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DIRECTED CATALYTIC ASYMMETRIC HYDROBORATION OF 1,1-DISUBSTITUTED ALKENES

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DIRECTED CATALYTIC ASYMMETRIC HYDROBORATION of

1,1-DISUBSTITUTED ALKENES

By

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

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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-disubtituted 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 β,γ-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 β,γ-unsaturated ester framework. The applicability of this method was further highlighted by successfully forming chiral β-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.

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i. Acknowledgements

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vi.List of Abbreviations

CAHB	Catalytic Asymmetric Hydroboration
9-BBN	9-Borabicyclo(3.3.1)nonane
TMDB	4,4,6-Trimethyl-1,3,2-dioxaborinane
BINAP	2,2'-*Bis*(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Bu	Butyl
DME	Dimethoxyethane
MS	Mass Spectrometry
ca	Circa
Calcd	Calculated
CatBD	Deutero Catecholborane
CatBH	Catecholborane
pinBH	pinacolborane
COD	Cyclooctadiene
ee	Enantiomeric excess
Cy	Cyclohexyl
nbd	Norbornadienyl
Mp	Melting Point
M	Molarity
NMR	Nuclear Magnetic Resonance

DCE	Dichloroethane
DCM	Dichloromethane
RT	Room temperature
Rac	Racemic
J	Coupling Constant
Eq	Equivalents
Aq	aqueous
Me	Methyl
Et	Ethyl
DMAP	Dimethylaminopyridine
EDCI	1-Ethyl-3-(dimethylaminopropyl)carbodiimide
DCC	N,N'-Dicyclohexylcarbodiimide
N	Normality
HRMS	High Resolution Mass Spectrometry
HPLC	High Pressure Liquid Chromatography
Min	Minute
IR	Infrared
Hz	Hertz

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 activity[2] (Figure 1). , Darvon™ has an analgesic property while Novrad™ has an antitussive property.
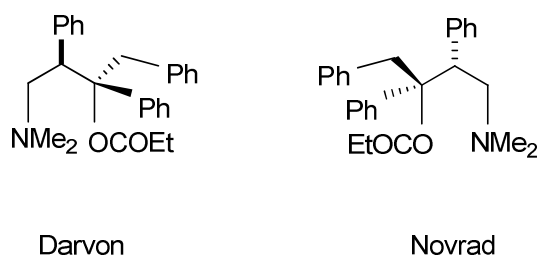
Figure1. Two Enantiomers of Proxyphene

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 alkylation[3] have been developed to the point that they are used routinely on an industrial scale.

William S. Knowles[4] in 1968 pioneered methods in enantioselective synthesis by
replacing the achiral triphenylphosphine ligands in Wilkinson's catalyst with the chiral
phosphine ligands. i.e., (Ph)P(Me)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.[5]
The continued growth of asymmetric catalysis have been advanced with the use of recent
techniques such as high-throughput screening and computational studies.[3,6]
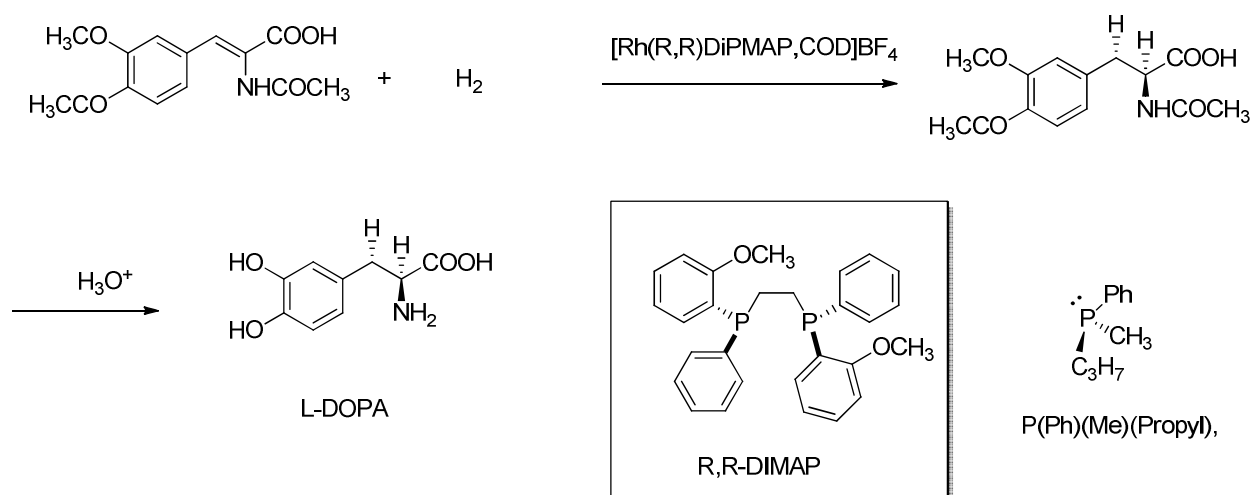
Figure 2. Enantioselective Hydrogenation Step in the Industrial Production of L-DOPA.

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.[7] This reaction involves the addition of hydrogen and a boron atom across the Π- 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).
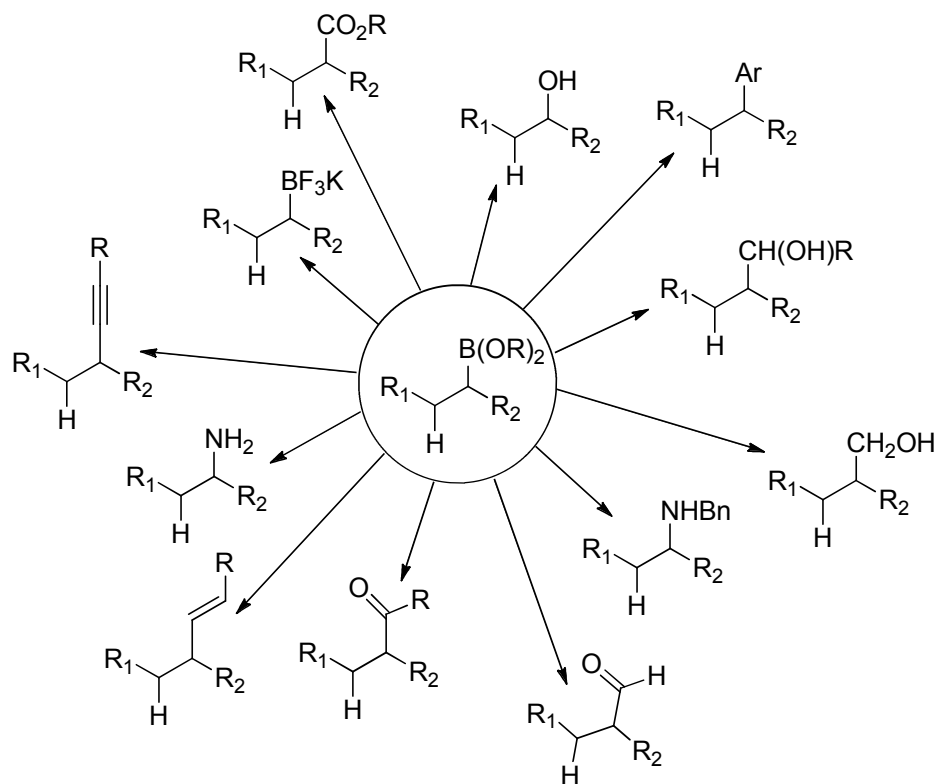
Figure 3. Functional Group Transformations of Chiral Organoboronate Intermediates

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_2O,

8% $Pd_2(dba)_3$, 8-12 equiv of PPh_3) (Figure 4).[12]
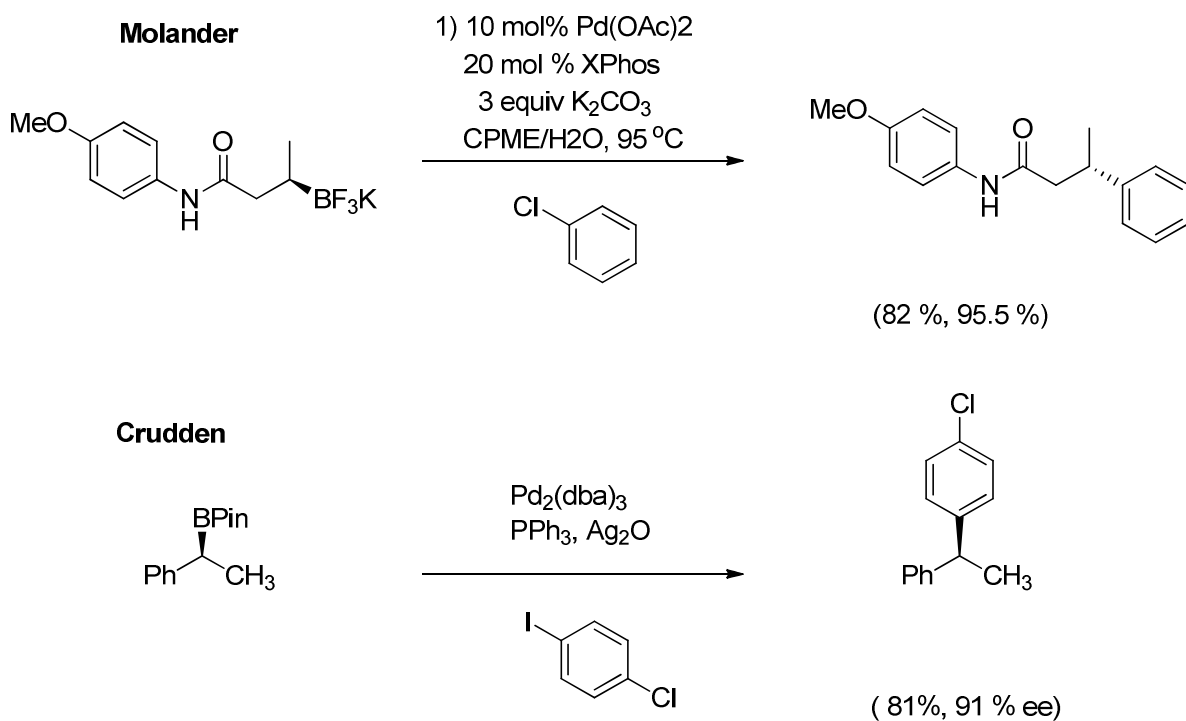
Figure 4. Carbon-Carbon Cross Coupling using Chiral Secondary Boronic Esters

The recent synthetic utility of boronate esters are summarized in (Figure 5).[13, 14, 15, 16]
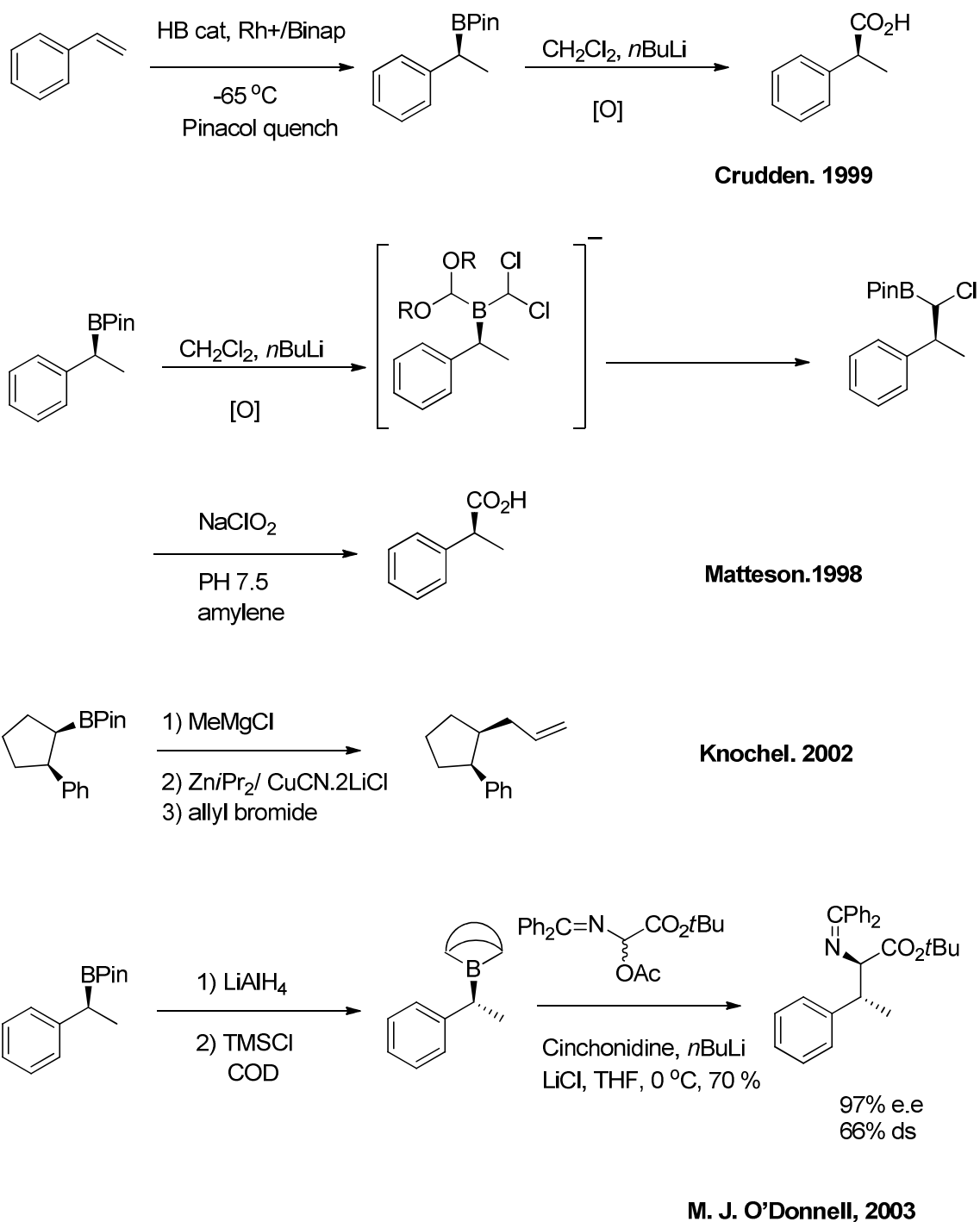
Figure 5. Representative Examples of Synthetic Reactions of Boronate Ester

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.[17]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).
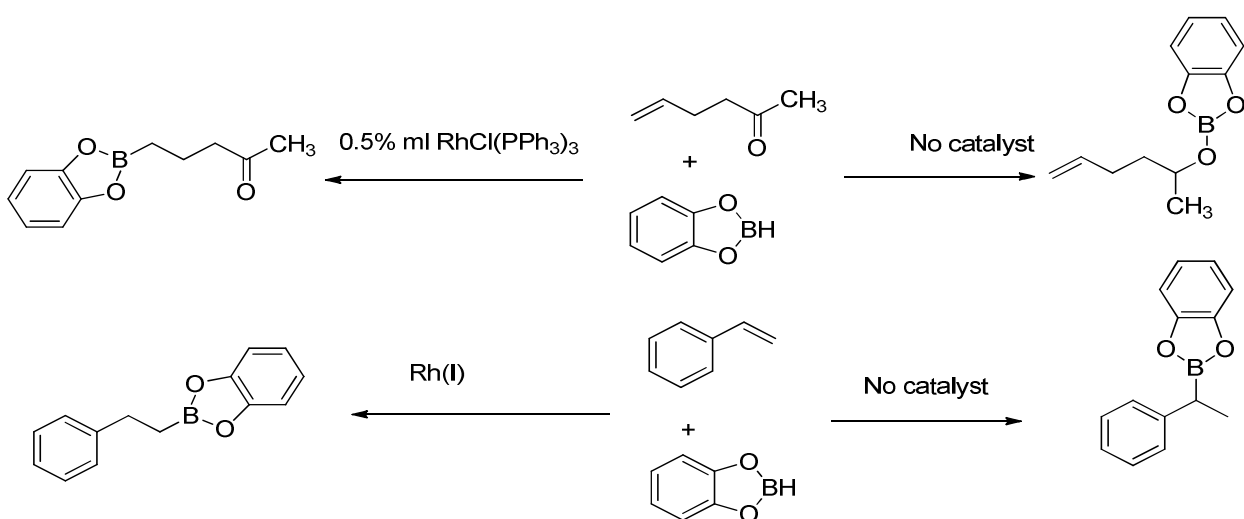
Figure 6. Rh(I)-Catalyzed/ non-Catalyzed Hydroboration Reaction using

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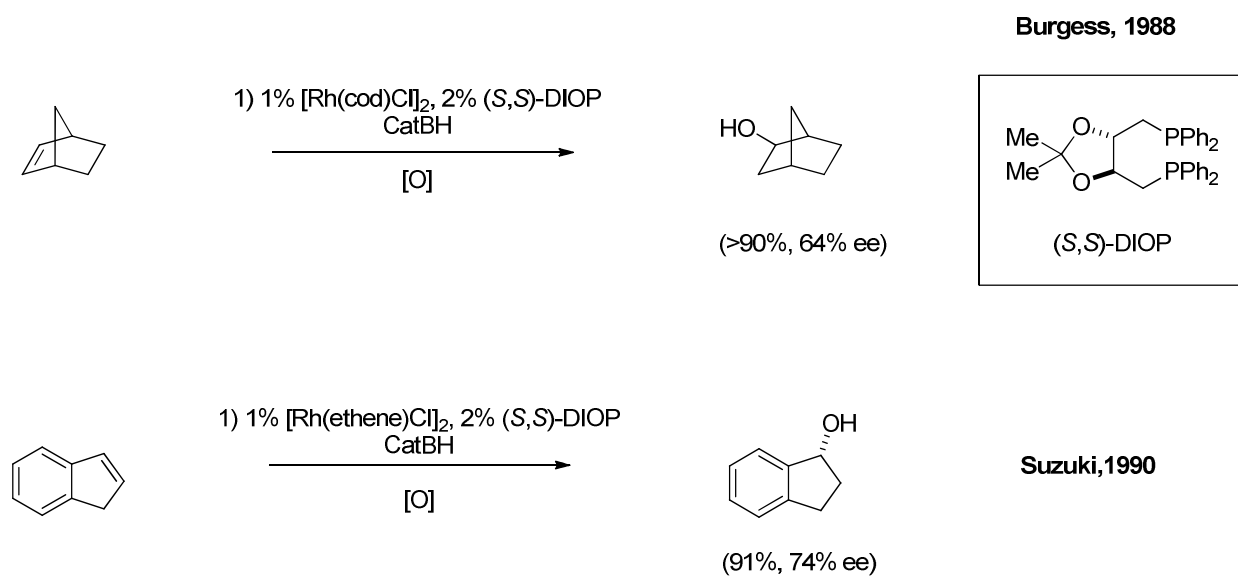
Figure 7. Early Enantioselective Hydroboration using Rhodium–Ligand Catalyst Combinations.

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).

Hayashi ,1989

1) 2% Rh(COD)$_2$BF$_4$, 2% (R)-BINAP
CatBH

2) aq NaOH, H$_2$O$_2$

(R)-BINAP
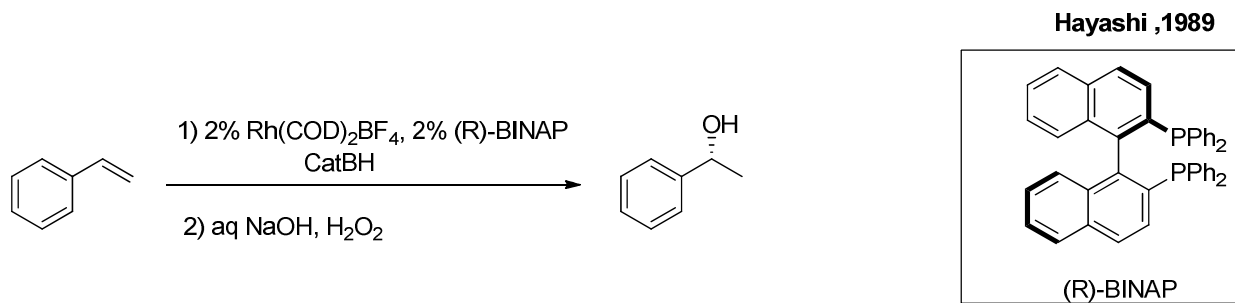
Figure 8. CAHB with Chiral Catalysts by Hayashi and Coworkers.

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.[22] 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.[23]With this system, high levels of selectivity were obtained indicative of an ether-directed reaction (75%) (Figure 9).
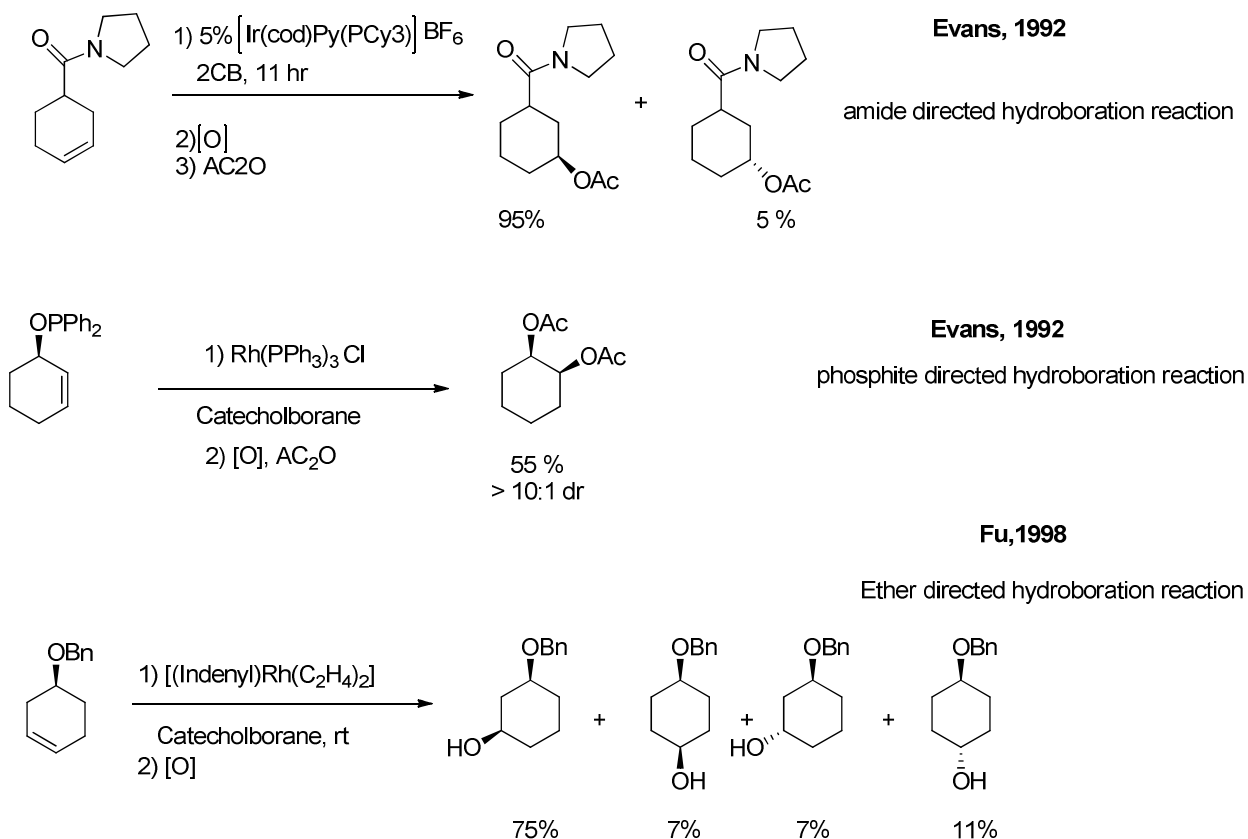
Figure 9. Examples of Directed Hydroboration

A further development of this chemistry was reported by Gevorgyan, et al;[24] 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[25] recently discussed the efficiency of amine in

the non-catalyzed directed hydroboration of a *β,γ*-unsaturated amine by THF·BH$_3$

followed by oxidative workup. The latter substrates exhibit 43:1 regioselectivity in favor

of the 3,5-disubstituted product (Figure 10).
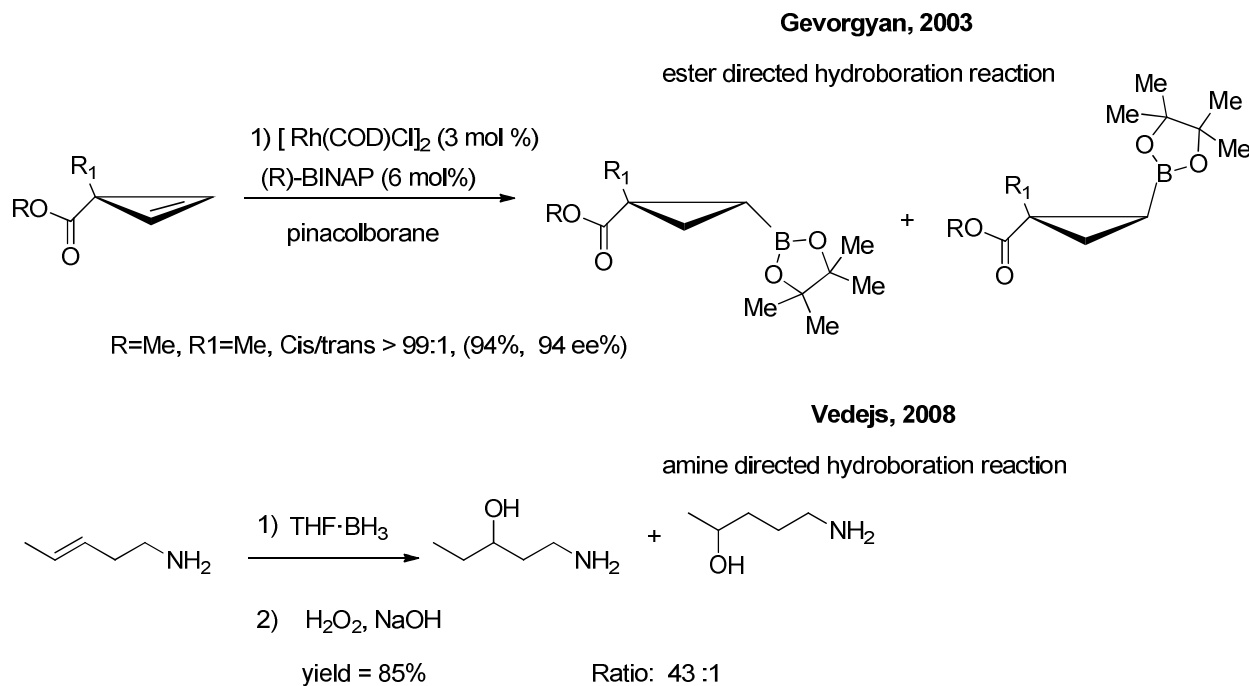
Figure 10. Representative Functional Groups Directed Hydroboration.

