To the Graduate Council:

I am submitting herewith a dissertation written by Su Yu entitled "Reactions of Unsaturated Carbonyl Compounds with Organoboranes." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

George W. Kabalka, Major Professor

We have read this dissertation
And recommend its acceptance:

Accepted for the Council:

Associate Vice Chancellor and
Dean of The Graduate School

Reactions of Unsaturated Carbonyl Compounds with Organoboranes

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Su Yu

December 1998

DEDICATION

I dedicate this dissertation to my parents,

Anli Pan（潘爱莉）

and

Xiao Rong Yu（虞孝荣）

ACKNOWLEDGEMENTS

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ABSTRACT

The kinetic data indicate that both the hydroboration of a terminal alkene and the reduction of a carbonyl compound with 9-BBN exhibit first-order kinetics. However, the reactivities of alkenes and ketones toward borane reagents are not equal. Thus, a study of competition reactions between carbon-carbon unsaturated bonds and carbonyl groups toward organoboranes has been carried out. Unhindered borane reagents such as 9-BBN are less chemoselective toward carbon-carbon unsaturated bonds and carbonyl groups than hindered borane reagents, such as dicyclohexylborane. Dicyclohexylborane selectively hydroborates a terminal alkene in the presence of either a ketone or an aldehyde. The hydroborations of olefinic ketones and aldehydes with dicyclohexylborane give the corresponding hydroxy ketones and aldehydes in good yields after oxidation with sodium perborate. Both terminal and internal alkynyl ketones and aldehydes can be selectively hydroborated by dicyclohexylborane in the presence of the carbonyl group. The reaction affords the corresponding olefins in high yields after protonation with acetic acid or dicarbonyl compounds in good yields after oxidation with sodium perborate.

The reaction of α,β-acetylenic ketones with dicyclohexylborane occurs via a 1,4-addition. Allenoxyborinates are generated as intermediates which then react with excess α,β-acetylenic ketones or other electrophiles. The reactions afford highly functionalized trisubstituted olefins in high yields.

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List of Abbreviations and Symbols

Ar	Aryl
9-BBN	9-Borabicyclo[3,3,1]nonane
BMS	Borane-dimethylsulfide
br s	Broad singlet
Bu	Butyl
BuLi	Butyllithium
°C	Degrees Celsius
CB	Catecholborane
$CDCl_3$	Chloroform-*d*
d	Doublet
ee	Enantiomeric excess
Et	Ethyl
Et_2O	Diethyl ether
GC	Gas Chromatograph
hext	hextet
Hz	Hertz
Ipc	Isopinocampheyl
IR	Infrared
J	Proton-proton coupling constant
K	Degrees Kelvin

m	multiplet
Me	Methyl
NMR	Nuclear magnetic resonance spectroscopy
[O]	Oxidation
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
pent	pentet
Ph	Phenyl
Pr	Propyl
q	Quartet
R	Alkyl
r.t.	Room temperature
s	Singlet
t	Triplet
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMANO	Trimethylamine-N-oxide
TMS	Tetramethylsilane

Chapter 1. Boranes in Organic Chemistry

1.1 Introduction

This dissertation is focused on the reactions of the alkenes, alkynes and carbonyl compounds with boranes. Thus, a brief overview of hydroboration and reduction using boranes will be presented. In addition, aldol reactions carried out via boron enolates are summerized because they provide a foundation for the chemistry summarized in Chapter 5.

1.2 Hydroboration

1.2.1 Historical

Organoboranes were first produced in 1859 by Frankland using the reactions of dialkylzincs with trialkoxyboranes (eqn 1-1)[1,2]. Boron hydrogen

$$3\ (C_2H_5)_2Zn\ +\ 2\ (C_2H_5O)_3B \longrightarrow 2\ (C_2H_5)_3B\ +\ 3\ Zn(OC_2H_5)_2$$

(eqn 1-1)

compounds, such as B_2H_6, B_4H_{10}, B_5H_{11} and $B_{10}H_{14}$, were prepared by Alfred Stork between 1910 and 1930[3]. However, these compounds remained of little interest to organic chemists due to their difficult and inconvenient preparation. In the 1940s, Schlesinger and Brown introduced a variety of methods for the facile production of both sodium tetrahydroborate and diborane (eqn 1-2) (eqn 1-3) (eqn 1-4)[4,5].

$$6\ LiH + 8\ BF_3 \xrightarrow{25^\circ C} B_2H_6 + 6\ LiBF_4 \qquad \text{(eqn 1-2)}$$

$$4\ NaH + B(OCH_3)_3 \xrightarrow{250^\circ C} NaBH_4 + 3\ NaOCH_3 \qquad \text{(eqn 1-3)}$$

$$3\ NaBH_4 + 4\ BF_3 \xrightarrow[25^\circ C]{\text{diglyme}} 2\ B_2H_6 + 3\ NaBH_4 \qquad \text{(eqn 1-4)}$$

Subsequent studies on the reactions of diborane with alkenes and alkynes were carried out by several groups[6,7,8,9]. It was found that the reactions were slow and required elevated temperatures. For example, the reaction of ethylene with diborane was completed only after heating to 100 °C for four days (eqn 1-5).[6]

$$6\ CH_2{=}CH_2 + B_2H_6 \xrightarrow[4\ days]{100^\circ C} 2\ (CH_3{-}CH_2)_3B \qquad \text{(eqn 1-5)}$$

Hydroboration was not synthetically useful until 1956 when Brown and his coworkers discovered a simple and rapid method for the adding of boranes to alkenes[10]. They noted that the unsaturated ester, ethyl oleate, consumed excess hydride while reducing the unsaturated carbonyl compound with $NaBH_4/AlCl_3$ in diglyme[11]. Further investigation showed that the double bond participated in the reaction. It was found that alkenes reacted readily with $NaBH_4/AlCl_3$ in diglyme at room temperature to produce the corresponding organoboranes in excellent yield (eqn 1-6)[10,12]. Similarly, sodium borohydride in the presence of boron halides

$$9\ RCH{=}CH_2 + 3\ NaBH_4 + AlCl_3 \xrightarrow[r.t.]{diglyme}$$

$$3\ (RCH_2CH_2)_3B + AlH_3 + 3\ NaCl \qquad \text{(eqn 1-6)}$$

readily transformed olefins into organoboranes with more efficient utilization of the hydride (eqn 1-7)[12,13].

$$12\ RCH{=}CH_2 + 3\ NaBH_4 + 4\ BF_3 \xrightarrow[r.t.]{diglyme}$$

$$4\ (RCH_2CH_2)_3B + 3\ NaBF_4 \qquad \text{(eqn 1-7)}$$

Diborane may be generated as a gas and then passed into other solvents such as THF to form the complex $BH_3{\bullet}THF$[14]. This solution turned out to be an effective and practical reagent for hydroboration reactions[15]. It is now commercially available and is the most commonly used hydroboration reagent.

The discovery in the 1950s that ether solvents strongly accelerated the addition of diborane to olefins led to extensive investigations which showed that the hydroboration of alkenes is rapid, regioselective and stereospecific[16,17,18,19,20,21].

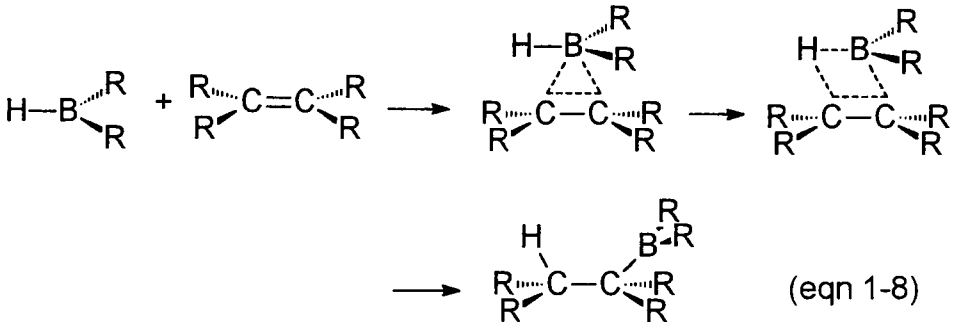
1.2.2 Hydroboration of Alkenes

Hydroboration constitutes the most important method for the preparation of organoboranes and has been applied to a wide variety of alkenes. The most common and useful application of the hydroboration reaction of alkenes is to

form anti-Markownikoff alcohols by oxidation of the product organoborane with hydrogen peroxide[22,23] or sodium perborate[24]. Oxidation of the organoborane gives essentially quantitative yields of the alcohol and proceeds with complete retention of configuration[24,25]. Analysis of the alcohols formed after oxidation serves to locate the precise position of the boron atom in the organoboranes and also establishes the stereochemistry of the hydroboration reactions[25].

1.2.2.1 Mechanism

The mechanism of hydroboration is believed to involve the addition of a monomeric borane to a carbon-carbon double bond via a four-center transition state to form an alkylborane (eqn 1-8).



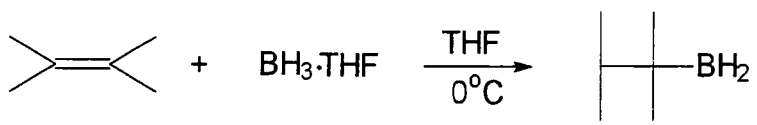
(eqn 1-8)

If the borane reagent is dimeric or complexed with a Lewis base, the first step is dissociation to free monomeric borane. The cyclic transition-state leads to the conclusion that hydroborations are diastereospecific and that regioselectivity is dominated by steric repulsions.

1.2.2.2 Hydroboration with Borane-Tetrahydrofuran

The reactions of alkenes with borane-tetrahydrofuran occur sequentially to give first monoalkylboranes, then dialkylboranes, and finally trialkylboranes. Unhindered alkenes react rapidly to produce the trialkylboranes[21,26,27]. However, in the case of more hindered alkenes such as trimethylethylene and tetramethylethylene, the reactions proceed rapidly only to the dialkylborane (disiamylborane, eqn 1-9)[28] or the monoalklborane stage (thexylborane, eqn 1-10)[29]. The remaining steps are very slow. Therefore, syntheses of

(eqn 1-9)



(eqn 1-10)

dialkylboranes and monoalkylboranes is possible by controlling the stoichiometry and the reaction conditions.

The regiochemistry of the hydroboration is determined primarily by steric factors, the boron atom has high preference for the less hindered carbon of the alkene. For example, simple 1-alkenes such as 1-hexene undergo hydroboration with BH_3•THF to place 94% of the boron at the terminal position with 6% at the 2-position[15, 30]. This distribution is not influenced by branching of the alkyl group while it is significantly affected by the substitution on the double bond (Figure 1-1)[30].

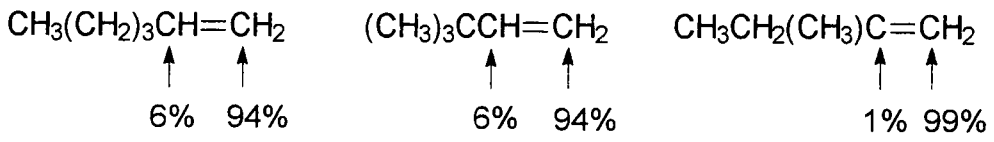


Figure 1-1. Regioselectivity of hydroboration of 1-alkenes with BH_3.THF

However, the regioselectivity is not always great and, in some cases, attack may occur at the alternative orientation. The site of boron placement for a number of representative alkenes is shown in Figure 1-2. As can be seen, a

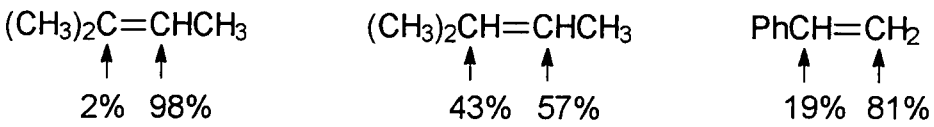
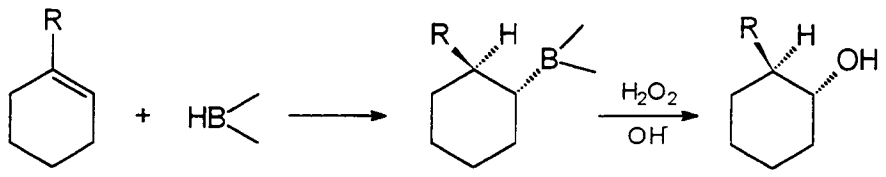


Figure 1-2. Sites of attack on alkenes by BH_3.THF

similar preference for the less substituted position is exhibited in internal olefins. On the other hand, there is no significant discrimination between the two position of an internal olefin containing alkyl groups[30]. An aryl group substituted on the double bond causes increased placement of the boron atom adjacent to the benzene ring. This distribution is altered by substituents in the ring[31]. The presence of a 3-alkyl substituent of cycloalkene exerts little directive influence on the reaction with BH_3•THF [32].

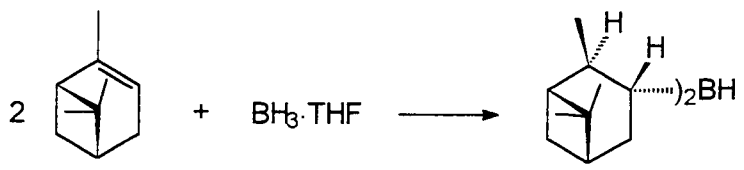
The stereochemistry of the addition of the B-H bond to a double bond proceeds in a *syn*-fashion [16,21,26]. When the two faces of the double bond are

sterically differentiated, addition occurs preferentially from the less hindered face. The hydroboration of 1-methylcyclohexene, followed by oxidation with alkaline hydrogen peroxide results in the formation of pure *trans*-2-methylcyclohexanol (eqn 1-11)[33]. This indicates that the hydroboration reaction must involves a *syn*



(eqn 1-11)

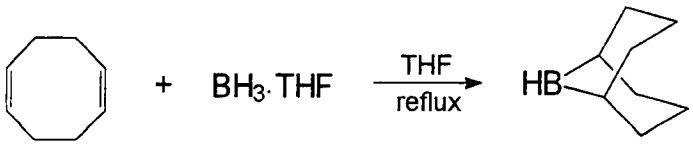
addition of the hydrogen-boron bond to the double bond since the hydrogen peroxide oxidation proceeds with retention of configuration[25]. The reaction of optically pure α-pinene with BH_3•THF gives a single type of dialkylborane with >99% ee (eqn 1-12)[15,34]. This dialkylborane is synthetically useful for asymmetric hydroboration.



(eqn 1-12)

1.2.2.3 Hydroboration with 9-BBN

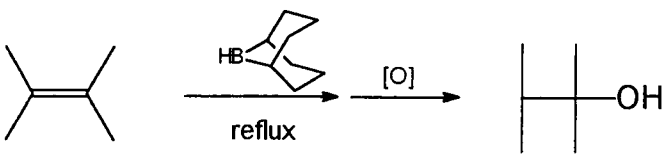
9-Borabicyclo[3,3,1]nonane (9-BBN) is prepared by the hydroboration of 1,5-cyclooctadiene with BH_3•THF, followed by thermal isomerization of the mixture of dialkylboranes at 65 °C (eqn 1-13)[35,36]. The procedure using 1,2-



(eqn 1-13)

dimethoxyethane instead of THF as solvent gives high purity, large needles of crystalline 9-BBN dimer which show considerable stability. They are stable in air for brief periods[37]. 9-BBN solutions and the crystalline reagent are commercially available. It has been widely used as a hydroborating reagent [38,39].

The reaction of 9-BBN with olefins is slower than that of BH_3•THF and other dialkylboranes. However terminal olefins react readily at 25°C. Less reactive internal olefins require either an excess of the reagent or longer reaction times[40]. Hydroboration reactions with 9-BBN can be carried out in refluxing THF due to the remarkable thermal stabilities of 9-BBN and B-R-9-BBN. 9-BBN has been found to be the least hindered dialkylborane known. It can be used to hydroborate fairly hindered alkenes such as 2,3-dimethyl-2-butene which fails to react with other dialkylboranes (eqn 1-14)[41].



(eqn 1-14)

9-BBN shows substantially greater steric regioselectivity than borane. 9-BBN places 99.9% of boron at the terminal position of 1-hexene. Even more surprising is the fact that 9-BBN places 98.2% boron at 2-carbon of *cis*-4-methyl-2-pentene. Examples of reaction regioselectivities exhibited by 9-BBN are given

in Figure 1-3. 9-BBN also shows great stereoselectivity in the hydroboration of cyclic alkenes (eqn 1-15, 1-16, 1-17)[42].

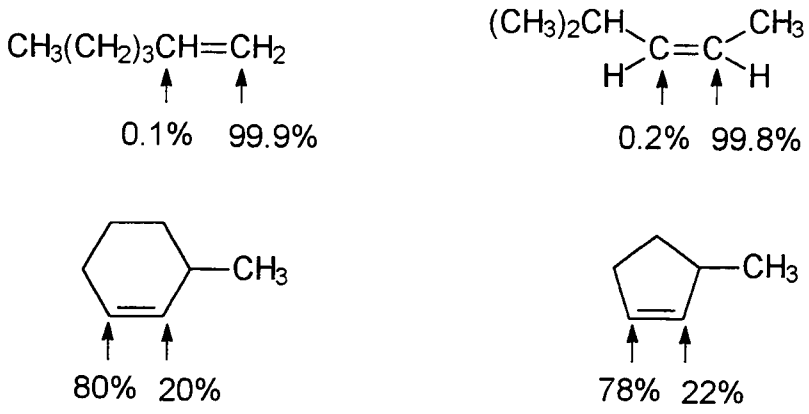
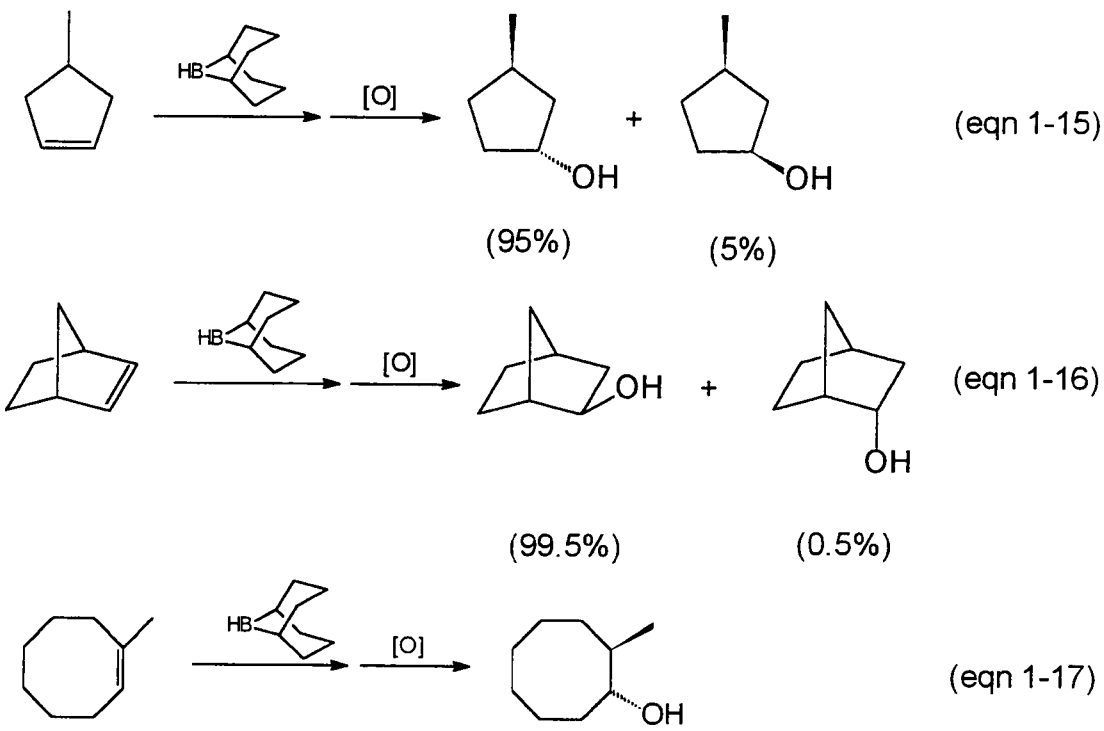
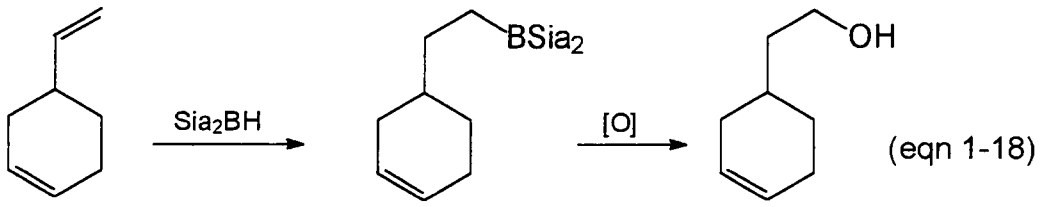


Figure 1-3. Regioselectivity of hydroboration of alkenes with 9-BBN



1.2.2.4 Hydroboration with Disiamylborane

Disiamylborane is prepared by the reaction of two molar equivalents of 2-methyl-2-butene with one molar equivalent of BH_3 (eqn 1-9). Hydroborations involving disiamylborane are highly sensitive to the structures of the olefins. The rates of reactions of alkenes with disiamylborane vary over a much greater range than hydroborations using BH_3•THF[43,44]. The reagent reacts with terminal alkenes such as 1-hexene much faster than with internal alkenes such as *trans*-2-hexene. *Cis* alkenes react considerably faster than *trans* alkenes[44,45]. The relative rates for the reactions of cyclopentene, cycloheptene and cyclooctene with disiamylborane are 1:19:69 [38]. These characteristics make it possible to selectively hydroborate the most open double bond in a compound containing two or more double bond (eqn 1-18)[45].



(eqn 1-18)

Disiamylborane is more hindered than BH_3•THF. The regioselectivity of hydroboration reactions involving alkenes and disiamylborane is substantially greater than those involving BH_3•THF, but it is usually a little lower than that of 9-BBN. Disiamylborane places 99% of boron on the terminal carbon of 1-hexene. Styrene undergoes hydroboration with disiamylborane to place 98% of the boron

at the terminal position. The reagent also shows great regioselectivity for the less hindered carbon of 4-methyl-2-pentene (Figure 1-4)[45,46].

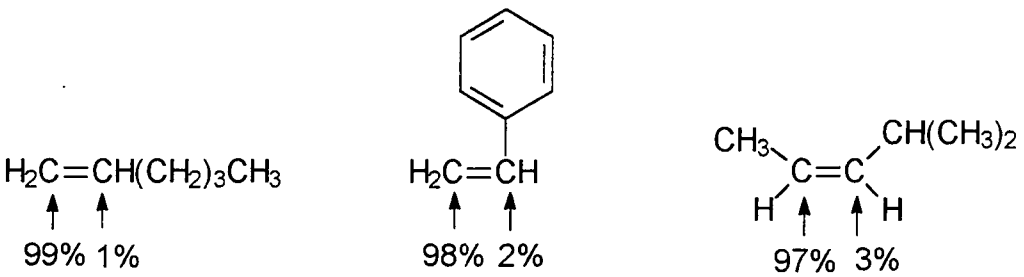
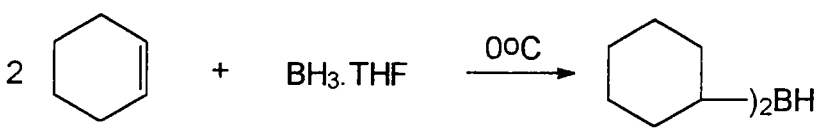


Figure 1-4. Regioselectivity of Hydroboration of Alkenes with Disiamylborane

1.2.2.5 Hydroboration with Dicyclohexylborane

Dicyclohexylborane is readily prepared via the stoichiometric hydroboration of cyclohexene with BH_3•THF. The reaction proceeds rapidly to the dicyclohexylborane stage, but only very slowly beyond that point (eqn 1-19)[47]. Dicyclohexylborane precipitates out of the solution and forms a white solid dimer.



(eqn 1-19)

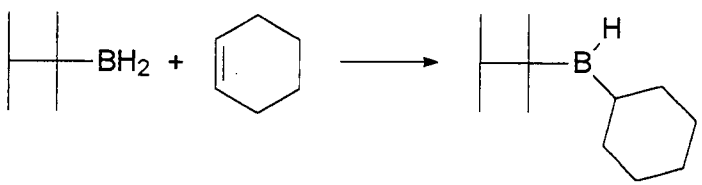
Dicyclohexylborane is similar in hydroborating properties to disiamylborane. However, dicyclohexylborane has remarkable advantages over disiamylborane. First, siamyl groups are thermally unstable and are readily isomerized to less bulky groups during heating[48]. Second, when the elimination

of an alkene is a competing side reaction, dicyclohexylborane is a better hydroborating reagent than disiamylborane because elimination of 2-methyl-2-butene is easier than elimination of cyclohexene[49]. Third, dicyclohexylborane is a solid which is stable for extended periods when stored under dry nitrogen[21]. The completion of hydroboration reactions involving dicylohexylborane is self-indicating because the hydroboration products dissolve in ether solution. However, due to the historical precedence, dicyclohexylborane has not been as thoroughly studied as disiamylborane.

1.2.2.6 Hydroboration with Thexylborane

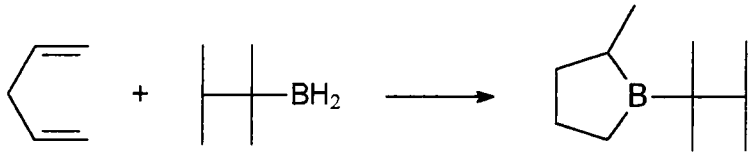
Thexylborane is readily prepared by treating one mole of BH_3•THF with one mole of 2,3-dimethyl-2-butene (eqn 1-10)[50,51]. It is the most widely used monoalkylborane hydroborating reagent. However, the tertiary alkyl group is not stable and slowly isomerizes to a primary alkyl group at 20 °C[51]. Addition of a molar equivalent of N,N-diethylaniline makes the reagent more stable and thus better a hydroborating reagent.

Hydroboration of 1-alkenes with thexylborane produces the corresponding thexyldialkylboranes[50]. The reaction of more hindered alkenes, such as cyclohexene, can give thexylmonoalkylboranes in good yields by controlling the stoichiometry (eqn 1-20)[51]. The "mixed" dialkylboranes are effective reagents for



(eqn 1-20)

the hydroboration of alkenes with low steric requirements. One of the most useful reactions with thexylborane is the synthesis of cyclic derivatives by hydroboration of dienes (eqn 1-21)[52]. Under kinetic control, there is a strong preference for formation of five- and seven-membered rings.



(eqn 1-21)

The regioselectivity of hydroboration reactions with thexylborane is somewhat better than that of reactions with borane-THF. Thexylborane places 94% of boron on the terminal carbon of 1-alkenes and 94% of boron at the terminal position of styrene (Figure 1-5)[50].

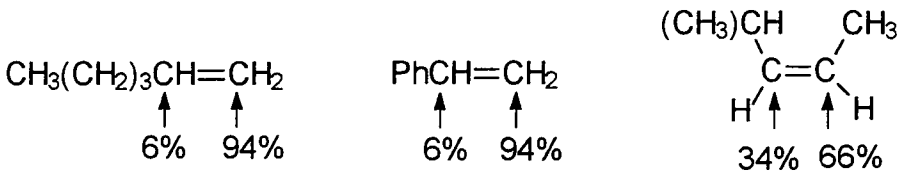


Figure 1-5. Regioselectivity of hydroboration of alkenes with thexylborane

1.2.2.7 Hydroboration with Monohalogenoboranes

Monohalogenoboranes are stronger Lewis acids than BH_3 because of electronic withdrawing properties of the halogens. They form strong complexes with ether solvents such as THF. Thus, in ether solvents, hydroborations are slow and reactions such as redistributions may occur[53]. Monochloroborane-

dimethyl sulfide is a convenient source of monohalogenoborane. The equilibration of a mixture of borane and trichloroborane dimethyl sufide complexes produces monochloroborane predominantly (>90%) (eqn 1-22)[54,55].

$$BCl_3 \cdot SMe_2 + 2\ BH_3 \cdot SMe_2 \rightleftharpoons 3\ BH_2Cl \cdot SMe_2 \quad \text{(eqn 1-22)}$$

$$BBr_3 \cdot SMe_2 + 2\ BH_3 \cdot SMe_2 \rightleftharpoons 3\ BH_2Br \cdot SMe_2 \quad \text{(eqn 1-23)}$$

The monobromoborane-dimethyl sulfide complex has also been prepared by a redistribution reaction (eqn 1-23)[54,55]. Both of the monohalogeno-borane dimethyl sufide complexes react readily with alkenes at 25 °C to form dialkylhalogeno-borane-dimethyl sufide complexes in high yields (eqn 1-24)[56,57].

$$H_2BX \cdot SMe_2 + 2\ RCH{=}CH_2 \longrightarrow (RCH_2CH_2)_2BX \cdot SMe_2 \quad \text{(eqn 1-24)}$$

The regioselectivity of the hydroboration of alkenes with monohalogeno-boranes is greater than that of borane and similar to that of dialkylboranes[53,58]. Some typical regioselectivities are shown in Figure 1-6.

1.2.2.8 Hydroboration with Dihalogenoboranes

Dihalogenoboranes form even stronger complexes with ether solvents such as diethyl ether than do the monohalogenoboranes[59]. The reactions of alkenes with dihalogenoboranes in diethyl ether are very slow. Dihalogeno-borane-dimethyl sulfide is more stable and easier to prepare by the equilibration

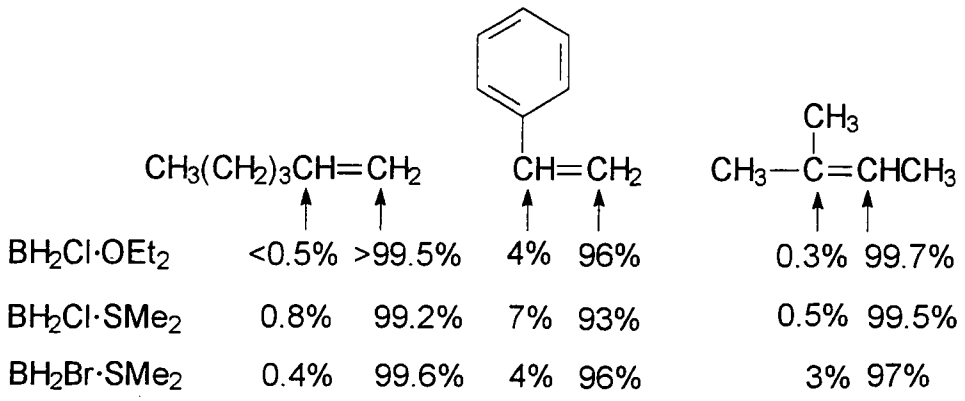
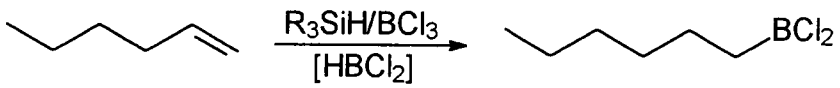


Figure 1-6. Regioselectivities of hydroboration of alkenes with monohalogenoboranes

of borane-THF and boron trihalide (eqn 1-25)[55,56]. The hydroboration of alkenes with dihalogenoborane, as a dimethyl sulfide complex, occurs at 25°C usually in the presence of trihalogen boron to decomplex the dimethyl sufide[60,61,62]. Alkyldihalogenoboranes are obtained as the major product.

$$BH_3{\cdot}SMe_2 + 2BX_3{\cdot}SMe_2 \rightleftharpoons 3\ BHX_2{\cdot}SMe_2 \qquad \text{(eqn 1-25)}$$

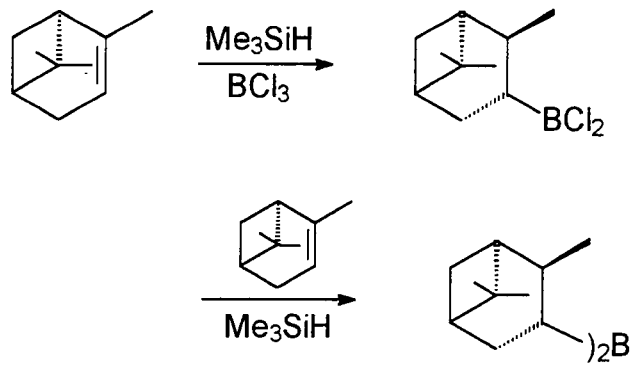
Recently, Matteson and his coworkers developed a convenient method for preparing dialkylhalogenoboranes by adding a mixture of trialkylsilane and alkene to boron trichloride (eqn 1-26)[63,64]. Presumably, $HBCl_2$ is generated by



(eqn 1-26)

the reaction of the trialkylsilane with boron trichloride. This solvent free borane is an extremely fast hydroborating reagent, which rapidly reacts with alkenes even

below -78 °C. Alkyldihalogenoboranes or dialkyhalogenoboranes can be prepared cleanly by controlling the ratio of reactants (eqn 1-27)[63,64].

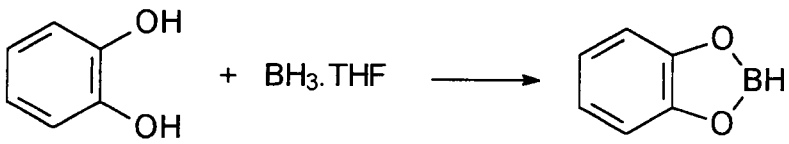


(eqn1-27)

The regioselectivity of hydroborations of alkenes with dihalogenoborane is similar to that of 9-BBN[61]. The most practical use of dihalogenoborane is that their hydroboration products are easily converted to the corresponding boronic acids and their esters.

1.2.2.9 Hydroboration with Catecholborane

Catecholborane is stable and is readily prepared by the reaction of catechol with borane-THF (eqn 1-28)[65,66]. However, it is a relatively sluggish



(eqn 1-28)

hydroborating reagent because π-bonding to oxygen partially fills the vacant *p*-orbital on boron and thus diminishes its Lewis acidity. The hydroboration of alkenes with catecholborane occurs at 100 °C[66,67]. The regioselectivity of

hydroboration with catecholborane appears to approach to that of disiamylborane[66]. Some examples are shown in Figure 1-7.

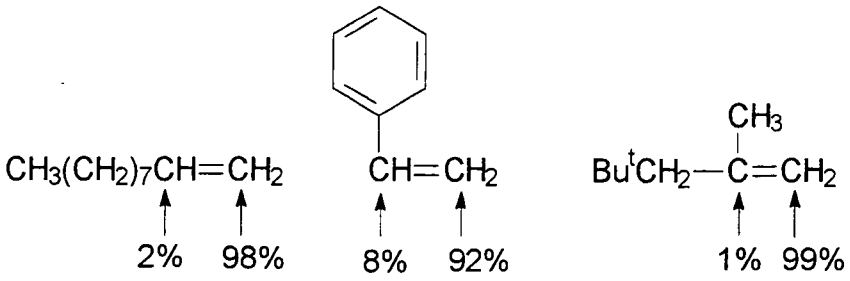
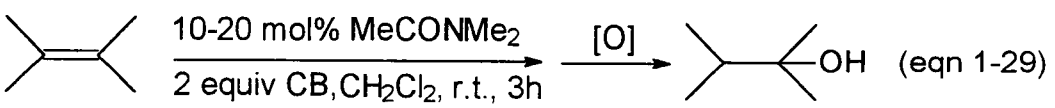


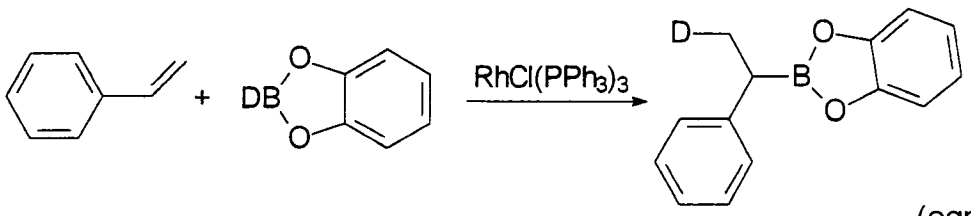
Figure 1-7. Regioselectivity of hydroboration of alkene with catecholborane

During the past ten years, a number of catalytic processes for hydroborations of alkenes with catecholborane have been developed[68,69]. These catalysts greatly accelerate the rates of reactions of alkenes with catecholborane and allow them to occur at room temperature[70,71]. For example, the hydroboration of mono-, di-, tri, and tetra-substituted olefins with catecholborane proceeds efficiently at room temperature in the presence of 10-20 mol% *N,N*-diemthylacetamide (eqn 1-29)[71]. Another important effect of the catalysts is that



(eqn 1-29)

the regioselectivity of hydroboration is sometimes changed remarkably[72,73]. For example, in the presence of Wilkinson's catalyst, the hydroboration of styrene leads exclusively to 1-phenylethanol after oxidation (eqn 1-30)[72].

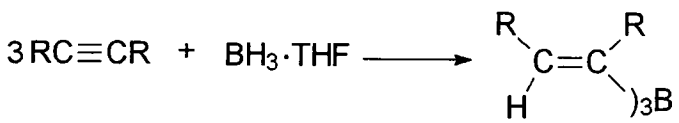


(eqn 1-30)

1.2.3 Hydroboration of Alkynes

1.2.3.1 Hydroboration with Boranes

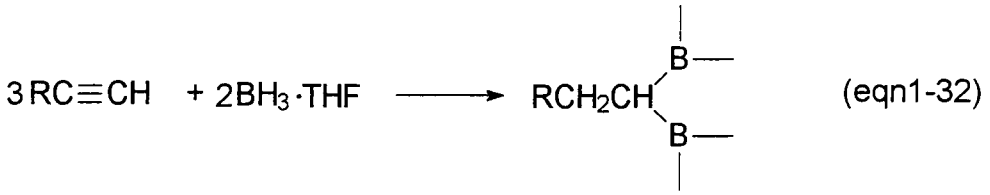
Alkynes readily undergo hydroboration to form either vinylboranes or diboron derivatives simply by controlling the amounts of the hydroborating agents. However, the hydroboration of alkynes involves the initial formation of a vinylborane derivative; thereafter a competition exists between unreacted alkyne and the vinylborane for the residual hydroborating reagent[74]. The hydroboration of internal alkynes with a stoichiometric amount of BH_3•THF predominantly forms the corresponding (*Z*)-trialkenylborane with a small proportion of the dihydroboration product (eqn 1-31)[75]. In the case of terminal alkynes, the initially



(eqn 1-31)

formed vinylborane appears to be more reactive than the residual alkyne, and preferential dihydroboration occurs[74]. An excess of BH_3•THF leads to total conversion to the dihydroboration products which are predominantly 1,1-diboryl

compounds (eqn 1-32)[76]. The regioselectivity of hydroboration reactions of alkynes with borane-THF is to place a greater percentage of the boron atoms at the less hindered carbon of the triple bond. The regioselectivity of internal alkynes is modest[75].



(eqn1-32)

1.2.3.2 Hydroboration with Borane Derivatives

The hydroboration of internal alkynes with one molar equivalent of 9-BBN gives vinylboranes as major products[77]. Further hydroboration of vinylboranes is slow, but can occur to form 1,1-diboryl compounds in 24 h at 25 °C[77]. The stoichiometric reaction of 9-BBN with terminal alkynes gives mainly 1,1-diboryl compounds. In contrast to 9-BBN, the reactions of internal and terminal alkynes with disiamylborane or dicylohexylborane in a 1:1 molar ratio forms vinylboranes. However, dihydroboration with these two agents is incomplete even with excess hydroborating agents[74,76,77,78].

The regioselectivities of the hydroboration of alkynes with dialkylboranes generally are greater than that of borane-THF. However, the regioselectivities are still modest in most case (Figure 1-8).

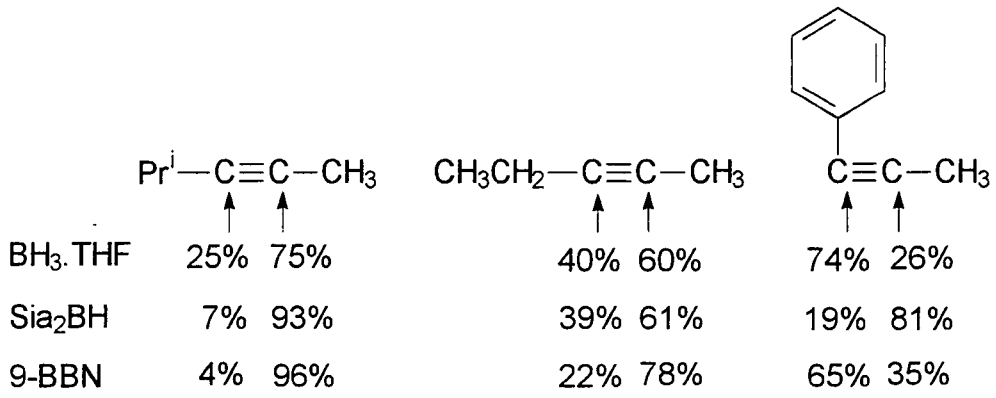
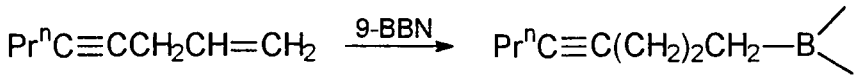


Figure 1-8. Regioselectivities of hydroboration of alkynes

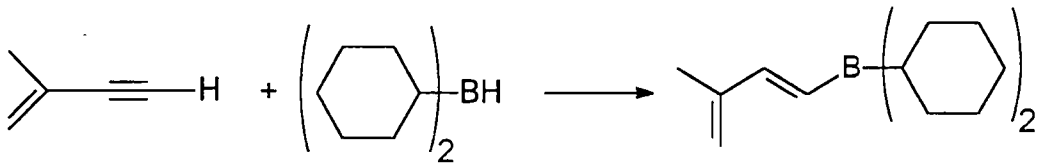
An interesting observation is that dibromoborane-dimethyl sulfide hydroborates internal alkynes faster than terminal alkynes[79] in contrast to most hydroborating reagents. The regioselectivity of dibromoborane-dimethyl sulfide is similar to that of 9-BBN.

1.2.3.3 Hydroboration of Enynes

Both alkenes and alkynes are readily hydroborated, thus there is a competition between the double bond and the triple bond of an enyne for the hydroboration reagent. The alkene group is generally hydroborated in preference to the alkyne group by 9-BBN, thereby permitting the synthesis of organoboranes containing an alkyne unit (eqn 1-33)[80]. In contrast to 9-BBN, disiamylborane and dicyclohexylborane react faster with the triple bond than the double bond of an enyne[81,82]. For example, dicyclohexylborane can be used for the synthesis of dienylborane (eqn 1-34)[83].



(eqn 1-33)



(eqn 1-34)

Catecholborane reacts at similar rates with of 1-alkenes and 1-alkynes, thus it is not a good reagent for the selective hydroboration of enynes[84]. Interestingly, dibromoborane-dimethyl sufide hydroborates internal alkynes faster than terminal alkenes, which could be synthetically useful for the selective hydroboration of an internal alkynes in the presence of a terminal alkene[79].

1.2.4 Hydroboration of Functional Derivatives

The hydroborations of alkenes and alkynes are very fast, thus many functional groups, such as halides, alkoxyl groups and esters, can be tolerated in hydroboration reactions. When the functional group is far away from the double bond or the triple bond, it has little influence on the hydroboration reaction. However, when the functional group is in close proximity to the double bond or the triple bond, it can have a marked effect on the reaction. Functional groups may dramatically change the regioselectivity of the reaction, and may cause the product organoboranes to be unstable[15,17,20].

1.2.4.1 Hydroboration of Vinyl Derivatives

Hydroboration of vinyl derivatives gives α- or β-substituted organoboranes depending on the nature of the substituents. The mesomeric effect (+M or -M) of the substituents influence the regioselectivities of the reactions[20].

The hydroboration of vinyl halides places the boron atom predominantly on the α-carbon atom (Figure 1-9)[85]. However, these organoboranes are unstable. They readily undergo α-transfer and elimination-rehydroboration reactions[17].

