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Organocatalytic acid mediated Mannich reactions and multicomponent boronate reactions to make chiral benzhydryls

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Boston University
ORGANOCATALYTIC ACID MEDIATED MANNICH REACTIONS
AND MULTICOMPONENT BORONATE REACTIONS
TO MAKE CHIRAL BENZHYDRILS

by

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ORGANOCATALYTIC ACID MEDIATED MANNICH REACTIONS
AND MULTICOMPONENT BORONATE REACTIONS
TO MAKE CHIRAL BENZHYDRILS

(Daniele RameLLa)

Boston University Graduate School of Arts and Sciences, 2013

Major Professor: Scott E. Schaus, Associate Professor of Chemistry

ABSTRACT

Since its discovery in 1912, the Mannich reaction has been widely utilized in organic chemistry to form C-C bonds. Reactivity of an enol with an imine allows for easy formation of a β-aminoketone. Enamines have also been widely utilized as convenient nucleophiles. In our work, unexpected reactivity of the γ position of β-enamidoesters in a Brønsted acid environment and high enantioselectivity of a Mannich reaction were achieved through chiral phosphoramidic acid catalysis. A novel class of chiral phosphoramidic acids was designed, synthesized from the corresponding diamines, with several sulfonyl N-protecting groups, and characterized. Their unique properties arise from their Brønsted acid nature, atropisomerism and ability to form complexes via H-bond. Once
prepared, such catalysts were successfully used as organocatalysts for the regio- and enantioselective Mannich reaction of β-enamidoesters and imines. Their activity is described as a method to reverse the regioselectivity of the nucleophile while achieving high enantioselectivities in the formation of chiral benzhydrils. A diverse range of imines has been tested, obtaining yields of up to 93% and enantioselectivities of up to 99:1. A few substituted enamines were also tested to study the influence of substituents on the regioselectivity. A mechanism for this reaction is proposed and kinetic studies confirmed that the reaction is first order in catalyst. The ozonolysis of the product of this Mannich reaction was performed to prove the absolute stereochemistry of the product; and a new efficient methodology for the asymmetric preparation of aminoacid β-phenyl-β-alanine benzyl ester is described. The reduction of the enamide moiety of the Mannich product was attempted via asymmetric hydrogenation and via hydride reduction to diastereomerically obtain 1,3-diamines, which are compounds of major synthetic interest. Unfortunately our attempts in this direction were not successful. Finally, a multicomponent reaction between an aldehyde, a substituted phenol, and a styrylboronate was developed as an alternative method for the preparation of chiral benzhydryls. This process is also organocatalytic and the methodology was optimized in the presence of 3-3’-disubstituted BINOLs. Yields up to 71% and enantioselectivities up to 96:4 were achieved. A mechanism for this organocatalytic reaction is also proposed.
Table of Contents

Acknowledgements ........................................................................................................ iv

Abstract .......................................................................................................................... ix

Table of Contents .............................................................................................................. xi

List of Tables .................................................................................................................... xiv

List of Figures ................................................................................................................... xvii

List of Schemes ................................................................................................................ xix

List of Abbreviations ....................................................................................................... xxvii

1. Chapter 1. Introduction. Organocatalysis and Chiral Bronsted Acids ............. 1

   1.1 Bronsted Acids ...................................................................................................... 1

   1.2 Chiral phosphoric and chiral phosphoramidic acids ........................................ 6

   1.3 Chiral phosphoramidic acids as catalysts ......................................................... 12

2. Chapter 2. Recent Advances in the Mannich reaction ................................... 14

   2.1 The Mannich reaction .......................................................................................... 14

   2.2 The asymmetric Mannich reaction ..................................................................... 17
2.3 Synthetic applications of the Mannich reaction .......................... 31

3. Chapter 3. Development of an asymmetric organocatalyzed Mannich reaction ................................................................. 42

3.1 Introduction ........................................................................... 42

3.2 Novel chiral phosphoramidic acids ................................. 53

3.3 Asymmetric Mannich reaction ........................................... 64

3.4 Absolute configuration elucidation .................................... 81

3.5 Asymmetric reduction of the enamine .......................... 83

3.6 Conclusions ......................................................................... 102

3.7 Experimental section ......................................................... 105

4. Chapter 4. Asymmetric multicomponent reaction ............. 137

4.1 Introduction ......................................................................... 137

4.2 Results ............................................................................... 158

4.3 Conclusions ......................................................................... 169

4.4 Experimental section ......................................................... 171
5. Conclusions ................................................................. 194

List of Journal Abbreviations ........................................... 200

References ........................................................................ 203

Curriculum Vitae ............................................................... 227
List of Tables

Table 1: Morita-Baylis-Hillman Reaction by McDougal and Wensley .................. 3

Table 2: Yamamoto’s catalytic Diels-Alder reaction. ........................................ 9

Table 3: Selected results for Yamamoto’s asymmetric catalytic 1,3-dipolar cycloaddition
........................................................................................................................................... 10

Table 4: Selected results from the catalyst optimization for the first enantioselective Fisher
indolization. ........................................................................................................................ 11

Table 5: Selected results for the SGP catalyzed Mannich Reaction. ....................... 30

Table 6: Kita’s work generating substituted \(\beta\)-enamidoesters. ............................ 44

Table 7: Selected results from the diamine substrate table of Sotoca’s work for the
preparation of benzodiazepines via Mannich reaction.............................................. 46

Table 8: Selected data from the catalyst screening and substrate scope of Sha Lou and Amal
Ting’s work on the asymmetric Mannich reaction catalyzed by cinchona alkaloids...... 49

Table 9: Aldehyde substrate scope of Akiyama’s work on Bronsted acid catalyzed Mannich
reaction.............................................................................................................................. 54

Table 10: Direct Mannich Reaction of acac catalyzed by Chiral phosphoric acid........ 56
Table 11: Three-Component Mannich Reaction

Table 12: Conditions screening for achiral Mannich reaction

Table 13: Reactivity of chiral phosphoramidic acids in Asymmetric Mannich Reaction.

Table 14: Conditions screening for enantioselective catalytic Mannich reaction

Table 15: Imine substrate scope

Table 16: Enamide substrate table

Table 17: Effect of catalyst $\textbf{181a}$ concentration on the initial rate of the catalytic Mannich reaction

Table 18: Selected data for condition and catalyst screening for metal catalyzed asymmetric hydrogenation

Table 19: Conditions and reagents screening for borohydride reduction of enamide

Table 20: Catalyst screen for the asymmetric allylboration of ketones

Table 21: Asymmetric arylboration of o-quinonemethides catalyzed by Chiral Brønsted Acids

Table 22: Optimization of the multicomponent boronate reaction for catalyst, temperature and time
Table 23: Optimization of multicomponent boronate reaction for catalyst concentration and temperature.
List of Figures

Figure 1: Chiral cyclic phosphoric acid diesters................................................................. 7

Figure 2: Bifuncionality of chiral Bronsted acids.............................................................. 8

Figure 3: Proposed nine-membered zwitterionic cyclic transition-state model of the phosphoric acid and aldimine. ................................................................. 55

Figure 4: Proposed nine-membered transition state for the Mannich Reaction's Transition state 172. ........................................................................................................... 57

Figure 5: Yields of the three-step preparation of nine chiral phosphoric catalysts. ....... 63

Figure 6: Curtin-Hammett principle rational for γ-regioselectivity in the Mannich reaction. ..................................................................................................................... 74

Figure 7: Plot of initial rate vs. catalyst concentration for the Mannich reaction.......... 80

Figure 8: Chiral phosphines screened as ligands in metal-catalyzed asymmetric hydrogenation ....................................................................................................... 92

Figure 9: Myristinins A 341, B 342, C 343, and D 344, potent DNA polymerase β inhibitors and DNA damaging agents. ................................................................. 155

Figure 10: Common Substituted Chromene Core 355...................................................... 157
Figure 11: Aldehyde substrate scope of multicomponent boronate reaction. ............... 165

Figure 12: Boronate substrate scope of multicomponent boronate reaction. ............... 166
List of Schemes

Scheme 1: Dixon catalytic addition of hydrazine 6 to imine 5 .................................................. 4

Scheme 2: Yamamoto asymmetric nitroso-Diels-Alder catalyzed by Brønsted acid........ 5

Scheme 3: Yamamoto asymmetric α-amination catalyzed by Brønsted acids........... 5

Scheme 4: Chiral phosphoric acid catalysis of Danishefsky Diene nucleophilic attack on aldehydes................................................................. 7

Scheme 5: Mechanism of the Mannich Reaction ................................................................. 15

Scheme 6: Direct catalytic Mannich reactions catalyzed by a Lewis acidic chiral nickel complex 40a with (A) β-ketophosphonates or (B) cyclic amides. ...................... 18

Scheme 7: Direct catalytic Mannich reaction catalyzed by Lewis acidic chiral nickel complex 40a with alkylimines......................................................... 18

Scheme 8: Preparation of chiral 1,2-diamines vie direct asymmetric Mannich reaction of chiral Nickel complexes................................................................. 19

Scheme 9: Preparation of β-aminated-β-ketoesters via direct Mannich reaction, aryl scope ................................................................. 20
Scheme 10: Preparation of β-aminated-β-ketoesters via direct Mannich reaction, ester scope ................................................................. 20

Scheme 11: Schiff base catalyzed nitro-Mannich reaction ........................................... 21

Scheme 12: Reverse selectivity in the Mannich reaction vs. the aldol reaction in presence of L-proline as a chiral auxiliary .............................................................. 23

Scheme 13: Reactions with imino glyoxylates .......................................................... 24

Scheme 14: First anti-selective Mannich reaction ...................................................... 25

Scheme 15: Cinchona alkaloid catalysis .................................................................... 26

Scheme 16: Hydroquinine-derived thiourea catalysis ................................................ 27

Scheme 17: Enantioselective phosphoric acid catalyzed reaction between an aromatic imine and the nucleophilic silylenolether ....................................................... 28

Scheme 18: Brønsted acid-assisted chiral Brønsted acid-catalysis ................................ 29

Scheme 19: Stereoelectronic control in the cyclization initiated by iminium ions to form exo-trig (A) and endo-trig (B) products ............................................................... 32

Scheme 20: Synthesis of Lycopodium alkaloid 101 .................................................. 33

Scheme 21: Stereoelectronically controlled synthesis of Porantherin alkaloid 107 ....... 35

Scheme 22: Schematic reaction path of the aza-Cope ±Mannich cyclization ........... 36
Scheme 23: Overman’s synthesis of (-)-strychnine (112). .................................................. 37

Scheme 24: Enantioselective domino Mannich - Michael reaction.................. 38

Scheme 25: Stevens and coworkers’ domino Reissert/Michael/Mannich cyclization of karachin (126) .................................................................................................................. 39

Scheme 26: Synthesis of bicyclic alkaloids............................................................ 40

Scheme 27: Preparation of Benzodiazepine through Mannich reaction............... 45

Scheme 28: First enantioselective Mannich reaction catalyzed by a chiral Bronsted acid. ............................................................................................................................................. 47

Scheme 29: General scheme of the studied Mannich reaction............................ 48

Scheme 30: Formation of quaternary centers via Mannich reaction of cyclic β-ketoesters. ........................................................................................................................................ 50

Scheme 31: Preparation of substituted chiral dihydropyrimidones via Mannich Reaction. ........................................................................................................................................ 51

Scheme 32: Synthesis of SNAP-7941 (163) via an asymmetric Biginelli and an assymetric Mannich reactions .................................................................................................................... 52

Scheme 33: Proposed mechanism and transtition state in Terada acatalytic Mannich reaction ........................................................................................................................................ 57
Scheme 34: Preparation of chiral Phosphoramidic acids................................. 62

Scheme 35: Plausible mechanism for Mannich reaction via chiral nucleophile .......... 76

Scheme 36: Plausible reaction mechanism for Mannich reaction via trimolecular transition state 197. .................................................................................................................. 77

Scheme 37: Mannich reaction monitored by ReactIR at different concentrations of catalyst to determine the order of reaction in catalyst................................................................. 78

Scheme 38: Ozonolysis of the product of the Mannich reaction to obtain enantiopure β-phenyl-β-alanine benzyl ester. ........................................................................................................... 82

Scheme 39: Cohen and Overman synthesis of batzelladine F. .................................. 84

Scheme 40: An example of application of chiral 1,3-diamines as ligands for metal catalysis. .................................................................................................................................................. 85

Scheme 41: Synthesis of chiral 1,3-diamines for use as ligands in metal catalysis........ 86

Scheme 42: Two carbon homologation of N,O-acetals for the synthesis of chiral 1,3-diamines. ................................................................................................................................. 87

Scheme 43: Asymmetric diastereoselective hydrogenation of dihydrositagliptin to Sitagliptin A in presence of PtO$_2$. ............................................................................................................. 88

Scheme 44: Asymmetric diastereoselective hydrogenation of dehydrositagliptin to Sitagliptin A in presence of chiral ruthenium complexes............................................... 89
Scheme 45: Zhang asymmetric hydrogenation of β-enaminiumesters ......................... 90

Scheme 46: Fox's asymmetric hydrogenation of α-enamidoesters .............................. 90

Scheme 47: Results of the attempts to the hydrogenation of the product of the Mannich reaction ................................................................................................................................................. 95

Scheme 48: Mechanism of the reduction of dienamines in presence of sodium borohydride. ........................................................................................................................................................................ 97

Scheme 49: Reduction of enamines in presence sodium cyanoborohydride. ............... 98

Scheme 50: Mechanism of Palmieri's methodology for a reductive alkylation of carbonyls. ........................................................................................................................................................................ 98

Scheme 51: Results of attempts to reduce the product of the Mannich Reaction in presence of hydridic reagents.................................................................................................................................................................................. 101

Scheme 52: Preparation of chiral Phosphoramidic acids............................................. 105

Scheme 53: Reaction for the preparation of β-enamidoesters..................................... 116

Scheme 54: Reaction for the preparation of Methoxycarbimmine 186 ...................... 118

Scheme 55: Reaction for the preparation of t-Butoxycarbimmines 150 .................... 120

Scheme 56: Mannich Reaction general scheme......................................................... 127
Scheme 57: Synthesis of β-phenyl-β-alanine via ozonolysis of the product of the Mannich reaction

Scheme 58: McCusker observation of exchange of the substituents of the boron

Scheme 59: Roush allylboration catalyzed by tartrates and tartrate amides

Scheme 60: Reaction mechanism proposed by Barnett and Moquist with single BINOL/Boronate exchange

Scheme 61: List and co-workers' acyl-Strecker multicomponent reaction catalyzed by chiral thiourea

Scheme 62: Gong and co-workers' enantioselective Biginelli reaction, catalyzed by a chiral Brønsted Acid

Scheme 63: Schaus and co-workers' asymmetric Petasis reaction catalyzed by VAPOL 29

Scheme 64: Jorgensen and co-workers' asymmetric Hantzsch synthesis of dihydropyridines

Scheme 65: Schreiber's asymmetric Passerini reaction catalyzed by a copper based chiral Lewis acid

Scheme 66: General Scheme of the Ugi four-component reaction
Scheme 67: Luan's work on homodimerization of dihydrochromenes catalyzed by Fe (III). ................................................................. 151

Scheme 68: Deuterium labelling studies for the elucidation of the mechanism of the homodimerization of dihydrochromenes. ........................................................................... 152

Scheme 69: Organocatalytic acid-driven multicomponent boronate reaction for the synthesis of chiral benzhydrils. ....................................................................................... 154

Scheme 70: Maloney Synthesis of Myristinin A ................................................................. 157

Scheme 71: Synthetic Route for Producing Catalysts 286 and 359 .............................. 159

Scheme 72: Synthetic Route for the preparation of styrylboronate 338 from ethynylbenzene. ......................................................................................................................... 160

Scheme 73: Detailed catalytic mechanism for the multicomponent boronate reaction and transition state with the rational for enantioselectivity. ............................................. 168

Scheme 74: Preparation of styrylboronates 338. ............................................................. 172

Scheme 75: Preparation of catalysts 286 and 359. .......................................................... 174

Scheme 76: General Scheme for aldehyde substrate scope of asymmetric multicomponent boronate reaction.................................................................................................... 177

Scheme 77: General Scheme for boronate substrate scope of asymmetric multicomponent boronate reaction.................................................................................................... 185
Scheme 78: Nine novel chiral phosphoramidic acids were designed and prepared. They were also applied to develop the methodology of a new asymmetric Mannich reaction.

Scheme 79: Synthesis of enantiopure aminoacids via oxonolysis of the product of the asymmetric Mannich reaction.

Scheme 80: Failed attempt to diastereoselectively hydrogenate the product of the asymmetric Mannich reaction.

Scheme 81: Failed attempts to reduce the enamine of the product of the asymmetric Mannich reaction with hydridic reagents.

Scheme 82: An asymmetric three-components reaction involving a boronate molecule as the nucleophile and catalyzed by chiral Brønsted acids was developed.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>BINAM</td>
<td>1,1'-binaphthalene-2,2'-diamine</td>
</tr>
<tr>
<td>BINAP</td>
<td>binaphthalene-2,2'-diyl)bis(diphenylphosphine)</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-binaphthalene-2,2'-diol</td>
</tr>
<tr>
<td>CAN</td>
<td>cerium ammonium nitrate</td>
</tr>
<tr>
<td>CSA</td>
<td>camphor sulfonic acid</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>de</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
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</table>
eqv  equivalents
er  enantiomeric ratio
ESI-MS  electrospray ionization mass spectrometry
h  hour
H$_8$BINOL  5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol
HMDS  hexamethyldisilazane
HPLC  high performance liquid chromatography
KIE  kinetic isotope effect
LDA  lithium diisopropylamide
LHMDS  lithium hexamethyldisilazide
M  molarity
min  minute
MHz  megahertz
mol  mole
MOM  methoxymethyl
NBS  N-bromosuccinimide

xxviii
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nd</td>
<td>not determined</td>
</tr>
<tr>
<td>NMI</td>
<td>(N)-methylimidazole</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>PMP</td>
<td>(para)-methoxyphenyl</td>
</tr>
<tr>
<td>PEG</td>
<td>polyethyleneglycol</td>
</tr>
<tr>
<td>PHANAP</td>
<td>4,12-di(diphenyl)phosphino[2.2]paracyclophane</td>
</tr>
<tr>
<td>PHANOL</td>
<td>4,12-dihydroxy[2.2]paracyclophane</td>
</tr>
<tr>
<td>pKA</td>
<td>acid dissociation constant</td>
</tr>
<tr>
<td>psi</td>
<td>Pounds per squared inch</td>
</tr>
<tr>
<td>RDS</td>
<td>rate determining step</td>
</tr>
<tr>
<td>ROESY</td>
<td>rotating frame Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>t(_{1/2})</td>
<td>half life</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
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Chapter 1. Introduction. Organocatalysis and chiral Brønsted Acids.

1.1 Brønsted Acid Catalysis

Protons have the ability to activate many organic functional groups through formation of hydrogen bonds with heteroatoms. Molecules able to donate protons have been used for decades as catalysts and reactants in organic reactions. Such molecules are known as Brønsted Acids, after Johannes Nicolaus Brønsted who proposed the acid theory along with Thomas Martin Lowry, who independently reported the same idea in 1923.

Mineral Brønsted acids, their properties and their strengths were already known in the Middle Ages by the first alchemists: the mixture of fuming nitric acid and concentrated hydrochloric acid in the ratio of 1:3, for example, was called Aqua regia (royal water). It was so named because it can dissolve the "royal metals", such as gold and platinum. By end of the nineteenth century, the use of Brønsted acids became systematic. One of the most famous examples of Brønsted acid catalysis is the Fisher esterification. Fischer esterification, or Fischer-Speier esterification, is the esterification of a carboxylic acid with an alcohol in the presence of an acid catalyst. The reaction was first described by Emil Fischer and Arthur Speier in 1895. Other common examples of Brønsted acid-catalyzed classic reactions include the nitration of benzene, hydrolysis of ethers, hydrolysis of esters...
and thousands of other reactions that chemists have discovered, invented or modified in almost one and a half centuries of organic chemistry.

Towards the end of the 1960s, synthetic organic chemists began to develop asymmetric organic reactions. However, it is only in the 1990s that most of the organic reactions have been performed enantioselectively using systems based on chiral Lewis acids. During the last years of the twentieth century the innovation of chiral acids as catalysts expanded from Lewis acids to include chiral Brønsted acids. Chiral Brønsted acids are compounds able to transfer their chiral information to the reaction via hydrogen bonds rather than metal chelation to favor facial selectivity.

1,1’-Bi-2-naphthols, commonly known as BINOLs, are among the most commonly used sources of chiral Brønsted acidity. A summary of the work carried out in our lab by McDougal and Wensley on an enantioselective Morita-Baylis-Hillman (MBH) reaction catalyzed by substituted octahydro-BINOL 3 is shown in Table 1. McDougal and Wensley were able to obtain the MBH adduct of cyclohexenone or cyclopentenone, and a range of aliphatic aldehydes in good yields and high enantioselectivity.
Table 1: Morita-Baylis-Hillman Reaction by McDougal and Wensley

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCH$_2$CH$_2$</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>(Z)-CH$_3$CH=CH(CH$_2$)$_2$</td>
<td>72</td>
<td>96</td>
</tr>
<tr>
<td>$c$-C$<em>6$H$</em>{11}$</td>
<td>71</td>
<td>96</td>
</tr>
<tr>
<td>$i$-Pr</td>
<td>82</td>
<td>95</td>
</tr>
<tr>
<td>PhCH=CH</td>
<td>39</td>
<td>81</td>
</tr>
</tbody>
</table>

An example of a very different system to which the same class of catalysts, substituted BINOLs, was applied is the work of Dixon and co-workers. In 2005, they reported that tetrol 7 catalyzed the addition of methyleneaminopyrrolidine to imines, producing $\alpha$-aminoazabicyclo[3.2.1]octanes in up to 75% ee.\textsuperscript{7} (Scheme 1).
A further example of the diverse applications of chiral BINOL derivatives as catalysts for enantioselective reactions is the hetero-Diels-Alder reaction reported in 2007 by Yamamoto and co-workers.\textsuperscript{10} The reaction of a diene with nitrosoarenes catalyzed by substituted BINOL \textbf{11} yielded bicyclketones in good yield and high enantioselectivity (\textbf{Scheme 2}), while the reaction of the same nitroso compound with an enamine resulted in enantioselective $\alpha$-amination. (\textbf{Scheme 3}).\textsuperscript{11} Many examples of Bronsted Acid catalyzed Mannich and Mannich-type reactions have also been reported in literature and will be discussed in Chapters 2 and 3.
Scheme 2: Yamamoto asymmetric nitroso-Diels-Alder catalyzed by Brønsted acid.

Scheme 3: Yamamoto asymmetric α-amination catalyzed by Brønsted acids.
1.2 Chiral phosphoric and phosphoramidic acids

An interesting class of chiral Brønsted acids is chiral phosphoric acids. Such organocatalysts have unique characteristics. Their cyclic structure allows formation of a ring structure, which can restricts free rotation. This characteristic feature cannot be found in other common Brønsted acids, such as carboxylic and sulfonic acids. Furthermore, the acidic proton can complex to a basic site on an electrophile via hydrogen-bonding while the phosphoryl oxygen can simultaneously function as a Lewis base through coordination to the nucleophile; thus, a phosphoric acid could serve as a bifunctional catalyst (Figure 2).

1.2.1. Phosphoric Acids as catalysts in Mannich and Mannich type reactions

1.2.1.1. State of the art

Chiral cyclic phosphoric acid 15 (Figure 1), derived from (R)-BINOL, was initially employed as a chiral resolving agent. In 1991, Wilen and co-workers used BINOL-
phosphoric acid to form the salts of chiral benzylic alcohols and was able to achieve chiral resolution by crystallization.\textsuperscript{12}

![Chemical Structure]

Figure 1: Chiral cyclic phosphoric acid diesters.

Beginning in 1995, chiral phosphoric acids were designed and synthesized as chiral organocatalysts. Inanaga and co-workers employed ytterbium (III) BINOL-phosphate as a catalyst for the hetero Diels–Alder reaction between aromatic aldehydes and Danishefsky diene (Scheme 4).\textsuperscript{13-20}

![Chemical Reaction]

Scheme 4: Chiral phosphoric acid catalysis of Danishefsky Diene nucleophilic attack on aldehydes.
In 2004, Akiyama reported that \((R)-3,3'\text{-di(4-nitrophenyl)}\text{-BINOL-phosphoric acid (15c)}\) exhibited catalytic activity as a chiral Brønsted acid.\(^{21}\) Terada also independently reported the catalytic activity of BINOL-phosphoric acids.\(^{22}\) At this point, chiral phosphoric acids were acknowledged as novel chiral catalysts.\(^{23}\) One of the main reasons chiral phosphoric acids have been extensively studied and successfully applied to a wide range of C-C bond forming reactions is their ability to work as bifunctional catalysts.\(^{24}\) They bear both a Brønsted-acidic site and a Brønsted-basic site, which are able to coordinate the nucleophile and electrophile via H-bonds. The 3,3'-substituents play a crucial role in attaining excellent enantioselectivity due to their steric interactions during the formation of the transition state complex (Figure 2).

Many examples of Brønsted acid and combined Lewis/Brønsted acid adducts to catalyze different systems can be found in the work of Hisashi Yamamoto.\(^{6-11,25-26}\) In 2006,
Yamamoto and co-workers reported a chiral phosphoramidate 21b catalyzed Diel-Alder reaction between ethylvinylketone and diene 20 in 95% yield and 92% ee enantioselectivity (Table 2). In 2008, they reported the application of the same class of catalysts to a 1,3-dipolar cycloaddition of nitrones to ethylvinyloxyether (Table 3).9

Table 2: Yamamoto’s catalytic Diels-Alder reaction.

