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

George W. Kabalka, Major Professor

We have read this dissertation
and recommend its acceptance:

Linda L. Magid

Accepted for the Council:

Associate Vice Chancellor and
Dean of The Graduate School

NEW REACTIONS OF CARBONYL COMPOUNDS WITH ORGANOBORANES AND HALOBORANES

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

David Tejedor

August 1998

DEDICATION

I dedicate this dissertation to my mother, Maria Julia Aragon, and my father, Jose Maria Tejedor, for their love and support. They have always encouraged me to strive for all my dreams.

I also dedicate this dissertation to my aunt Loli and my uncle Pedro for their love and for partially raising me to be who I am.

ACKNOWLEDGEMENTS

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ABSTRACT

The 1,2-addition of organoboranes to carbonyl compounds was investigated utilizing three different approaches. First, the reactions were irradiated with either ultrasound or microwaves, giving, in both cases, negative results. Second, efforts were directed to modify the transition state. Acyloxyboranes gave positive results but improvements will be necessary before the reaction is synthetically useful. Finally, fluorinated organoboranes were prepared in an effort to increase the Lewis acidity at the boron atom. Although no 1,2-addition was observed upon addition to carbonyl compounds, the study led to an unprecedented reaction. It was discovered that ketones react with aromatic aldehydes in non-nucleophilic solvents in the presence of boron trifluoride (and other anhydrous strong acids) to produce β-alkylstyrenes and the corresponding carboxylic acids.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

LIST OF ABBREVIATIONS AND SYMBOLS

AcOH	Acetic acid
aq	Aqueous
Ar	Aryl
9-BBN	9-Borabicyclo[3.3.1]nonane
b.p.	boiling point
Bu	Butyl
Bz	Benzyl
°C	Degrees Celsius
ChX	Cyclohexyl
cm^{-1}	Inverse centimeter
d	Doublet
DCC	1,3-Dicyclohexylcarbodiimide
DMS	Dimethyl sulfide
Δ	Heat
δ	Chemical shift
eq	Equivalent
eqn	Equation
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
exp	Experiment
g	Grams

GC	Gas chromatography
GC/MS	Gas Chromatography-Mass Spectroscopy
Hex	Hexyl
hr, hrs	Hour, hours
Hz	Hertz
i-Pr	Isopropyl
IR	Infrared
J	Coupling constant
kcal	Kilocalories
kHz	Kilohertz
KIPBH	Potassium triisopropoxyborohydride
M	Metal, Molarity
m	Multiplet
Me	Methyl
min	Minute
mL	Milliliter
mm	Millimeter
mmol	Millimole
m.p.	Melting point
NMR	Nuclear magnetic resonance spectroscopy
NR	No reaction
[O]	Oxidation
OTf	Triflate

Ph	Phenyl
ppm	Parts per million
Pr	Propyl
q	Quartet
R	Alkyl
R_2BX	Dialkylboron halide
RT	Room temperature
s	Singlet
t	Triplet
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane

PART A

THE SEARCH FOR THE 1,2-ADDITION OF ORGANOBORANES TO CARBONYL COMPOUNDS

CHAPTER I

ORGANOBORANES AND THE CARBONYL MOIETY IN ORGANIC SYNTHESIS

1.1 Introduction

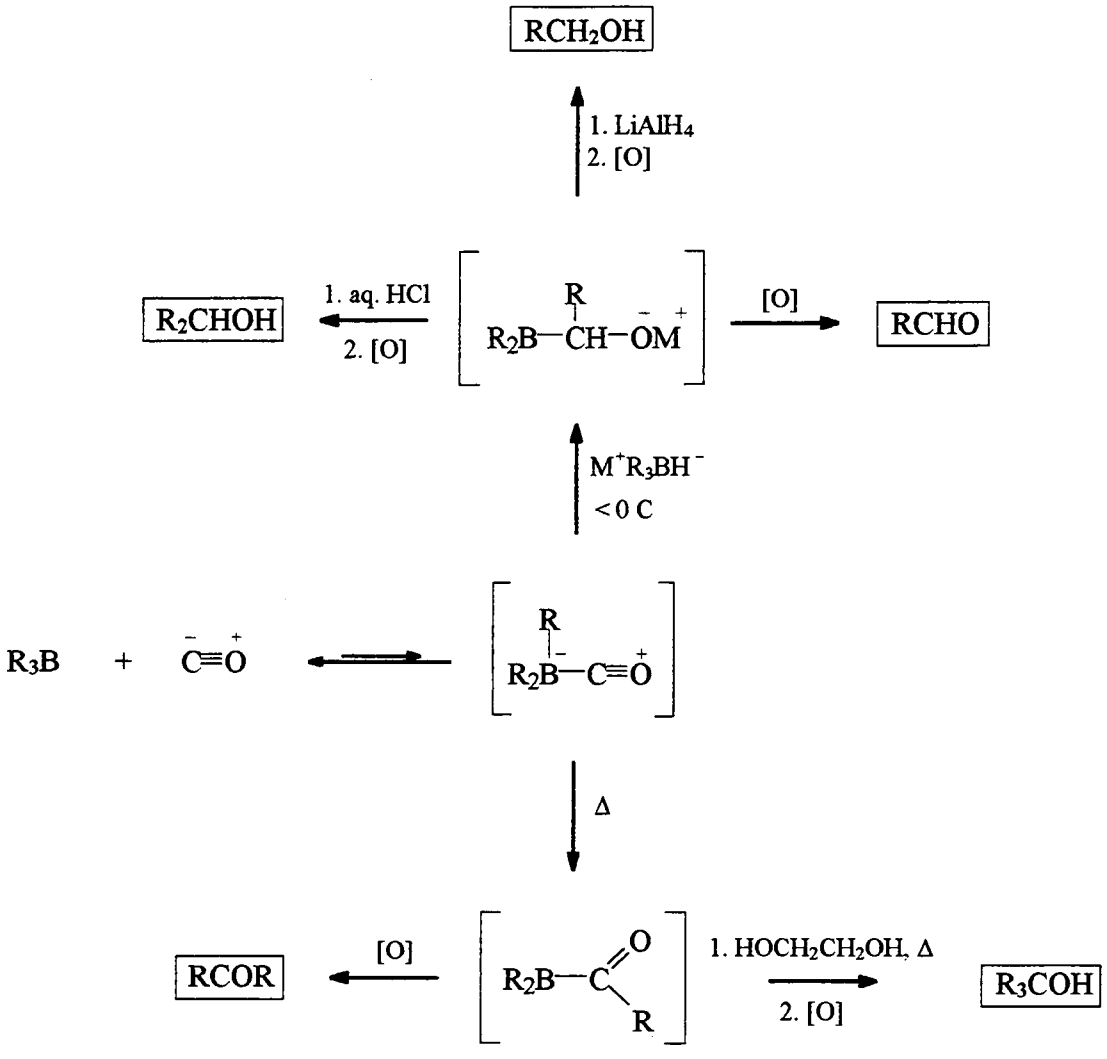
Organoboranes are used in a wide variety of organic syntheses and they currently play an important role in organic chemistry.[1] Perhaps their most important role is their use in carbon-carbon bond formation reactions. Part A of this dissertation is a summary of research directed at the development of new reactions in which carbon-carbon bonds are formed via the reaction of organoboranes and carbonyl compounds. A brief overview of previously developed reactions involving organoboranes and carbonyl reagents is presented.

1.2 Organoboranes and Carbonyl Reagents

1.2.1 Carbonylation of Organoboranes

The carbonylation reaction allows the migration of one, two or all three alkyl groups depending upon the reaction conditions. Consequently, it provides the opportunity to synthesize aldehydes, ketones and various types of alcohols from trialkylboranes and carbon monoxide (Scheme 1-1).[1]

Scheme 1-1. Carbonylation of Organoboranes.

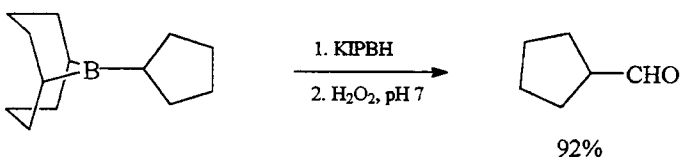


The reaction occurs via two distinguishable pathways depending on whether it is run in the presence or absence of a hydride reagent.

In the presence of a hydride reagent, such as potassium triisopropoxyborohydride (KIPBH) or lithium trimethoxyaluminum hydride (LTMA), the rate of carbon monoxide uptake is enhanced even at temperatures below 0 ^{0}C. The intermediate obtained can be directly oxidized to the homologated aldehyde,[2] treated with lithium aluminum hydride before oxidation to give the homologated alcohol,[3] or treated with acid, promoting a second alkyl migration, to give a secondary alcohol upon oxidation.[4]

Alternatively, in the absence of a hydride reagent, the reaction proceeds via a different pathway. At elevated temperatures (100 ^{0}C), oxidation in the presence of a small amount of water affords a ketone as a result of two alkyl migrations.[5] However, if oxidation is preceded by addition of ethylene glycol with further heating, a third migration is induced to afford a tertiary alcohol after oxidation.[6]

As representative examples, cyclopentanecarboxaldehyde can be synthesized via the carbonylation of 9-cyclopentyl-9-BBN in the presence of a hydride (eqn 1-1),[2] and tri-2-norbornylcarbinol from the carbonylation of tri-2-norbornylborane (eqn 1-2).[6] Both products are prepared in good yields.



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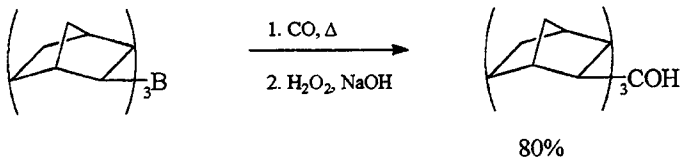
(1-1)

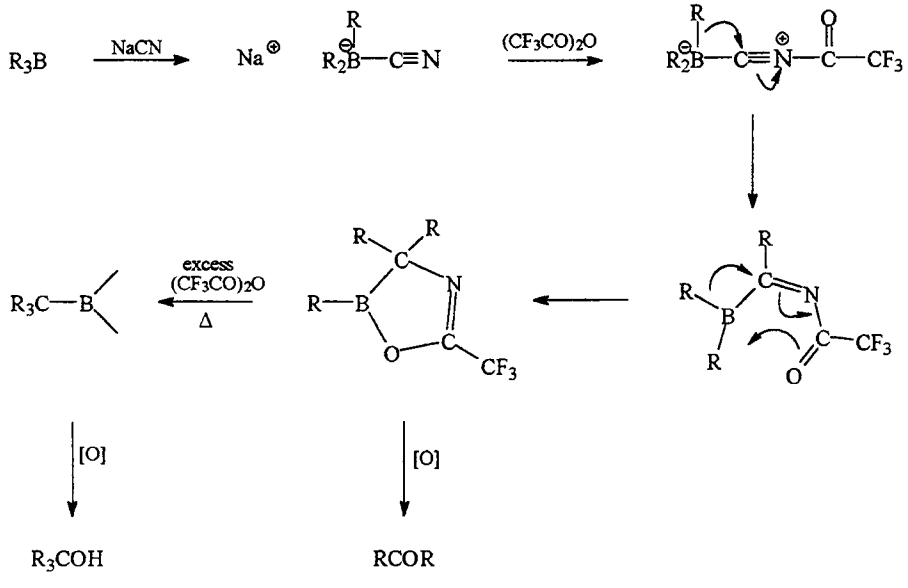


(1-2)

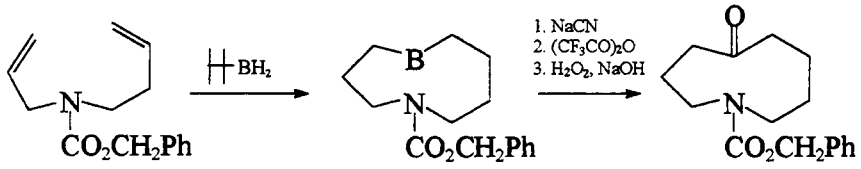
1.2.2 Cyanoborate Process

A simpler synthesis of ketones and tertiary alcohols from organoboranes can be achieved using the cyanoborate process. Trialkylboranes complex to alkali metal cyanides to give stable cyanotrialkylborate salts. However, multiple alkyl migrations can be induced by addition of an electrophilic reagent such as trifluoroacetic anhydride (Scheme 1-2).[7]

Scheme 1-2. Cyanoborate Process.



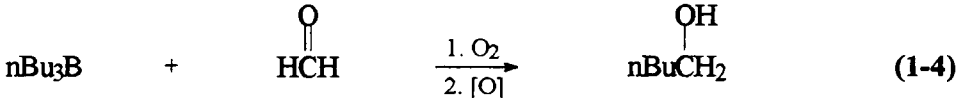
The intermediate resulting from a single migration has never been isolated. Instead, a double migration occurs to give, after oxidation, the corresponding ketone at ambient conditions,[8] or a tertiary alcohol if excess trifluoroacetic anhydride is added at slightly higher temperatures.[9] A thexylorganoborane is often used to maximize the desired alkyl migration when preparing ketones by this process (eqn 1-3)[10].



(1-3)

1.2.3 Alkylation of Formaldehyde

The first reported alkylation of an aldehyde using a trialkylborane was the addition of tributylborane to formaldehyde to give the homologated alcohol (eqn 1-4)[11] via a radical mechanism.



(1-4)

Since it has been shown that this reaction cannot be generalized to other aldehydes or ketones, and it only gives moderate yields of the alkylated products (29-79%),[11] its importance is more theoretical than experimental.

1.2.4 1,4-Addition to α,β-Unsaturated Carbonyl Compounds

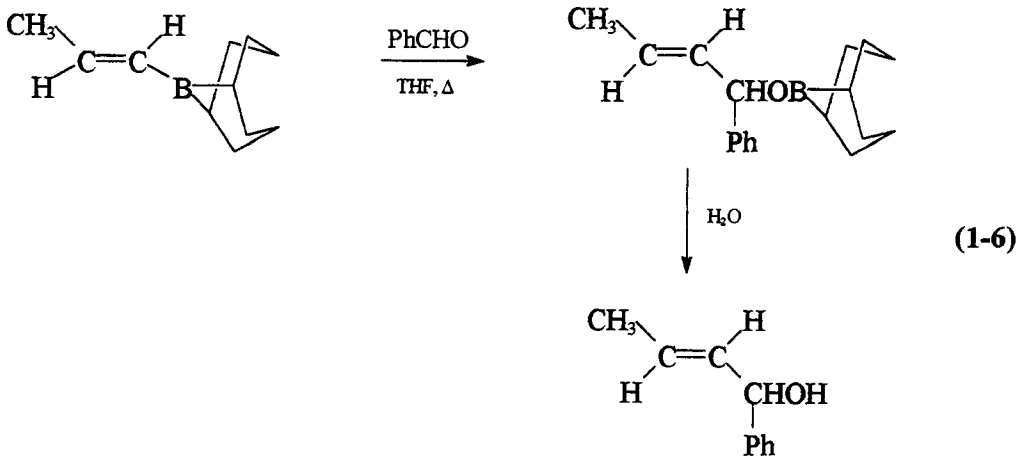
Trialkylboranes have been shown to add in a 1,4 manner to α,β-unsaturated carbonyl compounds producing in high yields, after hydrolysis, the corresponding alkylated product (eqn 1-5).[12,13]

$$R_3B + CH_2{=}C(CH_3){-}CHO + H_2O \longrightarrow RCH_2CH(CH_3)CHO + R_2BOH \quad \textbf{(1-5)}$$

Initially, the reaction was only successful if the double bond involved in the reaction was in the terminal position,[12] but it was later generalized to more substituted double bonds.[13] Like the alkylation of formaldehyde, this reaction has also been shown to proceed through a radical mechanism because the reaction rate is enhanced by radical initiators and inhibited by radical inhibitors.

1.2.5 Addition of B-Alkenylboranes

Vinyl groups can be added across the carbonyl group to give, upon work-up, the corresponding allylic alcohols with retention of configuration at the double bond (eqn 1-6).[14]

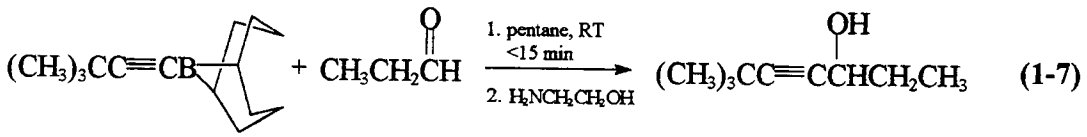


(1-6)

Although the yields are moderate (36-86%), this is a remarkably simple method for converting alkynes into allylic alcohols. A triple bond can be hydroborated to generate a vinylboron reagent and then added to a carbonyl compound to obtain the desired product. As shown in eqn. 1-6, the reaction works best when a B-alkenyl-9-BBN is used.[14]

1.2.6 Addition of B-Alkynylboranes

Alkynyl groups can also be added to ketones or aldehydes to give, after hydrolysis, the corresponding propargylic alcohol (eqn 1-7) in good to excellent yields (56-97%)[15]. B-Alkynyl-9-BBN reagents give the best yields while selectively reacting with aldehydes in the presence of ketones, and with unhindered ketones in the presence of hindered ketones.

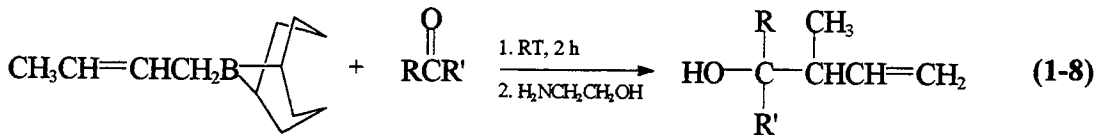


(1-7)

The extraordinary chemoselectivity, combined with the tolerance of various functional groups such as esters, nitriles, amides, acid chlorides, acetals, ketals and alkyl halides, make this method a useful alternative to other reaction involving alkylmetals.

1.2.7 Addition of B-Allylboranes

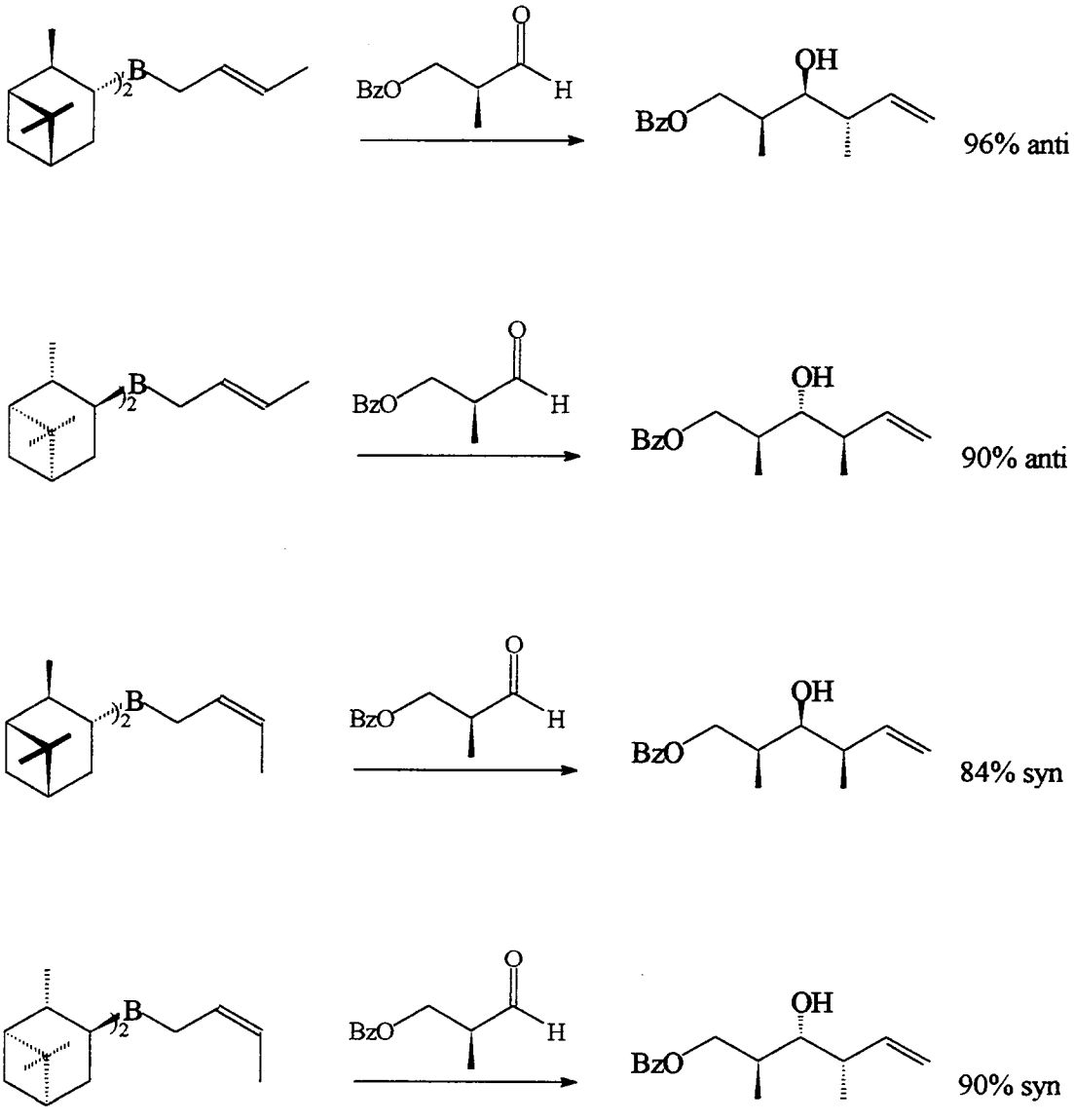
Allylboranes add readily to both aldehydes and ketones to form the corresponding homoallylic alcohols in excellent yields. This reaction has received a great deal of attention due to the importance of the resulting alcohols as intermediates in complex biosyntheses.[16] Although it has been shown that triallylboranes, as well as a wide range of allyl(dialkyl)boranes and diallyl(alkyl)boranes, can be used with positive results,[17] B-allyl-9-BBN compounds are usually the reagents of choice (eqn 1-8).[18]



(1-8)

The scope of the allyboration reaction is broadened by the use of optically active organoboranes. Alkyl groups derived from naturally occurring terpenes[19] and optically tartrate esters[20] have received most of the attention. The crotylboration of an optically active aldehyde using B-crotyldiisopinocampheyl-boranes is a perfect example of this remarkable selectivity (Scheme 1-3).[21]

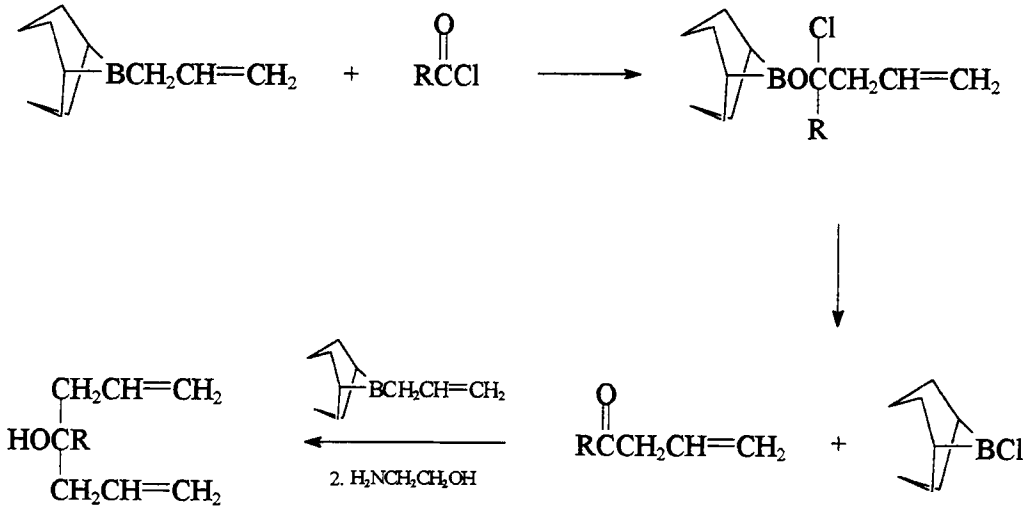
Scheme 1-3. Crotylboration of an Optically Active Aldehyde.



The configuration at the α-carbon of the aldehyde is retained in the product while the chirality of the organoborane controls the enantioselectivity and the double bond geometry of the crotyl group determines the diastereoselectivity.

The allylboration of acid chlorides, acid anhydrides, carboxylic acid esters and amides is also known[18]. The stoichiometry of these reactions, however, is two allyl groups to one carbonyl compound. The addition of B-allyl-9-BBN to an acid chloride (Scheme 1-4) to give a diallyl tertiary alcohol is representative.

Scheme 1-4. Allylboration of Acid Chlorides.



It is widely recognized that the ease of reactivity of B-allylboranes and their high selectivity are a consequence of a six-membered transition state (Figure 1-1).

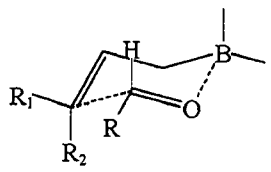
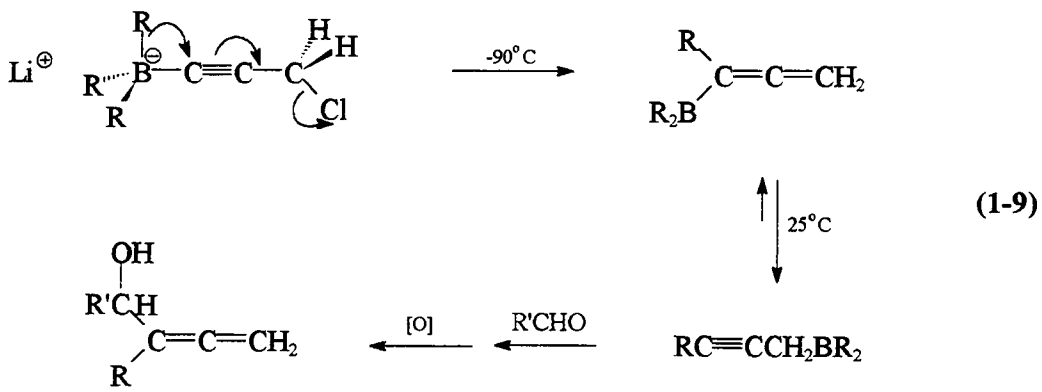


Figure 1-1. Transition State of Allylboration Reaction.

1.2.8 Addition of B-Propargylicboranes

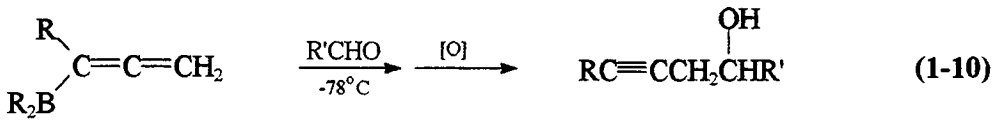
B-propargylicboranes, prepared by the reaction of trialkylboranes with lithium chloropropargylides, followed by equilibration at room temperature, add to carbonyl compounds to form α-allenic alcohols (eqn 1-9).[22]



(1-9)

The reaction proceeds via a six-membered transition state, in a manner analogous to the allylboration. Subsequently, the α-hydroxyallene yields are also high (73-89%).

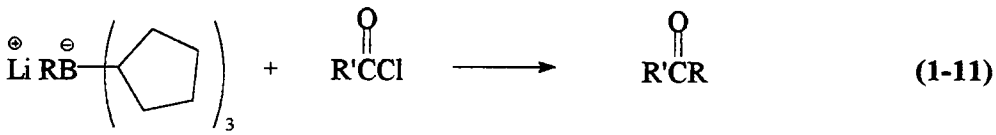
An interesting aspect of this reaction is that, if the B-allenicborane is not allowed to equilibrate, it can react at lower temperatures with the same carbonyl compound to give the homopropargylic alcohol, in excellent yields (eqn 1-10).[22]



(1-10)

1.2.9 Addition of Lithium Tetraorganoborates to Acyl Chlorides

Lithium tetraorganoborates, prepared from the reaction of triorganoboranes with an alkyllithium, alkylate acyl chlorides to form the corresponding ketones in moderate to high yields (eqn 1-11).[23] Unfortunately, other carbonyl compounds do not undergo the reaction.

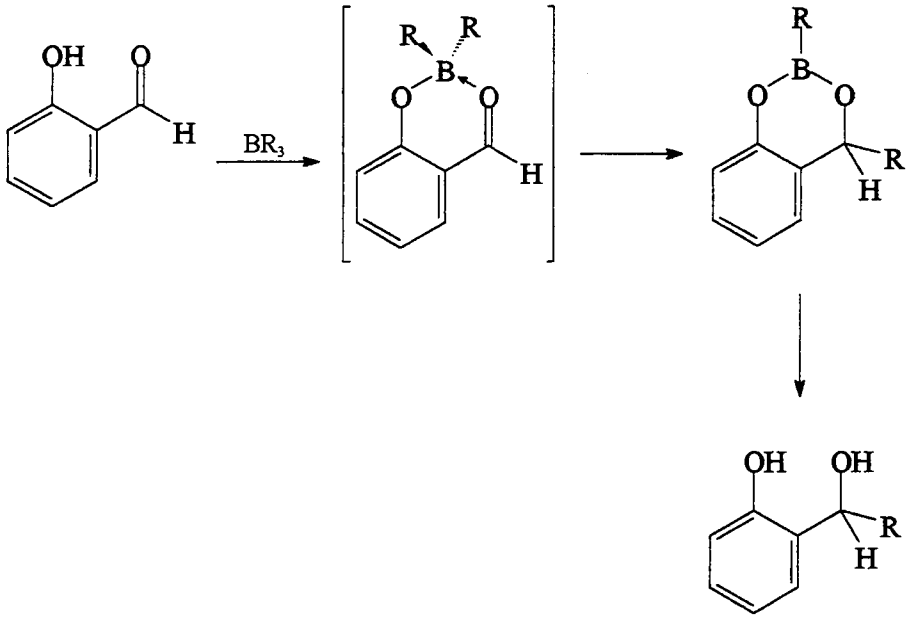


(1-11)

It has been shown that the reactive species is not the alkyllithium, which would afford the carbinol upon dialkylation, but the tetraorganoborate itself. Indeed, the alkyl group from the alkyllithium does not necessarily become the migrating group. It has been determined that primary alkyl groups migrate exclusively in the presence of secondary alkyl groups.

1.2.10 Addition of Trialkylboranes to o-Hydroxyarylaldehydes

An alkyl group is readily transferred across the carbonyl group of an *o*-hydroxyarylaldehyde to give the corresponding diol after work-up (eqn 1-12).[24]



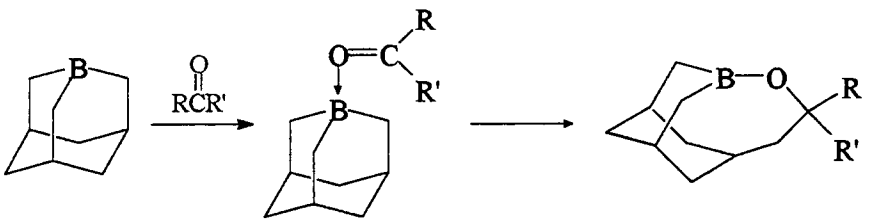
(1-12)

The yields of this reaction are moderate to good (47-83%), but its applications are limited because the hydroxy group must be ortho to the carbonyl group. It has been shown that arylaldehydes bearing *o*-methoxy groups are not alkylated by trialkylboranes.

The efficiency of the reaction is demonstrated by the results obtained upon addition of diisopinocampheylborane to salicylaldehyde, a typical reducing agent. Instead of the expected complete reduction, the product mixture contained 46% reduction and 16% alkylation. However, yields of the alkylation product are reduced by the use of a radical inhibitor, which suggests a radical mechanism.

1.2.11 Addition of 1-Boraadamantane

1-Boraadamantane is the only saturated organoborane known to alkylate aldehydes and ketones.[25] It does so by transferring one of its groups across the carbonyl group (eqn 1-13).