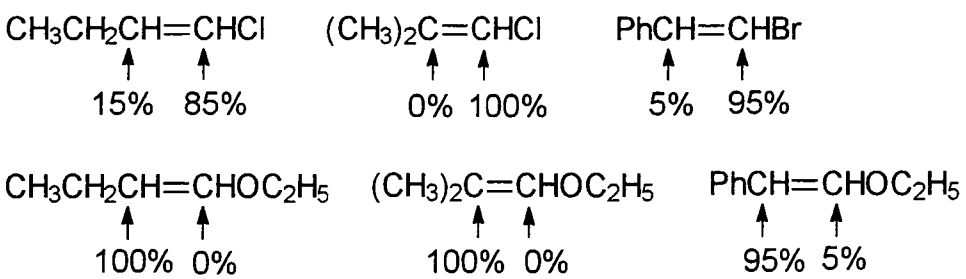
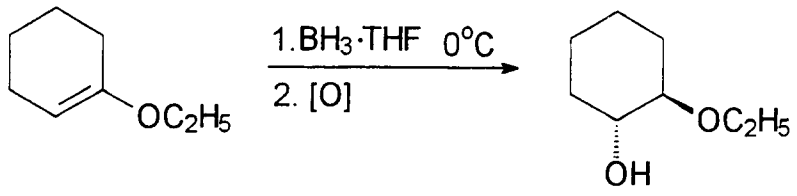


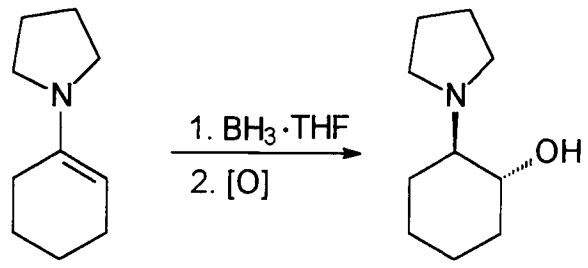
Figure 1-9. Regioselectivity of hydroboration of vinyl derivatives with BH_3-THF

Alkoxyl groups in enol ethers exhibit a marked influence on the regioselectivity of the hydroboration of enol ethers[85]. The boron atom is placed predominantly on the β-carbon atom (Figure 1-9). For example, hydroboration-oxidation of cyclic enol ethers gives the corresponding *trans*-2-alkoxy-1-alcohols in high yield (eqn 1-35)[85]. However, β-elimination of organoborane can occur in some cases[86].



(eqn 1-35)

The hydroboration of enamines gives mainly the β-aminoorganoborane due to the mesomeric effect of the nitrogen atom. Hydroboration-oxidation of cyclohexanone enamine derivatives gives the corresponding *trans*-amino-alcohols in good yields (eqn 1-36)[87].



(eqn 1-36)

1.2.4.2 Hydrobortion of Allylic Derivatives

The regioselectivity of hydroboration of allylic derivatives is affected by the electronegativity of the subsitituents[17]. Hydroboration of allyl derivatives (CH_2=$CHCH_2X$) gives mixture of β- and γ-boron derivatives. The percentage of the β-substituted organoboranes increases with increasing electronegativity of the substituent (Figure 1-10)[88]. Hydroboration of extended allylic systems

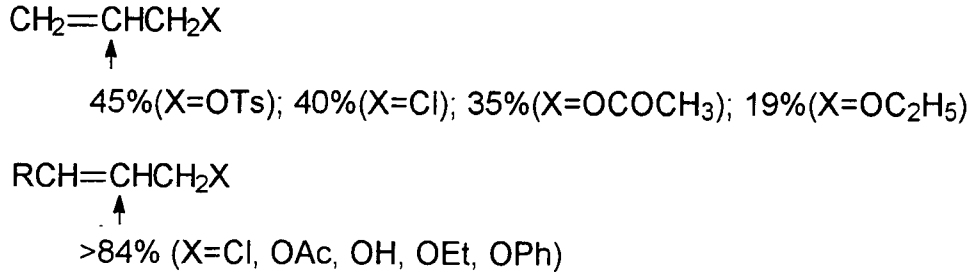
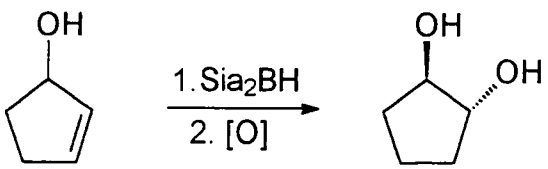


Figure 1-10. Regioselectivity of hydroboration of allylic derivatives with BH_3·THF

($RCH=CHCH_2X$) with borane-THF forms greater than 84% of the β-substituted organoborane in all cases. However, the β-substituted organoboranes can undergo elimination reactions especially if the substituents are good leaving groups, such as tosylates, halides and esters.

Hydroboration-oxidation of allylic alcohols gives 1,2-diols as major products [89]. Reaction of 3-hydroxycyclopentene with disiamylborane gives the *trans*-1,2-diol in 80% yield after oxidation (eqn 1-37)[90].



(eqn 1-37)

Hydroboration of allyl acetate with disiamylborane gives the 1,3-hydroxyl ester as major product after oxidation[88]. Reaction of crotyl acetate with borane-THF gives almost exclusive β-addition followed by rapid elimination-rehydroboration (eqn 1-38)[89].

$$RCH{=}CHCH_2OAc \xrightarrow[2.\ [O]]{1.\ BH_3\cdot THF} RCH_2CH_2CH_2OH \qquad \text{(eqn 1-38)}$$

1.2.4.3 Hydroboration of Unsaturated Carboxylic Acids and Derivatives

Hydroboration-oxidation of α,β-unsaturated carboxylic acids gives the saturated alcohols as major products, which are formed via reduction of the carboxylic acid group and hydroboration of the double bond followed by elimination-rehydroboration[91]. However, considerable amounts of 1,2-diols are formed at lower temperature[91].

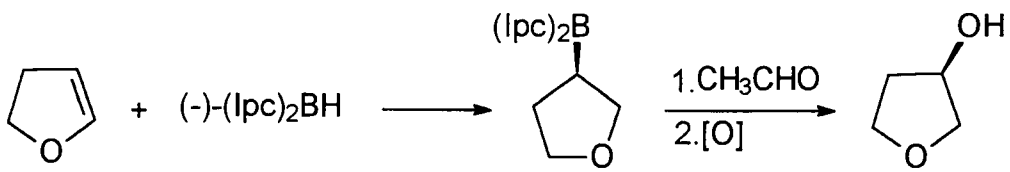
Hydroboration of α,β-unsaturated acid chlorides has been reported to proceed with some reduction of the acid chloride group[92]. Competitive hydroboration studies show the reaction of borane with esters is generally considerably slower than that with alkenes. Indeed, the double bond of unsaturated esters can be selectively hydroborated without reducing the ester group by borane-THF (eqn 1-39)[93].

$$CH_2{=}CH(CH_2)_nCO_2C_2H_5 \xrightarrow{Sia_2BH} Sia_2BCH_2CH_2(CH_2)_nCO_2C_2H_5 \qquad \text{(eqn 1-39)}$$

1.2.5 Asymmetric Hydroboration

1.2.5.1 Chiral Hydroboration Reagents

Optically active hydroborating reagents have been widely used in the asymmetric synthesis of organoboranes from alkenes. Diisopinocampheyl-borane, $(Ipc)_2BH$, is the most widely used asymmetric hydroborating reagent[94]. It is prepared by the hydroboration of α-pinene which is readily available in both enantiomers[95]. (R)-2-Butanol with 99% ee is obtained by the reaction of *cis*-2-butene with (-)-$(Ipc)_2BH$. However, only 63% ee is obtained for (S)-1-phenyl-1-propanol from *cis*-1-phenylpropene and (-)-$(Ipc)_2BH$[96]. In contrast to the mediocre results with acyclic olefins, diisopinocampheylborane reacts with five-membered heterocycles to give enantiomerically pure products (eqn 1-40)[97].

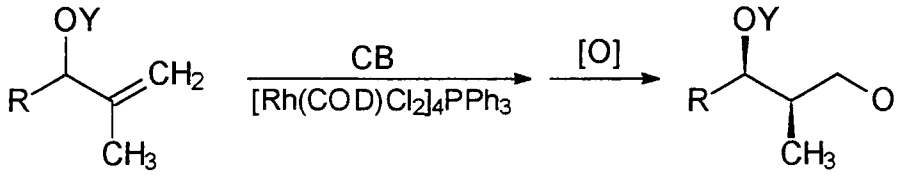


(eqn 1-40)

(R)-(R*,R*)-2,5-Dimethylborolane and its (S)-enantiomer are chiral hydroborating reagents that give exceptionally high asymmetric induction in all types of alkenes except disubstituted terminal alkenes[98]. Unfortunately, enantiomeric pure 2,5-dimethylborolane is very difficult to synthesize. Moreover, the compound is unstable during storage and must be used soon after preparation. All these factors are the obstacles to the practical use of (R)- or (S)-2,5-dimethylborolane.

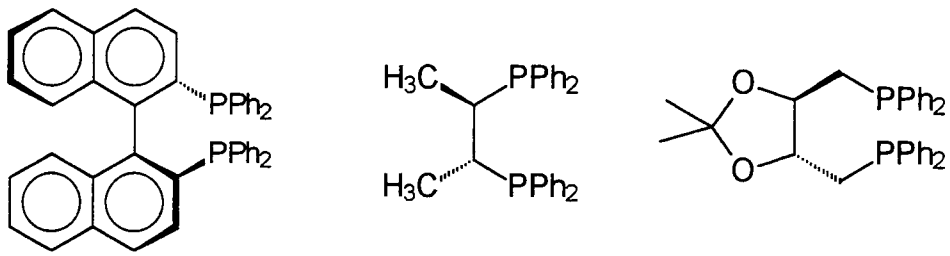
1.2.5.2 Catalytic Asymmetric Hydroboration

Most studies on catalytic asymmetric hydroboration are focused on the reactions of catecholborane. In the presence of catalysts, the regioselectivity of hydroboration with catecholborane is different from uncatalyzed hydroborations (see 1.2.2.8). A preference for *syn* selectivity has been observed in the rhodium catalyzed hydroboration of allylic alcohol derivatives (eqn 1-41)[99].



(eqn 1-41)

Asymmetric catalysts are also used to catalyze the hydroboration reactions. Asymmetric diphosphines are most often used as chiral ligands (Figure 1-10). Catecholborane, in the presence of a catalyst prepared from



(S)-BINAP (R,R)-CHIRAPHOS (R,R)-DIOP

Figure 1-11. Chiral ligands for hydroboration

$[Rh(COD)_2]BF_4$ and (R)-BINAP, converts styrene to (R)-1-phenylethanol after oxidation in 91% yield, 96.2% ee[100]. With a catalyst prepared from (+)-(S,S)-DIOP and [ClRh(C2H4)2], the hydroboration-oxidation of indene gives (-)-(R)-1-

indanol in 74% ee[101]. However, all methods developed to date are limited to certain alkenes. More general catalysts with high asymmetric induction for hydroborations are yet to be developed.

1.3 Reduction

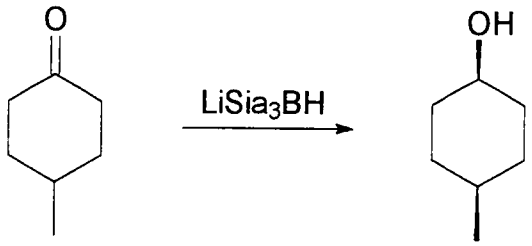
Boron-containing reducing reagents may be divided into two categories, nucleophilic reducing agents such as sodium borohydride and electrophilic reducing agents such as borane and its derivatives. Some functional groups, such as aldehydes and ketones, are readily reduced by both types of reducing agents. However, in many other cases, one type of reagent reduces compounds that may not be reduced by the other. The chemoselectivity exhibited by boron-containing reagents can be useful in organic synthesis.

1.3.1 Reduction with Hydroborates

As nucleophilic reducing reagents, borohydrides first attack electron-deficient centers in a compound. Changes of substitution at boron, counter-ion and solvents may affect the reactivity of the reagents[16]. Borohydrides decrease in reactivity towards functional groups in the order of acid chloride > aldehyde > ketone > ester > amide > alkyl halide[20]. Carboxylic acids and alkenes are not generally reduced by borohydrides.

Sodium tetrahydroborate is a very mild reducing reagent, readily reducing only acid chlorides, aldehydes and ketones. Altering the metal ion in the

tetrahydroborate increases the reducing power in the order of $NaBH_4$ < $LiBH_4$ < $Mg(BH_4)_2$ < $Al(BH_4)_3$[16]. Substituents on boron also change the reactivity of tetrahydroborate. Alkyl groups on boron increase the nucleophilicities of substituted hydroborates. Trialkylhydroborates ($M^+R_3BH^-$) are among the most powerful nucleophilic reducing agents. For example, the reducing power of $LiEt_3BH$ exceeds that of $LiAlH_4$. It readily reduces aliphatic halides[102] or sulphonate groups[103]. On the other hand, certain substituents, such as alkoxyl groups, decrease the reactivity of substituted tetrahydroborates. The reducing power of potassium triisopropoxyhydroborate is lower than that of sodium tetrahydroborate[104]. Substituents on boron may also affect the stereochemistry of borates. Bulky substituents, as in $Li(sec\text{-}Bu)_3BH$ and $LiSia_3BH$, introduce a large steric factor, which can control the stereochemistry of reductions (eqn 1-42).



(eqn 1-42)

Solvents also play an important role in the reduction with borohydrides. Solvents may increase or decrease the rate of reduction. Since reduction of carbonyl groups is strongly catalyzed by electrophilic attack at the carbonyl oxygen[105], protic solvents or a strongly coordinating cation may enhance reduction whereas solvents strongly dissolving the counter-ion decrease the rate

of reduction. Crown ethers[106], polar and aprotic solvents[107], or cations with poor coordinating ability[108] decrease the rate of reduction. In contrast to carbonyl compounds, the reduction of alkyl halides is not dependent on the electrophilic attack at the carbonyl oxygen. It is enhanced by conditions that render the anion 'naked'. Thus, sodium tetrahydroborate in dimethyl sulphoxide reduces alkyl halides in preference to ester or nitro groups[109] and sodium cyanotrihydroborate in hexamethylphosphoramide reduces alkyl halides in preference to aldehydes and ketones[110].

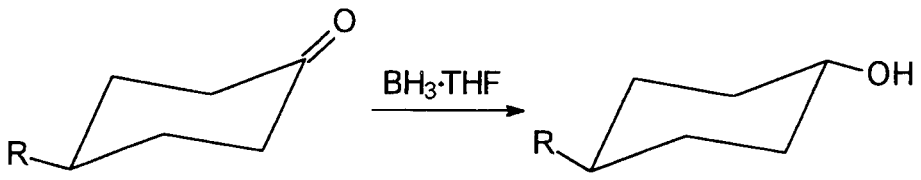
1.3.2 Reduction with Boranes and Derivatives

In contrast to borohydrides, boranes and their derivatives are electrophilic reducing reagents and attack groups at positions of high electron density. These reagents possess unique reducing characteristics. Borane derivatives readily reduce carboxylic acids, alkenes and alkynes, which are not reduced by borohydrides. Acid chlorides, which are readily reduced by borohydrides, are unreactive to boranes. This allows the selective reduction of an acid[111] or an amide[112] in the presence of an ester. The stereochemistry of the reduction of cyclic ketones using substituted boranes is superior to that of other reducing reagents. In addition, a number of borane derivatives have been developed for the asymmetric reduction of ketones.

1.3.2.1 Reduction of Aldehydes and Ketones

In general, aldehydes and ketones are rapidly reduced by borane-THF at 0°C to give the corresponding alcohols. Only benzophenone is reduced slowly[113]. Similar results are obtained using dialkylboranes in THF, though these reactions are usually slower[114].

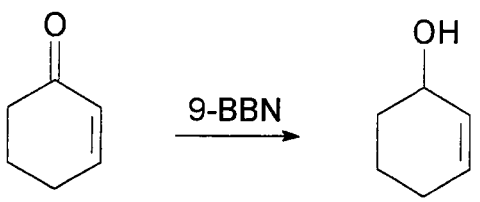
The reduction of unhindered cyclic ketones with borane-THF is steroselective and generally leads to the predominant formation of the more stable equatorial alcohols (eqn 1-43)[115]. Use of more sterically hindered borane



(eqn 1-43)

derivatives increases the formation of the less stable axial alcohols due to attack from the less hindered equatorial direction[116].

The reaction of α,β-unsaturated aldehydes and ketones with borane gives complicated results with three possibilities: hydroboration of carbon-carbon double bond, reduction of carbonyl group and 1,4-addition. Only a few examples which produce allylic alcohols are known[117]. Even in these cases, hydroboration of the carbon-carbon double bond competes as a side reaction. However, the

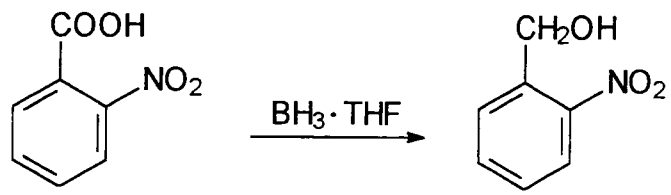


(eqn 1-44)

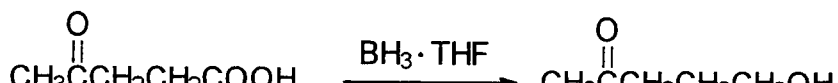
reaction of α,β-unsaturated cyclic ketones with 9-BBN in THF at 0 °C forms cyclic allylic alcohols quantitatively (eqn 1-44)[118].

1.3.2.2 Reduction of Carboxylic Acids

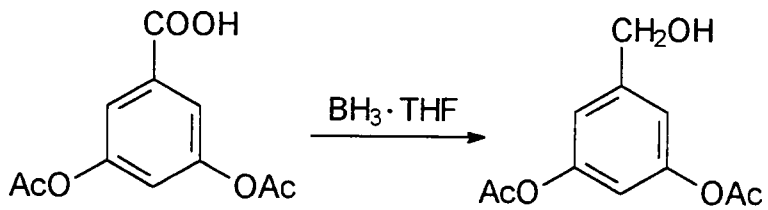
Both aliphatic and aromatic carboxylic acids are reduced by BH_3•THF rapidly and quantitatively to the corresponding primary alcohols under mild conditions. For aliphatic acids the reaction is extremely fast, being complete in 15 min at 0 °C, while 30 minutes is required at 25 °C in the case of aromatic acids. This provides a highly convenient synthetic method for the selective reduction of the carboxylic acid group in the presence of other functional groups. Carboxylic acids can be selectively reduced in the presence of the nitro group[119], nitrile[120], amine[121], ketone[122], ester[123] and amide[124] groups. Several examples are presented in equations 1-45, 1-46 and 1-47.



(eqn 1-45)



(eqn 1-46)



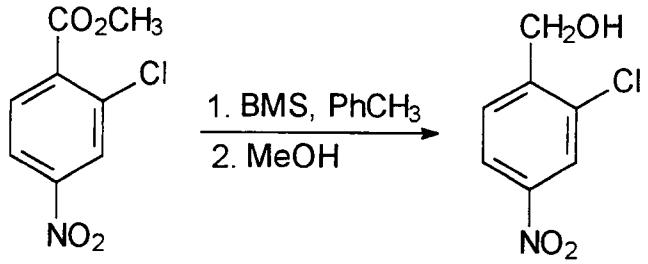
(eqn 1-47)

In reactions with disiamylborane, both aliphatic and aromatic acids liberate hydrogen quantitatively to form the anhydride of the acid and disiamylborinic acid, but no reduction occurs[114].

1.3.2.3 Reduction of Acid Chlorides, Esters and Lactones

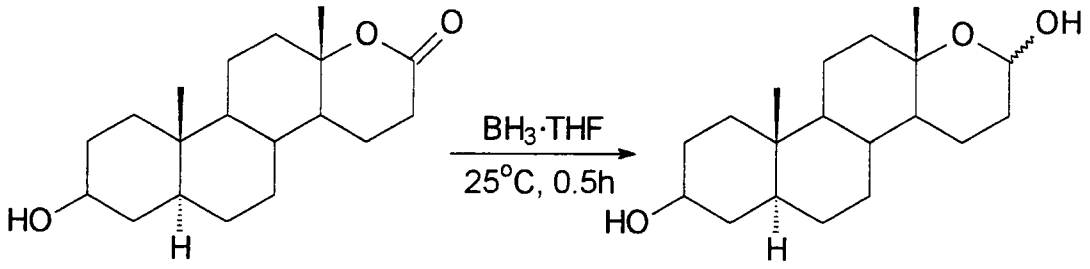
Reduction of aliphatic and aromatic acid chlorides with borane-THF generally proceeds very slowly, being only 50% complete in 48 hr[113]. Disiamylborane is inert toward aliphatic and aromatic acid chlorides[114]. However, it has been found that acid chlorides containing electronegative substituents on the α-carbon atom are more readily reduced than the parent acid chlorides[125].

Aliphatic acid esters and lactones are reduced relatively slowly with borane-THF. A 12-24h period is required for complete conversion to the corresponding alcohol[113]. Aromatic acid esters and lactones react extremely slowly with borane-THF consuming only 4-6% of the hydride in 24 hr[113]. The presence of electron-withdrawing substituents on the aromatic nucleus enhances the reactivity of the aromatic esters (eqn 1-48). In general, esters are inert to disiamylboranes in THF at 0 °C[114].



(eqn 1-48)

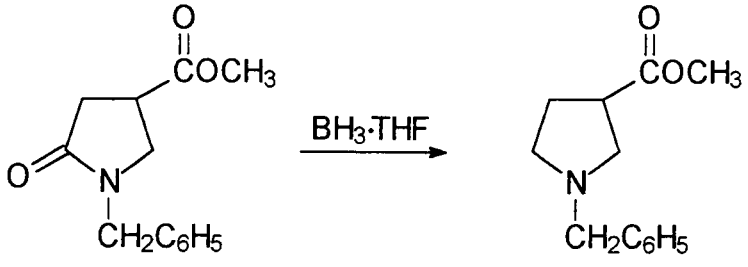
The reaction of δ-lactones with various borane reagents gives cyclic ethers in the presence of boron trifluoride[126]. Under carefully controlled conditions, the steroidal δ-lactones are converted to cyclic hemiacetals (eqn 1-49)[127].



(eqn 1-49)

1.3.2.4 Reduction of Amides

Primary, secondary, and tertiary amides derived from both aliphatic and aromatic carboxylic acids are rapidly reduced with borane-THF in refluxing THF[128]. The corresponding amine is obtained by acidic and basic hydrolysis in excellent yield. Amides are selectively reduced by borane-THF in the presence of esters (eqn 1-50)[129], while reduction fails with $LiAlH_4$.



(eqn 1-50)

Treatment of primary amides with dialkylboranes, such 9-BBN and Sia_2BH, in THF at 0 °C results in the rapid evolution of hydrogen. No reduction is observed[114]. However, tertiary amides are reduced by 9-BBN to give primary alcohols as major products (eqn 1-51)[130]. Disiamylborane also reacts with tertiary amides, but aldehydes rather than primary alcohols are obtained (eqn 1-52)[131].

$$PhCONMe_2 \xrightarrow{9\text{-BBN}} PhCH_2OH \qquad \text{(eqn 1-51)}$$

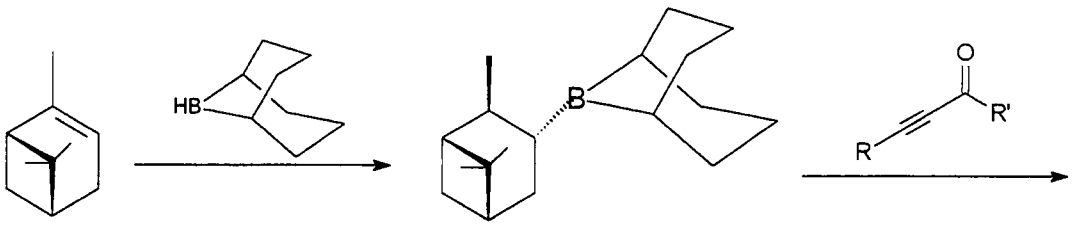
$$PhCONMe_2 \xrightarrow{Sia_2BH} PhCHO \qquad \text{(eqn 1-52)}$$

1.3.3 Asymmetric Reductions

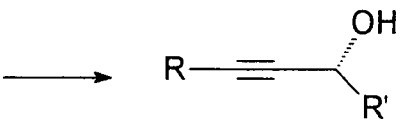
Another useful synthetic application of boron-containing reducing reagents is the asymmetrical reduction of carbonyl compounds[132,133]. High enantioselectivities have been achieved. The two major categories of enantioselective reductions include those that donate hydride by β-elimination of the boron and a hydride from alkylboranes, and those that donate hydride directly by breaking a B-H bond. Asymmetric boron reagents have been developed as reduction catalysts in recent years.

1.3.3.1 Reduction with Alkylboranes

The reaction of trialkylboranes with aldehydes to form alkenes and alcohols was first reported by Mikhailov's group[134]. Later the discovery of pinylborane made the reaction useful for reducing carbonyl compounds. Isopinocampheyl-9-BBN (Alpine-Borane), which is prepared from the hydroboration of (+) or (-)-α-pinene with 9-BBN, is most widely used for asymmetric reduction of propargylic ketones (eqn 1-53)[132]. Propargylic



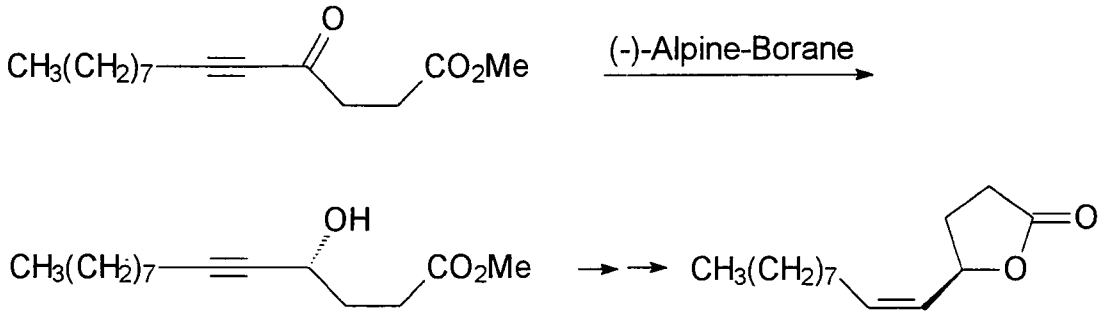
(-)-Alpine-Borane



(eqn 1-53)

alcohols are obtained in excellent enantiomeric purity by the reduction of propargylic ketones with Alpine-borane. An application of this reagent is the synthesis of the Japanese beetle pheromone from the alkynyl keto ester via propargylic alcohol ester (eqn 1-54)[135].

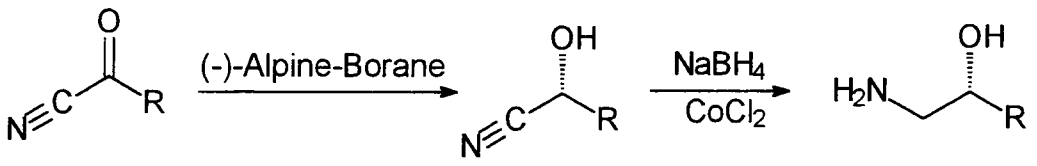
One problem with Alpine-Borane is that it can undergo reverse hydroboration to generate achiral 9-BBN, which is a much faster reducing agent than Alpine-Borane and leads to lowered ee's[136]. Running the reaction without a



(eqn 1-54)

solvent has been used to solve the problem. The highest enantioselectivity is achieved for ketones such as acetylenic ketones and acetophenone[137].

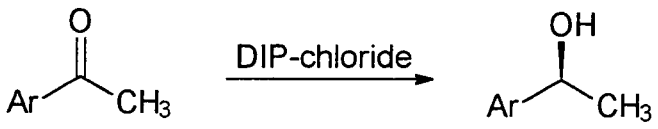
The cyano group is similar to the acetylenic group, and acyl cyanides are reduced by neat Alpine-Borane in 84-98% ee[138]. After treatment with sodium borohydride and cobaltous chloride in methanol, the reaction forms 1,2-amino acohols in high ee's (eqn 1-55).



(eqn 1-55)

An alternative to Alpine-Borane is the nopol benzyl ether analog[139], which is sold by the Aldrich Chemical Company as NB-Enantrane. Since this reagent possesses slightly higher steric requirements, the reduction of ketones with this reagent gives slightly higher ee's than Alpine-Borane. However, the reductions also tend to be slower.

Another useful reagent is diisopinocampheyboron chloride (DIP-chloride), which can be prepared by Matteson's method (eqn 1-27) or by the hydroboration of α-pinene with monochloroborane. The reaction of aryl alkyl ketones with DIP-

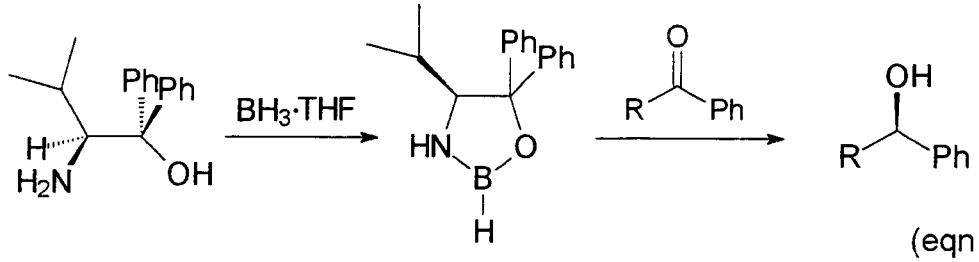


(eqn 1-56)

chloride yields (S)-arylalkanols in >90% ee's (eqn 1-56)[140]. DIP-chloride is also an excellent reagent for the conversion of propargylic ketones to highly enantiomeric pure propargylic alcohols[141].

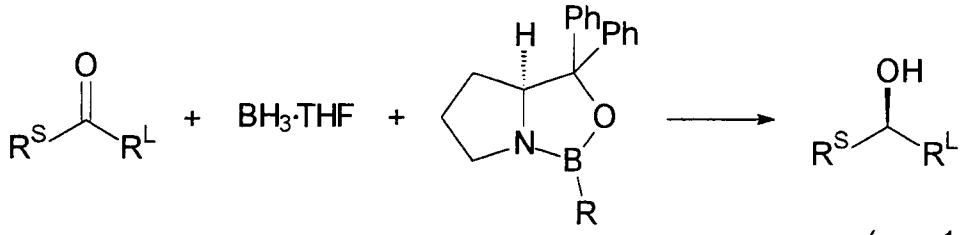
1.3.3.2 Reduction with Asymmetric B-H Compounds

In recent years, oxazaborolidines have emerged as important reagents in the enantioselective reduction of ketones. The first report of modest ee's in the reduction of acetophenone by BH_3•THF in the presence of amino alcohols derived from amino acids was made by Hirao and his coworker[142]. Soon, they found that a mixture of 1,1-diphenylvalinol with 2 moles of BH_3•THF reduces alkyl phenyl ketones to (R)-1-phenylalkanols in 94-96% ee (eqn 1-57)[143]. The



(eqn 1-57)

performance of the oxazaborolidines is greatly improved if the (S)-(-)-2-(diphenylmethoxy)pyrrolidine is used in place of the valine derivative. The resulting reagent is used as catalyst (5-10%) together with BH_3•THF. The reduction of ketones, having R^S=alkyl and R^L=aryl, yields alcohols with 89-90% ee's (eqn 1-58)[144].



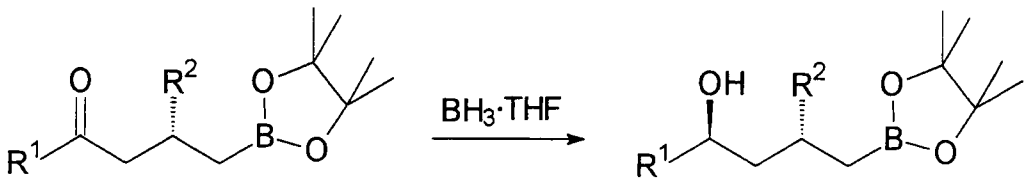
(eqn 1-58)

Certain allylic ketones, which are potentially useful for natural products synthesis, have been reduced by this reagent. Allylic alcohols having ee's >90% are obtained[145]. Another innovation introduced by Corey was the use of catecholborane as the reducing agent in place of BH_3•THF. Since catecholborane is more stable than BH_3•THF, the use of catecholborane can be helpful in avoiding competitive reductions of other functional groups[146]. In the presence of the Corey's reagent, catecholborane reduces 2-triisopropylsilyl-ethynyl alkyl ketones to chiral propargylic alcohols with 90-97% ee's in 91-100% yields[147].

Several research groups have developed other chiral 1,3,2-oxazaborolidines as efficient catalysts for the borane reduction of ketones[133]. For example, trimethylsilylethynyl alkyl ketones are reduced to acetylenic alcohols

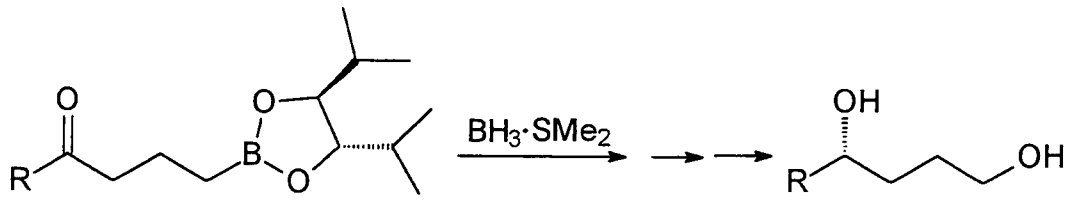
with 97% ee's in 95% yields by BH_3•THF in the presence of (R)-B-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine[148].

Remote asymmetric induction in γ-keto boronic esters is a valuable method for enantioselective reduction of ketones. 2-Alkyl-4-ketoalkylboronic esters, which are synthesized easily in racemic form from organozinc reagents, react with BH_3•THF to yield the 2,4-*anti* diasteromers in high 91-96% de's (eqn 1-59)[149].



(eqn 1-59)

A cyclic interaction in the postulated transition state accounts for the results. Asymmetric boronic esters with C_2 symmetry in ketoalkylboronic esters provide an asymmetric induction at the keto group. After oxidation, 1,4-diols with 92-98% ee are obtained (eqn 1-60)[150].



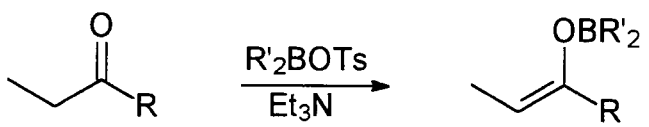
(eqn 1-60)

1.4 Boron Enolates

The reaction of boron enolates with aldehydes has been one of the most powerful reactions for stereocontrolled carbon-carbon bond formation[151]. The aldol reaction of boron enolates affords high levels of diastereoselectivity *via* highly ordered chair transition states. The stereochemistry of this reaction has been extensively studied [152]. In general, the reaction of (*Z*) enolates gives *syn*-aldol products, while the reaction of (*E*) enolates gives *anti*-aldol products. Thus, the selective preparation of (*Z*) or (*E*)-enolates is important to the diastereoselectivity of the aldol reaction. The diastereoselectivity is depended on the ratio of (*Z*)/(*E*) isomer.

1.4.1 Routes to Boron Enolates

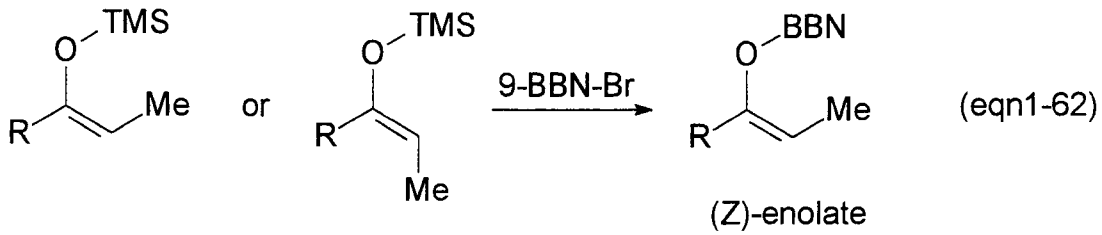
Enolates are usually generated by the reaction of ketones with R_2BX in the presence of amines. When X is a triflate group, the reaction of ethyl ketones gives (*Z*)-enolates predominantly (eqn 1-61)[153]. However, the ratio of *Z* enolates



(eqn 1-61)

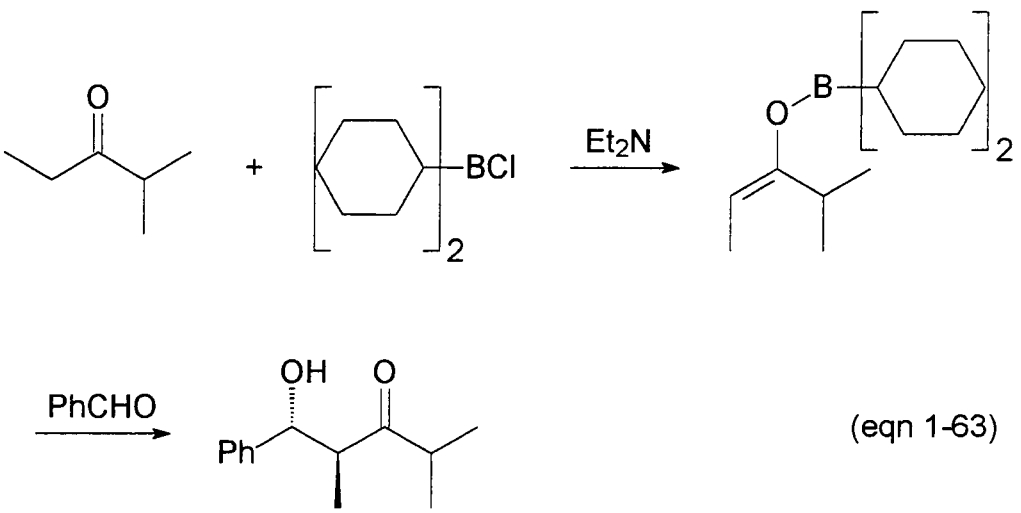
(Z)-enolate

and *E* enolates is lower for sterically hindered ketones. Recently, Evans and coworkers reported a new route to high purity of *Z* enolates from enol silylates (1-62)[154].



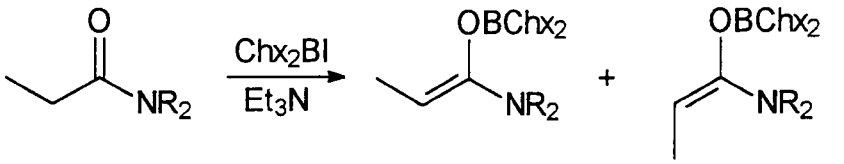
(eqn1-62)

In contrast to dialkylboron triflates, reaction of dialkylboron chlorides with ketones usually yields (*E*)-enolates[155,156]. For example, the reaction of chlorodicylohexylborane and triethylamine with ethyl isopropyl ketone forms the (*E*)-enolate with a >97:3 (*E*)/(*Z*) ratio (eqn 1-63)[156]. Reaction with benzadehyde yielded the *anti* β-hydroxy ketone.



(eqn 1-63)

N,N-Dialkyl ethyl amides react with dicyclohexylboron iodide in the presence of triethylamine to form either (*Z*) or (*E*) enolates, depending on the solvents used[157]. (*Z*)-Enolates are obtained predominantly when hexane is used as the solvent. On the other hand, (*E*)-enolates are the predominant products formed when carbon tetrachloride is used as the solvent (eqn 1-64).



(eqn 1-64)

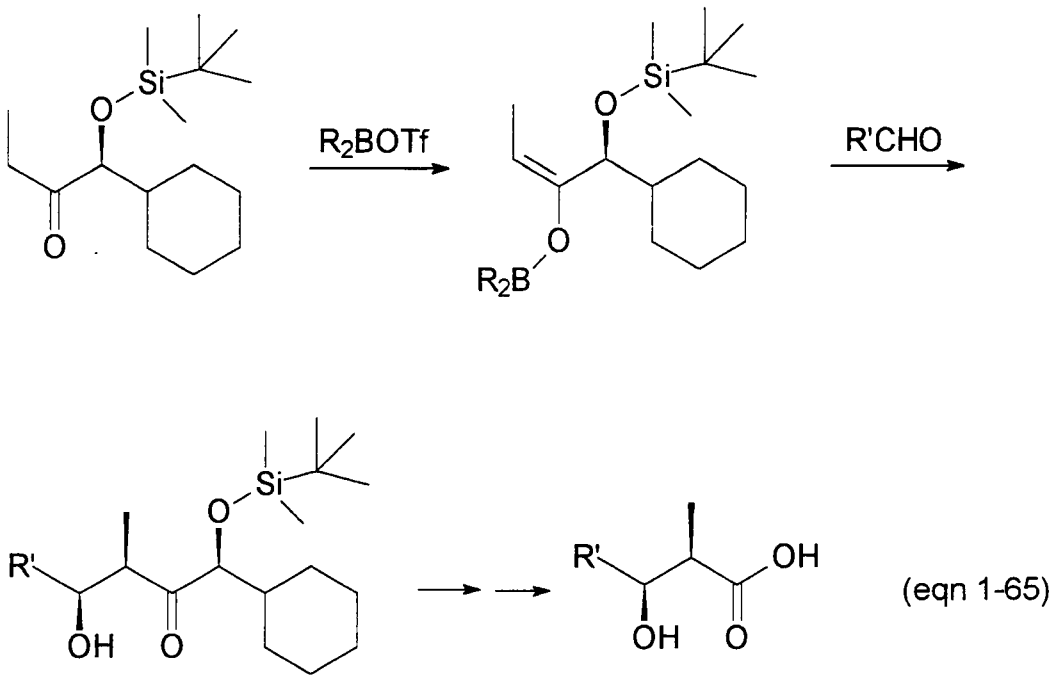
Solvent	(Z)-enolate	(E)-enolate
Hexane	>97%	<3%
CCl_4	<3%	>97%

1.4.2 Aldol Reaction with Chiral Boron Enolates

1.4.2.1 Chiral Enolate Carbon Skeletons

The diasteroselective aldol condesations can be made enantioselective by the use of appropriate chiral directors. There are two ways to introduce chiral directors into the reaction. One is the use of chiral auxiliaries attached to the carbonyl carbon. Another is the use of chiral ligands on the boron to promote enantio- and diastereoselective aldol reactions between achiral carbonyl compounds.

The first compound using chiral auxiliaries attached to the carbonyl carbon was derived from commercially available (S)-mandelic acid, then converted to a boron enolate (eqn 1-65)[158]. The reaction of this boron enolate with aldehydes affords carboxylic acids in high diastereoselectivity after desilylation. The drawback of this method is that the chiral director cannot be recovered and recycled.

