SYNTHESIS OF DIARYLIODONIUM SALTS FOR USE IN NUCLEOPHILIC SUBSTITUTION REACTIONS

A THESIS
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ABSTRACT

Diaryliodonium salts are a type of hypervalent iodine compound that are capable of arylating a variety of nucleophiles. Unsymmetrical diaryliodonium salts provide varying degrees of selectivity during reactions with nucleophiles where one aryl group is preferentially transferred to the nucleophile. It is the goal of this research to develop a diaryliodonium salt where the substituents on one of the aryl groups are modified in such a manner that it causes a nucleophile to couple with the other aryl group with >95% selectivity. This research finds practical application as it relates to Positron Emission Tomography (PET). Positron Emission Tompgraphy is an area of molecular imaging that is used to visualize human physiology by the detection of positron-emitting radiopharmaceuticals labeled with short lived positron-emitting radionuclides. Recent research has focused on efficiently introducing the [^{18}F]fluoride ion into an aryl group of diaryliodonium salts.

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LIST OF ABBREVIATIONS

PET = Positron Emission Tomography

λ = Lambda

TIPS = triisopropylsilyl

EDG = Electron Donation Group

EWG = Electron Withdrawing Group

Nu = Nucleophile

equiv = Equivalents

OTs = OTosylate

OTf = OTriflate

n-BuLi = normal- butyl lithium

Et_2O = diethyl ether

HR-MS = High Resolution Mass Spectrometry

g = gram

mol = mole

PTFE = Polytetrafluoroethylene

Pd = palladium

nmr = Nuclear Magnetic Resonance

m/z = mass / charge

CHAPTER 1

REVIEW

1.1 Introduction

Hypervalent iodine compounds have recently received considerable attention as mild, nontoxic, and selective reagents in organic synthesis.[1] They are efficient alternatives to toxic heavy metal based oxidants and expensive organometallic catalysts for many organic reactions.[2] Hypervalent iodine compounds are compounds that feature an iodine atom that exceeds the octet rule. The octet rule states that atoms combine in such a manner so that every atom has eight electrons in its valence shell. **Figure 1** shows an example of a hypervalent iodine compound in which the iodine atom has ten valence electrons. The compound in **Figure 1** is termed a lambda three (λ^3) hypervalent iodine compound. The λ^3 nomenclature is used to denote that the iodine atom exhibits the non-standard valence state of iodine (III).
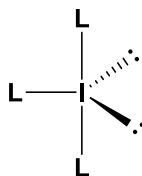
L = Ligand

I = Iodine

: = Lone Pair of Electrons

Figure 1

Diaryliodonium salts are just one branch of a wide range of λ^3 hypervalent iodine compounds. Diaryliodonium salts consist of a central iodine atom that is bonded to two aryl functional groups (R^1 and R^2), and anion (X^-) as shown in **Figure 2**. The term "salt" is used in chemistry to define a compound that is ionic. Diaryliodonium salts are ionic because they are comprised of a cation and an anion. Formally, the iodonium cation does not belong to the hypervalent species since it has only eight valence electrons on the iodine atom; however, in the modern literature diaryliodonium salts are commonly treated as ten electron hypervalent compounds, taking into account the closely associated anionic part of the molecule.[3] This close association is shown in **Figure 2** as a dashed line between the iodine atom and anion (X^-).
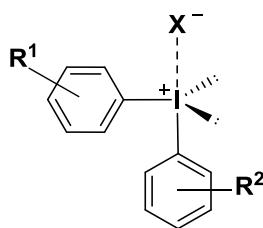
X = Cl, Br, I, OTf, OTs, BF$_4$, ...

Figure 2

X-Ray structural data for the overwhelming majority of diaryliodonium salts show significant secondary bonding between the iodine atom and the anion (X^-), with average bond distances within the range 2.3-2.7Å. Their structure has overall trigonal-bipyramidal geometry and the experimentally determined R-I-R bond angle is close to 90°. Key structural features of diaryliodonium salts available from numerous X-ray data

show that diaryliodonium salts generally have the least electronegative aryl group and both lone pairs of electrons residing in equatorial positions. The axial positions are occupied by the most electronegative aryl group and the anion (X⁻). Bonding in the diaryliodonium salt uses an essentially pure 5p iodine orbital for bonding with the two axial substituents. This is a hypervalent three-center four-electron bond (3c-4e bond) with two electrons from the doubly occupied 5p orbital on iodine and one electron from each of the axial substituents. The aryl group in the equatorial position is bound by a normal two-electron covalent bond with $5sp^2$ hybridization to form a C_{Ar}-I σ bond. The I-C bond lengths in diaryliodonium salts typically range from 2.00 to 2.10Å.

1.2 First Known Diaryliodonium Salt

The first known diaryliodonium salt was (4-iodophenyl)phenyliodonium bisulfate **2**. It was prepared in 1894 by Hartmann and Meyer.[4] This reaction is shown in **Scheme 1** by reacting iodosyl benzene **1** with sulfuric acid (H_2SO_4).
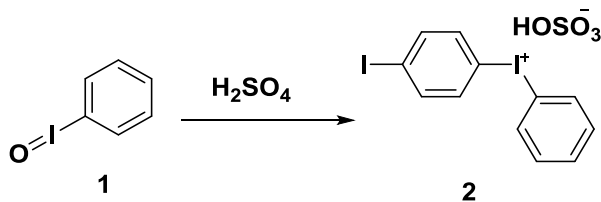
Scheme 1

1.3 Properties of Diaryliodonium Salts

Diaryliodonium salts are air and moisture stable compounds whose physical properties like melting point and solubility are strongly affected by the nature of the

anionic part of the molecule (X⁻).   Diaryliodonium salts come in two varieties, "symmetrical" and "unsymmetrical". A symmetrical diaryliodonium salt is shown below in **Figure 3**.   The salt is symmetrical because both aryl groups are identical. In **Figure 3** both aryl groups are simply phenyl groups.
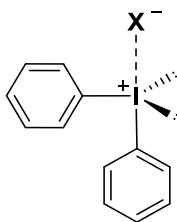
X = Cl, Br, I, OTf, OTs, BF$_4$, ...

Figure 3

An example of an unsymmetrical diaryliodonium salt is shown in **Figure 4**. The salt is unsymmetrical because the aryl groups are different from each other. In **Figure 4** one of the aryl groups is a phenyl group and the other aryl group is a 4-MeC$_6$H$_4$ group.
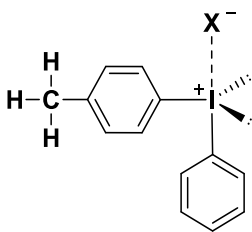
X = Cl, Br, I, OTf, OTs, BF$_4$, ...

Figure 4

Symmetrical diaryliodonium salts are generally preferable to unsymmetric salts because their use avoids selectivity issues in aryl-transfer reactions. Unsymmetrical

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diaryliodonium salts are desirable when it is necessary to transfer one aryl moiety with the other aryl moiety behaving as a "dummy ligand".[2] Selectivity issues arise because the aryl groups can often be differentiated electronically or sterically.[5] The general trend is that the more electron-deficient aryl moiety is transferred in enolate and heteroatom arylations whereas the more electron-rich aryl group is transferred in cross-coupling reactions.

1.4 Berry Pseudo-Rotation Involving Organo-λ^3-Iodanes

It is a general trend that diaryliodonium salts in the solid state feature the heteroatom (X^-) and the most electronegative aryl group in axial positions. When the diaryliodonium salt is dissolved into solution the salt is configurationally unstable and undergoes facile pseudo-rotation. Pseudo-rotation results in an exchange of the axial and equatorial ligands through bond bending. **Figure 5** shows schematically the reversible pseudo-rotation process whereby two equatorial bonds become axial bonds, while two axial bonds become equatorial bonds. In **Figure 5** the central sphere represents iodine and the small spheres (1-5) represent the substituents and/or lone pairs of electrons.
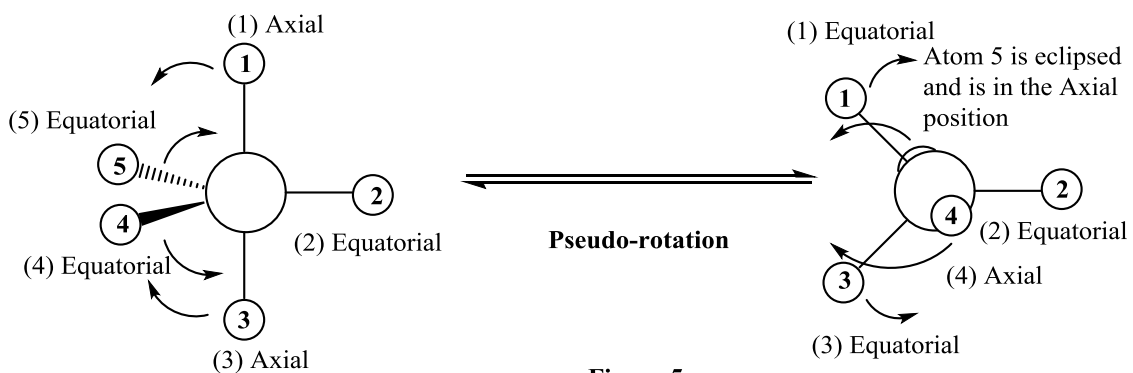
Figure 5

Figure 6 shows pseudo-rotation involving a diaryliodonium salt. Image **3** in **Figure 6** has the least electronegative aryl group (4-MeC$_6$H$_4$) located in the equatorial position and the more electronegative phenyl group located in the axial position. The (4-MeC$_6$H$_4$) aryl group is less electronegative than the phenyl group because the methyl group donates electron density to the aromatic ring through hyperconjugation. Image **3** undergoes pseudo-rotation whereby bond bending results in the (4-MeC$_6$H$_4$) group occupying the axial position and the phenyl group occupying the equatorial position as shown by **4**. A solution is expected to contain an equilibrium mixture of **3** and **4** with the major species being **3**.

Pseudo-rotation

X = Cl, Br, I, OTf, OTs, BF$_4$, ...

3   4
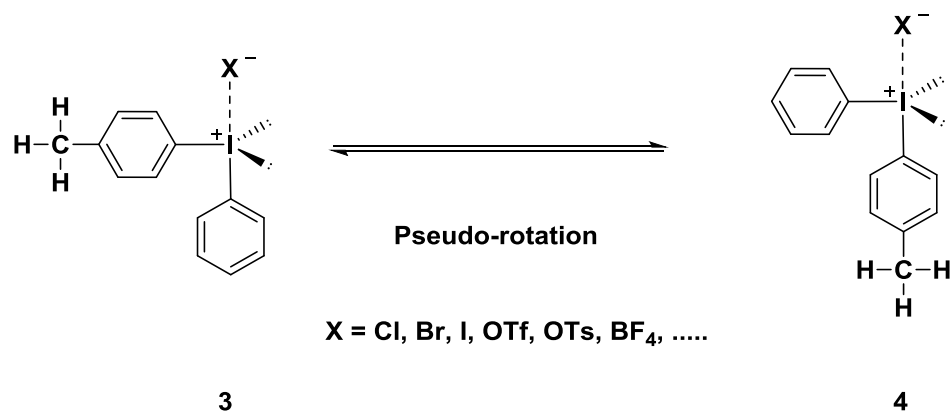
Figure 6

1.5 Reactivity Patterns of Organo-λ^3-Iodanes

Diaryliodonium salts are good reagents for transferring one of the aryl ligands to a variety of nucleophiles. This process begins by reacting a nucleophile **6** with the iodine atom of a diaryliodonium salt as shown in **Scheme 2**.
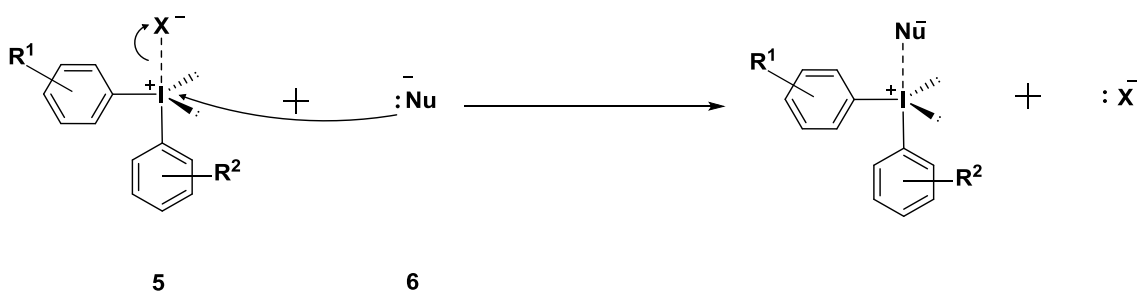
Scheme 2

The reaction in **Scheme 2** is referred to as a "ligand exchange" reaction. Heteroatoms like (X) in the diaryliodonium salt **5** are easily displaced by external nucleophiles **6**. A detailed mechanism of ligand exchange is not known, but experimental results show that ligand exchange happens by an associative mechanism as shown in **Scheme 3**. In **Scheme 3** the iodine atom of the diaryliodonium salt **7** is positively charged and is therefore electrophilic. A variety of nucleophiles react with the positively charged iodine at the C-I σ^* orbital and result in the intermediate formation of a trans tetracoordinated iodate with square planar arrangement **8**.

7   8   9   10
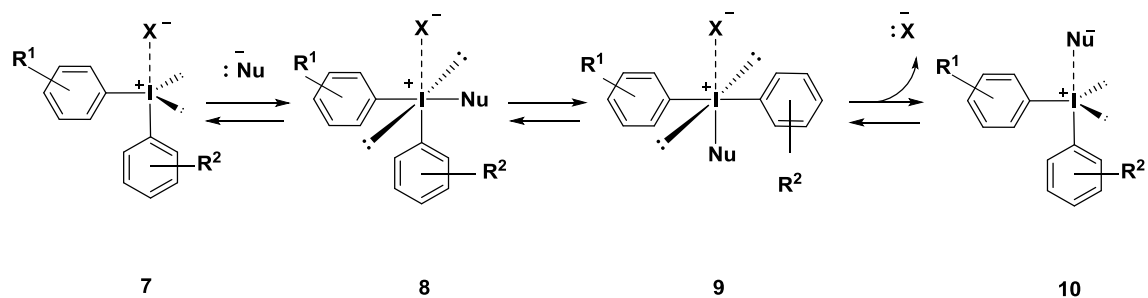
Scheme 3

The trans iodate isomerizes to a cis iodate **9** and elimination of a heteroatom ligand (X)
from the tetracoordinated iodate produces a new aryl-λ^3-iodane **10**. This ligand exchange
process generally proceeds with a low energy barrier and is rapid and reversible.[6]

The final step involved with transferring one of the aryl ligands to the nucleophile
is referred to as "ligand coupling". The term ligand coupling refers to the intramolecular
coupling of two ligands bonded to a hypervalent atom. A general schematic showing
ligand coupling is shown in **Scheme 4**.
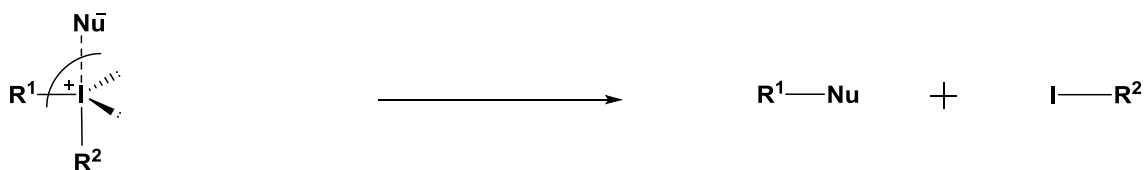
Scheme 4

The mechanism of ligand coupling is poorly understood but it is believed to be a
concerted mechanism that proceeds with retention of configuration of the ligands. The

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generally accepted mechanism of ligand coupling as it relates to unsymmetrical

diaryliodonium salts is shown in **Scheme 5**. In **Scheme 5** one of the aryl groups contains

an electron-donating group (EDG) and the other aryl group contains an electron-

withdrawing group (EWG). Structures **11** and **12** represent a diaryliodonium salt that is in

equilibrium and is being interconverted through pseudo-rotation. Structure **11** is believed

to be major species in the equilibrium mixture. The reason for this is because an EWG is

attached to the aryl group located in the axial position which causes that aryl group to be

more electronegative than the aryl group in the equatorial position. Structures **11** and **12**

can then coordinate with the nucleophile to form the transition states **13** and **14**

respectively. These transition states are believed to be formed by interaction of the

nucleophile with the ipso carbon atom of the aryl group in the equatorial position. **14** is a

more favorable transition state than **13** because both the negative charge on the aromatic

ring and the enhanced positive charge on the iodine(III) are stabilized by the substituents

more effectively. The coupling of the nucleophile to the equatorial aryl group is paralled

by a decoupling of the iodine atom from the same aryl group. The result of ligand

coupling is to produce **15** in the case of minor path products. The products in **16** are

produced in the case of the major path products.

