8-2000

Organoboranes in organic synthesis

Shane W. Kelley

To the Graduate Council:

I am submitting herewith a dissertation written by Shane W. Kelley entitled "Organoboranes in organic synthesis." I have examined the final electronic 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:

Clifton Woods, J. F. Feller

Accepted for the Council:

Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

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and recommend its acceptance:

Clifton Woods

Accepted for the Council:

Associate Vice Chancellor and
Dean of the Graduate School

ORGANOBORANES IN ORGANIC SYNTHESIS

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Shane Kelley

May 2000

DEDICATION

I dedicate this dissertation to Beth Ann, my princess, and to Jesus Christ, my Savior.

ACKNOWLEDGEMENTS

I would like to thank Dr. George Kabalka for his help, guidance and financial support. Everything he has done for me over the last five years has been appreciated. I also want to acknowledge my many labmates and friends who have made my graduate school experience an enjoyable one. They include Dr. Rama Malladi Reddy, Dr. Bhashkar Das, Dr. Kathy Bogas-Beauvais, Dr. Kathy Yang, Dr. Mike McGinnis, Dr. Bob Ober, Dr. Kevin Bennett, Christy Stine, George Pacer, Catherine Chidester, Ute Lipprandte and Nisha Natarajan. I especially wish to thank the following: our secretary, Ms. Pat McDaniel for helping keep things going; Dr. Max Hair for many serious and silly conversations and for just being Max; Dr. David Tejedor and Rob Singhaus for many, many memories on and off the golf course, Northeast Alabama will never be the same. This list would not and could not be complete without thanking my family, my church and my prayer partners Dan Knisley and Jeff Conrad. I could not have made it without their love and support

ABSTRACT

Aryl ketonetrisylhydrazones were found to react with trialkylboranes, in the presence of base, to generate the corresponding aromatic alkanes in good to excellent yields. Alkyl aldehydetrisylhydrazones also participate under the same reaction conditions to produce aliphatic alcohols in good yields upon oxidation. The effects of the solvent and the aromatic leaving group were also examined.

The Suzuki coupling of acid chlorides with trialkylboranes were also evaluated. Both aromatic and aliphatic acid chlorides were alkylated to generate the analogous ketone in good yields.

The synthesis of a boronated 1,5-diarylpyrrazole was attempted. Evidence suggests the desired product was produced.

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LIST OF ABBREVIATIONS AND SYMBOLS

Ar	Aryl
BBB	Blood Brain Barrier
BNCT	Boron Neutron Capture Therepy
BPA	*p*-Boronophenylalanine
BSH	Sodium Mercaptoundecahydrododecaborate
Bu	Butyl
^0C	Degree Celcius
$CDCL_3$	Chloroform-*d*
COX	Cyclooxygenase
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
Δ	Heat
d	Doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCME	Dichloromethyl Methyl Ether
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic Acid
ee	Enantiomeric Excess
Et	Ethyl
Hz	Hertz
J	Proton-Proton Coupling Constant
m	Multiplet
Me	Methyl
MeOH	Methanol

MeV	Mega Electron Volt
NCT	Neutron Capture Therepy
NMR	Nuclear Magnetic Resonance
NSAID	Non-steroidal Anti-inflammatory Drug
Nu	Nucleophile
[O]	Oxidation
PDT	Photodynamic Therepy
Ph	Phenyl
q	Quartet
R,R'	Alkyl or Aryl
s	Singlet
sec	Secondary
Sept	Septet
Sext	Sextet
t	Tertiary
t	Triplet
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane

MATERIALS

All materials were purchased from the indicated vendor and used without further purification unless otherwise stated.

Solvents

Acetone-d_6, Aldrich

Benzene, Aldrich

Chloroform-*d*, Aldrich

Diethyl Ether, Fisher, Distilled from sodium-benzophenone ketyl

Dimethylsulfoxide-d_6, Aldrich

Ethanol, AAPER

Ethyl Acetate, Fisher

Hexanes, Fisher

Methanol, Fisher, Distilled

Methylene Chloride, Fisher, Distilled from calcium hydride

Pentane, Acros

Tetrahydrofuran, fisher, Distilled from sodium-benzophenone ketyl

Water, House supply, Distilled

Gases

Nitrogen, National Welders

Reagents

Acetanilide, Aldrich

Acetophenone, Aldrich

Benzaldehyde, Aldrich, Distilled

Benzoyl Chloride, Aldrich

Benzophenone, Aldrich

Boron Trichloride (1.0 M in hexanes), Aldrich

2-Bromoacetophenone, Aldrich

3-Bromoacetophenone, Aldrich

4-Bromoacetophenone, Aldrich

Cyclohexylcarboxaldehyde, Aldrich

Cyclopropane Carboxylic acid Chloride, Aldrich

DBU, Aldrich, Distilled

cis-4-Decenal, Aldrich

1-Decene, Aldrich

Decanoic Acid, Aldrich

Diboron Pinacol Ester, Fronteir

2,5-Dichlorobenzenesulfonylhydrazide, Aldrich

2,6-Dimethyl-5-heptenal, Aldrich

2,2-Dimethylhexanal, Aldrich

Ethylene Glycol, Aldrich

4-Fluorobenzenesulfonylhydrazide, Aldrich

Heptaldehyde, Flucka

Isobutoyl Chloride, Aldrich

Isovaleroyl Chloride, Aldrich

Magnesium, Aldrich

2-Methoxyacetophenone, Aldrich

3-Methoxyacetophenone, Aldrich

4-Methoxyacetophenone, Aldrich

4-Methoxybenzenesulsonylhydrazide, Aldrich

4-Methylacetophenone, Aldrich

2-Methylpenatanal, Flucka

Methyl-*tert*-butyl Ether, Aldrich

Methyl Trifluoroacetate, Aldrich

2-Naphthylsulfonylhydrazide, Aldrich

2-Nitroacetophenone, Aldrich

3-Nitroacetophenone, Aldrich

4-Nitroacetophenone, Aldrich

4-Nitrobenzenesulfonylhydrazide, Aldrich

2,3,4,5,6-Pentafluorobenzenesulfonylhydrazide, Aldrich

Potassium Acetate, Aldrich

Propiophenone, Aldrich

Sodium Methoxide (25 wt.% inMeOH), Aldrich

Sodium Nitrite, Fisher

Sodium Perborate, Aldrich

Tetrakis(triphenyphosphine)palladium (0), Aldrich

TetramethylAmmonium Hydroxide (1.0 M in MeOH), Aldrich

Tin (II) Chlodire, Aldrich

p-Toluenesulfonic Acid, Aldrich

Tosyl Chloride, Aldrich

Tributylborane (1.0 M in THF), Aldrich

Trimethylborate, Aldrich

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

Trisyl Chloride, Aldrich

10-Undecenoyl Chloride, Aldrich

PART I

CARBON-CARBON BOND FORMING REACTIONS

CHAPTER 1

CARBON-CARBON BOND FORMING REACTIONS

1.A Introduction

The formation of carbon-carbon bonds is a fundamental goal of synthetic organic chemistry and organoboranes play an important role in attaining this goal. In Part I (Chapters 2 and 3) of this dissertation, the development of two methods that utilize trialkylboranes in the formation of new carbon-carbon bonds are described.

1.B Carbon-Carbon Bond Formation via Organoboranes: An Overview

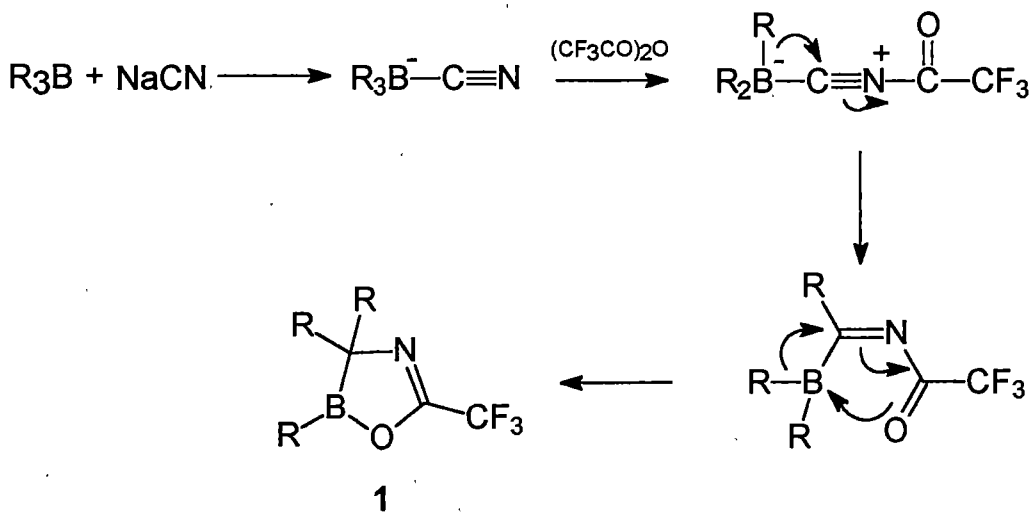
Boron containing molecules are extremely versatile. They are commonly used in products such as fuels and fuel additives, corrosion inhibitors, and herbicides.[1] Boron hydrides are excellent reagents for stereo-directed reductions of alkenes, alkynes and carbonyl compounds.[2] Boron compounds are also useful in asymmetric syntheses both as catalysts and intermediates.[3] Although these transformations are important, only the formation of carbon-carbon bonds will be discussed here. The remainder of this chapter is focused on a brief overview of reactions using organoboranes to form carbon-carbon

bonds.

1.B.1 Cyanoborate Process

Cyanotrialkylborate salts are formed when trialkylboranes and metal cyanides are allowed to react. These salts are stable and can be isolated. If the salts are exposed to electrophilic compounds, such as trifluoroacetic anhydride, the alkyl groups transfer from the boron to the neighboring carbon (Scheme 1-1).[4] At mild temperatures and using an equimolar concentration of the anhydride, **1** will form which will yield a ketone upon oxidation.[5] A tertiary alcohol is obtained, by migration of all three alkyl groups when excess anhydride and elevated temperatures are used.[6]

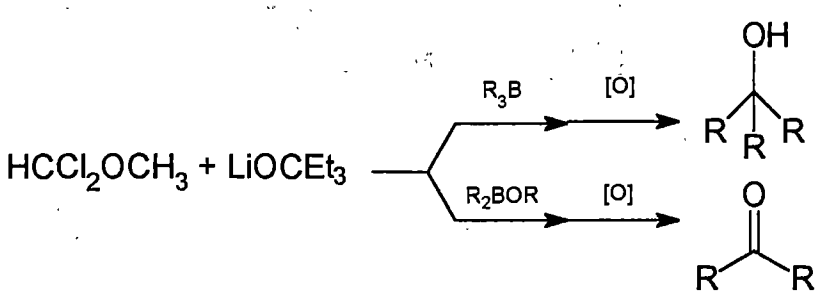
Scheme 1-1. The Cyanoborate Process.



1.B.2 DCME Reaction

Tertiary alcohols and ketones are produced in this method. A proton is first removed from the dichloromethyl methyl ether (DCME), through the use of a strong base, forming an anion that attacks either a trialkylborane or a dialkylborinic ester (Scheme 1-2). After migration of either two or three alkyl groups, the alcohol[7] or the ketone[8] is produced upon oxidation.

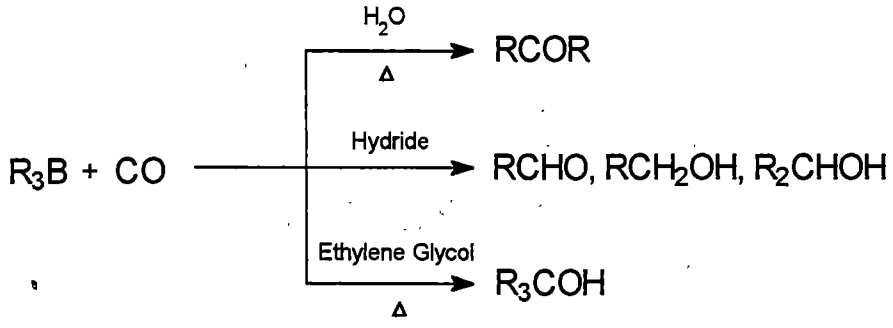
Scheme 1-2. The DCME Reaction.



1.B.3 Carbonylation

Another route to alcohols, as well as aldehydes and ketones, involves the reaction of trialkylboranes with carbon monoxide (Scheme 1-3). By varying the reaction conditions, the desired product can be obtained. For example, in the presence of boron hydrides, the carbonylation reaction proceeds at room temperature and yields an aldehyde upon oxidation.[9] However, if the intermediate is treated with lithium aluminum hydride[10] or acid[11] the alcohol product is obtained.

Scheme 1-3. Reaction of Trialkylboranes and Carbon Monoxide.



In the absence of hydride the reaction is sluggish and requires elevated temperatures in order to achieve an acceptable rate. A temperature of 100 °C is required at atmospheric pressure. Ketones are produced, in the presence of water under these conditions.[12] Tertiary alcohols can be formed when ethylene glycol is used instead of water and temperatures greater than 100 °C are utilized.[13]

1.B.4 Coupling of Trialkylboranes

The alkyl groups on a trialkylborane will couple with each other when a trialkylborane is exposed to aqueous silver nitrate and base (1-1).[22] Yields are good and many functional groups tolerate the reaction conditions

$$R_3B + R'_3B \xrightarrow[\text{Base}]{AgNO_3} R{-}R' \qquad (1\text{-}1)$$

There are several disadvantages to this type of reaction. First, coupling is statistical. This means, if equal amounts of both boranes are used, there will be a 1:1:2 ratio of the R-R, R'-R' and R-R' coupled products. This problem can be minimized if a large excess of one of the trialkylboranes is used. Second, molar masses of the R and R' groups must vary significantly so that the non-symmetric product can be separated from the symmetric products.

1.B.5 Reactions with Diazo Compounds

This alkylation procedure provides an excellent method for adding functionality to molecules. The reaction conditions are extremely mild and yields are high. Only one alkyl group will transfer (1-2) limiting unwanted side

$$R_3B + N_2CHX \rightarrow RCH_2X + N_2 \qquad (1\text{-}2)$$

reactions. The functional groups that are tolerated in this reaction include aldehydes[14], ketones[15], esters[16], and nitriles[16].

When the alkyl group transfers, nitrogen is evolved and rearrangement occurs to form a boron enolate (Scheme 1-4, **2**).[17] This enolate can then be hydrolyzed to generate the desired product. The formation of α-deuterio-[18] and α-haloketones[19] are possible when **2** is treated with D_2O and N-halosuccinimides respectively.

Mixed alkylboranes can not be used because they result in product

Scheme 1-4. Boron Enolate Formation.

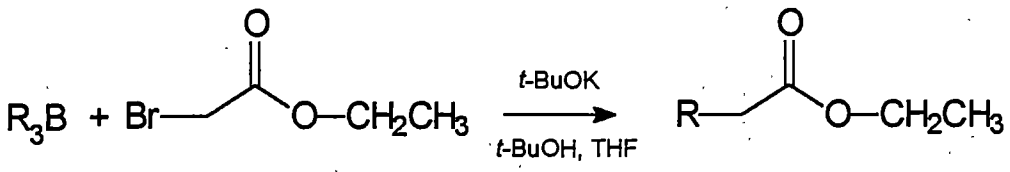
$$R_3B + N_2CHCHO \rightarrow [R_2BCHRCHO] \rightarrow \underset{\mathbf{2}}{R_2BOCH{=}CHR} \rightarrow \text{Products}$$

mixtures.[20] Mono and dichloroboranes can be used in the reaction and both give good yields of the desired products.[21]

1.B.6 α-Alkylation and Arylation

This reaction is similar to the diazo reaction discussed in the last section. α-Haloesters, ketones and nitriles are utilized along with a suitable base and a trialkylborane (Scheme 1-5).[23] In this method only one alkyl group transfers, replacing the halogen. Undesirable side reactions do not occur. Reaction temperatures are fairly mild and yields are good to excellent. A large variety of alkyl groups can be transferred and dialkylation can be accomplished if the α,α-dihalo species is utilized.[24]

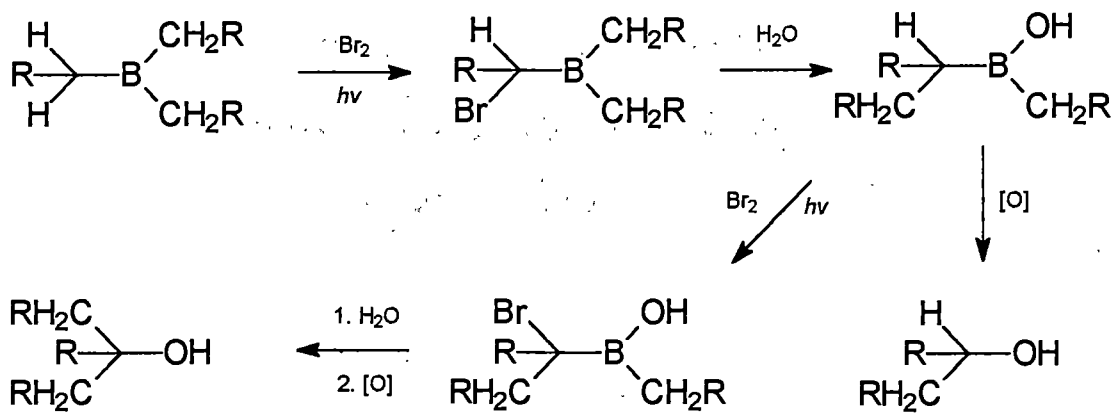
Scheme 1-5. α-Alkylation and Arylation.



1.B.7 α-Bromination Reaction

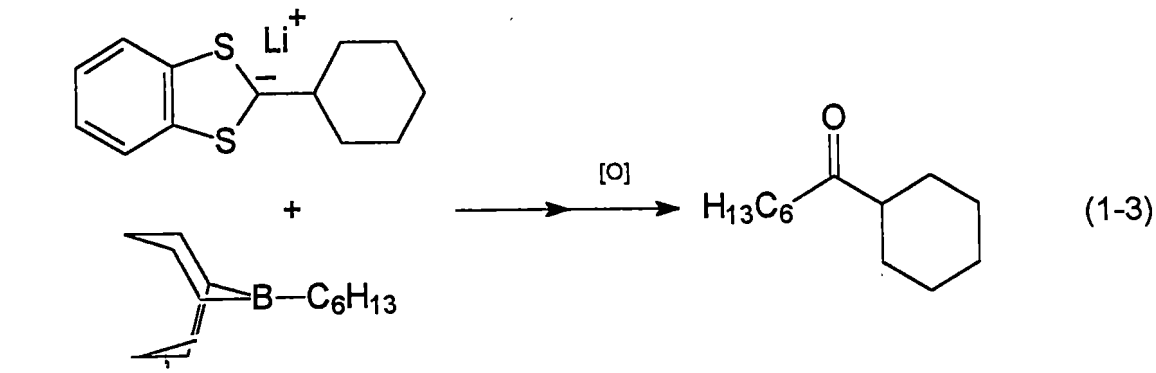
Highly substituted secondary and tertiary alcohols can be prepared using this method. The reaction is light induced and can be conducted using either trialkyboranes[25] or dialkylborinic acids.[26] If equimolar quantities of Br_2 are used, in the presence of water, only one alkyl group will transfer. A second equivalent of Br_2 is required for the second group to migrate (Scheme 1-6).

Scheme 1-6. Highly Substituted Alcohols via α-Bromination Reaction.

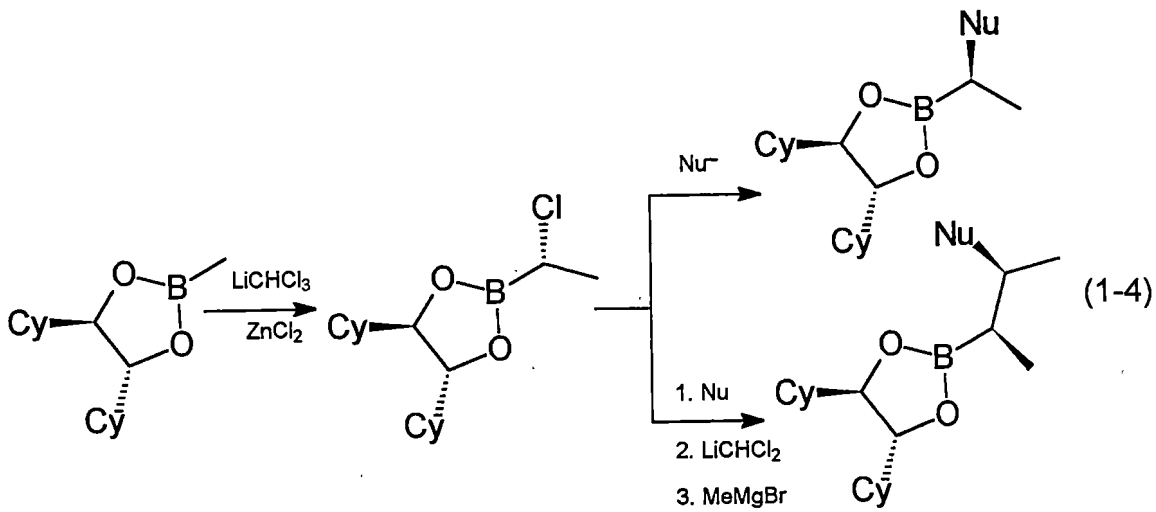


1.B.8 Acyl Carbanion Equivalent Reactions

There are several acyl equivalent anions that have been used to react with organoboranes to form carbon-carbon bonds. The most common anions are generated from the thioketals[27] (1-3) and dichloromethane[28] (1-4).



(1-3)

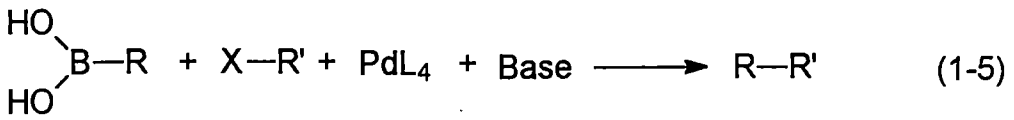


(1-4)

1.B.9 Suzuki Coupling

Suzuki coupling is an extremely useful reaction that utilizes a palladium catalyst and a base to couple an organic group from an organoboron with the organic portion of a halogenated molecule(1-5).[29] The boron compounds most often used are boronic acids, however, trialkylboranes are sometimes utilized.

The choice of the halogen is very important. Organic fluorides are unreactive and chlorides generate little product whereas iodides and bromides give the best results. Although not a halogen, the trifluorosulfonate group



(1-5)

(triflate, CF_3SO_3) works well but is more sensitive to the reaction conditions. The reactivity of the organic halide is also critical. Aryl halides readily react as do alkyne, alkene and allylic derivatives.[30] Alkyl halides react sluggishly.[31]

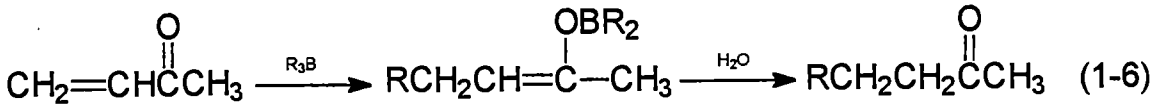
There are many bases that can be used, the only requirement is that they be ionic in nature. Acetates, carbonates and phosphates tend to give the highest yields. There are numerous catalysts to choose from, but palladium complexed with triphenylphosphine, acetate and chloride ligands are the most popular.

Suzuki reactions are usually run at the reflux temperature of the solvent of choice, however it was recently reported that solvent is not necessary.[32] The type of products obtained and a new category of Suzuki coupling will be discussed in Chapter 3.

1.B.10 1,4-Addition Reactions

Saturated organoboranes generally do not add to carbonyl groups, however they do readily participate in 1,4-additions to α,β-unsaturated systems (1-6).[33] The reaction conditons are mild and the reaction yields are excellent. This reaction was originally believed to proceed via a polar mechanism but experiments using free radical inhibitors proved otherwise.[34] The free radical

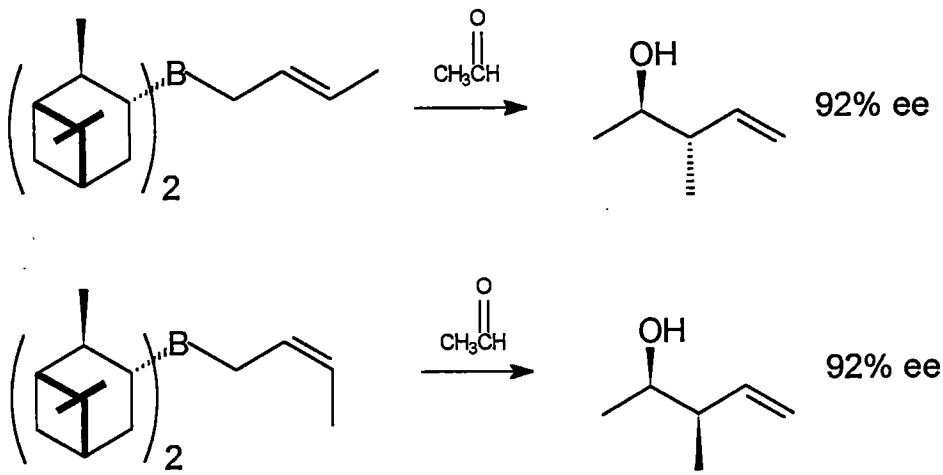
nature of the reaction was further confirmed when it was learned that initiators like oxygen allowed previously unreactive species to undergo addition.[35]



(1-6)

1.B.11 Allyl, Vinyl and Acetylboration

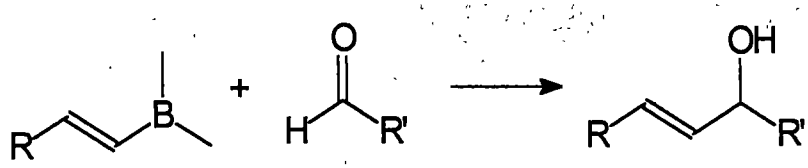
Although saturated organoboranes do not add to carbonyl compounds, their unsaturated counterparts successfully participate in 1,2-addition reactions. The reaction of allylboranes with a variety of aldehydes and ketones proceed in good yields and with high stereoselectivity (1-7).[36] Chiral alkyl groups on



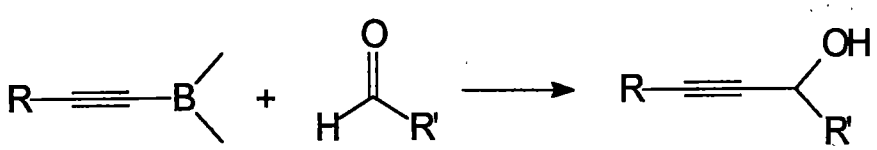
(1-7)

boron can be utilized to achieve a high degree of enantioselectivity while the double bond geometry accounts for the diasterioselectivity of these molecules.[37]

Vinyl groups can also add to a carbonyl group in a 1,2 fashion to yield α,β-unsaturated alcohols (1-8). The stereochemistry of the double bond can be manipulated by varying the conditions used.[38] Acetylboranes will also readily add to carbonyl compounds (1-9).[39]



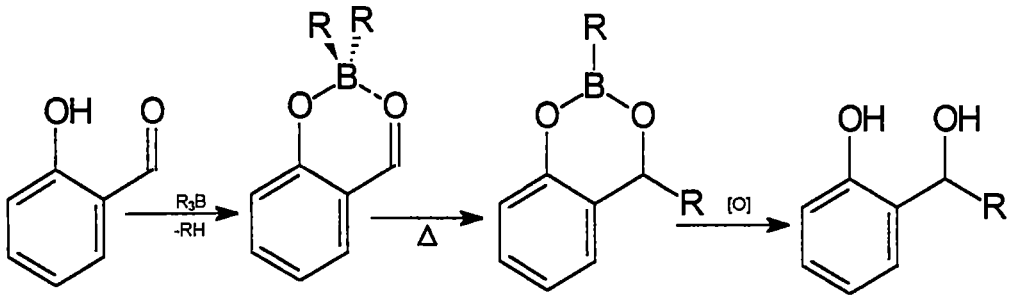
(1-8)



(1-9)

1.B.12 Alkylation of 2-Hydroxyarylaldehydes

As stated earlier, saturated trialkylboranes do not generally add to the carbonyl groups in organic compounds. However, addition will take place under certain conditions. One such case involves the reaction of trialkylboranes with 2-hydroxyaromatic aldehydes (1-10).[40] The reaction is general for a wide variety of boranes as well as hydroxy aryl aldehydes. The reaction does not proceed with 2-hydroxyaryl ketones or 2-alkoxyaryl aldehydes.