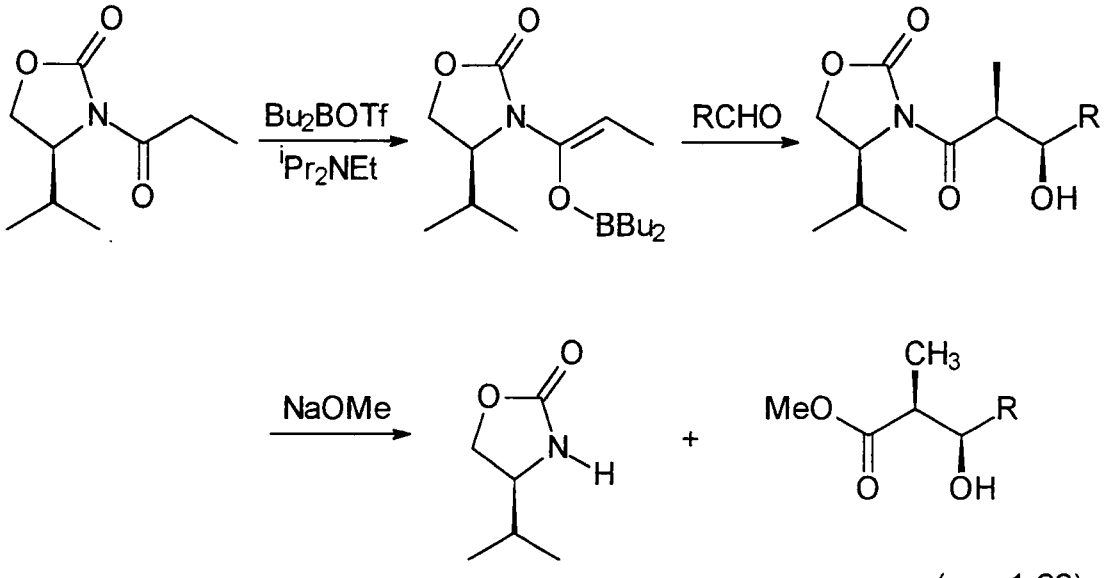


(eqn 1-65)

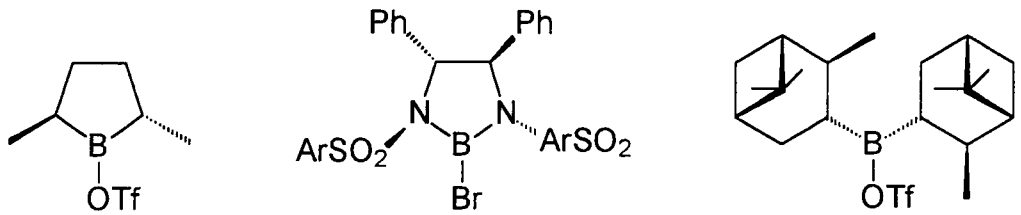
Evans and coworkers developed a method using chiral oxazolidine as the chiral director, which can be recovered. The (*Z*)-enolate is formed from the reaction of oxazolidine with Bu_2BOTf in the presence of diisopropyl ethyl amine[153]. It reacts with aldehydes to give β-hydroxyl esters in high yields and high ee's after methoxide cleavage (eqn 1-66).

1.4.2.2 Chiral Boryl Groups

Many chiral boron reagents used for asymmetric reductions or hydroborations are also good for the asymmetric aldol reaction of enolates. Several efficient chiral boron reagents used for producing enolates are illustrates in Figure 1-11.



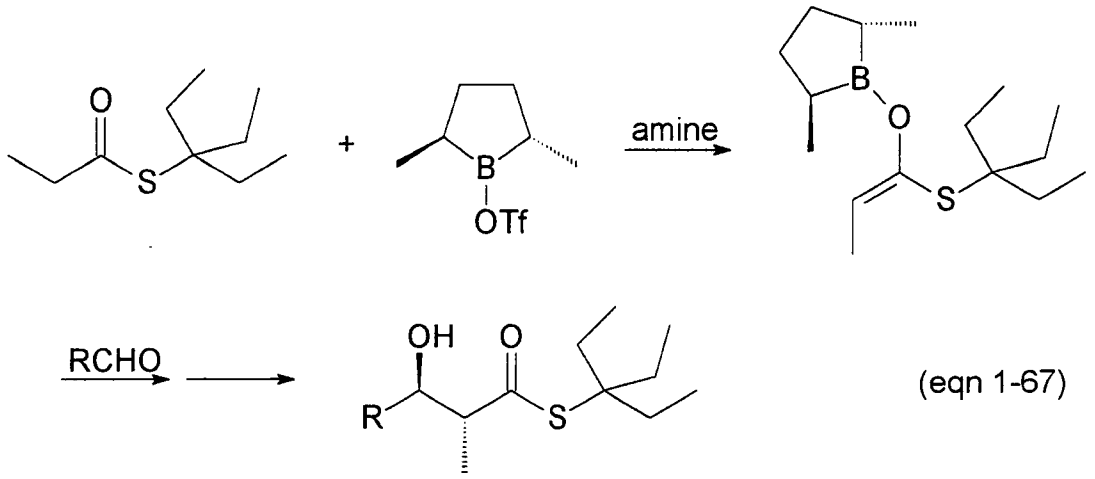
(eqn 1-66)



Masamune's reagent Corey's reagent (-)-(Ipc)$_2$BOTf

Figure 1-12. Chiral reagents for Aldol reactions with boron enolates

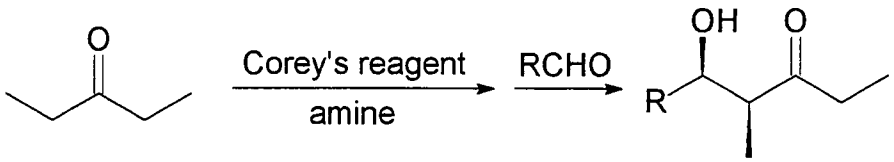
Masamune's chiral borolane serving as a chiral director in the aldol condensation gives excellent de and ee. For example, the reaction of (triethyl)methanethiol propionate with the chiral borolane results in formation of the (*E*)-enolate, which, with aldehydes, leads to anti α-methyl-β-hydroxy thiol esters in 94% de, 97-99% ee (eqn 1-67)[159].



(eqn 1-67)

94%de, 97-99%ee

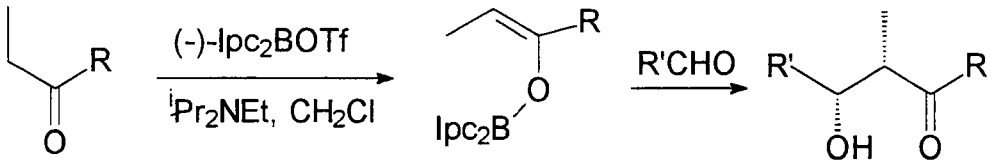
Although Masamune's reagent gives excellent de and ee, the difficulty in preparing the reagent limits the application of this method. In contrast to Masamune's reagent, Corey's reagent is easily prepared and more practical. The reaction of diethyl ketone with Corey's reagent yields the (*Z*)-enolate, which yielded the hydroxy ketones in 95-98% ee when reacted with aldehydes (eqn 1-68)[160].



(eqn 1-68)

95-98% ee

Both (-)- and (+)-Ipc_2BOTf are easily prepared in >99% ee in two steps from commercial grade (+) and (-)-α-pinene. The reaction of ethyl ketones with (-)-Ipc_2BOTf results in formation of the *Z* enolates which react with aldehydes to yield *syn* α-methyl-β-hydroxy ketones in moderate to high ee's (eqn 1-69)[161].



66-93% ee

(eqn 1-69)

1.5 Statement of Problem

In many molecules, especially in natural products, both carbonyl groups and carbon-carbon unsaturated bonds are present. The selective hydroboration of the carbon-carbon unsaturated bonds in the presence of a carbonyl group would be synthetically useful. As discussed in this chapter, the reactions of boron hydrides with alkenes and alkynes are very fast[16]. This permits the selective hydroboration of alkenes and alkynes in the presence of many functional groups, such as halogen groups, alkoxy groups, ester groups[15]. Ketones and aldehydes are also highly reactive toward boron hydrides, and selective hydroborations in the presence of ketones and aldehydes has been considered impossible[15]. The only way to hydroborate alkenes and alkynes in the presence of ketones and aldehydes involved the protection of the carbonyl groups by converting them to acetal and ketal groups[162]. However, in many cases, even acetals and ketals react with boron hydrides.

This dissertation summarizes research focused on the selective hydroboration of alkenes and alkynes in the presence of ketones and aldehydes. Practical methods for selective hydroboration have been developed during the course of this study.

Chapter 2. The Kinetic Study of Hydroboration of Alkenes and Reduction of Ketones.

2.1 Introduction

The hydroboration of alkenes and the reduction of ketones using borane reagents are widely utilized in organic syntheses[20]. However, many aspects of these reactions are still being delineated. Several different reaction mechanisms of hydroboration with BH_3 have been proposed[163]. The major problem in defining the mechanism of the hydroboration reaction has been the difficulty in obtaining accurate kinetic data. Boranes are sensitive to both oxygen and water and consequently must be handled under an inert atmosphere. Moreover, hydroborations with borane (BH_3) are complex, involving three consecutive addition reactions, three redistribution equilibria, and five monomer-dimer equilibria. Reductions of carbonyl compounds are prone to the same complexities. As a result, kinetics studies of the reactions of borane (BH_3) with both alkenes and carbonyl compounds have often been contradictory.

In order to overcome these difficulties, Brown and his coworkers conducted a series of kinetic experiments focused on hydroborations and reductions with dialkylboranes[164]. Dialkylboranes, which have only one boron hydride, dramatically simplify the overall reaction and consequently simplify kinetics studies. Because of the remarkable thermal stability and the high purity of the 9-BBN, the kinetics of 9-BBN reactions have been extensively studied by Brown and his coworkers. First-order kinetics were observed in the reaction of

reactive alkenes with 9-BBN which exists as a dimer[164b,164c]. The reaction of less reactive olefins with 9-BBN exhibited three-halves-order kinetics[164b,164c]. Similarly, first-order kinetics were found in the reduction of aldehydes and reactive ketones with 9-BBN, and three-halves-order kinetics were observed in the reduction of less reactive ketones[164e]. The kinetics of these reactions were accounted for in terms of a dissociation of the dimer into the monomer (eqn 2-1), followed by a reaction of the monomer with the olefin (eqn 2-2) or the aldehyde (eqn 2-3). For reactive alkenes and carbonyl compounds k_1 is the rate

$$(9\text{-BBN})_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2\ 9\text{-BBN} \qquad \text{(eqn 2-1)}$$

$$9\text{-BBN} + \text{olefin} \xrightarrow{k_2} \text{product} \qquad \text{(eqn 2-2)}$$

$$9\text{-BBN} + \text{aldehyde} \xrightarrow{k_2} \text{product} \qquad \text{(eqn 2-3)}$$

determining step whereas k_2 is the rate determining step for less reactive alkenes and carbonyl compounds. Three-halves-order kinetic behavior is observed in the hydroboration of many alkenes with the disiamylborane dimer[164k] and the borinane dimer support the dissociation mechanism[164i].

The techniques used in these kinetic studies were developed by Brown and his coworkers[164b,164c]. Initially, the kinetic studies of 9-BBN hydroborations were carried out by an indirect analytical technique[164b]. Aliquots of the reaction mixture were periodically withdrawn and quenched in an alcohol solution. The

samples were analyzed by GC for residual olefin by using an internal standard. This method gave reliable data, but was tedious and very time consuming. The accuracy of the kinetic data is limiting due to the limited number of aliquots taken and the indirect nature of the analytical technique. In 1980, a direct analytical technique using quantitative infrared spectrometry was introduced and used to carry out the kinetic study[164c]. 9-BBN exhibits a very strong infrared absorption at 1570 cm^{-1} due to the boron-hydrogen bridges. The reaction was followed by monitoring the absorption at 1570 cm^{-1}. Since no quenching procedure was needed using this technique, the errors inherent in the indirect quenching method were eliminated. This technique was extensively used to carry out various kinetic studies with 9-BBN by Brown and his coworker.

NMR spectroscopy has developed rapidly in recent years and has been widely applied to many quantitative kinetic studies. ^{11}B NMR would appear to be a reasonable technique for carrying out the kinetic studies of reactions with borane reagents. Each boron compound exhibits a unique ^{11}B resonance. The reactions can be followed by monitoring the disappearance of specific boron resonances as the reaction progresses. Compared to the infrared technique, this method provides variable temperature kinetic data since most NMR spectrometers are equipped with variable temperature probes. The preliminary results of a kinetic study of the reactions of 9-BBN with alkenes and carbonyl compounds using ^{11}B NMR spectrometer are presented in this chapter.

2.2 Results and Discussion

2.2.1 The Kinetics of the Reduction of Ketones with 9-BBN

2-Heptanone was chosen as a model ketone. The kinetics of the reduction of 2-heptanone with 9-BBN were measured by monitoring the ^{11}B-resonance of 9-BBN (0.5 M in THF) in a 5 mm quartz NMR tube. The NMR tube was placed into a NMR spectrometer which was maintained at 273 K. The rate of disappearance of the boron resonance of $(9\text{-BBN})_2$ at 32 ppm was monitored by acquiring spectra at specific intervals. The concentration of $(9\text{-BBN})_2$ was determined by integrating the resonance at 32 ppm.

Using Brown's protocols[184], three equations, $\ln C_0/C$ (first-order), $1/C-1/C_0$ (second-order) and $2^{1/2}[C^{-1/2}-C_0^{-1/2}]$ (three-halves), versus time were utilized to plot the data. The plots of the rate values computed using the three equations versus time are presented in Figure 2-1. As can be noted by examining Figure 2-1, the rate data which provides the best fit to the first-order rate equation (Figure 2-2). The data do not fit well to the second-order rate equation and three-halves-order rate equation. Changing the initial concentration of each of the reactants does not alter the first-order rate constant appreciably (Table 2-1, Figure 2-5 and Figure 2-6). The reaction of 2-heptanone with 9-BBN in 1:1 ratio was repeated twice (Figure 2-3 and Figure 2-4) and the rate constants were found to be consistent.

The kinetics derived utilizing ^{11}B NMR are consistent with the literature. The mechanism of the reaction of 2-heptanone with $(9\text{-BBN})_2$ thus involves the

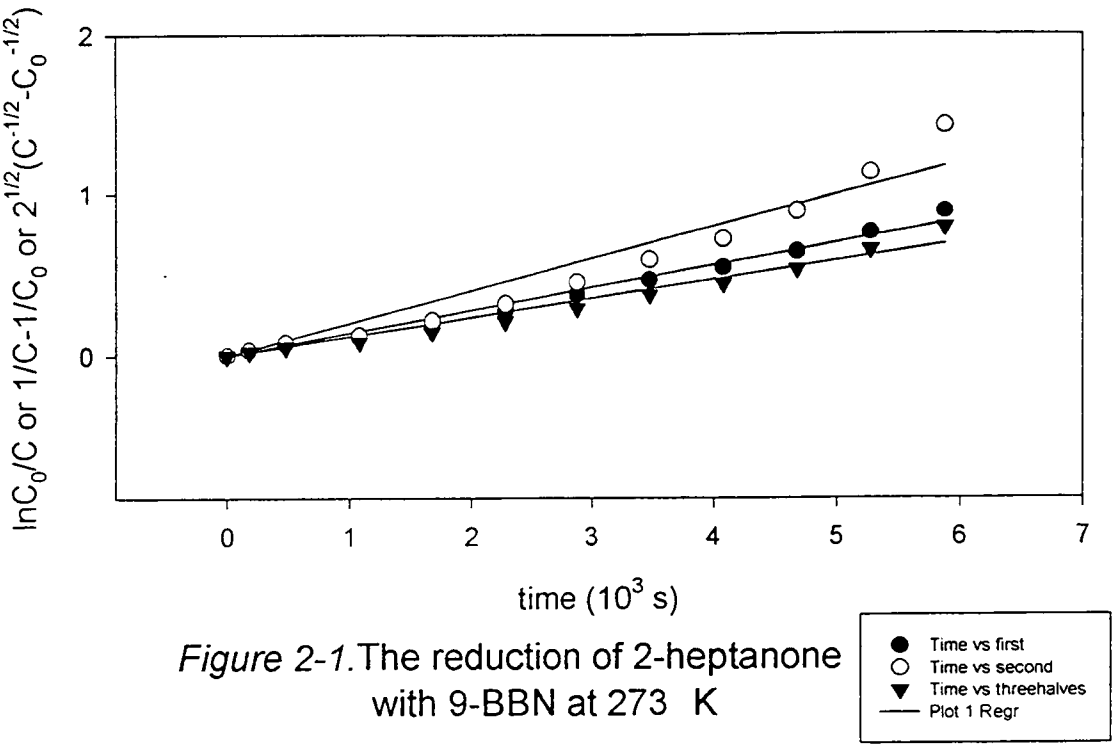


Figure 2-1. The reduction of 2-heptanone with 9-BBN at 273 K

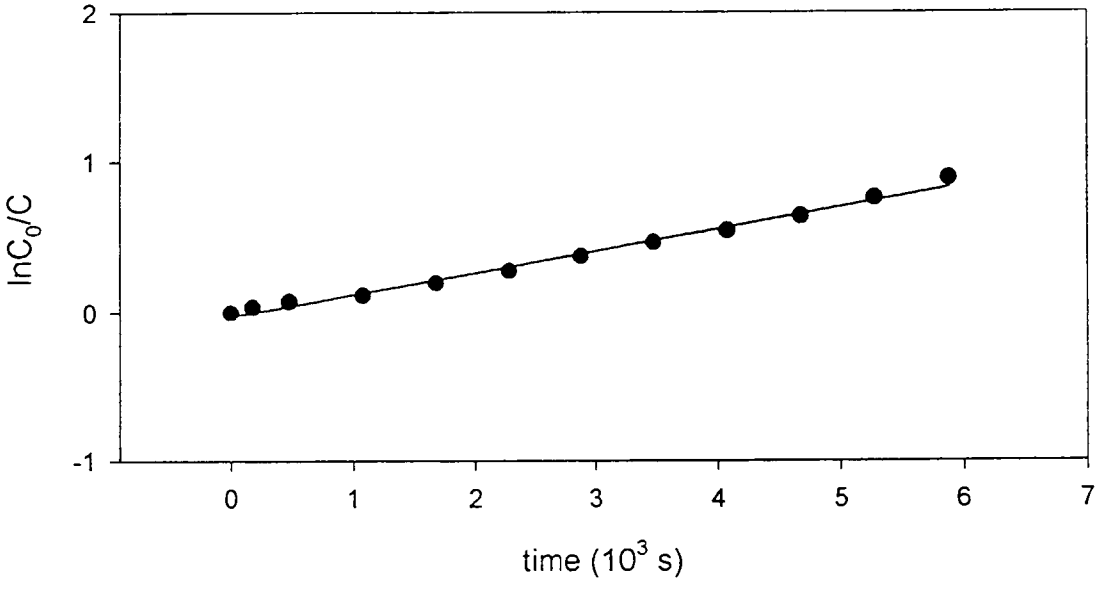


Figure 2-2. The reduction of 2-heptanone with 9-BBN at 273 K

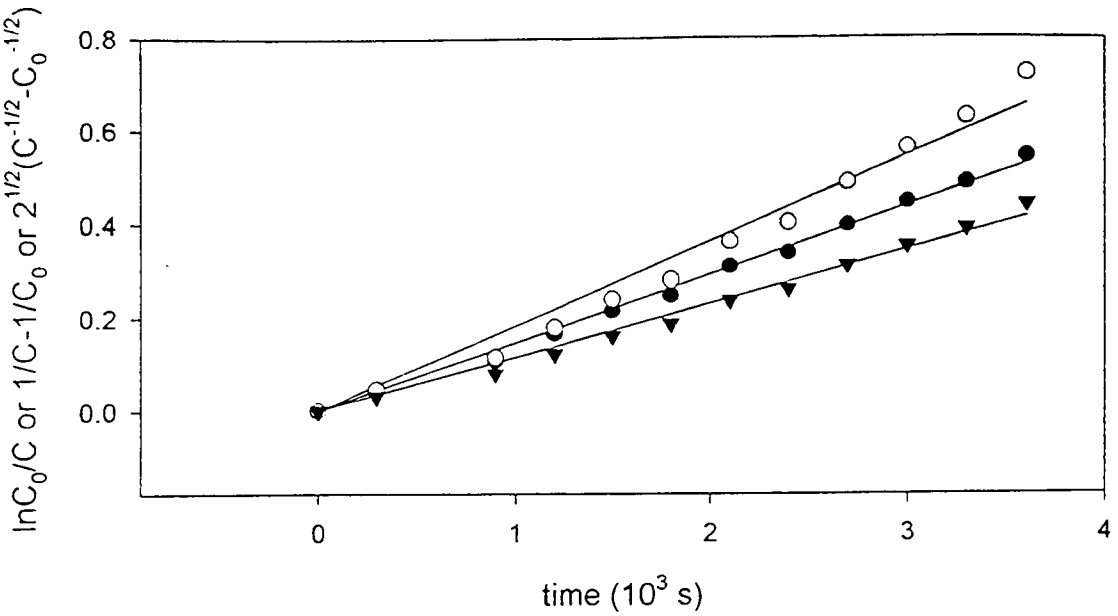


Figure 2-3. The reduction of 2-heptanone with 9-BBN at 273 K

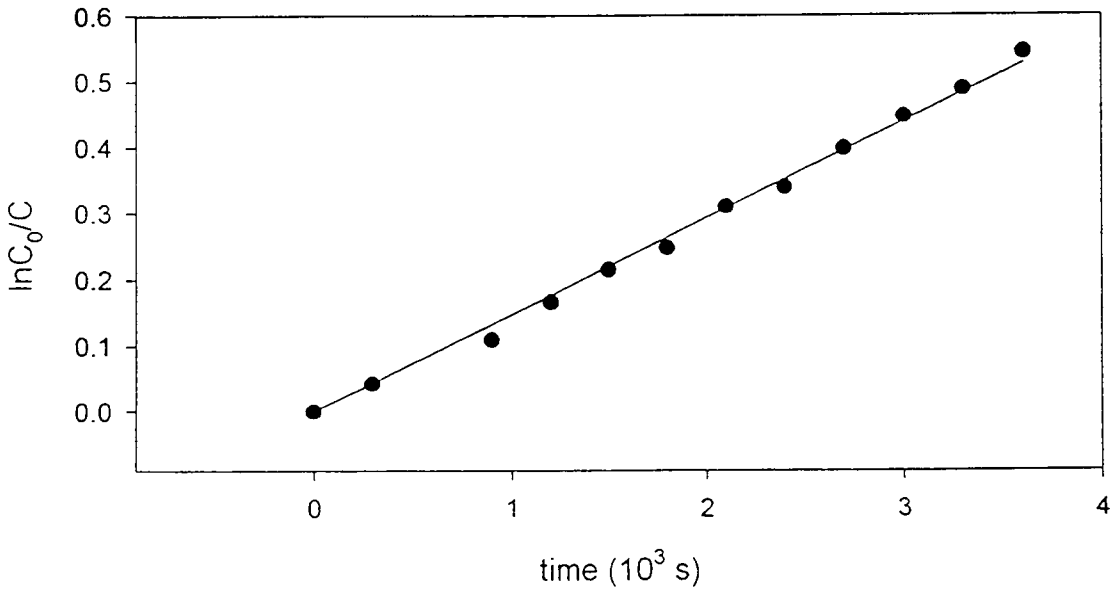


Figure 2-4. The reduction of 2-heptanone with 9-BBN at 273 K

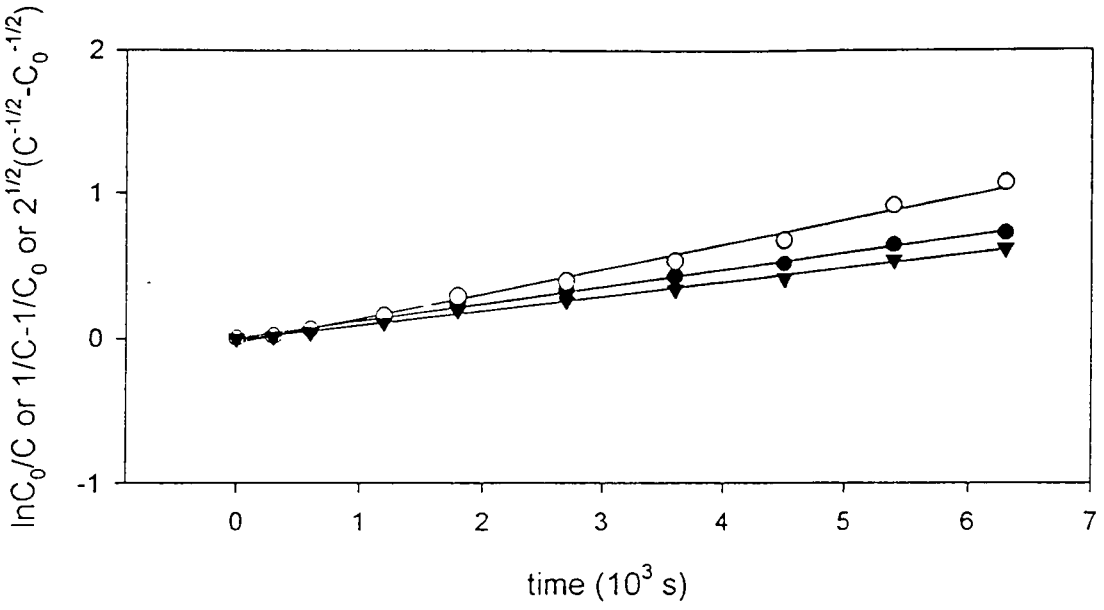


Figure 2-5. The reduction of 2-heptanone with 9-BBN at 276 K

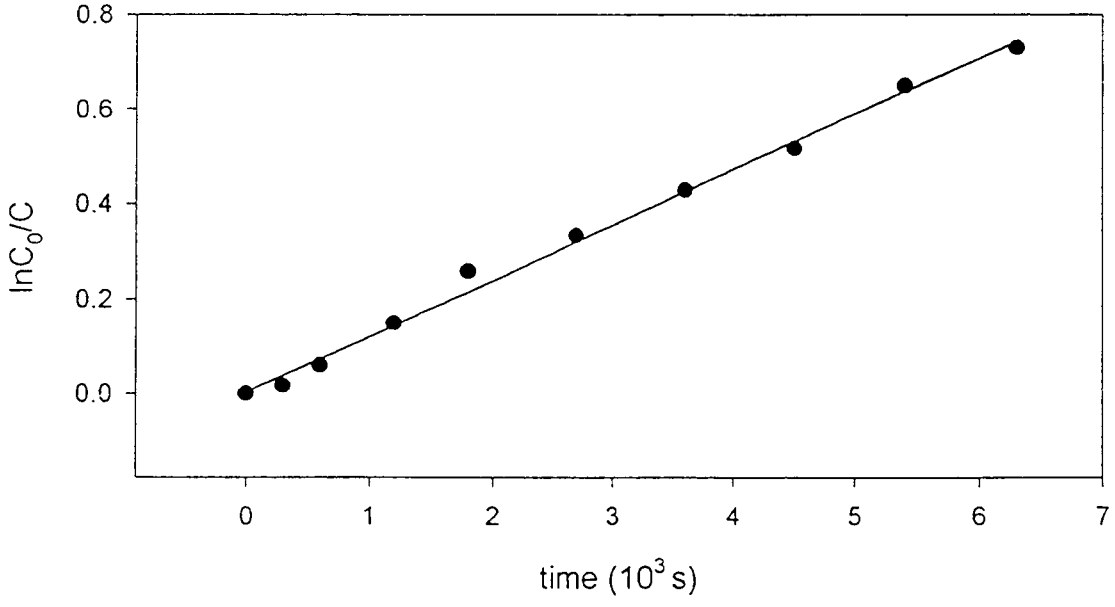


Figure 2-6. The reduction of 2-heptanone with 9-BBN at 276 K

Table 2-1. Rate constants for the reduction of 2-heptanone with 9-BBN in THF at 273 K.

Entry	Initial Concn, M		Rate Constant (k_1)
	$(9\text{-BBN})_2$	2-heptanone	$\times 10^{-4}\ s^{-1}$
1	0.25	0.25	1.46
2	0.25	0.25	1.40
3[a]	0.33	0.17	1.20

[a] This reaction was carried out at 276K.

dissociation of the 9-BBN dimer to the monomer followed by the reaction of the monomer with 2-heptanone (eqn 2-4).

This mechanism leads to the following kinetic expression (eqn 2-5), utilizing the usual steady state approximation.

$$(9\text{-BBN})_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2\ 9\text{-BBN}$$

$$9\text{-BBN} + 2\text{-heptanone} \xrightarrow{k_2} \text{product} \qquad \text{(eqn 2-4)}$$

$$-\frac{d[(9\text{-BBN})_2]}{dt} = k_1[(9\text{-BBN})_2]\left(\frac{{}^1/_2\, k_2[2\text{-heptanone}]}{k_{-1}[9\text{-BBN}]^2 + {}^1/_2\, k_2[2\text{-heptanone}]}\right)$$

(eqn 2-5)

If $^1/_2k_2$[2-heptanone] >> k_{-1}[9-BBN], equation 2-5 reduces to equation 2-6. Thus the reaction would behave like a unimolecular reaction and exhibit first-order kinetics. However, if $^1/_2k_2$[2-heptanone] << k_{-1}[9-BBN], equation 2-5 reduces to equation 2-7. Thus the reaction would exhibit three-halves-order

$$-\frac{d[(9\text{-BBN})_2]}{dt} = k_1[(9\text{-BBN})_2] \qquad \text{(eqn 2-6)}$$

$$-\frac{d[(9\text{-BBN})_2]}{dt} = {}^1/_2\,(k_1/k_{-1})^{1/2}k_2[(9\text{-BBN})_2]^{1/2}[2\text{-heptanone}] \qquad \text{(eqn 2-7)}$$

kinetics. If $^1/_2k_2$[2-heptanone] $\approx$ k_{-1}[9-BBN], the kinetics would fail to follow the simplified rate expressions, equation 2-6 and equation 2-7.

The kinetic data indicate that the reaction of 2-heptanone with 9-BBN follows the first-order kinetics. This suggests that 2-heptanone reacts with the 9-BBN monomer very rapidly and the dissociation of 9-BBN dimer is the rate-determined step. This was observed directly by ^{11}B spectroscopy. A solution of 9-BBN in THF reveals two resonances in ^{11}B spectrum, one (δ 32 ppm) is due to 9- BBN dimer and another (δ 17 ppm) is due to the 9-BBN monomer (Figure 2-7)[165]. The integrated ratio of these peaks is 2.8 to 1, which suggests that 9-BBN exists predominantly as the dimer in THF. After 2-heptanone was added, the monomer peak (δ 17 ppm) disappeared and the product peak (δ 60 ppm) appeared (Figure 2-8). This observation indicate that the reaction of the 9-BNN monomer with 2-heptanone is very fast. The rate of the reaction is determined only by the dissociation of the 9-BBN dimer.

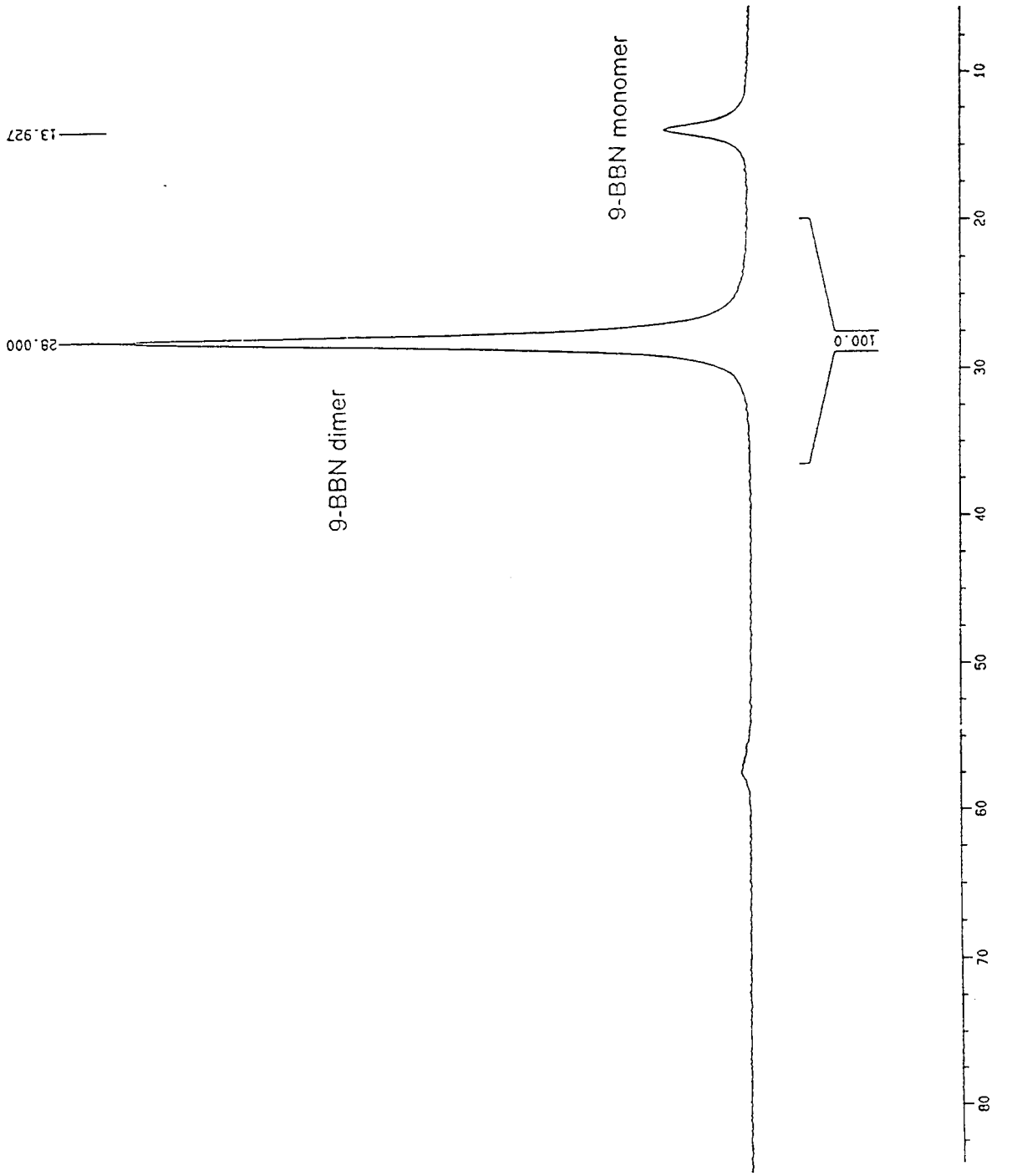


Figure 7. The solution of 9-BBN in THF

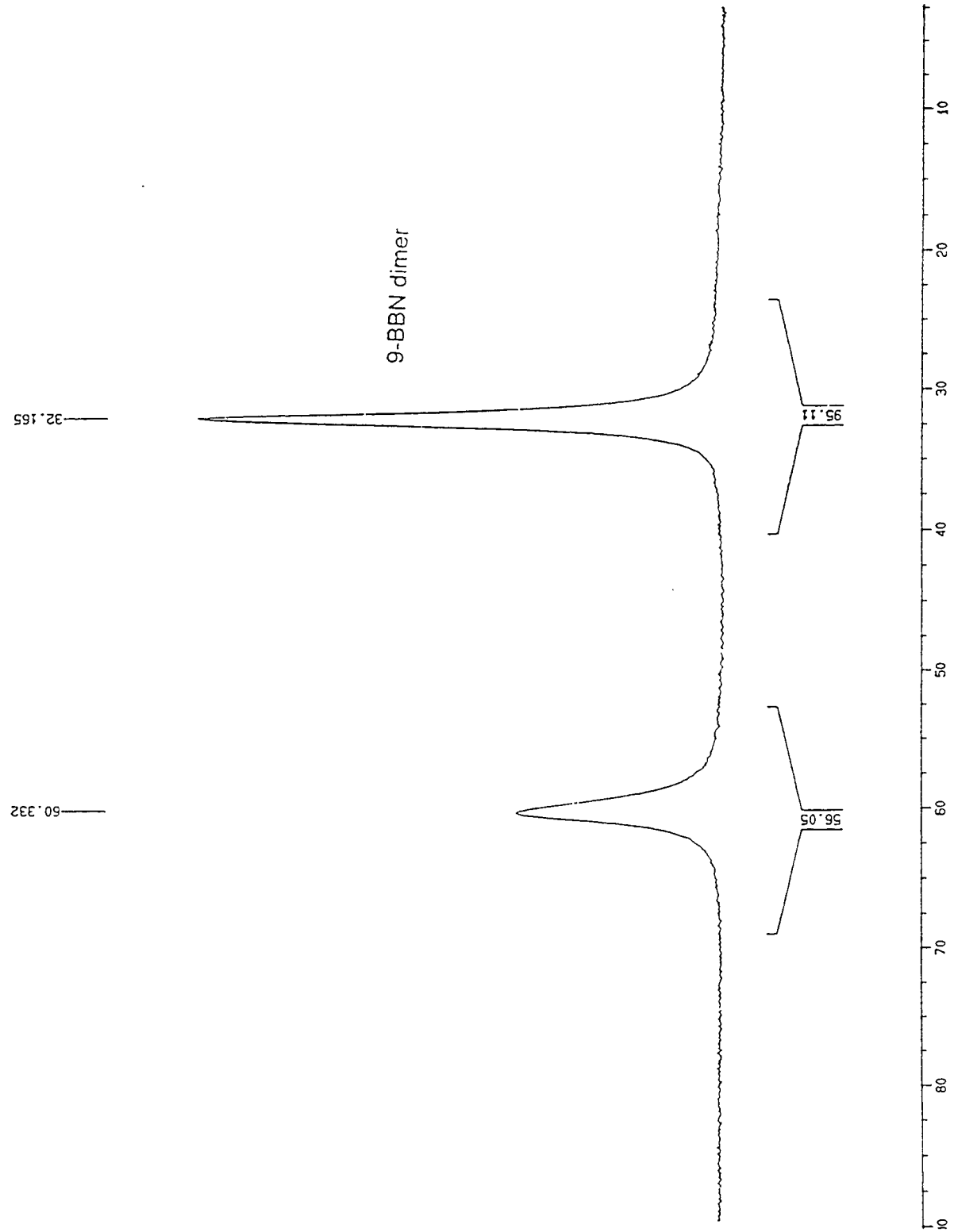


Figure 8. The reaction mixture of 9-BBN with 2-heptanone in THF

2.2.2 The Kinetics of the Hydroboration of Alkenes with 9-BBN

Terminal alkenes are very reactive toward to borane reagents. 1-Octene was chosen as a model terminal alkene for the kinetic study. The kinetics of the reaction of 1-octene with 9-BBN was studied by monitoring a solution of 1-octene (0.5 M in THF) and 9-BBN (0.5 M in THF) in a 5 mm quartz NMR tube.

The rate data were calculate respectively using the three rate equations, $\ln C_0/C$ (first-order), $1/C-1/C_0$ (second-order) and $2^{1/2}[C^{-1/2}-C_0^{-1/2}]$ (three-halves-order). Figure 2-9 contains the rate plot for the reaction of 1-octene with 9-BBN in THF at 273 K. The rate data most closely match the first-order rate equation (Figure 2-10), but not second-order and three-halves-order equations (correlation constants are summarized in the experimental section). This indicates that the reaction of 1-octene with 9-BBN in THF at 273 K follows first-order kinetics. Changing the initial concentration of each of the reactants did not alter the first-order rate constant (Table 2-2, Figure 2-11 and Figure 2-12).

Table 2-2. Rate constants for the hydroboration of 1-octene with 9-BBN in THF.

Entry	Temp.	Initial Concn, M		Rate Constant (k_1)
		$(9\text{-BBN})_2$	2-heptanone	$\times 10^{-4}$ s^{-1}
1	273 K	0.25	0.25	1.41
2	273 K	0.33	0.17	1.48
3	300 K	0.33	0.17	15.0

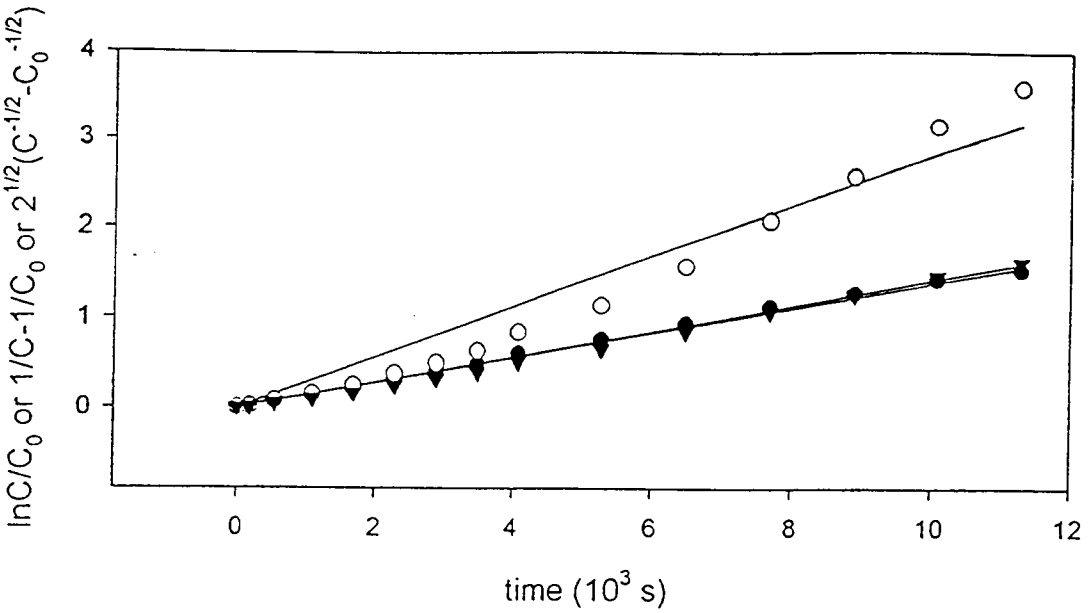
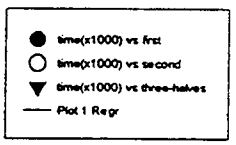


Figure 2-9. The hydroboration of 1-octene with 9-BBN at 273 K



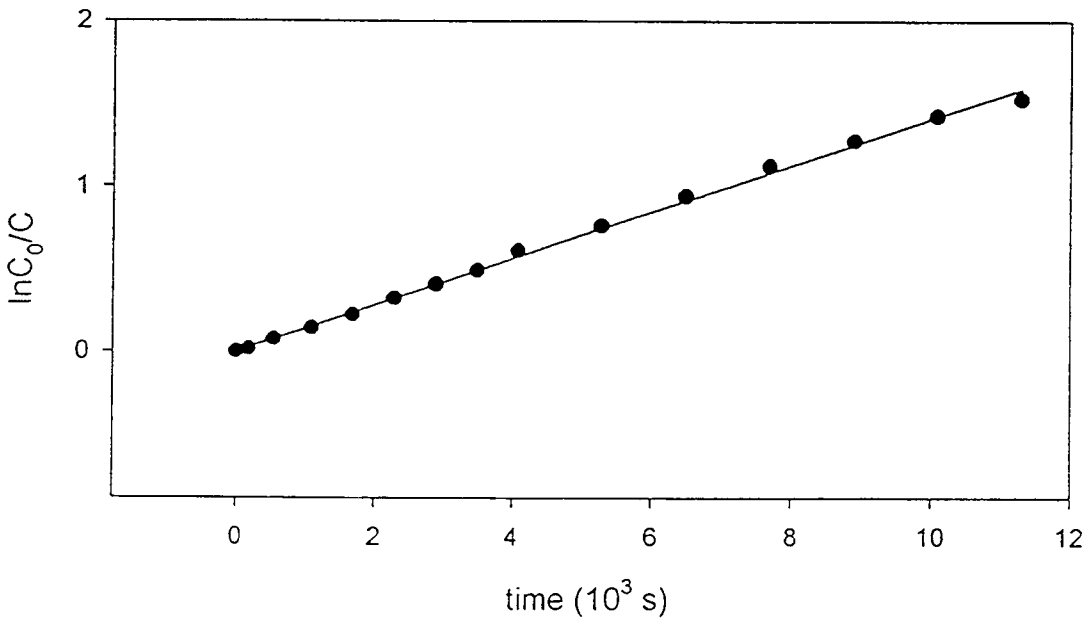


Figure 2-10. The hydroboration of 1-octene with 9-BBN at 273 K

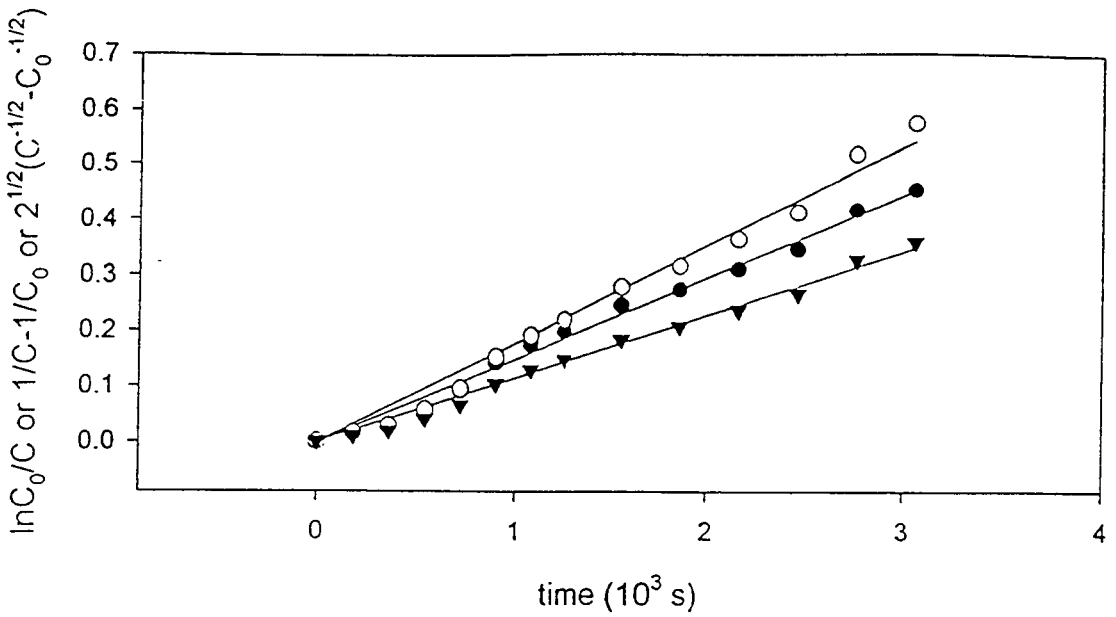


Figure 2-11. The hydroboration of 1-octene with 9-BBN at 273 K

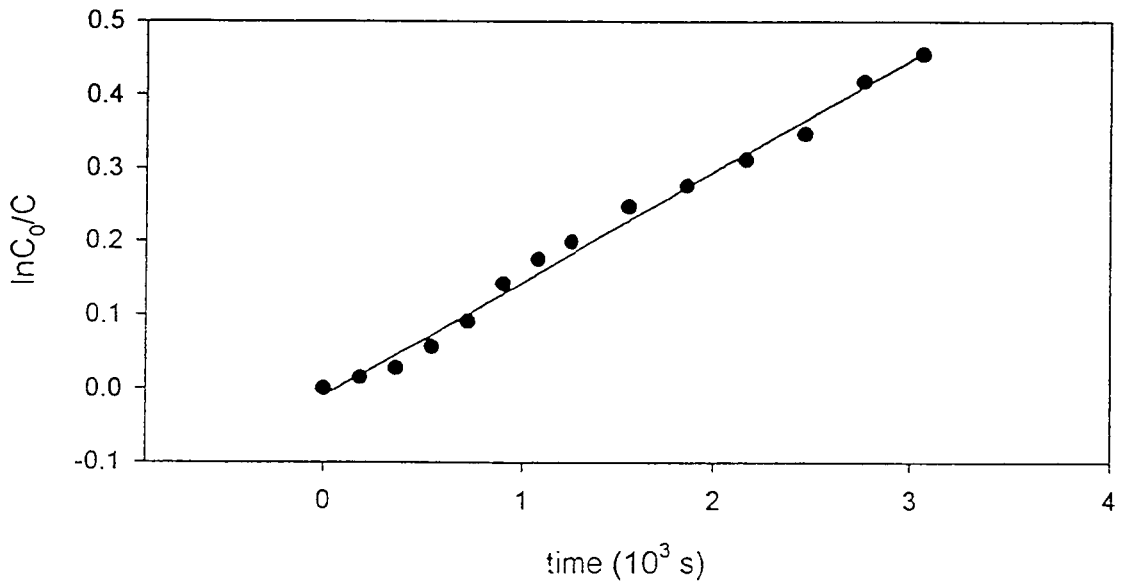


Figure 2-12. The hydroboration of 1-octene with 9-BBN at 273 K

The mechanism of the reaction was defined clearly by the kinetics. The reaction of 1-octene with $(9\text{-BBN})_2$ occurs by a dissociation of the 9-BBN dimer to the monomer, this is followed by the reaction of the monomer with 1-octene (eqn 2-8). As in the reaction of 1-octene 9-BBN, this mechanism leads

$$(9\text{-BBN})_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2\ 9\text{-BBN}$$

$$9\text{-BBN} + 1\text{-octene} \xrightarrow{k_2} \text{product} \qquad \text{(eqn 2-8)}$$

to the following kinetic expression (eqn 2-9), utilizing the usual steady state approximation.

$$-\frac{d[(9\text{-BBN})_2]}{dt} = k_1[(9\text{-BBN})_2]\left(\frac{{}^1/_2\, k_2[1\text{-octene}]}{k_{-1}[9\text{-BBN}]^2 + {}^1/_2\, k_2[1\text{-octene}]}\right)$$

(eqn 2-9)

If ${}^1/_2 k_2[1\text{-octene}] >> k_{-1}[9\text{-BBN}]$, the reaction would behave like a unimolecular reaction and exhibit first-order kinetics. However, if ${}^1/_2 k_2[1\text{-octene}] << k_{-1}[9\text{-BBN}]$, the reaction would exhibit three-halves-order kinetics. If ${}^1/_2 k_2[1\text{-octene}] \approx k_{-1}[9\text{-BBN}]$, the kinetics would fail to follow the simplified rate expressions and would be complicated.