EDG = Electron Donating Group

EWG = Electron Withdrawing Group
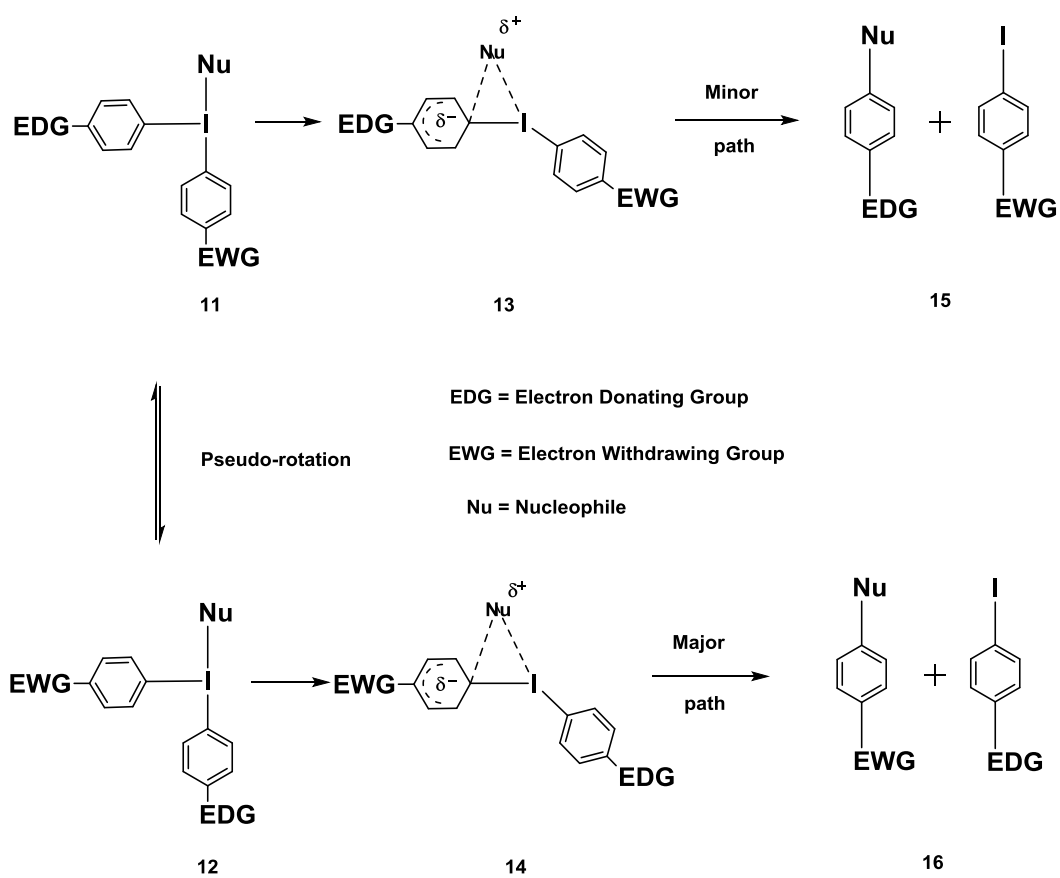
Nu = Nucleophile

Scheme 5

Scheme 6 shows an unsymmetrical diaryliodonium salt being taken through a ligand exchange reaction followed by pseudo-rotation and ligand coupling. The predicted results indicate that the nucleophile will couple with the more electronegative aryl group. In the case of **Scheme 6** the more electronegative aryl group is the one that is attached to the (EWG).

EDG—⟨ ⟩—Nu   +   I—⟨ ⟩—EWG

Minor Products

Nu $\delta-$
EDG—⟨ ⟩—I $\delta+$
EWG

Nu $\delta+$
EDG—⟨ ⟩—I $\delta+$
EWG

Unfavorable Transition State

Diaryliodonium Salt

EDG—⟨ ⟩—I
X $\delta-$
$\delta+$
EWG

Nu:⁻   X:⁻

Ligand Exchange

Pseudo-rotation

Nu $\delta-$
EWG—⟨ ⟩—I $\delta+$
EDG

Nu $\delta+$
EWG—⟨ ⟩—I $\delta+$
EDG

Favorable Transition State

EDG = Electron-Donating Group
EWG = Electron-Withdrawing Group
Nu = Nucleophile

EWG—⟨ ⟩—Nu   +   I—⟨ ⟩—EDG

Major Products
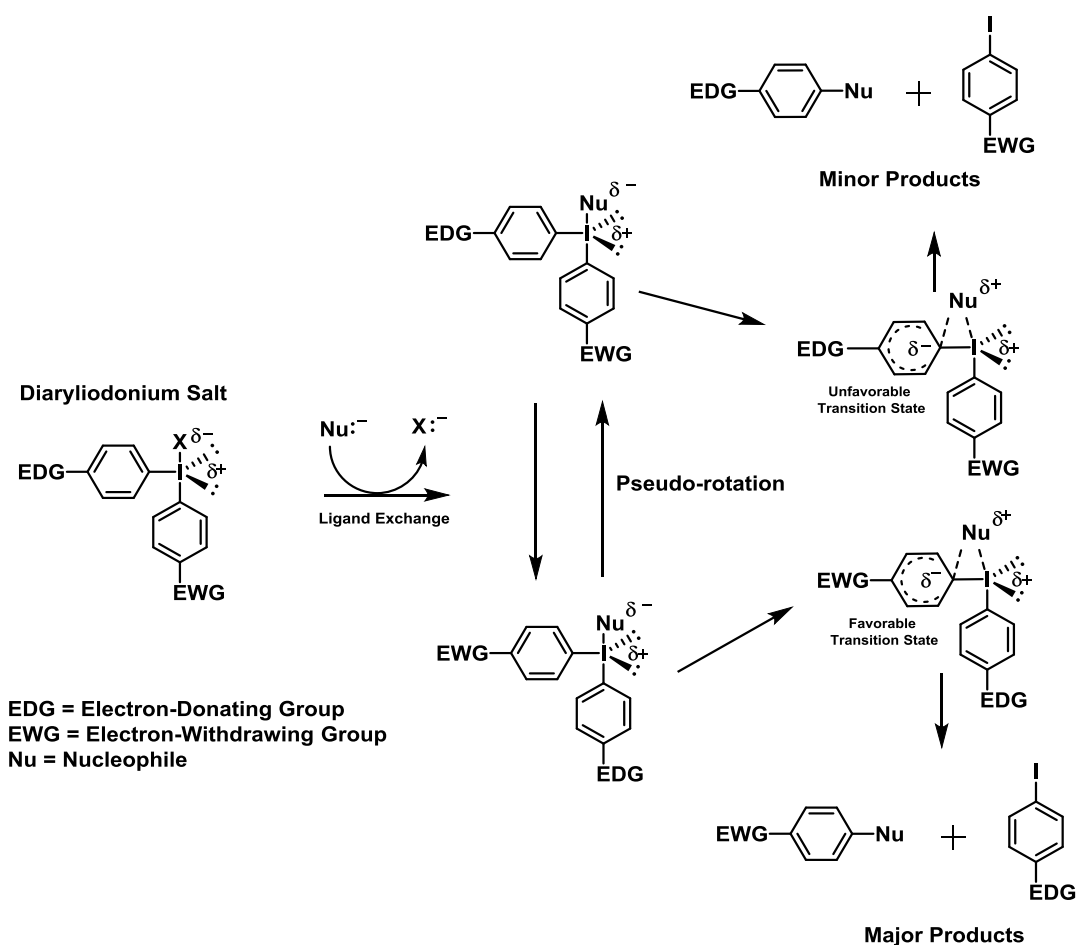
Scheme 6

1.6 Development of New Unsymmetrical Diaryliodonium Salts

Diaryliodonium salts represent an important class of λ^3-iodanes, particularily

useful as reagents for arylation of various nucleophiles.[2,7] The focus of this research is to

develop new diaryliodonium salts, $Ar_2I^+ X^-$, that will be used in reactions involving the

direct electrophilic arylation of various nucleophiles. Especially important are the

reactions of diaryliodonium salts with the fluoride anion, allowing efficient introduction

of fluorine into an aromatic ring via aromatic nucleophilic substitution. In recent years,

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nucleophilic fluorination reactions of diaryliodonium salts have found wide practical application in Positron Emission Tomography (PET) as a fast and convenient method for the introduction of the radioactive $[^{18}F]$-fluoride into radiotracer molecules. Positron Emission Tomography (PET) is a powerful and rapidly developing area of molecular imaging that is used to study and visualize human physiology by the detection of positron-emitting radiopharmaceuticals labeled with short-lived positron-emitting radionuclides ^{11}C, ^{18}F, ^{15}O, ^{13}N.[8-14]

1.7 Arylation of Heteroatom Nucleophiles

The use of diaryliodonium salts in arylation of heteroatom nucleophiles has been known for more than 80 years. Work by Beringer's group in the 1950's led to the phenylation of a wide range of organic and inorganic bases including alkoxides, phenoxides, benzoates, nitrites, sulfonamides, amines, sulfites, sulfinates and cyanides.[2] An example of a diaryliodonium salt **17** reacting with sodium alkoxide (Na$^+$ RO$^-$) to produce the phenylated alkoxide **18**, phenyl iodide **19**, and NaX is shown in **Scheme 7**.
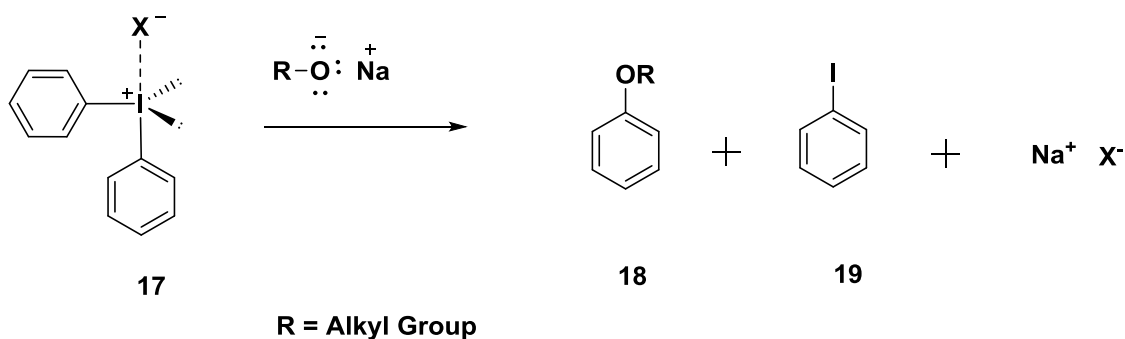
Scheme 7

1.8 Arylation of Oxygen Nucleophiles

A decade after Beringer's investigation, Crowder et al. reported the preparation of diaryl ethers using a method similar to Beringer. The method involves running the reactions in aqueous solution under reflux for several hours. Initial studies showed that the highest yield of diphenyl ether (72%) was obtained by refluxing diphenyliodonium bromide in water with an equimolar amount of sodium phenoxide. Substituted phenols gave diaryl ethers in 63-86% yields (**Scheme 8**).[15]
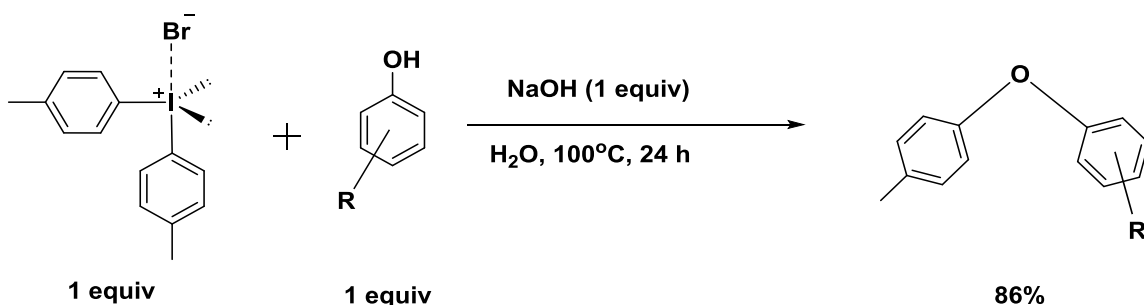
Scheme 8

This method has been applied to the synthesis of many polybrominated diphenyl ethers, which have a range of industrial applications.[16] Polymer-supported diaryliodonium salts have been used to prepare diaryl ethers and thioethers in moderate to good yields by reaction with either sodium aryloxides or arylthiolates.[17]

1.9 Arylation of Nitrogen Nucleophiles

While heterocycles have formed the bulk of the N-arylation investigations, it is nevertheless possible to arylate aliphatic substrates. For example, Kang et al. reported a method suitable for arylating secondary aliphatic amines, aromatic amines, azoles and amides using copper(I) iodide or [Cu(acac)$_2$] (**Scheme 9**).[18]
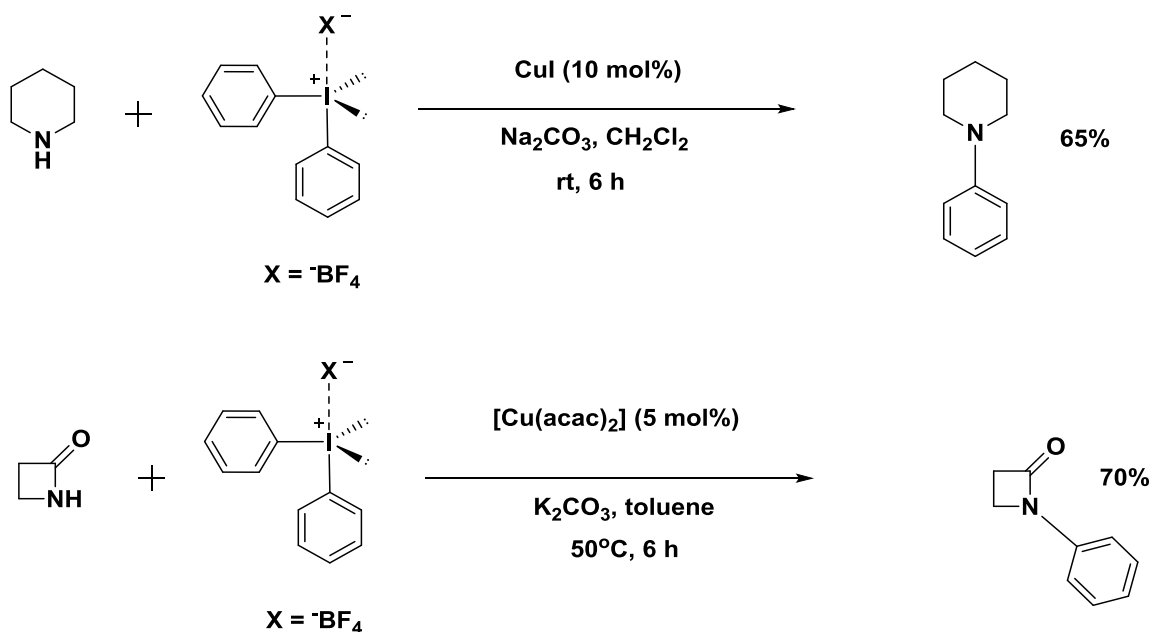
Scheme 9

