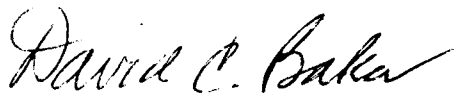


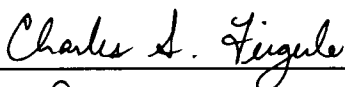
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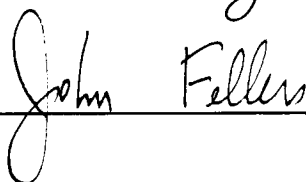
I am submitting herewith a dissertation written by John Thortan Maddox entitled "Alkylation of Aldehyde Arenesulfonylhydrazones Via Trialkylboranes". I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for 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

ALKYLATION OF ALDEHYDE ARENESULFONYLHYDRAZONES
VIA TRIALKYLBORANES

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

John Thortan Maddox

August 1995

DEDICATION

I dedicate this dissertation to my wife, Robin.

ACKNOWLEDGEMENTS

I want to acknowledge, first and foremost, Dr. George W. Kabalka for his help, guidance, and financial support for the past five years. He has provided an exceptional working and learning environment that has made my stay here an enjoyable one. I also want to acknowledge all the people that I have been privileged to know during my time in Dr. Kabalka's lab. I especially want to thank Dr. David Pace, Timothy Gotsick, Max Hair, Robert Beauvais, and my partner in the tosylhydrazone project, Kathy Bogas. Your laughter and company have meant more to me than I can adequately express.

ABSTRACT

A new methodology for delivering alkyl groups to carbonyl moieties via trialkylboranes was developed. This new reaction is a useful alternative to the traditional alkylmetal reactions.

Arenesulfonylhydrazone derivatives of aryl aldehydes are easily alkylated by trialkylboranes in the presence of base to give the corresponding substituted alcohols after oxidation. Both tosyl and trisyl derivatives may be utilized in this new reaction. The reaction tolerates several different functional groups thereby allowing functionalized alkyl groups to be transferred. The applicability of various blocked borane derivatives was also evaluated.

The methodology can be extended to alkyl aldehydes via the trisyl derivatives. The usefulness of blocked borane derivatives was evaluated.

Several approaches to the direct 1,2-addition of a trialkylborane to a carbonyl group were attempted. Future approaches to this problem were also discussed.

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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
CDCl ₃	Chloroform- <i>d</i>
Chx	Cyclohexyl
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCME	Dichloromethyl methyl ether
Δ	Heat
ee	Enantiomeric excess
Et ₂ O	Diethyl ether
GCMS	Gas Chromatograph-Mass Spectrometer
HMPA	Hexamethylphosphoramide
Hz	Hertz
Ipc	Isopinocampheyl
IR	Infrared

<i>J</i>	Proton-proton coupling constant
LAH	Lithium aluminum hydride
LG	Leaving group
LiHMDS	Lithium hexamethyldisilazide
m	multiplet
Me	Methyl
NMR	Nuclear magnetic resonance spectroscopy
[O]	Oxidation
Ph	Phenyl
PTC	Phase Transfer Catalysis
q	Quartet
R	Alkyl
RT	Room temperature
s	Singlet
t	Triplet
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
Ts	Tosyl (<i>p</i> -toluenesulfonyl)
Tris	Trisyl (2,4,6-triisopropylbenzenesulfonyl)

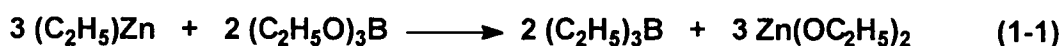
CHAPTER 1. ORGANOBORANES IN ORGANIC SYNTHESIS

1.1 Introduction

This dissertation concerns the use of organoboranes in the formation of new carbon-carbon bonds. A brief overview of organoborane chemistry is presented.

1.2 Historical Overview

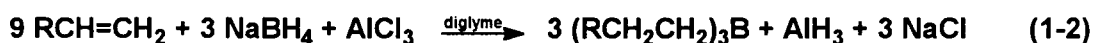
Organoborane chemistry began in 1859 when Frankland prepared triethylborane by reacting diethylzinc with triethoxyborane (eqn 1-1)¹. Subsequent researchers found



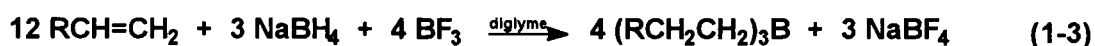
that other organometallics, such as Grignard reagents, would react with alkoxyboranes or boron trifluoride etherate in a similar fashion to produce trialkylboranes². These new reagents, however, were not utilized because their syntheses depended on the availability of more reactive organometallic reagents.

Organoborane reagents would not become synthetically useful until 1956, almost one hundred years after Frankland's discovery, when Brown and co-workers

discovered a simple, more convenient route to organoboranes. While investigating the reduction of carbonyl compounds with $\text{NaBH}_4/\text{AlCl}_3$ in diglyme, Brown noted that the unsaturated ester, ethyl oleate, consumed 2.4-2.5 moles of hydride rather than the 2.0 moles required for simple reduction³. Further investigation showed that the double bond was participating in the reaction. In fact, it was subsequently found that alkenes would react readily with $\text{NaBH}_4/\text{AlCl}_3$ in diglyme to produce the corresponding organoboranes in excellent yield (eqn 1-2)⁴.



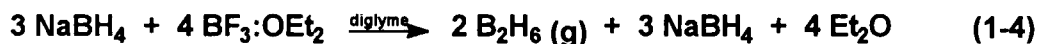
Replacement of AlCl_3 with BF_3 allowed utilization of all four hydrides present in NaBH_4 (eqn 1-3)⁵.



The NaBH_4 and AlCl_3 (or BF_3) reaction mixture generates diborane (B_2H_6) which reacts with the alkene *in-situ* to produce the organoborane. The reaction of diborane with an alkene is a more direct route to an organoborane than Frankland's original organometallic method (eqn 1-1). Earlier work had shown, however, that the reaction between alkenes and diborane was sluggish and required elevated temperatures and long reaction times⁶. It was Brown's fortuitous choice of an ether

solvent, diglyme, that allowed the hydroboration to proceed at a synthetically useful rate⁵.

Diborane may be generated *in-situ* as shown in equations 1-2 and 1-3 or it may be generated neat and dissolved in another solvent such as THF (eqn 1-4)⁷. Neat



diborane is rarely used as a hydroborating reagent as it is a gas and it spontaneously inflames in air. Instead, it is usually complexed with a donor molecule to form a 1:1 complex. Diborane is soluble in THF and it forms the complex $\text{BH}_3 \cdot \text{THF}$. This addition compound may be used as a solution in THF; it is commercially available and is the most commonly used hydroboration reagent. Another common source of BH_3 is $\text{BH}_3 \cdot \text{SMe}_2$ which is also known as BMS. This complex is significantly more stable than $\text{BH}_3 \cdot \text{THF}$ and may be handled and stored as a neat solution.

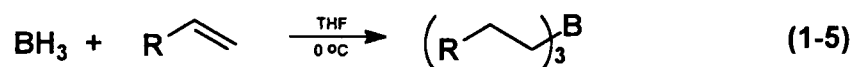
1.3 Hydroboration

Hydroboration is the most synthetically useful route to organoboranes. In contrast to Frankland's original organometallic method, hydroboration is operationally simpler and it allows a wide range of functionally substituted alkenes to be utilized. Because of the commercial availability of $\text{BH}_3 \cdot \text{THF}$, it and its derivatives are the most

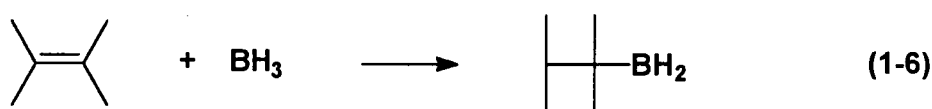
widely used hydroborating reagents today. What follows is a brief overview of the various permutations on the original hydroboration scheme.

1.3.1 Hydroboration with BH_3

Hydroboration of most simple alkenes with BH_3 proceeds rapidly at 0 °C utilizing all three hydrides present to produce the corresponding organoboranes (eqn 1-5). When the alkene is hindered, the reaction stops at the dialkylborane or



monoalkylborane stage. An example of this is the hydroboration of the hindered 2,3-dimethyl-2-butene which produces the monoalkylborane, *tert*-butylborane (eqn 1-6).



The hydroboration reaction predominantly proceeds in an *anti*-Markovnikoff fashion. The regioisomer distribution for a simple alkene, such as 1-hexene, is placement of 94% of the boron at the terminal carbon with 6% at the internal carbon of the original double bond. This distribution is not affected by branching of the alkyl group although it is significantly enhanced by increased substitution on the double bond (Figure 1-1)⁸.

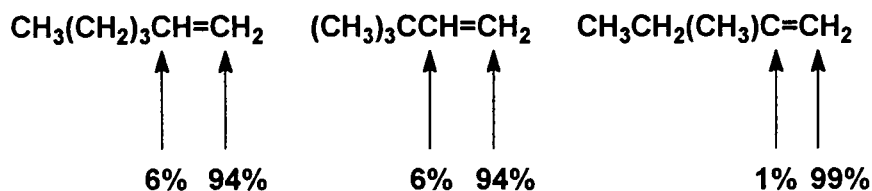


Figure 1-1. Regioselectivity of Hydroboration with BH_3 .

The regiochemistry of hydroboration is radically affected when heteroatoms are present on the double bond. Figure 1-2 illustrates the effect of placing a chlorine or

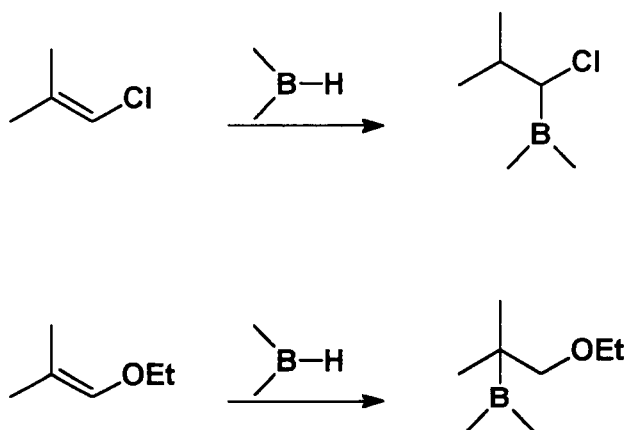


Figure 1-2. Hydroboration of Olefins Bearing Functional Groups.

an oxygen directly on the olefin. The electronegative chlorine directs the boron to the terminal carbon of the double bond whereas the oxygen substituent, which is capable

of donating electrons, directs the boron to the internal carbon⁹.

This scheme of reactivity suggests the mechanism shown in Figure 1-3 as the

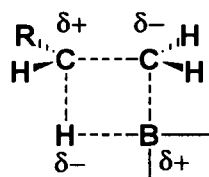
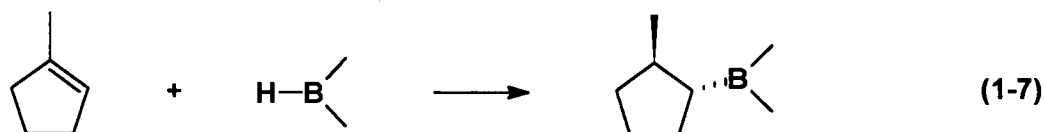


Figure 1-3. Mechanism of Hydroboration.

probable explanation of hydroboration regiochemistry. This four-center transition state, with the direction of addition controlled mainly by the B-H bond polarization, adequately rationalizes the regiochemistry of hydroboration with BH_3 ⁷.

Based on the mechanism shown in Figure 1-3, the hydroboration reaction should involve a *syn*-addition to the double bond. This, in fact, has been verified experimentally (eqn 1-7). It can also be shown that the addition occurs on the less hindered side of the double bond (eqn 1-8). The *syn*-addition of boron hydride was



later shown to be true for freely rotating acyclic systems as well¹⁰.



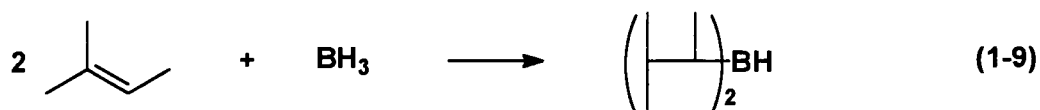
The hydroboration reaction tolerates many functional groups. This is due to the fact that the rate of reaction of BH_3 with carbon-carbon double and triple bonds is much faster than the rate of reaction of BH_3 with most functional groups. Functional groups such as esters, halogens, cyano, and ethers are easily tolerated during hydroborations with BH_3 and can be present in the alkene substrate⁷.

1.3.2 Hydroboration with BH_3 Derivatives

Because there are three active hydrides present in BH_3 , either one or two of them may be replaced with another group to modify the reactivity of the remaining boron-hydride bond. Commonly, the hydrides are replaced with "blocking groups", such as alkyl groups, to prevent the waste of a valuable substrate in subsequent reactions where only one group is transferred. Also, sterically bulky blocking groups augment the electronic regiochemical preference (Figure 1-3) which results in enhanced regioselectivities. What follows is a brief overview of some of the borane derivatives where two hydrides are replaced by blocking groups.

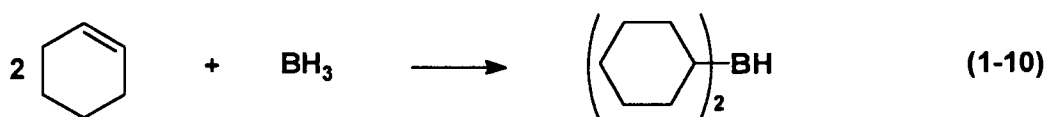
1.3.2.1 Disiamylborane and Dicyclohexylborane

The reaction of 2-methyl-2-butene with BH_3 may be stopped at the dialkylborane stage allowing isolation of the dialkylborane, disiamylborane (eqn 1-9).



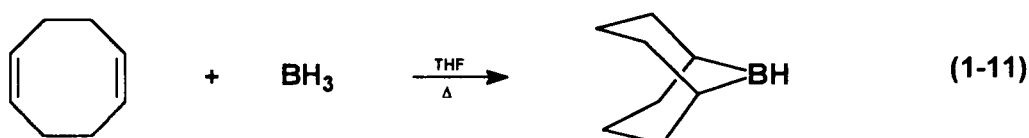
This reagent may then be used as a hydroborating agent. Disiamylborane shows an enhanced regioselectivity relative to BH_3 , placing 99% of the boron at the terminal position. Disiamylborane is also very sensitive to the structure of the alkene. For example, it will selectively hydroborate an acyclic double bond in the presence of a cyclic double bond¹¹.

Dicyclohexylborane is prepared in a similar fashion. When cyclohexene is hydroborated, the reaction stops at the dialkylborane stage (eqn 1-10). Dicyclohexylborane crystallizes out of solution as a dimer which is a remarkably stable, white solid. Its reactivity is similar to that of disiamylborane.



1.3.2.2 9-BBN

9-Borabicyclo[3.3.1]nonane (9-BBN) can be prepared by the cyclic hydroboration of 1,5-octadiene followed by thermal equilibration of the isomers in refluxing THF (eqn 1-11)¹². The dimer of 9-BBN may be recrystallized from



1,2-dimethoxyethane to give crystals which are remarkably stable, even in air, for short periods of time¹³. 9-BBN is one the most unhindered dialkylboranes known. This openness allows it to hydroborate fairly hindered alkenes such as 2,3-dimethyl-2-butene¹⁴.

9-BBN exhibits remarkable regioselectivity in hydroborating alkenes. It places 99.5% of the boron on the terminal carbon of 1-hexene. Even more surprising is the fact that 9-BBN will hydroborate alkenes in the presence of the more electron-rich alkynes, in contrast to other dialkylboranes¹⁵.

1.3.2.3 Dimethylborane

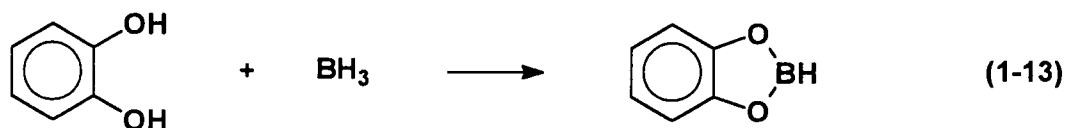
Dimethylborane is the simplest of the dialkylboranes. It is unavailable via hydroboration. It can be readily made, however, from the corresponding lithium dimethylborohydride (eqn 1-12)¹⁶. It exists in solution as its dimer. Dimethylborane



exhibits a regioselectivity similar to 9-BBN and disiamylborane, placing 99.5% of the boron on the terminal carbon of 1-hexene. Dimethylborane is useful in organoboron chemistry because the methyl groups typically do not participate in subsequent reactions.

1.3.2.4 Catecholborane

The reaction of BH_3 with catechol produces the dialkoxyborane, 1,3,2-benzodioxaborole or catecholborane (eqn 1-13)¹⁷. It is a solid at 0 °C and is quite



stable if stored at that temperature. It differs from the dialkylboranes cited previously in that two oxygen atoms serve as the blocking groups instead of alkyl groups. These oxygens also decrease the Lewis acidity of the boron atom making catecholborane less reactive than the dialkylboranes. It does however, hydroborate alkynes and alkenes readily at 70 °C and 100 °C, respectively, giving regioselectivities in the alkene case comparable to disiamylborane¹⁸.

One of the biggest applications of catecholborane is its use to form boronic

acids by hydrolysis of the corresponding alkyl derivatives¹⁸.

1.3.2.5 Haloboranes

Dibromoborane and dichloroborane are borane reagents in which two positions are blocked with halo groups (eqn 1-14). The dihaloboranes are generally supplied as



their etherate or dimethyl sulfide complexes. The dichloroborane complex requires the addition of a Lewis acid, such as BCl_3 , during hydroboration reactions^{19,20}. The dibromoborane dimethylsulfide complex does not require added Lewis acids but hydroboration reactions are heated to 40 °C to achieve reasonable reaction times²⁰.

Dibromo- and dichloroborane exhibit a regioselectivity similar to 9-BBN. One of the practical uses of these dihaloborane reagents is the conversion of their hydroboration products into the corresponding boronic acids and their esters²⁰.

1.3.3 Asymmetric Hydroboration^{21a}

As illustrated in previous sections, two hydrides on BH_3 may be replaced with blocking groups to create new, disubstituted boranes with radically different

properties. It is also possible to use chiral groups to modify BH_3 . This allows the introduction of asymmetry into the hydroboration products when prochiral alkenes are used as substrates.

Figure 1-4 shows some of the more common asymmetric hydroborating reagents. Diisopinocampheylborane, $(\text{Ipc})_2\text{BH}$, is the most widely used asymmetric

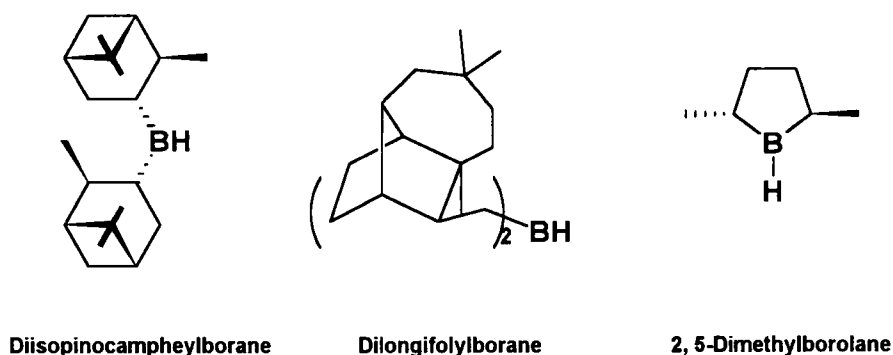
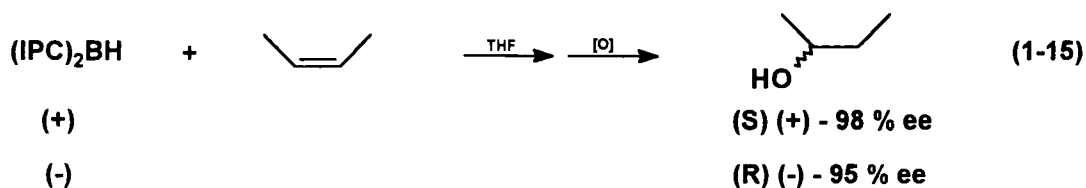


Figure 1-4. Common Asymmetric Hydroborating Reagents.

hydroborating reagent. It is synthesized by hydroboration of the naturally occurring terpene, α -pinene, which is readily available in both enantiomeric forms. $(\text{Ipc})_2\text{BH}$ can be prepared in an enantiopure form by allowing the reagent to equilibrate with excess α -pinene in THF at $0\text{ }^\circ\text{C}$ ²¹. Hydroboration-oxidation of *cis*-2-butene with the reagent so prepared produces the corresponding alcohol with an enantiomeric excess exceeding 95% (eqn 1-15). Both enantiomers are available, thus both enantiomeric products may be produced.



Diisopinocampheylborane works best with *cis*-disubstituted alkenes. Asymmetric induction is markedly lower with more sterically hindered alkenes.

Dilongifolylborane, $(\text{Lgf})_2\text{BH}$, is similar to diisopinocampheylborane in that both are derived from naturally occurring terpenes. Unlike α -pinene, however, longifolene is readily available in only one stereoisomeric form. Dilongifolylborane is a dimeric, crystalline solid which is remarkably stable for long periods of time²². Dilongifolylborane hydroborates aliphatic, trisubstituted alicyclic, and cyclic alkenes giving 60-78% ee's. It also hydroborates *cis*-disubstituted alkenes but the asymmetric induction is not as great as that obtained with diisopinocampheylborane.

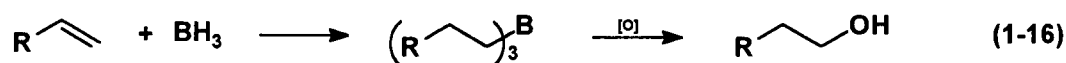
2,5-Dimethylborolane is perhaps the most robust of the asymmetric hydroborating reagents. It gives asymmetric inductions of 95-97% ee with all types of alkenes except disubstituted terminal alkenes²³. Unfortunately, it is very difficult to produce. If a viable, simple method of producing this compound could be found, it would be the asymmetric hydroboration reagent of choice.

1.4 Carbon-Heteroatom Bond Formation Via Organoboranes

One of the synthetic advantages of organoboranes is that the boron-carbon bond can be transformed into several different carbon-heteroatom bonds very easily. The following is an overview of several of the more common procedures.

1.4.1 Oxidation

The oxidation of organoboranes to generate alcohols is one the most widely used applications of organoborane technology (eqn 1-16). This operation provides a

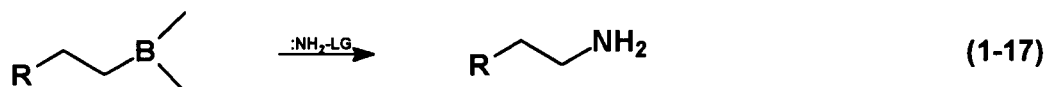


simple route to *anti*-Markovnikoff alcohols from alkenes. The classical procedure uses alkaline hydrogen peroxide to achieve this transformation²⁴. Other reagents which may be used include amine N-oxides²⁵, sodium percarbonate²⁶, sodium perborate²⁷, and molecular oxygen²⁸.

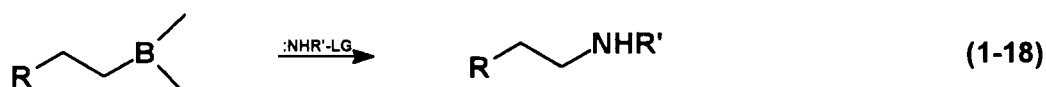
Oxidation of organoboranes with molecular oxygen has been adapted to produce oxygen-15 labeled butanol, a blood perfusion agent used in clinical PET studies²⁹. Oxygen-15 has a half-life of two minutes and the use of organoboranes allows rapid utilization of this isotope.

1.4.2 Amination

Organoboranes may be converted to primary amines by reaction with nitrogen reagents bearing a suitable leaving group (eqn 1-17). Typical reagents used



are hydroxylamine O-sulfonic acid^{30,31}, chloramine³¹, and hydrazoic acid³². Secondary amines may be synthesized by using the alkyl substituted derivatives of these reagents such as alkylazides³³ and alkylchloramines³⁴ (eqn 1-18).



Usually only one or two of the alkyl groups are transferred from the organoborane but this can be compensated for by using substituted organoboranes such as dimethylborane as the original hydroborating reagent^{31a}.

1.4.3 Protonolysis

The organoboranes are unique organometallic reagents in that they are stable to water, aqueous bases, and even aqueous mineral acids. They are, however, protonolyzed by carboxylic acids (eqn 1-19). Although two of the three alkyl groups



react rapidly in a trialkylborane, the third alkyl group requires rather vigorous conditions to protonolyze. Typically, organoboranes are refluxed with propionic acid in a high boiling solvent such as diglyme for two to three hours³⁵. The reaction is believed to proceed via a six-membered transition state and has been shown to occur with retention of configuration³⁶.

In contrast to trialkylboranes, organoboranes which contain groups that are capable of stabilizing negative charges, such as aryl and benzylic groups, are easily protonolyzed by water or base.

1.4.4 Halogenation

Organoboranes are resistant to reaction with halogens. However, in the presence of base, reaction occurs readily to produce the corresponding alkyl halides. Bromine reacts with trialkylboranes in the presence of base to produce alkyl bromides

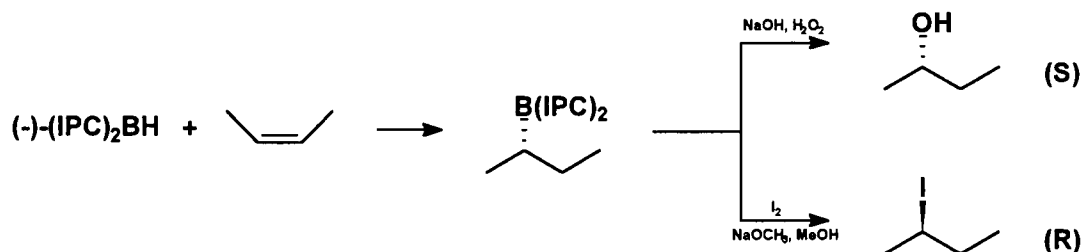
(eqn 1-20)³⁷. The reaction is unique among organoborane transformations in



that it proceeds with inversion of configuration^{38, 40b}.

Iodine likewise reacts with organoboranes in the presence of base to produce alkyl iodides³⁹. Like the bromination reaction, iodination proceeds with inversion of configuration as shown in Scheme 1-1⁴⁰.

Scheme 1-1. Inversion in the Iodination of Organoboranes.



The reaction of nitrogen trichloride with trialkylboranes produces alkyl chlorides with all three groups being transferred⁴¹. The reaction however, involves radicals and produces stereochemically mixed products.

A recent article reported that cesium fluoroxysulfate had been used to fluorinate aryl boronic acids⁴². The yields ranged from 25-50%.

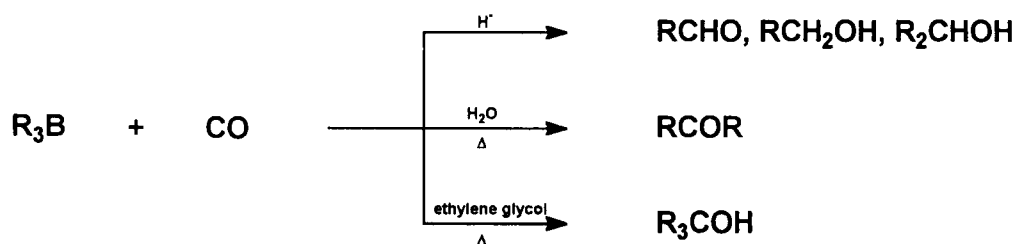
1.5 Carbon-Carbon Bond Formation Via Organoboranes

Perhaps the most fundamental reaction in organic synthesis is the formation of a carbon-carbon bond. Organoboranes are particularly useful in this transformation. What follows is a brief overview of some of the more common carbon-carbon bond forming reactions of organoboranes.

1.5.1 Carbonylation

Trialkylboranes react with carbon monoxide with one, two, or three alkyl groups migrating depending upon the reaction conditions (Scheme 1-2).

Scheme 1-2. Reaction of Organoboranes with Carbon Monoxide.



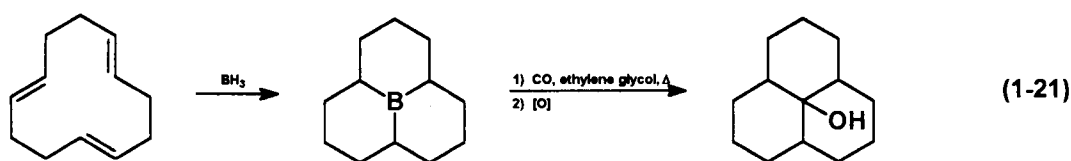
This makes possible the synthesis of various ketones, aldehydes, and homologated alcohols.

