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Br[o/]nsted Acid Catalyzed Asymmetric Allylation and Propargylation of Aldehydes

Pankaj Jain
University of South Florida, pankaj1@mail.usf.edu

Brønsted Acid Catalyzed Asymmetric Allylation and Propargylation of Aldehydes

by

Pankaj Jain

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Department of Chemistry
College of Arts and Sciences
University of South Florida

Major Professor: Jon Antilla, Ph.D.
Abdul Malik, Ph.D.
Roman Manetsch, Ph.D.
Peter Zhang, Ph.D.

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List of Schemes

List of Abbreviations

[α]	specific rotation
Å	angstrom(s)
Ac	acetyl
anhyd	anhydrous
aq	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonyl
9-BBN–H	9-borabicyclo[3.3.1]nonane
BINOL	1,1′-bi-2-naphthol
Bn	benzyl
BOC,	Boc *tert*-butoxycarbonyl
bp	boiling point
br	broad (spectral)
Bu, *n*-Bu	normal (primary) butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
B3LYP 3	parameter hybrid Becke exchange/ Lee–Yang–Parr correlation functional
°C	degrees Celsius
cat	catalytic
CBZ, Cbz	benzyloxycarbonyl
cm	centimeter(s)
cm^{-1}	wavenumber(s)
m-CPBA	*meta*-chloroperoxybenzoic acid
Cy	cyclohexyl
δ	chemical shift in parts per million downfield from tetramethylsilane
d	day(s); doublet (spectral)
DCC	*N,N*′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DIBALH	diisobutylaluminum hydride
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomer ratio
eq	equation
equiv	equivalent
er	enantiomer ratio
Et	ethyl
h	hour(s)
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
J	coupling constant (in NMR spectrometry)
k	kilo
L	liter(s)
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
μ	micro
m	multiplet (spectral); meter(s); milli
M	molar (moles per liter); mega
Me	methyl
MHz	megahertz
min	minute(s)
mM	millimolar (millimoles per liter)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methylsulfonyl (mesyl)
MTBE	methyl *tert*-butyl ether
m/*z*	mass-to-charge ratio
N	normal (equivalents per liter)
Ph	phenyl
ppm	part(s) per million
Pr	propyl
*i*Pr	isopropyl
py	pyridine
q	quartet (spectral)
rt	room temperature
s	singlet (spectral)
t	triplet (spectral)
TBS	*tert*-butyldimethylsilyl
temp	temperature
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	*N,N,N′,N*′-tetramethyl-1,2-ethylenediamine
Tr	triphenylmethyl (trityl)
Ts	*para*-toluenesulfonyl (tosyl)
TS	transition state

Abstract

Carbonyl allylation and propargylation reactions have been an important tool for the stereocontrolled formation of carbon-carbon bonds for synthetic chemists. The chiral homoallylic and homopropargylic alcohols obtained from these reactions serve as versatile intermediates for the synthesis of natural and pharmaceutical products. Over the past three decades and continuing on, various synthetic groups around the globe have directed their research towards the efficient synthesis of these chiral moieties. In spite extensive research, asymmetric allylation and propargylation reactions remain an enduring challenge in organic chemistry.

Chapter 1 of this thesis describes the first phosphoric acid catalyzed asymmetric allylboration of aldehydes. We found that the BINOL-derived phosphoric acids can efficiently catalyze the allylation reaction under specific conditions. Homoallylic alcohols were obtained in high yields and enantioselectivities from a wide variety of substrates. The optimized conditions were also found to be effective towards crotylboration of aldehydes.

Chapter 2 describes the extension of the Brønsted acid catalyzed allylboration methodology to the propargylation of aldehydes. Homopropargylic alcohols were obtained with high selectivities with TRIP-PA as the catalyst. Synthesis of various important synthetic scaffolds from these chiral alcohols is also presented.

The mechanistic insights studied by research groups of Kendall Houk and Jonathan Goodman have been outlined in chapter 3. These studies show that the major isomer is formed *via* a transition state involving the hydrogen bonding interaction between the hydroxyl group of the catalyst and the pseudoaxial oxygen of the boronate, with a stabilizing interaction of the phosphoryl oxygen to the formyl hydrogen. These insights helped us in developing new and highly efficient boronates that are described in the next chapter.

Chapter 4 illustrates the impact of the phosphoric acid catalyzed allylboration on the synthetic community and the reports emerging consequently. As the Computational studies suggests the clash of the methyl groups on the pinacol boronate with the bulky aromatic substituents on the catalyst plays an important role in controlling the absolute stereochemistry, new boronates were synthesized and utilized in allylation and propargylation reactions. These boronates gave much better selectivities for both allylboration and allenylboration of aldehydes compared to the previously reported methodologies with pinacol boronates. The extension of the methodology to utilize substituted allyl boronates as substrates in presence of chiral phosphoric acid is also presented in this chapter.

1 Enantioselective Allylboration of Aldehydes

Note to the Reader: This chapter (Pages 15-35) has been previously published and is utilized here with the permission of the publisher.

1.1. Asymmetric catalysis: Significance

Adequacy to control the three dimensional architecture of a molecule has revolutionized synthetic chemistry. Asymmetric synthesis is at a constant upswing and has opened new routes towards the preparation of chiral molecules. Chirality is a biologically important structural property exhibited not only by biomolecules like amino acids and sugars but also by many pharmaceutical drugs, agrochemicals, flavors and fragrances. Molecules are considered chiral when they are nonsuperimposable on their mirror images, each form called as an optical isomer or an enantiomer. One enantiomer of a particular molecule can have beneficial/desirable activity while the other enantiomer can have no/adverse activity.

Thalidomide is one of most notorious example showing that molecules that are so nearly identical in appearance can have completely diverse significance as a drug (Figure 1.1). Thalidomide in racemic form was introduced as an efficient sedative and had beneficial effects in morning sickness for pregnant women. However, later research has showed the R isomer of thalidomide was an effective drug but the S isomer was teratogen and was responsible for birth defects in more than 10,000 children worldwide.[1] Enantiomers are also of particular importance to the perfume industry as 17% of the enantiomers do not have similar scent. Limonene is well known example where its optical isomers are responsible for the distinct smell in oranges and

lemons (Figure 1.1). Enantiomers are also important to the food industry as each optical isomer might have distinctive taste. Aspartame, which is the LL isomer, is very sweet whereas the DD isomer has a bitter taste (Figure 1.1). Thus, both scientifically and economically, the development of methodologies that selectively give access to one enantiomer is very important. The need for competent asymmetric transformations is constantly rising. Along with higher yields and selectivities the reactions must also be economical and safe to the environment. Owing to its importance, numerous academic and industrial groups have directed major research towards the selective synthesis of chiral molecules.

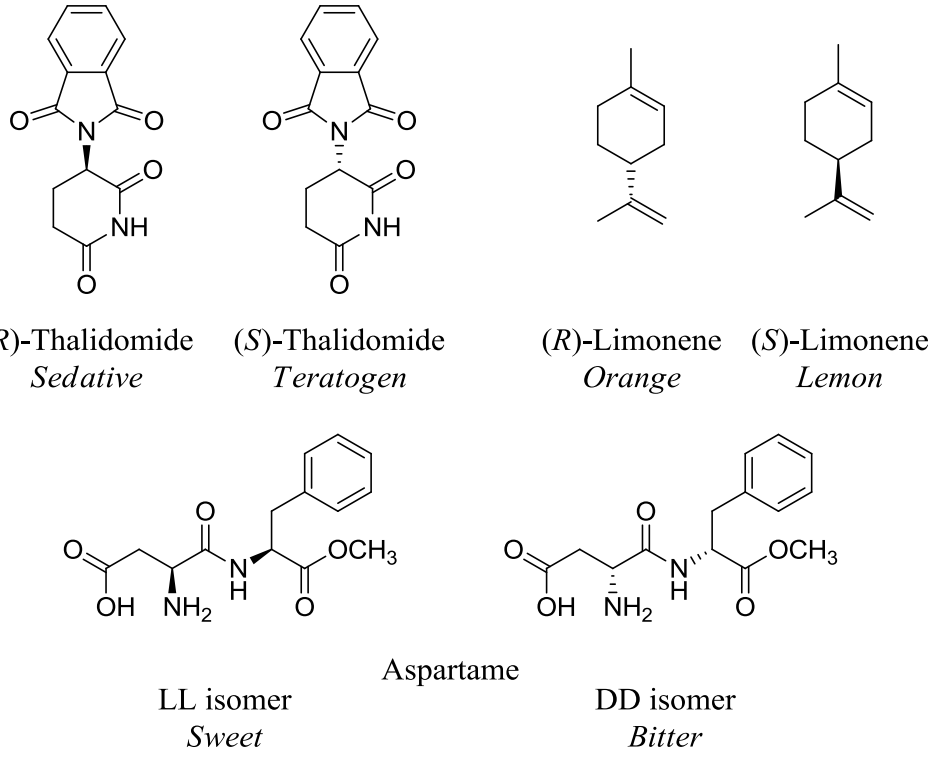


Figure 1.1 Significance of enantiomers

1.2 Enantioselective Allylation

Carbonyl allylation represents a powerful and an important process in synthetic organic chemistry.[2] In past three decades continuous efforts have been made towards the asymmetric

transformation of carbonyl compounds to optically pure homoallylic alcohols, which serve as versatile intermediates in the synthesis of natural products and pharmaceuticals.[2] Use of chiral homoallylic alcohols is one of the foremost strategies for the construction of polyketeides which approximately constitutes 20% of the small molecules therapeutics. Among the numerous syntheses which utilize allylation as a key step, three examples are shown were chiral homoallylic alcohols act as important building blocks in the construction of complex, medicinally important molecules. Epothilones, a newer class of anticancer drugs, have shown to be more efficient then taxanes with milder adverse effects. Homoallylic alcohols, obtained by allylation of the corresponding aldehydes, constituted two important fragments for the construction of Epothilone A (Figure 1.2).[3] (6S)-5,6-dihydro-6-[(2R)-2-hydroxy-6-phenylhexyl]-2H-pyran-2-one, a α,β-unsaturated-δ-lactone which shows antifungal properties was also utilized a homoallylic alcohol in its total synthesis (Figure 1.2).[4] Use of homoallylic alcohol as a key intermediate is also seen the total synthesis of the natural antibiotic fostriecin and its analogues (Figure 1.2).[5] Fostriecin, metabolite obtained from *Streptomyces pulveraceu*, shows antitumour activity against a broad range of cancerous cell lines.[6]

Many important methodologies directed towards the synthesis of homoallylic alcohols have emerged that include the additions of allylic silanes,[7] allylic stannanes,[8] allylic boranes/boronates,[9,10] allylic alcohols,[11] allylic acetates[12] and allylic halides[13] to carbonyl compounds. Among these the use of allylic silanes, allylic stannanes and allylic boranes/boronates as the allyl donors have been widely demonstrated. Depending on the stereochemical mode of reaction, in 1983 Denmark classified the allylation reactions into three categories (Figure 1.3).[14] Type I reagents react via the formation of a closed cyclic six-membered

transition state, making the geometry of the products predictable based on the stereochemistry of the starting materials. Thus the absolute configuration of two successive stereogenic centers can

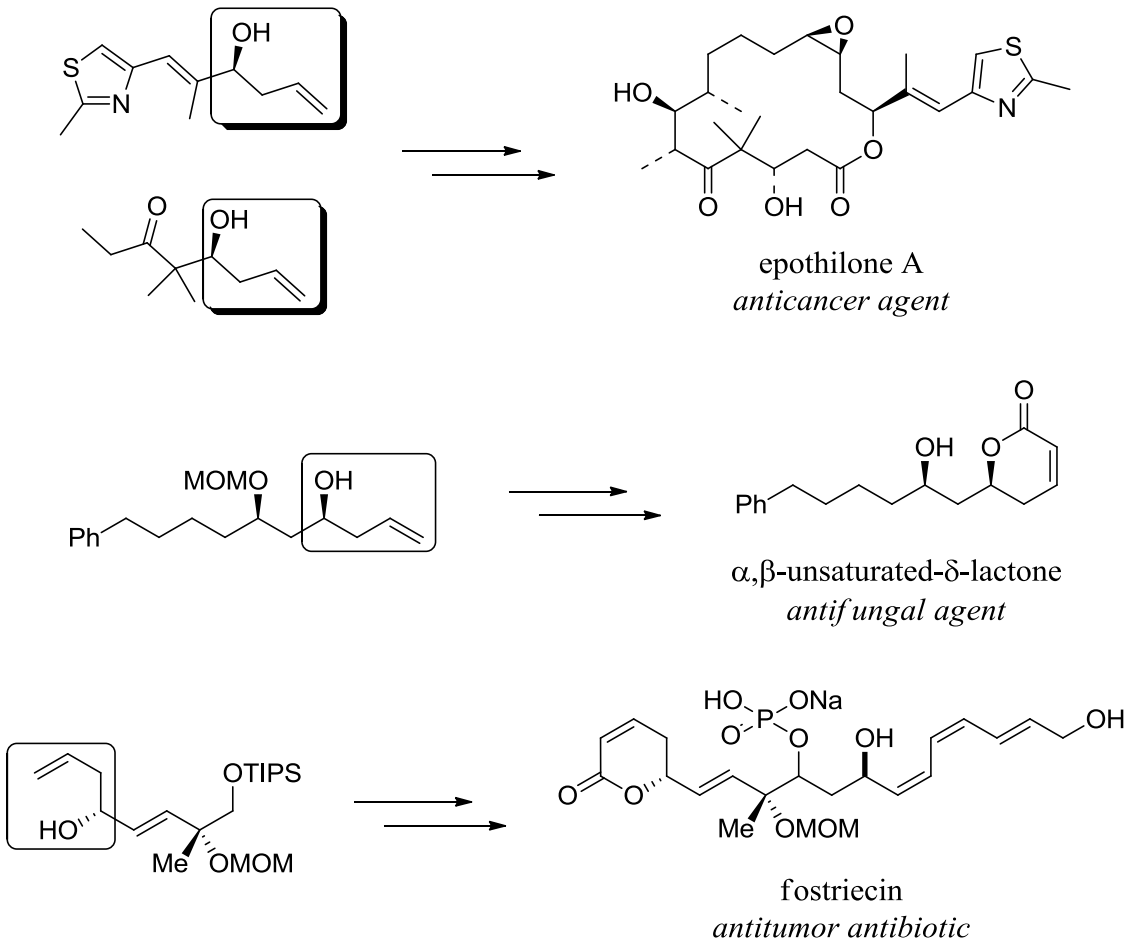


Figure 1.2 Synthesis of medicinal compounds from homoallylic alcohols

be controlled during the formation of one carbon-carbon bond. Under type I category, the *trans* isomer usually gives the *anti* products while the *cis* isomer gives the *syn* products. Allylic boron reagents and the allylic trichlorosilanes typically fall under the type I category. Type II class reagents generally react via open transition states where an external Lewis acid is required to activate the carbonyl group. As the reaction does not take place in closed transition states, Type II reagents are not usually diastereospecific and predominantly give *syn* products. Type III

reagents are rarely seen and they predominantly give anti products irrespective of the starting allylic geometry due to the pre-equilibration of the allylmetal species to more stable *E* isomer. Allylic organometallic reagents that are generated in situ from allylic halides catalyzed by chelating agents, fall under the type III category. Among all the three categories, type I reagents have gained utmost importance due to the high diastero- and enantiocontrol attained in the products formed.

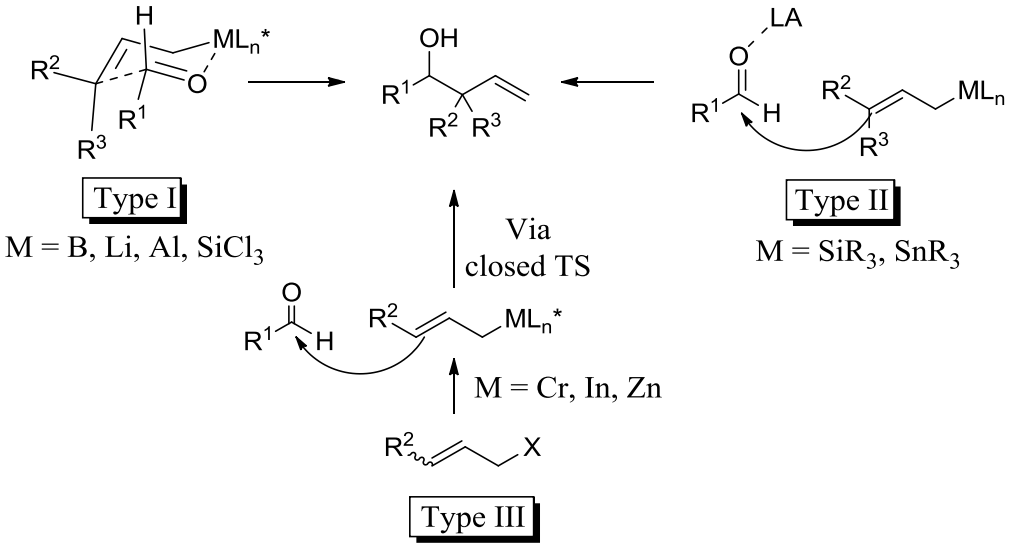


Figure 1.3 Mechanisms involving allylation reactions

1.3 Allylboration

Allylboration is the addition of the allylboron reagents to unsaturated substrates like aldehydes, ketones and imines.[9,10] Allylboron reagents are highly reactive and non-toxic allyl donors and are an ideal choice in allylation chemistry. In 1964, Mikhailov and Bubnov first reported the use of allylic organoboranes to allylate carbonyl compounds.[15] In 1979, Hoffmann recognized that *β*-methyl homoallylic alcohols with high diastereoselectivities are obtained when either (*E*)- or (*Z*)-crotylboronates are reacted with aldehydes.[16] He proposed that the boron

reagents are react with carbonyl compounds *via* the formation of a closed six-membered chair-like transition state, where the boron internally activates the carbonyl. This rigid cyclic transition state ensures high and predictable stereospecificity in the products formed.[16]

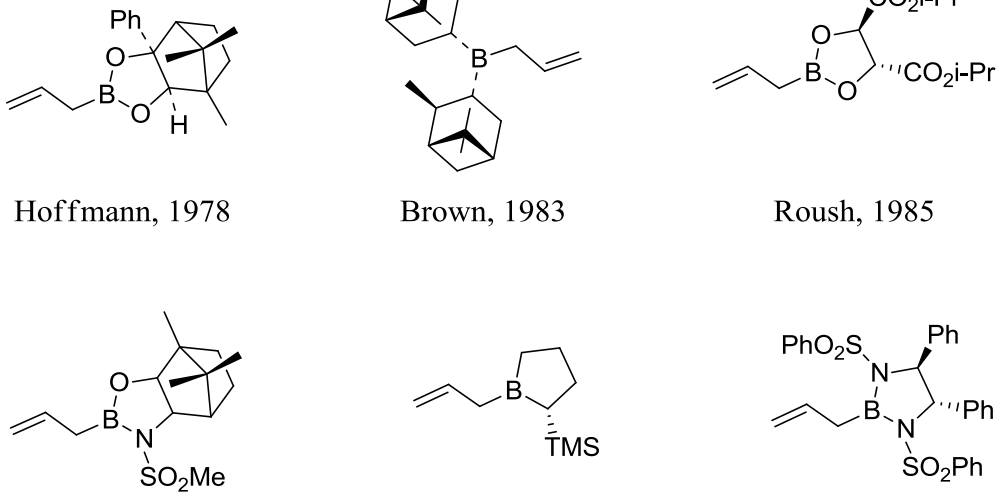
1.4 Chiral Auxiliary reagents

In the following years several chiral allylboron reagents were developed by Brown, Masamune, Roush, Corey and others (Figure 1.4).[9] The first chiral allyl reagents were synthesized from camphor-derived 1,2-diols by Hoffmann in 1978.[16] These systems did not give high stereoselectivities but were responsible for directing the future of the chiral allyl reagents. In 1983, Brown and Jadhav reported the synthesis of terpene based allylic boranes.[9a] Roush introduced the very recognizable class of tartrate-derived reagents in 1985.[9c] In 1988, Reetz developed the mixed O/N allylboronates which gave excellent enantiocontrol with aliphatic aldehydes.[9r] In the following year Masamune reported the use of *B*-allyl-2-(trimethylsilyl)borolane from an air-stable precursor.[9f] In 1989, Corey reported an efficient chiral allylborane from (*R*,*R*) or (*S*,*S*)-1,2-diamino-1,2-diphenylethane.[9g] More recently, Chong utilized an allyl reagent from chiral BINOL for the allylation of aldehydes.[9s] In 2005, Soderquist developed *B*-allyl-10-(trimethylsilyl)-9-borabicyclo[3.3.2]decane for the allyl- and crotylboration of aldehydes (Figure 1.4).[9n]

1.5 Brown's reagent

Among all the chiral auxiliaries developed, Brown's pinene-derived reagents[9a,b] have been most widely utilized for the generation of chiral homoallylic alcohols. Synthesis of Brown's reagents involves the hydroboration of the inexpensive precursor α-pinene, with chloroborane etherate giving the *B*-chlorodiisopinocamphylborane (Ipc_2BCl) which was treated with

allylmagnesium bromide at -78 °C to generate *B*-allyldiisopinocamphylborane as the chiral allylborane (Scheme 1.1).[9a] It is important to note that even after three decades of its discovery,

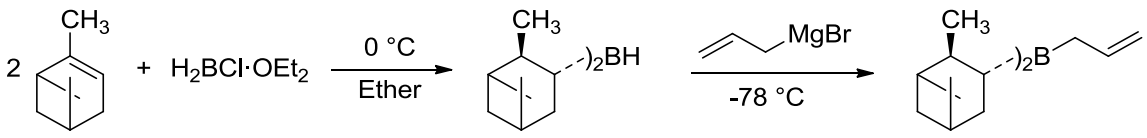


Hoffmann, 1978 | Brown, 1983 | Roush, 1985

Reetz, 1988 | Masamune, 1989 | Corey, 1989

Chong, 2004 | Soderquist, 2005

Figure 1.4 Chiral allylation reagents



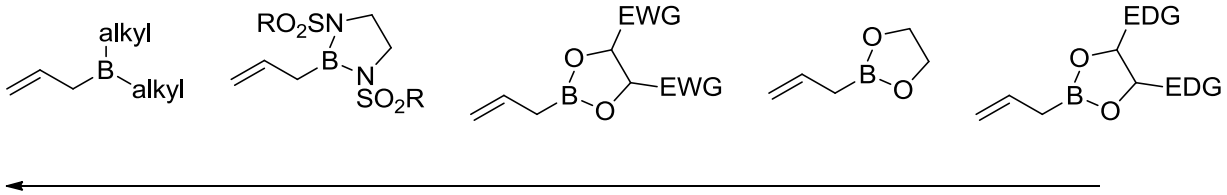
Scheme 1.1 Synthesis of Brown's Reagent for asymmetric allylation

use of Brown's pinene-derived allylating reagents is the method of choice for organic chemists.[17]

However the use of these reagents can be challenging as the reagents must be prepared and reacted at low temperatures and are highly air and moisture sensitive. Also, the stoichiometric generation of the isopinocampheol as the byproduct can sometimes complicate the product isolation.[18]

1.6 Reactivity and stability of allylic boron reagents

In General, allylic boranes are more reactive than the allylic boronates towards carbonyl allylation. The partial donation of electrons on the oxygen atoms to the empty p-orbital of boron is responsible for the lower reactivity of allyl boronates. Electron-donating or withdrawing substituents that reduce or increase the electrophilicity of the boron also play an important role in the reactivity of the boronate towards carbonyl allylation (Figure 1.5).



more reactive towards carbonyl compounds

EWG: electron-withdrawing groups, EDG: electron-donating groups

Figure 1.5 Reactivity of Allylboronates

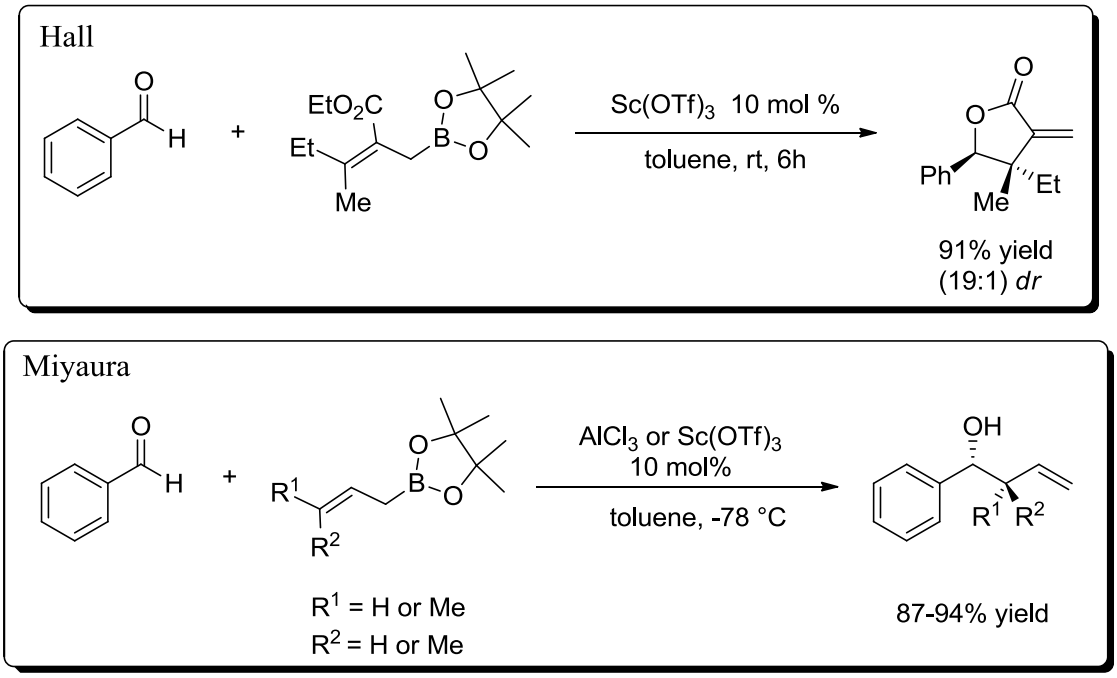
Allylic boronates are easier to handle when compared to allylic boranes as the former are more stable to atmospheric oxidation.[2] The boron-oxygen mesomeric effect is responsible for the relative stability of the allylic boronates. This makes the use of allylic boronates more desirable as they are stable to hydrolysis and can be effectively purified and isolated by chromatography on silica gel. Also, the substituted allyl boronates are stable to the borotropic rearrangements that are seen with substituted allyllic boranes.[2]

1.7 Lewis acid catalyzed allylboration

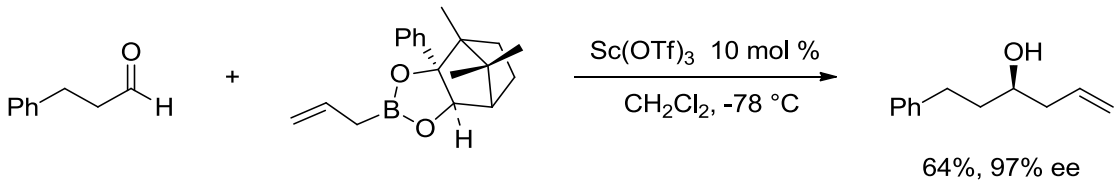
Dialkyl allylic boranes though have the advantage of being more reactive allylating reagents than the allylic boronic esters. Any attempts to increase the reactivity of the allylic boronates would lead to reduced stability. The allylboration reaction goes through the type I mechanism where the boron internally activates the carbonyl. Hence it would be right to assume that the presence of external activator would not benefit the reaction and the external activation could adversely affect the diastereoselectivities attained with these reactions. However, in 2002 Hall[10a] and Miyaura[10b] have independently shown that Lewis acids can accelerate the allylboration of aldehydes that use boronic esters as allyl reagents, while retaining the diastereoselectivity of the reaction (Scheme 1.2).[10a-d]

Hall reported that allylboration of aldehydes with 2-alkoxy carbonylallylboronates could be catalyzed by metal salts such as $Sc(OTf)_3$, $Cu(OTf)_2$, and $Yb(OTf)_3$. Even in the presence of external Lewis acid the reaction went through the type I mechanism, hence giving highly diastereoselective products (Scheme 1.2).[10a] In the same year Miyaura utilized Lewis acids like $AlCl_3$ and $Sc(OTf)_3$ for accelerating the reaction of aldehydes with simple allyl pinacolboronates. Miyaura also reported the use of chiral BINOL with these Lewis acids and achieved moderate enantioselectivities (39-51%) (Scheme 1.2).[10b] These were the first catalytic asymmetric allylboration of aldehydes which gave homoallylic alcohols with high diastereoselectivity.

In 2003 Hall reported the use of Lewis acids to accelerate the allylboration reaction when stoichiometric amounts of chiral substrates were used as allyl donors (Scheme 1.3). Hoffmann's camphor derived allylboronates were used as chiral substrates to react with a wide variety of aliphatic aldehydes. [10k]



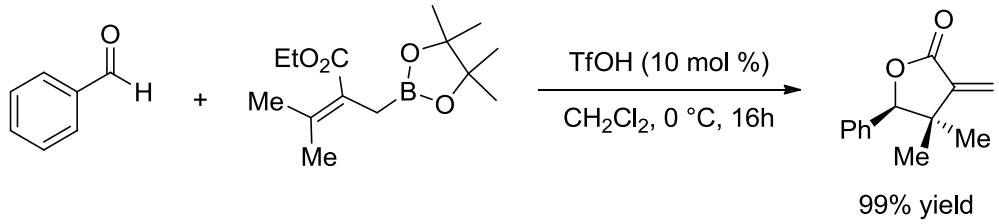
Scheme 1.2 Lewis acid catalyzed allylboration



Scheme 1.3 Lewis acid catalyzed allylborations with chiral boron reagents

1.8 Brønsted acid catalyzed allylboration

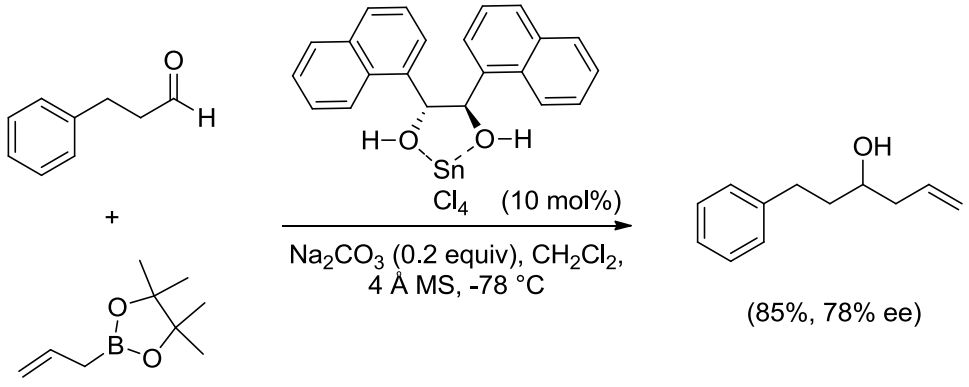
Followed by the reports on Lewis acid catalyzed allylborations, Hall reported the use of triflic acid, a Brønsted acid, for the allylboration of aldehydes in 2005 (Scheme 1.4). 10 mol% of triflic acid catalyzed the reaction between benzaldehyde and the 2-alkoxy carbonylallylboronate to give the respective lactones in near quantitative yields. [10d]



Scheme 1.4 Brønsted acid catalyzed allylboration

1.9 Lewis acid-assisted Brønsted acid catalyzed allylboration

Lewis acid-assisted chiral Brønsted acid (LBA) system was first developed by Yamamoto in 1994.[19] The proton in the LBA system is more acidic as the coordination of Lewis acids with Brønsted acid confines the orientation of the proton. In 2006, Hall introduced Yamamoto's chiral diol-SnCl4 complex to the allylboration chemistry.[10e] This Lewis acid assisted Brønsted acid catalyst proved to be an efficient catalyst for the allylboration of aldehydes. 78% enantioselectivity was obtained when hydrocinnamyl aldehyde was reacted with allyl boron pinacol ester with bis(napthyl)diol-$SnCl_4$ complex used as the catalyst (Scheme 1.5). The reaction also used sodium carbonate to scavenge the adventitious HCl that could be generated from $SnCl_4$ under reaction conditions.[10e] Later, an improved system was reported by Hall which



Scheme 1.5 Lewis acid-assisted Brønsted acid catalyzed allylboration

utilized a novel C_2-symmetric diols made from the hydrobenzoin skeleton.[10g] These diols with $SnCl_4$ gave much better enantioselectivities for the homoallylic alcohols formed. However, both these systems were more effective towards aliphatic aldehydes and gave only moderate selectivities with aromatic aldehydes.

1.10 Limitations of asymmetric allylation reactions

The versatility of homoallylic alcohols to serve as intermediates in the synthesis of various complex organic compounds makes it very important to prepare these alcohols in an asymmetric fashion with methods that are efficient and practical. In spite of the significant progress made towards the syntheses of non-racemic homoallylic alcohols, most of the current methods are limited by one or more drawbacks. These include: the difficulties associated with the synthesis of reagents, reagents that are very sensitive to air and/or moisture, use of tin derived reagents or catalysts, reactions that have to be performed at -78 °C, conditions suitable for either aliphatic or aromatic substrates only, high catalyst loading and lower reactivity of the reagents leading to narrow substrate scope. Even after three decades of its discovery, use of Brown's pinene-derived allylating reagents[9a,b] is the method of choice for organic chemists.[17] However the use of these reagents can be challenging as the reagents must be prepared and reacted at low temperatures (-78 °C) and are highly air and moisture sensitive. Also, the stoichiometric generation of the isopinocampheol as the byproduct can sometimes complicate the product isolation.[18] Because of the significance of asymmetric allylation reactions in organic synthesis especially in the polyketide construction; there is a clear need to develop a methodology for the synthesis of chiral homoallylic alcohols that can address most of the issues mentioned above.

1.11 Allylborations with boron pinacol ester

Pinacol-derived reagents have been excessively used in synthetic chemistry for an array of organic transformations.[20] Allyl reagents derived from pinacol have been an ideal choice for allylboration chemistry owing to its relative stability, optimal reactivity and non-toxicity. Most of the allyl reagents derived from pinacol are stable to hydrolysis and can be easily purified by chromatography on silica gel. This makes is easier to generate pinacol-derived allylic boronates with large range of functional groups, which is hard with boranes. Pinacol derived allyl- and crotylboronates are commercially available or can be easily synthesized from known literature methods.

1.12 Synthesis of Allyl boronic acid pinacol ester

Numerous ways to synthesize the allylboronic acid pinacol ester have been developed in past few years.[20] Direct reaction allyl magnesium bromide with trialkylborates followed by acid hydrolysis and addition of pinacol gives the allyl pinacol reagent in good yields (Figure 1.6, Eq. 1). Use of isopropoxypinacolborane as the boron source to react with Grignard reagents is also commonly used to obtain pinacol boronates (Figure 1.6, Eq. 2).[20] Morken reacted readily available allylic acetates with bis(pinacolato) diboron in presence of Ni/PCy_3 or Ni/PPh_3 complexes to get allyl boronates in high yields and good stereoselectivities (Figure 1.6, Eq. 3).[21] Boronates can also be easily accessed by reacting allylic halides with palladium catalysts like $Pd_2(dba)_3$, $PdCl_2$, Pd/C (Figure 1.6, Eq. 4).[20] In 2011, Singaram reported the synthesis of pinacoboronates by reacting aliphatic, aryl, heteroaryl, vinyl or allylic Grignard reagents with pinacol borane (Figure 1.6, Eq. 5).[22] Homologation of vinyl boronates can also be used to generate allyl boronates (Figure 1.6, Eq. 6). Copper, Iridium and platinum based catalysts have also been utilized to synthesize allyl boronates effectively.[20]

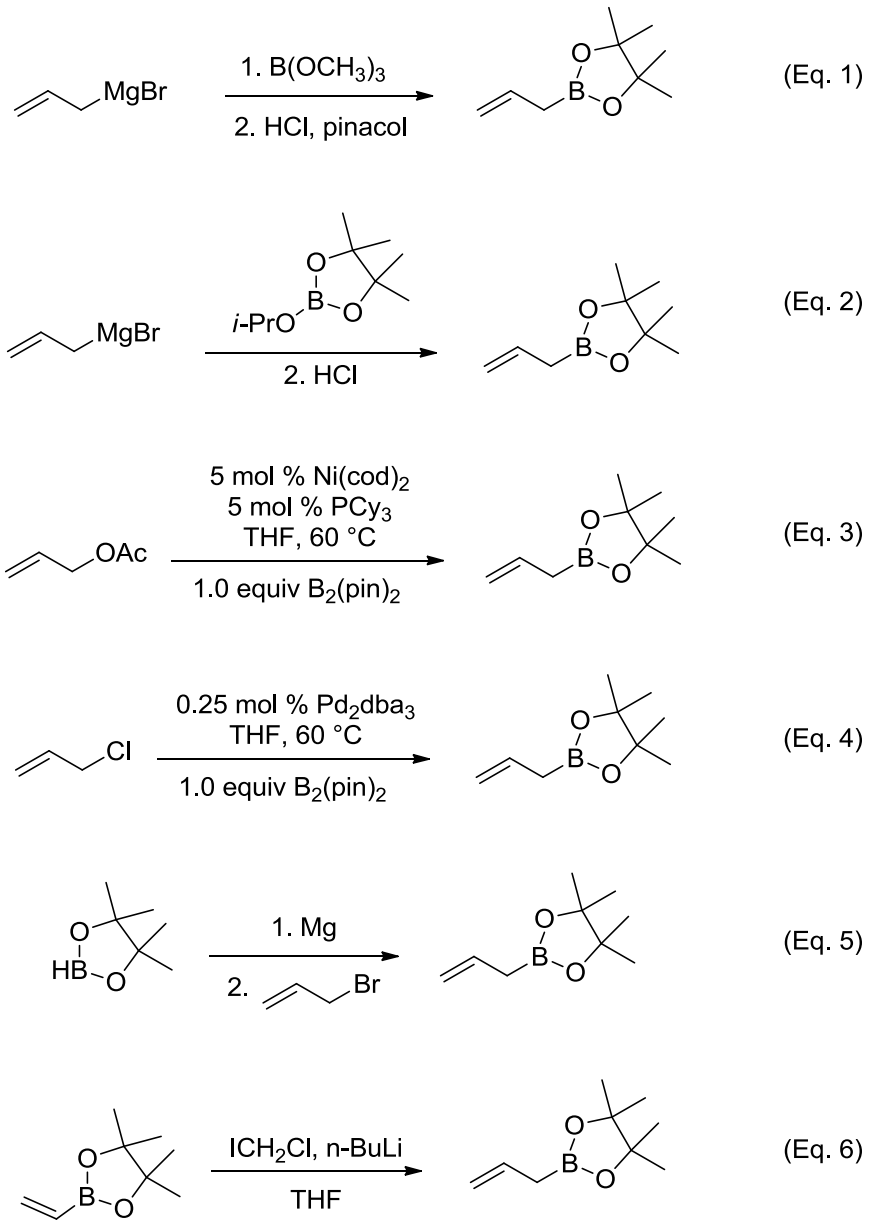


Figure 1.6 Synthesis of allyl boronic acid pinacol ester

1.13 BINOL-derived chiral phosphoric acids

Binaphthyl-derived chiral phosphoric acids (Figure 1.7) have been utilized as powerful catalysts in wide variety of asymmetric transformations.[23] These important chiral systems derived from BINOL were first reported independently by Akiyama and Terada in 2004.[24] Since then there has be huge interest across the globe to employ these Brønsted acidic systems in

carbon-carbon and carbon-heteroatom bond-forming reaction as well in oxidation and reduction reactions.[23] BINOL-derived chiral phosphoric acids possess some unique characteristics that make them potential catalysts in various non-racemic transformations. The catalyst, along with the Brønsted acidic site also has a Lewis basic site from the phosphoryl oxygen which gives it the potential to act as a bifunctional catalyst. The electronic and the steric properties of the catalyst can be controlled by altering the groups on the 3,3′-positions of the BINOL giving more options to optimize the reaction conditions. These catalytic systems with different substituents 3,3′-positions can be easily synthesized in few steps from commercially available BINOL in both enantiomeric forms.[23] Our lab focuses on the use of these systems in the wide array of reactions to attain chiral products. Although chiral PA catalysts have shown to work efficiently with an array of substrates, a very few reports have shown which utilization of aldehydes and ketones.[25] Hence, to expand the scope of chiral phosphoric acid catalysis into an important area of carbonyl activations, we investigated allylation of aldehydes.

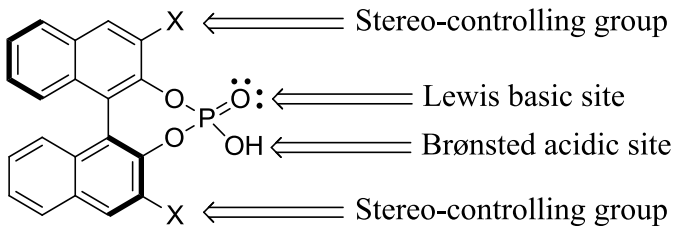


Figure 1.7 BINOL-derived phosphoric acid catalysts

1.14 Phosphoric acid catalyzed allylboration

The results obtained by Lewis acid and Lewis acid-assisted Brønsted acid catalyzed asymmetric allylboration reactions[10] encouraged us to investigate the chiral phosphoric acid catalyzed allylations. The goal of introducing phosphoric acid catalyzed allylboration using allyl pinacol boronate was to overcome the drawbacks encountered with current methods. Use of

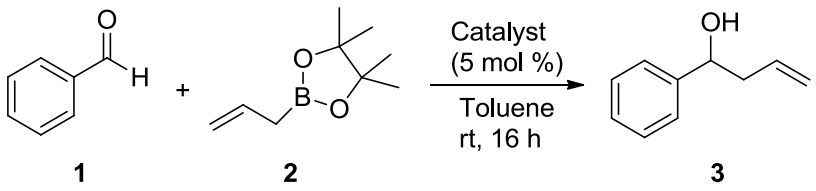
phosphoric acid as the catalyst eliminates the use of catalysts that are air/moisture sensitive and hard to synthesize/handle. Phosphoric acid as a Brønsted acid also prevents the use of catalysts that rely on toxic metals like tin and chromium. Similar advantages also make the use of allyl pinacol boronate as an attractive allyl donor as it is easy to synthesize, relatively stable and commercially available reagent.

1.15 Screening of catalysts and solvents

The investigation started with the reaction between benzaldehyde and allyl boronic acid pinacol ester in presence of a chiral phosphoric acid in toluene. Various BINOL-derived chiral phosphoric acids were screened to find the catalyst that gives the best selectivity at room temperatures (Table 1.1). Among all the catalysts that were studied TRIP-PA (**4e**) was found to be the most efficient catalyst along with H8-TRIP-PA (**4h**) which gave slightly less selectivity. Surprisingly, all the other catalysts showed very little or no selectivity giving almost racemic products. Interestingly, **4f** which is similar to TRIP-PA, having methyl groups instead of isopropyl groups, and **4c** which is very bulky catalyst also gave very low enantioselectivity. All the catalysts were re-screened as some of the catalysts tested could have been salts:[26] see detailed report in chapter 3.

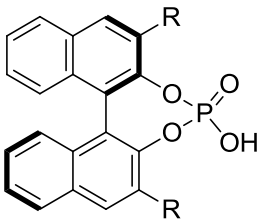
Various solvent were screened for the allylboration of benzaldehyde with TRIP-PA as the catalyst (Table 1.2). Non-coordinating solvents like toluene, *m*-xylene, benzene and methylene chloride were effective for the asymmetric synthesis of alcohol **3a**. Solvents like ether, tetrahydrofuran and ethyl acetate gave lower enantioselectivities with slow reaction rates. It was determined that toluene was the most suitable solvent, allowing for a 93% ee of **3a** at room temperature in a 1 hour reaction time (entry 8). The enantioselectivity was further improved by reducing the temperature to 0 °C (96% ee, entry 9) and -30 °C (98% ee, entry 10) in presence of

Table 1.1 Allylboration of aldehydes: Catalyst screening

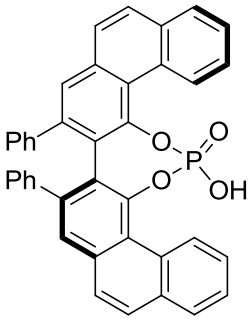


1 **2** **3**

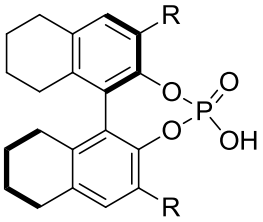
Entry	Catalyst	% Conversion	ee %
1	**4a**	100	4
2	**4b**	100	5
3	**4c**	100	4
4	**4d**	100	6
5	**4e**	100	93
5	**4f**	100	8
6	**4g**	100	6
7	**4h**	100	88



4a: R = $SiPh_3$
4b: R = 4-(β-Naph)-C_6H_4
4c: R = 9-anthryl
4d: R = Ph
4e: R = (2,4,6-*i*-Pr)-C_6H_2
4f: R = (2,4,6-CH_3)-C_6H_2



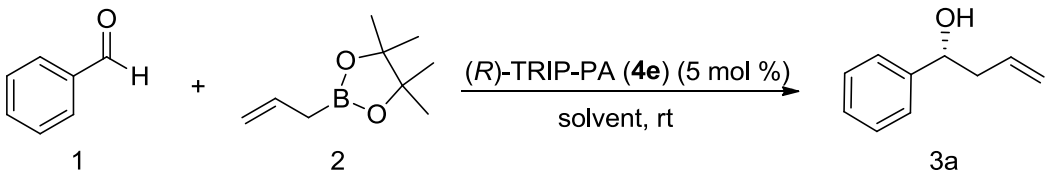
4g



4h: R = (2,4,6-*i*-Pr)-C_6H_2

5 mol % of the catalyst. It was fascinating to find that lowering the catalyst loading to 2.5 mol % allowed for a 97% ee (entry 11) and further lowering to 1 mol % (entry 12) still allowed for an impressive 95% enantioselectivity.

