

To the Graduate Council:

I am submitting herewith a dissertation written by Edgar Eugene Gooch III entitled "Iodination of Organic Compounds via Organoborane Intermediates: New Methods." I 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
George W. Kabalka, Major
Professor

We have read this dissertation
and recommend its acceptance:

Carl M. Schuler

Charles F. Brooks

Geo. E. Schweitzer

Accepted for the Council:

L. Evans Reed
Vice Chancellor
Graduate Studies and Research

IODINATION OF ORGANIC COMPOUNDS VIA
ORGANOBORANE INTERMEDIATES:
NEW METHODS

A Dissertation
Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Edgar Eugene Gooch III

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3051967

DEDICATION

The author wishes to dedicate this work to Dr. Albert L. Myers, Dr. Carl T. Bahner and Dr. Truett C. Patterson; they laid a firm foundation upon which the author's graduate career developed. This work has finally vindicated their belief in him.

This work is also dedicated to the author's wife, Marcia, who was "the catalyst responsible for the completion of the reaction."

ACKNOWLEDGEMENTS

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Thanks to the many others who assisted in the completion of this research (and curses to those who hindered it).

ABSTRACT

The incorporation of iodine into organic molecules can be accomplished through the use of organoboranes as synthetic intermediates. However, the iodination of organoboranes with molecular iodine is not suitable for the efficient incorporation of radioiodine into organic molecules since one-half of the radionuclide is lost as iodide.

The iodination of organoboranes, vinylboronic acids and arylboronic acids was studied, using iodine monochloride or sodium iodide/chloramine-T. Both synthetic methods were rapid and efficient methods for iodinating organic substrates, including those with functional groups.

The reactions provided maximum utilization of radioiodine in the synthesis of iodine-125 labeled compounds, both in preliminary tracer studies, and in experiments using carrier-free iodine-125.

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CHAPTER I

ORGANOBORANES AS SYNTHETIC INTERMEDIATES

A. History of Organoboranes

During the past twenty-five years, organoboranes have developed into an important class of synthetic intermediates. They are readily prepared via the hydroboration reaction, which was discovered by Nobel Laureate H. C. Brown and his co-worker B. C. Subba Rao. Organoboranes undergo a variety of reactions in which the boron atom is replaced by a different atom or functional group. Comprehensive treatments of organoborane synthesis and chemistry have appeared, and are beyond the scope of this work.¹⁻⁵

B. Synthesis of Organoboranes

The hydroboration reaction involves the addition of borane (BH_3) to an olefinic site in an organic molecule. The reaction is rapid, often being complete within seconds at 0°C .



The borane molecule can be added as the tetrahydrofuran complex ($\text{BH}_3\text{-THF}$) or generated in situ by the addition of boron trifluoride etherate to sodium borohydride.^{6,7}

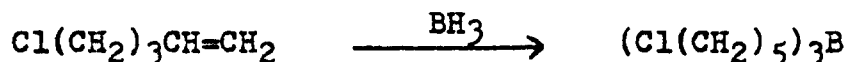
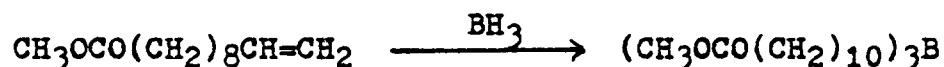
While borane will react with several different functional groups (Table I), the rates of reaction differ widely.

TABLE I. Relative reaction rates of various functional groups toward $\text{BH}_3\text{-THF}^{2,8}$

Functional Group	Product	Rate
carboxylic acid	alcohol	very fast
alcohol	boron ester ^a	very fast
olefin	organoborane	very fast
aldehyde, ketone	alcohol	fast
amide, nitrile	amine	slow
epoxide, ester	alcohol	slow
acid chloride	alcohol	very slow
nitro, ether	---	no reduction
carboxylic acid salt	---	no reduction
alkyl or aryl halide	---	no reduction
aromatic ring	---	no reduction

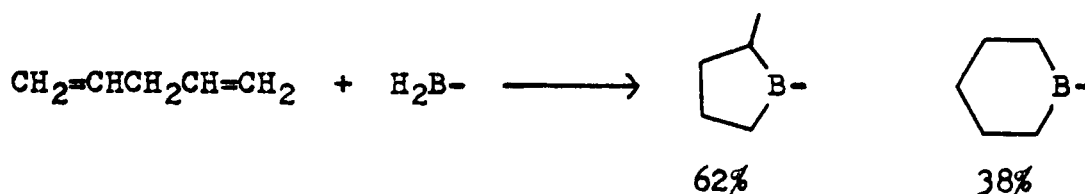
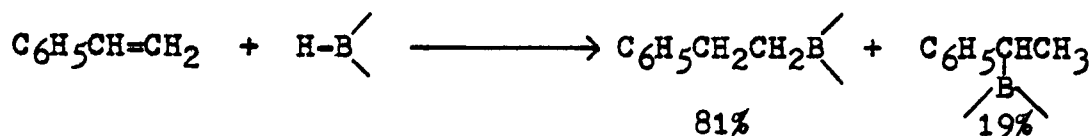
^a The alcohol is easily regenerated via dilute acid hydrolysis.

This makes selective changes of certain functional groups in the presence of other, less reactive functional groups possible. Since the hydroboration reaction is one of the fastest reactions studied, it can be accomplished in the presence of a number of reducible functional groups.

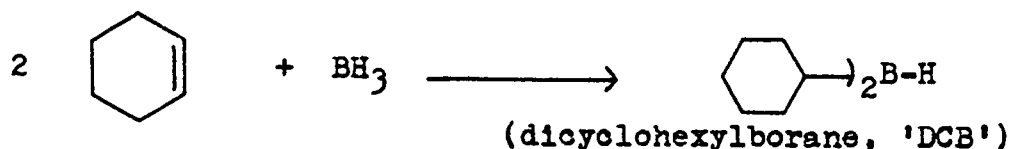
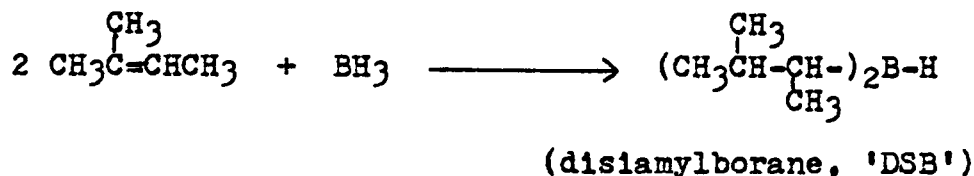


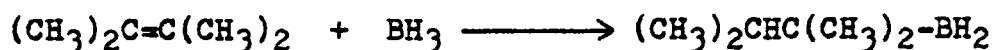
The hydroboration reaction is remarkably regio-specific. Terminal olefins undergo hydroboration to

place 94% of the boron on the less hindered carbon.⁹ Internal olefins also undergo hydroboration with similar directive effects. However, conjugation of the double bond with an aromatic group dramatically changes the regiochemistry.¹⁰ Hydroboration of terminal dienes also results in substantial amounts of isomers in which the boron is attached to a non-terminal carbon.¹¹

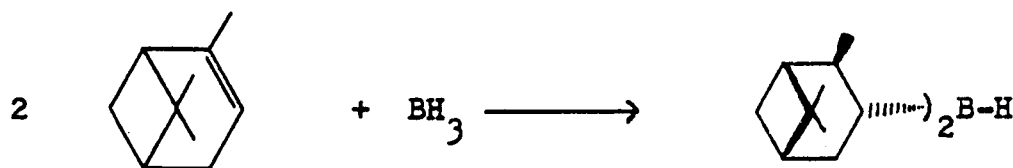


The hydroboration of more highly hindered olefins will often not reach the trialkylborane stage,¹² resulting in monoalkyl- and dialkylboranes. These intermediates can be also used as hydroborating agents to make mixed trialkylboranes.



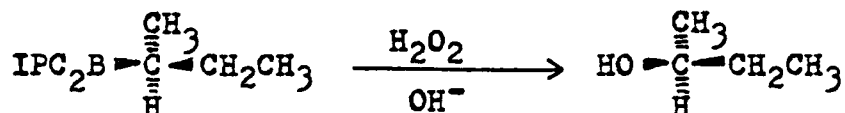
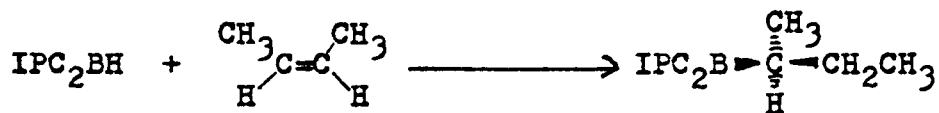


(thexylborane, 'ThB')



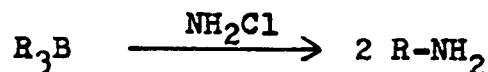
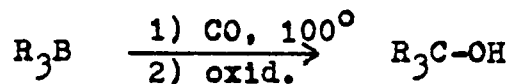
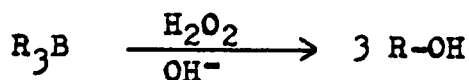
(diisopinocampheylborane, 'IPC₂BH')

These alkylborane reagents exhibit enhanced regioselectivity over $\text{BH}_3\text{-THF}$. Hydroboration of terminal olefins will occur to place 98-99% of the boron at the terminal carbon, even with styrene and 1,4-pentadiene.¹³ Since both enantiomers of α -pinene are available, diisopinocampheylborane can be used as an asymmetric hydroborating agent. Optically active organoboranes have been synthesized using IPC_2BH , and subsequently converted to other optically active compounds.¹⁴



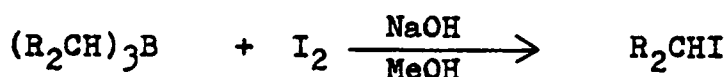
C. Reactions of Organoboranes

The ready formation of organoboranes would be of little consequence if they were unreactive; fortunately they are very reactive synthetic intermediates. In general, the reactions that organoboranes undergo involve replacement of the boron atom by other atoms of interest to organic chemists.^{1,2} These reactions are usually rapid, regiospecific and stereospecific.



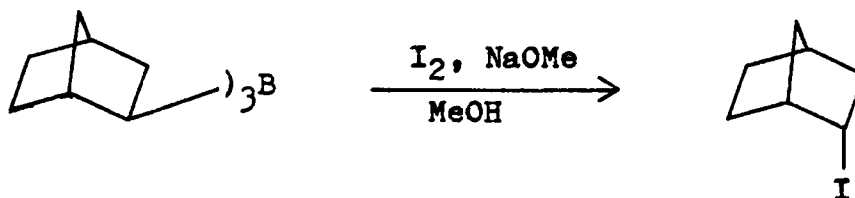
One of the reactions which organoboranes undergo is the replacement of boron with iodine. The reaction, first investigated by Long, was found to be slow and inefficient even at elevated temperatures.¹⁵ However, Brown found that a rapid reaction occurred between iodine and organoboranes in the presence of sodium hydroxide at 0°C.¹⁶ Two of the three alkyl groups attached to boron were regiospecifically iodinated when they were primary. Only one

of the three alkyl groups attached to boron were iodinated, under identical conditions, when they were secondary.

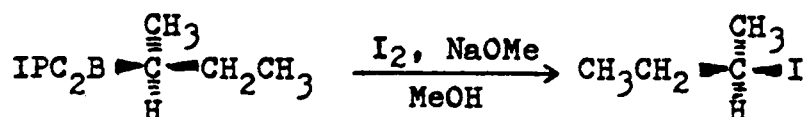


An improved procedure using forcing conditions was developed by Brown and De Lue.¹⁷ In the presence of sodium methoxide, primary alkyl groups on boron were quantitatively iodinated; only two of three secondary alkyl groups on boron were iodinated under the same conditions.

The iodination reaction was shown to occur in a stereoselective manner. The reaction occurs with inversion of configuration at the carbon undergoing substitution. The stereochemical studies were reported jointly by Brown and Kabalka.¹⁸ Brown's group studied the iodination of tri-exo-2-norbornylborane and found the major product to be endo-2-iodonorbornane.



Kabalka's group studied the iodination of diisopinocampheyl-(S)-2-butylborane. They obtained (R)-2-iodobutane as the sole product. Both products are consistent with stereochemical inversion of the carbon undergoing the substitution.



D. Potential of the Iodination Reaction for Radiopharmaceutical Synthesis

Recent advances in diagnostic nuclear medicine include the development of positron emission tomography (PET) and single photon emission computerized tomography (SPECT).^{19,20} These techniques require efficient radio-labeling methods for the synthesis of the required imaging agents. In order to achieve the high specific activity necessary for good imaging and yet minimize radiation dosage to the patient, relatively short-lived isotopes are employed ($t_{1/2}$ = 0.3 to 24 h). This restriction puts severe limitations on the number of effective synthetic methods which can be used for radiopharmaceuticals.

Synthetic routes for iodine incorporation are being developed extensively since iodine possesses a number of medicinally useful isotopes for both PET and SPECT scans.²¹ The use of radiiodine in organic synthesis will be discussed further in Chapter III.

Organoboranes are promising intermediates for the synthesis of radioiodine labeled pharmaceuticals. Many biologically active compounds containing carbon-carbon double bonds are available, and they can be readily converted to the corresponding organoboranes. These organoboranes might undergo the iodination reaction using radioiodine, producing radiopharmaceuticals for the PET and SPECT scanning techniques.