<table>
<thead>
<tr>
<th>Diene</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>15b</td>
<td>DCM</td>
<td>2</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>21a</td>
<td>DCM</td>
<td>2</td>
<td>91</td>
<td>9 (S)</td>
</tr>
<tr>
<td>19</td>
<td>21b</td>
<td>DCM</td>
<td>1</td>
<td>86</td>
<td>32 (R)</td>
</tr>
<tr>
<td>20</td>
<td>15b</td>
<td>Toluene</td>
<td>3</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>21a</td>
<td>Toluene</td>
<td>3</td>
<td>&lt;10</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>21b</td>
<td>Toluene</td>
<td>3</td>
<td>95*</td>
<td>92</td>
</tr>
</tbody>
</table>

*mixture of regioisomers.
Table 3: Selected results for Yamamoto's asymmetric catalytic 1,3-dipolar cycloaddition

<table>
<thead>
<tr>
<th>Catalyst (R group)</th>
<th>Yield (%)</th>
<th>endo:exo</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Catalyst 21x" /></td>
<td>92</td>
<td>90:10</td>
<td>76</td>
</tr>
<tr>
<td>adamantyl</td>
<td>92</td>
<td>96:4</td>
<td>84</td>
</tr>
</tbody>
</table>

In 2008, Yamamoto and co-workers also reported the application of chiral phosphoric acids to enantioselective protonation. Using the catalysis of 3,3’ disubstituted BINOL-phosphoric acids and phosphoramides, they were able to asymmetrically promote the tautomerization of silylenolethers to ketones. Through the application of this class of catalysts, in 2011, List and co-workers were able to obtain the first enantioselective Fisher indolization. The results are shown in Table 4; yields up to 98% and enantiomeric ratios up to 93.5:6.5 were reported.
Table 4: Selected results from the catalyst optimization for the first enantioselective Fisher indolization.

![Diagram](image)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Additive</th>
<th>X</th>
<th>% Y</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP</td>
<td>-</td>
<td>H</td>
<td>83</td>
<td>-</td>
</tr>
<tr>
<td>DPP</td>
<td>-</td>
<td>H</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>DPP</td>
<td>CG50</td>
<td>H</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>CG50</td>
<td>H</td>
<td>&lt;5</td>
<td>-</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Additive</th>
<th>X</th>
<th>% Y</th>
<th>er</th>
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<tr>
<td>15f</td>
<td>CG50</td>
<td>H</td>
<td>75</td>
<td>85:15</td>
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<td>27e</td>
<td>CG50</td>
<td>H</td>
<td>66</td>
<td>74:26</td>
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<tr>
<td>28f</td>
<td>CG50</td>
<td>H</td>
<td>98</td>
<td>93.5:6.5</td>
</tr>
<tr>
<td>29</td>
<td>CG50</td>
<td>H</td>
<td>52</td>
<td>49.5:50.5</td>
</tr>
<tr>
<td>28f</td>
<td>CG50 + 4Å MS</td>
<td>I</td>
<td>98</td>
<td>95:5</td>
</tr>
</tbody>
</table>
1.3 Chiral Phosphoramidic acids as catalysts

While chiral phosphoric acids have been extensively studied and successfully applied to a variety of organic reactions such as the asymmetric Mannich reaction, the closely related class of phosphoramidic acids has not been adequately developed. The preparation of these catalysts was described in a patent, but without reporting an application.

Our interest in this class of compounds arises from their unique characteristics. Their acidity is in the same range as some of the most common organic Brønsted acids, such as p-toluensulfonic acid and trifluoroacetic acid. If a class of chiral catalysts can be developed that regio, diastereo, and enantioselectively promotes reactions traditionally carried out in presence of simple Brønsted acids (p-TSA and TFA), they will have a very broad and diverse range of applications. In order to give a deeper insight to the mechanism of the transmission of the chiral information from the catalyst to the final products, a study of the mechanisms of such Brønsted acid asymmetrically catalyzed processes was crucial. A better understanding of the peculiarity of this class of compounds will help design further and broader applications. For these reasons, we have chosen to develop and thoroughly study the mechanisms of two quite different reactions: the Mannich reaction between an arylimine and a β-enamidoester, and a multicomponent boronate reaction catalyzed by substituted BINOLs. Both reactions are organocatalytic, Brønsted acid driven, and are
viable methods to asymmetrically prepare substituted chiral benzhydriils. Further steps were also taken to explore the synthetic applications of the products of the Mannich reactions, such as the ozonolysis of the enamide olefin to prepare enantiopure amino acids and the reduction of the same double bond to enantio- and diastereoselectively prepare chiral 1,3-diamines.
Chapter 2: Recent advances in the Mannich reaction.

2.1 The Mannich reaction

The aminoalkylation of enolizable compounds was described by several authors as early as the 19th century. However, Carl Mannich was the first to recognize the enormous significance of this reaction type, and it was he who extended the chemistry into a broad based synthetic methodology through systematic research. Since then, the reaction that now carries his name has developed into an important carbon-carbon bond-forming reactions in organic chemistry. In practice, enolizable aldehydes or ketones serve as the CH-acidic substrate for Mannich reactions. After activation of the aldehyde 1 by protonation, the amine 31 adds as a nucleophile the electrophilic carbonyl carbon, forming the protonated hemiaminal 32a. The tautomeric form of the protonated emiaminal 32b eliminates water to form the imine 33. The enol 34 then adds to the electrophilic carbon of imine 33, to form adduct 35, which upon deprotonation yields the β-amino ketone 36 (Scheme 5).
Despite having been widely studied and successfully applied in the synthesis of molecules of interest, the Mannich reaction maintains serious limitations: classically, enolizable aldehydes can not be used as electrophiles; the Mannich reaction can not be carried out in strongly basic environment; a widely applicable method to achieve regio, and stereoselectivities was never found; and several biproducts can form during the process. The efforts to overcome such limitations and the versatility of $\beta$-aminocarbonyl compounds as synthetic building blocks have led to the search for more readily accessible catalysts and more convenient methodologies. One key to success has been the use of pre-formed Mannich reagents. Some of the most commonly pre-formed reagents for the Mannich reaction include: imines, aminals, N- and O-acetals and iminium salts as
electrophile, and enols, enolates, enamines, boro-, silyl- and alkylenolethers as nucleophiles.

In general, the Mannich reaction is very versatile, but the main synthetic interest derives from the possibility of generating the resulting stereocenters for applications to the synthesis of complex molecules. In Section 2.2, a description of the most widely used methods to direct the selectivity of the Mannich reaction is reported.
2.2 The asymmetric Mannich reaction

2.2.1. Lewis acid catalysis

The asymmetric Mannich reaction is an important process for the highly enantioselective and diastereoselective formation of C–C bonds. Many protocols have been developed for asymmetric Lewis acid catalyzed Mannich reactions. Only some of the most recent publications will be reported here.

Dinuclear nickel metal catalysis has been applied to direct asymmetric Mannich-type reactions with high yield and stereoselectivity. In 2008, Matsunaga and Shibasaki\(^{30}\) reported the direct catalytic asymmetric Mannich-type reactions of β-keto phosphonates with aryl and heteroaryl N-Boc imines promoted by a homodinuclear Ni\(_2\)-Schiff base complex 40a (Scheme 6A). The resulting β-amino phosphonates were obtained in 43-90% yield, 20:1-2:1 dr, and 47-99% ee. Two years later, they developed the direct catalytic asymmetric vinylogous Mannich-type and Michael reactions of α,β-unsaturated γ-butyrolactam and N-Boc imines under dinuclear nickel catalysis.\(^{31}\) The dinuclear Ni-catalyzed reactions proceeded selectively at the γ-position, giving vinylogous Mannich adducts in 5:1-30:1 dr and 99% ee (Scheme 6B) and vinylogous Michael adducts in 16:1-30:1 dr and 93-99% ee (Scheme 7).
Scheme 6: Direct catalytic Mannich reactions catalyzed by a Lewis acidic chiral nickel complex 40a with (A) β-ketophosphonates or (B) cyclic amides.

Scheme 7: Direct catalytic Mannich reaction catalyzed by Lewis acidic chiral nickel complex 40a with alkylimines.
Hong and co-workers\textsuperscript{32} described a practical and highly efficient enantio- and diastereoselective route to \textit{syn} configured \(\alpha,\beta\)-diamino acids employing a chiral Ni(II) complex of glycine and \(\alpha\)-amino sulfones. This process forms a carbon-carbon bond and two stereogenic centers in a single step (Scheme 8), representing an attractive route to the synthesis \(\alpha,\beta\)-diamino acids.

Scheme 8: Preparation of chiral 1,2-diamines via direct asymmetric Mannich reaction of chiral Nickel complexes.

In 2011, Kang and Kim developed the highly efficient catalytic enantioselective Mannich reaction of \(\alpha\)-fluoro-\(\beta\)-ketoesters, catalyzed by chiral palladium complexes \textbf{51}, which are air and moisture stable.\textsuperscript{33} The desired \(\beta\)-aminated products were obtained in good to high yields, and high enantioselectivities (up to 99\% ee) were observed for all the substrates examined in this work. This method provided a practical entry for the preparation of chiral \(\beta\)-aminated \(\alpha\)-fluoro-\(\beta\)-ketoesters derivatives (Scheme 9 and 10).
Matsunaga and Shibasaki described the full details of a catalytic asymmetric syn-selective nitro-Mannich reaction promoted by heterobimetallic Cu/Sm/dinucleating Schiff base complexes. In the published work, they demonstrated the effectiveness of the heterobimetallic transition metal/rare earth metal bifunctional catalysis with ligand 40b (Scheme 11). The first-generation system prepared from Cu(OAc)$_2$/Sm(O-iPr)$_3$/40b 1:1:1 with an achiral phenol additive was partially successful for achieving the syn-selective, catalytic,
asymmetric nitro-Mannich reaction. The application of this catalytic system to a broad range of substrates remained a problematic limitation of the first-generation system. After mechanistic studies on the catalyst prepared from Sm(O-iPr)$_3$, they re-optimized the catalyst preparation method, and a catalyst derived from Sm$_3$O(O-iPr)$_{13}$ showed broader substrate generality as well as higher reactivity and stereoselectivity compared to Sm(O-iPr)$_3$. They were able to apply the optimal system with Sm$_3$O(O-iPr)$_{13}$ to various aromatic, heteroaromatic, and isomerizable aliphatic N-Boc imines, giving products in 66-99% ee and syn/anti $>20:1$-$13:1$.

Scheme 11: Schiff base catalyzed nitro-Mannich reaction
2.2.2. Organocatalysis

In recent years, organocatalyzed versions of asymmetric Mannich processes have been increasingly reported and used in a rapidly growing number of applications. This review provides an overview of the recent history of the asymmetric organocatalyzed Mannich reaction, including scope and limitations, and application of different catalyst systems. The most important organocatalytic approaches can be organized in three classes: (i) chiral amines (via enamine formation) as chiral auxiliaries, (ii) chiral Brønsted bases, and (iii) chiral Brønsted acids as catalysts.

2.2.2.1. Catalysis via chiral auxiliary

Chiral amines have the possibility to react with Mannich donors such as ketones or aldehydes. The resulting chiral enamines can add to a Mannich acceptor, usually a prochiral aldimine, thereby introducing one or two chiral centers in the Mannich product. The catalytic cycle is completed by regeneration of the amine catalyst through hydrolysis.

The first example was published in 1981 by Dieter Seebach.\textsuperscript{35-37} The proline substituent on the nitrogen of the enamine (nucleophile) directed the face-selective addition to the aldehyde with the R group in the less hindered orientation in the case of the aldol reaction (57a) to produce adduct 58a. In the case of the Mannich reaction \textit{via} 57b instead, the presence of the R\textsubscript{1} group on the imine’s nitrogen and the \textit{trans} configuration of the
double bond, allowed only one orientation of the imine during the formation of the hydrogen-bond complex between the nitrogen lone pair and the proline proton, overcoming the R-R\textsuperscript{2} steric hinderance. This caused a reversal of facial selectivity, which resulted in the opposite stereochemistry in the final product 58b. (Scheme 12).\textsuperscript{35-37}

![Scheme 12: Reverse selectivity in the Mannich reaction vs. the aldol reaction in presence of L-proline as a chiral auxiliary.](image-url)

In 2000, List broadened the application of proline to the direct three-component asymmetric Mannich reaction.\textsuperscript{39} List and co-workers reported a one-pot, three-component reaction involving a ketone, aldehyde and a primary amine, which provided the desired
Mannich product in enantiopure form. Shortly thereafter, the Barbas group published similar results on proline-catalyzed asymmetric Mannich reactions. They independently discovered the previously mentioned one-pot three-component proline-catalyzed asymmetric Mannich reaction. Their focus quickly turned to conditions involving pre-formed imines. In 2002, a highly enantioselective proline-catalyzed reaction of ketones with PMP-protected ethyl iminoglyoxylate was reported, which gave the corresponding β-keto-α-amino acid derivatives in high yields (Scheme 13).

Mechanistically, the stereochemical outcome of all of these reactions can be explained by invoking a transition state as depicted in Scheme 12. The stereochemical repulsion between the PMP-group and the proline moiety, in combination with protonation of the imine by the acid-functionality of proline, accounts for a si-face addition to the (E)-aldimine by the si-face of the (E)-enamine formed by the ketone and proline. This model
explains the stereochemical outcome of many similar reactions that have appeared in literature.

In 2002, Barbas and co-workers reported a \((R)\)-proline (RMP) catalyzed asymmetric Mannich-type reaction of unmodified aldehydes \(68\) with PMP-protected imino ethyl glyoxylate \(66\), which proceeded in a highly \emph{anti}-selective manner to produce adduct \(69\) (Scheme 14).\(^{40}\)

\[
\begin{array}{c}
\text{O} \\
\text{R'} \\
\text{EtO}_2\text{C} \\
\text{H} \\
\end{array} \quad \text{PMP} \quad \text{D-proline (20 mol\%)} \quad \text{DMSO, r.t.} \quad \begin{array}{c}
\text{O} \\
\text{HN} \text{ CO}_2\text{Et} \\
\text{R''} \\
\end{array}
\]

Scheme 14: First \emph{anti}-selective Mannich reaction.

2.2.2.2. Catalysis via Brønsted bases: the use of Cinchona alkaloids

In the previous examples, the crucial C–C-bond forming step occurred through the reaction of an enamine nucleophile with a protonated imine. The protonation of the imine is essential to render it sufficiently electrophilic to react with the enantiomerically pure nucleophilic enamine.

It is, however, also possible to react nucleophiles with neutral imines, although in these cases an electron-withdrawing substituent on the imine nitrogen is generally required
for adequate reactivity. The nucleophile is often derived from an acidic methylene compound. Deprotonation with a chiral amine, provides a chiral ion pair of which the anion reacts with the Mannich acceptor in an enantioselective fashion. The presence of a thiourea moiety can enhance the reaction, most likely through cooperative hydrogen bonding with the imine precursor, thereby rendering it more active towards nucleophilic attack. In 2005, Schaus and co-workers reported the development of a diastereo- and enantioselective direct Mannich reaction of β-ketoesters 70 to acyl aryl imines 71 catalyzed by alkaloids cinchonine 73 and cinchonidine 74 (Scheme 15). The reaction generated enantioenriched dihydropyrimidones and β-amino alcohols 72.42-43

![Scheme 15: Cinchona alkaloid catalysis.](image-url)
Schaus and co-workers also found that the hydroquinine-derived thiourea $77$ could serve as an effective catalyst as well. The reaction between dimethyl malonate $76$ and a variety of methyl carbamate-protected aromatic imines $75$ afforded the corresponding Mannich adducts $78$ in good selectivities and nearly quantitative yields (Scheme 16).  

![Scheme 16: Hydroquinine-derived thiourea catalysis.](image)

2.2.2.3. Catalysis via Brønsted acids

A third pathway for enantioselective organocatalyzed Mannich reactions proceeds via enantiopure Brønsted acids. In this case the acid protonates the imine, leading to an iminium ion with an enantiopure counterion. This coordinating counterion directs the
incoming nucleophile and leads to an optically active Mannich product. Most often, the acids involved are readily accessible enantiopure phosphoric acids.

An early example was reported by Akiyama and co-workers. They synthesized a series of chiral phosphates, and phosphoric acid 81 provided the best combination of yield and enantioselectivity. Reaction of the aromatic aldimines 79 with silyl ketene acetal 80 (80a: R₁ = R₂ = Me) catalyzed by 81 afforded the Mannich bases 82 in excellent yield (98–100%) and reasonable enantioselectivity (80–89% ee). Addition of monosubstituted silyl ketene acetals 80 (80b: R₁ = H, R₂ = Me, Bn) to aromatic aldimines 79 led to highly syn-selective reactions (dr 87:13 to 95:5 (syn:anti)), while the enantioselectivity was also maintained (81–96% ee). In addition, it was concluded that the hydroxy-substituent on the ortho-position of the protecting group was essential to ensure high levels of enantioselectivity (Scheme 17).

Scheme 17: Enantioselective phosphoric acid catalyzed reaction between an aromatic imine and the nucleophilic silylenoether.
Schoepke and co-workers reported the first enantioselective Brønsted acid-assisted, chiral Brønsted acid-catalyzed, direct Mannich reaction of poorly reactive acetophenone.\(^{45}\) They reasoned that activation of the aldimine should occur via ion pair formation with the chiral Brønsted acid, while activation of the ketone donor must be mediated by an achiral acid which cannot form an ion pair with the aldimine. Elaborating on this concept, the reaction of acetophenone with the N-4-chlorophenyl-protected aldimine 83 was investigated using the chiral BINOL-phosphate 85 in combination with acetic acid, which led to a high selectivity (76% ee) (Scheme 18).

Scheme 18: Brønsted acid-assisted chiral Brønsted acid-catalysis.

In Chapter 3 of this dissertation, our work on the use of chiral Bronsted acids as catalysts for an asymmetric Mannich reaction to influence the regioselectivity of a β-enamidoester nucleophile, while maintaining high enantioselectivity, will be described.
2.2.3. Enzyme catalyzed Mannich reaction

In 2012, He and co-workers reported the first and only enzyme catalyzed asymmetric Mannich reaction using protease type XIV from *Streptomyces griseus* (SGP) in acetonitrile. They were able to achieve yields of up to 87%, enantioselectivities up to 82% e.e., and diastereoselectivities up to 88:12 (syn:anti) (Table 5).47

Table 5: Selected results for the SGP catalyzed Mannich Reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>dr (syn:anti)</th>
<th>e.e. (syn) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Protease type XIV from <em>Streptomyces</em></td>
<td>66</td>
<td>85:15</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>griseus (SGP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>28</td>
<td>41:59</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Albumin from chicken egg white</td>
<td>23</td>
<td>46:54</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Albumin from bovine serum</td>
<td>21</td>
<td>58:42</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>SGP denatured with urea</td>
<td>87</td>
<td>48:52</td>
<td>8</td>
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<tr>
<td>6</td>
<td>Urea</td>
<td>28</td>
<td>39:61</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>SGP pretreated with 2.5 mM Cu$^{2+}$</td>
<td>62</td>
<td>88:12</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>SGP pretreated with 25 mM Cu$^{2+}$</td>
<td>61</td>
<td>87:13</td>
<td>77</td>
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<tr>
<td>9</td>
<td>SGP pretreated with 250 mM Cu$^{2+}$</td>
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<td>43:57</td>
<td>9</td>
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<tr>
<td>10</td>
<td>SGP pretreated with 2.5 mM Ag$^{+}$</td>
<td>60</td>
<td>88:12</td>
<td>82</td>
</tr>
<tr>
<td>11</td>
<td>SGP pretreated with 2.5 mM Ag$^{+}$</td>
<td>65</td>
<td>82:18</td>
<td>74</td>
</tr>
<tr>
<td>12</td>
<td>SGP pretreated with 2.5 mM Ag$^{+}$</td>
<td>67</td>
<td>38:62</td>
<td>8</td>
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</table>
2.3. Synthetic applications of the Mannich reaction

The inter- and intramolecular versions of the Mannich reaction are both very important methods for the preparation of *aza*-cyclic products from acyclic precursors. The practicality of the Mannich reaction is well documented in a multitude of syntheses of alkaloids.\(^{48-50}\) In contrast to the intermolecular Mannich reaction, the intramolecular variant is not restricted to aminomethylation, but can also be applied to aminoalkylations. Its chemoselectivity also offers a much wider range of potential applications. Furthermore, the regio and stereoselectivity of the intramolecular Mannich reaction are governed by a series of rules that allow the prediction of the reaction path as an important precondition for the synthesis of natural products. Thus, Baldwins’ selection rules, developed for the cyclization of olefins, can be applied to iminium ions. Cyclic products can be formed according to either an exocyclic-trigonal (A) or an endocyclic-trigonal process (B) (Scheme 19).\(^{49,51-52}\)
Scheme 19: Stereoelectronic control in the cyclization initiated by iminium ions to form exo-trig (A) and endo-trig (B) products.

The stereochemical pathway of a nucleophilic addition to an iminium ion is often controlled by stereoelectronic factors (Scheme 19)\textsuperscript{53} because of the antiperiplanar conformation of the electron pair of the nucleophile and the incoming electrophile. Reliable predictions can therefore be made about the stereoselectivity of the cyclization. An excellent example of this stereocontrolled reaction is in Heathcock’s synthesis of \textit{Lycopodium} alkaloid 101 (Scheme 20).\textsuperscript{54, 55}
The starting material, a mixture of 96 and 99, which are epimeric at C2, cyclizes to give the single isomer 98 in 66% yield. This result can be explained by assuming an equilibration of the starting material after hydrolysis of the protecting group; a cyclization via the transition state 100 is impossible for stereoelectronic reasons: the electrophile is inaccessible by the enol. Thus the final cyclization proceeds through intermediate 97 with the ketone in an axial position. In this synthetic sequence another major advantage of...
parallel epimeric syntheses is exemplified: regio- and stereochemical considerations are reduced to a minimum with both epimers leading to the same product.\textsuperscript{56}

Similarly, the stereoelectronically controlled Mannich cyclization is responsible for the diastereoselective construction of the quadricycle in the synthesis of the \textit{Porantherin} alkaloid \textbf{107} (Scheme 21). The formations of the four rings are formally a sequence of two multicomponent Mannich reactions. Initial addition of the nitrogen to one of the ketones, followed by intramolecular Mannich addition of the enolized tautomer of the other ketone determines the formation of rings \textit{A} and \textit{B}. Thus, the nitrogen adds to the aldehyde forming a cyclic iminium ion (ring \textit{C}), this step is followed by a second intramolecular Mannich addition of the enole formed on the ketone to the iminium ion to form ring \textit{D}.\textsuperscript{57}
There are many examples of syntheses of natural products in which Mannich cyclizations have been used to construct a) pyrrolidines, b) piperidines, c) bicycloalkaloids with nitrogen as the bridge atom, and d) carbocyclic products. The sequence of cationic aza-Cope rearrangement and Mannich cyclization (Scheme 22) in which pyrrolidines (both mono- and polycyclic) are formed has served many groups in their work relating to the total synthesis of alkaloids.
Scheme 22: Schematic reaction path of the aza-Cope ±Mannich cyclization.

The synthesis of (-)-strychnine (112) by the Overman group represents one of the highlights of the sequential cationic aza-Cope rearrangement/Mannich reaction strategy.\textsuperscript{58} In contrast to the route of Woodward, who chose to prepare strychnine from isostrychnine (111), Overman utilized a route involving the Wieland - Gumlich aldehyde 113 (Scheme 23).\textsuperscript{59-61} After initial formation of the iminium ion 115 through addition of the nitrogen to paraformaldehyde, a pericyclic aza-Cope reaction broke the five member ring forming a new iminium ion and an enol (116). The Mannich type addition of the enol to the iminium ion formed the five-membered heterocycle and the six membered cycle 117. Through further steps of dehydrogenation, conjugate addition and acetal formation allowed for the formation of the Wieland-Gumlich aldehyde 113, final precursor for the synthesis of strychnine 112. The central step, involving the aza-Cope/Mannich tandem for the transformation of precursor 114 into 117, was obtained in the excellent yield of 98%.
Another example of a tandem system involving a Mannich reaction is the intermolecular Mannich/Michael domino reactions, which was successfully applied to the synthesis of a range of piperidine alkaloids by Waldmann and co-workers in 1996 and 1997. (Scheme 24). Upon activation of electrophile 118 via coordination with the Lewis acidic catalyst 120, the TMS protected enol 119 added to the imine forming a nucleophilic amine and an electrophilic $\alpha,\beta$-unsaturated ketone, which then reacted intramolecularly
via a Michael addiction to form adduct 121 as a precursor for the syntheses of yohimbine and reserpine-type alkaloids.\textsuperscript{63}

![Diagram of reactions](image)

Scheme 24: Enantioselective domino Mannich - Michael reaction.