Table 1.2 Optimization of allylboration reaction with TRIP-PA as catalyst



1 2 3a

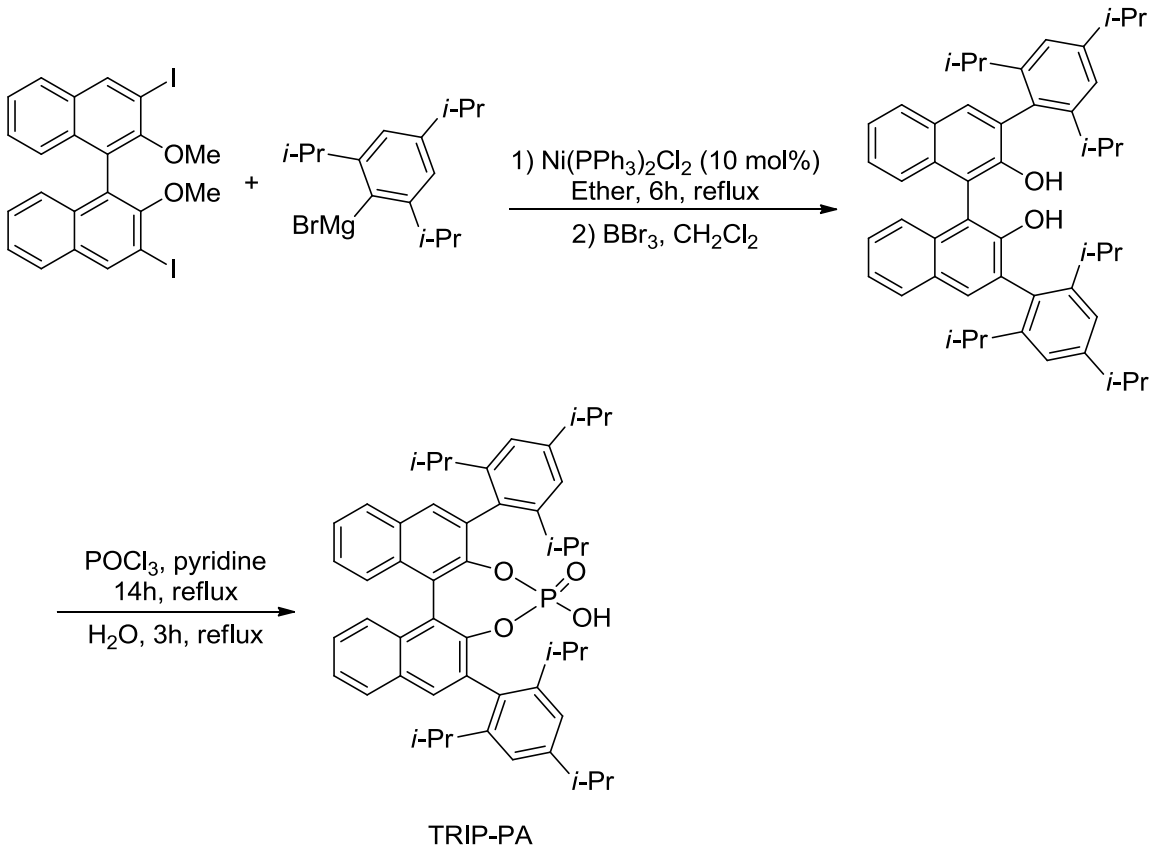
entry	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	ether	16	99	35
2	DCM	16	99	88
3	THF	48	51	6
4	m-xylene	48	99	89
5	EtOAc	24	76	29
6	CH_3CN	48	55	33
7	benzene	2	99	92
8	toluene	1	99	93
9	toluene[d]	4	99	96
10	toluene[e]	16	99	98
11	toluene[e,f]	16	99	97
12	toluene[e,g]	16	99	95

[a] Reaction conditions: 1 (0.10 mmol), 2 (0.12 mmol), 5 mol % (R)-TRIP-PA, unless otherwise specified. [b] Isolated yield. *c* Determined by chiral HPLC analysis. [d] Reaction conducted at 0 °C. e Reaction conducted at -30 °C. [f] 2.5 mol % catalyst used. [g] 1 mol % catalyst used.

1.16 TRIP phosphoric acid

Many differently substituted binaphthyl-phosphoric acids have been developed since the introduction of these chiral catalysts by Akiyama and Terada in 2004.[23] The 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (**4e**, abbreviated TRIP or TRIP-PA) was first reported by List in 2005 for the asymmetric hydrogenation of imines.[26] This catalyst with bulky 3,3′-positions on the binaphthol core proved to be powerful Brønsted acid

catalyst in terms of activity and selectivity and has found wide applications in various asymmetric transformations. The catalyst can be easily synthesized or obtained commercially from sigma in both *R* and *S* forms. The key step involves the nickel-catalyzed Kumada coupling of the BINOL derivate X with triisopropylphenyl magnesium bromide (Scheme 1.6). During the synthesis this catalyst can be easily contaminated with metal impurities from silica gel purifications or the metal catalysts/reagents used in its synthesis.[26] Forming phosphate salts reduces the free acid catalyst in the product, reducing its efficacy in truly Brønsted acid catalyzed reactions. Hence it is extremely important to thoroughly wash the TRIP catalyst with hydrochloric acid after the final step.



Scheme 1.6 Synthesis of TRIP-PA

1.17 Substrate scope

The optimized reaction conditions were effective in promoting the asymmetric allylboration of a wide range of aldehydes, allowing for an extremely efficient reaction (Table 1.3). The substrate scope extended to electron-rich (alkyl- and alkoxy- groups on benzaldehyde: entries 5-7) and electron-poor aromatic aldehydes (chloro-, bromo-, nitro- groups on benzaldehyde: entries 2-4). An ester functional group was tolerated in the chemistry (entry 8) and also several hindered aldehydes were effectively allylated (entries 7, 9 and 10). We were particularly pleased to find that heteroaryl (entry 12), α,β-unsaturated aldehydes (entries 13 and 14) and aliphatic aldehydes (entries 15 and 16) were found to be allylated efficiently with high enantioselectivity. The only limits on enantioselectivity were found upon further evaluation of aliphatic aldehydes (entries 17 and 18).

We believe these examples represent the first case where a chiral Brønsted acid activates allyl boronate esters, in the absence of a Lewis acid, in a highly enantioselective catalytic process.

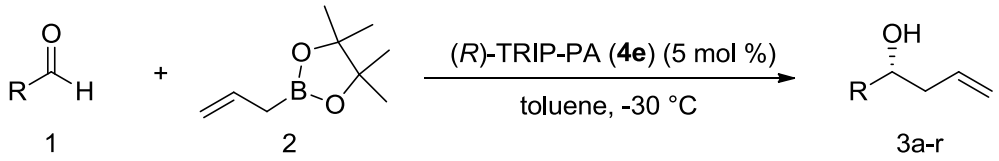
1.18 Crotylboration of aldehydes

We were very pleased to find that (*R*)-**TRIP-PA** also promoted the crotylboration of benzaldehyde with high diastereo- and enantioselectivities (Table 1.4). Use of (*E*)-crotyl boronate **5a** provided the *anti*-isomer **6a** exclusively with 96% ee at room temperature (entry 1) and >99% ee at 0 °C (entry 2) using the general reaction conditions. When employing the (*Z*)-crotyl boronate **5b** the *syn*-isomer **6b** was obtained exclusively with 94% ee at -30 °C.

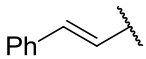
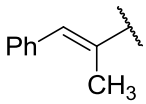
1.19 Initial mechanistic insights

The reaction mechanism for this interesting activation was investigated by Goodman's and

Table 1.3 Substrate scope for chiral phosphoric acid catalyzed allylboration

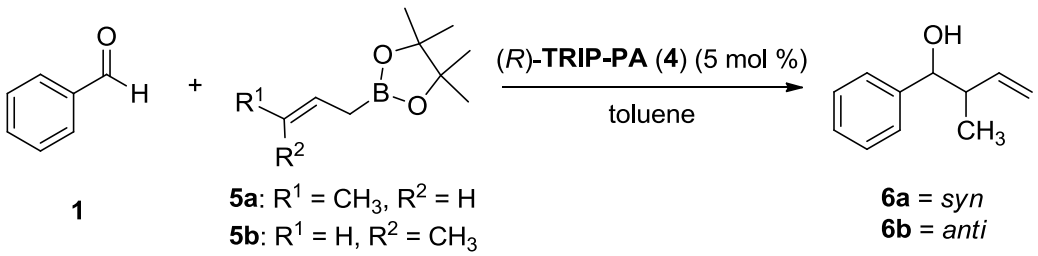


1 2 3a-r

entry	R	product	yield (%)[b]	ee (%)[c]
1	Ph	3a	99	98d
2	4-ClC$_6$H$_4$	3b	98	99
3	4-BrC$_6$H$_4$	3c	99	99
4	4-NO$_2$C$_6$H$_4$	3d	98	98
5	4-MeOC$_6$H$_4$	3e	95	98
6	3-MeOC$_6$H$_4$	3f	96	97
7	2-MeC$_6$H$_4$	3g	97	93
8	4-CO$_2$MeC$_6$H$_4$	3h	96	96
9	1-naphthyl	3i	93	98
10	9-anthryl	3j	94	91
11	piperonyl	3k	98	98
12	2-thienyl	3l	91	96
13		3m	94	96
14		3n	93	93
15	Bn	3o	98	90
16	PhCH$_2$CH$_2$	3p	96	87[e]
17	BnOCH$_2$	3q	92	79
18	c-C$_6$H$_{11}$	3r	98	73

[a] Reaction Conditions: 1 (0.1 mmol), 2 (0.12 mmol), 5 mol % (R)-TRIP-PA, unless otherwise specified. [b] Isolated yield. c Determined by chiral HPLC analysis. d When this reaction was performed with (S)-TRIP-PA the opposite enantiomer of 3a was obtained in 98% yield and 97% ee under otherwise identical conditions. [e] In this case the opposite (S) enantiomer was observed using the (R)-TRIP-PA catalyt.

Table 1.4 Crotylboration of benzaldehyde



1

5a: $R^1 = CH_3$, $R^2 = H$
5b: $R^1 = H$, $R^2 = CH_3$

6a = *syn*
6b = *anti*

entry	R^1	R^2	temp	**6a** : **6b**[b]	yield (%)[c]	ee (%)[d]
1	CH_3	H	rt	*anti* only	96	96
2	CH_3	H	0 °C	*anti* only	96	99
3	H	CH_3	0 °C	*syn* only	95	94

[a] Reaction Conditions: **1** (0.1 mmol), **5** (0.12 mmol), 5 mol % (***R***)-**TRIP-PA**, unless otherwise specified. [b] Determined by ^{1}H NMR. [c] Isolated Yield. [d] Determined by chiral HPLC analysis.

Houk's laboratory independently (see chapter 4).[27] Our initial report on Brønsted acid catalyzed allylboration explained some plausible mechanistic insights. The observed diastereoselectivity in the crotylation strongly suggests that the allylboration proceeds via a type I mechanism involving a chair-like six-membered cyclic transition state similar to previous uncatalyzed reactions involving allyl boronates.[9] Recent work by Hall[10f-g] and Schaus,[10k] suggest that activation by protonation of the boronate oxygen could be involved. Similarly, Lewis acid promoted boronate activation has also been previously invoked.[10a,b] As the basis to a working hypothesis, we proposed in our initial report that activation via protonation of the boronate oxygen by the chiral phosphoric catalyst would provide a reasonable explanation for the reactivity. Chapter 4 includes the detailed results of the theoretical calculations performed by the research labs of Goodman and Houk independently. These studies show that the major isomer is formed *via* a transition state involving the hydrogen bonding interaction between the hydroxyl group of the catalyst and the pseudoaxial oxygen of the boronate, with a stabilizing interaction of the phosphoryl oxygen to the formyl hydrogen.

1.20 Conclusions

In conclusion we have developed a simple and highly efficient chiral phosphoric acid catalyzed allylboration of aldehydes. The protocol provides a high yielding and a highly enantioselective method for the synthesis of homoallylic alcohols from simple starting materials. The high diastereoselctivites attained suggests that the reaction proceeds via a type I mechanism involving a chairlike six-membered cyclic transition state similar to the uncatlyzed allylborations. The reaction is shown to highly general, with a broad substrate scope that covers aryl, heteroaryl, α,β-unsaturated and aliphatic aldehydes. The reaction conditions are also shown to be effective for the catalytic enantioselective crotylation of aldehydes. The usefulness of this organocatalytic reaction is highlighted by the stability and commercial availability of the substrates and the catalyst. This work also has the potential of opening new vistas for chiral phosphoric acid-catalyzed activation that was not previously evident.

1.21 Experimental

General Considerations: All reactions were carried out in flame-dried screw-cap test tubes and were allowed to proceed under a dry argon atmosphere with magnetic stirring. Toluene was purified by passing through a column of activated alumina under a dry argon atmosphere. Aldehydes were purchased from commercial sources and were distilled prior to use. TRIP catalyst was prepared from chiral BINOL according to the known literature procedure.[26] Thin layer chromatography was performed on Merck TLC plates (silica gel 60 F_{254}). Visualization was accomplished UV light (256 nm), with the combination of ceric ammonium molybdate as indicator. Flash column chromatography was performed with Merck silica gel (230-400 mesh). Enantiomeric excess (ee) was determined using a Varian Prostar HPLC with a 210 binary pump and a 335 diode array detector. Optical rotations were performed on a Rudolph Research

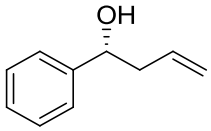
Analytical Autopol IV polarimeter (λ 589) using a 700-μL cell with a path length of 1-dm. ^{1}H NMR and ^{13}C NMR were recorded on a Varian Inova-400 spectrometer with chemical shifts reported relative to tetramethylsilane (TMS). All the compounds were known compounds and were characterized by comparing their ^{1}H NMR and ^{13}C NMR values to the reported values.

General procedure for the allylboration of aldehydes

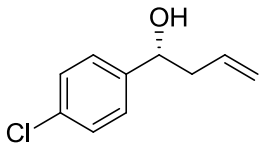
A screw-cap reaction tube with a stir bar was evacuated, flame-dried, and back-filled with argon. To this tube was added the (*R*)-TRIP-PA catalyst **4** (5 mol %), freshly distilled aldehyde (0.1 mmol) and 1.5 ml of dry toluene. The reaction mixture was then cooled to -30 °C followed by the addition of allylboronic acid pinacol ester **2** (0.12 mmol), dropwise over 30 seconds. The mixture was stirred overnight at this temperature and then directly loaded on a silica gel column, the crude product was purified by flash chromatography using ethyl acetate and hexanes (1 : 9).

General procedure for the crotylboration of benzaldehyde

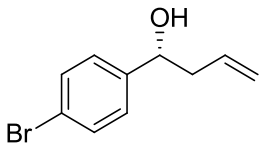
A screw-cap reaction tube with a stir bar was evacuated, flame-dried, and back-filled with argon. To this tube was added the (*R*)-TRIP-PA catalyst **4** (5 mol %), freshly distilled benzaldehyde (0.10 mmol) and 1.5 ml of dry toluene. The reaction mixture was then cooled to required temperature followed by the addition of crotyl boronic acid pinacol ester **5** (0.12 mmol), dropwise over 30 seconds. The mixture was stirred overnight at this temperature. Next day 1 ml of 1M HCl was added and the reaction was stirred for 15 minutes. Proton NMR of the crude mixture was collected and then the product was purified by flash chromatography using ethyl acetate and hexanes (1 : 9).



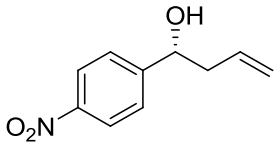
(*R*)-1-Phenyl-but-3-en-1-ol (3a): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 99 % yield with spectral properties reported in literature.[28] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 99/1, 0.7 mL/min), t_{major} = 29.27 min, t_{minor} 34.44 min; ee = 98%. $[\alpha]^{24}_D$ = +55.74 (c = 0.98, $CHCl_3$). The reported value[28] for the *R*-enantiomer (95% ee) is $[\alpha]_D$ = +56.5 (c = 1.0, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.20 (m, 5H), 5.85-5.71 (m, 1H), 5.16-5.10 (m, 2H), 4.72 (dd, *J* = 7.6, 5.6 Hz, 1H), 2.54-2.43 (m, 2H), 2.00 (br s, 1H).



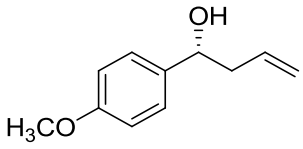
(*R*)-1-(4-Chloro-phenyl)-but-3-en-1-ol (3b): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 98% yield with spectral properties reported in literature.[29] Enantiomeric excess was determined by HPLC with a chiralcel AD-H column (hexane/iPrOH = 99/1, 1.0 mL/min), t_{major} = 26.59 min, t_{minor} = 28.55 min; ee = 99%. $[\alpha]^{24}_D$ = +63.3 (c = 1.14, $CHCl_3$). The reported value[29] for the *R*-enantiomer (94% ee) is $[\alpha]_D$ = +61.4 (c = 1.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 1H), 2.39-2.52 (m, 2H), 4.66-4.73 (m, 1H), 4.96-5.20 (m, 2H), 5.69-5.83 (m, 1H), 7.18-7.35 (m, 4H).



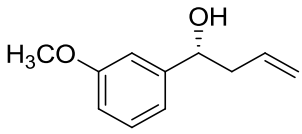
(*R*)-1-(4-Bromo-phenyl)-but-3-en-1-ol (3c): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 99% yield with spectral properties reported in literature.[28] Enantiomeric excess was determined by HPLC with a chiralcel OJ-H column (hexane/iPrOH = 95/5, 0.4 mL/min), t_{minor} = 25.61 min, t_{major} = 28.16 min; ee = 99%. $[\alpha]^{24}_{D}$ = +25.82 (c = 0.91, Benzene). The reported value[28] for the *R*-enantiomer (96% ee) is $[\alpha]_D$ = +23.2 (c = 1.17, Benzene). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 5.83-5.71 (m, 1H), 5.18-5.13 (m, 2H), 4.69 (dd, *J* = 7.6, 4.8 Hz, 1H), 2.52-2.39 (m, 2H), 2.06 (br s, 1H).



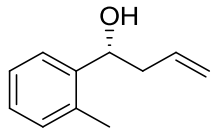
(*R*)-1-(4-Nitro-phenyl)-but-3-en-1-ol (3d): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 98% yield with spectral properties reported in literature.[30] Enantiomeric excess was determined by HPLC with a chiralcel AS-H column (hexane/iPrOH = 97/3, 0.7 mL/min), t_{major} = 52.09 min, t_{minor} = 54.52 min; ee = 98%. $[\alpha]^{24}_{D}$ = +65.87 (c = 1.07, $CHCl_3$). The reported value[30] for the *R*-enantiomer (97% ee) is $[\alpha]_D$ = +64.2 (c = 0.8, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 5.86-5.72 (m, 1H), 5.24-5.17 (m, 2H), 4.89 (m, 1H), 2.61-2.55 (m, 1H), 2.52-2.44 (m, 1H) 2.31 (br s, 1H).



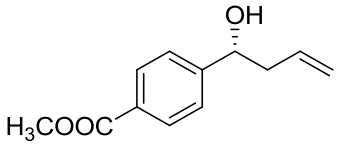
(*R*)-1-(4-Methoxy-phenyl)-but-3-en-1-ol (3e): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 95% yield with spectral properties reported in literature.[29] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 98/2, 1.0 mL/min), t_{major} = 18.64 min, t_{minor} = 22.87 min; ee = 98%. $[\alpha]^{24}_{D}$ = +30.84 (c = 1.01, Benzene). The reported value[29] for the *R*-enantiomer (95% ee) is $[\alpha]_{D}$ = +30.5 (c = 1.0, Benzene). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 5.83-5.72 (m, 1H), 5.16-5.09 (m, 2H), 4.69 (m, 1H), 3.78 (s, 3H), 2.50 (m, 2H), 1.95 (br s, 1H).



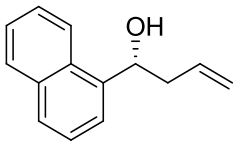
(*R*)-1-(3-Methoxy-phenyl)-but-3-en-1-ol (3f): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 96% yield with spectral properties reported in literature.[31] Enantiomeric excess was determined by HPLC with a chiralcel OJ-H column (hexane/iPrOH = 98/2, 0.8 mL/min), t_{minor} = 28.63 min, t_{major} = 30.17 min; ee = 97%. $[\alpha]^{24}_{D}$ = +53.81 (c = 0.89, Benzene). The reported value[31] for the *R*-enantiomer (73% ee) is $[\alpha]_{D}$ = +41.0 (c = 2.22, Benzene). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.22 (m, 1H) 6.94-6.89 (m, 2H), 6.82-6.78 (m, 1H), 5.85-5.47 (m, 1H), 5.19-5.10 (m, 2H), 4.67-4.72 (m, 1H), 3.80 (s, 3H), 2.56-2.42 (m, 2H), 1.95 (br s, 1H).



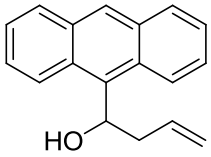
(*R*)-1-*o*-Tolyl-but-3-en-1-ol (3g): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 97% yield with spectral properties reported in literature.[28] Enantiomeric excess was determined by HPLC with a chiralcel AD-H column (hexane/iPrOH = 95/5, 0.5 mL/min), t_{major} = 13.89 min, t_{minor} = 16.32 min; ee = 93%. $[\alpha]^{24}_{D}$ = +68.8 (c = 1.11, Benzene). The reported value[28] for the *R*-enantiomer (97% ee) is $[\alpha]_{D}$ = +75.5 (c = 1.0, Benzene).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.8 Hz, 1H), 7.28-7.12 (m, 3H) 5.22-5.14 (m, 2H), 4.97 (dd, *J* = 8.0, 4.8 Hz, 1H), 2.54-2.40 (m, 2H), 2.35 (s, 3H), 2.02 (br s, 1H).



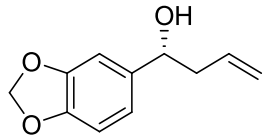
(*R*)-Methyl 4-(1-hydroxybut-3enyl)benzoate (3h): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 96% yield with spectral properties reported in literature.[32] Enantiomeric excess was determined by HPLC with a chiralcel AD-H column (hexane/iPrOH = 95/5, 0.6 mL/min), t_{major} = 23.67 min, t_{minor} = 26.84 min; ee = 96%. $[\alpha]^{24}_{D}$ = 27.84 (c = 1.31, Benzene).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 5.83-5.72 (m, 1H), 5.17-5.12 (m, 2H), 4.79 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.90 (s, 3H), 2.56-2.41 (m, 2H), 2.24 (br s, 1H).



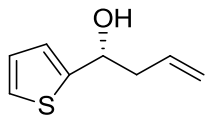
(*R*)-1-Naphthalen-1-yl-but-3-en-1-ol (3i): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 93% yield with spectral properties reported in literature.[28] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 90/10, 0.5 mL/min), t_{minor} = 16.44 min, t_{major} = 26.73 min; ee = 98%. $[\alpha]^{24}_{D}$ = +98.63 (c = 1.06, Benzene). The reported value[28] for the *R*-enantiomer (92% ee) is $[\alpha]_{D}$ = +97.3 (c = 1.0, Benzene).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 7.1 Hz, 1H), 7.55-7.45 (m, 3H), 6.00-5.87 (m, 1H), 5.58-5.52 (m, 1H), 5.28-5.16 (m, 2H), 2.80-2.56 (m, 2H), 2.14 (br s, 1H).



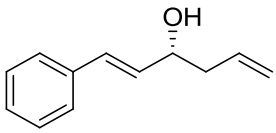
(*R*)-1(anthrcen-9-yl)but-3-en-1-ol (3j): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 93% yield with spectral properties reported in literature.[33] Enantiomeric excess was determined by HPLC with a chiralcel AD-H column (hexane/iPrOH = 95/5, 1.0 mL/min), t_{major} = 17.60 min, t_{minor} = 21.29 min; ee = 91%. $[\alpha]^{24}_{D}$ = +17.38 (c = 1.85, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72-8.60 (m, 2H), 8.39 (s, 1H), 8.02-7.97 (m, 2H), 7.51-7.42 (m, 4H), 6.29 (dd, *J* = 6.3 Hz, 1H), 6.01-5.90 (m, 1H), 5.29-5.10 (m, 2H), 3.24-3.15 (m, 1H), 2.89-2.81 (m, 1H), 2.25 (br s, 1H).



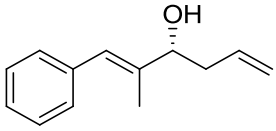
(*R*)-1-(Benzo[d][1,3]dioxol-5-yl)but-3-en-1-ol (3k): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 98% yield with spectral properties reported in literature.[32] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 98/2, 1.0 mL/min), t_{major} = 22.37 min, t_{minor} = 27.64 min; ee = 98%. $[\alpha]^{24}_{D}$ = +35.53 (c = 0.95, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (m, 1H), 6.81-6.75 (m, 2H), 5.95 (s, 2H), 5.84-5.72 (m, 1H), 5.18-5.11 (m, 2H), 4.65 (t, *J* = 6.8 Hz, 1H), 2.46 (t, *J* = 6.4 Hz, 2H), 1.96 (br s, 1H).



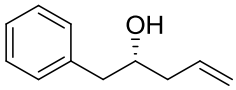
(*R*)-1-Thiophen-2-yl-but-3-en-1-ol (3l): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 91% yield with spectral properties reported in literature.[34] Enantiomeric excess was determined by HPLC with a chiralcel OJ-H column (hexane/iPrOH = 93/7, 0.5 mL/min), t_{minor} = 21.37 min, t_{major} = 24.59 min; ee = 96%. $[\alpha]^{24}_{D}$ = -12.33 (c = 1.07, $CHCl_3$). The reported value[35] for the *R*-enantiomer (95% ee) is $[\alpha]_D$ = +9.7 (c = 1.0, EtOH).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.24 (m, 1H), 6.98-6.94 (m, 2H), 5.87-5.76 (m, 1H), 5.20-5.14 (m, 2H), 4.96-5.00 (m, 1H), 2.63-2.59 (m, 2H), 2.10-2.11 (m, 1H).



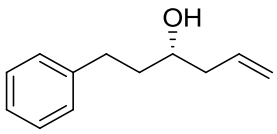
(*R*),(*E*)-1-Phenyl-hexa-1,5-dien-3-ol (3m): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 94% yield with spectral properties reported in literature.[28] Enantiomeric excess was determined by HPLC with a chiralcel AS-H column (hexane/iPrOH = 95/5, 1.0 mL/min), t_{major} = 8.00 min, t_{minor} = 9.04 min; ee = 96%. $[\alpha]^{24}_{D}$ = -9.76 (c = 1.12, Et_2O). The reported value[28] for the *R*-enantiomer (97% ee) is $[\alpha]_D$ = -12.3 (c = 1.0, Et_2O).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.21 (m, 5H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.23 (dd, *J* = 16.0, 6.4 Hz, 1H), 5.90-5.80 (m, 1H), 5.20-5.14 (m, 2H), 4.35 (ddd, *J* = 6.8, 6.0, 6.0 Hz, 1H), 2.45-2.33 (m, 2H), 1.80 (br s, 1H).



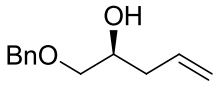
(*R*),(*E*)-2-Methyl-1-phenyl-hexa-1,5-dien-3-ol (3n): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 93% yield with spectral properties reported in literature.[36] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 97/3, 1.0 mL/min), t_{major} = 10.85 min, t_{minor} = 12.64 min; ee = 93%. $[\alpha]^{24}_{D}$ = +2.37 (c = 0.79, $CHCl_3$). The reported value[36] for the *R*-enantiomer (50% ee) is $[\alpha]_D$ = +1.1 (c = 1.15, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82-1.84 (m, 1H), 1.87-1.88 (m, 3H), 2.34-2.48 (m, 2H), 4.17-4.25 (m, 1H), 5.11-5.21 (m, 2H), 5.77-5.88 (m, 1H), 6.52 (s, 1H), 7.18-7.35 (m, 5H).



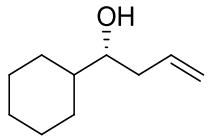
(*R*)-1-Phenylpent-4-en-2-ol (3o): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 98% yield with spectral properties reported in literature.[37] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 97/3, 0.5 mL/min), t_{minor} = 15.51 min, t_{major} = 19.65 min; ee = 90%. $[\alpha]^{24}_{D}$ = -12.20 (c = 1.01). The reported value[37] for the *R*-enantiomer (97% ee) is $[\alpha]_D$ = -14.24 (c = 0.65, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.20 (m, 5H), 5.94-5.80 (m, 1H), 5.20-5.12 (m, 2H), 3.93-3.84 (m, 1H), 2.86-2.70 (m, 2H), 2.38-2.18 (m, 2H), 1.7 (br s, 1H).



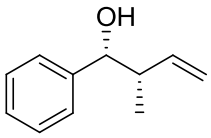
(*S*)-1-Phenylpent-4-en-2-ol (3p): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 96% yield with spectral properties reported in literature.[28] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 95/5, 1.0 mL/min), t_{major} = 8.76 min, t_{minor} = 13.29 min; ee = 87%. $[\alpha]^{24}_{D}$ = -25.4 (c = 0.97, Benzene). The reported value[28] for the *S*-enantiomer (86% ee) is $[\alpha]_D$ = -26.4 (c = 1.0, Benzene).^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76-1.84 (m, 2H), 2.14-2.37 (m, 2H), 2.64-2.86 (m, 2H), 3.62-3.72 (m, 1H), 5.08-5.19 (m, 2H), 5.72-5.98 (m, 1H), 7.13-7.32 (m, 5H).



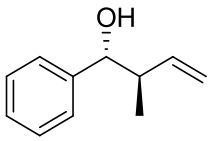
(*S*)-1-Benzyloxy-pent-4-en-2-ol (3q): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 92% yield with spectral properties reported in literature.[38] Enantiomeric excess was determined by HPLC with a chiralcel AS-H column (hexane/iPrOH = 97/3, 0.5 mL/min), t_{minor} = 20.91 min, t_{major} = 25.09 min; ee = 79%. $[\alpha]^{24}_{D}$ = -1.26 (c = 1.27, $CHCl_3$). The reported value[38] for the *R*-enantiomer (53% ee) is $[\alpha]_D$ = +0.9 (c = 2.5, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.24 (m, 5H), 5.87-5.75 (m, 1H), 5.13-5.06 (m, 2H), 4.54 (s, 2H), 3.92-3.84 (m, 1H), 3.50 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.36 (dd, *J* = 9.6, 7.6 Hz, 1H), 2.35 (br s, 1H), 2.25 (t, *J* = 6.8 Hz, 2H).



(*R*)-1-Cyclohexyl-but-3-en-1-ol (3r): Following the general procedure for the allylation of aldehydes, the title compound was obtained in 98% yield with spectral properties reported in literature.[28] Enantiomeric excess was determined by formation of 3,5 dinitrobenzoate ester of the title compound followed by HLPC with a chiralcel OD-H column (hexane/iPrOH = 95/5, 1.0 mL/min), t_{major} = 10.97 min, t_{minor} = 11.76 min; ee = 73%. $[\alpha]^{24}_{D}$ = +5.24 (c = 1.0, EtOH). The reported value[2] for the *R*-enantiomer (93% ee) is $[\alpha]_D$ = +13.7 (c = 1.0, EtOH).^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91-1.32 (m, 4H), 1.55-1.87 (m, 7H), 2.16-2.08 (m, 1H), 2.30-2.37 (m, 1H), 3.42-3.35 (m, 1H), 5.16-5.10 (m, 2H), 5.90-5.78(m, 1H).



1-Methyl-1-phenyl-but-3-en-1-ol (6a): Following the general procedure for the crotylboration of aldehydes, the syn product was obtained when cis-crotylboronic acid pinacol ester was used at – 30 °C, in 95% yield with spectral properties reported in literature.[28] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 95/5, 1.0 mL/min), t_{minor} = 7.17 min, t_{major} = 8.32 min; ee = 93%. $[\alpha]^{24}_{D}$ = +19.27 (c = 2.27, $CHCl_3$). The absolute configuration of the syn isomer was found to be (1*R*,2*S*) by comparing with the literature.[28] ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (d, *J* = 6.8 Hz, 3H), 1.94-1.96 (m, 1H), 2.52-2.62 (m, 1H), 4.60 (dd, *J* = 5.5 Hz, 1H), 5.01-5.07 (m, 2H), 5.70-5.80 (m, 1H), 7.22-7.35 (m, 5H).



1-Methyl-1-phenyl-but-3-en-1-ol (6b): Following the general procedure for the crotylboration of aldehydes, the anti product was obtained when *trans*-crotylboronic acid pinacol ester was used at – 0 °C, in 96% yield with spectral properties reported in literature.[28] Enantiomeric excess was determined by HPLC with a chiralcel AD-H column (hexane/iPrOH = 98/2, 1.0 mL/min), t_{minor} = 12.73 min, t_{major} = 13.77 min; ee = 99%. $[\alpha]^{24}_{D}$ = 98.97 (c = 2.27, $CHCl_3$). The absolute configuration of the anti isomer was found to be (1*R*,2*R*) by comparing with the literature.[28] ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d, *J* = 6.8 Hz, 3H), 2.13 (br s, 1H), 2.41-2.60 (m, 1H), 4.36 (d, *J* = 7.8 Hz, 1H), 5.12-5.26 (m, 2H), 5.66-5.86 (m, 1H), 7.20-7.37 (m, 5H).

1.22 References

1) Rouhi, M. Thalidomide. Chem. Eng. News **2005**, *83*, 122.

2) For reviews, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, p 1. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293. (c) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter10, pp 299-402. (d) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 11, 403-490. (c) (d) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2793. (e) Lachance, H.; Hall, D. G. *Org. React.* **2008**, *73*, 1. (f) Yus, M.;Gonzalez-Gomez, J. C.; Foubelo, F. *Chem. Rev*. **2011**, *111*, 7774−7854.

3) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974.

4) Raoelison, G. E.; Terreaux, C.; Queiroz, E. F.; Zsila, F.; Simonyi, M.; Antus, S.; Randriantsoa, A.; Hostettmann, K. Helv. Chim. Acta 2001, 84, 3470.

5) (a) Fujii, K.; Maki, K.; Kanai, M.; Shibasaki, M. Org. Lett. 2003, 5, 733. (b) Maki, K.; Motoki, R.; Fujii, K.; Kanai, M.; Kobayashi, T.; Tamura, S.; Shibasaki, M. J. Am. Chem. Soc. 2005, 127, 17111

6) (a) Tunac, J. B.; Graham, B. D.; Dobson, W. E. J. Antibiot. 1983, 36, 1595. (b) Stampwala, S. S.; Bunge, R. H.; Hurley, T. R.; Wilmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. J. Antibiot. 1983, 36, 1601.

7) For selected examples see: (a) Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, *68*, 5593. (b) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556. (c) Kobayashi, S.; Nishio, K. *Synthesis* **1994**, 457. (d) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem*. **1994**, *59*, 6161 (e) Denmark, S. E.;

Fu, J. *J. Am. Chem. Soc*. **2000**, *122*, 12021. (f) Malkov, A. V.; Dufková, L.; Farrugia, L.; Kočovský, P. *Angew. Chem., Int. Ed*. **2003**, *42*, 3274. (g) Malkov, A. V.; Ramírez-López, P.; Biedermannová, L.; RulíšeK, L.; Dufková, L.; Kotora, M.; Zhu, F.; Kočovský, P. *J. Am. Chem. Soc*. **2008**, *130*, 5341.

8) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc*. **1993**, *115*, 7001. (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc*. **1993**, *115*, 8467. (c) Xia, G.; Shibatomi, K.; Yamamoto, H. *Synlett* **2004**, 2437. (d) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc*. **2003**, *125*, 1708. (e) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc*. **1996**, *118*, 4723.

9) For selected examples of chirally modified allyl reagents, see: (a) Brown, H. C. and Jadhav, P. K. *J. Am. Chem. Soc*. **1983**, *105*, 2092. (b) Brown, H. C. and Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (c) Roush, W. R., Walts, A. E., and Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (d) Chen, M., Handa, M., and Roush, W. R. *J. Am. Chem. Soc*. **2009**, *131*, 14602. (e) Kister, J., DeBaillie, A. C., Lira, R., and Roush, W. R. *J. Am. Chem. Soc*. **2009**, *131*, 14175. (f) Short, R. P. and Masamune, S. *J. Am. Chem. Soc*. **1989**, *111*, 1892. (g) Corey, E. J., Yu, C. M., and Kim, S. S. *J. Am. Chem. Soc*. **1989**, *111*, 5495. (h) Seebach, D., Beck, A. K., Imwinkelzied, R., Roggo, S., and Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954. (i) Riediker, M. and Duthaler, R. O. *Angew. Chem., Int. Ed. Engl*. **1989**, *28*, 494. (j) Panek, J. S. and Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594. (k) Kinnaird, I. W. A., Ng, P. Y., Kubota, K., Wang, X., and Leighton, J. L. *J. Am. Chem. Soc*. **2002**, *124*, 7920. (l) Hackman, B. M., Lombardi, P. J., and Leighton, J. L. *Org. Lett*. **2004**, *6*, 4375. (m) Wu, T. R., Shen, L., and Chong, J. M. *Org. Lett*. **2004**, *6*,

2701. (n) Burgos, C. H., Canales, E., Matos, K., and Soderquist, J. A. *J. Am. Chem. Soc*. **2005**, *127*, 8044. (o) Gonzalez, A. Z., Roman, I. G., Alicea, E., Canales, E., and Soderquist, J. A. *J. Am. Chem. Soc*. **2009**, *131*, 1269. (p) Althaus, M., Mahmood, A., Suarez, J. R., Thomas, S. P., and Aggarwal, V. K. *J. Am. Chem. Soc*. **2010**, *132*, 4025. (q) Kim, H.; Ho, S.; Leighton, L. *J. Am. Chem. Soc*. **2011**, *133*, 6517. (r) Reetz, M. T.; Zierke, T. *Chem. Ind.* **1988**, 663. (s) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701.

10) For examples of catalytic allylborations, see: (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586. (b) Ishiyama, T.; Ahiko, T. –A.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414. (c) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518. (d) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808. (e) Rauniyar, V.; Hall, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2426. (f) Hall, D. G. *Synlett* **2007**, 1644. (g) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481. (h) Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236. (i) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8911. (j) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660. (k) Barnett, D. S.; Moquist, P. N.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8679. (l) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. J. Am. Chem. Soc. 2003, 125, 10160−10161.

11) For reviews on use of allyl alcohols, see: Tamaru, Y. *Eur. J. Org. Chem*. **2005**, 2647.

12) For selected examples, see: (a) Zanoni, G.; Gladiali, S.; Marchetti, A.; Piccinini, P.; Tredici, I.; Vidari, G. *Angew. Chem., Int. Ed*. **2004**, *43*, 846. (b) Ngai, M.-Y.; Kong, J.-R.; Krische, M. J. *J. Org. Chem*. **2007**, *72*, 1063. (c) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed*. **2009**, *48*, 34. (d) Kim, I. S.; Ngai, M.-Y.;

Krische, M. J. *J. Am. Chem. Soc*. **2008**, *130*, 6340. (e) Zbieg, J. R.; Moran, J.; Krische, M. J. *J. Am. Chem. Soc*. **2011**, *133*, 10582. (f) R. A.-M; Dechert-Schmitt; Schmitt, D. C.; Krische, M. J. *Angew. Chem., Int. Ed*. **2013**, *125*, 3277.

13) For selected examples, see: (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc*. **1977**, *99*, 3179. (b) Miller, J. J.; Sigman, M. S. *Angew. Chem., Int. Ed*. **2008**, *47*, 771. (c) McManus, H. A.; Cozzi, P. G.; Guiry, P. J. *Adv. Synth. Catal*. **2006**, *348*, 551 (d) Haddad, T. D.; Hirayama, L. C.; Singaram, B. *J. Org. Chem*. **2010**, *75*, 642.

14) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655

15) Mikhailov, B. M.; Bubnov, Y. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1964**, 1874.

16) (a) Hoffmann, R. W. and Ladner, W. Tetrahedron Lett. 1979, 20, 4653. (b) Hoffmann, R. W.; Zeiss, H. J. *Angew*. *Chem*., *Int. Ed. Engl.* **1979**, *18*, 306. (c) Hoffmann, R. W.; Zeiss, H. J. *J. Org. Chem.* **1981**, *46*, 1309.

17) For recent selected examples, see: (a) Trost, B. M.; Rey, J. *Org. Lett.* **2012**, *14*, 5632. (b) Albury, A. M. M.; Jennings, M. P. *J. Org. Chem*. **2012**, *77*, 6929. (c) Kikumori, M.; Yanagita, R.C.; Tokuda, H.; Suzuki, N.; Nagai, H.; Suenaga, K.; Irie K. *J. Med. Chem*. **2012**, *55*, 5614. (d) Wang, B.; Hansen, T. M.; Wang, T.; Wu, D.; Weyer, L.; Ying, L.; Engler, M. M.; Sanville, M.; Leitheiser, C.; Christmann, M.; Lu, Y.; Chen, J.; Zunker, N.; Cink, R. D.; Ahmed, F.; Lee, C.-S.; Forsyth, C. J. *J. Am. Chem. Soc*. **2011**, *133*, 1484. (e) Zhu, K.; Panek, J. S. *Org. Lett*. **2011**, *13*, 4652– 4655. (f) Martinez-Solorio, D.; Belmore, K. A.; Jennings, M. P. *J. Org. Chem.* **2011**, *76*, 3898. (g) Kumar, P.; Pandey, M.; Gupta, P.; Naidu., V.; Dhavale, D. D. *Eur. J. Org. Chem*. **2010**, *36*, 6993.

18) For selected examples, see: (a) Ireland, R. E.; Armstrong, J. D., III; Lebreton, J.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc*. **1993**, *115*, 7152. (b) Ramachandran,

P. V.; Prabhudas, B.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem*. **2004**, *69*, 6294. (c) Gao, D.; O'Doherty, G. A. *Org. Lett*. **2005**, *7*, 1069. (d) Gao, D.; O'Doherty, G. A. *J. Org. Chem*. **2005**, *70*, 9932 (e) Liu, D.; Xue, J.; Xie, Z.; Wei, L.; Zhang, X.; Li, Y. *Synlett* **2008**, 1526.

19) Ishihara, K., Kaneeda, M., and Yamamoto, H. J. Am. Chem. Soc. 1994, 116, 11179.

20) For representative reviews, see: (a) Brown, H. C.; Singaram, B. *Pure Appl. Chem*. **1987**, *59*, 879. (b) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457. (c) Asymmetric Synthesis, 2nd ed.; Christmann, M.; Braese, S., Eds.; Wiley-VCH: Weinheim, 2008 (d) Thomas, S. P.; French, R. M.; Jheengut, V.; Aggarwal, V. K. *Chem. Rec*. **2009**, *9*, 24 (e) Hugo, H.; Hall, D. Org. React. 2008, 73, 1. (f) Boronic Acids*: Preparation and Application in Organic Synthesis, Medicine and Materials*, 2nd ed. Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2011.

21) Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett*. **2012**, *14*, 1416.

22) Clary, J.W.; Rettenmaier, T. J.; Snelling, R.; Bryks, W.; Banwell, J.; Wipke, W. T. Singaram, B. *J. Org. Chem.* **2011**, *76*, 9601.

23) (a) Akiyama, T. *Chem. Rev*. **2007**, *107*, 5744. (b) Terada, M. *Chem. Commun*. **2008**, 4097.

24) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804.

25) (a) Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4122. (b) Momiyama, N.; Tabuse, H.; Terada, M. *J. Am. Chem. Soc.* **2009**, *131*, 12882. (c) Sun, F.-L.; Zeng, M.; Gu, Q.; You, S.-L. *Chem. Eur. J.* **2009**, *15*, 8709.

