DEVELOPMENT OF ANION-BINDING APPROACHES TO ASYMMETRIC CATALYSIS

by

NISHA MITTAL

A Dissertation submitted to the

Graduate School-New Brunswick

Rutgers, The State University of New Jersey

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

Graduate Program in Chemistry and Chemical Biology

Written under the direction of

Professor Daniel Seidel

And approved by

_____

_____

_____

_____

New Brunswick, New Jersey

May, 2014

ABSTRACT OF THE DISSERTATION

Development of Anion-Binding Approaches to Asymmetric Catalysis

By NISHA MITTAL

Dissertation Director:
Professor Daniel Seidel

The dual catalytic approach in asymmetric catalysis has gained considerable attention in recent times. Many otherwise inefficient and unattainable chemical processes can be accomplished by this approach. Outlined within this dissertation are recent efforts in improving the overall efficiency of this process as well as expanding this method involving nucleophilic/anion-binding catalysis to the kinetic resolution of allylic amines and 1,2-diamines. An efficient catalytic system has been identified through targeted structural modifications of both the achiral nucleophilic catalyst and the chiral anion-binding co-catalyst. This has resulted in increased selectivities while simultaneously allowing for significantly reduced catalyst loadings. Based on the mechanistic insight into the anion binding approach for the kinetic resolution of amines, we established that there was a 1:1 catalyst to benzoate anion binding ratio.

Cooperative approaches in which Brønsted acids act in concert with other Brønsted acids or (thio) urea co-catalysts have gained significance. This study describes the synthesis of a new class of chiral conjugate-base-stabilized Brønsted acid catalysts and a new concept for cooperative hydrogen bonding/ Brønsted acid catalysis. These chiral Brønsted acids contain a carboxylic acid group which is connected via an appropriate linker to an anion receptor moiety such as a thiourea. Substrate protonation by the catalyst results in the association of the conjugate base with the anion recognition site, resulting in the formation of a rigid catalyst/substrate ion pair. We were able to successfully apply this concept to the catalytic enantioselective Povarov and Pictet-Spengler reactions.

DEDICATION

To my parents and my husband, for always believing in me and giving me motivation to succeed.

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my principal advisor, Professor Daniel Seidel, for his guidance, support and imparting in me his thorough and keen sense of perfection throughout my graduate research at Rutgers University. I will always be grateful to you for enlightening me and helping me in becoming a more organized and self-reliant person. You were always there for discussions and suggestions which have helped me to solve research related problems. Your dedication has greatly inspired me and I would like to thank you from the bottom of my heart for helping me in achieving my goals.

I would like to thank my committee members; Professor Lawrence J. Williams, Professor Kai C. Hultzsch and Dr. Harold B. Wood. I am really grateful to you, for your valuable time, suggestions and guidance.

To all the past and present members of the Seidel group−it was a great experience working with all of you. Invaluable discussions over our group coffee time, sharing fun times, lunches and many other things have been a great motivation throughout my Ph.D. career. The best part of being in the Seidel group was everyone was always willing to discuss and provide help with work related problems at any time. I have learnt a lot of things from the group members. It was pleasure working with Dr. Indubhusan Deb, Dr. Deepankar Das, Dr. Chandra Kanta De, Dr. Eric G. Klauber, Matthew Richers, Longle Ma, Tejas K.Shah, Aaron X. Sun, Diana X. Sun, Chang Min, Weijie Chen, Abbas Sanchawala and Chenfei Zao. Special thanks to Dr. Indubhusan Deb for providing prompt help and advice. I am greatly indebted to Dr. Deepankar Das for his constant support inside and outside the lab. You were a wonderful colleague and are an awesome friend, who has always of great help and a source of motivation. I am really thankful to you for your suggestions and many other things which are difficult to express. Special thanks to Diana X. Sun, it was a wonderful experience working with you. You are a great colleague and friend to work with. Your dedication and liveliness has always inspired me all the time. I am really

indebted to you. I would also like to thank Aaron X. Sun and Michael Haibach for helpful discussions and suggestions. I would like to convey my sincere thanks to Tom Emge for his help and support for all crystallography related questions.

I would like to thank my parents who are behind all my achievements. I am indebted to you for making me capable and be independent in establishing my career. I am thankful to my brother, Gaurav Mittal, sister, Isha Gupta and my brother- in-law, Sachin Gupta for always helping me and specially convincing my father for allowing me to come to United States to pursue my career. This journey began only when they showed confidence in my abilities. I am also thankful to my grandparents and my in-laws for their love and support.

I am greatly thankful to my husband, Rochak Vig for his unconditional love and support. You were always there for me as a childhood friend, lover and now as a husband to motivate and encourage me throughout my life. I am really short of words in expressing my gratitude towards you. I am not sure what I would have done without your help and support.

Last but not the least my acknowledgement is reserved for all my friends and cousins. Without them this would not have been possible. I am thankful to my friends in India, Rashi Bansal, Neha Grover and Aditi Kejriwal, they are my childhood friends and have always loved me and believed in me. I would like to thank all my friends, Abhishek, Shweta, Rubal, Gayatree, Rekha, Pallavi, Manik and Reddy. A special thanks to Dr. Prasad Subramaniam whom I know since my masters and who is one person I have always counted on. You were always there for me in all my good and some real tough times at Rutgers. I am really thankful to you for your love and support. I am greatly indebted to Saket Kharsikar, who was always a great source of inspiration and motivation. I will always remember you saying" I know you can do it". Lastly, I am really thankful to Soma Mandal who has been a true friend always. You were always there for me for the problems I had in my personal or professional life. You have always motivated me and tried to point out wherever I was wrong and guided me to the right things. I have always looked upon you as a sister and close friend. Thank you for all the help.

Table of Contents

List of Tables

List of Figures

List of Schemes

Abbreviations, Symbols and Units

δ	Chemical shift
π	Pi
Å	Angstrom
μL	Microliter
μW	Microwave
°	Degree
°C	Degree Celsius
%	Percent
acac	Acetylacetonate
AcCl	Acyl chloride
AcOH	Acetic acid
AgOAc	Silver Acetate
app	Apparent
atm	Atmospheric pressure
BA	Benzoic Anhydride
BINOL	1,1'-Bi-2-naphthol
Boc_2O	Di-*tert*-Butoxycarbonyl
Br	Bromide
br	Broad
Bu	Butyl
Bn	Benzyl
C_6D_6	Deuterated benzene
$(CD_3)_2SO$	Deuterated dimethyl sulfoxide
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
cm	Centimeter
cm^{-1}	Inverse centimeter
comp	Complex
conv	Conversion
cp_2ZrCl_2	Bis(cyclopentadienyl)zirconium dichloride
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethylsulfoxide

dr	Diastereoselectivity
ee	Enantiomeric excess
equiv	Equivalents
ESI-MS	Electron spray ionization mass spectrometry
Et	Ethyl
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
EtOH	Ethanol
FT-IR	Fourier transform infrared spectroscopy
g	Gram
h	Hour
H	Hydrogen, Proton
^{1}H NMR	Proton Nuclear Magnetic Resonance
H_2O	Water
HPLC	High Pressure Liquid Chromatography
Hz	Hertz
*i*Pr	Isopropyl
iPr_2NEt	*N*,*N*-diisopropylethylamine
*i*PrOH	Isopropanol
J	Coupling constant
KBr	Potassium bromide
m	Multiplet
M	Molar
Me	Methyl
MeOH	Methanol
mg	Milligram
MHz	Megahertz
min	Minute
mL	Milliliter
mM	Millimolar
mmol	Millimole
mol	Mole
mp	Melting point
MS	Molecular sieves
MTBE	Methyl *tert*-butyl ether

m/*z*	Mass to charge ratio
NMR	Nuclear magnetic resonance
OAc	Acetate
OBz	Benzoate
Ph	Phenyl
PPh_3	Triphenylphosphine
ppm	Parts per million
ppy	4-Pyrrolydinopyridine
*p*TSA	*p*-Toluenesulfonic acid
q	Quartet
R_f	Retention factor
rt	Room temperature
s	Singlet
t	Triplet
*t*Bu	Tertiary butyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMSCl	Trimethylsilyl chloride
v/v	Volumetric ratio

Chapter I

Introduction

1.1 Background

Asymmetric catalysis has become a convenient tool for adding complexity to molecules. Many catalytic systems are based on metal complexes with chiral ligands,[1] enzymes[2] and a variety of organocatalysts.[3] Due to increasing demand and immense potential, there has been a significant development in this vast pool of catalytic processes.

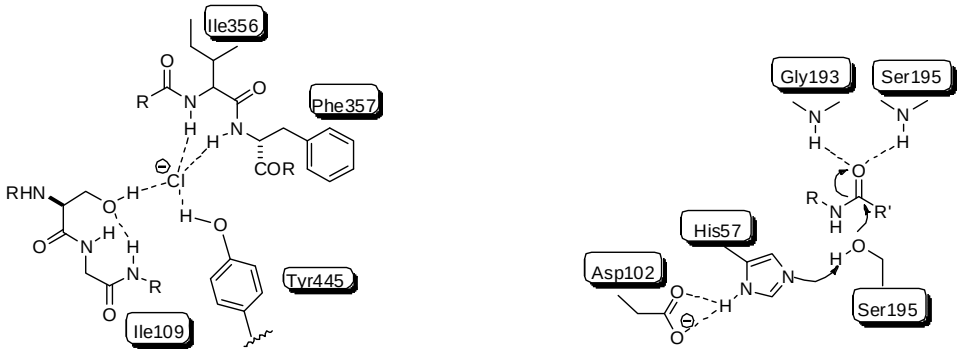
The propensity to develop environmental friendly synthesis has encouraged the growth of "metal free catalysis," or organocatalysis over the past two decades.[3d,3e] Typically, organocatalytic methods involve less sensitive conditions. The motivation to develop greener chemistry has led to tremendous development in the structural diversity of organocatalysts. These catalysts have displayed great potential for a number of chemical transformations. Organocatalysis can be classified into many subfields such as hydrogen bonding catalysis, iminium/enamine catalysis, phase transfer catalysis, Brønsted acid catalysis and nucleophilic/Lewis basic catalysis. Notably, organocatalysts employed in each of these methods can be categorized into more than one class and have the potential to activate more than one type of substrate.

1.2 Hydrogen Bonding Catalysis

In recent years, development of small molecule hydrogen bonding donors has increased considerably and has become a major part of the field of organocatalysis.[4] There is a close relationship between anion recognition,[5] active site consideration in enzyme catalysis and organocatalysis involving hydrogen bonding. For example, **A** displays binding of the chloride

anion by hydrogen bonding donors in the chloride channel, whereas in **B** the negatively charged oxygen atom is stabilized by hydrogen bonding in the active site of a serine protease enzyme (Figure 1.1).[6]

***Figure 1.1*: Anion Recognition in Biological Systems**

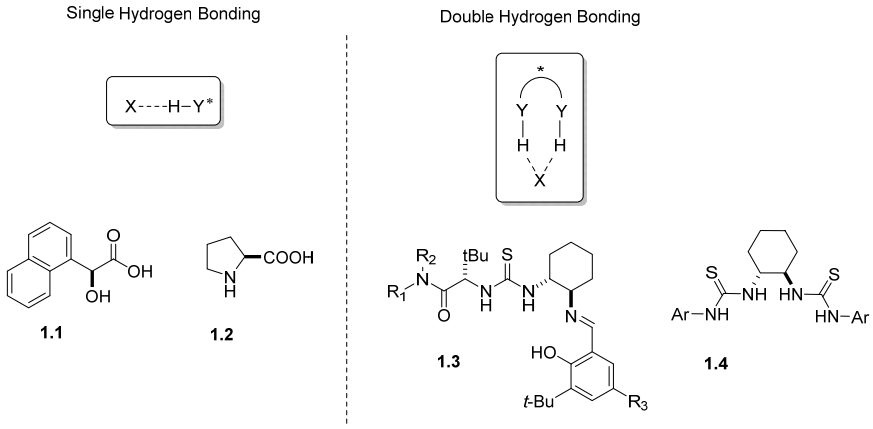


A. Cl^- binding site in chloride channel **B.** Oxyanion intermediate

The field of organocatalysis has been greatly inspired by various biological systems and as such, over the last decade new classes of catalysts have emerged. Many organocatalysts have been designed to mimic enzymatic mechanisms.[7] Also, mechanisms of several organocatalytic reactions have found correspondence with biological reactions. It has long been known that non-covalent interactions such as hydrogen bonding play a significant role in the majority of enzyme-catalyzed biological processes.[8]

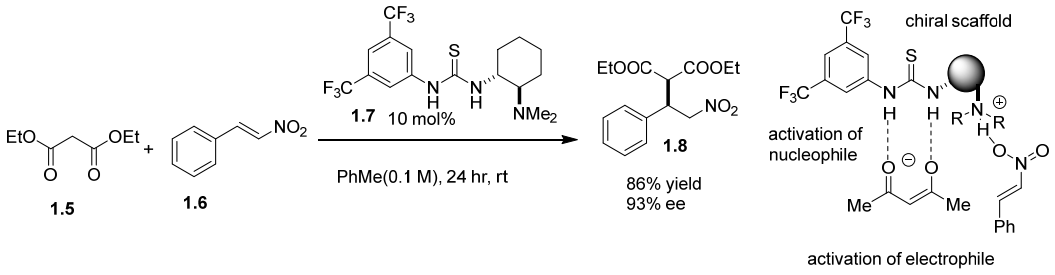
Many chiral HB catalysts linked with various types of structural and functional frameworks have been established. The source of chirality in thiourea catalysts may arise from 1,2-aminoindanol, 1,2-cyclohexanediamine, amino acids, BINAM, cinchona alkaloids, etc. They commonly include single or double hydrogen bonding donor sites (Figure 1.2). Organocatalysts such as chiral diols, proline and hydroxyl acids are examples of single hydrogen bond donors. Significant contributions in this area have been made by Yamamoto, Rawal, List and many others.[9]

***Figure 1.2*: Single vs Double Hydrogen Bonding**



Elegant contributions from Jacobsen, Corey, Nagasawa and others introduced several HB catalysts which activate the substrate primarily through double hydrogen bonding.[10] In addition to the concept of single or double hydrogen bonding sites, bifunctional catalysts contain a secondary site that is either weakly Lewis basic or acidic. In 2003, Takemoto reported a bifunctional catalyst (**1.7**) containing both a thiourea moiety as the hydrogen bonding site and an amine group as the Lewis basic site.[11] Catalyst **1.7** promoted Michael addition of 1,3-dicarbonyl compounds to nitrostyrene in high yields and enantioselectivity (Scheme 1.1).

***Scheme 1.1*: Bifunctional Catalysis**

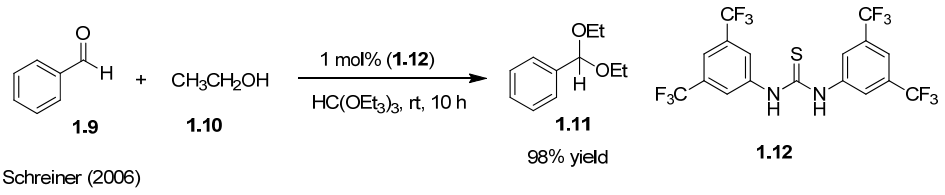


1.3 Chiral Ion Pair Catalysis

1.3.1 Anion Binding

Anion recognition is a vital component of hydrogen bonding catalysis.[6] Binding of anions to (thio) urea moieties via hydrogen bonding as well as other non-covalent interactions is responsible for small molecule catalysis in a number of reactions. The potential of (thio) urea derivatives to act as excellent anion receptors was revealed by Wilcox and Hamilton in 1992.[12] Since then, there has been a tremendous growth in the number of catalytic enantioselective transformations involving anion binding. The success of these reactions is largely dependent on the strength of the anion bound to the hydrogen bonding receptor, which is in close proximity to the positively charged electrophile. The resulting ion pair formed is particularly strong in nonpolar solvents.

***Scheme 1.2*: Acetalization Reaction Using Thiourea Hydrogen Bonding Catalyst**



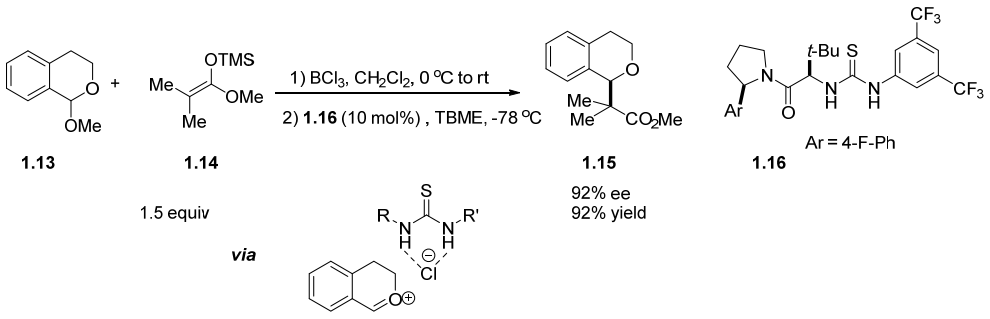
1.9 **1.10** **1.11** 98% yield **1.12**

Schreiner (2006)

Schreiner and co-workers demonstrated the ability of thiourea to bind the oxyanions in an acetalization reaction[13] (Scheme 1.2). In the proposed mechanism, the thiourea catalyst (**1.12**) activated the carbonyl of the aldehyde or ketone via double hydrogen bonding. The catalyst acted as a partial proton donor to the carbonyl, which was then followed by the nucleophilic attack of the alcohol. The products were obtained in high yields and most of the results were comparable to that obtained in the presence of *p*-toluenesulfonic acid monohydrate as the catalyst. Later, in the same year, this group showed the anion binding of oxyanions in the addition of aliphatic amines and alcohols to epoxides.[14]

Halide anions are recognized as good hydrogen bond acceptors. Jacobsen's group reported the binding of a thiourea catalyst to a halide anion in nucleophilic additions to *N*-acyliminium ions[15] in Pictet Spengler cylization[16] and Mannich type reactions.[17]

***Scheme 1.3*: Addition to Oxocarbenium Ion**

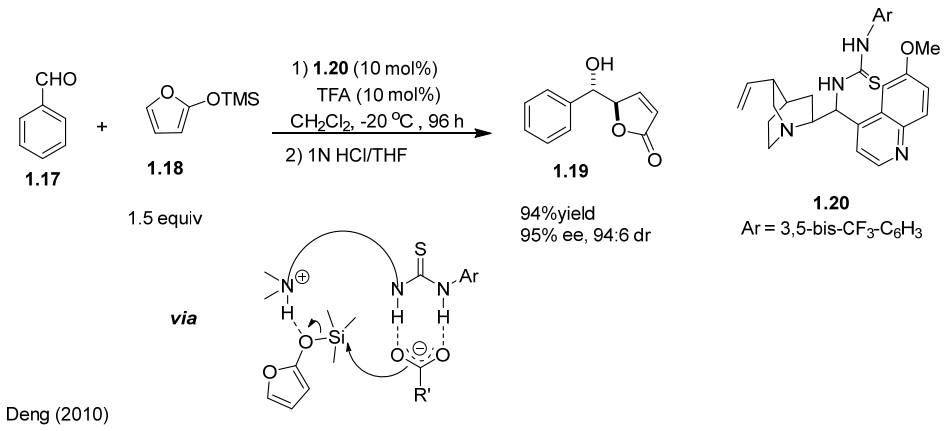


Jacobsen (2008)

In 2008, Jacobsen et al. disclosed the enantioselective addition of silyl ketene acetals to an in situ generated oxocarbenium ion.[18] This reaction provided substituted isochromans in high yield and enantioslectivity (Scheme 1.3). Recognition of cyanide ion (CN^-) in anion recognition was reported by the same group in the Strecker reaction of *N*-allylimines.

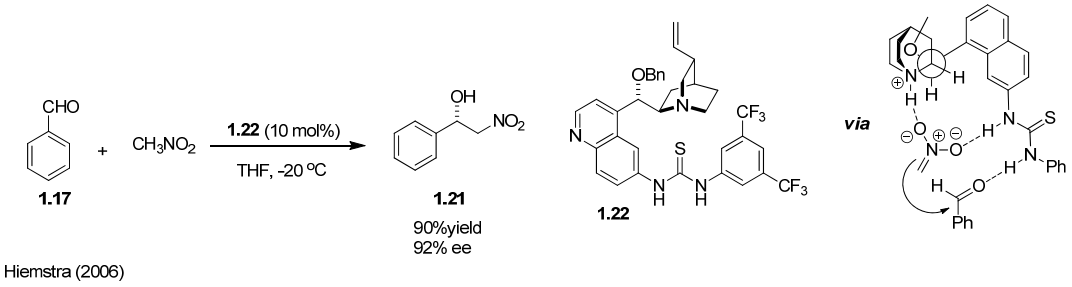
Carboxylates are predominantly found in biological systems and are also widely known to bind the (thio) urea receptors. Some examples of carboxylate binding to the hydrogen bonding catalysts, specifically in the decarboxylation type reactions, were shown by Rouden,[19] Wennemers and Lubkoll.[20] A more recent example was provided by Deng and co-workers where they developed a carboxylate amine salt catalyst prepared from mixing a carboxylic acid and a thiourea amine.[21] This amine salt was employed to catalyze a vinylogous aldol reaction of silyoxy furans (Scheme 1.4). It was hypothesized that the carboxylate bound to the thiourea activates the silyoxy furan and also helps in the silyl transfer to the aldolate product.

***Scheme 1.4*: Vinylogous Aldol Reaction of Silyoxy Furan**



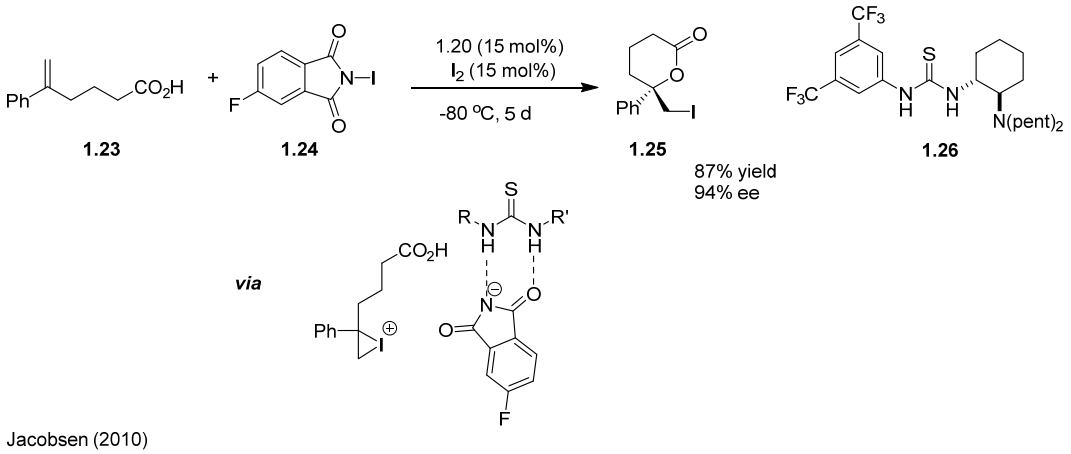
In addition to the resemblance of the thio (urea) derivatives to the guanidinium ions, Kelly[22] and Hamilton[23] observed that the negative charge on the nitronate ion helps it to strongly bind to the hydrogen bonding catalysts. In 2006, Hiemstra and co-workers reported the addition of nitromethane to aromatic aldehydes (Henry reaction) in the presence of 10 mol% of thiourea substituted cinchona catalyst. High enantioselectivity and yields were obtained (Scheme 1.5).[24]

***Scheme 1.5*: Thiourea Catalyzed Enantioselective Henry Reaction**



Catalytic enantioselective iodolactolization is a challenging reaction due to high reactivity of the iodonium ion. In 2010, Jacobsen group reported this reaction by employing a *tert*-amino urea catalyst (Scheme 1.6).[25] It was proposed that the binding of the phthalimide to the urea leads to deprotonation of the carboxylic acid. Upon cyclization, the resulting lactones are formed in high yield and enantioselectivity.

***Scheme 1.6*: Catalytic Asymmetric Iodolactolization**



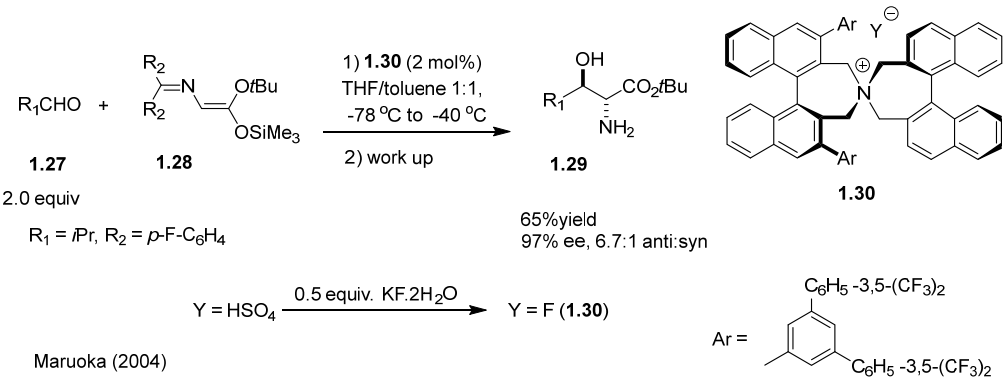
Jacobsen (2010)

1.3.2 Phase Transfer Catalysis

Phase transfer catalysis (PTC) is a kind of heterogeneous catalysis in which a phase transfer catalyst promotes the migration of a reactant from one phase to another where reaction occurs.[26] Environmentally friendly solvents and reagents, milder reaction conditions and easy operation in large scale have made this process attractive and useful.[27] In 1978, Wynberg and co-workers reported the first example of a Michael addition of nitromethane to chalcones catalyzed by chiral quarternary ammonium salt.[28] A highly efficient enantioselective PTC reaction was reported by researchers at Merck in the methylation of indanone.[29] Since then, phase transfer catalysts have been shown to catalyze a number of reactions enantioselectively.

Quarternary ammonium or phosphonium salts are typically employed in presence of anionic reactants. Traditionally, cinchona derived salts were employed as phase transfer catalysts. Important contributions by Shioiri[30] and Corey[31] displayed the use of cinchona ammonium salt derivatives. Ooi and Maruoka introduced C_2-symmetric binaphthyl ammonium salts such as **1.30** which turned out to be an effective catalyst in the asymmetric Mukayama aldol transformation, furnishing products in good yields and high enantioselectivities (Scheme 1.7).[32]

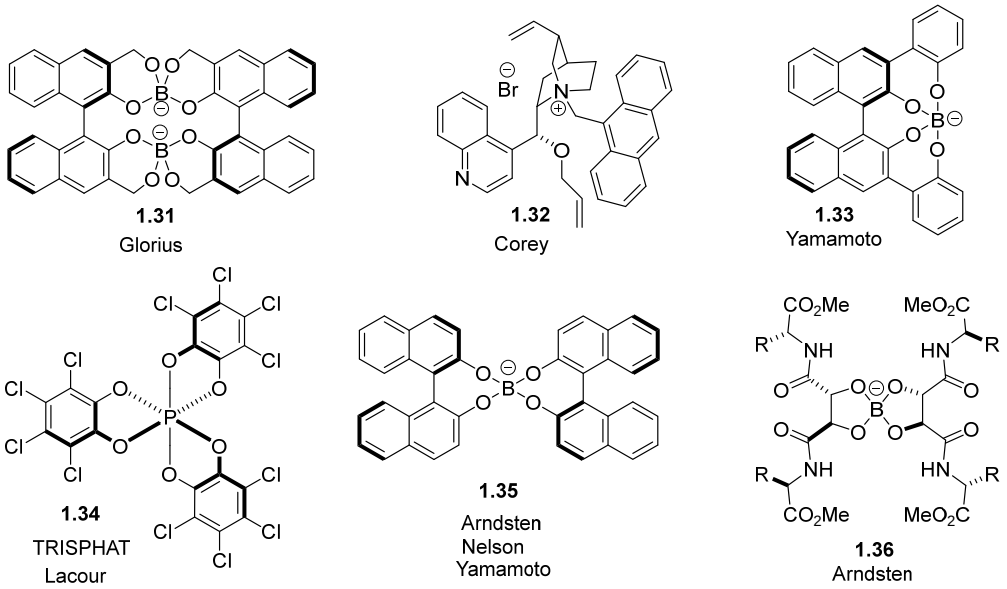
Scheme 1.7: **Mukaiyama Aldol Reaction Catalyzed by Chiral Ammonium Salt**



Chiral borates are the most common chiral anion phase transfer catalysts. Arndtsen introduced the use of a chiral counteranion such as chiral borate anion with an achiral metal complex for enantioselective olefin aziridination[33] and cyclopropanation.[34] In this pioneering work, asymmetry was induced solely by the chiral counteranion, while in other methods chirality transfer occurred upon various ionic interactions during catalysis. Other notable contributions were made by Yamamoto,[35] Nelson[36] and Leitner.[37] In a more recent example, Glorius and coworkers reported a dianionic chiral borate complex **1.31**, which was used as an efficient NMR shift reagent and a chiral resolving agent for *trans*-1,2-diaminocyclohexane and *trans*-1,2-diphenylethane-1,2-diamine (Figure 1.3).[38]

Lacour and co-workers reported a hexacoordinated phosphonium phase transfer catalyst. The presence of chlorine atoms on the D_3-symmetric tris(tetrachlorobenzenediolato)phosphate(V) anion (**1.34**) provided configurational stability to the molecule.[39] Furthermore, it helped in imparting lipophilicity to the anion, hence helping the ion pair to stay intact even in aqueous media. This catalyst was successfully employed for asymmetric epoxidation, providing ee of up to 76%.[40]

***Figure 1.3*: Chiral Phase Transfer Catalysts**



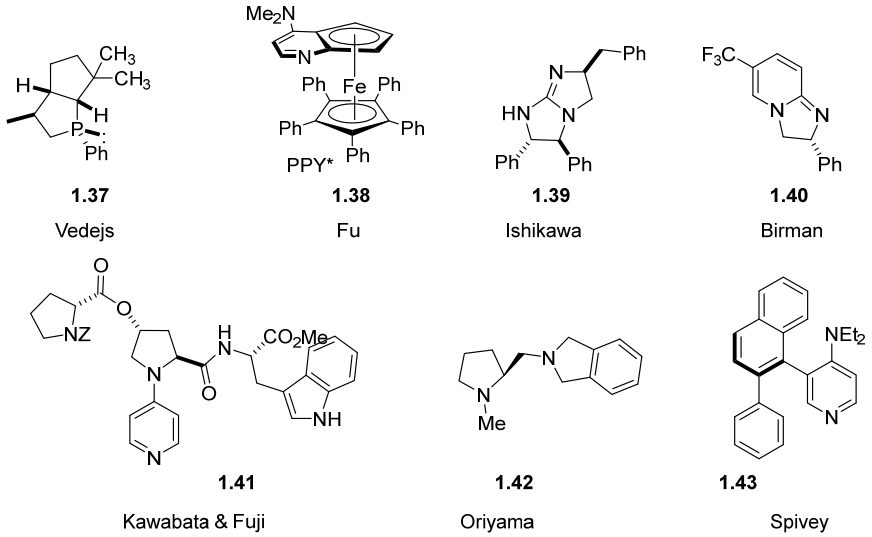
1.4 Nucleophilic Catalysis

The ubiquity of nucleophilic catalysts has led to their widespread application in organocatalysis.[41] While a wide array of catalytic systems has been dependent on metal catalysts, Lewis acids or organometallic agents, the demand of nucleophilic catalysts to induce asymmetry has grown rapidly. A library of these catalysts has been developed over the decades. Amongst these, tertiary phosphines, tertiary amines, imidazoles and pyridines have been shown to promote a number of reactions (Figure 1.4).[41c,42]

Significant inspiration for the development of nucleophilic catalysts has been drawn from biological processes.[41b] Specifically, chiral amine catalysts have stood out amongst the class of nucleophilic catalysts.[43] Some of them have also been categorized as Lewis basis. Upon carbonyl activation, the formation of enamine or iminium ions have been extensively studied as a

key concept and is now a matured field of organocatalysis.[44] However, mechanistically, sometimes it is difficult to differentiate between Lewis base or nucleophilic catalysis.

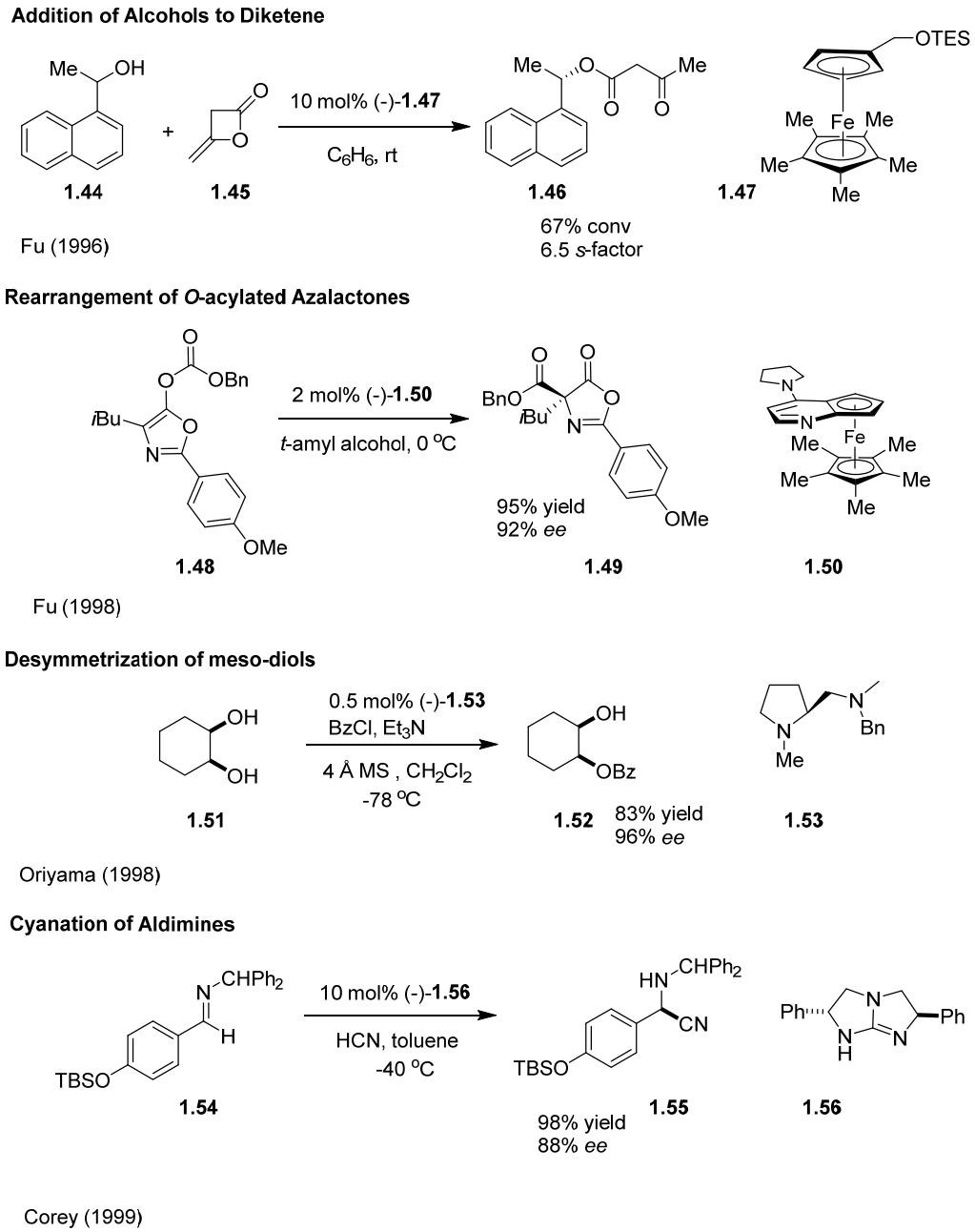
***Figure 1.4*: Common Chiral Nucleophilic Catalysts**



Chiral amine nucleophilic catalysts are known to catalyze a number of chemical processes, importantly, addition of alcohols to ketenes,[45] rearrangement of *O*-acylated azalactones,[46] desymmetrization of meso-diols,[47] cyanation of aldimines[10b] and many others (Figure 1.5).[48] Amongst several nitrogen based nucleophilic catalysts, DMAP in particular possesses exceptional properties.[49]

Due to its versatile nature, DMAP has been frequently used as nucleophilic catalyst for several reactions. It is known to accelerate reactions such as acylation process by several orders of magnitude.[49a,50] Pioneering contribution by Fu et al. introduced chiral version of DMAP for kinetic resolution of amines.[41a,51] Since then, several attempts for synthesis of chiral DMAP analogues have been made. However, in most cases, due to tedious synthesis, its applicability has been limited to a few examples.

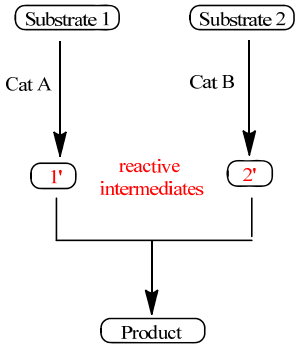
***Figure 1.5*: Application of Nucleophilic Catalysts**



1.5 Dual Catalysis

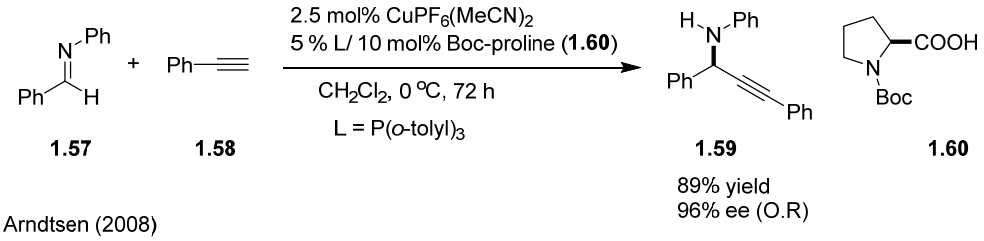
Several otherwise unachievable and inefficient catalytic processes have been accomplished by a dual catalysis approach. A dual catalytic method involves two different catalysts that work simultaneously to separately activate both the electrophile and the nucleophile in order to carry out a single chemical process (Figure 1.6).[52] Compared to the use of single catalysts, dual catalysis has been successful in achieving greater efficiencies for many chemical reactions.

***Figure 1.6*: Dual Catalysis Approach**



Traditionally, Lewis acid catalysts have been used in combination with various chiral ligands to promote many chemical transformations.[1b] Arndsten and co-workers demonstrated a merger of hydrogen bonding and metal catalysis in an asymmetric imine alkynylation reaction.[53] In this method, it was proposed that the imine gets activated by Boc-proline via hydrogen bonding, while the alkyne is activated by the Cu^{I}-phosphine complex (Scheme 1.8). Products were obtained in high yields and enantioselectivities, thereby showing the potential of the dual catalytic approach.

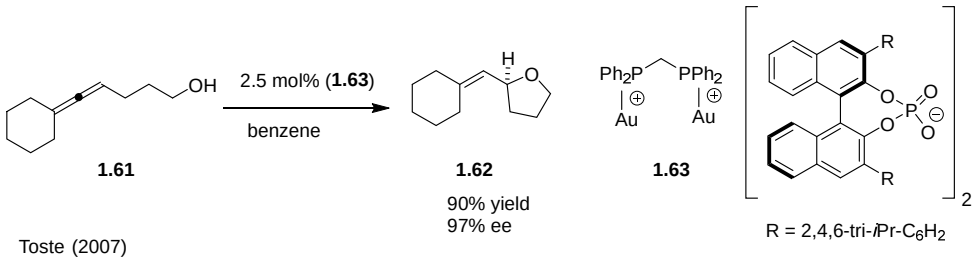
***Scheme 1.8*: Asymmetric Imine Alkynylation**



Arndtsen (2008)

A more common approach to dual catalysis involves transition metal catalysts and chiral Brønsted acid catalysts such as phosphoric acid catalysts.[54] Au(I) is known to activate alkenes and alkynes. However, relatively few reports are known for enantioselective transformations. In 2007, Toste demonstrated the use of a Au(I) phosphine complex in combination with a chiral phosphoric acid catalyst for enantioselective allenol cyclization reaction (Scheme 1.9).[55] Later, the Trost group employed this strategy to various other chemical transformations such as the ring opening of meso-aziridinium ions, and the enantioselective syntheses of pyrazolidines, isoxazolidines and tetrahydrooxazines.[56]

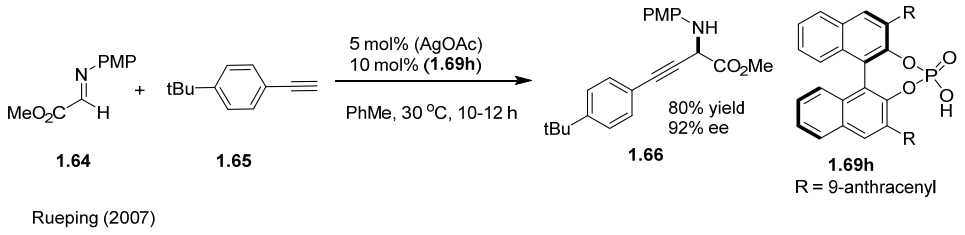
***Scheme 1.9*: Allenol Cylization via Chiral Au(I) Phosphine Complex**



Toste (2007)

Rueping and co-workers reported enantioselective alkynylation of α-imino esters in the presence of AgOAc and chiral phosphoric acid. Here, dual catalysis occurs when the protonated imine and the phosphate forms an ion pair. Concurrently, the alkyne is activated by silver acetate, which then gets delivered to the iminium ion (Scheme 1.10).[57]

Scheme 1.10: **Asymmetric Alkynylation of α-imino esters**



Rueping (2007)

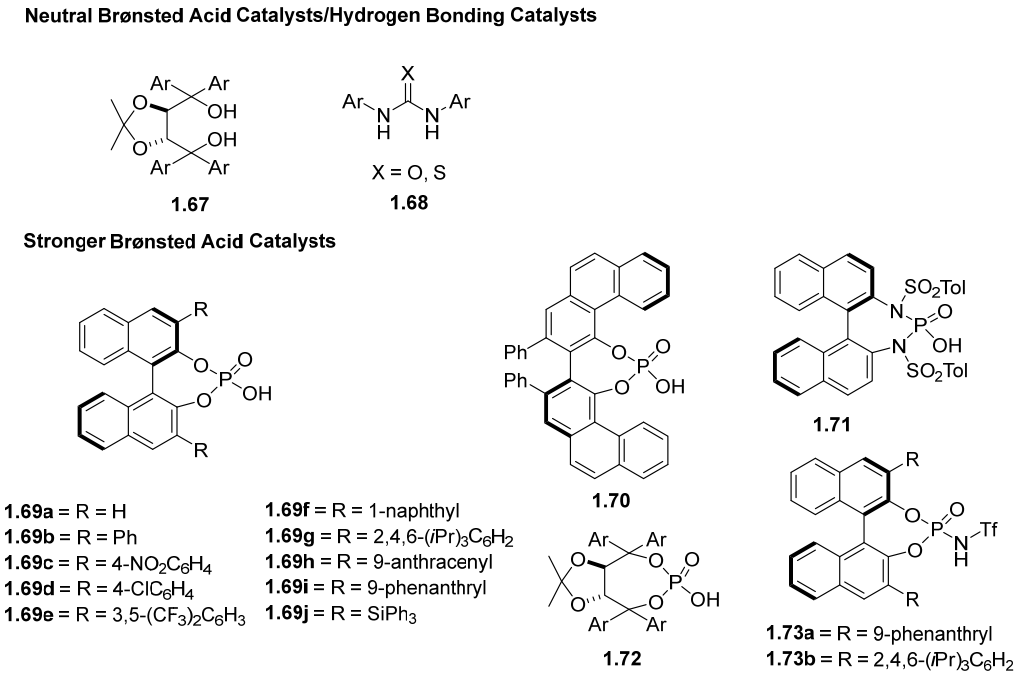
Other pioneering contributions to the combined transition metal and chiral phosphoric acid approach were made by List, Krische, Che, Hu, Gong and many others.[58] In addition, other synergistic strategies involving a chiral Lewis acid catalyst and different chiral catalysts (apart from chiral phosphoric acids) have been applied to a wide array of reactions. This includes the synthesis of α-allyl carbonyls, enamine catalysts and reactions of α,β-unsaturated carbonyls.[59] Overall, addressing problems of catalyst compatibility along with the challenges associated with dual catalysis has paved the way for the success of many otherwise inefficient and unattainable chemical processes.

1.6 Brønsted Acid Catalysis

As alluded to earlier, Lewis acid catalysis has been an integral part of the history of asymmetric catalysis.[1b,60] Due to its versatility and huge applicability in a number of reactions, this area of catalysis has been extensively exploited. On the other hand, Brønsted acid catalysts were typically employed for the synthesis of esters and acetals or hydrolysis and other related reactions. However, in contrast to Lewis acid catalysts, Brønsted acid catalysts are generally bench stable and easy to handle. Due to the attractive features of these organocatalysts,[3b,3c,3e] there has been significant development in this area of catalysis. In the past decade, Brønsted acid catalysts have appeared to dominate a number of enantioselective transformations, including many carbon-carbon bond forming reactions.[4b,61]

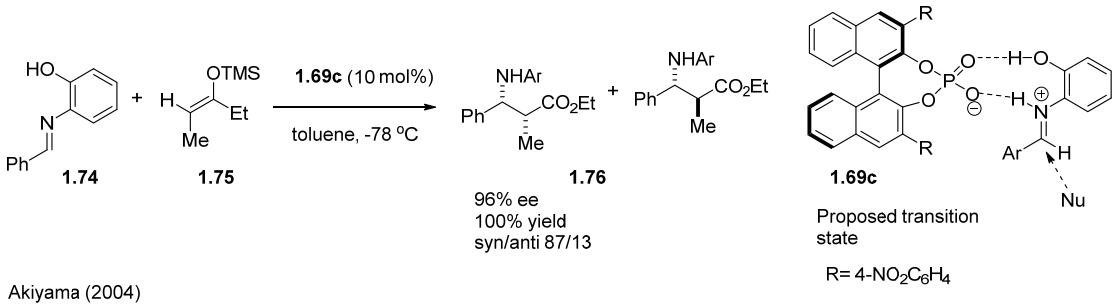
Brønsted acid catalysts can be neutral, such as (thio)urea catalysts,[62] or TADDOL-type catalysts.[9a,63] These catalysts mostly activate the substrates via hydrogen bonding. BINOL analogs or phosphoric acids contain rigid backbones and are much stronger than the neutral Brønsted acid catalysts (Figure 1.7). Specifically, phosphoric acids have gained much attention due to their exceptional structural and chemical properties.[61a,64] They can also act as bifunctional catalysts since they have a Brønsted acidic site (the proton on the hydroxyl group) and a Lewis basic site (sp^2 oxygen), while the substituents on the 3,3'-position provide a way to control stereoselectivity.

***Figure 1.7*: Common Chiral Brønsted Acid Catalysts**



In 2004, Akiyama and Terada independently reported the use chiral phosphoric acids in enantioselective Mannich-type reactions.[65] Akiyama and co-workers employed **1.69c** for addition of silyl ketene acetals to *N*-aryl imines, which provided products in high yields and selectivities. The hydroxyl group on the imine substrate plays a key role in formation of a nine-membered transition state and, thereby, in the enantioselective outcome of the reaction (Scheme 1.11).

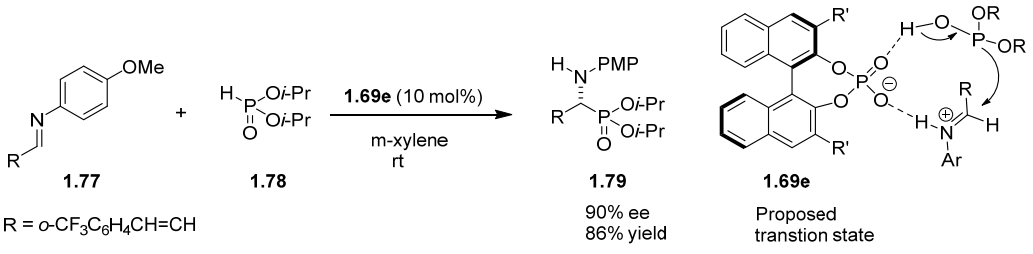
***Scheme 1.11*: Chiral Phosphoric Acid Catalyzed Mannich-type Reaction**



Akiyama (2004)

Later, in 2005, the same group reported hydrophosphonylation between aldimines and diisopropyl phosphites catalyzed by **1.69e**.[66] Activation of the aldimine via protonation and simultaneous activation of the nucleophile by the phosphonyl oxygen brings the two substrates in close proximity to each other and facilitates *re* facial attack

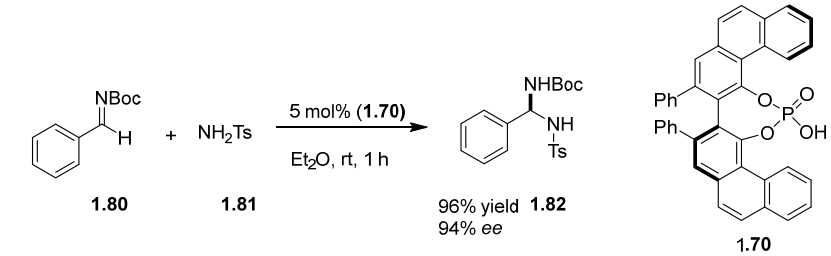
***Scheme 1.12*: Enantioselective Hydrophosphonylation of Imines**



Akiyama (2005)

Furthermore, in addition to carbon or phosphorus nucleophiles, nitrogen-containing nucleophiles such as amides have also been used as nucleophilic partners in Mannich type reactions. Antilla and co-workers employed a novel biphenanthrol derived phosphoric acid **1.70** (VAPOL) for this transformation (Scheme 1.13).[67] The aminal products were formed in high enantioselectivties.

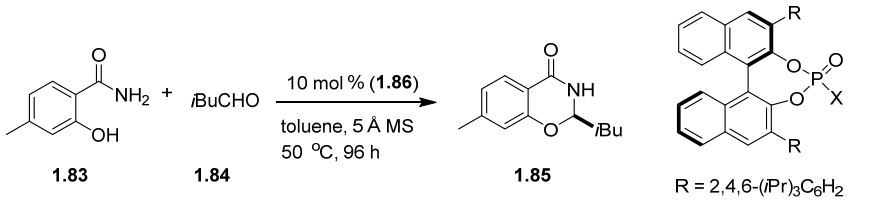
Scheme 1.13: **VAPOL Catalyzed Imine Amidation**



Antilla (2006)

In order to achieve even stronger Brønsted acid catalysts for substrates which are harder to activate (aldehydes, ketones etc.), *N*-trifyl phosphoramides by Yamamoto *et.al.*[68] and chiral disulfonimides by List *et.al.* were developed.[69] Additionally, the Antilla group extended the aminal formation to *N*,*O*-acetalization,[70] List and co-workers showed a broader scope for this reaction using a novel *N*-phosphinyl phosphoramide Brønsted acid catalyst. A broad range of hydroxyl amides and aldehydes were tested providing *N*,*O*- acetals with high level of enantioselectivity (Scheme 1.14).[71] The presence of the X group on the chiral Brønsted acid allowed its fine-tuning, making **1.80** an attractive Brønsted acid catalyst.

Scheme 1.14**: Enantioselective *N*, *O*-Acetalization *via* Chiral Phosphinyl Phosphoramide**

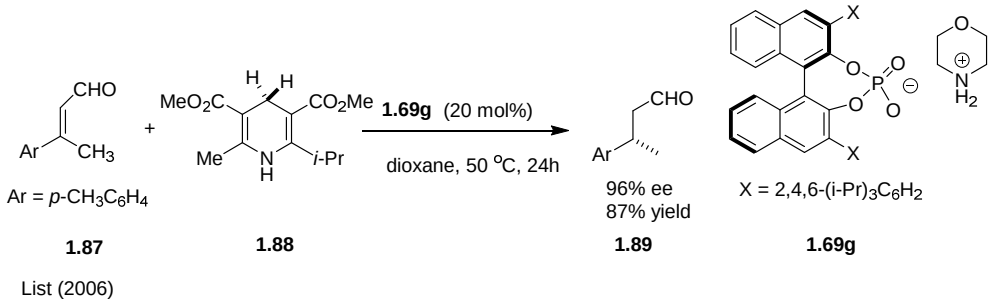


List (2010)

List and co-workers reported a counter ion directed asymmetric transfer hydrogenation of α,β-unsaturated aldehydes.[72] Introduction of this new strategy of counter ion directed catalysis

enabled the expansion of iminium ion catalysis. The reduced products were obtained in excellent yields and enantioselectivities (Scheme 1.15).

***Scheme 1.15*: Asymmetric Transfer Hydrogenation**



It can be concluded that chiral Brønsted acid catalysts, specifically chiral phosphoric acids, are facile and highly efficient organocatalysts. Tremendous development in this field of organocatalysis has expanded their utility and has enabled a number of chemical transformations for which previous catalytic methods were unsuitable.

1.7 Objective

Enantioselective catalysis via small molecules as hydrogen bond donors has opened new avenues in asymmetric catalysis. The growing interest in this area of research has led to the synthesis of a large number of catalysts with various frameworks. These catalysts have been widely employed for several inefficient and unattainable chemical processes leading to the synthesis of many biologically and pharmaceutically relevant compounds. Although various approaches to organocatalysis have been elucidated in the literature, some challenges to each of these strategies still remain.

The primary goal of this dissertation is to develop various anion binding approaches for organocatalysis, which would overcome the shortcomings of previously reported organocatalytic

methods. Chapter II focuses on a combined hydrogen bonding and nucleophilic catalysis approach. It has been previously applied to the kinetic resolution of benzylic and propargyl amines by our group. Chapter II includes extension of this approach to the kinetic resolution of allylic amines, a detailed study of the variation of nucleophilic catalysts (with application to benzylic amines), the kinetic resolution of 1,2-diamines and a detailed mechanistic insight into our proposed anion binding strategy for kinetic resolution of amines. Chapter III presents a dual catalysis approach to the Steglich rearrangement and enantioselective additions to isoquinolines. Chapter IV describes the synthesis of a new class of conjugate-base-stabilized Brønsted acid catalysts and the introduction of a hydrogen bonding and Brønsted Acid cooperative approach. It also includes application of this approach to the enantioselective Povarov and Pictet-Spengler reactions.

References:

(1) a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134; b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

(2) a) Höhne, M.; Bornscheuer, U. T. *ChemCatChem* **2009**, *1*, 42; b) Lee, J. H.; Han, K.; Kim, M.-J.; Park, J. *Eur. J. Org. Chem.* **2010**, 999.

(3) a) List, B. *Chem. Rev.* **2007**, *107*, 5413; b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; c) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; d) Bertelsen, S.; Jorgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178; e) List, B. *Adv. Synth. Catal.* **2004**, *346*, 1021.

(4) a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713; b) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289; c) Yu, X.; Wang, W. *Chemistry – An Asian Journal* **2008**, *3*, 516.

(5) Mangani, S.; Ferraroni, M. *Supramolecular Chemistry of Anions, Wiley, New York* **1997**.

(6) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187.

(7) Breslow, R. *Chem. Soc. Rev.* **1972**, *1*, 553.

(8) Fersht, A. *Structure and Mechanism in Protein Science, Freeman, New York* **1999**.

(9) a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146; b) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094; c) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080; d) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798; e) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.

(10) a) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012; b) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157; c) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416; d) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 153; e) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217.

(11) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

(12) a) Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369; b) Albert, J. S.; Hamilton, A. D. *Tetrahedron Lett.* **1993**, *34*, 7363; c) Smith, P. J.; Reddington, M. V.; Wilcox, C. S. *Tetrahedron Lett.* **1992**, *33*, 6085.

(13) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434.

(14) Kleiner, C. M.; Schreiner, P. R. *Chem. Commun.* **2006**, 4315.

(15) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577.

(16) a) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404; b) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.

(17) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 6700.

(18) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198.

(19) Amere, M.; Lasne, M.-C.; Rouden, J. *Org. Lett.* **2007**, *9*, 2621.

(20) Lubkoll, J.; Wennemers, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 6841.

(21) Singh, R. P.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2010**, *132*, 9558.

(22) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072.

(23) Linton, B. R.; Goodman, M. S.; Hamilton, A. D. *Chem. -Eur. J.* **2000**, *6*, 2449.

(24) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 929.

(25) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2010**, *49*, 7332.

(26) a) Lacour, J.; Hebbe-Viton, V. *Chem. Soc. Rev.* **2003**, *32*, 373; b) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222; c) Lacour, J.; Moraleda, D. *Chem. Commun.* **2009**, 7073.

(27) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656.

(28) Colonna, S.; Hiemstra, H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1978**, 238.

(29) Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.

(30) Ando, A.; Miura, T.; Tatematsu, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 1507
.

(31) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

(32) Ooi, T.; Taniguchi, M.; Doda, K.; Maruoka, K. *Adv. Synth. Catal.* **2004**, *346*, 1073.

(33) Llewellyn, D. B.; Adamson, D.; Arndtsen, B. A. *Org. Lett.* **2000**, *2*, 4165.

(34) Llewellyn, D. B.; Arndtsen, B. A. *Tetrahedron: Asymmetry* **2005**, *16*, 1789.

(35) a) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561; b) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520.

(36) Carter, C.; Fletcher, S.; Nelson, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1995.

(37) Chen, D.; Sundararaju, B.; Krause, R.; Klankermayer, J.; Dixneuf, P. H.; Leitner, W. *ChemCatChem* **2010**, *2*, 55.

(38) Loewer, Y.; Weiss, C.; Biju, A. T.; Fröhlich, R.; Glorius, F. *J. Org. Chem.* **2011**, *76*, 2324.

(39) Lacour, J.; Monchaud, D.; Marsol, C. *Tetrahedron Lett.* **2002**, *43*, 8257.

(40) Lacour, J.; Linder, D. *Science* **2007**, *317*, 462.

(41) a) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412; b) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601; c) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109.

(42) a) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432; b) De Rycke, N.; Couty, F.; David, O. R. P. *Chem. -Eur. J.* **2011**, *17*, 12852.

(43) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985

.

(44) MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

(46) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532.

(47) Oriyama, T.; Imai, K.; Sano, T.; Hosoya, T. *Tetrahedron Lett.* **1998**, *39*, 3529.

(48) Müller, C. E.; Schreiner, P. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 6012.

(49) a) Steglich, W.; Hoefle, G. *Angew. Chem. Int. Ed.* **1969**, *8*, 981; b) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129.

(50) Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk SSSR, Ser. Khim* **1967**, *176*, 97.

(51) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542.

(52) a) Allen, A. E.; MacMillan, D. W. C. *Chemical Science* **2012**, *3*, 633; b) Stegbauer, L.; Sladojevich, F.; Dixon, D. J. *Chemical Science* **2012**, *3*, 942.

(53) Lu, Y.; Johnstone, T. C.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2009**, *131*, 11284.

(54) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem. -Eur. J.* **2010**, *16*, 9350.

(55) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.

(56) a) Hamilton, G. L.; Kanai, T.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 14984; b) LaLonde, R. L.; Wang, Z. J.; Mba, M.; Lackner, A. D.; Toste, F. D. *Angew. Chem. Int. Ed.* **2010**, *49*, 598.

(57) Rueping, M.; Antonchick, A. P.; Brinkmann, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 6903.

(58) a) Liao, S.; List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 628; b) Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16448; c) Liu, X.-Y.; Che, C.-M. *Org. Lett.* **2009**, *11*, 4204; d) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182; e) Hu, W.; Xu, X.; Zhou, J.; Liu, W.-J.; Huang, H.; Hu, J.; Yang, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782-7783; f) Li, C.; Wang, C.; Villa-Marcos, B.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 14450.

(59) a) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4387; b) Ibrahem, I.; Córdova, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1952; c) Sun, T.; Hou, G.; Ma, M.; Zhang, X. *Adv. Synth. Catal.* **2011**, *353*, 253.

(60) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(61) a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744; b) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999; c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; d) Pihko, P. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2062.

(62) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299.

(63) a) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846; b) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 92.

(64) Connon, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3909.

(65) a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356; b) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.

(66) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583.

(67) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696.

(68) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626.

(69) García-García, P.; Lay, F.; García-García, P.; Rabalakos, C.; List, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 4363.

(70) Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216.

(71) Vellalath, S.; Čorić, I.; List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 9749.

(72) Mayer, S.; List, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4193.

Chapter-II

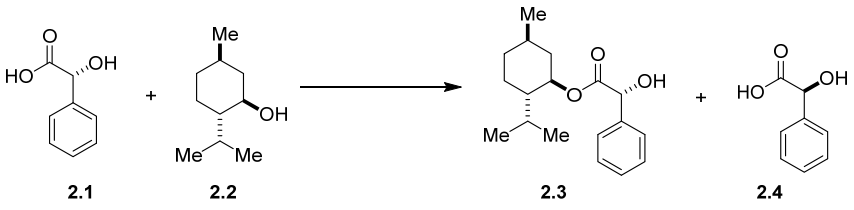
Kinetic Resolution of Amines

2.1 Background

Enantiomerically pure chiral amines are important building blocks in the synthesis of many biologically active compounds. They have largely been used as chiral auxiliaries, resolving agents and precursors in the syntheses of many neurological, immunological, anti-infective and antiemetic drugs.[1] The absolute configuration/stereochemistry of these chiral amines defines their pharmacological properties.[2] Despite their widespread application and importance, the development of bio catalytic methods for their preparation has been limited.[3] Amongst these, kinetic resolution of their racemates using lipases and acylases as enzymes has been the most popular method.[4]

In addition to the enzymatic methods, classical resolution via crystallization has been traditionally employed. In 1899, first attempts were made by Marckwald and McKenzie. They were able to isolate the less reactive *l*-mandelic acid from racemic mandelic acid, using (-)-menthol as the resolving agent (Scheme 2.1).[5] One drawback of these methods is the use of stoichiometric amounts of the chiral resolving reagent.

Scheme 2.1: **Kinetic Resolution of Mandelic Acid**



2.1 **2.2** **2.3** **2.4**

Marckwald & McKenzie (1899)

While, non-enzymatic kinetic resolution has gained significant importance, resolution via small molecule catalysis has remained a challenge. Kinetic resolution is defined as a process where two enantiomers of a racemate show different rates of reactivities in a particular reaction condition. Typically, the rate of reaction with fast reacting enantiomer is much more than the slow reacting enantiomer ($k_f >> k_s$). The efficiency of a kinetic resolution is measured in terms of the selectivity factor *s* which corresponds to relative rates of reactivities of the two enantiomers. It is defined as $s= k_f/k_s$.[6]

The following equation is used to calculate the *s*-factor :

$$\boldsymbol{s} = \frac{\boldsymbol{ln}\big((\mathbf{1}-\boldsymbol{C})(\mathbf{1}-\boldsymbol{ee})\big)}{\boldsymbol{ln}\big((\mathbf{1}-\boldsymbol{C})(\mathbf{1}+\boldsymbol{ee})\big)}$$

The conversion can be calculated using NMR, GC/MS or more commonly HPLC analysis. Conversion C can be calculated using the equation $\boldsymbol{C} = \frac{\boldsymbol{ee_{SM}}}{\boldsymbol{ee_P + ee_{SM}}}$, where $\boldsymbol{ee_p}$ is the enantiomeric excess of the product and $\boldsymbol{ee_{SM}}$ is the enantiomeric excess of the unreacted starting material. The *s*-factor can be determined using the calculated conversion and *ee* from either the product $\boldsymbol{ee_p}$, or recovered starting material $\boldsymbol{ee_{SM}}$, using the following equations:

$$\boldsymbol{s} = \frac{\boldsymbol{ln}\big((\mathbf{1}-\boldsymbol{C_{HPLC}})(\mathbf{1}-\boldsymbol{ee_P})\big)}{\boldsymbol{ln}\big((\mathbf{1}-\boldsymbol{C_{HPLC}})(\mathbf{1}+\boldsymbol{ee_P})\big)}$$

$$\boldsymbol{s} = \frac{\boldsymbol{ln}\big((\mathbf{1}-\boldsymbol{C_{HPLC}})(\mathbf{1}-\boldsymbol{ee_{SM}})\big)}{\boldsymbol{ln}\big((\mathbf{1}-\boldsymbol{C_{HPLC}})(\mathbf{1}+\boldsymbol{ee_{SM}})\big)}$$

Generally, *s*-factors ≥ 10 are considered useful. Although a maximum yield of 50% makes kinetic resolutions inefficient, relatively inexpensive racemates, the small amount of resolving reagent required and the possibility of obtaining high selectivity for the recovered

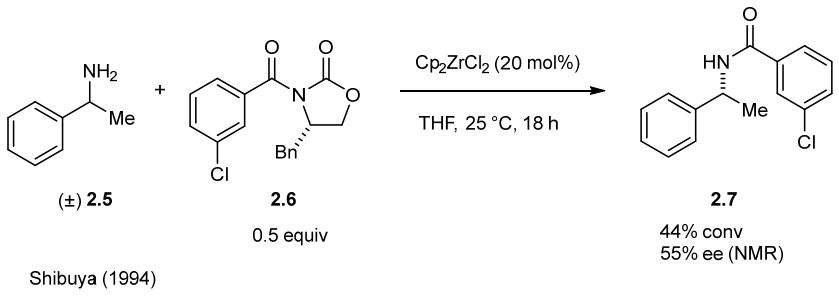
starting material make this approach attractive.

2.1.1 Chiral Acylating Reagents for Kinetic Resolutions

Enzymes are remarkable catalysts for instilling asymmetry in a number of organic compounds. Acylative enzymes like lipases have been extensively utilized in the synthesis of chiral amino acids, amides and alcohols via kinetic resolution.[4] Intrigued by the efficiency of these biocatalysts, many groups have developed small molecule catalysts for resolution via acylation.

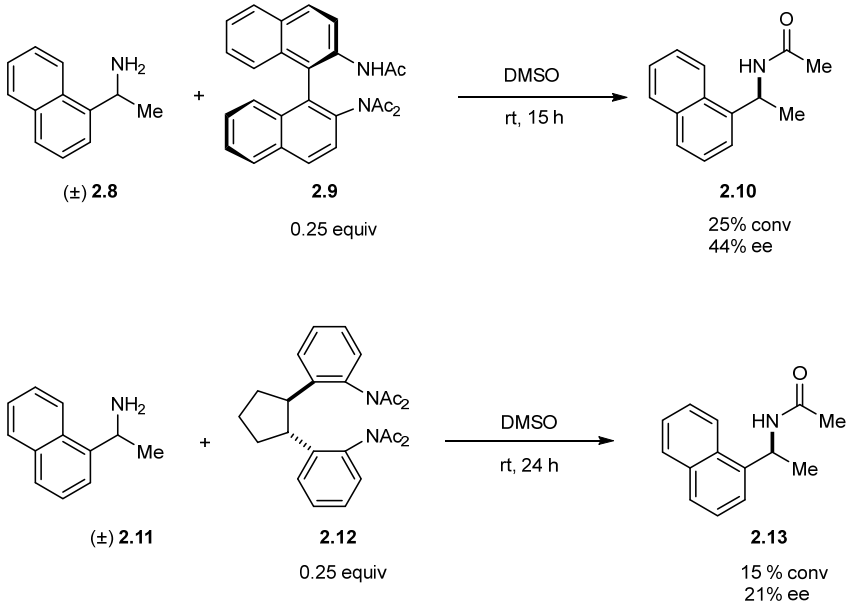
The first example of a non-enzymatic kinetic resolution process for amines was reported in 1994 by Shibuya and co-workers (Scheme 2.2).[7] Straight chain primary amines were resolved chemo-selectively using chiral *N*-acyl-2-oxazolidinones as acylating reagents in the presence of Cp_2ZrCl_2 as a Lewis acid.