These domino sequences can also be applied intramolecularly, as in the synthesis of the alkaloid karachin 123 (Scheme 25).\textsuperscript{64-65} In this example, a domino sequence takes place as follows: a Reissert reaction (122 to 124) is succeeded by a Michael reaction (124 to 125) and then another Mannich reaction (125 to 123). Three C-C bonds are formed sequentially. This example demonstrates the efficiency with which Mannich cyclizations can be carried out, and displays atom economy.\textsuperscript{63} When berberin 122 is treated with excess of the diene for 18 h at 100°C, the yield of the overall sequence is 66%.

\[ Y = 24\text{–}62\% \]
\[ \text{dr} = 88:12\text{–}98:2 \]
\[ \text{er (for } R=H) = 63:37 \]
The syntheses of bicyclic systems which, in analogy to tropinone 126, have nitrogen as the bridging atom are considered classic examples of this methodology (Scheme 26).
Scheme 26: Synthesis of bicyclic alkaloids.
The synthesis of anatoxin A 127, carried out by Robinson in 1917, and those of ferrugitin 128 by Hess, and epibatidin 129 by Trudell, are still frequently used today for the synthesis of these pharmacologically active materials.

In this chapter, we saw that the Mannich reaction is an important synthetic methodology. It was applied to the synthesis of several different molecules, both inter and intramolecularly. Few different methodologies have been developed to direct the stereoselectivity of the reaction. In Chapter 3, we will discuss an advancement in the Brønsted acid catalyzed Mannich reaction, where excellent regioselectivity is combined with good enantioselectivity.
Chapter 3: Asymmetric Organocatalyzed Mannich Reaction.

Synthesis of novel chiral phosphoramidic acids and their application as organocatalysts in the Mannich reaction.

3.1 Introduction

As demonstrated in Chapter 2, the Mannich reaction can be catalyzed by Brønsted acids. Imine formation involves the nucleophilic addition of an amine to a carbonyl group followed by dehydration to a Schiff base. The Schiff base electrophile reacts in the second step with the nucleophilic carbon of an enolizable compound. During the reaction, a stereogenic center is formed at the carbon originally bearing the carbonyl. The Mannich reaction has been studied under several different conditions and two different ways to direct the enantioselectivity are known: use of a chiral amine as an auxiliary or use of a chiral catalyst.

In this chapter, we will see how the application of chiral phosphoric acid catalysts to the reaction between an imine and a β-ketoester led to the discovery of an unexpected reversal in regioselectivity. After a brief review of previous work done by the Schaus laboratory on the asymmetric Mannich reaction, we will describe how the design,
preparation and application of the novel class of chiral phosphoramidic acids led to maintaining high enantioselectivity with reversal of the usual regioselectivity.

3.1.1. Reactivity of β-ketoesters as nucleophiles in the Mannich reaction

In 2007, Kita unexpectedly found that, in the presence of Brønsted acids as catalysists, β-enamidoesters formed from β-ketoesters 146 reacted in the γ-position instead of in the α-position as was expected. Initially, one of the amino groups of diamine 139 forms the enamine intermediate from the ketone moiety of the β-ketoester, enolizing the α-position. Thus, the kinetically favored reaction with the minor γ-tautomer happens intramolecularly to form the seven member ring of product 141. The Curtin-Hammett principle that favors the reaction of the minor tautomer is thoroughly discussed in Section 3.3.2. In their work, Kita and co-workers were able to perform the reaction on a variety of aromatic aldehydes and β-ketoesters (Table 6).
Table 6: Kita's work generating substituted β-enamidoesters.

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Product 1" /></td>
<td>39</td>
<td><img src="image2.png" alt="Product 2" /></td>
<td>74</td>
</tr>
<tr>
<td><img src="image3.png" alt="Product 3" /></td>
<td>57</td>
<td><img src="image4.png" alt="Product 4" /></td>
<td>62</td>
</tr>
<tr>
<td><img src="image5.png" alt="Product 5" /></td>
<td>62</td>
<td><img src="image6.png" alt="Product 6" /></td>
<td>48</td>
</tr>
<tr>
<td><img src="image7.png" alt="Product 7" /></td>
<td>68</td>
<td><img src="image8.png" alt="Product 8" /></td>
<td>48</td>
</tr>
<tr>
<td><img src="image9.png" alt="Product 9" /></td>
<td>56</td>
<td><img src="image10.png" alt="Product 10" /></td>
<td>46</td>
</tr>
<tr>
<td><img src="image11.png" alt="Product 11" /></td>
<td>27</td>
<td><img src="image12.png" alt="Product 12" /></td>
<td>69</td>
</tr>
<tr>
<td><img src="image13.png" alt="Product 13" /></td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In the following year, two independent studies were published utilizing different diamines.\textsuperscript{71-72} Kita and co-workers were able to perform the reaction in presence of an aromatic diamine, \textit{o}-phenyldiamine 144, to prepare 1,5-benzodiazepine derivatives 144. They also were able to perform the reaction in presence of a wide variety of aldehydes and \(\beta\)-ketoesters. The parent reaction is shown in Scheme 27.

\[
\begin{align*}
\text{142} & \quad \text{143} & \quad \text{139b} & \quad \text{144} \\
\text{Acid (10 mol\%)} & \quad \text{DCE, reflux} & \quad \text{Y = 60 \%}
\end{align*}
\]

Scheme 27: Preparation of Benzodiazepine through Mannich reaction.

Sotoca and co-workers performed the first stereoselective version of this intramolecular Mannich reaction, using \((R,R)-1,2\)-cyclohexyldiamine. Although no enantioselectivity was detected, the \textit{trans} product was observed for the first time. A variety of aryl aldehydes, diamines and carboxylic/amidic substrates was investigated, and the methodology proved to be robust for the tested substrates (Table 7).
Table 7: Selected results from the diamine substrate table of Sotoca's work for the preparation of benzodiazepines via Mannich reaction.

<table>
<thead>
<tr>
<th>Product</th>
<th>% Y</th>
<th>cis/trans</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>37</td>
<td>cis</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>99</td>
<td>cis</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>94</td>
<td>2 : 1</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>89</td>
<td>2.5 : 1</td>
</tr>
</tbody>
</table>

Ar\(\text{H}\) 145 131 \[\xrightarrow{4 \text{ Å MS, toluene}}\] 146

4 Å MS, toluene

110 °C, 24 h
3.1.2. Chiral Brønsted acid catalysis in the Mannich reaction and aim of the work

As described extensively in Section 2.2.2., the Mannich reaction has been studied under the catalysis of a variety of Lewis and Brønsted acids. In 2006, Masahiro Terada performed the first enantioselective Mannich addition of an enamine onto an imine catalyzed by a chiral phosphoric acid (Scheme 28).\textsuperscript{73-74}

![Scheme 28: First enantioselective Mannich reaction catalyzed by a chiral Bronsted acid.](image)

The asymmetric Mannich reaction of \(\beta\)-ketoesters and arylimines has also been reported in literature, but prior to this work there had been no example of a system where the \(\gamma\)-reactivity discussed in Section 3.1.1 could be combined with high enantioselectivity. Chapter 3 of this dissertation describes how a new class of catalysts was designed, prepared, characterized, and successfully applied to develop an asymmetric methodology.
for a regio and enantioselective Mannich reaction between an $\alpha$-enamidoester and an arylimine for the synthesis of chiral benzhydryls. Scheme 29 shows the general reaction of this work.

![Scheme 29: General scheme of the studied Mannich reaction.](image)

3.1.3. Preliminary studies on the Mannich reaction

In 2005, Lou, Ting and Schaus designed and developed a cinchona alkaloid directed enantioselective Mannich reaction of $\beta$-ketoesters to aryl imines. Four different alkaloids were described as catalysts and a wide range of substrates were successfully reacted (Table 8). The methodology gave excellent results, proving robust for most of the tested substrates. Yield were consistently very high, above 80%, and in many cases almost quantitative conversion was obtained. Enantiomeric excesses were also excellent, with most of the values exceeding 90%.
Table 8: Selected data from the catalyst screening and substrate scope of Sha Lou and Amal Ting's work on the asymmetric Mannich reaction catalyzed by cinchona alkaloids.

![Chemical structures](140, 153, 154)

<table>
<thead>
<tr>
<th>Aryl</th>
<th>R1</th>
<th>R2</th>
<th>Catalyst</th>
<th>Yield</th>
<th>dr</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenyl</td>
<td>Allyl</td>
<td>t-Butyl</td>
<td>cinchonine</td>
<td>85</td>
<td>3:1</td>
<td>80</td>
</tr>
<tr>
<td>Phenyl</td>
<td>Allyl</td>
<td>t-Butyl</td>
<td>quinine</td>
<td>86</td>
<td>1:1</td>
<td>60</td>
</tr>
<tr>
<td>Phenyl</td>
<td>Allyl</td>
<td>Ethyl</td>
<td>cinchonine</td>
<td>91</td>
<td>2:1</td>
<td>86</td>
</tr>
<tr>
<td>Phenyl</td>
<td>Allyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>99</td>
<td>3:1</td>
<td>92</td>
</tr>
<tr>
<td>Phenyl</td>
<td>Allyl</td>
<td>Methyl</td>
<td>cinchonidine</td>
<td>96</td>
<td>2:1</td>
<td>90</td>
</tr>
<tr>
<td>Phenyl</td>
<td>Allyl</td>
<td>Methyl</td>
<td>quinine</td>
<td>90</td>
<td>1:1</td>
<td>60</td>
</tr>
<tr>
<td>Phenyl</td>
<td>Allyl</td>
<td>Methyl</td>
<td>quinidine</td>
<td>95</td>
<td>1:1</td>
<td>65</td>
</tr>
<tr>
<td>Phenyl</td>
<td>Methyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>99</td>
<td>20:1</td>
<td>94</td>
</tr>
<tr>
<td>Phenyl</td>
<td>Methyl</td>
<td>Methyl</td>
<td>cinchonidine</td>
<td>95</td>
<td>20:1</td>
<td>90</td>
</tr>
<tr>
<td>Phenyl</td>
<td>Methyl</td>
<td>Methyl</td>
<td>quinine</td>
<td>97</td>
<td>4:1</td>
<td>60</td>
</tr>
<tr>
<td>Phenyl</td>
<td>Methyl</td>
<td>Methyl</td>
<td>quinidine</td>
<td>98</td>
<td>5:1</td>
<td>65</td>
</tr>
<tr>
<td>Phenyl</td>
<td>Methyl</td>
<td>Allyl</td>
<td>cinchonine</td>
<td>91</td>
<td>2:1</td>
<td>90</td>
</tr>
<tr>
<td>4-Cl-C₆H₄</td>
<td>Allyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>93</td>
<td>1:1</td>
<td>83</td>
</tr>
<tr>
<td>4-F-C₆H₄</td>
<td>Allyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>98</td>
<td>1:1</td>
<td>93</td>
</tr>
<tr>
<td>3-F-C₆H₄</td>
<td>Allyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>98</td>
<td>1:1</td>
<td>91</td>
</tr>
<tr>
<td>3-CH₃-C₆H₄</td>
<td>Allyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>96</td>
<td>1:1</td>
<td>96</td>
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<tr>
<td>3-CF₃-C₆H₄</td>
<td>Allyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>99</td>
<td>1:1</td>
<td>90</td>
</tr>
<tr>
<td>3,4-(OCH₂O)-C₆H₄</td>
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<td>Methyl</td>
<td>cinchonine</td>
<td>95</td>
<td>1:1</td>
<td>80</td>
</tr>
<tr>
<td>2-C₆H₅O</td>
<td>Allyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>81</td>
<td>1:1</td>
<td>93</td>
</tr>
<tr>
<td>2-C₆H₅S</td>
<td>Allyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>84</td>
<td>1:1</td>
<td>92</td>
</tr>
<tr>
<td>2-Naphtyl</td>
<td>Allyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>96</td>
<td>5:1</td>
<td>95</td>
</tr>
<tr>
<td>4-Cl-C₆H₄</td>
<td>Methyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>81</td>
<td>10:1</td>
<td>81</td>
</tr>
<tr>
<td>4-F-C₆H₄</td>
<td>Methyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>87</td>
<td>10:1</td>
<td>91</td>
</tr>
<tr>
<td>3-F-C₆H₄</td>
<td>Methyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>99</td>
<td>1:1</td>
<td>92</td>
</tr>
<tr>
<td>3-CH₃-C₆H₄</td>
<td>Methyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>88</td>
<td>1:1</td>
<td>90</td>
</tr>
<tr>
<td>2-C₆H₅O</td>
<td>Methyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>83</td>
<td>1:1</td>
<td>90</td>
</tr>
<tr>
<td>2-C₆H₅S</td>
<td>Methyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>86</td>
<td>1:1</td>
<td>93</td>
</tr>
<tr>
<td>2-Naphtyl</td>
<td>Methyl</td>
<td>Methyl</td>
<td>cinchonine</td>
<td>95</td>
<td>20:1</td>
<td>94</td>
</tr>
</tbody>
</table>
The authors extended this method to cyclic β-ketoesters, enantio- and
diastereoselectively obtaining quaternary stereogenic centers adjacent to a chiral
benzhydridil (Scheme 30). Subsequently, Lou and Schaus applied this method as the initial
step in the preparation of substituted chiral dihydropyrimidones. The carbamate moiety,
initially installed on the imine as a protecting group, was converted to an asymmetric urea
by reacting the allyl ester with an isocyanate in presence of catalytic Pd(PPh₃)₄ and
barbituric acid. The urea reacts intramolecularly with the ketone to form the cyclized
enamine in the presence of catalytic acetic acid under microwave conditions. The full
process is shown in Scheme 31.

Scheme 30: Formation of quaternary centers via Mannich reaction of cyclic β-ketoesters.
Scheme 31: Preparation of substituted chiral dihydropyrimidones via Mannich Reaction.

An alternative method for the preparation of substituted chiral dihydropyrimidones is an asymmetric Biginelli reaction, involving a β-ketoester, an aromatic aldehyde and a urea, in presence of a chiral phosphoric acid. During these studies the option of pre-forming the enamine on the β-ketoester before reacting it with the aldehyde was explored and the surprising γ-reactivity discussed in Section 3.1.1 was observed. This fueled our efforts to design a catalytic system based on a chiral Brønsted acid, capable of
tautomizerizing the enamine while simultaneously directing the attack onto the imine (Scheme 32).

Scheme 32: Synthesis of SNAP-7941 (163) via an asymmetric Biginelli and an assymetric Mannich reactions.
3.2. Novel chiral phosphoramidic acids

As previously discussed, chiral Brønsted acids have been successfully applied to a broad range of organic reactions as organocatalysts (see Chapter 1), and the Mannich reaction was performed asymmetrically in the presence of such catalysts (see Section 2.2.3). In this Section, after a brief summary of the applications to the asymmetric Mannich reaction of a specific class of chiral Brønsted acids, chiral phosphoric acids, as reported in recent literature, the design and preparation of a novel class of chiral phosphoramidic acids is described.

3.2.1. Phosphoric acids as catalysts in Mannich and Mannich type reaction

3.2.1.1. State of the art

As mentioned in Chapter 1, in 1999, Akiyama and co-workers found that phosphoric acid 15c (Figure 1, Section 1.2.1.1.) is effective as a catalyst for a number of aldimines and ketene silyl acetals (Table 9). The Mannich-type reaction exhibited high syn selectivity, and the enantioselectivity of the syn isomer was as high as 96%.
Akiyama proposed a transition state with dual coordination of the electrophile to the catalyst, through a nine-membered zwitterionic cyclic transition-state consisting of the aldmine and the phosphoric acid (Figure 3), on the basis of experimental results and theoretical simulation of the transition state. The nine-membered cyclic structure and the aromatic stacking interaction between the 4-nitrophenyl group and the N-aryl group fix the
geometry of the aldimine in the transition state; *si*-facial attack is disfavored due to the steric hindrance of the 3,3'-aryl substituents.

![Figure 3: Proposed nine-membered zwitterionic cyclic transition-state model of the phosphoric acid and aldimine.](image)

In 2004, Uraguchi and Terada, found that chiral phosphoric acid 15d (Figure 1, Section 1.2.1.1.) catalyzed the Mannich reaction of 2,4-pentandione with aldimines; and they were able to successfully prepare the corresponding adducts in great yields and good enantioselectivities (Table 10).
Table 10: Direct Mannich Reaction of acac catalyzed by Chiral phosphoric acid.

<table>
<thead>
<tr>
<th>Ar</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>99</td>
<td>95</td>
</tr>
<tr>
<td>p-MeC₆H₄</td>
<td>98</td>
<td>94</td>
</tr>
<tr>
<td>p-BrC₆H₄</td>
<td>96</td>
<td>98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ar</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-FC₆H₄</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>o-MeC₆H₄</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>99</td>
<td>92</td>
</tr>
</tbody>
</table>

During their mechanistic studies, Terada and co-workers obtained computational and NMR data to support the transition state 172 shown in Figure 4 rationalizing the origin of the enantioselectivity. Hydrogen-bond coordinations of the imine to the acidic proton
of the phosphoric acid and of the proton on the hydrogenophosphate with the oxygen of the chiral phosphoric acid favor the approach of the two substrates with facial selectivity.

Figure 4: Proposed nine-membered transition state for the Mannich Reaction’s Transition state 172.

Mechanistic studies carried out by You during his research, as well as results independently obtained by Terada,\textsuperscript{81} support a proposed mechanism where the enantioselectivity is derived from the bis-coordination of the catalyst to both substrates (Scheme 33).

Scheme 33: Proposed mechanism and transition state in Terada acatalytic Mannich reaction.
Several three-component direct Mannich reactions were also reported; a meaningful example is the work, published in 2006, by Gong and co-workers. Several H$_8$-BINOL derivatives were employed to promote the multicomponent one-pot Mannich reaction between an aromatic aldehyde, phenylamine and a 6-membered cyclic ketone.$^{81}$ Cyclohexanone derivatives turned out to be good substrates for this process (Table 11).

Table 11: Three-Component Mannich Reaction

<table>
<thead>
<tr>
<th>X</th>
<th>Ar</th>
<th>cat.</th>
<th>yield (%)</th>
<th>dr</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_2$</td>
<td>p-CF$_3$C$_6$H$_4$</td>
<td>15e</td>
<td>90</td>
<td>72/23</td>
<td>94</td>
</tr>
<tr>
<td>CH$_2$</td>
<td>p-NCC$_6$H$_4$</td>
<td>15e</td>
<td>92</td>
<td>86/14</td>
<td>91</td>
</tr>
<tr>
<td>CH$_2$</td>
<td>p-FC$_6$H$_4$</td>
<td>15e</td>
<td>67</td>
<td>81/19</td>
<td>95</td>
</tr>
<tr>
<td>O</td>
<td>p-O$_2$NC$_6$H$_4$</td>
<td>15e</td>
<td>94</td>
<td>92/8</td>
<td>90</td>
</tr>
<tr>
<td>BocN</td>
<td>p-O$_2$NC$_6$H$_4$</td>
<td>15e</td>
<td>99</td>
<td>80/20</td>
<td>91</td>
</tr>
<tr>
<td>S</td>
<td>p-O$_2$NC$_6$H$_4$</td>
<td>15a</td>
<td>97</td>
<td>92/8</td>
<td>95</td>
</tr>
<tr>
<td>S</td>
<td>p-CF$_3$C$_6$H$_4$</td>
<td>15a</td>
<td>82</td>
<td>92/8</td>
<td>95</td>
</tr>
</tbody>
</table>

15a: R = H
15e: R = 4-I-Ph
3.2.1.2. Chiral phosphoramidic acids

Chiral phosphoric acids have been successfully applied to a variety of organic reactions, while the closely related class of phosphoramidic acids is less developed. The difference in pKₐ between phosphoric acids (2-2.5 in toluene) and phosphoramidic acids (1-2 in toluene) allows the application of the latter to a complimentary range of reactions. Furthermore, the presence of tridentate nitrogens atoms directly bonded to the phosphorus allows for easier functionalization. Although the preparation of such catalysts is described in a patent registered by Terada and co-workers in 2005 and in a paper published in 2006; no satisfactory enantioselective application has been reported.

3.2.2. Properties of chiral phosphoramidic acids

We designed phosphorodiamidic acids as chiral catalysts in view of the following four points:

1) Use of a readily available and relatively inexpensive chiral source: (R)-BINAM, (R,R)-1,2-cyclohexyldiamine, (R,R)-1,2-diphenyl-1,2-ethylenediamine and (R)-2,3,9,10-tetrahydro-1H-5,13-ethano-4,8-(methe-no)benzodiamine were the backbones to be investigated.
2) Suitable acidity to promote the reaction: the acidity of these new catalysts needs to be in the same range (pKₐ ~ 0 to 2) as some of the most common organic Brønsted acids, such as p-toluensulfonic acid or trifluoroacetic acid. If a new class of chiral catalysts can regio-, diastereo- and enantioselectively promote reactions that have traditionally been carried out in presence of simple Brønsted acids (p-TSA and TFA), a very broad and diverse range of applications can be expected for them. The Mannich reaction was studied under non-asymmetric conditions in the presence of p-toluensulfonic acid, which has a pKₐ around 1 in toluene and related solvents. Phosphorodiamidic acids also have pKa values in the same range; they are in fact more acidic than other chiral phosphoric acids.

3) Cyclic structure to attain high asymmetric induction: the rigid structure of a ring is crucial to the enantioselectivity due to its ability to coordinate the substrates in a fixed conformation, which results in less degrees of freedom.

4) The appropriate choice of the substituents at the N,N’-positions is crucial for realization of high enantioselectivity. This is mostly due to the steric interaction between the N-substituents and the substrates during the formation of the transition state complex (see Scheme 34 in Section 3.3.2.1. for the detailed proposed mechanism); if the substituent is not large enough, the facial selectivity suffers, while if the substituent is too bulky, there is insufficient coordination and the reaction is poorly or un-catalyzed. Both cases result in a loss in enantioselectivity.
3.2.3. Results

Contrary to what was obtained by Terada in 2006\textsuperscript{80} in the reaction of β-ketoesters and benzimines catalyzed by the achiral catalyst 2-hydroxy-1,3-ditosyl-2,3-dihydro-1H-benzo[d][1,3,2]diazaphosphole 2-oxide, our initial application of the BINAM-derived phosphoric acid to the reaction, produced a 95:5 ratio between the γ- and the α-addition products. The origin of this unusual reactivity will be further explained with the Curtin-Hammett principle in Section 3.3.2.

3.2.3.1. Design and preparation of novel chiral phosphoramidic acids

Upon observation of this unique regioselectivity, we decided to thoroughly evaluate this synthetic system. Since the asymmetric induction of the direct Mannich reaction described for β-diketones by Terada in 2006 was low, structural modification of the phosphorodiamidic acid catalyst was necessary. This was done by changing the chiral diamine backbone and/or the substituents on the nitrogen atoms. The only known preparation for such molecules was the one included in the aforementioned patent by Terada. For this reason, inspired by the synthesis of similar molecules,\textsuperscript{88-89} we designed the preparation shown in Scheme 34.
Scheme 34: Preparation of chiral Phosphoramidic acids.

As the first step of the synthesis, diamine $\text{178}$ was reacted with the sulfonyl chloride to install the substituent onto the nitrogen. Product $\text{179}$ was then deprotonated with $n$-butyllithium followed by treatment with dichloromethylphosphite to form the nitrogen-phosphorus bonds. The reaction was quenched with hydrogen peroxide to oxidize the phosphorus from P(III) to P(V) yielding the chiral methyl phosphorodiamidate $\text{180}$. Subjection of $\text{180}$ to potassium cyanide deprotected the phosphorodiamidate through $\text{S}_2\text{N}\text{2}$ reaction on the methyl, to yield the desired chiral phosphorodiamidic acid $\text{181}$. By varying the diamine backbone as well as the N-protecting group, nine different catalysts were successfully prepared, as shown in the Figure 5.
Figure 5: Yields of the three-step preparation of nine chiral phosphoric catalysts.
3.3. Asymmetric Mannich reaction

3.3.1. Methodology development and results

3.3.1.1. Preliminary studies.

During preliminary studies conducted under the catalysis of \( p \)-toluenesulfonic acid, five different imine protecting groups were tested: benzoyl (185), methylcarbamyl (186), \( t \)-butylcarbamyl (150), \( p \)-toluene sulfonyl (187) and \( P,P \)-diphenylphosphinoyl (188). \( p \)-Toluenesulfonyl and \( P,P \)-diphenylphosphinoyl protected imines proved unreactive; the starting material was consistently recovered. Benzoyl protected arylimines tended to decompose under these conditions, while the best imine protecting groups were methylcarbamate and \( t \)-butylcarbamate. Catalyst loading, solvent, time and temperature effects were also evaluated in achiral conditions. The best conditions were found to be: 10 mol % catalyst in a 0.3 M solution of substrate in \( \alpha,\alpha,\alpha \)-trifluorotoluene. The reactions were stirred for 20 h at 4°C in the case of the methylcarbamate protected imine, or at room temperature in the case of \( t \)-butylcarbamate protected imines (Table 12).
Table 12: Conditions screening for achiral Mannich reaction

<table>
<thead>
<tr>
<th>Imine</th>
<th>[p-TSA] (mol %)</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
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<td>5</td>
<td>DCM</td>
<td>0</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>185</td>
<td>5</td>
<td>DCM</td>
<td>20</td>
<td>20</td>
<td>decomp.</td>
</tr>
<tr>
<td>185</td>
<td>5</td>
<td>PhCF₃</td>
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<td>20</td>
<td>49</td>
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</tr>
<tr>
<td>185</td>
<td>5</td>
<td>PhCF₃</td>
<td>20</td>
<td>20</td>
<td>decomp.</td>
</tr>
<tr>
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<td>PhCF₃</td>
<td>0</td>
<td>20</td>
<td>71</td>
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<td>79</td>
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<tr>
<td>186</td>
<td>5</td>
<td>PhCF₃</td>
<td>0</td>
<td>30</td>
<td>54</td>
</tr>
<tr>
<td>186</td>
<td>5</td>
<td>PhCF₃</td>
<td>20</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>150</td>
<td>-</td>
<td>PhCF₃</td>
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<tr>
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<tr>
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<td>0</td>
</tr>
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<tr>
<td>187</td>
<td>10</td>
<td>PhCF₃</td>
<td>20</td>
<td>20</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>188</td>
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<td>20</td>
<td>0</td>
</tr>
<tr>
<td>188</td>
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<td>&lt; 5</td>
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<tr>
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<td>decomp.</td>
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<td>20</td>
<td>decomp.</td>
</tr>
<tr>
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<td>PhCF₃</td>
<td>40</td>
<td>20</td>
<td>decomp.</td>
</tr>
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3.3.1.2. Application and screening of chiral phosphoramidic acids as catalysts

After a first condition screening was completed under achiral conditions (Table 12), a second one was carried out in the presence of the chiral phosphoramidic catalysts, for substrates 186 and 150. The nine catalysts (Figure 6) were then screened with each methylcarbamate and t-butyldimethylcarbamate protected benzimines. (Table 13). As expected, the steric hindrance of the protecting group on the nitrogen of the diamine core of the catalysts helped enhance the stereoselectivity of the reaction. Exceptions are the reactions catalyzed by acids bearing naphthylsulfonyl substituents (Entries 4 and 17 in Table 13). The steric congestion between the t-butyl and the naphthyl groups may prevent the formation of a tight hydrogen bond complex between substrates and catalyst, resulting in low observed selectivity. Also, the methylsulfonyl substituent on 181f appears to be too small to induce high stereoselectivity (Entries 12 and 13 in Table 13). The diamine core of catalysts 181c and 181e, derived from (1R,2R)-(−)-1,2-diaminocyclohexane, and 181d, built on [2.2]-paracyclophane-pseudo-ortho-diamine, exhibit dramatically different geometries than every other catalyst prepared. The poor to modest yields and selectivities seen with these catalysts likely arise from the inability to form the necessary transition state complex (Entries 5-9 in Table 13). Catalysts built on (1R,2R)-(−)-1,2-diphenylethylendiamine and on (R)-(−)-1,1’-binaphtyl-2,2’-diamine display the best reactivity. In conclusion, the best catalyst structures have been found to be 181d and 183i.
(Entries 3 and 16 in Table 13) for the methoxycarbamate protected imine and 181a, 181g and 181h (Entries 2, 11 and 15 in Table 13) for the t-butoxycarbamate protected imine.

