Chiral Boro-Phosphates in Asymmetric Catalysis: 1,4-reduction of Enones and Reductive Aldol

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Chiral Boro-Phosphates in Asymmetric Catalysis:

1,4-reduction of Enones and Reductive Aldol

by

Susana Sorina López

A dissertation submitted in partial fulfillment of
the requirements for the degree of
Doctorate of Philosophy
Department of Chemistry
College of Arts and Sciences
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March 18, 2016

Keywords: Enantioselective synthesis, 1,4-reduction, BINOL-derived boro-phosphate catalysts, α, β-unsaturated enones, ketones, reductive aldol, organocatalysis, boro-phosphate catalysis

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Dedication

Les dedico esta tesis a mi madre y padre, Susana y Oscar López. Gracias por sacrificar tanto con el fin de ayudar a hacer mi sueño realidad. Sin ustedes yo nunca habría tenido la fuerza para seguir para adelante a través de todos los obstáculos y momentos difíciles que estaban en mi camino. No hay palabras para expresar mi gratitud. Los quiero con todo mi corazón.

To my loving husband Brian R. Jacobs. You stood by me during one of the toughest times in my life. You gave me comfort when I was sad, encouragement when I wanted to give up and shared in my joy in moments of happiness. I love you more than words will ever be able to express. Thank you for your unconditional love.
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I want to give an extra special thanks to a group of people that I hold very near and dear. My amazing crew of undergraduate researchers; Lucas Hernandez, Josh McBride, Josue Liriano, Arielis Estevez-Davila and Nicholas Clough, who each brought something special to our little group. What I learned from each of you has influenced me in ways that have left a lasting impression and I will carry our friendship with me always. I also want to thank Dr. Guilong Li, who was a fountain of knowledge, my mentor in the lab and will be a friend for life. Lastly, I want to give my gratitude to Dr. James Leahy, without whose unwavering support and guidance I would not have gained the strength to carry on during the tough times. You have all made this possible and I thank you.
Table of Contents

List of Tables ......................................................................................................................... v
List of Figures ............................................................................................................................ vi
List of Schemes ........................................................................................................................ viii
List of Abbreviations ................................................................................................................. ix
Abstract ....................................................................................................................................... xiv

Chapter 1 Applications of privileged ligands in asymmetric catalysis................................. 1
1.1 Background.......................................................................................................................... 1
1.2 Evolution of BINOL derived catalysts .............................................................................. 3
   1.2.1 Chiral BINOL-phosphoric acids ............................................................................... 3
   1.2.2 Chiral BINOL-derived metal phosphates ................................................................. 4
1.3 Chiral BINOL derived boro-phosphates catalyst .............................................................. 5
1.4 Summary ............................................................................................................................. 10

Chapter 2 Boro-phosphate catalyzed asymmetric 1,4-reduction of α, β-unsaturated enones..... 11
2.1 Background ......................................................................................................................... 11
2.2 1,4-reduction of α, β-unsaturated enones ......................................................................... 14
   2.2.1 Catalyst Screening ...................................................................................................... 14
   2.2.2 Solvent Screening ...................................................................................................... 16
2.3 Substrate synthesis and scope ......................................................................................... 18
2.4 Results and Discussion ..................................................................................................... 20
2.5 Mechanistic Observations ............................................................................................... 26
   2.5.1 Comparison of enone geometry ............................................................................... 26
   2.5.2 Comparison of α-naphthyl or β-naphthyl substituents .......................................... 27
2.6 Summary ........................................................................................................................... 32
2.7 Experimental ...................................................................................................................... 33
   2.7.1 General Considerations ............................................................................................ 33
   2.7.2 General procedure for the reduction of α, β-unsaturated enones ......................... 34
      (S)-1,3-diphenylbutan-1-one (2a) .................................................................................. 35
      (S)-3-(naphthalen-2-yl)-1-phenylbutan-1-one (2b) ....................................................... 36
      (R)-3-(naphthalen-1-yl)-1-phenylbutan-1-one (2c) ....................................................... 36
      (S)-3-(4-methoxyphenyl)-1-phenylbutan-1-one (2d) ................................................... 37
      (S)-1-(4-methoxyphenyl)-3-phenylbutan-1-one (2e) ................................................... 38
      (S)-3-(4-fluorophenyl)-1-phenylbutan-1-one (2f) ......................................................... 38
      (S)-1-(4-fluorophenyl)-3-phenylbutan-1-one (2g) ......................................................... 39
      (R)-1-phenyl-3-(4-(trifluoromethyl)phenyl)butan-1-one (2h) ............................... 40
(S)-3-(4-chlorophenyl)-1-phenylbutan-1-one (2i) .......................... 40
(S)-1-phenyl-3-(thiophen-2-yl)butan-1-one (2j) .......................... 41
(S)-4-(4-oxo-4-phenylbutan-2-yl)benzonitrile (2k) ......................... 42
(S)-1,3-diphenylpentan-1-one (2l) ........................................... 42
(S)-4-methyl-1,3-diphenylpentan-1-one (2m) .............................. 43
(S)-3-cyclohexyl-1,3-diphenylpropan-1-one (2n) ......................... 44
(S)-3-methyl-1,5-diphenylpentan-1-one (2p) .............................. 44

Chapter 3 Boro-phosphate catalyzed asymmetric reductive aldol ......................................................... 46
3.1 Background ........................................................................... 46
3.2 Methodology ......................................................................... 47
3.3 Results and Discussion ......................................................... 48
3.4 Summary ................................................................................ 50
3.5 Experimental ......................................................................... 51
  3.5.1 General considerations .................................................... 51
    Compound (3.2a): ................................................................. 52
    Compound (3.2b): ................................................................. 52
    Compound (3.2c): ................................................................. 53
    Compound (3.2d): ................................................................. 53
    Compound (3.2e): ................................................................. 54
    Compound (3.2f): ................................................................. 55

References .............................................................................. 56

Appendix I .............................................................................. 63
  Preparation and characterization of catalysts ............................... 63
    General Considerations ......................................................... 63
    Synthesis of (R) 2,2'-bis(methoxymethoxy)-1,1'-binaphthalene: ...... 64

Appendix II .............................................................................. 68
  Preparation and characterization of reaction substrates .................. 68
    General Considerations ......................................................... 68
    General procedure for the synthesis of ethyl esters ..................... 69
    Synthesis of Weinreb amides ................................................... 76
    Synthesis of α, β-unsaturated ketones ..................................... 83

Appendix III ............................................................................ 92
  Chemical vendor information .................................................... 92

Appendix IV ............................................................................. 94
  1H NMR spectra of 1,4-reduction starting material and product ....... 94
  (E)-1, 3-diphenylbut-2-en-1-one ............................................... 94
  1,3-diphenylbutan-1-one .......................................................... 95
  (E)-3-(naphthalen-2-yl)-1-phenylbut-2-en-1-one ......................... 96
  3-(naphthalen-2-yl)-1-phenylbutan-1-one .................................... 97
  (E)-3-(naphthalen-1-yl)-1-phenylbut-2-en-1-one ......................... 98
### Appendix VI

HPLC chromatograms of reductive aldol reaction

- **Compound (3.2a)**: ........................................................................................................ 138
- **Compound (3.2b)**: ........................................................................................................ 139
- **Compound (3.2d)**: ........................................................................................................ 140
- **Compound (3.2e)**: ........................................................................................................ 141

### Appendix V

HPLC Spectra for 1,4-reduction of α, β-unsaturated ketones

- 1,3-diphenylbutan-1-one ................................................................................................... 124
- 3-(naphthalen-2-yl)-1-phenylbutan-1-one .......................................................................... 125
- 3-(naphthalen-1-yl)-1-phenylbutan-1-one .......................................................................... 126
- 3-(4-methoxyphenyl)-1-phenylbutan-1-one ...................................................................... 127
- 1-(4-methoxyphenyl)-3-phenylbutan-1-one ...................................................................... 128
- 3-(4-fluorophenyl)-1-phenylbutan-1-one .......................................................................... 129
- 1-(4-fluorophenyl)-3-phenylbutan-1-one .......................................................................... 130
- 3-(4-chlorophenyl)-1-phenylbutan-1-one .......................................................................... 131
- 4-(4-oxo-4-phenylbut-2-yl)benzonitrile ........................................................................... 133
- 1,3-diphenylpentan-1-one ............................................................................................... 134
- 3-cyclohexyl-1,3-diphenylpropan-1-one .......................................................................... 135
- 3,4,4-trimethyl-1-phenylpent-2-en-1-one ......................................................................... 136
- 3-methyl-1,5-diphenylpentan-1-one ................................................................................ 137
- 3,4,4-trimethyl-1-phenylpentan-1-one ........................................................................... 138
- 3,4,4-trimethyl-1-phenylpentan-1-one ........................................................................... 139
- 3,4,4-trimethyl-1-phenylpentan-1-one ........................................................................... 140
- 3,4,4-trimethyl-1-phenylpentan-1-one ........................................................................... 141
List of Tables

Table 1. Screening of various BINOL-derived PA catalysts ........................................ 16
Table 2. Screening of various solvents with (R)-PA1 catalyst .................................. 17
Table 3. Re-screening of catalysts with similar substituents at the 3, 3’-positions ........ 20
Table 4. Boro-phosphate catalyzed 1,4-reduction of α, β-unsaturated ketones .......... 22
Table 5. Reductions of α, β-unsaturated ketones with variation at the β-position ...... 23
Table 6. Geometry of enone influence in boro-phosphate reduction ...................... 24
Table 7. Substrate scope of methodology ............................................................... 25
Table 8. Effect of enone geometry on product outcome ......................................... 27
Table 9. Selectivity comparison of (R)-PA1 and (R)-PA2 ...................................... 28
Table 10. Reductive aldol substrate scope ............................................................ 49
List of Figures

Figure 1. Privileged ligands and scaffolds used in asymmetric synthesis ........................................... 2
Figure 2. Chiral metal complexes ........................................................................................................... 3
Figure 3. Structural features of BINOL-derived phosphoric acid catalyst ........................................... 4
Figure 4. Structural features of BINOL-derived phosphate salt ............................................................ 5
Figure 5. Asymmetric reduction of ketones catalyzed by phosphoric acid derivatives ......................... 7
Figure 6. Proposed formation of boro-phosphate catalyst .................................................................... 8
Figure 7. Proposed formation of boro-phosphate catalyst .................................................................. 9
Figure 8. Interaction of boro-phosphate catalyst, borane and substrate .............................................. 9
Figure 9. MacMillan et al. Enantioselective Organocatalytic Hydride Reduction ........................... 12
Figure 10. *tert*-butyl valinate and chiral TRIP-PA ............................................................................. 12
Figure 11. List enantioselective conjugate transfer hydrogenation ......................................................... 13
Figure 12. MacMillan organocatalytic transfer hydrogenation of cyclic enones ................................. 13
Figure 13. Reactive sites of α, β-unsaturated ketones ......................................................................... 14
Figure 14. Chiral phosphoric acid catalysts used in methodology screening ...................................... 15
Figure 15. Traditional synthesis of α, β-unsaturated ketones via HWE reaction ............................... 18
Figure 16. Route for the synthesis of α, β-unsaturated ketones .......................................................... 19
Figure 17. Different conformations of E/Z-isomers .............................................................................. 26
Figure 18. Computational methods used for structural studies .......................................................... 29
Figure 19. Representation of the simplified model................................................................. 30
Figure 20. Simplified structural model.................................................................................. 30
Figure 21. Structures of (R)-PA1 and (R)-PA2 .................................................................... 31
Figure 22. (R)-PA1 and (R)-PA2 transition state computational model............................... 32
Figure 23. Stereochemical preferences of the (E)- and (Z)-enolate in the aldol reaction....... 47
Figure 24. Proposed mechanism of reductive aldol................................................................ 48
List of Schemes

Scheme 1.  Monsanto synthesis of L-Dopa................................................................. 2
Scheme 2.  Catalytic hydrogenation of (S)-Naproxen ................................................. 3
Scheme 3.  Chiral Brønsted acid catalyzed allylboration of aldehydes............................. 6
Scheme 4.  Chiral Brønsted acid catalyzed propargylation of aldehydes............................. 7
Scheme 5.  Takaya BINAP-Ru (II) transfer hydrogenation ............................................. 11
Scheme 6.  Synthesis of specialized Weinreb ylide....................................................... 19
Scheme 7.  Synthesis of α, β-unsaturated ketones via HWE ........................................ 19
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
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UV ultraviolet
Abstract

The biological activity of the pharmaceutical drugs often depends on how it fits with a receptor making stereochemistry a key component. Selective reactions can limit or avoid the mixture of enantiomers obtained. One such reaction is the selective reduction of a carbon-carbon double bond in the presence of a carbonyl. Although efficient, current asymmetric synthesis methods have limitations such as harsh reaction conditions, the high costs of chiral catalysts and the toxicity of the metal-based catalysts. Catalysts derived from small organic molecules have become an attractive alternative which have been explored more rigorously in recent years. Using a BINOL-derived boro-phosphate catalyst, we have developed a methodology that selectively reduces the carbon-carbon double bond of linear \( \alpha, \beta \)-unsaturated ketones, exclusively giving the corresponding saturated ketone. To the best of our knowledge, this reaction is the first of its kind to accomplish this transformation and results give high yields of >93% and enantioselectivities >90% at room temperature. Furthermore, the products of this novel reaction can be subjected to a choice electrophile, in example benzaldehyde, to afford diastereoselective tertiary alcohol products with enantioselectivities of >88% and diastereoselectivities of up to 99:1.
Chapter 1 Applications of privileged ligands in asymmetric catalysis

1.1 Background

Asymmetric catalysis is one of the most prominent areas of organic synthesis due to the ever growing need to make chiral drugs economically and enantiomerically pure.\textsuperscript{1,2} While the field has achieved major breakthroughs in the last three decades, there are challenges that still limit the efficiency of catalytic asymmetric methods.\textsuperscript{3} One such limitation in asymmetric catalysis is being able to develop new chiral ligands which can lead to the discovery of new catalytic reactions.\textsuperscript{4,5} Although many approaches exists that can be employed in asymmetric synthesis, the use of a chiral catalyst to control the stereochemical outcome of a reaction is one of the most commonly used strategies. The desire to design cost effective catalysts that can achieve high levels of enantioselective control has piqued the interest of researchers in this vast field.\textsuperscript{6} While these catalysts have evolved in past decades from transition metal catalysts to organocatalysts, they share the same general composition in that the stereochemical control is obtained from the chirality of the ligand or scaffold. Despite the fact that there are a plethora of these chiral ligands exist\textsuperscript{7}, there is a particular group that exhibit extraordinary reactivity providing higher levels of stereochemical in a wide range of reactions. Generally referred to as “privileged ligands”, BINAP (2, 2’- diphenylphosphino-1, 1’-binapthyl), BINOL (1, 1’-bi-2-napthol), Bis (oxazoline), salen complexes, and cinchona alkaloid derivatives possess exceptional reactivity and selectivity for a
wide range of reactions.

Figure 1. Privileged ligands and scaffolds used in asymmetric synthesis

These types of chiral ligands have been successfully applied in the synthesis of enantiopure drugs on an industrial scale. In 1968, Knowles created one of the first asymmetric catalysts by replacing the achiral triphenylphosphine ligands in Wilkinson's catalyst with the chiral phosphine ligands. Experimentally, when used for an asymmetric hydrogenation, this catalyst gave a low 15% ee. Knowles later applied this method when he synthesized the key intermediate of L-3, 4-dihydroxyphenylalanine (L-Dopa) while working for the Monsanto Company. By using rhodium and the chiral (R,R)-1,2-Bis[(2-methoxyphenyl)(phenylphosphino)]ethane, better known as (R,R)-DIPAMP (scheme 1), he successfully obtained the hydrogenated product with an ee of 95%. However, metal ligand catalysts have drawbacks in that they are expensive, produce toxic waste and the removal of the catalyst can prove tedious.
Ryoji Noyori, one of the most notable pioneers in the field of asymmetric catalysis, designed and developed the BINAP ligand. The chiral BINAP-Ru (II) complexes have been used to efficiently catalyze the asymmetric hydrogenation of acrylic acids.\textsuperscript{13}

![Figure 2. Chiral metal complexes](image)

Figure 2. Chiral metal complexes

(S)-Naproxen was successfully prepared by hydrogenation of acrylic acid \textsuperscript{1} with (S)-BINAP-Ru (II) catalyst (Scheme 3), which is an example of the utility of this methodology.\textsuperscript{14} This impact that this ligand has had in the field of catalysis earned Noyori the Nobel Prize in chemistry in 2001.

1.2 Evolution of BINOL derived catalysts

1.2.1 Chiral BINOL-phosphoric acids

Although reports dating as far back as 1971 exist on the use of BINOL-phosphoric acids as chiral resolving agents, it would be another 30 years before BINOL-derived chiral phosphoric acids would gain mainstream popularity. In 2004, Akiyama and Terada independently reported on the development of a new class of chiral Brønsted acids.\textsuperscript{15} Both BINAP and BINOL ligands are based on a biphenyl core which can be fine-tuned by varying the substituents at the 3, 3’-positions. The BINOL-derived phosphoric acids differ from the BINOLate complexes in that they have a Brønsted acidic phosphoryl moiety. In the BINOLate complexes, the phosphoric acid moiety is
replaced by a transition metal which behaves as Lewis acid. The defining feature that makes BINOL derived phosphoric acid catalysts unique is how the “pocket” surrounds the binding site. The large aryl groups confine the substrate, effectively transferring the stereochemical information to the substrate. The presence of the Lewis acidic phosphoryl moiety in proximity to the acidic proton potentially allows for bifunctional catalysis assisting in various non-racemic transformations.