(1-13)

What is remarkable about this reaction is not its versatility, but the fact that it proceeds via complexation of the trialkylborane to the carbonyl compound. Trialkylboranes have lower Lewis acidities and complex to carbonyl compounds only weakly. This is demonstrated by IR and ^{11}B NMR data. When 1-boraadamantane is added to an aldehyde or ketone at room temperature, the C=O stretch in the IR is shifted 70-80 cm^{-1} to a lower frequency, and the ^{11}B NMR peak is shifted upfield to –19.7 ppm (p-methoxybenzaldehyde complex). These values contrast the observations for other trialkylboranes, which cause only a slight shift in the C=O frequency in the IR and generate a peak in the ^{11}B NMR spectrum around 86 ppm. Furthermore, the observed acidity is comparible to that of BF_3, an excellent Lewis acid.

When the complex is heated (>50 °C), alkylation takes place instead of reduction by β-hydride transfer (Section 1.2.12).

1.2.12 Trialkylborane Reduction of Carbonyl Compounds

Trialkylboranes are not considered to be reducing agents, but in fact, they can reduce aldehydes by β-hydride transfer. Certain hindered B-alkyl-9-BBN compounds can be used to selectively reduce aldehydes in the presence of a reactive ketone such as cyclohexanone under mild conditions.[26]

Benzaldehyde is particularly prone to β-hydride reduction. Even tri-n-alkylboranes can reduce it at temperatures as low as 65 °C in 24 hours or 25 °C in 6 days.[27]

1.3 Statement of Problem

An important number of carbon-carbon bond formation methods involve the addition of traditional organometallic compounds, such as organolithium or Grignard reagents, to the carbonyl moiety. These methods have been enormously helpful to synthetic organic chemists, however, they also have limitations. For example, their strong basicity leads to reduction, condensation and enolization side reactions. Another drawback is that they react with a large number of functional groups.

The development of an alternative method to traditional organometallic reactions utilizing organoboranes has been of great interest to synthetic chemists because such a method would provide several benefits. These include milder conditions, tolerance to a broader variety of functional groups, stability towards many protic solvents, and the possibility of inducing asymmetry in the product. A

number of reactions between organoboranes and carbonyl compounds are now known (Section 1.2), however, a general simple addition of organoboranes to carbonyl compounds has not been successful.

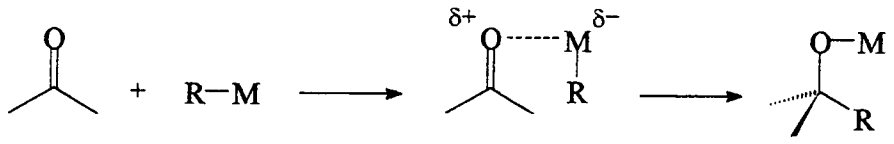
Chapter 2 (Part A) of this dissertation includes a brief discussion on the difficulties encountered in the Grignard-like addition of alkyl groups to carbonyl compounds. This is followed by a detailed description of the author's attempts to overcome this lack of reactivity.

CHAPTER 2

1,2 ADDITION OF ORGANOBORANES TO CARBONYL COMPOUNDS: AN INVESTIGATION

2.1 Introduction

With the exception of 1-boraadamantane (Section 1.2.11), saturated organoboranes fail to add to aldehydes and ketones in an ionic, Grignard-like fashion (eqn 2-1).



(2-1)

Thermodynamically, the 1,2-addition is favored even though alkylation does not occur. In the overall reaction, the C-B bond and the π-bond of the C=O are broken. These bonds have energies of approximately 80 kcal/mol[28] and 60 kcal/mol,[29] respectively. The bonds formed would be a B-O bond and a C-C bond, with approximate energies of 120 kcal/mol[30] and 80 kcal/mol[31] respectively. The overall reaction is thus energetically favored by 60 kcal/mol.

Why does the direct alkylation fail when the allyboration occurs so readily (Section 1.2.7)? The answer presumably lies in an unfavorable transition state: A four-membered versus a six-membered transition state.

It is well known that some organometallic compounds are capable of alkylating carbonyl compounds. There is a direct relationship between the ionic character of the M-C bond and the ability of the metal to add the alkyl group in a 1,2-fashion. When compared to metals which succesfully alkylate aldehydes and ketones, boron forms bonds to carbon with a lower percent ionic character. This, presumably, leads to a lower reactivity (Table 2.1).[31] The lower reactivity of trialkylboranes when compared to other organometallic compounds or other organoboranes such as dialkylboranes is evidenced by their inability to dimerize. More reactive species such as RMgBr, Me_3Al and R_2BH are known to exist in the dimeric form.[32]

Table 2-1. Carbon-Metal Bond % Ionic Character and Type of Reaction.

C-M	% Ionic Character	Reaction with Carbonyl
C-Na	47	enolization
C-Li	43	1,2-addition
C-Mg	35	1,2-addition
C-Al	22	1,2-addition, side rxns.
C-Zn	18	1,2-addition, some cases
C-Cd	15	1,2-addition
C-Hg	9	1,2-addition
C-B	6	1,2-addition

Three approaches to enhance the reactivity of trialkylboranes with the carbonyl moiety were envisioned. First, experiments could be designed to supply sufficient energy to exceed the activation energy. Secondly, modifications could be made to the reactants so that the transition state would resemble that of the allylboration reaction. Finally, modifications could be made such that the boron atom would be made more Lewis acidic in order to increase its complexation ability. What follows in this chapter is the author's research on these subjects.

2.2 High Energy Experiments

Simply heating a mixture of a trialkylborane with aldehydes or ketones has been shown to give only the carbonyl reduction product (Section 1.2.12). Since the 1,2-addition to the carbonyl moiety is not successful under mild conditions, attempts were made to exceed the activation energy of the desired reaction using other methods.

2.2.1 Ultrasonics

Ultrasound has been successfully used in organic synthesis to accelerate the rate of certain reactions while improving the yield of products. The literature on ultrasonic reactions is broad. It has been used, for example, to generate dichlorocarbenes from $NaOH/CHCl_3$,[33] the Simmons–Smith cyclopropanation of olefins using zinc-diiodomethane,[34] the reduction of aryl halides with $LiAlH_4$,[35] and the heterogeneous reduction of halo derivatives of group IVB elements.[36] In

organoborane chemistry it has also been used to accelerate the rate of slow hydroborations,[37] in the synthesis of trialkylboranes via transmetallation reactions,[38] and in the formation of arylboronic acids.[39]

Unfortunately, the alkylation of aldehydes using a trialkylborane was not successful. In our experiment, an equimolar mixture of benzaldehyde and tributylborane in THF was irradiated with ultrasound (Fisher Scientific, Model 550 Sonic Dismembrator, 190 watts, 20 KHz) for 30 minutes. After oxidative work-up, the organic products were analyzed by GCMS. Neither alkylation nor other reaction products were found and only unreacted benzaldehyde was recovered.

2.2.2 Microwaves

Although microwaves are generally associated with the heating of foods, chemists have found them useful in organic synthesis. Microwaves cause dipolar molecules to rotate, and thus absorb energy, which is normally dissipated as heat. The effect of microwaves is not solely thermal because reactions performed using conventional heating take longer.[40] The efficiency of microwaves can be seen for example in peptide hydrolysis, which can be achieved in 15 minutes under microwave radiation instead of the normal overnight heating. Another example is the oxidation of alcohols to ketones or aldehydes by ferrous nitrate. The oxidation is completed within one minute instead of several hours.[40,41]

The reaction of benzaldehyde with tributylborane under microwave radiation in a solvent free environment was first investigated. In only 3 minutes of microwave radiation in a conventional microwave oven nearly 50% reduction of

benzaldehyde to benzyl alcohol was achieved (β-hydride reduction, Section 1.2.12). Unfortunately, the desired alkylation did not take place, although the ease of carbonyl reduction under these mild conditions could be useful. More studies could be done in the future to find synthetic applications for the reduction of benzaldehyde and/or other carbonyl compounds.

2.3 Six-Membered Ring Approach

Because six-membered ring transition states are known to be more favorable than four-membered ring transition states, it is appeared reasonable to attempt the alkylation of carbonyl compounds by introducing two additional nuclei into the transition state in order to lower its energy (Figure 2-1).

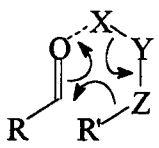


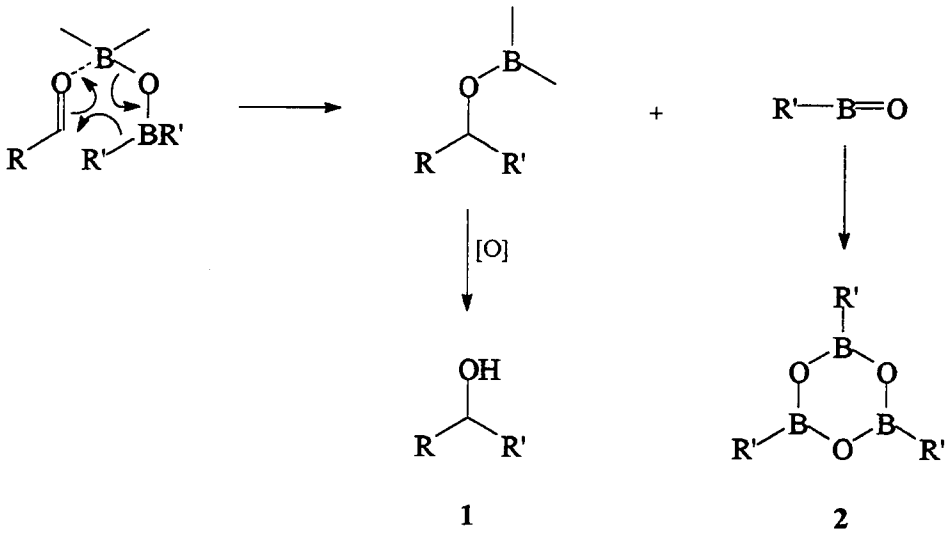
Figure 2-1. Six-Membered Ring Transition State.

Various attempts have been made utilizing this approach. In every case, boron would either complex to the carbonyl compound through the oxygen atom (X), deliver the alkyl group (Z) or both.

2.3.1 Borinic Anhydrides

Borinic anhydrides are readily formed from the reaction of dialkylboranes with borinic acids. If an unsymmetrical borinic anhydride is utilized, it seems reasonable that the more Lewis acidic of the two boron atoms would complex to the oxygen of the carbonyl moiety. The desired alkyl transfer might then occur from the non-complexed boron atom (Scheme 2-1). The alcohol (**1**) would then be synthesized upon oxidation of the borinic ester. The byproduct would be the stable boroxin (**2**).

Scheme 2-1. Borinic Anhydride Approach.



Early attempts were made with symmetrical borinic anhydrides (**3**) but the reaction proved to be unsuccessful.[42,43] In an effort to increase the ability of the

organoborane to complex to the carbonyl compound, two different unsymmetrical borinic anhydrides (**4** and **5**) were synthesized (Figure 2-2).

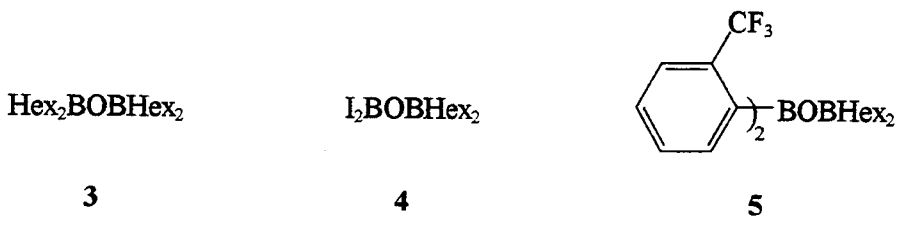


Figure 2-2. Borinic Anhydrides.

Borinic anhydride **4** was prepared from the reaction of diiodoborane (prepared *in situ*)[44] with dihexylboronic acid.[1] The presence of **4** was confirmed by two resonances in the ^{11}B-NMR spectrum. The more Lewis acidic of the two boron atoms appeared at 19 ppm. The dialkylboron atom appeared, as expected, as a broader peak centered at 55 ppm. The reaction of **4** with benzaldehyde however, produced no alkylation or other products of interest.

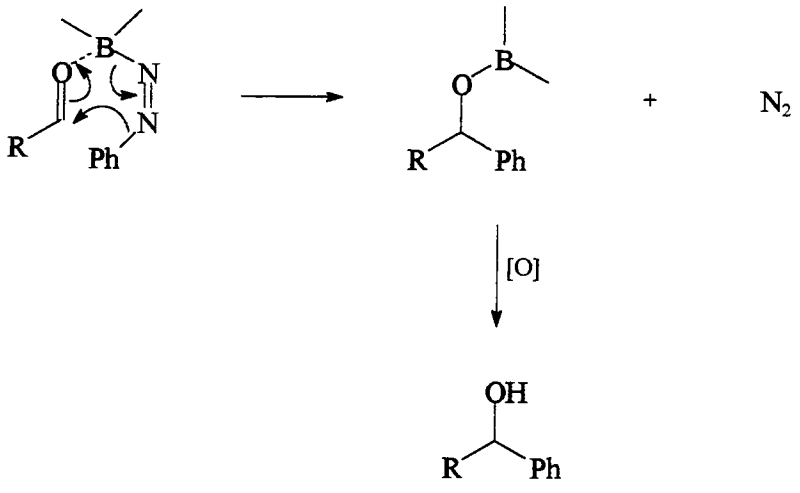
Borinic acid **5** was prepared from the reaction of dicyclohexylborane[1] with bis-(2-α,α,α-trifluorotolyl)borinic acid (prepared from boron tribromide and the Grignard of 2-bromo-α,α,α-trifluorotoluene, followed by hydrolysis). ^{11}B-NMR showed broad resonances at 55 and 47 ppm. Unfortunately, no reaction was observed upon addition of **5** to benzaldehyde.

Future research could be directed to further increase the Lewis acidity of one of the two boron atoms in borinic anhydrides.

2.3.2 Phenyldiazeneboranes

Although this approach would be limited to the addition of aryl groups, due to the instability of diazene compounds, it appeared that the liberation of nitrogen gas as a byproduct would significantly enhance the ease of reactivity towards carbonyl compounds (Scheme 2-2).

Scheme 2-2. Phenyldiazeneborane Approach.



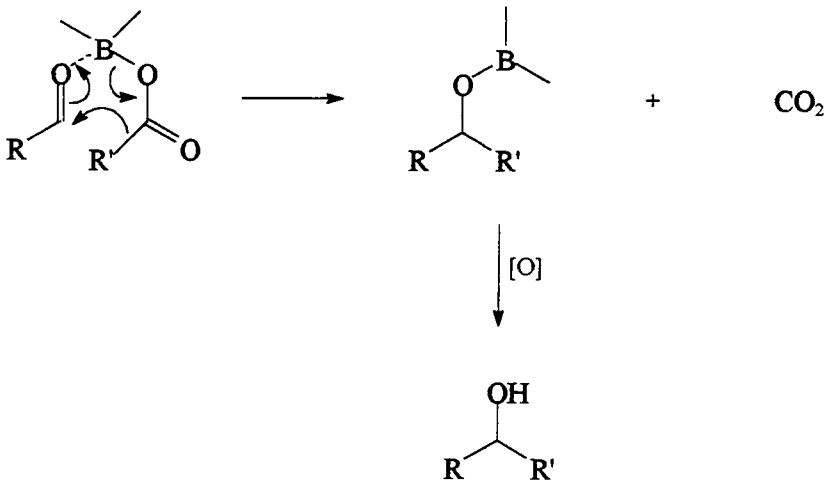
Phenyldiazene was prepared following literature procedures[45] and immediately allowed to react with 9-BBN to form the desired organoborane with liberation of hydrogen gas. The low concentrations required due to the instability of the diazene compounds in solution (< 0.01 M) precluded obtaining a ^{11}B-NMR spectrum of the resulting product. Immediate gas evolution was observed after the addition of 9-BBN and was taken as evidence of the formation of the desired phenyldiazeneborane compound. Unfortunately, no further reaction was observed upon addition of benzaldehyde.

Due to the limitations of this reaction and the difficulties encountered forming the diazene compounds, this approach was abandoned.

2.3.3 Acyloxyboranes

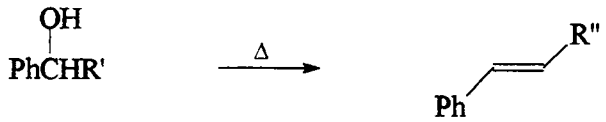
The reaction of a borane such as 9-BBN with carboxylic acids affords the corresponding acyloxyboranes. It was postulated that these agents might alkylate carbonyl compounds by releasing carbon dioxide (Scheme 2-3).

Scheme 2-3. Acyloxyborane Approach.



Various acyloxyboranes were prepared by reacting propionic acid with 9-BBN, dichloroborane and dibromoborane. In refluxing THF, these compounds failed to react with benzaldehyde.[42,43] Reasoning that at more elevated temperatures the decarboxylation should take place, the reaction of acyloxy-9-BBN with benzaldehyde was studied using a steel bomb. Indeed, at higher

temperatures the desired alkylation was observed, followed by dehydration of the intermediate to give the styrene derivative **6** (eqn 2-2) in moderate yields.



(2-2)

6

The major product arose however from the β-hydride reduction (Section 1.2.12) of benzaldehyde. In an effort to prevent the reduction product from competing with the alkylation of benzaldehyde, boranes bearing no β-hydrogens were investigated. The yields of the desired products were, however, not enhanced (Table 2-2).

Table 2-2. Reactions of Acyloxyboranes with Benzaldehyde.

Organoborane	R'	T (°C)	Alkylation (%)[a]	Reduction (%)[a]
9-BBN	Ethyl	390	43	57
9-BBN	Pentyl	390	20	80
9-BBN	Ethyl	200	0	50
catecholborane	Ethyl	390	27	0
catecholborane	Pentyl	390	< 5	0
dimethylborane	Ethyl	300	< 5	0
dimethylborane	Ethyl	360	9	0
dicyclohexylborane	Ethyl	350	30	30

[a] GC yieds

It was found that no alkylation took place at temperatures below 200 °C, which gives this method little synthetic value. This reaction was successful with aliphatic aldehydes and gave only traces of the desired product when benzophenone was used instead of benzaldehyde.

In separate experiments, attempts were made to carry out the reaction of an acyloxy-9-BBN with benzaldehyde under microwave and ultrasonic radiaton, but the results in both cases were negative.

Future research could be directed to the synthesis of other organoborane reagents which might give better yields of the desired products (**6**). Efforts could also be made to search for a catalyst that would aid in the decarboxylation at more reasonable temperatures in order to make it synthetically useful.

2.3.4 Other Approaches Involving Six-membered Transition States

Attempts have been made in the past[42] to react trialkylboranes with carbonyl compounds in the presence of reagents that could supply the two missing atoms of the desired six-membered ring transition state. To further examine this concept, 1,3-dicyclohexylcarbodiimide (DCC) was chosen as a possible reagent because it has an electrophilic center which could complex to the carbonyl moiety and a nucleophilic center which could complex to the organoborane (Figure 2-3).

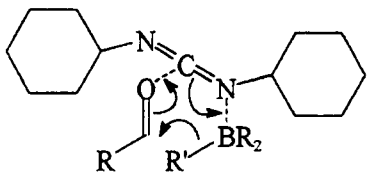


Figure 2-3. Transition State Involving DCC.

Unfortunately, when tributylborane was reacted with benzaldehyde in the presence of DCC no alkylation occurred. Benzaldehyde was reduced (Section 1.2.12) and DCC neither enhanced nor reduced the rate of this reduction.

2.4 Lewis Acidity of Organoboranes

The first step in the addition of organometallic reagents to the carbonyl moiety is the complexation of the metal to the carbonyl oxygen. As noted in Section 1.2.11, 1-boraadamantane is the only trialkylborane that forms a strong complex with aldehydes and ketones, therefore, experiments were devised to modify the organoborane in order to increase its Lewis acidity and its complexation ability. It should be noted that Lewis acidic boranes bearing good leaving groups induce enolization of the carbonyl compound and can lead to aldol type reactions.[46] A variety of approaches had been attempted in the past with no success.[42,47] These included, for example, the use of nitroboranes and triphenylphosphineboranes.[42]

2.4.1 Fluorinated Arylboranes

Fluorinated aryl substituents are excellent electron withdrawing groups and at the same time poor leaving groups, therefore, it was postulated that they would be good candidates for enhancing the Lewis acidity of boranes. *o*-Benzotrifluorodihexylborane (Figure 2-4, R = Hex) was synthesized from *o*-benzotrifluoromagnesium bromide and dihexylbromoborane. Both starting materials were prepared *in situ* from readily available starting materials.[1]

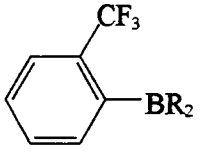


Figure 2-4. o-Benzotrifluorodialkylborane.

Unfortunately, the reagent failed to react with either benzaldehyde or heptanal.

2.4.2 Alkyldifluoroboranes

Although alkyldifluoroboranes (RBF_2) are readily prepared from alkylboronic acids and boron trifluoride,[48] there are few reports of their use in the literature. They were particularly attractive because the boron-fluoride bond is more stable than any of the boron-halogen bonds. Additionally, these compounds are potent Lewis acids.

Difluorohexylborane was prepared via the reaction of hexylboronic acid with boron trifluoride in hexanes. Complete formation of product was evidenced by the appearance of a triplet (J = 83 Hz) at δ 28.8 ppm (Figure 2-5). When an equimolar amount of benzaldehyde was added to a solution of difluorohexylborane in hexanes, a white solid precipitated out of solution. This solid proved to be a stable difluorohexylborane–benzaldehyde complex which was readily cleaved by ether to afford BF_3-etherate and benzaldehyde. 1-Boraadamantane (Section 1.2.11) formed a similar complex at room temperature and the alkylation was induced only at higher temperatures. The solid was thus heated in hexanes to reflux for 24 hours, followed by $NaBO_3$ oxidation. Although the solid dissolved readily upon heating, analysis of the products by GCMS showed only unreacted benzaldehyde and the expected 1-hexanol.

In a separate experiment, heptanal was added to a solution of hexyldifluoroborane in hexanes. Rather than a precipitate, a yellow solution was formed. The reaction mixture was heated to reflux overnight and analyzed after oxidation. No alkylation product was found. Instead, 72% of 2-pentyl-2-nonenal was isolated. This product was the result of the acid catalyzed self-condensation of heptanal followed by dehydration.

We concluded that alkyldifluoroboranes would not alkylate carbonyl compounds; They act as Lewis catalysts to promote aldol type reactions. However, further investigation of the properties of such compounds (and eventually boron trifluoride) led to the findings which are detailed in Part B of this dissertation.

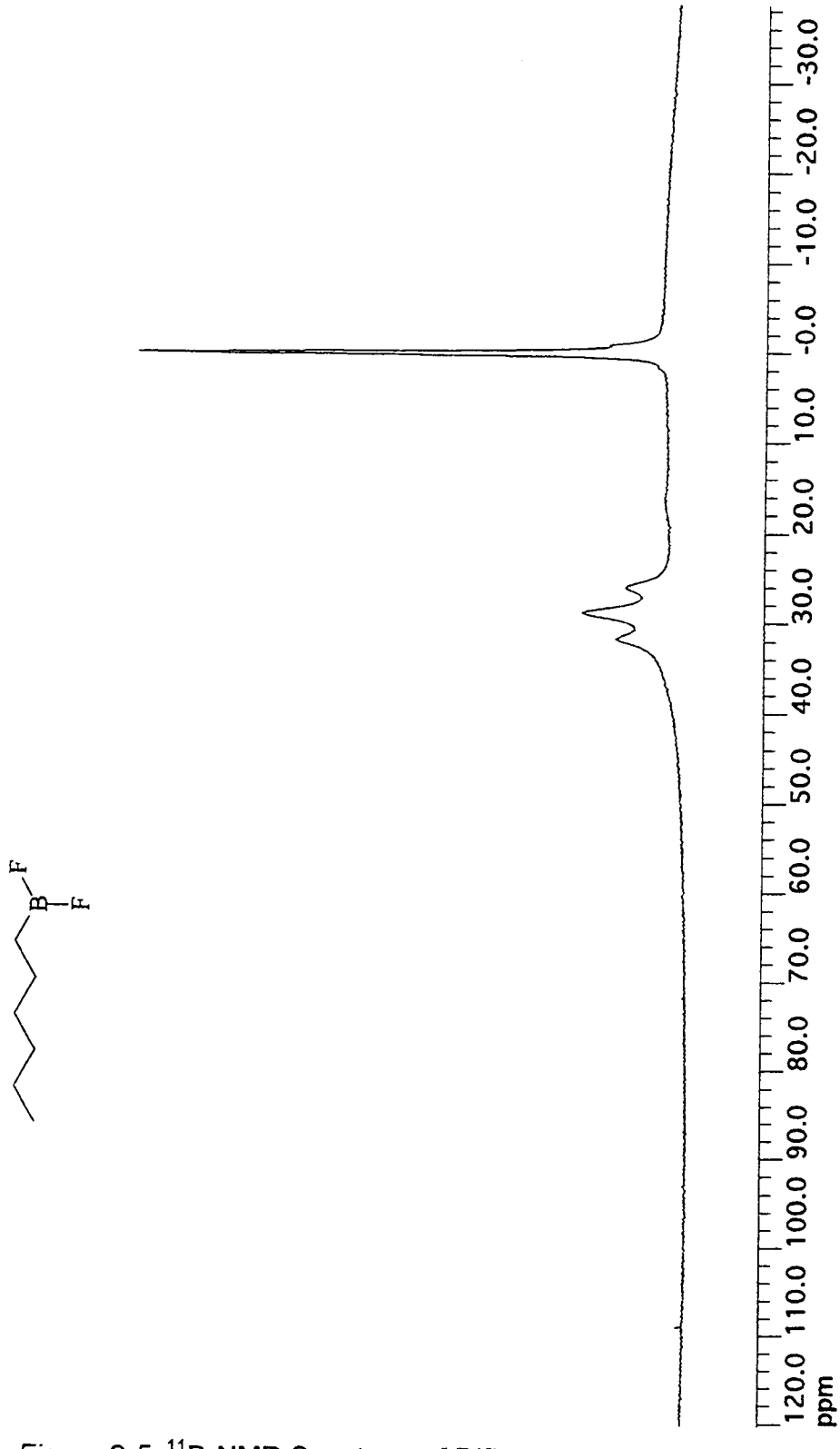


Figure 2-5. ^{11}B-NMR Spectrum of Difluorohexylborane.

2.5 Conclusion

A wide variety of organoboranes react with carbonyl compounds to generate new carbon-carbon bonds. However, unlike other organometallic reagents, trialkylboranes fail to add to the carbonyl group in a 1,2-manner with the exception of 1-boraadamantane.

Three different approaches were devised in an attempt to overcome this lack of reactivity. First, reactions were irradiated with either ultrasound or microwaves giving, in both cases, negative results. Second, efforts were directed to modify the transition state from a four to a six-membered ring. Acyloxyboranes gave positive results but improvements will be necessary before the reaction is synthetically useful. Finally, fluorinated organoboranes were prepared in an effort to increase the Lewis acidity at the boron atom. Although no 1,2-addition was observed upon addition to carbonyl compounds, further studies on alkyldifluoroboranes and boron trifluoride led to a new methodology for the synthesis of β-alkylstyrenes and carboxylic acids from readily available ketones and aromatic aldehydes. Our findings are discussed in Part B of this dissertation.

2.6 Experimental

All reactions were performed in oven-dried glassware under a nitrogen atmosphere and with continuous magnetic stirring. Air and moisture sensitive compounds were introduced via syringe or cannula through a rubber septum. All

solvents were dried and distilled prior to use. Products were purified by flash chromatography using 230-400 mesh ASTM 60 silica gel. All ^{1}H and ^{13}C-NMR spectra were recorded on a 250 MHz Bruker AC250 spectrometer. All ^{1}H and ^{13}C-NMR data were obtained in $CDCl_3$ solution, chemical shifts (δ) are reported in ppm relative to TMS, and coupling constants (J) are given in Hz. All ^{11}B-NMR were recorded on a JEOL FX90Q spectrometer. ^{11}B-NMR chemical shifts are reported relative to $BF_3{\cdot}OEt_2$. All GCMS data were obtained using a Hewlett Packard 5890 Series GC System equipped with a 5970 Mass Selective Detector.

2.6.1 Reaction of Benzaldehyde and Tributylborane Under Ultrasonic Irradiation.

A solution containing benzaldehyde (5.0 mmol) and tributylborane (5.0 mmol) in THF (20 mL) was irradiated with ultrasound (Fisher Scientific, Model 550 Sonic Dismembrator, 190 watts, 20 kHz) for 30 minutes at a 30% intensity. The reaction mixture was oxidized with $NaBO_3{\cdot}4H_2O$ and the organic products were extracted into ether. Analysis of the products revealed only unreacted benzaldehyde.

2.6.2 Reaction of Benzaldehyde and Tributylborane Under Microwave Irradiation.

A solution containing benzaldehyde (3.0 mmol) and tributylborane (3.0 mmol) was irradiated with microwaves (Sharp, Model R-4A38, 1000 watts, 2450 MHz) for 3 minutes. The reaction mixture was oxidized with $NaBO_3{\cdot}4H_2O$ and the organic products were extracted into ether. GCMS data revealed approximately 50% reduction of benzaldehyde to benzyl alcohol and no other products.

*2.6.3 Reaction of Borinic Anhydrides **4** and **5** with Benzaldehyde.*

Borinic anhydride **4** was prepared via the reaction of diiodoborane (prepared in situ, 5.0 mmol)[44] and dihexylboronic acid (5.0 mmol)[1] in THF (10 mL). Benzaldehyde (5.0 mmol) was added to the reaction mixture containing **4** and the mixture was stirred overnight at room temperature. The reaction mixture was oxidized with $NaBO_3 \cdot 4H_2O$ and the organic products were extracted into ether. Analysis of the mixture revealed 1-hexanol, 1-iodohexane and benzaldehyde. No alkylation product was detected.

Borinic anhydride **5** was prepared via the reaction of dicyclohexylborane (prepared in situ, 3.0 mmol)[1] and bis-(2-α,α,α-trifluorotolyl)borinic acid (prepared in situ from boron tribromide and 2-bromo-α,α,α-trifluorotoluenemagnesium bromide, 3.0 mmol).[1] Benzaldehyde (3.0 mmol) was added to the reaction mixture containing **5** and the mixture was stirred overnight at room temperature. The reaction mixture was oxidized with $NaBO_3 \cdot 4H_2O$ and the organic products were extracted into ether. Analysis of the products revealed cyclohexanol, 2-α,α,α-trifluomethylphenol, and benzaldehyde. No alkylation product was detected.

2.6.4 Reaction of Phenylhydrazine with 9-BBN and Benzaldehyde.

To a solution of phenylhydrazine (prepared in situ, 1.0 mmol)[45] was added 9-BBN (0.5 M in THF, 2.0 mL) and the reaction mixture was stirred at room temperature for 15 minutes. Benzaldehyde (1.0 mmol) was added to the solution

and the mixture was stirred at room temperature for 5 hours. The reaction mixture was oxidized with $NaBO_3 \cdot 4H_2O$ and the organic products were extracted into ether. ^{1}H-NMR data revealed no products from the alkylation of benzaldehyde.

2.6.5 Reaction of Acyloxyboranes with Benzaldehyde.

Acyloxyboranes (Table 2-2) were prepared via reaction of propanoic acid and pentanoic acid with the corresponding dialkylboranes (equimolar amounts reacted in ether solvent at 0 °C for 1 hour). 9-BBN and catecholborane were purchased (Aldrich Chemical Company) and used as received. Dimethylborane and dicyclohexylborane were prepared following literature procedures.[1] Acyloxyboranes (3.0 mmol) were allowed to react with benzaldehyde (3.0 mmol) in ether (10 mL) for 0.5 hour at temperatures ranging from 200-390 °C in a steel bomb placed in a Kugelrohr. The reaction mixtures were oxidized with $NaBO_3 \cdot 4H_2O$ and the organic products were extracted into ether. GC yields (Table 2-2) were obtained using undecane as the internal standard.

2.6.6 Reaction of Benzaldehyde and Tributylborane in the Presence of Dicyclohexylcarbodiimide (DCC).

A mixture of benzaldehyde (6.8 mmol), tributylborane (6.8 mmol) and DCC (6.8 mmol) was stirred in THF (10 mL) at reflux for 12 hours. The reaction mixture was oxidized with $NaBO_3 \cdot 4H_2O$ and the organic products were extracted into ether. Benzyl alcohol 0.51 g (70% yield) was isolated by flash

chromatography using silica gel and 10% EtOAc/hexanes as the eluent. No alkylation product was obtained.