Finally, the reaction was screened for solvent, reagent ratio, temperature and concentration conditions in presence of the catalysts that afforded the best results. The choice of α,α,α-trifluorotoluene was based on the results of a solvent screen; it yielded higher conversions than regular toluene and higher selectivities than methylene chloride. α,α,α-Trifluorotoluene is in fact more polar than toluene, enhancing the solubility of the catalyst and, at the same time, doesn’t interfere with the formation of the transition state complex as coordinating solvents such as dichloromethane could do. An excess of 1.5 equivalents of enamido is helpful to increase the yield of the reaction. (Table 14)
Table 13: Reactivity of chiral phosphoramidic acids in Asymmetric Mannich Reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Cat.</th>
<th>Yield</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>186</td>
<td>181a</td>
<td>44</td>
<td>72:18</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>181a</td>
<td>82</td>
<td>98:2</td>
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<tr>
<td>3</td>
<td>186</td>
<td>181b</td>
<td>44</td>
<td>74:26</td>
</tr>
<tr>
<td>4</td>
<td>150</td>
<td>181b</td>
<td>57</td>
<td>67:33</td>
</tr>
<tr>
<td>5</td>
<td>186</td>
<td>181c</td>
<td>69</td>
<td>55:45</td>
</tr>
<tr>
<td>6</td>
<td>150</td>
<td>181c</td>
<td>23</td>
<td>81:19</td>
</tr>
<tr>
<td>7</td>
<td>186</td>
<td>181e</td>
<td>59</td>
<td>51:49</td>
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<td>8</td>
<td>186</td>
<td>181d</td>
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<td>64:48</td>
</tr>
<tr>
<td>9</td>
<td>150</td>
<td>181d</td>
<td>&lt;5</td>
<td>76:24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Cat.</th>
<th>Yield</th>
<th>er</th>
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</thead>
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<tr>
<td>10</td>
<td>186</td>
<td>181g</td>
<td>52</td>
<td>72:18</td>
</tr>
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<td>11</td>
<td>150</td>
<td>181g</td>
<td>82</td>
<td>95:5</td>
</tr>
<tr>
<td>12</td>
<td>186</td>
<td>181f</td>
<td>68</td>
<td>62:38</td>
</tr>
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<td>13</td>
<td>150</td>
<td>181f</td>
<td>30</td>
<td>72:28</td>
</tr>
<tr>
<td>14</td>
<td>186</td>
<td>181h</td>
<td>53</td>
<td>71:19</td>
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<td>15</td>
<td>150</td>
<td>181h</td>
<td>55</td>
<td>94:6</td>
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<td>16</td>
<td>186</td>
<td>181i</td>
<td>48</td>
<td>73:27</td>
</tr>
<tr>
<td>17</td>
<td>150</td>
<td>181i</td>
<td>15</td>
<td>57:43</td>
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</tbody>
</table>

Reaction conditions: Enamide 151 (0.45 mmol) and catalyst (0.03 mmol) were dissolved in PhCF$_3$ (1 mL). Imine 4 (0.30 mmol) was added and the reaction was stirred for 20 h.

*Isolated % yield. *b*Determined by chiral HPLC. *c*Reaction was cooled at 4 °C.
Table 14: Conditions screening for enantioselective catalytic Mannich reaction

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Imine</th>
<th>151:imine</th>
<th>Solvent [reaction]</th>
<th>Temp. (°C)</th>
<th>catalyst</th>
<th>[Catalyst] (mol %)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Er (R:S)</th>
</tr>
</thead>
<tbody>
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<td>1:1</td>
<td>PhCF₃(0.3M)</td>
<td>0</td>
<td>181g</td>
<td>5</td>
<td>20</td>
<td>40</td>
<td>76:24</td>
</tr>
<tr>
<td>186</td>
<td>1.5:1</td>
<td>PhCF₃(0.3M)</td>
<td>0</td>
<td>181g</td>
<td>5</td>
<td>20</td>
<td>61</td>
<td>68:32</td>
</tr>
<tr>
<td>186</td>
<td>2:1</td>
<td>PhCF₃(0.3M)</td>
<td>0</td>
<td>181g</td>
<td>5</td>
<td>20</td>
<td>72</td>
<td>66:34</td>
</tr>
<tr>
<td>186</td>
<td>1:1.5</td>
<td>PhCF₃(0.3M)</td>
<td>0</td>
<td>181g</td>
<td>5</td>
<td>20</td>
<td>34</td>
<td>74:26</td>
</tr>
<tr>
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<td>1:1</td>
<td>PhCF₃(0.2M)</td>
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<td>181g</td>
<td>5</td>
<td>20</td>
<td>63</td>
<td>69:21</td>
</tr>
<tr>
<td>186</td>
<td>1:1</td>
<td>PhCF₃(0.1M)</td>
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<td>181g</td>
<td>5</td>
<td>20</td>
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</tr>
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<td>20</td>
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<td>66:34</td>
</tr>
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<td>DCM(0.3M)</td>
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<td>181g</td>
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<td>65:35</td>
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<tr>
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<td>150</td>
<td>1:1</td>
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</table>
3.3.1.3. Substrate screening

Catalyst 181a was chosen as the model catalyst for screening a variety of \( t \)-butylcarbamate substituted imines due to strong catalytic activity and ease of preparation compared with BINAM derived catalysts. A variety of imines were tested to study the influence of substituents on the reactivity and stereoselectivity. The results of the substrate scope are shown in Table 15. A variety of aromatic (Entries 1-8 in Table 15) and aliphatic imines (Entries 8 and 9 in Table 15) were screened to prove the wide applicability of this reaction. All tested substrates gave good yields (72-93%) and selectivities (91:9 to 99:1). These results show how both electron-deficient (Entries 7 and 9 in Table 15) and electron-rich substrates (Entries 3, 4, 6 and 8 in Table 15) are tolerated. Sterically hindered imines (Entries 5, 6 and 8 in Table 15) are also well tolerated.
Table 15: Imine substrate scope.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Y</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>98:2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>83</td>
<td>98:2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>92:8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>79</td>
<td>96:4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>91:9</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>87</td>
<td>99:1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>76</td>
<td>99:1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>93</td>
<td>98:2</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>65</td>
<td>99:1</td>
<td></td>
</tr>
</tbody>
</table>
In order to further study the unexpected regioselectivity, substituted enamides were also subjected to the reaction conditions: the results for these substrates are reported in Table 16.

Table 16: Enamide substrate table

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield$^a$</th>
<th>er$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image150.png" alt="Substrate 150" /></td>
<td>82</td>
<td>98:2</td>
</tr>
<tr>
<td>2</td>
<td><img src="image151.png" alt="Substrate 151" /></td>
<td>71</td>
<td>94:6</td>
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<td>3</td>
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<tr>
<td>4</td>
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</tr>
<tr>
<td>5</td>
<td><img src="image181a.png" alt="Substrate 181a" /></td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td><img src="image181a.png" alt="Substrate 181a" /></td>
<td>Trace</td>
<td>-</td>
</tr>
</tbody>
</table>
The substrate in entry 1 is reported as a reference. Substitution in the α-position (entry 2, in Table 16) has minimal effect on the reactivity, likely because it further disfavors the α-position leaving the reactive γ position unhindered. In contrast, any substitution on the γ-position (Entries 3-5 in Table 16) turns off the reactivity of the nucleophile, presumably due to steric hindrance at the reactive position.

3.3.2. Mechanistic studies

3.3.2.1. Proposed mechanism

It is known that the α-position of a β-ketoester is the most likely to be enolized, due to the possibility of delocalizing the negative charge on two carbonyl π-systems through resonance. However, under Brønsted acidic conditions, ketenamines are also known to isomerize.\(^9\) If the minor thermodynamic isomer γ (191) is kinetically more reactive than the major isomer α (194), the product that will form is the product derived from the minor isomer. The product distribution depends proportionally upon the ΔΔG\(^{‡}\). This is illustrated as an effect of the Curtin-Hammett Principle in Figure 6. This rational was supported by the substrate table in Table 16 (see Section 3.3.1.3).
Figure 6: Curtin-Hammett principle rational for $\gamma$-regioselectivity in the Mannich reaction.
Two plausible mechanism could instead explain the enantioselectivity. The first, proceeds via a transition state in which the catalyst forms two H-bonds with the nucleophile, gaining stabilization from the formation of a six membered ring, while the electrophile is activated via protonation of the imine 150 to iminium 193. The rigid conformation of the nucleophile and its double coordination with the catalyst promotes chiral delivery, resulting in the enantioselectivity of the reaction. This mechanism is also in agreement with the kinetic data shown in Section 3.3.2.2 (Scheme 35).

A second reasonable mechanism instead, similar to the one proposed by Terada (Scheme 33 in Section3.2.1.1), is shown in Scheme 36. According to our model, after the initial tautomerization of the enamide from the more stable but less reactive α-enamidoester to the less stable but more reactive γ-enamidoester, bis-H-boding complex formation occurs between the acidic proton of the catalyst and the lone pair of the imine’s nitrogen, and between the proton on the enamide’s nitrogen and the oxygen of the phosphamidic acid. The two sulfonyl groups force the imine to approach the adduct from the lower face of the enamide. Successive proton transfers re-form the enamide 194 and the catalyst. From the model of the complex, the R enantiomer 194 would be preferred.
Scheme 35: Plausible mechanism for Mannich reaction via chiral nucleophile
Scheme 36: Plausible reaction mechanism for Mannich reaction via trimolecular transition state 197.

3.3.2.2. Kinetic studies

In order to support the proposed bimolecular hydrogen bonded complex transition state, the kinetics of this Mannich type reaction were studied as a function of the catalyst’s
concentration, and monitored by React-IR. (Scheme 36 and Table 17). It was not possible to go higher in catalyst load than 15 mol%, due to its limited solubility in trifluorotoluene.

![Scheme 37: Mannich reaction monitored by ReactIR at different concentrations of catalyst to determine the order of reaction in catalyst.](image)

The solution was stirred at room temperature for 4 hours and the C=N stretch of imine 150 was monitored at 1530 cm\(^{-1}\) by ReactIR in real time. A measurement was taken every 2 minutes and the initial rate was calculated on the first 30 minutes of reaction. Five measurements were performed for each concentration and averaged. The results are shown in Table 17.
Table 17: Effect of catalyst 181a concentration on the initial rate of the catalytic Mannich reaction.

<table>
<thead>
<tr>
<th>Catalyst 181a mol %</th>
<th>Rate M (mmol/min)</th>
<th>Rate st dev (x10^2)</th>
<th>Yield^a</th>
<th>ee^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>0.88</td>
<td>0.04</td>
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<td>2.5</td>
<td>2.2</td>
<td>0.05</td>
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<td>1.91</td>
<td>50</td>
</tr>
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<td>10.0^c</td>
<td>8.82</td>
<td>0.16</td>
<td>3.09</td>
<td>53</td>
</tr>
<tr>
<td>15.0^c</td>
<td>13.2</td>
<td>0.18</td>
<td>4.03</td>
<td>62</td>
</tr>
</tbody>
</table>

Reaction conditions: Enamide 151 (0.45 mmol) and catalyst 181a (0.03 mmol) were dissolved in PhCF₃ (3 ml). Imine 150 (0.30 mmol) was added and the reaction was stirred for 20 h. ^aIsolated yield. ^bDetermined by chiral HPLC. ^cThe solubility of the catalyst in trifluorotoluene is around 8 mM (10 mol%) Reactions with higher concentration of catalyst are not clear solutions before the beginning of the reaction. The product precipitates upon formation.

**Figure 7** shows a plot of the initial rate of reaction (initial 20 minutes) *versus* the concentration of the catalyst. The experiment was repeated five times in order to calculate the experimental error. The considerably large experimental errors represented by the error bars are due to a few different effects. Firstly, the product of the reaction tends to precipitate while forming, this makes the reaction mixture partially heterogeneous, increasing the noise in the measurement. Additionally, at higher concentrations, the catalyst is only partially soluble; it is solubilized by the formation of the complex but it is not possible to assume that the catalyst concentration is constant throughout the reaction; this may explain
the low value for the result at 14 mM of concentration in catalyst. The data shown in the plot in Figure 7 were interpreted as only partially linear. The trend is linear in a region of catalyst concentration between 4 and 10 mM (red values on the plot in Figure 7), suggesting that the reaction is first order in catalyst, but it deviates from linearity at low (blu values in Figure 7) and high (black value in Figure 7) catalyst concentrations. We interpreted this observation as the possibility of a change in mechanism.

Figure 7: Plot of initial rate vs. catalyst concentration for the Mannich reaction.
3.4. Absolute configuration elucidation

3.4.1. Ozonolysis and preparation of enantioenriched β-phenyl-β-alanine benzyl ester

To confirm the expected absolute stereochemistry, the product was converted into β-phenyl-β-alanine benzyl ester 203 via ozonolysis of the enamide double bond, and the optical rotation was compared with the reported literature value.91 (Scheme 38) The product of the Mannich reaction 190 was quantitavely ozonolyzed to adduct 201. The terminal amide of 201 was transterified to benzyl ester upon reaction with benzyl alcohol. The other amide was then subjected to hydrolyzation in presence of p-TSA to obtain β-phenyl-β-alanine benzyl ester 190, in an overall yield of 24%. Comparison with optical
rotation values from literature ([α]_D = -5.2° for the S enantiomer) confirmed that the product of the Mannich reaction has an excess of R enantiomer.

Scheme 38: Ozonolysis of the product of the Mannich reaction to obtain enantiopure β-phenyl-β-alanine benzyl ester.
3.5. Asymmetric reduction of the enamine

3.5.1. Synthetic interest of asymmetric 1,3-diamines

Enantiomerically enriched 1,3-diamines are very important chiral building blocks in the synthesis of natural products and pharmacologically active compounds. The work of Cohen and Overman is an example of total synthesis based on the preparation of enantioenriched 1,3-diamines. In 2001, they carried out the enantioselective total synthesis of batzelladine F 209. The first phase of this synthesis consisted of the conversion of hydroxybutyrate 204 into the relative diamine 205 in 58% yield, over 5 steps (Scheme 39).92 A similar diamine bearing a nonyl chain had been previously prepared as a precursor to batzelladine B.93
Enantioenriched 1,3-diamines are also of great use as chiral ligands. Generally, in conjunction with chiral bidentate phosphines, diamines are also used as chiral ligands in metal catalysis. An example is the asymmetric hydrogenation work reported in 2007 by Grasa and co-workers. In this work, the diamine ligand was tuned for application in the reduction of various substrates. The design was based on changing the nature of the diamine ligand as well as on increasing the chain length of the diamine ligand from 1,2 to the 1,3- and 1,4-homologues (Scheme 40).
Scheme 40: An example of application of chiral 1,3-diamines as ligands for metal catalysis.

The preparation of such 1,3-diamines typically requires 4 steps (Scheme 41). For example, after initial enantioselective reduction of 1,3-diketone 214 to (anti)-1,3-diol 215 in presence of a chiral ruthenium catalyst, the hydroxyl groups were protected as mesylates, then displayed with azides via S_N2 reactions. The resulting 1,3-diazide 216 was then reduced to diamine 217 in the presence of palladium on carbon and hydrogen gas. Despite the good overall yield of 58% over five steps in Overman’s work in preparing diamine 205, and the relatively well established methods used by Grasa, illustrated in Scheme 40, it is
evident that a more expedient method to prepare such building blocks would be of great value.

Scheme 41: Synthesis of chiral 1,3-diamines for use as ligands in metal catalysis.

For this reason, much effort has been devoted to the development of new effective methods to access these compounds. Only a few asymmetric syntheses of 1,3-diamines have been described, contrary to their 1,2-diamine counterparts. Kobayashi and Terada have developed an elegant two-step synthesis of 1,3-diamines 222 by reaction of enamides (enecarbamates) 220 with pre-formed N-acylimines or N-acylaminoethers followed by reduction of the resulting aminooimine 221 (Scheme 42); but not many other robust methods have been currently reported in literature.
Scheme 42: Two carbon homologation of N,O-acetals for the synthesis of chiral 1,3-diamines.

The use of 1,3-diamines as ligands in catalysis, coupled with the limited number of synthetic approaches to this diamine class, suggest the importance of developing viable methods for the asymmetric preparation of chiral 1,3-diamines. For this reason, we attempted the asymmetric reduction of the product of the Mannich reaction described in Section 3.4 to obtain enantio- and diastereo-enriched 1,3-diamines. A variety of methods
have been developed to reduce enamines, which can be distinguished as asymmetric catalytic hydrogenations or hydride-based reductions.

3.5.2. Asymmetric hydrogenation of enamines

3.5.2.1. Previously reported methods

In 2007, Krska and Shutlz reported their studies on asymmetric hydrogenations. As Merck employees, their main focus was to develop an efficient reduction of a β-enamidoamide for the total synthesis of sitagliptin A. Sitagliptin A is the active principle of Januvia®, a drug used to treat type II diabetes. The stereoselectivity of the hydrogenation was achieved through installation of a chiral auxiliary on the nitrogen of the enamide, in the presence of platinum oxide as the catalyst (Scheme 43).

Scheme 43: Asymmetric diastereoselective hydrogenation of dihydrositagliptin to Sitagliptin A in presence of PtO₂.
Alternatively, using a chiral bidentate phosphine ligand to form a chiral rhodium complex, high enantioselectivity in the preparation of amino amide 226 was also achieved (Scheme 44). In 2009, Hansen and co-workers, also completed a one-pot total synthesis of dehydrositagliptin 225, followed by asymmetric reduction to generate sitagliptin.\textsuperscript{101-104}

Scheme 44: Asymmetric diastereoselective hydrogenation of dehydrositagliptin to Sitagliptin A in presence of chiral ruthenium complexes.

Other meaningful results of asymmetric hydrogenation of enamidoesters were independently reported by Zhang\textsuperscript{105-106} (Scheme 45) and by Fox\textsuperscript{107} (Scheme 46). Zhang and co-workers were able to asymmetrically hydrogenate a $\beta$-enamonium ester in presence of bidentate phophine ligand 228 and an iridium (II) salt, while Fox and co-workers
reported the asymmetric hydrogenation of α-enamidoesters in presence of the bidentate phosphino ligand Et-DuPhos and a rhodium salt.

Scheme 45: Zhang asymmetric hydrogenation of β-enaminiumesters

Scheme 46: Fox's asymmetric hydrogenation of α-enamidoesters

3.5.2.2. Results

In attempt to achieve the reduction of the enecarbamates, a large variety of systems and several different variables were screened for the hydrogenation, according to the
reaction shown in Table 18. We initially utilized ruthenium and rhodium salts and screened a variety of chiral bidentate phosphine ligands (Figure 8), in the presence of light and positive pressure of hydrogen gas (balloon), all without success. Upon the failure of rhodium and ruthenium to achieve reduction, more reactive metals were examined, including iridium, nickel, palladium and platinum, but none of these metals yielded the desired product under standard conditions. Therefore, the conditions were altered to higher concentrations of catalyst, higher temperatures or higher pressures of hydrogen. A higher concentration of catalyst did not change the results of the reaction, as no product was observed. At higher temperatures, combined with much higher hydrogen pressures (> 80 psi), the starting material decomposed via cleavage of the C-C bond formed during the Mannich reaction. The benzylic position, activated by the presence of the nitrogen is sensitive to the presence of a transition metal under strongly reducing conditions (Scheme 47).
Figure 8: Chiral phosphines screened as ligands in metal-catalyzed asymmetric hydrogenation
Table 18: Selected data for condition and catalyst screening for metal catalyzed asymmetric hydrogenation

<table>
<thead>
<tr>
<th>Metal salt</th>
<th>Ligand</th>
<th>Temp. (°C)</th>
<th>H₂ Press. (psi)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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</thead>
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<td>Rh(COD)OTf</td>
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Raney Ni  -  60  80  24  -  
Raney Ni  -  60  120  24  < 5  
H-cube Ni  -  40  10  -  -  
H-cube Ni  -  45  80  -  -  

Scheme 47: Results of the attempts to the hydrogenation of the product of the Mannich reaction.

In either case, the desired product was not forming; under mild conditions no reactivity was observed, while in a more aggressive reducing environment the molecule
decomposed. We thus decided to look into alternative, non metal-catalyzed ways to reduce the enamide.

3.5.3. Alternative asymmetric reduction methods of enamides with hydridic reagents

Due to the failure of the hydrogenation of 190, we decided to look into literature reports of a method to reduce enamines using hydridic reagents in presence of a catalytic amount of a Brønsted acid. Such methods have long been established, deriving from classing reductive amination of ketones and aldehydes.

3.5.3.1. Previously reported methods

The union of sodium borohydride with carboxylic acids has been reported many times in literature as a versatile and efficient reducing protocol.\textsuperscript{109-110} These acyloxyborohydride species are able to reduce a wide variety of functional groups like indoles, quinolines, isoquinolines and related heterocycles; they can also reduce imines, enamines, oximes, enamides, and similar functional groups. They reduce amides and nitriles, aryl alcohols and ketones, aldehydes in the presence of ketones, and β-hydroxyketones to 1,3-diols stereoselectively.
For the reduction of enamines, one of the first reports using borohydrides in the presence of Brønsted acids to yield substituted amines is the work of Marshall and Johnson in 1963. Their original paper describes an improved procedure for the reduction of steroidal enamines and also shed light on the mechanism of this type of reduction (Scheme 48).108

Scheme 48: Mechanism of the reduction of dienamines in presence of sodium borohydride.

Their first significant observation was that there was no reaction between the dienamine 255 (3,4-dehydroconessine) and sodium borohydride until acetic acid was added to the reaction mixture. This suggested that there is no direct reduction of the double bond, but rather the reaction proceeded via protonation to iminium ion followed by direct hydrid addition. A few years later, sodium cyanoborohydride was introduced as a reagent, and although the enamine group itself is resistant to reduction with this reagent, the rapid and reversible protonation of the enamine double bond generates a reducible iminium salt. Simple enamines are rapidly reduced by sodium cyanoborohydride at a pH of 5 in a THF/methanol solvent mixture (Scheme 49).108
Scheme 49: Reduction of enamines in presence sodium cyanoborohydride.

Many other applications of this reductive method followed over many years, including the work of Gribble,\textsuperscript{110} Effenberger\textsuperscript{111} and, more recently, that of Palmieri and co-workers. Palmieri reported a one-pot organo-lithiation/reduction of β-enaminoesters for the production of tertiary γ-aminoalcohols. (Scheme 51).\textsuperscript{112-113}

Scheme 50: Mechanism of Palmieri's methodology for a reductive alkylation of carbonyls.
3.5.3.2. Results

Following the procedures reported in the aforementioned publications and in others, we attempted the reduction of the enamine in the presence of a borohydride and a Brønsted acid. We expected that this protocol would yield a mixture of diastereoisomers, in the hope of obtaining the desired 1,3-diamine. The hydridic reagents we tried were sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, lithium borohydride (Table 19).
Table 19: Conditions and reagents screening for borohydride reduction of enamide

![Chemical Structures](image)

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We applied these hydrides in presence of 1% of strong acid solution. 6 M hydrochloric acid in water, 2 N hydrochloric acid in water, 2 N hydrochloric acid in diethyl
ether, and various concentrations of acetic acid in water were tested. Solvents were also screened: methanol, ethanol and various solutions of methanol and water (Scheme 51). Unfortunately, this method did not yield any desired product, as the starting material for this reaction, the product of the asymmetric Mannich reaction, was returned unreacted.

