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THE ADDITION OF IODINE TO VINYL BORONIC ACID INTERMEDIATES IN THE PRESENCE OF ALUMINA

A Thesis

Presented for the

Master of Science

Degree

The University of Tennessee, Knoxville

William R. Sponholtz, III

December 1990

DEDICATION

To my parents, the best friends in the world...

ACKNOWLEDGEMENTS

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A special thanks go to God...because all things are possible through him.

ABSTRACT

There is no general methodology to convert (E)-1-alkenyl boronic acids into all the 1-halo-1-alkenes (F, Cl, and Br) with complete retention of configuration. Thus, it is the goal of this research to obtain a mild methodology whereby the boron moiety in (E)-1-alkenyl boronic acids is replaced by iodine with retention of configuration utilizing gamma alumina catalysis.

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Chapter I

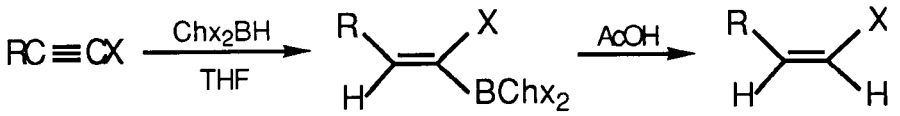
Introduction

In 1913 Hevesey proposed using radioactive isotopes as tracers for medicinal and biochemical use.[1] Recently radiohalogens, especially the iodine-123 isotope, have been used successfully as tracers in the medical community.[2] Due to the ideal decay characteristics of iodine-123 (half-life 13.3 hours) and its ready availability, interest in the development of new synthetic routes for the incorporation of iodine into organic compounds has risen considerably. It is the utility of isotopically labelled vinyl iodide tracers in particular that has caused chemists to look for mild and rapid methods to incorporate iodine into organic molecules. The following is a brief overview that examines the different techniques now being employed for the formation of vinyl iodides.

In the last decade the most convenient method for the highly stereoselective synthesis of (E)- and (Z)-1-halo-1-alkenes involves organoborane intermediates. The organoboranes are prepared in a highly regio- and stereoselective manner via a terminal alkyne. From the vinyl boranes the E and Z haloalkene isomers may be produced in high yields.

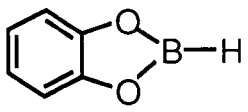
Zweifel and Arzoumanian in 1967 reported one of the first highly stereoselective syntheses of (Z)-1-halo-1-alkenes by hydroborating 1-halo-alkynes with dicyclohexylborane followed by protonolysis with acetic acid (eq. 1).[3]

(1)



Since 1967, several different hydroborating reagents have appeared.[4] These hydroborating reagents add only once to the alkyne, and in a highly regio- and stereoselective fashion. A classic example of one of the new hydroborating reagents is 1,3,2-benzodioxaborole **1** (catecholborane).[5] The results reported in Table

1



I clearly show the versatility of the directive effects of the monohydroboration of 1-alkynes with catecholborane at 70^0 C .[5]

The (E)- or (Z)-1-halo-1-alkenes can be produced via the catechol ester **2** or from the boronic acid **3** (eq. 2).[6]

(2)

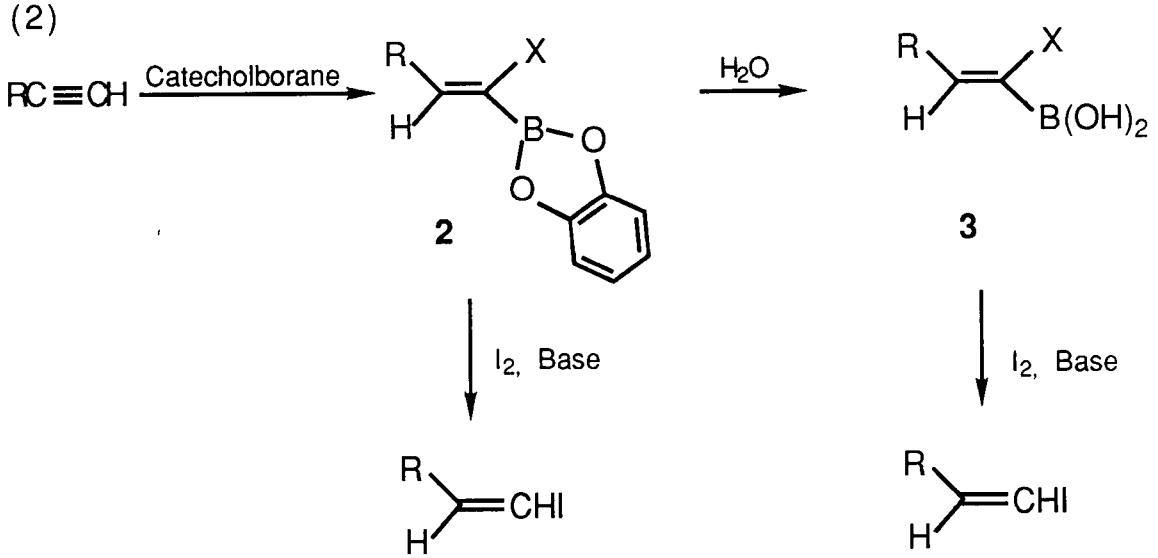


TABLE 1

The Directive Effects in the Monohydroboration of 1-Alkynes with Catecholborane at 70^0 C.

Alkyne	Total yield[a]	% Composition[b] α Product[c]	β Product[c]
1-Pentyne	92	93 (93)[d]	7 (7)[d]
1-Hexyne	90	93 (94)[d]	7 (6)[d]
1-Cyclohexylethyne	93	98	2
1-Phenylethyne	85[e]	91	9
3,3-Dimethyl-1-butyne	94	101	0
3-Chloropropyne	85	81 (83)[d]	19 (17)[d]
3-Bromopropyne	88	87	13

[a]By GLC analysis.

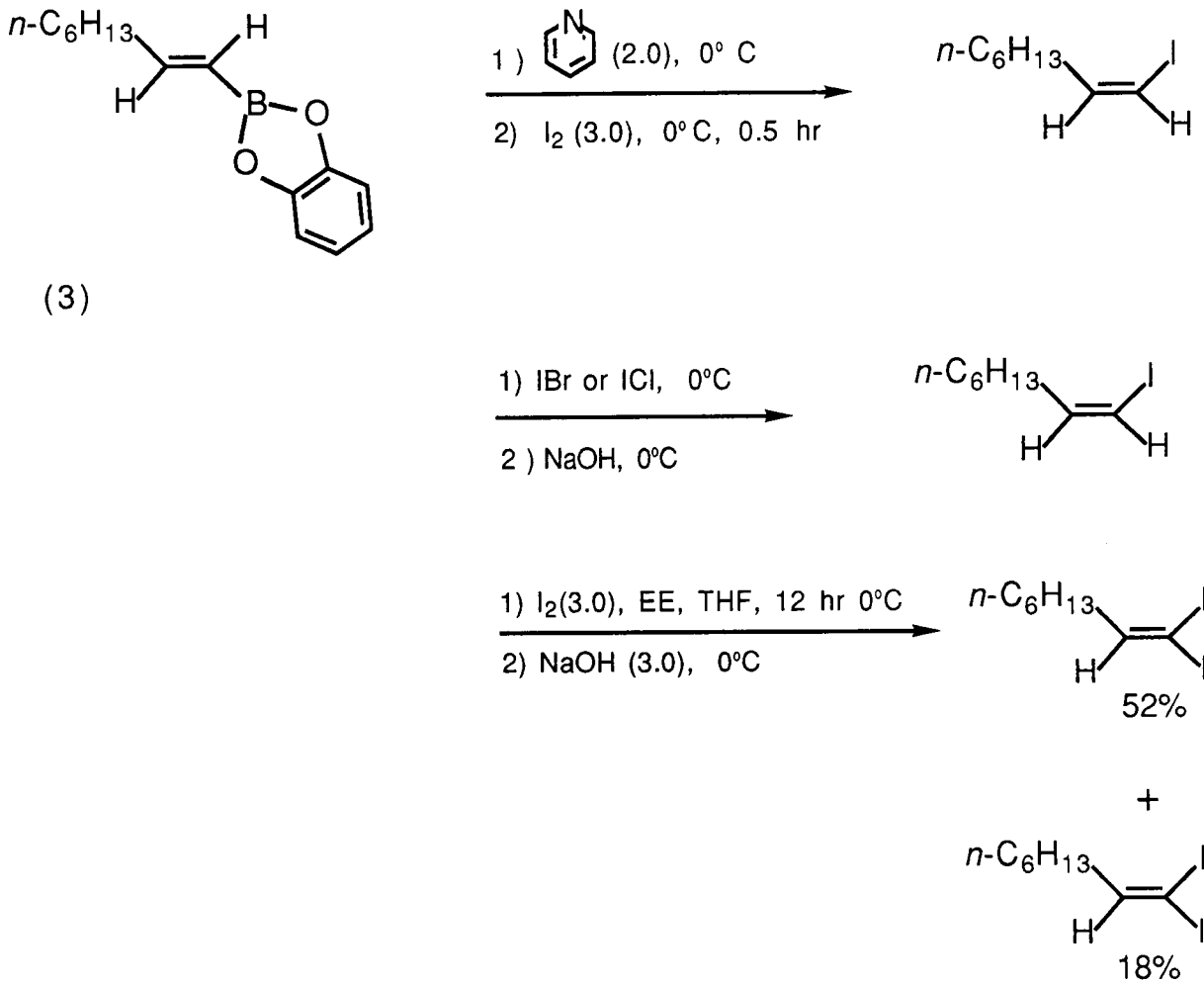
[b]Of the distilled product.

[c]Position of the attachment of boron in R-Cβ=CαH.

[d]Estimated by NMR (by GLC).

[e]By isolation of the product.

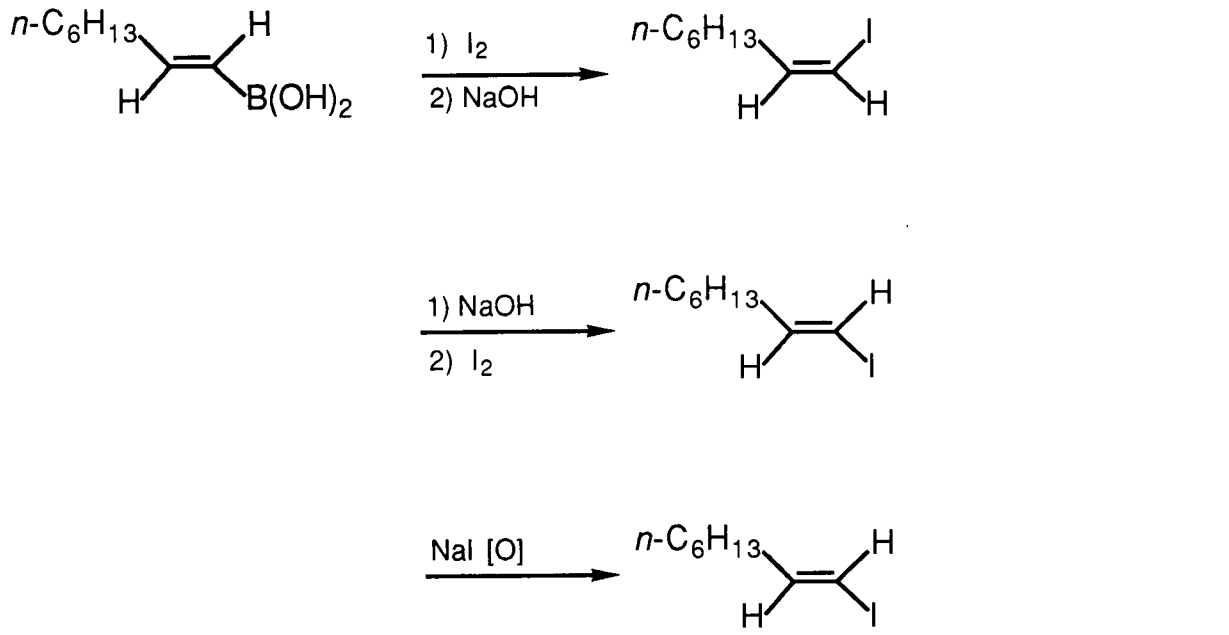
The catechol ester adduct can yield the Z isomer or a mixture of the E and Z isomers, as the following reactions indicate (eq. 3).[6]



(3)

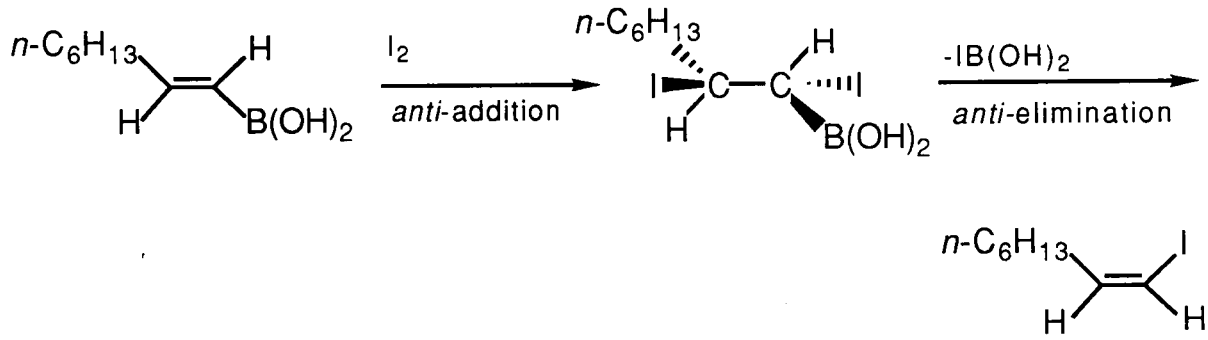
The most versatile and reliable organoborane is the boronic acid intermediate. The boronic acid has a long shelf life and is stable to air for long periods of time (providing there is moisture in the air to avoid forming the anhydride). Furthermore, treatment of the boronic acid under different reaction conditions will yield either E or Z vinyl halides as equation 4 demonstrates.

(4)



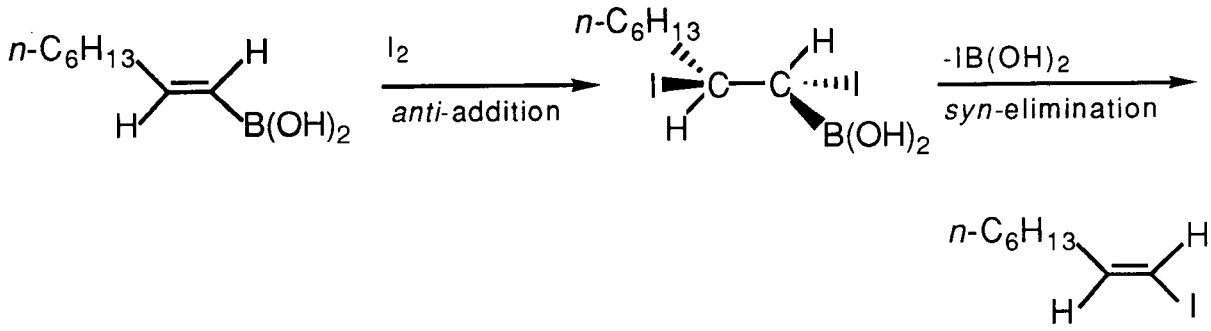
Mechanisms for these reactions are poorly understood. One can, however, rationalize formation of the Z isomer by the *anti*-addition of iodine followed by the *anti*-deboronoiodination (eq. 5).

(5)



Likewise, the E isomer may arise by the *anti*-addition of iodine followed by *syn*-deboronoiodination (eq. 6).[8]

(6)



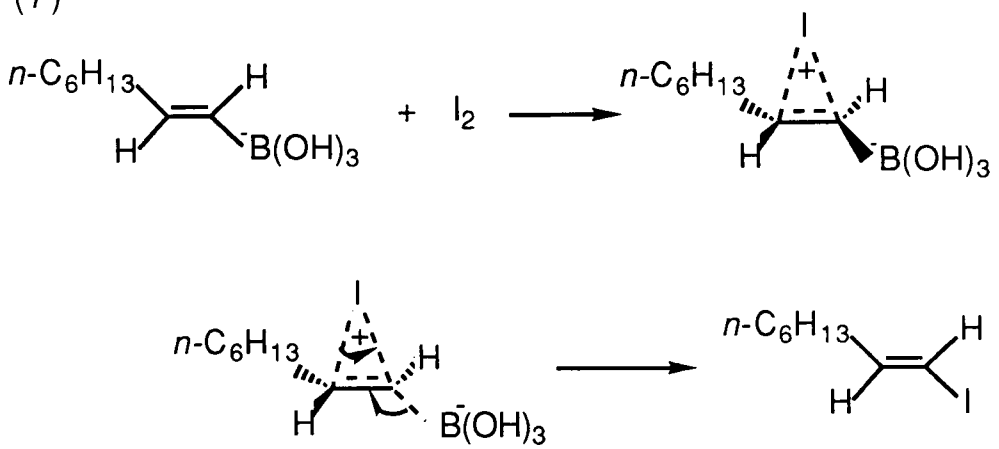
However, when the reaction is run in the presence of a mild base and at low temperatures, this *syn*-elimination is unlikely. Moreover, the time involved (30 minutes) is insufficient for any significant addition of iodine, and several experiments performed by Brown and coworkers further help to negate this addition-elimination mechanism.[9] First, 1.2 mmol of iodine was added to a stirred mixture of 3.0 mmol of (E)-1-octenylboronic acid in ether and 9.0 mmol of sodium hydroxide. This resulted in the disappearance of the iodine color instantaneously. In addition, analysis of the ethereal layer revealed that (E)-1-iodo-1-octene had formed (.44, 1.02, and 1.21 mmol in 1, 5, and 15 minutes, respectively). A similar reaction was performed to examine the addition of iodine across the double bond. First, 3.0 mmol of boronic acid was treated with 1.2 mmol of iodine in the absence of base. After 10 minutes, the excess iodine was destroyed with sodium thiosulfate and then base was added. A yield of less than 2% of the vinyl iodide product was recovered (eliminating the quick addition of iodine across the double bond).[9]

An analogous mechanism which has been postulated for the iodination of vinyl silanes to yield (E)-1-iodo-1-alkenes could also be

imagined for boronic acids.[10] This would involve the direct displacement of the neutralized (tetravalent) boronic acid moiety with iodine. But under similar reaction conditions phenylboronic acid and other alkyl boronic acids fail to yield the corresponding iodides. Thus, direct displacement of the boron moiety can also be ruled out.[11]

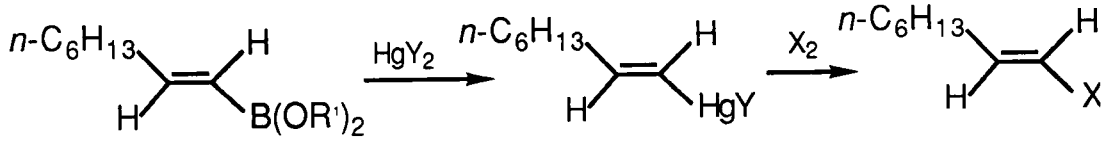
These facts suggest a mechanism that involves a fast reaction of the neutralized vinyl boronic acid with iodine to form an iodonium ion intermediate. This intermediate is then converted to the (E)-1-vinyl iodide rather slowly (eq. 7).[12]

(7)



In an attempt to show how versatile alkenylboronic acids are as intermediates in synthesis, Brown devised a synthesis which converts the organoboranes to organomercury compounds.[13] It is well-known that alkenylboronic acids react with mercury (II).[14] Thus, Brown hypothesized that transmetalation of (E)-1-alkenylboronic acids or esters with mercury (II) salts followed by halogenation would provide a general synthesis of vinylhalo compounds (eq. 8).

(8)



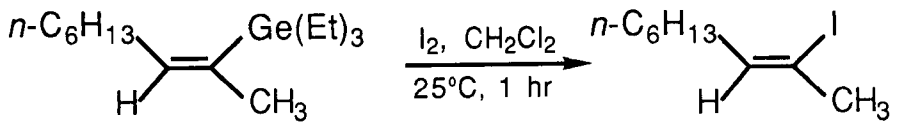
Y=$OCOCH_3$; X=Cl, Br, and I

It should be noted that there is no general methodology to convert (E)-1-alkenylboronic acids or esters into all the 1-halo-1-alkenes (F, Cl, I, and Br) with complete retention of configuration.[7] Unfortunately, the vinylmercurial intermediate yielded a different mixture of E and Z isomers as the halogen was varied. More specifically, the iodination of the vinylmercurials gave the same results as the direct iodination of the boronic acid. Thus, the iodination of mercury intermediates does not offer any significant advantage over the direct iodination of the boronic acid.[15]

Vinyl iodides have also been synthesized by many other reactions. For example, the reduction of 1-iodo-1-octyne with diimide yields (Z)-1-iodo-1-octene in greater than 99% purity (85% yield).[16] In contrast, (E)-1-iodo-1-octene can be synthesized in greater than 99% purity (75% yield) from a terminal alkyne by treatment with diisobutylaluminum hydride followed by the addition of iodine.[17]

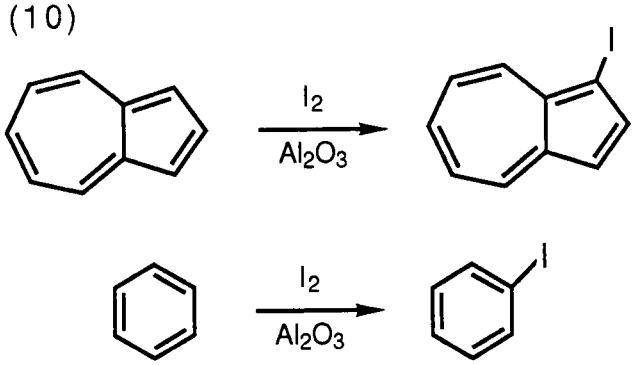
Many methods have also been reported which use organometallics as intermediates in the synthesis of vinyl halides. The vinyl germanes are excellent examples of metal intermediates that react with the electrophile iodine. The vinyl germanes proceed to haloalkenes with greater than 95% retention of configuration (eq. 9).[18]

(9)



Metal oxides, such as gamma alumina, with surface properties which are not duplicated in the solution phase, are the newest, most interesting environment in which to catalyze iodination reactions. Although alumina first appeared in the chemical literature in 1797[19], it has only been quite recently that advances leading to the understanding of alumina have been made. Most of the currently accepted ideas on alumina stem from the theories of Peri[20] and Knozinger and Ratnasamy[21]. Their theories suggest that a wide range of organic reactions may take place on the surface due to partially exposed oxide anions (which may function as bases or nucleophiles), partially exposed aluminum cations (which may function as Lewis acids), and hydroxyl groups of varying Bronsted acidity. A classic example of iodination using the dehydrated surface of gamma alumina (for dehydration procedure see the following reference) was demonstrated by Pagni, Kabalka, and Boothe.[22] They iodinated benzene, toluene, and azulene by allowing the substrate to adsorb onto the activated alumina along with iodine (eq. 10).

(10)



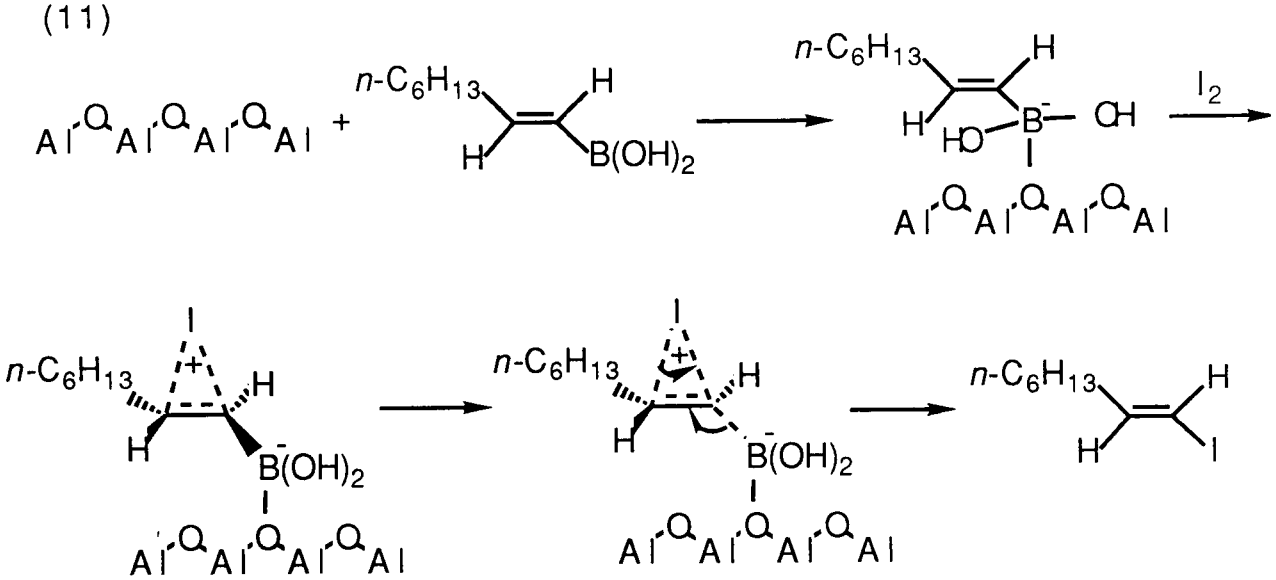
It is this type of pioneering work by Pagni and Kabalka demonstrating iodination of a diverse group of unsaturated substrates in the presence of gamma alumina, that has given rise to this research.[23] Thus, it is the goal of this research to obtain a mild methodology whereby the boron moiety in (E)-1-alkenylboronic acids is replaced by iodine with retention of configuration utilizing gamma alumina catalysis.

Chapter II

Results and Discussion

In solution, it is believed that the neutralized vinyl boronic acid is the precursor for the fast reaction with iodine to form an intermediate which is then slowly converted to the vinyl iodide. Therefore, it was hypothesized that the exposed oxide anions on the surface of alumina could react with the boronic acid to form the tetravalent neutralized vinyl boronic acid, thereby allowing iodine to react with the alkene (eq. 11). The following chapter describes the results of this hypothesis.

(11)



The iodination of vinyl boronic acids was performed using a procedure called the slurry method. This involved the following: .001 mol of the boronic acid was dissolved in 15 ml of ether and added to 10 grams of activity grade 1 Brockman neutral alumina.

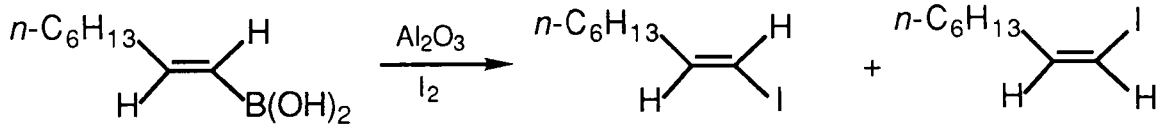
The ether was then removed under vacuum leaving behind the boronic acid-alumina complex. An equimolar amount of iodine in 10 ml ether was then added to the boronic acid-alumina complex. The reaction was allowed to run for several hours. Aliquots were periodically removed and analyzed by gas chromatography (GC). The yields of the iodinated products were determined by injecting a known amount of decane as the standard into the reaction mixture and analyzing the mixture by GC. The amount of standard used corresponded to a theoretical yield of 50% of the product.

Reactions of Boronic Acids with Iodine in the Presence of Alumina

A. (E)-1-Octenylboronic Acid

(E)-1-Octenylboronic acid was treated with iodine for two hoursusing the method described above for two hours, and a mixture of two iodinated products was observed by GC (eq. 12).

(12)



After the reaction proceeded for two hours a ^1H NMR spectrum was obtained (Fig. 1&2) on the reaction mixture. The vinylic protons for (E)-1-iodo-1-octene matched the peaks reported by Brown and coworkers (6.5 ppm d/t, 1H; 5.96 ppm d, J=15Hz, 1H).[24] The vinylic protons for (Z)-1-iodo-1-octene also matched the peaks reported by Andeeva and coworkers (6.07 ppm m, 2H).[25] Thus, a mixture of (E)- and (Z)-1-octenyl iodide in approximately a 1:1 ratio had been formed.