2.6.7 Reaction of 2-Benzotrifluorodicyclohexylborane with Benzaldehyde.

A solution of 2-benzotrifluorodicyclohexylborane (prepared in situ from dicycloxexylborane and 2-benzotrifluoromagnesium bromide, 2.6 mmol)[1] and benzaldehyde (2.6 mmol) in THF (10 mL) was stirred at room temperature for 12 hours. The reaction mixture was oxidized with $NaBO_3 \cdot 4H_2O$ and the organic products were extracted into ether. Analysis of the products revealed no products arising from alkylation of benzaldehyde.

2.6.8 Reaction of Difluorohexylborane with Benzaldehyde.

A solution of difluorohexylborane (prepared in situ from hexylboronic acid and BF_3, 6 mmol)[48] and benzaldehyde (15 mmol) in hexanes (10 mL) was stirred at reflux for 24 hours. The reaction mixture was quenched with H_2O (10 mL) and the organic products were extracted into ether. Analysis of the products revealed unreacted benzaldehyde.

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PART B

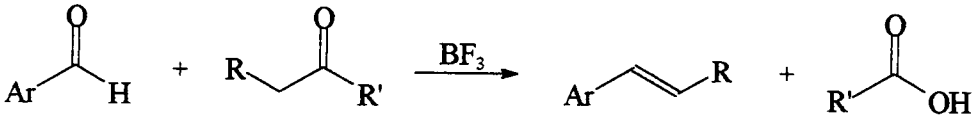
REACTION OF KETONES WITH AROMATIC ALDEHYDES IN THE PRESENCE OF BORON TRIFLUORIDE

CHAPTER 1

SYNTHESIS OF (E)-β-ALKYLSTYRENES VIA THE REACTION OF KETONES WITH AROMATIC ALDEHYDES IN THE PRESENCE OF BORON TRIFLUORIDE

1.1 Introduction

During our investigation centered on new carbon-carbon bond formation reactions via organoboranes, we discovered an unprecedented reaction of ketones with aromatic aldehydes in the presence of boron trifluoride. Part B of this dissertation describes this new synthetic method which affords (E)-β-alkylstyrenes and carboxylic acids (eqn 1-1).



(1-1)

In order to gain a better understanding of the significance of this study, an overview of the chemistry related to this new reaction will first be presented.

1.1.1 Boron Trifluoride

Boron trifluoride is a colorless, nonflammable gas with a boiling point of -100 °C. It is soluble in solvents such as carbon tetrachloride, chloroform, saturated hydrocarbons, benzene and carbon disulfide.[1] It easily forms coordination complexes with molecules having at least one unshared pair of electrons, a wide variety of which are commercially available.

Boron trifluoride, in the free form or as a complex, has been extensively studied in organic chemistry. For the most part, it has been associated with polymerization, condensation and alkylation reactions.

1.1.1.1 Polymerization Reactions

The polymerization of alkenes in the presence of BF_3 is probably one of the most investigated acid catalyzed reactions. It is known that in the absence of water (or other protic species), boron trifluoride does not react with olefins,[2] but in the presence of traces of water, it forms a protic acid which brings about a rapid cationic polymerization of the olefin.[3] Related reactions include the cyclotrimerization of aliphatic aldehydes in the presence of boron trifluoride ethyl etherate[4] and the ring-opening polymerization of cyclic ketene acetals.[5]

1.1.1.2 Condensation Reactions

Condensation reactions promoted by boron trifluoride are numerous. For example, one important synthetic method for the preparation or carboxylic acids

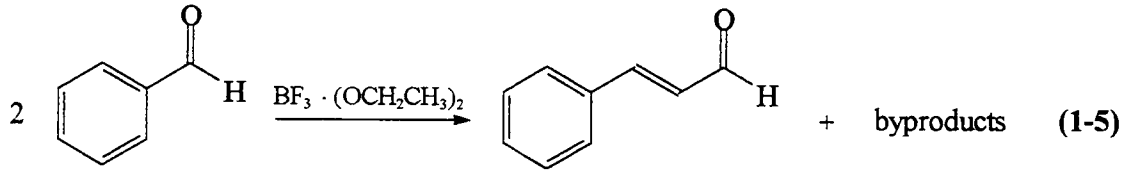
is the condensation of carbon monoxide with alcohols[6] (eqn 1-2), ethers[7] (eqn 1-3), or olefins[8] (eqn 1-4) in the presence of BF_3.

$$RCH_2OH + CO \xrightarrow{BF_3} RCH_2\overset{O}{\overset{\|}{C}}-OH \qquad \textbf{(1-2)}$$

$$ROR + 2\,CO \xrightarrow[H_2O]{BF_3} R\overset{O}{\overset{\|}{C}}-OH \qquad \textbf{(1-3)}$$

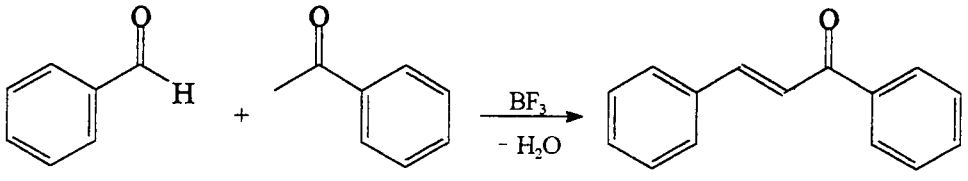
$$CH_2{=}CH_2 + CO \xrightarrow[H_2O]{BF_3} CH_3CH_2\overset{O}{\overset{\|}{C}}-OH \qquad \textbf{(1-4)}$$

The self-condensation of benzaldehyde in the presence of boron trifluoride ethyl etherate has also been reported. Even below room temperature, benzaldehyde is slowly converted into cinnamaldehyde (eqn 1-5) via a reaction that includes the cleavage of diethyl ether.[9]



(1-5)

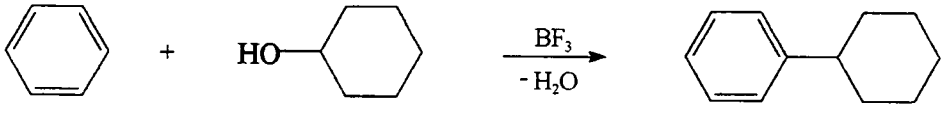
The condensation of acetophenone with benzaldehyde saturated with boron trifluoride is closely related to our study and has been reported to produce benzalacetophenone in 66% yield (eqn 1-6).[10] It is important to point out that the authors did not identify any products arising from the cleavage of acetophenone or the β-hydroxyketone intermediate.



(1-6)

1.1.1.3 Alkylation of Aromatic Hydrocarbons

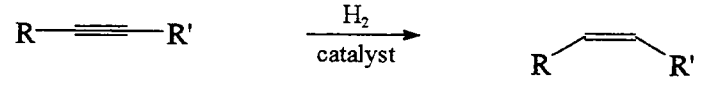
Boron trifluoride is one of a variety of Lewis acids commonly used in the Friedel-Crafts alkylation of aromatic hydrocarbons. Numerous examples are know in which alkenes, alcohols, alkyl halides or ethers are used for the alkylation of benzene or its derivatives.[11] A representative example, commonly found in organic chemistry textbooks,[12] is the reaction of cyclohexanol and benzene (eqn 1-7).



(1-7)

1.1.2 β-Alkylstyrenes

β-Alkylstyrenes, an important type of 1,2-disubstituted alkenes, are accessible via a variety of well known methods. Some of these include the reduction of alkynes (eqn 1-8 and 1-9),[13] the Wittig reaction and its variations (eqn 1-10),[13,14] the Heck coupling reaction (eqn 1-11),[13,15] and various elimination reactions (eqn 1-12).[13]



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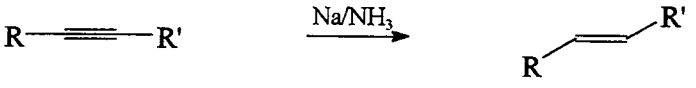

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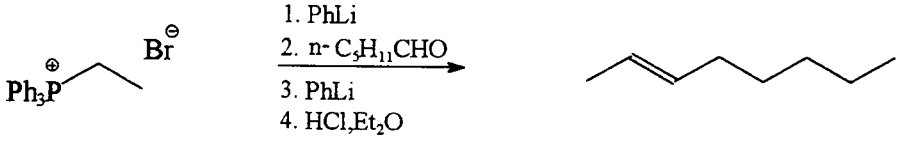

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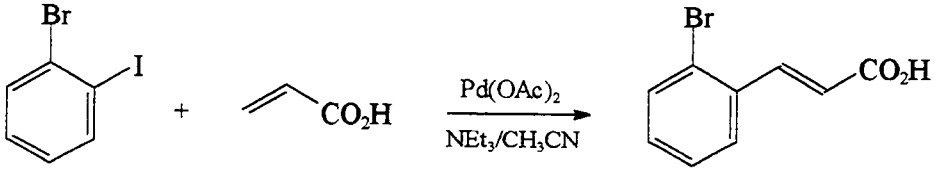


(1-11)

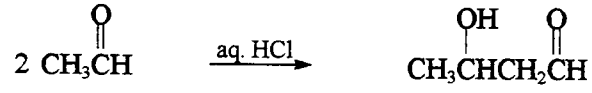
(1-12)

New methods have recently been reported confirming the importance of β-alkylstyrenes in organic synthesis. Some of the recent methods involve β-nitrostyrenes,[16] alkenylzinc reagents[17] and β-hydroxysulfones[18] as starting materials.

With the wide range of synthetic methods available, the factors that most often determine the method chosen for a particular synthesis are stereoselectivity (E/Z ratios), product yields, availability of the starting materials and tolerance of functional groups. The new method described in this dissertation will be compared to the other existing methodologies.

1.1.3 Aldol Condensations

Aldol (3-hydroxybutanal) was first reported in 1872 by Wurtz as the product from the self-condensation of acetaldehyde in aqueous acid (eqn 1-13).[19,20] Although it was not the first reaction of this type, it has since given its name to the self-condensation or mixed-condensation of aldehydes and ketones. The self-condensation of acetone was first reported by Kane in 1838 to give mesityl oxide (eqn 1-14).[21]



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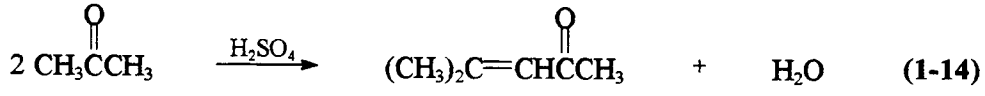


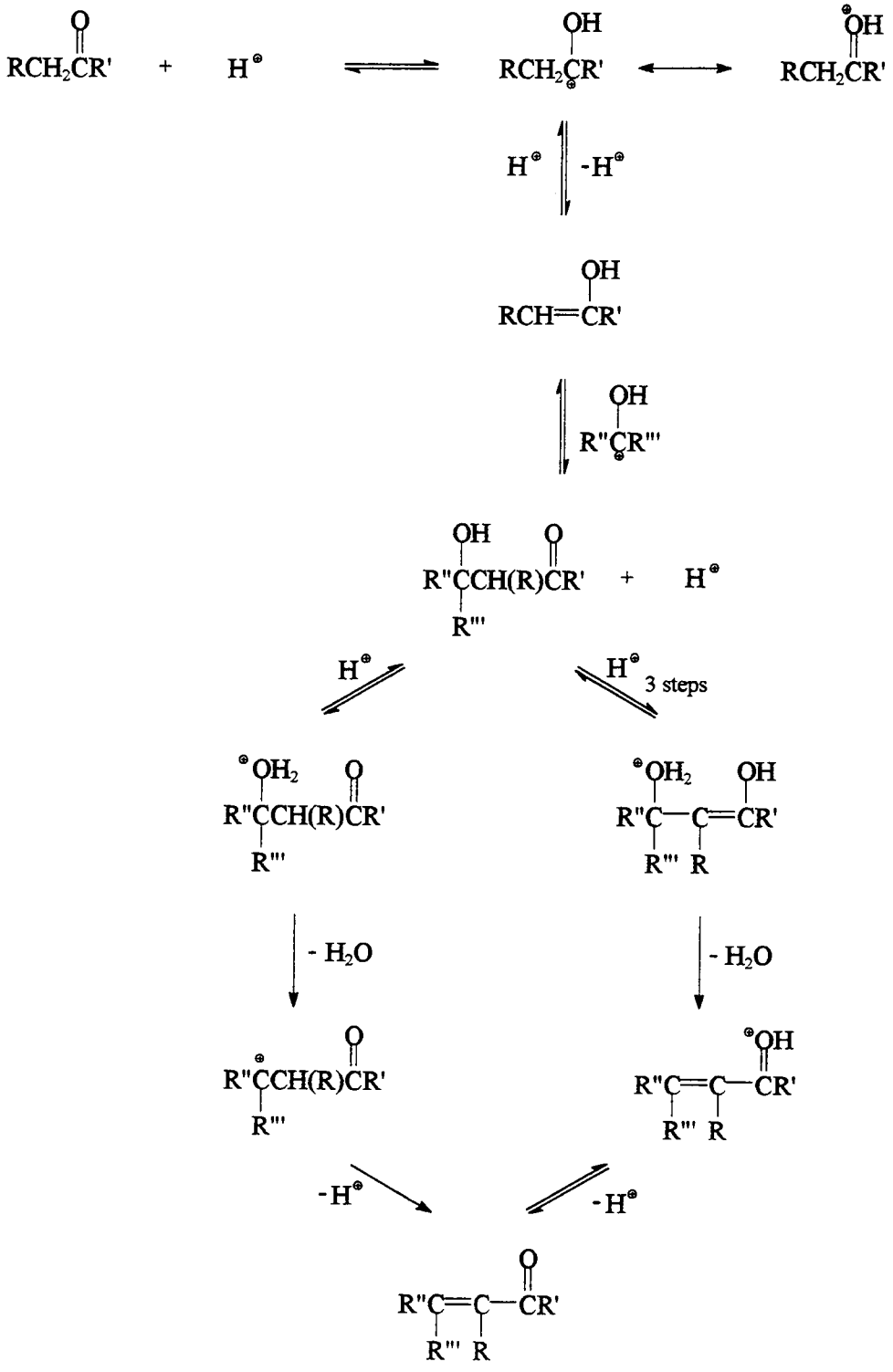
(1-14)

The aldol condensation and "aldol-type" reactions (i.e. Reformatsky,[22] Knoevenagel,[23] Claisen,[24] etc...) have received a tremendous amount of attention over the years. Although both base- and acid-mediated methods have been studied, this dissertation focuses on acid-catalyzed aldol chemistry. The acid-catalyzed mechanism (Scheme 1.1) involves the condensation of two carbonyl compounds followed, in the majority of the cases, by a rapid dehydration of the β-hydroxycarbonyl intermediate. The dehydration occurs via one of two distinguishable pathways depending on the stability of the carbocation. For example, 4-(*p*-methoxyphenyl)-4-hydroxy-2-butanone undergoes dehydration via a carbocation intermediate while 4-(*p*-nitrophenyl)-4-hydroxy-2-butanone dehydrates via an enolization pathway.[25]

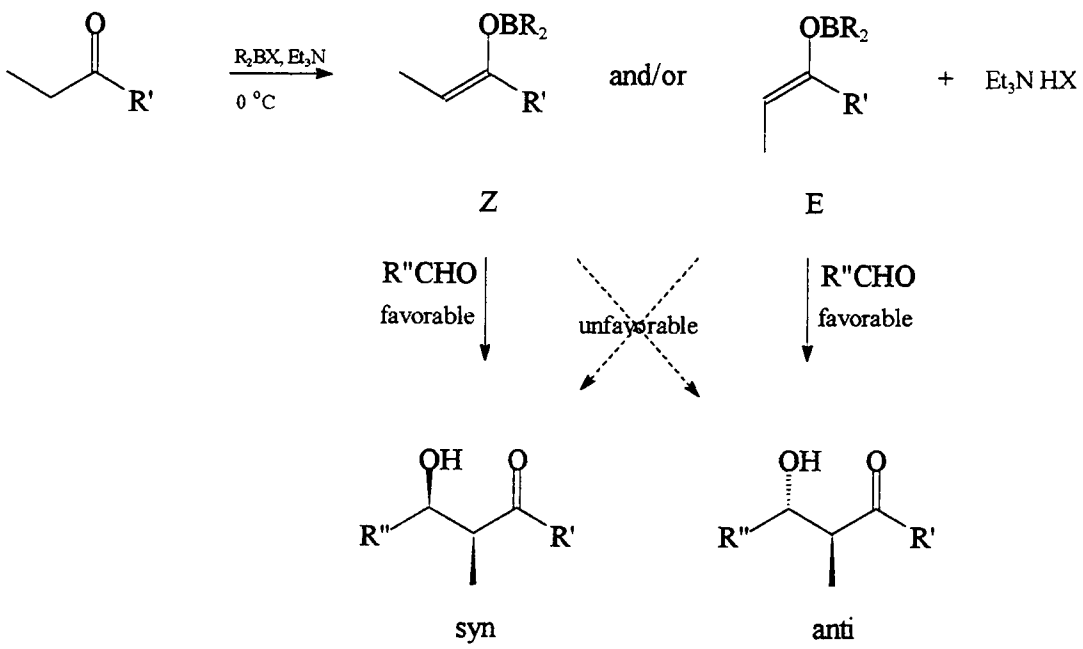
In most cases, the acid-catalyzed aldol condensations are carried out in strong aqueous acid and lead to the α,β-unsaturated carbonyl compounds. Other reaction conditions that lead to dehydrated products have also been reported. For example, Equation 1-6 illustrated the condensation of acetophenone with benzaldehyde in the presence of boron trifluoride. Additionally, 2-butanone has been found to react with benzaldehyde and HCl in the absence of solvent or in an aprotic solvent such as benzene to give, upon base work-up, the α,β-unsaturated ketone.[26,27]

More recent aldol condensation studies have led to new methods for the asymmetric synthesis of β-hydroxyketones. For example, R_2BX (X=Cl, Br, I, OTf) have often been used to selectively produce *syn* or *anti* β-hydroxyketones without leading to dehydration products (Scheme 1-2).[28]

Scheme 1-1. Mechanism of Acid Catalyzed Aldol Condensation.



Scheme 1-2. Asymmetric Aldol Condensation.



1.2 Synthesis of β-Alkylstyrenes

1.2.1 Reaction in the Presence of Difluorohexylborane

We initially examined the properties of difluorohexylborane in the aldol condensation of 5-nonanone with benzaldehyde. A non-nucleophilic solvent such as hexane was chosen because fluoroboranes are more Lewis acidic when not complexed to a Lewis base. When the reaction mixture was analyzed by GC/MS, 1-phenyl-1-pentene was found among the products. The generation of this alkene could be rationalized if a C-C bond cleavage at the aldol intermediate had occurred, followed by dehydration. Among the remaining products,

β-hydroxyketone (from the aldol condensation), pentanoic acid and two dimers of 1-phenyl-1-pentene were also found.

Three experiments were performed in which the ratio of starting materials was varied. The results are summarized in Table 1-1.

Table 1-1. Ratio Study; $HexBF_2$, 5-Nonanone and Benzaldehyde.[a]

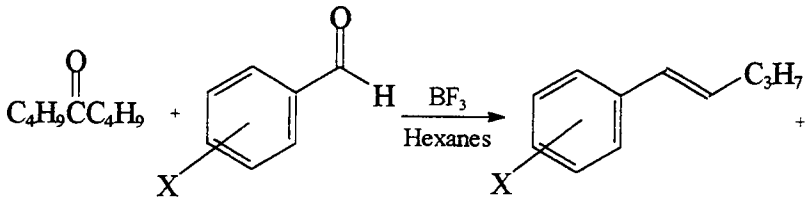
Exp.	$HexBF_2$	5-nonanone	benzaldehyde	Alkene[b]	Aldol[b,c]	Dimer[b,e]
1[d]	1.0	1.0	1.5	49 %	0 %	0 %
2[d]	1.0	1.7	1.1	12 %	40 %	0 %
3	1.6	1.0	1.1	0 %	0 %	75 %

[a] Reactants stirred in hexanes at room temperature for 12 hours. [b] Yields based on limiting reagent. [c] β-hydroxyketone. [d] GC/MS analysis revealed unreacted starting materials. [e] Mixture of two (shown by GC/MS analysis) unidentified compounds of twice the molecular weight of the alkene.

This study indicated that the best results can be obtained by adding excess benzaldehyde. The results revealed that the alkene product is not stable under reaction conditions in which excess of the Lewis acid was present. Before an attempt was made to maximize the yield of the alkene under these reaction conditions, the reaction was repeated using boron trifluoride as the Lewis acid.

1.2.2 Reaction in the Presence of Boron Trifluoride

We felt that commercially available boron trifluoride would be a more convenient reagent than difluorohexylborane. Indeed, when 5-nonanone (**1**) was reacted with benzaldehyde (**2a**) in hexanes, and in the presence of boron trifluoride, 1-phenyl-1-pentene (**3a**) and pentanoic acid (**4**) were obtained (eqn 1-15).



1 **2** **3** **4**

a: X = H
b: X = 2-Cl
c: X = 3-Cl
d: X = 4-Cl
e: X = 2-Br
f: X = 3-Br
g: X = 4-Br
h: X = 2-NO_2
i: X = 3-NO_2
j: X = 4-NO_2
k: X = 4-CH_3
l: X = 4-CF_3
m: X = 3-OCH_3
n: X = 2-CO_2H
o: X = 3-OH

1.2.2.1 Reaction Time and Temperature

In an effort to define the reaction conditions which maximize the yield of the desired styrene product, reaction time and temperature were examined. The results are summarized in Table 1-2. This study indicates that the reaction appears to be very time dependent due to the ease of polymerization of the styrenyl product in the presence of boron trifluoride. It also shows that refluxing the reactions is more effective than room temperature.

Table 1-2. Reaction of **1** with **2a** in the Presence of BF_3.[a]

Entry	Time	Temperature	Yield (%)[b]
1	20 hr	RT	60
2	43 hr	RT	< 5[c]
3	0.5 hr	reflux	61
4	1 hr	reflux	78
5	3 hr	reflux	42[c]

[a] Reaction carried out in hexane using 30% excess benzaldehyde. [b] (E)-1-phenyl-1-pentene (**3a**); isolated yields based on 5-nonanone. [c] GC/MS confirms dimerization of the product.

1.2.2.2 Ratio of Starting Materials

A second study was performed to determine the ratio of starting materials which would lead to the optimum yields of the alkene product. This study was performed utilizing 3-chlorobenzaldehyde (**2c**, X = 3-Cl) instead of benzaldehyde because of the lower tendency of the product (E)-1-(3-chlorophenyl)-1-pentene (**3c**, X = 3-Cl) to dimerize under the reaction conditions. The results are summarized in Table 1-3. The study reveals that excess aldehyde results in increased yields. However, similar results can be achieved using equimolar quantities of the starting materials by increasing the reaction time from 2 hrs to 3 hours. We conclude from these studies that equimolar amounts of the aldehyde and the ketone can be used as long as the products are resistant to

polymerization (generally aryl aldehydes bearing an electron withdrawing group). An excess of the aldehyde is more effective for those reactions yielding alkenes that are readily polymerized.

Table 1-3. Reaction of **1** with **2c** in the Presence of BF_3.

Entry	Ketone	Aldehyde	Time[a]	Yield (%)[b]
1	1.0 eq	1.0 eq	2 hr	76[c]
2	1.0 eq	1.0 eq	3 hr	84
3	1.0 eq	1.3 eq	2 hr	78[c]
4	1.0 eq	1.3 eq	2.5 hr	89
5	1.0 eq	1.5 eq	2 hr	84[c]
6	1.0 eq	2.0 eq	2 hr	90

[a] Reflux in hexanes. [b] Isolated yields of (E)-1-(3-chlorophenyl)-1-pentene (**3c**).

[c] GC/MS reveals unreacted 5-nonanone.

1.2.2.3 Reaction Solvents

The reaction of 3-chlorobenzaldehyde (**2c**) with 5-nonanone (**1**) was studied in different solvents. The results of this study are presented in Table 1-4.

The most significant result is that a non-nucleophilic solvent is required for the reaction to take place. A nucleophilic solvent such as ethyl ether completely inhibits the reaction. Complexed boron trifluoride apparently loses its ability to promote the aldol condensation of the starting materials because unreacted 5-

nonanone and 3-chlorobenzaldehyde were recovered when diethyl ether was used as the reaction solvent. The optimized yield of 1-(3-chlorophenyl)-1-pentene (**3c**) in dichloromethane is lower than in any other non-nucleophilic solvent studied. A possible explanation might be that dichloromethane, being more polar, the olefin enhances the cationic polymerization of the olefinic product. In fact, GC/MS analyses confirmed the formation of the dimeric species after 3 hours, thus lowering the yield of the desired product.

Table 1-4. Solvent Study of the Reaction of **1** with **2c**.

Entry	Solvent	Time	Temperature	% Yield [a]
1	Ether	12 hr	RT	0
2	Hexane	2.5 hr	68-70 °C	89
3	CCl_4	2 hr	76-77 °C	53
4	CCl_4	4 hr	76-77 °C	75
5	CCl_4	6 hr	76-77 °C	91
6	CH_2Cl_2	2 hr	40 °C	67
7	CH_2Cl_2	3 hr	40 °C	75
8	CH_2Cl_2	4 hr	40 °C	62
9	Toluene	2 hr	110 °C	75
10	Toluene	4 hr	110 °C	84

[a] Isolated yields of (E)-1-(3-chlorophenyl)-1-pentene.

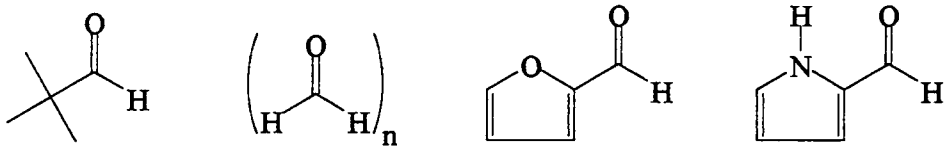
Hexane, carbon tetrachloride and toluene gave excellent results. The only appreciable difference was a slight increase in the reaction rate when hexane was used. For safety and economic reasons, hexane appears to be the ideal solvent.

1.2.2.4 Aromatic Aldehydes vs. Non-Aromatic Aldehydes

The reaction of ketones with aromatic aldehydes in the presence of boron trifluoride to yield β-alkylstyrenes and carboxylic acids (eqn 1-1) proceeds readily. Unfortunately, the reaction cannot be generalized to aliphatic aldehyes which would result in the synthesis of aliphatic 1,2-disubstituted alkenes. When 5-nonanone was reacted with heptanal in the presence of boron trifluoride, the only products observed in the GC/MS and ^{1}H-NMR spectra were the β-hydroxyaldehyde obtained from the self-condensation of heptanal and the β-hydroxyketone obtained from the mixed-condensation.

Reactions were also carried out with non-enolizable aldehydes to avoid the self-condensation product. For example, pivalaldehyde (2,2-dimethylpropanal, **5**) was allowed to react with 5-nonanone in the presence of boron trifluoride in refluxing hexane, but no olefin product was obtained. The same reaction was attempted in toluene (higher refluxing temperature) with no change in the outcome. Similarly, paraformaldehyde (**6**) was reacted with a higher molecular weight ketone (1,3-diphenyl-2-propanone) and only an identified black tar was obtained.

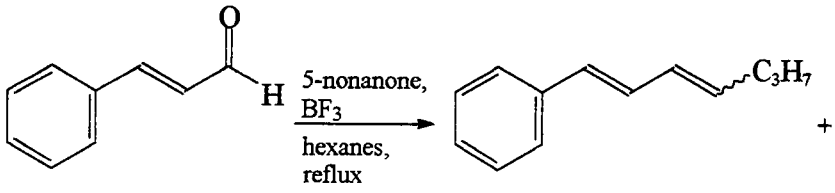
Heterocyclic compounds **7** (2-furaldehyde) and **8** (pyrrole-2-carboxaldehyde) gave similar results upon their reaction with 5-nonanone. Black tars were obtained, presumably from the polymerization of the aldehydes. These results were somewhat expected because dienic compounds such as cyclopentadiene have been reported to polymerize readily in the presence of boron trifluoride.[1b,29]



5 **6** **7** **8**

Figure 1-1. Non-Enolizable Aldehydes.

Finally, *trans*-cinnamaldehyde (**9**) produced the conjugated diene (**10**) in 4% and 5% yield in two separate experiments in which reaction solvents were varied (eqn 1-16). The low yields were attributed to the ease of polymerization of the diene product.[1b,29] The trans-trans / trans-cis ratio was not as high as the E/Z ratios obtained for styrenyl products. ^{1}H-NMR data was used to calculate a 4:1 ratio of the corresponding isomers (E/Z). Further research will be required to identify reaction conditions which would lead to higher yields.



(9) **(10)**

Benzaldehyde and a large number of substituted benzaldehydes have been found to give the corresponding β-alkylstyrene derivatives upon reaction with 5-nonanone and boron trifluoride (refer to eqn 1-15). The yields obtained are largely dependent on the nature of the substituent, being generally higher for instances where electron withdrawing groups are present, a fact attributed to the stability of the styrenyl products under the reaction conditions. The common byproduct of the reactions leading to **3a-3n** was pentanoic acid. Although it was identified in the GC/MS and NMR spectra, it was not isolated in every reaction as a part of this study. As an example, an isolated yield of 84% of pentanoic acid was obtained from the reaction of benzaldehyde (**2a**) leading to 1-phenyl-1-pentene (**3a**). Table 1-5 contains a summary of the different aromatic aldehydes investigated to date as well as the corresponding reaction conditions and yields.

Table 1-5. Reaction of Substituted Benzaldehydes with 5-Nonanone in the Presence of BF_3.[a]

Aldehyde	Time	Product[b] (%)	(E/Z)[c]
2a	1 hr	**3a** (78)	97:3
2b	4 hr	**3b** (91)	98:2
2c	2.5 hr	**3c** (89)	95:5
2d	4 hr	**3d** (91)	94:6
2e	4 hr	**3e** (88)	98:2
2f	2.5 hr	**3f** (92)	95:5
2g	4 hr	**3g** (86)	96:4
2h	4 hr	**3h** (8)	98:2
2i	2 hr	**3i** (83)	92:8
2j	1.5 hr	**3j** (49)	94:6
2k	2.5 hr	**3k** (66)	98:2
2l	4 hr	**3l** (82)	96:4
2m	1.5 hr	**3m** (20)	96:4
2n	1hr, 7hr	**3n** (0)[d]	----
2o	1 hr	**3o** (0)[d]	----

[a] Reaction carried out in hexane at reflux. [b] Spectral data are in agreement with the proposed structures. [c] Isomer ratios determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum. [d] An unidentified black tar was obtained.

Chloro- and bromo-substituted benzaldehydes (**2b**-**2g**) gave excellent yields of the corresponding alkenes (**3b**-**3g**). The yields were not sensitive to the regiochemistry of the substituent and the alkene products were found to be fairly stable to the reaction conditions. They were found, however, to slowly dimerize (evidenced by GC/MS and ^{1}H-NMR data) when the reaction times were lengthened.

Nitro-substituted benzaldehydes (**2h**-**2j**) were found to be very dependent on the substitution site. While 3-nitrobenzaldehyde (**2i**) gave an 83% yield of the corresponding alkene (**3i**), the yields were lower for both 4-nitro- and 2-nitrobenzaldehyde (**2j** and **2h**). The lower yields (49% and 8% respectively) can be rationalized by assuming that delocalization of the positive charge (Section 1.2.4; mechanism) places partial positive charges at the ortho and para carbons of the benzene ring. A nitro group at either of these positions would then be expected to destabilize the carbocation due to its powerful electron withdrawing properties. The dehydration product of the β-hydroxyketone (α,β-unsaturated ketone) intermediate was isolated in both cases. This is in accordance with mechanistic studies on *p*-nitro-substituted β-aryl-β-hydroxyketones which reveal that the dehydration does not occur via a carbocation. Instead, the studies suggested a mechanism which involves rate determining enolization (Scheme 1-1, Section 1.1.3).[25] To date, the 2-nitro- and 4-nitrobenzaldehydes (**2h** and **2j**) have been found to be the only aldehydes which have produced α,β-unsaturated ketones. As observed for the chloro- and bromo-substituted alkene products (**3b**-

3g), the nitro-substituted alkene products (**3h-3j**) were found to be fairly stable to the reaction conditions.