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.[26] For

research described later in this dissertation, it should be noted that Kono et al.[27] 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,[28] and Evans used it in his original
report of the catalyzed reaction.
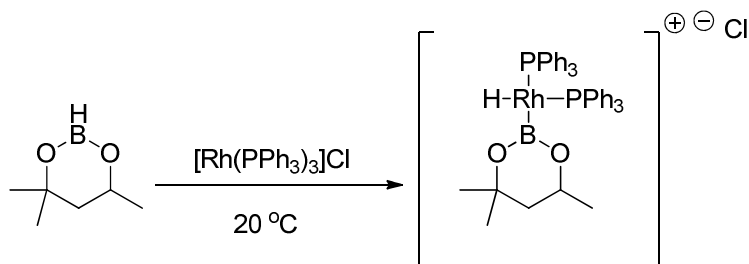
Figure 11. Oxidative Addition of TMDB with Wilkinson's Catalyst

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 perfluroroalkylethylenes 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 $RhCl(PPh_3)_3$, the reaction forms
the primary borane and, following the oxidative workup, the primary alcohol.[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).[30]
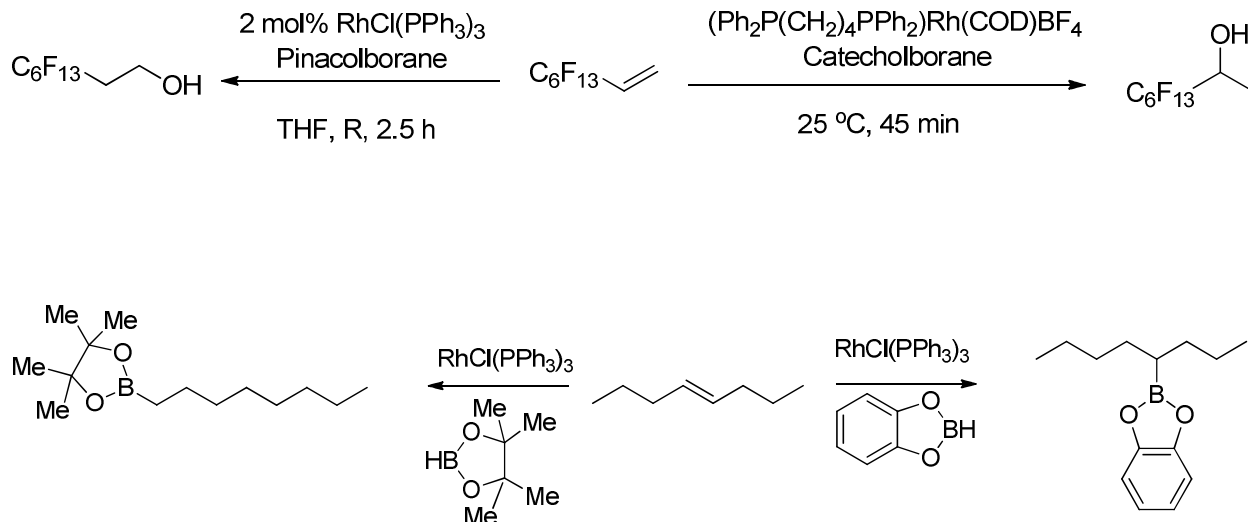
Figure 12. Regiochemical Reversal with Catecholborane and Pinacolborane

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 l,l- and 1,2-disubstituted olefins. Hayashi et.al, reported the significant contribution to catalytic enantioselective hydroboration,[20] 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)- l,l'-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,

diphsophanes are, by far, the most extensively used class of ligands; they show a wide

range of reactivity and enantioselectivity.[1] Some of the more successful examples are

discussed in the following paragraph.
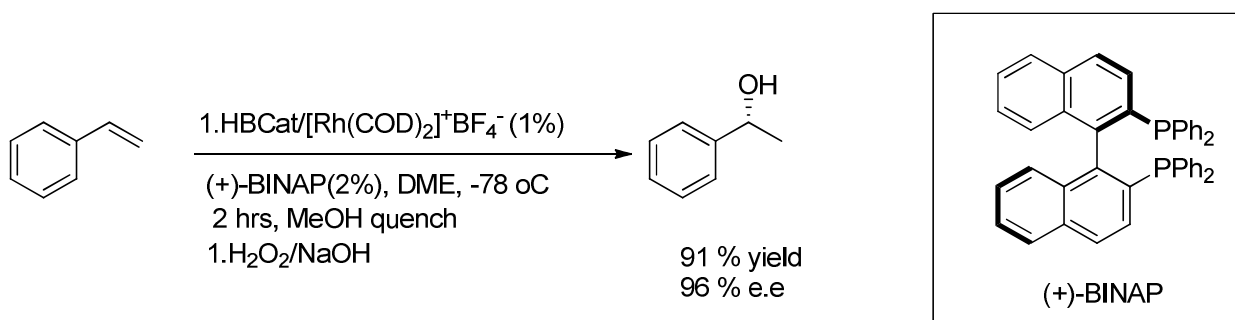
Figure 13. Hydroboration of Styrene with Rhodium Combined with BINAP Ligand.

Knochel[31] 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.[32] 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).
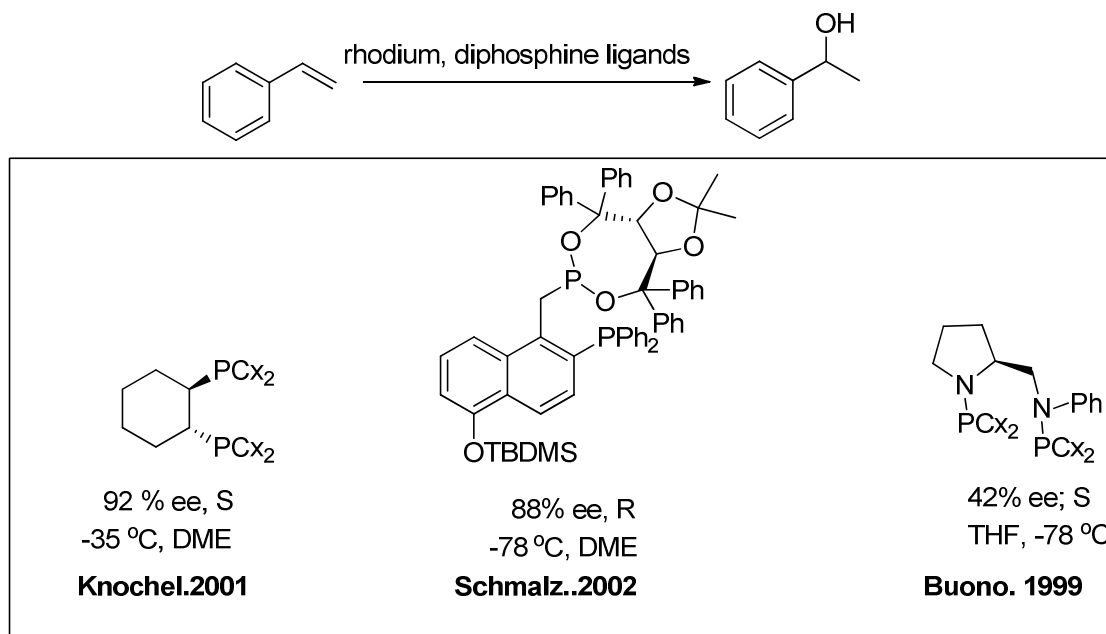
Figure 14. Recent Rhodium-Catalyzed CAHBs with Chelating *P,P*-Ligands.[1]

The Takacs group[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_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.[35] CAHB of *β,γ*-unsaturated Weinreb amides are

another directing group studied by the Takacs group.[36] The Weinreb amides add synthetic value since they readily undergo transformation to other functional groups. For example, the Weinreb amide shown furnishes the *β*-hydroxy acid after the oxidative workup of the product of TMDB addition using Rh(nbd)$_2$BF$_4$ in conjunction with phosphoramidite **L1** (77%, 92% ee) (Figure 15).
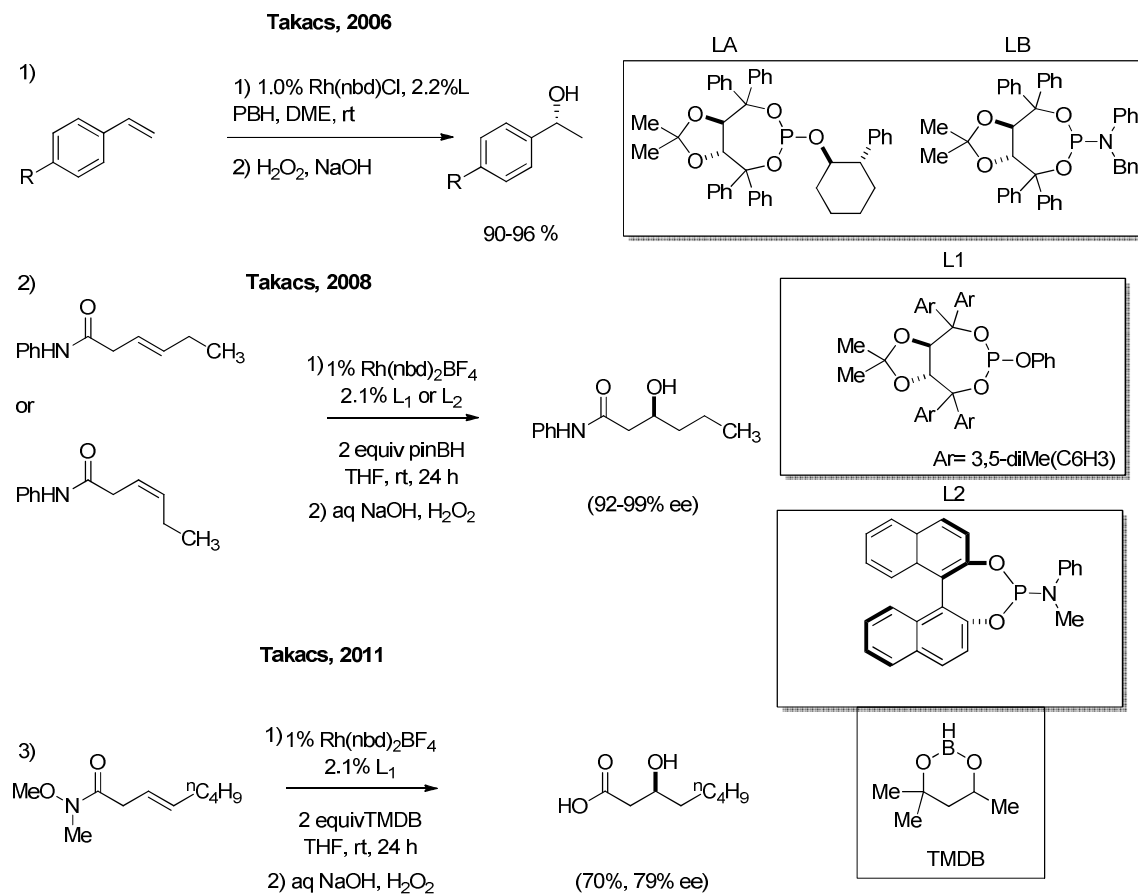
Figure 15. Highly Enantioselective CAHB with Chiral Monodentate Ligands Reported from the Takacs Group.

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[37] as well as by

Ziegler's[38]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 PPh$_3$ 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).

RhP$_3$Cl

+ P   -P

S= solvent
P= PPh$_3$

B(OR)$_2$

R

E

Cl   P
   Rh
A P   S

HB(OR)$_2$

Cl

(RO)$_2$B—Rh   P
            P

Me   R

D

P   H
Cl—Rh
      B(OR)$_2$
P

B

R

R

P   H
   Rh
(OR)$_2$B   P
      Cl

C
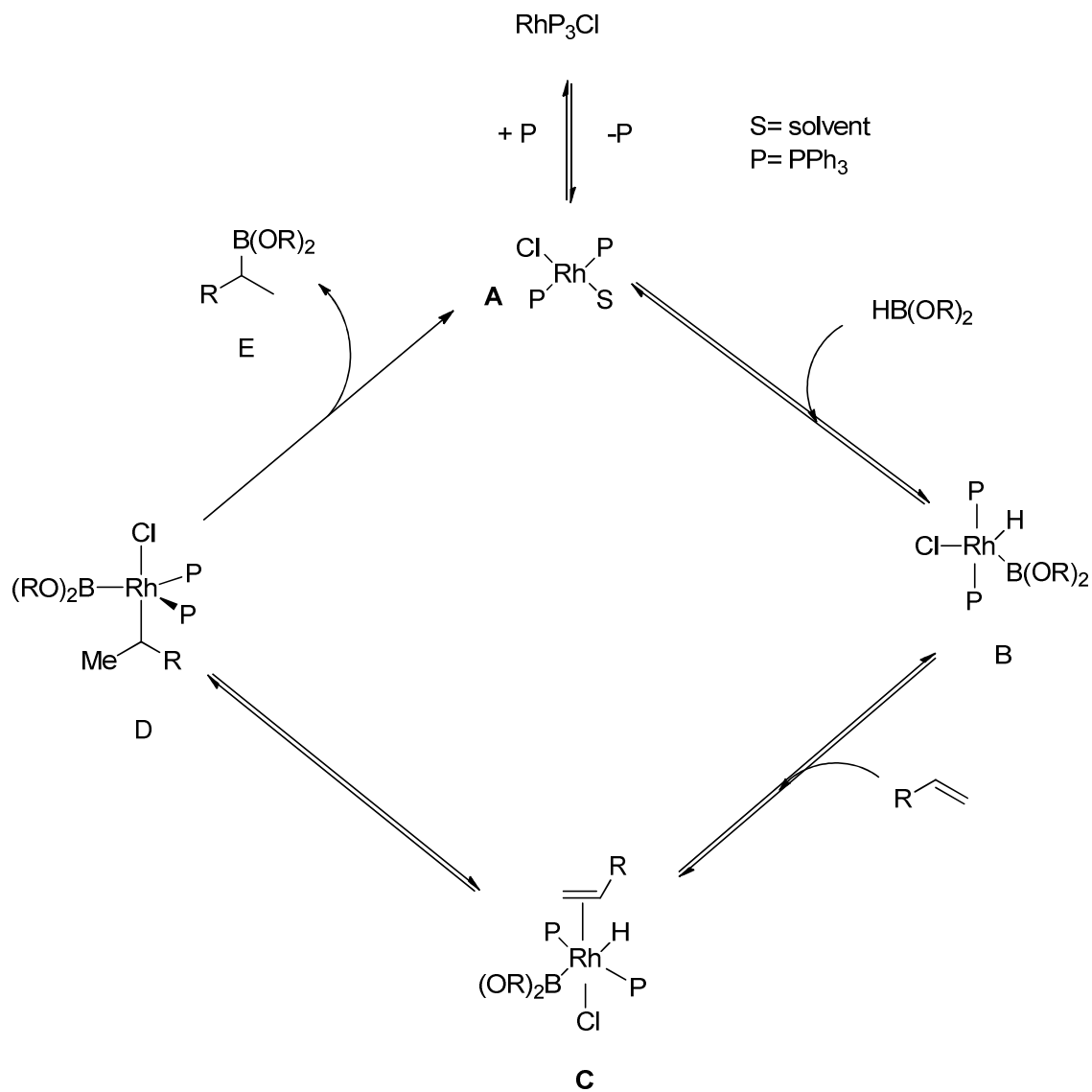
Figure 16. Proposed Rhodium Metal Catalyzed Hydroboration of Vinyl Arene.

In deuterium labeling studies, Evans[37,39] found that CatBD (deuterated catecholborane) behaved differently with different substrates in reactions catalyzed by RhCl(PPh$_3$)$_3$. 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).
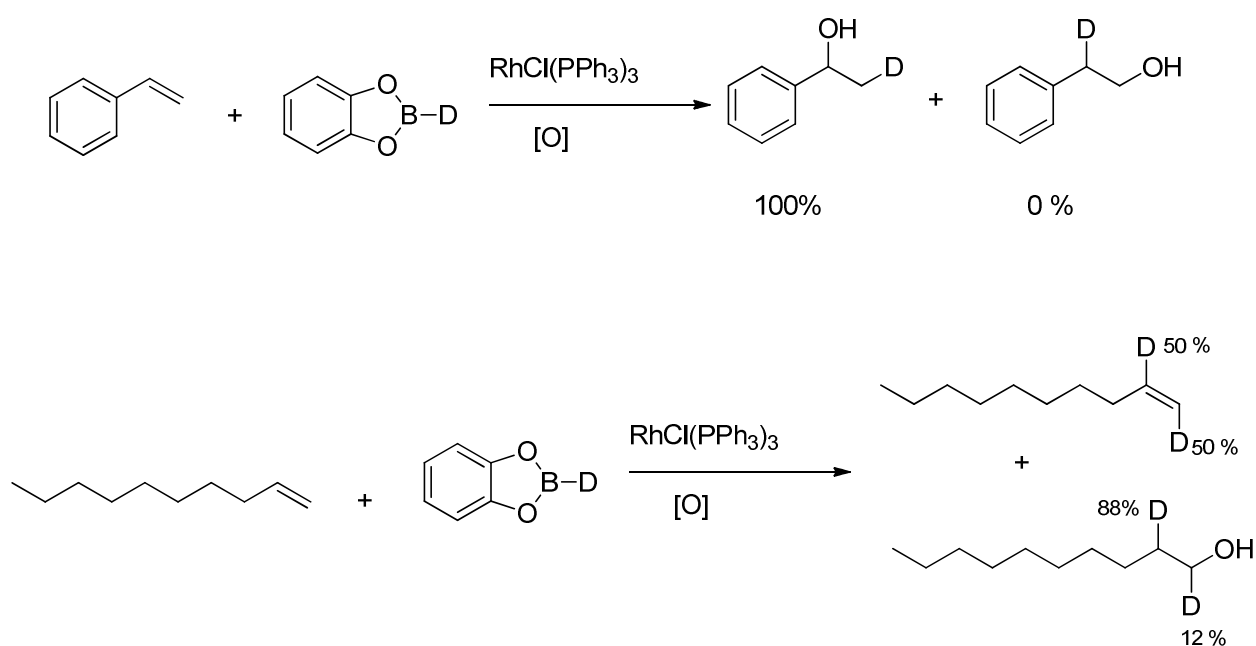
Figure 17. Deuterium Labeled Mechanistic Studies using Catecholborane.

1.8 Conclusion

As we have seen, catalytic asymmetric hydroboration (CAHB) is 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 β,γ-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 β,γ-unsaturated amides proceed to give

highly regioselective results, supporting a two point binding model for these substrates.

For example, the catalytic hydroboration reaction of β,γ-unsaturated amide **X10** followed

by oxidative work up forms the β-hydroxyamide (74%) with high yield; the

regioselectivity favoring the oxidation at the β- rather than γ-position is reported to be

20:1 (Scheme 1).
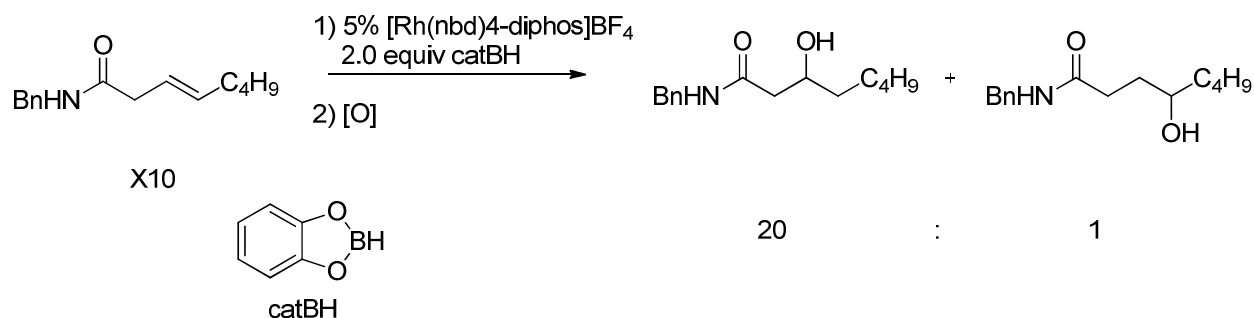
Scheme 1 Amide-directed rhodium-catalyzed hydroboration by evans et. al.

The Takacs group in 2008[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 **X11** (R1 = isopropyl) using **L1** proceeds in good yield (79%) and high enantioselectivity (97% ee).the effectiveness of the chiral ligands highlighted by structure **L2** varies for different substrates, giving a range of enantioselectivity (93-99%). The CAHB also proceeds with high regioselectivity; only 3-4% of the γ-isomer is formed under the described conditions for each substrate shown below in Scheme 2.
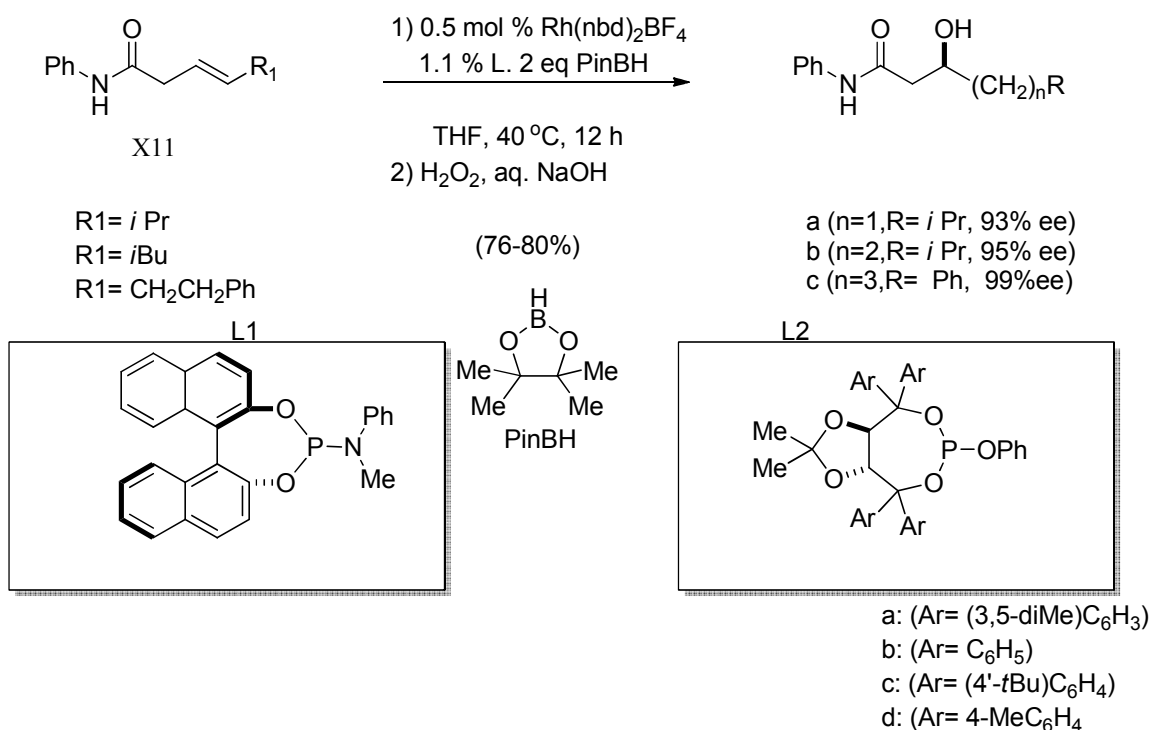
Scheme 2 Efficient directed CAHB of β,γ-unsaturated amides by takacs et al.

The Takacs group[41] provided, as previously mentioned, a new catalyst for the hydroboration reaction of β,γ–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.
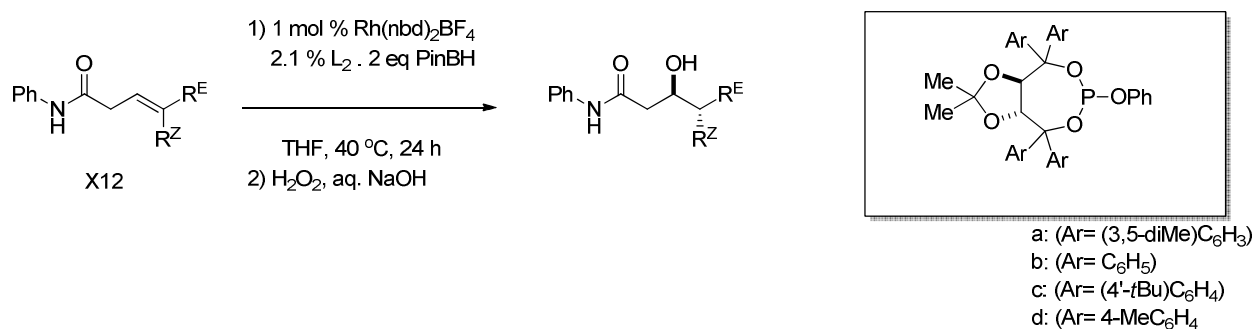
Ligand	R^E	R^Z	Yield %	ee%
L$_2$d	(CH$_2$)$_3$Ph	CH$_3$	81	95
L$_2$a	CH$_3$	(CH$_2$)$_3$Ph	83	95
L$_2$d	(CH$_2$)$_4$Ph	CH$_3$	79	93
L$_2$c	(CH$_2$)$_2$CH$_3$	CH$_3$	80	96
L$_2$d	CH$_3$	CH$_2$CH(CH$_3$)$_2$	81	91
L$_2$c	CH$_3$	CH(CH$_3$)$_2$	80	95

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 moities. 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[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).
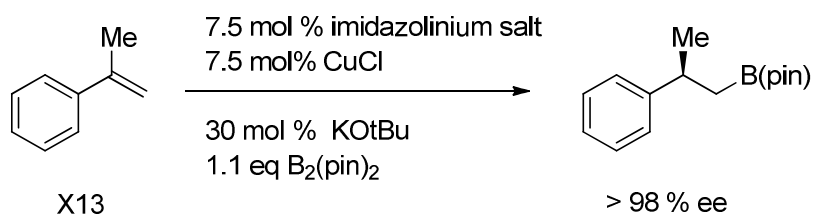
Scheme 4   NHC/Cu-catalyzed CAHB by hoveyda et al.