When trialkylboranes react with carbon monoxide in the presence of a hydride

reagent, such as potassium triisopropoxyborohydride (KIPBH), the rate of uptake of carbon monoxide is increased and the homologated aldehydes are obtained after oxidative work-up⁴³. Alkyl-9-BBN derivatives can be used to maximize the utilization of the alkyl group. Alternatively, the carbonylation intermediates may be treated with lithium aluminum hydride to form homologated alcohols⁴⁴ or they may be treated with acid, which induces migration of a second alkyl group, and then oxidized to give secondary alcohols⁴⁵.

The reaction of trialkylboranes with carbon monoxide is slow in the absence of hydride but the reaction does occur at elevated temperatures. If the reaction is performed at atmospheric pressure, at 100 °C, in the presence of a small amount of water, two alkyl groups migrate and oxidation of the intermediate produced gives ketones in excellent yields⁴⁶. As before, a mixed organoborane, such as a thexyl derivative, may be used to maximize the efficiency of the reaction.⁴⁷

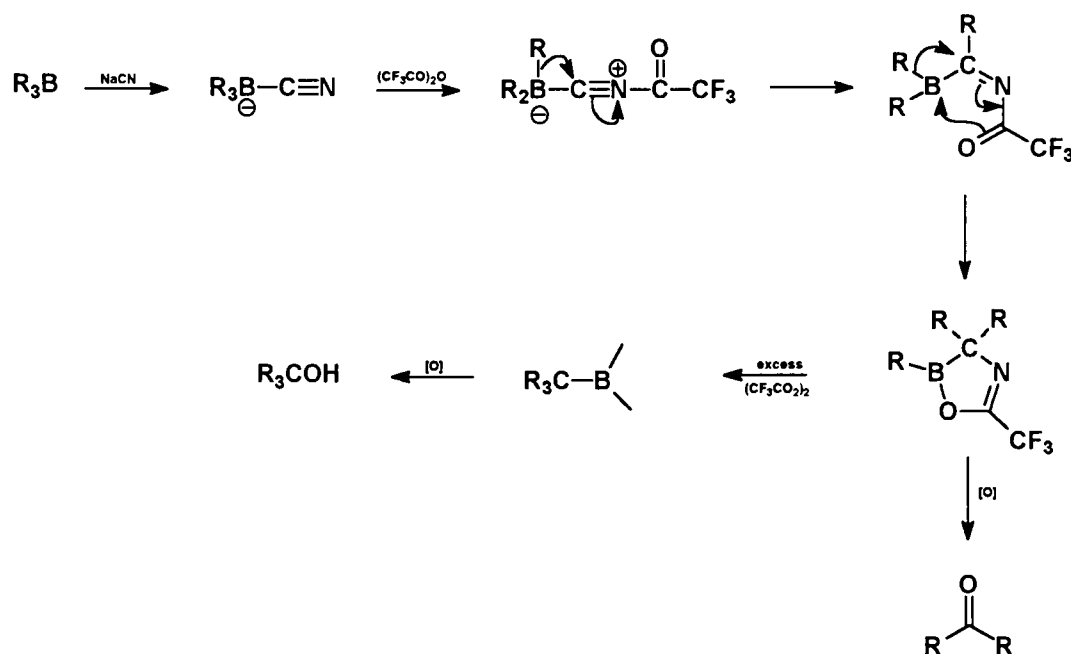
If water is excluded and the reaction is heated to a higher temperature in the presence of ethylene glycol, the third and last alkyl group will migrate to produce, after oxidation, the corresponding tertiary alcohol⁴⁸. This reaction can be used to prepare quite hindered tertiary alcohols which are not available via standard Grignard routes. This methodology can also be utilized to "stitch" a polyene together by hydroboration and then "rivet" the structure by carbonylation-oxidation (eqn 1-21)⁴⁹.



1.5.2 Cyanoborate Process

Trialkylboranes react with alkali metal cyanides to give the stable cyanotrialkylborate salts. These salts can be made to react further by the addition of an electrophilic reagent such as trifluoroacetic anhydride (Scheme 1-3)⁵⁰. Two groups

Scheme 1-3. The Cyanoborate Process.



initially migrate to produce an intermediate, which upon oxidation, gives a ketone⁵¹.

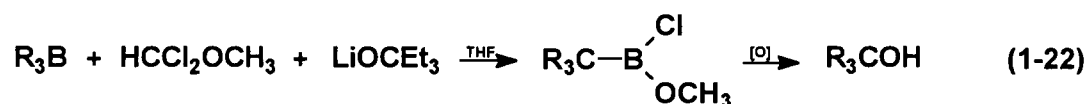
Thexylborane derivatives may be used to maximize the utilization of the alkyl groups⁵¹,

⁵². If the reaction is performed with an excess of trifluoroacetic anhydride and at a higher temperature, a third migration occurs to give an intermediate, which upon

oxidation, produces the tertiary alcohol⁵³. The cyanoborate process is a useful alternative to the carbonylation methodology in that it requires less forcing conditions to proceed.

1.5.3 DCME Reaction

A third approach to the synthesis of tertiary alcohols or ketones via organoboranes is the reaction of organoboranes with the anion of dichloromethyl ether (DCME) to give an intermediate which yields, after oxidation, the tertiary alcohol (eqn 1-22)⁵⁴. This is a milder alternative to the carbonylation reactions as it occurs at



25 °C. If the reaction is performed with an alkoxydialkylborane⁵⁵, easily prepared from the corresponding dialkylchloroborane⁵⁶, ketones are obtained.

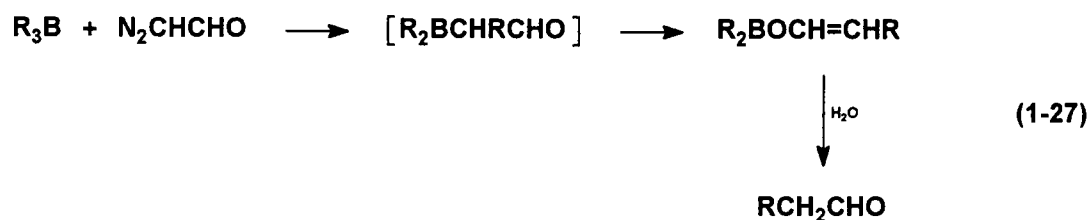
1.5.4 Reactions with Diazo Compounds

Trialkylboranes readily react with various α -diazocarbonyl compounds. Diazoacetaldehyde (eqn 1-23)⁵⁷, diazoacetone (eqn 1-24)⁵⁸, ethyl diazoacetate (eqn 1-25)⁵⁹, and diazoacetonitrile (eqn 1-26)⁵⁹ all react with trialkylboranes under mild



conditions to give excellent yields of the alkylated products.

Only one alkyl group migrates, which expels nitrogen from the diazo compound, to give an intermediate which spontaneously rearranges to the boron enolate (eqn 1-27)⁶⁰. Treatment of this boron enolate with water produces the corresponding two-carbon homologated product. Hydrolysis with D₂O gives the



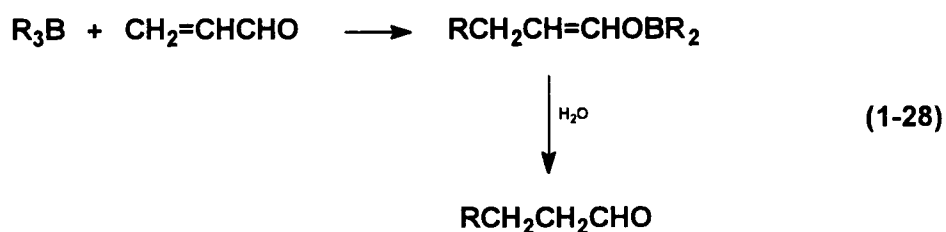
α -deuterioketones⁶¹ and halogenation with N-halosuccinimides produces the α -haloketones⁶².

This methodology suffers two distinct disadvantages. First, only one alkyl group is transferred. Second, the reaction rate and the yield decrease when bulky alkyl groups are present on the boron^{59a}. Typically, dialkylboron reagents such as 9-

BBN are used to surmount these problems. That solution, however, does not work with this reaction due to competitive migration of the cyclooctyl group. When 9-BBN is used, for example, the cyclooctyl ring preferentially migrates instead of the desired alkyl group⁶³. If a dichloro- or monochloroborane reagent is used, however, the yields of the homologated product increase and there is no competitive migration of the blocking chloro groups⁶⁴.

1.5.5 1,4-Addition Reactions

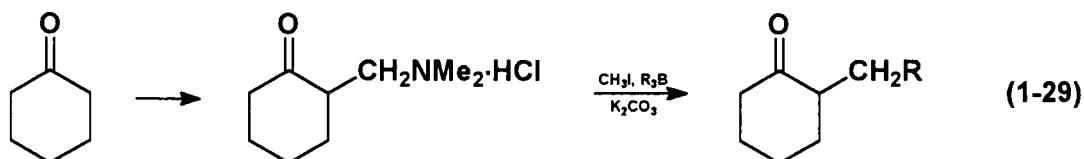
Saturated organoboranes are typically unreactive toward carbonyl addition. They do, however, readily add in a conjugate fashion to α,β -unsaturated systems to give, after hydrolysis, the corresponding alkylated product (eqn 1-28)^{65,66}.



Initially, the reaction was thought to proceed via a polar mechanism with the alkyl group being transferred via a six-membered transition state⁶⁷. Later, it was discovered that the reaction is actually radical in nature since the radical inhibitor galvinoxyl inhibits the reaction⁶⁷. In fact, it was subsequently found that free radical initiators such as oxygen increased the rate of reaction for substrates that were

sluggish or unreactive under the original conditions⁶⁸. Only one alkyl group is transferred in the reaction but alkyl group transfer can be maximized by the use of blocked boranes such as the diphenylalkylboranes⁶⁹.

The reaction appears to be general for a wide variety of α,β -unsaturated systems including the enol tautomer of β -dicarbonyl compounds (with photochemical irradiation)⁷⁰ and the α,β -unsaturated aldimines⁷¹. One particularly elegant application of this methodology is the reaction of organoboranes with Mannich bases which, when quaternized *in situ*, produce the alkylated ketone product in good yield (eqn 1-29)⁷².

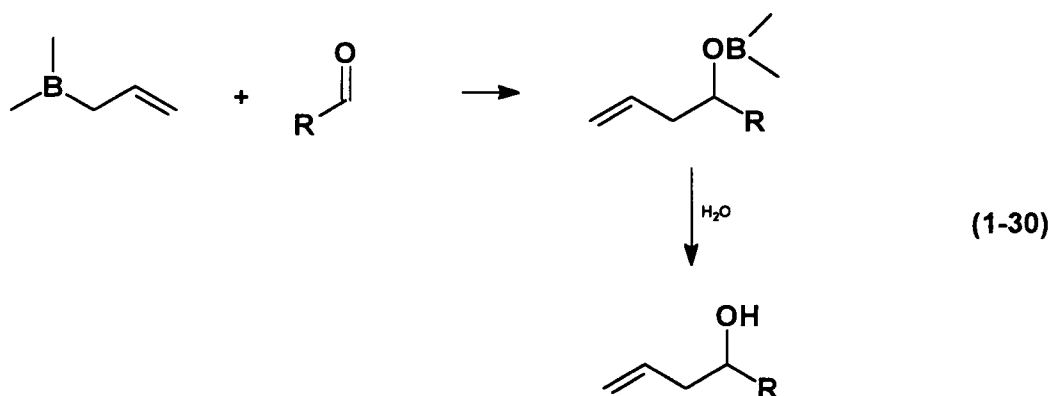


1.5.6 Unsaturated Organoborane Reactions

This introduction has thus far only dealt with the transfer of saturated alkyl groups from boron to carbon moieties. In addition, a large number of studies have been performed on the transfer of unsaturated alkyl groups from boron to carbon. In this section, this research is reviewed with special attention to the transfer of unsaturated alkyl groups from boron to carbonyl carbons.

1.5.6.1 Allylboration

Allylboron compounds react in an extremely facile manner with aldehydes and ketones to produce the corresponding homoallylic alcohols (eqn 1-30)⁷³.



Triallylborane reacts with carbonyl compounds but the reaction requires heating to transfer all three allyl groups⁷⁴. It is simpler to use either the dialkylallylboranes such as B-allyl-9-BBN⁷⁵ or dialkoxyallylboranes⁷⁶. Only the allyl group is transferred and the reaction proceeds at, or below, room temperature.

The reaction presumably proceeds via a six-membered transition state (Figure 1-5). This closely associated transition state allows control of asymmetric

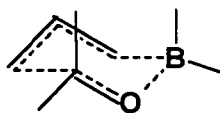
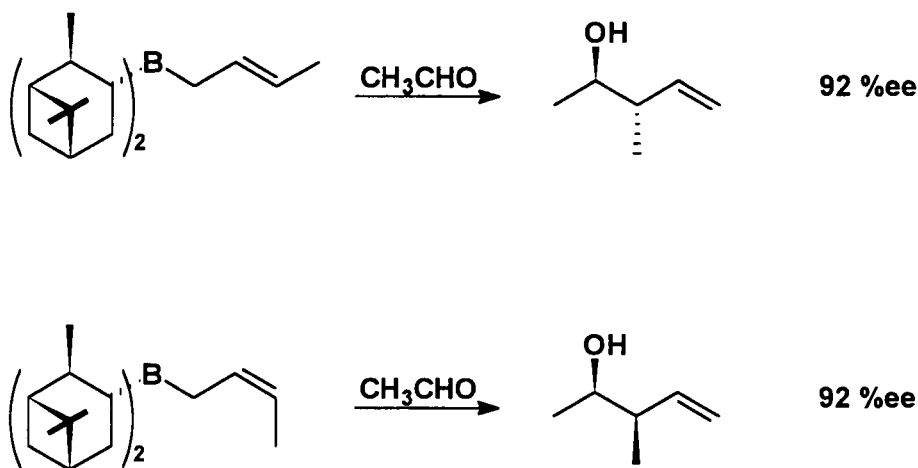


Figure 1-5. Transition State of Allylboration Reaction.

induction in the product through introduction of chiral modifying groups on the boron. Alkyl groups derived from naturally occurring terpenes⁷⁷ and optically active tartrate esters⁷⁸ have been used to achieve remarkable selectivities. If a crotyl group is used, instead of an allyl, control of two developing stereocenters is possible (Scheme 1-4)⁷⁹. The chiral blocking group controls the enantioselectivity while the double bond

Scheme 1-4. Crotylboration.

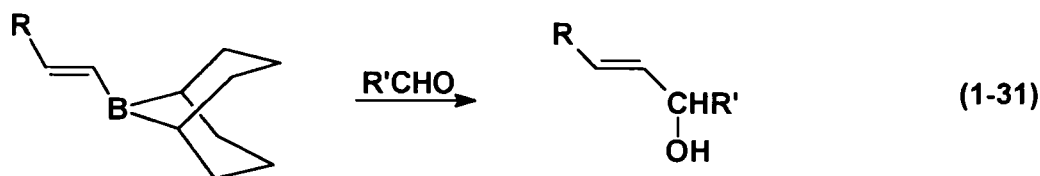


geometry of the crotyl group determines the diastereoselectivity.

1.5.6.2 Vinylboranes

B-Alkenyl-9-BBN derivatives, prepared by the hydroboration of terminal

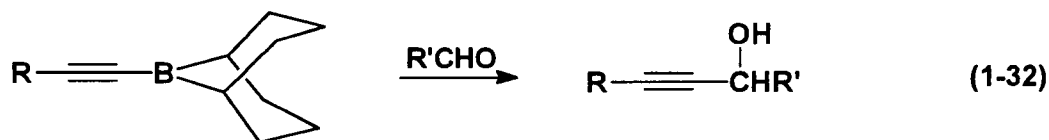
alkynes with 9-BBN, add to carbonyl groups in a Grignard-like fashion to produce the corresponding allylic alcohols (eqn 1-31)⁸⁰. The stereochemistry of the



alkenylborane is retained in the allylic alcohol product. The reaction occurs under relatively forcing conditions (16 hours in refluxing THF) and gives only moderate to good yields (36-86%). The reaction tolerates functional groups which may be incompatible with traditional organometallic reagents. For example, the alkenyl borane derived from 5-chloro-1-pentyne is readily transferred using this methodology.

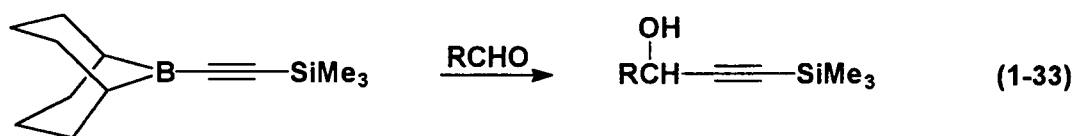
1.5.6.3 Alkynylboranes

In contrast to the vinylboranes cited in the previous section, *B*-alkynyl-9-BBN derivatives, prepared from the lithium acetylide and *B*-methoxy-9-BBN⁸¹, react smoothly and quickly at room temperature with aldehydes to give the corresponding propargylic alcohols in excellent yields (eqn 1-32)⁸². The reaction takes place with both aldehydes and ketones. Because of the alkynylboranes low basicity, the reaction tolerates functional groups such as esters, nitriles, halides, and acetals. In addition,



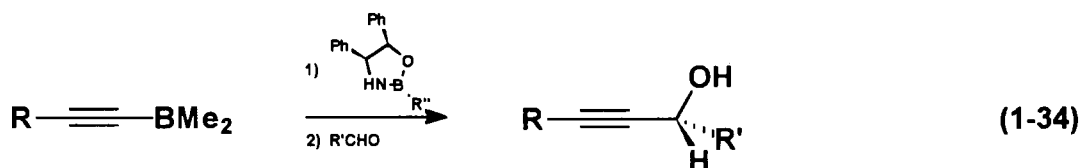
the *B*-alkynyl-9-BBN compounds exhibit remarkable chemoselectivity. The reagents will preferentially react with an aldehyde in the presence of a ketone and with a less-hindered ketone in the presence of a more hindered ketone⁸². This combination of mild basicity and chemoselectivity makes the alkynylboranes useful alternatives to the more traditional alkynyl metals.

Recently, researchers reported the preparation of *B*-[2-(trimethylsilyl)ethynyl]-9-borabicyclo[3.3.1]nonane and its reaction with ketones and aldehydes (eqn 1-33)⁸³.



This reagent is the functional equivalent of the unavailable *B*-ethynyl-9-BBN ($\text{R} = \text{H}$, eqn 1-32). The reagent was reported to produce good yields of the corresponding trimethylsilyl protected propargylic alcohols.

Corey recently reported a modification of this reaction which produces excellent yields of optically active propargylic alcohols (eqn 1-34)⁸⁴. By utilizing his proline-derived oxazaborolidines, he was able to accelerate the reaction and control the asymmetric induction at the developing stereocenter resulting in production of enantiomeric excesses of 85-96%.



1.5.7 1,2-Addition Reactions

In contrast to the unsaturated analogues, saturated trialkylboranes do not typically add to carbonyl compounds in a 1,2, or Grignard-like, fashion (eqn 1-35).



The reaction shown in eqn 1-35 is energetically favorable. The two bonds that are formed (the B-O and the C-C bonds) have energies of 120 kcal/mol⁸⁵ and 80 kcal/mol respectively. The two bonds broken (the C-O and the C-B bonds) have energies of approximately 60 kcal/mol⁸⁶ and 80 kcal/mol⁸⁷ respectively. The overall reaction, then, is thermodynamically favored by approximately 60 kcal/mol.

The earliest attempts at carbonyl alkylation via trialkylboranes consisted of simply heating a mixture of the organoborane and aldehyde to high temperatures. Instead of the desired alkylation, reduction via β -hydride elimination occurred (eqn 1-36)⁸⁸. In fact, it was subsequently shown that *B*-alkyl-9-BBN derivatives readily



reduce benzaldehyde under very mild conditions⁸⁹. The reduction was found to proceed via a six-membered cyclic transition state rather than a dehydroboration - reduction pathway (Fig 1-6).

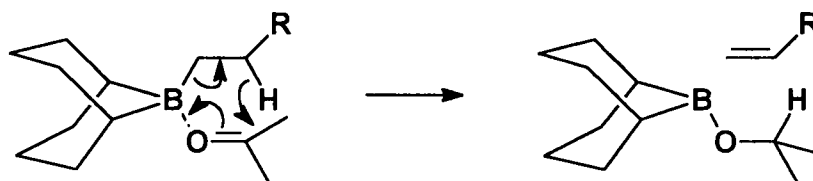


Figure 1-6. Reduction of Carbonyl Groups with *B*-Alkyl-9-BBN.

While the reduced carbonyl compound is clearly the major product in these reactions, alkylation products have been observed as minor components of the reaction mixture when a trialkylborane and a carbonyl compound were heated to 300 °C in the presence of hydroquinone⁹⁰.

As illustrated in the preceding paragraphs, the straightforward addition of a simple trialkylborane to a carbonyl moiety is not easily achieved. What follows are the few examples of successful alkylations of carbonyls using saturated organoborane compounds.

1.5.7.1 Free-Radical Alkylation of Formaldehyde Via Trialkylboranes

In the absence of air, monomeric formaldehyde reacts rapidly with tributylborane to produce the reduced product, di-*n*-butylmethylborinate, and 1-butene (eqn 1-37). In the presence of air, however, the reaction proceeds through an



alkylation pathway producing the one-carbon homologated product (eqn 1-38)⁹¹.



This is the first reported example of a direct 1,2-addition of a simple trialkylborane to a carbonyl group. Unfortunately, the reaction does not appear to be general for all aldehydes. It is general, though, for several trialkylboranes (Table 1-1).

Table 1-1. Reaction of R_3B with CH_2O in the Presence of Air.

R_3B	% yield $\text{RCH}_2\text{OH}^{(a)}$
Tri- <i>n</i> -butyl	78
Tri- <i>n</i> -octyl	79
Tri- <i>n</i> -isobutyl	29
Tri- <i>n</i> -sec-butyl	45

^(a)Yield based on one group migrating.

The alkylation reaction is thought to be free-radical in nature, as iodine completely inhibits the alkylation pathway producing the reductive dealkylation compound as the sole product. The following free-radical mechanism is proposed for the alkylation. Oxygen reacts with the trialkylborane to produce an alkyl radical (eqn 1-39). This then reacts with formaldehyde to produce an alkoxy radical (eqn 1-40). The alkoxy radical can then displace an alkyl radical from another molecule of trialkylborane to produce the homologated product and regenerate the alkyl radical



(eqn 1-41). The reduction pathway, which occurs under inert atmosphere conditions, is thought to proceed via a six-member transition state (Figure 1-6)^{89,91}.

Due to the availability of more general and efficient routes for one carbon homologation of trialkylboranes this reaction has received little attention.

1.5.7.2 Lithium Tetraorganoborate Additions to Carbonyl Compounds

Negishi and co-workers reported, in 1975, that lithium tetraorganoborates underwent a smooth reaction with acyl chlorides to produce the corresponding ketones in good yield (eqn 1-42)⁹². The lithium tetraorganoborate is easily prepared from the



corresponding alkyllithium and trialkylborane. The reaction is general for a wide variety of acyl chlorides and trialkylboranes (Table 1-2).

Table 1-2. Reaction of Lithium Tetraorganoborates with Acyl Chlorides.

R	R'	R''	Product	%yield
<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	Ph	<i>n</i> -C ₄ H ₉ COPh	80
<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	(<i>n</i> -C ₄ H ₉) ₂ CO	53
<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	CH ₂ =CH(CH ₂) ₈	<i>n</i> -C ₄ H ₉ CO(CH ₂) ₈ CH=CH ₂	69
PhCH ₂	<i>n</i> -C ₄ H ₉	Ph	PhCH ₂ COPh	88
<i>n</i> -C ₄ H ₉	<i>c</i> -C ₃ H ₉	MeO ₂ C(CH ₂) ₂	<i>n</i> -C ₄ H ₉ CO(CH ₂) ₂ CO ₂ Me	76

Primary alkyl groups are transferred preferentially over secondary alkyl groups. The trialkylborane produced in the reaction may be recovered quantitatively and reused. The reacting species is postulated to be the lithium tetraorganoborate. No prior dissociation to organoborane and alkyllithium is thought to occur. Based on these observations, Negishi states that this reaction may be considered an

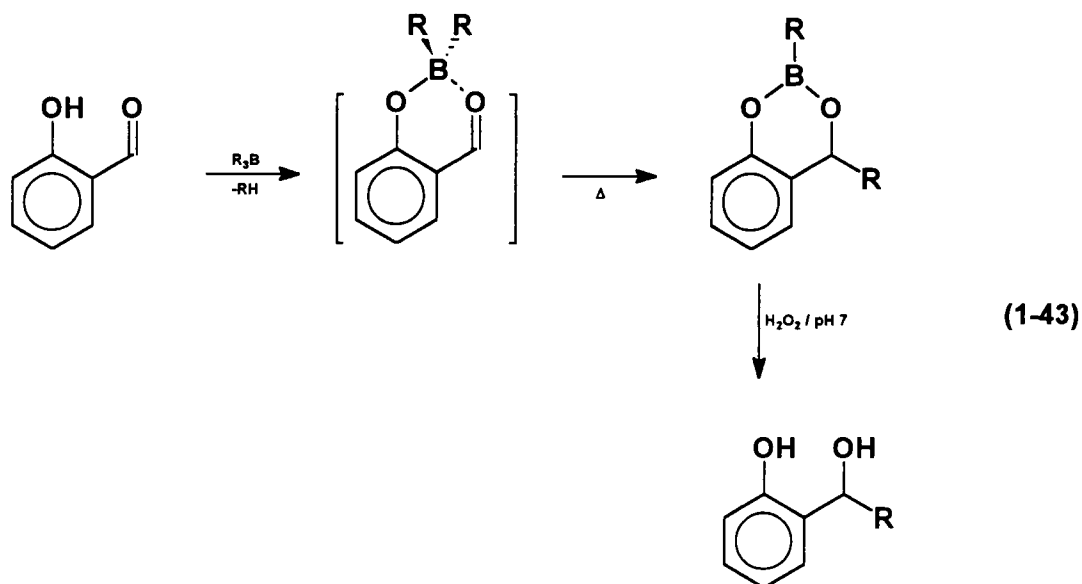
organoborane-moderated reaction of an organolithium with an acyl halide^{92a}. This moderation allows one to produce only the keto product instead of the carbinol product which typically is formed in reactions of acyl halides and alkyllithium reagents. Also, this moderation affords some degree of chemoselectivity as the reaction may be performed with groups containing other carbonyl functionalities such as esters (Table 1-2, entry 5).

Lithium tetraorganoborates do not react with typical electrophiles such as methyl iodide, dimethyl sulfate, cyclohexanone, or propylene oxide^{92c}. However, the reaction of lithium *tetra-n*-butylborate with benzyl chloride at 125 °C has been reported to give the alkylation product 1-phenylpentane in 5 % yield⁹³.

Suzuki has reported a modification of this methodology using copper (I) methyltrialkylborates⁹⁴. The reaction of these copper (I) borates with acyl halides is similar to the reaction shown in equation 1-42. The copper (I) methyltrialkylborates may also be used to perform a 1,4-addition to acrylonitrile and ethyl acrylate⁹⁵ and to alkylate benzyl bromides⁹⁶.

1.5.7.3 Alkylation of *o*-Hydroxyarylaldehydes Via Trialkylboranes

The carbonyl group of an *o*-hydroxyarylaldehyde may be easily alkylated with a trialkylborane (eqn 1-43)⁹⁷.



The reaction appears to be general for both trialkylborane and *o*-hydroxyarylaldehyde (Table 1-3).

Table 1-3. Reaction of Trialkylboranes with *o*-Hydroxyarylaldehydes.