***Scheme 2.2*: Chiral Oxazolidinone as Acyl Transfer Reagent**



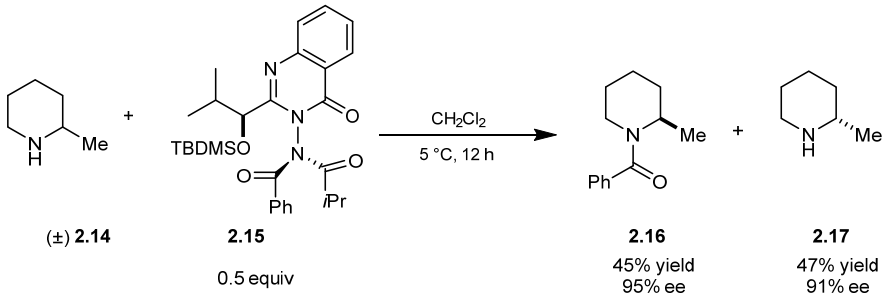
Murakami *et al*. reported a BINAM-based triacetoxy acetylating reagent (**2.9**) for the enantioselective *N*-acylation of secondary amines.[8] Interestingly, the reaction worked best in polar solvents like DMSO. This group later introduced a unique acetylating reagent with a cyclopentane backbone (**2.12**) which gave lower selectivities compared to the BINAM-backbone reagent (Scheme 2.3).[9]

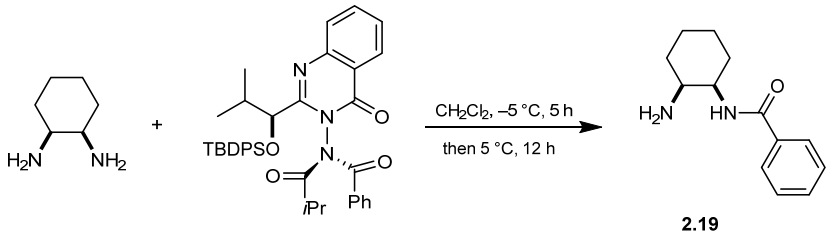
***Scheme 2.3*: *N*-Acylation by Chiral Aniline Derivatives**



In 2000, Atkinson and co-workers employed a single diastereomer of axially chiral diacylamino quinazolinone (DAQ) **2.15** as an acylating reagent.[10] It resolved 2-methyl piperidine with high selectivity. It was proposed that the enantioselectivity was largely controlled by the chiral axis along the N–N bond in DAQ. Later in 2007, Al-Sehemi and co-workers applied the other enantiomer of **2.15** to the desymmetrization of *meso*-1, 2-cyclohexanediamine to obtain the benzoylated product with high selectivity (Scheme 2.4).[11]

***Scheme 2.4*: Chiral 3-(*N*, *N*-diacylamino) quinazolin-4(3H)-one as Acylating Reagent**



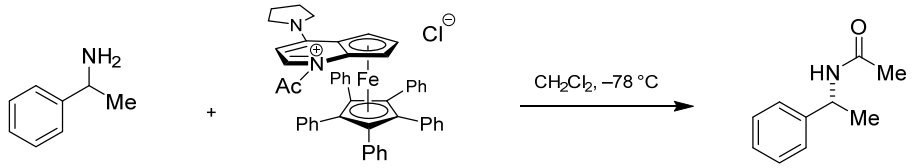


2.18 **2.15** **2.19**
91% yield
95% ee

Atkinson (2007)

Fu and co-workers introduced *N*-acylated Ph-PPY* (**2.20**), a new planar chiral derivative of PPY, which efficiently resolved benzylic amines in high enantioselectivity at –78 °C. Although this process required 8 equivalents of amine and gave lower conversions, this catalyst was a significant advance in the field of kinetic resolution compared to previously reported chiral acylation catalysts (Scheme 2.5).[12]

***Scheme 2.5*: Chiral PPY Ferrocene as an Acyl Transfer Reagent**

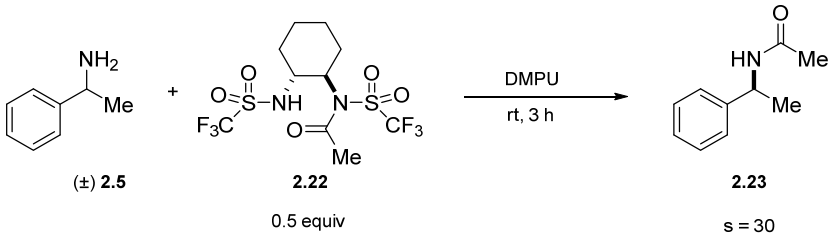


(±) **2.5** **2.20** **2.21**
8 equiv 1 equiv 87% ee

Fu (2000)

In 2004, Mioskowski *et al.* described a (1*S*, 2*S*)-cyclohexane-1, 2-diamine-based reagent for the enantioselective acylation of racemic primary amines. Acetylated product was obtained in high levels of selectivity (*s*-factor up to 30) at room temperature (Scheme 2.6). A remarkable dependency on solvent was observed. Switching from nonpolar solvents like toluene to polar solvents like DMSO and DMPU, gave higher *s*-factor and reversal of selectivity.[13] Later, Kagan *et al*. reported asymmetric amplification of amines using the racemic form of Mioskowski reagent.[14]

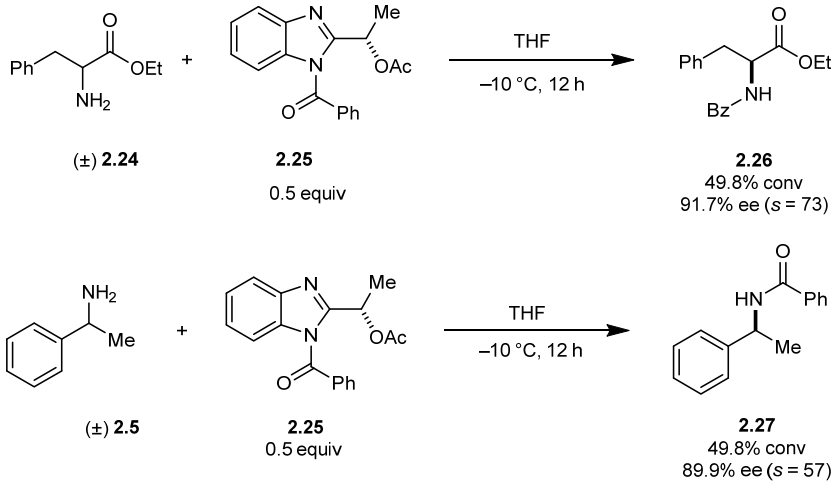
***Scheme 2.6*: Acylation with a (1*S*, 2*S*)-Cyclohexane-1, 2-diamine Derivative**



Mioskowski (2004)

In 2007, a chiral benzimidazole was employed as an acylation reagent Karnik and co-workers to resolve racemic α-amino esters efficiently under mild conditions.[15] They were also able to apply the same acylating reagent to the kinetic resolution of benzylic amines. The inexpensive and readily available chiral benzimidazole makes this approach very attractive (Scheme 2.7).[16]

***Scheme 2.7*: Chiral Benzimidazole Acyl Transfer Reagent**

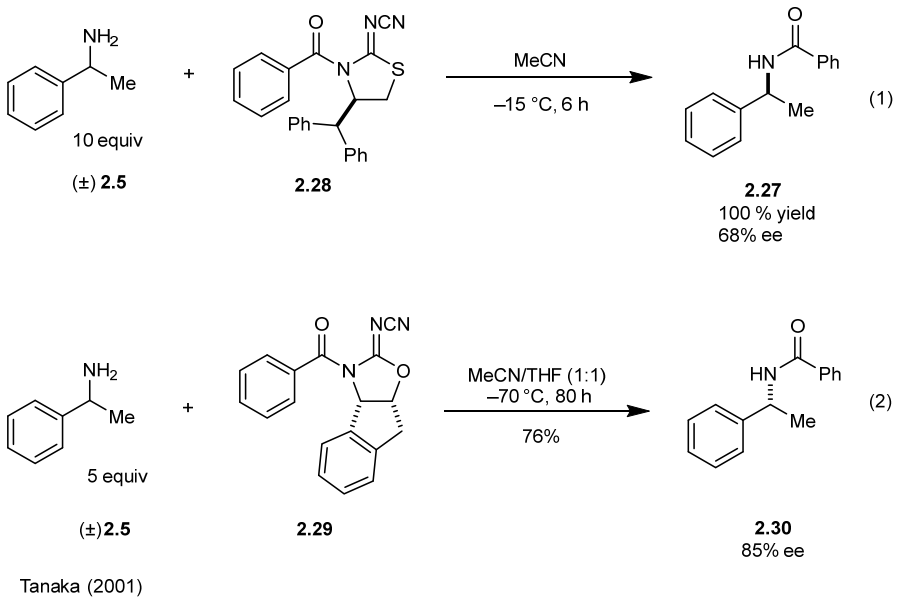


Karnik (2007)

Earlier studies by Tanaka and co-workers showed that acyl-2-(*N*-cyanoimino) thiazolidine (3-acyl-NCT) can be used effectively for the acylation of amines, alcohols and thiols (Scheme 2.8, eq. 1).[17] In 2001, they showed chiral acyl-2-(*N*-cyanoimino) oxazolidine can

resolve benzylic amines with good selectivities and high conversion (Scheme 2.8, eq. 2).[18]

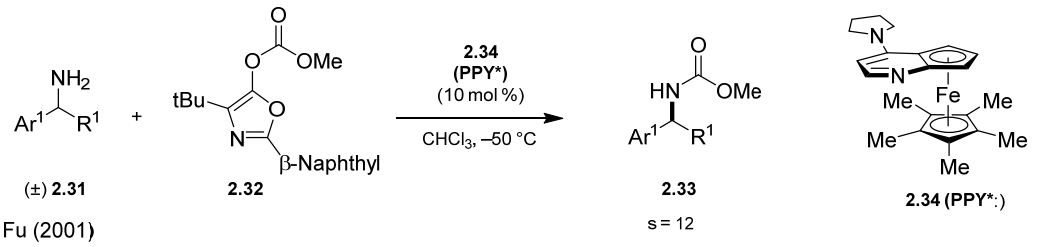
***Scheme 2.8*: Chiral Thiazolidine as Acylating Reagent**



2.1.2 Kinetic Resolution of Amines by Chiral Catalysts

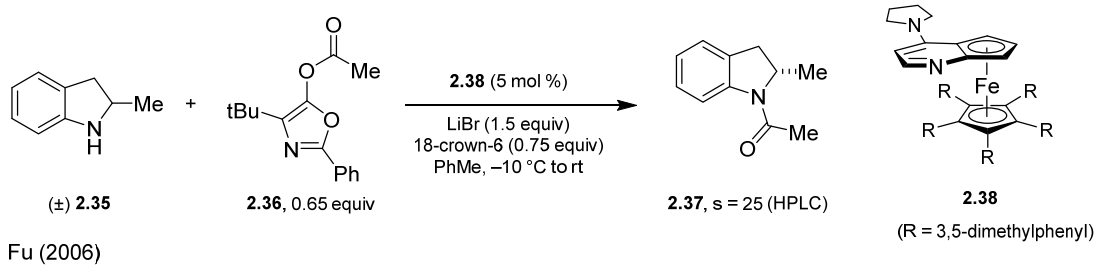
Nitrogen-based heterocycles encompass a broad range of nucleophilic catalysts.[19] The structural diversity possible in these heterocycles has driven the field of organocatalysis.[20] Amongst these compounds, 4-(dimethylamino) pyridine (DMAP) has proved to be an efficient nucleophilic catalyst.[21] Many chiral derivatives of DMAP have been successfully applied to the kinetic resolution of alcohols.[22] Due to the high nucleophilicity of amines in comparison to alcohols, the resolution of amines via small molecule catalysis has been a challenge. In order for the kinetic resolution to proceed efficiently, the catalytic acyl transfer to the nucleophilic amine should be much faster than the background reaction rate between the racemic amine and the acylating reagent.

***Scheme 2.9*: Chiral PPY catalyst for Kinetic Resolution of Amines**



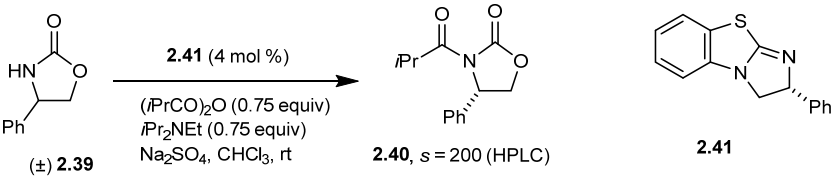
The first example of the kinetic resolution of amines using a chiral DMAP analogue was developed by Fu and co-workers (Scheme 2.9).[23] An *O*-acylated azalactone was employed as the acylating reagent. Performing the reaction at –50 ℃ and adding the acylating reagent in two batches led to moderate to good *s*-factors. Benzylic amines bearing a substituent at the ortho-position yielded higher *s*-factors around 27, but para-substituted benzylic amines led to similar results. Furthermore, several vital contributions have been made to the kinetic resolution of amines and some of their less nucleophilic derivatives. Some examples are shown in the following Schemes.

Scheme 2.10*: Kinetic Resolution of Indolines by PPY



The chiral PPY derivative (**2.38**) used for the resolution of benzylic amines proved to be inefficient for the kinetic resolution of indolines. Changing R from methyl to 3,5-dimethylphenyl drastically improved selectivity (Scheme 2.10).[24] However, when the reaction was run at room temperature, the rate increased at the expense of selectivity. The use of smaller crown ethers or different salts as additives also lowered the *s*-factors.

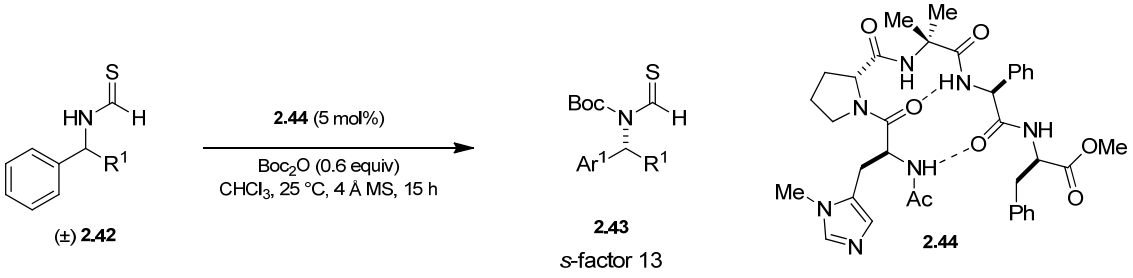
***Scheme 2.11*: Kinetic Resolution of 2-Oxazolidinones**



Birman (2006)

The benzotetraamisole (BTM) based chiral nucleophilic catalyst was introduced by Birman and co-workers in 2006 (Scheme 2.11).[25] The BTM catalyst promoted highly enantioselective acylation of 2-oxazolidinones with *s*-factors as high as 200. However, this catalyst gave nearly racemic product in the kinetic resolution of indolines.

***Scheme 2.12*: Kinetic Resolution of Thioformamides**



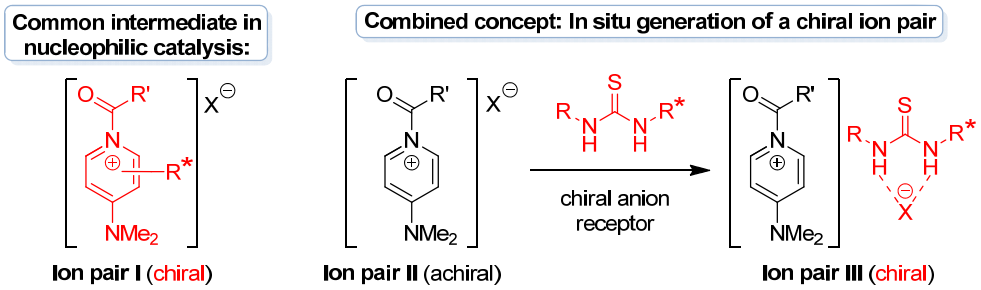
Miller (2010)

In 2010, the Miller group demonstrated the kinetic resolution of the less nucleophilic thioformamides via a nucleophilic peptide based catalyst (Scheme 2.12).[26] Boc-anhydride was used as the acylating reagent after activation by the histidine residue in the catalyst. As a result, enantioenriched thioformamides with moderate selectivities were generated, which could later be transformed into amines.

2.2 Concept

As discussed above, the inherent nucleophilicity of amines has restricted their resolution via small molecule catalysis. In 2009, Drs. Chandra Kanta de and Eric G. Klauber from our group introduced a new concept for the kinetic resolution of amines using simple starting materials (Figure 2.1).[27]

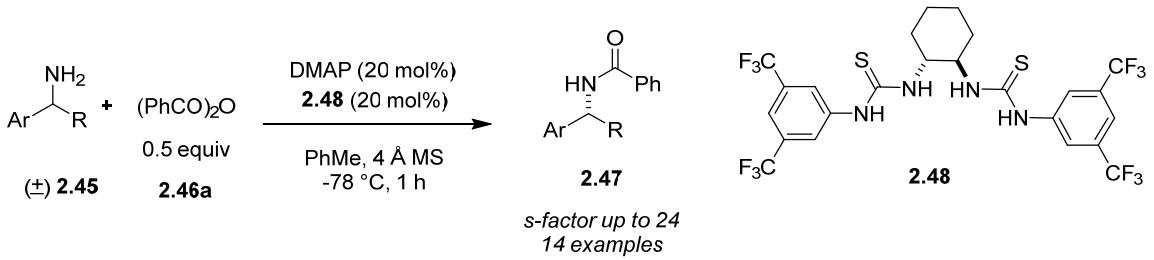
***Figure 2.1*: Approach towards Nucleophilic Catalysis**



Upon combining a simple nucleophilic catalyst[21d,28] such as DMAP with an acylating reagent achiral ion pair **II** is formed. The addition of a chiral catalyst, which is capable of binding to the anion of ion pair **II** via hydrogen-bonding (HB) interactions, establishes a second equilibrium that results in the formation of chiral ion pair **III**.[29] It was hypothesized that chiral ion pair **III** is more reactive and/or present in higher concentrations as compared to achiral ion pair **II**. This favors a scenario in which the amine preferentially reacts with chiral ion pair **III** over achiral ion pair **II** or unmodified acylating reagent, thereby allowing for an efficient kinetic resolution.

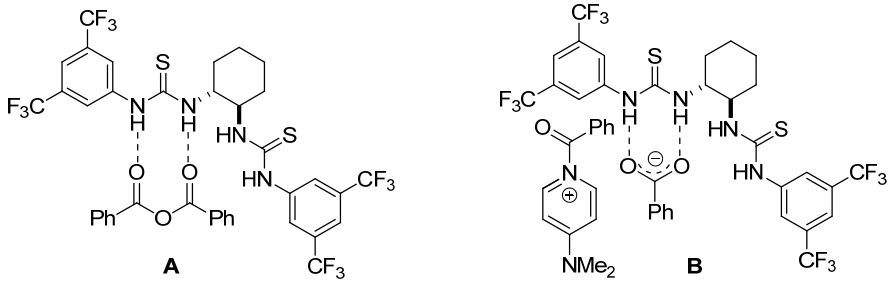
In comparison to the previously reported approach[12,21b] where ion pair **I** is chiral by virtue of the cation, this approach possesses a few key advantages. First, readily available achiral nucleophilic catalyst (tedious syntheses of chiral DMAP analogues can be avoided) and second would be a more soluble and electrophilic ion pair **III** in comparison to ion pair **II**.

***Scheme 2.13*: Kinetic Resolution of Benzylic Amines**



This concept was successfully applied to the kinetic resolution of benzylic amines[27] in presence of 20 mol % of Nagasawa's bisthiourea catalyst (**2.48**). A wide range of benzylic amines were tested and *s*-factors up to 24 were obtained (Scheme 2.13).

***Figure 2.2*: Modes of Activation of the Anhydride**

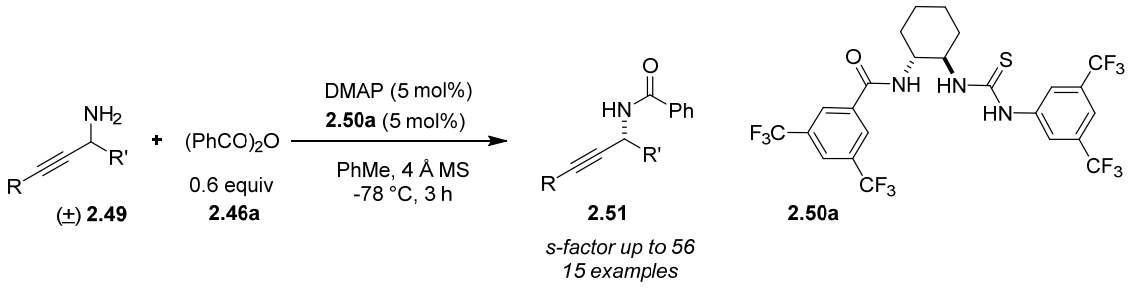


Two possible activation modes were hypothesized for the title reaction (Figure 2.2). In activation mode A, the anhydride is directly activated by the HB catalyst. Under the optimized reaction conditions, this activation mode was found to be inferior to activation mode B (*s*-factor = 1.4 in presence of **2.48** as the only catalyst). The concentration of the DMAP/pyridinium species in the reaction mixture was dependent on molarity and the reaction worked best under dilute conditions (a detailed mechanistic study is discussed in section 2.6).

To obtain a more efficient HB catalyst with lower catalyst loading, the basic catalyst framework was modified. The main idea behind the design of these catalysts was to fix one side of the previously employed bisthiourea catalyst, while fine-tuning the steric and electronic properties on the other side. The modification in the catalyst structure helped to understand the

role of the second thiourea moiety and obtain a 'second-generation catalyst' capable of generating even higher s-factors at lower catalyst loadings. The amide thiourea catalyst (**2.50a**) obtained in this manner, was able to resolve propargylic amines with *s*-factors up to 56. In addition, catalyst loading was lowered from 20 mol % to 5 mol % (Scheme 2.14).[30]

***Scheme 2.14*: Kinetic Resolution of Propargylic Amines**



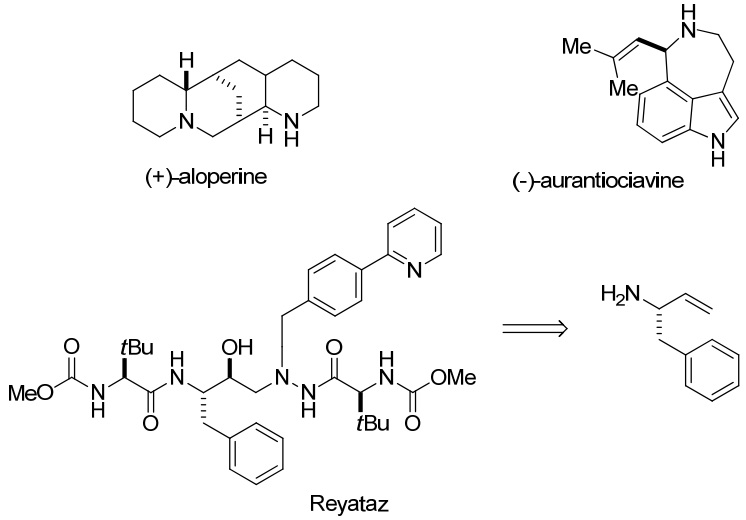
A diverse collection of propargylicic amines were resolved with good to excellent selectivities. Propargylic.amines with substituents at different positions of the phenyl ring were well accommodated. However, substitution at position 3 of the phenyl ring gave the highest *s*-factors.

2.3 Kinetic Resolution of Allylic Amines

2.3.1 Significance and Background

Several amino acids and therapeutic agents include allylic amines in the core structure. These are useful building blocks of (+)-aloperine,[31] (-)-aurantiociavine,[32] Reyataz[33] and many others (Figure 2.3).[34]

***Figure 2.3*: Allylic Amines in Natural Products and Drugs**



Allylic amines have been asymmetrically synthesized via the aza-Claisen rearrangement,[34c,35] allylic amination,[36] vinylation of protected imines[37] and many other methods.[38] Typically, these methods produce secondary or tertiary allylic amines whereas primary allylic amines can be synthesized via kinetic resolution of the corresponding racemates. Although, a number of reports are known for the kinetic resolution of allylic alcohols,[39] the kinetic resolution of allylic amines has remained a challenge.

After the successful application of our second generation catalyst (**2.50a**) to the kinetic resolution of propargylic amines, we applied the optimized conditions to the kinetic resolution of allylic amines.

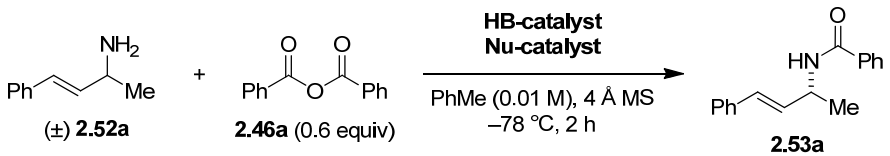
2.3.2 Results and Discussion

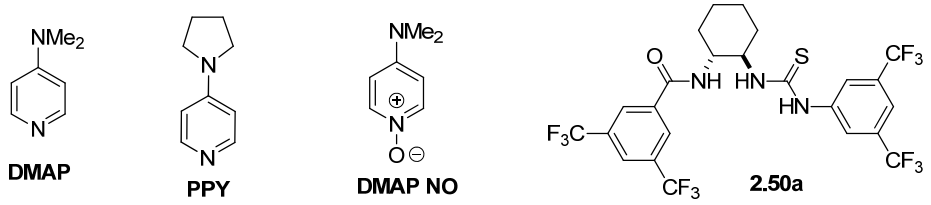
2.3.2.1 Optimization

We initiated our efforts to develop and efficient resolution procedure for primary allylic amines by exposing **2.52**to the optimized resolution conditions previously developed for the propargylic amines.[30] These conditions yielded a conversion of 55% and *s*-factor[6] of 12 (Table 2.1, entry 1). However, in the absence of any HB catalyst or in the presence of DMAP or PPY as the only catalyst but under otherwise identical conditions gave 8% conversion. Notably, this background reaction rate in the case of allylic amines was higher than that observed in the case of benzylic or propargylic amines (<2% conversion in case of latter, entries 4-6, Table 2.1). This observation indicated a higher nucleophilicity for allylic amines. In order to lower the background reactivity a co-catalyst more nucleophilic than DMAP was employed. DMAP *N*-oxide gave nearly identical results (entry 2) as DMAP, whereas catalysts with higher nucleophilicity than DMAP, such as PPY, increased the *s*-factor to 14 (entry 3).

In order to further investigate the background rates, we performed a number of experiments where the reaction time was reduced from 2 hours to 30 min. (entries 7–12). PPY was a better nucleophilic co-catalyst for the title reaction, this observation became more clear on comparing entries 10 and 11.[21a,28b,40] In combination with catalyst **2.50a**, PPY yielded 55% conversion and an *s*-factor of 13, whereas DMAP only gave 33% conversion (*s*-factor = 9.5). Consistent with our previous studies, catalyst **2.50a** was capable of catalyzing the reaction by itself, presumably through direct activation of benzoic anhydride via HB. However, this process was inefficient with regard to selectivity (*s*-factor = 1.6, entry 12).

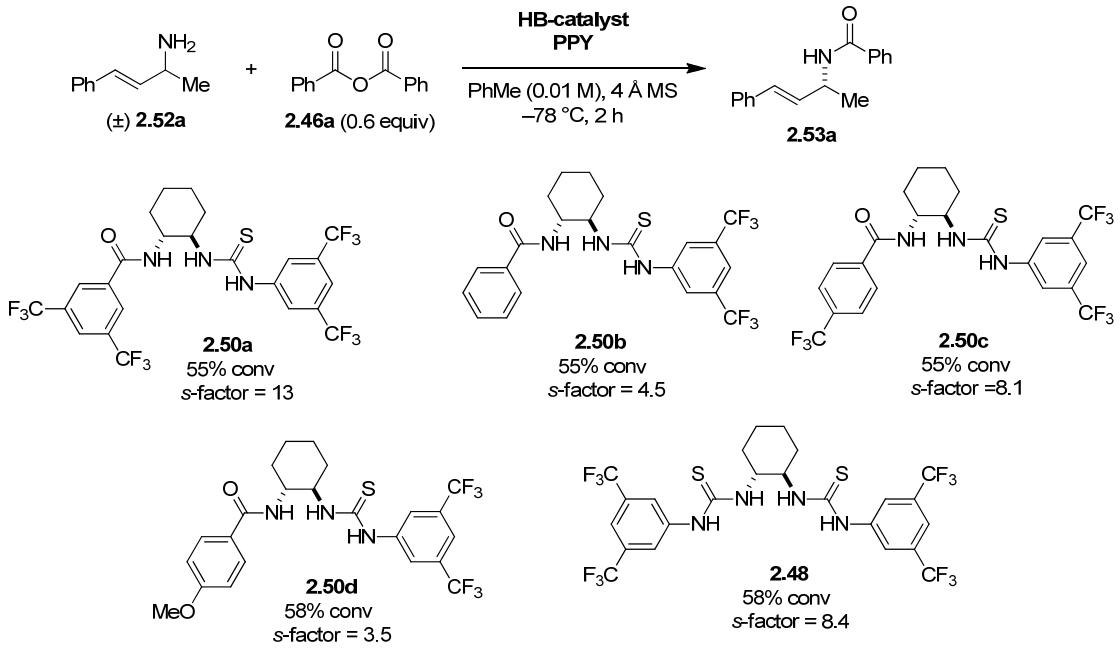
***Table 2.1*: Evaluation of Reaction Conditions**





entry	HB-catalyst (mol%)	Nu-catalyst (mol%)	time (min)	conversion (%)	*s*-factor
1	**2.50a (5)**	DMAP (5)	120	55	12
2	**2.50a (5)**	DMAP.NO (5)	120	57	12
3	**2.50a (5)**	PPY (5)	120	55	14
4	none	none	120	8	N/A
5	none	DMAP (5)	120	8	N/A
6	none	PPY (5)	120	8	N/A
7	none	none	30	2	N/A
8	none	DMAP (5)	30	2	N/A
9	none	PPY (5)	30	2	N/A
10	**2.50a (5)**	PPY (5)	30	55	13
11	**2.50a (5)**	DMAP (5)	30	33	9.5
12	**2.50a (5)**	None	30	29	1.6

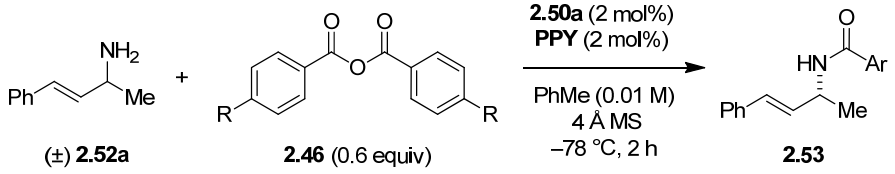
***Scheme 2.15*: Evaluation of Hydrogen Bonding Catalysts**



Other chiral hydrogen bonding catalysts were subsequently evaluated. Although, high conversion was achieved, all other HB catalysts (except **2.50a**) led to inferior results (Scheme 2.15). Surprisingly, employing lower catalyst loadings of 2 mol% of each **2.50a** and PPY produced results similar to those obtained at 5 mol% catalyst loadings (*s*-factor of 14 compared to *s*-factor 13 with latter). However, attempts to reduce the catalyst loading further to 1 mol% slightly decreased the reaction efficiency. Nevertheless, a respectable *s*-factor of 12 was still observed.

It was vital to reduce the background rate as allylic amines showed greater reactivity towards anhydrides. In an attempt to further achieve this rate reduction, various less reactive anhydrides were tested (Table 2.2). Introducing a *p*-methyl group to the benzoic anhydrides increased the *s*-factor from 14 to 16 (entry 2). However, using the even less reactive *p*-MeO-benzoic anhydride led to lower conversion and selectivity (entry 3). Replacing the methyl group with a bulkier *tert*-butyl group gave a much lower *s*-factor, even though this anhydride was more reactive.

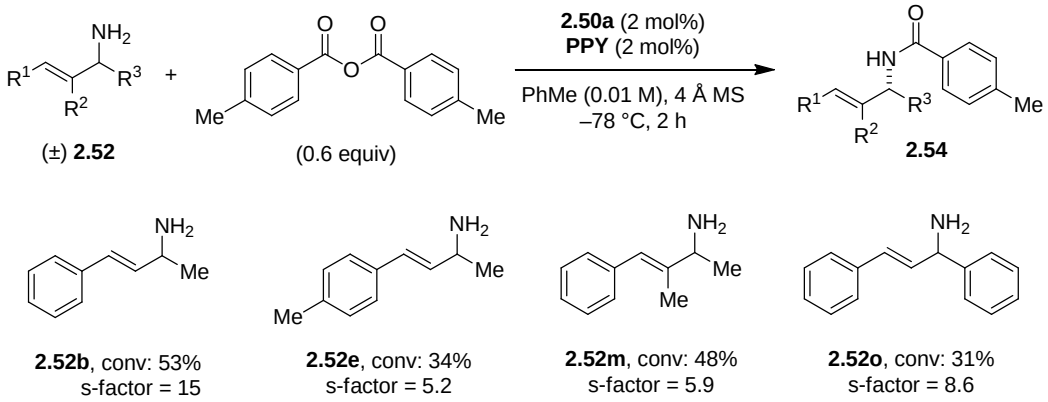
***Table 2.2*: Evaluation of Different Anhydrides**



entry	anhydride	product	conversion (%)	*s*-factor
1	**2.46a** (R = H)	**2.53a**	55	14
2	**2.46b** (R = Me)	**2.53b**	54	16
3	**2.46c** (R = OMe)	**2.53c**	18	9.2
4	**2.46d** (R = *t*Bu)	**2.53d**	53	5.6

To expand the scope with the improved selectivities, we initially used **2.46b** as the acylating reagent for the allylic amine resolution. Some results of this survey are shown in Scheme 2.16.

***Scheme 2.16*: Scope of Resolution with Anhydride 2.46b**

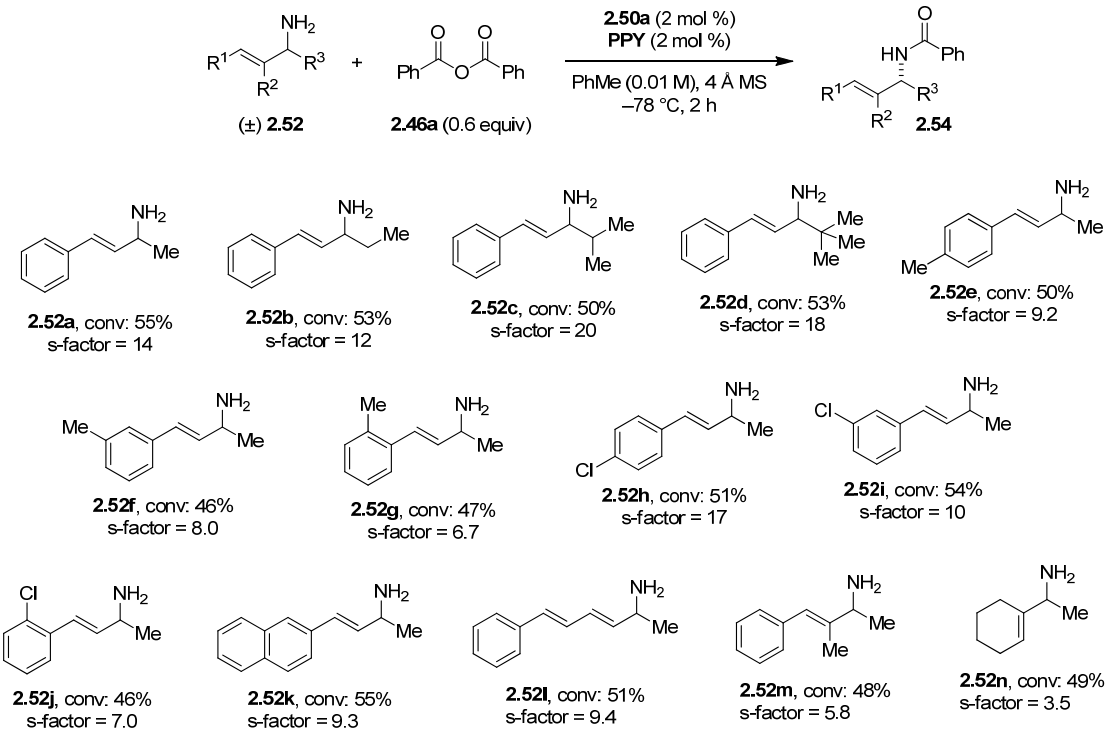


In a few cases, better *s*-factors were obtained with **2.46b** as compared to **2.46a**. However, this trend was not maintained throughout the scope. In many cases, both conversions and selectivities were both lowered upon using **2.46b**. Hence, benzoic anhydride **2.46a** remained the acylating reagent of choice.

2.3.2.2 Scope of the Reaction

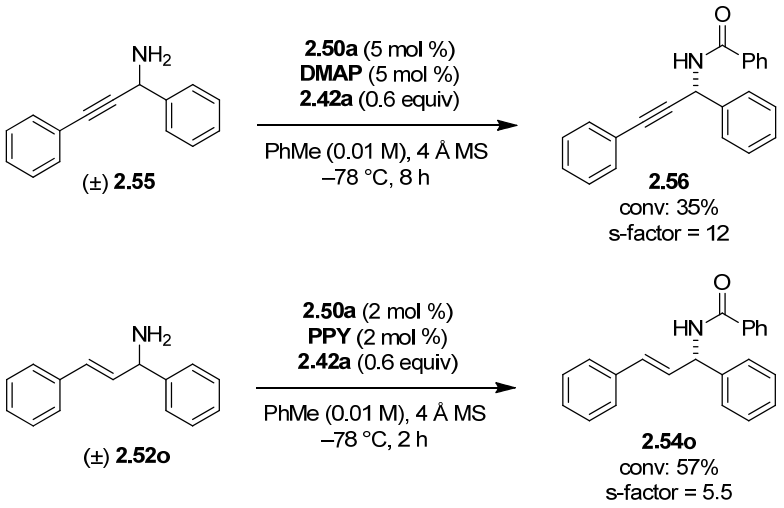
A broader range of allylic amines[41] were resolved by utilizing the optimized reaction conditions with benzoic anhydride **2.46a** as the acylating reagent (Scheme 2.17). An exchange of methyl for ethyl in the parent substrate led to a drop in *s* factor. However, introducing bulkier substituents like *iso*-propyl and *tert*-butyl led to higher *s*-factors. Substituents such as methyl and chloro at different positions of the phenyl ring in the parent amines were also tolerated.

***Scheme 2.17*: Scope of Allylic Amines**



Substrates with extended π-systems such as **2.52k** and **2.52l** were also resolved with good selectivity. The tri-substituted allylic amine **2.52m** gave a modest level of selectivity (*s*-factor = 5.9). Amine **2.52n** gave a poor result (*s*-factor = 3.5), suggesting the importance of the conjugation of the allylic amine to another π- system.

***Scheme 2.18*: Comparison of Propargylic and Allylic Amines**



In kinetic resolution of propargylic amines, it was observed that introducing an aliphatic side chain gave higher selectivities in contrast to a phenyl ring.[30] Our catalytic system was able to differentiate between the two ring systems resulting in *s*-factor of 12. In addition, product **2.55** was obtained in the same absolute configuration like other products which illustrated the control of propargylic over phenyl. Following the trend, in our present system product **2.54o** was obtained with the same configuration, although it was resolved with modest *s*-factor of 5.5.

2.3.3 Summary

In conclusion, we were able to resolve a diverse collection of allylic amines using small molecule catalysis. A dual catalysis approach where an achiral nucleophilic catalyst PPY was used in combination with an HB catalyst **2.50a** was applied and racemic allylic amines were resolved with moderate to good *s*-factors.

2.4 Kinetic Resolution of Benzylic Amines: Dependency of Selectivity on Achiral Cocatalyst

2.4.1 Background

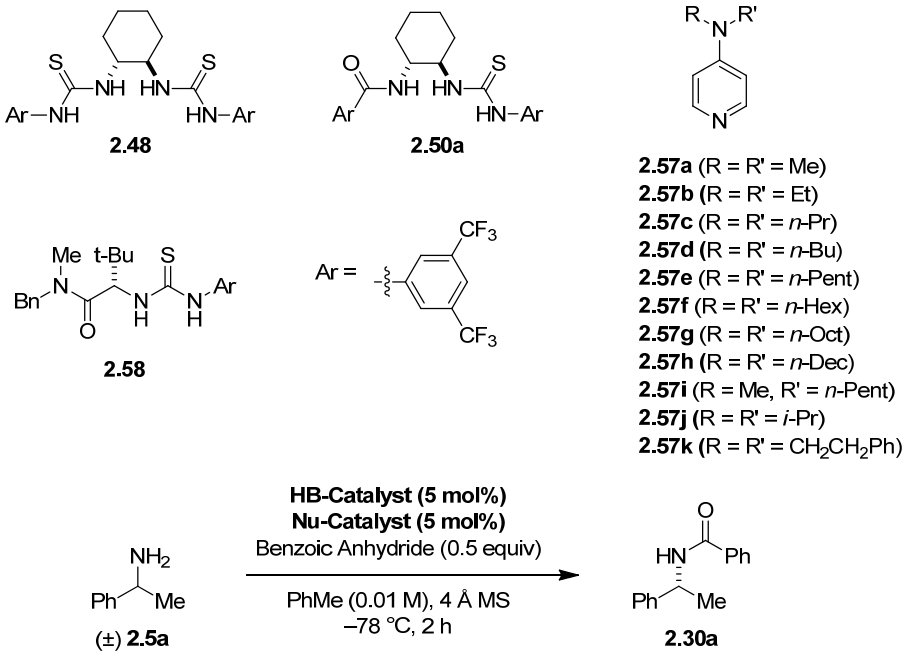
A dual catalytic approach with DMAP was shown in the previous sections where an acyl pyridinium species combines with a chiral anion receptor /hydrogen bonding (HB)[20d,29h,42] catalyst to form a chiral ion pair,[29a-d,43] allowing the amine to react preferentially with it. The crucial role of DMAP led us to consider that its replacement by other nucleophilic cocatalysts might present an avenue for further improvement of selectivity. In addition to the changes in selectivity that could be brought about by simple structural modifications, we hypothesized that an increase in nucleophilicity may lead to more efficient catalysis. Furthermore, as catalyst **2.50a** displays relatively poor solubility in toluene and after observing that the reaction mixture was heterogeneous at -78°C in many cases, we focused our attention on identifying a more soluble nucleophilic catalyst in order to obtain higher selectivities. Hence, a nucleophilic cocatalyst more soluble than DMAP was thought to potentially improve the overall efficiency of the process by enabling the formation of a more soluble chiral ion pair. However, better stabilization and solubility of the resulting acylpyridinium species obtained from the 4-(di alkylamino)pyridine could account for its superiority over other nucleophilic catalysts.

2.4.2 Results and Discussion

2.4.2.1 Optimization

A structurally diverse collection of 22 nucleophilic cocatalysts encompassing a broad range of nucleophilicities[40b,40c,44] was evaluated in combination with amide-thiourea catalyst **2.50a** (Table 2.3).

***Table 2.3*: Evaluation of Catalysts**



entry	HB-catalyst (5 mol %)	Nu-catalyst (5 mol %)	conversion (%)	s-factor
1	**2.50a**	-	34	1.9
2	**2.50a**	**2.57a**	41	13
3	**2.50a**	**2.57b**	50	24
4	**2.50a**	**2.57c**	49	27
5	**2.50a**	**2.57d**	49	22
6	**2.50a**	**2.57e**	50	22
7	**2.50a**	**2.57f**	46	18
8	**2.50a**	**2.57g**	50	19
9	**2.50a**	**2.57h**	49	18
10	**2.50a**	**2.57i**	44	17
11	**2.50a**	**2.57j**	48	25
12	**2.50a**	**2.57k**	46	8.9
13	**2.48**	**2.57c**	49	11
14	**2.58**	**2.57c**	36	1.3

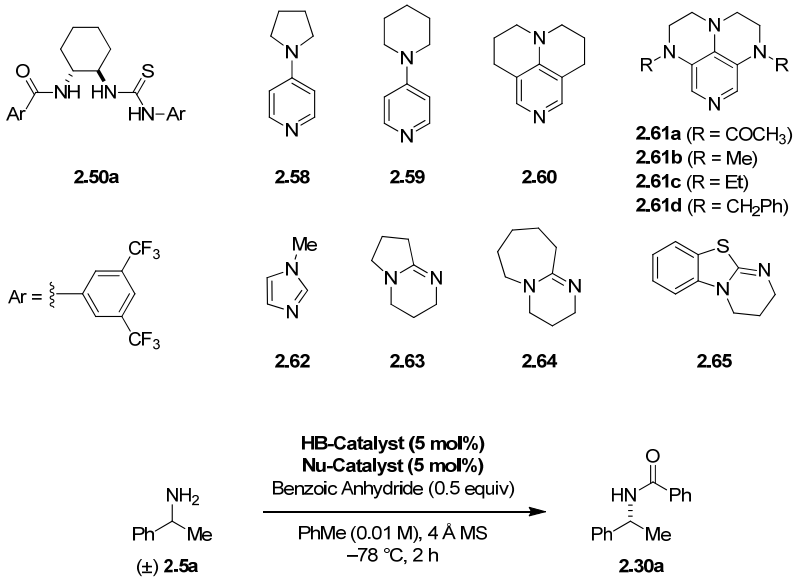
All experiments were conducted with 5 mol % catalyst loadings. As reported earlier, catalyst **2.50a** was active in the absence of any cocatalysts, but led to very poor resolution (s-factor = 1.9). On the other hand, the combination of DMAP and **2.50a** gave an s-factor of 13 at 41% conversion (entry 2).

Remarkably, under our optimized resolution conditions, the simple switch from DMAP to 4-diethylaminopyridine (**2.57b**) led to an increase in *s*- factor to 24 (entry 3). Another dramatic increase in selectivity (*s*-factor = 27) was observed upon switching to the di-*n*-propylamine group in catalyst **2.57c**. There was a slight decrease in the *s*-factor to 22 on moving to di-*n*-butylamine (**2.57d**, entry 5). Further extension of the alkyl chain[45] led to a drop-off in *s*-factors (entries 6–10). Interestingly, for alkyl groups beyond *n*-pentyl, the *s*-factor remained nearly constant at 18.

Although, increasing the carbon chain length further did not show any significant improvement, no direct correspondence between the increasing sterics and the level of selectivity was observed (entries 6 − 10, 12). Two isomers of 4-di-*n*-propylaminopyridine (**2.57c**) were tested: 4-(*N*-methyl-*N*-pentylamino)pyridine (**2.57i**) and 4-diisopropylaminopyridine (**2.57j**). While the latter cocatalyst reached almost the same level of selectivity as **2.57c**, the former showed selectivity similar to the longer chain analogues. Interestingly, even the sterically hindered di-isopropylamine substituent on the pyridine (**2.57j**) resolved **2.5a** with high selectivity (entry 11).[46]

The best nucleophilic catalyst from our study of di-*n*-alkylaminopyridines (**2.57c**) was tested with the bis-thiourea catalyst (**2.48**), resulting in a slightly lower s-factor of 11 (entry 13). Thiourea **2.58**, developed by the Jacobsen group, was previously shown to be an excellent anion-binding catalyst for a number of reactions, but was inefficient in the amine resolution (entry 14)

***Table 2.4*: Evaluation of Nucleophilic Cocatalysts**



entry	HB-catalyst (5 mol %)	Nu-catalyst (5 mol %)	conversion (%)	*s*-factor
1	**2.50a**	**2.58**	50	15
2	**2.50a**	**2.59**	38	12
3	**2.50a**	**2.6**	50	6.6
4	**2.50a**	**2.61a**	< 5	ND
5	**2.50a**	**2.61b**	50	7.7
6	**2.50a**	**2.61c**	45	6
7	**2.50a**	**2.61d**	46	4.1
8	**2.50a**	**2.62**	30	1.3
9	**2.50a**	**2.63**	17	1
10	**2.50a**	**2.64**	21	1
11	**2.50a**	**2.65**	26	1.1

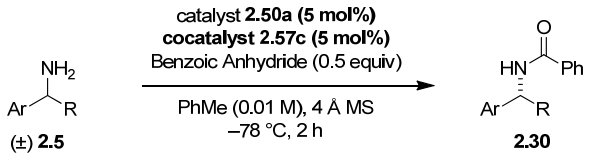
Consistent with our observation in the kinetic resolution of allylic amines,[47] PPY (**2.58**) provided a slight improvemnt in *s*-factor over DMAP in the resolution of benzylic amines (Table 2.4, entry 1). In contrast, 4-(piperidino)pyridine (**2.59**) and pyridonaphthyridine (**2.60**), led to inferior results (entries 2 and 3). Attempts to use a catalyst with enhanced nucleophilicities, such as 3,4,5-triaminopyridines and its congeners (**2.61a-d**),[48] did not give satisfactory results (entry 4–6). Amidine-type catalysts such as *N*-methylimidazole (**2.62**), DBN (**2.63**) and DBU (**2.64**) as

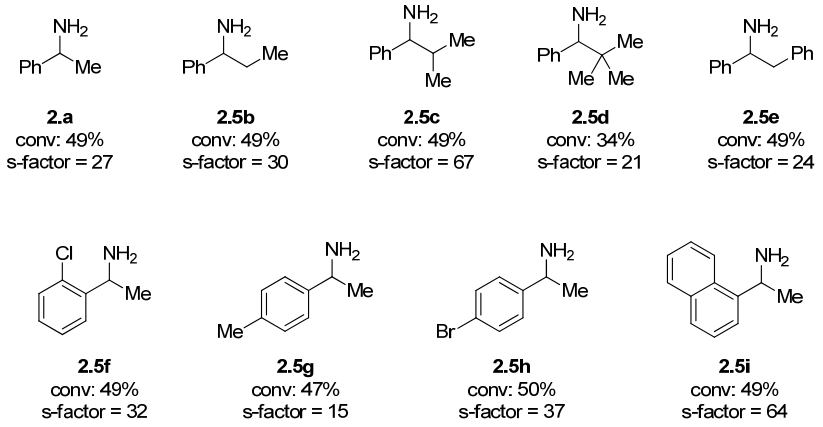
well as isothiourea **2.65** which acts as an acylation catalyst for alcohols, were completely ineffective (entries 7–10).[46]

2.4.2.2 Scope of Benzylic Amines

With the optimized conditions in hand, a number of benzylic amines were resolved efficiently via benzoylation with benzoic anhydride in the presence of 5 mol % of each, catalyst **2.50a** and cocatalyst **2.57c** (Figure 2.4). For all benzylic amines tested, significant improvements were obtained compared to our previous catalytic system.[27]

***Figure 2.4*: Scope of Benzylic Amines**





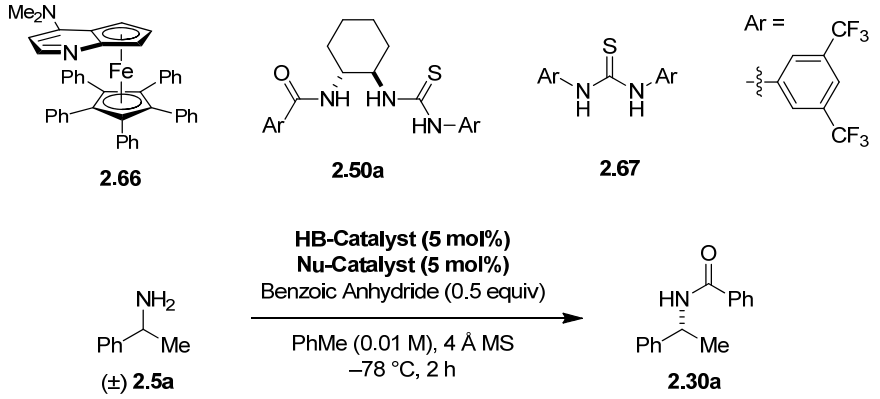
Even though the replacement of methyl (**2.5a**) with ethyl (**2.5b**) in the parent amine only gave a small increase in the s-factor, the introduction of a bulkier group like isopropyl (**2.5c**) led to a significant increase in the selectivity (s-factor = 67.0). This substrate **(2.5c)** provided the highest level of selectivity in our approach thus far. The even more sterically encumbered *t*-butyl group (**2.5d**) led to a drop in s-factor. Substitution of the phenyl-ring in different positions was also readily accommodated. Introduction of an electron withdrawing halogen atom in the para or ortho position also led to good selectivity (**2.5e**, **2.5f**). Presence of a methyl group in the para position (**2.5h**) was also a viable substrate and showed modest selectivity.

Differentiation between phenyl and benzyl was readily achieved as evidenced by substrate **2.5e**, for which an *s*-factor of 24 was obtained. An excellent result was achieved for substrate **2.5i** (*s*-factor = 64). Here, the presence of an extended conjugated system had noticeable influence and might lead to additional stabilizing interactions of one substrate enantiomer with the intermediate ion pair.

2.4.2.3 Further Studies

Seminal work by Fu *et al.* demonstrated the potential of *N*-alkyl substituents on the pyridine ring as nucleophilic catalysts. Intrigued by the possibility to observe matched and mismatched products, a relatively distinct approach to our current method was evaluated. Fu's planar chiral DMAP catalyst **(–)-2.62** was employed in combination with the chiral HB-catalyst **2.50a** (Table 2.5)

***Table 2.5*: Evaluation of PPY* as Nucleophilic Catalyst**



entry	HB-catalyst (mol %)	Nu-catalyst (mol %)	conversion (%)	*s*-factor
1	**2.50a**	**2.66**	36	1.8
2	**2.50a**	*ent*-**2.66**	33	1.9
3	-	*ent*-**2.66**	20	1
4	**2.67**	*ent*-**2.66**	34	1

Unfortunately both enantiomers **(–)-2.66** and *ent* **(–)-2.66** provided inferior selectivity (entries 1 and 2) and the catalyst by itself (in absence of HB catalyst) gave only 20% conversion and no selectivity. Furthermore, the incorporation of a chiral nucleophilic catalyst **(–)-2.66** with an achiral catalyst **2.67** gave better conversion but no resolution. Other catalyst combinations may prove to be more efficient, and there are tremendous opportunities for future investigations of nucleophilic catalysis in the presence of anion-binding additives.

2.4.3 Summary

In summary, we have identified 4-(di *n*-propylamino)pyridine as a more efficient nucleophilic catalyst than DMAP for the kinetic resolution of benzylic amines. In presence of 5 mol % each of HB catalyst **2.50a** and **2.57c**, benzylic amines were resolved with remarkable improvements and *s*-factors up to 67 were obtained.

2.5 Kinetic Resolution of 1,2-Diamines

2.5.1 Significance and Background

Chiral vicinal diamines are widely found in many asymmetric catalysts and drug molecules.[49] Despite the popularity of these chiral amines in several organic building blocks, synthetic methods for their development have remained underdeveloped. Recently, many diastereoselective[49-50] and enantioselective[49,51] methods have been applied to their synthesis. The most commonly known methods involve classical resolution of C_2-symmetrical 1,2-diamines requiring stoichiometric amounts of chiral resolving agents.[52] Highly desirable small-molecule catalyzed kinetic resolutions of racemic 1,2-diamines have remained elusive. Even in the realm of enzymatic catalysis, kinetic resolutions of racemic diamines have been limited to relatively few examples such as *trans*-1,2-cyclohexane and *trans*-1,2-cyclopentane diamines.[53]

In addition to high background rate due to high nucleophilicity of amines, diamines possess an additional problem of diacylation. This challenge was faced in the desymmetrization

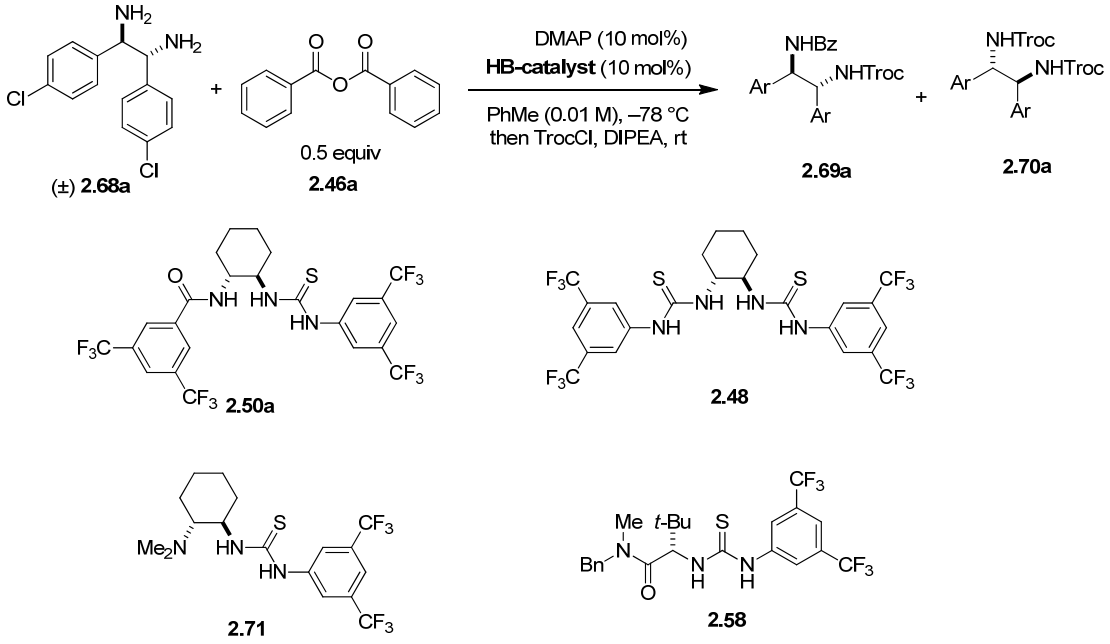
of *meso*-diamines because of the known propensity of diamines to readily undergo diacylation even in the presence of excess diamine, resulting in mixtures of unmodified diamine and diacyl-diamines.[54] In the process to resolve 1,2-diamines, the resolution of the monoacylated amine could also occur. While this scenario could potentially be advantageous, our goal was to find the best conditions that favor diamine mono-acylation.

2.5.2 Results and Discussion

2.5.2.1 Optimization

With the newly improved catalytic system in hand, we initiated our efforts to develop the kinetic resolution of 1,2-diamines with model substrate **2.68a** (Table 2.6). Interestingly, after one hour in the absence of any catalyst, mono-benzoyl diamine and di-benzoyl diamine were obtained in a 5.6:1 ratio and the conversion was 15 %. In the same reaction time with only DMAP present the conversion increased to 32% and the ratio of mono-benzoyl diamine to di-benzoyl diamine was 4:1. In these experiments, conversion was measured by ^{1}H NMR. Although, catalyst **2.50a** catalyzed the reaction in the absence of DMAP (in 30 min), essentially no resolution occurred.

***Table 2.6*: Evaluation of HB catalysts**



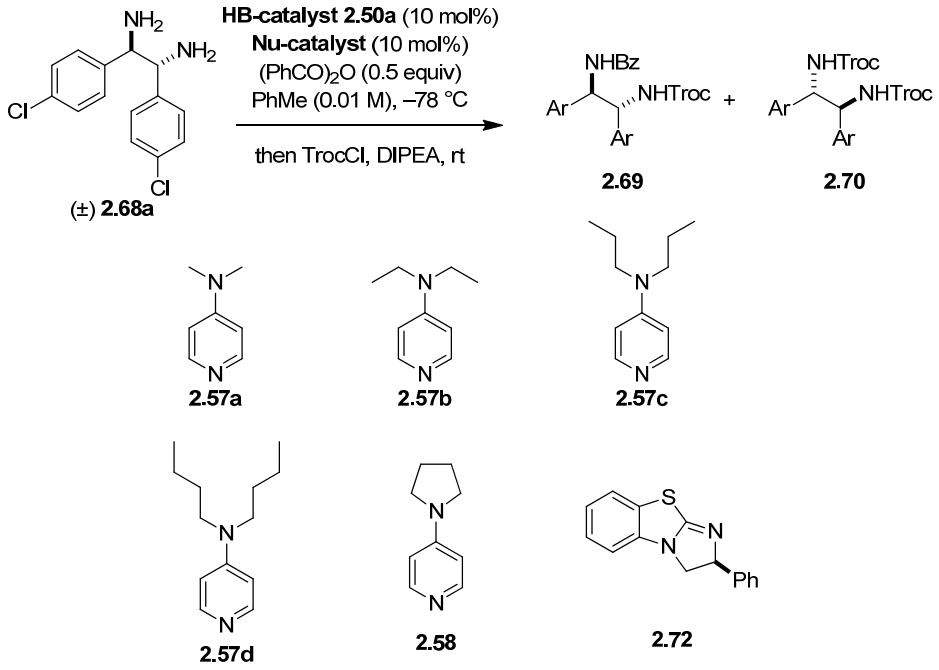
entry	HB-catalyst	Nu-catalyst	time (min)	yield (%) **2.69a**/**2.70a**	*ee* (%) **2.69a**/**2.70a**	conversion (%)	*s*-factor
1	**2.50a**	**2.57a**	30	44/41	56/46	45	5.5
2[a]	**2.50a**	**2.57a**	30	41/47	46/27	37	3.5
3[b]	**2.50a**	**2.57a**	30	46/45	46/44	49	4.1
4[c]	**2.50a**	**2.57a**	30	47/45	47/49	51	4.4
5	**2.48**	**2.57a**	40	46/40	50/43	46	4.5
6	**2.71**	**2.57a**	120	39/49	13/9	41	1.4
7	**2.58**	**2.57a**	120	41/44	Rac	ND	1

[a] With 0.6 equiv. of NEt_3. [b] With 3 Å MS instead of 4 Å MS.[c] With 5 Å MS instead of 4 Å MS.

Under our dual catalytic approach, when a combination of HB catalyst **2.50a** and DMAP was employed, a conversion of 45% and a *s*-factor[6] of 5.5 was obtained with a reaction time of thirty minutes. Upon addition of triethylamine (0.6 equiv), the *s*-factor decreased slightly to 3.5 (entry 2). In order to improve the reaction conditions, different molecular seives were employed. Neither 3Å (entry 3) nor 5Å (entry 4) molecular sieves gave better results than with 4Å molecular sieves. Nagasawa's bisthiourea catalyst[42c] **2.48** which worked well with the benzylic amine resolution , gave a slightly lower *s*-factor (enrty 5). Other HB catalysts like Takemoto's catalyst[55] **2.71** required a longer reaction time and resulted in lower selectivities (entry 6). Furthermore, Jacobsen's catalyst **2.58** gave no resolution (entry 7).

We then surveryed a variety of nucleophilic cocatalysts in combination with HB catalyst **2.50a** (Table 2.7). Even though the replacement of DMAP with PPY led to improvement in the selectivity in the kinetic resolution of allylic[47] and benzylic amines[56], it led to a drop in s-factor for the diamines (entry 1). Consistent with our previous results (discussed in section 2.4) for 4-di-*n*-alkylaminopyridines, nucleophilic catalyst **2.57b** gave a sharp increase in *s*-factor (13, entry 2).[56] Upon employing our best nucleophilic catalyst for the kinetic resolution of benzylic amines to the current system, there was a significant rise in selectivity and an *s*-factor of 30 was obtained.

***Table 2.7*: Evaluation of Nucleophilic Catalysts**



entry	HB-catalyst	Nu-catalyst	time (min)	yield (%) **2.69a/2.70a**	ee (%) **2.69a/2.70a**	conversion (%)	*s*-*F*actor
1	**2.50a**	**2.58**	10	42/46	51/48	48	4.9
2	**2.50a**	**2.57b**	25	45/42	75/64	46	13
3	**2.50a**	**2.57c**	25	44/46	83/86	51	30
4	**2.50a**	**2.57d**	25	44/45	75/78	51	16
5[a]	**2.48**	**2.57c**	50	46/42	81/74	48	21
6	-	**2.57a**	180	24/64	-4/-6	ND	~1

[a] 5 mol% of each **2.50a** and **2.57c** was employed

While, changing the carbon chain from di-*n*-propyl to di-*n*-butyl did not lead to any improvements, comparable results were obtained with **2.57b** (s-factor = 16, entry 4). Although the reason for this dramatic increase in the selectivity from using DMAP to 4-di-*n*-propylaminopyridines is not yet understood, these modified catalysts demonstrated a more pronounced effect than expected from our previous results.[56]

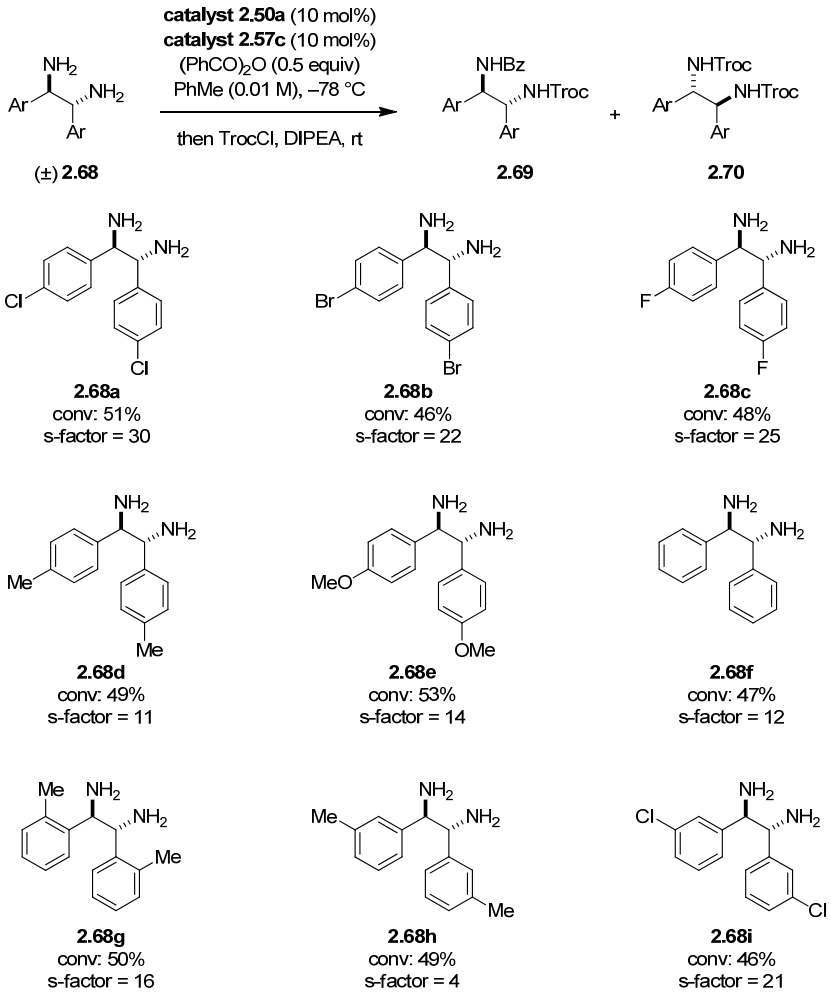
Benztetramisole (**2.72**), a chiral nucleophilic catalyst, introduced by Birman and co-workers[39c] catalyzed the reaction in absence of the HB catalyst but unfortunately did not provide any resolution. Combining Schreiner's achiral HB thiourea catalyst[57] (**2.67**) with chiral

nulceophilic catalyst **2.72** promoted the reaction but this process was not selective and a s-factor of 1.0 was obtained.