Two other substituted benzaldehydes bearing electron-withdrawing groups were studied. 4-(Trifluoromethyl)benzaldehyde (**2l**) gave the corresponding alkene (**3l**) in 82% yield. 2-Carboxybenzaldehyde (**2n**) failed to produce the desired alkene (**3n**). Since 2-nitrobenzaldehyde (**2h**) gave the poorest yield among the nitro-substituted benzaldehydes, the results given by **2n** should not lead to the conclusion that all carboxybenzaldehydes fail to generate styrenyl products under the reaction conditions. It is possible that the carboxy group at the 2-position might influence the lactol formation by decreasing the nucleophilicity of the hydroxy (Section 1.2.4). The carboxy group could increase the electron density of the hydroxy group through hydrogen bonding making the latter less reactive. Further studies could evaluate the reaction of 3-carboxy- and 4-carboxybenzaldehyde with 5-nonanone in the presence of boron trifluoride to determine how the carboxy- group influences the reaction.

Generally, substituted benzaldehydes bearing electron-donating groups produce lower yields because the styrenyl products are more prone to polymerization under the reaction conditions. For example, 4-tolualdehyde (**2k**) gave the corresponding alkene (**3k**) in 66% yield. Similar yields are expected for other alkyl-substituted benzaldehydes.

3-Hydroxybenzaldehyde (**2o**) failed to produce alkene (**3o**). Instead a black tar was obtained after only a few minutes. GC/MS analysis of the organic

solution revealed that pentanoic acid had been formed in good yields, suggesting that **3o** had initially formed but then polymerized very rapidly.

Finally, 3-anisaldehyde (3-methoxybenzaldehyde, **2m**) gave the corresponding alkene (**3m**) in 20% yield. Similar to the reaction of 3-hydroxybenzaldehyde (**2o**), a black tar was obtained, suggesting partial polymerization of the product. A study revealed that shorter reaction times lead to an incomplete reaction, while longer reaction times lead to a the disappearance of the starting aldehyde and lower yields of the alkene (**3m**) due to its rapid polymerization.

1.2.2.5 Aromatic Aldehydes vs. Aromatic Ketones

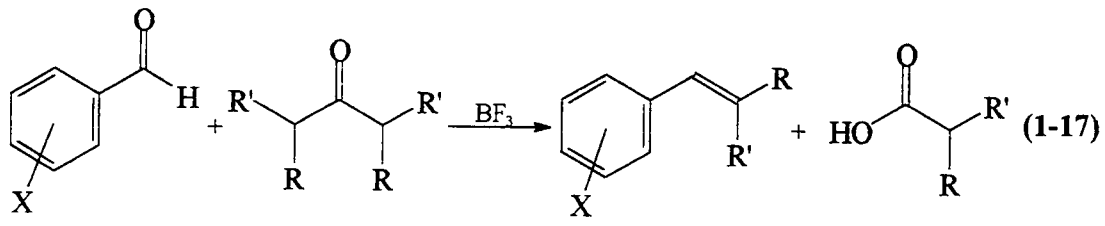
In Section 1.2.2.4, the results obtained from the reaction of various aromatic aldehydes with 5-nonanone in the presence of boron trifluoride were presented. To confirm our predictions that aliphatic ketones would fail to react with aromatic ketones due to their lower reactivity in aldol-type condensations, 5-nonanone was allowed to react with benzophenone under typical reaction conditions (boron trifluoride, refluxing hexanes and 2 hours). GC/MS analysis of the reaction mixture revealed unreacted starting materials and no trace of the desired α-phenylstyrenyl derivative.

1.2.2.6 Ketones

As noted earlier (Section 1.1, eqn 1-1), at least one of the α-carbons of the carbonyl compound must posses a hydrogen (this is a consequence of the initial aldol condensation which requires the removal of an α-hydrogen). But with ketones, two different products can be expected if the ketone is unsymmetrical and if both α-carbons have a hydrogen attached. In our studies, we have found that the nature of the ketone plays a crucial role in the reaction conditions necessary to optimize the yields of the desired olefin. The results obtained to this date are presented in four different categories according to four different types of ketones: Symmetrical ketones, methyl ketones, phenyl ketones and other unsymmetrical ketones.

1.2.2.6.1 Symmetrical Ketones

As noted, the reaction of 5-nonanone (dibutylketone) with substituted benzaldehydes and other aldehydes in the presence of boron trifluoride was studied in detail (Section 1.2.2.4). Two additional types of symmetrical ketones with substituted benzaldehydes in the presence of boron trifluoride were investigated: (1) acyclic ketones (eqn 1-17) and (2) cyclic ketones (eqn 1-18). The results are combined and summarized in Table 1-6.

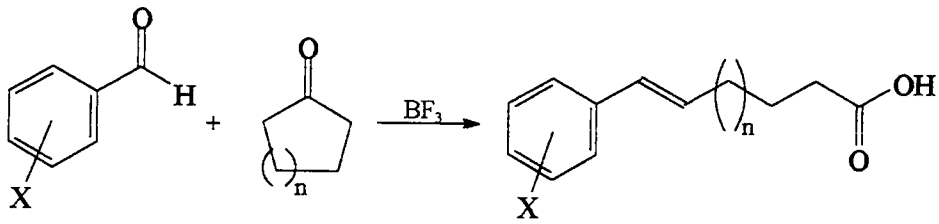


2

1: R' = H, R = Pr
11: R' = R = H
12: R' = H, R = Me
13: R' = H, R = Ph
14: R' = R = Me

3: R' = H, R = Pr
15: R' = R = H
16: R' = H, R = Me
17: R' = H, R = Ph
18: R' = R = Me

4: R' = H, R = Pr
19: R' = R = H
20: R' = H, R = Me
21: R' = H, R = Ph
22: R' = R = Me



2

23: n = 1
24: n = 2
25: n = 4

26: n = 1
27: n = 2
28: n = 4

Table 1-6. Reaction of Symmetrical Ketones with Substituted Benzaldehydes in the Presence of BF_3.[a]

Aldehyde	Ketone	Time	Product (%)[b]	(E/Z)[c]
2a	**1**	1 hr	**3a** (78)	97:3
2c	**1**	2.5 hr	**3c** (89)	95:5
2a	**11**	1.5 hr[d]	**15a** (0)[e]	----
2c	**12**	2.5 hr	**16c** (50)	96:4
2a	**13**	3 hr	**17a** (48)	>99:1
2d	**13**	4 hr	**17d** (43)	>99:1
2a	**14**	1 hr	**18a** (5)[f]	NA
2a	**23**	> 1hr	**26a** (0)[e]	----
2a	**24**	> 1hr	**27a** (0)[e]	----
2e	**25**	3 hr	**28e** (20)[g]	[h]

[a] Reaction carried out in hexanes at reflux unless otherwise noted. [b] Spectral data are in agreement with the proposed structures. [c] Isomer ratios determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum. [d] Reaction carried out in carbon tetrachloride to aid in ^{1}H-NMR analysis of crude products. [e] Red-brown oil obtained (indicating polymerization); followed by TLC. [f] Average yield of three reactions (4%, 5% and 6%). [g] Reaction carried out in toluene due its higher boiling point; ^{1}H-NMR yield; pure product was difficult to isolate from impurities. [h] Exact ratio of isomers could not be determined due to the impurities in the sample; mainly (E)-isomer.

Unlike 5-nonanone (**1**), which was found to produce excellent yields of the corresponding olefins, the reaction of acetone (**11**) with benzaldehyde (**2a**) in the presence of boron trifluoride proved to be unsuccessful. Upon addition of the benzaldehyde to the reaction mixture containing the acetone-boron trifluoride complex (white solid), a rapid formation of a red oil occurred. GC/MS and NMR analyses, after quenching the reaction with water, revealed no styrene. Styrene is apparently produced in the reaction but it polymerizes rapidly under the reaction conditions. Red or brown oils have been reported to be produced in the boron trfluoride polymerization of alkenes.[30]

Results tabulated in Table 1-6 suggest that the stability of the styrenyl product increases not only when electron-withdrawing groups are present in the benzene ring but also when the styrene derivative is substituted at the β-position. It appears that the rate of polymerization under the reaction conditions is decreased by increasing steric hindrance at the double bond in styrene and 1,2-disubstituted alkenes **3** and **16**.

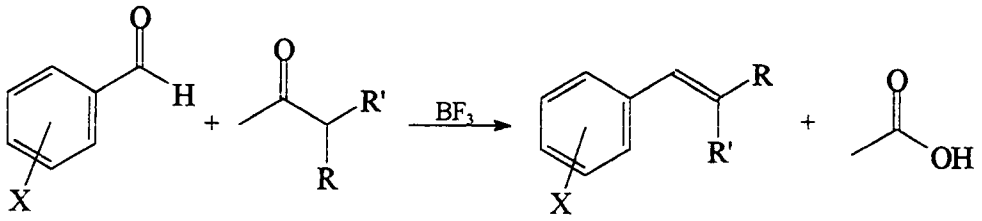
The yields obtained for stilbene (**17a**) and 4-chlorostilbene (**17d**) from the reaction of dibenzylketone (1,3-diphenyl-2-propanone, **13**) and the corresponding aldehydes were only moderate (48% and 43% respectively). A side product, the corresponding α,β-unsaturated ketone, was common to both reactions. The intervention of the dehydration reaction is attributed to a more sterically hindered intermediate in the cleavage reaction. One phenyl group is *alpha* to the hydroxy group and *alpha* to the carbonyl group in the β-hydroxyketone.

Interestingly, the reaction of cyclic ketones with benzaldehyde in the presence of boron trifluoride etherate and ethylene glycol has been reported, eqn 1-18.[31] The same authors did not report a similar reaction for acyclic ketones. In our studies, cyclopentanone (**23**) and cyclohexanone (**24**) failed to produce the desired products (**26** and **27** respectively), while cyclooctanone (**25**) has been found to give a low yield of the styrenyl carboxylic acid (**28**).

Another area of current study involves the reaction of ketones having at least one secondary group bonded to the carbonyl group. Unexpected results have been observed for ketones such as diisopropyl ketone (2,4-dimethyl-3-pentanone, **14**). GC/MS and ^{1}H- and ^{13}C-NMR analyses of the main reaction product strongly suggest an unexpected reaction of 2-methyl-1-phenyl-1-propene (β,β-dimethylstyrene) (**18a**) with benzaldehyde (**2a**). The identification of this major product and the relevance of this side reaction are the subject of a parallel study.

1.2.2.6.2 Methyl Ketones

Methyl ketones (2-ketones) have been found to react such that the methyl group can be used as a sacrificial group. Thus, the aldol condensation occurs preferably through the methylene side of the ketone (this is common to acid-catalyzed aldol condensations; eqn 1-19).



(1-19)

2			19
	29: R' = H, R = Me	**16:** R' = H, R = Me	
	30: R' = H, R = Pr	**3:** R' = H, R = Pr	
	31: R' = H, R = Bu	**34:** R' = H, R = Bu	
	32: R' = Me, R = Me	**18:** R' = Me, R = Me	
	33: R' = Me, R = Et	**35:** R' = Me, R = Et	

Because methyl ketones are more accessible than symmetrical ketones, the optimization of the yields of the desired alkenes would represent an important advantage to this new synthetic method. As with symmetrical ketones, the best results are obtained from the overall addition of a primary alkyl group to the reacting aldehyde. Results obtained to date are summarized in Table 1-7. This study shows that, although the methyl group is preferably sacrificed, reaction conditions that yield high chemoselectivities still need to be developed.

Following the trend observed for the symmetrical ketones (Section 1.2.2.6.1), (E)-1-(3-chlorophenyl)-1-propene (**16c**) was produced in lower yield (21%) than (E)-1-(3-chlorophenyl)-1-pentene (52%, **3c**) and (E)-1-(3-chlorophenyl)-1-hexene (58%, **34c**). Similar complications to those observed in the reaction of diisopropylketone (Section 1.2.2.6.1) have been found in the reactions of methylisopropyl ketone (3-methyl-2-butanone, **18**) and *sec*-butylmethyl ketone (3-methyl-2-pentanone, **35**).

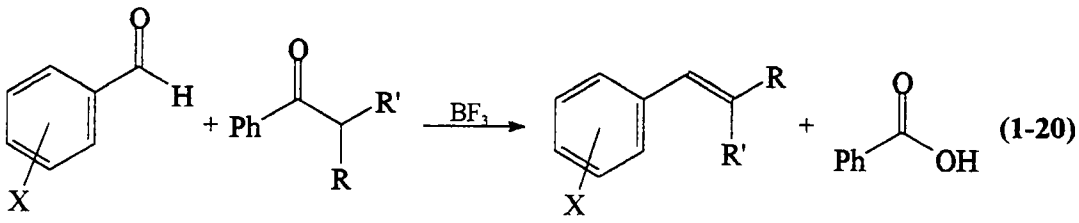
Table 1-7. Reaction of Methyl Ketones with Substituted Benzaldehydes in the Presence of BF_3.[a]

Aldehyde	Ketone	Time	Product (%)[b]	(E/Z)[c]
2c	**29**	2.5 hr	**16c** (21)	96:4
2c	**30**	2.5 hr	**3c** (52)	[d]
2c	**31**	2.5 hr	**34c** (58)	98:2
2a	**32**	1 hr	**18a** (5)	NA
2a	**33**	1.25 hr	**35a** (7)[e]	[f]

[a] Reaction carried out in hexanes at reflux. [b] Spectral data are in agreement with the proposed structures. [c] Isomer ratios determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum. [d] E/Z ratio was not obtained. [e] Mixture of **35a** and R' = Et, R = Me. [f] Ratio of isomers could not be obtained due to the lack of non-overlapping signals in the ^{1}H-NMR spectrum.

1.2.2.6.3 Phenyl Ketones

The reaction of phenyl ketones with aromatic aldehydes in the presence of boron trifluoride is of interest because a single product arises from the mixed-aldol condensation (eqn 1-20). The study of the reaction conditions, in an effort to maximize the yields of the desired styrenyl products, is currently underway. Preliminary results indicate that the cleavage of the aldol-condensation intermediate proceeds as expected (Table 1-8).



2	**36:** R' = H, R = Me	**16:** R' = H, R = Me	**42**
	37: R' = H, R = Pr	**3:** R' = H, R = Pr	
	38: R' = H, R = CH_2CH_2Cl	**40:** R' = H, R = CH_2CH_2Cl	**43:** 4-Fluoro-$PhCO_2H$
	Ph = 4-Fluorophenyl		
	39: R' = Et, R = Ph	**41:** R' = Et, R = Ph	

Table 1-8. Reaction of Phenyl Ketones with Substituted Benzaldehydes in the Presence of BF_3.[a]

Aldehyde	Ketone	Time	Product (%)[b]	(E/Z)[c]
2b	**36**	4 hr	16b (22)	[d]
2b	**37**	4 hr	3b (50)	96:4
2d	**38**	4 hr	40c (26)	96:4
2c	**39**	18 hr	41 (0)[e]	----
2a	**39**	5 hr[f]	41 (0)[e]	----

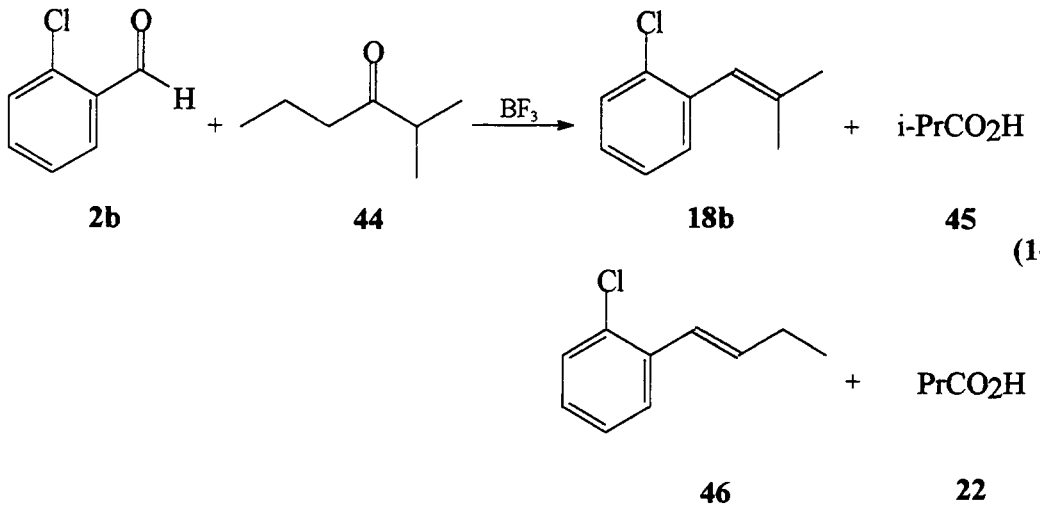
[a] Reaction carried out in hexanes at refluxing unless otherwise noted. [b] Spectral data are in agreement with the proposed structures. [c] Isomer ratios determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum. [d] Not available. [e] Starting materials recovered. [f] Reaction carried out neat at 150 °C.

The dehydration of the aldol condensation intermediate appears to compete with olefin formation, lowering the yields of the desired products. Reaction conditions are currently being sought which will produce higher olefin yields. A promising result was observed for the reaction of 4'-fluoro-4-chlorobutyrophenone **38**. The formation of (E)-4-chloro-1-(4-chlorophenyl)-1-butene (**40d**) indicates that certain functional groups will be tolerated in the reaction of substituted ketones.

2-Phenylbutyrophenone (**39**) was reacted under the usual reaction conditions (refluxing hexanes) with 3-chlorobenzaldehyde in the presence of boron trifluoride but no products were observed. The reaction was repeated in the absence of solvent at 150 °C but the results were the same, suggesting that steric effects prevent the reaction.

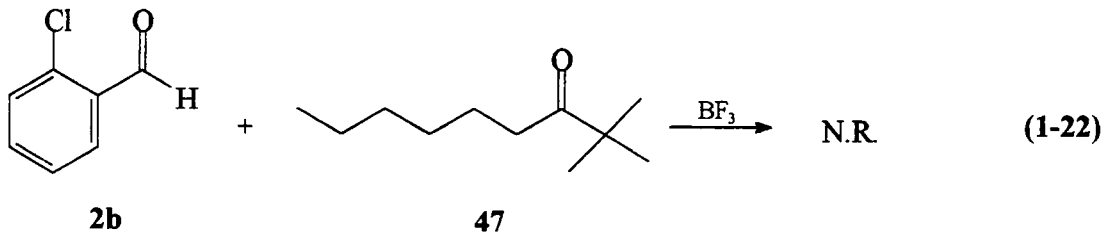
1.2.2.6.4 Other Ketones

While it has been established that primary groups and secondary groups participate more readily than the methyl group in the aldol condensation step, it was necessary to establish the selectivity of the addition of a ketone bearing a primary and a secondary group. The reaction of 2-methyl-3-hexanone (**44**) with 2-chlorobenzaldehyde (**2b**) in the presence of boron trifluoride was studied (eqn 1-21). A 13% yield of the product from the primary group addition (**46**) was obtained along with a 4% yield of the product from the secondary group addition (**18b**). These results seem to indicate that the primary group adds more readily



than the secondary group, but this is misleading. The low yield of **18b** can be attributed to the its destruction via a side reaction with the starting aldehyde, a process that was previously discussed (Section 1.2.2.6.1). The ease of addition is thus; 2° groups > 1° groups > methyl group, which is consistent with the results obtained in the acid catalyzed aldol condensation of asymmetrical ketones.[19]

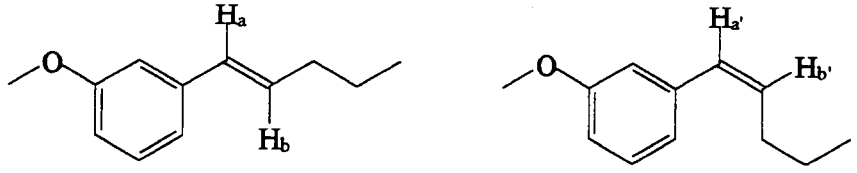
Finally, a ketone bearing a primary and a tertiary group was investigated. 2,2-Dimethyl-3-nonanone (**47**) was allowed to react with 2-chlorobenzaldehyde (**2b**) in the presence of boron trifluoride (eqn 1-22). GC/MS analysis of the reaction mixture revealed that no products were formed, suggesting that steric hindrance prevented the aldol condensation from taking place.



2b **47**

1.2.2.7 Configuration of the Double Bond

The formation of β-alkylstyrenes via the reaction of ketones with aromatic aldehydes in the presence of boron trifluoride is stereoselective. Tables 1-5 through 1-8 show that the E/Z ratios given by this reaction are excellent, E-isomer being the major product formed. We used ^{1}H-NMR for the identification of each isomer, as well as for the calculation of the E/Z ratios. To serve as an example, Figure 1-2 contains the structures of (E)- and (Z)-1-(3-methoxyphenyl)-1-pentene (**3m**). This is followed by a reproduction of the section of the ^{1}H-NMR spectrum containing the olefinic protons (Figures 1-3, 1-4 and 1-5). The observed coupling constants are: J_{Ha-Hb} = 15.9 Hz and $J_{Ha'-Hb'}$ = 11.7 Hz.



(E)-isomer (Z)-isomer

Figure 1-2. (E) and (Z) Isomers of 1-(3-Methoxyphenyl)-1-pentene (**3m**).

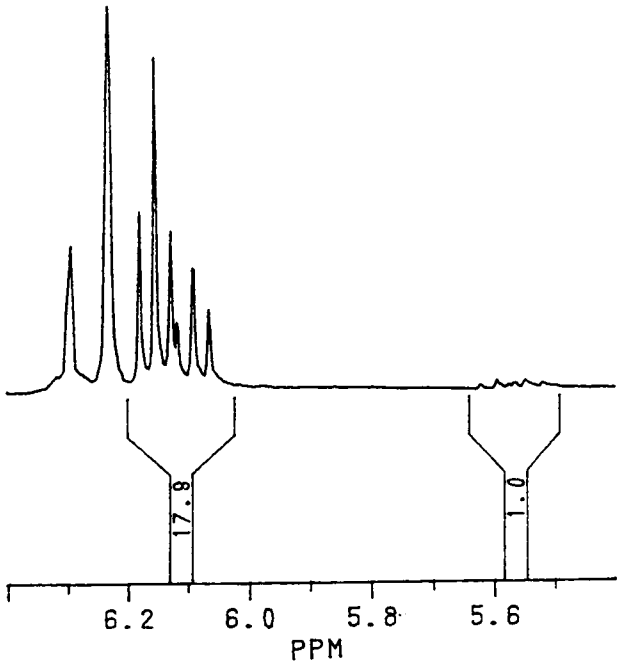
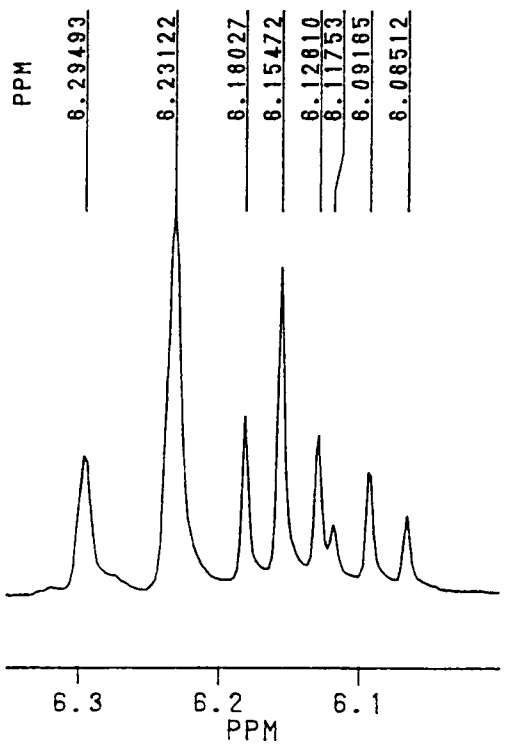


Figure 1-3. ^{1}H-NMR Spectrum of H_a, H_b, and $H_{b'}$.



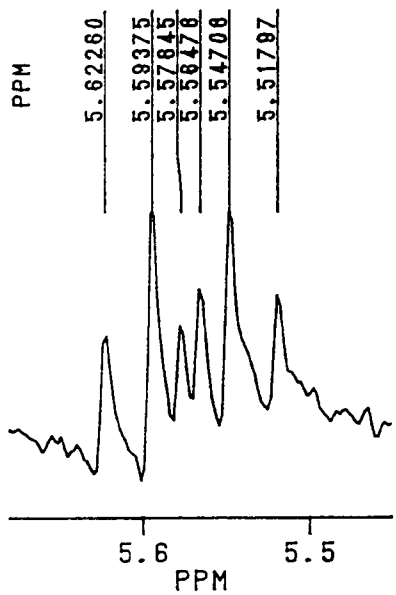


Figure 1-4. ^{1}H-NMR Spectrum of H_a and H_b. *Figure 1-5.* ^{1}H-NMR Spectrum of $H_{b'}$.

1.2.2.8 Boron Trifluoride vs. Other Lewis Acids

Boron trifluoride (as well as alkyldifluoroborane) in non-nucleophilic solvents promotes an unexpected reaction of aliphatic ketones with aromatic aldehydes. In order to determine the role played by boron trifluoride in the reaction, a study was carried out to determine the efficiency of other Lewis and protic acids. Although they differ in efficiency, a large number of acids were found to promote the new reaction. This is a remarkable finding considering that the aldol condensation of carbonyl compounds has been extensively studied for well over a hundred years.[19] The results obtained are shown in Table 1-9. These results indicate that both Lewis acids and protic acids are capable of promoting the reaction. However, even the strongest protic acids were found to be much less efficient than the majority of the Lewis acids studied. Boron trifluoride and boron trifluoride complexes were found to give the highest yields.

Interestingly, the only acids producing any significant amount of the α,β-unsaturated ketone were the two hydrated acids (boron trifluoride dihydrate and *p*-toluenesulfonic acid monohydrate). This strongly suggests that anhydrous conditions are necessary to avoid the typical aldol condensation products. We conclude that the presence of water (a nucleophile) allows the β-hydroxyketone intermediate to dehydrate instead of fragmenting by the cleavage of the C-C bond that leads to the styrenyl product. Thus, the concentration of water (nucleophile) appears to determine the extent to which the styrenyl product is formed. This is also observed with boron trifluoride etherate. While the use of

Table 1-9. Reaction of 5-Nonanone (**1**) with 2-Chlorobenzaldehyde (**2b**) in the Presence of Various Lewis and Protic Acids.[a]

Entry	Acid[b]	Yield of Alkene (%)[c]	Yield of Aldol (%)[d]
1[e]	BF_3	74	0
2[e]	$BF_3{\cdot}OEt_2$	72	0
3[e]	$BF_3{\cdot}CH_3CO_2H$	79	0
4	$BF_3{\cdot}H_2O$	60	26
5[e]	$AlCl_3$	30	0
6[e]	$TiCl_4$	9	0
7[e]	$ZnCl_2$	Traces	0
8	BBr_3	Traces	0
9	*p*-Toluene$SO_3H{\cdot}H_2O$	32	60
10	CF_3SO_3H	~20[g]	0
11[e]	CF_3CO_2H	<5	0
12[e,f]	$C_7F_{15}CO_2H$	<5	~5

[a] Reaction carried out in carbon tetrachloride at reflux for 2 hours. [b] 3 equivalents (except for BF_3 which was bubbled into the solution). [c] (E)-1-(2-chlorophenyl)-1-pentene (**3b**); Isolated yields. [d] α,β-unsaturated ketone. [e] GC/MS analysis showed unreacted starting materials. [f] It is possible that the acid was not completely anhydrous. [g] Product polymerized during isolation.

boron trifluoride etherate complex leads to good yields of the desired product, boron trifluoride in ether solvent fails to produce product.

As a consequence of these results, we are investigating the reaction conditions that maximize the efficiency of one or more of the boron trifluoride complexes. Additionally, previously troublesome reactions that produced low or moderate yields of the desired styrenyl products in the presence of boron trifluoride are being reinvestigated using different boron trifluoride complexes in an effort to increase the yields.

1.2.3 Reaction in the Presence of Boron Trifluoride Etherate

Boron trifluoride etherate was chosen for the study because it is familiar to organic chemists, it is readily available, it is inexpensive and it is also more easily handled than boron trifluoride gas. The first study was performed to evaluate different solvents at room temperature. The results are summarized in Table 1-10. As expected, a nucleophilic solvent such tetrahydrofuran (THF) failed to produce the desired styrenyl product because, apparently, boron trfluoride etherate loses its ability to promote the condensation of the starting materials. The rate of product formation varied in the four non-nucleophilic solvents studied. For safety and economic reasons, we concluded that hexane is also the ideal solvent for this reaction.

Table 1-10. Reaction of 5-Nonanone (**1**) and 2-Chlorobenzaldehyde (**2b**) in the Presence of Boron Trifluoride Etherate in Various Solvents at Room Temperature.

Entry	Solvent	Time	Yield (%)[a]
1	THF	24 hr	0
2	Hexane	24 hr	70
3	CCl_4	24 hr	58
4	CCl_4	32 hr	67
5	Toluene	24 hr	37
6	CH_2Cl_2	24 hr	68

a Isolated yields of (E)-1-(2-chlorophenyl)-1-pentene (**3b**).

An additional study was performed to determined whether boron trifluoride etherate is catalytic. The reactions were carried out in refluxing hexanes for 1 hour. The results are summarized in Table 1-11 and they reveal that the reaction is indeed catalyzed by boron trifluoride etherate. The low yields obtained in the presence of 10% boron trifluoride etherate were attibuted to the catalyst being destroyed by impurities (i.e. moisture) in the starting materials (the normal fuming above the reaction mixture during quenching was not observed when 10% of the catalyst was used.)

Table 1-11. Reaction of 5-Nonanone (**1**) and 2-Chlorobenzaldehyde (**2b**) in the Presence of Different Amounts of Boron Trifluoride Etherate.[a]

Entry	BF_3 Etherate[b]	Time, Temperature	Yield (%)[c]
1	2.2	24 hr, RT	70
2	2.2	1hr, reflux	84
3	1.5	1hr, reflux	84
4	0.7	1hr, reflux	88
5	0.4	4hr, reflux	81
6	0.2	4hr, reflux	25
7	0.1	4hr, reflux	4

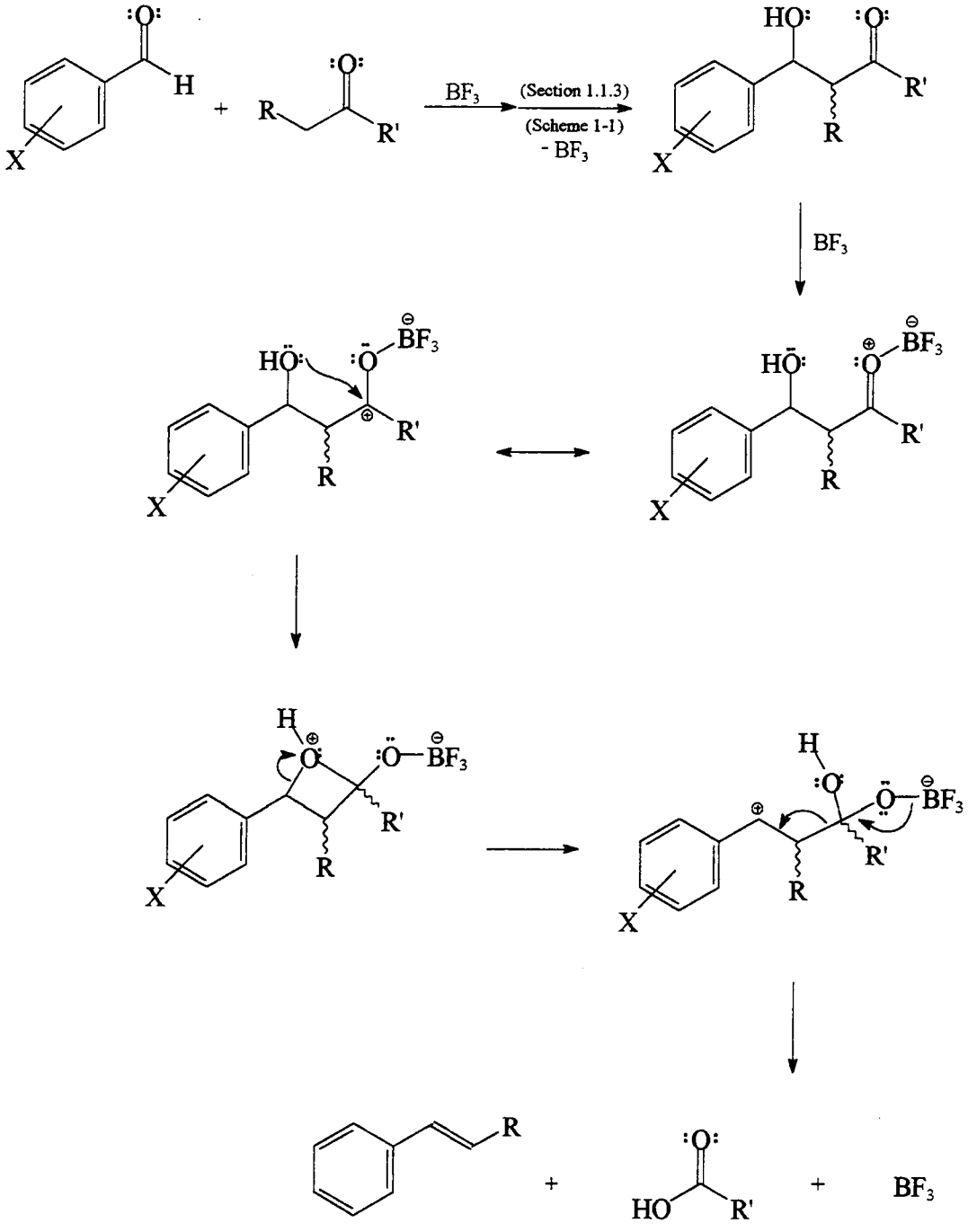
[a] Reaction carried out in hexanes. [b] Number of equivalents used (1.0 eq. of ketone and 1.1 of aldehyde). [c] Isolated yields of (E)-1-(2-chlorophenyl)-1-pentene (**3b**).