The stability of the enamine likely stems from conjugation with the ester. This, coupled with the steric hinderance from the trisubstituted olefin, makes the enamine resistant to reduction. In addition, the instability of the activated benzylic was a serious issue with hydrogenation. For these reasons, this project was no longer pursued.
3.6. Conclusion

The application of chiral Brønsted acids as organocatalysts in a Mannich reaction was studied. A new class of asymmetric phosphoramidic acids has been designed, prepared and characterized, accounting for pK\textsubscript{a} range, solubility in organic solvents and steric effects. Such catalysts were successfully applied to the asymmetric Mannich reaction between β-enamidoesters \textbf{151} and variously substituted imines reaching good yields and excellent regio- and enantioselectivities. A wide range of imine substrates has been tested to prove the applicability of the method to electron-poor and electron-rich, aromatic and non-enolizable, small and bulky imines.

Substituted β-enamidoesters have also been tested; substitution on the α-positions has proved to have no effect on the reactivity of the nucleophile affording product in good yields and enantioselectivities. On the other hand, substitution on the γ-position completely impeded the reaction. This finding supports the Curtin-Hammett principle which can be used to explain the reverse regioselectivity. A detailed mechanism was proposed to explain the enantioselectivity; the predicted product was the \textit{R} enantiomer.

The product of the Mannich reaction was subjected to ozonolysis and further modifications to obtain β-phenyl-β-alanine benzyl ester \textit{para}-toluenesulfonate salt. This was initially carried out with the goal of proving the absolute stereochemistry by comparison with literature values, but also gave an efficient method for the enantioselective
production of substituted aminoacids. The experimentally determined absolute configuration of the product matched the prediction obtained from the transition state model we proposed in our mechanism. This strongly supported our proposed model.

Kinetic studies were also carried out to determine the order of the reaction with respect to catalyst concentration. ReactIR data were collected at six different catalyst concentrations, five sets of data were take for each concentration and averaged. Although the experimental errors were fairly high, it was still possible to determine that the reaction was first order in catalyst.

Finally, the asymmetric reduction of enamides was attempted with the goal of obtaining an efficient method to enantio- and diastereoselectively access 1,3-diamines as important building blocks for synthesis of natural products and of ligands for metal catalysis. Such reduction was attempted first using asymmetric hydrogenation methods reported in literature. Unfortunately, this was not effective for our Mannich reaction product. Mild hydrogenation conditions returned the starting enamide, while more aggressive conditions cleaved the benzylic bond. After a large variety of attempts in presence of metals such as ruthenium, rhodium, iridium, palladium, platinum and nickel and the most diverse collection of ligands, at several different temperatures and hydrogen pressures, other methods were evaluated. Reduction of enamides with borohydrides in presence of Brønsted acids is described in literature and we decided to apply it to our system. Unfortunately, these conditions were also not successful as they returned the starting material or negligible traces of product. After attempting this reduction in various
conditions and with various hydridic reagents, the goal of asymmetrically reducing the product of the Mannich reaction to obtain 1,3-diamines was abandoned.
3.7. Experimental Section

3.2.4.1. General procedure for preparation of phosphoramidic catalysts.

In an oven dried 10 mL flask, the chiral diamine (4.7 mmol) was added. The flask was evacuated and filled with N₂. Pyridine (1 mL) was added and the solution stirred at r.t. for 30 min. The sulfonyl chloride (9.9 mmol) was added and the solution stirred at r.t. overnight. The solution was quenched with 1 mL of water, and the mixture stirred for 30 min. The reaction was extracted with 20 mL of ethyl acetate and two fractions of aqueous HCl (15 mL, 3 M), the organic layer collected, dried on NaSO₄ and evaporated. In a 10 mL
round bottom flask under argon the obtained product and anhydrous THF (5 ml) were added. The reaction was cooled to -78 °C. n-Butyl lithium (6.2 mL of a 1.6 M solution in hexanes) was slowly added. The reaction was allowed to warm up to r.t. and stirred for 2 hours. The reaction was cooled to -78 °C and methyl dichlorophosphite (0.62 mL, 5.2 mmol) was slowly added. The reaction was allowed to warm up to r.t. and stirred for two hours. The reaction was quenched with hydrogen peroxide (2 mL, excess) and the mixture was stirred for 2 hours. The mixture was extracted with 2 fractions of 25 mL of ethyl acetate and 25 mL of water, the organic layers combined, dried over sodium sulfate and evaporated. The obtained product was added to a 25 mL flask, and dissolved in N,N-dimethylformamide (5 ml). Potassium cyanide (35 mg, 5.2 mmol) was added, the reaction heated to 60°C and stirred for 4 hours. After allowing to cool to r.t., the reaction was quenched with 3 mL of 6 M HCl. The mixture was extracted with 25 mL of ethyl acetate and 25 mL of 6 M HCl, dried over sodium sulfate and evaporated to provide catalyst 181a. The product was recrystallized in 20 mL of diethyl ether to obtain a colorless powder (Scheme 52).
(4R,5R)-2-hydroxy-4,5-diphenyl-1,3-ditosyl-1,3,2-diazaphospholidine-2-oxide  181a.

Obtained a white powdery solid after recrystallization. (Yield after three steps = 36%); m.p. > 250°C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.48 (d, \(J = 8.1\) Hz, 4H), 7.07 (d, \(J = 8.1\) Hz, 4H), 7.03 (t, \(J = 8.1\) Hz, 2H), 6.95 (t, \(J = 8.1\) Hz, 4H), 6.65 (d, \(J = 8.1\) Hz, 4H), 5.50 (br, 2H), 4.45 (br, 2H), 2.32 (s, 6H); \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 169.9, 160.503, 153.1, 143.5, 136.5, 129.6, 93.7, 62.4, 26.8; HRMS (m/z): [M]+ calcd. for C\(_{28}\)H\(_{27}\)N\(_2\)O\(_6\)PS\(_2\), 582.1026; found, 582.1048.
(4R,5R)-2-hydroxy-1,3-bis(naphthalen-2-ylsulfonyl)-4,5-diphenyl-1,3,2-
diazaphospholidine 2-oxide 181b. ditosyl-1,3,2-diazaphospholidine-2-oxide 8. Obtained a white powdery solid after recrystallization. (Yield after three steps = 32%); m.p. > 250°C; 
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.12 (s, 2H), 7.92-7.63 (m, 6H), 7.62-7.38 (m, 6H), 7.27 (d, $J = 7.8$ Hz, 2H), 6.81 (d, $J = 7.5$ Hz, 4H), 6.64 (d, $J = 7.2$ Hz, 4H), 5.45 (br, 2H), 4.45 (br, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$167.6, 153.8, 151.9, 127.3, 127.1, 125.8, 125.2, 124.4, 124.0, 51.0, 44.6. HRMS (m/z): [M + Na]$^+$ calcd. for C$_{34}$H$_{27}$N$_2$O$_6$PS$_2$, 677.0946; found, 677.0975.
(3aR,7aR)-2-hydroxy-1,3-ditosyloctahydro-1H-benzo[de][1,3,2]diazaphosphole 2-oxide 181c. Obtained a white powdery solid after recrystallization. (Yield after three steps = 46%); m.p. > 250°C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.76 (d, $J = 7.0$ Hz, 4H), 7.32 (d, $J = 7.8$ Hz, 4H), 4.81 (br, 1H), 2.77 (br, 2H), 2.43 (s, 6H), 1.85 (br, 2H), 2.57 (br, 2H), 1.10 (br, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 143.8, 137.3, 130.0, 127.5, 56.9, 33.7, 24.5, 21.8; HRMS (m/z): [M]$^+$ calcd. for C$_{20}$H$_{25}$N$_2$O$_6$PS$_2$, 484.0970; found, 484.0892.
(3aR,7aR)-2-hydroxy-1,3-bis(naphthalen-2-ylsulfonyl)octahydro-1H-benzo[d]-[1,3,2]diazaphosphole 2-oxide 181c. Obtained a white powdery solid after recrystallization. (Yield after three steps = 41%); m.p. > 250°C; $^1$H NMR (300 MHz, CDCl$_3$): δ 8.59 (s, 2H), 8.19 (d, $J$ = 8.3 Hz, 2H), 7.93 (d, $J$ = 9.0 Hz, 2H), 7.87 (d, $J$ = 8.1 Hz, 2H), 7.69 (d, $J$ = 8.2 Hz, 4H), 4.86 (br, 1H), 4.65 (br, 2H), 3.10 (br, 2H), 2.83 (br, 2H), 2.62 (br, 2H), 2.30 (br, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 144.5, 141.7, 135.9, 133.9, 131.4, 127.9, 60.8, 36.7, 27.8, 24.9. HRMS (m/z): [M]$^+$ calcd. for C$_{26}$H$_{25}$N$_2$O$_6$PS$_2$, 556.0992; found, 556.0892.
2-hydroxy-1,3-ditosyl-2,3,9,10-tetrahydro-1H-5,13-ethano-4,8-(metheno)benzo[d][1,3,2]diazaphosphacyclododecine 2-oxide 181e. Obtained a white powdery solid after recrystallization. (Yield after three steps = 12%); m.p. > 250°C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.59 (d, $J = 8.1$ Hz, 4H), 7.20 (d, $J = 8.1$ Hz, 4H), 7.09 (br, 1H), 6.50 (d, $J = 8.0$ Hz, 2H), 6.36 (d, $J = 7.9$ Hz, 2H), 6.18 (s, 2H), 3.60 (dd, $J = 6.3$ Hz, 5.7, 2H), 2.98 (d, $J = 8.1$ Hz, 2H), 2.94 (d, $J = 8.4$ Hz, 2H), 2.69 (dd, $J = 13.8$ Hz, 6.4 2H), 2.36 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 143.9, 141.5, 136.0, 135.3, 133.8, 130.7, 129.8, 127.4, 123.7, 33.0, 21.8; HRMS (m/z): [M]$^+$ calcd. for C$_{30}$H$_{29}$N$_2$O$_6$PS$_2$, 608.1283; found, 608.1205.
(4R)-4-hydroxy-3,5-ditosyl-4,5-dihydro-3H-dinaphtho[2,1-d:1',2'-f][1,3,2]-
diazaphosphepine 4-oxide 181d. Obtained a white powdery solid after recrystallization.
(Yield after three steps = 28%); m.p. > 250°C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.13 (d, $J$ = 8.2 Hz, 4H), 8.00 (d, $J$ = 6.3 Hz, 4H), 7.92 (d, $J$ = 9.4 Hz, 2H), 7.57 (t, $J$ = 8.4 Hz, 4H), 7.44 (d, $J$ = 8.4 Hz, 4H), 2.38 (br, 1H), 2.17 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 166.9, 163.1, 159.9, 144.8, 135.1, 133.7, 128.7, 128.5, 126.9, 126.0, 120.1, 118.7, 26.8. HRMS (m/z): [M]$^+$ calcd. for C$_{34}$H$_{27}$N$_2$O$_6$PS$_2$, 654.1126; found, 654.1048.
(4R)-4-hydroxy-3,5-bis(methylsulfonyl)-4,5-dihydro-3H-dinaphtho[2,1-d:1', 2'-f][1,3,2]diazaphosphepine 4-oxide \(181f\). Obtained a white powdery solid after recrystallization. (Yield after three steps = 31%); m.p. > 250° C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.82 (d, \(J = 8.9\) Hz, 2H), 7.69 (d, \(J = 8.7\) Hz, 2H), 7.66 (d, \(J = 7.8\) Hz, 2H), 7.36 (t, \(J = 7.5\) Hz, 2H), 7.09 (t, \(J = 7.8\) Hz, 2H), 6.96 (d, \(J = 8.5\) Hz, 2H), 2.30 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 167.8, 151.3, 148.9, 140.9, 136.1, 131.2, 128.4, 123.8, 121.6, 21.6. HRMS (m/z): [M]+ calcd. for C\(_{22}\)H\(_{19}\)N\(_2\)O\(_4\)PS\(_2\), 502.0499; found, 502.0422.
(4R)-4-hydroxy-3,5-bis(phenylsulfonyl)-4,5-dihydro-3H-dinaptho[2,1-d:1',2'-f]-[1,3,2]diazaphosphepine 4-oxide 181h. Obtained a white powdery solid after recrystallization. (Yield after three steps = 27%); m.p. > 250°C; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.84 (d, $J = 7.8$ Hz, 4H), 7.74 (d, $J = 8.1$ Hz, 4H), 7.69 (d, $J = 8.1$ Hz, 4H), 7.56 (d, $J = 8.1$ Hz, 2H), 7.35 (t, $J = 7.8$ Hz, 2H), 7.21 (d, $J = 7.5$ Hz, 4H), 7.15 (d, $J = 8.1$ Hz, 4H), 7.10 (d, $J = 7.5$ Hz, 4H), 6.73 (d, $J = 8.1$ Hz, 2H), 6.68 (d, $J = 7.2$ Hz, 2H), 6.45 (t, $J = 7.5$ Hz, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 166.8, 161.3, 157.8, 144.9, 134.2, 131.4, 129.1, 128.6, 127.9, 127.1, 122.0, 119.7. HRMS (m/z): [M]$^+$ calcd. for C$_{32}$H$_{23}$N$_2$O$_6$PS$_2$, 626.0714; found, 626.0735.
(4R)-4-hydroxy-3,5-bis(naphthalen-2-ylsulfonyl)-4,5-dihydro-3H-dina-phtho[2,1-d:1',2'-f][1,3,2]diazaphosphepine 4-oxide 181i. Obtained a white powdery solid after recrystallization. (Yield after three steps = 21%); m.p. > 250°C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.84 (d, $J$ = 8.7 Hz, 2H), 7.71 (s, 2H), 7.53 (d, $J$ = 8.7 Hz, 2H), 7.53 (d, $J$ = 8.7 Hz, 2H), 7.34 (t, $J$ = 3.8 Hz, 4H), 7.27 (t, $J$ = 4.0 Hz, 4H), 7.24 (d, $J$ = 4.2 Hz, 2H), 6.87 (d, $J$ = 8.7 Hz, 2H), 6.77 (t, $J$ = 7.8 Hz, 2H), 6.56 (d, $J$ = 5.4 Hz, 4H), 3.92 (br, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 166.0, 160.6, 156.9, 143.7, 132.8, 129.0, 127.7, 126.4, 126.0, 125.1, 124.2, 120.4, 119.5, 118.9. HRMS (m/z): [M+Na]$^+$ calcd. for C$_{40}$H$_{27}$N$_2$O$_6$PS$_2$, 749.0946; found, 749.0983.

\[
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p-\text{TSA} \\
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\text{Toluene} \\
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\rightarrow \\
\text{O} \\ \text{O} \\
\text{NH} \\ 151
\]

Scheme 53: Reaction for the preparation of β-enamidoesters.

To a round bottom flask methyl carbamate (2.0 g, 27 mmol), the β-ketoester (27 mmol) and p-toluenesulfonyl chloride (110 mg, 0.64 mmol) were added. Toluene (30 mL) was added, the flask equipped with a Dean-Stark and a condenser, and the reaction refluxed for 15 hours. The reaction mixture was evaporated and chromatographed in 10-20% EtOAc:Hex. A white soft crystal was obtained (Scheme 53).

\[
\text{O} \\
\text{O} \\
\text{NH} \\
151
\]

(Z)-methyl 3-((methoxycarbonyl)amino)but-2-enoate 151. Obtained as a white crystal, (Yield = 92%) Mp: 74-75 (lit.72-73)\textsuperscript{109}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 10.61 (br, 1H),
4.93 (s, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 169.9, 155.0, 95.2, 87.3, 66.5, 52.7, 21.4.
3.7.2. Procedure for preparation of carbammylimines.

Carbammylimines have been prepared according to literature procedures.\textsuperscript{110}

3.7.2.1. Methylcarbammylimine 186.

![Scheme 54: Reaction for the preparation of Methoxycarbimmine 186.](image)

To an oven dry 250 mL round bottom flask equipped with stir bar and filled with dry argon 1,1,1,3,3,3-hexamethyldisilazane (15.58 mmol) was added. The reaction was cooled to 0 °C and butyllithium (15.58 mmol) was slowly added. The reaction was allowed to warm up to r.t. and stirred for 15 minutes. The reaction was cooled to 0 °C and benzaldehyde (15.58 mmol) was slowly added. The reaction was allowed to warm up to room temperature and stirred for 30 minutes. The hexanes were evaporated and the resulting slurry was distilled under vacuum (bp 95°C at 0.2 mmHg) as a pale yellow liquid. The silylimine distillate was dissolved in DCM (50 mL) and cooled to 0 °C (\textbf{Scheme 54}).
Methyl chloroformate (15.58 mmol) was added and the reaction was refluxed for 2 hours. The reaction mixture was cooled to r.t. and the volatiles evaporated under vacuum to yield a pale yellow oil.

(E)-methyl benzylidene carbamate 186. Obtained as a colorless oil, Yield over two steps = 54%; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.94 (s, 1H), 7.90 (d, $J = 8.1$ Hz, 2H), 7.56 (t, $J = 7.9$ Hz, 1H), 7.66 (t, $J = 8.3$ Hz, t), 3.89 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 171.6, 164.6, 134.2, 130.6, 129.2, 128.9, 54.3.
3.7.2.2. \textit{t}-butylcarbamylimines 150.

\begin{center}
\begin{tikzpicture}
    \node[below] at (0,0) {271};
    \node[below] at (1,0) {142};
    \node[below] at (2,0) {272};
    \node[below] at (3,0) {150};
    \node at (0.5,0.75) {MeOH/H\textsubscript{2}O 2:1 r.t., overnight};
    \node at (1.5,0.75) {TsONa H\textsubscript{2}CO\textsubscript{3}};
    \node at (2.5,0.75) {K\textsubscript{2}CO\textsubscript{3} THF, reflux, overnight};
    \node at (1.5,0.25) {Formic Acid 0.749 ml, 17.07 mmol};
    \node at (2.5,0.25) {2 g, 17.07 mmol};
\end{tikzpicture}
\end{center}

Scheme 55: Reaction for the preparation of \textit{t}-Butoxycarbimmines 150.

\textit{t}-Butylcarbamylimines 150 were prepared according to literature procedure.\textsuperscript{110} The aldehyde (17.07 mmol) and sodium phenylsulphinate (6.08 g, 34.1 mmol) were added to an Erlenmeyer flask and dissolved in MeOH (15 ml):water (30.0 ml). Formic acid (0.749 ml, 17.07 mmol) and \textit{t}-buthyl carbammate (2 g, 17.07 mmol) were added. The reaction was stirred at r.t. overnight. The precipitated white solid was filtered, washed with hexane and dried to yield a white soft intermediate. Potassium carbonate (11.80 g, 85 mmol) was added to an oven dried 250 mL flask. The flask containing the potassium carbonate was evacuated and flame dried and refilled with dry nitrogen. The intermediate was added and anhydrous THF (60 ml) was also added. The mixture was refluxed overnight. The mixture
was filtered through celite, the organic solution was evaporated to provide the desired product as a colorless oil (Scheme 55).
(E)-tert-butyl benzylidencarbamate 150a. Obtained as a colorless oil. Yield over two steps = 78%; \( ^1H \) NMR (300 MHz, CDCl\(_3\)): \( \delta \) 8.98 (s, 1H), 7.89 (d, \( J = 8.3 \) Hz, 2H), 7.52 (t, \( J = 8.2 \) Hz, 1H), 7.43 (t, \( J = 8.3 \) Hz, 2H), 1.57 (s, 9H); \( ^{13}C \) NMR (75 MHz, CDCl\(_3\)): \( \delta \) 167.6, 134.7, 130.0, 129.2, 127.4, 127.2, 28.5, 14.4.

(E)-tert-butyl 4-methylbenzylidencarbamate 150b. Obtained as a colorless oil. Yield over two steps = 76%; \( ^1H \) NMR (300 MHz, CDCl\(_3\)): \( \delta \) 8.82 (s, 1H), 7.76 (d, \( J = 7.8 \) Hz, 2H), 7.21 (d, \( J = 7.8 \) Hz, 2H), 2.36 (s, 3H), 1.54 (s, 9H); \( ^{13}C \) NMR (75 MHz, CDCl\(_3\)): \( \delta \) 171.4, 130.1, 129.5, 125.9, 28.5, 16.1.
(E)-tert-butyl 4-methoxybenzylidenecarbamate 150c. Obtained as a colorless oil, Yield over two steps = 55%; ¹H NMR (300 MHz, CDCl₃): δ 8.89 (s, 1H), 7.89 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.1 Hz, 2H), 3.88 (s, 3H), 1.59 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 189.7, 158.5, 153.8, 128.9, 126.1, 112.8, 66.2, 54.5, 27.2.

(E)-tert-butyl 4-(trifluoromethyl)benzylidenecarbamate 150d. Obtained as a colorless oil, Yield over two steps = 81%; ¹H NMR (300 MHz, CDCl₃): δ 8.79 (s, 1H), 7.95 (d, J =
8.3 Hz, 2H), 7.66 (d, $J = 8.2$ Hz, 2H), 1.41 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 167.7, 130.4, 130.1, 126.4, 126.1, 83.1, 28.4.

(\textit{E})-\textit{tert}-butyl 4-chlorobenzylidene carbamate 150e. Obtained as a colorless oil, Yield over two steps = 67%; $^1$H NMR (300 MHz, CDCl$_3$): δ 8.80 (s, 1H), 7.75 (d, $J = 8.2$ Hz, 2H), 7.20 (d, $J = 7.9$ Hz, 2H), 1.38 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 170.2, 163.0, 144.8, 131.7, 130.1, 129.9, 125.9, 82.3, 28.5.

(\textit{E})-\textit{tert}-butyl (3-phenylpropylidene) carbamate 150f. Obtained as a colorless oil, Yield over two steps = 34%; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.35-7.25 (m, 2H), 7.15-7.25 (m, 3H), 6.57 (t, $J = 10.2$ Hz, 2H), 6.39 (br, 1H), 6.26 (d, $J = 10.2$ Hz, 1H), 5.11 (br, 1H), 4.80
(q, $J = 8.0$ Hz, 2H), 3.28 (d, $J = 7.8$ Hz 2H), 1.45 (2s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 153.0, 140.1, 128.7, 128.5, 128.4, 128.2, 126.5, 126.3, 123.7, 106.4, 80.5, 31.9, 31.7, 27.9.

(N)-tert-butyl (2,2-dimethylpropylidene)carbamate 150g. Obtained as a colorless oil, Yield over two steps = 27%; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.07 (s, 1H), 1.53 (s, 9H), 1.19 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 164.5, 161.2, 76.5, 80.2, 31.2, 29.4, 25.8.

(E)-tert-butyl 3-methoxybenzylidenecarbamate 150h. Obtained as a colorless oil, Yield over two steps = 58%; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.70 (s, 1H), 7.37 (dd, $J = 2.5$ Hz, 1.5 Hz, 1H), 7.29 (dt, $J = 7.5$ Hz, 1.5 Hz, 1H), 7.24 (t, $J = 7.5$ Hz, 1H), 6.98 (ddd, $J = 7.5$ Hz, 1.5 Hz, 1H).
Hz, 2.5 Hz, 1.5 Hz, 1H), 3.74 (s, 3H), 1.50 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 162.4, 157.9, 148.9, 135.6, 130.1, 127.4, 111.4, 108.7, 82.0, 57.9, 31.5.

$^{(E)}$-5-(5,5-dimethyl-3-methylenehex-1-en-1-yl)-1,2,3-trimethylbenzene 150i. Obtained as a colorless oil, Yield over two steps = 61%; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.74 (s, 1H), 7.12 (s, 2H), 3.85 (s, 9H), 1.36 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 162.4, 154.3, 151.9, 137.8, 80.4, 58.7, 26.7.
3.7.3. General procedure for asymmetric catalytic Mannich reaction.

![Mannich Reaction general scheme](image)

Scheme 56: Mannich Reaction general scheme.

In an oven dry scintillation vial equipped with a stir bar and a dry nitrogen balloon, the enamide (0.30 mmol) and the catalyst (0.03 mmol) were added. Trifluorotoluene (1 mL) was added and the solution stirred at r.t. for 30 minutes. The imine is added and the reaction is stirred overnight at r.t. The crude mixture was purified through silica gel column chromatography (toluene:ethyl acetate 9:1), to yield the product as a white crystalline solid (Scheme 56).
(Z)-methyl 3,5-bis((methoxycarbonyl)amino)-5-phenylpent-2-enoate 190a. Obtained as a white powdery solid. TLC (Toluene:EtOAc, 9:1 v/v): \( R_f = 0.39 \); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 10.62 (br, 1H), 7.41-7.27 (m, 4H), 5.58 (br, 1H), 5.00 (br, 1H), 4.98 (s, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.59 (s, 3H), 3.11 (dd, \( J = 1.5 \) Hz, 0.1 Hz, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 170.6, 157.8, 155.4, 133.3, 130.0, 128.6, 128.4, 125.8, 80.1, 61.7, 28.2.