E. Statement of the Problem

We decided to apply the iodination reaction of organoboranes to the synthesis of radioiodine labeled compounds as a potential route to radiopharmaceuticals. We initially chose to synthesize ω -iodofatty acids due to current interest in radioiodinated fatty acids as potential heart imaging agents.²²⁻²⁴

A number of problems arose during the planning of the fatty acid synthesis. One problem involved the reported reduction of carboxylic acids by $\text{BH}_3\text{-THF}$,² the most commonly used hydroborating agent. Another problem involved the use of the strong base, sodium methoxide, to achieve complete utilization of the alkyl groups attached to boron. A third problem was the inefficient utilization of iodine. Using the published procedures, one-half of the iodine in the iodine molecule is lost as sodium iodide, a serious problem with respect to radiopharmaceutical synthesis due to the cost of radioiodine.

The purpose of this study was to develop more efficient methods of incorporating iodine into organic molecules using organoborane intermediates.

CHAPTER II

THE REACTION OF IODINE MONOCHLORIDE WITH ORGANOBORANES

A. Design of the Reagent

The development of new methods for introducing iodine into organic molecules required the development of an iodination reagent more efficient than molecular iodine. The new reagent would be of the form I-X, where X is an atom or functional group not containing iodine. (Thus, the loss of X would not reduce the radiochemical yields.) Ideally, X should be more electronegative than the iodine atom, and its anion should be more stable than iodide ion. This would avoid side reactions which incorporate X rather than I into the substrate. (In addition, the labeled reagent $^*\text{I-X}$ should be commercially available.) Iodine monochloride (ICl) satisfied the above criteria. It was chosen as the first reagent to be investigated.

B. Investigation of the Reaction in the Presence of Sodium Methoxide

The addition of three equivalents each of sodium methoxide and methanolic ICl to a solution of Tri-n-hexylborane in THF at 0°C resulted in a rapid disappearance of the ICl color. Immediate examination of the reaction mixture by gas chromatography indicated the presence of

1-iodohexane in high yield. The reaction was complete in less than one minute. Two of the three hexyl groups (66%) on boron were iodinated immediately. After sixty minutes at 0°C, a maximum yield of 75% (based on 1-hexene) was obtained. Longer reaction times resulted in lower yields. Identical results were obtained at 25°C.

In order to determine the reaction conditions necessary for optimum yield, a study was made in which the amounts of ICl and sodium methoxide were varied (Table II).

TABLE II. Stoichiometric study of the reaction of ICl with tri-n-hexylborane and sodium methoxide^a

Equivalents of ICl Used	Equivalents of Sodium Methoxide Used			
	1	2	3	4
1	32	28	--	--
2	37	66	67	--
3	41	75	89	90

^a Values given are percent yields based on 1-hexene; each value is the average of 3 gas chromatographic analyses.

The best yields (based on the limiting reagent, ICl) resulted when the number of equivalents of methoxide was one greater than the number of equivalents of ICl. More than one extra equivalent of methoxide resulted in lower yields, presumably due to dehydroiodination or displacement of iodide from iodohexane by the excess methoxide.

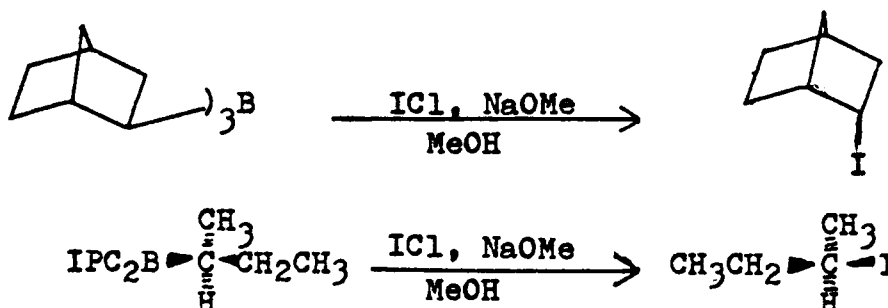
It was interesting to observe that no 2-iodohexane was formed in these reactions. The hydroboration of terminal olefins (such as 1-hexene) with BH_3 -THF is known to be regioselective but not regiospecific. About 6% of the alkyl groups in trihexylborane are attached to boron by the internal carbon of the original double bond.⁹ The product corresponding to the second isomer is observed in other reactions of organoboranes such as oxidation.²⁵ However, the 1-iodohexane produced in the iodination reaction was not contaminated by 2-iodohexane.

Along the same lines, the iodination of tricyclohexylborane with ICl resulted in the iodination of only one of three cyclohexyl groups (33%) attached to boron. These results, which parallel Brown's earlier results with molecular iodine,^{16,17} indicate a more facile iodination of primary alkyl groups versus secondary alkyl groups.

C. Stereochemical Studies

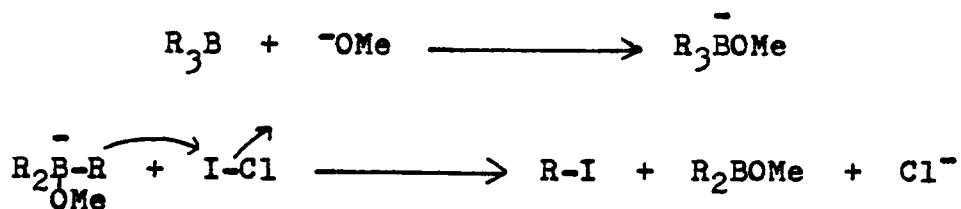
The stereochemical experiments described in Chapter One¹⁸ were repeated using ICl instead of iodine. Iodination of tri-exo-2-norbornylborane with ICl and sodium methoxide produced endo-2-iodonorbornane; the endo product underwent the previously observed isomerization to the exo isomer either upon extended treatment with base or under the influence of light. Diisopinocampheyl-(S)-2-butylborane (92% optically pure) was iodinated to produce (R)-2-iodobutane (87% optically pure, 94% optical yield). Again,

both products are consistent with a mechanism involving stereochemical inversion of the carbon undergoing the substitution.

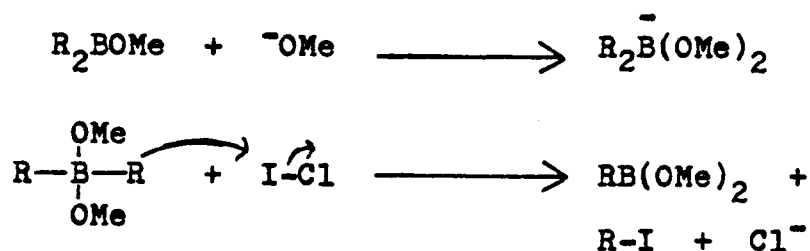


D. Conclusions Concerning the Reaction Mechanism

The results of the stereochemical and stoichiometric studies of the reaction are consistent with an $\text{S}_{\text{E}}2$ mechanism. The organoborane and methoxide ion first combine to form a borate complex which subsequently undergoes an electrophilic attack by ICl . This attack results in an intermolecular transfer of an alkyl group from boron to iodine with chloride as the leaving group. The boronic



ester intermediate combines with another methoxide ion and the process is repeated, transferring an alkyl group to another ICl molecule.



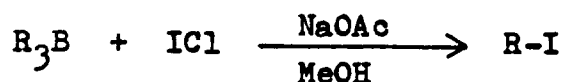
If R is a primary alkyl group the process occurs once more to produce a third molecule of alkyl iodide and trimethyl borate. The boronic ester $\text{RB}(\text{OMe})_2$ does not undergo further reaction if R is a secondary group.

E. Investigation of the Reaction in the Presence of Sodium Acetate

Iodine monochloride was chosen as an iodination agent because it offered the possibility of efficient utilization of iodine in its reaction with organoboranes. The rapidity of the reaction and the high yields produced suggested that forcing conditions might not be required. It was decided to investigate the use of a milder base in the iodination reaction. The successful application of milder bases would be beneficial in the iodination of functionalized molecules.

The addition of three equivalents each of methanolic sodium acetate and methanolic ICl to a solution of tri-n-hexylborane in THF at 0°C produced 1-iodohexane in 50%

yield. The reaction was considerably slower than when methoxide was used. The isolated product was greater than 95% pure by NMR and GC analyses. The reaction was faster at 25°C, producing higher yields. As before, no 2-iodohexane was observed.



Apparently, secondary alkyl groups are less reactive than primary alkyl groups. This conclusion is supported by the observations that no 2-iodohexane is observed as a product in the iodination of tri-n-hexylborane and that the iodination of tricyclohexylborane produces low yields of iodocyclohexane.

A study of the stoichiometry of the reaction was performed (Table III). The results of the study paralleled

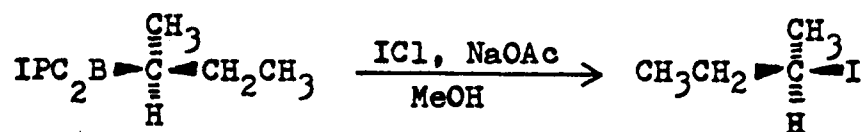
TABLE III. Stoichiometric study of the reaction of ICl with tri-n-hexylborane and sodium acetate^a

Equivalents of ICl Used	Equivalents of Sodium Acetate Used		
	1	2	3
1	22	33	20
2	34	58	65
3	30	59	66

^a Values given are percent yields based on 1-hexene; each value is the average of 3 gas chromatographic analyses.

those of the methoxide study (Table II, page 11), except that the maximum yield (based on 1-hexene) was 66% when using sodium acetate. (Brown's earlier studies of molecular iodine and sodium hydroxide produced results similar to the ICl results.)¹⁶

The reaction of diisopinocampheyl-(S)-2-butylborane with ICl and sodium acetate was investigated. The reaction produced (R)-2-iodobutane in 95% optical yield, again demonstrating inversion of configuration about the carbon undergoing substitution.

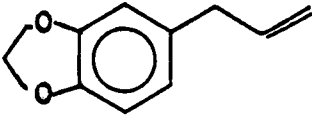
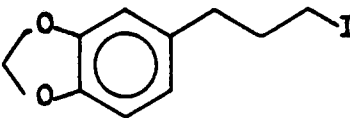
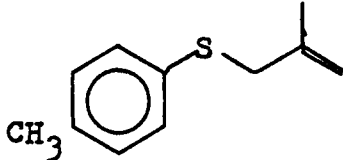
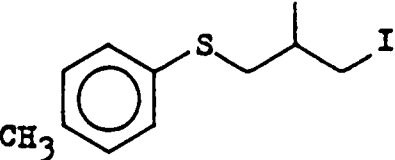


F. Iodination of Organoboranes Containing Other Functional Groups

Due to the variety of functional groups which are present in biologically active molecules, reactions which incorporate isotopes into potential radiopharmaceuticals must occur under very mild conditions. While sodium methoxide is too harsh a base, the use of the milder base, sodium acetate, permits the iodination of organoboranes containing many different sensitive functional groups.

Several functionalized terminal olefins were converted to the corresponding primary alkyl iodides via iodination with ICl and sodium acetate (Table IV). No measures were

TABLE IV. Conversion of several terminal olefins to the corresponding primary alkyl iodides.

Olefin ^a	Alkyl Iodide ^b	Isolated Yield ^c
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{I}$	80
$\text{ClCH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$	$\text{ClCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{I}$	82
$\text{C}_6\text{H}_5\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$	$\text{C}_6\text{H}_5\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{I}$	88
		75
		97

^a The olefins were hydroborated with BH_3 -THF; iodinations were run with 2 equiv of ICl and 3 equiv of NaOAc at 25°C for 45 min.

^b Products showed IR, NMR and mass spectra which were consistent with structure.

^c Based on ICl , which corresponds to two of three alkyl groups on boron iodinated.

taken to protect the various functional groups during the transformation. The alkyl iodides were isolated in good to excellent yield and were characterized by spectral methods. In every case the functional groups in the molecules survived intact.

G. Conclusion

It was found that ICl behaved like molecular iodine in its reaction with organoboranes. In the presence of base, an electrophilic substitution occurs to regiospecifically and stereospecifically replace boron with iodine. Forcing conditions can be employed to increase the yield of the reaction, but are not required. In the presence of mild base the reaction is tolerant of functional groups present in the substrate.

H. Experimental

General. Melting points were measured on a Laboratory Devices Mel-Temp using standard laboratory thermometers. All melting and boiling points are uncorrected. IR samples were run as neat films on a Perkin Elmer Model 727 spectrometer and were calibrated with polystyrene. NMR spectra were recorded on a Varian T-60A spectrometer with tetramethylsilane (TMS) as an internal standard. NMR samples were run either neat or in an appropriate solvent. Chemical shifts are reported in parts per million (δ) downfield from TMS. Mass spectra were recorded on an HP-5982

mass spectrometer with HP-5934 data package, using electron impact ionization (EI), secondary ion mass spectrometry (SIMS), or chemical ionization (CI) with methane as the secondary ion source.

Optical rotations were measured on a Rudolph Instruments MP-7 photoelectric polarimeter using a sodium D lamp and a 10-mm cell. Each observed rotation is the average of three measured values. Specific rotations were calculated using the formula:

$$\text{Specific rotation} = \frac{\text{observed rotation}}{\text{pathlength(dm)} \times \text{density(g/mL)}}$$

Gas chromatographic (GC) analyses were performed on a Varian Model 1700 dual column instrument with a 1.5 m x $\frac{1}{8}$ in. SE-30 column (20% on Chromsorb W) and a 1.8 m x $\frac{1}{8}$ in. Carbowax C-20M column (20% on Chromsorb W). Decane, undecane, dodecane, tridecane and tetradecane were used as internal standards. The relative response ratio between the standards and the reaction products was determined by GC of authentic samples of the reaction products with the standards. Chromatographic isolation of the reaction products was performed wither by flash chromatography on silica gel,²⁶ or thin layer chromatography (TLC) on silica gel (2000 μ L Fisher Uniplate).

Experiments involving air sensitive compounds were performed in glassware equipped with septum inlet and a

rubber septum (Aldrich). Each experimental system was closed to the atmosphere except for an outlet through a mercury bubbler, and was flame dried and cooled under a continuous flow of nitrogen before use. A nitrogen atmosphere was maintained in the system until the reaction was complete. Reagents were added through oven-dried, nitrogen-flushed syringes equipped with stainless steel needles.