More recently, Carroll and Wood published a transition metal free route to diarylamines in good yields where they also investigated the influence of the anion and chemoselectivity aspects (**Scheme 10**).[19]

Scheme 10
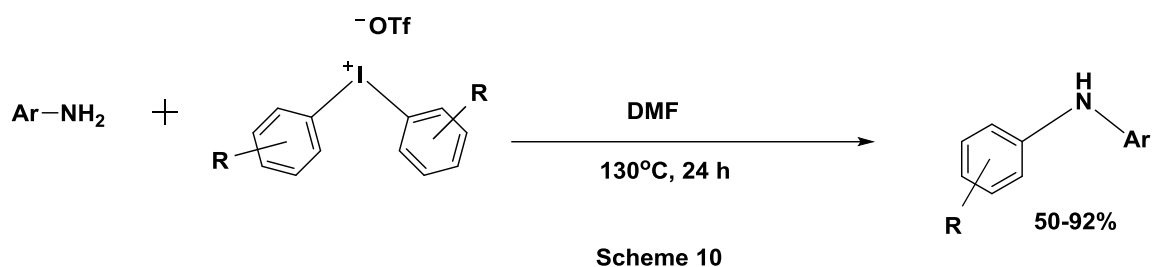
1.10 Arylation of Fluorine Nucleophiles

Fluorine-18 labeled arenes are used in Positron-Emission Tomography (PET). The synthesis of such radio-labeled compounds through nucleophilic attack of [^{18}F]fluoride on diaryliodonium salts has been studied extensively by Carroll and Widdowson (**Scheme 11**).[20]

Scheme 11
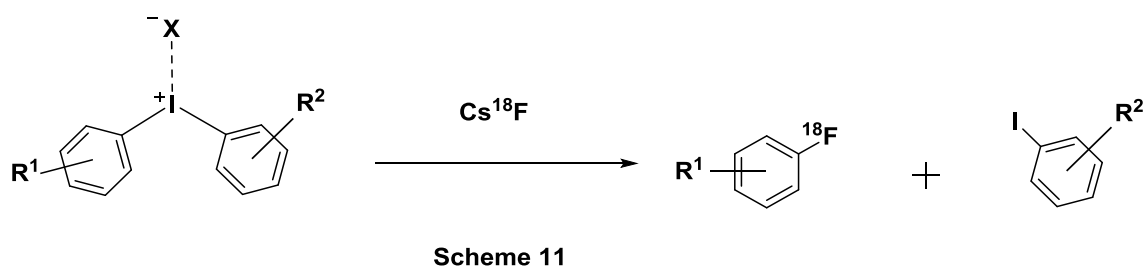
Advantages of using diaryliodonium salts as precursors are that arenes with a wide range of substitution patterns can be readily prepared.[2]

1.11 Selectivity of Diaryliodonium Salts

It is the goal of this research to synthesize diaryliodonium salts that can be used in aromatic nucleophilic substitution reactions with selectivity >95%. **Scheme 6** illustrates that from two different transition states both major and minor products can be formed. This research attempts to develop a diaryliodonium salt where one of the aryl groups has the proper combination of electronic and steric properties such that it forces the nucleophile to couple with the other aryl group exclusively. The aim is to develop a "dummy ligand" aryl group to which the nucleophile can not couple. The diaryliodonium salt that is believed to display the proper combination of desired properties is shown in **Figure 7**.

Triisopropylsilyl Group (TIPS)

Tosylate Group (OTs)
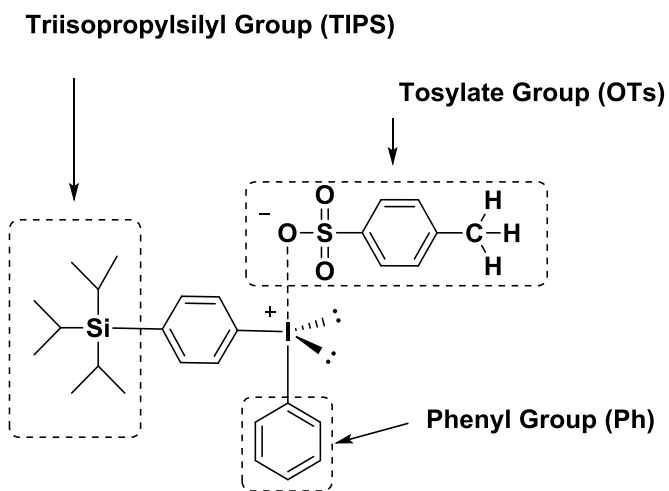
Phenyl Group (Ph)

Figure 7

The salt in **Figure 7** features a phenyl group in the axial position. The phenyl group is

representative of the electron withdrawing group (EWG). The phenyl group was chosen

as the (EWG) because of the stabilizing effect it provides to the salt. The aryl group in

the equatorial position is the 4-triisopropylsilylphenyl group (TIPS). The 4-

triisopropylsilylphenyl group was chosen as the electron donating group (EDG) because

of its electronic and steric influence. The TIPS group donates electron density toward the

aromatic ring to which it is attached. This enhanced electron density causes that aromatic

ring to have a slight negative charge. This negative charge makes if difficult for a

nucleophile to couple with that aromatic ring since it would require a lone pair of

electrons from the nucleophile to move toward a negatively charged ring. This is

unlikely to happen since like charges repel each other. The expected result is that the

nucleophile would couple with the least electron rich aromatic ring which is the phenyl

ring in this case.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Preparation of (4-iodophenyl)triisopropylsilane

A. Introduction

Synthesis of the desired diaryliodonium salt as it is shown in **Figure 7** required a series of reactions. The first of those reactions is shown in **Scheme 12**. 1,4-diiodobenzene **20** is reacted with n-butyllithium using Et_2O as the solvent. The reaction is run at -78^oC for 2 hours. This reaction produces the iodophenyl anion **21** and iodobutane **22**. The iodobutane **22** is a byproduct and it is removed under vacuum. The reaction of 1,4-diiodobenzene **20** with n-butyllithium is a halogen-metal exchange reaction where the metal (lithium) is exchanged for the halogen (iodine). The reaction proceeds in the direction of forming the more stable organolithium reagent. By use of the very basic n-butyllithium, halogens at more acidic sp^2-hybridized carbons are readily exchanged to give the corresponding lithium compound **21**.

Scheme 12

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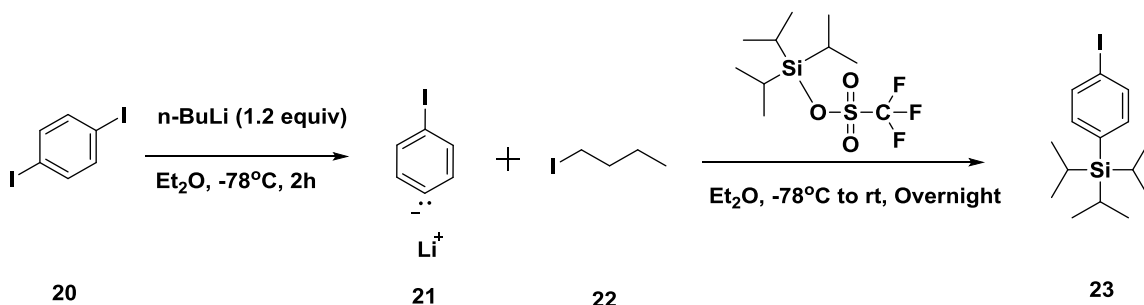
The mechanism for the reaction of 1,4-diiodobenzene **20** with n-butyllithium is shown in **Scheme 13**.
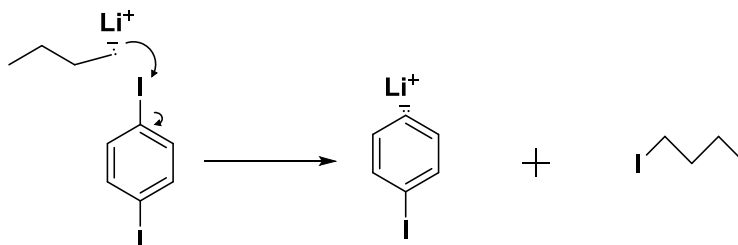
Scheme 13

The second step of the reaction in **Scheme 12** involves the addition of triisopropylsilyltrifluoromethanesulfonate (TIPS-triflate) to the reaction mixture. The mechanism for this reaction is shown in **Scheme 14**. The iodophenyl anion **24** reacts with the TIPS-triflate **25** in a S_N2 type reaction. The silicon-oxygen bond of the TIPS-triflate molecule is quite polar. This polarity difference results in a slight positive charge on the silicon atom and a slight negative charge on the oxygen atom. The iodophenyl anion **24** attacks the silicon atom causing a new carbon-silicon bond to form. At the same time that the carbon-silicon bond is being formed the silicon-oxygen bond is breaking with both of the silicon-oxygen bonding electrons moving to the oxygen atom. This reaction is motivated by the excellent leaving group ability of the triflate group. The triflate anion **27** is an excellent leaving group because of its ability to spread its negative charge over three oxygen atoms through resonance stabilization.
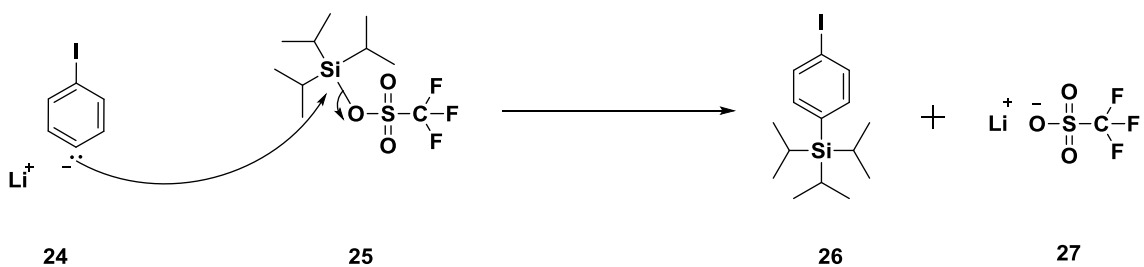
Scheme 14

The desired product from **Scheme 14** is (4-iodophenyl)triisopropylsilane **26**. Lithium-triflate **27** is a byproduct that is removed on the silica column.

B. Results and Discussion

The first 80 attempts at the reaction set in **Scheme 12** yielded unexpected and undesired results. The desired product from **Scheme 12** is (4-iodophenyl)triisopropylsilane. However, the actual product was (4-iodophenyl)-O-triisopropylsilane. Both the desired and undesired products are shown in **Table 1**. The undesired product contains an extra oxygen atom. This discrepancy was initially realized when the High Resolution Mass Spectrometry (HR-MS) result showed a product with 16 molecular weight units higher than the expected result. The molecular weight of oxygen is 16 g/mol. The source of this extra oxygen atom was difficult to pinpoint. It was hypothesized that the extra oxygen atom came from air or water that inadvertently found its way into the reaction flask. The reaction flask had always been purged with argon before the beginning of each reaction so it was initially assumed that there was water in

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the Et_2O or that the 1,4-diiodobenzene contained some residual water. Several reactions were then attempted where anhydrous Et_2O was used directly from a newly purchased sealed container. The reaction results still indicated that the undesired oxygen containing products were formed. (Et_2O) was then ruled out as the source of the undesired oxygen. Next a heat gun was used to heat the starting material (1,4-diiodobenzene) and the reaction flask sufficiently enough while under vacuum to remove any possible water in the starting material. Again, the reaction results showed that the undesired oxygen containing product was being formed. The starting material 1,4-diiodobenzene was then ruled out as the source of oxygen. After many more attempts at this reaction a chance encounter in which argon was being used to purge the reaction flask showed a slight leakage of argon through a closed valve. The valve on the reaction flask uses a standard polytetrafluoroethylene (PTFE) stopcock. The PTFE stopcock was new and did not show any signs of defect. However, it appeared that the sealing surface between the PTFE stopcock and the ground glass joint of the reaction flask was insufficient for this reaction. Depending on the direction of the pressure differential this allowed gasses to travel either into or out from the flask. This reaction is run at -78°C for 2 hours. This low temperature created a low pressure inside the flask. The atmospheric air pressure was then enough to force air into the reaction flask and react with the 4-iodophenyl anion. Once the source of oxygen in the undesired product was discovered it became necessary to use vacuum grease combined with extensive parafilm wrapping to make the contents of the reaction flask sealed from atmosphere.
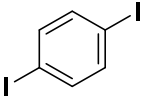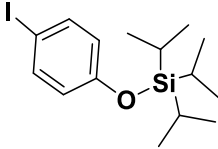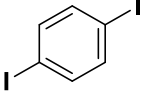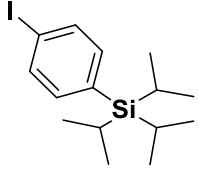
Substrate	Product
	UNDESIRED
	DESIRED

Table 1.

C. Summary

The reaction to produce (4-iodophenyl)triisopropylsilane requires a totally inert atmosphere. It is recommended that similar reactions be conducted in a dry glove box to insure that inert atmosphere is maintained in the reaction vessel throughout the reaction.