The kinetic data obtained by NMR spectroscopy indicate that the reaction of 1-octene with 9-BBN follows first-order kinetics. This suggests that 1-octene reacts with the 9-BBN monomer very rapidly ($^1/_2k_2$[1-octene] >> k_{-1}[9-BBN]) and the dissociation of 9-BBN dimer is the rate-determined step. This was observed directly using the ^{11}B spectroscopy. The solution of 9-BBN in THF shows two peaks in ^{11}B spectrum, one (δ 32 ppm) is 9-BBN dimer and another (δ 17 ppm) is the 9-BBN monomer[165]. This suggests that the monomer in the solution of 9-BBN in THF exist in equilibrium with 9-BBN dimer. After 1-octene is added, the monomer peak (δ 17 ppm) disappears and the product peak (δ 68 ppm) appears (Figure 2-13). These data indicate that the reaction of the monomer with 1-octene is very fast and the rate of the reaction is determined only by the dissociation of the 9-BBN dimer.

More importantly, the calculated rate constants of the hydroboration of 1-octene with 9-BBN in THF at 0 °C is in excellent agreement with those observed for the reduction of 2-heptanone with 9-BBN in THF at 0 °C. For example, the average of first-order rate constant for the hydroboration of 1-octene with 9-BBN in THF at 0 °C is 1.45×10^{-4} s^{-1}, which is consistent with average of the first-order rate constant for the reduction of 2-heptanone, 1.43×10^{-4} s^{-1}. This strongly supports the dissociation mechanism for these reactions with 9-BBN. Since the dissociation of $(9\text{-BBN})_2$ is rate limiting, the rate constants for the hydroboration of reactive alkenes and the reduction of reactive ketones are the same.

The kinetic study of the reaction of 1-octene with 9-BBN in THF at 300 K

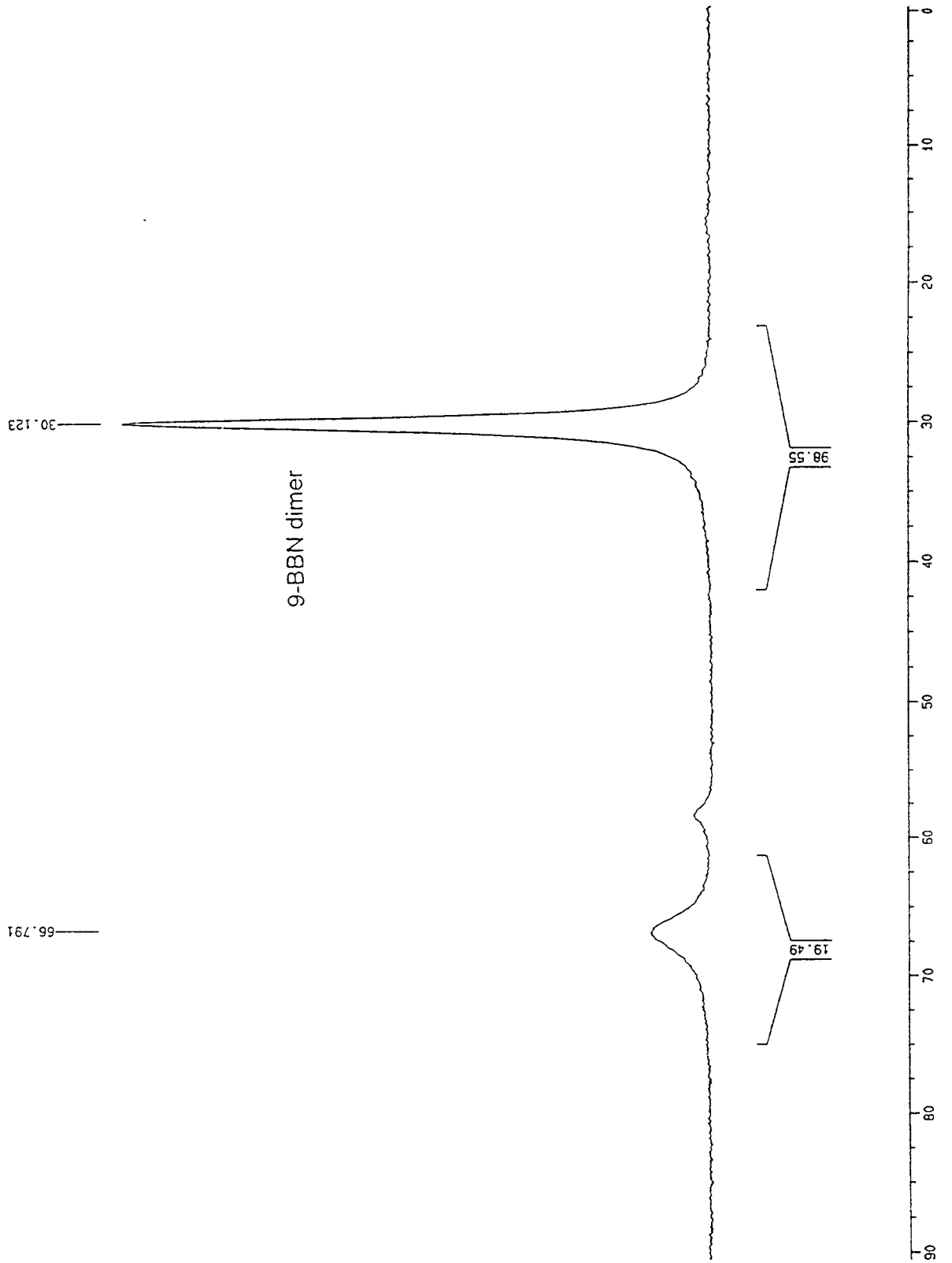


Figure 13. The reaction mixture of 9-BBN with 1-Octene in THF

was also carried out. However, the reaction was extremely fast and was completed in 7 to 8 minutes. Only four data points were collected during this peroid. The rate plot of the reaction is shown in Figure 2-14. Although four points do not provide sufficient data for an accurate kinetics study, they provide an approximate rate constant of the reaction. As can be seen in figure 2-14, the rate data most closely fit a first-order rate equation. Thus the reaction of 1-octene with 9-BBN in THF at 300 K also follows first-order kinetics. The rate constant for this reaction is 15.0×10^{-4} s^{-1}, which is in a good agreement with the results obtained by Brown. The first-order rate constants obtained by Brown for the reduction of acetone[164k] and hydroboration of 1-hexene[164c] with 9-BBN in THF at 25 °C were 13.7×10^{-4} s^{-1} and 14.2×10^{-4} s^{-1}, respectively.

2.3 Conclusion

A convenient method for monitoring reactions with 9-BBN using ^{11}B NMR spectroscopy has been developed. Its application to the study of the hydroboration of alkenes with 9-BBN and the reduction of ketones with 9-BBN confirmed the earlier proposed dissociation mechanism. The hydroboration of a terminal alkene with 9-BBN in THF at 0 °C exhibits first-order kinetics; the reduction of a reactive ketone with 9-BBN also follows first-order kinetics. Although the reactions possess the same first-order rate constant, they do not have the same reactivity toward the 9-BBN monomer. The difference in the reactivity of a terminal alkene and a reactive ketone toward to borane reagents will be discussed in the next chapter.

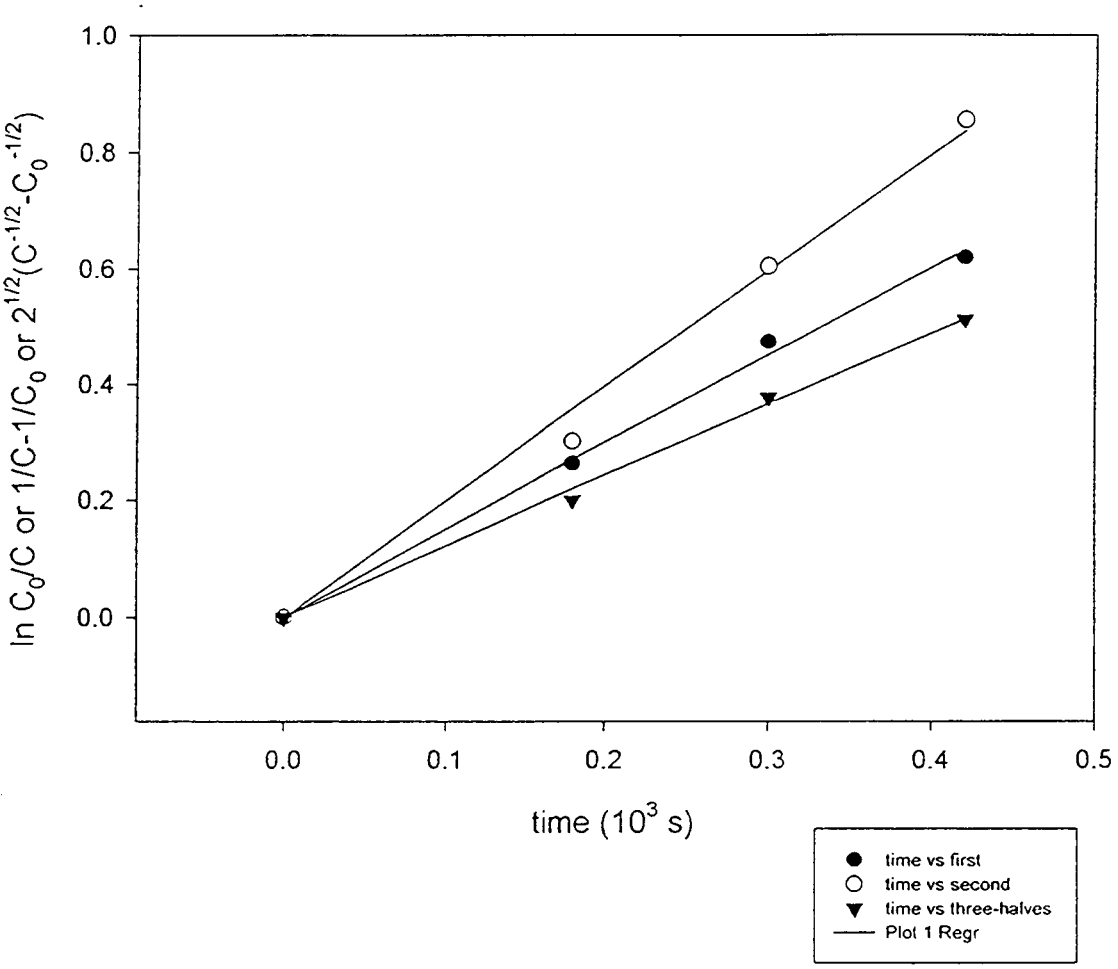


Figure 2-14. The hydroboration of 1-octene with 9-BBN at 300 K

2.4 Experimental

All glassware, syringes and needles were dried in an oven heated to 250 °C for at least 12 hours and cooled under argon prior to use. All solvents were dried and distilled prior to use. 2-Heptanone and 1-octene, obtained from Aldrich Chemical Company, were purified by distillation prior to use. 9-BBN dimer was prepared as described in the literature[37] and was purified by recrystallization from monoglyme. Quartz NMR tubes (5 mm) were used to avoid the boron interference present in pyrex NMR tubes. ^{11}B Spectra were recorded on a 400 MHz Bruker AMX-400 spectrometer.

General kinetics procedure. The reaction of 2-heptanone with 9-BBN in THF at 273 K. A solution of 9-BBN in THF (0.20 mmol, 0.40 mL of 0.50 M in THF), which was prepared by adding 9-BBN (2.5 mmol, 0.30 g) to THF (5 mL), was placed into a 5 mm quartz argon-flushed NMR tube which is sealed with a septa. The solution was cooled to 273 K and then a pre-cooled solution of 2-heptanone in THF (0.20 mmol, 0.40 mL of 0.50 M) was added to the NMR tube. The NMR tube was placed in spectrometer, which was maintained at 273 K in advanced. The reaction was followed by acquiring ^{11}B spectra at given time intervals. Integration of peaks present in ^{11}B spectra was carried out after the experiment. All data were computed using Sigma-plot. The plots were drawn and rate constants were calculated using Sigma-plot. Correlation coefficients are as following: first-order = 0.997, second-order = 0.986, three-halves-order = 0.993.

The reaction of 2-heptanone with 9-BBN in THF at 276 K was carried out by adding a solution of 2-heptanone in THF (0.13 mmol, 0.25 mL of 0.50 M) to the solution of 9-BBN (0.25 mmol, 0.50 mL of 0.50 M in THF). The kinetic study was carried out as previously described.

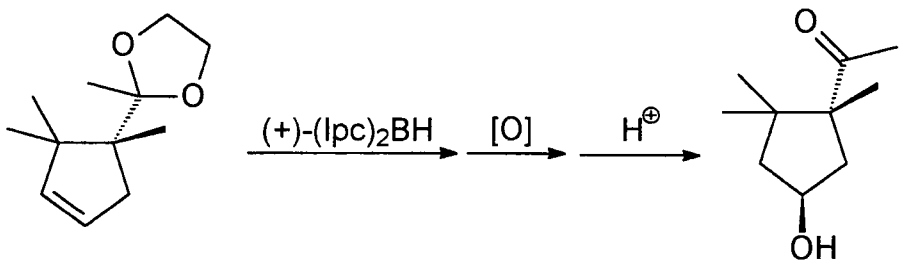
The reaction of 1-octene with 9-BBN in THF at 273 K. A solution of 9-BBN in THF (0.2 mmol, 0.4 mL of 0.5 M in THF), which was prepared by adding 0.3 mg of 9-BBN to 5 mL THF, was placed into a 5 mm quartz argon-flushed NMR tube which is sealed with a spectrum. The solution was cooled to 273 K and then a pre-cooled solution of 1-octene in THF (0.2 mmol, 0.4 mL of 0.5 M) was added to the NMR tube. The NMR tube was placed into the spectrometer, which was maintained at 273 K in advanced. The reaction was followed by acquiring ^{11}B spectra at given intervals of time. Integration of ^{11}B resonances was carried out after the experiment. All data were computed using Sigma-plot. The plots were drawn and rate constants were calculated using Sigma-plot.

Reactions of 1-octene with 9-BBN in THF at 273 K with a different initial concentrations of reactants were carried out by adding the solution of 1-octene in THF (0.13 mmol, 0.25 mL of 0.50 M) to a solution of 9-BBN (0.25 mmol, 0.50 mL of 0.50 M in THF). The kinetic study was carried out as described previously. Correlation coefficients are as following: first-order = 0.998, second-order = 0.974, three-halves-order = 0.995. The reaction at 300 K was carried out by equilibrating the spectrometer at 300 K.

Chapter 3. The Selective Hydroboration of Alkenes in the Presence of Ketones and Aldehydes

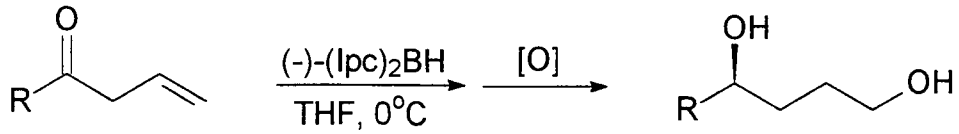
3.1 Introdution

Boron hydride reagents have been utilized extensively in organic synthesis[15,20]. They have proven to be valuable for the selective reduction of carbonyl compounds as well as for the stereoselective hydroboration of alkenes and alkynes[15,20]. Because of the effectiveness of borane reagents in reducing aldehydes and ketones, hydroboration reactions involving substrates containing these functional groups are often carried out by either converting the carbonyl group to a less reactive functionality (eqn 2-1)[162,166] or by modifying the



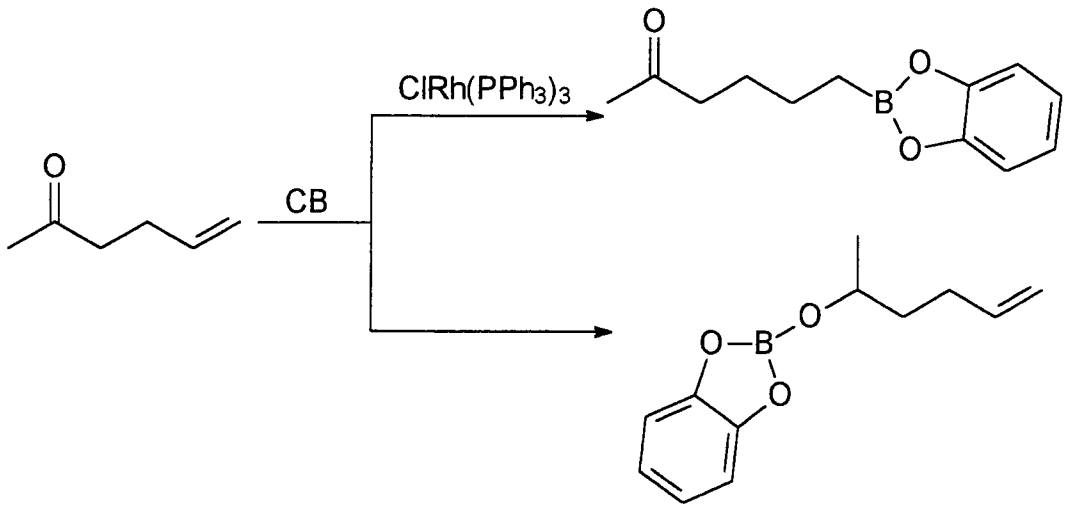
(eqn 2-1)

hydroborating agent[167]. Otherwise, reduction of the carbonyl moiety might compete with the desired hydroboration reaction. For example, α,β-unsaturated aldehydes and ketones are reduced rapidly and quantitatively to the corresponding allylic alcohols by 9-BBN (eqn 1-44)[118]. Similarly, the hydroboration of allyl ketones with diisopinocampheyborane produces enantiomerically enriched 1,4-diols via an intramolecular reduction (eqn 2-2)[168].



(eqn 2-2)

Diols are also the final products (after oxidation) when olefinic ketones are reduced by either borane[169a] or thexylborane[169b]. These latter reports and related examples, such as one involving a hydroboration with catecholborane in the presence of Wilkinson's catalyst (eqn 2-3)[170], indicate that it might be possible to selectively hydroborate alkenes in the presence of aldehydes and



(eqn 2-3)

ketones.

Based on the kinetic results obtained in Chapter 2, a study was conducted which was focused on the selective hydroboration of alkenes in the presence of ketones and aldehydes. This chapter details the results of the study. Solvents,

temperatures, reaction times and addition order of the reactants were investigated. Optimum conditions were developed to obtain a selective hydroboration of an alkene in the presence of both ketones and aldehydes. A number of alkenyl ketones and aldehydes were sucessfully hydroborated and hydroxy ketones and aldehydes were obtained in high yield after oxidation of the intermediate organoboranes.

3.2 Competitive Study of Reactions between Ketones, Aldehydes and Alkenes

Brown and his coworkers carried out extensive research on the reactions of alkenes and carbonyl compounds with a variety of boron hydrides[164]. Their kinetic data indicate that both the hydroboration of terminal alkenes as well as the reduction of most aldehydes and some ketones by 9-BBN follow first-order kinetics[164c,164d]. Although they exhibit first-order rate constants when reduced by borane reagents, aldehydes, ketones, and alkenes have different overall reductiion rates. For example, aldehydes are more reactive toward 9-BBN than alkenes but 9-BBN reacts faster with certain alkenes than with ketones[170]. Brown's results were supported by the experiments described in Chapter 2. We felt that the reactivity differences might be amplified such that a selective hydroboration of alkenes could be achieved in the presence of ketones and aldehydes.

In order to evaluate the reactivity differences between ketones, aldehydes and alkenes, competitive reactions were conducted. Accordingly, a mixture of

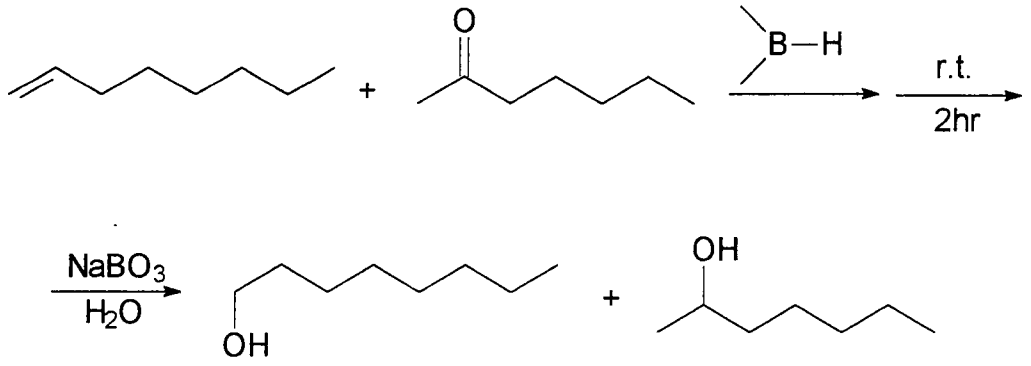
one equivalent of a ketone or an aldehyde and one equivalent of an alkene was allowed to react with one equivalent of a boron hydride. After appropriate time intervals, the mixture was oxidized using sodium perborate[24]. The reaction products were then extracted into ether, and analyzed by GC using an internal standard. The correction factors related to the GC responses were measured and used to determine the GC yield of the products.

3.2.1 Investigation of the Reaction of 1-Octene and 2-Heptanone with Borane Reagents

3.2.1.1 Choice of Borane Reagents

1-Octene and 2-heptanone were chosen as model compounds to react with a variety of borane reagents. A mixture of one equivalent of 1-octene and one equivalent of 2-heptanone was added to a solution of one equivalent of a boron hydride at room temperature. After stirring for two hours, the mixture was oxidized to obtain the corresponding alcohol. The reaction products were extracted into ether and decane was added as an internal standard. The yields of products were determined by GC analysis.

There were two possible major products in this reaction: 1-octanol which arose via the hydroboration of 1-octene, and 2-heptanol which was the product of reduction of 2-heptanone (eqn 3-4). Their relative yields reflect the reactivity toward the borane reagent. A variety of common borane reagents were tested. The results are presented in Table 3-1.



(eqn 3-4)

Table 3-1. The reaction of 1-octene and 2-heptanone with various borane reagents at room temperature.

Entry	Borane Reagent	Ratio of 1-Octanol to 2-Heptanol[a,b]
1	BH_3•THF	99:1[c]
2	BMS	97:3[c]
3	9-BBN	93:7
4	$(c\text{-}C_6H_{11})_2BH$	100:0
5	Sia_2BH	97:3
6	Catecholborane	0:100[d]
7	BH_3•$N(C_2H_5)_3$	--[e]

[a] Ratios obtained by GC analysis

[b] Overall combined yields ranged from 90 to 100%

[c] 2-Octanol was also formed in small quantities.

[d] Only 10% of 2-heptanol detected after 2hrs reaction.

[e] No reaction occurred.

Analysis of the data in Table 3-1 indicates that the reactivities of a terminal alkene and an acyclic aliphatic ketone toward boron hydrides are quite different. 1-Octanol, the product of hydroboration of 1-octene, was obtained as a major product along with less than 5% percent of 2-heptanol in most cases except when catecholborane was used. These data suggest that a terminal alkene is much more reactive toward most borane reagents than an acyclic aliphatic ketone.

Although most hydroborate 1-octene in preference to reducing 2-heptanone, the boron hydrides do differ in their reactivities. 9-BBN is less chemoselectivity than most of the boron hydrides, while dicyclohexylborane is very chemoselective and none of the ketones is reduced. BH3•THF and $BH3•SMe_2$ also exhibit good chemoselectivity in the reactions. Disiamylborane, however, is less selective than dicyclohexylborane.

As noted earlier, 9-BBN is the least sterically hindered dialkylborane[169]. The bicyclic system results in the boron atom being more open than it is in other borane reagents. Because of the openness of the boron atom in 9-BBN, hydroboration of alkenes and reduction of ketones with 9-BBN is less susceptible to steric effects than other dialkylboranes[38,170]. This might be the reason that 9-BBN attacks the oxygen of carbonyl more easily than other borane reagents. In contrast to 9-BBN, dicyclohexylborane, whose dimer precipitates out of THF, is very sterically hindered. Disiamylborane, which is similar to dicyclohexylborane, is reported to be more sensitive to steric effects than 9-BBN[38].

Dicyclohexylborane is considered more hindered than disiamylborane and it should show more sensitivity toward steric effects. This appears to be the case.

As noted in Table 3-1, the competition reaction of catecholborane gave only the reduction product, 2-heptanol. It is known that catecholborane is a sluggish hydroborating reagent because the oxygens donate electrons to boron atom which diminishes the Lewis acidity of boron. When catecholborane was allowed to react with a mixture of 1-octene and 2-heptanone at room temperature for two hours, no hydroboration product formed and only 10% of 2-heptanol was obtained. Although the reduction of ketones with catecholborane is slow, the results suggest that acyclic aliphatic ketones are more reactive toward catecholborane than terminal alkenes. A longer reaction time would simply result in more complete reduction of the ketone.

As expected, the borane-triethylamine complex did not react with ether of 1-octene or 2-heptanone. The borane-triethylamine complex is a very stable complex.

Overall, a terminal alkene can be successfully hydroborated in the presence of a ketone utilizing essentially all of the common hydroborating reagents except catecholborane. 9-BBN is less chemoselective than the more hindered hydroborating reagents; dicyclohexylborane is quite effective at hydroborating a terminal alkene in the presence of a ketone.

3.2.1.2 Temperature Effect

Reactions of 1-octene and 2-heptanone with a variety of boranes were carried out at various temperatures for two hours. After oxidation with sodium perborate, the reaction products were extracted into ether. The ether solution was analyzed by GC. The results are presented in Table 3-2.

As can be noted form the data in Table 3-2, temperature had little effect on the chemoselectivity of the borane reagents in most cases. BH_3•THF exhibited similar selectivities toward 1-octene and 2-heptaone at 0 °C, 25 °C, 68 °C. BH_3•SMe_2, dicyclohexylborane and disiamylborane also showed little change in selectivity between 0 °C and 25 °C. Temperature did affect the selectivity of 9-BBN. At 0 °C, 9-BBN gave a 69:31 ratio of 1-octanol and 2-heptanol. But this appeared to be due to an unexpected side reaction. 9-BBN reacts with both 1-octene and 2-heptanone very slowly at 0 °C. After two hours, when the sodium perborate and water were added, 2-heptanone was rapidly reduced by the organoborate complex which was formed *in situ* by the reaction of 9-BBN with $NaBO_3$. The phenomenon was also observed in the reaction of 1-octene and 2-heptanone with BH_3•THF at -78 °C. Only reduction products were detected in these cases.

As can be seen from the data in Table 2, the total yields were not significantly affected by temperature except when 9-BBN was used. The hydroboration and the reduction were both generally very rapid at 0 °C and 25 °C. However, the reactions with 9-BBN were slow at 0 °C and thus these

Table 3-2. The reaction of 1-octene and 2-heptanone with a variety of borane reagents at different temperature.

Entry	Reaction temperature	Borane reagents	Ratio of 1-Octanol 2-heptanol[a]	Yield[b]
1	0 °C	BH_3•THF	97:3[c]	98%[d]
2	25 °C	BH_3•THF	99:1[c]	100%[d]
3	68 °C	BH_3•THF	98:2[c]	100%[d]
4	0 °C	9-BBN	69:31	61%
5	25 °C	9-BBN	93:7	90%
6	68 °C	9-BBN	89:11	95%
7	0 °C	$(c\text{-}C_6H_{11})_2BH$	100:0	88%
8	25 °C	$(c\text{-}C_6H_{11})_2BH$	100:0	93%
9	0 °C	Sia_2BH	96:4	92%
10	25 °C	Sia_2BH	97:3	90%
11	0 °C	BMS	96:4[c]	100%[d]
12	25 °C	BMS	97:3[c]	100%[d]
13	0 °C	catecholborane	0:100	9%
14	25 °C	catecholborane	0:100	10%
15	0 °C	BH_3•$N(C_2H_5)_3$	--	--
16	25 °C	BH_3•$N(C_2H_5)_3$	--	--

[a] Ratios obtained by GC analysis.

[b] total yields of 1-octanol and 2-heptanol.

[c] 2-Octanol also formed in small quantities.

[d] overall yields including 1-octanol, 2-octanol, and 2-heptanol.

reactions were carried out at 25 °C. On the other hand, at room temperature, disiamylborane is subject to both isomerization and redistribution reactions, which might decrease the total yield of the reaction. Thus, the reaction with disiamylborane should be carried out at 0 °C to obtain the highest yields. The reaction with dicyclohexylborane is self-indicating because dicycohexylborane is insoluble in THF while the products of the reaction are soluble in THF. The reactions are complete in two hours at 0 °C. At room temperature, the reaction is faster and is completed in an hour. Running the reaction at room temperature is more efficient and was used in the latter reactions.

3.2.1.3 Order of Addition

The order of the addition of borane reagents might affect the reactions with 1-octene and 2-heptanone. It would appear that adding the borane reagents to a mixture of 1-octene and 2-heptanone would be best since the borane reagent would be the limiting reagent.

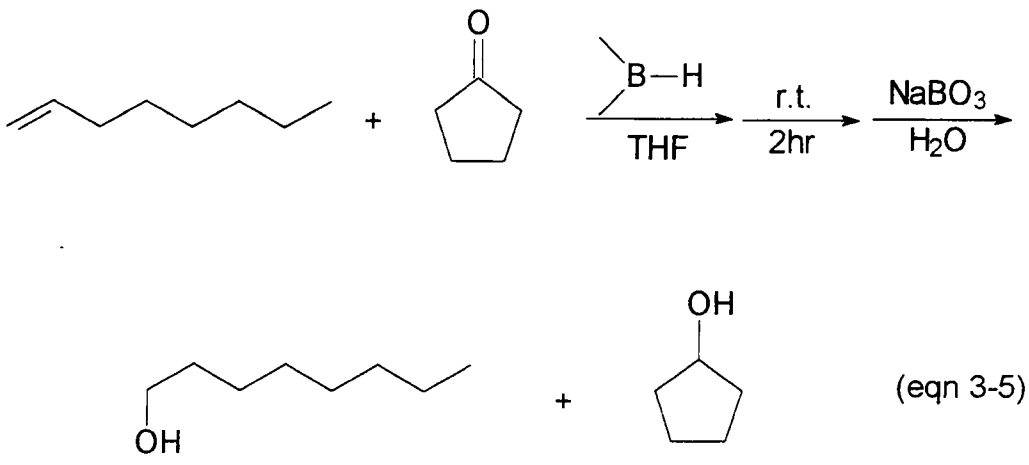
Method A and method B were used to carry out reactions. Method A: One equivalent of borane reagent was added to a mixture of one equivalent of 1-octene and one equivalent of 2-heptanone in THF at room temperature. The reaction mixture was stirred for two hours, then sodium perborate and water were added to the reaction mixture. After extraction into ether, the ether solution was analyzed by GC. Method B: a mixture of one equivalent of 1-octene and one equivalent of 2-heptanone in THF was added to one equivalent of borane reagent at room temperature. The reaction mixture was stirred for two hours,

then sodium perborate and water were added to the reaction mixture. After extraction into ether, the ether solution was analyzed by GC.

The reactions with a variety of borane reagents were carried out by both Method A and Method B. The results showed that the order of addition is not crucial to the selectivity of the reaction with 1-octene and 2-heptanone at 25 °C. However, when dicyclohexylborane is used as hydroborating reagents, method B is more convenient because the slurry of dicyclohexylborane in THF is difficult to transfer. When BH_3•THF, BMS and 9-BBN in THF were used as borane reagents, Method A was used to carry out the reactions because of the convenience of handling.

3.2.2 Investigation of the Reaction of 1-Octene and Cyclopentanone with Borane Reagents

Cyclopentanone is present in a number of important naturally occurring molecules. Selective hydroboration in the presence of cyclopentanone would be synthetically useful. Cyclopentanone was reported to be more reactive toward 9-BBN than a terminal alkene[164d]. More hindered borane reagents such as dicylcohexylborane might be able to hydroborate alkenes in the presence of cyclopentanone. As a probe, we allowed 1-octene and cyclopentanone to react with a limited quantity of the various borane reagents. The mixtures were then oxidized with sodium perborate (eqn 3-5). The ratio of two possible products, 1-octanol from hydroboration of 1-octene and cyclopentanol from reduction of cyclopentanone was determined by GC. The results are presented in Table 3-3.



(eqn 3-5)

Table 3-3. The reaction of 1-octene and cylopentanone with various borane reagents.

Entry	Borane Reagents	Ratio of 1-Octanol to cyclopentanol[a,b]
1	BH_3•THF	94:6[c]
2	BMS	89:11[c]
3	9-BBN	34:66
4	Sia_2BH	92:8
5	$(c\text{-}C_6H_{11})BH$	100:0

[a] Ratios obtained by GC analysis

[b] Overall combined yields ranged from 90 to 100%

[c] 2-Octanol was also formed in small quantities.

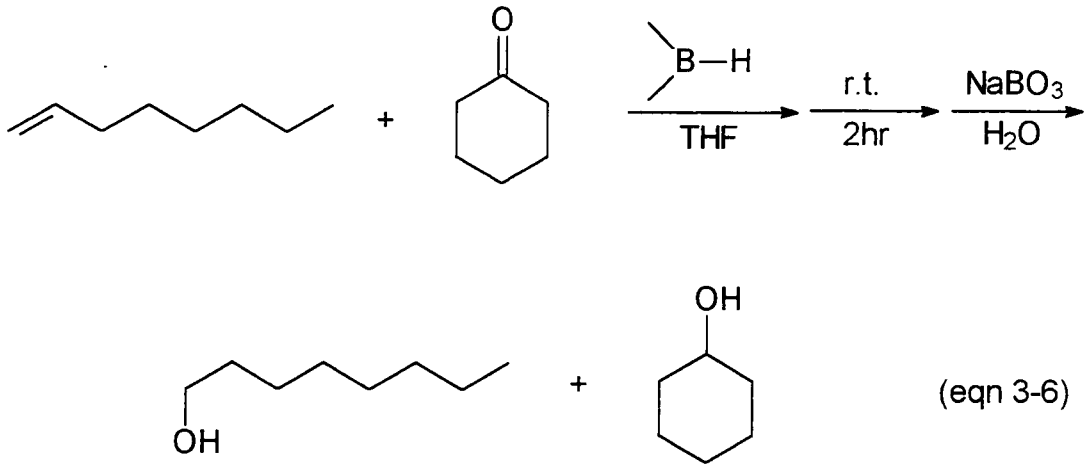
As can be seen from data in Table 3-3, cyclopentanone competes more effectively than 2-heptanone for the borane reagents. Compared to the ratio of

97:3 for the reaction of 1-octene and 2-heptanone with BMS, 1-octene and cyclopentanone gave only 89:11 ratio of 1-octanol to cyclopentanol. 9-BBN reduced cyclopentanone preferentially which is consistent with the result obtained from the previous study[164d]. Disiamylborane also exhibits a lower selectivity. However, hydroboration is still the major reaction except when 9-BBN is used as the hydroborating reagent. Dicyclohexylborane gives only the hydroboration product. Dicyclohexylborane is the most effective at hydroborating a terminal alkene in the presence of a cyclopentanone.

3.2.3 Investigation of the Reaction of 1-Octene and Cyclohexanone with Borane Reagents

Cyclohexanone is also a common moiety in natural products. Cyclohexanone is even more reactive toward 9-BBN than cyclopentanone. The relative rate of the reaction of cyclohexanone with 9-BBN compared to that of cyclopentanone is about 4:1[164d]. It is reported that cyclohexanone is much more reactive than a terminal alkene toward 9-BBN [164d]. These data suggest that cyclohexanone might compete more efficiently for borane reagents than cyclopentanone. 1-Octene was chosen as a model terminal alkene. One equivalent of the borane reagent was allowed to reacted with the mixture of one equivalent of 1-octene and one equivalent of cyclohexanone at room temperature for two hours. The reaction mixture was then oxidized by sodium perborate (eqn 3-6). The ratio of 1-octanol, the hydroboration product, to cyclohexanol, the

reduction product, was determined by GC. The results are presented in Table 3-4.



(eqn 3-6)

Table 3-4. The reaction of 1-octene and cyclohexanone with various borane reagents.

Entry	Borane Reagents	Ratio of 1-Octanol to cyclohexanol[a,b]
1	BH_3•THF	83:17[c]
2	BMS	78:22[c]
3	9-BBN	24:76
4	Sia_2BH	84:16
5	$(c\text{-}C_5H_{11})_2BH$	100:0

[a] Ratios obtained by GC analysis

[b] Overall combined yields ranged from 90 to 100%

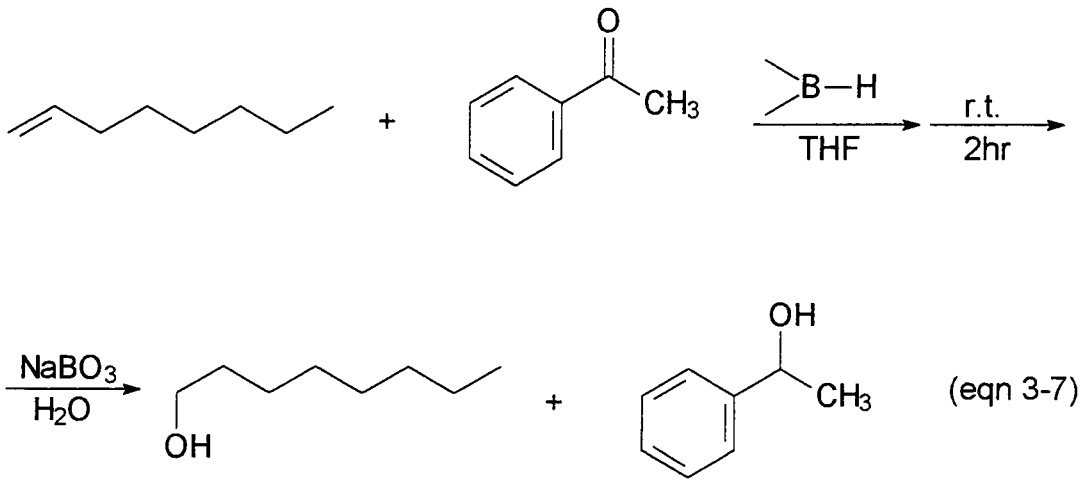
[c] 2-Octanol was also formed in small quantities.

The data in Table 3-4 indicate that cyclohexanone competes more effectively for borane reagents than does cyclopentanone. Cyclohexanone is reduced efficiently by 9-BBN in the presence of 1-octene such that cyclohexanol was the major product. The ratio of the hydroboration product to the reduction product decreased in the reactions involving BH_3•THF, BMS, and disiamylborane. This indicates that cyclohexanone is more reactive toward borane reagents than both acyclic ketones and cyclopentanone. However, except for 9-BBN, the reactions with borane reagents still give the hydroboration product as major product. Dicyclohexylborane hydroborates the terminal alkene without reducing cyclohexanone. This unique property of dicyclohexylborane makes it synthetically useful at selectively hydroborating terminal alkenes in presence of ketones.

3.2.4 Investigation of the Reaction of 1-Octene and Acetophenone with Borane Reagents

Aromatic ketones exhibit reactivity differences when compared to aliphatic ketones. Because of the aromatic ring, the carbonyl group is less polarized than it is in aliphatic ketones. This diminishes the reactivity of the carbonyl group. The reduction of benzophenone with either borane-THF or disiamylborane has been found to be considerably slower than the reduction of alkyl ketones and aldehydes[113,114]. This suggest that the selective hydroboration of a terminal alkene in the presence of an aromatic ketones might be possible using these borane reagents.