Figure 3. Structural features of BINOL-derived phosphoric acid catalyst

The ability to alter the groups on the 3, 3′-positions of the BINOL backbone provides versatility and more options for optimizing the reaction conditions. These catalytic systems with different substituents 3, 3′-positions can be easily synthesized in few steps from commercially available BINOL in both enantiomeric forms.

1.2.2 Chiral BINOL-derived metal phosphates

Structurally similar to chiral phosphoric acids, chiral metal phosphates have been found to behave as mild Lewis acid catalysts. Much like the phosphoryl moiety of the BINOL-derived phosphoric acids, the transition metals provide their own unique reactivity.
The mode by which the metal and the substrate interact in the presence of the chiral ligand can provide enhanced selectivity for certain reactions. Although there are several hypotheses on the mode of activation of the metal phosphates the two most commonly accepted forms involve the phosphate anion acting as a counterion for the metal or a ligand.

Characterizing the interaction of the phosphate anion with the metal, the metal behaves as a Lewis acid, while the phosphoric acid retains its Lewis basic site. Also, the ability of a metal located within the cavity of the ligand to accept electron density further enhances the catalyst’s ability to behave as an effective Lewis acid. This is a key feature that allows for the activation of substrates possessing a reactive lone pair. Additionally, the multiple metal centers commonly possess multiple coordination sites (figure 2), which can heighten the adaptability of how the chiral phosphate controls the chiral space surrounding the metal center.

1.3 Chiral BINOL derived boro-phosphates catalyst

In 2010, Antilla et al reported a new high-yielding and highly enantioselective chiral Brønsted acid-catalyzed allylboration of aldehydes. This approach gave a highly general methodology, with a broad substrate scope that covers aryl, heteroaryl, α, β-unsaturated, and aliphatic aldehydes.22
Due to their importance as intermediates in both natural product synthesis and the synthesis of pharmaceuticals, several methodologies have been developed for the synthesis of chiral homoallylic alcohols. Many of the allylation methodologies reported in recent years make use of allylic silanes, allylic stannanes and allylic boranes/boronates. Unfortunately, these allylation reagents are difficult to prepare or are air/moisture-sensitive. Also, the use of undesirable metal-based catalysts such as tin, or substrates lead to toxic byproducts which makes these methods less than desirable.

In 2012, Antilla et. al, reported a versatile and highly enantioselective chiral Brønsted acid catalyzed method for the propargylation of aldehydes to provide a range of chiral homopropargylic alcohols (scheme 4). At the time of the publication, alternative catalytic methods had been limited to the use of allenyllic or propargylic metal-based reagents or intermediates. Application of the previously reported methodology by the Antilla group (scheme 3) to the enantioselective propargylation of aldehydes proved successful. The methodology was simple and
highly efficient, demonstrating broad synthetic utility, and was the first Brønsted acid-catalyzed propargylation of aldehydes for the synthesis of chiral homopropargylic alcohols.

Scheme 4. Chiral Brønsted acid catalyzed propargylation of aldehydes

The Antilla group reported yet another successful methodology for the asymmetric reduction of ketones utilizing a chiral Brønsted acid as a precatalyst. This reduction used catecholborane (CatBH) as the reducing agent, to give a highly enantioselective formation of chiral secondary alcohols (figure 5). It was the first time chiral Brønsted acids as precatalysts were used in this type of transformation. The reaction methodology was found to have a broad substrate scope giving the desired secondary alcohols in yields up to 98% and enantioselectivities of up to 95%.

Figure 5. Asymmetric reduction of ketones catalyzed by phosphoric acid derivatives
It was during this study in which the proposed pre-catalyst underwent a more rigorous investigation. If in fact a different catalyst was forming when the phosphoric acid and the borane reagent were mixed, there should be an observable change in the shifts of the reagents by $^{11}$B NMR.

Equal amounts of the chosen phosphoric acid catalyst and catecholborane were mixed using deuterated toluene as the solvent under argon. As the two components mixed in the solvent, the evolution of gas was observed which suggested that a reaction was indeed taking place (figure 6).

![Figure 6. Proposed formation of boro-phosphate catalyst](image)

The proton coupled $^{11}$B NMR spectrum provided further evidence that a reaction had taken place due to the noticeable change of the resonance for catecholborane. The peak for catecholborane in the $^{11}$B NMR spectrum was observed as a doublet at $\delta=28.73$ ppm, which differed from the upfield singlet seen in the spectrum of the solution containing the phosphoric acid and catecholborane mixture.

Based on these findings, it was proposed that upon premixing, the phosphoric acid and catecholborane form a new boro-phosphonate catalyst via the mechanism in figure 6. The evolution of gas observed occurs when the hydride of catecholborane deprotonates the hydroxyl group on the phosphoric acid. In turn, the oxygen of the acid forms a bond with the boron of the catecholborane.
Once the new catalytic species forms, the Lewis basic character of the phosphoryl group increases the nucleophilicity of the catecholborane in the reaction. Furthermore, the boron of the catecholborane moiety on the catalyst, activates the carbonyl of the reaction substrate forming a chair like transition state shown in figure 7.
The hydride of the free catecholborane adds to the carbonyl of the reaction substrate generating the boro-phosphate catalyst ready to repeat. During the entire process the biaryl scaffold provides the chiral environment in which the reaction is taking place.

1.4 Summary

Asymmetric catalysis has evolved in the last decade, expanding the scope of interest beyond the traditional transition metal catalyst and organocatalysts. Even so, the search still continues to find efficient and convenient reaction conditions to obtain products enantio- and chemo-selectively. The versatility of catalytic systems with different substituents at the 3, 3′ -positions opens the door to explore the effectiveness of this catalyst in reactions not previously studied. The commercial availability of BINOL in both enantiomeric forms adds to the ease of accessing and creating novel catalytic systems that can be used in a wide range of reactions. The effective use of BINOL-derived phosphoric acid catalysts in past reactions gives promising potential for application in other reactions which have yet to be investigated. Similarly, the excellent enantioselectivity obtained from the new derivative of the well-known chiral phosphoric acid catalysts, makes the boro-phosphate a potential candidate for use in reactions still lacking mild conditions and efficient methodologies.
Chapter 2 Boro-phosphate catalyzed asymmetric 1,4-reduction of α, β-unsaturated enones

2.1 Background

Catalytic asymmetric hydrogenations of functionalized olefins have been widely investigated, and they can successfully be performed with modified ruthenium, rhodium and iridium chiral complexes.\(^{28,29}\) It is important to note, that catalytic asymmetric hydrogenations of functionalized olefins such as enamides, α, β-unsaturated carboxylic acids and esters, allylic and homoallylic alcohols have been widely studied and examined. Although compounds with stereogenic centers at the α- or β-position to a carbonyl group are synthetically important, they have been less studied. The ability to control the regioselectivity of the enone would eliminate obtaining an undesired product.\(^{30}\)

In 1995, Takaya\(^{31}\) and co-workers employed BINAP-Ru (II) complexes as catalysts to hydrogenate exo-cyclic enones, and they obtained 2-alkyl-substituted cyclic ketones with up to 98% ee (scheme 7). In this case, there were limitations in that conversion of 2-aryl substituted substrates gave a product with only 9% ee and the reactions only worked under high pressure and elevated heat.

![Scheme 5. Takaya BINAP-Ru (II) transfer hydrogenation](image)
The results obtained by Takaya and co-workers proved to further advance the investigations on hydrogenation reactions, but room for improvement still existed.

![Figure 9. MacMillan et al. Enantioselective Organocatalytic Hydride Reduction](image)

Others, such as List and MacMillan, found that organocatalytic transfer hydrogenations using Hantzsch esters (figure 9) provided excellent enantioselectivity.

![Figure 10. tert-butyl valinate and chiral TRIP-PA](image)

List\textsuperscript{32} reported an efficient and highly enantioselective conjugate transfer hydrogenation of $\alpha$, $\beta$-unsaturated ketones catalyzed by a salt shown in figure 10, made from tert-butyl valinate and a chiral phosphoric acid catalyst (TRIP). However, for linear enones these methodologies had limitations affording an ee max of only 70% (figure 11).
MacMillan\textsuperscript{33} reported a new organocatalytic strategy for the first enantioselective organocatalytic transfer hydrogenation of cyclic enones. This reaction (figure 12) provided access to $\alpha$-substituted cycloalkenones chemoselectively, in high yield and 74\% ee.

Although advances have been made in the field of asymmetric synthesis, the ability to enantioselectively create stereogenic carbon centers still faces challenges. The necessity to develop strategies to perform such a transformation is driven by need to synthesize biologically active molecules containing hydrogen containing stereogenic carbon centers.\textsuperscript{34,35} Problems arise due to the reactive nature of both the carbonyl and alkenic double bond.\textsuperscript{36,37}
Figure 13. Reactive sites of α, β-unsaturated ketones

To date, a plethora of methods have been reported which allow for the chemo- and enantioselective reduction of the carbonyl moiety of α, β-unsaturated ketones.\textsuperscript{38,39} However, methods which chemoselectively target the carbon-carbon (figure 13) double bond are rare\textsuperscript{40}, with the majority relying on organometallic catalysts. Although efficient enantioselective transfer hydrogenation strategies are known in the literature for cyclic α, β-unsaturated ketones and aldehydes, methodologies for linear systems are limited.\textsuperscript{22,27}

2.2 1,4-reduction of α, β-unsaturated enones

2.2.1 Catalyst Screening

We began our investigation by determining which PA catalyst (figure 14) would be the best promoter for the reaction. Several (R)-BINOL-derived PA catalysts were synthesized as well as a (R)-VAPOL-derived PA. Reactions catalyzed by PA catalysts derived from the H\textsubscript{8}-BINOL share similar qualities with the BINOL-derived PA catalysts, but differ in solubility and steric effects due to the hydrogenated portion of the scaffold.\textsuperscript{41} With this in mind, it was beneficial to see if modification of the scaffold as well as the substituents at the 3, 3'-positions may enhance the selectivity.
This series of PA catalysts were screened with (E)-1, 3-diphenyl-2-buten-1-one as the enone, pinacolborane (HBPin) as the reducing agent in anhydrous toluene at 50°C (Table 1). Under these conditions, (R)-BINOL-derived PA1 (table 1, entry 1, 68% ee) and PA2 (entry 2, 52% ee) were the best performing catalysts with a conversion to product >90%. The PA catalyst derived from (R)-H₈-BINOL, PA4 (table 1, entry 4, 41% ee) did not show any significant improvement in enantioselectivity and the (R)-VAPOL-derived PA9 (table 1, entry 7) gave the worst overall result with only a 4% conversion to product.
Although these results showed promise, the reaction needed to be heated to reach completion. Unfortunately, as the reaction temperature increased, the enantioselectivity decreased. Heating the reaction to 50°C in toluene gave the best results considering the effects of heating on the enantioselectivity. Albeit moderate, these initial results encouraged us to use (R)-PA1 and (R)-PA2 as our choice PA catalysts.

2.2.2 Solvent Screening

Since the 1,4-reduction in toluene required heating, other solvents were investigated. An ideal solvent would allow for the reaction to be run at lower temperatures while proceeding to

### Table 1. Screening of various BINOL-derived PA catalysts

<table>
<thead>
<tr>
<th>entry</th>
<th>PA</th>
<th>conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PA1</td>
<td>90</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>PA2</td>
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<tr>
<td>3</td>
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<td>2</td>
</tr>
<tr>
<td>7</td>
<td>PA9</td>
<td>4</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>PA11</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>PA12</td>
<td>62</td>
<td>11</td>
</tr>
<tr>
<td>10</td>
<td>PA13</td>
<td>32</td>
<td>12</td>
</tr>
</tbody>
</table>

*R Reactions conditions: (E)-1?a (0.25 mmol), PA catalyst (10 mol%), solvent (1.0 mL), 24h reaction time, under argon.*

*Measured by 1H NMR. *Enantiomeric ratios determined by HPLC using Chiralcel OD-H column; nd = not determined. *All reactions at 50°C*
completion. If in the end toluene proved to be the best solvent, the reaction temperature would need to be addressed.

Table 2. Screening of various solvents with \( (R) \)-PA1 catalyst

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>temperature</th>
<th>conversion (%)(^b)</th>
<th>ee (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>50°C</td>
<td>90</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>50°C</td>
<td>100</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>cyclohexane</td>
<td>50°C</td>
<td>100</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>toluene</td>
<td>rt</td>
<td>44</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>( m )-xylenes</td>
<td>rt</td>
<td>27</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>( p )-xylenes</td>
<td>rt</td>
<td>26</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>methyl cyclohexane</td>
<td>rt</td>
<td>100</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>cyclopentane</td>
<td>rt</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>benzene</td>
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<td>53</td>
<td>76</td>
</tr>
<tr>
<td>10</td>
<td>hexane</td>
<td>rt</td>
<td>37</td>
<td>70</td>
</tr>
<tr>
<td>11</td>
<td>1,4-dioxane</td>
<td>rt</td>
<td>23</td>
<td>70</td>
</tr>
<tr>
<td>12</td>
<td>cyclohexane</td>
<td>rt</td>
<td>100</td>
<td>87</td>
</tr>
</tbody>
</table>

\(^a\) Reactions conditions: (E)-1a (0.25 mmol), PA catalyst (10 mol %), solvent (1.0 mL), 24 h reaction time, under argon.\(^b\) Measured by 1H NMR. \(^c\) Enantiomeric ratios determined by HPLC using Chiralcel AD-H column; \( \text{nd} \) = not determined.

We continued our investigation by conducting an extensive solvent screening as shown in table 2, at room temperature. Ideally, a reaction that can proceed to completion at room temperature would provide the most convenient conditions. Along with simplifying the reaction conditions, using a lower reaction temperature would also improve the enantioselectivity. Although high conversion was achieved with toluene at 50°C, at room temperature only 44% (table 2, entry 4) conversion was observed. At room temperature, aromatic solvents such as \( m- \)
xylenes (table 2, entry 5) and \( p \)-xylenes (table 2, entry 6) gave poor conversion to product, while benzene (table 2, entry 9) performed similar to toluene in conversion and selectivity. We then proceeded to examine the reaction in aliphatic solvents. Linear aliphatic solvent, hexanes (table 3, entry 10) gave moderate enantioselectivity (70% ee), but gave only 37% conversion to product. To our delight, in cyclohexane (table 2, entry 12), the reaction gave full conversion proving to be the best solvent, showing a dramatic increase in enantioselectivity at room temperature (87% ee).

2.3 Substrate synthesis and scope

Inspired by our preliminary findings, various \( \beta \), \( \beta \)-disubstituted \( \alpha \), \( \beta \)-unsaturated ketones were synthesized to be screened for the substrate scope. The \( \alpha \), \( \beta \)-unsaturated ketones were synthesized (figure 15) via a Horner-Wadsworth-Emmons olefination to the \( \alpha \), \( \beta \)-unsaturated ethyl ester, which can then be readily converted to the Weinreb amide.\(^{42}\) This method allowed for variation at the \( R_1 \), \( R_2 \) and \( R_3 \) positions and worked fairly well for most disubstituted ketones giving \( \alpha \), \( \beta \)-unsaturated ethyl esters.

At this stage we found that while it was easy to separate the E/Z \( \alpha \), \( \beta \)-unsaturated ethyl ester isomers formed, not all were so proved easily separate by column chromatography. Due to these complications, we also explored alternative methods for the synthesis our test substrates.
In order to expedite the route to the desired \(\alpha, \beta\)-unsaturated ketones, we improved the method by which the Weinreb amide can be accessed. With slight improvements upon a lesser known strategy, the ylide was synthesized with the Weinreb amide moiety (scheme 6).

Once synthesized, specialized ylide can be stored and used at a later time which provides added convenience to this alternative synthetic pathway. The ylide can then be used to synthesize the \(\beta, \beta\)-disubstituted \(\alpha, \beta\)-unsaturated Weinreb amides in two-steps from various commercially available ketones or aldehydes shown in scheme 7.

Simple Grignard addition to the Weinreb amide installs the group at \(R^3\), providing rapid access to a wide variety of \(\alpha, \beta\)-unsaturated ketones.
2.4 Results and Discussion

With the test substrates in hand, we re-examined the PA catalysts bearing similar aromatic substituents at the 3, 3′-position. Originally, the catalysts were tested using enone 1a, pinacolborane (HBPin) as the reducing agent in anhydrous toluene at 50°C (Table 1). These conditions showed that (R)-PA1 gave the best selectivity prompting us to use (R)-PA1 for the solvent screening. The results of the solvent screening showed cyclohexane as the best performing solvent at room temperature, eliminating the need to use heat for the reaction. We proceeded to screen catalysts (R)-PA1, (R)-PA2, (R)-PA3 and (R)-PA4 in cyclohexane to rule out any possibility of finding a more selective catalyst.

Table 3. Re-screening of catalysts with similar substituents at the 3, 3′-positions

<table>
<thead>
<tr>
<th>entry</th>
<th>PA</th>
<th>conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PA1</td>
<td>100</td>
<td>(R) 87</td>
</tr>
<tr>
<td>2</td>
<td>PA2</td>
<td>100</td>
<td>(S) 91</td>
</tr>
<tr>
<td>3</td>
<td>PA3</td>
<td>93</td>
<td>(R) 39</td>
</tr>
<tr>
<td>4</td>
<td>PA4</td>
<td>100</td>
<td>(R) 58</td>
</tr>
</tbody>
</table>

*a Reactions conditions: (E)-1a (0.25 mmol), PA catalyst (10 mol %), solvent (1.0 mL), 24h reaction time, under argon. Measured by 1H NMR.  
*b Enantiomeric ratios determined by HPLC using Chiralcel AD-H column. 
*c Designation of R and S was determined by comparison with literature retention times.
It is well known that the biaryl scaffold of BINOL-derived catalysts can be tuned by changing the group at the 3, 3'-positions. We observed this effect when the results showed a wide variation in the enantioselectivity. Overall, *(R)-PA2* emerged as the best PA catalyst demonstrating superior enantiocontrol (table 3, entry 2) and we proceeded to use this catalyst to examine the substrate scope.

