DIRECTED CATALYTIC ASYMMETRIC HYDROBORATION OF 1,1-DISUBSTITUTED ALKENES

Mohammad Odeh Bani Khaled

Follow this and additional works at: https://digitalcommons.unl.edu/chemistrydiss

Part of the Chemistry Commons

Bani Khaled, Mohammad Odeh, "DIRECTED CATALYTIC ASYMMETRIC HYDROBORATION OF 1,1-DISUBSTITUTED ALKENES" (2012). Student Research Projects, Dissertations, and Theses - Chemistry Department. 35.

https://digitalcommons.unl.edu/chemistrydiss/35

This Article is brought to you for free and open access by the Chemistry, Department of at DigitalCommons@University of Nebraska - Lincoln. It has been accepted for inclusion in Student Research Projects, Dissertations, and Theses - Chemistry Department by an authorized administrator of DigitalCommons@University of Nebraska - Lincoln.
DIRECTED CATALYTIC ASYMMETRIC HYDROBORATION of

1,1-DISUBSTITUTED ALKENES

By

Mohammad Bani Khaled

A Thesis
Presented to the Faculty of
The Graduate College at the University of Nebraska
In Partial Fulfillment of Requirements
For the Degree of Master of Science

Major: Chemistry

Under the Supervision of Professor James M. Takacs

Lincoln, Nebraska

July 2012
Directed Catalytic Asymmetric Hydroboration (CAHB) of 1,1-Disubstituted Alkenes

Mohammad Bani Khaled M.S.
University of Nebraska, 2012

Adviser: James M. Takacs:

Since the beginning of catalytic asymmetric hydroboration (CAHB) in 1989, many new approaches have been developed. Developing an efficient method of catalytic asymmetric hydroboration to produce useful chiral organoboranes is still a challenge due to limited success with a small range of substrates. Typically, effective CAHB requires the presence of vinylarene moiety or a particular substitution pattern around the alkene. One area of research in the Takacs group has been to expand this substrate scope by incorporating two-point binding to direct the reaction to one regioisomer selectively. CAHB of two-point binding substrates in the presence of simple chiral monophosphite and monophosphoramidite ligands is an attractive approach to overcome this challenge.

One of the long standing challenges is the catalytic asymmetric hydroboration of 1,1-disubstituted alkenes. Although practical and highly enantioselective conjugate addition and hydroboration utilizing stoichiometric amounts of chiral borane of 1,1-disubstituted alkenes by Hoveyda, Mazet, and Soderquist have been demonstrated, CAHB of 1,1 disubstituted alkenes remain a significant challenge. Herein, we report an elegant solution of this problem using two-point binding. For example, this reaction can be
carried out by treatment of the $\beta,\gamma$-disubstituted alkene unsaturated amide with Rh(nbd)$_2$BF$_4$ and ligands TADDOL-derived monophosphite or BINOL-derived monophosphoramidite. High catalytic activity (62%), high regioselectivity (> 96%), and enantioselectivities up to 94% were obtained with the $\beta,\gamma$-unsaturated ester framework. The applicability of this method was further highlighted by successfully forming chiral $\beta$-substituted butyrolactones, the key precursor for the synthesis of biologically active natural products including lignans. This method also enables for the efficient preparation of trifluoroborate salts to provide chiral reagents for the Suzuki-Miyaura cross coupling reaction.
Table of Contents

i. Acknowledgments ................................................................. I

ii. Index of Figures .................................................................. II

iii. Index of Schemes ............................................................... III

iv. Index of Tables .................................................................. IV

v. List of Abbreviations ............................................................ VI

1. Introduction ........................................................................ 1

1.1. Development of asymmetric synthesis ................................... 1

1.2. The Versatility of organoboranes ........................................ 4

1.3. Background of transition metal catalyzed hydroboration .............. 7

1.4. Directed hydroboration ........................................................... 9

1.5. Hydroboration reagents .......................................................... 11

1.6. Enantioselective hydroborations ............................................. 13

1.7. Mechanism of rhodium-catalyzed hydroboration ..................... 17

1.8. Conclusion ......................................................................... 20

2. Carbonyl-directed Catalytic Asymmetric Hydroboration (CAHB) of 1,1-
disubstituted alkenes ................................................................. 21

2.1. Background: Amide directing hydroboration of β,γ-disubstituted alkene .... 21

2.2. Previous Attempts of Enantioselective Hydroboration of 1,1-Disubstituted
Alkenes………………………………………………………………………………………………………………………24

2.3. Investigation of CAHB of 1,1-disubstituted Alkenes contained a β,γ-unsaturated carbonyl framework…………………………………………………………………………….26

2.4. The influence of boranes in CAHB of 1,1-disubstituted alkene……………….33

2.5. A More Detailed Summary of pinBH Data for Comparison Purposes ……….37

2.6. Exploration into application of bornates ………………………………………………………………41

3.1. Catalytic asymmetric hydroboration of β,γ-unsaturated ester and Weinreb amides………………………………………………………………………………………………..43

3.2. Catalytic asymmetric hydroboration of 1,1-disubstituted Weinreb amides…50

3.3. Potential applications of the directed CAHB of unsaturated esters in synthesis53

4. Concluding Remarks……………………………………………………………………………………………………56

5. Experimental Data……………………………………………………………………………………………………60

6. References………………………………………………………………………………………………………………94

7. Chapter 7 Spectra Appendix………………………………………………………………………………..9
i. Acknowledgements

It is a pleasure to thank my supervisor, Professor James M. Takacs who has invaluable help of constructive comments throughout the thesis works and with his patience and knowledge whilst allowing me to work in the his research lab.

I would like to express my appreciation to many people who have helped me in the research lab: Dr. Mark Helle, Sean Smith, Nathan Thacker, Kazuya Toyama, Scott A. Pettibone and Andy Geis, For their kind assistance with giving advice, writing thesis, helping with various applications in the lab, and so on. And sincere thanks to all my friends outside the chemistry department.

I also thank the graduate chair of chemistry department Professor Jody Redepenning for his support and invaluable assistance on both an academic and a personal level since the start of my classes work in 2009.

I am grateful to the secretaries and staff in the chemistry departments in Nebraska-Lincoln, for helping the department to run smoothly, for assisting me in many academic issues. My acknowledgements also goes to all the technicians of chemistry department for their co-operation

Last but not least, I wish to thank my beloved wife for her kindness, moral support during my study, encouragement and for every moment she has patience with me, To her I dedicate this thesis.
ii: Index of Figures

Figure 1: Two Enantiomers of Proxyphene ................................................................. 1

Figure 2: Enantioselective Hydrogenation Step in the Industrial Production of L-DOPA 2

Figure 3: Functional Group Transformations of Chiral Organoboronate Intermediates… 4

Figure 4: Carbon-Carbon Cross Coupling using Chiral Secondary Boronic Esters……… 5

Figure 5: Representative Examples of Synthetic Reaction of Boronate Ester……………. 6

Figure 6: Rh(I)-Catalyzed/ non-Catalyzed Hydroboration Reaction using Catechoborane (CatBH) ...................................................................................................................... 7

Figure 7: Early Enantioselective Hydroboration using Rhodium–Ligand Catalyst
Combinations ................................................................................................................... 8

Figure 8: CAHB with Chiral Catalysts by Hayashi and Coworkers .............................. 9

Figure 9: Examples of Directed Hydroboration ........................................................... 10

Figure 10: Representative Functional Groups Directed Hydroboration .................... 11

Figure 11: Oxidative Addition of TMDB with Wilkinson’s Catalyst ......................... 12

Figure 12: Regiochemical Reversal with Catecholborane and Pinacolborane……….. 13

Figure 13: Hydroboration of Styrene with Rhodium Combined with BINAP
Ligand……. 14

Figure 14: Recent Rhodium-Catalyzed CAHBs with Chelating \( P>P \)-Ligands …… 15

Figure 15: Highly Enantioselective CAHB with Chiral Monodentate Ligands Reported from the Takacs Group ........................................................................................................... 16

Figure 16: Proposed Rhodium Metal Catalyzed Hydroboration of Vinyl Arene......... 18

Figure 17: Deuterium Labeled Mechanistic Studies using Catecholborane ………… 19
iii. Index of Schemes

Scheme 1: Amide-directed rhodium-catalyzed hydroboration by evans et. al. ...........21

Scheme 2: Efficient directed CAHB of β,γ-unsaturated amides by takacs et al ..........22

Scheme 3: amide directed catalytic hydroboration of trisubstituted alkenes by takacs. et. al.................................................................23

Scheme 4: NHC/Cu-catalyzed CAHB by hoveyda et al ..........................24

Scheme 5: Iridium-catalyzed CAHB of α-methylstyrene by mazet et al ..............25

Scheme 6: Example of stoichiometric asymmetric hydroboration of by soderquist. et. al. ...........................................................................................................25

Scheme 7: The influence of boranes structure in CAHB of β,γ-unsaturated weinreb amide..........................................................33

Scheme 8: Catalytic hydroboration of 3-methyl-3-butenoic acid phenyl amide X16 with variety of boranes.................................................................34

Scheme 9 Catalytic hydroboration of X16 phenyl amide with variety of ligands.....39

Scheme 10 Subsequent transformations of organoboronate ..................................42

Scheme 11: Catalytic hydroboration of tert-butyl esters with TMDB and L2a Ligand.48

Scheme 12: Catalytic hydroboration of 5-methyl-3-methylidenehexanoic acid weinreb amides X29 with pinBH.................................................................50

Scheme 13: Attempted route for the preparation of β-phenyl-γ-butyrolactone.........52

Scheme 14: Representative examples of applications of CAHB of 3-methyl-3-butoenoic acid tert-butyl ester X23.................................................................53

Scheme 15: Preparation of biologically active chiral β-substituted-γ-lactones via CAHB .................................................................55
iv. Index of Tables

**Table 1:** Catalytic hydroboration of 3-methyl-3-butenolic acid phenyl amide X16 with TMDB .................................................................................................................... 27

**Table 2:** Catalytic hydroboration of 3-methylidene-pentanoic acid phenyl amide X17 with TMDB .................................................................................................................... 29

**Table 3:** Catalytic hydroboration of 1,1-disubstituted phenyl amide phenyl amide X(18), X(19) and X(20) with TMDB ........................................................................................................ 29

**Table 4:** Catalytic hydroboration of 1,1-disubstituted phenyl amide X21 and X22 with TMDB .................................................................................................................... 32

**Table 5:** Catalytic hydroboration of 3-methyl-3-butenolic acid phenyl Amide X16 with variety of boranes .......................................................................................................................... 35

**Table 6:** Catalytic hydroboration of 3-Cyclohexyl-3-butenolic acid phenyl amide X19 with variety of boranes .......................................................................................................................... 36

**Table 7:** Catalytic hydroboration of 1,1-disubstituted phenyl amides X17,X18,X20 with pinBH .......................................................................................................................... 37

**Table 8:** Catalytic hydroboration of 1,1-disubstituted phenyl amides X21 and X22 with pinBH .......................................................................................................................... 38

**Table 9:** Catalytic hydroboration of X16 phenyl amide with variety of ligands ....... 40

**Table 10:** Catalytic hydroboration of 3-methyl-3-butenolic acid tert-butyl ester X23 with pinBH .......................................................................................................................... 45

**Table 11:** Catalytic hydroboration of 3-methyl-3-butenolic acid tert-butyl ester X23 with TMDB .......................................................................................................................... 46
Table 12: Catalytic hydroboration of 3-benzyl-3-butenolic acid tert-butyl with pinBH and TMDB ................................................................. 47

Table 13: Catalytic hydroboration of tert-butyl esters with TMDB and L2a ligand…… 49

Table 14: The results of catalytic hydroboration of 5-methyl-3-methylidenehexanoic acid weinreb amides X29 with pinBH and TMDB ................................................................. 51

Table 15: Summarizing the results ......................................................................................... 57
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAHB</td>
<td>Catalytic Asymmetric Hydroboration</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-Borabicyclo(3.3.1)nonane</td>
</tr>
<tr>
<td>TMDB</td>
<td>4,4,6-Trimethyl-1,3,2-dioxaborinane</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2’-<em>Bis</em>(diphenylphosphino)-1,1’-binaphthyl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>DME</td>
<td>Dimethoxyethane</td>
</tr>
<tr>
<td>MS</td>
<td>Mass Spectrometry</td>
</tr>
<tr>
<td><em>ca</em></td>
<td>Circa</td>
</tr>
<tr>
<td>Calcd</td>
<td>Calculated</td>
</tr>
<tr>
<td>CatBD</td>
<td>Deutero Catecholborane</td>
</tr>
<tr>
<td>CatBH</td>
<td>Catecholborane</td>
</tr>
<tr>
<td>pinBH</td>
<td>pinacolborane</td>
</tr>
<tr>
<td>COD</td>
<td>Cyclooctadiene</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>nbd</td>
<td>Norbornadienyl</td>
</tr>
<tr>
<td>Mp</td>
<td>Melting Point</td>
</tr>
<tr>
<td>M</td>
<td>Molarity</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>DCE</td>
<td>Dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>RT</td>
<td>Room temperature</td>
</tr>
<tr>
<td>Rac</td>
<td>Racemic</td>
</tr>
<tr>
<td>J</td>
<td>Coupling Constant</td>
</tr>
<tr>
<td>Eq</td>
<td>Equivalents</td>
</tr>
<tr>
<td>Aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>DMAP</td>
<td>Dimethylaminopyridine</td>
</tr>
<tr>
<td>EDCI</td>
<td>1-Ethyl-3-(dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'-Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>N</td>
<td>Normality</td>
</tr>
<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Pressure Liquid Chromatography</td>
</tr>
<tr>
<td>Min</td>
<td>Minute</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
</tbody>
</table>
Chapter 1- Introduction

1.2 Development of asymmetric synthesis

Asymmetric synthesis is a fundamental technology for producing enantiomerically pure materials which play a particularly important role in science and industry.¹ For example, proxyphene has two enantiomers and each one has a different biological activity² (Figure 1). Darvon™ has an analgesic property while Novrad™ has an antitussive property.

![Figure 1. Two Enantiomers of Proxyphene](image)

A small amount of chiral, enantiomerically pure catalyst can, in principle, effectively promote reactions and lead to the formation of large amounts of enantiomerically pure compounds. Some of these products may be very difficult to form by any other accessible method. Intensive research efforts have been devoted to the development of selective and practical asymmetric catalytic protocols and a large variety of chiral ligands and catalytic systems have been developed for asymmetric reactions in industry and academia.³ Catalytic chiral reactions such as hydrogenation,¹ oxidation,³ and alkylation³ have been developed to the point that they are used routinely on an industrial scale.
William S. Knowles in 1968 pioneered methods in enantioselective synthesis by replacing the achiral triphenylphosphine ligands in Wilkinson's catalyst with the chiral phosphine ligands, i.e., \((\text{Ph})\text{P}(\text{Me})\text{Pr}\), and employed this modified catalyst in asymmetric hydrogenation reactions. This experiment gave only a modest level of asymmetric induction (15% enantiomeric excess (ee)) but set the stage for the field to rapidly advance. Further research into the nature of the chiral ligand led to DIPAMP. This latter method of creating asymmetric compounds has been effectively utilized in the hydrogenation step of the industrial production of L-DOPA. This discovery of accelerating production of L-DOPA was one among the first economical and efficient method to generate chiral compounds by asymmetric catalysis using chemical catalysts.

The continued growth of asymmetric catalysis have been advanced with the use of recent techniques such as high-throughput screening and computational studies.

![Figure 2](image.png)

**Figure 2.** Enantioselective Hydrogenation Step in the Industrial Production of L-DOPA.
The Takacs group has been among the leaders in developing directed catalytic asymmetric hydroboration (CAHB) reactions for the preparation of chiral organoboranes. The reaction bears some similarity to catalytic asymmetric hydrogenation as will be seen in this dissertation.
1.2 The Versatility of organoboranes

Hydroboration reactions are one of the most important processes to produce organoboronates from alkenes (C=C and C-C triple bonds under readily accessible conditions. This reaction involves the addition of hydrogen and a boron atom across the \( \pi \)-system of a double or triple bond. It has gained considerable attention because it possesses unique properties such as proceeding under much milder conditions to produce synthetic intermediates such as organoboronates that can be easily converted into secondary products with wide range of functional groups.\(^8,9,10\) (Figure 3).

![Figure 3. Functional Group Transformations of Chiral Organoboronate Intermediates](image)

Many protocols that utilize chiral organoboronates reactions have emerged. For example, Molander\(^{11}\) reported the stereospecific Suzuki-Miyaura cross coupling of enantio-
enriched alkyltrifluoroborates (10 mol % of Pd(OAc)$_2$ and 20 mol % of XPhos).

Interestingly, this reaction was shown to be very efficient with a variety of substrates and gives the product with complete inversion of configuration. Crudden also provided successful example of cross-coupling using chiral secondary boronic esters and palladium to regioselectively form product with retention of enantioselectivity (0.15 mmol of Ag$_2$O, 8% Pd$_2$(dba)$_3$, 8-12 equiv of PPh$_3$) (Figure 4).$^{12}$

![Figure 4. Carbon-Carbon Cross Coupling using Chiral Secondary Boronic Esters](image-url)
The recent synthetic utility of boronate esters are summarized in (Figure 5).\textsuperscript{13, 14, 15, 16}

**Figure 5.** Representative Examples of Synthetic Reactions of Boronate Ester
1.3 Background of transition metal catalyzed hydroboration

Männig and Nöth’s in 1985 reported the first catalytic hydroboration reaction using tris(triphenylphosphine)chlororhodium (I) (Wilkinson’s catalyst to catalyze the addition of catecholborane (CatBH) across a double bond. This led to a rapid increase in interest toward developing a highly efficient catalytic process for the synthesis of enantiopure organoboronates via transition metal-catalyzed reactions with high levels of regio- and stereochemical control. There can be significant differences in reactivity between catalyzed and non-catalyzed reactions of the same substrate. For instance, metal-catalyzed hydroboration of unsaturated ketones in the presence of 1 mol % of RhCl(PPh$_3$)$_3$ led to the product resulting from the addition of catecholborane to the double bond whereas the hydroboration by catecholborane without the catalyst led to the addition of catecholborane to the carbonyl group. The difference between catalyzed and non-catalyzed reactions is also seen in hydroboration of styrene. Catalyzed hydroboration favors the Markovnikov addition products (after C-B bond oxidation) while the non-catalyzed reaction produces the anti-Markovnikov addition product (Figure 6).

**Figure 6.** Rh(I)-Catalyzed/ non-Catalyzed Hydroboration Reaction using Catecholborane (CatBH).
Suzuki \(^{18}\) and Burgess \(^{19}\) studied the control of regioselectivity and diastereoselectivity of the catalyzed and non-catalyzed hydroborations of allylic compounds. In 1988, the Burgess group reported the first example of a catalytic asymmetric hydroboration (CAHB) reaction. They subjected 1,2-disubstituted olefins, for example norbornene, to catalytic hydroboration conditions by CatBH using ([Rh(cod)Cl] \(^2\) and the chiral diphosphine, (R,R)-DIOP. The reactions proceed smoothly to furnish norbornol (90%, 64% ee). Suzuki employed Rh(I) in combination with (S,S)-DIOP with indene and also obtained moderate enantioselectivity in the CAHB (91%, 74% ee) (Figure 7).