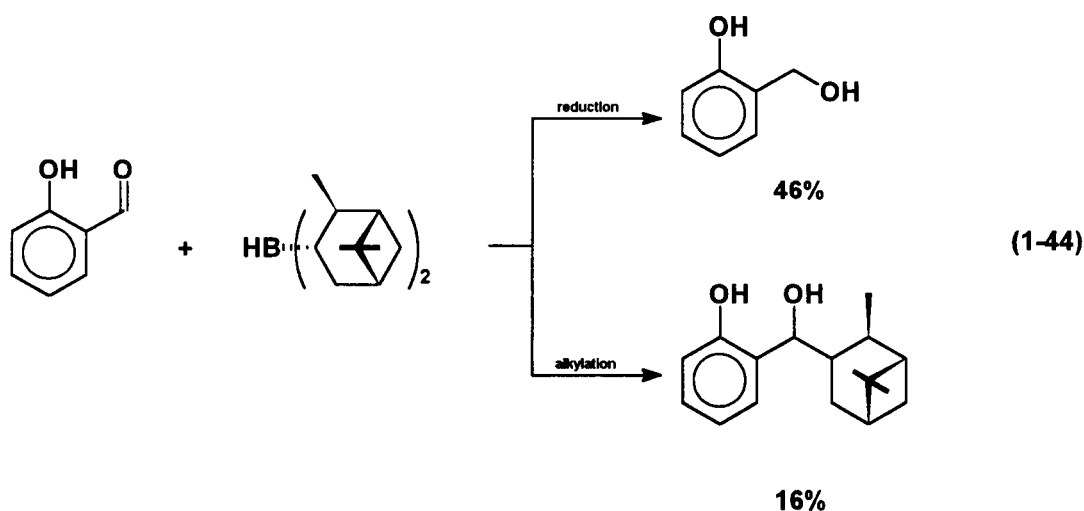
<i>o</i> -Hydroxyarylaldehyde	Trialkylborane	% Yield ^(a)
salicylaldehyde	Tricyclohexyl	83
salicylaldehyde	Tri- <i>n</i> -butyl	57
salicylaldehyde	Trinorbornyl	52
1-formyl-2-naphthol	Tricyclohexyl	69
1-formyl-2-naphthol	Tri- <i>n</i> -butyl	53
1-formyl-2-naphthol	Trinorbornyl	47

^(a)Yield based on one group migrating.

A hydroxy group *ortho* to a formyl group is necessary for the reaction to occur. The attempted alkylation of *o*-methoxybenzaldehyde resulted in the complete recovery of starting material. Likewise, reactions attempted using *o*-hydroxyacetophenone resulted in the reduction of the carbonyl group rather than alkylation.

Addition of the radical inhibitor galvinoxyl depresses the yield of the reaction presented in entry 1 of Table 1-3 from 83% to 46%. This suggests the reaction may proceed by a free-radical mechanism similar to the well-known 1,4 addition reactions⁶⁷.

The authors demonstrated the facile nature of this alkylation by comparing the competing products in the reduction of salicylaldehyde with diisopinocampheylborane (eqn 1-44). Sixteen percent of the alkylated product was produced illustrating the ease of the alkylation. HPLC and NMR analysis of the alkylated product indicated that no substantial diastereoselectivity had occurred. This may be taken as further evidence of



a free-radical mechanism.

1.5.7.4 1-Boraadamantane

1-Boraadamantane (Figure 1-7) is one of the most unusual organoboranes. It is unique in that the boron is not trigonal but rather is forced into a pyramidal

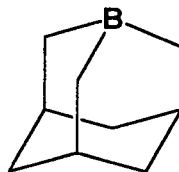
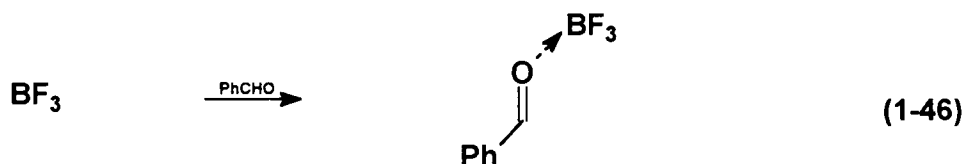
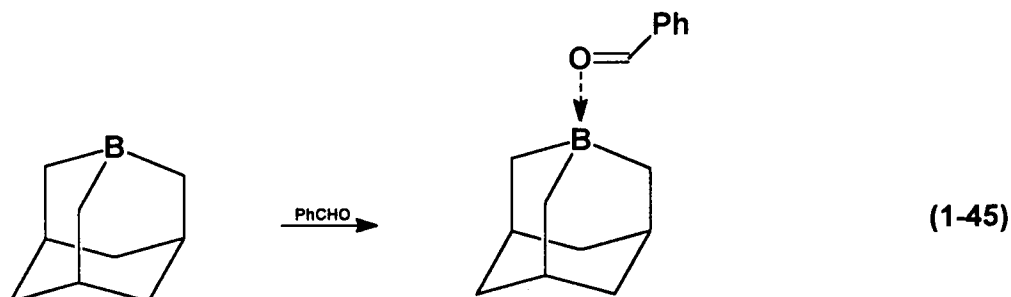


Figure 1-7. 1-Boraadamantane.

geometry by the adamantyl structure⁹⁸. Because of this sp^3 hybridization, 1-boraadamantane exhibits enhanced reactivity and complexing ability versus ordinary trialkylboranes. For example, 1-boraadamantane forms complexes with pyridine and triethylamine which do not dissociate even at 200 °C^{98a,b}. 1-Boraadamantane also reacts with carbonyl compounds to form strong complexes (eqn 1-45). The IR absorption band for the complexed carbonyl in benzaldehyde is shifted 70-75 cm^{-1} to a lower frequency compared to the free carbonyl compound⁹⁹. This is comparable to the 70-80 cm^{-1} shift that occurs when BF_3 complexes with benzaldehyde (eqn 1-46)¹⁰⁰. Thus, 1-boraadamantane appears to be of comparable Lewis acidity as BF_3 which is extraordinary for a trialkylborane.

1-Boraadamantane is a solid, colorless substance which sublimes to give well-formed prisms^{98c}. It may be prepared in good yield as shown in Scheme 1-5.

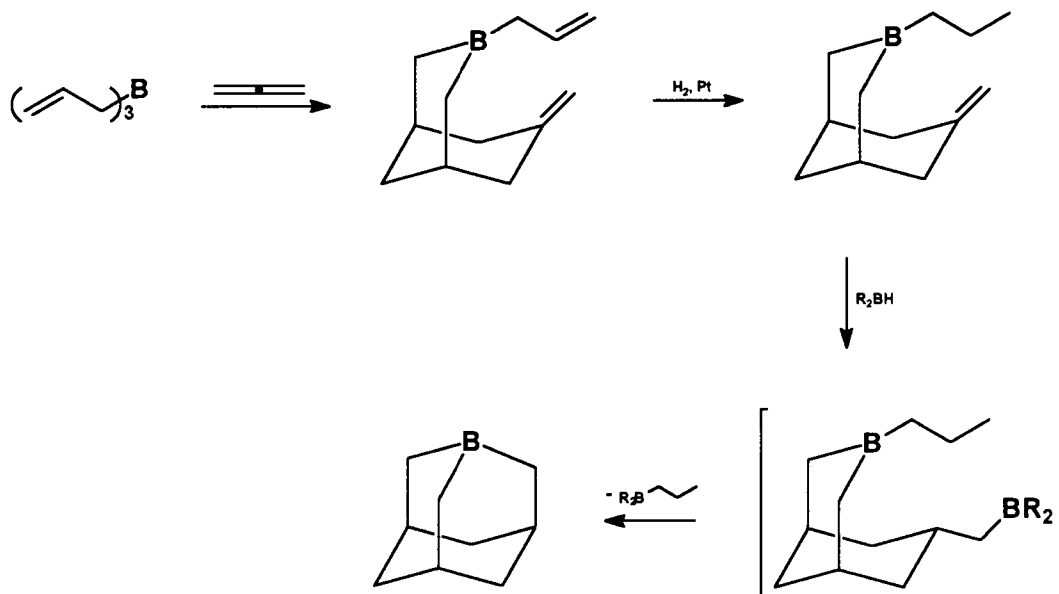
Condensation of triallylborane with allene gives 3-allyl-7-methylene-3-



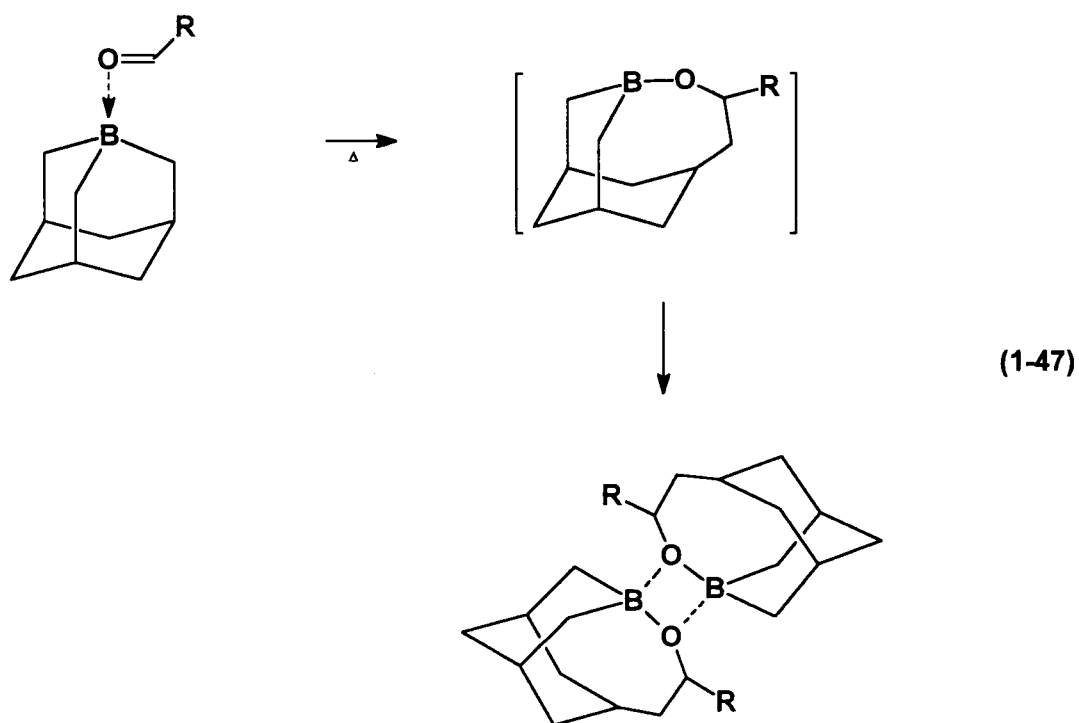
borabicyclo[3.3.1]nonane. The free allyl group is then hydrogenated to give the propyl derivative. Hydroboration of the resulting product with a dialkylborane gives a transient compound which cyclizes and eliminates a trialkylborane to give 1-boraadamantane in good yield^{98c,101}.

1-Boraadamantane undergoes several standard organoborane reactions with great ease. It may be carbonylated to produce 1-adamantyl alcohol¹⁰¹, aminated in a short synthesis of 1-azaadamantane¹⁰², or allowed to react with Wittig reagents to produce 4-alkyl-3-borahomoadamantanes¹⁰³.

Scheme 1-5. Preparation of 1-Boraadamantane.

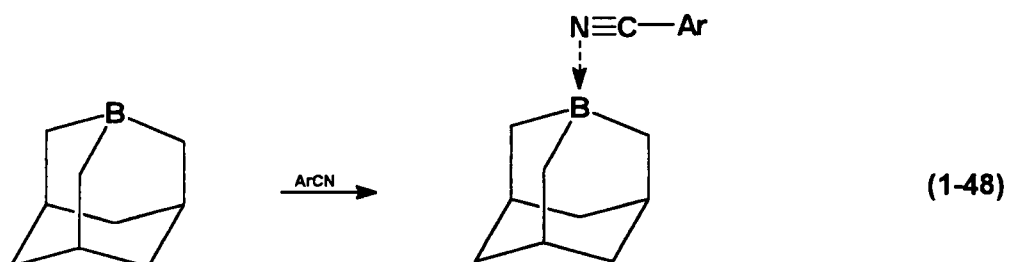


It is 1-boraadamantane's reaction with carbonyl compounds that is especially interesting and merits its inclusion in this introduction. The complex formed when 1-boraadamantane reacts with a carbonyl compound (eqn 1-45), when heated, undergoes a rearrangement to produce a 5-substituted derivative of 4-oxa-3-bora-1,1-bihomoadamantane which exists as a dimer (eqn 1-47)⁹⁹. One alkyl group has migrated from boron to carbon in a 1,2 fashion. This reaction follows the traditional organometallic route; that is, complexation of the metal with the carbonyl oxygen followed by alkyl group transfer. It has been suggested that the remarkable complexing ability and Lewis acidity of 1-boraadamantane is responsible for this

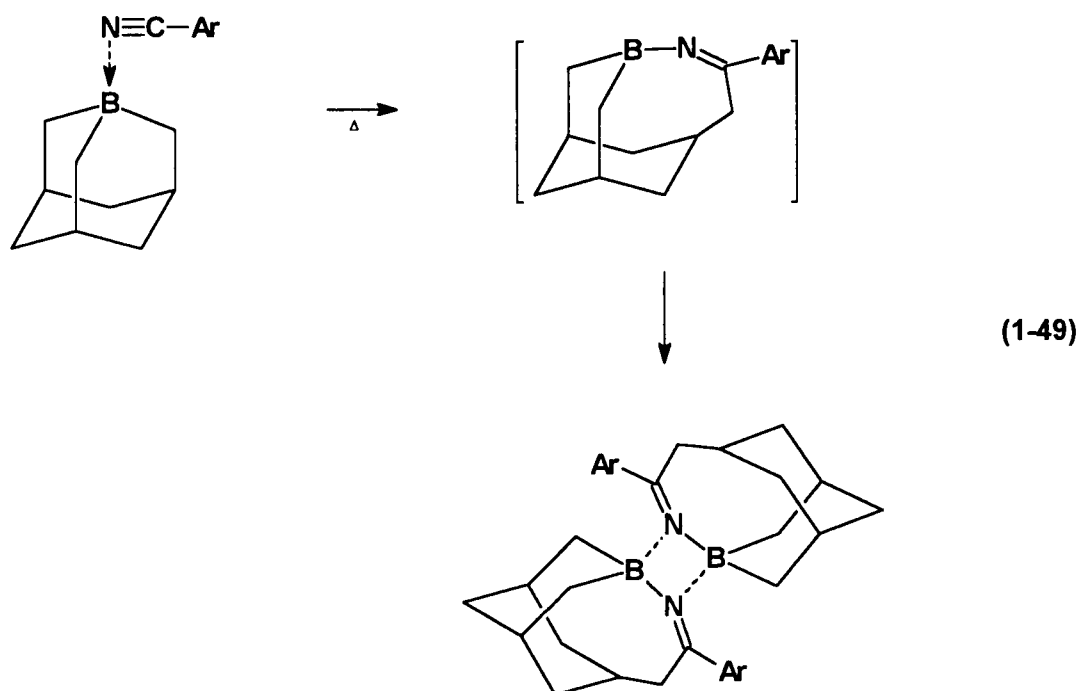


extraordinary reaction with carbonyls.

1-Boraadamantane undergoes a similar reaction with aromatic nitriles¹⁰⁴. 1-Boraadamantane reacts with aromatic nitriles to produce the corresponding complexes in good yields (eqn 1-48). As with the carbonyl complexes, when the nitrile



complexes are heated to 200 °C, they undergo a similar rearrangement with one migration taking place to give the dimer shown (eqn 1-49). This reaction, like the reaction with carbonyl compounds, is unprecedented in organoborane chemistry.



The usefulness of 1-boraadamantane's reactions with carbonyl compounds is diminished by the carbocyclic nature of the products formed. No method has yet appeared in the literature utilizing this chemistry to deliver simple alkyl groups to carbonyl compounds. If this could be realized, it would be a significant contribution.

1.6 Statement of Problem

The 1,2-addition of a trialkylborane to a carbonyl compound or derivative would be a valuable addition to organic methodology. The utilization of a boron reagent in such a manner would have several benefits. First, use of an organoborane reagent would eliminate many of the side reactions (such as enolization, condensation, and reduction) that are associated with the strongly basic, traditional organometallic reagents¹⁰⁵; organoboron reagents are not basic and are stable to many protic solvents such as alcohols and water. Second, organoboranes tolerate a wide variety of functional groups which makes available an almost unlimited selection of moieties that can be transferred⁷; functional groups such as halides, esters, and nitriles, which are not compatible with traditional organometallics, could theoretically be incorporated in reactions using an organoborane reagent. Finally, as shown in section 1.3.3, it is possible to incorporate chiral auxiliaries in the organoborane reagent in order to induce asymmetry in the product molecule; using this methodology, one could then readily perform stereocontrolled alkylations of carbonyl compounds. This is not easily accomplished with traditional organometallics¹⁰⁶.

This dissertation summarizes research focused on a study of the alkylation of arenesulfonylhydrazone derivatives of aryl and aliphatic aldehydes via trialkylboranes to produce the corresponding substituted alcohols in good to excellent yields. This reaction is the equivalent of a 1,2-addition of a trialkylborane to a carbonyl. Further,

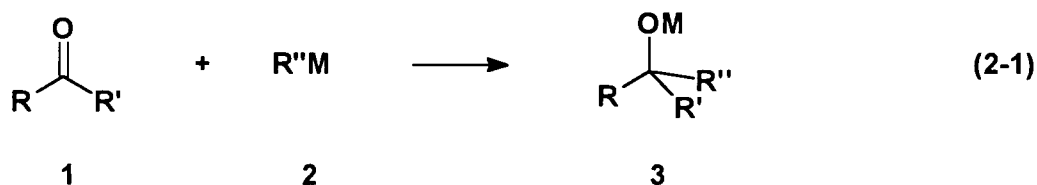
this dissertation also delineates various approaches which have been examined in an attempt to achieve the direct addition of a trialkylborane to a carbonyl moiety.

Finally, possible avenues for future research are suggested.

**CHAPTER 2. ALKYLATION OF ARYL ALDEHYDE
ARENESULFONYLHYDRAZONES VIA TRIALKYLBORANES**

2.1 Introduction

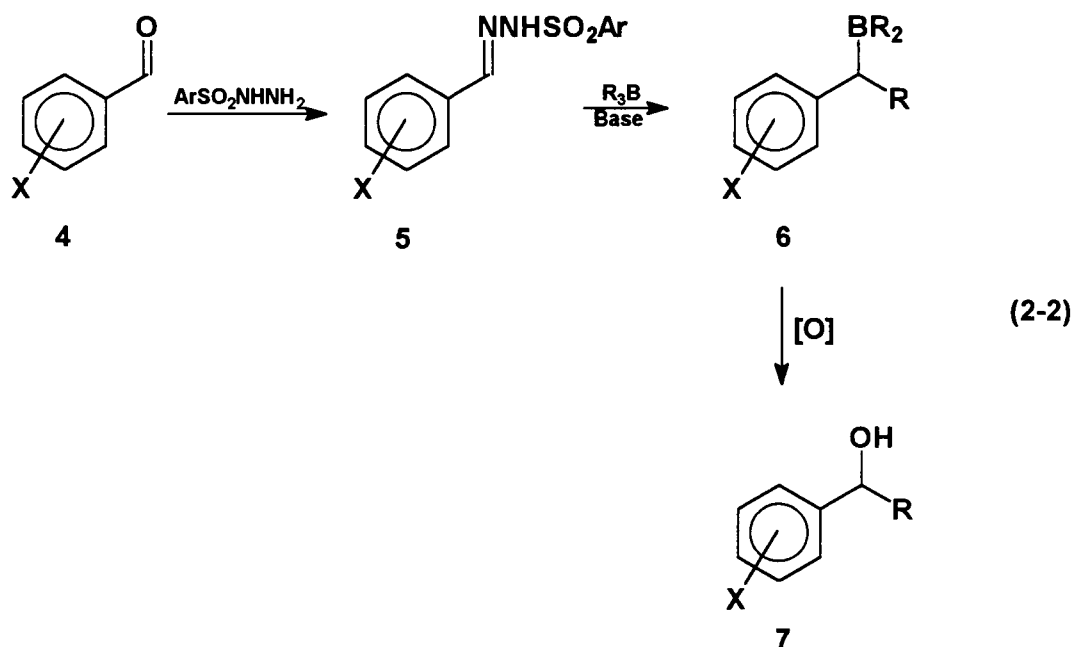
The formation of carbon-carbon bonds is a fundamental transformation in organic chemistry. One of the most utilized methods for achieving this conversion is the reaction of an alkylmetal reagent with a carbonyl compound (eqn 2-1). Typically, only active alkylmetal reagents such as organomagnesium¹⁰⁷, organolithium¹⁰⁸,



or organozinc¹⁰⁹ are used but their basicity limits their reactions to non-functionalized alkyl groups. Organoboranes tolerate a wide variety of functional groups and their use in carbonyl addition reactions would make it possible to transfer a wide selection of alkyl groups. As shown in Chapter 1, however, saturated organoboranes do not typically participate in carbonyl addition reactions.

This chapter details the development of a new alkylation reaction which allows the achievement of the overall 1,2-addition of a saturated organoborane to a carbonyl

compound: the alkylation of arenesulfonylhydrazones. Trialkylboranes react with aryl aldehyde arenesulfonylhydrazone derivatives, **5**, in the presence of a non-nucleophilic base to produce new trialkylboranes, **6**, which may be oxidized to give the corresponding alcohols, **7** (eqn 2-2). Alcohol **7** is equivalent to the product of a



1,2-addition of the trialkylborane to the starting aldehyde **4**.

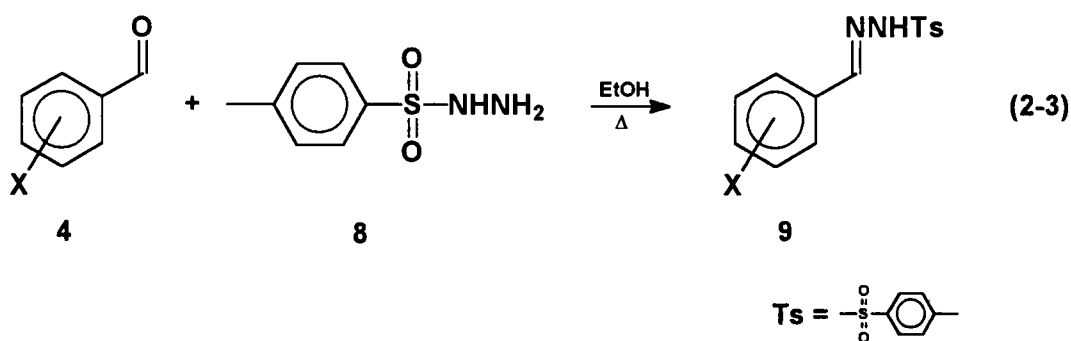
This chapter details the preparation of arenesulfonylhydrazone derivatives, **5**, and their subsequent alkylation via organoborane reagents to produce good yields of alcohols **7**.

2.2 Aryl Aldehyde Tosylhydrazones

The first arenesulfonylhydrazones to be studied were the readily available tosylhydrazones. The derivatizing agent, *p*-toluenesulfonylhydrazide, is commercially available and its hydrazone derivatives have been extensively studied and characterized.

2.2.1 Synthesis of Aryl Aldehyde Tosylhydrazones (9)

Aryl aldehyde tosylhydrazones, **9**, are stable, crystalline solids which are readily prepared by refluxing *p*-toluenesulfonylhydrazide, **8**, with the corresponding aryl aldehyde, **4**, in absolute ethanol (eqn 2-3)¹¹⁰. The resulting precipitate may



be purified by recrystallization from a minimum quantity of hot ethanol. Table 2-1 lists the substituted aryl aldehyde tosylhydrazones which were prepared for this study.

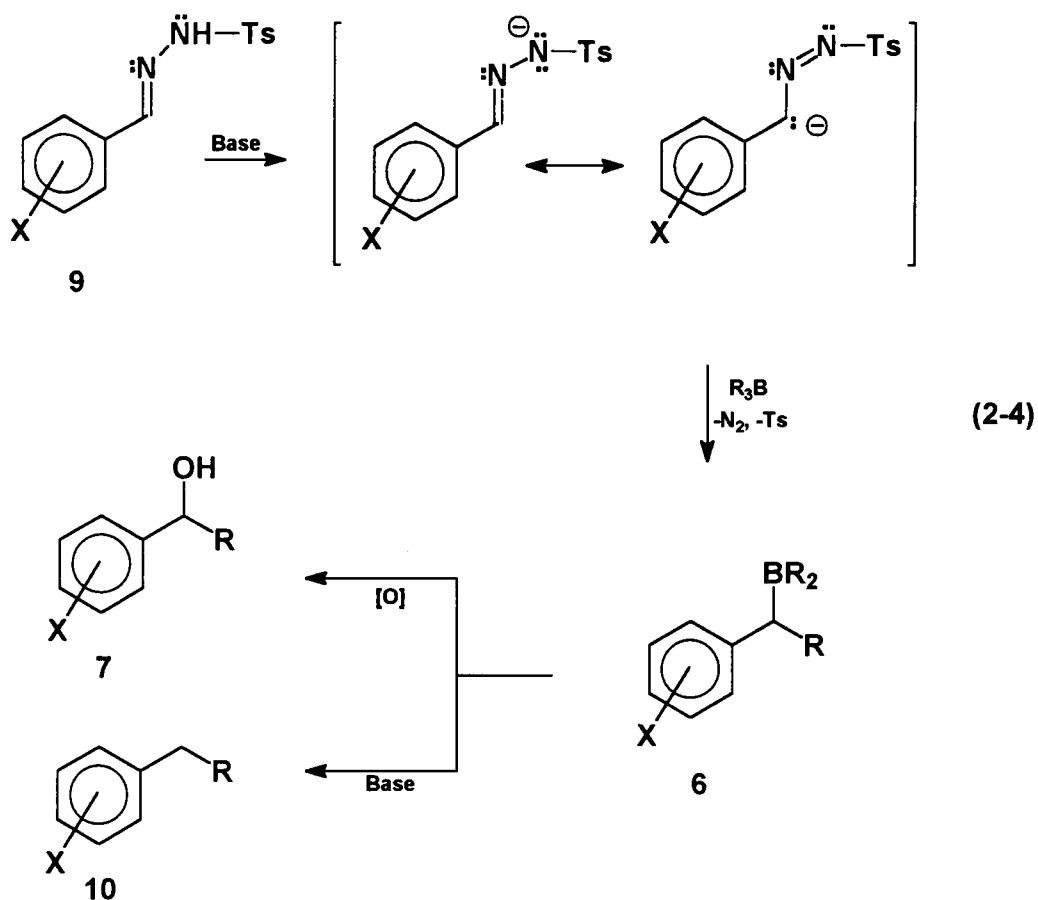
Table 2-1. Synthesis of Aryl Aldehyde Tosylhydrazones (**9**).

Entry	X	% yield ^(a)	m.p. (°C)
1	H (9a)	72	125.0 - 128.0
2	4-methyl (9b)	74	148.5 - 150.9
3	4-methoxy (9c)	89	110.0 - 112.0
4	3-methoxy (9d)	69	107.5 - 108.5
5	2-methoxy (9e)	85	157.0 - 160.0
6	4-chloro (9f)	67	163.5 - 165.3
7	4-bromo (9g)	80	172.0 - 176.0
8	3-bromo (9h)	72	114.5 - 117.5
9	2-bromo (9i)	84	165.0 - 167.5
10	3-nitro (9j)	79	159.1 - 160.2
11	4-nitro (9k)	81	156.8 - 158.2
12	2,4,6-trimethyl (9l)	85	162.8 - 166.0

^(a)Isolated yield based on starting aldehyde.

2.2.2 Choice of Base

The choice of base used in this alkylation reaction is dependent upon two factors. First, the base must be strong enough to remove the sulfonamide proton from the aryl aldehyde tosylhydrazone. Second, the base must be non-nucleophilic because the intermediate organoborane, **6**, produced in the reaction is easily hydrolyzed to the alkane, **10** (eqn 2-4)¹¹¹. In fact, if a nucleophilic base such as Bu₄NOH¹¹² or NaOH¹¹³ is used, excellent isolated yields of the corresponding aryl alkanes, **10**, are obtained.



Several bases were surveyed for possible use in this new reaction. Triethylamine, diisopropylethylamine, diethylamine, Proton Sponge (1,8-bis(dimethylamino)naphthalene), and lutidine produced little or no product. These hindered bases were not strong enough to remove the sulfonamide proton from the tosylhydrazone in the initial step of the reaction.

The strong kinetic bases, butyllithium, lithium hexamethyldisilazide (LiHMDS), and sodium hydride produced modest yields of the product alcohol. The chief

drawback to their use is that they form tosylhydrazone anion salts which precipitate out of solution. This impedes further reaction with the trialkylborane.

The hindered base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Figure 2-1), produced a 43 % yield of product alcohol in seven hours at room temperature. Simply heating the mixture to reflux in THF increased the yield of alcohol to 73 % in one

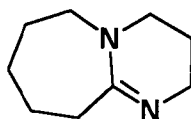


Figure 2-1. DBU

hour. DBU is a sufficiently strong base to produce the tosylhydrazone anion necessary for reaction with trialkylborane. It is also non-nucleophilic so it does not hydrolyze the intermediate organoborane produced in the reaction between the tosylhydrazone anion and the trialkylborane. Consequently, DBU was chosen as the standard base for this study.