Commercially available chemicals (Table V) were used as received except where noted. Methods of purification of commercial chemicals are also listed. BH_3 -THF complex, dicyclohexylborane, disiamylborane, thexylborane, diisopinocampheylborane and 9-borabicyclo(3.3.1)nonane (9-BBN) were prepared by the method of Brown.³ Triphenylborane was prepared by the method of Koster.²⁷

(-)- α -Pinene was prepared from (-)- β -pinene by the method of Settine,²⁸ and was purified by distillation through a spinning band column. The specific rotation of the (-)- α -pinene was found to be -47.4° , which corresponds to a 92% optical purity.^{14,28}

Trialkylboranes--general. An oven-dried, nitrogen-flushed, round-bottomed flask of appropriate size was equipped with magnetic stirring bar, reflux condenser, and gas outlet to a mercury bubbler and maintained under a nitrogen atmosphere. The alkene to be hydroborated was

TABLE V. Sources and methods of purification of commercial chemicals

Chemical and Abbreviation	Source ^a	Method of Purification ^b
Benzoyl chloride	E	
Boron trifluoride etherate	A	DL
Bromobenzene	F	
p-Bromotoluene	A	
Z-2-Butene	M	
Catecholborane (CB)	A	
Chloramine-T (CAT)	A	
Chloroform	F	AD
3-Chloro-2-methylpropene	A	D
5-Chloro-1-pentene	A	
5-Chloro-1-pentyne	Fa	
Cyclohexene	E	DL
Cyclopentanone	A	
1,5-Cyclooctadiene	A	DL
Decane	A	
Diglyme	An	VD
2,3-Dimethyl-2-butene	A	
Ethyl acetate	F	
Ethyl ether	F	
Ethynyl estradiol	S	
Heptane	E	
1-Hexene	A	DL
Iodine	B	
Iodine monochloride (ICl)	E	
Iodine-125 monochloride (¹²⁵ ICl)	N	
Iodobenzene	E	
Iodihexane	F	
Lithium aluminum hydride (LAH)	V	
Magnesium	F	
Mestranol	S	
Methanol	F	DM
2-Methyl-2-butene	A	
Methyl 10-undecenoate	E	
Morpholine	E	D
Nonane	A	
2-Norbornene	A	
1-Octene	A	DL
Pentane	E	
4-Pentene-1-ol	A	
Phenylboronic acid	A	
(-)- β -Pinene	C	D

TABLE V (continued)

Chemical and Abbreviation	Source ^a	Method of Purification ^b
Pyridine	F	
Safrole	A	
Sodium (metal)	F	
Sodium acetate (NaOAc)	F	
Sodium borohydride	A	
Sodium hydroxide	F	
Sodium iodide	F	
Sodium iodide-125 (Na ¹²⁵ I)	N	
Sodium thiosulfate	F	
Tetrahydrofuran (THF)	F	DL
p-Thiocresol	A	
p-Toluenesulfonic acid	M	
p-Toluenesulfonyl chloride	A	
Tridecane	F	
Triethylamine	E	
Undecane	A	
10-Undecenoic acid	MCB	
10-Undecenoyl chloride	A	
10-Undecynoic acid	Fa	

^a Sources: (A) = Aldrich Chemical Co.
 (An) = Ansul
 (B) = J. T. Baker Co.
 (C) = Crosby Chemical Co.
 (E) = Eastman Kodak Co.
 (F) = Fisher Scientific Co.
 (Fa) = Farchan
 (M) = Matheson
 (MCB) = Matheson, Coleman and Bell
 (N) = New England Nuclear
 (S) = Sigma
 (V) = Ventron

^b Methods of purification:

(AD) = acid wash (H₂SO₄) followed by
 distillation
 (D) = simple distillation
 (DL) = distillation from LAH
 (DM) = distillation from magnesium
 (VD) = vacuum distillation from LAH

added and dissolved in sufficient THF to make an approximately 2 M solution. The flask was cooled to 0°C and BH_3 -THF (~2 M) was added slowly by syringe. The reaction mixture was heated to 50°C for one hour, and cooled to room temperature.

Tri-n-hexylborane. 1-Hexene (18.8 mL, 150 mmol) in THF (5 mL) was hydroborated with BH_3 -THF (12.5 mL, 25 mmol) as described above. Additional THF was added to make a solution which was 1 M in tri-n-hexylborane.

Tricyclohexylborane. Cyclohexene (7.6 mL, 75 mmol) was hydroborated with BH_3 -THF (12.5 mL, 25 mmol) as described above. Additional THF was added to make a solution which was 1 M in tricyclohexylborane.

1-Iodohexane. To a 5-mL, oven-dried, nitrogen-flushed, round-bottomed flask equipped with magnetic stirring bar was added tri-n-hexylborane (1 mL of a 1 M solution, 1 mmol) and undecane (212 μL , 1 mmol). To this mixture was added sodium methoxide or sodium acetate (1-4 mL of a 1 M soln, 1-4 mmol) and ICl (1-3 mL of a 1 M soln, 1-3 mmol). The mixture was immediately analyzed by GC; the yields are reported in Tables II and III, pages 11 and 15.

Iodocyclohexane. To a 5-mL, oven-dried, nitrogen-flushed, round-bottomed flask with magnetic stirring bar was added tricyclohexylborane (1 mL of a 1 M soln, 1 mmol) and decane (195 μ L, 1 mmol). To this mixture was added sodium methoxide or sodium acetate (1-3 mL of a 1 M soln, 1-3 mmol) and ICl (1-3 mL of a 1 M soln, 1-3 mmol). The mixture was immediately analyzed by GC. A maximum yield of 1 mmol (33% based on cyclohexene) was observed.

2-Iodonorbornane. Norbornene (850 mg, 9 mmol) was hydroborated with BH_3 -THF (1.5 mL of a 2 M soln, 3 mmol) as described earlier. To the mixture was added sodium methoxide (9 mL of a 1 M soln, 9 mmol) and neat ICl (0.3 mL, 6 mmol). After 15 m stirring, the mixture was poured into 10 mL water and 1 mL CCl_4 and decolorized with 1 M sodium thiosulfate. The CCl_4 layer was separated and immediately examined by NMR; a signal corresponding to the methine proton of endo-2-iodonorbornane was observed at δ 4.60. After 10-15 m this signal had disappeared and another signal corresponding to the methine proton of the exo isomer was observed at δ 4.37.

(R)-2-Iodobutane. Diisopinocampheylborane in diglyme was prepared from α -pinene (92% optically pure) by the method of Brown.¹⁴ Z-2-Butene (26 mL, 300 mmol) was condensed in a cold trap and allowed to slowly distill into the IPC_2BH solution at -10°C . The solution was calculated

to be 0.68 M in diisopinocampheyl-(S)-2-butylborane.

A 500-mL, 3-neck, round-bottomed flask was fitted with two addition funnels, a mechanical stirrer, and was flame dried under nitrogen. The borane solution (100 mL, 68 mmol) was placed in the flask. Then methanolic sodium acetate (140 mL, of a 1 M soln, 140 mmol) and ICl in diglyme (50 mL of a 2.8 M soln, 140 mmol) were placed in the addition funnels. The flask was wrapped in aluminum foil; all subsequent operations were performed in a darkened lab in order to avoid racemization of the product. The two solutions were added simultaneously over 1 h at 25°C. The solution was stirred for an additional hour, then poured into 300 mL of ice water and 50 mL of pentane. The cold aqueous layer was washed with 5 x 50 mL pentane; the combined pentane extracts were washed with 5 x 50 mL of ice water (to remove diglyme) and 50 mL of cold NaCl solution. After drying (MgSO_4), the pentane was removed at atmospheric pressure; the product was distilled (bp 45°/60 torr) and found to be greater than 99% pure by GC. The optical rotation of the (R)-2-iodobutane was -4.36° (0.1 dm cell, density 1.56 g/mL); the specific rotation was calculated to be -27.95° (87% optical purity, 95% optical yield^{18,29}).

Iodination of functionalized olefins--general. Each olefin (30 mmol) was hydroborated with BH_3 -THF (5.0 mL of a 2 M soln, 10 mmol) at 0°C, then stirred for 1 h at 50° C.

Methanolic sodium acetate (30 mL of a 1 M soln, 30 mmol) and ICl (1.0 mL, 20 mmol) were added at 25°C and stirred for 45 m; the mixture was poured into water, decolorized with sodium thiosulfate, and extracted with 2 x 30 mL of ether. The combined ether layers were dried (MgSO_4) and the ether removed. The product was isolated by chromatography.²⁶

1-Iodohexane. 1-Hexene (3.75 mL, 30 mmol) was hydroborated with BH_3 -THF and iodinated with ICl as described above. Yield 5.08 g (80% based on ICl). The product was greater than 99% pure by GC and exhibited spectral properties identical with an authentic sample.

5-Chloro-1-iodopentane. 5-Chloro-1-pentene (3.1 g, 30 mmol) was hydroborated with BH_3 -THF and iodinated with ICl as described above. Yield 3.79 g (82% based on ICl); bp 30-31°C/0.1 torr; mass spectrum (EI) m/e 232.3, calcd 232.5; IR 1300 (C-Cl), 1200 (C-I) cm^{-1} ; NMR (CDCl_3) δ 1.8 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.2 (t, 2H, CH_2I), 3.6 (t, 2H, CH_2Cl).

1-Benzoxo-5-iodopentane. 5-Benzoxo-1-pentene (5.7 g, 30 mmol), prepared by a published procedure,²⁵ was hydroborated with BH_3 -THF and iodinated with ICl as described above. Yield 5.63 g (88% based on ICl); bp 125°C/0.25 torr; mass spectrum (EI) m/e 318.1, calcd 318.2; IR 1705 (C=O), 1205 (C-I) cm^{-1} ; NMR (neat) δ 1.7 (br envelope, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.0 (t, 2H, CH_2I), 4.2 (t, 2H, CH_2O), 7.6 (m, 5H, ArH).

3-(3,4-(Methylenedioxy)phenyl)-1-iodopropane. Safrole (4.9 g, 30 mmol) was hydroborated with BH_3 -THF and iodinated with ICl as described above. Yield 4.32 g (75% based on ICl); bp $105^\circ\text{C}/0.08$ torr; mass spectrum (EI) m/e 290.2, calcd 290.1; IR 1490 (C=C), 1440 (C=C), 1250 (OAr), 1210 (C-I), 1040 (CH_2O), 940 (ArH), 800 (ArH) cm^{-1} ; NMR (neat) δ 2.0 (m, 2H, CH_2), 2.6 (t, 2H, CH_2I), 3.1 (t, 2H, ArCH_2), 5.8 (s, 2H, OCH_2O), 6.6 (s, 3H, ArH).

3-(p-Tolylthio)-2-methyl-1-iodopropane. 3-(p-Tolylthio)-2-methylpropene (5.35 g, 30 mmol), prepared by a published procedure,²⁵ was hydroborated with BH_3 -THF and iodinated with ICl as described above. Yield 5.94 g (97% based on ICl); bp $110^\circ\text{C}/0.1$ torr; mass spectrum (EI) m/e 306.2, calcd 306.2; IR 1195 (C-I), 800 (ArH) cm^{-1} ; NMR (neat) δ 1.0 (d, 3H, CH_3), 1.6 (m, 1H, CH), 2.2 (s, 3H, ArCH_3), 2.7 (d, 2H, CH_2I), 3.2 (d, 2H, SCH_2), 7.0 ($\text{A}_2'\text{X}_2'$, 4H, ArH).

CHAPTER III

SYNTHETIC APPLICATIONS OF THE REACTION OF IODINE MONOCHLORIDE WITH ORGANOBORANES

A. Background

The first use of radioactive isotopes in human studies was reported by Blumgart.³⁰ A saline solution which had been exposed to radon gas was injected into a subject and used to measure blood circulation. The use of simple inorganic radionuclides continued for years afterward. Most applications involved tracer studies using cyclotron-produced radionuclides. These studies included the use of radioiodine to measure thyroid function in rabbits and humans.^{31,32}

Due to its success in the thyroid studies, iodine-131 rapidly became the most widely utilized radiopharmaceutical. It was used not only to visualize the thyroid, but also to treat thyroid cancer and hyperactivity.³³ As the use of radioiodine was expanded to the synthesis of labeled organic molecules as potential radiopharmaceuticals, its importance increased. A variety of synthetic methods were developed, and the area has been reviewed.³⁴

The continued versatility of radioiodine is due in part to the availability of several different isotopes of varying half-lives and gamma emission energies (Table VI).

TABLE VI. Medically useful isotopes of iodine³³

Iodine Radionuclide	Half Life	Mode of Decay	Energy (MeV)
123	13.3 h	EC ^a	.159
125	60 d	EC gamma	.149 .028
128	25.0 m	beta gamma	2.12 .455
131	8.05 d	beta gamma	.608 .364

^a EC = Electron capture.

This allows the researcher to select the isotope most desirable for the experiment to be performed. For example, preliminary work on the synthesis of a potential radio-pharmaceutical could be performed with ¹²⁵I with its long half-life and low radiation energy. Then the successfully developed radiopharmaceutical would be synthesized with ¹³¹I or ¹²³I (for use in positron emission tomography). The latter isotopes have shorter half-lives (which minimizes radiation dosage to the patient); in addition, they have higher gamma energies for improved imaging.

B. Statement of the Problem

The reaction of iodine monochloride with organoboranes in the presence of sodium acetate is a mild, efficient method for the incorporation of iodine into organic

molecules. The mildness of the reaction should make it valuable for the synthesis of functionally complex molecules; also, the commercial availability of radioiodine-containing ICl makes the reaction potentially useful for radiopharmaceutical synthesis.