![Burgess, 1988](image)

![Suzuki, 1990](image)

**Figure 7.** Early Enantioselective Hydroboration using Rhodium–Ligand Catalyst Combinations.

The synthetic potential of CAHB was quickly realized, and a big step forward was made by Hayashi and coworkers; \(^{20}\) they demonstrated the switching of regioselectivity using a cationic phosphine-rhodium catalyst Rh(I) for the hydroboration of styrene derivatives to produce secondary benzylic boranes with high enantioselectivity (Figure 8).
1.4 Directed hydroboration

The development of directed catalytic hydroboration was initiated in 1980s. Evans found that the amide group can serve as a directing group with the best selectivity found using Crabtree’s iridium catalyst, although practical levels were found with rhodium, too. Both cyclic and acyclic substrates have been shown the proximal addition of boron demonstrating the directing ability of the amide group. Moreover; they achieved excellent diastereoselectivity with phosphite –directed hydroboration in combination of rhodium complexes. The reaction proceeds successfully in presence of stoichiometric amounts of Wilkinson’s catalyst and catecholborane followed by oxidative workup by basic hydrogen peroxide to cleave the phosphites. Although Evans carried out the pioneering work in directed catalytic asymmetric hydroboration, Fu later presented an efficient hydroboration by employing an indenyl ligand to provide coordinative saturation around the metal which is required for binding with the alkene moiety. With this system, high levels of selectivity were obtained indicative of an ether-directed reaction (75%) (Figure 9).

Figure 8. CAHB with Chiral Catalysts by Hayashi and Coworkers.
Figure 9. Examples of Directed Hydroboration

A further development of this chemistry was reported by Gevorgyan, et al., who used a pendant ester as a highly efficient directing functional group; esters provide a versatile functional group which can be used for further transformations. He employed [Rh(COD)Cl]₂ and pinacolborane to the 3,3-disubstituted cyclopropenes. The reaction proceeded effectively to furnish >99:1 cis-diastereoselectivity in excellent enantioselectivity up to 99 % ee. Vedejs recently discussed the efficiency of amine in the non-catalyzed directed hydroboration of a β,γ-unsaturated amine by THF-BH₃.
followed by oxidative workup. The latter substrates exhibit 43:1 regioselectivity in favor of the 3,5-disubstituted product (Figure 10).

![Chemical structure](image)

**Figure 10.** Representative Functional Groups Directed Hydroboration.

### 1.5 Hydroboration reagents

A number of boranes have been prepared and employed for the non-catalyzed hydroboration of a wide variety of cyclic and acyclic substrates. In contrast, CatBH and pinacolborane (pinBH) are by far the most popular boranes used in the catalyzed reaction; a wide range of transition metal complexes have been explored, too. Other reagents were also employed in catalytic hydroboration with variable success. For research described later in this dissertation, it should be noted that Kono et al. reported 4,4,6-trimethyl-1,3,2-dioxyborinane (TMDB) undergoes in the oxidative addition with Wilkinson’s catalyst (Figure 11). Woods and Strong also used this borane for the non-
catalyzed hydroboration reaction of many alkenes,\textsuperscript{28} and Evans used it in his original report of the catalyzed reaction.

\textbf{Figure 11.} Oxidative Addition of TMDB with Wilkinson’s Catalyst

The choice of borane employed in a hydroboration reaction can have a significant influence on the mechanism and regioselectivity of the catalyzed reaction. For instance, the reaction of perfluoroalkylethylenes with CatBH catalyzed by (DPPB)Rh(I) gives the internal secondary borane with very high regioselectivity and furnishes the secondary alcohol after oxidative workup. Employing pinBH with RhCl(PPh\textsubscript{3})\textsubscript{3}, the reaction forms the primary borane and, following the oxidative workup, the primary alcohol.\textsuperscript{29} Another example which highlights the important role of the borane in the selectivity of catalytic systems is in the hydroboration of 4-octene. When CatBH is used in combination with Wilkinson’s catalyst, the reaction gives the secondary alcohol in very high selectivity; in contrast, pinBH in the reaction proceeds with apparent alkene isomerization to give the primary alcohol after oxidative workup (Figure 12).\textsuperscript{30}
Figure 12. Regiochemical Reversal with Catecholborane and Pinacolborane

1.6 Enantioselective hydroborations

The enantioselective construction of chiral molecules is an important issue because many natural compounds have chiral centers.\(^1\) Since the pioneering work of Männig and Nöth, much effort has been directed toward creating enantiomerically enriched stereocenters with boron as a substituent. As discussed above, modest levels of enantioselectivity were reported by Burgess and Suzuki for the CAHB of 1,1- and 1,2-disubstituted olefins.

Hayashi et al., reported the significant contribution to catalytic enantioselective hydroboration,\(^2\) they also establish several new and broadly applicable improvements including modifications of the ligand and catalyst in the enantioselective process. This reaction is performed with a cationic rhodium catalyst combined with (+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP). The cationic rhodium/BINAP complex was highly active. For instance, the hydroboration reaction of styrene proceeds to completion in 30 min even at -30 °C with 1 mol % of the catalyst.
The successes of employing BINAP as a chiral ligand in a variety substrates demonstrates that the BINAP is one of the best ligands in enantioselective hydroboration reactions. However, even its scope for CAHB is rather limited. In the case of styrene substrates, electron rich olefins give higher enantioselective than the electron poor substrates. The sterically hindered substrate like ortho-substituted styrenes shows low yield and low enantioselectivity. α or β-substitution of the double bond generally lead to low enantioselectivities with this particular ligand (Figure 13). Nonetheless, diphosphoanes are, by far, the most extensively used class of ligands; they show a wide range of reactivity and enantioselectivity. Some of the more successful examples are discussed in the following paragraph.

![Figure 13](image_url)

**Figure 13.** Hydroboration of Styrene with Rhodium Combined with BINAP Ligand.

Knochel\(^3\) reported preparation of the dicyclohexylbis(phosphane), shown in Figure 14, and reported that it gave high chemo-, regio- and enantioselectivity in the rhodium-catalyzed hydroboration with CatBH. He employed this system on a number of para-, meta- and ortho-styrenes to furnish a range of enantioselectivity (76-93 %) with one exception (p-CF\(_3\), 58 % ee). Buono reported that the bis(aminophosphane) gives results within the range of (42-77 % ee) in styrene system.\(^3\) The accumulated results of ligand screenings suggest that changing the ligand backbone has a profound effect on the yield, regioselectivity and enantioselectivity of these reactions (Figure 14).
The Takacs group\textsuperscript{34} studied the CAHB reaction of styrene and styrene derivatives using effective TADDOL-derived monodentate ligands such as phosphite LA and phosphoramidite LB. These ligands furnish highly enantioselective products in combination with a Rh(nbd)Cl derived catalyst. Many of the styrene derivatives were examined with pinBH and CatBH for comparison purposes. Introducing electron donating group such as -OMe at para position in styrene produced (96%, 93% ee) with ligand LA and (96%, 94% ee) with ligand LB. A strong inductive electron withdrawing group (e.g., CF\textsubscript{3}) in the same position produced (96%, 90% ee) with ligand LA and (92%, 90% ee) with ligand LB (Figure 15).

Related TADDOL-derived ligands and BINOL-derived phosphoramidites are also useful with substrates that exploit the directing ability of amide functional group to promote the CAHB with two point binding between olefin moiety and the amide to rhodium as a model to explain their effectiveness.\textsuperscript{35} CAHB of $\beta,\gamma$-unsaturated Weinreb amides are
another directing group studied by the Takacs group.\textsuperscript{36} The Weinreb amides add synthetic value since they readily undergo transformation to other functional groups. For example, the Weinreb amide shown furnishes the \(\beta\)-hydroxy acid after the oxidative workup of the product of TMDB addition using \(\text{Rh(nbd)}_2\text{BF}_4\) in conjunction with phosphoramidite \(L1\) (77\%, 92\% ee) (Figure 15).

**Figure 15.** Highly Enantioselective CAHB with Chiral Monodentate Ligands Reported from the Takacs Group.

**1.7 Mechanism of rhodium-catalyzed hydroboration**

The key to achieving a successful hydroboration reaction is developing an efficient and useful method to produce a boronate ester with a high degree of regio-, diastereo-, and/or enantioselectivity by applying chiral ligands to introduce the enantioselectivity in the
outcome. Experimentally, it has been found that the reaction is sensitive to many different factors, including the catalyst nature, borane reagents, solvents, temperature, and the interplay between steric and electronic effects on the substrate.

Männing and Nöth carried out an investigation to provide experimental evidence. They proposed the first generally accepted mechanism of the rhodium-catalyzed hydroboration as shown in Figure 16. This model was established on the basis of the observations of the reaction between catecholborane with Wilkinson’s catalyst and it is supported by deuterium studies in case of vinylboronates and alkane formation as well as by Ziegler’s density functional theory calculations.

The reaction pathway is a dissociative mechanism involving rhodium (I) oxidatively adding the B-H bond of catecholborane, followed by alkene coordination with simultaneous dissociation of an additional PPh₃ group. Migratory insertion of the alkene into the Rh-H bond with a subsequent reductive elimination of the alkylboronate ester completes the catalytic cycle (Figure 16).
Figure 16. Proposed Rhodium Metal Catalyzed Hydroboration of Vinyl Arene.

In deuterium labeling studies, Evans\textsuperscript{37,39} found that CatBD (deuterated catecholborane) behaved differently with different substrates in reactions catalyzed by RhCl(PPh\textsubscript{3})\textsubscript{3}. The two key substrates were styrene and 1-decene. Remarkably, the reactions with styrene proceed to complete conversion to form 1-phenyl-2-deuterioethanol without any hydride migration or deuterium scrambling that would indicate reversible reaction. The observed
deuterium distribution was much different upon the rhodium-catalyzed addition of CatBD to 1-decene under the same conditions. Evans suggested that the mechanism is reversible from rhodium alkyl complex back to the alkene. The considerable amount of deuterium on the terminal carbon in both substrates furthermore suggests that the regio-determining step in the catalytic cycle is the selective reductive elimination from the primary alkyl rhodium complex (Figure 17).

![Figure 17. Deuterium Labeled Mechanistic Studies using Catecholborane.](image-url)
1.8 Conclusion

As we have seen, catalytic asymmetric hydroboration (CAHB) is a valuable method for the synthesis of enantiomerically organoboronate compounds. However, the ability of prior technology to reliably produce defined classes of enantiopure products in a predictable manner is limited in 1,2-disubstituted and monosubstituted alkenes (vinyl arenes) using catalysts employing more complex, chelating ligands.

The thesis goal is to expand and develop the generality of directed CAHB of alkenes by focusing on the directed CAHB of two-point binding substrates in the β,γ-unsaturated carbonyls framework. The use of catalysts derived from simple, readily accessible monophosphite and monophosphoramidite ligands demonstrating high efficiency in stereochemical control of the reaction and to obtain high enantiopure products will be seen in this dissertation.
Chapter 2: Carbonyl-directed Catalytic Asymmetric Hydroboration (CAHB) of 1,1-disubstituted alkenes

2.1 Background: Amide directing hydroboration of $\beta,\gamma$-disubstituted alkene.

Catalytic asymmetric hydroboration (CAHB) is potentially a powerful tool for preparation of chiral organoborane molecules. Advantages of organoborane reagents include the numerous reactions than can be used to convert organoboranes to useful organic substructures and the ease with which their properties can be tuned.\(^{40}\) Evans and co-workers\(^{22}\) elegantly demonstrated the efficiency of the amide moiety in accelerating and directing the regiochemical course of catalyzed hydroboration reactions. It is noteworthy that the hydroborations of acyclic $\beta,\gamma$-unsaturated amides proceed to give highly regioselective results, supporting a two point binding model for these substrates. For example, the catalytic hydroboration reaction of $\beta,\gamma$-unsaturated amide $X10$ followed by oxidative work up forms the $\beta$-hydroxyamide (74%) with high yield; the regioselectivity favoring the oxidation at the $\beta$- rather than $\gamma$-position is reported to be 20:1 (Scheme 1).

\[
\begin{align*}
\text{Scheme 1} \quad &\text{Amide-directed rhodium-catalyzed hydroboration by evans et. al.}
\end{align*}
\]
The Takacs group in 2008\textsuperscript{35} reported an efficient procedure for amide directed CAHB by pinacol borane (pinBH) demonstrating that two-point binding substrates can undergo reaction with high enantioselectively using Rh(I) complexes of several chiral monodentate phosphorus ligands derived from simple chiral diols such as TADDOL and BINOL. For example, CAHB of X\textsubscript{11} (R\textsubscript{1} = isopropyl) using L\textsubscript{1} proceeds in good yield (79\%) and high enantioselectivity (97% ee). The effectiveness of the chiral ligands highlighted by structure L\textsubscript{2} varies for different substrates, giving a range of enantioselectivity (93-99\%). The CAHB also proceeds with high regioselectivity; only 3-4\% of the $\gamma$-isomer is formed under the described conditions for each substrate shown below in Scheme 2.

\begin{scheme}
1) 0.5 mol % Rh(nbd)\textsubscript{2}BF\textsubscript{4}  
1.1 \% L, 2 eq PinBH  
THF, 40 °C, 12 h  
2) H\textsubscript{2}O\textsubscript{2}, aq. NaOH

Scheme 2 Efficient directed CAHB of $\beta,\gamma$-unsaturated amides by takacs et al.

The Takacs group\textsuperscript{41} provided, as previously mentioned, a new catalyst for the hydroboration reaction of $\beta,\gamma$-disubstituted unsaturated phenyl amides. This catalyst
proved to be effective for many of the previously problematic cases, and generally allowed the reactions to proceed under mild conditions. Based on these findings the highly selective CAHB reactions in trisubstituted alkenes were also successfully developed. The combination of Rh(nbd)$_2$BF$_4$ with simple TADDOL derived phenyl monophosphite ligands in presence of pinBH furnished products in high enantiopurity as shown below in Scheme 3.

![Scheme 3](image)

<table>
<thead>
<tr>
<th>Ligand</th>
<th>R$^E$</th>
<th>R$^E'$</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>L$_2$d</td>
<td>(CH$_2$)$_3$Ph</td>
<td>CH$_3$</td>
<td>81</td>
<td>95</td>
</tr>
<tr>
<td>L$_2$a</td>
<td>CH$_3$</td>
<td>(CH$_2$)$_3$Ph</td>
<td>83</td>
<td>95</td>
</tr>
<tr>
<td>L$_2$d</td>
<td>(CH$_2$)$_4$Ph</td>
<td>CH$_3$</td>
<td>79</td>
<td>93</td>
</tr>
<tr>
<td>L$_2$c</td>
<td>(CH$_2$)$_2$CH$_3$</td>
<td>CH$_3$</td>
<td>80</td>
<td>96</td>
</tr>
<tr>
<td>L$_2$d</td>
<td>CH$_3$</td>
<td>CH$_2$CH(CH$_3$)$_2$</td>
<td>81</td>
<td>91</td>
</tr>
<tr>
<td>L$_2$c</td>
<td>CH$_3$</td>
<td>CH(CH$_3$)$_2$</td>
<td>80</td>
<td>95</td>
</tr>
</tbody>
</table>

**Scheme 3** Amide directed catalytic hydroboration of trisubstituted alkenes by takacs, et al.
2.2 Previous Attempts of Enantioselective Hydroboration of 1,1-Disubstituted Alkenes

Building on the work of Evans and Takacs, we proposed to expand the scope of substrates for directed CAHB to include γ,β-unsaturated amide substrates contained 1,1-disubstituted alkene moieties. The previous studies in the directed CAHB are described in the context of (E)- and (Z)-1,2-disubstituted and 1,2,2-trisubstituted alkenes. There are a few examples of the non-directed CAHB of 1,1-disubstituted alkenes. Hoveyda\textsuperscript{42,43} reported the net non-directed CAHB of 1,1-disubstituted vinylarene substrates using chiral Cu-based bidentate N-heterocyclic carbene (NHC) complexes with bis(pinacolato)diboron. Although this study demonstrates that 1,1-disubstituted alkenes readily react with CAHB with high enantioselectivity and regioselectivity, only selected vinylarenes are successful, and it requires the use of bis(pinacolato)diboron. In particular, the successful substrates require a large size difference between the alkene substituents (Scheme 4).

![Scheme 4](image)

Significant progress has been made recently in the design and development protocol for CAHB of 1,1-disubstituted alkenes by Mazet et al.\textsuperscript{44} Highly selective and highly efficient
iridium catalysts were found to be effective for the CAHB of 1-methylstyrene by pinBH. For example, using ligand LL, iridium-catalyzed CAHB gives the terminal product with high regio- and enantioselectivity (92%, 92% ee). The versatile chiral organoborane product proved useful for subsequent Suzuki cross-coupling reactions (Scheme 5).

**Scheme 5** Iridium-catalyzed CAHB of α-methylstyrene by Mazet et al.

Soderquist and coworkers developed a useful stoichiometric reagent for the asymmetric hydroboration of 1,1-disubstituted alkenes. Their chiral 9-borabicyclononane derivative exhibited remarkable enantioselectivity for 2-tert-butylpropene, and good selectivity for other methyldiene substrates, for example, α-methylstyrene shown below (Scheme 6).

**Scheme 6** Example of stoichiometric asymmetric hydroboration of by Soderquist et al.
2.3 Investigation of CAHB of 1,1-disubstituted Alkenes contained a $\beta$, $\gamma$-unsaturated carbonyl framework.

We began by examining the possibility of using simple 1,1-disubstituted alkenes contained within a $\beta,\gamma$-unsaturated carbonyl framework to generate enantiomerically pure organoboranes starting with the substrate that contains the methyl substituent in $\beta$-position. Our protocol (described in detail below) seeks to reduce the number of potential catalysts and ligands screened by taking into account the prior art (i.e., successful catalyst precursors and chiral ligands) available in the group. Based on our own precedents, we can compare results to expectations and we modify the system according to prior trends saving time and effort. We had established that simple TADDOL-derived phosphite and phosphoramidite ligands afford high levels of enantioselectivity in the rhodium-catalyzed asymmetric hydroborations of acyclic $\beta,\gamma$-unsaturated amides with pinacolborane (pinBH). A BINOL-derived monophosphoramidite was also shown to be among the most successful ligands for these substrates. The initial investigations employ Rh(nbd)$_2$BF$_4$ since prior studies have shown that a readily dissociable counterion is essential. As in prior studies, this investigation used both pinBH (vide infra) and 4,4,6-trimethyl-1,3,2-dioxaborinane (TMDB) to screen the CAHB of 3-methyl-3-butenoic acid phenyl amide X16 as shown in Table 1 for CAHB by TMDB.
Table 1 Catalytic hydroboration of 3-methyl-3-butenolic acid phenyl amide X16 with TMDB

![Chemical Structure](image)

1) 1% Rh(nbd)$_2$BF$_4$
2.1% L
2 equiv TMDB
THF, 40 °C
2) aq NaOH, H$_2$O$_2$

<table>
<thead>
<tr>
<th>Ligand</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2b</td>
<td>40</td>
<td>88</td>
</tr>
<tr>
<td>L2c</td>
<td>62</td>
<td>84</td>
</tr>
<tr>
<td>L2d</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>L2a</td>
<td>81</td>
<td>94</td>
</tr>
<tr>
<td>L1</td>
<td>80</td>
<td>63</td>
</tr>
<tr>
<td>L3a</td>
<td>72</td>
<td>-10</td>
</tr>
</tbody>
</table>

* % Yield and % ee are of the γ-hydroxyamide isomer
Amide X16 was screened in the CAHB by TMDB with a series of TADDOL-derived ligands to determine their influence on yield, regioselectivity and enantioselectivity. The overall highest level of enantioselectivity was obtained from the CAHB of X16 by TMDB using Rh(nbd)$_2$BF$_4$ in combination with L2a. CAHB of X16 under those conditions affords γ-dioxaborato amide X(16)-1 in moderate yield but excellent enantiomeric purity (60%, 94% ee). CAHB of the substrate with ligand L2b affords the γ-dioxaborato amide X(16)-1 in very good levels of enantiomeric purity (88% ee, Table 1). CAHB of the same substrate with other TADDOL-derived ligands, that is, L2c and L2d, also afford the respective γ-dioxaborato amide in similarly good levels of enantiomeric purity (80-84% ee, entries 3 and 2, respectively). However, directed CAHB of the same substrate using phosphoramidite ligand L3a (and some related ligands, data not included in Table 1) results in very low enantioselectivity, although the yield is quite reasonable (72%, 10% ee). The BINOL-derived monophosphoramidite ligand L1 gave moderate levels of enantioselectivity (80%, 63% ee).

