Ligand Transfer Reactions of Hypervalent Iodine Reagents with Phosphorus Compounds

by

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A thesis

presented to the University of Waterloo

in fulfillment of the

thesis requirements for the degree of

Master of Science

in

Chemistry

Waterloo, Ontario, Canada, 2018

Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Many hypervalent iodine compounds are used as versatile reagents in synthetic organic chemistry. Hypervalent iodine reagents are capable of oxidizing trivalent phosphorus compounds into pentavalent, by transferring their heteroatom ligands onto phosphorus. These pentavalent phosphorus compounds can have a different reactivity profile than either the hypervalent iodine(III) reagents or the parent phosphorus(III) compounds. As such, in addition to their applications in organic reactions, they are utilized in fields such as medicinal chemistry, biochemistry, and chemical biology. The goal of this project is to synthesize pentavalent phosphorus species from trivalent phosphorus compounds using relatively cheap, environmentally benign, hypervalent iodine reagents.

Chapter 1 describes the attempted synthesis of dihalo- and diacyloxytriphenyl-phosphoranes. In this study we successfully synthesized and isolated Ph_3PF_2 through the reaction of $TolIF_2$ and Ph_3P. This reaction was monitored using ^{31}P NMR spectroscopy which revealed clean conversion of Ph_3P to Ph_3PF_2, which was relatively fast in chloroform. In the similar way, we treated Ph_3P with hypervalent iodine reagents (diacetoxyiodo)benzene, bis(trifluoroacetoxyiodo)benzene and a chlorinated cyclic iodane. Even though the expected phosphoranes have not been observed, we found that the Ph_3P/hypervalent iodine reagent system can be utilized for functionalization of alcohols. When a set of primary, secondary and tertiary alcohols were treated with Ph_3P/hypervalent iodine reagent system, the conversion of primary alcohols to the corresponding fluoride, acetate, trifluoroacetate or chloride, respectively, were feasible. The reactivity of secondary and tertiary alcohols varied depending on the Ph_3P/hypervalent iodine reagent system.

Chapter 2 describes the halogenation of secondary phosphine oxides and subsequent reaction with various nucleophiles. We found that the presence of electron donating substituents on the aromatic ring gave better results on fluorination compared with the parent diphenylphosphine oxide. Chlorination of secondary phosphine oxides in the presence of a nucleophile like ethanol led to the formation of phosphinates with excellent yields.

Acknowledgements

I would like to thank my supervisor Dr. Graham Murphy for giving me an opportunity to pursue my master's degree under his guidance. It is with immense gratitude that I acknowledge all the support, guidance, and the patience, he offered me for the past two years.

I would like to thank my advisory committee, Dr. Michael Chong and Dr. Eric Fillion for all their support. I would like to extend my gratitude to Dr. Rick Marta, Dr. Laura Ingram and Julie Goll whom with I had the opportunity to work as a teaching assistant. It was a great learning experience.

I would like to thank Jan Venne for all her support with NMR.

There are no words to express my gratitude to my fellow colleagues in the Murphy lab. I always considered myself lucky to be part of such a wonderful group. I owe my deepest gratitude to Richard Tran for everything he has done for me from day one itself. Even after his graduation, he spent time to edit my thesis. I am indebted to Jason Tao not only for answering my questions, but, also finding time to edit my thesis even though he was busy with his thesis submission. I take this opportunity to thank Dr. Zhensheng Zhao for sharing the fumehood and for all the fun time we had together. I also take this opportunity to thank Myriam St. Onge Carle for her help with NMR studies and Dr. Leanne Racicot for her help with GCMS. I am thankful to Tristan Chidley for paying attention to all my doubts. I would like to express my gratitude to Liam Britt and also to former members Dr. Kaivalya Kulkarni and Abhinandan Shyamsundar.

I would like to thank my cousin Athulya for all her help with auto formatting word. Last, but not the least I would like to thank my husband Eljo and our kids Adish and Eva for their love, encouragement, and support for the entire period.

To Eljo, Adish and Eva

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List of Abbreviations

3c-4e	Three centre-four electron
DCDMH	Dichlorodimethylhydantoin
DCM	Dichloromethane
DCE	1,2-Dichloroethane
DEAD	Diethyl azodicarboxylate
DFP	Diisopropylfluorophosphate
DIAD	Diisopropyl azodicarboxylate
DMF	*N*,*N*-dimethyl formamide
equiv	Molar equivalent
et al.	And others
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
GCMS	Gas chromatography-mass spectrometry
gem	Geminal
HVI	Hypervalent iodine
in situ	In the reaction mixture
IR	Infrared Spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
L	Ligand
LRMS	Low Resolution Mass Spectrometry
MO	Molecular orbital
m.p.	Melting point
NMR	Nuclear Magnetic Resonance
OPs	Organophosphorus compounds
PIDA	(Diacetoxyiodo)benzene
PIFA	[Bis(trifluoroacetoxy)iodo]benzene

PhCl	Chlorobenzene
PhIO	Iodosylbenzene
R	Any group in which a carbon or hydrogen atom is attached to the rest of the molecule
rt	Room temperature
SPO	Secondary phosphine oxide
TCICA	Trichloroisocyanuric acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TolI	*p*-Iodotoluene
$TolIF_2$	*p*-(Difluoroiodo)toluene

Chapter 1: Hypervalent Iodine Reagents and Triphenylphosphine

1.1 Introduction to Hypervalent Iodine Compounds

Iodine is the heaviest, non radioactive, least electronegative and most polarizable halogen on the periodic table.[1] The common oxidation state of iodine is -1, but this value can vary up to +7. Compounds containing an iodine atom in higher oxidation states are termed as hypervalent iodine (HVI) compounds. The term "hypervalent" was first used by J.I. Musher to describe atoms of molecules containing oxidation state higher than the lowest stable oxidation state.[2] Today, IUPAC defines hypervalency is "the ability of an atom in a molecular entity to expand its valence shell beyond the limits of the Lewis octet rule".[3]

1.1.1 Structure and Bonding

Depending on the oxidation state of the central iodine atom, organic hypervalent iodine reagents are categorized into two structural types: trivalent iodine derivatives (**1** and **2** in Figure 1.1) and pentavalent iodine derivatives (**3** in Figure 1.1).[4] According to IUPAC nomenclature iodine(III) compounds and iodine(V) compounds are called λ^3-iodanes and λ^5-iodanes, respectively. In λ^5-iodanes, the iodine atom possesses 12 valence electrons and has a square bipyramidal geometry in which an organic group, R, and an unshared electron pair occupy the apical positions while the electronegative ligands reside at the equatorial positions. In λ^3-iodanes of the general formula RIL_2 (**1**), the central iodine atom possesses 10 electrons and has a distorted trigonal bipyramidal geometry with two heteroatom ligands occupying the apical positions, while a carbon substituent and two lone pairs of electrons are distributed at the equatorial positions

(Figure 1.1).[4] The I–L bond lengths in these compounds are found to be longer than an average I–L covalent bond and can be explained due to the formation of a so-called hypervalent bond.

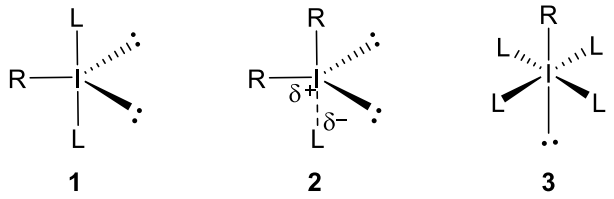


Figure 1.1: Typical structural types of organo-λ^3-iodanes and λ^5-iodanes

One way of explaining hypervalent bonding in λ^3-iodanes is through the 3-centre-4-electron bond model (3c–4e), first proposed by G. C. Pimentel[5] and R. E. Rundel[6] in 1951 on the basis of molecular orbital (MO) theory. In RIL_2 compounds, the iodine atom and the two apical ligands are involved in forming the 3c–4e bond. The filled 5p orbital of the central iodine atom interacts with the half-filled orbitals of two ligands leads to the formation of three MOs: bonding, nonbonding, and antibonding molecular orbitals. The four electrons occupy the lowest energy bonding and nonbonding molecular orbitals. Among which the highest occupied nonbonding molecular orbital has a node at the central iodine atom and the electron density is localized at the apical ligands. As a result, the central iodine atom is highly electrophilic (Figure 1.2).[1]

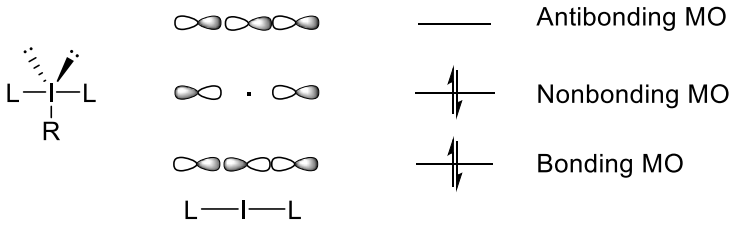


Figure 1.2: Molecular orbital diagram of the 3c–4e bond in λ^3-iodanes

1.1.2 Examples of HVI Reagents

Since their discovery by Willgerodt in 1886,[7] HVI reagents have been widely used in many organic syntheses, especially in the past three decades,[1] due to their mild reaction conditions, their commercial availability,[8] their ease of handling and their relatively low cost. Some of the most commonly used iodine(III) and iodine(V) reagents are illustrated in Figure 1.3.[4]

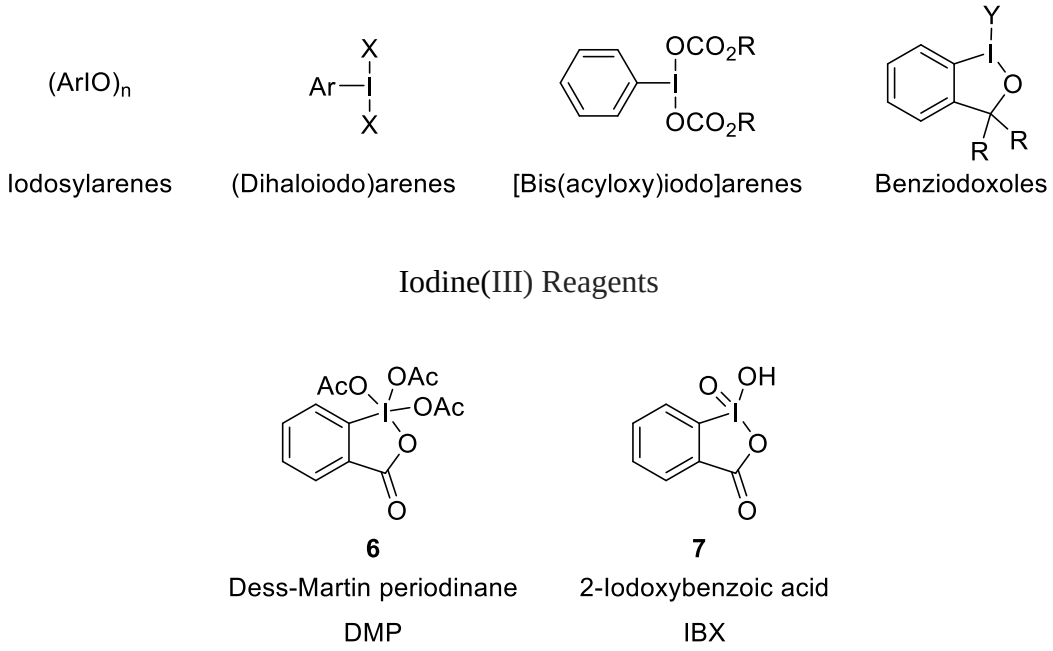


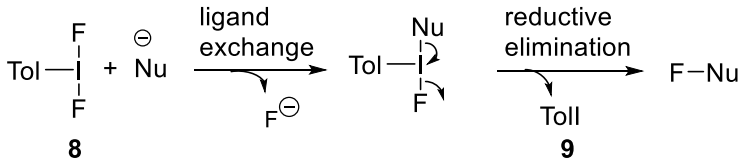
Figure 1.3: Main classes of some hypervalent iodine reagents

Iodosylarenes are examples of iodine(III) reagents. They are used in organic synthesis as selective oxidants and electrophilic ligand transfer reagents.[9] Among iodosyl compounds, iodosylbenzene (PhIO, **4**) is the most important one and is prepared by the hydrolysis of (diacetoxyiodo)benzene (**5**) using aqueous sodium hydroxide. Due to its polymeric nature, PhIO cannot be recrystallized.[9] Iodosylbenzene can be easily converted to $PhIX_2$ derivatives by reacting with the respective acids HX.[9] (Dihaloiodo)arenes are effective halogenating reagents while aryl

iodine(III) carboxylates are found to be useful in oxidative functionalization of organic substrates. Benziodoxole and benziodoxolone based hypervalent iodine reagents are well known for transferring their exocyclic ligands.[10] 2-Iodoxybenzoic acid (IBX, **6**) and Dess-Martin periodinane (DMP, **7**) are well-known iodine(V) reagents and they have been extensively used as mild and highly selective reagents for a variety of synthetically useful oxidative transformations.[11]

1.1.3 Reactivity of λ³-Iodanes

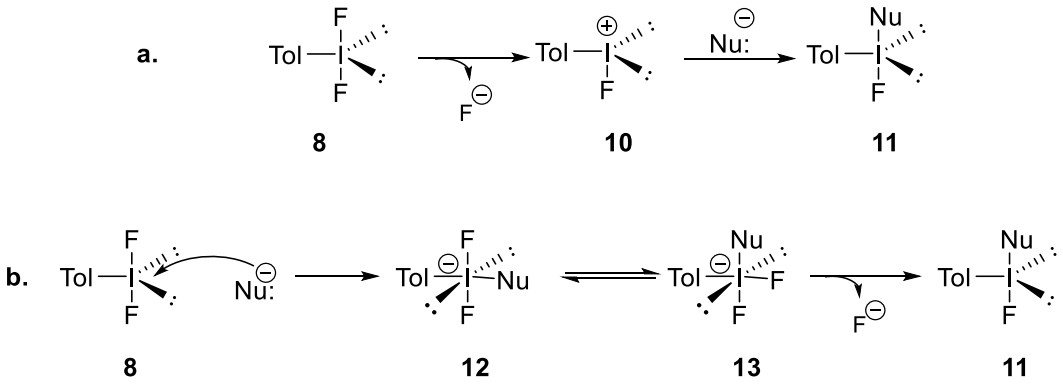
The reactivity associated with λ³-iodanes depends on the number of carbon ligands and heteroatom ligands.[12] Iodanes with two carbon ligands are very useful for transferring one of the carbon ligands to various nucleophiles while λ³-iodanes with two heteroatom ligands ($ArIL_2$) are effective oxidizing agents. In the typical reactions of $ArIL_2$ compounds (*e.g. p*-(difluoroiodo)toluene, $TolIF_2$, **8**), the initial step involves the exchange of ligands on the iodine atom with nucleophiles, followed by reductive elimination of *p*-iodotoluene (TolI, **9**) (Scheme 1.1).[1]



Scheme 1.1: Ligand exchange and reductive elimination in aryl-λ³-iodane

Two mechanistic pathways have been proposed for the ligand exchange reactions of λ³-iodanes: associative and dissociative (Scheme 1.2). In the dissociative pathway, the elimination of a ligand from aryl-λ³-iodane **8** leads to the formation of a dicoordinated iodonium ion **10**, which then reacts with the nucleophile to form a new aryl-λ³-iodane **11**. In solution, the cationic iodonium species is coordinated with solvent moleules.[1] This pathway is less likely to occur due to the low stability of the dicoordinated iodonium ion.

In the associative pathway, ligand exchange starts from the addition of an external nucleophile to the central iodine atom of the λ^3-iodane **8**, which results in the formation of a *trans* square planar species **12**. The *trans* intermediate isomerizes to the *cis* form **13** and the ligand dissociates to form **11**. The overall process can be summarized as a ligand exchange between a heteroatom ligand with the external nucleophile through an addition-elimination sequence.[12]



Scheme 1.2: Dissociative (a) and associative (b) pathways for ligand exchange of aryl-λ^3-iodanes

The key to the reactivity of aryl-λ^3-iodanes is their ability to undergo reductive elimination in which iodine(III) is reduced to monovalent iodine. Ochiai described the λ^3-iodanyl group as a "hypernucleofuge" due to its excellent leaving group ability.[12] Other important reactions associated with hypervalent iodine reagents such as radical reactions and single-electron transfer reactions are beyond the scope of this thesis.[13]

This thesis focuses on using hypervalent(III) iodine reagents as oxidants to easily access the chemistry of pentavalent phosphorous reagents. HVI reagents pertinent to this thesis are bis(acyloxyiodo)arenes, such as (diacetoxyiodo)benzene (PIDA, **7**) and bis(trifluoroacetoxyiodo)benzene (PIFA, **14**), *p*-(difluoroiodo)toluene (TolIF$_2$, **8**),

(dichloroiodo)benzene ($PhICl_2$, **15**) and the cyclic chlorobenziodoxole (**16**) (Figure 1.4). Some reactions of these HVI reagents are described in the remainder of this section.

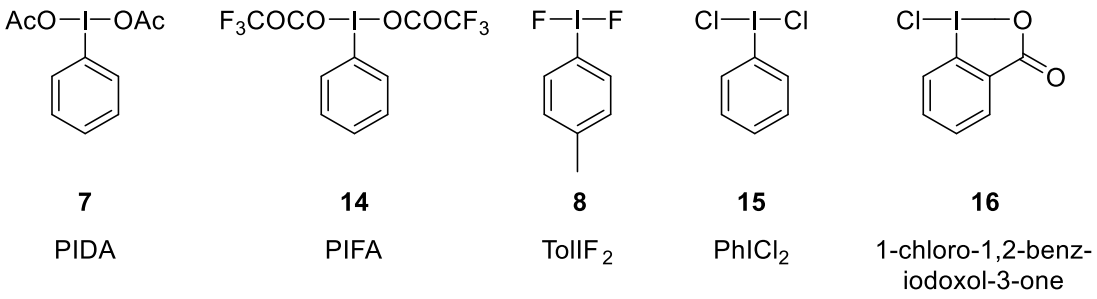
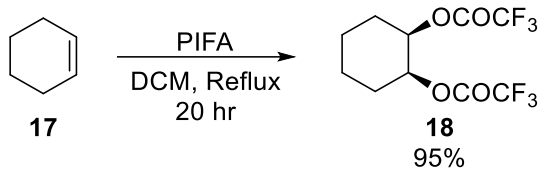


Figure 1.4: HVI reagents relevant to the thesis

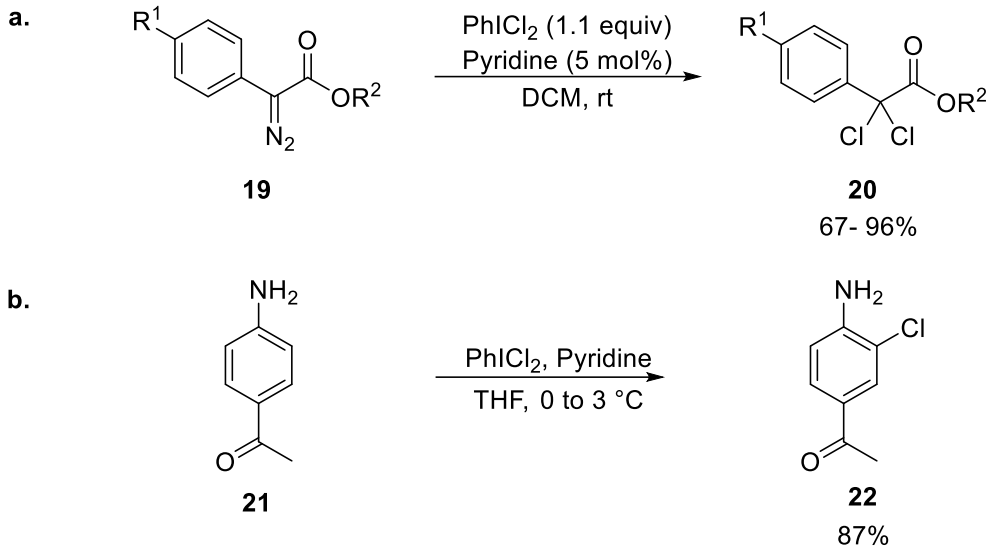
Both PIDA and PIFA are commercially available and are widely used as oxidants. They are capable of oxidizing alkenes,[14] alkynes,[15] aldehydes, and ketones.[14] Celik and coworkers reported the reaction of PIFA with alkenes to form bis(trifluoroacetates) with a *syn*- addition of the two trifluoroacetoxy groups (Scheme 1.3).[16]



Scheme 1.3: Synthesis of bis(trifluoroacetates)

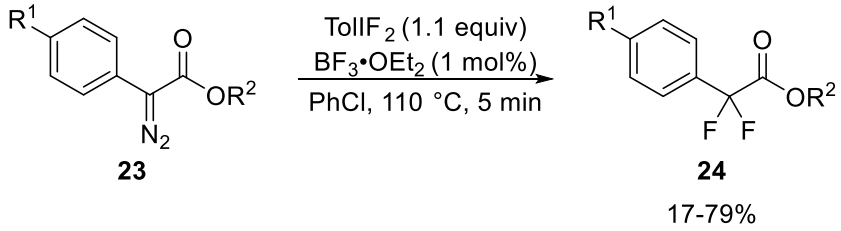
Both (difluoroiodo)arenes and (dichloroiodo)arenes are widely used in organic synthesis as halogenating or oxidizing reagents.[9] (Dichloroiodo)benzene is a useful reagent for chlorination of a wide range of organic compounds, such as alkenes[17] and ketones.[18] *gem*-Dichlorination of phenylacetate derivatives were reported by Murphy and *et al.* in 2013 (Scheme 1.4. a).[19] Monochlorination of 4-aminoacetophenone on a large scale using $PhICl_2$ was reported by Zanka and *et al.* (Scheme 1.4. b).[20] Recently, $PhICl_2$ was effectively employed in the oxidative

chlorination of triphenylphosphine and further reaction with carboxylic acids, amides and alcohols.[21]



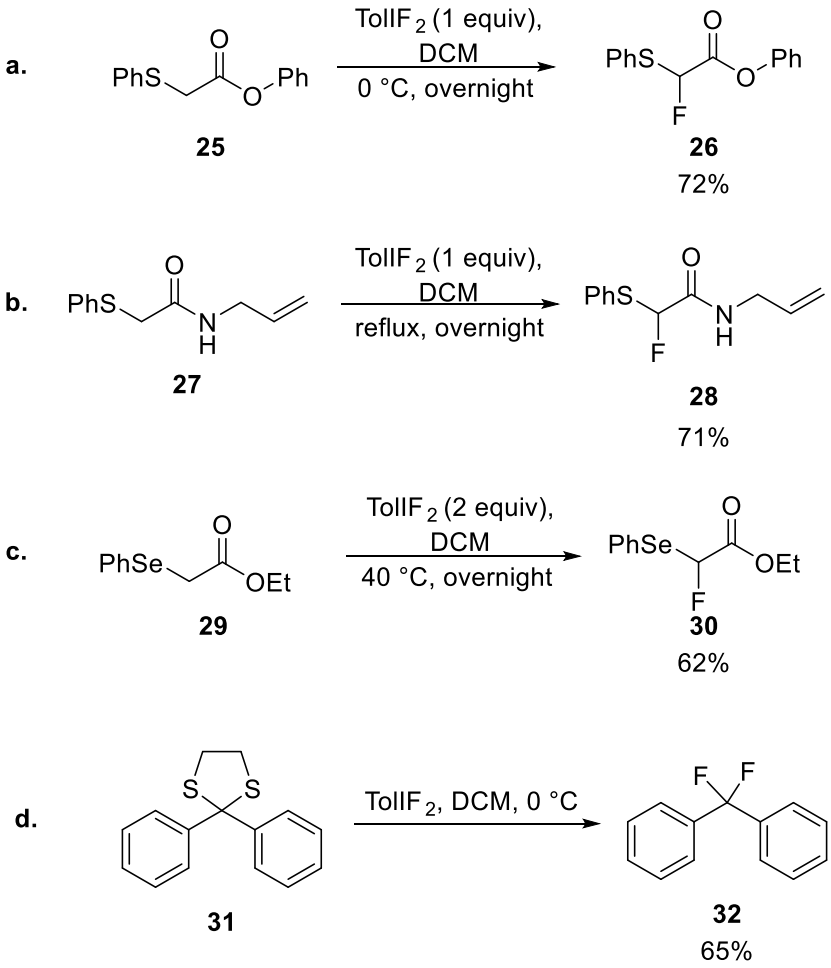
Scheme 1.4: Chlorination reactions with $PhICl_2$

The general methods employed for the synthesis of $TolIF_2$ are either by oxidative addition of fluorine to *p*-iodotoluene using an electrophilic fluorinating agent, or by exchanging the ligand of existing other iodine(III) compounds with fluoride.[4] $TolIF_2$ is an effective surrogate for elemental fluorine.[22] $TolIF_2$ can be a source of both electrophilic and nucleophilic fluorine and this property makes it a very useful reagent in many reactions. An example of this is the *gem*-difluorination of phenylacetate derivatives reported by Murphy and *et al*. in 2013 (Scheme 1.5).[19]



Scheme 1.5: α,α-Difluorination of aryl diazoacetate derivatives

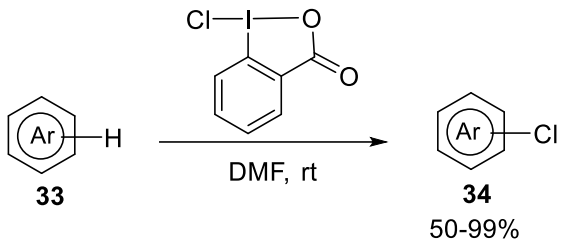
$TolIF_2$ is useful in the synthesis of α-monofluorosulfides from α-phenylsulfanylated esters[23] and amides[24] (Scheme 1.6. a and b). The authors claimed that the reaction pathway for these reactions involved an initial nucleophilic attack of sulfur atom on the electrophilic iodine centre. In a similar way, $TolIF_2$ is found to produce α-monofluorinated products with α-selenocarboxylic acid derivatives (Scheme 1.6. c).[25] *gem*-Difluorination of diarylthioketals with $TolIF_2$ has been reported by Motherwell *et al.*(Scheme 1.6. d).[26]



Scheme 1.6: Fluorination reactions of sulfur and selenium compounds with $TolIF_2$

Benziodoxole and benziodoxolone reagents are heterocyclic compounds in which iodine and oxygen are incorporated into the five membered ring with various substituents attached to

iodine.[8] In 2006, Togni *et al* reported the use of benziodoxol(on)e-based reagents for electrophilic trifluoromethylation of nucleophilic substrates.[27] Benziodoxol(on)e-based reagents are very effective in tosyloxylation of ketones,[28] bromination of anisole,[29] alkynylation *etc*. depending on the ligand attached to iodine. Xue *et al.*, reported 1-chloro-1,2-benziodoxol-3-one (**16**) as an efficient chlorinating reagent for various nitrogen containing heterocycles and selected classes of arenes (Scheme 1.7).[30]



Scheme 1.7: Electrophilic chlorination of arenes and heterocycles

1.2 Introduction to Organophosphorus Compounds

The element phosphorus was discovered in 1669 by H. Brandt[31] and since then, phosphorus compounds have received persistent attention from the scientific community. The ability of phosphorus to form bonds with both electronegative and electropositive elements leads to the existence of a wide range of phosphorus compounds. Organophosphorus compounds (OPs) contain organic moieties which are either directly bonded to phosphorus or bonded through a heteroatom such as oxygen, sulfur or nitrogen.[32] They have been used worldwide as reagents in organic synthesis, agrochemicals (e.g., insecticides, herbicides and plant growth regulators), medicinal compounds (e.g., anticancer, antiviral and antibacterial agents), flame retardants for fabrics and plastics, plasticizing and stabilizing agents in the plastic industry, additives in the petroleum products field, and corrosion inhibitors.[33]

There are several methods for classifying organophosphorus compounds. The early known OPs have three or four atoms directly bonded to phosphorus and are known as trivalent or tetravalent phosphorus compounds, respectively. Over time, more and more OPs were synthesized, in which, one, two, five or six atoms are attached to phosphorus. As a result, a new scheme has been developed to classify OPs in which a *coordination number* has been assigned to phosphorus depending on the number of atoms directly attached to it. For example, phosphines, having the general formula R_3P, are 3-coordinate compounds and are denoted by the symbol σ^3. The total number of bonds, which reflects the valency of phosphorus is described by λ. Therefore, triphenylphosphine (Ph_3P) is 3-coordinate with a total of 3 bonds and fully described as σ^3, λ^3. Some other examples are shown in Table 1.1.[33]

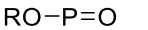
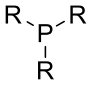
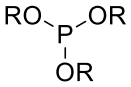
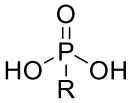
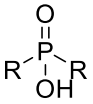
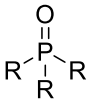
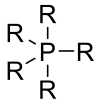
Designation	Coordination #	Structure R = a carbon group	Class Name
σ^1, λ^1	1		Phosphinidenes
σ^2, λ^3	2		Oxophosphines
σ^3, λ^3	3	 	Phosphines Trialkylphosphites
σ^4, λ^5	4	  	Phosphonic acids Phosphinic acids Phosphine oxides
σ^5, λ^5	5		Phosphoranes

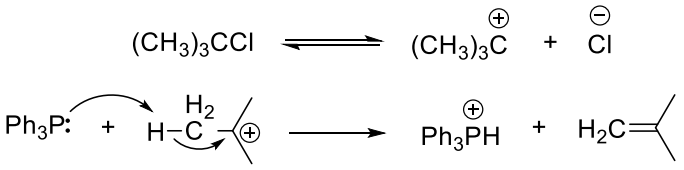
Table 1.1: An organization of some organophosphorus species

1.2.1 Phosphorus(III) Compounds

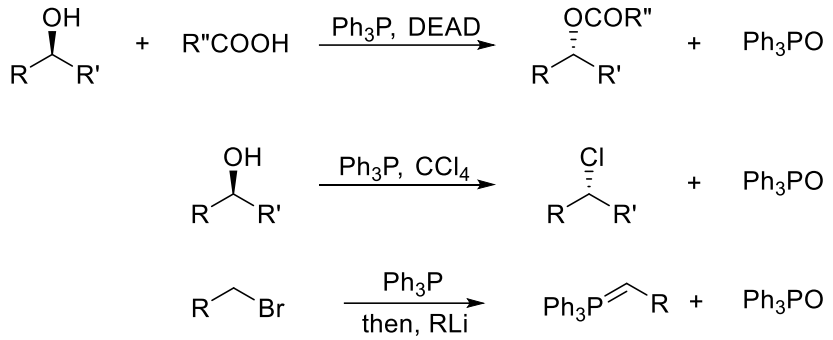
These compounds have the general formula R_3P where R can be hydrogen, alkyl, aryl, alkoxy, halogen *etc*. In general, the reactivity of phosphorous(III) compounds are dictated by the presence of the lone pair of electrons on the phosphorus atom that enables them to perform nucleophilic attack. Trivalent phosphorus compounds that contain one hydroxyl group are considered as derivatives of phosphinous acid, and will be discussed further in Chapter 2.