Acetophenone was chosen as the representative aromatic ketone and allowed to compete with a terminal alkene, 1-octene, for boron hydrides. One equivalent of 1-octene and one equivalent of acetophenone were allowed to react with one equivalent of the borane reagent at room temperature for two hours. The reaction mixture was then oxidized by sodium perborate (eqn 3-7) and analyzed by GC. The ratios of 1-octanol obtained from the hydrobration to 1-phenylethanol obtained from the reduction of acetophenone are listed in the Table 3-5.



(eqn 3-7)

As summarized in the Table 3-5, 1-octene can be selectively hydroborated in the presence of acetophenone utilizing essentially all of the common hydroborating agents. Once again, 9-BBN exhibited the least chemoselectivity among the borane reagents. The ratio of the reaction products using 9-BBN was only 76:24. As discussed earlier, aromatic ketones are less reactive toward

Table 3-5. The reaction of 1-octene and acetophenone with various borane reagents.

Entry	Borane Reagents	Ratio of 1-Octanol to 1-Phenylethanol[a,b]
1	BH_3•THF	100:0[c]
2	BMS	94:6[c]
3	9-BBN	76:24
4	Sia_2BH	100:0
5	$(c\text{-}C_6H_{11})_2BH$	100:0

[a] Ratios obtained by GC analysis

[b] Overall combined yields ranged from 90 to 100%

[c] 2-Octanol was also formed in small quantities.

borane reagents due to the electronic effects. The result is that even BH_3•THF and disiamylborane selectively hydroborated the terminal alkene without reducing the aromatic ketone. Not surprisingly, the reaction with dicyclohexylborane gave 100 percent of the hydroboration product.

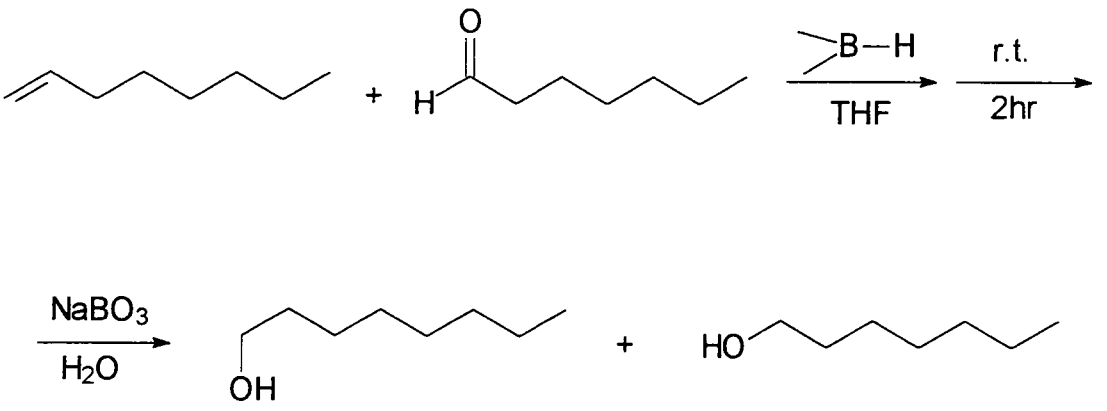
3.2.5 Investigation of the Reaction of 1-Octene and Heptanal with Borane Reagents

3.2.5.1 Choice of Borane Reagents

Aliphatic aldehydes are readily reduced by borane reagents. They are more reactive toward borane reagents than ketones. Aliphatic aldehydes are

reduced by 9-BBN 80 times faster than aliphatic ketones[164d]. Therefore, aldehydes might compete more effectively for borane reagents.

Heptanal, a model aldehyde, and 1-octene were reacted with a limited quantity of a variety of borane reagents. One equivalent of heptanal and one equivalent of 1-octene were reacted with one equivalent of the borane reagent in THF. After stirring at room temperature for two hours, the reaction mixture



(eqn 3-8)

was oxidized by sodium perborate (eqn 3-8). The hydroboration of 1-octene afforded 1-octanol, while the reduction of heptanal afforded 1-heptanol. The ratio of these two products in the reaction mixture was determined by GC. The results are presented in Table 3-6.

The data in Table 3-6 reveal that heptanal competed with 1-octene much more effectively than ketones. In the reactions of BH_3•THF, BMS and thexylborane, about a fifty-percent yield of 1-heptanol was obtained. Thus

heptanal has almost the same reactivity toward BH_3•THF, BMS and thexylborane as 1-octene. Heptanal was predominantly reduced by 9-BBN, which suggests that an aliphatic aldehyde is much more reactive toward 9-BBN than a terminal alkene. Similarly, reactions involving monochloroborane and monobromoborane

Table 3-6. The reaction of 1-octene and heptanal with various borane reagents.

Entry	Borane Reagents	Ratio of 1-Octanol to 1-Heptanol[a,b]
1	BH_3•THF	45:55[c]
2	BMS	53:47[c]
3	Thexylborane	50:50
4	BH_2Cl•Me_2S	15:85
5	BH_2Br•Me_2S	30:70
6	Catecholborane	0:100
7	(+)-diisopinocampheyborane	43:57
8	9-BBN	16:84
9	Sia_2BH	71:29
10	$(c\text{-}C_6H_{11})_2BH$	82:18

[a] Ratios obtained by GC analysis

[b] Overall combined yields ranged from 90 to 100%

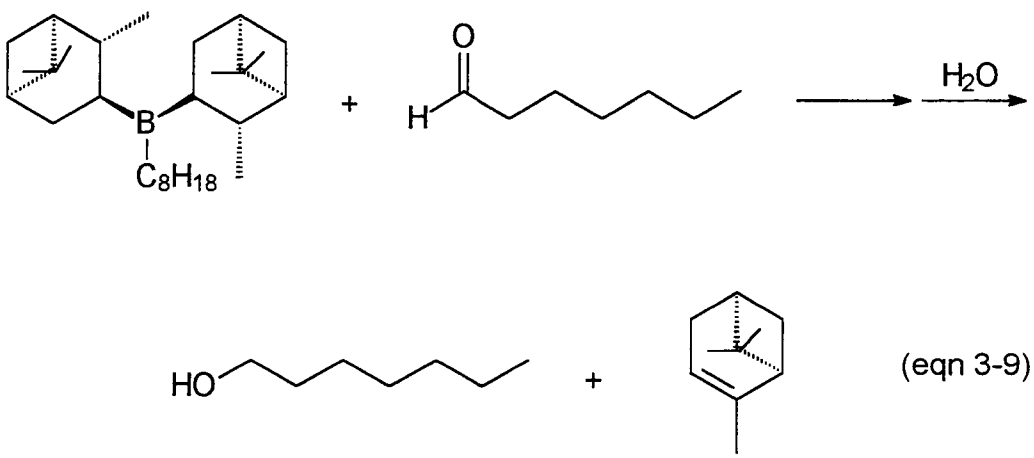
[c] 2-Octanol was also formed in small quantities.

[d] Reaction were carried out at 0°C for 3hrs.

[e] Total yield of reaction is 143%.

gave 1-heptanol as the major product. Monohaloborane are the effective reducing agents for aldehydes. However, reactions with hindered borane reagents, disiamylborane and dicylohexylborane, gave the hydroboration product, 1-octene, as the major product. Dicyclohexylborane exhibits the highest selectivity for hydroborating a terminal alkene in the presence of an aliphatic aldehyde.

The reaction of diisopinocampheylborane gave a 43:57 ratio of 1-octanol to 1-heptanal in greater than 100% yield. Presumably, some of the 1-heptanol arose from reduction of heptanal by diisopinocampheylborane. The rest of 1-heptanol was generated by reduction of the heptanal by octyldiisopinocamphey-borane[164], the product of the hydroboration of 1-octene with diisopropyl-campheylborane (eqn 3-9).



(eqn 3-9)

3.2.5.2 Choice of Solvents

The results presented in the previous section indicate that the highest selectivity which can be obtained between a terminal alkene and an aliphatic

aldehyde is 82:18, which was obtained by the reaction with dicylohexylborane. In order to improve the selectivity of the hydroboration with dicylohexylborane, solvent effects were evaluated by carrying out the reaction in different solvents.

One equivalent of 1-octene and one equivalent of heptanal were reacted with one equivalent of dicyclohexylborane in a variety of solvents. After stirring at room temperature for 2 hours, the reaction mixture was oxidized by sodium perborate. Then the mixture was analyzed by GC. The results are shown in Table 3-7.

Table 3-7. Solvent study on the reaction of 1-octene and heptanal with dicyclohexylborane.

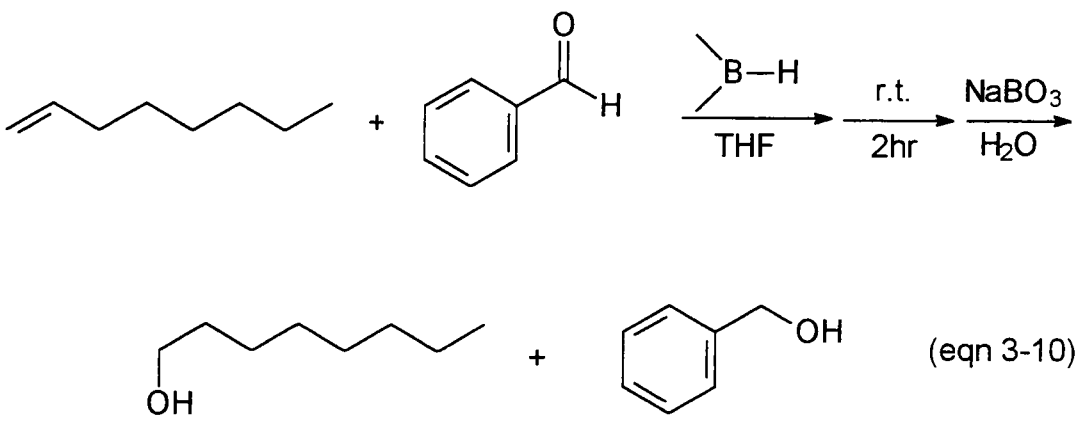
Entry	Solvents	Ratio of 1-octanol and 1-heptanol
1	THF	82:18
2	CH_2Cl_2	88:12
3	Et_2O	79:21
4	pentane	83:17

As shown in Table 3-7, solvents have a limited effect on the selectivity of dicyclohexylborane. Ether solvents, which are normally the best solvents for hydroboration, have lower selectivity. Perhaps a redistribution reaction occurs in these solvents. Non-etherate solvents gave a higher selectivity. Methylene

chloride is the best solvent among those tested at selectively hydroborating alkenes in the presence of aldehydes.

3.2.6 Investigation of the Reaction of 1-Octene and Benzaldehyde with Borane Reagents

Due to the electronic effects of the benzene ring, benzaldehyde is less reactive than aliphatic aldehydes. Thus, it might complete less effectively with a terminal alkene than aliphatic aldehydes. One equivalent of 1-octene and one equivalent of benzaldehyde were allowed to react with one equivalent of a variety of borane reagents (eqn 3-10). After stirring at room temperature for two hours,



(eqn 3-10)

the reaction mixture was oxidized using sodium perborate and the products were then analyzed by GC. The ratios of 1-octanol, the hydroboration product, to benzyl alcohol, the reduction product, are presented in Table 3-8.

As expected, benzaldehyde was less competitive with 1-octene than were the aliphatic aldehydes. The reactions with BH_3•THF, BMS, and 9-BBN afforded

Table 3-8. The reaction of 1-octene and benzaldehyde with various borane reagents.

Entry	Borane Reagents	Ratio of 1-Octanol to benzyl alcohol[a,b]
1	BH_3•THF	57:43[c]
2	BMS in THF	51:49[c]
3	9-BBN in THF	62:38
4	Sia_2BH in THF	75:25
5	$(c\text{-}C_6H_{11})_2BH$ in THF	85:15
6	$(c\text{-}C_6H_{11})_2BH$ in CH_2Cl_2	97:3

[a] Ratios obtained by GC analysis

[b] Overall combined yields ranged from 90 to 100%

[c] 2-Octanol was also formed in small quantities.

a nearly equal mixture of reduction product and hydroboration product, which suggests that benzaldehyde and 1-octene exhibit almost same reactivity toward unhindered borane reagents. The reactions with hindered borane reagents, such as disiamylborane and dicyclohexylborane, gave the hydroboration product as the major product. Dicyclohexylborane in methylene chloride has the highest selectivity for hydroborating a terminal alkene in the presence of an aromatic aldehyde.

3.2.7 Experimental

All glassware, syringes, and needles were dried in an oven heated to 250°C for at least 12 hours and cooled under argon prior to use. All solvents were dried and distilled prior to use. All chemicals obtained from Aldrich Chemical Company were used as received, or were purified by distillation prior to use.

Correction factors for reactants and products were measured prior to reactions. Each reactant and each product were carefully weighed and the weights recorded. An appropriate alkane, which served as an internal standard, was also weighed. These were mixed together in ether, samples were withdrawn and analyzed by GC to obtain the response ratios. The correction factors are calculated by the equation 3-11.

$$CF = (W_{\text{reactant or product}}/\text{Area}_{\text{reactant or product}})/(W_{\text{standard}}/\text{Area}_{\text{standard}}) \quad \text{(eqn 3-11)}$$

3.2.7.1 Reaction of 1-Octene and 2-Heptanone with a Variety of Borane Reagents.

General procedure for the reactions of 1-octene and 2-heptanone. Reaction of 1-octene and 2-heptanone with a limited quantity of BH_3•THF in THF. A mixture of 1-octene (3.0 mmol, 0.33 g, 0.47 mL) and 2-heptanone (3.0 mmol, 0.34 g, 0.42 mL) in THF (3 mL) was placed in a dry, argon-flushed, round-bottomed flask at room temperature. Borane (1.0 mmol, 1.0 mL of a 1.0 M

solution in THF) was added and the mixture was stirred at room temperature for 2 hours. Oxidation was achieved by adding $NaBO_3 \bullet 4H_2O$ (3 mmol, 0.46 g) and water (1 mL) and stirring the mixture at room temperature for another 2 hours. The reaction products were extracted into ether (3 × 15 mL) and decane (0.70 mmol, 0.10 g) was added as the internal standard. GC analysis indicated a ratio of 1-octanol to 2-heptanol of 99:1 (100% total yield).

The reaction was repeated at 0 °C. The ratio of 1-octanol to 2-heptanol obtained by GC was 97:3 (98% total yield). The reaction at 68 °C was carried out by refluxing the reaction mixture in THF. The ratio of 1-octanol to 2-heptanol was 98:2, and the yield was 100%.

Reaction of 1-octene and 2-heptanone with a limited quantity of BMS in THF. The reaction with BMS (1.0 mmol, 0.10 mL of 10 M dimethyl sulfide complex) at room temperature was carried out by the procedure described previously. Decane (0.68 mmol, 95 mg) was added as the internal standard. The ratio of 1-octanol to 2-heptanol obtained by GC was 97:3 with 100% total yield. The similar reaction was also carried out at 0 °C. The ratio of 1-octanol to 2-heptanol was 96:4, and the yield was 100%.

Reaction of 1-octene and 2-heptanone with a limited quantity of 9-BBN in THF. The reaction with 9-BBN (3.0 mmol, 6.0 mL of 0.5 M solution in THF) at room temperature was carried out by the general procedure described above, except that 1.4 g (9.0 mmol) of $NaBO_3 \bullet 4H_2O$ were used and decane

(0.74 mmol, 0.10 g) was added as the internal standard. The ratio of 1-octanol to 2-heptanol obtained by GC was 93:7 (90% total yield). A similar reaction was carried out at 0 °C. The ratio of 1-octanol to 2-heptanol was 69:31 and the yield was 61%. For the reaction at 68 °C which was carried out at reflux in THF, the ratio of 1-octanol to 2-heptanol was 89:11 and the yield was 95%.

Reaction of 1-octene and 2-heptanone with a limited quantity of catecholborane in THF. The reaction with catecholborane (3.0 mmol, 0.36 g, 0.32 mL) at room temperature was carried out as described previously. Decane (0.77 mmol, 0.11 g) was added as the internal standard. The ratio of 1-octanol to 2-heptanol obtained by GC was 0:100 in 10% yield. A similar reaction was carried out at 0 °C, the ratio of 1-octanol to 2-heptanol was 0:100, and the total yield was 9%.

Reaction of 1-octene and 2-heptanone with a limited quantity of disiamylborane in THF. Borane (2.0 mmol, 2.0 mL of 1.0 M solution in THF) was placed in a dry, argon-flushed, round-bottomed flask, which was then immersed in an ice-salt bath at -10 °C. 2-Methyl-2-butene (4.0 mmol, 0.28 g, 0.42 mL) was added dropwise and the mixture stirred at 0 °C for 2 hours to generate disiamylborane. A mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL) and 2-heptanone (2.0 mmol, 0.23 g, 0.28 mL) was added to the solution of disiamylborane in THF and the cooling bath was removed. The mixture was stirred at room temperature for two hours and oxidation was achieved by adding

$NaBO_3 \bullet 4H_2O$ (6.0 mmol, 0.92 g) and water (2 mL). The products were extracted into ether (3 × 15 mL). Decane (0.75 mmol, 0.11 g) was added to the ether layer as the internal standard. The ratio of 1-octanol to 2-heptanol obtained by GC analysis was 97:3 in 90% yield. For a similar reaction carried out at 0 °C, the ratio of 1-octanol to 2-heptanol was 96:4 and the yield was 92%.

Reaction of 1-octene and 2-heptanone with a limited quantity of dicyclohexylborane in THF. Borane (2.0 mmol, 2.0 mL of 1.0 M solution in THF) was placed in a dry, argon-flushed, round-bottomed flask, which was then immersed in an ice-water bath. Cyclohexene (4.0 mmol, 0.33 g, 0.41 mL) was added dropwise and the mixture was stirred at 0 °C for 1 hour. A mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL) and 2-heptanone (2.0 mmol, 0.23 g, 0.28 mL) was added to the slurry of dicyclohexylborane in THF and the cooling bath was removed. The mixture was stirred at room temperature for two hours. Oxidation was achieved by adding $NaBO_3 \bullet 4H_2O$ (6.0 mmol, 0.92 g) and water (2.0 mL). The reaction products were extracted into ether (3 × 15 mL). Decane (0.70 mmol, 0.10 g) was added to the ether solution as the internal standard. The ratio of 1-octanol to 2-heptanol obtained by GC analysis was 100:0 in 93% yield. For a similar reaction carried out at 0 °C, the ratio of 1-octanol to 2-heptanol was 100:0 and the yield was 88%.

3.2.7.2 Reaction of 1-Octene and Cyclopentanone with a Variety of Borane Reagents

General procedure for the reactions of 1-octene and cyclopentanone. Reaction of 1-octene and cyclopentanone with a limited quantity of BH_3•THF in THF. A mixture of 1-octene (3.0 mmol, 0.33 g, 0.47 mL) and cyclopentanone (3.0 mmol, 0.25 g, 0.27 mL) in THF (3.0 mL) was placed in a dry, argon-flushed, round-bottomed flask at room temperature. Borane (1.0 mmol, 1.0 mL of a 1.0 M solution in THF) was added and the mixture was stirred at room temperature for 2 hours. Oxidation was achieved by adding $NaBO_3$•$4H_2O$ (3.0 mmol, 0.46 g) and water (1.0 mL) and stirring the mixture at room temperature for another 2 hours. The reaction mixture was extracted into ether (3 × 15 mL) and decane (0.70 mmol, 0.10 g) was added to the ether solution as the internal standard. GC analysis indicated the yield ratio of 1-octanol to cyclopentanol was 94:6 with 93% total yield.

Reaction of 1-octene and cyclopentanone with a limited quantity of BMS in THF. The reaction with BMS (1.0 mmol, 0.10 mL of 10 M dimethyl sulfide complex) at room temperature was carried out by the general procedure described as above. Decane (0.70 mmol, 0.10 g) was added as the internal standard. The ratio of 1-octanol to cyclopentanol obtained by GC was 89:11 and the yield was 96%.

Reaction of 1-octene and cyclopentanone with a limited quantity of 9-BBN in THF. The reaction with 9-BBN (3.0 mmol, 6.0 mL of 0.5 M solution in THF) at room temperature was carried out by the general procedure described previously, except that 1.4 g of $NaBO_3 \bullet 4H_2O$ (9.0 mmol) was used. Decane (0.70 mmol, 0.10 g) was added as the internal standard. The ratio of 1-octanol to cyclopentanol obtained by GC was 34:66 and the yield was 90%.

Reaction of 1-octene and cyclopentanone with a limited quantity of disiamylborane in THF. The mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL) and cyclopentanone (2.0 mmol, 0.17 g, 0.18 mL) was added to the solution of 2.0 mmol disiamylborane, which was prepared as described previously. Oxidation was carried out using 0.92 g (6.0 mmol) of $NaBO_3 \bullet H_2O$. Decane (0.77 mmol, 0.11 g) was added as the internal standard. The ratio of 1-octanol to cyclopentanol obtained by GC was 92:8 and the yield was 91%.

Reaction of 1-octene and cyclopentanone with a limited quantity of dicyclohexylborane in THF. The mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL) and cyclopentanone (2.0 mmol, 0.17 g, 0.18 mL) was added to the slurry of 2 mmol dicyclohexylborane, prepared as described previously. The oxidation was achieved using 0.92 g (6.0 mmol) of $NaBO_3 \bullet H_2O$. Decane (0.77 mmol, 0.11 g) was added as the internal standard. The ratio of 1-octanol to cyclopentanol obtained by GC was 100:0 and the yield was 90%.

3.2.7.3 Reactions of 1-Octene and Cyclohexanone with a Variety of Borane Reagents.

General procedure for the reactions of 1-octene and cyclohexanone. Reaction of 1-octene and cyclohexanone with a limited quantity of BH_3•THF in THF. A mixture of 1-octene (3.0 mmol, 0.33 g, 0.47 mL) and cyclohexanone (3.0 mmol, 0.29 g, 0.32 mL) in THF (3 mL) was placed in a dry, argon-flushed, round-bottomed flask at room temperature. Borane (1.0 mmol, 1.0 mL of a 1.0 M solution in THF) was added and the mixture was stirred at room temperature for 2 hours. Oxidation was achieved by adding $NaBO_3$•$4H_2O$ (3.0 mmol, 0.46 g) and water (1 mL) and stirring the mixture at room temperature for an additional 2 hours. The reaction mixture was extracted into ether (3 × 15 mL) and decane (0.70 mmol, 0.10 g) was added as the internal standard. GC analysis indicated a ratio of 1-octanol to cyclohexanol was 83:17 and the yield was 95%.

Reaction of 1-octene and cyclohexanone with a limited quantity of BMS in THF. The reaction with BMS (1.0 mmol, 0.1 mL of 10 M dimethyl sulfide complex) at room temperature was carried out as described previously. Decane (0.70 mmol, 0.10 g) was added as the internal standard. The ratio of 1-octanol to cyclohexanol, obtained by GC, was 78:22 and the yield was 92%.

Reaction of 1-octene and cyclohexanone with a limited quantity of 9-BBN in THF. The reaction with 9-BBN (3.0 mmol, 6.0 mL of 0.5 M solution in

THF) at room temperature was carried out by the general procedure described previously, except that 1.4 g of $NaBO_3 \bullet 4H_2O$ (9.0 mmol) was used. Decane (0.77 mmol, 0.11 g) was added as the internal standard. The ratio of 1-octanol to cyclohexanol, obtained by GC, was 24:76 and the yield was 95%.

Reaction of 1-octene and cyclohexanone with a limited quantity of disiamylborane in THF. A mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL) and cyclohexanone (2.0 mmol, 0.20 g, 0.21 mL) was added to a solution of 2.0 mmol disiamylborane, which was prepared as described previously. Decane (0.77 mmol, 0.11 g) was added as the internal standard. The ratio of 1-octanol to cyclohexanol, obtained by GC, was 81:19 and the yield was 88%.

Reaction of 1-octene and cyclohexanone with a limited quantity of dicyclohexylborane in THF. The mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL) and cyclohexanone (2.0 mmol, 0.20 g, 0.21 mL) was added to the slurry of 2.0 mmol dicyclohexylborane, which was prepared as described previously. Decane (0.77 mmol, 0.11 g) was added as the internal standard. The ratio of 1-octanol to cyclohexanol, obtained by GC, was 100:0 and the yield was 90%.

3.2.7.4 Reactions of 1-Octene and Acetophenone with a Variety of Borane Reagents.

General procedure for the reactions of 1-octene and acetophenone. Reaction of 1-octene and acetophenone with a limited quantity of BH_3•THF in THF. A mixture of 1-octene (3.0 mmol, 0.33 g, 0.47 mL) and acetophenone (3.0 mmol, 0.36 g, 0.35 mL) in THF (3 mL) was placed in a dry, argon-flushed, round-bottomed flask at room temperature. Borane (1.0 mmol, 1.0 mL of a 1.0 M solution in THF) was added and the mixture was stirred at room temperature for 2 hours. Oxidation was achieved by adding $NaBO_3$•$4H_2O$ (3.0 mmol, 0.46 g) and water (1.0 mL) and stirring the mixture at room temperature for an addtional 2 hours. The reaction mixture was extracted into ether (3 × 15 mL) and decane (0.77 mmol, 0.11 g) was added as the internal standard. GC analysis indicated the ratio of 1-octanol to 1-phenylethanol was 100:0 and the yield was 95%.

Reaction of 1-octene and acetophenone with a limited quantity of BMS in THF. The reaction with BMS (1.0 mmol, 0.10 mL of 10 M dimethyl sulfide complex) at room temperature was carried out as described previously. Decane (0.70 mmol, 0.10 g) was added as the internal standard. The ratio of 1-octanol to 1-phenylethanol obtained by GC was 94:6 and the yield was 94%.

Reaction of 1-octene and acetophenone with a limited quantity of 9-BBN in THF. The reaction with 9-BBN (3.0 mmol, 6.0 mL of 0.50 M solution in

THF) at room temperature was carried out by the general procedure described previously, except that 1.4 g of $NaBO_3 \bullet 4H_2O$ (9.0 mmol) was used. Decane (0.77 mmol, 0.11 g) was added as the internal standard. The ratio of 1-octanol to 1-phenylethanol, obtained by GC, was 76:24 and the yield was 95%.

Reaction of 1-octene and acetophenone with a limited quantity of disiamylborane in THF. A mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL) and acetophenone (2.0 mmol, 0.24 g, 0.23 mL) was added to the solution of 2.0 mmol disiamylborane, which was prepared as described previously. Oxidation was achieved using 0.92 g (6.0 mmol) of $NaBO_3 \bullet H_2O$. Decane (0.70 mmol, 0.10 g) was added as the internal standard. The ratio of 1-octanol to 1-phenylethanol, obtained by GC, was 100:0 and the yield was 88%.

Reaction of 1-octene and acetophenone with a limited quantity of dicyclohexylborane in THF. A mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL) and acetophenone (2.0 mmol, 0.24 g, 0.23 mL) was added to the slurry of 2 mmol dicyclohexylborane, which as described previously. Oxidation was achieved using 0.92 g (6.0 mmol) of $NaBO_3 \bullet H_2O$. Decane (0.77 mmol, 0.11 g) was added as the internal standard. The ratio of 1-octanol to 1-phenylethanol, obtained by GC, was 100:0 and the yield was 96%.

3.2.7.5 Reactions of 1-Octene and Heptanal with a Variety of Borane Reagents.

General procedure for the reactions of 1-octene and heptanal.

Reaction of 1-octene and heptanal with a limited quantity of BH_3•THF in THF. A mixture of 1-octene (3.0 mmol, 0.33 g, 0.47 mL) and heptanal (3.0 mmol, 0.34 g, 0.42 mL) in THF (3.0 mL) was placed in a dry, argon-flushed, round-bottomed flask at room temperature. Borane (1.0 mmol, 1.0 mL of a 1.0 M solution in THF) was added and the mixture was stirred at room temperature for 2 hours. Oxidation was achieved by adding $NaBO_3$•$4H_2O$ (3 mmol, 0.46 g) and water (1 mL) and stirring the mixture at room temperature for an additional 2 hours. The reaction mixture was extracted into ether (3 × 15 mL) and decane (0.70 mmol, 0.10 g) was added as the internal standard. GC analysis indicated the ratio of 1-octanol to 1-heptanol was 45:55 and the yield was 96%.

Reaction of 1-octene and heptanal with a limited quantity of BMS in THF. The reaction with BMS (1.0 mmol, 0.10 mL of 10 M dimethyl sulfide complex) at room temperature was carried out as described previously. Decane (0.70 mmol, 0.10 g) was added as the internal standard. The ratio of 1-octanol to 1-heptanol, obtained by GC, was 53:47 and the yield was 91%.

Reaction of 1-octene and heptanal with a limited quantity of monochloroborane in CH_2Cl_2. The reaction of monochloroborane dimethyl

sulfide complex (2.0 mmol, 0.21 mL) with a mixture of 1-octene (4.0 mmol, 0.44 g, 0.63 mL) and heptanal (4.0 mmol, 0.46 g, 0.56 mL) in CH_2Cl_2 (8.0 mL) at room temperature was carried out as described previously. Decane (0.77 mmol, 0.11 g) was added as the internal standard. The ratio of 1-octanol to 1-heptanol, obtained by GC, was 15:85 and the yield was 92%.

Reaction of 1-octene and heptanal with a limited quantity of monobromoborane in CH_2Cl_2. The reaction of monobromoborane dimethyl sulfide complex (2.0 mmol, 0.20 mL of 1.0 M solution in CH_2Cl_2) with the mixture of 1-octene (4.0 mmol, 0.44 g, 0.63 mL) and heptanal (4.0 mmol, 0.46 g, 0.56 mL) in CH_2Cl_2 (6.0 mL) at room temperature was carried out as described previously. Decane (0.70 mmol, 0.10 g) was added as the internal standard. The ratio of 1-octanol to 1-heptanol, obtained by GC, was 30:70 and the yield was 95%.

Reaction of 1-octene and acetophenone with a limited quantity of 9-BBN in THF. The reaction with 9-BBN (3.0 mmol, 6.0 mL of 0.50 M solution in THF) at room temperature was carried out as described previously. Oxidation was achieved using 1.4 g of $NaBO_3 \bullet 4H_2O$ (9.0 mmol) was used. Decane (0.77 mmol, 0.11 g) was added as the internal standard. The ratio of 1-octanol to 1-phenylethanol, obtained by GC, was 76:24 and the yield was 95%.

Reaction of 1-octene and heptanal with a limited quantity of thexylborane in THF. Borane tetrahydrofuran (2.0 mmol, 2.0 mL of 1.0 M solution in THF) was placed in a dry, argon-flushed, round-bottomed flask, which was then immersed in an ice-salt bath maintained at -10 °C. 2,3-Dimethyl-2-butene (2.0 mmol, 2.0 mL of 1.0 M solution in THF) was added dropwise and the mixture stirred at 0°C for 2 hours to form thexylborane. A mixture of 1-octene (4.0 mmol, 0.44 g, 0.63 mL) and heptanal (4.0 mmol, 0.46 g, 0.56 mL) was added to the solution of thexylborane in THF and the mixture stirred at 0 °C for three hours. Oxidation was achieved by adding $NaBO_3 \bullet 4H_2O$ (12 mmol, 1.84 g) and water (4.0 mL) and the products were extracted into ether (3 × 15 mL). Decane (0.85 mmol, 0.12 g) was added to the reaction mixture as the internal standard. The ratio of 1-octanol to 1-heptanol, obtained by GC, was 50:50 and the yield was 85%.

Reaction of 1-octene and heptanal with a limited quantity of diisopinocampheylborane in THF. Borane (2.0 mmol, 2.0 mL of 1.0 M solution in THF) was placed in a dry, argon-flushed, round-bottomed flask, which was then immersed in an ice-water bath. α-(+)-Pinene (4.0 mmol, 0.54 g, 0.64 mL) was added dropwise and the mixture was stirred at 0 °C for 2 hours to form diisopinocampheylborane. A mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL) and heptanal (2.0 mmol, 0.23 g, 0.28 mL) was added to the slurry of diisopinocampheylborane in THF and the cooling bath was removed. The mixture was stirred at room temperature for an additional two hours. Oxidation

was achieved by adding $NaBO_3 \bullet 4H_2O$ (6.0 mmol, 0.92 g) and water (2 mL), and the products were extracted into ether (3 × 15 mL). Decane (0.70 mmol, 0.10 mg) was added to the reaction mixture as the internal standard. The ratio of 1-octanol to 1-heptanol, obtained by GC, was 43:57 and the yield was 143%.

Reaction of 1-octene and heptanal with a limited quantity of disiamylborane in THF. A mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL) and heptanal (2.0 mmol, 0.23 g, 0.28 mL) was added to a solution of 2.0 mmol disiamylborane, prepared as described previously. Decane (0.77 mmol, 0.11g) was added as the internal standard. The ratio of 1-octanol to 1-heptanol, obtained by GC, was 71:29 and the yield was 84%.

Reaction of 1-octene and heptanal with a limited quantity of dicyclohexylborane in THF. A mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL) and heptanal (2.0 mmol, 0.23 g, 0.28 mL) was added to the slurry of 2.0 mmol dicyclohexylborane, prepared as described previously. Decane (0.77 mmol, 0.11 g) was added as the internal standard. The ratio of 1-octanol to 1-heptanol, obtained by GC, was 82:18 and the yield was 95%.

Reaction of 1-octene and heptanal with a limited quantity of dicyclohexylborane in CH_2Cl_2. Dicyclohexylborane (2.0mmol) in THF was prepared as described previously. The THF was removed under vaccum and CH_2Cl_2 (4 mL) was added. A mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL)

and heptanal (2.0 mmol, 0.23 g, 0.28 mL) was added to the slurry of 2.0 mmol dicyclohexylborane in CH_2Cl_2. After stirring at room temperature for 2 hours, 4 mL of a mixture of THF and ethanol (1:1) was added to the reaction mixture. Oxidation was achieved by adding $NaBO_3 \bullet 4H_2O$ (6 mmol, 0.92 g) and water (2 mL). The ratio of 1-octanol to 1-heptanol, obtained by GC, was 88:12 and the yield was 97%.

Similar reactions were carried out in pentane and in ether. The ratio of 1-octanol to 1-heptanol was 83:17 and 79:21, respectively.

Reaction of 1-octene and heptanal with a limited quantity of catecholborane in THF. The reaction with catecholborane (2.0 mmol, 0.24 g, 0.21 mL) at room temperature was carried out as described previously. Decane (0.61 mmol, 0.87 g) was added as the internal standard. The ratio of 1-octanol to 1-heptanol, obtained by GC, was 0:100 and the yield was 100%.

3.2.7.6 Reactions of 1-Octene and Benzaldehyde with a Variety of Borane Reagents.

General procedure for the reactions of 1-octene and benzaldehyde. Reaction of 1-octene and benzaldehyde with a limited quantity of $BH_3 \bullet THF$ in THF. A mixture of 1-octene (3.0 mmol, 0.33 g, 0.47 mL) and benzaldehyde (3.0 mmol, 0.32 g, 0.30 mL) in THF (3 mL) was placed in a dry, argon-flushed, round-bottomed flask at room temperature. Borane (1.0 mmol, 1.0 mL of a 1.0 M

solution in THF) was added and the mixture was stirred at room temperature for 2 hours. Oxidation was achieved by adding $NaBO_3 \bullet 4H_2O$ (3.0 mmol, 0.46 g) and water (1 mL) and stirring the mixture at room temperature for 2 hours. The reaction products were extracted into ether (3 × 15 mL) and decane (0.77 mmol, 0.11 g) was added as the internal standard. The mixture was then analyzed by GC, indicating the ratio of 1-octanol to benzyl alcohol was 57:43 and the yield was 91%.

Reaction of 1-octene and benzaldehyde with a limited quantity of BMS in THF. The reaction with BMS (1.0 mmol, 0.10 mL of 10 M dimethyl sulfide complex) at room temperature was carried out as described previously. Decane (0.92 mmol, 0.13 g) was added as the internal standard. The ratio of 1-octanol to benzyl alcohol, obtained by GC, was 51:49 and the yield was 90%.

Reaction of 1-octene and benzaldehyde with a limited quantity of 9-BBN in THF. The reaction with 9-BBN (3.0 mmol, 6.0 mL of 0.5 M solution in THF) at room temperature was carried out as described previously. Oxidation was achieved using 1.38 g of $NaBO_3 \bullet 4H_2O$ (9.0 mmol). Decane (0.11 mmol, 0.15 g) was added as the internal standard. The ratio of 1-octanol to 1-phenylethanol, obtained by GC, was 62:38 and the yield was 96%.

Reaction of 1-octene and benzaldehyde with a limited quantity of disiamylborane in THF. A mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL) and

benaldehyde (2.0 mmol, 0.21 g, 0.20 mL) was added to the solution of 2.0 mmol disiamylborane, prepared as described previously. Decane (0.10 mmol, 0.14 g) was added as the internal standard. The ratio of 1-octanol to benzyl alcohol, obtained by GC, was 75:25 and the yield was 90%.

Reaction of 1-octene and benzaldehyde with a limited quantity of dicyclohexylborane in THF. A mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL) and benzaldehyde (2.0 mmol, 0.21 g, 0.20 mL) was added to the slurry of 2.0 mmol dicyclohexylborane, prepared as described previously. Decane (0.92 mmol, 0.13 g) was added as the internal standard. The ratio of 1-octanol to benzyl alcohol, obtained by GC, was 84:16 and the yield was 93%.

Reaction of 1-octene and benzaldehyde with a limited quantity of dicyclohexylborane in CH_2Cl_2. A mixture of 1-octene (2.0 mmol, 0.22 g, 0.33 mL) and benzaldehyde (2.0 mmol, 0.21 g, 0.20 mL) was added to the slurry of 2.0 mmol dicyclohexylborane in CH_2Cl_2, prepared by as described previously. Decane (0.85 mmol, 0.12 g) was added as the internal standard. The ratio of 1-octanol to benzyl alcohol, obtained by GC, was 97:3 and the yield was 92%.

3.3 Selective Hydroboration of Alkenyl Ketones and Aldehydes

3.3.1 Introduction

As discussed in the previous section, a terminal alkene can be successfully hydroborated in the presence of a ketone using essentially all of the common hydroborating agents except 9-BBN. However, only hindered borane reagents can selective hydroborate a terminal alkene in the presence of an aldehyde. Unhindered borane reagents prefer to reduce aldehydes rather than hydroborate alkenes. Among the borane reagents studied, dicyclohexylborane is the most effective at hydroborating terminal alkenes in the presence of ketones and aldehydes. It hydroborates terminal alkenes without reducing ketones and affords greater than 82 percent of the hydroboration products in the presence of aldehydes. It is logical that dicyclohexylborane would be effective at hydroborating the carbon-carbon bond of alkenyl ketones and aldehydes. Therefore, we examined the ability of dicyclohexylborane to selectively hydroborate the carbon-carbon bond of alkenyl ketones and aldehydes.

3.3.2 Results and Discussion

A variety of alkenyl ketones and aldehydes were allowed to react with dicyclohexylborane (Table 3-9). One molar equivalent of an olefinic ketone or aldehyde was added to one molar equivalent of dicyclohexylborane in THF. After the reaction mixture was stirred at room temperature for two hours, oxidation was

Table 3-9. The hydroboration of olefinic carbonyl compounds with dichyclohexylborane.

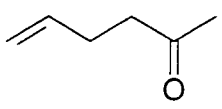
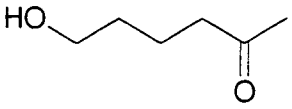
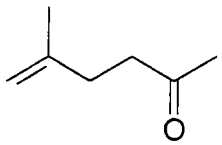
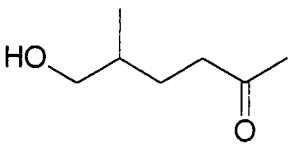
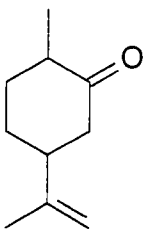
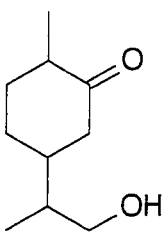
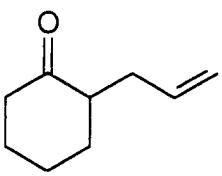
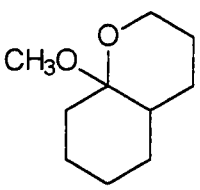
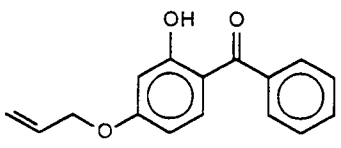
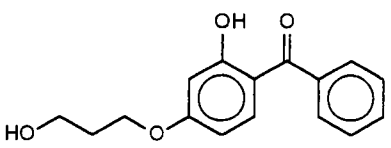
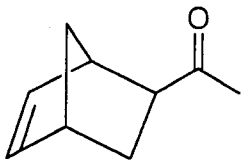
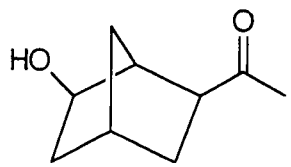
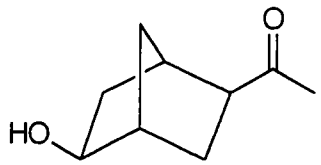
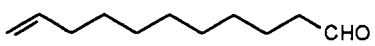
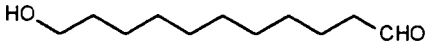
Entry	Substrate	Product[a]	Yield(%)[b]
1[c]			76
2			80
3[c]			77
4[d]			80
5[e]			78

Table 3-9. The hydroboration of olefinic carbonyl compounds with dicyclohexylborane (continued).

Entry	Substrates	Products[a]	Yields(%)[b]
6		 and 	68
7			50

[a] Known compounds exhibited physical and spectral characteristics in accord with literature values and new compounds were characterized by spectral and elemental analysis or HRMS.

[b] Isolated yield.

[c] Up to 10% of the corresponding diols were isolated.

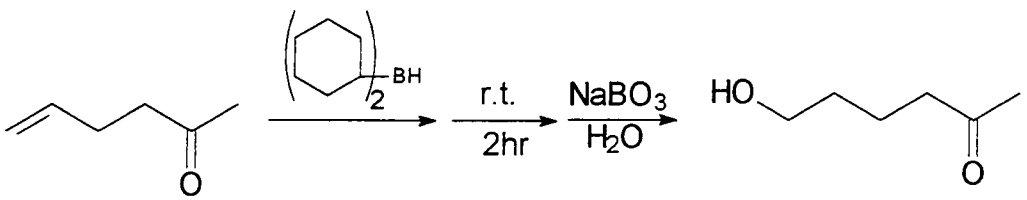
[d] Acetal formed by the reaction of the crude product with methanol in the presence of TsOH.

[e] Two equivalents of dicyclohexylborane were utilized.

achieved by adding $NaBO_3 \bullet H_2O$. The results indicate that hydroxyaldehydes and hydroxyketones can be prepared in good yields (Table 3-9).

3.3.2.1 Reaction of Terminal Alkenyl Ketones

5-Hexen-2-one (entry 1 in Table 3-9) reacted with dicyclohexylborane forming 6-hydroxy-2-hexanone as the major product (eqn 3-11). This suggests that dicyclohexylborane can selectively hydroborate a terminal alkene in the compound containing a carbonyl group. Interestingly, no "simple" reduction product, 5-hydroxy-1-hexene, was detected in this reaction. However,

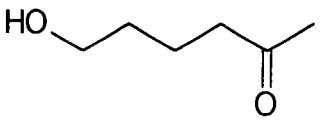
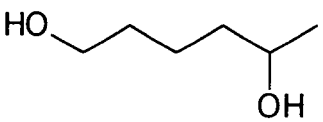


(eqn 3-11)

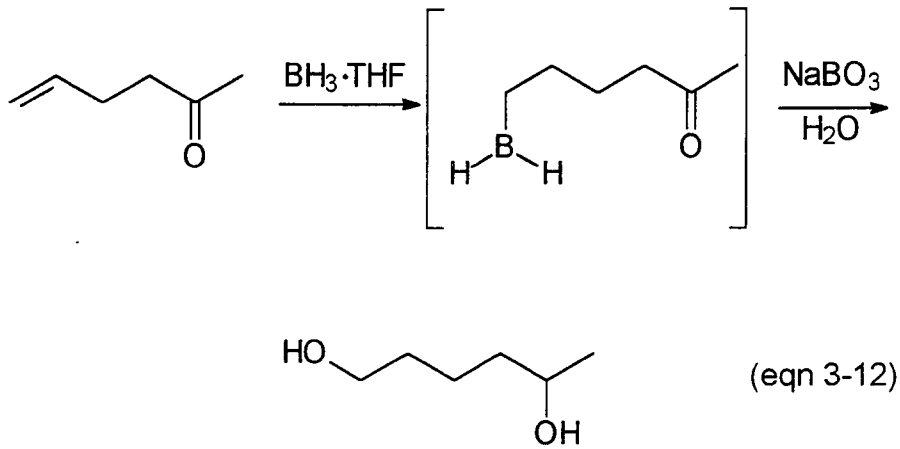
overreduction to the diol product was found to be a side reaction (about 8%). Excess dicyclohexylborane afforded more of the diol. Presumably, the hydroboration product forms an intramolecular complex between oxygen and boron, which activates the carbonyl group to attack by the borane reagents.