Encouraged by the results obtained with arguably the simplest methylidene substrate X16, we continued our investigation into more highly substituted ones, focusing on the interplay of alkene and the catalyst as it influences the yield and enantioselectivity. Table 2 gives a quick view of the major screening results from the CAHB of X17 by TMDB and highlights the levels of asymmetric inductions obtained from the screening. Not surprisingly, the results of directed CAHB of X17 are similar to those obtained with X16. The reaction proceeded smoothly to selectively form the γ-dioxaborato amides in enantioselectivities up to 90% ee.
Table 2 Catalytic hydroboration of 3-methylidene-pentanoic acid phenyl amide X17 with TMDB

<table>
<thead>
<tr>
<th>Ligand</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2a</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>L2c</td>
<td>55</td>
<td>83</td>
</tr>
<tr>
<td>L2d</td>
<td>50</td>
<td>71</td>
</tr>
<tr>
<td>L1</td>
<td>52</td>
<td>58</td>
</tr>
</tbody>
</table>

We have developed a highly efficient coordinative catalytic system. One of the major advantages of this catalyst system is the general applicability to multiple 1,1-disubstituted alkenes. In order to explore the stereochemistry and the regiochemistry of the other substituents, we employed the same catalytic system in X18 which has the isobutyl substituents in the β-position. Interestingly these experiments gave similar enantioselectivity induction as X16 and very high regioselectivity. For example CAHB of the substrate X18 with ligands L2a affords the respective γ-dioxaborato amides X(18)-1 in excellent levels of enantiomeric purity (95% ee, Table 3).
Table 3  Catalytic hydroboration of 1,1-disubstituted phenyl amide X(18),X(19) and X(20) with TMDB

![Chemical Structures]

<table>
<thead>
<tr>
<th>Ligand</th>
<th>% yield</th>
<th>% ee</th>
<th>Ligand</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2a</td>
<td>72</td>
<td>95</td>
<td>L2b</td>
<td>30</td>
<td>55</td>
</tr>
<tr>
<td>L2c</td>
<td>72</td>
<td>91</td>
<td>L2c</td>
<td>70</td>
<td>82</td>
</tr>
<tr>
<td>L2d</td>
<td>70</td>
<td>80</td>
<td>L2d</td>
<td>71</td>
<td>70</td>
</tr>
<tr>
<td>L1</td>
<td>50</td>
<td>55</td>
<td>L2a</td>
<td>79</td>
<td>90</td>
</tr>
<tr>
<td>L3a</td>
<td>60</td>
<td>39</td>
<td>L1</td>
<td>62</td>
<td>55</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ligand</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2c</td>
<td>75</td>
<td>88</td>
</tr>
<tr>
<td>L2d</td>
<td>55</td>
<td>86</td>
</tr>
<tr>
<td>L2a</td>
<td>79</td>
<td>93</td>
</tr>
<tr>
<td>L1</td>
<td>45</td>
<td>50</td>
</tr>
</tbody>
</table>

* % Yield and % ee are representative of the γ-hydroxyamide isomer
Our initial objective in this investigation had been to design a useful chiral catalytic system capable of operating a diverse set of substrates. It was apparent from the screenings of previous substrates that there was no significant steric difference between them. While we have observed significant success with these systems, we are aware of the limitations inherent in alkene substituent pattern so we felt that it is important to introduce a bulky substituent and experimentally explore the aspects of reactivity. We therefore selected X19 and X20 where we observed that these substrates can react with CAHB and afford high enantiomeric excess. For instance, while CAHB of X19 produces X(19)-1 in moderate yields (79%, 90% ee. Table 3), X20 affords X(20)-1 in nearly same higher yield (79%, 93% ee. Table 5).

Although currently confined to a small window of substrates, the following investigation introduces a new olefin pattern. We synthesized and studied X21 and X22 substrates that may hold greater potential for constructing a biological target molecules. Products furnished from these reactions are structurally stable and may be employed for subsequent Pd-catalyzed cross-coupling. Under the same conditions, these substrates had furnished highly enantiopure products up to 94% with very good regioselectivity when L2a has been employed.
Table 4  Catalytic hydroboration of 1,1-disubstituted phenyl amide X21 and X22 with TMDB

![Chemical structure of X21 and X22](image)

<table>
<thead>
<tr>
<th>Ligand</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2a</td>
<td>72</td>
<td>94</td>
</tr>
<tr>
<td>L2c</td>
<td>59</td>
<td>77</td>
</tr>
<tr>
<td>L2b</td>
<td>60</td>
<td>78</td>
</tr>
<tr>
<td>L1</td>
<td>61</td>
<td>56</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ligand</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2a</td>
<td>70</td>
<td>92</td>
</tr>
<tr>
<td>L2c</td>
<td>59</td>
<td>75</td>
</tr>
<tr>
<td>L1</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>

*% Yield and % ee are representative of the γ-hydroxyamide isomer
2.4 The influence of boranes in CAHB of 1,1-disubstituted alkene

The Takacs group\textsuperscript{36} studied the reactivity of boranes in directed CAHB and found that the nature of the structure of the borane is a key factor in the determining level of enantioselectivity. For example, CAHB of the test substrate illustrated in Scheme 7 by B\textsubscript{1}, a five-membered ring borane, gives product in lower enantiomeric excess (75\%, 83\% ee) than the six-membered ring homologue B\textsubscript{4} (78, 96\% ee).

\begin{itemize}
\item B\textsubscript{1}: seven-membered ring borane
\item B\textsubscript{2}: six-membered ring borane
\item B\textsubscript{3}: five-membered ring borane
\item B\textsubscript{4}: six-membered ring borane
\end{itemize}

\begin{align*}
\text{MeO} & \quad \text{O} & \quad \text{NH} & \quad \text{C}_2\text{H}_4 \\
\text{Me} & \quad \quad \text{Me} & \quad \quad \text{H} \\
\text{Me} & \quad \quad \text{Me} & \quad \quad \text{O} & \quad \quad \text{BH} \\
75 & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \text{Scheme 7} \quad \text{The influence of boranes structure in CAHB of } \beta, \gamma\text{-unsaturated weinreb amide.}
Table 5 summarizes the chemical yield, regioselectivity (i.e., % $\gamma$- and % $\beta$-products formed) and enantioselectivity for the $\gamma$-product as a function of borane in the CAHBs of X16; the same chiral catalyst system formed from L2a is used in each case. The results obtained using the six-membered ring dioxaborinanes, that is B2 and B4, are on average more selective (average of 87% ee) than those obtained on average using the five-membered ring dioxaborolanes, B1 and B3 (66% ee). Furthermore, the $\gamma$ / $\beta$ ratio with B2 and B4, are on average higher (average of 6.3) than those obtained on average using, B1 and B3 (average of 2.3). The two six-membered ring boranes, the trimethyl derivative B2 (TMDB, 94% ee) and pinacol-like tetramethyl derivative B4 (91% ee), afford quite similar results. Comparing specific five- and six-membered ring boranes with similar methyl substitution patterns finds some differences. For example, B1 affords with L2a (66%, 60% ee) while B4 affords (82%, 91 ee%). It was on the basis of this short study that TMBD (B2) was selected for the screenings of phenyl amides (X16-X22). During the hydroboration reaction, the majority of boranes led to form $\gamma$-products as major products with considerable amount of undesirable products such as $\beta$-products, this perhaps due to the size of alkyl group at $\beta$- position (scheme 8).

Scheme 8 Catalytic hydroboration of 3-methyl-3-butenolic acid phenyl Amide X16 with variety of Boranes.
Table 5  Catalytic hydroboration of 3-methyl-3-butenoic acid phenyl Amide X16 with variety of boranes.

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>γ %</td>
<td>% ee (γ)</td>
<td>β %</td>
<td>γ %</td>
</tr>
<tr>
<td>L2a</td>
<td>66</td>
<td>60</td>
<td>34</td>
<td>81</td>
</tr>
<tr>
<td>L2b</td>
<td>65</td>
<td>50</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>L2c</td>
<td>58</td>
<td>52</td>
<td>36</td>
<td>62</td>
</tr>
<tr>
<td>L2d</td>
<td>62</td>
<td>48</td>
<td>23</td>
<td>60</td>
</tr>
<tr>
<td>L1</td>
<td>75</td>
<td>62</td>
<td>11</td>
<td>80</td>
</tr>
</tbody>
</table>

* Yield determined by crude $^1$H NMR with mesitylene as an internal standard; enantioselectivities determined by HPLC analysis.
We also examined the borane influence on the catalytic efficiency and level of enantioselectivity in another substrate X19 with the expectation that it would provide additional insight into the reaction. A similar trend in enantioselectivity is found for the CAHB of X19 compared to X16. TMDB (B2) give high enantioselectivity (90% ee). However, unlike X16, only small amount of the β-isomer are formed presumably due to increased steric hindrance at the β-position due to the cyclohexyl substituent. As discussed earlier in this chapter, reagents and conditions have been identified for which directed CAHB is very efficient with TMDB enabling the asymmetric hydroboration of 1,1-disubstituted substrates to be developed into a highly enantiomeric and practical reaction.

**Table 6** Catalytic hydroboration of 3-cyclohexyl-3-butenolic acid phenyl amide X19 with variety of boranes

<table>
<thead>
<tr>
<th>L</th>
<th>γ %</th>
<th>% ee (γ)</th>
<th>β %</th>
<th>γ %</th>
<th>% ee (γ)</th>
<th>β %</th>
<th>γ %</th>
<th>% ee (γ)</th>
<th>β %</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2a</td>
<td>79</td>
<td>60</td>
<td>3</td>
<td>74</td>
<td>70</td>
<td>7</td>
<td>79</td>
<td>90</td>
<td>3</td>
</tr>
<tr>
<td>L2c</td>
<td>78</td>
<td>55</td>
<td>3</td>
<td>74</td>
<td>70</td>
<td>7</td>
<td>70</td>
<td>82</td>
<td>3</td>
</tr>
<tr>
<td>L2d</td>
<td>75</td>
<td>5</td>
<td>4</td>
<td>78</td>
<td>60</td>
<td>3</td>
<td>71</td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>L1</td>
<td>58</td>
<td>64</td>
<td>3</td>
<td>76</td>
<td>50</td>
<td>2</td>
<td>62</td>
<td>55</td>
<td>2</td>
</tr>
<tr>
<td>L3</td>
<td>70</td>
<td>-15</td>
<td>5</td>
<td>45</td>
<td>40</td>
<td>3</td>
<td>30</td>
<td>-55</td>
<td>5</td>
</tr>
</tbody>
</table>

* The yield determined by 1H-NMR, the enantiomeric excess determined by HPLC.
2.5 A More Detailed Summary of pinBH Data for Comparison Purposes

While some data are presented in the preceding two tables, we studied the efficiency and selectivity of CAHB with pinBH (B1) in greater detail since this reagent has often been used for catalyzed hydroboration and is commercially available, stable, easily stored and (if needed) easily prepared. Neither the borane reagents nor the modified catalysts were able to reach the enantioselectivity and regioselectivity obtained from TMDB. The results of this study are summarized in tables 7, 8 & 9.

Table 7 Catalytic hydroboration of 1,1-disubstituted phenyl amides X17, X18 and X20 with pinBH.

![Chemical Structure Image]

<table>
<thead>
<tr>
<th>Ligand</th>
<th>% yield</th>
<th>% ee</th>
<th>Ligand</th>
<th>Yield</th>
<th>% ee</th>
<th>Ligand</th>
<th>Yield</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2a</td>
<td>63</td>
<td>67</td>
<td>L2a</td>
<td>68</td>
<td>60</td>
<td>L2a</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>L2c</td>
<td>60</td>
<td>68</td>
<td>L2c</td>
<td>71</td>
<td>55</td>
<td>L2c</td>
<td>72</td>
<td>65</td>
</tr>
<tr>
<td>L2d</td>
<td>64</td>
<td>53</td>
<td>L2d</td>
<td>65</td>
<td>45</td>
<td>L2d</td>
<td>71</td>
<td>60</td>
</tr>
<tr>
<td>L1</td>
<td>57</td>
<td>50</td>
<td>L3a</td>
<td>75</td>
<td>-32</td>
<td>L1</td>
<td>60</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>L1</td>
<td>64</td>
<td>62</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*% Yield and % ee are representative of the γ-hydroxyamide isomer
The CAHB of the X18 substrate proceeds smoothly and goes to completion when using pinBH borane. However, the enantioselectivity induction is not improved when changing the borane source from TMDB to pinBH the same trend observed in X21 and X22. The summary of this screening are located in Table 8.

**Table 8** Catalytic hydroboration of 1,1-disubstituted phenyl amides X21 and X22 with pinBH

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield</th>
<th>ee %</th>
<th>Ligand</th>
<th>Yield</th>
<th>e.e %</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2a</td>
<td>62</td>
<td>60</td>
<td>L2a</td>
<td>64</td>
<td>67</td>
</tr>
<tr>
<td>L2c</td>
<td>72</td>
<td>51</td>
<td>L2c</td>
<td>68</td>
<td>45</td>
</tr>
<tr>
<td>L2b</td>
<td>63</td>
<td>43</td>
<td>L1</td>
<td>53</td>
<td>40</td>
</tr>
<tr>
<td>L1</td>
<td>75</td>
<td>34</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*% Yield and % ee are representative of the γ-hydroxyamide isomer
Overall, 4,4,6-trimethyl-1,3,2-dioxaborinane (TMDB (B2)), has been also found to be an excellent borane reagent for directed CAHB; it is generally more reactive and selective than pinBH and yet stable and easily prepared.\textsuperscript{47}

To survey the role of the ligands, we have done CAHB using Rh\((\text{nbd})_2\text{BF}_4\) in conjunction with TADDOL-derived monophosphite, TADDOL-derived phosphoramidites or BINOL-derived monophosphoramidite and pinBH affords, after oxidative work-up, $\beta$-hydroxyamides. The results are summarized in Table 9.

\begin{scheme}
\begin{center}
\begin{tikzpicture}
\node [text width=\textwidth,align=center] {\textbf{Scheme 9} Catalytic hydroboration of X16 phenyl amide with variety of ligands.};
\end{tikzpicture}
\end{center}
\end{scheme}
Regardless of the ligand used (i.e., TADDOL-derived monophosphite, TADDOL-derived phosphoramidite, or BINOL-derived monophosphoramidite), CAHB with pinBH affords the γ-hydroxy amide as the major product (Table 9). However, the various ligands do affect the product ratio suggesting that small changes in the ligand scaffold alters the topography at the site of catalysis in a significant way. The TADDOL-derived monophosphites (i.e., \textbf{L2a}, \textbf{L2b}, \textbf{L2c} and \textbf{L2d}) behave similarly giving predominantly the corresponding γ-hydroxy product after oxidative workup. Among the ligands studied here, this group ligand gives the highest amount of β-hydroxy product. For example, CAHB with \textbf{L2a}, and \textbf{L2c} yield 34\% & 36\% of the β-product, respectively. Directed

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Ligand} & \textbf{γ %} & \textbf{% ee} & \textbf{β %} \\
\hline
\textbf{L2b} & 65 & 50 & 24 \\
\textbf{L2d} & 62 & 48 & 23 \\
\textbf{L2c} & 58 & 52 & 36 \\
\textbf{L2a} & 66 & 60 & 34 \\
\hline
\textbf{L1} & 75 & 62 & 11 \\
\hline
\textbf{L3a} & 92 & -18 & 1 \\
\textbf{L3c} & 92 & -40 & 1 \\
\hline
\textbf{L3d} & 90 & -34 & 1 \\
\textbf{L3b} & 89 & -15 & 2 \\
\hline
\end{tabular}
\caption{Catalytic Hydroboration of \textbf{X16} phenyl amide with variety of ligands}
\end{table}
CAHB of X16 by pinBH with TADDOL-derived phosphoramidites L3a, L3b, L3c and L3d give high yield 89-92% of the γ-product indicating very high regioselectivity; less than 2% of the β-isomer is found with these ligands. Unfortunately, the level of enantioselectivity induced by those ligands is low, only an average of 32% ee. Similarly, the BINOL-derived phosphoramidite generates the γ-hydroxy product predominantly but with a modest level of enantioselectivity (75, 62% ee). Finally, it is also noteworthy that enantioswitching is observed in the some cases for the CAHB of X16 by pinBH. Enantioswitching describes the situation where similar ligand scaffolds of the same absolute configuration give enantiomeric products. For example, compare the results obtained with L3c give -40 % ee while L2a give 60% ee. There is no general mechanistic rationale accounting enantioswitching. Similarly, it is difficult to rationalize why the yield changes with small structural and electronic changes in the ligands. These differences may simply reflect significant and essential differences in catalyst reactivity, structure, and/or the reaction mechanism.

2.6 Exploration into application of boronates

The CAHB of 1,1-disubstituted substrates exhibits high selectivity producing chiral organoboronate derivatives which can be either be oxidized to give the non-racemic chiral alcohol or potentially used in other transformations. To illustrate the latter, treating the chiral organoboronate with KHF2 gives the trifluoroborate salt. These can be used in Suzuki-Miyaura coupling. For example, organoboronate is obtained in good yield (53%) from X16 (R=Me). Scheme 10 shows the subsequent transformations to illustrate its synthetic utility.
Scheme 10  (a)  aq NaOH, H₂O₂; (b) KHF₂, MeOH/H₂O; (c) 5%Pd(OAc)₂, 10% RuPhos, Ar-X, K₂CO₃, toluene/H₂O, 80 °C (Ar-X= Chlorobenzene.yield=81%).

In summary the directed CAHB of 1,1-disubstituted alkene has proven to be rewarding. High level of high levels of regio- and enantioselective control can results in CAHB of a β,γ-unsaturated amide framework. Furthermore, we also studied directed CAHB of 1,1-disubstituted alkenes consisting of a more synthetically versatile directing groups in the following Chapter.
Chapter 3.1 Catalytic asymmetric hydroboration of $\beta,\gamma$-unsaturated ester and Weinreb amides

The use of a phenyl amide as a directing group has played a major role in the direct CAHB reaction developed in the Takacs group as is apparent from the results described in Chapter 2. For example, CAHB of $X_{18}$ by 4,4,6-trimethyl-1,3,2-dioxaborinane (TMDB) catalyzed by Rh(nbd)$_2$BF$_4$ in conjunction with the TADDOL-derived phosphite $L_{2a}$ affords -dioxaborato amide $X(18)$-1 in excellent enantiomeric purity (72%, 95% ee); only a trace of the $\beta$-substituted product is found (<3%). We sought to expand the scope of the directed CAHB of 1,1-disubstituted alkene by opening options for subsequent chemistry. Accordingly, we investigated other directing groups for the 1,1-disubstituted alkenes at hand. In this chapter, we report that the tert-butyl ester moiety promotes the directed CAHB utilizing the same chiral rhodium catalyst. For example, CAHB of $X_{23}$ affords $X(23)$-1 in the similar yield and similarly high enantiomeric purity as the corresponding phenyl amide. The reaction proceeds with good regiocontrol as well; only a trace amount of the $\beta$-hydroxy ester is formed. Oxidative workup with basic hydrogen peroxide leads to cyclization of the $\gamma$-hydroxy ester to the $\gamma$-lactone.