26) . Both enantiomers of **TRIP-PA** (*R* and *S*) are commercially available or easily prepared from BINOL using a literature procedure see: (a) Klussmann, M.; Hoffmann, S.;. Wakchaure, V.; Goddard, R.; *List*, B. *Synlett 2010*, 14, 2189. Asymmetric Propargylation of Aldehydes

27) For computational aspects of chiral-BINOL phosphoric acid catalyzed allylboration and propargylations, see: (a) Grayson, M. N.; Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc*. **2012**, *134*, 2716. (b) Wang, H.; Jain, P.; Antilla, J. C.; Houk, K. N. *J. Org. Chem*. **2013**, *78*, 1208. (c) Grayson, M. N.; Goodman, J. M. *J. Am. Chem. Soc*. **2013**, *135*, 6142.

28) Wadamoto, M.; Ozasa, N.; Yanagigawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, *68*, 5593.

29) Wu. T. R.; Shen, L.; Chong, M. *Org. Lett.* **2004**, *6*, 2701.

30) Burgos, C. H.; Canales, E.; Matos, K.; Soderquiest, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044.

31) Zheng, Y.; Zhou, J.; Loh. T. *Org. Lett.* **1999**, *11*, 1855.

32) Kim, I. S.; Ngai, M.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891.

33) Bold, G.; Duthaler, R. D.; Riediker, M. *Angew. Chem.* **1989**, *101*, 491.

34) Singh, S.; Kumar, S.; Chimni, S. S. *Tetrahedron Asym.* **2002**, *13*, 2679.

35) Xia, G; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 2554.

36) Malkov, A.; Dufkova, L.; Farrugia, L.; Kocovsky, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3674.

37) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481.

38) Lee, J.; Miller, J. J.; Hamilton, S. S.; Sigman, S. S. *Org. Lett.* **2005**, *7*, 1837.

2 Asymmetric Propargylation of Aldehydes

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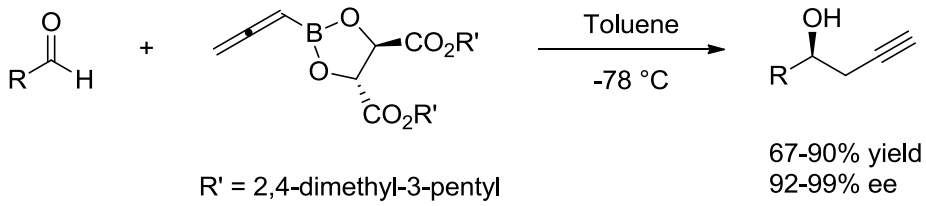
2.1 Introduction

Carbonyl propargylation reaction represents a very important transformation in organic synthesis producing homopropargylic alcohols. Enantiomerically pure homopropargylic alcohols are highly useful intermediates, with broad synthetic utility. The terminal alkyne functionality serves as a synthetic handle for cross-coupling, metathesis, and heterocycle synthesis.[1] The addition of allenic or propargylic reagents to carbonyl compounds is mechanistically similar to the analogous reaction with allylic reagents. Though many useful and innovative methods exist for the synthesis of homoallylic alcohols,[2] the enantioselective synthesis of homopropargylic alcohols remains arduous. Two main complications are 1) the lower reactivity of the allenylic and propargylic substrates in comparison to allylic substrates, and 2) the difficulties associated with controlling the reaction regioselectivity.[3] Herein, we describe a highly enantioselective catalytic method for the preparation of homopropargylic alcohols.

Many current methods for enantioselective propargylation reactions rely upon the use of chiral reagents.[4] Alternative catalytic methods have been developed, but are limited to the use of allenylic or propargylic metal-based reagents or intermediates.[2a,5] Despite notable work, many of these methods are restricted by one or more limitations. Among them are 1) the use of reagents that are relatively difficult to prepare or are unstable to air and/or moisture, 2) the use of undesirable metal reagents or catalysts, and 3) regioselectivity concerns.

2.2 Chiral reagents

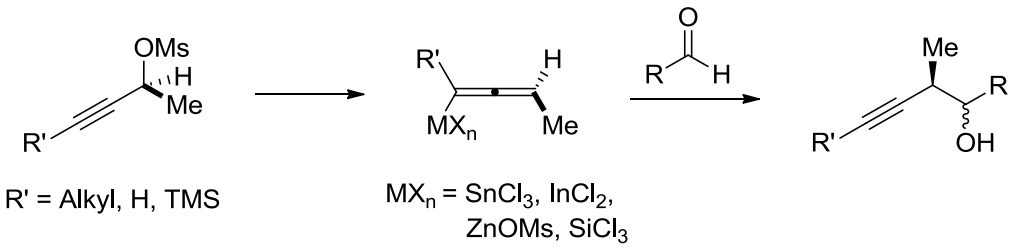
In 1982, Yamamoto reported the first asymmetric propargylation of carbonyl compounds by adding tartarate-derived chiral allenyl boronic esters to aldehydes (Scheme 2.1).[4b] Homopropargylaic alcohols were obtained with excellent regiocontrol and enantioselectivities. As the reaction proceeds via cyclic transition state, the regioselectivities were effectively controlled with the reaction occurring only at the γ-position of allenyl boron reagent.



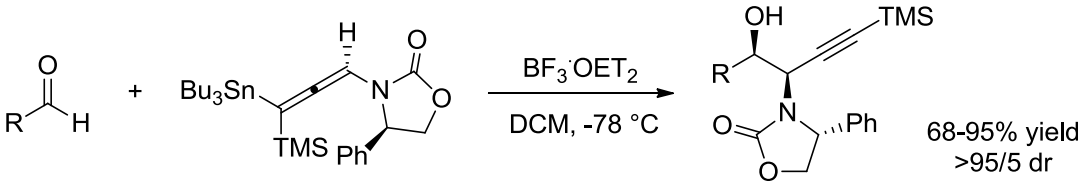
Scheme 2.1 Yamamoto's propargylation using tartarate-derived boronates

Marshall and co-workers made significant contributions to the asymmetric carbonyl propargylation reactions by utilizing chiral allenic organometallic reagents like allenylstannanes, allenylsilanes, allenyl zinc and indium reagents.[6] All these reagents were synthesized in situ from chiral propargylic mesylate intermediates and the corresponding metal reagents. The homopropargylic alcohols were synthesized with multiple chiral centers and high diastereoselectivities (Scheme 2.2). These alcohols with more than one stereocenters served as valuable intermediates in polyketide construction.

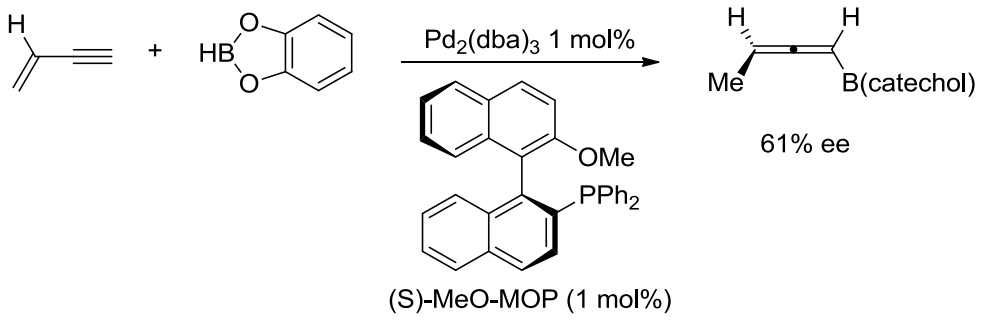
Hegedus efficiently synthesized α-oxazolidinonylallenylstannanes and reacted them with broad range of aldehydes in presence of $BF_3 \cdot OEt_2$ to obtain β-hyroxypropargylamines with high *syn* diastereoselectivities (Scheme 2.3).[7a]



Scheme 2.2 Marshall's synthesis of chiral homopropargylic alcohols



Scheme 2.3 Synthesis of β-hyroxypropargylamines

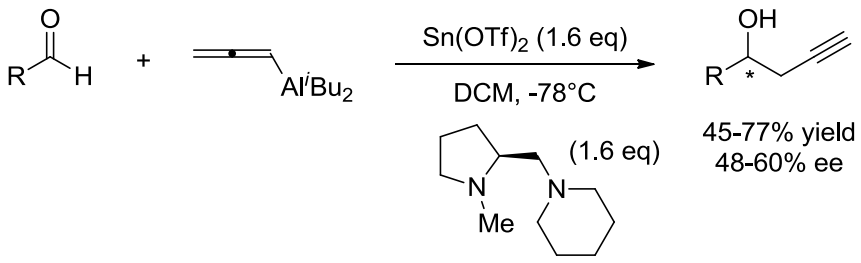


Scheme 2.4 Hayashi's synthesis of homopropargyl alcohols

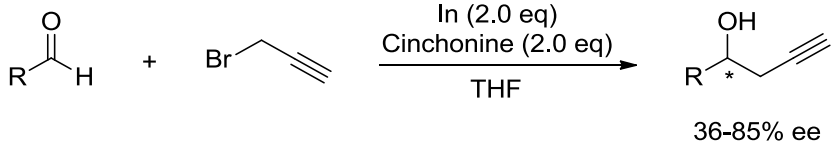
Hayashi reported the asymmetric propargylation of aldehydes with moderate selectivities via the in situ formation of a chiral allene by reacting catecholborane with but-1-en-3-yne in presence of chiral monodentate phosphine ligand and catalytic amounts of chiral palladium complex (Scheme 2.4).[7b]

2.3 Stoichiometric external chiral source

Mukaiyama reported the propargylation of aldehydes allenic aluminum reagents with 1.6 equivalents of chiral diamine and tin triflate (Scheme 2.5). Though this reaction gave only moderate enantioselectivities (48-60%) it showed excellent regioselectivities.[8a] Loh reported good enantioselectivities with indium mediated propargylations with stoichiometric amounts of cinchona alkaloids under Barbier-type conditions (Scheme 2.6).[8b] This method was successfully used in the total synthesis of bongkrekic and isobongkrekic acids.[8c]



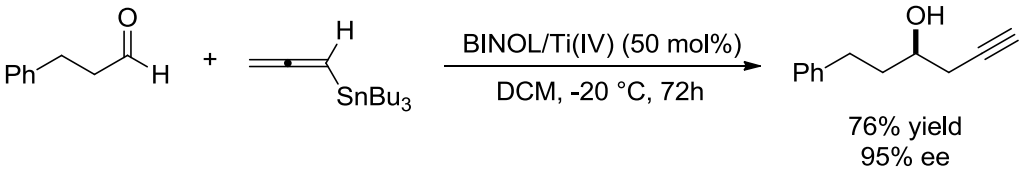
Scheme 2.5 Asymmetric propargylation with chiral diamine as external chiral source



Scheme 2.6 Use of chichona alkaloids as external chiral source

In 1994, Keck extended his allylation method to the propargylation of aldehydes. Allenyl stannane reacted with aldehydes in the presence of stoichiometric amounts for BINOL/Ti(IV) complex (Scheme 2.7).[8d] It was later discovered that the addition of stoichimetric amounts of

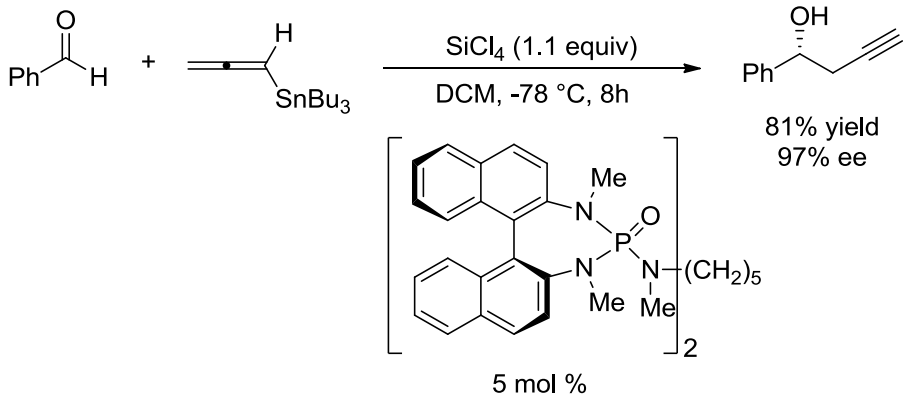
$B(OMe)_3$ or *i*-$PrSBEt_2$ enhanced the reaction rate for propargylation of aldehydes and also made it possible to use only catalytic amounts of Lewis acids.



Scheme 2.7 Keck's asymmetric propargylation

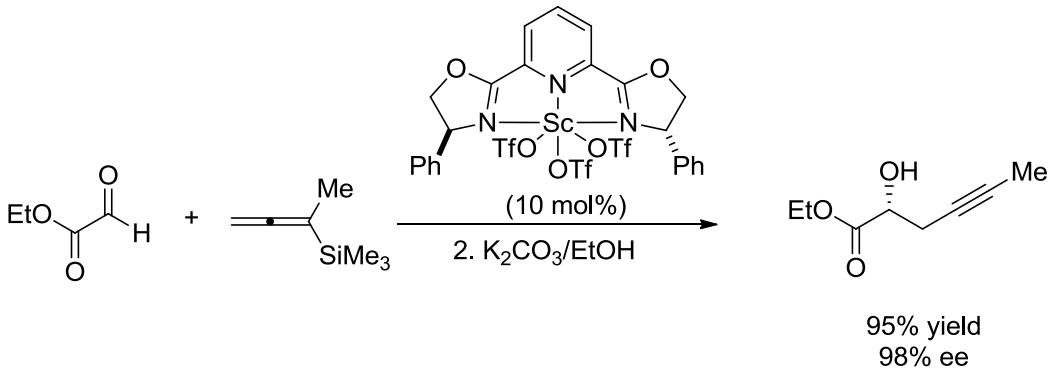
2.4 Catalytic methods

Chiral phosphoramides (5 mol%) with $SiCl_4$ were used by Denmark to carryout propargylation of aldehydes with allenyl stannanes (Scheme 2.8).[9a] This methodology provided the homopropargylic alcohols in high yields and enantioselectivities.



Scheme 2.8 Synthesis of homopropargylic alcohols with phosphoramide as catalyst

Allenic trimethylsilanes were utilized by Evans to propargylate ethyl glyoxalate with the bis(oxazolinyl)pyridine-scandium triflate as catalyst to obtain the homopropargyl alcohols with excellent yields and enantioselectivities (Scheme 2.9).[9b]



Scheme 2.9 Propargylation with bis(oxazolinyl)pyridine-scandium triflate as catalyst

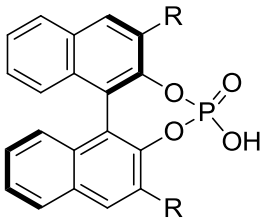
2.5 Limitations of the current asymmetric propargylation reactions

The versatility of homopropargylic alcohols to serve as intermediates in the synthesis of various complex organic compounds makes it very important to prepare these alcohols in an asymmetric fashion with methods that are very efficient and practical. Though significant progress made towards allylation reaction, the mechanistically similar propargylation reaction has been sparsely studied. The main reason being the lower reactivity of the propargyl reagents compared to the allyl reactions and the difficulties associated with controlling the regioselectivity of the reaction. Most the current methods are limited by one or more drawbacks. These include: the difficulties associated with the synthesis of reagents, reagents that are very sensitive to air and/or moisture, use of tin derived reagents or catalysts, reactions that have to be performed at -78 °C, conditions suitable for either aliphatic or aromatic substrates only, high catalyst loading and lower reactivity of the reagents leading to narrow substrate scope.

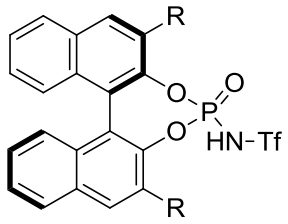
2.6 Optimization of propargylation reaction

In the past decade, Lewis and Brønsted acid-catalyzed allylboration reactions have fascinated the synthetic community.[10,11] However, this methodology remains relatively undeveloped for the more challenging allenylboration of aldehydes. Following our work on the development of a

chiral phosphoric acid-catalyzed allylboration,[11] we examined the extension of our methodology to the enantioselective propargylation of aldehydes. We began our investigation with the reaction of benzaldehyde and allenyl boronic acid pinacol ester. Boronate **2** is a relatively stable, non-toxic and commercially available reagent. The C-C bond formation proceeded smoothly in the presence of various chiral acid catalysts (Figure 2.1),[12] with complete control over the regioselectivity (Table 1.1). **PA5**[13] afforded product **3** with the highest enantioselectivity, when toluene was used as the reaction solvent. An increase to 87% *ee* was seen with the use of higher catalyst loading, in the presence of 4Å M.S. (entry 13). The enantioselectivity could be further increased, when the reaction was conducted at lower reaction temperatures of 0 °C (entry 14) and -20 °C (entry 15), albeit with longer reaction times.



PA1: R = $SiPh_3$
PA2: R = β-Napthyl
PA3: R = 9-anthryl
PA4: R = α-Napthyl
PA5: R = (2,4,6-*i*-Pr)-C_6H_2
PA6: R = (3,5-CF_3)-C_6H_3



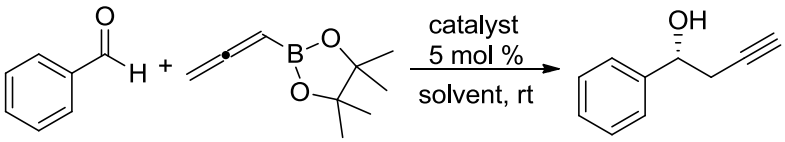
PA7: R = (2,4,6-*i*-Pr)-C_6H_2

Figure 2.1 Catalysts screened for asymmetric propargylation

2.7 Substrate scope

With the optimized conditions in hand,[14] a variety of aldehydes with different electronic and steric properties were tested to study the scope and the limitation of the developed methodology (Table 2.2). The reaction proved tolerant to electron-donating and electron-withdrawing groups (**1a-1j**), giving excellent yields and enantioselectivities (92-96% ee). The methodology was

Table 2.1Optimization of asymmetric porpargylation



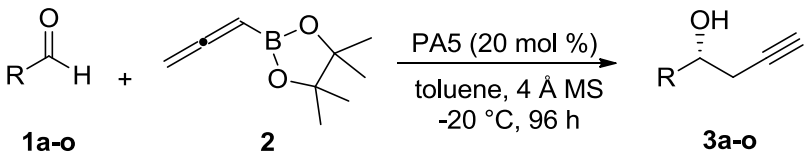
1 **2** **3**

entry	catalyst[b]	solvent	time (h)	yield (%)[c]	ee (%)[d]
1	PA1	toluene	40	94	0
2	PA2	toluene	40	93	7
3	PA3	toluene	40	92	20
4	PA4	toluene	40	95	9
5	PA5	toluene	40	91	74
6	PA6	toluene	40	93	4
7	PA7	toluene	40	94	16
8	PA5	benzene	40	89	62
9	PA5	DCM	40	87	43
10	PA5	$PhCF_3$	40	94	68
11	PA5	p-xylene[e]	40	92	75
12	PA5	toluene[e]	40	92	77
13	PA5	toluene[e,f]	24	93	87
14	PA5	toluene[e,f,g]	64	96	90
15	PA5	toluene[e,f,h]	72	94	91

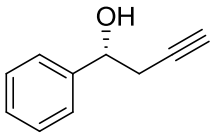
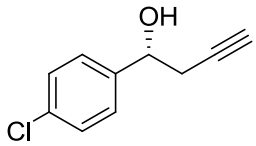
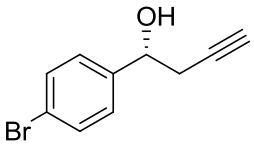
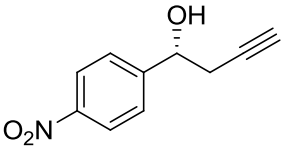
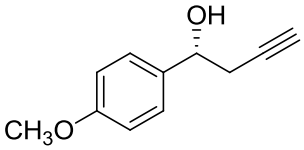
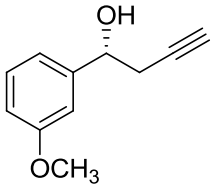
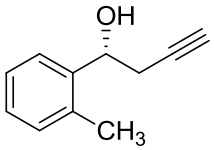
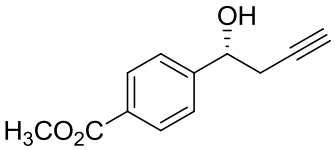
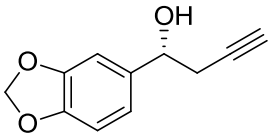
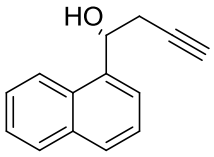
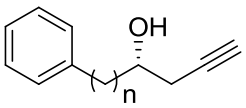
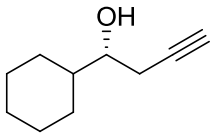
[a] Reaction conditions: 1 (0.10 mmol), 2 (0.12 mmol), catalyst (5 mol %), unless otherwise specified. [b] All catalysts were washed with 6 M HCl after purification by column chromatography. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] Reaction conducted in presence of 4Å M.S. [f] 20 mol % catalyst used. [g] Reaction conducted at 0 °C. [h] Reaction conducted at -20 °C.

extended to aliphatic aldehydes (**1k-1m**), furnishing the corresponding homopropargylic alcohol products **3k-m** in 77-82% *ee*.

Table 2.2 Substrate scope for asymmetric propargylation



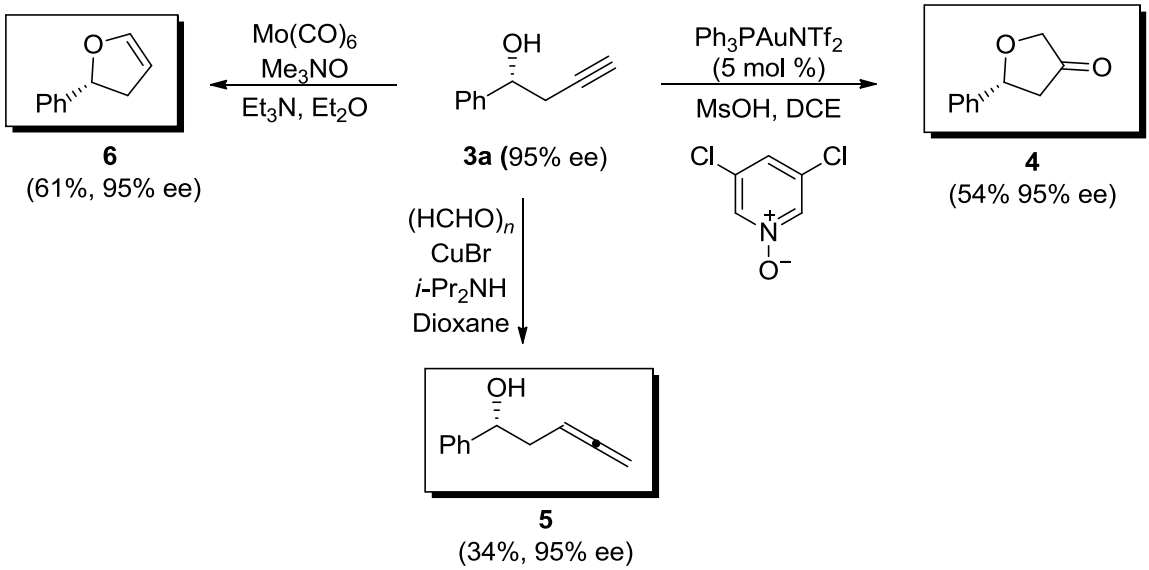
1a-o **2** **3a-o**

		
94%, 91% ee, **3a**	95%, 93% ee, **3b**	93%, 93% ee, **3c**
		
96%, 93% ee, **3d**[b]	87%, 92% ee, **3e**	92%, 96% ee, **3f**
		
91%, 92% ee, **3g**[b]	94%, 91% ee, **3h**[b]	92%, 94% ee, **3i**[b]
		
93%, 91% ee, **3j**	90%, 79% ee, **3k**[c] (n=1) 92%, 82% ee, **3l** (n=2)	89%, 77% ee, **3m**[d]

[a] Reaction conditions: 1 (0.20 mmol), 2 (0.30 mmol), PA5 (20 mol %). Yields are of isolated product. Enantioselectivity was determined by chiral HPLC. The products were determined to be (R) based on comparison to chiral HPLC analysis and optical rotation data reported in the literature. [b] The products were determined to be (R) by analogy. [c] (S) isomer was obtained. [d] Enantioselectivity was determined by 1H NMR after conversion to the corresponding Mosher ester.

2.8 Synthetic scaffolds synthesized from homopropargylic alcohols

We prepared several important synthetic scaffolds, previously unprepared from enantio-enriched homopropargylic alcohols (Scheme 2.10). Chiral dihydrofuran-3-ones, such as **4**, are important building blocks[15] for the synthesis of biologically active compounds. Despite their importance, a general enantioselective synthesis for this class of molecule has yet to be reported. We successfully transformed **3a**[16] into dihydrofuran-3-one **4**, by employing gold-catalyzed reaction methodology developed by Zhang and co-workers,[17] with complete preservation of the enantiomeric excess. Crabbe´ homologation of **3a** provided optically active 3,4-allenol **5**, which has the potential to serve as a substrate in natural product synthesis.[18] Chiral dihydrofuran **6**, currently dependent on the Heck reaction for its synthesis,[19] was obtained through a molybdenum-mediated cycloisomerization of **3a**, based on methodology developed by McDonald and co-workers.[20]



Scheme 2.10 Synthesis of important chiral moieties

2.9 Mechanistic insights

It is our belief that the propargylation proceeds via a six- membered cyclic transition state, where catalyst activation operates by protonation of the boronate oxygen. To further understand the mechanism and stereoselectivity of this phosphoric acid-catalyzed propargylation reaction, we performed theoretical calculations. Calculated energies of different pathways for allylboration[21] and propargylation showed that Brønsted acids form a strong hydrogen bond with the pseudo-equatorial oxygen of the allenyl boronate. The detailed results of the theoretical calculations performed by the research labs of Goodman and Houk independently are discussed in chapter 4.

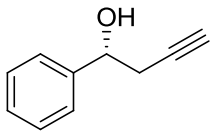
2.10 Conclusion

In summary, we have developed the first Brønsted acid-catalyzed propargylation of aldehydes, for the synthesis of chiral homopropargylic alcohols. The reaction is simple and highly efficient, demonstrating broad synthetic utility. The usefulness of this organocatalytic reaction is highlighted by the stability and commercial availability of the substrates and the catalyst. The homopropargylic alcohols were converted to different synthetic scaffolds while retaining the chiral center to demonstrate its versatility and utility. We believe the reaction proceeds via a type I mechanism, similar to the allylation reaction, involving a chairlike six-membered cyclic transition state. The hydrogen bonding between the catalyst and boronate oxygen might have an important role in catalysis and attaining enantioselectivity. This methodology makes it much easier to synthesize chiral homopropargylic alcohols and hence has the potential to increases the use of these versatile intermediates in organic synthesis.

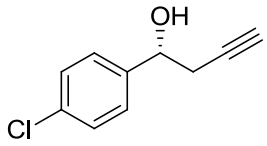
2.11 Experimental

General Considerations: All reactions were carried out in flame-dried screw-cap test tubes and were allowed to proceed under a dry argon atmosphere with magnetic stirring. Toluene was purified by passing through a column of activated alumina under a dry argon atmosphere. Aldehydes were purchased from commercial sources and were distilled prior to use. TRIP catalyst was prepared from chiral BINOL according to the known literature procedure. Thin layer chromatography was performed on Merck TLC plates (silica gel 60 F_{254}). Visualization was accomplished UV light (256 nm), with the combination of ceric ammonium molybdate or potassium permanganate as indicator. Flash column chromatography was performed with Merck silica gel (230-400 mesh). Enantiomeric excess (ee) was determined using a Varian Prostar HPLC with a 210 binary pump and a 335 diode array detector. Optical rotations were performed on a Rudolph Research Analytical Autopol IV polarimeter (λ 589) using a 700-μL cell with a path length of 1-dm. ^{1}H NMR and ^{13}C NMR were recorded on a Varian Inova-400 spectrometer with chemical shifts reported relative to tetramethylsilane (TMS). All the compounds were known compounds and were characterized by comparing their ^{1}H NMR and ^{13}C NMR values to the reported values.

General procedure for the propargylation of aldehydes: A screw-cap reaction tube loaded with a stir bar and 4 Å MS (100 mg) was evacuated, flame-dried, and back-filled with argon. To this tube was added the (*R*)-TRIP-PA catalyst **PA5** (20 mol %), freshly distilled aldehyde (0.20 mmol) and 1.5 ml of dry toluene. The reaction mixture was then cooled to -20 °C followed by the addition of allenylboronic acid pinacol ester **2** (0.30 mmol), slowly over 30 seconds. The mixture was stirred for 96 hours at this temperature and then directly loaded on to a silica gel column and was purified by flash chromatography using ethyl acetate and hexanes (1 : 9).

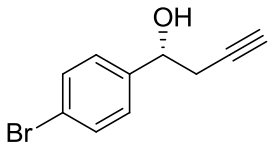


(*R*)-1-Phenyl-but-3-yn-1-ol (3a): Following the general procedure for the propargylation of aldehydes in 2 mmol scale (benzaldhyde), the title compound was obtained in 95 % yield with spectral properties reported in literature.[22] (94% yield, 91% ee was obtained when the reaction was run at 0.2 mmol scale following the general procedure for propargylation). Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 95/5, 1.0 mL/min), t_{major} = 10.49 min, t_{minor} 12.81 min; ee = 95%. $[\alpha]^{25}_{D}$ = +10.10 (c = 0.9, MeOH). The reported value[22] for the *R*-enantiomer (98% ee) is $[\alpha]^{24}_{D}$ = +12.9 (c = 1.55, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.21 (m, 5H), 4.86 (td, *J* = 6.5, 2.6 Hz, 1H), 2.69 – 2.55 (m, 2H), 2.36 (s, 1H), 2.06 (t, *J* = 2.8 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.39, 128.45, 127.96, 125.70, 80.62, 72.30, 70.94, 29.42

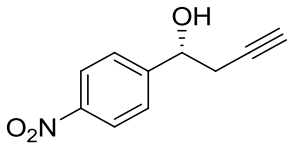


(*R*)-1-(4-Chloro-phenyl)-but-3-yn-1-ol (3b): Following the general procedure for the propargylation of aldehydes, the title compound was obtained in 95 % yield with spectral properties reported in literature.[23,24] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 98/2, 1.0 mL/min), t_{major} = 18.56 min, t_{minor} = 20.32 min; ee = 93%. $[\alpha]^{25}_{D}$ = +21.50 (c = 2.7, $CHCl_3$). The reported value[24] for the *S*-enantiomer (88% ee) is $[\alpha]^{20}_{D}$ = -35.9 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 4H), 4.83 (td, *J* =

6.5, 3.1 Hz, 1H), 2.69 – 2.51 (m, 2H), 2.40 (d, J = 3.3 Hz, 1H), 2.06 (t, J = 2.6 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.08, 133.91, 128.84, 127.38, 80.39, 71.85, 71.56, 29.70.

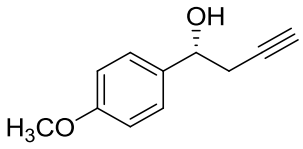


(*R*)-1-(4-Bromo-phenyl)-but-3-yn-1-ol (3c): Following the general procedure for the propargylation of aldehydes, the title compound was obtained in 93 % yield with spectral properties reported in literature.[25] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 98/2, 1.0 mL/min), t_{major} = 20.00 min, t_{minor} = 22.15 min; ee = 93%. $[\alpha]^{25}_D$ = +19.52 (c = 2.15, $CHCl_3$). The reported value[25] for the *S*-enantiomer (81% ee) is $[\alpha]_D$ = -28.4 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.36 (m, 2H), 7.29-7.15 (m, 2H), 4.85-4.72 (m, 1H), 2.66-2.50 (m, 2H), 2.37 (br s, 1H), 2.07-1.97 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.59, 131.78, 127.71, 122.03, 80.34, 71.87, 71.58, 29.64.

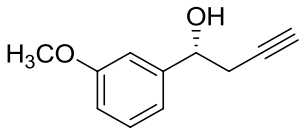


(*R*)-1-(4-Nitro-phenyl)-but-3-yn-1-ol (3d): Following the general procedure for the propargylation of aldehydes, the title compound was obtained in 96 % yield with spectral properties reported in literature.[26] Enantiomeric excess was determined by HPLC with a chiralcel OJ-H column (hexane/iPrOH = 90/10, 1.0 mL/min), t_{minor} = 29.81 min, t_{major} = 32.92 min; ee = 93%. $[\alpha]^{25}_D$ = +3.48 (c = 0.37, $CHCl_3$). The absolute configuration was determined by analogy.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.09 (m, 2H), 7.68 – 7.45 (m, 2H), 5.02-4.95 (m, 1H), 2.75-2.56 (m, 3H), 2.10 (td, *J* = 2.6, 0.6 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 149.64, 147.79, 126.87, 123.88, 79.57, 72.18, 71.50, 29.70.

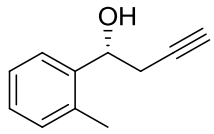


(*R*)-1-(4-Methoxy-phenyl)-but-3-yn-1-ol (3e): Following the general procedure for the propargylation of aldehydes, the title compound was obtained in 87 % yield with spectral properties reported in literature.[24,25] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 90/10, 1.0 mL/min), t_{major} = 8.64 min, t_{minor} = 10.53 min; ee = 92%. $[\alpha]^{25}_D$ = +33.60 (c = 1.45, $CHCl_3$). The reported value[24] for the *S*-enantiomer (89 % ee) is $[\alpha]^{28}_D$ = -36.2 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 6.92 – 6.86 (m, 2H), 4.84 (t, *J* = 6.4 Hz, 1H), 3.81 (s, 3H), 2.66-2.60 (m, 2H), 2.30 (br s, 1H), 2.07 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.56, 134.87, 127.23, 114.08, 81.03, 72.21, 71.08, 55.51, 29.61.

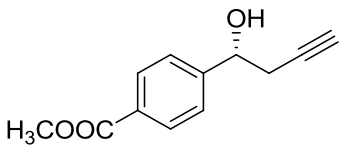


(*R*)-1-(3-Methoxy-phenyl)-but-3-yn-1-ol (3f): Following the general procedure for the propargylation of aldehydes, the title compound was obtained in 92 % yield with spectral properties reported in literature.[27] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 98/2, 1.0 mL/min), t_{major} = 34.28 min, t_{minor} = 39.96 min; ee =

96%. $[\alpha]^{25}_D$ = +7.09 (c = 0.34, $CHCl_3$). The absolute configuration was determined by analogy. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 1H), 6.97 – 6.90 (m, 2H), 6.82 (ddd, *J* = 8.2, 2.4, 1.1 Hz, 1H), 4.83 (td, *J* = 6.4, 3.4 Hz, 1H), 3.80 (s, 3H), 2.64 – 2.59 (m, 2H), 2.38 (d, *J* = 3.5 Hz, 1H), 2.06 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.95, 144.35, 129.74, 118.22, 113.68, 111.49, 80.86, 72.46, 71.21, 55.45, 29.65.

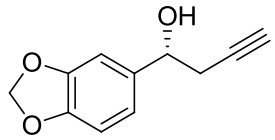


(*R*)-1-*o*-Tolyl-but-3-yn-1-ol (3g): Following the general procedure for the propargylation of aldehydes, the title compound was obtained in 91 % yield with spectral properties reported in literature.[25] Enantiomeric excess was determined by HPLC with a chiralcel AD-H column (hexane/iPrOH = 98/2, 1.0 mL/min), t_{major} = 16.61 min, t_{minor} = 21.21 min; ee = 92%. $[\alpha]^{25}_D$ = +35.57 (c = 1.96, $CHCl_3$). The reported value[25] for the *S*-enantiomer (89 % ee) is $[\alpha]^{25}_D$ = -63.2 (c = 0.58, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.4 Hz, 1H), 7.26-7.20 (m, 3H), 5.10 (dd, *J* = 7.3, 5.4 Hz, 1H), 2.62 – 2.57 (m, 2H), 2.35 (s, 3H), 2.32 (br s, 1H), 2.07 (td, *J* = 2.6, 0.8 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.69, 134.80, 130.66, 127.96, 126.55, 125.27, 81.13, 70.97, 69.10, 28.48, 19.27.

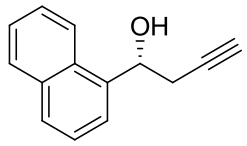


(*R*)-Methyl 4-(1-hydroxybut-3ynyl)benzoate (3h): Following the general procedure for the propargylation of aldehydes, the title compound was obtained in 94 % yield with spectral

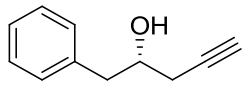
properties reported in literature.[28] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 90/10, 1.0 mL/min), t_{major} = 11.67 min, t_{minor} = 16.43 min; ee = 91%. $[\alpha]^{25}_{D}$ = +33.33 (c = 2.04, $CHCl_3$). The absolute configuration was determined by analogy. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 4.97 – 4.86 (m, 1H), 3.90 (d, *J* = 0.7 Hz, 3H), 2.76 – 2.50 (m, 3H), 2.07 (td, *J* = 2.6, 0.7 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.06, 147.63, 129.96, 129.88, 125.94, 80.24, 72.03, 71.60, 52.34, 29.60.



(*R*)-1-(Benzo[d][1,3]dioxol-5-yl)but-3-yn-1-ol (3i): Following the general procedure for the propargylation of aldehydes, the title compound was obtained in 92 % yield with spectral properties reported in literature.[29] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 95/5, 1.0 mL/min), t_{major} = 15.99 min, t_{minor} = 21.40 min; ee = 94%. $[\alpha]^{25}_{D}$ = +3.91 (c = 1.70, $CHCl_3$). The absolute configuration was determined by analogy. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 – 6.72 (m, 3H), 5.95 (s, 2H), 4.79 (td, *J* = 6.4, 3.0 Hz, 1H), 2.60 (dd, *J* = 6.6, 2.6 Hz, 2H), 2.33 (d, *J* = 3.2 Hz, 1H), 2.08 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.07, 147.56, 136.82, 119.54, 108.40, 106.58, 101.36, 80.90, 72.50, 71.30, 29.79.

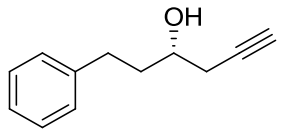


(*R*)-1-(Naphthalen-1-yl)but-3-yn-1-ol (3j): Following the general procedure for the propargylation of aldehydes, the title compound was obtained in 93 % yield with spectral properties reported in literature.[24,30] Enantiomeric excess was determined by HPLC with a chiralcel OJ-H column (hexane/iPrOH = 90/10, 1.0 mL/min), t_{minor} = 19.52 min, t_{major} = 24.85 min; ee = 91%. $[\alpha]^{25}_{D}$ = +60.64 (c = 1.96, PhH). The reported value[24] for the *S*-enantiomer (84 % ee) is $[\alpha]^{28}_{D}$ = -53.2 (c = 1, PhH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.3 Hz, 1H), 7.92 – 7.78 (m, 2H), 7.72 (d, *J* = 7.1 Hz, 1H), 7.58 – 7.45 (m, 3H), 5.67 (dd, *J* = 8.1, 4.0 Hz, 1H), 2.95-2.85 (m, 1H), 2.81-2.71 (m, 1H), 2.56 (br s, 1H), 2.15 (t, *J* = 2.4 Hz, 1H).^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.00, 133.99, 130.39, 129.25, 128.70, 126.50, 125.85, 125.61, 123.17, 122.97, 81.17, 71.46, 69.51, 28.90.

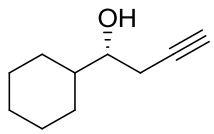


(*R*)-1-Phenylpent-4-yn-2-ol (3k): Following the general procedure for the propargylation of aldehydes, the title compound was obtained in 90 % yield with spectral properties reported in literature.[29] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 99/1, 1.0 mL/min), t_{minor} = 20.80 min, t_{major} = 23.85 min; ee = 79%. $[\alpha]^{25}_{D}$ = +0.53 (c = 0.55, $CHCl_3$). The absolute configuration was determined by analogy. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.13 (m, 5H), 4.06 – 3.88 (m, 1H), 2.95-2.78 (m, 2H), 2.49 – 2.30 (m,

2H), 2.09 (t, J = 2.7 Hz, 1H), 1.95 (d, J = 4.4 Hz, 1H).[13]C NMR (100.6 MHz, $CDCl_3$) δ 137.87, 129.61, 128.83, 126.90, 80.82, 71.33, 71.03, 42.70, 26.64.

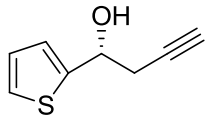


(*S*)-1-Phenylhex-5-yn-3-ol (3l): Following the general procedure for the propargylation of aldehydes, the title compound was obtained in 92 % yield with spectral properties reported in literature.[31] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 90/10, 1.0 mL/min), t_{major} = 6.97 min, t_{minor} = 9.67 min; ee = 82 %. $[\alpha]^{25}_D$ = -13.51 (c = 1.38, $CHCl_3$). The reported value[24] for the *R*-enantiomer (42 % ee) is $[\alpha]^{28}_D$ = +8.70 (c = 0.4, $CHCl_3$). [1]H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.08 (m, 5H), 3.83-3.70 (m, 1H), 2.86-2.63 (m, 2H), 2.50 – 2.24 (m, 2H), 2.05 (t, J = 2.6 Hz, 1H), 1.96 (d, J = 5.2 Hz, 1H), 1.90-1.82 (m, 2H).[13]C NMR (100.6 MHz, $CDCl_3$) δ 141.84, 128.65, 128.63, 126.14, 80.85, 71.22, 69.32, 37.99, 32.10, 27.72.

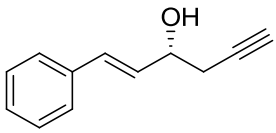


(*R*)-1-Cyclohexyl-but-3-en-1-ol (3m): Following the general procedure for the propargylation of aldehydes, the title compound was obtained in 89 % yield with spectral properties reported in literature.[24,31,32] Enantiomeric excess was determined to be 77 % by [1]H NMR of the crude

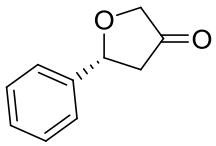
material after esterification with (*R*)-MTPACl by comparing the singlets at δ 3.62 (major) and 3.54 (minor).[24] $[\alpha]^{25}_{D}$ = +7.70 (c = 0.35, $CHCl_3$). The reported value[32] for the *R*-enantiomer (59% ee) is $[\alpha]^{20}_{D}$ = +7 (c = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54-3.45 (m, 1H), 2.50 – 2.27 (m, 2H), 2.05 (t, *J* = 2.6 Hz, 1H), 1.95 – 1.39 (m, 7H), 1.31 – 0.91 (m, 5H).^{13}C NMR (100.6 MHz, $CDCl_3$) δ 84.92, 74.23, 70.90, 42.72, 29.24, 28.39, 26.59, 26.33, 26.17, 24.85.



(*R*)-1-Thiophen-2-yl-but-3-yn-1-ol (3n): Following the general procedure for the propargylation of aldehydes, the title compound was obtained in 90 % yield with spectral properties reported in literature.[27] Enantiomeric excess was determined by HPLC with a chiralcel OJ-H column (hexane/iPrOH = 90/10, 1.0 mL/min), t_{minor} = 16.79 min, t_{major} = 18.16 min; ee = 77 %. $[\alpha]^{25}_{D}$ = -12.32 (c = 0.34, EtOH). The reported value[3] for the *S*-enantiomer (87 % ee) is $[\alpha]^{28}_{D}$ = +21.1 (c = 0.25, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 1H), 7.05 – 6.92 (m, 2H), 5.11 (t, *J* = 6.2 Hz, 1H), 2.79 – 2.69 (m, 2H), 2.46 (br s, 1H), 2.09 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 126.92, 125.19, 124.34, 80.22, 71.74, 68.76, 29.81.

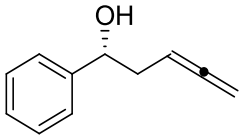


(*R*),(*E*)-1-Phenylhex-1-en-5-yn-3-ol (3o): Following the general procedure for the propargylation of aldehydes, the title compound was obtained in 86 % yield with spectral properties reported in literature.[22,31] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 90/10, 1.0 mL/min), t_{major} = 9.33 min, t_{minor} = 12.77 min; ee = 65 %. $[\alpha]^{25}_{D}$ = -42.17 (c = 0.27, PhH). The reported value[22] for the *R*-enantiomer (86 % ee) is $[\alpha]^{24}_{D}$ = -59.3 (c = 1.35, PhH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.18 (m, 5H), 6.65 (dd, *J* = 16.0, 0.9 Hz, 1H), 6.27 (dd, *J* = 15.9, 6.3 Hz, 1H), 4.46 (q, *J* = 5.4 Hz, 1H), 2.61 – 2.45 (m, 2H), 2.13 (br s, 1H), 2.08 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.55, 131.56, 130.18, 128.81, 128.11, 126.81, 80.42, 71.34, 70.93, 27.96.