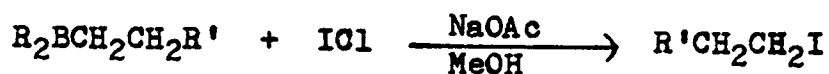
However, two aspects of the reaction needed to be addressed before it could be successfully applied to the synthesis of radiopharmaceuticals. First, utilization of the alkyl groups on boron during the iodination required optimization. Second, the complete utilization of radioiodine had to be confirmed.

The purpose of the study was to develop methods for improving the utilization of the organic substrate; and to evaluate the use of radioiodine in the reaction of ICl with organoboranes.

C. Iodination of Mixed Organoboranes

As noted earlier, the hydroboration of several hindered olefins such as 2-methyl-2-butene, cyclohexene, α -pinene and 2,3-dimethyl-2-butene can be controlled to produce dialkylboranes of the general formula R_2BH . These dialkylboranes are themselves excellent hydroborating agents exhibiting enhanced regioselectivity in their addition to terminal olefins (compared to BH_3 -THF). Thus, they can be used to synthesize organoboranes of the general formula $R_2BCH_2CH_2R'$, where R represents a secondary alkyl group.

The more facile iodination of primary alkyl groups versus secondary groups suggests that mixed trialkylboranes could provide a more efficient conversion of primary alkyl groups to primary alkyl iodides. Thus, in the reaction of ICl with tri-n-hexylborane (Table III, page 15), use of only one equivalent of ICl results in a maximum yield of 33% (corresponding to the quantitative iodination of one of three alkyl groups attached to boron). One would then expect that the primary group in a mixed trialkylborane would be selectively iodinated.



The iodination of several mixed trialkylboranes was investigated. 1-Hexene was hydroborated with 9-borabicyclo(3.3.1)nonane (9-BBN), disiamylborane (DSB), dicyclohexylborane (DCB), and thexylborane (ThB). The yields varied widely (Table VII). The iodination of 9-hexyl-9-BBN and thexyl-di-n-hexylborane produced low to moderate yields. In contrast, the use of alkyldisiamylboranes markedly enhanced the conversion of primary alkyl groups to the 1-iodoalkanes. The iodination of hexyldisiamylborane yielded 1-iodohexane in 90% yield after stirring overnight. (The reaction is slower than the iodination of tri-n-hexylborane.) Analysis of the reaction mixture by GC

TABLE VII. Iodination of several hexyldialkylboranes with ICl and base^a

Dialkylborane	Base	Yield(%) ^b
9-BBN	NaOMe	38
9-BBN	NaOAc	26
ThB	NaOMe	62
DSB	NaOMe	90
DSB	NaOAc	90
DCB	NaOMe	90
DCB	NaOAc	90

^a 1-Hexene was hydroborated with one equiv of the dialkylborane at 0-25°C for one hour, then treated with one equiv each of base and ICl at 25°C.

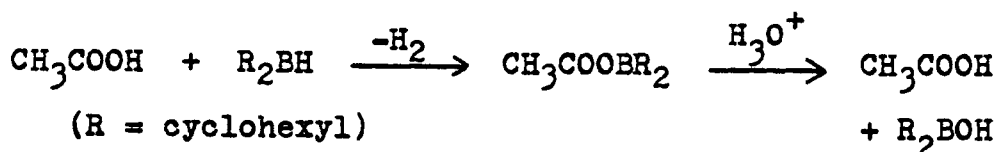
^b Isolated, based on 1-hexene.

indicated the presence of impurities with lower retention times than iodoheptane; presumably these were due to competing reactions involving iodination of the siamyl groups.

The iodination of hexyldicyclohexylborane yielded 1-iodohexane in 90% yield. This reaction was as rapid as the iodination of tri-n-hexylborane. No evidence of side reactions (formation of iodocyclohexane) was observed by GC.

Dicyclohexylborane was chosen for further studies. The use of DCB offers other advantages in addition to the improved utilization of alkyl groups. The reagent exhibits enhanced regioselectivity over BH_3 -THF in the hydroboration

of terminal olefins, as discussed earlier. In addition, the rapid reduction of carboxylic acids by BH_3 -THF (Table I, page 2) does not occur with DCB; instead a borinic ester is formed. The borinic ester undergoes a rapid hydrolysis in dilute aqueous acid to regenerate the carboxylic acid. The use of an extra equivalent of DCB for the hydroboration



of an olefinic carboxylic acid is adequate for the formation of the organoborane.

A series of functionally substituted olefins were converted to the corresponding primary alkyl iodides using DCB for the hydroboration and ICl/NaOAc for the iodination (Table VIII). The synthetic utility of DCB was further demonstrated by the selective hydroboration-iodination of the terminal double bond in Z-4,14-pentadecadienoic acid. No addition of DCB or ICl to the internal double bond was observed.

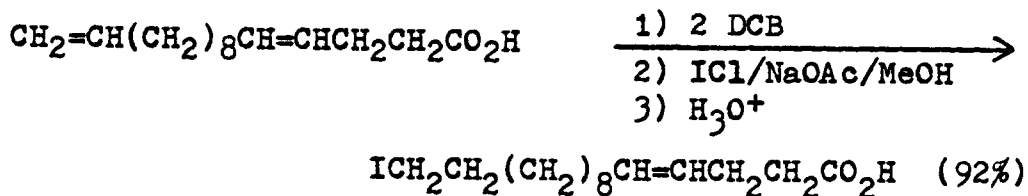
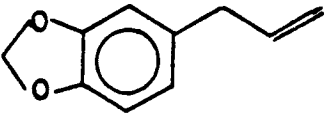
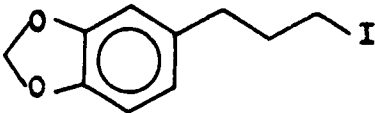
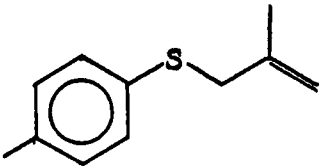
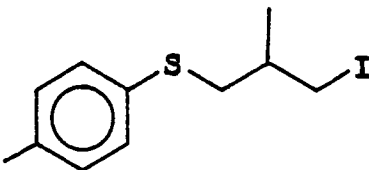


TABLE VIII. Iodination of alkyldicyclohexylboranes with ICl and sodium acetate

Olefin ^a	Product ^b	Yield (%)
$\text{CH}_2=\text{CH}(\text{CH}_2)_8\text{CO}_2\text{CH}_3$	$\text{ICH}_2\text{CH}_2(\text{CH}_2)_8\text{CO}_2\text{CH}_3$	95
$\text{CH}_2=\text{CH}(\text{CH}_2)_{24}\text{CO}_2\text{CH}_3$	$\text{ICH}_2\text{CH}_2(\text{CH}_2)_{24}\text{CO}_2\text{CH}_3$	73
$\text{C}_6\text{H}_5\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$	$\text{C}_6\text{H}_5\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{I}$	95
		75
		80
$\text{CH}_2=\text{CH}(\text{CH}_2)_n\text{CO}_2\text{H}^c$	$\text{ICH}_2\text{CH}_2(\text{CH}_2)_n\text{CO}_2\text{H}$	
where n =	8	89
	13	89
	16	95
	19	90

^a Olefins hydroborated with 1 equiv of DCB, then iodinated with 1 equiv each of ICl and NaOAc at 25°C.

^b Products exhibited IR, NMR and MS which were consistent with structure; products were compared with authentic samples where available.

^c 2 equiv DCB used in the hydroboration.

D. Synthesis of Labeled Molecules with ^{125}ICl

Iodine monochloride was chosen as an alternative iodination reagent to molecular iodine due to the more efficient utilization of radioiodine in the labelling of organic molecules. This aspect of the reaction required evaluation before the reagent could be successfully applied to the synthesis of radiopharmaceuticals.

The evaluation of ICl as a radioiodine reagent was affected by using ^{125}ICl in the presence of sodium acetate to iodinate a series of organoboranes (Table IX). During the evaluation, the iodination of the organic compounds was performed as before. The isolated products were assayed to determine their specific activities, which were then compared to the original activity of the ^{125}ICl .

The iodination of five trialkylboranes yielded the corresponding labeled primary alkyl iodides in good chemical yield. Furthermore, the specific activity of the products was virtually identical to the activity of the starting ^{125}ICl (within experimental error).

E. Conclusion

In the iodination of organic compounds via organoborane intermediates, the use of dicyclohexylborane as a hydroborating agent for terminal olefins is a superior alternative to $\text{BH}_3\text{-THF}$. The iodination of such mixed trialkylboranes utilizes the alkyl substrate more efficiently

TABLE IX. Synthesis of several iodoalkanes using sodium acetate and ^{125}ICl

Organoborane	Product	Yields ^a
$(\text{CH}_3(\text{CH}_2)_5)_3\text{B}$	$\text{CH}_3(\text{CH}_2)_5\text{I}$	66/66
$(\text{Cl}(\text{CH}_2)_5)_3\text{B}$	$\text{Cl}(\text{CH}_2)_5\text{I}$	82/82
$(\text{C}_6\text{H}_5\text{CO}_2(\text{CH}_2)_5)_3\text{B}$	$\text{C}_6\text{H}_5\text{CO}_2(\text{CH}_2)_5\text{I}$	88/88
$(\text{C}_7\text{H}_5\text{O}_2\text{CH}_2\text{CH}_2\text{CH}_2)_3\text{B}$	$\text{C}_7\text{H}_5\text{O}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{I}$	60/58
$(\text{C}_7\text{H}_7\text{SCH}_2\text{C}(\text{CH}_3)\text{CH}_2)_3\text{B}$	$\text{C}_7\text{H}_7\text{SCH}_2\text{C}(\text{CH}_3)\text{CH}_2\text{I}$	59/59
$\text{R}_2\text{B}(\text{CH}_2)_{10}\text{CO}_2\text{BR}_2^{\text{b}}$	$\text{I}(\text{CH}_2)_{10}\text{CO}_2\text{H}$	91/75
$\text{R}_2\text{B}(\text{CH}_2)_{15}\text{CO}_2\text{BR}_2^{\text{b}}$	$\text{I}(\text{CH}_2)_{15}\text{CO}_2\text{H}$	73/73

^a First value is chemical yield; second value is radiochemical yield.

^b R = cyclohexyl

than conventional trialkylboranes. In addition the use of ICl instead of molecular iodine provides maximum utilization of available radioiodine for the labelling of organic molecules.

F. Experimental

General. The analytical equipment and general techniques used have been described in Chapter II (p. 15). 15-Hexadecenoic acid and ethyl-4,14-pentadecadienoate were prepared according to published procedures.^{35,36}

The assays of radioactivity were performed on a Packard 5220 Auto-Gamma Scintillation Spectrometer. Samples were counted for one minute and corrected for background. The radioactivity of each sample was calculated by the formula:

$$\text{activity (mCi)} = \frac{\text{observed counts/min}}{60 \text{ sec/min} \times 3.7 \times 10^7 \text{ sec}^{-1} \text{ mCi}^{-1}}$$

The chemical and radiochemical purity of the labeled products were determined by TLC on silica gel. The pure unlabeled compounds were applied adjacent to the labeled ones. In all cases, over 95% of the radioactivity on the plate was associated with a single spot having an R_f value identical to that of the unlabeled material. Radiochemical yields were calculated using the formula:

$$\text{Radiochemical yield} = \text{chemical yield} \times \frac{\text{product activity}}{\text{iodine activity}}$$

^{125}ICl (New England Nuclear) was received in a CCl_4 solution with an activity of approximately 50 mCi/mol. This was diluted to approximately 5 mCi/mol with ICl before use. Fresh ^{125}ICl (less than 15 days old) was

always used; radiochemical yields were observed to drop considerably when radioiodine older than 2½-3 weeks was used.

Test of ^{125}ICl for full potency. An aliquot (5 μL) of ^{125}ICl in CCl_4 was added to 1 mL of aqueous sodium thiosulfate to reduce the ^{125}ICl to iodide. The solution was extracted with ether (1 mL). The ether and aqueous layers were separately assayed for activity. If more than 10% of the total activity was observed in the ether layer, the supply of ^{125}ICl was not used for any iodinations.

4,14-Pentadecadienoic acid. Ethyl 4,14-pentadecadienoate (1.50 g, 5.62 mmol) was added to 3 N NaOH (3.0 mL, 9 mmol) and 8 mL water. The solution was refluxed for 2½ h, then cooled and stirred at 25°C overnight. After acidification with HCl, the solution was extracted with pentane and the pentane removed. The product was isolated by flash chromatography²⁶ (silica gel, 5% ethyl acetate/ligroin). Yield 762 mg (57%); NMR (CDCl_3) δ 1.0 (br s, 12H, alkyl), 1.4-2.0 (br envelope, 8H, $=\text{CCH}_2$ and $\text{CH}_2\text{CO}_2\text{H}$), 4.5-5.3 (br envelope, 5H, $\text{CH}=\text{CH}$ and $\text{CH}=\text{CH}_2$), 10.5 (s, 1H, CO_2H).

18-Nonadecenoic acid. 1 2.9 M solution of methylmagnesium chloride in THF (3.4 mL, 10 mmol) was added to 8-bromooctanoic acid (2.23 g, 10 mmol) in 30-40 mL THF at -20°C. Lithium coppertetrachloride (2 mL of a 0.2 M

soln, 0.4 mmol) was added followed by a solution of a Grignard reagent (10 mmol) prepared from magnesium (240 mg, 0.01 g-atom) and 11-bromoundecane (2.33 g, 10 mmol), and stirred 3 h at -20°C . The solution was allowed to warm to room temperature and stirred overnight, then poured into a mixture of ice, ether and dilute H_2SO_4 . This was extracted three times with ether. The combined ether extracts were acidified and washed with water and saturated NaCl (aq) and dried (MgSO_4). Evaporation of the ether left a white solid (yield 80%) which was recrystallized from ligroin or ligroin/ CHCl_3 ; mp $59-60^{\circ}\text{C}$; IR 1642 ($\text{CH}=\text{CH}_2$), 1710 (CO_2H), 2860 and 2930 (CH_2) cm^{-1} ; NMR (CCl_4) δ 1.23 (br s, 28H, alkyl), 2.1 (m, 4H, $=\text{CH}-\text{CH}_2$ and $\text{CH}_2\text{COO}-$), 4.7-6.03 (m, 3H, $\text{CH}=\text{CH}_2$), 11.9 (s, 1H, CO_2H).