In evaluating the directed CAHB of $X_{23}$, several BINOL-derived phosphoramidite, TADDOL-derived phosphite, and phosphoramidite ligands derivatives were examined from the list shown below. The reactivity and enantioselectivity vary widely. Overall, directed CAHB of the tert-butyl ester derivatives with pinBH gives good reactivity with moderate enantiomeric induction; generally they afford results similar to those obtained from the corresponding phenyl amide substrate. For example, the CAHB of the $X_{23}$ in
presence of $\textbf{L2a}$ and pinBH furnish, after oxidation, $\gamma$-hydroxy alcohol in (57, 81% ee); the CAHB of the phenyl amide $\textbf{X16}$ in presence of $\textbf{L2a}$ and pinBH furnish $\gamma$-hydroxy alcohol (66, 60% ee). Certain ligands derived from the TADDOL scaffold afford catalysts that exhibit good enantioselectivity. For example, the parent TADDOL-derived phenylphosphite $\textbf{L2c}$ affords $\textbf{X(23)-1}$ in 75% ee and the corresponding (3,5-dimethyl)phenyl analogue $\textbf{L2d}$ gives 69% ee (Table 10).
The previous screening of phenyl amide substrates it was found that TMDB increases the enantioselectivity compared to pinBH. It was therefore expected that directed CAHB of the tert-butyl ester substrates by TMDB would again give higher levels of enantioselectivity. As summarized in Table 11, this proved to be the case. The enantioselectivity increases in each case; L2a gives the highest enantiomeric excess (94%) among the group of ligands. For example, the CAHB of the X23 in presence of L2a and TMDB furnish γ-hydroxy alcohol (63, 94% ee) and in presence of L2d furnish γ-hydroxy alcohol (63, 92% ee). It is worth noting that the BINOL-derived phosphoramidite L1 also gives improved enantioselectivity, 82% ee with TMDB, as compared to 72% ee with pinBH. The high degree of stereoselectivity obtained with the tert-butyl ester moiety should provide a powerful method for stereoselective construction of a chiral intermediate for target-directed synthesis.

Table 10  Catalytic hydroboration of 3-methyl-3-butoenoic acid tert-butyl ester X23 with pinBH.

<table>
<thead>
<tr>
<th>Ligands</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2a</td>
<td>57</td>
<td>81</td>
</tr>
<tr>
<td>L2c</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>L2d</td>
<td>52</td>
<td>69</td>
</tr>
<tr>
<td>L1</td>
<td>49</td>
<td>72</td>
</tr>
<tr>
<td>L3</td>
<td>58</td>
<td>-10</td>
</tr>
</tbody>
</table>
Table 11 Catalytic hydroboration of 3-methyl-3-butenolic acid tert-butyl ester X23 with TMDB.

<table>
<thead>
<tr>
<th>Ligands</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2a</td>
<td>63</td>
<td>94</td>
</tr>
<tr>
<td>L2c</td>
<td>60</td>
<td>88</td>
</tr>
<tr>
<td>L2d</td>
<td>63</td>
<td>92</td>
</tr>
<tr>
<td>L1</td>
<td>50</td>
<td>82</td>
</tr>
<tr>
<td>L3a</td>
<td>59</td>
<td>-23</td>
</tr>
</tbody>
</table>

To explore the scope a second tert-butyl ester substrate bearing an alkyl substituent in β-position was prepared. The benzyl group was chosen because it often enables more rapid and efficient access to structurally novel chemical libraries. The results of the CAHB of X24 by pinBH and TMDB are summarized in tables 12. For the three ligands examined, the regio and enantioselectivity observed was higher than the corresponding reaction with pinBH. The highlight of this study was the regioselectivity of the products, generating a single regioisomer at the γ-position.
Table 12  Catalytic hydroboration of 3-benzyl-3-butenolic acid tert-butyl X24 with pinBH and TMDB.

<table>
<thead>
<tr>
<th>Ligands</th>
<th>Yield %</th>
<th>ee %</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2a</td>
<td>64</td>
<td>61</td>
<td>80</td>
<td>95</td>
</tr>
<tr>
<td>L2b</td>
<td>62</td>
<td>57</td>
<td>72</td>
<td>82</td>
</tr>
<tr>
<td>L2c</td>
<td>51</td>
<td>30</td>
<td>79</td>
<td>92</td>
</tr>
</tbody>
</table>

From the studies conducted above and those carried out by others in the Takacs group, it was concluded that, for the 1,1-disubstituted substrates under investigation, the levels of asymmetric induction are highest for CAHB by TMDB using catalysts modified by the 3,5-diMe(TADDOL)POPh ligand (i.e., L2a). Thus, L2a was the best ligand to work with in exploring the reactions of other substrates in the hopes of developing a catalytic system to construct novel target molecules and use this strategy for chemical synthesis. Further screening reactions were carried out to continue to investigate the scope of this reaction with respect to the β-substituent (Scheme 11). The results are summarized in Table 13. In
each case, the lactone was produced in moderate to good yield and in 90-95% ee; only trace amounts of the β-regioisomer products were observed.

Scheme 11 Catalytic hydroboration of tert-butyl esters with TMDB and L2a ligand.
Table 13  The results of catalytic hydroboration of tert-butyl esters with TMDB and L2a ligand.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ester</th>
<th>Product</th>
<th>Yield</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>X23</td>
<td><img src="image" alt="Ester" /></td>
<td><img src="image" alt="Product" /></td>
<td>62</td>
<td>94</td>
</tr>
<tr>
<td>X24</td>
<td><img src="image" alt="Ester" /></td>
<td><img src="image" alt="Product" /></td>
<td>80</td>
<td>95</td>
</tr>
<tr>
<td>X25</td>
<td><img src="image" alt="Ester" /></td>
<td><img src="image" alt="Product" /></td>
<td>65</td>
<td>91</td>
</tr>
<tr>
<td>X26</td>
<td><img src="image" alt="Ester" /></td>
<td><img src="image" alt="Product" /></td>
<td>76</td>
<td>91</td>
</tr>
<tr>
<td>X27</td>
<td><img src="image" alt="Ester" /></td>
<td><img src="image" alt="Product" /></td>
<td>63</td>
<td>94</td>
</tr>
<tr>
<td>X28</td>
<td><img src="image" alt="Ester" /></td>
<td><img src="image" alt="Product" /></td>
<td>61</td>
<td>90</td>
</tr>
</tbody>
</table>
3.2 Catalytic asymmetric hydroboration of 1,1-disubstituted weinreb amides

We also briefly examined the potential of using Weinreb amides at the directing group for directed CAHB. Weinreb amide derivatives are also useful functional groups for further synthetic transformation. CAHB of Weinreb amide X29 by CatBH and pinBH was screened using Rh(nbd)2BF4 in conjunction with TADDOL-derived phosphite ligands and BINOL-derived monophosphoramidite ligands; the results are summarized in Table 14. Using pinBH, the level of enantioselectivity is generally low. For example, the CAHB of X29 by pinBH using L2c gives the γ-hydroxy product in 50% yield and 50% ee. CAHB of the same substrate by TMDB generally gives improved levels of enantioselectivity generally across the series of TADDOL- and BINOL-derived monophosphites and phosphoramidites. For example, CAHB of X29 by TMDB using L2a generates the γ-hydroxy products in 91% ee, however, the yield (45%) remains only modest in these preliminary experiments.

Scheme 12 Catalytic hydroboration of 5-methyl-3-methylidenehexanoic acid weinreb amides X29 with pinBH and TMDB.
Table 14 The results of catalytic hydroboration of 5-methyl-3-methylidenehexanoic acid weinreb amides X29 with pinBH and TMDB

<table>
<thead>
<tr>
<th>Ligands</th>
<th>Yield %</th>
<th>ee %</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2a</td>
<td>48</td>
<td>45</td>
<td>45</td>
<td>91</td>
</tr>
<tr>
<td>L2c</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>L2d</td>
<td>40</td>
<td>30</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>L1</td>
<td>20</td>
<td>25</td>
<td>38</td>
<td>20</td>
</tr>
</tbody>
</table>

* % Yield and % ee are representative of the γ-hydroxyamide isomer

The results in Table 13 suggest that the methodology should be very amenable to the stereoselective construction of chiral γ-hydroxy esters and β-substituted-γ-lactones. We attempted to construct the γ-phenyl lactone X30, a precursor to (R)-(−)-baclofen, which is a therapeutically effective GABAB receptor agonist. Unfortunately, this reaction did not proceed smoothly and the desired products were not formed cleanly under this condition because of alkene reduction and β-substitution. Although this application failed, the methodology has been successfully used by others in the Takacs group to prepare lignan precursors in good yield and high enantiomeric purity. Other potential applications are discussed in the following section.
Scheme 13  Attempted route for the preparation of β-phenyl-γ-butyrolactone

3.3 Potential applications of the directed CAHB of unsaturated esters in synthesis.

The rhodium-catalyzed directed CAHB reaction is developing into one of the most versatile and general methods developed for the preparation of highly enantiomeric selectivity of organoboronates. We envision that this method will ultimately serve in the asymmetric synthesis of variety of heterocyclic and carbocyclic compounds that found application in both medicinal and material chemistry. In the case of β,γ-unsaturated amides and esters, 1,1-disubstituted substrates react to form products with a high degree of regio- and enantioselectivity. For example, CAHB of X23 followed by work up with hydrogen peroxide and aqueous sodium hydroxide yields lactone X(23)-1 in excellent enantiomeric purity (62%, 94% ee). This lactone offers unique advantages as an intermediate for asymmetric synthesis and has been used in asymmetric total synthesis (Scheme 14). For example, Riaz reported the isolation and separation of the desired isomer of this lactone and used it to carry out a more expeditious and efficient synthesis of xyloketal. The latter compound has attracted attention due to its unusual C₃-symmetric structure and it’s as a potent inhibitor of acetylcholine esterase.
Scheme 14 Representative examples of applications of CAHB of 3-methyl-3-butenoic acid tert-butyl ester X23.
CAHB of \textbf{X23} followed by mild oxidative workup (NaBO$_3$, THF/H$_2$O) gives $\beta$-hydroxy ester \textbf{X(23)-2} (Scheme 14). The latter compound has served as a key intermediate in several total syntheses, for example, in the multi-step synthesis of amphidinolide X.\textsuperscript{53} The latter compound was the first macrodiolide consisting of polyketide-derived diacid and diol units isolated from natural sources; it possesses moderate cytotoxicity against L1210 and KB cell lines.\textsuperscript{54} Fujimoto\textsuperscript{55} used the same intermediate in his synthesis of muscone, the component of musk used in many perfumes. Nakamura\textsuperscript{56} prepared stink bug pheromones from this same intermediate.

Other $\beta$-substituted- $\gamma$-lactones prepared by directed CAHB have similarly found used as intermediates in asymmetric total syntheses. For example, Lee used $\gamma$-butyrolactones \textbf{X(26)-1} in a key step of his synthesis of enantiomerically pure Pregabalin\textsuperscript{TM}, an anticonvulsant drug used for neuropathic pain.\textsuperscript{57} Peter reported the alkylation of $\beta$-benzyl-$\gamma$-butyrolactone \textbf{X(24)-1} enroute to several symmetric and unsymmetric lignan homologs (Scheme 15).\textsuperscript{49}
Scheme 15  Preparation of biologically active chiral $\beta$-substituted-$\gamma$-lactones via CAHB

In summary, the recent development of directed CAHB reactions directly produce chiral intermediates that are associated with natural products synthesis and it is expected that the continued development of these methodologies will contribute to other new applications in asymmetric total synthesis.
Chapter 4: Concluding remarks

We provided efficient method in catalytic hydroboration of 1,1-disubstituted alkene using two-point binding methodology. This method furnishes chiral organoboronates in high enantiomeric purity. The reactions of several 1,1-disubstituted alkenes within a $\beta, \gamma$-unsaturated carbonyl framework including phenyl amide, esters, Weinreb amide under several reaction conditions and catalyst systems were investigated in this thesis. Since a little change in topography of chiral ligands has direct influence in the hydroboration outcomes, we postulated that the use of an assortment of TADDOL- and BINOL-derived monophosphites and phosphoramidites could serve as suitable ligands for selective directed hydroboration for 1,1-disubstituted alkene. Using structurally-similar boranes has significant effects not only on the regioselectivity but also on the enantioselectivity of the products.

The presence of directing group can serve an efficient tool in controlling the stereoselectivity in CAHB. To test this hypothesis in 1,1-didubstituted alkene within a $\beta, \gamma$-unsaturated carbonyl framework, the X16 substrate was subjected to the CAHB in presence of 1% Rh(nbd)$_2$BF$_4$ in combination with 2.1% 3,5-diMe(TADDOL)POPh (L2a) and 4,4,6-trimethyl-1,3,2-dioxaborinane (TMDB (B2)) affords $\gamma$-dioxaborato amide X(16)-1 in good yield and excellent enantiomeric purity (53%, 95% ee); and tert-butyl ester were proven to be an excellent directing moieties in the CAHB of 1,1-disubstituted alkenes. For example, the X23 substrate was subjected to the CAHB in presence of 1% Rh(nbd)$_2$BF$_4$ in conjunction with 2.1% 3,5-diMe(TADDOL)POPh and TMDB produced $\gamma$-dioxaborato ester X(23)-1 in good yield and excellent enantiomeric purity (62%, 94% ee). The Weinreb amide also permits the efficient two-point binding
from the carbonyl and olefin moieties. For example, CAHB of Weinreb amide derivative X29 gave promising results (45%, 91% ee).

The 1,1-disubstituted alkenes substrates investigated within this study involve varying degrees of reactivity and enantioselectivity with many ligands and boranes. The most promising results are listed in Table 15.

**Table 15** Results of CAHB of 1,1-disubstituted alkene

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Substrate 1" /></td>
<td>53</td>
<td>95</td>
</tr>
<tr>
<td><img src="image2.png" alt="Substrate 2" /></td>
<td>60</td>
<td>92</td>
</tr>
<tr>
<td><img src="image3.png" alt="Substrate 3" /></td>
<td>80</td>
<td>95</td>
</tr>
<tr>
<td><img src="image4.png" alt="Substrate 4" /></td>
<td>72</td>
<td>90</td>
</tr>
<tr>
<td><img src="image5.png" alt="Substrate 5" /></td>
<td>71</td>
<td>93</td>
</tr>
<tr>
<td><img src="image6.png" alt="Substrate 6" /></td>
<td>73</td>
<td>94</td>
</tr>
<tr>
<td><img src="image7.png" alt="Substrate 7" /></td>
<td>55</td>
<td>94</td>
</tr>
<tr>
<td>Substrate</td>
<td>Yield %</td>
<td>ee %</td>
</tr>
<tr>
<td>-----------</td>
<td>---------</td>
<td>------</td>
</tr>
<tr>
<td><img src="image1" alt="Substrate 1" /></td>
<td>62</td>
<td>94</td>
</tr>
<tr>
<td><img src="image2" alt="Substrate 2" /></td>
<td>65</td>
<td>91</td>
</tr>
<tr>
<td><img src="image3" alt="Substrate 3" /></td>
<td>78</td>
<td>91</td>
</tr>
<tr>
<td><img src="image4" alt="Substrate 4" /></td>
<td>80</td>
<td>95</td>
</tr>
<tr>
<td><img src="image5" alt="Substrate 5" /></td>
<td>67</td>
<td>92</td>
</tr>
<tr>
<td><img src="image6" alt="Substrate 6" /></td>
<td>63</td>
<td>94</td>
</tr>
<tr>
<td><img src="image7" alt="Substrate 7" /></td>
<td>45</td>
<td>91</td>
</tr>
</tbody>
</table>
The ability to produce chiral organoboronates through CAHB of two bond binding substrate provides unique opportunities for the accomplishment of verity enantioselective reactions. This protocol offers highly regio-and enantioselectivity, making them extremely powerful tools for synthesis of stereochemically products.
Chapter 5: Experimental Data

**General procedures.** Reactions were carried out in a dry nitrogen atmosphere. Dichloromethane (DCM) and tetrahydrofuran (THF) were freshly distilled under the following conditions: THF from sodium metal and benzophenone, and DCM from calcium hydride. HPLC solvents were filtered through Millipore filter paper. When indicated in the following procedures, solvents were degassed by freezing under reduced pressure followed by a dry nitrogen atmosphere thaw (3–4 times). 4,4,6-Trimethyl-1,3,2-dioxaborinane TMDB was distilled immediately before use. All synthesized compounds were purified with flash chromatography using EMD Silica Gel 60 Geduran®, distilled via short path distillation, or trituated. Thin Layer Chromatography analyses were performed on Analtech Silica Gel HLF (0.25 mm) precoated analytical plates and visualized with use of handheld short wavelength UV light, iodine stain (I\(_2\) and EMD Silica Gel 60 Geduran®) or vanillin stain (ethanol, H\(_2\)SO\(_4\), and vanillin). HPLC analyses were performed with use of an ISCO model 2360 HPLC and Chiral Technologies, Inc. chiral HPLC columns (Chiralcel OD; column: 250 x 4.6 mm) Data were recorded and analyzed with ChromPerfect chromatography software (version 5.1.0). NMR spectra were recorded on 600, 400, and 300 MHz Bruker Advance NMR spectrometers using residue CHCl\(_3\) (δ 7.27 ppm) or CDCl\(_3\) (δ 77.0 ppm) for reference unless otherwise specified. Peaks are expressed as m (unresolved multiplet), q (quartet), t (triplet), d (doublet) or s (singlet). IR spectra were recorded using an Avatar 360 FT-IR. Optical rotations were measured as solutions, 1.0 g/100 mL in chloroform unless indicated otherwise, and recorded using an Autopol III automatic polarimeter. HRMS analyses were performed by the Nebraska Center for Mass Spectrometry.
Representative procedure for the preparation of allylic acid

\[
\text{Cl} = \text{Mg, I}_2 \xrightarrow{\text{CO}_2, \text{aq HCl}} \text{HO-}
\]

**Preparation of 3-methyl-3-butenolic acid (X1):** Magnesium turnings and a few crystals of iodine were added to 400 mL of freshly distilled THF (dry) in three necked 1000 mL round bottom flask equipped with a stir bar and condenser. The allylic chloride (16.21 g, 180 mmol) was diluted by twice its volume with THF and added to a dropping funnel. A portion of the allyl chloride solution (ca. 50 mL) was added to the magnesium turnings; exothermic reaction ensued causing the THF to reflux. (Note: if the mixture did not heat to reflux, more allyl chloride (ca 20 mL) was added and the mixture gently heated to reflux using a heat gun). The remaining allyl chloride solution was added dropwise at a rate sufficient to maintain a gentle reflux. Upon complete addition, the cooling reaction was allowed to stir for 30 min under N\textsubscript{2} turning milky white. The mixture was cooled to -78°C (30 min). Afterwards, a steady stream of CO\textsubscript{2} blanketed the mixture for (ca 1 h). The temperature was slowly allowed to increase to 0 °C by removing the cold bath. The pH was then adjusted to 10-11 by the addition of cold 2 M aq NaOH and extracted with diethyl ether three times. The mixture was then acidified with cold 4 M HCl to pH 2-3 and extracted three times with diethyl ether. The organic solvent was concentrated under reduced pressure to affords after flash chromatography on silica gel (50:50 Hexanes:Ethyl acetate), the title compound (6g, 33%) as a light yellow oil; TLC analysis \( R_f \) 0.30 (50:50 hexanes :dichloromethane); \(^1\text{H}\) NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) 11.82 (1H, br s, OH), 4.96 and 4.89 (2H, s’s, d), 3.09 (2H, s, b), 1.84 (3H, s, e); \(^{13}\text{C}\) NMR (100
Representative procedure for the preparation of allylic alcohols.\(^{58}\)

General procedure illustrated for the preparation of 2-methylene-4-phenylbutan-1-ol (X2): Into a flame-dried three-neck RBF with condenser and a dropping funnel under N\(_2\) was added THF (40 mL), magnesium turnings (2g, 88 mmol) and a tiny crystal of I\(_2\). A solution of (2-bromoethyl) benzene (8.0 g, 88 mmol) in THF (10 mL) was added drop wise while reaction was initiated by heating with a heat gun. After the addition of (2-bromoethyl) benzene was complete, the reaction was stirred for 3 hours. The mixture was then cooled to 0 °C and transferred via cannula into a cooled (-70 °C) suspension of copper iodide (5.0 mmol, 50 mol %) and propargyl alcohol (10.0 mmol) in dry toluene (15 mL), which was followed by a natural warming to room temperature. After complete conversion of the starting material (ca. 18 h) the reaction mixture was cooled to 0 °C, quenched by the addition of saturated NH\(_4\)Cl and extracted with diethyl ether (3 X 30 mL). The combined extracts were dried (anhyd. MgSO\(_4\)). The solvent was evaporated and the crude product purified by flash chromatography (85:15 Hexane: ethyl acetate) to afford the title compound (2.5 g, 58 %) as a colorless oil; TLC analysis R\(_f\) 0.50 (60:40 hexanes:ethyl acetate); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.36-7.33 (2H, t, \(J = 8\), g,g'), 7.27-
7.25 (3H, d, J=8, h,h’, i), 5.12 and 4.98 (2H, s’s, c), 4.14(2H, s, a), 2.87(2H, t, J=4, d)
2.41(2H, t, J=8, e), 2.34 (1H, br s, OH); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ148.44(b), 141.09
(f), 128.40(h,h’), 128.38(g,g’), 125.96(i), 109.05(c), 65.92(a), 34.66 (e), 34.30(d); IR
(neat) 3325 (OH stretch), 2922 (OH bend), 1018, 1056, 1453(C-O stretch), 647, 729.
HRMS (FAB) calcd. for C$_{11}$H$_{14}$O (M+Na): 185.0942, found 185.0939 m/z.