Substrates containing an aromatic ring at R$^1$ and a -CH$_3$ at R$^2$ at the β-position. Based on the excellent result obtained with *(E)-1, 3-diphenyl-2-buten-1-one*, we proceeded to try our methodology on α,β-unsaturated ketones substrates in which the R$^1$, R$^3$=aryl groups had electron-withdrawing (table 4, entry 2h, 2k) or electron-donating substituents (table 4, entry 2d). We were pleased to observe that these substrates reacted extremely well and were reduced with high enantioselectivity. Also, heterocyclic substituents at R$^1$ did not diminish the reactivity or the enantioselectivity of the reaction (table 4, entry 2j).
Although chalcones with an aliphatic substituent at R₂ were reduced, we were disappointed by the moderate results obtained using the two catalyst with best selectivity (table 5). The poor selectivity for substrates with aliphatic substituents at R₁ and R₂ suggested that the aromatic ring at the β-position plays a key role in the selectivity of the reaction (table 5, entry 2o).
This can be observed in table 5, entry 2p in which again there is only moderate selectivity with an aromatic ring tethered to an aliphatic chain at the β-position. Even with an aromatic group directly attached to the β-position (table 5, entry 2p), the group at R² appears to also have an influence in the selectivity of the reaction. Replacing the -CH₃ group at R² with a -CF₃ group stopped the reaction from taking place with no reaction being observed in table 5, entry 2q.
Furthermore, we were impressed to observe that when the catalyst loading for (R)-PA2 was lowered to 2 mol %, the reaction proceeded to full conversion with 94% ee. Similarly, even at a low catalyst loading of 1 mol % full conversion was achieved, albeit with a moderate drop to 88% ee. Overall, a catalyst loading of 2 mol % was used for the methodology (table 7).
The substituents that had a significant impact on the enantioselectivity of the reaction were those with either an α-naphthyl or β-naphthyl or aliphatic chain at R\textsuperscript{1}. We were surprised to observe that the substrate with α-naphthyl at the R\textsuperscript{1} position gave better selectivity with (R)-PA\textsubscript{1}, the catalyst bearing an α-naphthyl at the 3, 3’-positions (table 7, entry 2c). Similarly, the substituent with a β-naphthyl at R\textsuperscript{1} gave better selectivity with (R)-PA\textsubscript{2}, which had β-naphthyl groups at the 3, 3’-positions (table 7, entry 2b). When compared to the reported literature values, the experimental values (\textsuperscript{1}H NMR, optical rotation, HPLC, etc.) of the products synthesized were in accordance to the published values. This information allowed us to establish the relative and absolute stereochemistry of the compounds. The results we observed with these substrates prompted us to investigate the mechanism of the reaction to try to better understand the selectivity.
2.5 Mechanistic Observations

2.5.1 Comparison of enone geometry

It is well known that cyclic $\alpha$, $\beta$-unsaturated ketones, such as 2-cyclohexanone, are locked into the $s$-trans conformation.\textsuperscript{43} However, for acyclic substrates such as 1, 3-diphenyl-2-buten-1-one (dypnone), its two geometrical isomers can undergo $s$-cis/$s$-trans conformational equilibrium (figure 17). This becomes important due to the fact that the geometry of the enone bears importance on the enantioselectivity of the reaction. The trans-$s$-cis conformation of ($E$)-dypnone has been shown to be the most stable conformation of this substrate, while the ($Z$)-dypnone is overall unstable.\textsuperscript{44} To further investigate the reactivity of each isomer, mixtures of different ratios of $E/Z$-isomers were subjected to the reaction conditions.

![Figure 17. Different conformations of $E/Z$-isomers](image)

As shown in table 8, when the reaction is performed with a mixture of $E/Z$ isomers, the enantioselectivity decreases (table 8, entry 4, and entry 5). There was also an observable decrease
in the conversion of the reaction. A 1:1 mixture of E/Z isomers (table 3, entry 3) demonstrated that after 24 hours, there was only a 50% conversion to product observed by $^1$HNMR.

Table 8. Effect of enone geometry on product outcome

<table>
<thead>
<tr>
<th>entry</th>
<th>(E)-1a</th>
<th>(Z)-1a</th>
<th>conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>0</td>
<td>92</td>
<td>94</td>
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<tr>
<td>5</td>
<td>0</td>
<td>100</td>
<td>21</td>
<td>39</td>
</tr>
</tbody>
</table>

*a Reactions conditions: (E)-1a (0.25 mmol), PA catalyst (10 mol %), solvent (1.0 mL) under argon at room temperature. *$^b$Enantiomeric ratios were determined by HPLC by using a Chiralcel AD-H column. *$^c$Designation of R and S was determined by comparison with literature retention times.

The enantioselectivity dropped from 94% ee (table 8, entry 1) to 70% ee (table 8, entry 3). This suggests that the selectivity also depends on the geometry of the substrate and that the (Z)-isomer is less reactive under the conditions (table 8, entry 5). Taking into considerations the relative stabilities of the conformations of each isomer, one can speculate that the poor reactivity and selectivity of (Z)-dypone can be attributed to its unfavorable conformations. For the ideal enantioselectivity, it is preferable to use the reaction conditions on isomerically pure (E)-enone (table 8, entry 1).

2.5.2 Comparison of α-naphthyl or β-naphthyl substituents on 3, 3’- position of PA

The most interesting results are observed in substrates bearing α-naphthyl or β-naphthyl substituents at R. When the chalcone bearing the β-naphthyl substituent at the β-carbon was subjected to the reaction condition using (R)-PA1 (3, 3’=α-naphthyl) or (R)-PA2 (3, 3’=β-naphthyl), only a minor difference was observed in enantioselectivity. However,
when the chalcone bearing the $\alpha$-naphthyl substituent at the $\beta$-carbon was treated in the same fashion, there was a dramatic difference in enantioselectivity. For this substrate (table 4, entry 3), (R)-PA1 emerged as the superior catalyst resulting in an 87% ee.

Table 9. Selectivity comparison of (R)-PA1 and (R)-PA2

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>PA1 ee (%)</th>
<th>PA2 ee (%)</th>
<th>entry</th>
<th>substrate</th>
<th>PA1 ee (%)</th>
<th>PA2 ee (%)</th>
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<td>(S) 91</td>
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<td>(S) 87</td>
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<td>(R) 80</td>
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<tr>
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<td>(R) 87</td>
<td>(S) 41</td>
<td>7</td>
<td>MeO</td>
<td>(R) 84</td>
<td>(S) 94</td>
</tr>
</tbody>
</table>

* Reactions conditions: (E)-17a (0.20 mmol), PA catalyst (10 mol %), solvent (1.0 mL) under argon at room temperature. Enantiomeric ratios were determined by HPLC by using a Chirasil-AD-H column chromatography. Reaction using (S)-BINOL-derived catalyst. Designation of R and S was determined by comparison with literature retention times.

Furthermore, although (R)-BINOL was used to synthesize the catalysts used for the study, we were intrigued by the fact there was a switch in the conformation of the resulting product. Under the same conditions, the substrates reduced using (R)-PA1 preferentially gave the (R)-enantiomer (table 9, entry 1), whereas in reactions with (R)-PA2 were selective for the (S)-enantiomer (table 9, entry 2). When the (S)-BINOL-derived PA1 and PA2 were used (table 4, entry 2) a change in selectivity was observed in which now the (S)-PA1 and (S)-PA2 gave the (S)-enantiomer and the (R)-enantiomer respectively.
To better understand why such a switch in selectivity was observed, computational studies were conducted to gather insight into the mechanism of the reaction. The Becke, three-parameter, Lee-Yang-Par (B3LYP) calculations tend to be the most commonly used methods for computational chemistry practitioners. When trying to examine organic reactions, B3LYP works particularly well for organic molecules and was the density functional method of choice used by our collaborator Eri Yamamoto, a graduate student in the lab of Dr. Masahiro Yamanaka at Rikkyo University in Tokyo, Japan.

![Chemical structure](image)

**Figure 18. Computational methods used for structural studies**

For the study of the catalyst structure, a chemical model and the density functional theory (DFT) computational method were used. Various conformations (local minimum structures) of (R)-PA1 and (R)-PA2 were optimized at the ONIOM (B3LYP/6-31G*: HF/3-21G) level. To elucidate the stereocontrol of PA1 and PA2 catalyzed 1,4-reduction of α, β-unsaturated ketone, the initial DFT calculations were performed in on a simplified chemical model (figure 19) in which the aryl rings and the methyl groups of the pinacolborane were removed.
The two diastereomeric TSs \([\text{TS}_R \text{ leading to (R)-product, TS}_S \text{ leading to (S)-product}]\) were located at the B3LYP/6-31G* level. In both \(\text{TS}_S\) and \(\text{TS}_R\), the phosphoro-boronic catalytic simultaneously activates \(\alpha, \beta\)-unsaturated ketone and boron on Lewis acidic boron and Lewis basic phosphoryl oxygen, respectively, to form cyclic TS.

This indicates that the relative stability of the diastereomeric TSs depends on the asymmetric reaction space constructed by the 3, 3’-substituents.
Detailed density functional theory (DFT) for the transition state energy of the reactions included those for the different isomers (s-cis and s-trans) of compound 1a. Also, the relative orientation of the 3, 3’-naphthyl group was explored (figure 21). The conformations bearing the hydrogen bond between the naphthyl-H at the ortho position and the phosphoryl oxygen are relatively stabilized.

The computational model (figure 22) shows that hydrogen bonding stabilizes the transition state between the borate-O and phenyl of the substrate in TS_R. Also, the calculated bond length between the phosphoryl-O and naphthyl-H is shorter in TS_S than TS_R. The energy difference between TS_R and TS_S can be attributed to the destabilization of the hydrogen bonding caused by the steric repulsion induced by the methyl of the substrate and 3, 3’-substituent of the catalyst.
Disruption of this interaction is fundamental to the energy difference observed leading to a preference of PA1 for the (R)-enantiomer. Therefore, it is the steric interaction of the substituents at the β-carbon and the 3, 3’-substituents of the PA (Figure 17) which influence the facial selectivity leading to the respective major enantiomer.

2.6 Summary

Under the optimized conditions of our methodology, the BINOL-derived boro-phosphate catalyst successfully reduced linear α, β-unsaturated ketones are selectively reduced at the carbon-carbon double bond, giving the corresponding saturated ketone in yields and enantioselectivities >93% with 2 mol % catalyst loading. α, β-Unsaturated ketones substrates with
electron withdrawing or electron donating substituents on the R$_1$, R$_3$=aryl groups did not exhibit reduced the enantioselectivity, and heterocyclic groups at R$_1$ were well-tolerated. The computational studies suggest that the stereoelectronic effects of the substituents at the β-carbon and the 3, 3’-substituents of the PA influence the facial selectivity that leads to the respective major enantiomer.

2.7 Experimental
2.7.1 General Considerations

Unless otherwise noted, all reactions were carried out in flame-dried screw-cap test tubes and were allowed to proceed under a dry argon atmosphere with magnetic stirring. Anhydrous solvents were purchased from commercial sources and used without further purification. Ketones were purchased from commercial sources and used without further purification. PA catalysts were prepared from chiral BINOL according to the known literature procedure. Thin layer chromatography was performed on Merck TLC plates (silica gel 60 F$_{254}$). Ketones were purchased from commercial sources without any further purification. Thin layer chromatography was performed on Merck TLC plates (silica gel 60 F$_{254}$). Visualization was accomplished using UV light (256 nm), p-anisaldehyde or potassium permanganate stain as indicator. Flash column chromatography was performed with Merck silica gel (230-400 mesh). Analytical Autopol IV polarimeter (589) using a 700-µL cell with a path length of 1-dm. $^1$H NMR and $^{13}$C NMR were recorded on a Varian Inova-400 spectrometer with chemical shifts reported relative to tetramethylsilane (TMS). Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. All the compounds were known compounds and were characterized by comparing their $^1$H NMR and $^{13}$C NMR values those reported in the literature. Enantioselectivity was determined using a Varian Prostar HPLC and
Chiralcel AD-H, OD-H, or AS-H chiral columns. All reactions were conducted in triplicate to ascertain reproducibility.

2.7.2 General procedure for the reduction of $\alpha$, $\beta$-unsaturated enones

\[
\begin{align*}
\text{R}^2 \text{C} &= \text{R}^1 \underset{\text{O}}{\text{C}} \text{R}^3 \\
\text{(R)-PA (2 mol%), HBPin (1.5 equiv.)} \\
\text{cyclohexane, rt, 24h} \\
\rightarrow \\
\text{R}^1 \text{C} &= \text{R}^2 \underset{\text{O}}{\text{C}} \text{R}^3
\end{align*}
\]

A screw-cap reaction tube loaded with a stir bar was evacuated, flame-dried, and back-filled with argon. Once the screw-cap reaction tube was cooled to room temperature, (R)-PA catalyst PA2 (2 mol %) and anhydrous cyclohexane (0.5ml) were added and left to stir. To this mixture was added HBpin (1.5 equiv.) and the mixture was stirred approximately 1 minute before adding $\alpha$, $\beta$-unsaturated ketone (0.25 mmol) in anhydrous cyclohexane (0.5ml). The reaction mixture was monitored by TLC (hexanes/EtOAc 10:1) and stirred at room temperature for 12-24 hours at room temperature. Upon completion the reaction was quenched with deionized water (1.0ml) and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude residue was then purified by flash chromatography. The eluent was collected in Fisherbrand™ disposable borosilicate glass tubes with plain end (Cat. No. 14-961-29 16x100mm) and the corresponding fractions were visualized by TLC using UV light (256 nm). The fractions containing the desired product were then collected and concentrated in vacuo. Enantiomeric excess was determined by chiral normal phase HPLC. The details of column type and run conditions are described below.

The relative stereochemistry ($R$ or $S$) was assigned based on the published literature values by assigning the experimental retention times to the literature retention times. In the literature$^{47}$, the first peak to elute was designated to be the ($S$)-enantiomer and the second peak to elute off the column was designated to be the ($R$)-enantiomer. Based on this published data, we assigned the
corresponding stereochemical designation to our chromatographic data. The assignment for the peak with the experimental optical rotation values were compared to the published literature values and determined to coincide based on the assignment by spectroscopic data of the published work. Absolute configuration was assigned by analogy based on the optical rotation data of known compounds reported in the literature and the sign of optical rotation is noted.

\[
\text{Absolut configuration was assigned by analogy based on the optical rotation data of known compounds reported in the literature and the sign of optical rotation is noted.}
\]

\[
\text{(S)-1,3-diphenylbutan-1-one (2a): Following the general procedure for the reduction of } \alpha, \beta-\text{unsaturated enones, purification by column chromatography (hexane/EtOAc, 10:1} \rightarrow \text{5:1) and preparative TLC (hexane/EtOAc, 5:1) the title compound was obtained as a white solid in 96 \% yield. The spectroscopic data was consistent with the literature data, the absolute configuration was assigned in comparison of the optical rotation reported and relative stereochemistry was assigned based on the HPLC retention times reported in the literature. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), t_{\text{major}} = 7.185 \text{ min}, t_{\text{minor}} = 9.131 \text{ min}; ee = 94\%. [\alpha]_{D}^{25} = +0.71 (c=1.87, CHCl}_3)\text{, literature value }^{28} [\alpha]_{D}^{R} = +0.57 (c=1.0, CHCl}_3) 81\% \text{ ee, S enantiomer; } ^1\text{H NMR (400 MHz, CDCl}_3): } \delta 7.93 (d, J = 7.2 \text{ Hz}, 2H), 7.59-7.51 (m, 1H), 7.48-7.40 (m, 2H), 7.35-7.18 (m, 5H), 3.58-3.43 (m, 1H), 3.30 (dd, J = 16.5, 5.4 Hz, 1H), 3.18 (dd, J = 16.5, 8.4 Hz, 1H), 1.34 (d, J = 6.9 Hz, 3 H); ^13\text{C NMR (100 MHz, CDCl}_3): } \delta 199.1, 146.6, 137.3, 133.0, 128.6, 128.1, 126.9, 126.3, 47.0, 35.6, 21.9.\]

35
(S)-3-(naphthalen-2-yl)-1-phenylbutan-1-one (2b): Following the general procedure for the reduction of \(\alpha, \beta\)-unsaturated enones, purification by column chromatography (hexane/EtOAc, 10:1 \(\rightarrow\) 5:1) and preparative TLC (hexane/EtOAc, 5:1) the title compound was obtained as a yellow oil in 96% yield. The spectroscopic data was consistent with the literature data, the absolute configuration was assigned in comparison of the optical rotation reported and relative stereochemistry was assigned based on the HPLC retention times reported in the literature.\(^49\)

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), \(t_{\text{major}} = 12.321\) min, \(t_{\text{minor}} = 15.865\) min; \(S\)-enantiomer= 95% ee. \([\alpha]^{25}_D = +1.14\) (c=0.97, CHCl\(_3\)), literature value\(^50\) \([\alpha]^{20}_D = -4.54\) (c=0.44, CHCl\(_3\)) \(R\)-enantiomer=97% ee;

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.93\) (d, \(J = 7.2\) Hz, 2H), 7.81-7.76 (m, 3H), 7.69 (s, 1H), 7.55-7.48 (m, 1H), 7.47-7.35 (m, 5H), 3.74-3.60 (m, 1H), 3.39 (dd, \(J = 16.5, 5.7\) Hz, 1H), 3.26 (dd, \(J = 16.5, 8.1\) Hz, 1H), 1.41 (d, \(J = 6.9\) Hz, 3H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 199.0, 144.1, 137.3, 133.6, 133.0, 132.3, 128.6, 128.2, 128.1, 127.7, 127.6, 126.0, 125.8, 125.4, 125.0, 45.0, 35.7, 21.9.