Both isomers were prepared independently by known procedures. The E isomer was made by Brown's method[26] and its

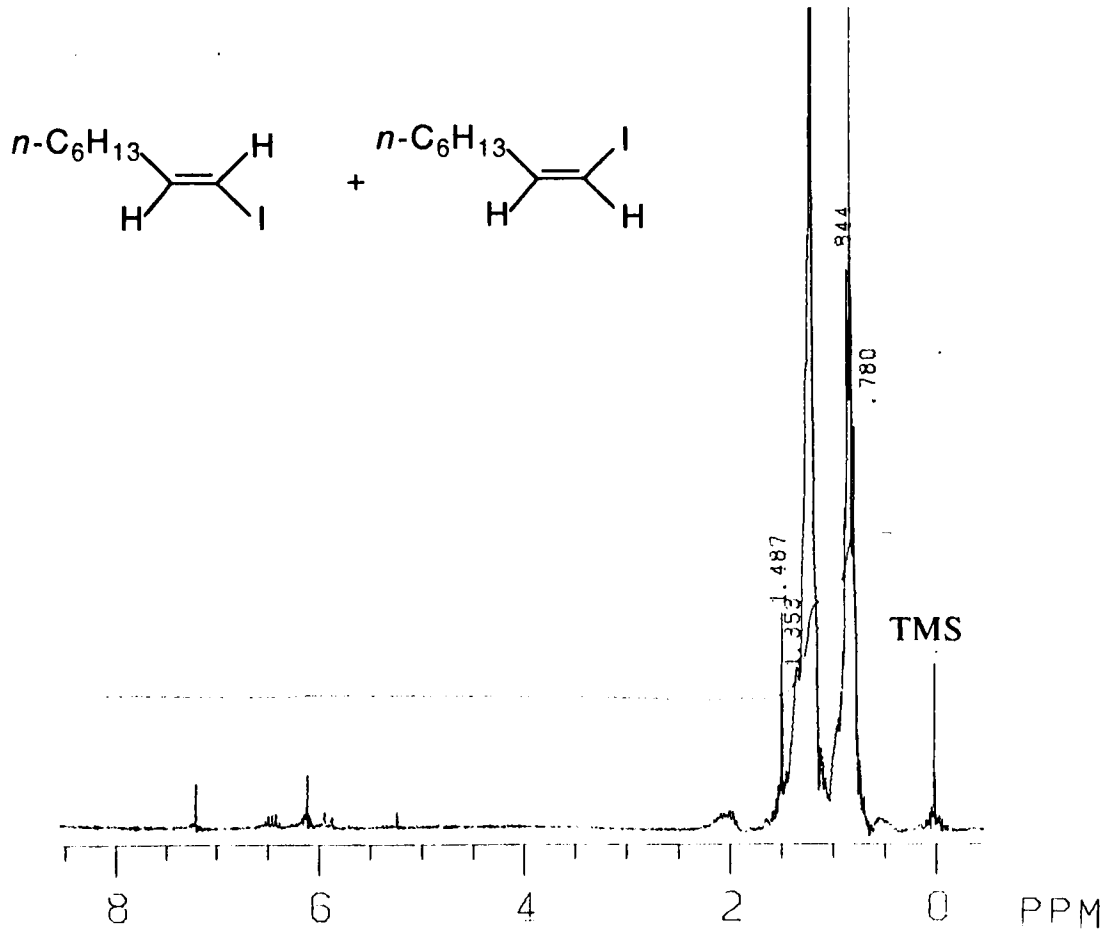


FIGURE 1. ^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of (E)- and (Z)-1-Iodo-1-octene Derived from Slurry Method.

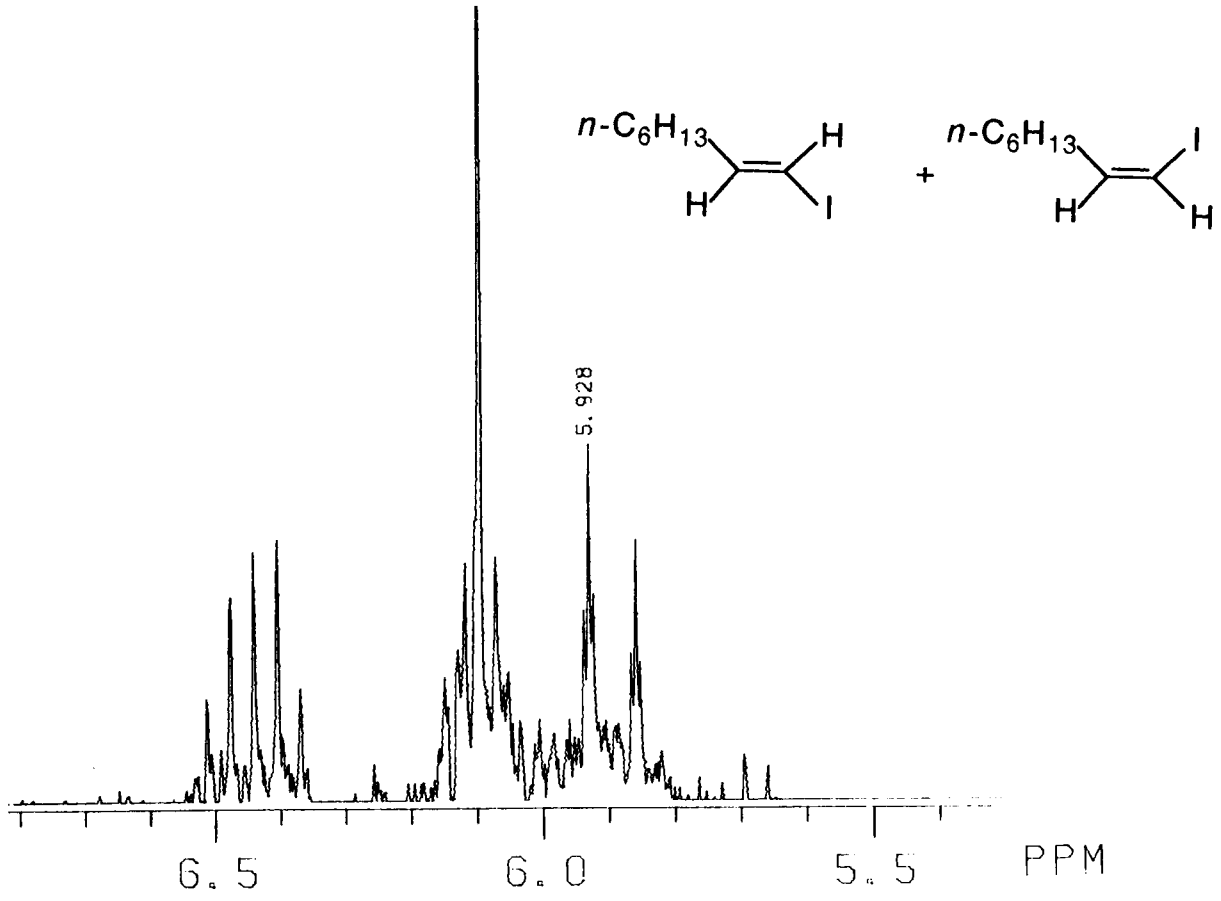


FIGURE 2. ^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of Vinylic Peaks of (E)- and (Z)-1-Iodo-1-octene Derived from Slurry Method.

^{1}H NMR spectrum was obtained (6.5 ppm d/t, 1H; 5.96 ppm d, J=15Hz, 1H; 2.1 ppm m, 2H; 1.4 ppm m, 8H; .8 ppm t, 3H) (Fig. 3). The Z isomer was also made by a Brown procedure[27] and its ^{1}H NMR spectrum was also obtained (6.07 ppm m, 2H; 2.1 ppm m, 2H; 1.4 ppm m, 8H; .8 ppm t, 3H) (Fig. 4). The isomers were then injected separately and the different retention times noted on the GC.

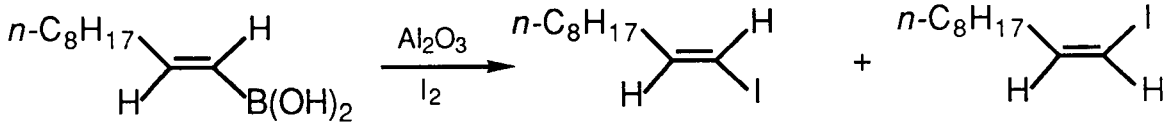
To substantiate further that the E and Z isomers were formed in the slurry method GC mass spectrometry (GC/MS) was then performed. The two peaks with 8.618 and 8.892 minutes retention times both had the same fragmentation patterns and molecular weight, proving them to be geometric isomers (Fig. 5&6).

A kinetics study monitoring the formation of the E and Z isomers was performed (using GC) to determine the E:Z ratio (Fig. 7) and % yield (Fig. 8) as a function of time. A maximum yield of 61% (24 hrs.) was reported for the 1:1 molar ratio of boronic acid and iodine on unactivated alumina.

B. (E)-1-Decenylboronic Acid

(E)-1-Decenylboronic acid reacted with iodine using the procedure described above, and a mixture of two iodinated products was obtained (eq. 13).

(13)



A ^{1}H NMR spectrum of the reaction mixture was obtained and the E and Z isomer vinylic peaks were clearly seen (Z isomer: 6.15 ppm m, 2H; E isomer: 6.48 ppm d/t, 1H; 5.95 ppm d, J=15Hz, 1H) (Fig. 9&10).

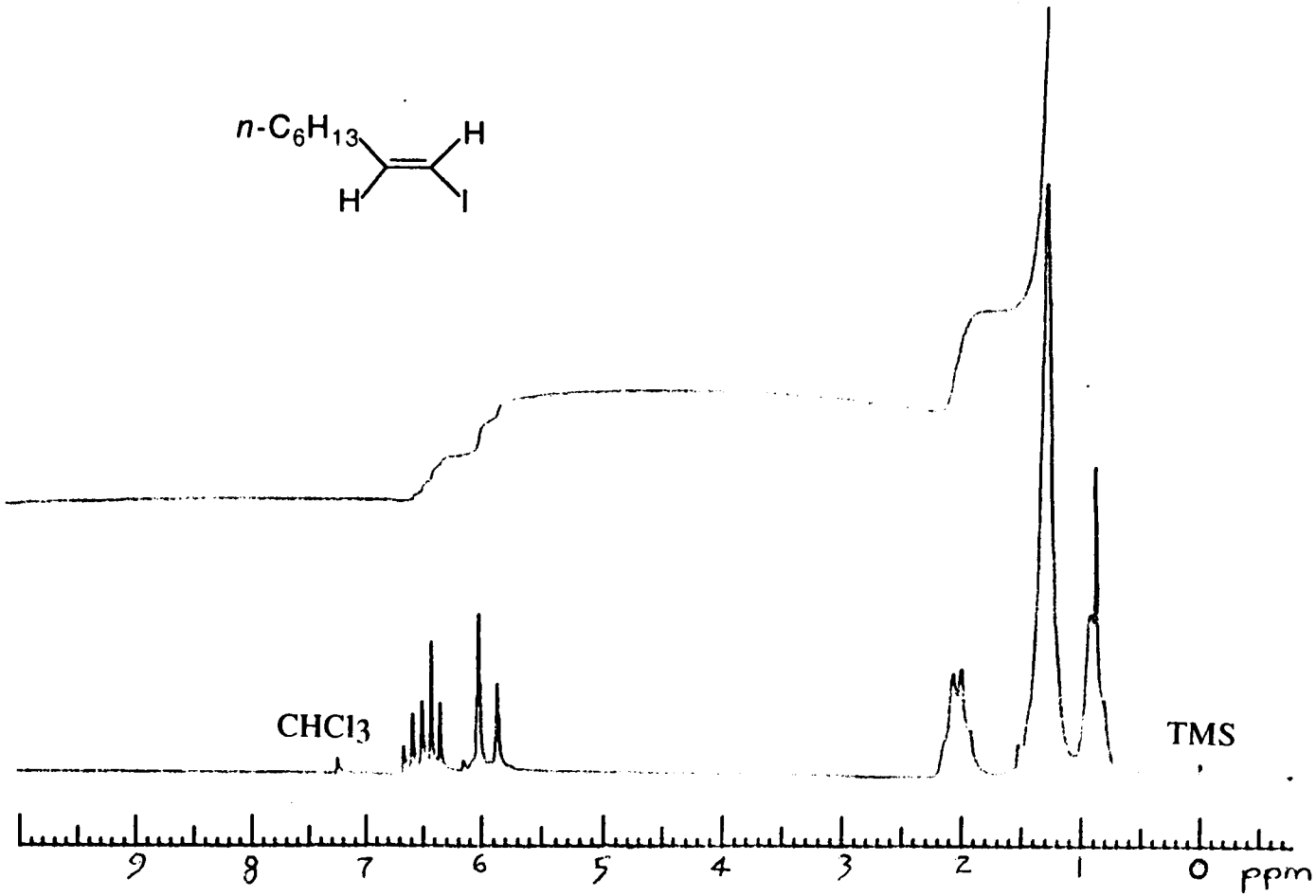


FIGURE 3. ^{1}H NMR (90 MHz, $CDCl_3$) Spectrum of (E)-1-Iodo-1-octene Derived from Brown's Method.

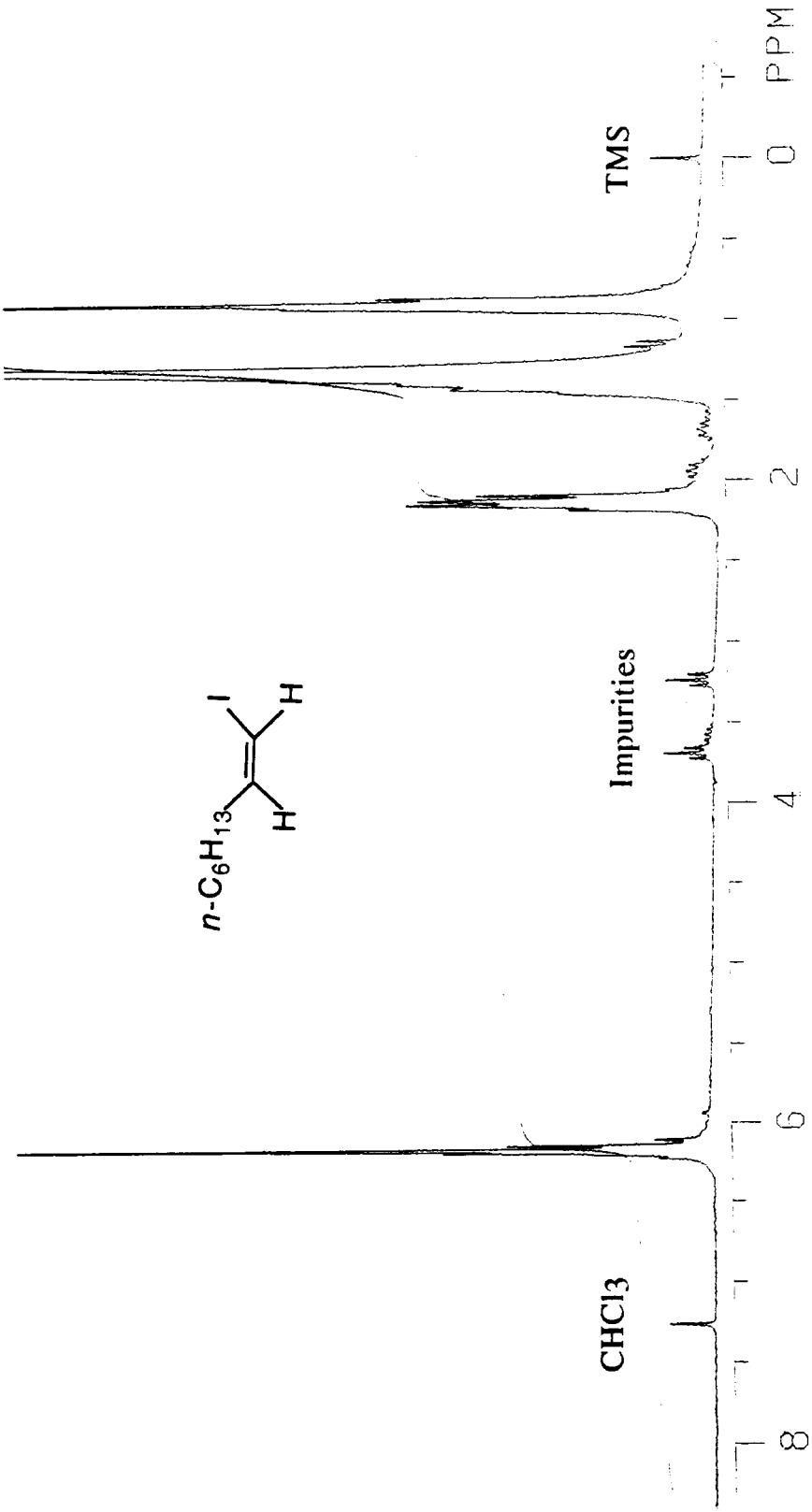


FIGURE 4. ^{1}H NMR (200 MHz, CDCl3) Spectrum of (Z)-1-Iodo-1-octene.

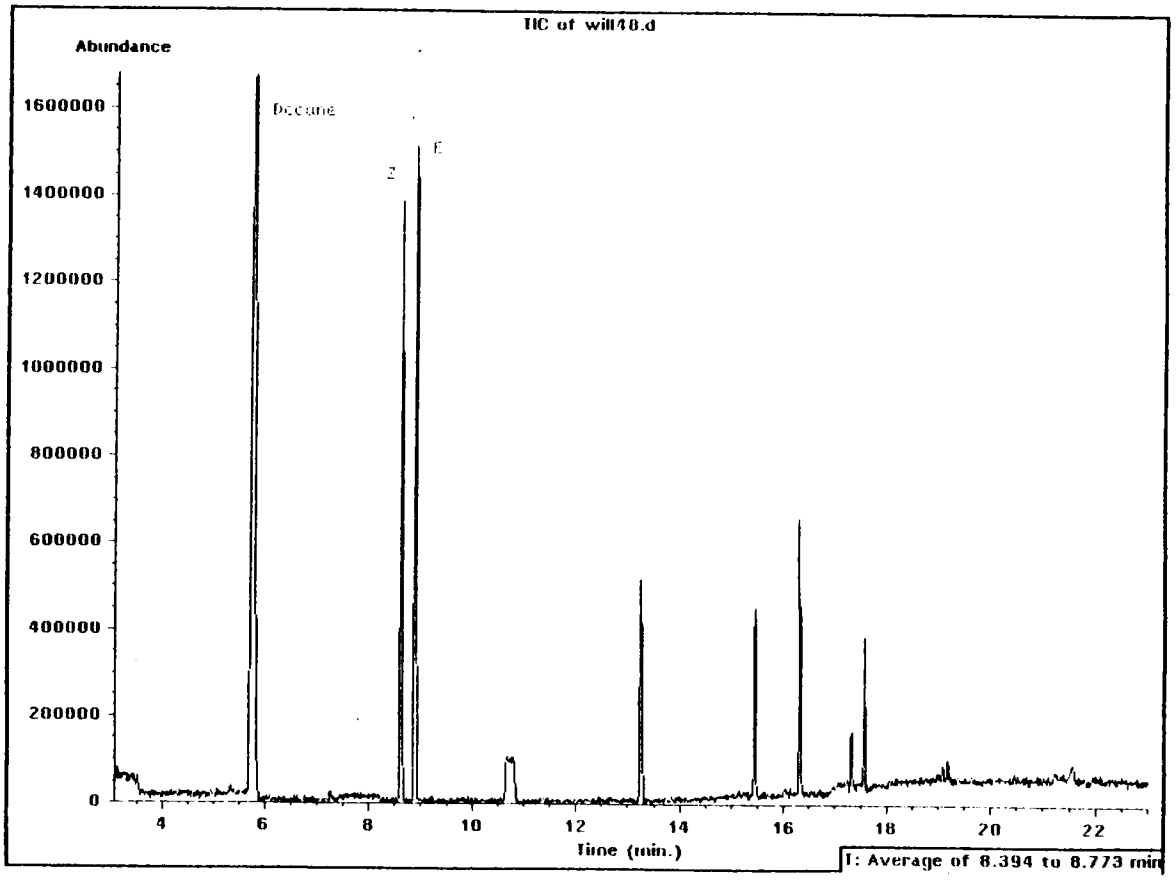


FIGURE 5. GC of (E)- and (Z)-1-Iodo-1-octene Derived from Slurry Method Indicating Retention Times of E and Z Isomer (8.892 and 8.618 minutes, respectively).

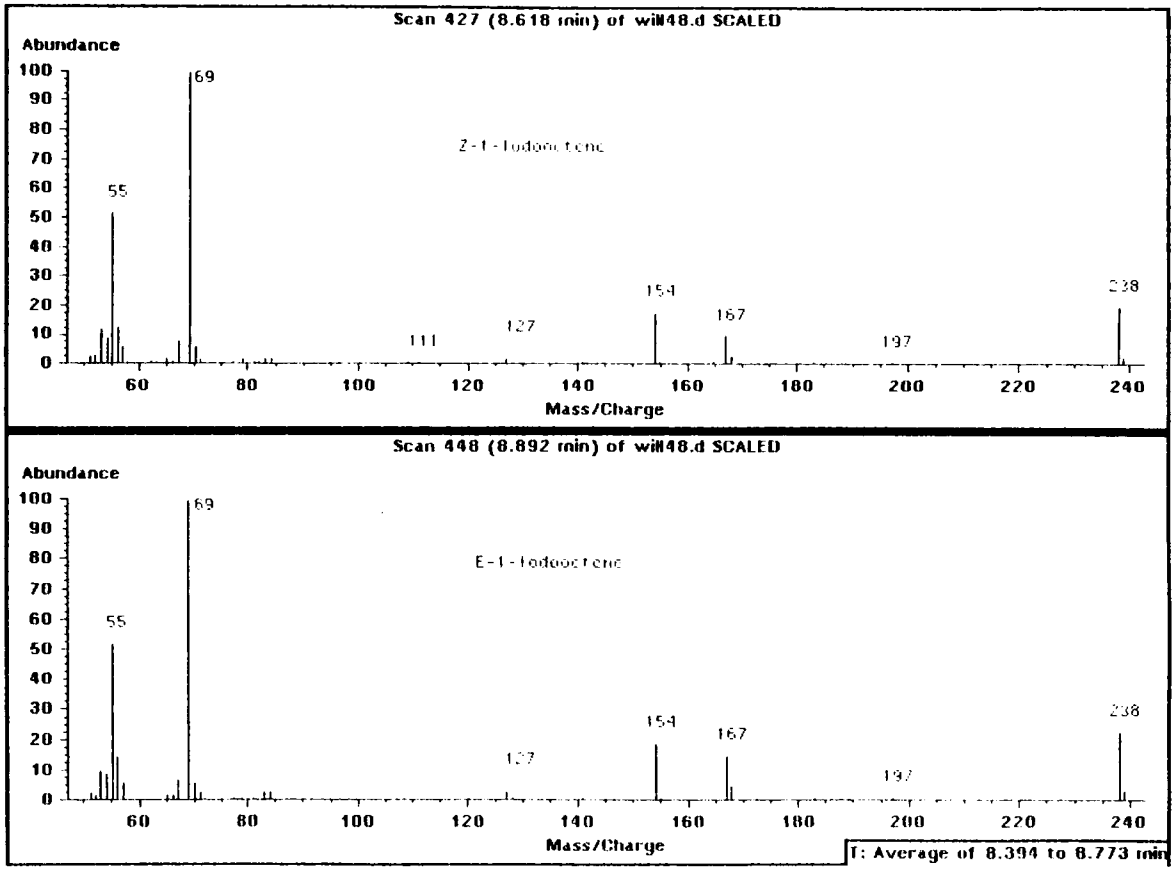


FIGURE 6. GC/MS of (E)- and (Z)-1-Iodo-1-octene Derived from Slurry Method, Showing Same Fragmentation Pattern and Overall Molecular Weight.

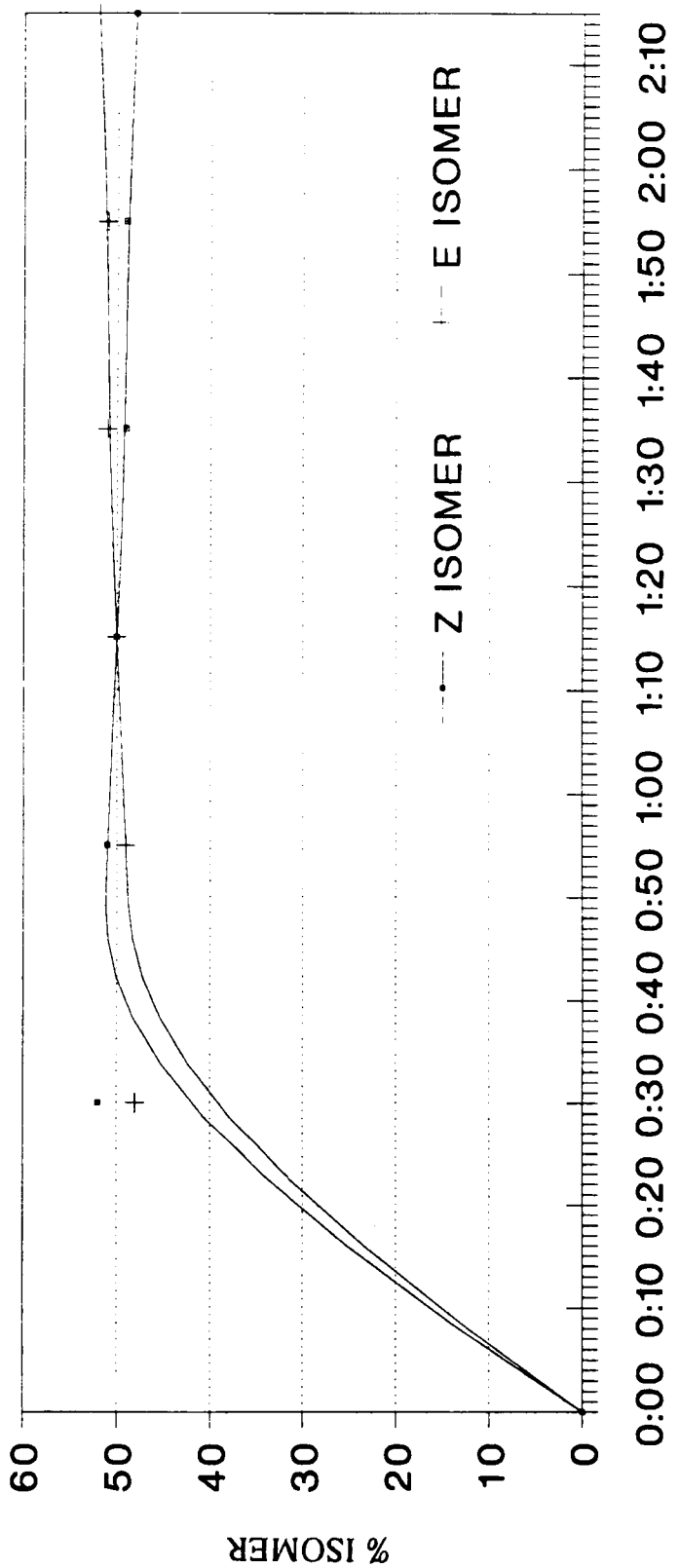


FIGURE 7. Relative Yields of (E)- and (Z)-1-Iodo-1-octene Derived from Slurry Method vs Time.