21-Docosenoic acid. This compound was prepared as described above for 18-nonadecenoic acid, using 11-bromoundecanoic acid (2.65 g, 10 mmol) instead of 8-bromooctanoic acid. Yield 80%; mp $65-67^{\circ}\text{C}$; IR 1642, 1710, 2860, 2930 cm^{-1} ; NMR (CCl_4) δ 1.23 (br s, 34H, alkyl), 2.1 (m, 4H, $=\text{CH}-\text{CH}_2$ and $\text{CH}_2\text{COO}-$), 4.7-6.0 (m, 3H, $\text{CH}=\text{CH}_2$), 11.9 (s, 1H, CO_2H).

Iodination of 9-hexyl-9-BBN. 1-Hexene (625 μL , 5 mmol) was hydroborated with 9-BBN (7.5 mL of a 0.67 M soln, 5 mmol) for 1 h at 25°C . Sodium acetate or sodium methoxide (5 mL of a 1 M soln, 5 mmol) was added followed

by ICl (250 μ L, 5 mmol) and undecane (636 μ L, 3 mmol). The mixture was analyzed by GC; yields 38% with sodium methoxide and 26% with sodium acetate.

Iodination of thexyl-di-n-hexylborane. 1-Hexene (250 μ L, 2 mmol) was hydroborated with thexylborane prepared from BH_3 -THF (0.5 mL of a 2 M soln, 1 mmol) and 2,3-dimethyl-2-butene (119 μ L, 1 mmol) at 0°C for 1 h. Sodium methoxide (2 mL of a 1 M soln, 2 mmol), ICl (50 μ L, 1 mmol) and undecane (212 μ L, 1 mmol) were added and the mixture analyzed by GC; yield 62%.

Iodination of hexyldisiamylborane. 1-Hexene (125 μ L, 1 mmol) was hydroborated with disiamylborane prepared from BH_3 -THF (0.5 mL of a 2 M soln, 1 mmol) and 2-methyl-2-butene (0.5 mL of a 4 M soln, 2 mmol) at 0°C for 1 h. Sodium acetate or sodium methoxide (2 mL of a 1 M soln, 2 mmol) and methanolic ICl (1 mL of a 1 M soln, 1 mmol) were added, followed by undecane (212 μ L, 1 mmol). The mixture was analyzed by GC; yield 90%.

Iodination of hexyldicyclohexylborane. 1-Hexene (125 μ L, 1 mmol) was hydroborated with dicyclohexylborane prepared from BH_3 -THF (0.5 mL of a 2 M soln, 1 mmol) and cyclohexene (202 μ L, 2 mmol) at 0°C. Sodium acetate or sodium methoxide (2 mL of a 1 M soln, 2 mmol) and methanolic ICl (1 mL of a 1 M soln, 1 mmol) were added, followed by undecane (212 μ L, 1 mmol). GC yield 90%.

Methyl 11-iodoundecanoate. Methyl 10-undecenoate (1.12 mL, 5 mmol) was hydroborated with dicyclohexylborane (DCB--5 mL of a 1 M soln, 5 mmol) at 0°C. Iodination was accomplished with sodium acetate (10 mL of a 1 M soln, 10 mmol) and methanolic ICl (5 mL of a 1 M soln, 5 mmol) at 0-25°C. The mixture was poured into water, decolorized with sodium thiosulfate, and extracted with pentane. The dried pentane extracts were evaporated and the product isolated by flash chromatography.²⁶ Yield 1.55 g (95%); mass spectrum (EI) m/e 199 (M - 127), calcd 326; IR 1740 (C=O) cm⁻¹; NMR (CDCl₃) δ 1.1-1.2 (br s, 16H, alkyl), 2.25 (t, 2H, CH₂CO₂), 3.28 (t, 2H, CH₂I), 3.58 (s, 3H, OCH₃).

1-Benzoxo-5-iodopentane. 5-Benzoxo-1-pentene (0.81 mL, 5 mmol) was hydroborated with DCB (5 mL of a 1 M soln, 5 mmol) at 0°C, and iodinated with sodium acetate (10 mL of a 1 M soln, 10 mmol) and methanolic ICl (5 mL of a 1 M soln, 5 mmol) at 0-25°C. The product was isolated as described above. Yield 1.51 g (95%); the product showed properties identical to an authentic sample.

3-(3,4-(Methylenedioxy)phenyl)-1-iodopropane. Safrole (0.74 mL, 5 mmol) was hydroborated with DCB (5 mL of a 1 M soln, 5 mmol) at 0°C, and iodinated with sodium acetate (10 mL of a 1 M soln, 10 mmol) and methanolic ICl (5 mL of a 1 M soln, 5 mmol) at 0-25°C. The product was isolated as described above. Yield 1.08 g (75%); the product showed properties identical to an authentic sample.

3-(p-Tolylthio)-2-methyl-1-iodopropane. 3-(p-Tolylthio)-2-methylpropene (0.90 mL, 5 mmol) was hydroborated with DCB (5 mL of a 1 M soln, 5 mmol) at 0°C, and iodinated with sodium acetate (10 mL of a 1 M soln, 10 mmol) and methanolic ICl (5 mL of a 1 M soln, 5 mmol) at 0-25°C. The product was isolated as described above. Yield 1.19 g (80%); the product showed properties identical to an authentic sample.

Methyl 27-iodoheptacosanoate. Methyl 26-heptacosenoate (100 mg, 0.24 mmol) was hydroborated with DCB (0.24 mL of a 1 M soln, 0.24 mmol) at 0°C, and iodinated with sodium acetate (0.5 mL of a 1 M soln, 0.5 mmol) and methanolic ICl (0.25 mL of a 1 M soln, 0.25 mmol) at 0-25°C. The product was isolated as described above. Yield 97 mg (73%); mp 66°C; mass spectrum (SIMS) m/e 550.7, calcd 550.7.

11-Iodoundecanoic acid. 10-Undecenoic acid (1.84 g, 10 mmol) was hydroborated with DCB (20 mL of a 1 M soln, 20 mmol) at 0°C, and iodinated with sodium acetate (20 mL of a 1 M soln, 20 mmol) and methanolic ICl (10 mL of a 1 M soln, 10 mmol) at 0-25°C. The reaction mixture was poured into water, decolorized with sodium thiosulfate, and acidified with HCl. The aqueous solution was extracted with pentane, the pentane extracts evaporated and the product isolated via flash chromatography²⁶ on silica gel. Yield 2.79 g (89%); mp 47-50°C; mass spectrum (CI) 313.4 (M + 1),

calcd 312.2; NMR (CDCl_3) δ 1.2 (s, 14H, alkyl), 2.1 (m, 4H, $\text{CH}_2\text{CO}_2\text{H}$ and $\text{CH}_2\text{CH}_2\text{I}$), 3.0 (t, 2H, CH_2I), 11.9 (s, 1H, CO_2H).

16-Iodoheptadecanoic acid. 15-Hexadecenoic acid (100 mg, 0.4 mmol) was hydroborated with DCB (0.8 mL of a 1 M soln, 0.8 mmol) at 0°C , and iodinated with sodium acetate (0.8 mL of a 1 M soln, 0.8 mmol) and methanolic ICl (0.4 mL of a 1 M soln, 0.4 mmol) at $0-25^\circ\text{C}$. The product was isolated as described above for 11-iodoundecanoic acid. Yield 136 mg (89%); mp $71-72^\circ\text{C}$; mass spectrum (SIMS) m/e 382.6, calcd 382.4; NMR (CDCl_3) δ 1.2 (s, 24H, alkyl), 2.1 (m, 4H, $\text{CH}_2\text{CO}_2\text{H}$ and $\text{CH}_2\text{CH}_2\text{I}$), 3.0 (t, 2H, CH_2I), 11.9 (s, 1H, CO_2H).

19-Iodononadecanoic acid. 18-Nonadecenoic acid (100 mg, 0.34 mmol) was hydroborated with DCB (0.68 mL of a 1 M soln, 0.68 mmol) at 0°C , and iodinated with sodium acetate (0.68 mL of a 1 M soln, 0.68 mmol) and methanolic ICl (0.34 mL of a 1 M soln, 0.34 mmol) at $0-25^\circ\text{C}$. The product was isolated as described above for 11-iodoundecanoic acid. Yield 136 mg (95%); mp $70-71.5^\circ\text{C}$; mass spectrum (SIMS) m/e 424.5, calcd 424.5; NMR (CDCl_3) δ 1.2 (s, 30H, alkyl), 2.1 (m, 4H, $\text{CH}_2\text{CH}_2\text{I}$ and $\text{CH}_2\text{CO}_2\text{H}$), 3.0 (t, 2H, CH_2I), 11.9 (s, 1H, CO_2H).

22-Iododocosanoic acid. 21-Docosenoic acid (100 mg, 0.3 mmol) was hydroborated with DCB (0.6 mL of a 1 M soln, 0.6 mmol) at 0°C , and iodinated with sodium acetate (0.6 mL

of a 1 M soln, 0.6 mmol) and methanolic ICl (0.3 mL of a 1 M soln, 0.3 mmol) at 0-25°C. The product was isolated as described above for 11-iodoundecanoic acid. Yield 126 mg (90%); mp 71-72°C; mass spectrum (SIMS) m/e 466.5, calcd 466.5; NMR (CDCl₃) δ 1.2 (s, 36H, alkyl), 2.1 (m, 4H, CH₂CH₂I and CH₂CO₂H), 3.0 (t, 2H, CH₂I), 11.9 (s, 1H, CO₂H).

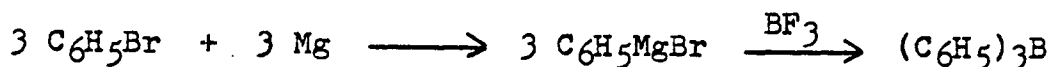
15-Iodo-4-pentadecenoic acid. 4,14-Pentadecadienoic acid (762 mg, 3.2 mmol) was hydroborated with DCB (6.4 mL of a 1 M soln, 6.4 mmol) at 0°C, and iodinated with sodium acetate (6.4 mL of a 1 M soln, 6.4 mmol) and methanolic ICl (3.2 mL of a 1 M soln, 3.2 mmol) at 0-25°C. The product was isolated as described above for 11-iodoundecanoic acid. Yield 1.08 g (92%); mp 55-60°C; NMR (CDCl₃) δ 1.2 (s, 16H, alkyl), 1.6-2.4 (br envelope, 6H, CH₂CH=CHCH₂CH₂CO₂H), 3.0 (t, 2H, CH₂I), 5.2 (m, 2H, CH=CH), 11.9 (s, 1H, CO₂H).

CHAPTER IV

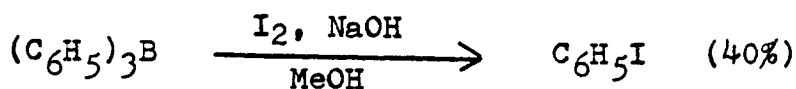
THE REACTION OF IODINE MONOCHLORIDE WITH OTHER BORON COMPOUNDS

A. Background

The chemistry of triarylboranes has not been developed as extensively as that of trialkylboranes. This is due to the fact that the triarylboranes cannot be prepared via the hydroboration reaction. The only practical synthesis of triarylboranes involves the reaction of aryl Grignard reagents with boron halides or alkoxides.²⁷

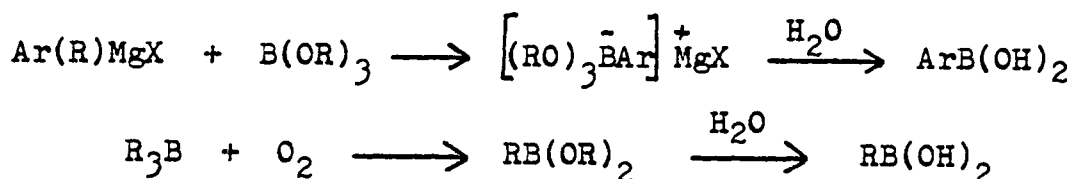


The chemistry of triphenylborane has recently been explored.³⁷ The iodination of triphenylborane parallels that of other secondary trialkylboranes; one of the three phenyl groups is iodinated in the presence of base.