**Preparation of 2-cyclohexyl-2-propenol (X3):** Following the general
procedure, cyclohexylmagnesium chloride (45 mL of a 2.0 M solution in THF, 90 mmol)
and propargyl alcohol affords the title compound (3.33 g, 79%) as a colorless oil after
flash chromatography over silica gel (80:20 hexanes:ethyl acetate); TLC analysis $R_f$ 0.40
(75:25 hexanes:ethyl acetate); $^1$H NMR (300 MHz, CDCl$_3$) δ 5.00 and 4.86(2H, s’s, c),
4.10(2H, s, a), 2.00–1.85(2H, m, a, OH), 1.85–1.70 (4H, m, e,e’, f,f’), 1.70–1.65(1H, m,
g), 1.30–1.10(5H, m, e,e, f,f’, g); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 154.53(b), 107.40(c),
65.05(a), 41.25(d), 32.43(e,e’), 26.70(f,f’), 26.29(g); IR (neat) 3306 (O-H stretch), 2850,
1649, 1060, 1019 (C-O stretch), 889, 625 cm$^{-1}$; HRMS (EI) calcd. for C$_9$H$_{16}$O: 140.1201,
found 140.1204 m/z.
Preparation of 2-Phenyl-2-propenol (X4): Following the general procedure, phenylmagnesium bromide (90 mL of a 1.0 M solution in THF, 90 mmol) and propargyl alcohol affords, after flash chromatography on silica gel (80:20 hexanes:ethyl acetate), the title compound (3.08 g, 77%) as a light yellow oil; TLC analysis $R_f$ 0.30 (75:25 hexanes:ethyl acetate); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.55–7.45 (2H, m, e,e’), 7.45–7.30 (3H, m, f,f’, g), 5.50 and 5.39 (2H, s’s, c), 4.55 (2H, s, a), 2.28 (1H, br s, OH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 147.30 (b), 138.60 (d), 128.53 (f,f’), 127.94 (g), 126.10 (e,e’), 112.55 (c), 64.87 (a); IR (neat) 3370 (O-H stretch), 2945, 2883, 1735, 1632, 1495, 1444, 1372, 1239, 1043 (C-O stretch), 1024, 902, 778, 706, 609 cm$^{-1}$.

Representative procedure for the preparation of allylic carbonates.$^{59}$

Preparation of 2-phenylethyl ethyl carbonate (X5): To a cooled (0 °C) solution of the allyl alcohol (50 mmol) and dry pyridine (100 mmol) in THF (100 mL) was added ethyl chloroformate (50 mmol) dropwise over 10 min. The mixture was stirred at room temperature for 3 h and then partitioned between dilute aq. hydrochloric acid and ether (ca. 150 mL each). The aqueous phase was extracted with an additional potion of ether,
the combined organic layers washed with brine, and dried (anhyd. MgSO₄). Following evaporation of the solvent, flash chromatography on silica gel (90:10 hexanes:ethyl acetate) gave the title compound (9.37 g, 80%) as a color less oil; TLC analysis Rₜ 0.70 (90:10 hexanes:ethyl acetate); ^1^H NMR (300 MHz, CDCl₃) δ 7.33(2H, m, g,g’), 7.22-7.25(3H, m, k,k’, i), 5.16 and 5.06(2H, s’s, f), 4.64(2H, s, d), 4.24(2H, q, J=4, b), 2.84(2H, t, J=8, h), 2.45(2H, t, J=8, g), 1.36(3H, t, J=5, a); ^1^C NMR (100 MHz, CDCl₃) δ 155(c), 142.93(e), 141.53(i), 128(k,k’), 128.37(g,g’), 126.00(l),113.43(f), 70.12(d), 64.06(b), 34.76(g), 34.02(h), 14.31(a); IR (neat) 1742 (C-O stretch), 1374, 1435, 1496 (C-O stretch), 2933(CH sp² stretch), 698, 908, 1007; HRMS (FAB) calcd. for C₁₄H₁₈O₃(M+Na): 257.1154, found 257.1154 m/z.

Preparation of 2-cyclohexylallyl ethyl carbonate (X6): To a cooled (0 °C) solution of 2-cyclohexylallyl alcohol (2.80 g, 20 mmol) and pyridine (3.16 g, 40 mmol) in THF (30 mL) was added ethyl chloroformate (2.17 g, 20 mmol) dropwise over a period of 10 min. The resultant reaction mixture was allowed to stir for 3 h and then diluted with a solution of dilute HCl (15 mL). The mixture was extracted with diethyl ether (3 x ca. 20 mL) and the combined organic extracts were dried (anhyd. MgSO₄) and concentrated under reduced pressure. Flash chromatography on silica gel (95:5 hexanes:ethyl acetate) afforded the title compound (3.69 g, 87%) as a colorless oil; TLC analysis Rₜ 0.75 (95:5 hexanes:ethyl acetate); ^1^H NMR (300 MHz, CDCl₃) δ 5.04 and 4.96 (2H, s’s, f), 4.60 (2H, s, d), 4.20 (2H, q, J = 7.1 Hz, b), 2.00–1.90 (1H, m, g), 1.90–1.75 (4H, m, h,h’, i,i’),
1.75–1.65 (1H, m, j), 1.31 (3H, t, J = 7.1 Hz, a), 1.30–1.10 (5H, h,h’ , i,i’, j); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 155.07 (c), 148.66 (e), 111.07 (f), 69.35 (d), 63.92 (b), 41.19 (g), 32.09 (h,h’), 26.56 (i,i’), 26.21 (j), 14.25 (a); IR (neat) 2926, 2853, 1742 (C=O stretch), 1649, 1448, 1374, 1241 (C-O stretch), 1004, 908, 890, 790, 630 cm\(^{-1}\); HRMS (Cl) calcd. for C\(_{12}\)H\(_{21}\)O\(_3\) (M+H): 213.1491, found 213.1493 m/z.

**Preparation 2-Phenylallyl ethyl carbonate (X7):** Following the representative procedure, 2-phenylallyl alcohol (2.68 g, 20 mmol) afforded, after flash chromatography on silica gel (95:5 hexanes:ethyl acetate), the title compound (3.46 g, 84%) as a colorless oil; TLC analysis \(R_f\) 0.75 (95:5 hexanes:ethyl acetate); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.50–7.45 (2H, m, h,h’), 7.45–7.30 (3H, m, i,i’, j), 5.60 and 5.45 (2H, s’s, f), 5.06 (2H, s, d), 4.23 (2H, q, J = 7.1 Hz, b), 1.33 (3H, t, J = 7.1 Hz, a); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 155.06 (c), 142.15 (e), 137.86 (g), 128.54 (i,i’), 128.14 (j), 126.04 (h,h’), 115.62 (f), 68.87 (d), 64.15 (b), 14.25 (a); IR (neat) 2984, 1740 (C=O stretch), 1634, 1375, 1242 (C-O stretch), 1006, 910, 872, 789, 705, 547 cm\(^{-1}\).
Representative procedure for the preparation of disubstituted βγ-unsaturated esters.

Preparation of 3-methylidene-5-phenylpentanoic acid ethyl ester (X8): A stirred solution of the allylic carbonate (5 mmol) and Pd(PPh₃)₄ (22.4 mg, 0.1 mmol) was blanketed with a head space of CO to 60 psi. The resulting mixture was warmed to 50 °C and stirred (24 h). Afterwards, the cooled reaction mixture was partitioned between ether/water. The organic layer was dried and concentrated, and the residue was purified by column chromatography on silica (80:20 hexanes:ethyl acetate) to give the title compound (0.490 g, 45%) as a colorless oil: TLC analysis Rₜ 0.70 (90:10 hexanes:ethyl acetate); H NMR (300 MHz, CDCl₃) δ 7.31(2H, m, j,j'), 7.19-7.29( 3H, m, i), 1.27(3H, t, J=8, a), 4.99 and 4.97(2H, s’s, f), 4.14(2H, q, J=8, b), 3.10(2H, s, d), 2.79(2H, t, J=8, g), 2.43(2H, t, J=8, h), 1.27(3H, t, J=8, a); C NMR (75 MHz, CDCl₃) δ 171.48(c), 141.95(e), 141.72(i), 128.49(k, k’), 128.35(j,j’), 125.91(i), 114.02(f), 60.69(b), 42.27(d), 37.59(g), 33.96(h), 14.24(a); IR (neat) 2934 (CH sp² stretch), 1735 (C=O stretch), 1154, 1367, 1387 (CO stretch), 746, 654. HRMS (FAB) calcd. For C₁₁H₁₄O₂ (M+H): 218.1307, found 219.1389 m/z.
Preparation of 2-phenylethyl ethyl acid

![Chemical structure]

Preparation of 3-Methylidene-5-phenylpentanoic acid (X9): To the compound (230 mg, 26 mmol) **X8** was added methanol 1 mL and 2 N KOH (9 mL), and stirred overnight at room temperature. The resultant basic solution was extracted with dichloromethane (2 x 15 mL) and then acidified. The acidic aqueous layer was extracted with dichloromethane (3 x 30 mL) and the combined organic extracts were dried (anhyd. MgSO₄) and concentrated under reduced pressure. The crude residue was then purified via flash chromatography on silica gel (50:50 hexanes:ethyl acetate) to afford the title compound (184 mg g, 63%) as a light yellow oil; TLC analysis Rf 0.50 (50:50 hexanes:ethyl acetate); **¹H NMR** (400 MHz, CDCl₃) δ 11.10 (1H, br s, OH), 7.34-7.30 (2H, m, J= 8, h,h’), 7.28-7.21 (3H, m, J= 8, i,i’, j), 5.05 and 5.03 (2H, s’s, d), 3.16 (2H, s, b), 2.81 (2H, t, J=8, e), 2.47 (2H, t, J=8, f); **¹³C NMR** (100 MHz, CDCl₃) δ 178.03(a), 141.54(c), 141.23(g), 128.40(i, i’), 128.35(h,h’), 125.98 (j), 114.79(d), 41.91(b), 37.48(e), 33.95(f); IR (neat) 3026(OH stretch), 2926 (OH bending), 1703 (C=O stretch), 1216, 1293, 1406(C-O stretch), 967, 768, 765. cm⁻¹. HRMS (ESI) calcd. For **C₁₂H₁₄O₂** (M+Na): 213.0891, found 213.0813 m/z.
Representative procedure for the preparation of $\beta,\gamma$-unsaturated amides

![Chemical structure]

Preparation of 3-methyl-3-butenoic acid phenyl amide (X16): To a cooled (0 °C) solution of 3-methyl-3-butenoic acid (501 mg, 5.0 mmol) in dichloromethane (DCM, 10 mL) was added aniline (560 mg, 6.0 mmol) and $N,N$-dimethylamino pyridine (DMAP, 61 mg, 0.50 mmol). After the resulting mixture was allowed to stir for 0.5 h at the same temperature, $N,N$-dicyclohexylcarbodiimide (DCC, 1.14 g, 5.5 mmol) was added in one portion and allowed to warm to room temperature. After an overnight stir, the reaction mixture was filtered and the filtrate was washed with dilute HCl (2 x 15 mL, 1M). The organic layer was dried (anhyd. MgSO$_4$) and concentrated under reduced pressure. Flash chromatography on silica gel (75: 25 hexanes:ethyl acetate) affords the title compound (570 mg, 65%) as a white solid: mp 97–99 °C; TLC analysis $R_f$ 0.30 (75:25 hexanes:ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.65 (1H, br s, NH), 7.53 (2H, d, $J = 8.0$ Hz, c,c’), 7.33 (2H, t, $J = 7.6$ Hz, b,b’), 7.13 (1H, t, $J = 7.2$ Hz, a), 5.09 and 5.02 (2H, s’s, h), 3.15 (2H, s, f), 1.88 (3H, s, i); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 168.58 (e), 140.35 (d), 137.80 (g), 128.98 (b,b’), 124.36 (a), 119.79 (c,c’), 116.09 (h), 47.41 (f), 22.46 (i); IR (neat) 3291 (N-H stretch), 3060, 2953, 2921, 2865, 1657 (C=O stretch), 1638, 1595, 1525 (N-H bend), 1440, 1307, 1251 (C-N stretch), 1162, 869, 738, 688, 617 cm$^{-1}$. 
Preparation of 3-Methylidene-5-phenylpentanoic acid phenyl amide (X21):

Following the general procedure, 3-methylene-5-phenylpentanoic acid (1 g, 5.25 mmol) affords, after flash chromatography on silica gel (75:25 hexanes:ethyl acetate), the title compound (484 mg, 61%) as a white solid: mp 79–80 °C; TLC analysis $R_f$ 0.40 (75:25 hexanes:ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48(2H, d, $J$ = 8.0 Hz, l,l’), 7.40–7.30 (3H, m, c,c’, NH), 7.30–7.25(2H, m, b,b’), 7.25–7.20(3H, m, m,m’,n), 7.14(1H, t, $J$ = 6.8 Hz, a), 5.16 and 5.12 (2H, s’s, h), 3.19(2H, s, f), 2.86 (2H, t, $J$ = 8.0 Hz, j), 2.50(2H, t, $J$ = 8.4 Hz, i); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 168.31(e), 143.69(d), 141.21 (k), 137.66 (g), 128.99 (b,b’), 128.44 (l,l’), 128.35 (m,m’), 126.06 (n), 124.38 (a), 119.69 (c,c’), 115.75 (h), 46.25 (f), 37.44 (i), 33.91 (j); IR (neat) 3237 (N-H stretch), 3185, 3061, 3025, 1652 (C=O stretch), 1596, 1541 (N-H bend), 1469, 1443, 1398, 1346, 1247 (C-N stretch), 1193, 961, 897, 747, 694, 616 cm$^{-1}$; HRMS (EI) calcd. for C$_{19}$H$_{21}$NO: 279.1623, found 279.1649 m/z.

Preparation of 3-Cyclohexyl-3-butenoic acid phenyl amide (X19): follow the same procedure describe above with carbonylation, A mixture of 2-cyclohexylallyl ethyl carbonate (1.06 mg, 5.0 mmol) and Pd(PPh$_3$)$_4$ (116 mg, 0.10 mmol) was put under a pressurized (60 psi) atmosphere of carbon monoxide. The mixture was heated (50 °C) for
24 h and then allowed to cool to room temperature and ambient pressure. The resultant black mixture was run over a silica plug to afford the crude $\beta,\gamma$-unsaturated ethyl ester. The crude residue was taken up in a mixture of Methanol (5 mL) and aqueous 2 M Potassium hydroxide (50 mL) and stirred overnight at room temperature. The resultant basic solution was extracted with dichloromethane (2 x 15 mL) and then acidified. The acidic aqueous layer was extracted with dichloromethane (3 x 30 mL) and the combined organic extracts were dried (anhyd. MgSO$_4$) and concentrated under reduced pressure. The crude $\beta,\gamma$-unsaturated acid (537 mg, 3.2 mmol) was used in the next step without further purification.

Following the general amidation procedure with DCC, the crude $\beta,\gamma$-unsaturated acid affords, after flash chromatography on silica gel (80:20 hexanes:ethyl acetate), the title compound (469 mg, 39%, 3 steps) as a white solid: mp 81–83 ºC; TLC analysis $R_f$ 0.40 (75:25 hexanes:ethyl acetate); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.62 (1H, br s, NH), 7.51 (2H, d, $J$ = 7.8 Hz, c,c’), 7.34 (2H, t, $J$ = 8.1 Hz, b,b’), 7.12 (1H, t, $J$ = 7.5 Hz, a), 5.15 and 5.06 (2H, s’s, h), 3.19 (2H, s, f), 2.05–1.95 (1H, m, i), 1.90–1.65 (5H, m, k,k’, l,j,j’), 1.30–1.10 (5H, m, j,j’,k,k’, l); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.85 (e), 150.39 (d), 137.72 (g), 129.00 (b,b’), 124.31 (a), 119.65 (c,c’), 113.79 (h), 44.06 (i), 44.42 (f), 32.18 (j,j’), 26.48 (k,k’), 26.09 (l); IR (neat) 3330 (N-H stretch), 2921, 2848, 1665 (C=O stretch), 1596, 1514 (N-H bend), 1436, 1346, 1245 (C-N stretch), 1167, 956, 905, 749, 691, 586 cm$^{-1}$; HRMS (ESI) calcd. for C$_{16}$H$_{21}$NaNO (M+Na): 266.1521, found 266.1526 m/z.
Preparation of 3-Phenyl-3-butenoic acid phenyl amide (X20): Following the general procedure, 2-phenylallyl ethyl carbonate (1.03 g, 5.0 mmol) affords, after flash chromatography on silica gel (75:25 hexanes:ethyl acetate), the title compound (215 mg, 18%, 3 steps) as a white solid: mp 90.5–93.5 ºC; TLC analysis \( R_f \) 0.40 (75:25 hexanes:ethyl acetate); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.60–7.50 (3H, m, j,j’,NH), 7.45–7.35 (5H, m, c,c’,k,k’,l), 7.35–7.25 (2H, m, b,b’), 7.10 (1H, t, \( J = 7.5 \) Hz, a), 5.78 and 5.41 (2H, s’s, h), 3.65 (2H, s, f); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 168.35 (e), 142.08 (d), 138.76 (i), 137.61 (g), 128.94 (b,b’), 128.82 (j,j’), 128.47 (l), 125.78 (k,k’), 124.43 (a), 119.84 (c,c’), 117.44 (h), 45.14 (f); IR (neat) 3248 (N-H stretch), 3192, 3135, 3085, 2929, 1804, 1656 (C=O stretch), 1597, 1554 (N-H bend), 1484, 1441, 1338, 1232 (C-N stretch), 1162, 896, 770, 752, 688 cm\(^{-1}\).