2.2 Preparation of (4-tributyltinphenyl)triisopropylsilane

A. Introduction

The next step involved in the synthesis of the desired diaryliodonium salt from **Figure 7** is to produce (4-tributyltinphenyl)triisopropylsilane**. Scheme 15** shows the reaction for producing (4-tributyltinphenyl)triisopropylsilane **29.** (4-tributyltinphenyl)triisopropylsilane **29** is prepared using the (4-iodophenyl)triisopropylsilane **28** that was prepared in the previous section and reacting it with bis(tributyltin) using palladium as a catalyst.
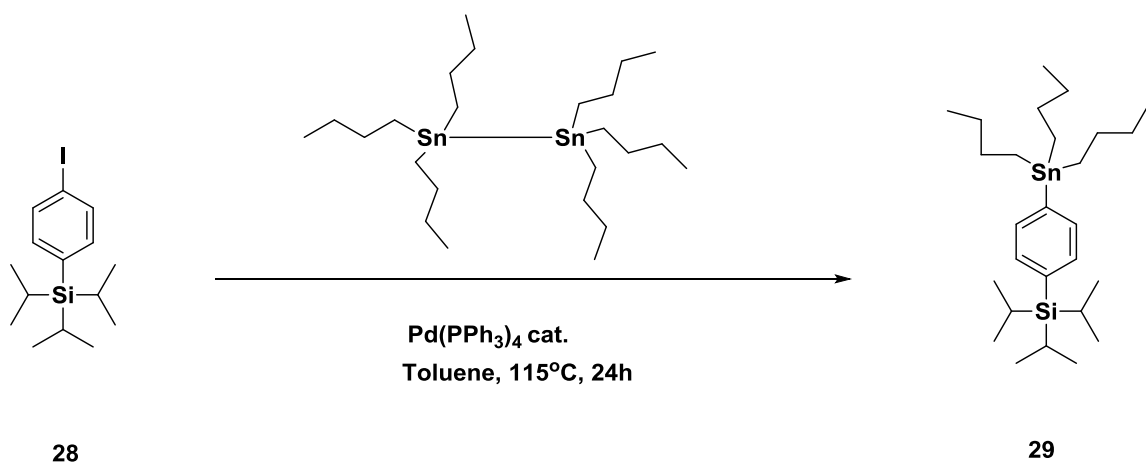
Scheme 15

This reaction is a modified version of the Migita-Kosugi-Stille coupling reaction. The

Migita-Kosugi-Stille coupling reaction results in new carbon-carbon bond formation. In

Scheme 15 the coupling reaction results in the formation of a new carbon-tin bond. The

exact mechanism of **Scheme 15** is not known but the generally accepted pathway for

Scheme 15 is shown in **Figure 8**.
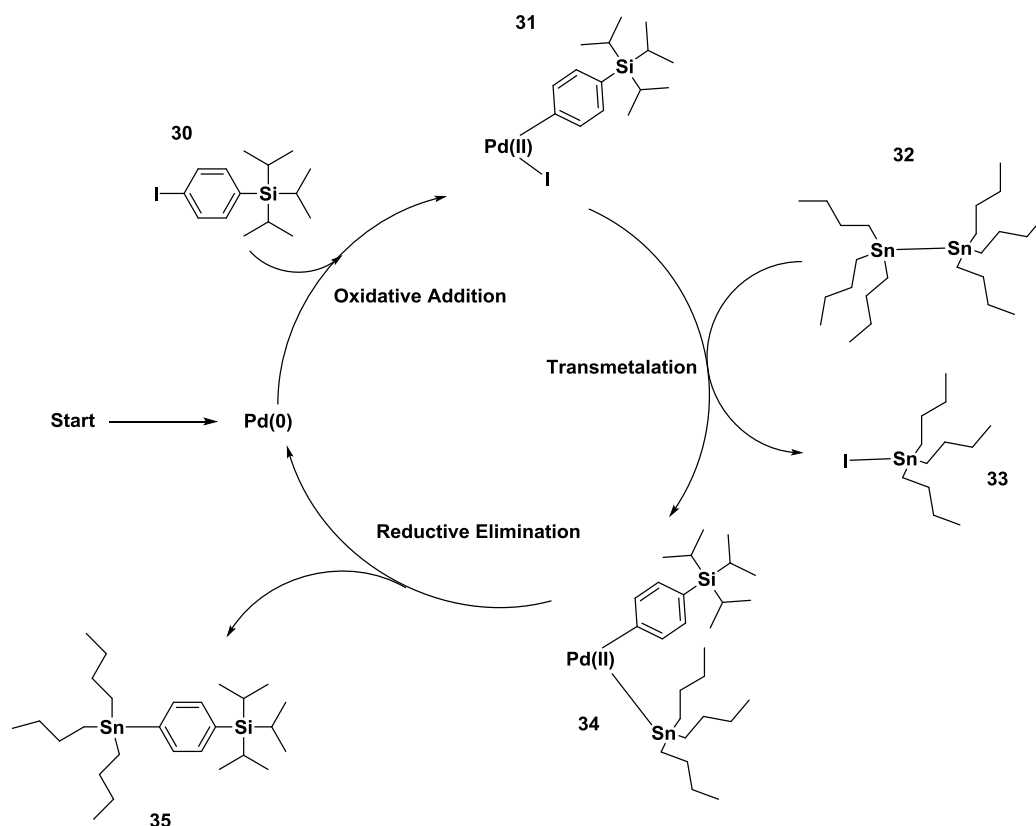
Figure 8

The "start" point on the left in **Figure 8** represents the palladium catalyst initially in the

zero oxidation state where it is coordinated with 4-triphenylphosphene groups. The

palladium catalyst then reacts with the (4-iodophenyl)triisopropylsilane **30** in an

oxidative addition reaction to produce **31**. **Image 31** shows that palladium has been

oxidized to Pd(II) state with iodine and TIPS-phenyl as ligands. **31** then reacts with

bis(tributyltin) **32** in a transmetalation reaction whereby ligands are exchanged between

the two metals. The iodine in **31** is exchanged with a tributyltin group from **32** to

produce iodotributyltin **33** and Pd(II) coordinated to TIPS-phenyl and tributyltin ligands

34. The final step on this pathway is the reductive elimination reaction whereby the TIPS-phenyl and tributyl ligands couple with each other to form the product (4-tributyltinphenyl)triisopropylsilane **35**. The reductive elimination process results in the reduction of Pd(II) back into Pd(0), thus regenerating the catalyst.

B. Results and Discussion

The reaction in **Scheme 15** is a straightforward process that involves initially charging the reaction flask with the starting material **30**, bis(tributyltin) **32**, palladium catalyst and toluene. This reaction mixture begins the heating process as an orange solution and after the toluene reflux temperature of ~115°C is reached it turns black. During the heating process a light argon purge was maintained through the reaction flask.

C. Summary

The tributyltin ligand was successfully coupled to the TIPS-phenyl ligand in the presence of palladium catalyst.

2.3 Preparation of (4-triisopropylsilylphenyl)phenyliodonium tosylate

A. Introduction

Scheme 16 shows the general preparation method for forming **(4-triisopropylsilylphenyl)phenyliodonium tosylate 37**. The **(4-tributyltinphenyl)triisopropylsilane 36** that was prepared in the previous section is combined into a reaction flask with Koser's Reagent - hydroxy(tosyloxy)iodobenzene (HTIB) in methylene chloride. The reaction mixture is then stirred at room temperature overnight.
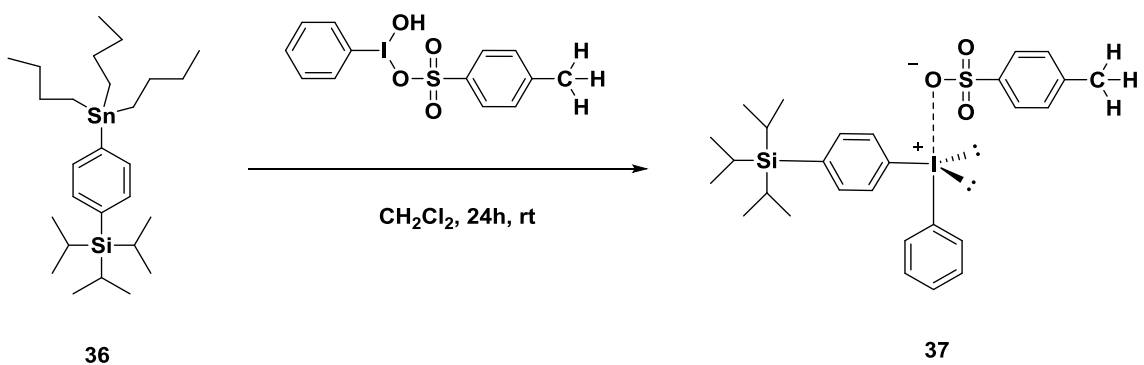
Scheme 16

The mechanism for the reaction in **Scheme 16** is shown in **Scheme 17**. (4-tributyltinphenyl)triisopropylsilane **38** is nucleophilic and shifts a pair of pi electrons to the electrophilic iodine atom of Koser's reagent **39**. The tosylate group is a very stable anion due to resonance and it breaks it's bond with iodine. The λ^3-iodane intermediate **40** has a positive charge on the aromatic ring. The tin-carbon bond breaks from the intermediate **40** which allows the aromaticity to reform in the ring. The hydroxyl group

in **42** is very reactive toward the tributyltin cation and ligand exchange takes place where

the hydroxyl group on iodine is replaced by the tosylate group. This produced the desired

diaryliodonium salt **43** and tributyltin-hydroxide **44**. The tributyltin-hydroxide **44** is a

byproduct and is removed during the ether washes.

Scheme 17
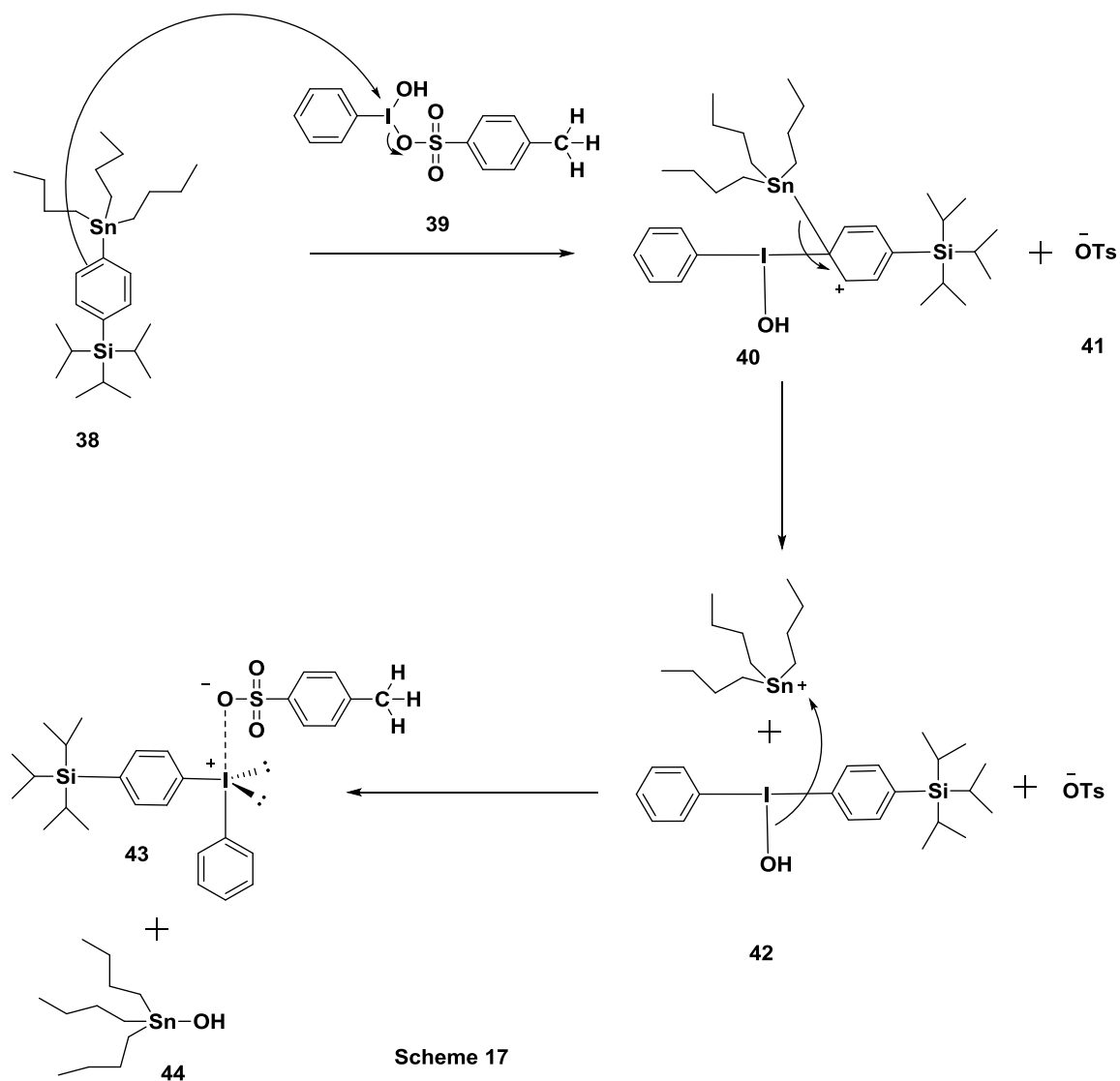
B. Results and Discussion

This is a straightforward reaction to carryout. (4-tributyltinphenyl)triisopropylsilane is a clear liquid and Koser's reagent is a white solid that dissolves in methylene chloride. The reaction flask therefore initially contains a clear mixture. As the salt product forms it begins to precipitate out of solution as a white solid. This reaction produces several byproducts and the product requires several washes in Et_2O to remove the byproducts. Iodoxybenzene ($PhIO_2$) is also produced in this reaction. After several Et_2O washes the white solid product was filtered and the filter was washed with methylene chloride to dissolve the desired product and leave the $PhIO_2$ on the filter.

C. Summary

A new unsymmetrical diaryliodonium salt was produced which can be used to analyze the selectivity of various nucleophiles in nucleophilic arylation reactions.

2.4 Preparation of (4-triisopropylsilylphenyl)phenyliodonium bromide

A. Introduction

The preparation of (4-triisopropylsilylphenyl)phenyliodonium bromide **46** is shown in **Scheme 18**.

Scheme 18
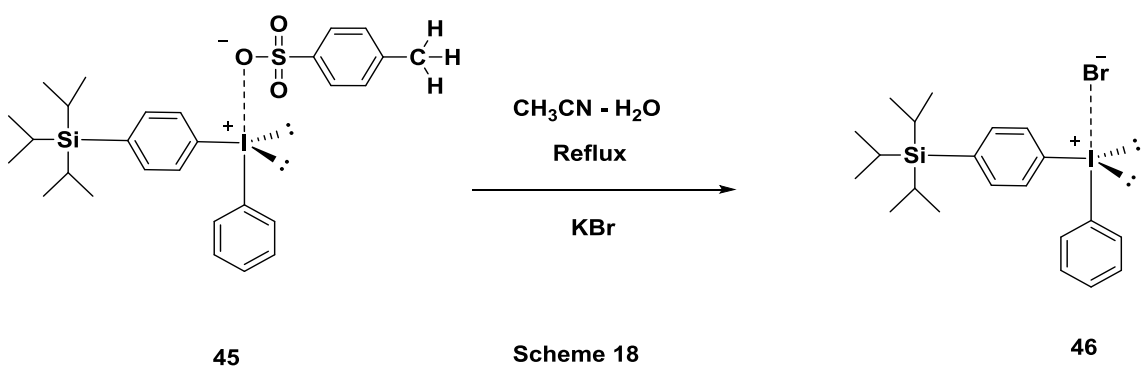
The process involves using the diaryliodonium salt (tosylate) **45** as the starting material and then adding acetonitrile-water and potassium bromide. Tosylate is the more stable anion as compared to the bromide anion therefore the bromide replaces tosylate as a ligand on the iodine atom to produce (4-triisopropylsilylphenyl)phenyliodonium bromide **46**.

B. Results and Discussion

The reaction in **Scheme 18** is a ligand exchange reaction. The reaction is only carried out long enough for ligand exchange to take place. If the reaction time was longer it would potentially cause ligand coupling whereby bromine would couple with an

aryl group.   Crystals of (4-triisopropylsilylphenyl)phenyliodonium bromide were analyzed using X-ray analysis.   The result showed that the solid state of the (4-triisopropylsilylphenyl)phenyliodonium bromide salt had the TIPS-phenyl aryl group in the equatorial position.   The result agrees with the theory of hypervalent iodine bonding for λ^3 iodanes whereby the most electronegative ligands (phenyl and bromide) are located in the axial positions and the more electron rich aryl group (TIPS-phenyl) is located in the equatorial position.

C. Summary

The properties of diaryliodonium salts can be modified by ligand exchange of the anionic portion of the molecule.

2.5 Reaction of (4-triisopropylsilylphenyl)phenyliodonium tosylate with
sodium azide

A. Introduction

The main goal of this research was to produce a diaryliodonium salt that is capable of arylating nucleophiles with a high degree of selectivity.   It was the hypothesisized that

the nucleophile would couple with the least electron rich ring of the diaryliodonium salt.