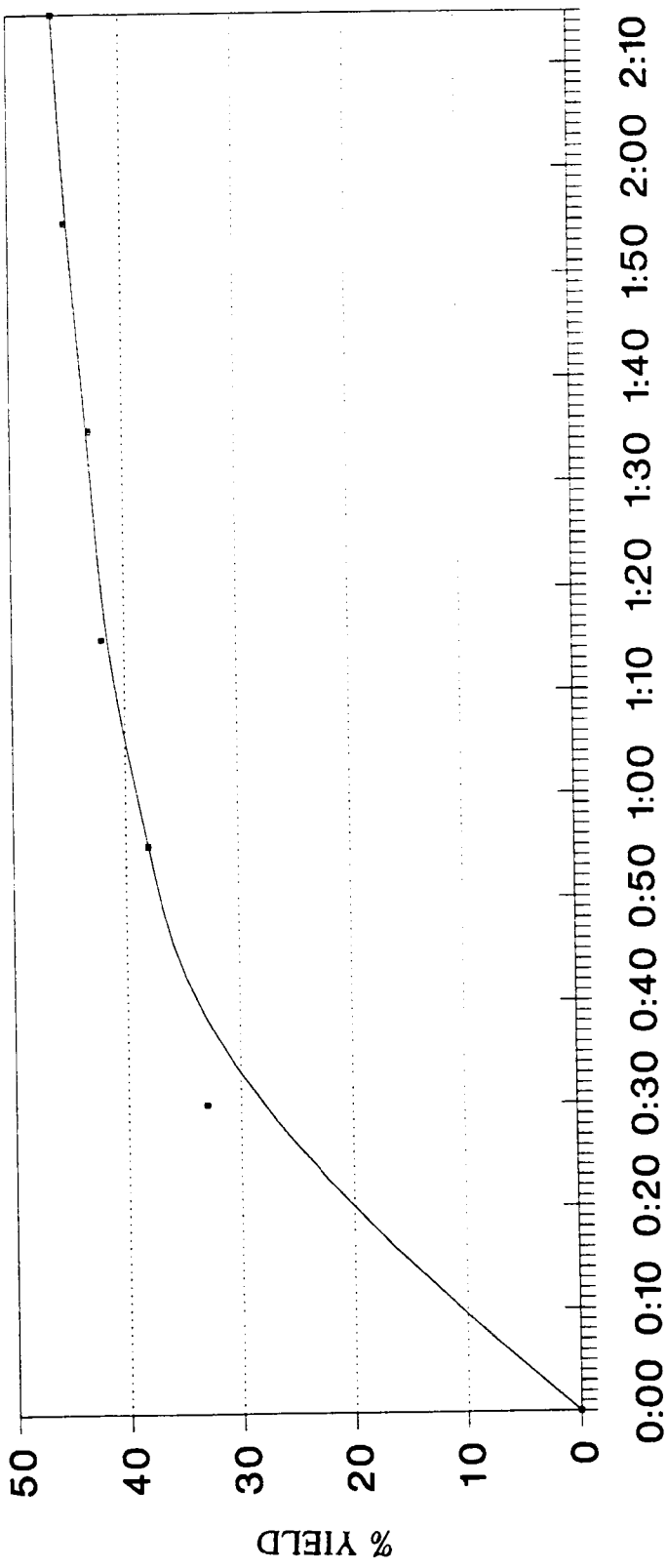


FIGURE 8. Overall % Yield of (E)- and (Z)-1-Iodo-1-octene Derived from Slurry Method vs Time.

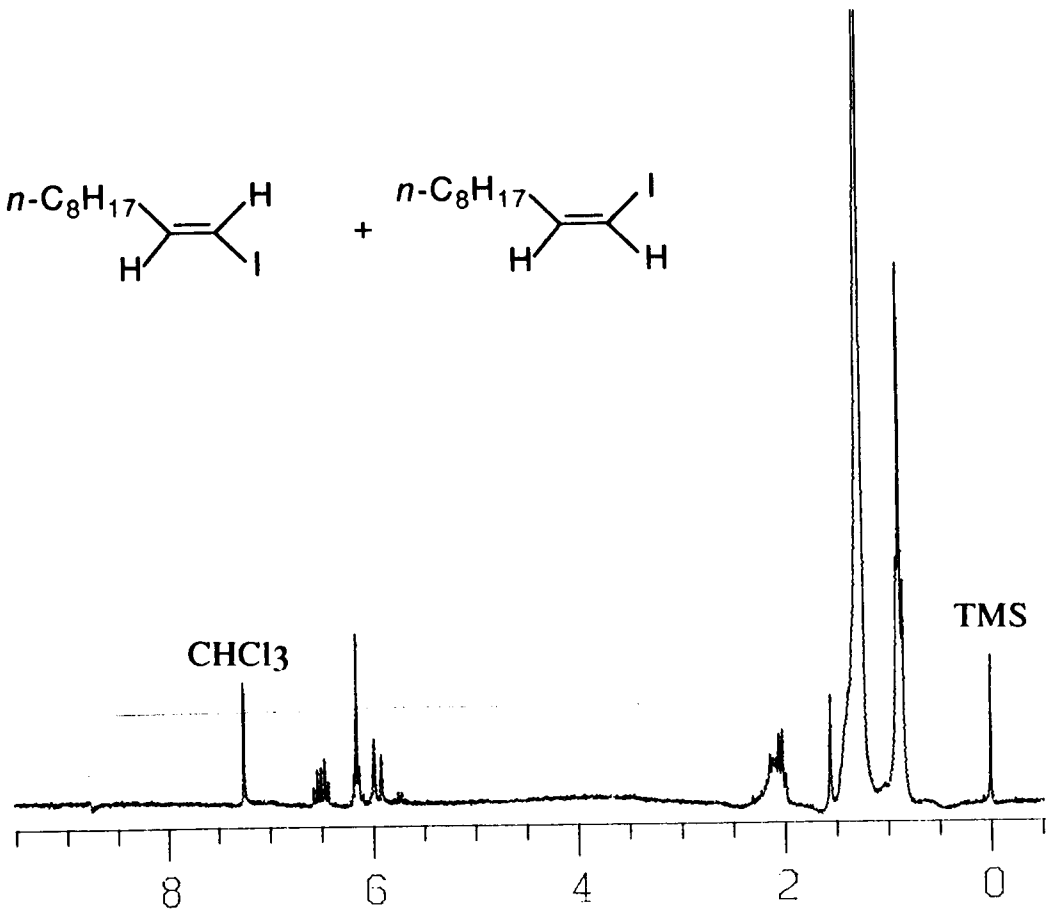


FIGURE 9. ^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of (E)- and (Z)-1-Iodo-1-decene Derived from Slurry Method.

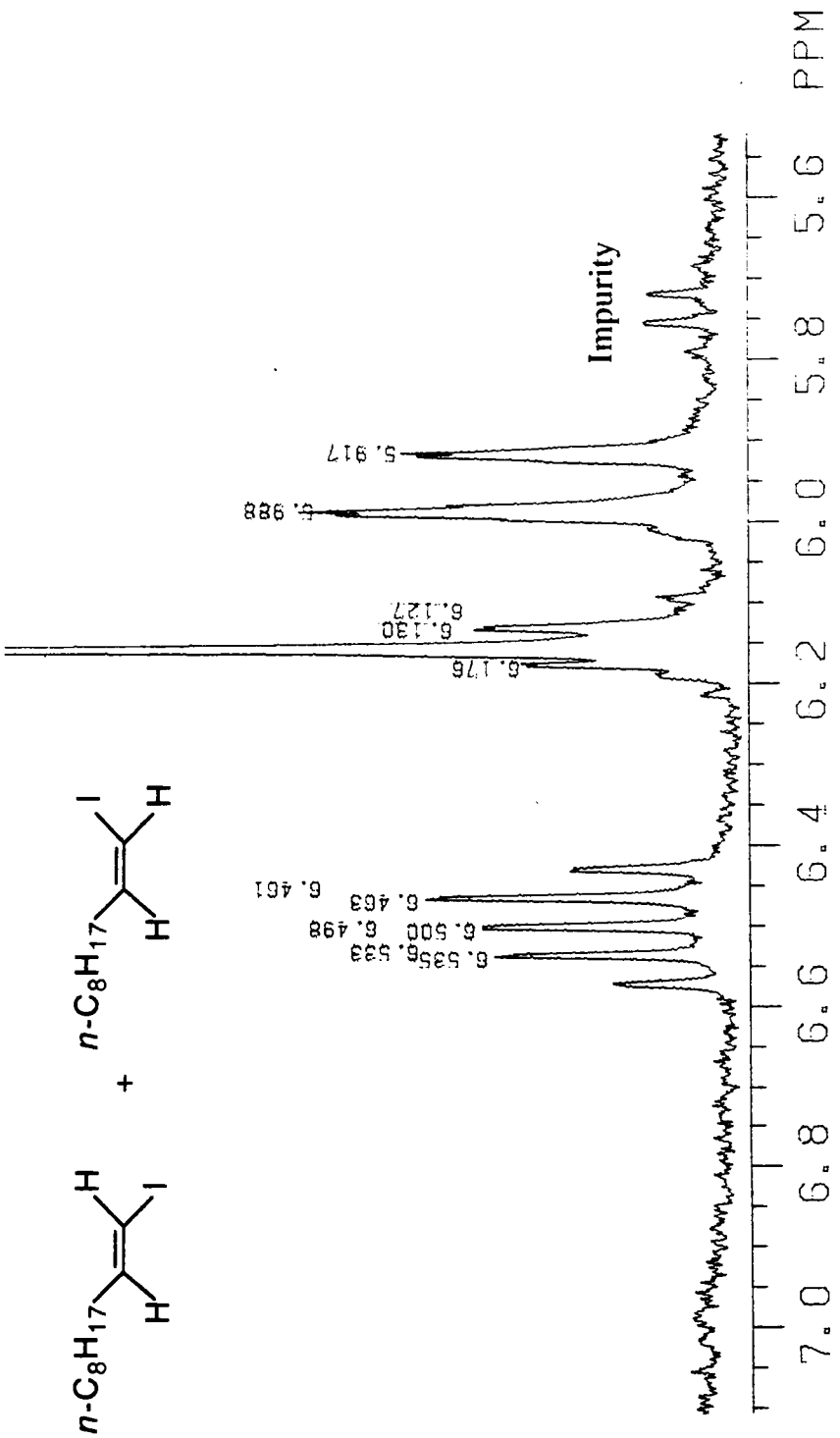


FIGURE 10. ^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of Vinylic Peaks of (E)- and (Z)-1-Iodo-1-decene Derived from Slurry Method.

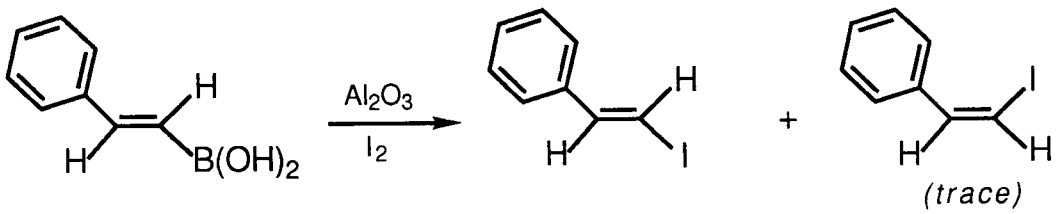
The E isomer was made by Brown's procedure[28] and its ^1H NMR spectrum was recorded (6.48 ppm d/t, 1H; 5.95 ppm d, J=15Hz, 1H) (Fig. 11&12). The E isomer and the reaction mixture were then injected separately into the GC to determine retention times for each isomer.

A kinetics study monitoring the formation of the E and Z isomers was performed (using GC) to determine the E:Z ratio (Fig. 13) and % yield (Fig. 14) as a function of time. A maximum yield of 66% (24 hrs.) was reported for the 1:1 molar ratio of boronic acid and iodine on unactivated alumina.

C. (E)-2-Phenylethenylboronic Acid

(E)-2-Phenylethenylboronic acid was treated with iodine using the reaction conditions previously described (eq. 14), and only one iodinated product was seen in the ^1H NMR spectrum (7.44 ppm d, J=15Hz, 1H; 6.80 ppm d, J=15Hz, 1H) (Fig. 15).

(14)



(E)-1-iodo-2-phenyl-1-ethene was then made by Brown's method[28] and its ^1H NMR peaks matched those of the product using the slurry method. The peaks observed in both reactions matched those reported by Brown and coworkers for (E)-1-iodo-2-phenyl-1-ethene.[29]

Close examination of the GC/MS revealed that a trace amount of another product had formed. The unknown product's MS

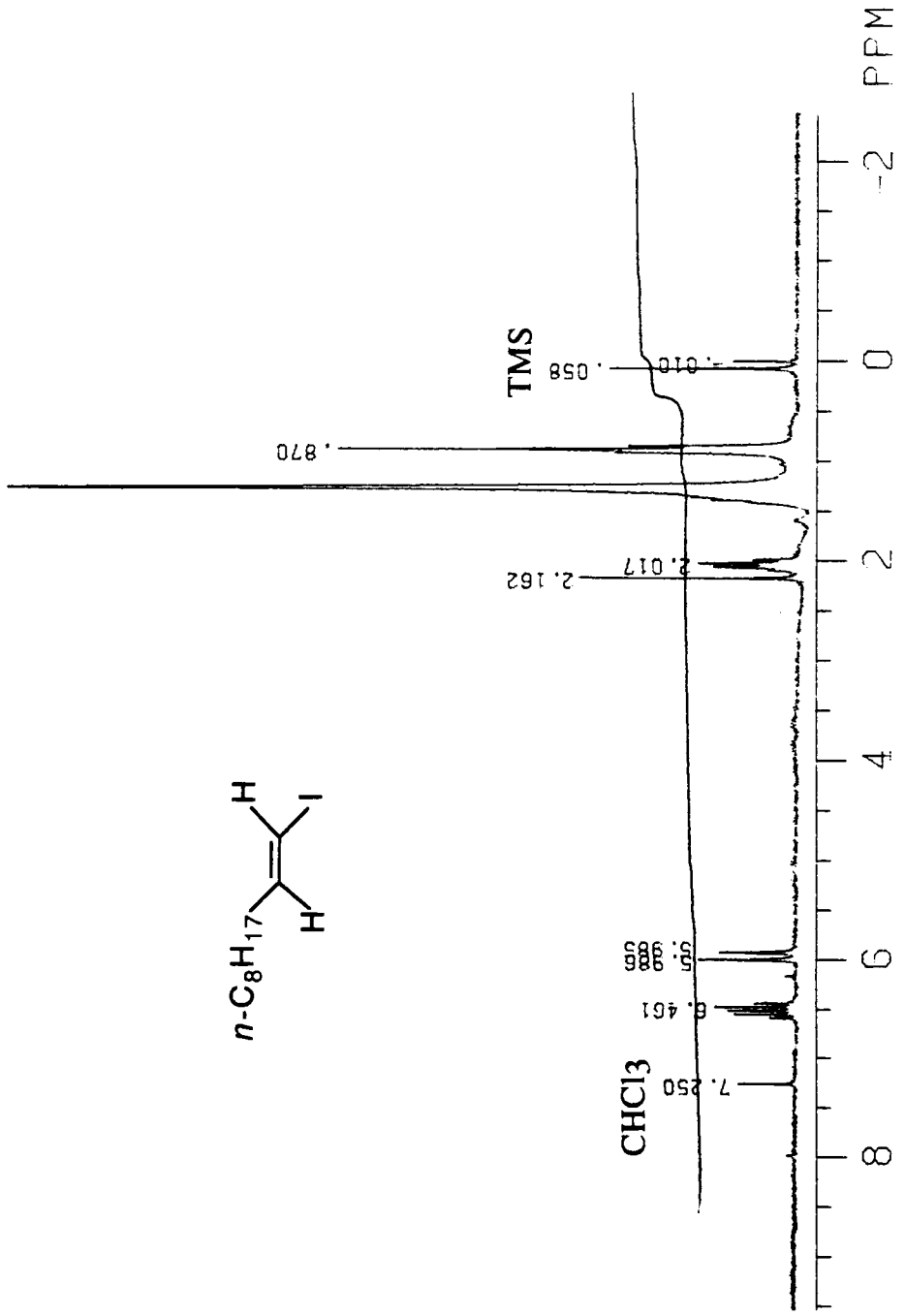


FIGURE 11. ^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of (E)-1-Iodo-1-decene Derived from Brown's Method.

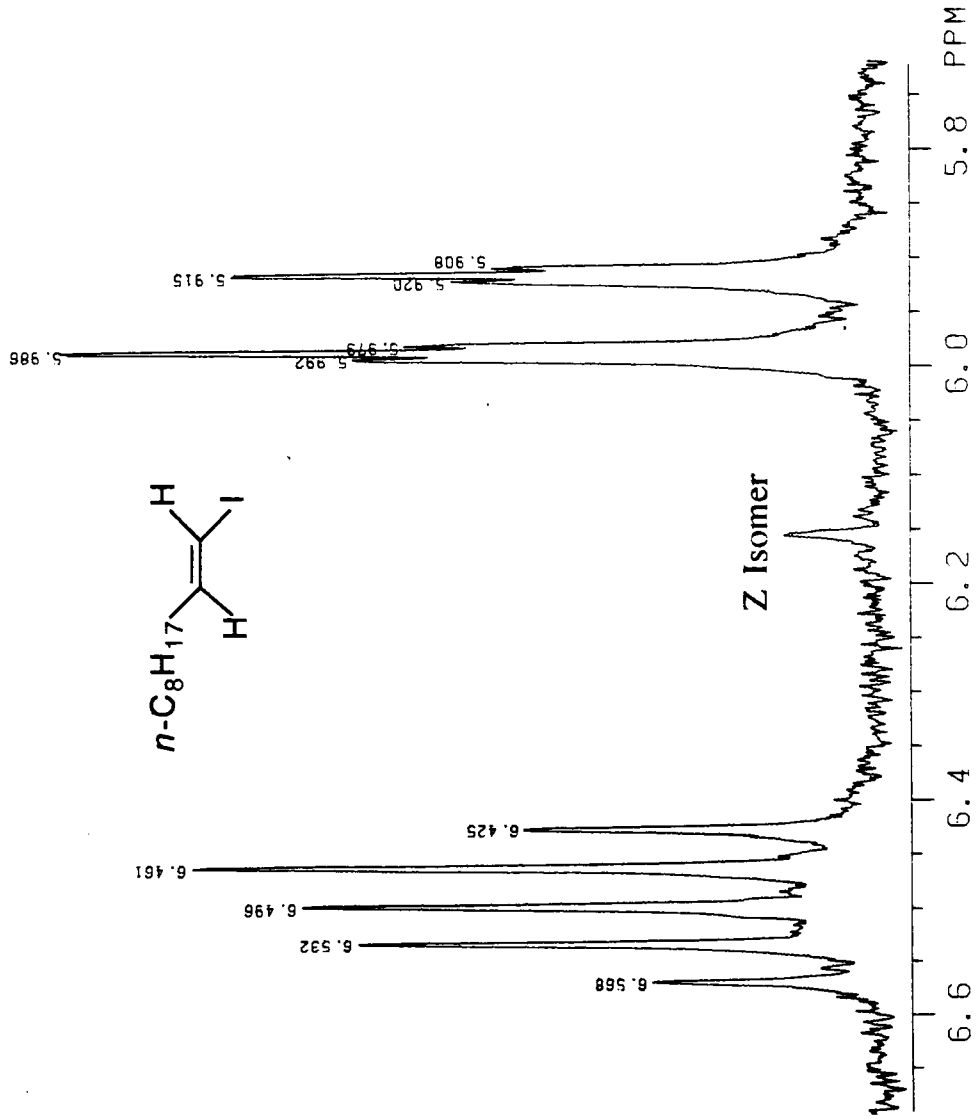


FIGURE 12. ^{1}H NMR (200 MHz, CDCl3) Spectrum of Vinylic Peaks of (E)-1-Iodo-1-decene Derived from Brown's Method.

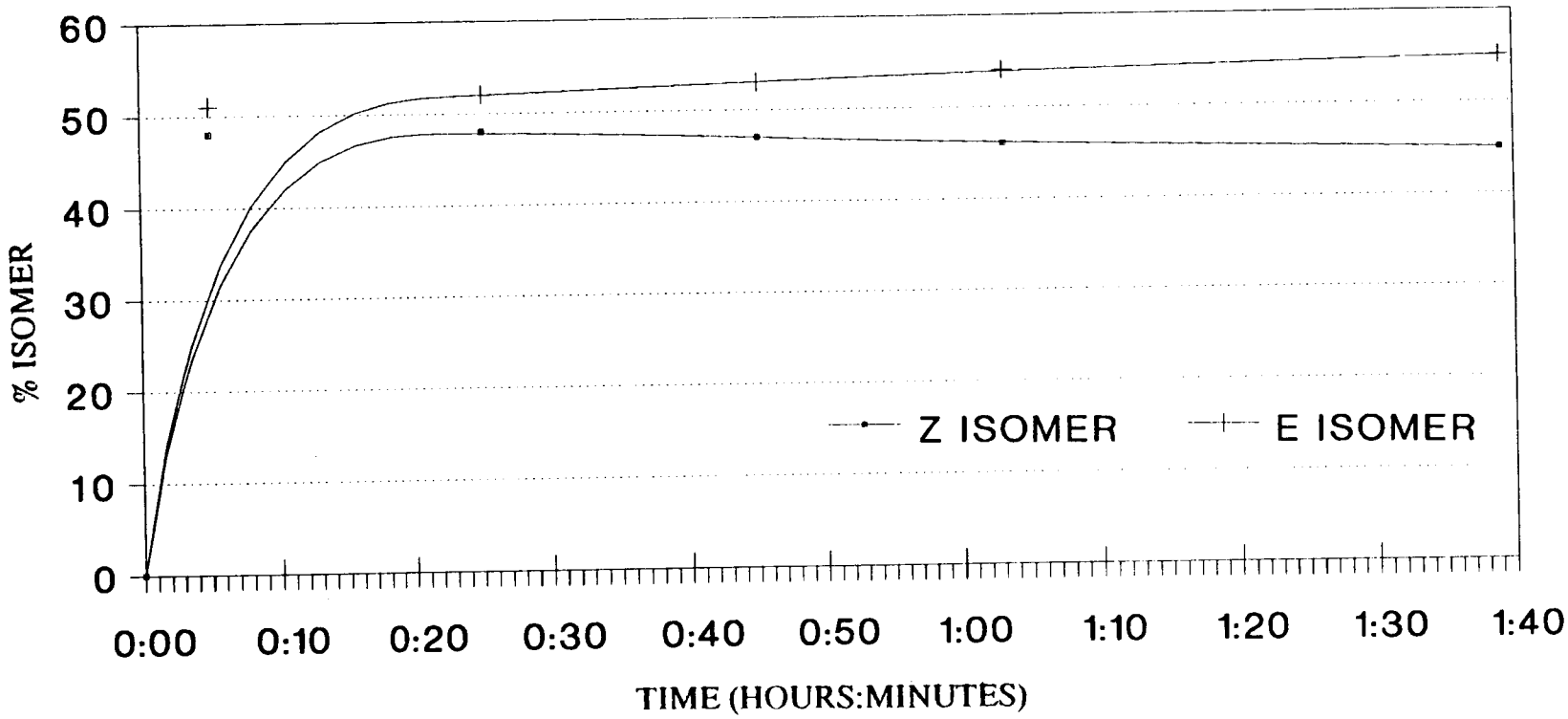


FIGURE 13. Relative Yields of (E)- and (Z)-1-Iodo-1-decene Derived from Slurry Method vs Time.

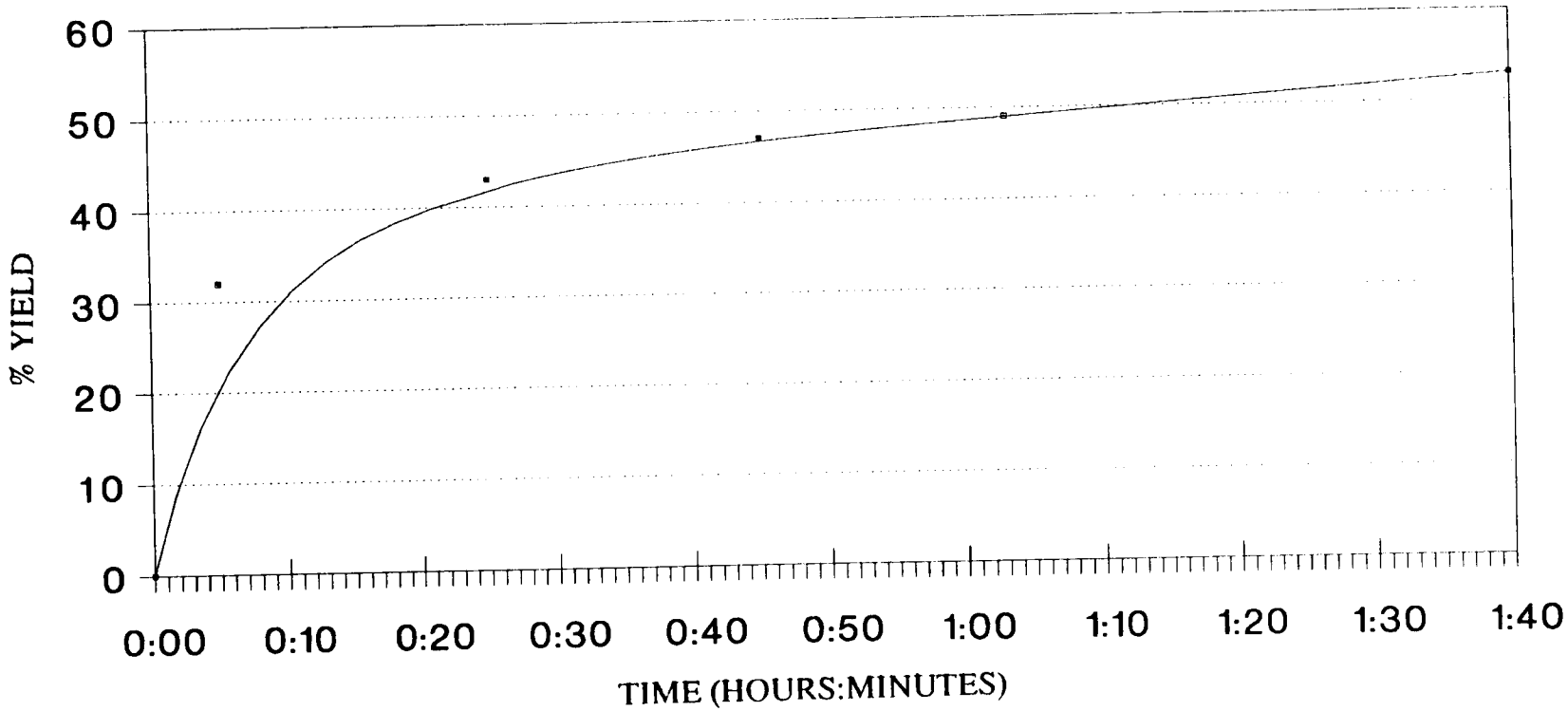


FIGURE 14. Overall % Yield of (E)- and (Z)-1-Iodo-1-decene Derived from Slurry Method vs Time.