The preliminary results presented in Tables 1-10 and 1-11, lead us to conclude that boron trifluoride etherate will be the acid of choice for the new reaction of aliphatic ketones with aromatic aldehydes.

1.2.4 Reaction Mechanism

Based on the results obtained to date, we propose the following mechanism (Scheme 1-3).

Scheme 1-3. Proposed Mechanism for the Reaction of Aliphatic Ketones with Aromatic Aldehydes in the Presence of BF_3 in Non-Nucleophilic Solvents.



The use of boron trifluoride in the proposed mechanism is representative of the acids which have been shown to promote the reaction.

The mechanism involves the formation of a mixed aldol product followed by the rapid formation and subsequent non-synchronous ring opening of a lactol intermediate. The proposed fragmentation is reminiscent of two-step Grob[32] fragmentations that have been reported for N-halo-α-amino acids[33] and cyclobutane hemiacetals[34] as well as the acid catalyzed fragmentation of β-hydroxyacetals.[35,36]

We have not observed significant amounts of α,β-unsaturated ketones (when boron trifluoride or other anhydrous strong acids were used) that would form from the dehydration of the β-hydroxyketone intermediate. We attribute this fact to the absence of nucleophilic spices that could aid in the removal of the α-proton. Because the elimination of water is not observed, we believe that a strong acid such as boron trifluoride activates the carbonyl group in a such a way that an intramolecular nucleophilic attack by the hydroxy group occurs to form a lactol intermediate. The consistent formation of (E)-alkene products, as well as the fact that aromatic aldehydes appear to be required would point toward a carbocation intermediate generated by a non-synchronous fragmentation of the lactol intermediate. (This is supported by the fact that the fragmentation of *syn* and *anti* β-hydroxyketones lead to the same (E)-alkene products, Part B, Chapter 2). A carbocation intermediate is also supported by the fact that nitro-substituted benzaldehydes behave differently. While 3-nitrobenzaldehyde (**2i**) led to good yields of the corresponding product, 2-nitrobenzaldehyde (**2h**) and 4-

nitrobenzaldehyde (**2j**) led to poor yields. This is consistence with a benzylic carbocation for which resonance structures place positive charge density at the 2- and 4-positions in the ring.

Finally, although previously reported results contradict each other regarding the isomerization of alkenes in the presence of boron trifluoride,[37,38] we found that a mixture of (Z) and (E)-alkenes does not isomerize under the reaction conditions.

1.3 Conclusion

The reaction of ketones with aromatic aldehydes in the presence of boron trifluoride (and other acids) produces β-alkylstyrenes as well as carboxylic acids (eqn 1-1). This new reaction is synthetically and theoretically important. Several features of this reaction make it synthetically useful: (1) The starting materials are readily available and inexpensive. (2) The reaction is stereoselective and the yields of (E)-alkenes are moderate to excellent. (3) Moderate reaction temperatures and non-nucleophilic solvents are effective. (4) The reactions are relatively rapid. (5) Initial results indicate that methylene groups react more efficiently than methyl groups, which permits the use of readily accessible methyl ketones. (6) The reaction may provide a useful alternative to the Baeyer-Villiger oxidation reaction.[39]

The theoretical importance arises from the fact that acid-catalyzed aldol condensations have been studied since the self-condensation of acetone was

first reported in 1838 by Kane[21] with no precedent of the new reaction having been reported. This reaction could serve as a precedent for using boron trifluoride and other anhydrous strong acids in non-nucleophilic solvents.

1.4 Experimental

All reactions were performed in oven-dried glassware under a nitrogen atmosphere and with continuous magnetic stirring. Air and moisture sensitive compounds were introduced via syringe or cannula through a rubber septum. All solvents were dried and distilled prior to use. Products were purified by flash chromatography using 230-400 mesh ASTM 60 silica gel. All melting points and microboiling points are uncorrected and were obtained using a MEL-TEMP melting point apparatus. All ^{1}H and ^{13}C-NMR spectra were recorded on a 250 MHz Bruker AC250 spectrometer. All ^{1}H and ^{13}C-NMR data were obtained in $CDCl_3$ solution, chemical shifts (δ) are given in ppm relative to TMS, and coupling constants (J) are given in Hz. All ^{11}B-NMR were recorded on a JEOL FX90Q spectrometer. ^{11}B-NMR chemical shifts are relative to $BF_3{\cdot}OEt_2$. All elemental analyses were performed by Atlantic Microlabs, Norcross, Georgia. All GC/MS data were obtained using a Hewlett Packard 6890 Series GC System equipped with a 5973 Mass Selective Detector or a Hewlett Packard 5890 Series GC System equipped with a 5970 Mass Selective Detector.

1.4.1 Difluorohexylborane[40]*:* see experimental section in Part A.

*1.4.2 Reaction of 5-Nonanone (**1**) with Benzaldehyde (**2a**) Using Different Quantities of Difluorohexylborane: Synthesis of 1-Phenyl-1-pentene (**3a**),*[41] *1-Hydroxy-1-phenyl-2-propyl-3-heptanone*[42] *and Dimers of **3a** of Unidentified Structures.*

To a solution of difluorohexylborane (2.93 mmol, prepared from 2.93 mmol of hexylboronic acid and BF_3, Section 1.4.1) in hexanes (10 mL) was added 5-nonanone (0.427 g, 3.00 mmol) and the solution stirred for 1 hour at room temperature. Benzaldehyde (0.478 g, 4.50 mmol) was added to the solution and the mixture was stirred at room temperature for 12 hours. The reaction was quenched with distilled water (10 mL) and the organic products were extracted into ether (3 x 10 mL) using a separatory funnel and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the product isolated by flash chromatography using silica gel (30 mm column, hexanes as eluent) to obtain the least polar product: 0.208 g (49% yield) of 1-phenyl-1-pentene (**3a**): ^{1}H-NMR ($CDCl_3$/TMS) δ 7.33 – 7.14 (m, 5H), 6.29 (d, 1H, J = 15.9), 6.18 (dt, 1H, J = 15.9, 6.7), 2.20 – 2.11 (m, 2H), 1.55 – 1.40 (m, 2H), 0.94 (t, 3H, J = 7.4); ^{13} C-NMR ($CDCl_3$) δ 137.95, 130.85, 129.95, 128.43, 126.73, 125.91, 35.12, 22.55, 13.71; GCMS (EI) m/z (relative intensity) 146 (M^+, 29), 117 (100), 115 (44), 104 (34), 91 (31).

The procedure was repeated using difluorohexylbenzaldehyde (2.93 mmol), 5-nonanone (0.717 g, 5.04 mmol) and benzaldehyde (0.329 g, 3.10

mmol). The products were flash chromatographed using silica gel and hexanes to give 0.050 g (12% yield) of **3a** (spectral data was consistent with sample previously prepared), and 0.266 g (40% yield) of 1-hydroxy-1-phenyl-2-propyl-3-heptanone (44:56 *syn:anti* ratio determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum). ^{1}H-NMR ($CDCl_3$/TMS) δ 7.33 – 7.25 (m, 5H), 4.80 (d, J = 6.0) and 4.74 (d, J = 7.2) (1H), 2.95 – 2.80 (m, 2H), 2.45 – 2.00 (m, 2H), 1.78 – 1.05 (m, 8H), 0.87 – 0.76 (m, 6H).

The procedure was repeated using difluorohexylbenzaldehyde (4.76 mmol), 5-nonanone (0.415 g, 2.92mmol) and benzaldehyde (0.346 g, 3.26 mmol). The products were flash chromatographed using silica gel and hexanes to give 0.319 (74% yield) of a mixture of two dimers (the GC/MS spectrum revealed two peaks having twice the molecular weight of **3a**) of unidentified structures. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.33 – 7.06 (m, 10H), 6.80 (t, 1H, J = 7.3), 4.00 - 3.89 (m, 1H), 3.16 – 3.05 (m) and 2.98 – 2.87 (m, 1H), 2.48 – 2.36 (m) and 2.27 – 2.15 (m) (1H), 1.85 – 1.10 (m, 8H), 0.92 – 0.81 (m, 6H); GCMS (EI) m/z (relative intensity) (a) 292 (M^+, 7), 235 (29), 129 (21), 115 (31), 91 (100); (b) 292 (M^+, 15), 235 (59), 193 (22), 179 (33), 178 (25), 129 (29), 115 (37), 91 (100).

*1.4.3 Reaction of 5-Nonanone (**1**) and Benzaldehyde (**2a**) in the Presence of BF_3 at Various Times and Temperatures: Synthesis of **3a**.*[41]

A small excess of BF_3 was bubbled into a solution of 5-nonanone (0.420 g, 2.95 mmol) in hexanes (10 mL). The reaction flask was flushed with nitrogen

to remove excess BF_3 . Benzaldehyde (0.407 g, 3.84 mmol) was added to the reaction mixture and the contents were stirred at room temperature for 20 hours. The reaction was quenched with distilled water (10 mL) and the organic products were extracted into ether (3 x 10 mL) using a separatory funnel and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the mixture was purified by flash chromatography with silica gel in a 30 mm column using hexanes as the eluent. This produced 0.259 g (60% yield) of 1-phenyl-1-pentene (**3a**); spectral data was consistent with previously prepared sample.

The procedure was repeated using 5-nonanone (0.411 g, 2.89 mmol) and benzaldehyde (0.399 g, 3.76 mmol). The contents were stirred at room temperature for 43 hours. GC/MS data revealed traces (< 5% yield) of **3a** and a large amount of dimers of **3a**.

The procedure was repeated in hexanes at reflux while vaying the reaction times: (0.5 hours), 5-nonanone (0.427 g, 3.00 mmol), benzaldehyde (0.414 g, 3.90 mmol) produced 0.268 g (61% yield) of **3a**; (1.0 hour), 5-nonanone (0.606 g, 4.26 mmol), benzaldehyde (0.588 g, 5.54 mmol) produced 0.486 g (78% yield) of **3a**; (3.0 hours), 5-nonanone (0.427 g, 3.00 mmol), benzaldehyde (0.414 g, 3.90 mmol) produced 0.184 g (42% yield) of **3a**; spectral data was consistent with previously prepared sample.

*1.4.4 Reaction of 5-Nonanone (**1**) with Various Amounts of 3-Chlorobenzaldehyde (**2c**) in the Presence of BF_3: Synthesis of (E)-1-(3-Chlorophenyl)-1-pentene (**3c**).*[43]

A small excess of BF_3 was bubbled into a solution of 5-nonanone (0.385 g, 2.71 mmol) in hexanes (10 mL). The reaction flask was flushed with nitrogen to remove excess BF_3 . 3-Chlorobenzaldehyde (0.381 g, 2.71 mmol) was added to the reaction mixture and the contents refluxed for 2 hours. The reaction was quenched with distilled water (10 mL) and the product was extracted into ether (3 x 10 mL) using a separatory funnel and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the mixture was purified by flash chromatography with silica gel in a 30 mm column using hexanes as the eluent. This produced 0.372 g (76% yield) of **3c**: ^{1}H-NMR ($CDCl_3$/TMS) δ 7.31 (s, 1H), 7.19 - 7.11 (m, 3h), 6.34 (d, 1H, *J* = 15.9), 6.24 (dt, 1H, *J* = 15.9, 6.2), 2.21 - 2.13 (m, 2H), 1.52 - 1.41 (m, 2H), 0.93 (t, 3H, *J* = 7.3); ^{13}C-NMR ($CDCl_3$) δ 139.81, 134.37, 132.55, 129.61, 128.65, 126.64, 125.81, 124.12, 35.02, 22.38, 13.68; GCMS (EI) m/z (relative intensity) 180 (M^+, 46), 151 (84), 138 (85), 115 (100), 103 (18), 89 (17); b.p. = 230-231 °C/730 mm Hg; lit. b.p. = 125-127°C/18mm for 60% *E*: 40% *Z* mixture.

The procedure was repeated with different ratios of starting materials and different reaction times: 5-nonanone (0.427 g, 3.00 mmol), 3-chlorobenzaldehyde (0.422 g, 3.00 mmol) refluxed for 3 hours to give 0.455 g, (84% yield) of **3c**; 5-nonanone (0.314 g, 2.21 mmol), 3-chlorobenzaldehyde (0.422 g, 2.87 mmol) refluxed for 2 hours to give 0.311 g, (78% yield) of **3c**; 5-nonanone (0.548 g, 3.85

mmol), 3-chlorobenzaldehyde (0.704 g, 5.01 mmol) refluxed for 2.5 hours to give 0.619 g, (89% yield) of **3c**; 5-nonanone (0.357 g, 2.51 mmol), 3-chlorobenzaldehyde (0.529 g, 3.77 mmol) refluxed for 2 hours to give 0.381 g, (84% yield) of **3c**; 5-nonanone (0.358 g, 2.52 mmol), 3-chlorobenzaldehyde (0.708 g, 5.04 mmol) refluxed for 2 hours to give 0.410 g, (90% yield) of **3c**; spectral data was consistent with previously prepared sample.

*1.4.5 Reaction of 5-Nonanone (**1**) with 3-Chlorobenzaldehyde (**2c**) in the Presence of BF_3 in Different Solvents: Synthesis of (E)-1-(3-Chlorophenyl)-1-pentene (**3c**).*[43]

A small excess of BF_3 was bubbled into a solution of 5-nonanone (0.548 g, 3.85 mmol) in hexanes (10 mL). The reaction flask was flushed with nitrogen to remove excess BF_3. 3-Chlorobenzaldehyde (0.704 g, 5.01 mmol) was added to the reaction mixture and the contents refluxed for 2.5 hours. The reaction was quenched with distilled water (10 mL) and the product was extracted into ether (3 x 10 mL) using a separatory funnel and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the mixture was purified by flash chromatography with silica gel in a 30 mm column using hexanes as the eluent. This produced 0.619 g (89% yield) of **3c**.

The procedure was repeated in different solvents and different reaction times; reaction was unsuccessful in ethyl ether; 5-nonanone (0.304 g, 2.14 mmol), 3-chlorobenzaldehyde (0.391 g, 2.78 mmol) refluxed in CCl_4 for 2 hours gave 0.204 g (53% yield) of **3c**; 5-nonanone (0.351 g, 2.47 mmol), 3-

chlorobenzaldehyde (0.451 g, 3.21 mmol) refluxed in CCl_4 for 4 hours gave 0.334 g (75% yield) of **3c**; 5-nonanone (0.350 g, 2.47 mmol), 3-chlorobenzaldehyde (0.450 g, 3.20 mmol) refluxed in CCl_4 for 6 hours gave 0.404 g (91% yield) of **3c**; 5-nonanone (0.558 g, 3.92 mmol), 3-chlorobenzaldehyde (0.716 g, 5.10 mmol) refluxed in CH_2Cl_2 for 2 hours gave 0.471 g (67% yield) of **3c**; 5-nonanone (0.516 g, 3.63 mmol), 3-chlorobenzaldehyde (0.663 g, 4.72 mmol) refluxed in CH_2Cl_2 for 3 hours gave 0.490 g (75% yield) of **3c**; 5-nonanone (0.543 g, 3.82mmol), 3-chlorobenzaldehyde (0.699 g, 4.97 mmol) refluxed in CH_2Cl_2 for 4 hours gave 0.429 g (62% yield) of **3c**; 5-nonanone (0.398 g, 2.80 mmol), 3-chlorobenzaldehyde (0.512 g, 3.64 mmol) refluxed in toluene for 2 hours gave 0.377 g (75% yield) of **3c**; 5-nonanone (0.427 g, 3.00 mmol), 3-chlorobenzaldehyde (0.548 g, 3.90 mmol) refluxed in toluene for 4 hours gave 0.455 g (84% yield) of **3c**; spectral data was consistent with previously prepared sample.

*1.4.6. 1-Phenyl-1-3-heptadiene (**10**)*

A small excess of BF_3 was bubbled into a solution of 5-nonanone (0.613 g, 4.31 mmol) in hexanes (10 mL). The reaction flask was flushed with nitrogen to remove excess BF_3. *trans*-Cinnamaldehyde (0.740 g, 5.60 mmol) was added to the reaction mixture and the contents refluxed for 9.25 hours. The reaction was quenched with distilled water (10 mL) and the product was extracted into ether (3 x 10 mL) using a separatory funnel and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the mixture was purified

by flash chromatography with silica gel in a 30 mm column using hexanes as the eluent. This produced 0.030 g (4% yield) of **10**. *Trans-trans/trans-cis* = 4:1, determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.43 – 7.15 (m, 5H), 7.07 (dd, J = 15.5, 11.0) and 6.76 (dd, J = 15.7, 10.3) (1H), 6.52 (d, J = 15.6) and 6.43 (d, J = 15.7) (1H), 6.21 – 6.12 (m, 1H), 5.82 (dt, J = 15.1, 7.0) and 5.53 (dt, J = 10.7, 7.7) (1H), 2.32 – 2.08 (m, 2H), 1.54 – 1.32 (m, 2H), 0.98 – 0.83 (m, 3H). Spectral data are in agreement with the proposed structures.

*1.4.7 General Procedure for the Reactions of Ketones with Aldehydes in the Presence of BF_3: (E)-1-Phenyl-1-pentene (**3a**).*[41]

A small excess of BF_3 was bubbled into a solution of 5-nonanone (**1**) (0.606 g, 4.26 mmol) in hexanes (10 mL). The reaction flask was flushed with nitrogen to remove excess BF_3. Benzaldehyde (**2a**) (0.588 g, 5.54 mmol) was added to the reaction mixture and the contents were heated to reflux for one hour. The reaction was quenched with distilled water (10 mL) and the product was extracted into ether (3 x 10 mL) using a separatory funnel and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the mixture was purified by flash chromatography with a minimum of 7 inches of silica gel in a 30 mm column using hexanes as the eluent. This produced 0.486 g (78% yield) of **3a**: (E/Z) = 97:3 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum; spectral data was consistent with previously prepared sample.

*1.4.7.1 (E)-1-(2-Chlorophenyl)-1-pentene (**3b**).*[44]

(E)-1-(2-Chlorophenyl-1-pentene (**3b**) was prepared, as described previously from 5-nonanone (**1**) (0.713 g, 3.90 mmol), BF_3 and 2-chlorobenzaldehyde (**2b**) (0.538 g, 5.07 mmol) with 4 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.638 g (91% yield) of **3b**. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.50 (dd, 1h, *J* = 7.6, 1.9), 7.32 (dd, 1H, *J* = 7.6, 1.6), 7.24 -7.08 (m, 2H), 6.75 (d, 1H, *J* = 15.8), 6.20 (dt, 1H, *J* = 15.8, 7.0), 2.28 – 2.19 (m, 2H), 1.59 – 1.44 (m, 2H), 0.97 (t, 3H, *J* = 7.4); ^{13}C-NMR ($CDCl_3$) δ 135.99, 133.89, 132.50, 129.55, 127.77, 126.68, 126.58, 126.18, 35.24, 22.42, 13.70; GCMS (EI) m/z (relative intensity) 180 (M^+, 37), 151 (65), 138 (78), 125 (30), 115 (100), 103 (24), 89 (22); b.p. = 228 °C/730 mm Hg; lit. b.p. = 80-90 °C/0.01 mm Hg; (E/Z) = 98:2 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.7.2 (E)-1-(3-Chlorophenyl)-1-pentene (**3c**).*[43]

(E)-1-(3-Chlorophenyl)-1-pentene (**3c**) was prepared, as described previously, from 5-nonanone (**1**) (0.548 g, 3.85 mmol), BF_3 and 3-chlorobenzaldehyde (**2c**) (0.704 g, 5.01 mmol) with 2 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.619 g (89% yield) of **3c**. (E/Z) = 98:2 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum; spectral data was consistent with previously prepared sample.

*1.4.7.3 (E)-1-(4-Chlorophenyl)-1-pentene (**3d**).*[18,44]

(E)-1-(4-Chlorophenyl)-1-pentene (**3d**) was prepared, as described previously, from 5-nonanone (**1**) (0.516 g, 3.63 mmol), BF_3 and 4-chlorobenzaldehyde (**2d**) (0.663 g, 4.72 mmol) with 4 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.596 g (91% yield) of **3d**. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.23 (s, 4H), 6.32 (d, 1H, J = 16.0), 6.18 (dt, 1H, J = 16.0, 6.6), 2.21 – 2.12 (m, 2H), 1.55 – 1.41 (m, 2H), 0.94 (t, 3H, J = 7.3); ^{13}C-NMR ($CDCl_3$) δ 136.41, 131.67, 129.98, 128.71, 128.53, 127.07, 35.03, 22.41, 13.68; GCMS (EI) m/z (relative intensity) 180 (M^+, 32), 151 (90), 138 (38), 125 (15), 115 (100); b.p. = 231 °C/730 mm Hg; lit. b.p. = 80-90 °C/0.01 mm Hg; (E/Z) = 94:6 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.7.4 (E)-1-(2-Bromophenyl)-1-pentene (**3e**).*

(E)-1-(2-Bromophenyl)-1-pentene (**3e**) was prepared, as described previously, from 5-nonanone (**1**) (0.485 g, 3.41 mmol), BF_3 and 2-bromobenzaldehyde (**2e**) (0.820 g, 4.43 mmol) with 4 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.675 g (88% yield) of **3e**. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.49 (td, 2H, J = 7.8, 1.4), 7.22 (t, 1H, J = 7.3), 7.03 (td, 1H, J = 7.7, 1.6), 6.71 (d, 1H, J = 15.7), 6.16 (dt, 1H, J = 15.7, 7.0), 2.27 – 2.18 (m, 2H), 1.59 – 1.44 (m, 2H), 0.96 (t, 3H, J = 7.4); ^{13}C-NMR ($CDCl_3$) δ 137.71, 134.01, 132.77, 128.79, 128.04, 127.31, 126.79,

123.12, 35.12, 22.36, 13.67; GCMS (EI) m/z (relative intensity) 224 (M^+, 12), 182 (22), 1445 (10), 116 (100), 103 (15), 89 (14); Anal. calcd. for $C_{11}H_{13}Br$: C, 55.69; H, 5.82. Found: C, 58.54; H, 5.81; b.p. = 242 °C/730 mm Hg; (E/Z) = 98:2 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.7.5 (E)-1-(3-Bromophenyl)-1-pentene (**3f**).*[45]

(E)-1-(3-Bromophenyl)-1-pentene (**3f**) was prepared, as described previously, from 5-nonanone (**1**) (0.420 g, 2.95 mmol), BF_3 and 3-bromobenzaldehyde (**2f**) (0.710 g, 3.84 mmol) with 4 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.609 g (92% yield) of **3f**. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.46 (t, 1H, J = 1.8), 7.31 – 7.06 (m, 3H), 6.27 (d, 1H, J = 15.9), 6.18 (dt, 1H, J = 15.9, 6.1), 2.20 – 2.12 (m, 2H), 1.55 – 1.40 (m, 2H), 0.94 (t, 3H, J = 7.3); ^{13}C-NMR ($CDCl_3$) δ 140.10, 132.57, 129.89, 129.55, 128.74, 128.55, 124.55, 122.67, 35.01, 22.37, 13.68; GCMS (EI) m/z (relative intensity) 224 (M^+, 12), 182 (20), 145 (12), 116 (100), 103 (10), 89 (11), 77 (10); b.p. = 251 °C/730 mm Hg; Anal. calcd. for $C_{11}H_{13}Br$: C, 55.69; H, 5.82. Found: C, 58.54; H, 5.81; (E/Z) = 95:5 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.7.6 (E)-1-(4-Bromophenyl)-1-pentene (**3g**).*[18,46]

(E)-1-(4-Bromophenyl)-1-pentene (**3g**) was prepared, as described previously, from 5-nonanone (**1**) (0.358 g, 2.52 mmol), BF_3 and 4-bromobenzaldehyde (**2g**) (0.606 g, 3.28 mmol) with 4 hours at reflux in hexane.

The product was flash chromatographed using silica gel and hexanes to give 0.488 g (86% yield) of **3g**. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.35 (d, 2H, *J* = 8.5), 7.13 (d, 2H, *J* = 8.5), 6.26 (d, 1H, *J* = 16.0), 6.15 (dt, 1H, *J* = 16.0, 6.4), 2.17 – 2.09 (m, 2H), 1.53 – 1.38 (m, 2H), 0.93 (t, 3H, *J* = 7.4); ^{13}C-NMR ($CDCl_3$) 136.80, 131.74, 131.44, 128.74, 127.40, 120.31, 35.03, 22.38, 13.68; GCMS (EI) m/z (relative intensity) 224 (M^+, 10), 195 (12), 182 (11), 116 (100), 89 (9); b.p. = 258 °C/730 mm Hg; lit. b.p. = 105 °C/0.05 mm Hg; (E/Z) = 96:4 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.7.7 (E)-1-(2-Nitrophenyl)-1-pentene (**3h**).*[47]

(E)-1-(2-Nitrophenyl)-1-pentene (**3h**) was prepared, as described previously, from 5-nonanone (**1**) (0.798 g, 5.61 mmol), BF_3 and 2-nitrobenzaldehyde (**2h**) (1.102 g, 7.29 mmol) with 4 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.086 g (8% yield) of **3h**. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.87 (dd, 1H, *J* = 8.1, 1.1), 7.61 – 7.52 (m, 2H), 7.33 (td, 1H, *J* = 7.3, 1.1), 6.84 (d, 1H, *J* = 15.6), 6.23 (dt, 1H, *J* = 15.6, 6.9), 2.29 – 2.20 (m, 2H), 1.57 – 1.48 (m, 2H), 0.97 (t, 3H, *J* = 7.3); ^{13}C-NMR ($CDCl_3$) δ 136.67, 133.38, 132.73, 128.37, 127.28, 125.04, 124.31, 35.18, 22.18, 13.63; GCMS (EI) m/z (relative intensity) 191 (M^+, 5), 146 (27), 132 (33), 120 (60), 115 (71), 92 (100), 77 (72); (E/Z) = 98:2 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.7.8 (E)-1-(3-Nitrophenyl)-1-pentene (**3i**).*

(E)-1-(3-Nitrophenyl)-1-pentene (**3i**) was prepared, as described previously, from 5-nonanone (**1**) (0.607 g, 4.27 mmol), BF_3 and 3-nitrobenzaldehyde (**2i**) (0.839 g, 5.55 mmol) with 2 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.677 g (83% yield) of **3i**. ^{1}H-NMR ($CDCl_3$/TMS) δ 8.17 (t, 1H, *J* = 1.9), 8.03 – 7.99 (m, 1H), 7.64 – 7.60 (m, 1H), 7.43 (t, 1H, *J* = 8.0), 6.44 (d, 1H, *J* = 15.3), 6.40 – 6.30 (m, 1H), 2.27 – 2.19 (m, 2H), 1.60 – 1.45 (m, 2H), 0.97 (t, 3H, *J* = 7.4); ^{13}C-NMR ($CDCl_3$) δ 148.54, 139.65, 134.40, 131.74, 129.22, 127.80, 121.27, 120.36, 34.97, 22.20, 13.64; GCMS (EI) m/z (relative intensity) 191 (M^+, 23), 149 (100), 115 (61), 103 (25), 89 (11), 77 (15); b.p. = 294-296 °C/730 mm Hg (decomposes); Anal. calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.84; H, 6.84; N, 7.11; (E/Z) = 92:8 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.7.9 (E)-1-(4-Nitrophenyl)-1-pentene (**3j**).*

(E)-1-(4-Nitrophenyl)-1-pentene (**3j**) was prepared, as described previously, from 5-nonanone (**1**) (0.462 g, 3.25 mmol), BF_3 and 4-nitrobenzaldehyde (**2j**) (0.638 g, 4.23 mmol) with 1.5 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.304 g (49% yield) of **3j**. ^{1}H-NMR ($CDCl_3$/TMS) δ 8.12 (d, 2H, *J* = 8.9), 7.45 (d, 2H, *J* = 8.9), 6.45 – 6.42 (m, 2H), 2.28 – 2.20 (m, 2H), 1.60 – 1.43 (m, 2H), 0.97 (t, 3H, *J* = 7.3); ^{13}C-NMR ($CDCl_3$) δ 146.26, 144.34, 136.29, 128.12, 126.19,

123.77, 35.11, 22.01, 13.59; GCMS (EI) m/z (relative intensity) 191 (M^+, 12), 149 (64), 119 (14), 116 (100), 115 (73), 91 (14), 77 (15); b.p. = 306-308°C/730 mm Hg (decomposes); Anal. calcd. for $C_{11}H_{13}NO_2$; C, 69.09; H, 6.85; N, 7.32. Found: C, 68.99; H, 6.87; N, 7.32; (E/Z) = 94:6 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.7.10 (E)-1-(4-Tolyl)-1-pentene (**3k**).*[48]

(E)-1-(4-Tolyl)-1-pentene (**3k**) was prepared, as described previously, from 5-nonanone (**1**) (0.427 g, 3.00 mmol), BF_3 and 4-tolualdehyde (**2k**) (0.666 g 3.90 mmol) with 2.5 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.317 g (66% yield) of **3k**. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.222 (d, 2H, J = 8.1), 7.07 (d, 2H, J = 8.1), 6.34 (d, 1H, J = 15.8), 6.14 (dt, 1H, J = 15.8, 6.8), 2.30 (s, 3H), 2.20 – 2.11 (m, 2H), 1.54 – 1.40 (m, 2H), 0.94 (t, 3H, J = 7.3); ^{13}C-NMR ($CDCl_3$) δ 136.34, 135.16, 129.83, 129.71, 129.11, 125.29, 35.10, 22.60, 21.06, 13.70; GCMS (EI) m/z (relative intensity) 160 (M^+, 30), 145 (6), 131 (100), 115 (23), 91 (33); b.p. = 236-237 °C/730 mm Hg; (E/Z) = 98:2 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.7.11 (E)-1-(4-α,α,α-Trifluorotolyl)-1-pentene (**3l**).*

(E)-1-(4-α,α,α-Trifluorotolyl)-1-pentene (**3l**) was prepared, as described previously, from 5-nonanone (**1**) (0.427 g, 3.00 mmol), BF_3 and 4–α,α,α-trifluorotolualdehyde (**2l**) (0.679 g, 3.90 mmol) with 4 hours at reflux in hexane.