1.2.1.1 Triphenylphosphine (Ph_3P)

Triphenylphosphine is a widely used phosphorus(III) compound. Triphenylphosphine and its derivatives have found widespread use as ligands in transition-metal chemistry.[34] The presence of a lone pair of electrons makes them good nucleophiles that take part in reactions at electron deficient centres. Compared to amines, phosphines are generally weaker bases;[31] however, there are cases where phosphines can be used as an effective base, such as reaction between Ph_3P with *t*-butyl chloride, when refluxed in formic acid, to give 2-methyl-1-propene, presumably by the mechanism shown in Scheme 1.8.[31] Triphenylphosphine is used in many organic reactions such as Mitsunobu,[35] Appel,[36] and Wittig (Scheme 1.9). In most of its reaction, Ph_3P is converted to triphenylphosphine oxide. The driving force in these reactions is the formation of the strong P=O bond (544 kJ/mol).[37]

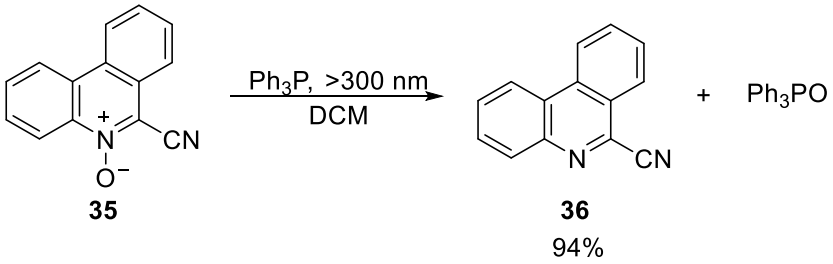


Scheme 1.8: Reaction in which Ph_3P acts as a base



Scheme 1.9: Mitsunobu reaction, Appel reaction and synthesis of Wittig reagents

Triphenylphosphine is also used as a reducing agent. For example, Ph_3P can be used in the reduction of organic peroxides, leading to the formation of either alcohols, carbonyl compounds, or epoxides.[38] Even though dimethyl sulfide is widely used in the reductive decomposition of ozonides to ketones and aldehydes, triphenylphosphine is an alternative to this, especially due to its lack of unpleasant odour. Triphenylphosphine is used as a reducing agent for N-oxides, especially for aromatic amine oxides. Kaneko *et al.* found that irradiation of aromatic amine oxides in the presence of Ph_3P led to the formation of deoxygenated products (Scheme 1.10)[39]. An attractive feature of this reaction is that the photolysis of aromatic amine N-oxides took place at room temperature while the earlier methods require heating above 200 °C.[40]

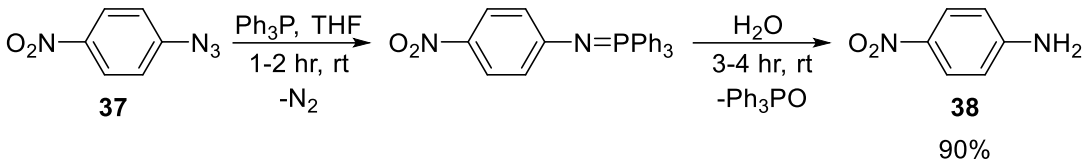


35 **36**
94%

Scheme 1.10: Reduction of aromatic N-oxides

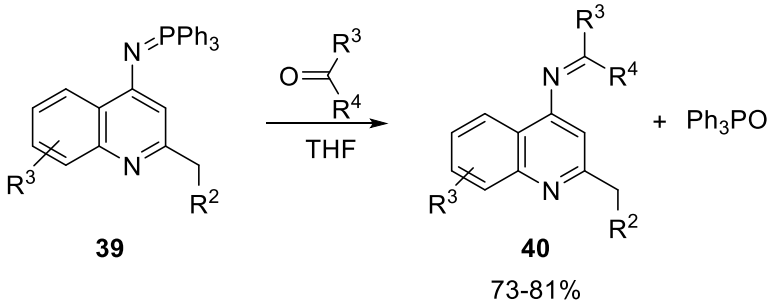
Another well-known reaction involving Ph_3P is the Staudinger reaction[41] in which organic azides are converted to iminophosphoranes. If this reaction is carried out in the presence of water,

the *in situ* formed iminophosphoranes are hydrolyzed to give amines and Ph_3PO (Scheme 1.11).[42] Thus, the Staudinger reaction serves as a very mild and chemoselective method for the reduction of organic azides to amines, a transformation which is otherwise accomplished by catalytic hydrogenation, reduction with lithium aluminum hydride or diborane.[38]



Scheme 1.11: Synthesis of amines from azides

Iminophosphoranes are found to be reactive towards electrophiles. The aza-Wittig reaction is an example in which iminophosphoranes react with carbonyl compounds to produce imines (Scheme 1.12) [38,43] This is an efficient method for the construction of carbon-nitrogen double bonds in mild reaction conditions.



Scheme 1.12: Example of Aza-Wittig reaction

1.2.2 Dihalotriphenylphosphoranes (Ph_3PX_2)

Halogenation of Ph_3P leads to the formation of dihalotriphenylphosphoranes (triphenylphosphine dihalides) represented by the chemical formula Ph_3PX_2. Several studies have been conducted on the structural diversity exhibited by dihalotriphenylphosphoranes and are summarized as in Figure 1.5.[44]

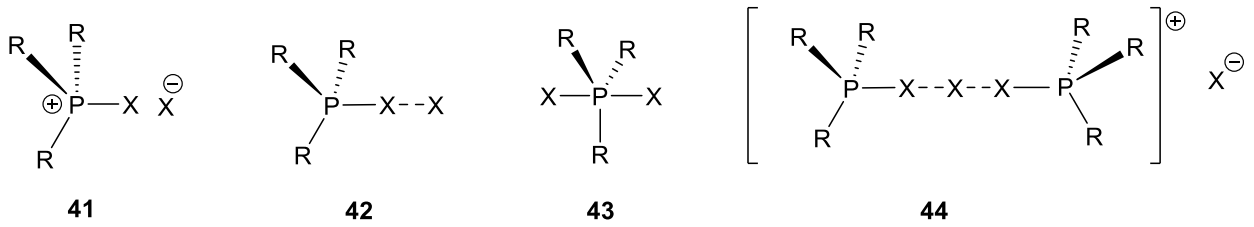


Figure 1.5: The principle dihalophosphorane structures

It is believed that a delicate balance exists between ionic and covalent forms of these compounds in solution.[44] The first successful attempts to reveal the structures of dihalotriphenylphosphoranes was done by Wiley and Stine in 1967.[45] By comparing the effects of Lewis acids on dichlorotriphenylphosphorane (Ph_3PCl_2**)** and by monitoring ^{31}P NMR, they hypothesized that, in acetonitrile, Ph_3PCl_2 completely ionized to form phosphonium chloride (**41** in Figure 1.5, where X = Cl) while in nitrobenzene it exists as a pentavalent species (**43**, where X = Cl) or as $R_3PCl^+R_3PCl^-_3$. Similar characteristics are observed for dibromotriphenylphosphorane (Ph_3PBr_2). In 1991, Godfrey and co-workers proposed a four-coordinate 'spoke' structure **42** (in Figure 1.5, X = I) for diiodotriphenylphosphorane (Ph_3PI_2) in the solid state by X-ray crystallographic studies.[46] They regarded it as a "frozen transition state" in the reaction sequence from **45** to **41** as shown in Figure 1.6.

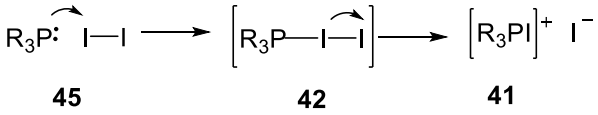


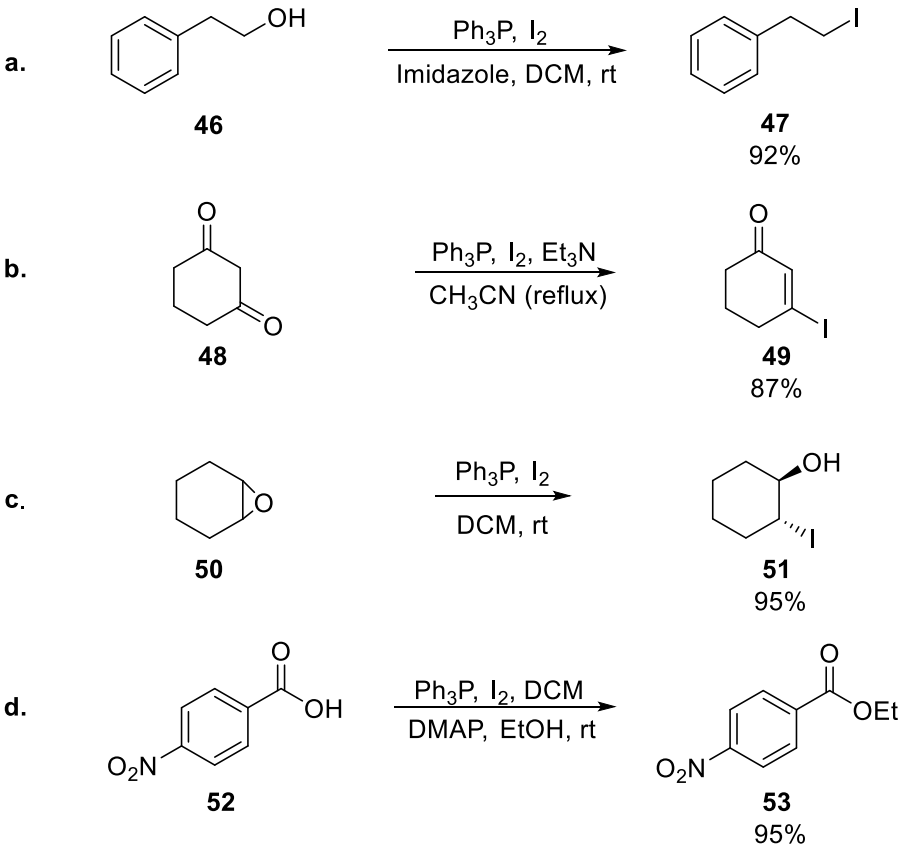
Figure 1.6: Suggestion for the four co-ordinate structure of Ph_3PI_2

X-ray crystallographic studies of Ph_3PCl_2 obtained by the reaction between 1:1 stoichiometric ratio of triphenylphosphine and chlorine gas in dichloromethane showed that it exists as a dinuclear ionic species **44** (X= Cl, in Figure 1.5).[47] This is supported by Giheany *et*

al.,[44] who suggested that this structure is stabilized by five-centre-six-electron hypervalent interactions.

1.2.2.1 Diiodotriphenylphosphorane (Ph_3PI_2)

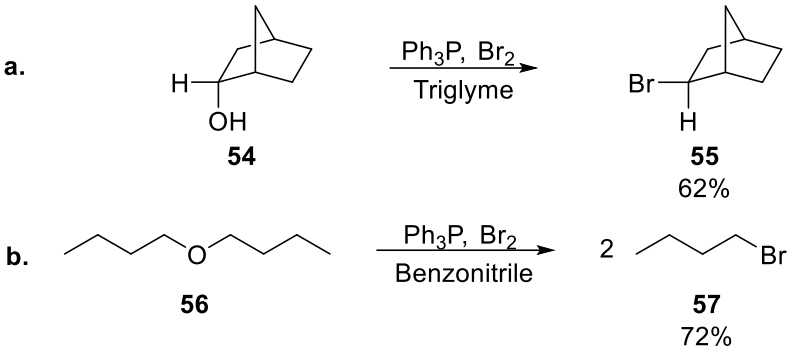
Diiodotriphenylphosphorane (Ph_3PI_2) is generally prepared by the reaction of iodine with triphenylphosphine. Usually Ph_3PI_2 is synthesized *in situ* and used in the conversion of primary and secondary alcohols into alkyl iodides (Scheme 1.13. a),[48] β-diketones into β-iodo α,β-unsaturated ketones (Scheme 1.13. b),[49] vicinal diols into alkenes,[50] and to synthesize iodohydrins from epoxides (Scheme 1.13. c).[51] In 2009, Sardarian and others reported its use in the one pot synthesis of carboxylic acid esters (Scheme 1.13. d).[52]



Scheme 1.13: Reactions of diiodotriphenylphosphorane

1.2.2.2 Dibromotriphenylphosphorane (Ph_3PBr_2)

Dibromotriphenylphosphorane (Ph_3PBr_2) is mainly prepared by the reaction between bromine and triphenylphosphine.[53,54] In 1965, Weinberg and others reported its use for converting *endo* norbornanol to *exo* norbornyl bromide (Scheme 1.14. a).[55] It is useful in the cleavage of dialkyl ethers to give the corresponding alkyl bromides (Scheme 1.14. b),[56] as well as the formation of aromatic compounds from endoxides.[57] Finally, it also converts alcohols to alkyl bromides,[58] and β-diketones into β-bromo enones.[49]



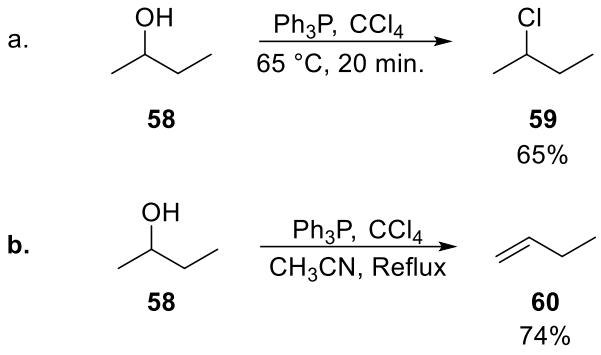
Scheme 1.14: Reactions of dibromotriphenylphosphorane

1.2.2.3 Dichlorotriphenylphosphorane (Ph_3PCl_2)

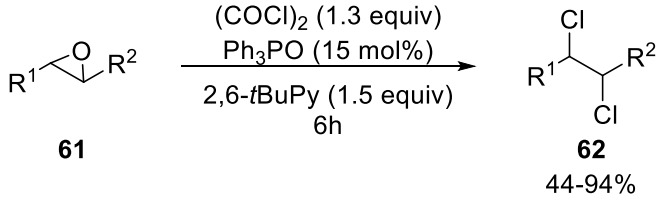
Dichlorotriphenylphosphorane (Ph_3PCl_2) is a very useful chlorinating agent. It can be synthesized by the reaction between triphenylphosphine with other chlorinating reagents such as chlorine gas,[58] hexachloroacetone,[59] phosphorus pentachloride,[60] carbon tetrachloride,[36] *etc*. Since all these reactions involve toxic reagents, scientists have investigated alternative reagents for the synthesis of Ph_3PCl_2. Denton *et al.* reported the chlorination of alcohols using oxalyl chloride and catalytic amount of triphenylphosphine oxide.[61] The downside of this reaction is the formation of the waste products carbon dioxide and carbon monoxide. Recently Murphy and co-workers[21] disclosed a dependable method to synthesize Ph_3PCl_2 in which they used $PhICl_2$, a less toxic surrogate for chlorine, with triphenylphosphine.

Several studies had been conducted to establish the structure of Ph_3PCl_2 in different solvents. In 1967, ^{31}P NMR data of Ph_3PCl_2 in acetonitrile (CH_3CN) and nitrobenzene prompted Wiley and Stine to propose that the compound completely ionized in CH_3CN (**41**) while the pentavalent form (**43**) predominated in nitrobenzene.[62] This finding was further supported by Harris and Ali by conductometric experiments.[63] Denny *et al.* reported that the chemical shifts were affected by the amount of chlorinating agent added. They found that in CH_3CN, when one or more moles of chlorine was added, the major absorption shifted to negative values and it reached -65 ppm when a large excess of chlorine was added.[64] In 2006, Zhao and co-workers investigated the products from the reaction of Ph_3P with C_2Cl_6 in various polar and nonpolar solvents and the process was traced by ^{31}P NMR.[65] The chemical shifts were different depending on the different solvents, thus pointing to the existence of the ionic or covalent forms of Ph_3PCl_2. A similar work has been conducted by Murphy *et al*. using Ph_3PCl_2, synthesized from Ph_3P and $PhICl_2$ in different solvents and the results are in agreement with the existence of both forms.[21]

Dichlorotriphenylphosphorane is a useful reagent for the conversion of alcohols to the corresponding chlorides.[58] Appel proposed its use as a chlorinating as well as dehydrating agent.[36] When the reaction between alcohols and triphenylphosphine was carried out using CCl_4 as the solvent , the resulting product was the corresponding alkyl chloride, but if the reaction of secondary alcohols were carried out in CH_3CN or dichloromethane (DCM), dehydration took place to form olefins (Scheme 1.15).[66] Ph_3PCl_2 is also useful for chlorinating carboxylic acids, epoxides, aldehydes and as a dehydration agent for amides, ureas and aldoximes.[67] Denton *et al.* reported the dichlorination of epoxides via the *in situ* formation of chlorophosphonium salt from oxalyl chloride and a catalytic amount of triphenylphosphine oxide (Scheme 1.16)[68]



Scheme 1.15: Reactions of dichlorotriphenylphosphorane



Scheme 1.16: Dichlorination of epoxides

1.2.2.4 Difluorotriphenylphosphorane (Ph_3PF_2)

Apart from other dihalophosphoranes, Ph_3PF_2 exists only in its covalent form, having a trigonal bipyramidal geometry with the halogen atoms occupying the axial positions. The three phenyl rings in the equatorial position secured a propeller like arrangement (Figure 1.7).[69]

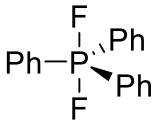
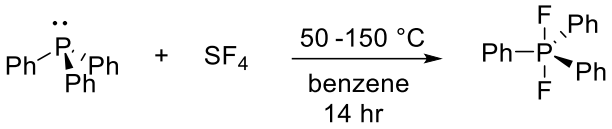


Figure 1.7: Structure of difluorotriphenylphosphorane

Several methods were reported for the synthesis of Ph_3PF_2. In 1960, Smith reported the preparation of Ph_3PF_2 from triphenylphosphine using sulfur tetrafluoride (SF_4) as an oxidative fluorinating agent. The reaction took 14 hours for completion with temperature ranging from 50

to 150 °C, in an overall yield of 69% (Scheme 1.17).[70] Smith also reported that, under these conditions, triphenylphosphine oxide can be used instead of Ph_3P to provide Ph_3PF_2 in 67% yield.



Scheme 1.17: Smith's synthesis of difluorotriphenylphosphorane

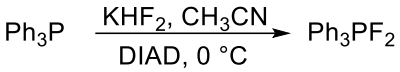
In 1965, Firth and colleagues prepared Ph_3PF_2 from tetrafluorohydrazine and triphenylphosphine with shorter reaction times than Smith's method; however, the yield was only 45% (Equation 1).[71] The major drawback of this method was the use of the highly hazardous reagent tetrafluorohydrazine.

$$2\ Ph_3P + N_2F_4 \longrightarrow 2\ Ph_3PF_2 + N_2 \qquad (1)$$

The reaction between triphenylphosphine and mercuric fluoride was reported in 1992 by Doxsee and colleagues, where Ph_3PF_2 was obtained in 71% yield with mercury as the byproduct. A downside of this reaction was the formation of toxic mercury and also the reaction took 42 hours for completion (Equation 2).[72]

$$Ph_3P + HgF_2 \xrightarrow[42\ hr]{benzene} Ph_3PF_2 + Hg \qquad (2)$$

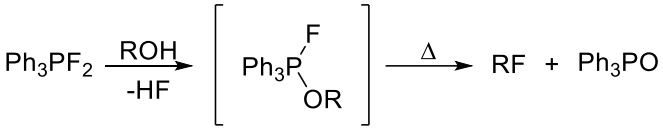
A facile method for the synthesis of Ph_3PF_2 was reported by Harvey and Jenkins using a Mitsunobu-type reaction. It was accomplished by the reaction between potassium hydrogen fluoride and triphenylphosphine in presence of diisopropyl azodicarboxylate. The reaction is carried out at 0 °C and the yield was 67% of the desired Ph_3PF_2 (Scheme 1.18).[73]



Scheme 1.18: Synthesis of Ph_3PF_2 by Mitsunobu reaction

In addition to these methods, other preparations for the synthesis of Ph_3PF_2 have been reported that use toxic reagents such as carbonyl difluoride,[74] trifluoroamine oxide,[75] or hexafluoroacetone.[76]

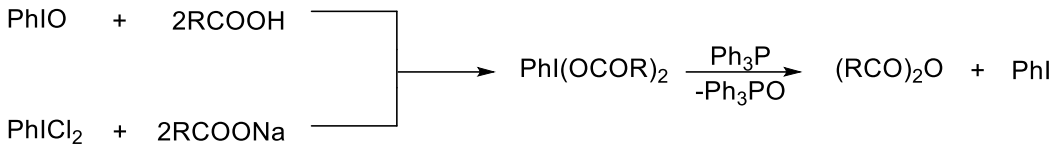
In 1968, Kobayashi and Akashi reported the only reaction in which Ph_3PF_2 was used in the synthesis of alkyl fluorides from alcohols (Scheme 1.19).[77] They prepared alkyl fluorides by heating different alcohols with Ph_3PF_2 at 150-170 °C for 5-7 hours in acetonitrile. The yield of the alkyl fluoride varied from 30-78%.



Scheme 1.19: Synthesis of alkyl fluoride using Ph_3PF_2 by Kobayashi and colleagues

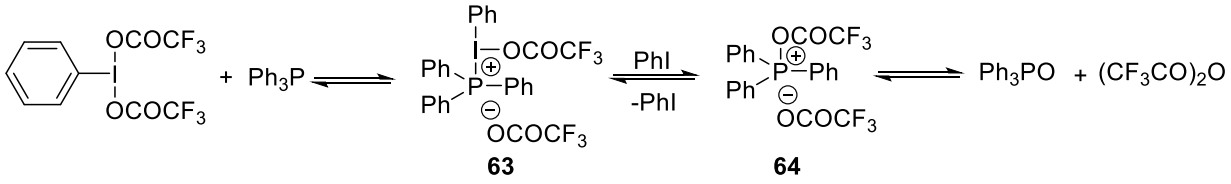
1.3 Reactions of Ph_3P and Hypervalent Iodine Reagents

Hypervalent iodine reagents such as iodosylbenzene[78] and bis(*m*-chloroperbenzoyloxy) iodobenzene[79] are known to oxidize phosphines to phosphine oxides.[80] In 1987, Varvoglis and Gallos reported that bis(acyloxyiodo)benzenes can react with triphenylphosphine at room temperature to yield carboxylic anhydrides and triphenylphosphine oxide.[80] They also reported a one-pot conversion of acids and their salts to anhydrides via the formation of bis(acyloxyiodo)benzenes as depicted in Scheme 1.20.



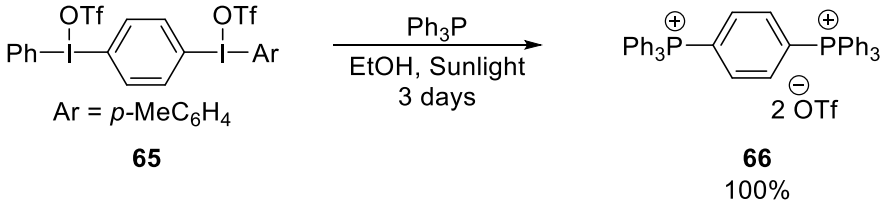
Scheme 1.20: Reaction of bis(acyloxyiodo)benzenes with triphenylphosphine

In the proposed mechanism for the formation of trifluoroacetic anhydride, they suggested a phosphonium salt (**63**) is formed by the attack of phosphorus on iodine. Compound **63** is then transformed into an acyloxyphosphonium salt (**64**) and finally to the anhydride through the attack of the trifluoroacetate ion onto **64** (Scheme 1.21).



Scheme 1.21: Mechanism for the formation of trifluoroacetic anhydride

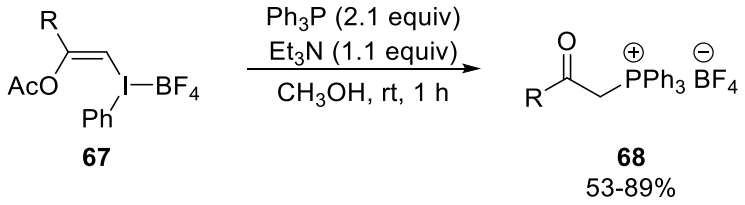
The reaction between triphenylphosphine and (*p*-phenylene)bis(aryliodonium) ditriflate was reported by Kitamura *et al*. (Scheme 1.22).[81] This reaction led to the formation of (*p*-phenylene)bis(triphenylphosphonium) ditriflate.



Scheme 1.22: Synthesis of (*p*-phenylene)bis(triphenylphosphonium) ditriflate

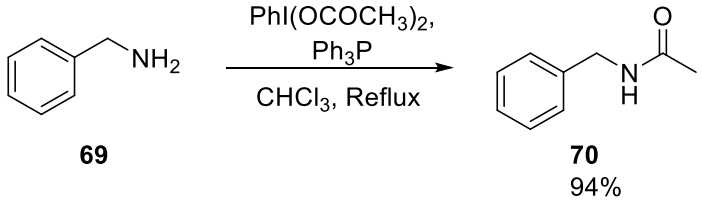
In 2002, Ochiai *et al.* developed an efficient method for *in situ* generation of α-λ^3-iodanyl ketones from β-acetoxyvinyl iodanes (**67**) in the presence of trimethylamine and methanol via an

ester exchange reaction of the β-acetoxy group. When this reaction was conducted in the presence of triphenylphosphine at room temperature generated β-ketophosphonium salts (**68**) (Scheme 1.23) which were shown to be viable Wittig reagents with aldehydes.[82]



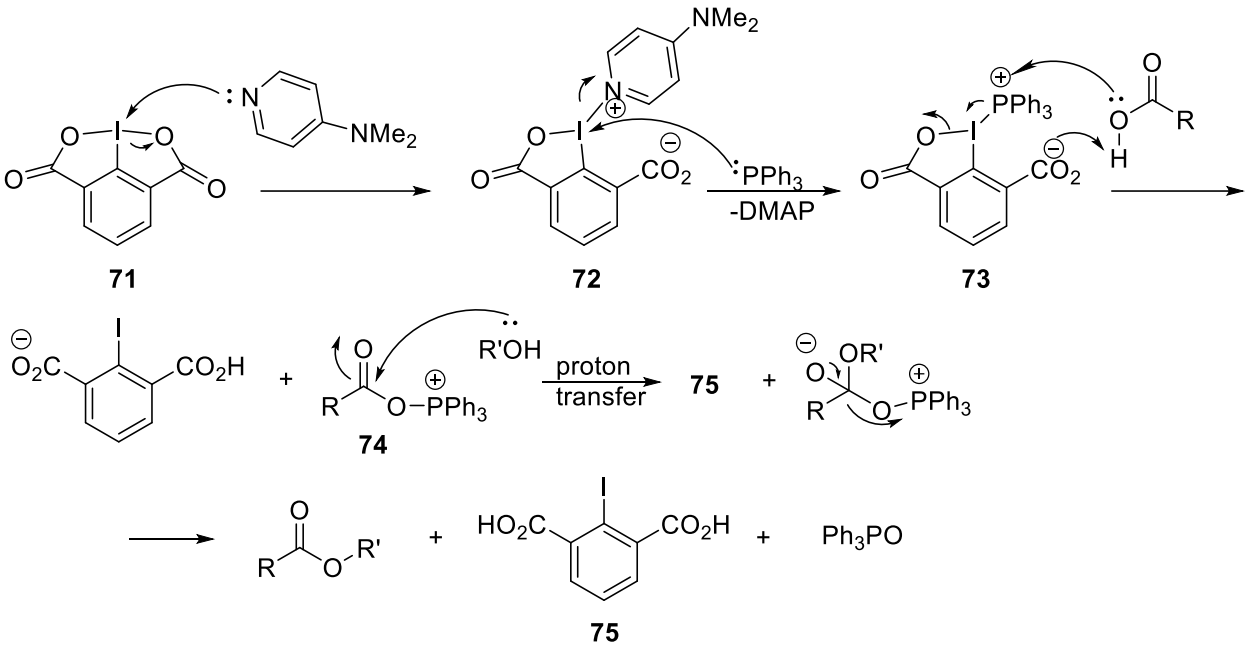
Scheme 1.23: Synthesis of β-ketophosphonium salts

Makowiec and Rachon described the reaction between bis(acyloxyiodo)benzenes with triphenylphosphine in the presence of methanol. They also used this system for the synthesis of various amides by using benzylamine in place of methanol (Scheme 1.24).[83]



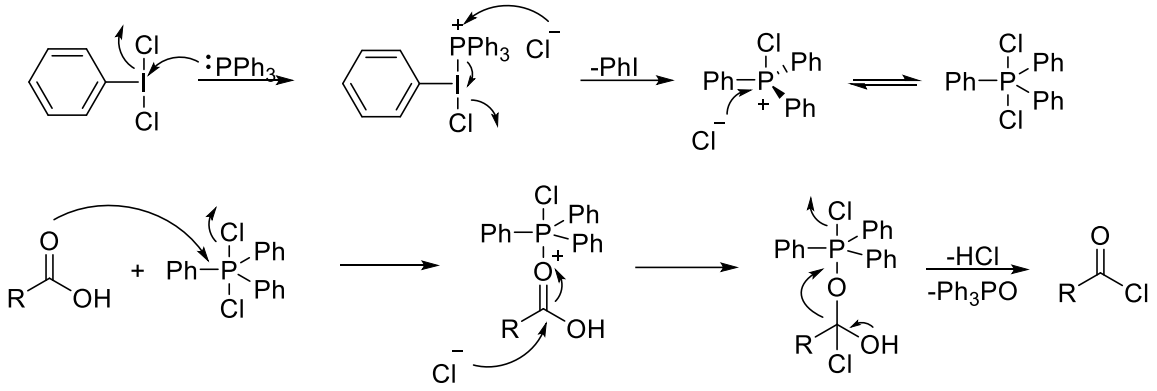
Scheme 1.24: Syntheses of amides

In 2012, Zhang and co-workers effectively used iodosodilactone/4-dimethylaminopyridine (DMAP)/Ph_3P for the synthesis of esters and amides.[84] In this reaction, the key step is the formation of acyloxyphosphonium ion (**74**). In the initial step, iodosodilactone was activated by DMAP resulted in the formation of zwitterion **72** which then underwent ligand exchange with Ph_3P to give the more reactive zwitterion **73.** The key intermediate, **74**, formed when carboxylic acid reacts with **73**. And in the final step, the activated species **74** was attacked by an alcohol to give the ester product (Scheme 1.25).



Scheme 1.25: Mechanism of iodosodilactone mediated esterifications proposed by Zhang *et al.*

Recently the Murphy group was successful in synthesizing acyl chlorides by activating triphenylphosphine with (dichloroiodo)benzene (Scheme 1.26).[21] Both the ligands on (dichloroiodo)benzene were transferred onto Ph_3P resulting in the formation of Ph_3PCl_2. The *in situ* formed Ph_3PCl_2 then reacts with carboxylic acids as described in the literature[85] to yield acyl chlorides (Scheme 1.26), which eventually led to the formation of esters and amides by reacting with suitable nucleophiles. This reaction has been extended to the deoxygenative chlorination of alcohols.



Scheme 1.26: Mechanism for the synthesis of Ph_3PCl_2 from Ph_3P and $PhICl_2$ and subsequent reaction with carboxylic acids

These reactions show that Ph_3P, in combination with hypervalent iodine reagents, can be used to functionalize alcohols.

1.4 Functionalization of Alcohols

Alcohols constitute an important class of compounds in organic chemistry. Menthol, cholesterol, and retinol are examples of some naturally occurring alcohols (Figure 1.8).