Representative procedure of preparing phenyl amide via tert-butyl ester approach

Preparation of 5-methyl-3-methylidenehexanoic acid phenyl amide (X18): To tert-butyl ester X26 (595 mg, 3.0 mmol) was added trifluoroacetic acid (CF\(_3\)CO\(_2\)H, 8 mL)
followed by a 1 h stir at room temperature. The mixture was concentrated under reduced pressure, taken up in ethyl acetate (15 mL), and washed with dilute sodium hydroxide (3 x 10 mL, 2 M). The basic aqueous layer was acidified and extracted with dichloromethane (3 x 15 mL). The combined organic extracts were dried (anhyd. MgSO₄) and concentrated under reduced pressure to afford the crude β,γ-unsaturated acid (320 mg, 2.0mmol) which was used in the next step without further purification.

Following the general amidation procedure with DCC, the crude β,γ-unsaturated acid affords, after flash chromatography on silica gel (80:20 hexanes:ethyl acetate), the title compound (390 mg, 60%) as a white solid: mp 90–92.5 ºC; TLC analysis R₅ 0.40 (75:25 hexanes:ethyl acetate); ¹H NMR (300 MHz, CDCl₃) δ 7.87 (1H, br s, NH), 7.53 (2H, d, J = 8.1 Hz, c,c’), 7.32 (2H, t, J = 8.1 Hz, b,b’), 7.11 (1H, t, J = 7.5 Hz, a), 5.09 and 5.06 (2H, s’s, h), 3.13 (2H, s, f), 2.02 (2H, d, J = 6.9 Hz, i), 1.90–1.75 (1H, m, j), 0.91 (6H, d, J = 6.6 Hz, k,k’); ¹³C NMR (75 MHz, CDCl₃) δ 168.92 (e), 143.29(d), 137.90 (g), 128.94 (b,b’), 124.30 (a), 119.84 (c,c’), 116.17 (h), 45.67 (f), 45.63 (j), 25.96 (i), 22.41 (k,k’); IR (neat) 3290 (N-H stretch), 2953, 2921, 2865, 1657 (C=O stretch), 1638, 1595, 1530 (N-H bend), 1440, 1393, 1307, 1295, 1251 (C-N stretch), 1223, 1162, 1120, 996, 869, 738, 668, 617 cm⁻¹; HRMS (Cl) calcd. for C₁₄H₂₀NO (M+H): 218.1545, found 218.1539 m/z.
Preparation 3-Methylidene-pentanoic acid phenyl amide (X17): Following the general procedure, 3-ethyl-3-butenoic acid tert-butyl ester X25 (511 mg, 3.0 mmol) affords, after flash chromatography on silica gel (75:25 hexanes:ethyl acetate), the title compound (362 mg, 64%, 2 steps) as a white solid: mp 101–102 °C; TLC analysis Rf 0.40 (75:25 hexanes:ethyl acetate); 1H NMR (400 MHz, CDCl$_3$) δ 7.62 (1H, br s, NH), 7.52 (2H, d, J = 8.0 Hz, c,c’), 7.33 (2H, t, J = 7.6 Hz, b,b’), 7.12 (1H, t, J = 7.6 Hz, a), 5.11 and 5.06 (2H, s’s, h), 3.17 (2H, s, f), 2.18 (2H, q, J = 7.2 Hz, i), 1.11 (3H, t, J = 7.2 Hz, j); 13C NMR (100 MHz, CDCl$_3$) δ 168.72 (e), 146.09(d), 137.79 (g), 128.98 (b,b’), 124.33 (a), 119.74 (c,c’), 113.92 (h), 46.23 (f), 28.89 (i), 12.12 (j); IR (neat) 3240 (N-H stretch), 3187, 2955, 2839, 1658 (C=O stretch), 1595, 1544 (N-H bend), 1488, 1444, 1400, 1352, 1297, 1252 (C-N stretch), 1187, 969, 759, 693 cm$^{-1}$; HRMS (CI) calcd. for C$_{12}$H$_{16}$NO (M+H): 190.1232, found 190.1237 m/z.

Preparation 3-Methylidene-6-phenylhexanoic acid phenyl amide (X22): Following the general procedure, tert-butyl ester X31 (781 mg, 3.0 mmol) affords, after flash chromatography on silica gel (80:20 hexanes:ethyl acetate), the title compound (476 mg, 57%, 2 steps) as a white solid: mp 51–53 °C; TLC analysis Rf 0.50 (75:25 hexanes:ethyl acetate); 1H NMR (400 MHz, CDCl$_3$) δ 7.60 (1H, br s, NH), 7.52 (2H, d, J = 7.9 Hz,
75

m,m’), 7.40–7.35 (2H, m, c,c’), 7.35–7.25 (2H, m, b,b’), 7.25–7.20 (3H, m, n,n’,o), 7.15
(1H, t, J = 7.3 Hz, a), 5.13 and 5.11 (2H, s’s, h), 3.18 (2H, s, f), 2.66 (2H, t, J = 7.7 Hz, k), 2.22 (2H, t, J = 7.4 Hz, i), 1.90–1.80 (2H, m, j); ^13C NMR (100 MHz, CDCl_3) δ
168.71 (e), 144.20 (d), 141.98 (l), 137.71 (g), 129.02 (b,b’), 128.44 (m,m’), 128.37 (n,n’), 125.87 (o), 124.43 (a), 119.83 (c,c’), 115.20 (h), 46.06 (f), 35.52 (i), 35.42 (k), 29.24 (j).

Representative procedure for the preparation of β,γ-unsaturated tert-butyl esters

\[
\text{O} \quad \xrightarrow{1)} \quad \text{LDA} \quad \text{NiBr}_2, \quad \text{2-bromopropene} \quad \text{O}
\]

Preparation of 3-methyl-3-butenolic acid tert-butyl ester (X23): To a cooled (-78 °C) solution of N,N-diisopropylamine (4.2 mL, 30 mmol) in THF (5 mL) was slowly added n-butyllithium (12 mL of a 2.5 M soln. in hexanes, 30 mmol). The resultant mixture was allowed to stir for 0.5 h at the same temperature before the dropwise addition of tert-butyl acetate (4.0 mL, 30 mmol). The reaction mixture was allowed to stir for an additional 0.5 h and the generated tert-butyl lithioacetate solution was used in the next step.

To a cooled (-78 °C) suspension of nickel bromide (2.76 g, 12.6 mmol) in THF (15 mL) was added n-butyllithium (2 mL of a 2.5 M soln. in hexanes, 5 mmol). After the resultant black mixture was allowed to stir for 15 min, 2-bromopropene (2.66 mL, 30 mmol) was added followed by the tert-butyl lithioacetate solution prepared in the previous step. The reaction was allowed to slowly rise to room temperature and stirred for an additional 1 h. The reaction mixture was quenched by the addition of dilute HCl (15 mL, 1 M) and then extracted with diethylether (2 x 20 mL). The combined organic
extracts were dried (anhyd. MgSO₄) and concentrated under reduced pressure. Flash chromatography over silica gel (80:20, hexanes:dichloromethane) affords the title compound (2.34 g, 50%) as a light yellow oil; TLC analysis R_f 0.50 (50:50 hexanes:dichloromethane); ¹H NMR (300 MHz, CDCl₃) δ 4.88 and 4.82 (2H, s’s, f), 2.93 (2H, s, d), 1.80 (3H, s, g), 1.45 (9H, s, a,a’,a’’); ¹³C NMR (75 MHz, CDCl₃) δ 170.72 (c), 139.13 (e), 114.09 (f), 80.42 (b), 44.79 (d), 27.99 (a,a’,a’’), 22.38 (g); IR (neat) 3075, 2976, 2934, 1728 (C=O stretch), 1647, 1455, 1366, 1258 (C-O stretch), 1139, 690, 843 cm⁻¹.

Preparation of 3-Methyldenepentanoic acid tert-butyl ester (X25): Following the general procedure, 2-bromobutene (4.1 g, 30 mmol) affords, after flash chromatography on silica gel (80:20 hexanes:dichloromethane), the title compound (2.9 g, 59%) as a light yellow oil; TLC analysis R_f 0.55 (50:50 hexanes:dichloromethane); ¹H NMR (400 MHz, CDCl₃) δ 4.91 and 4.88 (2H, s’s, f), 2.97 (2H, s, d), 2.12 (2H, q, J = 7.6 Hz, g), 1.46 (9H, s, a,a’,a’’), 1.06 (3H, t, J = 7.6 Hz, h); ¹³C NMR (100 MHz, CDCl₃) δ 170.99 (c), 144.65 (e), 111.83 (f), 80.40 (b), 43.47 (d), 28.78 (g), 28.01 (a,a’,a’’), 12.02 (h); IR (neat) 2935, 2848, 1731 (C=O stretch), 1653, 1391, 1252 (C-O stretch), 1145, 1122, 1040, 948, 761, 576 cm⁻¹.
Preparation of 3-phenyl-3-butenoic acid tert-butyl ester (X27): Following the general procedure, (1-bromovinyl)benzene (4.36 g, 24 mmol) affords, after flash chromatography on silica gel (80:20 hexanes:dichloromethane), the title compound (2 g, 38%) as a light yellow oil; TLC analysis $R_f$ 0.50 (50:50 hexanes:dichloromethane); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40–7.30 (2H, m, j,j’), 7.30–7.20 (3H, m, i,i’, k), 5.01 and 4.95 (2H, s’s, f), 3.48 (2H, s, g), 2.92 (2H, s, d), 1.49 (9H, s, a,a’,a’’); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.60 (c), 141.71 (g), 140.16 (e), 128.29 (h,h’), 127.64 (i,i’), 125.94 (j), 115.72 (f), 80.70 (b), 42.73 (d), 27.89 (a,a’,a’’).

Preparation of 3-(2-phenylethyl)-3-butenoic acid tert-butyl ester (X28): Following the general procedure, 2-bromo-4-phenylbutene (4.13 g, 20 mmol) affords, after flash chromatography on silica gel (75:25 hexanes:dichloromethane), the title compound (2.03 g, 42%) as a light yellow oil; TLC analysis $R_f$ 0.60 (50:50 hexanes:dichloromethane); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.40–7.30 (2H, m, k,k’), 7.30–7.20 (3H, m, j,j’, l), 4.99 and 4.97 (2H, s’s, f), 3.03 (2H, s, d), 2.83 (2H, t, $J = 7.5$ Hz, h), 2.46 (2H, t, $J = 8.4$ Hz, g), 1.51 (9H, s, a,a’,a’’); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.80 (c), 142.47 (i), 141.85 (e), 128.35 (j,j’, k,k’), 125.88 (l), 113.64 (f), 80.58 (b), 43.49 (d), 37.72 (g), 34.05 (h), 28.08
(a,a’,a”); IR (neat) 3028, 2978, 2931, 1726 (C=O stretch), 1647, 1496, 1454, 1366, 1255
(C-O stretch), 1139, 1030, 956, 896, 841, 744, 697 cm⁻¹.

**Representative preparation of tert-butyl esters via of vinyl**

![Representation of tert-butyl esters](image)

**Preparation of 3-iso-butyl-3-butenoic acid tert-butyl ester (X26):** To a mixture of
2,3-dibromopropene (7.01 g, 35 mmol) and copper chloride (173 mg, 1.8 mmol) in THF
(30 mL) was slowly added isobutylmagnesium bromide (40 mmol, 13.8 mL of a 2.9 M
solution in THF) at room temperature. After a 5 h stir, the reaction was quenched with
satd. aq. ammonium chloride (30 mL) and then extracted with diethyl ether (3 x 30 mL).
The combined organic extracts were dried (anhyd. MgSO₄) and concentrated under
reduced pressure. The crude residue was taken up in hexanes, passed through a short
silica plug, and concentrated under reduced pressure. The resultant crude 2-bromo-4-
methylpentene (4.25 g, 26 mmol) was used in the next step without further purification.

Following the general procedure for the nickel-catalyzed substitution of vinyl
bromides, crude vinyl bromide prepared in the previous step affords, after flash
chromatography on silica gel (70:30, hexanes:dichloromethane), the title compound (3.12
g, 45%) as a light yellow oil: TLC analysis Rf 0.50 (50:50 hexanes:dichloromethane); ¹H
NMR (400 MHz, CDCl₃) δ 4.91 and 4.87 (2H, s’s, f), 2.92 (2H, s, d), 1.98 (2H, d, J = 7.2
Hz, g), 1.95–1.85 (1H, m, h), 1.46 (9H, s, a,a’,a”), 0.89 (6H, d, J = 6.6 Hz, i,i’); ¹³C NMR
(100 MHz, CDCl₃) δ 170.90 (c), 141.96 (e), 114.33 (f), 80.36 (b), 45.79 (d), 43.03 (g),
28.00 (a,a’,a”), 25.75 (h), 22.38 (i,i’); IR (neat) 2969, 2912, 1722 (C=O stretch), 1431, 1376, 1177 (C-O stretch), 1117, 884, 826, 740, 521 cm⁻¹.

**Preparation of 3-Benzyl-3-butenoic acid tert-butyl ester (X24):** Following the general procedure, crude 2-bromo-3-phenylpropene prepared from 2,3-dibromopropene (7.01 g, 35 mmol) and phenylmagnesium bromide (40 mmol, 40 mL of a 1.0 M solution in THF) affords, after flash chromatography on silica gel (80:20, hexanes:dichloromethane), the title compound (4.40 g, 54%) as a light yellow oil; TLC analysis R_f 0.60 (50:50 hexanes:dichloromethane); ¹H NMR (300 MHz, CDCl₃) δ 7.40–7.30 (2H, m, j,j’), 7.30–7.20 (3H, m, i,i’,k), 5.01 and 4.95 (2H, s’s, f), 3.48 (2H, s, g), 2.92 (2H, s, d), 1.49 (9H, s, a,a’,a”); ¹³C NMR (75 MHz, CDCl₃) δ 170.75 (c), 142.43 (h), 138.97 (e), 129.17 (i,i’), 128.39 (j,j’), 126.30 (k), 115.26 (f), 80.59 (b), 42.68 (g), 42.40 (d), 28.06 (a,a’,a”); IR (neat) 2978, 1725 (C=O stretch), 1647, 1494, 1366, 1253 (C-O stretch), 1137, 966, 898, 838, 728, 696, 628 cm⁻¹.

**Preparation 3-(3-phenylpropyl)-3-butenoic acid tert-butyl ester (X31):** Following the general procedure, crude 2-bromo-5-phenylpentene prepared from 2,3-
dibromopropene (4.02 g, 20 mmol) and 2-phenylethylmagnesiumbromide (15 mmol) affords, after flash chromatography on silica gel (75:25 hexanes:dichloromethane), the title compound (2.23 g, 57%) as a light yellow oil; TLC analysis R_f 0.60 (50:50 hexanes:dichloromethane); ^1H NMR (300 MHz, CDCl_3) δ 7.35–7.25 (2H, m, l,l'), 7.25–7.15 (3H, m, k,k’, m), 4.94 and 4.93 (2H, s’s, f), 2.97 (2H, s, d), 2.65 (2H, t, J = 7.6 Hz, i), 2.17 (2H, t, J = 7.5 Hz, g), 1.90–1.75 (2H, m, h), 1.46 (9H, s, a,a’,a’’); ^13C NMR (75 MHz, CDCl_3) δ 170.93 (c), 142.74 (j), 142.33 (e), 128.45 (k,k’), 128.31 (l,l’), 125.74 (m), 113.30 (f), 80.54 (b), 43.35 (d), 35.50 (g), 35.47 (i), 29.14 (h), 28.03 (a,a’,a”); IR (neat) 3026, 2933, 2863, 1726 (C=O stretch), 1645, 1496, 1366, 1255 (C-O stretch), 1140, 897, 839, 744, 695 cm^{-1}.

**Representative procedure for rhodium-catalyzed asymmetric hydroboration**

![Chemical structure](image)

**Preparation of (3R)-4-Hydroxy-3-methylbutanoic acid phenyl amide (X(16)-1):** A stock solution (2.0 mL) containing Rh(nbd)_2BF_4 (2.6 mM) and (3,5-dimethyl-TADDOL)POPh (L, 5.6 mM) in THF was prepared. To the resulting yellow solution [Rh(nbd)_2BF_4 (2.0 mg, 0.0053 mmol) and (3,5-dimethyl-TADDOL)POPh (L2a, 7.8 mg, 0.011 mmol)] was slowly added over the course of 15 min a solution of 1,1-disubstituted alkene X16 (92.45 mg, 0.528 mmol) in THF (2.0 mL). To the reaction mixture was slowly added a solution of 4,4,6-trimethyl-1,3,2-dioxaborinane (TMDB, 135 mg, 1.1 mmol) in THF (1.0 mL) over the course of 0.5 h. After an additional 24 h stir, Afterwards, the reaction mixture was re-cooled (0 °C), diluted with THF (15 mL) and
quenched by the slow addition of methanol (6 mL) followed by the dropwise addition of 3 N aq. NaOH (8 mL) and 30% H₂O₂ (1 mL), the resultant mixture was extracted with dichloromethane (2 x 10 mL). The combined organic extracts were dried (anhdy. MgSO₄) and then concentrated under reduced pressure. Flash chromatography on silica gel (60:40 hexanes:ethyl acetate) affords the title compound (52%, 95% ee) as a white solid: mp 115–117 ºC; TLC analysis Rₖ 0.70 (50:50 hexanes:ethyl acetate); chiral HPLC analysis (Chiralcel-IC, 80:20 hexanes: isopropanol) showed peaks at 17 minutes (3% (R)) and 21 minutes (97% (S)); ¹H NMR (300 MHz, CDCl₃) δ 8.21 (1H, br s, OH), 7.51 (2H, d, J = 7.8 Hz, c,c’), 7.30 (2H, t, J = 7.6 Hz, b,b’), 7.10 (1H, t, J = 7.4 Hz, a), 3.70–3.55 (1H, m, h), 3.55–3.40 (2H, m, h, OH), 2.52 and 2.29 (2H, overlapping dd’s, J₁ = 14.0 Hz, 6.8 Hz, J₂ = 14.0 Hz, 6.00 Hz, f), 2.30–2.20 (1H, m, g), 1.00 (3H, d, J = 6.7 Hz, i); ¹³C NMR (75 MHz, CDCl₃) δ 171.71 (e), 137.88 (d), 128.94 (b,b’), 124.40 (a), 120.19 (c,c’), 67.46 (h), 42.16 (f), 33.36 (g), 17.03 (i); HRMS (CI) calcd. for C₁₁H₁₆NO₂ (M+H): 194.1181, found 194.1180 m/z.