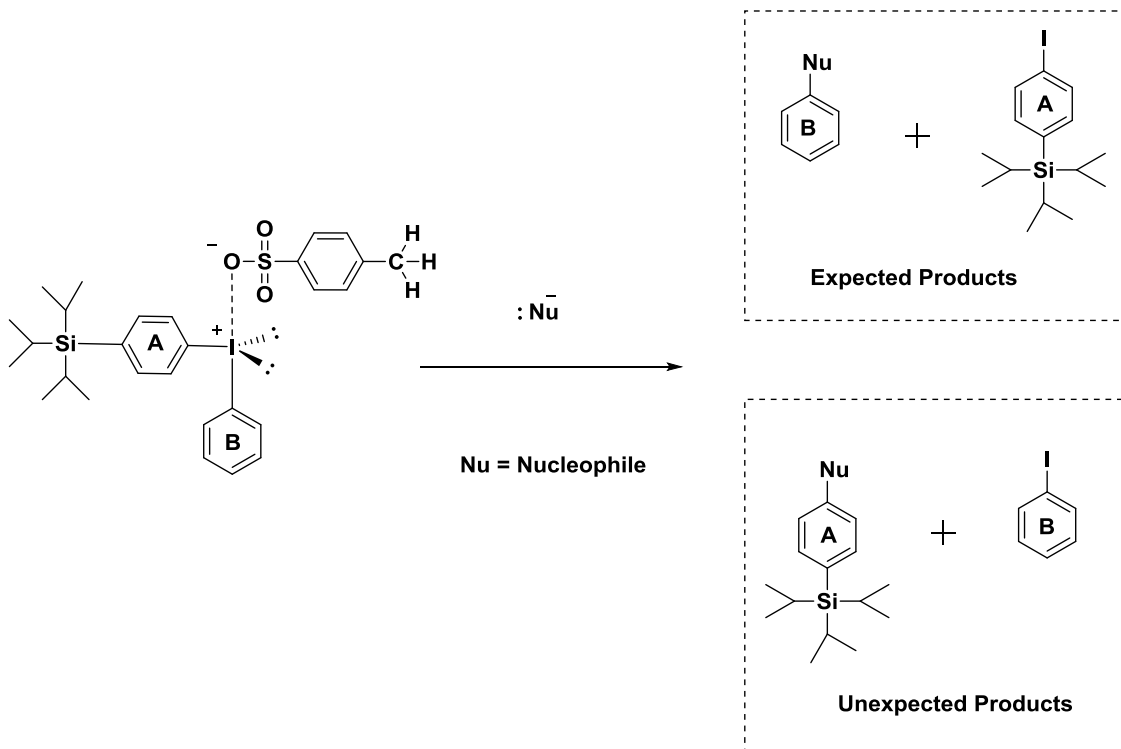An example of the expected result is shown in **Figure 9**.

Figure 9

From **Figure 9** it was believed that the presence of the TIPS group on the phenyl ring (A) would provide the necessary electronic and steric influences such that it would protect phenyl ring (A) from being attacked by the nucleophile. It was believed that the nucleophile would exclusively couple with phenyl ring (B).

The reaction shown in **Scheme 19** was conducted to test the selectivity theory of the arylation of nucleophiles. Sodium azide (NaN$_3$) was source of the nucleophile (N$_3^-$).
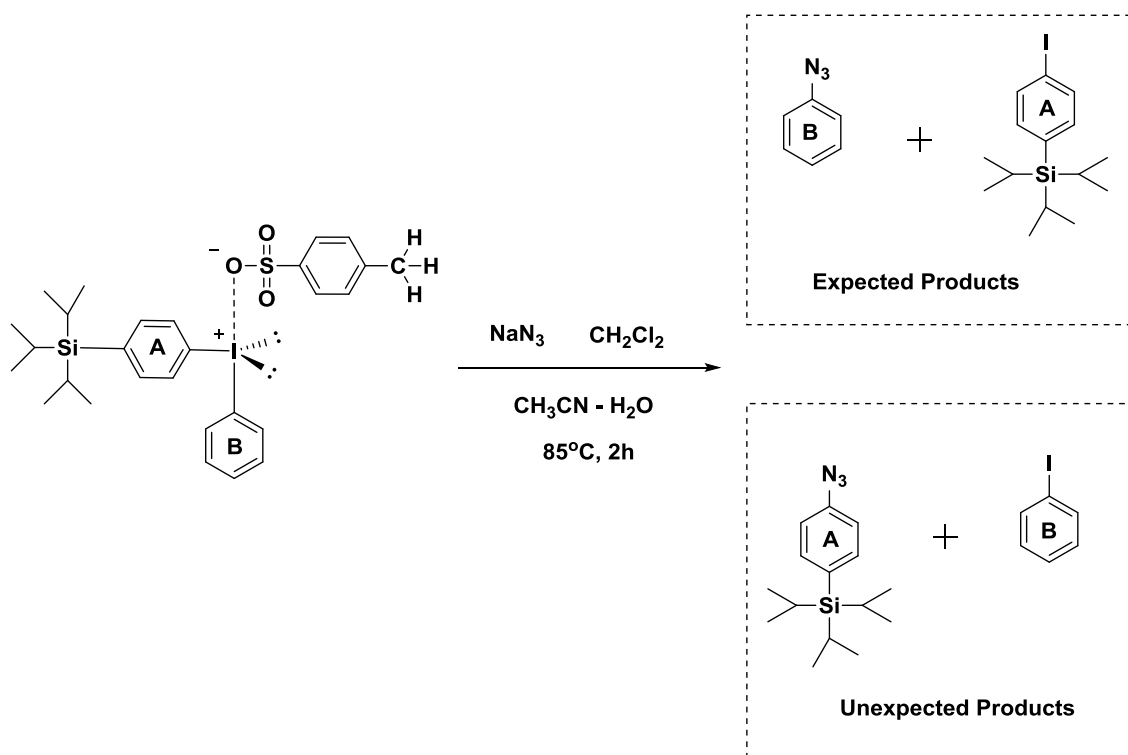
Scheme 19

B. Results and Discussion

The results of the reaction in **Scheme 19** were unexpected in that the unexpected products were formed over the expected products by a ratio of 2.6 : 1. This result is in opposition to the general theory that the nucleophile would add to the least electron rich ring. The expectation that the TIPS group would protect phenyl ring (A) from attack by the nucleophile was shown to be not correct. The results appeared to show that the nucleophile preferred to couple with the more electron rich ring. A theory for this unexpected result is that the phenyl ring (A) containing the TIPS group is big and bulky therefore it requires more room within the diaryliodonium salt molecule as compared with the smaller phenyl ring (B).   This idea is explained with **Figures 10** and **11**.

32

In **Figure 10** the TIPS-phenyl group is located in the equatorial position. The iodine-carbon bond that is attached to the TIPS-phenyl group has two neighbors at 90° separation. Those two neighbors are the tosylate and phenyl groups which both reside in the axial position. The iodine-carbon bond of the TIPS-phenyl group also has two neighbors at 120° of separation. Those two neighbors are the two lone pairs of electrons.
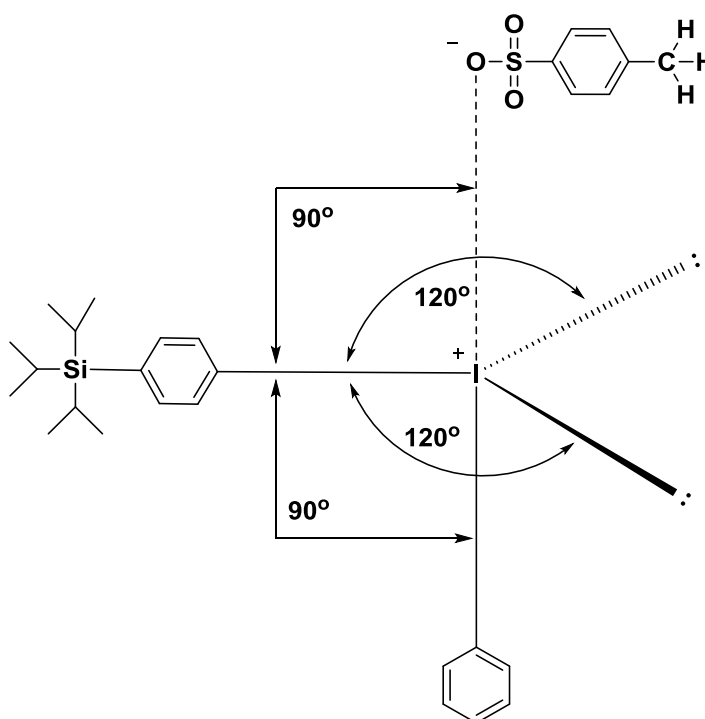

Figure 10

In **Figure 11** the TIPS-phenyl group is located in the axial position. The iodine-carbon bond that is attached to the TIPS-phenyl group has three neighbors at 90° and another neighbor at 180°. It is suggested that the molecule shown in **Figure 11** is not likely to form in solution because the presence of three neighbors at 90° forces the TIPS-phenyl

group to stay in the equatorial position. It appears necessary that the TIPS-phenyl group

reside in the equatorial position because it is roomier than the axial position. It is from

the equatorial position that the nucleophile is believed to couple with an aryl group. This

would explain why the major product associated with the reaction between the

diaryliodonium salt (tosylate) and the nucleophile produces selectivity with the

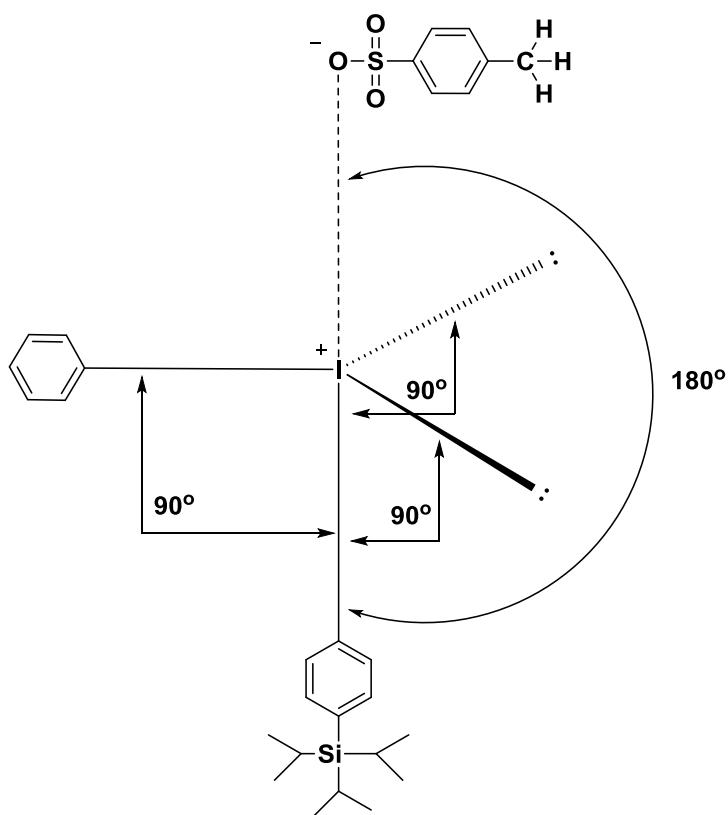nucleophile preferring the more electron rich aromatic ring.

Figure 11

Further unexplained results were discovered from the reaction in **Scheme 19**.

While the crude and isolated ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra

show patterns consistent with the two molecules in **Figure 12**, the HR-MS data for

molecule **48** indicates that it has a m/z ratio of 278.1. This would make it impossible for

the N_3 group to be attached to the TIPS-phenyl ring since its m/z ratio is 275.1818.
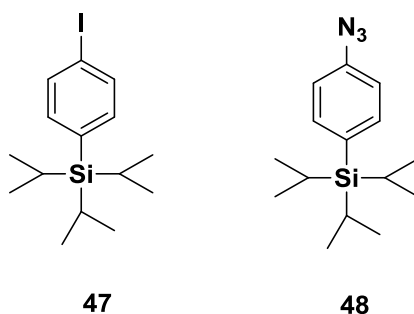

47   48

Figure 12

The results indicate that the major product formed from the reaction in **Scheme 19** is

shown in **Figure 13**. There is a question mark (?) in the *para* position of the molecule in

Figure 13 because it's identity is unknown. The ^{1}H nmr spectra of the molecule in

Figure 13 indicates the presence of the TIPS hydrogens and the four hydrogens on the

aromatic ring. The ^{1}H nmr spectra does not show any other proton peaks. The ^{13}C nmr

spectra shows six peaks which is consistent with the two carbons from the TIPS group

plus the four carbons from the aromatic ring. The ^{13}C nmr spectra does not show any

other carbon peaks. The results from the HR-MS analysis indicate that the molecule in

Figure 13 has a molecular weight of 278.1g/mol. Subtracting off the molecular weight

of the TIPS-phenyl species (233g/mol) from the 278.1g/mol would mean the question

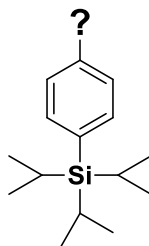mark (?) has a total molecular weight of 45.1g/mol.

Figure 13

C. Summary

An unsymmetrical diaryliodonium salt was reacted with a nucleophile in order to probe the selectivity of the arylation of the nucleophile. For the specific reaction conditions used in this experiment it was believed that the more electron rich aryl group coupled with a nucleophile to a greater extent than the less electron rich aryl group. Inconclusive data concerning the exact identity of the major species formed in this reaction hinders the ability to state conclusively that the selectivity of the azide anion is greater for the TIPS-phenyl group as opposed to the phenyl group.

This research should continue to identify the unknown compound in **Figure 13**. A variety of other nucleophiles should also be used in similar reactions with diaryliodonium salts to compare the selectivity results among differing nucleophiles.

CHAPTER 3

EXPERIMENTAL

3.1 General Methods

All melting points were determined in an open capillary tube with a Mel-temp II$^{®}$ melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian ^{UNITY} INOVA 500 MHz NMR spectrometer at 500 MHz (^{1}H NMR), and 125 MHz (^{13}C NMR); chemical shifts are reported in parts per million (ppm). ^{1}H and ^{13}C chemical shifts are referenced relative to the tetramethylsilane. GC-MS analysis was carried out with a HP 5890A Gas Chromatograph using a 5970 Series mass selective detector.

3.2 Materials

All commercial reagents were ACS reagent grade and used without further purification. All silica gel columns were performed using 63-200μm, 60Å silica gel from Dynamic Adsorbents, Inc.

3.3 Synthesis of Compounds

(4-iodophenyl)triisopropylsilane

Note: It is critical to maintain an inert atmosphere inside the reaction flask during this reaction. 1,4-diiodobenzene (660 mg, 2.00 mmol) was placed into the reaction flask. The flask was then filled with argon and sealed tightly. Anhydrous Et$_2$O (5mL) was added to the flask using a syringe and the mixture was stirred at room temperature for

several minutes to maximize the dissolving of 1,4-diiodobenzene. The reaction flask was then immersed into a -78 °C acetone/dry ice bath. Then 1.8 mL (4.5 mmol) of 2.5 M n-BuLi was added dropwise to the mixture. The mixture was stirred for 2 hours at -78 °C. Then TIPSOTf (0.660 mL (2.47 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred overnight at room temperature. The mixture was then evaporated under vacuum to give a yellow solid. The yellow solid was dissolved in ethyl acetate and applied to a silica gel column using 100% hexane as the eluent. 4-Iodophenyl triisopropylsilane fractions were collected and concentrated on rotary evaporator to give oily white solid. Yield 150 mg (21%) of oily white solid. ^{1}H NMR (500 MHz, CDCl$_{3,}$): δ 7.74-7.73 (m, 2 H), 7.26-7.25 (m, 2 H), 1.42 (sep, J=7.5 Hz, 3H), 1.09 (d, J=7.5 Hz, 18H). ^{13}C NMR (125MHz, CDCl$_3$): δ 136.9, 136.6, 134.4, 95.7, 18.5, 10.7; HRMS (EI) calculated for C$_{15}$H$_{25}$ISi ([M]$^+$): 360.0770, found: 360.0776.