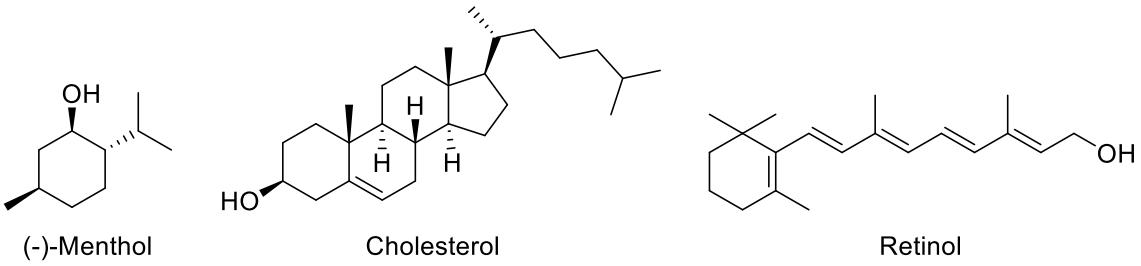


Figure 1.8: Examples of naturally occurring alcohols

Applications of alcohols vary from using as fuels, antiseptics, artificial flavours, beverages *etc*. They can be easily converted to various other functional groups as shown in Figure 1.9.

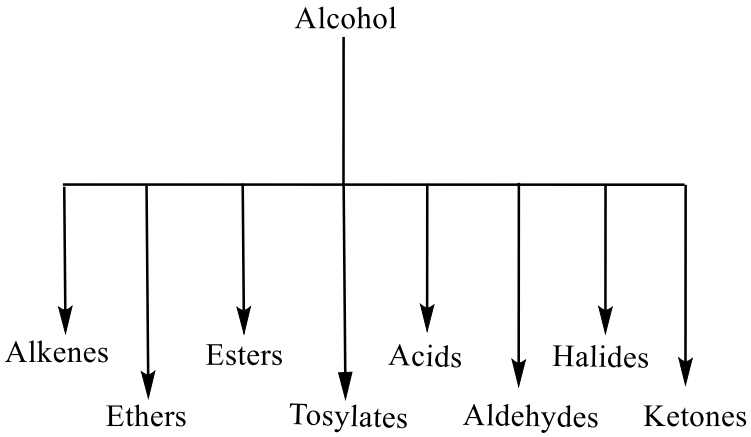
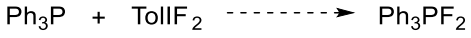


Figure 1.9: Functionalization of alcohols

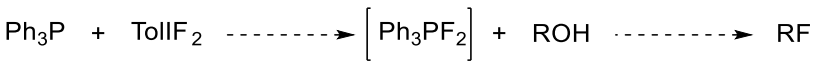
1.5 Proposal

Earlier protocols to producing Ph_3PF_2 employed toxic reagents,[74-76] generated hazardous by products,[72] and involved long reaction time.[70,72] Previous work by Murphy *et al.*, has shown that synthesis of Ph_3PCl_2 was achieved by treating triphenylphosphine with $PhICl_2$.[21] The success of this work prompted us to believe that the corresponding fluorination reaction is attainable using $TolIF_2$ (Scheme 1.27).



Scheme 1.27: Proposal for the synthesis of Ph_3PF_2

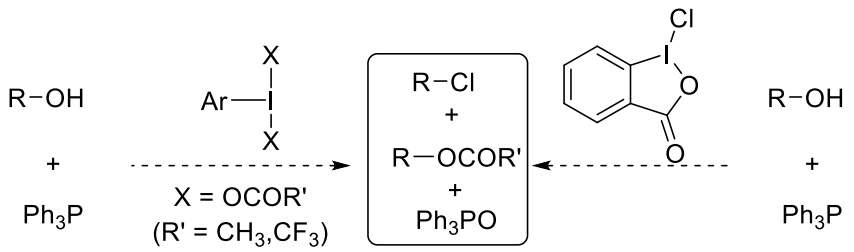
Depending on the success of this reaction, we would like to expand it to the synthesis of alkyl fluorides via the *in situ* formation of Ph_3PF_2 (Scheme 1.28).



Scheme 1.28: Proposal for the synthesis of alkyl fluorides

Since there are limited examples for the reaction between Ph_3P/hypervalent iodine reagent system with alcohols, we decided to expand the scope of this reaction. Hypervalent iodine reagents

such as PIFA, PIDA, and cyclic chloro(benzoyloxy)iodane were chosen for this study and the *in situ* formed phosphoranes were used to functionalize 1°, 2° and 3° alcohols (Scheme 1.29).



Scheme 1.29: Proposal for the functionalization of alcohols

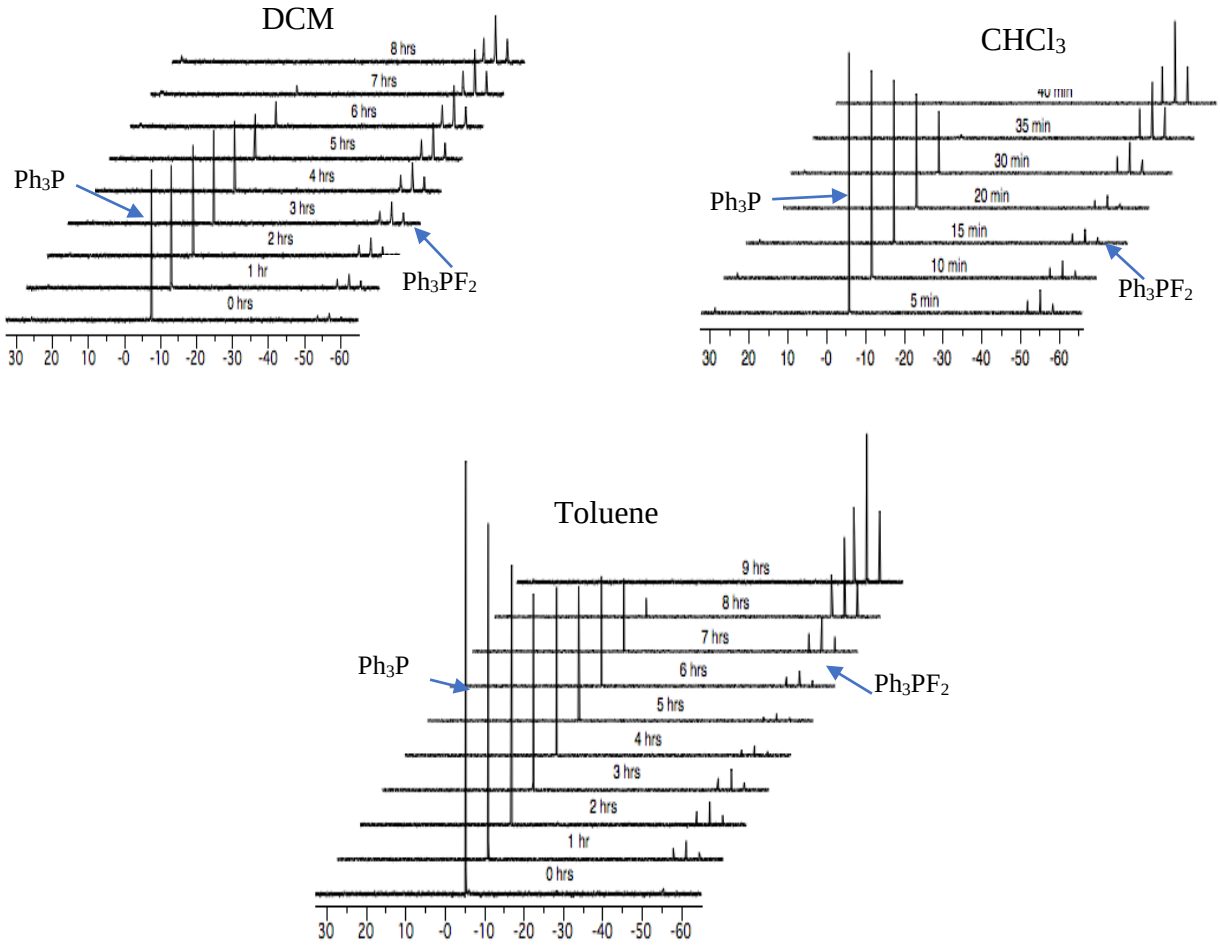
1.6 Synthesis of Difluorotriphenylphosphorane and Alkyl Fluorides

Preliminary studies for the synthesis of Ph_3PF_2 were first conducted in DCM in an NMR tube by mixing triphenylphosphine and a slight excess of *p*-(difluoroiodo)toluene at room temperature. The ^{31}P NMR spectrum showed the appearance of a triplet at -55 ppm with a coupling constant of 660 Hz, which is in close agreement with the values reported for Ph_3PF_2.[73] Monitoring the reaction using ^{31}P NMR spectroscopy at regular intervals showed the gradual disappearance of the triphenylphosphine peak at -5 ppm (Figure 1.10).

Previous work in the Murphy group proved that the nature of the solvent can influence Ph_3PCl_2 to exist in either an ionic tetra coordinated or a penta-coordinated structure.[21] Even though there has been no reported evidence for the ionic form of Ph_3PF_2, the reaction was conducted in various solvents to search for its existence. Other solvents that were tested include chloroform ($CHCl_3$), tetrahydrofuran (THF), toluene, diethyl ether (Et_2O) and dimethylformamide (DMF), and it was found that the choice of solvent does not affect the structure of Ph_3PF_2.

To study the evolution of Ph_3PF_2, ^{31}P NMR spectra were taken over a period of several hours, looking at the disappearance of Ph_3P (-5 ppm) and appearance of Ph_3PF_2 (around -55ppm). These experiments were conducted by dissolving 1 equiv of Ph_3P in different solvents in an NMR

tube and then adding 1.05 equivalent of $TolIF_2$ (Figure 1.10 and Table 1.2). The reaction time varied for different solvents. For example, the reaction was complete in 30 minutes in $CHCl_3$ (entry 1, Table 1.2) and for other solvents it varied from 8 to more than 48 hours. It was observed that Ph_3P was not completely converted to Ph_3PF_2 in the polar aprotic solvent DMF even after 48 hours (entry 6). The reaction conducted in Et_2O took almost 29 hours for completion (entry 2), which may be attributed to reagent's low solubility in diethyl ether. The reaction time associated with DCM varied from 3 to 7 hours. The reaction was fast in $CHCl_3$ compared to other solvents. When the reagent ($TolIF_2$) loading was increased, the conversion of Ph_3P to Ph_3PF_2 was faster (entry 7-9 in Table 1.2). It was believed that increasing the concentration of available iodane in solution would make the reaction occur faster.



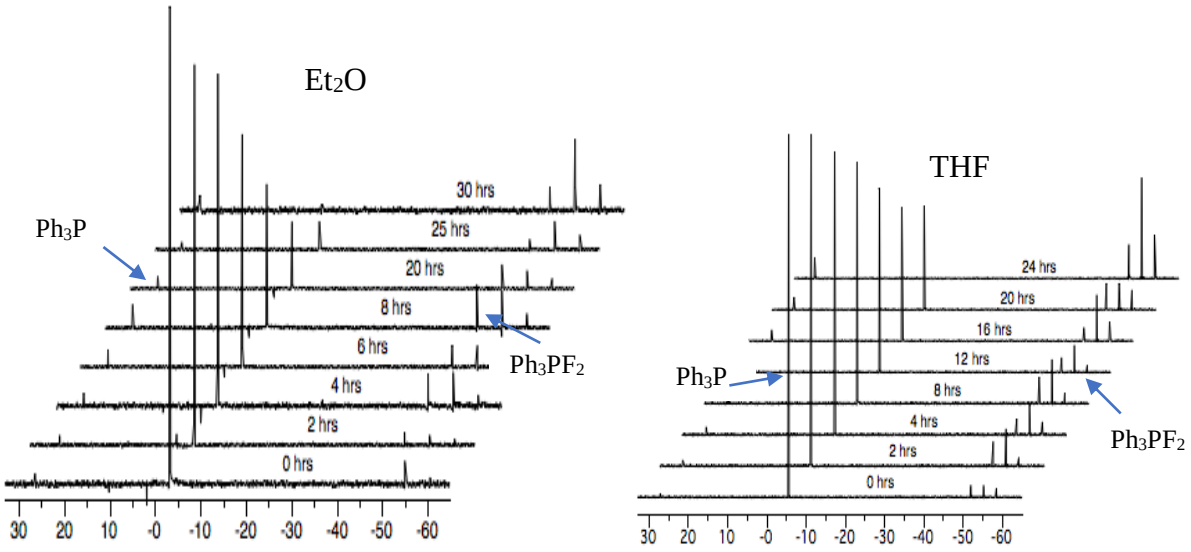
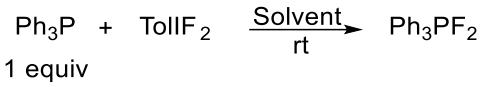


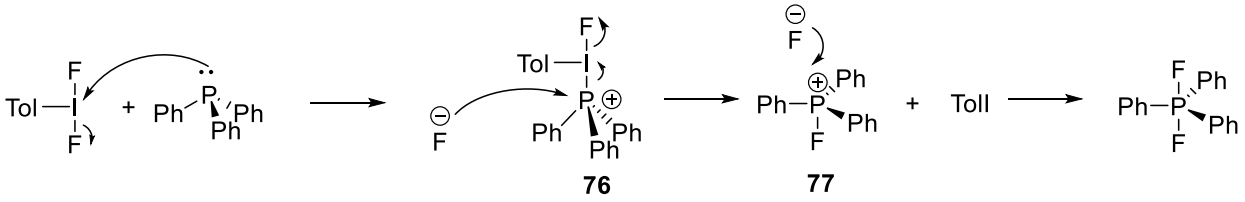
Figure 1.10: The stack ^{31}P NMR spectra of the mixture of Ph_3P and $TolIF_2$ in different solvents.



Entry	Solvent	Equivalents of $TolIF_2$	Time
1	Chloroform	1.05	30 minutes
2	Dichloromethane	1.05	3-7 hours
3	Toluene	1.05	8 hours
4	Tetrahydrofuran	1.05	20 hours
5	Diethyl ether	1.05	29 hours
6	Dimethylformamide	1.05	> 48 hours
7	Dichloromethane	1.2	< 10 minutes
8	Chloroform	1.1	< 10 minutes
9	Toluene	2	< 1 hour

Table 1.2: Solvent effect on reaction time for the reaction between Ph_3P and $TolIF_2$

The reaction was proposed to proceed through the mechanism shown in Scheme 1.30. The nucleophilic attack of Ph_3P at the electrophilic iodine of $TolIF_2$ resulted in the formation of a phosphonium ion intermediate (**76**), replacing one of the fluorine ligands. The fluoride ion then attacked the phosphonium ion leading to the formation of TolI and Ph_3PF_2.

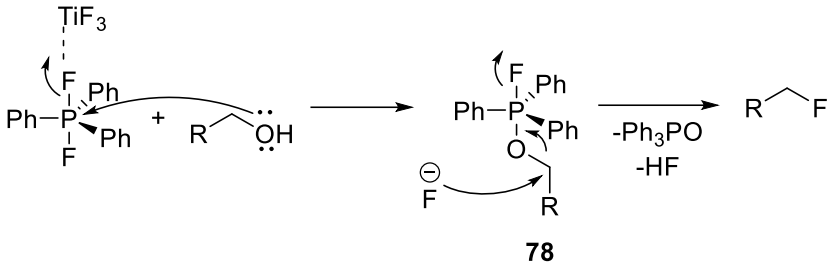


Scheme 1.30: Plausible mechanism for the synthesis of difluorotriphenylphosphorane

Once Ph_3PF_2 was obtained, the next step was to conduct the deoxygenative fluorination of alcohols, as reported earlier.[77] The earlier synthesis of alkyl fluoride achieved by Kobayashi *et al.* involved heating the alcohol with 2 equiv of Ph_3PF_2 at 150-170 °C for 5-7 hours in acetonitrile. When the reaction of Ph_3PF_2 with benzyl alcohol was conducted in acetonitrile at refluxing temperature no formation of the corresponding fluoride was observed. Wiley and Stine [62] proposed that in the presence of a Lewis acid, Ph_3PCl_2 was completely converted to the ionic form. We decided to add a Lewis acid to the reaction to check whether this was possible with Ph_3PF_2. When the experiment was conducted in a sealed vial at 110 °C in toluene using benzyl alcohol, Ph_3PF_2 and 10 mol% $BF_3{\cdot}OEt_2$, formation of a trace amount of benzyl fluoride was observed (^{19}F NMR, δ = -206.88 ppm),[86] but due to its volatility no benzyl fluoride was recovered. In the presence of Lewis acid, the phosphorus may become more electrophilic and thus facilitate the nucleophilic attack by the alcohol.

The formation of alkyl fluoride from Ph_3PF_2 was believed to proceed through the following mechanism (Scheme 1.31). In the presence of alcohol, a phosphonium intermediate (**78**) was

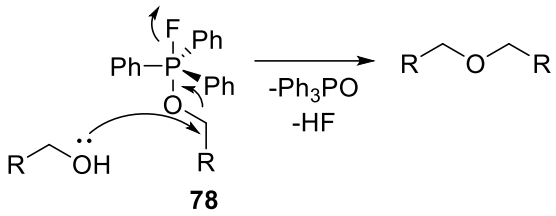
formed by eliminating one of the fluoride ligand from Ph_3PF_2. The attack of the fluoride ion on **78** led to the formation of alkyl fluoride and triphenylphosphine oxide. The driving force in this reaction was the formation of triphenylphosphine oxide.



Scheme 1.31: Plausible mechanism for the synthesis of alkyl fluoride

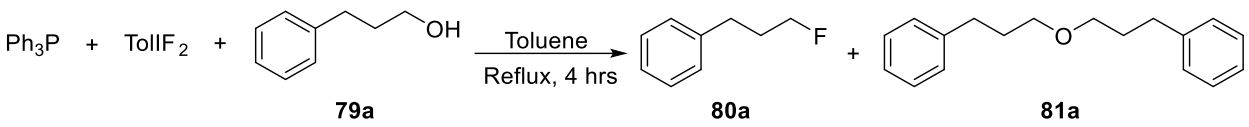
The substrate was changed to 4-methoxybenzyl alcohol, 2-naphthalenemethanol and finally to 3-phenylpropanol in the hope that the increase in molecular weight would provide a stable alkyl fluoride to isolate. Though the formation of the corresponding fluorides were observed in ^{19}F NMR, purification by column chromatography did not give any product.

It was observed that instead of isolating Ph_3PF_2, the reaction was also feasible when it was made *in situ* from Ph_3P and $TolIF_2$. So further reactions were carried out as a one-pot synthesis in which alcohol is treated with Ph_3P and $TolIF_2$ with the assumption that Ph_3P is quantitatively converted to Ph_3PF_2. Analysis of the ^1H NMR spectrum of the crude reaction mixture of 3-phenylpropanol with Ph_3P and $TolIF_2$ indicated the formation of corresponding alkyl fluoride (**80a**) along with ether product (**81a**).[87] It was proposed that the alcohol outcompeted fluoride as the nucleophile leading to the formation of ether (Scheme 1.32).



Scheme 1.32: Plausible mechanism for the formation of ether

Purification by column chromatography yielded the fluoride product along with ether. Interestingly, when the product mixture was kept under high vacuum, only the ether remained. Different additives were used in the reaction mixture to find out whether they improve the yield. Though Ph_3PF_2 was completely consumed, the slight excess of $Ph_3P/TolIF_2$ was not sufficient for the complete consumption of alcohol **79a**. The conversion of 3-phenylpropanol to **80a** and **81a** was determined using ^1H NMR by integrating the methylene protons attached to the -OH group, and is recorded in Table 1.3. When GaF_3 and AlF_3 were used the ether product predominated (entry 2 &3, Table 1.3). With TiF_3, 27% of the alcohol was converted to alkyl fluoride and 50% to ether product (entry 1). In all these reactions, the rest of the mass was accounted by the unreacted alcohol. The reaction conducted by increasing the reagent loading and also by adding the substrate dropwise over 1 hour also did not make significant change (entry 8). It was believed that the dropwise addition will reduce the concentration of the alcohol in the reaction and thus by reduce the nucleophilic attack of the alcohol on the intermediate **78.**



79a 80a 81a

Entry	Ph_3P	$TolIF_2$	Lewis acid (mol%)	% Conversion	
				80a	**81a**
1	1.06	1.13	TiF_3 (10)	27	50
2	1.06	1.13	GaF_3 (10)	12	36
3	1.06	1.13	AlF_3 (10)	8	45
4	1.06	1.17	FeF_3 (10)	0	ND[a]
5	1.06	1.13	BiF_3 (10)	0	ND
6	1.06	1.17	InF_3 (10)	0	ND
7	1.06	1.10	$Et_3N.3HF$ (15)	Trace	24
8	2.5	2.6	TiF_3 (10)	33	50

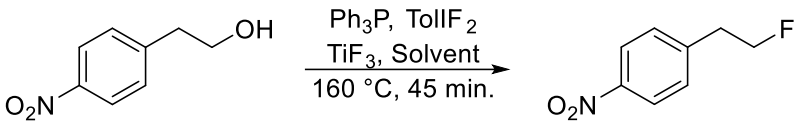
[a]Not Determined

Table 1.3: Screening of additives

Since the purification only resulted in the isolation of the ether product, an internal standard was used to determine the yield of the alkyl fluoride product. The compound 4-fluorotoluene was initially chosen as an internal standard by analyzing the ^{19}F NMR spectrum; however, this did not give accurate results due to difficulty associated with base line corrections. The next option was the use of hexamethyldisiloxane (HMDSO) to analyze the ^{1}H NMR spectrum, but that also failed. It was believed that the by-product of the reaction, HF, reacts with HMDSO which leads to its decomposition. Duroquinone was another option, but the peaks could not be resolved from that of the alkyl protons. Finally, cyclohexene became the optimal internal standard. The ^{1}H NMR yield

was calculated using the alkane protons for 1-fluoro-3-phenylpropane (**80a**) and the alkene protons for 1-fluoroundecane (**80h**).

The substrate was changed to 4-nitrophenethyl alcohol (**79b**), which was synthesized according to the literature procedure from 4-nitrophenylacetic acid.[88] An increase in the reaction temperature to 160 °C, produced better result. The reaction in toluene using 3 equivalents of $Ph_3P/TolIF_2$ led to the complete consumption of starting material and gave 55% of 1-(2-fluoroethyl)-4-nitrobenzene (entry 1, Table 1.4). Changing the solvent to chlorobenzene (PhCl) resulted in better result (entry 2). This may be attributed to the slight polarity difference between the two solvents. Compared to toluene, the more polar PhCl promotes the nucleophilic attack of fluoride on intermediate **78,** rather than the alcohol. Increasing the loading of TiF_3 did not make a significant difference (entry 3), while the yield dropped when TiF_3 loading was decreased to 5 mol% (entry 4). Any further attempts to decrease the amount of $Ph_3P/TolIF_2$ led to a decrease in yield (entry 5-7)



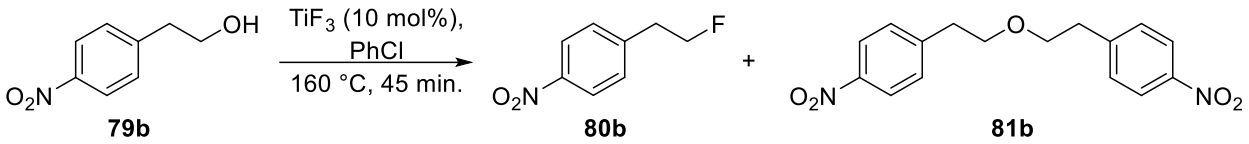
79b **80b**

Entry	Ph_3P (equiv)	$TolIF_2$ (equiv)	TiF_3 (mol%)	Solvent	% Yield[a] [% yield][b]
1	3	3.3	10	Toluene	55
2	2	2.1	10	PhCl	75
3	2	2.1	25	PhCl	[73]
4	2	2.1	5	PhCl	[52]
5	1.2	1.3	10	PhCl	[48]
6	1.4	1.5	10	PhCl	[53]
7	1.5	1.6	10	PhCl	[69]

[a]Isolated yield. [b]NMR yield

Table 1.4: Screening of reaction conditions for the synthesis of 1-(2-fluoroethyl)-4-nitrobenzene

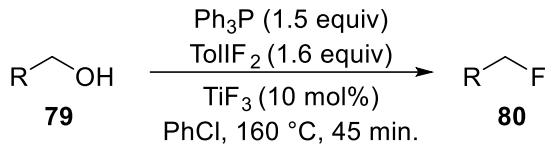
When the reaction was carried out using 1.5 equiv of reagent ($Ph_3P/TolIF_2$), the resulting Ph_3PF_2 was completely consumed within 45 minutes with less than 10% of **75b** remaining unreacted. Purification of the product by column chromatography produced 63% of 1-(2-fluoroethyl)-4-nitrobenzene and 12% of the ether product (entry 1, Table 1.5). A reaction was conducted under similar conditions using freshly prepared Ph_3PF_2. The slight increase in the yield observed (entry 2) may be due to more consumption of the alcohol when Ph_3PF_2 was used. Since the one pot synthesis of alkyl fluoride (entry 1) does not require the isolation of Ph_3PF_2 and gave almost the same result as entry 2, this method is more viable for the synthesis of alkyl fluorides.

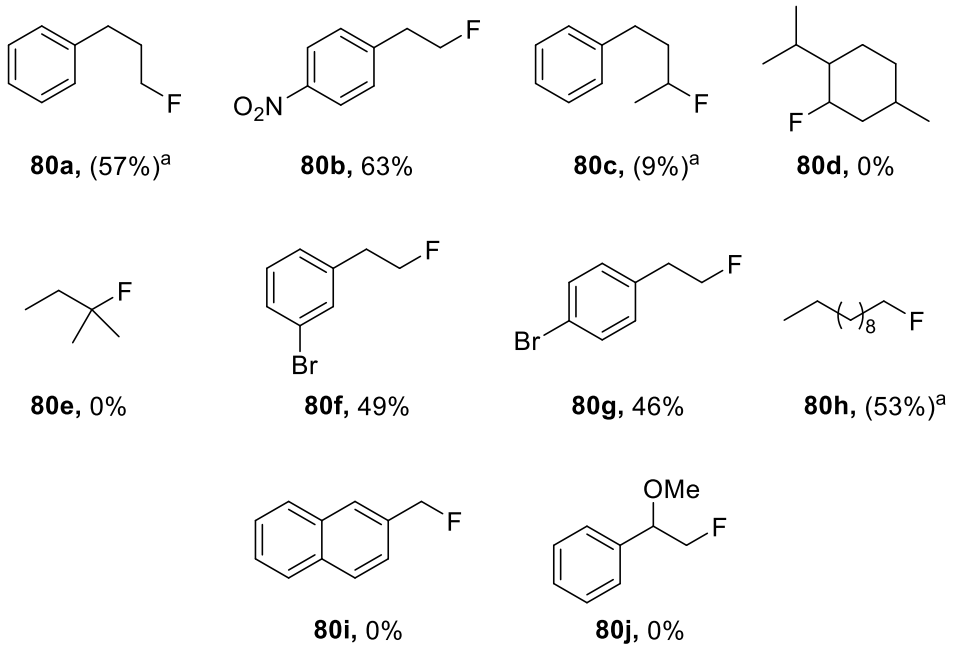


Entry	Reagent loading	% Yield	
		80b	**81b**
1	Ph_3P (1.5 equiv) $TolIF_2$ (1.6 equiv)	63	12
2	Ph_3PF_2 (1.5 equiv)	66	15

Table 1.5: Comparing the yield of 1-(2-fluoroethyl)-4-nitrobenzene

A number of alcohols were subjected to the conditions shown in Scheme 1.33 and found that phenethyl alcohols substituted in the *para* and *meta* positions gave moderate yield (**80b**, **80f**, **80g**). All the primary alcohols underwent deoxygenative fluorination reaction to give moderate yield. Secondary alcohol **79c** gave the alkyl fluoride **80c** only in 9% yield. Fluorination of the sterically congested *t*-amyl alcohol **80e** failed, which may be attributed to the poor rates of S_N2 reactions on tertiary substrates.





80a, (57%)[a] **80b,** 63% **80c,** (9%)[a] **80d,** 0%

80e, 0% **80f,** 49% **80g,** 46% **80h,** (53%)[a]

80i, 0% **80j,** 0%

[a] ^{1}H NMR yield

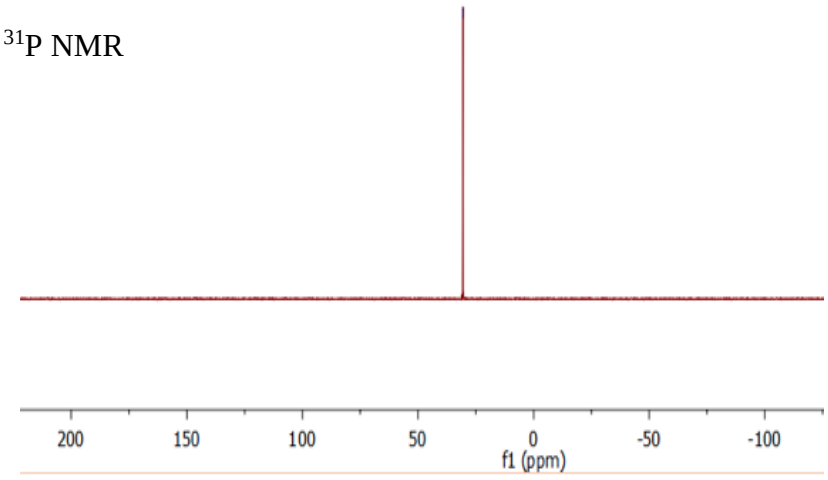
Scheme 1.33: Synthesis of alkyl fluorides

Though the temperature was the same, our methodology has some advantages over the method developed by Kobayashi *et al.*[77]According to Kobayashi's method, Ph_3PF_2 was synthesized from Ph_3P and the toxic SF_4, which took almost 10 hours for completion at a temperature of 150 °C. In our method Ph_3PF_2 was synthesized *in situ* and utilized for the deoxygenative fluorination. Another striking difference was the reaction time; our method required 45 minutes using 1.5 equiv of $Ph_3P/TolIF_2$ where as in, Kobayashi's method the reaction took 8 hours for completion with 2 equiv of Ph_3PF_2. This may be due to the difference in the choice of solvent and also due to the presence of TiF_3. Though there is no evidence for the existence of

Ph_3PF_2 in ionic form, the electrophilicity of phosphorus may be enhanced in the presence of TiF_3, thus increasing the reaction rate.

1.7 Synthesis of Trifluoroacetates

The next goal was to determine whether the synthesis of diacyloxytriphenylphosphoranes were feasible using hypervalent iodine reagents PIFA and PIDA with triphenylphosphine. Varvoglis reported the formation of trifluoroacetic anhydride from PIFA and Ph_3P,[80] and Makowiec and *et al.* investigated the reaction between methanol, Ph_3P and dibenzoyloxyiodobenzene.[83] To the best of our knowledge, the combined use of Ph_3P and PIFA in the functionalization of alcohols have not been reported.[80] In an attempt to gain some insight into the reaction mechanism, triphenylphosphine was treated with a slight excess of PIFA in $CDCl_3$ at room temperature. The ^{31}P NMR spectrum was analyzed to observe the trifluoroacetate ligand transfer from iodine to phosphorus. Triphenylphosphine was consumed within 5 minutes and only a signal for triphenylphosphine oxide was detected (Figure 1.11). Analysis of the ^{19}F NMR spectrum confirmed the presence of trifluoroacetic anhydride at δ -75.23 ppm which was in agreement with spectrum obtained from a pure sample of trifluoroacetic anhydride (δ -75.28 ppm).