The product was flash chromatographed using silica gel and hexanes to give 0.529 g (82% yield) of **3l**. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.51 (d, 2H, *J* = 8.3), 7.39 (d, 2H, *J* = 8.3), 6.40 (d, 1H, *J* = 16.0), 6.30 (dt, 1H, *J* = 16.0, 6.2), 2.24 - 2.16 (m, 2H), 1.57 – 1.43 (m, 2H), 0.95 (t, 3H, *J* = 7.3); ^{13}C-NMR ($CDCl_3$) δ 141.46, 133.83, 128.78, 126.03, 125.43, 125.37, 35.13, 22.35, 13.66; GCMS (EI) m/z (relative intensity) 214 (M^+, 30), 185 (58), 177 (100), 165 (45), 145 (18), 115 (34); Anal. calcd. for $C_{12}H_{13}F_3$: C, 67.28; H, 6.12. Found: C, 67.39; H, 6.05; (E/Z) = 96:4 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.7.12 (E)-1-(3-Methoxyphenyl)-1-pentene (**3m**).*[49]

(E)-1-(3-Methoxyphenyl)-1-pentene (**3m**) was prepared, as described previously, from 5-nonanone (**1**) (0.309 g, 2.17 mmol), BF_3 and 3-anisaldehyde (**2m**) (0.373 g, 2.82 mmol) with 1.5 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.076 g (20% yield) of **3m**. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.20 (t, 1H, *J* = 7.8), 6.94 (d, 1H, *J* = 7.6), 6.89 (d, 1H, *J* = 2.0), 6.74 (dd, 1H, *J* = 8.2, 2.3), 6.36 (d, 1H, *J* = 15.9), 6.21 (dt, 1H, *J* = 15.9, 6.4), 3.80 (s, 3H), 2.23 – 2.14 (m, 2H), 1.61 – 1.43 (2H), 0.95 (t, 3H, *J* = 7.3); ^{13}C-NMR ($CDCl_3$) δ 159.23, 139.37, 131.22, 129.74, 129.33, 118.54, 112.33, 111.21, 55.07, 35.02, 22.32, 13.66; GCMS (EI) m/z (relative intensity) 176 (M^+, 30), 147 (87), 134 (32), 115 (55), 91 (100), 77(37); (E/Z) = 96:4 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.8 General Procedure for the Reactions of Symmetrical Ketones with Aromatic Aldehydes in the Presence of BF_3: (E)-1-(3-Chlorophenyl)-1-pentene (**3c**).*[43] See Section 1.4.5

*1.4.8.1 (E)-1-(3-Chlorophenyl)-1-propene (**16c**).*[50]

(E)-1-(3-Chlorophenyl)-1-propene (**16c**) was prepared, as described previously, from 3-pentanone (**12**) (0.360 g, 4.18 mmol), BF_3 and 3-chlorobenzaldehyde (**2c**) (0.764 g, 5.43 mmol) with 2.5 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.319 g (50% yield) of **16c**. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.29 (s, 1H), 7.20 – 7.11 (m, 3H), 6.33 (d, 1H, *J* = 16.1), 6.21 (dq, 1H, *J* = 16.1, 6.2), 1.87 (d, 3H, *J* = 5.4); ^{13}C-NMR ($CDCl_3$) δ 139.80, 134.39, 129.80, 129.64, 127.34, 126.65, 125.76, 124.00, 14.44; GCMS (EI) m/z (relative intensity) 152 (M^+, 43), 125 (12), 117 (100), 115 (67), 91 (18); (E/Z) = 96:4 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.8.2 (E)-Stilbene (**17a**).*[51]

(E)-Stilbene (**17a**) was prepared, as described previously, from 1,3-diphenyl-2-propanone (**13**) (0.698 g, 3.32 mmol), BF_3 and benzaldehyde (**2a**) (0.528 g, 4.98 mmol) with 3 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.284 g (48% yield) of **17a**. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.49 (d, 4H, *J* = 7.4), 7.33 (d, 4H, *J* = 7.33), 7.30 – 7.20 (m, 2H), 7.09 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 137.29, 128.64, 127.56, 126.47;

GCMS (EI) m/z (relative intensity) 180 (M^+, 100), 179 (98), 178 (65), 165 (56), 152 (18) 89 (32), 76 (22); m.p. = 122–123 °C; lit. m.p. = 122–124 °C; (E/Z) > 99:1 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.8.3 (E)-4-Chlorostilbene (**17d**).*[52]

(E)-4-Chlorostilbene (**17d**) was prepared, as described previously, from 1,3-diphenyl-2-propanone (**13**) (0.604 g, 2.93 mmol), BF_3 and 4-chlorobenzaldehyde (**2d**) (0.535 g, 3.81 mmol) with 4 hours at reflux in hexane. The product was flash chromatographed using silica gel and 5% EtOAc/hexanes to give 0.270 g (43% yield) of **17d**. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.51 – 7.26 (m, 9H), 7.05 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 136.98, 135.84, 133.16, 129.31, 128.83, 128.72, 127.85, 127.64, 127.36, 126.54; GCMS (EI) m/z (relative intensity) 214 (M^+, 60), 179 (100), 89 (39), 76 (43); m.p. = 126-127 °C; lit. m.p. = 126 -128 °C; (E/Z) > 99:1 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.8.4 2-Methyl-1-phenyl-1-propene (**18a**).*[51]

2-Methyl-1-phenyl-1-propene (**18a**) was prepared, as described previously, from 1,3-dimethyl-2-pentanone (**14**) (0.388 g, 3.40 mmol), BF_3 and benzaldehyde (**2a**) (0.541 g, 5.10 mmol) with 1 hour at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.028 g

(6% yield) of **18a**. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.30 – 7.20 (m, 5H), 6.27 (s, 1H), 1.90 (s, 3H), 1.86 (s, 3H); spectral data in agreement with the proposed structure.

*1.4.8.5 (E)-9-(2-Bromophenyl)-8-nonenoic Acid (**28e**).*

(E)-9-(2-Bromophenyl)-8-nonenoic Acid (**28e**) was prepared, as described previously, from cyclooctanone (**25**) (0.372 g, 3.04 mmol), BF_3 and 2-bromobenzaldehyde (**2e**) (1.125 g, 6.08 mmol) with 4 hours at reflux in hexane. The product was flash chromatographed using silica gel and 15% EtOAc, 1% AcOH/hexanes to give 0.326 g of a mixture containing **28e**. Calculated ^{1}H-NMR yield is 20% for **28e**. ^{1}H-NMR ($CDCl_3$/TMS) δ 10 – 12 (broad s, 1H), 7.72 – 7.00 (m, 4H), 6.70 (s, 1H, *J* = 15.8), 6.15 (dt, 1H, *J* = 15.8, 7.0), 2.45 –2,15 (m, 4H), 1.73 – 1.20 (m, 8H); Spectral data are in agreement with the proposed structure.

*1.4.9 General Procedure for the Reactions of Methyl Ketones with Aromatic Aldehydes in the Presence of BF_3: (E)-1-(3-Chlorophenyl)-1-hexene (**34c**).*

A small excess of BF_3 was bubbled into a solution of 2-heptanone (**31**) (0.313 g, 2.74 mmol) in hexanes (10 mL). The reaction flask was flushed with nitrogen to remove excess BF_3 . 3-Chlorobenzaldehyde (**2c**) (0.501 g, 3.56 mmol) was added to the reaction mixture and the contents refluxed for 2.5 hours. The reaction was quenched with distilled water (10 mL) and the product was extracted into ether (3 x 10 mL) using a separatory funnel and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the

mixture was purified by flash chromatography with silica gel in a 30 mm column using hexanes as the eluent. This produced 0.311g (58% yield) of **34c**: ^{1}H-NMR ($CDCl_3$/TMS) δ 7.30 (s, 1H), 7.17 – 7.11 (m, 3H), 6.28 (d, 1H, *J* = 15.9), 6.18 (dt, 1H, *J* = 15.9, 6.1), 2.21 – 2.13 (m, 2H), 1.45 – 1.25 (m, 4H), 0.91 (t, 3H, *J* = 6.9); ^{13}C-NMR ($CDCl_3$) δ 139.74, 134.31, 132.62, 129.49, 128.40, 126.54, 125.72, 124.01, 32.57, 31.27, 22.18, 13.82; GCMS (EI) m/z (relative intensity) 194 (M^+, 26), 151 (59), 140 (33), 138 (100), 117 (21), 116(54) 115 (76); Anal. calcd. for $C_{11}H_{13}Cl$; C, 74.03; H, 7.77. Found: C, 73.97; H, 7.75; (E/Z) = 98:2 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.9.1 (E)-1-(3-Chlorophenyl)-1-pentene (**3c**).*[43]

(E)-1-(3-Chlorophenyl)-1-pentene (**3c**) was prepared, as described previously, from 2-hexanone (**30**) (0.608 g, 6.06 mmol), BF_3 and 3-chlorobenzaldehyde (**2c**) (0.842 g 7.93 mmol) with 2.5 hours at reflux in hexanes. The product was flash chromatographed using silica gel and hexanes to give 0.569 g (52% yield) of **3c**; spectral data was consistent with previously prepared sample.

*1.4.9.2 (E)-1-(3-Chlorophenyl)-1-propene (**16c**).*[50]

(E)-1-(3-Chlorophenyl)-1-propene (**16c**) was prepared, as described previously, from 2-butanone (**29**) (0.238 g, 3.29 mmol), BF_3 and 3-chlorobenzaldehyde (**2c**) (0.555 g, 3.95 mmol) with 2.5 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give

0.126 g (21% yield) of **16c**; spectral data was consistent with sample prepared previously; (E/Z) = 96:4 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.9.3. 2-Methyl-1-phenyl-1-propene (**18a**).*[51]

2-Methyl-1-phenyl-1-propene (**18a**) was prepared, as described previously, from 3-methyl-2-butanone (**32**) (0.252 g, 3.00 mmol), BF_3 and benzaldehyde (**2a**) (0.478 g, 4.50 mmol) with 1 hour at reflux in hexanes. The product was flash chromatographed using silica gel and hexanes to give 0.020 g (5% yield) of **18a**; spectral data was consistent with previously prepared sample.

*1.4.9.4 1-Phenyl-2-methyl-1-butene (**35a**).*[53]

1-Phenyl-2-methyl-1-butene (**35a**) was prepared, as described previously, from 3-methyl-2-pentanone (**33**) (0.449 g, 4.48 mmol), BF_3 and benzaldehyde (**2a**) (0.618 g, 5.82 mmol) with 1.25 hours at reflux in hexanes. The product was flash chromatographed using silica gel and hexanes to give 0.032g (7% yield) of **18a** (mixture of (E) and (Z)-isomers). Ratio of isomers could not be obtained due to the lack of non-overlapping signals in the ^{1}H-NMR spectrum; spectral data are in agreement with the proposed structure.

*1.4.10 General Procedure for the Reactions of Phenyl Ketones with Aromatic Aldehydes in the Presence of BF_3: (E)-1-(2-Chlorophenyl)-1-pentene (**3b**).*[44]

A small excess of BF_3 was bubbled into a solution of valerophenone (**37**) (0.480 g, 2.96 mmol) in hexanes (10 mL). The reaction flask was flushed with nitrogen to remove excess BF_3 . 2-Chlorobenzaldehyde (**2b**) (0.541 g, 3.85 mmol) was added to the reaction mixture and the contents refluxed for 4 hours. The reaction was quenched with distilled water (10 mL) and the product was extracted into ether (3 x 10 mL) using a separatory funnel and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the mixture was purified by flash chromatography with silica gel in a 30 mm column using hexanes as the eluent. This produced 0.267g (50% yield) of **3b**; spectral data was consistent with previously prepared sample; (E/Z) = 96:4 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.10.1 (E)-1-(2-Chlorophenyl)-1-propene (**16b**).*

(E)-1-(2-Chlorophenyl)-1-propene (**16b**) was prepared, as described previously, from propiophenone (**36**) (0.134 g, 1.00 mmol), BF_3 and 3-chlorobenzaldehyde (**2c**) (0.141 g, 1.00 mmol) with 4 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.033 g (22% yield) of **16b**; ^{1}H-NMR ($CDCl_3$/TMS) δ 7.46 (d, 1H, J = 7.6), 7.31 (d, 1H, J = 7.5), 7.23 – 7.06 (m, 2H), 6.77 (d, 1H, J = 15.9), 6.22 (dq, 1H, J = 15.9, 6.7), 1.91 (d, 3H, J = 6.5); GCMS (EI) m/z (relative intensity) 154 (26), 152

(M^+, 79), 117 (100), 115 (77); spectral data are in agreement with the proposed structure.

*1.4.10.2 (E)-4-Chloro-1-(4-chlorophenyl)-1-butene (**40d**).*

(E)-4-Chloro-1-(4-chlorophenyl)-1-butene (**40d**) was prepared, as described previously, from 4-chloro-4'-fluorobutyrophenone(**38**) (1.252 g, 6.05 mmol), BF_3 and 4-chlorobenzaldehyde (**2d**) (1.063 g, 7.56 mmol) with 4 hours at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.316 g (26% yield) of **40d**; ^{1}H-NMR ($CDCl_3$/TMS) δ 7.25 (s, 4H), 6.42 (d, 1H, *J* = 15.8), 6.16 (dt, 1H, *J* = 15.8, 6.9), 3.60 (t, 2H, *J* = 6.9), 2.69 – 2.60 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 135.51, 132.94, 131.53, 128.62, 127.34, 126.52, 43.85, 36.01; GCMS (EI) m/z (relative intensity) 202 (14), 200 (M^+, 22), 153 (36), 151 (100), 129 (21), 128 (24), 127 (16), 116 (64), 115 (74); Anal. calcd. for $C_{10}H_{10}Cl_2$: C, 59.73; H, 5.01. Found: C, 59.55; H, 4.98; (E/Z) = 94:6 determined by integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.11. Reaction of 2-Methyl-3-hexanone (**44**) with 2-Chlorobenzaldehyde (**2b**).*

A small excess of BF_3 was bubbled into a solution of 2-Methyl-3-hexanone (**44**) (0.457 g, 4.00 mmol) in hexanes (10 mL). The reaction flask was flushed with nitrogen to remove excess BF_3 . 2-Chlorobenzaldehyde (**2c**) (0.731 g, 5.20 mmol) was added to the reaction mixture and the contents refluxed for 4 hours. The reaction was quenched with distilled water (10 mL) and the product was extracted into ether (3 x 10 mL) using a separatory funnel and dried over

anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the mixture was purified by flash chromatography with silica gel in a 30 mm column using hexanes as the eluent. This produced 0.112 g of a mixture of two alkenes (**18b**) and (**46**). **18b/46** = 21:79 determined by the integration of non-overlapping signals in the ^{1}H-NMR spectrum.

*1.4.12 General Procedure for the Reactions of 5-Nonanone (**1**) with 2-Chlorobenzaldehyde (**2b**) in the Presence of Various Acids: (E)-1-(2-Chlorophenyl)-1-pentene (**3b**)[44] Using BF_3:AcOH Complex.*

To a mixture of 5-Nonanone (**1**) (0.356 g, 2.50 mmol) and 2-Chlorobenzaldehyde (**2b**) (0.387 g, 2.75 mmol) in 5 mL of CCl_4 was added boron trifluoride-acetic acid complex (7.50 mmol). The reaction mixture was stirred for 2 hours at reflux. The reaction was quenched with distilled water (10 mL) and the product was extracted into ether (3 x 10 mL) using a separatory funnel and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the mixture was purified by flash chromatography with silica gel in a 30 mm column using hexanes as the eluent. This produced 0.353 g (79% yield) of **3b**; spectral data was consistent with previously prepared sample.

The same conditions (2.50 mmol of **1**, 2.75 mmol of **2b**, 5 mL of CCl_4, 2 hours at reflux, 7.50 mmol of acid) were repeated for the following acids: Boron trifluoride etherate, boron trifluoride dihydrate, aluminum chloride, titanium (IV) chloride, zinc chloride, boron tribromide, *p*-toluenesulfonic acid monohydrate, trifluoromethylsulfonic acid, trifluoroacetic acid, and perfluorooctanoic acid. Boron

trifluoride was bubbled into a mixture of **1** and **2b** (i.e. Section 1.4.3). Isolated yields of **3b** are reported in Table 1-9; spectral data was consistent previously prepared sample.

*1.4.13 General Procedure for the Reactions of 5-Nonanone (**1**) with 2-Chlorobenzaldehyde (**2b**) in the Presence of Boron Trifluoride Etherate in Different Solvents: (E)-1-(2-Chlorophenyl)-1-pentene (**3b**).*[44]

To a mixture of 5-Nonanone (**1**) (0.356 g, 2.50 mmol) and 2-Chlorobenzaldehyde (**2b**) (0.387 g, 2.75 mmol) in 5 mL of hexanes was added boron trifluoride etherate (7.50 mmol). The reaction mixture was stirred for 24 hours at RT. The reaction was quenched with distilled water (10 mL) and the product was extracted into ether (3 x 10 mL) using a separatory funnel and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the mixture was purified by flash chromatography with silica gel in a 30 mm column using hexanes as the eluent. This produced 0.319 g (70% yield) of **3b**. The same procedure was repeated in toluene (0.165 g, 37% yield of **3b**), in CH_2Cl_2 (0.306g, 68% yield of **3b**), in CCl_4 (0.260 g, 58% yield of **3b**) and in THF (**3b** failed to form); spectral data was consistent with previously prepared sample.

*1.4.14 General Procedure for the Reactions of 5-Nonanone (**1**) with 2-Chlorobenzaldehyde (**2b**) in the Presence of Various Quantities of Boron Trifluoride Etherate: (E)-1-(2-Chlorophenyl)-1-pentene (**3b**).*[44]

(E)-1-(2-Chlorophenyl)-1-pentene (**3b**) was prepared, as described previously (Section 1.4.13), from 5-Nonanone (**1**) (0.356 g, 2.50 mmol), 2-Chlorobenzaldehyde (**2b**) (0.387 g, 2.75 mmol) and boron trifluoride etherate (2.2 eq.) with 1 hour at reflux in hexane. The product was flash chromatographed using silica gel and hexanes to give 0.380 g (84 % yield) of **3b**. The same procedure was repeated using boron trifluoride etherate in different amounts: (1.5 eq.) gave 0.381 g (84% yield) of **3b**. (0.7 eq.) gave 0.395 g (88% yield) of **3b**. (0.4 eq.) gave 0.364 g (81% yield) of **3b**. (0.2 eq.) gave 0.114 g (25% yield) of **3b**. (0.1 eq.) gave 0.018 g (4% yield) of **3b**; spectral data was consistent with previously prepared sample.

1.4.15 Exposure of a Mixture of (E)- and (Z)-1-Phenyl-1-heptene to General Reaction Conditions.

A small excess of BF_3 was bubbled into a solution of 1,3-diphenyl-2-propanone (0.406 g, 1.93 mmol) in hexanes (10 mL). The reaction flask was flushed with nitrogen to remove excess BF_3. Benzaldehyde (0.266 g, 2.51 mmol) was added to the reaction mixture and the contents refluxed for 1.25 hours. A mixture of (E)- and (Z)-1-phenyl-1-heptene (prepared following literature procedures,[14] 48:52 by integration of non-overlapping signals in the ^{1}H-NMR spectrum, 0.346 g, 1.84 mmol) was added to the reaction in progress and the mixture was further refluxed for 0.5 hours. The organic products were isolated as described previously to yield 0.340 g of olefinic products. ^{1}H-NMR analysis reveals no isomerization of the 1-phenyl-1-heptene mixture.

CHAPTER 2

BORON TRIFLUORIDE INDUCED FRAGMENTATION OF β-ARYL β-HYDROXY KETONES

2.1 Introduction

During the study of the synthesis of β-alkylstyrenes via the reaction of ketones with aromatic aldehydes in the presence of boron trifluoride in non-nucleophilic solvents (Part B, Chapter 1, eqn 1-1), we postulated the formation of an aldol condensation intermediate as part of the reaction mechanism (Section 1.2.4). ^{1}H-NMR and ^{13}C-NMR studies, however, did not detect the formation of any appreciable amount of the aldol product during the reaction of 5-nonanone and benzaldehyde in the presence of boron trifluoride. We attributed these observations to a slow aldol condensation reaction, followed by a rapid fragmentation. In order to validate the hypothesis that aldol intermediates undergo a fragmentation reaction that leads to styrenyl products, various β-hydroxy ketones were synthesized and their reactions in the presence of boron trifluoride were investigated. The results of this study are summarized in this chapter.

2.2 Synthesis of β-Aryl β-hydroxy Carbonyl Compounds

In recent years, a variety of boron reagents have been developed which efficiently control the stereochemistry of the resulting β-hydroxy ketones.[28,42] β-Aryl β-hydroxy ketones are often difficult to isolate due to their prepotency to dehydrate to the more stable α,β-unsaturated ketones. However, Brown's method,[28,42] which involves the formation of boron enolates, proved to be successful in their preparation. Flash chromatography was used for their isolation and no noticeable dehydration was observed when stored at room temperature. Thus, β-aryl β-hydroxy ketones **48** through **55** and β-alkyl β-hydroxy ketone **56** (Figure 2-1) were prepared for further reactions with boron trifluoride.

Anticipating that the fragmentation reaction may be general for other β-hydroxy carbonyl compounds, a readily accessible β-hydroxy ester **57** was prepared via the Refortmaski[22] condensation of ethylbromo acetate and benzophenone.

2.3 Reaction of β-Hydroxy Ketones with Boron Trifluoride

Based on the results obtained in the β-alkylstyrene studies (Part B, Chapter 1), we anticipated variable reactivities for the β-hydroxy ketones in Figure 2-1. In addition, the stability of the resultant products would also vary.

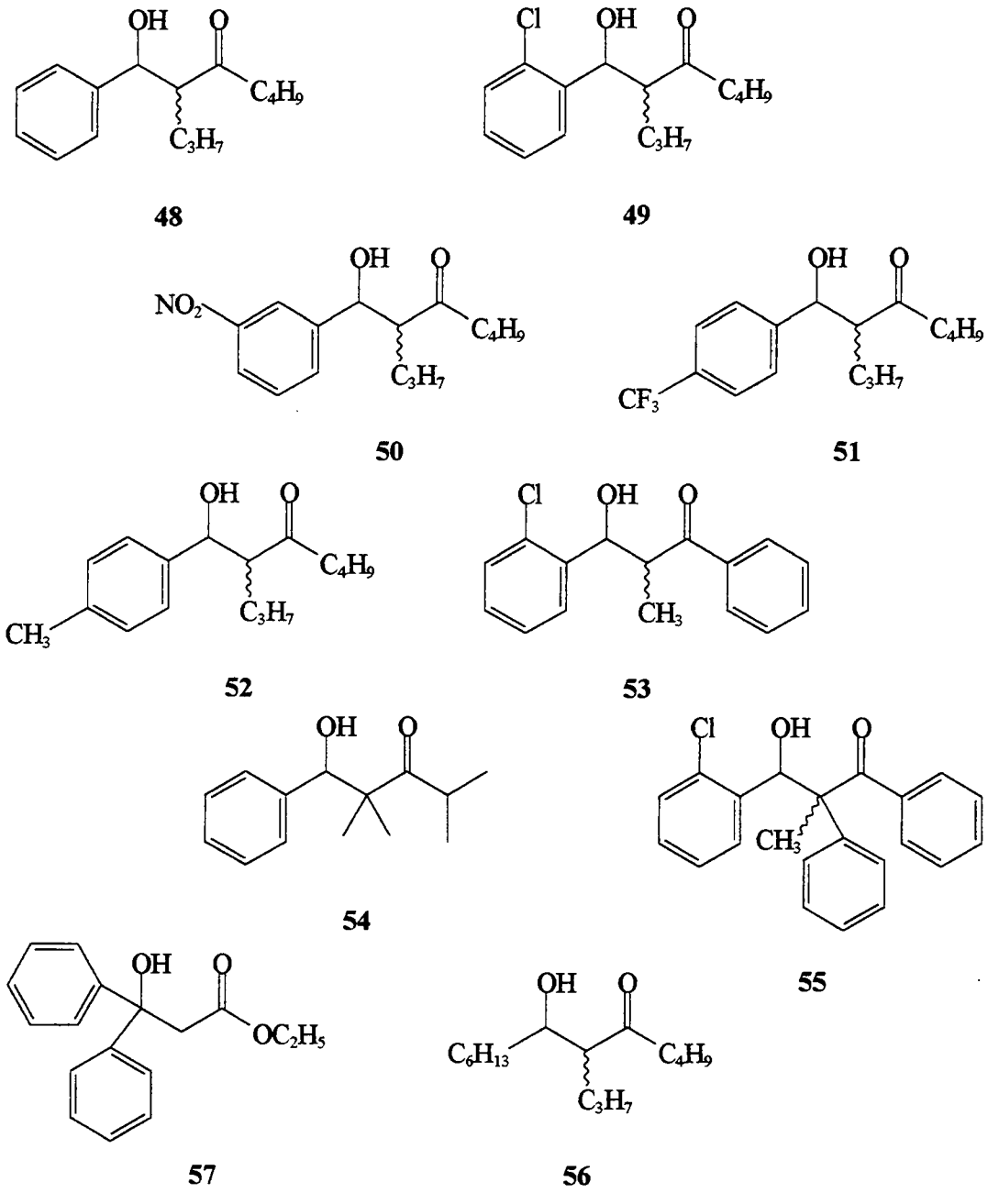
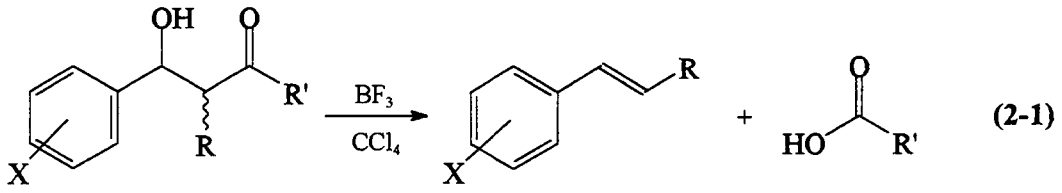


Figure 2-1. β-Hydroxy Carbonyl Compounds Prepared.

Initial experiments were performed with 1-hydroxy-1-phenyl-2-propyl-3-heptanone (**48**). Indeed, when compound **48** was reacted with boron trifluoride, the corresponding (E)-β-alkylstyrene was produced (eqn 2-1).



(2-1)

As anticipated, the formation of the products via the direct fragmentation of **48** occurred much more rapidly, and under milder conditions, than from the reaction of 5-nonanone with benzaldehyde. These observations clarify why a short-lived aldol condensation product was not detected in the previous NMR studies (Section 2.1). The results from the reaction of boron trifluoride with β-hydroxyketones **48** through **56** are summarized in Table 2-1. They parallel those obtained earlier in the sequential aldol condensation-fragmentation reaction in that the best yields were obtained when the aromatic ring was substituted with an electron-withdrawing group and when R' (eqn 2-1) was an aliphatic group. The yields, however, were consistently lower. This fact was attributed to the loss of product due to dimerization and polymerization reactions during the addition and removal of excess boron trifluoride gas from the reaction flask.

Table 2-1. Reaction of β-Hydroxy Ketones with Boron Trifluoride.[a]

β-Hydroxy Ketone	Time	Temperature	Yield (%)[b]
48	10 min	RT	54
49	30 min	RT	72
50	20 min	RT	62
51	30 min	RT	51[c]
51	5 hr	reflux	62
52	5 min	RT	50
53	4 hr	reflux	33
54	> 30 min[d]	reflux	traces[e]
55	30 min	RT	0[f]
56	> 30 min[d]	reflux	0[g]

[a] Reaction carried out in CCl4. [b] Isolated yield of corresponding 1-aryl-1-alkene: Mixtures of *syn* and *anti* β-hydroxy ketones produced , predominantly, (E)-isomer. [c] GC/MS and ^{1}H-NMR analyses of reaction mixture reveals retro aldol products. [d] Reaction followed by TLC for 4 hours. [e] GC/MS analysis reveals a mixture of retro aldol products and high molecular weight unidentified compounds. [f] Retro aldol products recovered quantitatively. No alkene detected by GC/MS analysis even in refluxing toluene for 48 hours. [g] Dehydration leads to α,β-unsaturated ketone.

The fragmentation of the β-hydroxyketone was rapid and, generally, side reactions were not observed (other than dimerization or polymerization of alkene). However, **51** suffered a competitive retro aldol reaction which lowered the yield of the corresponding alkene. In this case, the yield could be enhanced by increasing the reaction time and temperature (in Part B, Chapter 1, we demonstrated that the aldol condensation-fragmentation sequence required heating for longer periods of time).

The reaction of β-hydroxyketones obtained via aldol condensation of ketones bearing at least one secondary alkyl group proved to be problematic (Section 1.2.2.6). Steric hindrance and side reactions appear to be responsible for the lack of product formation. A β-alkyl-β-hydroxyketone (**56**) slowly dehydrates during its reaction with boron trifluoride, demonstrating that an aromatic group beta to the carbonyl is necessary in order to stabilize the proposed cabocation intermediate.

2.4 Reaction of a β-aryl β-Hydroxy Ester with Boron Trifluoride.

In a preliminary attempt to determine whether other β-aryl-β-hydroxy-carbonyl compounds could undergo the new fragmentation reaction, compound **59** was allowed to react with boron trifluoride. Only the dehydration product was obtained. Further research will be needed to determine whether β-aryl-β-hydroxy acids and β-aryl-β-hydroxy aldehydes lead to styrenyl products.

2.5 Conclusion

β-Aryl-β-hydroxyketones are cleaved by boron trifluoride in non-nucleophilic solvents to give β-alkylstyrenes and the corresponding carboxylic acid. The reaction generally occurs rapidly at room temperature. As described in Part B, Chapter 1, the reaction appears to proceed via a non-synchronous Grob fragmentation pathway.

Although the reaction is not an effective method for synthesizing styrenyl products, it provides valuable information in regarding possible mechanisms for the reaction of ketones with aromatic aldehydes in the presence of boron trifluoride. Additionally, it is as an example of an unprecedented fragmentation reaction.

2.6 Experimental

The general experimental conditions parallel those summarized in Section 1.4.

*2.6.1 General Procedure for the Synthesis of β-Hydroxyketones: 1-Hydroxy-1-phenyl-2-propyl-3-heptanone (**48**).*[28]

The β-hydroxy ketones were prepared via literature procedures.[28,41] To a stirred solution of bromodicyclohexylborane[54] (5.0 mmol) in CH_2Cl_2 (5 mL), triethylamine (5.0 mmol) and pentane (10 mL) was added 5-nonanone (0.71 g,

5.0 mmol). The reaction mixture was stirred at 0 °C for 2 hours and then cooled to -78 °C. Benzaldehyde (0.53 g, 5.0 mmol) was added to the reaction mixture at -78 °C and the mixture allowed to warm up to room temperature. The reaction was stirred overnight. Methanol (10 mL) and 30% H_2O_2 (2.5 mL) were then added at 0 °C followed by stirring for 5 hrs. The product was extracted into ether (3 x 10 mL) using a separatory funnel and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the mixture purified by flash chromatography (silica gel, 10% EtOAc/hexanes as the eluent) to obtain 0.43 g (34% yield) of **48** (mixture of *syn* and *anti* isomers). ^{1}H-NMR ($CDCl_3$/TMS) δ 7.34 – 7.23 (m, 5H), 4.82 – 4.72 (m, 1H), 3.06 (broad s, 1H), 2.93 – 2.86 (m, 1H), 2.39 – 2.23 (m, 2H), 1.70 – 1.10 (m, 6H), 0.90 – 0.77 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ (216.12, 215.16), (142.74, 142.07), (128.38, 128.28), 127.67, 126.13, (75.63, 74.09), (58.85, 56.14), (45.00, 44.61), (31.78, 29.53), 24.91, 22.09, (20.99, 20.48), (14.22, 14.06), 13.76; spectral data are in agreement with the proposed structure.

*2.6.1.1 1-(2-Chlorophenyl)-1-hydroxy-2-propyl-3-heptanone (**49**).*

1-(2-Chlorophenyl)-1-hydroxy-2-propyl-3-heptanone (**49**) was prepared as described previously, using bromo-9-BBN (5.0 mmol) in CH_2Cl_2 (5 mL), 5-nonanone (0.71 g, 5.0 mmol), pentane (10 mL), triethylamine (5.0 mmol) and 2-chlorobenzaldehyde (0.70 g, 5.0 mmol). The product was flash chromatographed using silica gel and 10% EtOAc/hexanes to give 1.2 g (84% yield) of **49** (mostly

anti isomer). ^{1}H-NMR ($CDCl_3$/TMS) δ 7.62 (dd, 1H, *J* = 7.7, 1.6), 7.35 – 7.21 (m, 3H), 5.26 (d, 1H, *J* = 2.4), 3.5 (broad s, 1H), 3.09 – 3.03 (m, 1H), 2.72 – 2.38 (m, 3H), 1.90 – 1.25 (m, 10H), 0.92 (t, 3H, *J* = 7.3), 0.76 (t, 3H, *J* = 7.3); ^{13}C-NMR ($CDCl_3$) δ 216.74, 138.52, 131.13, 129.34, 125.52, 128.47, 126.74, 69.81, 53.69, 44.03, 27.08, 25.32, 22.23, 21.26, 14.14, 13.80; spectral data are in agreement with the proposed structure.