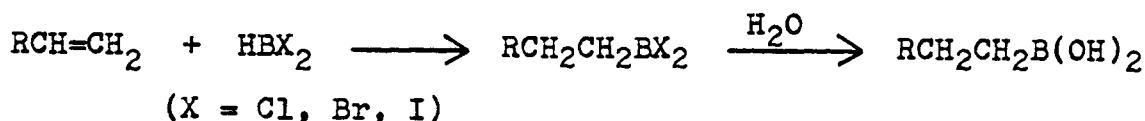


The chemistry of boronic acids has been reviewed by Torssell.³⁸ Alkyl- and arylboronic acids are typically prepared via the reaction of a Grignard reagent with

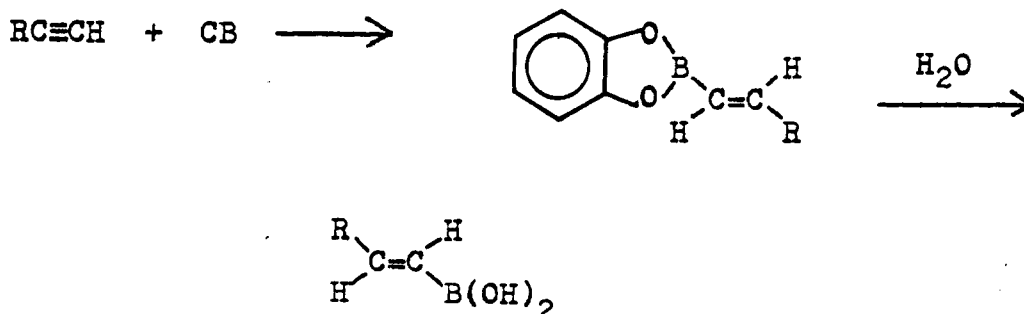
trialkylborates followed by hydrolysis. Alkylboronic acids may also be made by controlled oxidation of organoboranes followed by hydrolysis.³⁹



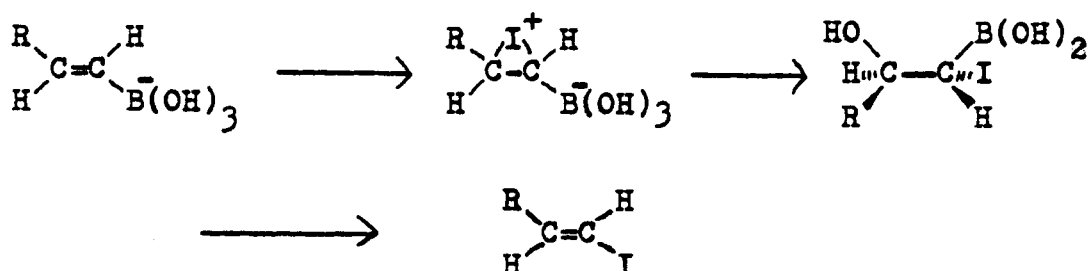
A newer reaction involving hydroboration using dihalo-borane/methyl sulfide complexes to produce alkyl dihalo-boranes has been reported.^{40,41} These intermediates also provide boronic acids upon hydrolysis.



(E)-1-Alkenylboronic acids and 1-alkylboronic acids are also available. Catecholborane (CB) hydroborates alkynes at 70° (and olefins at 100°) to produce the (E)-1-alkenyl- (or 1-alkyl-) 1,3,2-benzodioxaboroles, which are hydrolyzed to the boronic acids.⁴²

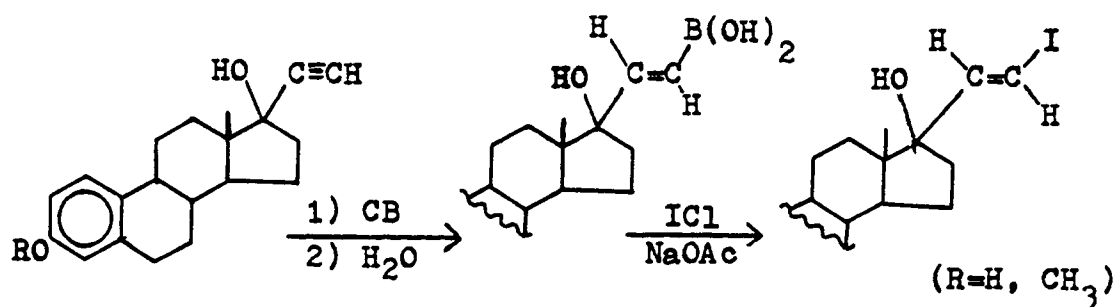


The halogenation of (E)-1-alkenylboronic acids has been studied by Brown.^{43,44} The proposed mechanism for iodination involves an initial addition of HOI to the double bond of the boronic acid, followed by a syn-elimination to produce the iodide.



It was decided to investigate the reaction of boronic acids with ICl in order to evaluate their potential as synthetic intermediates. In addition, the iodination of triphenylborane (as a model for triarylboranes) was investigated.

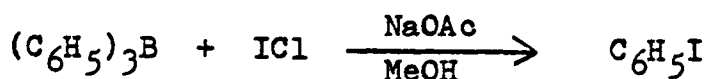
The potential utility of vinyl and aryl iodides labeled with radioiodine in nuclear medicine is significant. Boronic acids could be useful intermediates in the synthesis of these compounds. For example, 17 α -(2-ethynyl)- $\Delta^{1,3,5}$ -estratrien-3,17 β -diol (ethynyl estradiol) and its 3-methyl ether (mestranol) could be converted to the corresponding 17 α -(E)-2-iodovinyl- $\Delta^{1,3,5}$ -estratrien-3,17 β -diol and its 3-methyl ether by hydroboration with CB followed by hydrolysis and subsequent iodination with ICl.



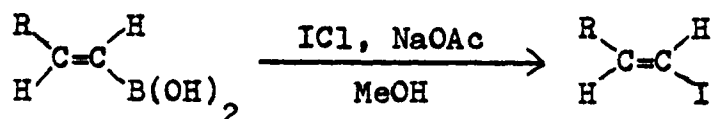
These labeled iodovinyl steroids are potential estrogen receptor site agents.⁴⁵ They could be used in positron emission tomography to visualize estrogen-dependent tissues such as breast tumors. For example, the conversion of ethynyl estradiol and mestranol to the corresponding 17 α -(2-iodoethynyl) derivatives by replacement of the acetylenic hydrogen has been reported.⁴⁶ The carrier-free ¹²⁵I compounds were also synthesized, and found to be receptor site active in vitro.

B. Results and Discussion

Triphenylborane was prepared by a published procedure²⁷ and iodinated with methanolic ICl and sodium methoxide at 25°C. The result paralleled the earlier study.³⁷ GC analysis indicated the formation of iodobenzene in 31% yield, which corresponds to 95% iodination of one of three phenyl groups on boron.



The iodination of (E)-1-hexenylboronic acid at 25°C produced (E)-1-iodohexene in 30-50% yield. The reaction was more efficient when run at -78° to 25°C, producing a 90% yield by GC; the product was isolated in 68% yield.



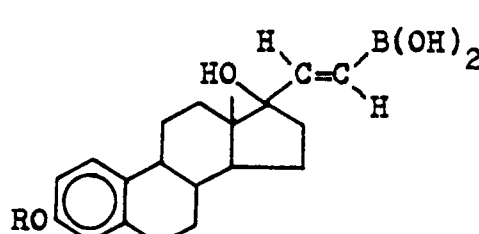
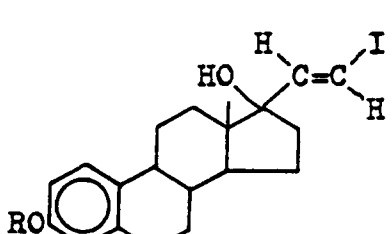
This prompted us to investigate the iodination of the 2-alkyl-1,3,2-benzodioxaboroles which are used to synthesize the boronic acids. Hydroboration of 1-octene with CB produced 2-octyl-1,3,2-benzodioxaborole; unfortunately, the iodination produced no 1-iodooctane.

The iodination of boronic acids was quite tolerant of functional groups in the substrate. Several functionalized (E)-1-alkenylboronic acids were synthesized and iodinated in good yield, including the two steroids (Table X).

The success of the alkenylboronic acids prompted us to investigate the iodination of arylboronic acids. Phenylboronic acid and p-tolylboronic acid⁴⁷ were iodinated in good yields at 25°C (Table X).



TABLE X. Synthesis of several alkenyl and aryl iodides from the boronic acids using ICl

Starting Material ^a	Product ^b	Yield ^c
$(C_6H_5)_3B$	C_6H_5I	(31)
$C_6H_5B(OH)_2$	C_6H_5I	(83)
$p-CH_3C_6H_4B(OH)_2$	$p-CH_3C_6H_4I$	70 (91)
$CH_3CH_2CH_2CH_2$ $\begin{array}{c} \diagup \\ C \\ \diagdown \end{array} \begin{array}{c} H \\ B(OH)_2 \end{array}$	$CH_3CH_2CH_2CH_2$ $\begin{array}{c} \diagup \\ C \\ \diagdown \end{array} \begin{array}{c} H \\ I \end{array}$	68 (90)
$ClCH_2CH_2CH_2$ $\begin{array}{c} \diagup \\ C \\ \diagdown \end{array} \begin{array}{c} H \\ B(OH)_2 \end{array}$	$ClCH_2CH_2CH_2$ $\begin{array}{c} \diagup \\ C \\ \diagdown \end{array} \begin{array}{c} H \\ I \end{array}$	73 (90)
$CH_3OCO(CH_2)_8$ $\begin{array}{c} \diagup \\ C \\ \diagdown \end{array} \begin{array}{c} H \\ B(OH)_2 \end{array}$	$CH_3OCO(CH_2)_8$ $\begin{array}{c} \diagup \\ C \\ \diagdown \end{array} \begin{array}{c} H \\ I \end{array}$	70
		$R = CH_3$ 88 $R = H$ 64

^a Alkenylboronic acids were prepared by hydroboration of the terminal alkynes with CB followed by hydrolysis; arylboronic acids were prepared via the Grignard reagents.

^b Products were characterized by IR, NMR and MS.

^c Yields in parentheses were obtained by GC analysis.

Finally, the ethynyl estradiol and mestranol boronic acids were synthesized and iodinated with ^{125}ICl in high radiochemical yield.

C. Experimental

Triphenylborane.²⁷ A 500-mL, 3-neck, round-bottomed flask with septum inlet was fitted with an addition funnel, mechanical stirrer, reflux condenser, gas outlet to a Hg bubbler, and flame dried and cooled under nitrogen. A nitrogen atmosphere was maintained throughout the course of the reaction and subsequent isolation of the product. The flask was charged with boron trifluoride etherate (14.2 g, 100 mmol) and ether (25 mL). Phenylmagnesium bromide prepared from bromobenzene (51.8 g, 330 mmol) and magnesium (8.3 g, 0.33 g-atom) in 250 mL ether was slowly added. A slow reflux began after 20 m and continued until the addition was complete (2.5 h). The reflux condenser was replaced (under nitrogen) by a distillation head, condenser and receiver. Some of the ether was distilled off. The system was cooled and heptane (200 mL) was added. The distillation was resumed and the rest of the ether and some heptane were removed. Cooling of the heptane solution provided the crystalline product; mp 143-145°C. Yield not determined.

p-Tolylboronic acid.⁴⁷ A 250-mL, 3-neck, round-bottomed flask with septum inlet was fitted with an addition funnel, magnetic stirring bar, reflux condenser, gas outlet to a Hg bubbler, and flushed with nitrogen. The flask was charged with trimethylborate (15.6 g, 150 mmol) and cooled to -78°C . p-Tolylmagnesium bormide made from p-bromotoluene (25.6 g, 150 mmol) and magnesium (3.65 g, 0.15 g-atom) in 30 mL ether was added over 1 h. The solution was allowed to warm to 0°C and added slowly with stirring to cold 10% aqueous H_2SO_4 . The aqueous layer was washed with 2 x 50 mL ether; the combined ether layers were evaporated, and the residue dissolved in dilute HCl and filtered. Cooling of the solution provided the crystalline product. Yield 8.6 g (42%); mp $259-260^{\circ}\text{C}$.

Preparation of vinylboronic acids--general. The alkyne was placed in a dry, nitrogen-flushed, round-bottomed flask. One equivalent of catecholborane (CB) was added and the mixture heated to 70°C for 3 h, then cooled. A large excess of water was added (slowly at first, to destroy excess CB) and the mixture stirred overnight. The solid boronic acids were filtered and washed with copious amounts of water to remove catechol.

Iodination of boronic acids--general. The vinylboronic acid was dissolved in THF and cooled to 0°C or -78°C . Two equivalents of methanolic sodium acetate (1 M)

and one equivalent of methanolic ICl (1 M) were added and the mixture stirred 30 m, poured into water, and decolorized with sodium thiosulfate. The product was extracted into ether and isolated by chromatography.

(E)-1-Iodohexene. 1-Hexyne (5.75 mL, 50 mmol) was hydroborated with CB (5.38 mL, 50 mmol). The yield of (E)-1-hexenylboronic acid was 5.85 g (92%); mp 99-100°C; NMR (CDCl₃) δ 0.9 (m, 3H, CH₃), 1.4 (m, 4H, CH₂CH₂CH₃), 2.1 (m, 2H, CH₂CH=C), 5.4 (d, 1H, C=CHB(OH)₂, J = 17 Hz), 6.5 (d of triplets, 1H, CH₂CH=C, J = 17 Hz, J' = 7 Hz).

The boronic acid (1.70 mg, 1.33 mmol) was iodinated with sodium acetate and ICl (1.3 mL of a 1 M soln, 1.3 mmol). The yield was 90%; NMR (CCl₄) δ 0.9 (m, 3H, CH₃), 1.4 (m, 4H, CH₂CH₂CH₃), 2.1 (m, 2H, CH₂CH=C), 5.85 (d, 1H, C=CHI), 6.25 (m, 1H, CH₂CH=C).

(E)-1-Iodo-5-chloro-1-pentene. 5-Chloro-1-pentyne (8.7 g, 85 mmol) was hydroborated with CB (9.44 mL, 85 mmol). The yield of the boronic acid was 9.11 g (73%); mass spectrum (EI) m/e 148.2, calcd 148.4; NMR (CDCl₃) δ 1.4-2.2 (m, 4H, CH₂CH₂CH₂Cl), 3.2 (t, 2H, CH₂Cl), 5.4 (d, 1H, CH=CHB(OH)₂, J = 17 Hz), 6.5 (m, 1H, CH=CHB).