(R)-3-(naphthalen-1-yl)-1-phenylbutan-1-one (2c): Following the general procedure for the reduction of \(\alpha, \beta\)-unsaturated enones, purification by column (hexane/EtOAc, 10:1 \(\rightarrow\) 5:1) and preparative TLC (hexane/EtOAc, 5:1) the title compound was obtained as a white solid in 91% yield. The spectroscopic data was consistent with the literature data, the absolute configuration was assigned in comparison of the optical rotation reported and relative stereochemistry was
Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), $t_{\text{major}} = 11.0463 \text{ min}$, $t_{\text{minor}} = 15.029 \text{ min}$; ee = 87%. $[\alpha]_{25}^{25} = -1.99 \text{ (c=0.82, CHCl}_3$); $^1$HNMR (400 MHz, CDCl$_3$) $\delta 7.99 \text{ (s, 1H), 7.82} - 7.74 \text{ (m, 3H), 7.65 (s, 1H), 7.42 (dd, } J = 23.4, 5.3 \text{ Hz, 4H), 7.32 (t, } J = 6.0 \text{ Hz, 3H), 3.60 (s, 1H), 3.21 (s, 1H), 2.98 (s, 1H), 1.56 - 1.43 \text{ (m, 3H); } ^{13}$CNMR (100 MHz, CDCl$_3$) $\delta 199.04, 140.36, 136.88, 134.49, 132.69, 132.34, 129.14, 128.83 - 128.51, 128.51 - 128.30, 128.06, 127.25, 126.97, 125.28, 123.21, 47.35, 37.39, 20.64.

(S)-3-(4-methoxyphenyl)-1-phenylbutan-1-one (2d): Following the general procedure for the reduction of $\alpha$, $\beta$-unsaturated enones, purification by column (hexane/EtOAc, 10:1$\rightarrow$5:1) and preparative TLC (hexane/EtOAc, 5:1) the title compound was obtained as a white solid in 92 % yield. The spectroscopic data was consistent with the literature data, the absolute configuration was assigned in comparison of the optical rotation reported and relative stereochemistry was assigned based on the HPLC retention times reported in the literature. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), $t_{\text{major}} = 12.703 \text{ min}$, $t_{\text{minor}} = 17.621; S$-enantiomer= 90% ee. $[\alpha]_{31.4}^{20} = +2.33 \text{ (c=0.98, CHCl}_3$), literature value$^{50} [\alpha]_{24.0}^{20} = -6.87 \text{ (c=1.39, CHCl}_3$, $R$-enantiomer= $>98$% ee; $^1$HNMR (400 MHz, CDCl$_3$): $\delta 7.92 \text{ (d, } J = 7.2 \text{ Hz, 2H), 7.58-7.40 (m, 3H), 7.18 (d, } J = 8.7 \text{ Hz, 2H), 6.84 (d, } J = 8.7 \text{ Hz, 2H), 3.77 (s, 3H), 3.48-3.39 (m, 1H), 3.26 (dd, } J = 16.5, 6.0 \text{ Hz, 1H), 3.14 (dd, } J =16.5, 8.1 \text{ Hz, 1H), 1.31 (d, } J = 6.9 \text{ Hz, 3H); } ^{13}$CNMR (100 MHz, CDCl$_3$): $\delta 199.3, 158.0, 138.7, 137.3, 133.0, 131.0, 128.6, 128.1, 127.8, 113.9, 55.3, 47.3, 34.9, 22.1.
(S)-1-(4-methoxyphenyl)-3-phenylbutan-1-one (2e): Following the general procedure for the reduction of \( \alpha, \beta \)-unsaturated enones, purification by column (hexane/EtOAc, 10:1→5:1) and preparative TLC (hexane/EtOAc, 5:1) the title compound was obtained as a white solid in 72% yield. The spectroscopic data was consistent with the literature data, the absolute configuration was assigned in comparison of the optical rotation reported and relative stereochemistry was assigned based on the HPLC retention times reported in the literature.\(^5\) Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), \( t_{\text{major}} = 19.662 \text{ min}, \ t_{\text{minor}} = 30.605 \text{ min}; \ ee = 93\% \). \([\alpha]^{25}_{D} = -0.91 \text{ (c=0.66, CHCl$_3$)}\); \(^1\)HNMR (400 MHz, CDCl$_3$) \( \delta 7.92 \text{ (d, J = 8.9 Hz, 2H)}, 7.32-7.26 \text{ (m, 4H)}, 7.21-7.17 \text{ (m, 1H)}, 6.91 \text{ (d, J = 8.9 Hz, 2H)}, 3.86 \text{ (s, 3H)}, 3.53-3.45 \text{ (m, 1H)}, 3.24 \text{ (dd, J = 16.2, 5.7 Hz, 1H)}, 3.13 \text{ (dd, J = 16.2, 8.4 Hz, 1H)}, 1.33 \text{ (d, J = 7.0 Hz, 3H)}\); \(^13\)CNMR (100 MHz, CDCl$_3$) \( \delta 198.1, 163.8, 147.1, 130.8, 130.7, 128.9, 127.3, 126.6, 114.1, 55.9, 47.1, 36.2, 22.3\). HRMS calculated for C$_{17}$H$_{18}$O$_2$: 277.1199; found 277.1206.

(S)-3-(4-fluorophenyl)-1-phenylbutan-1-one (2f): Following the general procedure for the reduction of \( \alpha, \beta \)-unsaturated enones, purification by column (hexane/EtOAc, 10:1→5:1) and preparative TLC (hexane/EtOAc, 5:1) the title compound was obtained as a white solid in 95% yield. The spectroscopic data was consistent with the literature data, the absolute configuration was assigned in comparison of the optical rotation reported and relative stereochemistry was
assigned based on the HPLC retention times reported in the literature.\textsuperscript{50} Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), $t_{\text{major}} = 8.948$ min, $t_{\text{minor}} = 11.630$ min; S-enantiomer = 91\%. $[\alpha]^{25}_D = +1.12$ (c=1.3, CHCl$_3$), literature value\textsuperscript{50} $[\alpha]^{28.8}_D = -1.21$ (c=1.54, CHCl$_3$) $R$-enantiomer =>98\% ee; $^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 1.30 (d, J = 6.8 Hz, 3H), 3.17 (dd, J = 7.6, 16.8 Hz, 1H), 3.27 (dd, J = 6.0, 16.8 Hz, 1H), 3.48–3.53 (m, 1H), 6.95–7.00 (m, 2H), 7.21–7.26 (m, 2H), 7.42–7.46 (m, 2H), 7.53–7.57 (m, 1H), 7.90–7.92 (m, 2H); $^{13}$CNMR (100 MHz, CDCl$_3$) $\delta$ 198.57, 163.68, 161.59, 143.40, 143.37, 136.95, 132.71, 128.65, 128.43, 128.05, 127.98, 115.65, 115.43, 47.93, 38.19, 21.12.

![Structure of 2g](image)

(S)-1-(4-fluorophenyl)-3-phenylbutan-1-one (2g): Following the general procedure for the reduction of $\alpha$, $\beta$-unsaturated enones, the title compound was obtained in 92\% yield. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), $t_{\text{major}} = 8.749$ min, $t_{\text{minor}} = 11.421$ min; ee = 95\%. $[\alpha]^{25}_D = -2.11$ (c=1.58, CHCl$_3$); $^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 7.83 – 7.79 (m, 2H), 7.31 – 7.24 (m, 4H), 7.16 (s, 1H), 7.13 – 7.06 (m, 2H), 3.45 (s, 1H), 3.15 (s, 1H), 2.93 (s, 1H), 1.44 – 1.30 (m, 3H); $^{13}$CNMR (100 MHz, CDCl$_3$) $\delta$ 199.04, 166.40, 146.61, 133.79, 130.89 – 130.23, 128.41 – 128.20, 127.32 – 126.92, 126.60, 116.98 – 114.69, 47.9, 38.8, 21.12.
(R)-1-phenyl-3-(4-(trifluoromethyl) phenyl)butan-1-one (2h): Following the general procedure for the reduction of α, β-unsaturated enones, purification by column (hexane/EtOAc, 10:1→5:1) and preparative TLC (hexane/EtOAc, 5:1) the title compound was obtained as a white solid in 93% yield. The spectroscopic data was consistent with the literature data, the absolute configuration was assigned in comparison of the optical rotation reported and relative stereochemistry was assigned based on the HPLC retention times reported in the literature. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), $t_{\text{major}} = 7.137 \text{ min}$, $t_{\text{minor}} = 9.755 \text{ min}$; R-enantiomer= 96% ee. $[\alpha]_{25}^{D} = -4.20 \ (c=0.96, \text{ CHCl}_3$), literature value $[\alpha]_{24.0}^{D} = -5.22 \ (c=0.78, \text{ CHCl}_3$) R-enantiomer= 89% ee; ¹HNMR (400 MHz, CDCl₃) δ 1.36 (d, $J = 7.19 \text{ Hz}$, 3H), 3.23 (dd, $J = 7.6, 16.7 \text{ Hz}$, 1H), 3.32 (dd, $J = 6.4, 16.8 \text{ Hz}$, 1H), 3.56–3.60 (m, 1H), 7.38–7.46 (m, 3H), 7.54–7.56 (m, 3H), 7.90–7.93 (m, 2H); ¹³CNMR (100 MHz, CDCl₃) δ 21.8, 35.3, 46.5, 124.2 (q, 1 $J = 270.8 \text{ Hz}$), 125.5 (q, 3 $J = 4.1 \text{ Hz}$), 127.2, 128.0, 128.5 (q, 2 $J = 32.1 \text{ Hz}$), 128.6, 133.1, 137.0, 150.6, 198.4.

(S)-3-(4-chlorophenyl)-1-phenylbutan-1-one (2i): Following the general procedure for the reduction of α, β-unsaturated enones, purification by column (hexane/EtOAc, 10:1→4:1) and hexane/EtOAc, 4:1) and preparative TLC (hexane/EtOAc, 4:1) the title compound was obtained as a white solid in 92% yield. The spectroscopic data was consistent with the literature data and
the absolute configuration was assigned in comparison of the optical rotation with the literature value. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), \( t_{\text{major}} = 9.041 \text{ min, } t_{\text{minor}} = 12.659 \text{ min; } S\text{-enantiomer} = 92\% \). \( [\alpha]^{25}_D = -1.24 \text{ (c=1.1, CHCl}_3\text{), literature value}^{50} [\alpha]^{24.0}_D = -1.76 \text{ (c=1.30, CHCl}_3\text{) } S\text{-enantiomer}= 95\% \text{ ee; } ^1\text{HNMR (400 MHz, CDCl}_3\text{)}: \delta 7.94-7.91 \text{ (m, 2 H), 7.58-7.43 \text{ (m, 3 H), 7.28-}
7.19 \text{ (m, 4 H), 3.53-3.47 \text{ (m, 1 H), 3.27 \text{ (dd, J = 16.6, 6.3, 1 H), 3.18 \text{ (dd, J = 16.6, 7.8, 1 H), 1.32 \text{ (d, J = 6.8, 3 H); } ^1\text{CNMR (100 MHz, CDCl}_3\text{)} \delta 198.88, 145.19, 137.23, 133.31, 132.05, 128.82, 128.48, 128.24, 47.01, 35.14, 22.17.}

(S)-1-phenyl-3-(thiophen-2-yl)butan-1-one (2j): Following the general procedure for the reduction of \( \alpha, \beta \)-unsaturated enones, purification by column (hexane/EtOAc, 4:1) and preparative TLC (hexane/EtOAc, 4:1) the title compound was obtained as a white solid in 93\% yield. The spectroscopic data was consistent with the literature data, the absolute configuration was assigned in comparison of the optical rotation reported and relative stereochemistry was assigned based on the HPLC retention times reported in the literature. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), \( t_{\text{major}} = 8.161 \text{ min, } t_{\text{minor}} = 9.559 \text{; } S\text{-enantiomer} = 87\% \text{ ee. } [\alpha]^{33.3}_D = +1.37 \text{ (c=0.97, CHCl}_3\text{), literature value}^{50} [\alpha]^{24.0}_D = -1.42 \text{ (c=2.04, CHCl}_3\text{), } R\text{-enantiomer}= >98\% \text{ ee; } ^1\text{HNMR (400 MHz, CDCl}_3\text{)} \delta 7.88 – 7.77 \text{ (m, 8H), 7.42 \text{ (s, 4H), 7.38 – 7.33 \text{ (m, 8H), 7.01 – 6.86 \text{ (m, 12H), 3.41 \text{ (s, 3H), 3.13 \text{ (s, 3H), 2.80 \text{ (s, 3H), 1.53 – 1.39 \text{ (m, 12H); } ^1\text{CNMR (100 MHz, CDCl}_3\text{)} \delta 201.06, 146.12, 136.88, 132.69, 128.83 – 128.46, 128.46 – 128.30, 126.26, 125.39, 123.47, 48.68, 40.25, 21.05.}
(S)-4-(4-oxo-4-phenylbutan-2-yl)benzonitrile (2k): Following the general procedure for the reduction of α, β-unsaturated enones, purification by column (hexane/EtOAc, 4:1) and preparative TLC (hexane/EtOAc, 4:1) the title compound was obtained as a white solid in 92% yield. The spectroscopic data was consistent with the literature data, the absolute configuration was assigned in comparison of the optical rotation reported and relative stereochemistry was assigned based on the HPLC retention times reported in the literature. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), \( t_{\text{major}} = 18.6 \text{ min} \), \( t_{\text{minor}} = 24.32 \text{ min} \); ee = 87% ee. \([\alpha]^{25}_D = +2.04 \) (c=1.10, CHCl\(_3\)); \(^1\)HNMR (400 MHz, CDCl\(_3\)) \( \delta \): 7.81 – 7.69 (m, 8H), 7.67 – 7.54 (m, 8H), 7.54 – 7.40 (m, 12H), 7.39 – 7.32 (m, 8H), 3.49 (s, 3H), 3.17 (s, 3H), 2.87 (s, 3H), 1.44 – 1.31 (m, 12H); \(^{13}\)CNMR (100 MHz, CDCl\(_3\)) \( \delta \): 199.04, 152.37, 136.88, 133.24 – 133.03, 132.69, 128.83 – 128.45, 128.45 – 128.30, 126.61 – 126.40, 119.12, 106.7, 47.93, 38.80, 21.12.

(S)-1,3-diphenylpentan-1-one (2l): Following the general procedure for the reduction of α, β-unsaturated enones, purification by column (hexane/EtOAc, 4:1) and preparative TLC (hexane/EtOAc, 4:1) the title compound was obtained as a white solid for screening purposes. The spectroscopic data was consistent with the literature data, the absolute configuration was assigned in comparison of the optical rotation reported and relative stereochemistry was assigned based on the HPLC retention times reported in the literature. Enantiomeric excess was determined by
HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), t\textsubscript{major} = 5.454 min, t\textsubscript{minor} = 6.427 min; S-enantiomer= 66\% ee. [\alpha]\textsuperscript{25}_{D} = +2.52 (c=0.97, CHCl\textsubscript{3}), literature value\textsuperscript{28} [\alpha]\textsuperscript{RT}_{D} = +2.49 (c=1.1, CHCl\textsubscript{3}) S-enantiomer= 89\% ee; \textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}): \delta = 7.81-7.83 (m, 2H), 7.43-7.47 (m, 1H), 7.33-7.37 (m, 2H), 7.08-7.23 (m, 5H), 3.14-3.25 (m, 3H), 1.68-1.75 (m, 1H), 1.51-1.62 (m, 1H), 0.78 (t, 3H, J = 7.5 Hz); \textsuperscript{13}CNMR (100 MHz, CDCl\textsubscript{3}): \delta = 199.1, 144.6, 137.2, 132.9, 128.5, 128.4, 128.0, 127.6, 126.2, 45.7, 43.1, 29.3, 12.2.