Significant progress has been made recently in the design and development protocol for CAHB of 1,1-disubstituted alkenes by Mazet et al.[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).
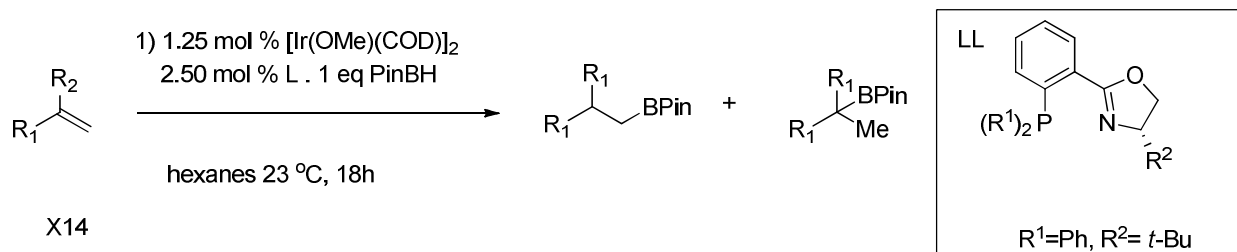
Scheme 5 Iridium-catalyzed CAHB of α-methylstyrene by Mazet et al.

Soderquist and coworkers developed a useful stoichiometric reagent for the asymmetric

hydroboration of 1,1-disubstituted alkenes.[45] Their chiral 9-borabicyclononane derivative

exhibited remarkable enantioselectivity for 2-tert-butylpropene, and good selectivity for

other methylidene substrates, for example, α-methylstyrene shown below (Scheme 6).
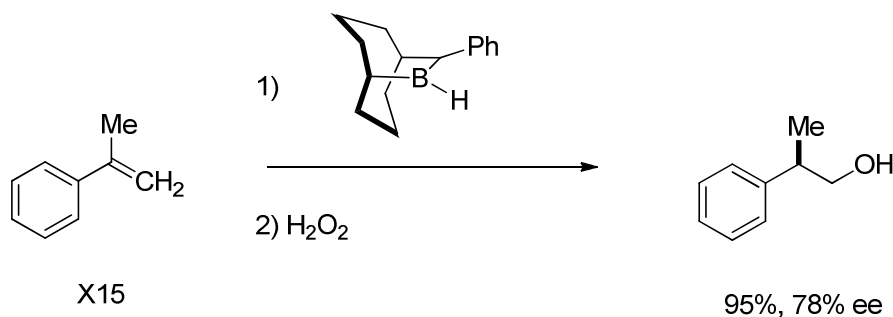
Scheme 6 Example of stoichiometric asymmetric hydroboration of by Soderquist et al.

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

We began by examining the possibility of using simple 1,1-disubstituted alkenes contained within a *β,γ*-unsaturated carbonyl framework to generate enantiomerically pure organoboranes starting with the substrate that contains the methyl substituent in *β*-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 *β,γ*-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 $Rh(nbd)_2BF_4$ 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-butenoic acid phenyl amide **X16** with

TMDB
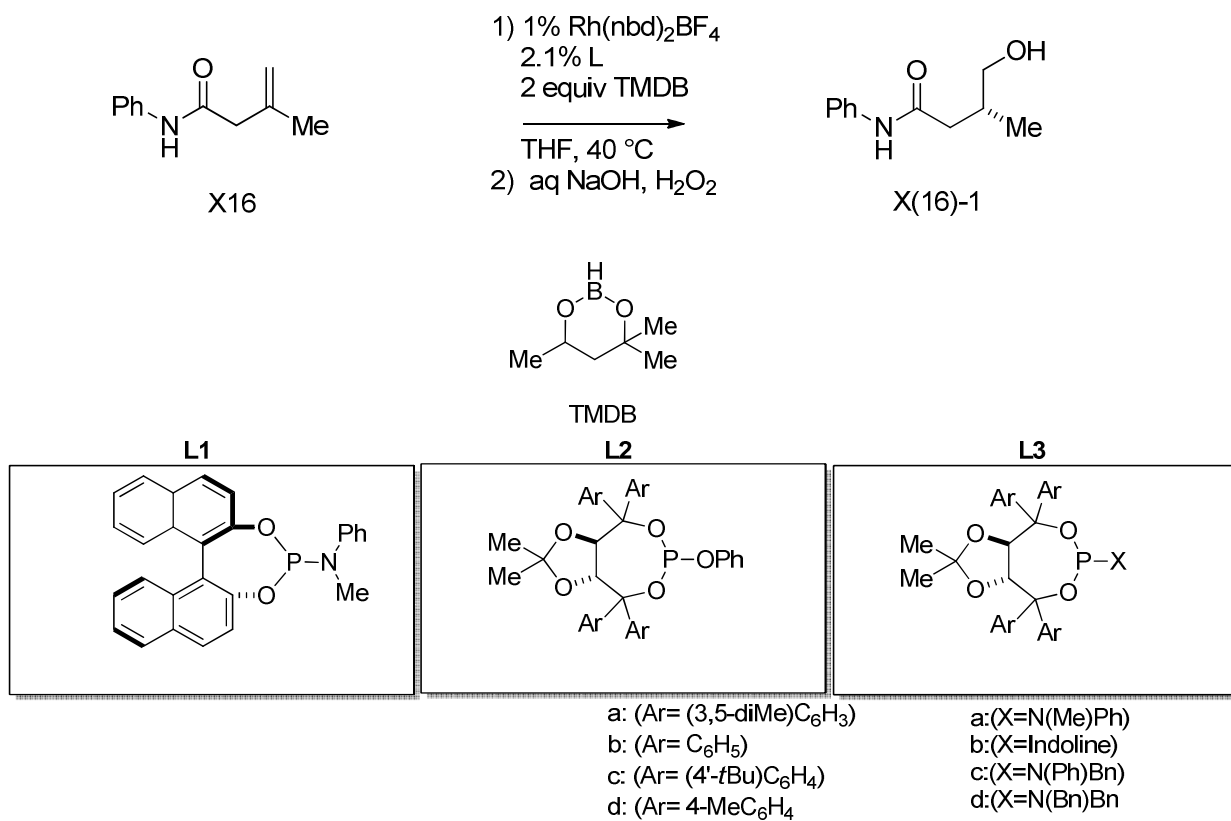
Ligand	% yield	% ee
L2b	40	88
L2c	62	84
L2d	60	80
L2a	81	94
L1	80	63
L3a	72	-10

* % 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
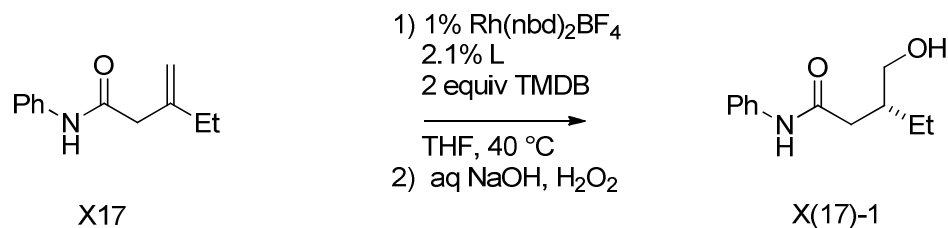
Ligand	% yield	% ee
L2a	70	90
L2c	55	83
L2d	50	71
L1	52	58

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

X18, R=*i*Bu
X19, R=c-C$_6$H$_{11}$
X20, R=C$_6$H$_5$

1) 1% Rh(nbd)$_2$BF$_4$
   2.1% L
   2 equiv TMDB

THF, 40 °C

2) aq NaOH, H$_2$O$_2$

X(18)-1
X(19)-1
X(20)-1
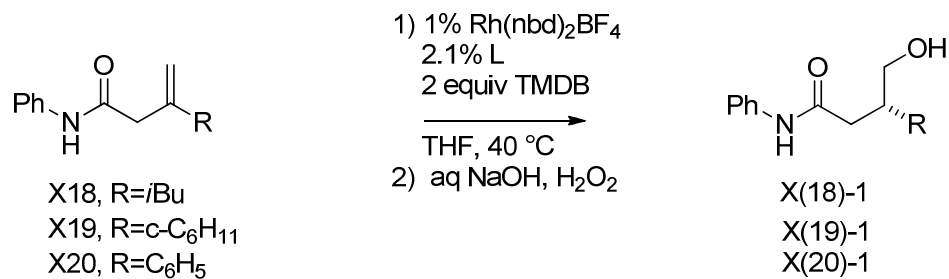
Ligand	% yield	% ee
L2a	72	95
L2c	72	91
L2d	70	80
L1	50	55
L3a	60	39

Ligand	% yield	% ee
L2b	30	55
L2c	70	82
L2d	71	70
L2a	79	90
L1	62	55

Ligand	% yield	% ee
L2c	75	88
L2d	55	86
L2a	79	93
L1	45	50

* % 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

X21, R=(CH₂)₂Ph
X22, R=(CH₂)₃Ph

X(21)-1
X(22)-1
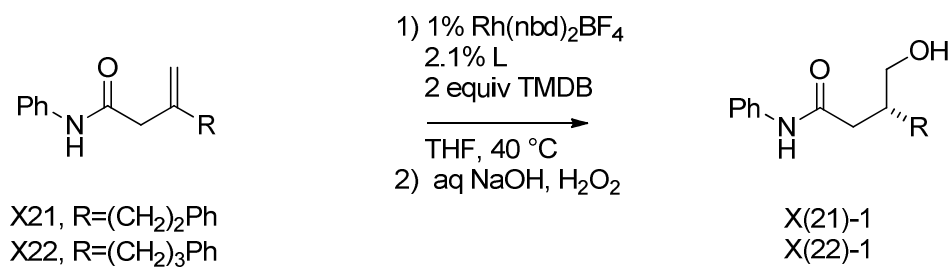
Ligand	% yield	% ee
L2a	72	94
L2c	59	77
L2b	60	78
L1	61	56

Ligand	% yield	% ee
L2a	70	92
L2c	59	75
L1	40	50

*% 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[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 **B1**, a five-membered ring borane, gives product in lower enantiomeric excess (75%, 83% ee) than the six-membered ring homologue **B4** (78, 96% ee).

B1	B2	B3	B4
75 (83 ee%)	77(92 ee%)	40(81 ee%)	78(96 ee%)

B5	B6	B7	B8
16(14 ee%)	10(50 ee%)	79(84 ee %)	81(97 ee%)
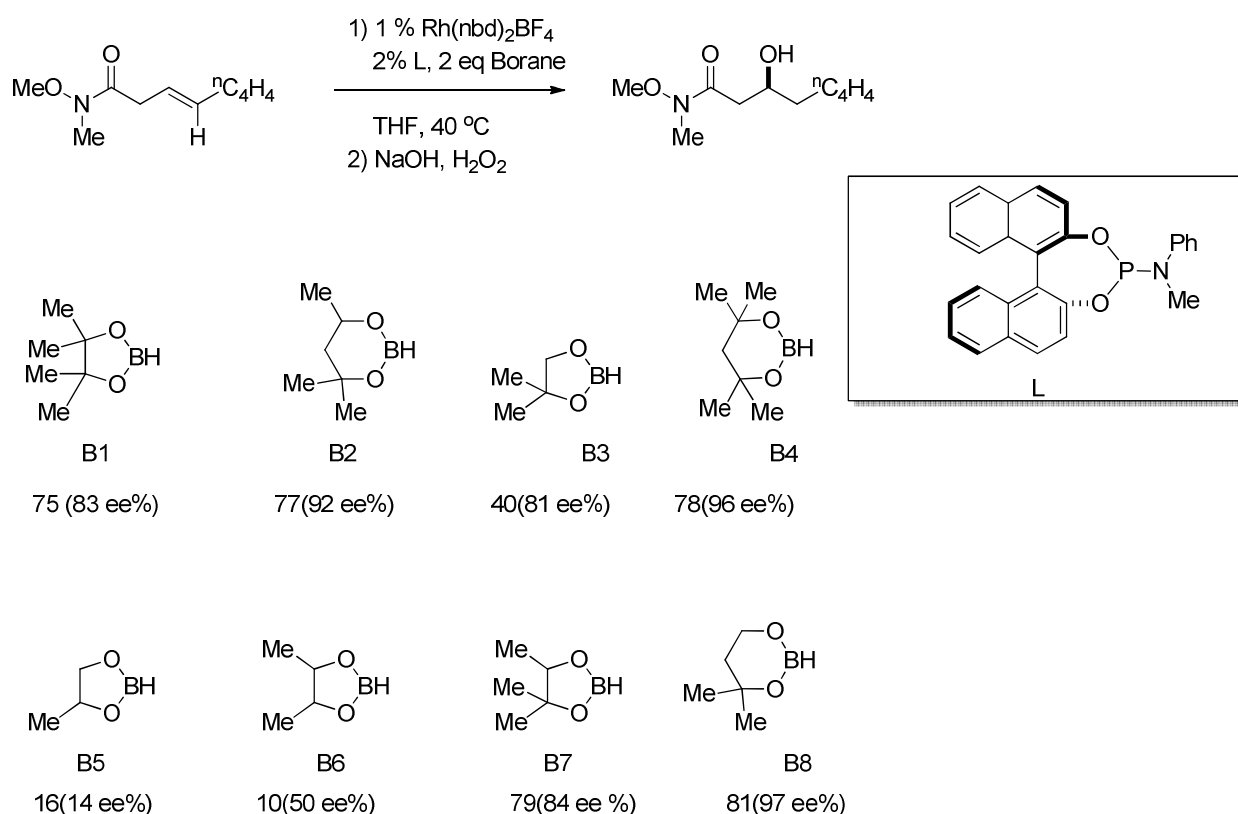
Scheme 7 The influence of boranes structure in CAHB of β,γ-unsaturated weinreb amide.

Table **5** summarizes the chemical yield, regioselectivity (i.e., % γ- and % β-products

formed) and enantioselectivity for the γ-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 γ / β 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 γ-products as major products

with considerable amount of undesirable products such as β- products, this perhaps due to

the size of alkyl group at β- position (scheme 8).
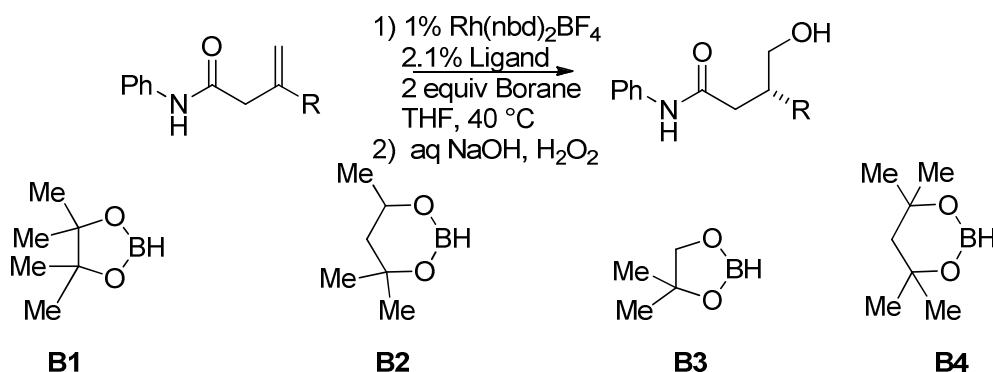
Scheme 8 Catalytic hydroboration of 3-methyl-3-butenoic acid phenyl Amide **X16** with

variety of Boranes.

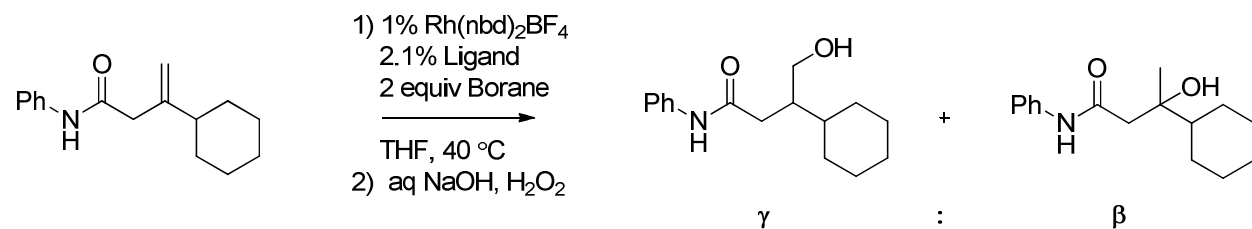**Table 5** Catalytic hydroboration of 3-methyl-3-butenoic acid phenyl Amide **X16** with variety of boranes.

L	B1			B2			B3			B4		
	γ %	% **ee** (γ)	β %	γ %	% **ee** (γ)	β%	γ %	% **ee** (γ)	β%	γ %	% **ee** (γ)	β %
L2a	66	60	34	81	94	13	53	75	41	82	91	12
L2b	65	50	24	40	88	30	36	73	28	64	89	5
L2c	58	52	36	62	84	25	31	79	43	80	79	10
L2d	62	48	23	60	80	30	34	75	41	79	87	10
L1	75	62	11	80	63	18	65	65	22	78	66	7

* 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-butenoic acid phenyl amide **X19** with variety of boranes

L	B1			B2			B3		
	γ %	% ee (γ)	β %	γ %	% ee (γ)	β%	γ %	% ee (γ)	β%
L2a	79	60	3	74	70	7	79	90	3
L2c	78	55	3	74	70	7	70	82	3
L2d	75	5	4	78	60	3	71	70	2
L1	58	64	3	76	50	2	62	55	2
L3	70	-15	5	45	40	3	30	-55	5

* The yield determined by ^{1}H-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.[46] 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.
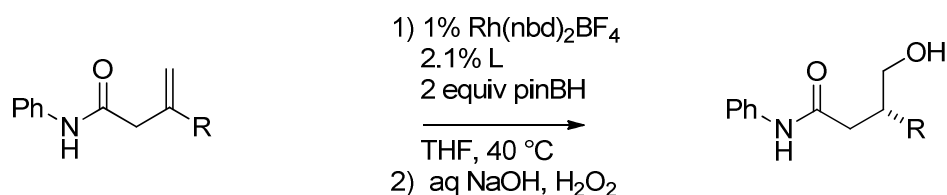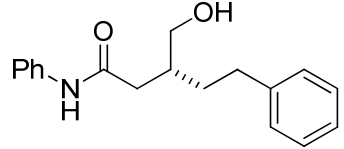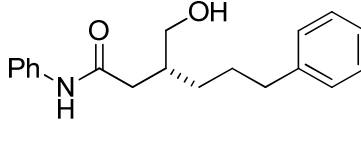

Ligand	% yield	% ee	Ligand	Yield	% ee	Ligand	Yield	ee %
L2a	63	67	L2a	68	60	L2a	80	75
L2c	60	68	L2c	71	55	L2c	72	65
L2d	64	53	L2d	65	45	L2d	71	60
L1	57	50	L3a	75	-32	L1	60	53
-	-	-	L1	64	62	-	-	-

*% 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.

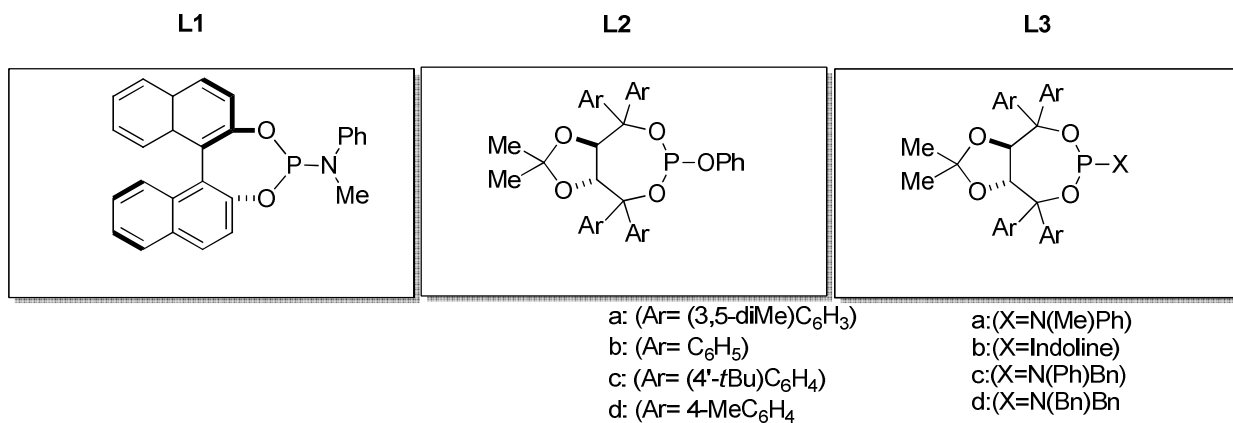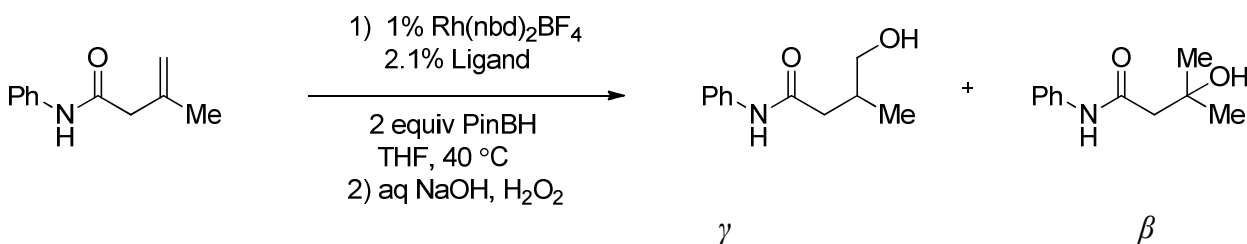**Table 8** Catalytic hydroboration of 1,1-disubstituted phenyl amides **X21 and X22** with pinBH
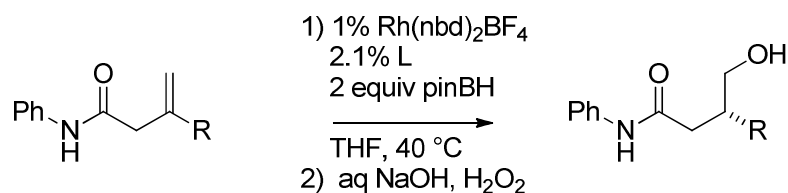
Ligand	Yield	ee %	Ligand	Yield	e.e %
L2a	62	60	L2a	64	67
L2c	72	51	L2c	68	45
L2b	63	43	L1	53	40
L1	75	34	-	-	-

*% 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.[47]

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

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

Table 9 Catalytic Hydroboration of **X16** phenyl amide with variety of ligands

Ligand	γ %	% ee	β %
L2b	65	50	24
L2d	62	48	23
L2c	58	52	36
L2a	66	60	34
L1	75	62	11
L3a	92	-18	1
L3c	92	-40	1
L3d	90	-34	1
L3b	89	-15	2

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., **L2a**, **L2b**, **L2c** and **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 **L2a**, and **L2c** yield 34% & 36% of the β-product, respectively. Directed

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.[48] 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 KHF_2 gives the trifluoroborate salt. These can be used in

Suzuki-Miyaura coupling.[11] For example, organoboronate is obtained in good yield

(53%) from **X16 (R=Me)**. Scheme 10 shows the subsequent transformations to illustrate

its synthetic utility.
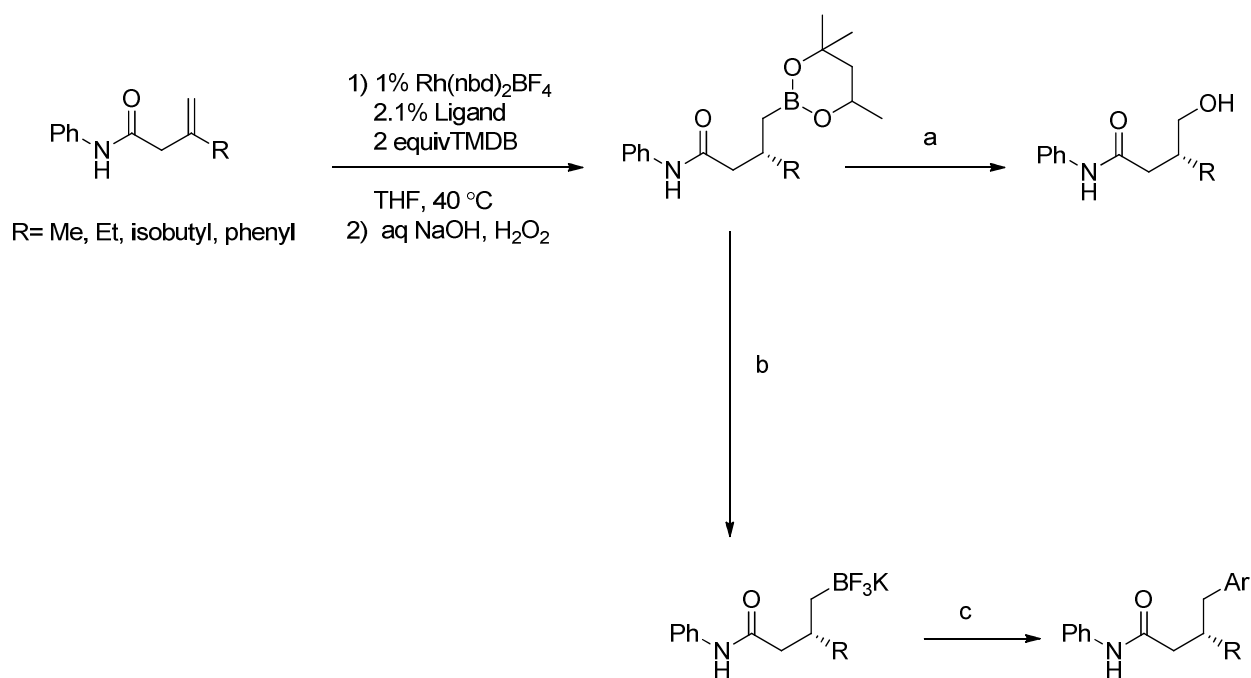
Scheme 10 (a) aq NaOH, H$_2$O$_2$; (b) KHF$_2$, MeOH/H$_2$O; (c) 5%Pd(OAc)$_2$, 10% RuPhos, Ar-X, K$_2$CO$_3$, toluene/H$_2$O, 80 °C (Ar-X= Chlorobenzene.yield=81%).