The boronic acid (5.92 g, 40 mmol) was iodinated with sodium acetate and ICl (40 mL of a 1 M soln, 40 mmol). The yield was 7.0 g (76%); mass spectrum (EI) m/e 230.2 (58%) and 232.2 (17%), calcd 230.5 and 232.5; NMR (CCl₄)

δ 2.0 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$), 3.45 (t, 2H, CH_2Cl), 6.0 (d, 1H, $\text{C}=\text{CHI}$, $J = 15$ Hz), 6.2 (d, of triplets, 1H, $\text{CH}_2\text{CH}=\text{CHI}$).

Methyl (E)-11-iodo-10-undecenoate. Methyl 10-undecynoate (1.6 g, 8 mmol) was prepared by the reaction of 10-undecynoic acid with diazomethane, then hydroborated with CB (0.88 mL, 8 mmol). The yield of the boronic acid was 1.7 g (87%); mp $48-50^\circ\text{C}$; mass spectrum (EI) m/e 316.9, calcd 316.1; NMR (CDCl_3) δ 1.3 (br s, 12H, alkyl), 2.35 (br envelope, 4H, $\text{CH}_2\text{CH}=\text{}$ and $\text{CH}_2\text{CO}_2\text{Me}$), 3.6 (s, 3H, OCH_3), 5.38 (d, 1H, $\text{C}=\text{CHB}(\text{OH})_2$, $J = 17$ Hz), 6.4 (m, 1H, $\text{CH}=\text{CHB}$).

The boronic acid (198 mg, 0.81 mmol) was iodinated with sodium acetate and ICl (0.81 mL of a 1 M soln, 0.81 mmol). The yield was 183 mg (70%); mass spectrum (EI) m/e 197 ($M - 127$), calcd 324.2; NMR (CDCl_3) δ 1.35 (br s, 12H, alkyl), 2.35 (br envelope, 4H, $\text{CH}_2\text{CH}=\text{}$ and $\text{CH}_2\text{CO}_2\text{Me}$), 3.6 (s, 3H, OCH_3), 5.85 (d, 1H, $\text{CH}=\text{CHI}$, $J = 14$ Hz), 6.4 (m, 1H, $\text{CH}=\text{CHI}$).

17 α -(E)-2-iodovinyl- $\Delta^{1,3,5}$ -estratrien-3,17 β -diol-3-methyl ether. Mestranol (3.1 g, 10 mmol) was hydroborated with CB (1.1 mL, 10 mmol). The yield of the boronic acid was 3.64 g (98%); mp $148-150^\circ\text{C}$; mass spectrum (EI) m/e 312.6 ($M - 44$), calcd 356.6; NMR (CD_3SOCD_3) δ 0.9 (s, 3H, CH_3), 1.0-2.8 (br envelope, 15H, steroid nucleus), 3.6 (s, 3H, OCH_3), 5.4 (d, 1H, $\text{C}=\text{CHB}(\text{OH})_2$, $J = 17.5$ Hz), 6.5-7.2 (complex m, 4H, ArH and $\text{CH}=\text{CHB}$).

The boronic acid (364 mg, 1 mmol) was iodinated with sodium acetate and ICl (1 mL of a 1 M soln, 1 mmol). The product was isolated by preparative TLC on silica gel (ligroin/ethyl acetate/methanol (200:25:25), $R_f = 0.5$). The yield was 385 mg (88%); mass spectrum (CI) m/e 439 ($M + 1$), calcd 438; NMR (CCl_4) δ 0.9 (s, 3H, CH_3), 1.0-2.8 (br envelope, 15H, steroid nucleus), 3.6 (s, 3H, OCH_3), 6.2 (d, 1H, $C=CHI$), 6.4-7.2 (complex m, 4H, ArH and $CH=CHI$).

17 α -(E)-2-iodovinyl- $\Delta^{1,3,5}$ -estratrien-3,17 β -diol.

Ethynyl estradiol (300 mg, 1 mmol) was hydroborated with CB (0.11 mL, 1 mmol). The boronic acid was isolated by preparative TLC on silica gel (ligroin/ethyl acetate/methanol (250:35:35), $R_f = 0.25$). Yield 173 mg (50%); mass spectrum (EI) m/e 298.6 ($M - 44$), calcd 342.6; NMR (CD_3SOCD_3) δ 0.9 (s, 3H, CH_3), 1.2-2.8 (br envelope, 15H, steroid nucleus), 5.4 (d, 1H, $CH=CHB(OH)_2$, $J = 17$ Hz), 6.5-7.2 (complex m, 4H, ArH and $CH=CHB$).

The boronic acid (100 mg, 0.28 mmol) was iodinated with sodium acetate and ICl (0.28 mL of a 1 M soln, 0.28 mmol). The product was isolated by preparative TLC on silica gel (ligroin/ethyl acetate/methanol (200:35:35), $R_f = 0.2$). Yield 76 mg (64%); mass spectrum (EI) m/e 424, calcd 424; NMR ($CDCl_3$) δ 0.9 (s, 3H, CH_3), 1.1-2.9 (br envelope, 15H, steroid nucleus), 6.6 (d, 1H, $CH=CHI$), 6.8-7.2 (complex m, 4H, ArH and $CH=CHI$).

Attempted iodination of 2-(1-octyl)-1,3,2-benzodioxaborole. 1-Octene (2.35 mL, 15 mmol) was heated with CB (1.65 mL, 15 mmol) at 100°C for 16 h. To 0.5 mL (2.09 mmol) of the organoboronic ester was added neat ICl (100 μ L, 2 mmol). No 1-iodooctane was observed by GC analysis.

Iodobenzene from triphenylborane. Triphenylborane (247 mg, 1 mmol) was iodinated with sodium methoxide and methanolic ICl (3.0 mL of a 1 M soln, 3 mmol). Undecane (212 μ L, 1 mmol) was added and the mixture analyzed by GC; yield 194 mg (31%).

Iodobenzene from phenylboronic acid. Phenylboronic acid (122 mg, 1 mmol) was iodinated with sodium acetate and methanolic ICl (1 mL of a 1 M soln, 1 mmol). Undecane (212 μ L, 1 mmol) was added and the mixture analyzed by GC; yield 170 mg (83%).

p-Iodotoluene. p-Tolylboronic acid (136 mg, 1 mmol) was iodinated with sodium acetate and methanolic ICl (1 mL of a 1 M soln, 1 mmol). Undecane (212 μ L, 1 mmol) was added and the mixture analyzed by GC; yield 198 mg (91%).

CHAPTER V

THE REACTION OF ORGANOBORANES WITH SODIUM IODIDE AND CHLORAMINE-T

A. Background and Statement of the Problem

Several methods for the incorporation of radioiodine into organic molecules (in addition to the use of ICl) are currently in use.³⁴ These include radioiodine exchange involving iodo-substituted reagents, the addition of I₂ to double bonds and the Sandmeyer reaction. The oxidation



of iodide ion with mild reagents such as chlorine, nitrite and chloramine-T are also commonly employed.

The oxidation procedures were of particular interest to us because of the lack of long term stability of ¹²⁵ICl (pages 37 and 38) and the problems associated with the handling of this corrosive reagent.

Synthetic chemists have incorporated iodine into organic molecules via oxidation of iodide ions for years,^{48,49} and it is clear that the reacting species is some form of

electropositive iodine. Since the reaction of organoboranes with ICl involves an $\text{S}_{\text{E}}2$ reaction of a borate complex with a positively polarized iodine, it is possible that a reaction might occur between a borate complex and iodide ion in the presence of an oxidizing agent.

Chloramine-T was chosen as the first reagent to be investigated since its chemistry has been extensively reviewed.⁵⁰

B. Results and Discussion

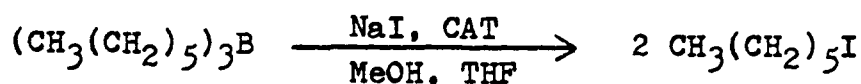
The addition of methanolic chloramine-T to a mixture of tri-n-hexylborane in THF, methanolic sodium acetate and aqueous sodium iodide at 25°C resulted in the appearance of a brown color, which rapidly disappeared. Within two minutes, GC analysis indicated that 1-iodohexane was present in good yield. A study of the stoichiometry of the reaction was carried out as before (Table XI).

TABLE XI. Stoichiometric study of the reaction of tri-n-hexylborane with iodide and chloramine-T^a

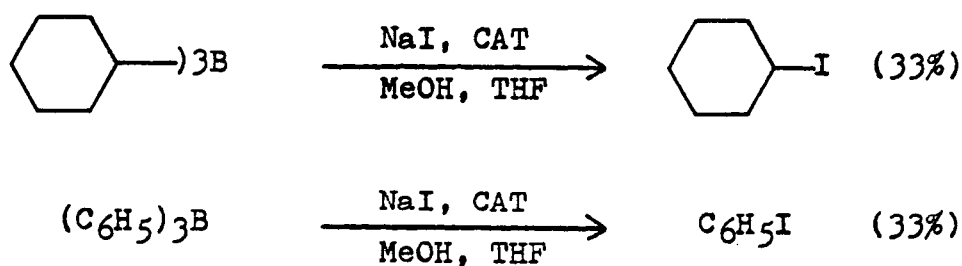
Equivalents of Iodide		Equivalents of Sodium Acetate								
		1			2			3		
		1	2	3	1	2	3	1	2	3
of CAT	1	30	31	31	31	33	32	24	31	32
	2	33	57	55	33	65	57	33	60	66
	3	26	48	69	21	54	53	24	48	65

^a Values given are percent yields based on 1-hexene; each value is the average of three GC analyses.

The best yields (based on the limiting reagent, sodium iodide) resulted when the number of equivalents of sodium acetate and chloramine-T were one greater than the number of equivalents of iodide. These results paralleled the earlier studies using ICl (Tables II and III, pages 11 and 15). The maximum yield based on 1-hexene was 66%. No 2-iodohexane was observed as a product.

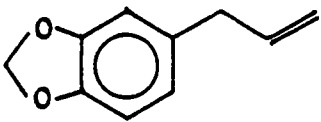
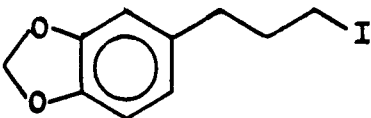
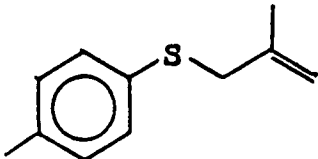
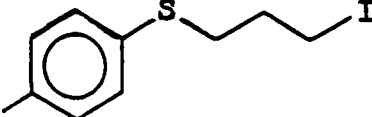


The iodination of tricyclohexylborane produced iodo-cyclohexane in a maximum yield of 33%. Once again, primary alkyl groups are more readily iodinated than secondary groups. The iodination of triphenylborane produced iodobenzene in 33% yield also.



The tolerance of the new iodination method towards functionality in the substrate was evaluated. Several terminal olefins containing functional groups were converted to the corresponding primary alkyl iodides (Table XII) via iodination with sodium iodide/chloramine-T. No measures

TABLE XII. Conversion of several terminal olefins to alkyl iodides using iodide/chloramine-T

Olefin ^a	Alkyl Iodide ^b	Isolated Yield ^c
$\text{C}_6\text{H}_5\text{CO}_2(\text{CH}_2)_3\text{CH}=\text{CH}_2$	$\text{C}_6\text{H}_5\text{CO}_2(\text{CH}_2)_5\text{I}$	94
$\text{CH}_3\text{OCO}(\text{CH}_2)_8\text{CH}=\text{CH}_2$	$\text{CH}_3\text{OCO}(\text{CH}_2)_{10}\text{I}$	94
		78
		99
$\text{CH}_2=\text{CH}(\text{CH}_2)_{16}\text{CO}_2\text{H}^{\text{d}}$	$\text{ICH}_2\text{CH}_2(\text{CH}_2)_{16}\text{CO}_2\text{H}$	89
$\text{CH}_2=\text{CH}(\text{CH}_2)_{19}\text{CO}_2\text{H}^{\text{d}}$	$\text{ICH}_2\text{CH}_2(\text{CH}_2)_{19}\text{CO}_2\text{H}$	91

^a Olefins were hydroborated with BH_3 -THF at 0°C , then iodinated with 2 equiv NaI and 3 equiv each of NaOAc and chloramine-T.

^b The products exhibited properties identical to those of authentic samples.

^c Based on the limiting reagent, NaI.

^d Olefins hydroborated with 2 equiv DCB, then iodinated with 1 equiv NaI and 2 equiv each of NaOAc and Chloramine-T.

were taken to protect the functional groups during the transformation. In all cases, the functional groups survived intact, and the products were isolated in good yields.

The iodination of vinyl and arylboronic acids with iodide/chloramine-T was investigated. The reaction was found to be solvent dependent; poor yields were obtained in solvents which did not dissolve the boronic acids completely. With the proper solvents, good yields were obtained (Table XIII).

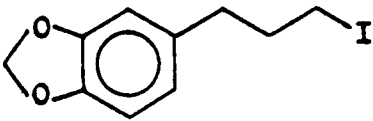
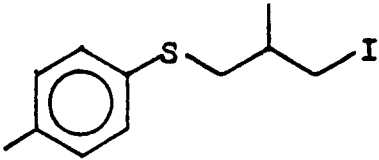
TABLE XIII. Iodination of some alkenyl- and arylboronic acids with iodide/chloramine-T^a

Iodide	Solvent	Yield (%)
$\text{ICH}_2\text{CH}_2\text{CH}_2\begin{array}{c} \diagup \text{H} \\ \text{C}=\text{C} \\ \diagdown \text{I} \\ \text{H} \end{array}$	MeOH	45
	H ₂ O/THF	80
C ₆ H ₅ I	MeOH	<5
	H ₂ O/THF	75
p-CH ₃ C ₆ H ₄ I	MeOH	74
	H ₂ O/THF	40

^a The corresponding boronic acids were iodinated with 2 equiv each of acetate and chloramine-T and 1 equiv of iodide.