(1-10)

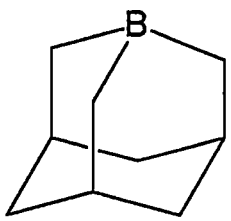
1.B.13 1-Boraadamantane

The caged structure of 1-boraadamantane (Figure 1-1) causes the boron to exhibit a non-planar geometry which contrasts to the planar geometry found normal trialkylboranes.[41] This unique structure allows 1-boraadamantane to react with carbonyl compounds. However, the usefulness of this method is minimal. No alkyl group other than those present in the adamantane migrate under the conditions used.

1.B.14 Lithium Tetraalkylborate Addition to Acid Chlorides

Lithium tetraalkylborates react with acid chlorides to produce ketones in

Figure 1-1. 1-Boraadamantane.



high yields (1-11).[42] Both aromatic and aliphatic acid chlorides participate in this reaction but primary alkyl groups transfer preferentially.

$$LiBRR'_3 + ClOCR'' \rightarrow RCOR'' + R'_3B \qquad (1\text{-}11)$$

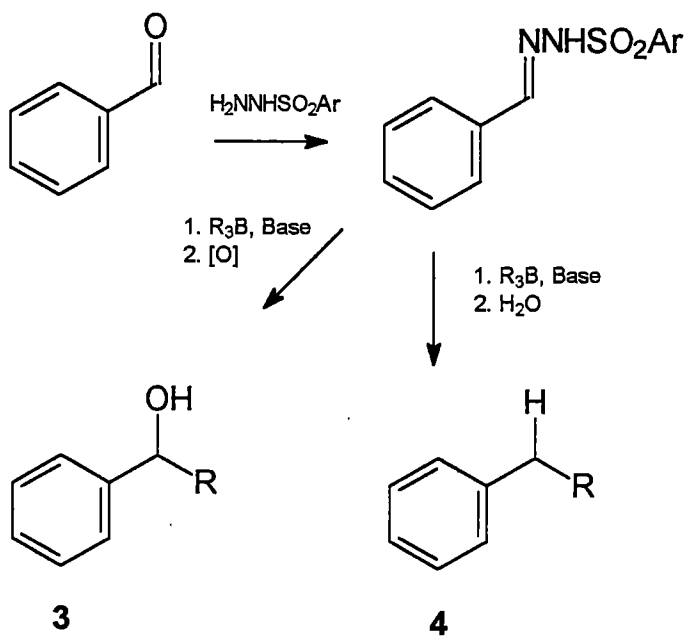
The tetraorganoborate is easily prepared from the corresponding trialkylborane and alkyllithium species. The trialkylborane produced in the reaction can be quantitatively recovered and reused. This suggests that the organolithium compound is responsible for the alkylation. However, alkyl groups from the original boron reagent participate in the reaction along with the alkyl group from the organolithium reagent. In addition, it is known that alkyllithium species yield alcohols when allowed to react with acid chlorides.

1.B.15 Alkylation of Aromatic Aldehyde Arylsulfonylhydrazones

Aromatic aldehydes can easily be converted to arylsulfonylhydrazones. These hydrazones can then react further with trialkylboranes, in the presence of base, to form the alkylated alcohol **3** or aryl alkane **4** (Scheme 1-7).[43] The formation of **3** is equivalent to a 1,2-addition of a borane to a carbonyl group. This reaction is general for all aromatic aldehydes and product yields are good to excellent. The reaction is usually carried out at reflux in THF and a wide variety of functional groups tolerate the reaction conditions (Table 1-1).

The choice of base is dependant on the product desired.

Scheme 1-7. Alkylation of Aromatic Aldehyde Arylsulfonylhydrazone via Trialkylborane.



3 **4**

Table 1-1. Functional Groups Transferred in the Synthesis of Alcohol **3**.

R	% Yield
$-CH_2(CH_2)_3CH_2Cl$	76
$-CH_2(CH_2)_3CH_2CN$	72
$-CH_2(CH_2)_9CO_2CH_3$	75
Cyclohexyl	68
$-CH_2(CH_2)_4CH_3$	51

Non-nucleophilic bases are required if the alcohol **3** is desired. However, a nucleophilic base is more effective if the alkane **4** is the target compound.

This reaction will be discussed in greater detail in the next chapter.

1.C Statement of Purpose

This reaction will be discussed in greater detail in the next chapter.

The present discussion has focused on carbon-carbon bond forming reactions using organoboron compounds. It is always important to synthetic organic chemists to expand or develop new technologies involving the formation of carbon-carbon bonds. The remaining two chapters in Part I contain a description of the author's contributions to these important areas of research.

Chapter 2 is focused on a study of the reaction of carbonyl arylsulfonylhydrazones with organoboranes (section 1.B.14). The discussion includes studies of the reaction conditions and the expansion of the methodology to aromatic ketones and aliphatic aldehydes. A brief review of previous results will also be presented.

Chapter 3 contains a description of the application of Suzuki coupling methodology to acid chlorides. The chapter also contains a review of other metal-mediated couplings of acid chlorides.

CHAPTER 2

ALKYLATION OF CARBONYL ARYLSULFONYLHYDRAZONES VIA TRIALKYLBORANES

2.A Introduction

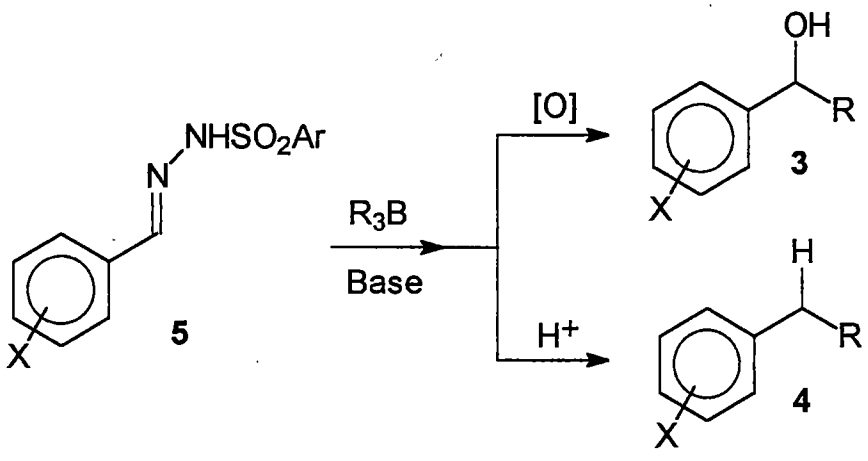
Hydrazones and sulfonylhydrazones are important intermediates in synthetic organic chemistry. They are commonly used to convert aldehydes and ketones into olefins (Bamford-Stevens and Shapiro reactions)[44], alkanes (Wolff-Kishner reaction)[45], indoles (Fischer indole synthesis)[46] and diazo compounds.

Chapter 1 contained a description of the important role boron plays in the chemistry of carbon-carbon bond formation. The discussion included a synopsis of a newly developed method that utilizes arylsulfonylhydrazones and trialkylboranes (section *1.B.14*). The discussion in Chapter 2 addresses the extent to which this methodology can be applied to solving synthetic problems and contains a brief review of previous findings.

2.B Prior Results[43]

As noted in Chapter 1, aromatic aldehydes are easily converted to the corresponding arenesulfonylhydrazones (**5**). These hydrazones can then react

with trialkylboranes, in the presence of an appropriate base, to form either an alcohol (**3**) or an alkane (**4**) (2-1). Two series of arenesulfonylhydrazones have been examined prior to the current study. They were substituted benzaldehyde derivatives of 4-methylbenzenesulfonyl- (tosyl, **5a**) and 2,4,6-triisopropylbenzenesulfonyl- (trisyl, **5b**) hydrazones (Figure 2-1). Tables 2-1 and 2-2 contains a summery of the results obtained. Both the tosyl- and the



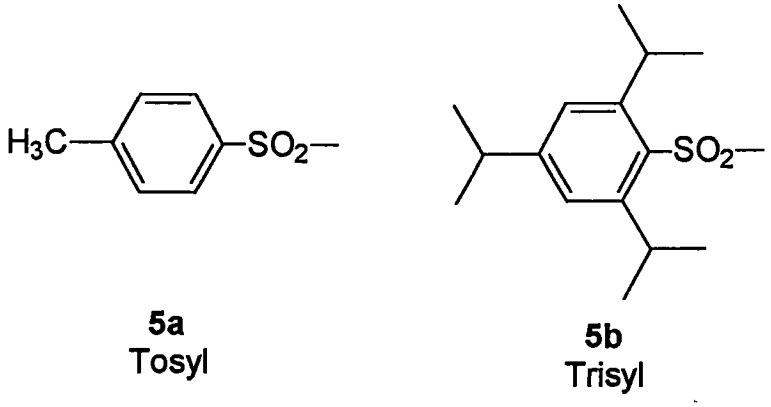


Figure 2-1. Structure of the Tosyl and Trisyl Groups.

Table 2-1. Product Yields of **3** and **4** From Tosylhydrazone **5a**.

Entry	X	Yield of **5a**	Yield of **3**	Yield of **4**
1	3-Nitro	79	91	NA
2	4-Nitro	81	98	NA
3	2-Bromo	84	92	80
4	3-Bromo	72	89	78
5	4-Bromo	80	94	80
6	H	72	80	73
7	2-Methoxy	85	93	86
8	3-Methoxy	69	89	76
9	4-Methoxy	89	83	71
10	2,4,6-Trimethyl	85	NA	90
11	4-Methyl	74	90	83

Table2-2. Product Yields of **3** and **4** From Trisylhydrazone **5b**.

Entry	X	Yield of **5b**	Yield of **3**	Yield of **4**
1	3-Nitro	80	96	NA
2	4-Nitro	74	95	NA
3	2-Bromo	54	92	0
4	3-Bromo	54	96	83
5	4-Bromo	68	93	86
6	H	87	93	90
7	2-Methoxy	54	NA	88
8	3-Methoxy	62	NA	76
9	4-Methoxy	62	68	80
10	2,4,6-Trimethyl	29	NA	91
11	4-Methyl	61	88	87

trisylhydrazones gave good to excellent yields of both the alcohols (**3**) and the alkanes (**4**).

The choice of base is dependent on the product desired. If alcohol **3** is the preferred product, a non-nucleophilic base is required. However, the opposite is true for the alkane product **4**. Table 2-3 contains the results of a base study conducted for the synthesis of 1-phenylpentane. Hydroxide was found to be the most efficient nucleophilic base for this transformation. Whereas DBU (Figure 2-2) was found to be the most effective non-nucleophilic base in a different study.

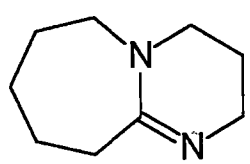


Figure 2-2. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Table 2-3. Base Study Results for the Synthesis of 1-Phenylpentane.

Base	% Yield of 1-Phenylpentane
Diethylamine	8
DBU	21
NaOH	91
Bu_4NOH	86
Lutidine	0

Trialkylboranes appear to be the only boranes that can be utilized in this methodology. When borane derivatives such as hexyldibromoborane and hexylcatecholborane (Figure 2-3) were used, no appreciable quantity of product was obtained.

Two mechanistic pathways have been proposed for this reaction. Both involve an initial proton abstraction from the starting hydrazone to form anion **6** (Scheme 2-1). The mechanisms differ only in the timing of the loss of the tosyl moiety.

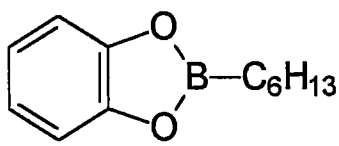
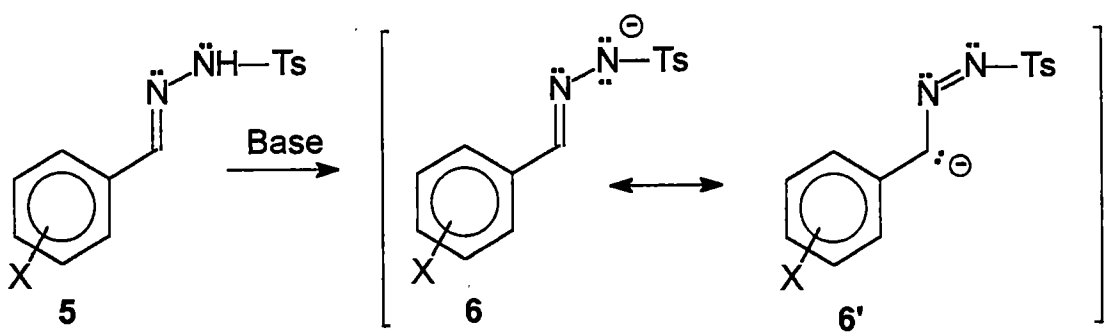


Figure 2-3. Hexylcatecholborane.

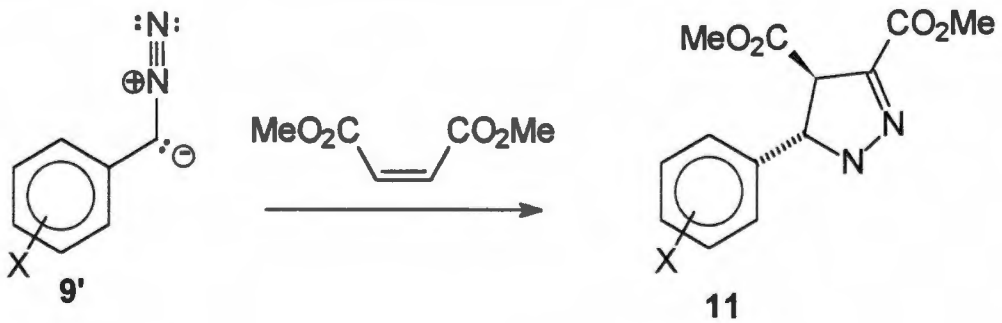
Scheme 2-1. Initial Mechanistic Step.



Pathway 1 (Scheme 2-2) is thought to involve an anionic route in which intermediate **6'** reacts with the trialkylborane creating the electron-rich organoborate **7**. An alkyl group transfers from the boron atom as nitrogen and the tosyl group leave in a concerted fashion forming a new trialkylborane **8**.

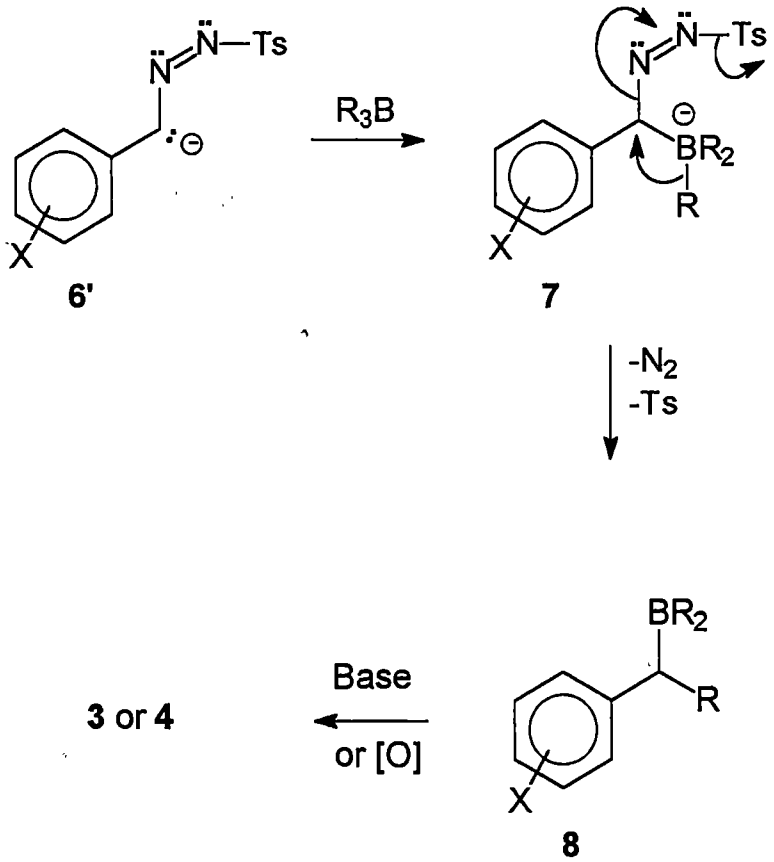
Pathway 2 (Scheme 2-3) is thought to involve the loss of the tosyl group to form diazo intermediate **9**. The trialkylborane then reacts with **9'** creating the new organoborate complex **10**. Compound **8** is then produced after alkyl transfer and nitrogen extraction.

Several attempts have been made to ascertain which pathway is the correct one. The most interesting experiment involved the use of dimethyl maleate in an effort to trap diazo **9'** (2-2).[48] When the experiment was attempted, no pyrrazole product **11** was detected. It is not clear if this was due to the lack of a diazo intermediate or if the loss of nitrogen was faster than the capture reaction. Therefore no firm conclusions can be made at this time. There are several other reaction parameters that remain unexplored. The remainder of this chapter will address these.

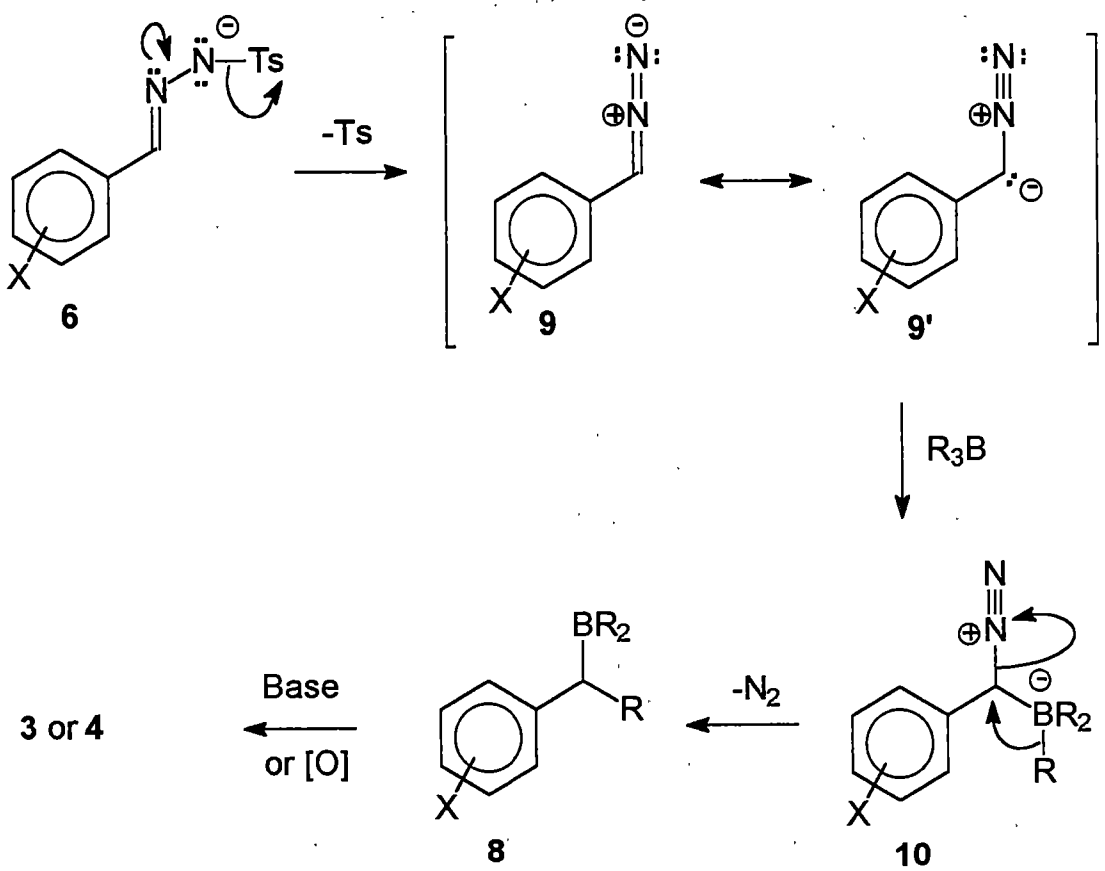


9' **11** (2-2)

Scheme 2-2. Pathway 1: The Anion Route.



Scheme2-3. Pathway 2: The Diazo Route.

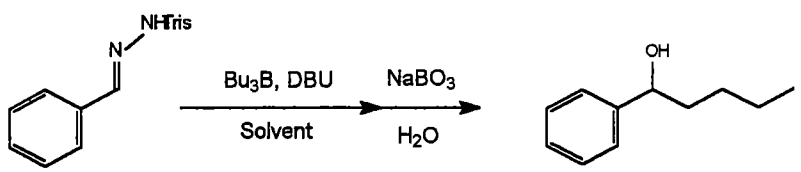


2.C Current Results

2.C.1 Solvent Study

The first parameter studied concerned the role of the solvent. Since the proposed mechanistic pathways both involve anion **6,** it was assumed that a polar, non-protic solvent would be the most effective. Several solvents were investigated using the synthesis of 1-phenyl-1-pentanol as the model reaction (Table 2-4). As expected the polar, non-protic ethers were the most effective. Polar, protic solvents, such as methanol, resulted in good yields of the alkane products but none of the desired alcohol. This is due to the ability of the solvent to act as a Lewis base, attacking trialkylborane **8**, and thus producing the protonalized product **4** instead.

Table 2-4. Solvent Efficiency in the Synthesis of 1-Phenyl-1-pentanol.



Entry	Solvent	% Yield
1	Ether	81
2	Dichloromethane	0
3	Pentane	12
4	THF	90
5	Methanol	79[a]

a) Alkane product only, no alcohol product found.

2.C.2 Leaving Group Study

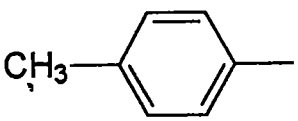
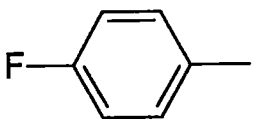
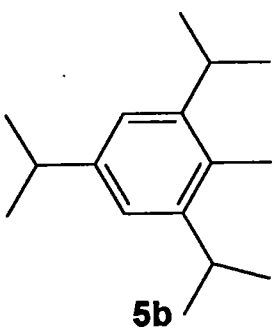
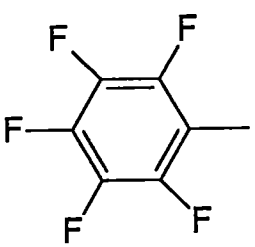
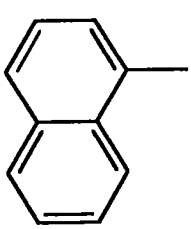
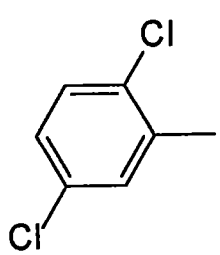
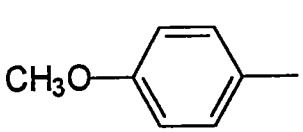
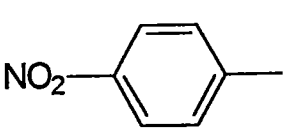
Earlier studies took advantage of the well known chemical behavior of the tosyl- and trisyhydrazones.[49] It was important to ascertain what effect changing the aromatic leaving group would have on the product yields. A variety of benzaldehyde arenesulfonylhydrazones were synthesized and the results summarized in Table 2-5. The hydrazones were prepared by stirring a methanolic solution of benzaldehyde with the desired arenesulfonylhydrazide. Unlike the tosyl (**5a**) and trisyl (**5b**) species, which precipitated out of solution and could be used without further purification, the hydrazones in Table 2-5 required at least one recrystallization from hot methanol. Hydrazone **5f** could not be isolated.

All of the hydrazones were subjected to the alkylation protocol and they produced varying yields of 1-phenylpentane. Compound **5f** was synthesized *in situ* but generated none of the desired product. Table 2-6 contains the results of the investigation.