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 *β,γ*-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 **X18** by 4,4,6-trimethyl-1,3,2-

dioxaborinane (TMDB) catalyzed by $Rh(nbd)_2BF_4$ in conjunction with the TADDOL-

derived phosphite **L2a** affords -dioxaborato amide **X(18)-1** in excellent enantiomeric

purity (72%, 95% ee); only a trace of the *β*-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 **X23** 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 *β*-hydroxy ester is formed. Oxidative

workup with basic hydrogen peroxide leads to cyclization of the *γ*-hydroxy ester to the

γ-lactone.

In evaluating the directed CAHB of **X23**, 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 **X23** in

presence of **L2a** and pinBH furnish, after oxidation, γ-hydroxy alcohol in (57, 81% ee);

the CAHB of the phenyl amide **X16** in presence of **L2a** and pinBH furnish γ-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 **L2c** affords **X(23)-1** in 75% ee and the corresponding (3,5-

dimethyl)phenyl analogue **L2d** gives 69 % ee (Table 10).
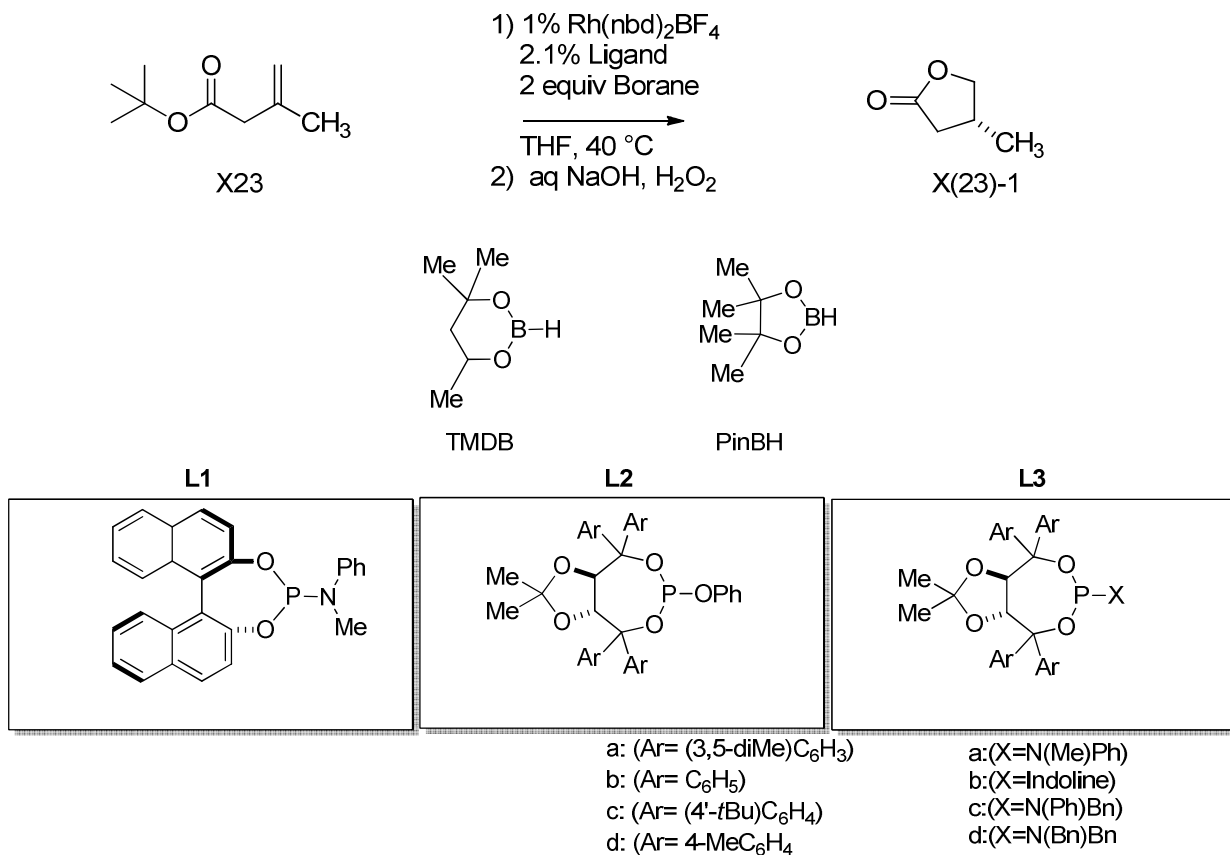
Table 10 Catalytic hydroboration of 3-methyl-3-butenoic acid *tert*-butyl ester **X23** with pinBH.

Ligands	Yield %	ee %
L2a	57	81
L2c	50	75
L2d	52	69
L1	49	72
L3	58	-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 11 Catalytic hydroboration of 3-methyl-3-butenoic acid *tert*-butyl ester **X23** with TMDB.

Ligands	Yield %	ee %
L2a	63	94
L2c	60	88
L2d	63	92
L1	50	82
L3a	59	-23

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.[49] 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-butenoic acid *tert*-butyl **X24** with

pinBH and TMDB.
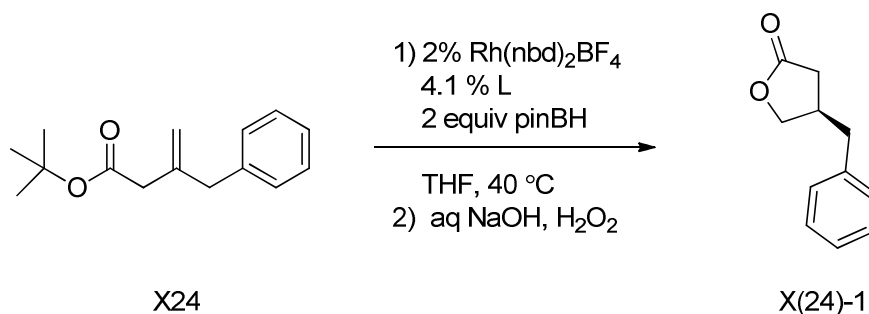
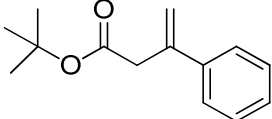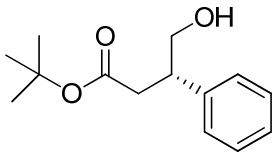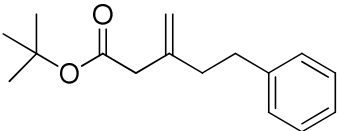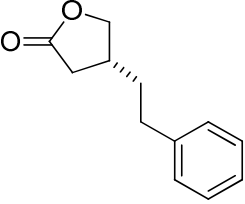| Ligands	pinBH		TMDB	
	Yield %	**ee %**	**Yield %**	**ee %**
L2a	64	61	80	95
L2b	62	57	72	82
L2c	51	30	79	92
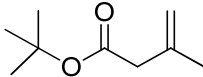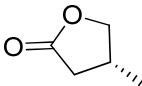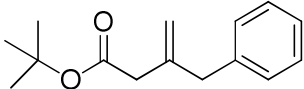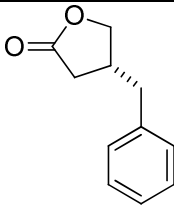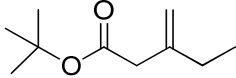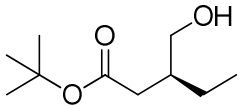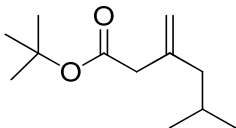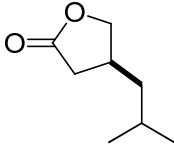
From the studies conducted above and those carried out by others in the Takacs group, it

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.
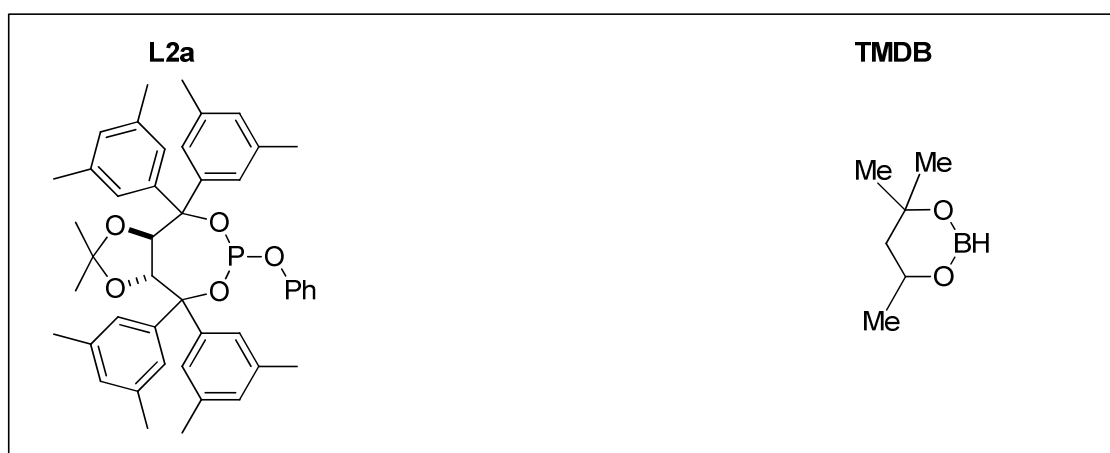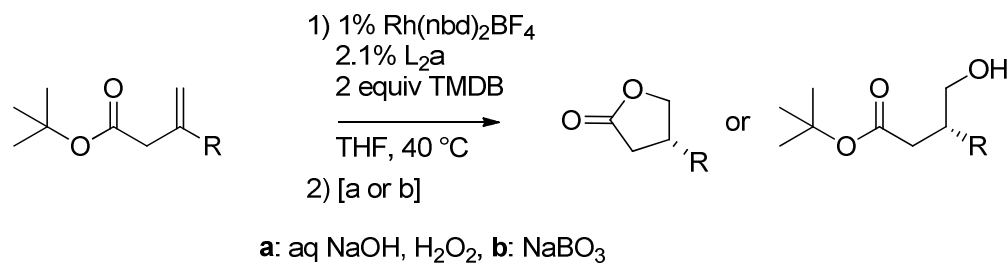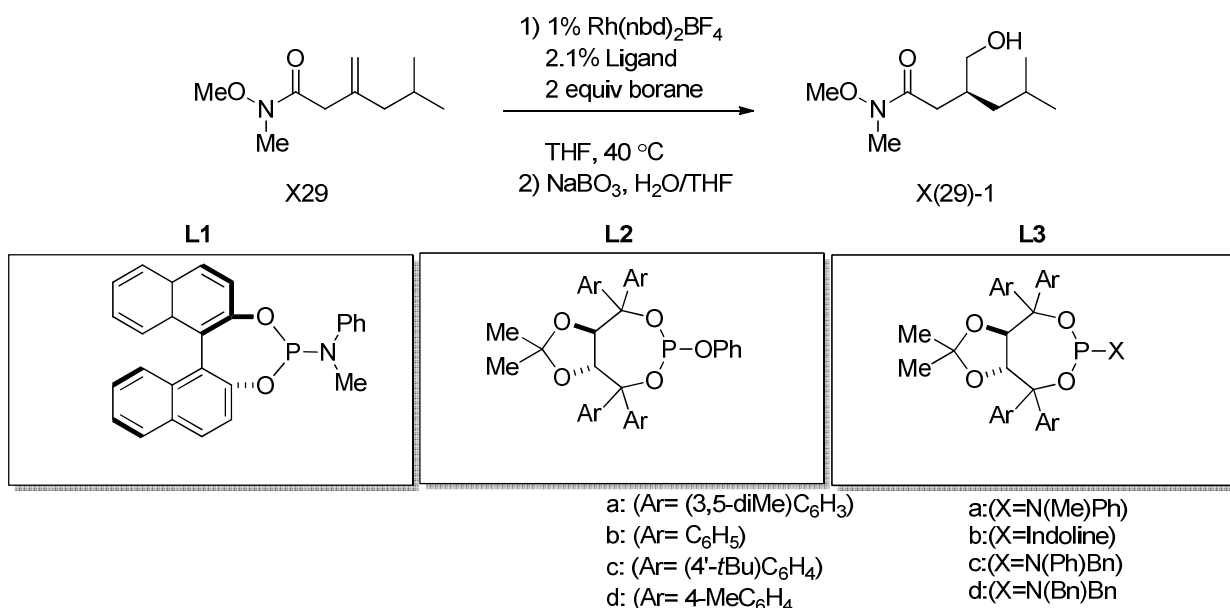

Scheme 11 Catalytic hydroboration of *tert*-butyl esters with TMDB and **L2a** ligand .

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

Entry	Ester	Product	Yield	ee%
X23			62	94
X24			80	95
X25			65	91
X26			76	91
X27			63	94
X28			61	90
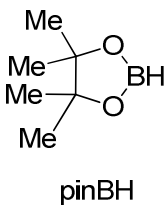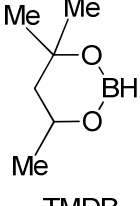
3.2 Catalytic asymmetric hydroboration of 1,1-disubstituted weinreb amides

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 $Rh(nbd)_2BF_4$ 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 TMBD 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

Ligands	pinBH		TMDB	
	Yield %	**ee %**	**Yield %**	**ee %**
L2a	48	45	45	91
L2c	50	50	50	75
L2d	40	30	30	70
L1	20	25	38	20

* % 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,[50] which is a therapeutically effective GABAB receptor agonist.[51] 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.
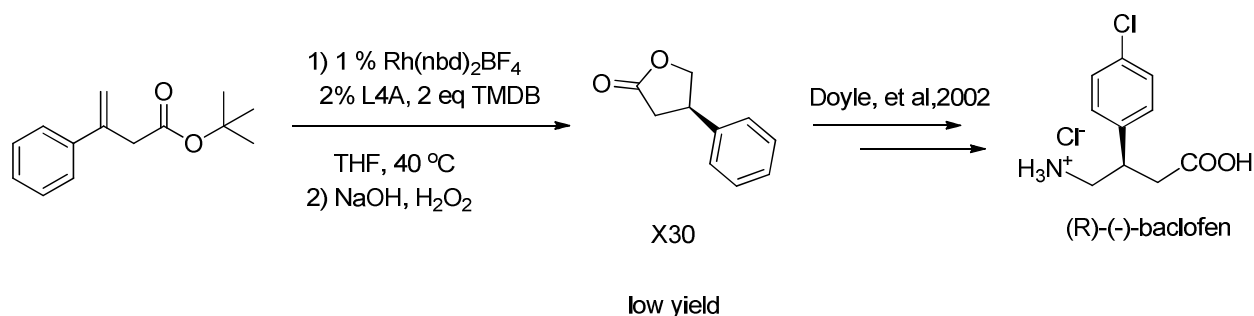
Scheme 13 Attempted route for the preparation of *β*-phenyl-*γ*-butyrolactone

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.[1,2,3,6] 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 C$_3$-symmetric structure and it's as a potent inhibitor of acetylcholine esterase.[52]
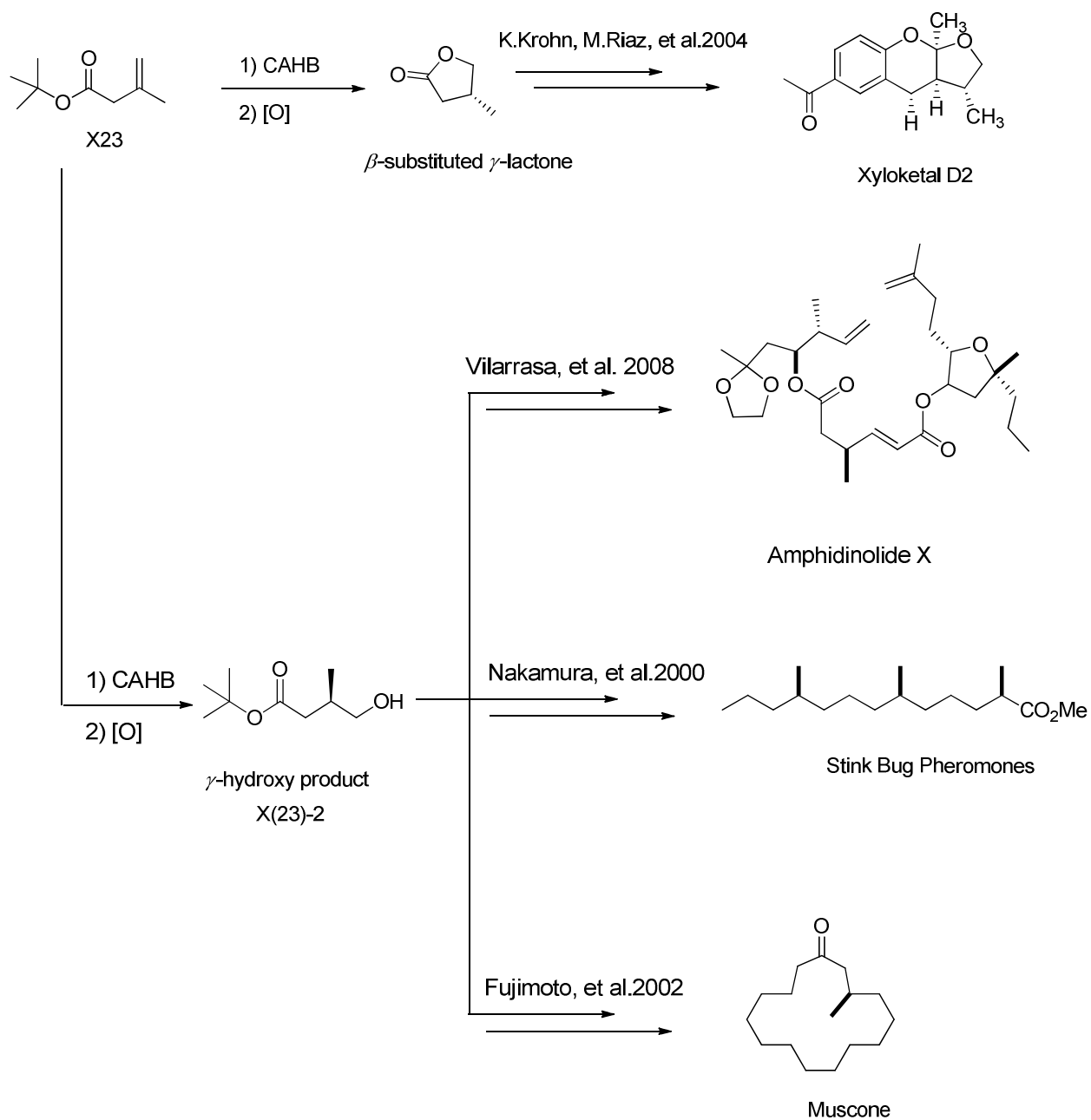
Scheme 14 Representative examples of applications of CAHB of 3-methyl-3-butenoic

acid *tert*-butyl ester **X23**.

CAHB of **X23** followed by mild oxidative workup (NaBO$_3$, THF/H$_2$O) gives β-hydroxy ester **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.[53] The latter compound was the first macrodiolide consisting of polyketide-derived diacid and diol units isolated from natural sources; it possesses moderate cytotoxicitiy against L1210 and KB cell lines.[54] Fujimoto[55] used the same intermediate in his synthesis of muscone, the component of musk used in many perfumes. Nakamura[56] prepared stink bug pheromones from this same intermediate.

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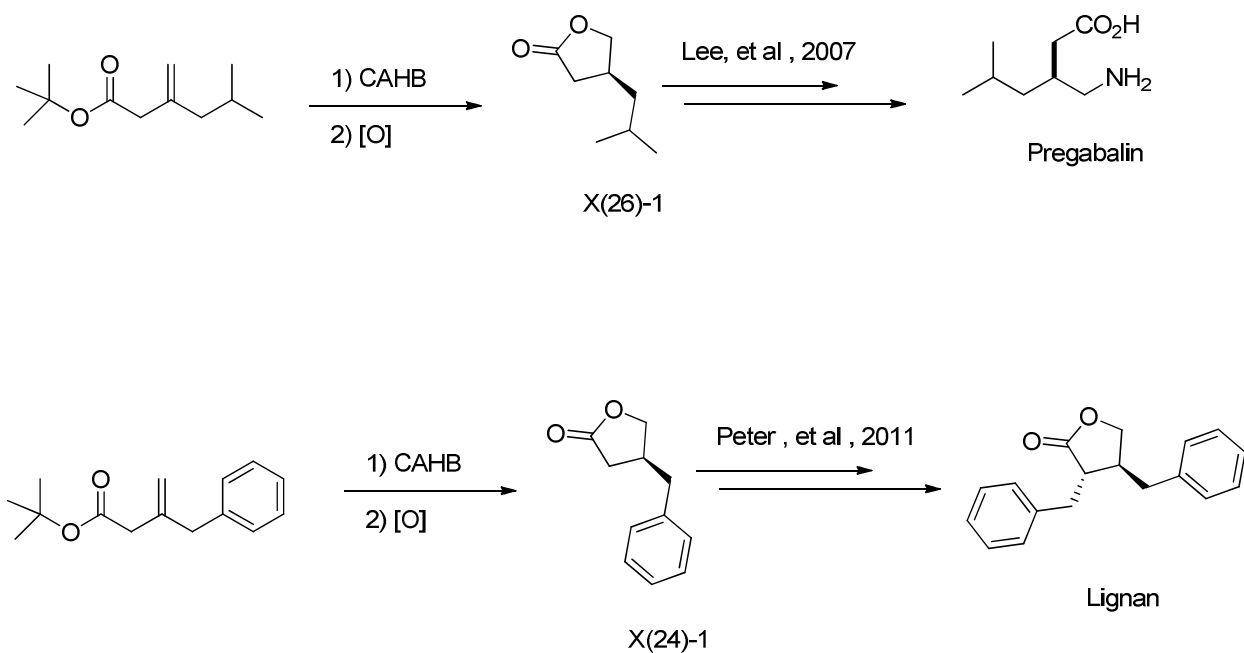
Scheme 15 Preparation of biologically active chiral *β*-substituted-*γ*-lactones via CAHB

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.
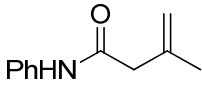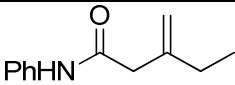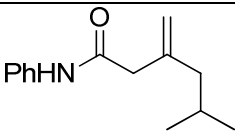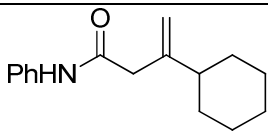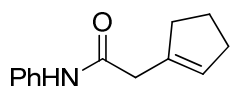
Chapter 4: Concluding remarks
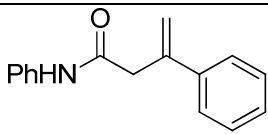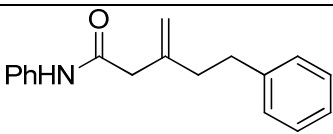
We provided efficient method in catalytic hydroboration of 1,1-disubsituted alkene using two-point binding methodology. This method furnishes chiral organoboronates in high enantiomeric purity. The reactions of several 1,1-disubstitued alkenes within a β, γ-unsaturated carbonyl framework including phenyl 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.
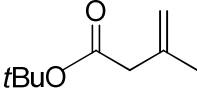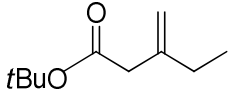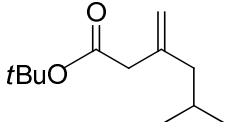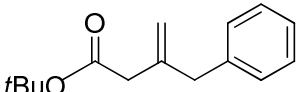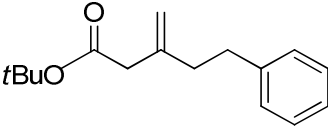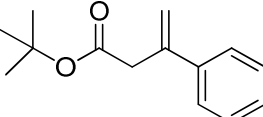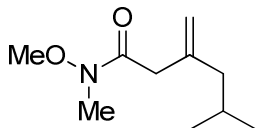
The presence of directing group can serve an efficient tool in controlling the stereoselectivity in CAHB. To test this hypothesis in 1,1-didubstituted alkene within a β, γ-unsaturated carbonyl framework, the **X16** substrate was subjected to the CAHB in presence of 1 % Rh(nbd)$_2$BF$_4$ in combination with 2.1% 3,5-diMe(TADDOL)POPh (**L2a**) and 4,4,6-trimethyl-1,3,2-dioxaborinane (TMDB (**B2**)) affords γ-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 1,1disubstituted 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 γ-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

Substrate	Yield %	ee %
	53	95
	60	92
	80	95
	72	90
	71	93
	73	94
	55	94

| Substrate	Yield %	ee %
*t*BuO	62	94
*t*BuO	65	91
*t*BuO	78	91
*t*BuO	80	95
*t*BuO	67	92
O	63	94
MeO–N(Me)	45	91

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 triturated. 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_2SO_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
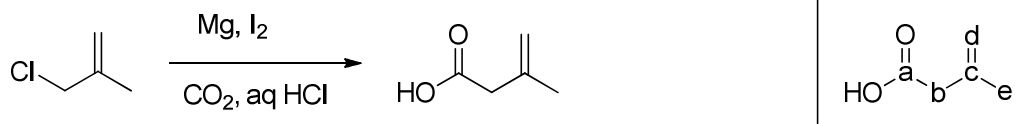
Preparation of 3-methyl-3-butenoic acid (X1): Magnesium turnings and a few

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_2 turning milky white. The

mixture was cooled to -78°C (30 min). Afterwards, a steady stream of CO_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}H NMR (CDCl$_3$, 400 MHz) δ 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}C NMR (100

MHz, CDCl$_3$) δ 177.97 (a), 137,06 (c), 115.60 (d), 43.31 (b), 22,62 (e) ; IR (neat)

2975.5(CH sp^2 stretch) and 1652 cm^{-1}.