2.5.2.2 Substrate Scope of 1,2-diamines

A number of racemic 1,2-diaryl-1,2-diaminoethanes were resolved efficiently under our optimized conditions (Scheme 2.19).

***Scheme 2.19*: Substrate Scope**



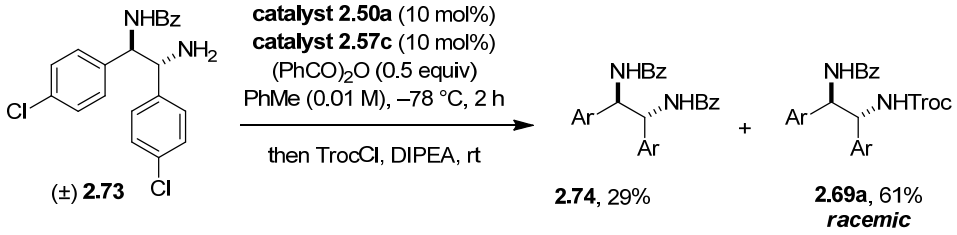
Consistent with our obervation in other amine systems,[47,56,58] amines with electron withdrawing groups were resolved with higher *s*-factors as compared to the electron rich substrates. The reason behind this trend was likely to be the higher background rate in case of the electron rich amines. However, introducing methyl (**2.68d**) or methoxy (**2.69e**) group in the para

position of the aryl group provided good selectivities. Substituents at other positions of the aryl ring such as in **2.68g** and **2.68i** were also well accomodated. Overall, our catalytic system was quite acitve for the resolution of racemic 1,2-diaryl-1,2-diaminoethanes and less than 5% of the bis-benzoylated products were formed in all substrates.

2.5.2.3 Further Studies

Although only a small amount of the dibenzoylated product was formed, we wanted to explore if it could effect the selectivity of the overall process. A second resolution process could occur, which is the reaction between the monobenzoylated product (**2.73**) and the excess benzoic anhydride left in the reaction mixture (experiment outlined in Scheme 2.20).

***Scheme 2.20*: Evaluation of a Potential Second Resolution Process**



The above reaction was considerably slower and after two hours of reaction time, the dibenzoylated product was formed with only 29% conversion (by ^{1}H-NMR analysis of the crude reaction mixture). The left over unreacted starting material was converted to the corresponding troc product, which was found to be racemic. This experiment proved that the second resolution process did not occur and small amounts of the dibenzoylated product did not effect the selectivities of the products.

2.5.3: Summary

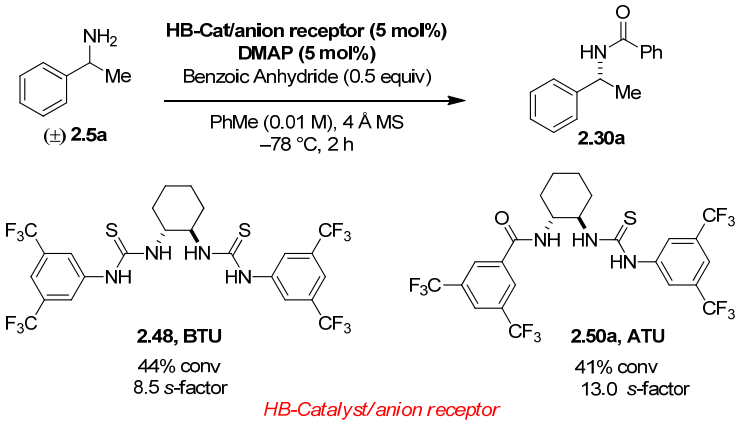
In summary, we have reported the first example of a small-molecule catalytic approach to the kinetic resolution of diamines. A number of 1,2-diaryl-1,2-diaminoethanes were efficiently

resolved by monobenzoylation, using a catalytic amount of a chiral amide-thiourea anion-receptor in combination with an achiral nucleophilic cocatalyst.

2.6: Kinetic Resolution of Amines: Mechanistic Insight

As part of our recent study to develop the kinetic resolution of propargylic amines,[30] we explored various structural modifications of the basic bis-thiourea (**2.48**) catalyst framework. The amide-thiourea catalyst (**2.50a**) was found to provide superior results. This catalyst also showed better selectivities in the resolution of benzylic amines as compared to **2.48** (Scheme 2.21).[27,30]

Scheme 2.21: Comparison of Hydrogen Bonding Catalysts 4.28 and .250a



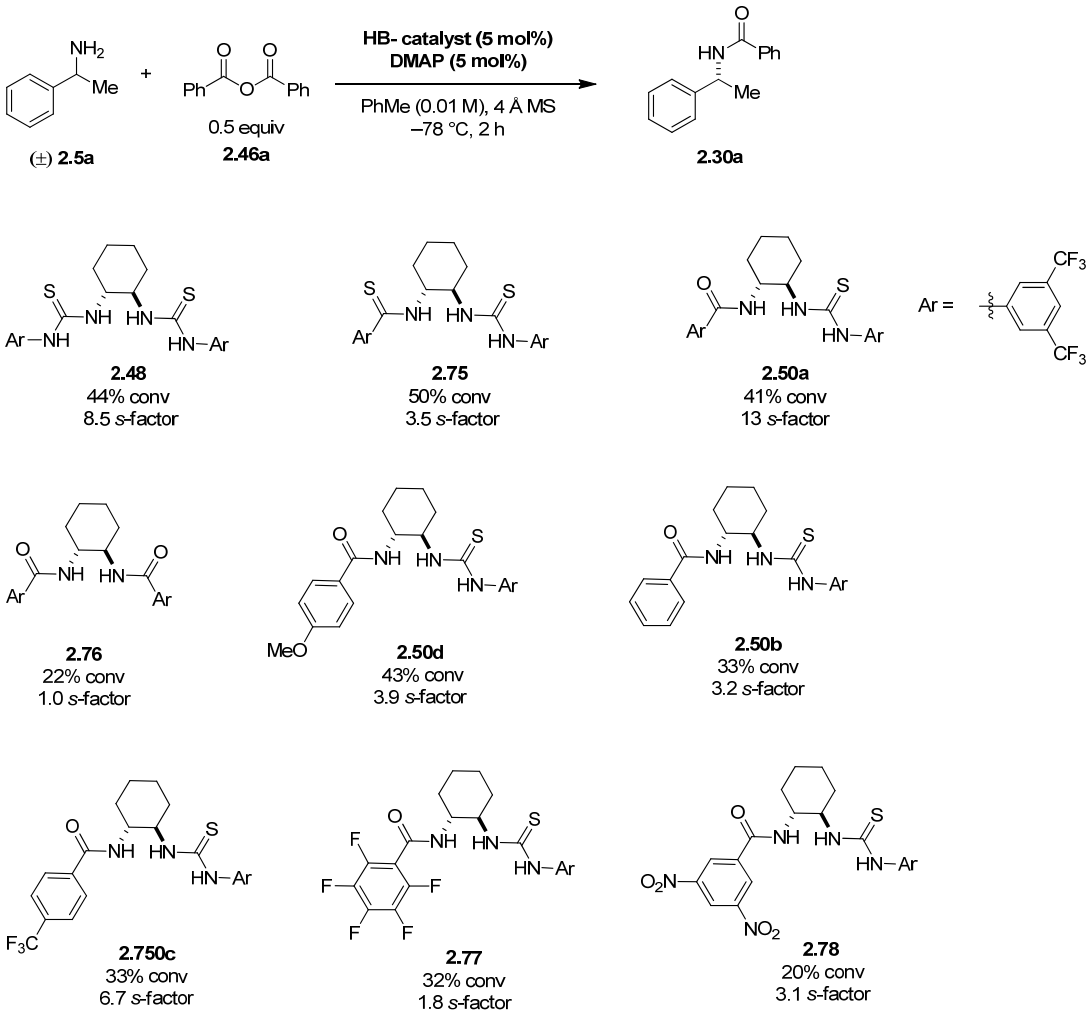
2.6.1 Evaluation of Different Hydrogen Bonding Catalysts

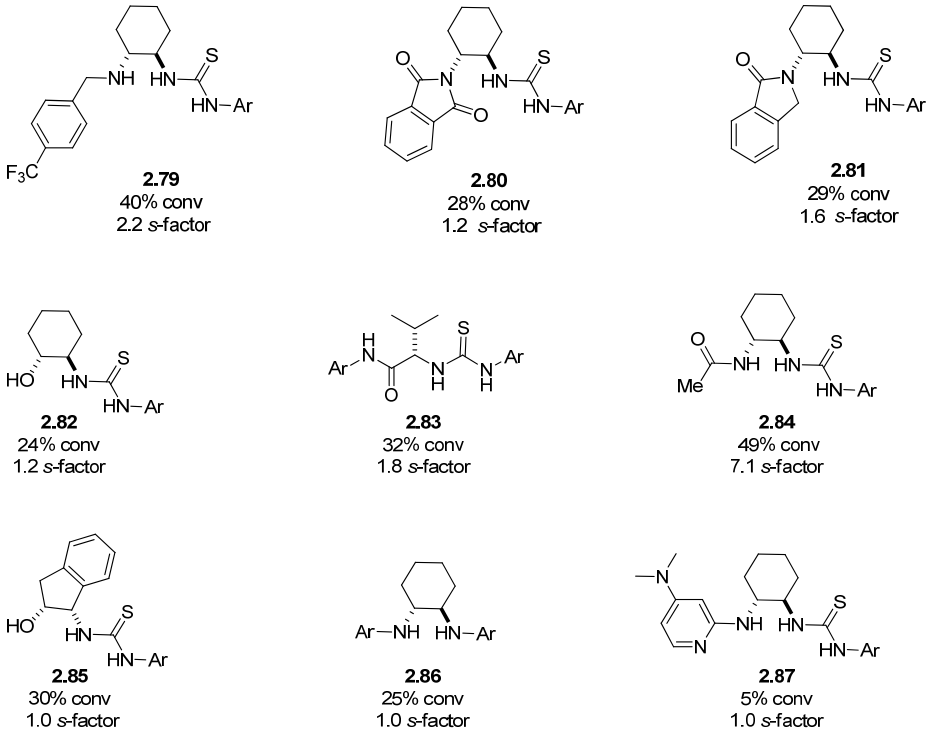
To obtain a better understanding of what structural components are important for efficient catalysis, a range of potential catalysts were tested in the resolution of benzylic amines (Scheme 2.22). Several hydrogen bonding catalysts (HB-catalysts) were tested by fixing one side of the model catalyst **2.48** and diversifying the electronic properties on the other side. **2.50d**, **2.50b**, **2.50c**, **2.77**, **2.78** lowered the selectivity drastically as compared to **2.50a**. Introducing a cyclic imide in **2.80** and cyclic amide **2.81** also lowered the *s*-factor. To evaluate the exceptional behavior of **2.50a**, substituting a simple secondary amine in place of an amide functionality in **2.84** provided very low selectivity. Other catalysts like **2.83** and **2.85** which also behave as

bifunctional catalysts provided poor selectivity. **2.87** with DMAP as the internal nucleophile (in absence of DMAP) gave very low conversion and no resolution.

These studies implied that the presence of one thiourea moiety is essential as is the presence of a free amide *N*-H. Also, catalysts with more acidic *N*-H protons are more active and give higher *s*-factors and the substitution of amide for amine is detrimental. Furthermore, substitution of amide for thioamide results in poorer catalyst performance despite the expected increase in *N*-H acidity.

Scheme 2.22: Evaluation of Different Catalysts.

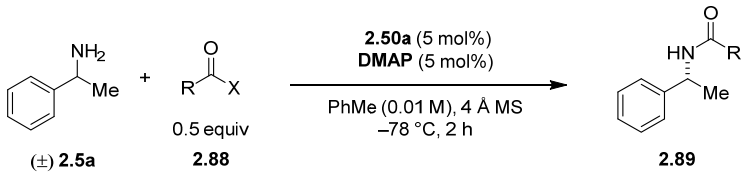




2.6.2 Variation of Acylating Reagent

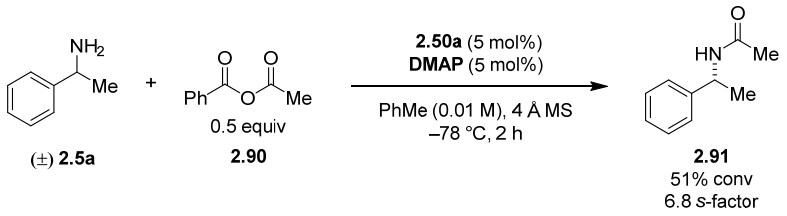
We began to explore different acylating reagents in order to understand the reaction parameters more closely (Table 2.8). Changing the benzoate counteranion to fluoride or chloride led to poor selectivity. A reasonable *s*-factor was obtained with acetic anhydride. Benzoic anhydride proved to be superior to benzoyl halides. This result demonstrated the benzoate ion's superior binding compared to other anions. The mixed anhydride of benzoic and acetic acid exclusively provided the acetylated product (Scheme 2.23).

Table 2.8: **Evaluation of Acylating Reagents.**



entry	acylating reagent	conv (%)	*s*-factor
1	PhCOCl	50	2.4
2	PhCOF	34	3.1
3	PhCOBr	39	1
4	MeCOCl	43	1.4
5	$(MeCO)_2O$	43	6.7
6	$(PhCO)_2O$	41	13
7	$(4\text{-}MePhCO)_2O$	38	12.8
8	$(4\text{-}OMePhCO)_2O$	3.6	4.8

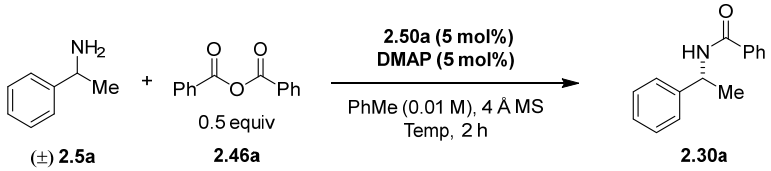
***Scheme 2.23*: Mixed Anhydride as Acylating Reagent**



2.6.3 Variation of Reaction Temperature

In our initial study, cryogenic conditions were found to be essential in order to minimize background reactivity.[27,30,47] In a more detailed study, we found that *s*-factors drop off gradually as the reaction temperature is increased (Table 2.9).

***Table 2.9*: Evaluation of Reaction Temperature**

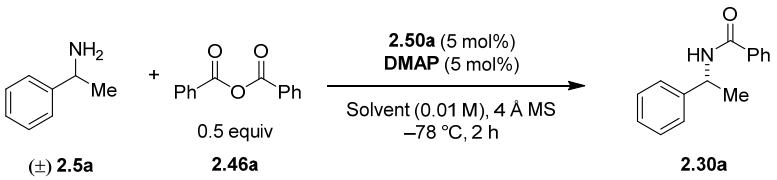


entry	temp (°C)	conv (%)	*s*-factor
1	–40	50	7.5
2	–60	50	10
3	–78	41	13

2.6.4: Evaluation of Solvents

Based on the results in Table 2.9, we limited our evaluation of solvents to those that can operate at –78 °C (Table 2.10).

***Table 2.10*: Evaluation of Solvents**



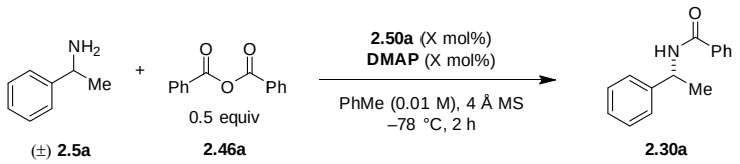
entry	solvent	conversion (%)	*s*-factor
1	Toluene	41	13
2	Hexanes	17	1
3	EtOAc	19	1.5
4	MTBE	38	1.4
5	Toluene/hexanes (1:1)	50	12
6	Mesitylene/hexanes (1:1)	42	5.6

Hexanes and polar solvents like ethyl acetate and MTBE provided inferior results. Toluene was found to be superior to all other solvents studied. Mixtures of less polar solvents, such as toluene and hexanes, gave high conversion but reduced *s*-factor (entry 5). A combination of mesitylene/hexanes, (entry 6) lowered the *s*-factor drastically.

2.6.5: Effect of Catalyst Loading & Dilution Study

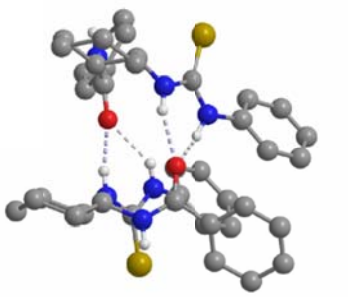
In the kinetic resolution of propargylic amines we had observed that a catalyst loading of 5 mol % for both DMAP and **2.50a** provided higher s-factors than those resulting from a 10 or 20 mol% loading.[30] This trend also applied to the case of benzylic amines (Table 2.11). Partial self-aggregation of the catalyst observed in the solid state (Figure 2.6) could account for the lower selectivities. However, catalyst loadings below 5 mol% led to reduced s-factors.

***Table 2.11*: Evaluation of Catalyst Loading**



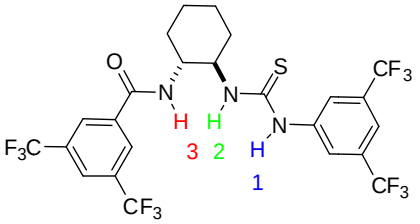
entry	**2.50a** (mol%)	DMAP (mol%)	Time (h)	Conversion (%)	s-factor
1	10	10	2	50	8.6
2	5	5	2	41	13
3	2	2	4	48	8.6
4	1	1	4	43	5.1

***Figure 2.5*: Crystal Structure of HB-Catalyst 2.50a**



The crystal structure in Figure **2.5** shows the self-association/dimer formation of the **2.50a** catalyst in the solid state. In order to establish whether this type of aggregation also occurs in solution, ^{1}H NMR spectra of **2.50a** were recorded at varying concentrations (Figure 2.6 & Table 2.12). This study was initially conducted in $CDCl_3$. Due to the low solubility of the **2.50a**, 0.04 M was the highest possible concentration obtained. Upon decreasing the concentration, the NH1 and NH2 thiourea protons demonstrated a significant upfield shift. An upfield shift was also observed for the NH3 proton, albeit to a much lesser extent. These observations are consistent with the formation of a dimer at higher concentrations, and significant de-aggregation at lower concentrations. Consistent with the observations in the solid state, the NH3 proton does not appear to be involved directly (via HB) in the aggregation.

***Figure 2.6*: Dilution Study of 2.50a in $CDCl_3$**



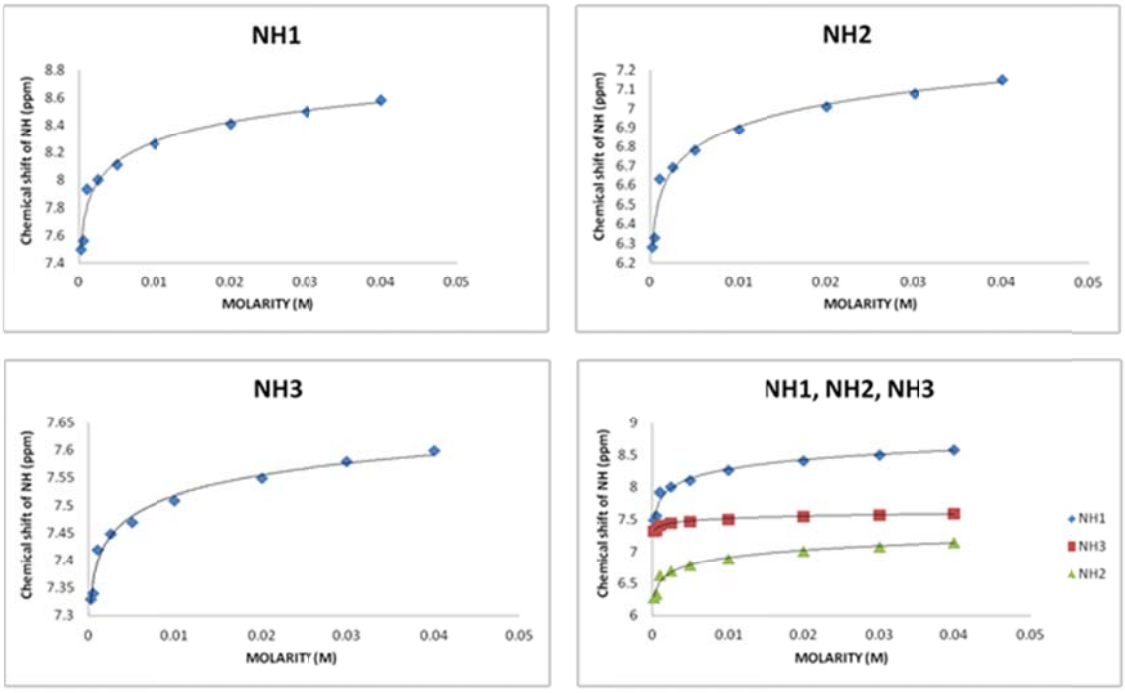
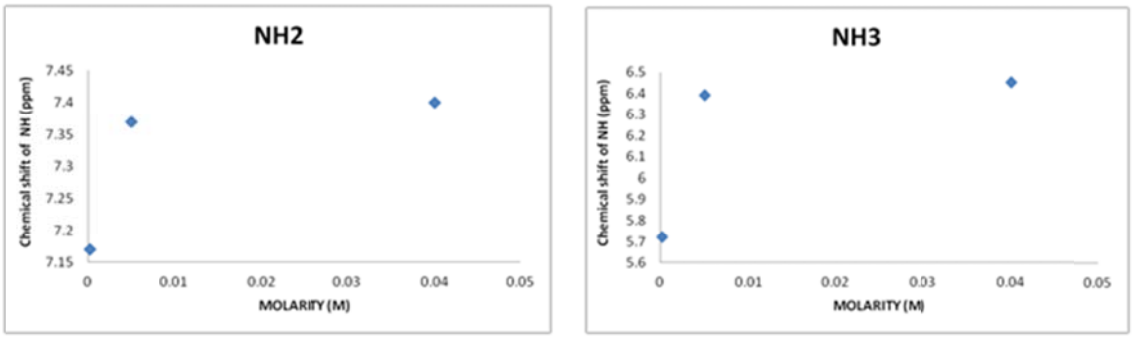


***Table 2.12*: Dilution Study of 2.50a in $CDCl_3$**

entry	molarity	NH1	NH2	NH3
1	0.04	8.58	7.15	7.6
2	0.03	8.5	7.08	7.58
3	0.02	8.41	7.01	7.55
4	0.01	8.26	6.89	7.51
5	0.005	8.11	6.78	7.47
6	0.0025	8	6.69	7.45
7	0.001	7.93	6.63	7.42
8	0.0005	7.56	6.33	7.34
9	0.00025	7.5	6.28	7.33

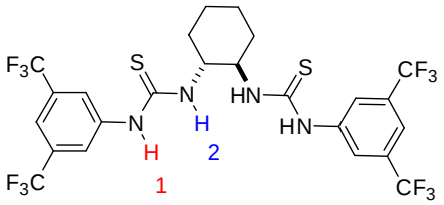
A more limited dilution study was also performed in toluene, which was the solvent used in the reaction (Figure 2.7). ^{1}H NMR spectra were obtained of the 0.04 M (saturated), 0.005 M and 0.00025 M solutions of **2.50a** catalyst. Following the previous trend, the dilution of **2.50a** in toluene-d8 also engendered upfield shifts of NH2 and NH3 whereas there was no significant difference in the shift for NH1. This study was also conducted in benzene-d6, but the use of this solvent did not provide conclusive NMR spectra at dilute conditions.

Figure 2.7: **Dilution Study of 2.50a in Toluene-d**



The aggregation behavior of **2.48** was also investigated. Due to the greater solubility of **2.48** as compared to **2.50a** in $CDCl_3$, a broader range of concentrations was surveyed (Figure 2.8 & Table 2.13). Upon dilution, a gradual upfield shift of the NH protons was observed, whereas at higher concentrations, the value leveled off after 0.04 M.

***Figure 2.8*: Dilution Study of 2.48 in $CDCl_3$**



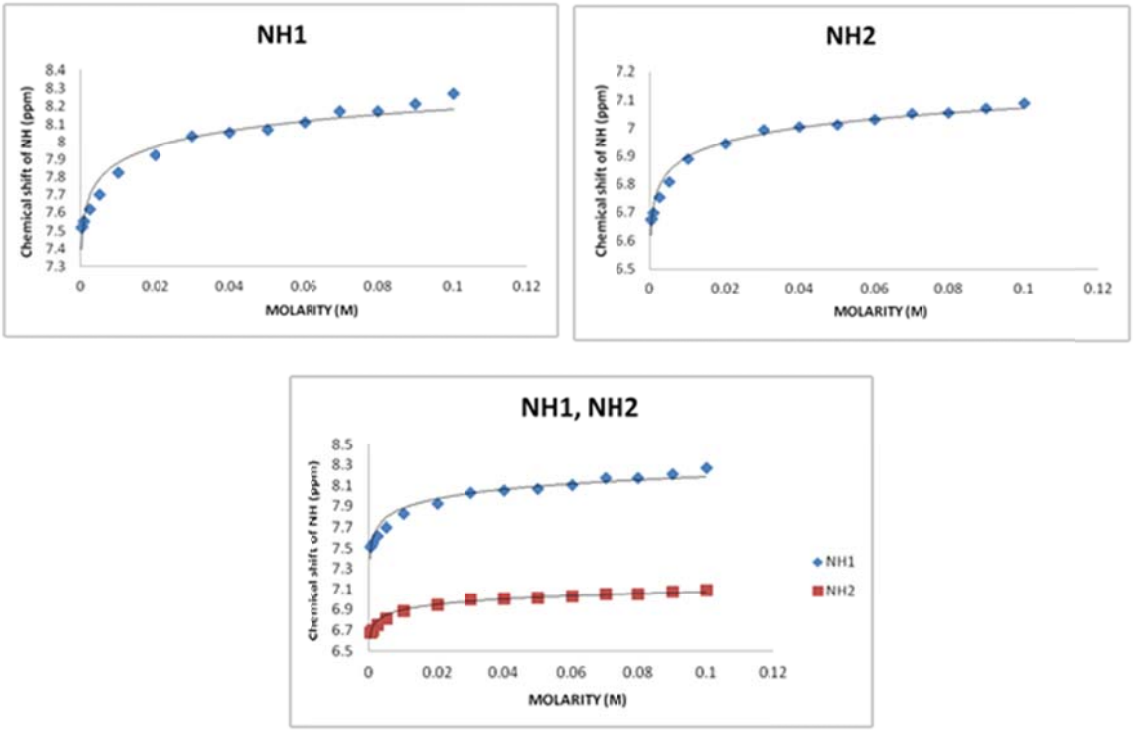


***Table 2.13*: Dilution Study of 2.48 in $CDCl_3$**

entry	molarity	NH1	NH2
1	0.1	8.27	7.09
2	0.09	8.21	7.07
3	0.08	8.17	7.06
4	0.07	8.17	7.05
5	0.06	8.11	7.03
6	0.05	8.07	7.01
7	0.04	8.05	7.00
8	0.03	8.03	6.99
9	0.02	7.92	6.95
10	0.01	7.82	6.89
11	0.005	7.69	6.81
12	0.0025	7.62	6.75
13	0.001	7.55	6.70
14	0.0005	7.52	6.68
15	0.00025	7.52	6.67

The dilution study of **2.48** was also conducted in benzene-d6. Toluene was not chosen because its aromatic proton signals overlapped with the NH signals of **2.48**. In C_6D_6, 0.04 M was the maximum concentration attainable and an analogous but more pronounced trend for the NH shift was observed (Figure 2.9 & Table 2.14). Thus, this experiment indicated that self-aggregation of **2.48** occurs at higher concentrations.

***Figure 2.9*: Dilution Study of 2.48 in C_6D_6**

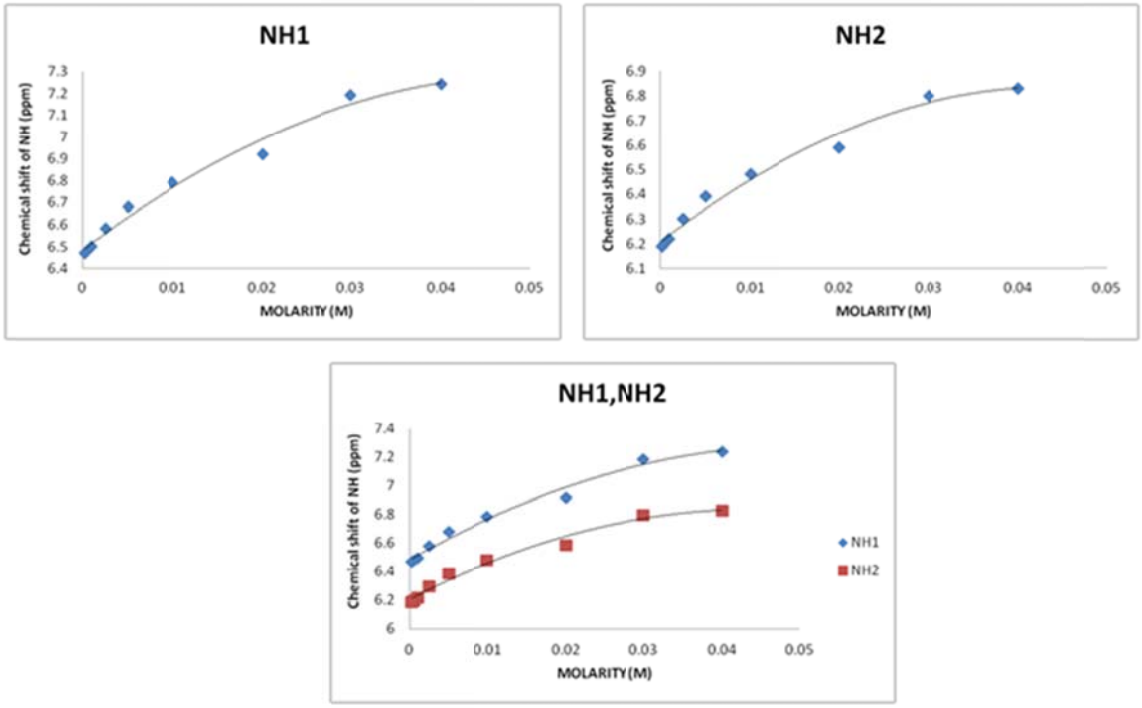


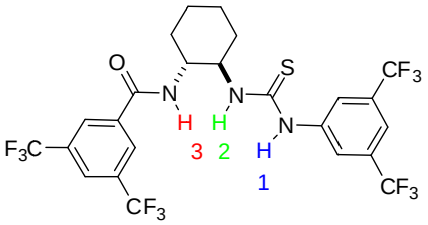
***Table 2.14:* Dilution Study of 2.48 in C_6D_6**

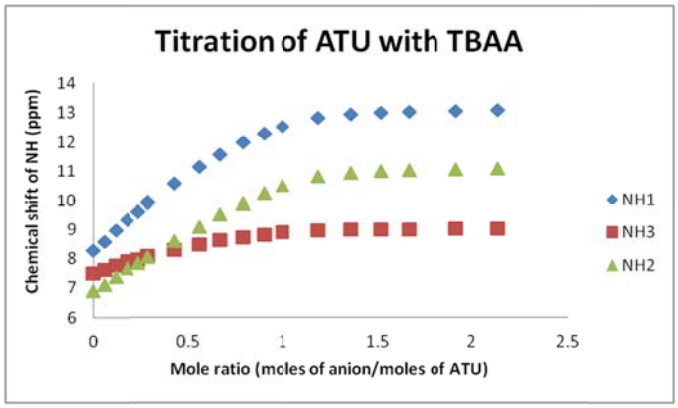
entry	molarity	NH1	NH2
1	0.04	7.29	6.84
2	0.03	7.19	6.71
3	0.02	7.02	6.65
4	0.01	6.80	6.52
5	0.005	6.74	6.43
6	0.0025	6.63	6.34
7	0.001	6.50	6.23
8	0.0005	6.49	6.21
9	0.00025	6.45	6.17

2.6.6: Anion Binding Study

In order to gain insights into how the **2.50a** catalyst interacts with anions, we performed several anion binding studies that were monitored by ^{1}H-NMR. The results from the titration of **2.50a** with tetrabutylammonium acetate (TBAA) are shown in Figure 2.10. A substantial shift was observed in all three NH signals upon increasing the mole fraction of the anion.

Figure 2.10: **Titration of 2.50a with Tetrabutylammonium Acetate (TBAA)**





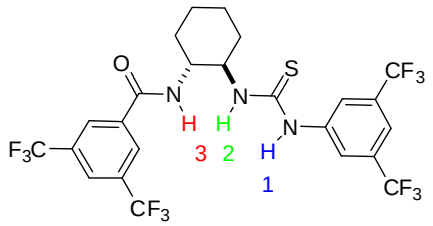
ATU = Catalyst **2.50a**

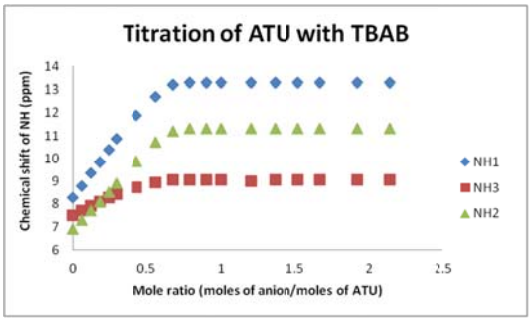
***Table 2.15*: Titration of 2.50a with Tetrabutylammonium Acetate (TBAA)**

entry	mole ratio (anion/**2.50a**)	NH1 (ppm)	NH2 (ppm)	NH3 (ppm)
1	0	8.26	6.88	7.48
2	0.06	8.57	7.1	7.61
3	0.12	8.96	7.38	7.76
4	0.18	9.33	7.66	7.9
5	0.24	9.63	7.89	8
6	0.29	9.94	8.09	8.12
7	0.43	10.6	8.64	8.33
8	0.56	11.1	9.11	8.51
9	0.68	11.6	9.53	8.66
10	0.79	12	9.91	8.77
11	0.9	12.3	10.2	8.86
12	1	12.5	10.5	8.93
13	1.19	12.8	10.8	9.01
14	1.36	12.9	10.9	9.03
15	1.52	13	11	9.04
16	1.67	13	11	9.04
17	1.92	13.1	11	9.05
18	2.14	13.1	11.1	9.05

An analogous titration was performed with tetra butyl ammonium benzoate (TBAB) (Figure 2.11& Table 2.16). Here, a more substantial downfield shift was observed for all NH signals. For both TBAA and TBAB, the NH signals of the thiourea functionality (NH1 & NH2) experienced a more substantial downfield shift than that of NH3. This is consistent with the results obtained from the computational analysis, which suggest intramolecular hydrogen bonding of NH3 to the thiourea sulfur, but no direct involvement of NH3 in anion binding.

***Figure 2.11*: Titration of 2.50a with Tetrabutylammonium (TBAB)**





ATU = Catalyst **2.50a**

***Table 2.16*: Titration of 2.50a with Tetrabutylammonium (TBAB)**

entry	mole ratio (anion/**2.50a)**	NH1 (ppm)	NH2 (ppm)	NH3 (ppm)
1	0	8.26	6.88	7.48
2	0.06	8.79	7.27	7.7
3	0.12	9.35	7.69	7.91
4	0.18	9.85	8.09	8.09
5	0.24	10.4	8.52	8.27
6	0.29	10.9	8.92	8.43
7	0.43	11.9	9.86	8.72
8	0.56	12.7	10.7	8.94
9	0.68	13.2	11.2	9.05
10	0.79	13.3	11.2	9.06
11	0.9	13.3	11.3	9.07
12	1	13.3	11.3	9.07
13	1.19	13.3	11.3	9
14	1.36	13.3	11.3	9.07
15	1.52	13.3	11.3	9.06
16	1.67	13.3	11.3	9.06
17	1.92	13.3	11.3	9.06
18	2.14	13.3	11.3	9.05

The anion binding studies (Figures 2.10, 2.11 & Table 2.15, 2.16) of the **2.50a** catalyst indicated 1:1 binding of the catalyst to the anion (benzoate or acetate). This was based on the observation that the chemical shifts for all three NH's remains nearly constant upon reaching a mole ratio of one. To confirm 1:1 binding, a UV-Vis study was conducted (Figure 2.13). Stock solutions of **2.50a** and TBAB of the same concentration (0.064 mM) were prepared. The absorbance of samples with different host (**2.50a**)/guest (TBAB) ratio but the same total volume were recorded. A job plot (Figure 2.14) was obtained by plotting $\Delta A*X_{host}$ versus X_{host} where ΔA represents $A-A_{obs}$ (A = absorbance of **2.50a** at zero anion concentration; A_{obs} = observed absorbance for the samples). The results are consistent with the proposed 1:1 binding.

***Figure 2.12*: UV-Vis Titration Curve of 2.50a vs. TBAB**

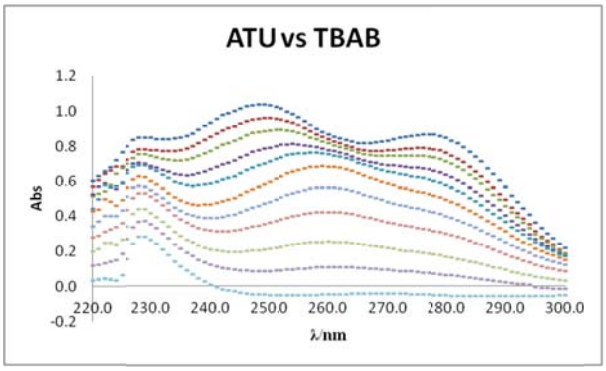
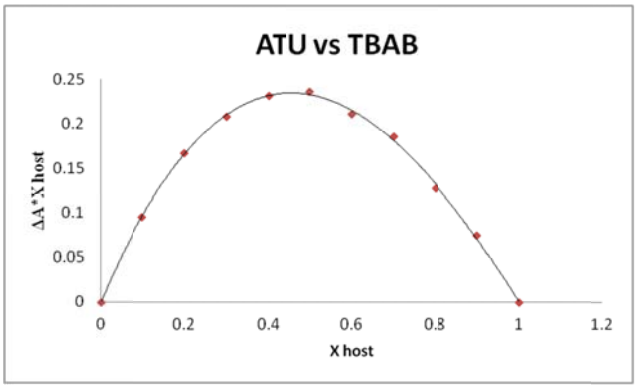


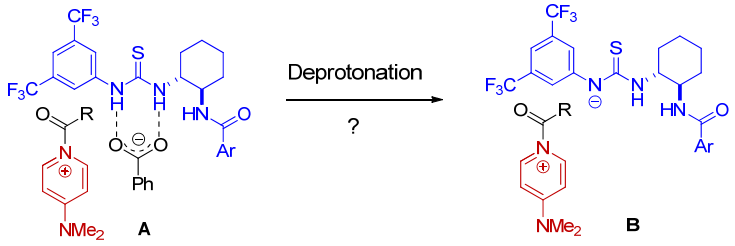
***Figure 2.13*: Job Plot for Titration of 2.50a vs TBAB at 248 nm.**



2.6.7: Deprotonation of Amide Thiourea Catalyst (2.50a)

In light of a recent study by the Schreiner group[59] we hypothesized that different ion pairs could play a role in this reaction (Scheme 2.24). In order to investigate the possibility of catalyst deprotonation and its implications for the mechanism of the reaction, **2.50a** was exposed to a number of different bases, including triethylamine, DMAP, Hünig's base and α-methyl benzylamine. Interestingly, in some cases we observed the apparent disappearance of one of the thiourea N-H signals in the ^{1}H NMR. However, virtually no change was observed in the corresponding ^{13}C and ^{19}F NMR spectra. We speculated that the changes we observed in the ^{1}H NMR's could be due to HB and/or a fast exchange process.

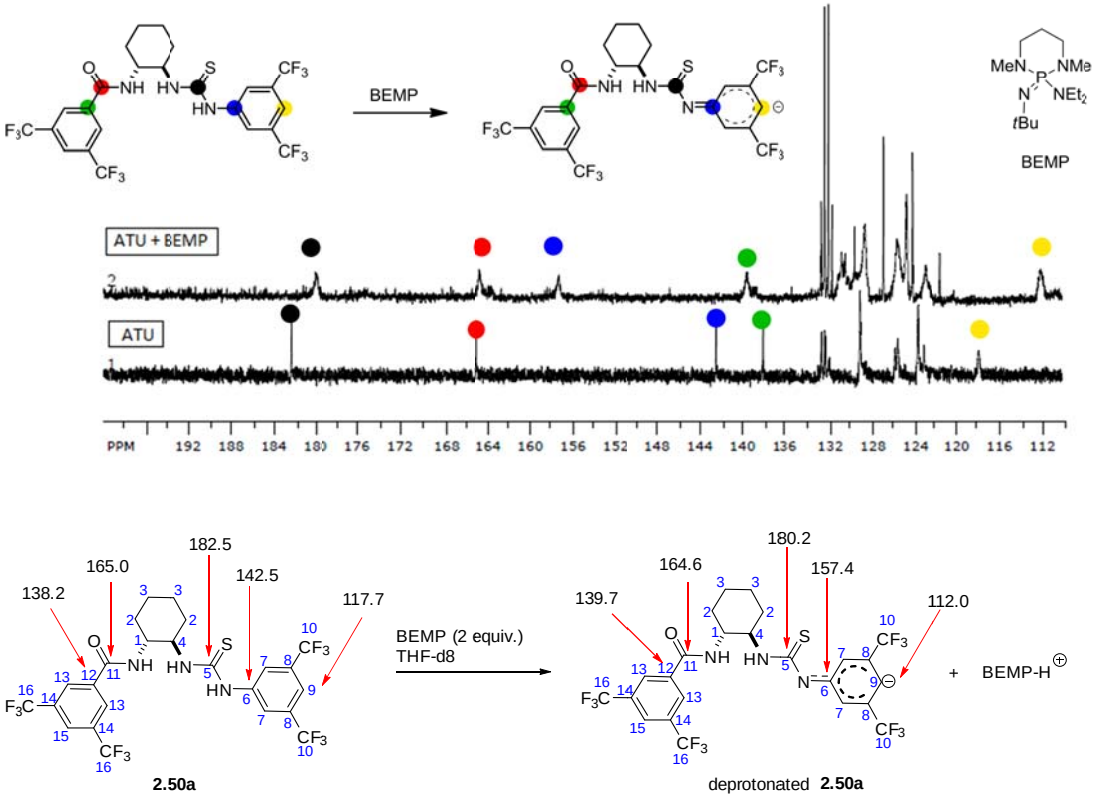
***Scheme 2.24*: Two Potentially Relevant Ion Pairs**



When a much stronger base, BEMP (2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) was added to **2.50a** (in toluene-d8), a significant change in the ^{13}C NMR spectrum was observed. Due to the poor solubility of the catalyst in toluene, the same experiment was repeated in THF-d8 (Figure 2.14). The **2.50a** catalyst behaved similarly after the addition of BEMP, regardless of the solvent used. Upon addition of two equiv. of BEMP to the 0.01M solution of **2.50a** (in THF), an upfield shift of C5 by 2.3 ppm was observed. It was proposed that the reason for this shift could be the deprotonation of the most acidic proton (NH1). Thereafter, the negative charge generated on the nitrogen atom of the thiourea moiety would delocalize into the aromatic ring. As a result, C6 acquired partial double-bond character, which in turn, shifted its signal downfield from 142.5 ppm to 157.5 ppm. C9 is

also affected as its ^{13}C signal moves upfield by 4.3 ppm. These observed changes and a comparison of the ^{1}H and ^{13}C spectra of the catalyst **2.50a** with its spectra in its deprotonated form, suggested deprotonation of the thiourea NH in presence of BEMP. It can be concluded from these experiments that the catalyst **2.50a** could only deprotonate in presence of strong base such as BEMP. Furthermore, it also suggested that the catalyst does not deprotonate under our reaction conditions for kinetic resolution of amines, hence favoring binding mode **A** in comparison to binding mode **B**.

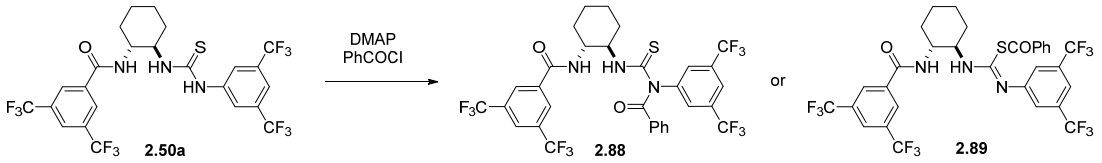
***Figure 2.14*: Deprotonation of 2.50a in THF-d8 using BEMP**



2.6.8: Benzoylation of the 2.50a Catalyst

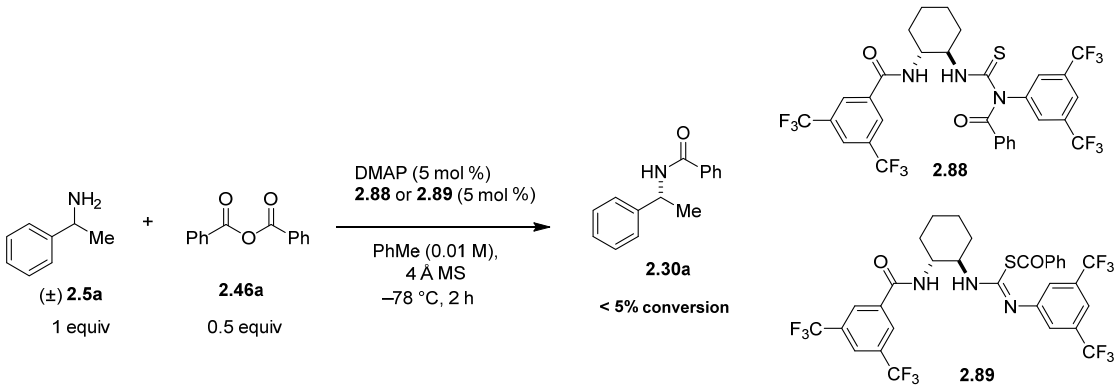
We had previously observed that **2.50a** was slowly benzoylated at elevated temperatrues (Scheme 2.25). The corresponding benzoylation product was prepared independently, but the site of the benzoylation has yet to be established.

***Scheme 2.25*: Benzoylation of 2.50a**



When the benzoylated **2.50a** was used in place of **2.50a** in a standard kinetic resolution experiment, less than 5% conversion was obtained (Scheme 2.26). This finding effectively ruled out the relevance of this compound to the catalytic cycle.

***Scheme 2.26*: Attempted Kinetic Resolution of Benzylic Amine Using Benzoylated 2.50a**



2.6.9 Computational Studies

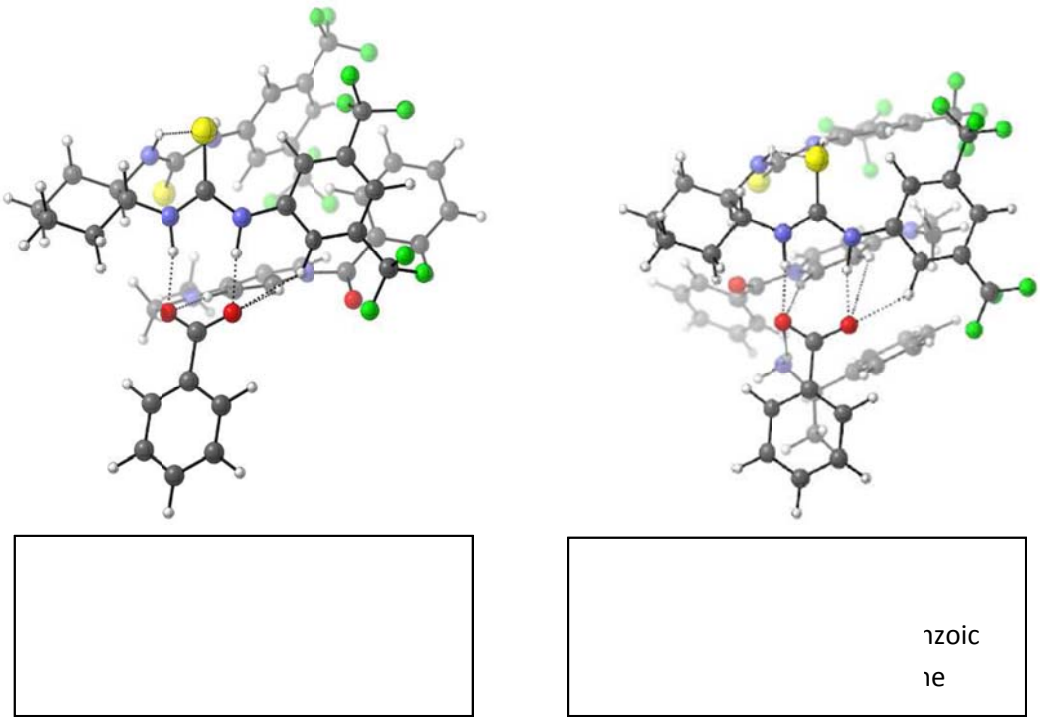
To investigate in detail our proposed mechanistic pathway, computational studies were performed by our collaborators Schreiner et.al. The theoretical studies were based on the benzoylation of propargylic amines and phenylethyl amines. It was found that the thiourea prefers binding to the acetate ion in comparison to the benzoate anion. The dissociation energies are higher for the acetate-thiourea complex at room temperature (rt) or at 0 K. Whereas for the benzoate-thiourea complex the dissociation energies are negative or show a small positive value at 0 K.

Other complexes between the thiourea and phenylethyl amine or between the thiourea and the DMAP showed lower positive dissociation energy values at 0 K, but the energies were

negative at rt or in solution. Therefore, it was proposed that no hydrogen bonding occurs between these complexes at room temperature. Cooling might favor these complexes with lower dissociation energies.

Our mechanistic model involves strong hydrogen bonding between the thiourea and the benzoate. To study this in detail, Schreiner et.al computated the ternary complex between the thiourea, DMAP and benzoic anhydride and the quaternary complex between the thiourea, DMAP benzoic anhydride and amine. Figure 2.15 displays the lowest lying ternary and quaternary complexes with Nagasawa's catalyst **2.48.**

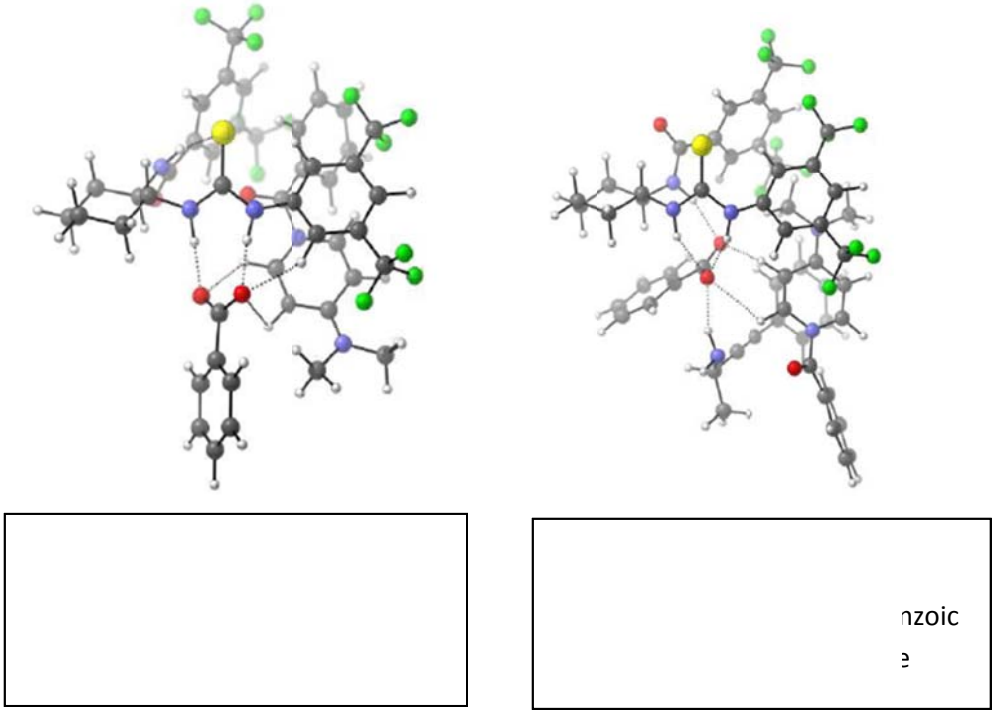
***Figure 2.15*: Ternary and Quaternary Complexes of HB-catalyst 2.48**



In the lowest lying complexes with the bis thiourea catalyst, it was observed that the NH protons of the thiourea show double hydrogen bonding to the oxygen of the benzoate ion (Figure 2.15). One of the oxygens of the benzoate further coordinates to the acidic proton present at the *ortho* position of the aryl group of the thiourea. The sulfur atom of the thiourea links to the

second thiourea via hydrogen bonding. In addition, interactions between the benzoate oxygen and *ortho* protons of DMAP and also between the benzoate oxygen and amine NH (complex **B**) were observed. These coordination modes helped to stereochemically fix the benzoate through π-π stacking with a thiourea aryl ring.

***Figure 2.16*: Ternary and Quaternary Complexes of HB-catalyst 2.50a**



This identical double hydrogen bonding trend was observed for the amide thiourea catalyst (**2.50a)** as well. The NH of the amide moiety binds to the sulfur atom of the thiourea. Additional binding modes were observed between the benzoate and the *ortho* protons of the DMAP. Both aryl groups of the catalyst helped to hold DMAP and its benzoyl group in place via π-π stacking. In complex **B** (Figure 2.16), only one aryl group of the catalyst helped to stereochemically fix DMAP whereas, upon addition of the propargylic amine, additional interactions such as binding of the NH of the propargylic amine to the benzoate and π-π stacking between the amine and DMAP were observed.

2.6.10: Summary

In summary, a dual catalytic approach involving an achiral nucleophilic catalyst employed in combination with a chiral hydrogen bonding catalyst is discussed. Its application has been extended to the kinetic resolution of allylic amines and also to the kinetic resolution of 1,2-diamines. With lower catalyst loadings and shorter reaction times, a diverse collection of substrates with substituents having different electronic properties have been resolved with high *s*-factors. A detailed study of nucleophilic catalysts was conducted. A more efficient nucleophilic catalyst 4-(di *n*-propylamino)pyridine was found which led to remarkable improvement in selectivity for the kinetic resolution of benzylic amines as compared to that previously reported by our group. In addition, a mechanistic study for the dual catalytic approach was conducted. Dilution study experiments supported our previous observation of catalyst self-aggregation at higher concentrations. The titration experiments and the UV-Vis experiments favored 1:1 anion binding of the catalyst to the anion (benzoate or acetate). The HB catalyst **2.50a** did not deprotonate in the presence of bases such as triethylamine, Hunig's base etc. The deprotonation was only observed in the presence of a very strong base like BEMP. This result ruled out the possibility of catalyst deprotonation under the employed reaction conditions. Additional support to the mechanistic model was provided by various computational studies performed by our collaborators. A number of ternary and quaternary complexes were computed and many stable complexes were found, which favored double hydrogen bonding of one thiourea (Nagasawa bis thiourea **2.48** or the amide thiourea catalyst **2.50**) to the oxygen atom on the benzoate ion. At least one of the oxygens on the benzoate binds to the *ortho*-protons of DMAP. In addition, the hydrogen bonding interactions between the NH proton of the amine and the oxygen atom of the benzoate was also observed. Other hydrogen bonding linkage was seen between the NH proton of the amide or the second thiourea of the catalyst, to the sulfur of the first thioure of the HB catalyst. Furthermore, π-π stacking was observed between the DMAP aryl ring and the amine

aryl ring, the DMAP aryl ring and the thiourea phenyl ring, and the benzoate phenyl and second thiourea or amide moiety. Overall, these interactions helped to stereochemically fix DMAP, the benzoyl group on DMAP and the amine with the HB catalyst. They also support the higher selectivities observed for the aromatic substrates in comparison to those obtained from the aliphatic ones (π-π stacking).

Experimental Section

A Kinetic Resolution of Allylic Amines

General Procedure for the Synthesis of Racemic Allylic Amines:

A mixture of ketone (3.0 mmol, 1.0 equiv.), titanium(IV) isopropoxide 1.82 mL (1.71 g, 6.0 mmol, 2.0 equiv.) and 2 M ammonia in ethanol (7.5 mL, 15 mmol, 5.0 equiv.) was stirred under nitrogen dry round bottom flask at room temperature for 12 hours. Sodium borohydride (0.170 g, 4.5 mmol, 1.5 equiv.) was then added and the resulting mixture was stirred at room temperature for an additional 12 hours. A second batch of sodium borohydride (0.056 mg, 1.5 mmol, 0.5 equiv.) was added and stirred for an additional 12 hours. The reaction was quenched with 2 M ammonium hydroxide (10 mL). The resulting inorganic precipitate was filtered through celite and washed with ethyl acetate. The aqueous solution is acidified with 1 M HCl (pH < 4). The resulting solution was extracted with ethyl acetate (3 x 20 mL). The aqueous layer was then treated with aqueous 10% sodium hydroxide (pH 10 – 12) and extracted with ethyl acetate (5 x 50 mL). The combined organic layers were washed with brine, then dried with anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure and the crude product was purified by flash chromatography (99:1 EtOAc/NEt_3→90:10:1 EtOAc/MeOH/ NEt_3).

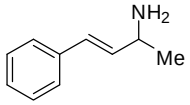
General Procedure for Kinetic Resolutions of Allylic Amines:

A flame dried round bottom flask was charged with benzoic anhydride (34.0 mg, 0.150 mmol, 0.6 equiv.) and 4Å MS (100 mg). PPY (0.74 mg, 0.005 mmol, 0.02 equiv.) in 1 mL of toluene was added. Freshly distilled toluene (21.0 mL) was added and the reaction mixture was cooled to –78 ºC over 15 min and a solution of catalyst (3.13 mg, 0.005 mmol, 0.02 equiv.) in 2 mL of toluene was added. After 15 min, a solution of amine (0.25 mmol) in 1 mL of toluene was added and the reaction mixture was stirred at –78 ºC for 2 hours. The reaction was quenched by adding 3.0 M MeMgCl in THF (0.500 mmol, 0.167 mL) at –78 ºC and stirring was continued for another 10

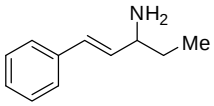
minutes. Excess Grignard reagent was quenched with 1 M aq HCl (5 mL) solution. The reaction mixture was allowed to warm to room temperature and was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with 5 mL of 1 M HCl, then brine. The combined organic extracts were then dried with anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure and the crude product was purified by flash chromatography. The unreacted amine was isolated by basifying the aqueous layer with 15% NaOH (pH 10) and subsequent extraction with diethyl ether (5 x 50 mL). The combined organic layers were washed with brine, and then dried with anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure. The crude material was benzoylated following a standard procedure. The second runs were conducted using the general procedure without any modifications.

Characterization Data of Racemic Amines

(*E*)-4-phenylbut-3-en-2-amine (2.52a): Following the general procedure, compound **2.52a** was obtained as a clear oil in 75% yield (330 mg). Rf = 0.60 (EtOAc/MeOH 4:1 v/v); IR (neat) cm^{-1}; 3277, 3024, 2962, 1577, 1493, 1448, 1369, 966, 693. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (app d, *J* = 9.1 Hz, 2H), 7.30 (app t, *J* = 7.6 Hz, 2H), 7.21 (app t, *J* = 7.3 Hz, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.20 (dd, *J* = 15.9, 6.7 Hz, 1H), 3.71–3.60 (m, 1H), 1.55 (br s, 2H), 1.25 (d, *J* = 6.5 Hz, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 136.2, 128.5, 127.7, 127.2, 126.2, 49.3, 23.9; *m/z* (ESI-MS) 147.7 $[M+H]^+$.

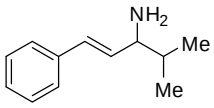


(*E*)-1-phenylpent-1-en-3-amine (2.52b): Following the general procedure, compound **2.52b** was obtained as a clear oil in 67% yield (322 mg). Rf = 0.42 (EtOAc/MeOH 4:1 v/v); IR (neat) cm^{-1}; 3282, 3024, 2961, 1577, 1492, 1449, 1371, 965, 747, 693. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (app d, *J* = 7.7 Hz, 2H), 7.33– 7.25 (comp, 2H), 7.21 (app t, *J* = 7.2 Hz, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.13 (dd, *J* = 15.9, 7.2, Hz, 1H), 3.40–3.34 (m, 1H), 1.68–1.49 (comp, 2H), 1.44 (br s, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).; ^{13}C



NMR (100 MHz, $CDCl_3$) 137.2, 134.8, 129.0, 128.5, 127.2, 126.2, 55.6, 30.7, 10.5; *m/z* (ESI-MS) 161.9 $[M+H]^+$.

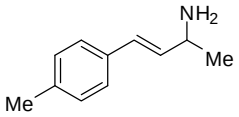
(*E*)-4-methyl-1-phenylpent-1-en-3-amine (2.52c): Following the general procedure, compound



2.52c was obtained as a clear oil in 55% yield (291 mg). Rf = 0.66 (EtOAc/MeOH 4:1 v/v); IR (neat) cm^{-1}; 3368, 3284 3024, 2957, 1598, 1577, 1493, 1448, 1383, 1366, 966, 747, 693. ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (app d, *J* = 7.9 Hz, 2H), 7.29 (app t, *J* = 7.6 Hz, 2H), 7.20 (app t, *J* = 7.3 Hz, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.16 (dd, *J* = 15.9, 7.4 Hz, 1H), 3.23 (app t, *J* = 6.6 Hz, 1H), 1.78–1.64 (m, 1H), 1.41 (br s, 2H), 1.04–0.89 (comp, 6H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 133.2, 129.5, 128.3, 126.9, 126.0, 59.6, 34.0, 18.6, 18.5.; *m/z* (ESI-MS) 175.9 $[M+H]^+$.

(*E*)-4,4-dimethyl-1-phenylpent-1-en-3-amine (2.52d): Following the general procedure, compound **2.52d** was obtained as a clear oil in 48% yield (272 mg). Rf = 0.70 (EtOAc/MeOH 4:1 v/v); IR (neat) cm^{-1}; 3380, 3310, 3025, 2957, 1598. 1492, 1475, 1448, 1362, 967, 755, 692. ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (app d, *J* = 8.3 Hz, 2H), 7.31 (app t, *J* = 7.6 Hz, 2H), 7.22 (app t, *J* = 6.6 Hz, 1H), 6.48 (d, *J* = 15.8 Hz, 1H), 6.24 (dd, *J* = 15.8, 7.9 Hz, 1H), 3.18 (app d, *J* = 7.9 Hz, 1H), 1.28 (br s, 2H), 0.96 (s, 9H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 132.0, 130.3, 128.5, 127.1, 126.2, 63.3, 34.6, 26.3.; *m/z* (ESI-MS) 189.9 $[M+H]^+$.

(*E*)-4-(*p*-tolyl)but-3-en-2-amine (2.52e): Following the general procedure, compound **2.52e** was



obtained as a clear oil in 60% yield (291 mg). Rf = 0.18 (EtOAc/MeOH 4:1 v/v); IR (neat) cm^{-1}; 3362, 3275, 3086, 2960, 1631, 1513, 1452, 1370, 1140, 967, 731. ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.33 (dd, *J* = 15.9, 6.7 Hz, 1H), 3.86–3.78 (m, 1H), 2.50 (s, 3H), 1.93 (br s, 2H), 1.43 (d, *J* = 6.5 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 134.6, 134.0, 128.8, 127.4, 125.8, 48.9, 23.5, 20.8.; *m/z* (ESI-MS) 161.1 $[M]^+$.

(*E*)-4-(*m*-tolyl)but-3-en-2-amine (2.52f): Following the general procedure, compound **2.52f** was obtained as a clear oil in 73% yield (353 mg). Rf = 0.29 (EtOAc/MeOH 4:1 v/v); IR (neat) cm^{-1}; 3361, 3276, 3021, 2960, 1603, 1583, 1451, 1370, 1140, 965, 776. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.11 (comp, 3H), 7.00 (d, *J* = 6.8 Hz, 1H), 6.40 (d, J = 15.9 Hz, 1H), 6.16 (dd, J = 15.9, 6.7 Hz, 1H), 3.70–3.48 (m, 1H), 2.31 (br s, 3H), 1.78 (br s, 2H), 1.22 (d, *J* = 6.5 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 136.7, 135.3, 128.0, 127.7, 127.6, 126.6, 123.1, 48.9, 23.4, 21.0.; *m/z* (ESI-MS) 161.1 $[M]^+$.

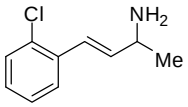
(*E*)-4-(*o*-tolyl)but-3-en-2-amine (2.52g): Following the general procedure, compound **2.52g** was obtained as a clear oil in 74% yield (360 mg). Rf = 0.34 (EtOAc/MeOH 4:1 v/v); IR (neat) cm^{-1}; 3360, 3277, 3018, 2961, 1601, 1485, 1459, 1370, 1143, 966, 748. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 6.3 Hz, 1H), 7.23–7.04 (comp, 3H), 6.67 (d, *J* = 15.7 Hz, 1H), 6.09 (dd, *J* = 15.7, 6.7 Hz, 1H), 3.69 (m, 1H), 2.34 (s, 3H), 1.78 (br s, 2H), 1.27 (d, *J* = 6.5 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 135.5, 130.5, 127.4, 126.3, 125.9, 125.8, 49.8, 24.2, 20.1.; *m/z* (ESI-MS) 161.1 $[M]^+$.