There are several items in Table 2-6 that merit discussion. First, **5b**, **5d** and **5h** all produced excellent product yields. The effectiveness of **5b** can be attributed to the steric bulk of the leaving group, whereas **5d** and **5h** rely on electronic (resonance) factors. It is interesting that the electron-donating methoxy and the electron-withdrawing nitro compounds gave statistically equivalent results.

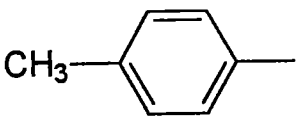
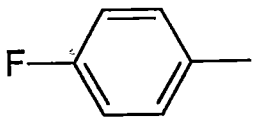
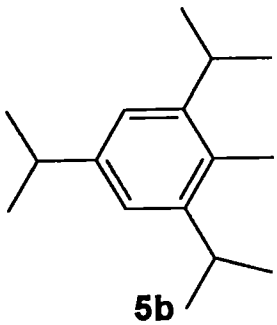
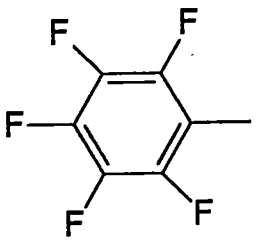
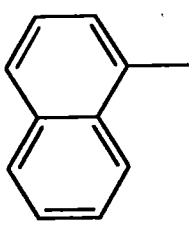
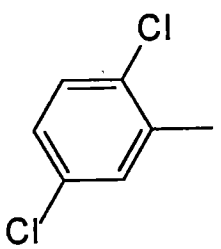
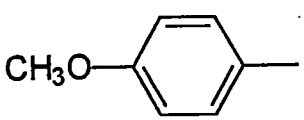
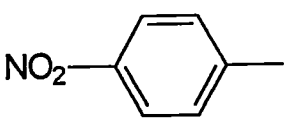
Second, the stability of the hydrazones was extremely sensitive to the

Table 2-5. Synthesis of Benzaldehyde Arenesulfonylhydrazone **5**.

Entry	Ar	Yield of **5**[a]	Entry	Ar	Yield of **5**[a]
1	 **5a**	72	5	 **5e**	76
2	 **5b**	87	6	 **5f**	0
3	 **5c**	87	7	 **5g**	89
4	 **5d**	76	8	 **5h**	68

a) Isolated yields.

Table 2-6. Synthesis of 1-Phenylpentane from **5**.

Entry	Ar	Yield[a]	Entry	Ar	Yield[a]
1	 **5a**	83	5	 **5e**	80
2	 **5b**	93	6	 **5f**	0
3	 **5c**	9	7	 **5g**	52[b]
4	 **5d**	92	8	 **5h**	90

a) Isolated Yields
b) NMR Yield

number of halogen atoms attached to the aromatic ring. As the number increases, the stability decreases (**5e**>**5g**>**5f**).

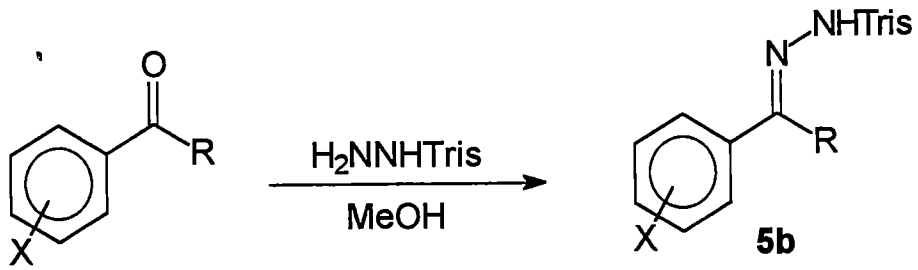
This characteristic may shed some light on the mechanism question. It would appear that increasing the number of electron-withdrawing groups on the aromatic ring promotes the expulsion the arylsulfinate anion, thus generating the diazo species. Since the product yields diminish in proportion to the increase in electron-withdrawing groups, it would appear that the anion pathway (Scheme 2-2) is the more likely mechanistic route.

Due to the fact that the trisylhydrazone (**5b**) derivatives led to the highest product yields and were the most accommodating compounds to prepare, it was decided to utilize them for the remaining studies.

2.C.3 Aromatic Ketone Trisylhydrazones

The study then progressed to the application of the technology to aromatic ketones. Table 2-7 contains the results of this investigation. As expected, product yields were lower than those of the aryl aldehyde counterparts (Tables 2-2 and 2-5) due to crowding around the carbonyl center. The trisylhydrazones of the aromatic ketone were also more difficult to prepare. Most of the hydrazone intermediates did not easily precipitate from solution. In general, hydrazone preparation involved removal of the solvent under reduced pressure and the recrystallization of the resulting solid from hot methanol.

Table 2-7. Aromatic Ketone Trisylhydrazones **5b**.



5b

Entry	X	R	% Yield of **5b**[a]
1	2-NO_2	Me	34
2	3-NO_2	Me	50
3	4-NO_2	Me	65
4	2-Br	Me	36
5	3-Br	Me	78
6	H	Me	85
7	H	Et	59
8	H	Ph	5
9	2-CH_3O	Me	45
10	3-CH_3O	Me	71
11	4-CH_3O	Me	65
12	4-CH_3	Me	44

a) Isolated Yields.

2.C.4 Alkylation of Aromatic Ketone Trisylhydrazones ***5b***.

Aryl ketone trisylhydrazones undergo the new reaction to generate alkanes (**4**) in moderate to good yields. As expected product yields are lower than their aldehyde counterparts. A survey of the data in Table 2-8 reveals that isolated yields are good with the exception of entries 3 and 7. The reaction site of these compounds would be quite hindered, thus resulting in the lower output. The obvious exception is entry 8. It is similar to entries 3 and 7 in that the reaction site would also be crowded. However, the oxygen most likely aids the reaction by complexing with the boron atom (Figure 2-4) and holding the intermediate in a favorable position for the reaction to proceed.

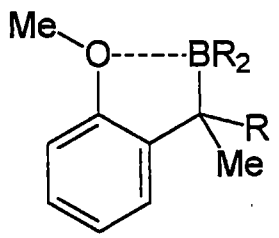
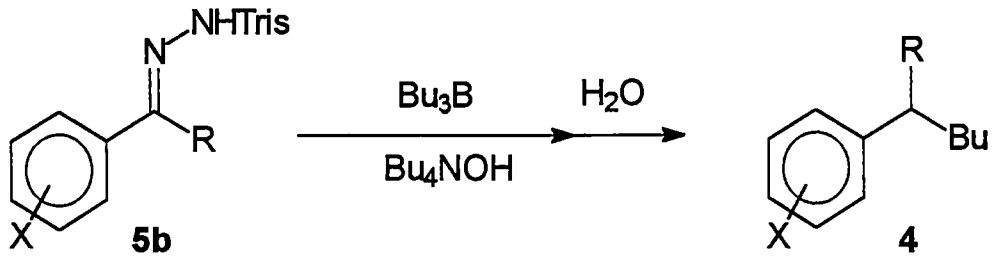


Figure 2-4. Structure of Possible Oxygen Aided Intermediate.

Table 2-8. Reaction of **5b** with Tributylborane to Produce Alkane **4**.



Entry	X	R	% Yield of **4**[a]
1	3-NO_2	Me	34
2	4-NO_2	Me	85
3	2-Br	Me	35
4	H	Me	74
5	H	Et	82
6	H	Ph	7
7	2-CH_3O	Me	93
8	4-CH_3O	Me	82
9	4-CH_3	Me	83

a) Isolated Yields.

2.C.5 Alkylation Using More Hindered Trialkylboranes

It was of interest to explore the use of more hindered trialkylboranes as alkylating agents. Tri-*sec*-butylborane (Figure2-5) was used to alkylate various trisylhydrazones of aromatic aldehydes and ketones. The results are summarized in Table 2-9.

2.C.6 Alkyl Aldehyde Trisylhydrazones

Trisylhydrazones of aliphatic aldehydes and ketones are known but are generally not isolable.[49c] Therefore, in this study all alkyl carbonyl trisylhydrazones were prepared *in situ* and used within 30 minutes of preparation. Alkyl aldehyde trisylhydrazones react nicely with both tri-*n*-butyl and tri-*sec*-butylborane to give good product yields of the alcohol products **13** (Table 2-10). Aliphatic aldehydes with single branching at the α-carbon also take part in the reaction (entries 2,3,4 and 8). Double α-branched aldehydes (entry 6) and alkyl ketones do not participate.

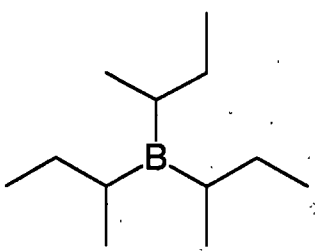
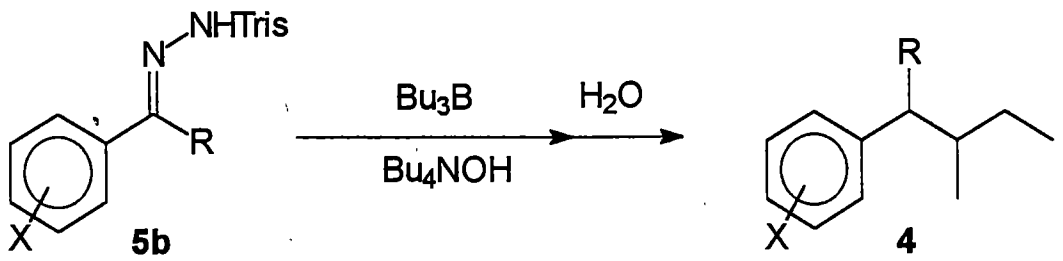
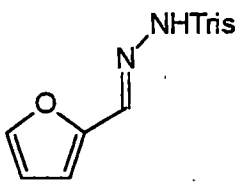


Figure 2-5. Tri-*sec*-butylborane.

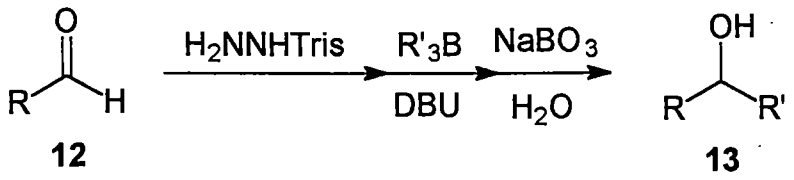
Table 2-9. Reaction of **5b** with Tri-sec-butylborane to Produce Alkane **4**.



Entry	X	R	% Yield of **4**[a]
1	3-NO_2	H	91
2	4-NO_2	H	38
3	4-NO_2	Me	62
4	4-Br	H	53
5	2-CH_3O	H	93
6	3-CH_3O	H	94
7	H	H	63
8		H	48

a) Isolated Yields.

Table 2-10. Synthesis of Alcohol **13** From Aliphatic Aldehyde **12**.



12 **13**

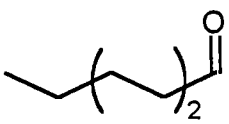
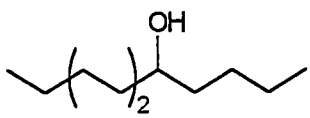
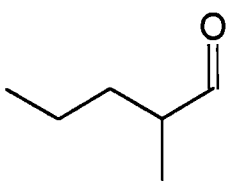
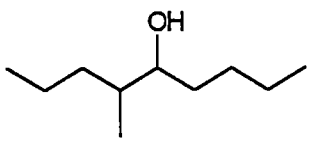
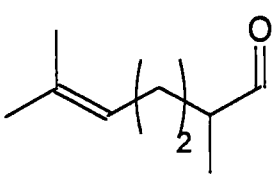
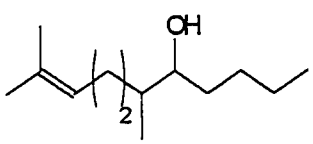
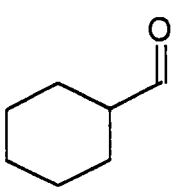
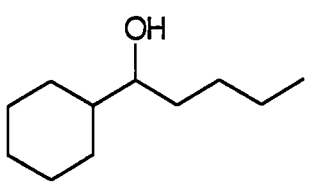
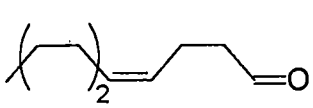
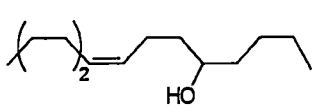
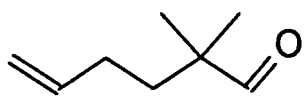
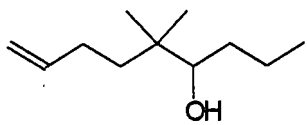
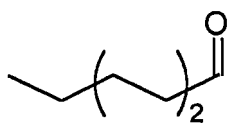
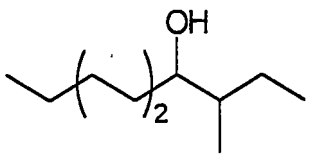
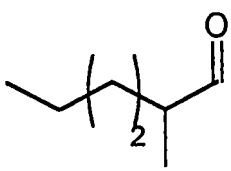
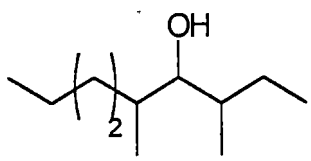
Entry	Aldehyde	R'	Product	% Yield of **13**[a]
1		*n*-Butyl		74
2		*n*-Butyl		65
3		*n*-Butyl		29[b]
4		*n*-Butyl		62[b]
5		*n*-Butyl		40[b]

Table 2-10. (Continued).

6		*n*-Butyl		0
7		*sec*-Butyl		12
8		*sec*-Butyl		49

a) Isolated Yields.
b) Dehydration Product.

2.D Experimental

2.D.1 General

All ^{1}H and ^{13}C NMR spectra were obtained 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. Elemental analyses were performed by Atlantic Microlabs, Norcross, Georgia.

All glassware, syringes, and needles were dried in an oven heated to 250 ^{0}C for at least 12 hours and cooled under nitrogen prior to use. All solvents were dried and distilled prior to use.[50] Reactions were magnetically stirred and monitored by TLC.

Products were purified by flash chromatography using 230-400 mesh ASTM 60 Å silica gel.[51]

2.D.2 Synthesis of 2,4,6-Triisopropylbenzenesulfonylhydrazide[49b]

To a round-bottomed 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. After the addition, the mixture was stirred at 0 °C for 3 hours and then distilled water was added to dissolve any solids that formed. The mixture

was transferred to a separatory funnel, the aqueous phase was discarded and the organic layer was washed with ice-cold brine. The organic phase was then dried over anhydrous sodium sulfate for 3 hours, filtered and the solvent removed under reduced pressure. Pentane (100 mL) was added to the resulting solid and the mixture was 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 phosphorous pentoxide for 24 hours to give a yield of 21.4 g (82 %): mp 115.0-116.0 °C; lit. mp 118-120 °C.

2.D.3 General Procedure for the Synthesis of Benzaldehyde Arenesulfonyl-hydrazones

To a stirred solution of the arylsulfonylhydrazide (11 mmol) in anhydrous methanol (45mL) was added the benzaldehyde (1.1 g, 10mmol). The solution was stirred at room temperature for 1 hour and was then placed in a refrigerator overnight. The resulting solid was collected by vacuum filtration and washed with 3 x 5 mL of cold methanol. If no precipitate formed, the solvent was removed under reduced pressure. All products were recrystallized from hot ethanol.

Newly prepared derivatives were analyzed by NMR and purity was determined by elemental analyses.

*2.D.3.1 Benzaldehyde Tosylhydrazone (**5a**)*[52]

This material was prepared from freshly distilled benzaldehyde (3.2 g, 30 mmol) and *p*-toluenesulfonylhydrazide (5.6 g, 30 mmol) to produce an isolated yield of 5.9 g, 72%: mp 126.5-128.0 ^{0}C; literature mp 127-128 ^{0}C.

*2.D.3.2 Benzaldehyde Trisylhydrazone (**5b**)*[53]

This material was prepared from freshly distilled benzaldehyde (1.2 g, 10 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide (1.1 g, 10 mmol) to produce an isolated yield of 3.4 g, 87%: mp 186.5-187.5 ^{0}C; literature mp 188-189 ^{0}C.

*2.D.3.3 Benzaldehyde 2-Naphthylenesulfonylhydrazone (**5c**)*

This material was prepared from freshly distilled benzaldehyde (1.2 g, 10 mmol) and 2-naphthylenesulfonylhydrazide (2.2 g,10 mmol) to produce an isolated yield of 2.4 g, 87%: mp 153.5-155.0 ^{0}C: ^{1}H-NMR (DMSO-d_6) δ 11.96 (s, 1H), 8.84 (d, 1H, J = 8.6 Hz), 8.29 (d, 1H,J = 7.5 Hz), 8.25 (d, 1H, J = 8.3 Hz), 8.06 (d, 1H, J = 8.1 Hz), 7.90 (s, 1H), 7.80-7.61 (m, 3H), 7.48-7.44 (m, 2H), 7.33-7.30 (m, 3H) ; ^{13}C-NMR (DMSO-d_6) δ 145.85, 134.48, 133.72, 133.54, 129.90, 129.72, 128.87, 128.66, 127.89, 127.72, 126.90, 126.60, 124.93, 124.63. Anal. calcd. for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03. Found: C, 65.66; H, 4.52; N, 9.05.

*2.D.3.4 Benzaldehyde 4-Methoxybenzenesulfonylhydrazone (**5d**)*

This material was prepared from freshly distilled benzaldehyde (1.2 g, 10 mmol) and 4-methoxybenzenesulfonylhydrazide (2.0 g,10 mmol) to produce an isolated yield of 2.2 g, 76%: mp 124.5-126.0 ^{0}C: ^{1}H-NMR (DMSO-d_6) δ 11.35 (s, 1H), 7.89 (s, 1H), 7.79 (d, 2H, J = 8.7 Hz), 7.55-7.53 (m, 2H), 7.39-7.38 (m,3H), 7.11 (d, 2H, J = 8.7 Hz), 3.80 (s, 3H); ^{13}C-NMR (DMSO-d_6) δ 162.53, 146.79, 133.66, 130.56, 129.99, 129.36, 126.74, 126.66, 114.34, 55.61. Anal. calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.91; H, 4.86; N, 9.65. Found: C, 57.95; H, 4.96; N, 9.76.

*2.D.3.5 Benzaldehyde 4-Fluorobenzenesulfonylhydrazone (**5e**)*

This material was prepared from freshly distilled benzaldehyde (1.2 g, 10 mmol) and 4-fluorobenzenesulfonylhydrazide (1.9 g,10 mmol) to produce an isolated yield of 2.1 g, 76%: mp 104.5-106.0 ^{0}C: ^{1}H-NMR (acetone-d_6) δ 10.24 (s, 1H), 8.08-7.93 (m, 3H), 7.64-7.58 (m, 2H), 7.43-7.32 (m, 5H); ^{13}C-NMR (acetone-d_6) δ 164.47 (d,J = 251.8 Hz), 147.52, 135.32, 133.53, 130.27(d, J = 10.0 Hz), 130.15. 128.75, 126.80, 116.44 (d, J = 22.8 Hz). Anal. calcd. for $C_{13}H_{11}FN_2O_2S$: C, 56.11; H, 3.98; N,10.07. Found: C, 56.12; H, 4.05 ; N,10.16.

*2.D.3.6 Benzaldehyde 2,3,4,5,6-pentafluorobenzenesulfonylhydrazone (**5f**)*

The synthesis was attempted using freshly distilled benzaldehyde and 2,3,4,5,6-pentafluorobenzenesulfonylhydrazide. No product could be isolated.

*2.D.3.7 Benzaldehyde 2,5-Dichlorobenzenesulfonylhydrazone (**5g**)*

This material was prepared from freshly distilled benzaldehyde (1.2 g, 10 mmol) and 2,5-dichlorobenzenesulfonylhydrazide (2.4 g, 10 mmol) to produce an isolated yield of 2.9 g, 89%: mp 115-116 ^{0}C: ^{1}H-NMR (acetone-d_6) δ 8.33 (s, 1H), 8.24 (d, 1H, J = 2.4 Hz), 7.85 (s, 1H), 7.56-7.26 (m, 7H); ^{13}C-NMR (acetone-d_6) δ 146.71, 139.21, 135.21, 134.64, 134.20, 133.67, 132.42, 131.21, 130.88, 129.59, 127.90. Anal. calcd. for $C_{22}H_{10}Cl_2N_2O_2S$: C, 47.43; H, 3.06; N, 8.51. Found: C, 47.40; H, 3.10; N, 8.57.

*2.D.3.8 Benzaldehyde 4-Nitrobenzenesulfonylhydrazone (**5h**)*

This material was prepared from freshly distilled benzaldehyde (1.2 g, 10 mmol) and 4-nitrobenzenesulfonylhydrazide (2.2 g, 10 mmol) to produce an isolated yield of 2.1 g, 68%: mp 140.0-142.0 ^{0}C: ^{1}H-NMR (DMSO-d_6) δ 11.87 (s, 1H), 8.42 (d, 2H, J = 8.8 Hz), 8.14 (d, 2H, J=8.8 Hz), 7.96 (s, 1H), 7.59-7.55 (m, 2H), 7.39-7.37 (m, 3H); ^{13}C-NMR (DMSO-d_6) δ 149.97, 148.34, 144.24, 133.36, 130.36, 128.83, 126.96, 124.96, 124.62. Anal. calcd. for $C_{13}H_{11}N_3O_4S$: C, 51.14; H, 3.63; N,13.76. Found: C, 50.87; H, 3.71; N,13.61.

2.D.4 General Procedure for the Synthesis of Aromatic Ketone Trisylhydrazones

To a stirred solution of 2,4,6-triisopropylbenzenesulfonylhydrazide (3.3 g, 11 mmol) in anhydrous methanol (45) was added the ketone (10 mmol) and 5 drops of concentrated HCl. The solution was stirred at room temperature for 1

hour and then was placed in a refrigerator overnight. The resulting solid was collected by vacuum filtration. If no precipitate formed, the solvent was removed under reduced pressure. All compounds were recrystallized from hot methanol.

Newly prepared derivatives were analyzed by NMR and purity was determined by elemental analyses.

2.D.4.1 2-Nitroacetophenone Trisylhydrazone

This material was prepared from 2-nitroacetophenone and 2,4,6-triisopropylbenzenesulfonylhydrazide to produce an isolated yield of 34%: mp 171.0-173.0 ^{0}C (dec.): ^{1}H-NMR (DMSO-d_6) δ 10.90 (s, 1H),7.89-7.86 (m,1H), 7.70-7.63 (m, 1H), 7.58-7.57 (m, 1H), 7.44-7.41 (m, 1H), 7.16 (s, 2H), 4.16 (sept, 2H, J = 6.9 Hz), 2.87 (sept, 1H, J = 6.9 Hz), 2.12 (s, 3H), 1.17 (d, 6H, J = 6.9 Hz), 1.08 (d, 12H, J = 6.9 Hz); ^{13}C-NMR (DMSO-d_6) δ 153.48, 150.49, 148.94, 147.81, 134.27, 133.06, 132.02, 129.93, 129.66, 124.16, 123.32, 33.26, 26.46, 24.37, 23.34.

2.D.4.2 3-Nitroacetophenone Trisylhydrazone

This material was prepared from 3-nitroacetophenone (0.33 g, 2.0 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide to produce an isolated yield of 0.45 g, 34%: ^{1}H-NMR (DMSO-d_6) δ 11.08 (s, 1H), 8.69-8.67 (m, 1H), 8.39-8.32 (m, 1H), 8.19-8.15 (m, 1H), 7.99 (d, 1H, J = 7.7 Hz), 7.70 (dt, 1H. J = 8.0 Hz), 7.23 (s, 2H), 4.31 (sept, 2H, J = 6.7 Hz), 2.89 (sept, 1H, J = 6.9 Hz), 2.26 (s, 3H),

1.20-1.17 (m, 18H); ^{13}C-NMR (DMSO-d_6) δ 152.76, 150.46, 147.88, 132.90, 132.20, 129.90, 124.41, 123.53, 120.04, 33.29, 28.89, 24.51, 23.31, 14.12.

2.D.4.3 4-Nitroacetophenone Trisylhydrazone

This material was prepared from 4-nitroacetophenone (1.7 g, 10 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide to produce 2.9 g, 65%: mp 163.3-164.7 °C: ^{1}H-NMR (DMSO-d_6) δ 11.19 (s, 1H), 8.17 (d, 2H, J = 8.9 Hz), 7.82 (d, 2H, J = 8.9 Hz), 7.22 (s, 2H), 4.30 (sept, 2H, J = 6.7 Hz), 2.24 (s, 3H), 2.88 (sept, 1H, J = 6.9 Hz), 1.18 (overlapping d's, 18H,J = 6.6 Hz and 6.7 Hz); ^{13}C-NMR (DMSO-d_6) δ 152.79, 150.49, 147.65, 147.39, 143.64, 132.30, 126.87, 123.53, 123.38, 33.29, 28.96, 24.55, 23.31, 14.04. Anal. calcd. for $C_{22}H_{29}N3O4S$: C, 61.23; H,6.78; N, 9.74. Found: C, 61.13; H, 6.83; N, 9.82.

2,D.4.4 2-Bromoacetophenone Trisylhydrazone

This material was prepared from 2-bromoacetophenone (1.9 g, 10 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide to produce an isolated yield of 36%: mp 140.0-141.5 °C: ^{1}H-NMR (DMSO-d_6) δ 10.82 (s, 1H), 6.97 (d, 1H, J = 7.0 Hz), 7.34-7.12 (m, 5H), 4.23 (sept, 2H, J = 6.7 Hz), 2.88 (sept, 1H, J = 6.9 Hz), 2.14 (s, 3H), 1.18 (d, 6H, J = 6.9 Hz), 1.10 (d, 12H, J = 6.7 Hz); ^{13}C-NMR (DMSO-d_6) δ 152.52, 151.58, 150.54, 140.38, 132.78, 130.13, 130.00, 127.47, 123.34, 120.44, 33.34, 28.79, 24.45, 23.40, 18.43. Anal. calcd. for $C_{23}H_{31}BrN_2O_2S$: C, 57.61; H, 6.52; N, 5.84. Found: C, 57.38; H, 6.49; N, 5.76.