The other standard conditions for this study were chosen in a similar manner. Heating the reaction to reflux in THF until the starting material had disappeared as evidenced by TLC was found to give the best yields of product. Also, because of its availability, tributylborane was chosen as the standard trialkylborane for the initial part of this study.

2.2.3 Choice of Oxidant

This new alkylation reaction has, as its last step, the oxidation of the intermediate organoborane, **6**, to the product alcohol, **7** (eqn 2-2). Compound **6** is a benzylic organoborane and, as noted, is particularly susceptible to hydrolysis to the alkane. Because of this, use of the classical sodium hydroxide-hydrogen peroxide oxidation procedure must be avoided as the nucleophilic hydroxide anion reduces the yield of alcohol produced¹¹.

Sodium perborate ($\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$) is a stable, easily handled, solid oxidant which has an excellent shelf life. It has been shown to be an efficient oxidizing agent for trialkylboranes²⁷. The oxidations proceed at room temperature under conditions less stringent than the classical procedure. Use of this oxidant produced the corresponding alcohols in good yield (Table 2-2). Some alkane is produced as a by-product since water is added with the sodium perborate and some hydrolysis occurs (eqn 2-5).

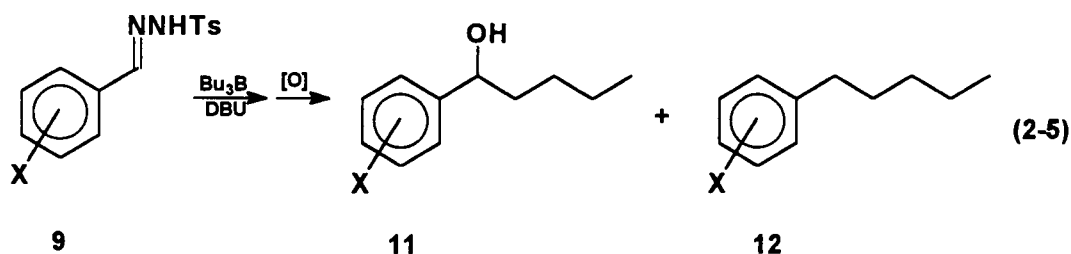


Table 2-2. Synthesis of Aryl Alcohols (**11**) via Oxidation by Sodium Perborate.

Entry	X	Time (hr)	% Yield 11 ^(a)	% Yield 12 ^(a)
1	H (9a)	0.5	73	15 ^(b)
2	4-methyl (9b)	1.5	83	5 ^(b)
3	4-methoxy (9c)	3	71	8 ^(b)
4	3-methoxy (9d)	1.5	76	15
5	2-methoxy (9e)	1.5	86	14
6	2, 4, 6-trimethyl (9l)	1	90	0
7	4-bromo (9g)	1	30	70
8	4-nitro (9i)	1	0	87

^(a)Isolated yield based on tosylhydrazone. ^(b)GC yield.

The reaction times listed in Table 2-2 are the times required for the starting material to disappear as evidenced by TLC.

The reaction tolerates substituents on the ring. The methoxy and methyl substituted tosylhydrazones give good yields of alcohol **11**. The three methoxy substrates (entries 3-5) demonstrate that the substituent may be present at any position on the ring. The hindered 2,4,6-trimethyl derivative, which is prepared from mesitaldehyde, produces an excellent yield of alcohol which suggests that the reaction is insensitive to steric effects present in the tosylhydrazone.

The 4-bromobenzaldehyde (**9g**) and 4-nitrobenzaldehyde (**9i**) tosylhydrazones produced alkane product rather than alcohol. These *para*, electron-withdrawing substituents apparently stabilize the benzylic anion formed during the hydrolysis of the intermediate organoborane making the formation of the alkane more favored. A less

basic oxidant was needed for these derivatives.

Peracetic acid has been used to oxidize water sensitive organoboranes¹¹⁴. Use of peracetic acid with reactants bearing electron-withdrawing substituents increased the yield of alcohol dramatically (Table 2-3). The use of peracetic acid reversed the result obtained with sodium perborate in the 4-bromobenzaldehyde case (entry 3). Several substrates bearing electron-withdrawing groups were used in the reaction and most gave excellent yields of alcohol **11** with the rest of the product mixture being the hydrolysis by-product **12**. The three bromo derivatives (entries 3-5) demonstrate, again, that the position of the substituent has little or no effect on the yield of the reaction. The yield with benzaldehyde tosylhydrazone (**9a**) was essentially the same as that obtained with the sodium perborate oxidation (entry 1).

Table 2-3. Synthesis of Aryl Alcohols (**11**) via Oxidation by Peracetic Acid.

Entry	X	Time (hr)	% Yield 11 ^(a)	% Yield 12 ^(a)
1	H (9a)	0.5	74	17
2	4-chloro (9f)	0.5	80	15 ^(b)
3	4-bromo (9g)	1	80	17
4	3-bromo (9h)	1	78	18
5	2-bromo (9i)	1	80	17 ^(b)
6	3-nitro (9j)	1	62	23
7	4-nitro (9k)	1	0	84

^(a)Isolated yield based on starting tosylhydrazone. ^(b)GC yield.

The 3-nitro derivative (entry 6) produced a low yield of alcohol compared to the other entries due to the tremendous electron withdrawing properties of the nitro group. In fact, when the nitro group was *para* to the original carbonyl (entry 7), only the alkane product was produced. Both oxidizing procedures ($\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ and peracetic acid) produced only alkane from the 4-nitro substrate. Use of an anhydrous oxidant such as trimethylamine N-oxide (TMANO)^{25a} also resulted in production of alkane (Table 2-4). Apparently the 4-nitro group stabilizes the incipient benzylic anion involved in the hydrolysis of the intermediate organoborane to such an extent that it becomes the sole reaction pathway. Use of the anhydrous TMANO oxidation did not increase the yield of alcohol obtained with the 3-nitro derivative, **9j** (entry 2).

Table 2-4. Synthesis of Aryl Alcohols (**11**) via Oxidation by TMANO.

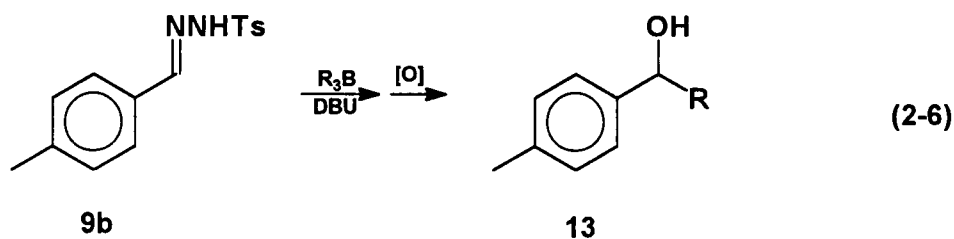
Entry	X	Time (hr)	% Yield 11 ^(a)	% Yield 12 ^(a)
1	H (9a)	0.5	83	--
2	3-nitro (9j)	1	64	24
3	4-nitro (9k)	1	0	84

^(a)Isolated yield based on tosylhydrazone.

It did, however, increase the yield of alcohol produced from benzaldehyde tosylhydrazone, **9a** (entry 1).

2.2.4 Use of Functionalized Organoboranes

An advantage of this new alkylation reaction is that functionalized alkyl groups can be incorporated into the product alcohol (eqn 2-6). As stated in Chapter 1, this



is difficult to achieve with traditional organometallic reagents. Several functional groups may be present in the alkyl group transferred in this new alkylation reaction (Table 2-5). Table 2-5 lists the alkenes used to generate the functionalized organoboranes and the yields of the respective alcohols after reaction with *p*-tolualdehyde tosylhydrazone, **9b**. Entries 1-3 demonstrate that a halo, cyano, and ester group are readily transferred using this methodology. Entries 4 and 5 demonstrate that secondary groups may be transferred as well.

Table 2-5. Synthesis of Functionalized Aryl Alcohols (**13**).

Entry	Alkene	R	% Yield 13 ^(a)
1	5-chloro-1-pentene	-CH ₂ (CH ₂) ₃ CH ₂ Cl (13a)	76
2	5-cyano-1-pentene	-CH ₂ (CH ₂) ₃ CH ₂ CN (13b)	72
3	Methyl-10-undecenoate	-CH ₂ (CH ₂) ₉ CO ₂ CH ₃ (13c)	75
4	Cyclohexene	-Chx ^(b) (13d)	68
5	2-butene	-CH(CH ₃)CH ₂ CH ₃ (13e)	51

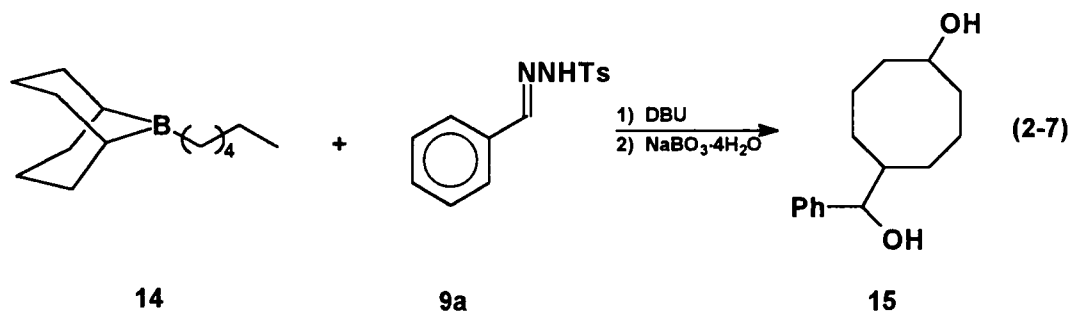
^(a)Isolated yield based on starting tosylhydrazone. ^(b)Chx = cyclohexyl.

2.2.5 Use of Borane Derivatives

From the beginning of this study, it was recognized that the stoichiometry of the reaction was one equivalent of organoborane to one equivalent of aryl aldehyde tosylhydrazone. Only a single group is transferred from the three available on the trialkylborane. This is not uncommon in organoborane chemistry and, in fact, it occurs in many reactions of trialkylboranes. When it does occur, borane derivatives with two positions "blocked" are utilized to conserve alkene substrate. What follows is a description of an investigation into the applicability of these "blocked" derivatives to this new alkylation reaction.

2.2.5.1 9-BBN

Hexyl-9-BBN, **14**, was prepared according to the literature procedure⁷. When it was reacted with benzaldehyde tosylhydrazone, **9a**, the diol **15** was isolated in 59% yield (eqn 2-7). Compound **15** results from preferential reaction of the cyclooctyl-

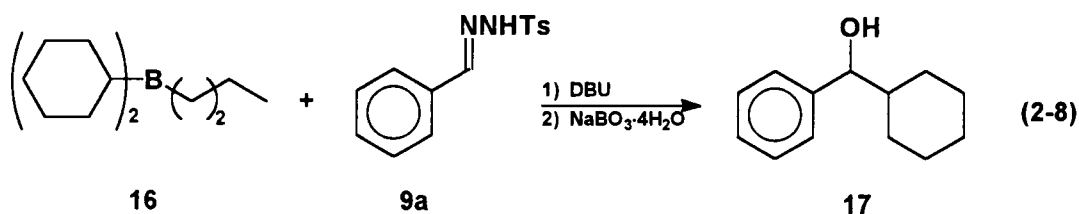


boron bond instead of the hexyl-boron bond.

A similar result had been noted previously. When alkyl-9-BBN compounds were used in the mechanistically similar reaction with α -diazocarbonyl compounds, preferential migration of the cyclooctyl ring was observed⁶³.

2.2.5.2 Dicyclohexylborane

Butyldicyclohexylborane, **16**, was prepared according to the literature procedure⁷. When it was treated with DBU and benzaldehyde tosylhydrazone, **9a**, a 60% isolated yield of cyclohexylphenylmethanol, **17**, was isolated (eqn 2-8). As

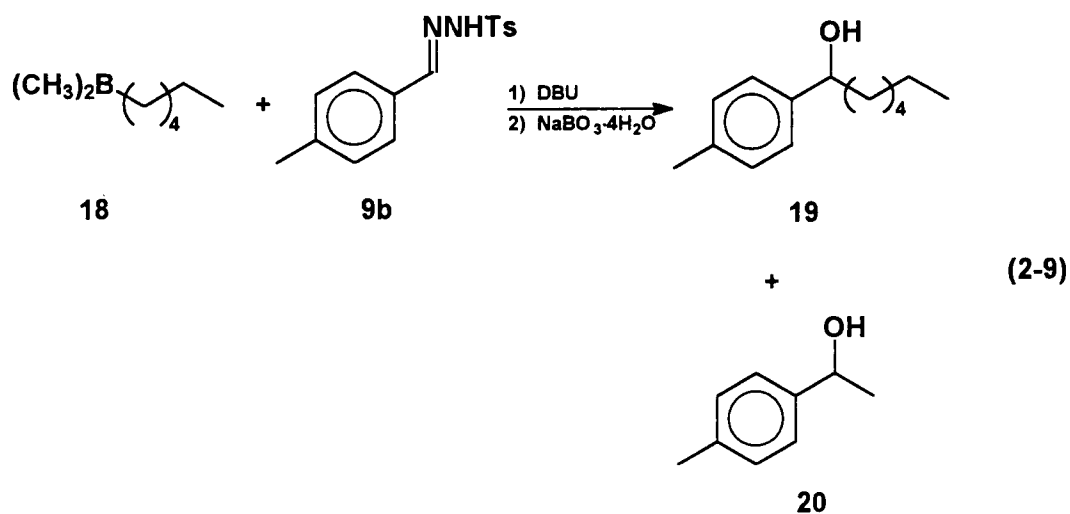


in the 9-BBN case, the blocking group migrated preferentially, instead of the intended alkyl group.

2.2.5.3 Dimethylborane

Dimethylborane is often used as a blocked borane derivative because the methyl groups tend to have a very low migratory aptitude. Hexyldimethylborane, **18**, was prepared according to the literature procedure¹⁶ and allowed to react with *p*-

tolualdehyde tosylhydrazone, **9b**, and DBU (eqn 2-9). After oxidation and work-up, a



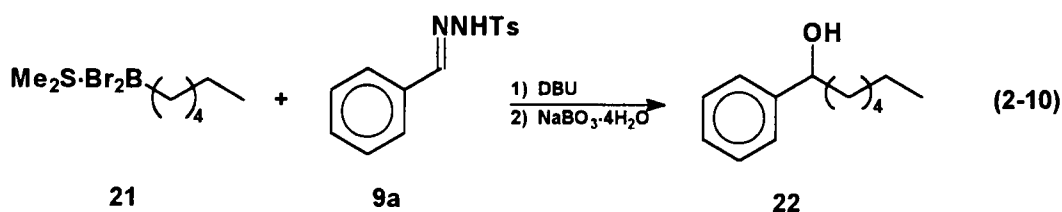
41 % isolated yield of the desired product, 1-*p*-tolylheptan-1-ol, **19**, was isolated. A 53 % yield of the competitive product **20** was also detected. The methyl group appears to have migrated as well as the intended alkyl group. A 41:53 ratio is close to the 33:66 ratio expected if both groups had the same migratory aptitude.

2.2.5.4 Dihaloalkylboranes

Dihaloalkylboranes were investigated as possible reactants. Dihaloalkylboranes are typically more reactive than trialkylboranes due to their increased Lewis acidity. Dichloroalkylboranes have previously been used in the mechanistically similar reaction of α -diazocarbonyl compounds with organoboranes (Chapter 1.5.4)⁶⁴ and it was felt

that they would function similarly in this new technology.

The dimethylsulfide complex of dibromohexylborane, **21**, was prepared according to the literature procedure²⁰ and added to a solution of benzaldehyde tosylhydrazone, **9a**, in THF followed by the addition of DBU (eqn 2-10). After



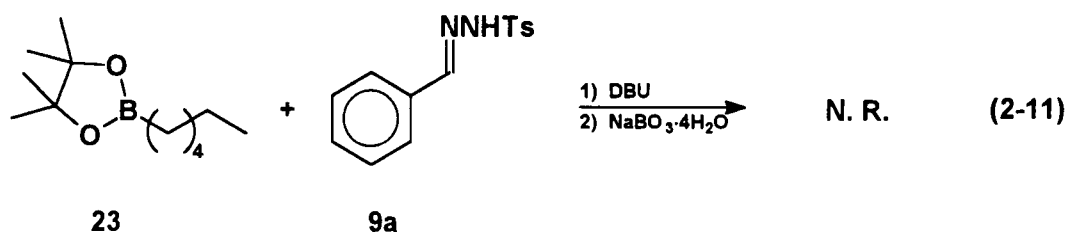
oxidation and work-up, a 16% yield of alcohol **22** was isolated. Reversing the addition, by adding **21** to a solution of **9a** and DBU, resulted in a lower yield of 4%.

Dichlorohexylborane was also prepared²⁰ and allowed to react with *p*-tolualdehyde tosylhydrazone and DBU. No product was produced as evidenced by TLC.

The dihaloboranes are apparently too acidic for this reaction. Due to their enhanced Lewis acidity, they presumably form complexes with the nitrogens of the tosylhydrazone or DBU and do not react further.

2.2.5.5 Pinacol Hexylboronate

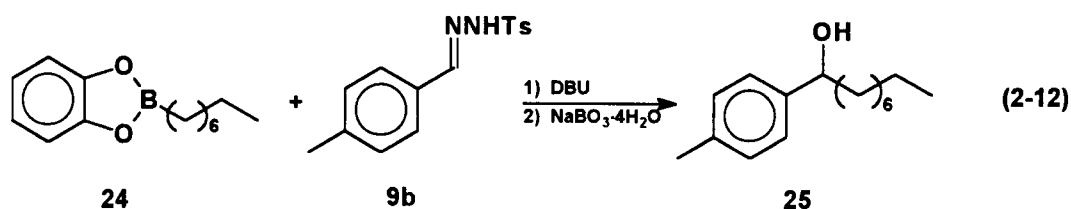
In an attempt to use a borane derivative less reactive than the haloboranes, pinacol hexylboronate, **23**, was prepared from the corresponding dibromohexylborane²⁰. Reaction of **23** with benzaldehyde tosylhydrazone, **9a**, and DBU produced no product alcohol (eqn 2-11). The boronic ester is a poor Lewis acid



due to the back donation of electron density from the oxygen atoms and does not participate in the reaction.

2.2.5.6 Catecholborane

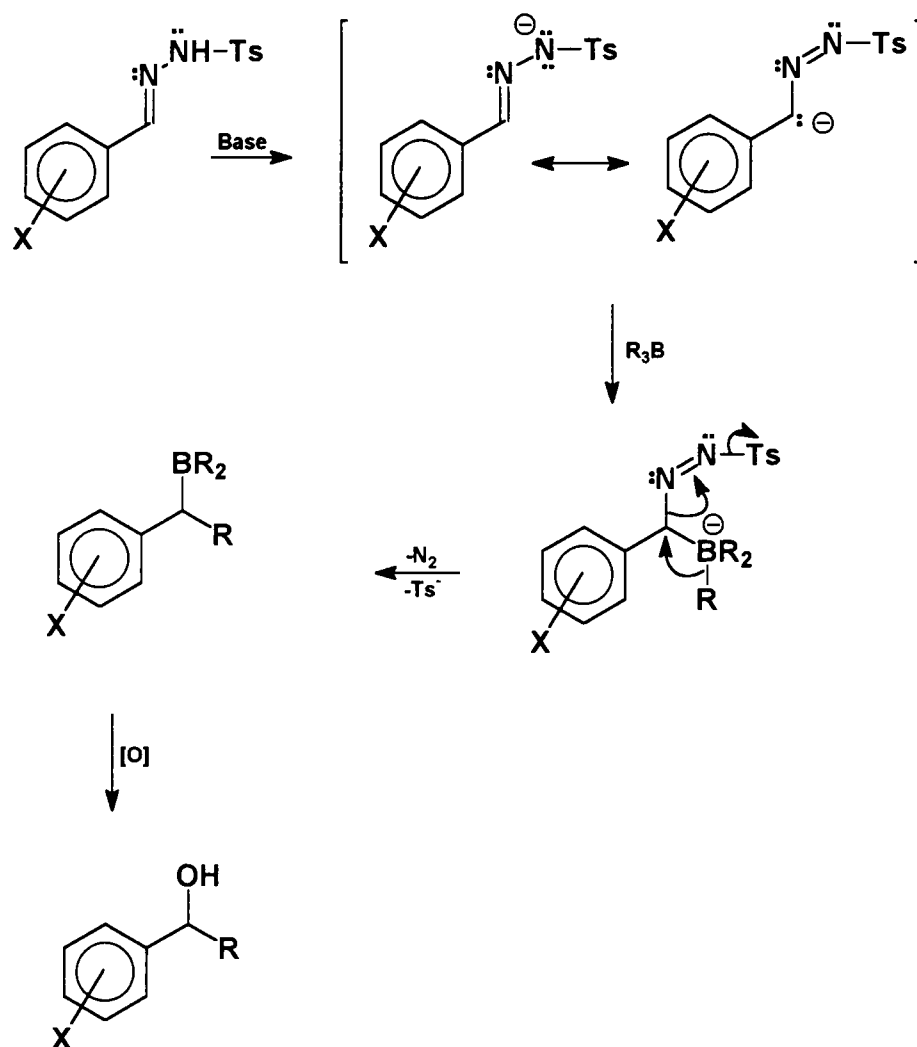
B-Octylcatecholborane, **24**, was prepared according to the literature procedure¹⁸. It is a boronic ester like pinacol hexylboronate, **23**, but **24** is more Lewis acidic due to the presence of the electron-withdrawing benzene ring. Reaction of **24** with *p*-tolualdehyde tosylhydrazone, **9b**, and DBU produced a 27% isolated yield of alcohol **25** (eqn 2-12). No competition product was isolated because the oxygens do not migrate.



2.2.6 Mechanism of Reaction

There are two possible mechanistic courses by which the new reaction may proceed. In the first, the anion mechanism, removal of a proton from the starting tosylhydrazone would generate an anion (Scheme 2-1). The trialkylborane then reacts with this anion to generate an electron-rich organoborate complex which spontaneously undergoes a 1,2-borotropic shift, expelling nitrogen and the *p*-toluenesulfinate anion, to produce a new trialkylborane. This trialkylborane can then be oxidized to the desired product alcohol. The intermediate benzylic borane, as noted previously, can also be hydrolyzed to the corresponding alkane by nucleophilic bases¹¹¹⁻¹¹³.

Scheme 2-1. Anion Mechanism.

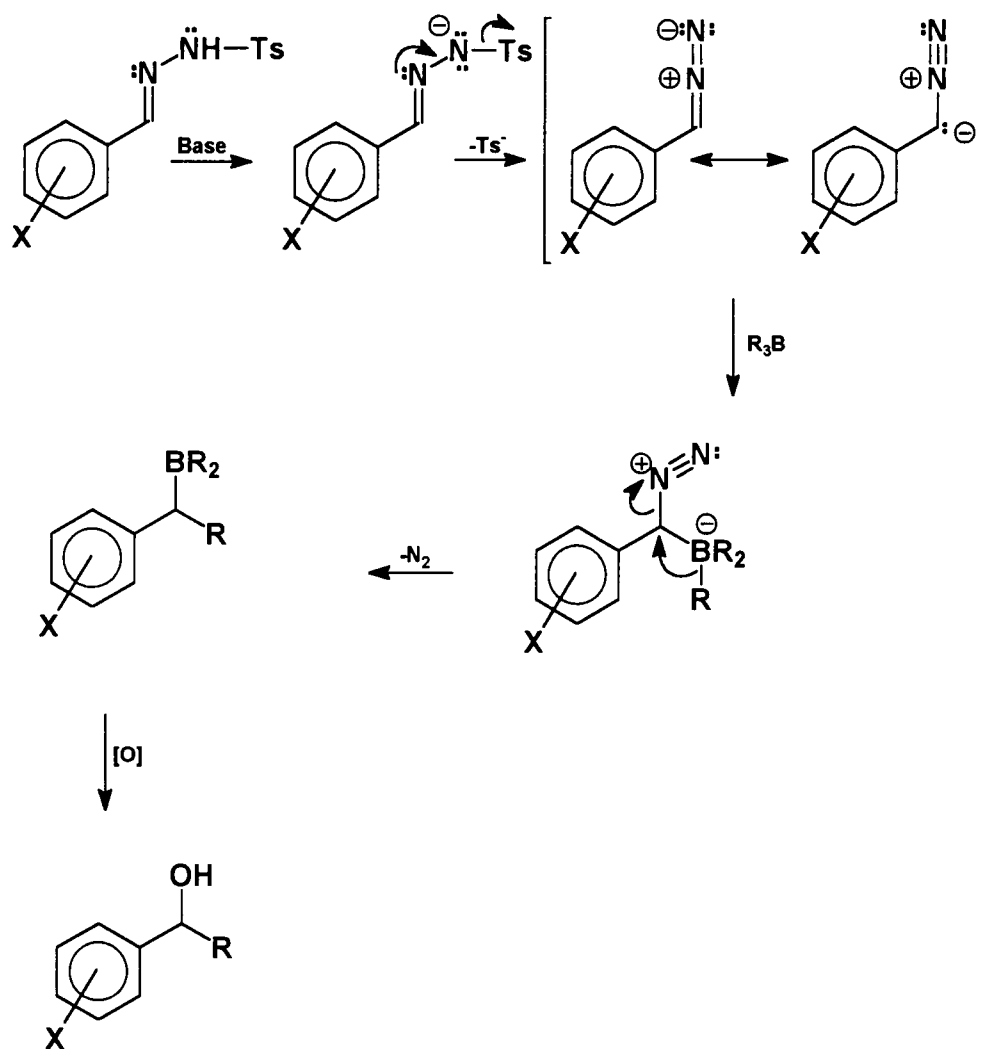


Alternatively, the reaction may proceed via a diazo mechanism (Scheme 2-2). Removal of a proton from the aryl aldehyde tosylhydrazone would generate the anion, as in the previous mechanism. This anion, however, would decompose to the intermediate diazo compound before reacting with the trialkylborane. The borate complex, once formed, would undergo a spontaneous 1,2-borotropic shift, expelling nitrogen, to generate a new trialkylborane which would then be oxidized to the product alcohol.

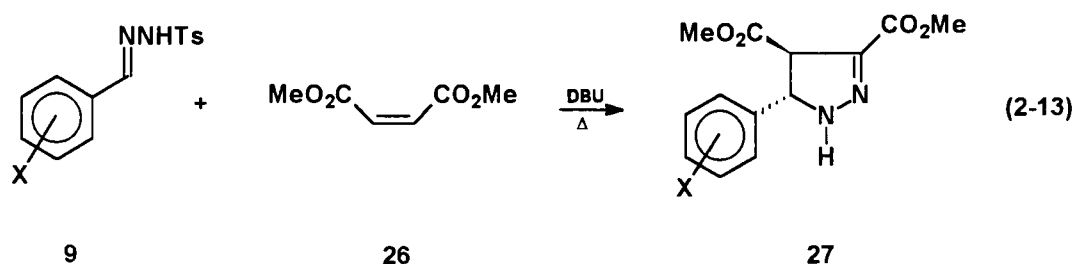
Both mechanisms are similar to that postulated for the reaction of α -diazocarbonyl compounds with trialkylboranes⁵⁷⁻⁵⁹. The difficulty in elucidating which mechanism is operative lies in the fact that they differ only in the timing of the tosyl group loss.

Tosylhydrazones have been used to generate diazo compounds¹¹⁵. This reaction is known as the Bamford-Stevens reaction and it has been extensively studied. Generation of an aryl diazo compound, such as that shown in Scheme 2-2, is possible under the conditions employed in this methodology. When *p*-tolualdehyde tosylhydrazone was treated with DBU in the absence of organoborane under the standard reaction conditions, a deep red color formed which can be attributed to the formation of a diazo compound. Also, when the pentane extracts of this reaction mixture were examined by IR, a sharp band at 2050 cm^{-1} was noted. The characteristic IR band of aryl diazo compounds has been reported to be in the range 2020-2060 cm^{-1} ^{115c}. Generation of diazo intermediates is, then, feasible under these conditions.