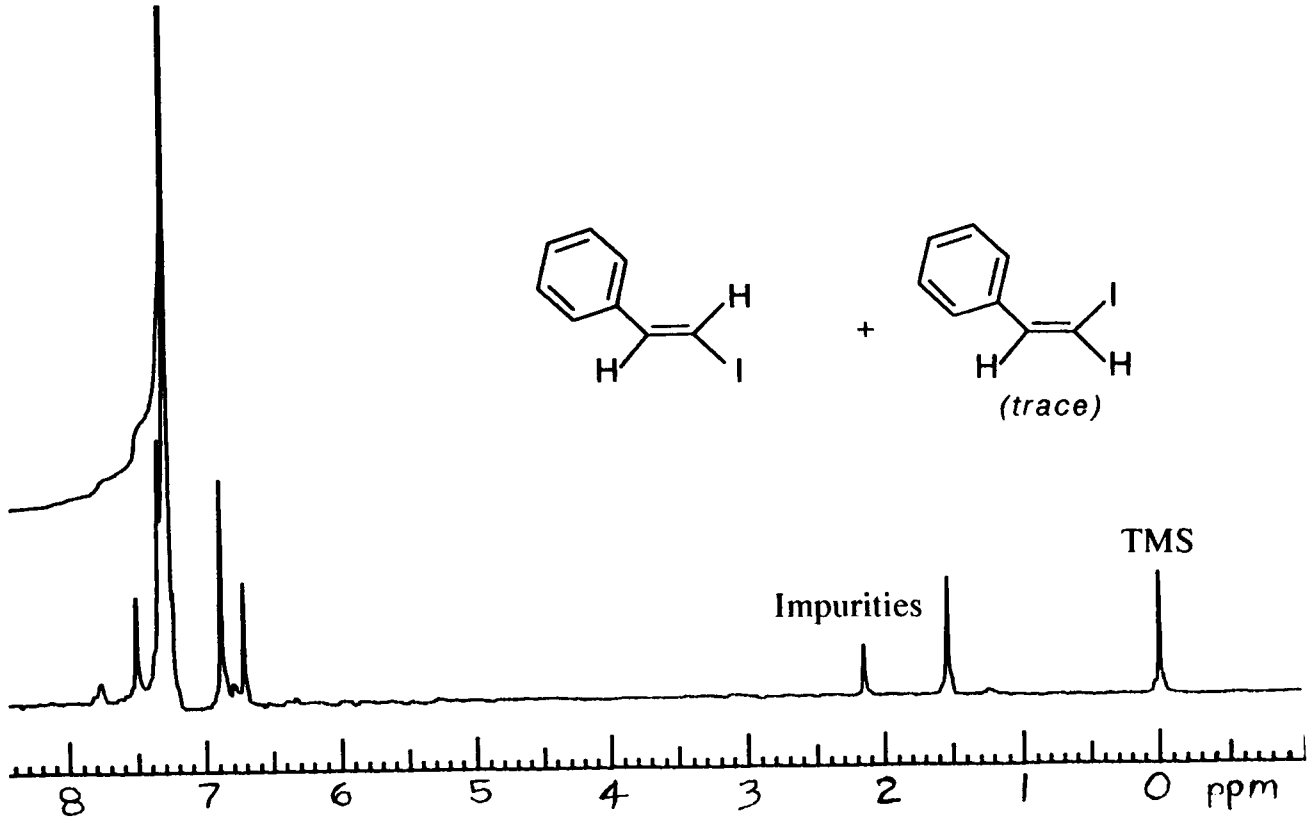


FIGURE 15. ^{1}H NMR (90 MHz, $CDCl_3$) Spectrum of (E)- and (Z)-1-Iodo-2-phenyl-1-ethene Derived from Slurry Method.

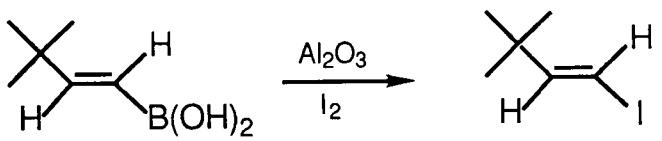
fragmentation pattern and molecular weight were the same as the E isomer (Fig. 16&17). Thus, less than 1% of the Z isomer was also formed.

A kinetics study monitoring the formation of the E isomer was performed (using GC) to determine the overall % yield (Fig. 18). GC/MS calculations revealed that greater than 99% of the E isomer had formed with only a trace amount of the Z isomer. A maximum yield of 96% (24 hrs.) was reported for the 1:1 molar ratio of boronic acid and iodine on unactivated alumina.

D. (E)-3,3-Dimethyl-1-butenylboronic Acid

Treatment of (E)-3,3-dimethyl-1-butenylboronic acid (eq. 15) with iodine, using the reaction conditions previously described, yielded only (E)-3,3-dimethyl-1-iodo-1-butene.

(15)



A ^1H NMR of the reaction product was obtained and the peaks matched those reported by Brown (6.4 ppm d, J=14Hz, 1H; 5.4 ppm d, J=14Hz, 1H).[13] (E)-3,3-dimethyl-1-iodo-1-butene was also made by Brown's method[28] and the ^1H NMR peaks matched those of the product obtained using the slurry method.

A kinetics study monitoring the formation of the E isomer was performed (using GC) to determine the % yield (Fig.20). GC calculations indicated that there was no trace of the Z isomer. A maximum yield of 55% was recorded (15 minutes) but then

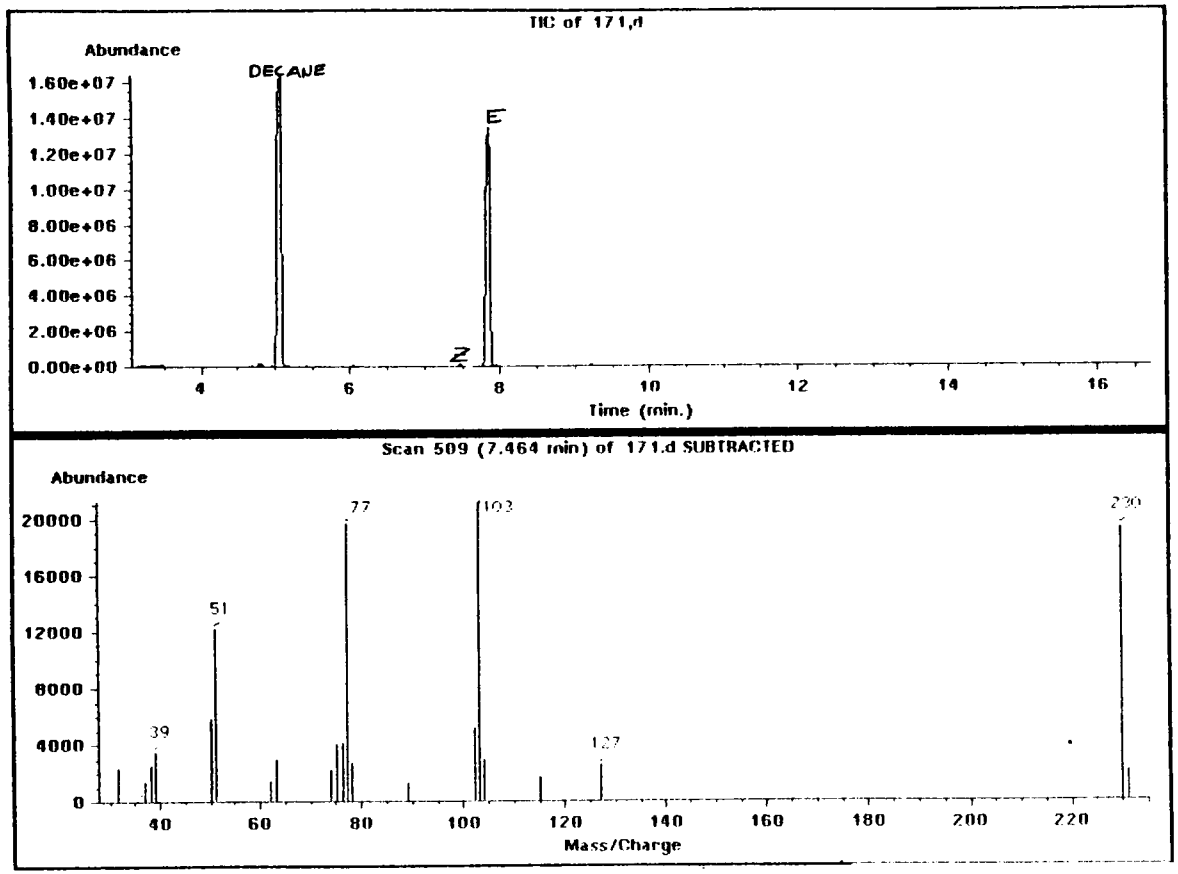


FIGURE 16. GC of (E)- and (Z)-1-Iodo-2-phenyl-1-ethene Derived from Slurry Method Indicating Retention Times of E and Z Isomer (7.846 and 7.464 minutes, respectively). MS of Z Isomer Showing Fragmentation and Molecular Weight.

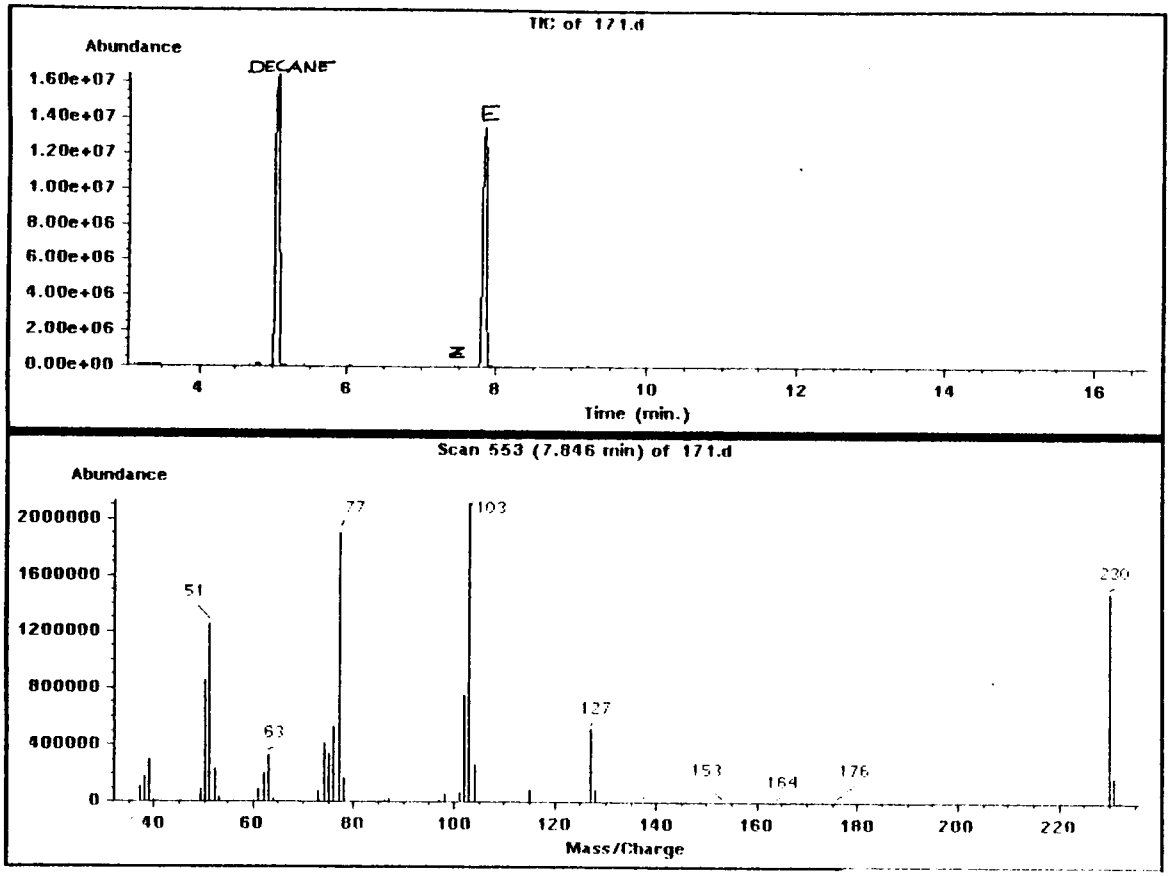


FIGURE 17. GC of (E)- and (Z)-1-Iodo-2-phenyl-1-ethene Derived from Slurry Method Indicating Retention Times of E and Z Isomer (7.846 and 7.464 minutes, respectively). MS of E Isomer Showing Matching Fragmentation Pattern and Molecular Weight as Z Isomer.

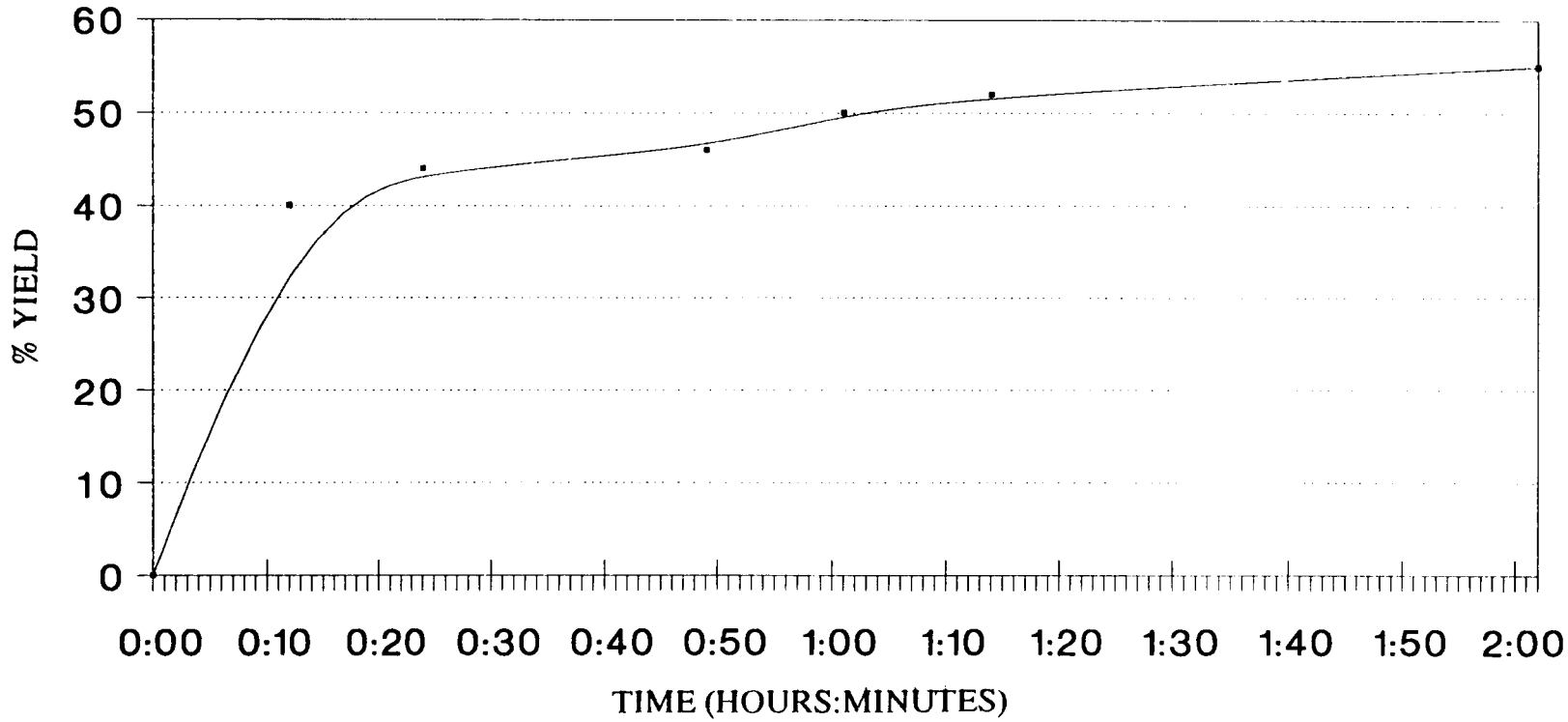


FIGURE 18. Overall % Yield of (E)- and (Z)-1-Iodo-2-phenyl-1-ethene Derived from Slurry Method vs Time.

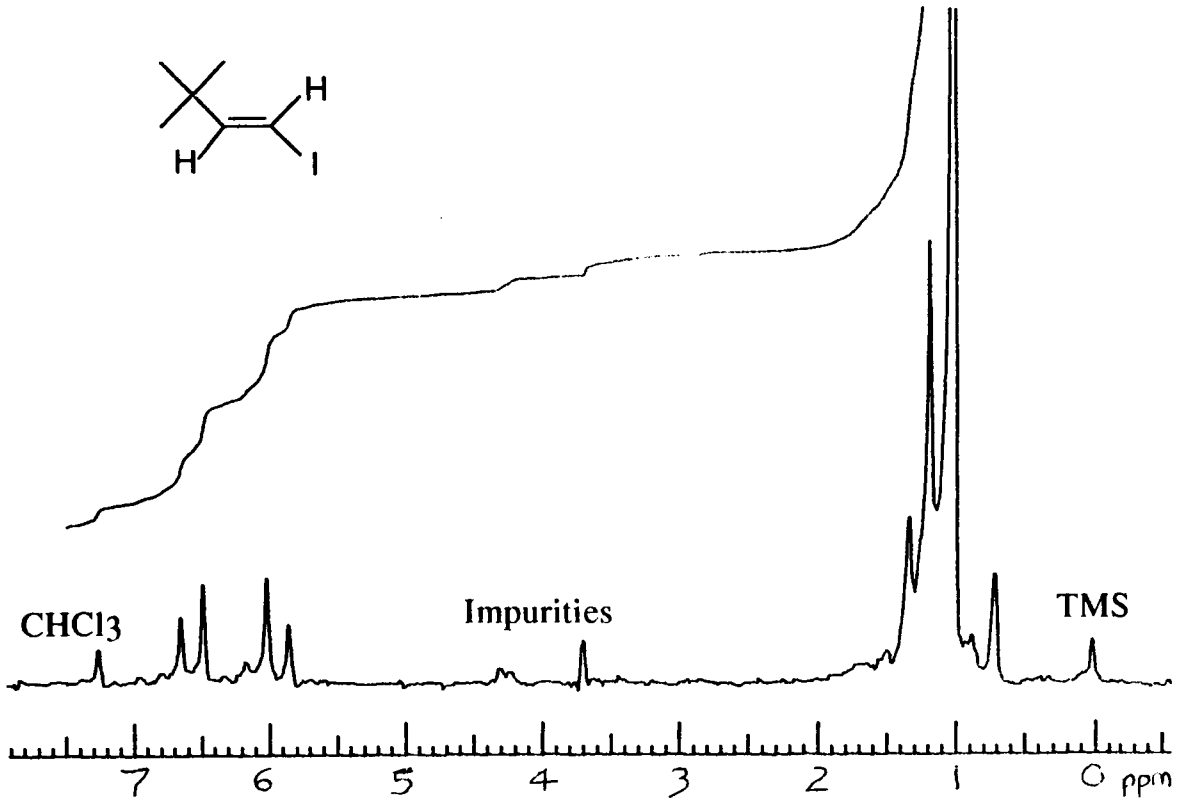


FIGURE 19. ^{1}H NMR (90 MHz, $CDCl_3$) Spectrum of (E)-3,3-Dimethyl-1-Iodo-1-butene Derived from Slurry Method.

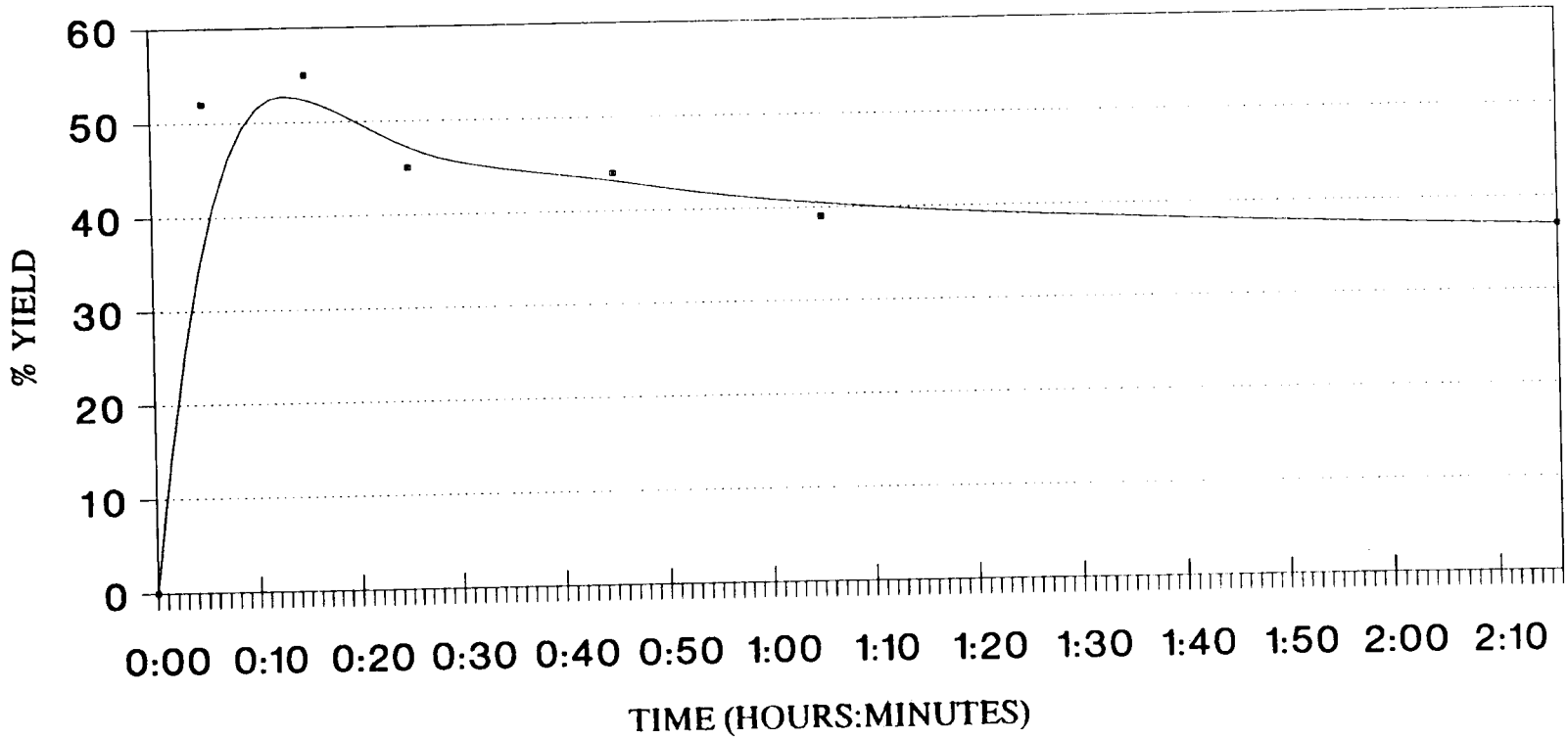


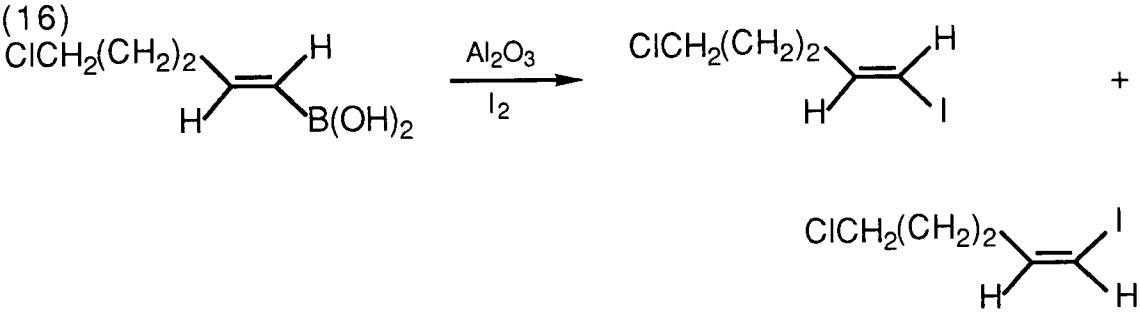
FIGURE 20. Overall % Yield of (E)-3,3-Dimethyl-1-Iodo-1-butene Derived from Slurry Method vs Time.

dropped off inexplicably to 24% (24 hrs.) for the 1:1 molar ratio of boronic acid and iodine on unactivated alumina.

E. (E)-5-Chloro-1-pentenylboronic Acid

(E)-5-Chloro-1-pentenylboronic acid (eq. 16) was treated with iodine using the method previously described and a mixture of two iodinated products was obtained.

(16)



After the reaction was allowed to proceed for two hours, a ^1H NMR spectrum was obtained on the reaction mixture (6.43 ppm d/t, 1H; 6.2 ppm m, 2H; 5.9 ppm d, 1H) (Fig. 21), and the observed peaks matched those reported by Brown and coworkers for (E)- and (Z)-5-chloro-1-iodo-1-pentene.[30] To determine GC retention times of both products the E isomer, prepared independently by Brown's method,[28] was injected into the GC and its retention time noted.

A kinetics study monitoring the formation of the E and Z isomers was performed (using GC) to determine the relative yields of E:Z products (Fig. 22) and the % yield (Fig. 23) as a function of time. A 82% yield was reported as the maximum yield (50 min.) for a 1:1 molar ratio of boronic acid and iodine on unactivated alumina. This unexpected high yield in such a short amount of time could possibly be due to the electron withdrawing inductive effect of the chloro group, but much is still uncertain.

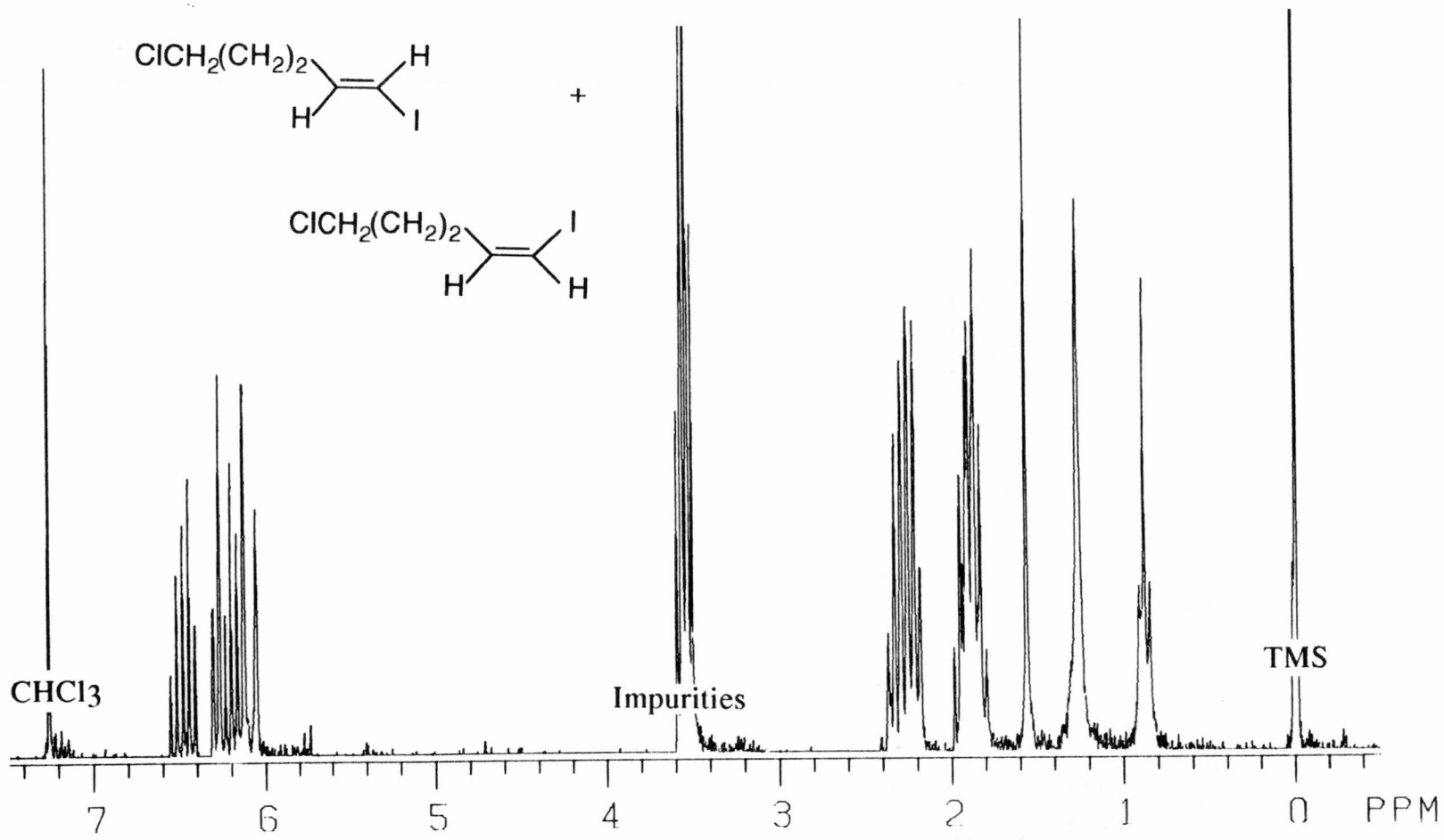


FIGURE 21. ^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of (E)- and (Z)-5-Chloro-1-Iodo-1-pentene Derived from Slurry Method.