(*E*)-4-(4-chlorophenyl)but-3-en-2-amine (2.52h): Following the general procedure, compound **2.52h** was obtained as a clear oil in 61% yield (334 mg). Rf = 0.30 (EtOAc/MeOH 4:1 v/v); IR (neat) cm^{-1}; 3364, 3280, 3026, 2961, 1592, 1490, 1369, 1091, 1012, 967, 806. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.18 (comp, 4H), 6.38 (d, *J* = 15.9 Hz, 1H), 6.14 (dd, *J* = 15.9, 6.6, Hz, 1H), 3.65–3.59 (m, 1H), 1.36 (br s, 2H), 1.21 (d, *J* = 6.5 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 135.6, 132.6, 128.5, 127.3, 126.4, 49.1, 23.7.; *m/z* (ESI-MS) 181.7 $[M+H]^+$.

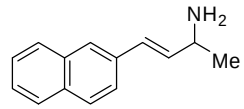
(*E*)-4-(3-chlorophenyl)but-3-en-2-amine (2.52i): Following the general procedure, compound **2.52i** was obtained as a clear oil in 51% yield (278 mg). Rf = 0.34 (EtOAc/MeOH 4:1 v/v); IR (neat) cm^{-1}; 3363, 3272, 3023, 2961, 1593,

1474, 1427, 1370, 1094, 964, 777, 684. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.22–7.07 (comp, 3H), 6.35 (d, *J* = 15.9 Hz, 1H), 6.16 (dd, *J* = 15.9, 6.5 Hz, 1H), 3.65–3.59 (m, 1H), 1.86 (br s, 2H), 1.20 (d, *J* = 6.5 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 137.3, 134.2, 129.5, 127.0, 126.4, 126.0, 124.3, 49.0, 23.5.; *m/z* (ESI-MS) 181.9 $[M+H]^+$.

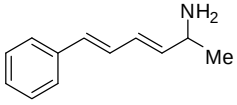
(*E*)-4-(2-chlorophenyl)but-3-en-2-amine (2.52j): Following the general procedure, compound **2.52j** was obtained as a clear oil in 57% yield (311 mg). Rf = 0.47 (EtOAc/MeOH 4:1 v/v); IR (neat) cm^{-1}; 3362, 3276, 3058, 2961, 1590, 1470, 1438, 1369, 1050, 1034, 966, 750. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (app dd, *J* = 7.7, 1.6 Hz, 1H), 7.32 (app dd, *J* = 7.9, 1.3 Hz, 1H), 7.19 (app t, *J* = 7.5 Hz, 1H), 7.13 (app td, *J* = 7.6, 1.7 Hz, 1H), 6.83 (d, *J* = 15.8 Hz, 1H), 6.18 (dd, *J* = 15.8, 6.7 Hz, 1H), 3.72 – 3.67 (m, 1H), 1.40 (br s, 2H), 1.25 (d, *J* = 6.5 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 135.2, 132.8, 129.5, 128.2, 126.7, 126.7, 124.0, 49.4, 23.7.; *m/z* (ESI-MS) 181.8 $[M+H]^+$.



(*E*)-4-(naphthalen-2-yl)but-3-en-2-amine (2.52k): Following a modified general procedure, where 7.5 ml dichloromethane was added as co-solvent, compound **2.52k** was obtained as a clear oil in 71% yield (420 mg). Rf = 0.16 (EtOAc/MeOH 4:1 v/v); IR (neat) cm^{-1}; 3363, 3273, 3054, 2960, 1626, 1596, 1450, 1324, 1140, 963, 745. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (app t, *J* = 7.6 Hz, 3H), 7.71 (s, 1H), 7.60 (app d, *J* = 8.6 Hz, 1H), 7.52–7.35 (m, 2H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.33 (dd, *J* = 15.9, 6.6 Hz, 1H), 3.86–3.51 (m, 1H), 1.37 (br s, 2H), 1.29 (d, *J* = 6.1 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 134.5, 133.5, 132.7, 128.0, 127.7, 127.7, 127.5, 126.0, 125.8, 125.5, 123.5, 49.2, 23.8.; *m/z* (ESI-MS) 198.1 $[M+H]^+$.

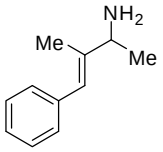


(*3E,5E*)-6-phenylhexa-3,5-dien-2-amine (2.52l): Following a modified general procedure, where 7.5 ml dichloromethane was added as co-solvent, compound **2.52l** was obtained as a clear oil in 48% yield (255 mg). Rf = 0.24



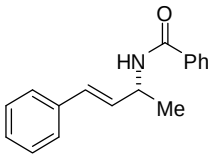
(EtOAc/MeOH 4:1 v/v); IR (neat) cm^{-1}; 3364, 3277, 3022, 2960, 1596, 1490, 1447, 1367, 1072, 1028, 988, 747. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.34 (comp, 2H), 7.30 (app t, *J* = 7.6 Hz, 2H), 7.21 (app tt, *J* = 8.5, 1.2 Hz, 1H), 6.75 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.28 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.81 (dd, *J* = 15.2, 6.6 Hz, 1H), 3.69–3.47 (m, 1H), 1.34 (br s, 2H), 1.21 (d, *J* = 6.5 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 131.5, 128.7, 128.5, 128.2, 127.3, 126.2, 48.9, 23.8.; *m/z* (ESI-MS) 174.0 $[M+H]^+$.

(*E*)-3-methyl-4-phenylbut-3-en-2-amine (2.52m): Following the general procedure, compound **2.52m** was obtained as a clear oil in 70% yield (339 mg). Rf = 0.24 (EtOAc/MeOH 4:1 v/v); IR (neat) cm^{-1}; 3372, 3022, 2963, 1598, 1491, 1443, 1371, 1101, 856, 739, 698. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (app t, *J* = 7.6 Hz, 2H), 7.25 (app d, *J* = 7.5 Hz, 2H), 7.19 (app t, *J* = 7.3 Hz, 1H), 6.44 (s, 1H), 3.61–3.57 (m, 1H), 1.86 (s, 3H), 1.76 (br s, 2H), 1.25 (d, *J* = 6.6 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 137.9, 128.8, 127.9, 126.0, 123.4, 54.6, 22.1, 13.7.; *m/z* (ESI-MS) 161.1 $[M]^+$.



Characterization Data of Products

(*R,E*)-*N*-(4-phenylbut-3-en-2-yl)benzamide (2.54a): Following the general procedure, compound **2.54a** was obtained as a white solid in 49% yield (31.0 mg). mp = 117–119 ºC; Rf = 0.31 (Hexanes/EtOAc 3:1 v/v); $[\alpha]_D^{20}$ +13.2 (c 1.0, $CHCl_3$, 68.2% *ee*); IR (KBr) cm^{-1}; 3277, 2964, 1624, 1536, 1491, 1311, 966, 751, 692. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.0 Hz, 1H), 7.49 (m, 1H), 7.42 (app t, *J* = 7.3 Hz, 2H), 7.36 (app d, *J* = 7.6 Hz, 2H), 7.30 (app t, *J* = 7.5 Hz, 2H), 7.27–7.09 (m, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.40–6.07 (comp, 2H), 5.01–4.96 (m, 1H), 1.45 (d, *J* = 6.7 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 136.6, 134.6, 131.4, 130.8, 129.9, 128.5, 127.6, 126.9, 126.4, 46.9, 20.6.; *m/z* (ESI-MS) 252.1 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 17.7 min (major) and t_R = 34.0 min. The recovered starting material was benzoylated and the *ee* was determined by HPLC (85.0% *ee*, *S*-enantiomer).



Calculated conversion = 56; **s = 14**. Second run: conversion = 53; **s = 14** (benzoylated product: 31.0 mg, 49% yield, 70.6% *ee*; benzoylated starting material: 80.4% *ee*, *S*-enantiomer). The absolute configuration of the recovered amine **7a** ($[\alpha]_D^{20}$ –11.0 (c 1.0, $CHCl_3$, 80.4% *ee*) was assigned by comparison with the compound reported in the literature[4] ($[\alpha]_D^{20}$ +25.8 (c 1.16, $CHCl_3$, >99% *ee*).

(*R,E*)-*N*-(1-phenylpent-1-en-3-yl)benzamide (2.54b): Following the general procedure, compound **2.54b** was obtained as a white solid in 45% yield (30.1 mg). mp = 125–127 ºC; Rf = 0.35 (Hexanes/EtOAc 3:1 v/v); $[\alpha]_D^{20}$ +17.2 (c 1.0, $CHCl_3$, 68.6% *ee*); IR (KBr) cm^{-1}; 3336, 2960, 1636, 1520, 1488, 1321, 960, 753, 692. ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.1 Hz, 2H), 7.54–7.47 (m, 1H), 7.46–7.39 (comp, 2H), 7.39–7.34 (comp, 2H), 7.30 (app t, *J* = 7.6 Hz, 2H), 7.26–7.20 (m, 1H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.20 (dd, *J* = 15.9, 6.4 Hz, 1H), 6.16 (app s, 1H), 4.82–4.74 (m, 1H), 1.85–1.68 (comp, 2H), 1.03 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 136.7, 134.8, 131.4, 130.9, 129.6, 128.6, 128.5, 127.6, 126.9, 126.4, 52.8, 28.3, 10.4.; *m/z* (ESI-MS) 266.2 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 17.4 min (major) and t_R = 21.2 min. The recovered starting material was benzoylated and the *ee* was determined by HPLC (76.0% *ee*, *S*-enantiomer). Calculated conversion = 53; **s = 12**. Second run: conversion = 52; **s = 12** (benzoylated product: 29.2 mg, 44% yield, 69.0% *ee*; benzoylated starting material: 74.0% *ee*, *S*-enantiomer).

The absolute configuration was assigned by analogy.

(*R,E*)-*N*-(4-methyl-1-phenylpent-1-en-3-yl)benzamide (2.54c): Following the general procedure, compound **2.54c** was obtained as a white solid in 45% yield (32.2 mg). mp = 134–136 ºC; Rf = 0.40 (Hexanes/EtOAc 3:1 v/v); $[\alpha]_D^{20}$ +10.5 (c 1.0, $CHCl_3$, 79.2% *ee*); IR (KBr) cm^{-1}; 3277, 2965, 1629, 1533, 1489, 1323, 968, 752, 696. ^1H NMR (500 MHz, $CDCl_3$) δ 7.84–7.80 (comp, 2H), 7.54–7.48 (m, 1H), 7.44 (app t, *J* = 7.4 Hz, 2H), 7.39–7.34 (comp, 2H), 7.30 (app t, *J*

= 7.6 Hz, 2H), 7.23 (app t, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 15.9 Hz, 1H), 6.28 (d, *J* = 8.8 Hz, 1H), 6.20 (dd, *J* = 15.9, 6.8 Hz, 1H), 4.72 (dd, *J* = 15.1, 6.8 Hz, 1H), 2.06–1.99 (m, 1H), 1.04 (d, *J* = 2.2 Hz, 3H), 1.03 (d, *J* = 2.1 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 136.7, 134.9, 131.6, 131.4, 128.6, 128.5, 128.2, 127.5, 126.9, 126.4, 56.8, 32.8, 18.9, 18.6.; *m/z* (ESI-MS) 280.2 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 14.1 min (major) and t_R = 17.6 min. The recovered starting material was benzoylated and the *ee* was determined by HPLC (76.2% *ee*, *S*-enantiomer). Calculated conversion = 49; **s = 20**. Second run: conversion = 51; **s = 19** (benzoylated product: 32.7 mg, 46% yield, 77.4% *ee*; benzoylated starting material: 80.8% *ee*, *S*-enantiomer). The absolute configuration was assigned by analogy.

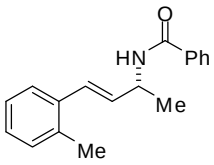
(*S*,*E*)-*N*-(4,4-dimethyl-1-phenylpent-1-en-3-yl)benzamide (2.54d): Following the general procedure, compound **2.54d** was obtained as a white solid in 46% yield (34.1 mg). mp = 105–107 ºC; Rf = 0.45 (Hexanes/EtOAc 3:1 v/v); $[\alpha]_D^{20}$ +7.0 (c 1.0, $CHCl_3$, 76.0% *ee*); IR (KBr) cm^{-1}; 3276, 2963, 1632, 1540, 1491, 1335, 971, 765, 692. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.79 (m, 2H), 7.51 (app t, *J* = 7.3 Hz, 1H), 7.48–7.43 (comp, 2H), 7.39–7.34 (comp, 2H), 7.30 (app t, *J* = 7.6 Hz, 2H), 7.23 (app t, *J* = 7.3 Hz, 1H), 6.60 (d, *J* = 15.7 Hz, 1H), 6.25 (dd, *J* = 15.8, 7.3 Hz, 1H), 6.23 (app s, 1H), 4.72 (dd, *J* = 9.6, 7.3, Hz, 1H), 1.06 (s, 9H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 136.8, 135.0, 132.3, 131.4, 128.6, 128.5, 127.5, 126.8, 126.8, 126.4, 59.7, 35.1, 26.5.; *m/z* (ESI-MS) 294.1 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 10.9 min (major) and t_R = 14.0 min. The recovered starting material was benzoylated and the *ee* was determined by HPLC (78.9% *ee*, *R*-enantiomer). Calculated conversion = 51; **s = 17**. Second run: conversion = 55; **s = 19** (benzoylated product: 33.7 mg, 47% yield, 73.0% *ee*; benzoylated starting material: 90.2% *ee*, *S*-enantiomer). The absolute configuration was assigned by analogy.

(*R,E*)-*N*-(4-p-tolylbut-3-en-2-yl)benzamide (2.54e): Following the general procedure, compound **2.54e** was obtained as a white solid in 50% yield (33.0 mg). mp = 115–117 ºC; Rf = 0.35 (Hexanes/EtOAc 3:1v/v); $[\alpha]_D^{20}$ +17.9 (c 1.0, $CHCl_3$, 62.8% *ee*); IR (KBr) cm^{-1}; 3307, 3027, 2964, 1633, 1528, 1488, 1277, 694. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.4 Hz, 2H), 7.56–7.37 (comp, 3H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.18–7.06 (comp, 2H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.23 (dd, *J* = 16.0, 5.7 Hz, 1H), 6.19 (app s, 1H), 4.99–4.94 (m, 1H), 2.34 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H).;^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 137.4, 134.7, 133.8, 131.4, 129.8, 129.7, 129.2, 128.5, 126.9, 126.3, 46.9, 21.1, 20.7.; *m/z* (ESI-MS) 266.1 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 12.7 min (major) and t_R = 15.2 min. The recovered starting material was benzoylated and the *ee* was determined by HPLC (63.6% *ee*, *S*-enantiomer). Calculated conversion = 50; **s = 8.3** Second run: conversion = 49; **s = 10** (benzoylated product: 32.0 mg, 48% yield, 67.6% *ee*; benzoylated starting material: 65.2% *ee*, *S*-enantiomer). The absolute configuration was assigned by analogy.

(*R,E*)-*N*-(4-m-tolylbut-3-en-2-yl)benzamide (2.54f): Following the general procedure, compound **2.54f** was obtained as a white solid in 45% yield (32.3 mg). mp = 75–77 ºC; Rf = 0.35 (Hexanes/EtOAc 3:1 v/v); $[\alpha]_D^{20}$ +19.1 (c 1.0, $CHCl_3$, 63.4% *ee*); IR (KBr) cm^{-1}; 3305, 3028, 2973, 1634, 1533, 1488, 1295, 693. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87–7.74 (comp, 2H), 7.55–7.41 (comp, 3H), 7.24–7.11 (comp, 3H), 7.06 (app d, *J* = 7.0 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 6.29–6.24 (comp, 2H), 5.00–4.94 (m, 1H), 2.34 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 138.0, 136.5, 134.6, 131.4, 130.6, 130.5, 130.0, 128.5, 128.4, 127.1, 126.89, 123.5, 46.9, 21.3, 20.6..; *m/z* (ESI-MS) 266.2 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 15.0 min (major) and t_R = 20.7 min. The recovered starting material was benzoylated and the *ee* was determined by HPLC (56.8% *ee*, *S*-

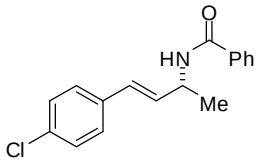
enantiomer). Calculated conversion = 47; **s = 7.8**. Second run: conversion = 45; **s = 8.2** (benzoylated product: 28.0 mg, 42% yield, 66.0% *ee*; benzoylated starting material: 53.1% *ee*, *S*-enantiomer). The absolute configuration was assigned by analogy.

(*R,E*)-*N*-(4-o-tolylbut-3-en-2-yl)benzamide (2.54g): Following the general procedure, compound **2.54g** was obtained as a white solid in 44% yield (29.0 mg). mp = 96–98 ºC; Rf = 0.33 (Hexanes/EtOAc 3:1 v/v); $[\alpha]_D^{20}$ +16.8 (c 1.0, $CHCl_3$, 59.1% *ee*); IR (KBr) cm^{-1}; 3302, 3059, 2972, 1634, 1538, 1488, 1275, 665. ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.3 Hz, 2H), 7.60–7.30 (comp, 4H), 7.20–7.04 (comp, 3H), 6.82 (d, *J* = 15.8 Hz, 1H), 6.22 (d, *J* = 7.6 Hz, 1H), 6.14 (dd, *J* = 15.8, 5.9 Hz, 1H), 5.02–4.96 (m, 1H), 2.34 (s, 3H), 1.47 (d, *J* = 6.8 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 135.7, 135.4, 134.7, 132.1, 131.4, 130.2, 128.5, 127.9, 127.5, 126.9, 126.0, 125.6, 47.2, 20.8, 19.7.; *m/z* (ESI-MS) 266.1 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 17.5 min (major) and t_R = 30.0 min. The recovered starting material was benzoylated and the *ee* was determined by HPLC (48.8 % *ee*, *S*-enantiomer).

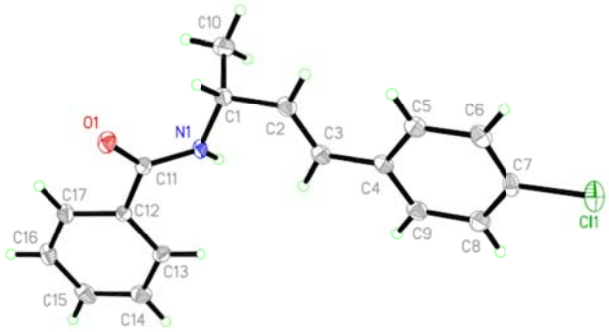


Calculated conversion = 45; **s = 6.2**. Second run: conversion = 49; **s = 7.2** (benzoylated product: 31.4 mg, 47% yield, 60.2 % *ee*; benzoylated starting material: 58.6 % *ee*, *S*-enantiomer). The absolute configuration was assigned by analogy.

(*R,E*)-*N*-(4-(4-chlorophenyl)but-3-en-2-yl)benzamide (2.54h): Following the general procedure, compound **2.54h** was obtained as a white solid in 47% yield (33.8 mg). mp = 157–159 ºC; Rf = 0.29 (Hexanes/EtOAC 3:1 v/v); $[\alpha]_D^{20}$ +26.5 (c 1.0, $CHCl_3$, 74.8% *ee*); IR (KBr) cm^{-1}; 3301, 2967, 1636, 1526, 1489, 1293, 1090, 965, 704. ^1H NMR (500 MHz, $CDCl_3$) 7.80 (d, *J* = 7.1 Hz, 2H), 7.50 (app t, *J* = 7.4 Hz, 1H), 7.42 (app t, *J* = 7.5 Hz, 2H), 7.31–7.18 (comp, 4H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.27 (d, *J* = 7.7 Hz, 1H), 6.23 (dd, *J* = 16.0, 5.7 Hz, 1H), 5.06–4.81 (m, 1H), 1.43 (d, *J* = 6.8 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 135.1, 134.5, 133.2, 131.5, 131.5, 128.7,



128.6, 128.5, 127.6, 126.9, 46.8, 20.6.; *m/z* (ESI-MS) 286.1 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 95/15, Flow rate = 1 mL/min, UV = 254 nm, t_R = 10.3 min and t_R = 12.8 min (major). The recovered starting material was benzoylated and the *ee* was determined by HPLC (75.8% *ee*, *S*-enantiomer). Calculated conversion = 50; **s = 16**. Second run: conversion = 51; **s = 17** (benzoylated product: 33.0 mg, 46% yield, 75.8% *ee*; benzoylated starting material: 79.6% *ee*, *S*-enantiomer). The absolute configuration was assigned by X-ray crystallography:

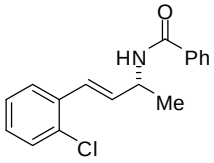


The enantioenriched amide **2.54h** was recrystallized from hexanes/ethyl acetate. The enantiopure amide (>99% ee) was crystallized from hexanes/ethyl acetate through slow diffusion at room temperature. The requisite CIF file has been submitted to the journal.

(*R,E*)-*N*-(4-(3-chlorophenyl)but-3-en-2-yl)benzamide (2.54i): Following the general procedure, compound **2.54i** was obtained as a white solid in 48% yield (34.6 mg). mp =96–98ºC; Rf = 0.29 (Hexanes/EtOAc 3:1 v/v); $[\alpha]_D^{20}$ +17.4(c 1.0, $CHCl_3$, 63.5% *ee*); IR (KBr) cm^{-1}; 3302, 3061, 2974, 1634, 1537, 1488, 1292, 964, 710. ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.6 Hz, 2H), 7.52–7.40 (comp, 3H), 7.35 (s, 1H), 7.24–7.16 (comp, 3H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.27 (dd, *J* = 16.0, 5.7 Hz, 1H), 6.22 (d, *J* = 7.6 Hz, 1H), 4.96 (dd, *J* = 13.5, 6.8 Hz, 1H), 1.44 (d, *J* = 6.8 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 138.5, 134.4, 132.4, 131.5, 129.7, 128.5, 127.5, 126.9, 126.2, 124.7, 46.8, 20.6.; *m/z* (ESI-MS) 286.1 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 254 nm, t_R = 18.8 min (major) and t_R = 31.5

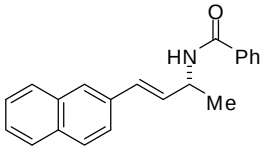
min. The recovered starting material was benzoylated and the *ee* was determined by HPLC (75.2% *ee*, *S*-enantiomer). Calculated conversion = 54; **s = 9.9**. Second run: conversion = 54; **s = 10** (benzoylated product: 35.1mg, 49% yield, 64.5% *ee*; benzoylated starting material: 76.8% *ee*, *S*-enantiomer). The absolute configuration was assigned by analogy.

(*R*,*E*)-*N*-(4-(2-chlorophenyl)but-3-en-2-yl)benzamide (2.54j): Following the general procedure, compound **2.54j** was obtained as a white solid in 46% yield (33.2 mg). mp = 104–106 ºC; Rf = 0.29(Hexanes/EtOAc 3:1 v/v); $[\alpha]_D^{20}$ +17.4 (c 1.0, $CHCl_3$, 57.6% *ee*); IR (KBr) cm^{-1}; 3337, 2979, 1633, 1524, 1486, 1323, 1274, 961, 761, 696. ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.9 Hz, 2H), 7.56–7.47 (comp, 2H), 7.43 (app t, *J* = 7.7 Hz, 2H), 7.34 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.24–7.11 (comp, 2H), 6.98 (d, *J* = 16.0 Hz, 1H), 6.29 (dd, *J* = 16.0, 5.4 Hz, 1H), 6.22 (d, *J* = 7.7 Hz, 1H), 5.01 (dd, *J* = 12.9, 6.1 Hz, 1H), 1.48 (d, *J* = 6.8 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 134.8, 134.6, 133.8, 133.1, 131.5, 129.6, 128.6, 128.6, 126.9, 126.8, 126.8, 126.0, 46.8, 20.5.; *m/z* (ESI-MS) 286.2 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 254 nm, t_R = 11.3 min (major) and t_R = 17.2 min. The recovered starting material was benzoylated and the *ee* was determined by HPLC (65.4% *ee*, *S*-enantiomer). Calculated conversion = 53; **s = 7.1**.



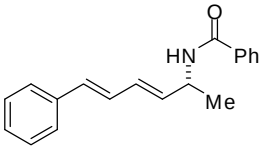
Second run: conversion = 38; **s = 6.9** (benzoylated product: 24.6 mg, 34% yield, 64.8% *ee*; benzoylated starting material: 40.4% *ee*, *S*-enantiomer). The absolute configuration was assigned by analogy.

(*R*,*E*)-*N*-(4-(naphthalen-2-yl)but-3-en-2-yl)benzamide (2.54k): Following the general procedure, compound **2.54k** was obtained as a white solid in 52% yield (39.0 mg). mp = 125–127 ºC; Rf = 0.28 (Hexanes/EtOAc 3:1v/v); $[\alpha]_D^{20}$ +12.7 (c 1.0, $CHCl_3$, 62.4% *ee*); IR (KBr) cm^{-1}; 3303, 3056, 2791, 1634, 1533, 1489, 1271, 665. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88–7.73 (comp, 5H), 7.71 (s, 1H), 7.57



(app d, *J* = 8.6 Hz, 1H), 7.53–7.29 (comp, 5H), 6.73 (d, *J* = 15.9 Hz, 1H), 6.48–6.29 (comp, 2H), 5.11–4.95 (m, 1H), 1.49 (d, *J* = 5.5 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 134.6, 134.0, 133.5, 132.9, 131.4, 131.2, 130.0, 128.5, 128.1, 127.9, 127.6, 126.9, 126.4, 126.2, 125.8, 123.5, 46.9, 20.7.; *m/z* (ESI-MS) 302.4 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 38.3 min and t_R = 47.7 min (major). The recovered starting material was benzoylated and the *ee* was determined by HPLC (76.3% *ee*, *S*-enantiomer). Calculated conversion = 55; **s = 9.7**. Second run: conversion = 54; **s = 8.9** (benzoylated product: 36.8 mg, 49% yield, 61.7% *ee*; benzoylated starting material: 72.7% *ee*, *S*-enantiomer). The absolute configuration was assigned by analogy.

***N*-((*R,3E,5E*)-6-phenylhexa-3,5-dien-2-yl)benzamide (2.54l):** Following the general procedure, compound **2.54l** was obtained as a white solid in 48% yield (33.6 mg).



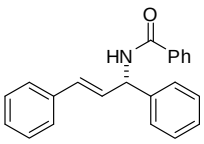
mp = 140–142 ºC; Rf = 0.33 (Hexanes/EtOAc 3:1 v/v); $[\alpha]_D^{20}$ +16.5 (c 1.0, $CHCl_3$, 65.8% *ee*); IR (KBr) cm^{-1}; 3282, 2964, 1632, 1531, 1488, 1343, 1286, 992, 747, 691. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (app d, *J* = 7.0 Hz, 2H), 7.50 (app dd, *J* = 9.7, 3.7 Hz, 1H), 7.46–7.41 (comp, 2H), 7.38 (app d, *J* = 7.3 Hz, 2H), 7.31 (app t, *J* = 7.5 Hz, 2H), 7.26–7.17 (m, 1H), 6.76 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.55 (d, *J* = 15.7 Hz, 1H), 6.40 (dd, *J* = 15.7, 10.9 Hz, 1H), 6.14 (d, *J* = 7.6 Hz, 1H), 5.88 (dd, *J* = 15.3, 5.7 Hz, 1H), 4.91 (app dq, *J* = 13.0, 6.6 Hz, 1H), 1.41 (d, *J* = 6.8 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 137.1, 134.9, 134.6, 132.7, 131.4, 130.4, 128.6, 128.5, 128.1, 127.6, 126.9, 126.3, 46.7, 20.6.; *m/z* (ESI-MS) 278.0 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 38.9 min and t_R = 50.2 min (major). The recovered starting material was benzoylated and the *ee* was determined by HPLC (66.8% *ee*, *S*-enantiomer). Calculated conversion = 50; **s = 9.5**. Second run: conversion = 52; **s = 9.3** (benzoylated product: 35.0 mg, 51% yield, 64.4% *ee*; benzoylated starting material: 68.8% *ee*, *S*-enantiomer). The absolute configuration was assigned by analogy.

(*R,E*)-*N*-(3-methyl-4-phenylbut-3-en-2-yl)benzamide (2.54m): Following the general procedure, compound **2.54m** was obtained as a white solid in 48% yield (31.8 mg). mp = 55–57 ºC; Rf = 0.35 (Hexanes/EtOAc 3:1 v/v); $[\alpha]_D^{20}$ +4.9 (c 1.0, $CHCl_3$, 55.4% *ee*); IR (KBr) cm^{-1}; 3304, 3057, 2975, 1636, 1533, 1489, 1272, 697. ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.7 Hz, 1H), 7.58–7.46 (comp, 1H), 7.43 (app t, *J* = 7.7 Hz, 2H), 7.32 (app t, *J* = 7.6 Hz, 2H), 7.26 (app d, *J* = 7.7 Hz, 2H), 7.21 (app t, *J* = 7.3 Hz, 1H), 6.54 (s, 1H), 6.24 (d, *J* = 7.7 Hz, 1H), 4.91–4.79 (m, 1H), 1.93 (s, 3H), 1.46 (d, *J* = 6.8 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 138.8, 137.5, 134.7, 131.4, 130.5, 128.9, 128.8, 128.5, 128.0, 126.9, 126.4, 125.1, 51.9, 19.8, 15.4.; *m/z* (ESI-MS) 266.0 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 254 nm, t_R = 7.7 min (major) and t_R = 27.0 min. The recovered starting material was benzoylated and the *ee* was determined by HPLC (51.2% *ee*, *S*-enantiomer). Calculated conversion = 48; **s = 5.7**. Second run: conversion =47; **s = 5.8** (benzoylated product: 29.2 mg, 44% yield, 56.5% *ee*; benzoylated starting material: 50.1% *ee*, *S*-enantiomer). The absolute configuration was assigned by analogy.

***(R)*-*N*-(1-cyclohexenylethyl)benzamide (2.54n):** Following the general procedure, compound **2.54n** was obtained as a clear oil in 46% yield (26.5 mg). Rf = 0.45 (Hexanes/EtOAc 3:1 v/v); $[\alpha]_D^{20}$ +7.2 (c 1.0, $CHCl_3$, 40.2% *ee*); IR (neat) cm^{-1}; 3300, 3059, 2928, 1634, 1536, 1489, 1336, 1274, 694. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.4 Hz, 2H), 7.47 (app t, *J* = 7.1 Hz, 2H), 7.40 (app t, *J* = 7.5 Hz, 3H), 6.14 (d, *J* = 7.2 Hz, 1H), 5.67 (s, 1H), 4.71–4.48 (m, 1H), 2.29–1.82 (comp, 4H), 1.66–1.54 (comp, 4H), 1.31 (d, *J* = 6.8 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 138.3, 134.9, 131.2, 128.4, 126.8, 121.6, 50.1, 25.8, 24.9, 22.7, 22.3, 19.4.; *m/z* (ESI-MS) 229.1 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 6.8 (major) and t_R = 10.3 min. The recovered starting material was benzoylated and the *ee* was determined by HPLC (38.7% *ee*, *S*-enantiomer). Calculated conversion = 49; **s =3.4**. Second

run: conversion = 48; **s = 3.5** (benzoylated product: 25.7 mg, 45% yield, 41.8% *ee*; benzoylated starting material: 39.0% *ee*, *S*-enantiomer). The absolute configuration was assigned by analogy.

(*S,E*)-*N*-(1,3-diphenylallyl)benzamide (2.54o): Following the general procedure, compound **5o**



was obtained as a white solid in 55% yield (43.0 mg). $[\alpha]_D^{20}$ –6.0 (c 1.0, $CHCl_3$, 49.2% *ee*); The spectral data was consistent with the literature.[5] HPLC Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 254 nm, t_R = 17.3 min and t_R = 38.3 min (major). The recovered starting material was benzoylated and the *ee* was determined by HPLC (64.9% *ee*, *R*-enantiomer). Calculated conversion = 57; **s = 5.5.** Second run: conversion =57; **s = 5.4** (benzoylated product: 40.2 mg, 51% yield, 48.7 % *ee*; benzoylated starting material: 63.4% *ee*, *R*-enantiomer). The absolute configuration of recovered amine **3o** ($[\alpha]_D^{20}$ +10.0 (c 1.0, CH_2Cl_2, 64.9% *ee*) was assigned by comparison with the compound reported in the literature[6,7] ($[\alpha]_D^{16}$ +38.2 (c 0.86, CH_2Cl_2, 87% *ee*). The absolute configuration of product **5o** ($[\alpha]_D^{20}$ –6.0 (c 1.0, $CHCl_3$, 49.2% *ee*) was further confirmed by comparison with the opposite enantiomer reported in the literature ($[\alpha]_D^{23}$ +20.4 (c 1.0, $CHCl_3$, 95% *ee*).

B General Procedure for Kinetic Resolutions:

A flame dried round bottom flask was charged with benzoic anhydride (28.0 mg, 0.125 mmol, 0.5 equiv.) and 4Å MS (100 mg), followed by addition of toluene (18 mL). Nucleophilic catalyst (0.0125mmol, 0.05 equiv.) in 1 mL of toluene was added. The resulting solution was stirred at room temperature for 5 min and then cooled to –78 ºC over 15 min. A solution of HB catalyst (7.82 mg, 0.0125 mmol, 0.05 equiv.) in 4 mL of toluene was added. After 15 min, a solution of amine (0.25 mmol) in 2 mL of toluene was added and the reaction mixture was stirred at –78 ºC for 2 hours. The reaction was quenched by adding 3.0M MeMgCl in THF (0.500 mmol, 0.167 mL) at –78 ºC. The reaction mixture was then stirred for another 10 minutes. Excess Grignard

reagent was quenched with 1M aqueous HCl (5 mL) solution. The reaction mixture was allowed to warm to room temperature and was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with 5 mL of 1M HCl, then brine. The combined organic extracts were then dried with anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure and the crude product was purified by flash chromatography.

Characterization Data of Products

(*R*)-*N*-(2-Methyl-1-phenylpropyl)benzamide (2.30c): Following the general procedure, compound **2.30c** was obtained as a white solid in 49% yield (31.0 mg). mp = 105–107 ºC; R_f 0.21 (Hexanes/EtOAc 8:2 v/v); $[\alpha]_D^{20}$ +18.2 (c 1.0, $CHCl_3$, 91.6% *ee*); IR (KBr) cm^{-1} 3279, 3065, 2955, 1632, 1579, 1491, 700. ^1H NMR (500 MHz, $CDCl_3$) δ 7.79–7.66 (comp, 2H), 7.48–7.38 (m, 1H), 7.37–7.32 (comp, 2H), 7.31–7.21 (comp, 4H), 7.20–7.15 (m, 1H), 6.38 (app d, *J* = 8.1 Hz, 1H), 4.90 (app t, *J* = 8.3 Hz, 1H), 2.17–2.03 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 3H); 0.83 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 141.5, 134.8, 131.4, 128.6, 128.5, 127.2, 127.0, 126.9, 59.4, 33.6, 19.8, 18.9.; *m/z* (ESI-MS) 254.2 $[M+H]^+$;HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R =7.3 min (major) and t_R = 9.0 min. The recovered starting material was benzoylated and the *ee* was determined by HPLC (88.9% *ee*, *S*-enantiomer). Calculated conversion = 49; **s = 68**. Second run: conversion = 49; **s = 66** (benzoylated product: 31.0 mg, 49% yield, 91.5% *ee*; benzoylated starting material: 88.2% *ee*, *S*-enantiomer). The absolute configuration of **2c** ($[\alpha]_D^{20}$ +16 (c 0.6, $CHCl_3$, 91.6% *ee*) was assigned by comparison with the amine reported in literature[60] ($[\alpha]_D^{20}$ +6.4 (c 0.6, $CHCl_3$, 88.0% *ee).*

(*R*)-*N*-(2,2-Dimethyl-1-phenylpropyl)benzamide (2.30d): Following the general procedure, compound **.2.30d** was obtained as a white solid in 34% yield (23.0 mg). mp = 124–126 ºC; R_f 0.31 (Hexanes/EtOAc 8:2 v/v); $[\alpha]_D^{20}$ –25 (c 1.0, $CHCl_3$, 86.8% *ee*); IR (KBr) cm^{-1} 3411, 3056, 2959, 1640, 1521, 1488, 702. ^1H NMR (500 MHz, $CDCl_3$) δ 7.84–7.73 (comp, 2H), 7.54–7.47 (m, 1H), 7.46–7.40 (comp, 2H), 7.37–7.21 (comp, 5H), 6.75 (app d, *J* = 8.5 Hz, 1H), 5.05 (d, *J* = 9.3 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 140.0, 135.0, 131.3, 128.6, 128.0, 127.8, 127.1, 126.8, 61.9, 35.1, 26.1; *m/z* (ESI-MS) 268.3 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 0.5 mL/min, UV = 254 nm, t_R = 26.0 min (major) and t_R = 28.7 min. The recovered starting material was benzoylated and the *ee* was determined by HPLC (43.2% *ee*, *S*-enantiomer). Calculated conversion = 33; **s = 22**. Second run: conversion = 31; **s = 21** (benzoylated product: 22.0 mg, 33% yield, 86.5% *ee*; benzoylated starting material: 38.5% *ee*, *S*-enantiomer). The absolute configuration of **2d** was assigned by analogy

C Kinetic Resolution of 1,2-Diamines

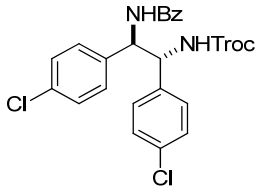
General Procedure for the Resolution and Protection of Racemic Diamines:

A flame dried round bottom flask was charged with benzoic anhydride (22.6 mg, 0.1 mmol, 0.5 equiv.) and powdered 4Å MS (100 mg). Freshly distilled toluene (10 mL) and N,N-dipropylpyridine-4-amine (3.6 mg, 0.02 mmol, 0.1 equiv.) in 1 mL of toluene was added. The resulting mixture was cooled to –78 °C over 15 min and a solution of catalyst **1** (12.5 mg, 0.02 mmol, 0.1 equiv.) in 6 mL of toluene was added. After 15 min, a solution of diamine (0.2 mmol) in 3 mL of toluene was added slowly along the inner side of the flask and the reaction mixture was stirred at –78 °C. When benzoic anhydride could no longer be detected by TLC analysis, an ethanolic ammonia solution (2 M, 2 mL) was added. The reaction mixture was allowed to warm to rt, diluted with 10 mL of a 1:1 water/brine mixture and extracted with EtOAc (5 x 30 mL). After drying with anhydrous sodium sulfate, the organic layer was concentrated under reduced

pressure and dissolved in 10 mL of CH_2Cl_2. The solution was cooled to 0 °C and Hünig's base and Troc-Cl were added slowly. After completion of the reaction, the resulting mixture was concentrated under reduced pressure and purified by flash chromatography.

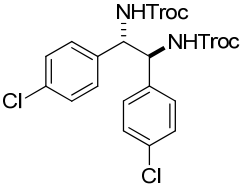
Characterization Data of Products

2,2,2-Trichloroethyl((1*R*,2*R*)-2-benzamido-1,2-bis(4-chlorophenyl)ethyl)carbamate (2.69a):



Following the general procedure, compound **2.69a** was obtained as a white solid in 44% yield (49 mg); mp = 222–224 °C; R_f = 0.21 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ –29.2 (c 0.5, $CHCl_3$, 83% ee); IR (KBr) 3334, 3053, 2947, 2364, 1713, 1640, 1529, 1492, 1277, 1148, 1094, 1015, 820, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.7 Hz, 2H), 7.65–7.32 (comp, 6H), 7.31–7.25 (m, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.06 (app t, *J* = 7.1 Hz, 3H), 6.20 (d, *J* = 8.0 Hz, 1H), 5.45 (app t, *J* = 9.2 Hz, 1H), 5.16–4.93 (m, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 155.5, 137.2, 136.8, 133.3, 132.1, 132.0, 129.1, 129.0, 128.7, 127.1, 122.4, 122.2, 95.1, 74.6, 60.5, 59.1; m/z(ESI-MS) 561.9 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.5 min (major) and t_R = 8.4 min (minor).

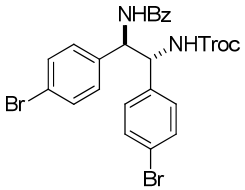
Bis(2,2,2-trichloroethyl)((1*S*,2*S*)-1,2-bis(4-chlorophenyl)ethane-1,2-diyl)dicarbamate



(**2.70a**): Following the general procedure, compound **2.70a** was obtained as a white solid in 46% yield (58.0 mg); mp = 205–207 °C; R_f = 0.48 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ +36.7 (c 0.5, $CHCl_3$, 86% ee); IR (KBr) 3330, 2952, 1710, 1537, 1278, 1144, 1093, 820, 721 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.4 Hz, 4H), 7.03 (d, *J* = 8.4 Hz, 4H), 5.91 (br s, 2H), 4.97 (dd, *J* = 5.6, 2.4 Hz, 2H), 4.82 (d, *J* = 12.0 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0 136.1, 134.3, 129.1 128.6, 95.2, 74.7, 60.4; m/z (ESI-MS) 633.4$[M+H]^+$; HPLC:

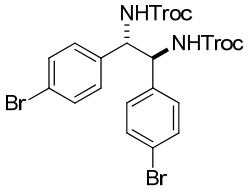
Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, Flow rate = 0.5 mL/min, UV = 230 nm, t_R = 20.6 min (major) and t_R = 27.5 min (minor). Calculated conversion = 51; **s = 30**.

2,2,2-Trichloroethyl((1*R*,2*R*)-2-benzamido-1,2-bis(4-bromophenyl)ethyl)carbamate (2.69b):



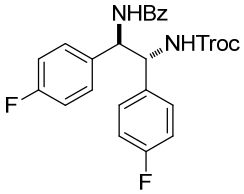
Following the general procedure, compound **2.69b** was obtained as a white solid in 41% yield (53 mg); mp = 218–219 °C; R_f = 0.20 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ –27.8 (c 0.5, $CHCl_3$, 83% ee); IR (KBr) 3334, 3055, 2950, 2362, 1715, 1642, 1531, 1492, 1280, 1148, 1097, 1015, 822, 728 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 8.82 (d, *J* = 9.5 Hz, 1H), 8.59 (d, *J* = 9.5 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 2H), 7.60–7.50 (comp, 2H), 7.49–7.37 (comp, 5H), 7.36–7.20 (comp, 4H), 5.64–5.55 (m, 1H), 5.32–5.23 (m, 1H), 4.78 (d, *J* = 12.5 Hz, 1H), 4.66 (d, *J* = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 166.0, 154.1, 139.2, 139.1, 134.1, 131.6, 131.5, 131.4, 129.0, 128.8, 128.3, 128.0, 127.9(7), 127.2, 96.0, 73.3, 58.4, 56.3; m/z (ESI-MS) 650.4 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 8.4 min (major) and t_R = 5.8 min (minor).

Bis(2,2,2-trichloroethyl)((1*S*,2*S*)-1,2-bis(4-bromophenyl)ethane-1,2-diyl)dicarbamate



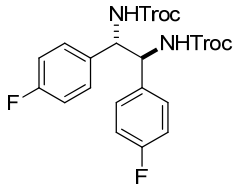
(2.70b): Following the general procedure, compound **2.70b** was obtained as a white solid in 42% yield (60 mg); mp = 208–210 °C; R_f = 0.45 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ +19.3 (c 0.5, $CHCl_3$, 70% ee); IR(KBr) 3330, 3058, 2954, 1716, 1529, 1489, 1248, 1148, 1075, 1011, 818, 725, 568 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.3 Hz, 4H), 6.97 (d, *J* = 8.3 Hz, 4H), 5.95 (br s, 2H), 5.06–4.91 (m, 2H), 4.81 (d, *J* = 12.0 Hz, 2H), 4.64 (d, *J* = 12.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 136.6, 132.0, 128.9, 126.4,, 95.2, 74.7, 60.3; m/z (ESI-MS) 721.9 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 5.4 min (major) and t_R = 6.4 min (minor). Calculated conversion = 46; **s = 22**.

2,2,2-Trichloroethyl((1*R*,2*R*)-2-benzamido-1,2-bis(4-fluorophenyl)ethyl)carbamate (2.69c):



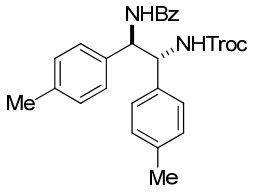
Following the general procedure, compound **2.69c** was obtained as a white solid in 40% yield (42 mg); mp = 211–213 °C; R_f = 0.19 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^{D}_{20}$ –31.3 (c 0.5, $CHCl_3$, 83% ee); IR (KBr) 3332, 3056, 2366, 1715, 1640, 1532, 1490, 1148, 1097, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.4 Hz, 2H), 7.57–7.48 (m, 1H), 7.48–7.37 (comp, 2H), 7.21–7.07 (comp, 4H), 7.01–6.84 (comp, 4H), 6.19 (d, *J* = 8.1 Hz, 1H), 5.47 (dd, 10.7, 8.1 1H), 5.05 (dd, 10.7, 8.1 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 155.5, 134.3, 133.8, 133.4, 131.9, 129.1(5), 129.1(2), 129.0(9), 129.0(6), 128.6, 127.0, 115.8 (d, $J_{C\text{-}F}$ = 21.0 Hz), 115.7 (d. $J_{C\text{-}F}$ = 21.0 Hz), 95.1, 74.5, 60.6, 59.2; m/z (ESI-MS) 528.3 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.5 min (major) and t_R = 8.0 min (minor).

Bis(2,2,2-trichloroethyl)((1*S*,2*S*)-1,2-bis(4-fluorophenyl)ethane-1,2-diyl)dicarbamate (2.70c):



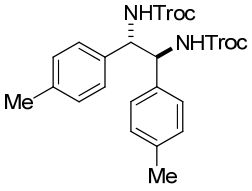
Following the general procedure, compound **2.70c** was obtained as a white solid in 45% yield (54 mg); mp = 202–203 °C; R_f = 0.41 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^{D}_{20}$ +29.4 (c 0.5, $CHCl_3$, 78% ee); IR(KBr) 3331, 3055, 2952, 1714, 1530, 1490, 1248, 1148, 820, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.11–7.01 (comp, 4H), 6.98–6.87 (comp, 4H), 5.89 (br s, 2H), 5.00–4.91 (m, 2H), 4.82 (d, *J* = 12.0 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 161.3, 155.0, 133.6, 129.0, 128.9, 115.13(d, $J_{C\text{-}F}$ = 21.8 Hz), 95.2, 74.7, 60.5; m/z (ESI-MS) 600.2 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 7.0 min (major) and t_R = 8.7 min (minor). Calculated conversion = 48; **s = 25**.

2,2,2-Trichloroethyl((1*R*,2*R*)-2-benzamido-1,2-di-*p*-tolylethyl)carbamate (2.69d): Following



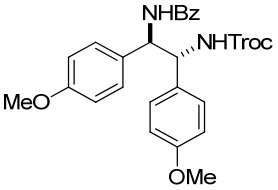
the general procedure, compound **2.69d** was obtained as a white solid in 44% yield (45 mg); mp = 229–231 °C; $[\alpha]^{D}_{20}$ –21.5 (c 0.5, $CHCl_3$, 69% ee); R_f = 0.21 (Hexanes/EtOAc 6:1 v/v); IR (KBr) 3336, 3060, 1720, 1630, 1542, 1261, 1152, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, 7.6 Hz, 2H), 7.53–7.47 (m, 1H), 7.45-7.39 (comp, 2H), 7.19–7.06 (comp, 4H), 7.05–6.97 (comp, 4H), 6.05 (d, *J* = 8.1 Hz, 1H), 5.54–4.47 (m, 1H), 5.10–5.03 (m, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 2.27 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.6, 155.4, 137.8, 137.6, 135.5, 135.1, 133.8, 131.7, 129.3(5), 129.3, 128.5, 127.4, 127.3, 117.6, 95.2, 74.5, 60.8, 59.2, 21.0(8), 21.0(7); m/z (ESI-MS) 520.5 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 210 nm, t_R = 6.8 min (major) and t_R = 5.1 min (minor).

Bis(2,2,2-trichloroethyl)((1*S*,2*S*)-1,2-di-*p*-tolylethane-1,2-diyl)dicarbamate (2.70d):



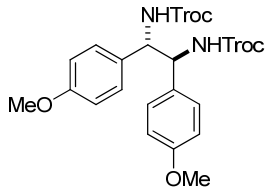
Following the general procedure, compound **2.70d** was obtained as a white solid in 44% yield (51 mg); mp = 165–168 °C; R_f = 0.44 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^{D}_{20}$ +17.3 (c 0.5, $CHCl_3$, 67% ee); IR (KBr) 3318, 3061, 1706, 1636, 1541, 1257, 1152, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, *J* = 7.6 Hz, 4H), 6.98 (d, *J* = 7.6 Hz, 4H), 5.82 (br s, 2H), 5.03–4.96 (m, 2H), 4.80 (d, *J* = 12.0 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 2H), 2.27 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 137.8, 134.9, 129.3, 127.2, 95.4, 74.6, 60.5, 21.1; m/z (ESI-MS) 592.2 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 7.0 min (major) and t_R = 8.9 min (minor). Calculated conversion = 49; **s = 11**.

2,2,2-Trichloroethyl((1*R*,2*R*)-2-benzamido-1,2-bis(4methoxyphenyl)ethyl)carbamate (2.69e):



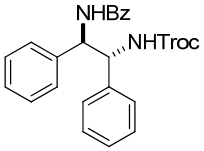
Following the general procedure, compound **2.69e** was obtained as a white solid in 45% yield (49 mg); mp = 210–213 °C; R_f = 0.10 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ –15.5 (c 0.5, $CHCl_3$, 70% ee); IR (KBr) 3330, 2950, 2831, 1718, 1637, 1515, 1250, 1176, 1028, 827, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82–7.78 (comp, 2H), 7.51–7.46 (m, 1H), 7.45–7.38 (comp, 2H), 7.17–7.07 (comp, 2H), 6.84–6.78 (comp, 4H), 6.70–6.60 (comp, 2H), 6.54 (d, J=10.0 Hz, 1H), 5.89–5.82 (m, 1H), 5.52–5.45 (m, 1H), 4.63 (d, *J* = 12,0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 3.97 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 159.2, 159.0, 155.4, 133.8, 131.7, 130.9, 130.3, 128.7, 128.6, 128.5(3), 128.5(2), 127.1, 114.0, 95.2, 74.5, 60.6, 59.1, 55.2.; m/z (ESI-MS) 552.6 $[M+H]^+$; HPLC: Daicel Chiralpak OJ-H, hexane/*i*-PrOH = 93/7, Flow rate = 1 mL/min, UV = 230 nm, t_R = 20.3 min (major) and t_R = 16.3 min (minor).

Bis(2,2,2-trichloroethyl)((1*S*,2*S*)-1,2-bis(4-methoxyphenyl)ethane-1,2-diyl)dicarbamate



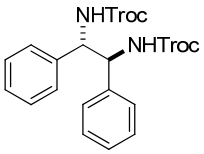
(2.70e): Following the general procedure, compound **2.70e** was obtained as a white solid in 44% yield (55mg); mp = 170–172 °C; R_f = 0.20 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ +22.4 (c 0.5, $CHCl_3$, 80% ee); IR (KBr) 3331, 2953, 2836, 1701, 1614, 1516, 1250, 1180, 1031, 831, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.01 v (d, *J* = 8.5 Hz, 4H), 6.75 (d, *J* = 8.5 Hz, 4H), 5.81 (br s, 2H), 5.02–4.91 (m, 2H), 4.81 (d, *J* = 12.0 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 2H), 3.75 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 154.9, 130.0, 128.5, 114.0, 95.4, 74.6, 60.4, 55.2; m/z (ESI-MS) 623.8 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 11.5 min (major) and t_R = 9.9 min (minor). Calculated conversion = 53; **s = 14**.

2,2,2-Trichloroethyl ((1*R*,2*R*)-2-benzamido-1,2-diphenylethyl)carbamate (2.69f): Following



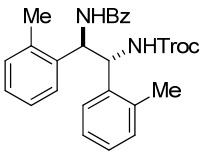
the general procedure, compound **2.69f** was obtained as a white solid in 40% yield (39 mg); mp = 187–190 °C; R_f = 0.19 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^{D}_{20}$ – 24.0 (c 0.5, $CHCl_3$, 72% ee); IR (KBr) 3333. 3053, 2925, 1717, 1653, 1637, 1528, 1144, 1082, 1027, 821, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 2H), 7.54–7.47 (m, 1H), 7.46–7.39 (comp, 2H), 7.29–7.13 (comp, 10H), 6.15 (d, *J* = 8.2 Hz, 1H), 5.58–5.49 (m, 1H), 5.18–5.06 (m, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 155.5, 138.5, 138.0, 133.8, 131.8, 128.7(2), 128.6(8), 128.6, 128.2, 128.0, 127.5, 127.4, 127.1, 95.2, 74.5, 61.3, 59.8.; m/z (ESI-MS) 493.2 $[M+H]^+$; Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 11.0 min (major) and t_R = 8.8 min (minor).

Bis(2,2,2-trichloroethyl) ((1*S*,2*S*)-1,2-diphenylethane-1,2-diyl)dicarbamate(2.70f): Following



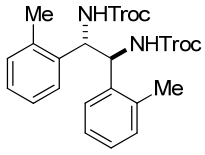
the general procedure, compound **2.70f** was obtained as a white solid in 42% yield (47 mg); mp = 147–150 °C; R_f = 0.41 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^{D}_{20}$ +24.9 (c 0.5, $CHCl_3$, 65% ee); IR (KBr) 3329, 3061, 2955, 1705, 1541, 1254, 1148, 1082, 1027, 820, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.16 (comp, 6H), 7.15–7.01 (comp, 4H), 5.93 (br s, 2H), 5.09–4.98 (m, 2H), 4.82 (d, *J* = 12.0 Hz, 2H), 4.63 (d, *J* = 12.0, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 137.8, 128.7, 128.2, 127.3, 95.3, 74.7, 61.1; m/z (ESI-MS) 564.1 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 6.1 min (major) and t_R = 7.4 min (minor). Calculated conversion = 47; **s = 12**.

2,2,2-Trichloroethyl((1*R*,2*R*)-2-benzamido-1,2-di-*o*-tolylethyl)carbamate (2.69g): Following



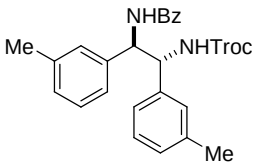
the general procedure, compound **2.69g** was obtained as a white solid in 41% yield (43 mg); mp = 220–222 °C; R_f = 0.24 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ – 21.0 (c 0.5, $CHCl_3$, 76% ee); IR (KBr) 3328, 3061, 1713, 1636, 1541, 1257, 1152, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 2H), 7.61–7.47 (comp, 3H), 7.46–7.39 (comp, 2H), 7.27–7.17 (comp, 2H), 7.15–7.07 (comp, 3H), 7.03–6.93 (comp, 2H), 6.02–5.89 (comp, 2H), 5.52–5.45 (m, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 2.08 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 155.7, 136.8, 136.2, 136.6, 136.1, 133.8, 131.8, 130.7, 130.6, 128.6, 128.1, 127.9, 127.1, 126.6, 126.5, 126.4, 126.3, 95.1, 74.5, 56.8, 55.2, 19.3, 19.2(7); m/z (ESI-MS) 520.7 $[M+H]^+$; Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 8.8 min (major) and t_R = 7.1 min (minor).

Bis(2,2,2-trichloroethyl)((1*S*,2*S*)-1,2-di-*o*-tolylethane-1,2-diyl)dicarbamate (2.70g):



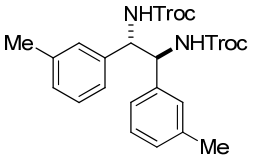
Following the general procedure, compound **2.70g** was obtained as a white solid in 44% yield (52 mg); mp = 177–178 °C; $[\alpha]^D_{20}$ +23.1 (c 0.5, $CHCl_3$, 75% ee); R_f = 0.47 (Hexanes/EtOAc 6:1 v/v); IR (KBr) 3320, 3055, 2950, 1707, 1650, 1527, 1255, 713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.5 Hz, 2H), 7.20 (app t, *J* = 7.4 Hz, 2H), 7.11 (app t, *J* = 7.4 Hz, 2H), 6.96 (d, *J* = 7.5 Hz, 2H), 5.92 (br s, 2H), 5.40 (dd, *J* = 5.9, 2.3 Hz, 2H), 4.82 (d, *J* = 12.0 Hz, 2H), 4.64 (d, *J* = 12.0 Hz, 2H), 2.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 136.7, 136.2, 130.7, 128.1, 126.4, 126.3(7), 95.3, 74.7, 56.5, 19.2; m/z (ESI-MS) 592.2 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 7.2 min (major) and t_R = 9.0 min (minor). Calculated conversion = 50; **s = 16**.

Bis(2,2,2-trichloroethyl)((1*R*,2*R*)-1,2-di-*m*-tolylethane-1,2-diyl)dicarbamate (2.69h):



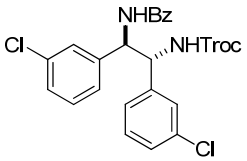
Following the general procedure, compound **2.69h** was obtained as a white solid in 40% yield (41 mg); mp = 199–201 °C; IR (KBr) 3337, 3056, 2947, 1718, 1653, 1527, 1254, 711, 568 cm^{-1}; R_f = 0.24 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ –14.2 (c 0.5, $CHCl_3$, 45% ee); ^1H NMR (500 MHz, , $CDCl_3$) 7.79 (d, *J*= 7.5Hz, 2H), 7.53-7.47 (m, 1H), 7.46–7.38 (comp, 2H), 7.20–7.07 (comp, 4H), 7.06-6.97 (comp, 4H), 6.01 (d, *J*= 8.4 Hz, 1H), 5.53–5.47 (m, 1H), 5.10-5.04 (m, 1H), 4.71 (d, J=12.0 Hz, 1H), 4.55 (d, J= 12.0 Hz, 1H), 2.26 (s, 3H), 2.27(s, 3H); ^{13}C NMR (125 MHz, , $CDCl_3$) δ 167.7, 155.4, 138.4, 138.3, 138.2(6), 138.0, 133.8, 131.7, 128.8, 128.7, 128.5, 128.4(7), 128.2, 128.0, 127.1, 124.6, 95.2, 74.5, 61.1, 59.5, 21.3, 21.2(8); m/z (ESI-MS) 520.8 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 8.6 min (major) and t_R = 5.7 min (minor).

Bis(2,2,2-trichloroethyl) ((1*S*,2*S*)-1,2-di-*m*-tolylethane-1,2-diyl)dicarbamate (2.70h):



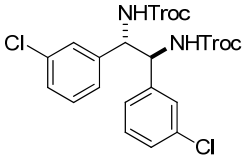
Following the general procedure, compound **2.70h** was obtained as a white solid in 41% yield (48 mg); mp = 190–192 °C; R_f = 0.46 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ +12.4 (c 0.5, $CHCl_3$, 44% ee); IR (KBr) 3318, 3055, 2950, 1707, 1650, 1527, 1255, 713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14–7.07 (comp, 2H), 7.06–6.98 (comp, 2H), 6.90 (s, 2H), 6.86 (d, J= 7.4 Hz, 2H), 5.88 (br s, 2H), 5.02–4.96 (m, 2H), 4.82 (d, *J* = 12.0 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 2H), 2.25 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 138.4, 137.7, 128.9, 128.5, 128.0, 124.5, 95.4, 74.6, 60.8, 21.3; m/z (ESI-MS) 592.2 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.0 min (major) and t_R = 16.3 min (minor). Calculated conversion = 49; **s = 4.0**.

2,2,2-Trichloroethyl((1*R*,2*R*)-2-benzamido-1,2-bis(3-chlorophenyl)ethyl)carbamate (2.69i):



Following the general procedure, compound **2.69i** was obtained as a white solid in 39% yield (43 mg); mp = 203–205 °C; R_f = 0.21 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ –27.7 (c 0.5, $CHCl_3$, 82% ee); IR (KBr) 3336, 3061, 2949, 1714, 1636, 1528, 1252, 1084, 702 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.47 (s, 1H), 7.64 (d, *J* = 7.2, 2H), 7.58–7.34 (comp, 10H) 7.37–7.26(m, 1H), 6.82 (br s, 1H), 5.17 (d, *J* = 6.3 Hz, 1H), 4.68 (d, *J* = 6.3 Hz, 1H), 4.04 (s, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 166.1, 154.1, 142.5, 142.4(8), 134.0, 132.8, 132.7(6), 131.5, 129.9, 128.3, 127.1, 127.0(9), 127.0, 126.9, 126.8, 125.8, 125.5, 96.0, 73.4, 58.4, 56.3; m/z (ESI-MS) 561.9 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.2 min (major) and t_R = 7.6 min (minor).

Bis(2,2,2-trichloroethyl)((1*S*,2*S*)-1,2-bis(3-chlorophenyl)ethane-1,2-diyl)dicarbamate (2.70i):



Following the general procedure, compound **2.70i** was obtained as a white solid in 43% yield (54 mg); mp = 199–202 °C; R_f = 0.48 (Hexanes/EtOAc 6:1 v/v); $[\alpha]^D_{20}$ +25.5 (c 0.5, $CHCl_3$, 70% ee); IR (KBr) 3331, 2952, 1709, 1537, 1277, 1144, 1092, 821 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 8.30 (d, *J* = 8.2 Hz, 2H), 7.50 (s, 2H), 7.36–7.26 (comp, 6H), 5.20 (d, *J* = 8.1 Hz, 2H), 4.72 (d, *J* = 12.4 Hz, 2H), 4.68 (d, *J* = 12.4 Hz, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 154.1, 142.2, 132.9, 130.1, 127.2, 126.7, 125.5, 96.0, 73.4, 58.3; m/z (ESI-MS) 633.4 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 6.8 min (major) and t_R = 8.0 min (minor). Calculated conversion = 46; **s = 21.**

References:

(1) a) Gottwald, D. M.; Roaznski, I. R. *Expert Opin. Invest. Drugs* **1999**, *8*, 1673; b) Jann, M. W. *Pharmacotherapy* **2000**, *20*, 1-12; c) Juaristi, E.; León-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441-2495.

(2) a) Snyder, H. S.; Tayler, M. K. *Science* **1970**, *168*, 1487; b) Hajos, T. G.; Garattin, S. *J. Pharm. Pharmacol.* **1973**, *25*, 418.

(3) a) Alexeeva, M.; Carr, R.; Turner, N. J. *Org. Biomol. Chem.* **2003**, *1*, 4133; b) Paetzold, J.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 17620.

(4) a) Azov, V. A. *Sci. Synth.* **2009**, *40a*, 419; b) Gotor-Fernandez, V.; Gotor, V. *Curr. Opin. Drug Discovery Dev.* **2009**, 12; c) Höhne, M.; Bornscheuer, U. T. *ChemCatChem* **2009**, *1*, 42; d) Turner, N. J. *Nat. Chem. Biol.* **2009**, *5*, 567; e) Lee, J. H.; Han, K.; Kim, M.-J.; Park, J. *Eur. J. Org. Chem.* **2010**, 999.

(5) Marckwald, W.; McKenzie, A. *Ber* **1899**.

(6) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(7) Yokomatsu, T.; Arakawa, A.; Shibuya, S. *J. Org. Chem.* **1994**, *59*, 3506.

(8) Kondo, K.; Kurosaki, T.; Murakami, Y. *Synlett* **1998**, 725.

(9) Yang, J. S.; Kondo, K.; Murakami, Y. *Chin. Chem. Lett.* **2001**, *12*, 1.

(10) Al-Sehemi, A. G.; Atkinson, R. S.; Fawcett, J.; Russell, D. R. *Tetrahedron Lett.* **2000**, *41*, 2239.

(11) Al-Sehemi, A. G. M. *J. King Abdulaziz Univ., Sci.* **2007**, 11.

(12) Ie, Y.; Fu, G. C. *Chem. Commun.* **2000**, 119.

(13) Srseniyadis, S.; Valleix, A.; Wagner, A.; Mioskowski, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 3314.

(14) a) Satyanarayana, T.; Kagan, H. B. *Chem. Eur. J.* **2006**, *12*, 5785; b) Satyanarayana, T.; Kagan, H. B. *Tetrahedron* **2007**, *63*, 6415.

(15) Karnik, A. V.; Kamath, S. S. *J. Org. Chem.* **2007**, *72*, 7435.

(16) Karnik, A. V.; Kamath, S. S. *Tetrahedron Asymmetry* **2008**, *19*, 45.

(17) Tanaka, T.; Fang, X.; Azuma, T.; Uchida, S.; Ishida, T.; In, Y.; Iwata, C.; Maezaki, N. *J. Chin. Chem. Soc. (Taipei)* **2000**, *47*, 865.

(18) Maezaki, N.; Furusawa, A.; Uchida, S.; Tanaka, T. *Tetrahedron* **2001**, *57*, 9309.

(19) a) Delaney, E. J.; Wood, L. E.; Klotz, I. M. *J. Am. Chem. Soc.* **1982**, *104*, 799; b) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226; c) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601; d) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351.

(20) a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726-3748; b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; c) List, B. *Chem. Rev.* **2007**, *107*, 5413; d) Müller, C. E.; Schreiner, P. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 6012.

(21) a) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129; b) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412; c) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985; d) Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570.

(22) a) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069; b) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809-1810; c) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169; d) Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154; e) Spivey, A. C.; Arseniyadis, S.; Fekner, T.; Maddaford, A.; Leese, D. P. *Tetrahedron* **2006**, *62*, 295.

(23) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem. Int. Ed.* **2001**, *40*, 234.

(24) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264.

(25) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536.

(26) Fowler, B. S.; Mikochik, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 2870.

(27) De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060.

(28) a) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542; b) Spivey, A. C.; Arseniyadis, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 5436; c) Vedejs, E.; Jure, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3974; d) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.

(29) a) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803; b) Llewellyn, D. B.; Adamson, D.; Arndtsen, B. A. *Org. Lett.* **2000**, *2*, 4165; c) Lacour, J.; Hebbe- Viton, V. *Chem. Soc. Rev* **2003**, *32*, 373; d) Kang, S. O.; Begum, R. A.; Bowman-James, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 7882; e) Mayer, S.; List, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4193; f) Hamilton, G. L.; Kanai, T.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 14984; g) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577; h) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198; i) Caltagirone, C.; Gale, P. A. *Chem. Soc. Rev.* **2009**, *38*, 520; j) Schreiner, P. R. *Science* **2010**, *327*, 965.

(30) Klauber, E. G.; De, C. K.; Shah, T. K.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 13624.

(31) Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700.

(32) Krishnan, S.; Bagdanoff, J. T.; Ebner, D. C.; Ramtohul, Y. K.; Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 13745.

(33) Blacker, A. J.; Roy, M.; Hariharan, S.; Headley, C.; Upare, A.; Jagtap, A.; Wankhede, K.; Mishra, S. K.; Dube, D.; Bhise, S.; Vishwasrao, S.; Kadam, N. *Organic Process Research & Development* **2010**, *15*, 331.

(34) a) Burgess, K.; Liu, L. T.; Pal, B. *J. Org. Chem.* **1993**, *58*, 4758; b) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444; c) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225; d) Suyama, T. L.; Gerwick, W. H. *Org. Lett.* **2008**, *10*, 4449.