(4-tributyltinphenyl)triisopropylsilane

4-iodophenyl triisopropylsilane (170 mg, 0.472 mmol), toluene (8 mL), 477 μL of bis(tributyltin) (0.477 mL, 0.944 mmol) and Pd(PPh$_3$)$_4$ (54.3 mg, 0.047 mmol) were mixed in a flask. The flask was fitted with a continuous purge stream of argon gas and the pot temperature was set to 115 °C. The mixture was stirred at 115 °C for 24 hours. The mixture was then evaporated to remove the solvent, which resulted in a black oil/solid mixture in the flask. The black oil/solid mixture was combined with several mL of hexane and then was applied to a silica gel column. The silica column was flushed with hexane and the (4-tributyltinphenyl)triisopropylsilane fractions were collected and

concentrated to give a clear oil. Yield 100 mg (40%) of clear oil. ^{1}H NMR (500 MHz, CDCl$_{3,}$): δ 7.41 (s, 4 H), 1.72-0.68 (m, J=7.5 Hz, 48 H). ^{13}C NMR (125MHz, CDCl$_3$): δ 142.4, 135.6, 134.7, 134.1, 29.1, 27.4, 18.6, 13.7, 10.8, 9.5; HRMS (ESI) calculated for C$_{27}$H$_{52}$SiSn ([M]$^+$): 524.2860, found: 524.2859.

(4-triisopropylsilylphenyl)phenyliodonium tosylate

4-(tributyltinphenyl)triisopropyl silane (105 mg, 0.2 mmol), PhI(OTs)OH (78.4 mg, 0.2 mmol) and CH$_2$Cl$_2$ (3 mL) were placed in a flask and the flask was purged with argon and then stirred for 48 hours. The reaction mixture was then evaporated to remove the CH$_2$Cl$_2$ leaving behind a white solid. Et$_2$O (5 mL) was then added to the flask and the resulting white suspension was stirred for 8 hours. The precipitate was filtered and the filter was washed with CH$_2$Cl$_2$ to give a clear solution. Evaporation of this solution gave a white solid. Yield 40 mg (33%); mp 169°C-170°C. ^{1}H NMR (500 MHz, CDCl$_{3,}$): δ 7.98-7.96 (m, 2H), 7.88-7.86 (m, 2H), 7.67-7.66 (m, 2H), 7.61 (t, J=8.5 Hz, 1H), 7.52-7.51 (m, 2H), 7.45 (t, J=7.5 Hz, 2H), 7.10-7.09 (m, 2H), 2.32 (s, 3H), 1.37 (sep, J=7.0 Hz, 3H), 1.05-1.03 (m, 18H) . ^{13}C NMR (125MHz, DMSO): δ 140.3, 138.4, 138.0, 135.9, 134.4, 132.7, 132.3, 128.5, 126.0, 117.8, 116.4, 21.3, 18.7, 10.4; (ESI-positive) calculated for C$_{21}$H$_{30}$ISi ([M]$^+$): 437.1161, found: 437.1159

(4-triisopropylsilylphenyl)phenyliodonium bromide

The mixture of 14mg (0.023 mmol) of TIPS-iodonium tosylate, 1.2 mL of CH_3N, 100 μL H_2O, 13 mg (0.109 mmol) of KBr was refluxed at 85°C until clear solution was formed. The mixture was then allowed to cool slowly to room temperature which caused product crystals to form. The mixture was placed in refrigerator overnight. The mixture was then filtered and washed with Et_2O. The crystals were removed from the filter as a white solid. Yield 4mg (34%); mp 152°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99-7.98 (m, 2 H), 7.91-7.89 (m, 2 H), 7.55 (t, J=7.5 Hz, 1H), 7.49-7.47 (m, 2 H), 7.41 (t, J=7.5 Hz, 2 H), 1.36 (sep, J=7.0 Hz, 3H), 1.04-1.02 (m, 18H). ^{13}C NMR (125MHz, $CDCl_3$): δ 140.3, 138.1, 134.8, 132.9, 131.7, 131.4, 120.8, 120.1, 18.5, 10.7; (ESI-positive) calculated for $C_{21}H_{30}ISi$ ([M]$^+$): 437.1161, found: 437.1163.

Single crystals of (4-triisopropylsilylphenyl)phenyliodonium bromide suitable for X-ray crystallographic analysis were obtained by slow crystallization from the dichloromethane/hexane solution. X-ray diffraction data for (4-triisopropylsilylphenyl)phenyliodonium bromide were collected on Rigaku RAPID II Image Plate system using graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å) at 123 K. The structure was solved by the Patterson method (SHELXS 86) and refined by full-matrix least-squares refinement on F2 using Crystals for Windows program. Crystal data for (4-triisopropylsilylphenyl)phenyliodonium bromide $C_{21}H_{30}BrISi$: M 517.36, a = 9.07770(10) b = 14.3030(2), c = 35.499(3) Å, α= 90.00, β = 90.00, γ = 90.00 , V = 4609.1(3), R-Factor = 4.54.

<div align="center">

(4-azidophenyl)triisopropylsilane

</div>

Reaction of (4-triisopropylsilylphenyl)phenyliodonium tosylate with NaN$_3$. The mixture of 33 mg (0.054 mmol) of TIPS-iodonium, 1.0 mL CH$_3$CN and 10.5 mg (0.161 mmol) NaN$_3$ was heated for 2 h at 85 $^\circ$C. After that CH$_2$Cl$_2$ (5.0 mL) and H$_2$O (3.0 mL) were added under stirring and organic layer was separated and dried with Na$_2$SO$_4$; organic solvent was evaporated and the residue was dried in vacuum (0.2-0.4 mm) for 10 h. Under these conditions PhN$_3$ and PhI evaporated from the mixture of products leaving 16 mg of mixture TIPS-C$_6$H$_4$-N$_3$ and TIPS-C$_6$H$_4$-I in 2.6:1 ratio (see NMR). TIPS-C$_6$H$_4$-N$_3$ and TIPS-C$_6$H$_4$-I were separated from each other by PTLC using 100% Hexane as the solvent. TIPS-C$_6$H$_4$-N$_3$ was isolated as light brown oil. ^{1}H NMR (500 MHz, CDCl$_3$,): δ 7.47 (m, 2 H), 7.02 (m, 2 H), 1.38 (sep, J=7.5 Hz, 3H), 1.07 (d, J=7.5 Hz, 18H). ^{13}C NMR (125MHz, CDCl$_3$): δ 140.3, 136.7, 131.4, 118.2, 18.5, 10.8; (ESI-positive) calculated for C$_{15}$H$_{25}$N$_3$Si ([M]$^+$): 275.1818, found: 278.1

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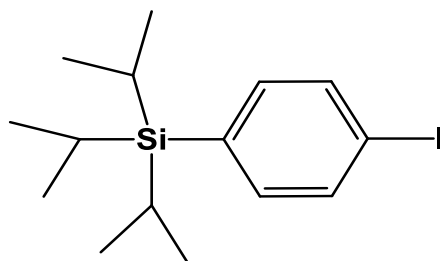
TIPS - Iodobenzene

^{1}H NMR
Solvent - CDCl$_3$
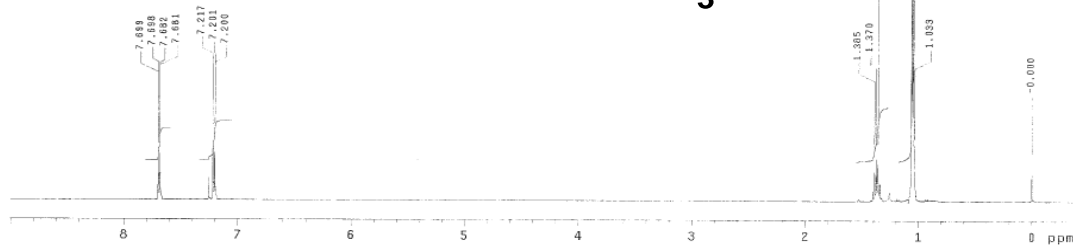
TIPS - Iodobenzene

^{13}C NMR
Solvent - CDCl$_3$

136.931
136.630
134.360
95.663
77.303
77.047
76.794
18.690
18.602
18.521
18.496
18.463
10.835
10.674

220   200   180   160   140   120   100   80   60   40   20   0   ppm

^{1}H NMR
Solvent - CDCl$_3$

7.260
1.085
1.082
1.069
1.066
0.893
0.884
0.000

8   7   6   5   4   3   2   1   ppm
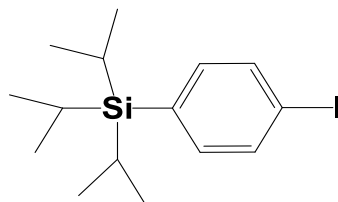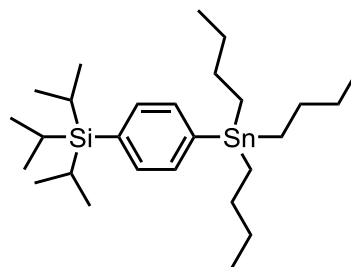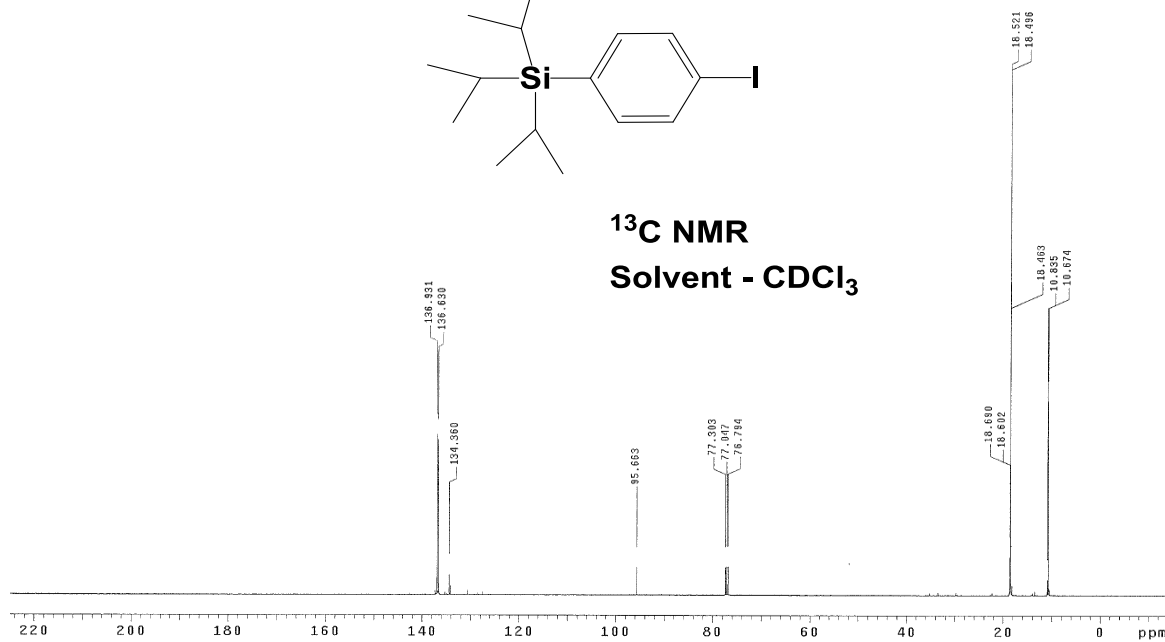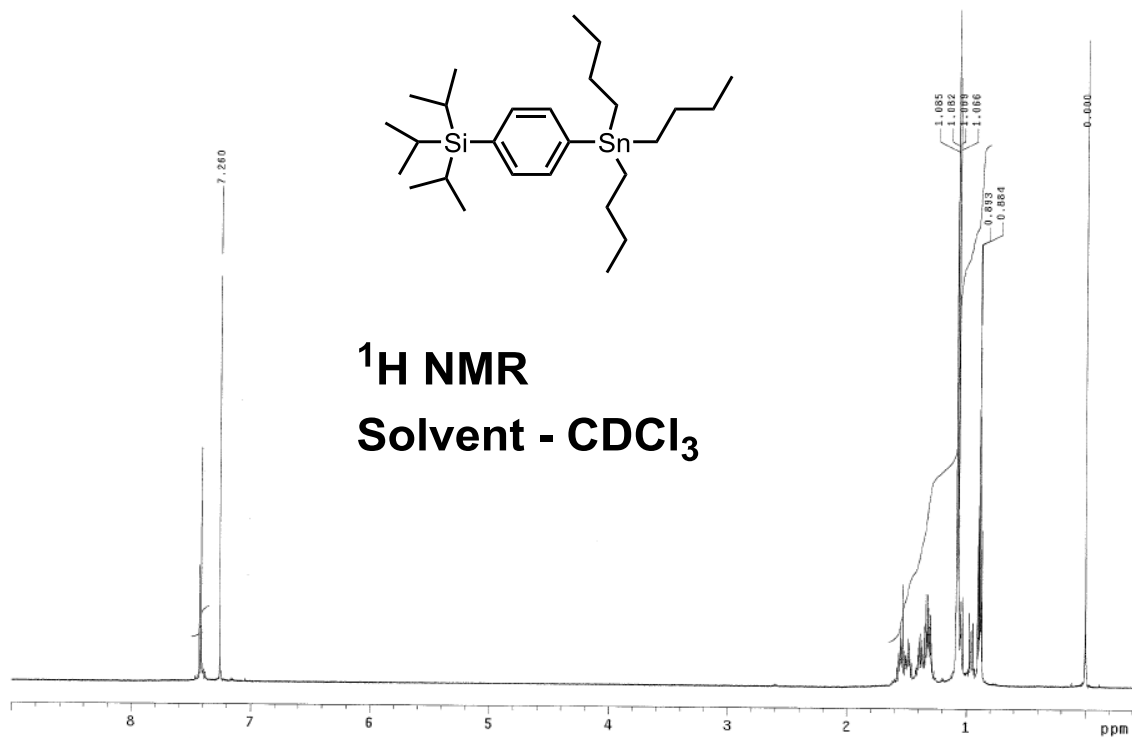
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Pulse Sequence: s2pul
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 Temp. 25.0 C / 298.1 K
Operator: vzteach2
File: 00432
INOVA-500 "nmr500"

 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.300 sec
 Width 30154.5 Hz
 1000 repetitions
 OBSERVE C13, 125.6570835 MHz
 DECOUPLE H1, 499.7320016 MHz
 Power 38 dB
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 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 131072
Total time 38 min, 29 sec
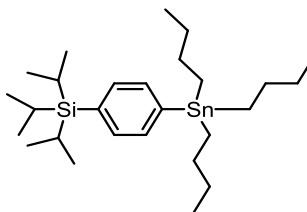
¹H NMR