5-Hexen-2-one was allowed to react with a variety of borane reagents. The results are presented in Table 3-10. As can be seen by examining Table 3-10, dicyclohexylborane, disiamylborane and 9-BBN react with 5-hexen-2-one to give the hydroboration product, 6-hydroxy-2-hexanone, as the major product. BH_3•THF effectively hydroborates the alkenyl group of 5-hexen-2-one. However,

Table 3-10. The reactions of 5-hexen-2-one with a variety of borane reagents

Borane Reagent		
$(c\text{-}C_6H_{11})_2BH$	76%	5%
Sia_2BH	65%	6%
9-BBN	61%	~10%
BH_3·THF	10%	40%
BMS	8%	30%

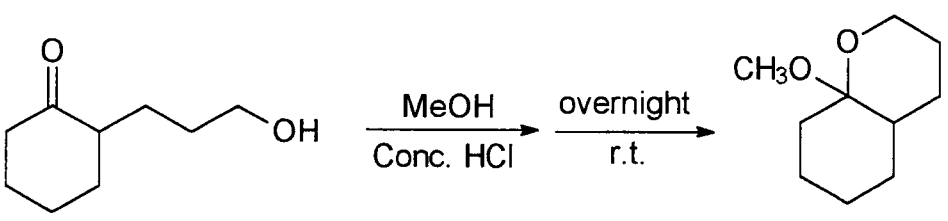
the diol is the major product of the reaction of 5-hexen-2-one with BH_3•THF (eqn 3-12). It is assumed that the hydroboration of the alkenyl group by one hydride of BH_3•THF occurs first, then an intramolecular reduction of the carbonyl group by the hydroboration product is faster than intermolecular hydroboration of the alkenyl group. BMS reacts in a similar fashion. Therefore, only dialkylboranes are effective at hydroborating olefinic groups in the alkenyl ketones.



(eqn 3-12)

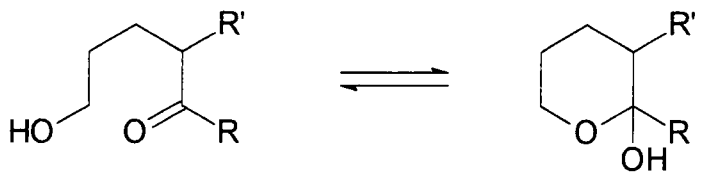
The reaction of 5-methyl-5-hexen-2-one (entry 2, Table 3-9) with dicyclohexylborane forms 6-hydroxy-5-methyl-2-hexanone after oxidation. The methyl group substituted at the 5-position has no effect on the selective hydroboration of the olefinic group.

Terminal alkenes can be selectively hydroborated by dicyclohexylborane when a cyclohexanone is present in the molecule (entries 3 and 4, Table 3-9). No "simple" reduction product forms, but diols are the side products. In the case of 2-allyl-cyclohexanone, the product could not be separated from cyclohexanol. The crude product was then reacted with methanol in the presence of TsOH to form an acetal, which was isolable (eqn 3-13).



(eqn 3-13)

In fact, many of the products (entries 1 to 4, Table 3-9) exist as a mixture of the acyclic hydroxyl ketone and the cyclic hemiacetal (eqn 3-14). NMR evidence suggests an equilibrium consisting of about 50% of hydroxyl ketone and 50% of hemiacetal, which is consistent with the literature report[171].

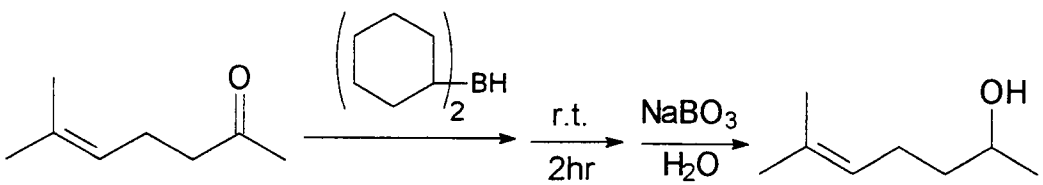


(eqn 3-14)

Two equivalents of dicyclohexylborane were utilized to react with 4-allyoxy-2-hydroxybenzophenone because of the presence of the hydroxyl group. 4-(3-Hydroxypropanoxy)-2-hydroxybenzophenone was obtained in good yield. No "simple" reduction product was observed.

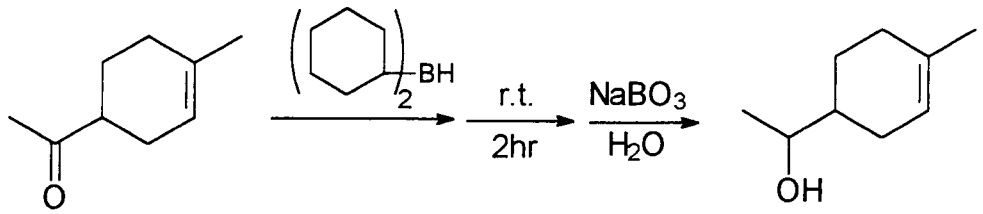
3.3.2.2 Reaction of Internal Alkenyl Ketones

Internal alkenes are less reactive toward borane reagents than terminal alkenes[172]. Therefore, internal alkenes compete much less effectively with ketones toward dicyclohexylborane than do terminal alkenes. 6-Methyl-5-hepten-2-one was allowed to react with dicyclohexylborane. After addition with $NaBO_3 \bullet H_2O$ and water, 6-hydroxy-2-methyl-2-heptene (eqn 3-15), was obtained



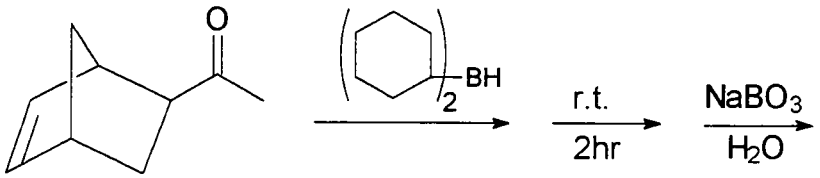
(eqn 3-15)

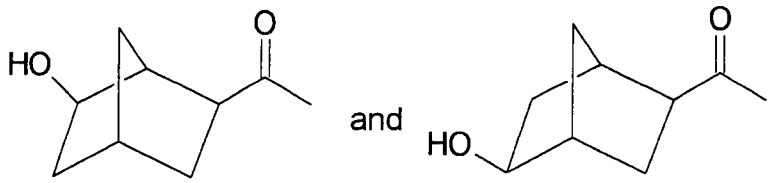
as the major product. Similarly, the reaction of 4-acetyl-1-methyl cylcohexene with dicyclohexylborane formed predominantly the reduction product, 4-(1-hydroxyethyl)-1-methyl cyclohexene (eqn 3-16).



(eqn 3-16)

Norbornene has been reported to be more reactive toward 9-BBN than are terminal alkenes[172] due to the bicyclic system causing the carbon-carbon double bond to be highly strained. This also makes it possible to hydroborate the carbon-carbon double bond of norbornene using dicyclohexylborane without reducing the carbonyl group. Acetylnorbornene (entry 6, Table 3-9) (eqn 3-17)



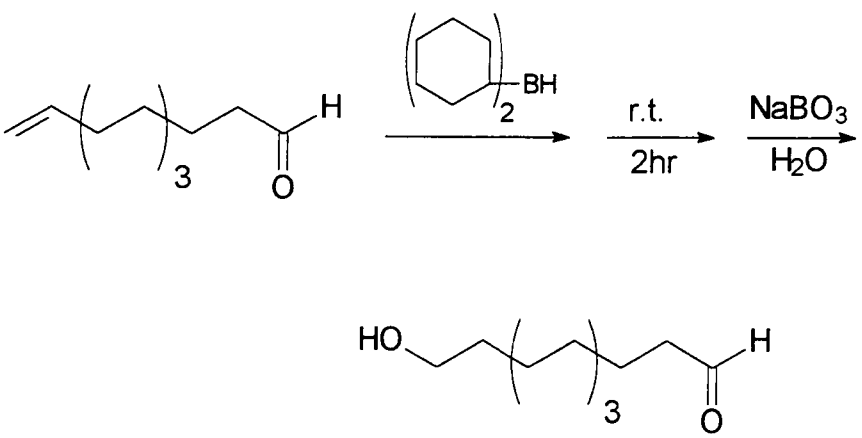


(eqn 3-17)

reacts with dicyclohexylborane to form 2-acetyl-5-hydroxynorbornanol and 2-acetyl-6-hydroxynorbornanol as major products.

3.3.2.3 Reaction of Alkenyl Aldehydes

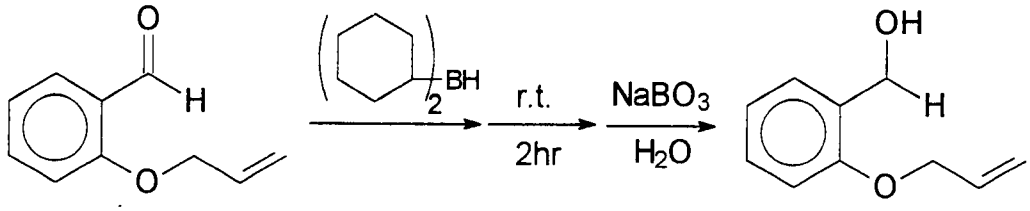
Aldehydes would be expected to compete more effectively with an alkene for borane reagents than would ketones. The reaction of 10-undecenal (entry 7, Table 3-9) with dicyclohexylborane form about 50% of the hydroboration product, 11-hydroxyundecanal (eqn 3-18). A trace of "simple" reduction product, 11-



(eqn 3-18)

hydroxy-1-undecene, is also observed from the TLC analysis. The reaction was also carried out using dicyclohexylborane in CH_2Cl_2. The yield is slightly higher, 55%. A trace of the reduction product was found by TLC.

The reaction of 2-allyoxybenzaldehyde with dicyclohexylborane affords the reduction product, 2-allyoxybenzyl alcohol, as the major product in 46% yield (eqn 3-19). About 20% of the diol is also formed, and only 5% of desired



(eqn 3-19)

hydroboration product is detected. The reduction product is the major product even when the reaction is carried out in CH_2Cl_2. Since the reduction of a carbonyl group with borane reagents has been reported to proceed via a complex of between the carbonyl oxygen and boron atom [170], the electron-releasing allyoxyl group at the ortho position of benzene ring increases the rate of reduction by increasing the electron density of carbonyl oxygen.

3.3.3 Conclusion

The terminal alkenyl group in alkenyl ketones and aldehydes can be selectively hydroborated by dicyclohexylborane. Except for norbornene derivatives, the reactions of internal alkenyl ketones with dicyclohexylborane produce reduction products as the major products. The hydroboration of olefinic ketones and aldehydes with dicyclohexylborane gives the corresponding hydroxy ketones and aldehydes in good yields after oxidation with sodium perborate.

3.3.4 Experimental

All glassware, syringes and needles were dried in an oven heated to 250°C for at least 12 hours and cooled under argon prior to use. All solvents were dried and distilled prior to use. Alkenyl ketones and alkenyl aldehydes, obtained from Aldrich Chemical Company, were purified by distillation prior to use. All borane reagents were obtained from Aldrich Chemical Company, and were used as received. Reactions were magnetically stirred and monitored by TLC analysis. Products were purified by flash chromatography.

All ^{1}H and ^{13}C NMR spectra were recorded on a 250 MHz Bruker AC250 spectrometer. Elemental analyses were performed by Altantic Microlabs, Norcross, Georgia.

General procedure for the preparation of hydroxyketones and hydroxyaldehydes. The synthesis of 6-Hydroxy-2-hexanone[173]: Borane (5.0 mmol, 5.0 mL of a 1.0 M solution in THF) was placed in a dry, argon-flushed, round-bottomed flask which was then immersed in an ice water bath. Cyclohexene (10.0 mmol, 0.82 g, 1.0 mL) was added dropwise and the mixture stirred at 0 °C for 1 hour. 5-Hexen-2-one (5.0 mmol, 0.49 g, 0.58 mL) was then added to the slurry of dicyclohexylborane in THF. The cooling bath was removed and the mixture stirred for 2 hours at room temperature. Oxidation was achieved by adding $NaBO_3 \bullet 4H_2O$ (15 mmol, 2.3 g) and water (5 mL) and stirring the mixture at room temperature for 2 hours. The product was extracted into ether (3 x 15 mL), the solvent removed under pressure, and 6-hydroxy-2-

hexanone (0.44g, 76% yield) was isolated by flash chromatography. ^{1}H NMR ($CDCl_3$/TMS) δ ppm 3.62 (*t*, *J* = 6.1 Hz, 2H), 2.59 (*br s*, 1H), 2.49 (*t*, *J* = 6.8 Hz, 2H), 2.16 (*s*, 3H), 1.73 -1.50 (*m*, 4H); ^{13}C NMR($CDCl_3$/TMS) δ ppm 209.38, 61.96, 43.15, 31.87, 19.73, 19.72.

The synthesis of 6-hydroxy-5-methyl-2-hexanone: The reaction of 5-methyl-5-hexen-2-one (4.0 mmol, 0.45 g, 0.52 mL) with dicyclohexylborane (4.0 mmol), prepared as described previously, yielded 80% of a cyclic and acyclic mixture (50:50) of 6-hydroxy-5-methyl-2-hexanone. ^{1}H NMR ($CDCl_3$/TMS) δ ppm 3.55-3.42 (*m*, 2H), 2.97 (*br s*, 0.5H) 2.61-2.46 (*m*, 1.5H), 2.16 (*s*, 1.5H), 1.81-1.35 (*m*, 5.5H), 0.91 (*d*, *J* = 6.6 Hz, 1.5H), 0.82 (*d*, *J* = 6.3 Hz, 1.5H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm 209.58, 94.50, 67.18, 60.50, 41.06, 35.15, 34.85, 30.06, 29.94, 29.72, 27.56, 26.65, 17.05, 16.39, HRMS Calcd. for $C_7H_{14}O_2$: 130.099 Found: 130.096.

The synthesis of 2-methyl-5-(1-methyl-2-ydroxylethyl)-cyclohexanone[174]: The reaction of 2-methyl-5-(1-methylethenyl)cyclohexanone (4.0 mmol, 0.61 g, 0.66 mL) with dicyclohexylborane (4.0 mmol), prepared as described previously, yielded 77% of 2-Methyl-5-(1-methyl-2-ydroxylethyl)-cyclohexanone. ^{1}H NMR ($CDCl_3$/TMS) δ ppm 3.59-3.44 (*m*, 2H), 2.49-1.26 (*m*, 9H), 1.01 (*d*, *J* = 6.4Hz, 2H), 0.94 (*d*, *J* = 6.9 Hz) and 0.91 (*d*, *J* = 6.9Hz) (total 3H); ^{13}C NMR($CDCl_3$/TMS) δ ppm 213.72, 213.45, 65.45, 65.36, 46.17, 44.83

(44.83), 43.91, 41.57, 41.37, 40.19, 40.00, 34.97 (34.97), 29.71, 27.51, 14.20 (14.20), 13.05, 12.71.

The synthesis of 1-methoxy-2-oxabicyclo[4.4.0]decane[175]: 2-Allyoxycyclohexanone (4.0 mmol, 0.55 g, 0.60 mL) was reacted with dicyclohexylborane (4.0 mmol), prepared as described previously. Then the crude hydroxy ketone was reacted with methanol in the presence of TsOH and concentrated HCl to yield: 70% of 1-methoxy-2-oxabicyclo[4.4.0]decane. ^{1}H NMR($CDCl_3$/TMS) δ ppm 3.72-3.56 (*m*, 2H), 3.22-3.16 (*m*, 3H), 1.98-1.12 (*m*, 13H); ^{13}C NMR($CDCl_3$/TMS) δ ppm 98.34, 60.87, 46.34, 44.44, 31.74, 29.45, 26.36, 25.88, 24.72, 22.67.

The synthesis of 4-(2-propenoxy)-2-hydroxybenzophenone: The reaction of 4-allyoxy-2-hydroxybenzophenone (2.0 mmol, 0.51 g) with dicyclohexylborane (4.0 mmol), prepared as described previously, yielded 78% of 4-(2-propenoxy)-2-hydroxybenzophenone. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 12.66 (*s*, 1H), 7.61 - 7.44 (*m*, 6H), 6.50 (*d*, *J* = 2.2Hz, 1H), 6.38 (*dd*, *J* = 8.9, 2.2Hz, 1H), 4.13 (*t*, *J* = 6.0Hz, 2H), 3.80 (*t*, *J* = 6.0Hz, 2H), 2.66 (*s*, 1H), 2.02 (*p*, *J* = 6.0 Hz, 2H); ^{13}C NMR ($CDCl^3$/TMS) δ ppm: 199.85, 166.04, 165.40, 138.01, 135.13, 131.32, 128.64 (128.64), 128.12 (128.12), 112.93, 107.42, 101.53, 65.32, 59.14, 31.61. Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92; Found: C, 70.66; H, 5.91.

The synthesis of 2-acetyl-5-hydroxynorbornane and 2-acetyl-6-hydroxynorbornane[176]: The reaction of 2-acetylnorbornene (4.0 mmol, 0.54 g, 0.54 mL) with dicyclohexylborane (4.0 mmol), prepared as described previously, yielded 68% of 2-acetyl-5-hydroxynorbornane and 2-acetyl-6-hydroxy-norbornane. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 3.85-3.62 (*m*, 1H), 3.05-1.12 (*m*, 13H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 209.79, 209.64, 209.28, 73.98, 73.68, 73.38, 69.72, 60.20, 53.39, 52.79, 51.43, 50.13, 47.30, 47.03, 44.65, 43.70, 41.70, 41.21, 39.17, 38.85, 36.27, 34.93, 32.07, 31.63, 31.17, 29.44, 29.23, 28.63, 28.42, 26.76, 25.06.

The synthesis of 11-hydroxyundecanal[177]: The reaction of 10-undecenal (4.0 mmol, 0.67 g, 0.83 mL) with dicyclohexylborane (4.0 mmol), prepared as described previously, yielded 50% of 11-hydroxyundecanal. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 9.76 (*t*, *J* = 1.3 Hz, 1H), 3.61 (*t*, *J* = 6.6Hz, 2H), 2.65 (*s*, 1H), 2.43 (*dt*, *J* = 7.3, 1.6 Hz, 2H). 1.65-1.53 (*m*, 4H), 1.29 (*br s*, 12H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 202.71, 62.47, 43.63, 32.51, 29.26, 29.11 (29.11), 28.90, 25.54, 21.82, 13.89.

Chapter 4. The Selective Hydroboration of Alkynes in the Presence of Ketones and Aldehydes

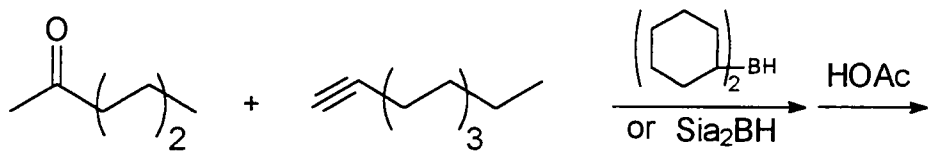
4.1 Introduction

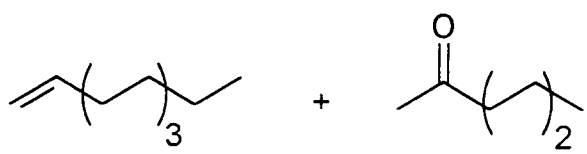
As discussed in the previous chapter, terminal alkenes can be selectively hydroborated by dicyclohexylborane in the presence of ketones and aldehydes. Like alkenes, alkynes react with borane reagents very rapidly. They would also be expected to compete with ketones and aldehydes for borane reagents.

The hydroborations of alkynes with different borane reagents are unique. The reaction of internal alkynes with a stoichiometric amount of BH_3•THF forms (*Z*)-trialkenylboranes with a small proportion of 1,1-diborylalkane. In the case of terminal alkynes, dihydroboration products are formed even when the correct stoichiometry for monohydroboration is used[74,75,76]. The stoichiometric reaction of 9-BBN with terminal alkynes also gives the 1,1-diboryl compounds predominantly[77]. On the other hand, the reactions of internal and terminal alkynes with disiamylborane or dicyclohexylborane in 1:1 molar ratio yields vinylboranes cleanly[78]. In general, when alkenes and alkynes are both present, 9-BBN is more reactive toward alkenes than alkynes while disiamylborane and dicylohexylborane are more reactive toward alkynes than alkenes. Thus, disiamylborane and dicyclohyexylborane would appear to be useful for hydroborating alkynes in the presence of ketones and aldehydes.

4.2 Competitive Study of Reactions of Alkynes and Ketones with Dialkylboranes

1-Decyne and 2-heptanone were chosen as a pair of model compounds to compete with both dicyclohexylborane and disiamylborane. A mixture of one equivalent of 1-decyne and one equivalent of 2-heptanone was added to one equivalent of dicyclohexylborane or disiamylborane in THF. After stirring at room temperature for 2 hours, the reaction was quenched using acetic acid (eqn 4-1).





(eqn 4-1)

100% 100% (recovered)

The reaction mixture was then analyzed by GC. The results revealed that 1-decene was formed quantitatively and 100 percent of the ketone was recovered in both reactions. Thus a terminal alkyne can be successfully hydroborated in the presence of a ketone by either dicyclohexyborane or disiamylborane. Dicyclohexylborane was chosen for reactions of alkynyl ketones and aldehydes later since it has several advantages over disiamylborane (discussed in section 1.2.2.5).

4.3 Synthesis of Alkynyl Ketones and Aldehydes

Alkynyl ketones and aldehydes can be readily prepared by oxidation of alkynyl alcohols[177,178], which are commercial available. Alkynyl aldehydes and ketones were prepared from the corresponding alcohols by oxidation with PCC (eqn 4-2 and eqn 4-3). The oxidation of primary alcohols with PCC was

$$RC{\equiv}C(CH_2)_nCH_2OH \xrightarrow[CH_2Cl_2]{PCC} \xrightarrow[2\text{-}3\ hrs]{r.t.} RC{\equiv}C(CH_2)_nC(=O)H \quad \text{(eqn 4-2)}$$

$$R'C{\equiv}C(CH_2)_nCH(OH)R'' \xrightarrow[CH_2Cl_2]{PCC} \xrightarrow[overnight]{r.t.} R'C{\equiv}C(CH_2)_nC(=O)R'' \quad \text{(eqn 4-3)}$$

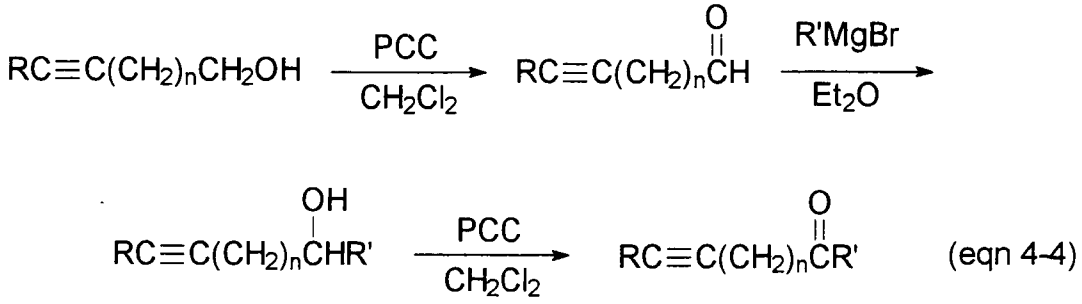
complete in 3 hours and the yields were high (about 80%). The oxidation of secondary alcohols with PCC was slower. The results of the oxidations of a variety of alkynyl alcohols are present in Table 4-1.

The primary alcohols are commercial available. Secondary alcohols were prepared via reactions of Grignard reagents with alkynyl aldehydes which were prepared by oxidation of the primary alcohols. The advantage of this method is that a variety of alkynyl alcohols can be prepared by using different Grignard reagents. Alkynyl ketones were then obtained by oxidation the secondary alcohols (eqn 4-4). Total yields ranged from 50% to 60%.

Table 4-1. Preparation of alkynyl ketones by oxidation of alkynyl alcohols with PCC.

Entry	Substrate	Product	Yield[a]
1	$HC\equiv C(CH_2)_8CH_2$ (OH)	$HC\equiv C(CH_2)_8CH$ (O)	75%
2	$HC\equiv C(CH_2)_8CHCH_3$ (OH)	$HC\equiv C(CH_2)_8CCH_3$ (O)	57%
3	$HC\equiv C(CH_2)_8CHCH_2CH_3$ (OH)	$HC\equiv C(CH_2)_8CCH_2CH_3$ (O)	65%
4	$HC\equiv C(CH_2)_3CHPh$ (OH)	$HC\equiv C(CH_2)_3CPh$ (O)	70%
5	$CH_3C\equiv C(CH_2)_8CH_2$ (OH)	$CH_3C\equiv C(CH_2)_8CH$ (O)	83%
6	$CH_3C\equiv C(CH_2)_8CHCH_3$ (OH)	$CH_3C\equiv C(CH_2)_8CCH_3$ (O)	56%
7	$CH_3C\equiv C(CH_2)_8CHPh$ (OH)	$CH_3C\equiv C(CH_2)_8CPh$ (O)	86%

[a] Isolated yields.

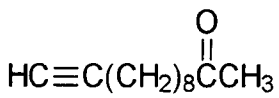
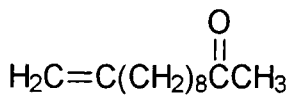
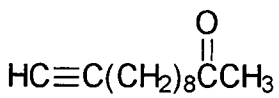
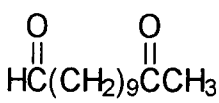
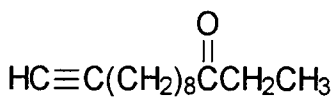
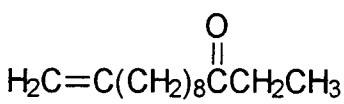
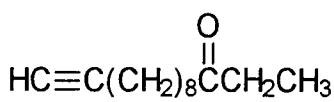
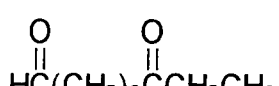
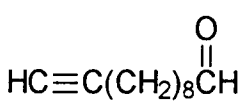
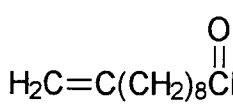
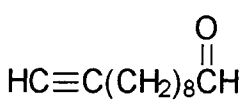
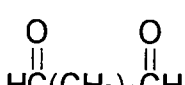
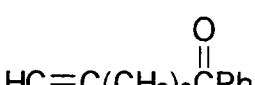
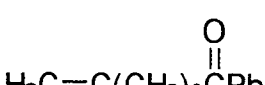
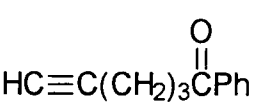
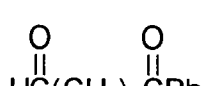


(eqn 4-4)

4.4 Investigation of the Reaction of Terminal Alkynyl Ketones and Aldehydes with Dicyclohexylborane

The results summarized in section 4.2 suggest that the triple bonds in terminal alkynyl ketones and aldehydes might be selectively hydroborated using dicyclohexylborane. A variety of terminal alkynyl carbonyl compounds were reacted with dicyclohexylborane to probe the ability of dicyclohexylborane to selectively hydroborate terminal alkynes in the presence of both aldehydes and ketones. One equivalent of the alkynyl carbonyl compound was added to one equivalent of dicyclohexylborane. The mixture was stirred at room temperature for one hour to complete the reaction. Two different methods, protonation with acetic acid and oxidation with sodium perborate, were used to quench the reactions. The corresponding olefinic ketones and aldehydes were obtained after protonation, and the corresponding dicarbonyl compounds were obtained after oxidation. The results are present in Table 4-2.

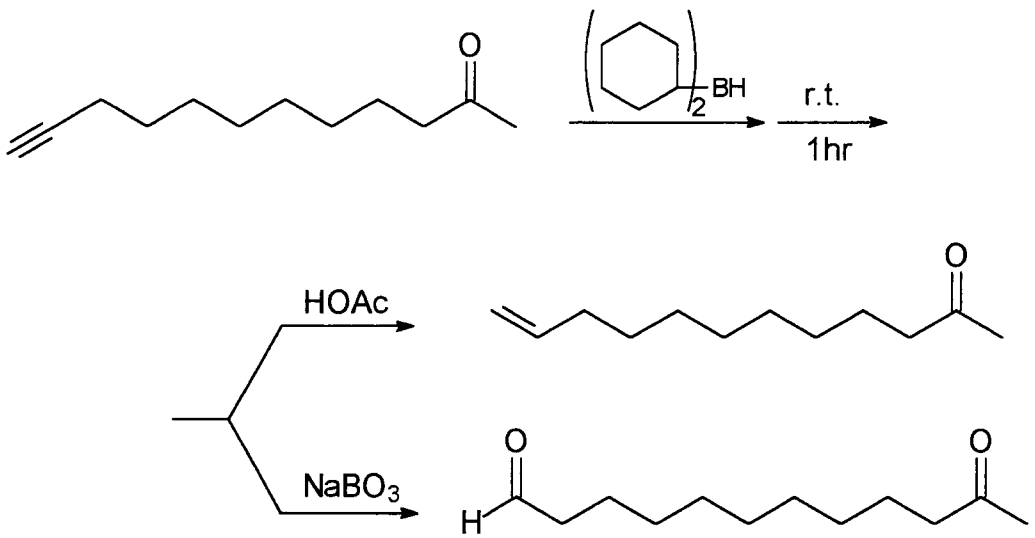
Table 4-2. The hydroboration of termianl alkynyl ketones and aldehdyes with dicyclohexylborane.

Entry	Substrate	Work-up	Product[a]	Yield (%)[b]
1		Protonation		94%
2		Oxidation		76%
3		Protonation		83%
4		Oxidation		68%
5		Protonation		90%
6		Oxidation		50%
7		Protonation		85%
8		Oxidation		50%

[a] Known compounds exhibited physical and spectral characteristics in accord with literature values, and new compounds were characterized by spectral and elemental analysis or HRMS.

[b] Isolated yields.

The data in Table 4-2 indicate that the terminal alkynyl group in alkynyl ketones and aldehydes can be selectively hydroborated without reducing the carbonyl group. For example, the reaction of 11-dodecyn-2-one with dicyclohexylborane gave 11-dodecen-2-one in 94% yield after protonation and 11-oxododecanal in 76% yield after oxidation (eqn 4-5). The carbon-carbon triple

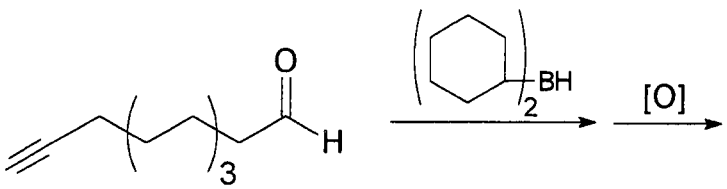


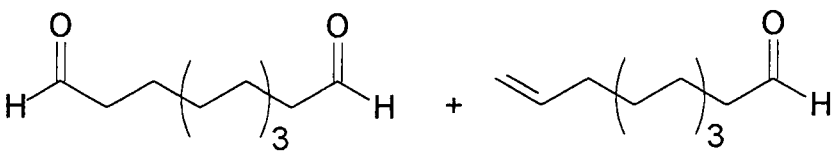
(eqn 4-5)

bond of 1-phenyl-5-hexyn-1-one was hydroborated without reducing the aromatic carbonyl moiety (entries 7 and 8, Table 4-2). Even in the presence of the aldehyde, the alkynyl group was selectively hydroborated to form the corresponding alkenyl aldehyde in excellent yield after protonation (entry 5 and 6, Table 4-2).

As can been seen by analyzing the data in Table 4-2, protonation with acetic acid afforded olefinic ketones and aldehydes in excellent yields, while

oxidation with sodium perborate gave dicarbonyl compound in good yields. One side reaction in the oxidation work-up involves the over-oxidation of aldehydes to the carboxylic acids; another side reaction involves the inadvertent protonation of the vinyl organoborane under the oxidation conditions. Several reagents were used to oxidize the intermediate organoborane (eqn 4-6). Up to 15% of the





Oxidant		
$NaBO_3 \cdot 4H_2O$	50%	15%
TMANO	40%	20%
Peracetic Acid	0%	90%

(eqn 4-6)

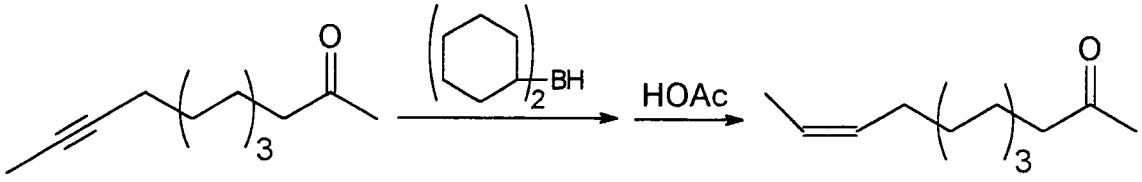
olefinic carbonyl compound was obtained after oxidation with sodium perborate. Oxidation with trimethylamine N-oxide (TMANO)[179] also resulted in the production of olefinic carbonyl compounds. Apparently the intermediate organoborane is susceptible to protonolysis even by a Lewis base. Oxidation with peracetic acid[180] in acetic acid gave only the protonation product. The

results summarized in equation 4-6, indicate that sodium perborate is the best oxidant.

4.5 Investigation on the Reaction of Internal Alkynyl Ketones and Aldehydes with Dicyclohexylborane

Internal alkynes are less reactive toward borane reagents than terminal alkynes due to steric effects. Thus, internal alkynes might compete with ketones and aldehydes less effectively than terminal alkynes for borane reagents. A variety of internal alkynyl ketones and aldehydes were allowed to react with dicyclohexylborane in order to evaluate the relative reactivities of the internal alkynyl moiety and the carbonyl moiety towards dicyclohyexylborane. One equivalent of alkynyl ketone or aldehyde was added to one equivalent of dicyclohexylborane. After stirring at room temperature for one hour, the reaction was quenched using acetic aicd (Table 4-3).

As shown in Table 4-3, internal alkynyl ketones and aldehydes can be successfully hydroborated by dicyclohexylborane. The reaction of 11-tridecyn-2-one with dicyclohexylborane afforded (*Z*)-11-tridecen-2-one in excellent yield after protonation with acetic acid (eqn 4-7). The carbon-carbon triple bond of 1-



(eqn 4-7)

Table 4-3. The hydroboration of internal alkynyl ketones and aldehdyes with dicyclohexylborane.

Entry	Substrate	Product[a]	Yield (%)[b]
1	$CH_3C{\equiv}C(CH_2)_8\overset{O}{\overset{\|\|}{C}}CH_3$	(Z)-$CH_3CH{=}CH(CH_2)_8\overset{O}{\overset{\|\|}{C}}CH_3$	88%
2	$CH_3C{\equiv}C(CH_2)_8\overset{O}{\overset{\|\|}{C}}H$	(Z)-$CH_3CH{=}CH(CH_2)_8\overset{O}{\overset{\|\|}{C}}H$	71%
3	$CH_3C{\equiv}C(CH_2)_8\overset{O}{\overset{\|\|}{C}}Ph$	(Z)-$CH_3CH{=}CH(CH_2)_8\overset{O}{\overset{\|\|}{C}}Ph$	90%

[a] Known compounds exhibited physical and spectral characteristics in accord with literature values, and new compounds were characterized by spectral and elemental analysis or HRMS.
[b] Isolated yields

phenyl-10-dodecyn-1-one was hydroborated by dicyclohexylborane without reducing the aromatic ketone. Even in the presence of a aldehyde, the internal alkynyl group was selectively hydroborated to form the (*Z*)-alkenyl aldehyde in high yield after protonation (entry 2, Table 4-3).

4.6 Conclusion

Both terminal and internal alkynyl ketones and aldehydes can be selectively hydroborated by dicyclohexylborane in the presence of the carbonyl group. The reaction affords the corresponding olefins in high yields after

protonation with acetic acid or the dicarbonyl compounds in good yields after oxidation with sodium perborate.

4.7 Experimental

All glassware, syringes and needles were dried in an oven heated to 250°C for at least 12 hours and cooled under argon prior to use. All solvents were dried and distilled prior to use. Alkynyl alcohols, obtained from Aldrich Chemical Company, were purified by distillation prior to use. All borane reagents and Grignard reagents were obtained from Aldrich Chemical Company, and were used as received. Reactions were magnetically stirred and monitored by TLC. Products were purified by flash chromatography.

All ^{1}H and ^{13}C NMR spectra were recorded on a 250 MHz Bruker AC250 spectrometer. Elemental analyses were performed by Atlantic Microlabs, Norcross, Georgia.

Synthesis of 10-undecynal[178]: To a stirred mixture of dry pyridinium chlorochromate (45 mmol, 9.7 g) in anhydrous methylene chloride (40 mL), 11-hydroxy-1-udecyne (30 mmol, 5.0 g) in anhydrous methylene chloride (4.0 mL) was added in one portion. The reaction mixture was stirred for 2-3 hours at ambient temperature. Then anhydrous ether (40 mL) was added and the supernatant solution decanted from the black gum. The residue was thoroughly washed with anhydrous ether, the ether washes combined and the ether removed under reduced pressure. 10-Undecynal (3.5 g, 70% yield) was isolated

by flash chromatography. ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 9.79 (s, 1H), 2.42 (dt, *J* = 6.8, 2.6 Hz, 2H), 2.18 (dt, *J* = 6.8, 2.4 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.75-1.21 (m, 12H); ^{13}C NMR ($CDCl_3$/TMS) δ (ppm): 212.54, 84.14, 68.10, 43.96, 31.87, 29.83, 29.20, 28.95, 28.64, 23.42, 18.78.

Synthesis of 11-dodecyn-2-one[178]: A well-stirred ethereal solution of methylmagnesium bromide (11 mmol, 3.8 mL of 3.0 M solution in ether) was placed in a dry, argon-flushed, round-bottomed flask, which was then immersed in an ice-water bath. 10-Undecynal (1.5 g, 9.0 mmol) in ether (10 mL) was added dropwise and the ice bath was then removed. The reaction mixture was stirred at room temperature overnight. The Grignard complex was decomposed by addition of a saturated aqueous ammonium chloride solution. The products were extracted into ether (3 × 20 mL), the ether extracts were combined and the solvent removed under reduced pressure. 11-Hydroxy-1-dodecyne (1.7 g) was obtained and was used without further purification.

11-Hydroxy-1-dodecyne (7.0 mmol, 1.7 g) was added in one portion to a stirred mixture of dry PCC (11 mmol, 2.3 g) in methylene chloride (10 mL). The reaction mixture was stirred for two days at room temperature. Anhydrous ether (10 mL) was added and the supernatant solution decanted from the black gum. The residue was thoroughly washed with anhydrous ether. The ether washes combined and the solvents removed under reduced pressure. The product, 11-dodecyn-2-one (0.74 g, 53% yield), was purified by flash chromatography. ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.42 (t, *J* = 7.3 Hz, 2H), 2.16 (dt, *J* = 6.8, 2.6 Hz,

2H), 2.13 (s, 3H), 1.94 (t, J = 2.6 Hz, 1H), 1.60-1.26 (m, 12H); ^{13}C NMR ($CDCl_3$/TMS) δ (ppm): 209.13, 84.62, 68.04, 43.70, 29.76, 29.18, 29.05, 28.84, 28.60, 28.38, 23.75, 18.32.

Synthesis of 12-tridecyn-3-one: A well-stirred ethereal solution of ethylmagnesium bromide (12 mmol, 4.0 mL of 3.0 M solution in ether) was placed in a dry, argon-flushed, round-bottomed flask which was then immersed in an ice-water bath. 10-Undecynal (1.6 g, 9.9 mmol) in ether (10 mL) was added dropwise and the ice bath was then removed. The reaction mixture was stirred at room temperature overnight. The Grignard complex was decomposed by addition of a saturated aqueous ammonium chloride solution. The mixture was extracted into ether (3 × 20 mL). The ether extracts were combined and the solvent was removed under reduced pressure. 11-Hydroxy-1-tridecyne (1.3 g) was obtained and was used without further purification.

Crude 11-hydroxy-1-tridecyne (6.7 mmol, 1.3 g) was added in one portion to a stirred mixture of dry PCC (10 mmol, 2.2 g) in methylene chloride (10 mL). The reaction mixture was stirred for two days at room temperature. Anhydrous ether (10 mL) was added and the supernatant solution decanted from the black gum. The residue was thoroughly washed with anhydrous ether (3 × 20 mL). The ether washes combined and the solvents removed under reduced pressure. The product, 12-tridecyn-3-one (1.13 g, 86% yield), was purified by flash chromatography. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 2.41 (t, J = 7.3 Hz, 4H), 2.16 (dt, J = 6.8, 2.6 Hz, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.57-1.30 (m, 12H), 1.05 (t, J =

7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$/TMS) δ (ppm): 211.59, 84.46, 67.95, 42.22, 35.68, 29.06, 28.77, 28.51, 28.29, 23.73, 18.21, 7.67.

Synthesis of 1-phenyl-5-hexyn-1-one[181]: 5-Hexynal was prepared via oxidation of 6-hydroxy-1-hexyne (51 mmol, 5.0g) with PCC (76 mmol, 16 g) in methylene chloride (60 mL) using the procedure described above. The crude 5-hexynal (1.0 g) was obtained and was used without further purification.

A well-stirred ethereal solution of phenylmagnesium bromide (13 mmol, 4.2 mL of 3.0 M solution in ether) was placed in a dry, argon-flushed, round-bottomed flask, which was then immersed in an ice-water bath. The crude 5-hexynal (1.0 g, 10 mmol) in ether (10 mL) was added dropwise and the ice bath was then removed. The reaction mixture was stirred at room temperature overnight. The Grignard complex was decomposed by addition of a saturated aqueous ammonium chloride solution. The mixture was extracted into ether (3 × 20 mL). The ether extracts were combined and the solvent was removed under reduced pressure. 6-Phenyl-6-hydroxy-1-hexyne (1.2 g) was obtained and was used without further purification.

Crude 6-phenyl-6-hydroxy-1-hexyne (6.6 mmol, 1.2 g) was added in one portion to a stirred mixture of dry PCC (10 mmol, 2.2 g) in methylene chloride (10 mL). The reaction mixture was stirred for overnight at room temperature. Anhydrous ether (10 mL) was added and the supernatant solution decanted from the black gum. The residue was thoroughly washed with anhydrous ether (3 × 20 mL). The ether washes combined and the solvents removed under reduced

pressure. The product, 1-phenyl-5-hexyn-1-one (0.83 g, 71% yield), was obtained by flash chromatography. ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 7.97 (d, J = 7.3 Hz, 2H), 7.58-7.42 (m, 3H), 3.12 (t, J = 7.1Hz, 2H), 2.33 (dt, J = 6.9, 2.5 Hz, 2H), 2.02-1.91 (m, 3H); ^{13}C NMR ($CDCl_3$/TMS) δ (ppm): 199.39, 136.83, 132.95, 128.49, 127.92, 83.63, 69.07, 36.91, 22.65, 17.81.