(R,Z)-methyl 5-((tert-butoxycarbonyl)amino)-3-((methoxycarbonyl)amino)-5-phenylpent-2-enoate 190b. Obtained as a white powdery solid. TLC (Toluene:EtOAc, 9:1 v/v): \( R_f = 0.41 \); \([\alpha]_D = +5.8 \) (0.1 M in DCM); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 10.62 (br, 1H), 7.39-7.31 (m, 4H), 5.15 (br, 1H), 5.02 (br, 1H), 4.90 (s, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 1.35 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 168.1, 154.2, 153.2, 152.6, 127.6, 126.3, 124.9, 96.2, 63.3, 62.3, 53.0, 51.7, 50.1, 39.7, 27.2.
(R,Z)-methyl 5-((tert-butoxycarbonyl)amino)-3-((methoxycarbonyl)amino)-5-(p-tolyl)pent-2-enoate 190c. Obtained as a white powdery solid. TLC (Toluene:EtOAc, 9:1 v/v): \( R_f = 0.43 \); \([\alpha]_D = +5.9 \) (0.1 M in DCM); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta 10.61 \) (br, 1H), 7.22 (d, \( J = 10.0 \) Hz, 2H), 7.12 (d, \( J = 10.0 \) Hz, 2H), 5.12 (br, 1H), 5.01 (br, 1H), 4.98 (s, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.30 (dd, \( J = 13.3 \) Hz, 3.3 Hz), 1.39 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta 169.1, 137.0, 129.3, 125.8, 97.2, 52.7, 51.1, 28.2, 21.1 \).

(R,Z)-methyl 5-((tert-butoxycarbonyl)amino)-3-((methoxycarbonyl)amino)-5-(4-methoxyphenyl)pent-2-enoate 190d. Obtained as a white powdery solid. TLC (Toluene:EtOAc, 9:1 v/v): \( R_f = 0.42 \); \([\alpha]_D = +5.9 \) (0.1 M in DCM); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta 10.62 \) (br, 1H), 7.26 (dd, \( J = 6.7 \) Hz, 3.3 Hz, 2H), 7.19 (dt, \( J = 6.0 \) Hz, 1.6 Hz,
1H), 6.87-6.80 (m, 2H); $^1$C NMR (75 MHz, CDCl$_3$): $\delta$ 158.8, 127.6, 127.1, 114.0, 100.0, 55.3, 52.7, 51.1, 28.3.

(R,Z)-methyl 5-((tert-butoxycarbonyl)amino)-3-((methoxycarbonyl)amino)-5-(4-(trifluoromethyl) phenyl)pent-2-enoate 190e. Obtained as a white powdery solid. TLC (Toluene:EtOAc, 9:1 v/v): $R_f$ = 0.38; $[\alpha]_D$ = +5.3 (0.1 M in DCM); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.61 (br, 1H), 7.53 (d, $J$ = 8.2 Hz, 2H), 7.07 (d, $J$ = 8.4 Hz, 2H), 5.19 (d, $J$ = 8.5 Hz, 1H), 5.04 (br, 1H), 5.01 (s, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 3.35 (d, $J$ = 12.2 Hz, 1H), 2.89 (br, 1H), 1.38 (s, 9H); $^1$C NMR (75 MHz, CDCl$_3$): $\delta$ 168.0, 136.1, 132.4, 128.2, 127.6, 127.2, 124.7, 64.7, 63.3, 53.2, 29.4.

(R,Z)-methyl 5-((tert-butoxycarbonyl)amino)-5-(4-chlorophenyl)-3-((methoxycarbonyl)amino)pent-2-enoate 190f. Obtained as a white powdery solid. TLC (Toluene:EtOAc, 9:1 v/v): $R_f$ = 0.37; $[\alpha]_D$ = +6.2 (0.1 M in DCM); $^1$H NMR (300 MHz,


CDCl$_3$: $\delta$ 7.25 (d, $J = 6.9$ Hz, 2H), 7.21 (d, $J = 11.2$ Hz, 1.0 Hz, 1H), 1.38 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 161.5, 160.8, 130.0, 128.8, 126.3, 122.6, 122.2, 121.3, 118.6, 59.6, 58.2, 54.6, 53.4, 25.8, 24.2, 23.4

(5S,Z)-methyl 5-((tert-butoxycarbonyl)amino)-7-(cyclohexa-2,4-dien-1-yl)-3-((methoxycarbonyl)-amino)hept-2-enoate 190g. Obtained as a white powdery solid. TLC (Toluene:EtOAc, 9:1 v/v): $R_f = 0.49$; $[\alpha]_D = +6.4$ (0.1 M in DCM); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.81 (d, $J = 1.2$ Hz, 2H), 7.42 (d, $J = 1.1$ Hz, 2H), 7.38 (t, $J = 1.3$ Hz, 1H), 5.44 (br, 1H), 5.29 (br, 1H), 4.97 (s, 1H), 3.84 (d, $J = 6.7$, 1H), 3.37 (s, 3H), 3.27 (s, 3H), 2.59 (d, $J = 5.8$ Hz), 2.03 (s, 2H), 1.79 (s, 2H), 1.01 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$):
δ 168.0, 166.6, 136.1, 132.7, 128.2, 127.6, 127.2, 126.0, 125.8, 125.1, 123.7, 64.6, 63.3, 53.2, 30.1, 29.4.

(R,Z)-methyl 5-((tert-butoxycarbonyl)amino)-3-((methoxycarbonyl)amino)-6,6-dimethylhept-2-enoate 190h. Obtained as a white powdery solid. TLC (Toluene:EtOAc, 9:1 v/v): Rf = 0.53; [α]D = +5.6 (0.1 M in DCM); 1H NMR (300 MHz, CDCl3): δ 5.15 (br, 1H), 5.03 (br, 1H), 4.96 (s, 1H), 3.84 (s, 3H), 3.64 (s, 3H), 3.39 (d, J = 7.9, 1H), 2.92 (br, 1H), 1.68 (s, 9H), 1.48 (s, 9H); 13C NMR (75 MHz, CDCl3): δ 172.4, 157.2, 155.5, 152.4, 89.2, 53.1, 52.1, 41.5, 28.5, 25.8, 21.0.

(R,Z)-methyl 5-((tert-butoxycarbonyl)amino)-3-((methoxycarbonyl)amino)-5-(3-methoxyphenyl)pent-2-enoate 190i. Obtained as a white powdery solid. TLC
(Toluene:EtOAc, 9:1 v/v): R_f = 0.41; [α]_D = +6.4 (0.1 M in DCM); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 10.59 (br, 1H), 7.24 (t, J = 10.0 Hz, 1H), 6.93 (d, J = 6.7 Hz, 1H), 6.88 (t, J = 2.0 Hz, 1H), 6.77 (dd, J = 9.0 Hz, 2.0 Hz, 1H), 5.16 (br, 1H), 4.99 (br, 1H), 4.96 (s, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H), 1.41 (s, 9H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): δ 169.1, 129.7, 118.2, 112.7, 100.0, 55.2, 52.7, 51.1, 48.4, 28.2.

\( (R,Z) \)-methyl 5-((tert-butoxycarbonyl)amino)-3-((methoxycarbonyl)amino)-5-(3,4,5-trimethoxyphenyl)-pent-2-enoate 190j. Obtained as a white powdery solid. TLC (Toluene:EtOAc, 9:1 v/v): R_f = 0.51; [α]_D = +4.1 (0.1 M in DCM); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 6.51 (s, 2H), 5.11 (br, 1H), 5.07 (br, 1H), 4.97 (s, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H), 3.34 (d, J = 7.4 Hz, 1H), 2.85 (br, 1H), 1.44 (s, 9H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): δ 166.5, 152.5, 136.9, 134.5, 18.2, 127.9, 103.4, 64.8, 63.5, 61.4, 56.9, 53.6, 29.5.
3.7.4. Determination of absolute stereochemistry.

3.7.4.1. Ozonolysis.

![Scheme 57: Synthesis of β-phenyl-β-alanine via ozonolysis of the product of the Mannich reaction.](image)

The product of the Mannich reaction 190 (50.0 mg, 0.13 mmol) was dissolved in DCM (5mL). The solution was cooled to -78 C and O₃ was bubbled in the reaction for 15 minutes. The flow of ozone was stopped, the reaction quenched with dimethyl sulfide, allowed to warm to r.t. and stirred for 2 hours. All the volatile compounds were evaporated...
under vacuum and the product was obtained as a white solid. The product was purified by silica gel column chromatography (Toluene, EtOAc 9:1 to 8:1). The product of the ozonolysis 201 was then dissolved in benzyl alcohol (5ml) and stirred at 60 C for 5 hours. After cooling to r.t., the mixture was extracted with water/DCM (3 x 25 ml), the organic fractions were collected, dried over sodium sulfate, the solvent evaporated under vacuum and the product 202 obtained as a white solid. The solid was dissolved in DCM (5 ml) and para-toluensulfonic acid (excess, 0.15 mmol) was added. The mixture was stirred at r.t. overnight. The mixture was extracted in water/DCM (3 x 25 ml), the organic fractions were collected, dried over sodium sulfate and the solvent was evaporated under vacuum to provide the product 203 as a white solid (Scheme 57). The β-phenyl-β-alanine benzyl ester was dissolved in methanol and the [α]D was measured (+3.1 (0.1 M in methanol)) and compared with the literature value91 (-2.5 (0.1 M in methanol for the S enantiomer).

3.7.4.2. Characterization of β-phenyl-β-alanine benzyl ester.

(R)-3-(benzyloxy)-3-oxo-1-phenylpropan-1-aminium p-toluensulfonate 203. [α]D = +3.1 (0.1 M in methanol); 1H NMR (300 MHz, CDCl3): δ 7.45-7.12 (m, 14H), 5.21 (s, 2H), 4.76 (t, J = 6.8 Hz, 2H), 3.34 (dd, J = 8.9 Hz, 1.5 Hz, 1H), 3.34 (br d, J = 9.2 Hz, 1H), 2.10
(s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 175.4, 143.6, 139.1, 137.2, 136.2, 135.8, 130.1, 128.7, 128.5, 126.7, 125.4, 125.0, 124.8, 71.4, 49.3, 38.4, 21.3.
Chapter 4: Asymmetric Multicomponent Reaction.

Development of an asymmetric organocatalyzed multicomponent reaction of phenols, aldehydes and boronates.

4.1. Introduction

Since the asymmetric reduction of the enamide moiety of the product of the Mannich reaction, described in Section 3.5, was unsuccessful, we decided to direct our efforts toward the development of a synthetic methodology to asymmetrically prepare chiral benzhydrls under the catalysis of chiral Brønsted acids. In this chapter, the development of an asymmetric multicomponent boronate reaction to achieve this goal is described.

4.1.1. Boron based nucleophiles

4.1.1.1. Boronic acids and boronates

Boranes are Lewis acidic because of the empty p orbital on the boron atom. In general, classical boron Lewis acids, such as boron trifluoride etherate, are used stoichiometrically in organic transformations, and under anhydrous conditions to prevent the hydrolysis to boric acid. Arylboronic acids also act as Brønsted acids and have been
used since the early ‘60s as catalytic promoters and reagents. Their ability to exchange their aryl substituent has led to their use as nucleophiles for the formation of carbon-carbon bonds in cross coupling. Due to the difference in electronegativity, a partial negative charge is localized on the carbon directly bonded to the boron atom, hence, it is a modest nucleophile. Investigations of boronates, which have esters in place of boronic acids, also began in the same period, when McCusker first observed exchange of the substituents of the boron. When two different boronates where mixed together, the two species would exchange ligands and form mixed boronate esters (Scheme 58).

Scheme 58: McCusker observation of exchange of the substituents of the boron.

Based on the results obtained in 1982 by Yamamoto with tartrate ligands for the formation of chiral boronates, Roush investigated the first implementation of such ligands to synthesize chiral allylboronate reagent 278a, and completed a significant body of work showing their utility as reagents. Although these boronates gave only
moderate selectivities when coupled with prochiral aldehydes, their utility was well established in diastereoselective allylboration reactions using chiral aldehydes as substrates, and have since been used in many natural product syntheses.\textsuperscript{126-129} Theoretical calculations suggested an attractive nO→p* C-O interaction between one of the ester lone-pairs and the boron-activate aldehyde carbonyl as a likely explanation for facial selectivity 279 (Scheme 59).

Based on the proposed transition state model, Roush designed cyclic tartrate amides as ligands for chiral boronate reagents 278b and 278c.\textsuperscript{130-131} These allylboronates gave

\begin{equation}
\text{Roush allylboration catalyzed by tartrates and tartrate amides.}
\end{equation}
higher enantioselectivities upon reactions with prochiral aldehydes when compared to diisopropyltartrate-derived allylboronate 278a.

More recently, Schaus laboratory’s research has set a major focus on reactions involving boronates as nucleophiles. In 2005, Sha Lou and Philip Moquist reported a new catalytic method for the allylboration of ketones using diisopropoxyallylboronate as a nucleophile. From a thorough catalyst screen, their investigations revealed 3,3’-disubstituted BINOLs as suitable catalysts for allylboration. Analysis of different substitutions identified 3,3’-Br2BINOL 286 as the optimal catalyst for the reaction (Table 20).
Table 20: Catalyst screen for the asymmetric allylboration of ketones.

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<th>Catalyst</th>
<th>% Y</th>
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<td>-</td>
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<td>282</td>
<td>19</td>
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<td>83:17</td>
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<tr>
<td>287</td>
<td>78</td>
<td>82.5:17.5</td>
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<table>
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<th>e.r.</th>
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<td>68</td>
<td>55:45</td>
</tr>
<tr>
<td>289</td>
<td>76</td>
<td>71:29</td>
</tr>
<tr>
<td>290</td>
<td>72</td>
<td>68:32</td>
</tr>
<tr>
<td>291</td>
<td>25</td>
<td>53:47</td>
</tr>
</tbody>
</table>

Nuclear magnetic resonance and mass spectrometry studies, conducted by Moquist and Barnett in 2009, strongly supported that the proposed mechanism proceeds via a single
exchange of one of the alkoxy esters of the boron with one of the hydroxyls of the catalyst. This leaves the other hydroxyl group free to activate the substrate via coordination and direct the facial selectivity of the nucleophilic attack (Scheme 60). In Section 4.2., we will see how this influences the enantioselectivity of the new multicomponent reaction we have developed.

Scheme 60: Reaction mechanism proposed by Barnett and Moquist with single BINOL/Boronate exchange
4.1.2. Multicomponent reactions

One of the major current challenges in organic synthesis is the creation of molecular diversity and complexity from simple and readily available substrates. Therefore, the development of processes that allow the formation of several bonds in a single operation is highly desirable. Multicomponent reactions \(132\) (MCR) are convergent chemical processes that involve the well defined condensation of more than two reactants to form a product that contains significant portions of all reactants, ideally all atoms.\(^{133}\) In this way, very high levels of atom efficiency can be reached, while avoiding time-consuming isolation and purification of synthetic intermediates.\(^{134-137}\) Through reducing the number of reaction steps and starting from simple, inexpensive starting materials, the cost of constructing highly diverse and complex small molecules is reduced to a minimum. In addition, both waste production and expenditure of human labor are significantly reduced. The most valuable MCRs allow systematic variations and exhibit the possibility of automation\(^{138-140}\) by their experimental simplicity. For these reasons, such MCRs are especially suitable for combinatorial synthesis\(^{141-142}\) and diversity-oriented synthesis.\(^{143-148}\) Multicomponent reactions have been extensively applied to the synthesis of large libraries of potentially bioactive and densely functionalized molecules,\(^{148-149}\) and to a lesser extent, to the total synthesis of complex molecules.\(^{150-154}\) Moreover, the identification of therapeutic protein targets is achieved in a systematic way by high-throughput screening\(^{152-154}\) of numerous candidates. Other advantages of the most useful multicomponent
approaches are the high selectivities and environmentally friendly procedures. Thus, MCRs quite closely approach the realization of the ideal synthesis, capable of delivering target compounds in a single pot.\textsuperscript{155}

4.1.2.1. Asymmetric multicomponent reactions

As we have seen in Chapter 2, a multicomponent reaction that can be catalyzed by chiral Brønsted acids is the Mannich reaction, a condensation of amine derivatives, enolizable carbonyl compounds and non-enolizable aldehydes. Other multicomponent reactions which have been widely studied and developed asymmetrically include the Strecker reaction, the Biginelli reaction, the Petasis reaction, the Hantsch reaction, the Passerini reaction and the Ugi reaction.
The asymmetric Strecker reaction was first described by Kobayashi and co-workers in 2000 as a transition-metal catalyzed reaction,\textsuperscript{156-157} and then reported in its organocatalytic version by Pan and List\textsuperscript{158} in 2007. This three-component acyl-Strecker reaction was catalyzed by chiral thiourea as a simplification of the Jacobsen–Strecker procedure that involves three separate steps to furnish the $\alpha$-amino nitrile derivatives.\textsuperscript{159}\textsuperscript{-160}

In the first step, imine formation occurs on the aldehyde 148. This is followed by nucleophilic addition of the newly formed imine onto the carbonyl cyanide 301 with elimination of cyanide. Finally, the cyanide ion adds to the acyliminium ion to yield adduct 304. List reported the formation of adduct 304 in excellent yield and high enantioselectivity under the catalysis of thiourea 303 (Scheme 61).

![Scheme 61: List and co-workers' acyl-Strecker multicomponent reaction catalyzed by chiral thiourea.](image-url)
The Biginelli reaction, discovered by Pietro Biginelli in 1893, is a condensation of aldehydes, (thio)urea and β-ketoesters to give functionalized dihydropyrimidines or the 2-thio analogs. The first highly enantioselective Biginelli dihydropyrimidine synthesis was developed by Zhu and co-workers in 2005 and involved the use of a new chiral ytterbium Lewis acid catalyst. The first organocatalytic enantioselective Biginelli reaction was reported in 2006 by Gong and co-workers, as catalyzed by chiral phosphoric acids. In presence of (R)-3,3′-diphenyl-H8-binaphthyl phosphoric acid (27g), Gong obtained very high enantioselectivities in the reaction of an aldehyde 1, a urea 305 and a β-ketoester 306, for the formation of the cyclic adduct 307 (Scheme 62).

Scheme 62: Gong and co-workers' enantioselective Biginelli reaction, catalyzed by a chiral Brønsted Acid.
The Petasis multicomponent reaction, firstly developed by Petasis in 1993, involves the condensation of amines, carbonyl derivatives and aryl- or vinylboronic acids for the preparation of amine derivatives. The first catalytic enantioselective Petasis reaction was developed in Schaus laboratory as the reaction between styryl boronates 302, secondary amines 303 and ethyl glyoxylate 304, in presence of chiral biphenol 29, to prepare adduct 305 (Scheme 64). The publications of Takemoto and Yuan followed in subsequent years. 

Scheme 63: Schaus and co-workers' asymmetric Petasis reaction catalyzed by VAPOL 29
The Hantzsch multicomponent reaction involves the cyclocondensation of aldehydes $312$, β-keto esters $306$, and a nitrogen source such as ammonium acetate or primary amine $313$, to construct dihydropyridines $315$. As the Hantzsch pyridine synthesis was described as early as 1882, this reaction is one of the pioneering and most venerable MCRs. An asymmetric three-component Hantzsch-type reaction for the construction of DHPs was developed by Jørgensen and co-workers, representing the first organocatalytic enantioselective one-pot synthesis of optically active DHPs. (Scheme 64)

Scheme 64: Jørgensen and co-workers' asymmetric Hantzsch synthesis of dihydropyridines
The Passerini three-component reaction involves the condensation of carbonyl compounds, carboxylic acids and isocyanides to afford α-acyloxy carboxamides. Schreiber and co-workers applied chiral tridentate Lewis acidic Cu(II) complexes 318 to activate the carbonyl species and control the stereochemical outcome of the Passerini three-component reaction (Scheme 65).  

\[ \text{Scheme 65: Schreiber's asymmetric Passerini reaction catalyzed by a copper based chiral Lewis acid} \]
The Ugi four-component reaction, first described in 1959, involves the condensation of carbonyl derivatives, amines, carboxylic acids and isocyanides to afford α-amino acid derivatives (Scheme 66). The Ugi reaction is the most studied and widely used MCR reaction, enabling a high degree of diversity in the preparation of new α-amino acids. Thus far, a catalytic enantioselective version of the Ugi multicomponent reaction has not been reported.

Scheme 66: General Scheme of the Ugi four-component reaction
4.1.4. Novel multicomponent boronate reaction

In this chapter, we will describe how the nucleophilic boronate addition chemistry developed from the Schaus laboratory led to the discovery and development of a novel asymmetric multicomponent reaction of a styryl boronate, a phenol and an aromatic aldehyde, catalyzed by substituted BINOLs as chiral Brønsted acids.

4.1.4.1. Previous work

In 2011, Luan and Schaus reported the homodimerization of dihydrochromenes catalyzed by iron (III) chloride (Scheme 67). The mechanism of the dimerization was investigated via deuterium labeling experiments, and a conjugated ortho-quinone methide was prepared as an intermediate to support the proposed mechanism. (Scheme 68)

Scheme 67: Luan's work on homodimerization of dihydrochromenes catalyzed by Fe (III).
Scheme 68: Deuterium labelling studies for the elucidation of the mechanism of the homodimerization of dihydrochromenes.

From this observation, the idea for a nucleophilic boronate arylation of $o$-quinonemethides followed and a new synthetic methodology for the preparation of chiral benzhydrols was reported in 2012.\textsuperscript{178} Due to the low stability of $o$-quinonemethides, Luan re-designed the system so that the boronate could be added to the \textit{in situ} formed $o$-quinonemethides, with no required isolation (Table 21).
Table 21: Asymmetric aryloboration of o-quinonemethides catalyzed by Chiral Brønsted Acids.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>% Y</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>285</td>
<td>PhCH₃</td>
<td>54</td>
<td>86:14</td>
</tr>
<tr>
<td>286</td>
<td>PhCH₃</td>
<td>76</td>
<td>97:3</td>
</tr>
<tr>
<td>286</td>
<td>PhCF₃</td>
<td>70</td>
<td>96:4</td>
</tr>
<tr>
<td>286</td>
<td>DCM</td>
<td>75</td>
<td>95:5</td>
</tr>
<tr>
<td>286</td>
<td>THF</td>
<td>72</td>
<td>90:10</td>
</tr>
<tr>
<td>287</td>
<td>PhCH₃</td>
<td>65</td>
<td>92.5:7.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>% Y</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>330</td>
<td>PhCH₃</td>
<td>65</td>
<td>90:10</td>
</tr>
<tr>
<td>331</td>
<td>PhCH₃</td>
<td>73</td>
<td>97:3</td>
</tr>
<tr>
<td>289</td>
<td>PhCH₃</td>
<td>66</td>
<td>74:26</td>
</tr>
<tr>
<td>290</td>
<td>PhCH₃</td>
<td>57</td>
<td>50:50</td>
</tr>
<tr>
<td>332</td>
<td>PhCH₃</td>
<td>47</td>
<td>52:48</td>
</tr>
<tr>
<td>333</td>
<td>PhCH₃</td>
<td>72</td>
<td>77:23</td>
</tr>
</tbody>
</table>

R = R=H
R = Br
R = Ph
R = 2,4,6-(CH₃)₃C₆H₂
R = 9-anthracyl
In this chapter, we describe how we were able to design a one-pot multicomponent variant of this boronate chemistry in order to develop an organocatalytic enantioselective multicomponent reaction for the synthesis of highly enantioenriched benzhydrils (Scheme 69).