Scheme 2-2. Diazo Mechanism



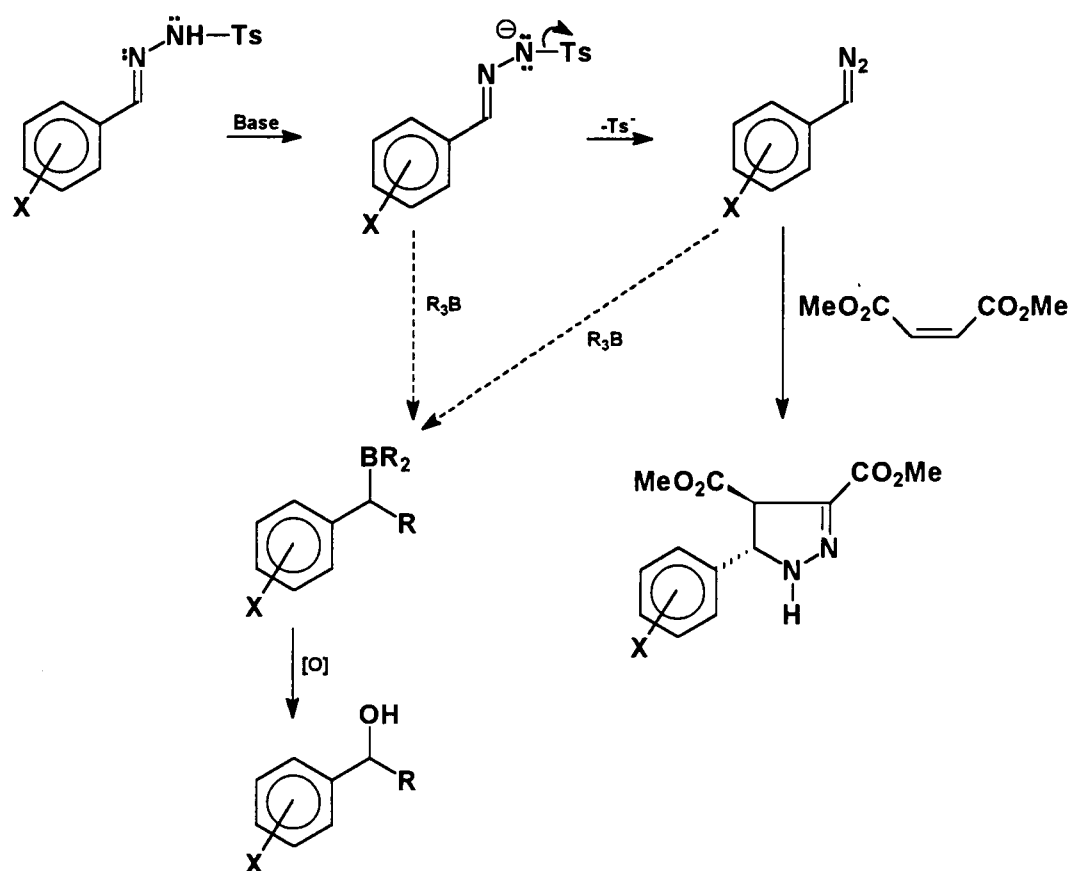
One possible method to probe the mechanism involves addition of a reagent which would compete with the trialkylborane for the diazo intermediate, if it were present. One such reagent is dimethyl maleate (**26**). Dimethyl maleate reacts with aryl diazo compounds via a 1,3-dipolar cycloaddition to generate *trans*-5-aryl-4,5-dihydro-1H-pyrazole-3,4-dicarboxylic acid dimethyl esters, **27** (eqn 2-13)¹¹⁶.



Reaction of *p*-tolualdehyde tosylhydrazone **9b** with **26** and DBU in the absence of trialkylborane in refluxing THF produced a 76% isolated yield of **27b**.

If dimethyl maleate competed successfully with trialkylborane for the diazo intermediate, no alcohol product would be observed and this would support the diazo mechanism. When the competition experiment (Scheme 2-3) was performed, an 80% isolated yield of alcohol (trialkylborane reaction) was produced and none of the pyrazoline, **27**, was detected. The reaction was repeated, beginning at reflux temperature, in an attempt to help dimethyl maleate compete more effectively. Once again, a 77% yield of alcohol was produced. These results suggest one of two things. Either the reaction proceeds via the anion mechanism and no diazo intermediate is formed or, the reaction of the trialkylborane with the diazo intermediate is faster than the cycloaddition with dimethyl maleate. In any case, the question is still open and current research is directed at solving this problem.

Scheme 2-3. Competition Experiment.

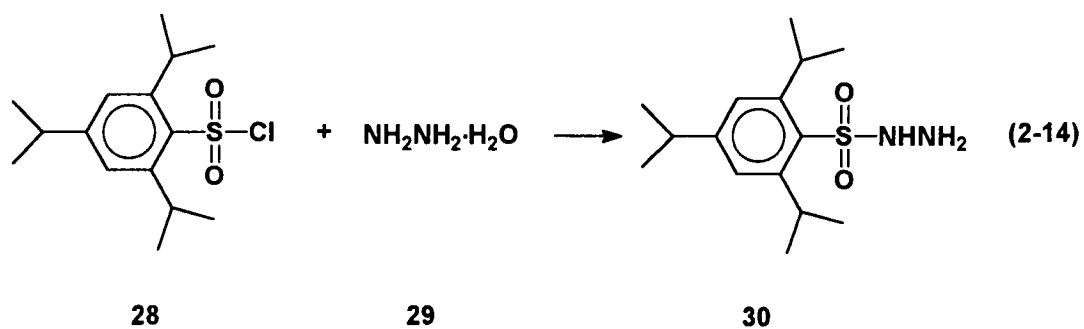


2.3 Aryl Aldehyde Trisylhydrazones

After establishing that aryl aldehyde tosylhydrazones were suitable substrates for the new alkylation reaction, it was of interest to explore whether other arenesulfonylhydrazones would function as well. The 2,4,6-triisopropylbenzenesulfonylhydrazones (trisylhydrazones) have been prepared and their reactions studied previously in the literature. The trisyl moiety has proven superior to the tosyl group in production of di-imide from the arenesulfonylhydrazides¹¹⁷ and in the production of diazoalkanes from the arenesulfonylhydrazones¹¹⁸. It was felt that the trisyl's increased reactivity would also manifest itself in the new alkylation reaction.

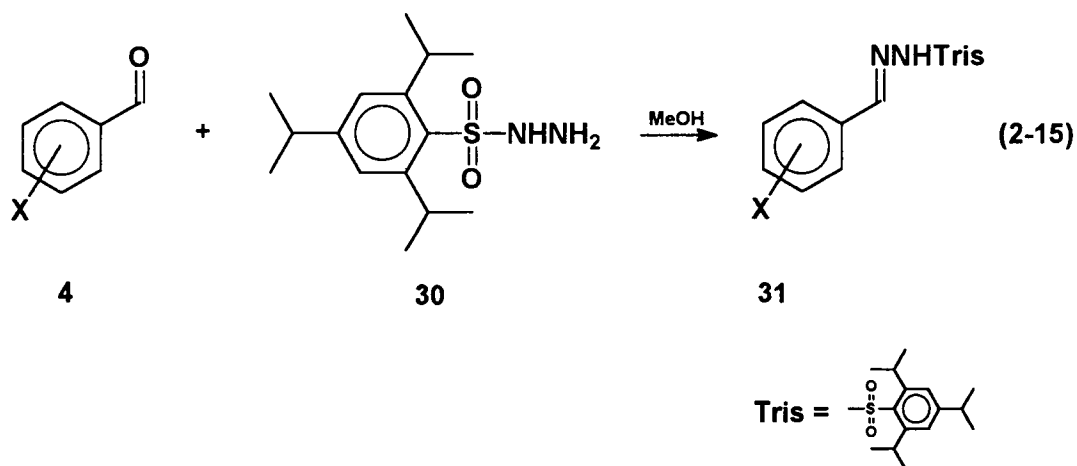
2.3.1 *Synthesis of 2,4,6-Triisopropylbenzenesulfonylhydrazide (30)*

The derivatizing agent, 2,4,6-triisopropylbenzenesulfonylhydrazide (TPSH), is commercially available. It may, however, be simply and inexpensively prepared from the readily available sulfonyl chloride **28** and hydrazine hydrate (eqn 2-14)¹¹⁷. TPSH was prepared and isolated as a snow-white solid in 80-85% yield. It is a reasonably stable and easily handled material. It was stored in an amber bottle in a cold room to prevent decomposition.



2.3.2 Synthesis of Aryl Aldehyde Trisylhydrazones (31)

Aryl aldehyde trisylhydrazones, **31**, are stable, crystalline solids which can be readily prepared by adding the corresponding aryl aldehyde to a solution of TPSH in anhydrous methanol (eqn 2-15)¹¹⁸. The resulting precipitate may be



recrystallized from a minimum quantity of hot ethanol. Table 2-6 lists several substituted aryl aldehyde trisylhydrazones which were prepared for this study.

Table 2-6. Synthesis of Aryl Aldehyde Trisylhydrazones (**31**).

Entry	X	% yield ^a	m.p. (°C)
1	H (31a)	87	186.5 - 187.5
2	4-methyl (31b)	61	186.7 - 188.7
3	4-methoxy (31c)	62	159.0 - 163.5
4	3-methoxy (31d)	62	187.0 - 188.5
5	2-methoxy (31e)	54	164.5 - 165.5
6	4-bromo (31g)	68	197.0 - 197.8
7	3-bromo (31h)	54	230 - 233
8	2-bromo (31i)	71	153.0 - 155.2
9	2, 4, 6-trimethyl (31l)	29	133.0 - 135.0
10	2-chloro (31m)	72	154.5 - 158.0

^(a)Isolated yield based on starting aldehyde

2.3.3 Typical Results

The aryl aldehyde trisylhydrazone derivatives were tested as possible substrates in the alkylation reaction (eqn 2-16). The derivatives, **31**, produced the alcohols, **11**, in excellent yields and, in fact, they proceeded under very mild conditions. Whereas the tosyl derivatives required heating to reflux in THF, the trisyl derivatives reacted at room temperature to give comparable or enhanced yields of product (Table 2-7).

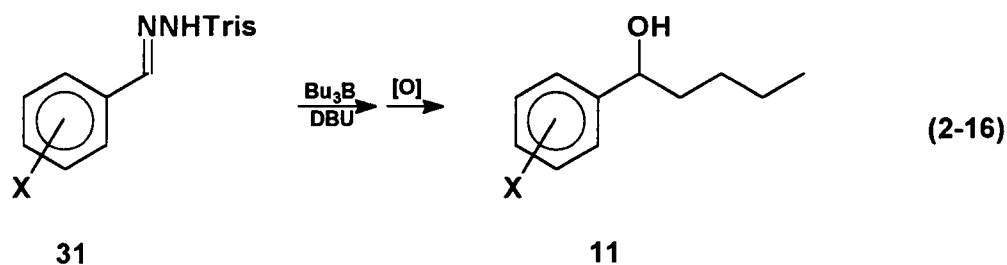


Table 2-7. Synthesis of Aryl Alcohols (11).

Entry	X	Trisyl % Yield 11 ^(a)	Time (hr)	Tosyl % Yield 11 ^(a)	Time (hr)
1	H (31a)	90	2	73	0.5
2	4-methyl (31b)	87	2	83	1.5
3	4-methoxy (31c)	80	3	71	3
4	3-methoxy (31d)	76	1	76	1.5
5	2-methoxy (31e)	88	1	86	1.5
6	4-bromo (31g)	86	1	80	1
7	3-bromo (31h)	83	1	78	1
8	2-bromo (31i)	0 ^(b)	1	80	1
9	2, 4, 6-trimethyl (31l)	91	1	90	1
10	2-chloro (31m)	0 ^(c)	1	--	--

^(a)Isolated yield based on starting hydrazone. ^(b)89% yield of alkane product isolated. ^(c)82% yield of alkane product isolated.

The standard oxidizing procedures described earlier were used for the trisyl derivatives. Sodium perborate ($\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$) was used to oxidize entries 1-5 and 9

while peracetic acid was used to oxidize the entries bearing electron-withdrawing substituents (6-8 and 10). Both the electron-withdrawing and electron-donating groups, on all positions on the ring, gave good yields of product. Even the hindered 2,4,6-trimethyl derivative produced an excellent yield of alcohol product.

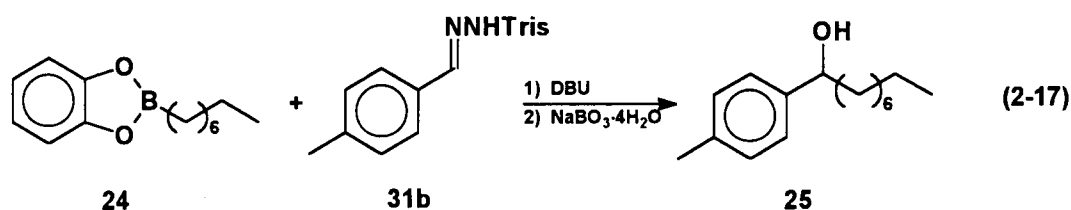
Anomalous results were obtained when electron-withdrawing substituents were present in the *ortho* position (entries 8 and 10). Instead of alcohol, a good yield of the corresponding alkane product was isolated. It was initially hypothesized that the increased basicity of the trisyl anion together with the *ortho* effects of the electron-withdrawing substituents contributed to the production of the alkane product. However, when this concept was tested by forming the intermediate organoborane from the 2-bromobenzaldehyde tosylhydrazone derivative and treating it with the trisyl anion, no alkane product was produced. Current research is directed at examining these unusual results.

2.3.4 Use of Borane Derivatives

As in the tosylhydrazone case, the stoichiometry of the alkylation reaction between aryl aldehyde trisylhydrazones and tributylborane was one to one. Only one alkyl group is transferred in the reaction. It was therefore of interest to determine if one of the "blocked" derivatives of borane may be employed to conserve alkene substrate.

2.3.4.1 Catecholborane

B-Octylcatecholborane, **24**, was prepared according to the literature procedure¹⁸. Reaction of **24** and *p*-tolualdehyde trisylhydrazone, **31b**, and DBU at room temperature produced a 48% yield of alcohol **25** (eqn 2-17). This was the highest yield obtained with a blocked borane derivative. Repeating the reaction at reflux in THF led to a lower yield of 28% of **25**. Apparently the higher temperature



led to decomposition of the starting trisylhydrazone.

2.4 Experimental

All ¹H and ¹³C NMR spectra were recorded on a 250 MHz Bruker AC250 spectrometer. All melting points are uncorrected and were recorded using a MEL-TEMP melting point apparatus equipped with a Glas-Col digital thermometer. Micro-boiling points were recorded using the same apparatus. Elemental analyses were

performed by Atlantic Microlabs, Norcross, Georgia.

All glassware, syringes, and needles were dried in an oven heated to 250 °C for at least 12 hours and cooled under Ar prior to use. All solvents were dried and distilled prior to use¹¹⁹. Reactions were magnetically stirred and monitored by TLC. Products were purified by flash chromatography on 230-400 mesh ASTM 60 Å silica gel¹²⁰.

2.4.1 Benzaldehyde Tosylhydrazone (**9a**)¹²¹

This procedure is general for all aryl aldehyde tosylhydrazones. To a solution of *p*-toluenesulfonylhydrazide (5.62 g, 30.2 mmol) in absolute ethanol (17 mL) was added benzaldehyde (2.82 g, 26.6 mmol). The reaction mixture was stirred and heated to reflux for ten minutes. The mixture was cooled and the precipitated product collected. This was recrystallized from hot ethanol to give 5.26 g (72 % yield) of **9a**: m.p. = 125.0 - 128.0 °C; lit. m.p. = 127 - 128 °C.

2.4.2 4-Methylbenzaldehyde Tosylhydrazone (**9b**)¹²²

4-Methylbenzaldehyde tosylhydrazone (**9b**) was prepared, as described previously, from 4-methylbenzaldehyde (3.25 g, 27.1 mmol) and *p*-toluenesulfonylhydrazide (5.59 g, 30.0 mmol). The product was recrystallized from hot ethanol to give 5.82 g (74% yield) of **9b**: m.p. = 148.5 - 150.9 °C; lit. m.p. =

115 - 116 °C.

2.4.3 4-Methoxybenzaldehyde Tosylhydrazone (**9c**)¹²³

4-Methoxybenzaldehyde tosylhydrazone (**9c**) was prepared, as described previously, from 4-methoxybenzaldehyde (1.37 g, 10.1 mmol) and *p*-toluenesulfonylhydrazide (2.07 g, 11.1 mmol). The product was recrystallized from hot ethanol to give 2.73 g (89% yield) of **9c**: m.p. = 110.0 - 112.0 °C; lit. m.p. = 112 - 114 °C.

2.4.4 3-Methoxybenzaldehyde Tosylhydrazone (**9d**)

3-Methoxybenzaldehyde tosylhydrazone (**9d**) was prepared, as described previously, from 3-methoxybenzaldehyde (3.69 g, 27.1 mmol) and *p*-toluenesulfonylhydrazide (5.59 g, 30.0 mmol). The product was recrystallized from hot ethanol to give 5.73 g (69% yield) of **9d**: m.p. = 107.5 - 108.5 °C; Anal. calcd for C₁₅H₁₆N₂O₃S: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.26; H, 5.34; N, 9.25.

2.4.5 2-Methoxybenzaldehyde Tosylhydrazone (**9e**)¹²⁴

2-Methoxybenzaldehyde tosylhydrazone (**9e**) was prepared, as described previously, from 2-methoxybenzaldehyde (3.68 g, 27.0 mmol) and *p*-

toluenesulfonylhydrazide (5.60 g, 30.0 mmol). The product was recrystallized from hot ethanol to give 7.00 g (85 % yield) of **9e**: m.p. = 157.0 - 160.0 °C; lit. m.p. = 165 - 167 °C; Anal. calcd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.29; H, 5.30; N, 9.28.

2.4.6 4-Chlorobenzaldehyde Tosylhydrazone (**9f**)¹²⁵

4-Chlorobenzaldehyde tosylhydrazone (**9f**) was prepared, as described previously, from 4-chlorobenzaldehyde (1.41 g, 10.0 mmol) and *p*-toluenesulfonylhydrazide (2.10 g, 11.3 mmol). The product was recrystallized from hot ethanol to give 2.07 g (67% yield) of **9f**: m.p. = 163.5 - 165.3 °C; lit. m.p. = 148 - 151 °C.

2.4.7 4-Bromobenzaldehyde Tosylhydrazone (**9g**)

4-Bromobenzaldehyde tosylhydrazone (**9g**) was prepared, as described previously, from 4-bromobenzaldehyde (5.01 g, 27.1 mmol) and *p*-toluenesulfonylhydrazide (5.61 g, 30.1 mmol). The product was recrystallized from hot ethanol to give 7.63 g (80% yield) of **9g**: m.p. = 172.0 - 176.0 °C; Anal. calcd for $C_{14}H_{13}N_2O_2SBr$: C, 47.60; H, 3.71; N, 7.93. Found: C, 47.68; H, 3.77; N, 7.98.

2.4.8 3-Bromobenzaldehyde Tosylhydrazone (**9h**)

3-Bromobenzaldehyde tosylhydrazone (**9h**) was prepared, as described previously, from 3-bromobenzaldehyde (5.02 g, 27.1 mmol) and *p*-toluenesulfonylhydrazide (5.60 g, 30.0 mmol). The product was recrystallized from hot ethanol to give 6.93 g (72% yield) of **9h**: m.p. = 114.5 - 117.5 °C; Anal. calcd for $C_{14}H_{13}N_2O_2SBr$: C, 47.60; H, 3.71; N, 7.93. Found: C, 47.79; H, 3.81; N, 8.01.

2.4.9 2-Bromobenzaldehyde Tosylhydrazone (**9i**)

2-Bromobenzaldehyde tosylhydrazone (**9i**) was prepared, as described previously, from 2-bromobenzaldehyde (4.64 g, 25.1 mmol) and *p*-toluenesulfonylhydrazide (5.22 g, 28.0 mmol). The product was recrystallized from hot ethanol to give 7.46 g (84% yield) of **9i**: m.p. = 165.0 - 167.5 °C; Anal. calcd for $C_{14}H_{13}N_2O_2SBr$: C, 47.60; H, 3.71; N, 7.93. Found: C, 47.77; H, 3.76; N, 8.00.

2.4.10 3-Nitrobenzaldehyde Tosylhydrazone (**9j**)¹²⁶

3-Nitrobenzaldehyde tosylhydrazone (**9j**) was prepared, as described previously, from 3-nitrobenzaldehyde (4.09 g, 27.1 mmol) and *p*-toluenesulfonylhydrazide (5.59 g, 30.0 mmol). The product was recrystallized from

hot ethanol to give 6.82 g (79% yield) of **9j**: m.p. = 159.1 - 160.2 °C; lit. m.p. = 160 - 161 °C.

2.4.11 4-Nitrobenzaldehyde Tosylhydrazone (**9k**)¹²⁶

4-Nitrobenzaldehyde tosylhydrazone (**9k**) was prepared, as described previously, from 4-nitrobenzaldehyde (4.08 g, 27.0 mmol) and *p*-toluenesulfonylhydrazide (5.59 g, 30.0 mmol). The product was recrystallized from hot ethanol to give 6.98 g (81% yield) of **9k**: m.p. = 156.8 - 158.2 °C; lit. m.p. = 158 °C.

2.4.12 2,4,6-Trimethylbenzaldehyde Tosylhydrazone (**9l**)¹²⁷

2,4,6-Trimethylbenzaldehyde tosylhydrazone (**9l**) was prepared, as described previously, from 2,4,6-trimethylbenzaldehyde (1.49 g, 10.1 mmol) and *p*-toluenesulfonylhydrazide (2.24 g, 12.0 mmol). The product was recrystallized from hot ethanol to give 2.70 g (85% yield) of **9l**: m.p. = 162.8 - 166.0 °C; lit. m.p. = 158.0 - 160.0 °C.

2.4.13 Alkylation of Tosylhydrazones with Tributylborane: Oxidation with Sodium Perborate.

The following compounds were prepared by the reaction of the corresponding tosylhydrazone with DBU and tributylborane followed by oxidation with sodium perborate ($\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$). The synthesis of 1-phenylpentan-1-ol (**11a**) is representative.

2.4.13.1 1-Phenylpentan-1-ol (**11a**)¹²⁸

To a flame-dried, argon flushed, 50 mL, round-bottom flask equipped with a side-arm, reflux condenser, stir bar, argon inlet, and mercury bubbler was added **9a** (0.833 g, 3.00 mmol). **9a** was dissolved in dry THF (17 mL) followed by the addition of tributylborane (3.0 mmol, 3.0 mL of a 1.0 M solution in THF). DBU (0.45 mL, 3.0 mmol) was added and the reaction flask placed in an oil bath. The reaction was heated to a gentle reflux until the tosylhydrazone disappeared as evidenced by TLC (0.5 hrs). The reaction mixture was cooled under argon and placed in a room temperature water bath. Distilled water (10 mL) and sodium perborate (1.38 g, 8.97 mmol) were added. The reaction was stirred vigorously for 2 hours. The reaction mixture was then transferred to a separatory funnel and the product extracted into ether (3 x 10 mL). The extracts were washed with brine (1 x 20 mL) and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure and the crude product flash chromatographed using 8 inches of silica gel in a

50 mm column with 17% EtOAc/Hexanes. This produced 0.36 g (73% yield) of **11a**: $^1\text{H-NMR}$ (CDCl_3/TMS) δ 7.37-7.18 (m, 5H), 4.60 (t, 1H, $J = 6.67$ Hz), 2.22-2.05 (br s, 1H), 1.86-1.57 (m, 2H), 1.45-1.14 (m, 4H), 0.87 (t, 3H, $J = 6.96$ Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 144.96, 128.34, 127.37, 125.88, 74.60, 38.76, 27.93, 22.56, 13.95.

2.4.13.2 1-*p*-Tolylpentan-1-ol (**11b**)¹²⁹

1-*p*-Tolylpentan-1-ol (**11b**) was prepared, as described previously, from **9b** (0.866 g, 3.00 mmol). The crude product was flash chromatographed using 6.5 inches of silica gel in a 50 mm column with 9% EtOAc/Hexanes to give 0.45 g (83% yield) of **11b**: $^1\text{H-NMR}$ (CDCl_3/TMS) δ 7.21 (d, 2H, $J = 8.09$ Hz), 7.13 (d, 2H, $J = 8.06$ Hz), 4.59 (t, 1H, $J = 6.67$ Hz), 2.33 (s, 3H), 2.03-1.86 (br s, 1H), 1.84-1.59 (m, 2H), 1.44-1.23 (m, 4H), 0.87 (t, 3H, $J = 6.90$ Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 141.98, 137.02, 129.03, 125.82, 74.46, 38.68, 27.98, 22.57, 21.02, 13.93. Anal. calcd for $\text{C}_{12}\text{H}_{18}\text{O}$: C, 80.85; H, 10.18. Found: C, 80.57; H, 10.29.

2.4.13.3 1-(4-Methoxyphenyl)pentan-1-ol (**11c**)¹³⁰

1-(4-Methoxyphenyl)pentan-1-ol (**11c**) was prepared, as described previously, from **9c** (0.913 g, 3.00 mmol). The crude product was flash chromatographed using 8 inches of silica gel in a 50 mm column with 18% EtOAc/Hexanes to give 0.41 g (71% yield) of **11c**: b.p. = 281 °C (733.2 mm Hg); lit. b.p. = 160 °C (14 mm Hg); $^1\text{H-}$

NMR (CDCl₃/TMS) δ 7.25 (d, 2H, J = 8.59 Hz), 6.87 (d, 2H, J = 8.67 Hz), 4.58 (t, 1H, J = 6.71 Hz), 3.79 (s, 3H), 1.99 (br s, 1H), 1.88-1.57 (m, 2H), 1.45-1.14 (m, 4H), 0.88 (t, 3H, J = 6.93 Hz); ¹³C-NMR (CDCl₃) δ 158.93, 137.10, 127.09, 113.74, 74.21, 55.20, 38.64, 27.99, 22.54, 13.94.

2.4.13.4 1-(3-Methoxyphenyl)pentan-1-ol (**11d**)¹³¹

1-(3-Methoxyphenyl)pentan-1-ol (**11d**) was prepared, as described previously, from **9d** (0.913 g, 3.00 mmol). The crude product was flash chromatographed using 6.5 inches of silica gel in a 40 mm column with 10% EtOAc/Hexanes to give 0.45 g (76% yield) of **11d**: ¹H-NMR (CDCl₃/TMS) δ 7.29-6.75 (m, 4H), 4.60 (t, 1H, J = 6.59 Hz), 3.79 (s, 3H), 2.17-2.04 (br s, 1H), 1.84-1.61 (m, 2H), 1.45-1.24 (m, 4H), 0.88 (t, 3H, J = 6.83 Hz); ¹³C-NMR (CDCl₃) δ 159.67, 146.71, 129.33, 118.20, 112.80, 111.37, 74.53, 55.13, 38.71, 27.92, 22.55, 13.93. The alkane product, 1-methoxy-3-pentylbenzene (**12d**)¹³², was also isolated to give 0.080 g (15% yield): ¹H-NMR (CDCl₃/TMS) δ 7.23-6.67 (m, 4H), 3.78 (s, 3H), 2.57 (t, 2H, J = 7.73 Hz), 1.69-1.52 (m, 2H), 1.39-1.27 (m, 4H), 0.89 (t, 3H, J = 6.77 Hz); ¹³C-NMR (CDCl₃) δ 159.56, 144.57, 129.10, 120.82, 114.17, 110.77, 55.05, 35.98, 31.50, 31.04, 22.51, 13.99.

2.4.13.5 1-(2-Methoxyphenyl)pentan-1-ol (**11e**)¹³³

1-(2-Methoxyphenyl)pentan-1-ol (**11e**) was prepared, as described previously, from **9e** (0.914 g, 3.00 mmol). The crude product was flash chromatographed using 8 inches of silica gel in a 50 mm column with 10% EtOAc/Hexanes to give 0.50 g (86% yield) of **11e**: ¹H-NMR (CDCl₃/TMS) δ 7.32-7.19 (m, 2H), 6.98-6.83 (m, 2H), 4.85 (t, 1H, *J* = 6.55 Hz), 3.84 (s, 3H), 2.61 (br s, 1H), 1.84-1.69 (m, 2H), 1.45-1.26 (m, 4H), 0.89 (t, 3H, *J* = 6.87); ¹³C-NMR (CDCl₃) δ 156.54, 132.72, 128.10, 126.90, 120.67, 110.48, 70.87, 55.20, 36.99, 28.21, 22.57, 13.97. The alkane product, 1-methoxy-2-pentylbenzene (**12e**)¹³⁴, was also isolated to give 0.076 g (14% yield): ¹H-NMR (CDCl₃/TMS) δ 7.20-7.09 (m, 2H), 6.91-6.79 (m, 2H), 3.80 (s, 3H), 2.60 (t, 2H, *J* = 7.70 Hz), 1.65-1.50 (m, 2H), 1.38-1.27 (m, 4H), 0.94-0.85 (m, 3H); ¹³C-NMR (CDCl₃) δ 157.44, 131.35, 129.70, 126.69, 120.27, 110.21, 55.20, 31.80, 30.08, 29.53, 22.55, 14.01.