(35) a) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412; b) Fischer, D. F.; Barakat, A.; Xin, Z. W.; E.;, M.; Peters, R. *Chem. Eur. J.* **2009**, *15*, 8722.

(36) a) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301; b) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031; c) Bower, J. F.; Jumnah, R.; Williams, A. C.; Williams, J. M. J. *J. Chem. Soc. Perk. T 1* **1997**, 1411; d) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164; e) Gnamm, C.; Franck, G.; Miller, N.; Stork, T.; Broedner, K.; Helmchen, G. *Synthesis* **2008**, *20*, 3331; f) Nagano, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2009**, *131*, 4200.

(37) a) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883; b) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875; c) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12644; d) Reynolds, T. E.; Binkley, M. S.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 5227.

(38) a) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680; b) Trost, B. M.; Fandrick, D. R.; Brodmann, T.; Stiles, D. T. *Angew. Chem. Int. Ed.* **2007**, *46*, 6123; c) Jiang, H.; Holub, N.; Jørgensen, K. A. *Proc. Nat. Acad. Sci.* **2010**, *107*, 20630.

(39) a) Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chem. Commun.* **2000**, 1009; b) Vedejs, E.; MacKay, J. A. *Org. Lett.* **2001**, *3*, 535; c) Birman, V. B.; Li, X. M. *Org. Lett.* **2006**, *8*, 1351.

(40) a) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem. Int. Ed.* **1978**, *17*, 569; b) Heinrich, M. R.; Klisa, H. S.; Mayr, H.; Steglich, W.; Zipse, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4826; c) Held, I.; Villinger, A.; Zipse, H. *Synthesis* **2005**, *2005*, 1425.

(41) Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463.

(42) a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289; b) Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580; c) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589; d) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6576; e) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299; f) MacMillan, D. W. C. *Nature* **2008**, *455*, 304; g) Rampalakos, C.; Wulff, W. D. *Adv. Synth. Catal.* **2008**, *350*, 1785; h) Birrell, J. A.; Desrosiers, J.-N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 13872.

(43) a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744; b) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.

(44) a) Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. *Chem. -Eur. J.* **2005**, *11*, 4751; b) Fischer, C. B.; Xu, S.; Zipse, H. *Chem. -Eur. J.* **2006**, *12*, 5779; c) Brotzel, F.; Kempf, B.; Singer, T.; Zipse, H.; Mayr, H. *Chem. -Eur. J.* **2007**, *13*, 336; d) Lutz, V.; Glatthaar, J.; Würtele, C.; Serafin, M.; Hausmann, H.; Schreiner, P. R. *Chem. -Eur. J.* **2009**, *15*, 8548.

(45) Spivey, A. C.; Leese, D. P.; Zhu, F.; Davey, S. G.; Jarvest, R. L. *Tetrahedron* **2004**, *60*, 4513.

(46) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007**, *9*, 37.

(47) Klauber, E. G.; Mittal, N.; Shah, T. K.; Seidel, D. *Org. Lett.* **2011**, *13*, 2464.

(48) a) Singh, S.; Das, G.; Singh, O. V.; Han, H. *Org. Lett.* **2007**, *9*, 401; b) Rycke, N. D.; Berionni, G.; Couty, F. o.; Mayr, H.; Goumont, R.; David, O. R. P. *Org. Lett.* **2010**, *13*, 530.

(49) a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew Chem Int Edit* **1998**, *37*, 2581-2627; b) Savoia, D. *Top. Organomet. Chem.* **2005**, *15*, 1; c) Kizirian, J.-C. *Chem. Rev.* **2007**, *108*, 140.

(50) a) Roland, S.; Mangeney, P. *Eur. J. Org. Chem.* **2000**, *2000*, 611; b) Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 4747; c) So, S. M.; Mui, L.; Kim, H.; Chin, J. *Acc. Chem. Res.* **2012**, *45*, 1345.

(51) a) Nishiwaki, N.; Rahbek Knudsen, K.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2992-2995; b) Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731; c) Uraguchi, D.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 14088.

(52) a) Pikul, S.; Corey, J. E. *Org. Synth.* **1993**, *71*, 22; b) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939.

(53) a) Alfonso, I.; Astorga, C.; Rebolledo, F.; Gotor, V. *Chem. Commun.* **1996**, 2471; b) Luna, A.; Alfonso, I.; Gotor, V. *Org. Lett.* **2002**, *4*, 3627; c) Berkessel, A.; Ong, C. M.; Nachi, M.; Neudorfl, M. J. *ChemCatChem* **2010**, *2*, 1215.

(54) a) Zhang, Z.; Yin, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *Org. Lett.* **2003**, *5*, 3399; b) Verma, S. K.; Acharya, B. N.; Kaushik, M. P. *Org. Lett.* **2010**, *12*, 4232.

(55) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

(56) Mittal, N.; Sun, D. X.; Seidel, D. *Org. Lett.* **2012**, *14*, 3084.

(57) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217.

(58) De, C. K.; Mittal, N.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 16802.

(59) Hrdina, R.; Müller, C. E.; Wende, R. C.; Lippert, K. M.; Benassi, M.; Spengler, B.; Schreiner, P. R. *J. Am. Chem. Soc.* **2011**, *133*, 7624.

(60) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 2484-2491.

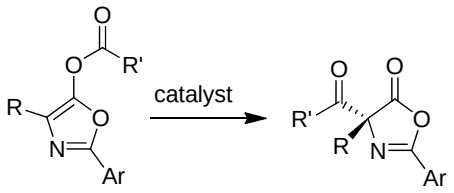
Chapter III

A Dual Catalysis Approach to the Asymmetric Steglich Rearrangement and Enantioselective Addition of Azlactones to Isoquinolines

3.1 Background

The analogues of α,α-disubstituted amino acids display a wide range of biological and chemical properties. Peptides containing this class of amino acids exhibit several interesting biomimetic properties, including resistance against chemical[1] and enzymatic degradation.[2] The growing interest in these amino acids and their derivatives has led to the development of asymmetric methods for their preparation.[3] These α,α-disubstituted amino acids or their derivatives can be synthesized via electrophilic alkylation of amino acid enolates,[4] electrophilic α-amination of α-branched carbonyl compounds,[5] nucleophilic addition to multiple C–N bonds[6] or stereospecific ring opening and rearrangement reactions.[7]

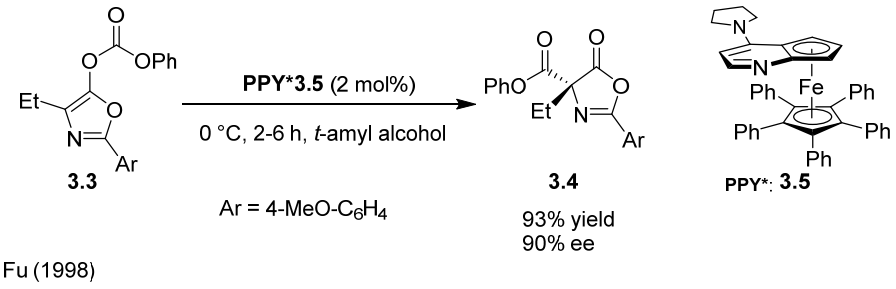
***Figure 3.1*: Enantioselective *O* to *C* Acyl Transfer of Azlactones**



3.1 **3.2**

Amongst the known methods, the Steglich reaction, which involves rearrangement of an *O*-acylated azlactone to the corresponding *C*-acylated product, has proved to be a valuable strategy (Figure 3.1).[8] First attempts were made by Steglich in 1970 wherein he showed that this transformation can be performed in the presence of nucleophilic catalysts such as DMAP and PPY.[8a,9] This rearrangement leads to the formation of a new C–C bond and a new quaternary stereogenic center.

***Scheme 3.1*: First Catalytic Enantioselective Steglich Rearrangement**



Fu (1998)

In 1998, Ruble and Fu introduced the first catalytic enantioselective example of the Steglich rearrangement.[10] In their studies, the dependency of enantioselectivity on the 2-substituent of the *O*-acylated product was observed and it was found that Ar = 4-OMe-C_6H_4 provided the highest selectivity. Under optimized conditions, all substrates (varying R group) were rearranged to *C*-acylated products with excellent yields and enantioselectivity (Scheme3.1). Utility of these products by converting them to dipeptide and α-methylserine derivatives was also reported.

***Figure 3.2*: Classic Approach: Chiral Nucleophilic Catalyst**

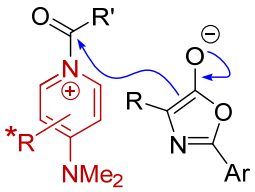
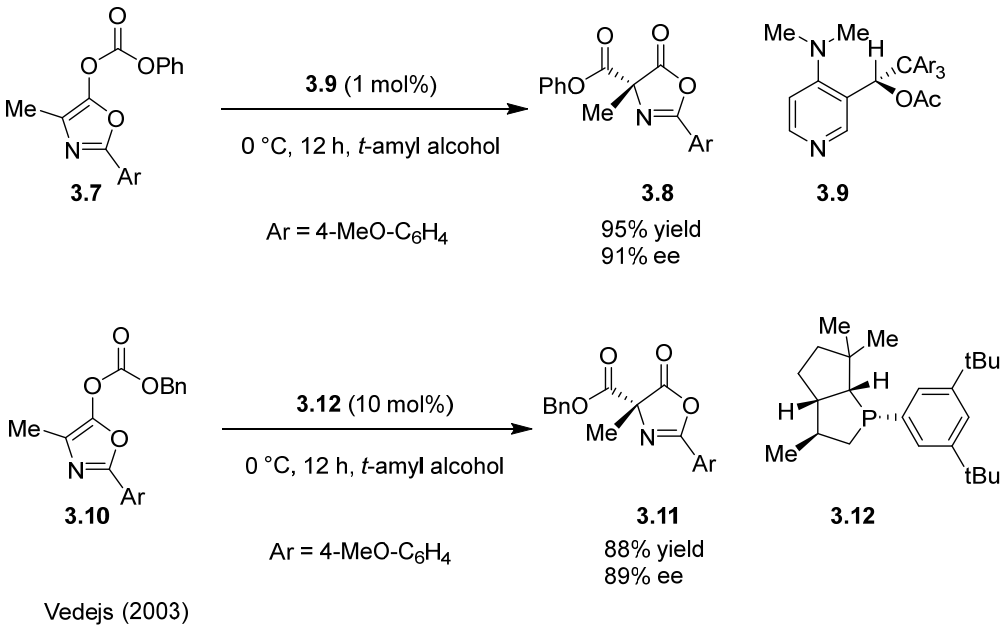


Figure 3.2 displays the mechanistic pathway involved in the Steglich rearrangement, catalyzed by nucleophilic catalysts that are mostly chiral variants of 4-(dimethylamino) pyridine (DMAP). Rearrangements of azlactones via other chiral catalysts are discussed in the following section.

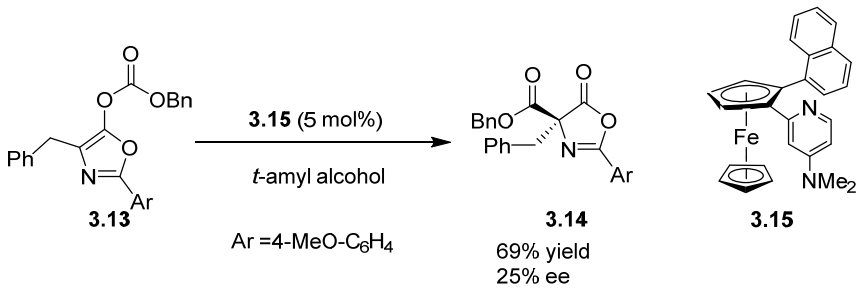
***Scheme 3.2*: Vedejs Chiral Nucleophilic Catalysts for Azlactones Rearrangement**



Vedejs (2003)

In 2003, Vedejs and coworkers synthesized a new class of chiral pyridine derivatives. It was observed that the catalyst **3.9** was more selective in the transfer of the phenyoxycabonyl group as compared to the benzyloxycarbonyl group (Scheme 3.2).[11] Whereas upon employing catalyst **3.12**, opposite trend was observed and the reaction was more selective for benzyloxycarbonyl group.[12] However, both of these methods provided rearranged products in excellent yields and ee values.

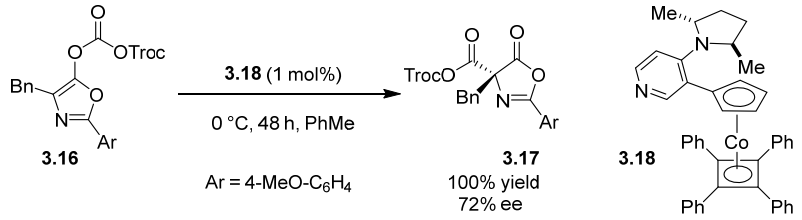
***Scheme 3.3:* DMAP Based Planar Chiral Ferrocene Catalyst**



Johannsen (2005)

Inspired by the development of chiral nucleophilic catalysts for various acyl transfer processes, in 2005 the Johannsen group introduced a new chiral DMAP catalyst with a planar chiral ferrocene backbone.[13] It was hypothesized that the selectivity of the catalyst was largely dependent on the chiral environment surrounding the pyridine unit (2-position of the pyridine ring). In this design, catalyst activity could be fine-tuned by modifying the substituents on the pyridine ring. Although the synthesis of this catalyst was shorter than the synthesis of previously reported chiral nucleophilic catalysts, it yielded lower selectivity (25%ee) (Scheme 3.3).

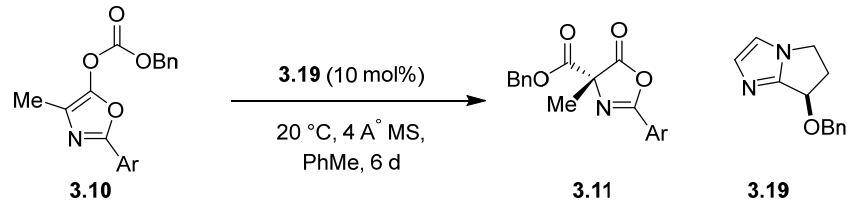
***Scheme 3.4*: Azlactone Rearrangement via Chiral Cobaltocene Catalyst**



Richards (2006)

Another elegant contribution was made by the Richards group in 2006.[14] They disclosed a highly active nucleophilic catalyst, which was easily derived in three steps from (*S*,*S*)-hexane-2,5-diol. It was hypothesized that the introduction of a bulky Cobaltocene in the 3-position of the pyridine ring would lead to high nucleophilicity and optimum stereocontrol. With only 1 mol% of the catalyst **3.18**, the rearranged product was obtained in quantitative yield and moderate selectivity. Other important contribution in this regard was made by Smith and co-workers.[15]

***Scheme 3.5:* Chiral Bicyclic Imidazole as Nucleophilic Catalyst**

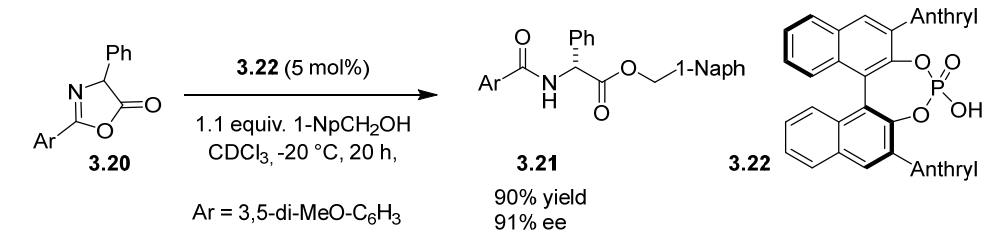


Zhang (2010)

A more recent example was provided by Zhang and co-workers, where a new type of chiral bicyclic imidazole nucleophilic catalyst was introduced.[16] Although the rearrangement reaction with catalyst **3.19** required a longer reaction time as compared to the other reported catalysts, it could be employed at ambient temperature to provide enantioenriched rearranged products high yields (Scheme 3.5).

In addition to the Steglich rearrangement reactions, chiral enantioenriched derivatives of α-amino acids can also be obtained by ring opening reactions of azlactones via dynamic kinetic resolution (DKR) process. One of the earliest examples was discovered by Seebach and co-workers.[17] They resolved racemic azlactones with moderate levels of enantioselectivity using titanium taddolates in stoichiometric and substoichiometric amounts.[18] Other important contributions were made by Hua,[19] Fu,[20] and many others.[21]

***Scheme 3.6*: DKR of Azlactone via Chiral Phosphoric Acid**

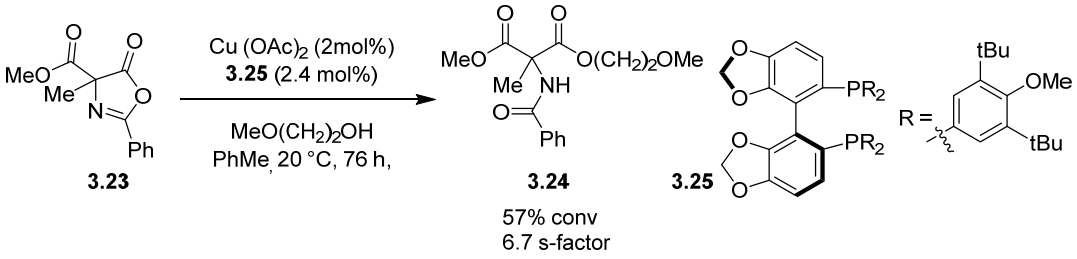


Birman (2010)

Enantioselective alcoholysis has proven to be an important method for the dynamic kinetic resolution of azlactones in the preparation of amino acid derivatives. Initially, Birman group reported benzotetramisole (BTM) as the acyl transfer catalyst for the above process.[22] Later in the same year, this group disclosed the first application of a chiral phosphoric acid to the enantioselective alcoholysis of azlactones via DKR (Scheme 3.6).[23] Regardless of the nature of the substituent, this method was particularly effective for 4-aryl-substituted-substrates. This

study demonstrated the potential of the application of Brønsted acids to asymmetric acylation reactions.

***Scheme 3.7*: Kinetic Resolution of Azlactones**



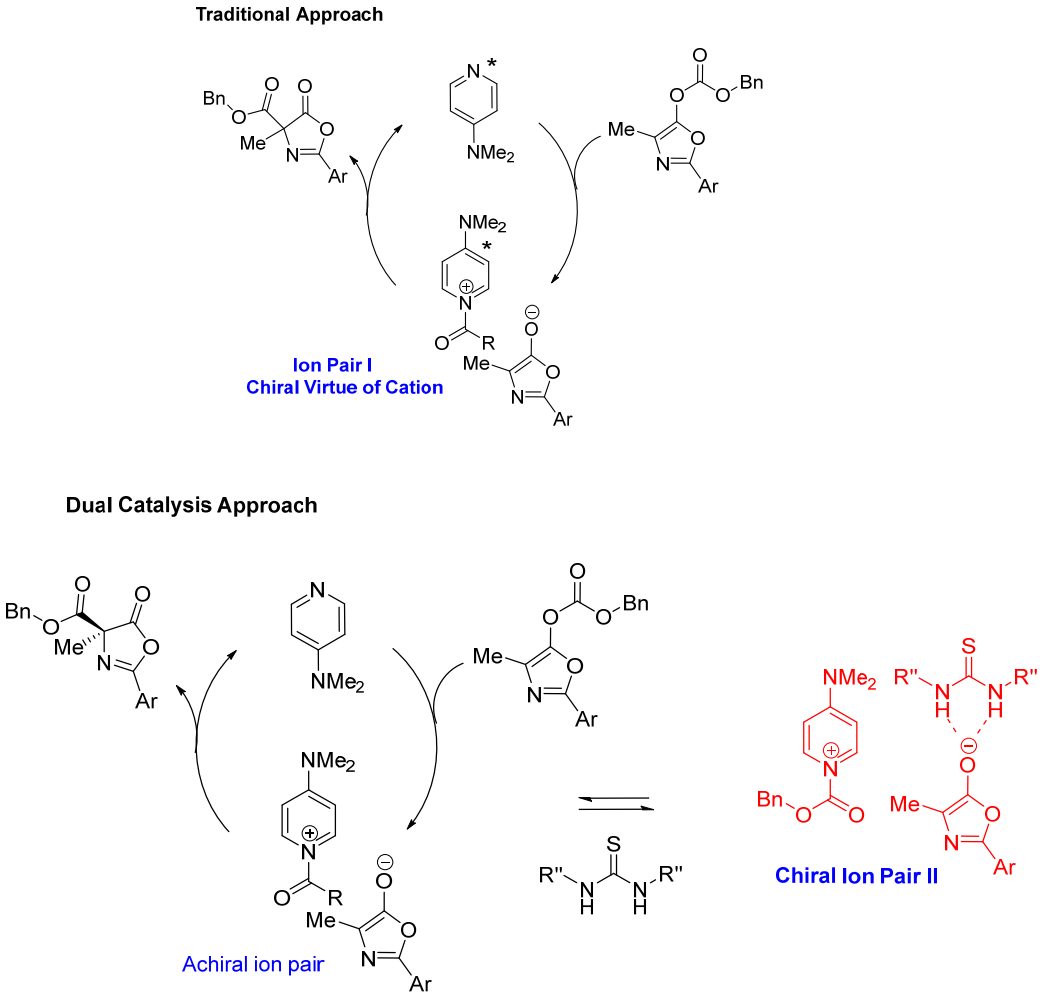
Tokunaga (2006)

Furthermore, dynamic kinetic resolution of azlactones can also be accomplished with metal catalysts. In 2006, Togunaka reported the first example of the resolution of disubstituted azlactones with homogeneous catalysts.[24] Upon employing only 2 mol% of copper acetate and 2.4 mol% of **3.25**, moderate levels of selectivity was obtained (Scheme 3.7).

3.2: A Dual Catalysis Approach for the Steglich Rearrangement

In chapter two, we described a dual catalytic approach, where simple achiral nucleophilic catalysts such as DMAP or PPY were combined with a chiral hydrogen bonding catalyst. Intrigued by the successful application of this approach to the kinetic resolution of various classes of amines,[25] we (with Dr. Chandra Kanta De) extended this concept to the Steglich rearrangement.

***Figure 3.3*: Comparison of Traditional Approach vs Dual Catalysis Approach**



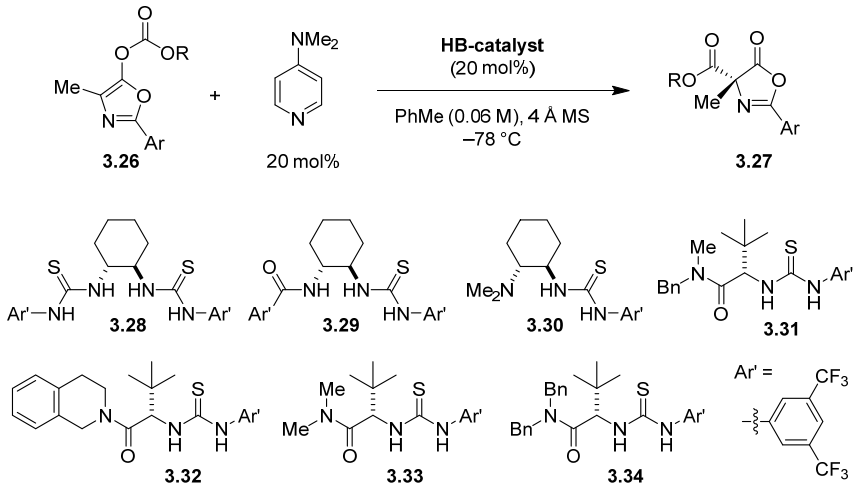
Most traditional approaches for the Steglich rearrangement proceed through chiral ion pair **I** (Figure 3.3). This ion pair would form upon combination of an achiral nucleophilic catalyst and the *O*-acylated azlactone. However, achiral ion pair formed between an achiral nucleophilic catalyst and the azlactone would be rendered chiral upon combining with the chiral hydrogen bonding catalyst.[26] The resulting ion pair II was hypothesized to serve as a better acylating[27] reagent than ion pair **I**. Also, the binding of ion pair **I** with an anion receptor[28] would make ion pair **II** more electrophilic, thereby making the process selective.

3.2.1 Results and Discussion

3.2.1.1 Optimization

We initiated our efforts by combining various hydrogen bonding catalysts (20 mol%) with DMAP (20 mol%) at –78 °C in toluene (Table 3.1). In most cases, short reaction times were observed. Hydrogen bonding catalysts **3.28** and **3.29** which were successfully employed in the kinetic resolution and desymmetrization of amines, provided inferior results in this study.

***Table 3.1*: Evaluation of Hydrogen Bonding Catalysts[a]**



entry	R	Ar	HB-Catalyst	time (h)	yield (%)	ee (%)
1	Ph	4-MeO-C_6H_4	**3.28**	4	57	12
2	Ph	4-MeO-C_6H_4	**3.29**	4	54	10
3	Ph	4-MeO-C_6H_4	**3.3**	4	44	–74
4	Ph	4-MeO-C_6H_4	**3.31**	4	72	79
5	Ph	4-MeO-C_6H_4	**3.32**	4	77	71
6	Ph	4-MeO-C_6H_4	**3.33**	4	52	55
7	Ph	4-MeO-C_6H_4	**3.34**	4	58	47
8[b]	Bn	4-MeO-C_6H_4	**3.31**	8	52	60
9	Ph	1-naphthyl	**3.31**	5	53	85
10	Ph	3,5-di-MeO-C_6H_3	**3.31**	1	70	89

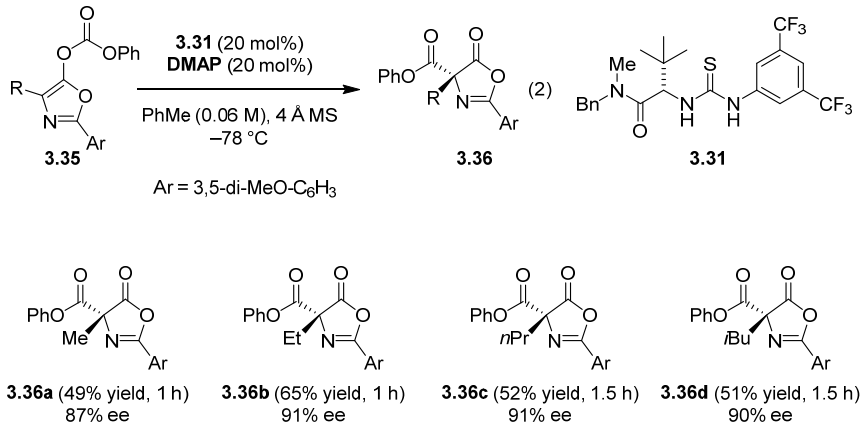
[a]Reactions were performed on a 0.1 mmol scale. [b]Reaction was perfomed at -60 °C.

Promising results were obtained with the Takemoto catalyst[29] (**3.30**, entry 3) but the highest level of selectivity was observed with catalyst **3.31** (79% ee, entry 4), which was previously developed by the Jacobsen group.[28c] Increasing the temperature from –78 °C to –60 °C lowered both the selectivity and the yield of the reaction (entry 8). According to previously reported studies, the nature of the migratory group and the electronic nature of the aryl group significantly affect the overall selectivity of the reaction. In all cases, presence of the phenoxycarbonyl group provided better results than the benzyloxycarbonyl group. A short survey of the aryl groups in **3.26** was carried out. Changing the aryl group to the 1-naphthyl group gave 85% ee but lowered the yield. In addition, substituting 3,5-di-MeO-C_6H_3 was more effective and increased the selectivity to 89% ee (entry 10) Interestingly, this change also significantly decreased the reaction time from four hours to one hour. Reason for this observation was most likely the increase in the nucleophilicity of the anionic intermediate. Importantly, the use of DMAP as the only catalyst under otherwise identical conditions led to very slow reactions. These combined observations nicely illustrate the unique reactivity profile of this dual catalytic system.

3.3.2.2 Scope of the Azlactone Rearrangement

The scope of the azlactone rearrangement was explored under the optimized conditions (Scheme 3.8). Straight chain alkyl groups like methyl, ethyl, *n*-propyl and even the sterically hindered isobutyl group also yielded excellent selectivities. Consistent with earlier accounts, the rearranged products were unstable on silica gel.[11] Thus, even though the reaction completed quickly, the resulting yields were relatively low.

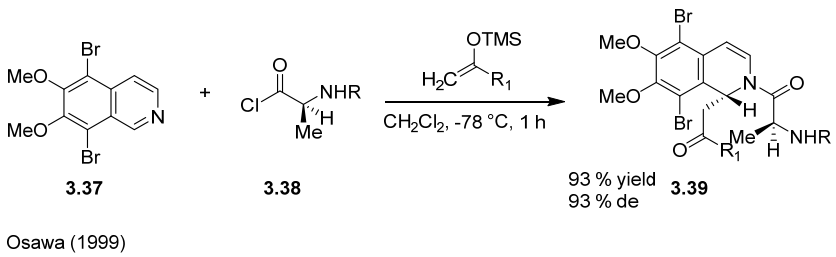
***Scheme 3.8*: Scope of the Azlactone Rearrangement**



3.3: Functionalization of Isoquinolines

Isoquinolines and their derivatives are important structural motifs in many medicinal and biologically active compounds.[30] Enantioselective nucleophilic addition of various carbon nucleophiles to isoquinolines has been the most valuable strategy in the functionalization of isoquinolines and the synthesis of their derivatives. Catalytic enantioselective additions to isoquinolines have been limited to relatively few examples,[31] whereas significant efforts have focused on the catalytic enantioselective preparation of α,β-diamino acid derivatives.[32] Amongst these, enantioselective alkylations and arylations via Grignard[33] or organolithium[34] additions has been the most common approach

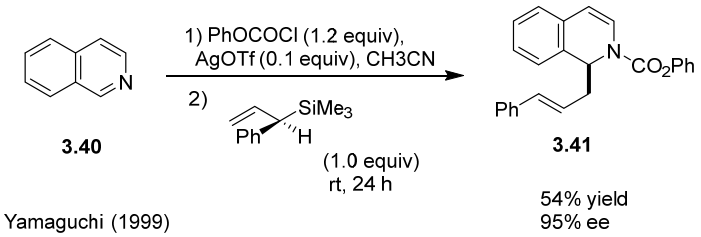
***Scheme 3.9*: Nucleophilic Addition via Acyl Chloride Derived from *L*-Alanine**



Osawa (1999)

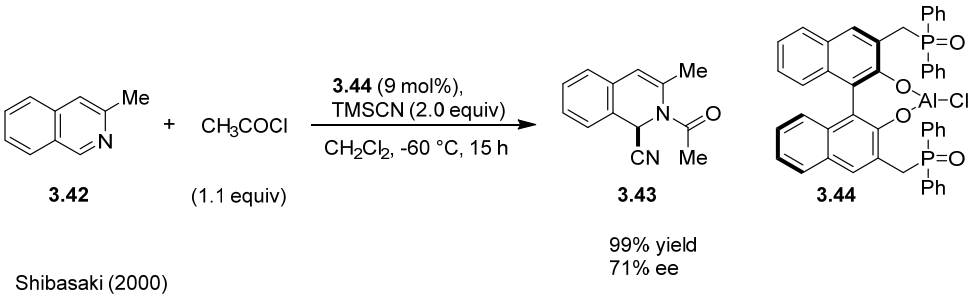
In 1999, Osawa group demonstrated the addition of a silyl ketene acetal to 6,7-dimethoxyisoquinoline in the presence of an acid chloride derived from L-alanine. Addition of the silyl ketene acetal to the acyl quinolinium salt formed in situ was efficient and provided **3.39** in high yield and diastereoselectivity (Scheme 3.9).[35]

***Scheme 3.10*: Addition of Chiral Allylsilanes to Isoquinolines**



In 1999, Yamaguchi et. al. disclosed a highly enantioselective version of this addition reaction by reacting chiral allylsilanes with activated *N*-acylquinolinium ions to provide 1-allyl-1,2-dihydroisoquinolines in moderate yields and high ee's (Scheme 3.10).[36]

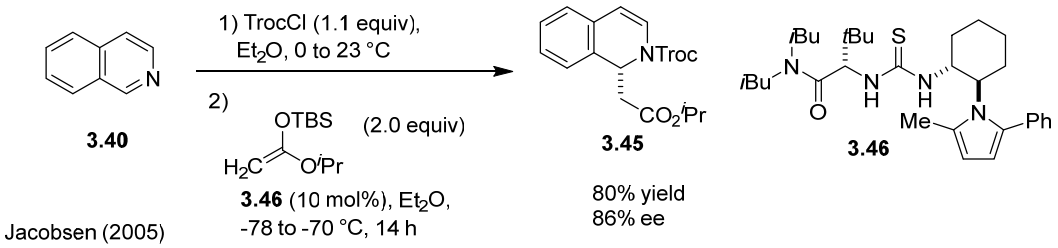
***Scheme 3.11*: Asymmetric Reissert Reaction**



In 2000, nearly a century after the introduction of the racemic Reissert reaction, Shibasaki and co-workers reported the first enantioselective version of this reaction using bifunctional catalysis.[31a] A Lewis acid-Lewis base bifunctional catalyst was employed with 9 mol % catalyst loading and isoquinoline derivatives were obtained with moderate selectivity. However, these bifunctional catalysts were more suitable for quinolines as they provided quinoline derivatives in higher

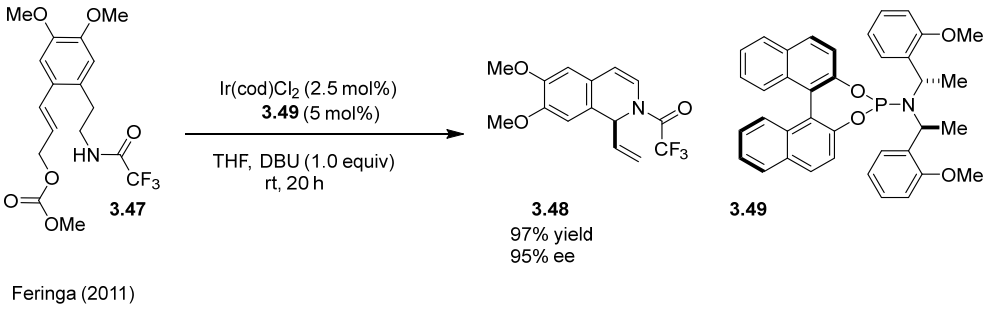
enantioselectivities. The nitrile compounds thus obtained were converted to tetrahydroquinoline-2-carboxylate without any effect on the selectivity (Scheme 3.11).

***Scheme 3.12*: Addition reaction of Isoquinolines by Thiourea Catalyst**



In 2005, Jacobsen's group employed a chiral thiourea catalyst for the addition of silyl ketene acetals to activated isoquinolium ions. Upon using 1.1 equivalents of Troc chloride as the acylating reagent and two equivalents of the silyl ketene acetal, dihydroisoquinoline products were obtained in good yields and enantioselectivity (Scheme 3.12).[31d]

***Scheme 3.13*: Asymmetric Allylic Amidation**

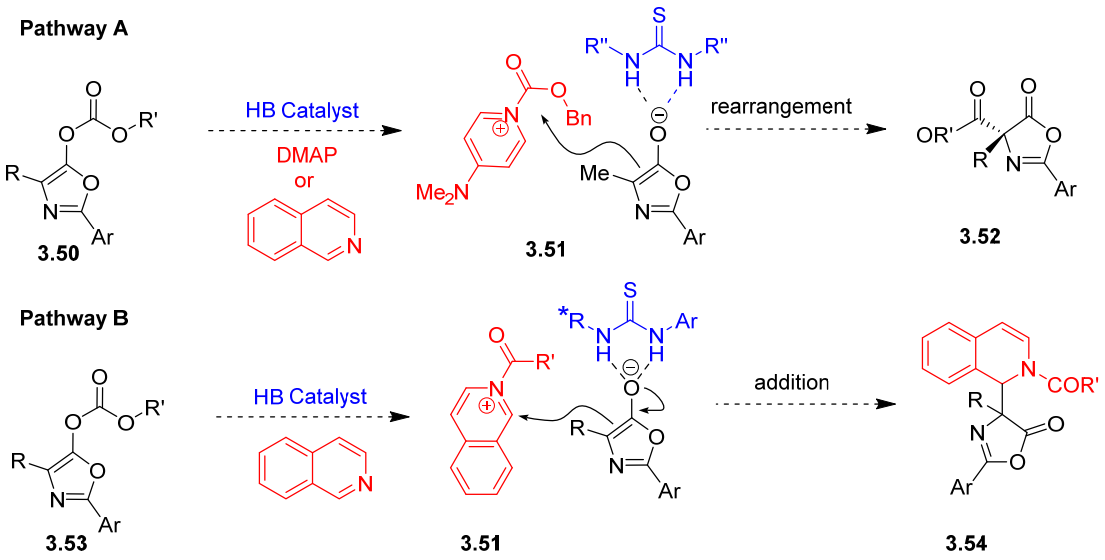


A more recent example was disclosed by the Feringa group. In 2011, they reported enantioselective intramolecular Iridium-catalyzed allylic amidation, resulting in the formation of chiral tetrahydroisoquinoline derivatives. With only 2.5 mol% catalyst loading, products were formed in high yields and enantioselectivities (Scheme 3.13).[37]

3.4 Enantioselective Reaction of Isoquinolines with Azlactones

In order to extend our current methodology for the Steglich rearrangement, we considered alternate reaction pathways by replacing the co-catalyst DMAP with isoquinoline as the nucleophilic species. Due to the lesser nucleophilicity of the isoquinoline in comparison to DMAP, we employed stoichiometric amounts of isoquinoline in the reaction mixture. It was observed that the anionic rearranged product was trapped by the acyl isoquinoline derivative, leading to the synthesis of the addition products.

***Figure 3.4*: Plausible Reaction Pathways for Reaction between Azlactone and DMAP or Isoquinoline**



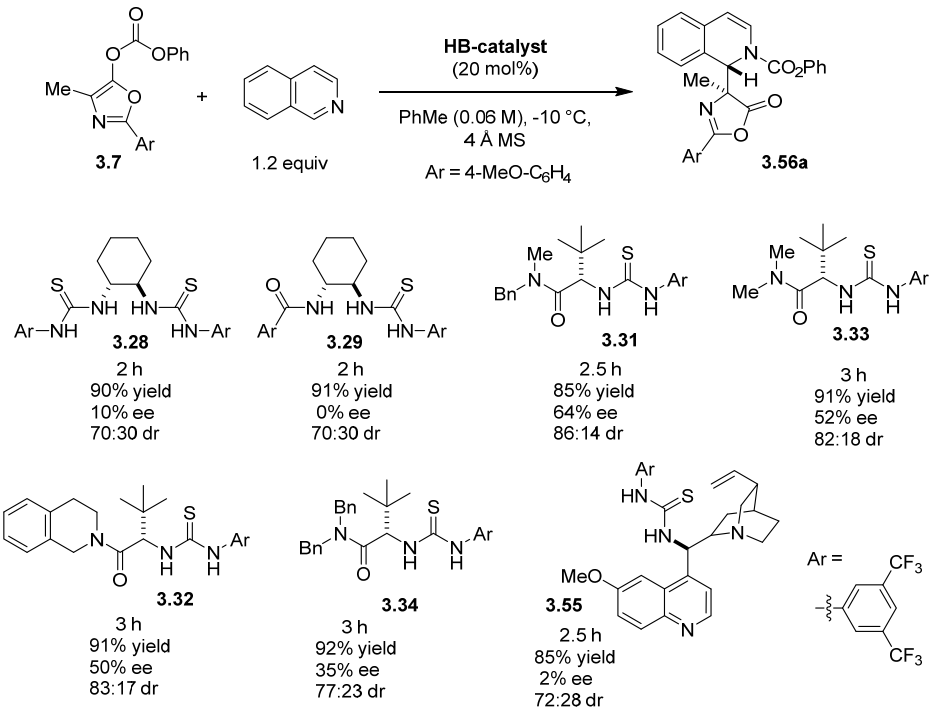
We envisioned that the *O*-acylated azlactone **3.50** would form ion pair **3.51** upon combining with the isoquinoline and the HB catalyst. Ion pair **3.51** could undergo pathway **A** and rearrange in a usual manner to form *C*-acylated azlactone **3.52**. Alternatively, in pathway **B** where instead of isoquinoline acting as a nucleophilic promoter, the enolate ion could attack isoquinoline at its 1-position to give rise to the highly functionalized α,β-diamino acid derivative **3.54** (Figure 3.4).

3.4.1 Results and Discussion

3.4.1.1 Optimization

Isoquinoline, being much less nucleophilic than DMAP gave little or nearly no product formation when exposed to our optimum conditions for the Steglich rearrangement. Hence, this reaction was carried out at elevated temperatures. Although catalyst **3.31** was the most efficient for the rearrangement reactions to begin with, we explored the effects of other catalysts on the addition reaction. All other catalysts, except **3.31**, provided high yields but notably lower selectivities. Bifunctional cinchona alkaloid based HB catalyst **3.55**, amide thiourea catalyst **3.29** and Nagasawa's catalyst **3.28** were all inefficient for this process. Catalyst **3.28** provided the best results.

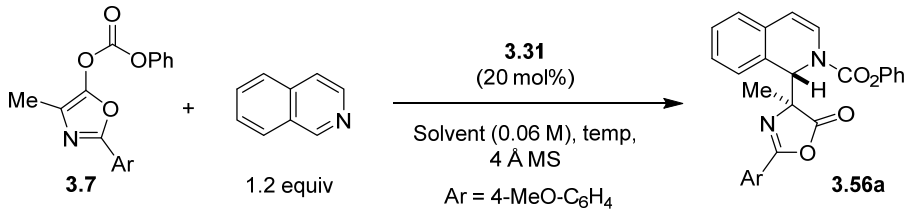
***Scheme 3.14*: Evaluation of Hydrogen Bonding Catalysts**



With the optimum catalyst **3.31** in hand, we performed the reaction in various solvents. Upon employing **3.31** as catalyst in toluene, product **3.56** was isolated in 85% yield with 86:14 dr

and 64% ee. This reaction was completed in 2.5 hours (Scheme 3.14). The title reaction was tested in other less polar solvents such as MTBE, mesitylene and a significant improvement in selectivity was observed (entry 2 and 3, Table 3.2). Interestingly, under the same conditions but in the absence of the HB-catalyst, the reaction went to completion in 11.5 hours and **3.60** was formed in 95% yield (dr = 64:36), indicating a substantial background reaction rate. Upon lowering the temperature from –10 °C to –20 °C, the reaction time and diastereoselectivity increased whereas the enantioselectivity remained moderate (entry 4).

***Table 3.2*: Solvent Screening**



entry	temp (°C)	solvent	time (h)	yield (%)	dr	ee (%)
1	–10	PhMe	2.5	85	86:14	64
2	–10	TBME	4	86	84:16	69
3	–10	mesitylene	3	88	88:12	73
4	–20	mesitylene	10	88	92:08	77
5[a]	–20	pentane	24	65	92:08	82
6	–25	mes/pent(2:1)	14	91	95:05	88
7	–25	mes/pent(1:1)	17	90	96:04	91
8	–25	mes/pent(1:2)	22	92	96:04	93
9	–25	mes/hex (1:2)	20	91	91:09	84
10[a]	–25	mes/pent(1:2)	27	92	96:04	93
11 [a,b]	–25	mes/pent(1:3)	24	61	96:04	93
12 [a,b]	–25	mes/pent(1:4)	24	52	95:05	93

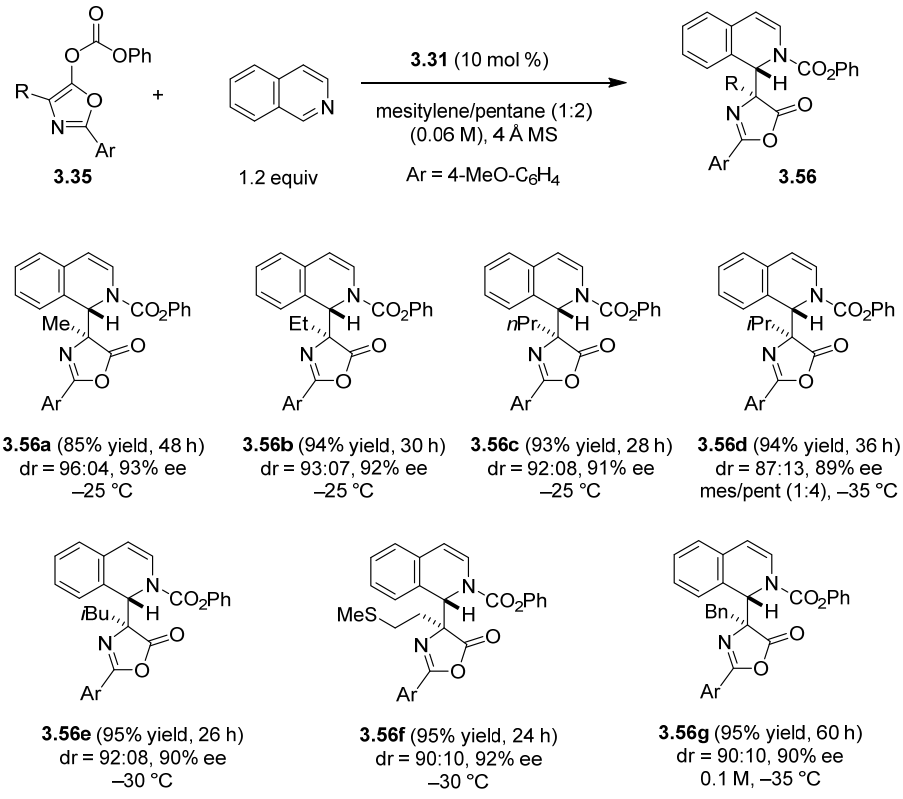
[a] Reaction was incomplete, [b] reactions were run with 10 mol % catalyst loading

Similar results were obtained upon employing pentane as the solvent (entry 5). However, in this case, the reaction did not complete even after 24 hours. Gratifyingly, a solvent pair of mesitylene and pentane improved the selectivity drastically. A systematic study of the effects of

employing different ratios of these two solvents was then performed. The best result was obtained with a 1:2 mixture of mesitylene and pentane (92% yield with 96:04 dr and 93% ee, entry 8) at –25 °C. In addition, lowering the catalyst loading from 20 mol% to 10 mol% only increased the reaction time slightly whereas dr, yield and selectivity remained the same (entry 10). It was observed that under the optimized conditions, the reaction displayed a certain level of heterogeneity that appeared to be beneficial to the outcome of the reaction. This effect could possibly be due to product precipitation driving the reaction forward.[38] However, after a certain point, further increasing the heterogeneity lowered the yields. This observation was most likely due to the decreased solubility of the starting materials (entries 11 and 12).

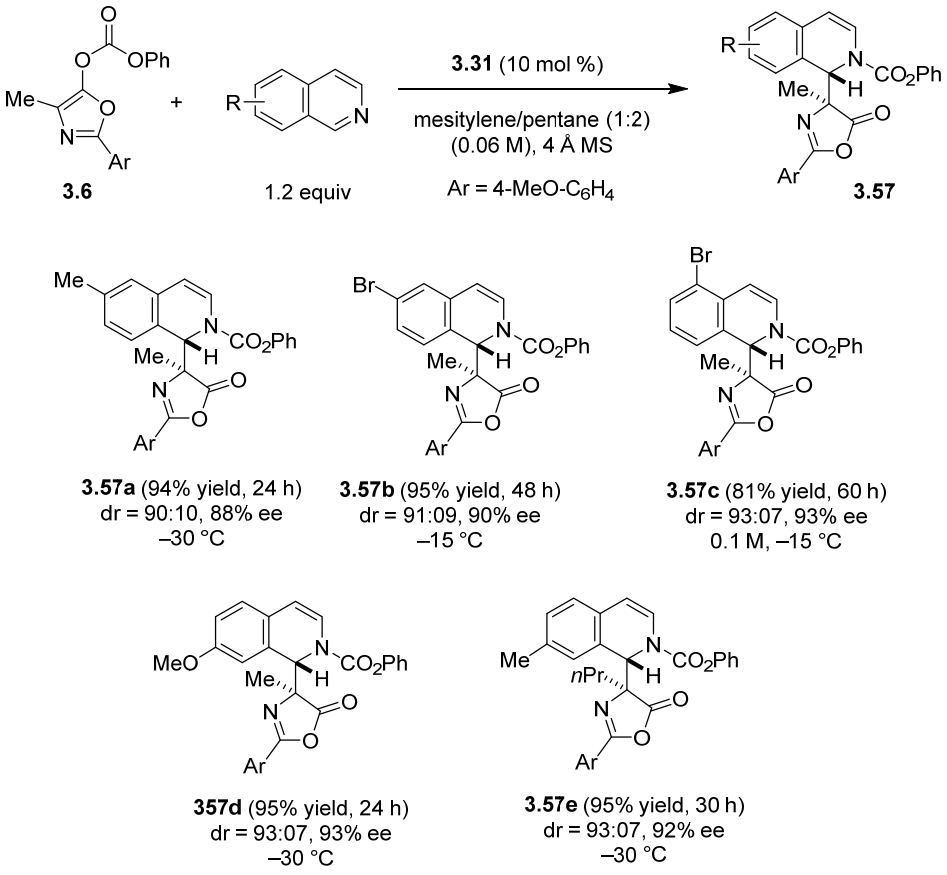
3.4.1.2: Scope of the Reaction

***Scheme 3.15*: Scope of the Reaction: Variation of the Azlactone**



Under the optimized conditions, addition reactions between unsubstituted isoquinoline and azlactones with various alkyl groups provided products in high yields and enantioselectivities. Both straight chain and branched alkyl substituents on the azlactone were well-adapted to the reaction. Interestingly, azlactone with an isopropyl group substituent also yielded the product with high selectivity, even though it failed to give any product for the Steglich rearrangement.

***Scheme 3.16*: Scope of the Reaction: Variation of the Isoquinoline**



Reaction of the methyl-substituted azlactone with different isoquinolines also provided products with high levels of enantioselectivity and diastereoselectivity. Although introducing an electron withdrawing group on the isoquinoline ring increased the reaction time (due to decreased nucleophilicity), both electron-rich and electron-donating substituents at different positions of the isoquinoline ring were well-accommodated.

3.5: Summary

In summary, we successfully extended the application of our dual catalytic approach to the Steglich rearrangement, where *O*-acylated azlactones were efficiently rearranged to the corresponding *C*-acylated products. This study further established the potential and utility of combining a chiral HB-catalyst with a simple achiral nucleophilic catalyst. We also demonstrated that replacing the nucleophilic catalyst with a stoichiometric amount of isoquinoline enabled an unprecedented reaction of *O*-acylated azlactones. Gratifyingly, this new reaction provided rapid access to densely functionalized α,β-diamino acid derivatives.

Experimental Section

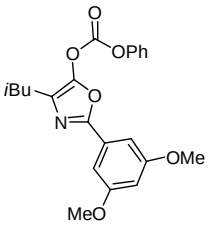
Selected Characterization Data of *O*-Acylated Azlactones

2-(3,5-dimethoxyphenyl)-4-methyloxazol-5-yl phenyl carbonate (3.35a): mp = 104–106 ºC; IR (KBr) 2962, 2924, 1786, 1602, 1555, 1225, 1209, 1195, 1052, 732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (tt, *J* = 8.5, 2.1 Hz , 2H), 7.35–7.28 (comp, 3H), 7.12 (d, *J* = 2.3 Hz, 2H), 6.54 (app t, *J* = 2.3 Hz, 1H), 3.85 (s, 6H), 2.21(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 154.8, 150.7, 150.0, 145.7, 129.8, 128.6, 126.9, 120.7, 120.5, 103.6, 103.6, 55.6, 10.4; *m/z* (ESI-MS) 355.9 $[M+H]^+$.

2-(3,5-dimethoxyphenyl)-4-ethyloxazol-5-yl phenyl carbonate (3.35b): mp = 125–127 ºC; IR (KBr) 2971, 2939, 2839, 1800, 1599, 1555, 1207, 1157, 1065, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (app t, *J* = 7.6 Hz, 2H), 7.31 (app t, *J* = 7.9 Hz, 3H), 7.14 (d, *J* = 2.2 Hz, 2H), 6.54 (app t, *J* = 2.2 Hz, 1H), 3.84 (s, 6H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 154.8, 150.7, 150.2, 155.0, 129.8, 128.7, 126.8, 126.0, 120.4, 103.6, 103.6, 55.5, 55.5, 18.4, 12.3; *m/z* (ESI-MS) 370.9 $[M+H]^+$.

2-(3,5-dimethoxyphenyl)-4-propyloxazol-5-yl phenyl carbonate (3.35c): mp = 71–73 ºC; IR (KBr) 2963, 2927, 2841, 1789, 1599, 1552, 1231, 1158, 732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (app t, *J* = 7.6 Hz, 2H), 7.35–7.27 (comp, 3H), 7.13 (d, *J* = 2.4 Hz, 2H), 6.54 (app t, *J* = 2.4 Hz, 1H), 3.85 (s, 6H), 2.53 (t, *J* = 7.5 Hz, 2H), 1.80–1.68 (m, 2H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 154.9, 150.7, 150.2, 145.5, 129.8, 128.8, 126.8, 124.8, 120.5, 103.7, 103.4, 55.6, 26.9, 21.2, 13.7; *m/z* (ESI-MS) 383.9 $[M]^+$.

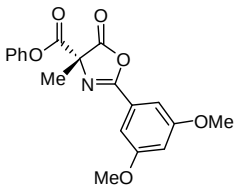
2-(3,5-dimethoxyphenyl)-4-isobutyloxazol-5-yl phenyl carbonate (3.35d): mp = 69–71 ºC; IR (KBr) 2965, 2934, 1782, 1597, 1552, 1232, 1155, 1044, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44(tt, *J* = 7.4,2.1 Hz, 2H), 7.35–7.27(comp, 3H), 7.13 (d, *J* = 2.3 Hz, 2H), 6.54(appt, *J* = 2.3 Hz, 1H), 3.85(s, 6H), 2.42(d, *J* = 7.2 Hz, 2H), 2.11(sept, *J* = 6.7 Hz, 1H), 0.99(d, *J* = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 154.9, 150.7, 150.2, 146.1, 129.8, 128.8, 126.8, 124.1, 120.5, 103.7, 103.4, 55.6, 33.9, 27.6, 22.3; *m/z* (ESI-MS) 398.0 $[M+H]^+$.



General Procedure for the Rearrangements of *O*-Acylated Azlactones:

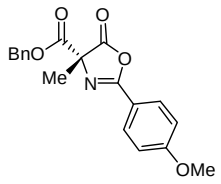
A flame dried 2 dram sample vial was charged with azlactone (0.20 mmol, 1.0 equiv.), catalyst (0.04 mmol, 0.2 equiv.) and 4Å MS (50 mg). Anhydrous toluene (2.2 mL) was added and the reaction mixture was stirred at room temperature for 5 min. It was then cooled to –78 ºC over 15 min. and a solution of DMAP (0.04 mmol) in 1.1 mL of toluene was added and the reaction mixture was stirred at –78 ºC. The reaction was monitored by TLC. The reaction mixture was purified by flash chromatography without doing any work up.

(*R*)-phenyl 2-(3,5-dimethoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazole-4-carboxylate (3.36a): Following the general procedure, compound **3.36a** was obtained as colorless oil in 49% yield. Rf = 0.18 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ +5.4 (c 1.0, $CHCl_3$, 87% ee); IR (neat) 2938, 1819, 1768, 1647, 1596, 1492, 1458, 1428, 1360, 1343, 1206, 1159, 1103, 1065, 1023, 916, 842 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (app t, *J* = 7.9 Hz, 2H), 7.30–7.20 (comp, 3H), 7.15–7.07 (comp, 2H), 6.70 (app t, *J* = 2.4 Hz, 1H), 3.86 (s, 6H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 164.5, 163.6, 161.0, 150.2, 129.5, 126.7, 126.5, 121.0, 120.9, 106.5, 105.9, 73.0, 55.7, 20.4; *m/z* (ESI-MS) 355.9 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 280 nm, t_R = 7.8 min (major) and t_R = 8.8 min (minor).



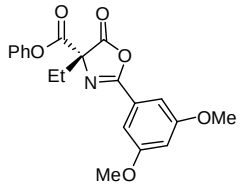
Determination of the absolute configuration of the rearranged products:

(*R*)-benzyl 2-(4-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazole-4-carboxylate (3.36e):

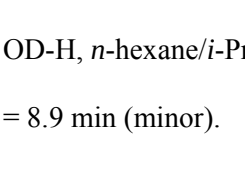


Following the general procedure, except the reaction was run at –60 ºC and compound **3.36e** was obtained as colorless oil in 52% yield. The absolute configuration of compound (*R*)-**3.36e** ($[\alpha]_D^{20}$ +27.6 (c 1.0, $CHCl_3$, 60% ee) was assigned by comparison with the (*S*)-enantiomer reported in the literature ($[\alpha]_D^{20}$ –55 (c 0.95, $CHCl_3$, 90.6% ee). The absolute configuration of the rearranged products (**3.36a**–**3.36d**) was thus assigned by analogy.

(*R*)-phenyl 2-(3,5-dimethoxyphenyl)-4-ethyl-5-oxo-4,5-dihydrooxazole-4-carboxylate (3.36b): Following the general procedure, compound **3.36b** was obtained as colorless oil in 65% yield. Rf = 0.36 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ +37.3 (c 1.0, $CHCl_3$, 91% ee); IR (neat) 2971, 2939, 1817, 1765, 1650, 1696, 1492, 1458, 1428, 1360, 1344, 1315, 1206, 1159, 1064, 1034, 913, 846, 743, 727 cm^{-1}; ^1H NMR δ 7.38 (app t, *J* = 7.9 Hz, 2H), 7.29–7.24 (m, 1H), 7.23 (app d, *J* = 2.4 Hz, 2H), 6.70 (app t, *J* = 2.4 Hz, 1H), 3.86 (s, 6H), 2.52–2.32 (m, 2H), 1.01 (t, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 164.3, 163.5, 161.0, 150.2, 129.5, 126.7, 126.5, 121.1, 106.5, 106.3, 105.9, 105.8, 55.7, 55.7, 27.3, 7.7; *m/z* (ESI-MS) 369.9 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 280 nm, t_R = 7.1 min (major) and t_R = 8.9 min (minor).

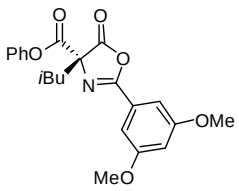


(*R*)-phenyl 2-(3,5-dimethoxyphenyl)-5-oxo-4-propyl-4,5-dihydrooxazole-4-carboxylate (3.36c): Following the general procedure, compound **2c** was obtained as colorless oil in 52% yield. Rf = 0.42 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ +138.8 (c 1.0, $CHCl_3$, 91% ee); IR (neat) 2965, 2936, 2876, 2842, 1819, 1766, 1649, 1595, 1492, 1458, 1427, 1360, 1343, 1315, 1206, 1159, 1110, 1065, 1036, 969, 914, 845,



743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (app t, *J* = 7.9 Hz, 2H), 7.27–7.23 (m, 1H), 7.22 (app d, *J* = 2.4 Hz, 2H), 6.70 (app t, *J* = 2.4 Hz, 1H), 3.85 (s, 6H), 2.47–2.22 (m, 2H), 1.55–1.23 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 164.3, 163.4, 161.0, 150.2, 129.5, 126.7, 126.5, 121.0, 106.4, 105.8, 76.9, 36.3, 16.8, 13.7; *m/z* (ESI-MS) 383.9 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 280 nm, t_R = 6.5 min (major) and t_R = 7.9 min (minor).

(*R*)-phenyl 2-(3,5-dimethoxyphenyl)-4-isobutyl-5-oxo-4,5-dihydrooxazole-4-carboxylate (3.36d): Following the general procedure, compound **3.36d** was obtained as colorless oil in 51% yield. Rf = 0.45 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ +3.6 (c 1.0, $CHCl_3$, 90% ee); IR (neat) 2961, 1818, 1771, 1650, 1595, 1492, 1459, 1427, 1361, 1343, 1316, 1206, 1159, 1121, 1066, 1041 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (app t, *J* = 7.9 Hz, 2H), 7.28–7.21 (comp, 3H), 7.14–7.08 (comp, 2H), 6.71 (app t, *J* = 2.3 Hz, 1H), 3.86 (s, 6H), 2.52 (dd, *J* = 14.4, 5.5 Hz, 1H), 2.19 (dd, *J* = 14.4, 7.4 Hz, 1H), 1.82 (sept, *J* = 6.7 Hz, 1H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 164.5, 163.1, 161.0, 150.2, 129.5, 129.0, 128.2, 126.8, 126.5, 121.0, 106.3, 105.9, 76.5, 55.7, 42.7, 24.6, 23.8, 23.0; *m/z* (ESI-MS) 398.0 $[M+H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 280 nm, t_R = 6.1 min (major) and t_R = 7.2 min (minor).



General Procedure for Azlactone and Isoquinoline Reaction:

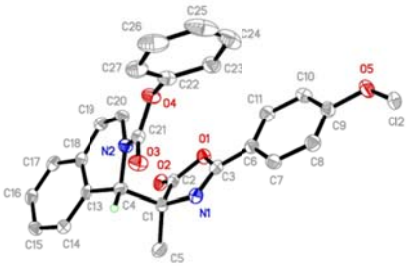
A flame dried 2 dram sample vial was charged with azlactones (0.20 mmol, 1.0 equiv.), catalyst (0.02 mmol, 0.1 equiv.) and 4Å MS (50 mg). Anhydrous pentane (2.2 mL) was added and the reaction mixture was stirred at room temperature for 5 min. It was then cooled to –25 ºC over 15 min. and a solution of isoquinoline (0.24 mmol) in 1.1 mL of mesitylene was added and the reaction mixture was stirred at –25 ºC. The reaction was monitored by TLC and when the

starting material was consumed, the reaction was quenched by adding 0.2 mL of 10 mol % of DMAP solution in DCM at –25 ºC and stirring was continued for another 10 minutes. The reaction mixture was purified by flash chromatography without doing any work up.

Characterization Data of Products

(*S*)-phenyl 1-((*S*)-2-(4-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazol-4-yl)isoquinoline-2(1H)-carboxylate (3.56a): Following the general procedure, compound **3.56a** was obtained as a white solid in 85% yield. mp = 69–71 ºC; Rf = 0.50 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ –175.69 (c 1.0, $CHCl_3$, 93% ee); dr = 96:04; IR (KBr) 3063, 2935, 1814, 1728, 1648, 1512, 1321, 1197, 1016, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): the compound exists as a 2:1 mixture of carbamate rotamers (* denotes the proton(s) corresponding to the minor rotamer), δ 7.86–7.80 (m, 2H), 7.80–7.77 (m, 2H*), 7.46–7.40 (comp, 2H*), 7.40–7.34 comp, 2H) , 7.33–7.21 (comp, 5H, 5H*), 7.19 (app dd *J* = 7.7, 1.1 Hz, 1H), 7.13 (app dd *J* = 7.7, 1.1 Hz, 1H*), 7.12–7.07 (comp, 2H*), 6.96–6.89 (comp, 2H, 2H*), 6.10 (d, *J* = 7.7 Hz, 1H *), 6.03 (d, *J* = 7.7 Hz, 1H), 5.91 (s, 1H*), 5.87 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H*), 1.60 (s, 3H*), 1.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 178.8, 163.2, 163.1, 160.2, 160.0, 152.3, 152.0, 150.9, 150.6, 137.7, 131.9, 131.5, 129.7, 129.7, 129.5, 129.4, 129.0, 128.8, 127.8, 127.5, 127.4, 127.2, 126.9, 126.0, 126.0, 125.9, 128.9, 125.6, 125.0, 124.9, 124.8, 121.5, 121.5, 117.9, 117.8, 114.0, 114.1, 111.9, 111.2, 73.7, 73.4, 61.2, 60.1, 55.4, 55.4, 21.2, 20.3, 19.9; *m/z* (ESI-MS) 476.8 $[M+Na]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.5 mL/min, UV = 280 nm, major diastereomer: t_R = 20.4 min (minor) and t_R = 27.6 min (major), minor diastereomer: t_R = 22.5 min (minor) and t_R = 25.7 min (major).

The enantioenriched product **3.56a** was recrystallized from EtOAc/hexanes and the absolute configuration was assigned by X-ray crystallography.



The requisite CIF has been submitted to the journal.

(*S*)-phenyl 1-((*S*)-4-ethyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazol-4-yl)isoquinoline-2(1H)-carboxylate (3.56b): Following the general procedure, compound **3.56b** was obtained as a white solid in 94% yield. mp = 63–65 ºC; R_f = 0.56 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ –183.5 (c 1.0, $CHCl_3$, 92% ee); dr = 93:07; IR (KBr) 2967, 2935, 1810, 1729, 1650, 1512, 1323, 1197, 1025, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): the compound exists as a 2:1 mixture of carbamate rotamers (* denotes the proton(s) corresponding to the minor rotamer), δ 7.89–7.79 (m, 2H, 2H*), 7.46–7.40 (comp, 2H*), 7.40–7.34 (comp, 2H), 7.33–7.20 (comp, 5H, 5H*), 7.17 (d, *J* = 7.7 Hz, 1H), 7.14–7.05 (comp, 1H*, 2H, 2H*), 6.98–6.90 (comp, 2H, 2H*), 6.09 (d, *J* = 7.7 Hz, 1H*), 6.03 (d, *J* = 7.7 Hz, 1H), 5.95 (s, 1H*), 5.92 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H*), 2.28–2.2.10 (m, 1H, 1H*), 2.09–2.1.92 (m, 1H, 1H*), 0.77 (t, *J* = 7.4 Hz, 3H*), 0.73 (t, *J* = 7.4, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 178.1, 163.2, 163.1, 160.6, 160.4, 152.2, 152.0, 150.9, 150.7, 132.0, 131.5, 129.7, 129.4, 129.4, 129.4, 128.9, 128.8, 127.8, 127.5, 127.4, 127.2, 126.1, 126.0, 126.0, 125.8, 125.6, 125.0, 124.9, 124.7, 121.5, 121.5, 117.8, 117.7, 114.1, 114.1, 112.1, 111.4, 78.9, 78.2, 77.2, 61.1, 60.2, 55.4, 26.5, 26.1, 8.1, 8.0; *m/z* (ESI-MS) 468.7 $[M]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 0.5 mL/min, UV = 280 nm, major diastereomer: t_R = 49.7 min (minor) and t_R = 99.6 min (major), minor diastereomer: t_R = 54.6 min (minor) and t_R = 92.6 min (major). Due to the overlap of one of the enantiomer of the minor diastereomer with the major enantiomer

of the major diastereomer, the ee was determined by calculated dr from ^{1}H NMR. The absolute configuration was assigned by analogy.