2.D.4.5 3-Bromoacetophenone Trisylhydrazone

This material was prepared from 3-bromoacetophenone (1.9 g, 10 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide to produce an isolated yield of 78%: mp 180.0-181.5 ^{0}C (dec.): ^{1}H-NMR (DMSO-d_6) δ 10.92 (s, 1H), 7.71-7.70 (m, 1H), 7.58-7.49 (m, 2H), 7.32-7.23 (s over m, 3H), 4.30 (sept, 2H, J = 6.7 Hz), 2.89 (sept, 1H, J = 6.8 Hz), 1.19 (d, 12H, J = 6.6 Hz), 1.17 (d, 6H, J = 6.8 Hz); ^{13}C-NMR (DMSO-d_6) δ 150.70, 150.48, 148.40, 139.84, 132.29, 131.89, 130.39, 128.05, 125.05, 123.47, 121.78, 33.32, 28.89, 24.56, 23.37, 13.95 18.43. Anal. calcd. for $C_{23}H_{31}BrN_2O_2S$: C, 57.61; H, 6.52; N, 5.84. Found: C, 57.87; H, 6.45; N, 6.01.

2.D.4.6 Acetophenone Trisylhydrazone[53]

This material was prepared from acetophenone (1.2 g, 10 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide to produce an isolated yield of 3.4 g, 85%: mp 166.5-167.5, lit mp 172-173 ^{0}C: ^{1}H-NMR (Acetone-d_6) δ 7.70-7.76 (m, 2H), 7.33-7.28 (m, 5H), 4.41 (sept, 1H, J = 6.8 Hz), 2.93 (sept, 1H, J = 6.9 Hz) 1.26, 1.22 (overlappin d's, 18H, J = 6.8 Hz and 6.9 Hz); ^{13}C-NMR (Acetone-d_6) δ 153.50, 155.07, 138.21, 133.87, 133.70, 129.38, 128.94, 124.41, 34.77, 30.41, 30.30, 25.60, 23.82.

2.D.4.7 Propiophenone Trisylhydrazone

This material was prepared from propiophenone (1.3 g, 10 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide to produce an isolated yield of 2.4 g, 59 %:

^{1}H-NMR (DMSO-d_6) δ 7.59-7.56 (m, 2H), 7.32-7.29 (m, 3H), 7.21 (s, 2H), 4.30 (sept, 2H, J = 6.7 Hz), 3.16 (s, 3H), 2.88 (sept, 1H, J = 6.8 Hz), 2.72 (q, 2H, J = 7.4 Hz), 1.19 (d, 12H, J = 4.8 Hz), 1.16 (d, 6H, J = 4.7 Hz), 0.98 (t, 3H, J = 7.4 Hz); ^{13}C-NMR (DMSO-d_6) δ 153.80, 152.59, 150.54, 132.54, 129.02, 128.26, 125.92, 123.44, 33.33, 28.96, 24.65, 23.37, 19.58, 10.43. Anal. calcd. for $C_{24}H_{34}N_2O_2S$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.65; H, 8.34; N, 6.65.

2.D.4.8 Benzophenone Trisylhydrazone[49b]

This material was prepared from benzophenone (1.8 g, 10 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide to produce an isolated yield of 1.6 g, 34 %: ^{1}H-NMR ($CDCl_3$/TMS) δ 7.66 (s, 1H), 7.57-7.53 (m, 3H), 7.49-7.41 (m, 2H), 7.34-7.18 (m, 7H), 4.17 (sept, 2H, J = 6.7 Hz), 2.91 (sept, 1H, J = 6.9 Hz), 1.29, 1.25 (overlapping d's, 18H, J = 6.9 Hz and 7.4 Hz). ^{13}C-NMR ($CDCl_3$) δ 153.36, 151.37, 131.25, 130.03, 129.73, 128.41, 128.08, 127.52, 123.80, 34.18, 30.07, 25.00, 23.55.

2.D.4.9 2-Methoxyacetophenone Trisylhydrazone

This material was prepared from 2-methoxyacetophenone (1.5 g, 10 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide to produce an isolated yield of 1.5 g, 36 %: mp 160.5-162.0 °C: ^{1}H-NMR (DMSO-d_6) δ 10.57 (s, 1H), 7.32-7.25 (m, 1H), 7.19 (s, 2H), 6.99-6.96 (m, 2H), 6.84-6.78 (m, 1H), 4.26 (sept, 2H, J = 6.7 Hz), 3.71, (s, 3H), 2.88 (sept, 1H, J = 6.9 Hz), 2.10 (s, 3H), 1.18 (d, 6H, J = 6.9 Hz), 1.12

(d, 12H, J = 6.7 Hz); ^{13}C-NMR (DMSO-d_6) δ 156.70, 152.40, 152.29, 150.52, 132.48, 130.17, 128.96, 123.32, 119.99, 111.62, 55.39, 33.28, 28.82, 24.51, 23.36, 17.97. Anal. calcd. for $C_{24}H_{34}N_2O_3S$: C, 66.94; H, 7.96; N, 6.50. Found: C, 66.93; H, 8.06; N, 6.58.

2.D.4.10 3-Methoxyacetophenone Trisylhydrazone

This material was prepared from 3-methoxyacetophenone (0.75 g, 5.0 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide to produce an isolated yield of 1.4 g, 64 %: ^{1}H-NMR (DMSO-d_6) δ 10.75 (s, 1H), 7.25-7.07 (m, 5H), 6.91-6.88 (m, 1H), 4.31 (sept, 2H, J = 6.9 Hz), 3.68 (s, 3H), 2.88 (sept, 1H, J = 6.9 Hz), 2.17 (s, 3H), 1.18 (d, 12H, J = 6.7 Hz), 1.16 (d, 6H, J = 6.9 Hz); ^{13}C-NMR (DMSO-d_6) δ 159.13, 152.58, 150.42, 149.68, 139.06, 132.39, 129.17, 123.40, 118.38, 114.53, 111.44, 55.02, 33.30, 28.85, 24.55, 23.33, 14.25.

2.D.4.11 4-Methoxyacetophenone Trisylhydrazone

This material was prepared fro 4-methoxyacetophenone (1.5 g, 10 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide to produce an isolated yield of 2.3 g, 65 %: ^{1}H-NMR (DMSO-d_6) δ 7.54 (d, 2H, J = 8.8 Hz), 7.21 (s, 2H), 6.84 (d, 2H, J = 8.8 Hz), 4.32 (sept, 2H, J = 6.7 Hz), 3.73 (s, 3H), 3.38 (s, 1H), 2.88 (sept, 1H, J = 6.9 Hz), 2.15 (s, 3H), 1.19 (d, 12H, J = 4.9 Hz), 1.16 (d, 6H, J = 4.8 Hz); ^{13}C-NMR (DMSO-d_6) δ 160.11, 152.50, 150.50, 150.28, 132.62, 130.04, 127.33, 123.41, 113.51, 55.19, 33.32, 28.95, 24.63, 23.37, 13.99.

2.D.4.12 4-Methylacetophenone Trisylhydrazone

This material was prepared from 4-methylacetophenone (1.3 g, 10 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazide to produce an isolated yield of 0.22 g, 5 %: ^{1}H-NMR (DMSO-d_6) δ 10.65 (s, 1H), 7.48 (d, 2H, J = 8.0 Hz), 7.21 (s, 1H), 7.11 (d, 2H, J = 8.0 Hz), 4.31 (sept, 2H, J = 6.7 Hz), 2.88 (sept, 1H, J = 6.9 Hz), 2.25 (s, 3H), 2.15 (s, 3H), 1.18 (d, 12H, J = 6.5 Hz), 1.17 (d, 6H, J = 6.3 Hz); ^{13}C-NMR (DMSO-d_6) δ 152.52, 150.47, 150.22, 136.70, 134.80, 132.54, 128.89, 125.77, 123.37, 33.29, 28.92, 24.56, 23.34, 20.66, 13.97.

2.D.5 General Procedure for the Synthesis of Arylalkane **4**.

The ketone trisylhydrazone (3.00 mmol) was dissolved in THF (15 mL) contained in a nitrogen-flushed, round bottomed flask equipped with a side arm, reflux condenser and stirring bar. Tributylborane (3.0 mmol, 3.0 mL of a 1.0 M solution in THF) was added via syringe followed by Bu_4NOH (3.0 mmol, 3.0 mL of a 1.0 M solution in MeOH). The reaction mixture was heated at reflux in THF and was monitored by TLC. Upon completion, the reaction was cooled to room temperature and water (10 mL) was added. The product was extracted into ether (3 x 15 mL). The combined organic layers were washed with saturated brine solution (25 mL) and dried over anhydrous $MgSO_4$. The phases were separated, the solvent removed under reduced pressure and the product was purified by flash

chromatography using a 20-mm diameter column, packed with silica gel, and eluted with a solvent system of 9% ethyl acetate in hexanes.

2.D.5.1 3-(1-Methylpentyl)-1-nitrobenzene

This material was prepared from 3-nitroacetophenone trisylhydrazone (0.86 g, 2.0 mmol) to produce an isolated yield of 0.14 g, 34%. ^{1}H-NMR ($CDCl_3$/TMS) δ 8.05-8.02 (m, 2H), 7.53-7.26 (m, 2H), 2.81 (sext, 1H, J = 7.1 Hz), 1.+60 (q, 2H, J = 7.6 Hz), 1.34-1.10 (d over M, 7H, d at 1.27, J = 6.9 Hz), 0.85 (t, 3H, J = 6.7 Hz); ^{13}C-NMR ($CDCl_3$) δ 149.96, 148.42, 133.41, 129.10, 121.85, 121.00, 39.82, 37.84, 29.72, 22.83, 21.97, 13.94.

2.D.5.2 4-(1-Methylpentyl)1-nitrobenzene

This material was prepared from 4-nitroacetophenone trisylhydrazone (1.34 g, 3.00 mmol) to produce an isolated yield of 0.56 g, 85%. ^{1}H-NMR ($CDCl_3$/TMS) δ 8.15 (d, 2H, J = 8.7 Hz), 7.34 (d, 2H, J = 8.7 Hz), 2.81 (sext, 1H, J = 7.0 Hz), 1.60 (q, 2H, J = 7.5 Hz), 1.30-1.10 (d over m, 7H, d is at 1.26, J = 6.9 Hz), 0.85 (t, 3H, J = 7.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 155.75, 146.18, 127.70, 123.52, 39.96, 37.67, 29.65, 22.55, 21.80, 13.83. Anal. calcd. for $C_{12}H_{17}NO_2$: C, Found:

2.D.5.3 2-(1-Methylpentyl)-1-bromobenzene

This material was prepared from 2-bromoacetophenone trisylhydrazone (1.1 g, 2.2 mmol) to give an isolated yield of 0.76 g, 35%: ^{1}H-NMR ($CDCl_3$/TMS) δ

7.54-7.51 (m, 1H), 7.27-7.21 (m, 2H), 7.06-6.99 (m, 1H), 3.24 (sext, 1H, J = 7.0 Hz), 1.72-1.08 (d over m, 9H, d at 1.17, J = 6.9 Hz), 0.87 (t, 3H, J = 7.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 146.90, 132.74, 127.55, 127.25, 127.13, 124.77, 37.93, 37.12, 29.99, 22.76, 21.17, 14.04.

2.D.5.4 (1-Methylpentyl)benzene[54]

This material was prepared from acetophenone trisylhydrazone (0.92 g, 3.0 mmol) to produce an isolated yield of 0.27 g, 74%. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.20-7.10 (m, 5H), 2.66 (sext, 1H, J = 7.0 Hz), 1.50 (dq, 2H, J = 8.0 Hz and 2.4 Hz), 1.36-1.04 (d over m, 7H, d is at 1.16, J = 6.8 Hz), 0.84 (t, 3H, J = 7.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 147.92, 128.16, 126.91, 125.64, 39.87, 38.09, 29.87, 22.69, 22.23, 13.93.

2.D.5.5 (1-Ethylpentyl)benzene[55]

This material was prepared from propiophenone trisylhydrazone (0.56 g, 3.1 mmol) to produce an isolated yield of 0.43 g, 82%. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.29-7.23 (m, 2H), 7.18-7.10 (m, 3H), 2.38 (pent, 1H, J = 5.3 Hz), 1.72-1.48 (m, 4H), 1.31-1.04 (m, 4H), 0.82 (t, 3H, J = 6.9 Hz), 0.76 (t, 3H, J = 6.9 Hz); ^{13}C-NMR ($CDCl_3$) δ 128.13, 27.98, 127.73, 125.72, 47.92, 36.30, 29.88, 29.75, 22.83, 14.01, 12.17.

2.D.5.6 1,1-Diphenylpentane[56]

This material was prepared from bezophenone trisylhydrazone (1.1 g, 2.4 mmol) to produce an isolated yield of 0.035 g, 7%. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.30-7.11 (m, 10H), 3.87 (t, 1H, J = 7.8 Hz), 2.03 (q, 2H, J = 6.7 Hz), 1.38-1.20 (m, 4H), 0.86 (t, 3H, J = 7.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 145.38, 128.36, 127.88, 125.98, 51.38, 35.46, 30.25, 22.72, 13.99.

2.D.5.7 2-(1-Methylpentyl)-1-anisole[57]

This material was prepared from 2-methoxyacetophenone trisylhydrazone (1.3 g, 3.0 mmol) to produce an isolated yield of 0.78 g, 93%. ^{1}H-NMR ($CDCl_3$ /TMS) δ 7.25-7.12 (m, 2H), 6.95-6.83 (m, 2H), 3.81 (s, 3H), 3.18 (sext, 1H, J = 7.1 Hz), 1.61-1.48 (m, 2H), 1.37-1.15 (d over m, 7H, d is at 1.18, J = 7.1 Hz), 0.86 (t, 3H, J = 7.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 157.00, 138.26, 128.70, 128.40, 120.55, 110.47, 55.35, 38.83, 31.89, 29.70, 22.81, 20.94, 14.04.

2.D.5.8 4-(1-Methylpentyl)-1-anisole[58]

This material was prepared from 4-methoxyacetophenone trisylhydrazone (0.80 g, 1.9 mmol) to produce an isolated yield of 0.29 g, 82%. ^{1}H-NMR ($CDCl_3$ /TMS) δ 7.08 (d, 2H, J = 8.5 Hz), 6.82 (d, 2H, J = 8.5 Hz), 3.76 (s, 3H), 2.60 (pent, 1H, J = 7.0 Hz), 1.52 (q, 2H, J = 7.1 Hz), 1.34-1.07 (d over m, 7H, d is at 1.19, J = 6.9 Hz), 0.84 (t, 3H, J = 6.9 Hz); ^{13}C-NMR ($CDCl_3$) δ 157.64, 140.05, 127.74, 113.80, 55.10, 39.06, 38.33, 29.95, 22.75, 22.50, 14.01.

2.D.5.9 4-(1-Methylpentyl)-1-toluene[59]

This material was prepared from 4-methylacetophenone trisylhydrazone (0.83 g, 2.0 mmol) to produce an isolated yield of 0.29 g, 83%. ^{1}H-NMR ($CDCl_3$ /TMS) δ 7.08 (s, 4H), 2.62 (sext, 1H, *J* = 7.1 Hz), 2.31 (s, 3H), 1.59-1.50 (m, 2H), 1.31-1.12 (d over m, 7H, d at 1.21, *J* = 7.0 Hz), 0.85 (t, 3H, *J* = 6.7 Hz): ^{13}C-NMR ($CDCl_3$) δ 144.95, 135.07, 128.95, 128.82, 39.51, 38.22, 29.97, 22.81, 22.44, 20.97, 14.02.

2.D.5.10 3-(2-methylbutyl)-1-nitrobenzene

This material was prepared from 3-nitrobenzaldehyde trisylhydrazone (0.86 g, 2.0 mmol) to produce an isolated yield of 0.35 g, 91%. ^{1}H-NMR ($CDCl_3$/TMS) δ 8.07-8.02 (m, 2H), 7.50-7.39 (m, 2H), 2.75 (dd, 1H, *J* = 6.2 Hz), 2.47 (dd, 1H, *J* = 8.2 Hz), 1.68 (sept, 1H, *J* = 6.7 Hz), 1.48-1.32 (m, 1H), 1.30-1.12 (m, 1H), 0.94 (t, 3H, *J* = 7.3 Hz), 0.88 (d, 3H, *J* = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ 148.18, 143.63, 135.35, 128.86, 123.78, 120.82, 42.80, 38.47, 29.03, 18.67, 11.32.

2.D.5.11 4-(2-Methylbutyl)-1-nitrobenzene

This material was prepared from 4-nitrobenzaldehyde trisylhydrazone (0.86 g, 2.0 mmol) to produce an isolated yield of 0.15 g, 38%. ^{1}H-NMR ($CDCl_3$/TMS) δ 8.13 (d, 2H, *J* = 8.6 Hz), 7.30 (d, 2H, *J* = 8.6 Hz), 2.47 (dd, 1H, *J* = 6.2 Hz), 1.73-1.63 (m, 1H), 1.44-1.04 (m, 3H), 0.92 (t, 3H, *J* = 7.4 Hz), 0.85 (d, 3H, *J* = 6.8 Hz);

^{13}C-NMR ($CDCl_3$) δ 130.79, 129.83, 123.49, 123.37, 119.12, 43.10, 36.53, 29.15, 18.60, 11.68.

2.D.5.12 4-(1,2-Dimethylbutyl)-1-nitrobenzene

This material was prepared from 4-nitroacetophenone trisylhydrazone (1.3 g, 3.0 mmol) to produce an isolated yield of 0.38 g, 62%. ^{1}H-NMR ($CDCl_3$/TMS) δ 8.16 (d, 2H, *J* = 7.1 Hz), 7.80 (d, 2H, *J* = 7.1 Hz), 3.43 (pent, 1H, *J* = 6.5 Hz), 1.78-1.66 (m, 1H), 1.56-1.43 (m. 1H), 1.24 (d, 6H, *J* = 6.5 Hz), 0.97 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR ($CDCl_3$) δ 146.36, 145.81, 125.16, 123.77, 123.53, 56.90, 29.18, 19.91, 11.19, 10.26.

2.D.5.13 4-(2-Methylbutyl)-1-bromobenzene

This material was prepared from 4-bromobenzophenone trisylhydrazone (0.67 g, 1.5 mmol) to produce an isolated yield of 0.17 g, 53%. ^{1}H-NMR ($CDCl_3$ /TMS) δ 7.38 (d, 2H, *J* = 8.3 Hz), 7.01 (d, 2H, *J* = 8.3 Hz), 2.60, (d, 1H, *J* = 6.2 Hz), 2.55 (d, 1H, *J* = 6.2 Hz), 2.35-2.26 (m, 1H), 1.64-1.07 (m over m, 2H), 0.89 (t, 3H, *J* = 7.3 Hz), 0.83 (d, 3H, *J* = 6.7 Hz); ^{13}C-NMR ($CDCl_3$) δ 140.59, 131.10, 130.89, 119.29, 42.64, 36.55, 29.06, 18.61, 11.42.

2.D.5.14 2-(2-Methylbutyl)-1-anisole

This material was prepared from 2-methoxyacetophenone trisylhydrazone (0.75 g, 1.8 mmol) to produce an isolated yield of 0.30 g, 93%. ^{1}H-NMR ($CDCl_3$

/TMS) δ 7.20-7.06 (m, 2H), 6.89-6.81 (m, 2H), 3.78 (s, 3H), 2.64 (dd, 1H, *J* = 6.2 Hz), 2.37 (dd, 1H, *J* = 8.0 Hz), 1.72-1.61 (m, 1H), 1.44-1.31(m, 1H), 1.26-1.08 (m, 1H), 0.90 (t, 3H, *J* = 7.3 Hz), 0.83 (d, 3H, *J* = 6.7 Hz); ^{13}C-NMR ($CDCl_3$) δ 130.83, 128.74, 120.05, 110.23, 55.17, 37.41, 35.08, 29.45, 19.06, 11.50.

2.D.5.15 3-(2-Methylbutyl)-1-anisole

This material was prepared from 3-methoxybenzaldehyde Trisylhydrazone (1.2 g, 1.8 mmol) to produce an isolated yield of 0.31 g, 94%: ^{1}H-NMR ($CDCl_3$/TMS) δ 7.25-7.15 (m, 1H), 6.75-6.70 (m, 3H), 3.79 (s, 3H), 2.60 (dd, 1H, *J* = 6.2 Hz), 2.33 (dd, 1H, *J* = 8.1 Hz), 1.70-1.55 (m, 1H), 1.43-1.13 (m, 2H), 0.98-0.84 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ 159.49, 143.38, 128.95, 121.89, 115.00, 110.75, 55.07, 43.40, 36.48, 31.60, 29.22, 22.57.

2.D.5.16 (2-Methylbutyl)benzene

This material was prepared from benzaldehyde trisylhydrazone (0.39 g, 1.0 mmol) to produce an isolated yield of 0.094 g, 63%.^{1}H-NMR ($CDCl_3$/TMS) δ 7.30-7.13 (m, 5H), 2.66 (dd, 1H, *J* = 6.2 Hz), 2.39 (dd, 1H, *J* = 8.0 Hz), 1.45-1.34 (m, 1H), 1.26-1.11 (m, 1H), 0.90 (t, 3H, *J* = 7.3 Hz), 0.85 (d, 3H, *J* = 6.7 Hz); ^{13}C-NMR ($CDCl_3$) δ 141.90, 129.16, 128.04, 125.54, 43.35, 36.68, 29.20, 18.94, 11.48.

*2.D.5.17 2-(2-Methyl*butyl)furan

This material was prepared from 2-furancarboxaldehyde trisylhydrazone (1.1 g, 3.0 mmol) to produce an isolated yield of 0.20 g, 48%. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.29-7.28 (m, 1H), 6.28-6.26 (m, 1H), 5.98-5.96 (m, 1H), 2.61 (dd, 1H, J = 6.2 Hz), 2.42 (dd, 1H, J = 7.7 Hz), 1.77-1.66 (m, 1H), 1.47-1.28 (m, 1H), 1.26-1.08 (m, 1H), 0.93-0.84 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ 155.57, 140.65, 109.96, 105.63, 35.05, 34.24, 29.131, 19.09, 11.37.

2.D.6 General Proceedure for the Synthesis of Aliphatic Alcohol ***13.***

To a roundbottom flask equipped with a magnetic stir bar and septum was added the 2,4,6-triisopropylbenzenesulfonylhydrazide (0.895 g, 3.00 mmol). THF was added to creat a clear, colorless solution. The aldehyde (3.00 mmol) is added and the solution stirred at room temperature for 30 minutes. The solution was passed through a short column of celite/anhydrous Na_2SO_4directly into the reaction flask. The trialkylborane (3.00 mmol) was added followed by DBU (0.67 mL, 4.5 mmol). The reaction was heated to reflux until TLC indicated the reaction was complete. The solution was cooled to room temperature and sodium perborate (1.44 g, 9.36 mmol) and water (10 mL) was added. After stirring for 30 minutes the product was extracted into ether (3 x 10 mL). The combined organic layer was washed with saturated brine solution (20 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the product purified on a silica gel flash column.

2.D.6.1 Undecan-5-ol[60]

This material was prepared from heptanal (3.00 mmol) according to the general procedure to give an isolated yield of 0.38 g, 74%. ^{1}H-NMR ($CDCl_3$/TMS) δ 3.74-3.44 (m, 1H), 1.56-1.04 (m, 17H), 1.04-0.72 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ 72.02, 37.51, 37.18, 31.84, 29.36, 27.84, 25.60, 22.75, 22.60, 14.04.

2.D.6.2 4-Methylnonan-5-ol[61]

This material was prepared from 2-methylpentanal (3.00 mmol) according to the general procedure to give an isolated yield of 0.21 g, 65%. ^{1}H-NMR ($CDCl_3$ /TMS) δ 3.54-3.39 (m, 1H), 1.59-1.05 (m, 12H), 0.98-0.80 (m, 9H); ^{13}C-NMR ($CDCl_3$) 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, 13.50.

2.D.6.3 6,10-Dimethyl-9-undecen-5-ol

This material was prepared from 2,6-dimethyl-5-heptenal (0.42 g, 3.0 mmol) according to the general procedure to give an isolated yield of 0.17 g, 29%. Product isolated is the dehydrated product. ^{1}H-NMR ($CDCl_3$/TMS) δ 5.15-5.10 (m, 2H), 3.47 (q, 4H, J = 7.0 Hz), 2.04-1.97 (m, 2H), 1.68 (s, 6H), 1.60(s, 3H), 1.53-1.10 (m, 4H), 0.89 (t, 3H, J = 6.9 Hz).

2.D.6.4 1-Cyclohexylpentan-1-ol

This material was prepared from cyclohexane carboxaldehyde (0.33 g, 3.0 mmol) according to the general procedure to give an isolated yield of 0.32 g, 62%. Product isolated is the dehydrated product. ^{1}H-NMR ($CDCl_3$/TMS) δ 2.14-1.94 (m, 4H), 1.71-1.39 (m, 4H), 1.32-1.23 (m, 9H), 1.97-0.83 (m, 5H);

2.D.6.5 8-Tetradecen-5-ol

This material was prepared from *cis*-4-decanal (0.46 g, 3.0 mmol) according to the general procedure to give an isolated yield of 0.25 g, 40%. Product isolated is the dehydrated product. ^{1}H-NMR ($CDCl_3$/TMS) δ 5.40-5.37 (m, 4H), 2.04-2.01 (m, 4H), 1.43-1.23 (m, 12H), 0.91-0.83 (m, 6H).

2.D.6.6 6,6-Dimethyl-9-decan-5-ol

This material was prepared from *cis*-4-decanal (0.33 g, 3.0 mmol) according to the general procedure. No product was obtained.

2.D.6.7 3-Methyldecan-4-ol

This material was prepared from heptanal (3.0 mmol) according to the general procedure to give an isolated yield of 12%. ^{1}H-NMR ($CDCl_3$/TMS) δ 3.30 (m, 1H), 1.97-1.53 (m, 15H), 0.95-0.78 (m, 9H); ^{13}C-NMR ($CDCl_3$) δ 75.10, 74.86, 40.90, 40.15, 35.00, 34.86, 32.45, 30.05, 26.42, 22.40, 15.00.