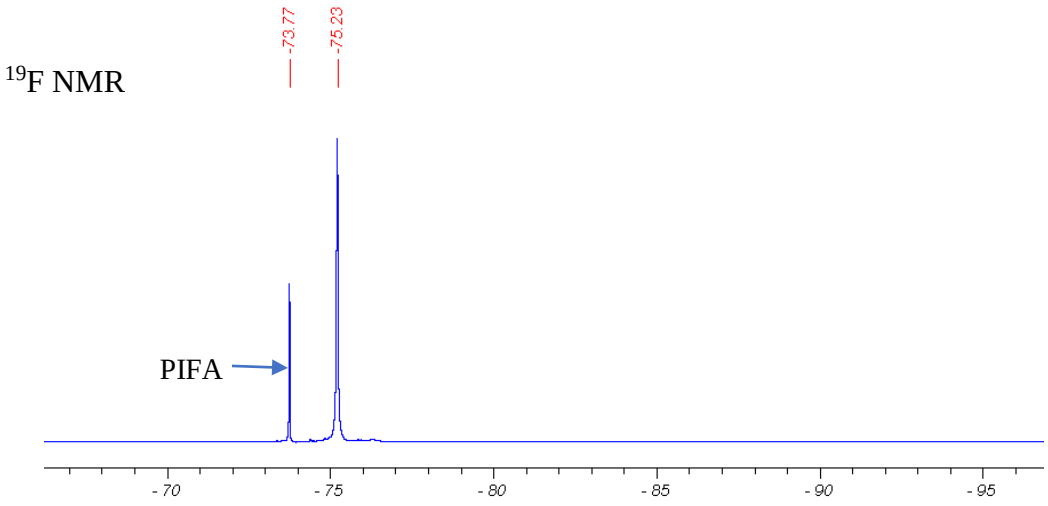
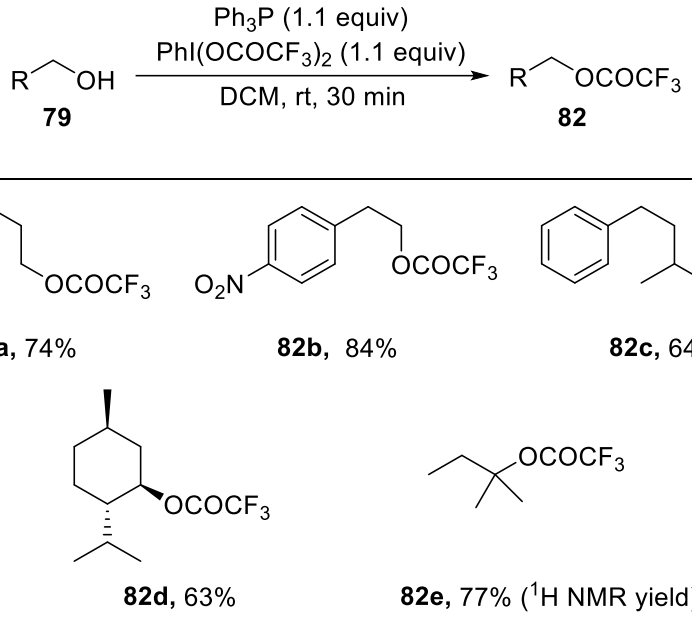


Figure 1.11: ^{31}P and ^{19}F NMR spectra for the attempted synthesis of $Ph_3P(OCOCF_3)_2$

The next step of this project was to analyze how this reaction proceeds in the presence of an alcohol. The model substrate chosen to conduct this experiment was 4-nitrophenethyl alcohol. To a solution of the alcohol in DCM was added Ph_3P and PIFA and the reaction progress was monitored by TLC. Within half an hour, the starting alcohol was completely consumed. The ^1H NMR showed a clean spectrum of the 4-nitrophenethyl 2,2,2-trifluoroacetate (**82b**) and no starting material observed. Purification of the crude reaction mixture by column chromatography led to only isolation of the starting material. The outcome was the same even after the reaction was repeated. This led to the conclusion that the product was being hydrolyzed during column chromatography. To prevent hydrolysis, the silica was treated with 1% triethylamine in hexane, but this only resulted in recovery of 81% of the starting material. An alternative was to make the silica more acidic, by treating it with 0.2% trifluoroacetic acid in hexane, and to our delight, 84% trifluoroacetate product was recovered (**82b**, Scheme 1.34). The next alcohol studied was 3-phenyl-1-propanol, and this produced the 3-phenylpropyl 2,2,2-trifluoroacetate product in 74% yield (**82a**). The substrate scope was then expanded to secondary and tertiary alcohols and the results are summarized in Scheme 1.34. Compared to primary alcohols, the recovered yield for

secondary trifluoroacetates was low. The stereochemistry assigned to **82d** was confirmed by comparison of its ^{1}H NMR spectrum with the chemical shifts reported on the literature.[89] Since the ^{1}H NMR spectrum revealed the complete consumption of starting material without having any unidentified by product, led to the conclusion that the low yield was not due to a reactivity problem, but rather due to decomposition of product while on column. The yield for tertiary trifluoroacetate (**82e)** was calculated by ^{1}H NMR, comparing with the hydrogens on the sp^2 carbon of cyclohexene. Overall the reaction was fairly consistent on primary, secondary and tertiary alcohols and the trifluoroacetate products were recovered in 63-84% yield.



Scheme 1.34: Reaction of PIFA with Ph_3P and alcohols

1.8 Synthesis of Acetates

The next hypervalent iodine chosen to study was PIDA. Though Makoweic and Rachon reported (diacyloxyiodo)benzene/PR_3 system as an acylating agent for methanol, no specific example for PIDA/Ph_3P system has been mentioned.[83] The only reported synthesis of diacetoxytriphenylphosphorane ($Ph_3P(OAc)_2$) relied on *in situ* oxidation of Ph_3P using

$Ph_3P/Br_2/NH_4OAc$ mixed reagent system.[90] So we envisioned that a direct synthesis from PIDA and Ph_3P would offer a significant improvement in ease of reaction. Monitoring the reaction between Ph_3P and PIDA using ^{31}P NMR spectroscopy was conducted at room temperature in $CDCl_3$ with the expectation to observe the reported $Ph_3P(OAc)_2$ peak (δ = 45.0 ppm).[90] Contradictory to PIFA, very little consumption of Ph_3P occurred after five minutes and phosphine remained after 24 hours. When the reaction mixture was heated to reflux, Ph_3P was completely consumed within three hours and analysis of the ^1H NMR spectrum revealed the presence of acetic anhydride (δ 2.19 ppm) as the fate of the acetate ligands (Figure 1.12).

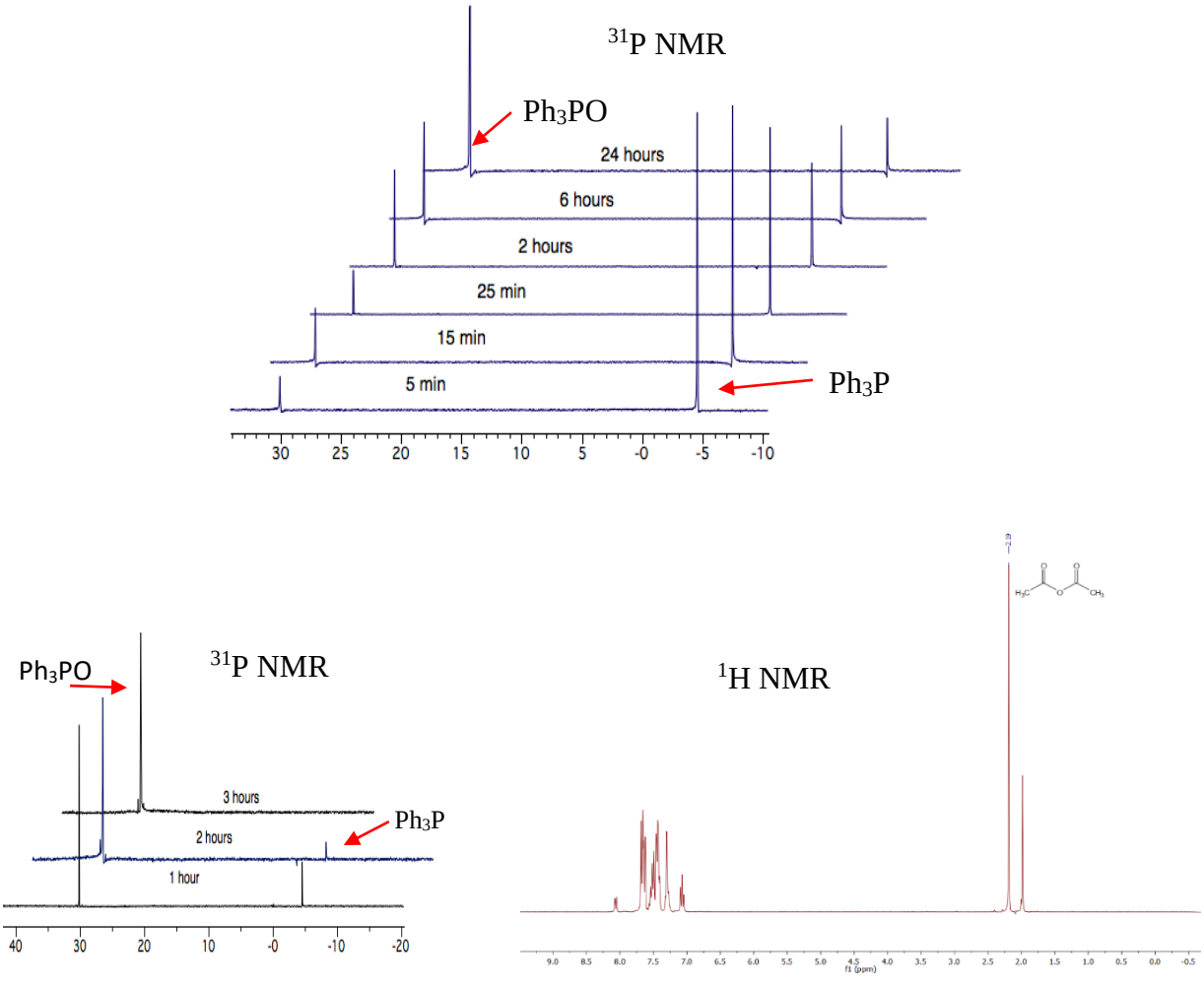
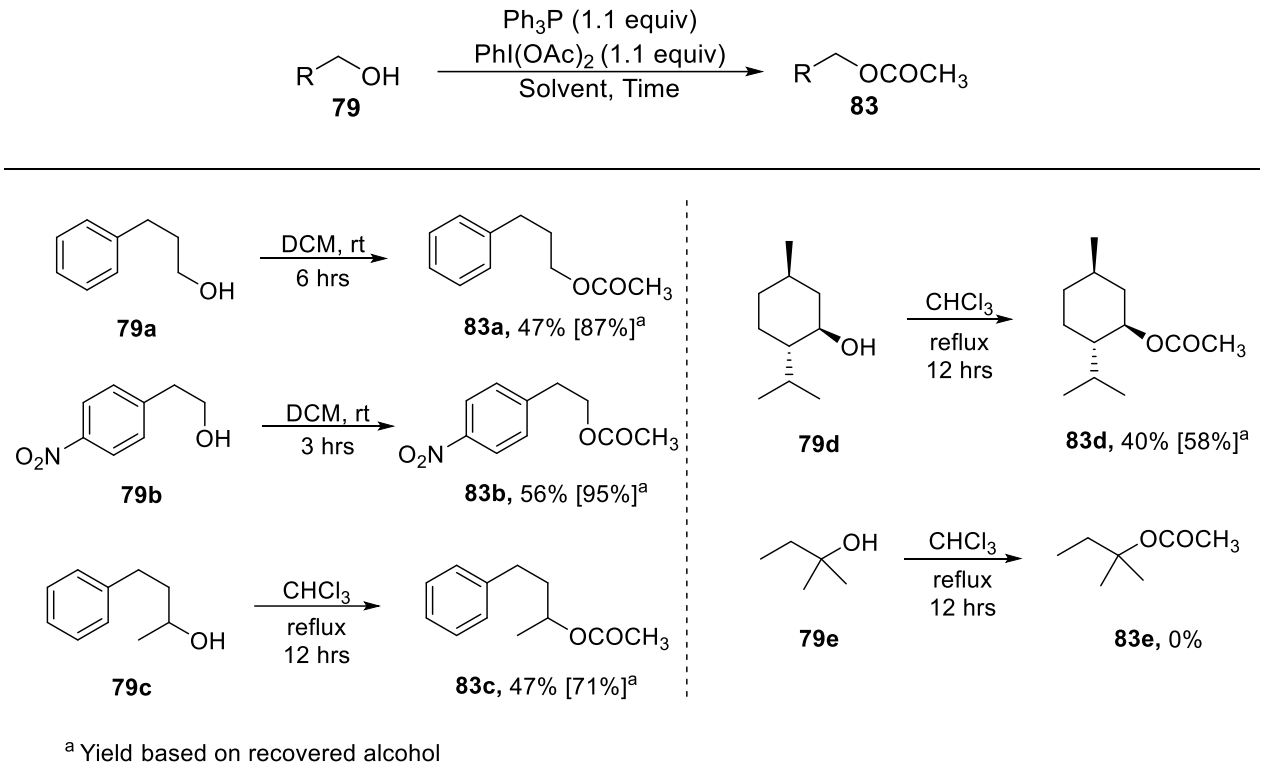


Figure 1.12: Attempted synthesis of $Ph_3P(OAc)_2$

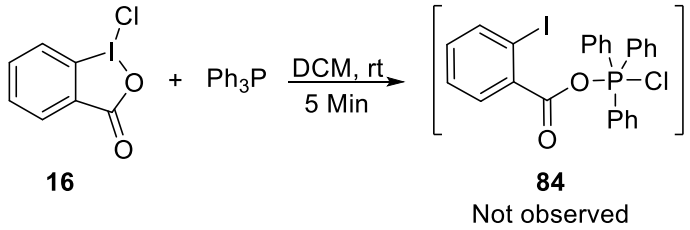
Acetylation of alcohols using PIDA/Ph_3P was slow at room temperature and the starting material was not consumed fully, even after Ph_3P was completely converted to the phosphine oxide. The high reactivity of the PIFA/Ph_3P system was attributed to the more electrophilic nature at the carbonyl carbon due to the strong electron withdrawing trifluoromethyl (CF_3) group. Attempting to acetylate primary alcohols with PIDA/Ph_3P system led to isolation of unreacted starting material and moderate yields of the desired acetate product. Unfortunately, the acetylation of secondary alcohols with PIDA/Ph_3P at room temperature did not give the desired acetate product. This was overcome by refluxing in $CHCl_3$ overnight for 12 hours and the acetate products were obtained in moderately good yields (**83c** and **83d**, Scheme 1.35). A tertiary alcohol did not undergo acetylation even after refluxing in $CHCl_3$ for 12 hours.



Scheme 1.35: Synthesis of acetates

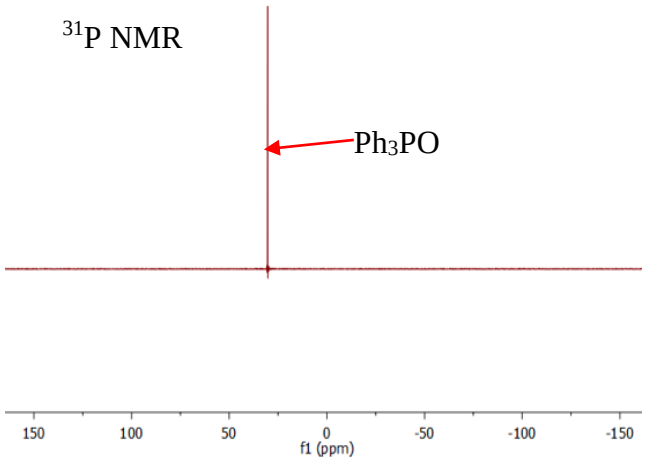
1.9 Functionalization of Alcohols Using Cyclic Chloro(benzoyloxy)-iodane

The ability of cyclic iodanes to transfer their ligands to triphenylphosphine was attempted next. The cyclic iodane chosen to conduct this study was the cyclic chloro(benzoyloxy)iodane (**16**). Similar to the previous case, preliminary studies were conducted using ^{31}P NMR spectroscopy in an attempt to detect the phosphorane **84** (Scheme 1.36). Ph_3P and iodane **16** was dissolved in DCM and the ^{31}P NMR spectrum was taken to observe phosphorane **84**, but instead, only triphenyl phosphine oxide was observed within 5 minutes. The ^{1}H NMR spectrum contained a set of signals which matched those previously reported for 2-iodobenzoyl chloride (Figure 1.13).[91]



16 **84**
Not observed

Scheme 1.36: Attempted synthesis phosphorane **84**



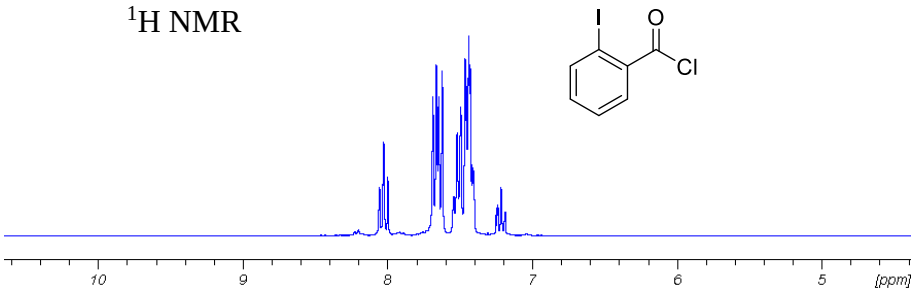
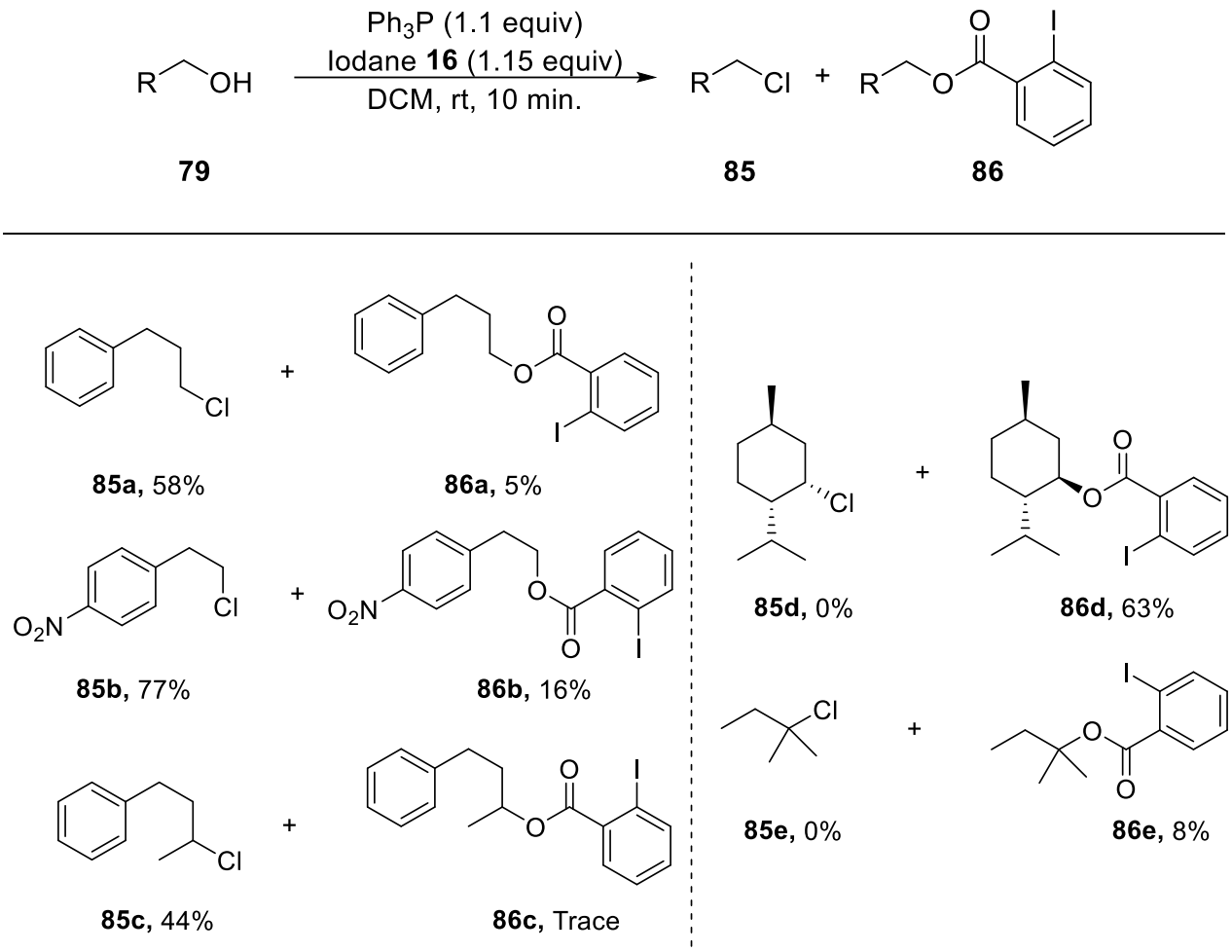


Figure 1.13: Attempted synthesis of disubstituted triphenylphosphorane **84**

As in the previous cases, a small group of alcohols were subjected to reacting with Ph_3P and iodane **16** in DCM at room temperature. Monitoring by TLC indicated the complete consumption of the starting alcohol within 10 minutes. Analysis of the ^1H NMR spectrum obtained from the crude reaction mixture of 4-nitrophenethylalcohol with Ph_3P and **16**, revealed the presence of two products; the corresponding alkyl chloride (**85b**) and the 2-iodobenzoate ester (**86b**, Scheme 1.37) as the minor product. Similar results were observed when 3-phenylpropanol was used as the starting material also. Other alcohols were studied and in the case of 4-phenyl-2-butanol, the major product was 3-(chloropropyl)benzene (**85c**) and 34% of unreacted starting material was recovered. Sterically congested *l*-menthol and tertiary amyl alcohol required heating to reflux in DCM and gave only the iodobenzoate product (**86d** and **86e**). The stereochemistry assigned to **86d** was based on the reported chemical shift for (—)-menthyl 2-iodobenzoate.[92]

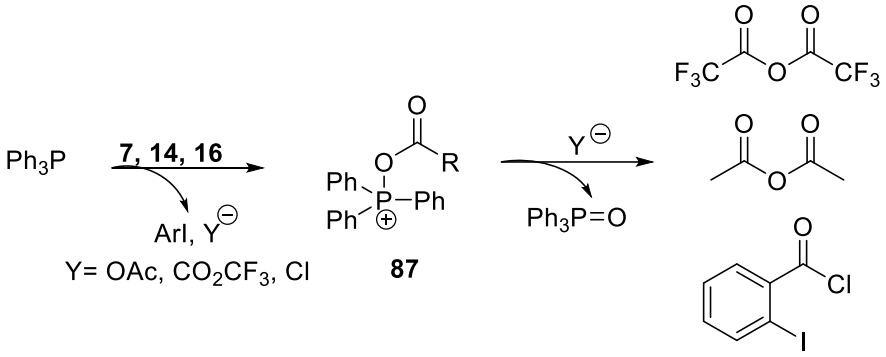


Scheme 1.37: Syntheses of chlorides and iodobenzoate esters

1.10 General Mechanism for the Functionalization of Alcohols via Phosphoranes.

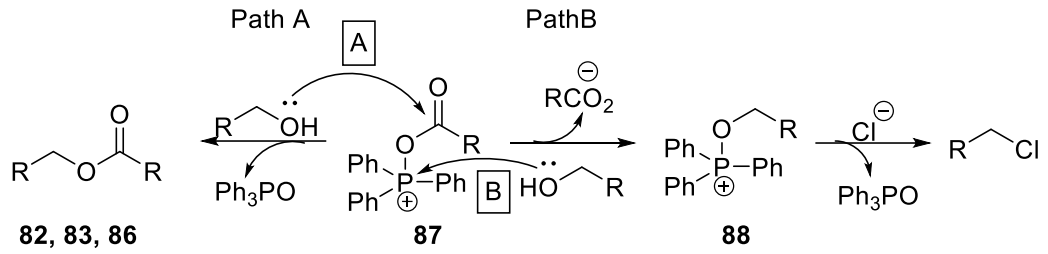
From the NMR studies, it was concluded that hypervalent iodine reagents PIDA (**7**), PIFA (**14**), and cyclic iodane **16** reacted with PPh_3 according to the mechanism suggested by Varvoglis (Scheme 1.38).[80] In short, transfer of the ligand Y on the iodane to Ph_3P, followed by reductive elimination, or nucleophilic displacement, leads to the formation of an acyloxyphosphonium

intermediate (**87**). The displaced ligand, Y, then attacks the activated carboxylate on intermediate **87** to give triphenylphosphine oxide and the corresponding anhydride or benzoyl chloride products.



Scheme 1.38: Mechanism for the synthesis of phosphoranes

When the activation of Ph_3P using reagents **7**, **14**, **16** was carried out in the presence of alcohols, the intermediate **87** still forms. In the case of iodane **7** and **14**, the alcohol attacks at the carbonyl carbon on the phosphonium intermediate **87** (Scheme 1.39, Path A).[93,83] In the case of iodane **16**, attack could either occur at the activated carboxylate (Path A), or at the phosphonium ion (Path B) to generate intermediate **88**, which could terminate through nucleophilic chlorination. The stereochemistry associated with trifluoroacetate product **82d** and the acetate product **83d** also pointed out that iodane **7** and **14** does not follow Path B. If the reaction occurs through Path B, the trifluoroacetate or acetate ion attacks the intermediate **88** and the reaction will proceed with inversion of configuration. In the case of iodane **16**, the primary and secondary alcohol attacks the electrophilic phosphorus centre, rather than the carbonyl, resulting in the formation of **88**. We assumed that in the case of hindered alcohols, Path A preferred due to steric hindrance from the bulky groups on acylphosphonium ion **87**.



Scheme 1.39: Reaction pathways for the functionalization of alcohols

1.11 Conclusion

The synthesis of Ph_3PF_2 has been achieved by the reaction between iodane **8** ($TolIF_2$) and Ph_3P. Fluorination reactions with $Ph_3P/TolIF_2$ gave moderate yields for primary alcohols while secondary and tertiary alcohols failed, under these reaction conditions. In the case of iodane **7** (PIDA), **14** (PIFA), and **16** (cyclic iodane) no phosphoranes were observed, instead deoxygenative ligand coupling occurred. Primary, secondary, and tertiary alcohols reacted with these iodanes and Ph_3P to give alkyl chlorides, acetates, trifluoroacetates, and 2-iodobenzoates in moderate to good yield. Iodane **8** shows Appel-type reactivity while acylation reactions dominated with iodanes **7** and **14.** The chemoselectivity observed with iodane **16** was related to the steric hindrance and/or nucleophilicity of the alcohol, giving alkyl chlorides with unhindered alcohols and benzoates with hindered alcohols.

1.12 Experimental Procedures for Chapter 1

1.12.1 General Experimental Details

Reactions were carried out in oven-dried glassware under a positive nitrogen atmosphere. Transfer of anhydrous solvents and reagents was accomplished with oven-dried needles. Solvents were dried and purified using a JC Meyer solvent purification system, and were used without further purification. Thin layer chromatography was performed on glass plates pre-coated with 0.25 mm

Kieselgel 60 F254 (Silicycle). Flash chromatography columns were packed with 230-400 mesh silica gel (Silicycle). ^{1}H NMR spectra were recorded at 300 or 500 MHz, and are reported (ppm) relative to the residual chloroform peak (7.26 ppm) and coupling constants (*J*) are reported in hertz (Hz). Carbon NMR spectra (^{13}C NMR) were recorded at 125 or 75 MHz and are reported (ppm) relative to the center line of the triplet from chloroform-d (77.00 ppm). Phosphorus NMR spectra (^{31}P NMR) were recorded at 121 or 202 MHz, and were reported (ppm) relative to the peak of 85% H_3PO_4 (0 ppm). Fluorine NMR spectra (^{19}F NMR) were recorded at 282 MHz, and were reported (ppm) relative to the peak of trifluoroacetic acid (-76.53 ppm). Mass spectra were performed on a ThermoFisher Scientific Q-Exactive hybrid mass spectrometer using positive electrospray ionization (ESI). Accurate masses were recorded with a mass resolution of 70,000. ESI samples were infused at 5 μL/min in 1:1 CH_3OH/H_2O+0.1% formic acid. Melting points were determined on a Melt-Temp II.

1.12.2 Synthesis of *p-(*Difluoroiodo)toluene (8)

$TolIF_2$ was synthesized by the addition of 3N sodium hydroxide (29 mL, 143 mmol) to (diacetoxyiodo)toluene (8.4 g, 25 mmol) and stirring at room temperature for three hours. The resulting *p*-iodosotoluene (TolIO) was filtered, washed with water (2 x 100 mL), then chloroform (100 mL) and suction dried. TolIO was transferred to a Teflon bottle and was suspended in dicholoromethane (40 mL). To this was added conc. aq. HF dropwise (approximately 9 mL). The aqueous layer was decanted and the organic layer was concentrated to dryness under a stream of nitrogen to yield a light yellow solid. The light yellow solid was recrystallized using a mixture of hexanes and $CHCl_3$ to yield *p-(*difluoroiodo)toluene as a white solid (4.10 g, 64%). **m.p.** 98 – 102 °C. Spectral data were consistent with the reported values.[94]

1.12.3 Synthesis of (Dichloroiodo)benzene (15)

Iodobenzene (2.0 g, 9.8 mmol), was suspended in 5% sodium hypochlorite (household bleach, 60 mL) and stirred vigorously at room temperature. To this was added concentrated hydrochloric acid (20 mL) dropwise over 5 minutes. The yellow suspension was allowed to stir for 5 minutes. Filtration of the suspension, followed by washing with H_2O (200 mL) and petroleum ether (50 mL) gave an yellow solid which was spread on a watch glass and allowed to air-dry in the dark overnight in a desiccator to give $PhICl_2$ as a pale yellow solid (2.5 g, 93%).[95]

1.12.4 Synthesis of Difluorotriphenylphosphorane

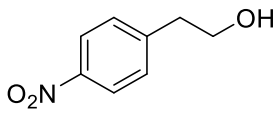
Triphenylphosphine (0.265 g, 1.01 mmol) was dissolved in $CHCl_3$ (3 mL) in a round bottom flask, and to this was added *p*-(difluoroiodo)toluene (0.273 g, 1.07 mmol, 1.05 equiv), and the reaction was stirred for 30 minutes at room temperature. The solvent was evaporated and the resulting residue was triturated with cold 20% DCM in Et_2O. The solid was filtered and washed with minimum amount of cold 20% DCM in Et_2O to provide Ph_3PF_2 as a white solid in 74% yield (**m.p.** 154 °C). Spectral data were consistent with the reported values.[73]

1.12.5 General Procedure A: Synthesis of Alcohols (79)

Alcohols which were not readily available were prepared according to the literature starting from their corresponding carboxylic acids.[88] In a round bottom flask was added the acid (1.0 equiv) and THF (0.2 M) under argon. The reaction mixture was cooled to 0 °C temperature in an ice-water bath and vigorously stirred while sodium borohydride (2.5 equiv) was added portionwise over 15 minutes with a 5 minute interval between each addition. $BF_3{\cdot}OEt_2$ (1.50 equiv) was then added slowly and the reaction mixture was warmed to room temperature and allowed to stir for 3.5 hours. Following this, the reaction mixture was again cooled to 0 °C in an ice-water bath while 10% HCl (aq.) was slowly added with vigorous stirring for 5 minutes. 5% NaOH (aq.) was then slowly added

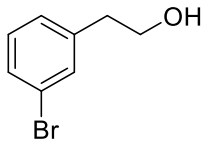
and the reaction was stirred for an additional 5 minutes. THF was then removed by rotary evaporation and the crude mixture was extracted with EtOAc three times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, concentrated by rotary evaporation, and purified by column chromatography.