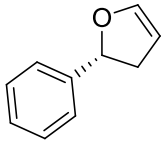


(*R*)-5-phenyldihydrofuran-3-one (4): Following Zhang's gold catalysis procedure,[28] while using 3,5-dichloropyridine *N*-oxide as the oxidant, the title compound was obtained in 54 % yield with spectral properties reported in literature.[28] Enantiomeric excess was determined by HPLC with a chiralcel OJ-H column (hexane/iPrOH = 90/10, 1.0 mL/min), t_{minor} = 20.27 min, t_{major} = 21.41 min; ee = 95 %. $[\alpha]^{25}_{D}$ = +67.61 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.32 (m, 5H), 5.29 (dd, *J* = 9.5, 6.3 Hz, 1H), 4.25 (d, *J* = 17.0 Hz, 1H), 4.02 (d, *J* = 17.0 Hz,

1H), 2.87 (dd, J = 17.9, 6.3 Hz, 1H), 2.55 (dd, J = 17.9, 9.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.38, 140.18, 128.94, 128.54, 126.07, 79.57, 71.95, 44.94.



(*R*)-1-phenylpenta-3,4-dien-1-ol (5): Following the reported procedure[33] the title compound was obtained in 34 % yield with spectral properties reported in literature.[33,34] Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/iPrOH = 90/10, 1.0 mL/min), t_{major} = 6.07 min, t_{minor} = 7.01 min; ee = 95 %. $[\alpha]^{25}_D$ = +45.88 (c = 0.60, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 4H), 7.31 – 7.27 (m, 1H), 5.12 (p, J = 7.0 Hz, 1H), 4.77 (t, J = 6.5 Hz, 1H), 4.72 (dt, J = 6.7, 2.8 Hz, 2H), 2.52 – 2.40 (m, 2H), 2.17 (br s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.70, 143.83, 128.63, 127.82, 126.06, 86.32, 75.28, 73.84, 38.70.



(*R*)-2-phenyl-2,3dihydrofuran (4): Following the literature procedure,[35] the title compound was obtained in 61 % yield with spectral properties reported in literature.[36] Enantiomeric excess was determined to be >94 % by chiral GC (80 °C for 2 min, increase 1 °C/min for 38 min, cyclodex-B column), t_{minor} = 18.65 min, t_{major} = 18.95 min; $[\alpha]^{25}_D$ = -28.10 (c = 0.23, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.24 (m, 5H), 6.49 – 6.43 (m, 1H), 5.53 (dd, J = 10.7, 8.4 Hz, 1H),

5.01 – 4.94 (m, 1H), 3.14 – 3.05 (m, 1H), 2.67 – 2.58 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.54, 143.26, 128.73, 127.84, 125.81, 99.24, 82.57, 38.07.

2.12 References

1) For selected examples, see: a) B. M. Trost, J. Dumas, M. Villa, *J. Am. Chem. Soc.* **1992**, *114*, 9836-9845. b) F. E. McDonald, M. M. Gleason, *J. Am. Chem. Soc.* **1996**, *118*, 6648-6659. c) D. R. Schmidt, S. J. O'Malley, J. L. Leighton, *J. Am. Chem. Soc.* **2003**, *125*, 1190-1191. d) P. T. O'Sullivan, W. Buhr, M. A. A. Fuhry, J. R. Harrison, J. E. Davies, N. Feeder, D. R. Marshall, J. W. Burton, A. B. Holmes, *J. Am. Chem. Soc.* **2004**, *126*, 2194-2207. e) B. M. Trost, G. Dong, *Nature,* **2008**, 456, 485-488. f) A. Francais, A. Leyva, G. Etxebarria-Jardi, S. V. Ley, *Org. Lett.* **2010**, *12*, 340-343.

2) For selected examples, see: a) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763-2794. b) H. C. Brown, P. K. Jadhav, *J. Am. Chem. Soc.* **1983**, *105*, 2092-2093. c) E. J. Corey, C. M. Yu, S. S. Kim, *J. Am. Chem. Soc.* **1989**, *111*, 5495-5496. d) G. E. Keck, K. H. Tarbet, L. S. Geraci, *J. Am. Chem. Soc.* **1993**, *115*, 8461-8462. e) C. H. Burgos, E. Canales, K. Matos, J. A. Soderquist, *J. Am. Chem. Soc.* **2005**, *127*, 8044-8049. f) H. Lachance, D. G. Hall, *Org. React.* **2008**, *73*, 1. g) M. Chen, M. Handa, W. R. Roush, *J. Am. Chem. Soc.* **2009**, *131*, 14602-14603. h) M. Althaus, A. Mahmood, J. R. Suarez, S. P. Thomas, V. K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 4025-4028.

3) H. Yamamoto, in comprehensive Organic Synthesis : Propargyl and *Allenyl Organometallics,* ed. C. H. Heathcock, Pergamon, Oxford, 1991, vol. 2, pp. 81-98.

4) a) N. Ikeda, I. Arai, H. Yamamoto, *J. Am. Chem. Soc.* **1986**, *108*, 483-486. b) R. Haruta, M. Ishiguro, N. Ikeda, H. Yamamoto, *J. Am. Chem. Soc.* **1982**, *104,* 7667-7669. c) E. J. Corey, C.–M. Yu, D.–H. Lee, *J. Am. Chem. Soc.* **1990**, *112,* 878-879. d) K.–C. Lee, M.–

J. Lin, T.–P. Loh, *Chem. Commun.* **2004**, 2456-2457. e) C. Lai, J. A. Soderquist, *Org. Lett.* **2005**, *7*, 799-802.

5) a) For reviews on asymmetric propargylation, see: a) C.–H. Ding, X.–L. Hou, *Chem. Rev.* **2011**, *111*, 1914-1937. For selected examples, see: b) G. P. Boldrini, E. Tagliavini, C. Trombini, A. Umani-Ronchi, *J. Chem. Soc., Chem. Commun.* **1986**, 685–686. c) N. Minowa, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3697–3704. d) G. E. Keck, D. Krishnamurthy, X. Chen, *Tetrahedron Lett.* **1994**, *35*, 8323–8324. e) C.–M. Yu, S.-K. Yoon, H.–S. Choi, K. Baek, *Chem. Commun.* **1997**, 763–764. f) C.–M. Yu, S.–K. Yoon, K. Baek, J.–Y. Lee, *Angew. Chem.* **1998**, *110*, 2504-2506; *Angew. Chem. Int. Ed.* **1998**, *37*, 2392–2395. g) K. Iseki, Y. Kuroki, Y. Kobayashi, *Tetrahedron: Asymmetry*, **1998**, *9*, 2889–2894. h) S. E. Denmark, T. Wynn, *J. Am. Chem. Soc.* **2001**, *123*, 6199–6200. i) D. A. Evans, Z. K. Sweeney, T. Rovis, J. S. Tedrow, *J. Am. Chem. Soc.* **2001**, *123*, 12095–12096. j) H. Hanawa, D. Uraguchi, S. Konishi, T. Hashimoto, K. Maruoka, *Chem.-Eur. J.* **2003**, *9*, 4405–4413. k) M. Inoue, M. Nakada, *Org. Lett.* **2004**, *6*, 2977–2980. l) M. Naodovic, G. Xia, H. Yamamoto, *Org. Lett.* **2008**, *10*, 4053–4055. m) D. R. Fandrick, K. R. Fandrick, J. T. Reeves, Z. Tan, W. Tang, A. G. Capacci, S. Rodriguez, J. J. Song, H. Lee, N. K.; Yee, C. H. Senanayake, *J. Am. Chem. Soc.* **2010**, *132*, 7600-7601. n) D. L. Usanov, H. Yamamoto, *Angew. Chem.* **2010**, *122*, 8245-8348; *Angew. Chem. Int. Ed.* **2010**, *49*, 8169 –8172. o) S.–L. Shi, L.–W. Xu, K. Oisaki, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 6638-6639. p) J. Chen, B. Captain, N. Takenaka, *Org. Lett.* **2011**, *13*, 1654-1657. q) B. M. Trost, M.–Y. Ngai, G. Dong, *Org. Lett.* **2011**, *13*, 1900-1903. r) For the lone example of catalytic asymmetric propargylation not involving the use of

allenylic or propargylic metal reagents or intermediates, see chiral biphenol catalyzed allenylboration of ketones: D. S. Barnett, S. E. Schaus, *Org. Lett.* **2011**, *13*, 4020-4023.

6) (a) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (b) Marshall, J. A. *Chem. Rev. 2000*, 100, 3163. (c) Marshall, J. A. J. Org. Chem. 2007, 72,8153.

7) (a) Ranslow, P. B. D.; Hegedus, L. S.; de los Rios, C. *J. Org. Chem*. **2004**, *69*, 105. (b) Matsumoto, Y.; Naito, M.; Uozumi, Y.; Hayashi, T. *J. Chem. Soc., Chem. Commun* **1993**, 1468.

8) (a) Minowa, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **1987**, *60,* 3697. (b) Loh, T.-P.; Lin, M.-J.; Tan, K.-L. *Tetrahedron Lett.* **2003**, *44*, 507. (c) Francais, A.; Leyva, A.; Etxebarria-Jardi, G.; Ley, S. V. *Org. Lett*. **2010**, *12*, 340. (d) Keck, G. E.; Krishnamurthy, D.; Chen, X. *Tetrahedron Lett*. **1994**, *35*, 8323.

9) (a) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc*. **2001**, *123*, 6199. (b) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc*. **2001**, *123*, 12095.

10) For selected examples, see: a) J. W. J. Kennedy, D. G. Hall, *J. Am. Chem. Soc.* **2002**, *124*, 11586-11587. b) T. Ishiyama, T.–A. Ahiko, N. Miyaura, *J. Am. Chem. Soc.* **2002**, *124*, 12414-12415. c) S. H. Yu, M. J. Ferguson, R. McDonald, D. G. Hall, *J. Am. Chem. Soc.* **2005**, *127*, 12808-12809. d) V. Rauniyar, D. G. Hall, *Angew. Chem.* **2006**, *118*, 2486-2488; *Angew. Chem., Int. Ed.* **2006**, *45*, 2426-2428. e) V. Rauniyar, H. Zhai, D. G. Hall, *J. Am. Chem. Soc.* **2008**, *130*, 8481-8490. f) For chiral biphenols catalyzed allylborations see: S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2006**, *128*, 12660-12661. S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2007**, *129*, 15398-15404. D. S. Barnett, P. N. Moquist, S. E. Schaus, *Angew.Chem. Int. Ed.* **2019**, *48*, 8679-8682.

11) (a) P. Jain, J. C. Antilla, *J. Am. Chem. Soc.* **2010**, *132*, 11884-11886. For reduction of ketones using phosphoric acid derived catalysts, see: (b) Z. Zhang, P. Jain, J. C. Antilla, *Angew. Chem.* **2011**, *123*, 11153-11156; *Angew. Chem., Int. Ed.* **2011**, *50*, 10961-10964.

12) For reviews on phosphoric acid catalysis, see: a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744-5758. b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713-5743. c) M. Terada, *Chem. Commun.* **2008**, 4097-4112.

13) Both enantiomers of **TRIP-PA** (*R* and *S*) are commercially available or easily prepared from BINOL using a literature procedure: S. Hoffmann, A. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590-7593; *Angew. Chem., Int. Ed.* **2005**, *44*, 7424-7427.

14) Though benzaldehyde showed >90% conversion within 48 h at -20 °C, the reaction time was not further optimized and all the substrates were allowed to react for 96 h to ensure complete conversion.

15) A Scifinder search of compounds with the dihydrofuran-3-one moiety resulted in more than 5000 entries with reported biological activities.

16) 95% *ee* was obtained for **3a** when the reaction was run on a larger scale (2 mmol, benzaldehyde) when comared to a run on the 0.2 mmol scale (91% *ee*) under identical conditions.

17) L. Ye, L. Cui, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 3258-3259.

18) (a) P. Crabbe´, B. Nassim, M.–T. Robert-Lopes, Org. Synth. 1985, 63, 203. b) S. Ma, H. Hou, S. Zhao, G. Wang, *Synthesis* **2002**, 1643-1645. c) X. Cheng, X. Jiang, Y. Yu, S. Ma. *J. Org. Chem.* **2008**, *73*, 8960-8965. d) V. Coeffard, M. Aylward, P. J. Guiry, *Angew. Chem.* **2009**, *121*, 9316-9319; *Angew. Chem., Int. Ed.* **2009**, *48*, 9152-9155. e) R. W. Bates, Y. Lu, *Org. Lett.* **2010**, *12*, 3938-3941.

19) For selected examples, see: a) W.–M. Dai, K. K. Y. Yeung, Y. Wang, *Tetrahedron* **2004**, *60*, 4425-4430. b)W. Wu, Q. Peng, D. Dong, X. Hou, Y. Wu, *J. Am. Chem. Soc.* **2008**, *130*, 9717–9725.

20) F. E. McDonald, C. B. Connolly, M. M. Gleason, T. B. Towne, K. D. Treiber, *J. Org. Chem.* **1993**, *58*, 6952-6953.

21) M. J. Frisch, et al. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

22) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199–6200.

23) Hirayama, L. C.; Dunham, K. K.; Singaram, B. *Tetrahedron Lett.* **2006**, *4*. 5173-5176.

24) Usanov, D. L.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 8169 – 8172

25) Trost, B. M.; Ngai, M.-Y.; Dong, G. *Org. Lett.* **2011**, *13*, 1900-1903

26) Maddess, M. L.; Lautens, M. *Org. Lett.* **2005**, *7*, 3557-3560.

27) Ma, X.; Wang, J. –X.; Li, S.; Wang, K. –H. Huang, D. Tetrahedron 2009, 65, 8683-8689.

28) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258.

29) Li, Q. –R.; Gu, C. –Z.; Yin, H. *Chin. J. Chem.* **2006**, *24*, 72-78.

30) Minowa, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3697–3704.

31) Tummatorn, J.; Dudley, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 5050-5051.

32) Chen, J.; Captain, B.; Takenaka, N. *Org. Lett.* **2011**, *13*, 1654-1657.

33) Cheng, X.; Jiang, X.; Yu, Y.; Ma. S. *J. Org. Chem.* **2008**, *73*, 8960-8965.

34) Coeffard, V.; Aylward, M.; Guiry, P. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9152.

35) McDonald, F. E.; Connolly, C. B.; Gleason, M. M.; Towne, T. B.; Treiber, K. D. *J. Org. Chem.* **1993**, *58*, 6952.

36) Dai, W. –M.; Yeung, K. K. Y.; Wang, Y. *Tetrahedron* **2004**, *60*, 4425-4430

3 Mechanistic insights into the chiral phosphoric acid catalyzed allylation and propargylation of aldehydes

Note to the Reader: This chapter has been previously published and is utilized here with the permission of the publisher. Computational studies were done by research groups of Houk and Goodman.

3.1 Introduction

In 2010, we the reported the 1,1′-Bi-2-naphthol-derived phosphoric acid catalyzed allylboration of aldehydes.[1] The protocol provides a high yielding and a highly enantioselective method is shown to highly general, with a broad substrate scope that covers aryl, heteroaryl, α,β-unsaturated and aliphatic aldehydes. The high diastereoselctivites attained suggests that the reaction proceeds via the type I mechanism involving a chairlike six-membered cyclic transition state similar to the uncatlyzed allylborations.[2] In early 2012 we reported the extension of our methodology towards the propargylation of aldehydes.[3] The methodology used TRIP-PA as the catalyst and allenyl boronic acid pinacol ester for the asymmetric propargylation of aldehydes. Inspired by this work many interesting asymmetric transformations have been published in last 2 years,[4] where TRIP-PA was still found to be the most efficient catalyst. Owing to the importance of these reactions to the synthetic community, several mechanistic papers were published that helped us in better understanding the origins of stereoselectivities for the asymmetric allylation and propargylation reactions.[5-7]

3.2 Houk's intial insights

The first mechanistic insights were studied by Houk for the asymmetric propargylation of aldehydes and reported in our asymmetric propargylation manuscript.[3] It is our belief that the propargylation proceeds via a six- membered cyclic transition state, where catalyst activation operates by protonation of the boronate oxygen. To further understand the mechanism and stereoselectivity of this phosphoric acid-catalyzed propargylation reaction, we performed theoretical calculations. Calculated energies of different pathways for allylboration[8] and propargylation showed that Brønsted acids form a strong hydrogen bond with the pseudo-equatorial oxygen of the allenyl boronate. A computed transition state structure involving protonation is shown in Figure 3.1.

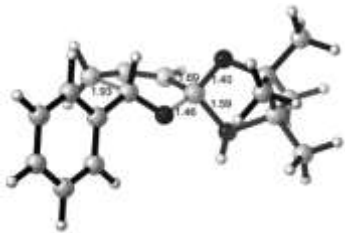


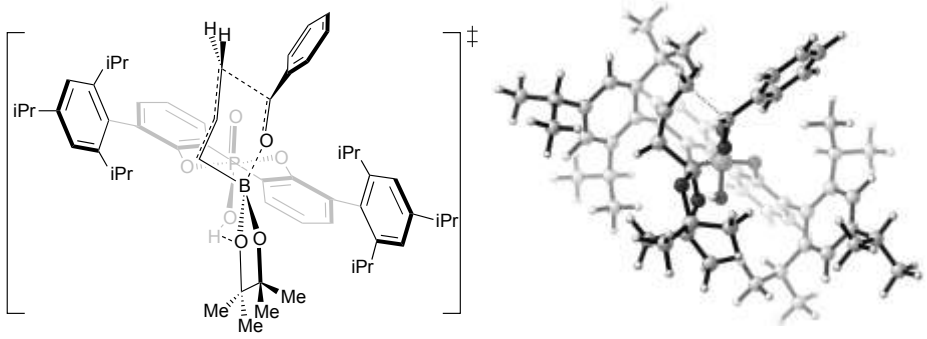
Figure 3.1 Transition state for the Brønsted acid-catalyzed propargylation reaction

To explore the origins of the enantioselectivity, we studied the transition state structures for the propargylation reaction, where the phosphoric acid catalyst activates the pseudo-equatorial oxygen of the allenyl boronate. Biphenol (BIPOL)-derived phosphoric acid was used as the model, in place of the fully derived BINOL phosphoric acid, to reduce the computational time. Catalyst **PA5**, bearing a 2,4,6-triisopropylphenyl group at the 3,3'-positions, provides high experimental enantioselectivity. Thus, the diastereomeric transition states of the *re*-face and *si*-face attack involving the BIPOL model of **PA5** were compared. Transition states **TSr1** and **TSs1**

are represented in Figure 3.2. *Re*-face attack (**TSr1**) is predicted to be more favored than *si*-face attack (**TSs1**) by 1.3 kcal/mol. This is in agreement with the 74% *ee* obtained experimentally.

Figure 3.2 shows a lack of obvious steric differences in the transition states. H-H distances are 2.4Å or more. However, the distortion of the catalyst is larger in **TSs1** than in **TSr1** by about 1.2 kcal/mol. This distortion relieves steric repulsions that would otherwise occur. The preference for *re*-facial selectivity is therefore the result of the larger distortion of the catalyst-boronate complex in **TSs1**.

TSr1 (0.0)



TSs1 (+1.3)

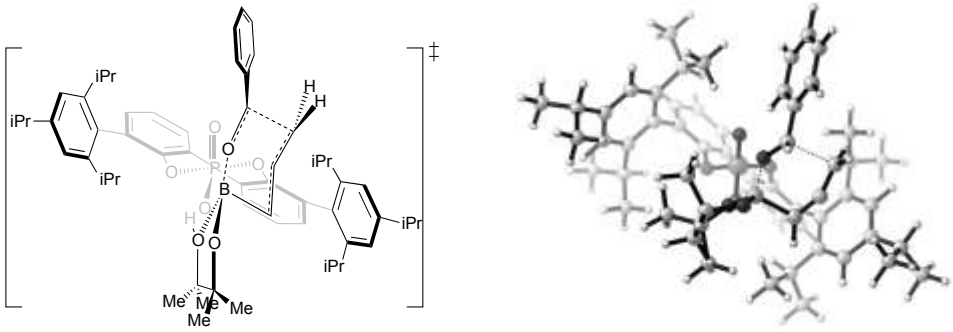


Figure 3.2 Optimized structures of TSr1 and TSs1. Relative energies (kcal/mol) are shown in parentheses.

The origins of the differences in distortion energies of the catalyst-boronate complex in the two TSs can be visualized from geometries of the catalyst in the TSs. Figure 3.3a shows the catalyst-boronate complex structure in **TSr1**. Here, the dioxaborolane ring has no significant steric interaction with the catalyst, and the dihedral angle between the 2,4,6-triisopropylphenyl substituent and the BIPOL core is 74°, almost the same as the dihedral angle of 72° in the optimized catalyst. Figure 3.3b shows the catalyst-boronate complex structure in **TSs1**, with the dioxaborolane ring on the left. The methyl groups (circled in 3.3b) of the dioxaborolane ring and the isopropyl groups of the catalyst (circled in 3.3b) are close to each other. In order to minimize such steric repulsions, the 2,4,6-triisopropylphenyl substituent is rotated around the bond to the BIPOL phenyl core with a dihedral angle of 78°. This is a 6° rotation away from the dihedral angle in the optimized catalyst (72°). The asymmetric induction can be rationalized by differences in distortion energies originating from the steric interactions between the substrates and the bulky 3,3'-substituents on the catalyst.

For other catalysts screened experimentally, calculations showed the absence of an energy difference between *re*/*si* attack diastereomeric transition states, suggesting why these catalysts gave low enantioselectivities.

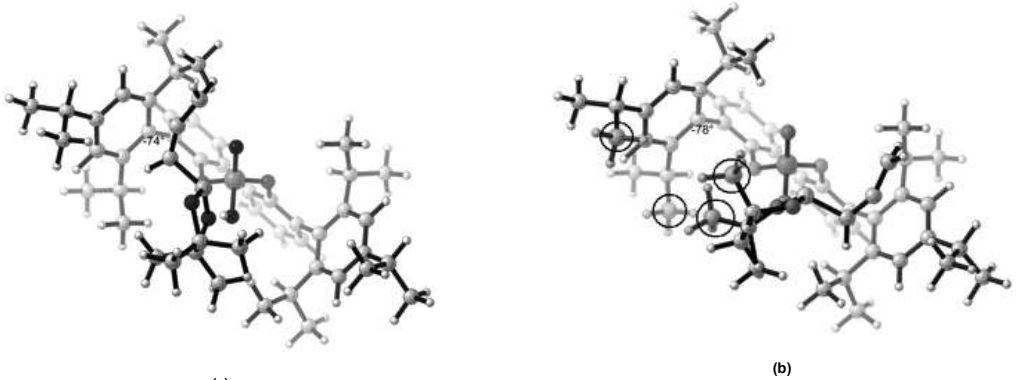


Figure 3.3 (a) 3D structure of TSr1 without benzaldehyde. (b) 3D structure of TSs1 without benzaldehyde.

In summary, Houk's mechanistic studies show the catalyst activating the reaction by forming a strong hydrogen bond with the pseudo-equatorial oxygen of the boronate. The high enantioselectivity obtained with catalyst **PA5** originates from steric interactions between the methyl groups of the allenylboronate, the bulky catalyst substituents, and the resulting distortion of the catalyst.

3.3 Goodman's report on allylboration

Later in 2012, Goodman published his studies on the 1,1′-Bi-2-naphthol-derived phosphoric acid catalyzed asymmetric allylboration of aldehydes.[5] Theoretical studies were performed using buta-1,3-diene-1,4-diol-phosphoric acid as the representation of the catalyst for the initial studies. Jaguar program (version 7.6) was used for the quantum mechanical calculations. For the uncatalyzed reaction of benzaldehyde and the allyl boronic acid pinacol ester, four transition states (TSs) were identified with the phenyl groups at the pseudoaxial or pseudoequatorial in the corresponding boat and chair conformations. The $\Delta G^{\ddagger}$ values suggested the chair conformation with the equatorial phenyl group as the most stable transition state with $\Delta G^{\ddagger}$ of 14.0 kcal mol^{-1} (Figure 3.4).

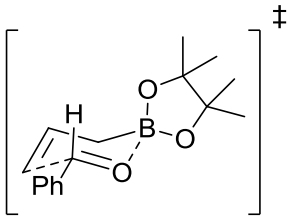


Figure 3.4 Preferred uncatalyzed transition state for allylboration of benzaldehyde

Different possible transition states were reviewed with buta-1,3-diene-1,4-diol-phosphoric acid as the model catalyst instead of the BINOL-derived catalyst (Figure 3.5). The TS **I** was calculated based on the plausible transition state reported in our original paper where the

hydrogen bonding between the phosphoric acid proton and the oxygen of the boronate is shown. The $\Delta G^{\ddagger}$ values for I from B3LYP/6-31G was calculated to 2.2 kcal mol^{-1}, much lower than the activation barrier for the uncatalyzed reaction. TS **II** showing the direct activation of the aldehyde by the phosphoric acid proton gave a high $\Delta G^{\ddagger}$ value of 14.4 kcal mol^{-1}. Transition states **III** and **IV** show the possibility of formation of the 10-membered ring with high $\Delta G^{\ddagger}$ values of 26.3 and 20.4 kcal mol^{-1} respectively. The most stable transition state was found to be **V** involving the hydrogen bonding interaction between the hydroxyl group of the catalyst and the pseudoaxial oxygen of the boronate, with a stabilizing interaction of the phosphoryl oxygen to the formyl hydrogen. This transition state had the shortest oxygen-hydrogen (1.47 Å), boron-oxygen (1.50 Å) and carbon-carbon (2.11Å) bond distances giving the tightest transition state with the lowest energy.

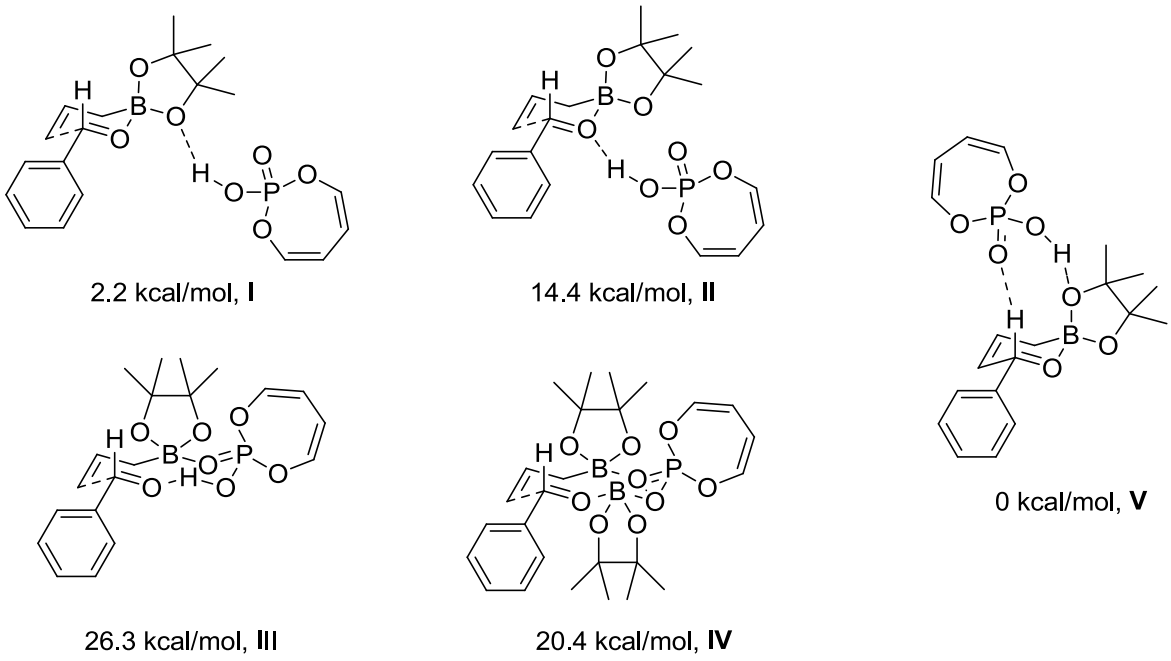


Figure 3.5 Possible transition states catalyzed by a model phosphoric acid

After employing buta-1,3-diene-1,4-diol-phosphoric acid as the model catalyst (R)-3,3′-bis(2,4,6-trimethylphenyl)-1,1′-bi-2-phenol derived phosphoric acid was used for calculations as

more similar model to the real catalyst.[5] A similar observation was made where the transition state with the dual interaction between the catalyst and the substrates had the lowest energy. Then using the ONIOM for different pathways the transition states for the full catalyst was located. This also followed the same trend as seen with earlier models where the ten-membered ring transition states were disfavoured and the six-membered rings were more favoured having lower energy. When the energy barrier for re-face attack and the si-face attack was calculated for the transition states with dual activation, an energy difference of 6.7 kcal mol^{-1} was observed. This difference is majorly responsible for the stereoselectivity observed in the products formed. Calculated from the Boltzmann ratios, this high difference in energies should give enantioselectivities >99.9%.

Since the experimental results showed the lowest enantiomeric excess for cyclohexanecarbaldehyde, the transition states were located for the *re*-face and the *si*-face attack. The energy difference in both the transition states was calculated to be 3.8 kcal mol^{-1}, which is much lower than the corresponding energy difference for benzaldehyde (6.7 kcal mol^{-1}) explaining the lower enantioselectivity.[5]

3.4 Houk's reinvestigation for allylation and propargylation reactions

After the initial independent reports by Houk[3] and Goodman[5] pointed out at two different transition states responsible for the stereoselectivity of the reaction (Figure 3.6), Houk reinvestigated the chiral BINOL-phosphoric acid catalyzed allylboration and propargylation reactions using several levels of DFT calculations.[6] In order to study the enantioselectivity of the catalysis, the two different models were evaluated. In addition, B3LYP-D3 was used, which includes dispersion energies,[9] to calculate the transition state energies, which may also be important to such systems. Using biphenol (BIPOL)-derived phosphoric acid as the model

catalyst, it was found that the two competing models are comparable in energy. The diastereomeric TSs involved in allylborations and propargylations for **PA1** were located using fully DFT optimization, and the calculated energies by B3LYP and B3LYP-D3 indicated that both pathways were involved for these systems. Goodman's model with axial coordination has a lower energy for *re*-face attack TS, which leads to the major enantiomeric product. However, in our calculations, for *si*-face attack TS, our model is more stable than Goodman's model, which indicated that the minor enantiomeric TS comes from equatorial coordination of the catalyst.

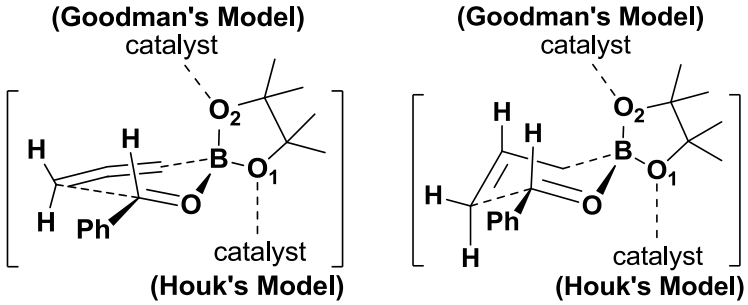


Figure 3.6 Two models for the chiral phosphoric acid-catalyzed allylborations and propargylations of benzaldehyde

3.4.1 Reinvestigation of the reaction mechanism

The allylboration reaction proceeds via a closed six-membered chair-like transition state.[10] There are three possible coordination positions for the catalyst hydroxyl group: the two boronate oxygens or the aldehyde oxygen (Figure 3.7). In Goodman's and our models, the phosphoric acid forms a hydrogen bond with the boronate oxygens: either the pseudo-equatorial oxygen (path i: eq), or the pseudo-axial oxygen (path ii: ax). The other plausible mechanistic pathway is the phosphoric acid forming a H-bond with the oxygen of the aldehyde (path iii).

In order to evaluate these different pathways, we first explored transition states where each of the oxygens was protonated. All calculations were performed with the Gaussian 09 package.[8] Geometries were fully optimized in the gas phase and characterized by frequency calculations

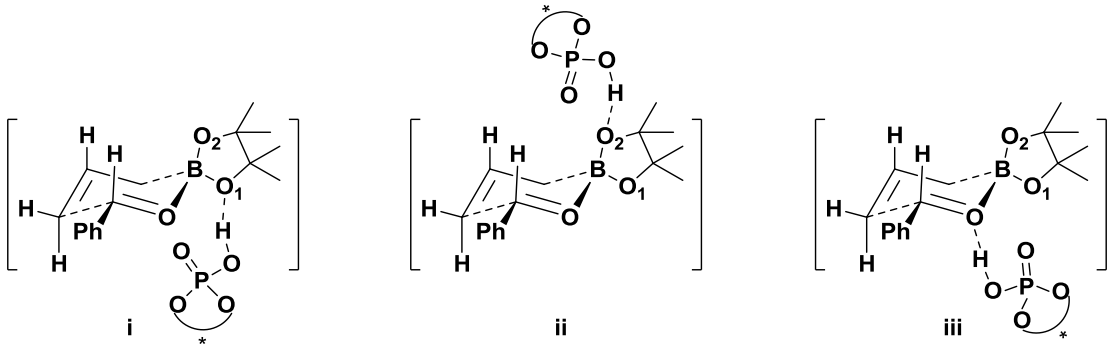


Figure 3.7 Three possible sites of coordination in the phosphoric acid-catalyzed allylboration reaction

using B3LYP functional and 6-31G* basis set. Free energies were calculated for each stationary point. The optimized chairlike transition state structure of the uncatalyzed reaction is shown in Figure 3.8, and the transition states for the three possible sites of protonation are shown in Figure 3.9 along with their relative Gibbs free energies.

As shown in Figure 3.9, the pathways involving protonation of boronate oxygens (**TS1**: 0.0 kcal/mol, **TS2**: +3.6 kcal/mol) are more favorable than **TS3** (+4.3 kcal/mol) which involves protonation of the aldehyde oxygen. Protonation of a B-O increases the electrophilicity of the boronate and lowers the activation energy.[11] This finding is in agreement with Hall's experimental observations[12] and Fujimoto's theoretical studies[13] of similar Lewis acid catalyzed allylboration reactions. Similarly, for propargylations, protonation of boronate oxygens accelerates more than protonation of aldehyde (See Supporting Information for reference 6).

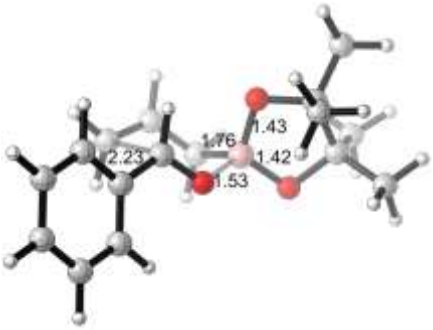


Figure 3.8 Optimized transition state of the uncatalyzed allylboration of benzaldehyde at the B3LYP/6-31G* level of theory.

TS1 (0.0) **TS2** (+3.6) **TS3** (+4.3)

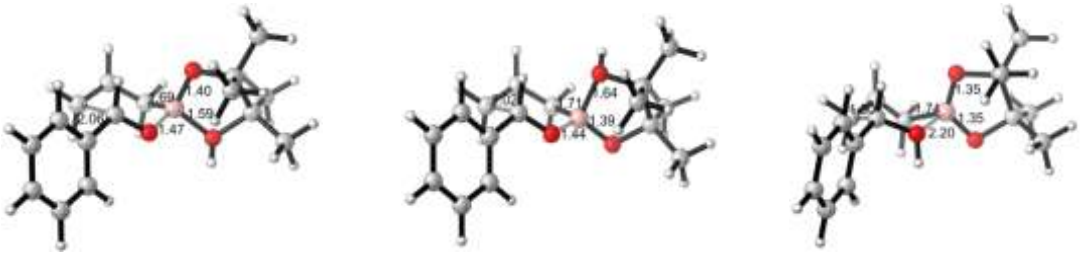


Figure 3.9 Optimized transition states of different mechanisms at the B3LYP/6-31G* level of theory. Bond lengths are given in Å. Relative free energies (kcal/mol) are shown in parentheses

3.4.2 Model of the phosphoric acid-catalyzed allylboration reaction

The mechanistic studies reported above illustrate that activation of boronate oxygens are more favorable than activation of aldehyde oxygen. This phenomenon is also found in Goodman's model study calculations. In order to better understand the boronate activation pathways, catalyst **PA** without Ar substituents was then employed to study both paths i and ii in more detail. In order to reduce the computational cost, the biphenol (BIPOL)-derived phosphoric acid was initially used as the model instead of the BINOL-derived phosphoric acid. This kind of

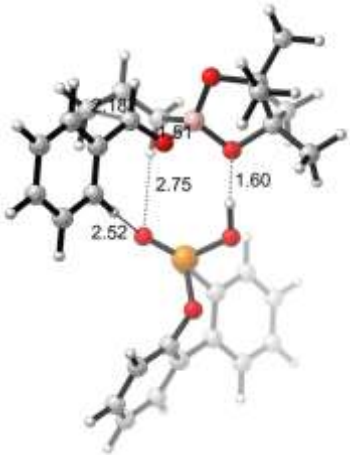
truncating has previously been justified by Yamanaka, Akiyama and Goodman in their studies.[14] Replacement of the binaphthyl backbone with a smaller biaryl does not significantly alter the geometry around the reaction center.

In both pathways i (eq) and ii (ax), the catalyst interacts with the allylboronate by a single hydrogen bond, and the orientation of the phosphate with respect to the substrate is not fixed. As a result, the remaining parts of the catalyst are conformationally flexible, and there are many possible diastereomeric transition state structures with different orientations of the catalyst. To explore all accessible conformations of the transition states, a conformational search was performed (See Supporting Information of reference 6: Figure S1).

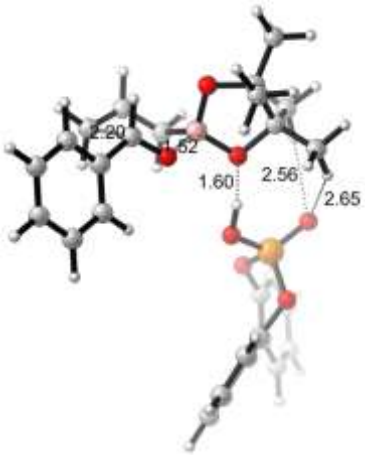
For pathway i, two low energy transition state structures, **TS4** and **TS4'**, were located for the phosphoric acid-catalyzed allylboration reaction (Figure 3.10). In **TS4**, the lowest energy minimum for i, the phosphoryl oxygen was near the six-membered transition state; in **TS4'**, the phosphoryl oxygen is away from the six-membered ring, but next to the boronate methyls. **TS4'** is 1.4 kcal/mol less stable than **TS4**. Since B3LYP may underestimate the aromatic and dispersion interactions in such systems, a method which is expected to treat such interactions more accurately was used to calculate the energy differences between different transition states as well. The energy difference between **TS4** and **TS4'** is calculated to be 2.0 kcal/mol with B3LYP-D3, which includes a dispersion energy correction. For pathway ii, involving H-bonds to the pseudo-axial boronate oxygen, two different diastereomeric transition state conformers, **TS5** and **TS5'** were also found (Figure 3.10b). **TS5**, in which the phosphoryl oxygen is situated over the six-membered ring TS, was more energetically favorable than **TS5'** by 3.0 kcal/mol. B3LYP-D3 calculation gave an energy difference of 3.5 kcal/mol between **TS5** and **TS5'**. This order of stability between **TS5** and **TS5'** was also observed by Goodman's et al.[5]

(a) Pathway i

TS4 0.0 (0.7)

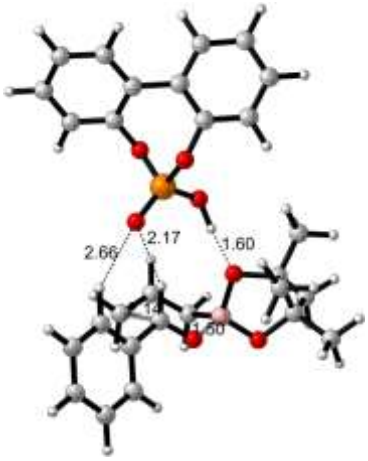


TS4' 1.4 (2.7)



(b) Pathway ii

TS5 0.2 (0.0)



TS5' 3.2 (3.5)

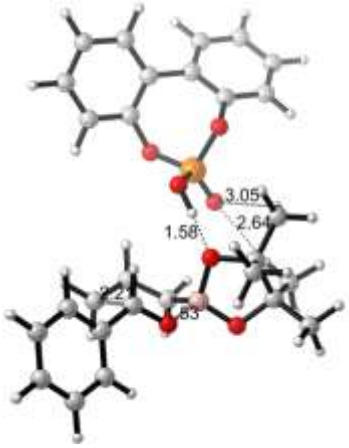


Figure 3.10 Optimized transition state structures of (a) TS4, TS4' in pathway i (eq) and (b) TS5, TS5' in pathway ii (ax) at the B3LYP/6-31G* level of theory

In order to study the origin of the energy differences between the different transition state conformers, electrostatic potentials were computed. They are shown for the uncatalyzed reaction transition state **TS** in Figure 3.11. The formyl H, allyl Hs and phenyl Hs are more positive than the Hs on boronate methyls. This indicates that there can be stabilizing electrostatic attractions between the phosphoryl oxygen and those positive Hs. The stabilized interactions between electronegative parts of Lewis acids and the formyl H has been proposed by Corey before,[15] as well as in Goodman's model. Here, **TS4** was more stable than **TS4'** and **TS5** was more stable than **TS5'**. The extra stabilization of **TS4** and **TS5** comparing to **TS4'** and **TS5'** came from the extra attractive P=O···H-C interactions, either with the aldehyde H in **TS5** or the phenyl and allyl Hs in **TS4**.

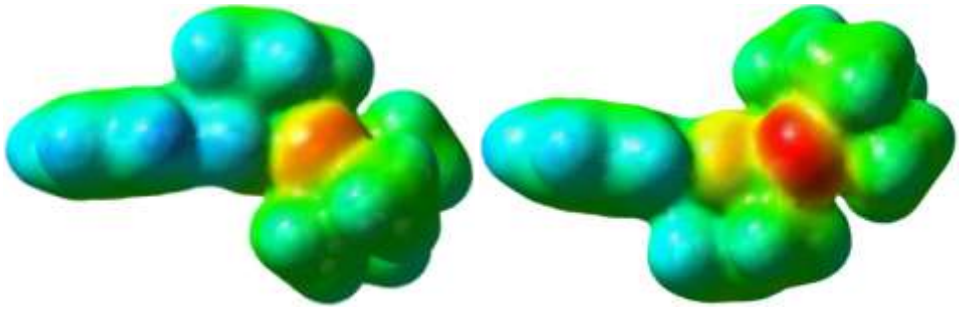


Figure 3.11 Top and bottom view of electrostatic potential of TS. Red: negative ESP; Blue: positive ESP; Green: neutral.

By comparing the most stable TSs in two pathways, **TS4** is calculated to be 0.2 kcal/mol more stable than **TS5** by B3LYP, but 0.7 kcal/mol less stable than **TS5** using B3LYP-D3. In the Goodman et al. work, when buta-1,3-diene-1,4- diol-phosphoric acid, which contains no aromatic rings was used as the model catalyst, the two competing pathways are differentiated by 2.2 kcal/mol. In our studies, the model catalyst (biphenol-derived phosphoric acid) resembles more the real catalysts in the experiment, and the two different pathways are calculated to be

similar in energy. This is likely due to the role of the additional aromatic rings in our model catalyst. The energy differences we calculate are quite small, suggesting that both of them may be involved in the reactions.

On the basis of these investigations, the "two-point binding models" of two different pathways shown in Figure 3.12 appear to operate for phosphoric acid catalyzed allylborations. The models consider two interactions between the catalyst and the substrates, which provide relative rigidity to the transition state. In what we will refer to as **A** (for axial), which is the same as Goodman's model, the acidic H of the catalyst forms a hydrogen bond with the pseudo-axial oxygen of boronate. In **E** (for equatorial), the hydroxyl group of the catalyst H-bonds to the pseudo-equatorial oxygen of boronate. The second interaction comes from the electrostatic attractions between the phosphoryl oxygen and relatively positive Hs.

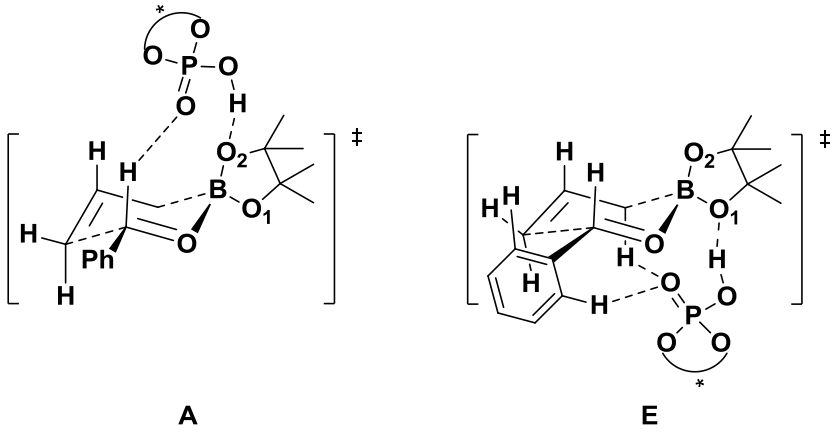


Figure 3.12 Models for the phosphoric acid-catalyzed allylboration reaction

3.4.3 Origins of Enantioselectivity

The model studies described above indicated that both of the transition states in the two models, **A** and **B**, are likely to be involved in the reactions. To explore the origins of the

enantioselectivity of the catalysis, the 3,3'-substituted BIPOL model for the binaphthol catalyst **PA1** was employed, and both transition states, **A** and **E**, were computed. Catalyst **PA1** bearing the 2,4,6-triisopropylphenyl group on the 3,3'-positions gave high enantioselectivity experimentally. The diastereomeric transition states for *re*-face **(r)** and *si*-face attack **(s)** involving BIPOL model of **PA1** were explored. The transition states involved were fully optimized, in contrast to Goodman's ONIOM calculations for these systems, **TSr1-E**, **TSs1-E** are located for **E** and **TSr1-A**, **TSs1-A** are located for **A**. These are shown in Figure 3.13.