***(S)*-phenyl 1-((*S*)-4-propyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazol-4-yl)isoquinoline-2(1H)-carboxylate (3.56c):** Following the general procedure compound **3.56c** was obtained as a white solid in 93% yield. mp = 56–58ºC; R_f = 0.63 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ –177.6 (c 1.0, $CHCl_3$, 91% ee); dr = 92:08; IR (KBr) 2960, 2932, 1811, 1731, 1650, 1511, 1320, 1197, 1026 742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) the compound exists as a 1.7:1 mixture of carbamate rotamers (* denotes the proton(s) corresponding to the minor rotamer), δ 7.87–7.81 (m, 2H), 7.80–7.77 (m, 2H*), 7.43 (app t, *J* = 7.7 Hz, 2H*), 7.37 (app t, *J* =7.7 Hz, 2H), 7.33–7.20 (comp, 5H, 5H*), 7.17 (d, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H*), 7.11–7.06 (comp, 2H, 2H*), 6.99–6.90 (comp, 2H, 2H*), 6.10 (d, *J* = 7.7 Hz, 1H*), 6.04 (d, *J* = 7.7 Hz, 1H), 5.97 (s, 1H*), 5.92 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H*), 2.15 (td, *J* = 12.6, 4.8Hz, 1H, 1H*), 2.01 (td, *J* = 12.6, 4.4 Hz, 1H*), 1.92 (td, *J* = 12.6, 4.5 Hz, 1H), 1.25–0.94 (m, 2H, 2H*), 0.90 (t, *J* = 7.3 Hz, 3H*), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 178.3, 163.2, 163.1, 160.4, 160.2, 152.2, 152.1, 150.9, 150.7, 137.7, 132.0, 131.6, 129.7, 129.7, 129.5, 129.4, 128.9, 128.8, 127.8, 127.4, 127.2, 126.9, 126.0, 126.0, 126.0, 125.8, 125.6, 125.0, 124.9, 124.8, 121.6, 121.5, 117.8, 117.7, 114.1, 114.1, 112.1, 111.5, 78.3, 78.0, 61.3, 60.3, 55.4, 35.5, 34.9, 21.2, 17.3, 17.2, 13.9, 13.8; *m/z* (ESI-MS) 482.8 $[M]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.5 mL/min, UV = 280 nm, major diastereomer: t_R = 14.1 min (minor) and t_R = 21.2 min (major), minor diastereomer: t_R = 15.7 min (minor) and t_R = 19.3 min (major). The absolute configuration was assigned by analogy.

(*S*)-phenyl 1-((*S*)-4-isopropyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazol-4-yl)isoquinoline-2(1H)-carboxylate (3.56d): Following the general procedure, except the reaction was run in mesitylene/pentane (1:4) at –35 ºC and compound **3.56d** was obtained as a white solid in 94% yield. mp = 63–65 ºC; Rf = 0.70 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ –122.6 (c 1.0, $CHCl_3$, 89% ee); dr = 87:13; IR (KBr) 2957, 1811, 1731, 1650, 1511, 1320, 1197, 1053, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.4:1 mixture of carbamate rotamers (* denotes the proton(s) corresponding to the minor rotamer), δ 7.98–7.90 (m, 2H), 7.90–7.86 (m, 2H*), 7.49–7.27 (comp, 6H, 6H*), 7.25–7.10 (comp, 2H, 2H*), 7.01–6.85 (comp, 4H, 4H*), 6.31 (s, 1H*), 6.24 (s, 1H), 6.06–5.96 (m, 1H, 1H*), 3.89 (s, 3H), 3.85 (s, 3H*), 2.37–2.25 (m, 1H, 1H*), 1.43 (d, *J* = 6.7 Hz, 3H*), 1.30 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 177.5, 163.2, 163.2, 161.7, 160.6, 152.1, 151.7, 151.0, 150.8, 137.7, 132.3, 131.8, 129.9, 129.8, 129.7, 129.7, 129.6, 129.4, 129.3, 129.0, 128.9, 128.5, 128.3, 127.4, 127.4, 127.1, 127.1, 126.9, 125.8, 125.8, 125.8, 125.0, 124.9, 124.8, 124.7, 124.3, 121.7, 121.5, 118.2, 118.1, 114.2, 114.1, 114.1, 114.0, 112.6, 112.4, 79.2, 77.7, 58.5, 57.4, 55.5, 55.5, 55.4, 55.4, 31.3, 31.2, 31.0, 26.9, 21.2, 17.6, 17.5, 17.4, 17.4, 17.3; *m/z* (ESI-MS) 482.9 $[M]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.2 mL/min, UV = 280 nm, major diastereomer: t_R = 35.0 min (minor) and t_R = 47.2 min (major), minor diastereomer: t_R = 36.1 min (minor) and t_R = 49.8 min (major). The absolute configuration was assigned by analogy.

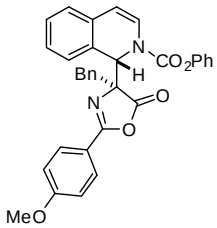
(*S*)-phenyl 1-((*S*)-4-isobutyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazol-4-yl)isoquinoline-2(1H)-carboxylate (3.56e): Following the general procedure, except the reaction was run at –30 ºC and compound **3.56e** was obtained as a white solid in 95% yield. mp = 59–61 ºC; Rf = 0.66 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ –176.43 (c 1.0, $CHCl_3$, 90% ee); dr = 92:08; IR

(KBr) 2957, 1810, 1731, 1649, 1607, 1511, 1455, 1353, 1320, 1258, 1197, 1053, 777, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.4:1 mixture of carbamate rotamers (* denotes the proton(s) corresponding to the minor rotamer r), δ 7.88–7.82 (m, 2H), 7.81–7.76 (m, 2H*), 7.46–7.40 (comp, 2H*), 7.39–7.33 (comp, 2H), 7.33–7.19 (comp, 5H, 5H*), 7.17–7.02 (comp, 3H, 3H*), 7.00–6.89 (comp, 2H, 2H*), 6.09 (d, *J* = 7.7, 1H*), 6.03 (d, *J* = 7.7 Hz, 1H), 5.93 (s, 1H*), 5.88 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H*), 2.10–1.96 (m, 2H, 2H*), 1.60–1.44 (m, 1H, 1H*), 0.89 (d, *J* = 6.7 Hz, 3H*), 0.85 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H*), 0.78 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 178.8, 163.1, 160.0, 159.8, 152.2, 150.9, 150.7, 137.7, 132.1, 131.6, 129.7, 129.6, 129.5, 129.4, 129.3128.9, 128.8, 127.9, 127.5, 127.4, 127.1, 126.9, 126.0, 125.8, 125.7, 125.6, 124.9, 124.9, 124.7, 121.6, 121.4, 118.0, 117.9, 114.1, 114.1, 112.2, 111.7, 77.5, 77.4, 62.1, 61.1, 55.4, 55.4, 41.9, 41.3, 25.0, 24.1, 23.2, 23.1, 21.2; *m/z* (ESI-MS) 519.0 $[M+Na]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.5 mL/min, UV = 280 nm, major diastereomer: t_R = 13.2 min (minor) and t_R = 19.3 min (major), minor diastereomer: t_R = 14.3 min (minor) and t_R = 16.8 min (major). The absolute configuration was assigned by analogy.

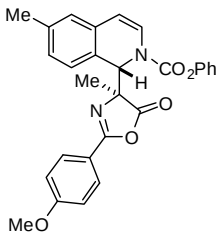
(*S*)-phenyl 1-((*S*)-2-(4-methoxyphenyl)-4-(2-(methylthio)ethyl)-5-oxo-4,5-dihydrooxazol-4-yl)isoquinoline-2(1H)-carboxylate (3.56f): Following the general procedure, except the reaction was run at –30 ºC and compound **3.56f** was obtained as a white solid in 95% yield. mp = 52–55ºC; Rf = 0.86 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ –175.35 (c 1.0, $CHCl_3$, 92% ee); dr = 90:10; IR (KBr) 2917, 1812, 1729, 1646, 1511, 1321, 1197, 1171, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.8:1 mixture of carbamate rotamers (* denotes the proton(s) corresponding to the minor rotamer), δ 7.86–7.77 (m, 2H, 2H*), 7.46–7.40 (comp, 2H*), 7.40–7.34 (comp, 2H), 7.33–7.20 (comp, 4H, 4H*), 7.18–7.04 (comp, 4H, 4H*), 7.00–6.90 (comp, 2H, 2H*), 6.10 (d, *J* = 7.6 Hz, 1H*), 6.05 (d, *J* = 7.6 Hz, 1H), 5.94 (s, 1H*), 5.90 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H*), 2.55–2.31 (comp, 3H, 3H*), 2.30–

2.20 (m, 1H, 1H*), 2.02 (s, 3H*), 2.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 178.0, 163.3, 163.2, 160.9, 160.8, 152.2, 152.0, 150.8, 150.6, 137.7, 131.9, 131.5, 129.9, 129.8, 129.5, 129.4, 129.1, 128.9, 128.6, 128.1, 127.9, 127.6, 127.5, 127.3, 126.8, 128.1, 127.9, 127.6, 127.5, 127.3, 126.8, 126.0, 125.9, 125.6, 125.5, 125.0, 124.9, 124.8, 121.5, 121.4, 117.7, 117.6, 114.1, 114.1, 112.1, 111.5, 71.2, 61.4, 60.4, 55.4, 32.6, 32.0, 28.7, 27.0, 21.1, 15.3, 15.2; *m/z* (ESI-MS) 514.6 $[M]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.5 mL/min, UV = 280 nm, major diastereomer: t_R = 24.5 min (minor) and t_R = 31.7 min (major), minor diastereomer: t_R = 21.9 min (minor) and t_R = 27.9 min (major). The absolute configuration was assigned by analogy.

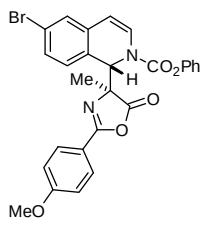
(*S*)-phenyl 1-((*S*)-4-benzyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazol-4-yl)isoquinoline-2(1H)-carboxylate (3.56g): Following the general procedure, except the reaction was run in 0.1 M concentration and at –35 ºC. Compound **3.56g** was obtained as a white solid in 95% yield. mp = 49–51 ºC; Rf = 0.73 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ –269.38 (c 1.0, $CHCl_3$, 90% ee); dr = 90:10; IR (KBr) 3030, 2932,1813, 1728, 1649, 1512, 1321, 1197, 977, 740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 2:1 mixture of carbamate rotamers (* denotes the proton(s) corresponding to the minor rotamer), δ 7.74–7.62 (m, 2H, 2H*), 7.50–7.36 (comp, 4H, 4H*), 7.34–7.25 (comp, 3H, 3H*), 7.25–7.05 (comp, 9H, 9H*), 6.92–6.82 (comp, 2H, 2H*), 6.21–6.07 (comp, 2H, 2H*), 3.81 (s, 3H), 3.81 (s, 3H*), 3.50 (d, *J* = 13.0 Hz, 1H*), 3.48 (d, *J* = 13.0 Hz, 1H), 3.31 (d, *J* = 13.0 Hz, 1H*), 3.24 (d, *J* = 13.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 177.3, 162.9, 162.9, 160.0, 159.9, 152.3, 152.1, 150.9, 150.6, 133.8, 133.6, 131.9, 131.5, 130.4, 130.3, 129.5, 129.4, 129.4, 129.0, 128.8, 127.9, 127.9, 127.8, 127.7, 127.5, 127.2, 127.1, 126.9, 126.1, 126.0, 126.0, 125.9, 125.7, 125.0, 124.9, 124.8, 121.5, 121.4, 121.4, 117.7, 117.6, 113.9, 113.9, 112.1, 111.5, 79.1, 78.5, 77.2, 61.0, 60.2, 55.3, 39.3, 38.8; *m/z* (ESI-MS) 552.9 $[M+Na]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 280 nm,



major diastereomer: t_R = 19.6 min (minor) and t_R = 32.6 min (major), minor diastereomer: t_R = 17.0 min (minor) and t_R = 25.9 min (major). The absolute configuration was assigned by analogy.



(*S*)-phenyl 1-((*S*)-2-(4-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazol-4-yl)-6-methylisoquinoline-2(1H)-carboxylate (3.57a): Following the general procedure, except the reaction was run at –30 ºC and compound **3.57a** was obtained as a white solid in 94% yield. mp = 61–63 ºC; Rf = 0.50 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ –108.71 (c 1.0, $CHCl_3$, 88% ee); dr = 90:10; IR (KBr) 2933, 1816, 1729, 1605, 1512, 1321, 1200, 1016, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.9:1 mixture of carbamate rotamers (* denotes the proton(s) corresponding to the minor rotamer), δ 7.67–7.80 (m, 2H, 2H*), 7.44–7.39 (comp, 2H*), 7.39–7.34 (comp, 2H), 7.25–7.13 (comp, 3H, 3H*), 7.12–7.05 (comp, 3H, 3H*), 6.98–6.89 (comp, 3H, 3H*), 6.05 (d, *J* = 8.1 Hz, 1H*), 5.98 (d, *J* = 8.1 Hz, 1H), 5.86 (s, 1H*), 5.82 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H*), 2.31 (s, 3H*), 2.30 (s, 3H), 1.58 (s, 3H*), 1.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 178.8, 163.2, 163.1, 160.2, 160.0, 152.2, 152.0, 150.9, 150.7, 138.8, 138.6, 131.8, 131.3, 129.8, 129.8, 129.4, 129.4, 129.4, 128.2, 127.9, 127.8, 127.5, 127.0, 125.9, 125.8, 125.6, 125.5, 124.8, 123.1, 123.0, 121.6, 121.5, 118.0, 117.9, 114.1, 114.1, 112.0, 111.3, 73.5, 73.2, 61.0, 60.0, 55.4, 21.2, 21.1, 20.4, 19.9; *m/z* (ESI-MS) 468.8 $[M]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.5 mL/min, UV = 280 nm, major diastereomer: t_R = 19.6 min (minor) and t_R = 26.3 min (major), minor diastereomer: t_R = 21.6 min (minor) and t_R = 23.0 min (major). The absolute configuration was assigned by analogy.

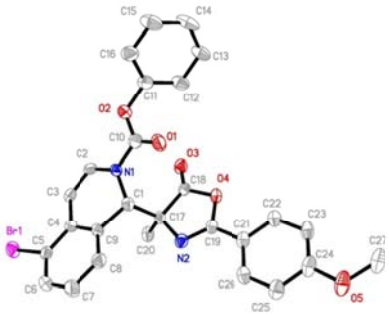


(*S*)-phenyl 6-bromo-1-((*S*)-2-(4-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazol-4-yl)isoquinoline-2(1H)-carboxylate (3.57b): Following the general procedure, except the reaction was run at –15 ºC and compound **3.57b** was obtained as a white solid in 95% yield. mp = 57–59 ºC; Rf = 0.53

(DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ –134.771 (c 1.0, $CHCl_3$, 90% ee); dr = 91:09; IR (KBr) 2966, 1817, 1730, 1648, 1512, 1349, 1197, 1016, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): the compound exists as a 2:1 mixture of carbamate rotamers (* denotes the proton(s) corresponding to the minor rotamer), δ 7.88–7.80 (m, 2H, 2H*), 7.45–7.35 (comp, 4H, 4H*), 7.31–7.21 (comp, 2H, 6H*), 7.18 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.98–6.92 (m, 2H, 2H*), 6.01 (d, *J* = 7.6 Hz, 1H*), 5.95 (d, *J* = 7.7 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H*), 1.57 (s, 3H*), 1.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 163.3, 160.4, 160.2, 152.1, 150.8, 150.5, 133.9, 133.5, 130.2, 129.9, 129.8, 129.5, 129.5, 129.4, 129.2, 127.6, 127.5, 126.9, 126.2, 126.1, 126.0, 124.8, 124.7, 123.0, 122.8, 121.5, 121.4, 117.7, 117.6, 114.2, 114.2, 110.5, 109.8, 77.2, 73.3, 73.0, 60.7, 59.6, 55.5, 20.2, 19.8; *m/z* (ESI-MS) 533.2 $[M+H]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1.0 mL/min, UV = 280 nm, major diastereomer: t_R = 12.9 min (minor) and t_R = 37.6 min (major), minor diastereomer: t_R = 16.1 min (minor) and t_R = 27.9 min (major). The absolute configuration was assigned by analogy.

(*S*)-phenyl 5-bromo-1-((*S*)-2-(4-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazol-4-yl)isoquinoline-2(1H)-carboxylate (3.57c): Following the general procedure, except the reaction was run in 0.1 M and at –15 ºC. Compound **3.57c** was obtained as a white solid in 81% yield. mp = 62–64 ºC; Rf = 0.56 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ –162.0 (c 1.0, $CHCl_3$, 93% ee); dr = 93:07; IR (KBr) 2935, 1815, 1724, 1643, 1511, 1353, 1197, 1016, 741 cm^{-1};. ^1H NMR (500 MHz, $CDCl_3$): the compound exists as a 2:1 mixture of carbamate rotamers (* denotes the proton(s) corresponding to the minor rotamer), δ 7.83–7.78 (m, 2H), 7.78–7.74 (m, 2H*), 7.51–7.45 (m, 1H, 1H*), 7.44–7.35 (comp, 2H, 2H*), 7.32–7.20 (comp, 4H, 4H*), 7.12 (d, *J* = 8.9 Hz, 2H), 7.07 (d, *J* = 8.9 Hz, 2H*), 6.97–6.88 (comp, 2H, 2H*), 6.48 (d, *J* = 8.0 Hz, 1H*), 6.42 (d, *J* = 8.0 Hz, 1H), 5.87 (s, 1H*), 5.83 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H*), 1.59 (s, 3H*), 1.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 163.2, 160.2, 152.1, 150.8, 150.5, 133.1, 132.9, 131.6,

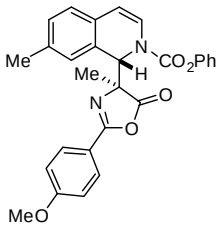
131.2, 129.8, 129.5, 129.4, 128.3, 128.0, 127.9, 127.8, 127.3, 127.0, 126.7, 126.6, 126.2, 126.0, 121.5, 121.4, 120.4, 117.7, 114.2, 114.1, 110.5, 109.8, 73.7, 61.1, 60.2, 61.2, 55.5, 20.2, 19.8; *m/z* (ESI-MS) 532.5 $[M]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.5 mL/min, UV = 280 nm, major diastereomer: t_R = 22.6 min (minor) and t_R = 28.0 min (major), minor diastereomer: t_R = 25.0 min (minor) and t_R = 26.8 min (major). The enantioenriched product **3.57c** was recrystallized from EtOAc/hexanes and the absolute configuration was assigned by X-ray crystallography.



The requisite CIF has been submitted to the journal.

(*S*)-phenyl 7-methoxy-1-((*S*)-2-(4-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazol-4-yl)isoquinoline-2(1H)-carboxylate (3.57d): Following the general procedure, except the reaction was run at –30 ºC and compound **3.57d** was obtained as a white solid in 95% yield. mp = 59–61 ºC; Rf = 0.43 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ –102.50 (c 1.0, $CHCl_3$, 93% ee); dr = 93:07; IR (KBr) 2935, 1816, 1726, 1648, 1511, 1257, 1199, 1016, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): the compound exists as a 2.3:1 mixture of carbamate rotamers (* denotes the proton(s) corresponding to the minor rotamer), δ 7.87–7.80 (m, 2H, 2H*), 7.50–7.34 (comp, 2H*, 2H), 7.25–7.20 (comp, 2H, 2H*), 7.16–7.06 (comp, 2H, 2H*), 7.05–7.00 (m, 1H, 1H*), 6.98–6.90 (comp, 2H, 2H*), 6.90–6.85 (m, 1H, 1H*), 6.84–6.76 (m, 1H, 1H*), 6.06 (d, *J* = 7.7 Hz, 1H*),

6.00 (d, *J* = 7.5 Hz, 1H), 5.85 (s, 1H*), 5.81 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H*), 3.82 (s, 3H, 3H*), 1.59 (s, 3H*), 1.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 178.8, 163.2, 163.1, 160.2, 160.0, 159.9, 158.8, 152.4, 152.0, 150.9, 150.6, 129.7, 129.7, 129.4, 129.4, 129.4, 127.5, 127.4, 126.1, 126.0, 125.9, 125.8, 125.0, 124.6, 123.5, 122.8, 121.5, 121.5, 121.4, 117.9, 117.8, 114.5, 114.4, 114.1, 114.1, 113.5, 113.4, 111.7, 110.9, 77.2, 73.5, 73.2, 61.2, 60.3, 55.4, 55.4, 53.4, 20.3, 19.8; *m/z* (ESI-MS) 484.6 $[M]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.5 mL/min, UV = 280 nm, major diastereomer: t_R = 23.9 min (minor) and t_R = 29.5 min (major), minor diastereomer: t_R = 27.2 min (minor) and t_R = 29.5 min (major). Due to the overlap of one of the enantiomer of the minor diastereomer with the major enantiomer of the major diastereomer, the ee was determined by calculated dr from ^{1}H NMR. The absolute configuration was assigned by analogy.



(*S*)-phenyl 1-((*S*)-2-(4-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazol-4-yl)-7-methylisoquinoline-2(1H)-carboxylate (3.57e): Following the general procedure, except the reaction was run at –30 ºC and compound **3.57e** was obtained as a white solid in 95% yield. mp = 60–62 ºC; Rf = 0.56 (DCM/Et_2O 50:1 v/v); $[\alpha]_D^{20}$ –123.25 (c 1.0, $CHCl_3$, 92% ee); dr = 93:07; IR (KBr) 2940, 1815, 1728, 1650, 1512, 1352, 1200, 1016, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.9:1 mixture of carbamate rotamers (* denotes the proton(s) corresponding to the minor rotamer), δ 7.86–7.82 (m, 2H), 7.82–7.78 (m, 2H*), 7.44–7.39 (comp, 2H*), 7.39–7.34 (comp, 2H), 7.24–7.20 (comp, 2H), 7.15–7.04 (comp, 4H, 4H*), 7.00 (app t, *J* = 7.6Hz, 1H, 1H*), 6.97–6.90 (comp, 2H, 2H*), 6.08 (d, *J* = 7.5 Hz, 1H*), 6.01 (d, *J* = 7.5 Hz, 1H), 5.86 (s, 1H*), 5.82 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H*), 2.37 (s, 3H*), 2.36 (s, 3H), 1.60 (s, 3H*), 1.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 178.8, 163.2, 163.1, 160.2, 160.0, 152.3, 152.0, 150.9, 150.7, 137.4, 137.1, 129.8, 129.7, 129.7, 129.5, 129.4, 129.3, 128.8, 128.4, 128.2, 126.0, 125.9, 125.9, 125.8, 124.9, 124.7, 124.6, 124.0, 121.5, 121.5, 118.0, 117.8, 114.1, 114.0,

112.0, 11.3, 77.2, 73.6, 73.2, 61.2, 60.2, 55.4, 21.4, 21.4, 20.4, 20.0; *m/z* (ESI-MS) 468.8 $[M]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.5 mL/min, UV = 280 nm, major diastereomer: t_R = 18.4 min (minor) and t_R = 27.9 min (major), minor diastereomer: t_R = 20.7 min (minor) and t_R = 26.0 min (major). The absolute configuration was assigned by analogy.

References:

(1) Polinelli, S.; Broxterman, B. Q.; Schoemaker, E. H.; Boesten, J. H. W.; Crisma, M.; Valle, G.; C., T.; Kamphuis, J. *Bioorg. Med. Chem.* **1992**, *5*, 453.

(2) Khosla, C. M.; Stachowiak, K.; Smeby, R. R.; Bumpus, M. F.; Piriou, F.; K., L.; Fermandjian, S. *Proc. Natl. Acad.Sci. U. S. A.* **1981**, *78*, 757.

(3) a) Vogt, H.; Brase, S. *Org. Biomol. Chem.* **2007**, *5*, 406; b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569; c) Clayden, J.; Donnard, M.; Lefranc, J.; Tetlow, D. J. *Chem. Commun.* **2011**, *47*, 4624.

(4) a) Cativiela, C.; Díaz-de-Villegas *, M. a. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645; b) Ma, D.; Ding, K. *Org. Lett.* **2000**, *2*, 2515.

(5) a) Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1367; b) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.

(6) a) Davis, F. A.; Lee, S.; Zhang, H.; Fanelli, D. L. *J. Org. Chem.* **2000**, *65*, 8704; b) Borg, G.; Chino, M.; Ellman, J. A. *Tetrahedron Lett.* **2001**, *42*, 1433.

(7) a) Satoh, T.; Fukuda, Y. *Tetrahedron* **2003**, *59*, 9803; b) Miyashita, M.; Mizutani, T.; Tadano, G.; Iwata, Y.; Miyazawa, M.; Tanino, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 5094.

(8) a) Steglich, W.; Hoefle, G. *Tetrahedron Lett.* **1970**, *11*, 4727; b) Nasveschuk, C. G.; Rovis, T. *Org. Biomol. Chem.* **2008**, *6*, 240; c) Mosey, R. A.; Fisk, J. S.; Tepe, J. J. *Tetrahedron: Asymmetry* **2008**, *19*, 2755; d) Alba, A. N. R.; Rios, R. *Chem.-Asian J.* **2011**, *6*, 720.

(9) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem. Int. Ed.* **1978**, *17*, 569.

(10) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532.

(11) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368.

(12) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166.

(13) Seitzberg, J. G.; Dissing, C.; Søtofte, I.; Norrby, P.-O.; Johannsen, M. *J. Org. Chem.* **2005**, *70*, 8332.

(14) Nguyen, H. V.; Butler, D. C. D.; Richards, C. J. *Org. Lett.* **2006**, *8*, 769.

(15) Joannesse, C.; Johnston, C. P.; Concellón, C.; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 8914.

(16) Zhang, Z.; Xie, F.; Jia, J.; Zhang, W. *J. Am. Chem. Soc.* **2010**, *132*, 15939.

(17) Seebach, D.; Jaeschke, G.; Gottwald, K.; Matsuda, K.; Formisano, R.; Chaplin, D. A.; Breuning, M.; Bringmann, G. *Tetrahedron* **1997**, *53*, 7539.

(18) Gottwald, K.; Seebach, D. *Tetrahedron* **1999**, *55*, 723.

(19) Xie, L.; Hua, W.; Chan, A. S. C.; Leung, Y.-C. *Tetrahedron: Asymmetry* **1999**, *10*, 4715.

(20) Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154.

(21) a) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 807; b) Terada, M.; Nii, H. *Chem. -Eur. J.* **2011**, *17*, 1760.

(22) Yang, X.; Lu, G.; Birman, V. B. *Org. Lett.* **2010**, *12*, 892.

(23) Lu, G.; Birman, V. B. *Org. Lett.* **2010**, *13*, 356.

(24) Tokunaga, M.; Kiyosu, J.; Obora, Y.; Tsuji, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4481.

(25) a) De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060; b) Klauber, E. G.; De, C. K.; Shah, T. K.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 13624; c) Klauber, E. G.; Mittal, N.; Shah, T. K.; Seidel, D. *Org. Lett.* **2011**, *13*, 2464.

(26) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

(27) Müller, C. E.; Schreiner, P. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 6012.

(28) a) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434; b) Kotke, M.; Schreiner, R. P. *Synthesis* **2007**, 779; c) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404; d) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968-970; e) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187; f) Singh, R. P.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2010**, *132*, 9558; g) Birrell, J. A.; Desrosiers, J.-N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 13872.

(29) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

(30) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449.

(31) a) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327; b) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 6801; c) Alexakis, A.; Amiot, F. *Tetrahedron: Asymmetry* **2002**, *13*, 2117; d) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 6700; e) Ahamed, M.; Todd, M. H. *Eur. J. Org. Chem.* **2010**, *2010*, 5935.

(32) a) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167; b) Weiner, B.; Szymanski, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2010**, *39*, 1656.

(33) a) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509; b) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072.

(34) Richter-Addo, G. B.; Knight, D. A.; Dewey, M. A.; Arif, A. M.; Gladysz, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 11863.

(35) Itoh, T.; Nagata, K.; Miyazaki, M.; Ohsawa, A. *Synlett* **1999**, 1154.

(36) Yamaguchi, R.; Tanaka, M.; Matsuda, T.; Fujita, K.-i. *Chem. Commun.* **1999**, 2213.

(37) Teichert, J. F.; Fañanás-Mastral, M.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 688.

(38) Li, L.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 12248.

Chapter IV

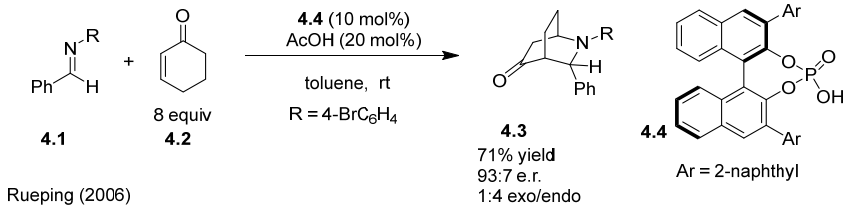
Conjugate-Base-Stabilized Brønsted Acids as Powerful Asymmetric Catalysts

4.1 Background

The field of asymmetric Brønsted acid catalysis has experienced rapid growth over the last decade.[1] Seminal studies by Akiyama[2] and Terada[3] have greatly accelerated the development in this area. In particular, chiral phosphoric acids are versatile catalysts and have been widely employed in an ever increasing number of asymmetric transformations.[4] In addition to the activation of the substrate via hydrogen bonding, these chiral acids are also anticipated to show dual catalytic action in some cases.[1c] In a continuing trend, catalysts that surpass the acidity of phosphoric acids are being prepared for the purpose of activating moderately basic substrates via asymmetric ion-pairing catalysis.[5]

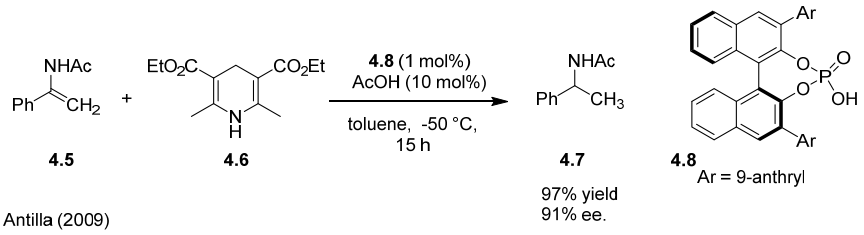
Cooperative approaches in which Brønsted acids act in concert with either another Brønsted acid[6] or with a (thio) urea catalyst[7] have emerged and shown exceptional reactivity for certain enantioselective transformations. Amongst these combinatorial approaches, the one involving both (thio) urea catalyst and Brønsted acids have opened new avenues in organocatalysis.

***Scheme 4.1*: Double Brønsted Acid Catalyzed Asymmetric Synthesis of Isoquinuclidines**



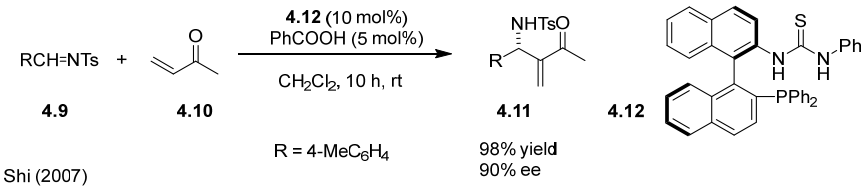
In 2006, Rueping and co-workers reported an example of double Brønsted acid catalyzed asymmetric synthesis of isoquinuclidines (Scheme 4.1). The plausible mechanism involved the activation of both electrophile and the nucleophile, where the chiral phosphoric acid activated the imine and the nucleophile was activated by the achiral Brønsted acid via keto-enol tautomerism. This reaction provided a direct way to synthesize highly enantioenriched isoquinuclidines in high yields.

***Scheme 4.2*: Hydrogenation of Enamides via Dual Acid Catalytic System**



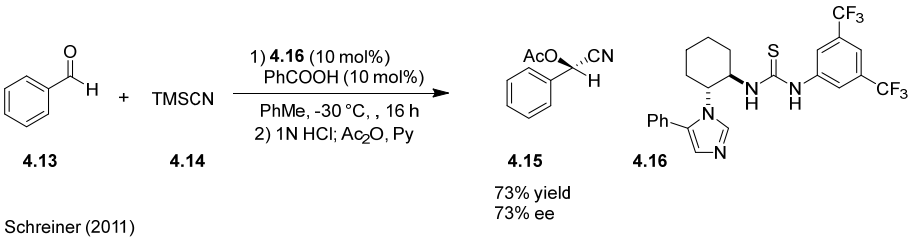
Antilla et al. employed a dual acid catalytic system for hydrogenation of enamides. Using a substoichiometric amount of the chiral phosphoric acid (1 mol%) in combination with the acetic acid (10 mol%), provided products in excellent yields and selectivities (Scheme 4.2). The dual catalytic system provided significant enhancement in reactivity of the reaction as compared to the one obtained by chiral phosphoric acid itself.

***Scheme 4.3*: Asymmetric Aza-Morita-Baylis-Hillman Reaction**



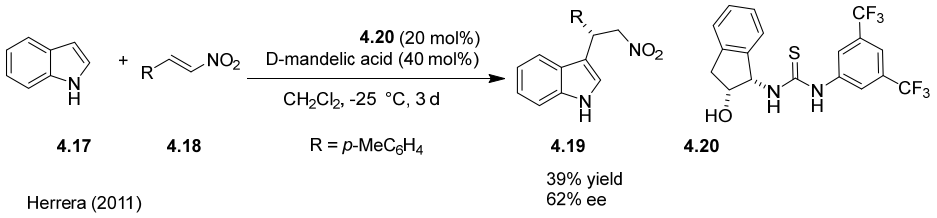
In 2007, Shi and coworkers introduced this cooperative approach in asymmetric Aza-Morita-Baylis-Hillman reaction (Scheme 4.3).[7a] The newly synthesized thiourea-phosphine catalyst **4.12** was employed in combination with benzoic acid and products were obtained in good to excellent yields and *ee* values.

***Scheme 4.4*: Asymmetric Cyanosilylation of Aldehydes**



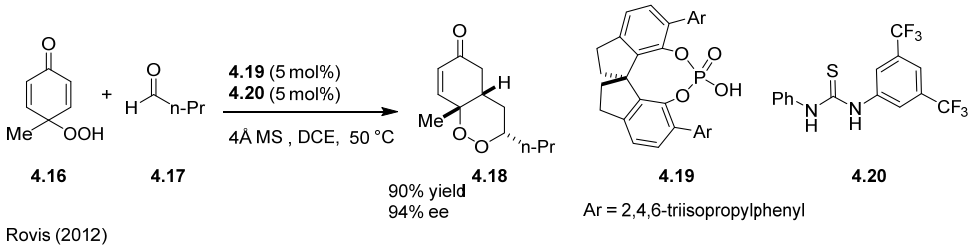
In 2008, Schreiner et al. demonstrated an efficient method for the alcoholysis of styrene oxides employing a catalytic system comprised of mandelic acid (1 mol%) and *N*,*N*-bis-[3,5-(trifluoromethyl)phenyl]-thiourea (1 mol%).[7b] The alkoxy alcohols were formed in high regioselectivity and excellent yields. Later in 2011, this group reported the addition of TMSCN to aldehydes utilizing a combination of imidazole based thio urea catalyst and benzoic acid with 10 mol% catalyst loading of each (Scheme 4.4).[7c] A wide variety of cyanohydrin acetates were obtained in good yields and moderate selectivities. Mechanistic studies were also performed which showed the presence of hydrogen bonding between the thiourea catalyst and the Brønsted acid catalyst.

***Scheme 4.5*: Enantioselective Friedel-Crafts Alkylation of Indoles**



Herrera and coworkers reported an example of Friedel-Crafts alkylation of indoles by employing a combination of a thiourea catalyst and D-mandelic acid.[7d] Although, moderate selectivity and yield were obtained, the combination of both catalysts showed an overall enhancement in results as compared to that of using each of the catalysts separately (Scheme 4.5).

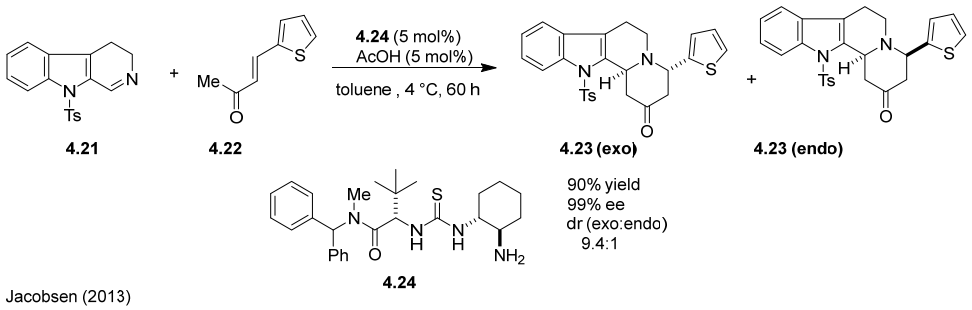
***Scheme 4.6*: Asymmetric Synthesis of 1,2,4-Trioxanes via Desymmetrization of Peroxyquinols**



In 2012, Rovis and coworkers demonstrated a distinct approach to cooperative catalysis. A chiral phosphoric acid in combination with a an achiral thiourea catalyst was employed (Scheme 4.6).[7f] This

combined catalytic system was utilized to synthesize optically active 1,2,4-Trioxanes via desymmetrization of peroxyquinols. All products were formed with excellent yields and high ee values. The 1,2,4-trioxane products were derivatized and were shown to exhibit potency as cancer cell inhibitors.

***Scheme 4.7*: Enantioselective Aza-Diels Alder Reaction of Enones**



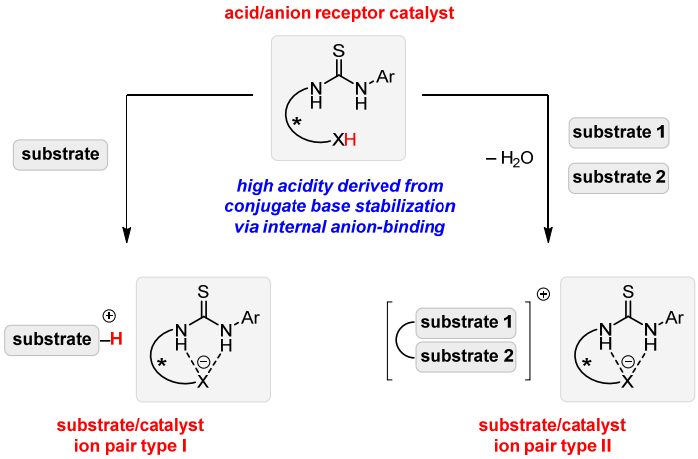
Jacobsen (2013)

A recent example based on the cooperative mechanism was demonstrated by Jacobsen et al. in [4 + 2] cycloaddition of enones to cyclic imines (Scheme 4.7). The hydrogen bond donor containing an amine group helped in activation of the enone by forming dienamine, whereas the imine was activated by the achiral Brønsted acid. With this dual catalytic approach, enantioenriched complex indolo- and benzoquinolizidine compounds were formed in high level of enantioselectivity and yields.

4.2 Concept

We introduced a complementary concept for asymmetric Brønsted acid catalysis that merges certain features of previous approaches while offering some unique advantages. Most of the previously reported methods for cooperative catalysis involved the use of a chiral Brønsted acid or a chiral HB catalyst in conjunction with an achiral Brønsted acid. We envisioned a chiral Brønsted acid in which the acidic site of the catalyst is tethered to a hydrogen bonding site such as a thiourea, which acts an appropriate linker to an anion receptor moiety (Figure 4.1).

***Figure 4.1*: Internal Anion-Binding Concept for Asymmetric Brønsted Acid/Chiral Anion Catalysis**



Upon substrate protonation, the conjugate base associates with the anion recognition site, [8] resulting in the formation of a substrate/catalyst ion pair of type I. Alternatively, the catalyst could facilitate the condensation of two different substrates, leading to the formation of an ion pair of type II. While the anion may still interact with the substrate via hydrogen bonding in the type I ion pair, hydrogen bonding should be reduced significantly in the type II ion pair, resulting in strict ion-pairing. Importantly, both types of ion pairs feature a rigid anion that should facilitate an efficient transfer of chirality. We have applied our concept to the enantioselective Povarov reaction with secondary amines[9] and the Pictet Spengler reaction.

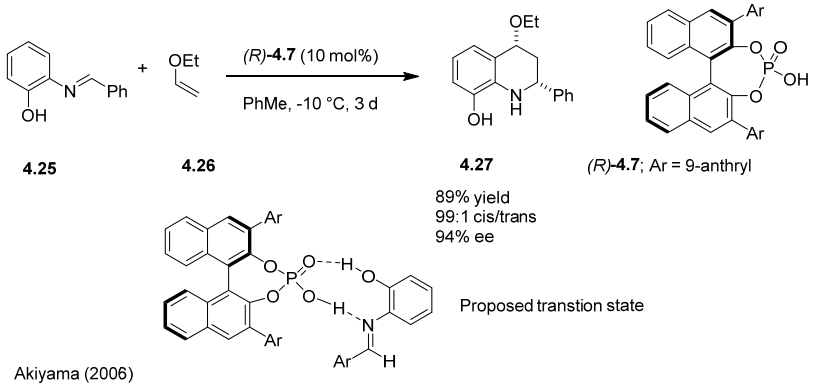
4.3 Catalytic Enantioselective Povarov Reaction

4.3.1 Background

Heterocyles containing a nitrogen atom are an important class of organic compounds which have found significant applications in pharmaceutical, medicinal and agrochemical industries. These include compounds with a tetrahydroquinoline ring system which is a common structural feature of many drugs and therapeutic agents (Figure 4.3).[10] Due to popularity of these compounds as important scaffolds in drug candidates and many other biologically active compounds, a number of asymmetric methods have been developed for their synthesis. Amongst these, the Povarov reaction is one such technique, involving

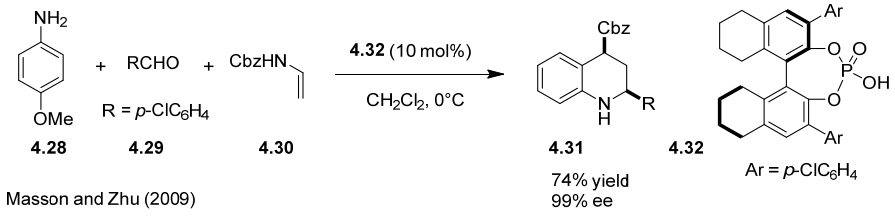
a [4+2] cycloaddition reaction between *N*-aryl imines and electron-rich olefins resulting in the formation of tetrahydroisoquinoline derivatives.[11] Interest in the asymmetric Povarov reaction has grown in recent years. Impressive results have been achieved with chiral Lewis acids,[12] although most studies have focused on asymmetric Brønsted acid catalysis.[13]

***Scheme 4.8*: Asymmetric Inverse Electron Demand Aza Diels Alder Reaction**



In 2006, a pioneering contribution in this regard was made by Akiyama and co-workers (Scheme 4.8).[13a] An aldimine synthesized from an aromatic aldehyde and an *o*-hydroxyaniline was allowed to react with an ethyl vinyl ketone to provide a tetrahydroquinoline derivative favoring the *cis* isomer. The proposed transition state involved a nine-membered cyclic structure where the hydroxyl group in the aldimine hydrogen bonds to the phosphoric acid and plays a key role in imparting enantioselectivity in the products.

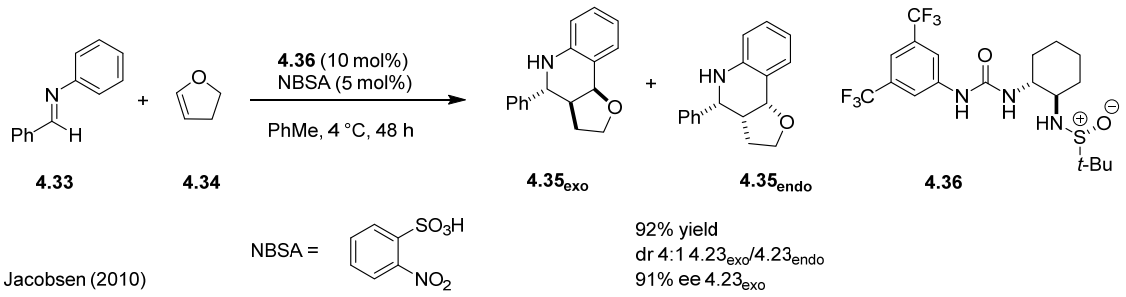
***Scheme 4.9*: Chiral Brønsted Acid Catalyzed Three Component Povarov Reaction**



In 2009, Masson and Zhu demonstrated an enantioselective three component Povarov reaction catalyzed by a chiral Brønsted acid derived from octahydro *(R)*-BINOL (Scheme 4.6).[13b] Here, a three component reaction between various aromatic or aliphatic aldehydes, anilines and benzyl *N*-vinyl carbamate was reported. The resulting (2,4-*cis*)-amino-2-aryl(alkyl)-tetrahydroisoquinolines were formed

in high enantioselectivities. A short synthesis of Torcetrapid involving the enantioselective Povarov reaction as one of the key steps was also reported.

***Scheme 4.10*: Asymmetric Povarov Reactions via Cooperative Catalysis of NBSA and Chiral Urea**



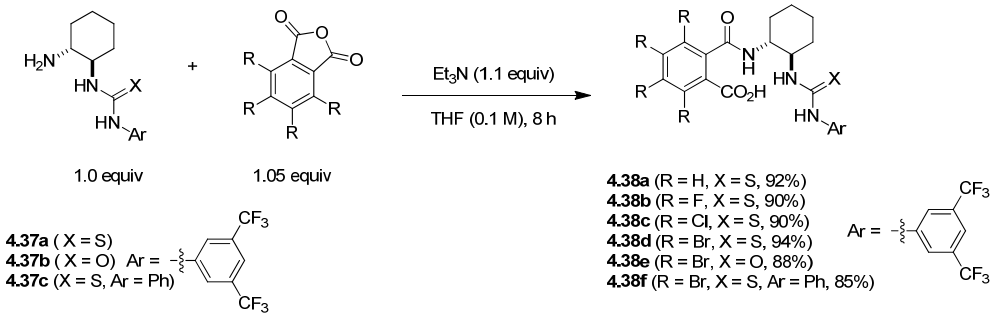
Most of the Brønsted acid catalysis of the Povarov reaction has been limited to chiral phosphoric acids.[13c-e] In 2010, Jacobsen and coworkers demonstrated a cooperative catalysis approach using a combination of *o*-nitrobenzenesulfonic catalyst (NBSA) and a chiral urea catalyst (Scheme 4.7).[7h] Addition of 2,3-dihydrofuran to *N*-aryl imines was chosen as the model reaction. The cyclized products were obtained in excellent diastereoselectivity and enantioselectivity. The optimized conditions were applied to the addition of various other nucleophiles as well.

4.3.2 Results and Discussion

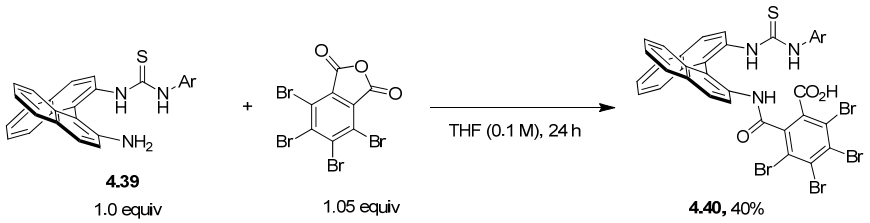
4.3.2.1 Design and Synthesis of Chiral Brønsted Acid Catalysts

Due to the relatively weak acidities of carboxylic acids, the use of chiral carboxylic acids for substrate activation has been limited to relatively few examples.[14] We prepared a number of chiral acids containing a carboxylic acid connected to a hydrogen bonding site such as (thio) urea. The internal stabilization of a conjugate base such as a carboxylate would provide certain key advantages. In addition to lowering the pK_a value of an acid, it would help to reduce hydrogen bonding interactions between the carboxylate anion and the protonated substrate. More importantly, the internal covalent attachment of the acidic site to the anion receptor moiety as opposed to the dual catalytic approach (Figure 4.1) would circumvent the potential issue of background reactivity.

***Scheme 4.11*: Chiral Brønsted Acid Catalysts with 1,2-Cyclohexanediamine Backbone**

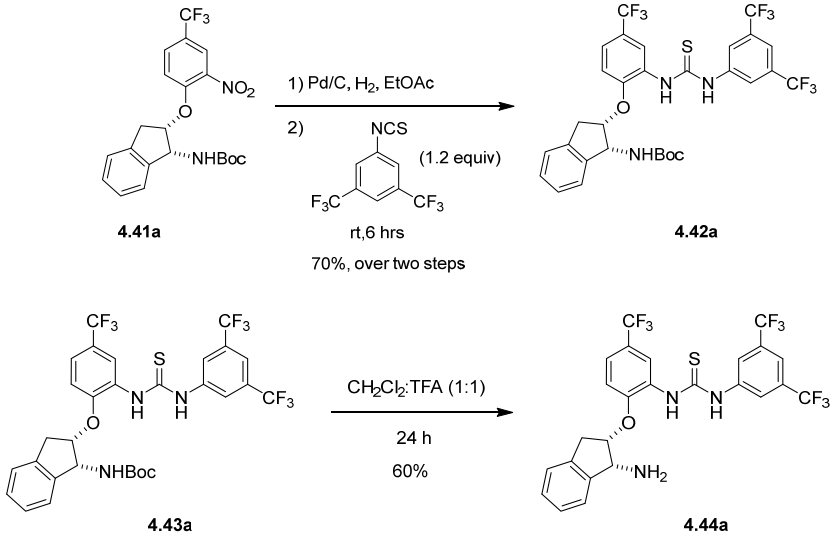


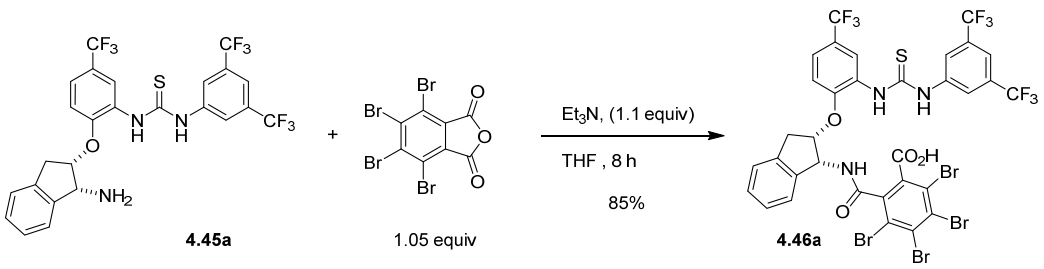
***Scheme 4.12*: Chiral Brønsted Acid Catalysts with 1,1′ -Binaphthyl-2,2′ -diamine Backbone**



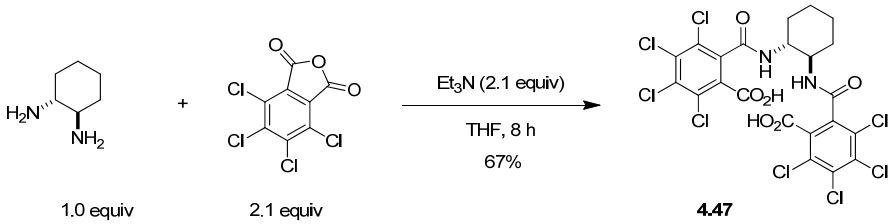
Catalysts **4.38a-4.38g** were prepared in one step from the corresponding phthalic anhydride and the monothiourea compounds (Scheme 4.11 & 4.12). Catalyst **4.46** was synthesized from a three step procedure from the known compound **4.41**, which was originally derived from *cis*-aminoindanol (Scheme 4.14). Chiral diacid catalyst **4.47** was prepared in one step from 1,2-cyclohexanediamine and tetrachloro phthalic anhydride.

***Scheme 4.13:* Chiral Brønsted Acid Catalyst with *cis*-Aminoindanol Backbone**





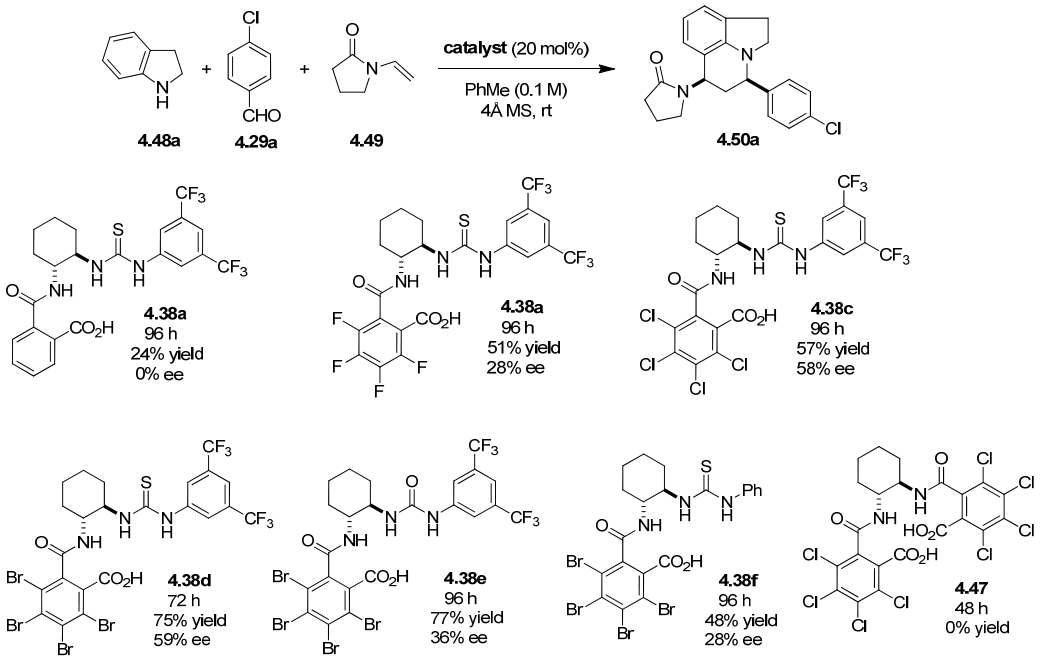
***Scheme 4.14*: Synthesis of Chiral Diacid Catalyst**

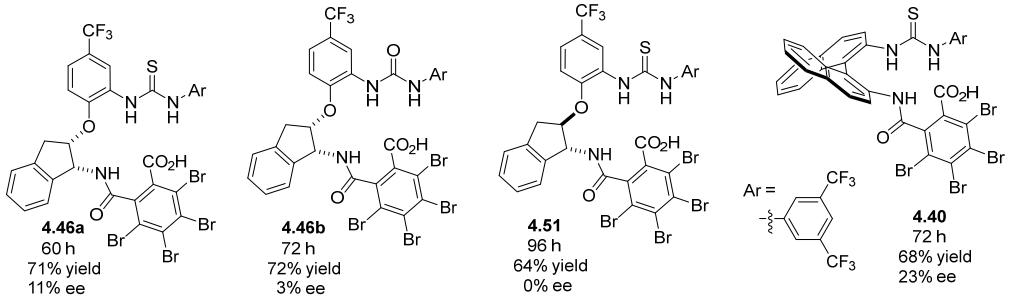


4.3.2.2 Optimization

A number of chiral carboxylic acids synthesized were evaluated for the three component Povarov reaction with indoline (Scheme 4.15). Catalyst **4.38a**, which was derived from phthalic anhydride and 1,2-cyclohexanediamine mono thiourea, promoted the reaction but provided racemic product.

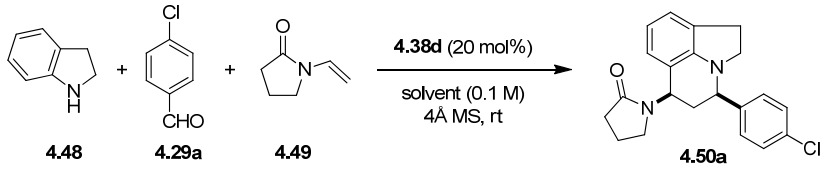
***Scheme 4.15*: Evaluation of Chiral Brønsted Acid Catalysts**





Tetrafluoro-catalyst **4.38b** displayed a drastic improvement in reactivity and selectivity. The corresponding tetrachloro-catalyst **4.38c** provided another marked increase in enantioselectivity. The tetrabromo catalyst **4.38d** displayed an almost identical level of selectivity, but a dramatic increase in reactivity was observed. The presence of urea as the hydrogen bonding site in catalyst **4.38e** gave inferior results. Introducing an unsubstituted phenyl ring on the thiourea in catalyst **4.38f** lowered the selectivity and the diacid catalyst **4.47** completely failed to catalyze the reaction. Catalysts derived from *cis* or *trans* indanol backbones provided resulted in low ee (catalysts **4.46a**, **4.46b & 4.51**). (R)-BINAM-based catalyst **4.40** also showed moderate levels of reactivity, albeit with poor selectivity.

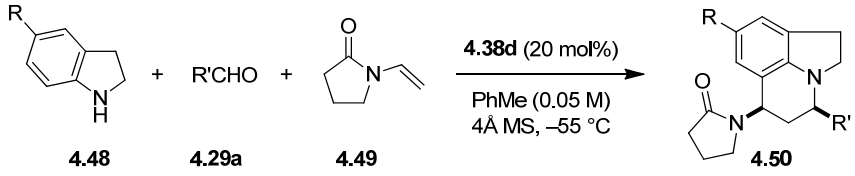
***Table 4.1*: Solvent Study**



entry	solvent	time (h)	yield (%)	ee (%)
1	Toluene	72	75	59
2	CH_3CN	12	77	0
2	CH_2Cl_2	7	81	17
3	Et_2O	30	79	34
4	MTBE	15	85	31
5	THF	48	74	0

Amongst various chiral Brønsted acid catalysts evaluated, catalyst **4.38d** provided the most promising results. Upon performing the reaction in solvents more polar than toluene (with 20 mol% of **4.38d**) increased the reactivity but the selectivity of the reaction was markedly reduced (Table 4.1). However, performing the reaction in toluene and lowering the temperature to 0 °C increased the selectivity from 59% to 71%. Further lowering the temperature to -55 °C and increasing the equivalents of **4.29a** and **4.49** to two equivalents resulted in formation of **4.50a** in 94% yield and 92% ee in 110 hours.

***Table 4.2*: Substrate Scope with Different Indolines and Aldehydes**



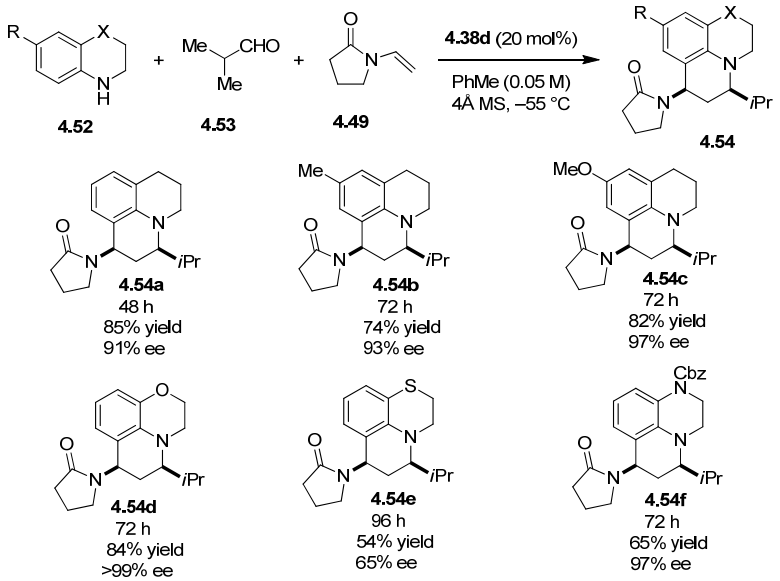
4.48 **4.29a** **4.49** **4.50**

entry	R	R′	time (h)	product	yield (%)	ee (%)
1	H	4-Cl-C_6H_4	110	**4.50a**	94	92
2	Cl	4-Cl-C_6H_4	120	**4.50b**	59	84
3	Br	4-Cl-C_6H_4	120	**4.50c**	76	86
4	Me	4-Cl-C_6H_4	96	**4.50d**	82	90
5	H	4-Br-C_6H_4	96	**4.50e**	86	95
6	H	4-F-C_6H_4	96	**4.50f**	76	93
7	H	4-CN-C_6H_4	96	**4.50g**	92	91
8	H	3-MeO-C_6H_4	96	**4.50h**	93	92
9	H	2-Me-C_6H_4	120	**4.50i**	80	92
10	H	2-MeO-C_6H_4	120	**4.50j**	59	93
11	H	C_6H_5	120	**4.50k**	71	79
12	H	3,4-Cl_2-C_6H_3	96	**4.50l**	88	87
13	H	*i*Pr	24	**4.50m**	96	94
14	H	*i*Bu	26	**4.50n**	53	95
15	H	*t*Bu	96	**4.50o**	65	>99
16	H	neopentyl	96	**4.50p**	91	95
17	H	cyclohexyl	96	**4.50q**	51	90
18	H	cyclopentyl	12	**4.50r**	82	88

The scope of the enantioselective Povarov reaction was explored under the optimized conditions (Table 4.2). To begin with, 4-chlorobenzaldehyde was combined with indolines bearing different substituents at the 5-position to provide tetrahydroquinolines in moderate to good yields and selectivities (entries 1–4). The Povarov reaction between unsubstituted indoline and an electronically diverse collection of aromatic aldehydes was also very well accommodated. (entries 5–12). To our delight, aliphatic aldehydes were also viable substrates and provided products with excellent ee values (entries 13–18).

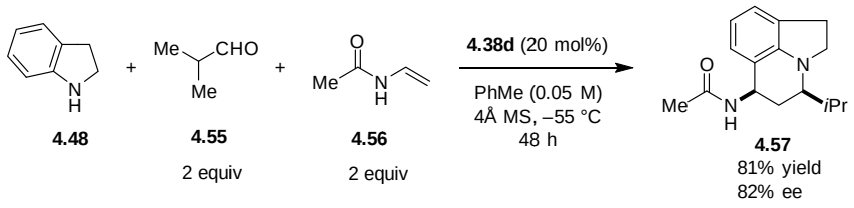
The scope of the reaction was extended to different secondary amines with isobutaraldehyde as the aldehyde (Scheme 4.16). A number of tetrahydroquinolines were tolerated with high levels of enantioselectivity, particularly substrate **4.54d** was produced with nearly perfect enantioselectivity. However, the corresponding sulfur analogue (**4.49e**) was isolated in only 54 percent yield and 65% ee. Additionally, tetrahydroquinoxaline-containing product **4.49f** was obtained with moderate yield and excellent selectivity.

***Scheme 4.16*: Substrate Scope with Different Secondary Amines**



Upon extending the scope in terms of the dienophile, *N*-vinylacetamide **4.56** proved to be a viable substrate (Scheme 4.17). However, substituted versions of **4.34** were unreactive, while simple vinyl ethers reacted sluggishly.

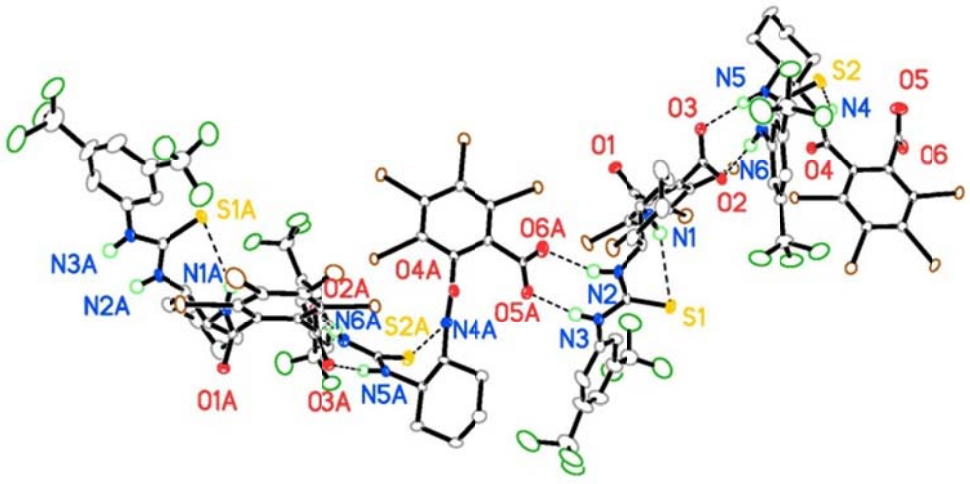
***Scheme 4.17*: *N*-vinylacetamide as Dienophile**



4.3.3 Further Studies

To obtain insights into the nature of conjugate base stabilization in the anionic form of **4.38d**, we prepared the corresponding tetrabutylammonium salt. The X-ray crystal structure of this salt is depicted in Figure 4.2. Interestingly, the individual units were found to hydrogen bond in an intermolecular fashion, resulting in a helical chain-type superstructure. Individual catalyst units interact through binding of the carboxylate anion to the thiourea site of the neighboring molecule. In addition, the amide N-H proton is engaged in an internal hydrogen bonding interaction with the thiourea sulfur atom of the same molecule, an interaction that likely increases the acidity of the thiourea site, thus contributing to better anion-binding. It remains to be established whether or not this particular type of catalyst aggregation is relevant in the catalytic cycle.

***Figure 4.2*: X-ray Crystal Structure of the Tetrabutylammonium Salt of Catalyst 4.38d (four repeating units)[a]**



[a] For clarity, tetrabutylammonium cations are not shown and only selected hydrogen atoms are depicted.

4.3.4 Summary

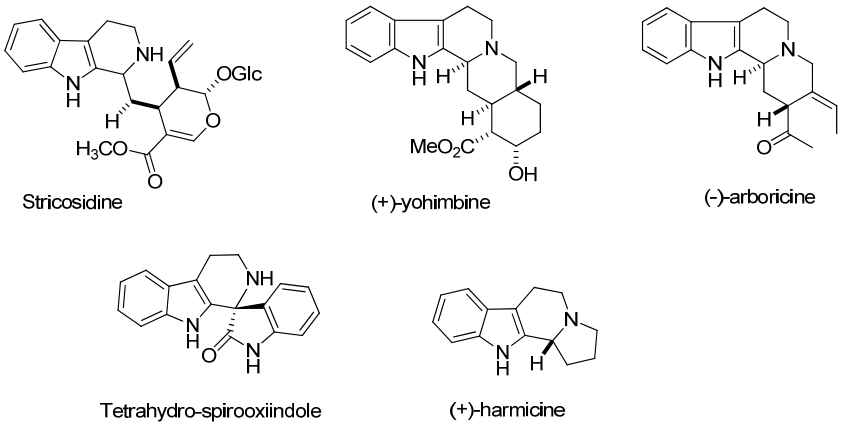
In summary, we have introduced conjugate-base-stabilized Brønsted acid catalysis as a new and highly generalizable concept for asymmetric catalysis. The power of this design was demonstrated in the context of the first catalytic enantioselective Povarov reaction involving secondary aromatic amines such as indoline and tetrahydroquinoline.