**Representative procedure for the preparation of allylic alcohols.**[58]
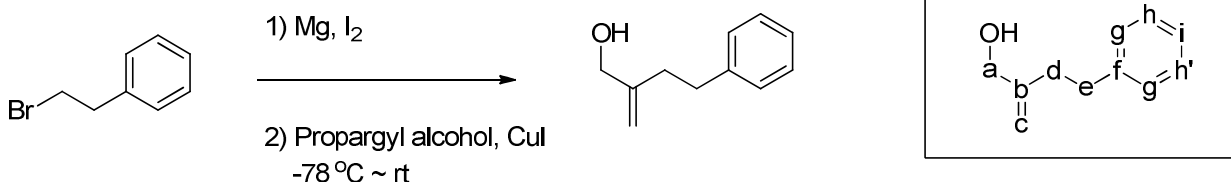
General procedure illustrated for the preparation of 2-methylene-4-phenylbutan-1-ol (X2): Into a flame-dried three-neck RBF with condenser and a dropping funnel under N$_2$ was added THF (40 mL), magnesium turnings (2g, 88 mmol) and a tiny crystal of I$_2$. A solution of (2-bromoethyl) benzene (8.0 g, 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) δ 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.
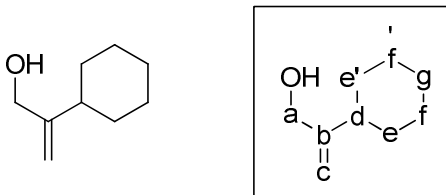

Preparation of Preparation of 2-cyclohexyl-2-propenol (X3): Following the general

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.
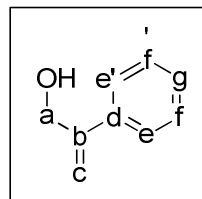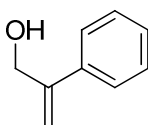
Preparation of 2-Phenyl-2-propenol (X4): Following the general procedure,

phenylmagnesium bromide (90 mL of a 1.0 M solution in THF, 90 mmol) and propargyl

alchol 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$_3$) δ 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$_3$) δ 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$^{-1.}$

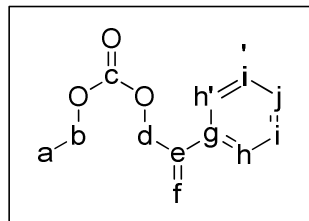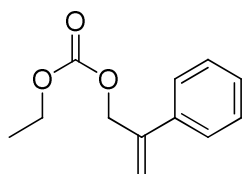**Representative procedure for the preparation of allylic carbonates** [59]
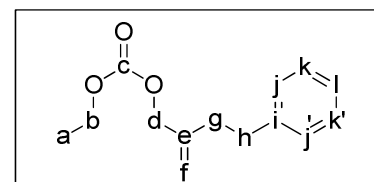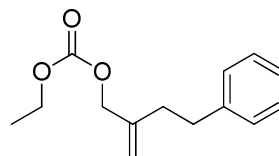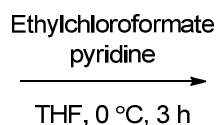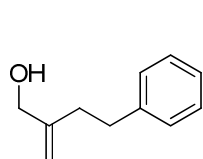
Preparation of 2-phenylethyl ethyl carbonate (X5): To a cooled (0 °C) solution of

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. $MgSO_4$). 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 R_f 0.70

(90:10 hexanes:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$)

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 sp[2] stretch), 698, 908, 1007; HRMS (FAB) calcd. for

$C_{14}H_{18}O_3$(M+Na): 257.1154, found 257.1154 m/z.
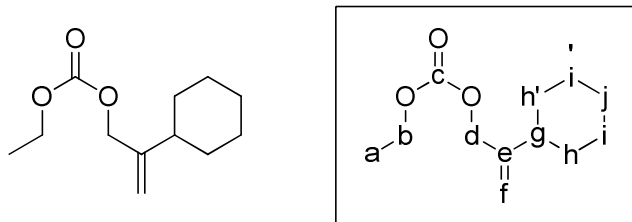
Preparation of 2-cyclohexylallyl ethyl carbonate (X6): To a cooled (0 °C) solution

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. $MgSO_4$) 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 R_f 0.75 (95:5

hexanes:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) 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, m, h,h', i,i', j); ^{13}C NMR

(75 MHz, CDCl$_3$) δ 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 (CI) 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$_3$) δ

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$_3$) δ

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 β,γ-unsaturated esters.
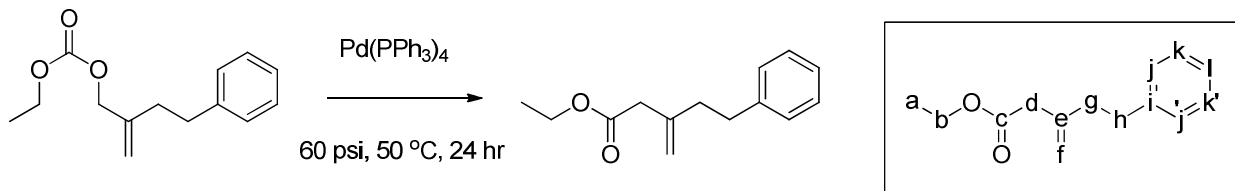
Preparation of 3-methylidene-5-phenylpentanoic acid ethyl ester (X8): A stirred solution of the allylic carbonate (5 mmol) and Pd(PPh$_3$)$_4$ (22.4 mg, 0.1 mmol) was blanketed with a head space of CO to 60 psi. The resulting mixture was warmed to 50 °C and stirred (24 h). Afterwards, the cooled reaction 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 R$_f$ 0.70 (90:10 hexanes:ethyl acetate); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.31(2H, m, j,j'), 7.19-7.29(3H, m, k,k', l), 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); ^{13}C NMR (75 MHz, CDCl$_3$) 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 sp^2 stretch), 1735 (C=O stretch), 1154, 1367, 1387 (CO stretch),746, 654.HRMS (FAB) calcd. For C$_{11}$H$_{14}$O$_2$ (M+H): 218.1307, found 219.1389 m/z.
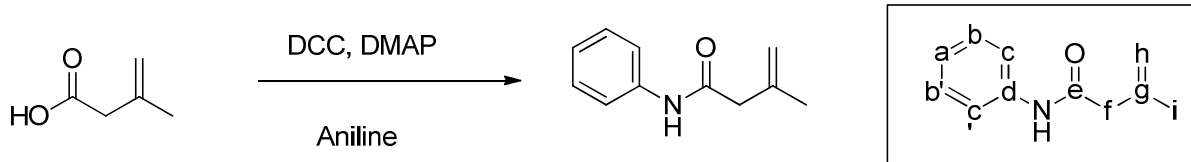
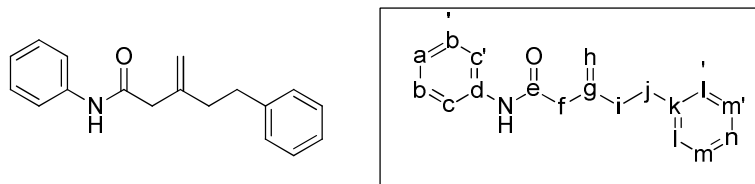## Preparation of 2-phenylethyl ethyl acid
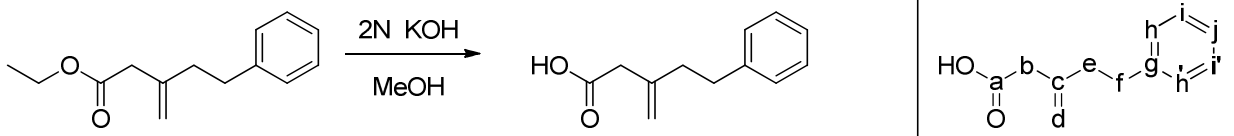
Preparation of 3-Methylidene-5-phenylpentanoic acid (X9): To the compound (
230 mg, 26 mmol) **X8** was added methanol 1 mL and 2 N KOH (9 mL), and stirred
overnight at room temperature. The resultant basic solution was extracted with
dichloromethane (2 x 15 mL) and then acidified. The acidic aqueous layer was extracted
with dichloromethane (3 x 30 mL) and the combined organic extracts were dried (anhyd.
$MgSO_4$) 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 R_f 0.50 (50:50
hexanes:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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
stetch), 1216, 1293, 1406(C-O stretch), 967, 768, 765. cm^{-1}. HRMS (ESI) calcd. For
$C_{12}H_{14}O_2$ (M+Na): 213.0891, found 213.0813 *m/z*.

**Representative procedure for the preparation of β,γ-unsaturated amides** [60]

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):
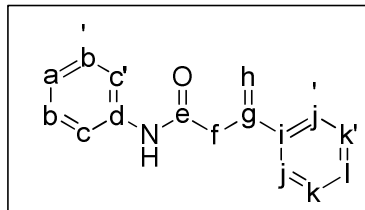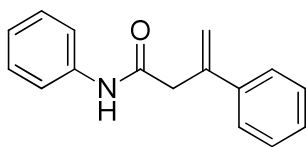
Following the general procedure, 3-methylene-5-phenylpentanoic acid (1 g, 5.25 mmol) affords, after flash chromatography on silica gel (75:25 hexanes:ethyl acetate), the title compound (484 mg, 61%) as a white solid: mp 79–80 °C; TLC analysis R_f 0.40 (75:25 hexanes:ethyl acetate); ^{1}H NMR (400 MHz, CDCl$_3$) δ 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$_3$) δ 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.
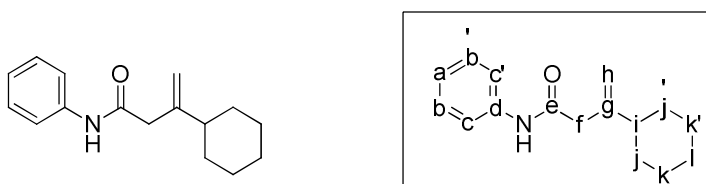
Preparation of 3-Cyclohexyl-3-butenoic acid phenyl amide (X19): follow the same procedure describe above with carbonylation, A mixture of 2-cyclohexylallyl ethyl carbonate   (1.06 mg, 5.0 mmol) and Pd(PPh$_3$)$_4$ (116 mg, 0.10 mmol) was put under a pressurized (60 psi) atmosphere of carbon monoxide. 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 β,γ-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 β,γ-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 β,γ-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 ℃; TLC analysis R_f

0.40 (75:25 hexanes:ethyl acetate); ^{1}H NMR (300 MHz, CDCl₃) δ 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, CDCl₃) δ 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 °C; TLC analysis R_f 0.40 (75:25

hexanes:ethyl acetate); ^{1}H NMR (300 MHz, CDCl$_3$) δ 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); ^{13}C NMR (75 MHz, CDCl$_3$) δ 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
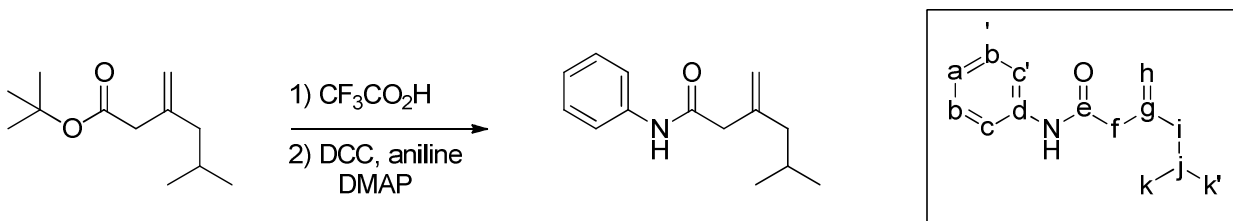
Preparation of 5-methyl-3-methylidenehexanoic acid phenyl amide (X18): To

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. $MgSO_4$) 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 R_f 0.40 (75:25 hexanes:ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) 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'); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CI) calcd. for $C_{14}H_{20}NO$ (M+H): 218.1545, found 218.1539 *m/z*.
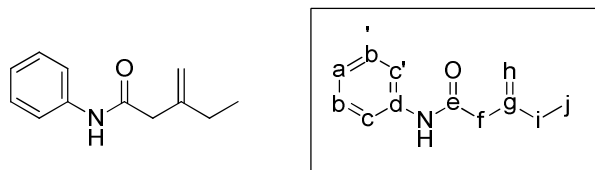
Preparation 3-Methylidene-pentanoic acid phenyl amide (X17): Following the general procedure, 3-ethyl-3-butenoic acid *tert*-butyl ester **X25** (511 mg, 3.0 mmol) affords, after flash chromatography on silica gel (75:25 hexanes:ethyl acetate), the title compound (362 mg, 64%, 2 steps) as a white solid: mp 101–102 °C; TLC analysis R_f 0.40 (75:25 hexanes:ethyl acetate); ^{1}H 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); ^{13}C 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*.
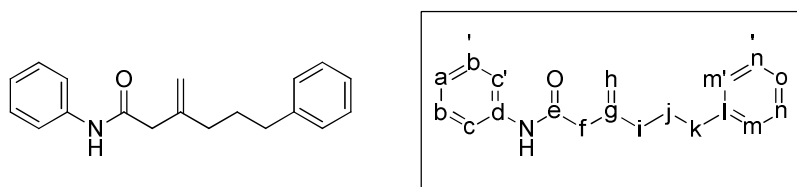
Preparation 3-Methylidene-6-phenylhexanoic acid phenyl amide (X22): Following the general procedure, *tert*-butyl ester **X31** (781 mg, 3.0 mmol) affords, after flash chromatography on silica gel (80:20 hexanes:ethyl acetate), the title compound (476 mg, 57%, 2 steps) as a white solid: mp 51–53 °C; TLC analysis R_f 0.50 (75:25 hexanes:ethyl acetate); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60 (1H, br s, NH), 7.52 (2H, d, J = 7.9 Hz,

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); ^{13}C 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 [61]
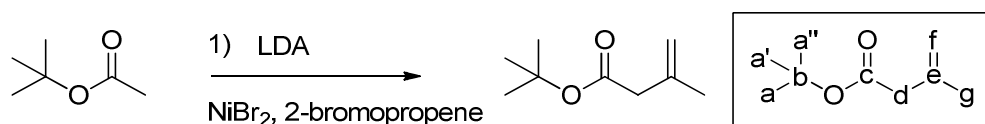
Preparation of 3-methyl-3-butenoic acid *tert*-butyl ester (X23): To a cooled (-78

°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. MgSO$_4$) 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); ^{1}H NMR (300 MHz, CDCl$_3$) 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"); ^{13}C NMR (75 MHz, CDCl$_3$) 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}.
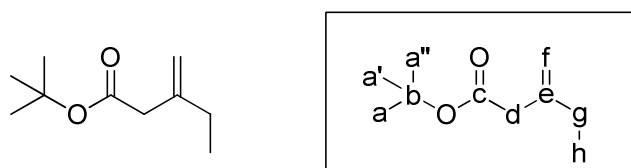
Preparation of 3-Methylidenepentanoic acid *tert*-butyl ester (X25): Following

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); ^{1}H

NMR (400 MHz, CDCl$_3$) 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); ^{13}C NMR (100 MHz, CDCl$_3$) 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}.
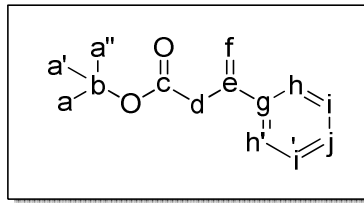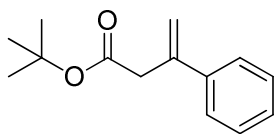
Preparation of 3-phenyl-3-butenoic acid *tert*-butyl ester (X27): Following the

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$_3$) 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"); ^{13}C NMR (75 MHz,

CDCl$_3$) δ 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").
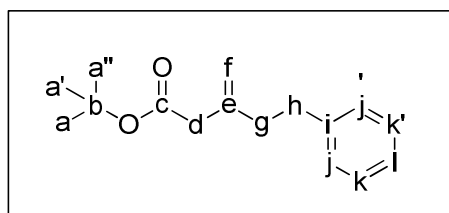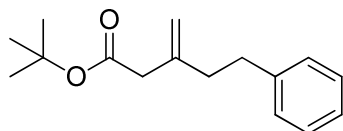
Preparation of 3-(2-phenylethyl)-3-butenoic acid *tert*-butyl ester (X28): Following

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$_3$) δ 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$_3$) δ 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 of *tert*-butyl esters via of vinyl** [62]
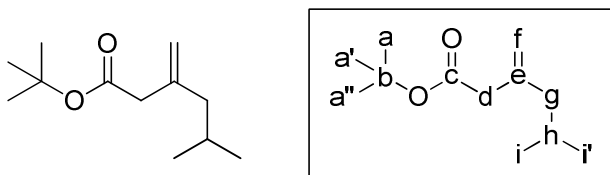
Preparation of 3-*iso*-butyl-3-butenoic acid *tert*-butyl ester (X26): To a mixture of 2,3-dibromopropene (7.01 g, 35 mmol) and copper chloride (173 mg, 1.8 mmol) in THF (30 mL) was slowly added isobutylmagnesium bromide (40 mmol, 13.8 mL of a 2.9 M solution in THF) at room temperature. After a 5 h stir, 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. MgSO$_4$) 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 R_f 0.50 (50:50 hexanes:dichloromethane); ^{1}H NMR (400 MHz, CDCl$_3$) 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'); ^{13}C NMR (100 MHz, CDCl$_3$) 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}.
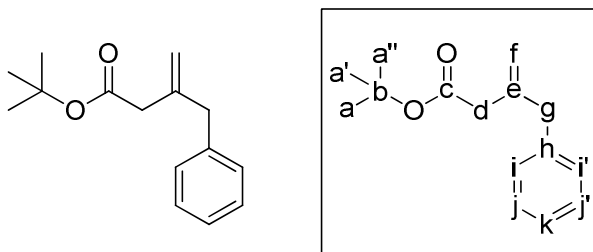

Preparation of 3-Benzyl-3-butenoic acid *tert*-butyl ester (X24): Following the

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); ^{1}H NMR (300 MHz, CDCl$_3$) 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"); ^{13}C NMR (75 MHz, CDCl$_3$) 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}.
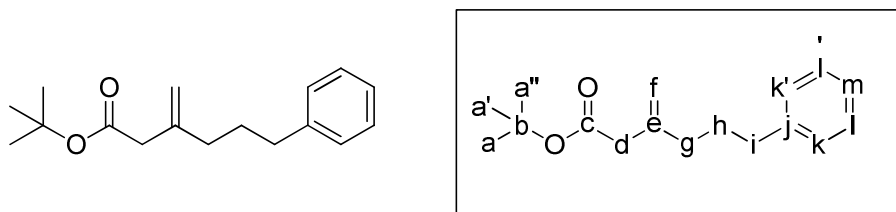
Preparation 3-(3-phenylpropyl)-3-butenoic acid *tert*-butyl ester (X31): Following

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); ^{1}H 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''); ^{13}C 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
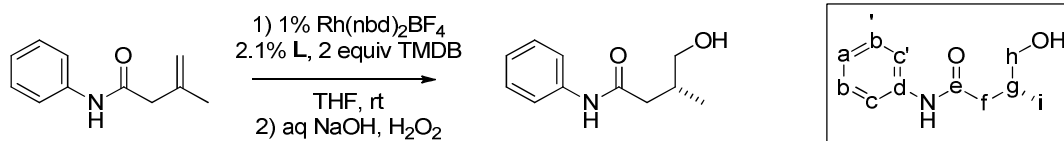
Preparation of (3*R*)-4-Hydroxy-3-methylbutanoic acid phenyl amide (X(16)-1): A

stock solution (2.0 mL) containing Rh(nbd)$_2$BF$_4$ (2.6 mM) and (3,5-dimethyl-

TADDOL)POPh (**L**, 5.6 mM) in THF was prepared. To the resulting yellow solution

[Rh(nbd)$_2$BF$_4$ (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 ^{o}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% H_2O_2 (1 mL), the resultant mixture was extracted with dichloromethane (2 x 10 mL). The combined organic extracts were dried (anhyd. $MgSO_4$) and then concentrated under reduced pressure. Flash chromatography on silica gel (60:40 hexanes:ethyl acetate) affords the title compound (52%, 95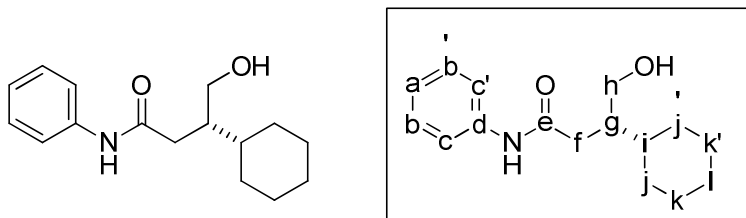% ee) as a white solid: mp 115–117 ºC; TLC analysis R_f 0.70 (50:50 hexanes:ethyl acetate); chiral HPLC analysis (Chiralcel-IC,

80:2 0 hexanes: isopropanol) showed peaks at 17 minutes (3% (R)) and 21 minutes (97 % (S)); ^{1}H NMR (300 MHz, CDCl$_3$) 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, J_1 = 14.0 Hz, 6.8 Hz, J_2 = 14.0 Hz, 6.00 Hz, f), 2.30–2.20 (1H, m, g), 1.00 (3H, d, J = 6.7 Hz, i); ^{13}C NMR (75 MHz, CDCl$_3$) 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 $C_{11}H_{16}NO_2$ (M+H): 194.1181, found 194.1180 *m/z*.
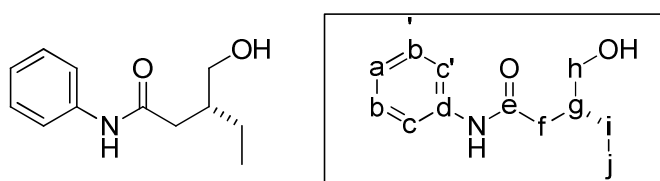
Preparation of (3*R*)-3-Ethyl-4-hydroxybutanoic acid phenyl amide (X(17)-1):
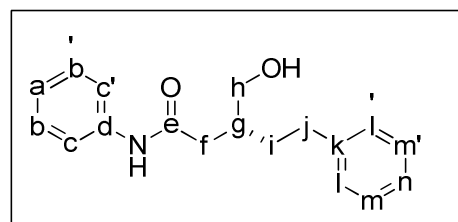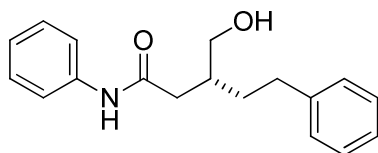
Following the general procedure, 1,1-disubstituted alkene **X17** (99.85 mg, 0.528 mmol) affords, after flash chromatography on silica gel (60:40 hexanes:ethyl acetate), the title compound (65.61 mg, 60%) as a white solid: mp 118–119.5 ºC; TLC analysis R_f 0.50

(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$_3$) δ 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$_3$) δ 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).
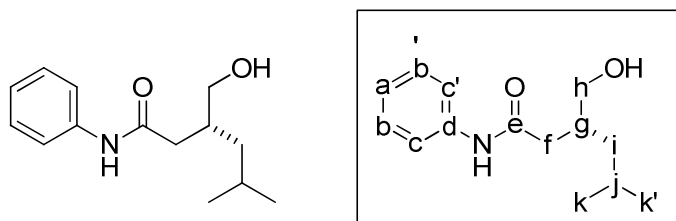
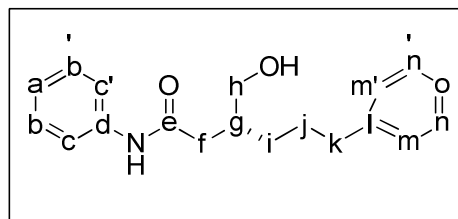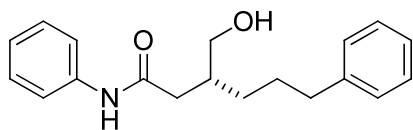**Preparation of (3*R*)-3-*iso*-butyl-4-hydroxybutanoic acid phenyl amide (X(18)-1):**
Following the general procedure, 1,1-disubstituted alkene **X18** (114.65mg, 0.528 mmol) affords, after flash chromatography on silica gel (80:40 hexanes:ethyl acetate), the title compound (89.39 mg, 72%) as a white 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$_3$) δ 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$_3$) δ 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 ºC; 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$_3$) δ 7.71 (1H, br s, NH), 7.50 (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), 3.79 (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$_3$) δ 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).
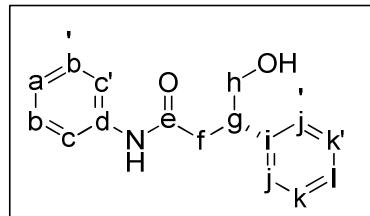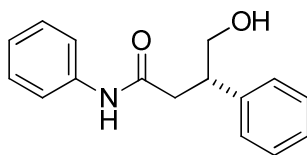
Preparation of (3*S*)-4-Hydroxy-3-phenylbutanoic acid phenyl amide (X(20)-1):

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 R_f 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)); ^{1}H NMR (300 MHz, DMSO-d_6) 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, J_1 = 14.8 Hz, 5.9 Hz, J_2 = 14.8 Hz, 8.9 Hz, f); ^{13}C NMR (75 MHz, DMSO-d_6) 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 (3*R*)-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$_3$) δ 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$_3$) δ 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 ºC; 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$_3$) δ 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 [57]
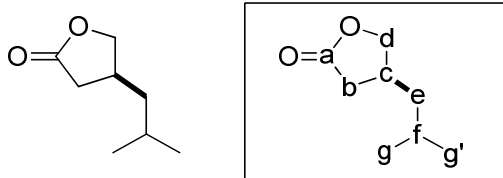
Preparation of (4S)-4-isobutylbutyrolactone (X(26)-1): 1,1-disubstituted alkene **X26** (102 mg, 0.528 mmol) was subjected to standard CAHB conditions . The resultant reaction mixture was diluted with an additional 10 mL of THF followed by slow addition of NaOH (6 mL of a 3 M aqueous soln.) and dropwise 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)

2956, 2903, 1773 (C=O stretch), 1469, 1420, 1367, 1216, 1168 (C-O stretch), 1011, 913, 838, 730, 646, 557 cm^{-1}.
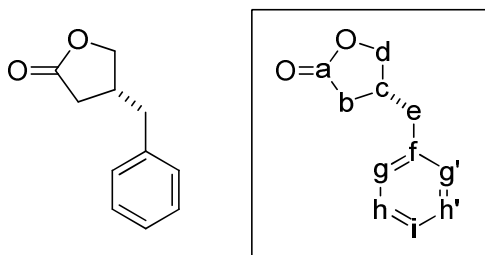