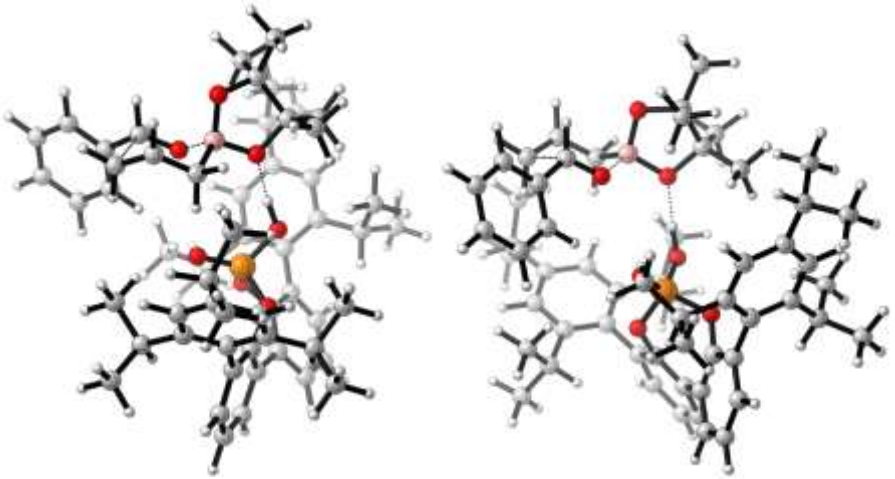
In the equatorial coordination model **E**, the *re*-face attack **TSr1-E** is predicted to be more favored than the *si*-face attack **TSs1-E** by 2.0 kcal/mol. In the axial coordination model **A**, **TSr1-A** is more stable than **TSs1-A** by 6.1 kcal/mol using B3LYP calculations, which is consistent with Goodman's ONIOM calculations on these two TSs, which gives an energy difference of 6.7 kcal/mol.

In contrast to Goodman's ONIOM calculations that both *re* and *si* TSs are substantially energetically preferable in **A** over **E**, our fully optimized structure energies show that transition states resembling both models contribute to selectivity. That is, using the B3LYP-D3 energetics, the relative rates of reaction via **TSr1-A**, **TSr1-E**, **and TSs1-E** will be 1:0.05:0.001. Use of **A** only predicts far too high selectivity. The energy difference between the most stable *re*-face **(r)** attack transition state **TSr1-A** and the most stable *si*-face **(s)** attack transition state **TSs1-E** is 2.6 kcal/mol by B3LYP, which is in close agreement with the 93% ee observed experimentally. Solvation energy calculations using PCM model with toluene as the solvent does not change the energy difference very much, which gives a number of 3.1 kcal/mol.

(a) *re*-face attack (b) *si*-face attack

E

TSr1-E 0.6(1.8) **TSs1-E** 2.6 (4.0)



A

TSr1-A 0.0 (0.0) **TSs1-A** 6.1 (7.5)

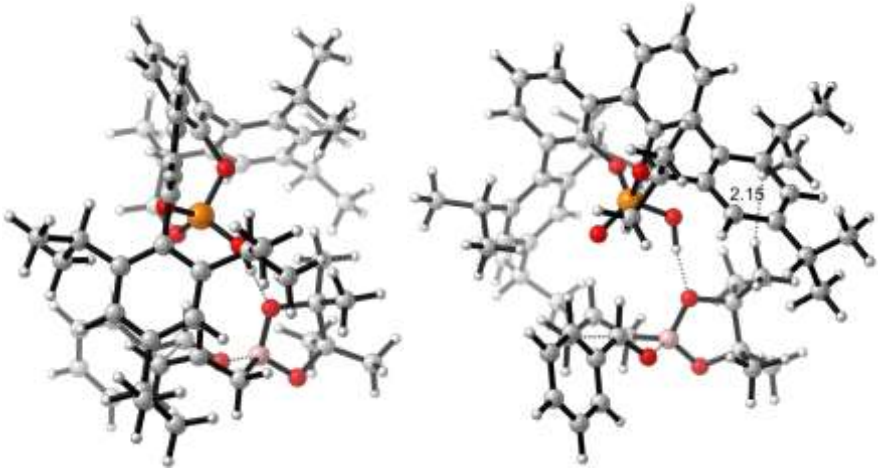


Figure 3.13 Optimized structures of TSr1-E and TSs1-E for E, TSr1-A and TSs1-A for A

Based on these calculations, we compare the two competing models for each enantiomeric TS (*re* or *si*), respectively. In Goodman's paper, the large preference for **A** comes from both

steric and electronic factors. In the case of *re*-TSs, our calculations, in agreement with Goodman's results, show **A** (**TSr1-A**) is more stable than **E** (**TSr1-E**). Inspection of the two diastereomeric TSs show they are both free of steric problems by inspecting all the H-H distances inside; all H-H distances are 2.4 Å or more. The stabilities between two TSs is then perhaps because formyl H-bond strength inside **A** (**TSr1-A**) is stronger than the electrostatic interactions between phosphoryl oxygen and relative positive Hs in **E** (**TSr1-E**).

Our calculations show that **A** (**TSs1-A**) is much less favorable than **E** (**TSs1-E**) for *si*-TSs. In our fully optimized TS structures **TSs1-A** and **TSs1-E**, both of them have an almost linear H-bond arrangement. However, **A** (**TSs1-A**) has a longer H-bond distance (1.65 Å) and corresponding weaker H-bond strength than that in **E** (**TSs1-E**) (1.59 Å); this is opposite from Goodman's ONIOM calculated structures. We find a steric difference between the two models. Inspection of **A** (**TSs1-A**) shows that the pinacol group is orientated toward the bulky pocket of the catalyst, and there is one significant steric repulsion between an isopropyl H on the catalyst and a methyl H on the boronate; separated by only 2.15 Å; such steric repulsions are not found in **E** (**TSs1-E**). As a result, both electronic and steric factors make **A** (**TSs1-A**) less favorable than **E** (**TSs1-E**) in our calculated structures for *si*-TSs.

After comparing the two competing models, it is then necessary to investigate the origins of different stabilities between *re* and *si* TSs in each model, respectively. In **A**, the stabilities between **TSr1-A** and **TSs1-A** are due to steric factors. One significant steric repulsion between isopropyl H on the catalyst and methyl H on the boronate, separated by only 2.15 Å, was found for **TSs1-A**; by contrast **TSr1-A** is free of steric congestion. These steric factors are believed to control the stabilities of two diastereomeric TSs in **A** in Goodman's studies as well.

In **E**, however, as mentioned above, there are no obvious steric differences in the two transition states **TSr1-E** and **TSs1-E**. To gain insights into the origins of the energy difference between **TSr1-E** and **TSs1-E**, the distortion energy (ΔE_d) and interaction energy (ΔE_i) of the transition states were performed. This method has been used previously to understand 1,3-dipolar and Diels-Alder cycloadditions.[16] **TSr1-E** and **TSs1-E** are divided into two parts: catalyst-boronate complex **1A** and the benzaldehyde **1B** (Figure 3.13) with the geometries fixed at the transition state geometries. The calculated distortion energy ΔE_d of **1B** in **TSr1-E** (+12.2 kcal/mol) is almost the same as that in **TSs1-E** (+12.3 kcal/mol). There is also no interaction energy ΔE_i difference between **TSr1-E** (-41.3 kcal/mol) and **TSs1-E** (-41.2 kcal/mol) which means all of the stabilizing and destabilizing interactions between **1A** and **1B** in the two TSs are similar. The preference for *re*-facial selectivity is therefore the result of the larger distortion of catalyst-boronate complex **1A** in **TSs1-E**. **1A** is more heavily distorted in **TSs1-E** (+33.9 kcal/mol) than in **TSr1-E** (+32.1 kcal/mol) by 1.8 kcal/mol.

The origins of the differences in distortion energies of **1A** in the two TSs can be visualized from the **1A** geometries, as shown in Figure 3.14 and 3.15. In Figure 3.15, which shows the **1A** structure in **TSs1-E**, the dioxaborolane ring is on the left, and the methyl groups on the dioxaborolane ring and isopropyl groups of catalysts are close to each other (green atoms in Figure 3.15). In order to minimize such steric repulsions, the 2,4,6-triisopropylphenyl substituent is rotated around the bond to the BIPOL phenyl core with a dihedral angle of 80^o. This is an 8^o rotation away from the dihedral angle in the optimized catalyst (72^o). Due to the distortion of the catalyst, the green atoms (Figure 3.15) are all far away, resulting in no steric repulsions. In other words, the catalyst undergoes conformational changes to avoid unfavorable steric interactions in **TSs1-E**. Figure 3.15 shows the **1A** structure in **TSr1-E**. Here, the dioxaborolane ring is far from

the catalyst, and the dihedral angle between 2,4,6-triisopropylphenyl substituent and the BIPOL core is 72°, the same as the dihedral angle of 72° in the optimized catalyst. The asymmetric induction can be rationalized by differences in distortion energies originating from avoiding the steric interactions between the substrates and the bulky 3,3'-substituents on the catalysts.

TSr1-E **TSs1-E**

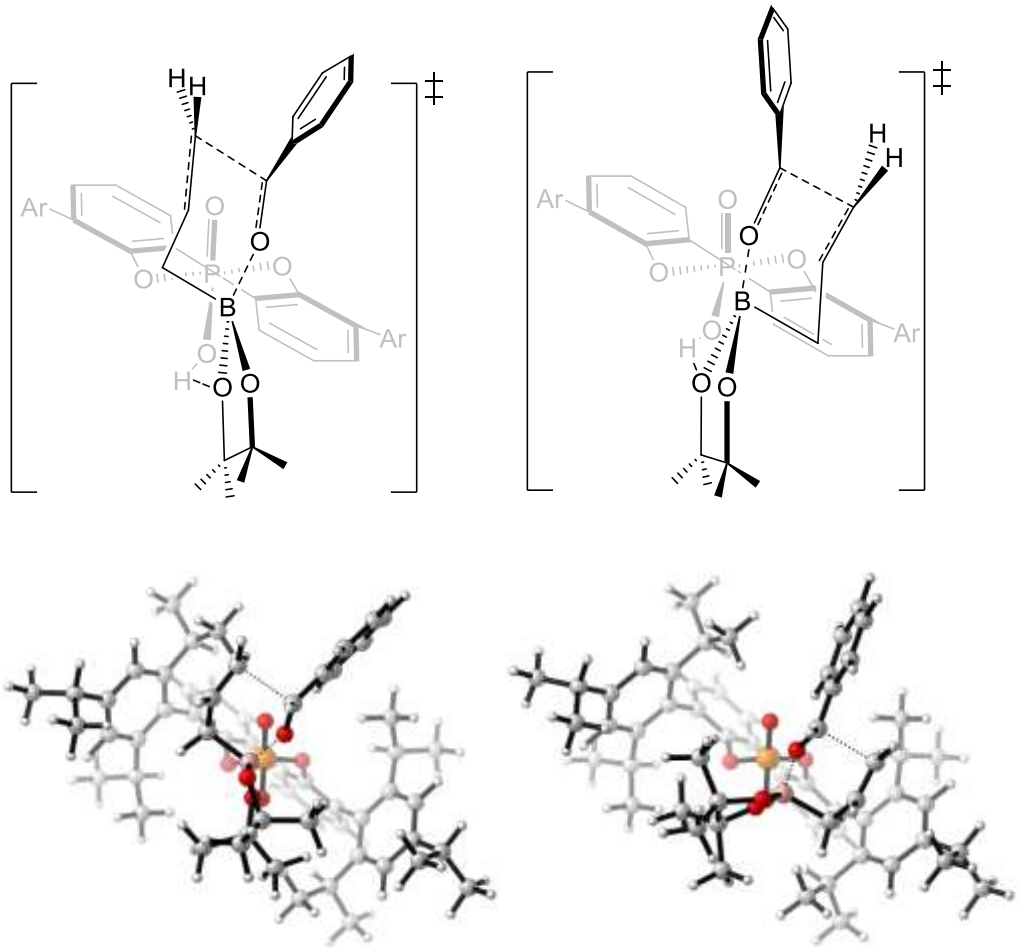


Figure 3.14 Side view of TSr1-E and TSs1-E

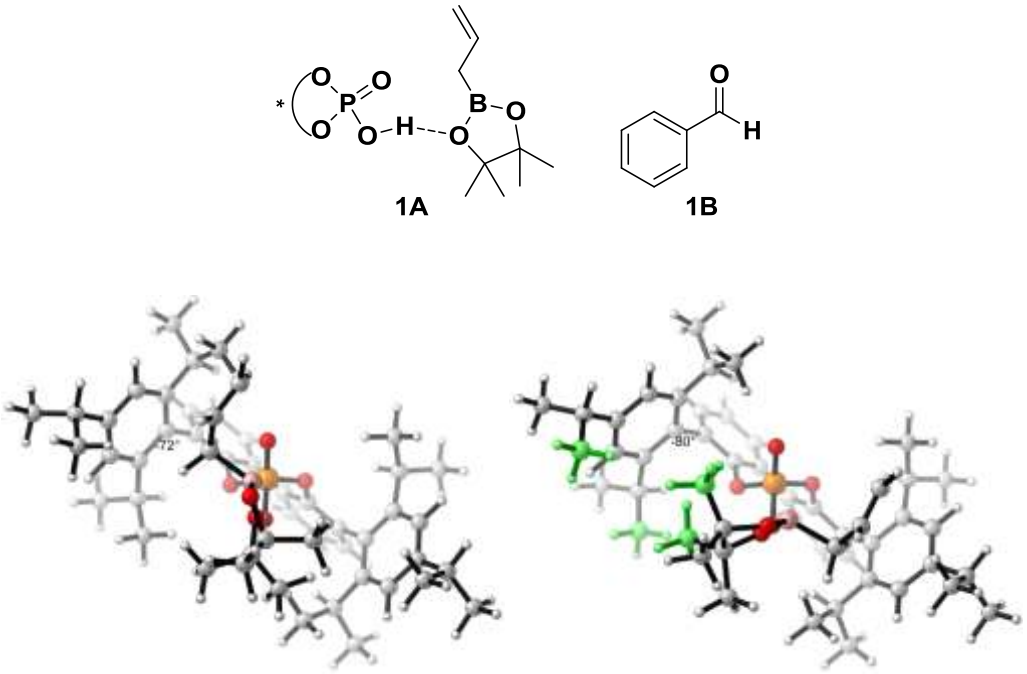


Figure 3.15 3D structures of 1A in TSr1-E and 3D structures of 1A in TSs1-E

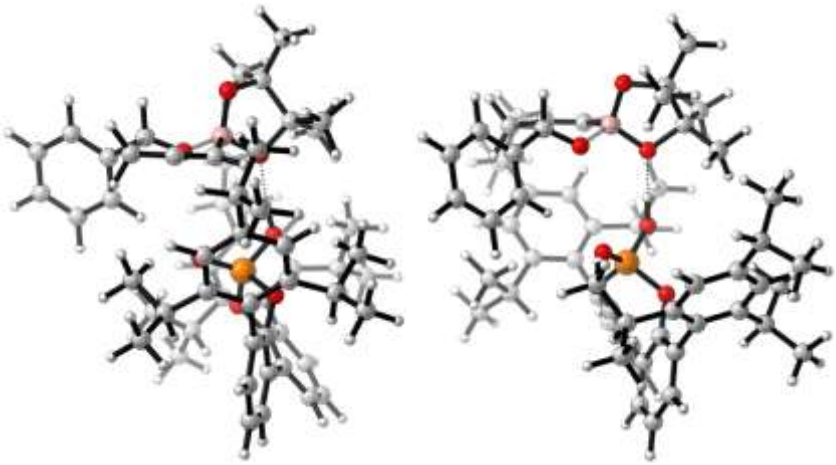
After investigating the allylboration reaction, we then reinvestigated the propargylborations. The propargylboration proceeds via a six-membered cyclic transition state similar to that for allylborations. Once again, the catalyst could activate the reaction by forming a hydrogen bond with either of the boronate oxygens. The transition state structures of propargylation involving the phosphoric acid catalyst **PA1** using both **E** and **A** were studied. As before, diastereomeric transition states **TSr1'-E** and **TSs1'-E** were located for **E**, and **TSr1'-A** and **TSs1'-A** were located for **A** (Figure 3.16).

As in the allylboration analysis, for *re*-face **(r)** attack, **A** (**TSr1'-A**) is more stable than **E** (**TSr1'-E**) by 2.7 (or 3.5) kcal/mol. For *si*-face **(s)** attack, **A** (**TSs1'-A**) is less stable than **E** (**TSs1'-E**) by 1.3 (or 1.2) kcal/mol. The energy difference between the most stable *re*-face **(r)** attack transition state **TSr1'-A** and the most stable *si*-face **(s)** attack transition state **TSs1'-E** is

(a) *re*-face attack (b) *si*-face attack

E

TSr1'-E 2.7 (3.5) **TSs1'-E** 4.0 (5.1)



A

TSr1'-A 0.0 (0.0) **TSs1'-A** 5.3 (6.3)

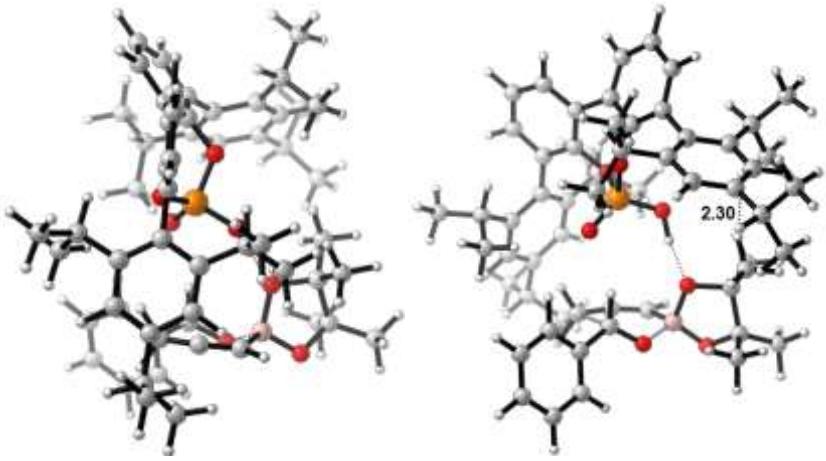


Figure 3.16 Optimized structures of TSr1'-E and TSs1'-E for E, TSr1'-A and TSs1'-A for A

4.0 (or 5.1) kcal/mol, overestimating the stereoselectivities as compared to the 74% ee observed experimentally.

Our studies on propargylations still showed that for *re*-TSs, **A** is more favorable; while **E** is more favorable for *si*-TSs. The **A** and **E** transition states leading to *re* attack are both lower in energy than **E** transition state that leads to *si* attack.

In **E**, the calculated distortion energy ΔE_d of benzaldehyde in **TSr1'-E** (+17.4 kcal/mol) is almost the same as that in **TSs1'-E** (+17.5 kcal/mol), so is the interaction energy ΔE_i for the two transition states. The preference for *re*-facial selectivity still comes from the larger distortion of catalyst-boronate complex in **TSs1'-E**. The catalyst-boronate complex is calculated to be more heavily distorted in **TSs1'-E** (+45.9 kcal/mol) than in **TSr1'-E** (+44.7 kcal/mol) by 1.2 kcal/mol.

3.5 Goodman's studies on propargylation

After the studies on the chiral phosphoric acid catalyzed allylboration of aldehydes[5] Goodman studied the propargylation of aldehydes.[7] Very similar results were observed for the propargylation reaction where the DFT calculations proved that the reaction proceeds via a cyclic six-membered transition state. The dual activation involving the interaction of the acidic proton on the catalyst with the boronate oxygen and the interaction of the phosphoryl oxygen with the formyl hydrogen forms the most stable transition state.[7]

Initial investigation was done using the model catalyst as 1,3-diene-1,4-diol-phosphoric acid (Figure 3.17). **I** shows the activation by hydrogen bonding to the boronate oxygen with the $\Delta G^{\ddagger}$ value of 4.8 kcal mol^{-1}. High energy barriers were seen with transition states involving the direct activation of aldehyde by the phosphoric acid proton with **II**, **III** and **IV** having $\Delta G^{\ddagger}$ values of 9.0, 13.0 and 18.2 kcal mol^{-1}. The transition states involving the hydrogen bonding with the axial

boronate oxygen was investigated with (**V**) and without (**VI**) the dual interaction with the formyl hydrogen. Similar to the allylboration studies the hydrogen bonding with the pseudoaxial oxygen with the dual interaction with aldehyde hydrogen gave the most stable transition state.[7]

Further studies with (*R*)-3,3′-bis(2,4,6-trimethylphenyl)-1,1′-bi-2-phenol derived phosphoric acid as the model catalyst were performed. A similar observation was made where the transition state with the dual interaction between the catalyst and the substrates, involving the hydrogen bonding with the pseudoaxial boronate oxygen and an additional interaction from the phosphoryl oxygen and the formyl hydrogen, had the lowest energy.[7]

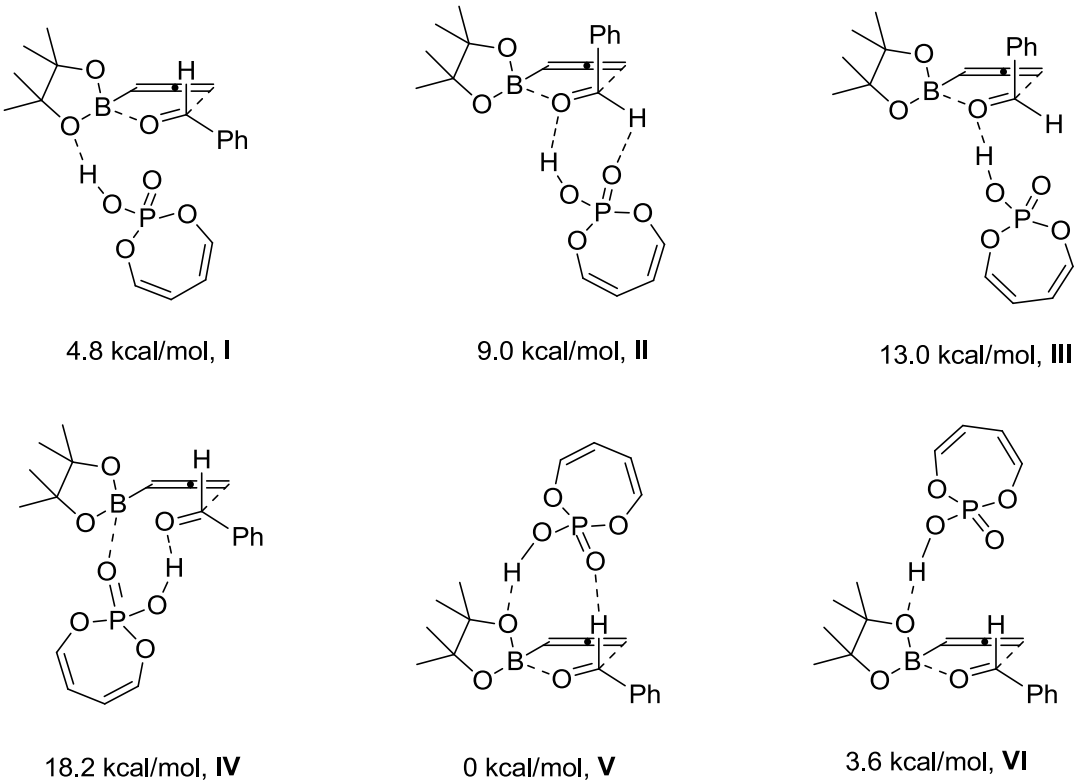


Figure 3.17 TS's for the propargylation reaction with a model catalyst

3.6 Conclusion

Houk's initial calculations show the catalyst activating the reaction by forming a strong hydrogen bond with the pseudo-equatorial oxygen of the boronate. In contrast, Goodman's studies show that the major isomer is formed *via* a transition state involving the hydrogen bonding interaction between the hydroxyl group of the catalyst and the pseudoaxial oxygen of the boronate, with a stabilizing interaction of the phosphoryl oxygen to the formyl hydrogen. Houk's reinvestigated the chiral phosphoric acid-catalyzed enantioselective allylboration and propargylboration reactions. Transition states with either boronate oxygen hydrogen-bonded to the phosphoric acid were studied. The catalyst is able to activate the boronate by forming a hydrogen bond either with the pseudo-equatorial oxygen (**E**) or the pseudo-axial oxygen of boronate (**A**); the phosphoryl oxygen interacts with relatively positive Hs of the substrate through electrostatic attractions, which provides further stabilization of the TS, and two-point orientation of the catalyst.

For *re*-face attack, both equatorial and axial coordination gives TSs that are free of steric repulsions, with **A** more favorable than **E.** The relative stability of A is due to the formyl H-bond strength in **A**. For *si*-face attack, to give the minor enantiomer, our calculations showed that **A** is less favorable than **E**. Steric factors make the more crowded **A** less stable than the less crowed **E**.

Calculations show that the enantioselectivity observed experimentally originates from larger distortions of the catalyst in the minor enantiomeric TS, which is the result of avoiding the repulsive interactions between the bulky 3,3'-substituents in the catalyst and the substrates. The pinacol boronate methyls have an important role, and these groups could be altered to influence stereoselectivities. These investigations might help direct future enantioselective catalysis development for allylboration and propargylboration reactions.

3.7 References

1) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884

2) (a) Hoffmann, R. W. and Ladner, W. *Tetrahedron Lett*. **1979**, *20*, 4653. (b) Hoffmann, R. W.; Zeiss, H. J. *Angew*. *Chem*., *Int. Ed. Engl.* **1979**, *18*, 306. (c) Hoffmann, R. W.; Zeiss, H. J. *J. Org. Chem.* **1981**, *46*, 1309.

3) Jain, P.; Wang, H.; Houk, K. N.; Antilla, J. C. *Angew. Chem., Int. Ed*. **2012**, *51*, 1391.

4) (a) Zhang, Z.; Jain, P.; Antilla J. C. *Angew. Chem. Int. Ed*. **2011**, *50*, 10961. (b) Reddy, L. R. *Org. Lett*. **2012**, *14*, 1142. (c) Chen, M.; Roush, W. R. *J. Am. Chem. Soc*. **2012**, *134*, 10947. (d) Xing, C.-H.; Liao, Y. –X.; Zhang, Y.; Sabarova, D.; Bassous, M.; Hu, Q. –S. *Eur. J. Org. Chem*. **2012**, 1115. (e) Reddy, L. R. *Chem. Commun*., **2012**, *48*, 9189 (f) Tsai, A. S.; Chen, M.; Roush, W. R. *Org. Lett.* **2013**, *15*, 1568. (g) Fustero, S.; Rodriguez, E.; Lazaro, R.; Herrera, L.; Catalan, S.; Barrio, P. *Adv. Synth. Catal.* **2013**, *355*, 1058. (h) Incerti-Padillos, C. A.; Kabeshov, M. A.; Malkov, A. V. *Angew. Chem. Int. Ed*. **2013**, *52*, 5338. (i) Miura, T.; Nishida, Y.; Morimoto, M.; Murakami, M. *J. Am. Chem. Soc*. **2013**, *135*, 11497. (j) Reddy, B. V. S.; Reddy, P. J.; Reddy, C. S. *Tetrahedron Lett*. **2013**, *54*, 5185.

5) Grayson, M. N.; Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc*. **2012**, *134*, 2716.

6) Wang, H.; Jain, P.; Antilla, J. C.; Houk, K. N. *J. Org. Chem*. **2013**, *78*, 1208.

7) Grayson, M. N.; Goodman, J. M. *J. Am. Chem. Soc*. **2013**, *135*, 6142.

8) M. J. Frisch, et al. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004

9) (a) For dispersion correction, see: (a) Grimme, S. *J. Comput. Chem.* **2006**, *27*, 1787-1799. (b) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104. For application of dispersion corrected DFT in computational chemistry, see: (c) McMullin, C. L.; Jover, J.; Harvey, J. N.; Fey, N. *Dalton Trans.* **2010**, *39*, 10833-10836. (d)

Antoline, J. E.; Krenske, E. H.; Lohse, A. G.; Houk, K. N.; Hsung, R. P. *J. Am. Chem. Soc.* **2011**, *133*, 14443-14451.

10) (a) Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 1236–1240. (b) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692–10697.

11) (a) Omoto, K.; Fujimoto, H. *J. Org. Chem.* **1998**, *63*, 8331–8336. (b) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868–1874.

12) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518-4519.

13) Sakata, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 12519–12526.

14) For theoretical studies on the chiral phosphoric acid catalysis, see: (a) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756–6764. (b) Simo´n, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 8741–8747. (c) Simo´n, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 4070–4077. (d) Simo´n, L.; Goodman, J. M. *J. Org. Chem.* **2010**, ***75***, 589–597. (e) Simo´n, L.; Goodman, J. M. *J. Org. Chem.*, **2011**, ***76***, 1775–1788. (f) Marcelli, T.; Hammar, P.; Himo, F. *Chem. Eur. J.* **2008**, *14*, 8562–8571. (g) Akiyama, T.; Morita, H.; Bachu, P.; Mori, K.; Yamanaka, M.; Hirata, T. *Tetrahedron*. **2009**, *65*, 4950–4956. (h) Shi, F.-Q.; Song, B.-A. *Org. Biom. Chem.* **2009**, *7*, 1292–1298. (i) Yamanaka, M.; Hirata, T. *J. Org. Chem.* **2009**, *74*, 3266–3271. (j) Gridnev, I. D.; Kouchi, M.; Sorimachi, K.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 497-500.

15) (a) Corey, E. J.; Rohde, J. J.; Fischer, A.; Azimioara, M. D. *Tetrahedron Lett.* **1997**, *38,* 33-36. (b) Corey, E. J.; Rohde, J. J. *Tetrahedron Lett.* **1997**, *38*, 37-40. (c) Corey, E. J.; David B. S.; Thomas, W. L. *Tetrahedron Lett.* **1997**, *38*, 1699-1702.

16) (a) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10187-10198. (b) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646-10647. (c) Ess, D. H.; Jones, G. O.;

Houk, K. N. *Org. Lett.* **2008**, *10*, 1633-1636. (d) Garcı´a, J. I.; Martı´nez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1998**, *120*, 2415-2420. (e) Sbai, A.; Branchadell, V.; Ortun˜o, R. M.; Oliva, A. *J. Org. Chem.* **1997**, *62*, 3049-3054.

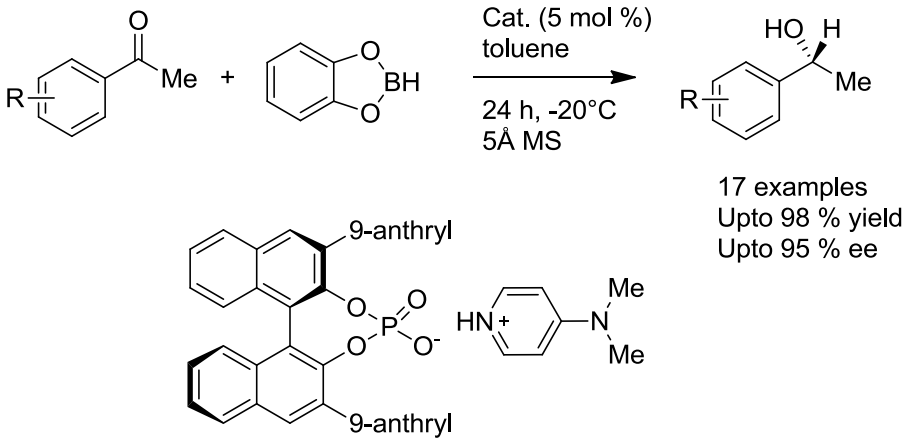
4 Further advances in the Brønsted acid catalyzed allylation and propargylation

4.1 Impact of TRIP-PA catalyzed allylboration on the synthetic community

In 2010 we reported a simple and highly efficient chiral phosphoric acid catalyzed allylboration of aldehydes.[1] TRIP-PA (5 mol %), a commercially available catalyst, effectively catalyzed the reaction at -30 °C with allyl boronic acid pinacol ester as the allyl donor (see chapter 1). This was the first report where a Brønsted acid catalyzed the allylboration of aldehydes in the absence of a Lewis acid.[2] Inspired by this work many interesting reports have been published in last 2 years,[3-14] where TRIP-PA was still found to be the most efficient catalyst.

4.1.1 Reduction of ketones

After the discovery of the Brønsted acid catalyzed allylboration of aldehydes, where the acid activates the reaction by forming a strong hydrogen bond with the oxygen of the allylboronate, we started exploring other reactions that could be similarly catalyzed. Zuhui, a postdoc in our lab, envisioned that similar activation could also be used to selectively reduce ketones with borohydrides. When catachol borate was used to reduce various ketones in the presence of a chiral phosphoric acid, secondary alcohols were obtained with high selectivities (Scheme 4.1).[3] At first we assumed that the selectivity was obtained due to the formation of hydrogen bond between the catalyst and the oxygen of the boronate

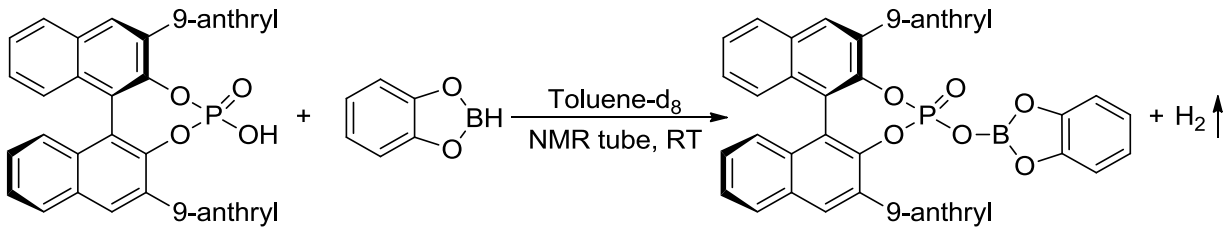


Scheme 4.1 Phosphoric acid catalyzed reduction of ketones

However when mechanistic studies were performed, very different results was observed. When the acid catalyst was treated with equivalent amount of catecholborane, evolution of hydrogen gas was observed (Scheme 4.2). ^{11}B NMR experiment of this mixture showed that the resonance for catacholborane (δ = 28.73 ppm, doublet, J = 194 Hz) shifted upfield to 22.13 ppm as a singlet. These results clearly prove that a new boronate species is formed when phosphoric acid is interacted with the catecholborane via the loss of hydrogen. In this new boronate species formed, the boron center is believed to act as a Lewis acid to activate the carbonyl, while the P=O moiety can act as a Lewis base to increase the nucleophilicity of catachol boroane. Also, the addition of DMAP as an additive helps in obtaining better selectivity by the altering the reactictivity/sterics of the catalyst system, by coordinating with the boron (seen in ^{11}B NMR experiment).[3] This new system formed by the reaction of catecholbornane and a chiral phosphoric acid could serve as a potential Lewis acid catalyst in various transformations.

4.1.2 Reddy's Work with propargylation

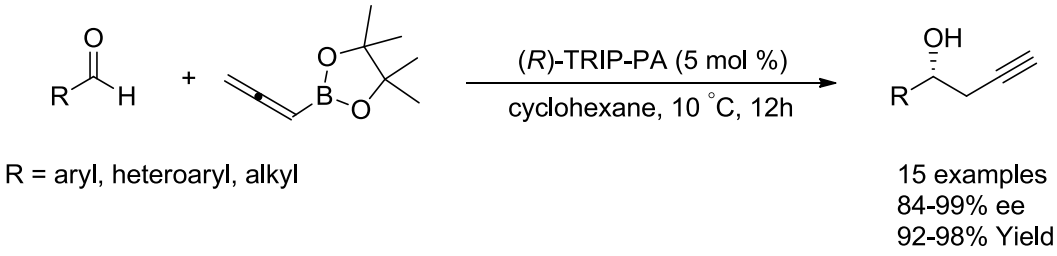
The Brønsted acid catalyzed allylboration methodology was efficiently extended to the



Scheme 4.2 Generation of the chiral boronate in situ

propargylation of aldehydes utilizing TRIP-PA as the catalyst by our group[4] (see chapter 3) followed by Reddy[5,8] and Roush.[6,9]

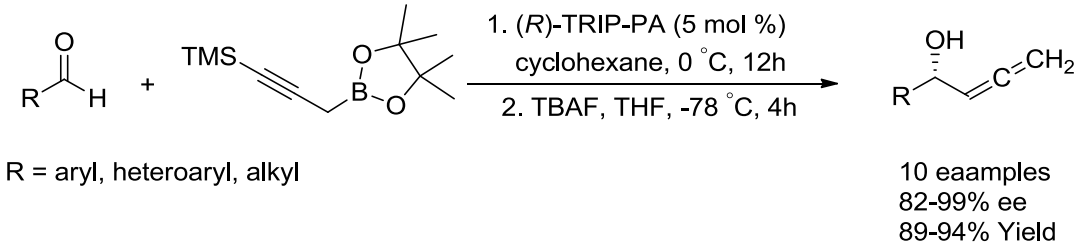
Reddy from Novartis Pharmaceuticals Corporation reported the propargylation of aldehydes with TRIP-PA as the catalyst.[5] Though very similar to our report on propargylation, he discovered that cyclohexane was a superior solvent when compared to toluene. The reaction was performed on various aromatic, heteroaromatic and aliphatic aldehydes with allenyl boronic acid pinacol ester as the propargyl donor and 5 mol % of the phosphoric acid catalyst. Under catalytic conditions the reaction was carried out at 10 °C for 12 hours to get enantioselectivities ranging from 84-99% (Scheme 4.3).[5]



Scheme 4.3 Reddy's propargylation of aldehydes

4.1.3 Reddy's Work with allenylation

Reddy also extended our methodology to allenylation of aldehydes with the same catalytic system.[8] TMS propargyl boronate was reacted with different aldehydes in presence of TRIP-PA to give α-allenic alcohols after desilyation in 82-99 % enantioselectivities (Scheme 4.4). Good yields and enantioselectivities were obtained for various aromatic heteroaromatic and aliphatic aldehydes.[8]



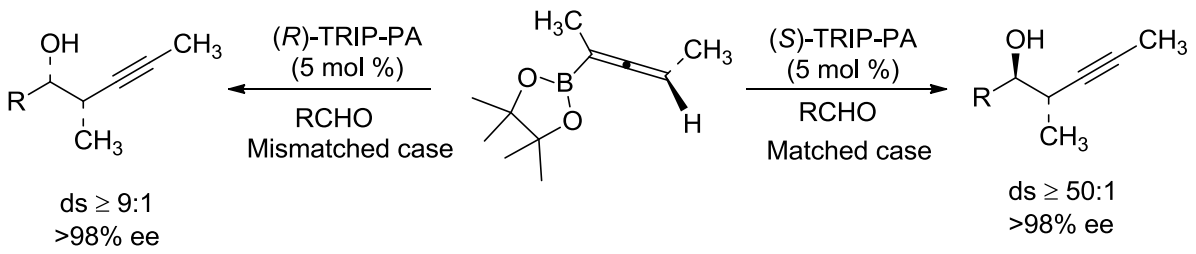
Scheme 4.4 Reddy's allenylation of aldehydes

4.1.4 Roush's Work

In 2012, Roush synthesized chiral *anti*- and *syn*-homopropargyl alcohols using the TRIP-PA catalyst.[6] Aldehydes were reacted with chiral allenyl boronates to synthesize homopropargyl products in high diastereo- and enatio-control (Scheme 4.5). The geometry of the methyl groups introduced in the products is controlled by the stereochemistry of the allenylboronate, while the phosphoric acid catalyst controls the stereochemistry of the hydroxyl center. Thus using *R* and *S* isomers of the catalyst gave syn- and anti-homopropargylic alcohols respectively. The methodology was utilized in the preparation of *anti*, *anti*-stereotriads, the synthesis of which quite challenging with aldol and crotylation reactions.[6]

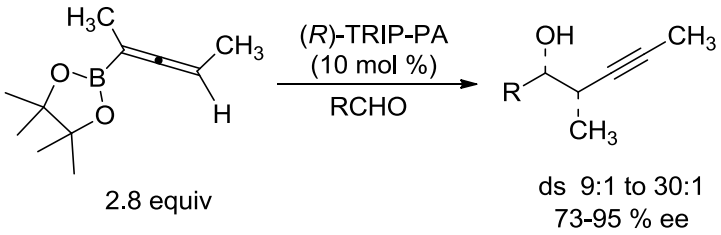
4.1.5 Roush's kinetic resolution

Roush also reported the TRIP-PA catalyzed allenylboration of aldehydes by the kinetic



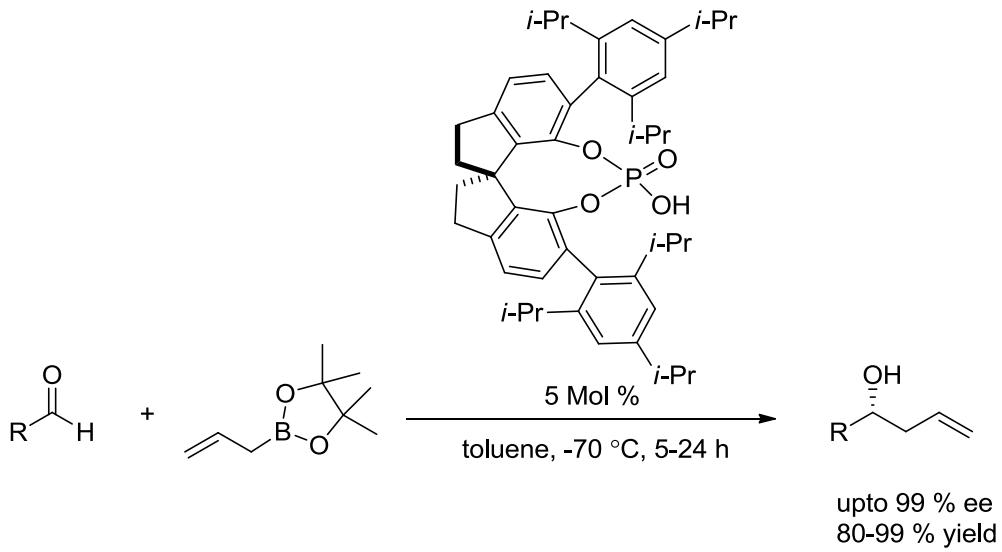
Scheme 4.5 Roush's propargylation with chiral boronates

resolution of nonchiral allenylboronates.[9] *Anti*-homopropargyl alcohols were obtained when 2.8equiv of allenyl pinacol boronate was reacted with aldehydes in presence of 10 mol% of the chiral phosphoric acid (Scheme 4.6). The products were obtained in 83-95% yields with diastereoselectivities up to 20:1 and enantioselectivities upto 95%. Three consecutive stereocenters were obtained to give anti, anti-homopropargyl when a chiral aldehyde was used.[9]



Scheme 4.6 Kinetic resolution for the synthesis of homopropargylic alcohols

Hu successfully employed the 1,1′-spirobiindane-7,7′-diol (SPINOL) derived phosphoric acids for the asymmetric allylboration of aldehydes.[7] This methodology also used allyl boronic acid pinacol ester as the allyl source with toluene as the solvent (Scheme 4.7). This system gave slightly better selectivities when compared to our phosphoric acid catalyzed methodology. However the reaction was run at lower temperatures (-70 °C) for longer periods of time (5-24 h). The reaction conditions also gave excellent diastereoselectivities and enantioselectivities for the crotylboration of aldehydes.[7]



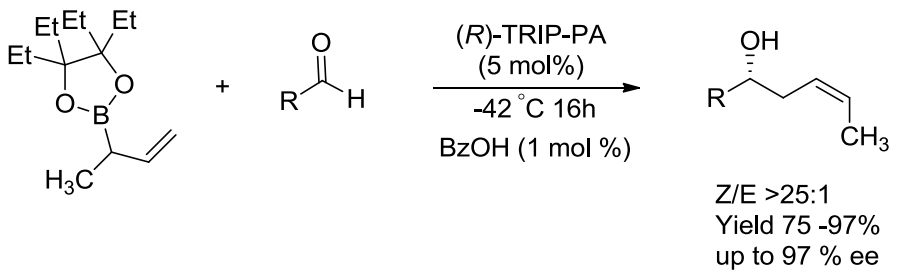
Scheme 4.7 Hu's allylation with SPINOL-derived phosphoric acid

4.1.6 Malkov's Kinetic resolution for allylboration

More recently, Malkov used TRIP-PA as the catalyst to synthesize *Z*-homoallylic alcohols via the kinetic resolution of racemic allylboronates.[11] Excess of racemic secondary boronate was reacted with aldehydes in the presence of TRIP-PA as the catalyst (Scheme 4.8). The tetraethyl analogue of the allylboronate identified by the quantum chemical calculations gave better selectivities compared to the pinacol allylboronate. Most of the homoallylic alcohols were obtained with remarkable Z selectivity (>25:1) and high enantiomeric purity. Use of benzoic acid as an additive enhanced the reaction rate for the phosphoric acid catalyzed allylboration of aldehydes. The conditions were shown to effectively catalyze a wide range of aldehydes giving predominantly the *cis*-isomer with excellent enantioselectivites.[11]

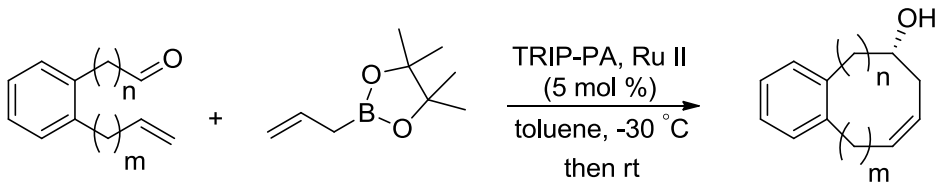
4.1.7 Barrio's relay catalysis

Barrio synthesized six- and seven-membered benzo- and heteroaryl-fused cyclic homoallylic alcohols by tandem phosphoric acid catalyzed allylboration and ring closing



Scheme 4.8 Malkov's Kinetic resolution for allylboration reaction

metathesis (Scheme 4.9).[10] It was interesting to see that the phosphoric acid catalyst was compatible with the ruthenium catalyst and the reaction could be performed in one pot. The methodology shows good substrate scope which gave access to a broad range of cyclic homoallylic alcohols some of which had limited accessibility with existing synthetic procedures. [10]

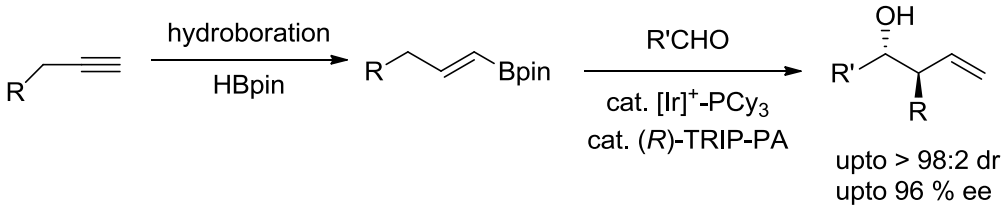


Scheme 4.9 Barrio's relay catalysis

4.1.8 Murakami's synthesis of chiral homoallylic alcohols from alkenes

Murakami reported a highly efficient synthesis of anti homoallylic alcohols from terminal alkynes and aldehydes.[12] The reaction conditions involve the use of a cationic iridium complex and a chiral phosphoric acid. Various (*E*)-2-alkenylboronates were synthesized in situ by the olefin transposition of respective 3- and 5-alkenylboronates, catalyzed by the cationic iridium (I) complex. It was exiting to find that the cationic iridium complex and the chiral phosphoric acid work in a relay and are compatible with each other. The hydroboration of terminal alkynes

followed by the transposition and the allylboration catalyzed by TRIP-PA gives the homoallylic alcohols in high diastereo- and enantio-selectivities (Scheme 4.10).[12]



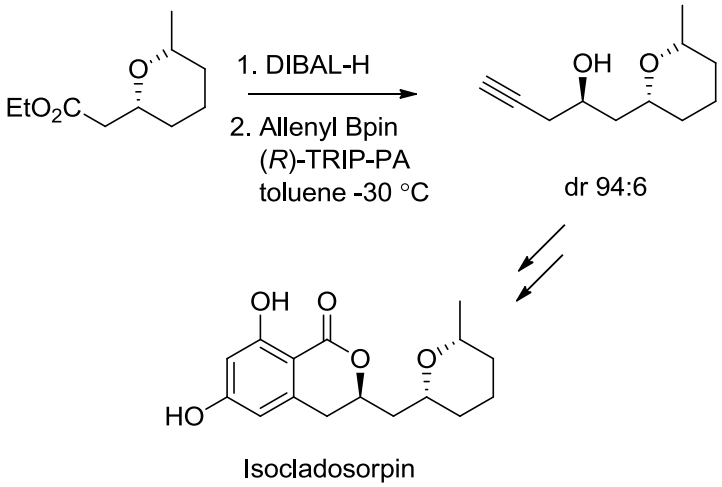
Scheme 4.10 Murakami's synthesis of chiral homoallylic alcohols from alkenes

4.1.9 Total synthesis of isocladosorpin

Reddy's group very recently reported the total synthesis of isocladosorpin[13] that was isolated from the fungus *cladosporium cladosporioides* in 1993. The promising biological activity of isocladosporin has interested many synthetic groups towards its total synthesis. Reddy's group utilized oxa-Michael reaction, asymmetric propargylation and the Alder-Rickerts reaction as the key steps in the total synthesis of this molecule. We were pleased to see that one of the key steps involving the asymmetric propargylation was carried out using our methodology. In the presence of TRIP-PA as the catalyst and the allenyl boronic acid pinacol ester as the propargyl source in toluene as the solvent yielded the respective homopropargyl alcohol with *dr* of 94:6 at -30 °C (Scheme 4.11). This homopropargylic alcohol was further transformed in multiple steps to synthesize isocladosorpin. [13]

4.2 Further improvement of the methodology

The methodology developed for the phosphoric acid catalyzed allylboration and propargylation of aldehydes is one of the most efficient and practical ways to attain chiral homoallylic and homopropargylic alcohols.[1,3] However this methodology like any other synthetic transformation has some room for improvement. Though the TRIP-PA catalyzed



Scheme 4.11 Total synthesis of isocladosorpin

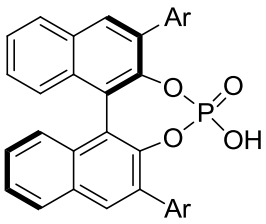
allylboration was very efficient towards a wide variety of substrates including aryl, heteroaryl, α,β-unsaturated aldehydes (91-99% ee), this system was slightly less efficient towards aliphatic substrates giving enantioselectivities in the range of 73-90%. Also, though good selectivities were obtained at room temperatures the reaction had to be performed at -30 °C to attain the very high selectivities.