1.12.5.1 Synthesis of 4-Nitrophenethyl alcohol (79b)



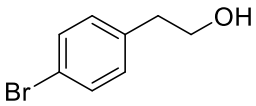
4-Nitrophenylacetic acid (1.004 g, 5.54 mmol, 1 equiv) was subjected to General Procedure **A**. Purification via column chromatography (80% EtOAc/Hexanes) gave **79b** (0.880 g, 95% yield) as a pale yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 3.92 (*app* q, *J* = 6.0 Hz, 2H), 2.97 (t, *J* = 6.0 Hz, 2H), 1.43 (t, *J* = 6.0 Hz, 1H). Spectral data were consistent with literature values.[96]

1.12.5.2 Synthesis of 3-Bromophenethyl alcohol (79f)



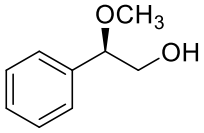
3-Bromophenylacetic acid (0.500 g, 2.33 mmol, 1 equiv) was subjected to General Procedure **A**. Purification via column chromatography (80% EtOAc/Hexanes) gave **79f** (0.389 g, 83% yield) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38-7.34 (m, 2H), 7.18-7.15 (m, 2H), 3.85 (t, *J* = 6.0 Hz, 2H), 2.83 (t, *J* = 6.0 Hz, 2H), 1.43 (br. s, 1H). Spectral data were consistent with literature values.[97]

1.12.5.3 Synthesis of 4-Bromophenethyl alcohol (79g)



4-Bromophenylacetic acid (0.501 g, 2.33 mmol, 1 equiv) was subjected to General Procedure **A**. Purification via column chromatography (80% EtOAc/Hexanes) gave **79g** (0.284 g, 61% yield) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 3.83 (t, *J* = 6.0 Hz, 2H), 2.81 (t, *J* = 6.0 Hz, 2H), 1.44 (br. s, 1H). Spectral data were consistent with literature values.[96]

1.12.5.4 Synthesis of (*R*)-2-Methoxy-2-phenylethanol (79j)

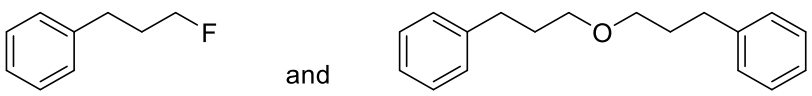


(*R*)-2-Methoxyphenylacetic acid (0.268 g, 1.61 mmol, 1 equiv) was subjected to General Procedure **A**. Purification via column chromatography (80% EtOAc/Hexanes) gave **79j** (0.148 g, 60 % yield) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 4.30 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.70-3.58 (m, 2H), 3.30 (s, 3H), 2.27 (br. s, 1H). Spectral data were consistent with literature values.[98]

1.12.6 General Procedure B: Synthesis of Alkyl Fluorides (80)

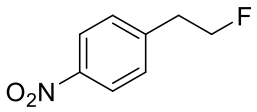
Into a sealable vial was added triphenylphosphine (1.5 equiv) and chlorobenzene (0.6 mL), and to this was added *p*-(difluoroiodo)toluene (1.6 eq), followed by TiF_3 (10 mol%) and the alcohol (1 equiv). The reaction vessel was sealed, immersed in a 160 °C oil bath and stirred for 45 minutes. The crude reaction mixture was cooled to room temperature and to it was added 5 µL of cyclohexene (for determination of the ^{1}H NMR yield). Otherwise, the reaction mixture was concentrated by rotatory evaporation and purified by column chromatography to give the alkyl fluorides.

1.12.6.1 Synthesis of 1-Fluoro-3-phenylpropane (80a) and Bis(3-phenylpropyl)ether (81a)



Phenyl-1-propanol (33 μL, 0.24 mmol) was subjected to General Procedure **B**, giving **80a** in 57% and **81a** in 21% ^{1}H NMR yield. Spectral data for **80a** and **81a** were consistent with literature values.[99]

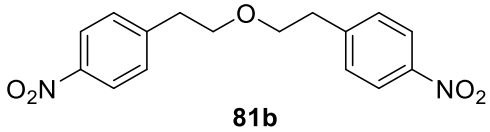
1.12.6.2 Synthesis of 1-(2-Fluoroethyl)-4-nitrobenzene (80b) and *p*-Nitrophenethylether (81b)



80b

4-Nitrophenethyl alcohol (0.040 g, 0.24 mmol, 1 equiv) was subjected to General Procedure **B**. Purification via column chromatography (20% EtOAc/Hexanes) gave **80b** (0.026 g, 63% yield) and **81b** (0.009 g, 12%).

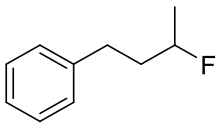
^{19}F NMR (282 MHz, $CDCl_3$) δ -217.28; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 4.67 (dt, *J* = 46.9, 6.0 Hz, 2H), 3.11 (dt, *J* = 25.7, 6.0 Hz, 2H). Spectral data were consistent with literature values.[100]



81b

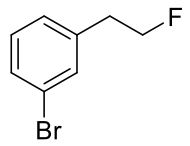
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.0 Hz, 4H), 7.31 (d, *J* = 9.0 Hz, 4H), 3.65 (t, *J* = 6.0 Hz, 4H), 2.93 (t, *J* = 6.0 Hz, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 147.0, 146.7, 129.7, 123.5, 70.9, 36.1.

1.12.6.3 Synthesis of (3-Fluorobutyl)benzene (80c)



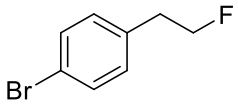
4-Phenyl-2-butanol (36 μL, 0.23 mmol) was subjected to General Procedure **B**, giving **80c** in 9% ^{1}H NMR yield. Spectral data for **80c** were consistent with literature values.[101]

1.12.6.4 Synthesis of 3-(2-fluoroethyl)-1-bromobenzene (80f)



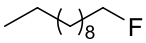
3-Bromophenethyl alcohol (0.053 g, 0.26 mmol, 1 equiv) was subjected to General Procedure **B**. Purification via column chromatography (5% EtOAc/Hexanes) gave **80f** (0.026 g, 48% yield) as a colourless oil. The yield was calculated from a mixture of **80f** and the corresponding ether product. **IR** (ATR) 2964, 2944, 1582, 1529, 1447, 1065, 928, 865 cm^{-1}; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -216.29; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43-7.41 (m, 2H), 7.23-7.19 (m, 2H), 4.66 (dt, *J* = 45.0, 5.0 Hz, 2H), 3.11 (dt, *J* = 25.0, 5.0 Hz, 2H); **LRMS**: EI calcd for C_8H_8BrF ($M^{+\cdot}$) 201.98; found 201.98 and 204.00.

1.12.6.5 Synthesis of 1-Bromo-4-(2-fluoroethyl)benzene (80g)



4-Bromophenethyl alcohol (0.048 g, 0.24 mmol, 1 equiv) was subjected to General Procedure **B**. Purification via column chromatography (10% EtOAc/Hexanes) gave **80g** (0.022 g, 45% yield) as a colourless oil. The yield was calculated from a mixture of **80g** and the corresponding ether product. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -216.27; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 6.0 Hz, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 4.60 (dt, *J* = 48.0, 6.0 Hz, 2H), 2.96 (dt, *J* = 24.0, 6.0 Hz, 2H).

1.12.6.6 Synthesis of 1-Fluoroundecane (80h)

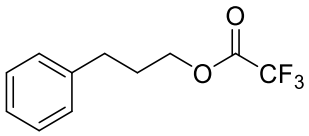


1-Undecanol (0.043 g, 0.25 mmol) was subjected to General Procedure **B**, giving **80h** in 53% ^{1}H NMR yield. Spectral data for **80h** were consistent with literature values.[102]

1.12.7 General Procedure C: Synthesis of Trifluoroaceatates (82)

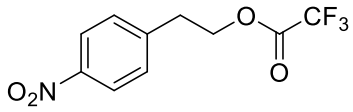
Into a conical flask was added the alcohol (1 equiv) and DCM (0.5 mL), and to this was added triphenylphosphine (1.1 equiv) and (bis(trifluoroacetoxy)iodo)benzene (1.1 equiv). The reaction mixture was stirred at room temperature for 30 minutes, concentrated by rotary evaporation and purified by column chromatography, acidifying the stationary phase with 0.2% trifluoroacetic acid in hexanes.

1.12.7.1 Synthesis of 3-Phenylpropyl 2,2,2-trifluoroacetate (82a)



3-Phenyl-1-propanol (56 μL, 0.41 mmol) was subjected to General Procedure **C**. The crude reaction mixture was purified via column chromatography (20% EtOAc/Hexanes) to give **82a** (0.070 g, 74% yield) as a colourless oil. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -75.35; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35-7.18 (m, 5H), 4.34 (t, *J* = 6.5 Hz, 2H), 2.75 (t, *J* = 7.4 Hz, 2H), 2.14-2.04 (m, 2H). Spectral data were consistent with literature values[103]

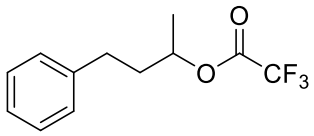
1.12.7.2 Synthesis of 4-Nitrophenethyl 2,2,2-trifluoroacetate (82b)



4-Nitrophenethyl alcohol (0.064 g, 0.38 mmol) was subjected to General Procedure **C**. The crude reaction mixture was purified via column chromatography (20% EtOAc/Hexanes) to give **82b** (0.085 g, 84% yield) as a pale yellow oil. **IR** (ATR) 2964, 2944, 1786, 1602, 1520, 1345, 1221,

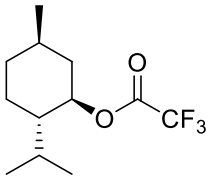
1150 cm^{-1}; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -75.27; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 4.59 (t, *J* = 6.6 Hz, 2H), 3.16 (t, *J* = 6.6 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.2 (q, *J* = 43.0 Hz), 147.2, 144.0, 129.8, 123.9, 114.4 (q, *J* = 285.4 Hz), 67.2, 34.4.

1.12.7.3 Synthesis of 1-Methyl-3-phenylpropyltrifluoroacetate (82c)



4-Phenyl-2-butanol (0.063 g, 0.42 mmol) was subjected to General Procedure **C**. The crude reaction mixture was purified via column chromatography (10% EtOAc/Hexanes) to give **82c** (0.066 g, 64% yield) as a colourless oil. **IR** (ATR) 2960, 1779, 1455, 1221, 1162, 907, 728, 698 cm^{-1}; **^{19}F NMR** (282 MHz, $CDCl_3$) δ -75.58; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34-7.16 (m, 5H), 5.11 (m, 1H), 2.74-2.60 (m, 2H), 2.15-1.87 (m, 2H), 1.39 (d, *J* = 6.3Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.1 (q, *J* = 41.5 Hz), 140.5, 128.6, 128.3, 126.3, 114.6 (q, *J* = 286.1Hz), 75.8, 37.1, 31.4, 19.5; **LRMS**: EI calcd for $C_{12}H_{13}F_3O_2$ ($M^{+\cdot}$) 246.09; found 246.12.

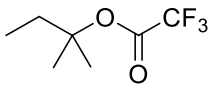
1.12.7.4 Synthesis of (–)-Menthyl 2,2,2-trifluoroacetate (82d)



(-)-Menthol (0.063 g, 0.41 mmol) was subjected to General Procedure **C**. The crude reaction mixture was purified via column chromatography (1:20 Et_2O/Pentane) to give **82d** (0.065 g, 63% yield) as a colourless oil. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -75.59; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.86 (td, *J* = 11.0, 4.5 Hz, 1H), 2.06-2.02 (m, 1H), 1.90-1.80 (m, 1H), 1.75-1.66 (m, 2H), 1.58-1.46

(m, 2H), 1.20-1.03 (m, 2H), 0.98-0.84 (m, 7H), 0.76 (d, *J* =7.0 Hz, 3H). Spectral data were consistent with literature values.[89]

1.12.7.5 Synthesis of 2-Methyl-2-butyltrifluoroacetate (82e)

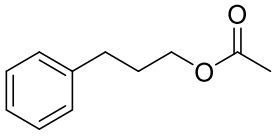


t-Amylalcohol (45 µL, 0.41 mmol) was subjected to General Procedure **C**, giving **82e** in 77% ^{1}H NMR yield. Spectral data for **82e** were consistent with literature values.[104]

1.12.8 General Procedure D: Synthesis of Acetates (83)

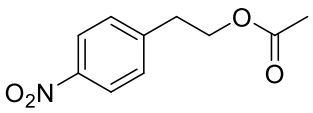
Into a conical flask was added the alcohol (1 equiv), DCM or $CHCl_3$ (0.5 mL) and triphenylphosphine (1.1 equiv). To this was added (diacetoxyiodo)benzene **7** (1.1 equiv) and the reaction mixture was stirred at either room temperature or reflux. The crude reaction mixtures were concentrated by rotary evaporation and purified by column chromatography.

1.12.8.1 Synthesis of 3-Phenylpropyl acetate (83a)



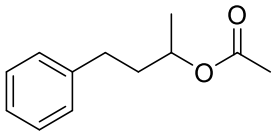
3-Phenyl-1-propanol (32 µL, 0.24 mmol) was subjected to General Procedure **D**, stirring for 6 hours at room temperature. The crude reaction mixture was purified via column chromatography (20% EtOAc/Hexanes) to give **83a** (0.020 g, 47% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31-7.17 (m, 5H), 4.08 (t, *J* = 6.6 Hz, 2H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.00 (s, 3H), 1.95 (m, 2H). Spectral data were consistent with literature values.[105]

1.12.8.2 Synthesis of 4-Nitrophenethyl acetate (83b)



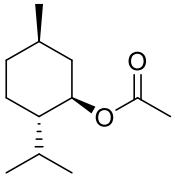
4-Nitrophenethyl alcohol (0.067 g, 0.40 mmol) was subjected to General Procedure **D**, stirring for 3 hours at room temperature. The crude reaction mixture was purified via column chromatography (50% EtOAc/Hexanes) to give **83b** (0.047 g, 56% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 4.30 (t, *J* = 6.7 Hz, 2H), 3.03 (t, *J* = 6.7 Hz, 2H), 2.00 (s, 3H). Spectral data were consistent with literature values.[105]

1.12.8.3 Synthesis of 1-Methyl-3-phenylpropylacetate (83c)



4-Phenyl-2-butanol (0.062 g, 0.41 mmol) was dissolved in $CHCl_3$ (0.5 mL) in a round bottom flask and to this was added triphenylphosphine (1.1 equiv) and (diacetoxyiodo)benzene (1.1 equiv). The reaction was fitted with a condenser and refluxed for 12 hours, concentrated by rotary evaporation and purified by column chromatography (20% EtOAc/Hexanes) to give **83c** (0.037 g, 47% yield) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 7.20-7.15 (m, 3H), 4.93 (m, 1H), 2.73-2.55 (m, 2H), 2.02 (s,3H), 1.99-1.74 (m, 2H), 1.24 (d, *J* = 6.2 Hz, 3H). Spectral data were consistent with literature values.[106]

1.12.8.4 Synthesis of (–)-Menthyl acetate (83d)

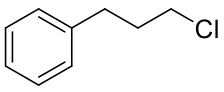


(–)-Menthol (0.064 g, 0.41 mmol) was dissolved in $CHCl_3$ (0.5 mL) in a round bottom flask and to this was added triphenylphosphine (1.1 equiv) and (diacetoxyiodo)benzene (1.1 equiv). The reaction was fitted with a condenser and refluxed for 12 hours, concentrated by rotary evaporation and purified by column chromatography (20% EtOAc/Hexanes) to give **83d** (0.032 g, 40% yield) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.65 (td, *J* = 4.4, 10.9 Hz, 1H), 2.01 (s, 3H), 1.99-1.91 (m, 1H), 1.89-1.78 (m, 1H), 1.72-1.60 (m, 2H), 1.53-01.28 (m, 2H), 1.10-0.91 (m, 2H), 0.90-0.84 (m, 7H), 0.74 (d, *J*= 7.0 Hz, 3H). Spectral data were consistent with literature values.[107]

1.12.9 General Procedure E: Synthesis of Chlorides (85) and Benzoates (86)

To a conical flask was added the alcohol (1 equiv) and CH_2Cl_2 (0.5 mL), followed by triphenylphosphine (1.1 equiv) and chloroiodane **16** (1.15 equiv). The reaction mixture was either stirred at room temperature for 10 minutes or reflux for 13 hours, then concentrated by rotary evaporation and purified by column chromatography, rendering the stationary phase slightly basic with 1% triethylamine in hexane.

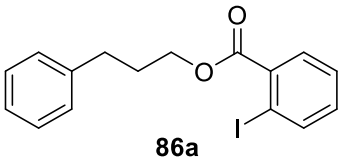
1.12.9.1 Synthesis of 3-(Chloropropyl)benzene (85a) and 3-Phenylpropyl 2-iodobenzoate (86a)



85a

3-Phenyl-1-propanol (58 μL, 0.43 mmol) was subjected to General Procedure **E** to give a crude reaction mixture that was purified via column chromatography (10% EtOAc/Hexanes) to give **85a** (0.038 g, 58% yield) and **86a** (0.008 g, 5% yield).

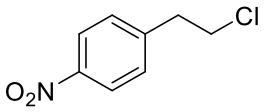
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.18 (m, 5H), 3.53 (t, *J* = 6.5 Hz, 2H), 2.78 (t, *J* = 7.3 Hz, 2H), 2.04-2.13 (m, 2H). Spectral data were consistent with literature values.[68]



86a

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, 6.9 Hz, 1H), 7.75 (dd, *J* = 6.1, 1.6 Hz, 1H), 7.43-7.36 (m, 1H), 7.32-7.12 (m, 6H), 4.36 (t, *J* = 6.5 Hz, 2H), 2.80 (t, *J* = 7.3 Hz, 2H), 2.16-2.04 (m, 2H).

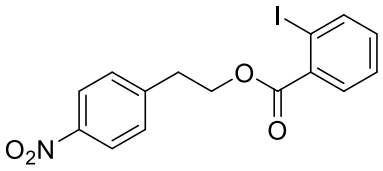
1.12.9.2 Synthesis of 1-(2-Chloroethyl)-4-nitrobenzene (85b) and 4-Nitrophenethyl 2-iodobenzoate (86b)



85b

4-Nitrophenethyl alcohol (0.069 g, 0.41 mmol) was subjected to General Procedure **E** to give a crude reaction mixture that was purified via column chromatography (20% EtOAc/Hexanes) to give **85b** (0.046 g, 61% yield) and **86b** (0.026 g, 16% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 3.76 (t, *J* = 6.9 Hz, 2H), 3.17 (t, *J* = 6.9 Hz, 2H). Spectral data were consistent with literature values.[108]

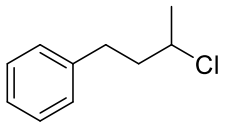


86b

IR (ATR) 3077, 2965, 1723, 1600, 1562, 1514, 1342, 1246, 1211, 1103, 740 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 6.8 Hz, 2H), 7.98-7.96 (m, 1H), 7.69-7.65 (m, 1H), 7.46-7.34 (m, 3H), 7.19-7.11 (m, 1H), 4.58 (t, *J* = 6.7 Hz, 2H), 3.20 (t, *J* = 6.6 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ

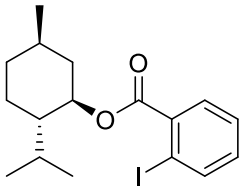
166.1, 146.9, 145.4, 141.3, 134.7, 132.7, 130.7, 129.8, 127.9, 123.7, 94.0, 64.9, 34.8; **LRMS**: EI calcd for $C_{15}H_{12}INO_4$ ($M^{+\cdot}$) 396.98; found 396.97.

1.12.9.3 Synthesis of (3-Chlorobutyl)benzene (85c)



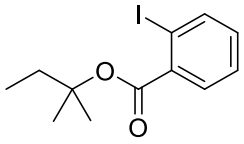
4-Phenyl-2-butanol (0.062 g, 0.42 mmol) was subjected to General Procedure **E** to give a crude reaction mixture that was purified via column chromatography (5% EtOAc/Hexanes) to give **85c** (0.031 g, 44% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33-7.21 (m, 5H), 4.06-3.95 (m, 1H), 2.91-2.70 (m, 2H), 2.06-1.99 (m, 2H), 1.54 (d, *J* = 6.0 Hz, 3H). Spectral data were consistent with literature values.[109]

1.12.9.4 Synthesis of (–)-Menthyl 2-iodobenzoate (86d)



(–)-Menthol (0.064 g, 0.41 mmol) was subjected to General Procedure **E**, fitting with a condenser and refluxing the reaction for 13 hours. The crude reaction mixture was concentrated by rotary evaporation and purified by column chromatography (20% EtOAc/Hexanes) to give **86d** (0.100 g, 63% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.9, Hz, 1H), 7.76 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.42 (*app.* t, *J* = 6.0 Hz, 1H), 7.15 (*app.* t, *J* = 6.0 Hz, 1H), 4.99 (td, *J* = 10.9, 4.4 Hz, 1H), 2.24-2.18 (m, 1H), 2.09-2.00 (m, 1H), 1.79-1.71 (m, 2H), 1.64-1.52 (m, 2H), 1.23-1.12 (m, 2H), 1.00-0.92 (m, 7H), 0.85 (d, *J* = 7.0 Hz, 3H). Spectral data were consistent with literature values.[92]

1.12.9.5 Synthesis of *t*-Amyl 2-iodobenzoate (86e)



t-Amylalcohol (46 µL, 0.42 mmol) was subjected to General Procedure **E**, fitting with a condenser and refluxing the reaction for 13 hours. The crude reaction mixture was concentrated by rotary evaporation and purified by column chromatography (5% EtOAc/Hexanes) to give **86e** (0.011 g, 8% yield). **IR** (ATR) 2974, 2926, 1722, 1584, 1462, 1289, 1129, 740 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.9, Hz, 1H), 7.68 (dd, *J* = 7.8, 1.67 Hz, 1H), 7.39-7.34 (*app*.t, *J* = 7.5Hz, 1H), 7.12-7.07(*app*. dt, *J* = 7.5, 1.4 Hz, 1H), 1.94 (q, *J* = 7.4Hz, 2H), 1.58 (s, 6H), 0.96 (t, *J* = 7.5Hz, 3H); **^{13}C NM**R (75 MHz, $CDCl_3$) δ 166.1, 141.0, 137.3, 131.9, 130.4, 127.8, 93.5, 85.2, 33.5, 25.6, 8.5; **LRMS**: EI calcd for $C_{12}H_{15}IO_2$ ($M^{+\cdot}$) 318.01; found 318.02

Chapter 2: Halogenation of Secondary Phosphine Oxides

2.1 Background

Phosphine oxides are phosphorus based compounds having the general formula $R_3P(O)$. In the case of organophosphine oxides, R = alkyl or aryl groups. In general, phosphine oxides can be divided into two classes depending on the number of substituents on the phosphorus atom.[110] Phosphine oxides with three substituents are called tertiary phosphine oxides, (e.g., triphenylphosphine oxide, **89**, Figure 2.1). Phosphine oxides having two substituents that are connected to phosphorus through carbon atoms are called secondary phosphine oxides (SPOs; e.g., diphenylphosphine oxide, **90**). If the two substituents are linked to phosphorus through an oxygen atom, they are called diorganophosphites or H-phosphonates, (e.g., diethyl phosphite, **91**). In this thesis, the halogenation of only secondary phosphine oxides (SPOs) and diorganophosphites are discussed.

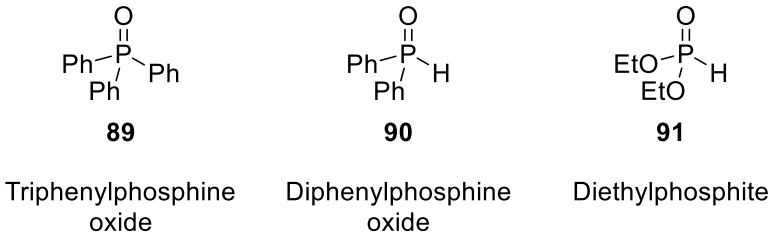
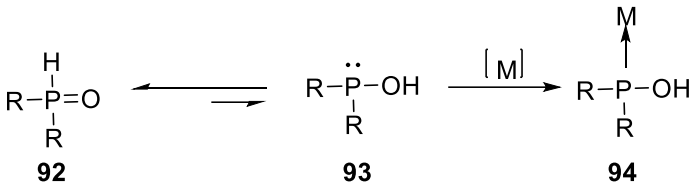


Figure 2.1: Examples of phosphine oxides

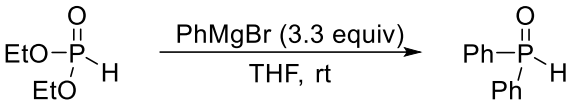
SPOs can be used to synthesize tertiary phosphines and they can also act as ligands in many metal-catalyzed reactions.[111,112] This is because of their tendency to tautomerize in solution to form the trivalent phosphinous acid (**93**) (Scheme 2.1). Several studies have been carried out to investigate the tautomeric properties of SPO's. The deuterium exchange and oxidation reactions carried out in the 1960's suggested that 4-coordinate (pentavalent) species (**92**) is dominant in most

instances.[113,114,115] The only compound that is known to exist in the trivalent form is bis(trifluoromethyl)phosphinous acid.[116] In 2011, Hoge *et al.* confirmed that the presence of electron withdrawing substituents on the phosphorus atom shifted the equilibrium towards the phosphinous acid.[117] Since secondary phosphine oxides can exist in the tautomeric trivalent form, they can act as nucleophiles in many reactions.



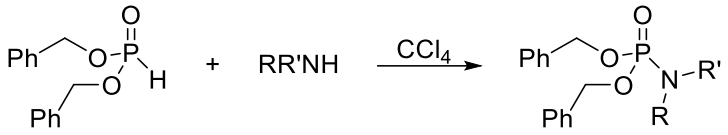
Scheme 2.1: Tautomerism in secondary phosphine oxides and the formation of metal complexes

The synthesis of secondary phosphine oxides from diorganophosphites is well documented in the literature.[118,119] For example, in a typical method, diethyl phosphite reacts with three equivalents of Grignard reagent to form the corresponding secondary phosphine oxide. Both of the ethoxy groups at the phosphorus atom are displaced by the alkyl- or aryl group of the Grignard reagent (Scheme 2.2)



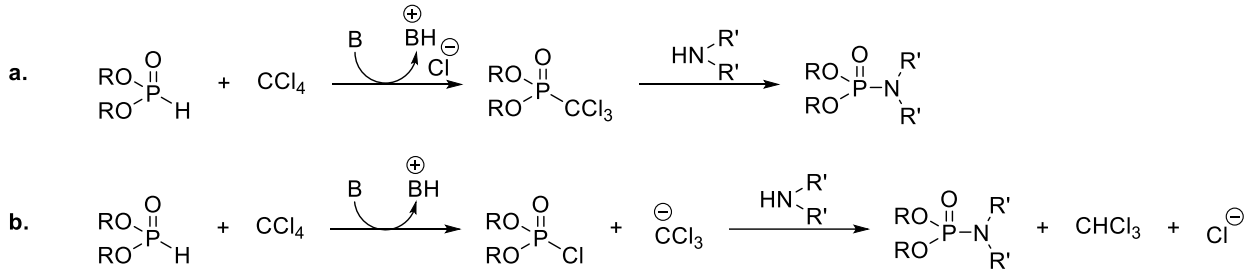
Scheme 2.2: Synthesis of secondary phosphine oxides

Another very useful reaction of dialkyl phosphites is the Atherton-Todd reaction, which was initially applied to the synthesis of phosphoramidates (Scheme 2.3)[120] by reacting dialkyl phosphites with amines in the presence of carbon tetrachloride (CCl_4).[121]



Scheme 2.3: Example of Atherton-Todd reaction

This reaction proceeds through the formation of a chlorophosphate intermediate which possesses electrophilic character and is capable of reacting with nucleophiles. Atherton and Todd suggested two possible mechanisms for the formation of phosphoroamidate (Scheme 2.4. a & b).[120,121] In mechanism a, phosphite reacts with CCl_4 in the presence of a base to form a trichloromethylphosphonate which undergoes further reaction with amine to yield phosphoramidate. The isolation of the intermediate trichloromethylphosphonate by various attempts was not successful. Mechanism b proceeds through the formation of an intermediate dialkylchlorophosphate.[122] This assumption was mainly based on an increase in the reaction rate when CCl_4 was replaced with $CBrCl_3$. They believed that it was due to the easier nucleophilic attack of the dilakylphosphite salt on bromine compared to CCl_4.



Scheme 2.4: Mechanism of Atherton-Todd reaction

Thus, halogenated derivatives of SPOs and diorganophosphites (here onwards, they are collectively called phosphinic halides) are found to be very useful compounds as they are easily converted to phosphinamides, phosphinates or phosphinothioates by reacting with nucleophiles.[123,124]

2.2 Halogenation of Secondary Phosphine Oxides

The majority of organophosphorus (OPs) compounds are used as insecticides, and phosphinic fluorides (P(O)F compounds) are well known as nerve agents. The toxicity associated with P(O)F compounds is well documented.[125,126,127,128] Amongst the nerve agents tabun, sarin, soman, cyclosarin and VX, three of them are P(O)F compounds (Figure 2.2).[129] They act by inhibiting the enzyme acetylcholinesterase (AChE) which affects the nervous system.

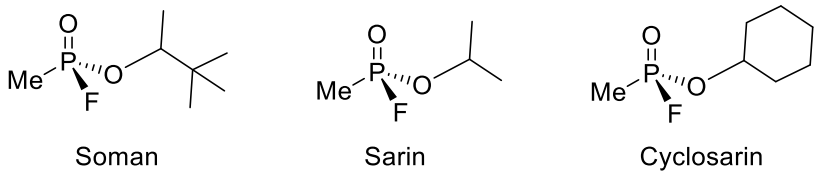
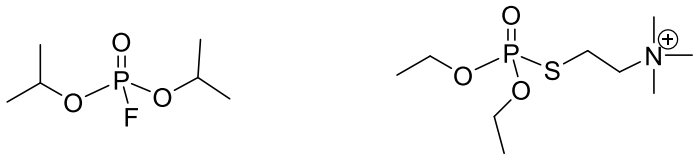


Figure 2.2: Examples of nerve agents

The principal role of AchE is to catalyze the hydrolysis of neurotransmitter acetylcholine into acetic acid and choline.[129] When this enzyme is inhibited, the amount of acetylcholine (ACh) at central and peripheral sites of the nerve system increases which eventually leads to convulsions and paralysis of the respiratory muscle.[130] AchE inhibitors can be classified into irreversible and reversible inhibitors. Organophosphorus compounds come under the category of irreversible AchE inhibitors.