Preparation of (3R)-3-Ethyl-4-hydroxybutanoic acid phenyl amide (X(17)-1):

Following the general procedure, 1,1-disubstituted alkene X₁₇ (99.85 mg, 0.528 mmol) affords, after flash chromatography on silica gel (60:40 hexanes:ethyl acetate), the title compound (65.61 mg, 60%) as a white solid: mp 118–119.5 ºC; TLC analysis Rₖ 0.50
(50:50 hexanes:ethyl acetate); Chiral HPLC analysis (Chiralcel-IC, 90:10 hexanes:isopropanol) showed peaks at 37 minutes (5.0% (R)) and 45 minutes (95.0% (S)); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.83 (1H, br s, NH), 7.52 (2H, d, $J = 7.9$ Hz, c,c’), 7.33 (2H, t, $J = 7.8$ Hz, b.b’), 7.12 (1H, t, $J = 7.3$ Hz, a), 3.78 (1H, dd, $J_1 = 10.5$ Hz, $J_2 = 3.0$ Hz, h), 3.59 (1H, dd, $J_1 = 10.5$ Hz, $J_2 = 6.8$ Hz, h), 2.87 (1H, br s, OH), 2.55–2.45 (2H, m, f), 2.10–2.00 (1H, g), 1.50–1.35 (2H, m, i), 0.98 (3H, t, $J = 7.4$ Hz, j); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.63 (e), 137.83 (d), 128.99 (c,c’), 124.38 (a), 119.99 (b,b’), 65.32 (h), 40.46 (f), 39.75 (g), 24.36 (i), 11.59 (j).

Preparation of (3R)-3-iso-butyl-4-hydroxybutanoic acid phenyl amide (X(18)-1):

Following the general procedure, 1,1-disubstituted alkene X18 (114.65mg, 0.528 mmol) affords, after flash chromatography on silica gel (80:40 hexanes:ethyl acetate), the title compound (89.39 mg, 72%) as a white solid: mp 92–94 ºC; TLC analysis $R_f$ 0.60 (50:50 hexanes:ethyl acetate); Chiral HPLC analysis (Chiralcel-IC, 90:10 hexanes:isopropanol) showed peaks at 26 minutes (2.0% (R)) and 29 minutes (96.0% (S)); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.88 (1H, br s, NH), 7.50 (2H, d, $J = 7.9$ Hz, c,c’), 7.32 (2H, t, $J = 7.8$ Hz, b,b’), 7.12 (1H, t, $J = 7.3$ Hz, a), 3.79 (1H, dd, $J_1 = 10.5$ Hz, $J_2 = 3.0$ Hz, h), 3.57 (1H, dd, $J_1 = 10.5$ Hz, $J_2 = 6.8$ Hz, h), 2.87 (1H, br s, OH), 2.55–2.45 (2H, m, f), 2.20–2.10 (1H, g), 1.69–1.66(1H, m, j), 1.28-1.22 (2H, m, i), 0.91 (6H, d, $J = 3$ Hz, k,k’); $^{13}$C NMR (75
MHz, CDCl$_3$) $\delta$ 171.61 (e), 137.84 (d), 128.97 (c,c’), 124.36 (a), 120.01 (b,b’), 65.76 (h), 40.90 (f), 40.72 (g), 35.78(j), 25.72(i), 22.78–22.66 (k,k’).

**Preparation of (3S)-3-cyclohexyl-4-hydroxybutanoic acid phenyl amide (X(19)-1):**

Following the general procedure, 1,1-disubstituted alkene X19 (128.38 mg, 0.528 mmol) affords, after flash chromatography on silica gel (60:40 hexanes:ethyl acetate), the title compound (99.28 mg, 72%) as a white solid: mp 88–89 °C; TLC analysis $R_f$ 0.60 (60:40 hexanes:ethyl acetate); Chiral HPLC analysis (Chiralcel-IC, 90:10 hexanes:isopropanol) showed peaks at 42 minutes (4.0% (R)) and 46 minutes (94.0% (S)); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.71 (1H, br s, NH), 7.50 (2H, d, $J = 7.9$ Hz, c,c’), 7.33 (2H, d, $J = 7.8$ Hz, b,b’), 7.12 (1H, t, $J = 7.3$ Hz, a), 3.79 (1H, m, h), 3.68 (1H, m, h), 2.69 (1H, br s, OH), 2.55–2.45 (2H, d, $J$=6.3, f), 2.00–1.93 (1H, m, g), 1.75-1.60 (5H, m, i, j,j’), 1.55–1.12(6H, m, k,k’ , l); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.61 (e), 137.84 (d), 128.97 (c,c’), 124.36 (a), 120.01 (b,b’), 64.44 (h), 43.38 (f), 39.55 (g), 38.88(i), 30.37(j,j’), 26.54,(k,k’), 26.84(l).
Preparation of (3S)-4-Hydroxy-3-phenylbutanoic acid phenyl amide (X(20)-1):

Following the general procedure, 1,1-disubstituted alkene X20 (125.19 mg, 0.528 mmol) affords, after flash chromatography on silica gel (60:40 hexanes:ethyl acetate), the title compound (95.64 mg, 71%) as a white solid: mp 95.5–97 ºC; TLC analysis Rf 0.50 (50:50 hexanes:ethyl acetate); Chiral HPLC analysis (Chiralcel-IC, 80:20 hexanes:isopropanol) showed peaks at 20 minutes (2.0% (R)) and 24 minutes (95.0% (S)); 1H NMR (300 MHz, DMSO-d6) δ 9.86 (1H, br s, NH), 7.51 (2H, d, J = 8.0 Hz, c,c’), 7.30–7.10 (7H, m, b,b’,j,j’, k,k’, l), 6.98 (1H, t, J = 7.3 Hz, a), 4.79 (1H, t, J = 5.2 Hz, OH), 3.65–3.50 (2H, m, h), 3.35–3.20 (1H, m, g), 2.82 and 2.60 (2H, overlapping dd’s, J1 = 14.8 Hz, 5.9 Hz, J2 = 14.8 Hz, 8.9 Hz, f); 13C NMR (75 MHz, DMSO-d6) δ 170.55 (e), 143.16 (d), 139.67 (i), 129.06 (j,j’), 128.55 (b,b’), 128.32 (k,k’), 126.64 (l), 123.40 (a), 119.45 (c,c’), 65.84 (h), 44.92(f).

Preparation of (3R)-4-Hydroxy-3-(2-phenylethyl)butanoic acid phenyl amide (X(21)-1): Following the general procedure, 1,1-disubstituted alkene X21 (139.99 mg, 0.528 mmol) affords, after flash chromatography on silica gel (60:40 hexanes:ethyl acetate), the title compound (109.14 mg, 73%) as a white solid: mp 81–83 ºC; TLC
analysis $R_f$ 0.50 (60:40 hexanes:ethyl acetate); Chiral HPLC analysis (Chiralcel-IC, 90:10 hexanes:isopropanol) showed peaks at 40 minutes (2.0% (R)) and 46 minutes (95.0% (S)); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.75 (1H, br s, NH), 7.50 (2H, d, $J = 7.8$ Hz, c,c’), 7.35–7.25 (4H, m, b,b’, l,l’), 7.25–7.15 (3H, m, m,m’, n), 7.13 (1H, t, $J = 7.4$ Hz, a), 3.85–3.75 (1H, m, h), 3.70–3.60 (1H, m, h), 2.92 (1H, br s, OH), 2.80–2.65 (2H, m, j), 2.55–2.45 (2H, m, f), 2.20–2.10 (1H, m, g), 1.80–1.65 (2H, m, i); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.32 (e), 141.89 (k), 137.75 (d), 129.01 (l,l’), 128.48 (b,b’), 128.37 (m,m’), 125.98 (n), 124.44 (a), 120.02 (c,c’), 65.36 (h), 40.60 (f), 37.77 (j), 33.41 (g), 33.11 (i); IR (neat) 1677 (C=O stretch), 1040, 1122 (C-O stretch), 3200 (OH stretch), 1399, 1439, 1409 (C-N stretch), 675, 829, 638 cm$^{-1}$; HRMS (CI) calcd. for C$_{18}$H$_{22}$NO$_2$ (M+H): 284.1651, found 284.1656 m/z.

Preparation of (3R)-3-Hydroxymethyl-6-phenylhexanoic acid phenyl amide

(X(22)-1): Following the general procedure, 1,1-disubstituted alkene X22 (147.39 mg, 0.528 mmol) affords, after flash chromatography on silica gel (60:40 hexanes:ethyl acetate), the title compound (109.83 mg, 70%) as a white solid: mp 78.5–80 °C; TLC analysis $R_f$ 0.50 (50:50 hexanes:ethyl acetate); Chiral HPLC analysis (Chiralcel-IC, 90:10 hexanes:isopropanol) showed peaks at 26 minutes (2.0% (R)) and 31 minutes (94.0% (S)); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.76 (1H, br s, NH), 7.51 (2H, d, $J = 7.8$ Hz, c,c’), 7.33–7.29 (4H, m, b,b’, m,m’), 7.23–7.17 (3H, m, n,n’, o), 7.13 (1H, t, $J = 7.4$ Hz, a),
3.75 (1H, m, h), 3.58 (1H, m, h), 2.65 (2H, m, k), 2.55–2.45 (2H, m, f), 2.20–2.10 (1H, m, g), 1.71-1.51 (2H, m, i), 1.51–1.45 (2H, m, j); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.21 (e), 141.89 (i), 137.75 (d), 129.01 (m,m’), 128.48 (b,b’), 128.37 (n.n’), 125.98 (o), 124.44 (a), 120.02 (c,c’), 65.36 (h), 40.10 (f), 38.04 (k), 32.60 (g), 31.08 (i), 20.06 (j).

**Representative procedure for preparation lactones**

Preparation of (4S)-4-isobutylbutyrolactone (X(26)-1): 1,1-disubstituted alkene X26 (102 mg, 0.528 mmol) was subjected to standard CAHB conditions. The resultant reaction mixture was diluted with an additional 10 mL of THF followed by slow addition of NaOH (6 mL of a 3 M aqueous soln.) and dropwise addition of H$_2$O$_2$ (0.6 mL of a 30% aqueous soln.). After a 2 h stir, sodium metabisulfite (Na$_2$SO$_5$, 4 mL of a 10% aqueous soln.) was added and the resultant mixture was acidified (6 M HCl) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried (anhyd. MgSO$_4$) and concentrated under reduced pressure. Flash chromatography on silica gel (75:25 hexanes:ethyl acetate) affords the title compound (58.6 mg, 78%) as a light yellow oil; TLC analysis $R_f$ 0.50 (75:25 hexanes:ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$) δ 4.41 (1H, dd, $J_1 = 8.8$ Hz, $J_2 = 8.1$ Hz, d), 3.88 (1H, dd, $J_1 = 8.9$ Hz, $J_2 = 8.6$ Hz, d), 2.70–2.55 (2H, m, b), 2.25–2.10 (1H, m, c), 1.65–1.50 (1H, m, f), 1.36 (2H, t, $J = 7.1$ Hz, e), 0.93 (3H, t, $J = 6.6$ Hz, g), 0.90 (3H, t, $J = 6.6$ Hz, g’); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 177.22 (a), 73.56 (d), 42.21 (e), 34.76 (b), 33.83 (c), 26.28 (f), 22.64 (g), 22.40 (g’); IR (neat)
Preparation of (3R)-4-benzylbutyrolactone (X(24)-1): Following the general procedure, 1,1-disubstituted alkene X24 (123 mg, 0.528 mmol) affords, after flash chromatography on silica gel (75:25 hexanes:ethyl acetate), the title compound (73.2 mg, 80%) as a light yellow oil; TLC analysis Rf 0.40 (75:25 hexanes:ethyl acetate); 1H NMR (400 MHz, CDCl3) δ 7.34 (2H, t, J = 7.2 Hz, h,h’), 7.27 (1H, d, J = 6.9 Hz, i), 7.17 (2H, d, J = 7.3 Hz, g,g’), 4.35 (1H, dd, J1 = 8.9 Hz, J2 = 8.9 Hz, d), 4.05 (1H, dd, J1 = 6.2 Hz, J2 = 6.1 Hz, d), 2.95–2.85 (1H, m, c), 2.85–2.75 (2H, m, e), 2.62 (1H, dd, J1 = 17.4 Hz, J2 = 7.9 Hz, b), 2.31 (1H, dd, J1 = 17.4 Hz, J2 = 6.9 Hz, b); 13C NMR (100 MHz, CDCl3) δ 176.84 (a), 138.25 (f), 128.81 (g,g’), 128.67 (h,h’), 126.83 (i), 72.66 (d), 38.95 (e), 37.18 (b), 34.25 (c); IR (neat) 2963, 2909, 1773 (C=O stretch), 1496, 1417, 1257, 1166 (C-O stretch), 1088, 1012, 910, 797, 731, 699, 638, 531 cm⁻¹.

Preparation of (3R)-4-methylbutyrolactone (X(23)-1): Following the general procedure, 1,1-disubstituted alkene X23 (82.43 mg, 0.528 mmol) affords, after flash
chromatography on silica gel (75:25 hexanes:ethyl acetate), the title compound (32.75 mg, 62%) as a light yellow oil; TLC analysis $R_f$ 0.60 (80:20 hexanes:ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.41 (1H, dd, $J_1 = 8.0$ Hz, $J_2 = 8.1$ Hz, d), 3.87 (1H, dd, $J_1 = 8.0$ Hz, $J_2 = 8.6$ Hz, d), 2.68–2.65 (2H, m, b), 2.17–2.15 (1H, m, c), 1.17 (3H, d, $J = 6.4$ Hz, e); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 177.21 (a), 74.68 (d), 34.14 (b), 30.40 (c), 17.94 (e).

**Preparation of (3R)-4-(phenylethyl)butyrolactone (X(28)-1):** Following the general procedure, 1,1-disubstituted alkene X28 (139.47 mg, 0.528 mmol) affords, after flash chromatography on silica gel (75:25 hexanes:ethyl acetate), the title compound (61.27 mg, 61%) as a light yellow oil; TLC analysis $R_f$ 0.40 (75:25 hexanes:ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 (2H, $J = 7.2$ Hz, i,i’), 7.26 (1H, d, $J = 7.0$ Hz, j), 7.17 (2H, d, $J = 7.3$ Hz, h,h’), 4.44 (1H, dd, $J_1 = 9.0$ Hz, $J_2 = 8.0$ Hz, d), 3.97 (1H, dd, $J_1 = 9.0$ Hz, $J_2 = 7.0$ Hz, d), 2.85–2.74 (2H, m, f), 2.75–2.53 (2H, m, b), 2.30–2.19 (1H, m, c), 1.89–1.74 (2H, m, e); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 177.06 (a), 138.23 (g), 128.80 (h,h), 128.67 (i,i’), 126.83 (j), 73.21 (d), 35.27 (e), 34.46 (b), 33.24 (f), 31.48 (c).
Representative procedure for preparation of γ-borylated product

**Preparation of (3R)-tert-butyl-3-((4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)methyl) pentanoate:** Following the representative procedure for rhodium-catalyzed asymmetric hydroboration of β,γ-unsaturated amides at room temperature, hydroboration of β,γ-unsaturated ester T3 (89.8 mg, 0.528 mmol) affords, after flash chromatography on silica gel (95:5 hexanes:ethyl acetate), the title compound (102.35 mg, 65%) as a yellow oil; TLC analysis Rf 0.60 (70:30 hexanes:ethyl acetate); 1H NMR (300 MHz, CDCl3) δ 4.22-4.11 (1H, m, j), 2.20-2.17 (2H, dd, J = 6.9 Hz, d), 2.04-1.95 (1H, m, e), 1.79-1.74 (1H, dd, J = 13.8 Hz, i), 1.50-1.41 (1H, m, i), 1.46 (9H, s, a,a’,a’’), 1.40-1.32 (2H, m, l), 1.28 (6H, s, h,h’), 1.24 (3H, d, J = 6.2 Hz, k), 0.88 (3H, t, J = 7.4 Hz, m), 0.69 (2H, d, J = 6.8 Hz, f); 13C NMR (75 MHz, CDCl3) δ 173.24 (c), 79.51 (b), 70.39 (g), 64.41 (j), 45.96 (i), 42.33 (d), 33.27 (e), 31.28 (h, h’), 28.94 (l), 28.16 (a,a’,a’’), 28.06 (f), 23.21 (k), 11.19 (m).

Representative procedure preparation of alcohol via oxidation with NaBO2.

**Preparation of (3R)-tert-butyl-3-(hydroxymethyl)-5-methylhexanoate (X26-1):** Following the general procedure for the CAHB of 1,1-disubstituted alkene X26, the
resultant reaction mixture was concentrated under reduced pressure and then taken up in THF (1.5 mL) and H₂O (1.5 mL). NaBO₃-tetrahydrate (40 mg, 0.26 mmol) was added to the resulting mixture. After a 2 h vigorous stir, the reaction was diluted with H₂O (3 mL) and diethylether (4 mL). The aqueous layer was extracted with diethylether (2 x 3 mL) and the combined organic extracts were dried (anhyd. MgSO₄) and concentrated under reduced pressure. The crude residue was purified via flash chromatography on silica gel (80:20 hexanes:dichloromethane) to afford the title compound (86.74 mg, 76%) as a light yellow oil; TLC analysis Rᵋ 0.50 (60:40 hexanes:ethyl acetate); \(^1\)H NMR (300 MHz, CDCl₃) δ 3.70–3.60 (1H, m, f), 3.60–3.40 (1H, m, f), 2.28 (2H, dd, J₁ = 4.4 Hz, J₂ = 2.5 Hz, d), 2.16 (1H, br s, OH), 2.10–2.00 (1H, m, e), 1.70–1.60 (1H, m, h), 1.47 (9H, s, a,a’,a”), 1.30–1.20 (2H, m, g), 0.92 (3H, d, J = 4.7 Hz, i), 0.90 (3H, d, J = 4.7 Hz, i’); \(^{13}\)C NMR (75 MHz, CDCl₃) δ 173.32 (c), 80.62 (b), 66.07 (f), 40.43 (g), 38.46 (d), 35.71 (e), 28.08 (a,a’,a”), 25.19 (h), 22.80 (i), 22.67 (i’).

**Preparation of tert-butyl 4-hydroxy-3-phenylbutanoate (X(27)-1):** Following the general procedure for the CAHB of 1,1-disubstituted alkene X₂₇, the resultant reaction mixture was concentrated under reduced pressure and then taken up in THF (1.5 mL) and H₂O (1.5 mL). NaBO₃-tetrahydrate (40 mg, 0.26 mmol) was added to the resulting mixture. After a 2 h vigorous stir, the reaction was diluted with H₂O (3 mL) and
diethylether (4 mL). The aqueous layer was extracted with diethylether (2 x 3 mL) and the combined organic extracts were dried (anhyd. MgSO₄) and concentrated under reduced pressure. The crude residue was purified via flash chromatography on silica gel (80:20 hexanes:dichloromethane) to afford the title compound (78.54 mg, 63%) as a light yellow oil: TLC analysis Rₜ 0.70 (75:25 hexanes:ethyl acetate);¹H NMR (400 MHz, CDCl₃) δ 7.39–7.31 (3H, m, i,i’,j), 7.25 (2H, d, J=8, h,h’), 3.84-3.70 (2H, m, f), 3.33 (1H, m, e), 2.73 and 2.60 (2H, m, d), 1.39 (9H, s, a,a’,a’’);¹³C NMR (75 MHz, CDCl₃) δ 171.92 (c), 141.12 (g), 128.61 (h,h’), 127.88 (i,i’), 126.70 (j), 80.66 (b), 67.03 (f), 41.10 (d), 38.66(e), 27.93 (a,a’,a’’).