The phosphoric acid catalyzed propargylation reaction was efficient and practical compared to the currently available methods, it did have some significant limitations: 1) High catalyst loading (20 mol %) was needed to attain high enantioselectivities. 2) The reaction had to be run for long periods of time (48-96 hours). 3) Moderate selectivities towards aliphatic substrates (77-82% ee).[3]

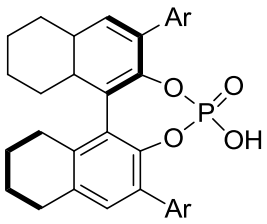
4.3 Insights from computational studies

Goodman[14a,c] and Houk[3,14b] independently reported the computational aspects for the chiral BINOL-derived phosphoric acid catalyzed allylboration of aldehydes. These studies show that the major isomer is formed *via* a transition state involving the hydrogen bonding interaction

between the hydroxyl group of the catalyst and the pseudoaxial oxygen of the boronate, with a stabilizing interaction of the phosphoryl oxygen to the formyl hydrogen. Computational studies also suggest that the clash of the methyl groups on the pinacol boronate (**B1** or **B3**) with the bulky aromatic substituents on the catalyst (**PA1**) plays an important role in controlling the absolute stereochemistry.[14] Keeping this in mind we predicted that increasing the bulk, either on the catalyst or the boronate should consequently affect the transition state and thus the enantioselectivity. We chose propargylation reaction over allylation for our initial studies, as the slower reaction rate of the former would aid us in better analyzing the reaction.



PA1: Ar = 2,4,6-*i*$Pr_3C_6H_2$
PA2: Ar = 2,4,6-Cyclohexyl$_3C_6H_2$
PA3: Ar = 9-anthryl

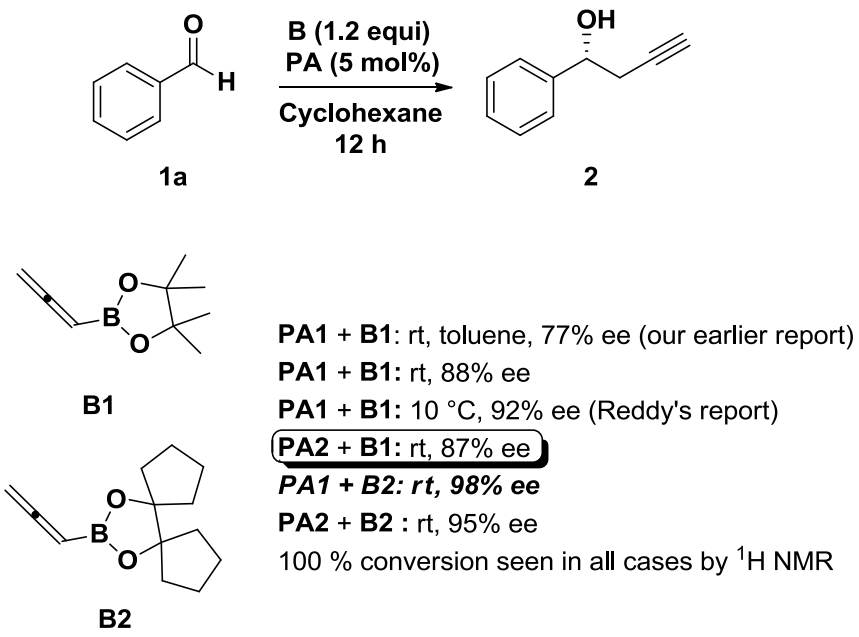


PA4 or (*R*)-H8-TRIP-PA: Ar = 2,4,6-*i*$Pr_3C_6H_2$

Figure 4.1 Catalysts rescreened for asymmetric allylboration and propargylation of aldehydes

4.4 Propargylation

Earlier we reported that TRIP-PA (**PA1,** Figure 4.1) catalyzed propargylation of benzaldehyde with allenyl boronic acid pinacol ester (**B1**) gave 77% ee at rt in toluene (91 % ee with 20 mol % catalyst at -20 °C).[3] When cyclohexane was used as solvent the ee improved to 88%, Reddy has shown that at 10 °C with cyclohexane as solvent, 92 % enantioselectivity can be achieved.[5] We started our investigation (Scheme 4.12) by reacting benzaldehyde (**1a**) with pinacol boronate **B1** using 2,4,6-cyclohexylbenzene substituted BINOL phosphoric acid (**PA2**)



Scheme 4.12 Optimization of the propargylation reaction, steric effect

as a bulkier catalyst instead of TRIP-PA. 87% ee was obtained with cyclohexane as solvent, which was similar to the selectivity attained when TRIP-PA was used. Since use of bulkier catalyst did not give us the desired result we focused on increasing the bulk on the boronate. Gratifyingly, when bi(cyclopentane)diol derived allenyl boronate **B2** was used 98% ee was attained at room temperature with 5 mol % catalyst loading. The major advantage of **B2**, synthesized by using commercially available bi(cyclopentyl)diol, was that it is similar to pinacol boronate in terms of reactivity and stability but gives superior selectivity. When the bulkier catalyst **PA2** was used along with the bulkier boronate **B2** slightly lower selectivity was seen (95 % ee).

4.4.1 Substrate scope with the new boronate

We then examined the substrate scope for the propargylation reaction with the boronate **B2** and **PA1** as catalyst (Table 4.1). Wide ranges of homopropargylic alcohols were obtained from

aryl (entry 1-8), heteroaryl (entry 9) and *α,β*-unsaturated (entry 10) aldehydes with high yields and enantioselectivites (92-99%). Boronate **B2** gave superior selectivities even at room temperature with reduced reaction times when compared the selectivity obtained with **B1** at lower temperatures.

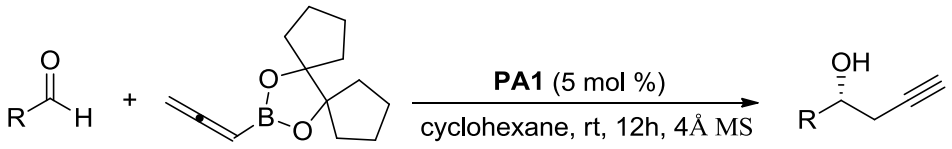
4.5 Allylboration

We then investigated the allylation of benzaldehyde (Scheme 4.13). Our earlier report on the reaction of benzaldehyde with **B3** gave 93% ee at room temperature with 5 mol % of **PA1**in toluene.[10] Use of **PA2** as a bulkier catalyst with pinacol derived allyl boronate **B3** gave 97% ee at room temperature with cyclohexane as solvent, which is equivalent to the enantioselectivity attained by **PA1** in cyclohexane. However, when bulkier boronate **B4** was used much desired results were obtained. The bi(cyclopentane)diol derived allyl boronate **B4** gave >99 ee at room temperature and the reaction was completed in less than 15 min. When the combination of bulkier catalyst **PA2** and the bulkier boronate **B4** was used, 98% ee was obtained. When the catalyst loading of **PA1** was reduced to 2 mol % and 1 mol % with **B4** at room temperature the enantioselectivity of >99% and 98% was obtained respectively with 100% conversion in < 15 min. Use of much bulkier, benzopinacol boronate gave racemic product.

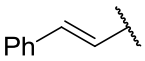
4.5.1 Substrate scope with new boronate

Substrate scope of the allylation reaction was then explored, employing method A, which utilizes 2 mol% of the catalyst at room temperature with cyclohexane as solvent (Table 4.2). It was found that a large range of aromatic compounds with electron-donating and electron-withdrawing groups at different positions of aromatic ring gave excellent yields and selectivities (entries 1-8). Hetero-aromatic and α,β-unsaturated aldehydes also gave the homoallylic alcohols with excellent enantioselectivities (entry 9, 10). *To our knowledge this is the first report of*

Table 4.1 Asymmetric propargylation of aldehydes with bi(cyclopentane)diol derived boronate B2



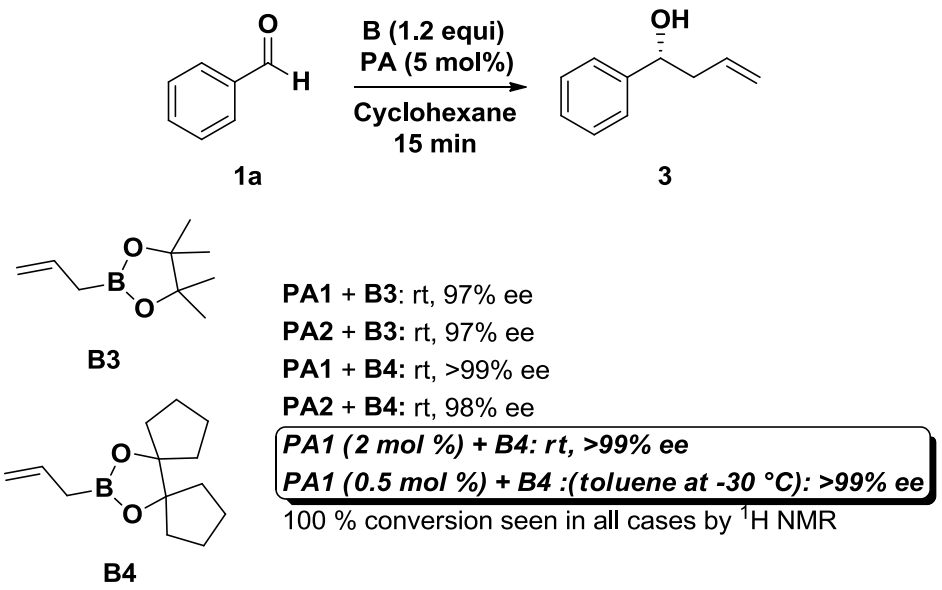
1a-j **B2** **2a-j**

entry	R	product	yield (%)[b]	ee (%)[c]
1	Ph	**2a**	94	98
2	4-BrC_6H_4	**2b**	94	99
3	4-$NO_2C_6H_4$	**2c**	93	98
4	4-$MeOC_6H_4$	**2d**	91	98
5	3-$MeOC_6H_4$	**2e**	96	96
6	2-MeC_6H_4	**2f**	94	93
7	4$CO_2MeC_6H_4$	**2g**	96	97
8	Piperonyl	**2h**	92	95
9	2-thienyl	**2i**	95	92
10		**2j**	94	92

[a] Reaction Conditions: All reactions were performed with **1** (0.10 mmol), **B2** (0.12 mmol), **PA1** 5 mol %, 50 mg 4 Å MS and 1 ml solvent at room temperature. [b] Isolated yield. [c] The products were determined to be *R* by chiral HPLC analysis and optical rotation data in literature.

catalytic or non-catalytic asymmetric allylboration of aldehydes at room temperature (mostly done at -78 ℃) with such high enantioselectivities.

Next we attempted to further reduce the catalyst loading by lowering the reaction temperature. With 0.5 mol % of the catalyst, at -30 °C in toluene (Table 4.2, method B),



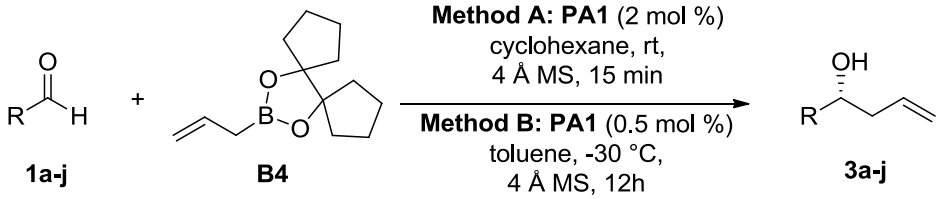
Scheme 4.13 Asymmetric allylation: Steric effect on enantioselectivity

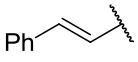
Among all the aldehydes used, 99 or higher ee was attained for more than half of the substrates with 0.5 mol % of the catalyst. It is important to note that at room temperature cyclohexane or methylcyclohexane gives superior selectivity compared to toluene but at temperatures below 0 °C toluene remains as a superior solvent. Using method A or method B, enantioselectivity of 96% or higher was achieved for all of the substrates examined. *To our knowledge 0.5 mol % is lowest catalyst loading for catalytic enantioselective allylation of aldehydes furnishing such high selectivities.*

4.6 Aliphatic aldehydes

Homoallylic alcohols obtained from aliphatic aldehydes are widely used in natural product synthesis. Our initial report with pinacol boronate **B3** with TRIP-PA as the catalyst showed moderate selectivity towards aliphatic aldehydes.[1] With hydrocinnamyl aldehyde (**1k**) as

Table 4.2 Asymmetric allylboration of aldehydes with bi(cyclopentane)diol derived boronate



entry	R	product	method	yield (%)[b]	ee (%)[c]
1	Ph	**3a**	A	95	>99
			B	94	98
2	4-BrC_6H_4	**3b**	A	96	>99
			B	95	>99
3	4-$NO_2C_6H_4$	**3c**	A	96	>99
			B	97	>99
4	4-MeOC_6H_4	**3d**	A	97	97
			B	96	96
5	3-MeOC_6H_4	**3e**	A	98	97
			B	95	>99
6	2-MeC_6H_4	**3f**	A	94	96
			B	96	>99
7	4CO_2MeC_6H_4	**3g**	A	93	96
			B	98	98
8	Piperonyl	**3h**	A	97	98
			B	97	>99
9	2-thienyl	**3i**	A	91	97
			B	93	98
10		**3j**	A	94	96
			B	97	99

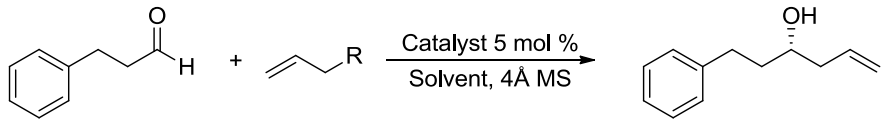
[a] Reaction Conditions: All reactions were performed with **1** (0.10 mmol), **B4** (0.12 mmol), **PA1** 0.5 or 2 mol %, 50 mg 4 Å MS and 1 ml solvent. [b] Isolated yield. [c] The products were determined to be *R* by chiral HPLC analysis and optical rotation data in literature.

substrate we further explored different boronates, solvents and also revisited some of the catalysts (Table 4.3). The best selectivity obtained after re-optimization with pinacol boronate **B3** was 90 % with methyl cyclohexane as solvent and TRIP-PA as the catalyst at -20 °C. When the boronate **B5** was used, interestingly, opposite isomer was seen with moderate selectivities (60-75% ee). The boronate **B6** gave racemic products. When the boronate **B7** was used low enatiocontrol (5-30%) was seen. When the bi(cyclopentane)diol derived boronate **B4** was used with TRIP-PA as the catalyst 81 and 72 % ee was obtained at room temperature and -30 °C respectively. Gratifyingly, when H8-TRIP-PA (**PA4**) was used, the enantioselectivity improved to 95 % with toluene as the solvent. Benzyloxyacetaldehyde (**1m)**, which gave only 79% ee with **B3** and TRIP-PA,[10] gave 95% selectivity with **B4** and H8-TRIP-PA as the catalyst, under similar conditions (Table 4.4, entry 3).

4.7 Substituted allylations

Substituted allylating reagents react with aldehydes to give a wide variety of homoallylic alcohols with vicinal stereocenters that can serve as versatile synthetic intermediates.[15] Hoffmann first recognized that *β*-methyl homoallylic alcohols with high diastereoselectivities are obtained when either (*E*)- or (*Z*)-crotylboronates are reacted with aldehydes.[16] This is possible as the reaction takes place *via* a rigid, cyclic, six membered transition state making the geometry of the products predictable based on the starting materials. Thus the absolute configuration of two successive stereogenic centers can be controlled during the formation of the one carbon-carbon bond. Crotylborations is one of the most important methods for the syntheses of polypropionate

Table 4.3 Re-optimization of conditions for asymmetric allylation of hydrocinnamyl aldehyde

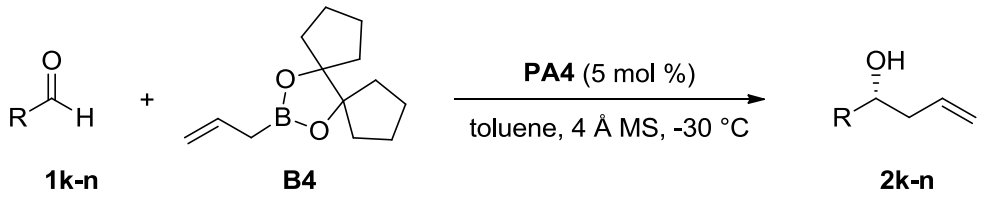


1k **B3-6** **3k**

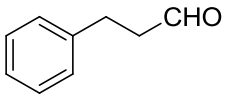
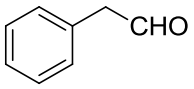
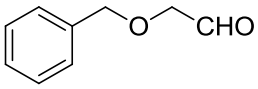
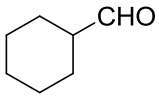
entry	R	catalyst	temp (°C)	Solvent	% Conversion[b]	ee (%)[c]
1		**PA1**	-30	toluene	100	87
2		**PA1**	-20	*me*-cyclohexane	100	90
3		**PA1**	-78	*me*-cyclohexane	100	53
4	**B3**	**PA2**	rt	cyclohexane	100	50
5		**PA3**	rt	cyclohexane	100	64
6		**PA4**	rt	cyclohexane	100	76
7		**PA1**	-70	toluene	100	75(*R*)
8		**PA1**	-70	*me*-cyclohexane	100	67(*R*)
9	**B5**	**PA2**	-70	toluene	100	60(*R*)
10	**B6**	**PA1**	-78	toluene	100	0
11		**PA1**	-78	*me*-cyclohexane	100	9
12		**PA2**	-78	*me*-cyclohexane	100	23
13		**PA1**	-30	*me*-cyclohexane	100	30
14	**B7**	**PA2**	-30	*me*-cyclohexane	100	5
15		**PA1**	rt	cyclohexane	100	81
16		**PA1**	-30	toluene	100	72
17		**PA3**	rt	cyclohexane	100	64
18	**B4**	**PA4**	rt	cyclohexane	100	86
19		**PA4**	**-30**	**toluene**	**100**	**95**

[a] Reaction Conditions: All reactions were performed with **1** (0.10 mmol), **B** (0.12 mmol), **PA** 5 mol %, 50 mg 4 Å MS and 1 ml solvent. [b] Determined by ^{1}H NMR analysis. [c] Ee determined by chiral HPLC analysis.

Table 4.4 Asymmetric allylboration of aliphatic aldehydes



1k-n **B4** **2k-n**

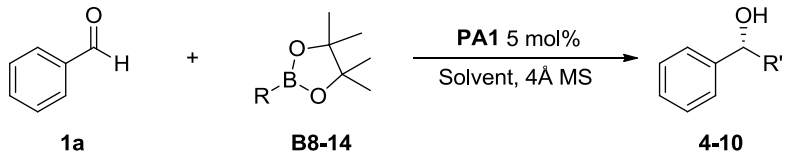
entry	R	product	yield (%)[b]	ee (%)[c]
1		**2k**	95	95
2		**2l**	93	>90
3		**2m**	96	95
4		**2n**		

[a] Reaction Conditions: All reactions were performed with **1** (0.10 mmol), **B4** (0.12 mmol), **PA4** 5 mol %, 50 mg 4 Å MS and 1 ml toluene. [b] Isolated yield. [c] Ee determined by chiral HPLC analysis.

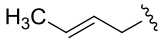
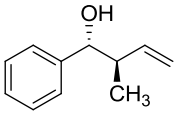
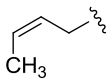
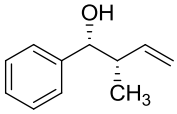
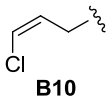
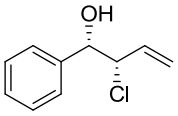
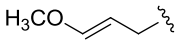
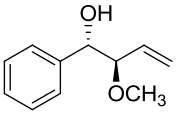
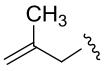
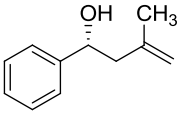
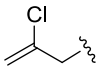
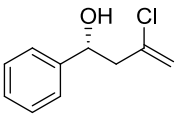
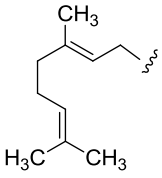
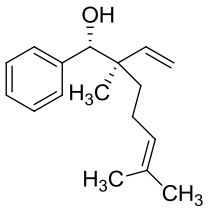
natural products.[15] When we reacted *trans*- and *cis*-crotylboronates (Table 4.5, **B8** and **B9**) with benzadehyde in cyclohexane with TRIP-PA as the catalyst, enantioselectivities of 98 % and 93 % were obtained with high diastereoselectivities (>20:1) (Table 4.5, entry 1, 2). It was exiting to find that such high enantioselectivities and diastereoselectivities could be attained at room

temperatures under catalytic conditions. Though crotylborations have been investigated a lot, substituents other than methyl at the γ-position of the allylboronate have been rarely studied. We synthesized[17] the (*Z*)-chloro allylboronate **B10** and reacted it with benzaldehyde with cyclohexane as solvent in presence of TRIP-PA as the catalyst. As expected the reaction was slower compared to the crotylboronate and was run for 24 hrs for complete conversions. The product **6** was obtained with 93% yield and 93% enantiomeric excess (entry 3). The homoallylic alcohols obtained from boronate **B10** can be easily transformed to vinyl epoxides, which serve as important intermediates in organic synthesis.[18] To study the effect of γ-alkoxyallylboronates on aldehydes under the catalytic conditions, (*E*)-methoxy allylboronate **B11** was synthesized using Ni-Catalyzed allylic borylation developed by Morken.[19] **B11** when reacted with benzaldehyde gave β-methoxy homoallylic alcohol **7** with 93% ee and 96 % yield with diastereomeric excess of >20:1 (entry 4). We also studied the *β*-methylallylation and the *β*-chloroallylation of aldehydes. 96% enantioselectivity was attained for **8** with 94% yield when boronate **B12** was reacted with benzaldehyde in toluene with **PA1** as the catalyst (entry 5). The presence of chloro group on the *β*-position of the boronate (**B13**) did not affect the reactivity as much as it did with the chloro-group at the *γ*-position (**B10**) and hence the reaction could be run at much lower temperatures. The best ee that could be attained after the allylation with boronate **B13** was 81% at -55 °C with 91% yield for homoallylic alcohol **9** (Table 4.5, entry 6). Reaction temperature higher or lower than -55 °C gave reduced enantioselectivity showing that temperature can play an important role in some of Brønsted acid catalyzed allylation reactions. To study the effect of a more challenging substrate, much bulkier boronate **B14** was synthesized from geranyl acetate following Morken's procedure.[19] 73 % ee was obtained for product **10** with high diastereoselectivities with the formation of two vicinal chiral centers including an all-carbon

Table 4.5 Asymmetric allylboration of benzaldehyde with substituted allylation reagents



1a **B8-14** **4-10**

Entry	R	Product	Yield[b]	dr[c]	ee[d]
1	 **B8**	 **4**	98	>20:1	99
2	 **B9**	 **5**	96	>20:1	93
3	 **B10**	 **6**	93	–	93
4	 **B11**	 **7**	94	>20:1	93
5	 **B12**	 **8**	94	NA	96
6	 **B13**	 **9**	91	NA	81
7	 **B14**	 **10**	92	–	75

[a] Reaction Conditions: All reactions were performed with **1** (0.10 mmol), **B** (0.13 mmol), **PA** 5 mol %, 50 mg 4 Å MS and 1 ml solvent. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Ee determined by chiral HPLC analysis.

quaternary carbon center (Table 4.5, entry 7).

4.8 Conclusion

The Brønsted acid catalyzed allylboration and the propargylation of aldehydes utilizing pinacol derived boronates have gained importance and have been utilized widely since its discovery. We attempted to further improve the methodology by screening different boronates and catalysts. Bi(cyclopentane)diol derived boronate reagents were found to be superior reagents compared to pinacol derived reagents for the Brønsted acid catalyzed allylation and propargylation reactions. Allylation can be done with 2 mol % of catalyst at room temperature or with 0.5 mol % catalyst at -30 °C. Propargylations can also be carried out at room temperatures with superior enantiocontrol with 5 mol % catalyst. Use of H8-TRIP-PA gives excellent enantioselectivities for aliphatic aldehydes with the boronate **B4**. Highly useful diastereoselctive allylations were studied with various allylating reagents giving excellent enatioselectivity and diasteroselectivity in most of the cases. The bi(cyclopentyl)diol derived boronates are suitable substitutes for pinacol boronates and may find useful applications not only in the other Brønsted acid catalyzed reactions but also in several other reactions that utilize pinacol boronates.

4.9 References

(1) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884.

(2) For examples of catalytic allylborations, see: (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586. (b) Ishiyama, T.; Ahiko, T. –A.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414. (c) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518.

(d) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808. (e) Rauniyar, V.; Hall, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2426. (f) Hall, D. G. *Synlett* **2007**, 1644. (g) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481. (h) Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236. (i) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8911. (j) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660. (k) Barnett, D. S.; Moquist, P. N.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8679.

(3) Zhang, Z.; Jain, P.; Antilla J. C. *Angew. Chem. Int. Ed*. **2011**, *50*, 10961.

(4) Jain, P.; Wang, H.; Houk, K. N.; Antilla, J. C. *Angew. Chem., Int. Ed*. **2012**, *51*, 1391.

(5) Reddy, L. R. *Org. Lett*. **2012**, *14*, 1142.

(6) Chen, M.; Roush, W. R. *J. Am. Chem. Soc*. **2012**, *134*, 10947.

(7) Xing, C.-H.; Liao, Y. –X.; Zhang, Y.; Sabarova, D.; Bassous, M.; Hu, Q. –S. *Eur. J. Org. Chem*. **2012**, 1115.

(8) Reddy, L. R. *Chem. Commun*., **2012**, *48*, 9189.

(9) Tsai, A. S.; Chen, M.; Roush, W. R. *Org. Lett.* **2013**, *15*, 1568.

(10) Fustero, S.; Rodriguez, E.; Lazaro, R.; Herrera, L.; Catalan, S.; Barrio, P. *Adv. Synth. Catal.* **2013**, *355*, 1058.

(11) Incerti-Padillos, C. A.; Kabeshov, M. A.; Malkov, A. V. *Angew. Chem. Int. Ed*. **2013**, *52*, 5338.

(12) Miura, T.; Nishida, Y.; Morimoto, M.; Murakami, M. *J. Am. Chem. Soc*. **2013**, *135*, 11497.

(13) Reddy, B. V. S.; Reddy, P. J.; Reddy, C. S. *Tetrahedron Lett*. **2013**, *54*, 5185.

(14) For computational aspects of chiral-BINOL phosphoric acid catalyzed allylboration and propargylations, see: (a) Grayson, M. N.; Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc*. **2012**, *134*, 2716. (b) Wang, H.; Jain, P.; Antilla, J. C.; Houk, K. N. *J. Org. Chem*. **2013**, *78*, 1208. (c) Grayson, M. N.; Goodman, J. M. *J. Am. Chem. Soc*. **2013**, *135*, 6142.

(15) For recent review on diastereoselective allylations, see: Yus, M.;Gonzalez-Gomez, J. C.; Foubelo, F. *Chem. Rev*. **2013**, *113*, 5595.

(16) (a) Hoffmann, R. W. and Ladner, W. Tetrahedron Lett. 1979, 20, 4653. (b) Hoffmann, R. W.; Zeiss, H. J. *Angew*. *Chem*., *Int. Ed. Engl.* **1979**, *18*, 306. (c) Hoffmann, R. W.; Zeiss, H. J. *J. Org. Chem.* **1981**, *46*, 1309.

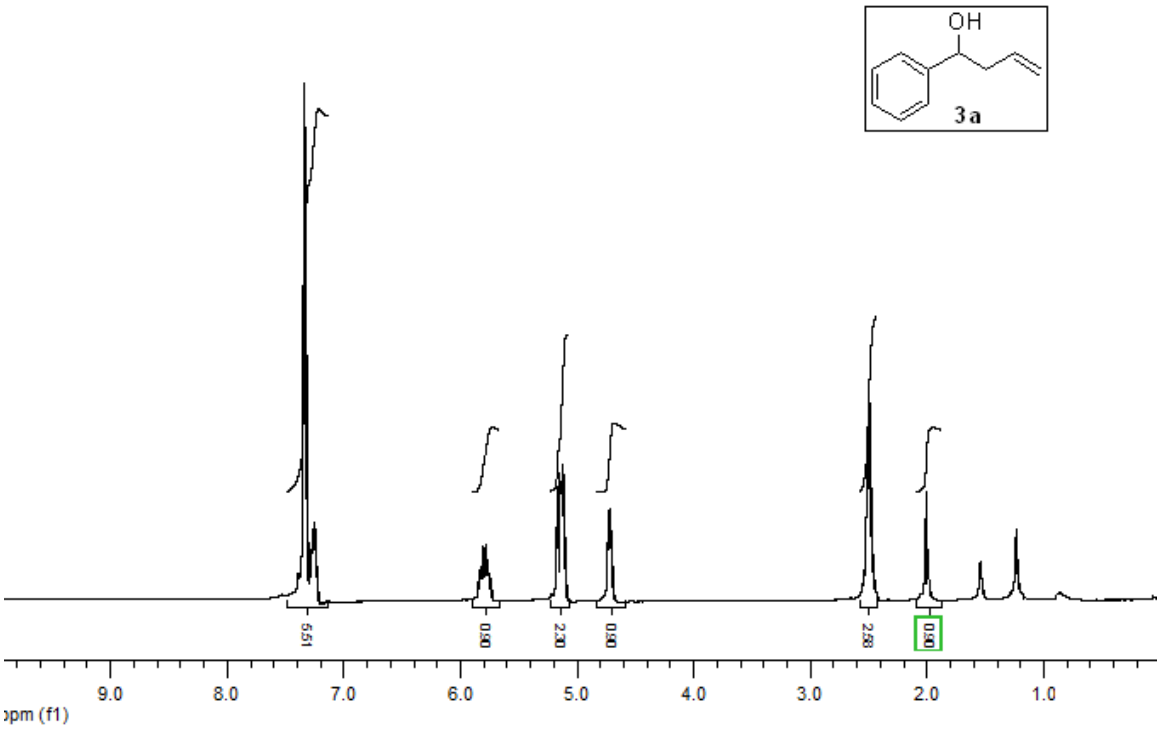
(17) The boronate **B10** was synthesized following a literature procedure with some modifications : Julia, M.; Verpeaux, J-. N.; Zahneisen, T. *Synlett* **1990**, 769.

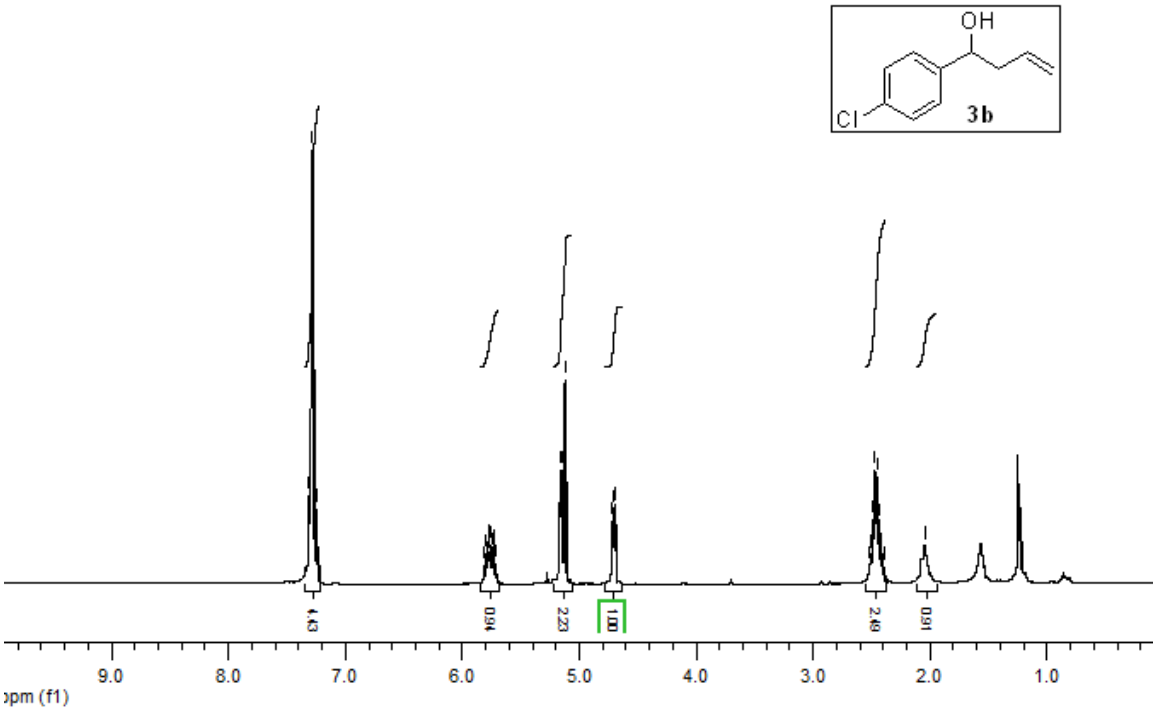
(18) (a) Smith, J. G. *Synthesis* **1984**, 629. (b) Marshall, J. A. *Chem. Rev*. **1989**, *89*, 1503. (c) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5.

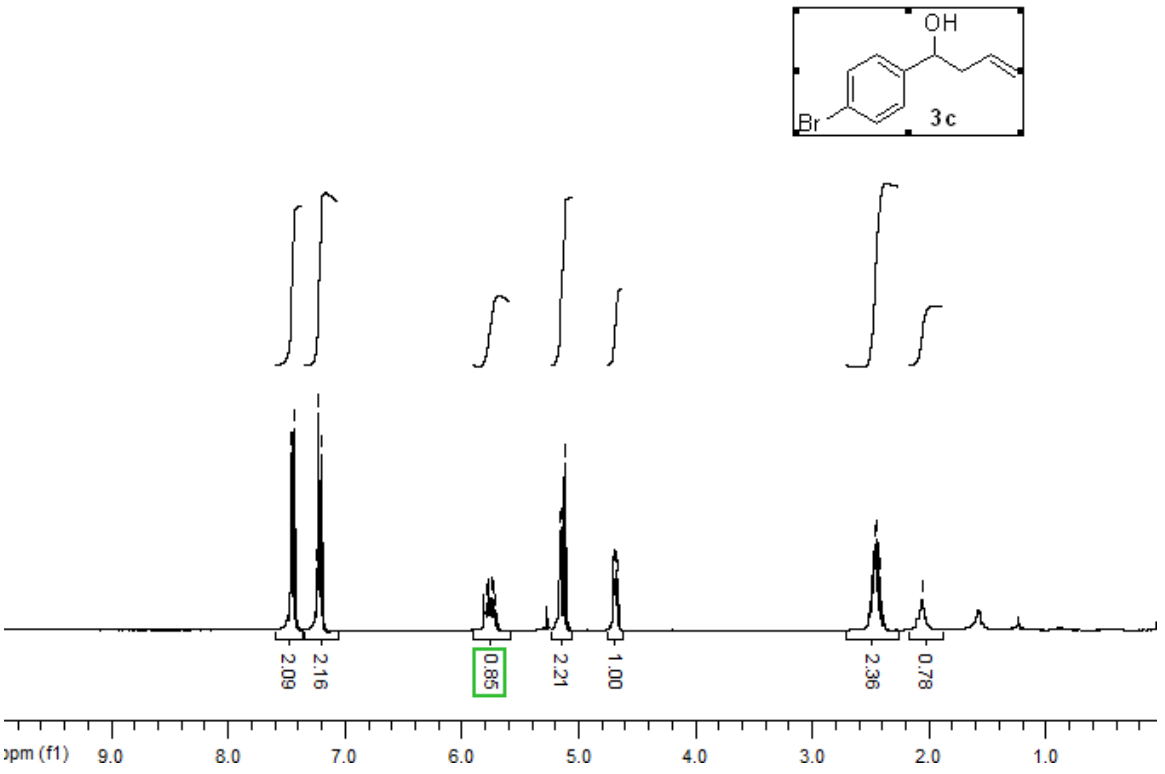
(19) Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett*. **2012**, *14*, 1416.