2.D.6.8 3,5-Dimethylnonan-4-ol

This material was prepared from 2-methylpentanal (3.0 g, 3.0 mmol) according to the general procedure to give an isolated yield of 0.24 g, 49%. ^{1}H-NMR ($CDCl_3$/TMS) δ 4.03 (t, 1H, *J* = 6.8 Hz), 1.98-1.85 (m, 1H), 1.66-1.15 (m, 14H), 1.01-0.80 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ 74.73, 34.45, 29.72, 28.23, 24.12, 23.75, 19.99, 18.78, 14.20.

CHAPTER 3

SUZUKI COUPLING OF ACID CHLORIDES WITH TRIALKYL BORANES

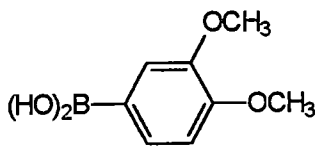
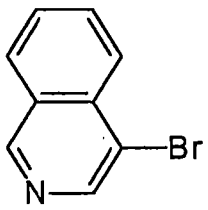
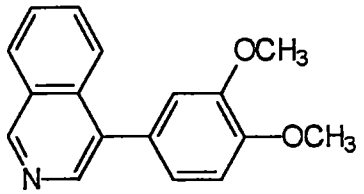
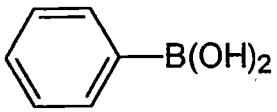
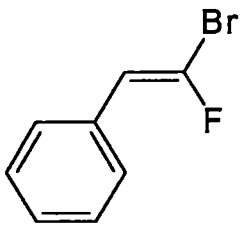
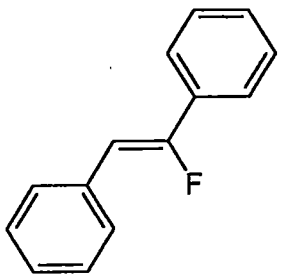
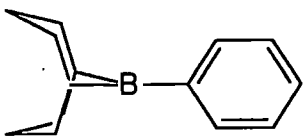
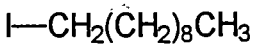
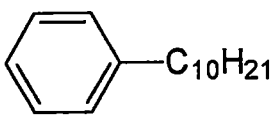
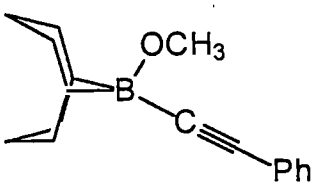
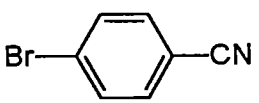
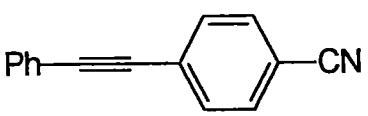
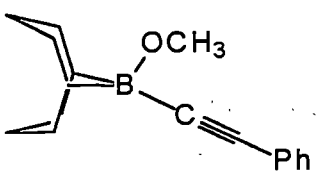
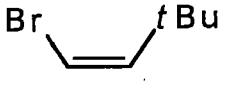
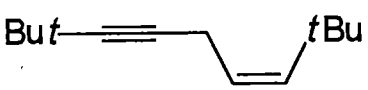
3.A Introduction

As noted in Chapter 1 (section *1.B.9*), the Suzuki coupling reaction is one of the most useful reactions in organic chemistry. Table 3-1 contains a list of the various types of compounds that can be constructed using the Suzuki reaction. It is apparent that this methodology is versatile and extremely valuable to synthetic chemists.

There is a large number of reports in the literature of Suzuki-like reactions involving the conversion of acid chlorides to ketones using a variety of metal catalysts (Table 3-2).[69] However, there are few accounts of acid chlorides being reacted with boron compounds. This is surprising since many of the metals used for the conversion of acid chlorides to ketones are difficult to use, require extreme reaction conditions and are plagued with problems such as high toxicity and low thermal stability. The use of boron compounds would alleviate many of these pitfalls.

Until recently, all of the reported reactions utilizing boron compounds in reactions with acid chlorides used tetraalkylborate salts. Negishi was the first to use the tetraalkylborates for the preparation of ketones.[42] He reported that

Table 3-1. Examples of Suzuki Coupling Reactions.

No.	Boron Compound	Halide/Triflate	Product (Yield)
1			 (95)[62]
2			 (86)[63]
3			 (55)[64]
4			 (93)[65]
5			 (56)[65]

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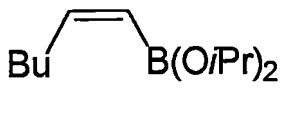
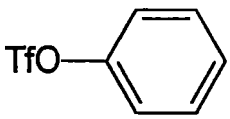
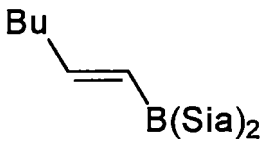
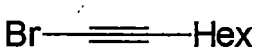
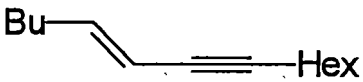
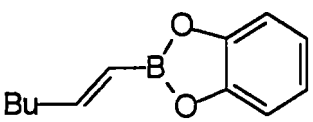
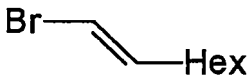
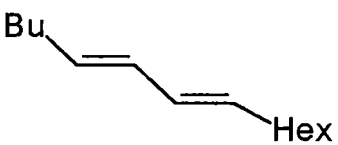
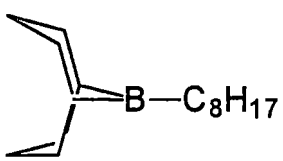
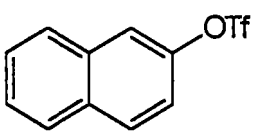
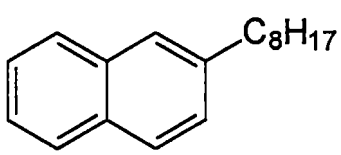
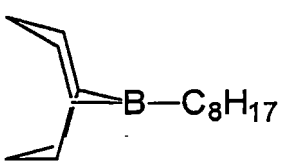
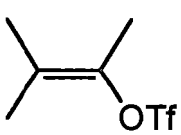
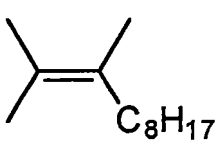
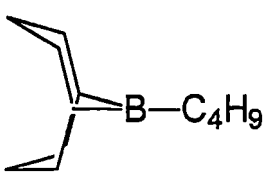
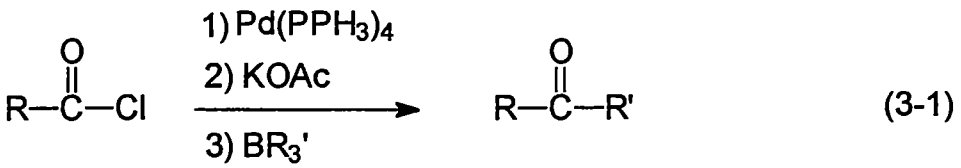
6			 (68)[67]
7			 (98)[68]
8			 (86)[68]
9			 (99)[67]
10			 (91)[67]
11		$IC_{10}H_{21}$	$C_{14}H_{30}$ (50)[64]

Table 3-2. Metals and Metal Combinations Used to Produce Ketones from Acid Chlorides.

Lithium[70]	Magnesium[71]	Magnesium Iron[72]	Titanium[73]	Zirconium[74]
Zinc Copper[75]	Vanadium[76]	Manganese[77]	Manganese Lithium Magnesium[78]	Manganese Copper[79]
Iron[80]	Cobalt[81]	Cobalt Zinc[81]	Rhodium[82]	Nickel[83]
Palladium[84]	Nickel Magnesium[85]	Palladium Tin[86]	Palladium Zinc[87]	Palladium Zinc Copper[88]
Palladium Magnesium Zinc[89]	Palladium Aluminum[90]	Palladium Silicon[91]	Palladium Lead[92]	Copper Lithium[93]
Copper Magnesium[94]	Copper Zinc[95]	Copper Zirconium[96]	Copper Aluminum[97]	Copper Tin[98]
Cadmium[99]	Mercury[100]	Gallium Lithium[101]	Indium[102]	Antimony[103]

lithium tetraalkylborates would react with acid halides at room temperature, in the absence of catalyst, to produce mixed ketones. Uemara then developed a similar reaction that utilized tetraalkylborates and a palladium catalyst to prepare aryl ketones.[104] Later, Bumagin modified and improved this method.[105]

Recently, this lab reported that acid chlorides would react with trialkylboranes, under Suzuki reaction conditions, to afford aliphatic and aromatic ketones in good yields (3-1).[106] Subsequently, it was reported that aryl ketones can be prepared using aromatic boronic acids and aroyl chlorides under related reaction conditions.[105,106] The development of an efficient method to couple acid chlorides with trialkylboranes is the subject of the remaining sections of this chapter.

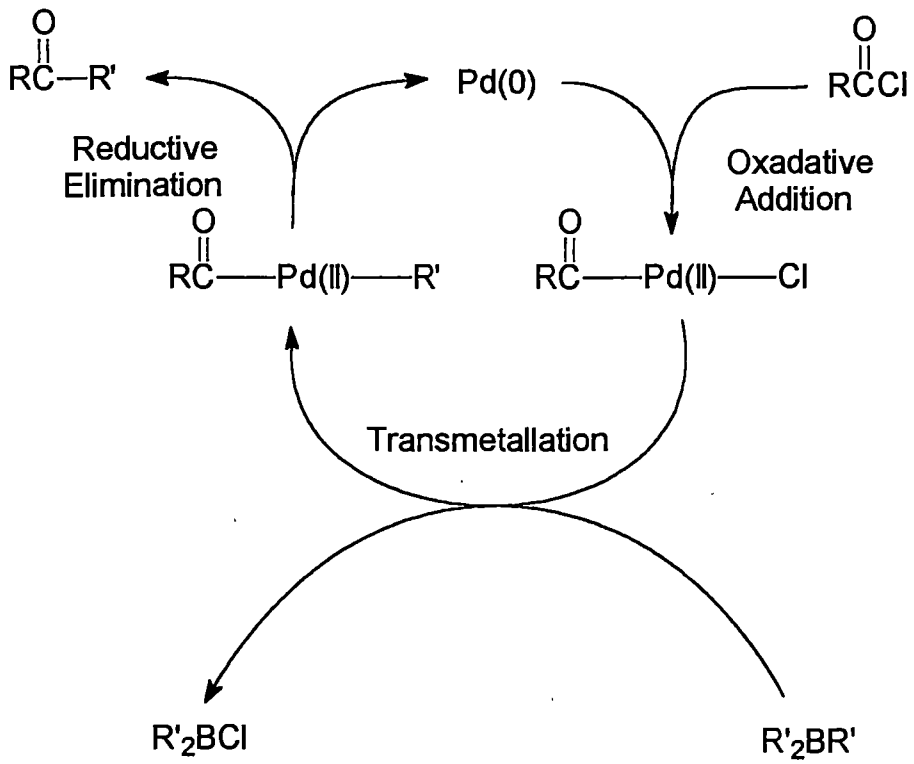


(3-1)

3.B Results

The quantity of palladium catalyst required was the first parameter studied. It was found that 20-40 mol % of the catalyst [tetrakis-(triphenylphosphine) palladium (0)] was necessary to obtain the maximum product yield (Entries 3-5, Table 3-3). This quantity is higher than that used in standard Suzuki coupling reactions and this might be due to differences in the transmetallation step (Scheme 3-1).[69]

Scheme 3-1. General Mechanism for Cross Coupling of Acid Chlorides with Trialkylboranes.



The mechanism of the reaction is presumed to involve the oxidative addition of the acid chloride to the palladium creating a palladium(II) chloride species. Transmetallation then occurs, creating a diorganopalladium(II) species . This intermediate then undergoes a reductive elimination to produce the ketone and regenerate the palladium (0) reagent.

The reaction temperature was also evaluated. A reasonable reaction time of three hours was achieved by conducting the experiments at reflux in THF (Entries 1-4, Table 3-3). The reaction does proceed at room temperature, however the reaction time is considerably longer (Entry 5, Table 3-3).

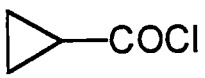
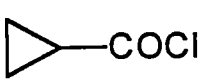
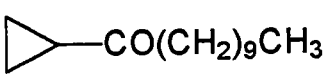
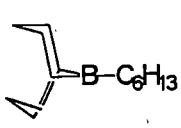
The reaction appears to be general in nature as aliphatic and aromatic acid chlorides participate equally well (Table 3-4). Also, alkenyl substituents easily tolerate the reaction conditions.

Table 3-3 . Reaction of Benzoyl Chloride With Tributylborane To Generate Valerophenone.[a]

Entry	$Pd(PPh_3)_4$	Temperature	Time (Hours)	Yield (%)[b]
1	0.05 mmol	65 °C	3	25
2	0.1 mmol	65 °C	3	41
3	0.2 mmol	65 °C	3	74
4	0.4 mmol	65 °C	3	75
5	0.2 mmol	21 °C	8	68

a) Equimolar concentrations of benzoyl chloride and tributylborane were used.
b) Isolated yields.

Table 3-4. Palladium Mediated Reaction of Acid Chloride With Trialkylborane.

No.	Acid Chloride	Trialkyl borane	Product	Yield (%)[a]
1	PhCOCl	$B(C_4H_9)_3$	$PhCO(CH_2)_3CH_3$	74
2	PhCOCl	$B(C_{10}H_{21})_3$	$PhCO(CH_2)_9CH_3$	68
3	$CH_3(CH_2)_8COCl$	$B(C_4H_9)_3$	$CH_3(CH_2)_8CO(CH_2)_3CH_3$	65
4	$CH_3(CH_2)_8COCl$	$B(C_{10}H_{21})_3$	$CH_3(CH_2)_8CO(CH_2)_9CH_3$	61
5	$(CH_3)_2CHCH_2COCl$	$B(C_4H_9)_3$	$(CH_3)_2CHCH_2CO(CH_2)_3CH_3$	56
6		$B(C_4H_9)_3$		38
7	$CH_2=CH(CH_2)_8COCl$	$B(C_4H_9)_3$	$CH_2=CH(CH_2)_8C(CH_2)_3CH_3$	65
8	$CH_2=CH(CH_2)_8COCl$	$B(C_{10}H_{21})_3$	$CH_2=CH(CH_2)_8C(CH_2)_9CH_3$	62
9	$(CH_3)_2CHCH_2COCl$	$B(C_{10}H_{21})_3$	$(CH_3)_2CHCH_2CO(CH_2)_9CH_3$	53
10	$(CH_3)_2CHCOCl$	$B(C_4H_9)_3$	$(CH_3)_2CHCO(CH_2)_3CH_3$	34
11		$B(C_{10}H_{21})_3$		35
12	PhCOCl		$PhCO(CH_2)_5CH_3$	47

a) Isolated yields.

3.C Conclusion

A new reaction using trialkylboranes in the Suzuki coupling of acid chlorides was developed. This protocol is advantageous in that the reaction temperatures are relatively mild and olifinic groups can be tolerated.

Further research should focus in four areas. First, the use of other acid halides should be explored. Suzuki coupling of other organohalides revealed a preference for the iodides and bromides. It would be interesting to see if this trend holds true for these acid derivatives.

Second, the use of mono and dihaloboranes in place of trialkylboranes should be investigated as an aid in efficiency. Under the current protocol, only one of three alkyl groups transfers from the trialkylborane. The use of the halogenated organoboron species would eliminate waste and could assist in the transmetallation process.

Third, this methodology could be used to create α,β-unsaturated ketones by transferring alkenyl and alkynyl groups from the boron species to the acid halide. Negishi reported that the tetraalkylborate method was not successful in this transformation,[87b] however the use of boronic acids or dichloroboranes may help facilitate the transfer.

Fourth, acid halides should be exposed to the solventless Suzuki process that is currently under development.[32] This procedure utilizes potassium fluoride-

doped alumina and it is possible that this basic surface may help increase product yields.

3.D Experimental

3.D.1 General

All ^{1}H and ^{13}C NMR spectra were recorded on a 250 MHz Bruker AC250 spectrometer. All glassware, syringes and needles were dried in an oven heated to 250 ^{0}C for at least 12 hours and then cooled under nitrogen prior to use. THF was dried over sodium benzophenone ketyl and distilled prior to use.[50] Reactions were magnetically stirred and monitored by TLC. Products were purified by flash chromatography using 230-400 mesh ASTM 60 Å silica gel.[51]

3.D.2 General Procedure for the Coupling of Acid Chlorides with Trialkylboranes.

Into a flame dried, nitrogen-flushed, 3-necked flask was placed the acid chloride (1.0 mmol) and palladium catalyst (0.2 mmol). THF (10 mL) was added and the mixture was stirred for 10 minutes. Potassium acetate (2.0 mmol) and trialkylborane (1.0 mmol) were introduced and the resulting mixture was heated at reflux (65 ^{0}C) for 3 hours. Upon cooling, the reaction was quenched with water (10 mL) and the aqueous layer extracted with ether (3 x 20 mL). The combined organic extracts were washed with saturated brine solution, dried over magnesium sulfate and the solvent removed at reduced temperature prior to

purification.

3.D.3 1-Phenyl-1-pentanone[108]

This material was prepared from benzoic acid chloride (1.0 mmol, 0.14 g) and tributylborane (1.0 mmol, 1.0 mL of 1.0 M solution in THF) to produce an isolated yield of 0.12 g, 74%, according to the general procedure. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.97-7.94 (m, 2H), 7.55-7.42 (m, 3H), 2.98 (t, 2H, J = 7.3 Hz), 1.75 (pent, 2H, J = 7.3 Hz), 1.40 (sext, 2H, J = 7.3 Hz), 0.95 (t, 3H, J = 7.3 Hz); ^{13}C-NMR ($CDCl_3$) δ 200.55, 137.06, 132.81, 128.51, 128.02, 38.31, 26.47, 22.47, 13.90.

3.D.4 1-Phenyl-1-undecanone[109]

This material was prepared from benzoic acid chloride (1.0 mmol, 0.14 g) and tridecylborane (1.0 mmol, 0.43 g) to produce an isolated yield of 0.17 g, 68%, according to the general procedure. Spectral data was consistent with previously prepared samples.

3.D.5 5-Tetradecanone[110]

This material was prepared from decanoic acid chloride (1.0 mmol, 0.19 g) and tributylborane (1.0 mmol, 1.0 mL of 1.0 M solution in THF) to produce an isolated yield of 0.15 g, 65%, according to the general procedure. ^{1}H NMR ($CDCl_3$/ TMS) δ 2.45-2.30 (m, 4H), 1.55-1.47 (m, 4H), 1.40-1.20 (m, 14H), 0.95-

0.83 (m, 6H). ^{13}C-NMR ($CDCl_3$) δ 211.64, 42.82, 42.51, 31.86, 29.42, 29.27, 25.99, 23.90, 22.65, 22.36, 14.07, 13.84.

3.D.6 10-Icosanone

This material was prepared from decanoic acid chloride (1.0 mmol, 0.19 g) and tridecylborane (1.0 mmol, 0.43 g) to produce an isolated yield of 0.18 g, 61%, according to the general procedure.

3.D.7 2-Methyl-4-octanone[111]

This material was prepared from 2-methylbutanoic acid chloride (1.0 mmol, 0.11 g) and tributylborane (1.0 mmol, 1.0 mL of 1.0 M solution in THF) to produce an isolated yield of 0.080 g, 56%, according to the general procedure. Spectral data was consistent with previously prepared samples.

3.D.8 1-Cyclopropyl-1-pentane[112]

This material was prepared from cyclopropanecarboxylic acid chloride (1.0 mmol, 0.11 g) and tributylborane (1.0 mmol, 1.0 mL of 1.0 M solution in THF) to produce an isolated yield of 0.050 g, 38%, according to the general procedure. ^{1}H NMR ($CDCl_3$/ TMS) δ 2.55 (t, 2H, J = 7.0 Hz), 1.94 (m, 1H), 1.3-1.7 (m, 4H), 0.93 (t, 3H, J = 7.0 Hz), 0.8-1.1 (m, 4H).

3.D.9 14-Pentadecen-5-one

This material was prepared from undecanoic acid chloride (1.0 mmol, 0.14 g) and tributylborane (1.0 mmol, 1.0 mL of 1.0 M solution in THF) to produce an isolated yield of 0.15 g, 65%, according to the general procedure. ^{1}H NMR ($CDCl_3$/ TMS) δ 5.85-5.70 (m, 1H), 5.05-4.85 (m, 2H), 2.38 9t, 4H, J = 7.3 Hz), 2.04-1.95 (m, 4H), 1.65-1.45 (m, 2H), 1.40-1.15 (m, 4H), 0.90 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 211.16,138.70, 113.96, 42.60, 42.32, 33.63, 29.14, 28.91, 28.75, 25.82, 23.70, 22.22, 13.67.

3.D.10 Heniicosen-11-one

This material was prepared from undecenoic acid chloride (1.0 mmol, 0.14 g) and tridecylborane (1.0 mmol, 0.43 g) to produce an isolated yield of 0.18 g, 62%, according to the general procedure. ^{1}H NMR ($CDCl_3$/ TMS) δ 4.05-3.95 (m, 3H), 2.42-2.22 (m, 4H), 2.65-2.50 (m, 6H), 1.35-1.1 (m, 20H), 0.95-0.85 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 211.61, 173.97, 127.13, 64.05, 42.80, 42.49, 34.39, 31.84, 30.71, 29.41, 29.25, 25.98, 25.02, 23.89, 22.64, 22.37, 19.14, 14.05.

3.D.11 2-Methyl-4-tetradecanone

This material was prepared from 2-methylbutanoic acid chloride (1.0 mmol, 0.12 g) and tridecylborane (1.0 mmol, 0.43 g) to produce an isolated yield of 0.12 g, 53%, according to the general procedure.

3.D.12 2-Methyl-3-heptanone[113]

This material was prepared from 2-methylpropanoic acid chloride (1.0 mmol, 0.11 g) and tributylborane (1.0 mmol, 1.0 mL of 1.0 M solution in THF) to produce an isolated yield of 0.040 g, 34%, according to the general procedure. Spectral data was consistent with previously prepared samples.

3.D.13 1-Cyclopropyl-1-undecane[114]

This material was prepared from cyclopropanecarboxylic acid chloride (1.0 mmol, 0.11 g) and tridecylborane (1.0 mmol, 0.43 g) to produce an isolated yield of 0.095 g, 35%, according to the general procedure. ^{1}H NMR ($CDCl_3$/ TMS) δ 2.53 (t, 2H, J = 7.0 Hz), 1.93 (m, 1H), 1.2-1.7 (m, 16H), 0.88 (t, 3H, J = 7.0), 0.8-1.1 (m, 4H).

3.D.14 1-Phenyl-1-heptanone[115]

This material was prepared from benzoic acid chloride (1.0 mmol, 0.14 g) and *B-n*-hexyl-9-BBN (1.0 mmol, 0.21 g) to produce an isolated yield of 0.090g, 47%, according to the general procedure. ^{1}H NMR ($CDCl_3$/ TMS) δ 7.98-7.94 (m, 2H), 7.49-7.43 (m, 3H), 2.96 (t, 2H, J = 7.4 Hz), 1.75-1.71 (m, 2H), 1.33-1.25 (m, 6H), 0.89 (t, 3H, J = 6.3 Hz); ^{13}C-NMR ($CDCl_3$) δ 200.58, 137.10, 132.82, 128.52, 128.03, 38.62, 31.64, 29.03, 24.33, 22.52, 14.02.

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PART II

BORONATED COX-2 INHIBITORS AS POTENTIAL BORON NEUTRON CAPTURE THEREPY AGENTS

CHAPTER 1

BNCT AND COX-2 INHIBITORS

1.A Introduction

Part II of this dissertation deals with inhibitors of the cyclooxygenase-2 (COX-2) enzyme[1] and their potential use in a form of cancer treatment known as boron neutron capture therapy (BNCT).[2]

1.B BNCT- Background and History

BNCT is a binary form of cancer treatment that utilizes the interaction between a thermal (slow) neutron and a boron-10 atom according to the follow reaction:

$$^{10}B + {}^{1}n_{th} \rightarrow {}^{11}B \rightarrow {}^{4}He + {}^{7}Li + Gamma + 2.31\ MeV \quad (1\text{-}1)$$

The toxicity of the nuclear decay products and the energy emitted is sufficient to destroy tissue within 10 microns or approximately one cell diameter. In order for BNCT to be effective, three critereia must be met. First, the boron carrier must be introduced to the tumor, normally via the blood. Second, there must be

access to a sufficiently powerful neutron source, normally a nuclear reactor. Appropriate reactors are currently available for this purpose in the United States, Japan and the Netherlands. Third, the ratio of the concentration of the boronated compound in the tumor to that in the normal tissue (or the blood) must be significantly larger than one.