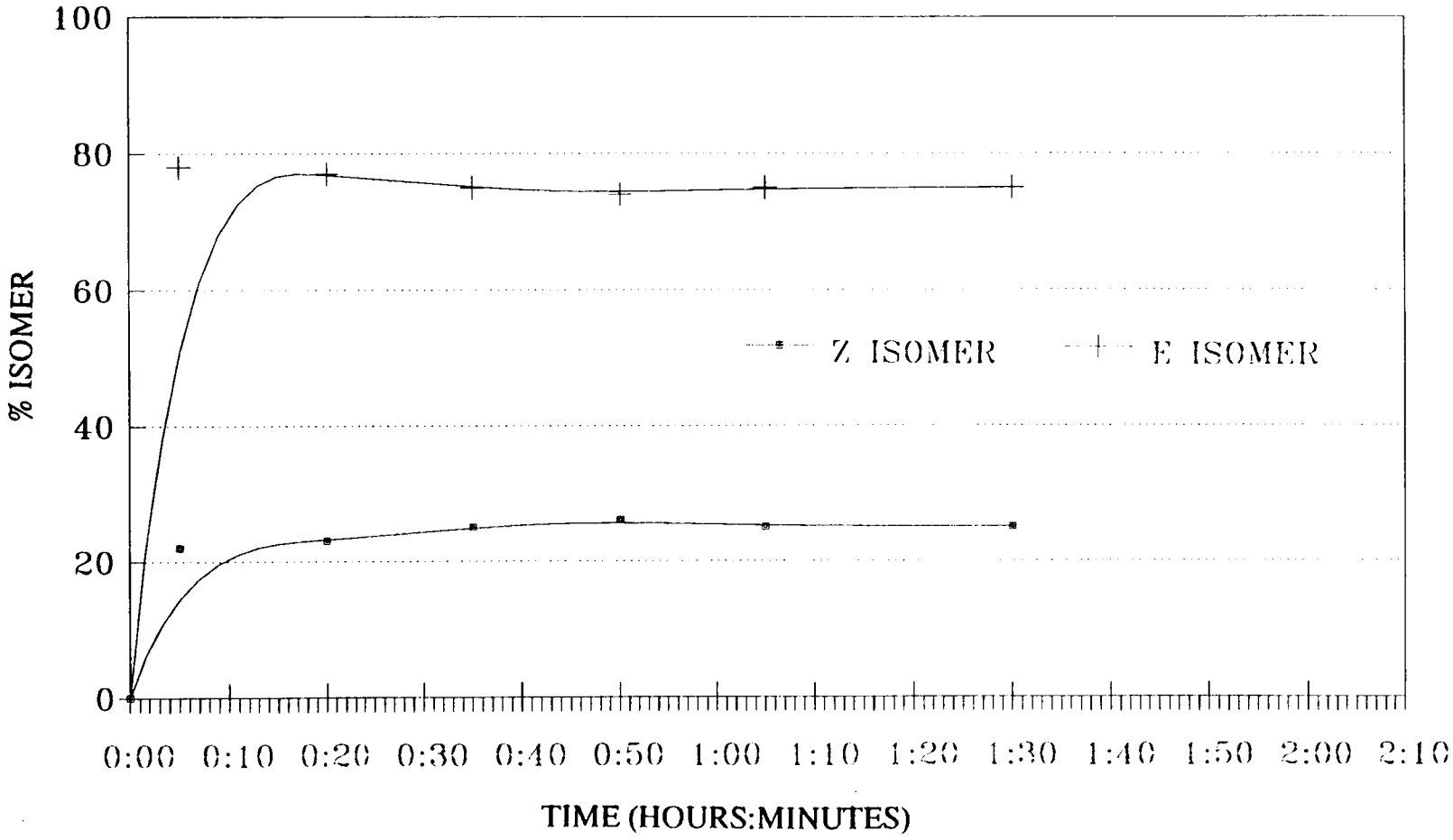


FIGURE 22. Relative Yields of (E)- and (Z)-5-Chloro-1-Iodo-1-pentene from Slurry Method vs Time.

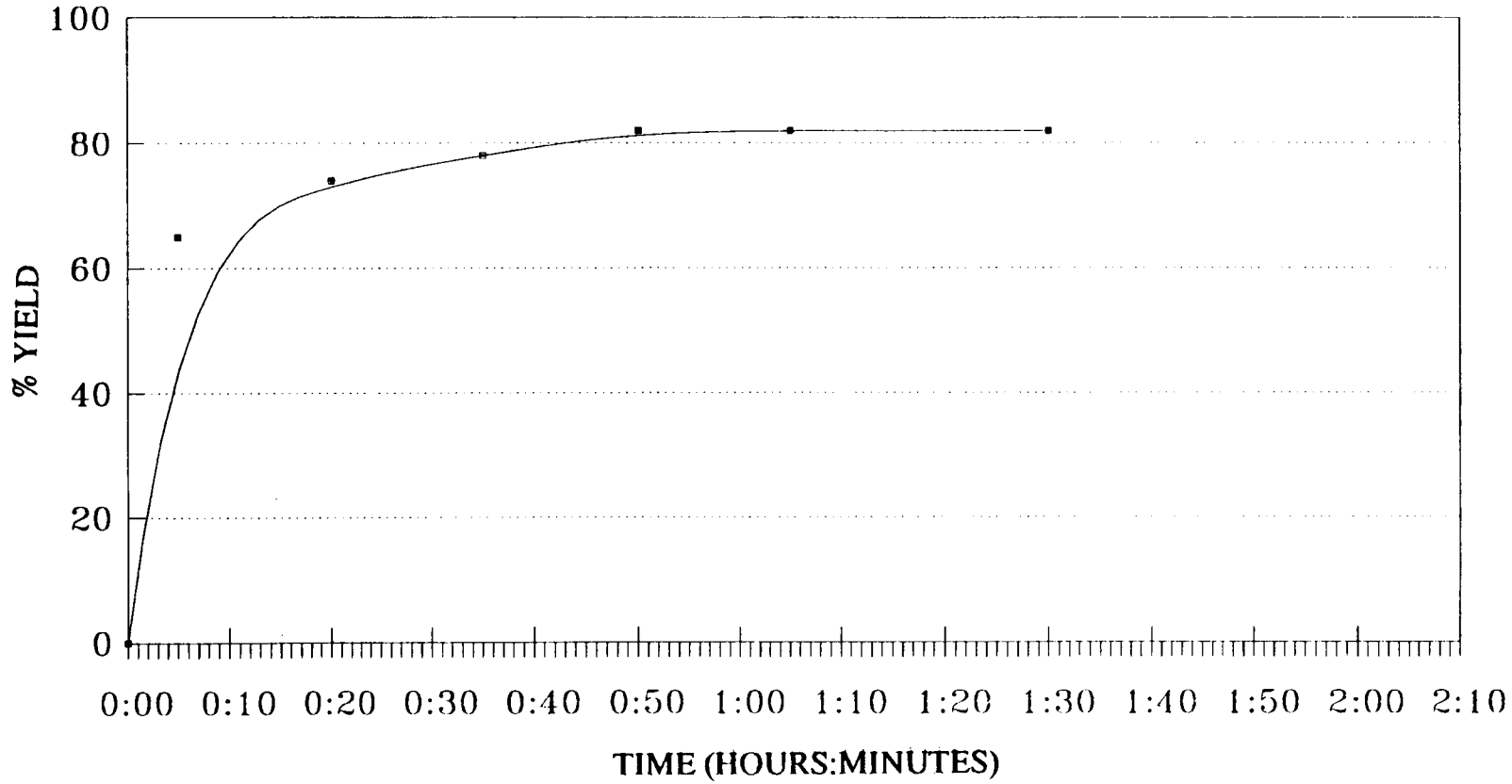
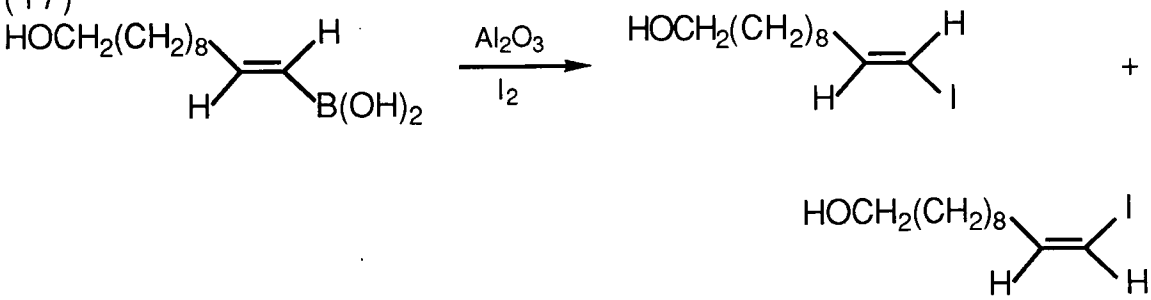


FIGURE 23. Overall % Yield of (E)- and (Z)-5-Chloro-1-Iodo-1-pentene Derived from Slurry Method vs Time.

F. (E)-11-Hydroxy-1-undecenylboronic Acid

(E)-11-Hydroxy-1-undecenylboronic acid (eq. 17) was treated with iodine using the method previously described and a mixture of two iodinated products was afforded.

(17)



After the reaction was allowed to proceed for two hours, a ^1H NMR spectrum was obtained on the reaction mixture (6.5 ppm m, 1H; 6.07 ppm m, 2H; 5.95 ppm d/t, 1H) (Fig. 24), and the vinylic proton peaks matched similar compounds described previously (i.e. long straight chain R groups) by Brown and coworkers[31] for the E and Z isomers. To determine GC retention times of both products the E isomer was prepared independently by Brown's method[28] (the alcohol group was protected with 1-(trimethylsilyl)-imidazole prior to injection into GC) and its retention time noted.

A kinetics study monitoring the formation of the E and Z isomers was performed (using GC) to determine the E:Z ratios (Fig. 25) and the % yield (Fig. 26) as a function of time. A 59% yield was reported as the maximum yield (24 hrs.) for a 1:1 molar ratio of boronic acid and iodine on unactivated alumina.

G. Other Boronic Acids

Phenylboronic acid was treated with iodine using the previously described slurry method (eq. 18) and Brown's method,[28]

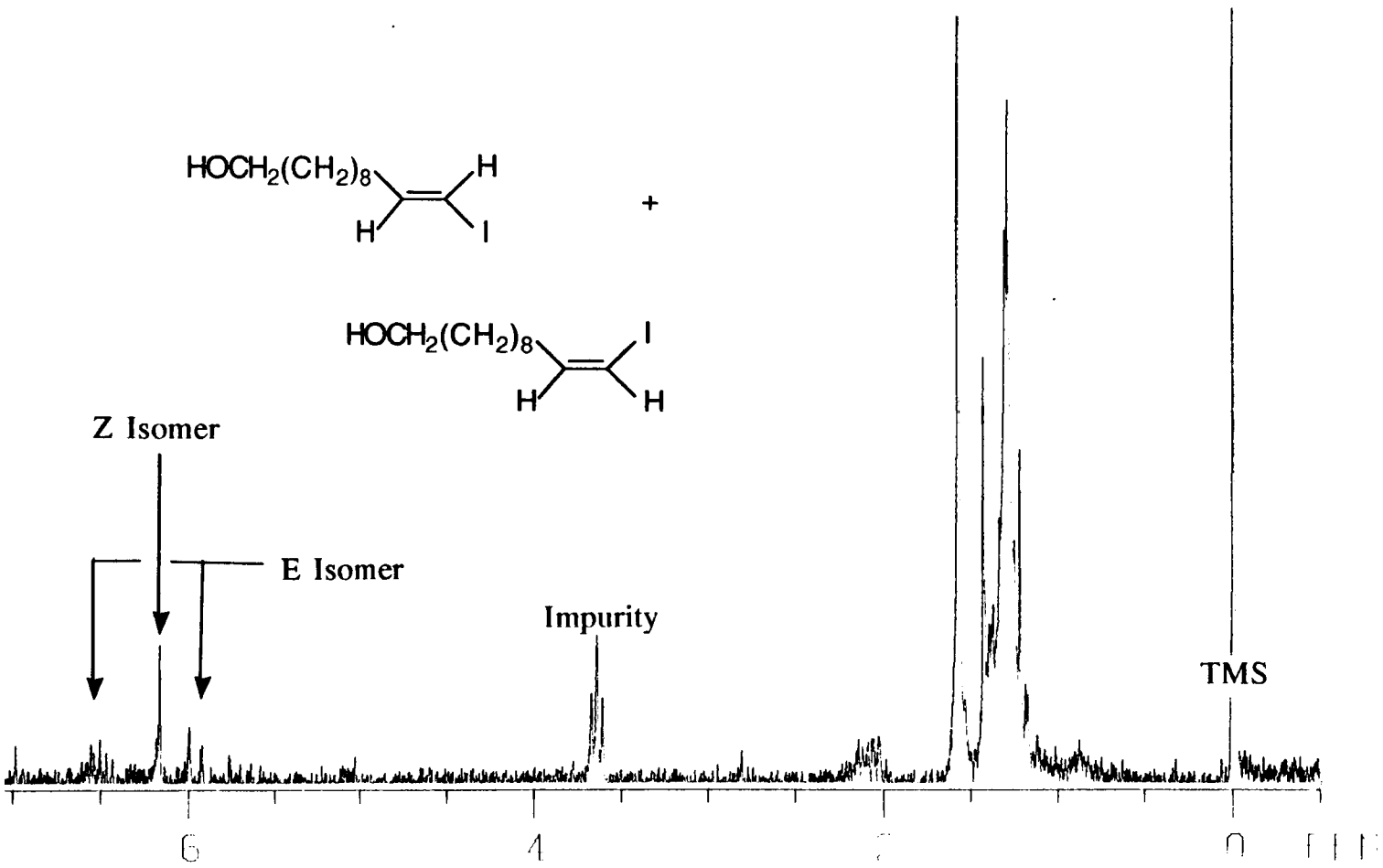


FIGURE 24. ^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of (E)- and (Z)-11-Hydroxy-1-iodo-1-undecene Derived from Slurry Method.

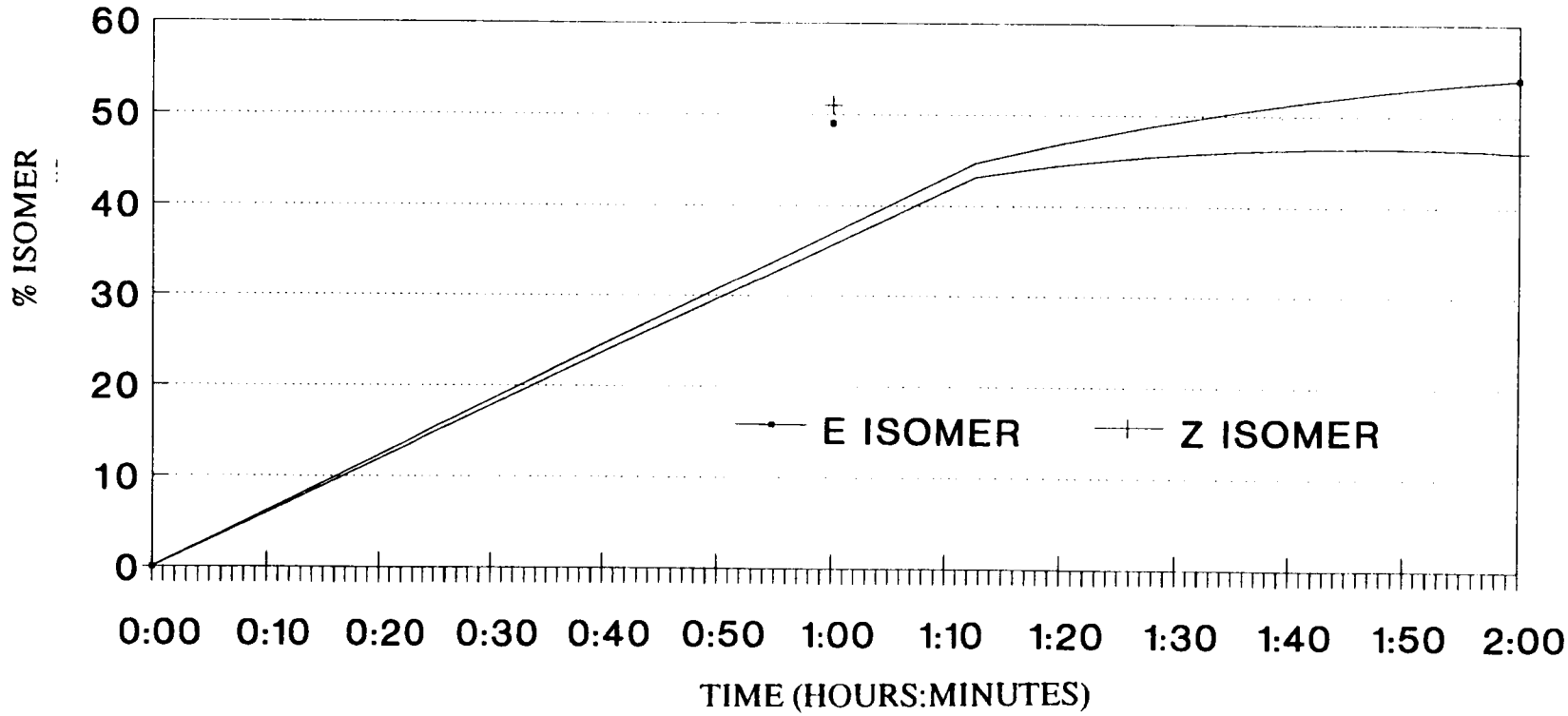


FIGURE 25. Relative Yields of (E)- and (Z)-11-Hydroxy-1-iodo-1-undecene Derived from Slurry Method.

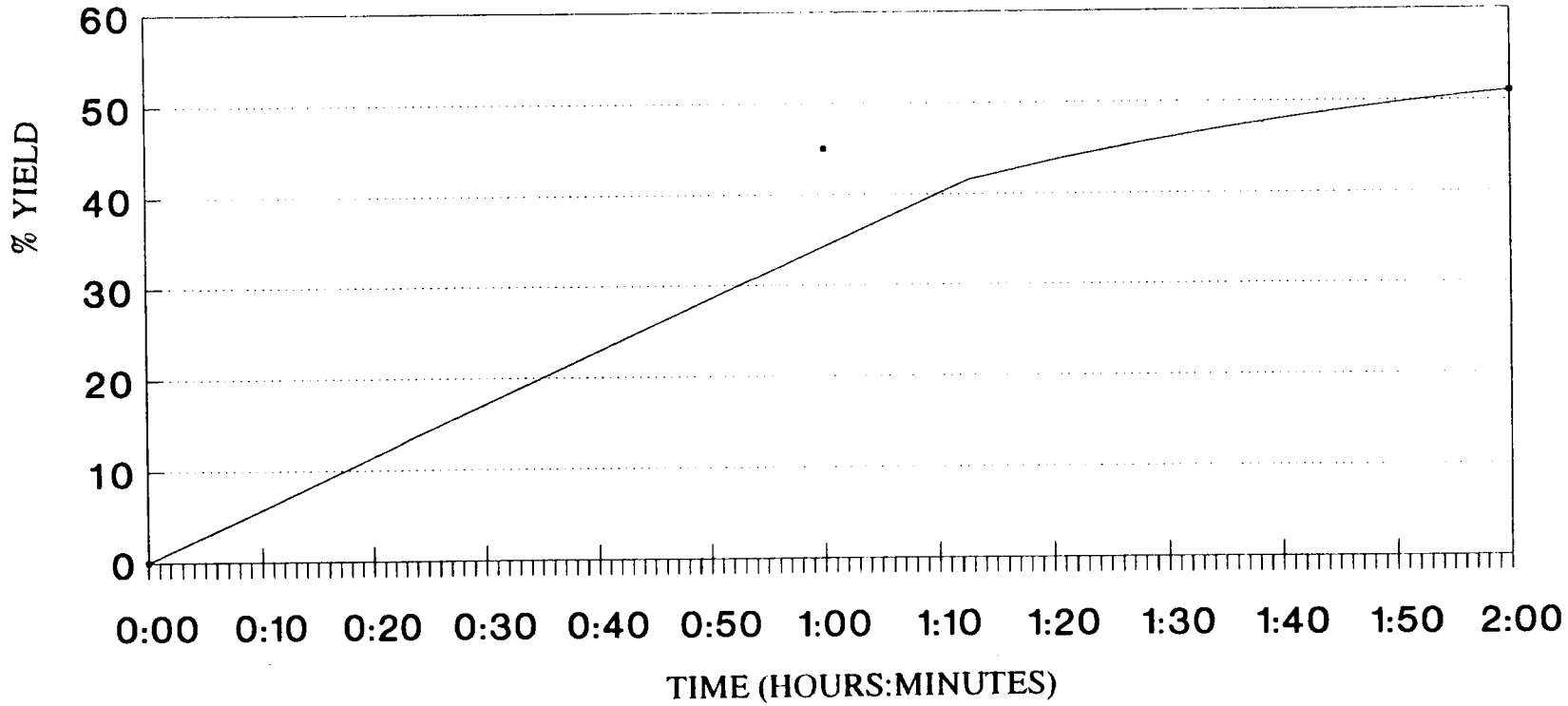
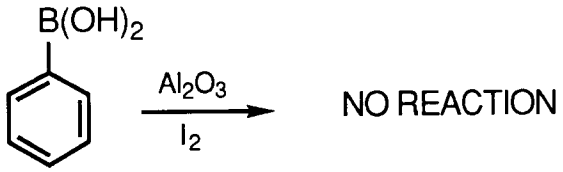


FIGURE 26. Overall % Yield of (E)- and (Z)-11-Hydroxy-1-iodo-1-undecene Derived from Slurry Method vs Time.

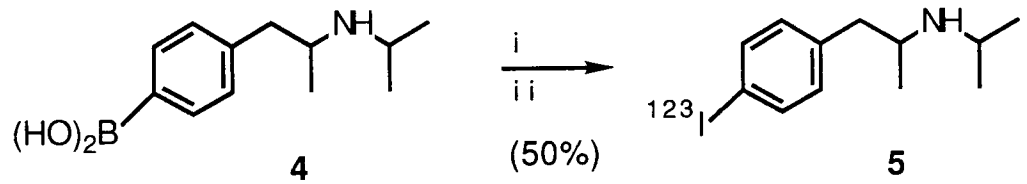
and after four hours no iodinated products were present by both methods (as indicated by ^1H NMR and GC).

(18)



This was an unexpected result because boronic acid **4** (eq. 19) reacts readily to form N-isopropyl p-iodoamphetamine **5**.[32]

(19)



4 **5**

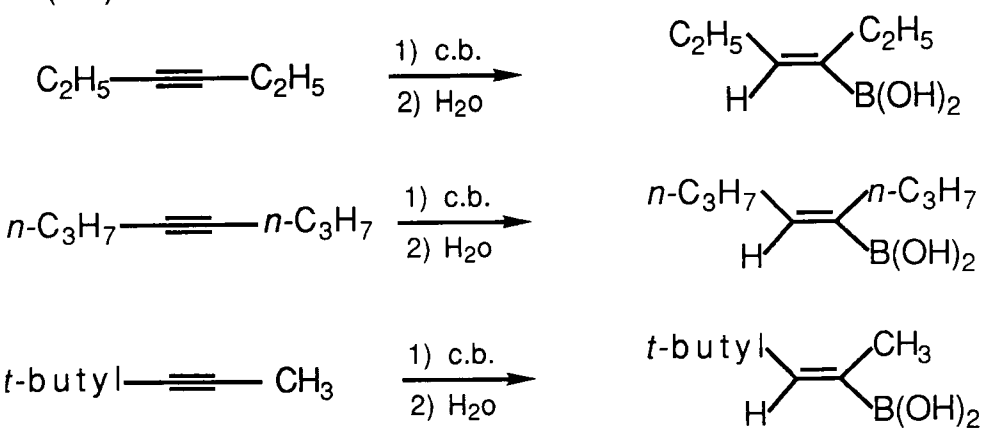
(i) $Na^{123}I$, HCl, Chloramine-T

(ii) NaOH

The nonreactivity of phenylboronic acid using the slurry method is perhaps due to the different reaction conditions, the different substrate used, and the nonreactivity of aromatic rings in substitution reactions (S_E2).

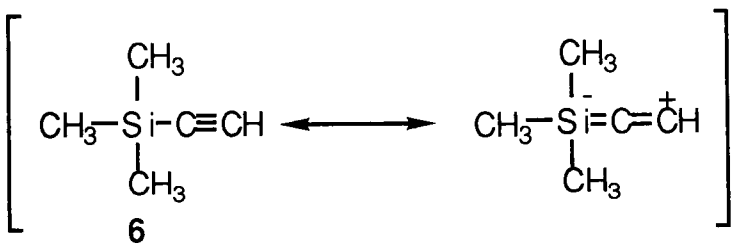
Several internal alkynes were hydroborated with catecholborane and the resultant internal cis boronic acids were, isolated (eq. 20). Addition of alumina and iodine (slurry method) produced no iodinated products. Addition of base and iodine (Brown's method[28]) also produced no iodinated products. Thus, the reaction seems to take another course with internal boronic acids.[7]

(20)



Trimethylsilyl acetylene (**6**) was also hydroborated with catecholborane, and a mixture of hydroborated adducts was obtained. The regioselectivity can be attributed to the pi electrons of the olefin overlapping with the d orbitals of the silcon (eq. 21). The result is a higher effective charge density at the beta than at the alpha carbon of the triple bond[33] as the following resonance structures indicate. Unfortunately, the mixture of hydroborated adducts could not be separated successfully; thus, no iodination reactions were undertaken.

(21)



6

H. Reaction Studies of a Model Compound: (E)-1-Octenylboronic Acid

In an attempt to optimize yields, to control the E:Z ratio, and to gain a better understanding of alumina and the boron moiety, several experiments were devised and performed.

1. Isomerization Studies

Recall that (E)- and (Z)-1-iodooctene are formed initially in a 1:1 ratio and that the percent of the E isomer increases over longer periods of time due to possible isomerization of the Z isomer to the more thermodynamically stable E isomer. It was hypothesized that either the E isomer was being formed first and then isomerizing to the Z isomer or the Z isomer was being formed first and then isomerizing to the E isomer. The E isomer isomerizing to the Z isomer seems highly unlikely based on thermodynamics; therefore, it seems reasonable that the Z isomer may be formed initially and then isomerizes to the E isomer. To test this hypothesis several control experiments were devised.

Pure (Z)-1-iodooctene (.001 mol) was added to 10 grams alumina and 15 ml ethyl ether to imitate the slurry method. Aliquots were removed every 15 minutes and analyzed by GC to see if the E isomer had formed. After 2.5 hours there was no evidence of the E isomer.

In a second experiment pure (Z)-1-iodooctene (.001 mol) was added to 10 grams alumina, 15 ml ethyl ether, and .0005 mol iodine. Aliquots were removed every 15 minutes and analyzed by GC for the formation of the E isomer. After 2 hours there was no evidence of the E isomer.

In a third and final experiment, pure (Z)-1-iodooctene (.001 mol) was exposed to 10 grams alumina, 15 ml ethyl ether, and .0005 mol of (E)-1-octenylboronic acid. Aliquots were removed every 15 minutes and analyzed for the presence of the E isomer. After 2 hours there was no evidence of the E isomer.

Every reactant combination was explored in an attempt to isolate the species that could catalyze the isomerization. No (E)-1-iodo-1-octene was formed through an isomerization pathway; thus, it can be concluded that (E)- and (Z)-1-iodo-1-octene are formed initially in approximately a 1:1 ratio by separate mechanistic pathways to be discussed later.