2.4.13.6 1-(2,4,6-Trimethylphenyl)pentan-1-ol (**11l**)

1-(2,4,6-Trimethylphenyl)pentan-1-ol (**11l**) was prepared, as described previously, from **9l** (0.949 g, 3.00 mmol). The crude product was flash chromatographed using silica gel and 8% EtOAc/Hexanes to give 0.56 g (90% yield) of **11l**: ¹H-NMR (CDCl₃/TMS) δ 6.80 (s, 2H), 5.15-5.06 (dd, 1H, *J* = 5.67, 8.46 Hz), 2.38 (s, 6H), 2.24 (s, 3H), 2.05-1.88 (m, 1H), 1.77 (br s, 1H), 1.75-1.62 (m, 1H), 1.59-1.20 (m, 4H), 0.90 (t, 3H, *J* = 7.03 Hz); ¹³C-NMR (CDCl₃) δ 137.10,

136.32, 135.92, 130.10, 71.46, 35.52, 28.76, 22.65, 20.66, 13.98. Anal. calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.26; H, 10.80.

2.4.14 Alkylation of Tosylhydrazones with Tributylborane: Oxidation with Peracetic Acid

The following compounds were prepared by the reaction of the corresponding tosylhydrazone with DBU and tributylborane followed by oxidation with peracetic acid. The synthesis of 1-phenylpentan-1-ol (**11a**) is representative.

2.4.14.1 1-Phenylpentan-1-ol (**11a**)

To a flame-dried, argon flushed, 50 mL, round-bottom flask equipped with a side-arm, reflux condenser, stir bar, argon inlet, and mercury bubbler was added **9a** (0.822 g, 3.00 mmol). **9a** was dissolved in dry THF (17 mL) followed by the addition of tributylborane (3.0 mmol, 3.0 mL of a 1.0 M solution in THF). DBU (0.45 mL, 3.0 mmol) was added and the reaction mixture heated to a gentle reflux until starting material disappeared as evidenced by TLC (0.5 hrs). The reaction mixture was cooled under argon and placed in an ice-water bath. Peracetic acid (10 mmol, 2.2 mL of a 32 wt% solution in acetic acid) was added slowly over the course of 8 minutes. After the addition was complete, the ice bath was removed and the reaction mixture allowed to stir at room temperature for one hour. A small amount

of sodium thiosulfate solution was then added to destroy any excess peracid. The reaction mixture was transferred to a separatory funnel, extracted with ether (3 x 10 mL), washed with saturated sodium bicarbonate solution (3 x 10 mL), washed with brine (1 x 20 mL) and dried over anhydrous MgSO_4 . Solvent was removed under reduced pressure and the crude product flash chromatographed using silica gel and 12% EtOAc/Hexanes to give 0.36 g (74% yield) of **11a**: Spectral data was consistent with sample prepared previously. Also isolated was 0.074 g (17% yield) of the alkane product, pentylbenzene (**12a**).

2.4.14.2 1-(4-Chlorophenyl)pentan-1-ol (**11f**)¹³⁵

1-(4-Chlorophenyl)pentan-1-ol (**11f**) was prepared, as described previously, from **9f** (0.926 g, 3.00 mmol). The crude product was flash chromatographed using 8 inches of silica gel in a 50 mm column with 15% EtOAc/Hexanes to give 0.48 g (80% yield) of **11f**: $^1\text{H-NMR}$ (CDCl_3/TMS) δ 7.29 (d, 2H, $J = 8.56$ Hz), 7.23 (d, 2H, $J = 8.56$ Hz), 4.58 (t, 1H, $J = 6.63$ Hz), 2.30 (br s, 1H), 1.82-1.53 (m, 2H), 1.43-1.11 (m, 4H), 0.88 (t, 3H, $J = 6.91$ Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 143.50, 133.00, 128.32, 127.13, 73.73, 38.64, 27.63, 22.38, 13.78.

2.4.14.3 1-(4-Bromophenyl)pentan-1-ol (**11g**)¹³⁶

1-(4-Bromophenyl)pentan-1-ol (**11g**) was prepared, as described previously,

from **9g** (1.06 g, 3.00 mmol). The crude product was flash chromatographed using silica gel and 12 % EtOAc/Hexanes to give 0.58 g (80 % yield) of **11g**: $^1\text{H-NMR}$ (CDCl_3/TMS) δ 7.46 (d, 2H, $J = 8.40$ Hz), 7.20 (d, 2H, $J = 8.37$ Hz), 4.61 (t, 1H, $J = 6.61$ Hz), 1.99 (br s, 1H), 1.82-1.61 (m, 2H), 1.41-1.18 (m, 4H), 0.88 (t, 3H, $J = 6.92$ Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 143.87, 131.46, 127.61, 121.12, 73.97, 38.79, 27.78, 22.51, 13.93. Anal. calcd for $\text{C}_{11}\text{H}_{15}\text{OBr}$: C, 54.34; H, 6.22. Found: C, 54.91; H, 6.27. The alkane product, 1-bromo-4-pentylbenzene (**12g**)¹³⁷, was also isolated to give 0.12 g (17 % yield).

2.4.14.4 1-(3-Bromophenyl)pentan-1-ol (**11h**)

1-(3-Bromophenyl)pentan-1-ol (**11h**) was prepared, as described previously, from **9h** (1.06 g, 3.00 mmol). The crude product was flash chromatographed using silica gel and 12 % EtOAc/Hexanes to give 0.57 g (78 % yield) of **11h**: $^1\text{H-NMR}$ (CDCl_3/TMS) δ 7.45-7.08 (m, 4H), 4.54 (t, 1H, $J = 6.57$ Hz), 1.96 (br s, 1H), 1.76-1.52 (m, 2H), 1.38-1.10 (m, 4H), 0.82 (t, 3H, $J = 6.86$ Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 147.29, 130.43, 129.95, 129.00, 124.49, 122.54, 73.95, 38.82, 27.78, 22.51, 13.94. Anal. calcd for $\text{C}_{11}\text{H}_{15}\text{OBr}$: C, 54.34; H, 6.22. Found: C, 54.42; H, 6.21. The alkane product, 1-bromo-3-pentylbenzene (**12h**)¹³⁸, was also isolated to give 0.12 g (18 % yield).

2.4.14.5 1-(2-Bromophenyl)pentan-1-ol (**11i**)¹³⁹

1-(2-Bromophenyl)pentan-1-ol (**11i**) was prepared, as described previously, from **9i** (1.06 g, 3.00 mmol). The crude product was flash chromatographed using silica gel and 10% EtOAc/Hexanes to give 0.59 g (80% yield) of **11i**: ¹H-NMR (CDCl₃/TMS) δ 7.57-7.06 (m, 4H), 5.10-5.01 (dd, 1H, *J* = 4.38, 7.84), 2.12 (br s, 1H), 1.86-1.61 (m, 2H), 1.54-1.31 (m, 4H), 0.91 (t, 3H, *J* = 6.98 Hz); ¹³C-NMR (CDCl₃) δ 143.92, 132.59, 128.64, 127.64, 127.28, 122.00, 72.90, 37.39, 27.92, 22.50, 13.98. Anal. calcd for C₁₁H₁₅OBr: C, 54.34; H, 6.22. Found: C, 54.24; H, 6.20.

2.4.14.6 1-(3-Nitrophenyl)pentan-1-ol (**11j**)

1-(3-Nitrophenyl)pentan-1-ol (**11j**) was prepared, as described previously, from **9j** (0.958 g, 3.00 mmol). The crude product was flash chromatographed using silica gel and 13% EtOAc/Hexanes to give 0.39 g (62% yield) of **11j**: ¹H-NMR (CDCl₃/TMS) δ 8.23-7.47 (m, 4H), 4.80 (t, 1H, *J* = 6.45 Hz), 2.16 (br s, 1H), 1.86-1.71 (m, 2H), 1.44-1.28 (m, 4H), 0.90 (t, 3H, *J* = 6.84 Hz); ¹³C-NMR (CDCl₃) δ 148.38, 147.08, 131.98, 129.31, 122.34, 120.86, 73.57, 39.02, 27.66, 22.49, 13.92. Anal. calcd for C₁₁H₁₅O₃N: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.98; H, 7.38; N, 6.42. The alkane product, 1-nitro-3-pentylbenzene (**12j**)¹⁴⁰, was also isolated to give 0.13 g (23% yield).

2.4.14.7 1-Nitro-4-pentylbenzene (12k)¹⁴¹

1-Nitro-4-pentylbenzene (**12k**) was prepared, as described previously, from **9k** (0.958 g, 3.00 mmol). The crude product was flash chromatographed using silica gel and 7% EtOAc/Hexanes to give 0.48 g (84% yield) of **12k**: b.p. = 282 °C (736.6 mm Hg); lit. b.p. = 126.5 - 127.2 °C (2.75 mm Hg); ¹H-NMR (CDCl₃/TMS) δ 8.14 (d, 2H, *J* = 8.68 Hz), 7.32 (d, 2H, *J* = 8.63 Hz), 2.71 (t, 2H, *J* = 7.70 Hz), 1.72-1.58 (m, 2H), 1.38-1.27 (m, 4H), 0.94-0.85 (m, 3H); ¹³C-NMR (CDCl₃) δ 150.79, 146.21, 129.10, 123.52, 35.79, 31.30, 30.61, 22.39, 13.89.

2.4.15 Alkylation of Tosylhydrazones with Tributylborane: Oxidation with Trimethylamine N-Oxide (TMANO)

The following compounds were prepared by the reaction of the corresponding tosylhydrazone with DBU and tributylborane followed by oxidation with TMANO. The synthesis of 1-phenylpentan-1-ol (**11a**) is representative.

2.4.15.1 1-Phenylpentan-1-ol (11a)

To a flame-dried, argon flushed, 50 mL, round-bottom flask equipped with a side-arm, reflux condenser, stir bar, argon inlet, and mercury bubbler was added **9a** (0.823 g, 3.00 mmol). **9a** was dissolved in dry THF (17 mL) followed by the addition of tributylborane (3.0 mmol, 3.0 mL of a 1.0 M solution in THF). DBU

(0.45 mL, 3.0 mmol) was added and the reaction heated to a gentle reflux until the starting material disappeared as evidenced by TLC (0.5 hrs). The reaction was then cooled and TMANO (10 mmol, 5.0 mL of a 2.0 M solution in CHCl_3) added. The reaction mixture was again heated to reflux and allowed to remain at that temperature for 23 hours. The reaction mixture was then cooled and transferred to a separatory funnel, extracted with ether (3 x 10 mL), washed with brine (1 x 20 mL), and dried over anhydrous MgSO_4 . The solvent was removed and the crude product was flash chromatographed using silica gel and 10% EtOAc/Hexanes to give 0.41 g (83% yield) of **11a**: Spectral data was consistent with sample prepared previously.

2.4.15.2 1-(3-Nitrophenyl)pentan-1-ol (**11j**)

1-(3-Nitrophenyl)pentan-1-ol (**11j**) was prepared, as described previously, from **9j** (0.958 g, 3.00 mmol). The crude product was flash chromatographed using silica gel and 13% EtOAc/Hexanes to give 0.40 g (64% yield) of **11j**: Spectral data was consistent with sample prepared previously. The alkane product, 1-nitro-3-pentylbenzene (**12j**), was also isolated to give 0.14 g (24% yield).

2.4.15.3 1-Nitro-4-pentylbenzene (**12k**)

1-Nitro-4-pentylbenzene (**12k**) was prepared, as described previously, from **9k** (0.958 g, 3.00 mmol). The crude product was flash chromatographed using silica gel

and 7% EtOAc/Hexanes to give 0.49 g (84% yield) of **12k**: Spectral data was consistent with sample prepared previously.

2.4.16 Use of Functionalized Organoboranes

A series of alcohols containing functional groups was prepared by the reaction of 4-methylbenzaldehyde tosylhydrazone, **9b**, with different trialkylboranes and DBU followed by oxidation. The synthesis of 6-chloro-1-*p*-tolylhexan-1-ol (**13a**) is representative.

2.4.16.1 6-Chloro-1-*p*-tolylhexan-1-ol (**13a**)

To a flame-dried, argon flushed, 50 mL, round-bottom flask equipped with a stir bar, argon inlet, and mercury bubbler was added 5-chloro-1-pentene (0.381 g, 3.64 mmol) and dry THF (2 mL). The reaction mixture was cooled in an ice-water bath and $\text{BH}_3 \cdot \text{THF}$ (1.3 mmol, 1.3 mL of a 1.0 M solution in THF) added. The reaction was stirred at 0 °C for 15 minutes. The ice bath was then removed and the reaction stirred at room temperature for two hours. To a separate flame-dried, argon flushed, 50 mL, round-bottom flask equipped with a side-arm, reflux condenser, stir bar, argon inlet, and mercury bubbler was added **9b** (0.346 g, 1.20 mmol) and dry THF (7 mL). The tris(5-chloro-1-pentyl)borane solution was transferred via a double-ended needle to the tosylhydrazone solution under argon and THF (2 mL) was used to

rinse the flask and needle. DBU (0.18 mL, 1.2 mmol) was then added and the reaction heated to a gentle reflux until the starting material disappeared as evidenced by TLC (3 hrs). The reaction was cooled to room temperature and oxidized with sodium perborate and worked-up according to the procedure reported earlier. The crude product was flash chromatographed using 7.5 inches of silica gel in a 40 mm column with 12% EtOAc/Hexanes to give 0.21 g (76% yield) of **13a**: $^1\text{H-NMR}$ (CDCl_3/TMS) δ 7.22 (d, 2H, $J = 8.08$), 7.15 (d, 2H, $J = 7.93$), 4.62 (t, 1H, $J = 6.59$), 3.50 (t, 2H, $J = 6.69$), 2.34 (s, 3H), 1.89 (br s, 1H), 1.84-1.65 (m, 4H), 1.50-1.21 (m, 4H); $^{13}\text{C-NMR}$ (CDCl_3) δ 141.77, 137.22, 129.13, 125.79, 74.30, 44.95, 38.73, 32.49, 26.75, 25.10, 21.06. Anal. calcd for $\text{C}_{13}\text{H}_{19}\text{OCl}$: C, 68.86; H, 8.45. Found: C, 68.77; H, 8.57.

2.4.16.2 7-Hydroxy-7-*p*-tolylheptanenitrile (**13b**)

7-Hydroxy-7-*p*-tolylheptanenitrile (**13b**) was prepared, as described previously, from 5-cyano-1-pentene (0.284 g, 2.98 mmol) and **9b** (0.289 g, 1.00 mmol) with 2.5 hours at reflux in THF and oxidation by sodium perborate. The crude product was flash chromatographed using 9 inches of silica gel in a 30 mm column with 50% EtOAc/Hexanes to give 0.16 g (72% yield) of **13b**: $^1\text{H-NMR}$ (CDCl_3/TMS) δ 7.22 (d, 2H, $J = 8.17$ Hz), 7.16 (d, 2H, $J = 8.09$ Hz), 4.67-4.59 (dd, 1H, $J = 6.12$, 6.92 Hz), 2.38-2.27 (overlapping s and d, 5H, $J = 7.02$ Hz), 1.87-1.57 (m, 5H), 1.55-1.24 (m, 4H); $^{13}\text{C-NMR}$ (CDCl_3) δ 141.64, 137.32, 129.16, 125.76, 119.67,

74.21, 38.51, 28.49, 25.26, 24.96, 21.06, 17.02; IR (cm⁻¹, neat): 3450, 2950, 2855, 2250, 1518, 1460, 1425; GCMS *m/z* 199 (m-H₂O).

2.4.16.3 12-Hydroxy-12-*p*-tolylododecanoic Acid Methyl Ester (13c)

12-Hydroxy-12-*p*-tolylododecanoic acid methyl ester (**13c**) was prepared, as described previously, from methyl 10-undecenoate (1.81 g, 9.15 mmol) and **9b** (0.865 g, 3.00 mmol) with 2 hours at reflux in THF and oxidation by sodium perborate. The crude product was flash chromatographed using 7 inches of silica gel in a 50 mm column with 15 % EtOAc/Hexanes to give 0.72 g (75 % yield) of **13c**: ¹H-NMR (CDCl₃/TMS) δ 7.22 (d, 2H, *J* = 8.11 Hz), 7.14 (d, 2H, *J* = 7.97 Hz), 4.61 (t, 1H, *J* = 6.65 Hz), 3.65 (s, 3H), 2.34 (s, 3H), 2.29 (t, 2H, *J* = 7.55 Hz), 1.91 (br s, 1H), 1.86-1.17 (m, 18H); ¹³C-NMR (CDCl₃) δ 174.29, 141.99, 137.04, 129.04, 125.82, 74.48, 51.37, 39.00, 34.07, 29.45, 29.34, 29.17, 29.09, 25.81, 24.90, 21.05. Anal. calcd for C₂₀H₃₂O₃: C, 74.96; H, 10.06. Found: C, 75.05; H, 10.14.

2.4.16.4 Cyclohexyl-*p*-tolylmethanol (13d)¹⁴²

Cyclohexyl-*p*-tolylmethanol (**13d**) was prepared, as described previously, from tricyclohexylborane¹⁴³ (3.1 mmol, 11 mL of a 0.28 M solution in THF) and **9b** (0.865 g, 3.00 mmol) with 6 hours at reflux in THF and oxidation by peracetic acid. The crude product was flash chromatographed using silica gel and 15 % EtOAc/Hexanes to

give 0.42 g (68% yield) of **13d**: $^1\text{H-NMR}$ (CDCl_3/TMS) δ 7.23-7.10 (m, 4H), 4.30 (d, 1H, $J = 7.27$ Hz), 2.38-2.30 (s, 3H), 2.08-1.93 (m, 2H), 1.83-1.51 (m, 4H), 1.43-0.82 (m, 7H); $^{13}\text{C-NMR}$ (CDCl_3) δ 140.65, 136.86, 128.77, 126.50, 79.12, 44.86, 29.24, 28.87, 26.39, 26.05, 25.97, 21.02.

2.4.16.5 2-Methyl-1-*p*-tolylbutan-1-ol (**13e**)¹⁴⁴

2-Methyl-1-*p*-tolylbutan-1-ol (**13e**) was prepared, as described previously, from tri-*sec*-butylborane (3.0 mmol, 3.0 mL of a 1.0 M solution in THF) and **9b** (0.865 g, 3.00 mmol) with 1.5 hours at reflux in THF and oxidation by peracetic acid. The crude product was flash chromatographed using 8 inches of silica gel in a 30 mm column with 12% EtOAc/Hexanes to give 0.27 g (51% yield) of **13e** as a pair of diastereomers: $^1\text{H-NMR}$ (CDCl_3/TMS) δ 7.23-7.11 (m, 4H), 4.51-4.36 (d, d, 1H, $J = 6.17, 7.07$ Hz), 2.34 (s, 3H), 1.86-1.58 (m, 2H), 1.45-0.99 (m, 2H), 0.98-0.70 (m, 6H); $^{13}\text{C-NMR}$ (CDCl_3) δ 141.20, 140.80, 137.20, 136.80, 128.83, 126.61, 126.31, 78.63, 78.03, 41.88, 41.56, 25.84, 24.93, 21.05, 15.08, 14.08, 11.60, 11.27.

2.4.17 Use of Borane Derivatives

A series of alcohols was prepared by the reaction of various borane derivatives with aryl aldehyde tosylhydrazones and DBU followed by oxidation. A representative procedure was presented in Section 2.4.13.1.

2.4.17.1 Reaction of Hexyl-9-BBN (14) with 9a

Hexyl-9-BBN (3.0 mmol) was prepared according to the literature procedure⁷ from 1-hexene (0.257 g, 3.05 mmol) and 9-BBN (3.0 mmol, 6.0 mL of a 0.5 M solution in THF) and allowed to react, as described previously, with **9a** (0.821 g, 2.99 mmol) and DBU (0.45 mL, 3.0 mmol) at reflux in THF for 1 hour. After oxidation with sodium perborate, the crude product was flash chromatographed using silica gel and 4% MeOH/CH₂Cl₂ to give 0.39 g (59% yield) of 5-(hydroxyphenyl-methyl)cyclooctanol (**15**)¹⁴⁵: ¹H-NMR (CDCl₃/TMS) δ 7.40-7.23 (m, 5H), 4.41 (d, 1H, J = 6.84 Hz), 4.01-3.85 (m, 1H), 2.00-1.14 (m, 14H); ¹³C-NMR (CDCl₃) δ 143.69, 128.30, 127.46, 126.61, 79.48, 72.09, 44.28, 36.12, 30.51, 28.57, 23.23, 22.84.

2.4.17.2 Reaction of Butyldicyclohexylborane (16) with 9a

Butyldicyclohexylborane (3.0 mmol) was prepared according to the literature procedure⁷ from BH₃·THF (3.0 mmol, 3.0 mL of a 1.0 M solution in THF), cyclohexene (0.492 g, 5.99 mmol) and excess 1-butene. It was allowed to react, as described previously, with **9a** (0.822 g, 3.00 mmol) and DBU (0.45 mL, 3.0 mmol) at reflux in THF for 30 minutes. After oxidation with peracetic acid, the crude product was flash chromatographed using silica gel and 6% EtOAc/Hexanes to give 0.34 g (60% yield) of cyclohexylphenylmethanol (**17**)¹⁴⁶: ¹H-NMR (CDCl₃/TMS) δ 7.38-7.21 (m, 5H), 4.35 (d, 1H, J = 7.19 Hz), 2.04-1.52 (m, 6H), 1.44-0.83 (m, 6H);

^{13}C -NMR (CDCl_3) δ 143.62, 128.14, 127.36, 126.61, 79.34, 44.95, 29.30, 28.79, 26.41, 26.08, 25.99.

2.4.17.3 Reaction of Hexyldimethylborane (18) with 9b

Hexyldimethylborane (3.0 mmol) was prepared according to the literature procedure¹⁶ from LiMe_2BH_2 (3.0 mmol, 6.0 mL of a 0.5 M solution in hexanes), 1-hexene (0.45 mL, 3.6 mmol), and TMSCl (0.38 mL, 3.0 mmol). It was allowed to react, as described previously, with **9b** (0.865 g, 3.00 mmol) and DBU (0.45 mL, 3.0 mmol) at reflux in THF for 3 hours. After oxidation with sodium perborate, the crude product was flash chromatographed using 7.5 inches of silica gel in a 50 mm column with 12% EtOAc/Hexanes to give 0.25 g (41% yield) of 1-*p*-tolylheptan-1-ol (**19**)¹⁴⁷: ^1H -NMR (CDCl_3/TMS) δ 7.23 (d, 2H, $J = 8.09$ Hz), 7.15 (d, 2H, $J = 8.05$ Hz), 4.61 (t, 1H, $J = 6.64$ Hz), 2.34 (s, 3H), 1.86-1.61 (m, 3H), 1.42-1.18 (m, 8H), 0.93-0.78 (m, 3H); ^{13}C -NMR (CDCl_3) δ 142.02, 137.10, 129.10, 125.85, 74.55, 39.06, 31.76, 29.21, 25.84, 22.60, 21.08, 14.04.

2.4.17.4 Reaction of B-Octylcatecholborane (24) with 9b

B-Octylcatecholborane was prepared according to the literature procedure¹⁸ from 1-octene (0.332 g, 2.96 mmol) and catecholborane (0.35 mL, 3.3 mmol). It was allowed to react, as described previously, with **9b** (0.865 g, 3.00 mmol) and DBU

(0.45 mL, 3.0 mmol) at reflux in THF for 4 hours. After oxidation with sodium perborate, the crude product was flash chromatographed using 9.5 inches of silica gel in a 50 mm column with 7% EtOAc/Hexanes to give 0.18 g (27% yield) of 1-*p*-tolylnonan-1-ol (**25**)¹⁴⁷: ¹H-NMR (CDCl₃/TMS) δ 7.23 (d, 2H, *J* = 8.10 Hz), 7.15 (d, 2H, *J* = 8.01 Hz), 4.62 (t, 1H, *J* = 6.66 Hz), 2.34 (s, 3H), 1.89-1.58 (m, 3H), 1.45-1.14 (m, 12H), 0.94-0.78 (m, 3H); ¹³C-NMR (CDCl₃) δ 141.99, 137.11, 129.09, 125.85, 74.55, 39.04, 31.85, 29.53, 29.24, 25.87, 22.63, 21.08, 14.07.

*2.4.18 trans-5-p-Tolyl-4,5-dihydro-1H-pyrazole-3,4-dicarboxylic Acid Dimethyl Ester (27b)*¹⁴⁸

To a flame dried, argon flushed, 50 mL, round-bottom flask equipped with a side-arm, reflux condenser, stir bar, argon inlet, and mercury bubbler was added **9b** (0.866 g, 3.00 mmol) and dimethyl maleate (0.435 g, 3.02 mmol). Dry THF (20 mL) was added followed by DBU (0.45 mL, 3.0 mmol) and the reaction heated to reflux for 1.5 hours. The reaction was then cooled to room temperature and distilled water (10 mL) added. The reaction mixture was transferred to a separatory funnel, extracted with ether (3 x 10 mL), washed with brine (1 x 20 mL), and dried over anhydrous MgSO₄. Solvent was removed under reduced pressure and the crude product was flash chromatographed using 7 inches of silica gel in a 40 mm column with 25% EtOAc/Hexanes to give 0.63 g (76% yield) of **27b**: ¹H-NMR (CDCl₃/TMS) δ 7.17 (s, 4H), 5.22 (d, 1H, *J* = 9.29 Hz), 4.02 (d, 1H, *J* = 9.33

Hz), 3.85 (s, 3H), 3.78 (s, 3H), 2.35 (s, 3H), 1.29-1.21 (br s, 1H); ^{13}C -NMR (CDCl_3) δ 170.86, 162.24, 138.63, 137.85, 136.24, 129.79, 126.10, 70.43, 57.93, 52.80, 52.25, 21.08.

2.4.19 Competition Experiment

The competition experiment was performed exactly like the synthesis of 1-*p*-tolylpentan-1-ol, **11b**, reported previously with the only difference being the addition of dimethyl maleate (0.433 g, 3.00 mmol) at the beginning of the reaction.

2.4.20 2,4,6-Triisopropylbenzenesulfonylhydrazide (**30**)¹¹⁷

To a round-bottom flask equipped with a magnetic stirrer, thermometer, and addition funnel was added 2,4,6-triisopropylbenzenesulfonyl chloride (26.3 g, 86.9 mmol) and THF (50 mL). The solution was cooled to -10°C in an ice-salt bath and hydrazine monohydrate (9.60 g, 192 mmol) was added over the course of 25 minutes. The temperature rose to 0°C during the addition. After the addition, the reaction mixture was stirred at 0°C (ice bath) for 3 hours and then distilled water (5 mL) was added to dissolve the solids. The mixture was then transferred to separatory funnel, the aqueous layer discarded, and the organic layer washed with ice-cold brine (3 x 20 mL). The organic layer was then dried over anhydrous Na_2SO_4 for 3 hours, filtered, and the solvent removed using a rotary evaporator below room temperature. Pentane

(100 mL) was added to the resulting solid and the mixture filtered. The solid was washed several times with pentane and then triturated with ice-cold water (4 x 100 mL). The solid was then dried *in vacuo* over P_2O_5 for 24 hours to give 21.4 g (82 % yield) of **30**: m.p. = 115.0 - 116.0 °C; lit. m.p. = 118 - 120 °C.

2.4.21 Benzaldehyde Trisylhydrazone (**31a**)¹¹⁸

The following procedure is general for the preparation of all aryl aldehyde trisylhydrazones. To a stirred solution of **30** (3.28 g, 11.0 mmol) in anhydrous methanol (45 mL) was added benzaldehyde (1.06 g, 9.97 mmol) in one portion. A solid immediately precipitated and the mixture was stirred at room temperature for one hour. At this point, the mixture was placed in the cold room overnight. The resulting solid was collected to give 3.36 g (87% yield) of **31a**: m.p. = 186.5 - 187.5 °C; lit. m.p. = 188 - 189 °C.

2.4.22 4-Methylbenzaldehyde Trisylhydrazone (**31b**)

4-Methylbenzaldehyde trisylhydrazone (**31b**) was prepared, as described previously, from **30** (3.30 g, 11.0 mmol) and 4-methylbenzaldehyde (1.22 g, 10.1 mmol). The product was recrystallized from hot ethanol to give 2.46 g (61 % yield) of **31b**: m.p. = 186.7 - 188.7 °C; Anal. calcd for $C_{23}H_{32}N_2O_2S$: C, 68.96; H, 8.05; N, 6.99. Found: C, 68.93; H, 8.06; N, 7.04.