\textbf{(S)-4-methyl-1,3-diphenylpentan-1-one (2m):} Following the general procedure for the reduction of \(\alpha\), \(\beta\)-unsaturated enones, purification by column (hexane/EtOAc, 4:1) and preparative TLC (hexane/EtOAc, 4:1) the title compound was obtained as a white solid for screening purposes. The spectroscopic data was consistent with the literature data, the absolute configuration was assigned in comparison of the optical rotation reported and relative stereochemistry was assigned based on the HPLC retention times reported in the literature.\textsuperscript{57} Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), t\textsubscript{major} = 8.134 min, t\textsubscript{minor} 9.715 min; S-enantiomer= 64\% ee. [\alpha]\textsuperscript{25}_{D} = +0.77 (c=1.09, CHCl\textsubscript{3}), literature value\textsuperscript{28} [\alpha]\textsuperscript{RT}_{D} = +0.75 (c=1.2, CHCl\textsubscript{3}) S-enantiomer= 97\% ee; \textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}): \delta = 7.86-7.89 (m, 2H), 7.50-7.54 (m, 1H), 7.40-7.43 (m, 2H), 7.23-7.27 (m, 2H), 7.13-7.19 (m, 3H), 3.66 (d, 2H, J = 6.9 Hz), 3.14-3.20 (m, 1H), 1.90-2.00 (m, 1H), 0.99 (d, 3H, J = 6.6 Hz), 0.79 (d, 3H, J = 6.9 Hz); \textsuperscript{13}CNMR (100 MHz, CDCl\textsubscript{3}): \delta = 199.3, 143.6, 137.3, 132.8, 128.4, 128.3, 128.0, 127.9, 126.1, 47.9, 42.6, 33.4, 21.1, 20.5.
(S)-3-cyclohexyl-1,3-diphenylpropan-1-one (2n): Following the general procedure for the reduction of α, β-unsaturated enones, purification by column (hexane/EtOAc, 4:1) and preparative TLC (hexane/EtOAc, 4:1) the title compound was obtained as a white solid for screening purposes. The spectroscopic data was consistent with the literature data and the absolute configuration was assigned in comparison of the optical rotation with the literature value. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), t_major = 10.650 min, t_minor = 12.384 min; S-enantiomer= 34% ee. [α]_{D}^{25} = -0.89 (c=0.85, CHCl₃), literature value [α]_{D}^{RT} = +5.6 (c=1.4, CHCl₃) R-enantiomer= 97% ee; $^{1}$HNMR (400 MHz, CDCl₃): $\delta$ = 7.86-7.88 (m, 2H), 7.50-7.54 (m, 1H), 7.39-7.43 (m, 2H), 7.22-7.26 (m, 2H), 7.13-7.17 (m, 3H), 3.42 (dd, 1H, J = 5.5, 15.5 Hz), 3.30 (dd, 1H, J = 8.0, 16.5 Hz), 3.17-3.21 (m, 1H), 1.48-1.87 (m, 6H), 0.83-1.25 (m, 5H); $^{13}$CNMR (100 MHz, CDCl₃): $\delta$ = 199.4, 143.8, 137.3, 132.7, 128.4, 128.3, 128.0, 127.9, 126.0, 47.1, 43.2, 42.6, 31.5, 30.9, 26.7, 26.6, 26.5.

(S)-3-methyl-1,5-diphenylpentan-1-one (2p): Following the general procedure for the reduction of α, β-unsaturated enones, purification by column (hexane/EtOAc, 4:1) and preparative TLC (hexane/EtOAc, 4:1) the title compound was obtained as a white solid for screening purposes. The spectroscopic data was consistent with the literature data, the absolute configuration was assigned in comparison of the optical rotation reported and relative stereochemistry was assigned based on the HPLC retention times reported in the literature. Enantiomeric excess was determined by
HPLC with a Chiralcel AD-H column (hexane/iPrOH = 99.5/0.5, 1.0 mL/min), $t_{\text{major}} = 10.941$ min, $t_{\text{minor}} = 12.591$ min; $S$-enantiomer = 56%. $[\alpha]^D_{25} = +6.7$ (c=1.0, CHCl$_3$), literature value$^{28}$ $[\alpha]^D_{\text{RT}} = +7.1$ (c=1.1, CHCl$_3$) $S$-enantiomer = 81% ee; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.92-7.94$ (m, 2H), 7.53-7.57 (m, 1H), 7.43-7.47 (m, 2H), 7.26-7.29 (m, 2H), 7.15-7.19 (m, 3H), 3.00 (dd, 1H, $J = 4.5$, 15.9 Hz), 2.81 (dd, 1H, $J = 7.9$, 15.9 Hz), 2.61-2.76 (m, 2H), 2.24-2.26 (m, 1H), 1.70-1.77 (m, 1H), 1.56-1.63 (m, 1H), 1.03 (d, 3H, $J = 6.4$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 200.0, 142.4, 137.3, 132.9, 128.9, 128.5, 128.4, 128.3, 128.1, 125.7, 46.0, 39.0, 33.6, 29.7, 20.1.$
Chapter 3 Boro-phosphate catalyzed asymmetric reductive aldol

3.1 Background

The use of tandem reactions is a highly efficient method in the synthesis of organic compounds. Methodologies that require multiple steps of reactions followed by purifications, reduce the efficiency of the reaction and increase the amount of time spent on purification and isolation of intermediates. Favorable tandem reactions would eliminate excessive use of reagents and solvents, making the reactions much more cost effective.

Optically active tertiary alcohols are important building blocks found in both naturally occurring and synthetic biologically active molecules. Developing reactions that can accomplish the formation of these moieties enantioselectively would find great use in the synthesis of pharmaceuticals. The aldol reaction is an example of a simple and efficient reaction that can provide access to tertiary alcohols starting from a ketone. The asymmetric reductive aldol reaction of α,β-unsaturated carbonyl compounds is an efficient tandem reaction which provides access to optically active tertiary alcohols. In the past, chiral catalysts with transition-metals such as boron and silane have been used to control the stereochemistry of these transformations. Although boron enolates are known to be remarkably useful intermediates for asymmetric aldol reactions, these reactions are still limited by the reactivity of the ketone.
3.2 Methodology

In synthetic organic chemistry, several methodologies that use organoboron compounds have been developed for carbon–carbon bonds. Organoboron compounds are touted as being a safer, environmentally-friendly alternative to organometallic reagents. Organometallic reagents produce toxic byproducts which at times are difficult to remove from the reaction mixture whereas boric acid is the primary byproduct in reactions using organoboron reagents. Similarly, their versatility have made them one of the most widely utilized reagents in aldol additions, aldol condensations and coupling reactions to name a few.

Since the early 1980s, boron enolates have been a major component in the aldol condensation reaction and the stereochemical control of the reaction has been in extensively studied.

Figure 23. Stereochemical preferences of the (E)- and (Z)-enolate in the aldol reaction

The reaction has been found to proceed via a Zimmerman-Traxler model, six-membered, chair like transition state with the stereochemical outcome being dependent on the configuration of the...
enolate. The high stereochemical control observed for boron-mediated aldol reactions, is attributed to the short bond length between the B-O (1.4-1.5Å) bond which allows for a tighter transition state that produces syn-aldol product for the (Z)-enolates and anti-aldol product for the (E)-enolate.\textsuperscript{81}

Guided by the results that were obtained from the boro-phosphate catalyzed reduction, we proceeded to examine introduction of benzaldehyde as the electrophile after formation of the boron enolate. Once the preceding phosphoboronate-catalyzed 1, 4-addition of the hydride takes place,

### 3.3 Results and Discussion

Having obtained successful results using the chiral BINOL-derived boro-phosphate catalyst to enantioselectively reduce of α, β-unsaturated enones to the corresponding ketone substrates, we were interested in expanding the utility of this transformation.

![Proposed mechanism of reductive aldol](Figure 24)

By adding the electrophile to the boron enolate (figure 25) formed in the reaction, it would be possible to use the stereocenter set when the hydride attacks at the β-position, can potentially
influence the facial selectivity of the reaction (figure 21). Furthermore, the (Z)-enolate that is formed in the reduction step would preferentially give the syn-aldol product. With this information it would be possible to determine the overall relative stereochemistry of the synthesized compounds.

Table 10. Reductive aldol substrate scope

<table>
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<th>major ee (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>minor ee (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>&gt;99</td>
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<sup>a</sup> Reactions conditions: (E)-1a (0.25 mmol), PA catalyst (10 mol %), solvent (1.0 mL) under argon at room temperature. <sup>b</sup> Enantiomeric ratios were determined by HPLC by using a Chiralcel OD+ or OD-H column.

Being that the reaction conditions used in the secondary reaction would be the same used in the initial reduction, we used the substrates with the best results for the reduction for the aldol (table 10). The reaction proceeded smoothly at room temperature to give the 1,4-reduced product.
as expected giving full conversion observed by TLC and $^1$H NMR in 24 hours using anhydrous cyclohexane as the solvent (table 10). Keeping the reaction under argon, benzaldehyde was then added to the reaction mixture. The diastereomeric ratios for the selected substrates showed excellent selectivity (up to 99% ee). The substrate that showed lowest selectivity compared to the other substrates examined was substrate 2b, but still showed high selectivity (table 10, entry 2). Overall, we were pleased to see that the results were as what were what we had expected, giving high enantioselectivity for the both the major and the minor diastereomers, with the exception being table 10, entry 2. For this case, the enantioselectivity of the minor enantiomer was only 52%. The substrates that had strong electron withdrawing substituents (table 10, entry 3) as well as weak electron withdrawing substituents (table 10, entry 6) gave the highest enantioselectivities for both the major and the minor diastereomer with very high diastereoselectivity (table 10, entry 3, and 66:1 dr) and (table 10, entry 6, 99:1 dr). Overall, the stereospecificity of the boron-mediated aldol in conjunction with the high enantioselectivity of the reduction step, would allow for the formation of three stereocenters with excellent enantioselectivity and diastereoselectivity.

3.4 Summary

The aldol reaction is one of the most well-known and used reactions in organic synthesis. Due its great synthetic utility and atom economy, the aldol reaction has assisted in the design and development of chiral catalysts. The use of a one-pot method to achieve an enantioselective tandem reaction is synthetically beneficial to assemble optically active tertiary alcohols. Using our boro-phosphate catalyzed 1,4-reduction of α, β-unsaturated enones methodology, we were able to sequentially react the enolate intermediate with benzaldehyde and obtain the aldol product. The reductive aldol products were obtained in good to excellent diastereomeric ratios (up to 99:1 dr). Further investigations are underway in order to provide stereochemical evidence and mechanistic rational.
3.5 Experimental
3.5.1 General considerations

Unless otherwise noted, all reactions were carried out in flame-dried screw-cap test tubes and were allowed to proceed under a dry argon atmosphere with magnetic stirring. Anhydrous solvents were purchased from commercial sources and used without further purification. Ketones were purchased from commercial sources and used without further purification. PA catalysts were prepared from chiral BINOL according to the known literature procedure. Thin layer chromatography was performed on Merck TLC plates (silica gel 60 F254). Ketones were purchased from commercial sources without any further purification. Thin layer chromatography was performed on Merck TLC plates (silica gel 60 F254). Visualization was accomplished using UV light (256 nm), p-anisaldehyde or potassium permanganate stain as indicator. Flash column chromatography was performed with Merck silica gel (230-400 mesh). Analytical Autopol IV polarimeter (589) using a 700-µL cell with a path length of 1-dm. $^1$H NMR and $^{13}$C NMR were recorded on a Varian Inova-400 spectrometer with chemical shifts reported relative to tetramethysilane (TMS). Data were recorded as follows: chemical shift in ppm from internal tetramethysilane on the G scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. All the compounds were known compounds and were characterized by comparing their $^1$H NMR and $^{13}$C NMR values those reported in the literature. Enantioselectivity was determined using a Varian Prostar HPLC and Chiralcel AD-H, OD-H, or AS-H chiral columns. All reactions were conducted in triplicate to ascertain reproducibility.
Compound (3.2a):

(2R, 3R)-2-((R)-hydroxy (phenyl) methyl)-1, 3-diphenylbutan-1-one

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 96/4, 0.8 mL/min), tR = 18.51 min (anti, major), 27.18 min (syn, major), 34.87 min (syn, minor), 42.98 min (anti, minor). $^1$HNMR (400 MHz, CDCl$_3$): $\delta$ 7.83 (dd, J = 7.4, 1.4 Hz, 2H), 7.47 – 7.24 (m, 11H), 7.24 – 7.14 (m, 2H), 5.84 (d, J = 10.6 Hz, 1H), 3.66 (dd, J = 10.8, 2.2 Hz, 1H), 3.29 (qd, J = 6.5, 2.1 Hz, 1H), 1.37 (d, J = 6.6 Hz, 3H), 1.28 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.28, 144.55, 142.77, 136.46, 132.13, 128.53, 128.40, 128.19, 128.05, 127.98, 127.77, 127.43, 126.03, 74.20, 54.88, 39.57, 20.60.

Compound (3.2b):

(2R, 3R)-2-((R)-hydroxy (phenyl) methyl)-3-(naphthalen-2-yl)-1-phenylbutan-1-one

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 96/4, 0.8 mL/min), tR = 18.83 min (anti, major), 11.89 min (syn, major), 16.61 min (syn, minor), 8.93 min (anti, minor). $^1$HNMR (400 MHz, CDCl$_3$): $\delta$ 7.85 – 7.64 (m, 6H), 7.45 – 7.15 (m, 11H), 5.42 (d, J = 10.1 Hz, 1H), 3.66 (dd, J = 10.0, 5.9 Hz, 1H), 3.31 (p, J = 6.5 Hz, 1H), 1.45 (s, 1H), 1.37 (d, J = 6.4 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.30, 146.09, 143.12, 137.01, 134.98,
Compound (3.2c):

(2R, 3R)-2-((R)-hydroxy (phenyl)methyl)-1-phenyl-3-(4-(trifluoromethyl)phenyl)butan-1-one

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 96/4, 0.8 mL/min), tR = 19.287 min (anti, major), 26.697 min (syn, major), 32.304 min (syn, minor). $^1$HNMR (400 MHz, CDCl$_3$): $\delta$ 7.76 (dd, $J = 7.5$, 1.2 Hz, 2H), 7.37 – 7.18 (m, 9H), 7.73 – 5.55 (m, 13H), 7.37 – 5.55 (m, 10H), 5.65 (d, $J = 1.6$ Hz, 1H), 4.43 (s, 1H), 3.66 (t, $J = 1.5$ Hz, 1H), 3.14 (qd, $J = 6.4$, 1.5 Hz, 1H), 1.36 (d, $J = 6.5$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.28, 146.57, 142.77, 136.46, 132.35, 132.13, 131.91, 131.70, 128.53, 128.40, 128.19, 127.77, 127.60, 127.43, 127.07, 127.04, 127.00, 126.97, 126.27, 126.21, 126.15, 126.10, 125.51, 123.41, 121.36, 74.16, 54.92, 39.84, 20.57.

Compound (3.2d):

(2R,3R)-2-((R)-hydroxy(phenyl)methyl)-3-(4-methoxyphenyl)-1-phenylbutan-1-one

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 96/4, 0.8 mL/min), tR = 37.46 min (anti, major), 32.34 min (syn, major), 26.78 min (syn, minor),
22.06 min (anti, minor). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.81 (dd, $J = 7.4, 1.3$ Hz, 2H), 7.48 – 7.27 (m, 5H), 7.27 – 7.11 (m, 5H), 6.99 (d, $J = 7.5$ Hz, 2H), 5.55 (d, $J = 9.2$ Hz, 1H), 3.80 (s, 3H), 3.66 (dd, $J = 12.1, 9.2$ Hz, 1H), 3.12 (dq, $J = 12.8, 6.5$ Hz, 1H), 1.30 (d, $J = 6.6$ Hz, 3H), 0.30 (s, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 206.28, 157.06, 142.77, 136.72, 136.46, 132.13, 128.53, 128.40, 128.19, 127.77, 127.57, 127.43, 114.04, 74.20, 56.10, 54.99, 39.57, 20.60.

Compound (3.2e):

(2R,3R)-1-(4-fluorophenyl)-2-((R)-hydroxy(phenyl)methyl)-3-phenylbutan-1-one

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 96/4, 0.8 mL/min), tR = 7.018 min (anti, major), 10.226 min (syn, major), 13.320 min (syn, minor), 16.172 min (anti, minor). $^1$H NMR (400 MHz, CDCl$_3$): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.67 – 7.58 (m, 2H), 7.34 – 6.53 (m, 12H), 5.31 (d, $J = 1.8$ Hz, 1H), 3.66 (dd, $J = 4.1, 1.9$ Hz, 1H), 3.43 (qd, $J = 6.6, 4.1$ Hz, 1H), 1.87 (s, 1H), 1.41 (d, $J = 6.6$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 217.91, 206.28, 167.86, 165.77, 144.55, 142.77, 133.64, 133.61, 130.88, 130.82, 128.19, 128.05, 127.98, 127.77, 127.43, 126.03, 115.05, 114.84, 74.20, 54.96, 39.52, 20.59.
Compound (3.2f):

(2R,3R)-3-(4-chlorophenyl)-2-((R)-hydroxy(phenyl)methyl)-1-phenylbutan-1-one

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/iPrOH = 96/4, 0.8 mL/min), tR = 37.458 min (anti, major), 32.373 min (syn, major), 26.781 min (syn, minor), 22.056 min (anti, minor). $^1$HNMR (400 MHz, CDCl$_3$): $\delta$ 8.66 – 5.50 (m, 15H), 5.53 (d, $J$ = 1.6 Hz, 1H), 5.53 (d, $J$ = 1.6 Hz, 1H), 3.66 (d, $J$ = 1.3 Hz, 1H), 3.40 (q, $J$ = 6.4 Hz, 1H), 1.87 (s, 1H), 1.42 (d, $J$ = 6.6 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.20, 142.80, 142.62, 135.98, 132.13, 131.69, 129.20, 128.52, 128.40, 128.19, 128.17, 127.77, 127.43, 74.20, 54.96, 39.57, 20.59.
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Appendix I

Preparation and characterization of catalysts

General Considerations

All reactions involving air or moisture sensitive reagents were performed under an argon in flame-dried glassware using standard syringe, cannula, or Schlenk techniques. Anhydrous tetrahydrofuran (THF), diethyl ether (Et₂O) and dichloromethane (CH₂Cl₂) were purchased from commercial sources and used without purification, unless otherwise stated. Prior to use, the potassium carbonate (K₂CO₃) was flame dried to remove moisture. Chloromethyl methyl ether was prepared according to the literature. (R)-BINOL and (S)-BINOL were purchased from commercial sources without any further purification. Thin layer chromatography was performed on Merck TLC plates (silica gel 60 F₂₅₄). Visualization was accomplished using UV light (256 nm), p-anisaldehyde or potassium permanganate stain as indicator. Flash column chromatography was performed with Merck silica gel (230-400 mesh). Analytical Autopol IV polarimeter (+589) using a 700-μL cell with a path length of 1-dm. ¹H NMR and ¹³C NMR were recorded on a Varian Inova-400 spectrometer with chemical shifts reported relative to tetramethylsilane (TMS). Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the G scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. All the compounds were known compounds and were characterized by comparing their ¹H NMR and ¹³C NMR values those reported in the literature.
Synthesis of \((R)\) 2,2'-bis(methoxymethoxy)-1,1'-binaphthalene:

\[(R)-2,2'-\text{bis(methoxymethoxy)}-1,1'-\text{binaphthalene} \text{ was prepared according to literature procedures.}\]  

\[
\begin{array}{c}
\text{OH} \\
\text{O} \\
\text{OMOM} \\
\end{array}
\xrightarrow{1. \text{NaH, THF, } 0^\circ\text{C } \xrightarrow{2. \text{MOM-Cl, } 0^\circ\text{C } \xrightarrow{\text{rt}}}
\begin{array}{c}
\text{OMOM} \\
\end{array}
\]

Synthesis of 3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene: To a stirred solution of 2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (17 mL/1 mmol) suspended in anhydrous Et₂O (20 mL) at -78 °C was added a solution of n-butyllithium (2.52 M in hexanes; 3 equiv.) and was stirred for 1 h. The mixture was then allowed to warm to room temperature and stirred for 3 h at which point the reaction mixture was re-cooled to -78 °C and iodine (3 equiv.) as a solid was added in one portion. The reaction mixture was stirred for 1 h then allowed to warm slowly to room temperature over four hours. Saturated aqueous ammonium chloride (40 mL) was added to the reaction mixture and the organic and aqueous phases separated. The aqueous phase was extracted with ethyl acetate (3 x 30 mL) and the combined organic phases were then washed with aqueous sodium sulfite (10 percent w/v; 30 mL), de-ionized water (10 mL) and brine (10 mL). The organic
layers were then dried over anhydrous sodium sulfate and dried in vacuo. The residue was purified by flash column chromatography (15:1 = silica gel/material, 15:1 hexane/EtOAc). The eluent was collected in Fisherbrand™ disposable borosilicate glass tubes with plain end (Cat. No. 14-961-29 16x100mm) and the corresponding fractions were visualized by TLC using UV light (256 nm). The fractions containing the desired product were then collected were concentrated in vacuo.