2. Activation Studies

The advantage of dehydrated Brockman activity 1 neutral alumina in catalyzing the iodination of alkenes has been clearly demonstrated by Pagni, Kabalka and coworkers.[34] Therefore, it was thought that by using dehydrated alumina in the slurry reaction, instead of alumina straight out of the bottle, E:Z ratios and yields might be altered.

The E:Z ratio for 1-iodooctene formed from the reaction with unactivated alumina changes from 48:52 at 5 minutes to 51:48 at 135 minutes and to 56:44 after 24 hours (Fig. 27). What is interesting is that the E:Z ratio changes less with activated alumina (Fig. 28). The reason for this anomaly is unclear.

The most significant finding was the difference in yields between activated and unactivated alumina. The yield was found to be at least twice as high with unactivated alumina as presented in Figure 29. There are many possible explanations for the lower yield using activated alumina, but much uncertaintity stills remains. For example, the desired product could interact with the alumina in such a way that it is destroyed or one of the starting materials (i.e. iodine) could be interacting with alumina in such a way that it hinders the

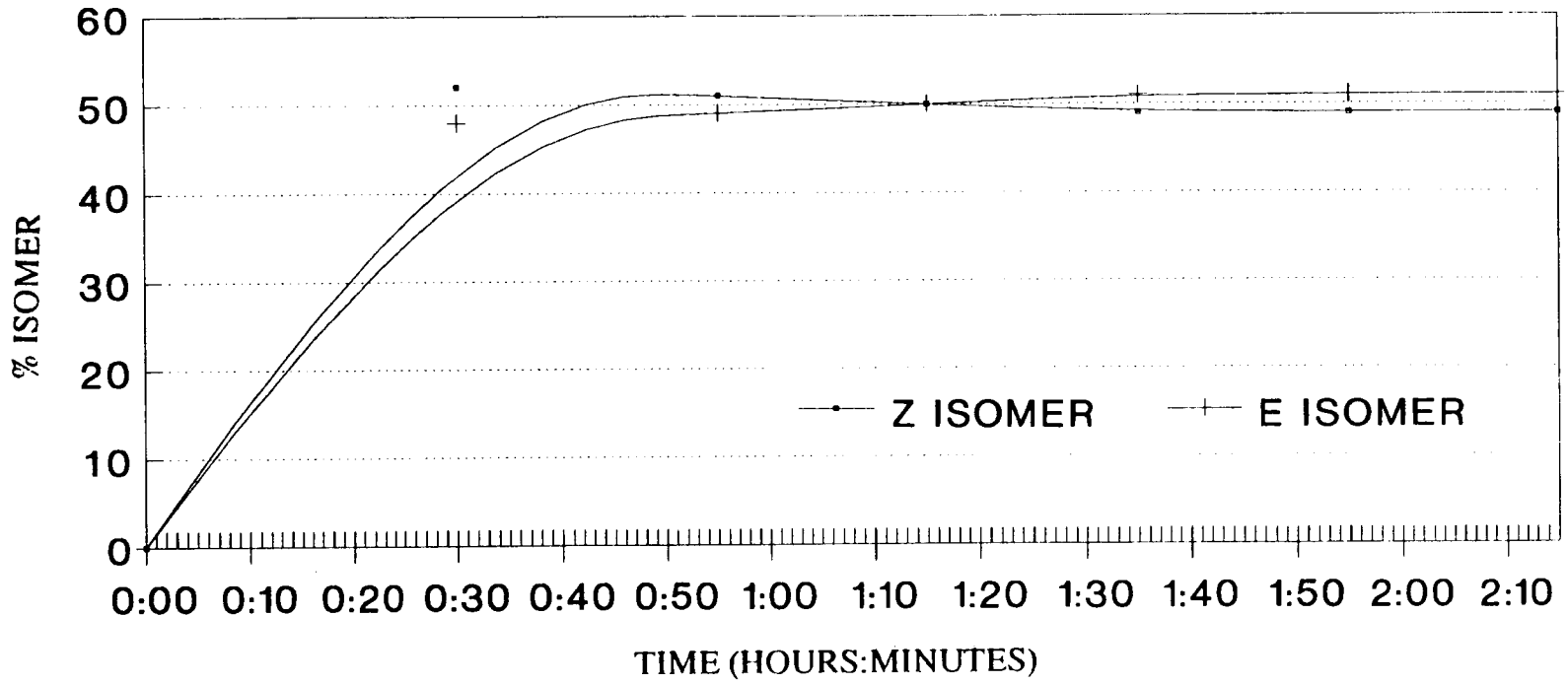


FIGURE 27. Relative Yields of (E)- and (Z)-1-Iodo-1-octene Derived from Slurry Method, Utilizing Unactivated Alumina and a 1:1 Molar Ratio of Iodine and 1-Octenylboronic Acid, vs Time.

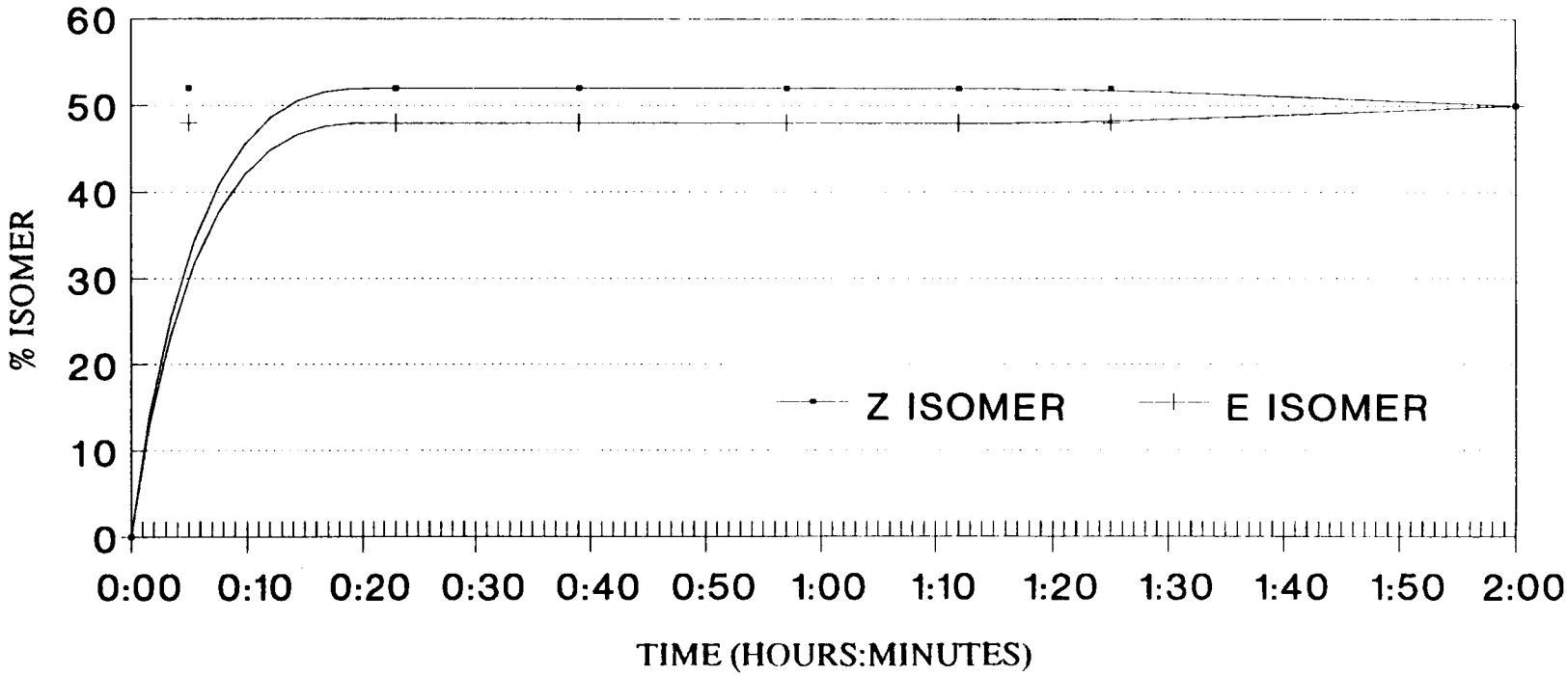


FIGURE 28. Relative Yields of (E)- and (Z)-1-Iodo-1-octene Derived from Slurry Method, Utilizing Activated Alumina and a 1:1 Molar Ratio of Iodine and 1-Octenylboronic Acid vs Time.

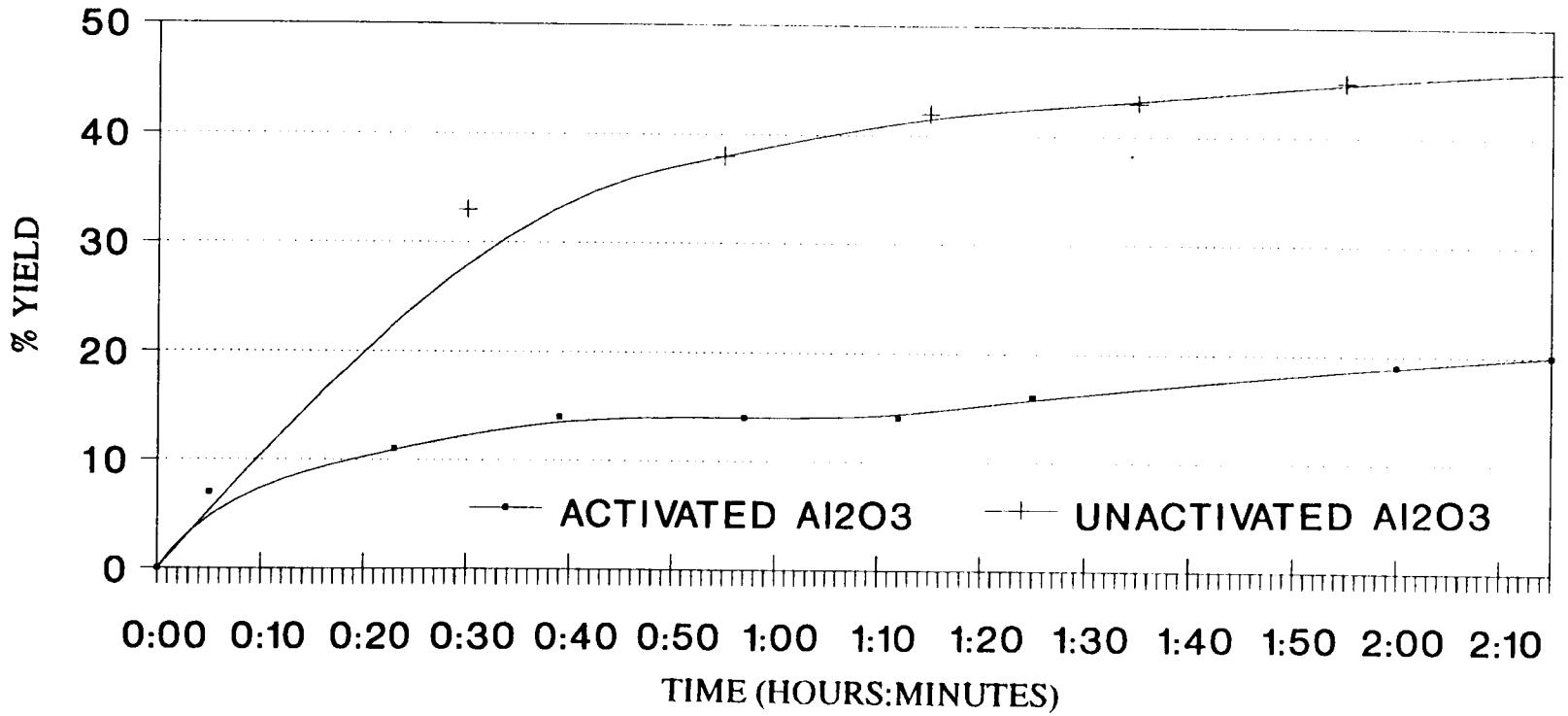


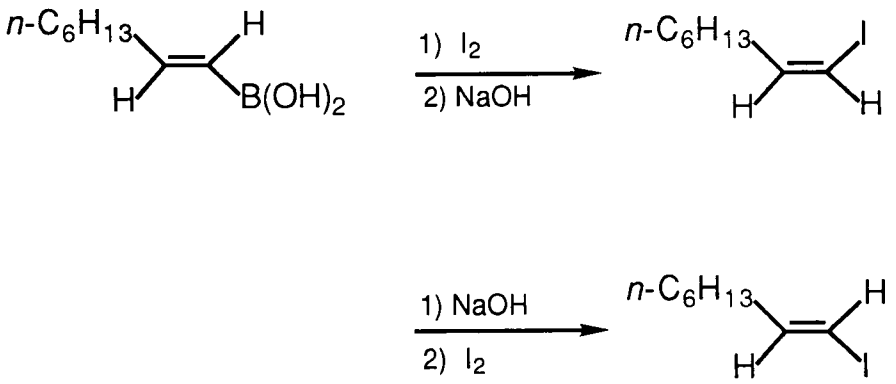
FIGURE 29. % Yield of 1-Iodo-1-octene Comparing Activated and Unactivated Alumina vs Time (1:1 Molar Ratio of Iodine and 1-Octenylboronic Acid).

production of the desired product. Much data are still needed to draw any specific mechanistic conclusions.

3. Reverse Additions

As mentioned previously, reverse addition of base and iodine (Brown's method[28]) favors the production of the Z isomer (eq. 22).[35]

(22)



In an attempt to change and/or control the approximate 1:1 ratio of geometric isomers being formed from (E)-1-octenylboronic acid with alumina and iodine, a reverse addition experiment was attempted. This involved the following: .001 mol of (E)-1-octenylboronic acid was dissolved in ether. To the ethereal solution was added .001 mol of molecular iodine. The solution was stirred for 5 minutes, and 10 grams of unactivated Brockman activity 1 neutral alumina was then added. The yields of the iodinated products were determined by injecting a known amount of decane as the internal standard into the reaction mixture and then analyzing the reaction mixture by removing aliquots periodically and performing GC.

a. Unactivated Alumina

The E:Z ratios did not change with this reverse addition method, but an unexpected result involving the yield was observed. The reverse addition method allows the reaction to proceed almost twice as fast as the previously described methodology. Using a 1:1 molar ratio of iodine and (E)-1-octenylboronic acid the reaction yield levels off at 70% in 20 minutes. Although a yield of greater than 99% was recorded in 24 hours, the reaction was relatively slow after 20 minutes. Thus, two equivalents of iodine were added in the reverse addition method in an attempt to obtain a 100% yield more quickly. A 100% yield of product was indeed obtained in less than 20 minutes using a 2:1 molar ratio of iodine and boronic acid with the reverse addition method. A graph showing the yields of 1 mol versus 2 mol of iodine using the reverse addition method is presented in Figure 30.

b. Activated Alumina

The reverse addition experiment was also attempted with activated alumina to see if the E:Z ratios and yield would be affected. Here again the E:Z ratio was unchanged and the reaction was faster. Using 2 equivalents versus 1 equivalent of iodine clearly doubles the reaction rate when the reverse addition method is used (Fig. 31).

The results of the reverse addition method comparing the effect of activated and unactivated alumina with a 1:1 molar ratio of iodine and boronic acid are graphed in Figure 32. Likewise, the results of the reverse addition method comparing activated and unactivated alumina with a 2:1 ratio of iodine and boronic acid are graphed in Figure 33.

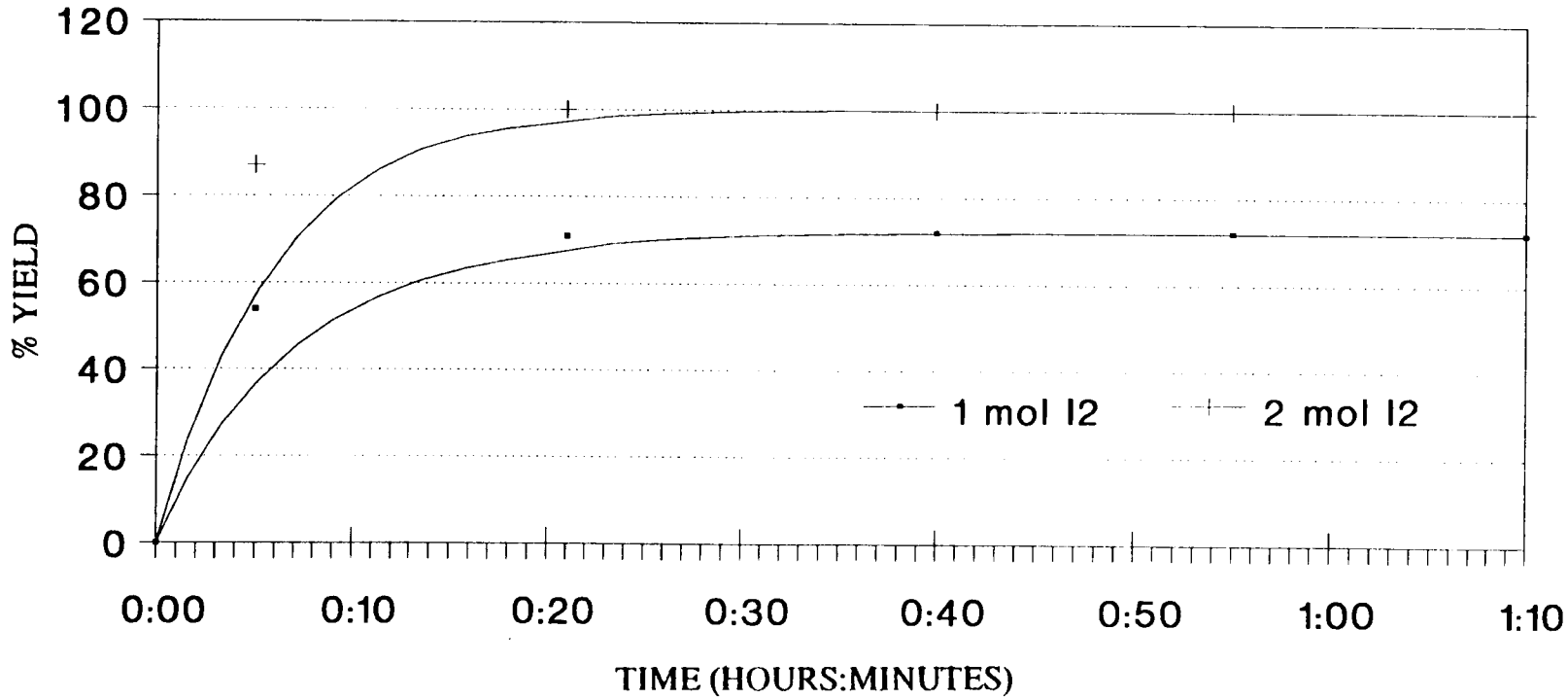


FIGURE 30. % Yield of 1-Iodo-1-octene Comparing 1 mole and 2 moles of Iodine on Unactivated Alumina vs Time.

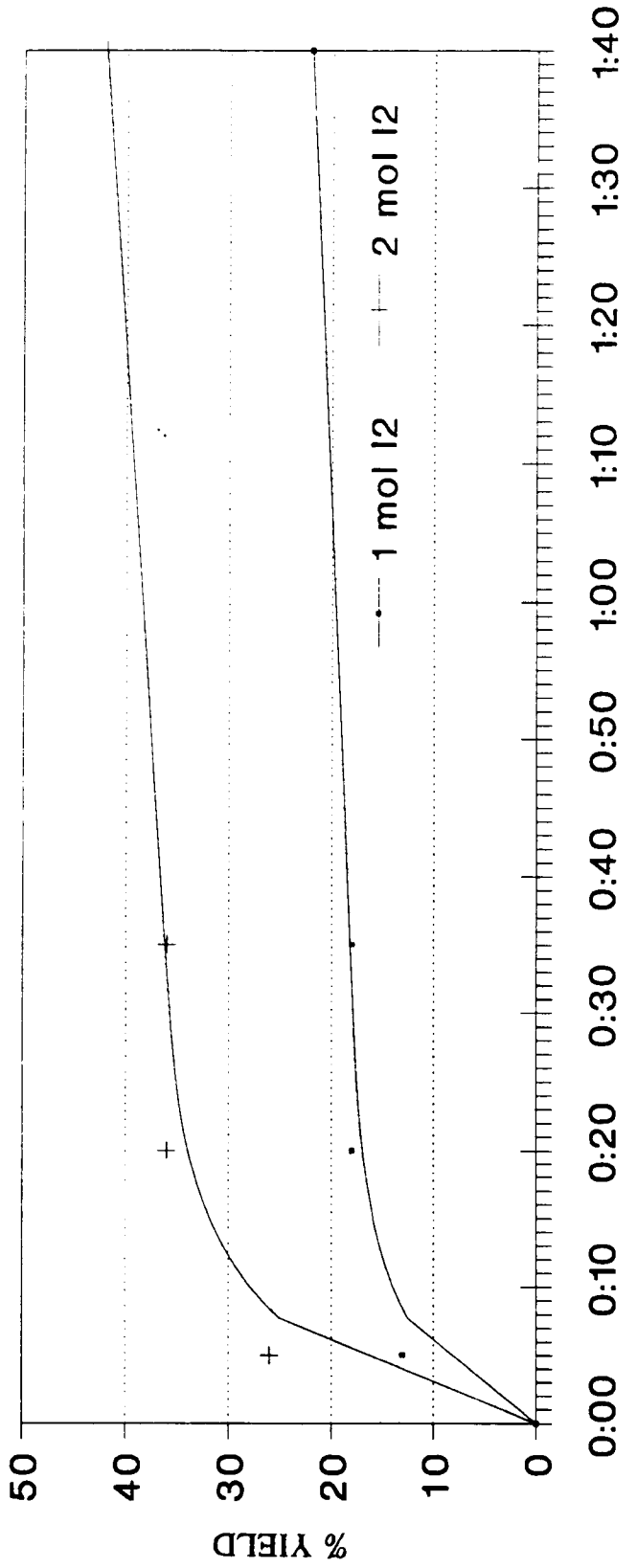


FIGURE 31. % Yield of 1-Iodo-1-octene Comparing 1 mole and 2 moles of Iodine on Activated Alumina vs Time.

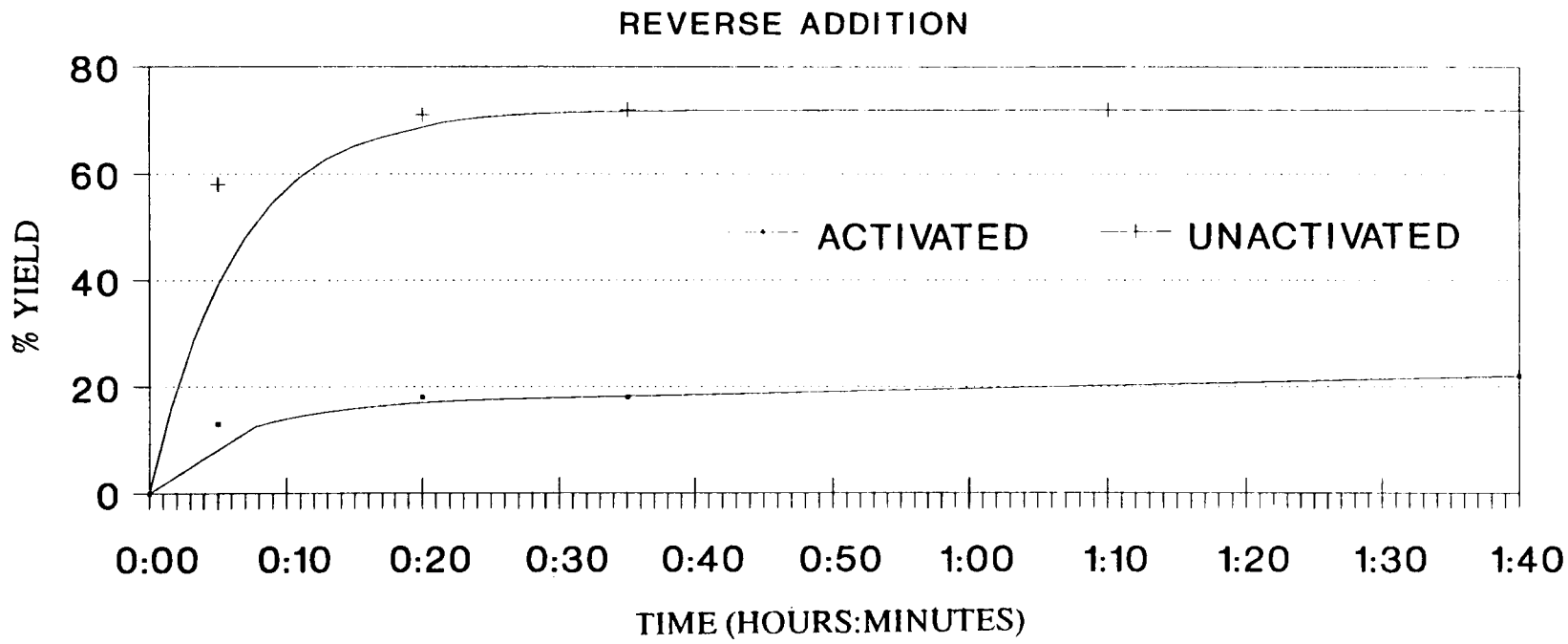


FIGURE 32. % Yield of 1-Iodo-1-octene Comparing Activated and Unactivated Alumina with a 1:1 Molar Ratio of Iodine and 1-Octenylboronic Acid vs Time.

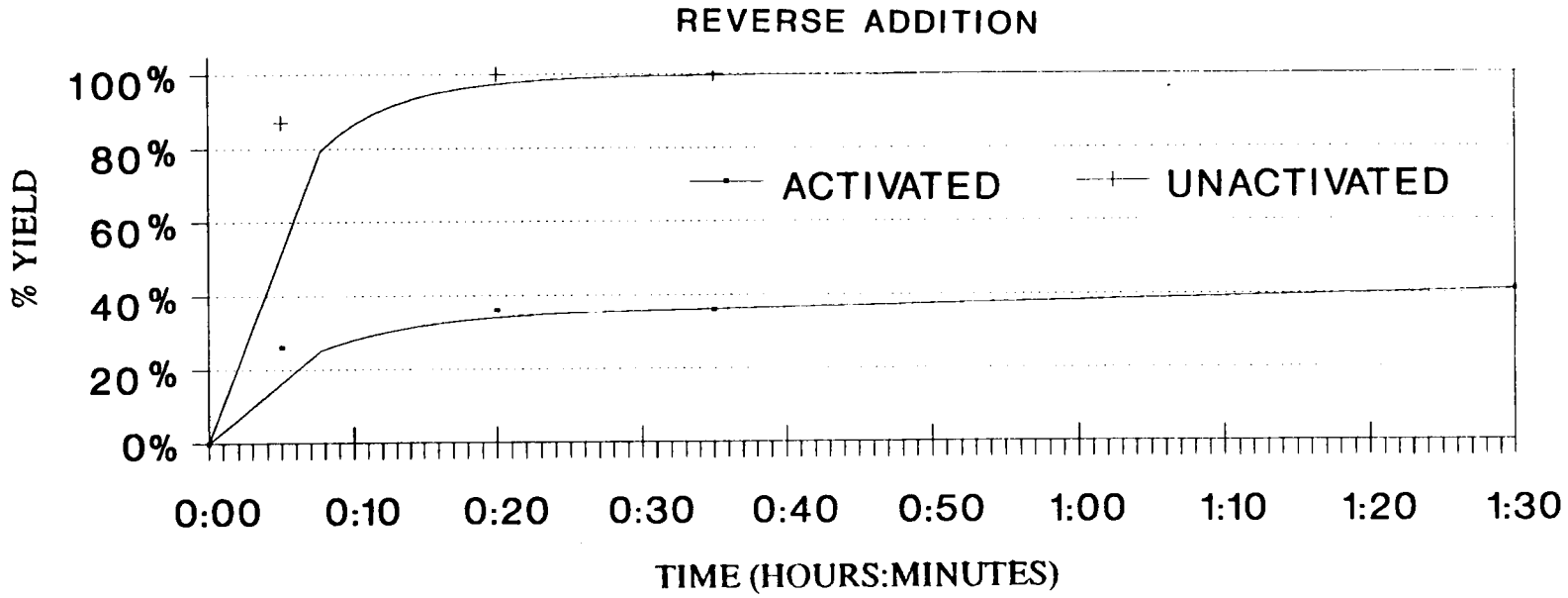


FIGURE 33. % Yield of 1-Iodo-1-octene Comparing Activated and Unactivated Alumina with a 2:1 Molar Ratio of Iodine and 1-Octenylboronic Acid vs Time.