2.4.23 4-Methoxybenzaldehyde Trisylhydrazone (**31c**)

4-Methoxybenzaldehyde trisylhydrazone (**31c**) was prepared, as described previously, from **30** (3.29 g, 11.0 mmol) and 4-methoxybenzaldehyde (1.36 g, 10.0 mmol). The product was recrystallized from hot ethanol to give 2.56 g (62 % yield) of **31c**: m.p. = 162.0 - 167.3 °C; Anal. calcd. for $C_{23}H_{32}N_2O_3S$: C, 66.31; H, 7.74; N, 6.72. Found: C, 66.49; H, 7.67; N, 6.95.

2.4.24 3-Methoxybenzaldehyde Trisylhydrazone (**31d**)

3-Methoxybenzaldehyde trisylhydrazone (**31d**) was prepared, as described previously, from **30** (3.29 g, 11.0 mmol) and 3-methoxybenzaldehyde (1.37 g, 10.0 mmol). The product was collected to give 2.59 g (62 % yield) of **31d**: m.p. = 187.0 - 188.5 °C; Anal. calcd. for $C_{23}H_{32}N_2O_3S$: C, 66.31; H, 7.74; N, 6.72. Found: C, 66.24; H, 7.78; N, 6.72.

2.4.25 2-Methoxybenzaldehyde Trisylhydrazone (**31e**)

2-Methoxybenzaldehyde trisylhydrazone (**31e**) was prepared, as described previously, from **30** (3.28 g, 11.0 mmol) and 2-methoxybenzaldehyde (1.38 g, 10.1 mmol). The product was recrystallized from hot ethanol to give 2.28 g (54 % yield) of **31e**: m.p. = 164.5 - 165.5 °C; Anal. calcd. for $C_{23}H_{32}N_2O_3S$: C, 66.31; H, 7.74; N, 6.72. Found: C, 66.17; H, 7.69; N, 6.79.

2.4.26 4-Bromobenzaldehyde Trisylhydrazone (**31g**)

4-Bromobenzaldehyde trisylhydrazone (**31g**) was prepared, as described previously, from **30** (3.31 g, 11.1 mmol) and 4-bromobenzaldehyde (1.86 g, 10.0 mmol). The product was recrystallized from hot ethanol to give 3.17 g (68% yield) of **31g**: m.p. = 197.0 - 197.8 °C; Anal. calcd. for $C_{22}H_{29}N_2O_2SBr$: C, 56.77; H, 6.28; N, 6.02. Found: C, 56.58; H, 6.19; N, 6.11.

2.4.27 3-Bromobenzaldehyde Trisylhydrazone (**31h**)

3-Bromobenzaldehyde trisylhydrazone (**31h**) was prepared, as described previously, from **30** (3.29 g, 11.0 mmol) and 3-bromobenzaldehyde (1.86 g, 10.1 mmol). The product was collected to give 2.54 g (54% yield) of **31h**: m.p. = 230 - 233 °C; Anal. calcd for $C_{22}H_{29}N_2O_2SBr$: C, 56.77; H, 6.28; N, 6.02. Found: C, 56.84; H, 6.23; N, 6.06.

2.4.28 2-Bromobenzaldehyde Trisylhydrazone (**31i**)

2-Bromobenzaldehyde trisylhydrazone (**31i**) was prepared, as described previously, from **30** (3.29 g, 11.0 mmol) and 2-bromobenzaldehyde (1.85 g, 10.0 mmol). The product was recrystallized from hot ethanol to give 3.31 g (71% yield) of **31i**: m.p. = 153.0 - 155.2 °C; Anal. calcd for $C_{22}H_{29}N_2O_2SBr$: C, 56.77; H, 6.28; N, 6.02. Found: C, 56.88; H, 6.33; N, 6.10.

2.4.29 2,4,6-Trimethylbenzaldehyde Trisylhydrazone (**31l**)

2,4,6-Trimethylbenzaldehyde trisylhydrazone (**31l**) was prepared, as described previously, from **30** (0.946 g, 3.17 mmol) and 2,4,6-trimethylbenzaldehyde (0.429 g, 2.89 mmol). The product was recrystallized from hot ethanol to give 0.358 g (29 % yield) of **31l**: m.p. = 133.0 - 135.0 °C; Anal. calcd for $C_{25}H_{36}N_2O_2S$: C, 70.05; H, 8.46; N, 6.54. Found: C, 70.15; H, 8.50; N, 6.49.

2.4.30 2-Chlorobenzaldehyde Trisylhydrazone (**31m**)

2-Chlorobenzaldehyde trisylhydrazone (**31m**) was prepared, as described previously, from **30** (3.30 g, 11.0 mmol) and 2-chlorobenzaldehyde (1.42 g, 10.1 mmol). The product was recrystallized from hot ethanol to give 3.04 g (72 % yield) of **31m**: m.p. = 159.0 - 161.0 °C; Anal. calcd for $C_{22}H_{29}N_2O_2SCl$: C, 62.76; H, 6.94; N, 6.65. Found: C, 62.66; H, 6.97; N, 6.64.

2.4.31 Alkylation of Trisylhydrazones with Tributylborane: Oxidation with Sodium Perborate

The following compounds were prepared by reaction of the corresponding trisylhydrazone with DBU and tributylborane followed by oxidation with sodium perborate. The synthesis of 1-phenylpentan-1-ol (**11a**) is representative.

2.4.31.1 1-Phenylpentan-1-ol (**11a**)

To a flame-dried, argon flushed, 50 mL, round-bottom flask equipped with a side-arm, reflux condenser, stir bar, argon inlet, and mercury bubbler was added **31a** (1.16 g, 3.00 mmol). This was dissolved in dry THF (17 mL) followed by the addition of tributylborane (3.0 mmol, 3.0 mL of a 1.0 M solution in THF). DBU (0.45 mL, 3.0 mmol) was added and the reaction stirred at room temperature. Gas evolution was immediately evident and there was a slight exotherm. The reaction was stirred until TLC indicated the disappearance of starting material (2 hours). The reaction flask was then placed in a room temperature water bath and distilled water (10 mL) and sodium perborate (1.43 g, 9.29 mmol) added. The reaction was stirred vigorously for 2 hours, the reaction mixture transferred to a separatory funnel, and the product extracted into ether (3 x 10 mL). The extracts were washed with brine (1 x 20 mL), dried over anhydrous MgSO₄ and the solvent removed. The crude product was flash chromatographed using silica gel and 11% EtOAc/Hexanes to give 0.44 g (90% yield) of **11a**: Spectral data was consistent with sample prepared previously.

2.4.31.2 1-*p*-Tolylpentan-1-ol (**11b**)

1-*p*-Tolylpentan-1-ol (**11b**) was prepared, as described previously, from **31b** (1.21g, 3.01 mmol). The crude product was flash chromatographed using 8 inches of silica gel in a 50 mm column with 8% EtOAc/Hexanes to give 0.47 g (87% yield) of **11b**: Spectral data was consistent with sample prepared previously.

2.4.31.3 1-(4-Methoxyphenyl)pentan-1-ol (11c)

1-(4-Methoxyphenyl)pentan-1-ol (**11c**) was prepared, as described previously, from **31c** (1.25 g, 3.00 mmol). The crude product was flash chromatographed using 8.5 inches of silica gel in a 50 mm column with 15% EtOAc/Hexanes to give 0.47 g (80% yield) of **11c**: Spectral data was consistent with sample prepared previously.

2.4.31.4 1-(3-Methoxyphenyl)pentan-1-ol (11d)

1-(3-Methoxyphenyl)pentan-1-ol (**11d**) was prepared, as described previously, from **31d** (1.25 g, 3.00 mmol). The crude product was flash chromatographed using 7.5 inches of silica gel in a 50 mm column with 10% EtOAc/Hexanes to give 0.44 g (76% yield) of **11d**: Spectral data was consistent with sample prepared previously. Also isolated was 0.12 g (23% yield) of the alkane product, 1-methoxy-3-pentylbenzene (**12d**): Spectral data was consistent with sample prepared previously.

2.4.31.5 1-(2-Methoxyphenyl)pentan-1-ol (11e)

1-(2-Methoxyphenyl)pentan-1-ol (**11e**) was prepared, as described previously, from **31e** (1.25 g, 3.00 mmol). The crude product was flash chromatographed using 7.5 inches of silica gel in a 50 mm column with 10% EtOAc/Hexanes to give 0.51 g (88% yield) of **11e**: Spectral data was consistent with sample prepared previously. Also isolated was 0.066 g (12% yield) of the alkane product, 1-methoxy-2-

pentylbenzene (**12e**): Spectral data was consistent with sample prepared previously.

2.4.31.6 1-(2,4,6-Trimethylphenyl)pentan-1-ol (**11l**)

1-(2,4,6-Trimethylphenyl)pentan-1-ol (**11l**) was prepared, as described previously, from **31l** (0.215 g, 0.502 mmol). The crude product was flash chromatographed using 7.5 inches of silica gel in a 30 mm column with 8% EtOAc/Hexanes to give 0.094 g (91% yield) of **11l**: Spectral data was consistent with sample prepared previously.

2.4.32 Alkylation of Trisylhydrazones with Tributylborane: Oxidation with Peracetic Acid

A series of alcohols was prepared by the reaction of the corresponding trisylhydrazone with DBU and tributylborane followed by oxidation with peracetic acid. The synthesis of 1-(4-bromophenyl)pentan-1-ol (**11g**) is representative.

2.4.32.1 1-(4-Bromophenyl)pentan-1-ol (**11g**)

To a flame-dried, argon flushed, 50 mL, round-bottom flask equipped with a side-arm, reflux condenser, stir bar, argon inlet, and mercury bubbler was added **31g** (1.40 g, 3.00 mmol). Dry THF (17 mL) was added followed by the addition of

tributylborane (3.0 mmol, 3.0 mL of a 1.0 M solution in THF). DBU (0.45 mL, 3.0 mmol) was added and the reaction stirred at room temperature. Vigorous gas evolution was immediately evident and there was a slight exotherm. The reaction was stirred until TLC indicated the disappearance of starting material (1 hour). The reaction flask was then placed in an ice-water bath and peracetic acid (10 mmol, 2.2 mL of a 32 wt% solution in acetic acid) added slowly. After addition was complete, the solution was stirred at room temperature for one hour. After this, a small amount of sodium thiosulfate solution was added, to destroy any excess peracid, followed by NaOH (30 mmol, 15 mL of a 2 N solution) to basify. The reaction mixture was transferred to a separatory funnel and extracted into ether (3 x 10 mL). The extracts were washed with brine (1 x 20 mL) and dried over anhydrous MgSO_4 . The solvent was removed and hexanes added to the crude material to produce a flocculent white solid. The solid was removed by filtration through a plug of celite and anhydrous Na_2SO_4 . Solvent was removed from the filtrate and the crude product was flash chromatographed using 8.5 inches of silica gel in a 50 mm column with 10% EtOAc/Hexanes to give 0.63 g (86% yield) of **11g**: Spectral data was consistent with sample prepared previously.

2.4.32.2 1-(3-Bromophenyl)pentan-1-ol (**11h**)

1-(3-Bromophenyl)pentan-1-ol (**11h**) was prepared, as previously described, from **31h** (1.40 g, 3.00 mmol). The crude product was flash chromatographed using

7.5 inches of silica gel in a 50 mm column with 8% EtOAc/Hexanes to give 0.60 g (83% yield) of **11h**: Spectral data was consistent with sample previously prepared.

2.4.32.3 1-Bromo-2-pentylbenzene (**12i**)¹⁴⁹

1-Bromo-2-pentylbenzene (**12i**) was prepared, as previously described, from **31i** (1.40 g, 3.00 mmol). The crude product was flash chromatographed using 7.0 inches of silica gel in a 50 mm column with 5% EtOAc/Hexanes to give 0.60 g (89% yield) of **12i**: ¹H-NMR (CDCl₃/TMS) δ 7.54-6.97 (m, 4H), 2.71 (t, 2H, *J* = 7.82 Hz), 1.67-1.54 (m, 2H), 1.41-1.29 (m, 4H), 0.95-0.86 (m, 3H); ¹³C-NMR (CDCl₃) δ 142.14, 132.71, 130.26, 127.28, 124.46, 36.16, 31.58, 29.63, 22.51, 14.02.

2.4.32.4 1-Chloro-2-pentylbenzene (**12m**)¹⁵⁰

1-Chloro-2-pentylbenzene (**12m**) was prepared, as previously described, from **31m** (1.26 g, 3.00 mmol). The crude product was flash chromatographed using 7 inches of silica gel in a 40 mm column with 9% EtOAc/Hexanes to give 0.45 g (82% yield) of **12m**: ¹H-NMR (CDCl₃/TMS) δ 7.37-7.08 (m, 4H), 2.74 (t, 2H, *J* = 7.79 Hz), 1.70-1.56 (m, 2H), 1.43-1.33 (m, 4H), 0.97-0.89 (m, 3H); ¹³C-NMR (CDCl₃) δ 140.45, 133.92, 130.30, 129.38, 127.02, 126.60, 33.56, 31.61, 29.45, 22.50, 14.00.

2.4.33 Reaction of B-Octylcatecholborane (24) with 31b

B-Octylcatecholborane was prepared according to the literature procedure¹⁸ from 1-octene (0.334 g, 2.98 mmol) and catecholborane (0.35 mL, 3.3 mmol) and was then allowed to react, as described previously, with **31b** (1.21 g, 3.02 mmol) and DBU (0.45 mL, 3.0 mmol) at room temperature in THF for 4 hours. After oxidation with sodium perborate, the crude material obtained was flash chromatographed using 8.5 inches of silica gel in a 50 mm column with 7% EtOAc/Hexanes to give 0.33 g (48% yield) of 1-*p*-tolylnonan-1-ol (**25**): Spectral data was consistent with sample previously prepared.

2.5 Conclusion

This chapter has described the development of a new alkylation reaction which is the synthetic equivalent of the 1,2-addition of a trialkylborane to a carbonyl compound. Both aryl aldehyde tosyl- and trisylhydrazones are readily alkylated with trialkylboranes in the presence of the non-nucleophilic base DBU to produce the corresponding substituted alcohols in excellent yields after oxidation. Several different functional groups may be present in either the hydrazone or the trialkylborane. The trisylhydrazones react more readily than the corresponding tosylhydrazones, producing the alcohol in excellent yields at room temperature. The common dialkylborane reagents migrate competitively with the intended alkyl group. Catecholborane is the

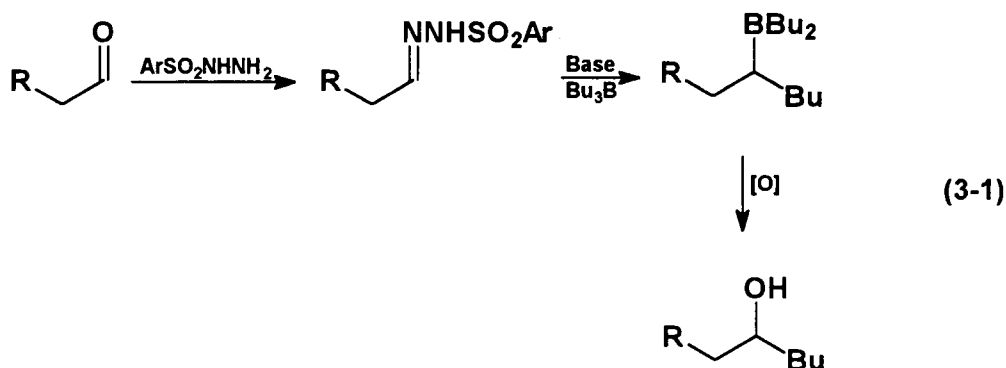
best blocking group tested thus far although the search for a more suitable group continues. Finally, two possible mechanistic courses for the reaction were presented.

Chapter 3 describes the application of this technology to alkyl aldehydes.

**CHAPTER 3. ALKYLATION OF ALKYL ALDEHYDE
ARENESULFONYLHYDRAZONES VIA TRIALKYLBORANES**

3.1 Introduction

Based on the successful alkylation of aryl aldehyde arenesulfonylhydrazones with trialkylboranes, it was of interest to determine whether this methodology could be extended to alkyl aldehydes (eqn 3-1). Based on the mechanisms proposed for



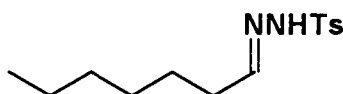
the reaction in Chapter Two, it was anticipated that the alkyl hydrazone substrates would be more sluggish to react. This is because the alkyl groups offer little or no stabilization for the developing negative charge at the original carbonyl carbon. The aryl groups, on the other hand, stabilize this developing charge through benzylic resonance and the electronegative nature of the benzene ring. Despite this drawback, it was desirable to determine if alkyl aldehyde substrates could be included in this new alkylation technology.

3.2 Alkyl Aldehyde Tosylhydrazones

As with the aryl aldehydes, the first arenesulfonylhydrazone derivatizing agent to be tested was *p*-toluenesulfonylhydrazide. The alkyl tosylhydrazones are well known and have been studied previously.

3.2.1 Synthesis of Alkyl Aldehyde Tosylhydrazones

Heptanal tosylhydrazone, **32** (Figure 3-1), was chosen as the model substrate for the study. It is readily prepared from heptanal and *p*-toluenesulfonylhydrazide and



32

Figure 3-1. Heptanal Tosylhydrazone **32**

it may be easily purified by recrystallization from ether¹⁵¹.

3.2.2 Typical Results

Several base and solvent combinations were tested to determine if **32** could be

alkylated with the standard trialkylborane, tributylborane (Table 3-1). The first attempt involved the use of DBU in refluxing THF, the protocol which succeeded with the aryl aldehyde tosylhydrazones. It, however, failed to produce any product with the alkyl substrate. Several other bases were tested in refluxing THF including NaOH, Bu₄NOH, BuLi, *t*-BuLi, and lithium diisopropylamide (LDA). None

Table 3-1. Attempted Alkylation of Heptanal Tosylhydrazone via Tributylborane.

Entry	Base	Solvent ^(a)	% Yield undecan-5-ol
1	DBU	THF	--
2	NaOH	THF	--
3	Bu ₄ NOH	THF	--
4	BuLi	THF	--
5	<i>t</i> -BuLi	THF	--
6	LDA	THF	--
7	NaOH	CH ₂ Cl ₂ /H ₂ O (PTC)	--
8	Bu ₄ NOH	MeOH	--
9	Bu ₄ NOH	MeOH/Hexanes	--
10	BuLi	HMPA	--
11	<i>t</i> -BuLi	HMPA	--

^(a)Reflux.

generated the desired product, undecan-5-ol. Use of Bu₄NOH in MeOH or MeOH/Hexanes also did not succeed. What were typically produced, instead of the desired product, were condensation products of heptanal or an azine by-product, **33** (Figure 3-2). Azines are a common by-product of diazo compounds which suggests that the diazo intermediate is being formed^{115b}. No alcohol product, however, could

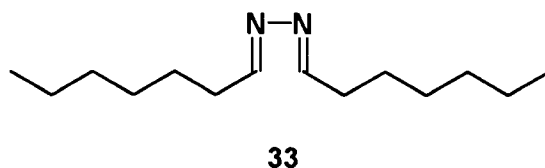


Figure 3-2. Azine By-product 33.

be detected.

Tosylhydrazones have been reported to be N-alkylated with NaOH and alkyl halides under phase transfer catalysis (PTC) conditions¹⁵². Adaptation of this technology to utilization of tributylborane also failed to produce any product.

Several of the strong kinetic bases, such as the alkyllithiums, produced a white solid when added to a solution of **32** and tributylborane in THF. This solid is presumably the "borate" complex, **34**, formed by reaction of the nitrogen of the tosylhydrazone anion with the boron of the tributylborane (Figure 3-3). A ¹¹B-NMR

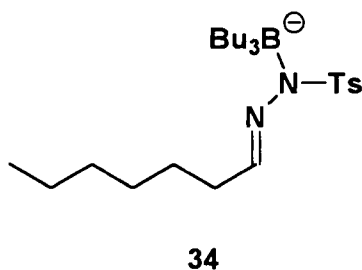


Figure 3-3. Presumed "Borate" Complex 34.

of the supernatant from a reaction in which the solid was present showed no boron

species present, suggesting that the tributylborane was trapped in the precipitated complex. Hexamethylphosphoramide (HMPA), a polar, aprotic solvent, was utilized in an attempt to solubilize this complex to allow the boron to react at the carbon of the original carbonyl instead of at the nitrogen. Reactions were performed using the strong bases BuLi and *t*-BuLi in neat HMPA but no product was produced (Table 3-1). However, when a 50:50 combination of HMPA:THF was used, product was generated (Table 3-2). The use of this new solvent combination together with

Table 3-2. Alkylation of Heptanal Tosylhydrazone via Tributylborane.

Entry	Base	Solvent ^(a)	% Yield undecan-5-ol ^(b)
1	LiHMDS	HMPA/THF	34
2	BuLi	HMPA/THF	29

^(a)Reflux. ^(b)Isolated yield based on heptanal tosylhydrazone.

a strong base such as lithium hexamethyldisilazide (LiHMDS) or BuLi produced approximately 30% of the intended product, undecan-5-ol. This was the highest yield of alkylated product produced from an alkyl aldehyde tosylhydrazone.

3.3 Alkyl Aldehyde Trisylhydrazones

Due to the apparent lack of reactivity of alkyl aldehyde tosylhydrazones, it was decided to test the alkyl aldehyde trisylhydrazones. The aryl trisyl derivatives had

reacted more readily than their tosyl counterparts and it was felt that this increased reactivity would be present in the alkyl derivatives as well.

3.3.1 Synthesis of Alkyl Aldehyde Trisylhydrazones

As before, the hydrazone derivative of heptanal, in this case heptanal trisylhydrazone, **35**, was chosen as the model substrate for the initial investigation (Figure 3-4). Unlike its tosylhydrazone counterpart, however, heptanal

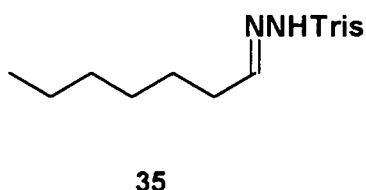


Figure 3-4. Heptanal Trisylhydrazone **35**.

trisylhydrazone is not isolable and must be prepared and used *in situ*¹⁵¹. Typically, heptanal and 2,4,6-triisopropylbenzenesulfonylhydrazide (TPSH) were dissolved in THF and allowed to stir at room temperature until TLC indicated hydrazone formation was complete. The THF solution of the heptanal trisylhydrazone was then dried with anhydrous MgSO_4 and filtered through a short column of celite/anhydrous Na_2SO_4 to remove the water generated during trisylhydrazone formation. The other alkyl aldehyde trisylhydrazone utilized in this study, 2-methylpentanal trisylhydrazone, **36**,

was prepared in a similar fashion (Figure 3-5).

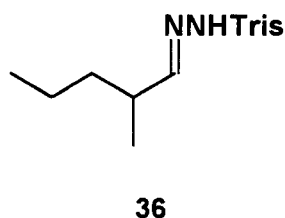


Figure 3-5. 2-Methylpentanal Trisylhydrazone **36**.

3.3.2 Typical Results

Unlike its tosyl counterpart, every base and solvent combination tested with **35** induced alkylation via tributylborane to produce undecan-5-ol (Table 3-3). The DBU/THF protocol, which worked for the aryl aldehyde trisylhydrazones, produced a

Table 3-3. Alkylation of Heptanal Trisylhydrazone via Tributylborane^(a).

Entry	Base	Solvent ^(b)	% Yield undecan-5-ol ^(c)
1	DBU	THF	57
2	DBU	THF ^(d)	47
3	KOH	MeOH	45
4	Bu ₄ NOH	THF	50
5	<i>t</i> -BuLi	THF	64

^(a)Heptanal trisylhydrazone formed from 1 equiv. heptanal and 1 equiv. TPSH and treated with 1 equiv. base. ^(b)Reflux. ^(c) Isolated yield based on starting aldehyde. ^(d)Reaction was sonicated instead of refluxed.

57% yield of product (entry 1). Sonication of the reaction mixture, in place of refluxing, did not produce an increase in yield. Several other bases, including KOH, Bu_4NOH , and $t\text{-BuLi}$ produced good yields of product. The strong base, $t\text{-BuLi}$, produced the highest yield of product, 64%.

Because the readily available and easily utilized base DBU produced a reasonable amount of product, it was of interest to see if the yield could be increased using this base. To this end, a study of the reaction using DBU was performed.

Because the trisilylhydrazone substrate must be prepared *in situ*, this step was studied initially to determine the effect it had on the final yield. As shown in Table 3-4, increasing the equivalents of the derivatizing agent TPSH from 1.0 to 1.25 did

Table 3-4. Study of the Alkylation of Heptanal Trisilylhydrazone via Tributylborane.

Entry	Aldehyde (equiv.)	TPSH (equiv.)	DBU (equiv.)	% Yield undecan-5-ol ^(a)
1	1.0	1.0	1.0	57
2	1.0	1.25	1.0	58
3	1.5	1.0	1.0	62
4	1.0	1.0	1.5	74
5	1.0	1.0	2.0	70

^(a)Isolated yield based on heptanal.

not increase the yield (entry 2). Because alkyl aldehydes sometimes exist in solution as trimers, it was thought that the amount of aldehyde available for reaction was less than that required. Increasing the amount of aldehyde, however, did not affect the

yield (entry 3).

When the amount of base was changed, however, the yield increased.

Increasing the amount of DBU to 1.5 equivalents increased the yield to 74 % (entry 4).

Increasing the amount further, to 2.0 equivalents, did not produce a concomitant increase in yield however (entry 5).

Presumably, some of the DBU was being lost to reaction with water generated from the initial formation of the trisylhydrazone. If this was indeed the case, it was thought that changing the drying agent might obviate the problem. The drying agent used to remove water in the reactions thus far had been anhydrous MgSO_4 . Changing to activated 4Å molecular sieves produced a 58 % yield of product, the same as that obtained with MgSO_4 . Using 4Å molecular sieves and allowing them to remain in the reaction mixture during the course of the reaction depressed the yield to 40 %.

Another aldehyde, 2-methylpentanal, was tested to determine if it too could be alkylated using this methodology (Table 3-5). Use of one equivalent of DBU produced a 45 % yield of the desired product (entry 1). Increasing this to 1.5 equivalents did not increase the yield (entry 2).

Table 3-5. Alkylation of 2-Methylpentanal Trisylhydrazone via Tributylborane.

Entry	Aldehyde (equiv.)	TPSH (equiv.)	DBU (equiv.)	%Yield 4-methylnonan- 5-ol ^(a)
1	1.0	1.0	1.0	45
2	1.0	1.0	1.5	42
3 ^(b)	1.0	1.0	1.0	39

^(a)Isolated yield based on 2-methylpentanal. ^(b)2 mol % of $\text{Rh}_2(\text{OAc})_4$ added.

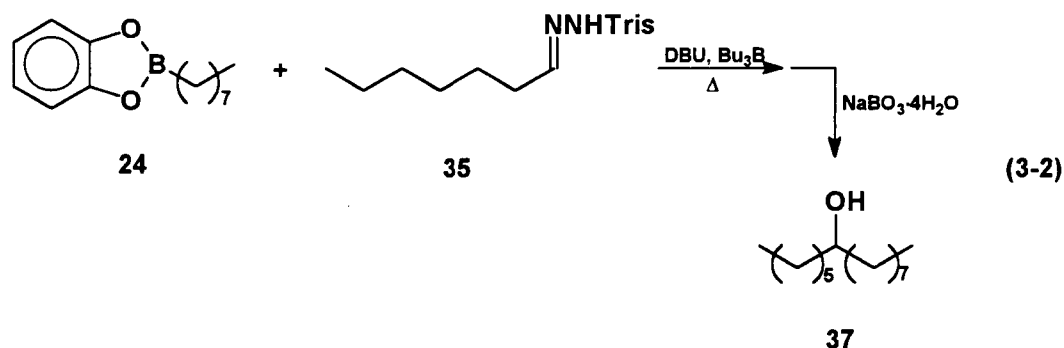
Both reactions produced a considerable amount of azine by-product. The appearance of this product suggests that the diazo intermediate is forming, but it is not reacting with the tributylborane. Dirhodium tetraacetate ($\text{Rh}_2(\text{OAc})_4$) has been used to promote reactions of diazo compounds¹⁵³ and it was felt that it might induce reaction in this case as well. Addition of this compound to the reaction of 2-methylpentanal trisylhydrazone, tributylborane, and DBU resulted in a 39% yield of the desired product (entry 3). It appears that the DBU complexed with the transition metal catalyst since the reaction mixture changed from the deep blue-green color of the catalyst to a dark burgundy upon the addition of the DBU. If this reaction were repeated, a base which would not complex with the rhodium catalyst would be needed.