4.4 Catalytic Enantioselective Pictet-Spengler Reaction

4.4.1 Significance and Background

The importance of tetrahydroisoquinolines and tetrahydro-β-carboline ring systems in the synthesis of alkaloids as well as in other biologically and synthetically relevant compounds has been known for over a hundred years.[15] After its seminal discovery in 1911,[16] the Pictet-Spengler reaction has been widely employed to synthesize these structural motifs.[15a,17] Particularly, this reaction has been successfully employed in the synthesis of many medicinally important compounds (Figure 4.3). Some of them have shown promising results in the treatment of diseases such as cancer, tuberculosis and malaria.[18]

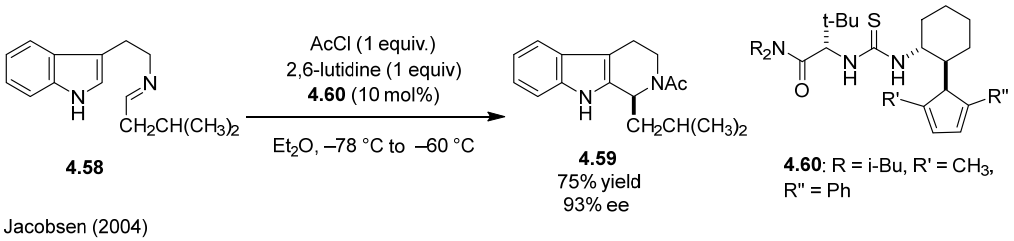
***Figure 4.3*: Some Examples of Biologically Relevant Compounds Containing β-Carboline Unit**



The racemic synthesis of β-carbolines via Pictet-Spengler reaction has been extensively studied.[19] These commonly involve strong Brønsted or Lewis acids as catalysts. However, enantioselective methods have been limited to only a few examples.[20] In addition, some indirect enantioselective methods are known for their preparation.[21] Despite the development of indirect methods, there is still no general solution to the prototypical Pictet-Spengler reaction of unmodified tryptamine with simple aldehydes. In

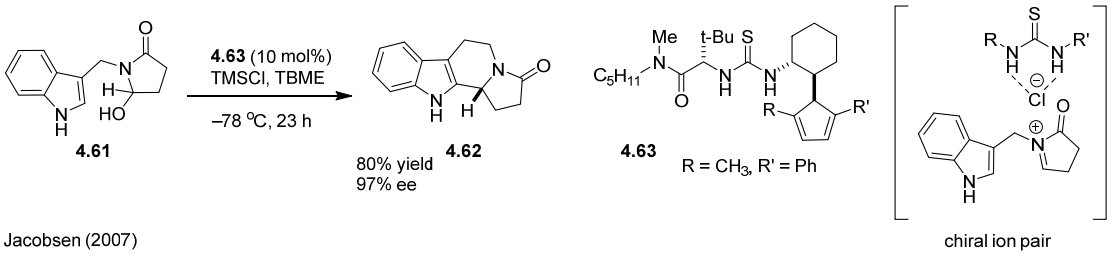
2004, a pioneering contribution by Jacobsen et al. demonstrated an acyl Pictet-Spengler reaction involving cyclization with in-situ-generated acyliminium ions, thus overcoming the inherently low reactivity of the corresponding imines (Scheme 4.18).[20b] Their strategy involved the use of a hydrogen bonding catalyst to activate weakly basic *N*-aclyiminium ions to form β-carbolines in good yield and high ee values.

***Scheme 4.18*: Enantioselective Acyl Pictet-Spengler Reaction**



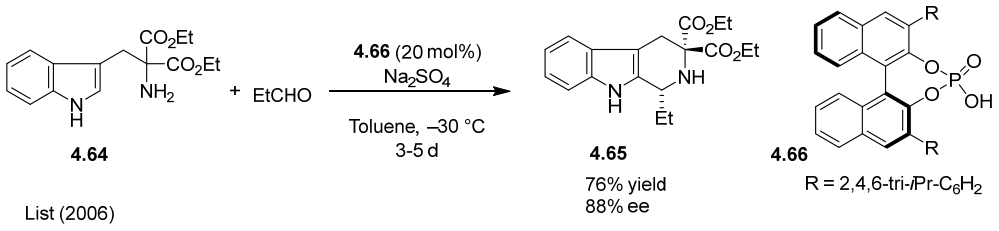
In 2007, Jacobsen et al. reported a mechanistic study on ion pair catalysis in the acyl Pictet-Spengler cyclization of hydroxyl lactams.[20c] The chloro lactam is formed in situ from the corresponding hydroxyl lactam, which upon chloride abstraction by the hydrogen bonding catalyst forms the *N*-acyliminium chloride-thiourea ion pair. The chloride abstraction was proposed to be the rate determining step and the cyclized products were formed in excellent yields and selectivity (Scheme 4.19).

***Scheme 4.19*: Pictet-Spengler Cylcization of Hydroxy Lactams**



Chiral phosphoric acids have been successfully applied to the activation of imines towards various nucleophiles. In 2006, List and co-workers displayed their use for the Pictet-Spengler cyclization between geminal diesters of tryptamines and a range of aldehydes (Scheme 4.20).[20k] Employing 20 mol% of **4.66** provided enantioenriched products in excellent yields.

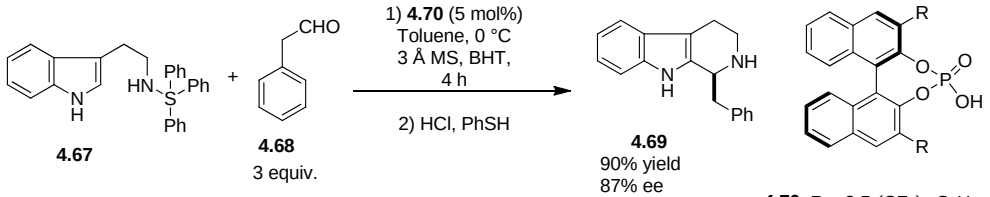
***Scheme 4.20*: Asymmetric Pictet-Spengler Reaction of Geminal Diester of Tryptamine**



List (2006)

Another application of chiral phosphoric acid catalysts towards the Pictet-Spengler reaction was shown by Hiemstra and co-workers in 2007. The in situ formed *N*-sulfenyltryptamines were allowed to react with a variety of aldehydes in the presence of only 5 mol% of **4.70**.[20j] It was proposed that the reaction proceeded via the formation of *N*-sulfenylinium ion. In addition, the presence of the sulfenyl group offered the advantage of facile removal after the cyclization reaction (Scheme 4.21).

***Scheme 4.21*: Pictet-Spengler Cyclization via *N*-Sulfenylinium Ion**

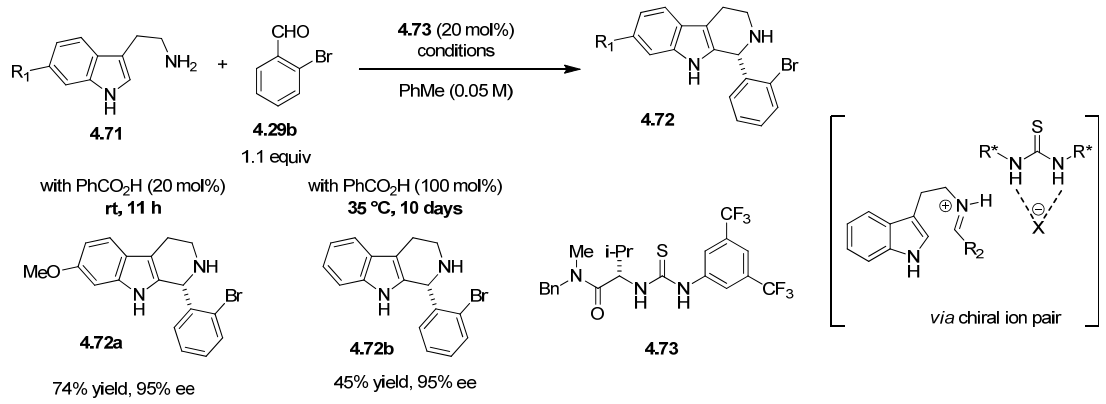


Hiemstra (2007)

Catalytic enantioselective Pictet-Spengler reactions have also been reported with relatively electrophilic imines derived from isatin and tryptamine.[18,22] Furthermore, interesting catalytic enantioselective cascade approaches have been disclosed that involve a diastereoselective Pictet-Spengler step.[21e,23] In 2009, Jacobsen and co-workers revealed a cooperative catalytic approach with a weak Brønsted acid and a hydrogen bonding catalyst, leading to the formation of unprotected tetrahydro-β-carboline products (Scheme 4.22).[20g] In most cases, the more nucleophilic 6-methoxytryptamine was employed with aldehydes in the presence of 20 mol% of benzoic acid (achiral co-catalyst) and chiral hydrogen bonding catalyst **4.67** and produced β-carbolines in excellent levels of enantioselectivities. A reaction of 6-methoxytryptamine with 2-bromobenzaldehyde, performed at rt for 11 h and catalyzed by 20 mol% of each a thiourea catalyst and benzoic acid, readily provided the corresponding product in good yield and excellent ee. In contrast, the otherwise identical reaction with unmodified tryptamine required

one equivalent of benzoic acid and elevated temperatures. Following an extended reaction time of 10 days, the expected product was isolated in moderate yield albeit with excellent ee. Later this cooperative approach was also applied to an iso-Pictet-Spengler reaction by the same group.[20i]

***Scheme 4.22*: Chiral Hydrogen Bonding Catalyst (thiourea) and Benzoic Acid as Catalysts**



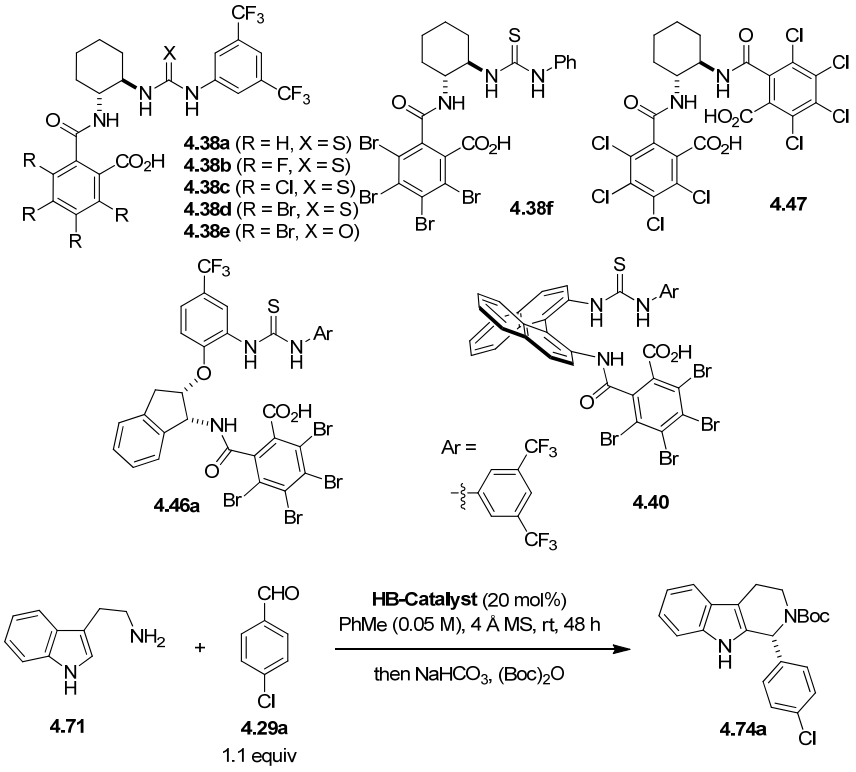
Jacobsen (2009)

4.4.2 Results and Discussion

4.4.2.1 Optimization

The major difficulty in rendering catalytic enantioselective Pictet-Spengler transformations lies in the relatively low electrophilicity of β-phenylethylamine or tryptamine-derived imines or iminium ions. A further challenge is posed by the enhanced basicity of the products over the starting materials, leading to problems of product inhibition and catalyst turnover. To overcome the low reactivity of tryptamine-derived iminium ions we wanted to test our concept of internally conjugate-base-stabilized Brønsted acid catalysis. We hypothesized, that in comparison to the cooperative approach involving an external achiral Brønsted acid, the cooperative action of a chiral Brønsted acid catalyst where an acidic functional group is covalently connected to an anion-recognition site would, upon substrate protonation, result in a rigid substrate/catalyst ion pair (Figure 4.1). Since hydrogen bonding between the ions is expected to be minimal in the latter scenario, the protonated substrate should display enhanced electrophilicity.

Table 4.3: **Evaluation of Chiral Brønsted Acid Catalysts**[a]



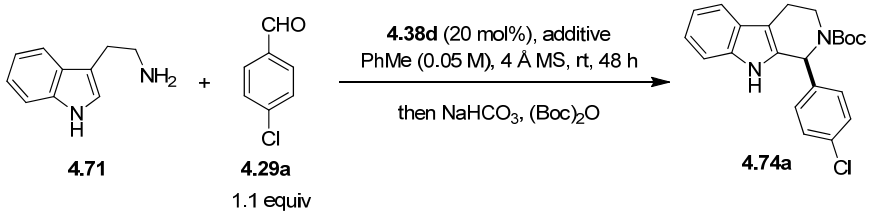
entry	HB-catalyst (5 mol%)	time (h)	yield (%)	ee (%)
1	**4.38a**	48	NR	-
2	**4.38b**	48	10	20
3	**4.38c**	48	33	92
4	**4.38d**	48	37	94
5	**4.38e**	48	9	66
6	**4.38f**	48	NR	-
7	**4.47**	48	NR	-
8	**4.46a**	48	NR	-
9	**4.40**	48	38	56
10	**4.38d**	72	36	94
11	**4.38d**	96	38	94

[a]Reactions were performed on a 0.2 mmol scale. Yields are isolated yields (over two steps) of chromatographically purified compounds.

We initiated our efforts by exposing tryptamine and *p*-chlorobenzaldehyde (1.1 equiv.) to a range of chiral acid catalysts containing a carboxylic acid group and thiourea as the hydrogen bonding moiety (Table 4.3). Due to the known sensitivity of the products[20g] and to facilitate ee determination, the initially formed tetrahydro-β-carbolines were Boc-protected prior to purification. Catalyst **4.38a** did not catalyze this transformation (entry 1). Catalyst **4.38b** yielded some product with poor selectivity, while catalyst **4.38c** showed a dramatic increase in selectivity with some increase in the yield of the reaction (entry 2 and 3). The corresponding tetrabromo catalyst **4.38d** gave identical results in terms of selectivity, with only a slight increase in the yield of the reaction (entry 4). However, the reaction was sluggish and moderately selective in the presence of a similar tetrabromo urea catalyst (**4.38e**, entry 5).

Furthermore, catalysts **4.38f** and **4.46a,** which promoted the Povarov reaction, were unsuccessful in catalyzing this transformation, whereas catalyst **4.47** was inactive for both reactions (entries 6-8). Encouraging results in terms of reactivity were observed with **4.40**. However, the selectivity was only moderate (entry 9). Even though catalyst **4.38d** demonstrated promising results, continuing the reaction for 72 or 96 hours in the presence of **4.38d** did not show any improvement in selectivity (entries 10 and 11). While these attempts illustrated the excellent selectivity profile of this new class of Brønsted acid catalysts for this otherwise challenging reaction, they are indicative of product inhibition and the issue of reactivity was yet to be solved.

***Table 4.4*: Evaluation of Acid Additives[a]**



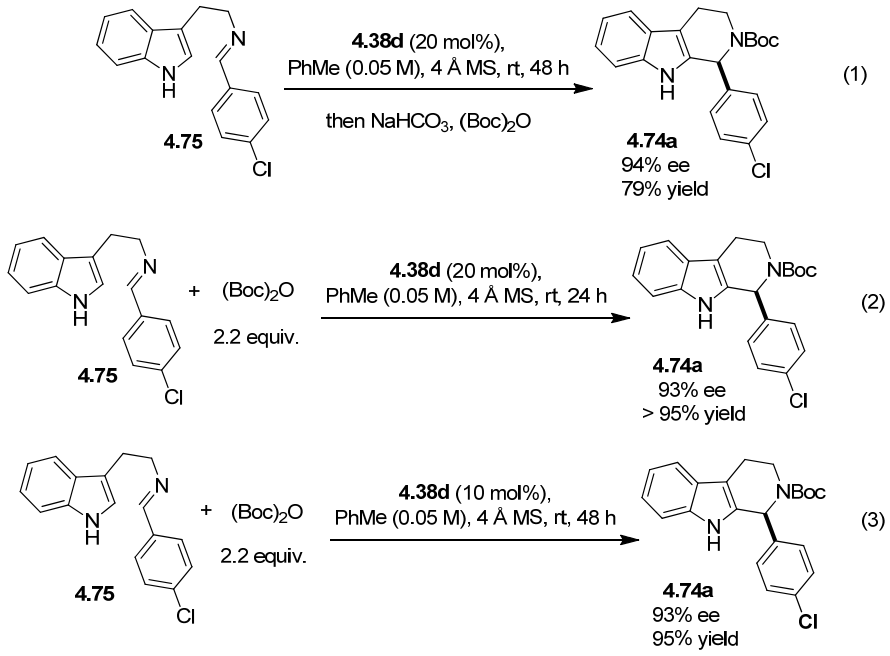
entry	additive (mol%)	yield (%)	ee (%)
1	Acetic acid (100)	37	85
2	Benzoic acid (100)	16	80
3	4-Trifluoromethyl benzoic acid (100)	41	79
4	Amberlyst 15 (200)	21	81
5	Amberlite CG-50 (200)	32	94
6	3,5-Bis(trifluoromethyl) benzoic acid (100)	81	36
7	Trifluoroacetic acid (100)	95	rac
8	Terephthalic acid (100)	37	94
9	Oxalic acid (100)	85	95
10	Malonic acid (100)	>95	93
11	Citric acid (100)	34	92
12[b]	Malonic acid (100)	48	94

[a] See footnote a, Table 4.3. [b] with 10 mol% of catalyst **4.38d**.

Continuing with the most promising catalyst **4.38d**, we began to explore reaction conditions in the presence of various acid additives (Table 4.4) in order to solve the problem of catalyst turnover. The rationale for these experiments is based on the idea that an achiral acid that by itself is incapable of promoting the racemic background reaction may serve to protonate the product thus freeing up the catalyst. Alternatively, a poorly soluble acidic additive may lead to the formation of relatively insoluble product salts, again facilitating catalyst turnover. A wide range of achiral Brønsted acid catalysts were tested. In most cases, identical or inferior results were obtained (entries 1-5). Much stronger acids offered better reactivity, but the reaction was either not selective or provided very poor selectivity (entries 6 & 7). Interestingly, strongly acidic but poorly soluble additives with more than one carboxylic acid group gave excellent yields and selectivities (entries 9 & 10), although terephthalic acid and citric acid were notable exceptions (entry 8 &11). In addition, employing 10 mol% of **4.38d** in the presence of 1 equivalent of malonic acid gave similar selectivity, albeit with lower reactivity (entry 12). Furthermore, it proved difficult to extend the use of malonic acid as an additive to other aldehydes.

At this point in the reaction development, the problem of product inhibition and low catalyst turnover remained to be solved. To explore this concept, we employed this alternate strategy where the preformed imine **4.75** was chosen as the starting material. It was considered that **4.75** was comparatively much less basic than the unprotected **4.74a** product (eq. 1, Scheme 4.23) and that in this way, the unprotected product, could efficiently be Boc-protected as it is formed, so that it would not act as a base and inhibit the catalyst.

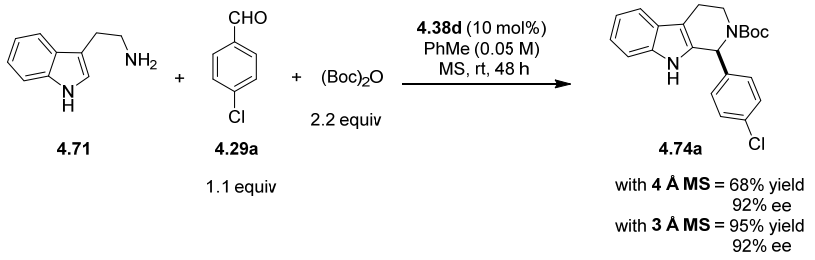
***Scheme 4.23*: Reaction with the Preformed Imine**



With an identical level of selectivity, a drastic improvement in reactivity was observed with the preformed imine. Under these conditions, with Boc anhydride already present in the reaction mixture, the product was formed in excellent yield and essentially no change in selectivity was observed (equation 2). Interestingly, lowering the catalyst loading to 10 mol% decreased the yield slightly, but no effect on selectivity was observed (equation 3). These experiments helped to circumvent the problem of product inhibition and also proved be a viable strategy that allowed for a reduction in catalyst loading to 10 mol%.

To facilitate this alternate pathway, we explored the in situ Boc-protection of the tetrahydro-β-carboline products. The aldehyde and tryptamine were allowed to first undergo imine formation in situ by stirring for 12 hours in the presence of molecular sieves prior to the addition of catalyst **4.38d** and $(Boc)_2O$. Upon performing the reaction under modified conditions resulted in drastic improvements in reactivity. Furthermore, replacing 4 Å MS with 3 Å MS increased the yield to 95% although the selectivity remained the same (Scheme 4.24).

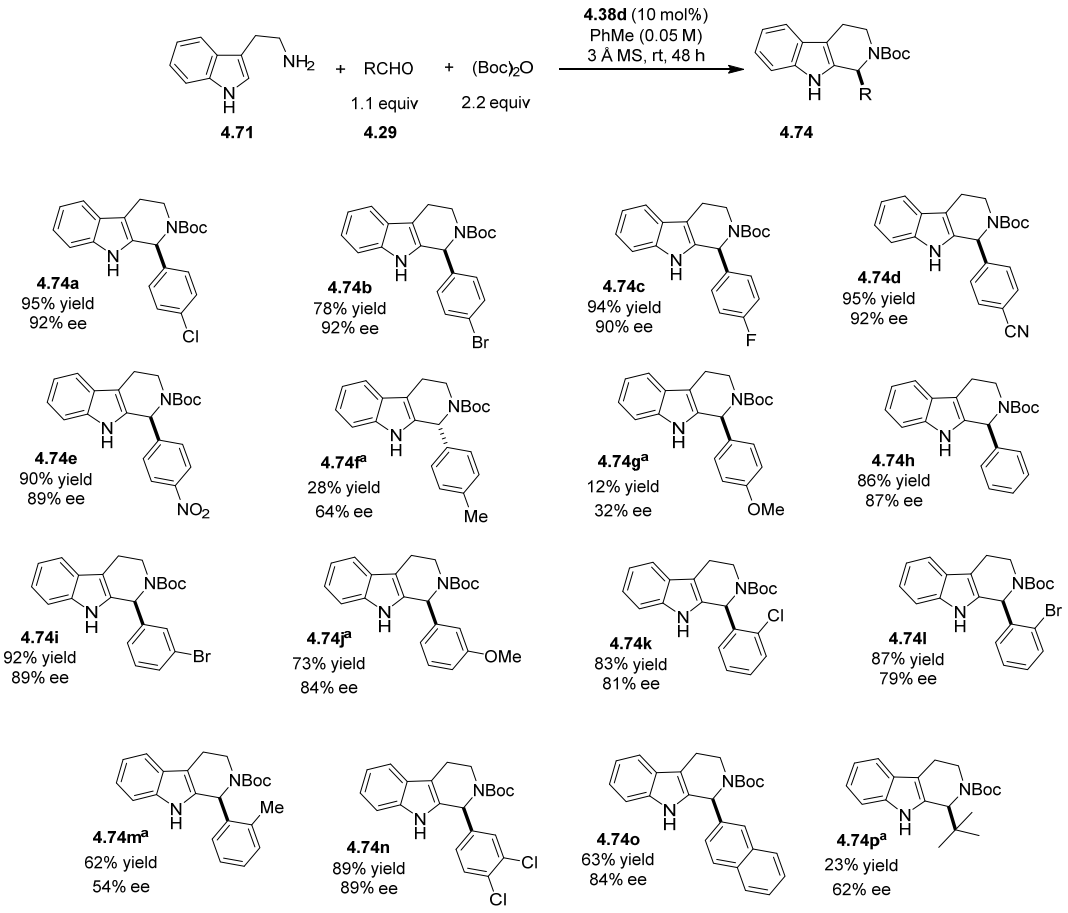
***Scheme 4.24*: Effect of Molecular Sieves**



4.4.2.2 Scope of Pictet-Spengler Reaction

A range of electronically diverse aldehydes were tested under these newly optimized conditions (Scheme 4.18). While, the presence of electron withdrawing substituents in the para position provided β-carbolines in high yields and enantioselectivities (**4.74a-4.74e**), substitution on other positions of the phenyl ring was also well accommodated. Simple benzaldehyde also produced the corresponding product (**4.74h**) in good selectivity. Surprisingly, a comparatively less reactive aldehyde with an electron-donating methoxy group provided product **4.74j** with good yield and selectivity. In contrast, substitution with the same substituent in the para position gave unsatisfactory results (**4.74g**). Ortho-tolualdehyde was also a viable substrate (**4.74m**). However, para-tolualdehyde, which is a much less reactive substrate in this reaction, provided inferior results **(4.74f).** In addition, disubstitution with two electron withdrawing groups on the aldehyde was also well tolerated to form **4.74i** in high yield and selectivity. Finally, aliphatic aldehydes provided poor yields and modest levels of selectivity in this reaction (Scheme 4.25).

***Scheme 4.25*: Scope of Pictet-Spengler Reaction**



[a] Reaction was run for 96h.

4.4.3 Summary

In summary, a selection of chiral Brønsted acid catalysts with a carboxylic acid group connected to a hydrogen bonding site such as (thio)urea were synthesized. A new concept involving internal stabilization of these catalysts by a conjugate base has been introduced. The potential of this design was demonstrated in the context of the first catalytic enantioselective three component Povarov reaction. In this reaction, secondary aromatic amines, such as indoline, and tetrahydroquinolines were formed in excellent yields and high levels of enantioselectivity. Another successful application of our newly introduced concept was demonstrated in the highly challenging enantioselective Pictet-Spengler reaction with unmodified substrates. A diverse collection of protected β-carbolines were prepared in good yields

and high level of enantioselectivities by combining unsubstituted tryptamine and a wide range of aldehydes.

Experimental Section

I Synthesis of Catalysts

General Procedure A: Preparation of catalysts **4.38a**–**4.38f**

To a solution of amino(thio)urea (2.59 mmol) in THF (0.1 M, 25.9 mL) in a 50 mL round bottom flask were added the anhydride (2.72 mmol) and triethylamine (2.85 mmol). The resulting mixture was stirred for 8 h. After full conversion of the amino(thio)urea as judged by TLC analysis, the reaction mixture was concentrated and then purified by flash silica gel chromatography using ethyl acetate as the eluent. The combined fractions were reduced to a volume of 40 mL and washed with 1 M HCl (2 × 20 mL). The combined aqueous layers were back-extracted with ethyl acetate (2 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Finally, the solvent was removed under reduced pressure and the resulting white solid was dried under high vacuum.

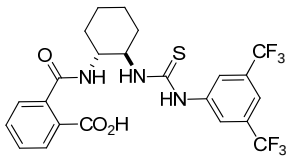
General Procedure B (4.41a to 4.42a)

To a solution of **4.41a** (2.3 mmol) in ethyl acetate (8.5 mL, 0.27 M), was added palladium on charcoal (10% w/w, 200 mg). The resulting suspension was placed under a hydrogen atmosphere following three cycles of a vacuum/hydrogen purge. The mixture was then stirred for 8 h at which point the starting material could no longer be detected by TLC analysis. Subsequently, 3,5-bistrifluoromethylisothiocyanate (1.2 equiv, 0.5 mL) was added and the reaction mixture stirred for an additional six hours. The reaction mixture was then concentrated under reduced pressure and the crude product purified by flash silica gel chromatography using EtOAc/Hexanes (1:1 v/v) as the eluent to give **4.42a** in 70 % yield. Compounds **4.42b** and **4.42c** were also prepared by following the above procedure.

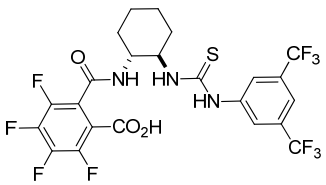
General Procedure C (4.43a to 4.44a)

To a solution of **4.43a** (1.47 mmol) in CH_2Cl_2 (2.1 mL, 0.7 M), TFA (2.1 mL) was added at 0 ºC. The resulting reaction mixture was then allowed to warm to room temperature. After stirring for 24 hours the reaction was quenched by adding saturated aqueous $NaHCO_3$ (10 mL). Dichloromethane was removed under reduced pressure and the remaining aqueous mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using a gradient of EtOAc/Hexanes (1:4) to EtOAc/Hexanes (3:2) to give **4.44a** in 60% yield. Compounds **4.44b** and **4.44c** were also prepared by following the above procedure.

2-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)carbamoyl)benzoic acid (4.38a): Following the general procedure **A**, monothiourea compound **4.37a** was combined with phthalic anhydride to provide **4.38a** as a white solid in 92% yield (1.3 g); mp = 169–171 ºC; R_f = 0.46 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +42.0 (c 1.0, EtOH); IR (KBr) 3323, 2927, 1691, 1572, 1535, 1318, 1207, 1121, 698 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 12.90 (s, 1H), 10.18 (s, 1H), 8.34 (br s, 1H), 8.29 (s, 2H), 8.08 (br s, 1H), 7.88–7.77 (m, 1H), 7.75 (s, 1H), 7.62–7.37 (comp, 3H), 4.40–4.18 (m, 1H), 4.02–3.86 (m, 1H), 2.29–2.14 (m, 1H), 2.08–1.91 (m, 1H), 1.86–1.66 (comp, 2H), 1.56–1.23 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 181.1, 169.5, 168.8, 142.9, 139.5, 131.8, 131.6, 130.9 (q, $J_{C\text{-}F}$ = 33.0 Hz), 130.2, 130.0, 128.6, 124.2 (q, $J_{C\text{-}F}$ = 272.1 Hz), 123.0, 117.0, 58.3, 52.9, 32.3, 32.2, 25.3, 25.2; *m/z* (ESI-MS) 534.0 $[M + H]^+$.

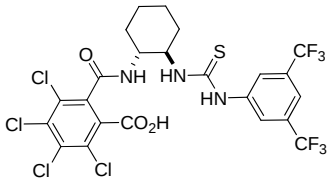


2-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)carbamoyl)-3,4,5,6-tetraflurobenzoic acid (4.38b): Following the general procedure **A**, monothiourea compound **4.37aa** was combined with tetrafluorophthalic anhydride to provide **4.38b** as a white solid in 90% yield (1.5 g); mp = 134–136 ºC; R_f = 0.17 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +43.0 (c 1.0, EtOH); IR (KBr) 3331, 2944, 1728,

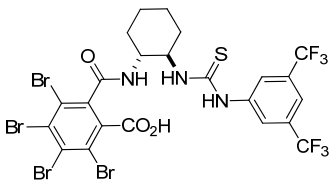


1633, 1541, 1475, 1384, 1278, 1181, 1108, 1066, 682 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 14.00 (br s, 1H), 10.02 (s, 1H), 8.69 (d, J = 8.3 Hz, 1H), 8.21 (s, 2H), 8.04 (br s, 1H), 7.70 (s, 1H), 4.47–4.14 (m, 1H), 3.97–3.82 (m, 1H), 2.29–2.03 (m, 1H), 2.01–1.85 (m, 1H), 1.79–1.58 (comp, 2H), 1.53–1.06 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 180.4, 162.5, 160.1, 146.1–143.8 (m), 144.6–142.4 (m), 142.0, 141.7–139.5 (m), 141.4–139.0 (m), 130.1 (q, $J_{C\text{-}F}$ = 32.7 Hz), 125.7 (q, $J_{C\text{-}F}$ = 272.6 Hz), 122.6–122.3 (m), 122.2–121.9 (m), 117.7–117.4 (m), 116.3–115.9 (m), 56.6, 52.3, 31.4, 31.0, 24.1; *m/z* (ESI-MS) 605.9 $[M + H]^+$.

2-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)carbamoyl)-3,4,5,6-tetrachlorobenzoic acid (4.38c): Following the general procedure **A**, monothiourea compound **4.37a** was combined with tetrachlorophthalic anhydride to provide **4.38c** as a white solid in 90% yield (1.6 g); mp = 170–172 ºC; R_f = 0.18 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +24.5 (c 1.0, EtOH); IR (KBr) 3328, 2932, 1709, 1627, 1541, 1385, 1317, 1278, 1182, 1131, 682, 653 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 14.25 (br s, 1H), 10.19 (s, 1H), 8.75 (d, J = 8.5 Hz, 1H), 8.27 (s, 2H), 7.99 (br s, 1H), 7.77 (s, 1H), 4.38–4.19 (m, 1H), 3.99–3.87 (m, 1H), 2.23–2.06 (m, 1H), 2.00–1.88 (m, 1H), 1.82–1.64 (comp, 2H), 1.48–1.20 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 180.9, 165.5, 163.6, 142.8, 136.6, 134.6, 133.8, 133.6, 131.0 (q, $J_{C\text{-}F}$ = 32.0 Hz), 130.2, 129.3, 124.2 (q, $J_{C\text{-}F}$ = 272.3 Hz), 123.0, 117.1, 57.8, 52.8, 32.2, 32.0, 24.9; *m/z* (ESI-MS) 669.7 ($^{35}Cl/^{35}Cl/^{35}Cl/^{35}Cl$) $[M + H]^+$; 671.6 ($^{35}Cl/^{35}Cl/^{35}Cl/^{37}Cl$) [M + H], 673.7 ($^{35}Cl/^{35}Cl/^{37}Cl/^{37}Cl$) $[M + H]^+$.



2-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)carbamoyl)-3,4,5,6-tetrabromobenzoic acid (4.38d): Following the general procedure **A**, monothiourea compound **4.37a** was combined with tetrabromophthalic anhydride to provide **4.38d** as a white solid in 94% yield (2.2 g); mp = 174–176 ºC; R_f = 0.21 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +10.7 (c 1.0, EtOH); IR (KBr) 3325, 2927, 1735, 1654, 1629, 1551, 1528, 1383, 1277, 1182, 1128, 678, 632 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ



14.1 (br s, 1H), 10.2 (s, 1H), 8.69 (d, J = 8.3 Hz, 1H), 8.27 (s, 2H), 7.99 (br s, 1H), 7.77 (s, 1H), 4.37–4.15 (m, 1H), 3.97–3.82 (m, 1H), 2.27–2.07 (m, 1H), 2.00–1.89 (m, 1H), 1.83–1.65 (comp, 2H), 1.51–1.22 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 180.9, 166.6, 165.0, 142.8, 139.0, 137.8, 130.9 (q, $J_{C\text{-}F}$ = 31.5 Hz), 130.7, 130.5, 124.1 (q, $J_{C\text{-}F}$ = 272.5 Hz), 123.4, 123.1, 122.4, 117.1, 57.7, 52.6, 32.0, 24.9; *m/z* (ESI-MS) 849.5 (^{79}Br/^{79}Br/^{79}Br/^{79}Br) $[M + H]^+$, 851.3 (^{79}Br/^{79}Br/^{79}Br/^{81}Br) $[M + H]^+$.

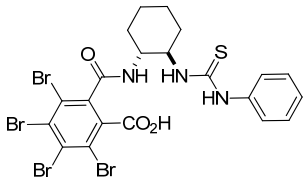
Tetrabutylammonium salt of 4.38d: Catalyst **4.38d** (20 mg, 0.024 mmol) was dissolved in 3 mL of dichloromethane. Tetrabutylammonium acetate (1 equiv, 7.1 mg) was added and the resulting solution was stirred for 12 h. Crystals suitable for X-ray crystallography were obtained through slow diffusion of hexanes into the dichloromethane solution at room temperature. The tetrabutylammonium salt of **4.38d** was characterized by X-ray crystallography (tetrabutylammonium cation not shown):

The requisite CIF has been deposited with the CCDC (deposition # 961074).

2-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)cyclohexyl)carbamoyl)-3,4,5,6-tetrabromobenzoic acid (4.38e): Following the general procedure **A**, monourea compound **4.37b** was combined with phthalic anhydride to provide **4.38e** as a white solid in 88% yield (1.9 g); mp > 200 ºC; R_f = 0.18 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ –1.0 (c 1.0, EtOH); IR (KBr) 3247, 2940, 2861, 1743, 1647, 1560, 1386, 1278, 1176, 1128, 684, 637 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 13.98 (br s, 1H), 9.22 (s, 1H), 8.55 (d, J = 8.4 Hz, 1H), 8.04 (s, 2H), 7.51 (s, 1H), 6.29 (d, J = 7.9 Hz,

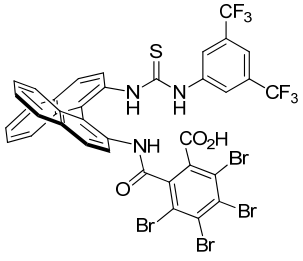
1H), 3.80–3.65 (m, 1H), 3.60–3.45 (m, 1H), 1.98–1.86 (m, 2H), 1.76–1.57 (comp, 2H), 1.46–1.18 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 165.7, 164.0, 154.4, 142.6, 138.3, 136.7, 130.6 (q, $J_{C\text{-}F}$ = 32.5 Hz), 129.8, 129.5, 123.3 (q, $J_{C\text{-}F}$ = 273.0 Hz), 122.4, 121.5, 117.2, 113.4, 52.1, 32.4, 31.1, 24.1, 23.9; *m/z* (ESI-MS) 833.4 (^{79}Br/^{79}Br/^{79}Br/^{79}Br) $[M + H]^+$, 855.3 (^{79}Br/^{79}Br/^{79}Br/^{79}Br) $[M + Na]^+$.

2,3,4,5-Tetrabromo-6-(((1*R*,2*R*)-2-(3-phenylthioureido)cyclohexyl)carbamoyl)benzoic acid (4.38f):



Following the general procedure **A**, monothiourea compound **4.37c** was combined with tetrabromophthalic anhydride to provide **4.38e** as a white solid in 85% yield (1.7 g); mp > 200 ºC; R_f = 0.15 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +3.83 (c 1.0, EtOH); IR (KBr) 3266, 2934, 1717, 1648, 1540, 1449, 1262, 695 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.06 (br s, 1H), 9.60 (br s, 1H), 8.67 (br s, 1H), 7.82–6.90 (comp, 5H), 4.45–4.07 (m, 1H), 3.96–3.65 (m, 1H), 2.39–2.04 (m, 2H), 1.81–1.52 (comp, 2H), 1.51–0.96 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 179.6, 165.7, 164.0, 139.2, 138.2, 136.9, 129.8, 129.5, 128.5, 124.0, 122.9, 122.5, 121.4, 56.9, 51.7, 31.4, 31.2, 24.1; *m/z* (ESI-MS) 713.5 (^{79}Br/^{79}Br/^{79}Br/^{79}Br) $[M + H]^+$, 715.4 (^{79}Br/^{79}Br/^{79}Br/^{81}Br) $[M + H]^+$, 717.7 (^{79}Br/^{79}Br/^{81}Br/^{81}Br) $[M + H]^+$.

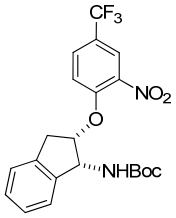
2-(((1*R*,2*R*)-2-(2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamoyl)-3,4,5,6-tetrabromobenzoic acid (4.40):



Tetrabromophthalic anhydride (0.95 mmol) was added to a solution of aminothiourea **4.39** (0.9 mmol) in THF (9.0 mL, 0.1 M). The resulting mixture was stirred for 24 h. After full conversion, the reaction mixture was concentrated and purified by flash silica gel chromatography with ethyl acetate as the eluent. The combined fractions were reduced to a volume of 40 mL and washed with 1 M HCl (2 × 20 mL). The combined aqueous layers were back-extracted with ethyl acetate (2 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure and drying under high vacuum, **4.40** was obtained as an off-white solid in 40% yield (0.55 g); mp > 200 ºC; R_f = 0.31 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ –3.0 (c 0.5, EtOH); IR (KBr) 3424, 1648, 1507,

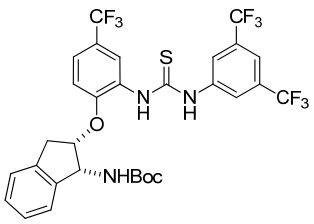
1381, 1278, 1179, 1135, 700, 681 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 14.3 (br s, 1H), 10.16–9.95 (comp, 2H), 9.31 (br s, 1H), 8.24–8.11 (comp, 2H), 8.09–7.98 (comp, 2H), 7.92 (br s, 2H), 7.84 (d, *J* = 8.8, 1H), 7.70 (s, 1H), 7.64 (d, *J* = 8.7, 1H), 7.59–7.39 (comp, 3H), 7.37–7.25 (m, 1H), 7.24–7.11 (m, 1H), 6.95 (d, *J* = 8.6, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 179.9, 165.9, 163.7, 144.4, 141.6, 141.4, 137.6, 136.7, 136.1, 135.5, 135.2, 133.9, 133.4, 133.3, 132.7, 132.6, 132.4, 132.3(7), 132.0, 130.7, 130.0(4), 130.0, 129.7(3) (q, $J_{C\text{-}F}$ = 33.0 Hz), 129.7 (q, $J_{C\text{-}F}$ = 32.2 Hz), 129.1–128.6 (m), 128.5–127.4 (m), 127.1–125.5 (m), 125.5–125.1 (m), 124.4–123.3 (m), 123.3 (q, $J_{C\text{-}F}$ = 272.7 Hz), 123.2 (q, $J_{C\text{-}F}$ = 272.7 Hz), 123.1–122.7 (m), 121.8, 121.6, 121.4, 117.2–116.8 (m), 109.8; *m/z* (ESI-MS) 1019.4 ($^{79}Br/^{79}Br/^{79}Br/^{79}Br$) $[M + H]^+$, 1023.2 ($^{79}Br/^{79}Br/^{81}Br/^{81}Br$) $[M + H]^+$.

***tert*-Butyl((1*R*,2*S*)-2-(2-nitro-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamate**



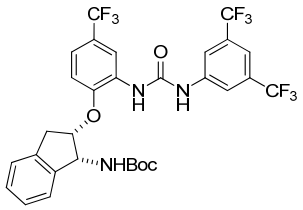
(4.41a): Following the reported procedure (4 mmol scale), compound **4.41a** was obtained as yellow solid in 75% yield (1.3 g); mp = 126–128 ºC; R_f = 0.35 (EtOAc/Hexanes 1:4 v/v); $[\alpha]_D^{20}$ +17.0 (c 1.0, EtOH); IR (KBr) 1693, 1545, 1517, 1335, 1289, 1161, 1128, 678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.37 (d, *J* = 6.9 Hz, 1H), 7.34–7.27 (comp, 3H), 7.22 (d, *J* = 6.9 Hz, 1H), 5.60–5.47 (comp, 2H), 5.39–5.31 (m, 1H), 3.35 (dd, *J* = 17.0, 4.7 Hz, 1H), 3.21 (app d, *J* = 17.0 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 153.8, 140.5, 139.6, 138.2, 131.2 (q, $J_{C\text{-}F}$ = 3.4 Hz), 128.6, 127.8, 125.1, 124.3, 123.9 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.3 (q, $J_{C\text{-}F}$ = 34.5 Hz), 123.0 (q, $J_{C\text{-}F}$ = 272.3 Hz), 115.8, 81.6, 80.1, 58.3, 36.9, 28.4; *m/z* (ESI-MS) 460.9 $[M + Na]^+$.

4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamate (4.42a): Following the general procedure **B**, compound **4.42a** was obtained as a white solid in 70% yield (1.1 g); mp = 186–188 ºC; R_f = 0.25 (EtOAc/Hexanes 1:4 v/v); $[\alpha]_D^{20}$ +56.4 (c 1.0, EtOH); IR (KBr) 2983, 1686, 1618, 1544, 1383, 1334, 1278, 1130, 1052, 700, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 9.38–9.22 (comp, 2H), 8.18 (s, 2H), 7.65 (s, 1H), 7.42 (d, *J* = 7.1 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.35–7.28

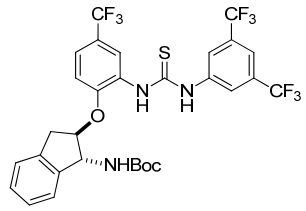


(comp, 2H), 7.27 (s, 1H), 7.20 (d, J = 7.1 Hz, 1H), 5.40–5.27 (m, 1H), 5.08 (d, J = 7.6 Hz, 1H), 4.85–4.69 (m, 1H), 3.47–3.26 (comp, 2H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 157.1, 151.4, 140.4, 139.3, 138.3, 132.0 (q, $J_{C\text{-}F}$ = 33.4 Hz), 131.6.–131.3 (m), 129.9.–129.6 (m), 128.1, 125.6, 125.4.–125.2 (m), 124.0 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.4 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.3 (app d, J = 3.2 Hz), 123.3, 122.2.–121.9 (m), 120.0, 119.9–119.6 (m), 118.7–118.2 (m), 83.4, 81.4, 58.0, 37.0, 28.5; *m/z* (ESI-MS) 701.9 [M + Na]$^+$.

***tert*-Butyl ((1*R*,2*S*)-2-(2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamate (4.42b):** Following the general procedure **B** (3,5-bistriflouromethylisocyanate (1.2 equiv, 0.5 mL) was used), compound **4.42b** was obtained as a white solid in 85% yield (1.3 g); mp = 108–110ºC; R_f = 0.40 (EtOAc/Hexanes 1:4 v/v); $[\alpha]_D^{20}$ +76.7 (c 0.5, EtOH); IR (KBr) 2985, 1671, 1615, 1551, 1475, 1387, 1279, 1245, 1131, 682 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.92 (s, 1H), 8.46 (s, 1H), 8.31 (s, 1H), 8.04 (s, 2H), 7.66 (s, 1H), 7.55–7.22 (comp, 6H), 7.21–7.08 (m, 1H), 5.43–5.21 (comp, 2H), 3.51–3.43 (m, 1H), 3.27–3.15 (m, 1H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 155.9, 152.1, 149.1, , 141.3, 140.8, 139.7, 130.9 (q, $J_{C\text{-}F}$ = 32.7 Hz), 128.9, 128.3, 127.2, 125.1, 124.5 (q, $J_{C\text{-}F}$ = 271.7 Hz), 123.2 (q, $J_{C\text{-}F}$ = 272.9 Hz), 124.1, 121.4 (q, $J_{C\text{-}F}$ = 32.6 Hz), 119.7 (app d, J = 4.1 Hz), 117.9–117..6 (m), 115.2–114.9, 114.8(8)–114.6, 112.9, 79.9, 78.2, 57.8, 37.2, 27.7; *m/z* (ESI-MS) 685.7 [M + Na]$^+$.



***tert*-Butyl((1*R*,2*R*)-2-(2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamate (4.42c):** Starting from *N*-Boc-(*R*,*R*)-*trans*-aminoindanol[8] and following the general procedure **B**, compound **4.42c** was obtained as an off white solid in 87% yield (1.4 g); mp = 85–87ºC; R_f = 0.25 (EtOAc/Hexanes 1:4 v/v); $[\alpha]_D^{20}$ -80.9 (c 0.5, EtOH); IR (KBr) 2983, 1618, 1474, 1444, 1383, 1334, 1278, 1130, 1052, 733, 681 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.47 (s, 1H), 9.68 (s, 1H), 8.26 (s, 2H), 8.20 (s, 1H), 7.76 (s, 1H), 7.58 (d, J = 8.4 Hz,



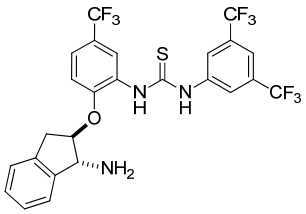
1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.24–7.15 (comp, 4H), 5.25–5.13 (comp, 2H), 3.54 (dd, *J* = 16.3 Hz, 7.1 Hz, 1H), 2.95 (dd, *J* = 16.2 Hz, 5.2 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 179.7, 155.6, 153.6, 141.4, 141.1, 138.9, 130.1 (q, $J_{C\text{-}F}$ = 33.0 Hz), 128.4, 128.1, 127.1, 124.6, 124.0, 124.2 (q, $J_{C\text{-}F}$ = 271.2 Hz), 123.5, 123.3, 123.2 (q, $J_{C\text{-}F}$ = 272.7 Hz), 123.0, 120.9 (q, $J_{C\text{-}F}$ = 32.4 Hz), 117.0, 114.5, 84.4, 78.2, 60.9, 36.3, 28.1; *m/z* (ESI-MS) 701.8 $[M + Na]^+$.

***tert*-Butyl ((1*R*,2*S*)-2-(2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamate (4.45a):** Following the general procedure **C**, compound **4.45a** was obtained as a white solid in 60% yield (0.512 g); mp = 86–88 ºC; R_f = 0.14 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +84.0 (c 0.5, EtOH); IR (KBr) 3284, 3049, 2965, 1617, 1545, 1473, 1443, 1382, 1334, 1174, 701, 682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s 1H), 7.76 (s, 2H), 7.53 (s, 1H), 7.34 (d, *J* = 8.6 Hz, 1H), 7.28–7.08 (comp, 4H), 7.02 (d, *J* = 8.6 Hz, 1H), 4.97–4.82 (m, 1H), 4.44 (d, *J* = 5.4 Hz, 1H), 3.17 (dd, *J* = 16.6, 5.5 Hz, 1H), 3.08 (dd, *J* = 16.7, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 151.9, 142.9, 139.9, 138.4, 131.8 (q, $J_{C\text{-}F}$ = 33.3 Hz), 129.0, 128.6, 127.7, 125.3, 124.9, 124.3 (q, $J_{C\text{-}F}$ = 33.3 Hz), 123.8 (q, $J_{C\text{-}F}$ = 271.6 Hz), 123.7–123.1 (m), 122.9 (q, $J_{C\text{-}F}$ = 272.6 Hz), 122.3–122.1 (m), 118.8–118.1 (m), 115.6–115.2 (m), 113.2, 82.4, 58.0, 36.5; *m/z* (ESI-MS) 850.1 $[M + H]^+$.

1-(2-(((1*R*,2*S*)-1-Amino-2,3-dihydro-1*H*-inden-2-yl)oxy)-5-(trifluoromethyl)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)urea (4.45b): Following the general procedure **C**, compound **4.45b** was obtained as a light brown solid in 72% yield (0.596 g); mp = 170–172 ºC; R_f = 0.15 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +39.3 (c 1.0, EtOH); IR (KBr) 3319, 3104, 1667, 1560, 1477, 1447, 1388, 1339, 1281, 1131, 702, 682 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.93 (s, 1H), 8.46 (s, 1H), 8.11 (s, 2H), 7.68 (s 1H), 7.64–7.57 (m, 1H), 7.542–7.40 (comp, 3H), 7.39–7.30 (comp, 3H), 5.48–5.39 (m, 1H), 5.03 (d, *J* = 5.6 Hz, 1H), 3.20 (dd, *J* = 16.9, 5.8 Hz, 1H), 3.31 (s, 2H), 3.20 (dd, *J* = 16.8, 2.8 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 152.4, 148.5, 141.6, 139.9, 137.8, 130.8 (q, $J_{C\text{-}F}$ = 33.1 Hz), 129.2 (app d, *J*

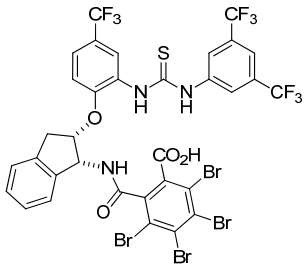
= 9.9 Hz), 127.3, 125.2, 124.9, 124.5 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.1 (q, $J_{C\text{-}F}$ = 272.2 Hz), 121.8 (q, $J_{C\text{-}F}$ = 32.2 Hz), 119.9–119.6 (m), 118.3–117.8 (m), 116.6–116.2 (m), 115.6, 114.8–114.4 (m), 113.2, 78.2, 55.8, 36.1; *m/z* (ESI-MS) 563.9 $[M + H]^+$.

***tert*-Butyl((1*R*,2*R*)-2-(2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-4-(trifluoromethyl)phenoxy)-**



2,3-dihydro-1*H*-inden-1-yl)carbamate (4.45c): Following the general procedure **C**, compound **4.45c** was obtained as an off white solid in 70% yield (0.597 g); mp = 54–56 ºC; R_f = 0.17 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ –65.4 (c 0.5, EtOH); IR (KBr) 3265, 3057, 2916, 1616, 1593, 1548, 1443, 1382, 1334, 1278, 1173, 1129, 701, 682 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 8.25 (s, 1H), 8.19 (s, 2H), 7.70 (s, 1H), 7.57–7.46 (comp, 2H), 7.45–7.35 (comp, 2H), 7.31–7.15 (comp, 4H), 4.97–4.88 (m, 1H), 4.49 (d, *J* = 4.4 Hz, 1H), 3.59 (dd, *J* = 16.5, 7.0 Hz 1H), 2.90 (dd, *J* = 16.4, 5.2 Hz, 1H), 1.25 (s, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 178.3, 152.9, 143.6, 142.9, 138.9, 130.5 (q, $J_{C\text{-}F}$ = 32.6 Hz), 129.9 (q, $J_{C\text{-}F}$ = 32.7 Hz), 129.4, 127.9, 126.9, 124.6, 124.4 (q, $J_{C\text{-}F}$ = 271.3 Hz), 124.3, 123.3 (q, $J_{C\text{-}F}$ = 272.6 Hz), 123.2–123.9 (m), 123.6–123.3 (m), 122.1–121.7 (m), 120.6 (q, $J_{C\text{-}F}$ = 32.4 Hz), 116.2–115.8 (m), 114.3, 86.9, 61.9, 36.3 ; *m/z* (ESI-MS) 579.7 $[M + H]^+$.

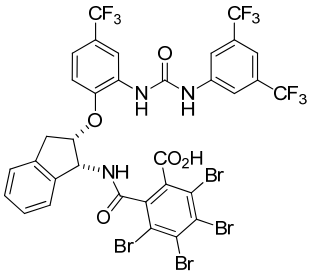
2-(((1*R*,2*S*)-2-(2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-4-(trifluoromethyl)phenoxy)-2,3-



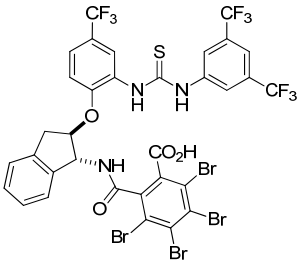
dihydro-1*H*-inden-1-yl)carbamoyl)-3,4,5,6-tetrabromobenzoic acid (4.46a): Following the general procedure **A**, monothiourea compound **4.45a** was combined with tetrabromophthalic anhydride to provide **4.46a** as a white solid in 85% yield (0.759 g); mp = 156–159 ºC; R_f = 0.57 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +65.8 (c 0.5, EtOH); IR (KBr) 3357, 1655, 1618, 1546, 1439, 1382, 1332, 1277, 1177, 1130, 681 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 14.32 (br s, 1H), 10.53 (br s, 1H), 9.45 (br s, 1H), 9.10–8.83 (m, 1H), 8.56 (s, 1H), 8.18 (s, 2H), 7.77 (s, 1H), 7.66–6.97 (comp, 6H), 6.03–5.77 (m, 1H), 5.48–5.26 (m, 1H), 3.43 (app d, *J* = 15.1 Hz, 1H), 3.17 (app d, *J* = 15.8 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 179.1, 166.4, 164.6, 151.8, 141.3, 140.4, 139.5, 137.5, 137.1, 130.2 (q, $J_{C\text{-}F}$

= 33.2 Hz), 129.8, 128.7, 128.2, 127.1, 126.4, 125.3, 124.9, 124.6, 124.2 (q, $J_{C\text{-}F}$ = 271.1 Hz), 123.4, 123.2 (q, $J_{C\text{-}F}$ = 272.8 Hz), 122.7, 122.2, 121.3, 120.8 (q, $J_{C\text{-}F}$ = 32.1 Hz), 117.2–116.7 (m), 114.5–114.0 (m), 79.7, 55.7, 36.9, *m/z* (ESI-MS) 1043.8 (^{79}Br/^{79}Br/^{79}Br/^{79}Br) $[M]^+$; 1044.5 (^{79}Br/^{79}Br/^{79}Br/^{79}Br) $[M]^+$.

2-(((1*R*,2*S*)-2-(2-(3-Argioureido)-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-yl)carbamoyl)-3,4,5,6-tetrabromobenzoic acid (4.46b): Following the general procedure **A**, monothiourea compound **4.45b** was combined with tetrabromophthalic anhydride to provide compound **4.46b** as a white solid in 90% yield (0.791 g); mp = 105–107 ºC; R_f = 0.56 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ +37.0 (c 0.5, EtOH); IR (KBr) 3338, 2938, 1712, 1652, 1549, 1444, 1386, 1338, 1179, 1133, 702, 682 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.41 (br s, 1H), 9.54 (br s, 1H), 9.03 (app d, *J* = 7.4 Hz, 1H), 8.45 (s, 1H), 8.23–7.98 (comp, 2H), 7.75 (s, 1H), 7.63 (s, 1H), 7.61–7.54 (comp, 2H), 7.49–6.71 (comp, 5H), 6.05–5.80 (m, 1H), 5.36–5.11 (m, 1H),), 3.56 (app d, *J* = 17.3 Hz, 1H), 3.27 (app d, *J* = 17.3 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 166.3, 164.4, 151.9, 148.5, 141.2, 140.2, 139.9, 137.3, 131.1 (q, $J_{C\text{-}F}$ = 31.5 Hz), 131.0 (q, $J_{C\text{-}F}$ = 32.6 Hz), 129.8, 129.4, 128.5, 125.1, 124.5, 124.6 (q, $J_{C\text{-}F}$ = 271.2 Hz), 123.3 (q, $J_{C\text{-}F}$ = 272.8 Hz), 122.6, 121.8, 121.5, 121.3, 121.0, 119.4, 116.7, 114.9, 114.6, 112.6, 80.4, 55.8, 37.3; *m/z* (ESI-MS) 1026.1 (^{79}Br/^{79}Br/^{79}Br/^{79}Br) $[M]^+$; 1028.2 (^{79}Br/^{79}Br/^{79}Br/^{81}Br) $[M]^+$.

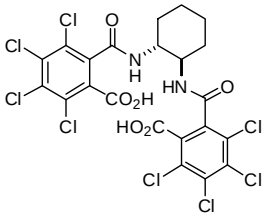


2-(((1*R*,2*R*)-2-(2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-4-(trifluoromethyl)phenoxy)-2,3-dihydro-1*H*-inden-1-yl)carbamoyl)-3,4,5,6-tetrabromobenzoic acid (4.46c): Following the general procedure **A**, monothiourea compound **4.45c** was combined with tetrabromophthalic anhydride to provide compound **4.46c** as an off white solid in 90% yield (0.804 g); mp = >200 ºC R_f = 0.45 (MeOH/EtOAc 5:95 v/v); $[\alpha]_D^{20}$ –92.5 (c 0.5, EtOH,); IR (KBr) 3417, 1652, 1548, 1382, 1332, 1278, 1174, 1131, 739, 681, 640 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.63 (br s, 1H), 9.92 (br s, 1H), 9.26 (d, *J* = 7.7 Hz, 1H), 8.25 (s, 2H), 8.11 (s, 1H), 7.75 (s, 1H), 7.61 (d, *J* = 8.1 Hz,



1H), 7.48 ((d, *J* = 8.1 Hz, 1H), 7.34 (app d, *J* = 6.4 Hz, 1H), 7.30–7.12 (comp, 3H, 5.64–5.51 (m, 1H), 5.14–5.0 (m, 1H), 3.62 (dd, *J* = 16.3 Hz, , *J* = 5.4 Hz, 1H), 3.02 (app d, *J* = 16.10 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 179.7, 166.4, 164.4, 153.7, 141.4, 139.9, 139.6, 137.6, 130.0 (q, J_{C-F} = 32.9 Hz), 129.6, 128.4, 128.1, 127.1, 125.3, 125.0, 124.7, 123.2 (q, J_{C-F} = 272.6 Hz), 124.0–123.8 (m), 123.8–123.6 (m), 123.5–123.1 (m), 122.8, 121.3, 121.0, 120.7, 120.5, 117.3–116.8 (m), 114.2, 83.4, 59.6, 36.8; *m/z* (ESI-MS) 1043.3 (^{79}Br/^{79}Br/^{79}Br/^{79}Br) $[M + H]^+$; 1046.3 (^{79}Br/^{79}Br/^{81}Br/^{81}Br) $[M]^+$.

6,6'-(((1*R*,2*R*)-Cyclohexane-1,2-diylbis(azanediyl))bis(carbonyl))bis(2,3,4,5-tetrachlorobenzoic acid)



(4.47): Tetrachlorophthalic anhydride (1.05 mmol) and triethylamine (1.05 mmol) were added to a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine (0.5 mmol) in THF (5.0 mL, 0.1 M). The resulting mixture was stirred for 12 h. The solvent was removed and the residue was re-dissolved in ethyl acetate (100 mL). This solution was washed with 1 M HCl (2 × 20 mL). The combined aqueous layers were back-extracted with ethyl acetate (2 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure and drying under high vacuum, **4.47** was obtained as a white solid in 67% yield (230 mg); mp = 198–200 ºC; R_f = 0.13 (MeOH/EtOAc 20:80 v/v); $[\alpha]_D^{20}$ –35.8 (c 0.2, EtOH,); IR (KBr) 3285, 2934, 1701, 1635, 1523, 1343, 1322, 1298, 1266, 649 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.2 (br s, 2H), 8.69–8.46 (comp, 2H), 3.98–3.77 (comp, 2H), 1.97–1.82 (comp, 2H), 1.73–1.54 (comp, 2H), 1.52–1.22 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 165.2, 163.1, 135.7, 135.4, 132.9, 132.8, 129.7, 128.6, 50.9, 28.5, 22.4, 22.3; *m/z* (ESI-MS) 686.5 (^{35}Cl/^{35}Cl/^{35}Cl/^{35}Cl) $[M + H]^+$, 688.6 (^{35}Cl/^{35}Cl/^{35}Cl/^{37}Cl) $[M + H]^+$.

II Enantioselective Povarov Reaction:Preparation and characterization data of products

General procedure D

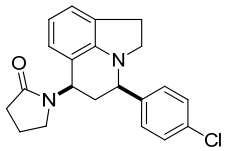
A flame dried vial was charged with aldehyde (0.4 mmol, 2 equiv), **4.38d** (34 mg, 0.04 mmol, 0.2 equiv) and powdered 4Å MS (100 mg). Freshly distilled toluene (4 mL) was added and the resulting mixture

was cooled to –55 °C over 15 min. The aromatic amine was then added (0.2 mmol, 1 equiv). After five minutes, 1-vinylpyrrolidin-2-one (**4.49**) (43 μL, 0.4 mmol, 2 equiv) was added and the reaction mixture was stirred at –55 °C. When indoline could no longer be detected by TLC analysis, triethylamine (1 mmol, 0.14 mL) was added. The reaction mixture was allowed to warm to rt, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated under reduced pressure and the crude product purified by flash chromatography.

General procedure E

A flame dried vial was charged with aldehyde (0.4 mmol, 2 equiv), **4.38d** (34 mg, 0.04 mmol, 0.2 equiv) and powdered 4Å MS (100 mg). Freshly distilled toluene (3 mL) was added and the resulting mixture was cooled to –55 °C over 15 min. A solution of the aromatic amine (0.2 mmol, 1 equiv) in 1 mL of toluene was then added. After five minutes, 1-vinylpyrrolidin-2-one (**4.49**) (43 μL, 0.4 mmol, 2 equiv) was added and the reaction mixture was stirred at –55 °C. When the amine could no longer be detected by TLC analysis, triethylamine (1 mmol, 0.14 mL) was added. The reaction mixture was allowed to warm to rt, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated under reduced pressure and the crude product purified by flash chromatography.

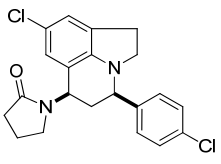
1-((4*R*,6*R*)-4-(4-chlorophenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one



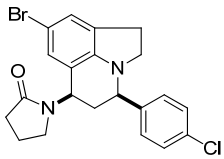
(4.50a): Following the general procedure **D**, compound **4.50a** was obtained as a white solid in 94% yield (66.2 mg); mp = 167–168 °C; R_f = 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +73.6 (c 0.4, $CHCl_3$, 92% *ee*); IR (KBr) 2952, 2912, 1686, 1478, 1455, 1270, 1013, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.28 (comp, 4H), 7.02 (d, *J* = 6.8 Hz, 1H), 6.81–6.66 (comp, 2H), 5.68 (dd, *J* = 10.7, 7.1 Hz, 1H), 3.99 (dd, *J* = 10.2, 3.4 Hz, 1H), 3.35–3.22 (comp, 3H), 3.02–2.90 (m, 1H), 2.88–2.80 (m, 1H), 2.78–2.68 (m, 1H), 2.57–2.38 (comp, 2H), 2.22–2.09 (comp, 2H), 2.07–1.96 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 150.8, 140.1, 133.2, 129.8, 128.8, 128.2, 124.2, 123.6, 119.4, 117.2, 62.3, 53.3, 47.6, 42.3, 36.6, 31.3, 28.7, 18.1; *m/z* (ESI–MS)

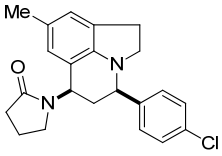
353.5 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 70/30, Flow rate = 1 mL/min, UV = 230 nm, t_R = 8.2 min (major) and t_R = 14.8 min (minor). The absolute configuration was assigned by analogy.

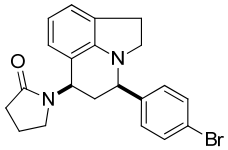
1-((4*R*,6*R*)-8-chloro-4-(4-chlorophenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (4.50b): Following the general procedure **E**, compound **4.50b** was obtained as a light brown solid in 59% yield (45.6 mg); mp =178–179 °C; R_f= 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +37.9 (c 0.3, $CHCl_3$, 84% *ee*); IR (KBr) 2961, 2929, 2835, 1683, 1480, 1466, 1286, 1202, 859, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (comp, 4H), 6.98 (s, 1H), 6.72 (s, 1H), 5.63 (dd, *J* = 11.2, 6.6 Hz, 1H), 3.97 (dd, *J* = 10.8, 2.8 Hz, 1H), 3.37–3.22 (comp, 3H), 3.03–2.88 (m, 1H), 2.86–2.70 (comp, 2H), 2.58–2.38 (comp, 2H), 2.22–1.99 (comp, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 149.4, 139.6, 133.6, 131.8, 129.0, 128.3, 124.5, 124.1, 123.9, 118.6, 62.4, 53.5, 47.4, 42.3, 36.4, 31.2, 28.6, 18.1; *m/z* (ESI–MS) 387.4 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 230 nm, t_R = 13.0 min (major) and t_R = 25.2 min (minor). The absolute configuration was assigned by analogy.