It is now clear from the previous experiments, that the optimal reaction conditions for terminal vinylic boronic acids reacting with iodine in the presence of alumina is with unactivated alumina, a two molar excess of iodine, and the reverse addition method.

I. Conclusion

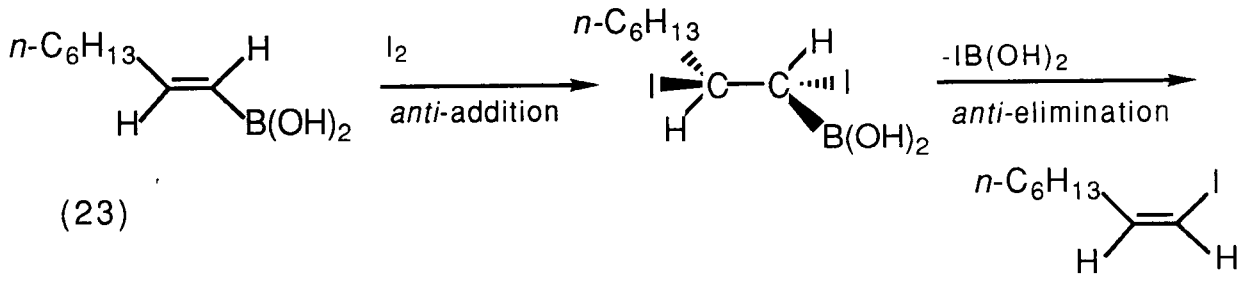
There are many interesting phenomena taking place when iodine reacts with terminal vinyl boronic acids in the presence of alumina. To address any one of the aspects with absolute certainty is not possible. Therefore, the following is a summary of postulations from current journals and research findings in an attempt to explain the product distribution for the reaction of iodine with boronic acids in the presence of alumina.

The first topic of interest is the interaction of alumina and the boron moiety. It has been clearly established from the pioneering work of Brown[36] that, for the vinylic boron group to be replaced by iodine, the boron group must first be tetravalent (neutralized by base or a nucleophile). Therefore, it can be hypothesized from this research that alumina is a significant enough neutralizing force for the boron moiety because it is replaced in the presence of iodine. The nature of this bond is unclear; it may be a coulombic electrostatic interaction or a full covalent bond between the unhybridized vacant p orbital of the trivalent boron and an oxygen of the alumina surface. Nevertheless, it is significant and does exist.

In an attempt to learn more about the interaction of the trivalent boron and the oxygen of the alumina, solid state boron NMR (SSBNMR) was employed. The major feature of SSBNMR is that

trigonal boron appears as a doublet whereas tetravalent boron appears as a singlet due to its having a relatively small quadrupolar coupling.[37] A sample of 1-octenylboronic acid was prepared in the presence of alumina, as described previously, and with 1% sodium tetraphenylboron as the internal standard. The spectrum obtained shows a single broad peak at 7.0 ppm relative to sodium tetraphenylboron (Fig. 34). This singlet further provides evidence of tetravalent boron and supports direct coordination of the alumina with the vacant unhybridized p orbital of the boron.[38]

In an attempt to explain how a mixture of geometric isomers is produced from straight chain vinyl boronic acids, one must be open minded to a possible mixture of mechanisms. The *anti*-addition of iodine to the alkene, followed by the *anti*- and *syn*-elimination mechanism affording the cis and trans isomers, respectively, is plausible (eq. 23).



(23)

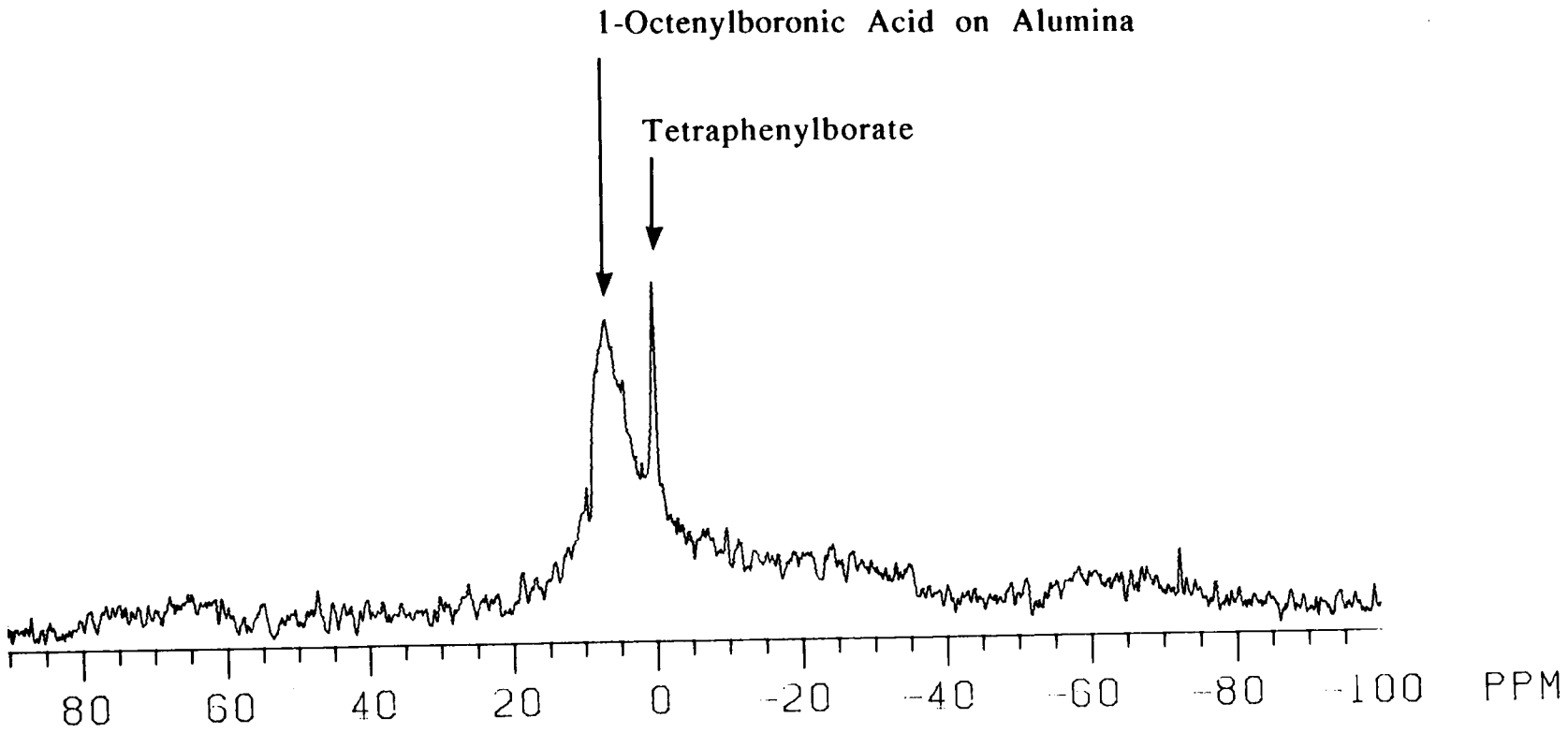
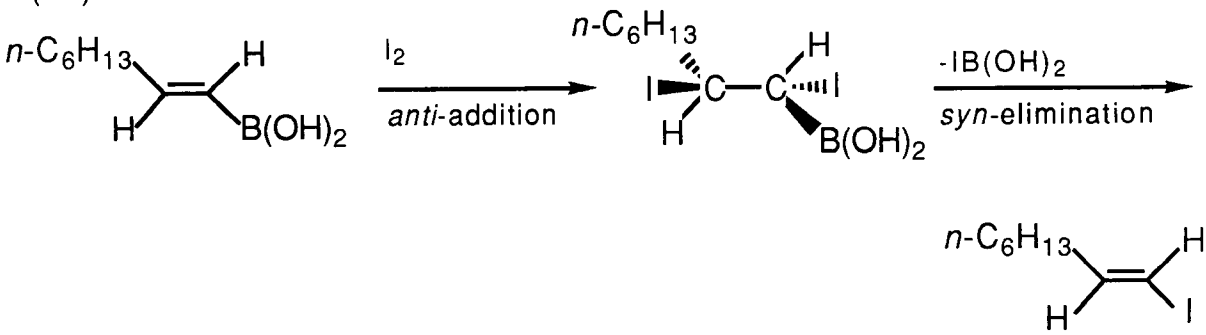


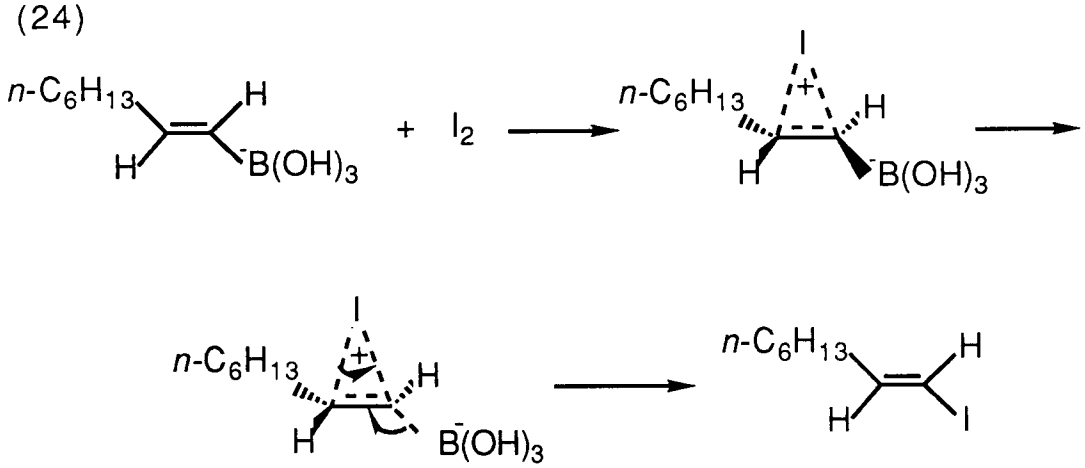
FIGURE 34. Solid State ^{11}B NMR (200 MHz, Sodium Tetraphenylborate) of 1-Octenylboronic Acid-Alumina Complex Showing Tetravalent Shift of 1-Octenylboronic Acid.

(23) con't



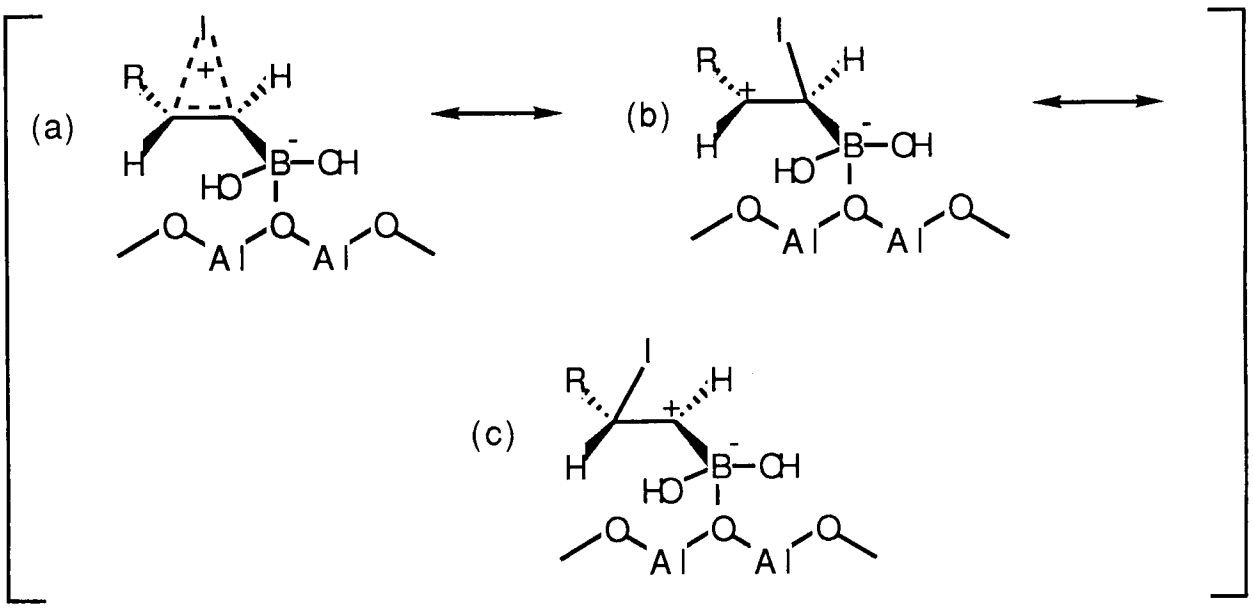
One could also imagine the iodine reacting with the alkene to form an iodonium ion which then undergoes some bond shifting to form the vinyl iodide (eq. 24). Yet, none of these possible mechanisms give a definite explanation for the distribution of products presented in this research.

(24)



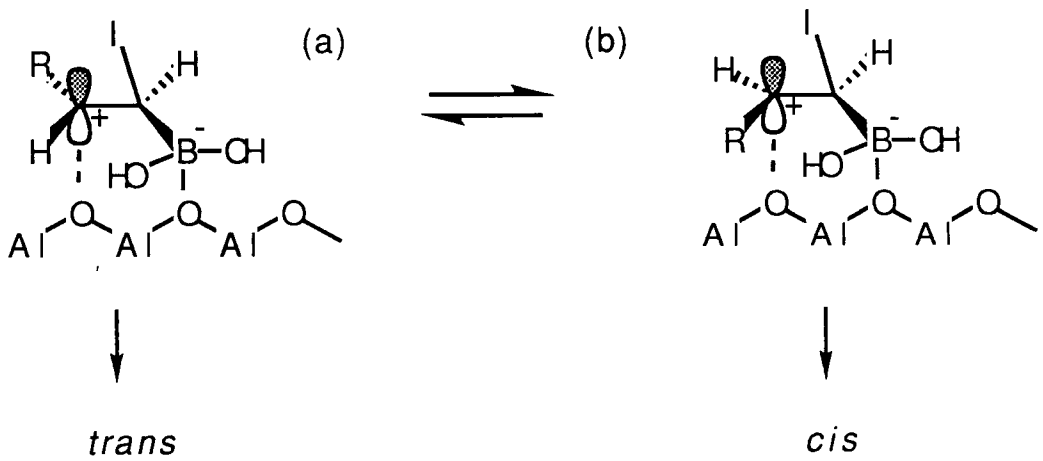
Examining the iodonium intermediate more closely, a plausible mechanism which accounts for the product distribution can be hypothesized. The iodonium ion intermediate is represented by the following three resonance contributors (a), (b), and (c) (eq. 25).

(25)



An even more stabilized iodonium ion intermediate can be imagined when the oxygen (from the surface of alumina) interacts with the electron deficient C_2 of the alkene (eq. 26).

(26)



In intermediate (b) (eq. 26) there could exist a steric effect between the tetravalent boron group and the R group (if the R group is large and bulky). Therefore, as the lone pairs of oxygen (from the surface

of alumina) approach the electron deficient C_2 of the alkene, the bulky R group will orientate itself trans to the tetravalent boron group, as depicted in intermediate (a). The trans orientation of intermediate (a) will then afford the trans vinyl iodide. This type of reasoning can account for the formation of only (E)-1-iodo-2-phenyl-1-ethene and (E)-3,3-dimethyl-1-butene from their corresponding trans vinyl boronic acids (i.e. none of the cis isomer was formed when large bulky R groups were present). Also, this type of reasoning can rationalize the formation of the 50:50 mixture of cis and trans vinyl iodides from straight chain R groups substituted on the alkene. For example, in these alkenes there is a minimal steric interaction between the tetravalent boron group and the straight chain R group as the lone pairs of the oxygen (from the surface of alumina) approach the electron deficient C_2 of the alkene. Therefore, the straight chain R group will orientate itself indiscriminately cis and trans to the tetravalent boron group (as seen in eq.26), affording a circa 50:50 mixture of cis and trans vinyl iodides. The R group could then have an effect not only on the geometric isomer ratio being produced, but also on the overall yield of the reaction. The overall percent yields and the E:Z ratios for the varying R groups are presented in Table 2. The reason for the various yields is uncertain.

The reaction between iodine, alumina, and the boronic acid moiety is a promising synthetic procedure for the radioiodination of medicinal compounds. The boronic acid-alumina complex is stable for long periods of time; therefore, one could imagine a packed

TABLE 2

The Overall Yields and E:Z Ratios For RCH=CHI Using the Slurry Method.[a]

	% Yield[b] (E:Z ratio)		
R Group	60 min.	120 min.	Max. Yield
n-C_6H_{13}	40 (50:50)	46 (51:49)	61 (56:44), 24 hrs
n-C_8H_{17}	49 (54:46)	54 (55:45)	66 (60:40), 24 hrs
C_6H_5	50 (99:1)	55 (99:1)	96 (99:1), 24 hrs
t-Butyl	39 (100:0)	37 (100:0)	55 (100:0), 15 min
$ClCH_2(CH_2)2$	82 (74:26)	76 (75:25)	82 (74:26), 50 min
$HOCH_2(CH_2)8$	45 (49:51)	51 (54:46)	59 (58:42), 24 hrs

[a] The slurry method described in the text uses a 1:1 molar ratio of iodine and boronic acid.

[b] The yields and E:Z ratios were determined by GC.

column of the boronic acid-alumina complex (made up industrially and sold as a kit) and then introducing radioactive iodine through the column (prior to use of the imaging agent at the hospital) affording pure radioactive vinyl iodine imaging agents ready for a patient's use.

Chapter III

Experimental

A. Materials

1. Solvents

Methylene Chloride, CH_2Cl_2, Mallinckrodt, ACS grade, was used as purchased.

Acetone, Mallinckrodt, ACS grade acetone was used without further purification.

Distilled Water, Departement distilled water was used without further purification.

Anhydrous Diethyl Ether, Ether, Mallinckrodt, ACS grade, anhydrous diethyl ether was used as purchased.

Hexanes, Mallinckrodt, ACS grade hexanes were used as purchased.

Tetrahydrofuran, THF, Fischer, pure grade THF was purified daily by distillation over excess lithium aluminum hydride or sodium benzophenone ketyl, which was prepared by adding 1-2 g of metallic sodium and 1-2 g of benzophenone to 500ml of THF to attain the characteristic deep blue or purple color. The distilled THF was stored under nitrogen.

2. Gases

Argon, Ar. MG Industries, prepurified Ar was used without further purification.

Nitrogen, N_2. MG Industries, prepurified N_2 was used without further purification.

3. Reagents

Normal Butyllithium, *n*-BuLi. Aldrich, *n*-BuLi (1.6 M in hexanes) was used as purchased.

Lithium Aluminum Hydride, LAH. Aldrich, LAH was used as received.

1-Octyne, 1-Decyne, 3,3-Dimethyl-1-butyne, Phenylacetylene, and 5-Chloro-1-pentyne, Farchan, was used as received.

Catecholborane, Aldrich, was used as received.

2-Methyl-2-butene, Phillips, was distilled from LAH prior to use.

Borane-Methyl sulfide, Aldrich, was dissolved in appropriate solvent to give an approximate 2.5 M solution. The reagent was stored at 0^0 C and standardized by measuring the hydrogen evolved on hydrolysis in a 1:1:1 mixture of glycerol, water, and methanol.

Sodium Metal, Fischer Scientific, reagent grade Na was used as purchased.

Iodine, Fischer, was used as received.

Glacial Acetic Acid, Fischer, was used as received.

Hydrogen Peroxide, 30%, Fischer, was used as received.

Magnesium Sulfate, Fischer, was used as received.

Sodium Thiosulfate, Aldrich, was used as received.

1-(Trimethylsilyl)-imidazole, Aldrich, was used as received.

B. Experimental Methods

1. Physical Properities and Analytical Methods

Nuclear magnetic resonance spectra were recorded either on a 90 MHz JEOL FX-90Q spectrometer or a 200 MHz NICOLET spectrometer. Samples were run in $CDCl_3$ with 1% tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in parts per million downfield from TMS.

Gas chromatograms were recorded with a Hewlett-Packard 5890A equipped with a 30 m x 1/8" column packed with 30% SE-30 by weight on Chromsorb W as the solid support.

GC/MS were recorded on the Hewlett-Packard 5970 series Mass Selective Detector.

2. Apparatus and Manipulation of Reagents

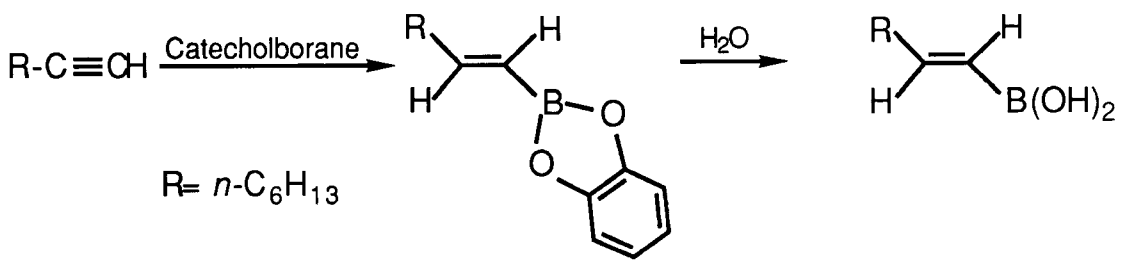
Due to the sensitivity of most organoborane compounds toward air, and in some cases water, catecholborane was transferred with a dry, argon-flushed syringe and allowed to react under an atmosphere of dry argon. All glassware, syringes, and needles were oven-dried at 100^0 C for 6 hours, assembled hot, and cooled under a stream of argon before use. The reactions were performed under a slight positive pressure of argon using a pressure-regulated argon source with a mercury bubbler.[39]

C. Experimental Procedures

1. Reaction of Alkynes with Catecholborane

The following literature procedure for the hydroboration of 1-octyne (eq. 27) developed by Brown is a representative example of a terminal alkyne reacting with catecholborane .[40]

(27)



a. 1-Octyne

A 50 ml flask containing a magnetic stirring bar was connected to a mercury bubbler by means of a tube containing a sidearm fitted with a rubber stopple. A stream of nitrogen was introduced through a hypodermic needle penetrating the rubber stopple, and the apparatus was dried by flaming. The apparatus was allowed to cool, and a static nitrogen pressure was maintained. With the aid of a hypodermic syringe, 4.29g (0.04 mol) of 1-octyne was introduced at 0^0 C followed by 4.84g (0.04 mol) of catecholborane. The stirred mixture was stirred for two hours at 70^0 C. The hydroborated adduct was cooled to room temperature and 100 ml of water was added. The mixture was stirred for two hours at room temperature to effect the hydrolysis of the ester. The white crystalline product was filtered and recrystallized from a mixture of ether and hexane (the boronic acid is soluble in ether and insoluble in hexane) to give 6.00 g (95% yield) of (E)-1-octenylboronic acid: mp 104-105^0 C; ^{1}H NMR (200 MHz, $CDCl_3$) (Fig. 35): 6.5 (1 H, m), 5.5 (1 H, d/t), 4.2 (2 H, OH, br), 2.1 (2 H, m), 1.4 (8 H, m), .8 (3 H, t).

b. Other Alkynes

All other terminal alkynes were hydroborated with catecholborane following the general procedure above for 1-octyne with a few exceptions. Table 3 lists the different reaction times and temperatures for each terminal alkyne examined.

2. Activation of Alumina

Brockman activity grade 1 neutral alumina was dehydrated (activated) by heating under vacuum (less than .5mm Hg) for 15 hours at 400^0 C utilizing the apparatus designed by Pagni.[41]

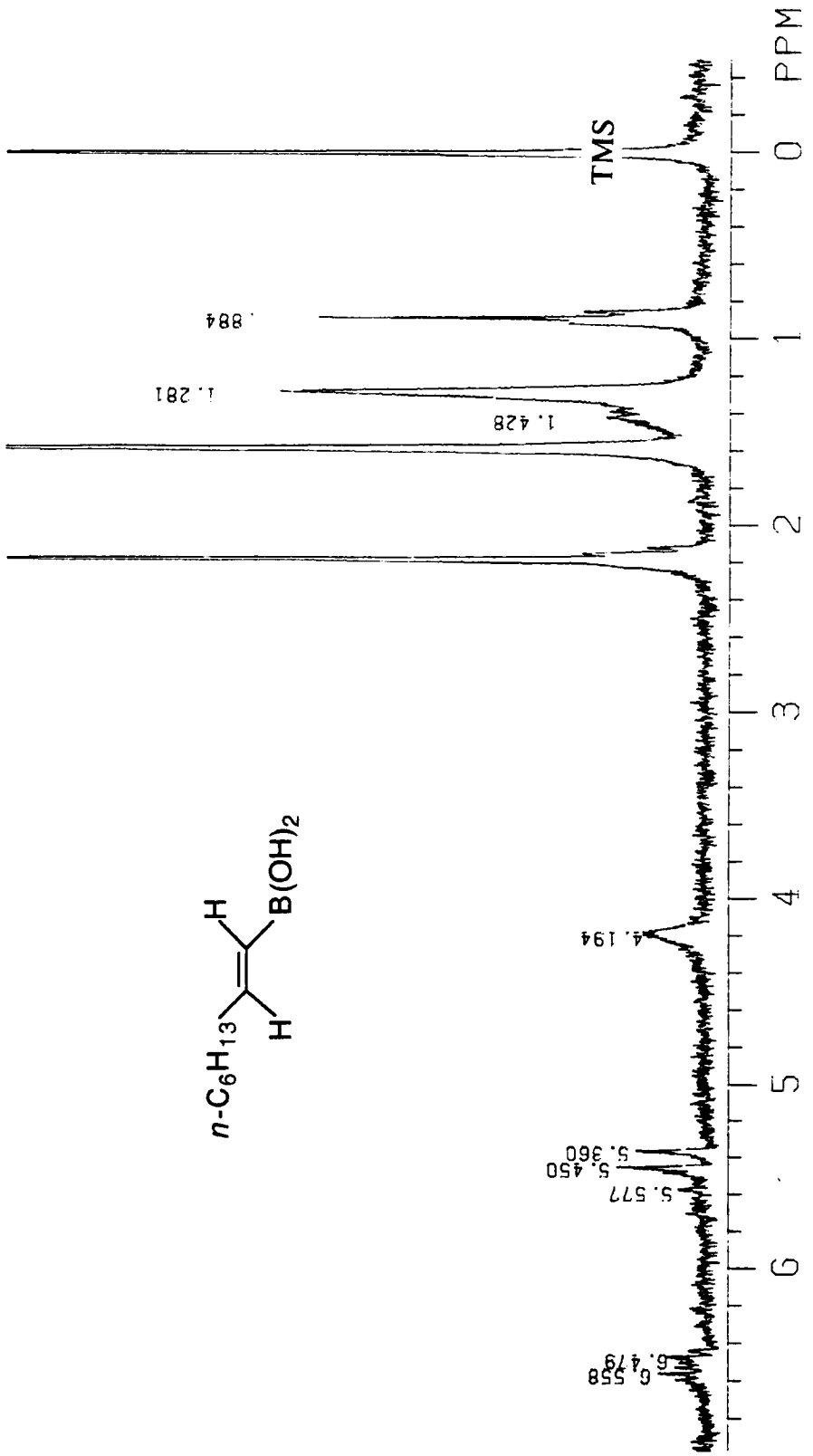


FIGURE 35. ^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of (E)-1-Octenylboronic Acid.