**General procedure for the synthesis of 3,3'-Diaryl-2,2'-Bis(methoxymethoxy)-1,1'-binaphthyls:** A mixture of DME (6.7mL/mmol) and 2M Na₂CO₃ (5.2 equiv.) was degassed with argon for 30 minutes prior to use in the reaction. The aryl boronic acid (3.5 equiv.), 3, 3'-diiodo-2, 2'-bis (methoxymethoxy)-1,1'-binaphthalene (1 equiv.), and tetrakis (triphenylphosphine) palladium (0) (1 mol%) were placed in a flame dried reaction flask. The degassed solvents were added to the mixture of solids via cannula, the reaction mixture was heated to reflux and monitored by TLC (1:1 DCM/hexane). Upon completion, the reaction mixture was allowed to cool to room temperature, diluted with DCM. Saturated aqueous ammonium chloride (40 mL) was added to the reaction mixture and the organic and aqueous phases separated and the washed brine (2 x 10 mL). The organic phase was dried over Na₂SO₄ and concentrated in vacuo. The crude product was purified by column chromatography (15:1 silica gel/material, 1:1 DCM/hexane). The eluent was collected in Fisherbrand™ disposable borosilicate glass tubes with plain end (Cat. No. 14-961-29 16x100mm) and the corresponding fractions were visualized by TLC using UV light (256 nm). The fractions containing the desired product were then collected were concentrated in vacuo to
give a light yellow solid in 98% yield. The spectroscopic data was in agreement with the reported literature values.\textsuperscript{84}

\textbf{Synthesis of 3,3'-diaryl-[1,1'-binaphthalene]-2,2'-diol:}

The (2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl) diaryl (1 equiv.) was suspended in a 2:1 MeOH/toluene solution. To the mixture was added 12N HCl (8.45 equiv.) and let stir for 6 hours a reflux. The reaction was diluted with EtOAc and organic phase was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. The product was used in the next step without further purification.

\textbf{Synthesis of 2,6-diaryl-4-hydroxydinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide:}

The 3, 3'-diaryl-[1, 1'-binaphthalene]-2, 2'-dil (1 equiv.) was suspended in pyridine (2.56mL/mmol) under argon. The reaction was cooled to 0°C and phosphorous oxychloride (2 equiv.) was added slowly dropwise at room temperature while stirring [\textbf{CAUTION: Phosphorus oxychloride may ignite other combustible materials (wood, paper, oil, etc.). Phosphorus oxychloride reacts violently with water}]. The suspension was heated to 95 °C for 12h hours and the let cool to room temperature, then cooled to 0°C. Deionized water (2 mL) was then added to the reaction mixture and the solution heated to 100 °C for 1 hour. Once again, the reaction was cooled to room temperature. DCM was used to extract the organic layer (3 x 30 mL) and the
combined organic phases were then washed de-ionized water (10 mL) and brine (10 mL), and the pyridine was removed by washing with 6N HCl (10 mL). The organic phase was dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography (15:1= silica gel/material, 98.5:1.5 DCM/MeOH). The eluent was collected in Fisherbrand™ disposable borosilicate glass tubes with plain end (Cat. No. 14-961-29 16x100mm) and the corresponding fractions were visualized by TLC using UV light (256 nm). The fractions containing the desired product were then collected were concentrated in vacuo. $^1$HNMR was used to determine the compounds isolated in the fractions. The product obtained was re-acidified by dissolving the solid in DCM and extracting the organic phase (3 x 10 mL) with 6N HCl. The combined aqueous layers were then washed with DCM (3 x 10 mL). The organic phase was dried over Na$_2$SO$_4$ and concentrated in vacuo.
Appendix II

Preparation and characterization of reaction substrates

General Considerations

Unless otherwise noted, all reactions were carried out under argon atmosphere in flame-dried glassware using standard syringe, cannula, and septa apparatus. Prior to use, the K$_2$CO$_3$ was flame dried to remove moisture. Anhydrous solvents and reagents were purchased from commercial sources and used without purification, unless otherwise stated. Ketones were purchased from commercial sources without any further purification. Thin layer chromatography was performed on Merck TLC plates (silica gel 60 F$^{254}$). Visualization was accomplished using UV light (256 nm), ceric ammonium molybdate, p-anisaldehyde, or potassium permanganate or as indicator. Flash column chromatography was performed with Merck silica gel (230-400 mesh). $^1$H NMR and $^{13}$C NMR were recorded on a Varian Inova-400 spectrometer with chemical shifts reported relative to tetramethylsilane (TMS). Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the G scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. All the compounds were known compounds and were characterized by comparing their $^1$H NMR and $^{13}$C NMR values those reported in the literature.
General procedure for the synthesis of ethyl esters

To a flame dried flask with magnetic stirrer was added sodium hydride (NaH) 60% dispersion in mineral oil [**CAUTION: Upon reaction of sodium hydride dispersion with water, H₂ and NaOH are formed. This hydrolysis reaction is vigorous and exothermic**] (1.75 equiv.) in anhydrous THF (12mL). The solution was cooled to 0°C and the triethyl phosphonoacetate (1.5 equiv.) was added slowly dropwise. The mixture was stirred at 0°C for 30 minutes. The ketone was then added and the mixture and was allowed to reflux, while monitored by TLC (hexanes/EtOAc 20:1). Upon completion, the reaction was quenched with a solution of saturated aqueous NaHCO₃ (100 mL) was added and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine (100 mL), dried with anhydrous Na₂SO₄ and concentrated in vacuo. The crude product was then purified by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The eluent was collected in Fisherbrand™ disposable borosilicate glass tubes with plain end (Cat. No. 14-961-29 16x100mm) and the corresponding fractions collected were concentrated in vacuo to give the desired ethyl ester.
**Ethyl (E/Z) 3-phenylbut-2-enoate (1aa):** Following the general procedure for the synthesis of ethyl esters, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a pale yellow oil in 93 % yield. The spectroscopic data was consistent with the literature.\(^{28}\) **E-isomer:** \(^{1}\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) 7.44 (m, 2 H), 7.33 (m, 3 H), 6.12 (s, 1 H), 4.19 (q, \(J = 7.1\) Hz, 2 H), 2.56 (s, 3 H), 1.29 (t, \(J = 7.1\) Hz, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)), \(\delta\) 166.8, 155.4, 142.1, 128.9, 128.4, 126.2, 117.0, 59.7, 17.8, 14.2; HRMS calculated for \([M + H]^+\)\(\text{C}_{12}\text{H}_{15}\text{O}_2\), 191.1072; found, 191.1065. **Z-isomer:** \(^{1}\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) 7.3 (m, 3 H), 7.18 (d, \(J = 6.0\) Hz, 2 H), 5.89 (s, 1 H), 3.97 (q, \(J = 7.1\) Hz, 2 H), 2.15 (s, 3 H), 1.06 (t, \(J = 7.1\) Hz, 3 H).

**ethyl (E)-3-(naphthalen-2-yl) but-2-enoate (1ab):** Following the general procedure for the synthesis of ethyl esters, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless oil, yield 97%. The spectroscopic data was consistent with the literature.\(^{85}\) \(^{1}\)HNMR (400 MHz, CDCl\(_3\)): \(d\) 7.93–7.79 (m,4H), 7.60–7.56(m,1H),7.50–7.45 (m, 2H), 6.28 (s, 1H), 4.27–4.20 (q,2H, \(J = 7.2\) Hz), 2.68 (s, 3H), 1.35–1.30 (t, 3H, \(J =7.2Hz\));\(^{13}\)C MR(100 MHz, CDCl\(_3\)): \(d\) 155.7, 139.9, 134.0, 133.6, 129.0, 128.7, 128.1, 127.2, 127.0, 126.4, 124.5, 118.0, 60.4, 18.4, 14.9. HRMS calcd for \([M + H]^+\)\(\text{C}_{16}\text{H}_{17}\text{O}_2\), 241.1228; found, 241.1230.
ethyl (\(E\))-3-(naphthalen-1-yl)but-2-enoate (1ac): Following the general procedure for the synthesis of ethyl esters, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless oil, yield 97%. The spectroscopic data was consistent with the literature.\(^8\) \(^6\)^1HNMR (400 MHz, CDCl\(_3\)): \(\delta \) 7.93 (dt, \(J = 7.3, 1.4 \) Hz, 1H), 7.89 – 7.72 (m, 2H), 7.68 (dd, \(J = 7.4, 1.5 \) Hz, 1H), 7.60 (t, \(J = 7.5 \) Hz, 1H), 7.51 – 7.41 (m, 2H), 6.54 (d, \(J = 0.6 \) Hz, 1H), 4.24 (q, \(J = 6.0 \) Hz, 2H), 2.23 (d, \(J = 0.6 \) Hz, 3H), 1.39 (t, \(J = 6.0 \) Hz, 3H). \(^1\)^3C NMR (100 MHz, CDCl\(_3\)) \(\delta \) 168.22, 153.26, 138.95, 131.85, 128.59, 128.33, 127.64, 125.95, 125.55, 125.31, 124.31, 121.97, 118.23, 61.16, 18.26, 14.69.

ethyl (\(E\))-3-(4-methoxyphenyl)but-2-enoate (1ad): Following the general procedure for the synthesis of ethyl esters, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless oil, yield 80%. The spectroscopic data was consistent with the literature.\(^8\) \(^7\)^1HNMR (400 MHz, CDCl\(_3\)): \(\delta \) 7.43–7.46(m, 2H), 6.87–6.90 (m, 2H), 6.10–6.11 (d, 1H, \(J = 1.2 \) Hz), 4.17–4.24(q, 2H, \(J = 7.2 \) Hz), 3.81 (s, 3H), 2.56 (d, 3H, \(J = 1.2 \) Hz ), 1.28–1.33 (t,3H, \(J = 7.2Hz\));\(^1\)\(^3\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta \) 167.5, 160.9, 155.3,134.8, 128.1, 115.8, 114.3, 60.2, 55.8, 18.1, 14.9; HRMS calcd for [M + H]\(^+\) \(\text{C}_{13}\text{H}_{17}\text{O}_3\), 221.1177; found, 221.1179.
ethyl (E)-3-(4-fluorophenyl)but-2-enoate (1ae): Following the general procedure for the synthesis of ethyl esters, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless oil in 80% yield. The spectroscopic data was consistent with the literature.\textsuperscript{88} \textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.44–7.48 (m, 2H), 7.02–7.08 (m, 2H), 6.09 (d, 1H, \(J = 1.2\) Hz), 4.18–4.25 (q,2H, \(J = 7.2\) Hz), 2.55–2.56 (d, 3H, \(J = 1.2\) Hz), 1.29–1.34 (t, 3H, \(J = 7.2\) Hz); \textsuperscript{13}CNMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 167.2, 165.4, 162.1, 154.7, 138.7, 128.6, 117.6, 60.4, 18.4, 14.8; HRMS calcd for [M + H]\(^+\) \(C_{12}H_{14}FO_2\) 209.0971; found, 209.0969.

ethyl (E)-3-(4-(trifluoromethyl)phenyl)but-2-enoate (1af): Following the general procedure for the synthesis of ethyl esters, purification flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless oil, yield 96%. The spectroscopic data was consistent with the literature.\textsuperscript{89} \textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.55–7.64 (m,4H), 6.15 (d, 1H, \(J = 1.5\) Hz), 4.20–4.27 (q, 2H, \(J = 7.2\) Hz), 2.58 (d, 3H, \(J = 1.2\) Hz), 1.30–1.35 (t, 3H, \(J = 7.2\) Hz); \textsuperscript{13}CNMR (100MHz, CDCl\textsubscript{3}): \(\delta\) 166.9, 154.2, 146.3, 127.1, 126.2, 125.9, 122.6, 119.5, 60.6, 18.4, 14.8; HRMS calcd for [M + H]\(^+\) \(C_{13}H_{14}F_3O_2\), 259.0936; found, 259.0932.
ethyl (E)-3-(4-chlorophenyl)but-2-enoate (1ag): Following the general procedure for the synthesis of ethyl esters, purification by column chromatography flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless oil, yield 82%. The spectroscopic data was consistent with the literature.\textsuperscript{90} \textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}): d 7.32–7.42(m, 4H), 6.10–6.12 (q, 1H, J = 1.2 Hz), 4.18–4.25 (q, 2H, J = 7.2 Hz), 2.55 (d, 3H, J = 1.2 Hz), 1.29–1.34 (t, 3H, J = 7.2 Hz); \textsuperscript{13}CNMR (100 MHz, CDCl\textsubscript{3}): d 167.1, 154.5, 141.1, 135.5, 129.2, 128.1, 118.0,60.4, 18.3, 14.8; HRMS calcd for [M + H]\textsuperscript{+} C\textsubscript{12}H\textsubscript{14}ClO\textsubscript{2}, 225.0677; found, 225.0679.

![1ah](image)

ethyl (E)-3-(4-cyanophenyl)but-2-enoate (1ah): Following the general procedure for the synthesis of ethyl esters, purification by column chromatography flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless oil, yield 51%. The spectroscopic data was consistent with the literature.\textsuperscript{91} \textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}): δ = 7.68 – 7.64 (m, 2H), 7.56 – 7.53 (m, 2H), 6.14 (q, J = 1.3 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.55 (d, J = 1.3 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H) ppm; \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ = 166.3, 153.1, 146.8, 132.5, 127.1, 119.8, 118.6, 112.6, 60.4, 17.9, 14.4.

![1ai](image)

ethyl (E)-3-phenylpent-2-enoate (1ai): Following the general procedure for the synthesis of ethyl esters, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless oil, yield 92%. The spectroscopic
data was consistent with the literature. \(^{92}\) \(^{1}\)HNMR (400 MHz, CDCl\(_3\)): \(\delta = 7.48 – 7.33\) (m, 5H), 6.01 (s, 1H), 4.21 (q, \(J = 7.1\) Hz, 2H), 3.11 (q, \(J = 7.5\) Hz, 2H), 1.32 (t, \(J = 7.1\) Hz, 3H), 1.08 (t, \(J = 7.5\) Hz, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 166.6, 162.2, 141.3, 129.0, 128.6, 126.8, 116.9, 60.0, 24.5, 14.5, 13.7\).

**ethyl \((E)\)-4-methyl-3-phenylpent-2-enoate (1aj):** Following the general procedure for the synthesis of ethyl esters, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless oil, yield 86%. The spectroscopic data was consistent with the literature. \(^{93}\) \(^{1}\)HNMR (400 MHz, CDCl\(_3\)): \(\delta = 7.35 – 7.28\) (m, 3H), 7.22 – 7.18 (m, 2H), 5.70 (s, 1H), 4.20 (q, \(J = 7.1\) Hz, 2H), 4.16 – 4.06 (m, 1H), 1.30 (t, \(J = 7.1\) Hz, 3H), 1.09 (d, \(J = 7.0\) Hz, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 167.2, 166.4, 140.9, 127.9, 127.8, 127.7, 118.7, 60.0, 29.7, 21.5, 14.4\).