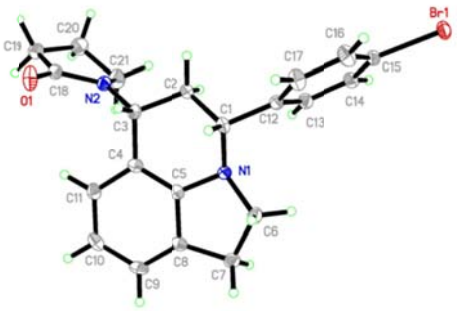


1-((4*R*,6*R*)-8-bromo-4-(4-chlorophenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (4.50c): Following the general procedure **E**, compound **4.50c** was obtained as a light brown solid in 76% yield (65.7 mg); mp = 184–185 °C; R_f = 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +19.2 (c 0.5, $CHCl_3$, 93% *ee*); IR (KBr) 2950, 2831, 1686, 1488, 1457, 1271, 1209, 822, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.31 (comp, 4H), 7.10 (s, 1H), 6.84 (s, 1H), 5.62 (dd, *J* = 11.0, 6.8 Hz, 1H), 3.96 (dd, *J* = 10.4, 3.2 Hz, 1H), 3.33–3.21 (comp, 3H), 3.00–2.88 (m, 1H), 2.87–2.78 (m, 1H), 2.78–2.68 (m, 1H), 2.58–2.36 (comp, 2H), 2.17–2.00 (comp, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 150.1, 139.6, 133.4, 132.1, 128.9, 128.2, 126.8, 126.7, 118.8, 111.2, 62.1, 53.3, 47.4, 42.3, 36.4, 31.2, 28.5, 18.1; *m/z* (ESI–MS) 433.4 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.4 min (major) and t_R = 16.4 min (minor). The absolute configuration was assigned by analogy.



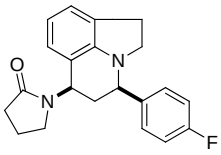
1-((4*R*,6*R*)-4-(4-chlorophenyl)-8-methyl-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (4.50d):  Following the general procedure **E**, compound **4.50d** was obtained as a white solid in 82% yield (60 mg); mp = 110–111 °C; R_f = 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +24.5 (c 0.5, $CHCl_3$, 90% *ee*); IR (KBr) 2947, 2915, 2886, 2820, 1686, 1487, 1426, 1268, 1014, 841, 525 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.26 (comp, 4H), 6.86 (s, 1H), 6.57 (s, 1H), 5.65 (dd, *J* = 10.9, 6.9 Hz, 1H), 3.91 (dd, *J* = 10.9, 2.5 Hz, 1H), 3.37–3.22 (comp, 3H), 3.02–2.87 (m, 1H), 2.86–2.75 (m, 1H), 2.73–2.60 (m, 1H), 2.58–2.39 (comp, 2H), 2.25 (s, 3H), 2.20–1.96 (comp, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 148.8, 140.3, 133.2, 130.2, 129.0, 128.8, 128.3, 124.6, 124.3, 117.0, 62.8, 53.8, 47.6, 42.3, 36.8, 31.4, 28.8, 21.0, 18.1; *m/z* (ESI–MS) 368.1 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 15.9 min (major) and t_R = 33.3 min (minor). The absolute configuration was assigned by analogy.

1-((4*R*,6*R*)-4-(4-bromophenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (4.50e):  Following the general procedure **D**, compound **4.50e** was obtained as a white solid in 86% yield (68.1 mg); mp = 201–202 °C; R_f = 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +17.3 (c 0.4, $CHCl_3$, 95% *ee*); IR (KBr) 2950, 2841, 1683, 1481, 1457, 1269, 1023, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 6.8 Hz, 1H), 6.79–6.69 (comp, 2H), 5.67 (dd, *J* = 10.6, 7.2 Hz, 1H), 3.98 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.37–3.22 (comp, 3H), 3.05–2.91 (m, 1H), 2.89–2.79 (m, 1H), 2.78–2.67 (m, 1H), 2.58–2.37 (comp, 2H), 2.22–2.08 (comp, 2H), 2.07–1.95 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 150.8, 140.7, 131.9, 129.9, 128.7, 124.3, 123.7, 121.4, 119.6, 117.3, 62.4, 53.4, 47.6, 42.3, 36.6, 31.4, 28.8, 18.2; *m/z* (ESI–MS) 399.8 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 230 nm, t_R = 12.7 min (major) and t_R = 28.8 min (minor). The absolute configuration of **3e** was assigned by X-ray crystallography:



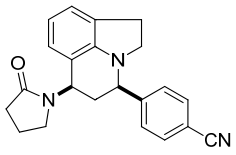
Compound **4.50e** was crystallized from hexanes/dichloromethane through slow diffusion at room temperature. The requisite CIF has been deposited with the CCDC (deposition # 960973).

1-((4*R*,6*R*)-4-(4-fluorophenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one



(4.50f): Following the general procedure **D**, compound **4.50f** was obtained as a white solid in 76% yield; mp = 181–182 °C; R_f = 0.29 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ + 55.6 (c 0.4, $CHCl_3$, 93% *ee*); IR (KBr) 2959, 2840, 1682, 1482, 1269, 1152, 842, 779 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.34 (comp, 2H), 7.13–7.00 (comp, 3H), 6.82–6.66 (comp, 2H), 5.69 (dd, *J* = 11.0, 6.8 Hz, 1H), 3.99 (dd, *J* = 10.6, 2.3 Hz, 1H), 3.37–3.22 (comp, 3H), 3.02–2.90 (m, 1H), 2.88–2.79 (m, 1H), 2.77–2.67 (m, 1H), 2.56–2.38 (comp, 2H), 2.26–2.09 (comp, 2H), 2.08–1.96 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 163.4, 161.5, 151.3, 137.7 (d, J_{C-F} = 3.2 Hz), 130.2, 128.7 (d, J_{C-F} = 8.1 Hz), 124.5, 123.9, 119.7, 117.5, 115.8 (d, J_{C-F} = 21.4 Hz), 62.5, 53.7, 48.0, 42.7, 37.1, 31.6, 29.1, 18.5; *m/z* (ESI–MS) 338.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 230 nm, t_R = 11.0 min (major) and t_R = 25.9 min (minor). The absolute configuration was assigned by analogy.

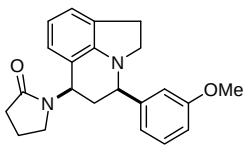
4-((4*R*,6*R*)-6-(2-oxopyrrolidin-1-yl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-4-yl)benzonitrile (4.50g):



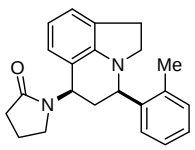
Following the general procedure **D**, compound **4.50g** was obtained as a white solid in 92% yield; mp = 124–126 °C; R_f = 0.20 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +8.7 (c 0.4, $CHCl_3$, 91% *ee*); IR (KBr) 2953, 2839, 2227, 1678, 1458, 1286, 1146, 1058, 730, 561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3

Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.12–7.01 (m, 1H), 6.82–6.73 (comp, 2H), 5.69 (dd, *J* = 10.2, 7.6 Hz, 1H), 4.08 (dd, *J* = 9.5, 4.2 Hz, 1H), 3.33–3.22 (comp, 3H), 3.06–2.95 (m, 1H), 2.92–2.82 (m, 1H), 2.79–2.67 (m, 1H), 2.55–2.41 (comp, 2H), 2.21–2.11 (comp, 2H), 2.07–1.97 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 150.3, 146.9, 132.7, 130.0, 127.9, 124.4, 123.9, 120.2, 118.6, 117.5, 111.7, 62.9, 53.6, 47.6, 42.4, 36.4, 31.4, 28.9, 18.2; *m/z* (ESI–MS) 344.3 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 70/30, Flow rate = 1 mL/min, UV = 230 nm, t_R = 12.9 min (major) and t_R = 31.0 min (minor). The absolute configuration was assigned by analogy.

1-((4*R*,6*R*)-4-(3-methoxyphenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (4.50h): Following the general procedure **D**, compound **4.50h** was obtained as a white solid in 93% yield (64.7 mg); mp = 165–167 °C; R_f = 0.21 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +32.3 (c 0.4, $CHCl_3$, 92% *ee*); IR (KBr) 2950, 2841, 1675, 1597, 1460, 1420, 1282, 1036, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (app t, *J* = 8.2 Hz, 1H), 7.13–6.96 (comp, 3H), 6.88–6.81 (m, 1H), 6.80–6.67 (comp, 2H), 5.68 (dd, *J* = 11.1, 6.6 Hz, 1H), 3.99 (dd, *J* = 10.7, 2.5 Hz, 1H), 3.82 (s, 3H), 3.37 (app t, *J* = 8.4 Hz, 1H), 3.34–3.22 (comp, 2H), 3.03–2.92 (m, 1H), 2.89–2.81 (m, 1H), 2.80–2.71 (m, 1H), 2.60–2.39 (comp, 2H), 2.27–2.11 (comp, 2H), 2.10–1.95 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 159.8, 160.0, 143.2, 129.9, 129.6, 124.1, 123.5, 119.2, 119.1(7), 117.1, 113.0, 112.2, 62.8, 55.1, 53.3, 47.7, 42.3, 36.6, 31.3, 28.7, 18.1; *m/z* (ESI–MS) 349.6 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 70/30, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.6 min (major) and t_R = 15.6min (minor). The absolute configuration was determined by analogy.

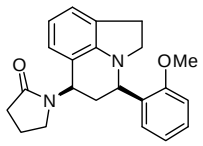


1-((4*R*,6*R*)-4-(o-tolyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (4.50i): Following the general procedure **D**, compound **4.50i** was obtained as a white solid in 80% yield (53.1 mg); mp = 89–91 °C; R_f = 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +19.2 (c 0.5, $CHCl_3$, 92% *ee*); IR (KBr) 2947, 2926, 2846, 1686, 1457, 1285, 1191, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 7.34–7.12 (comp, 3H), 7.03 (d, *J* = 7.0 Hz, 1H),

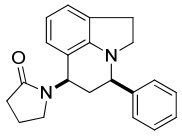


6.83–6.65 (comp, 2H), 5.70 (app t, J = 8.9 Hz, 1H), 4.36–4.22 (m, 1H), 3.46–3.33 (m, 1H), 3.27 (app t, *J* = 6.9 Hz, 2H), 3.06–2.92 (m, 1H), 2.90–2.79 (m, 1H), 2.76–2.64 (m, 1H), 2.57–2.41 (m, 2H), 2.36 (s, 3H), 2.18–2.07 (comp, 2H), 2.05–1.93 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 151.4, 139.3, 135.1, 130.6, 130.0, 127.1, 126.4, 124.3, 123.5, 123.4(8), 119.2, 117.3, 58.2, 53.5, 47.7, 42.4, 35.5, 31.4, 28.8, 19.2, 18.2; *m/z* (ESI–MS) 333.6 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 230 nm, t_R = 8.2 min (major) and t_R = 12.8 min (minor). The absolute configuration was assigned by analogy.

1-((4*R*,6*R*)-4-(2-methoxyphenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (4.50j): Following the general procedure **D**, compound **4.50j** was obtained as a white solid in 59% yield (41.1 mg); mp = 83–84 °C; R_f = 0.21 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +19.2 (c 0.5, $CHCl_3$, 93% *ee*); IR (KBr) 2952, 2837, 1683, 1457, 1243, 1026, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.29–7.22 (m, 1H), 7.05–6.98 (comp, 2H), 6.89 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.79–6.66 (comp, 2H), 5.70 (dd, *J* = 11.5, 6.4 Hz, 1H), 4.57 (dd, *J* = 11.1, 2.2 Hz, 1H), 3.82 (s, 3H), 3.44 (app t, *J* = 8.2 Hz, 1H), 3.27 (app t, *J* = 7.0 Hz, 2H), 3.05–2.93 (m, 1H), 2.89–2.80 (m, 1H), 2.78–2.67 (m, 1H), 2.58–2.37 (comp, 2H), 2.25–2.16 (m, 1H), 2.12–1.95 (comp, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 156.7, 151.4, 137.9, 130.1, 129.4, 128.2, 127.2, 124.3, 123.4, 120.7, 119.3, 110.5, 55.3, 55.1, 53.4, 47.7, 42.4, 35.0, 31.5, 28.8, 18.2; *m/z* (ESI–MS) 349.6 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.7 min (major) and t_R = 12.1 min (minor). The absolute configuration was assigned by analogy.



1-((4*R*,6*R*)-4-phenyl-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (4.50k): Following the general procedure **D**, compound **4.50k** was obtained as a white solid in 71% yield (45.1 mg); mp = 171–172 °C; R_f = 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +6.4 (c 0.5, $CHCl_3$, 79% *ee*); IR (KBr) 2949, 2914, 1689, 1478, 1450, 1272, 776 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.40 (comp, 2H), 7.37 (app t, *J* = 7.5 Hz, 2H), 7.34–7.27



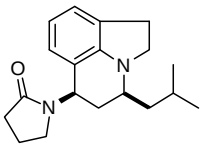
(m, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.83–6.66 (comp, 2H), 5.69 (dd, *J* = 11.3, 6.5 Hz, 1H), 4.02 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.42–3.21 (comp, 3H), 3.04–2.92 (m, 1H), 2.90–2.81 (m, 1H), 2.79–2.71 (m, 1H), 2.56–2.39 (comp, 2H), 2.27–2.11 (comp, 2H), 2.08–1.94 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 141.6, 129.9, 128.7, 127.7, 126.9, 124.3, 123.6, 119.3, 117.3, 63.0, 53.4, 47.8, 42.4, 36.8, 31.4, 28.8, 18.2; *m/z* (ESI–MS) 319.5 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.3 min (major) and t_R = 16.8 min (minor). The absolute configuration was assigned by analogy.

1-((4*R*,6*R*)-4-(3,4-dichlorophenyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (4.50l): Following the general procedure **D**, compound **4.50l** was obtained as a white solid in 88% yield (68.1 mg); mp = 151–152 °C; R_f = 0.30 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +19.2 (c 0.5, $CHCl_3$, 87% *ee*); IR (KBr) 2948, 2829, 1685, 1480, 1268, 1012, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 2.0 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.24 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.06–7.00 (m, 1H), 6.79–6.70 (comp, 2H), 5.66 (app t, 1H, *J* = 8.0 Hz), 3.96 (dd, *J* = 8.9, 4.8 Hz, 1H), 3.34–3.23 (comp, 3H), 3.05–2.92 (m, 1H), 2.90–2.80 (m, 1H), 2.79–2.68 (m, 1H), 2.59–2.37 (comp, 2H), 2.20–2.09 (comp, 2H), 2.04–1.98 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 150.5, 142.0, 132.9, 131.6, 130.8, 129.9, 128.9, 126.4, 124.3, 123.8, 119.9, 117.3, 62.1, 53.5, 47.6, 42.4, 36.6, 31.4, 28.8, 18.2; *m/z* (ESI–MS) 387.4 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 70/30, Flow rate = 1 mL/min, UV = 230 nm, t_R = 7.4 min (major) and t_R = 13.2 min (minor). The absolute configuration was assigned by analogy.

1-((4*R*,6*R*)-4-isopropyl-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (4.50m): Following the general procedure **D**, compound **4.50m** was obtained as a white solid in 96% yield (54.5 mg); mp = 159–160 °C; R_f = 0.29 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ 24.5 (c 0.5, $CHCl_3$, 94% *ee*); IR (KBr) 2956, 2842, 1683, 1460, 1420, 1287, 1269, 1206, 776, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 6.9 Hz, 1H), 6.71–6.56 (comp, 2H), 5.53 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.56 (app t, *J* = 7.5 Hz, 1H), 3.33–3.17 (comp, 2H), 3.02–2.76 (comp, 4H),

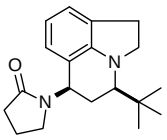
2.57–2.45 (comp, 2H), 2.14–1.96 (comp, 3H), 1.95–1.77 (comp, 2H), 0.96 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 151.6, 129.5, 124.2, 123.3, 118.8, 117.4, 62.3, 52.2, 47.9, 42.4, 31.5, 28.8, 28.7, 25.7, 19.1, 18.2, 14.8; *m/z* (ESI–MS) 285.9 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 85/15, Flow rate = 1 mL/min, UV = 230 nm, t_R = 7.0 min (major) and t_R = 8.0 min (minor). The absolute configuration was assigned by analogy.

1-((4*S*,6*R*)-4-isobutyl-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one (4.50n):



Following the general procedure **D**, compound **4.50n** was obtained as a colorless oil in 53% yield (31.6 mg); R_f = 0.30 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +19.2 (c 0.5, $CHCl_3$, 93% *ee*); IR (neat) 2944, 2840, 1678, 1454, 1277, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, *J* = 6.9 Hz, 1H), 6.79–6.56 (comp, 2H), 5.54 (dd, *J* = 11.6, 6.6 Hz, 1H), 3.74–3.60 (m, 1H), 3.32–3.15 (comp, 2H), 3.09–2.74 (comp, 4H), 2.57–2.39 (comp, 2H), 2.17 (ddd, *J* = 12.8, 6.5, 1.9 Hz, 1H), 2.08–1.94 (comp, 2H), 1.87–1.67 (comp, 2H), 1.63–1.51 (m, 1H), 1.47–1.32 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 151.3, 129.7, 124.3, 123.3, 119.1, 117.6, 56.2, 52.8, 47.3, 43.0, 42.4, 32.5, 31.5, 28.8, 24.5, 24.2, 22.0, 18.2; *m/z* (ESI–MS) 299.6 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 7.7 min (major) and t_R = 9.8 min (minor). The absolute configuration was assigned by analogy.

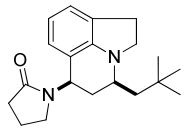
1-((4*R*,6*R*)-4-(tert-butyl)-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one



(4.50o): Following the general procedure **D**, compound **4.50o** was obtained as a colorless oil in 65% yield; R_f = 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +5.0 (c 0.8, $CHCl_3$, 99% *ee*); IR (neat) 2948, 2848, 1674, 1450, 1270, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 6.7 Hz, 1H), 6.78–6.54 (comp, 2H), 5.52 (dd, *J* = 11.8, 6.0 Hz, 1H), 3.87–3.67 (m, 1H), 3.32–3.18 (comp, 2H), 3.13–3.03 (m, 1H), 3.02–2.76 (comp, 3H), 2.58–2.45 (comp, 2H), 2.14–1.85 (comp, 4H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 151.7, 128.9, 123.8, 123.2, 118.8, 117.5, 66.3, 55.8, 48.0, 42.3, 34.0, 31.5, 29.3, 29.1, 28.3, 18.2; *m/z* (ESI–MS) 299.7 $[M+ H]^+$;

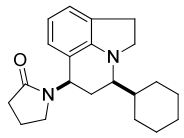
HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 0.5 mL/min, UV = 230 nm, t_R = 32.3 min (major). The absolute configuration was assigned by analogy.

1-((4*S*,6*R*)-4-neopentyl-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one



(4.50p): Following the general procedure **D**, compound **4.50p** was obtained as a colorless oil in 91% yield (56.9 mg); R_f = 0.30 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +7.4 (c 0.5, $CHCl_3$, 95% *ee*); IR (neat) 2950, 2850, 1680, 1456, 1274, 1206, 855, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 6.7 Hz, 1H), 6.82–6.55 (comp, 2H), 5.55 (dd, *J* = 11.6, 6.4 Hz, 1H), 3.71 (app t, *J* = 7.6 Hz, 1H), 3.30–3.22 (m, 1H), 3.21–3.14 (m, 1H), 3.03–2.78 (comp, 4H), 2.54–2.43 (comp, 2H), 2.18 (ddd, *J* = 13.0, 6.4, 2.1 Hz, 1H), 2.03–1.90 (comp, 3H), 1.77 (d, *J* = 14.0 Hz, 1H), 1.35 (dd, *J* = 14.5, 7.9 Hz, 1H), 0.95 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 151.6, 130.3, 124.3, 123.4, 119.3, 117.9, 55.5, 53.2, 47.3, 46.9, 42.3, 35.8, 31.5, 30.3, 29.9, 28.7, 28.6; *m/z* (ESI–MS) 314.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.9 min (major) and t_R = 11.9 min (minor). The absolute configuration was assigned by analogy.

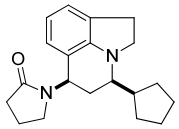
1-((4*R*,6*R*)-4-cyclohexyl-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one



(4.50q): Following the general procedure **D**, compound **4.50q** was obtained as a white solid in 51% yield (33.1 mg); mp = 156–158 °C; R_f = 0.29 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^D_{20}$ +23.5 (c 0.2, $CHCl_3$, 90% ee); IR (KBr) 2926, 2848, 1686, 1458, 1267, 1207, 776, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 6.8 Hz, 1H), 6.76–6.53 (comp, 2H), 5.52 (dd, *J* = 11.3, 6.5 Hz, 1H), 3.56 (app t, *J* = 7.0 Hz, 1H), 3.34–3.09 (comp, 2H), 3.01–2.77 (comp, 4H), 2.61–2.34 (comp, 2H), 2.05–1.86 (comp, 5H), 1.84–1.77 (comp, 2H), 1.75–1.65 (comp, 2H), 1.52 (d, *J* = 11.9 Hz, 1H), 1.31–1.14 (comp, 4H), 1.09–0.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 151.8, 129.5, 124.2, 123.3, 118.7, 117.3, 62.2, 52.3, 48.0, 42.4, 39.8, 31.5, 29.9, 28.8, 27.3, 26.9, 26.8(8), 26.6, 25.8, 18.2; *m/z* (ESI–MS) 326.0 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 8.5 min (major) and t_R = 11.3 min (minor). The

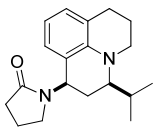
absolute configuration was assigned by analogy.

1-((4*R*,6*R*)-4-cyclopentyl-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-ij]quinolin-6-yl)pyrrolidin-2-one



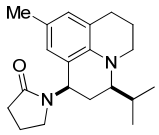
(4.50r): Following the general procedure **D**, compound **4.50r** was obtained as a white solid in 82% yield (50.8 mg); mp = 124–125 °C; R_f = 0.30 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ -4.4 (c 0.5, $CHCl_3$, 88% *ee*); IR (KBr) 2954, 2861, 1683, 1456, 1428, 1287, 1206, 1055, 842, 779, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, J = 6.8 Hz, 1H), 6.70–6.48 (comp, 2H), 5.47 (dd, *J* = 11.4, 6.3 Hz, 1H), 3.71–3.46 (m, 1H), 3.30–3.06 (comp, 2H), 3.00–2.76 (comp, 4H), 2.55–2.33 (comp, 2H), 2.28–2.09 (m, 1H), 2.00–1.88 (comp, 3H), 1.86–1.76 (m, 1H), 1.75–1.60 (comp, 2H), 1.59–1.43 (comp, 4H), 1.42–1.25 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 151.5, 129.4, 124.1, 123.2, 118.8, 117.4, 60.2, 52.9, 47.8, 47.7, 42.3, 42.2, 41.7, 31.5, 28.9, 27.9, 26.4, 25.7, 18.1; *m/z* (ESI–MS) 311.9 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.8 min (major) and t_R = 12.3 min (minor). The absolute configuration was assigned by analogy.

1-((1*R*,3*R*)-3-isopropyl-1,2,3,5,6,7-hexahydropyrido[3,2,1-ij]quinolin-1-yl)pyrrolidin-2-one (4.54a):



Following the general procedure **D**, compound **4.54a** was obtained as a white solid in 85% yield (50.6 mg); mp = 164–165 °C; R_f= 0.31 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +75.2 (c 0.5, $CHCl_3$, 91% *ee*); IR (KBr) 2954, 2840, 1685, 1464, 1280, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90–6.80 (m, 1H), 6.64–6.49 (comp, 2H), 5.43 (dd, *J* = 11.9, 5.5 Hz, 1H), 3.42–3.31 (m, 1H), 3.31–3.23 (comp, 2H), 3.23–3.16 (m, 1H), 2.85–2.68 (comp, 2H), 2.65–2.55 (comp, 1H), 2.55–2.43 (comp, 2H), 2.43–2.28 (m, 1H), 2.14–1.95 (comp, 3H), 1.94–1.72 (comp, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 144.5, 127.7, 124.4, 123.2, 120.1, 116.0, 61.4, 48.2, 45.0, 42.3, 31.4, 27.7, 27.2, 25.4, 22.8, 19.5, 18.2, 14.3; *m/z* (ESI–MS) 299.7 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.3 min (major) and t_R = 14.5 min (minor). The absolute configuration was assigned by analogy.

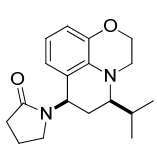
1-((1*R*,3*R*)-3-isopropyl-9-methyl-1,2,3,5,6,7-hexahydropyrido[3,2,1-ij]quinolin-1-yl)pyrrolidin-2-one



(4.54b): Following the general procedure **E**, compound **4.54b** was obtained as a white solid in 74% yield (46.3 mg); mp = 114–116°C; R_f = 0.28 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +38.4 (c 0.5, $CHCl_3$, 93% *ee*); IR (KBr) 2947, 2839, 1671, 1458, 1420, 1286, 1269, 1086, 1010, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.40 (s, 1H), 5.42 (dd, *J* = 12.0, 5.6 Hz, 1H), 3.38–3.30 (m, 1H), 3.29–3.20 (comp, 2H), 3.12 (app dt, *J* = 11.1, 3.5 Hz, 1H), 2.76–2.64 (comp, 2H), 2.61–2.45 (comp, 3H), 2.37–2.29 (m, 1H), 2.15 (s, 3H), 2.08–1.95 (comp, 3H), 1.86–1.76 (comp, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 142.5, 128.7, 125.4, 124.5, 123.8, 120.3, 61.4, 48.3, 45.0, 42.4, 31.5, 27.6, 27.3, 25.5, 23.0, 20.4, 19.6, 18.3, 14.3; *m/z* (ESI–MS) 314.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 6.7 min (major) and t_R = 7.9 min (minor). The absolute configuration was assigned by analogy.

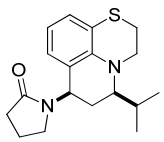
1-((1*R*,3*R*)-3-isopropyl-9-methoxy-1,2,3,5,6,7-hexahydropyrido[3,2,1-ij]quinolin-1-yl)pyrrolidin-2-one (4.54c): Following the general procedure **E**, compound **4.54c** was obtained as a white solid in 82% yield (53.8 mg); mp = 124–126 °C; R_f = 0.22 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +68.3 (c 0.7, $CHCl_3$, 97% *ee*); IR (KBr) 2962, 2928, 2835, 1683, 1485, 1285, 1193, 1082, 887, 865 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.47 (d, *J* = 2.8 Hz, 1H), 6.21 (d, *J* = 2.8 Hz, 1H), 5.48–5.38 (m, 1H), 3.67 (s, 3H), 3.38–3.18 (comp, 3H), 3.11–3.00 (m, 1H), 2.80–2.68 (m, 1H), 2.67–2.54 (comp, 2H), 2.53–2.45 (comp, 2H), 2.36–2.26 (m, 1H), 2.10–1.91 (comp, 4H), 1.89–1.72 (comp, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 151.0, 139.3, 125.9, 121.7, 113.6, 109.5, 61.5, 55.6, 48.4, 44.8, 42.4, 31.4, 27.8, 27.2, 25.3, 23.0, 19.6, 18.2, 14.3; *m/z* (ESI–MS) 329.9$[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 30.4 min (major) and t_R = 34.9 min (minor). The absolute configuration was assigned by analogy.

1-((5*R*,7*R*)-5-isopropyl-3,5,6,7-tetrahydro-2H-[1,4]oxazino[2,3,4-ij]quinolin-7-yl)pyrrolidin-2-one



(4.54d): Following the general procedure **D**, compound **4.54d** was obtained as a light red solid in 84% yield; mp = 183–184 °C; R_f = 0.28 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ -15.4 (c 0.5, $CHCl_3$, >99% *ee*); IR (KBr) 2945, 2865, 1724, 1636, 1541, 1475, 1384, 1181, 1108, 974, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.68–6.62 (m, 1H), 6.62–6.56 (m, 1H), 6.45–6.38 (m, 1H), 5.48 (dd, *J* = 12.1, 6.1 Hz, 1H), 4.36–4.26 (comp, 2H), 3.34 (app dt, *J* = 11.6, 2.4 Hz, 1H), 3.30–3.22 (m, 1H), 3.21–3.14 (m, 1H), 3.05 (ddd, *J* = 11.2, 3.3, 2.4 Hz, 1H), 2.91–2.79 (m, 1H), 2.55–2.45 (comp, 2H), 2.36–2.23 (m, 1H), 2.09–1.96 (comp, 2H), 1.94–1.74 (comp, 2H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 144.4, 134.4, 121.8, 118.6, 118.5, 115.1, 65.6, 60.5, 48.1, 42.3, 42.0, 31.4, 26.7, 24.5, 19.3, 18.1, 14.2; *m/z* (ESI–MS) 301.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 70/30, Flow rate = 1 mL/min, UV = 230 nm, t_R = 6.3 min (major). The absolute configuration was assigned by analogy.

1-((5*R*,7*R*)-5-isopropyl-3,5,6,7-tetrahydro-2H-[1,4]thiazino[2,3,4-ij]quinolin-7-yl)pyrrolidin-2-one



(4.54e): Following the general procedure **D**, compound **4.54e** was obtained as a light brown oil in 54% yield; R_f = 0.29 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ +35.7 (c 0.5, $CHCl_3$, 54% *ee*); IR (neat) 2955, 2845, 1694, 1472, 1364, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.02–6.96 (m, 1H), 6.59 (app t, *J* = 7.6 Hz, 1H), 6.52 (d, *J* = 7.5 Hz, 1H), 5.37 (dd, *J* = 12.1, 4.4 Hz, 1H), 3.76–3.66 (m, 1H), 3.36–3.18 (comp, 4H), 3.01–2.93 (comp, 2H), 2.58–2.46 (comp, 2H), 2.33–2.23 (m, 1H), 2.14–2.03 (comp, 2H), 1.94–1.81 (comp, 2H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 143.6, 126.9, 123.1, 121.3, 121.2, 117.8, 62.3, 48.0, 46.7, 42.5, 31.3, 29.4, 28.1, 26.0, 19.5, 18.3, 14.7; *m/z* (ESI–MS) 317.3 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 70/30, Flow rate = 1 mL/min, UV = 254 nm, t_R = 8.3 min (major), t_R = 10.3 min (minor). The absolute configuration was assigned by analogy.

(5*R*,7*R*)-benzyl-5-isopropyl-7-(2-oxopyrrolidin-1-yl)-2,3,6,7-tetrahydropyrido[1,2,3-de]quinoxaline-1(5H)-carboxylate (4.54f): Following the general procedure **E**, compound **4.54f** was obtained as a light brown oil in 65% yield (9:1 dr); R_f = 0.25 (Hexanes/EtOAc 60:40 v/v); $[\alpha]^{D}_{20}$ -3.2 (c 0.5, $CHCl_3$, 97% *ee*); IR (neat) 2961, 2933, 1689, 1386, 1278, 1132, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (major diastereomer): δ 7.46–7.28 (comp, 6H), 6.62 (app t, *J* = 7.7 Hz, 1H), 6.53 (d, *J* = 6.7 Hz, 1H), 5.42 (dd, *J* = 12.1, 4.6 Hz, 1H), 5.27 (d, *J* = 12.4 Hz, 1H), 5.18 (d, *J* = 12.4 Hz, 1H), 3.6 –3.41 (comp, 3H), 3.29–3.16 (comp, 3H), 2.96–2.86 (m, 1H), 2.49–2.46 (comp, 2H), 2.32–2.22 (m, 1H), 2.09 –2.03 (comp, 2H), 1.90–1.78 (comp, 2H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 154.0, 136.3, 128.5, 128.0, 127.9, 121.2, 121.1, 116.5, 67.5, 61.4, 47.9, 45.7, 42.4, 31.4, 27.5, 25.2, 19.4, 18.2, 14.5; *m/z* (ESI–MS) 434.9 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, t_R = 22.7 min (major), t_R = 34.7 min (minor). The absolute configuration was assigned by analogy.

III Catalytic Enantioselective Pictet-Spengler Reaction

General Procedure F: (used in Table 4.3 & 4.4)

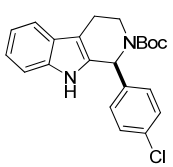
A flame dried 25 mL round bottom flask was charged with tryptamine (0.2 mmol, 1 equiv), and 4Å MS (100 mg). Toluene (2 mL) followed by catalyst (0.04 mmol, 0.2 equiv) and any additive was added and the resulting mixture stirred for two minutes under a nitrogen atmosphere. A solution of *p*-chlorobenzaldehyde (0.22 mmol, 1.1 equiv.) in 2 mL of toluene was added and the resulting mixture was stirred for two days. The reaction was quenched by adding a saturated, aqueous solution of $NaHCO_3$ (6 mL). A solution of Boc anhydride (0.44 mmol, 2.2 equiv) in 6 mL of ethyl acetate was added and the biphasic mixture was stirred for 4 hours. The crude reaction mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine and then dried with anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure and the crude product was purified by flash chromatography using a step gradient from EtOAc/hexanes (7:93 v/v) to EtOAc/hexanes (15:85 v/v).

General Procedure G: (Scope of the Reaction)

A flame dried 25 mL round bottom flask was charged with tryptamine (0.2 mmol, 1.0 equiv) and 3 Å MS (100 mg). Toluene (2 mL) was added and the reaction was stirred for two minutes under a nitrogen atmosphere. To the resulting mixture, aldehyde (0.22 mmol, 1.1 equiv) in 1 mL of toluene was added and the reaction mixture was stirred for 12 hours. Catalyst **1d** (0.02 mmol, 0.1 equiv) was added and Boc anhydride (0.44 mmol, 2.2 equiv) in 1 mL toluene was then added and the reaction was stirred for the designated time at room temperature. The reaction was quenched by adding saturated, aqueous $NaHCO_3$ (6 mL) and the biphasic mixture was stirred for an additional 3 hours. The reaction mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine and then dried with anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure and the crude product was purified by flash chromatography using a step gradient from EtOAc/hexanes (7:93 v/v) to EtOAc/hexanes (15:85 v/v).

Characterization Data of Products

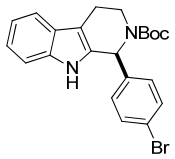
(*S*)-*tert*-Butyl 1-(4-chlorophenyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (2.74a):



Following the general procedure **G**, compound **2.74a** was obtained as a white solid in 95% yield (73 mg) and 92% ee; mp = 194–197 ºC; R_f = 0.46 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{25}$ +159.5.0 (c 0.45, CH_2Cl_2); IR (KBr) 3316, 2977, 2930, 1671, 1452, 1417, 1266, 1164, 1091, 915, 742 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer); ^1H NMR (500 MHz, ($CDCl_3$) δ ^1H NMR (500 MHz, ($CDCl_3$) δ 8.17–7.65 (m, 1H, 1H*), 7.56 (d, *J* = 7.6 Hz, 1H), 7.46–7.21 (comp, 5H), 7.21–7.08 (comp, 2H), 6.61–6.13 (m, 1H, 1H*), 4.55–4.08 (m, 1H, 1H*), 3.15–3.0 (m, 1H), 2.92 (app td, *J* = 14.0 Hz, *J* = 5.0 Hz, 1H), 2.86–2.73 (m, 1H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 139.2, 136.5, 134.1, 131.4, 129.9, 128.8, 126.9, 122.4, 119.9, 118.5 111.2, 111.0, 80.7, 54.1, 53.2, 38.5, 38.0, 28.7, 21.5; *m/z* (ESI-MS) 383.2 (^{35}Cl) $[M + H]^+$; 384.9 (^{37}Cl) [M + H]; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 0.5 mL/min, UV = 230 nm, t_R = 20.9 min (minor) and t_R = 23.7 min

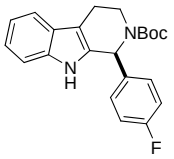
(major). The absolute configuration was assigned by analogy.

(*S*)-*tert*-Butyl 1-(4-bromophenyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (2.74b):



Following the general procedure **G**, compound **2.74b** was obtained as a white solid in 78% yield (67 mg) and 92% ee; mp = 185–187 ºC; R_f = 0.28 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{25}$ +127.4 (c 0.45, CH_2Cl_2); IR (KBr) 3317, 2976, 2928, 1671, 1486, 1416, 1366, 1292, 1163, 1011, 741 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.74 (br s, 1H*), 7.56 (d, *J* = 7.7 Hz, 1H), 7.50–7.36 (comp, 2H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.24–7.08 (comp, 4H), 6.58–6.05 (m, 1H, 1H*), 4.64–4.04 (m, 1H, 1H*), 3.06 (app td, *J* = 12.5 Hz, *J* = 4.0 Hz, 1H), 2.92 (app td, *J* = 15.8 Hz, *J* = 5.5 Hz, 1H), 2.86–2.72 (m, 1H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 139.5, 136.3, 131.6, 131.1, 130.0, 126.7, 122.2, 122.1, 119.7, 118.3, 111.0, 110.8, 80.5, 54.1, 53.1, 38.3, 37.7, 28.5, 21.4; *m/z* (ESI-MS) 427.2 (^{79}Br) $[M + H]^+$; 428.0 (^{81}Br) $[M]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 11.3 min (minor) and t_R = 13.0 min (major). The absolute configuration was assigned by analogy.

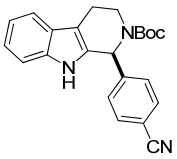
(*S*)-*tert*-Butyl 1-(4-fluorophenyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (2.74c):



Following the general procedure **G**, compound **2.74c** was obtained as a white solid in 94% yield (69 mg) and 90% ee; mp = 199–201 ºC; R_f = 0.22 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{25}$ +90.1 (c 0.45, CH_2Cl_2); IR (KBr) 3325, 2975, 2923, 1665, 1500, 1445, 1420, 1223, 1156, 1084, 729 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer; ^{1}H NMR (500 MHz, ($CDCl_3$) δ 8.04–7.65 (br s, 1H, 1H*), 7.55 (d, *J* = 7.7 Hz, 1H), 7.36–7.23 (comp, 3H), 7.22–7.08 (comp, 2H), 6.98 (app t, *J* = 8.3 Hz, 2H), 6.62–6.08 (m, 1H, 1H*), 4.61–4.05 (m, 1H, 1H*), 3.08 (app td, *J* = 12.7 Hz, *J* = 4.0 Hz, 1H), 2.92 (app td, *J* = 14.0 Hz, *J* = 4.9 Hz, 1H), 2.86–2.72 (m, 1H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 161.6, 154.9, 136.5 (d, J_{C-F} = 3.2 Hz), 136.4, 131.7, 130.2, 126.9, 122.3, 119.8, 118.5, 115.5 (d, J_{C-F} = 21.5 Hz), 111.2, 110.9, 80.6, 53.2, 38.4, 31.7, 29.9, 28.7, 22.8, 21.6, 14.3; *m/z* (ESI-MS) 367.7 [M +

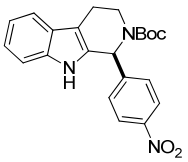
H]$^+$, 389.1 [M + Na]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.9 min (minor) and t_R = 13.1 min (major). The absolute configuration was assigned by analogy.

(*S*)-*tert*-Butyl 1-(4-cyanophenyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (2.74d):



Following the general procedure **G**, compound **2.74d** was obtained as a white solid in 95% yield (71 mg) and 92% ee; mp = 192–194 ºC; R_f = 0.26 (Hexanes/EtOAc 80:20 v/v); $[\alpha]_D^{25}$ +136.6 (c 0.45, CH_2Cl_2); IR (KBr) 3336, 2976, 2930, 1675, 1452, 1415, 1367, 1284, 1163, 1097, 743 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26–7.76 (m, 1H, 1H*), 7.68–7.48 (comp, 3H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.23–7.09 (comp, 2H), 6.69–6.12 (m, 1H, 1H*), 4.54–4.04 (m, 1H, 1H*), 3.10–2.98 (m, 1H), 2.92 (app td, *J* = 13.5 Hz, *J* = 4.9 Hz, 1H), 2.86–2.72 (m, 1H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 145.9, 136.5, 132.4, 130.3, 129.1, 126.8, 122.6, 120.0, 118.7, 118.6, 112.0, 111.3, 81.0, 64.6, 54.4, 53.4, 38.8, 38.0, 29.8, 28.6, 25.5, 21.5; *m/z* (ESI-MS) 374.1 [M + H]$^+$, 396.0 [M + Na]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.4 min (minor) and t_R = 20.4 min (major). The absolute configuration was assigned by analogy.

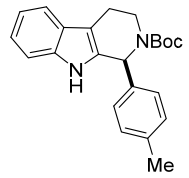
(*S*)-*tert*-Butyl 1-(4-nitrophenyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (2.74e):



Following the general procedure **G**, compound **2.74e** was obtained as a yellow solid in 90% yield (71 mg) and 89% ee; mp > 200 ºC; R_f = 0.33 (Hexanes/EtOAc 80:20 v/v); $[\alpha]_D^{25}$ +115.3 (c 0.45, CH_2Cl_2); IR (KBr) 3324, 2976, 2928, 1672, 1522, 1415, 1348, 1285, 1163, 1098, 741 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27–7.91 (comp, 3H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 1H) 7.25–7.11 (comp, 2H), 6.68–6.26 (m, 1H, 1H*), 4.61–4.09 (m, 1H, 1H*), 3.15–2.99 (m, 1H), 2.94 (app td, *J* = 13.8 Hz, *J* = 4.6 Hz, 1H), 2.88–2.76 (m, 1H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 147.8, 147.8, 147.7, 136.6, 130.3, 129.3, 129.2, 126.8, 123.8, 122.7, 120.0, 118.6, 111.3, 81.2, 54.3, 53.2, 38.9, 38.2, 29.9, 28.6, 21.5;

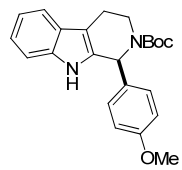
m/z (ESI-MS) 394.0 $[M + H]^+$, 415.9 $[M + Na]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 11.8 min (minor) and t_R = 24.9 min (major). The absolute configuration was assigned by analogy.

(*S*)-*tert*-butyl 1-(p-tolyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (2.74f): Following



the general procedure **G**, compound **2.74f** was obtained as a white solid in 28% yield (20 mg) and 64% ee; mp 180–182 ºC; R_f = 0.25 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{25}$ –27.1(c 0.45, CH_2Cl_2); IR (KBr) 3317, 2976, 2926, 1670, 1452, 1417, 1366, 1231, 1164, 1097, 740 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer); ^1H NMR (500 MHz, $CDCl_3$) δ 7.90–7.61 (m, 1H, 1H*), 7.56 (d, *J* = 7.6 Hz, 1H), 7.31–7.26 (m, 1H), 7.24–7.19 (comp, 2H), 7.19–7.08 (comp, 4H), 6.64–6.1 (m, 1H, 1H*), 4.60–3.96 (m, 1H, 1H*), 3.14 (app td, *J* = 12.7 Hz, *J* = 4.1 Hz, 1H), 2.92 (app td, *J* = 14.0 Hz, *J* = 5.3 Hz, 1H), 2.86–2.74 (m, 1H), 2.34 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 154.6, 136.2, 132.7, 132.1, 129.6, 126.8, 122.0, 119.6, 118.3, 113.8, 110.9, 110.7, 80.1, 55.3, 54.0, 53.1, 38.2, 37.4, 29.7, 28.5, 21.4; *m/z* (ESI-MS) 363.1 $[M + H]^+$, 384.9 $[M + Na]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 0.5 mL/min, UV = 230 nm, t_R = 19.4 min (major) and t_R = 21.7 min (major). The absolute configuration was assigned by analogy.

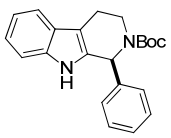
(*S*)-*tert*-butyl 1-(4-methoxyphenyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (4.74g):



Following the general procedure **G**, compound **4.74g** was obtained as a white solid in 12% yield (9 mg) and 32% ee; mp 180–182 ºC; R_f = 0.25 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{25}$ –27.1(c 0.45, CH_2Cl_2); IR (KBr) 3317, 2976, 2926, 1670, 1452, 1417, 1366, 1231, 1164, 1097, 740 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer); ^1H NMR (500 MHz, $CDCl_3$) δ 7.90–7.61 (m, 1H, 1H*), 7.56 (d, *J* = 7.6 Hz, 1H), 7.31–7.26 (m, 1H), 7.24–7.19 (comp, 2H), 7.19–7.08 (comp, 4H), 6.64–6.1 (m, 1H, 1H*), 4.60–3.96 (m, 1H, 1H*), 3.14 (app td, *J* = 12.7 Hz, *J* = 4.1 Hz, 1H), 2.92 (app td, *J* = 14.0 Hz, *J* = 5.3 Hz, 1H), 2.86–2.74 (m, 1H), 2.34 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 154.6, 136.2, 132.7, 132.1, 129.6, 126.8, 122.0, 119.6, 118.3, 113.8, 110.9, 110.7, 80.1, 55.3, 54.0, 53.1,

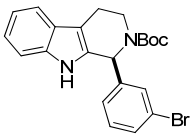
38.2, 37.4, 29.7, 28.5, 21.4; *m/z* (ESI-MS) 363.1 $[M + H]^+$, 384.9 $[M + Na]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 0.5 mL/min, UV = 230 nm, t_R = 19.4 min (major) and t_R = 21.7 min (major). The absolute configuration was assigned by analogy.

(*S*)-*tert*-Butyl 1-phenyl-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (4.74h): Following



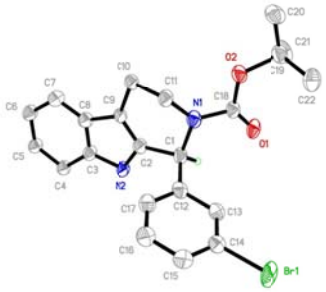
the general procedure **G**, compound **4.74h** was obtained as a white solid in 86% yield (60 mg) and 87% ee; mp > 200 ºC; R_f = 0.24 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{25}$ +130.8 (c 0.45, CH_2Cl_2); IR (KBr) 3333, 2972, 2920, 1668, 1539, 1453, 1416, 1280, 1163, 1089, 734 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer); ^1H NMR (500 MHz, $CDCl_3$) δ 8.02–7.62 (m, 1H, 1H*), 7.56 (d, *J* = 7.5 Hz, 1H), 7.38–7.22 (comp, 6H), 7.21–7.07 (comp, 2H), 6.73–6.06 (m, 1H, 1H*), 4.60–4.04 (m, 1H, 1H*), 3.13 (app t, *J* = 12.2 Hz, 1H), 2.89–2.87 (m, 1H), 2.86–2.73 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 140.5, 136.2, 131.8, 128.7, 128.5, 128.3, 128.0, 126.8, 122.0, 119.6, 118.3, 110.9, 110.7, 80.3, 54.6, 53.7, 38.1, 29.6, 28.5, 21.4; *m/z* (ESI-MS) 349.0 $[M + H]^+$, 371.0 $[M + Na]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 9.7 min (minor) and t_R = 12.3 min (major). The absolute configuration was assigned by analogy.

(*S*)-*tert*-Butyl 1-(3-bromophenyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (4.74i):



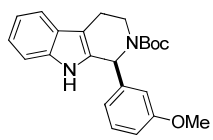
Following the general procedure **G**, compound **4.74i** was combined as a white solid in 92% yield (79 mg) and 89% ee; mp > 200 ºC; R_f = 0.24 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{25}$ +104.3 (c 0.45, CH_2Cl_2); IR (KBr) 3318, 2977, 2925, 1675, 1566, 1445, 1428, 1287, 1164 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer); ^1H NMR (500 MHz, $CDCl_3$) δ 8.05–7.62 (m, 1H, 1H*), 7.56 (d, *J* = 7.5 Hz, 1H), 7.48 (s, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.28–7.08 (comp, 4H), 6.65–6.01 (m, 1H, 1H*), 4.63–4.03 (m, 1H, 1H*), 3.10 (app td, *J* = 12.8 Hz, *J* = 3.8 Hz, 1H), 2.92 (app td, *J* = 14.3 Hz, *J* = 4.9 Hz, 1H), 2.87–2.74 (m, 1H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 142.8, 136.4, 131.3, 131.2, 131.0, 130.9, 130.1, 127.0, 126.7, 122.7, 122.3, 119.7, 118.4, 111.0, 80.6, 54.1, 53.3, 38.4, 37.9, 29.6, 28.4, 21.4; *m/z* (ESI-MS) 427.7 (^{79}Br) $[M + H]^+$, 428.9 (^{81}Br) $[M + H]^+$, 448.9 (^{79}Br) [M

+ Na]$^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 0.5 mL/min, UV = 230 nm, t_R = 31.2 min (minor) and t_R = 39.9 min (major). The absolute configuration of **4.74i** was assigned by X-ray crystallography.



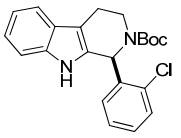
Compound **4.74i** was crystallized from hexanes/dichloromethane through slow diffusion at room temperature. The requisite CIF has been deposited to the journal.

(*S*)-*tert*-Butyl 1-(3-methoxyphenyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (4.74j):



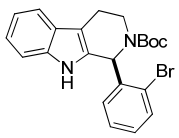
Following the general procedure **G**, compound **4.74j** was obtained as a white solid in 73% yield (55 mg) and 84% ee; mp 172–174 ºC; R_f = 0.35 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{25}$ +124.3 (c 0.45, CH_2Cl_2); IR (KBr) 3323, 2974, 2922, 1668, 1454, 1416, 1366, 1267, 1163, 741 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the minor rotamer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10–7.65 (m, 1H, 1H*), 7.55 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.24–7.09 (comp, 3H), 6.97–6.90 (m, 1H), 6.89–6.78 (comp, 2H), 6.61–6.13 (m, 1H, 1H*), 4.59–4.09 (m, 1H, 1H*), 3.75 (s, 3H), 3.15 (app td, *J* = 12.7 Hz, *J* = 4.0 Hz, 1H), 2.92 (app td, *J* = 14.1 Hz, *J* = 5.3 Hz, 1H), 2.85–2.74 (m, 1H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 154.7, 142.1, 136.3, 131.7, 129.4, 126.8, 122.0, 120.6, 119.5, 118.3, 114.1, 113.3, 110.9, 110.7, 80.2, 55.2, 54.5, 53.7, 38.3, 37.9, 28.5, 21.4; *m/z* (ESI-MS) 378.9 [M + H]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 14.7 min (minor) and t_R = 28.3 min (major). The absolute configuration was assigned by analogy.

(*S*)-*tert*-Butyl 1-(2-chlorophenyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (4.74k):



Following the general procedure **G**, compound **4.74k** was obtained as a white solid in 83% yield (64 mg) and 81% ee; mp > 200 ºC; R_f = 0.25 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{25}$ +56.9 (c 0.45, CH_2Cl_2); IR (KBr) 3313, 2980, 2920, 1677, 1549, 1458, 1393, 1366, 1163, 746 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer); ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.36–6.94 (comp, 6H), 6.61 (br s, 1H), 4.52 (br s, 1H, 1H*), 3.36 (br s, 1H, 1H), 3.07–2.73 (comp, 2H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 140.1, 136.2, 131.9, 129.8, 128.9, 128.1, 127.3, 126.5, 122.1, 119.6, 118.3, 111.0, 109.7, 80.4, 52.3, 40.2, 28.2, 21.1; *m/z* (ESI-MS) 383.1 (^{35}Cl) $[M + H]^+$; 385.0 (^{37}Cl) [M + H], 405.0 $[M + Na]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 0.5 mL/min, UV = 230 nm, t_R = 15.5 min (minor) and t_R = 19.9 min (major). The absolute configuration was assigned by analogy.

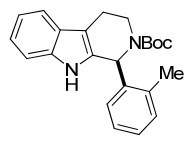
(*S*)-*tert*-Butyl 1-(2-bromophenyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (4.74l):



Following the general procedure **G**, compound **4.74l** was obtained as a white solid in 87% yield (74 mg) and 79% ee; mp > 200 ºC; R_f = 0.24 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{25}$ +65.7 (c 0.45, CH_2Cl_2); IR (KBr) 3322, 2976, 2923, 1677, 1466, 1394, 1366, 1278, 1163, 740 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer); ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.39–7.26 (comp, 2H), 7.24–7.20 (m, 1H), 7.19–7.00 (comp, 3H), 6.55 (br s, 1H, 1H*), 4.68–4.30 (m, 1H, 1H*), 3.68–3.32 (m, 1H, 1H*), 3.08–2.75 (comp, 2H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 136.2, 133.1, 131.9, 129.2, 127.9, 126.5, 122.1, 119.6, 118.3, 111.0, 109.4, 80.4, 54.6, 40.7, 29.5, 28.3, 21.1; *m/z* (ESI-MS) 427.7 (^{79}Br) $[M + H]^+$, 428.9 (^{81}Br) $[M + H]^+$, 448.9 (^{79}Br) $[M + Na]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 0.5 mL/min, UV = 230 nm, t_R = 15.5 min (minor) and t_R = 18.4min (major). The absolute configuration was

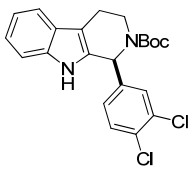
also assigned by comparison with the (*R*)-enantiomer reported in the literature ($[\alpha]_D^{25}$ = –105 (c 0.45, CH_2Cl_2, 95% ee.[20g]

(*S*)-*tert*-Butyl 1-(o-tolyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (4.74m): Following



the general procedure **G**, compound **4.74m** was obtained as a white solid in 62% yield (45 mg) and 54% ee; mp > 200 ºC; R_f = 0.28 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{25}$ +91.7 (c 0.45, CH_2Cl_2); IR (KBr) 3321, 2972, 2923, 1668, 1461, 1407, 1366, 1282, 1163, 740 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer); ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (br s, 1H, 1H*), 7.56 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.31–7.23 (comp, 2H), 7.22–7.10 (comp, 3H), 7.03 (app t, *J* = 7.3 Hz, 1H), 6.87–6.72 (m, 1H), 6.58 (br s, 1H, 1H*), 4.14 (br s, 1H, 1H*), 3.14 (app td, *J* = 12.7 Hz, *J* = 4.0 Hz, 1H), 2.99 (app td, *J* = 13.8 Hz, *J* = 5.3 Hz, 1H), 2.77 (app dd, *J* = 15.3Hz, *J* = 3.7 Hz, 1H), 2.56 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 138.3, 136.3, 132.8, 131.1, 129.4, 128.2, 127.2, 125.8, 122.2, 119.8, 118.3, 111.2, 110.9, 80.4, 52.3, 38.8, 29.9, 28.6, 21.2, 19.9; *m/z* (ESI-MS) 363.1 $[M + H]^+$, 385.3 $[M + Na]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 0.5 mL/min, UV = 230 nm, t_R = 12.7 min (minor) and t_R = 14.5 min (major). The absolute configuration was assigned by analogy.

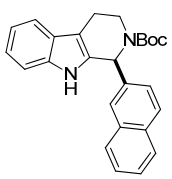
(*S*)-*tert*-Butyl 1-(3,4-dichlorophenyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate



(4.74n): Following the general procedure **G**, monourea compound **4.74n** was obtained as a white solid in 89% yield (74 mg) and 89% ee; mp > 200 ºC; R_f = 0.28 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{25}$ +97.3 (c 0.45, CH_2Cl_2); IR (KBr) 3319, 2977, 2929, 1670, 1468, 1416, 1366, 1266, 1163, 1032, 741 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer); ^1H NMR (500 MHz, $CDCl_3$) δ 8.29–7.65 (m, 1H, 1H*), 7.63–7.50 (m, 1H), 7.49–7.24 (comp, 3H), 7.23–6.92 (comp, 3H), 6.59–6.02 (m, 1H, 1H*), 4.66–3.96 (m, 1H, 1H*), 3.05 (app t, *J* = 12.0 Hz, 1H), 2.98–2.86 (m, 1H), 2.86–2.73 (m, 1H), 1.53 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 140.7, 136.3, 132.7, 132.2, 130.4,

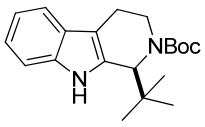
130.1, 127.6, 126.6, 122.4, 119.8, 118.4, 111.1, 80.7, 53.7, 52.8, 38.4, 37.8, 28.5, 21.4; *m/z* (ESI-MS) 417.1 ($^{35}Cl/^{35}Cl$) $[M + H]^+$, 418.0 ($^{35}Cl/^{37}Cl$) $[M]^+$, 421.5 ($^{37}Cl/^{37}Cl$) $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 10.5 min (minor) and t_R = 12.8 min (major). The absolute configuration was assigned by analogy.

(*S*)-*tert*-Butyl 1-(naphthalen-2-yl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (4.74o):



Following the general procedure **G**, compound **4.74o** was obtained as white solid in 63% yield (50 mg) and 84% ee; ; mp = 193–195 ºC; R_f = 0.24 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{25}$ +112.2 (c 0.45, CH_2Cl_2); IR (KBr) 3320, 2975, 2923, 1668, 1452, 1414, 1300, 1161, 740 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer); ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.79–7.72 (m, 1H), 7.72–7.64 (m, 1H), 7.64–7.57 (comp, 2H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.51–7.6 (comp, 2H), 7.35–7.27 (m, 1H), 7.24–7.08 (comp, 2H), 6.75–6.28 (m, 1H, 1H*), 4.56–4.12 (m, 1H, 1H*), 3.25–3.09 (m, 1H), 3.05–2.90 (m, 1H), 2.89–2.75(m, 1H), 1.53 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 138.2, 136.5, 133.2, 132.0, 128.6, 128.2, 127.8, 127.4, 127.0, 126.4, 122.3, 119.8, 118.5, 111.2, 111.0, 80.6, 55.1, 54.1, 38.4, 29.8, 28.7, 28.4, 21.6; *m/z* (ESI-MS) 399.0 $[M + H]^+$, 420.9$[M + Na]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 97/3, Flow rate = 1 mL/min, UV = 230 nm, t_R = 15.5 min (minor) and t_R = 18.8 min (major). The absolute configuration was assigned by analogy.

(*S*)-*tert*-butyl 1-(tert-butyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (4.74p):



Following the general procedure **G**, compound **4.74p** was obtained in 23% yield (15 mg) and 62% ee; mp > 200 ºC; R_f = 0.28 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{25}$ +32.2 (c 0.45, CH_2Cl_2); IR (KBr) 3304, 2973, 1668, 1454, 1417, 1365, 1260, 1162, 748 cm^{-1}; the compound exists as a mixture of carbamate rotamers (* denotes the proton(s) corresponding to the other rotamer); ^1H NMR (500 MHz, ($CDCl_3$) δ 7.95 (br s, 1H), 7.81 (br s, 1H*), 7.55–7.45 (comp, 2H), 7.36–7.30 (comp, 2H*), 7.21–7.14 (comp, 2H), 7.14–7.06 (comp, 2H*), 5.20–5.14 (m, 1H*), 4.98 (br s, 1H), 4.62 (d, *J* = 13.5 Hz, *J* = 6.0 Hz 1H*), 4.38 (d, *J* = 13.7 Hz, *J* = 5.6 Hz 1H),

3.49–3.38 (m, 1H), 3.38–3.28 (m, 1H*), 2.91–2.75 (comp, 2H), 2.74–2.65 (comp, 2H*), 1.54–1.44 (comp, 9H, 9H*), 1.17–1.03 (comp, 9H, 9H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8(4), 155.8(1), 155.4, 136.0, 135.9, 135.8, 132.8, 132.7, 132.2, 126.7, 121.9, 121.7, 121.6, 119.5, 119.3, 119.2, 118.1, 117.8, 117.7(6), 110.8, 110.7(7), 110.7(4), 110.6, 110.1, 109.9, 80.1, 79.7, 79.6, 59.8, 58.9, 58.8, 40.3, 40.2, 38.9, 37.7, 37.4, 37.3(7), 28.6, 28.4, 28.3, 28.2(6), 21.3, 20.8; *m/z* (ESI-MS) 329.2 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 0.5 mL/min, UV = 230 nm, t_R = 28.5 min (minor) and t_R = 36.5 min (major). The absolute configuration was assigned by analogy.

References:

(1) a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999; b) Terada, M. *Chem. Commun.* **2008**, 4097; c) Terada, M. *Synthesis* **2010**, 1929; d) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W.; Atodiresei, I. *Angew. Chem. Int. Ed.* **2011**, *50*, 6706.

(2) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.

(3) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

(4) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539.

(5) a) Lacour, J.; Hebbe-Viton, V. *Chem. Soc. Rev.* **2003**, *32*, 373; b) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187.

(6) a) Rueping, M.; Azap, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 7832; b) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141; c) Li, G.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 1075.

(7) a) Shi, Y.-L.; Shi, M. *Adv. Synth. Catal.* **2007**, *349*, 2129; b) Weil, T.; Kotke, M.; Kleiner, C. M.; Schreiner, P. R. *Org. Lett.* **2008**, *10*, 1513; c) Zhang, Z.; Lippert, K. M.; Hausmann, H.; Kotke, M.; Schreiner, P. R. *J. Org. Chem.* **2011**, *76*, 9764; d) Marqués-López, E.; Alcaine, A.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2011**, *2011*, 3700; e) Chen, X.; Zhu, W.; Qian, W.; Feng, E.; Zhou, Y.; Wang, J.; Jiang, H.; Yao, Z.-J.; Liu, H. *Adv. Synth. Catal.* **2012**, *354*, 2151; f) Rubush, D. M.; Morges, M. A.; Rose, B. J.; Thamm, D. H.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 13554; g) Geng, Y.; Kumar, A.; Faidallah, H. M.; Albar, H. A.; Mhkalid, I. A.; Schmidt, R. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 10089; h) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986.

(8) a) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434; b) Kotke, M.; Schreiner, R. P. *Synthesis* **2007**, 779; c) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198; d) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358; e) Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286; f) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030; g) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2010**, *49*, 7332; h) Singh, R. P.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2010**, *132*, 9558; i) Knowles, R. R.; Jacobsen, E. N. *Proc.*

Natl. Acad. Sci. U.S.A. **2010**, *107*, 20678; j) Kim, H. Y.; Oh, K. *Org. Lett.* **2011**, *13*, 1306; k) Birrell, J. A.; Desrosiers, J.-N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 13872; l) Beckendorf, S.; Asmus, S.; Mück-Lichtenfeld, C.; García Mancheño, O. *Chem. -Eur. J.* **2013**, *19*, 1581.

(9) Min, C.; Mittal, N.; Sun, D. X.; Seidel, D. *Angew. Chem. Int. Ed.* **2013**, ASAP.

(10) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.* **2011**, *111*, 7157.

(11) a) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721; b) Masson, G.; Lalli, C.; Benohoud, M.; Dagousset, G. *Chem. Soc. Rev.* **2013**, *42*, 902; c) Jiang, X.; Wang, R. *Chem. Rev.* **2013**, *113*, 5515.

(12) a) Sundararajan, G.; Prabagaran, N.; Varghese, B. *Org. Lett.* **2001**, *3*, 1973; b) Xie, M.; Liu, X.; Zhu, Y.; Zhao, X.; Xia, Y.; Lin, L.; Feng, X. *Chem. -Eur. J.* **2011**, *17*, 13800.

(13) a) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070; b) Liu, H.; Dagousset, G.; Masson, G. r.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598; c) Bergonzini, G.; Gramigna, L.; Mazzanti, A.; Fochi, M.; Bernardi, L.; Ricci, A. *Chem. Commun.* **2010**, *46*, 327; d) Wang, C.; Han, Z.-Y.; Luo, H.-W.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 2266; e) Dagousset, G.; Zhu, J.; Masson, G. *J. Am. Chem. Soc.* **2011**, *133*, 14804.

(14) a) Tohma, H.; Takizawa, S.; Watanabe, H.; Fukuoka, Y.; Maegawa, T.; Kita, Y. *J. Org. Chem.* **1999**, *64*, 3519; b) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080; c) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054; d) Ube, H.; Fukuchi, S.; Terada, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1203.

(15) a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797; b) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341; c) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278; d) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761; e) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532.

(16) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030.

(17) a) Luk, L. Y. P.; Bunn, S.; Liscombe, D. K.; Facchini, P. J.; Tanner, M. E. *Biochemistry* **2007**, *46*, 10153; b) Maresh, J. J.; Giddings, L.-A.; Friedrich, A.; Loris, E. A.; Panjikar, S.; Trout, B. L.; Stöckigt, J.; Peters, B.; O'Connor, S. E. *J. Am. Chem. Soc.* **2007**, *130*, 710; c) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 8538.

(18) Duce, S.; Pesciaioli, F.; Gramigna, L.; Bernardi, L.; Mazzanti, A.; Ricci, A.; Bartoli, G.; Bencivenni, G. *Adv. Synth. Catal.* **2011**, *353*, 860.

(19) a) Srinivasan, N.; Ganesan, A. *Chem. Commun.* **2003**, 916; b) Youn, S. W. *J. Org. Chem.* **2006**, *71*, 2521; c) Zhang, B.; Wee, A. G. H. *Chem. Commun.* **2008**, 4837; d) Lherbet, C.; Soupaya, D.; Baudoin-Dehoux, C.; André, C.; Blonski, C.; Hoffmann, P. *Tetrahedron Lett.* **2008**, *49*, 5449; e) Sharma, S. K.; Sharma, S.; Agarwal, P. K.; Kundu, B. *Eur. J. Org. Chem.* **2009**, *2009*, 1309; f) Selvakumar, J.; Makriyannis, A.; Ramanathan, C. R. *Org. Biomol. Chem.* **2010**, *8*, 4056.

(20) a) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405; b) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558; c) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404; d) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577; e) Bou-Hamdan, F. R.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2009**, *48*, 2403; f) Wanner, M. J.; Boots, R. N. A.; Eradus, B.;

Gelder, R. d.; van Maarseveen, J. H.; Hiemstra, H. *Org. Lett.* **2009**, *11*, 2579; g) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887; h) Herlé, B.; Wanner, M. J.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2011**, *76*, 8907; i) Lee, Y.; Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 5564; j) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 7485; k) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086.

(21) a) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117; b) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952; c) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916; d) Gomez-Monterrey, I. M.; Campiglia, P.; Bertamino, A.; Aquino, C.; Mazzoni, O.; Diurno, M. V.; Iacovino, R.; Saviano, M.; Sala, M.; Novellino, E.; Grieco, P. *Eur. J. Org. Chem.* **2008**, *2008*, 1983; e) Wu, X.; Dai, X.; Nie, L.; Fang, H.; Chen, J.; Ren, Z.; Cao, W.; Zhao, G. *Chem. Commun.* **2010**, *46*, 2733; f) Bernhardt, P.; Usera, A. R.; O'Connor, S. E. *Tetrahedron Lett.* **2010**, *51*, 4400.

(22) Badillo, J. J.; Silva-García, A.; Shupe, B. H.; Fettinger, J. C.; Franz, A. K. *Tetrahedron Lett.* **2011**, *52*, 5550.

(23) a) Zhang, W.; Franzén, J. *Adv. Synth. Catal.* **2010**, *352*, 499; b) Hong, B.-C.; Liao, W.-K.; Dange, N. S.; Liao, J.-H. *Org. Lett.* **2013**, *15*, 468.