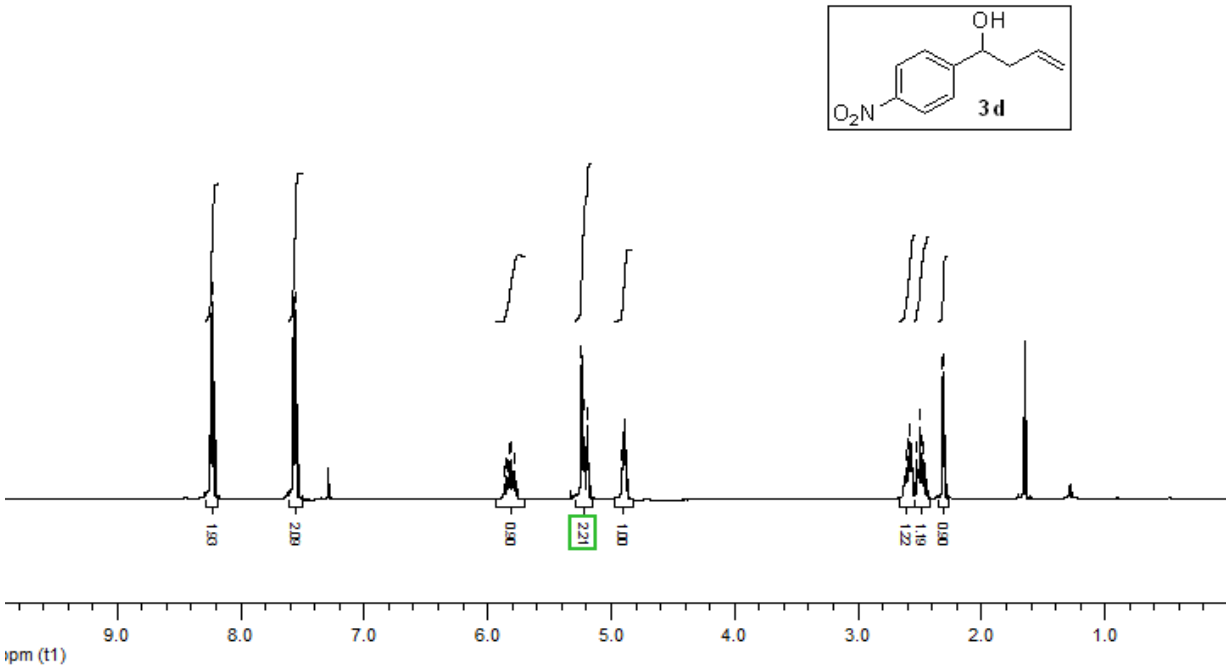
Appendix 1

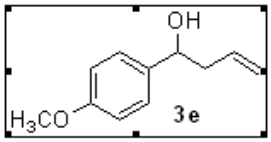
^{1}H NMR spectra for the compounds in chapter 1

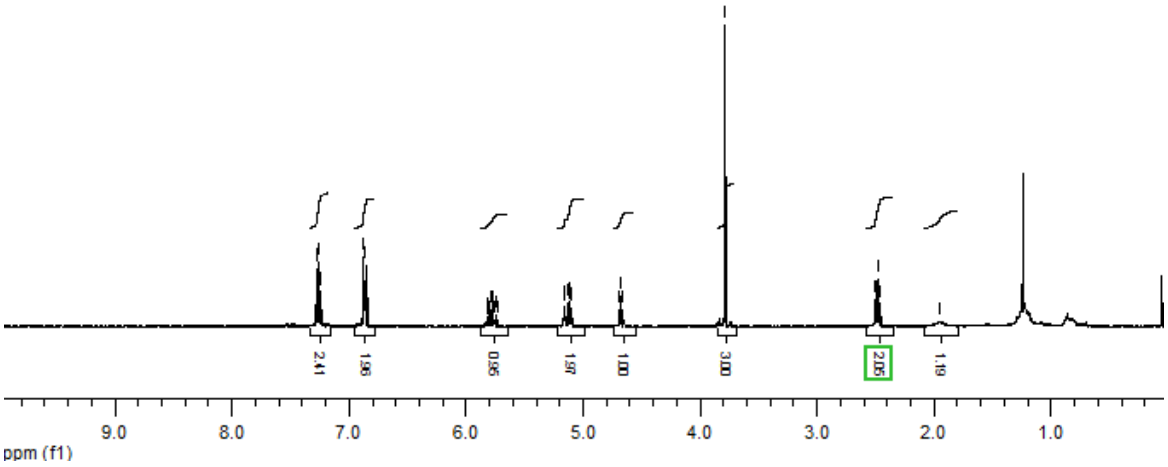


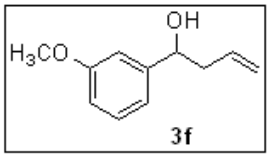


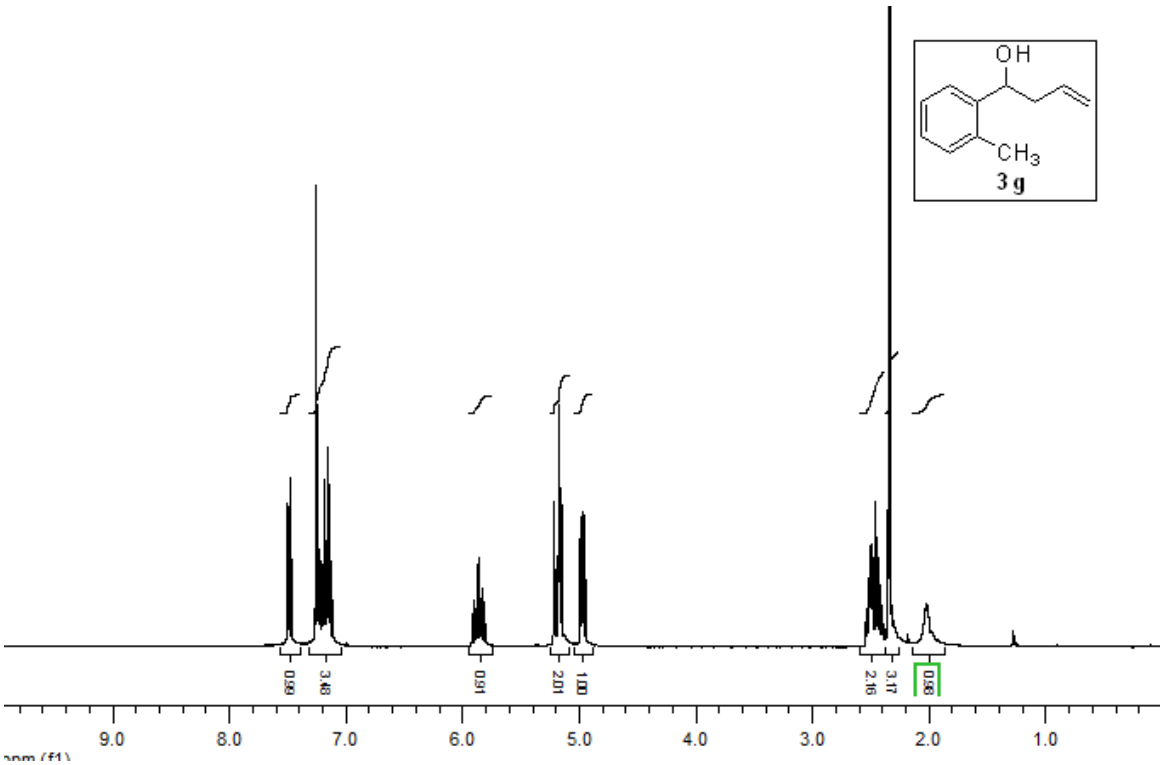


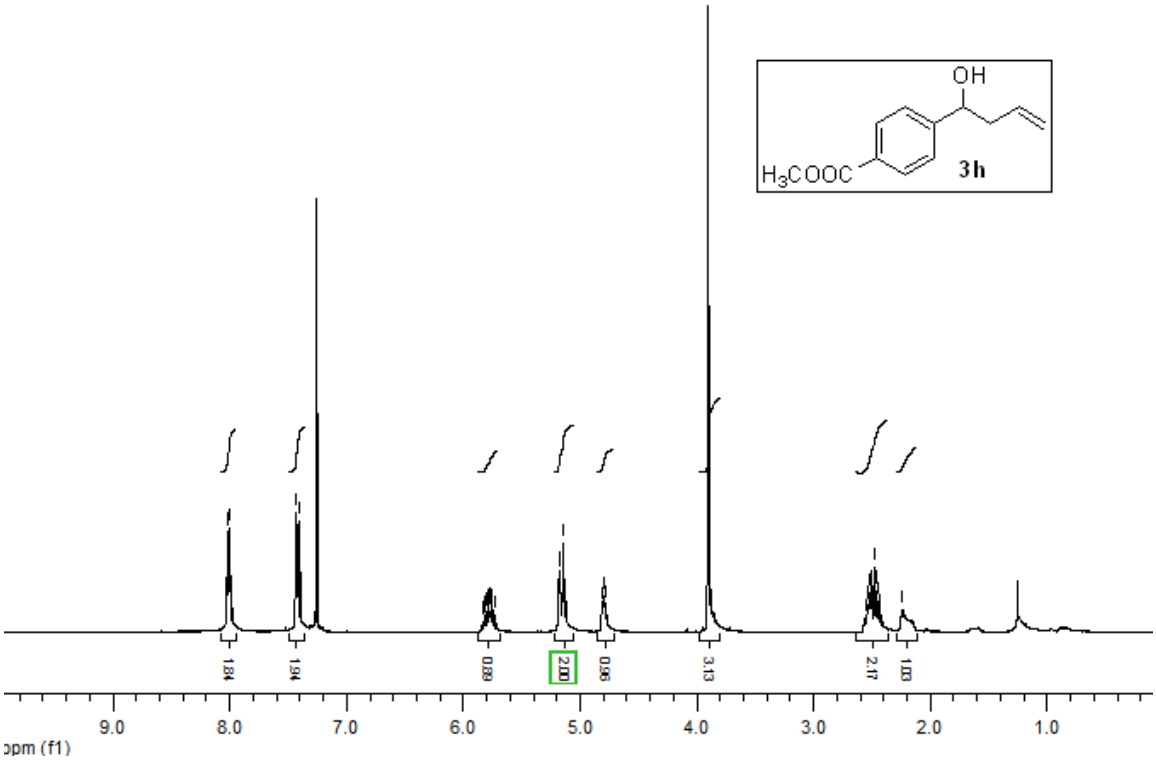


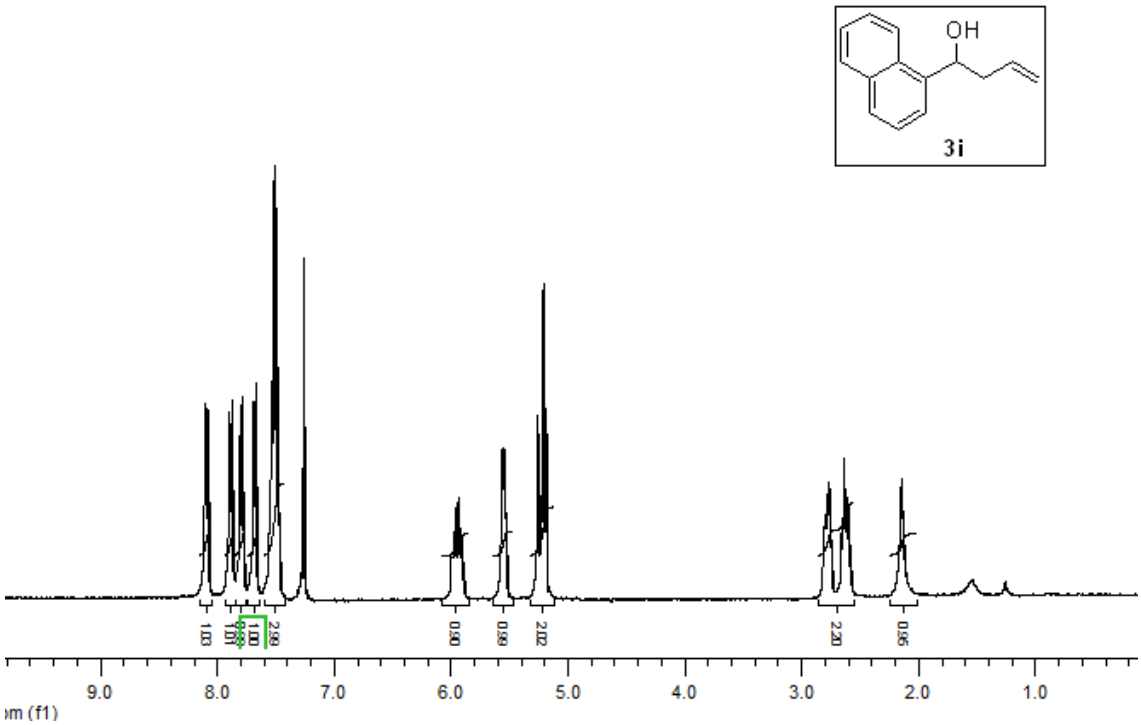


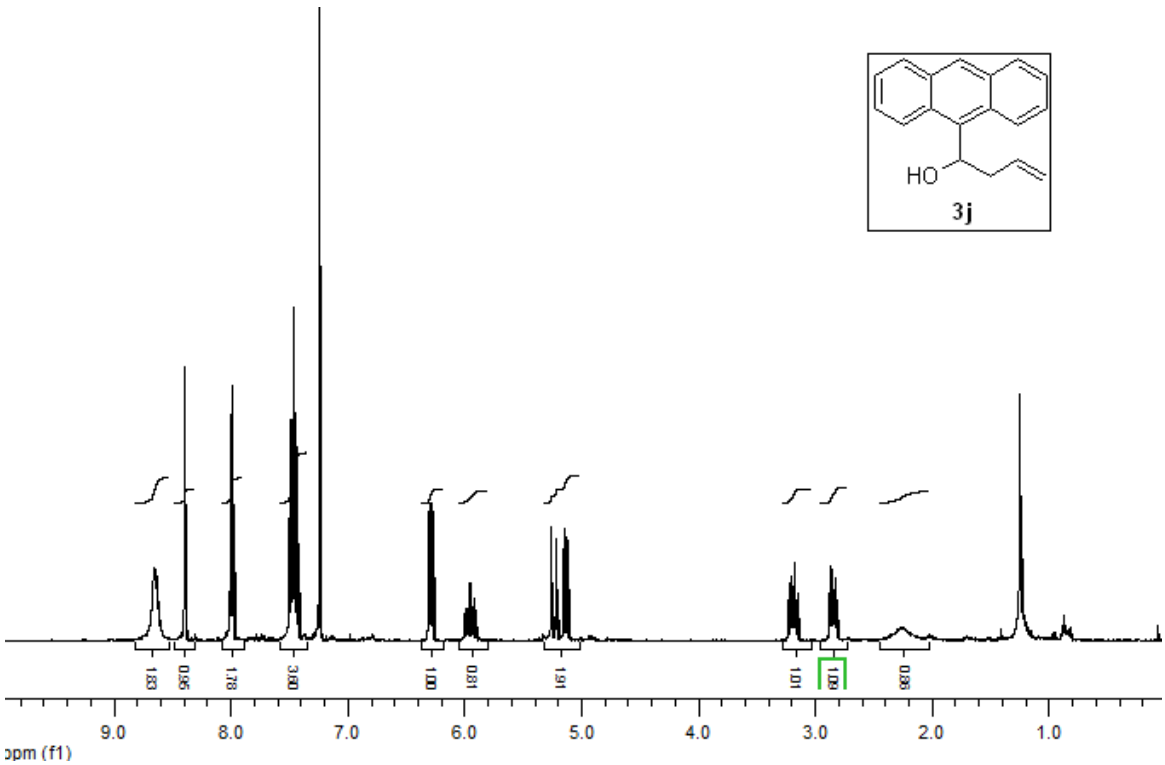


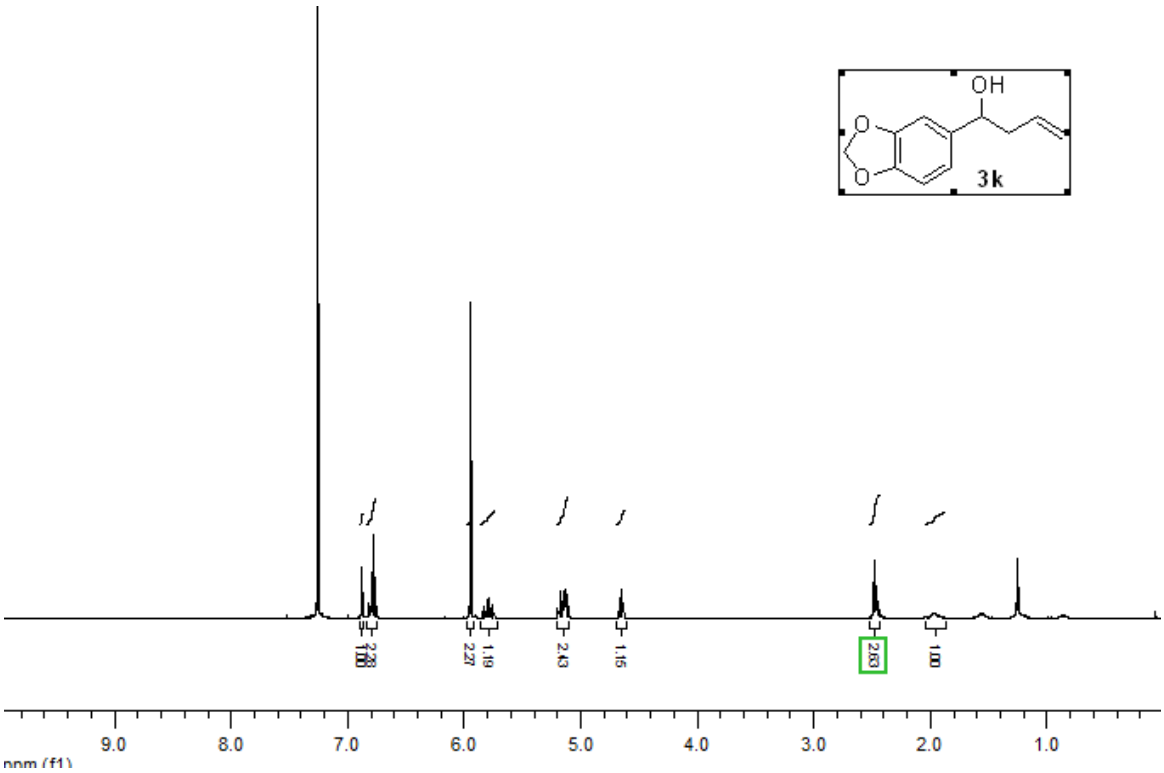


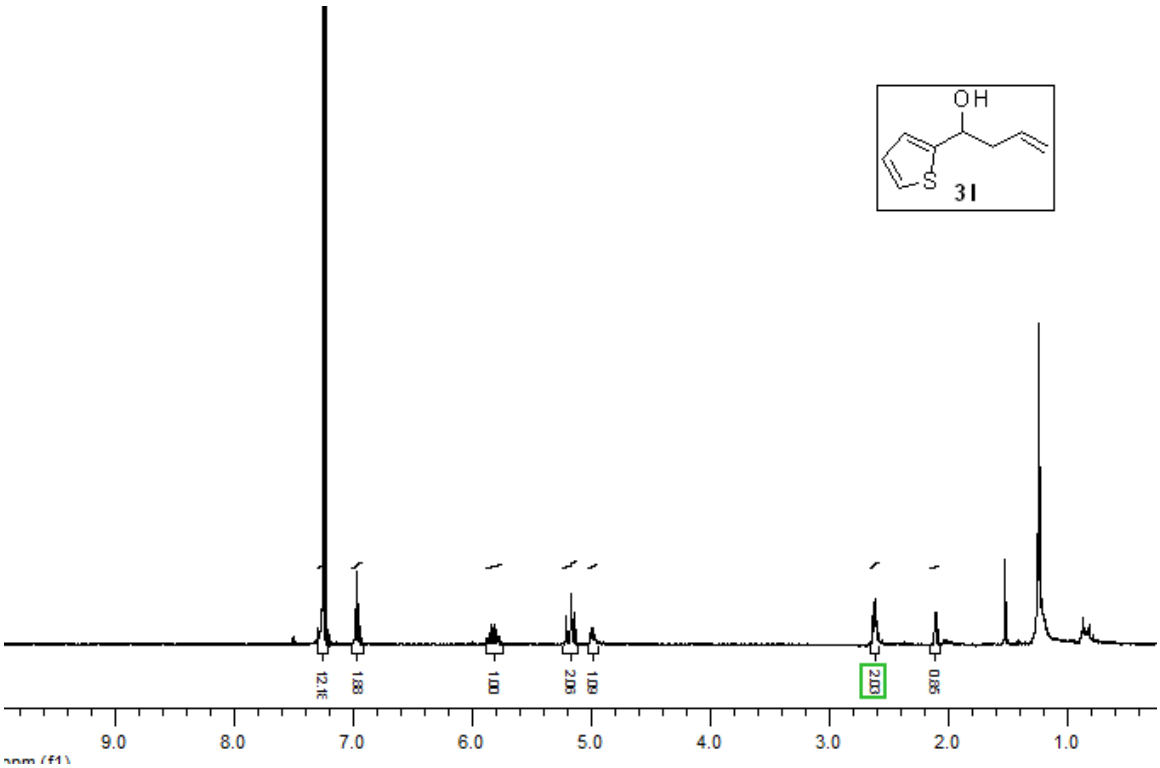


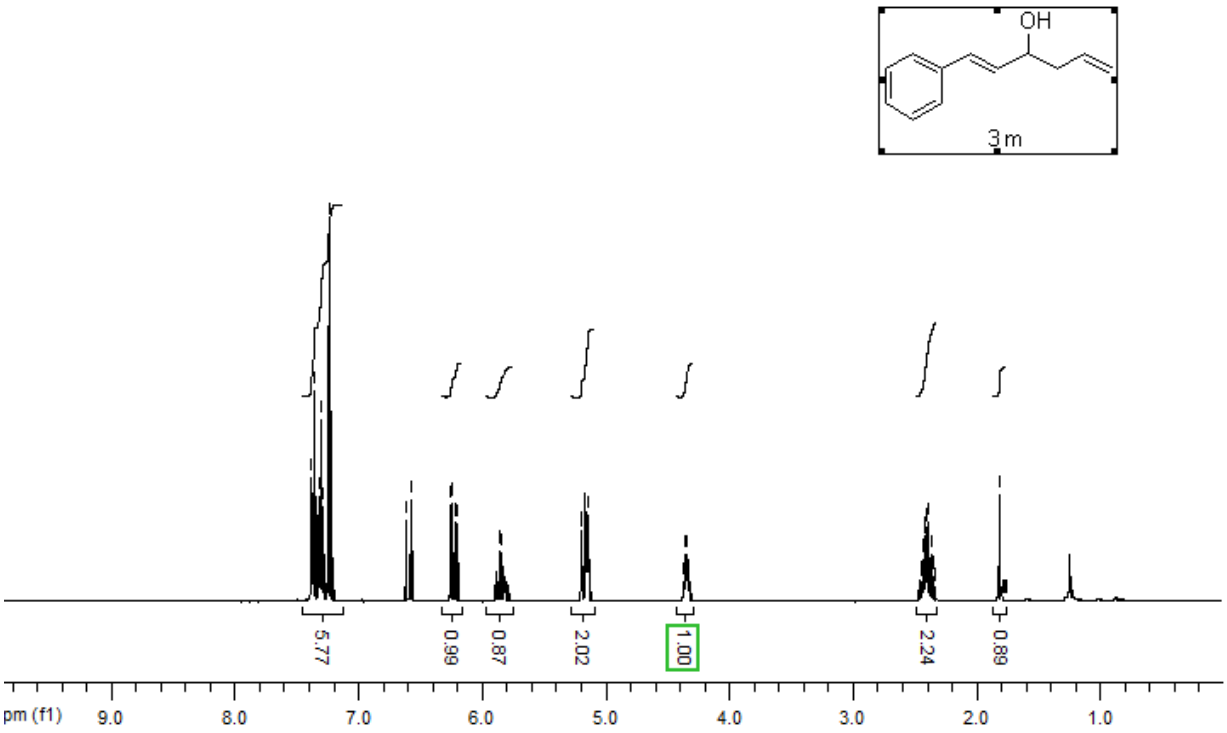


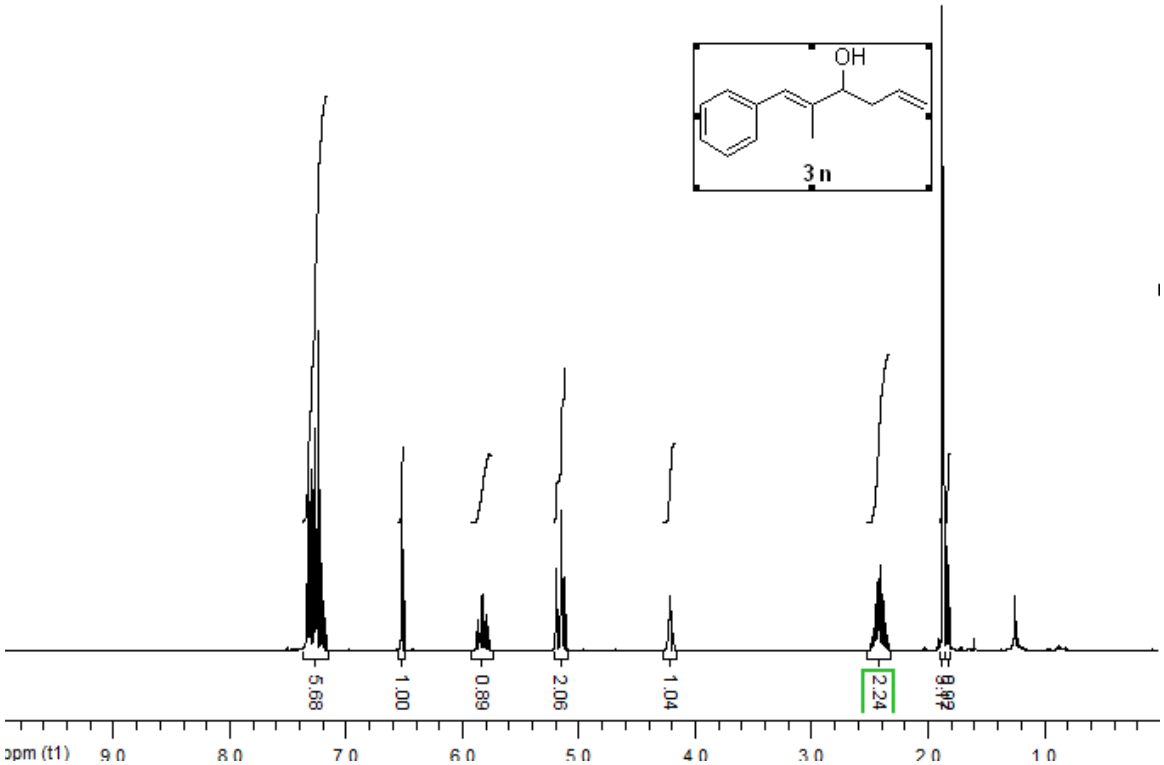


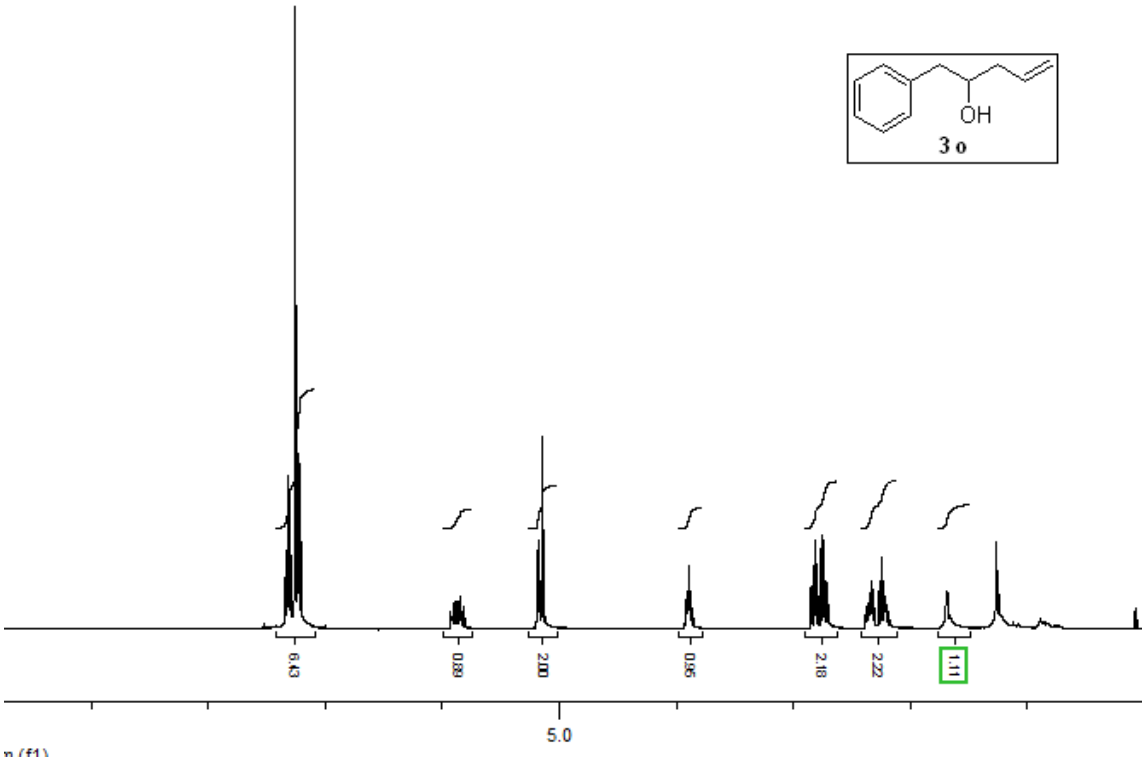


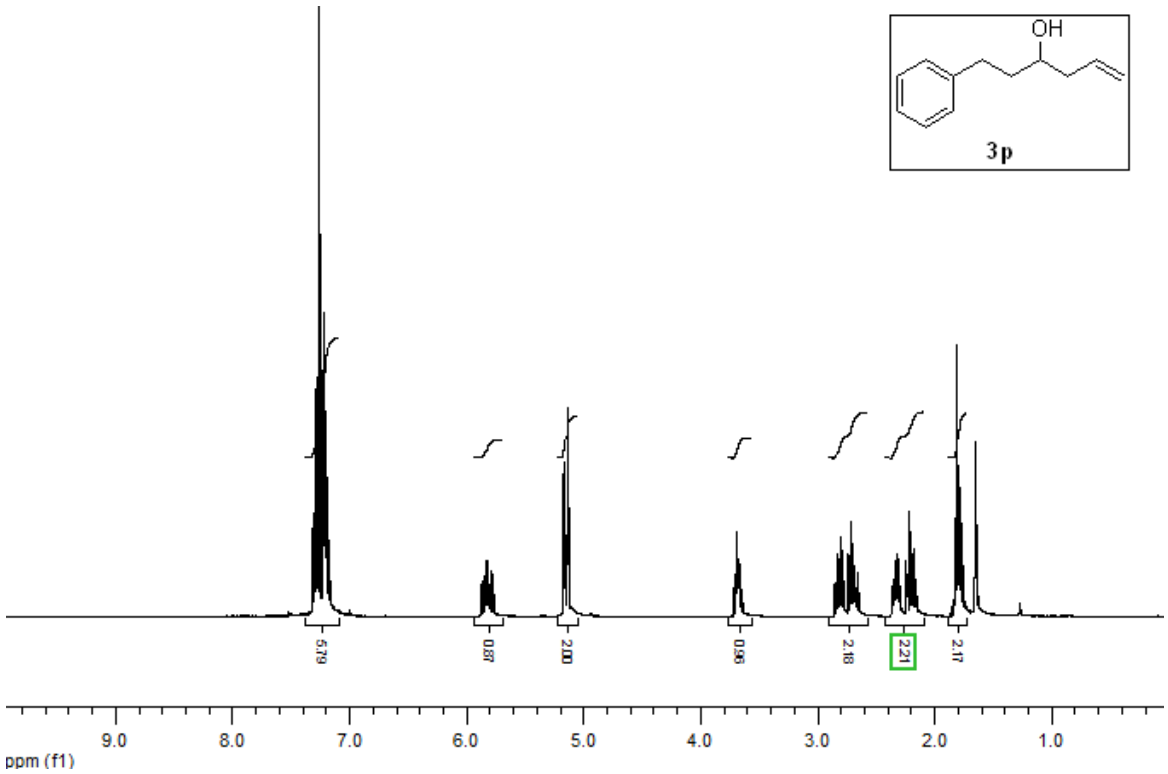


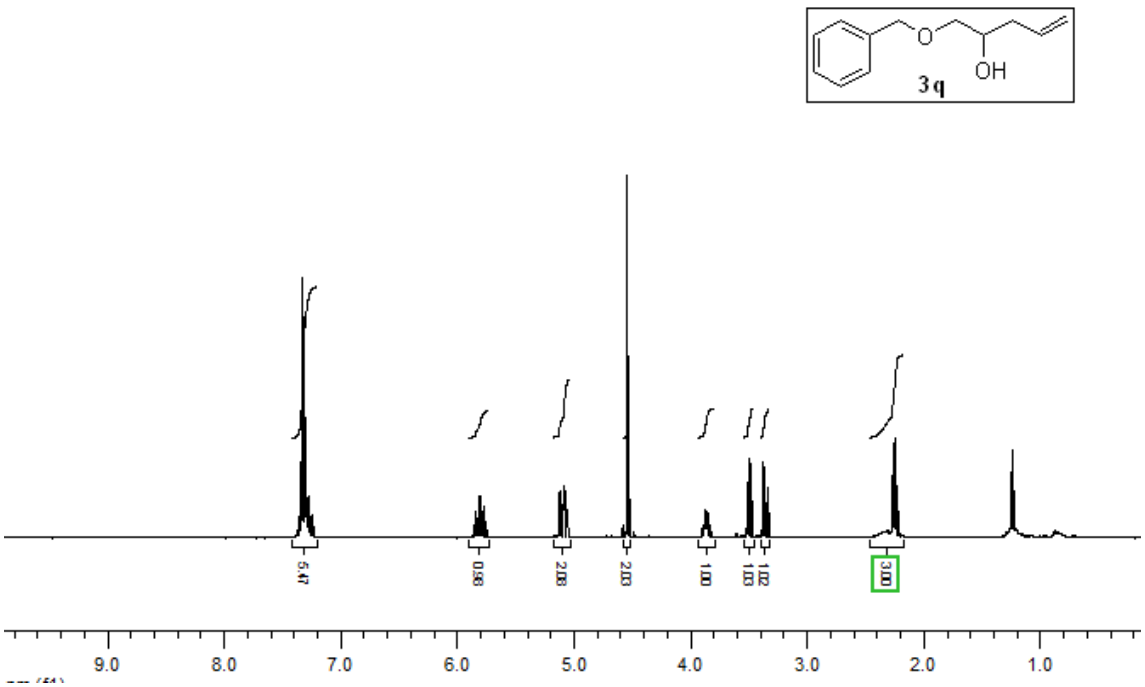


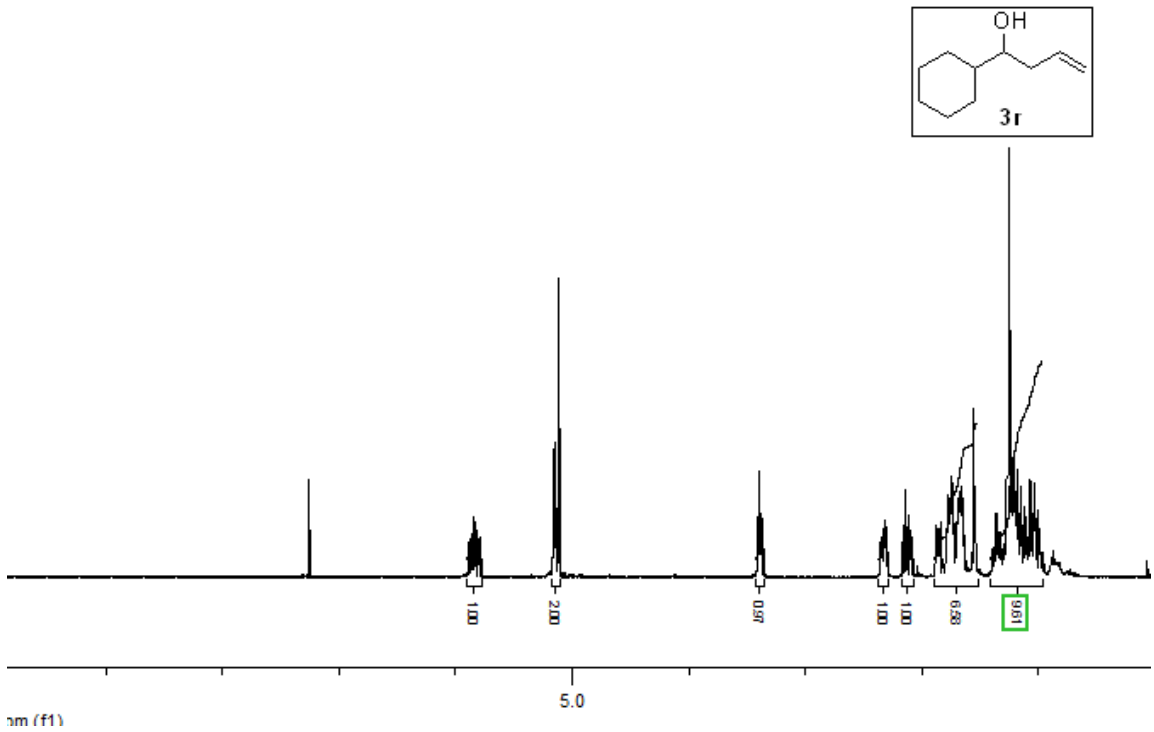


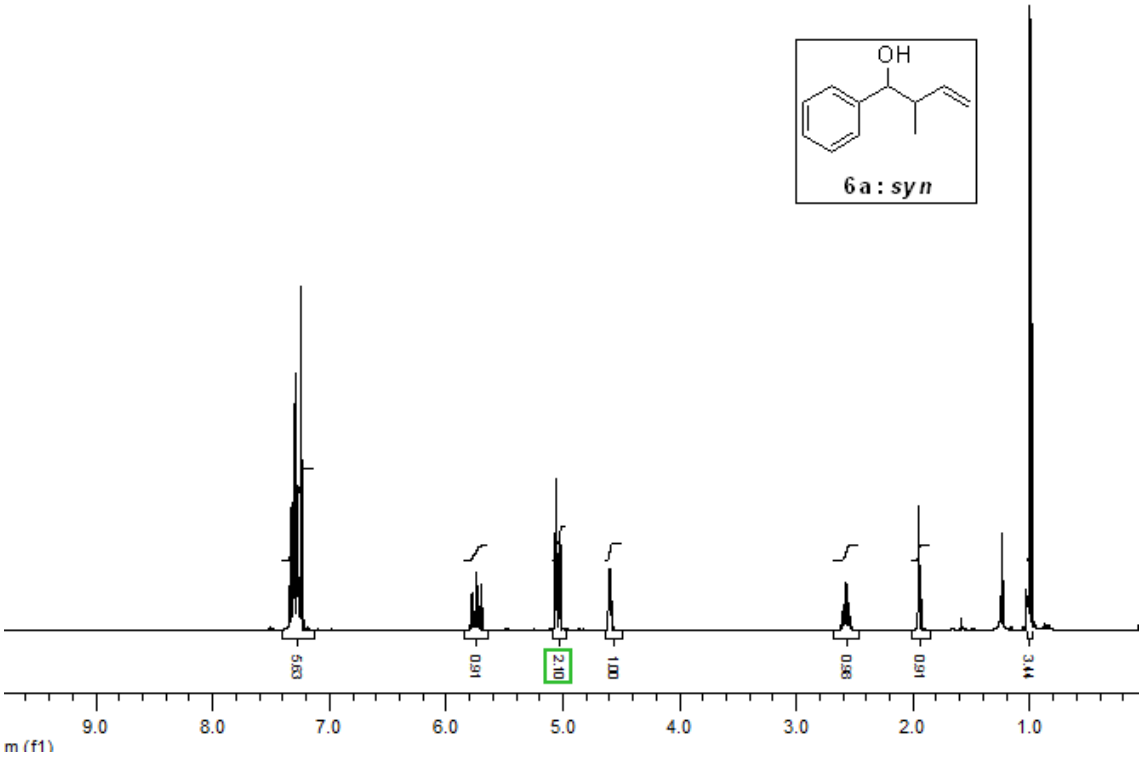


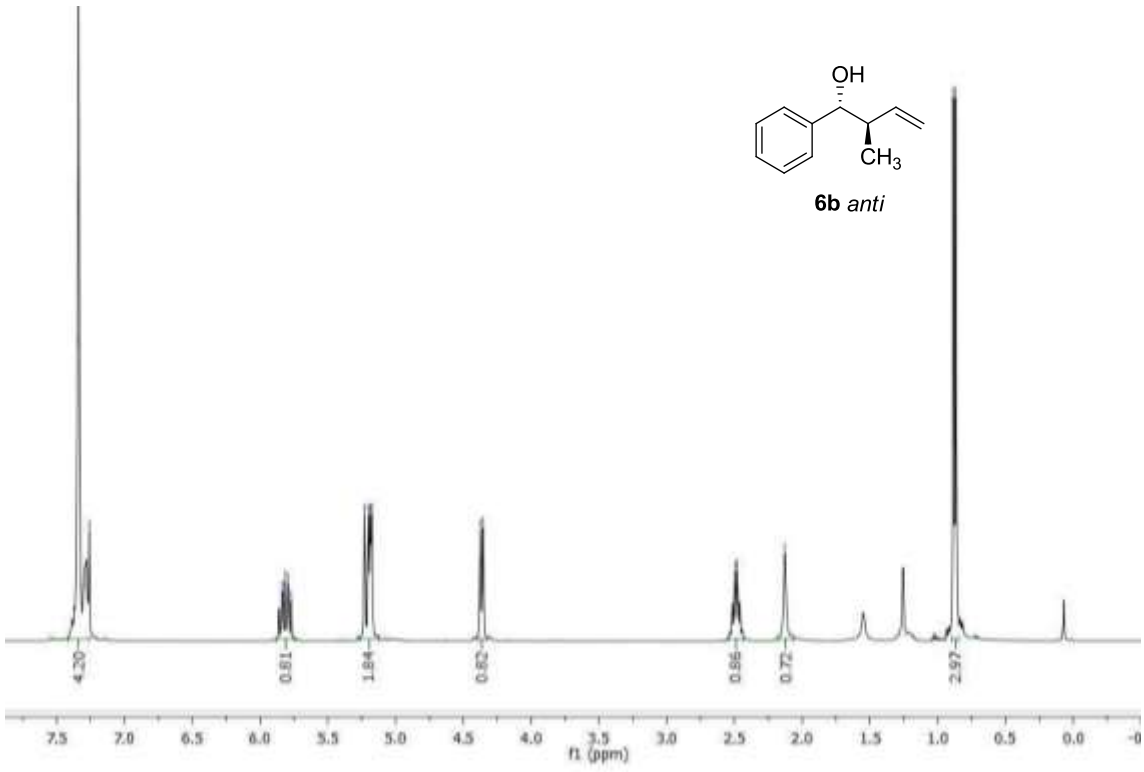






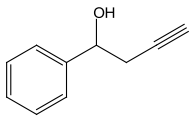






Appendix 2

^{1}H and ^{13}C NMR spectra for compounds in chapter 2



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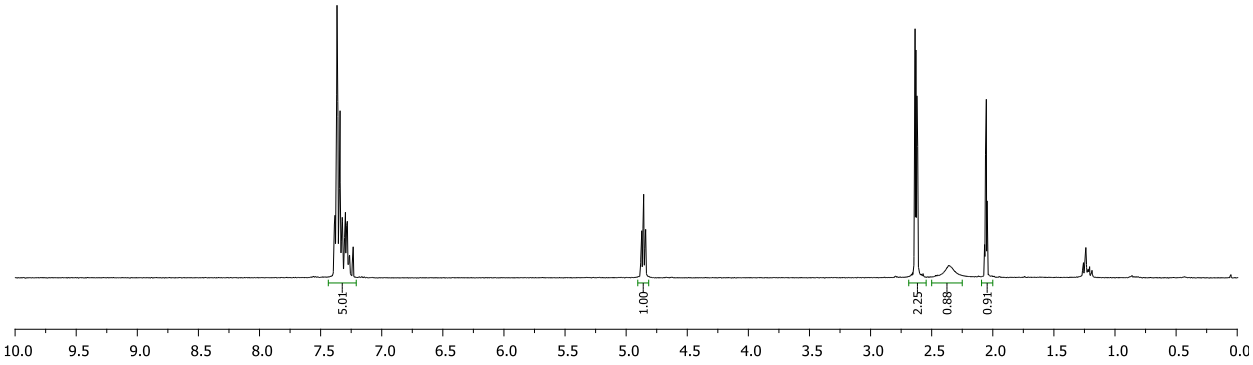

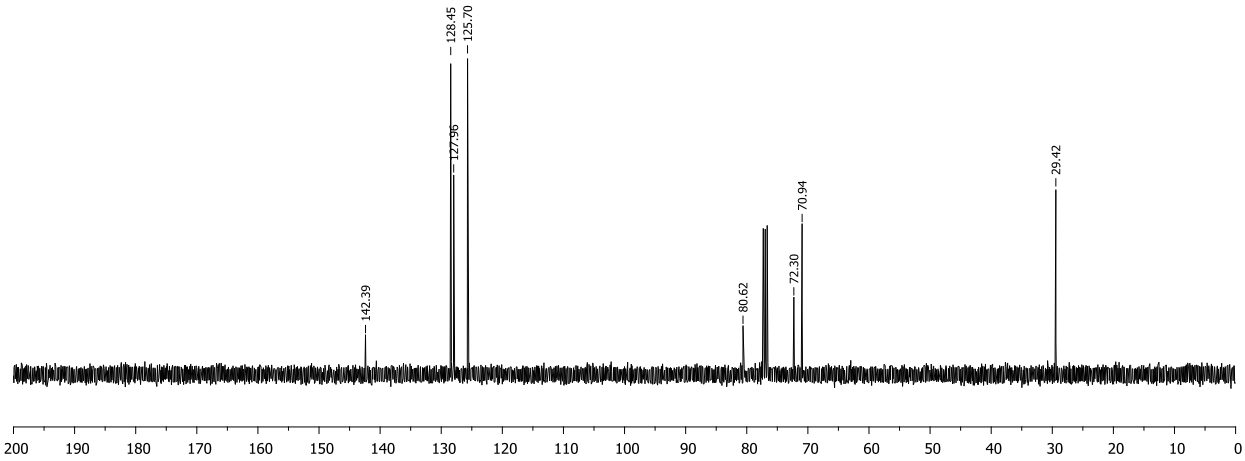

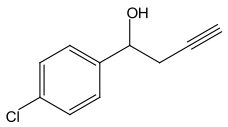

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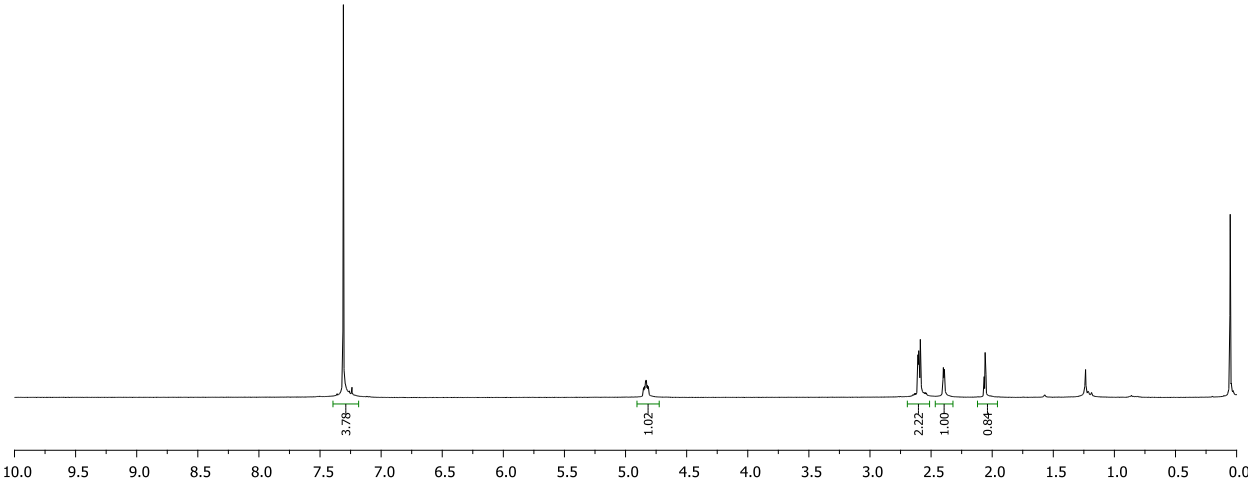