**ethyl \((E)\)-3-cyclohexyl-3-phenylacrylate (1ak):** Following the general procedure for the synthesis of ethyl esters, purification by column chromatography flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless oil, yield 33%. The spectroscopic data was consistent with the literature. \(^{94}\) \(^{1}\)HNMR (400 MHz, CDCl\(_3\)): \(\delta = 7.37 – 7.28\) (m, 3H), 7.12 – 7.05 (m, 2H), 5.83 (d, \(J = 1.0\) Hz, 1H), 3.95 (q, \(J = 7.1\) Hz, 2H), 2.31 – 2.18 (m, 1H), 1.86 – 1.72 (m, 4H), 1.33 – 1.08 (m, 6H), 1.03 (t, \(J = 7.1\) Hz,
3H); $^{13}$CNMR (100 MHz, CDCl$_3$): $\delta$ 166.7, 164.6, 140.7, 127.8, 127.3, 127.3, 116.1, 59.8, 47.5, 31.7, 26.6, 26.2, 14.0.

**ethyl (E)-3,4,4-trimethylpent-2-enoate (1al):** Following the general procedure for the synthesis of ethyl esters, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless oil, yield 70%. The spectroscopic data was consistent with the literature.$^{95}$ $^1$HNMR (400 MHz, CDCl$_3$): $\delta$ = 5.73 (q, J = 1.2 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 2.16 (d, J = 1.2 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.10 (s, 9H); $^{13}$CNMR (100 MHz, CDCl$_3$): $\delta$ 167.7, 167.4, 113.1, 59.7, 38.1, 28.7, 15.3, 14.5.

**ethyl (E)-3-methyl-5-phenylpent-2-enoate (1am):** Following the general procedure for the synthesis of ethyl esters, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless oil, yield 94%. The spectroscopic data was consistent with the literature.$^{96}$ $^1$HNMR (400 MHz, CDCl$_3$): $\delta$ 7.31 (m, 2H); 7.21 (m, 3H); 5.71 (m, 1H); 4.16 (q, 2H, J = 7.1 Hz); 2.80 (m, 2H); 2.46 (m, 2H); 2.23 (d, 3H, J = 1.2 Hz); 1.29 (t, 3H, J = 7.1 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.7, 158.9, 141.0, 128.4, 128.2, 126.0, 115.9, 59.4, 42.6, 33.9, 18.9, 14.3; HRMS calculated for C$_{14}$H$_{19}$O$_2$, 219.1402, found 219.1399.
Synthesis of Weinreb amides

\[
\begin{array}{c}
\text{R}_1 \text{C} = \text{O} \quad \text{R}_2 \\
\text{R}_1 \text{C} = \text{O} \quad \text{R}_2 \\
\end{array}
\]

To a flame dried flask with magnetic stirrer was added \( N, O \)-dimethylhydroxyamine HCl (2 equiv.) suspended in anhydrous THF (12mL). The ester obtained from reaction 1 (1 equiv.) was added and the mixture was cooled to -5°C. Once cooled, \( i \)-PrMgCl (4.3 equiv.) \textbf{[CAUTION: Flammable liquid. Water reactive. In case of fire, do not use water or carbon dioxide]} was slowly added dropwise and the reaction was allowed to stir and monitored by TLC (hexanes/EtOAc 20:1) until completion. Saturated aqueous ammonium chloride (40 mL) was added to the reaction mixture and the organic and aqueous phases separated. The aqueous phase was extracted with ethyl acetate (3 x 30 mL) and the combined organic phases were then dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The crude product was then purified by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The eluent was collected in Fisherbrand™ disposable borosilicate glass tubes with plain end (Cat. No. 14-961-29 16x100mm) and the corresponding fractions collected were concentrated in vacuo to give the desired Weinreb amide.
(E)-N-methoxy-N-methyl-3-phenylbut-2-enamide (1ba): Following the general procedure for the synthesis of Weinreb amides, purification flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a pale yellow liquid, 98%. The spectroscopic data was consistent with the literature.\(^\text{97}\) \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.51-7.45\) (m, 2H), 7.41-7.33 (m, 3H), 6.57 (s, 1H), 3.71 (s, 3H), 3.27 (s, 3H), 2.51 ppm (d, J=1 Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 168.0, 152.3, 143.0, 128.6, 128.5, 126.3, 116.0, 61.6, 32.4, 18.0\). HRMS calculated for C\(_{12}\)H\(_{15}\)NO\(_2\), 235.1208, found 235.1214.

(E)-N-methoxy-N-methyl-3-(naphthalen-2-yl) but-2-enamide (1bb): Following the general procedure for the synthesis of Weinreb amides, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a pale yellow liquid, 99% yield. The spectroscopic data was consistent with the literature.\(^\text{93}\) \(^1\)HNMR (400 MHz, CDCl\(_3\)) \(\delta 7.91\) (s, 1H), 7.85-7.78 (m, 3H), 7.59 (d, J = 11.2 Hz, 1H), 7.49-7.42 (m, 2H), 6.72 (s, 1H), 3.68 (s, 3H), 3.27 (s, 3H), 2.64 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 164.61, 147.28, 139.74, 134.51, 134.01, 129.74, 129.69, 128.21, 126.99, 126.50, 124.13, 123.41, 122.90, 57.58, 34.18, 18.05\). HRMS calculated for C\(_{16}\)H\(_{17}\)NO\(_2\): 255.1258, found 255.1263.
\((E)\)-\(N\)-methoxy-\(N\)-methyl-3-\(\text{naphthalen}-1-\text{yl}\) but-2-enamide (1bc): Following the general procedure for the synthesis of Weinreb amides, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a pale yellow liquid, 61% yield. The spectroscopic data was consistent with the literature.\(^{98}\)\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.97-7.94 (m, 1H), 7.85-7.83 (m, 1H), 7.79-7.76 (m, 1H), 7.48-7.41 (m, 3H), 7.31-7.29 (m, 1H), 6.42 (s, 1H), 3.63 (s, 3H), 3.27 (s, 3H), 2.60 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 167.5, 153.6, 142.6, 133.6, 130.2, 128.3, 127.7, 126.0, 125.8, 125.3, 125.1, 124.1, 118.9, 61.4, 32.1, 21.4. HRMS calculated for C\(_{16}\)H\(_{17}\)NO\(_2\): 255.1259, found 255.1258.

\((E)\)-\(N\)-methoxy-3-\(\text{4-methoxyphenyl}\)-\(N\)-methylbut-2-enamide (1bd): Following the general procedure for the synthesis of Weinreb amides, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a pale yellow liquid, 89% yield. The spectroscopic data was consistent with the literature.\(^{98}\)\(^1\)NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.45 (dd, \(J = 6.4, 1.6 \text{ Hz}, 2\text{H}\)), 6.90 (dd, \(J = 6.4, 1.6 \text{ Hz}, 2\text{H}\)), 6.55 (s, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.26 (s, 3H), 2.52 (d, \(J = 1.2 \text{ Hz}, 3\text{H}\)) ppm; \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 168.1, 160.0, 151.7, 135.0, 127.5, 114.1, 113.7, 61.5, 55.2, 32.1, 17.7. HRMS calculated for C\(_{14}\)H\(_{19}\)NO\(_3\): 235.1208, found 235.1214.
(E)-3-(4-fluorophenyl)-N-methoxy-N-methylbut-2-enamide (1be): Following the general procedure for the synthesis of Weinreb amides, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a pale yellow liquid, 70% yield. The spectroscopic data was consistent with the literature. HNMR (400 MHz, CDCl$_3$) δ 7.48-7.44 (m, 2H), 7.08-7.03 (m, 2H), 6.53 (s, 1H), 3.71 (s, 3H), 3.27 (s, 3H), 2.51 (d, J = 1.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.1, 150.2, 138.3, 127.4, 115.4, 114.7, 60.9, 31.6, 17.3. HRMS calculated for C$_{12}$H$_{14}$FNO$_2$, 239.0713, found 239.0717.

(E)-N-methoxy-N-methyl-3-(4-(trifluoromethyl) phenyl) but-2-enamide (1bf): Following the general procedure for the synthesis of Weinreb amides, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a pale yellow liquid, 81% yield The spectroscopic data was consistent with the literature. HNMR (400 MHz, CDCl$_3$) δ 7.64-7.58 (m, 4H), 6.63 (s, 1H), 3.73 (s, 3H), 3.28 (s, 3H), 2.54 (d, J = 1.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.1, 150.0, 146.2, 130.0, 126.3, 125.0, 123.8, 117.6, 61.2, 31.8, 17.5. HRMS calculated for C$_{13}$H$_{14}$F$_3$NO$_2$, 239.0713, found 239.0717.
(E)-3-(4-chlorophenyl)-N-methoxy-N-methylbut-2-enamide (1bg): Following the general procedure for the synthesis of Weinreb amides, purification flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a pale yellow liquid, 66% yield. The spectroscopic data was consistent with the literature. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.42-7.39 (m, 2H), 7.31-7.29 (m, 2H), 6.57 (s, 1H), 3.70 (s, 3H), 3.25 (s, 3H), 2.49 (s, 3H) ppm; $^{13}$CNMR (100 MHz, CDCl$_3$) δ 166.9, 150.0, 140.6, 133.8, 128.0, 127.0, 115.8, 60.9, 31.6, 17.1 ppm; HRMS calculated for C$_{12}$H$_{14}$ClNO$_2$: 239.0611, found 239.0718.

(E)-3-(4-cyanophenyl)-N-methoxy-N-methylbut-2-enamide (1bh): Following the general procedure for the synthesis of Weinreb amides, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a pale yellow liquid, 70% yield. The spectroscopic data was consistent with the literature. $^1$H NMR (100 MHz, CDCl$_3$) δ 7.74 (q, $J$ = 7.6 Hz, 4H), 6.22 (d, $J$ = 1.0 Hz, 1H), 3.84 (s, 3H), 3.37 (s, 3H), 2.05 (d, $J$ = 0.9 Hz, 3H). $^{13}$CNMR (100 MHz, CDCl$_3$) δ 206.04, 195.10, 164.61, 159.18, 158.39, 147.30, 143.53, 132.61, 127.14, 122.86, 119.12, 109.07, 81.03, 57.58, 48.04, 34.18, 18.05, 2.14, 19.59.
**(E)-N-methoxy-N-methyl-3-phenylpent-2-enamideate (1bi):** Following the general procedure for the synthesis of Weinreb amides, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a pale yellow liquid, 53% yield. The spectroscopic data was consistent with the literature.\(^{28}\)\(^1\)HNMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.44-7.41 (m, 2H), 7.36-7.27 (m, 3H), 6.46 (s, 1H), 3.63 (s, 3H), 3.22 (s, 3H), 3.06 (q, J = 7.2 Hz, 2H), 1.07 (t, J = 7.6 Hz, 3H) ppm; \(^{13}\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 166.8, 158.0, 141.1, 127.9, 127.8, 126.1, 115.1, 60.8, 31.5, 23.7, 13.0 ppm; HRMS calculated for C\(_{13}\)H\(_{17}\)NO\(_2\): 219.1260, found 219.1599.

**(E)-N-methoxy-N, 4-dimethyl-3-phenylpent-2-enamide (1bj):** Following the general procedure for the synthesis of Weinreb amides, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a pale yellow liquid, 70% yield. The spectroscopic data was consistent with the literature.\(^{85}\)\(^1\)HNMR (400 MHz, CDCl\(_3\)) \(\delta\) = 7.36-7.30 (m, 3H), 7.27-7.20 (m, 2H), 6.09 (br s, 1H), 3.90-4.00 (m, 1H), 3.68 (s, 3H), 3.25 (s, 3H), 1.40 (d, J = 7.1 Hz, 6H).
(E)-3-cyclohexyl-N-methoxy-N-methyl-3-phenylacrylamide (1bk): Following the general procedure for the synthesis of Weinreb amides, purification by flash column chromatography (silica gel/material = 15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless oil, 60% yield. The spectroscopic data was consistent with the literature. 

$^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 7.30–7.35 (m, 3H), 7.18–7.21 (m, 2H), 6.07 (s, 1H), 3.67 (s, 3H), 3.25 (s, 3H), 1.61–1.77 (m, 5H), 1.33–1.43 (m, 2H), 1.19–1.29 (m, 3H), 1.02–1.10 (m, 1H); $^{13}$CNMR (100 MHz, CDCl$_3$) $\delta$ 142.1, 127.8, 127.6, 127.1, 117.4, 61.4, 40.8, 32.6, 31.7, 26.4, 26.0.

(E)-N-methoxy-N, 3, 4, 4-tetramethylpent-2-enamide (1bl): Following the general procedure for the synthesis of Weinreb amides, purification by flash column chromatography (silica gel/material = 15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless liquid, 78% yield. The spectroscopic data was consistent with the literature.

$^1$HNMR (400 MHz, CDCl$_3$) $\delta$ 6.16 (s, 1H), 3.66 (s, 3H), 3.19 (s, 3H), 2.08 (s, 3H), 1.12 (s, 9H) ppm; $^{13}$CNMR (100 MHz, CDCl$_3$) $\delta$ 168.1, 161.1, 111.3, 60.4, 36.8, 31.5, 27.9, 14.1 ppm; HRMS calculated for C$_{16}$H$_{19}$NO$_2$: 185.1566, found: 185.1479.
(E)-N-methoxy-N\(,3\)-dimethyl-5-phenylpent-2-enamide (1bm): Following the general procedure for the synthesis of Weinreb amides, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a colorless liquid, 90% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.25 (dd, \(J = 9.0, 6.0\) Hz, 2H), 7.20 – 7.10 (m, 3H), 5.88 (d, \(J = 0.7\) Hz, 1H), 3.86 (s, 3H), 3.30 (s, 3H), 2.63 (t, \(J = 8.0\) Hz, 2H), 2.43 (t, \(J = 8.0\) Hz, 2H), 2.03 (d, \(J = 0.6\) Hz, 3H). \(^{13}\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 222.60, 165.57, 158.33, 150.29, 140.99, 128.85, 128.75, 126.52, 117.44, 88.01, 57.58, 41.13, 34.18, 34.14, 18.96, 19.69.

**Synthesis of \(\alpha, \beta\)-unsaturated ketones**

In a flame dried flask with magnetic stirrer was added Weinreb amide # (1 equiv.) suspended in THF (12mL). The reaction mixture was then cooled to -30°C and the corresponding Grignard reagent [**CAUTION:** Flammable liquid. Water reactive. In case of fire, do not use water or carbon dioxide. Reacts violently with water. May form explosive peroxides] (1.5 equiv.) was slowly added dropwise. The mixture was then allowed to warm to -5°C and monitored by TLC until completion. Saturated aqueous ammonium chloride (20 mL) was added to the reaction mixture and the organic and aqueous phases separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were then dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The crude product was then purified by flash.
column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The eluent was collected in Fisherbrand™ disposable borosilicate glass tubes with plain end (Cat. No. 14-961-29 16x100mm) and the corresponding fractions collected were concentrated in vacuo to give the desired α, β-unsaturated ketone.

![Diagram of 1a](image)

**(E)-1,3-diphenylbut-2-en-1-one (1a):** Following the general procedure for the synthesis of α, β-unsaturated ketones, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a yellow oil, 92% yield. The spectroscopic data was consistent with the literature.²⁸ **(E)-isomer:** ¹HNMR (400 MHz, CDCl₃) δ 7.99 (d, J = 7.0 Hz, 2H), 7.58-7.53 (m, 3H), 7.49-7.39 (m, 5H), 7.17 (q, J = 1.2 Hz, 1H), 2.60 (d, J = 1.2 Hz, 3H); ¹³CNMR (100 MHz, CDCl₃) δ 191.9, 155.2, 142.8, 139.4, 132.6, 129.2, 128.7, 128.6, 128.4, 126.6, 122.2, 19.0; HRMS calculated for C₁₆H₁₄O, 222.10; found 222.10. **(Z)-isomer:** ¹HNMR (400 MHz, CDCl₃) δ 7.84 (d, J = 4.0 Hz, 2H), 7.44 (t, J = 7.3 Hz, 1H), 7.34 (t, J = 5.0 Hz, 2H), 7.24-7.16 (m, 5H), 6.69 (q, J = 1.3 Hz, 1H), 2.31 (d, J = 1.4 Hz, 3H); ¹³CNMR (100 MHz, CDCl₃) δ 193.3, 152.6, 140.7, 138.1, 132.6, 128.9, 128.4, 128.2, 128.1, 127.5, 124.3, 26.7; HRMS calculated for C₁₆H₁₄O : 222.1110; found 222.1008.

![Diagram of 1b](image)

**(E)-3-(naphthalen-2-yl)-1-phenylbut-2-en-1-one (1b):** Following the general procedure for the synthesis of α, β-unsaturated ketones, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a yellow...
oil, 79% yield. The spectroscopic data was consistent with the literature.\textsuperscript{101} \textsuperscript{1}HNMR (CDCl\textsubscript{3}) \(\delta\) 8.00-8.05 (3H, m), 7.84-7.92 (3H, m), 7.70 (1H, dd, J = 8.6 Hz), 7.57 (1H, tt, J = 7.4, 1.3 Hz), 7.47-7.54 (4H, m), 7.32 (1H, d, J = 1.2 Hz), 2.71 (3H, d, J = 1.2 Hz); \textsuperscript{13}CNMR (CDCl\textsubscript{3}) \(\delta\) 192.0, 154.8, 139.9, 139.4, 133.5, 133.2, 132.5, 128.6, 128.5, 128.2, 128.3, 127.8, 126.7, 126.6, 126.2, 124.1, 122.5, 18.9.