3.3.3 Use of Borane Derivatives

As with the aryl aldehyde hydrazones, it was of interest to determine if any blocked borane derivatives could be utilized to deliver alkyl groups to the alkyl aldehyde trisylhydrazones.

3.3.3.1 Catecholborane

B-Octylcatecholborane, **24**, was prepared and reacted with heptanal trisylhydrazone (eqn 3-2). After oxidation and work-up, an 18% isolated yield of the



product, pentadecan-7-ol, **37**, was isolated proving that alkylcatecholborane derivatives can deliver alkyl groups to alkyl aldehyde trisylhydrazones albeit in low yields.

3.4 Experimental

The general experimental conditions parallel those summarized in Section 2.4.

3.4.1 Heptanal Tosylhydrazone (**32**)¹⁵¹

To a 250 mL, round-bottom flask equipped with a septum and stir bar was added 9.32 g (50.0 mmol) *p*-toluenesulfonylhydrazide and THF (100 mL). Heptanal (5.42 g, 47.5 mmol) was added and the solution stirred at room temperature for thirty minutes. After this, the THF was removed under reduced pressure below room temperature. The resulting cream-colored solid was recrystallized from hot ether to give 5.85 g (44% yield) of **32**: m.p. = 70.0 - 73.0 °C; lit. m. p. = 72 - 73 °C.

3.4.2 Alkylation of **32** Via Tributylborane

The following procedure for the alkylation reaction with LiHMDS is representative for the study involving various base and solvent combinations summarized in Tables 3-1 and 3-2. To a flame-dried, argon flushed, 50 mL, round-bottom flask equipped with a side-arm, reflux condenser, stir bar, argon inlet and mercury bubbler was added **32** (0.844 g, 2.99 mmol). This was dissolved in a 50:50 mixture of THF:HMPA (20 mL). Tributylborane (3.0 mmol, 3.0 mL of a 1.0 M solution in THF) was added via syringe. LiHMDS (3.0 mmol, 3.0 mL of a 1.0 M solution in THF) was added and the reaction mixture heated to reflux. The reaction mixture was heated until reaction stopped progressing as evidenced by TLC (21 hours). The reaction was then cooled and placed in a room temperature water bath. Distilled water (10 mL) and sodium perborate (1.41 g, 9.14 mmol) were added and the reaction stirred vigorously for 2 hours. The reaction mixture was then transferred to a separatory funnel, extracted with ether (3 x 10 mL), washed with water (2 x 20 mL) to remove HMPA, and washed with brine (1 x 20 mL). The ether extracts were dried over anhydrous MgSO₄. The solvent was removed and the crude product was flash chromatographed using silica gel and 9% EtOAc/Hexanes to give 0.18 g (34% yield) of undecan-5-ol¹⁵⁴: ¹H-NMR (CDCl₃/TMS) δ 3.74-3.44 (br m, 1H), 1.56-1.04 (m, 17H), 1.04-0.72 (m, 6H); ¹³C-NMR (CDCl₃) δ 72.02, 37.51, 37.18, 31.84, 29.36, 27.84, 25.60, 22.75, 22.60, 14.04; GCMS *m/z* 171 (M-1), 154 (m-H₂O).

3.4.3 Heptanal Trisylhydrazone (35)

As stated in the discussion, **35** is not isolable and must be prepared and used *in situ*. The following is a general procedure for the preparation. To a 25 mL, round-bottom flask equipped with a stir bar and septum was added TPSH (0.895 g, 3.00 mmol). THF (5 mL) was added to create a clear, colorless solution. Heptanal (0.340 g, 2.98 mmol) was diluted in THF (5 mL) and added to the TPSH solution at room temperature. The reaction mixture was then stirred at room temperature for 30 minutes. Anhydrous MgSO_4 was then added and the mixture filtered through a short column of celite/anhydrous Na_2SO_4 . THF (7 mL) was used to rinse the flask and column. The trisylhydrazone solution was typically filtered directly into a reaction flask and used immediately.

2-Methylpentanal trisylhydrazone (**36**) was prepared in an analogous fashion.

3.4.4 Alkylation of **35** Via Tributylborane

The following procedure is representative for reactions involving the base and solvent combinations shown in Tables 3-3 and 3-4. To a flame-dried, argon flushed, 50 mL, round-bottom flask equipped with a side-arm, reflux condenser, stir-bar, argon inlet, and mercury bubbler was added **35** (3.00 mmol) prepared as described in Section 3.4.3. Tributylborane (3.0 mmol, 3.0 mL of a 1.0 M solution in THF) was added followed by DBU (0.67 mL, 4.5 mmol). The reaction mixture was heated to reflux until TLC indicated the reaction was over (3 hrs). The mixture was then

cooled and oxidized with water (10 mL) and sodium perborate (1.44 g, 9.36 mmol) as described earlier. After the standard work-up and removal of solvent, the crude product was flash chromatographed using 8 inches of silica gel in a 50 mm column with 8% EtOAc/Hexanes to give 0.38 g (74% yield) of undecan-5-ol: Spectral data was consistent with previously prepared sample.

3.4.5 Alkylation of 2-Methylpentanal Trisilylhydrazone (**36**) Via Tributylborane

The following procedure is representative for the reactions summarized in Table 3-5. To a flame-dried, argon flushed, 50 mL, round-bottom flask equipped with a side-arm, reflux condenser, stir bar, argon inlet, and mercury bubbler was added **36** (3.00 mmol) prepared as described in Section 3.4.3. Tributylborane (3.0 mmol, 3.0 mL of a 1.0 M solution in THF) was added followed by DBU (0.45 mL, 3.0 mmol). The reaction was then heated until TLC indicated the reaction was complete (5 hrs). The reaction was then cooled and oxidized with water (10 mL) and sodium perborate (1.42 g, 9.25 mmol) as described earlier. After the standard work-up and removal of solvent, the crude product was flash chromatographed using 6.5 inches of silica gel in a 50 mm column with 7% EtOAc/Hexanes to give 0.21 g (45% yield) of 4-methylnonan-5-ol¹⁵⁵ as a pair of diastereomers: ¹H-NMR (CDCl₃/TMS) δ 3.54-3.39 (m, 1H), 1.59-1.05 (m, 12H), 0.98-0.80 (m, 9H); ¹³C-NMR (CDCl₃) δ 76.03, 75.18, 38.55, 37.90, 35.61, 34.16, 33.06, 28.46, 28.33, 22.78, 20.44, 15.21, 14.29, 14.04, 13.50; GCMS *m/z* 157 (M-1), 140 (m-H₂O).

3.4.6 Pentadecan-7-ol (**37**)¹⁵⁶

B-Octylcatecholborane was prepared according to the literature procedure from 1-octene (0.347 g, 3.09 mmol) and catecholborane (0.35 mL, 3.3 mmol). This and **35** (3.00 mmol), prepared as described in Section 3.4.3, were placed in a flame-dried, argon flushed, 50 mL, round-bottom flask equipped with a side-arm, reflux condenser, stir bar, argon inlet, and mercury bubbler. DBU (0.45 mL, 3.0 mmol) was added and the reaction mixture heated to reflux until TLC indicated reaction was over (6 hrs). The reaction mixture was cooled and oxidized with water (10 mL) and sodium perborate (1.42 g, 9.26 mmol) as described earlier. After the standard work-up and removal of solvent, the crude product was flash chromatographed using 9 inches of silica gel in a 50 mm column with 6% EtOAc/Hexanes to give 0.12 g (18% yield) of **37**: m.p. = 35.5 - 37.5 °C; lit. m.p. = 34 - 36 °C; ¹H-NMR (CDCl₃/TMS) δ 3.66-3.54 (m, 1H), 1.55-1.16 (m, 25H), 0.93-0.83 (m, 6H); ¹³C-NMR (CDCl₃) δ 72.03, 37.48, 31.84, 29.70, 29.56, 29.34, 29.26, 25.61, 22.59, 14.04; GCMS *m/z* 210 (m-H₂O).

3.5 Conclusion

This chapter summarizes data which show that the alkylation technology developed for aryl aldehydes can be extended to alkyl aldehydes. The reactions of the alkyl aldehyde tosylhydrazones are rather sluggish, producing alcohol product only

with strong bases and in polar aprotic solvent combinations. The alkyl aldehyde trisylhydrazones, however, react readily with a variety of bases to produce good yields of the alkylated products. It was found that reactions using DBU in refluxing THF, the protocol from the aryl aldehyde cases, gave a good yield of product in a reasonable time. Simply increasing the amount of DBU to 1.5 equivalents increased the yield. Finally, it was shown that B-octylcatecholborane can deliver an alkyl group to an alkyl aldehyde trisylhydrazone albeit in low yield.

Further research should expand upon this foundation by determining the generality of this methodology. This could be accomplished using several different aldehydes as substrates and determining the yield of alcohol produced from alkylation with tributylborane. Also, functionalized aldehydes and/or organoboranes could be evaluated. Finally, the search for a suitable blocking group for this reaction must continue. If a suitable blocking group was found, it would then be possible to use chiral modifiers to induce asymmetry in the product alcohol.

The following chapter presents various approaches attempted to achieve the direct 1,2-addition of an organoborane to a carbonyl compound.

CHAPTER 4. 1,2-ADDITION OF ORGANOBORANES TO CARBONYL COMPOUNDS

4.1 Introduction

Chapters 2 and 3 of this dissertation have illustrated the use of arenesulfonylhydrazone derivatives to achieve the overall 1,2-addition of organoboranes to carbonyl groups. It was shown that these derivatives provide the equivalent product of 1,2-addition, the substituted alcohols, in good to excellent yields for both aryl and alkyl aldehydes. What follows is an overview of various attempts to achieve the direct 1,2-addition of an organoborane reagent to a carbonyl compound. A summary of previous attempts is available¹⁵⁷.

Two basic approaches were taken. The first involved attempts to polarize the organoborane reagent, making it a better Lewis acid and, in turn, increasing the amount of complexation between it and the carbonyl. The second approach involved attempts to modify the reaction of allylborane reagents to deliver simple alkyl groups rather than allyl moieties. Both approaches will be detailed separately.

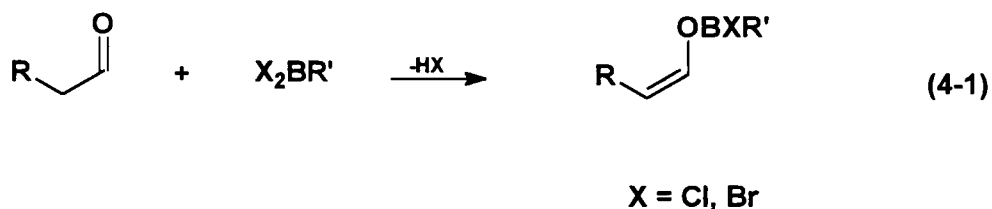
4.2 Polarization of the Organoborane Reagent

1-Boraadamantane (Section 1.5.7.4) is the only trialkylborane which adds in a

1,2-fashion to a carbonyl group. It does so according to the classical mechanism of complexation of the carbonyl oxygen by the metal followed by transfer of the alkyl group. As noted earlier, 1-boraadamantane readily forms isolable 1:1 addition complexes between the carbonyl oxygen and the adamantyl boron. Mild heating of these complexes causes an alkyl group to transfer. Ordinary trialkylboranes do not form addition complexes with carbonyl compounds as they are not sufficiently Lewis acidic. It was therefore reasoned that, if the Lewis acidity of the organoborane was increased, the amount of complexation between the organoborane and the carbonyl group would also increase and, with it, the likelihood of alkyl transfer.

4.2.1 Alkyldinitroborane

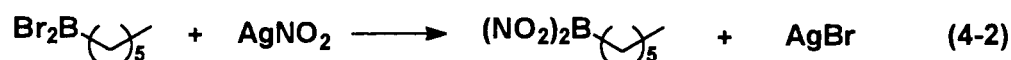
The most obvious choices for very Lewis acidic boranes are the dihaloboranes, dichloro- and dibromoborane. These, however, cannot be used since the halo groups are also good leaving groups and induce enolization of the carbonyl compound instead of delivering an alkyl group (eqn 4-1).



It was thought that a nitro group might increase the Lewis acidity of the

alkylborane but would not leave as readily as a halo group. A search of the literature indicated that simple nitroboranes had never been prepared.

Several attempts were made to form an alkydinitroborane. First, silver nitrite was added to dibromohexylborane in dichloromethane (eqn 4-2). The mixture was



reacted with an aldehyde such as benzaldehyde. Even though a yellow precipitate formed, which is attributable to AgBr, no alkylated product was detected. The reaction was repeated with sodium nitrite as the source of NO₂ to no avail.

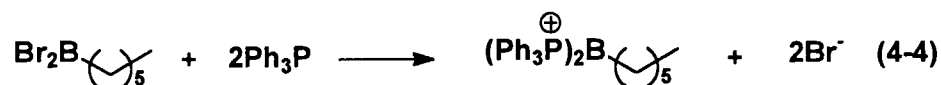
It was thought that two nitro groups on a single boron center might not be stable so an attempt was made to prepare a dialkylnitroborane. Dibutylboron triflate was treated with both silver nitrite and sodium nitrite but no alkylated product could be detected from a reaction with benzaldehyde (eqn 4-3).



4.2.2 Alkylbis(triphenylphosphine)borane

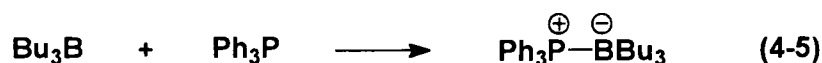
Triphenylphosphine was utilized in an attempt to increase the Lewis acidity of the organoborane. If an alkylbis(triphenylphosphine)borane could be formed, the

boron would be tremendously Lewis acidic. As with the dinitro studies, the triphenylphosphineborane was prepared from reaction with dibromohexylborane and triphenylphosphine (eqn 4-4). The mixture was reacted with benzaldehyde. No



product was detected. The reaction was repeated with dibutylboron triflate as the source of boron without success.

In a related reaction, triphenylphosphine was complexed with tributylborane and reacted with benzaldehyde (eqn 4-5). It was felt that the negatively charged



boron would be more likely to deliver an alkyl group (see Section 1.5.7.2). No alkylation product, however, was observed.

4.3 Six-Membered Transition State Approach

The reaction of allylboranes with carbonyl compounds (Section 1.5.6.1) has been well studied and is extensively used in the synthesis of new compounds. The reaction presumably proceeds via a six-membered chair-like transition state (Figure 4-

1). It was reasoned that replacement of key atoms in this reaction could enable an

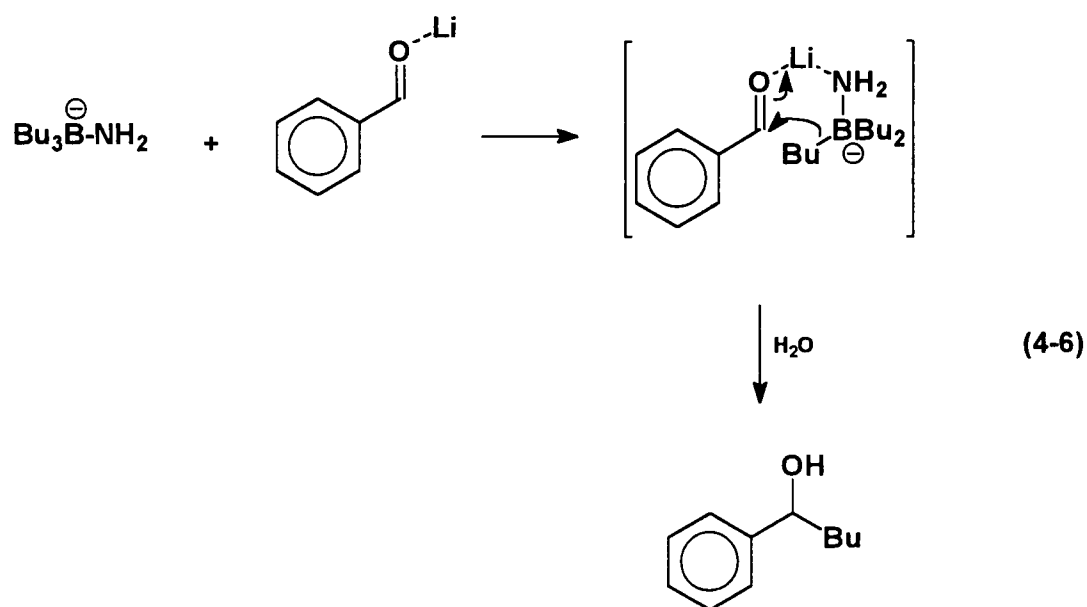


Figure 4-1. Six-Membered Transition States.

organoborane to deliver an alkyl group to a carbonyl (Figure 4-1). The boron could function as any of the three atoms marked X, Y, and Z.

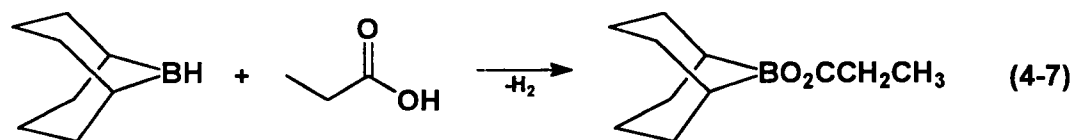
4.3.1 Amide Borate Complexes

The first experiment using this approach involved the reaction of tributylborane with sodium amide to form the amide borate complex. This intermediate was then treated with benzaldehyde which had been complexed with LiCl (eqn 4-6). It was postulated that the lithium cation would serve as a bridge to allow the borate complex to deliver an alkyl group. No alkylation product, however, was detected.

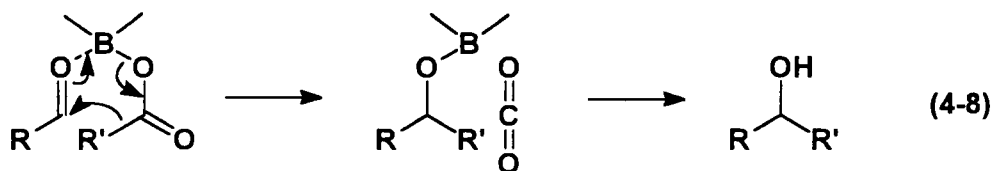


4.3.2 Acyloxyboranes¹⁵⁸

Another approach involved the use of acyloxyboranes which are readily prepared from 9-BBN and a carboxylic acid such as propionic acid (eqn 4-7). The compounds are especially attractive as they would simply release carbon dioxide



if they successfully alkylated carbonyl compounds (eqn 4-8).



Despite initial results which appeared encouraging, no alkylation product was detected.

The reaction was modified by utilizing dibromo- and dichloroborane instead of 9-BBN. The rationale for this change was that these more Lewis acidic boranes would complex more tightly with the carbonyls and allow the alkyl group to be delivered along with the expulsion of carbon dioxide. No alkylated product was detected.

4.3.3 Oxazaborolidine Chemistry¹⁵⁸

Another investigation involved an adaptation of Corey's oxazaborolidine catalyst system (Figure 4-2). These proline-derived catalysts have been used extensively to deliver hydrides to carbonyl groups stereospecifically ($R' = \text{H}$, $R'' = \text{methyl, phenyl, etc.}$)¹⁵⁹. It was thought that this system could also deliver an alkyl group. Treatment of benzaldehyde with an equivalent of the catalyst derived from proline, phenylboronic acid, and tributylborane ($R' = \text{butyl}$, $R'' = \text{phenyl}$) resulted in the production of no alkylated product. In fact, all that was isolated was the

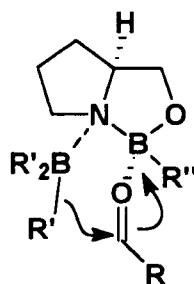


Figure 4-2. Corey's Oxazaborolidine Catalyst.

hemiaminal from prolinol and benzaldehyde (Figure 4-3).

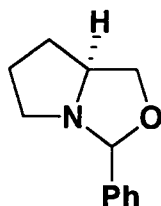


Figure 4-3. Hemiaminal from Benzaldehyde and Prolinol.

Corey has subsequently shown, however, that oxazaborolidine reagents will deliver alkynyl groups from alkynylboranes to carbonyl compounds (Section 1.5.6.3).

4.4 Future Research

There are several avenues along which future research could proceed. Further modification of the six-membered transition state approach may eventually prove fruitful. The lability of the R-Z bond (Figure 4-1) must be increased to allow delivery of the R group. If this could be accomplished, the approach could be successful.

New and unusual boranes such as that shown in Figure 4-4 could be synthesized in the hope that they would mimic 1-boraadamantane's complexing

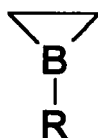
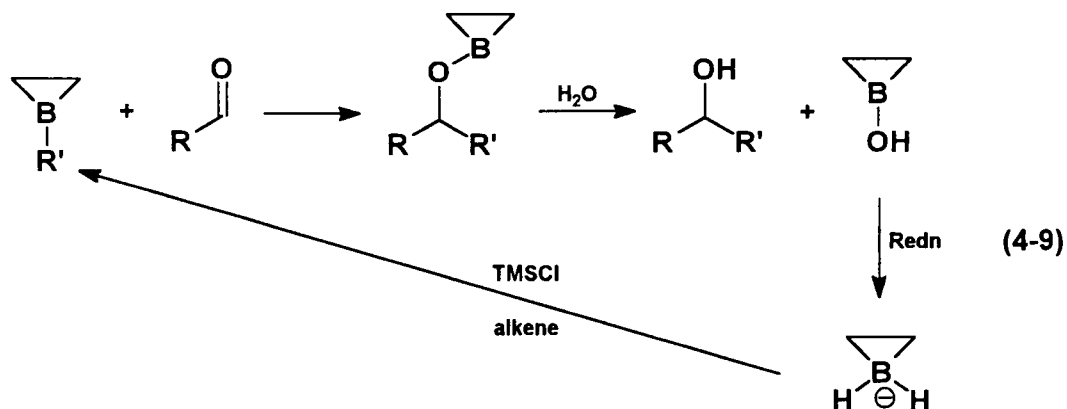


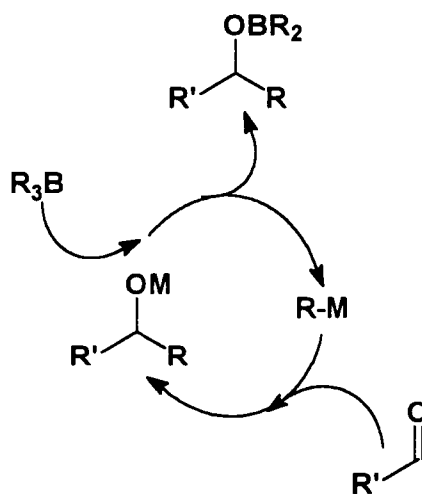
Figure 4-4. New and Unusual Borane.

ability. The boron atom in this borane should be very accessible as little steric hinderance is present. Also, the complexation of a carbonyl group would allow the boron to go from an sp^2 to an sp^3 geometry, which would relieve the I-strain in the ring. This would facilitate complexation and might enable delivery of an alkyl group. If this compound did deliver an alkyl group, the following chemistry should be possible (eqn 4-9).



Finally, a completely new paradigm for this reaction may be warranted. If a catalytic scheme such as that shown in Scheme 4-1 could be developed, it would

Scheme 4-1. Catalytic Approach.



achieve the goal of transferring an alkyl group from a boron to a carbonyl carbon.

Boron compounds readily undergo transmetalation reactions with atoms such as Zn and Mg so this scheme may be feasible.

4.5 Conclusion

This chapter contains a summary of several attempts to achieve the direct 1,2-addition of an organoborane to a carbonyl compound and the thinking that lay behind them. None of the approaches resulted in the transfer of an alkyl group from boron to carbon. Proposals for future research were also outlined.

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APPENDIX

Materials

Solvents

Chloroform, Mallinckrodt, used as received.

Chloroform-*d*, Aldrich Chemical, used as received.

Chloroform-*d* w/ 1 % TMS, Aldrich Chemical, used as received.

Diethyl ether, Mallinckrodt, distilled from sodium-benzophenone ketyl.

Ethanol, Quantum Chemical, used as received.

Ethyl acetate, Mallinckrodt, used as received.

Hexanes, Mallinckrodt, used as received.

Methanol, Mallinckrodt, used as received.

Methylene chloride, Mallinckrodt, used as received.

n-Pentane, Aldrich Chemical, used as received.

Tetrahydrofuran, Mallinckrodt, distilled from sodium-benzophenone ketyl.

Water (distilled), house supply.

Gases

Argon, MG Industries, passed through a column of Drierite and KOH.

Reagents

All reagents were purchased from indicated vendors and used without further purification unless otherwise indicated:

9-BBN, Aldrich Chemical.

Benzaldehyde, Eastman Kodak.

Borane-THF (1.0 M solution in THF), Aldrich Chemical.

2-Bromobenzaldehyde, Aldrich Chemical

3-Bromobenzaldehyde, Aldrich Chemical.

4-Bromobenzaldehyde, Aldrich Chemical.

1-Butene, Aldrich Chemical.

Butyllithium (1.6 M solution in hexanes), Aldrich Chemical.

tert-Butyllithium (1.7 M solution in pentane), Aldrich Chemical.

Catecholborane, Aldrich Chemical.

2-Chlorobenzaldehyde, Aldrich Chemical.

4-Chlorobenzaldehyde, Aldrich Chemical.

5-Chloro-1-pentene, Lancaster.

5-Cyano-1-pentene, Lancaster.

Cyclohexene, Aldrich Chemical, distilled from LAH.

1,8-Diazabicyclo[5.4.0]undec-7-ene, Aldrich Chemical, distilled from calcium hydride.

Dimethyl maleate, Aldrich Chemical.

Heptanal, Aldrich Chemical.

Hexamethylphosphoramide, Aldrich Chemical.

1-Hexene, Aldrich Chemical, distilled from LAH.

Hydrazine monohydrate, Aldrich Chemical.

Lithium aluminum hydride, Aldrich Chemical.

Lithium dimethylborohydride (0.5 M solution in hexanes), Aldrich Chemical.

Lithium hexamethyldisilazide (1.0 M solution in THF), Aldrich Chemical.

Magnesium sulfate (anhydrous), Mallinckrodt.

2-Methoxybenzaldehyde, Aldrich Chemical.

3-Methoxybenzaldehyde, Aldrich Chemical.

4-Methoxybenzaldehyde, Aldrich Chemical.

4-Methylbenzaldehyde, Aldrich Chemical.

2-Methylpentanal, Aldrich Chemical.

Methyl 10-undecenoate, Eastman Kodak, distilled from potassium carbonate.

3-Nitrobenzaldehyde, Aldrich Chemical.

4-Nitrobenzaldehyde, Aldrich Chemical.

1-Octene, Aldrich Chemical, distilled from LAH.

Peracetic acid (32 wt% solution in acetic acid), Aldrich Chemical.

Phosphorus pentoxide, Mallinckrodt.

Silica gel, 230-400 mesh, Baxter Scientific.

Sodium bicarbonate, Mallinckrodt.

Sodium chloride, Kroger.

Sodium hydroxide, Mallinckrodt.

Sodium perborate tetrahydrate, Fluka.

Sodium sulfate (anhydrous), Mallinckrodt.

Sodium thiosulfate, Mallinckrodt.

Tetrabutylammonium hydroxide (1.0 M solution in MeOH), Aldrich Chemical.

p-Toluenesulfonylhydrazide, Aldrich Chemical.

Tributylborane, Callery Chemical Corp., diluted in THF to make 1.0 M solution.

Tri-*sec*-butylborane (1.0 M solution in THF), Aldrich Chemical.

2,4,6-Triisopropylbenzenesulfonylchloride, Aldrich Chemical.

Trimethylamine N-oxide, Aldrich Chemical.

2,4,6-Trimethylbenzaldehyde, Aldrich Chemical.

Trimethylsilyl chloride, Lancaster.

VITA

John T. Maddox was born in Ashland, Kentucky on August 18, 1967. Upon graduating from West Carter High School in Olive Hill, Kentucky in May, 1985, he entered Morehead State University in Morehead, Kentucky, eventually graduating in May, 1990 with a Bachelor of Science degree (*magna cum laude*) in chemistry. He then entered graduate school at the University of Tennessee in Knoxville, Tennessee under the direction of Dr. George W. Kabalka. He has accepted a position as an Advanced Chemist in the Development and Control Group at Tennessee Eastman in Kingsport.

Chemical Genealogy



John Thorton Maddox
Ph. D. 1995 UT-Knoxville