Neutron capture therepy was first proposed by Gordon Locher in 1936.[3] Locher theorized that isotopes with large thermal neutron capture cross sections (Table 1-1) could readily be used for medicinal purposes, including the treatment

Table 1-1. Nuclides With High Thermal Neutron Capture Cross Sections (In Barns[a])[4]

^{10}B = 3850	^{149}Sm = 46000	^{169}Dy = 2620
^{6}Li = 870	^{155}Eu = 14000	^{199}Hg = 2500
^{113}Cd =24000	^{157}Gd = 200,000	^{235}U = 549

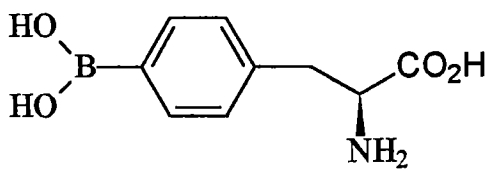
a) 1 Barn = 1×10^{-24} cm^2

of cancer. In 1940, Kruger[5] conducted *in vitro* studies on various types of neoplastic tissues. It was found that BNCT could be effective for the destruction of tumors. Kruger's findings also suggested that *in vivo* experiments would be successful if sufficient ^{10}B could be placed in the tumor. Several months later, Zahl, Cooper and Dunning[6] reported the results of *in vivo* BNCT studies carried out on mice with transplanted tumors. They reported that, after injecting the tumor with various boric acid solutions and then exposing the mice to neutron irradiation, significant reduction in the size of the tumors was observed. In

1952, Sweet and Javid proposed using BNCT to treat human brain tumors.[7] They injected varying concentrations of borax ($Na_2B_4O_7 \cdot 10H_2O$) intravenously into 58 patients with brain tumors. They found tumor to normal tissue ratios appeared adequate for BNCT and the concentration of ^{10}B in the scalp was low enough to not interfere with the procedure. Later that year, Sweet, Javid and Brownell, calculated the effects that BNCT would have on the brain.[8] The results, based on irradiation experiments performed at Brookhaven National Laboratories, suggested that BNCT was a viable method for treating tumors. However, the authors also found that the neutrons being used were not sufficiently penetrating to reach neoplastic tissue deep in the brain. Sweet and his co-workers reported the results of their BNCT studies conducted on human patients[9] and the initial results suggested that the treatment had reduced the size of the tumors in several of the patients. Unfortunately all patients died within one year of the initial treatment. Due to the lack of a dramatic success, BNCT treatments on human subjects were halted in the United States in 1962. However, human studies were initiated by Hiroshi Hatanaka in Japan in 1968.[10] Hatanaka was a member of Sweet's team in the US and chose to use a similar protocol for his experiments. Sodium mercaptoundecahydrododecaborate ($Na_2B_{12}H_{11}SH$, BSH), which Sweet used in his later trials, was used as the boron agent. The results of Hatanaka's work were striking, although some have questioned the empirical nature of his experiments and his inconsistent results.[1b] Of the 87 patients Hatanaka treated between 1968 and 1987, 18 lived more

than five years and nine of those lived in excess of 10 years.[11] Hatanaka's accomplishments kindled interest in BNCT around the world. Several groups in Japan began using BSH and *p*-boronophenylalanine (BPA, Figure 1-1) to treat brain and skin cancer.[12] The European Collaboration was formed and began treating patients in the late 1980's.[13] Clinical trials began again in the United States in 1994.[14] The American group has not had the success of the Japanese groups and they have been plagued by recurrence of many of the tumors. The results suggest that not all of the tumor is being treated. This could be due to poor neutron penetration or nonhomogeneous doses of boron-10 in the tumor. The slow pace of the Europeans and the modest results of the Americans has not diminished interest in BNCT. There are neutron sources and/or NCT centers being constructed currently in Hungary,The Czeck Republic, China, Slovenia, Sweden, Taiwan, Thailand, South America and the US.[15]

Figure 1-1. *p*-Boronophenylalanine.



BPA

1.C Potential Capture Agents

Although BSH and BPA are the only compounds currently being used in clinical trials, many groups have been diligently working on compounds that exhibit high tumor to normal tissue selectivity. In the following sections, a brief description is presented of the major classes of agents that are being explored.

1.C.1 Amino Acids and Amines

The brain is protected by a membrane called the blood-brain barrier (BBB). The purpose of the BBB is to keep hydrophilic compounds away from the delicate tissue of the brain and spinal cord.[1b] The blood-brain barrier is commonly weakened or non-existent at the site of neoplastic tissue. This fact, coupled with the knowledge that amino acids are the building blocks of the body, make amino acids an attractive ^{10}B carrier. Additionally, nitrogen containing compounds, such as amines, are often used as DNA markers.[16] It is reasoned that attaching a boronated marker to the DNA of the tumor cell would increase the odds of killing that cell by neutron irradiation.

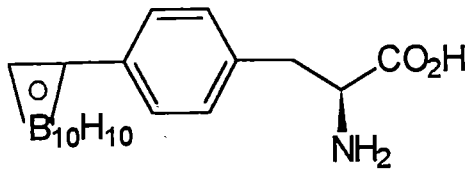
Of the compounds in this class, BPA and it's derivatives have been the most extensively studied.[17] As previously mentioned, BPA is one of only two compounds that is currently being used in human clinical trials. There have been many efforts made to alter the structure of this molecule in an attempt to increase it's hydrophilicity and boron concentration at the tumor site. The most

interesting alteration to BPA has been the addition of a carborane cage to the molecule (compound **1**, Table 1-2). These polyhedral compounds allow the boron concentration to increase at the tumor site without increasing the total number of carrier molecules. The most commonly used polyhedral boranes are the *ortho*, *meta* and *para* carborane shown as structures **7A-C,**.[18] Other naturally occurring amino acids, such as alanine and tyrosine, have also been derivatized (**2** and **3**) in this manner and examined as deliverly agents.[17d,e] Our lab has explored the non-naturally occurring amino acids **4**, **5** and **6**.[19]

It should be noted that carboranes are lipophilic. This means that, although the boron concentration can be increased due to a larger number of boron atoms per molecule, polarity decreases in the process. Therefore, hydrophilic groups have been introduced in an effort to counteract the lipophilic nature of the carboranes. Compounds **5, 8**[17f] and **9**[20] are examples of this approach.

The carborane technology has also been applied to amines and polyamines. Tumor specific, carborane containing compounds such as spermidine (**10**)[21], Hoechst 33258 (**11**)[22] and nitroimidizoles (**12**)[23] have shown decreased affinity for the tumor cell. Attempts are being made to improve the biodistribution characteristics of these compounds for use in BNCT.

Table 1-2. Amines and Amino Acids Being Studied as Potential BNCT Agents



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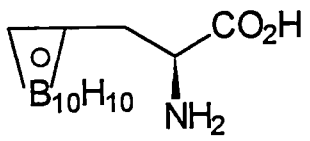

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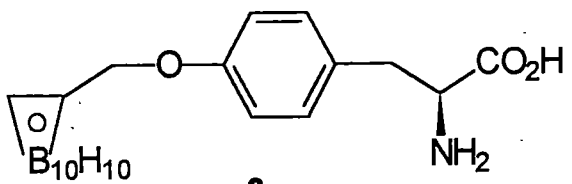

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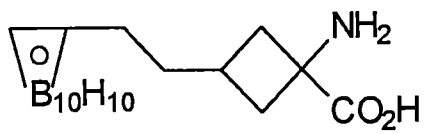

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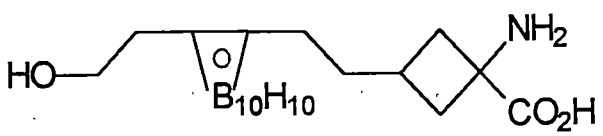

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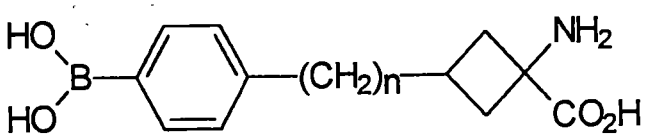

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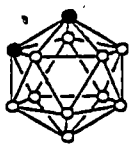
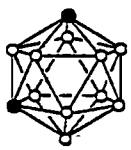
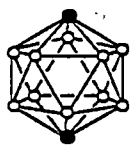


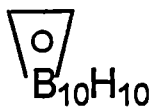
o-Carborane



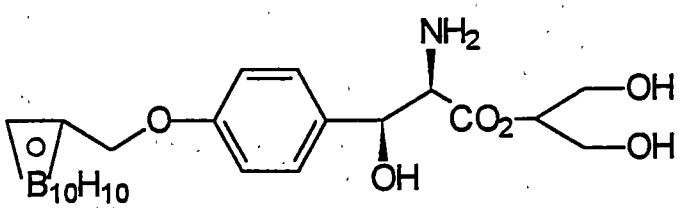
m-Carborane



p-Carborane



7A **7B** **7C** **7(General)**



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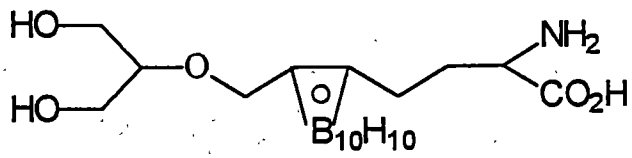

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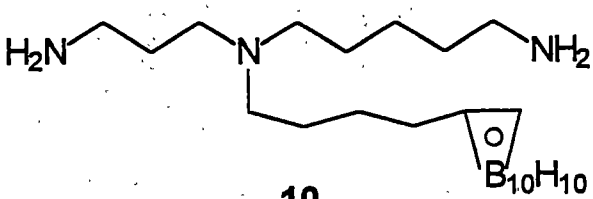

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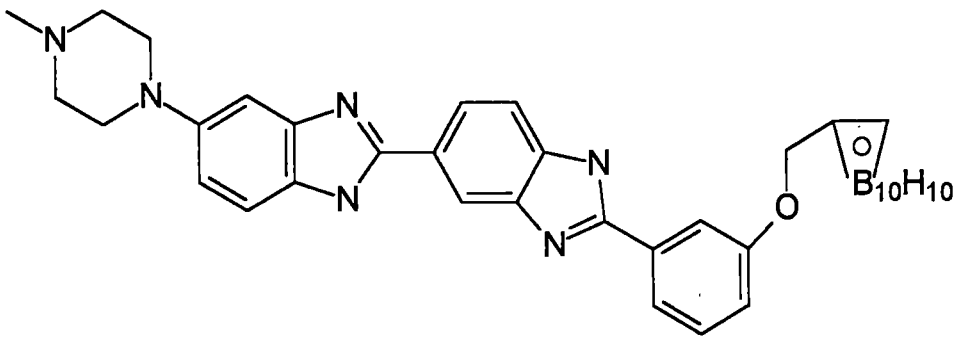

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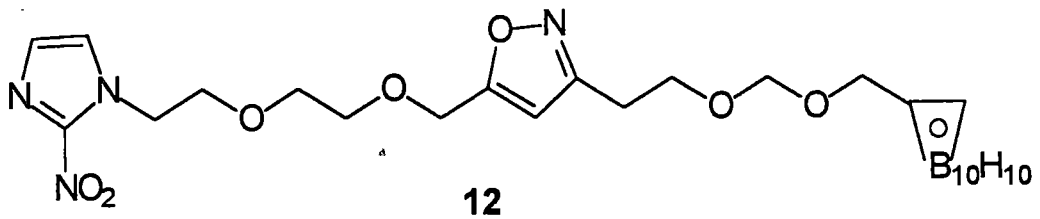


12

1.C.2 Nucleosides, Nucleotides and Nucleic Acids [26]

Nucleosides and nucleotides are building blocks for nucleic acids and are involved in many biological pathways.[24] The most well known nucleic acid is deoxyribonucleic acid or DNA. Due to its importance in the building of cells, it is easy to see why this class of compounds is being studied as a potential boron carrier. In fact it has been estimated that, by introducing boron into the cell nucleus via the DNA, the effectiveness of BNCT would double.[25]

Compounds in this class are composed of a sugar, an azo base and a phosphoric acid. Nucleosides do not have the phosphorous component. A large number of compounds of this type use uracil units as the base and have the general structure shown in Figure 1-2. The boron, usually as a carborane cage, has been placed in the uracil ring (**13**)[27], on the uracil ring (**14**)[28] and at various positions on the sugar (**15**,**16**, Table 1-3).[29] As described in the previous section, attempts have been made to increase the hydrophilicity of the carborane containing copounds.[30]

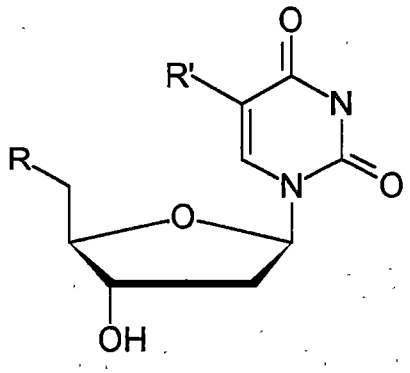
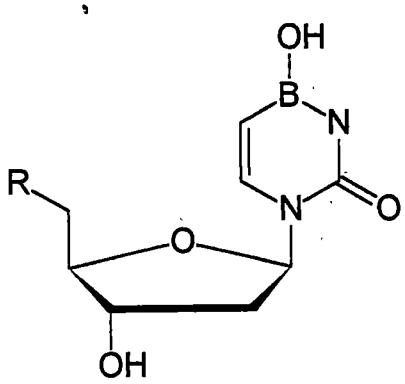


Figure 1-2. General Structure of Nucleosides and Nucleotides.

Table 1-3. Boron Containing Uracil Nucleosides and Nucleotides.



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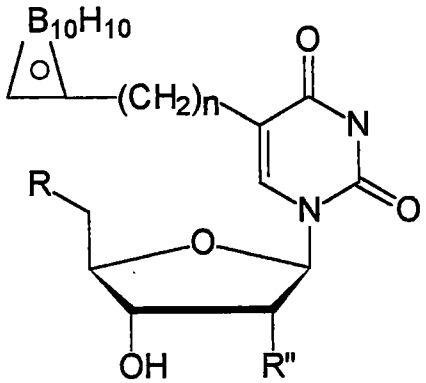

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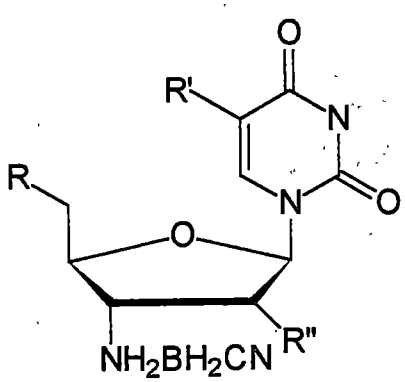

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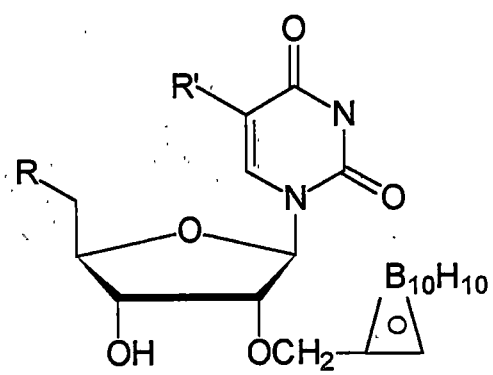


16

1.C.3 Antibodies and Immunoconjugates

Antibodies are proteins that bind to foreign substances in the body called antigens. To utilize antibodies for BNCT a boron containing group, called a conjugate, must be added to an antibody. The conjugate is generally attached to the antibody at a lysine residue via an amide bond (Figure 1-3). This approach has not been successful to date due to loss of activity of the antibody.[1b]

However, recently modifications have been reported which show promise.[32] Oligomeric carboranyl diphosphate ester conjugates (Figure 1-4) have been explored as an alternate method to utilize this technique. Early results indicate this may be a promising approach.[33]

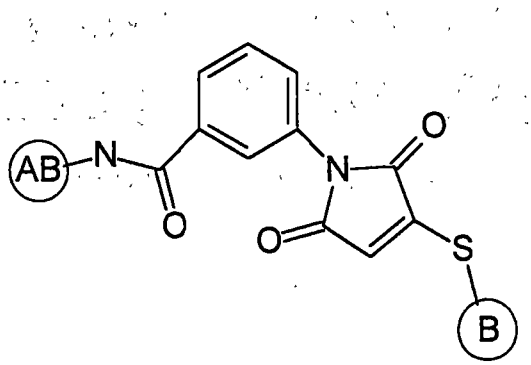


Figure 1-3. Example of Boronated Antibody.

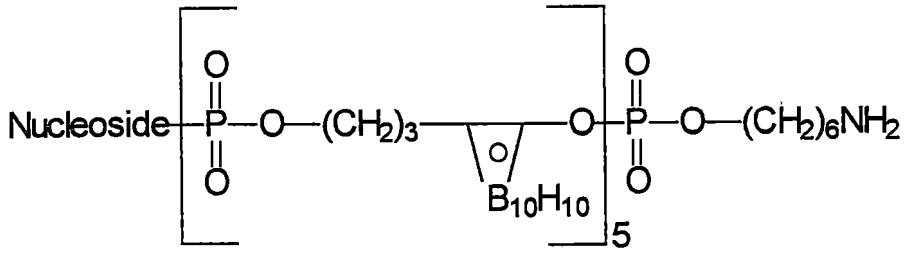


Figure 1-4. Carborane Containing Oligomeric Diphosphate Ester.

1.C.4 Porphyrins

Porphyrins are extremely important compounds in biological systems. For example, hemoglobin and all varieties of chlorophyl contain some type of porphyrin. Porphyrins are currently used in a binary cancer treatment known as photodynamic therepy (PDT).[1b,34] PDT studies have shown that porphyrins tend to localize in tumor cells and remain there indefinitely. Figure 1-5 contains an

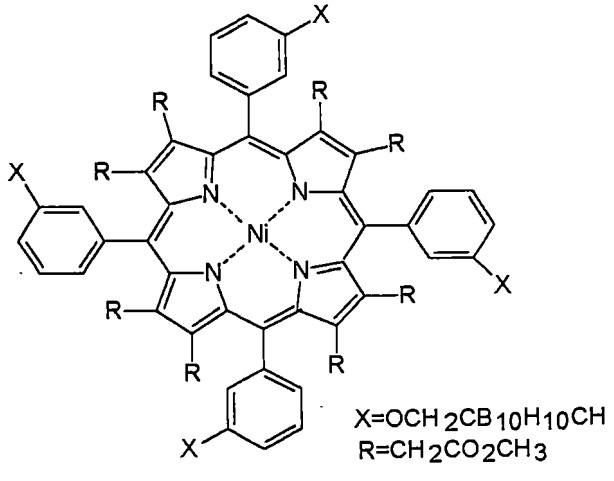


Figure 1-5. Carborane Containing Porphyrin.

example of a porphyrin that is currently of significant interest to scientists in the BNCT field.[35]

1.C.5 Liposomes

Liposomes are spherical lipid bilayers that form in aqueous media and have a large affinity for neoplastic tissue.[1d] They usually contain an aqueous center and are often used to deliver highly polar medications.[36] BSH[37], various polyhedral borane compounds[38] and highly polar amines, like those seen in Figure 1-6,[39] have been encapsulated in liposomes and appear to have significant potential as BNCT agents in initial studies. Boronated derivatives of naturally occuring steroids, such as cholesterol, have been encapsulated and are currently being evaluated.[40]

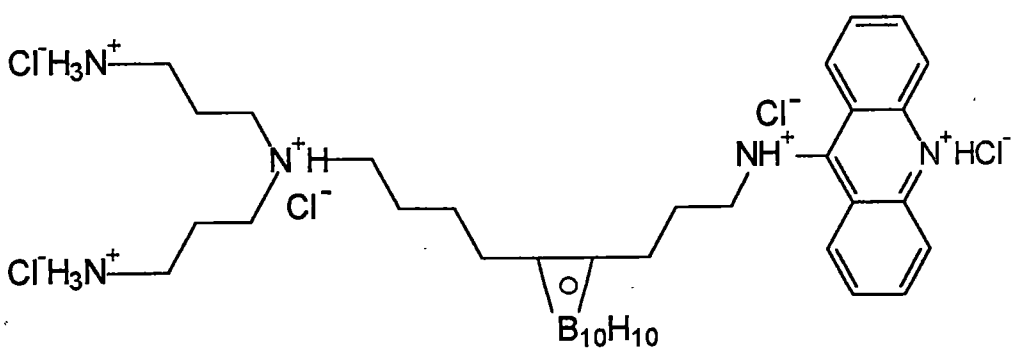


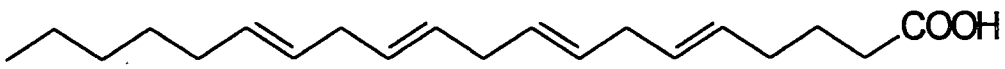
Figure 1-6. Example of a Highly Polar Amine.

1.C.6 Cyclooxygenase Inhibitors

It has recently been learned that two forms of the cyclooxygenase enzyme exist.[41] One form, called cyclooxygenase-1 (COX-1), expresses itself in most normal tissues, including the gastrointestinal tract, liver and kidneys.[1] The second form, known as cyclooxygenase-2 (COX-2), is present in inflammatory and cancer tissues.[1c,45,47,48] This fact makes COX-2 inhibitors excellent targets for a new class of compounds for the delivery of boron to cancer cells and for use in BNCT. The remainder of this chapter will briefly discuss the history of the COX enzyme and the various classes of COX-2 inhibitors that are currently available.

1.D Cyclooxygenase - History and Background

It has long been known that aspirin is both a pain reliever and anti-inflammatory agent. It is also well known that aspirin is damaging to the stomach and kidneys. For many years, research has been conducted to understand how aspirin and its analgesic relatives work. In 1971, J.R Vane began to unravel the mystery. Vane showed that aspirin and aspirin-like molecules called non-steroidal anti-inflammatory drugs (NSAIDs) inhibited the enzyme, called cyclooxygenase (COX), that produces prostaglandin.[1a] Prostaglandins are cyclopentanoic acids that are derived from aracidonic acid (Figure 1-7). These prostaglandins help regulate metabolism in the cell in which



Arachidonic acid

Figure 1-7. Structure of Aracidonic Acid.

they are created.[24] In 1990, it was discovered that there were actually two forms of the COX enzyme.[41] The two forms were designated COX-1 for the original and COX-2 for the new form. It was soon discovered that COX-1 was found in all cells but COX-2 was only expressed in inflammatory cells.[1c,47] It was also discovered that it was the inhibition of the COX-1 enzyme that caused the gastrointesinal problems.[43] The pharmaceutical industry invested immense resourses in an effort to develop, test and market a COX-2 specific inhibitor. Searle introduced Celebrex in 1999 and Merck soon followed with Vioxx (Figure 1-8). Johnson and Johnson, Japan Tobacco, Abbott, Boehringer-Ingelheim, American Home Products, Procter and Gamble and Dupont all have compounds in the developmental stages.[42] In addition to their analgesic and anti-inflammatory properties, COX-2 inhibitors may have potential in the treatment of Alzheimer's disease[44,48] and cancer of the colon, kidney and brain.[45,48]

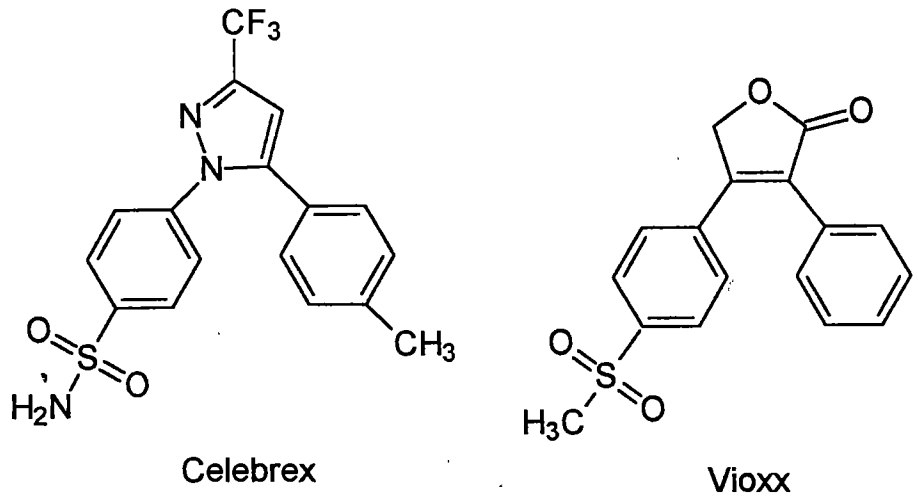


Figure 1-8. Structures of Celebrex and Vioxx.

1.E COX-2 Inhibitors

The following sections will describe the major classes of COX-2 inhibitors.

1.E.1 1,5-Diarylpyrrazole Derivatives

Celebrex belongs to this class of compounds being developed by Searle Pharmaceuticals.[46] Compounds in this class have the general structure presented in Figure 1-9 and can contain a large variety of substituents on the pyrrazole ring as well as the A aromatic ring. Ring C must contain a sulfonamide or methylsulfonyl group in order to be active. This class of compounds will be discussed in greater detail in chapter 2.

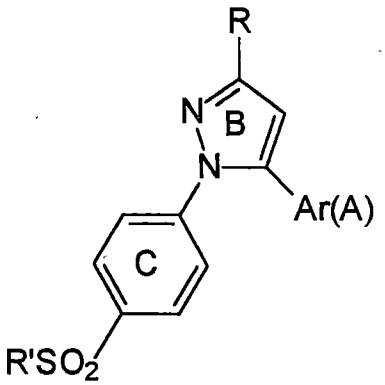


Figure 1-9. General Structure of 1,5-Diarylpyrrazole Derivatives

1.E.2 3,4-Diarylfuranone Derivatives

Vioxx is a member of this class of compounds with the general structure represented in Figure 1-10. In animal studies and human blood assay studies, Vioxx was shown to have a better selectivity for the COX-2 enzyme than Celebrex.[49] It should be noted that Merck, the makers of Vioxx, conducted this study and no independant corroboration has been found to support their claims. Merck has two other compounds in this class that have shown promise as COX-2 inhibitors. The are known as DFU[50] and L-784,512 (Figure 1-11).[51] Merck is also altering these two structures in an effort to improve the COX-2 selectivity.[52]

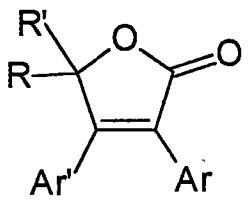


Figure 1-10. General Structure of 3,4-Diarylfuranone Derivatives.

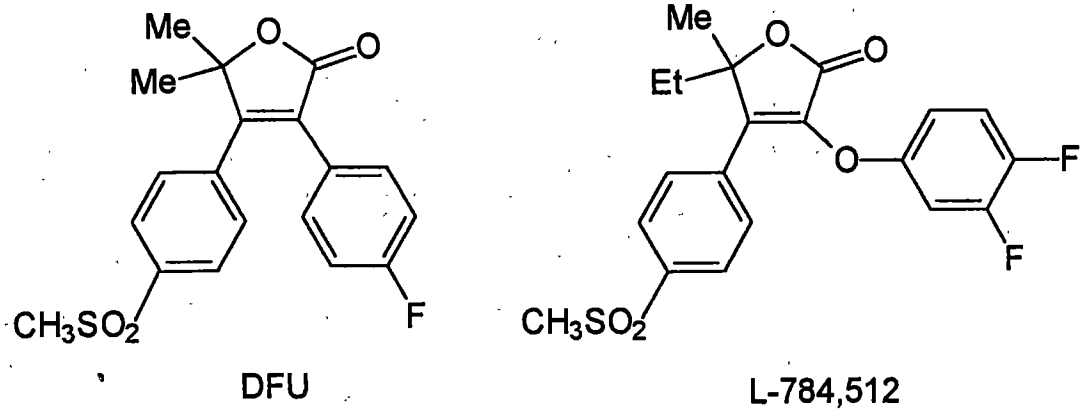


Figure 1-11. Structures of DFU and L-784,512.