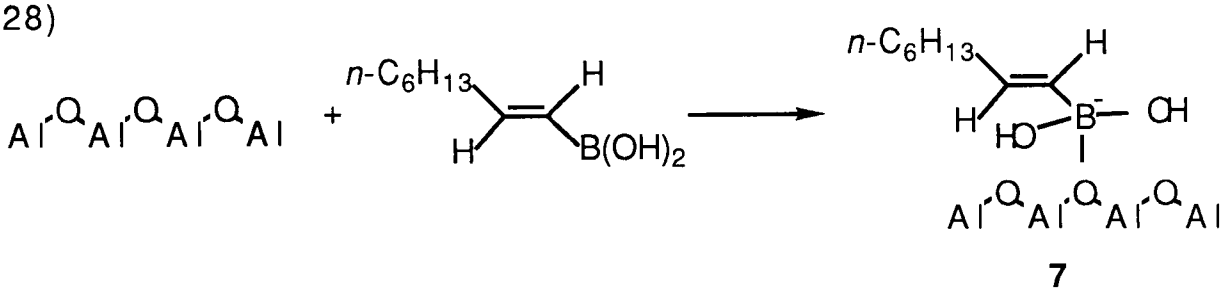
TABLE 3

Different Temperatures and Reaction Times forTerminal Alkynes Reacting with Catecholborane to Afford Optimum Results.

Alkyne	Temperature (^{0}C)	Time (hrs)
1-Decyne	70	2
3,3-Dimethyl-1-butyne	R.T	4 8
Phenylethyne	70	4
11-Hydroxy-1-undecyne	70	2
5-Chloro-1-pentyne	R.T.	2 4
4,4-Dimethyl-2-pentyne	70	8
3-Hexyne	70	4
4-Octyne	R.T.	4 8
Trimethylsilylacetylene	R.T	4 8

3. Preparation of the Alumina-Boronic Acid Complex (eq. 28)

(28)



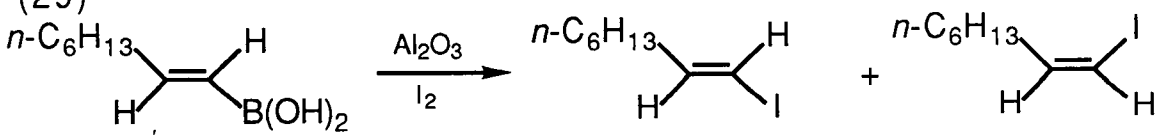
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To a 100 mL round-bottom flask equipped with magnetic stirring bar, 10 g of either activated or unactivated Brockman activity grade 1 alumina and 15 ml of ether were added. To the slurry mixture 0.001 mol of the desired boronic acid dissolved in 15 ml of ether was then added to the slurry mixture. The slurry was allowed to mix well for five minutes. The ether was then removed by evaporation and the boronic acid-alumina complex 7 remained.

4. Reaction of Alumina-Boronic Acid Complex with Iodine

a. (E)-1-Octenylboronic Acid (eq. 29)

(29)



Into a 100 mL round-bottom flask equipped with a magnetic stirring bar, the (E)-1-octenylboronic acid-alumina complex, prepared as described previously (10 g unactivated alumina and 0.0010 mol of desired boronic acid) was added. Ethyl ether (15 mL) and 0.00050 mol of decane (as the internal standard) were added to

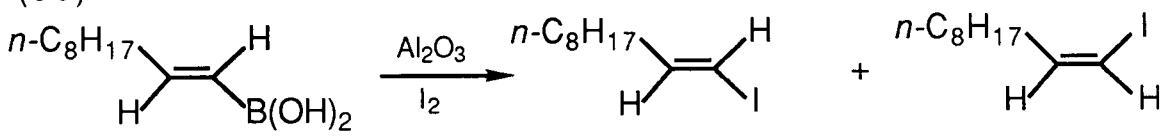
the flask and to the slurry was added 0.0010 mol of iodine dissolved in 25 mL of ether. The reaction was followed by GC by removal of 1 mL aliquots at convenient time intervals. A 65 % overall yield was obtained after 24 hours (a 56:44 ratio of E:Z isomers, respectively). After 24 hours the ether solution was decanted from the alumina. Upon removal of the solvent by evaporation, an oily product remained. The product compositionwas determined by ^1H NMR and GC/MS to be a mixture of (E)- and (Z)-1-iodo-1-octene.

NMR spectral characteristics of (E)-1-iodo-1-octene ($CDCl_3$) (ppm): 6.5 (1 H, m), 5.96 (1 H, d/t), 2.1 (2 H, m), 1.4 (8 H, m), .8 (3 H, t).

NMR spectral characteristics of (Z)-1-iodo-1-octene ($CDCl_3$) (ppm): 6.07 (2 H, m), 2.1 (2 H, m), 1.4 (8 H, m), .8 (3 H, t).

b. (E)-1-Decenylboronic Acid (eq. 30)

(30)



Into a 100 mL round-bottom flask equipped with a magnetic stirring bar, (E)-1-decenylboronic acid-alumina complex, prepared as described previously (10 g unactivated alumina and 0.0010 mol of desired boronic acid) was added. Ethyl ether (15 mL) and 0.00050 mol of decane (as the internal standard) was added into the flask and to the slurry was added 0.0010 mol of iodine dissolved in 25 mL of ether. The reaction was followed by GC by removal of 1 mL aliquots at convenient time intervals. A 66 % overall yield was obtained after

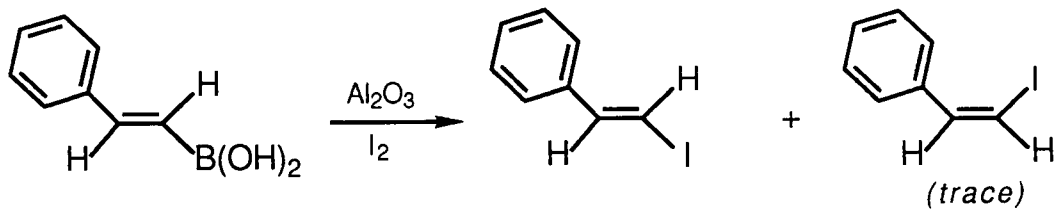
24 hours (a 57:43 ratio of E:Z isomers, respectively). After 24 hours the ether solution was decanted from the alumina. Upon removal of the solvent by evaporation, an oily product remained in the flask. The product composition was determined by ^1H NMR to be a mixture of (E)- and (Z)-1-iodo-1-decene.

NMR spectral characteristics of (E)-1-iodo-1-decene ($CDCl_3$) (ppm): 6.5 (1 H, m), 5.95 (1 H, d/t), 2.0 (2 H, m), 1.25 (12 H, m), .8 (3 H, t).

NMR spectral characteristics of (Z)-1-iodo-1-decene ($CDCl_3$) (ppm): 6.15 (2 H, m), 2.0 (2 H, m), 1.25 (12 H, m), .8 (3 H, t).

c. (E)-2-Phenylethenylboronic Acid (eq. 31)

(31)



Into a 100 mL round-bottom flaskequipped with a magnetic stirring bar, the (E)-2-Phenylethenylboronic acid-alumina complex as described previously (10 g unactivated alumina and 0.0010 mol of desired boronic acid)was added. Ethyl ether (15 mL) and 0.00050 mol of decane (as the internal standard) was added into the flask and to the slurry was added 0.0010 mol of iodine dissolved in 25 mL of ether. The reaction was followed by GC by removal of 1 mL aliquots at convenient time intervals. A 96% overall yield was obtained after 24 hours (greater than 99% E isomer). After 24 hours the ether solution was decanted from the alumina. Upon removal of the

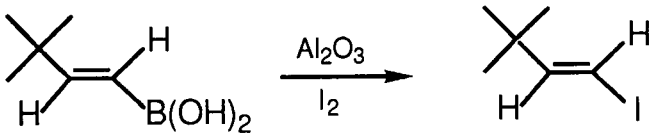
solvent by evaporation, an oily product remained in the flask. The product was determined by ^1H NMR to be (E)-1-iodo-2-phenyl-1-ethene. GC/MS revealed a trace of (Z)-1-iodo-2-phenyl-1-ethene to have been formed in the reaction.

NMR spectral characteristics of (E)-1-iodo-2-phenyl-1-ethene ($CDCl_3$) (ppm): 7.4 (1 H, d), 7.3 (5 H, s), 6.8 (1 H, d).

NMR spectral characteristics of (Z)-1-iodo-2-phenyl-1-ethene ($CDCl_3$) (ppm): 7.3 (5 H, s), 7.1 (2 H, m).

d. (E)-3,3-Dimethyl-1-butenylboronic Acid (eq. 32)

(32)

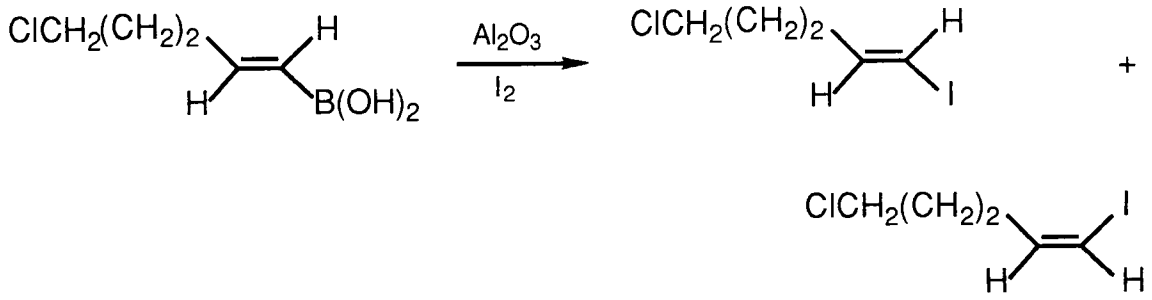


Into a 100 mL round-bottom flask equipped with a magnetic stirring bar, the (E)-3,3-Dimethyl-1-butenylboronic acid-alumina complex prepared as described previously (10 g unactivated alumina and 0.0010 mol of desired boronic acid) was added. Ethyl ether (15 mL) and 0.00050 mol of decane (as the internal standard) were added to the flask and to the slurry was added 0.0010 mol of iodine dissolved in 25 mL of ether. The reaction was followed by GC by removal of 1 mL aliquots at convenient time intervals. A 55% overall yield was determined after 15 minutes (greater than 99% E isomer). After 15 minutes the ether solution was decanted from the alumina. Upon removal of the solvent by evaporation, an oily product remained. The product was determined by ^1H NMR to be (E)-3,3-dimethyl-1-iodo-1-butene.

NMR spectral characteristics of (E)-3,3-dimethyl-1-iodo-1-butene ($CDCl_3$) (ppm): 6.4 (1 H, d), 5.4 (1 H, d), 1.2 (9 H, s).

e. (E)-5-Chloro-1-pentenylboronic Acid (eq. 33)

(33)



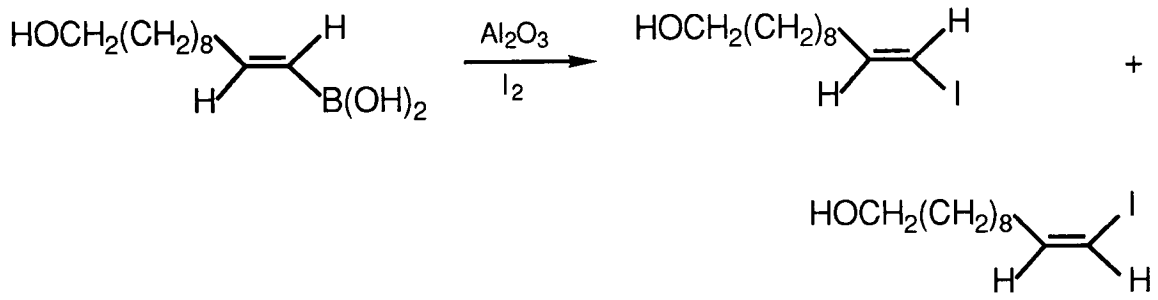
Into a 100 mL round-bottom flask equipped with a magnetic stirring bar, the (E)-5-Chloro-1-pentenylboronic acid-alumina complex prepared as described previously (10 g unactivated alumina and 0.0010 mol of desired boronic acid)was added. Ethyl ether (15 mL) and 0.00050 mol of decane (as the internal standard) were added to the flask and to the slurry was added 0.0010 mol of iodine dissolved in 25 mL of ether. The reaction was followed by GC by removal of 1 mL aliquots at convenient time intervals. A 86% overall yield was determined after 50 minutes (a 74:26 ratio of E:Z isomers respectively). After 50 minutes the ether solution was decanted from the alumina. Upon removal of the solvent by evaporation, an oily product remained. The product was determined by ^1H NMR to be a mixture of (E)- and (Z)-5-chloro-1-iodo-1-pentene.

NMR spectral characteristics of (E)-5-chloro-1-iodo-1-pentene ($CDCl_3$) (ppm): 6.43 (1 H, d/t), 6.1 (1 H, d), 3.55 (2 H, t), 2.25 (2 H, m), 1.9 (2 H, m).

NMR spectral characteristics of (Z)-5-chloro-1-iodo-1-pentene ($CDCl_3$) (ppm): 6.25 (2 H, m), 3.55 (2 H, t), 2.25 (2 H, m), 1.9 (2 H, m).

f. (E)-11-Hydroxy-1-undecenylboronic Acid (eq. 34)

(34)



Into a 100 mL round-bottom flask equipped with a magnetic stirring bar, the (E)-11-Hydroxy-1-undecenylboronic acid-alumina complex prepared as described previously (10 g unactivated alumina and 0.0010 mol of desired boronic acid)was added. Ethyl ether (15 mL) and 0.00050 mol of decane (as the internal standard) were added to the flask and to the slurry was added 0.0010 mol of iodine dissolved in 25 mL of ether. The reaction was followed by GC by removal of 1 mL aliquots at convenient time intervals. A 59 % overall yield was determined after 24 hours (a 58:42 ratio of E:Z isomers respectively). After 2 hours the ether solution was decanted from the alumina. Upon removal of the solvent by evaporation, an oily product remained. The product was determined by ^1H NMR to be a mixture of (E)- and (Z)-11-hydroxy-1-iodo-1-undecene.

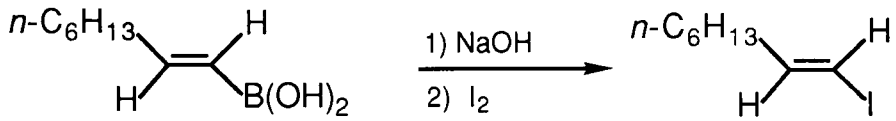
NMR spectral characteristics of (E)-11-hydroxy-1-iodo-1-undecene ($CDCl_3$) (ppm): 6.5 (1 H, d/t), 5.95 (1 H, d), 3.65 (2 H, m), .8-2.2 (16 H, m).

NMR spectral characteristics of (Z)-11-hydroxy-1-iodo-1-undecene ($CDCl_3$) (ppm): 6.07 (2 H, m), 3.65 (2 H, m), .8-2.2 (16 H, m).

5. Preparation of Standard Vinyl Iodides

a. (E)-1-Iodo-1-octene (eq. 35)

(35)

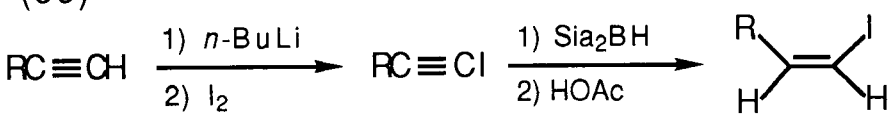


(E)-1-Octenylboronic acid (0.0050 mol, .78 g) was dissolved in ethyl ether (10 mL) in a 100 mL round-bottom flask, and a sodium hydroxide solution (7 mL, 3N) was added. The mixture was cooled to 0^0 C, and a solution of iodine (1.5g, 0.0060 mol) in ethyl ether (25 mL) was added. After stirring the mixture for 0.5 hours, the excess iodine was destroyed with a solution of saturated sodium thiosulfate. The ethereal layer was separated, and the aqueous layer was extracted with ether (2 x 25 mL). The combined ether extracts were washed with water (2 x 25 mL) and brine (1 x 25 mL) and dried over anhydrous magnesium sulfate. Upon removal of the ether by evaporation, .95 g (80% yield) of (E)-1-iodo-1-octene remained.

NMR spectral characteristics of (E)-1-iodo-1-octene ($CDCl_3$) (ppm): 6.5 (1 H, m), 5.96 (1 H, d/t), 2.1 (2 H, m), 1.4 (8 H, m), .8 (3 H, t).

b. (Z)-1-Iodo-1-octene (eq. 36)

(36)



R= n-C_6H_{13}

Into a 500 mL flask, equipped with a low temperature thermometer, magnetic stirrer and addition funnel and maintained under a nitrogen atmosphere, was placed 33.14 g (300.0 mmol) of 1-octyne and 150 mL of THF. The solution was cooled to -78^0 C (dry ice-acetone) and treated with 125 mL (300 mmol) of a 2.40 M solution of n-butyllithium in hexane. Following warming to 0-5^0 C (ice-water), 76.1 g (300 mmol) of iodine was added by means of a solid addition funnel while maintaining the temperature below 10^0 C during the addition. After warming to 25^0 C, the brown mixture was stirred for one hour and then was poured slowly into 100 mL of 10% HCl. The aqueous layer was extracted with three 50 mL portions of pentane, and the combined organic phase was washed with 30 mL of 6 N NaOH, two 30 mL portions of 10% Na_2SO_3 and four 30 mL portions of saturated NaCl. Following drying over $MgSO_4$ and removal of the solvent via rotatory evaporation, distillation through a 6 inch Vigreux column afforded 63.8 g (90%) of 1-iodo-1-octyne: bp 72-3^0 C (2.4 Torr); NMR (CCl_4) (ppm) 2.33 (2 H, t, J=6 Hz), 1.31 (8 H, m), 0.90 (3 H, t, J=6 Hz).

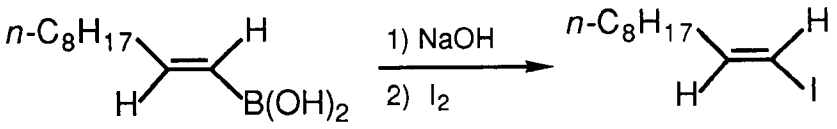
A dried 200 mL flask, fitted with a septum inlet and a magnetic stirring bar, was attached to a mercury bubbler. The flask

was flushed with dry nitrogen and then maintained under a static pressure of nitrogen. In the flask was placed 64.0 mL of a 1.00 M solution of borane-tetrahydrofuran. The flask was immersed in a salt-ice bath, and the temperature was lowered to -10^0 C. A hypodermic syringe was used to measure out 9.856 g (.1408 mol) of 2-methyl-2-butene, and the solution was then added slowly through the septum inlet to the stirred borane reagent over a period of approximately 15 minutes, maintaining the temperature at approximately 0^0 C. The reaction mixture was allowed to stand for two hours to complete the reaction. The 51.46 mL of the 1.00 M disiamylborane reagent thus obtained was allowed to react with 9.9 g (.042 mol) of 1-iodo-1-octyne under a nitrogen atmosphere at 0^0 C. The solution was then brought to room temperature and allowed to remain there for two hours to ensure completion of hydroboration. Protonolysis was then performed by adding 26 mL (10 equivalents) of anhydrous acetic acid and allowing the mixture to stir for two hours at room temperature. The entire mixture was then poured into ice water and taken up in ether. The disiamylboronic acid in the ether-tetrahydrofuran mixture was then oxidized by the addition of 36 mL of 6 N NaOH and 35 mL of 30% H_2O_2 at 0^0 C. After extraction and drying, distillation (1-10 mm Hg) afforded 5.1 mL (69%) of (Z)-1-iodo-1-octene.

NMR spectral characteristics of (Z)-1-iodo-1-octene ($CDCl_3$) (ppm): 6.07 (2 H, m), 2.1 (2 H, m), 1.4 (8 H, m), .8 (3 H, t).

c. (E)-1-Iodo-1-decene (eq. 37)

(37)

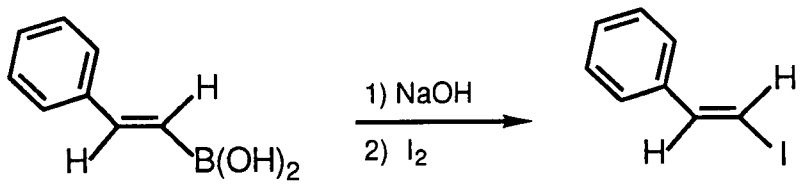


(E)-1-Decenyllboronic acid (0.0050 mol, .92 g) was dissolved in ethyl ether (10 mL) in a 100 mL round-bottom flask, and a sodium hydroxide solution (7 mL, 3N) was added. The mixture was cooled to 0^0 C, and a solution of iodine (1.5g, .0060 mol) in ethyl ether (25 mL) was added. After stirring the mixture for 0.5 hour, the excess iodine was reduceded with a solution of saturated sodium thiosulfate. The ethereal layer was separated, and the aqueous layer was extracted with ether (2 x 25 mL). The combined ether extracts were washed with water (2 x 25 mL) and brine (1 x 25 mL) and dried over anhydrous magnesium sulfate. Upon removal of the ether by evaporation, .81 g (61%) of (E)-1-iodo-1-decene remained.

NMR spectral characteristics of (E)-1-iodo-1-decene ($CDCl_3$) (ppm): 6.5 (1 H, m), 5.95 (1 H, d/t), 2.0 (2 H, m), 1.25 (12 H, m), .8 (3 H, t).

d. (E)-1-Iodo-2-phenyl-1-ethene (eq. 38)

(38)

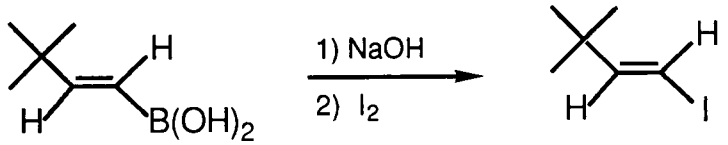


(E)-2-Phenylethenyllboronic acid (.0100 mol, 1.48 g) was dissolved in ethyl ether (20 mL) in a 100 mL round-bottom flask, and a sodium hydroxide solution (13 mL, 3N) was added. The mixture was cooled to 0^0 C, and a solution of iodine (3.5g, .014 mol) in ethyl ether (30 mL) was added. After stirring the mixture for 0.5 hour, the excess iodine was reduced with a solution of saturated sodium thiosulfate. The ethereal layer was separated, and the aqueous layer was extracted with ether (2 x 25 mL). The combined ether extracts were washed with water (2 x 25 mL) and brine (1 x 25 mL) and dried over anhydrous magnesium sulfate. Upon removal of the ether by evaporation, 1.6 g (69 % yield) of (E)-1-iodo-2-phenyl-1-ethene remained.

NMR spectral characteristics of (E)-1-iodo-2-phenyl-1-ethene ($CDCl_3$) (ppm): 7.4 (1 H, d), 7.3 (5 H, s), 6.8 (1 H, d).

e. (E)-3,3-Dimethyl-1-iodo-1-butene (eq. 39)

(39)



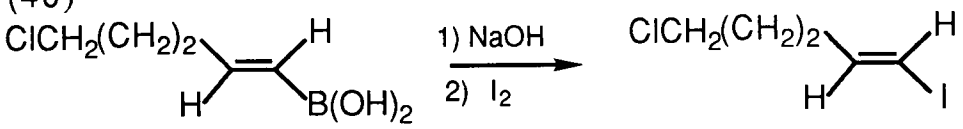
(E)-3,3-Dimethyl-1-butenylboronic acid (.0050 mol, .64 g) was dissolved in ethyl ether (10 mL) in a 100 mL round-bottom flask, and a sodium hydroxide solution (7 mL, 3N) was added. The mixture was cooled to 0^0 C, and a solution of iodine (1.5g, .0060 mol) in ethyl ether (25 mL) was added. After stirring the mixture for 0.5 hour, the excess iodine was reduced with a solution of saturated sodium thiosulfate. The ethereal layer was separated, and the aqueous layer

was extracted with ether (2 x 25 mL). The combined ether extracts were washed with water (2 x 25 mL) and brine (1 x 25 mL) and dried over anhydrous magnesium sulfate. Upon removal of the ether by evaporation, .54 g (52 % yield) of 3,3-dimethyl-1-iodo-1-butene remained.

NMR spectral characteristics of (E)-3,3-dimethyl-1-iodo-1-butene ($CDCl_3$) (ppm): 6.4 (1 H, d), 5.4 (1 H, d), 1.2 (9 H, s).

f. (E)-5-Chloro-1-iodo-1-pentene (eq. 40)

(40)

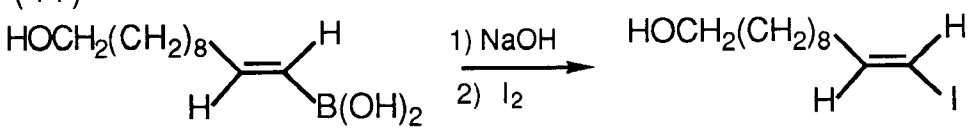


(E)-5-Chloro-1-pentenylboronic acid (.0030 mol, .44 g) was dissolved in ethyl ether (10 mL) in a 100 mL round-bottom flask, and a sodium hydroxide solution (5 mL, 3N) was added. The mixture was cooled to 0^0 C, and a solution of iodine(1.0g, .004 mol) in ethyl ether(20 mL) was added. After stirring the mixture for 0.5 hour, the excess iodine was reduceded with a solution of saturated sodium thiosulfate. The ethereal layer was separated, and the aqueous layer was extracted with ether (2 x 25 mL). The combined ether extracts were washed with water (2 x 25 mL) and brine (1 x 25 mL) and dried over anhydrous magnesium sulfate. Upon removal of the ether by evaporation, .589 g (85 % yield) of 3,3-dimethyl-1-iodo-1-butene remained.

NMR spectral characteristics of (E)-5-chloro-1-iodo-1-pentene ($CDCl_3$) (ppm): 6.43 (1 H, d/t), 6.1 (1 H, d), 3.55 (2 H, t), 2.25 (2 H, m), 1.9 (2 H, m).

g. (E)-11-Hydroxy-1-iodo-1-undecene (eq. 41)

(41)



(E)-11-Hydroxy-1-undecenylboronic acid (0.0030 mol, .64 g) was dissolved in ethyl ether (10 mL) in a 100 mL round-bottom flask, and a sodium hydroxide solution (5 mL, 3N) was added. The mixture was cooled to 0^0 C, and a solution of iodine (1.0g, .0040 mol) in ethyl ether (20 mL) was added. After stirring the mixture for 0.5 hour, the excess iodine was reduced with a solution of saturated sodium thiosulfate. The ethereal layer was seperated, and the aqueous layer was extracted with ether (2 x 25 mL). The combined ether extracts were washed with water (2 x 25 mL) and brine (1 x 25 mL) and dried over anhydrous magnesium sulfate. Upon removal of the ether by evaporation, .622 g (70 % yield) of (E)-11-hydroxy-1-iodo-1-undecene remained.

NMR spectral characteristics of (E)-11-hydroxy-1-iodo-1-undecene ($CDCl_3$) (ppm): 6.5 (1 H, d/t), 5.95 (1 H, d), 3.65 (2 H, m), .8-2.2 (16 H, m).

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VITA

William R. Sponholtz, III was born in Princeton, N.J. on August 3, 1964. He attended Hopewell Valley High School and Graduated in 1982. The following Fall he attended Stockton State College on a soccer scholarship. After injuries stopped him from playing soccer he decided to go back to school and enrolled at Pfeiffer College, Misenheimer, N.C. Upon receiving his Bachelor of Science degree on May 10, 1987 he accepted an Assistantship for Graduate School at The University of Tennessee, Knoxville. After his graduation in December of 1990 his whereabouts remain unknown...