*2.6.1.2 1-Hydroxy-1-(3-nitrophenyl)-2-propyl-3-heptanone (**50**).*

1-Hydroxy-1-(3-nitrophenyl)-2-propyl-3-heptanone (**50**) was prepared as described previously, using bromo-9-BBN (5.0 mmol) in CH_2Cl_2 (5 mL), 5-nonanone (0.71 g, 5.0 mmol), pentane (10 mL), triethylamine (5.0 mmol) and 3-nitrobenzaldehyde (0.76 g, 5.0 mmol). The product was flash chromatographed using silica gel and 10% EtOAc/hexanes to give 0.86 g (58% yield) of **50** (mostly *anti* isomer). ^{1}H-NMR ($CDCl_3$/TMS) δ 8.21 (s, 1H), 8.10 (d, 1H), 7.67 (d, 1H), 7.51 (t, 1H), 5.01 (d, 1H, *J* = 2.4), 3.66 (d, 1H, *J* = 2.4), 2.97 – 2.85 (m, 1H), 2.55 – 2.27 (m, 2H), 1.80 – 1.02 (m, 8H), 0.89 – 0.79 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ 215.22, 148.13, 144.26, 132.31, 129.10, 122.30, 121.00, 72.52, 57.72, 44.37 28.76, 24.97, 22.00, 20.85, 14.08, 13.64; spectral data are in agreement with the proposed structure.

*2.6.1.3 1-(4-α,α,α-Trifluorotolyl)-1-hydroxy-2-propyl-3-heptanone (**51**).*

1-(4-α,α,α-Trifluorotolyl)-1-hydroxy-2-propyl-3-heptanone (**51**) was prepared as described previously, using bromo-9-BBN (5.0 mmol) in CH_2Cl_2 (5

mL), 5-nonanone (0.71 g, 5.0 mmol), pentane (10 mL), triethylamine (5.0 mmol) and 4-α,α,α-trifluorotolualdehyde (0.87 g, 5.0 mmol). The product was flash chromatographed using silica gel and 10% EtOAc/hexanes to give 0.93 g (59% yield) of **51** (mostly *anti* isomer). ^{1}H-NMR ($CDCl_3$/TMS) δ 7.57 (d, 2H, *J* = 8.1), 7.41 (d, 2H, *J* = 8.1), 4.82 (d, 1H, *J* = 2.4), 3.56 (d, 1H, *J* = 2.4), 2.93 – 2.80 (m, 1H), 2.44 – 2.12 (m, 2H), 1.80 – 1.00 (m, 8H), 0.85 – 0.78 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ 215.25, 146.15, 129.6 (q), 126.50, 125.15, 125.10, 73.27, 58.32, 44.53 29.27, 24.96, 21.99, 20.85, 14.10, 13.64; spectral data are in agreement with the proposed structure.

*2.6.1.4 1-Hydroxy-2-propyl-1-(4-tolyl)-3-heptanone (**52**).*

1-Hydroxy-2-propyl-1-(4-tolyl)-3-heptanone (**52**) was prepared as described previously, using bromo-9-BBN (5.0 mmol) in CH_2Cl_2 (5 mL), 5-nonanone (0.71 g, 5.0 mmol), pentane (10 mL), triethylamine (5.0 mmol) and 4-tolualdehyde (0.59 g, 4.9 mmol). The product was flash chromatographed using silica gel and 10% EtOAc/hexanes to give **52** (mixture of isomers). ^{1}H-NMR ($CDCl_3$/TMS) δ 7.16 – 7.08 (m, 4H), 4.80 – 4.60 (m, 1H), 3.03 – 2.95 (m, 1H), 2.95 – 2.81 (m, 1H), 2.31 (s, 3H), 2.41 1.95 (m, 2H), 1.78 – 1.08 (m, 8H), 0.87 – 0.75 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ (216.01, 214.95), 139.13, 137.06, (128.97, 128.85), 126.04, (75.58, 74.09), (59.07, 58.24), (44.88, 44.52), (31,67, 29.84), 24.86, (22.05, 21.94), (20.94, 20.41), 14.17, 13.62; spectral data are in agreement with the proposed structure.

*2.6.1.5 3-(2-Chlorophenyl)-3-hydroxy-2-methylpropiophenone (**53**).*

3-(2-Chlorophenyl)-3-hydroxy-2-methylpropiophenone (**53**) was prepared as described previously, using bromo-9-BBN (5.0 mmol) in CH_2Cl_2 (5 mL), propiophenone (0.67 g, 5.0 mmol), pentane (10 mL), triethylamine (5.0 mmol) and 2-chlorobenzaldehyde (0.70 g, 4.9 mmol). The product was flash chromatographed using silica gel and 10% EtOAc/hexanes to give 0.64 g (47% yield) **53** (mostly *anti* isomer). ^{1}H-NMR ($CDCl_3$/TMS) δ 8.01 (d, 2H, *J* = 7.2), 7.71 (d, 1H, *J* = 7.3), 7.59 (d, 1H, *J* = 7.1), 7.49 (t, 2H, *J* = 7.0), 7.33 (td, 2H, *J* = 6.2, 2.2), 7.24 (dd, 1H, *J* = 5.4, 1.6), 5.55 (s, 1H), 4.05 (broad s, 1H), 4.15 – 3.88 (m, 1H), 1.10 (d, 3H, *J* = 7.3); ^{13}C-NMR ($CDCl_3$) δ 216.74, 138.62, 135.53, 133.68, 131.04, 129.26, 128.80, 128.65, 128.55, 128.40, 126.71, 69.70, 42.89, 10.37; spectral data are in agreement with the proposed structure.

*2.6.1.6 1-Hydroxy-2,2,4-trimethyl-1-phenyl-3-pentanone (**54**).*[55]

1-Hydroxy-2,2,4-trimethyl-1-phenyl-3-pentanone (**54**) was prepared as described previously, using bromo-9-BBN (5.0 mmol) in CH_2Cl_2 (5 mL), 2,4-dimethyl-3-pentanone (0.57 g, 5.0 mmol), pentane (10 mL), triethylamine (5.0 mmol) and benzaldehyde (0.53 g, 4.9 mmol). The product was flash chromatographed using silica gel and 10% EtOAc/hexanes to give 0.57 g (52% yield) **54**. ^{1}H-NMR ($CDCl_3$/TMS) δ 7.30 (m, 5H), 4.94 (d, 1H, *J* = 3.7), 3.20 (d, 1H, *J* = 3.8), 3.13 (septet, 1H), 1.14 (s, 3H), 1.09 (s, 3H), 1.05 (d, 6H, *J* = 6.8); ^{13}C-NMR ($CDCl_3$) δ 222.02, 140.11, 127.91, 127.67, 127.54, 78, 16, 52.61, 35.08, 22.64, 19.89, 17.53; spectral data are in agreement with the proposed structure.

*2.6.1.7 3-(2-Chlorophenyl)-3-hydroxy-2-methyl-2-phenylpropiophenone (**55**).*

3-(2-Chlorophenyl)-3-hydroxy-2-methyl-2-phenylpropiophenone (**55**) was prepared as described previously, using bromo-9-BBN (7.2 mmol) in CH_2Cl_2 (5 mL), 2-methyl-3-phenylpropiophenone (1.62 g, 7.2 mmol), pentane (10 mL), triethylamine (7.2 mmol) and 2-chlorobenzaldehyde (1.01 g, 7.2 mmol). The product was flash chromatographed using silica gel and 10% EtOAc/hexanes to give **55** (mostly one isomer). ^{1}H-NMR ($CDCl_3$/TMS) δ 7.58 – 7.03 (m, 15H), 5.75 (s, 1H), 3.78 (d, 1H, *J* = 12.9), 3.17 (broad s, 1H), 2.46 (d, 1H, *J* = 12.9), 1.18 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 213.10, 141.08, 138.80, 136.53, 133.71, 130.82, 130.00, 129.92, 129.52, 129.01, 128.09, 127.62, 126.70, 126.60, 126.47, 58.26, 43.80, 17.83; spectral data are in agreement with the proposed structure.

*2.6.1.8 7-Hydroxy-6-propyl-5-tridecanone (**56**).*

7-Hydroxy-6-propyl-5-tridecanone (**56**) was prepared as described previously, using bromo-9-BBN (7.2 mmol) in CH_2Cl_2 (5 mL), 5-nonanone (0.71 g, 5.0 mmol), pentane (10 mL), triethylamine (7.2 mmol) and heptanal (0.57 g, 5.0 mmol). The product was flash chromatographed using silica gel and 10% EtOAc/hexanes to give 0.69 g (54% yield) **56** (mostly *anti* isomer). ^{1}H-NMR ($CDCl_3$/TMS) δ 3.77 – 3.70 (m, 1H), 2.61 – 2.39 (m, 6H), 1.90 – 1.85 (m, 2H), 1.60 – 1.24 (m, 14H), 0.94 – 0.85 (9H); ^{13}C-NMR ($CDCl_3$) δ (representative peaks) 215.87, 71.66, 56.37, 44.15, 41.88, 14.31, 13.99, 13.81; spectral data are in agreement with the proposed structure.

*2.6.2 Synthesis of 3-Hydroxy-3,3-Diphenylethyl Propionate (**57**).*[22,56]

To Zinc powder (20 mmol) in THF (20 mL) was added benzophenone (20 mmol) and trimethyl borate (4.0 mL). With stirring, ethylbromo acetate (20 mmol) was added, all at once and, after 12 hrs, saturated aqueous NH_4Cl (10 mL) and methanol (10 mL) were added to quench the reaction. The product was flash chromatographed using silica gel and 5% EtOAc/hexanes to give a white solid (**57**). ^{1}H-NMR ($CDCl_3$/TMS) δ 7.45 – 7.18 (m, 10H), 5.10 (s, 1H), 4.06 (quartet, 2H, J = 7.1), 3.25 (s, 2H), 1.11 (t, 3H, J = 7.2); ^{13}C-NMR ($CDCl_3$) δ 172.71, 145, 90, 128.15, 127.00, 125.61, 60.86, 45.49, 13.92; spectral data are in agreement with the proposed structure.

*2.6.3 General Procedure for the Reaction of β-Hydroxy Ketones with Boron Trifluoride: (E)1-Phenyl-1-pentene (**3a**).*[41]

A small excess of BF_3 was bubbled over a stirred solution of 1-hydroxy-1-phenyl-2-propyl-3-heptanone (**48**) (0.083 g, 0.33 mmol). The reaction flask with flushed with nitrogen to remove excess BF_3 and the contents were stirred at room temperature for 10 min. The reaction was quenched with distilled water (10 mL) and the product was extracted into ether (3 x 10 mL) using a separatory funnel and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the mixture was purified by flash chromatography with silica gel in a 30 mm column using hexanes as the eluent to obtain 0.026 g (54% yield) of **3a**; spectral data was consistent with previously prepared sample.

*2.6.3.1 (E)-1-(2-Chlorophenyl)-1-pentene (**3b**).*[44]

(E)-1-(2-Chlorophenyl)-1-pentene (**3b**) was prepared as described previously, using 1-(2-Chlorophenyl)-1-hydroxy-2-propyl-3-heptanone (**49**) (0.154 g, 0.545 mmol) and BF_3. The reaction mixture was stirred at room temperature for 30 min. The product was flash chromatographed using silica gel and hexanes to give 0.072 mg (72% yield) of **3b**; spectral data was consistent with previously prepared sample.

*2.6.3.2 (E)-1-(3-Nitrophenyl)-1-pentene (**3i**).*

(E)-1-(3-Nitrophenyl)-1-pentene (**3i**) was prepared as described previously, using 1-hydroxy-1-(3-nitrophenyl)-2-propyl-3-heptanone (**50**) (0.325 g, 1.11 mmol) and BF_3. The reaction mixture was stirred at room temperature for 20 min. The product was flash chromatographed using silica gel and hexanes to give 0.132 mg (62% yield) of **3l**; spectral data was consistent with previously prepared sample.

*2.6.3.3 (E)-1-(4-α,α,α-Trifluorotolyl)-1-pentene (**3l**).*

(E)-1-(4-α,α,α-Trifluorotolyl)-1-pentene (**3l**) was prepared as described previously, using 1-(4-α,α,α-trifluorotolyl)-1-hydroxy-2-propyl-3-heptanone (**51**) (0.265 g, 0.838 mmol) and BF_3. The reaction mixture was stirred at reflux for 5 hours. The product was flash chromatographed using silica gel and hexanes to give 0.111 mg (62% yield) of **3l**; spectral data was consistent with previously prepared sample.

*2.6.3.4 (E)-1-(4-Tolyl)-1-pentene (**3k**).*[48]

(E)-1-(4-Tolyl)-1-pentene (**3k**) was prepared as described previously, using 1-hydroxy-2-propyl-1-(4-tolyl)-3-heptanone (**52**) (0.133 g, 0.500 mmol) and BF_3. The reaction mixture was stirred at room temperature for 5 min. The product was flash chromatographed using silica gel and hexanes to give 0.039 mg (50% yield) of **3k**; spectral data was consistent with previously prepared sample.

*2.6.3.5 (E)-1-(2-Chlorophenyl)-1-propene (**16b**).*

(E)-1-(2-Chlorophenyl)-1-propene (**16b**) was prepared as described previously, using 3-(2-chlorophenyl)-3-hydroxy-2-methylpropiophenone (**53**) (0.247 g, 0.900 mmol) and BF_3. The reaction mixture was stirred at reflux for 4 hours. The product was flash chromatographed using silica gel and hexanes to give 0.046 mg (33% yield) of **16b**; spectral data was consistent with previously prepared sample.

CHAPTER 3

FUTURE RESEARCH

3.1 Introduction

The discovery of the new reaction of ketones with aromatic aldehydes in the presence of boron trifluoride and other anhydrous strong acids opens the door to other research. Future research directions are outlined in this chapter.

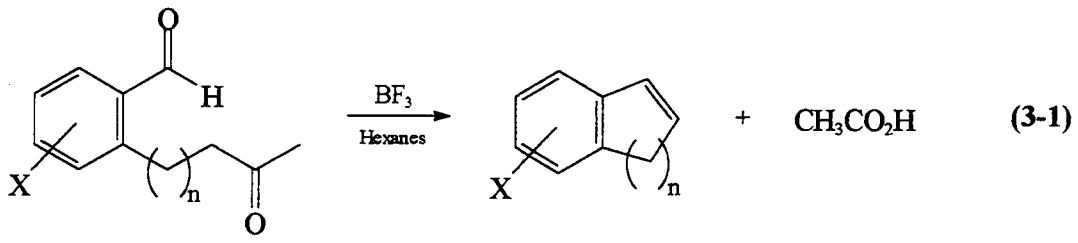
3.2 Oxidation of Ketones to Carboxylic Acids

Although Part B Chapter 1 was devoted to the synthesis of β-alkylstyrenes utilizing the new methodology, the formation of the corresponding carboxylic acids is also synthetically useful, and it could serve as an alternative to other oxidation methods such as the Baeyer-Villiger reaction[39] (refer to eqn 1-1). To date, we have isolated carboxylic acids on two occasions: The reaction of benzaldehyde with 5-nonanone led to 84% yield of pentanoic acid while the reaction of 2-chlorobenzaldehyde with valerophenone produced 86% yield of benzoic acid. These results illustrate that ketones are oxidized to the corresponding carboxylic acids in high yields.

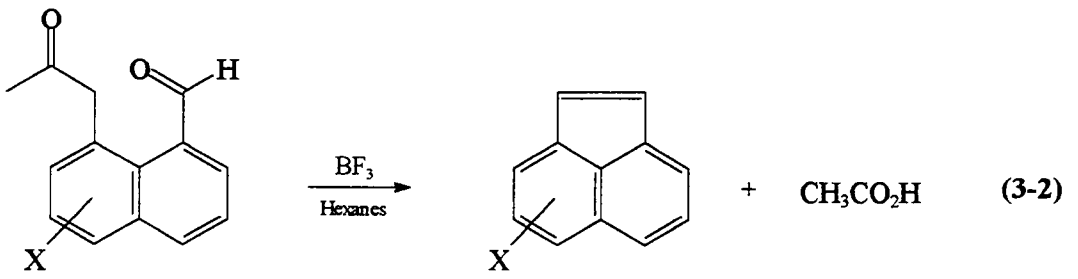
Phenyl ketones would be specially attractive because they would be expected to produce benzoic acids (under Baeyer-Villiger conditions, phenyl groups transfer more readily than aliphatic groups leading to aliphatic carboxylic esters). Additionally, inexpensive benzaldehyde could be used as the sacrificial reagent, making this methodology more appealing to the synthetic organic chemist.

3.3 Intramolecular Tandem Aldol-Grob Reaction Sequence

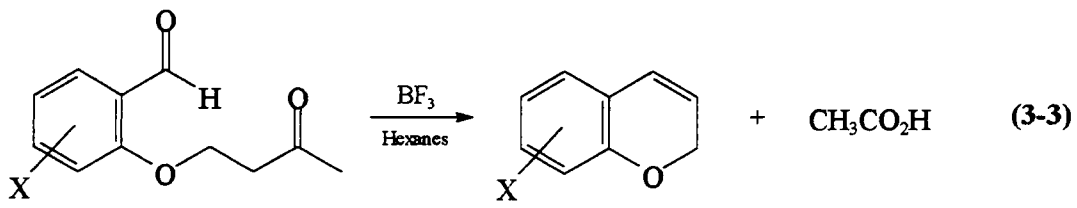
An overall intramolecular annulation reaction could be achieved if the aldol condensation step in the new reaction occurred intramolecularly. Equations **3-1**, **3-2** and **3-3** would then be feasible.



58 **59**



60 **61**



(3-3)

62 **63**

Boron trifluoride in hexanes is representative of the reagents found to promote the new aldol-Grob reaction sequence. Compounds such as indenes (**59**, n=1), 1,2-dihydronaphthylenes (**59**, n=2), acenaphthylenes (**61**) and 2H-benzopyrans (**63**) would be expected to be synthesized in good yields.

3.4 Fragmentation of β-Aryl-β-Hydroxy Aldehydes and β-Aryl-β-Hydroxy Acids

Boron trifluoride induced fragmentation of β-aryl-β-hydroxyketones is outlined in Part B, Chapter 2. However, it was found that β-aryl β-hydroxy esters simply dehydrated under the reaction conditions. It is possible that the ester acts as a nucleophile and aids in the removal of an α-hydrogen leading to the α,β-unsaturated ester. In order to gain a better understading of the fragmentation reaction, β-aryl-β-hydroxy aldehyes and acids could be investigated.

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APPENDIX

Materials

Gases

Argon (prepurified), National Welders and MG Industries.

Nitrogen (prepurified), National Welders and MG Industries.

Solvents

Acetic acid, Fisher Chemical Company.

Acetonitrile, Aldrich Chemical Company.

Benzene, Fisher Chemical Company.

Carbon Tetrachloride, Aldrich Chemical Company.

Chloroform-d, Aldrich Chemical Company.

Chloroform-d w/ 1% TMS, Aldrich Chemical Company.

Chloroform-d w/ 0.05% TMS, Isotec, Inc., Matheson Company.

Diethyl ether, Fisher Chemical Company.

Ethanol, Quantum Chemical Company.

Ethyl acetate, Fisher Chemical Company.

Hexanes, Fisher Chemical Company.

Methanol, Fisher Chemical Company.

Methylene Chloride, Fisher Chemical Company.

Pentane, Aldrich Chemical Company,

Tetrahydrofuran, Fisher Chemical Company.

Water (distilled), house supply.

Reagents

Acetone, Fisher Chemical Company.

Aluminum chloride, Fisher Chemical Company.

Ammonium chloride, Fisher Chemical Company.

9-BBN, Aldrich Chemical Company.

Benzaldehyde, Aldrich Chemical Company.

Benzophenone, Aldrich Chemical Company.

Benzyltriphenylphosphonium chloride, Aldrich Chemical Company.

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

Boron tribromide, Aldrich Chemical Company.

Boron trifluoride, MG Industries.

Boron trifluoride acetic acid complex, Aldrich Chemical Company.

Boron trifluoride dihydrate, Aldrich Chemical Company.

Boron trifluoride etherate, Aldrich Chemical Company.

2-Bromobenzaldehyde, Aldrich Chemical Company.

3-Bromobenzaldehyde, Aldrich Chemical Company.

4-Bromobenzaldehyde, Aldrich Chemical Company.

2-Bromo-α,α,α-trifluorotoluene, Aldrich Chemical Company.

2-Butanone, Aldrich Chemical Company.

4-Carboxybenzaldehyde, Aldrich Chemical Company.

Catecholborane, Aldrich Chemical Company.

2-Chlorobenzaldehyde, Aldrich Chemical Company.

3-Chlorobenzaldehyde, Aldrich Chemical Company.

4-Chlorobenzaldehyde, Eastman Chemical Company.

4-Chloro-4'-fluorobutyriphenone, Aldrich Chemical Company.

trans-Cinnamaldehyde, Aldrich Chemical Company.

Cyclohexanone, Fisher Chemical Company.

Cyclohexene, Aldrich Chemical Company.

Cyclooctanone, Fisher Chemical Company.

Cyclopentanone, Aldrich Chemical Company.

Dibromoborane-DMS (1.0 M in CH_2Cl_2), Aldrich Chemical Company.

Dichloroborane-DMS, Aldrich Chemical Company.

1,3-Dicyclohexylcarbodiimide, Aldrich Chemical Company.

Dimethylamine hydrochloride, Aldrich Chemical Company.

2,4-Dimethyl-3-pentanone, Aldrich Chemical Company.

1,3-Diphenyl-2-propanone, Aldrich Chemical Company.

Ethylbromo acetate, Aldrich Chemical Company.

2-Furaldehyde, Acros Chemical Company.

Heptanal, Aldrich Chemical Company.

2-Heptanone, Aldrich Chemical Company.

Hexanoic acid, Aldrich Chemical Company.

2-Hexanone, Aldrich Chemical Company.

1-Hexene, Aldrich Chemical Company.

Hexyllithium (2.0 M in hexane), Aldrich Chemical Company.

Hydrogen chloride (1.0 M in ether), Aldrich Chemical Company.

3-Hydroxybenzaldehyde, Eastman Chemical Company.

Iodine, Fisher Chemical Company.

Lead tetraacetate, Aldrich Chemical Company.

Lithium Aluminum Hydride (1.0 M in ether), Aldrich Chemical Company.

Magnesium, Fisher Chemical Company.

Magnesium Sulfate (anhydrous), Fisher Chemical Company.

3-Methoxybenzaldehyde, Aldrich Chemical Company.

3-Methyl-2-butanone, Aldrich Chemical Company.

Methylchloroformate, Aldrich Chemical Company.

2-Methyl-3-Hexanone, Aldrich Chemical Company.

Methyl iodide, Aldrich Chemical Company.

3-Methyl-2-pentanone, Aldrich Chemical Company.

2-Nitrobenzaldehyde, Aldrich Chemical Company.

3-Nitrobenzaldehyde, Aldrich Chemical Company.

4-Nitrobenzaldehyde, Aldrich Chemical Company.

5-Nonanone, Aldrich Chemical Company.

Paraformaldehyde, Aldrich Chemical Company.

Pentane, Aldrich Chemical Company.

3-Pentanone, Aldrich Chemical Company.

Perfluorooctanoic acid, 3M Chemical Company.

2-Phenylbutyrophenone, Aldrich Chemical Company.

Phenylhydrazine, Fisher Chemical Company.

Pivalaldehyde (2,2-dimethylpropanal or trimethylacetaldehyde), Aldrich Chemical Company.

Potassium hydroxide, Fisher Chemical Company.

Propionic acid, Aldrich Chemical Company.

Propiophenone, Aldrich Chemical Company.

Pyrrole-2-carboxaldehyde, Aldrich Chemical Company.

Silica gel, 230-400 mesh, Baxter Scientific Company.

Sodium bicarbonate, Mallinckrodt Company.

Sodium chloride, Kroger.

Sodium hydroxyde, Mallinckrodt Company.

Sodium perborate tetrahydrate, Aldrich Chemical Company.

Stilbene, Aldrich Chemical Company.

Titanium chloride, Aldrich Chemical Company.

4-Tolualdehyde, Aldrich Chemical Company.

p-Toluenesulfonic acid monohydrate, Aldrich Chemical Company.

Tributylborane, Aldrich Chemical Company.

Triethylamine, Aldrich Chemical Company.

Triethylenediamine, Aldrich Chemical Company.

Trifluoroacetic acid, Aldrich Chemical Company.

Trifluoromethylsulfonic acid, Aldrich Chemical Company.

4-α,α,α-Trifluorotolualdehyde, Aldrich Chemical Company.

Trimethylacetyl chloride, Aldrich Chemical Company.

Valerophenone, Aldrich Chemical Company.

Zinc, Fisher Chemical Company.

Zinc chloride, Fisher Chemical Company.

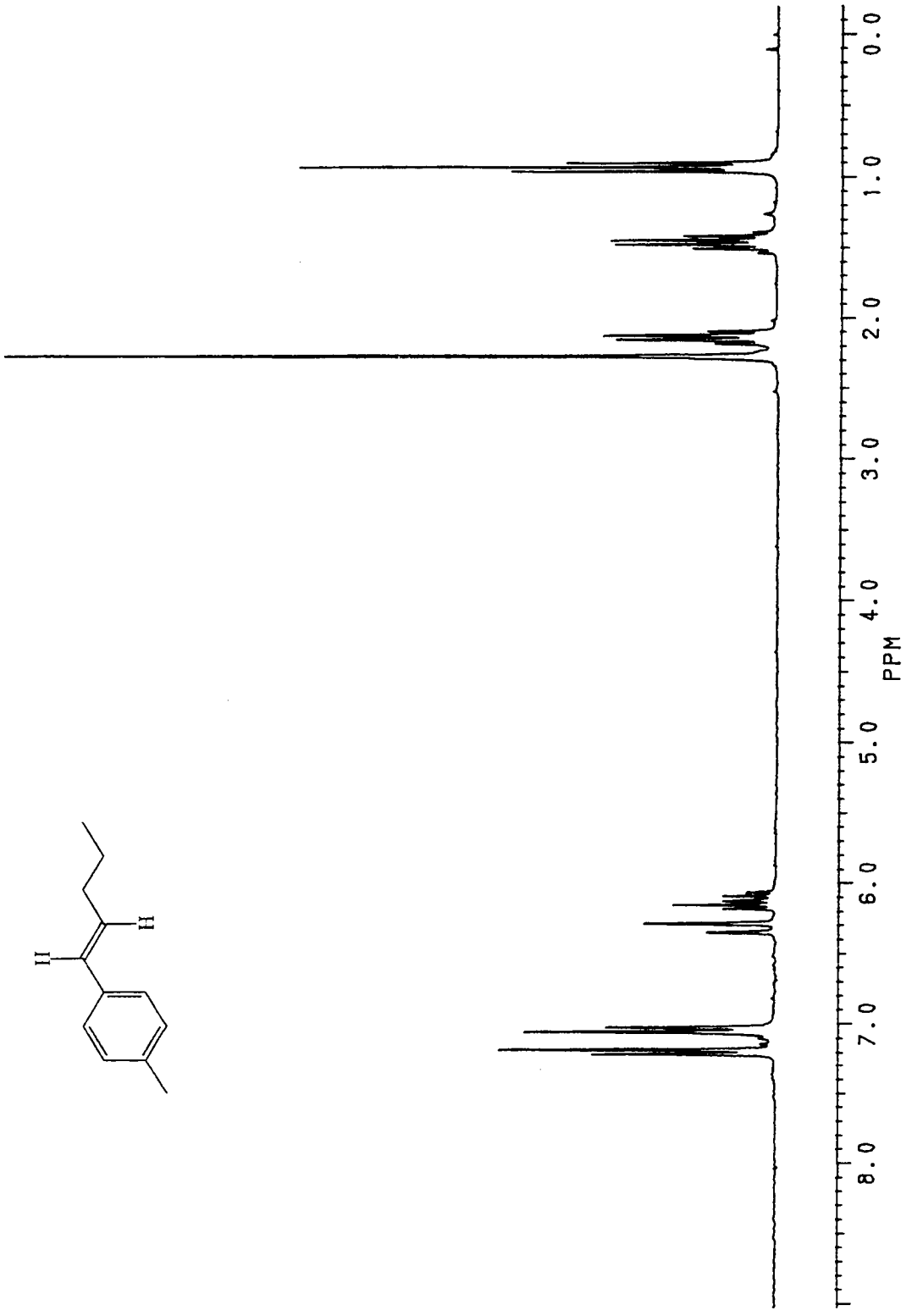

Figure A-1: ^{1}H-NMR Spectrum of (E)-1-(4-Tolyl)-1-pentene.

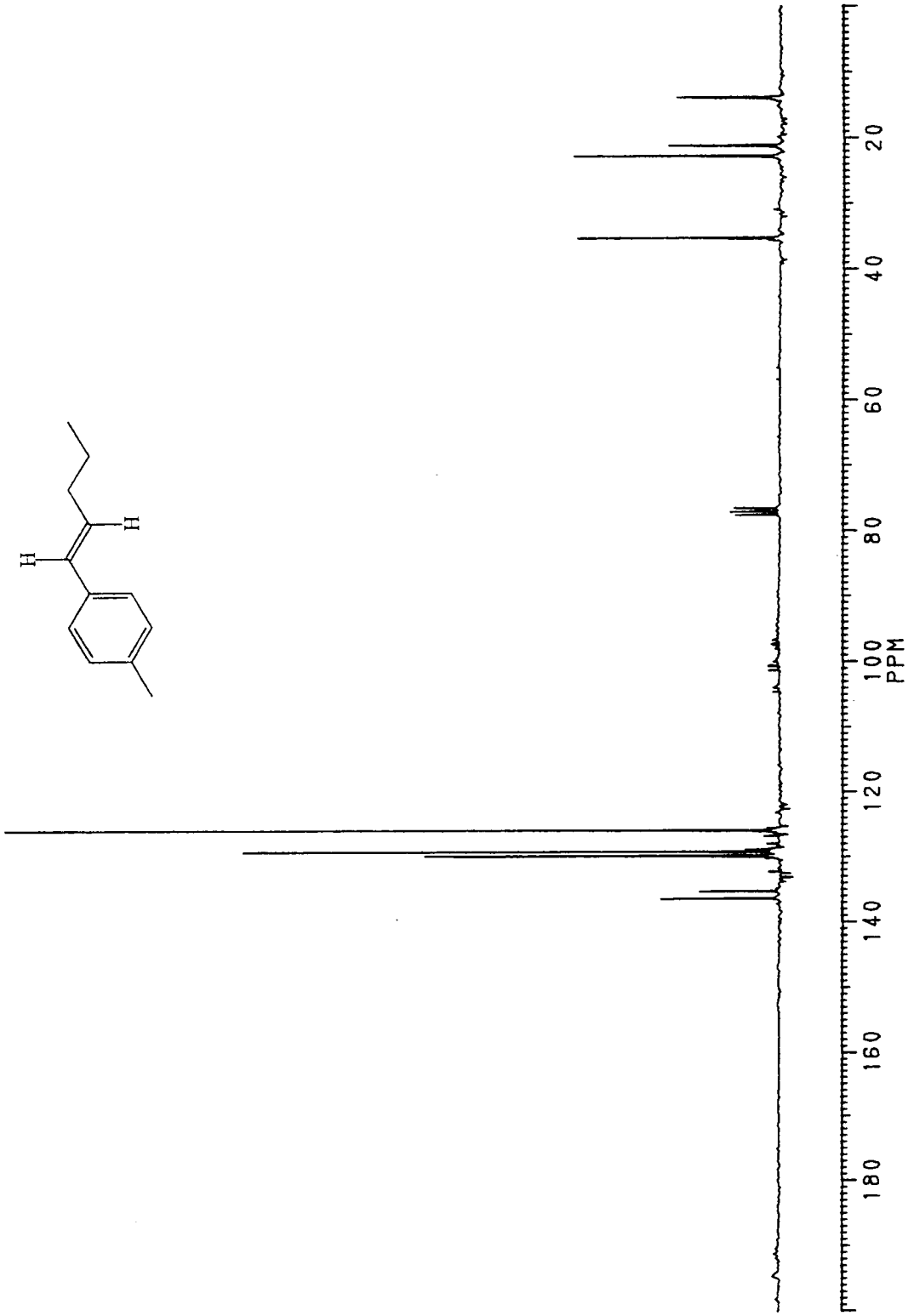

Figure A-2: ^{13}C-NMR Spectrum of (E)-1-(4-Tolyl)-1-pentene.