![Scheme 69: Organocatalytic acid-driven multicomponent boronate reaction for the synthesis of chiral benzhydrils.](image)

4.1.4.2. Chromenes as synthetic targets

Substituted chromene structures form the basis for many biologically interesting compounds, fueling the study and characterization of their syntheses. One class of compounds with a substituted chromene core is the flavan family of myristinins, first isolated by Sawadjoon and co-workers from *Myristica cinnamomea*. Some members of the class have been shown to exhibit activity both as potent COX-2 and DNA polymerase β inhibitors, as well as displaying some interesting antifungal activity against *Candida albicans*. In addition, two particularly interesting members of the family, myristinins A and D (Figure 9) have been shown to possess cytotoxicity against tumors cells through their
potent DNA damaging ability in addition to their DNA polymerase β inhibition, prompting a meticulous investigation of these compounds as prospective chemotherapeutic agents in tumor treatments.\textsuperscript{181-183}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9}
\caption{Myristinins A 341, B 342, C 343, and D 344, potent DNA polymerase β inhibitors and DNA damaging agents.}
\end{figure}

A significant portion of early research on these myristinins focused on their potential pharmacological similarity to the chemical constituents of \textit{Myristica fragrans} and the characterization of their absolute stereochemistries.\textsuperscript{182-183} Thus far, only a few myristinins have been synthesized due to their challenging polycyclic frameworks. Myristinin A was the first member of the class to be totally synthesized, via a diastereoselective linear sequence reported by Maloney and co-workers in 2005, but only in low yields.\textsuperscript{182} Shortly thereafter, the synthesis of the atropisomeric myristinin B/C was achieved through a similar pathway, but yields were still low (\textbf{Scheme 70}).\textsuperscript{183}
BnO-\text{OH} \quad \text{345} \quad \text{BnO} \quad \text{346} \quad \text{a, b, c, d} \quad \text{BnO} \quad \text{347} \quad \text{e, f, g} \quad \text{BnO} \quad \text{348}

\begin{align*}
\text{BnO} & \quad \text{349} \quad \text{R} = \text{H} \\
\text{BnO} & \quad \text{350} \quad \text{R} = \text{O}(\text{CH}_2\text{OH})
\end{align*}

351 \quad m

\begin{align*}
\text{BnO} & \quad \text{352} \quad (\text{CH}_2\text{O})_{10}\text{CH}_3 \\
\text{BnO} & \quad \text{353} \quad (\text{CH}_2\text{O})_{10}\text{CH}_3 \\
\text{HO} & \quad \text{354} \quad (\text{CH}_2\text{O})_{10}\text{CH}_3
\end{align*}

(a) 40\% (w/v) KOH in MeOH, MeOH, reflux, (97\%);
(b) ethyl chloroformate, NEt\text{3}, THF, 0 \text{ °C};
(c) \text{NaBH}_4, \text{H}_2\text{O}, (74\%, 2 steps);
(d) TBDMSCl, imidazole, DMF, (100\%);
(e) ADMIX-R, methanesulfonamide, t-BuOH/H\text{2O} (1:1), (84\%);
(f) \text{CH(OEt)}_3, cat. PPTS, \text{CH}_2\text{Cl}_2, (92\%);
(g) TBAF, THF, (100\%);
(h) \text{CH(OEt)}_3, PPTS, Cl\text{(CH}_2\text{Cl)}_2, 60 \text{ °C}, (89\%);
(i) \text{K}_2\text{CO}_3, \text{THF/MeOH} (1:1), (98\%);
(j) Dess-Martin periodinane, \text{CH}_2\text{Cl}_2, (94\%);
(k) L-selectride, LiBr, THF, -78 \text{ °C}, (78\%);
(l) \text{Ac}_2\text{O}, cat. DMAP, \text{CH}_2\text{Cl}_2, (93\%);
(m) DDQ, ethylene glycol, \text{CH}_2\text{Cl}_2, (79\%);
(n) TMSOTf, 1-(2,4,6-tris(benzyl oxy)phenyl)dodecan-1-one, THF, -35 to -5 \text{ °C}, (77\%);
(o) \text{K}_2\text{CO}_3, \text{THF/MeOH} (1:1), (100\%);
(p) PhO\text{(S)Cl}, DMAP, MeCN, 50 \text{ °C};
(q) \text{SnBu}_3\text{H}, cat. AIBN, toluene, 100 \text{ °C}, (65\%, 2 steps);
(r) \text{Pd(OH)}_2\text{C}, \text{H}_2, \text{THF/MeOH} (1:1), (75\%).
Scheme 70: Maloney Synthesis of Myristinin A

These setbacks in overall yield can be attributed to the inefficiency of executing long linear total syntheses: difficulty in designing the correct sequence of reactions to generate complex targets through multiple steps. In the synthesis of myristinin A conducted by Maloney, trans-2,4-1-(2,4,6-tris(benzyloxy) phenyl)-dodecan-1-one, which exhibits the major myristinin core structure, was accessed in thirteen steps, through a Lewis acid promoted condensation in THF with a trans-4-O-alkylated chroman. The total synthesis of the flavan took eighteen steps. The myristinins all share a common substituted chroman core structure (Figure 10), however, which is easier to access and is a recurring motif in many natural products.

Figure 10: Common Substituted Chromene Core 355.
4.2. Results

4.2.1. Substrates and catalyst preparation

As aforementioned (Section 4.1.4), goal of this project was the implementation of Luan’s addition of nucleophilic boronate reagents 335 on ortho-quinonemethides 334 (Table 21). This led to the discovery and optimization of a multicomponent reaction, where an aldehyde 339, a substituted phenol 337 and a styrylboronate 338 react together to form adduct 340. The reaction still proceeds via the formation of an ortho-quinonemethides, but has the advantage of being a one-pot system, with no need for the pre-formation of the reactive intermediate (Scheme 68).

To provide the necessary reagents and catalyst for the multicomponent reaction, (E)-diethyl styrylboronates and chiral disubstituted BINOL catalysts were prepared. During this study, the (E)-diethyl styrylboronates will be called simply “boronates”. To produce the 3,3’-disubstituted binaphthyl catalysts 286 or 359, the hydroxyl of BINOL 285 was protected as a methoxymethyl ether to create 356, which was brominated following lithiation by the addition of dibromotetrachloroethane to yield 357, or iodination via addition of iodine to yield 358. Subsequently, both 357 and 358 were deprotected and hydrolyzed in the presence of HCl to yield 286 and 359, respectively (Scheme 70).
In *Scheme 72*, the synthesis of \((E)\)-diethyl styrylboronate, the boronate used in creating the core structure, is delineated. Boronate 338 was prepared via hydroboration of phenylacetylene with catechol borane, followed by hydrolysis to produce 363, the boronic acid. Subsequently, 363 was converted to \((E)\)-diethyl styrylboronate 338. The boronate was air and moisture sensitive so it was stored in an airtight, tinted vial. Generally, this reaction was replicated in the syntheses of all other boronates, changing the aryl substitution of the alkyne.
4.2.2. Multicomponent boronate reaction

The multicomponent reactions were optimized with 337 and 338 with 15 mol % of catalyst. The enantioselectivity for each reaction was determined by HPLC, and the absolute stereochemistry assigned by comparison of the HPLC chromatograms of previously published results.\textsuperscript{167-168} Temperature and catalysts screenings were initially conducted, the results of which are reported in Table 22. From the temperature screen, it was observed that the reaction does not proceed at any temperature lower than 80°C. Subsequently, (R)-Br\textsubscript{2}-BINOL (286), and (R)-I\textsubscript{2}-BINOL (359) were tested as catalysts; since 286 afforded better selectivities, it was applied in all further screenings (Table 22).
Table 22: Optimization of the multicomponent boronate reaction for catalyst, temperature and time.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>286</td>
<td>40</td>
<td>24</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>286</td>
<td>80</td>
<td>6</td>
<td>23</td>
<td>94:6</td>
</tr>
<tr>
<td>3</td>
<td>286</td>
<td>80</td>
<td>12</td>
<td>42</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>286</td>
<td>80</td>
<td>24</td>
<td>81</td>
<td>94:6</td>
</tr>
<tr>
<td>5</td>
<td>286</td>
<td>80</td>
<td>36</td>
<td>84</td>
<td>90:10</td>
</tr>
<tr>
<td>6</td>
<td>286</td>
<td>80</td>
<td>48</td>
<td>83</td>
<td>86:14</td>
</tr>
<tr>
<td>7</td>
<td>359</td>
<td>40</td>
<td>24</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>359</td>
<td>80</td>
<td>6</td>
<td>19</td>
<td>87:13</td>
</tr>
<tr>
<td>9</td>
<td>359</td>
<td>80</td>
<td>12</td>
<td>35</td>
<td>89:11</td>
</tr>
<tr>
<td>10</td>
<td>359</td>
<td>80</td>
<td>24</td>
<td>76</td>
<td>90:10</td>
</tr>
</tbody>
</table>

Once optimal temperature and catalyst were determined, the effects of ethanol as an additive in the multicomponent reaction was assessed. It was found that the addition of 0.5 equivalents of ethanol had a positive effect on the reaction. This effect may be a
consequence of facilitating the boron ester exchange steps. A full discussion of the proposed mechanism is given in Section 4.2.

Running the multicomponent reaction in dichloromethane and PhCF₃ yielded no product, likely because both DCM and PhCF₃ have lower boiling points and, as mentioned above, the temperature must be at least 80 °C for the reaction to proceed. Both, the (R)-Br₂-BINOL and (R)-I₂-BINOL catalyzed reactions, exhibited modest to high yields along with good to excellent enantioselectivity ratios, but the 286 catalyzed reaction consistently gave higher yields and er’s (Entries 2-4). With this, the time allotted to running each reaction was optimized in an effort to give increased yields while retaining high er’s. Further reactions showed that neither decreasing nor increasing catalyst concentration would have an appreciable influence on yield or er (Table 23).
Table 23: Optimization of multicomponent boronate reaction for catalyst concentration and temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[cat. 286] (eq)</th>
<th>T (°C)</th>
<th>Yield (%)</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>80</td>
<td>49</td>
<td>94:6</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>120</td>
<td>38</td>
<td>89:11</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>80</td>
<td>81</td>
<td>96:4</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>120</td>
<td>57</td>
<td>86:14</td>
</tr>
<tr>
<td>5</td>
<td>0.3</td>
<td>80</td>
<td>74</td>
<td>95:5</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
<td>80</td>
<td>79</td>
<td>95:5</td>
</tr>
</tbody>
</table>

A ratio of sesamol : aldehyde : boronate of 1.5:1:2, at 80 °C, and in presence of 0.2 eq of catalyst and 0.5 eq of ethanol were the standard conditions chosen for the substrate screening of different boronates and aldehydes. Through this method, the versatility of the multicomponent reaction was confirmed. The substrate table also served the purpose of determining whether other combinations of aldehydes or boronates in the multicomponent
reaction could serve as viable substitutes in generating the myristinin core structure. Both
electron poor and electron rich substituents were investigated.

The complete substrate scope can be found in Figure 1 (aldehyde scope) and
Figure 12 (boronate scope). The multicomponent reaction failed with 2-naphthaldehyde
(not shown in Figure 11), aliphatic aldehydes (Figure 12, structures 340g and 340i), the
highly electron-rich aldehyde (Figure 11, structure 340h); and when aliphatic boronates
were used (Figure 12, structures 340q).
Figure 11: Aldehyde substrate scope of multicomponent boronate reaction.

\[ \text{Scheme 11:} \quad \text{Aldehyde substrate scope of multicomponent boronate reaction.} \]

\[ \begin{align*}
\text{337} & : 1.5 \text{ eqv} \\
\text{338} & : 2.0 \text{ eqv} \\
\text{142} & : 1.0 \text{ eqv} \\
\end{align*} \]

\[ \begin{align*}
\text{Tol} & : 1 \text{ mL} \\
\text{EtOH} & : 0.5 \text{ eq} \\
\text{80} \text{ °C, 24 h} & \\
\text{340} &
\end{align*} \]

\[ \begin{align*}
\text{340a} & : 77\% \text{y} \quad 95:5 \text{ er} \\
\text{340b} & : 52\% \text{y} * \quad 92:8 \text{ er} \\
\text{340c} & : 67\% \text{y} * \quad 96:4 \text{ er} \\
\text{340d} & : 62\% \text{y} \quad 94:6 \text{ er} \\
\text{340e} & : 75\% \text{y} \quad 96:4 \text{ er} \\
\text{340f} & : 40\% \text{y} \quad 88:12 \text{ er} \\
\text{340g} & \text{No observed reactivity} \\
\text{340h} & \text{Traces} \\
\text{340i} & \text{No observed reactivity} \\
\text{* = run at 60°C in PhCF}_3 \\
\end{align*} \]
Figure 12: Boronate substrate scope of multicomponent boronate reaction.
4.2.3. Proposed Mechanism for multicomponent boronate reaction

A detailed mechanism was proposed for this reaction sequence (Scheme 73). After initial exchange on the boronate between a sesamol molecule and ethanol, the second ethanol ligand is exchanged for the BINOL. Coordination of the aldehyde to the boron atom to form an “ate” complex, followed by nucleophilic addition of the α-position of the sesamol onto the activated aldehyde, occurs, forming benzylic alcohol 367 as intermediate. Rearomatization, followed by proton transfer allows for the formation of intermediate 368, which forms the ortho-quinone methide 369 upon ligand exchange, proton transfer and dehydration. Thus, intramolecular nucleophilic addition onto the activated ortho-quinone methide occurs asymmetrically under chiral induction of the chiral boron ligand (BINOL). After hydrolysis, product 340 is obtained, the catalyst is recovered and a molecule of ethyl dihydrogenborate 372 is formed as a byproduct.
Scheme 73: Detailed catalytic mechanism for the multicomponent boronate reaction and transition state with the rational for enantioselectivity.
4.3. Conclusions

Previously, the original Petasis reaction was modified to include boronates in place of boronic acids, and to use a phenol based nucleophile in place of the secondary amine reagent. A relatively inexpensive starting material, sesamol, undergoes a nucleophilic addition with selected aldehydes to in-situ generate an o-quinone methide. This intermediate then is a ready electrophile for the enantioselective boronate addition, to generate a compound that can be diastereoselectively cyclized to generate an analog of the myristin core structure.

Initially the methodology was optimized for a few parameters: relative concentration of reagents, additive ethanol and catalyst, temperature, solvent and concentration of the catalyst. Thus, a substrate table was built on a diverse variety of reagents with different substitutions with good results which support the scope of applying the presented multicomponent reaction to complex syntheses: both electron withdrawing and electron donating boronates as well as diversely substituted aromatic aldehydes were prepared and successfully utilized in this reaction. Aliphatic boronates didn’t yield any product.

In conclusion, a new enantioselective multicomponent reaction was developed as an implementation to a previously studied synthetic system to prepare chiral benzhydrils from readily available reagents. A catalytic mechanism was also proposed for this reaction,
rationalizing the enantioselectivity. Through further optimization, the scope of this multicomponent boronate reaction can be extended to other types of electrophiles, potentially including imines or ketones in place of the aldehyde and to different phenols in place of sesamol.
4.4. Experimental Section

4.4.1. General Information:

Sesamol was produced by Alfa Aesar. Benzaldehyde, catechol borane, and ethynylbenzene were produced by Aldrich. 1H NMR spectra were recorded using a Varian Utility Plus 300MHz, Varian Utility Plus 400MHz, or Varian 400 MHz VNMR spectrometer at ambient temperature. Multiplicities were expressed using the following abbreviations: s = singlet, d = double, t = triplet, q = quartet, m= multiplet, br = broad. Chiral HPLC was performed on an Agilent 1100 series HPLC System with a diode array detector. Chiral columns included ChiralpakR ADH (Chiral Technologies Inc., 25cm x 4.6mm I.D.) and ChiralcelR OD (Chiral Technologies Inc., 25cm x 4.6mm I.D.). Silica columns were run on Sorbent Technologies 60 Å silica gel; TLC was performed on EMD 0.25 mm silica gel 60-F plates.
4.4.2. General Procedure for the synthesis of styryl substituted boronates

The selected alkyne (25 mmol) was combined with catechol borane (3.0 g, 25.0 mmol) in a flame-dried flask under an argon atmosphere, and the mixture was heated for 1 h. 1.8 mL H2O was added to the resulting mixture and mixed for 1 h. The resultant precipitate was filtered and recrystallized from boiling water to yield 300 mg (E)-alkenyl boronic acids in the form of white solids. To the boronic acid was added anhydrous MgSO4 (3.0 g), 4 Å MS (3.0 g), CHCl3 (7.5 mL), and EtOH (7.5 mL), and the mixture was set on reflux for 15 h. Upon sufficiently stirred, the mixture was filtered and the resulting filtrate was concentrated and finally put under a high vacuum to yield the boronate in colorless, air-sensitive form (Scheme 74).
(E)-diethyl styryl boronate 338. After undergoing reflux, the mixture was filtered on celite and the solution was concentrated to yield a colorless oil, which was stored as a 2M solution in toluene. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.60 (m, 2H), 7.76-7.84 (m, 3H), 6.90 (d, J = 4.2 Hz, 1H), 5.84 (d, J = 4.2 Hz, 1H), 3.88 (q, J = 8.1 Hz, 4H), 1.12 (t, J = 8.2 Hz, 6H).
4.4.3. General Procedure for the synthesis of 3,3’-substituted BINOLs

To produce the disubstituted catalysts 286 or 359, 285 was protected with methoxymethyl ether to prepare 356, which underwent bromination via addition of electrophilic dibromotetrachloroethane to yield 357 or iodination via addition of electrophilic iodine to yield 358, after lithiation of the 3,3’ positions. Subsequently, both 357 and 358 were deprotected and hydrolyzed in the presence of HCl to yield 286 or 359, respectively, the 3,3’-disubstituted BINOL catalysts (Scheme 75).

Scheme 75: Preparation of catalysts 286 and 359.
Reaction to prepare \((R)-2,2'-\text{Bis(methoxymethoxy)}-1,1'-\text{Binaphthyl} \ (356)\). NaH (1.46 g, 60\% in oil, 36.5 mmol) was mixed in THF (75.0 mL) in a 500 mL round bottom flask at 0 °C under Ar. A solution of \((R)-2,2'\)-dihydroxy-1,1'-binaphthyl (4.75 g, 16.6 mmol) in THF (25.0 mL) was slowly added through a dropping funnel. The mixture was then stirred at 0 °C for 1 h, forming a pale green solution, and then allowed to warm up to rt for 15 min. Upon being recooled to 0 °C, chloromethyl methyl ether (2.77 mL, 36.5 mmol) was slowly added from the dropping funnel. The reaction was then warmed to rt for 4.5 h. Saturated aqueous NH\(_4\)Cl (50 mL) was added to the flask, and the solvent was removed in vacuo. The residue was then extracted with 75 mL CH\(_2\)Cl\(_2\). The organic layers were combined, washed with 25 mL brine, and dried over Na\(_2\)SO\(_4\). The solvent was then removed in vacuo. Resulting filtrate was crystallized by Hex/EtOAc to give a fine, white powder in quantitative yield. 1H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.88-8.14 (2 H, m), 7.76-7.84 (2 H, m), 7.10-7.62 (8 H, m), 4.97, 5.08 (4 H, d), 3.10 (6 H, s).
Reaction to produce \((R)-3,3’-\text{Dibromo-2,2’-Bis(methoxymethoxy)-1,1’-binaphthyl}\) (357). Intermediate 356 was treated with nBuLi (31.125 mL of a 1.6 M solution in hexane) at rt and the resulting mixture was quenched with dibromotetrachloroethane (electrolyte) (11.5 g, 35.33 mmol). The product was subsequently purified by column chromatography and concentrated down. The resulting filtrate was crystallized by Hex/EtOAc to give a fine, white powder. 1H NMR (CDCl3, 300 MHz) δ 8.25-8.30 (m, 2 H), 7.78-7.82 (m, 2 H), 7.18-7.48 (m, 6 H), 4.81, 4.82 (d, 4 H), 2.56 (s, 6 H).

Reaction to prepare \((R)-3,3’-\text{Dibromo-1,1’-binaphthyl}\) (286). Intermediate 357 (1.0 g, 2.92 mmol) was treated with 2 M HCl (3.0 mL) in 1:1 THF/MeOH (50.0 mL). The mixture was stirred and heated to reflux under Ar for 15 h. The resulting mixture was then concentrated and crystallized to afford a fine, white powder in 92% yield. 1H NMR CDCl3, 300 MHz) δ 8.33 (m, 2H), 8.01 (m, J = 8 Hz, 4H), 7.63 (m, 4H), 5.31 (s, J = 8 Hz, 2H).

4.4.4. General procedure for Multicomponent Reaction
Sesamol (42.0 mg, 0.03 mmol) was added to a dry reaction tube along with the selected catalyst (0.04 mmol). The tube was then capped and refilled with dry Argon. Solvent (1.0 mL), selected boronate (0.4 mmol), selected aldehyde (0.2 mmol), and EtOH (58.0 μL, 1.0 mmol) were then added via syringe injection. Subsequently, the mixture was allowed to stir in an oil bath at 80 °C for 24 hours. The product was then directly extracted through silica gel column chromatography (2-15% EtOAc:Hex) (Scheme 76).

4.4.4.1. Aldehyde substrate scope

![Scheme 76: General Scheme for aldehyde substrate scope of asymmetric multicomponent boronate reaction.](image)

Nine different aldehydes were used as substrates for the multicomponent reaction. The experimental results and data are listed below.
(R,E)-6-(1,3-diphenylallyl)benzo[d][1,3]dioxol-5-ol (340a) Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl styrylboronate (0.2 mL, 0.4 mmol), benzaldehyde (20.0 μL, 0.2 mmol), (R)-(−)-3,3′-Br₂-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. Silica gel purification gave a brown, highly viscous oil in 81% yield. 1H NMR (CDCl₃, 300 MHz) δ (7.40-7.11) (m, J = 5 Hz, 10H), 6.78 (m, J = 10 Hz, 2H), 6.31 (m, 2H), 5.97 (s, J = 10 Hz, 2H), 5.30 (s, 1H), 4.64 (d, 1H). 13C NMR (126 MHz, CDCl₃) δ 157.51, 147.04, 145.71, 140.64, 135.87, 132.62, 130.63, 130.22, 128.54, 127.52, 126.48, 125.34, 120.55, 113.18, 107.84, 100.06, 98.10, 46.45.

(S,E)-6-(1-(4-chlorophenyl)-3-phenylallyl)benzo[d][1,3]dioxol-5-ol (340b). Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl styrylboronate (0.2 mL, 0.4 mmol), p-Chlorobenzaldehyde (20.0 μL, 0.2 mmol), (R)-(−)-3,3′-Br₂-BINOL (11.4 mg, 0.04 mmol),
and EtOH (58.0 μL, 1 mmol) in trifluorotoluene (1.0 mL) for 24 hours at 60 °C. Silica gel purification gave a yellow, highly viscous oil in 52% yield. 1H NMR (500 MHz, CDCl3) δ 7.38 – 6.99 (m, 7H), 6.84 – 6.74 (m, 2H), 6.58 – 6.45 (m, 2H), 6.43 (s, 2H), 6.28 (dd, J = 15.9, 1.1 Hz, 1H), 5.79 (dd, J = 4.4, 1.4 Hz, 2H), 4.91 (d, J = 6.9 Hz, 1H), 4.51 (s, 1H).

13C NMR (126 MHz, CDCl3) δ 158.11, 147.94, 146.71, 141.84, 136.28, 133.02, 130.97, 129.93, 128.97, 128.64, 126.19, 125.01, 121.00, 112.88, 108.04, 100.26, 98.00, 54.05, 46.67.

(S,E)-6-(3-phenyl-1-(3-(trifluoromethyl)phenyl)allyl)benzo[d][1,3]dioxol-5-ol (340c). Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl styrylboronate (0.2 mL, 0.4 mmol), m-(trifluoromethyl)benzaldehyde (20.0 μL, 0.2 mmol), (R)-(−)-3,3′-Br2-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in trifluorotoluene (1.0 mL) for 24 hours at 60 °C. Silica gel purification gave a yellow, highly viscous oil in 67% yield. 1H NMR (500 MHz, CDCl3) δ 7.35 – 7.18 (m, 4H), 7.18 – 7.06 (m, 3H), 6.74 – 6.57 (m, 3H), 6.57 – 6.42 (m, 2H), 6.37 – 6.30 (m, 1H), 6.30 – 6.17 (m, 1H), 5.83 – 5.74 (m, 2H), 4.87 (t, J = 15.7 Hz, 1H), 4.59 (d, J = 9.1 Hz, 1H). 13C NMR (126 MHz, CHCl3) δ 148.04,
(S,E)-6-(1-(4-methoxyphenyl)-3-phenylallyl)benzo[d][1,3]dioxol-5-ol (340d). Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl styrylboronate (0.2 mL, 0.4 mmol), p-Methoxybenzaldehyde (20.0 μL, 0.2 mmol), (R)-(−)-3,3′-Br2-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. Silica gel purification gave a brown, highly viscous oil in 62% yield. 1H NMR (500 MHz, CDCl3) δ 7.38 – 6.99 (m, 8H), 6.84 – 6.74 (m, 2H), 6.58 – 6.45 (m, 2H), 6.37 (s, 1H), 6.26 (dd, J = 15.9, 1.1 Hz, 1H), 5.82 (dd, J = 4.4, 1.4 Hz, 2H), 4.88 (d, J = 6.9 Hz, 1H), 4.51 (s, 1H), 3.71 (s, 3H). 13C NMR (126 MHz, CDCl3) δ 157.51, 147.04, 145.71, 140.64, 135.87, 132.62, 130.63, 130.22, 128.54, 127.52, 126.48, 125.34, 120.55, 113.18, 107.84, 100.06, 98.10, 54.26, 46.45.
(S,E)-6-(1-(3-fluorophenyl)-3-phenylallyl)benzo[d][1,3]dioxol-5-ol (340e). Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl styrylboronate (0.2 mL, 0.4 mmol), m-Fluorobenzaldehyde (20.0 μL, 0.2 mmol), (R)-(−)-3,3′-Br2-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 ºC. Silica gel purification gave a brown, highly viscous oil in 62% yield. 1H NMR (500 MHz, CDCl3) δ 7.35 – 7.18 (m, 4H), 7.18 – 7.06 (m, 3H), 6.74 – 6.57 (m, 3H), 6.57 – 6.42 (m, 2H), 6.37 – 6.30 (m, 1H), 6.30 – 6.17 (m, 1H), 5.83 – 5.74 (m, 2H), 4.89 (t, J = 15.7 Hz, 1H), 4.62 (d, J = 9.1 Hz, 1H). 13C NMR (126 MHz, CHCl3) δ 148.04, 147.99, 146.78, 146.51, 141.71, 136.88, 135.81, 131.76, 131.07, 128.75, 128.56, 127.55, 126.38, 121.48, 121.47, 109.08, 108.80, 108.38, 101.11, 101.07, 47.77.

(S,E)-6-(1-(4-nitrophenyl)-3-phenylallyl)benzo[d][1,3]dioxol-5-ol (340f). Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl styrylboronate (0.2 mL, 0.4 mmol), p-
Nitrobenzaldehyde (20.0 μL, 0.2 mmol), (R)-(-)-3,3’-Br₂-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in trifluorotoluene (1.0 mL) for 24 hours at 60 °C. Silica gel purification gave a yellow, highly viscous oil in 40% yield. 1H NMR (500 MHz, CDCl₃) δ 7.35 – 7.18 (m, 4H), 7.18 – 7.06 (m, 3H), 6.74 – 6.57 (m, 3H), 6.57 – 6.42 (m, 2H), 6.37 – 6.30 (m, 1H), 6.30 – 6.17 (m, 1H), 5.83 – 5.74 (m, 2H), 4.97 (t, J = 15.7 Hz, 1H), 4.62 (d, J = 9.1 Hz, 1H). 13C NMR (126 MHz, CHCl₃) δ 149.13, 148.13, 146.97, 146.78, 141.35, 137.21, 133.21, 132.06, 132.07, 129.01, 128.86, 127.95, 126.51, 121.67, 121.46, 109.25, 108.99, 108.58, 100.87, 100.57, 99.24, 49.51.