1.E.3 Acetoxyphenyl Alkyl Sulfides

A group at the Vanderbilt University School of Medicine is developing a class of compounds that are related to the largest selling NSAID, aspirin. This group claims that compound **17** (Figure 1-12) and it's derivatives covalently bond to the enzyme and are quite potent in their selectivity.[53, 1e]

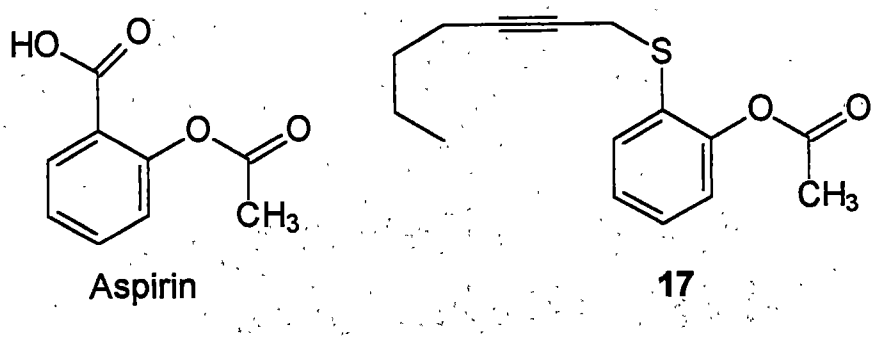


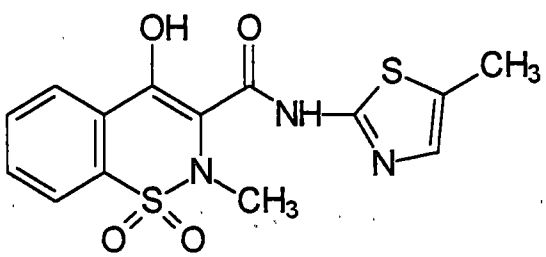
Figure 1-12. Aspirin and a Related Compound.

1.E.4 Thiazole Derivatives

Boehringer-Ingelheim's Meloxicam (Figure 1-13) is the most well known member of this group of compounds. Meloxicam was introduced as an NSAID before the COX-2 isoform was discovered[54], it is still being evaluated and is not currently being marketed as a specific COX-2 inhibitor.[55]

Merck has some unique thiazole-triazole derivatives which are claimed to be potent inhibitors of COX-2 and early tests have revealed biological activity.[56] Compound **18** (Figure 1-14) appears to be the most promising derivative but more testing is needed to determine if it is capable of competing with Vioxx.

Searle, a division of Monsanto and the maker of Celebrex, also has compounds in this class. Although **19** (Figure 1-14) is highly COX-2 selective it is not expected to be as effective as Celebrex. These compounds will continue to be studied in order to confirm this statement.[57]



Meloxicam

Figure 1-13. Structure of Meloxicam.

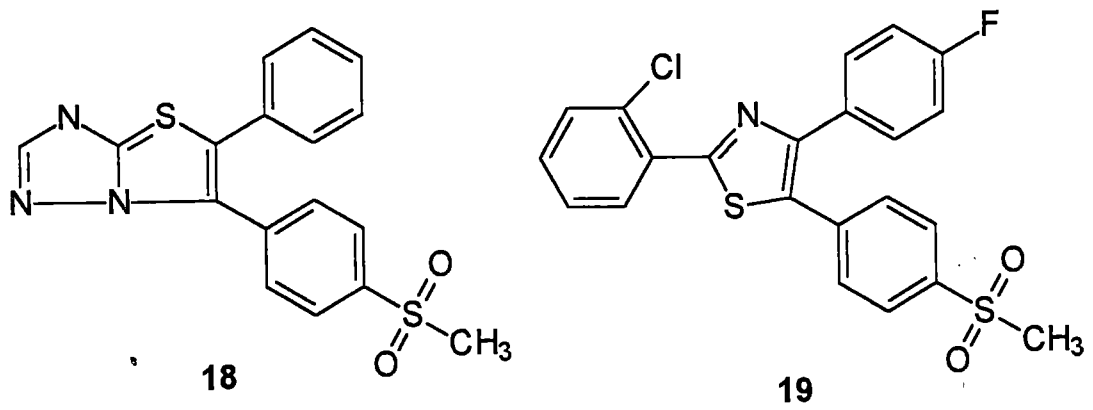


Figure 1-14. Structures of Two Thiazole Derivatives.

1.E.5 Oxazole Derivatives

Oxazoles are closely related to the thiazoles discussed in the previous section. The sulfur in the five membered ring is simply replaced with an oxygen. Searle Pharmaceuticals has made a series of 4,5-diaryloxazoles and they have found SC-299 (Figure 1-15) to be the most promising of these compounds.[63] Japan Tobacco has prepared a very similar compound known as JTE 522 (Figure 1-15).[64] Both molecules have been shown to be excellent COX-2 inhibitors and are now being subjected to pre-clinical testing.

1.E.6 Methylsulfanilid Containing Ethers and Thioethers

Compounds in this class differ from most other COX-2 selective NSAIDs in that they possess a sulfanilide connectivity ($R\text{-}NHSO_2R'$) as opposed to the more traditional sulfonamide and methylsulfonyl groups. Two of these

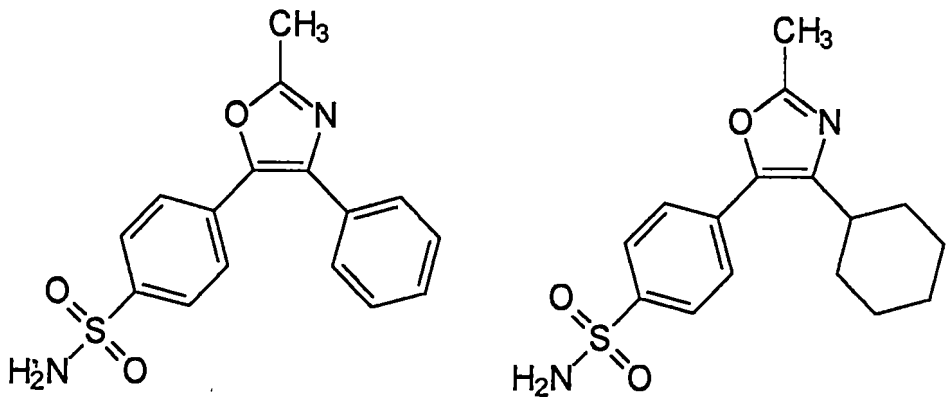
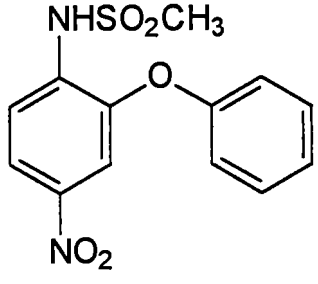


Figure 1-15. Structures of SC 299 and JTE 522.

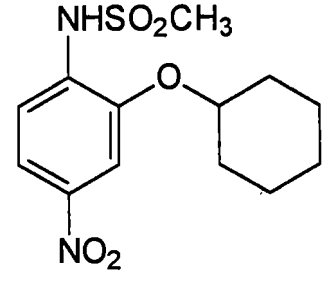
compounds, Nimesulide[58] and Taisho Pharmaceuticals' NS 398[59], have been on the market as pain relievers for some time. Both of these compounds display the analgesic abilities of NSAIDs without the gastrointestinal problems that are common with the non-specific COX inhibitors.[60] Nimesulide and NS 398 (Table 1-4) are similar in their ability to inhibit the COX-2 enzyme, but NS 398 has received more attention as an anticancer[61] and anticonvulsive[62] agent.

Also in this class are Flusilide from Ciba Geigy[65] and Merck's L-745,337.[66] Both of these compounds are undergoing further evaluation. Merck is also examining replacement of the difluorophenyl ring with various heteroatom

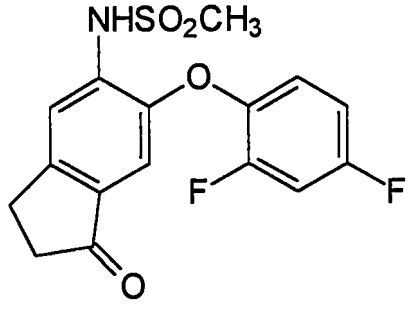
Table 1-4. Thioesters and Thioethers.



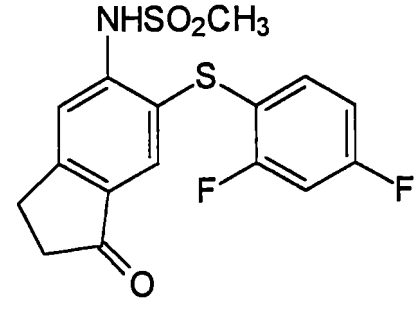
Nimesulide



NS 398



Flusolide



L-745,337

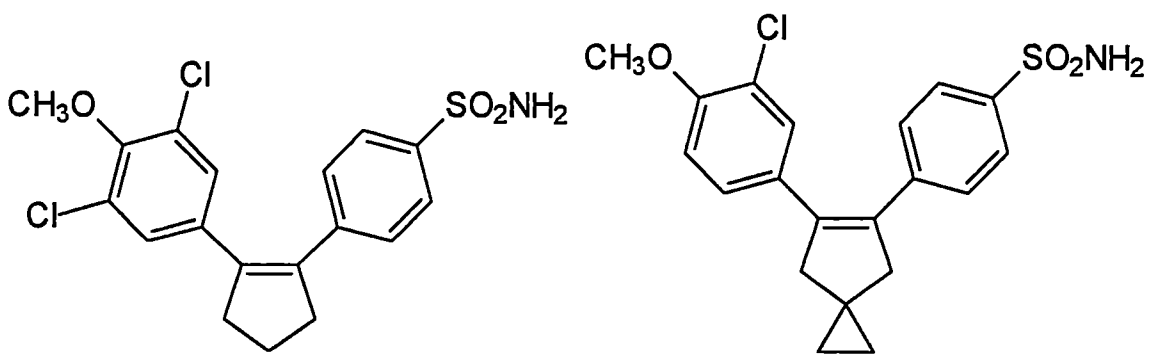
containing ring systems.[67]

1.E.7 Diarylcylopentenes and Spiro Derivatives

Searle Pharmaceutical is exploring compounds in this class. They have found both to be potent COX-2 inhibitors in pre-clinical testing and compounds **20**[68] and **21**[69] appear to be the most active (Figure 1-16).

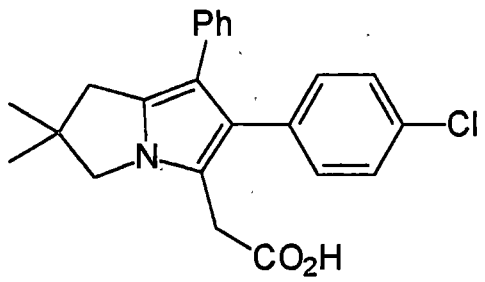
1.E.8 Pyrrolizines and Pyridines

There are several groups studying compounds in this group. All of these compounds are in pre-clinical stages of development. ML-3000 (Figure 1-17) is a pyrrolizine being developed in europe.[70] Merck is working on pyridines like **22** and **23** (Figure 1-18).[71] Apparently the heteroatom containing side chains on **23** are influencing the COX-2 potency, selectivity and activity of the compounds.



20 **21**

Figure 1-16. Diarylcyclpentene and Spiro Derivatives.

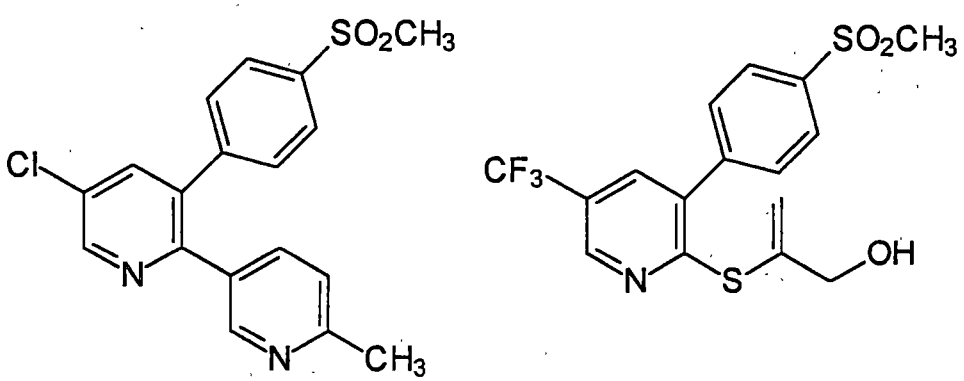


ML-3000

Figure 1-17. Structure of ML-3000.

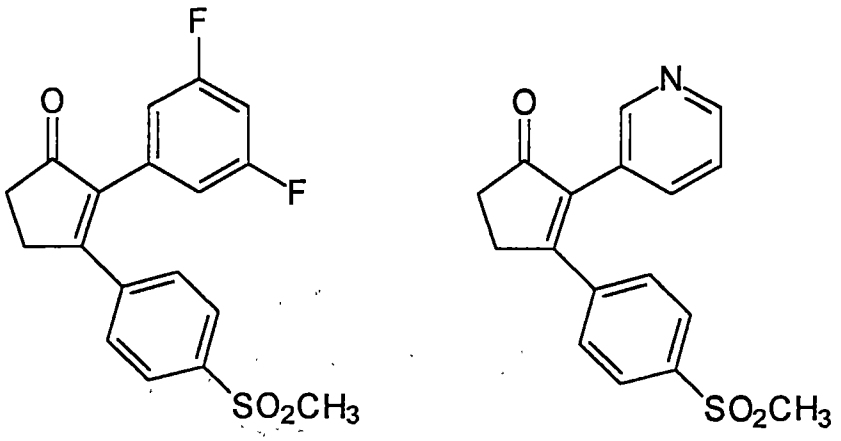
1.E.9 Cyclopentenone Derivatives

Merck is also interested in Vioxx derivatives that have a cyclopentenone central ring as opposed to a lactone. Compounds **24** and **25** (Figure 1-19) are very promising examples of these types of compounds. Merck claims that the halogen and pyridyl ring substitutions greatly increase the COX-2 selectivity.[72]



22 **23**

Figure 1-18. Pyridine Derivatives Being Developed by Merck.

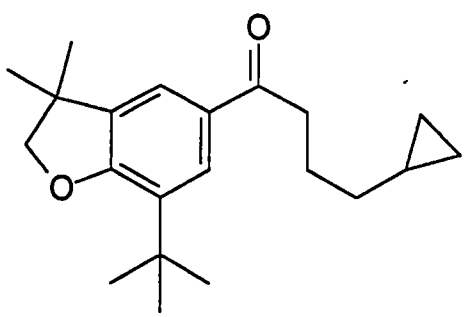


24 **25**

Figure 1-19. Cyclopentenone Derivatives.

1.E.10 Benzofuran Derivatives

Proctor and Gamble is developing benzofuran derivatives such as **26** (Figure 1-20).[73] They have examined heteroatom ring systems and found the furan to be the most active.[74] Early results also indicate that altering the alkyl side chain aids with solubility, selectivity and activity.[75]



26

Figure 1-20. Benzofuran Compound Being Developed By DuPont.

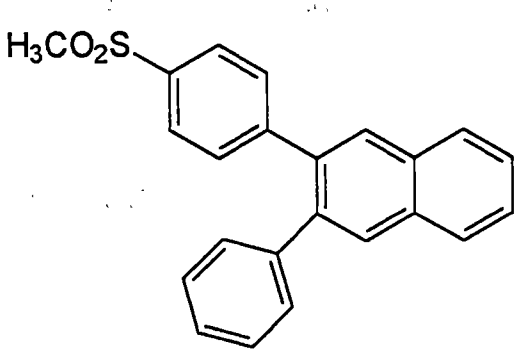
1.E.11 Terphenyl Derivatives

DuPont Pharmaceuticals is altering the central ring of terphenyl structures.[76] Compound **27** (Figure 1-21) appears to be the most selective for the COX-2 enzyme and is also the most bioavailable and active.

1.F Statement of Purpose

Although BNCT has potential as a cancer treatment, results to date in the United States have been moderate at best. This outcome is partially due to the lack of a boron carrier which selectively delivers high boron concentrations to the tumor.

It is known that high levels of prostaglandins are found in cancer tissues and this is attributed to the presence of COX-2 enzymes.[43,45] There is strong evidence that inhibiting the COX-2 enzyme reduces the formation of tumors and



27

Figure 1-21. Naphthalen Derivative of Terphenyl Compounds.

polyps in the intestines and colon.[45b]

It would appear that a highly COX-2 selective NSAID that also contain boron could be used to deliver boron to tumors and thus be used in BNCT. Chapter 2 describes attempts to prepare BNCT agents by altering compounds in the 1,5-diarylpyrrazole class.

CHAPTER 2

PRELIMINARY STUDIES ON THE SYNTHESES OF BORONATED 1,5-DIARYLPYRRAZOLES FOR USE AS POTENTIAL BNCT AGENTS

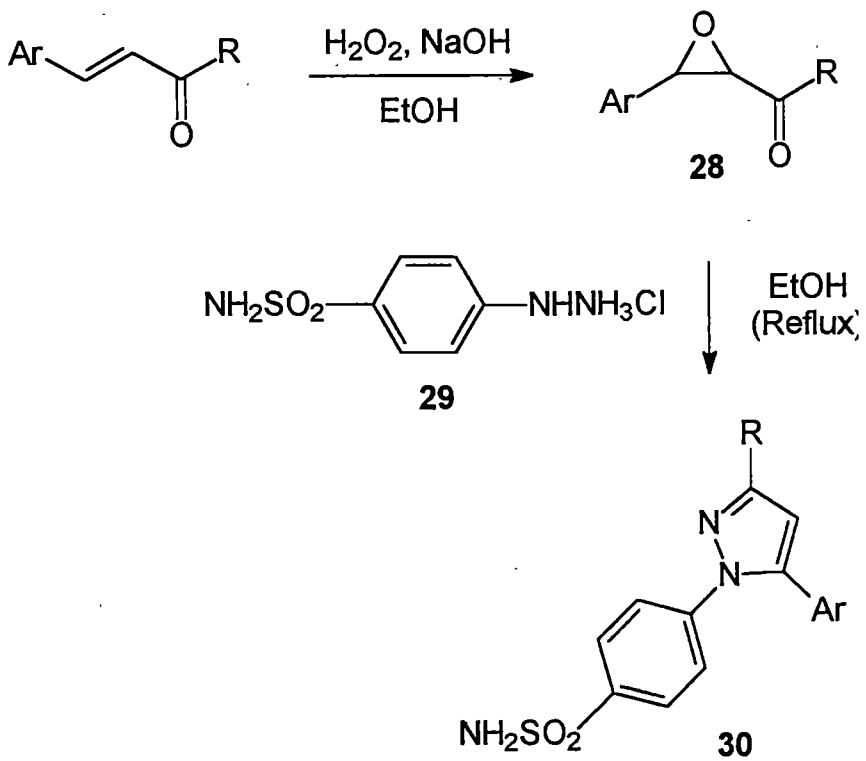
2.A Introduction

The COX-2 enzyme has been shown to express itself in large concentrations in inflammatory and tumor tissues.[1,45b] A number of compounds were described in Chapter 1 which have been, or are currently being, developed by industrial sources that inhibit the COX-2 enzyme selectively. Of special interest to cancer researchers is the apparent specificity of these new agents toward colon inflammation. Since the development of tumor selective boronated compounds is vital to the success of BNCT, it was decided to boronate these selective COX-2 inhibitors. This chapter details the author's efforts to synthesize boronated COX-2 inhibitors in the 1,5-diarylpyrrozole class.

2.B Syntheses of 1,5-Diarylpyrrazoles

This class of COX-2 inhibitors was developed by Searle Pharmaceuticals. There are two pathways used to prepare these compounds. In the first method, an α,β-unsaturated ketone is oxidized to epoxyketone **28** (Scheme 2-1).

Scheme 2-1. Synthesis of 1,5-Diarylpyrrazoles: Method 1.



Compound **28** is then condensed with the hydrochloride salt of (4-sulfamoylphenyl)hydrazine (**29**) to yield pyrrazole **30**. This method works well if R represented an alkyl group.

The second method utilizes the Claisen condensation of an acetophenone derivative with ethyl trifluoroacetate to produce diketone **31** (Scheme 2-2). Condensation with **29** yields the 1,5-product **30**. It should be noted that side product **32** was a major contaminant when the pure hydrazine was used. However when the hydrochloride salt **29** was utilized, **31** was produced almost exclusively. The second pathway was more general and was the method chosen for the synthesis of the new boronated compounds.

2.C Syntheses of Boronated 1,5-Diarylpyrazole 30

It was decided that a boronic acid group on ring C would constitute the simplest target molecule (Figure 2-1). The first step taken toward this target was

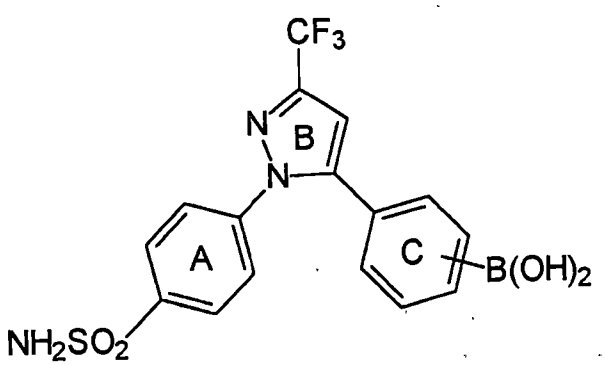
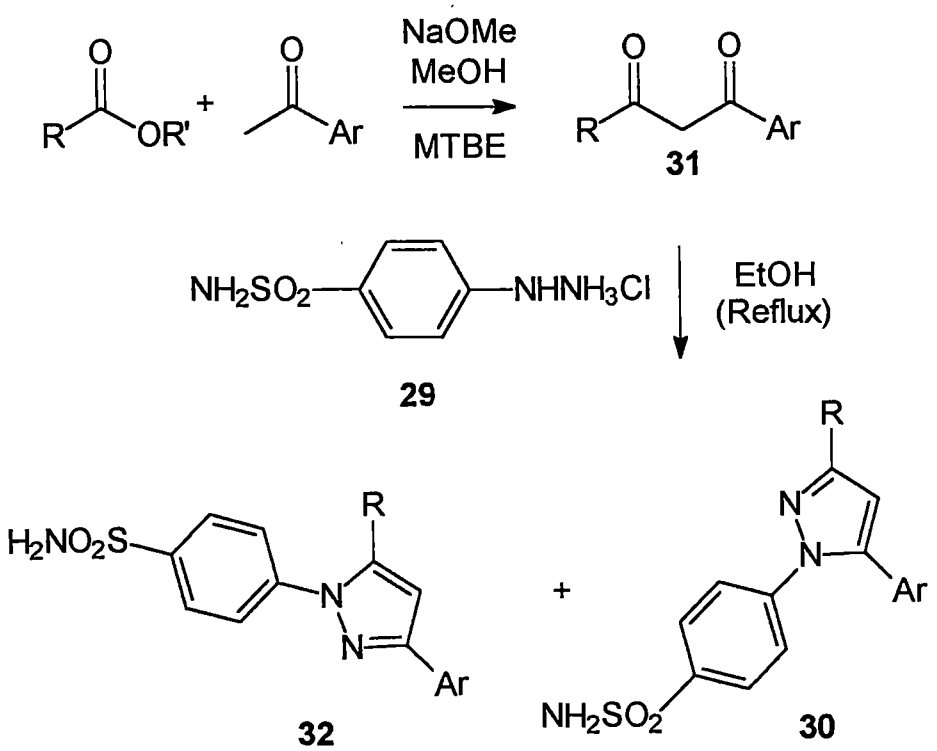


Figure 2-1. General Structure of Boronic Acid Target.

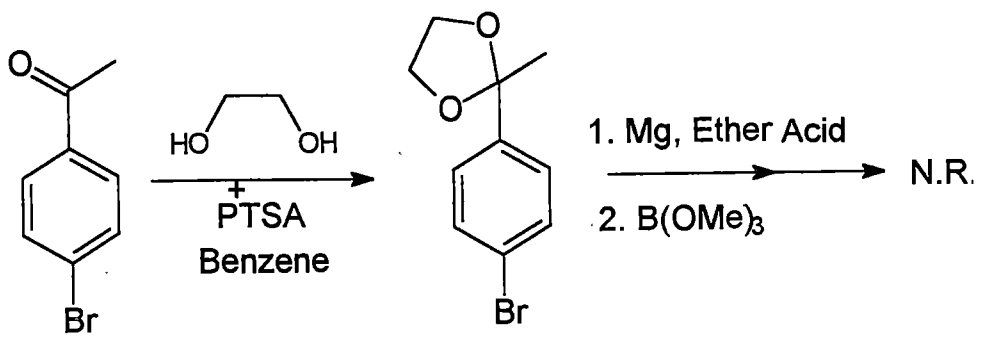
Scheme 2-2. Synthesis of 1,5-Diarylpyrrazoles: Method 2.



to prepare the boronic acid of 4-bromoacetophenone that could then be used in the Claisen condensation step.

This is usually accomplished by first protecting the ketone as the ethylene ketal and then making the Grignard reagent from the resulting intermediate (Scheme 2-3). The Grignard reagent would then be reacted with trimethylborate and quenched with aqueous acid. The ketal formation reaction was

Scheme 2-3. Attempted Synthesis of 4-Acetylphenylboronic Acid.



straightforward and gave high yields of the protected ketone. However, when the ketal was added to magnesium turnings in ether, no Grignard reagent formed. The addition of 1,2-dibromoethane, a known initiator for the Grignard reaction, and heat were unsuccessful in starting the reaction. In control experiments using bromobenzene, the Grignard reagent readily formed suggesting the ketal was detrimental to this protocol. Miyaura found success using magnesium powder to form the Grignard reagent.[77] However, when

magnesium powder was utilized little of the desired boronic acid product was obtained.