**General procedures for the preparation of L2a**

![Chemical structure of L2a preparation](image)

**Preparation of (3,5-dimethyl-TADDOL)POPh (L2a):** 3,5-Dimethyl-TADDOL was prepared as previously described⁶⁴. To a cooled solution (dry ice-acetone bath, -78 °C) of 3,5-imethyl-TADDOL (500 mg, 0.864 mmol) and triethylamine (TEA, 0.30 mL, 2.16 mmol) in dry, oxygen-free THF (35 mL) was added PCl₃ (0.07 mL, 0.86 mmol) in one portion. The resulting mixture was allowed to slowly warm to room temperature and stir over a total of ca. 12 h. Afterwards, the reaction mixture was filtered and the volatiles were removed on a vacuum line. The residue was dissolved in THF (5 mL) and the
resulting solution added (rapid addition) to a mixture of phenol (105.7 mg, 1.123 mmol) and TEA (0.18 mL, 1.3 mmol) in THF (35 mL). The resulting mixture was allowed to stir at room temperature for ca. 12 h. The resulting mixture was filtered and the volatiles were removed on a vacuum line. Flash chromatography on silica gel (97:3 hexanes:ethyl acetate) affords the title compound (412.0 mg, 68%) as a white foamy solid: mp 97.0-98.2 °C; TLC analysis $R_f$ 0.80 (95:5 hexanes: ethyl acetate); $[\alpha]_{D}^{20} = -120.0^\circ$ (c 0.5, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35-7.20 (6H, m), 7.15-7.05 (5H, m), 6.99 (2H, d, $J = 10.5$ Hz), 6.90 (2H, s), 6.86 (2H, d, $J = 7.6$ Hz), 5.33 (1H, d, $J = 8.2$ Hz), 5.17 (1H, d, $J = 8.2$ Hz), 2.40 (6H, s), 2.37 (6H, s), 2.32 (6H, s), 2.92 (6H, s), 0.99 (3H, s), 0.74 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 152.16 ($J_{CP} = 2.9$ Hz), 146.10 ($J_{CP} = 2.0$ Hz), 145.83, 141.23 (3.0 Hz), 141.02, 137.37, 136.99, 136.50, 136.29, 129.45, 129.07, 128.94, 128.78, 126.89, 126.84, 125.10, 125.08, 123.33, 120.89, 120.81, 112.65, 85.51 ($J_{CP} = 8.1$ Hz), 84.64 ($J_{CP} = 4.2$ Hz), 82.34 ($J_{CP} = 13.8$ Hz), 81.28 ($J_{CP} = 4.8$ Hz), 26.95, 26.48, 21.69, 21.59, 21.48 (overlapping peaks); $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 129.36; IR (neat) 2916, 2863 (P-O stretching), 1595, 1489, 1455, 1370, 1213 (C-O-C stretch), 1159, 1035, 939, 853, 800, 761, 689 cm$^{-1}$; HRMS (FAB) calcd. for C$_{45}$H$_{49}$O$_5$P (M+H): 701.3396, found 701.3409 m/z.

![Diagram](image.png)

**Preparation of 4,4,6-Trimethyl-1,3,2-dioxaborinane ((TMD)BH):** To a cooled (0 °C) solution of 2-methyl-2,4-pentanediol (1.54 g, 12 mmol) in dichloromethane (6 mL) was slowly added borane (BH$_3$, 1 mL of a 10 M solution in dimethylsulfide, 10 mmol) dropwise. After the resulting mixture was stirred for 1.5 h at the same
temperature, the ice bath was removed and the reaction was allowed to stir for an additional 0.5 h. Volatiles were carefully removed under reduced pressure (i.e., concentration via rotovap while the mixture was submerged in a room temperature water bath). After complete removal of dichloromethane and dimethylsulfide (SMe₂), the residue was purified via bulb-to-bulb distillation (160–165 °C) to afford the title compound (960 mg, 75%) as a colorless liquid: \( ^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 4.30–4.15 (1H, m, d), 3.84 (1H, q, \( J = 155.6 \) Hz, BH), 1.90–1.75 (1H, m, c), 1.60–1.45 (1H, m, c), 1.31 (3H, s, a), 1.29 (3H, s, a'), 1.26 (3H, d, \( J = 6.2 \) Hz, e); \( ^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 70.99 (b), 64.73 (d), 46.17 (c), 31.02 (a), 28.14 (a'), 22.93 (e); \( ^{11}\)B NMR (193 MHz, THF with residual CDCl₃) \( \delta \) 24.96 (d, \( J = 169.1 \) Hz); IR (neat) 2976 (CH sp\(^3\) stretch), 2879, 2400, 1495, 1427, 1384, 1291, 1156 (C-O stretch), 1094, 1024, 889, 789, 666 cm\(^{-1}\); HRMS (Cl) calcd. for C₆H₁₄BO₂ (M+H): 129.1087, found 129.1082 m/z.
Chapter 6 References


6. Alan Aitken, S. N. Kilenyi, Asymmetric synthesis, 1992


$^{1}H$ NMR X1

1D Proton NMR
$^{13}$C NMR X2

NAME: mob-080111 phenyl ethyl alcohol
EXPNO: 1
PROCNO: 1
Date_: 20110801
Time: 18.38
INSTRUM: spect
PROCNR: 1 mm GNP 10/13
FIDFROG: zgpm10
TD: 6516
SOLVENT: CDC13
NS: 783
DS: 23980.816 Hz
FDRES: 0.36591 Hz
AQ: 1.3664756 sec
RG: 1625.5
DM: 20.850 usec
DE: 6.50 usec
T2: 298.0 K
D1: 2.00000000 sec
D13: 0.03000000 sec
TDO: 1

CHANNEL f1
MOC1: 13C
F1: 10.00 usec
FL1: 0.50 dB
SF1: 100.6228298 MHz

CHANNEL f2
MOC2: 1H
FCPO: 70.00 usec
FL2: -3.35 dB
FL12: 13.34 dB
FL13: 13.34 dB
SF2: 400.1316000 Hz
SI: 32768
SF: 100.6127600 MHz
DSM: 1D
S2M: 0
LB: 1.00 Hz
DG: 0
IF: 1.40
1H NMR X9

1D Proton NMR

NAME     mob-080311-phenyl ethyl acid
EXPNO                 1 PROCNO                1 Date_          20110803 Time              13.33 INSTRUM           spect ...

1D Proton NMR
1D Proton

NAME         mob-111111
EXPNO                 1 PROCNO                1 Date_          20110829 Time              10.59
INSTRUM               spect PROBHD          5 mm QNP 1H/13 PULPROG        zg30
TD                32768 SOLVENT         CDC13
NS                 8 DS                     2 SNH             5995.204 Hz FIDRES        0.182959 Hz AQ           2.7329011 sec RG                362
DW               83.400 usec DE              6.50 usec TE             673.2 K D1           1.00000000 sec TD0                   1
======== CHANNEL f1 ========
NUC1                1H P1                 15.00 usec PL1        -4.40 dB SFO1       300.1318534 MHz SI            32768 SF          300.1300000 MHz WDW                  EM SSB                   0 LB                 0.30 Hz GB                    0 PC                 1.00

1H NMR X16
$^{13}$C NMR X16

NAME     mob-111111 13c
EXPNO                1
PROCNO                1
Date_          20110829
Time              11.44
INSTRUM                spect
PROBHD                5 mm QNP 1H/13
PULPROG                zgpg30
TD                 32768
SOLVENT                CDC13
NS                 896
DS                     4
SWH              17985.611 Hz
FIDRES         0.548877 Hz
AQ          0.9110004 sec
RG                 11585.2
DW                 27.800 usec
DE                 6.50 usec
TE              673.2 K
D1           2.0000000000 sec
D11           0.0300000000 sec
TD0                1

======== CHANNEL f1 ========
NUC1                13C
P1                 10.00 usec
PL1              5.00 dB
SFO1               75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                1H
PCPD2                70.00 usec
PL2               -4.40 dB
PL12              8.98 dB
PL13              8.98 dB
SFO2   300.1312005 MHz
SI                32768
SF          75.4677490 MHz
MDW               EM
SSB                 0
LB                 1.00 Hz
GB                 0
PC                 1.40
$^{13}$C NMR X17
$^1\text{H NMR X18}$
$^{13}$C NMR X18
$^{1}H$ NMR X19
$^{13}$C NMR X19
$^{1}H$ NMR X21

1D Proton NMR
$^{13}$C NMR X21
$^1$H NMR X22
$^{13}$C NMR X22
$^1$H NMR X23
$^{13}\text{C}\text{ NMR X23}$
$^1$H NMR X24
$^{13}$C NMR X24
$^1$H NMR X25
$^1$H NMR X26
$^{13}$C NMR X28
$^1\text{H NMR X31}$
$^{13}$C NMR X31
$^1$H NMR X(16)-1

1D Prt

- $7.632$
- $7.534$
- $7.338$
- $7.267$
- $7.219$
- $7.137$
- $3.796$
- $3.779$
- $3.753$
- $3.726$
- $3.700$
- $3.673$
- $3.647$
- $3.620$
- $3.593$
- $3.567$
- $3.540$
- $3.513$
- $3.486$
- $3.459$
- $3.432$
- $3.406$
- $3.380$
- $3.353$
- $3.327$
- $3.300$
- $3.274$
- $3.247$
- $3.221$
- $3.194$
- $3.168$
- $3.141$
- $3.114$
- $2.987$
- $2.961$
- $2.934$
- $2.908$
- $2.881$
- $2.854$
- $2.828$
- $2.801$
- $2.774$
- $2.748$
- $2.721$
- $2.694$
- $2.668$
- $2.641$
- $2.614$
- $2.588$
- $2.561$
- $2.534$
- $2.508$
- $2.481$
- $2.454$
- $2.428$
- $2.401$
- $2.374$
- $2.347$
- $2.320$
- $2.294$
- $2.267$
- $2.240$
- $2.213$
- $2.186$
- $2.160$
- $2.133$
- $2.106$
- $2.079$
- $2.052$
- $2.025$
- $1.998$
- $1.971$
- $1.944$
- $1.917$
- $1.890$
- $1.864$
- $1.837$
- $1.810$
- $1.784$
- $1.757$
- $1.730$
- $1.703$
- $1.676$
- $1.649$
- $1.622$
- $1.595$
- $1.568$
- $1.541$
- $1.514$
- $1.487$
- $1.460$
- $1.433$
- $1.406$
- $1.379$
- $1.352$
- $1.325$
- $1.298$
- $1.271$
- $1.244$
- $1.217$
- $1.190$
- $1.163$
- $1.136$
- $1.109$
- $1.082$
- $1.055$
- $1.028$
- $0.991$
- $0.864$
- $0.837$
- $0.810$
- $0.783$
- $0.756$
- $0.730$
- $0.703$
- $0.676$
- $0.650$
- $0.623$
- $0.596$
- $0.569$
- $0.543$
- $0.516$
- $0.489$
- $0.462$
- $0.436$
- $0.409$
- $0.383$
- $0.356$
- $0.330$
- $0.303$
- $0.276$
- $0.250$
- $0.223$
- $0.197$
- $0.170$
- $0.144$
- $0.118$
- $0.092$
- $0.066$
- $0.040$
- $0.014$
- $-0.014$
- $-0.040$
- $-0.066$
- $-0.092$
- $-0.118$
- $-0.144$
- $-0.170$
- $-0.197$
- $-0.223$
- $-0.250$
- $-0.276$
- $-0.303$
- $-0.330$
- $-0.356$
- $-0.383$
- $-0.409$
- $-0.436$
- $-0.462$
- $-0.489$
- $-0.516$
- $-0.543$
- $-0.569$
- $-0.596$
- $-0.623$
- $-0.650$
- $-0.676$
- $-0.703$
- $-0.730$
- $-0.756$
- $-0.783$
- $-0.810$
- $-0.837$
- $-0.864$
- $-0.991$
- $-1.028$
- $-1.055$
- $-1.082$
- $-1.109$
- $-1.136$
- $-1.163$
- $-1.190$
- $-1.217$
- $-1.244$
- $-1.271$
- $-1.298$
- $-1.325$
- $-1.352$
- $-1.379$
- $-1.406$
- $-1.433$
- $-1.460$
- $-1.487$
- $-1.514$
- $-1.541$
- $-1.568$
- $-1.595$
- $-1.622$
- $-1.649$
- $-1.676$
- $-1.703$
- $-1.730$
- $-1.757$
- $-1.784$
- $-1.810$
- $-1.837$
- $-1.864$
- $-1.890$
- $-1.917$
- $-1.944$
- $-1.971$
- $-2.001$
- $-2.028$
- $-2.055$
- $-2.082$
- $-2.109$
- $-2.136$
- $-2.163$
- $-2.190$
- $-2.217$
- $-2.244$
- $-2.271$
- $-2.298$
- $-2.325$
- $-2.352$
- $-2.379$
- $-2.406$
- $-2.433$
- $-2.460$
- $-2.487$
- $-2.514$
- $-2.541$
- $-2.568$
- $-2.595$
- $-2.623$
- $-2.650$
- $-2.676$
- $-2.703$
- $-2.730$
- $-2.757$
- $-2.784$
- $-2.810$
- $-2.837$
- $-2.864$
- $-2.891$
- $-2.918$
- $-2.945$
- $-2.972$
- $-3.000$

**NAME**: mob-081611-methyl phenyl alcohol

**EXPNO**: 1

**PROCNO**: 1

**Date**: 20110816

**Time**: 17:04

**SN**: 1

**SOLVENT**: CDCl3

**DS**: 2

**DR**: 8278.146 Hz

**FIDRES**: 0.126314 Hz

**AQ**: 3.9584243 sec

**RG**: 362

**DM**: 60.400 usec

**DE**: 6.50 usec

**TE**: 2.88 K

**TD**: 1.000000000 sec

**DD**: 1

**CHANNEL**: f1

**MRC1**: 16

**F1**: 12.00 usec

**F1**: -2.00 dB

**SPC1**: 400.1328710 MHz

**S**: 32768

**SF**: 400.1300000 MHz

**MDM**: EM

**LS**: 0.30 Hz

**lb**: 1.00
$^{13}$C NMR X(16)-1

**NAME**
mob-081611-methyl phenyl alcohol 13c

**EXPNO**
1

**PROCNO**
1

**TD**
163513

**CS**
1.00 Hz

**GB**
0.00 ppm

**PC**
1.40

**DATE_**
20110816

**DO**
4

**SSB**
0

**LB**
1.00 Hz

**DS**
0.00 ppm

**DI**
2.00000000 sec

**DT**
0.00000000 sec

**DS**
1

**CHANNEL F1**

**C0**
131

**F1**
10.00 usec

**F12**
0.00 us

**SFD1**
100.6229298 MHz

**CHANNEL F2**

**C2F1**
wait111

**PCo2**
70.00 usec

**F1**
-3.74 dB

**F2**
3.34 dB

**SFD2**
400.1310005 MHz

**SS**
2.7968

**WE**
100.61276MHz

**LB**
0

**GC**
0

**PC**
1.40
\textbf{13C NMR X(17)-1}

\begin{verbatim}
NAME     mob-062612-3  13 c
EXPNO    1
PROCNO   1
Date_    20120626
Time     11.04
INSTRUM  spect
PROBHD   5 mm QNP 1H/13
PULPROG  zgpf30
TD       32768
SOLVENT  CDC13
NS       507
DG       4
SWH      17985.611 Hz
FIDRES   0.548877 Hz
AQ       0.9110004 sec
RG       11585.2
DW       27.800 usec
DE       6.50 usec
TE       298.0 K
D1       2.000000000 sec
D11      0.030000000 sec
TD0      1

======== CHANNEL f1 ========
NUC1     13C
P1       10.00 usec
PL1      5.20 dB
SF01     75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2  walt216
NUC2     1H
PCPD2    70.00 usec
PL2      2.20 dB
PL12     19.10 dB
PL13     19.10 dB
SF02     300.1312005 MHz
SI       32768
SF       75.4677490 MHz
NDW      EM
SSB      0
LR       1.00 Hz
GB       0
PC       1.40
\end{verbatim}
$^1$H NMR X(21)-1

1D Proton NMR
$^{13}$C NMR X(21)-1

13C

NAME     mob-081711-phenyl ethyl amide
EXPNRO       1
PROCNO       1
Date          20110817
Time           12:54
INSTRUM       spect
PROCNOD       5 mm QNP 1H/13
PULPROG      zgpp30
TD             65336
SOLVENT       CDCl3
HS            947
DS              4
DMN     23980.814 Hz
FDKRES      0.365918 Hz
AQ            1.3664756 sec
RG            1625.5
DM    20.850 usec
DE              6.50 usec
TE              298.0 K
D1         2.00000000 sec
D11        0.00000000 sec
D20            1

-------- CHANNEL f1 --------
NUC1        13C
P1           10.00 usec
P11          0.50 dB
SP01       100.6228298 MHz

-------- CHANNEL f2 --------
NUC2        1H
PCHD2      70.00 usec
PL2         -3.35 dB
PL12        13.34 dB
PM12        13.34 dB
SP02    400.1316005 MHz
ST          32768
ST         100.6127890 MHz
MDW           EDM
ASB              0
LB             1.00 Hz
GB              0
PC             1.40
### 13C NMR X(26)-1

<table>
<thead>
<tr>
<th>ppm</th>
<th>177.23</th>
<th>175.36</th>
<th>162.76</th>
<th>144.21</th>
<th>136.76</th>
<th>126.28</th>
<th>117.64</th>
<th>106.40</th>
</tr>
</thead>
</table>

---

**NAME**  mob-062612- 6  13 c  
**EXPNO**  1  
**PROCNO**  1  
**Date_**  20120626  
**Time**  12.15  
**INSTRUM**  spect  
**PROBHD**  5 mm QNP 1H/13  
**PULPROG**  zgpq30  
**TD**  32768  
**SOLVENT**  CDC13  
**NS**  63  
**DS**  4  
**SWH**  17985.611 Hz  
**FIDRES**  0.548877 Hz  
**AQ**  0.9110004 sec  
**RG**  16384  
**DW**  27.800 usec  
**DE**  6.50 usec  
**TE**  298.0 K  
**D1**  2.00000000 sec  
**D11**  0.03000000 sec  
**TD0**  1  

====== CHANNEL f1 ======
**NUC1**  13C  
**P1**  10.00 usec  
**PL1**  5.20 dB  
**SFO1**  75.4752953 MHz

====== CHANNEL f2 ======
**CPDPRG2**  waltz16  
**NUC2**  1H  
**PCPD2**  70.00 usec  
**PL2**  2.20 dB  
**PL12**  19.10 dB  
**PL13**  19.10 dB  
**SFO2**  300.1312005 MHz  
**SI**  32768  
**SF**  75.4677490 MHz  
**WDW**  EM  
**SSB**  0  
**LB**  1.00 Hz  
**GB**  0  
**PC**  1.40

---

The image contains a graph of the 13C NMR spectrum with peaks labeled at various ppm values.
\textbf{\textsuperscript{1}H NMR X(24)-1}

\begin{verbatim}
NAME       mob-062612-2
EXPNO       1
PROCNO      1
Date_       20120626
Time        10.39
INSTRUM     spect
PROBHD      5 mm QNP 1H/13
PULPROG     zg30
TD          32768
SOLVENT     CDCl3
NS          5
DS          2
SNH         5995.204 Hz
FIDRES      0.182959 Hz
AQ           2.7329011 sec
RG           114
DW           83.400 usec
DE           6.50 usec
TE           298.0 K
D1          1.00000000 sec
TD0          1

======== CHANNEL f1 ========
NUC1       1H
P1          10.00 usec
PL1        2.20 dB
SFO1      300.1318534 MHz
SI          32768
SF          300.1300000 MHz
WDW        EM
SSB          0
LB          0.30 Hz
GB          0
PC           1.00
\end{verbatim}
13C NMR X(24)-1