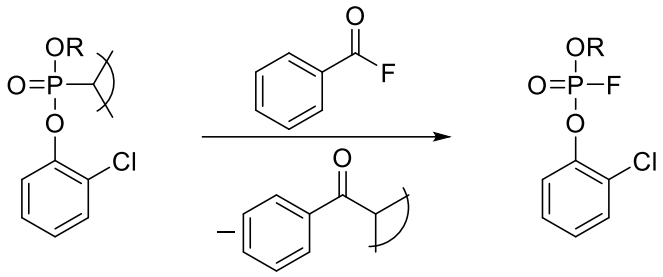
Apart from the toxicity associated with organophosphorus compounds, they have been used in ophthalmology as therapeutic agents in the treatment of chronic glaucoma. Diisopropyl fluorophosphates (DFP) and echothiophate are examples of two pharmacologically useful OPs (Figure 2.3).[129] Phosphorofluoridates play an important role as mechanistic probes for enzyme reactions[126] and are recognized as selective phosphorylating agents in synthesis.[131]



Diisopropylfluorophosphate (DFP) Echothiophate

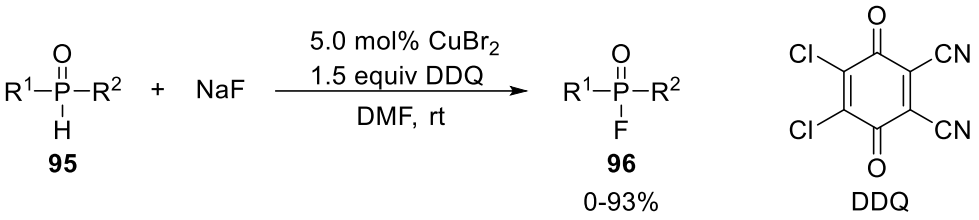
Figure 2.3: Pharmacologically useful OPs

Previous methods for the synthesis of phosphinic fluorides falls into two categories; either halogen metathesis with a metal fluoride, or reaction of an activated fluorine source.[131] Fluorination reactions using thionyl fluoride[132] on a limited number of phosphorus species has been reported by Michalski *et al.* The same group reported the synthesis of nucleoside phosphorofluoriates by the reaction between phosphoroazolides with benzoyl fluoride (Scheme 2.5).[133]



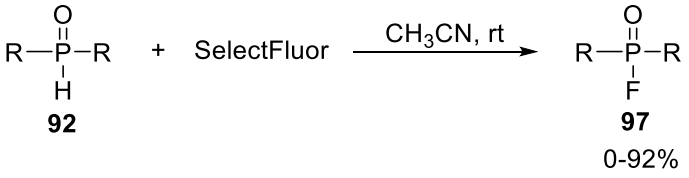
Scheme 2.5: Synthesis of nucleoside phosphorofluoridates

Recently Yang *et al.* reported the synthesis of phosphinic fluorides via oxidative coupling between SPO's and sodium fluoride (NaF). In this reaction DDQ is used as the oxidizing reagent and the reaction is catalyzed by Cu(II) bromide (Scheme 2.6).[134] This method gave excellent product yield for diphenyl phosphine oxides with electron donating substituents while the attempt to synthesize DFP failed under these reaction conditions.



Scheme 2.6: Synthesis of phosphinic fluorides by Yang *et al.*

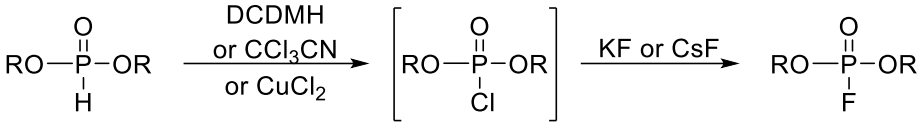
In 2016, Chen *et al.* achieved the fluorination of symmetrical SPOs using the electrophilic fluorinating reagent Selectfluor® (Scheme 2.7). The reaction proceeded smoothly at room temperature and they reported moderate to high yields for most of the substrates regardless of electron donating or electron withdrawing substituents on the aromatic ring. However, this method provided low yields of phosphinic fluorides derived from dialkyl derivatives. The failure to obtain dicyclopentylphosphinic fluoride is due to the steric hindrance between dicyclopentylphosphine oxides and bulky Selectfluor®. The Chen group also developed a protocol for the synthesis of phosphinic acids and phosphinates by trapping the *in situ* formed phosphinic fluorides with suitable nucleophiles.[135]



Scheme 2.7: Synthesis of phosphinic fluorides by Chen *et al.*

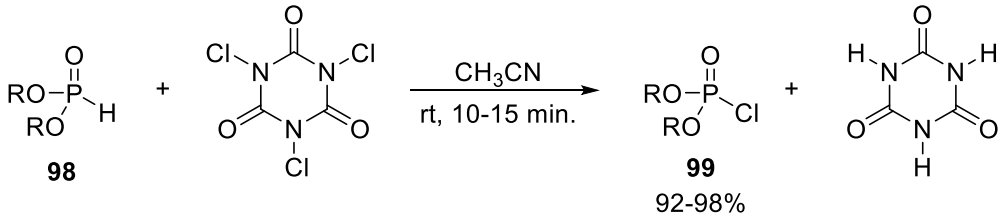
Before the development of the above mentioned methods, useful contributions to the fluorination of P(O)H compounds have been made by Kaushik, Dubey, and co-workers. In these methods, the fluorination reactions have been achieved by fluoride trapping of the *in situ* formed dialkyl chlorophosphates. They used a mixture of dichlorodimethylhydantoin (DCDMH),[136]

trichloroacetonitrile,[128] or $CuCl_2$[137] and alkali metal fluorides (i.e., KF or CsF) to accomplish the fluorination (Scheme 2.8).



Scheme 2.8: Synthesis of fluorophosphates by Kaushik *et al.*

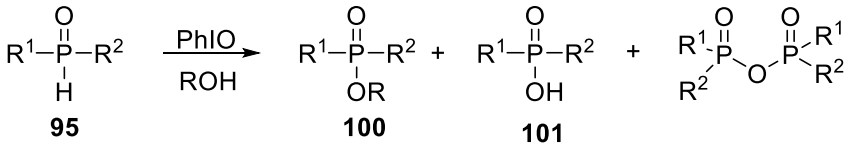
Phosphinic chlorides or dialkylchlorophosphates are important intermediates for many synthetic pathways. As such, the synthesis of these compounds has attracted much interest and has led to the development of many synthetic methods. The reagents used for the synthesis of phosphinic chlorides from P(O)H compounds varies from elemental chlorine,[125] sulfuryl chloride,[138] tellurium tetrachloride,[139] chloramines,[140] copper(II) chloride,[141] *N*,*N*'-dichloro bis(2,4,6-trichlorophenyl) urea,[142] *etc.* An unattractive feature of these reagents are that they are toxic, or react to give unwanted by-products. A very productive method for the synthesis of dialkylchlorophosphates using trichloroisocyanuric acid was reported by Kaushik *et al.* in 2005. This is a very rapid reaction occurring at room temperature and provides the phosphinic chlorides in over 90% yield (Scheme 2.9).[143]



Scheme 2.9: Synthesis of dialkylchlorophosphate using trichloroisocyanuric acid

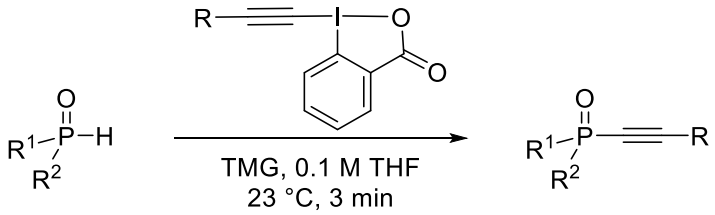
Due to the numerous applications of phosphinic chlorides as building blocks for many organophosphorus compounds, a one-pot synthesis in which trapping the *in situ* formed phosphinic chlorides with various nucleophiles is of great importance.

Though examples are limited, there are reactions involving hypervalent iodine reagents and secondary phosphine oxides. In 2002, Makowiec *et al.* described the synthesis of phosphinates (**100**) from P(O)H compounds using iodosyl benzene. This reaction was carried out in alcohol (Scheme 2.10). Makowiec group also investigated the reaction of secondary phosphine oxides with (diacetoxyiodo)benzene in the presence of alcohols and found that phosphinates (**100**) and phosphinic acids (**101**) are the products.[83]



Scheme 2.10: Synthesis of phosphinates using PhIO

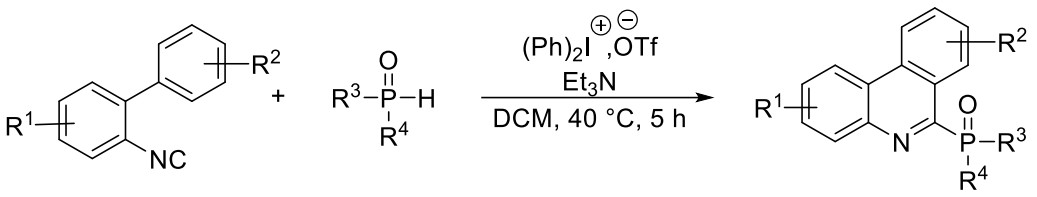
In 2014, Waser and Chen reported the alkynylation of secondary phosphine oxides with silyl, aryl and alkyl ethynyl benziodoxolone (EBX) reagents without using a transition metal catalyst (Scheme 2.11).



Scheme 2.11: Alkynylation of secondary phosphine oxides

The metal free synthesis of 6-phosphorylated phenanthridines from aryl isonitriles have been described by Lakhdar *et al*., in 2016.[144] This reaction proceeds through the formation of

phosphinoyl radicals from the combination of diphenyliodonium salt (Ph_2I^+ , ^-OTf) with triethylamine (Et_3N) in the presence of secondary phosphine oxides (Scheme 2.12).

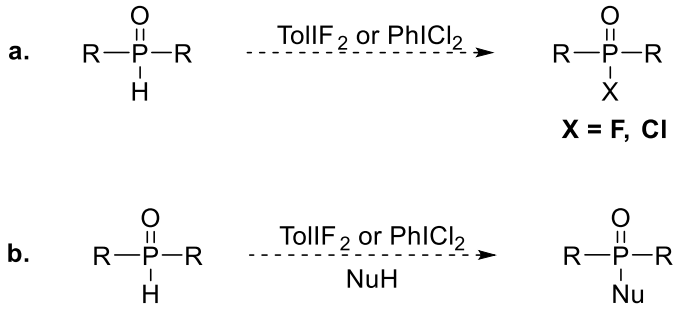


Scheme 2.12: Synthesis of 6-phosphorylated phenanthridines

To the best of our knowledge, (dihaloiodo)arenes have not been explored in the reactions of secondary phosphine oxides.

2.3 Proposal

There are various methods available for the halogenation of secondary phosphine oxides. Though some of them include toxic materials or long reaction times, the yield of the products were generally good.[125-128] The two most recent procedures for the synthesis of phosphinic fluorides were reported by Yang *et al.*[134] and Chen *et al.*[135] Even though these reactions were found to be very useful in the fluorination of secondary phosphine oxides, they were not effective for fluorinating diorganophosphites. Here we propose a new approach to the halogenation of secondary phosphine oxides and diorganophosphites using the commonly found hypervalent iodine reagents $TolIF_2$ and $PhICl_2$ (Scheme 2.13, a). We also propose a one pot synthesis of phosphinates, phosphinamides and phosphinothioates by incorporating O-, N-, and S- nucleophiles in the halogenation step (Scheme 2.13, b).

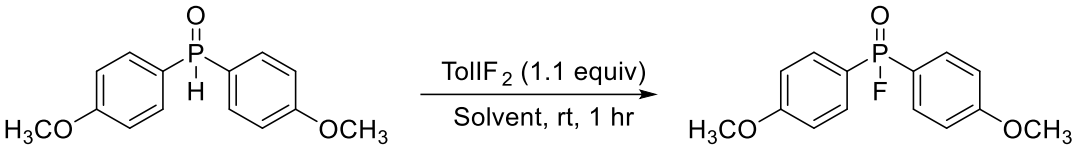


Scheme 2.13: Proposal for the halogenation reactions

2.4 Fluorination of Secondary Phosphine Oxides

The feasibility of the reaction was tested using commercially available diethyl phosphite (**91**). In a typical reaction, 1.0 equivalent of diethyl phosphite, 1.1 equiv of $TolIF_2$ and 0.3 mL of DCM was taken in a round bottom flask under nitrogen atmosphere and stirred at room temperature. The reaction progress was monitored by TLC, and the desired compound was visualized using a potassium permanganate stain. TLC analysis revealed the complete disappearance of diethyl phosphite within six hours. The analysis of the ^{31}P and ^{19}F NMR spectra of the reaction mixtures indicated the formation of diethyl phosphorofluoridate. The chemical shifts for diethyl phosphorofluoridate: a doublet at δ = -81.21 ppm in ^{19}F NMR and a doublet at -8.22 ppm in ^{31}P NMR with $J_{P\text{-}F}$ = 980 Hz and were in agreement with the reported values.[145] The attempt to purify diethyl phosphorofluoridate by flash column chromatography was not successful, presumably due to the hydrolysis of diethyl phosphorofluoridate when it was exposed to silica gel. Due to the toxicity associated with diethyl phosphorofluoridate[126,128,136] the reactions and the purification processes were performed in the fume hood and also, we decided to work with less toxic phosphinic fluorides to optimize the reaction conditions. For this purpose, a number of diaryl- and dialkyl secondary phosphine oxides were synthesized according to the known literature procedures.[118,119]

The synthesis of phosphinic fluorides from secondary phosphine oxides were investigated by using bis(4-methoxyphenyl)phosphine oxide (**92a**) as the model substrate. When 1 equivalent of **92a** was treated with 1.1 equivalent of $TolIF_2$ in 0.25 mL DCM (Table 2.1, entry 1), the starting material was consumed within an hour and both ^{31}P (a doublet at δ = 43.02) and ^{19}F NMR (a doublet at δ = -72.98, J_{P-F} = 1006 Hz) spectra of the crude reaction mixture showed the formation of the corresponding phosphinic fluoride (**97a**) which were in agreement with their reported values.[146] The ^{31}P NMR spectrum of the crude also indicated the formation another compound whose ^{31}P resonance occurred at δ = 35.21 ppm, which we believed to be bis(4-methoxyphenyl)phosphinic acid. Purification of the crude mixture by column chromatography resulted in 50% yield of the product **97a**. The reaction has been conducted in different solvents (Table 2.1) and was feasible in all the solvents tried, irrespective of whether chlorinated (entry 1-4), nonpolar (entry 5) or polar aprotic (entry 6-10). The best result of 58% was obtained using chlorobenzene (entry 3).



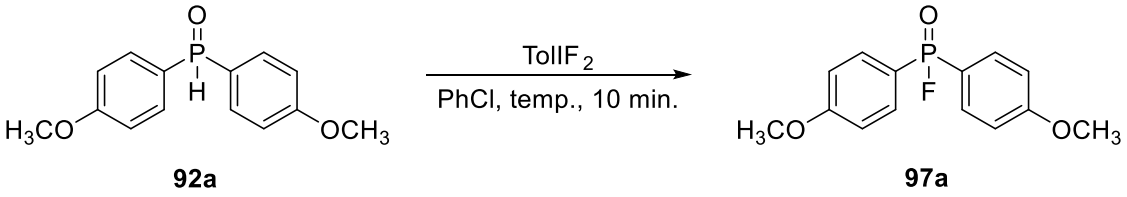
92a **97a**

Entry	Solvent	Yield
1	DCM	50%
2	DCE	53%
3	PhCl	58%
4	$CHCl_3$	46%
5	toluene	51%
6	Et_2O	49%
7	DMF	43%
8	CH_3CN	38%
9	THF	51%
10	CH_3COCH_3	31%

Table 2.1: Solvent screening for the fluorination of secondary phosphine oxides

In an attempt to maximize yield of **97a**, a reaction optimization study was performed. Since the reaction in PhCl gave the best result, it was chosen as the solvent for conducting further reactions. When the reactions were conducted at higher temperatures, a significant increase in the yield of **97a** was observed, and the reaction was completed within 10 minutes. When the oil bath temperature increased to 40 °C, the product yield went to 64% (entry 2, Table 2.2), and when the temperature was 60 °C, the yield was 69% (entry 3). Further increase in temperature did not make any significant difference and the yield started to decrease when the temperature was above 100

°C (entry 5-6). While increasing the loading of $TolIF_2$ did not affect the yield, it dropped to 55% with a decrease in the number of equivalents (entry 7-8).

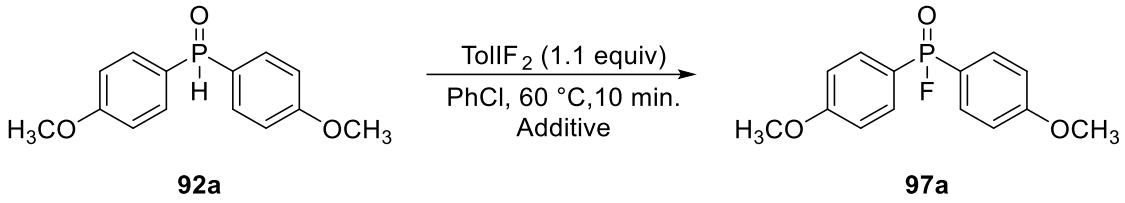


92a **97a**

Entry	$TolIF_2$	Temperature	Yield
1	1.1	rt	58%
2	1.1	40	64%
3	1.1	60	69%
4	1.1	80	69%
5	1.1	110	60%
6	1.1	reflux	64%
7	1.4	60	67%
8	1.02	60	55%

Table 2.2: Effect of temperature and reagent equivalents on fluorination

In some of the previous reactions, we noticed that a Lewis acid can activate $TolIF_2$ which resulted in an increase in the product yield. As per our continuous effort to increase the yield of **97a**, the effect of adding fluorinated Lewis acids to the reaction was studied (Table 2.3). It was found that BF_3•OEt_2 (entry 1-2) gave almost the same yield as without having any Lewis acid, and AlF_3 or GaF_3 (entry 7-8) gave 60 and 64% of the product **97a**, respectively, while with other Lewis acids, the yield dropped.



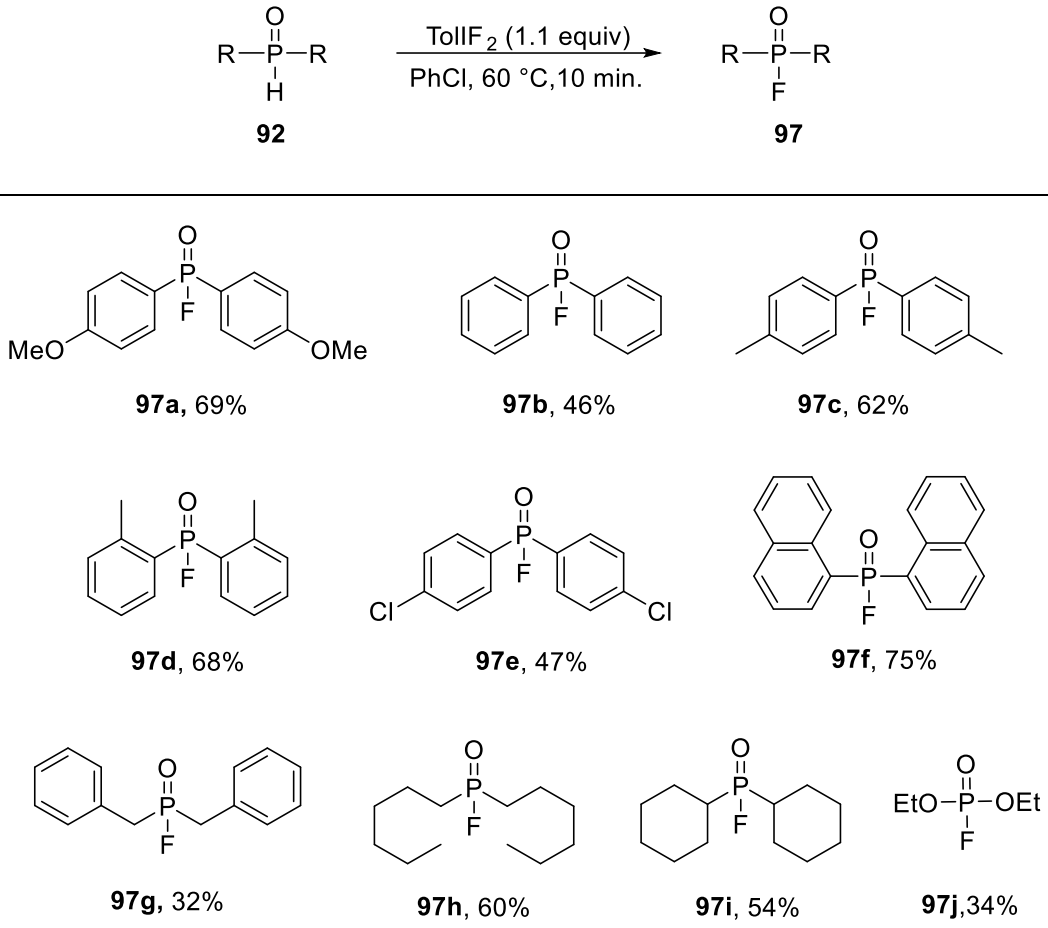
92a **97a**

Entry	Lewis acid	Yield
1	BF_3•OEt_2 (5 mol%)	67%
2	BF_3•OEt_2(10 mol%)	67%
3	TiF_3 (10 mol%)	57%
4	TiF_4 (10 mol%)	52%
5	FeF_3 (10 mol%)	57%
6	InF_3 (10 mol%)	57%
7	AlF_3 (10 mol%)	60%
8	GaF_3 (10 mol%)	64%
9	BiF_3 (10 mol%)	57%

Table 2.3: Effect of Lewis acids on fluorination of secondary phosphine oxides

To expand on the substrate scope of fluorination reactions of secondary phosphine oxides, a series of diaryl- and dialkylphosphine oxides were subjected to the optimized reaction conditions in which 1 equivalent of substrate is added to 1.1 equivalents of $TolIF_2$ in 0.25 mL chlorobenzene under a nitrogen atmosphere and the reaction mixture is stirred at 60 °C. Both dialkyl- and diarylphosphine oxides were compatible with reaction conditions and the corresponding fluorides (**97a-j)** were isolated in 32-75% yield (Scheme 2.14). Diarylphosphines possessing electron donating substituents were all viable and provided phosphinic fluorides (**97a**,**c**,**d**) in moderate yield (62-69%) compared to the parent unsubstituted diphenylphosphinic fluoride (**97b**) which gave only 46%. It is believed that the presence of electron donating substituents on the phenyl ring

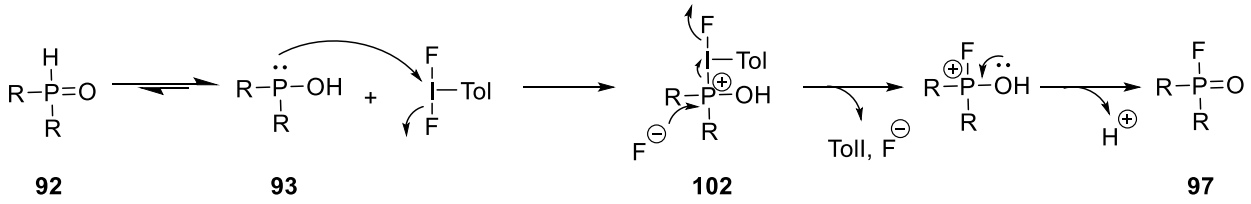
makes the diarylphosphine oxide more nucleophilic and thereby promoting the reaction with the electrophilic iodine on $TolIF_2$. An electron withdrawing substituent on the aromatic ring (**97e**) resulted in a low yield of 47% while di(naphthalen-1-yl)phosphinic fluoride (**97f**) gave the highest yield (75%). From the three dialkylphosphine oxides studied, dibenzyl- derivative (**97g**) gave only 32% yield, while the dihexyl- (**97h**) and dicyclohexylphosphine oxides (**97i**) afforded the corresponding phosphinic fluorides in 60% and 54% yield, respectively. The yield of diethylphosphorofluoridate (**97j**) was only 34%.



Scheme 2.14: Synthesis of phosphinic fluorides

A plausible mechanism for the fluorination of secondary phosphine oxides with $TolIF_2$ is suggested in Scheme 2.15. The secondary phosphine oxide (**92**) tautomerizes to the trivalent

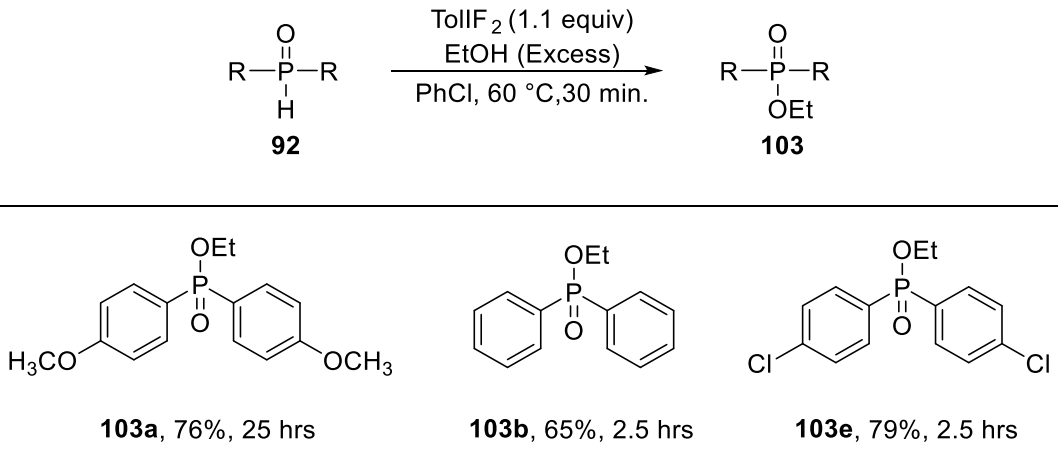
phosphinous acid **93** which acts as a nucleophile. The nucleophilic attack of compound **93** onto the electrophilic iodine centre on $TolIF_2$ leads to the formation of phosphonium ion intermediate **102**. The fluoride ion attacks the phosphonium ion intermediate, expelling TolI to form phosphinic fluoride **97**.



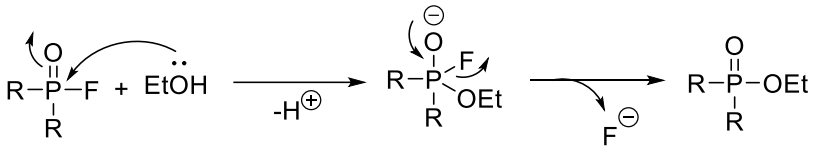
Scheme 2.15: Plausible mechanism for the fluorination of secondary phosphine oxides

It appeared that the formation of bis(4-methoxyphenyl)phosphinic acid may be due to the hydrolysis of **97a** by atmospheric moisture. To avoid this, a reaction was performed in the glove box and the ^{31}P NMR spectrum of the reaction mixture was analyzed and revealed that the signal at $\delta = 35.21$ ppm was still formed. Another possibility for the presence of moisture was either from substrate **92a** or from the reagent $TolIF_2$, but the use of recrystallized substrate and reagent could not prevent the formation of bis(4-methoxyphenyl)phosphinic acid. Even though a reaction was conducted in presence of activated molecular sieves, the result was the same. From the fluorination of secondary phosphine oxides, it was observed that extent of hydrolysis is correlated with the electronic stabilization offered to the phosphinic fluoride by its substituents (**97a** vs **97e**).

When the fluorination of **92a**, **92b** and **92e** were conducted in the presence of excess ethanol, the phosphinates **103a**, **103b**, and **103e** were formed in good yield compared to the fluorinated products (Scheme 2.16). Ethanol underwent further reaction with phosphinic fluorides, leading to the formation of ethyl phosphinates as shown in Scheme 2.17.



Scheme 2.16: Trapping of phosphinic fluorides with excess ethanol

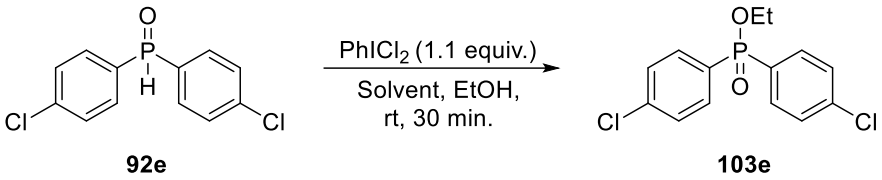


Scheme 2.17: Synthesis of phosphinates from phosphinic fluorides

2.5 Synthesis of Phosphinates via the *in situ* Formation of Phosphinic Chlorides

The success of the fluorination of secondary phosphine oxides led to the investigation of the analogous chlorination reactions using $PhICl_2$. From the previous reactions in our lab, it was observed that iodane based chlorination reactions are more feasible than fluorination.[19] Since fluorination took place with moderate yield, we expected no hurdles in the chlorination reactions. The feasibility of the reaction was tested by using bis(4-chlorophenyl)phosphine oxide (**92e**) as the model substrate. When 1 equiv of the model substrate was treated with 1.1 equivalent of $PhICl_2$ in 0.25 mL DCM, the starting material was consumed within five minutes and analysis of the spectrum of the reaction mixture obtained using ^{31}P NMR spectroscopy revealed a signal at δ 42.05. Unfortunately, there was no reported ^{31}P NMR for this compound to compare with. Analysis

of the crude reaction mixture using GCMS confirmed the formation of bis(4-chlorophenyl)phosphinic chloride. Because our attempts to purify the chlorinated product by column chromatography was unsuccessful, we decided to trap the *in situ* formed phosphinic chloride with excess ethanol. Purification of the crude reaction mixture by column chromatography provided **103e** in 92% yield (entry 1, Table 2.4). The oxidative chlorination reaction gave more than 80% yield in all attempted solvents, except DMF, no matter whether the solvent was chlorinated (entry 1-3), ethereal (entry 7) or nonpolar (entry 5). The reaction conducted in ethanol also gave 83% yield (entry 4) while the yield dropped to 68% in DMF (entry 8). These results are summarized in Table 2.4.

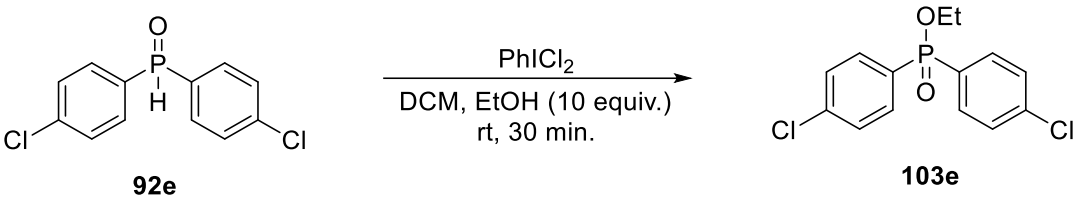


92e **103e**

Entry	Solvent	Yield
1	DCM	92%
2	PhCl	83%
3	DCE	85%
4	EtOH	83%
5	Toluene	85%
6	CH_3CN	83%
7	THF	81%
8	DMF	68%

Table 2.4: Solvent screening for the synthesis of phosphinates

Based on these observations, DCM was chosen to conduct further optimization studies. Because we were using approximately 30 equiv of ethanol for trapping the phosphinic chloride, we decided to reduce it to 10 equiv. When the number of equivalents of EtOH was dropped from 30 to 10, the subsequent drop in the yield was only 7% (Table 2.5, entry 1). So for further reactions, 10 equivalents of EtOH was used to trap phosphinic chlorides. Reducing the number of equivalents of $PhICl_2$ did not affect the yield (entry 2) while an increase in temperature resulted a drop in the yield (entry 3).