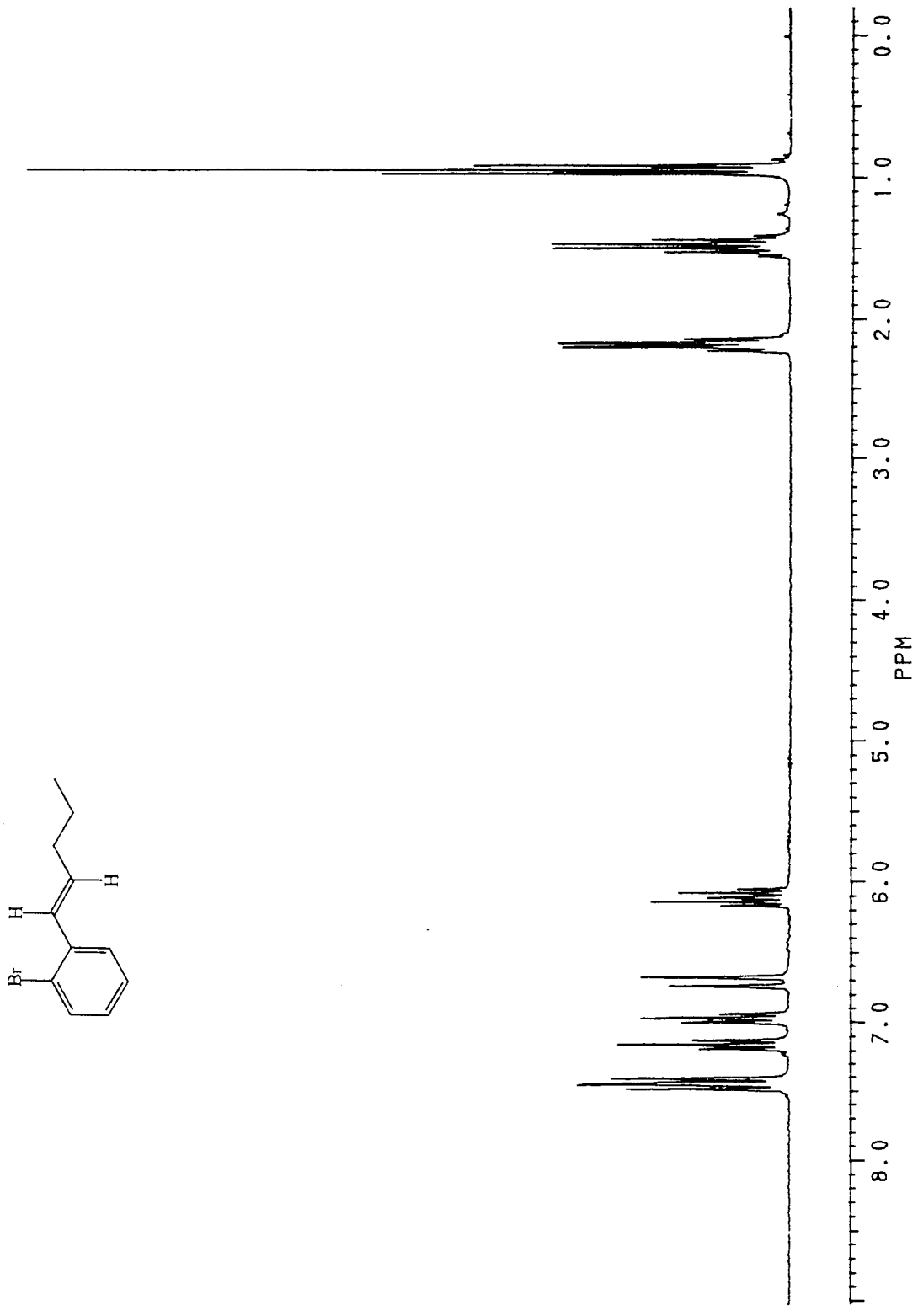

Figure A-3: ^{1}H-NMR Spectrum of (E)-1-(2-Bromophenyl)-1-pentene.

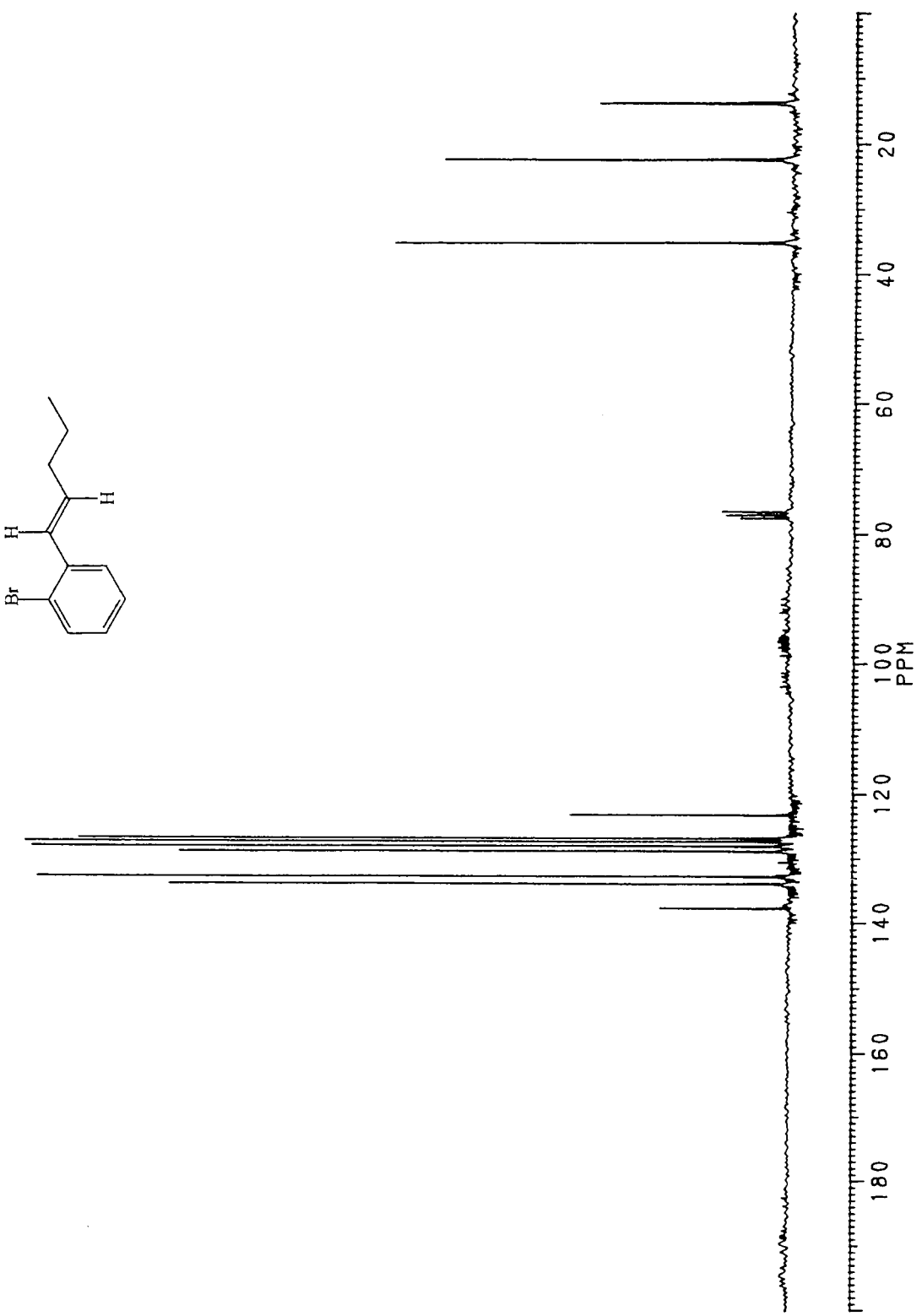

Figure A-4: ^{13}C-NMR Spectrum of (E)-1-(2-Bromophenyl)-1-pentene.

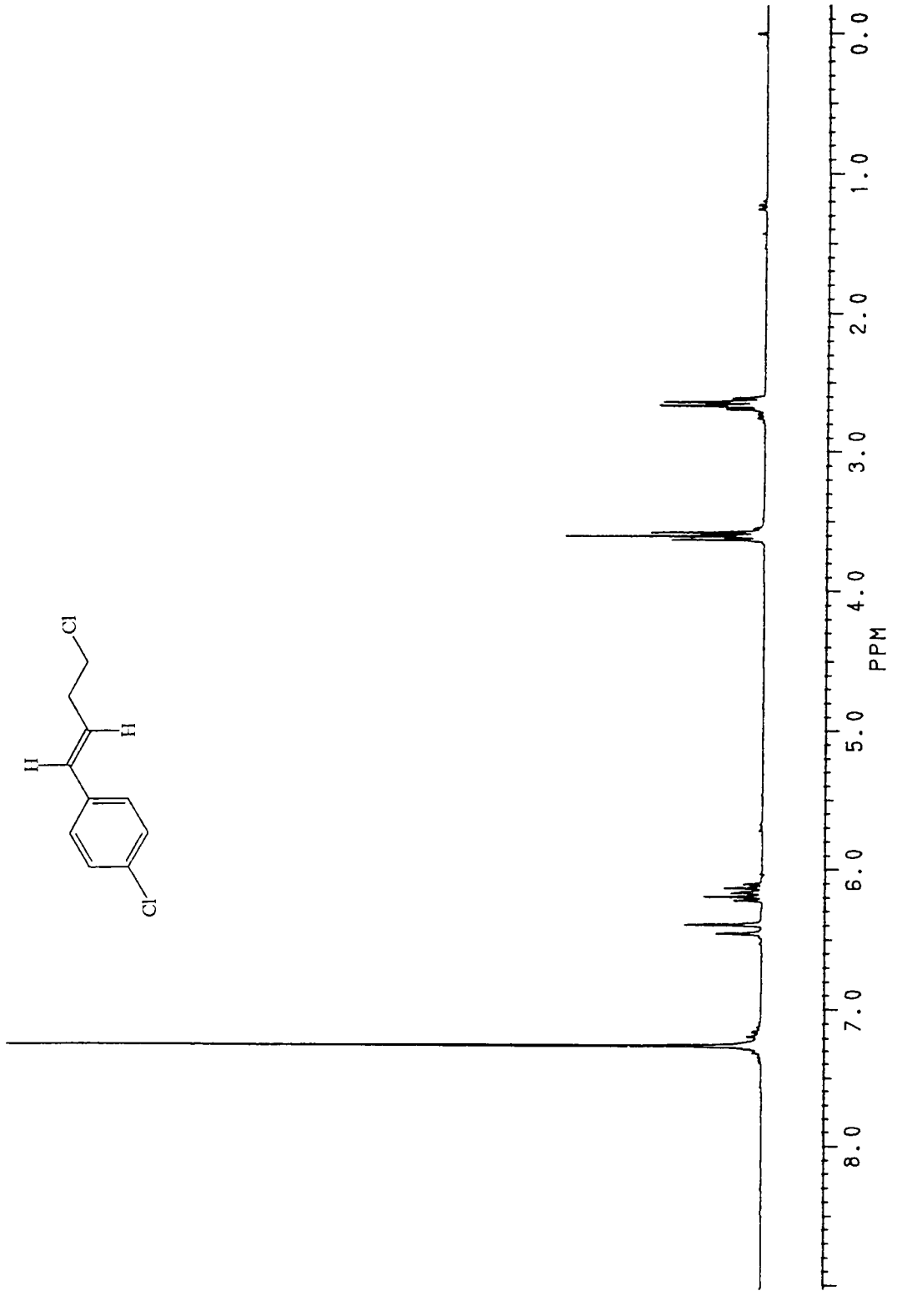

Figure A-5: ^{1}H-NMR Spectrum of (E)-4-Chloro-1-(4-chlorophenyl)-1-butene.

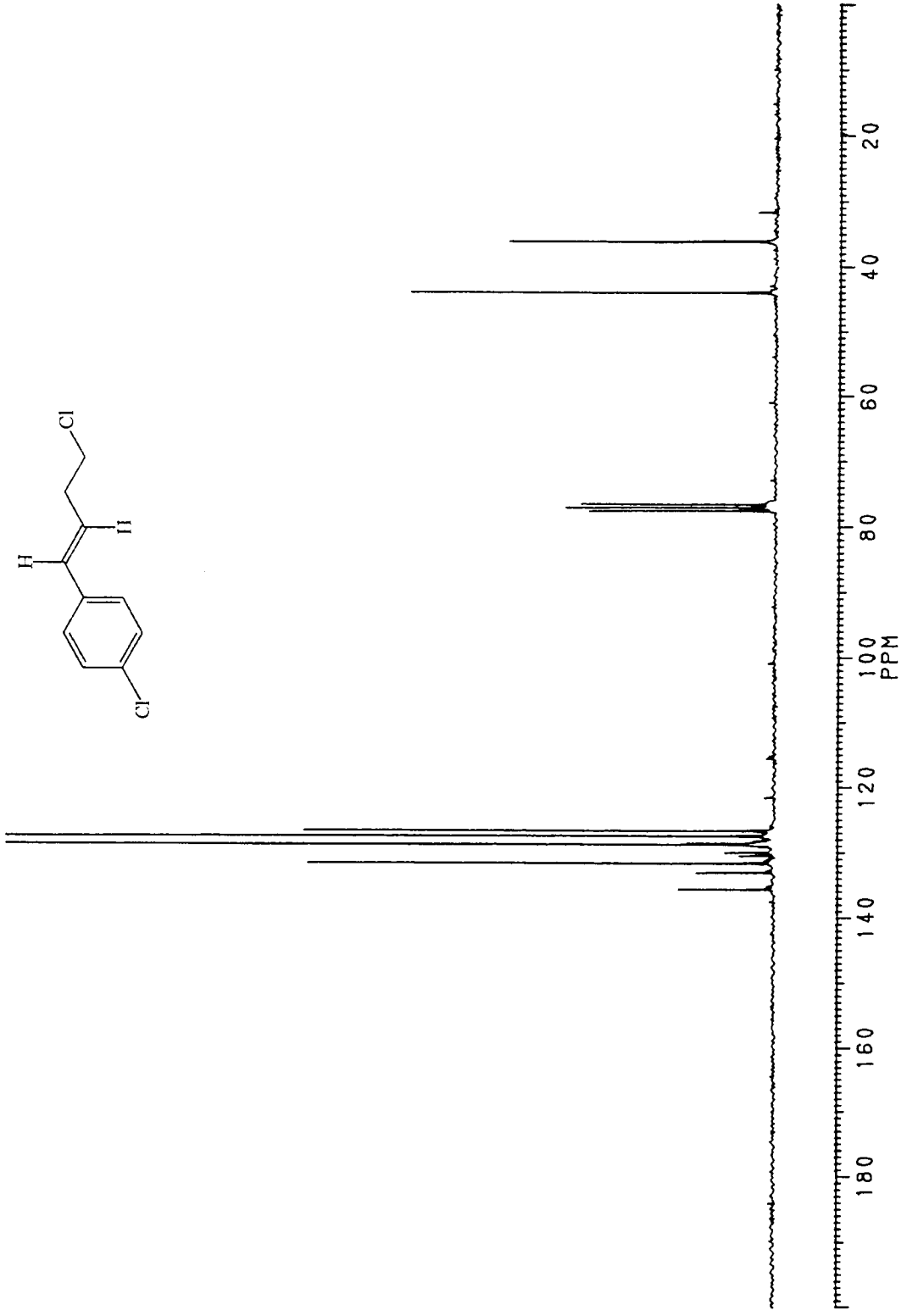

Figure A-6: ^{13}C-NMR Spectrum of (E)-4-Chloro-1-(4-chlorophenyl)-1-butene.

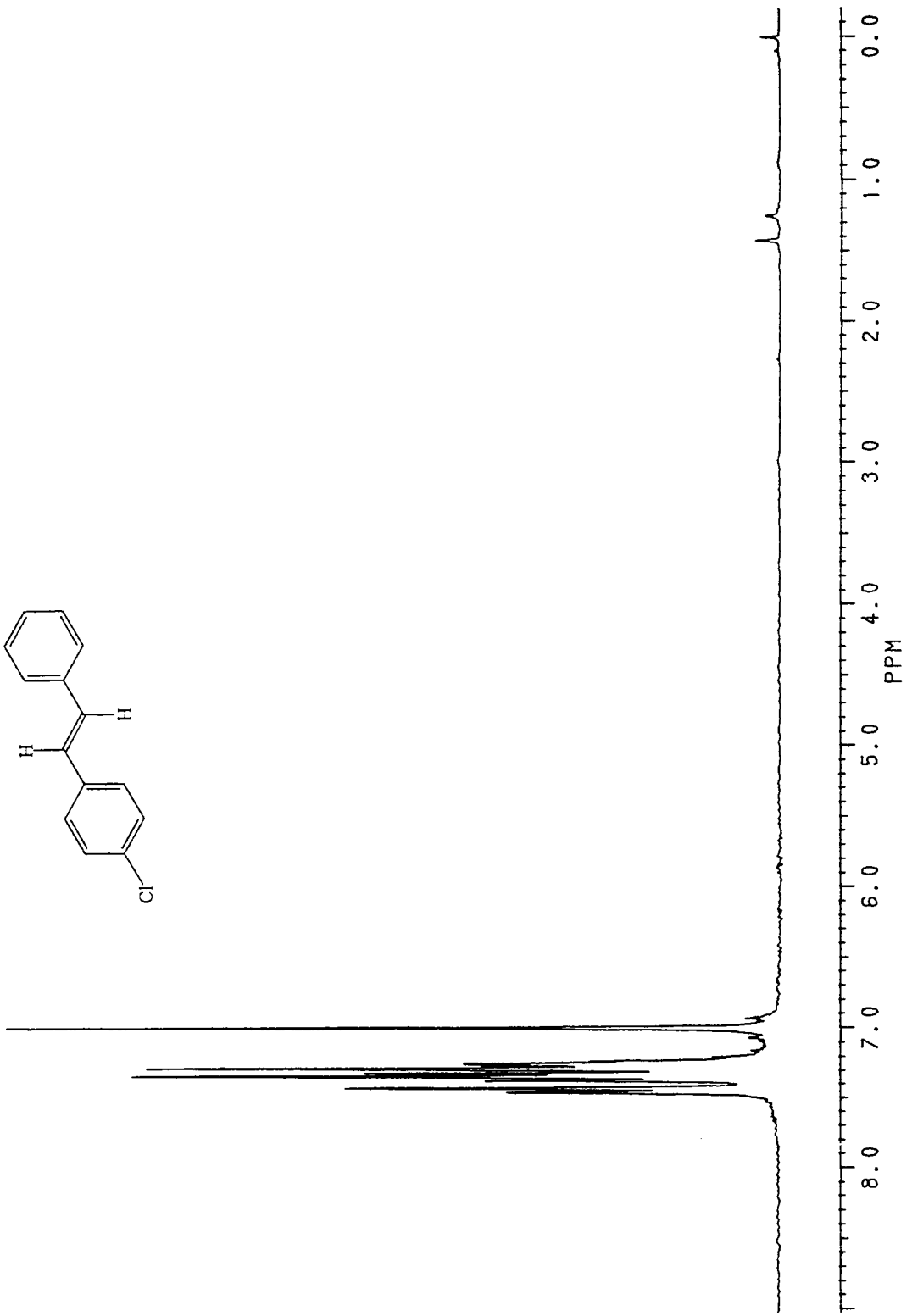

Figure A-7: ^{1}H-NMR Spectrum of (E)-4-Chlorostilbene.

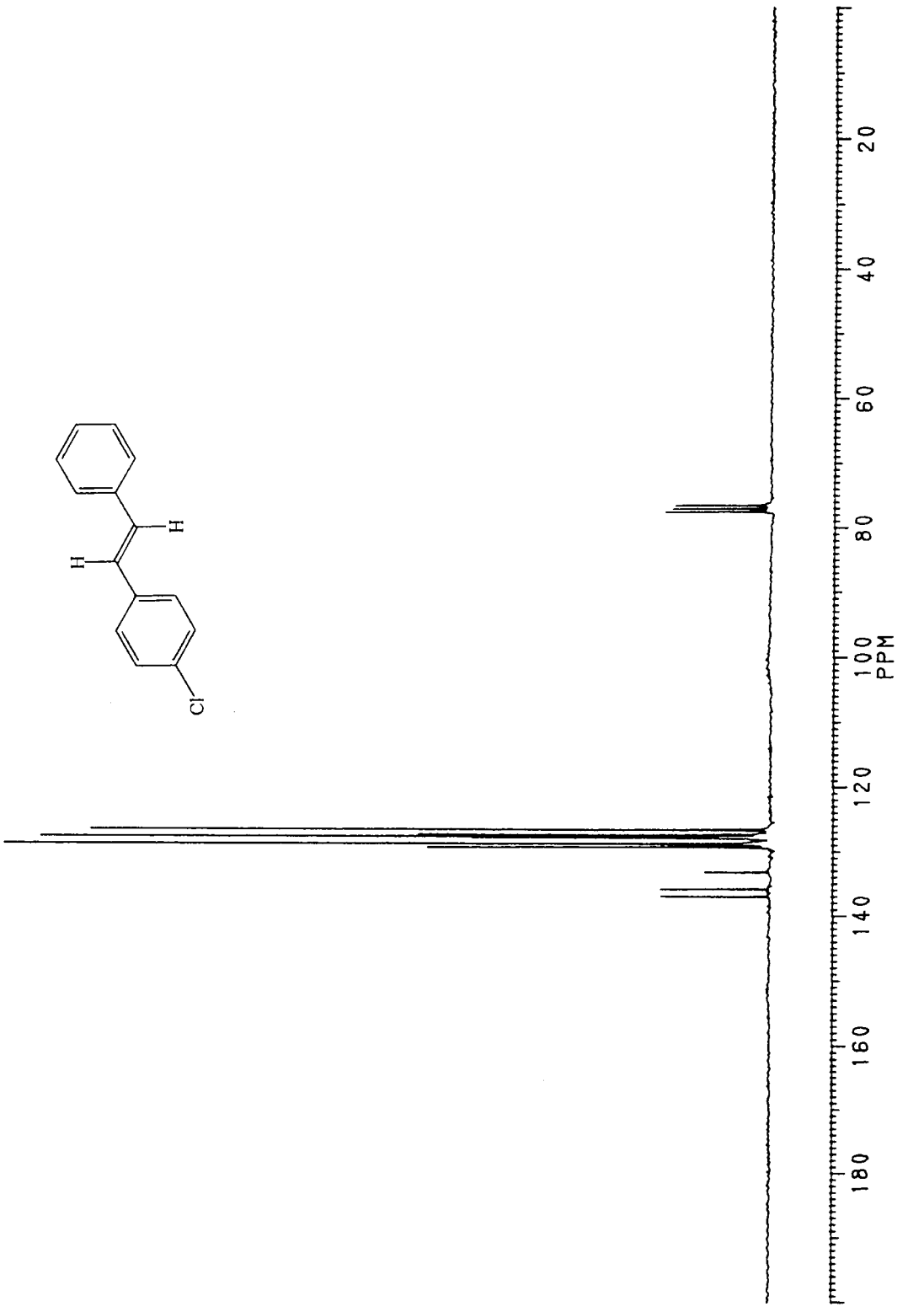

Figure A-8: ^{13}C-NMR Spectrum of (E)-4-Chlorostilbene.

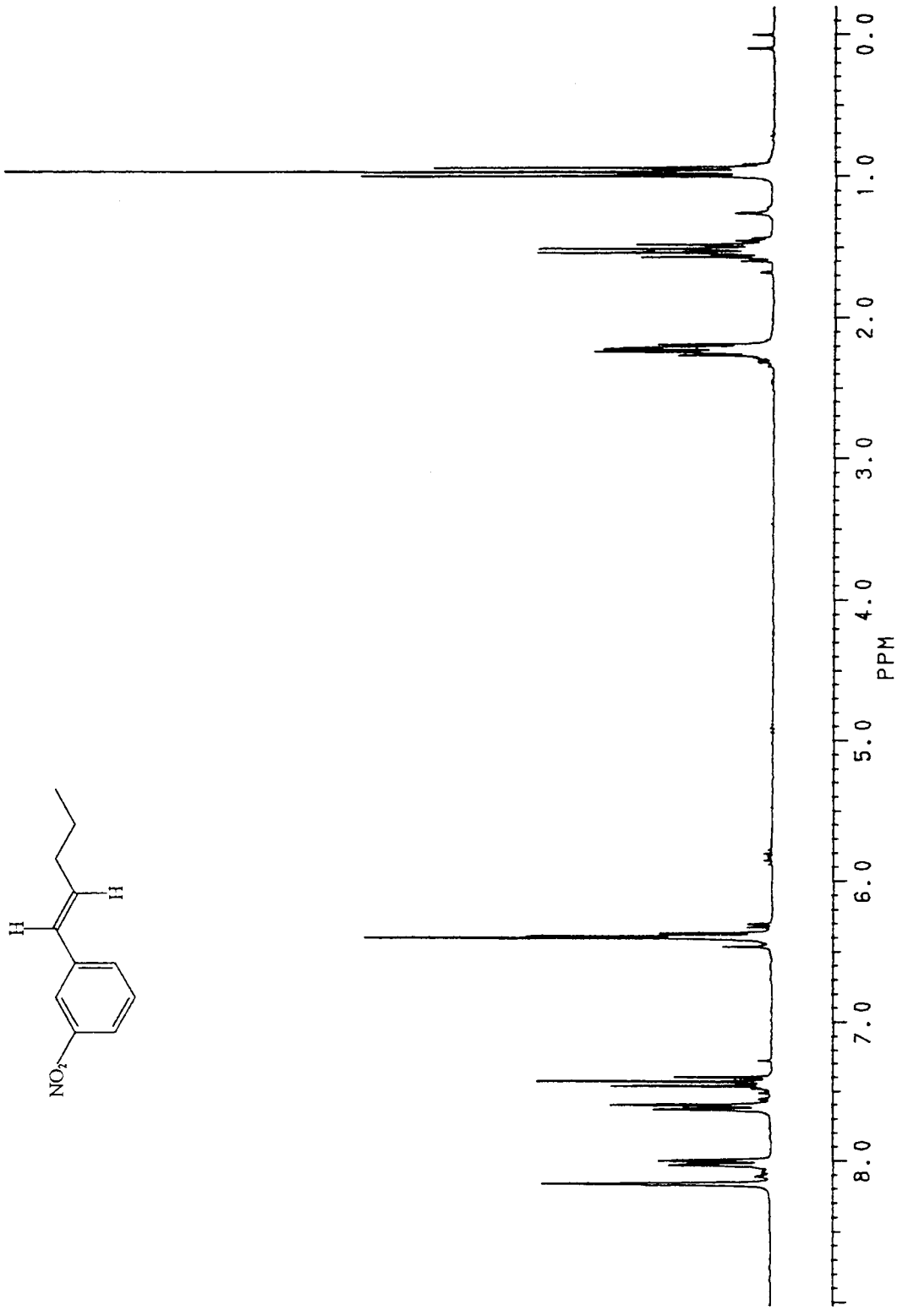

Figure A-9: ^{1}H-NMR Spectrum of (E)-1-(3-Nitrophenyl)-1-pentene.

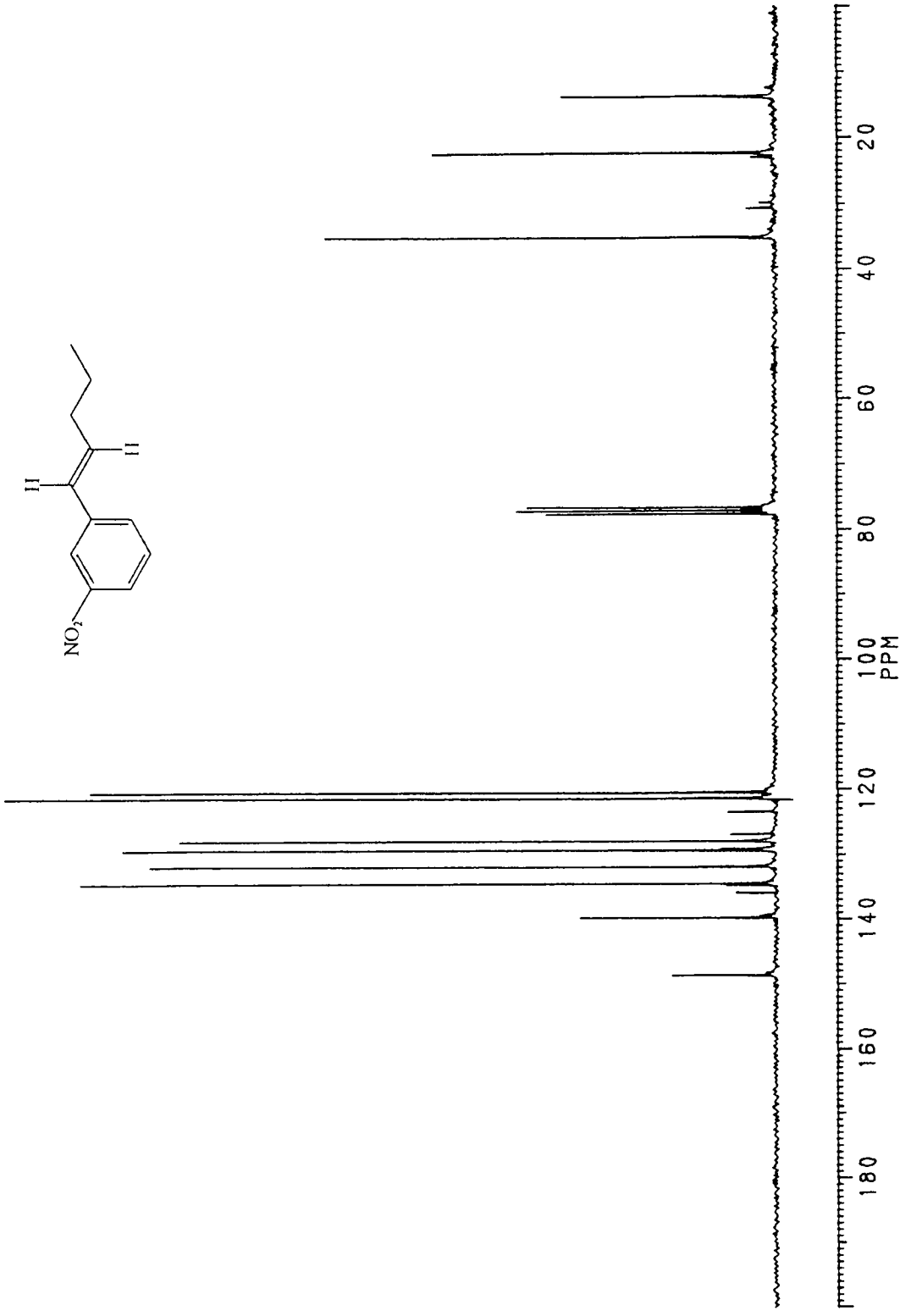

Figure A-10: ^{13}C-NMR Spectrum of (E)-1-(3-Nitrophenyl)-1-pentene.

VITA

David Tejedor was born in Madrid, Spain on November 3, 1970. He attended High School in Fuenlabrada, Spain and in Monroe, Washington where he graduated in June 1989. He entered North Idaho College on a cross country and track scholarship where he later received NJCAA All American Honors in academics and in track. He transferred to the University of Nevada-Reno in 1991 on another athletic scholarship, where he eventually graduated with a Bachelor of Science in Chemistry in December 1993. In August of 1994, he entered the University of Tennessee, Knoxville, joining the research group of Dr. George W. Kabalka. He intends to return to Tenerife, Spain where his family relocated and pursue a career in Chemistry.