Synthesis of 10-dodecynal: 10-Dodecynal was prepared via the oxidation of 12-hydroxy-2-dodecyne (27 mmol, 5.0 g) with PCC (42 mmol, 8.9 g) in methylene chloride (40 mL) using the general procedure. The product, 10-dodecynal (4.2 g, 83% yield), was obtained by flash chromatography. ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 9.76 (t, J = 1.8 Hz, 1H), 2.43 (dt, J = 7.3, 1.8 Hz, 2H), 2.13-2.08 (m, 2H), 1.77 (t, J = 2.5 Hz, 3H), 1.66-1.60 (m, 2H), 1.47-1.32 (m, 10H); ^{13}C NMR ($CDCl_3$/TMS) δ (ppm): 202.70, 79.13, 75.19, 43.74, 33.84, 29.11, 28.90, 28.66, 24.56, 21.93, 18.56, 3.28.

Synthesis of 11-tridecyn-2-one: A well-stirred ethereal solution of methylmagnesium bromide (11 mmol, 3.7 mL of 3.0 M solution in ether) was placed in a dry, argon-flushed, round-bottomed flask, which was then immersed in an ice-water bath. 11-Dodecynal (1.6 g, 8.8 mmol) in ether (10 mL) was added dropwise and the ice bath was then removed. The reaction mixture was stirred at room temperature overnight. The Grignard complex was decomposed by addition of a saturated aqueous ammonium chloride solution. The mixture was extracted into ether (3 × 20 mL). The ether extracts were combined and the

solvent was removed under reduced pressure. 12-Hydroxy-2-tridecyne (1.2 g) was obtained and was used without further purification.

12-Hydroxy-2-tridecyne (6.0 mmol, 1.19 g) was added in one portion to a stirred mixture of dry PCC (10.0 mmol, 2.15 g) in methylene chloride (10 mL). The reaction mixture was stirred for two days at room temperature. Anhydrous ether (10 mL) was added and the supernatant solution decanted from the black gum. The residue was thoroughly washed with anhydrous ether (3 × 20 mL). The ether washes combined and the solvents removed under reduced pressure. The product, 11-tridecyn-2-one (0.67 g, 56% yield), was obtained by flash chromatography. ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.42 (t, J = 7.3 Hz, 2H), 2.13-2.08 (m, 5H), 1.78 (t, J = 2.5 Hz, 3H), 1.59-1.30 (m, 12H); ^{13}C NMR ($CDCl_3$/TMS) δ (ppm): 209.19, 79.27, 75.27, 43.73, 29.75, 29.23, 28.99, 28.76, 23.78, 18.65, 3.39.

Synthesis of 1- phenyl-10-dodecyn-1-one: A well-stirred ethereal solution of phenylmagnesium bromide (9.1 mmol, 3.0 mL of 3.0 M solution in ether) was placed in a dry, argon-flushed, round-bottomed flask, which was then immersed in an ice-water bath. 10-Dodecynal (8.3 mmol, 1.5 g) in ether (10 mL) was added dropwise and the ice bath was then removed. The reaction mixture was stirred at room temperature overnight. The Grignard complex was decomposed by addition of a saturated aqueous ammonium chloride solution. The mixture was extracted into ether (3 × 20 mL). The ether extracts were combined and the solvent was removed under reduced pressure. 12-Phenyl-12-

hydroxy-2-dodecyne (1.63 g) was obtained and was used without further purification.

12-Phenyl-12-hydroxy-2-dodecyne (6.3 mmol, 1.6 g) was added in one portion to a stirred mixture of dry PCC (12 mmol, 2.5 g) in methylene chloride (15 mL). The reaction mixture was stirred for overnight at room temperature. Anhydrous ether (10 mL) was added and the supernatant solution decanted from the black gum. The residue was thoroughly washed with anhydrous ether (3 × 20 mL). The ether washes combined and the solvents removed under reduced pressure. The product, 1-phenyl-10-dodecyn-1-one (1.3 g, 86% yield), was obtained by flash chromatography. ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 7.98-7.94 (m, 2H), 7.58-7.41 (m, 3H), 2.95 (t, J = 7.1Hz, 2H), 2.14-2.07 (m, 2H), 1.78-1.67(m, 5H), 1.46-1.34 (m, 10H); ^{13}C NMR ($CDCl_3$/TMS) δ (ppm): 200.40, 137.04, 132.77, 128.46, 127.97, 79.27, 75.25, 38.52, 29.28, 28.98, 28.78, 24.28, 3.89.

General procedure for the preparation of alkenyl carbonyl compounds and dicarbonyl compounds. The hydroboration of 11-dodecyn-2-one is representative: BH_3•THF (2.0 mmol, 2.0 ml of a 1.0 M solution in THF) was placed in a dry, argon-flushed flask which was then immersed in an ice-water bath. Cyclohexene (4.0 mmol, 0.33g, 0.41 ml) was added dropwise and the mixture stirred at 0 °C for 1 hour to form dicyclohexylborane. 11-Dodecyn-2-one (2.0 mmol, 0.36 g) was then added to the slurry of dicyclohexylborane in THF. The cooling bath was removed and the mixture stirred for 1 hour at room temperature. Protonation was achieved by

adding glacial acetic acid (1.0 ml) and stirring the mixture at room temperature for 1 hour. 11-Dodecen-2-one[182] (0.34 g, 94% yield) was isolated after work up. ^{1}H NMR δ ppm: 5.88-5.72 (*m*, 1H), 5.02-4.90 (*m*, 2H), 2.41 (*t*, *J* = 7.4 Hz; 2H), 2.13 (*s*, 3H), 2.03 (*q*, *J* = 6.8 Hz, 2H), 1.56 (*m*, 2H), 1.28 (*m*, 10H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 209.08, 139.05 114.06, 43.70, 33.71, 29.72, 29.25 (29.25), 29.09, 29.00, 28.83, 23.78. Alternatively, oxidation could be achieved by adding of $NaBO_3 \bullet 4H_2O$ (6.0 mmol, 0.92 g) and water (2 ml) and stirring the mixture at room temperature for 2 hours. 11-Oxododecanal[183] (0.30 g, 76% yield) was isolated after work up. ^{1}H NMR δ ppm: 9.76 (*t*, *J* = 1.9 Hz, 1H), 2.45-2.39 (*m*, 4H), 2.14 (*s*, 3H), 1.62-1.56 (*m*, 4H), 1.29 (*m*, 10H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 209.07 202.64, 43.71, 43.58, 29.65, 29.10, 28.95, 23.65, 21.89.

Synthesis of 12-tridecen-3-one[176]: 12-Tridecen-3-one was prepared from the reaction of 12-tridecyn-3-one (2.0 mmol, 0.39 g) with dicyclohexylborane (2.0 mmol) in THF after protonation with acetic acid (1 mL). The procedure was the same as previously described. Yield 83% ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 5.85-5.72 (*m*, 1H), 5.03-4.90 (*m*, 2H), 2.46-2.36 (*m*, 4H), 2.03 (*q*, *J* = 6.9 Hz, 2H), 1.62-1.54 (*m*, 2H), 1.28 (*m*, 10H), 1.05 (*t*, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 211.81, 139.08, 114.06, 42.36, 35.78, 33.72, 29.23 (29.23), 29.00 (29.00), 28.84, 23.87, 7.77.

Synthesis of 11-oxotridecanal[184]: 11-Oxotridecanal was prepared from the reaction of 12-tridecyn-3-one (2.0 mmol, 0.39 g) with dicyclohexylborane (2.0 mmol) in THF after oxidation with $NaBO_3 \bullet H_2O$ (6.0 mmol, 0.92 g) and water (2 ml). The procedure was the same as previously described. Yield 68%. ^1H NMR ($CDCl_3$/TMS) δ ppm: 9.76 (*t*, *J* = 1.7 Hz, 1H) 2.46-2.37 (*m*, 6H), 1.59 (*m*, 4H), 1.29 (*br s*, 10H), 1.04 (*t*, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 211.52, 202.50, 43.64, 42.12, 35.58, 29.00, 23.66, 21.81, 7.58.

Synthesis of 10-undecenal[185]: 10-Undecenal was prepared from the reaction of 10-undecynal (2.0 mmol, 0.33 g) with dicyclohexylborane (2.0 mmol) in THF after protonation with acetic acid (1 mL). The procedure was the same as previously described. Yield 90%. ^1H NMR ($CDCl_3$/TMS) δ ppm: 9.76 (*t*, *J* = 1.9Hz, 1H), 5.89-5.73 (*m*, 1H), 5.03-4.90 (*m*, 2H), 2.42 (*dt*, *J* = 7.3, 1.9 Hz, 2H), 2.08-2.00 (*m*, 2H), 1.66-1.57 (*m*, 2H), 1.30 (*m*, 10H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 202.80, 139.08, 114.12, 43.87, 33.73, 29.23 (29.23), 29.11, 29.00, 28.84, 22.03.

Synthesis of 1,11-undecanedial[186]: 1,11-Undecanedial was prepared from the reaction of 10-undecynal (2.0 mmol, 0.33 g) with dicyclohexylborane (2.0 mmol) in THF after oxidation with $NaBO_3 \bullet H_2O$ (6.0 mmol, 0.92 g) and water (2 ml). The procedure was the same as previously described. Yield 50%. ^1H NMR ($CDCl_3$/TMS) δ ppm: 9.76 (*t*, *J* = 1.6 Hz, 2H), 2.42 (*dt*, *J* = 7.3, 1.6 Hz, 4H), 1.62

(*m*, 4H), 1.30 (*br s*, 10H); ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 202.74, 43.72, 29.10, 29.01, 28.97, 21.89.

Synthesis of 1-phenyl-5-hexen-1-one[187]: 1-Phenyl-5-hexen-1-one was prepared from the reaction of 1-Phenyl-5-hexyn-1-one (2.0 mmol, 0.51 g) with dicyclohexylborane (2.0 mmol) in THF after protonation with acetic acid (1.0 mL). The procedure was the same as previously described. Yield 85%, ^1H NMR ($CDCl_3$/TMS) δ ppm: 7.94 (*m*, 2H), 7.57-7.41 (*m*, 3H), 5.90-5.74 (*m*, 1H), 5.08-4.97 (*m*, 2H), 2.97 (*t*, *J* = 7.3 Hz, 2H), 2.15 (*q*, *J* = 7.3Hz, 2H), 1.84 (*p*, *J* = 7.3 Hz, 2H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 200.07, 137.95, 136.98, 132.80, 128.46, 127.92, 115.18, 37.60, 33.10, 23.21.

Synthesis of 6-oxo-6-phenylhexanal[188]: 6-Oxo-6-phenylhexanal was prepared from the reaction of 1-phenyl-5-hexyn-1-one (2.0 mmol, 0.51 g) with dicyclohexylborane (2.0 mmol) in THF after oxidation with $NaBO_3 \bullet H_2O$ (6.0 mmol, 0.92 g) and water (2.0 ml). The procedure was the same as previously described. Yield 66%. ^1H NMR ($CDCl_3$/TMS) δ ppm: 9.78 (*t*, *J* = 1.4 Hz, 1H), 7.96-7.93 (*m*, 2H), 7.59-7.43 (*m*, 3H), 3.03 (*t*, *J* = 6.8 Hz, 2H), 2.53-2.48 (*m*, 2H), 1.76-1.72 (*m*, 4H), ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 202.19, 199.69, 136.77, 132.94, 128.49, 127.89, 43.61, 38.00, 23.50, 21.59.

Synthesis of (*Z*)-10-dodecenal: (*Z*)-10-Dodecenal was prepared from the reaction of 10-dodecynal (2.0 mmol, 0.36 g) with dicyclohexylborane (2.0 mmol)

in THF after protonation with acetic acid (1.0 mL). The procedure was the same as previously described. Yield 71%. ^{1}H NMR δ ppm: 9.76 (*t*, *J* = 1.9 Hz, 1H). 5.43-5.41 (*m*, 2H), 2.42 (*dt*, *J* = 7.3, 1.9Hz, 2H), 2.07-1.98 (*m*, 2H), 1..78-1.53 (*m*, 5H) 1.30 (*br s*, 10H). ^{13}C NMR δ ppm: 202.82, 130.76, 123.63, 43.86, 29.45, 29.30 (29.30), 29.16, 26.79, 23.80, 22.06, 12.50. HRMS Calcd. for $C_{12}H_{22}O$. 182.167. Found: 182.167.

Synthesis of (*Z*)-11-tridecen-2-one: (*Z*)-11-Tridecen-2-one was prepared from the reaction of 11-tridecyn-2-one (2.0 mmol, 0.39 g) with dicyclohexylborane (2.0 mmol) in THF after protonation with acetic acid (1.0 mL). The procedure was the same as previously described. Yield 88%. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 5.47-5.32 (*m*, 2H), 2.41 (*t*, *J* = 7.4 Hz, 2H), 2.13 (*s*, 3H), 2.03-1.98 (*m*, 2H), 1.61-1.54 (*m*, 5H), 1.28 (*br s*, 10H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 209.19, 130.72, 123.53, 43.70, 29.72, 29.42, 29.27 (29.27), 29.10 (29.10), 26.72, 23.78, 12.64, HRMS Calcd for $C_{13}H_{24}O$ 196.182. Found 196.182.

Synthesis of 1-pheny-(*Z*)-10-dodecen-1-one: 1-Pheny-(*Z*)-10-dodecen-1-one was prepared from the reaction of 1-pheny-10-dodecen-1-one (2.0 mmol, 0.51 g) with dicyclohexylborane (2.0 mmol) in THF after protonation with acetic acid (1 mL). The procedure was the same as previously described. Yield 92%. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 7.98-7.94 (*m*, 2H), 7.58-7.41 (*m*, 3H), 5.47-5.35 (*m*, 2H), 2.96 (*t*, *J* = 7.2 Hz, 2H), 2.04-1.99 (*m*, 2H), 1.78-1.68 (*m*, 2H), 1.61-1.58 (*m*, 3H), 1.43-1.20 (*m*, 10H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 200.49, 137.07,

132.77, 130.77, 128.47 (128.47), 127.99 (127.99), 123.56, 38.55, 29.33 (29.33, 29.33), 29.18 (29.18), 26.77, 24.32, 12.50, Anal. Calcd. for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found, C 83.73; H, 10.20.

Chapter 5. The Reaction of α, β-Acetylenic Ketones with Dicylohexylborane: Stereoselective Synthesis of Functionalized Trisubstituted Olefins

5.1 Introduction

Trisubstituted olefins have been found in many naturally occurring biologically active compounds[189] such as terpenoids, pheromones, marolide antibiotics, marine products, etc. Examples (Figure 5-1) include the sex attractant propylure of the pink bollworm moth[190], farnesylacetone[191] which is an inhibitor of amino acid incorporation in a crab, the antibiotic conocandin[192] from a strain of *Hromococcus conorum*, and the antibiotic grifolin[193] from the mushroom

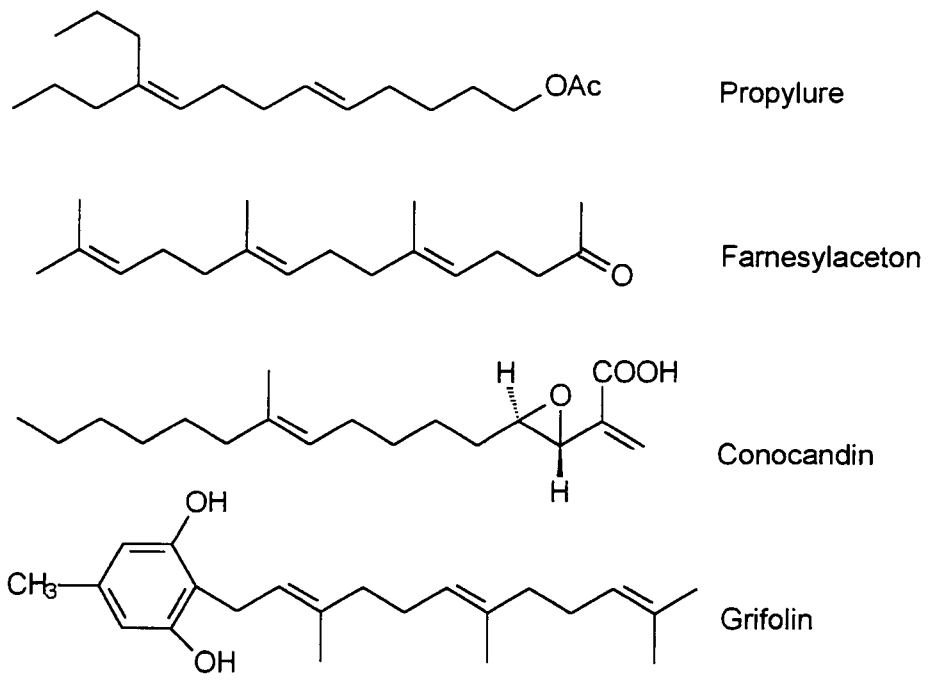
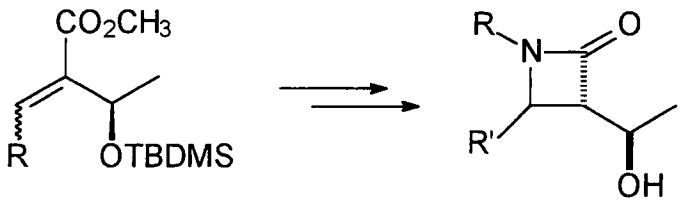


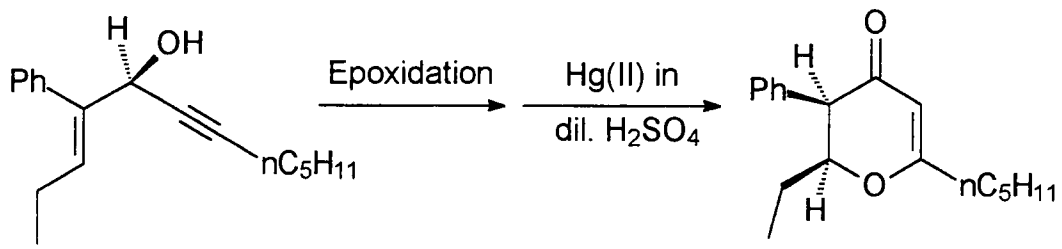
Figure 5-1. Some naturally occurring trisubstituted olefins

Albatrellus confluens. In addition to their importance in nature, trisubstituted olefins are key intermediates for further transformations leading to natural products[194]. For example, methyl 2-(1-(((1,1-dimethylethyl)dimethylsilyl)-oxy)ethyl)-2-butenoate is the key intermediate for the synthesis of the precursor of carbapenem antibiotics (eqn 5-1). 1-Alkynyl-2-alken-1-ols are the



(eqn 5-1)

intermediates for the preparation of 2,3-hydro-4*H*-pyran-4-ones which are present in many natural products (eqn 5-2). The ability to form carbon-carbon



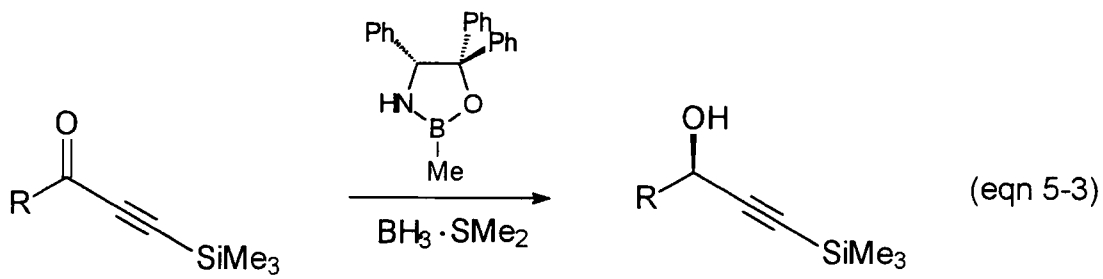
(eqn 5-2)

bonds rationally is the object of continuing vigorous research[195]. In this chapter, the synthesis of stereodefined, highly functionalized, trisubstituted olefins by the reaction of α,β-acetylenic ketones with dicyclohexylborane will be described.

5.2 The Reaction of α,β-Acetylenic Ketones with Dicyclohexylborane Trapped by Starting Ketones.

5.2.1 Introduction

As discussed in previous chapters, the carbon-carbon double bonds of unconjugated olefinic ketones and aldehydes can be selectively hydroborated by dicyclohexylborane. The carbon-carbon triple bonds of unconjugated alkynyl ketones and aldehydes can be also selectively hydroborated by dicyclohexylborane. However, the reactions of α,β-unsaturated ketones and aldehydes with various boron reagents proceed in different fashions. For example, Trombini and his coworkers reported that conjugated olefinic ketones react stereoselectively with dicyclohexylborane or (-)-diisopinocampheylborane to form boron enolates[196]. The carbonyl group in α,β-olefinic ketones is simply reduced by 9-BBN[118]. Enantioenriched propargylic alcohols have been obtained by reduction of α,β-acetylenic ketones using several different boron reagents, such as β-isopinocampheyl-9-BBN[197], B-chlorodiisopino-campheylborane[198] and BMS in the presence of chiral B-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine

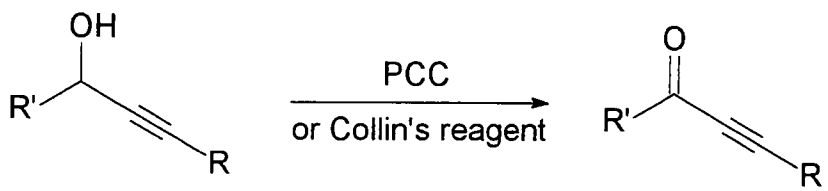


(eqn 5-3)

(eqn 5-3)[199]. However, to the best of our knowledge, no report on the reactions of α,β-acetylenic ketones with dialkylboranes other than 9-BBN has appeared in the literature.

5.2.2 The Synthesis of α,β-Acetylenic Ketones

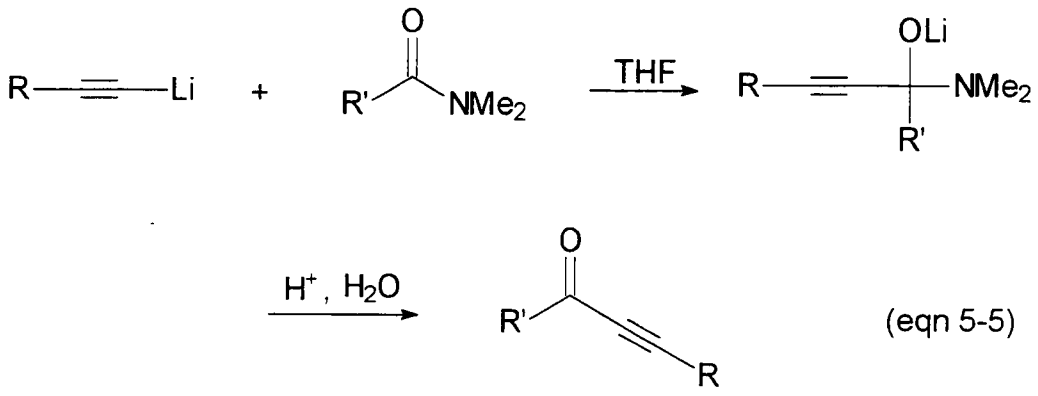
The most straightforward method for preparing α,β-acetylenic ketones is to oxidize the α,β-acetylenic alcohols since α,β-acetylenic alcohols are commercial available. However, the yields are low when α,β-acetylenic alcohols react with PCC or Collin's reagent (eqn 5-4)[177,178].



(eqn 5-4)

low yield

Acetylenic ketones can also be prepared by acetylation of acetylenes. The reaction of lithiated acetylenes with N,N-dialkylcarboxamides affords α,β-acetylenic ketones in good yield after the treatment with aqueous mineral acid (eqn 5-5, Table 5-1)[200]. N,N-Dimethylacetamide is inexpensive, commercially available. N,N- Dimethylbenzamide is also commercially available or can be readily prepared from the commercially available acid chlorides. Thus C(=O)Me and C(=O)Ph groups are readily introduced into the α,β-acetylenic ketones using this method.

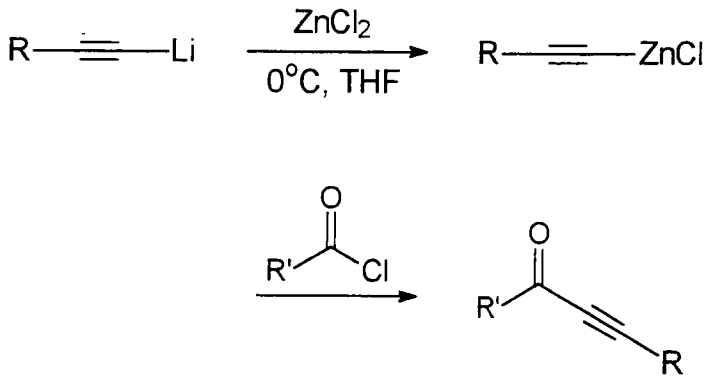


(eqn 5-5)

Table 5-1. The syntheses of α,β-acetylenic ketones from the reaction of alkynylithiums and *N,N*-dimethylcarboxamides.

Entry	Alkyne	Amide	Product	yield
1	$CH_3(CH_2)_5C{\equiv}CH$	$CH_3\overset{\overset{O}{\|}}{C}N(CH_3)_2$	$CH_3(CH_2)_5C{\equiv}C\overset{\overset{O}{\|}}{C}CH_3$	58%
2	$CH_3(CH_2)_2C{\equiv}CH$	$CH_3\overset{\overset{O}{\|}}{C}N(CH_3)_2$	$CH_3(CH_2)_2C{\equiv}C\overset{\overset{O}{\|}}{C}CH_3$	60%
3	$CH_3(CH_2)_2C{\equiv}CH$	$PhC(=O)N(CH_3)_2$	$CH_3(CH_2)_2C{\equiv}CC(=O)Ph$	65%
4	$(CH_3)_3CC{\equiv}CH$	$PhC(=O)N(CH_3)_2$	$(CH_3)_3CC{\equiv}CC(=O)Ph$	40%

α,β-Acetylenic ketones can also be prepared by the reaction of alkynylzinc chloride with acid chloride (eqn 5-6)[200]. Since a variety of acid chlorides



(eqn5-6)

are commercial available, this reaction provides a larger variety of carbonyl group. Solutions of alkynylzinc chloride, readily made from alkynyllithium and an equivalent amount of anhydrous zinc chloride in THF, reacted smoothly with acid chlorides. The reactions generally occurred at 20 °C except for the reaction of pivaloyl chloride which occurred at about 40 °C. A variety of α,β-acetylenic ketones were obtained in good yields (Table 5-2).

5.2.3 The Syntheses of Highly Functionalized Trisubstituted Olefins via the Reaction of α,β-Acetylenic Ketones with Dicyclohexylborane.

The reactions of α,β-acetylenic ketones with borane reagents offer three possible reaction pathways. Reduction of the carbonyl group produces propargylic alcohols, while 1,2-addition to the carbon-carbon double bond leads to α- or β-borylated ketones. 1,4-Addition to α,β-acetylenic ketones is also

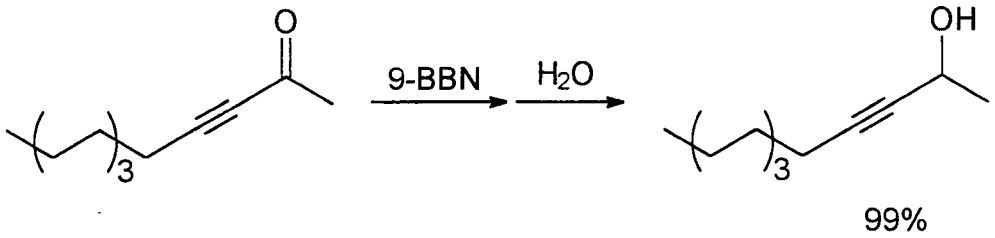
Table 5-2. The syntheses of α,β-acetylenic ketones from the reaction of alkynylzinc chlorides and acid chlorides.

Entry	Alkyne	Acid chlorides	Product	yield[a]
1	$CH_3(CH_2)_2C{\equiv}CH$	$(c\text{-}C_3H_5)\overset{O}{\overset{\|\|}{C}}Cl$	$(c\text{-}C_3H_5)\overset{O}{\overset{\|\|}{C}}C{\equiv}C(CH_2)_2CH_3$	92%
2	$CH_3(CH_2)_3C{\equiv}CH$	$(CH_3)_3C\overset{O}{\overset{\|\|}{C}}Cl$	$(CH_3)_3C\overset{O}{\overset{\|\|}{C}}C{\equiv}C(CH_2)_3CH_3$	95%
3	$PhC{\equiv}CH$	$(CH_3)_2CH\overset{O}{\overset{\|\|}{C}}Cl$	$(CH_3)_2CH\overset{O}{\overset{\|\|}{C}}C{\equiv}CPh$	85%
4[b]	$CH_3(CH_2)_2C{\equiv}CH$	$ClC(CH_2)_3C$ (O, O) Cl	$CH_2CC{\equiv}(CH_2)_2CH_3$ (O) / CH_2 / $CH_2CC{\equiv}C(CH_2)_2CH_3$ (O)	54%

[a] Isolated yields

[b] Two equivalent of alkyne and one equivalent of acid chloride were used.

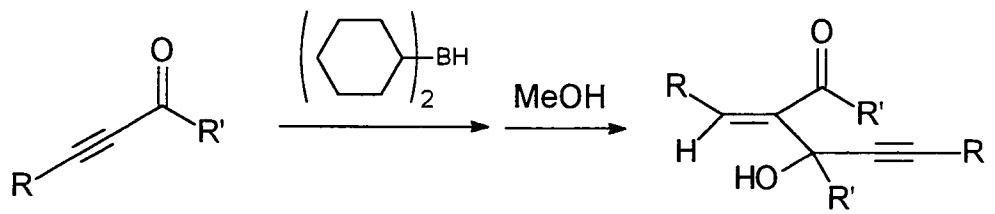
possible. As noted in the earlier chapters, dicyclohexylborane normally favors the carbon-carbon multiple bonds in non-conjugated unsaturated carbonyl compounds to yield hydroboration products whereas 9-BBN in more reactive toward the carbonyl groups. The reaction of 3-dodecyn-2-one with 9-BBN gave the reduction product, 3-dodecyn-2-ol, in 99% yield (eqn 5-7). The reaction of



99%

(eqn 5-7)

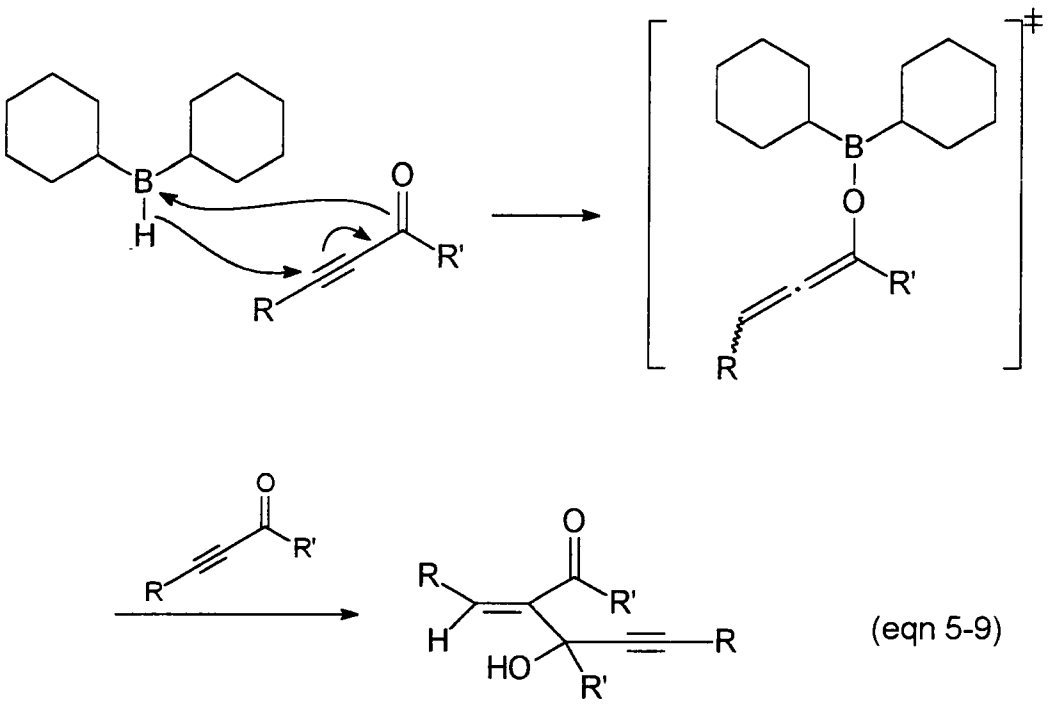
a molar equivalent of 3-heptyn-2-one with dicyclohexylborane gave complex results. However, when two molar equivalents of 3-heptyn-2-one were added to a slurry of dicyclohexylborane in THF at 0 °C, the reaction became clear and the only product isolated was 7-acetyl-6-hydroxy-6-methyl-7-undecan-4-yne after the reaction was quenched with methanol (eqn 5-8). Presumably, dicyclohexylborane added to 3-heptyn-2-one in an 1,4-fashion. The



(eqn 5-8)

corresponding allenoxyborinate was produced, and then underwent an aldol condensation with another mole of starting ketone (eqn 5-9).

To optimize the reaction conditions, the effects of reaction temperatures, solvents and stoichiometry were studied. The reaction of two molar equivalents



(eqn 5-9)

of 3-heptyn-2-one with a slurry of dicyclohexylborane in THF, which was prepared via the reaction of the one molar equivalent of BH_3•THF with two molar equivalent of cyclohexene, was carried out at different temperatures. The results are summarized in Table 5-3.

As shown in Table 5-3, temperature has little effect on the yield of the reaction of α,β-acetylenic ketones with dicyclohexylborane. It does affect the rate, thus the reaction does not occur at -78°C. The reaction at room temperature forms the product faster than the reaction at 0°C, thus room temperature was chosen for the study.

The effect of solvents on the reaction was evaluated by carrying out the reaction in different solvents. The results are presented in Table 5-4. As shown in

Table 5-4, the solvents had little effect on the reaction of α,β-acetylenic ketones with dicyclohexylborane.

Table 5-3. The reaction of 3-heptyn-2-one with dicyclohexylborane at different temperatures.

Entry	Reaction Temperature	yield[a]
1	0°C -> r.t., r.t. for 1 hr.	45%
2	0°C for 2 hr.	45%
3	-78°C, overnight	--[b]
4	-78°C -> r.t., r.t. for 1 hr.	45%

[a] Isolated yields.

[b] No reaction occurred.

Table 5-4. The reaction of 3-heptyn-2-one with dicyclohexylborane in different solvents.

Entry	Solvents	Yield[a]
1	THF	45%
2	CH_2Cl_2	45%
3	pentane	45%

[a] Isolated Yields.

Then 3-heptyn-2-one was allowed to react with excess dicyclohexylborane to investigate the stoichiometry of the reaction. One molar equivalent of 3-

heptyn-2-one was reacted with a slurry of dicyclohexylborane in THF, which was prepared from the reaction of 1.25 molar equivalent of BH_3•THF with 2.5 molar equivalent of cyclohexene. The yield of this reaction increased to 62% when 25% excess of boron hydride was used. This may indicate that the conjugate addition of the dicyclohexylborane is not quantitative.

A variety of α,β-acetylenic ketones (2 molar equivalents) were then allowed to react with dicyclohexylborane in THF, which was prepared from the reaction of 1.25 molar equivalents of BH_3•THF with 2.5 molar equivalents of cyclohexene, at room temperature. The results are presented in the Table 5-5.

As shown in Table 5-5, the expected products were obtained in good yields in all cases except that in which 2,2-dimethyl-4-nonyn-3-one (Entry 8, Table 5-5) was used as a substrate. The lack of reactivity could be due to the steric hindrance generated by the bulky tertiary butyl group which keeps the carbonyl group from reacting with the allenoxyborinate.

In the reaction of 4,11-pentadecadiyn-6,10-dione with dicyclohexylborane (Entry 7, Table 5-5), the intramolecular reaction competed with the intermolecular reaction. It was felt that diluting the reactants would benefit the intramolecular reaction. The reaction was carried out using different concentrations of 4,11-pentadecadiyn-6,10-dione to study the effect of concentration on the yield of desired product (Table 5-6). As can be seen by examining the data in Table 5-6, diluting the reactant increased the yield of desired product. When the reactant was diluted to 0.1M, the highest yield of desired product was obtained. Lowering the concentration further did not increase the yield of the reaction.

Table 5-5. The reaction of α,β-acetylenic ketones with dicyclohexylborane.

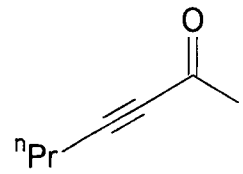
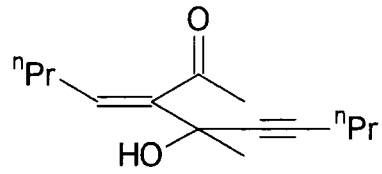
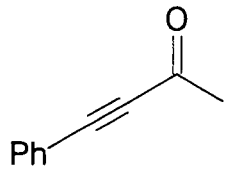
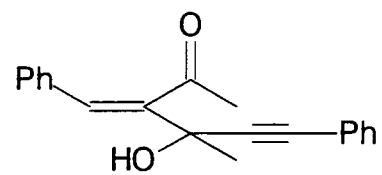
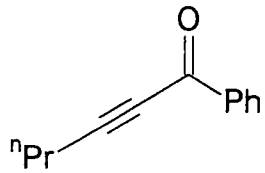
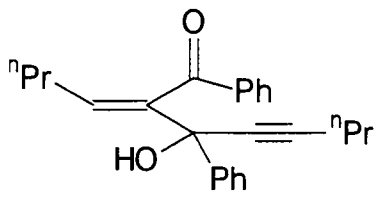
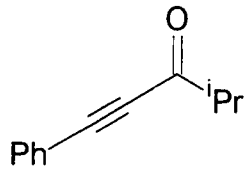
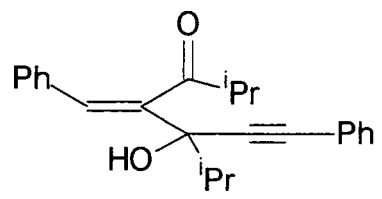
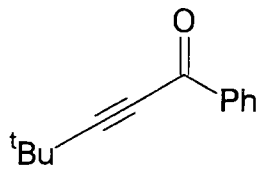
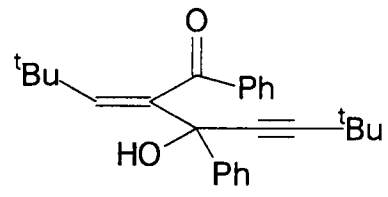
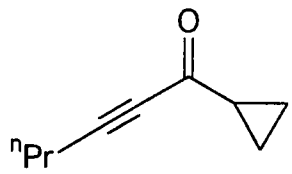
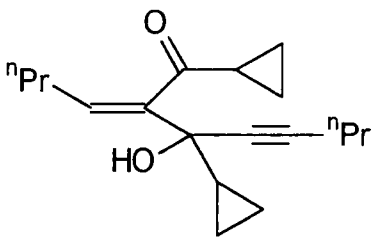
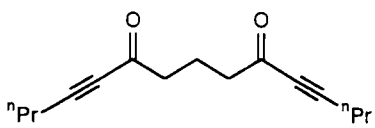
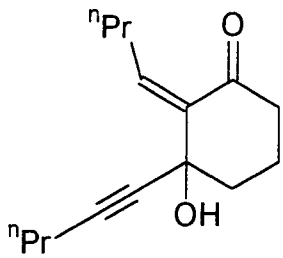
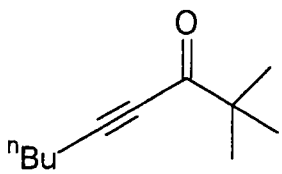
Entry	Substrate	Product	Yield
1			62%
2			72%
3			78%
4			72%
5			78%

Table 5-5. The reaction of α,β-acetylenic ketones with dicyclohexylborane (continued).

Entry	Substrate	Product[a]	Yield[b]
6			66%
7			55%
8[c]		----	--

[a] All new compounds were characterized by spectral and elemental analysis or HRMS.

[b] Isolated yields.

[c] None of the desired product was obtained.

Table 5-6. The reaction of dicyclohexylborane with 4,11-pentadecadiyn-6,10-dione in different concentrations.