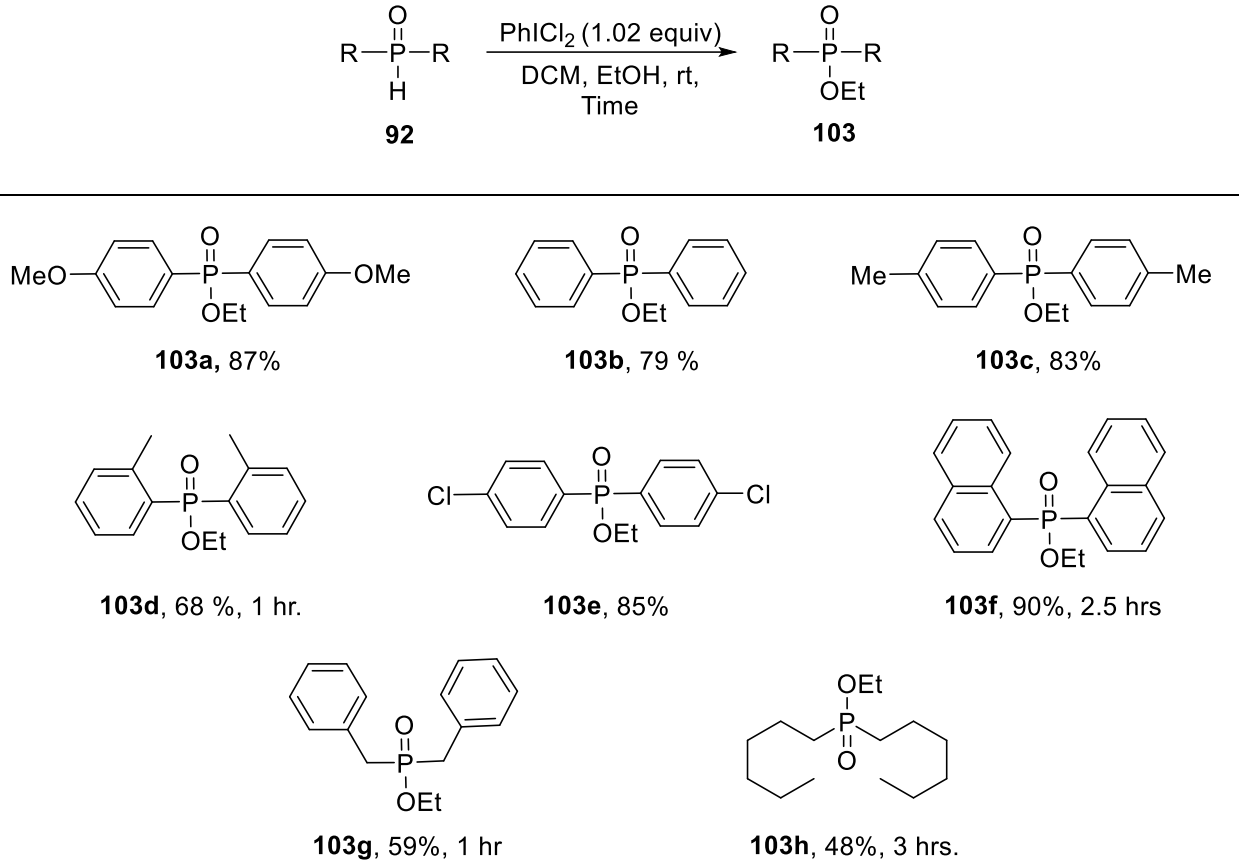


Entry	$PhICl_2$ (equiv)	Temperature	Yield
1	1.1	rt	85%
2	1.02	rt	85%
3	1.02	reflux	79%

Table 2.5: Yield of phosphinates based on temperature and reagent equivalents

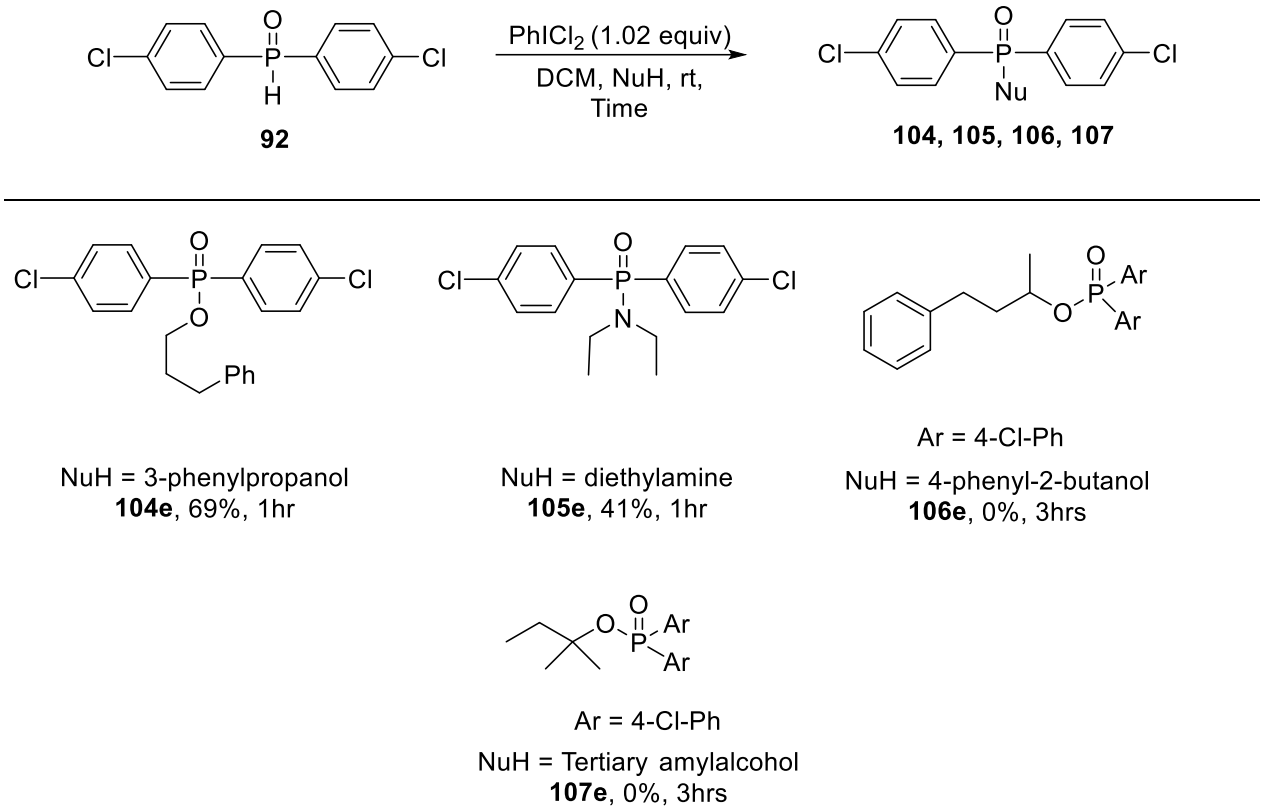
To investigate the scope of the one-pot coupling reaction for the synthesis of phosphinates, we applied the reaction conditions to a variety of secondary phosphine oxides and the results are summarized in Scheme 2.18. All of the diaryl substrates were high yielding, regardless of the substituent on the aryl ring. The ethyl di(naphthalen-1-yl)phosphinate (**103f**) was the highest yielding (90%) while di-*o*-tolylphosphine oxide gave the desired phosphinate (**103d**) in a moderate yield (68%). The yield was lower for dibenzyl (**103g**) and dihexyl (**103h**) derivatives (59% and 48% respectively). With most of the diaryl substrates (**103a-c, e**), the reaction completed within

30 minutes, while in other cases the reaction time varied from 1 to 3 hours. This may be either due to the presence of bulky group (**103d** and **103f**) near to phosphorus or the extra stability of the phosphinic chlorides due to the presence of electron donating group next to phosphorus.



Scheme 2.18: One pot coupling reaction for the synthesis of phosphinates

To test whether the one pot coupling reactions were feasible with other nucleophiles, we conducted reactions involving 3-phenylpropanol and diethylamine with bis(4-chlorophenyl)phosphine oxide (Scheme 2.19). The yield for the corresponding phosphinate and phosphinamide was 67% and 41%, respectively. No phosphinate product formed when secondary and tertiary alcohols were used. The failure to obtain (**106e**, **107e**) might be explained by the steric hindrance between alcohol and bis(4-chlorophenyl)phosphinic chloride.



Scheme 2.19: Synthesis of phosphinates and phosphinamide

An experiment was conducted using ^{31}P NMR spectroscopy to monitor the conversion of secondary phosphine oxide to phosphinate via the formation of the intermediate phosphinic chloride. Since the conversion of di(naphthalen-1-yl)phosphine oxide (**92f**) to phosphinate (**103f**) took 2.5 hours for completion, **92f** was chosen for this study. 1 equiv of **92f** was added to a round bottom flask containing 1.1 equiv of $PhICl_2$ and excess ethanol in DCM. The reaction mixture was stirred for 10 minutes at room temperature and transferred to an NMR tube. The ^{31}P NMR spectrum was acquired at 15 minute intervals. By the time the first NMR was taken, all the starting material (**92f)** was converted to the corresponding phosphinic chloride and part of which already converted to the phosphinate product. The gradual conversion of di(naphthalen-1-yl)phosphinic chloride to the phosphinate **103f** is depicted in Figure 2.4. The ^{31}P NMR study has proven that phosphinates are formed from phosphinic chloride.

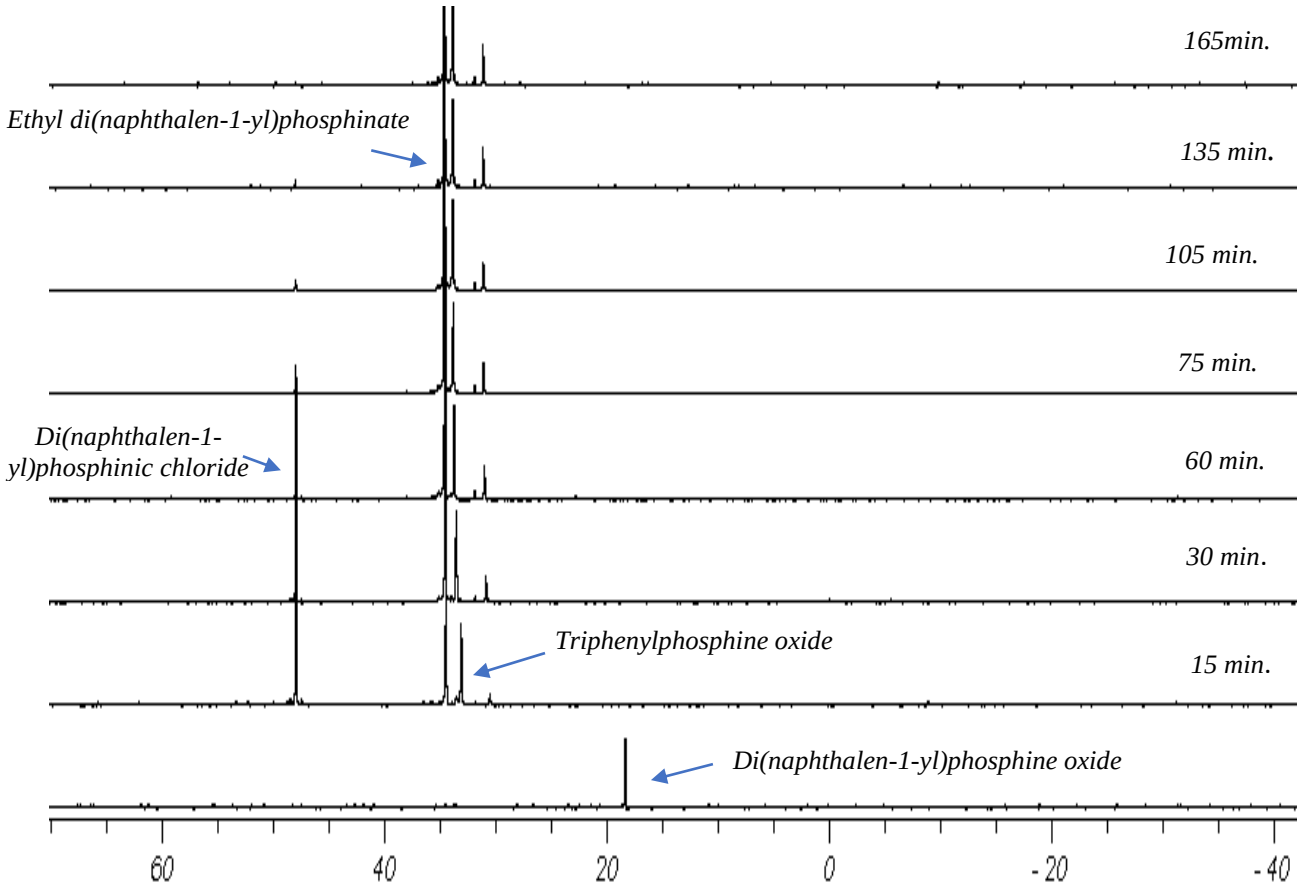


Figure 2.4: Stacked ^{31}P NMR spectra for the conversion of secondary phosphine oxide to phosphinate via phosphinic chloride

2.6 Conclusion

In conclusion, a novel method for the halogenation of secondary phosphine oxides using hypervalent iodine reagents was described. Diarylphosphine oxides having electron donating substituents provided moderately good yields for the fluorination reactions. The fluorination reaction was also feasible with dialkyl phosphine oxides, but the yield was low compared to diarylphosphine oxides. Additionally, the fluorination reaction required only 10 minutes for completion and this method can be extended to include the one pot synthesis of phosphinates. The chlorination reaction provided an easy access to synthesis of phosphinates and phosphinamides by incorporating appropriate nucleophiles in the reaction. The yield for the phosphinates obtained

from diarylphosphine oxides was good (68 - 90%). Dibenzyl and dihexyl phosphinates were obtained in 59% and 48% respectively. Secondary and tertiary alcohols could not produce the corresponding phosphinate. This may be attributed to the steric hindrance between the alcohol and the phosphinic chloride. When diethylamine was used in place of alcohol, the corresponding phosphinamide was produced in 41% yield.

2.7 Experimental Procedures for Chapter 2

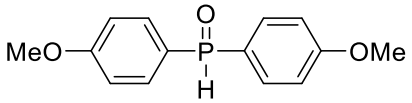
2.7.1 General Experimental Details

Reactions were carried out in oven-dried glassware under a positive nitrogen atmosphere. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes. Solvents were dried and purified using a JC Meyer solvent purification system, and were used without further purification. Thin layer chromatography was performed on glass plates pre-coated with 0.25 mm Kieselgel 60 F254 (Silicycle). Flash chromatography columns were packed with 230-400 mesh silica gel (Silicycle). Proton NMR spectra (^{1}H NMR) were recorded at 300 or 500 MHz, and are reported (ppm) relative to the residual chloroform peak (7.26 ppm) and coupling constants (*J*) are reported in hertz (Hz). Carbon NMR spectra (^{13}C NMR) were recorded at 125 or 75 MHz and are reported (ppm) relative to the center line of the triplet from chloroform-d (77.00 ppm). Phosphorus NMR spectra (^{31}P NMR) were recorded at 121 or 202 MHz, and were reported (ppm) relative to the peak of 85% H_3PO_4 (0 ppm). Fluorine NMR spectra (^{19}F NMR) were recorded at 282 MHz, and were reported (ppm) relative to the peak of trifluoroacetic acid (-76.53 ppm). Mass spectra were performed on a ThermoFisher Scientific Q-Exactive hybrid mass spectrometer using positive electrospray ionization (ESI). Accurate mass was recorded with a mass resolution of 70,000. ESI samples were infused at 5 μL/min in 1:1 CH_3OH/H_2O+0.1% formic acid. Melting points were determined on a Melt-Temp II.

2.7.1 General Procedure A: Synthesis of Secondary Phosphine Oxides

Secondary phosphine oxides are synthesized according to literature procedures with slight deviations.[118,119] Into a 250 mL two neck round bottom flask equipped with an addition flask and condenser, under nitrogen atmosphere, was added magnesium turnings (3.7 equiv.), a pinch of iodine crystals followed by 30 mL THF or diethyl ether. To this was added a small portion of alkyl or aryl bromide (3.6 equiv.) in 10 mL of THF or diethyl ether from the addition flask. If THF was taken as the solvent, the reaction mixture was heated to reflux. Once the reaction started refluxing, the remaining alkyl or aryl bromide was added dropwise. After the addition finished, the addition flask was rinsed with an additional 10 mL THF or diethyl ether. The resulting Grignard reagent was cannulated into another 250 mL two neck round bottom flask under nitrogen atmosphere and cooled to 0 °C. To this was added diethyl phosphite (1.0 equiv.) in 10 mL THF or diethyl ether dropwise from an addition flask. After the addition finished, the additional flask was rinsed with an additional 10 mL THF or diethyl ether and stirred at 0 °C for 15 more minutes. Then, the reaction mixture was allowed to stir for 3-6 hours at ambient temperature. It was again cooled to 0 °C and 40 mL 10% HCl was added dropwise followed by 50 mL diethyl ether. The organic layer was separated and the aqueous layer was extracted two times with 50 mL DCM. The organic layers were combined, dried with anhydrous magnesium sulfate, then filtered. The solvent was evaporated and the crude product was further purified by column chromatography.

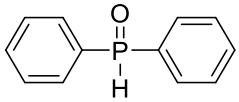
2.7.1.1 Synthesis of Bis(4-methoxyphenyl)phosphine oxide (92a)



General procedure **A** was applied to prepare the Grignard reagent from 4-bromoanisole (5.0 mL, 40 mmol) in diethyl ether and subjected to subsequent reaction with diethyl phosphite (1.4 mL, 10.86 mmol). The crude reaction mixture was purified via column chromatography (4%

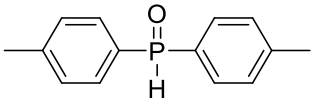
MeOH/EtOAc) to give **92a** (1.96 g, 69% yield) as a white solid. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 21.78 ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.03 (d, J_{P-H} = 477.0 Hz, 1H), 7.63-7.56 (m, 4H), 7.00-6.97 (m, 4H), 3.84 (s, 6H). Spectral data were consistent with literature values.[118]

2.7.1.2 Synthesis of Diphenylphosphine oxide (92b)



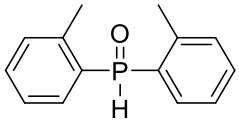
General procedure **A** was applied to prepare the Grignard reagent from bromobenzene (4.2 mL, 10.86 mmol) in diethyl ether and subjected to subsequent reaction with diethyl phosphite (1.4 mL, 10.86 mmol). The crude reaction mixture was purified via column chromatography (4% MeOH/EtOAc) to give **92b** (1.23 g, 56% yield) as a white solid. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 22.37; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 (d, J_{P-H} = 480.0 Hz, 1H), 7.73-7.66 (m, 4H), 7.46-7.47 (m, 6H). Spectral data were consistent with literature values.[118]

2.7.1.3 Synthesis of Di-*p*-tolylphosphine oxide (92c)



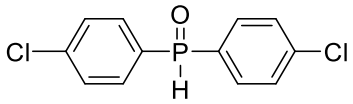
General procedure **A** was applied to prepare the Grignard reagent from 4-bromotoluene (6.8 g, 40 mmol) in diethyl ether and subjected to subsequent reaction with diethyl phosphite (1.7 mL, 13 mmol). The crude reaction mixture was purified via column chromatography (4% MeOH/EtOAc) to give **92c** (1.40 g, 46% yield) as a white solid. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 22.58; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.03 (d, J_{P-H} = 477.0 Hz, 1H), 7.56 (dd, J = 12.0 Hz, J = 9.0 Hz, 4H), 7.31-7.27 (m, 4H), 2.40 (s, 6H). Spectral data were consistent with literature values.[118]

2.7.1.4 Synthesis of Di-*o*-tolylphosphine oxide (92d)



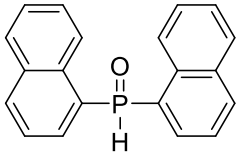
General procedure **A** was applied to prepare the Grignard reagent from 2-bromotoluene (4.8 mL, 40 mmol) in THF and subjected to subsequent reaction with diethyl phosphite (1.4 mL, 10.86 mmol). The crude reaction mixture was purified via column chromatography (EtOAc) to give **92d** (1.96 g, 79% yield) as a white solid. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 18.60 ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.19 (d, J_{P-H} = 474.0 Hz, 1H), 7.70 (dd, J = 15.0 Hz, J = 9.0 Hz, 2H), 7.45 (t, J = 6.0 Hz, 2H), 7.31 (t, J = 9.0 Hz, 2H), 7.24-7.21 (m, 2H), 2.36 (s, 6H). Spectral data were consistent with literature values.[118]

2.7.1.5 Synthesis of Bis(4-chlorophenyl)phosphine oxide (92e)



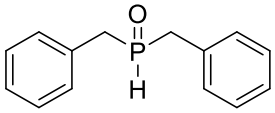
General procedure **A** was applied to prepare the Grignard reagent from 1-bromo-4-chlorobenzene (7.61 g, 40 mmol) in THF and subjected to subsequent reaction with diethyl phosphite (1.4 mL, 10.86 mmol). The crude reaction mixture was purified via column chromatography (80% EtOAc/hexanes) to give **92e** (2.29 g, 78% yield) as a white solid. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 19.80; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (d, J_{P-H} = 420.0 Hz, 1H), 7.65-7.58 (m, 4H), 7.51-7.47 (m, 4H). Spectral data were consistent with literature values.[118]

2.7.1.6 Synthesis of Di(naphthalen-1-yl)phosphine oxide (92f)



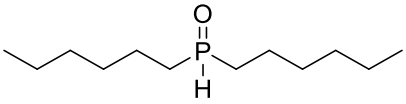
General procedure **A** was applied to prepare the titled Grignard reagent from 1-bromonaphthalene (5.6 mL, 40 mmol) in THF and subjected to subsequent reaction with diethyl phosphite (1.4 mL, 10.86 mmol). The crude reaction mixture was purified via column chromatography (80% EtOAc/hexanes) to give **92f** (2.11 g, 64% yield) as a white solid. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 18.27 ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.91 (d, J_{P-H} = 483.0 Hz, 1H), 8.38-8.34 (m, 2H), 8.08-8.05 (m, 2H), 8.01-7.98 (m, 1H), 7.95-7.91 (m, 3H), 7.57-7.52 (m, 6H). Spectral data were consistent with literature values.[147]

2.7.1.7 Synthesis of Dibenzylphosphine oxide (92g)



General procedure **A** was applied to prepare the titled Grignard reagent from benzylbromide (4.8 mL, 40 mmol) in diethyl ether and subjected to subsequent reaction with diethyl phosphite (1.7 mL, 13 mmol). The crude reaction mixture was purified via column chromatography (1% MeOH/EtOAc) to give **92g** (0.90 g, 30% yield) as a white solid. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 37.20 ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.27 (m, 6H), 7.21-7.18 (m, 4H), 6.97 (d, J_{P-H} = 471.0 Hz, 1H), 3.18 (d, J = 15.0 Hz, 4H). Spectral data were consistent with literature values.[148,119]

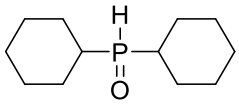
2.7.1.8 Synthesis of Dihexylphosphine oxide (92h)



General procedure **A** was applied to prepare the titled Grignard reagent from 1-bromohexane (5.6 mL, 40 mmol) in THF and subjected to subsequent reaction with diethyl phosphite (1.4 mL, 10.86 mmol). The white solid obtained after evaporating the solvent then recrystallized from hexanes to give the product **92h** (1.33 g, 56% yield). **^{31}P NMR** (121 MHz, $CDCl_3$) δ 36.10; **^{1}H NMR** (300

MHz, $CDCl_3$) δ 6.85 (d, J_{P-H} = 447.0 Hz, 1H), 1.83-1.59 (m, 10H), 1.43-1.27 (m, 10H), 0.88 (t, *J* = 6.0 Hz, 6H). Spectral data were consistent with literature values.[149]

2.7.1.9 Synthesis of Dicyclohexylphosphine oxide (92i)

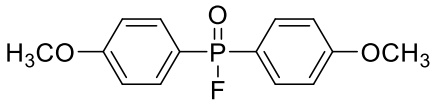


Into a 250 mL two neck round bottom flask equipped with an addition flask and condenser, under nitrogen atmosphere, was added magnesium turnings (0.83 g) and a pinch of iodine crystals. To this was added bromocyclohexane (4 mL, 32.5 mmol.) in 60 mL of diethyl ether dropwise from the addition flask with light heating (30 °C). After the addition finished, the reaction was heated to reflux for 1 hour. The reaction was then cooled to room temperature and then further cooled to -78 °C. To this was added diphenyl phosphite (1.6 ml, 8.5 mmol) in 60 mL of diethyl ether dropwise from an addition flask. The reaction was allowed to warm to room temperature overnight. The reaction was quenched by adding 35 g potassium carbonate in 50 ml ice water followed by filtration. The organic phase was separated and washed with water followed by saturated brine. The organic phase was then dried over magnesium sulfate, filtered, evaporated to dryness, and purified by column chromatography (2%EtOH/EtOAc) to give **92i** (0.17 g, 9.34%) as a white solid. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 50.66; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.32 (d, J_{P-H} = 429.0 Hz, 1H), 2.01-1.28 (m, 22H). Spectral data were consistent with literature values.[150]

2.7.2 General Procedure B: Synthesis of Phosphinic fluorides (97)

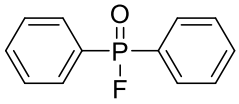
Into a round bottom flask was added *p*-(difluoroiodo) toluene (1.1 equiv), PhCl (0.25 mL), and the secondary phosphine oxide (1 equiv). The reaction mixture was stirred at 60 °C in an oil bath for 10 minutes, cooled, and then purified by column chromatography (ether/pentane).

2.7.2.1 Synthesis of Bis(4-methoxyphenyl)phosphinic fluoride (97a)



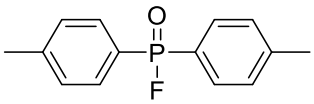
Bis(4-methoxyphenyl)phosphine oxide (0.039 g, 0.15 mmol) was subjected to General Procedure **B**. The crude reaction mixture was purified via column chromatography (ether) to give **97a** (0.029 g, 69% yield) as a colourless oil which solidified upon standing. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -72.98 (d, *J* = 1006.7 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$) δ 43.02 (d, *J* = 1003.1 Hz); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.75-7.68 (m, 4H), 6.99-6.95 (m, 4H), 3.83 (s, 6H). Spectral data were consistent with literature values.[146]

2.7.2.2 Synthesis of Diphenylphosphinic fluoride (97b)



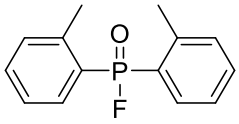
Diphenylphosphine oxide (0.030 g, 0.15 mmol) was subjected to General Procedure **B**. The crude reaction mixture was purified via column chromatography (80% ether/pentane) to give **97b** (15 mg, 46% yield) as a colourless oil. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -75.63 (d, *J* = 1018.0 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$) δ 41.90 (d, *J* = 1015.2 Hz); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.85-7.78 (m, 4H), 7.64-7.58 (m, 2H), 7.53-7.47 (m, 4H). Spectral data were consistent with literature values.[146]

2.7.2.3 Synthesis of Di-*p*-tolylphosphinic fluoride (97c)



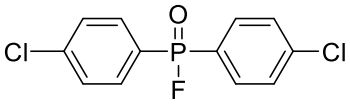
Di-*p*-tolylphosphine oxide (0.035 g, 0.15 mmol) was subjected to General Procedure **B**. The crude reaction mixture was purified via column chromatography (50% ether/pentane) to give **97c** (0.023 g, 62% yield) as a white solid. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -74.64 (d, *J* = 1012.4 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$) δ 43.23 (d, *J* = 1011.6 Hz); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.72-7.65 (m, 4H), 7.31-7.27 (m, 4H), 2.40 (s, 6H). Spectral data were consistent with literature values.[146]

2.7.2.4 Synthesis of Di-*o*-tolylphosphinic fluoride (97d)



Di-*o*-tolylphosphine oxide (0.035 g, 0.15 mmol) was subjected to General Procedure **B**. The crude reaction mixture was purified via column chromatography (50% ether/pentane) to give **97d** (0.025 g, 68% yield) as a colourless solid. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -75.44 (d, *J* = 1015.2 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$) δ 44.24 (d, *J* = 1016.4 Hz); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82-7.75 (m, 2H), 7.49 (t, 2H, *J* = 7.5 Hz), 7.33-7.24 (m, 4H), 2.43 (s, 6H). Spectral data were consistent with literature values.[146]

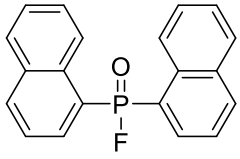
2.7.2.5 Synthesis of Bis(4-chlorophenyl)phosphinic fluoride (97e)



Bis(4-chlorophenyl)phosphine oxide (0.041 g, 0.15 mmol) was subjected to General Procedure **B**. The crude reaction mixture was purified via column chromatography, acidifying the stationary phase with 1% acetic acid in pentane (50% ether/pentane) to give **97e** (0.020 g, 47% yield) as a colourless oil. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -74.27 (d, *J* = 1020.8 Hz); **^{31}P NMR** (121 MHz,

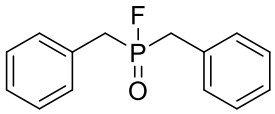
$CDCl_3$) δ 39.76 (d, *J* = 1016.4 Hz); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77-7.70 (m, 4H), 7.52-7.48 (m, 4H). Spectral data were consistent with literature values.[135]

2.7.2.6 Synthesis of Di(naphthalen-1-yl)phosphinic fluoride (97f)



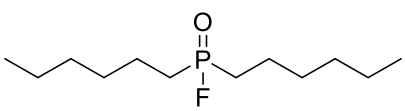
Di(naphthalen-1-yl)phosphine oxide (0.046 g, 0.15 mmol) was subjected to General Procedure **B**. The crude reaction mixture was purified via column chromatography (50% ether/pentane) to give **97f** (0.036 g, 75% yield) as a white solid. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -68.48 (d, *J* = 1018.0 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$) δ 45.47 (d, *J* = 1011.6 Hz); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.54-8.52 (m, 2H), 8.11-7.98 (m, 4H), 7.94-7.90 (m, 2H), 7.58-7.47 (m, 6H). Spectral data were consistent with literature values.[135]

2.7.2.7 Synthesis of Dibenzylphosphinic fluoride (97g)



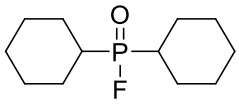
Dibenzylphosphine oxide (0.034 g, 0.15 mmol) was subjected to General Procedure **B**. The crude reaction mixture was purified via column chromatography (ether) to give **97g** (0.012 g, 32% yield) as a colourless oil. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -77.06 (d, *J* = 1037.8 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$) δ 59.79 (d, *J* = 1034.6 Hz); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37-7.29 (m, 6H), 7.25-7.21 (m, 4H), 3.22 (dd, *J* = 16.5, *J* = 9 Hz, 4H). Spectral data were consistent with literature values.[135]

2.7.2.8 Synthesis of Dihexylphosphinic fluoride (97h)



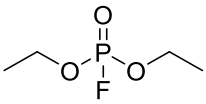
Dihexylphosphine oxide (0.033 g, 0.15 mmol) was subjected to General Procedure **B**. The reaction mixture was stirred at 60 °C in an oil bath for 30 minutes and the crude reaction mixture was purified via column chromatography (80% ether/pentane) by rendering the stationary phase acidic with 1% acetic acid in eluent to give **97h** (0.021 g, 60% yield) as a colourless oil which turned to a white solid gradually. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -78.67 (d, *J* = 1012.4 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$) δ 71.46 (d, *J* = 1012.8 Hz); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.88-1.76 (m, 4H), 1.69-1.55 (m, 4H), δ 1.44-1.25 (m, 12H), 0.87 (t, *J* = 6.0 Hz, 6H). Spectral data were consistent with literature values.[135]

2.7.2.9 Synthesis of Dicyclohexylphosphinic fluoride (97i)



Dicyclohexylphosphine oxide (0.032 g, 0.15 mmol) was subjected to General Procedure **B**. The reaction mixture was stirred at 60 °C in an oil bath for 30 minutes and the crude reaction mixture was purified via column chromatography (ether) by rendering the stationary phase acidic with 1% acetic acid in 50% ether/pentane to give **97i** (0.019 g, 54% yield) as a colourless needle like crystals. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -95.11 (d, *J* = 1034.9 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$) δ 72.04 (d, *J* = 1032.1 Hz); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.04-1.24 (m, 22H) Spectral data were consistent with literature values.[146]

2.7.2.10 Synthesis of Diethylphosphorofluoridate (97j)



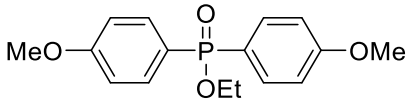
Diethyl phosphite (19 µL, 0.15 mmol) was subjected to General Procedure **B**. The crude reaction mixture was purified via column chromatography (ether) by rendering the stationary phase acidic

with 1% acetic acid in 50% ether/pentane to give **97j** (7.80 mg, 34% yield) as a colourless oil. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -81.24 (d, *J* = 975.7 Hz); **^{31}P NMR** (121 MHz, $CDCl_3$) δ -8.06 (d, *J* = 975.3 Hz); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.25 (q, *J* = 6.0 Hz, 4H), 1.38 (t, *J* = 6.0 Hz, 6H). Spectral data were consistent with literature values.[145]

2.7.3 General Procedure C: Synthesis of Phosphinates (103)

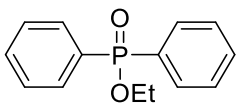
Into a round bottom flask was added dichloroiodobenzene (1.02 equiv), DCM (0.25 mL), and to this was added excess ethanol (0.1 mL) and the secondary phosphine oxide (1 equiv). The reaction mixture was stirred at room temperature for 30 minutes to 3 hours, concentrated *in vacuo*, then purified by column chromatography.