Preparation of (3R)-4-benzylbutyrolactone (X(24)-1):[63]Following the general procedure, 1,1-disubstituted alkene **X24** (123 mg, 0.528 mmol) affords, after flash chromatography on silica gel (75:25 hexanes:ethyl acetate), the title compound (73.2 mg, 80%) as a light yellow oil; TLC analysis R_f 0.40 (75:25 hexanes:ethyl acetate); ^{1}H NMR (400 MHz, CDCl$_3$) 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, J_1 = 8.9 Hz, J_2 = 8.9 Hz, d), 4.05 (1H, dd, J_1 = 6.2 Hz, J_2 = 6.1 Hz, d), 2.95–2.85 (1H, m, c), 2.85–2.75 (2H, m, e), 2.62 (1H, dd, J_1 = 17.4 Hz, J_2 = 7.9 Hz, b), 2.31 (1H, dd, J_1 = 17.4 Hz, J_2 = 6.9 Hz, b); ^{13}C NMR (100 MHz, CDCl$_3$) 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}.
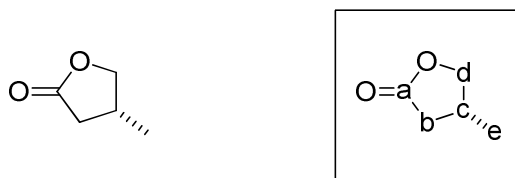
Preparation of (3R)-4-methylbutyrolactone (X(23)-1): Following the general procedure, 1,1-disubstituted alkene **X23** (82.43 mg, 0.528 mmol) affords, after flash

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$_3$) δ 4.41 (1H, dd, J_1 = 8.0 Hz, J_2 = 8.1 Hz, d), 3.87 (1H, dd, J_1 = 8.0Hz, 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$_3$) δ 177.21 (a), 74.68 (d), 34.14 (b), 30.40 (c), 17.94 (e).
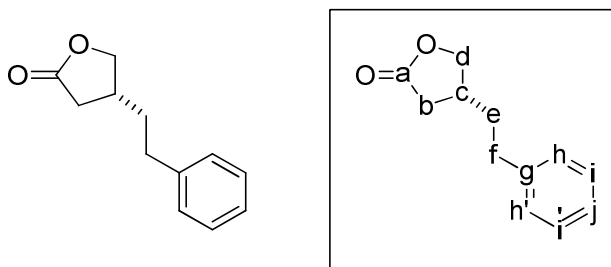
Preparation of (3*R*)-4-(phenylethyl)butyrolactone (X(28)-1): Following the general procedure, 1,1-disubstituted alkene **X28** (139.47 mg, 0.528 mmol) affords, after flash chromatography on silica gel (75:25 hexanes:ethyl acetate), the title compound (61.27 mg, 61%) as a light yellow oil; TLC analysis R_f 0.40 (75:25 hexanes:ethyl acetate); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33(2H, J= 7.2 Hz, i,i'), 7.26 (1H, d, J=7.0Hz, 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$_3$) δ 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
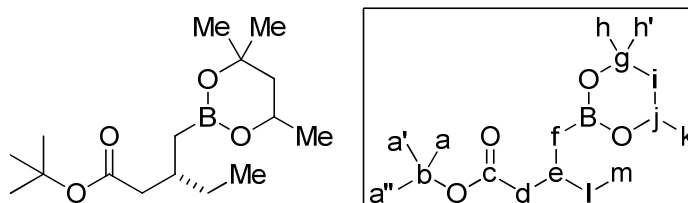
Preparation of (3R)-*tert*-butyl-3-((4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)methyl) pentanoate: Following the representative procedure for rhodium-catalyzed asymmetric hydroboration of β,γ-unsaturated amides at room temperature, hydroboration of β,γ-unsaturated ester **T3** (89.8 mg, 0.528 mmol) affords, after flash chromatography on silica gel (95:5 hexanes:ethyl acetate), the title compound (102.35 mg, 65 %) as a yellow oil; TLC analysis R_f 0.60 (70:30 hexanes:ethyl acetate); ^{1}H NMR (300 MHz, CDCl$_3$) 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); ^{13}C NMR (75 MHz, CDCl$_3$) 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 NaBO$_3$.
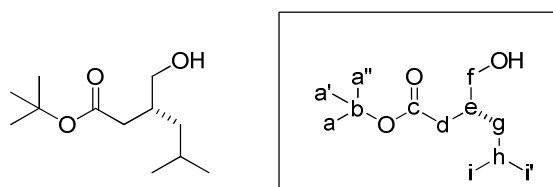
Preparation of (3R)-*tert*-butyl-3-(hydroxymethyl)-5-methylhexanoate (X(26)-1): Following the general procedure for the CAHB of 1,1-disubstituted alkene **X26**, the

resultant reaction mixture was concentrated under reduced pressure and then taken up in

THF (1.5 mL) and H_2O (1.5 mL). $NaBO_3$-tetrahydrate (40 mg, 0.26 mmol) was added to

the resulting mixture. After a 2 h vigorous stir, the reaction was diluted with H_2O (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. $MgSO_4$) 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 R_f 0.50 (60:40 hexanes:ethyl acetate); ^{1}H NMR (300 MHz,

$CDCl_3$) δ 3.70–3.60 (1H, m, f), 3.60–3.40 (1H, m, f), 2.28 (2H, dd, J_1 = 4.4 Hz, J_2 = 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, $CDCl_3$) 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').
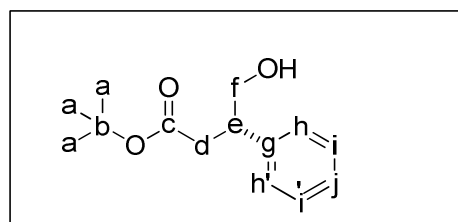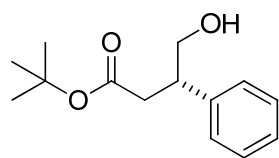
Preparation of *tert*-butyl 4-hydroxy-3-phenylbutanoate (X(27)-1): Following the

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

H_2O (1.5 mL). $NaBO_3$-tetrahydrate (40 mg, 0.26 mmol) was added to the resulting

mixture. After a 2 h vigorous stir, the reaction was diluted with H_2O (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. MgSO$_4$) 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 R_f 0.70 (75:25 hexanes:ethyl acetate); ^{1}H NMR (400 MHz,

CDCl$_3$) 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''); ^{13}C NMR (75 MHz, CDCl$_3$) 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
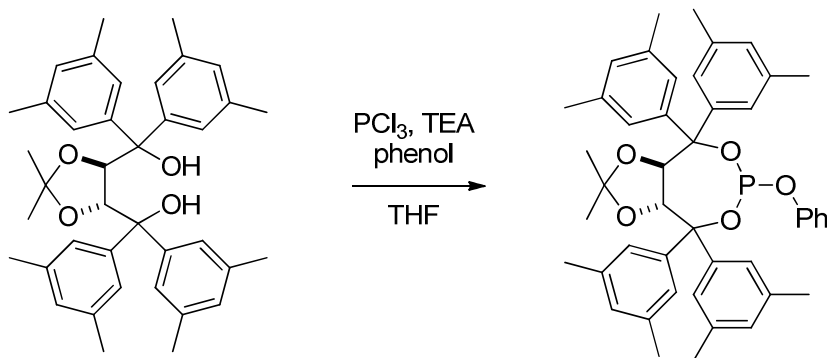
Preparation of (3,5-dimethyl-TADDOL)POPh (L2a): 3,5-Dimethyl-TADDOL

was prepared as previously described[64]. To a cooled solution (dry ice-acetone bath, -78

^{o}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 PCl$_3$ (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° (c 0.5, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 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$_3$) δ 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$_3$) δ 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.
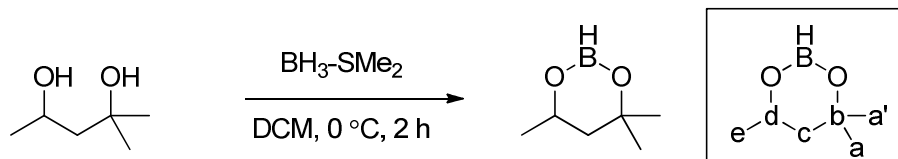
Preparation of 4,4,6-Trimethyl-1,3,2-dioxaborinane ((TMD)BH): To a cooled (0 °C) solution of 2-methyl-2,4-pentanediol (1.54 g, 12 mmol) in dichloromethane (6 mL) was slowly added borane (BH$_3$, 1 mL of a 10 M solution in dimethylsulfide, 10 mmol) dropwise. After the resulting mixture was stirred for 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 (SMe_2), 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $CDCl_3$) δ 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 (CI) calcd. for $C_6H_{14}BO_2$ (M+H): 129.1087, found 129.1082 m/z.

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Chapter 7: Spectra Appendix

^{1}H NMR X1

1D Proton NMR
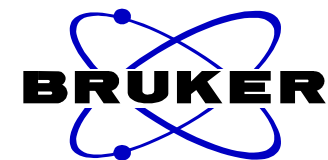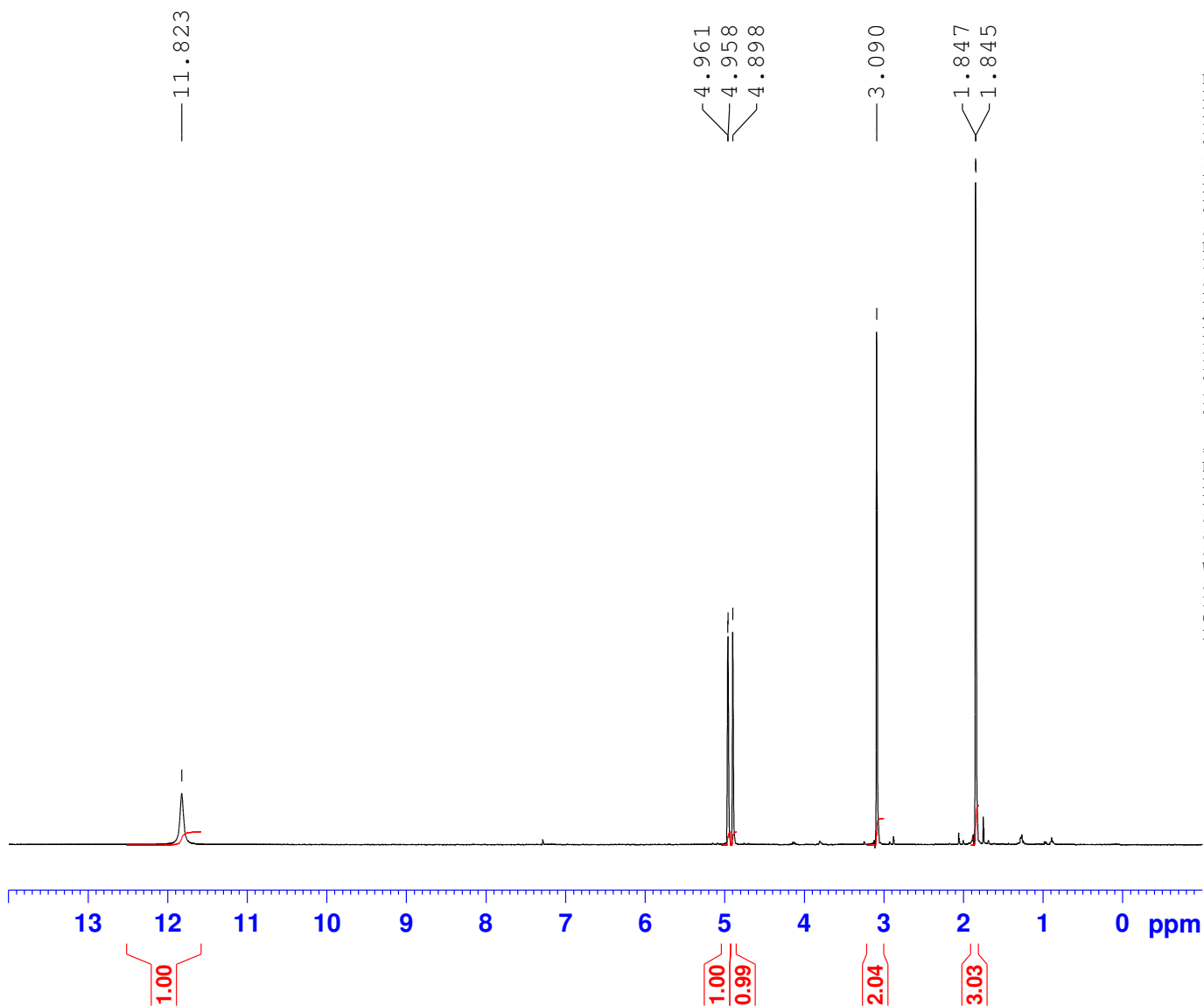
^{13}C NMR X1

13C

Peak labels (green): 178.28, 137.86, 115.29, 43.12, 22.31

180   160   140   120   100   80   60   40   20   ppm

100

¹H NMR X2

7.367
7.363
7.346
7.330
7.325
7.271
7.253

1 H Proton NMR

5.125
4.979

4.123

2.870
2.865
2.850
2.846
2.829
2.825
2.457
2.436
2.416
2.299

NAME   mob-090111-phenyl ethyl alcohole
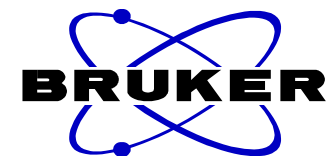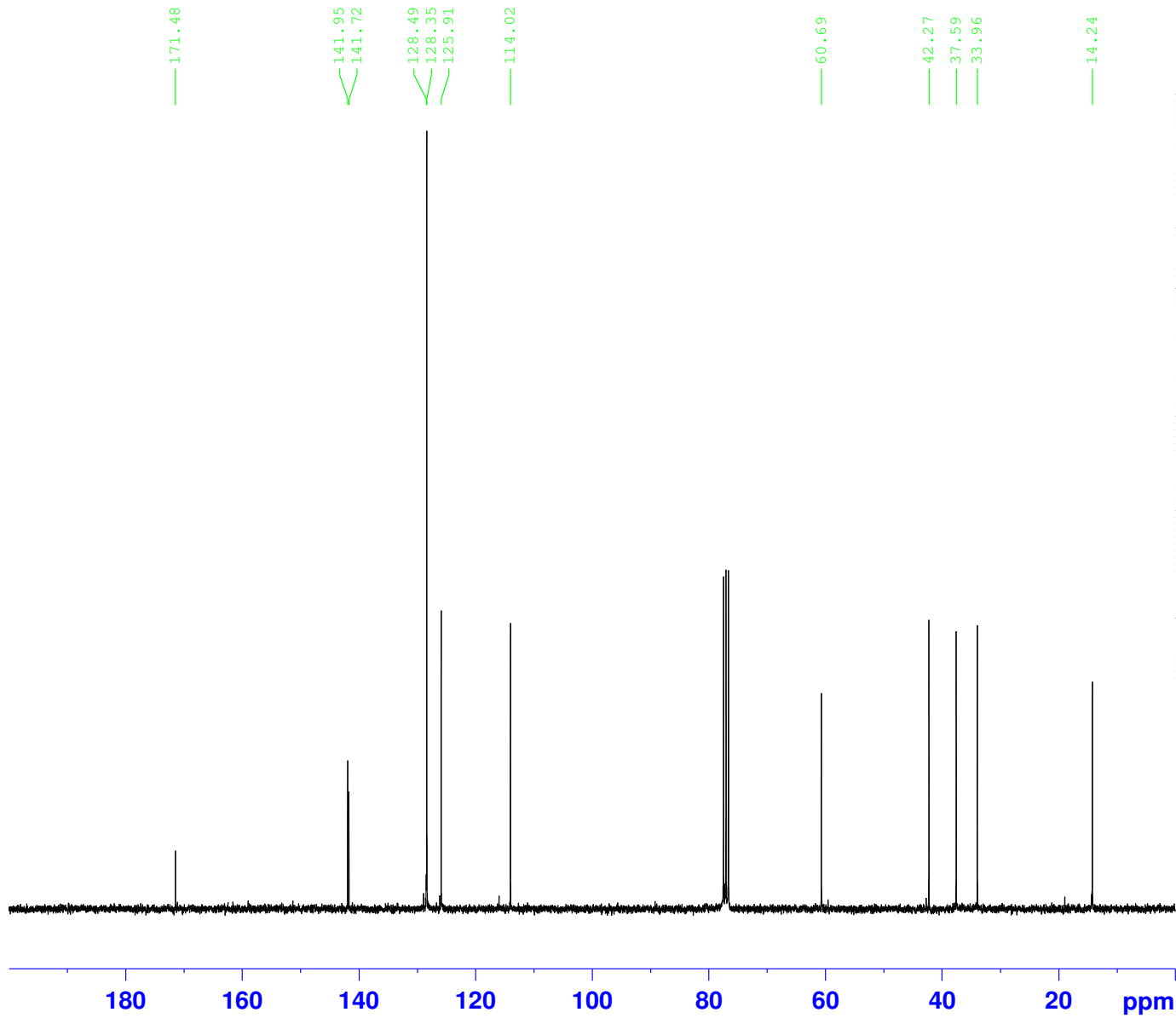EXPNO   1
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PULPROG   zg30
TD   65536
SOLVENT   CDCl3
NS   16
DS   2
SWH   8278.146 Hz
FIDRES   0.126314 Hz
AQ   3.9584243 sec
RG   28.5
DW   60.400 usec
DE   6.50 usec
TE   298.0 K
D1   1.00000000 sec
TD0   1

======== CHANNEL f1 ========
NUC1   1H
P1   12.00 usec
PL1   -2.30 dB
SFO1   400.1324710 MHz
SI   32768
SF   400.1300000 MHz
WDW   EM
SSB   0
LB   0.30 Hz
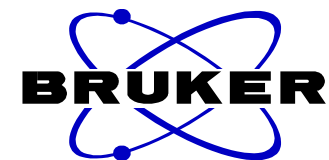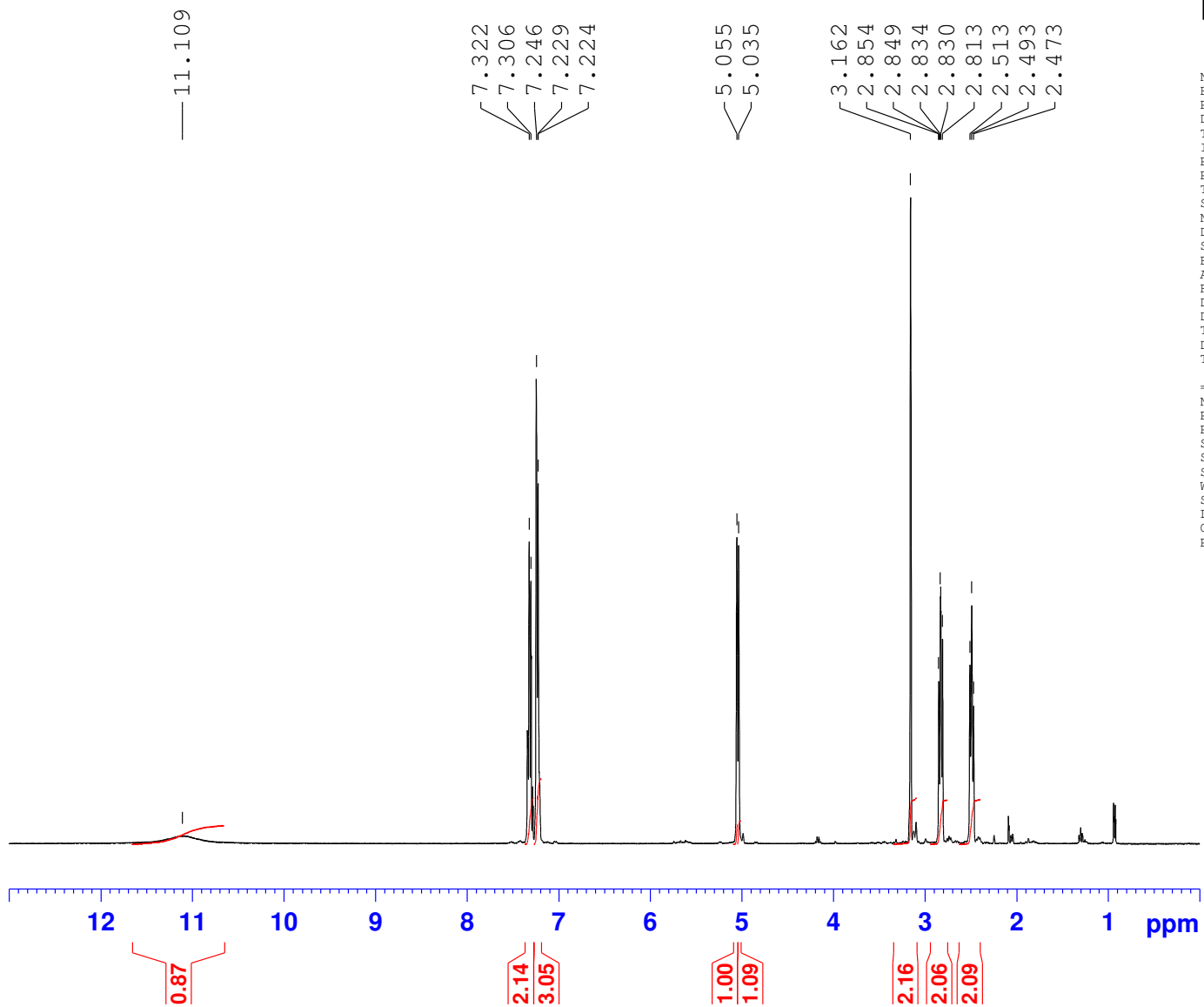GB   0
PC   1.00

ppm scale: 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

Integrations: 2.01 2.96   1.00 1.00   2.01   1.99 2.05 1.04

101

¹³C NMR X2

13C

148.44
141.89
128.40
128.38
125.96
109.85
77.47
77.15
76.83
65.92
34.66
34.30

180   160   140   120   100   80   60   40   20   ppm

¹**H NMR X5**

103

¹³C NMR X5

13C

Peak labels: 155.11, 142.93, 141.53, 128.40, 128.37, 126.00, 113.43, 77.47, 77.16, 76.84, 70.12, 64.06, 34.76, 34.02, 14.31