Solvent - CDCl₃
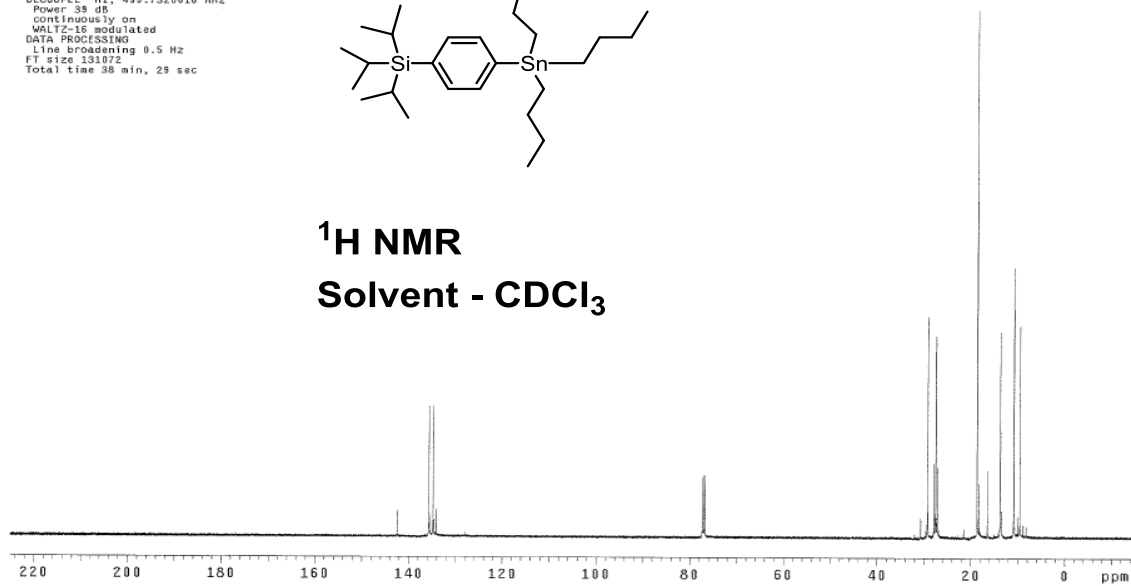
Diaryliodonium Salt
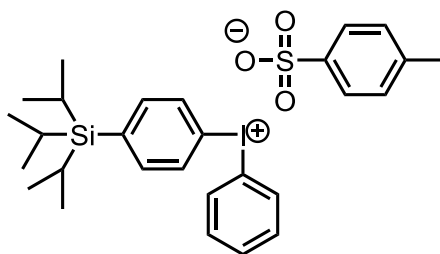
¹H NMR
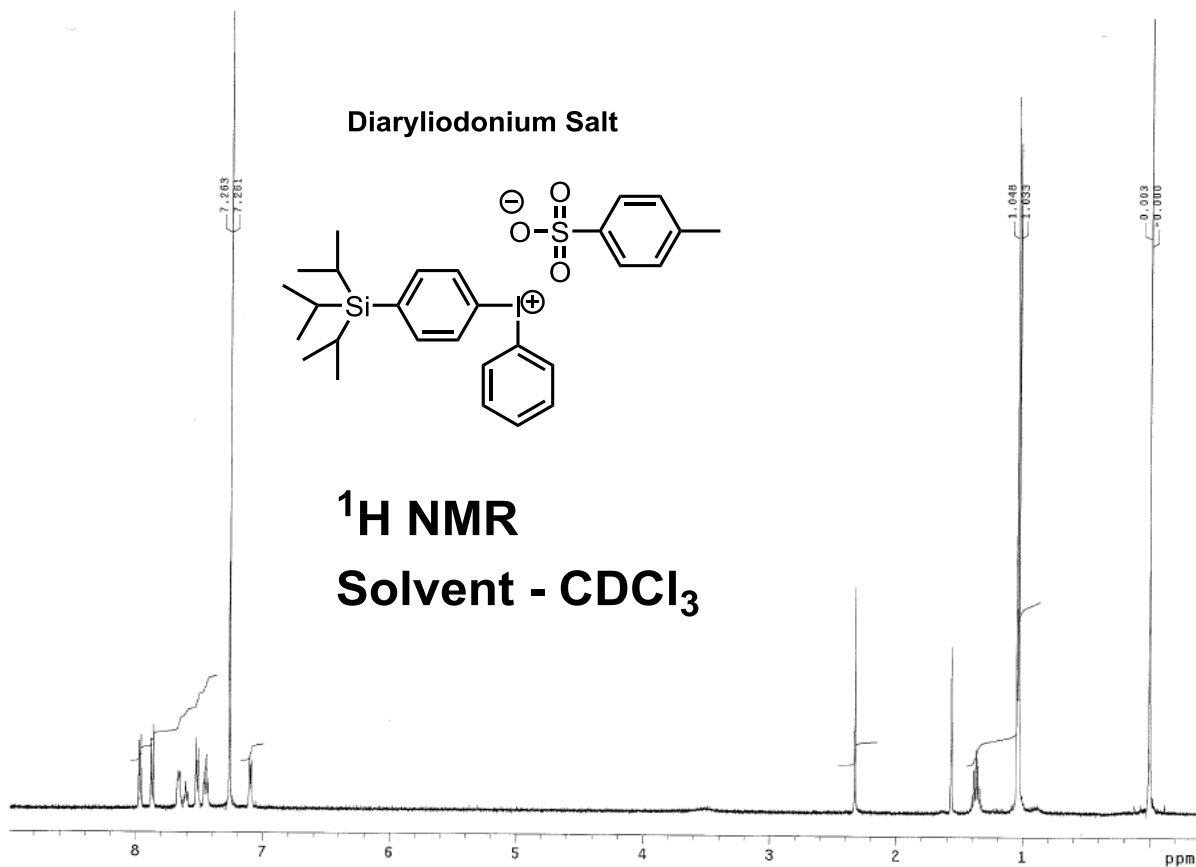
Solvent - CDCl₃

Diaryliodonium Salt
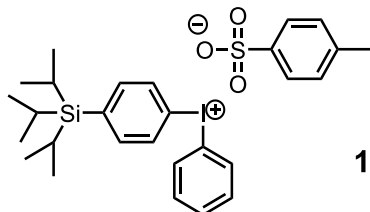
^{13}C NMR
Solvent - DMSO-d6
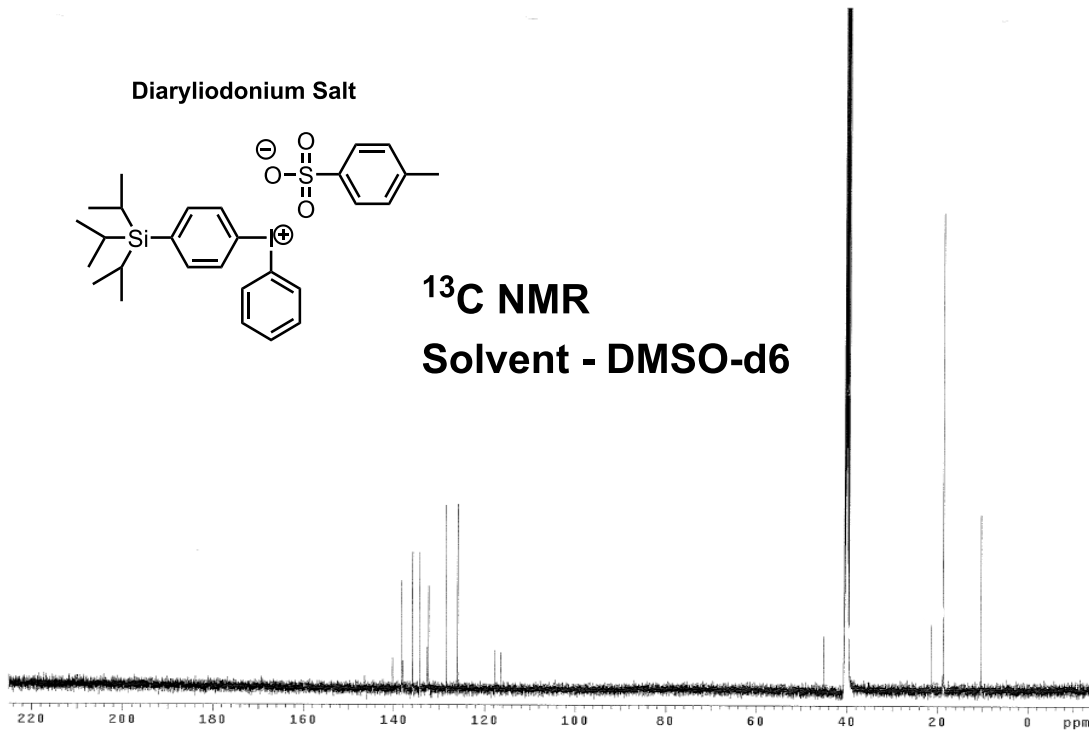
Sample ID: s_20140610_01
File: /home/vzteach2/vnmrsys/data/auto_2013.11.20_01/001485.fid

Pulse Sequence: s2pul
  Solvent: cdcl3
  Temp. 25.0 C / 298.1 K
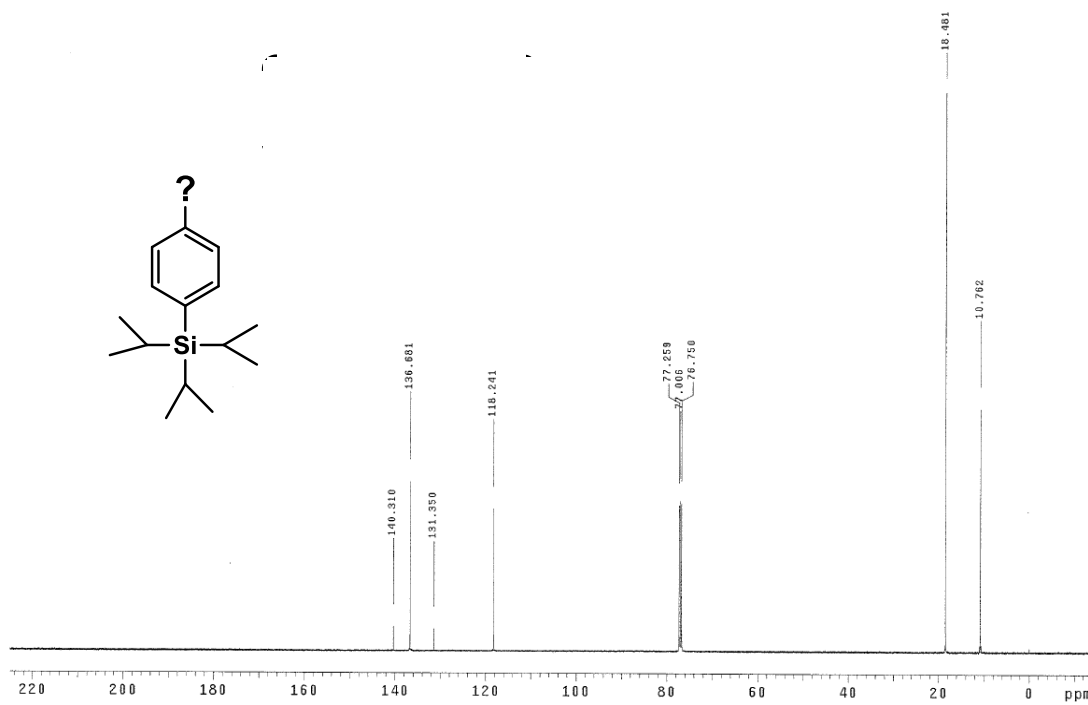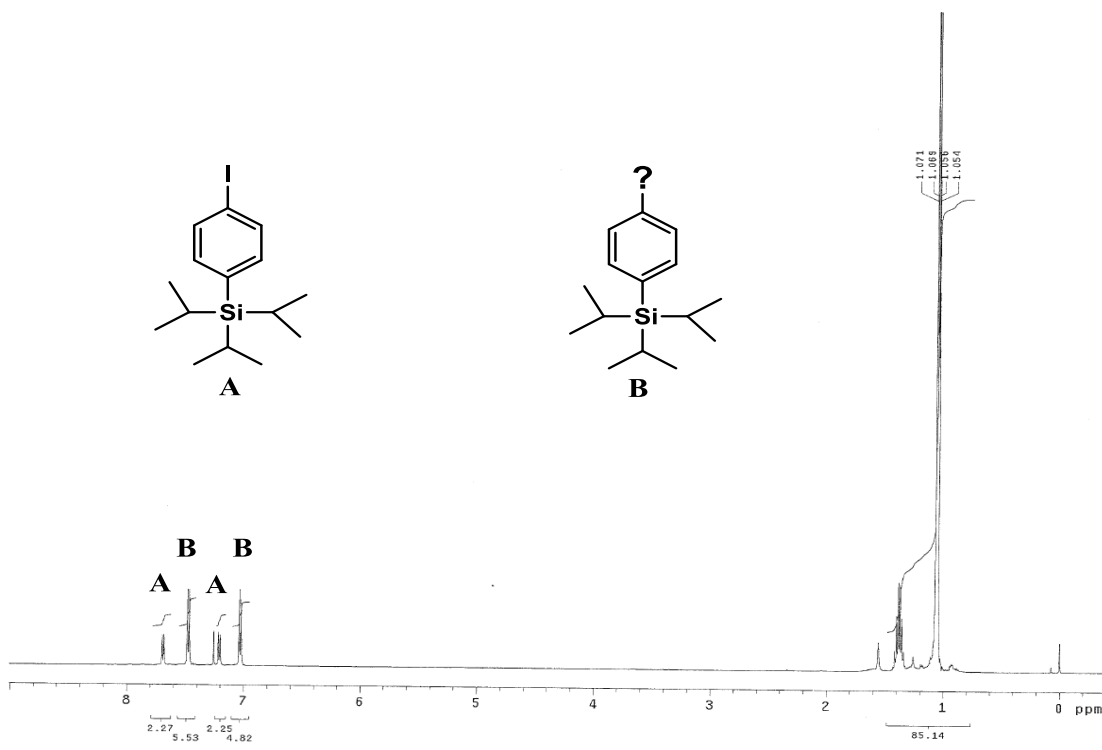Operator: vzteach2
File: 001485
INOVA-500 "nmr500"

  Relax. delay 1.000 sec
  Pulse 45.0 degrees
  Acq. time 2.049 sec
  Width 7996.0 Hz
  8 repetitions
OBSERVE H1, 499.7296730 MHz
DATA PROCESSING
  Resol. enhancement -0.0 Hz
FT size 65536
Total time 0 min, 31 sec