In order to successfully apply the iodination reaction of organoboranes with iodide/chloramine-T to the synthesis of radiopharmaceuticals, we needed to evaluate the utilization of radioiodine. The same series of compounds was used in the study as in Table XII. The corresponding labeled iodoalkanes were synthesized in high yields (Table XIV), and the specific activities of the products were identical to that of the Na^{125}I .

TABLE XIV. Iodination of several terminal olefins using Na^{125}I and chloramine-T

Labeled Product	Chemical/Radiochemical Yield
$\text{C}_6\text{H}_5\text{CO}_2(\text{CH}_2)_5\text{I}$	94/90
$\text{CH}_3\text{OCO}(\text{CH}_2)_8\text{CH}_2\text{CH}_2\text{I}$	94/94
	78/78
	99/99
$\text{ICH}_2\text{CH}_2(\text{CH}_2)_{16}\text{CO}_2\text{H}$	89/82
$\text{ICH}_2\text{CH}_2(\text{CH}_2)_{19}\text{CO}_2\text{H}$	91/89

C. Carrier-Free Experiments Using Radioiodine

The iodination of organoboranes with ICl and iodide/chloramine-T are efficient methods for the incorporation of radioiodine into organic compounds, as shown by preliminary experiments at the tracer level. However, a final set of experiments (run under quite different conditions) was required to complete the evaluation of these synthetic methods as routes to radiopharmaceuticals.

The actual use of a radiopharmaceutical for positron emission tomography requires the synthesis of the imaging agent on an ultramicro scale using carrier-free radioisotopes. The concentrations of the reagents are generally in the 10^{-9} to 10^{-18} M range; in addition, all reagents except the radionuclide are in great excess. To be successful for radiopharmaceutical synthesis, the synthetic method used must work under these conditions.

The iodination of 15-hexadecenoic acid with ^{125}ICl and the iodination of methyl 10-undecenoate with $^{125}\text{I}^-$ /chloramine-T were repeated at the ultramicro scale using the carrier-free iodine-125 (~ 2700 Ci/mole). The labeled products were obtained (identified by TLC). Thus, the methods are applicable to the synthesis of radiopharmaceuticals.

D. Experimental

General. The analytical equipment and commercial reagents used have been described in earlier chapters. Sodium iodide-125 (New England Nuclear) was received as an aqueous solution stabilized with sodium hydroxide; the activity was approximately 2500 Ci/mol. For the tracer studies this was diluted to approximately 5 mCi/mol with 1 M aqueous sodium iodide. For the carrier-free experiments, the undiluted isotope solutions were used as received.

1-Iodohexane. To a 5-mL, oven-dried, nitrogen-flushed, round-bottomed flask equipped with magnetic stirring bar was added tri-n-hexylborane (1 mL of a 1 M soln, 1 mmol), undecane (212 μ L, 1 mmol), sodium iodide (1-3 mL of a 1 M soln, 1-3 mmol), sodium acetate (1-3 mL of a 1 M soln, 1-3 mmol) and chloramine-T (CAT; 2-6 mL of a 0.5 M soln, 1-3 mmol). The mixture was analyzed by GC; the yields are reported in Table XI, page 58.

Iodocyclohexane. To a 5-mL, oven-dried, nitrogen-flushed, round-bottomed flask equipped with magnetic stirring bar was added tricyclohexylborane (1 mL of a 1 M soln, 1 mmol), decane (195 μ L, 1 mmol), sodium iodide and sodium acetate (1-3 mL of a 1 M soln, 1-3 mmol) and CAT (2-6 mL of 1 0.5 M soln, 1-3 mmol). GC analysis of the mixture indicated a maximum yield of 210 mg iodo-cyclohexane (33%).

Iodobenzene from triphenylborane. Triphenylborane (247 mg, 1 mmol) was iodinated with sodium iodide and sodium acetate (3 mL of a 1 M soln, 3 mmol) and chloramine-T (6 mL of a 0.5 M soln, 3 mmol). Undecane (212 μ L, 1 mmol) was added; GC analysis indicated a maximum yield of 33% of iodobenzene.

5-Benzoxo-1-iodopentane. 5-Benzoxo-1-pentene (0.49 mL, 3 mmol) was hydroborated with BH_3 -THF (0.5 mL of a 2 M soln, 1 mmol) at 0°C, and iodinated with sodium iodide and sodium acetate (2 mL of a 1 M soln, 2 mmol) and chloramine-T (4 mL of a 0.5 M soln, 2 mmol) at 25°C. The product was isolated by chromatography²⁶ on silica gel. Yield 574 mg (94%); the product exhibited properties identical to an authentic sample.

Methyl 11-iodoundecanoate. Methyl 10-undecenoate (0.67 mL, 3 mmol) was hydroborated with BH_3 -THF (0.5 mL of a 2 M soln, 1 mmol) at 0°C, and iodinated with sodium iodide and sodium acetate (2 mL of a 1 M soln, 2 mmol) and chloramine-T (4 mL of a 0.5 M soln, 2 mmol) at 25°C. The product was isolated by chromatography²⁶ on silica gel. Yield 613 mg (94%); the product exhibited properties identical to an authentic sample.

3-(3,4(Methylenedioxy)phenyl)-1-iodopropane. Safrole (0.45 mL, 3 mmol) was hydroborated with BH_3 -THF (0.5 mL of a 2 M soln, 1 mmol) at 0°C , and iodinated with sodium iodide and sodium acetate (2 mL of a 1 M soln, 2 mmol) and chloramine-T (4 mL of a 0.5 M soln, 2 mmol) at 25°C . The product was isolated by chromatography²⁶ on silica gel. Yield 453 mg (78%); the product exhibited properties identical to an authentic sample.

3-(p-Tolylthio)-2-methyl-1-iodopropane. 3-(p-Tolylthio)-2-methylpropene (0.54 mL, 3 mmol) was hydroborated with BH_3 -THF (0.5 mL of 1 2 M soln, 1 mmol) at 0°C , and iodinated with sodium iodide and sodium acetate (2 mL of a 1 M soln, 2 mmol) and chloramine-T (4 mL of a 0.5 M soln, 2 mmol) at 25°C . The product was isolated by chromatography²⁶ on silica gel. Yield 602 mg (99%); the product exhibited properties identical to an authentic sample.

19-Iodononadecanoic acid. 18-Nonadecenoic acid (100 mg, 0.34 mmol) was hydroborated with DCB (0.68 mL of a 1 M soln, 0.68 mmol) at 0°C , and iodinated with sodium iodide (0.34 mL of a 1 M soln, 0.34 mmol), sodium acetate (0.68 mL of a 1 M soln, 0.68 mmol) and chloramine-T (1.36 mL of a 0.5 M soln, 0.68 mmol) at 25°C . The product was isolated by chromatography²⁶ on silica gel. Yield 129 mg (89%); the product exhibited properties identical to an authentic sample.

22-Iododocosanoic acid. 21-Docosenoic acid (100 mg, 0.3 mmol) was hydroborated with DCB (0.6 mL of a 1 M soln, 0.6 mmol) at 0°C, and iodinated with sodium iodide (0.3 mL of a 1 M soln, 0.3 mmol), sodium acetate (0.6 mL of a 1 M soln, 0.6 mmol) and chloramine-T (1.2 mL of a 0.5 M soln, 0.6 mmol) at 25°C. The product was isolated by chromatography. Yield 127 mg (91%); the product exhibited properties identical to an authentic sample.

5-Iodo-1-pentyne. 5-Chloro-1-pentyne (10.5 mL, 85 mmol), sodium iodide (45.0 g, 300 mmol) and 2-butanone (600 mL) were refluxed for 18 h, and all but 50 mL of the butanone distilled off. Pentane (100 mL) was added, and the mixture was filtered. To the filtrate was added water (500 mL) and ether (250 mL). The organic layer was washed with 2 x 100 mL water and dried (MgSO₄). The solvent was removed under reduced pressure to yield the solid product. Yield 15.0 g (90%); NMR (CDCl₃) δ 1.05 (t, 2H, CH₂C $\equiv$ C), 2.0-2.4 (complex m, 3H, CH₂CH₂C $\equiv$ CH), 3.3 (t, 2H, CH₂I).

(E)-1,5-Diiodo-1-pentene. 5-Iodo-1-pentyne (12.5 g, 60 mmol) was hydroborated with CB (10.0 mL, 90 mmol) at 70°C for 6 h; water was slowly added to destroy excess hydride. The solid boronic acid was filtered and washed with water. Yield 11.5 g (80%); mass spectrum (EI) m/e

240.2, calcd 239.9; NMR (CDCl_3) δ 1.4-2.4 (complex m, 4H, $\text{CH}_2\text{CH}_2\text{C=}$), 3.3 (t, 2H, CH_2I), 5.4 (d, 1H, $=\text{CHB}(\text{OH})_2$, $J = 17 \text{ Hz}$), 6.5 (d, of triplets, 1H, $\text{CH}=\text{CHB}$).

The boronic acid (2.39 g, 10 mmol) was iodinated with sodium iodide (10 mL of a 1 M soln, 10 mmol), sodium acetate (20 mL of a 1 M soln, 20 mmol) and chloramine-T (40 mL of a 0.5 M soln, 20 mmol) at 25°C . The product was isolated by chromatography. Yield 1.45 g (45%); NMR (neat) δ 1.8-2.4 (complex m, 4H, $\text{CH}_2\text{CH}_2\text{CH=}$), 3.3 (t, 2H, CH_2I), 6.0 (d, 1H, $=\text{CHI}$, $J = 15 \text{ Hz}$), 6.5 (d, of triplets, 1H, $\text{CH}=\text{CHI}$, $J = 15 \text{ Hz}$, $J' = 6 \text{ Hz}$). When the reaction was repeated using water/THF instead of methanol the product was isolated in 80% yield.

Iodobenzene from phenylboronic acid. Phenylboronic acid (122 mg, 1 mmol) was iodinated with sodium iodide (1 mL of a 1 M soln, 1 mmol), sodium acetate (2 mL of a 1 M soln, 2 mmol) and chloramine-T (4 mL of a 0.5 M soln, 2 mmol) at 25°C . Undecane (212 μL , 1 mmol) was added; GC analysis indicated less than 5% yield.

The reaction was repeated using water/THF instead of methanol. The reaction mixture was extracted with 2 x 5 mL of pentane before the undecane was added. GC analysis indicated a 75% yield of iodobenzene.

p-Iodotoluene. p-Tolylboronic acid (136 mg, 1 mmol) was iodinated as described above for iodobenzene. Undecane

(212 μL , 1 mmol) was added; GC analysis indicated a 74% yield. The reaction was repeated using water/THF instead of methanol. The reaction mixture was extracted with 2 x 5 mL of pentane before the undecane was added. GC analysis indicated a 40% yield of p-iodotoluene.

Carrier-free 16-iodohexadecanoic acid iodine-125.

15-Hexadecenoic acid (0.5 mL of a 0.05 M soln, 25 μmol) was hydroborated with DCB (50 μL of a 1 M soln, 50 μmol) at 0°C, and iodinated with ^{125}ICl in CCl_4 (1.0 mL, 1.25 mCi) and sodium acetate (50 μL of a 1 M soln, 50 μmol) at 25°C. The solution was poured into 2% acetic acid (5 mL) and ligroin (5 mL). The aqueous layer was washed with ligroin (5 mL); the combined ligroin layers washed with aqueous NaCl (5 mL), and concentrated to 0.2 mL. The product was identified (p. 37) by TLC on silica gel (ligroin/ethyl acetate/methanol (79:20:1), $R_f = 0.35$).

Carrier-free methyl 11-iodoundecanoate iodine-125.

Methyl 10-undecenoate (0.22 mL, 1 mmol) was hydroborated with DCB (1 mL of a 1 M soln, 1 mmol) at 0°C. To THF (100 μL) was added the organoborane (1 μL , 1 μmol), sodium acetate (10 μL of a 0.1 M soln, 1 μmol), sodium iodide-125 (500 μL , 2.0 mCi), and chloramine-T (10 μL of a 0.1 M soln, 1 μmol) at 25°C. Water (1 mL) was added, and the mixture extracted with 2 x 0.5 mL pentane. The combined pentane layers were concentrated; the product was identified by TLC (ligroin/ethyl acetate (90:10) $R_f=0.7$).

CHAPTER VI

CONCLUSIONS OF THE STUDY

Organoboranes are useful synthetic intermediates for the incorporation of iodine into organic molecules. In the presence of base, boron is regiospecifically and stereospecifically replaced by iodine (either via ICl or iodide in the presence of chloramine-T). The reaction is quite tolerant of functionality in the organic substrate.

Maximum utilization of the alkyl substrate is possible using mixed trialkylboranes as intermediates. Vinyl- and arylboronic acids are also iodinated regiospecifically and stereospecifically.

Both synthetic methods provide maximum utilization of radioiodine in the synthesis of labeled compounds. The reactions can be successfully run under conditions favorable for the synthesis of carrier-free radiopharmaceuticals.

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VITA

Edgar Eugene Gooch III was born and raised in Knoxville, Tennessee. He attended Harrison-Chilhowee Baptist Academy, Seymour, Tennessee, graduating valedictorian in 1969. He received his B. S. degree in chemistry at Carson-Newman College in 1973, and immediately entered graduate school at the University of Tennessee, Knoxville. After one year he left graduate school.

He obtained an associate degree in computer programming at Knoxville Business College and took a job as a computer operator in west Knoxville. He married Marcia Lee Thomas, a native of Decatur, Georgia, in 1976.

He returned to graduate school at the University of Tennessee, Knoxville, attending classes part time in 1977. He was reinstated as a full time student in 1978, and has since been pursuing the Ph. D. degree. He has coauthored publications in the Journal of Organic Chemistry, the Journal of Labeled Compounds and Radiopharmaceuticals, Synthetic Communications, Chemical Communications, and Synthesis. He has presented papers at two regional meetings and one national meeting of the American Chemical Society.