200   180   160   140   120   100   80   60   40   20   0   ppm

^{1}H NMR X8

1D Proton

7.340
7.313
7.301
7.290
7.281
7.239
7.216
7.193

4.998
4.979

4.221
4.197
4.173
4.149

3.107
2.842
2.817
2.789
2.482
2.453
2.428

1.322
1.298
1.274

BRUKER
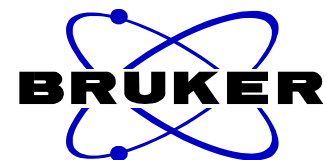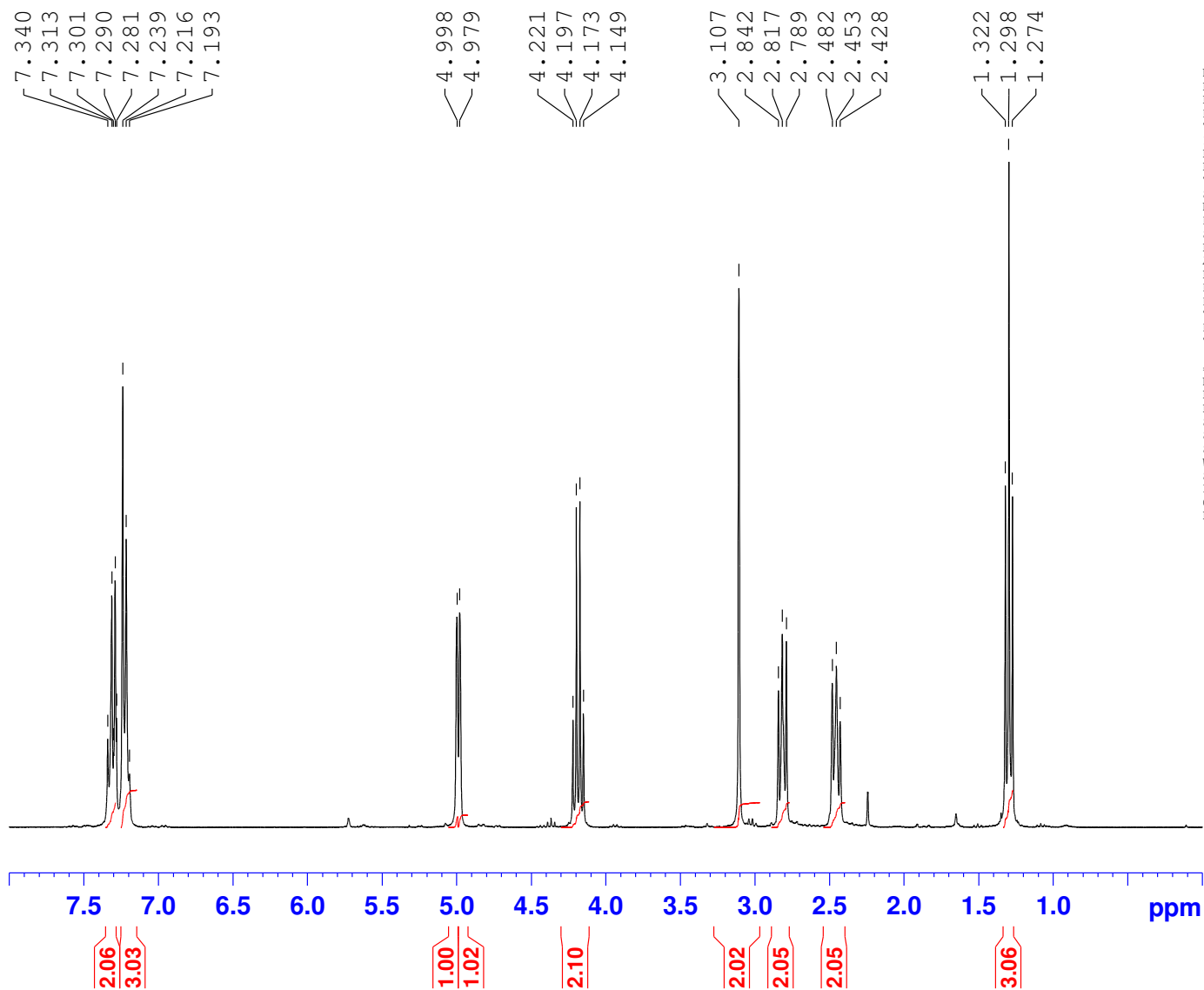
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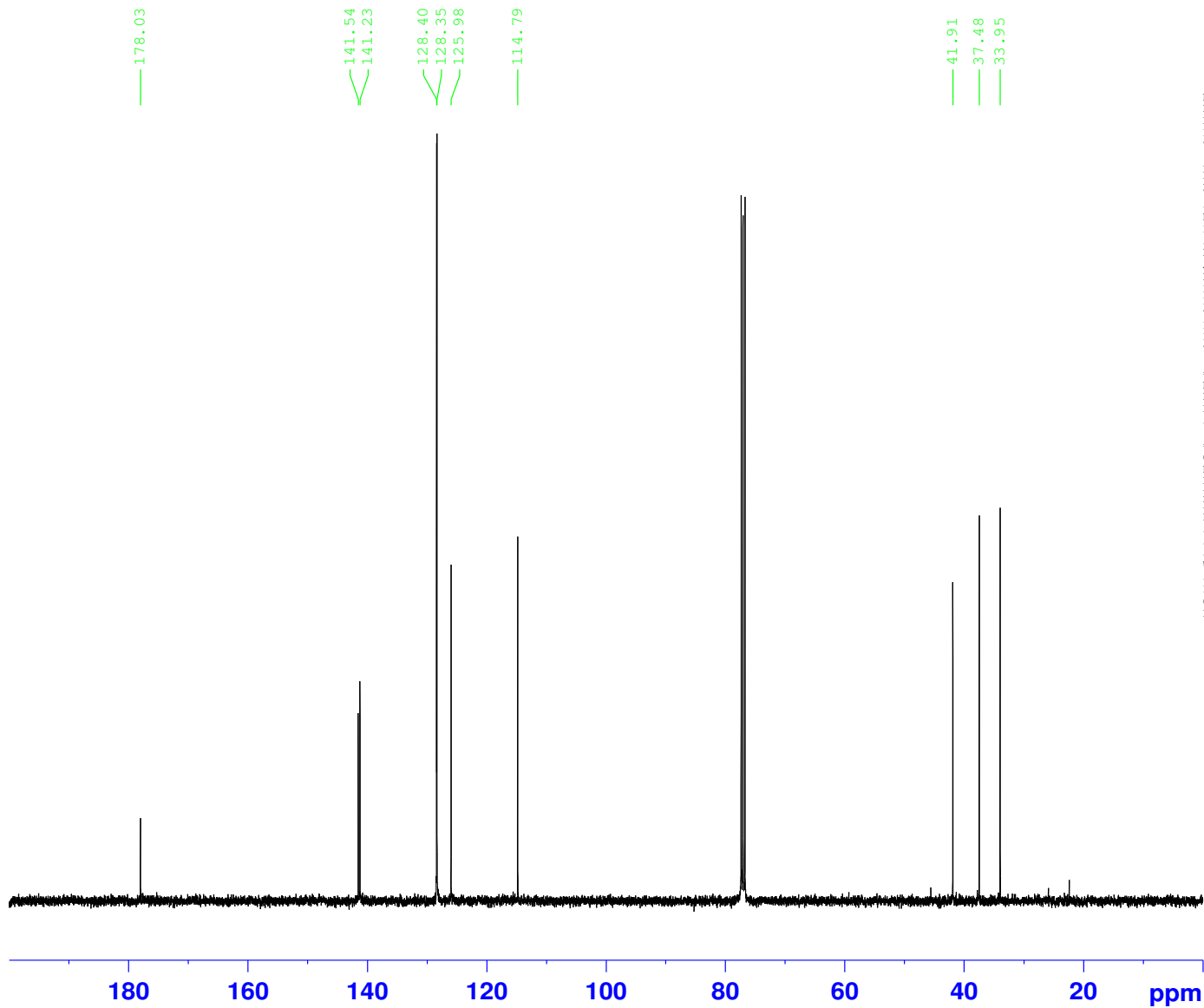EXPNO   1
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PULPROG   zg30
TD   32768
SOLVENT   CDC13
NS   6
DS   2
SWH   5995.204 Hz
FIDRES   0.182959 Hz
AQ   2.7329011 sec
RG   181
DW   83.400 usec
DE   6.50 usec
TE   673.2 K
D1   1.00000000 sec
TD0   1

======== 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
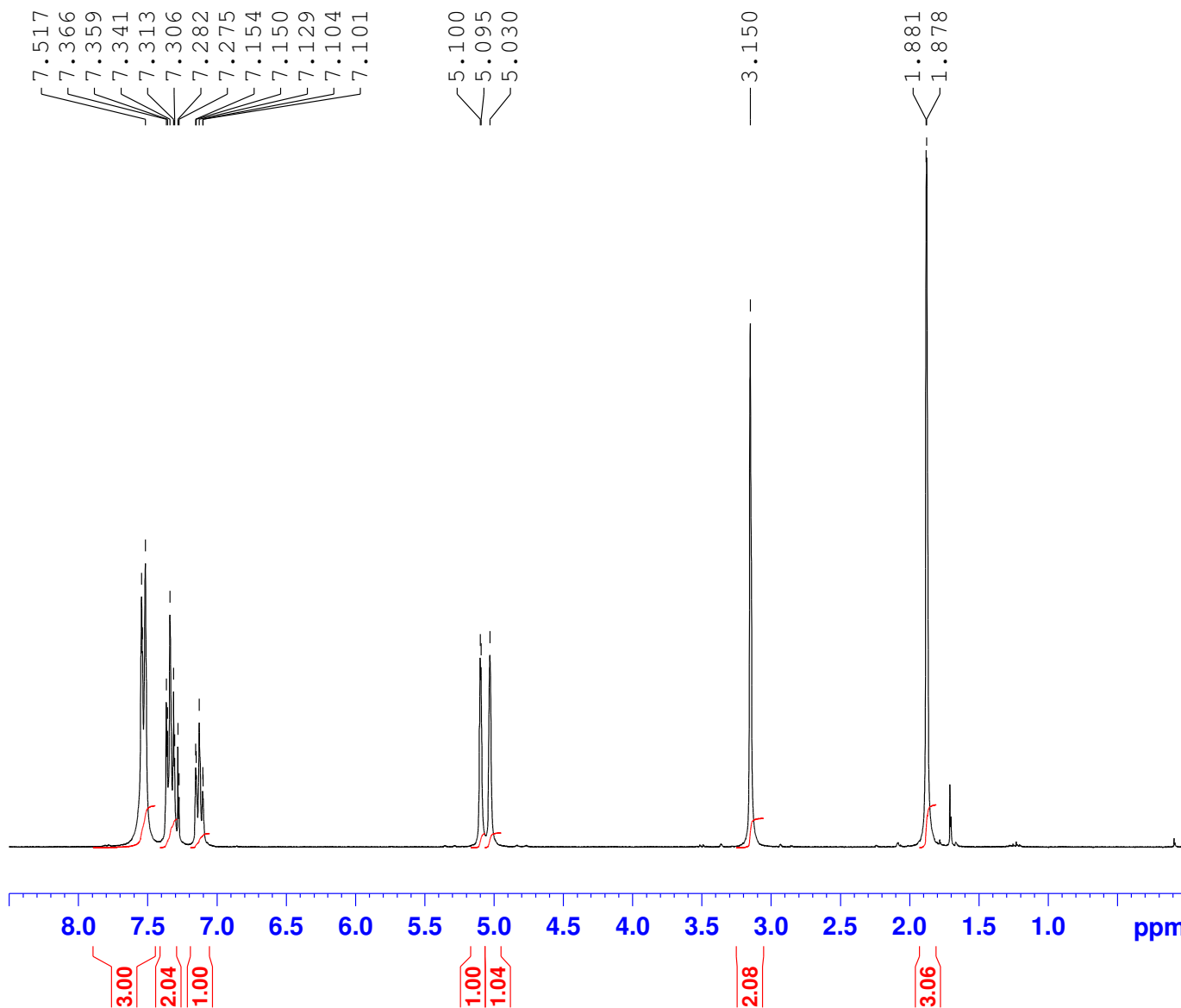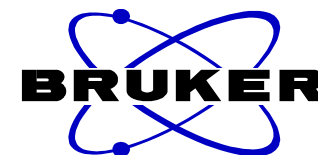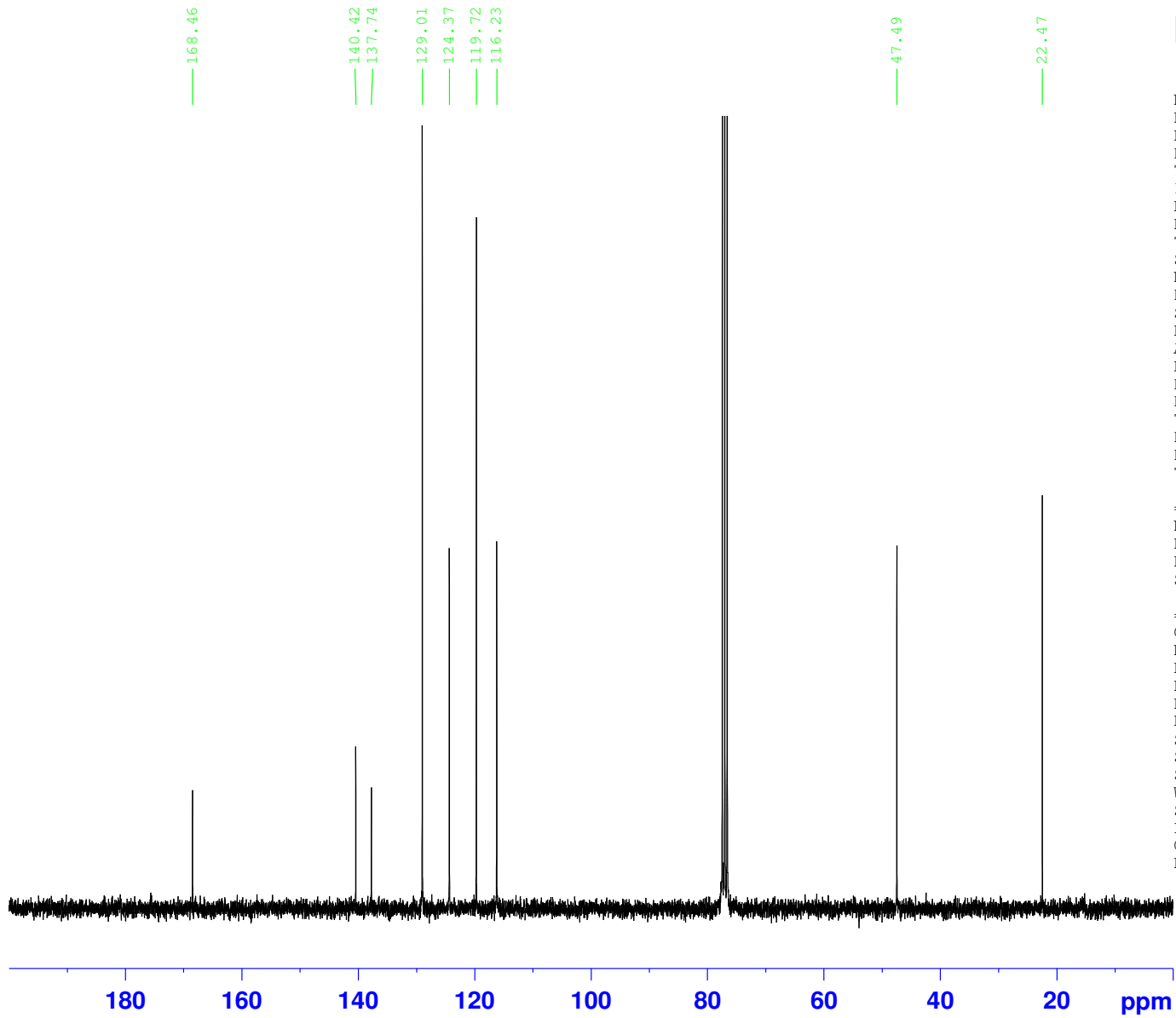GB   0
PC   1.00

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0   ppm

2.06 3.03 1.00 1.02 2.10 2.02 2.05 2.05 3.06

^{13}C NMR X8

¹H NMR X9

1D Proton NMR

11.109

7.322
7.306
7.246
7.229
7.224

5.055
5.035

3.162
2.854
2.849
2.834
2.830
2.813
2.513
2.493
2.473

12 11 10 9 8 7 6 5 4 3 2 1 ppm

0.87

2.14
3.05

1.00
1.09

2.16
2.06
2.09

107

^{13}C NMR X9

13C

178.03

141.54
141.23

128.40
128.35
125.98

114.79

41.91
37.48
33.95

180   160   140   120   100   80   60   40   20   ppm

108

¹H NMR X16

1D Proton

7.517
7.366
7.359
7.341
7.313
7.306
7.282
7.275
7.154
7.150
7.129
7.104
7.101

5.100
5.095
5.030

3.150

1.881
1.878

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   CDCl3
NS   8
DS   2
SWH   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

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0   ppm

3.00 2.04 1.00   1.00 1.04   2.08   3.06

109

^{13}C NMR X16

13C

Peak labels: 168.46, 140.42, 137.74, 129.01, 124.37, 119.72, 116.23, 47.49, 22.47

NAME   mob-111111 13c
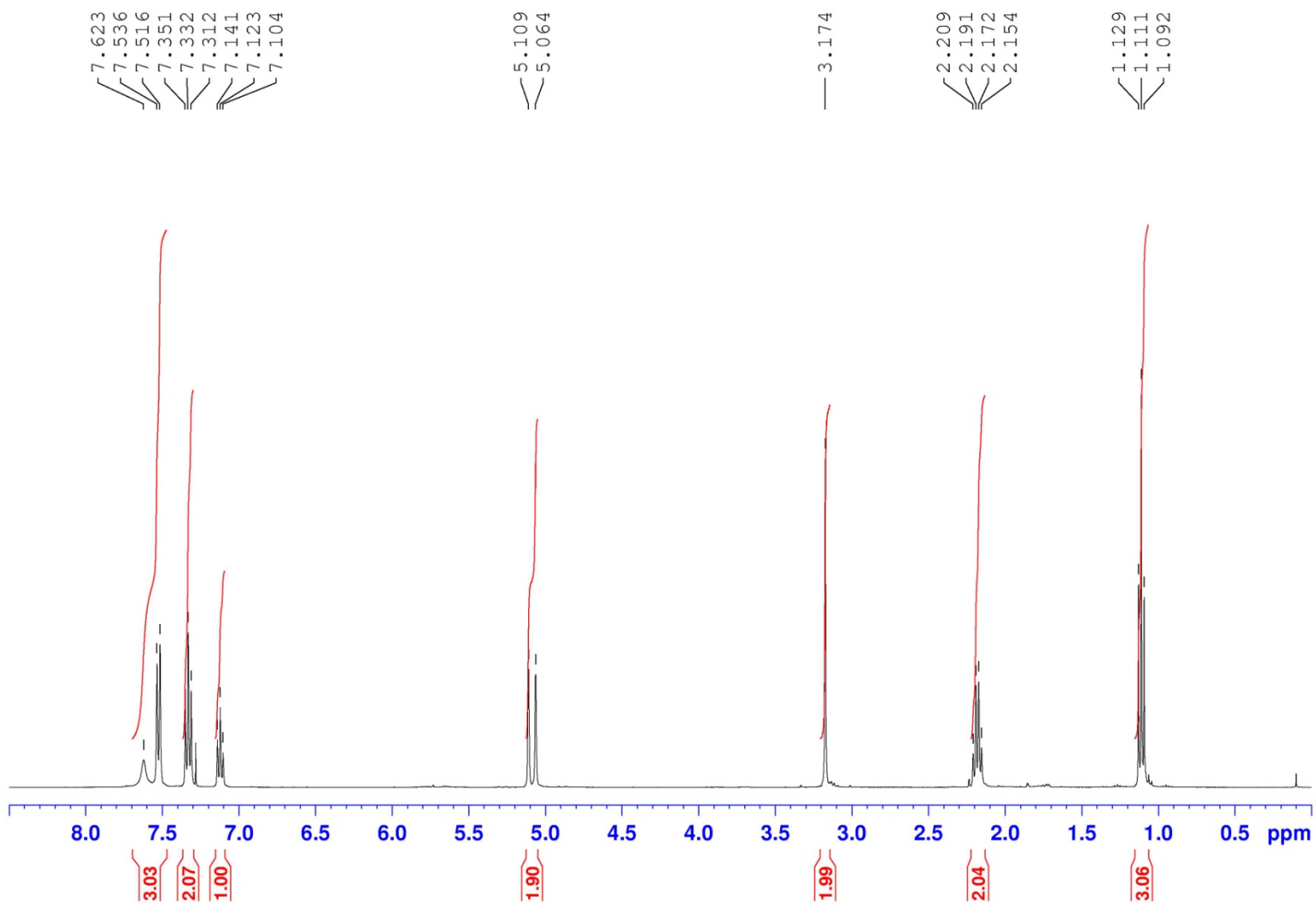EXPNO   1
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NS   896
DS   4
SWH   17985.611 Hz
FIDRES   0.548877 Hz
AQ   0.9110004 sec
RG   11585.2
DW   27.800 usec
DE   6.50 usec
TE   673.2 K
D1   2.00000000 sec
D11   0.03000000 sec
TD0   1

======== 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
WDW   EM
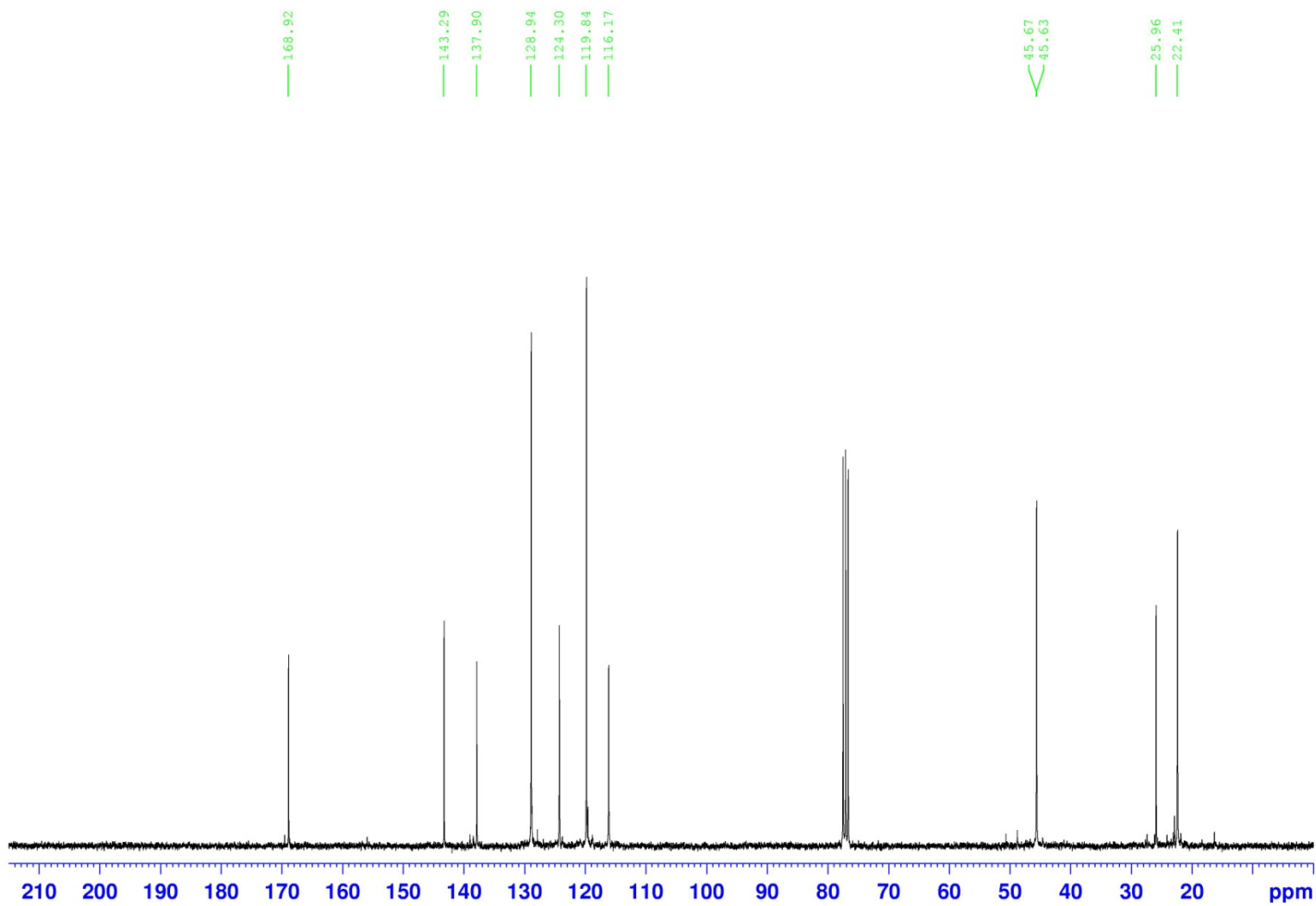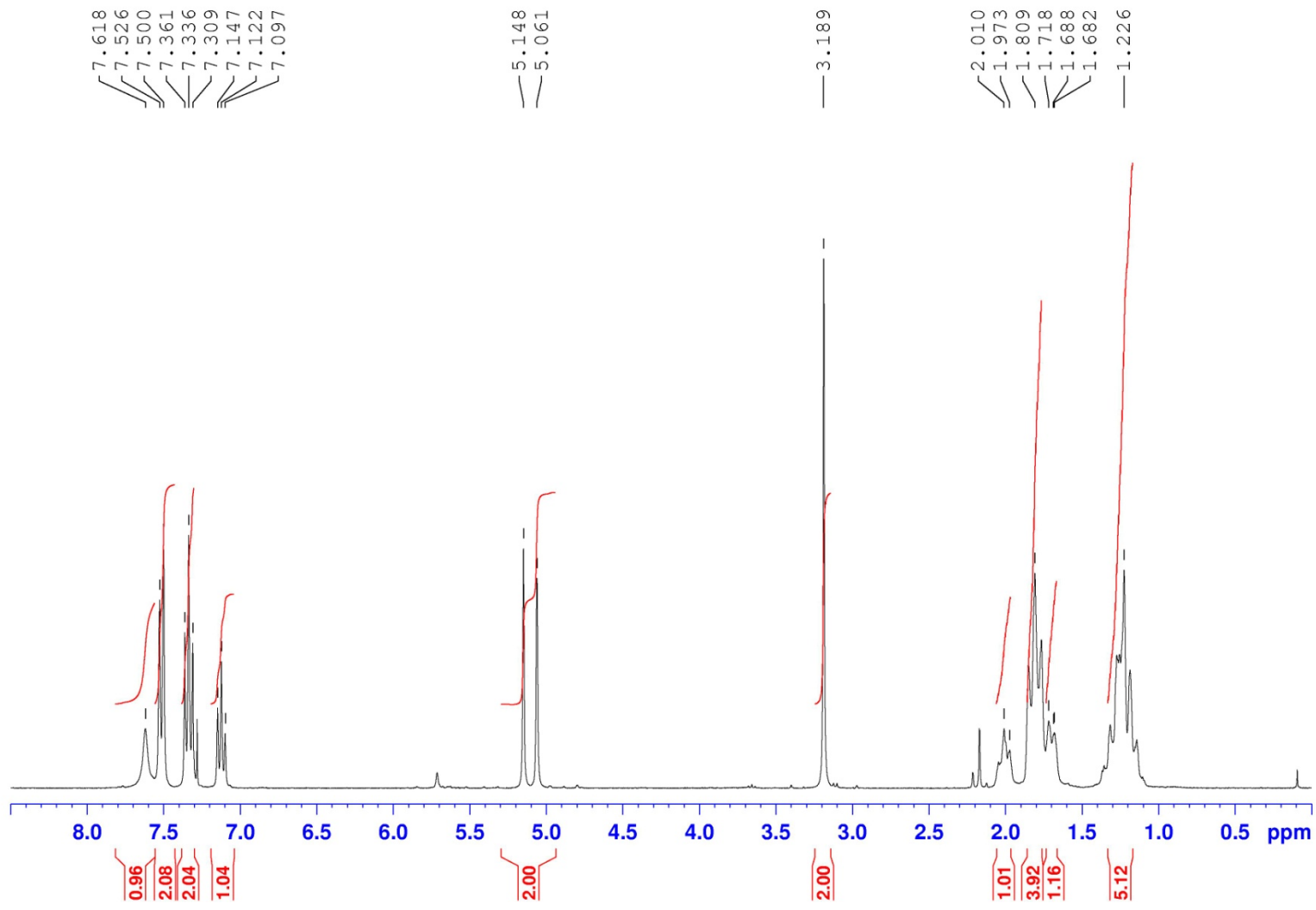SSB   0
LB   1.00 Hz
GB   0
PC   1.40

180 160 140 120 100 80 60 40 20 ppm

¹H NMR X17

7.623
7.536
7.516
7.351
7.332
7.312
7.141
7.123
7.104

5.109
5.064

3.174

2.209
2.191
2.172
2.154

1.129
1.111
1.092

| 8.0 | 7.5 | 7.0 | 6.5 | 6.0 | 5.5 | 5.0 | 4.5 | 4.0 | 3.5 | 3.0 | 2.5 | 2.0 | 1.5 | 1.0 | 0.5 | ppm |