Diaryliodonium Salt
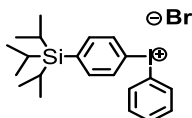
^{1}H NMR
Solvent - CDCl$_3$
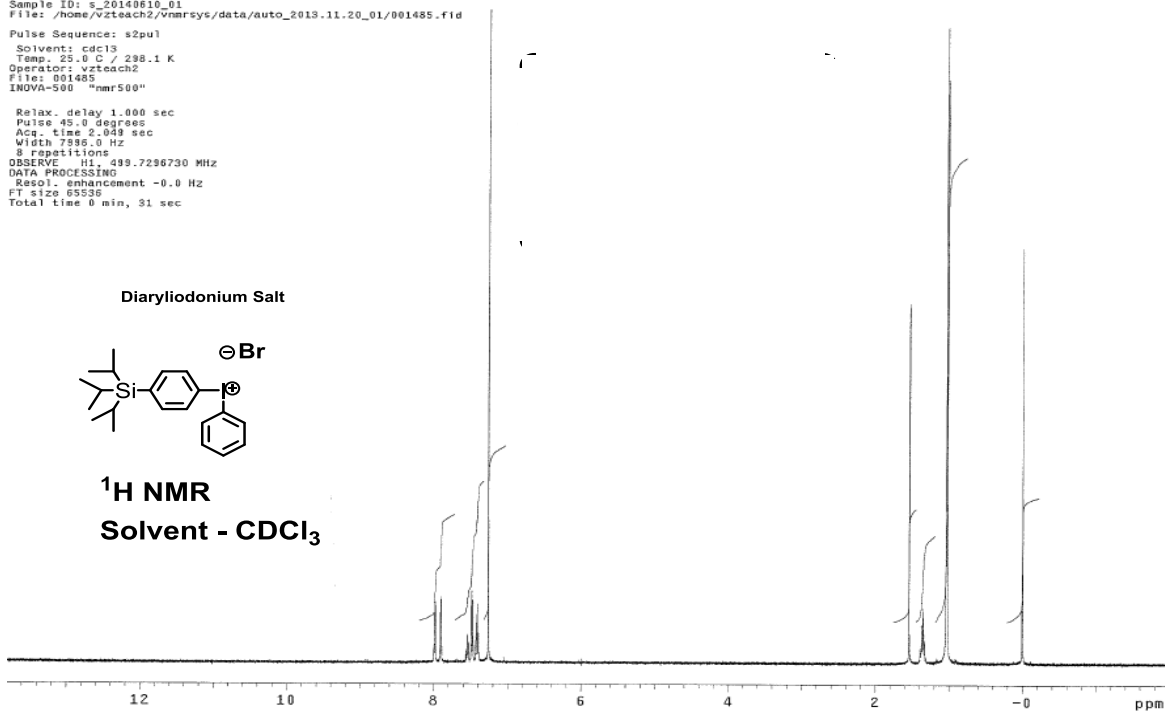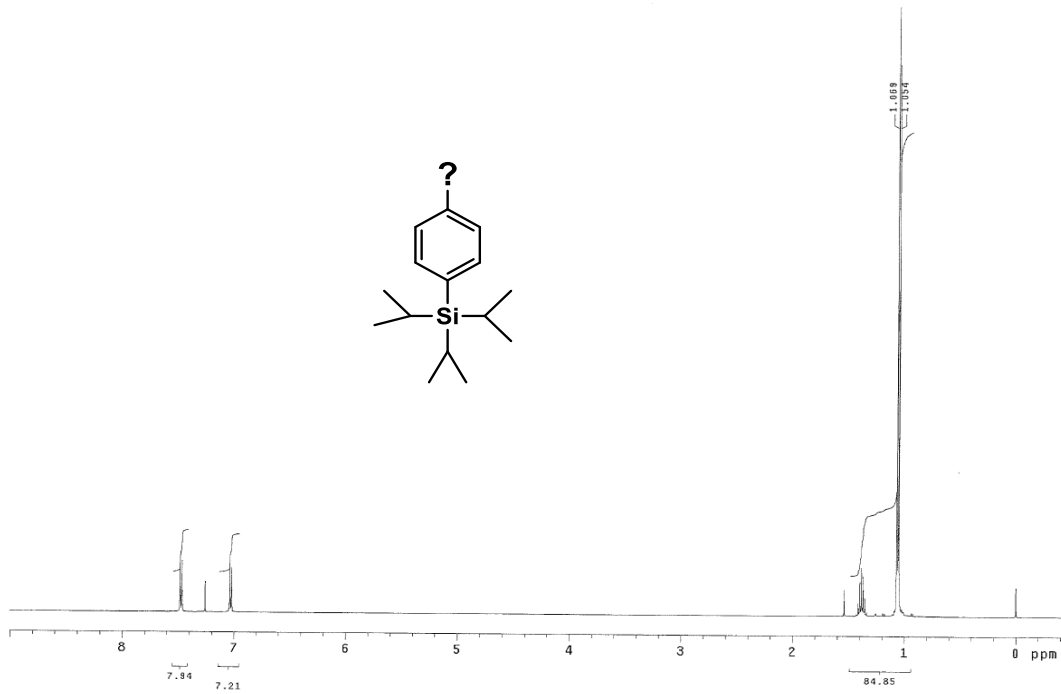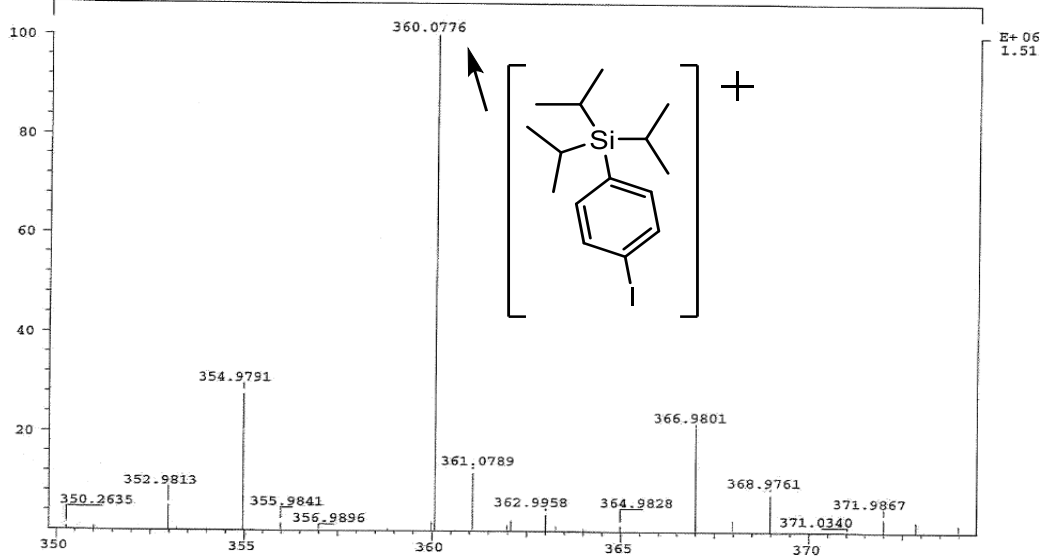
SPEC: e100970ph-c2   15-Apr-13   Elapse: 00:43.9   84
Samp: BK-35   Start : 13:47:52   84
Comm: 70 eV HR EI solids probe 4000 res
Mode: EI +VE +LMR ESCAN (EXP) UP HR NRM
Oper: Inlet :
Base: 367.0   Inten : 317769   Masses: 350 > 374
Norm: 360.1   RIC   : 2990329   #peaks: 30
Peak: 0.00 mmu
Data: CMASS : converted

Display Report

Acquisition Parameter

n/a	n/a	n/a	n/a	deflbias	1750 V
EndP	-4000 V	n/a	n/a	n/a	n/a

C27H52Si1Sn1, M ,524.29

50
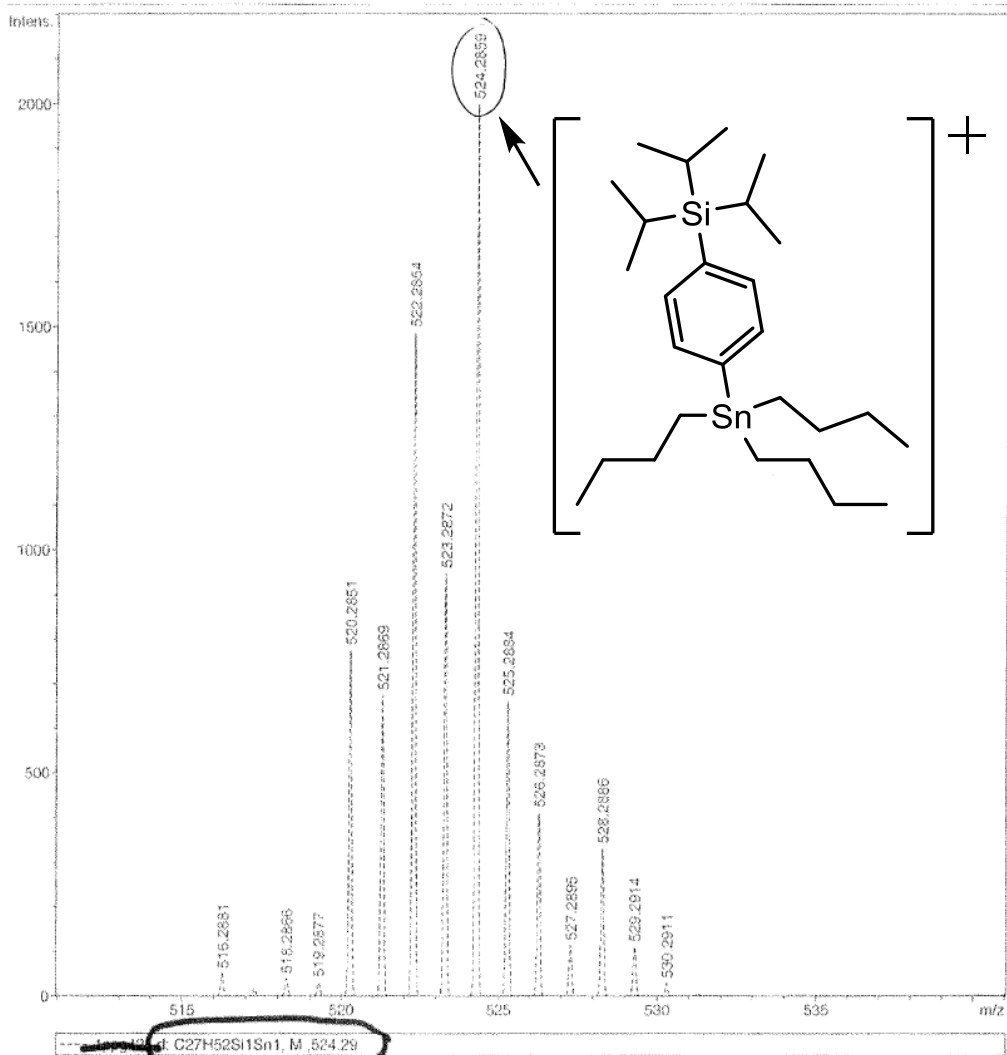
Generic Display Report (all)

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Bromide anion (Br⁻)

TIPS-phenyl Group

Iodine

Phenyl Group
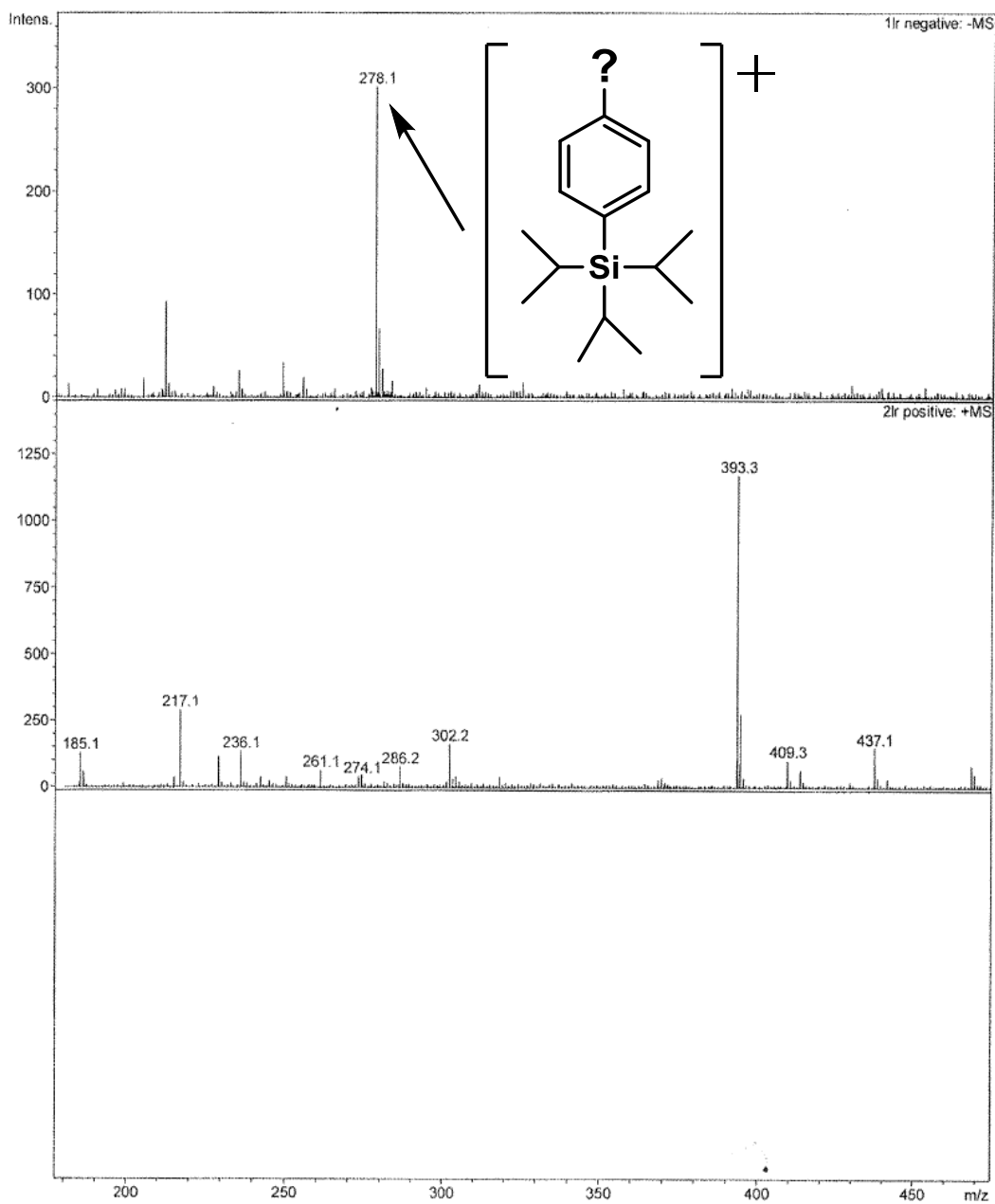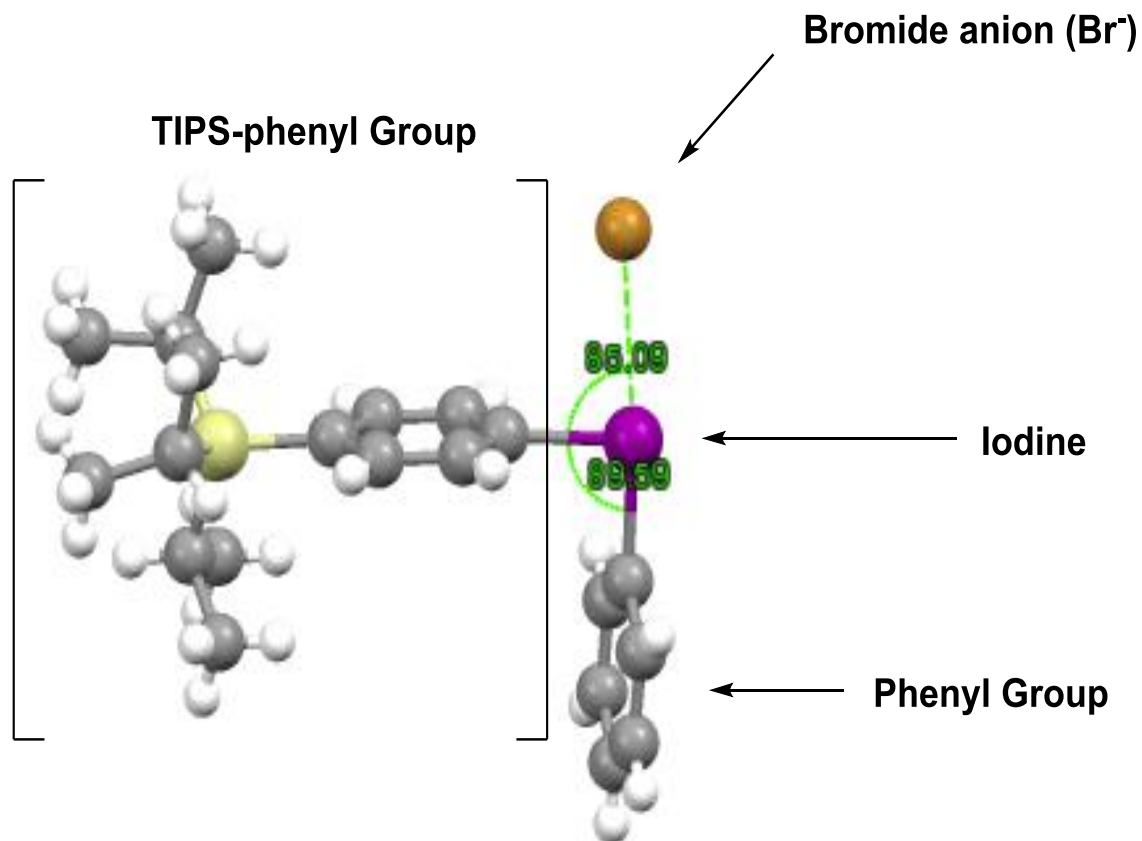
This image is the X-ray crystal structure obtained from

(4-triisopropylsilylphenyl)phenyliodonium bromide. It features the two most

electronegative substituents (bromide and phenyl) in the axial positions and the least

electronegative substituent (TIPS-phenyl) in the equatorial position.