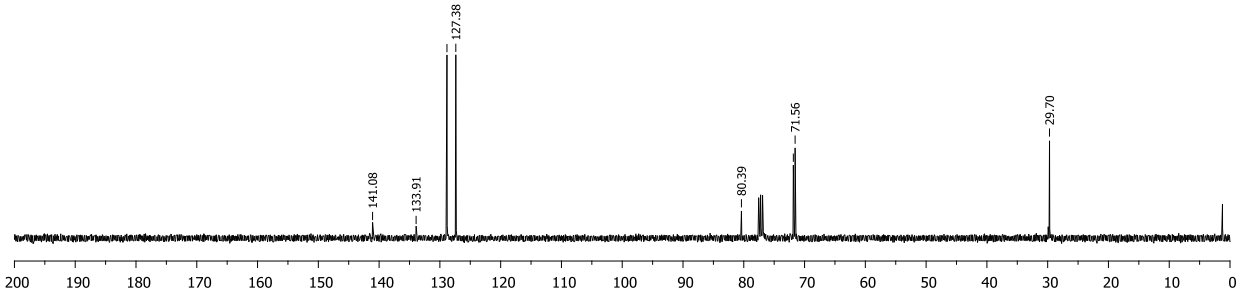

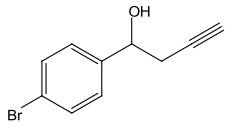

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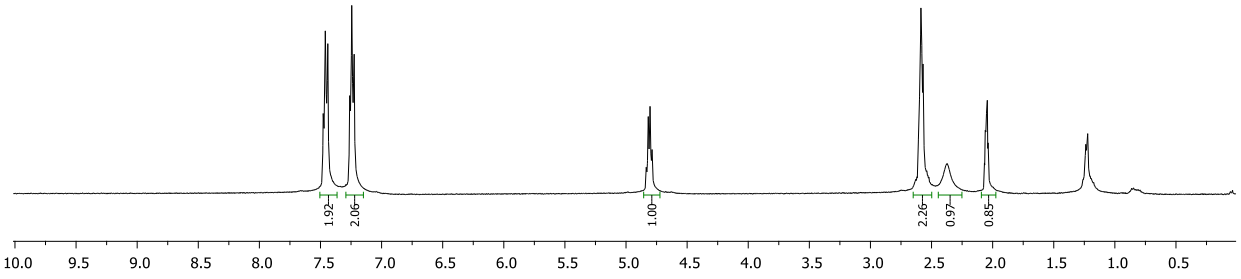

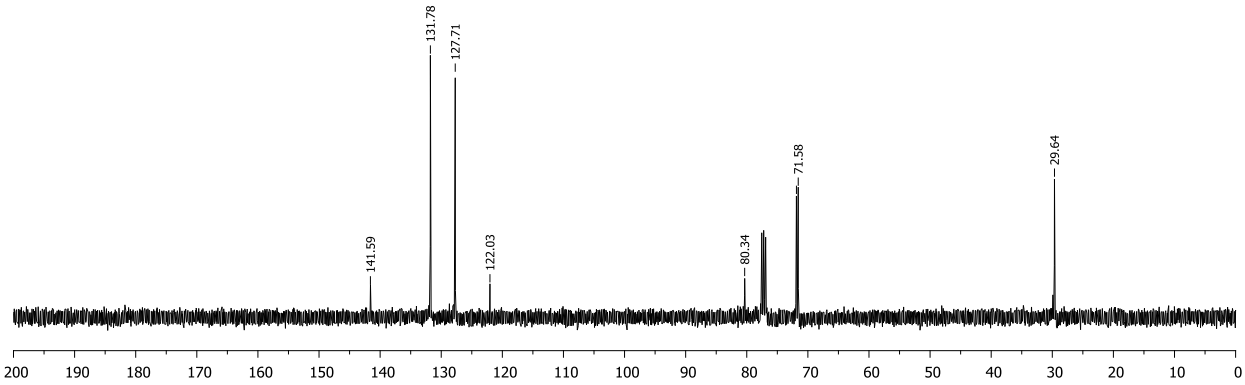

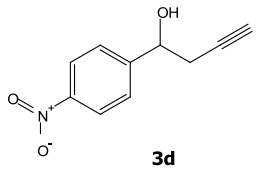

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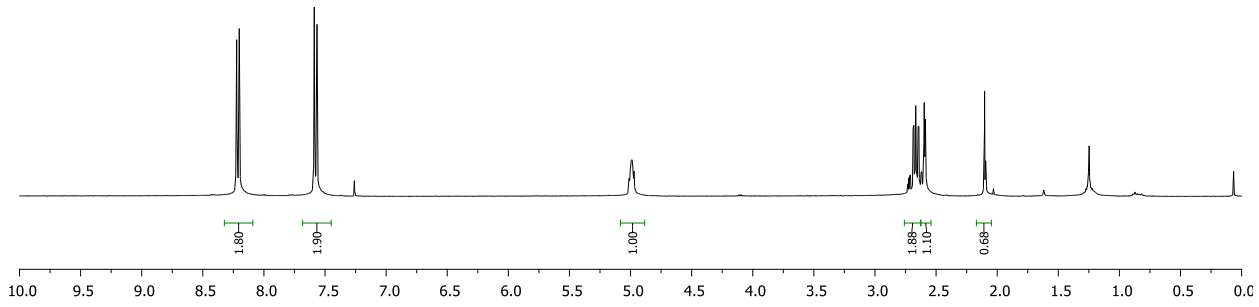

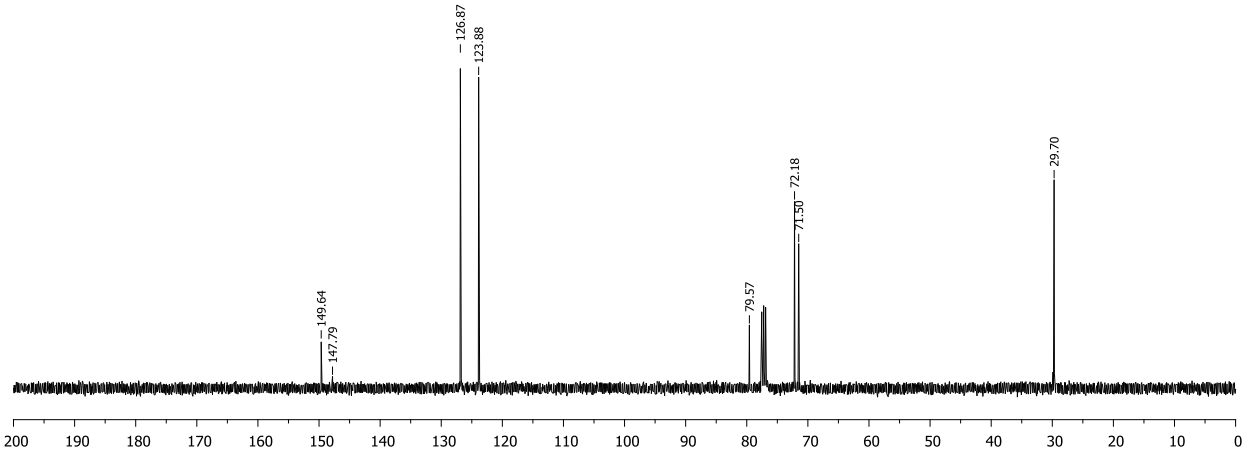

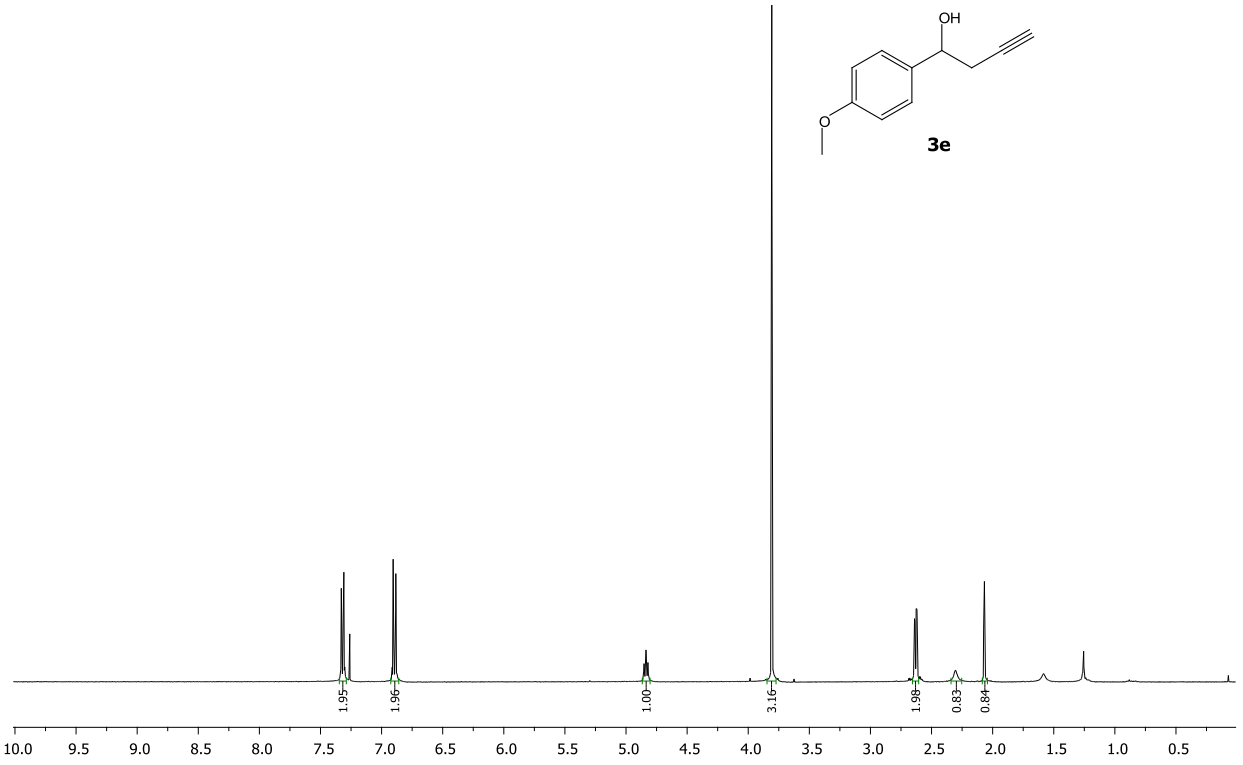

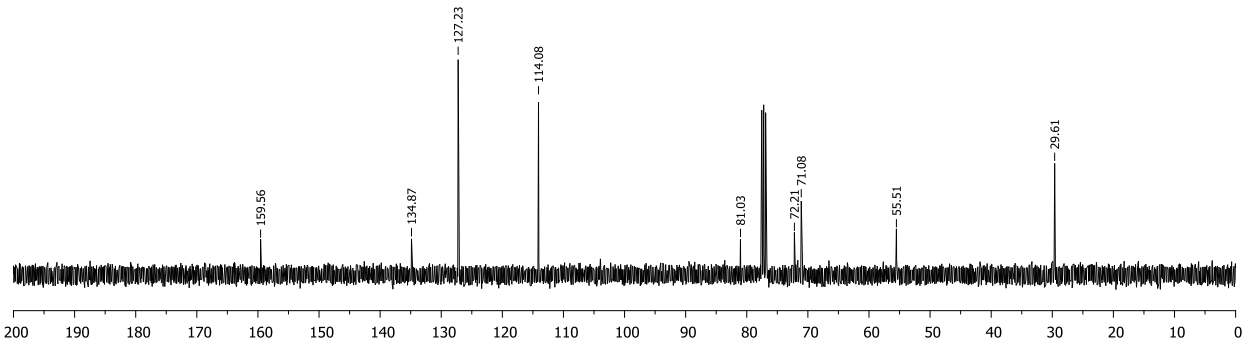

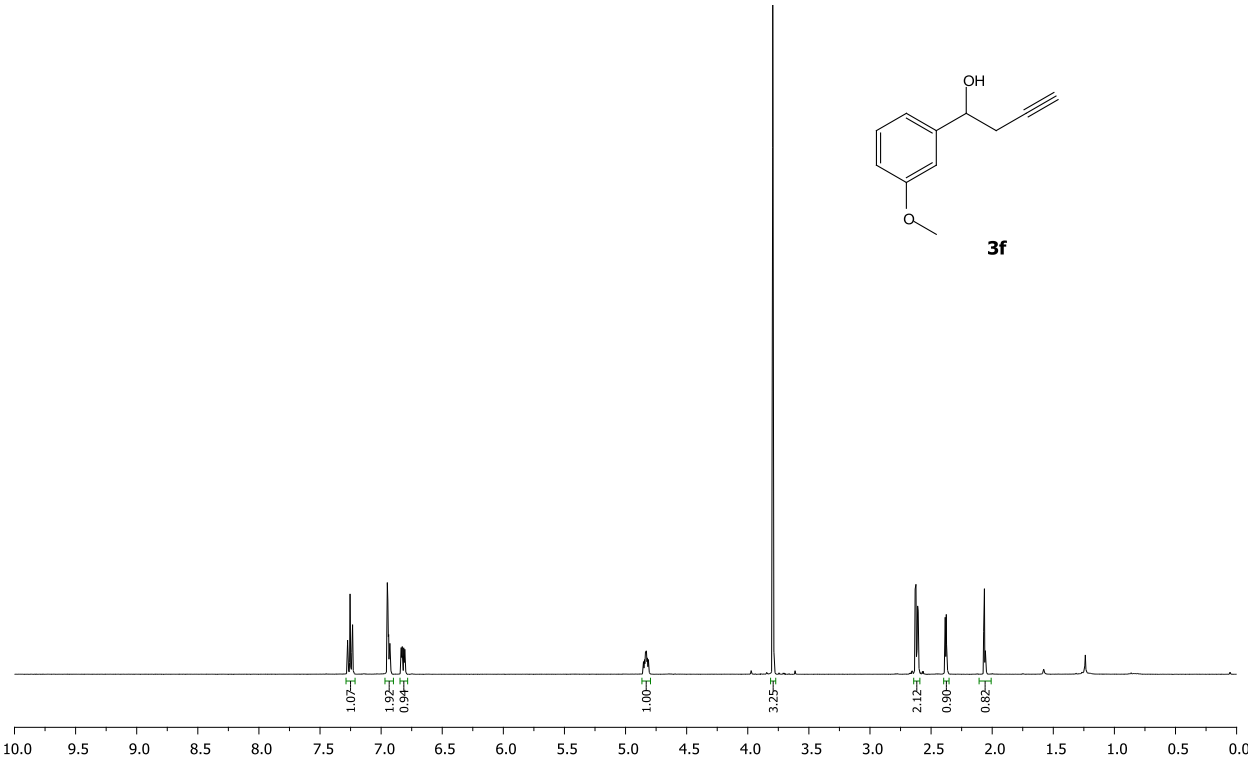

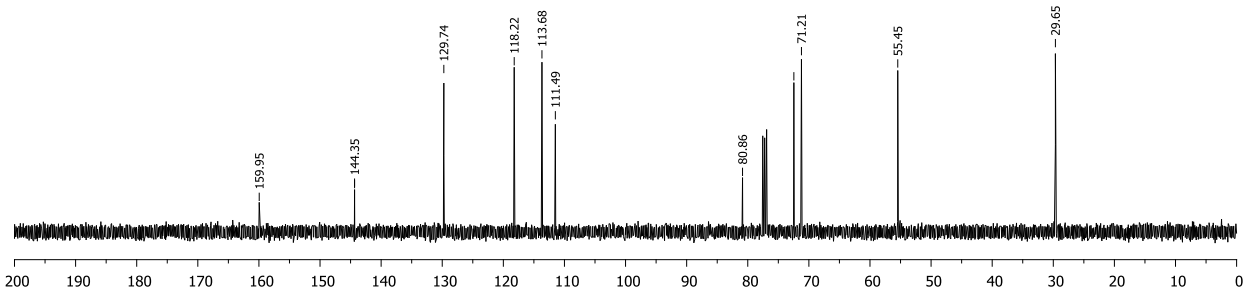

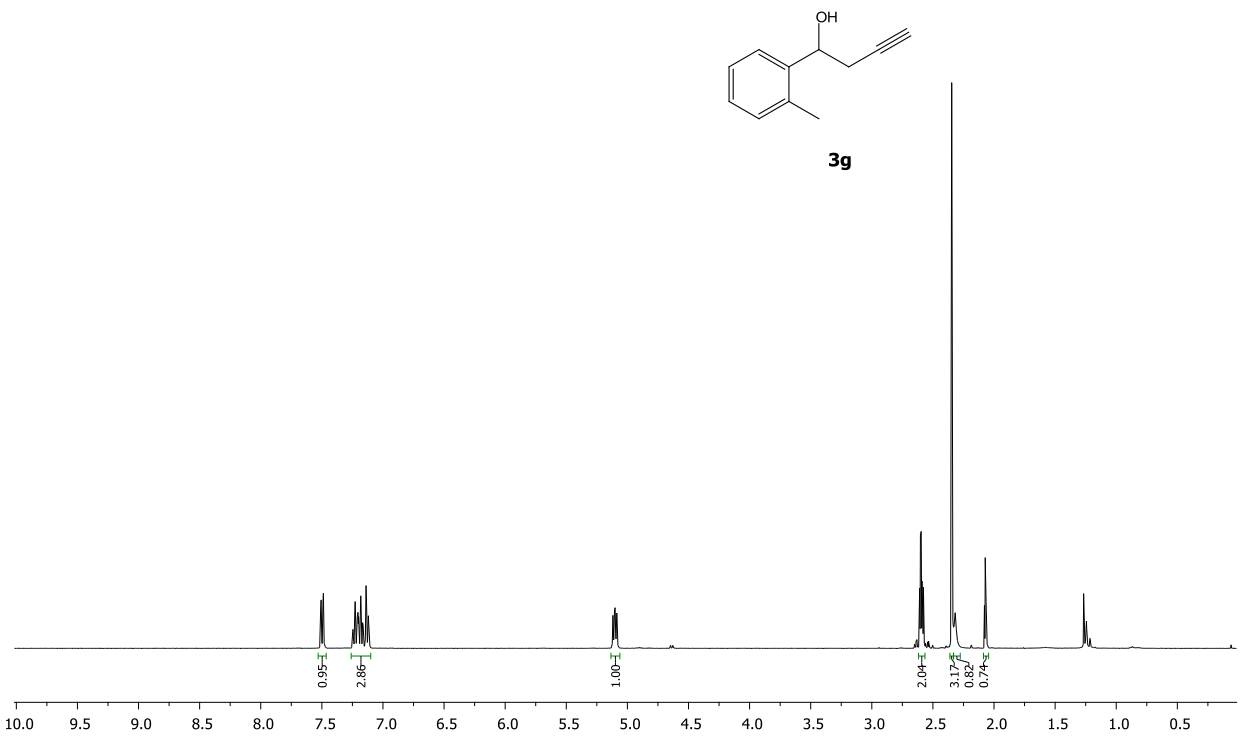

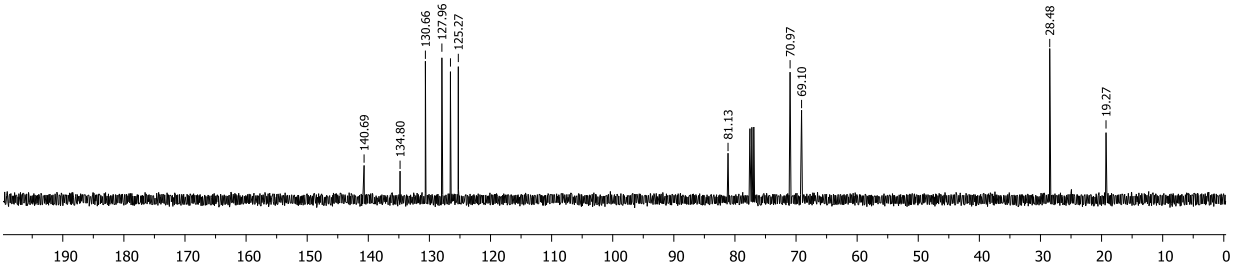

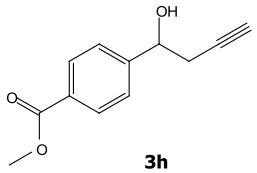

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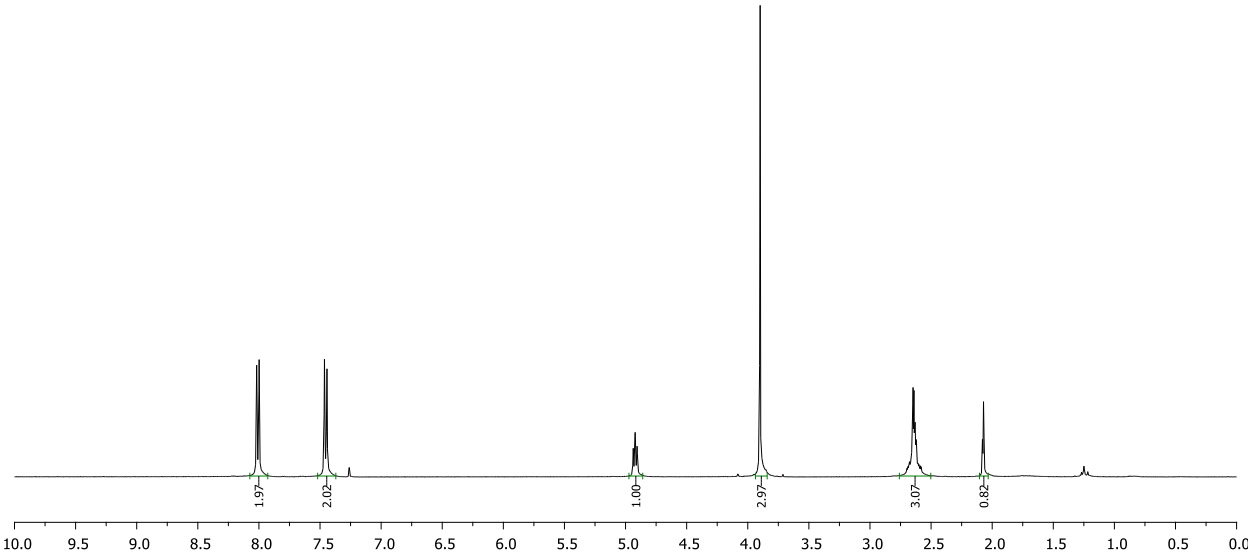

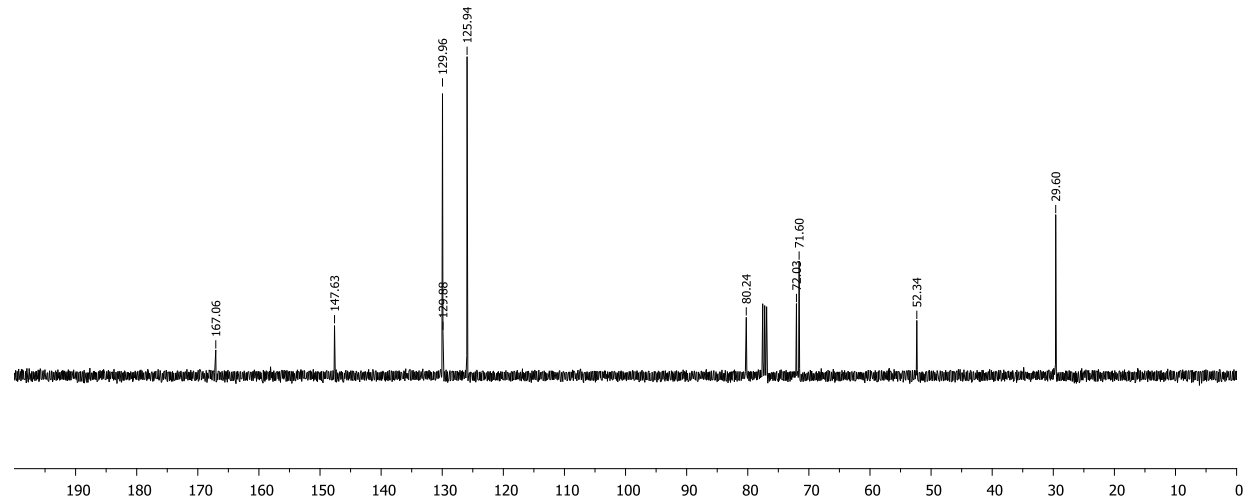

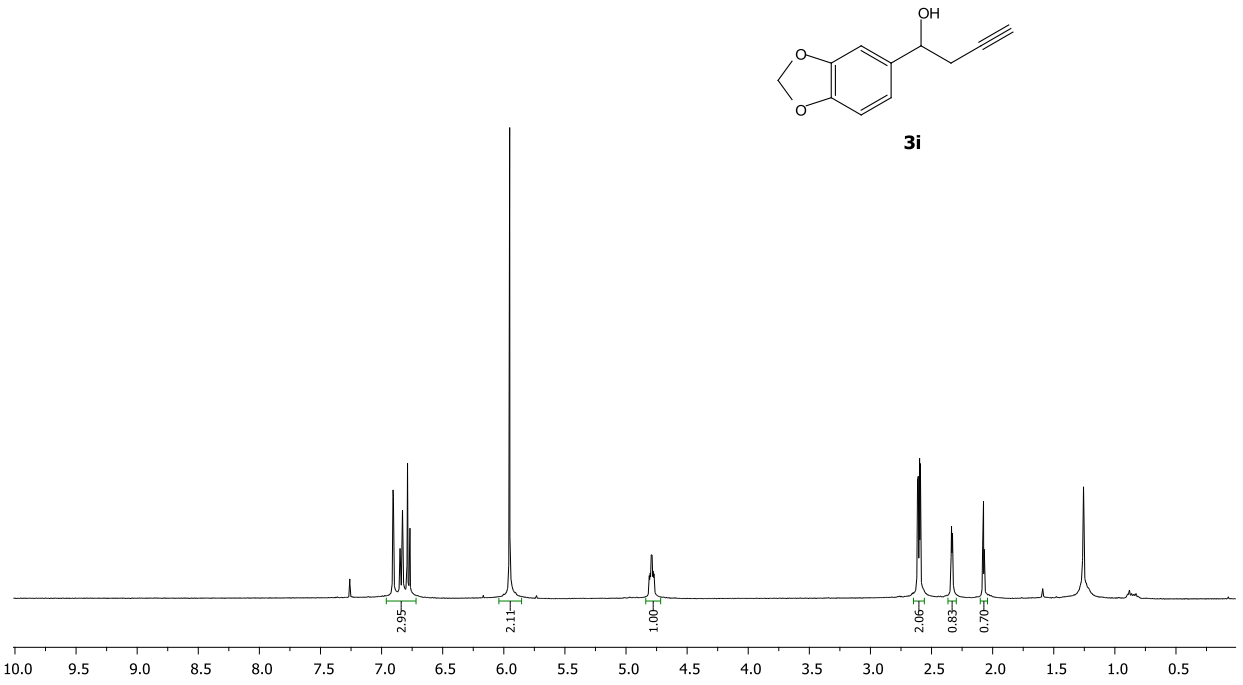

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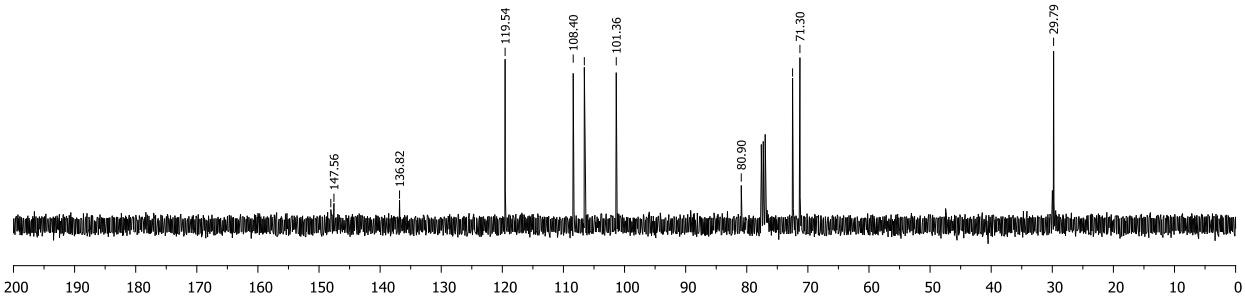

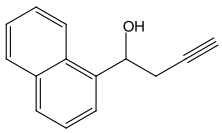

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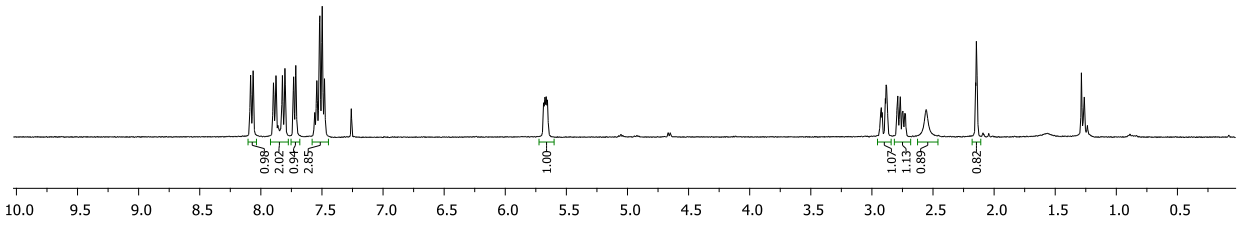

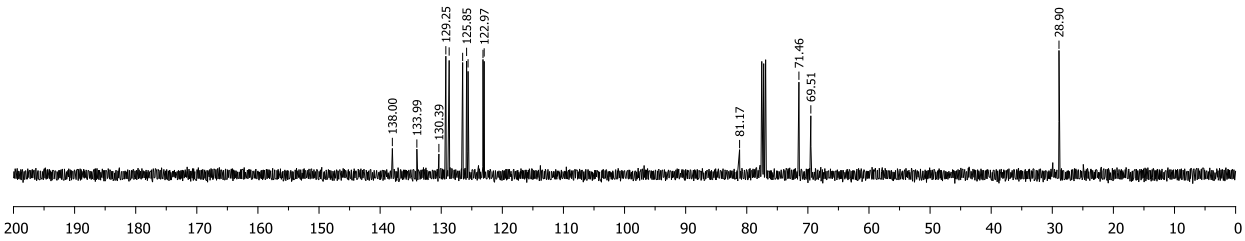

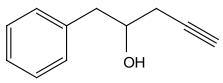

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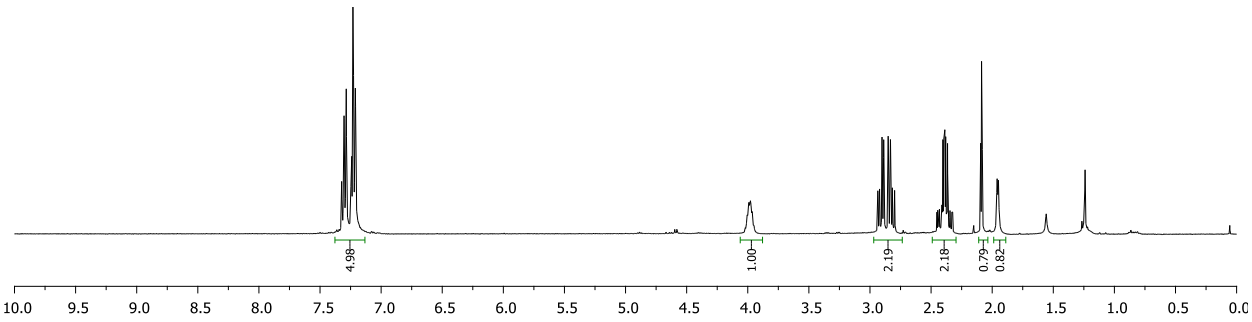

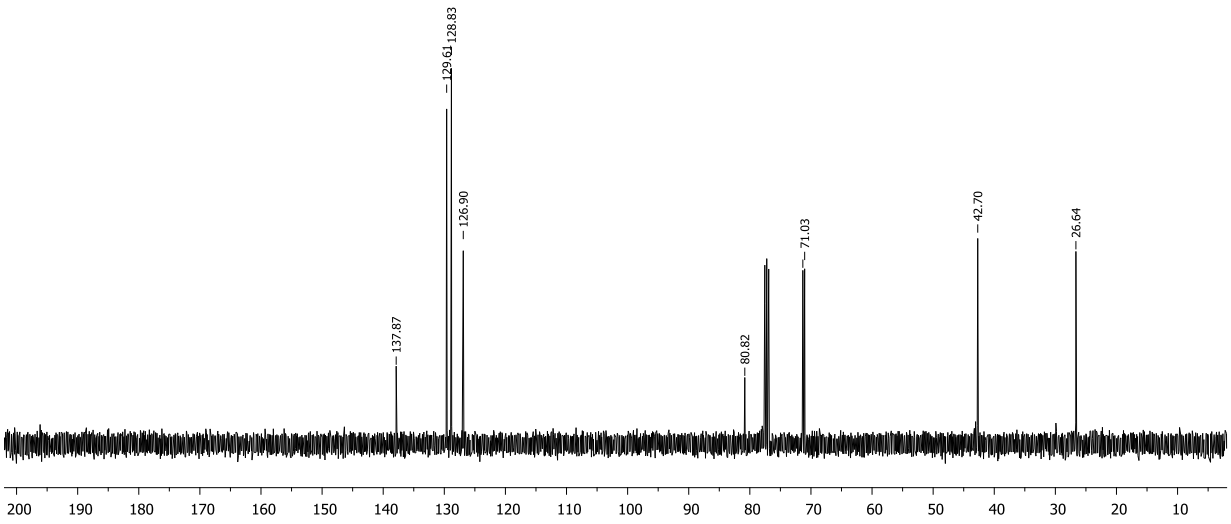

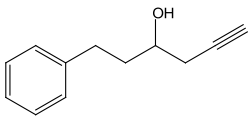

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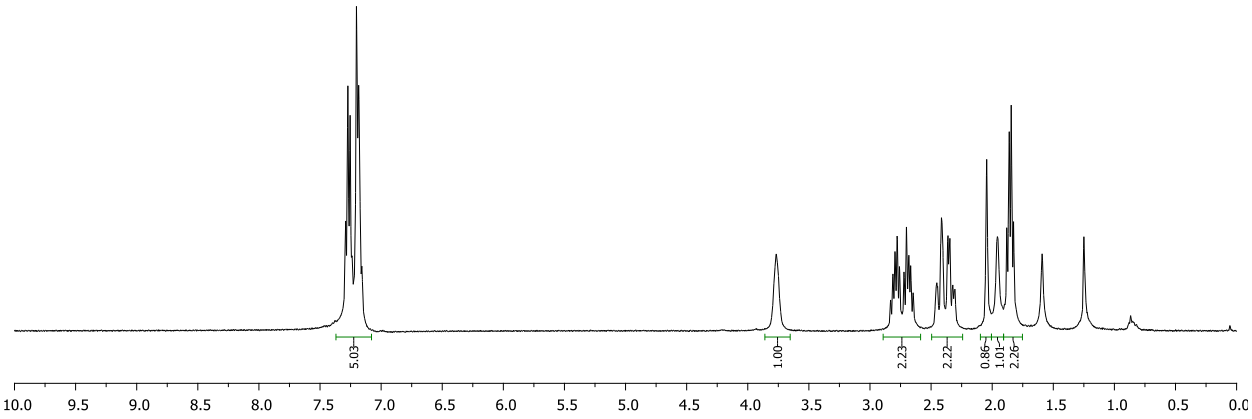

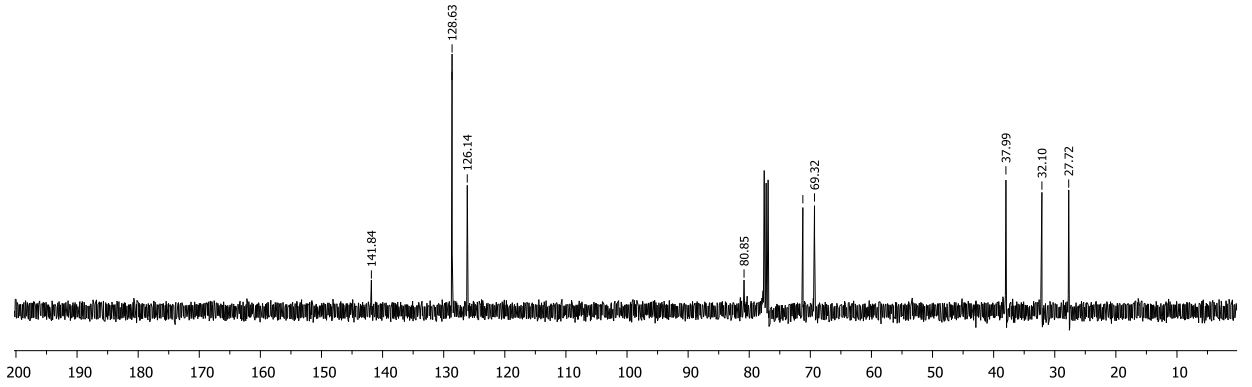

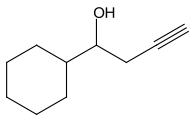

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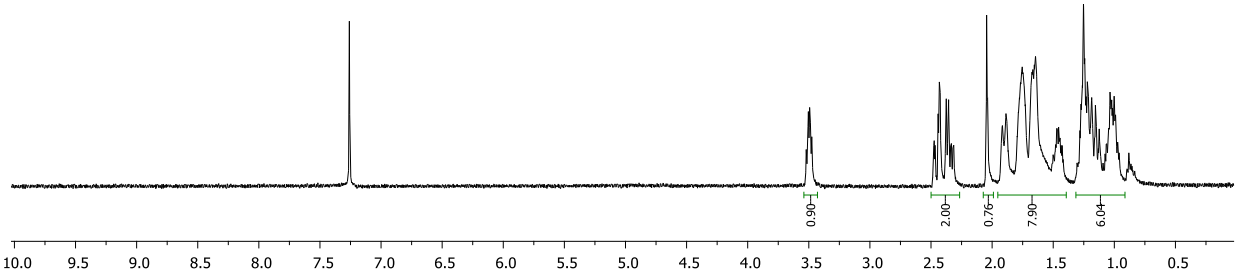

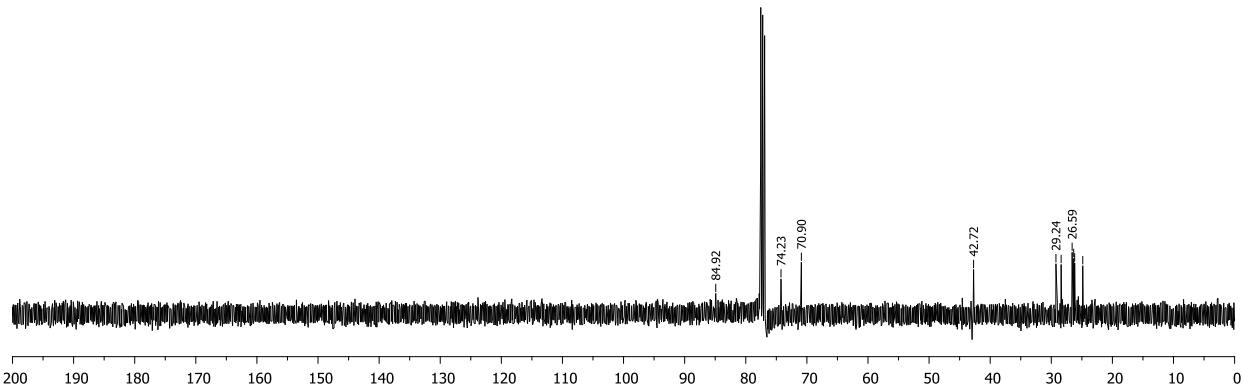

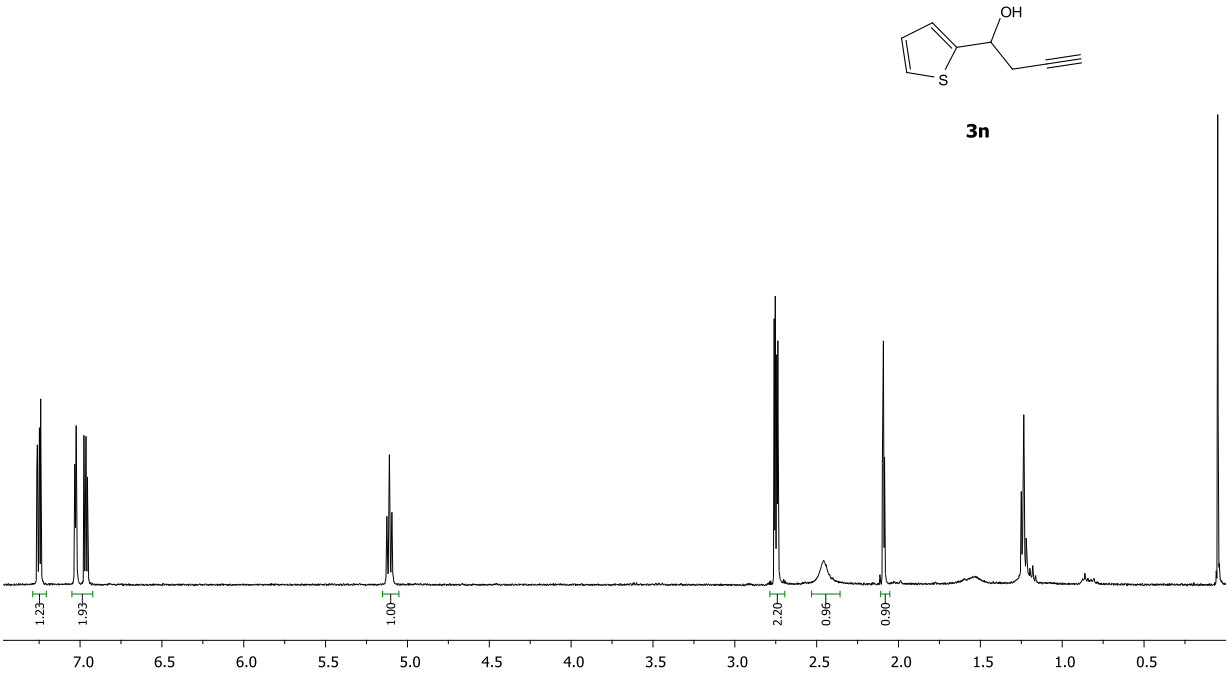

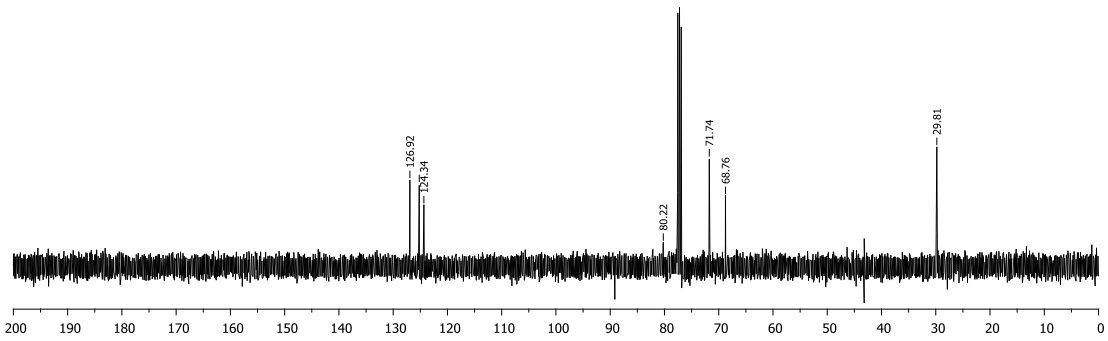

Appendix 3

Permissions