It was also discovered that the acetylphenylboronic acid would not undergo the Claisen condensation. A commercially available sample of the boronic acid was obtained and, even with a ten fold excess of the methoxide base, none of the desired diketone product was detected.

It has been shown that diboron pinacol ester (Figure 2-2) will react with aryl halides, in the presence of a palladium catalyst, to form the arylboronic esters in good to excellent yields.[78] The esters can then be hydrolyzed to the

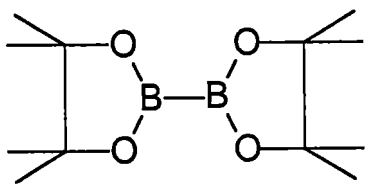
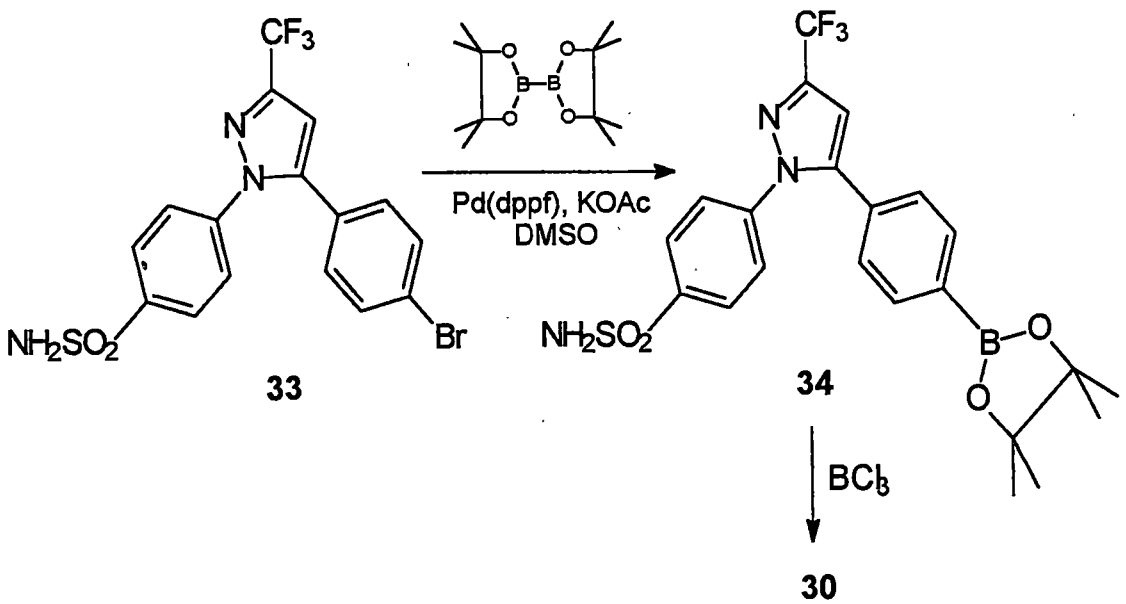


Figure 2-2. Diboron Pinacol Ester.

boronic acids. This reaction is also useful in that carbonyl groups do not need to be protected with this methodology.

It was next decided to use the diboron pinacol ester method and to apply it as the next to final step of the synthesis of **30** (Scheme 2-4). Although compound **33** was easily obtained according to the literature procedure[46] the boronic ester was not produced under the conditions listed. It is felt that the sulfonamide group interfered with the formation of the desired compound.

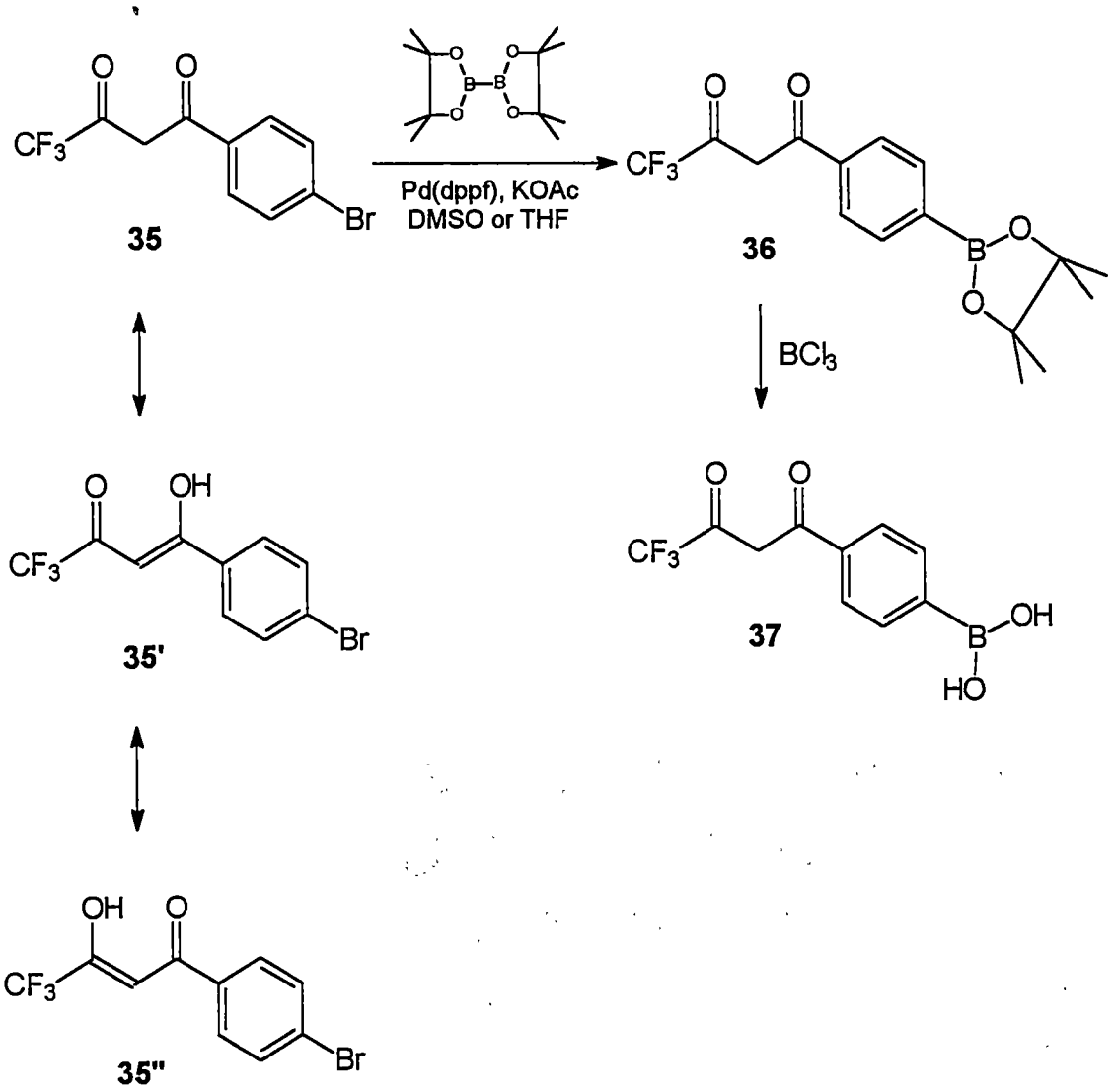
Scheme 2-4. Attempted Synthesis of the Boron Pinacol Ester of **33**.



No literature references could be found in which the diboron pinacol ester reaction had been executed in the presence of a free amine or a sulfonamide.

Next, the diboron technology was utilized to boronate the Claisen condensation product **35** (Scheme 2-5). These reactions are normally conducted in dry DMSO but it was found that THF was a more suitable solvent for the transformation. A red, viscous oil was obtained, however attempts to crystallize the sample were unsuccessful. An acceptable proton NMR spectrum of intermediate **31** could not be obtained and it was felt that this was due to the presence of enolates **35'** and **35"**. A boron-11 NMR spectrum suggested the boronic ester was present. Therefore the oil was allowed to reacte with **29** in refluxing ethanol in an attempt to produce 1,5-diarylpyrrazole **34**. Proton

Scheme 2-5. Attempted Synthesis of Compound **36**.



(Figure 2-3), carbon-13 (Figure 2-4) and boron-11 (Figure 2-5) spectra were obtained and strongly suggest the formation of compound **34** was accomplished. However, the presence of the brominated and boronic acid containing compounds were detected. Even after flash chromatography and recrystallization, the impurities were still present. A mass spectral analysis confirmed the presence of the bromide and boronic acid but also indicated the desired product was formed (Figure 2-6).

2.D Summary and Future Work

A synthetic route for the preparation of 4-[2-(4-sulfamoylphenyl)-5-trifluoromethyl-2H-pyrrazole-3-yl] phenylboronic acid (**34**) was developed. Although a pure sample of **34** has not been obtained, it is likely this pathway can be fruitful if modifications are made to remove undesired reagents.

Future work should focus on five areas. First, other solvents should be examined to see if they will produce a cleaner, higher yielding reaction. Solvents such as 1,4-dioxane[78] and dimethylformamide (DMF)[79] have been shown to generate high product yields in the palladium catalyzed diboron reaction. Second, other diboron and monoboronic esters might provide a smoother transformation to the desired compound **35**.[78] Third, the preparation of the boronic acid **30** should be pursued. If a pure sample of the boronic ester **35** can be obtained the boronic acid should easily be generated by hydrolysis with boron trichloride,[80] boron tribromide[78b] or sodium periodate.[78a] Fourth, other

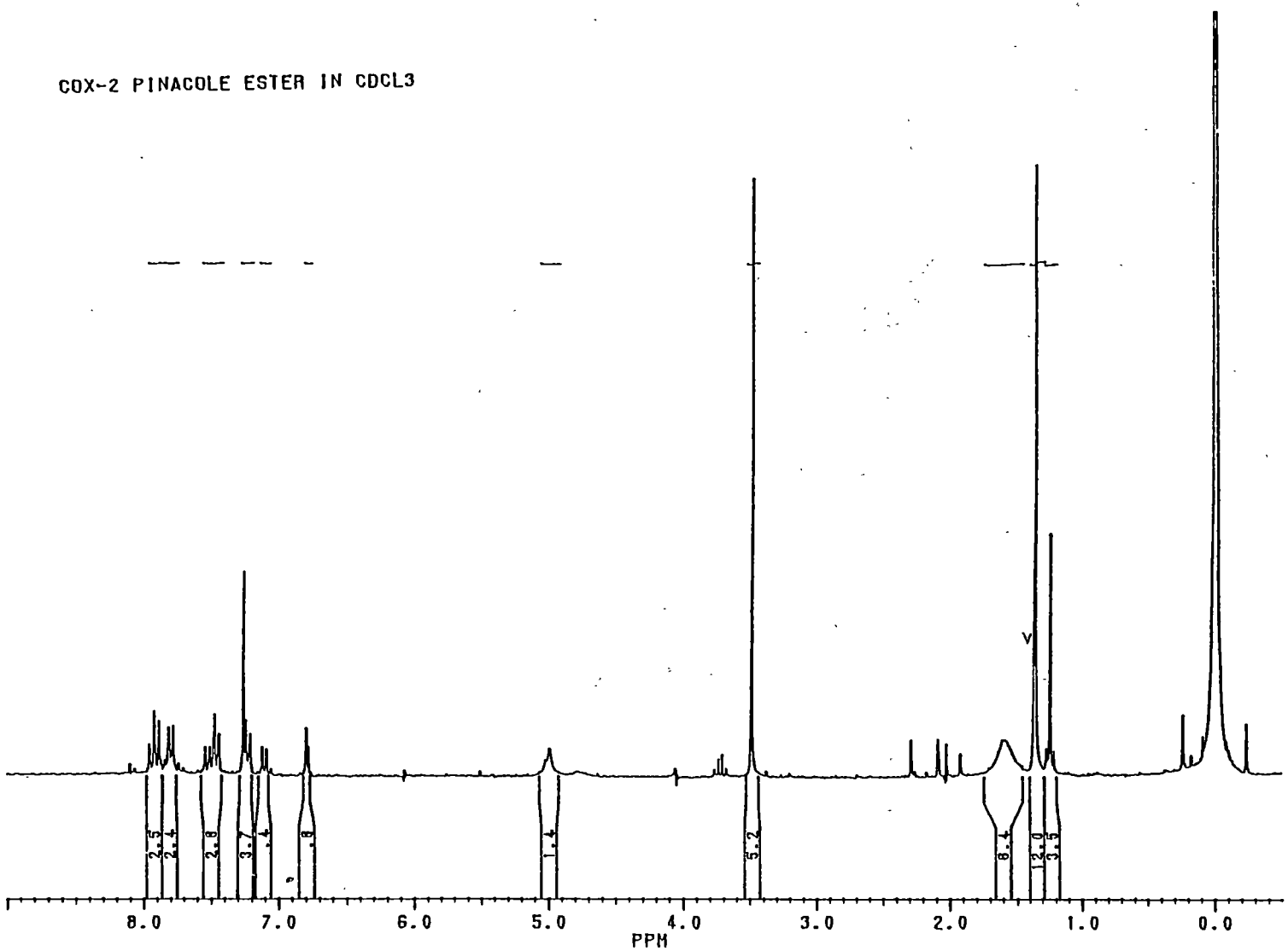


Figure 2-3. Proton Spectrum for **35**.

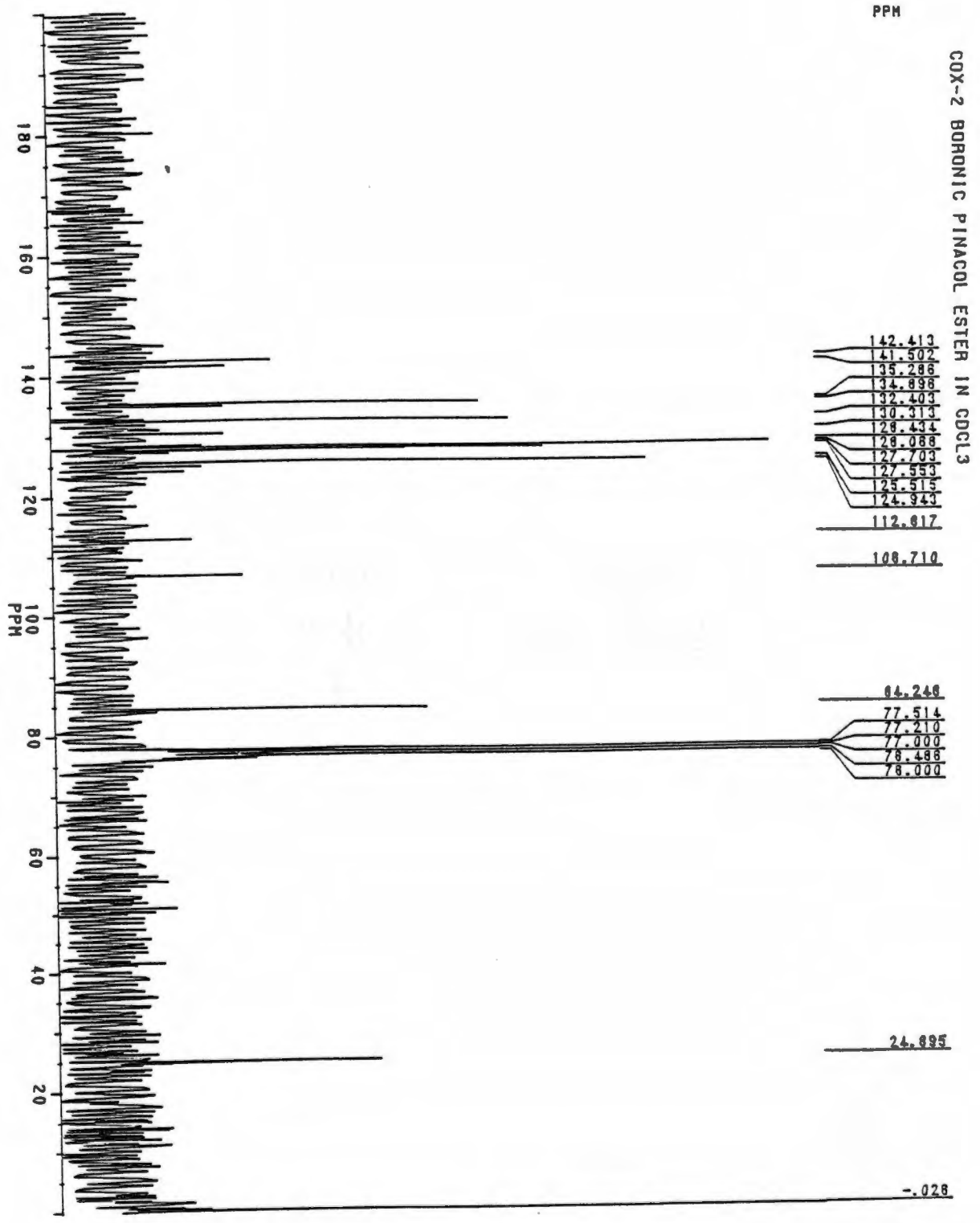


Figure 2-4. Carbon Spectrum for **35**.

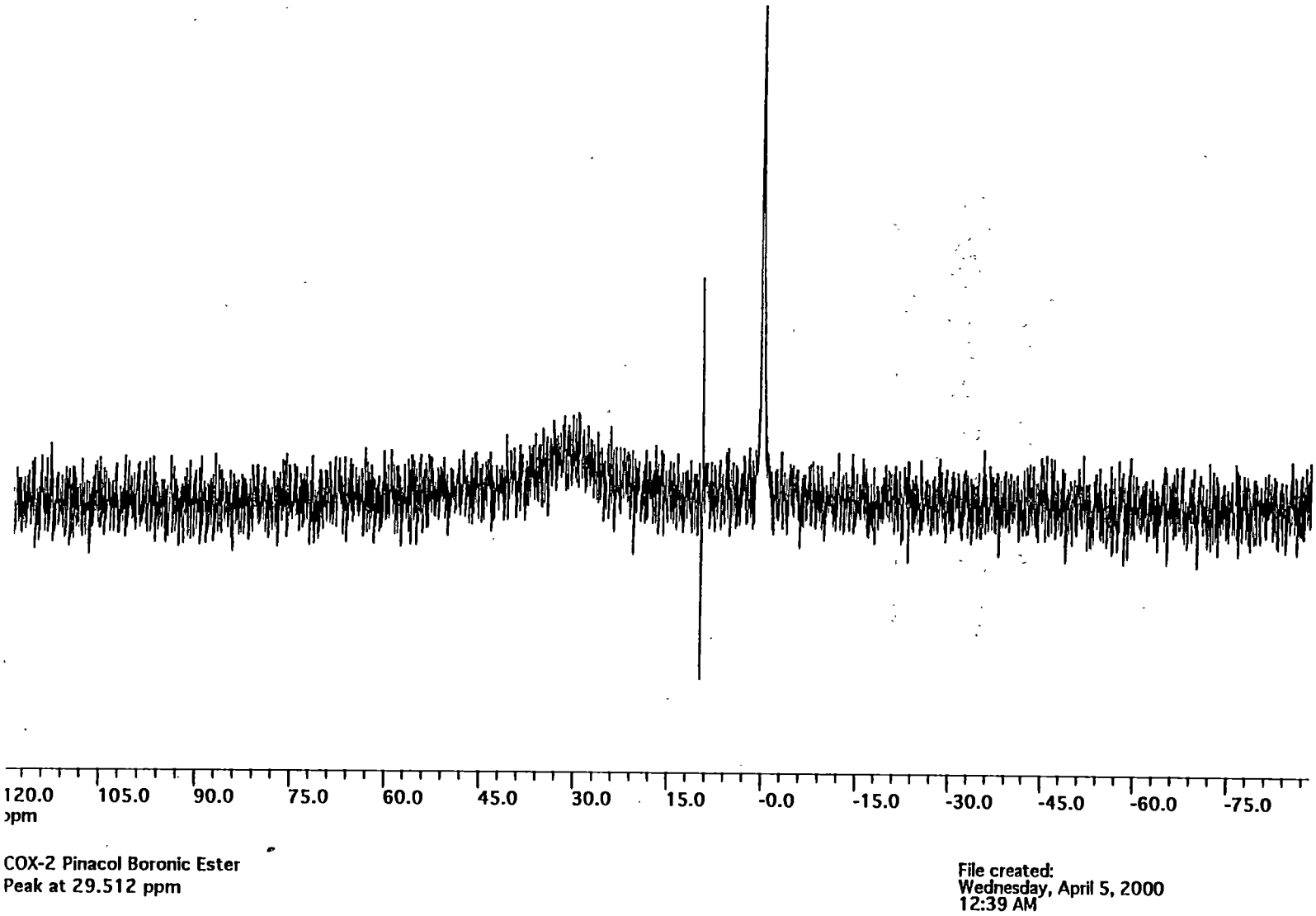


Figure 2-5. Boron Spectrum for **35**.

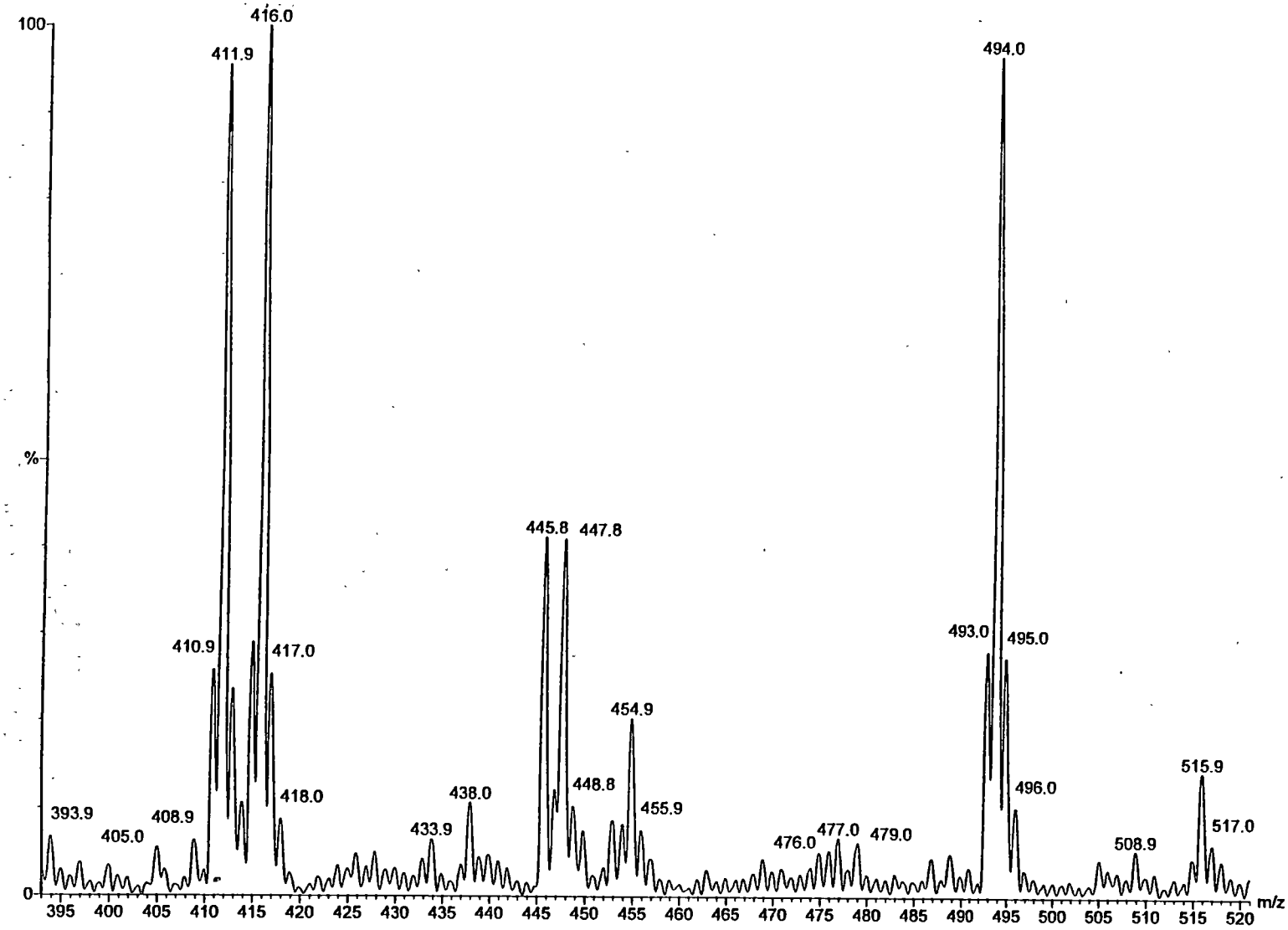


Figure 2-6. Mass Spectrum for **35**.

boronated groups, such as carboranes, should be incorporated in the synthesis of pyrrazole compounds. Fifth, other COX-2 inhibitors should be utilized for this study. Other structures may be more receptive to the boronation process and the boronated species may also be more selective toward tumor incorporation.

2.E Experimental

The ^{1}H- and ^{13}C-NMR spectra were run on a Brucker AC250 spectrometer and the ^{11}B-NMR spectrum was run on a JEOL FX90Q spectrometer. The nominal mass mass spectrum was run on a VG Quattro II electrospray mass spectrometer.

2.E.1 Compound ***35***

[ ] indicate probable contamination peaks. ^{1}H-NMR ($CDCL_3$/TMS) δ 7.90 (d, 2H, J = 8.2 Hz), [7.86 (d, 2H 7.54-7.44 (m, 2H), [7.26-7.21 (m, 4H)], 7.10 (d, 2H, J = 8.2 Hz), 6.80 (s, 1H), 4.99 (s, 2H), [3.49 (s, 5H)], 1.35 (s, 12H); ^{13}C-NMR ($CDCL_3$) δ 142.41, 141.50, 135.29, 134.90, 132.40, 130.31, 128.43, 128.07, 127.70, 127.55, 125.52, 124.94, 112.81, 106.71, 64.25, 24.90. ^{11}B-NMR (BF_3 Etherate) δ 29.51. Mass Spectrum (Protonated): m/z 494 mass of desired product, 446, 448, 416, 412.

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LIST OF REFERENCES

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