(E)-6-(4,4-dimethyl-1-phenylpent-1-en-3-yl)benzo[d][1,3]dioxol-5-ol (340g). Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl styrylboronate (0.2 mL, 0.4 mmol), Dimethylacetaldehyde (20.0 μL, 0.2 mmol), (R)-(-)-3,3’-Br₂-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. After the reaction work-up, no product was recovered.
(R,E)-6-(1-(furan-2-yl)-3-phenylallyl)benzo[d][1,3]dioxol-5-ol (340h). Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl styrylboronate (0.2 mL, 0.4 mmol), Furanaldehyde (20.0 μL, 0.2 mmol), (R)-(−)-3,3′-Br2-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. After the reaction work-up, the formation of traces only of product was observed. 1H NMR (500 MHz, CDCl3) δ 7.39 – 7.09 (m, 7H), 6.97 – 6.77 (m, 2H), 6.66 – 6.47 (m, 2H), 6.46 – 6.28 (m, 2H), 5.82 (dd, J = 2.1, 1.0 Hz, 2H), 5.17 (d, J = 7.0 Hz, 1H), 4.75 – 4.51 (m, 1H).

(E)-6-(1-cyclohexyl-3-phenylallyl)benzo[d][1,3]dioxol-5-ol (340i). Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl styrylboronate (0.2 mL, 0.4 mmol), Cyclohexanecarboxaldehyde (20.0 μL, 0.2 mmol), (R)-(−)-3,3′-Br2-BINOL (11.4 mg, 0.04
mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. After the reaction work-up, no product was recovered.
4.4.4.2. Boronate substrate scope

Ten different boronates were used as substrates for the multicomponent reaction (Scheme 77). The experimental results and data are listed below.

Scheme 77: General Scheme for boronate substrate scope of asymmetric multicomponent boronate reaction.
(E)-6-(3-(4-methoxyphenyl)-1-phenylallyl)benzo[d][1,3]dioxol-5-ol (340j). Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl p-Methoxystyrylboronate (0.2 mL, 0.4 mmol), benzaldehyde (20.0 μL, 0.2 mmol), (R)-(−)-3,3′-Br2-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. Silica gel purification gave a yellow, highly viscous oil in 81% yield. 1H NMR (500 MHz, CDCl3) δ 7.26 – 7.20 (m, 2H), 7.13 – 7.04 (m, 2H), 6.86 – 6.69 (m, 4H), 6.50 (s, 2H), 6.42 – 6.30 (m, 2H), 6.24 – 6.15 (m, 1H), 5.87 – 5.72 (m, 2H), 4.85 (d, J = 7.0 Hz, 1H), 4.63 (s, 1H), 3.72 (s, 3H). 13C NMR (126 MHz, CDCl3) δ 159.15, 158.49, 148.12, 146.69, 141.61, 133.87, 131.10, 129.69, 129.56, 129.00, 127.53, 121.76, 114.18, 113.96, 108.88, 101.04, 99.10, 55.28, 47.52.

(E)-6-(3-(naphthalen-2-yl)-1-phenylallyl)benzo[d][1,3]dioxol-5-ol (340k). Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl (2-napthyl)vinylboronate (0.2 mL, 0.4
mmol), benzaldehyde (20.0 μL, 0.2 mmol), (R)-(−)-3,3’-Br₂-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. Silica gel purification gave a yellow, highly viscous oil in 39% yield. 1H NMR (CDCl₃, 300 MHz) δ (7.40–7.11) (m, 10H), 6.78 (m, 4H), 6.31 (m, 4H), 5.97 (s, J = 10 Hz, 2H), 5.30 (s, 1H), 4.64 (d, 1H). 13C NMR (126 MHz, CDCl₃) δ 157.51, 147.04, 145.71, 140.64, 139.8, 137.1, 135.87, 132.62, 130.63, 130.22, 128.54, 127.52, 126.48, 125.34, 120.55, 113.18, 107.84, 100.06, 98.10, 46.45.

(E)-6-(1-phenyl-3-(3-(trifluoromethyl)phenyl)allyl)benzo[d][1,3]dioxol-5-ol (340l).

Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl m-trifluoromethylstyrylboronate (0.2 mL, 0.4 mmol), benzaldehyde (20.0 μL, 0.2 mmol), (R)-(-)-3,3’-Br₂-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. Silica gel purification gave a yellow, highly viscous oil in 75% yield. 1H NMR (500 MHz, CDCl₃) δ 7.35 – 7.18 (m, 4H), 7.18 – 7.06 (m, 3H), 6.74 – 6.57 (m, 3H), 6.57 – 6.42 (m, 2H), 6.37 – 6.30 (m, 1H), 6.30 – 6.17 (m, 1H), 5.83 – 5.74 (m, 2H), 4.87 (t, J = 15.7 Hz, 1H), 4.59 (d, J = 9.1 Hz, 1H). 13C NMR (126 MHz, CHCl₃) δ
(E)-6-(3-(4-chlorophenyl)-1-phenylallyl)benzo[d][1,3]dioxol-5-ol (340p). Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl p-Chlorostyrylboronate (0.2 mL, 0.4 mmol), benzaldehyde (20.0 μL, 0.2 mmol), (R)-(−)-3,3′-Br2-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. Silica gel purification gave a yellow, highly viscous oil in 58% yield. 1H NMR (500 MHz, CDCl3) δ 7.38 – 6.99 (m, 7H), 6.84 – 6.74 (m, 2H), 6.58 – 6.45 (m, 2H), 6.43 (s, 2H), 6.28 (dd, J = 15.9, 1.1 Hz, 1H), 5.79 (dd, J = 4.4, 1.4 Hz, 2H), 4.91 (d, J = 6.9 Hz, 1H), 4.51 (s, 1H). 13C NMR (126 MHz, CDCl3) δ 158.11, 147.94, 146.71, 141.84, 136.28, 133.02, 130.97, 129.93, 128.97, 128.64, 126.19, 125.01, 121.00, 112.88, 108.04, 100.26, 98.00, 54.05, 46.67.
(E)-6-(3-cyclohexyl-1-phenylallyl)benzo[d][1,3]dioxol-5-ol (340q). Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl (2-cyclohexyl)vinylboronate (0.2 mL, 0.4 mmol), benzaldehyde (20.0 μL, 0.2 mmol), (R)-(−)-3,3′-Br₂-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. After the reaction work-up, no product was recovered.

6-(benzofuran-3-yl(phenyl)methyl)benzo[d][1,3]dioxol-5-ol (340m). Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl benzofuran-3-ylboronate (0.2 mL, 0.4 mmol), benzaldehyde (20.0 μL, 0.2 mmol), (R)-(−)-3,3′-Br₂-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. Silica gel purification gave a yellow, highly viscous oil in 44% yield. 1H NMR (500 MHz, CDCl₃) δ 7.66 (dd, J = 7.8, 0.8 Hz, 1H), 7.56 (dd, J = 7.1, 1.2 Hz, 1H), 7.29 – 7.13 (m, 8H), 6.88 – 6.78 (m, 2H), 6.43 (s, 2H), 6.38 (dd, J = 8.5, 2.6 Hz, 1H), 6.33 (t, J = 2.5 Hz, 1H), 5.83 (s, 1H), 4.73 (s,
6-(benzo[b]thiophen-3-yl(phenyl)methyl)benzo[d][1,3]dioxol-5-ol (340n). Sesamol (42.0 mg, 0.3 mmol) was reacted with (E)-diethyl benzothiofuran-3-ylboronate (0.2 mL, 0.4 mmol), benzaldehyde (20.0 μL, 0.2 mmol), (R)-(−)-3,3′-Br₂-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. Silica gel purification gave a yellow, highly viscous oil in 48% yield. 1H NMR (500 MHz, CDCl₃) δ 7.66 (dd, J = 7.8, 0.8 Hz, 1H), 7.56 (dd, J = 7.1, 1.2 Hz, 1H), 7.29 – 7.13 (m, 8H), 6.88 – 6.78 (m, 2H), 6.43 (s, 2H), 6.38 (dd, J = 8.5, 2.6 Hz, 1H), 6.33 (t, J = 2.5 Hz, 1H), 5.83 (s, 1H), 4.73 (s, 1H). 13C NMR (126 MHz, CDCl₃) δ 159.83, 154.06, 148.18, 142.09, 140.05, 139.66, 130.67, 128.87, 128.62, 127.09, 124.18, 123.94, 123.26, 123.15, 122.20, 122.07, 106.14, 102.33, 57.98, 55.32.
(E)-6-(3-(4-(tert-butyl)phenyl)-1-phenyllallyl)benzo[d][1,3]dioxol-5-ol  \( (340o) \). Sesamol (42.0 mg, 0.3 mmol) was reacted with \((E)\)-diethyl \(p\)-(t-butoxy)styrlyboronate (0.2 mL, 0.4 mmol), benzaldehyde (20.0 μL, 0.2 mmol), \((R)\)\-(\(-\))-3,3’-Br\(_2\)-BINOL (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. Silica gel purification gave a yellow, highly viscous oil in 60% yield. 1H NMR (500 MHz, CDCl\(_3\)) \( \delta 7.38 - 6.99 \) (m, 7H), \( 6.84 - 6.74 \) (m, 2H), \( 6.58 - 6.45 \) (m, 2H), \( 6.43 \) (s, 2H), \( 6.28 \) (dd, \( J = 15.9, 1.1 \) Hz, 1H), \( 5.79 \) (dd, \( J = 4.4, 1.4 \) Hz, 2H), \( 4.91 \) (d, \( J = 6.9 \) Hz, 1H), \( 4.48 \) (s, 1H), \( 1.74 \) (s, 9H). 13C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 157.98, 148.16, 146.92, 142.04, 136.28, 132.89, 131.24, 130.05, 129.76, 128.84, 126.05, 125.01, 121.00, 112.88, 108.04, 100.26, 98.00, 54.05, 36.67, 29.98.

\( (E)\)-6-(1-phenyl-3-(thiophen-3-yl)allyl)benzo[d][1,3]dioxol-5-ol  \( (340r) \). Sesamol (42.0 mg, 0.3 mmol) was reacted with \((E)\)-diethyl benzofuran-3-ylboronate (0.2 mL, 0.4 mmol),
benzaldehyde (20.0 μL, 0.2 mmol), \((R)(-)-3',3'-\text{Br}_2\text{-BINOL}\) (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. Silica gel purification gave a yellow, highly viscous oil in 44% yield. 1H NMR (500 MHz, CDCl3) δ 7.35 – 7.27 (m, 2H), 7.27 – 7.20 (m, 2H), 7.18 – 7.10 (m, 3H), 6.96 – 6.86 (m, 1H), 6.82 (dt, \(J = 3.5, 1.1\) Hz, 1H), 6.60 (d, \(J = 2.2\) Hz, 1H), 6.58 – 6.50 (m, 1H), 6.39 (d, \(J = 6.5\) Hz, 1H), 6.36 (d, \(J = 2.3\) Hz, 1H), 5.91 – 5.73 (m, 2H), 5.17 (d, \(J = 7.1\) Hz, 1H), 4.62 (s, 1H). 13C NMR (126 MHz, CHCl3) δ 147.88, 147.05, 146.24, 141.80, 136.71, 131.69, 130.30, 128.56, 127.65, 126.95, 126.49, 125.36, 124.94, 121.23, 108.57, 101.18, 99.15, 43.74.

\((E)-6-(3-(3\text{-methoxyphenyl)}-1\text{-phenylallyl})\text{benzo}[d][1,3]\text{dioxol-5-ol}\) (340s). Sesamol (42.0 mg, 0.3 mmol) was reacted with 
\((E)-\text{diethyl }m\text{-}(\text{metoxy})\text{styrylboronate}\) (0.2 mL, 0.4 mmol), benzaldehyde (20.0 μL, 0.2 mmol), \((R)(-)-3',3'-\text{Br}_2\text{-BINOL}\) (11.4 mg, 0.04 mmol), and EtOH (58.0 μL, 1 mmol) in toluene (1.0 mL) for 24 hours at 80 °C. Silica gel purification gave a yellow, highly viscous oil in 32% yield. 1H NMR (500 MHz, CDCl3) δ 7.35 – 7.18 (m, 4H), 7.18 – 7.06 (m, 3H), 6.74 – 6.57 (m, 3H), 6.57 – 6.42 (m, 2H), 6.37 – 6.30 (m, 1H), 6.30 – 6.17 (m, 1H), 5.83 – 5.74 (m, 2H), 4.87 (t, \(J = 15.7\) Hz, 1H), 4.59 (d, \(J = 9.1\) Hz, 1H), 3.78 (s, 3H). 13C NMR (126 MHz, CHCl3) δ 148.04, 147.99, 146.78,
146.51, 141.71, 136.88, 135.81, 131.76, 131.07, 128.75, 128.56, 127.55, 126.38, 121.48, 121.47, 109.08, 108.80, 108.38, 101.11, 101.07, 99.10, 47.77.
Chapter 5. Conclusions

In this thesis we have reported that enantioenriched benzylic amines can be obtained through the use of asymmetric, organocatalytic, Bronsted acid driven reactions. In the first part of our work, unexpected reactivity of the $\gamma$ position of $\beta$-enamidoesters in a Brønsted acid environment was achieved with high enantioselectivity employing a Mannich reaction with chiral phosphoramidic acid catalysis (Scheme 78).

Scheme 78: Nine novel chiral phosphoramidic acids were designed and prepared. They were also applied to develop the methodology of a new asymmetric Mannich reaction.
A novel class of chiral phosphoramidic acids was designed, synthesized from the corresponding diamines, with several sulfonyl N-protecting groups, and characterized. Their unique properties arise from their Brønsted acid nature, atropisomerism and ability to form complexes via H-bonds (Scheme 79). Once prepared, such catalysts were successfully used as organocatalysts for the regio- and enantioselective Mannich reaction of β-enamidoesters with aryl imines. The application of these catalysts enabled regioselectivity of the β-enamido ester nucleophile to proceed through the γ-position, while achieving high enantioselectivities in the formation of chiral benzyl amines.

Scheme 79: Synthesis of enantiopure amino acids via oxonolysis of the product of the asymmetric Mannich reaction.
A diverse range of imines was tested, obtaining yields up to 93% and enantioselectivities up to 99:1. A mechanism for this reaction was proposed and kinetic studies confirmed that the reaction is first order in catalyst. The ozonolysis of the product of this Mannich reaction was performed to prove the absolute stereochemistry of the product; and a new efficient methodology for the asymmetric preparation of aminoacid \( \beta \)-phenyl-\( \beta \)-alanine benzyl ester was described (Scheme 80).

Scheme 80: Failed attempt to diastereoselectively hydrogenate the product of the asymmetric Mannich reaction.
The reduction of the enamide moiety of the Mannich product was attempted via asymmetric hydrogenation and via hydride reduction in order to diastereoselectively obtain 1,3-diamines, compounds of major synthetic interest. Unfortunately attempts in this direction were not successful (Scheme 80 and Scheme 81).

![Chemical Structure](image)

**Scheme 81**: Failed attempts to reduce the enamine of the product of the asymmetric Mannich reaction with hydridic reagents.

Finally, a multicomponent reaction between an aldehyde, a substituted phenol, and a styrylboronate was developed as an alternative method for the preparation of chiral benzhydrls. This process is also organocatalytic and the methodology was optimized in the presence of 3-3’ disubstituted BINOLs (Scheme 82). Yields up to 71% and enantioselectivities up to 96:4 were achieved. A mechanism for this organocatalytic reaction was also proposed.
Scheme 82: An asymmetric three-components reaction involving a boronate molecule as the nucleophile and catalyzed by chiral Brønsted acids was developed.

In conclusion, three major contributions to the field of organocatalysis were reported in this thesis: a novel class of chiral Bronsted acids to be employed as organocatalysts was designed and prepared, the methodology for a new highly regio and stereoselective Mannich reaction was developed and an organocatalytic asymmetric multicomponent boronate reaction was discovered.
List of Journal Abbreviations:

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<th>Abbreviation</th>
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<td>Acc. Chem. Res.</td>
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118. Diastereoselective and Enantioselective Aldehyde Addition-Reactions of 2-Allyl-1,3,2-Dioxaborolane-4,5-Dicarboxylic Esters, a Useful Class of Tartrate Ester Modified


Curriculum Vitae

DANIELE RAMELLA

1. Personal data:

First and Last Name: Daniele Ramella
Year of birth: 1983
Citizenship: Italian
Address: 483, Shirley Street (4A), Winthrop, MA, 02152-1322, US
Tel.: +1 (857) 919-7710
E-mail: ramella@bu.edu – daramella@gmail.com
Skype: Daniele Ramella – grignard83

2. Curriculum studiorum:

- **Primary and secondary education:**
  
o After elementary and middle schools, the high school “Liceo Scientifico Statale Giovanni Gandini” in Lodi, LO, Italy, was attended, and the final diploma was obtained in year 2001 (grade 94/100);

- **Undergraduate studies:**
  
o A bachelor degree in chemical sciences “Laurea di base in Scienze chimiche” (grade 107/110) was obtained in year 2004, a work for distinction on aquaporines was prepared, under the supervision of Prof. Maria Enrica Tira, Department of biochemistry of the Università degli Studi di Pavia, Italy.

- **Graduate studies:**
  
o A master of science in chemistry “Laurea specialistica in Scienze chimiche” was completed in year 2006 (grade 110/110). The master thesis “NiX₂Ln catalyzed cyclization of α,ω-dienes” was produced in the laboratories of the department “Katedra organické a jaderné chemie” of the Univerzita Karlova v Praze (Charles University in Prague, CZ) under the supervision of Prof. Martin Kotora (Univerzita Karlova v Praze)
and Prof. Giuseppe Faita (Università degli studi di Pavia) during an international cooperation funded by the EU exchange program Erasmus.

- The Italian state qualifying examination was successfully passed in June 2007, at Università degli studi di Pavia.

- A master of arts in chemistry was received in September 2010 from Boston University after course work and laboratory research on “Chiral Brønsted acid catalyzed Mannich reaction” were completed under the supervision of Ass. Prof. Scott E. Schaus, Department of chemistry, Boston University.

- A doctorate of philosophy in chemistry was received in September 2013 after course work and laboratory research were completed and this dissertation prepared, under the supervision of Ass. Prof. Scott E. Schaus, Department of chemistry, Boston University, and the sponsorship of the Fulbright Senatorial Commision.

3. Work experiences:

**Teaching Experience:**

- A period of six months of work (January-June 2005) in the university’s teaching laboratories was done as laboratory assistant in the Department of Organic Chemistry of the Università degli Studi di Pavia, contact person Prof. Angelo Albini.

- Chemistry in Italian language was taught for a period of 4 months (March-June 2006) as a substitute teacher in the bilingual high school “Gymnasium Ústavní 400” in Prague, CZ; Principal: RNDr. Helena Štěrbová.

- The following classes were taught for the course in Dairy Technologies of the educational program of Regione Lombardia, funded by the ESF:
  
  Spring 2007 – General Chemistry
  Spring 2008 – General Chemistry
  Coordinator: Mr. Luigi Passolungo.

- Science team coaching for the Boston University Academy is performed on a volunteer basis since 2009; contact person: Dr. Rosemary White, Teacher of Chemistry - (current)
The following teaching fellowships have been covered since May 2009 during Ph.D. studies at Boston University:

- **Summer 2009** - CH 204 laboratory – Organic Chemistry II
- **Fall 2009** – CH 203 laboratory – Organic Chemistry I
- **Spring 2010** – CH 212 laboratory – Intensive Organic Chemistry II
- **Summer 2010** – CH 203 laboratory – Organic Chemistry I
- **Fall 2010** – CH 211 laboratory – Intensive Organic Chemistry I
- **Fall 2011** – CH 203 discussion – Organic Chemistry I
- **Spring 2012** – CH 101 discussion – off sequence General Chemistry I
- **Summer 2012** – CH 101 discussion – General Chemistry I
- **Fall 2012** – CH 102 discussion – off sequence General Chemistry II
- **Spring 2013** – CH 101 discussion – General Chemistry I
- **Summer 2013** – CH 102 discussion - General Chemistry II
- **Summer 2013** – CH 101 lab – General Chemistry I

The following course for the SABIC 3 program of BU-CELOP (Center for English Language and Orientation Programs) is being taught:

- **Spring 2013** – CH pre-101 – General Chemistry
- **Spring 2014** – CH pre-101 – General Chemistry – *(current)*

Contact person: Gabrielle Wallace, Program administrator.

College classes are being taught as a postdoctoral faculty fellow at the Boston University Department of Chemistry since September 2013:

- **Fall 2013** – CH 102 discussion and laboratory – off-sequence General Chemistry II.
- **Spring 2014** – CH 101 discussion, laboratory and pre-lab lecture – off-sequence General Chemistry I – *(current)*

**Research and other work experience:**

The role of “Product Specialist” was covered for a brief period (September-October 2006) for BSN srl as specialist of HPLC methods for determining % CDT in human serum, under supervision of Dr. Giacinto Guercilena.

Researches about NIR and MIR applications to studies about transformation processes of dairy products and milk’s molecular interactions have been conducted at CRA-ILC (National Council for Researches in Agriculture – Institute for dairy sciences research).
for 9 months (October 2006- June 2007) under supervision of Dr. Roberto Giangiacomo.

- Synthesis of monomers for the development of new polibenzimidazoic polymers for proton transport membranes in fuel cells has been carried out for six months (June 2007- December 2007) under the supervision of Prof. PierPaolo Righetti, Dipartimento di Chimica Organica, Università degli Studi di Pavia.

- Mass spectrometry applications to the analysis and identification of the essential components of crop have been carried out under supervision of Dr. Aldo Tava, CRA-FLC (National council of researches in agriculture – Research center for crops and dairy productions) from January 2008 to September 2008.

- Independent research was carried out on Chiral Brønsted Acid catalyzed organic reactions from September 2008 to August 2013 during Ph.D. studies at Boston University in the laboratory of Ass. Prof. Scott E. Schaus.

- The role of Laboratory Safety Coordinator for Schaus Lab was covered from May 2010 to December 2012, in collaboration with the Research Safety Senior Specialist of the BU’s Environmental Health and Safety office, Mrs. Jenna Moar.

- Independent research is been carried out on nanowires from September 2013 as a postdoctoral faculty fellow at the department of chemistry of Boston University, under the supervision of Ass. Prof. Linda H. Doerrer. – (current)

4. Scientific publications:


~ Ramella, D.; Stidham, J.; Schaus, S.E. Asymmetric Mannich Reaction catalyzed by Chiral Bronsted Acids, manuscript in preparation.

5. Language skills:

(Skills are classified according to the “European language levels - Self Assessment Grid” available on-line at http://europass.cedefop.europa.eu/en/resources/european-language-levels-cefr)

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6. Affiliations:

- NGO Maria madre della Provvidenza
  Member (2003-2005)
  Treasurer (2003-2005)

- GSO San Fereolo sport club
  Volleyball player (1996-2004)
- GSO Sant’Alberto sport club
  Volleyball player (2004-2008)
  Volleyball coach (2005-2008)
  Assistant coaching director for the volleyball branch (2005)
  Coaching director for the volleyball branch (2006-2008)
  Vice-president (2006-2008)

- Italian Near Infra-Red Society
  Member (2007)

- American Chemical Society
  Member (2010)

- Boston University younger Chemists Committee
  Member (2008-current)
  Chair for graduate student affairs (2009-2010)
  President (2010-2011)
  President (2011-2012)

7. Hobbies and main volunteer experiences:

- Various pastoral activities and ministries, mostly regarding youth groups, have been carried out in several parishes in different times, accordingly with the place of residency. Such activities include: Sunday CCD teaching, organization of summer and winter camps, direction of musicals and other youth events.

- I was part of the choir of the parish of San Fereolo e Bassiano in Lodi, LO, Italy under the direction of Ing. Eugenio Ferrari from 1998 to 2005, and I am since 2010 part of the choir of the parish of St. John the Evangelist in Winthrop, MA, under the direction of Mr. Stephen Lee.

- I was part of the folkloric group “Terra del sole” as a dancer and singer from 1998 to 2005. Contact person: Felice Torre.
- The treasury of the NGO “Maria, Madre della Provvidenza”, branch of Lodi, Italy, was kept from year 2003 to 2005. During this period, international projects in Mostar, BiH, and Benin was carried out.

- Coaching for the summer program of “Soccer Nights” was performed in years 2009-2012 at the North Cambridge site.

- Coaching director for the program “Soccer Nights” 2012 at the East Boston site.

- Prison Ministry at the Essex County Sheriff Department House of Correction, Middleton, MA, since July 2012.

8. Brief self description:

Maybe not genial, but strong willed and good planner. Curious and open to new experiences, easily connecting with people. Always active, with a very broad range of interests. Effective communicator and good conversationalist.

9. Favorite citations:

- Memento audere semper. (Lat. = Remember to dare always; Gabriele D’Annunzio)

- Rien ne se perd, rien ne se crée, tout se transforme. (Fr. = Nothing is lost, nothing is created, everything is transforming; Antoine Lavoisier)

- To everything there is a season, and a time to every purpose under the heaven (Qt, 3:1)

- Acta est fabula, plaudite! (Lat. = The play is over, applaud!; Octavianus Augustus)