\textbf{(E)-3-(naphthalen-1-yl)-1-phenylbut-2-en-1-one (1c)}: Following the general procedure for the synthesis of \(\alpha\), \(\beta\)-unsaturated ketones, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a white solid, 25% yield. The spectroscopic data was consistent with the literature.\textsuperscript{102} \textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.01-7.96 (m,3), 7.92-7.88 (m, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.57-7.44 (m, 6H), 7.38 (dd, J = 7.0 Hz, 1.1Hz, 1H), 7.06 (q, J = 1.3 Hz, 1H), 2.68 (d, J = 1.3 Hz, 3H); \textsuperscript{13}CNMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 191.5, 156.9, 142.7, 139.1, 133.8, 132.7, 130.3, 128.7, 128.6, 128.4, 128.3, 126.5, 126.1, 125.5, 125.4, 125.1, 124.4, 22.6; HRMS calculated for C\textsubscript{20}H\textsubscript{16}O, 272.1099; found 272.1100.

\textbf{(E)-3-(4-methoxyphenyl)-1-phenylbut-2-en-1-one (1d)}: Following the general procedure for the synthesis of \(\alpha\), \(\beta\)-unsaturated ketones, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a yellow oil, 68% yield. The spectroscopic data was consistent with the literature.\textsuperscript{102} \textsuperscript{1}HNMR (400 MHz,
CDCl$_3$ δ 8.00-7.97 (m, 2H), 7.55 (t, J = 8.6 Hz, 3H), 7.47 (t, J = 7.3 Hz, 2H), 7.16 (d, J = 1.2 Hz, 1H), 6.95-6.93 (m, 2H), 3.86 (s, 2H), 2.60 (d, J = 1.2 Hz, 3H); $^{13}$CNMR (100 MHz, CDCl$_3$) δ 191.8, 160.6, 154.8, 139.6, 134.8, 132.3, 128.5, 127.9, 120.3, 113.9, 55.4, 18.6; HRMS calculated for C$_{17}$H$_{16}$O$_2$, 252.1150; found 252.1147.

(E)-1-(4-methoxyphenyl)-3-phenylbut-2-en-1-one (1e): Following the general procedure for the synthesis of α, β-unsaturated ketones, purification by flash column chromatography (silica gel/material = 15:1, hexanes/EtOAc = 30:1 → 10:1). The title compound was obtained as a yellow oil, 71% yield. The spectroscopic data was consistent with the literature.$^{103}$ $^1$HNMR (400 MHz, CDCl$_3$) δ 8.00 (2H, d, J = 8.9 Hz), 7.55-7.59 (2H, m), 7.37-7.45 (3H, m), 7.13 (1H, d, J = 1.2 Hz), 6.96 (2H, d, J = 8.9 Hz), 3.88 (3H, s), 2.57 (3H, d, J = 1.2 Hz); $^{13}$CNMR (100 MHz, CDCl$_3$) δ 190.7, 163.2, 153.7, 142.9, 132.2, 130.6, 128.9, 128.6, 126.4, 122.3, 113.7, 55.5, 18.8.

(E)-3-(4-fluorophenyl)-1-phenylbut-2-en-1-one (1f): Following the general procedure for the synthesis of α, β-unsaturated ketones, purification by column chromatography (silica gel, hexanes/EtOAc = 30:1 → 10:1). The title compound was obtained as a white solid, 91% yield. The spectroscopic data was consistent with the literature.$^{101}$ $^1$HNMR (400 MHz, CDCl$_3$) δ 7.88 – 7.76 (m, 2H), 7.65 – 7.49 (m, 3H), 7.49 – 7.43 (m, 2H), 7.19 – 7.12 (m, 3H), 2.12 – 2.08 (m, 3H). $^{13}$C
NMR (100 MHz, CDCl$_3$ $\delta$ 190.70, 178.42, 164.64, 162.54, 156.79, 138.81, 138.77, 138.01, 133.11, 128.72, 128.43, 128.41, 128.36, 120.75, 114.72, 114.51, 66.23, 52.01, 18.05, 3.43, 18.24.

(E)-1-(4-fluorophenyl)-3-phenylbut-2-en-1-one (1g): Following the general procedure for the synthesis of $\alpha$, $\beta$-unsaturated ketones, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1$\rightarrow$10:1). The title compound was obtained as a yellow oil, 54% yield. The spectroscopic data was consistent with the literature.$^{101}$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02 (2H, m), 7.55-7.59 (2H, m), 7.38-7.45 (3H, m), 7.15 (2H, t, $J$ =8.6 Hz), 7.12 (1H, s), 2.59 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 220.17, 190.70, 179.92, 166.41, 164.32, 156.79, 141.14, 134.71, 134.68, 131.03, 130.98, 127.95, 127.87, 126.43, 120.75, 115.67, 115.46, 65.47, 58.25, 18.05, 9.67, 2.97, 1.43, 4.25, 12.76.

(E)-1-phenyl-3-(4-(trifluoromethyl)phenyl) but-2-en-1-one (1h): Following the general procedure for the synthesis of $\alpha$, $\beta$-unsaturated ketones, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1$\rightarrow$10:1). The title compound was obtained as a white solid, 75% yield. The spectroscopic data was consistent with the literature.$^{104}$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.03 – 7.95 (m, 3H), 7.74 – 7.40 (m, 3H), 7.36 (d, $J$ = 7.4 Hz, 3H), 7.16 (s, $J$ = 1.3 Hz, 1H), 2.58 (d, $J$ = 1.2 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 190.70, 175.61, 156.79, 142.58, 138.01, 133.11, 131.07, 130.85, 130.64, 130.43, 128.72, 128.43,
127.60, 126.84, 126.81, 126.78, 126.74, 125.51, 125.45, 125.40, 125.34, 123.41, 121.32, 120.75, 70.61, 48.82, 18.05, 3.72, 18.25.

(E)-3-(4-chlorophenyl)-1-phenylbut-2-en-1-one (1i): Following the general procedure for the synthesis of α, β-unsaturated ketones, purification by column flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a yellow oil, 70% yield. The spectroscopic data was consistent with the literature. \(^{102}\) \(^1\)HNMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.98 (d, \(J = 2.8\) Hz, 2H), 7.56 (t, \(J = 7.3\) Hz, 1H), 7.52-7.46 (m, 4H), 7.39 (d, \(J = 8.7\) Hz, 2H), 7.14 (d, \(J = 1.2\) Hz, 1H), 2.56 (d, \(J = 1.2\) Hz, 3H); \(^{13}\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 191.8, 153.5, 141.1, 139.2, 135.2, 132.8, 128.9, 128.7, 128.4, 127.9, 122.5, 18.8; HRMS calculated for C\(_{16}\)H\(_{13}\)ClO: 256.0668; found 256.0612.

4-(4-oxo-4-phenylbutan-2-yl) benzonitrile (1k): Following the general procedure for the synthesis of α, β-unsaturated ketones, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a yellow oil, 70% yield. The spectroscopic data was consistent with the literature. \(^{105}\) \(^1\)HNMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.99-7.97 (m, 2H), 7.71 (dt, \(J = 8.1\) Hz, 1.7 Hz, 2H), 7.65 (dt, \(J = 8.1\) Hz, 1.7 Hz, 2H), 7.58 (t, \(J = 7.3\) Hz, 2H), 7.19 (q, \(J = 1.2\) Hz, 1H), 4.44-4.39 (m, 2H), 2.59 (d, \(J = 1.3\) Hz, 3H), 1.42 (t, \(J = 7.1\) Hz, 3H); \(^{13}\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 191.7, 152.1, 147.3, 138.8, 133.1, 132.6, 128.8,
128.5, 127.2, 124.5, 118.6, 112.6, 18.7; HRMS calculated for C₁₇H₁₃NO : 247.1001, found 247.0899.

(E)-1, 3-diphenylpent-2-en-1-one (1l): Following the general procedure for the synthesis of α, β-unsaturated ketones, purification flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a yellow oil, 81% yield. The spectroscopic data was consistent with the literature.¹¹¹HNMR (400 MHz, CDCl₃): δ = 8.01-8.05 (m, 2H), 7.40-7.60 (m, 8H), 7.08 (s, 1H), 3.12 (q, J = 7.4 Hz, 2H), 1.18 (t, J = 7.4 Hz, 3H); ¹³CNMR (100 MHz, CDCl₃): δ = 191.5, 161.4, 141.6, 139.3, 132.6, 129.0, 128.7, 128.6, 128.4, 126.9, 121.9, 25.1, 13.7; HRMS calculated C₁₇H₁₆O, 236.1012, found 236.0998.

(E)-4-methyl-1, 3-diphenylpent-2-en-1-one (1m): Following the general procedure for the synthesis of α, β-unsaturated ketones, purification flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a yellow oil, 88% yield. The spectroscopic data was consistent with the literature.¹¹¹NMR (400 MHz, CDCl₃): δ = 7.99-8.01 (m, 2H), 7.31-7.57 (m, 8H), 6.70 (s, 1H), 3.87-3.94 (m, 1H), 1.15 (d, J = 7.2 Hz, 6H); ¹³CNMR (100 MHz, CDCl₃): δ = 191.9, 165.6, 141.2, 138.9, 132.6, 128.5, 128.4, 127.9, 127.8, 127.6, 123.8, 30.7, 21.7; HRMS calculated for C₁₈H₁₈O: 250.1278. Found 250.1282.
(E)-3-cyclohexyl-1,3-diphenylprop-2-en-1-one (1n): Following the general procedure for the synthesis of $\alpha$, $\beta$-unsaturated ketones, purification flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a yellow oil, 76% yield. The spectroscopic data was consistent with the literature. $^8$ $^1$HNMR (400 MHz, CDCl$_3$): $\delta =$ 7.98-8.00 (m, 2H), 7.28-7.56 (m, 8H), 6.68 (s, 1H), 3.53-3.61 (m, 1H), 1.64-1.82 (m, 5H), 1.27-1.45 (m, 4H), 1.03-1.14 (m, 1H); $^{13}$CNMR (100 MHz, CDCl$_3$): $\delta =$ 191.8, 165.6, 141.9, 139.0, 132.6, 128.5, 128.4, 127.8, 127.7, 127.5, 123.8, 41.6, 31.8, 26.5, 26.1; HRMS calculated for C$_{21}$H$_{22}$O, 290.1604, found 290.1655.

(E)-3, 4, 4-trimethyl-1-phenylpent-2-en-1-one (1o): Following the general procedure for the synthesis of $\alpha$, $\beta$-unsaturated ketones, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a yellow oil, 70% yield. The spectroscopic data was consistent with the literature. $^{10}$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.13 (s, 9H), 1.20 (s, 9H), 2.16 (d, $J =$ 1.0 Hz, 3H), 3.70 (s, 2H), 4.67 (s, 1H), 5.08 (s, 1H), 6.76 (d, $J =$ 1.0 Hz, 1H), 7.40–7.56 (m), 7.83–8.03 (m).
(E)-3-methyl-1, 5-diphenylpent-2-en-1-one (1p): Following the general procedure for the synthesis of α, β-unsaturated ketones, purification by flash column chromatography (silica gel/material =15:1, hexanes/EtOAc = 30:1→10:1). The title compound was obtained as a yellow solid, 86% yield. The spectroscopic data was consistent with the literature.\textsuperscript{28} \textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}): δ = 7.76-7.79 (m, 2H), 7.21-7.53 (m, 8H), 6.62 (s, 1H), 2.89 (t, J = 7.8 Hz, 1H), 2.57 (t, J = 7.7 Hz, 1H), 2.23 (s, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ = 191.7, 157.9, 141.0, 139.1, 132.3, 128.5, 128.4, 128.3, 128.2, 126.1, 121.6, 43.1, 34.1, 19.9; HRMS calculated for C\textsubscript{18}H\textsubscript{18}O: 250.1399, found 250.1396.
### Appendix III

#### Chemical vendor information

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Appendix IV

$^1$HNMR spectra of 1,4-reduction starting material and product

(E)-1, 3-diphenylbut-2-en-1-one
1,3-diphenylbutan-1-one
(E)- 3-(naphthalen-2-yl)-1-phenylbut-2-en-1-one
3-(naphthalen-2-yl)-1-phenylbutan-1-one
(E)-3-(naphthalen-1-yl)-1-phenylbut-2-en-1-one
3-(naphthalen-1-yl)-1-phenylbutan-1-one
(E)-3-(4-methoxyphenyl)-1-phenylbut-2-en-1-one
3-(4-methoxyphenyl)-1-phenylbutan-1-one
\((E)-1-(4\text{-methoxyphenyl})-3\text{-phenylbut}-2\text{-en}-1\text{-one}\)
1-(4-methoxyphenyl)-3-phenylbutan-1-one
(E)-3-(4-fluorophenyl)-1-phenylbut-2-en-1-one
3-(4-fluorophenyl)-1-phenylbutan-1-one
(E)-1-(4-fluorophenyl)-3-phenylbut-2-en-1-one
1-(4-fluorophenyl)-3-phenylbutan-1-one
(E)-1-phenyl-3-(4-(trifluoromethyl)phenyl)but-2-en-1-one
1-phenyl-3-(4-(trifluoromethyl)phenyl)butan-1-one
$^{(E)}$-3-(4-chlorophenyl)-1-phenylbut-2-en-1-one
3-(4-chlorophenyl)-1-phenylbutan-1-one

![Chemical Structure](structure.png)
(E)-4-(4-oxo-4-phenylbut-2-en-2-yl)benzonitrile

NC

Me

O

Ph

1k
4-(4-oxo-4-phenylbutan-2-yl)benzonitrile
(E)-1,3-diphenylpent-2-en-1-one
1,3-diphenylpentan-1-one
(E)-4-methyl-1,3-diphenylpent-2-en-1-one

4-methyl-1,3-diphenylpentan-1-one
(E)-3-cyclohexyl-1,3-diphenylprop-2-en-1-one
3-cyclohexyl-1,3-diphenylpropan-1-one
(E)-3,4,4-trimethyl-1-phenylpent-2-en-1-one
3,4,4-trimethyl-1-phenylpentan-1-one
(E)-3-methyl-1,5-diphenylpent-2-en-1-one
3-methyl-1, 5-diphenylpentan-1-one
Appendix V

HPLC Spectra for 1,4-reduction of α, β-unsaturated ketones

1,3-diphenylbutan-1-one

![HPLC Spectra Image]
3-(naphthalen-2-yl)-1-phenylbutan-1-one
3-(naphthalen-1-yl)-1-phenylbutan-1-one
3-(4-methoxyphenyl)-1-phenylbutan-1-one

![Chemical Structure](image)
1-(4-methoxyphenyl)-3-phenylbutan-1-one
3-((4-fluorophenyl)-1-phenylbutan-1-one
$\text{1-}$(4-fluorophenyl)$\text{-3-phenylbutan-1-one}$
3-((4-chlorophenyl)-1-phenylbutan-1-one

![Chemical Structure](image)
1-phenyl-3-(thiophen-2-yl)butan-1-one

racemic

PA2
4-(4-oxo-4-phenylbutan-2-yl)benzonitrile
1,3-diphenylpentan-1-one
4-methyl-1,3-diphenylpentan-1-one

racemic

PA2
3-cyclohexyl-1,3-diphenylpropan-1-one
3-methyl-1,5-diphenylpentan-1-one

![Chemical Structure Image]
Appendix VI

HPLC chromatograms of reductive aldol reaction

Compound (3.2a):

(2R,3R)-2-((R)-hydroxy(phenyl)methyl)-1,3-diphenylbutan-1-one
Compound (3.2b):

(2R,3R)-2-((R)-hydroxy(phenyl)methyl)-3-(naphthalen-2-yl)-1-phenylbutan-1-one
Compound (3.2d):

(2R,3R)-2-((R)-hydroxy(phenyl)methyl)-3-(4-methoxyphenyl)-1-phenylbutan-1-one
Compound (3.2e):

(2R,3R)-1-(4-fluorophenyl)-2-((R)-hydroxy(phenyl)methyl)-3-phenylbutan-1-one
Compound (3.2f):

(2R,3R)-3-(4-chlorophenyl)-2-((R)-hydroxy(phenyl)methyl)-1-phenylbutan-1-one
About the Author

Susana Sorina López was born on September 23rd, 1980 in Miami Beach, Florida. She grew up in North Miami, Florida moving to Hollywood, Florida during her freshman year of high school where her parents, Oscar and Susana Mercedes López, still reside. In college, became a pre-medicine major at Barry University and discovered a passion for organic chemistry. She changed her major in the fall of 2004 to chemistry and began doing active research under the direction of Dr. George Fisher and Dr. Paul I. Higgs and did undergraduate research in the lab of Dr. Anthony J. Pearson of Case Western Reserve University in Cleveland, Ohio during the summer of 2005.

After graduating with a Bachelor of Science degree in the fall of 2005, Susana moved to Tallahassee, Florida to pursue her graduate studies at Florida State University working in the lab of Dr. Gregory B. Dudley. She published three peer-reviewed publications before earning her Master of Science degree in 2009. In 2011, Susana joined the lab of Dr. Jon C. Antilla and began her doctoral work on developing an enantioselective organocatalytic methodology for the reduction of α, β-unsaturated ketones. As a student in the lab of Dr. Antilla, she earned several awards including the 2011 Successful Latina Student Award, the 2012 Provost's Commendation for Outstanding Teaching by a Graduate Teaching Assistant Award, and was named a McKnight Dissertation Fellow for the 2015-2016 academic year. She obtained her Ph.D. in the spring of 2016. After several interviews for postdoctoral positions, she has decided to accept an offer at one of the top 10 schools in chemistry in the nation. She will begin her postdoctoral work in the fall of 2016 at Northwestern University in the lab of Dr. Karl Scheidt in Evanston, IL.