3.03 2.07 1.00   1.90   1.99   2.04   3.06

¹³C NMR X17

168   146   137   128   124   119   113   46.23   28.89   12.12

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

^{1}H NMR X18

¹³C NMR X18

168.92

143.29
137.90

128.94
124.30
119.84
116.17

45.67
45.63

25.96
22.41

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

114

^{1}H NMR X19

168.85
150.39
137.72
129.00
124.31
119.65
113.79
45.06
44.42
32.18
26.48
26.09

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0   ppm

^{1}H NMR X20

7.551
7.545
7.523
7.519
7.390
7.295
7.123
7.099
7.074

5.781
5.413

3.647

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

3.01 4.95 2.07 0.97

2.00

2.03

¹³C NMR X20

168.35

142.08
138.76
137.61

128.94
128.82
128.47
125.78
124.43
119.84
117.44

45.14

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

^{1}H NMR X21

1D Proton NMR

¹³C NMR X21

168.31

143.69
141.21
137.66
128.99
128.44
128.35
126.06
124.38
119.69
115.75

46.25
37.44
33.91

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

^{1}H NMR X22

7.599 7.537 7.518 7.369 7.350 7.304 7.285 7.231 7.211 7.192 7.164 7.146 7.128

5.133 5.107

3.178

2.683 2.663 2.644 2.237 2.219 2.200

1.861

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

0.96 1.99 2.08 1.95 3.19 1.15

2.00

2.08

2.03

2.12

2.13

¹³C NMR X22

168.71

144.20
141.98
137.71
129.02
128.44
128.37
125.87
124.43
119.83
115.20

46.06

35.52
35.42
29.24

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

¹H NMR X23

¹H NMR X24

7.354
7.350
7.325
7.320
7.303
7.281
7.265
7.261
7.243
7.216

5.008
4.947
4.943

3.480

2.921

1.487

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

1.96 3.01   2.00   1.94 1.97   8.99

170.75

142.43
138.97

129.17
128.39
126.30

115.26

80.59

42.68
42.40

28.06

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

^{1}H NMR X25

4.905
4.876

2.966

2.152
2.133
2.115
2.096

1.463

1.081
1.062
1.044

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

1.96

1.95

2.06

8.99

3.00

^{13}C NMR X25

^{1}H NMR X26

4.914
4.873

2.918

1.993
1.975
1.792

1.459

0.900
0.883

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

2.00

1.98

1.98
1.02

9.05

6.28

¹³C NMR X26

^{13}C NMR X26

170.90
141.96
114.33
80.36
45.79
43.03
28.00
25.75
22.38

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0   ppm

¹³C NMR X28

¹³C NMR X31

^{1}H NMR X(16)-1

1D Pro

7.632
7.534
7.515
7.358
7.338
7.320
7.286
7.283
7.148
7.131
7.113

3.736
3.727
3.709
3.700
3.550
3.532
3.506
2.617
2.563
2.546
2.528
2.510
2.391
2.376
2.355
2.341
2.327
2.310
2.293
2.279
2.263
1.698
1.062
1.045

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

0.89 1.94 1.98 0.98   1.00 1.00   1.89 2.05   1.26   3.00

135

171.18

137.77
129.01
124.40
119.97

67.59

42.31
33.28

17.10
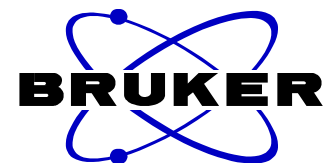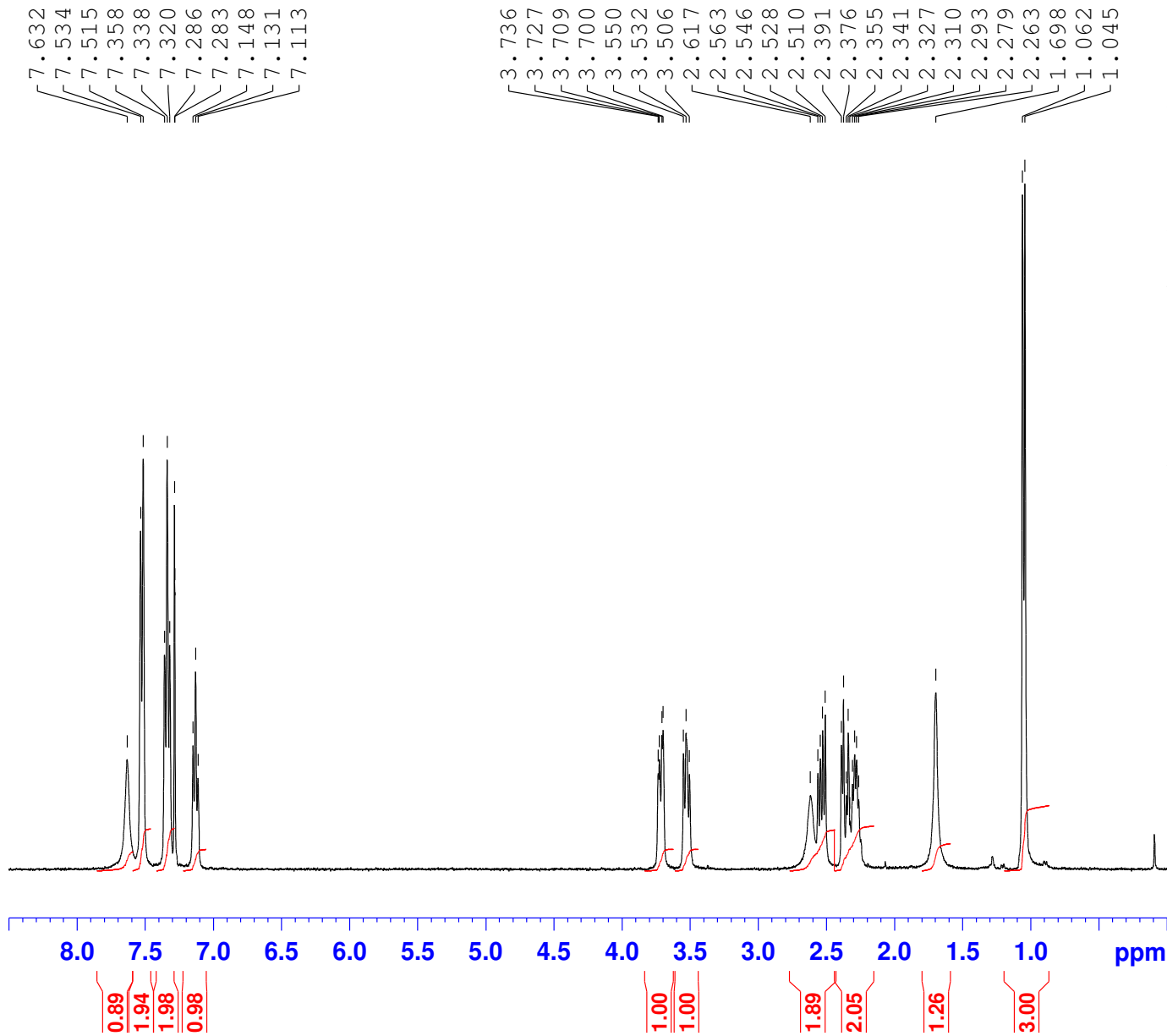
NAME   mob-081611-methyl phenyl alcohole 13c
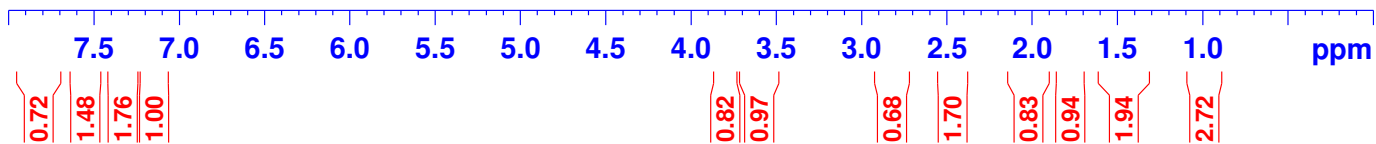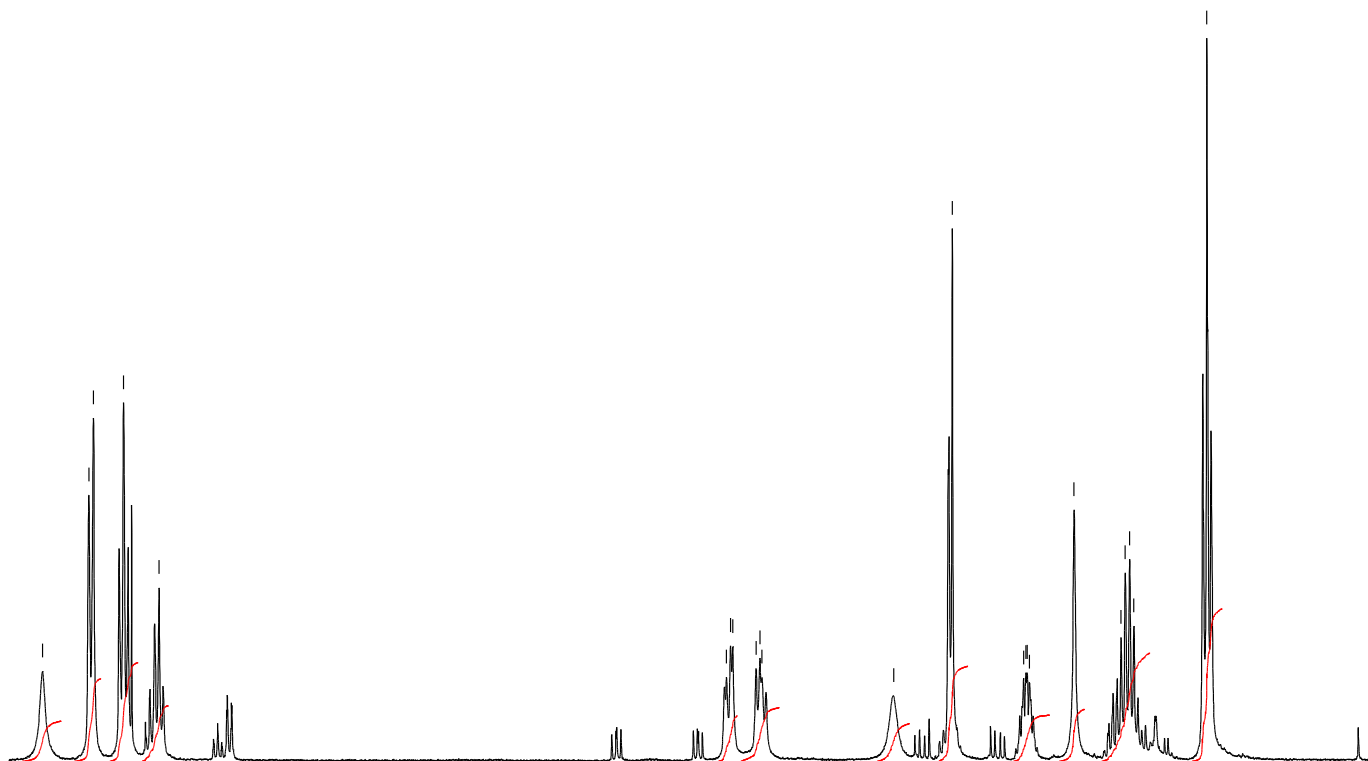EXPNO   1
PROCNO   1
Date_   20110816
Time   18.00
INSTRUM   spect
PROBHD 5 mm QNP 1H/13
PULPROG   zgpg30
TD   65536
SOLVENT   CDCl3
NS   749
DS   4
SWH   23980.814 Hz
FIDRES   0.365918 Hz
AQ   1.3664756 sec
RG   1625.5
DW   20.850 usec
DE   6.50 usec
TE   298.0 K
D1   2.00000000 sec
D11   0.03000000 sec
TD0   1

======== CHANNEL f1 ========
NUC1   13C
P1   10.00 usec
PL1   0.50 dB
SFO1   100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2   waltz16
NUC2   1H
PCPD2   70.00 usec
PL2   -3.35 dB
PL12   13.34 dB
PL13   13.34 dB
SFO2   400.1316005 MHz
SI   32768
SF   100.6127690 MHz
WDW   EM
SSB   0
LB   1.00 Hz
GB   0
PC   1.40

180   160   140   120   100   80   60   40   20   ppm

^{1}H NMR X(17)-1

^{13}C NMR X(17)-1

13c

171.60

137.83
129.28
128.98
124.36
119.98
115.12

65.31

40.43
39.75

24.35

11.58

200   180   160   140   120   100   80   60   40   20   0   ppm

138

¹H NMR X(21)-1

1D Proton NMR

7.359
7.340
7.321
7.304
7.284
7.223
7.212
7.205
7.133

3.837
3.812
3.673
3.660
2.744
2.728
2.712
2.607
2.527
2.512
2.182
2.170
1.828
1.810
1.794
1.774
1.755
1.738
1.718
1.701
1.683
1.663
1.624

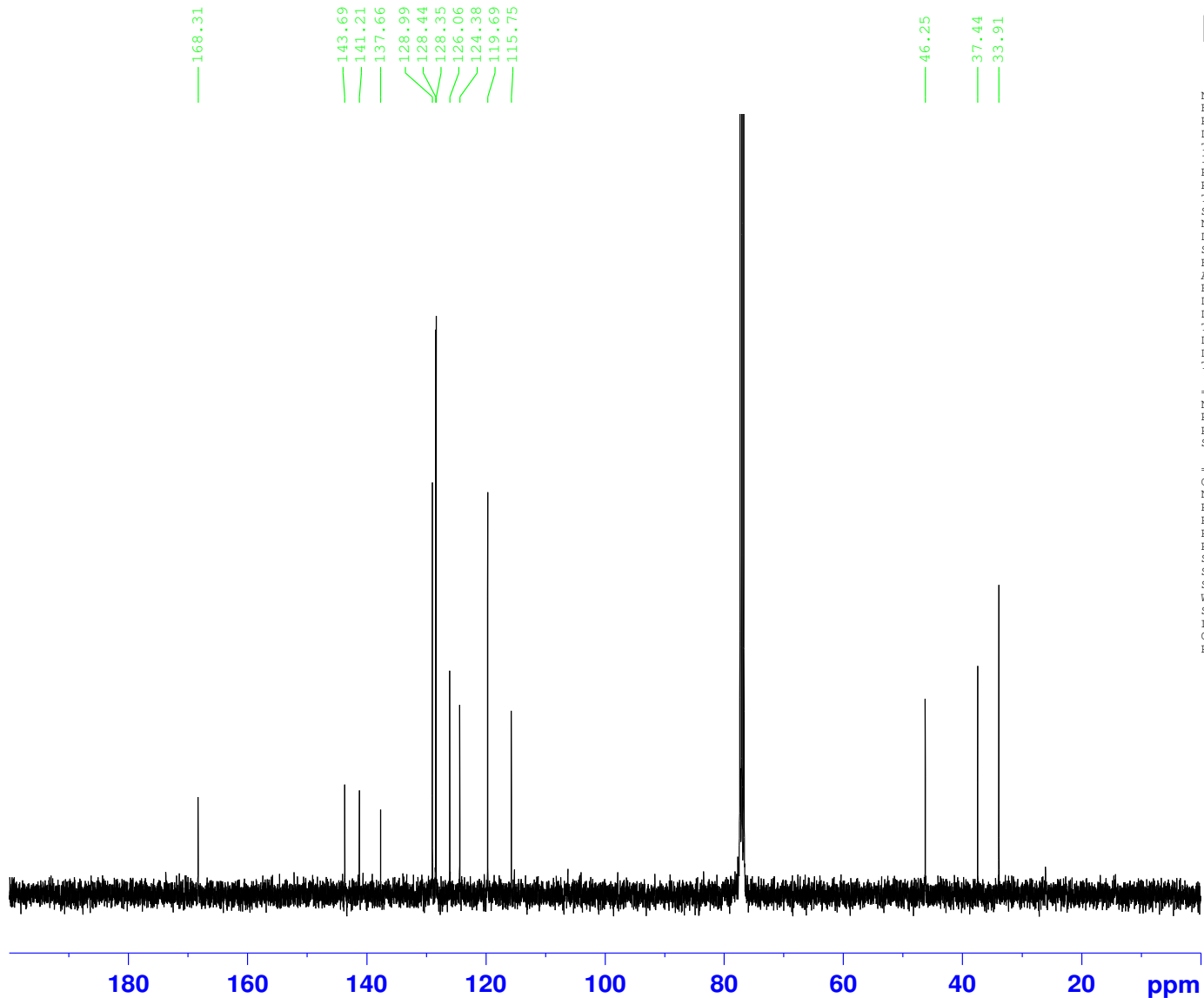NAME   mob-091911-phenyl ethyl alcohol
EXPNO   1
PROCNO   1
Date_   20110919
Time   13.40
INSTRUM   spect
PROBHD   5 mm QNP 1H/13
PULPROG   zg30
TD   65536
SOLVENT   CDCl3
NS   4
DS   2
SWH   8278.146 Hz
FIDRES   0.126314 Hz
AQ   3.9584243 sec
RG   362
DW   60.400 usec
DE   6.50 usec
TE   298.0 K
D1   1.00000000 sec
TD0   1

======== CHANNEL f1 ========
NUC1   1H
P1   10.00 usec
PL1   -4.00 dB
SFO1   400.1324710 MHz
SI   32768
SF   400.1300000 MHz
WDW   EM
SSB   0
LB   0.30 Hz
GB   0
PC   1.00

3.00 4.17 3.04 1.03   1.00 1.01   2.16 0.96 2.02   1.04   2.20 0.76

140

13C

Peak labels: 168.31, 143.69, 141.21, 137.66, 128.99, 128.44, 128.35, 126.06, 124.38, 119.69, 115.75, 46.25, 37.44, 33.91

BRUKER

NAME	mob-081711-phenyl ethyl amide
EXPNO	1
PROCNO	1
Date_	20110817
Time	12.54
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	947
DS	4
SWH	23980.814 Hz
FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	1625.5
DW	20.850 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	0.50 dB
SFO1	100.6228298 MHz

======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	70.00 usec
PL2	-3.35 dB
PL12	13.34 dB
PL13	13.34 dB
SFO2	400.1316005 MHz
SI	32768
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

180 160 140 120 100 80 60 40 20 ppm

¹H NMR X(26)-1

1D Proton

4.421
4.417

3.915
3.891
3.887

2.644
2.640
2.635
2.629
2.596
2.214
2.176
2.170
2.148
1.761
1.605
1.583
1.561
1.365

0.917

NAME   mob-062612-6
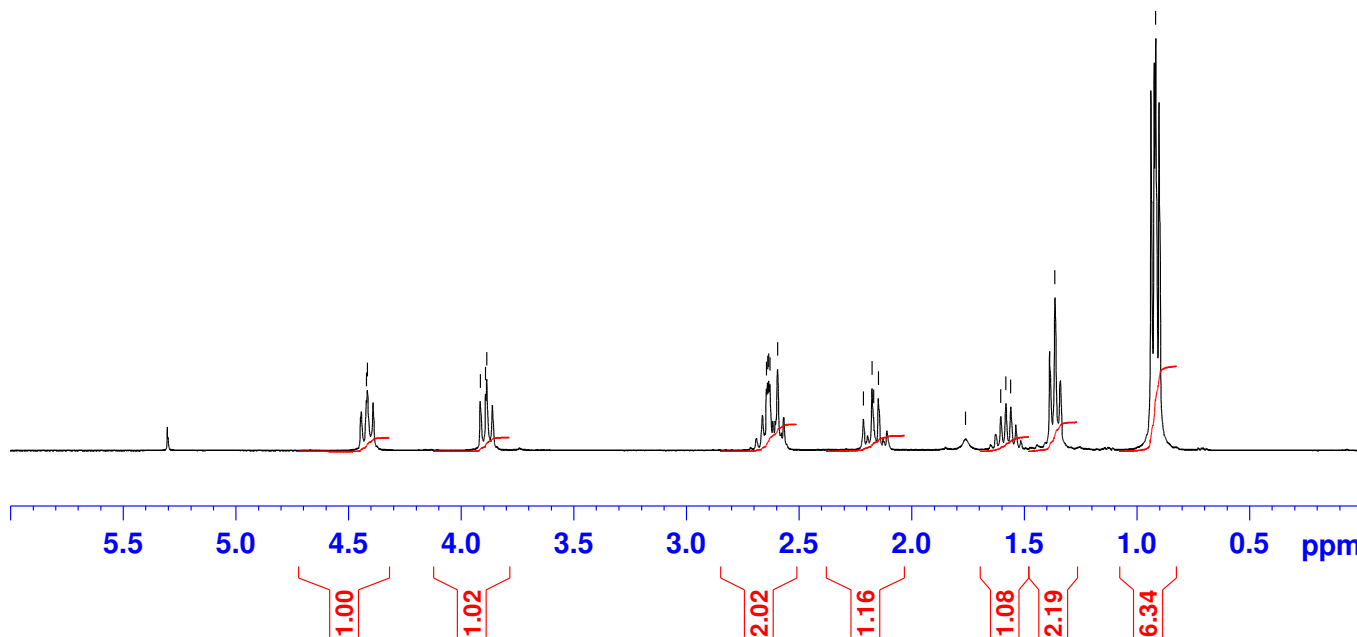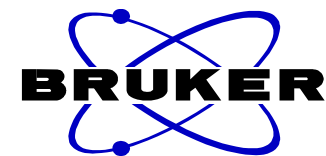EXPNO   1
PROCNO   1
Date_   20120626
Time   12.12
INSTRUM   spect
PROBHD   5 mm QNP 1H/13
PULPROG   zg30
TD   32768
SOLVENT   CDCl3
NS   4
DS   2
SWH   5995.204 Hz
FIDRES   0.182959 Hz
AQ   2.7329011 sec
RG   90.5
DW   83.400 usec
DE   6.50 usec
TE   298.0 K
D1   1.00000000 sec
TD0   1

======== CHANNEL f1 ========
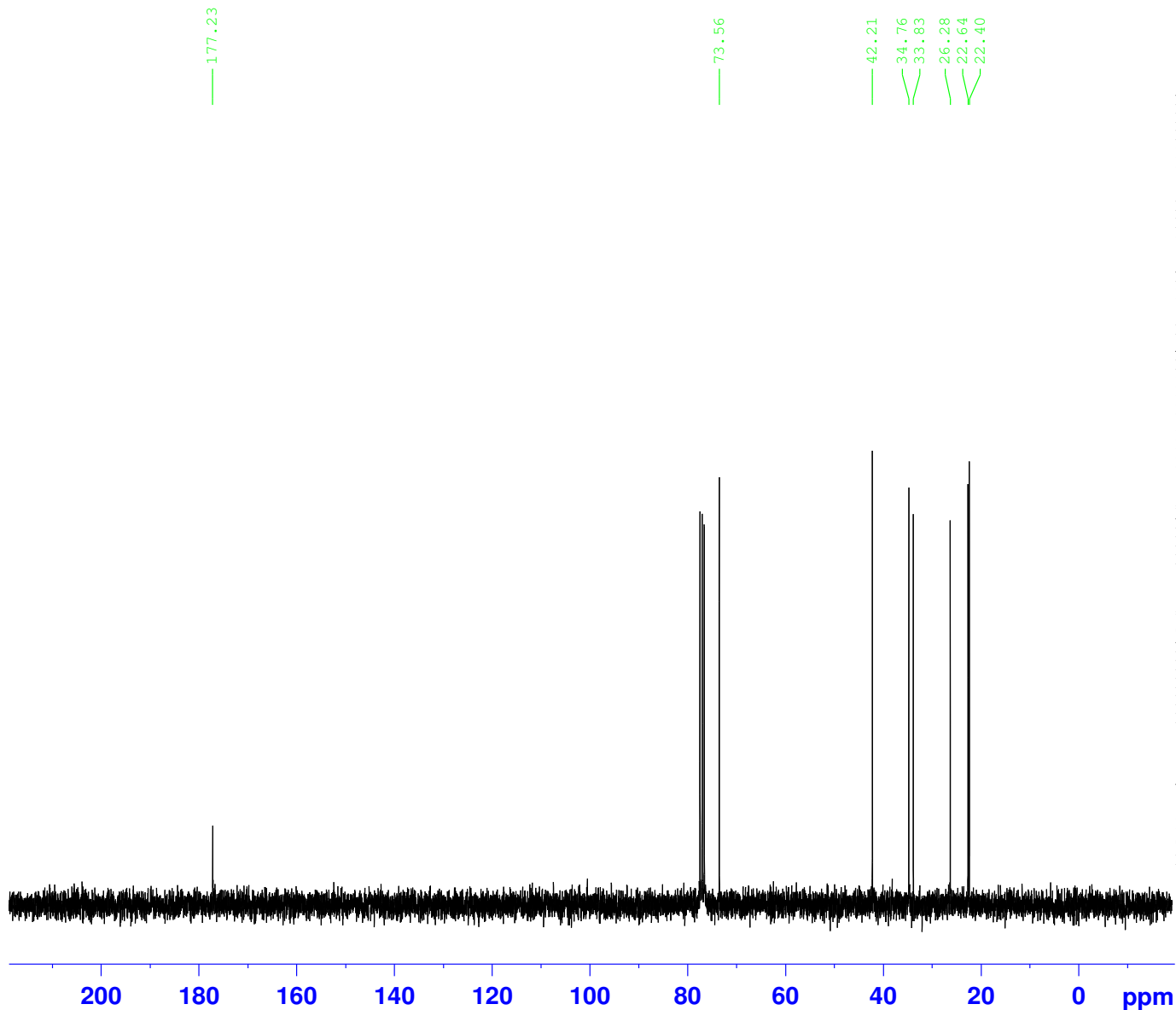NUC1   1H
P1   10.00 usec
PL1   2.20 dB
SFO1   300.1318534 MHz
SI   32768
SF   300.1300000 MHz
WDW   EM
SSB   0
LB   0.30 Hz
GB   0
PC   1.00

5.5   5.0   4.5   4.0   3.5   3.0   2.5   2.0   1.5   1.0   0.5   ppm

1.00   1.02   2.02   1.16   1.08 2.19   6.34

142

¹³C NMR X(26)-1

13C

177.23

73.56

42.21
34.76
33.83
26.28
22.64
22.40

200 180 160 140 120 100 80 60 40 20 0 ppm

143

^{1}H NMR X(24)-1

1D Proton

7.340
7.335
7.316
7.287
7.263
7.190
7.185
7.162

4.348
4.325
4.078
4.059
4.048

2.881
2.854
2.807
2.662
2.604
2.578
2.348
2.325
2.290
2.267

1.470

BRUKER

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
SWH	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

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

5.15   1.00 1.00   3.03 1.11 1.14

145

¹³C NMR X(24)-1

13C

176.84

138.24
128.81
128.67
126.83

72.66

38.94
37.17
34.25

200 180 160 140 120 100 80 60 40 20 0 ppm

146