Entry	Concentration of 4,11-pentadecadiyn-6,10-dione	Yield
1	0.7M	36%
2	0.3M	47%
3	0.1M	55%
4	0.05M	54%

Interestingly, the ^{1}H and ^{13}C NMR spectra of all products suggest that only one isomer is formed. The stereochemistry of the products was determined by NOESY NMR experiments. For example, the NOESY spectrum (Figure 5-2) of 7-acetyl-6-hydroxy-6-methyl-7-undecen-4-yne (Entry 1, Table 5-5) exhibited the diagnostic NOE cross peak between the olefinic proton (δ 6.04 ppm) and the methyl group (δ 1.63 ppm) on the hydroxyl substituted carbon. On the other hand, no NOE cross peak was observed between the olefinic proton and the methyl group (δ 2.41 ppm) of the acetyl group. Moreover, the methylene group (δ 2.20 ppm) next to the carbon-carbon double bond exibihited no NOE cross peak with the methyl group on the hydroxyl substituted carbon but a NOE cross peak with the methyl group of the acetyl group was observed. The data support a stereochemistry in which the olefinic proton is *trans* to the acetyl group. Presumably, the reaction of the allenoxyborinates with 3-heptyn-2-one occurs via a six-membered transition state in which the *n*-propyl group of the

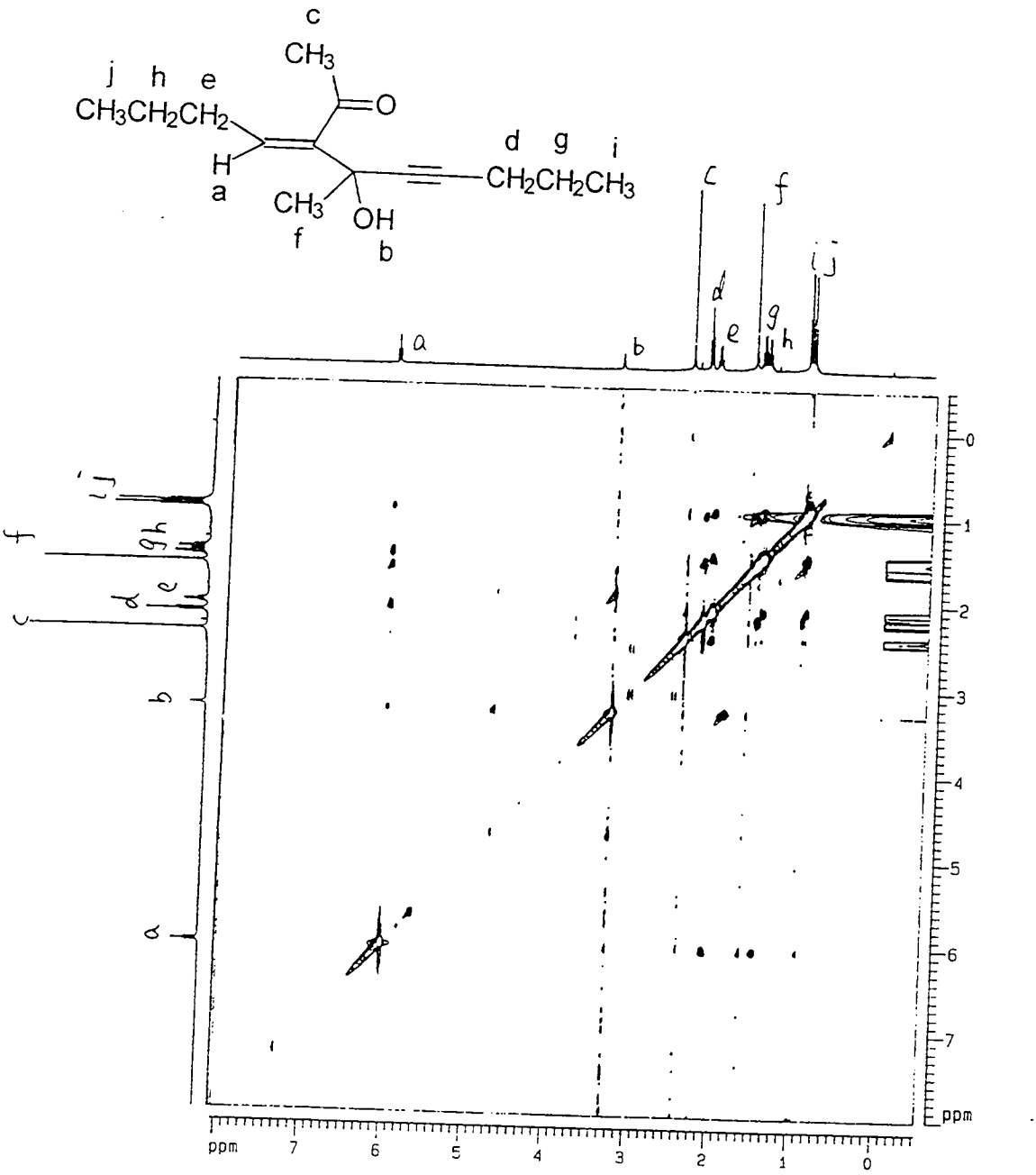
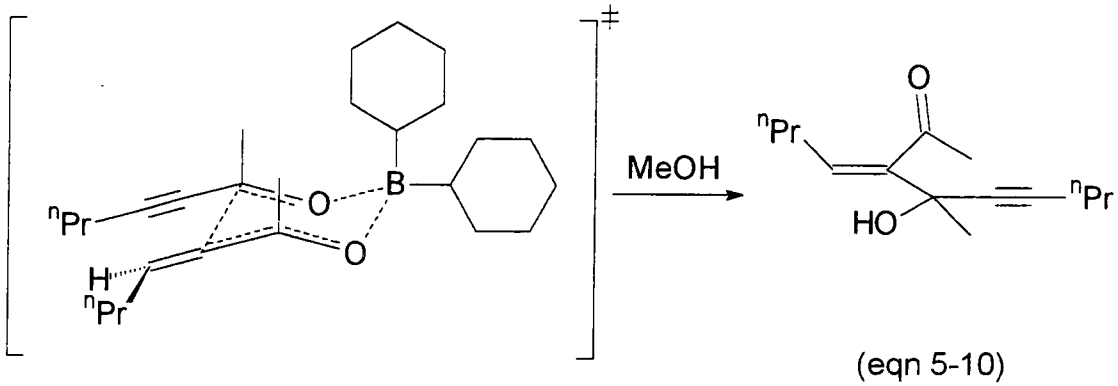


Figure 5-2. The NOESY spectrum of
7-Actyl-6-hydroxy-6-methyl-7-undecen-4-yne

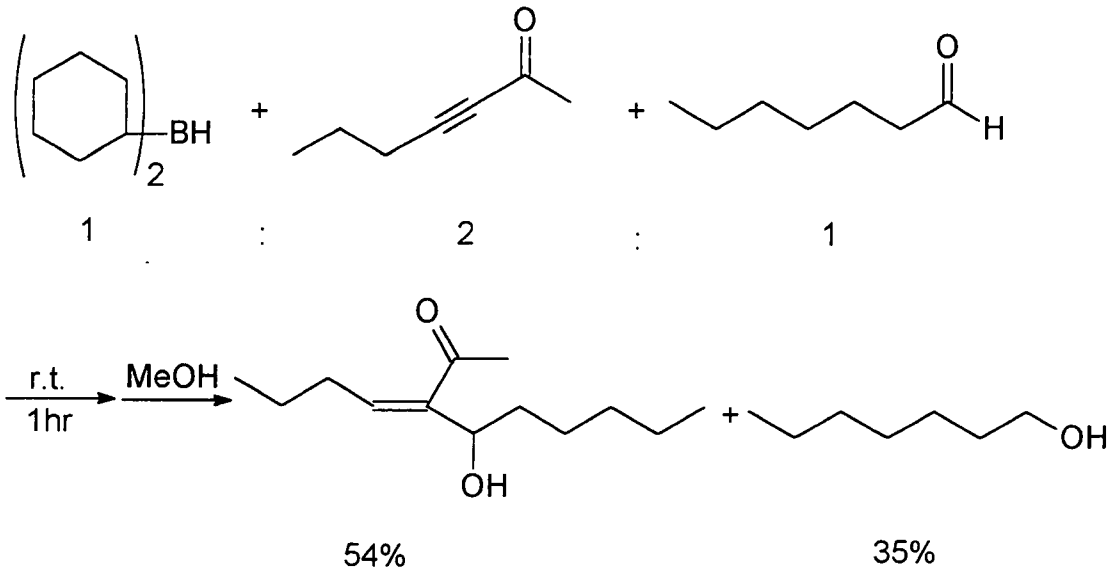
allenoxyborinate minimizes interactions with the methyl or pentynyl groups of 3-heptyn-2-one (eqn 5-10).



(eqn 5-10)

5.2.4 The Reaction of Allenoxyborinates with Other Electrophiles

Reactions of allenoxyborinates with other electrophiles, namely aldehydes, ketones, acid halides, were also investigated. The intermediate allenoxyborinates were found to be unstable at 0 °C and room temperature. Thus a mixture of two equivalents of α,β-acetylenic ketones and one equivalent of an electrophile was added to the slurry of dicyclohexylborane in THF. When aldehydes were used as electrophiles, the reactions gave the aldol products of the reaction of the allenoxyborinates with aldehydes (Table 5-7) as well as the products of the reduction of the aldehyde. For example, the reaction of dicyclohexylborane with a mixture of 3-heptyn-2-one and heptanal gave 54% of the aldol product of the reaction of the allenoxyborinate with heptanal and 35% of reduction product of heptanal, 1-heptanol (eqn 5-11). However, when an alkyl ketone was used in place of an aldehyde, only the product of the aldol reaction of



(eqn 5-11)

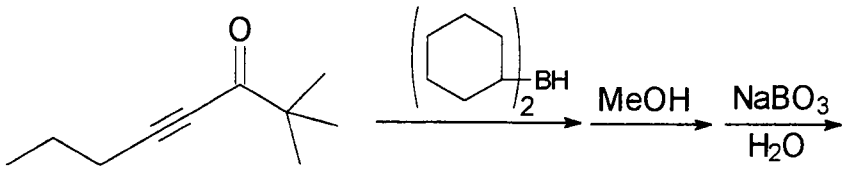
Table 5-7. The reactions of aldehydes as electrophiles.

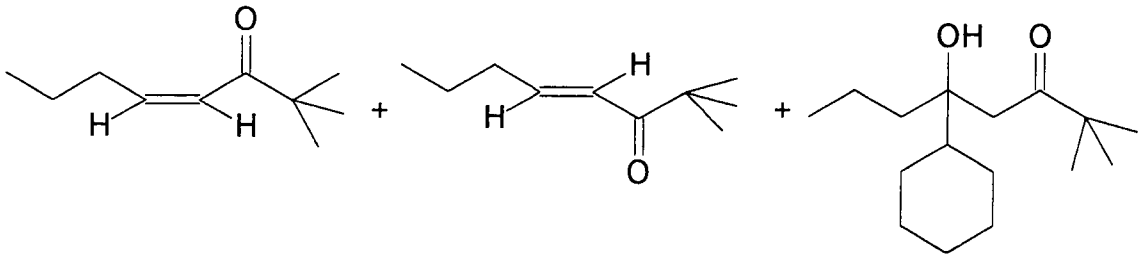
Entry	α,β-Acetylenic Ketones	aldehydes	Yields of aldol products of aldehydes
1	$CH_3(CH_2)_2C{\equiv}CC(=O)CH_3$	$CH_3(CH_2)_5C(=O)H$	54%
2	$PhC{\equiv}CC(=O)CH_3$	$CH_3CH_2C(=O)H$	45%
3	$PhC{\equiv}CC(=O)CH_3$	$PhC(=O)H$	40%

the allenoxyborinate with the starting α,β-acetylenic ketones was formed and the alkyl ketone was recovered. Similarly, reactions with an acid chloride gave only the product of the aldol reaction of the allenoxyborinate with the starting α,β-acetylenic ketones. These results suggest that aldehydes are more reactive toward allenoxyborinates than α,β-acetylenic ketones, whereas ketones and acid chlorides are less reactive toward allenoxyborinate than α,β-acetylenic ketones.

5.3 The Reaction of 2,2-Dimethyl-4-nonyl-3-one with Dicyclohexylborane

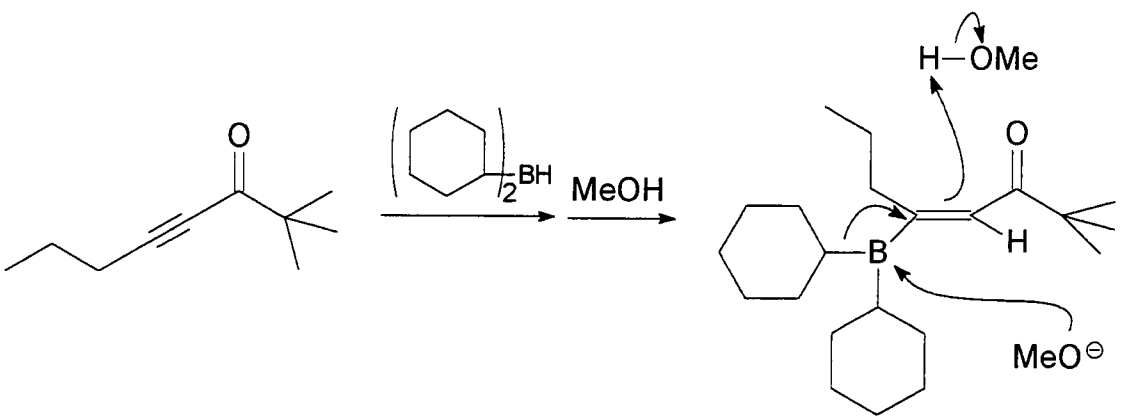
As noted in the previous section, the reaction of 2,2-dimethyl-4-nonyl-3-one with dicyclohexylborane did not form the aldol product of the reaction of the allenoxyborinate with starting 2,2-dimethyl-4-nonyl-3-one. The steric requirements of the bulky tertiary butyl group presumably keeps the carbonyl group from reacting with the allenoxyborinate. In order to study this reaction, one molar equivalent of 2,2-dimethyl-4-nonyl-3-one was reacted with dicyclohexylborane in THF, which was prepared from the reaction of 1.25 molar equivalents of BH_3•THF and 2.5 molar equivalents of cyclohexene. Then the reaction was quenched with methanol and oxidized using sodium perborate (eqn 5-11). (*E*)- and (*Z*)-2,2-Dimethyl-4-nonenyl-3-one were obtained in 60% yield. This suggests that the 1,4-addition of dicyclohexylborane to 2,2-dimethyl-4-nonyl-3-one occurred as the major reaction. Also noteworthy, 30% of 5-cyclohexyl-5-hydroxy-3-nonanone was obtained. Presumably, this compound was generated via the rearrangement of the vinylborane intermediate (eqn 5-12).

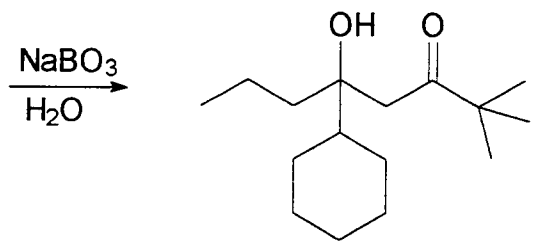




23% 37% 30%

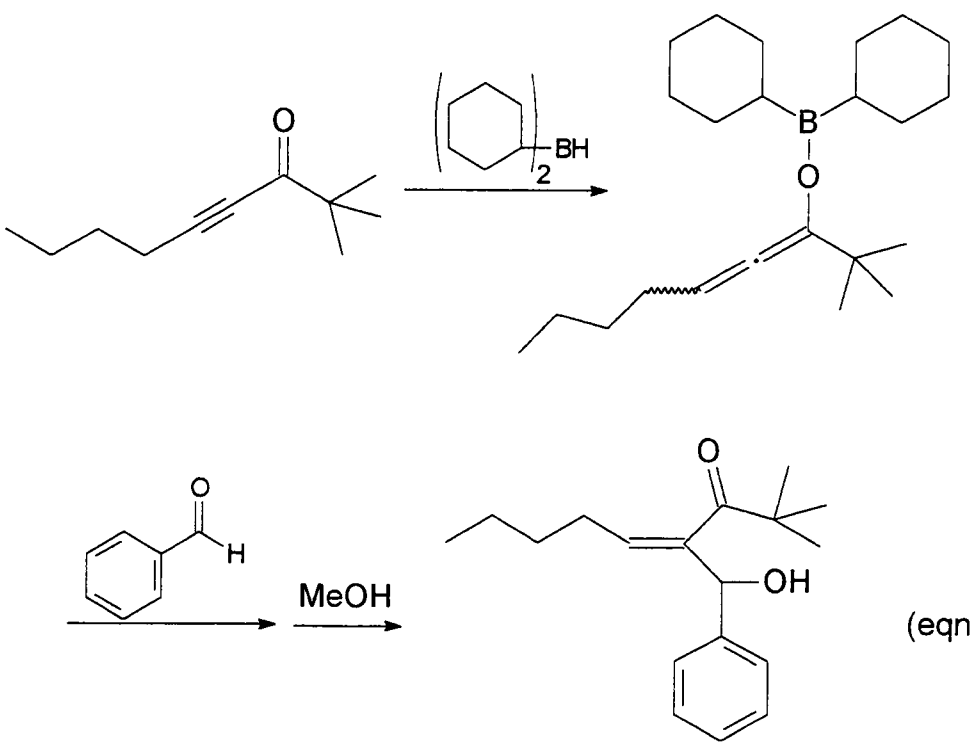
(eqn 5-11)





(eqn 5-12)

The allenoxyborinate obtained from the 1,4-addition of dicyclohexylborane to 2,2-dimethyl-4-nonyl-3-one was stable at 0 °C and at room temperature presumably due to the steric hindrance of the bulky tertiary butyl group. This made it possible to trap this allenoxyborinate by adding electrophiles. In this manner, the reduction of the aldehyde would be avoided in selective reactions with the allenoxyborinate. The reaction of 2,2-dimethyl-4-nonyl-3-one with dicyclohexyborane in THF, followed by the addition of benzaldehyde, gives the aldol product of the allenoxyborinate with benzaldehyde as the major product (eqn 5-13). Since the allenoxyborinate is generated in only about 60% yield,



(eqn 5-13)

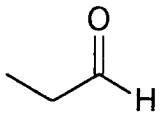
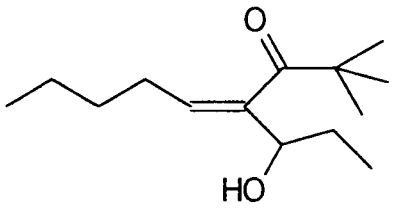
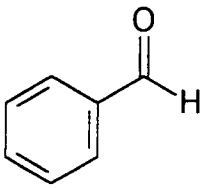
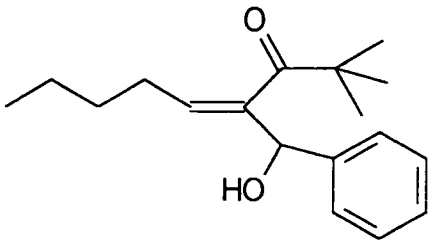
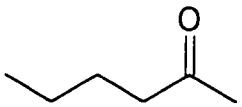
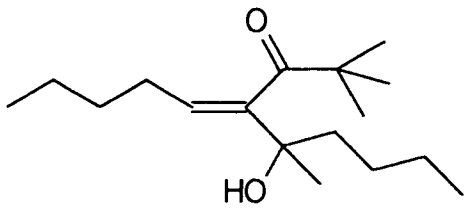
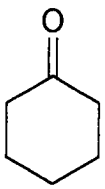
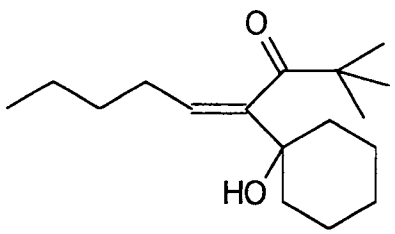
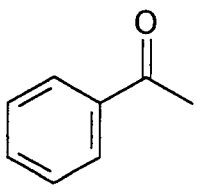
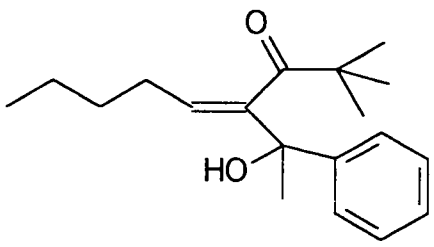
excess of 2,2-dimethyl-4-nonyl-3-one and dicyclohexylborane should be used when carrying out reactions with other electrophiles. The reaction of one molar equivalent of 2,2-dimethyl-4-nonyl-3-one with dicyclohexylborane, followed by

reaction with benzaldehyde, gives the aldol product in only 50% yield. Using a fifty percent excess of 2,2-dimethyl-4-nonyl-3-one and dicyclohexyborane gives the desired products in 75% yield. Two molar equivalents of 2,2-dimethyl-4-nonyl-3-one and dicyclohexylborane with one equivalent of benzaldehyde results in a quantitative formation of the aldol product.

A variety of ketones and aldehydes were then reacted with the allenoxyborinate generated by the reaction of 2,2-dimethyl-4-nonyl-3-one with dicyclohexylborane (Table 5-8). As can be seen from the data in Table 5-8, the reactions of the allenoxyborinate with aldehydes and ketones quantitatively forms the aldol product, the trisubstituted olefin. However, the allenoxyborinate did not react with acid chlorides.

Only one isomer of the trisubstituted olefin was obtained in these reactions. The stereochemistry was determined by a NOESY NMR experiment. For example, the NOESY spectrum of 2,2-dimethyl-4-(1-hydroxylpropyl)-4-nonen-3-one (Figure 5-3) shows a NOE cross peak between the olefinic proton and methinyl proton, which suggests the olefinic proton is *cis* to the methine group. Moreover, the tertiary butyl group exhibited no NOE cross peak with the olefinic proton but did show a NOE cross peak with the *n*-butyl group. This further supports the postulation that the olefinic proton is *cis* to the methyne group. The reaction of allenoxyborinates with aldehydes or ketones presumably occurs via a six-membered transition state in which the *n*-Bu group minimizes interactions with substituents on the aldehydes or ketones.

Table 5-8. The syntheses of 2,2-dimethyl-4-(1-hydroxyalkyl)-4-nonen-3-one

Entry	Electrophile	Product	Yield
1			100%
2			100%
3			100%
4			100%
5			100%

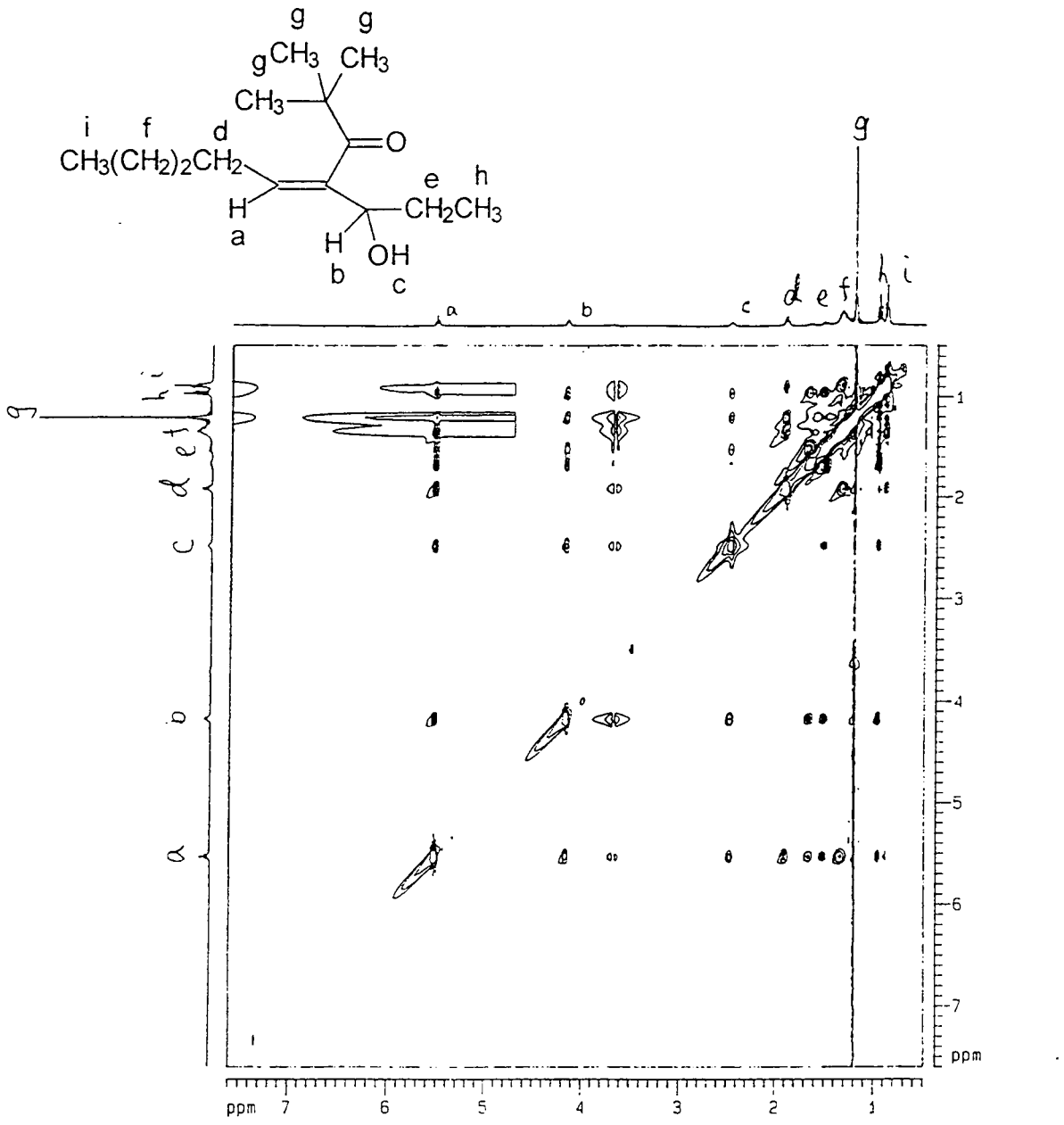


Figure 5-3. The NOESY spectrum of
2,2-dimethyl-4-(1-hydroxypropyl)-4-nonen-3-one

5.4 Conclusion

An efficient method for the stereoselective synthesis of highly functionalized trisubstituted olefins has been developed. Dicyclohexylborane adds to α,β-acetylenic ketones in a 1,4-fashion to generate allenoxyborinates which then react with the starting α,β-acetylenic ketones. The stereodefined, functionalized trisubstituted, olefins are obtained in high yields. The intermediate allenoxyborinate which is generated from the reaction of 2,2-dimethyl-4-nonyn-3-one with dicyclohexylborane can be trapped by other electrophiles such as aldehydes and ketones to form stereodefined trisubstituted olefins.

5.5 Experimental

All glassware, syringes and needles were dried in an oven heated to 250°C for at least 12 hours and cooled under argon prior to use. All chemicals were obtained from Aldrich Chemical Company. All borane reagents were used as received. Solvents and other reagents were purified by distillation prior to use. Reactions were magnetically stirred and monitored by TLC. Products were purified by flash chromatography.

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 250 MHz Bruker AC250 spectrometer. NOESY spectra were recorded on a 400 MHz Bruker AMX-400 spectrometer (D_1 = 3.0sec, P_1 = 8.4sec). Elemental analyses were performed by Atlantic Microlab Inc., Norcross, Georgia.

General procedure for the syntheses of α,β-acetylenic ketones via the reaction of lithiated acetylenes with N,N-dialkylcarboxamides. The synthesis of 3-heptyn-2-one[201]. A solution of butyllithium (50 mmol, 20 mL, 2.5M in hexane) was added dropwise to a solution of 1-pentyne (55 mmol, 3.7 g, 5.4 mL) in 45 mL of tetrahydrofuran with the temperature maintained below -30 °C. N,N-Dimethyl-acetamide (65 mmol, 5.7 g, 6.0 mL) was then added in one portion at approximately -30 °C. The mixture was warmed to room temperature. After an additional half hour, the solution was added to a vigorously stirred mixture of aqueous hydrochloric acid (12.5 g of 37% concentration) and ice water (100 mL). The pH of the aqueous phase was then adjusted to 6-7 by careful addition of concentrated aqueous K_2CO_3. The aqueous phase was extracted into ether (3 × 20 mL). The combined organic layer was washed twice with saturated aqueous sodium chloride (2 × 10 mL), and then dried over anhydrous $MgSO_4$. 3-Nonyn-2-one (3.3 g, 60% yield) was isolated by flash chromatography. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 2.34 (t, *J* = 7.0 Hz, 2H), 2.32(s, 3H), 1.61 (sext, *J* = 7.2 Hz, 2H), 1.01(t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 184.74, 93.76, 81.41, 32.63, 21.11, 20.72, 13.32.

The synthesis of 1-phenyl-2-hexyn-1-one[202]: 1-Phenyl-2-hexyn-1-one was prepared from the reaction of N,N-dimethylbenzamide (65 mmol, 9.8 g) with pentynyllithium (50 mmol) by the procedure described previously. The yield was 65%. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 8.14 (d, *J* = 7.0 Hz, 2H), 7.62-7.44 (m, 3H), 2.47 (t, *J* = 7.2 Hz, 2H),), 1.70 (sext, *J* = 7.2 Hz, 2H), 1.08 (t, *J* = 7.1 Hz, 3H). ^{13}C

NMR ($CDCl_3$/TMS) δ ppm: 178.07, 136.80, 133.74, 129.37, 129.37, 128.36, 96.50, 79.68, 21.26, 21.01, 13.45.

The synthesis of 1-phenyl-4,4-dimethyl-2-pentyn-1-one[203]: 1-Phenyl-4,4-dimethyl-2-pentyn-1-one was prepared via the reaction of N,N-dimethylbenzamide (65 mmol, 9.8 g) with 3,3-dimethylbutynyllithium, which was generated by the reaction of 3,3-dimethylbutyne (55 mmol, 4.5 g, 6.8 mL) with a solution of butyllithium (50 mmol , 20 mL, 2.5 M in hexane) as described previously. The yield was 40%. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 8.12 (d, J = 7.0 Hz, 2H), 7.62-7.43 (m, 3H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 178.17, 136.92, 133.68, 129.37, 129.35, 128.35, 103.78, 78.00, 30.07, 27.91.

General procedure for the syntheses of α,β-acetylenic ketones from the reaction of alkynylzinc chlorides and acid chlorides. The syntheses of 2,2-dimethyl-4-nonyn-3-one. A solution of butyllithium (50 mmol, 2.5 M, 20 mL in hexane) was added dropwise to a mixture of 1-hexyne (55 mmol, 4.5 g, 6.3 mL) in 25 mL of tetrahydrofuran with the temperature maintained below -50°C. Subsequently a solution of anhydrous zinc chloride (50 mmol, 6.8 g) in 25 mL THF was added at 0 °C. After an additional 10 min at 0 °C, pivaloyl chloride (60 mmol, 6.0 g, 7.4 mL) was added in one portion. The reaction mixture was warmed to 45 °C and was stirred for 30 minutes. The mixture was then added to a saturated solution of ammonium chloride (10 mL). Concentrated aqueous ammonia (10 mL) was added, and the mixture was vigorously shaken. After

separation of the layers, the aqueous layer was extracted with ether (3 × 20 mL). The organic solvent was removed under reduced pressure and 2,2-dimethyl-4-nonyn-3-one (8.6 g, 95%) was obtained by flash chromatography. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 2.24 (t, J = 7.0 Hz, 2H), 1.52(m, 4H), 1.21 (s, 9H), 1.01(t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 187.74, 93.96, 82.91, 32.63, 30.35, 30.17, 27.52, 22.14, 13.32.

The synthesis of 2-methyl-5-phenyl-4-pentyn-3-one[204]: 2-Methyl-5-phenyl-4-pentyn-3-one was prepared via the reaction of isobutyryl chloride (60 mmol, 6.4 g) with phenylacetylenylzinc chloride, which was generated from 2-phenylethyne (55 mmol, 5.6 g), a solution of butyllithium (50 mmol, 2.5 M, 20 mL in hexane) and zinc chloride (6.8 g). The procedure was described in the general procedure. The yield was 85%. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 7.57 (d, J = 7.0 Hz, 2H), 7.47-7.33 (m, 3H), 2.75 (sept, J = 7.2 Hz, 1H), 1.28 (s, 3H), 1.25 (s, 3H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 191.91, 132.86, 130.49, 128.49, 120.00, 91.41, 86.73, 42.96, 17.89.

The synthesis of 1-cyclopropanyl-2-hexyn-1-one: 1-Cyclopropanyl-2-hexyn-1-one was prepared from the reaction of cyclopropane carbonyl chloride (60 mmol, 6.2 g, 5.4 mL) with pentynylzinc chloride which was generated from 1-pentyne (55 mmol, 3.7 g), a solution of butyllithium (50 mmol, 2.5 M, 20 mL in hexane) and zinc chloride (6.8 g). The procedure was described in the general procedure. The yield was 92%. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 2.34 (t, J = 7.0

Hz, 2H), 2.05-1.97 (m, 1H), 1.61 (hext, J = 7.2 Hz, 2H), 1.24-1.18 (m, 2H), 1.05-0.99 (m, 5H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 188.36, 93.53, 78.82, 24.17, 21.11, 20.62, 13.23, 10.43.

The synthesis of 4,11-pentadecyne-5,10-dione: 4,11-Pentadecyne-5,10-dione was prepared from the reaction of glutaryl dichloride (30 mmol, 5.0 g, 3.8 mL) with pentynylzinc chloride, which was generated from 1-pentyne (55 mmol, 3.7 g), a solution of butyllithium (50 mmol, 2.5 M, 20 mL in hexane) and zinc chloride (6.8 g). The procedure was described in the general procedure. The yield was 54%. ^1H NMR ($CDCl_3$/TMS) δ ppm: 2.60 (t, J = 7.0 Hz, 4H), 2.35 (t, J = 7.2 Hz, 4H), 2.02 (p, J = 7.2 Hz, 2H), 1.61 (sext, J = 7.2 Hz, 4H), 1.02 (t, J = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 186.84, 94.30, 80.64, 43.94, 21.01, 20.62, 17.96, 13.21.

General procedure for the reaction of α,β-acetylenic ketones with dicyclohexylborane. The synthesis of 7-actyl-6-hydroxy-6-methyl-7-undecen-4-yne. Borane (1.25 mmol, 1.25 ml of a 1.00M solution in THF, was placed in a dry, argon-flushed round-bottomed flask which was then immersed in an ice-water bath. Cyclohexene (2.5 mmol, 0.21 g, 0.25 mL) was added dropwise and the mixture stirred at 0 °C for 1 hour. 3-Heptyn-2-one (2.0 mmol, 0.22 g) was then added to the slurry of dicyclohexylborane in THF. The cooling bath was removed and the mixture stirred for 1 hour at room temperature. Methanol (2.0 mL) was added to quench the reaction. The organic solvent

removed under pressure and 7-acetyl-6-hydroxy-6-methyl-7-undecen-4-yne (0.14 g, 62% yield) was obtained by flash chromatography. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 0.93 (*t*, *J* = 7.3 Hz, 3H), 1.50 (*sext*, *J* = 7.3 Hz, 4H), 1.63 (*s*, 3H), 2.09 (*q*, *J* = 7.4 Hz, 2H), 2.20 (*t*, *J* = 7.3 Hz, 2H), 2.42 (*s*, 3H), 3.35 (*s*, 1H), 6.04 (*t*, *J* = 7.7, 1H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 13.4, 13.6, 20.5, 21.9, 22.4, 29.8, 31.1, 32.9, 68.8, 82.6, 85.6, 130.5, 145.4, 207.2. Anal Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.83; H, 10.03.

The synthesis of 4-acetyl-1.5-diphenyl-3-hydroxy-3-methyl-4-penten-1-yne: 4-Acetyl-1.5-diphenyl-3-hydroxy-3-methyl-4-penten-1-yne was prepared via the reaction of 4-phenyl-3-butyn-2-one (2.0 mmol, 0.29 g, 0.29 mL) with dicyclohexyborane in THF using the general procedure. The product was obtained in 72% yield. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 1.88 (*s*, 3H) 2.13 (*s*, 3H), 3.95 (*s*, 1H), 7.23-7.35 (*m*, 9H), 7.41-7.45 (*m*, 2H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 29.0, 32.3, 69.6, 85.1, 90.6, 122.1, 128.2, 128.6, 128.7, 129.3, 131.6, 135.1, 144.9, 208.8. Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.54; H, 6.33.

The synthesis of 7-benzoyl-6-hydroxy-6-phenyl-7-undecen-4-yne: 7-Benzoyl-6-hydroxy-6-phenyl-7-undecen-4-yne was prepared via the reaction of 1-phenyl-2-hexyn-1-one (2.0 mmol, 0.34g) with dicyclohexylborane in THF using the general procedure. The product was obtained in 78% yield. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 0.71 (*t*, *J* = 3 Hz, 3H), 0.86 (*t*, *J* = 7.3 Hz, 3H), 1.27 (*sext*, *J*

= 7.3 Hz, 2H) 1.40 (*sext*, *J* = 7.3 Hz, 2H), 1.73 (*q*, *J* = 7.4 Hz, 2H), 2.13 (*t*, *J* = 7.0 Hz, 2H), 4.49 (*s*, 1H), 6.00 (*t*, *J* = 7.8 Hz, 1H), 7.23-7.42 (*m*, 5H), 7.50 - 7.53 (*m*, 1H), 7.63 - 7.67 (*m*, 2H), 7.80 - 7.84 (*m*, 2H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 13.4, 20.6, 21.7, 22.0, 31.6, 74.6, 81.8, 88.4, 126.4, 127.5, 127.8, 128.3, 129.5, 133.4, 134.0, 137.7, 141.8, 142.4, 200.5. Anal. Calcd for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56; Found: C, 83.14; H, 7.55.

The synthesis of 1.5-diphenyl-3-hydroxy-4-isobutyryl-3-isopropyl-4-penten-1-yne: 1.5-Diphenyl-3-hydroxy-4-isobutyryl-3-isopropyl-4-penten-1-yne was prepared via the reaction of 2-methyl-5-phenyl-4-pentyn-3-one (2.0 mmol, 0.34 g) with dicyclohexylborane in THF using the general procedure. The product was obtained as in 72% yield. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 0.94 (*d*, *J* = 6.8 Hz, 3H), 0.99 (*d*, *J* = 6.8 Hz, 3H), 1.12 (*d*, *J* = 6.8 Hz, 3H), 1.19 (*d*, *J* = 6.6 Hz, 3H), 2.48 (*sept*, *J* = 6.8 Hz, 2H), 3.40 (*s*, 1H), 7.21 - 7.36 (*m*, 8H), 7.39 (s, 1H), 7.47 - 7.51 (*m*, 2H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 17.0, 18.3, 18.7, 37.0, 41.6, 78.5, 87.6, 88.4, 122.3, 128.2, 128.4, 128.5, 128.7, 131.6, 132.8, 135.7, 143.7, 213.6. Anal. Calcd for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56. Found: C, 82.92; H, 7.70.

The synthesis of 6-benzoyl-5-hydroxyl-5-phenyl-2.2.8.8-tetramethyl-6-nonen-3-yne: 6-Benzoyl-5-hydroxyl-5-phenyl-2.2.8.8-tetramethyl-6-nonen-3-yne was prepared via the reaction of 4,4-dimethyl-1-phenyl-2-pentyn-1-one (2.0 mmol, 0.37 g) with dicyclohexylborane in THF using the general procedure. The product was obtained in 78% yield. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 0.88 (*s*, 9H),

1.01 (*s*, 9H), 3.57 (*s*, 1H), 5.85 (*s*, 1H) 7.20 - 741 (*m*, 5H), 7.47 - 7.53 (*m*, 1H), 7.60 - 7.63 (*m*, 2H), 7.90 - 7.93 (*m*, 2H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 27.2, 29.8, 30.3, 30.3, 33.5, 74.3, 80.7, 96.8, 126.5, 127.6, 127.7, 128.0, 129.9, 133.1, 138.7, 141.1, 142.8. Anal. Calcd for $C_{26}H_{30}O_2$: C, 83.38; H, 8.07. Found: C, 83.15; H, 8.01.

The synthesis of 7-cyclopropanecarbonyl-6-cyclopropanyl-6-hydroxyl-7-undecen-4-yne: 7-Cyclopropanecarbonyl-6-cyclopropanyl-6-hydroxyl-7-undecen-4-yne was prepared via the reaction of 1-cyclopropanyl-2-hexyn-1-one (2.0 mmol, 0.27 g) with dicyclohexylborane in THF using the general procedure. The product was obtained in 66% yield. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 0.48 - 0.52 (*m*, 3H), 0.72 (*m*, 1H), 0.92 - 1.05 (*m*, 8H), 1.20 - 1.28 (*m*, 4H). 1.45 - 1.57 (*m*, 4H), 2.16 - 2.29 (*m*, 4H), 3.89 (*s*, 1H), 8.26 (*t*, *J* = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 2.2, 2.4, 12.9, 13.3, 13.6, 19.7, 20.5, 21.9, 22.4, 23.5, 31.0, 73.8, 78.7, 86.6, 131.7, 144.8, 210.0. Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.84; H, 9.59.

The synthesis of 2-butylidene-3-hydroxy-3-(1-pentynyl)-cyclohexanone: 2-Butylidene-3-hydroxy-3-(1-pentynyl)-cyclohexanone was prepared via the reaction of 4,11-pentadecyne-5,10-dione (1.0 mmol, 0.23 g) with dicyclohexylborane in THF using the general procedure. The product was obtained in 55% yield. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 0.91 (*t*, *J* = 7.3 Hz, 3H), 0.99 (*t*, *J* = 7.3 Hz, 3H). 1.26 (*m*, 1H), 1.40 - 1.59 (*m*, 4H), 1.92 - 2.56 (*m*, 10H),

6.33 (*t*, *J* = 7.4 Hz, 1H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 13.3, 13.7, 19.5, 20.6, 21.9, 22.5, 30.5, 39.5, 42.2, 72.5, 81.3, 87.7, 136.8, 141.3, 202.9. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.79; H, 9.43.

General procedure for the syntheses of 2,2-dimethyl-4-(1-hydroxyalkyl)-4-nonen-3-one. The synthesis of 2.2-dimethyl-4-(1-hydroxypropyl)-4-nonen-3-one. Borane (2.5 mmol, 2.5 mL of a 1.0 M solution in THF) was placed in a dry, argon-flushed, round-bottomed flask which was then immersed in an ice-water bath. Cyclohexene (5.0 mmol, 0.41 g, 0.51 mL) was added dropwise and the mixture was stirred at 0 °C for 1 hour to generate dicyclohexylborane. 2,2-Dimethyl-4-nonyn-3-one (2.0 mmol, 0.33 g) was then added to the slurry of dicyclohexylborane in THF. The cooling bath was removed and the mixture was stirred at room temperature. After the white precipitate disappeared, propionaldehyde (1.0 mmol, 0.06 g, 0.07 mL) was added. The mixture was stirred at room temperature for an additional hour. Then methanol (2.0 ml) was added to quench the reaction. The organic solvent was removed under pressure and 2,2-dimethyl-4-(1-hydorxyl-propyl)-4-nonen-3-one (0.22g, 100% yield) was obtained by flash chromatography. ^1H NMR ($CDCl_3$/TMS) δ ppm: 0.88 (*t*, *J* = 6.8Hz, 3H), 0.96 (*t*, *J* = 7.3 Hz, 3H), 1.20 (*s*, 9H), 1.23 - 1.39 (*m*, 4H), 1.51 (*pent*, *J* = 7.2 Hz, 1H), 1.64 (*pent*, *J* = 7.2 Hz, 1H). 1.91 (*q*, *J* = 7.0 Hz, 2H), 2.21 (*br s*, 1H), 4.16 (*m*, 1H), 5.52 (*t*, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 9.8, 13.8, 22.2, 27.1, 27.2, 29.2, 29.7, 31.5, 43.9, 73.9,

127.5, 144.9, 217.1. Anal Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.11; H, 11.43.

The synthesis of 2.2-dimethyl-4-(1-hydroxy-1-phenylmethyl)-4-nonen-3-one: 2.2-Dimethyl-4-(1-hydroxy-1-phenylmethyl)-4-nonen-3-one was prepared via the reaction of benzaldehyde (1.0 mmol, 0.10 g, 0.10 mL) with the allenoxyborinate, which was generated using the general procedure. The product was obtained in 100% yield. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 0.84 (*t*, *J* = 7.0 Hz, 3H), 1.11 (*s*, 9H), 1.20 - 133 (*m*, 4H) 1.89 (*q*, *J* = 7.2 Hz, 2H), 2.91 (*d*, *J* = 5.1 Hz, 1H), 5.28 (*dt*, *J* = 7.6 Hz, 1.2 Hz, 1H), 5.36 (*d*, *J* = 5.1 Hz, 1H), 7.26 - 7.33 (*m*, 5H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 13.7, 22.2, 27.1, 27.2, 29.8, 31.2, 43.8, 75.3, 126.9, 127.7, 128.2, 130.1, 141.4, 144.5, 217.2. Anal Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.69; H, 9.65.

The synthesis of 7-hydroxy-7-methyl-6-trimethylacetyl-5-undecene: 7-Hydroxy-7-methyl-6-trimethylacetyl-5-undecene was prepared via the reaction of 2-hexanone (1.0 mmol, 0.10 g, 0.12 mL) with the allenoxyborinate, which was generated using the general procedure. The product was obtained in 100% yield. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 0.85 - 0.93 (*m*, 6H), 1.20 (*s*, 9H), 1.30 - 1.33 (*m*, 8H), 1.38 (*s*, 3H) 1.61 - 1.62 (*m*, 2H), 1.78 (*br s*, 1H), 1.90 (*q*, *J* = 7.2 Hz, 2H), 5.25 (*t*, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 13.8, 14.0, 22.2, 22.9, 25.9, 27.5, 27.6, 28.6, 29.9, 31.5, 43.1, 43.8, 74.6, 124.9, 148.5, 219.0. Anal Calcd for $C_{17}H_{32}O_2$: C, 76.07; H, 12.01. Found: C, 76.22; H, 11.89.

The synthesis of 4-(1-hydroxy-cyclohexyl)-4-nonen-3-one: 4-(1-Hydroxy-cyclohexyl)-4-nonen-3-one was prepared via the reaction of cyclohexanone (1.0 mmol, 0.10 g, 0.10 mL) with the allenoxyborinate, which was generated using the general procedure. The product was obtained in 100% yield. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 0.88 (*t*, *J* = 7.0 Hz, 3H), 1.08 - 1.14 (*m*, 2H), 1.20 (*s*, 9H), 1.27-1.37 (*m*, 4H), 1.52 - 1.58 (*m*, 6H), 1.81 - 1.94 (*m*, 5H), 5.36 (*t*, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 13.8, 21.7, 22.2, 25.3, 27.6, 29.9, 31.5, 38.3, 43.7, 73.1, 124.6, 150.4, 219.3. Anal Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.44; H, 11.21.

The synthesis of 4-(1-hydroxy-1-methyl-1-phenyl-methyl)-4-undecen-3-one: 4-(1-Hydroxy-1-methyl-1-phenyl-methyl)-4-undecen-3-one was prepared via the reaction of acetophenone (1.0 mmol, 0.12 g, 0.12 mL) with the allenoxyborinate, which was generated using the general procedure. The product was obtained in 100% yield. ^{1}H NMR ($CDCl_3$/TMS) δ ppm: 0.86 (*t*, *J* = 7.0 Hz, 3H), 1.01 (*s*, 9H), 1.21 - 1.35 (*m*, 4H), 1.70 (*s*, 3H), 1.86 - 1.96 (*m*, 2H), 3.22 (*s*, 1H), 5.40 (*t*, *J* = 7.6 Hz, 1H), 7.19 - 7.34 (*m*, 3H), 7.45 - 7.49 (*m*, 2H). ^{13}C NMR ($CDCl_3$/TMS) δ ppm: 13.7, 22.1, 27.2, 30.2, 30.4, 31.2, 43.9, 76.0, 125.8, 126.9, 127.8, 127.9, 146.2, 147.3, 219.6. Anal Calcd for $C_{19}H_{28}O_2$: C, 79.13; H, 9.78; Found: C, 79.13; H, 9.92.

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