2.7.3.1 Synthesis of Ethyl bis(4-methoxyphenyl)phosphinate (103a)



Bis(4-methoxyphenyl)phosphine oxide (0.039 g, 0.15 mmol) was subjected to General Procedure **C** for 30 minutes. The crude reaction mixture was purified via column chromatography (EtOAc) to give **103a** (0.040 g, 87% yield) as a colourless oil. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 33.20; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.73-7.67 (m, 4H), 6.93-6.91 (m, 4H), 4.04 (*app.*quint, *J* = 6.0 Hz, 2H), 3.80 (s,6H), 1.32 (t, *J* = 6.0 Hz, 3H). Spectral data were consistent with literature values.[151]

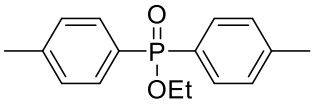
2.7.3.2 Synthesis of Ethyl diphenylphosphinate (103b)



Diphenylphosphine oxide (0.031 g, 0.15 mmol) was subjected to General Procedure **C** for 30 minutes. The crude reaction mixture was purified via column chromatography (80%

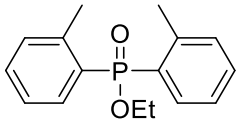
EtOAc/hexanes) to give **103b** (0.030 g, 79% yield) as a colourless oil. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 32.38; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.83-7.77 (m, 4H), 7.52-7.39 (m, 6H), 4.09 (*app.*quint, *J* = 6.0 Hz, 2H), 1.35(t, *J* = 6.0 Hz, 3H). Spectral data were consistent with literature values.[135]

2.7.3.3 Synthesis of Ethyl di-*p*-tolylphosphinate (103c)



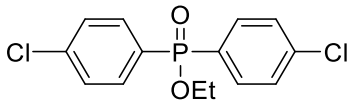
Di-*p*-tolylphosphine oxide (0.035 g, 0.15 mmol) was subjected to General Procedure **C** for 30 minutes. The crude reaction mixture was purified via column chromatography (50% EtOAc/hexanes) to give **103c** (0.034 g, 83% yield) as a colourless oil. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 33.22; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.70-7.64 (m, 4H), 7.24-7.21 (m, 4H), 4.05 (*app.*quint, *J* = 6.0 Hz, 2H), 2.35 (s, 6H), 1.33(t, *J* = 6.0 Hz, 3H). Spectral data were consistent with literature values.[151]

2.7.3.4 Synthesis of Ethyl di-*o*-tolylphosphinate (103d)



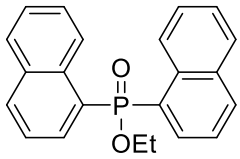
Di-*o*-tolylphosphine oxide (0.035 g, 0.15 mmol) was subjected to General Procedure **C** for 1 hour. The crude reaction mixture was purified via column chromatography (50% EtOAc/hexanes) to give **103d** (0.028 g, 68% yield) as a colourless oil. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 33.27; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92-7.86 (m, 2H), 7.39 (t, *J* = 6.0 Hz, 2H) 7.29-7.25 (m, 2H), 7.19-7.15 (m, 2H), 4.13-4.04 (m, 2H), 2.35 (s, 6H), 1.37(t, *J* = 6.0 Hz, 3H). Spectral data were consistent with literature values.[152]

2.7.3.5 Synthesis of Ethyl bis(4-chlorophenyl)phosphinate (103e)



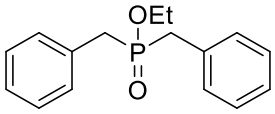
Bis(4-chlorophenyl)phosphine oxide (0.040 g, 0.15 mmol) was subjected to General Procedure **C** for 30 minutes. The crude reaction mixture was purified via column chromatography (50% EtOAc/hexanes) to give **103e** (0.040 g, 85% yield) as a colourless oil. **^{31}P NMR** (121 MHz, $CDCl_3$) δ 30.52; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.75-7.68 (m, 4H), 7.44-7.41 (m, 4H), 4.09 (*app*.quint, *J* = 6.0 Hz, 2H), 1.36 (t, *J* = 6.0 Hz, 3H). Spectral data were consistent with literature values.[135]

2.7.3.6 Synthesis of Ethyl di(naphthalen-1-yl)phosphinate (103f)



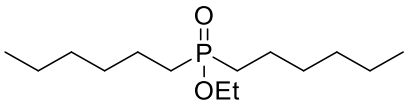
Di(naphthalen-1-yl)phosphine oxide (0.046 g, 0.15 mmol) was subjected to General Procedure **C** for 2.5 hours. The crude reaction mixture was purified via column chromatography (50% EtOAc/hexanes) to give **103f** (0.047 g, 90% yield) as a colourless oil. **IR** (ATR) 3048, 2981, 1591, 1569, 1487, 1247, 1080, 788 cm^{-1}; **^{31}P NMR** (121 MHz, $CDCl_3$) δ 35.16; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.62-8.60 (m, 2H), 8.15 (dd, *J* = 15 Hz, *J* = 6.0 Hz, 2H), 8.01 (d, *J* = 9.0 Hz, 2H), 7.87-7.84 (m, 2H), 7.52-7.47(m, 6H), 4.25-4.16(m, 2H), 1.38(t, *J* = 6.0 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.1 (d, *J* = 10.5 Hz), 133.7 (d, *J* = 10.5 Hz), 133.5 (d, *J* = 7.5 Hz), 133.0 (d, *J* = 9.8 Hz), 128.9, 128.9, 127.1, 126.9 (d, *J* = 78.8 Hz), 126.6 (d, *J* = 5.3 Hz), 124.7 (d, *J* = 14.3 Hz), 61.4 (d, *J* = 6.0 Hz), 16.5 (d, *J* = 6.8 Hz); **LRMS** (ESI) calcd for $C_{22}H_{19}O_2P$ $(M+H)^+$ 347.11; found 347.25.

2.7.3.7 Synthesis of Ethyl dibenzylphosphinate (103g)



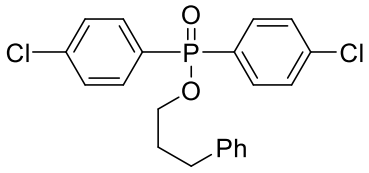
Dibenzylphosphine oxide (0.034 g, 0.15 mmol) was subjected to General Procedure **C** for 1 hour. The crude reaction mixture was purified via column chromatography (80% EtOAc/hexanes) to give **103g** (0.024 g, 59% yield) as a colourless oil. **IR** (ATR) 3048, 3013, 2904, 1602, 1560, 1465, 1351, 1112, 1083, 881 cm^{-1}; **^{31}P NMR** (121 MHz, $CDCl_3$) δ 48.84; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30-7.22 (m, 10H), 3.87 (*app.*quint, *J* = 6.0 Hz, 2H), 3.07 (d, *J* = 15 Hz, 4H), 1.14 (t, *J* = 6.0 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 131.6, 131.5, 129.9 (d, *J* = 6.0 Hz), 128.6.(d, *J* = 3.0 Hz), 126.9 (d, *J* = 3.0 Hz), 61.1 (d, *J* = 6.8 Hz), 36.1 (d, *J* = 86.3 Hz), 16.5 (d, *J* = 6.0 Hz); **LRMS** (ESI) calcd for $C_{16}H_{19}O_2P$ $(M+H)^+$ 275.11;found 275.17.

2.7.3.8 Synthesis of Ethyl dihexylphosphinate (103h)



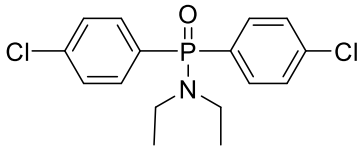
Dihexyllphosphine oxide (0.033 g, 0.15 mmol) was subjected to General Procedure **C** for 3 hours. The crude reaction mixture was purified via column chromatography (2% MeOH/EtOAc) to give **103h** (19 mg, 48% yield) as a colourless oil. **IR** (ATR) 2884, 2859, 2064, 1720, 1426, 1331, 1126, 1038, 946 cm^{-1}; **^{31}P NMR** (121 MHz, $CDCl_3$) δ 59.32**; ^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.02 (*app.*quint, *J* = 6.0 Hz, 2H), 1.72-1.62 (m, 4H), 1.57-1.47 (m, 4H), 1.37-1.26 (m, 15H), 0.86 (t, *J* = 6.0 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 59.9 (d, *J* = 6.8 Hz), 31.2, 30.5 (d, *J* = 15.0 Hz), 28.1 (d, *J* = 88.5 Hz), 22.3, 21.7 (d, *J* = 3.8 Hz), 16.6 (d, *J* = 6.0 Hz); **LRMS** (ESI) calcd for $C_{14}H_{31}O_2P$ $(M+H)^+$ 264.21;found 264.25.

2.7.3.9 Synthesis of 3-Phenylpropyl bis(4-chlorophenyl)phosphinate (104e)



Bis(4-chlorophenyl)phosphine oxide (0.041 g, 0.15mmol) was subjected to General Procedure **C** for 1 hour using 3-phenylpropanol instead of ethanol. The crude reaction mixture was purified via column chromatography (50% EtOAc/hexanes) to give **104e** (0.042 g, 69% yield) as a colourless oil. **IR** (ATR) 3051, 2997, 1691, 1462, 1104, 1018, 806, 761, 622 cm^{-1}, **^{31}P NMR** (121 MHz, $CDCl_3$) δ 30.03; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.72-7.66 (m, 4H), 7.44-7.40 (m, 4H), 7.29-7.24 (m, 2H), 7.20-7.13 (m, 3H), 4.01 (q, *J* = 6.0 Hz, 2H), 2.73 (t, *J* = 6.0 Hz, 2H), 2.09-2.00 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 140.6, 139.0 (d, *J* = 3.0 Hz), 133.1, 132.9, 129.7 (d, *J* = 139.5 Hz), 129.1 (d, *J* = 13.5 Hz), 128.5, (d, *J* = 6.8 Hz), 126.1, 64.6 (d, *J* = 6.0 Hz), 32.0 (d, *J* = 6.8 Hz), 31.9; **LRMS** (ESI) calcd for $C_{21}H_{19}Cl_2O_2P$ ($M^{+\cdot}$)405.05; found 405.17 and 407.08.

2.7.3.10 Synthesis of *P,P*-bis(4-chlorophenyl)-*N,N*-diethylphosphinic amide (105e)



Into a round bottom flask was added dichloroiodobenzene (1.02 equiv), DCM (0.25 mL), and to this was added the secondary phosphine oxide (1 equiv). The reaction mixture was stirred at room temperature for 5 minutes and diethyl amine (10 equiv) was added to this over two minutes and stirred at room temperature for 1 hour. The crude reaction mixture was purified via column chromatography (EtOAc) to give **105e** (0.021 g, 41% yield) as a colourless oil. **IR** (ATR) 3012, 2976, 1583, 1481, 1019, 1013, 975, 732, 603 cm^{-1}; **^{31}P NMR** (121 MHz, $CDCl_3$) δ 29.81; **^{1}H NMR**

(300 MHz, $CDCl_3$) δ 7.81-7.77(m, 4H), 7.46-7.44 (m, 4H), 3.10-3.03 (m, 4H), 1.12 (t, *J* = 6.0 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.4 (d, *J* = 3.8 Hz), 133.7 (d, *J* = 9.8 Hz), 130.7 (d, *J* = 130.5 Hz), 128.9 (d, *J* = 12.8 Hz), 39.3 (d, *J* = 3.8 Hz), 14.1 (d, *J* = 4.5 Hz); **LRMS** (ESI) calcd for $C_{16}H_{18}Cl_2NOP$ ($M^{+\cdot}$)342.05; found 342.17 and 344.17.

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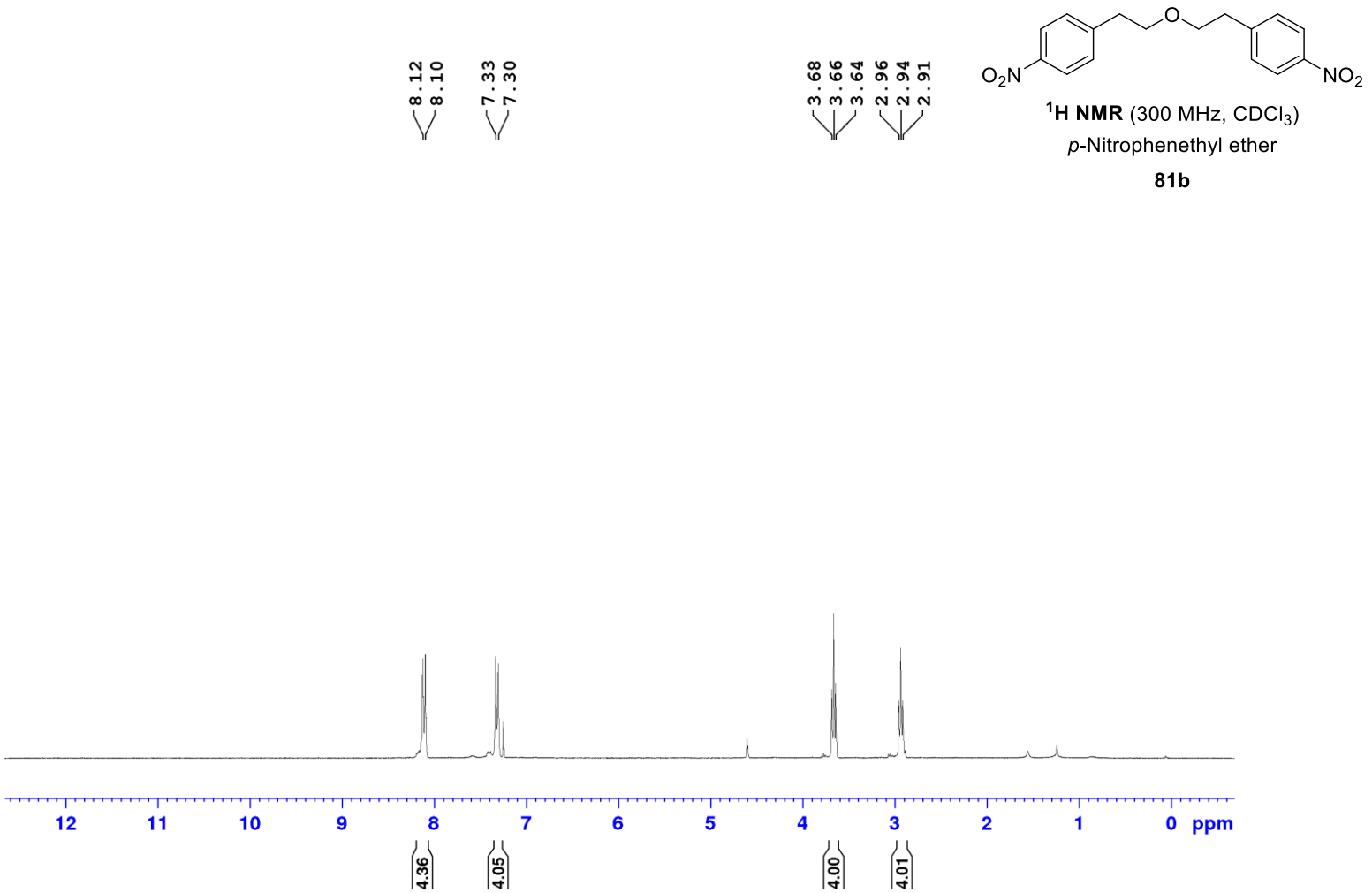
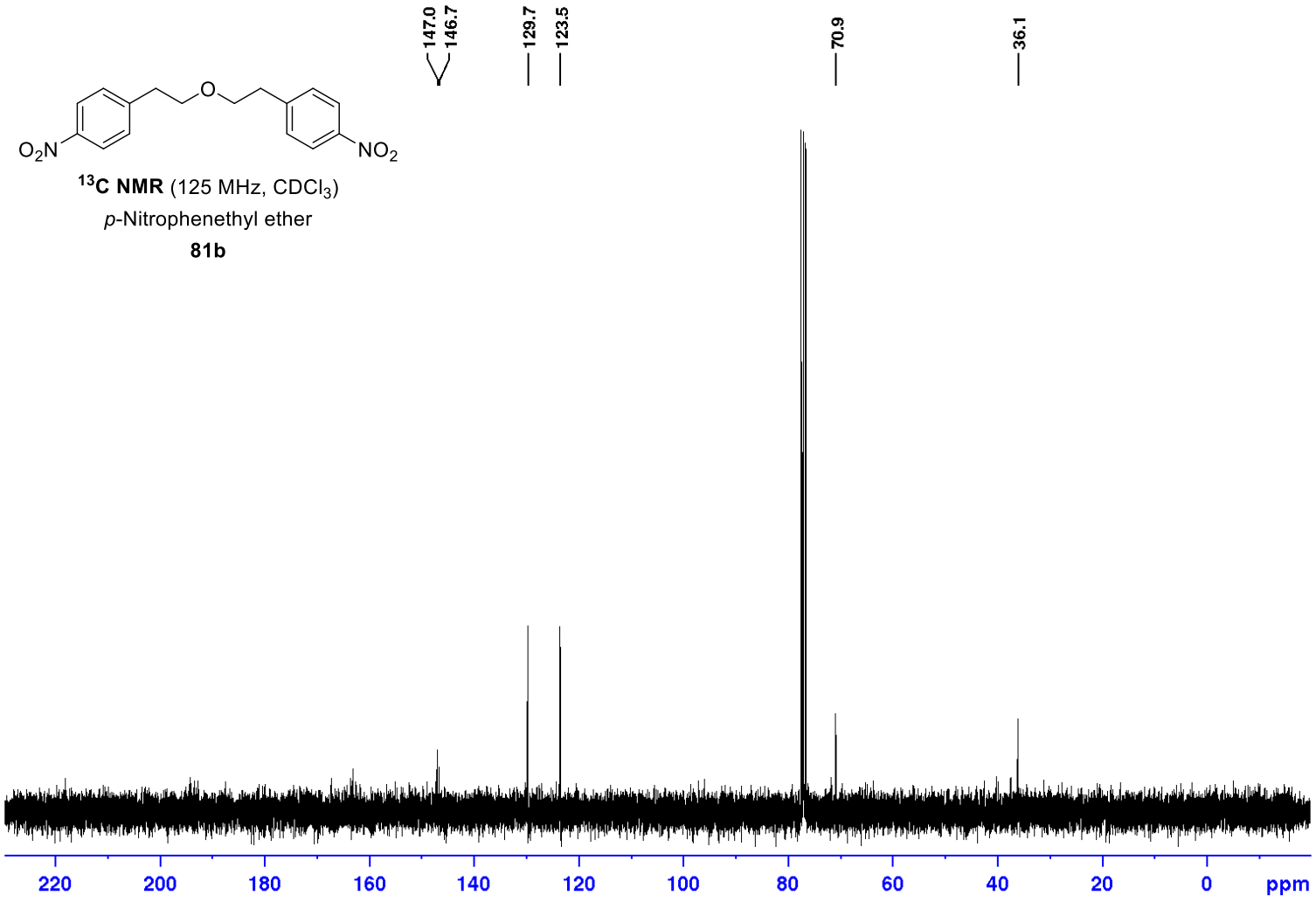
APPENDIX A: CHAPTER 1 NMR SPECTRA

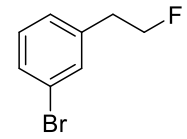




^{13}C NMR (125 MHz, $CDCl_3$)

p-Nitrophenethyl ether

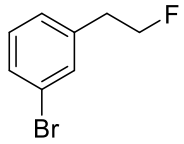
81b

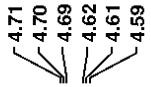


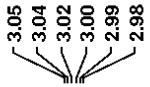
^{19}F NMR (282 MHz, $CDCl_3$)

3-(2-Fluoroethyl)-
1-bromobenzene

80f



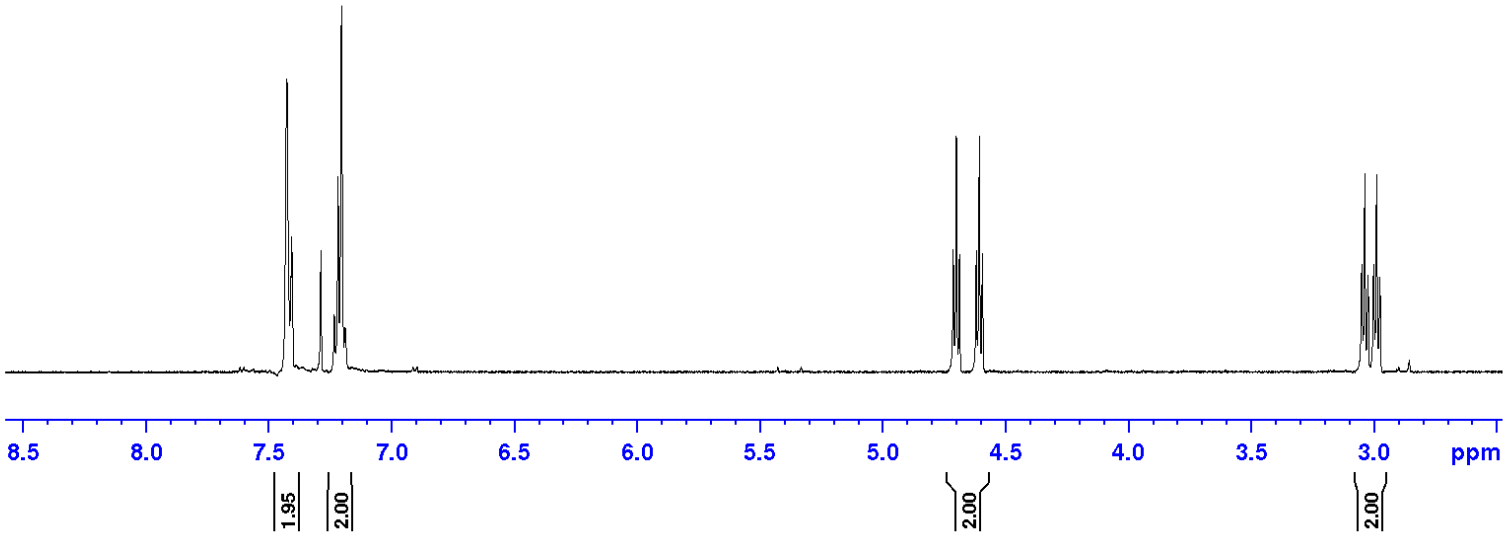


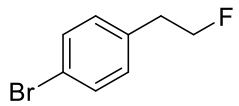


^{1}H NMR (300 MHz, $CDCl_3$)

3-(2-Fluoroethyl)-
1-bromobenzene

80f

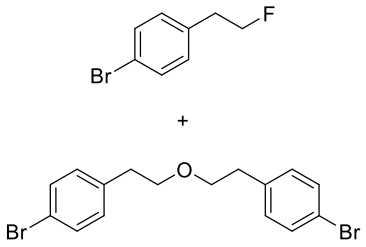




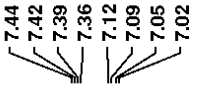
^{19}F NMR (282 MHz, $CDCl_3$)

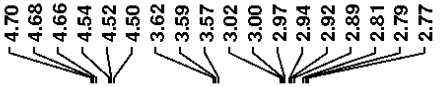
1-Bromo-4-(2-fluoroethyl)-benzene

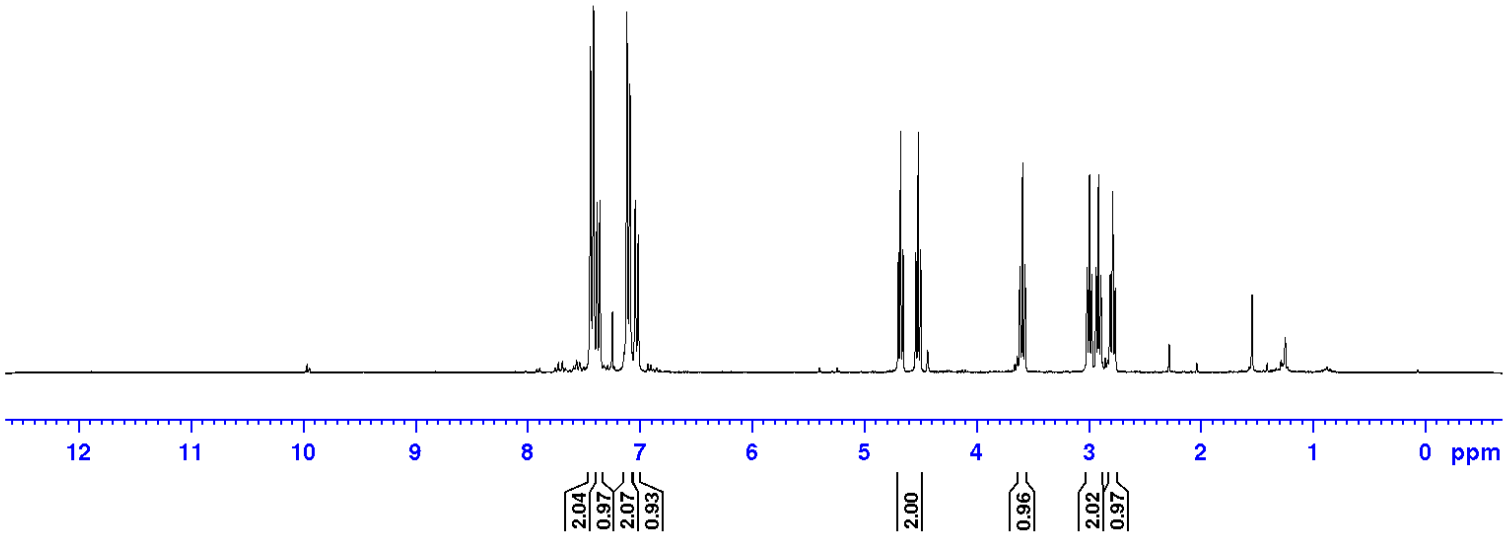
80g

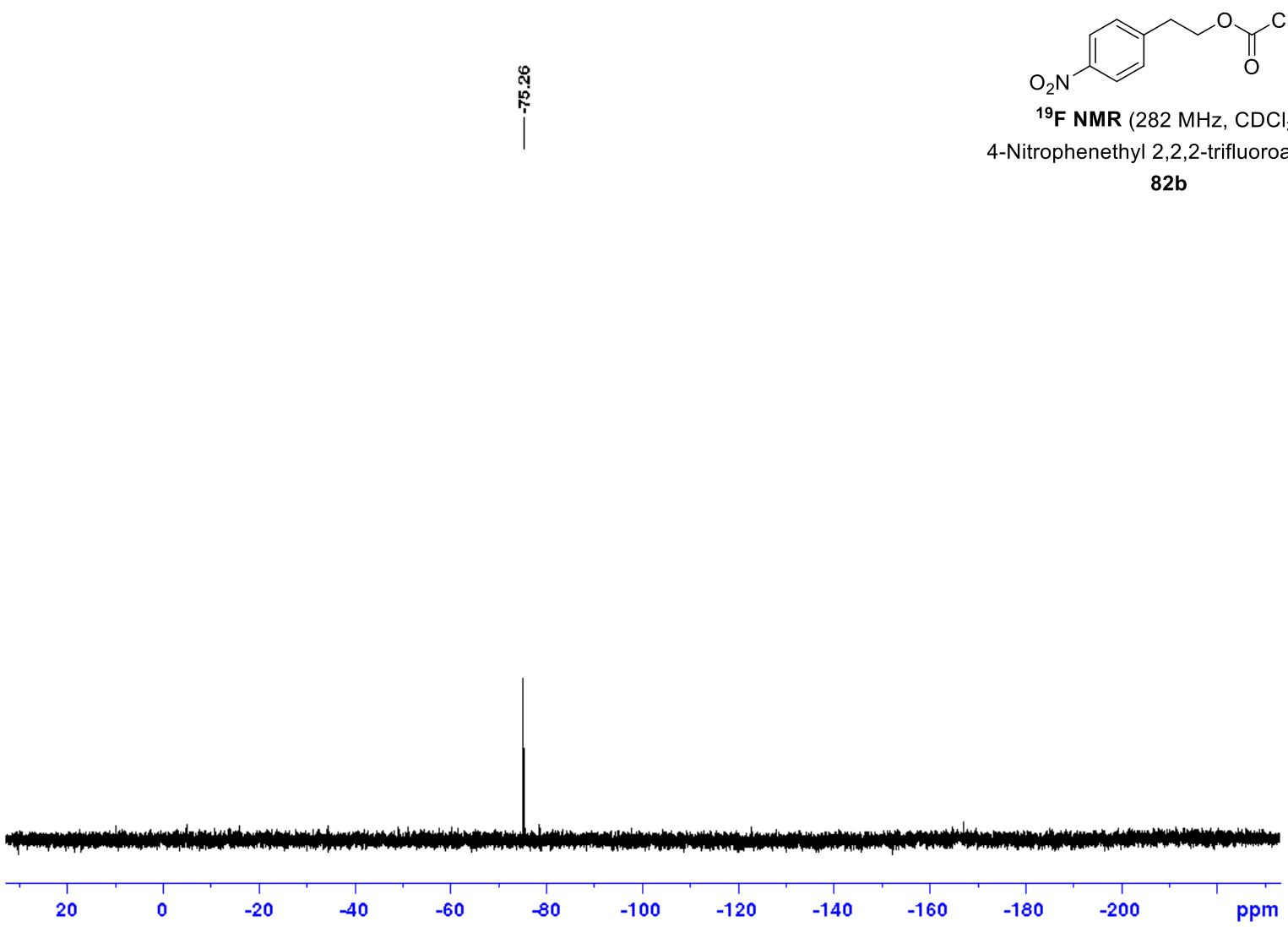


^{1}H NMR (300 MHz, $CDCl_3$)





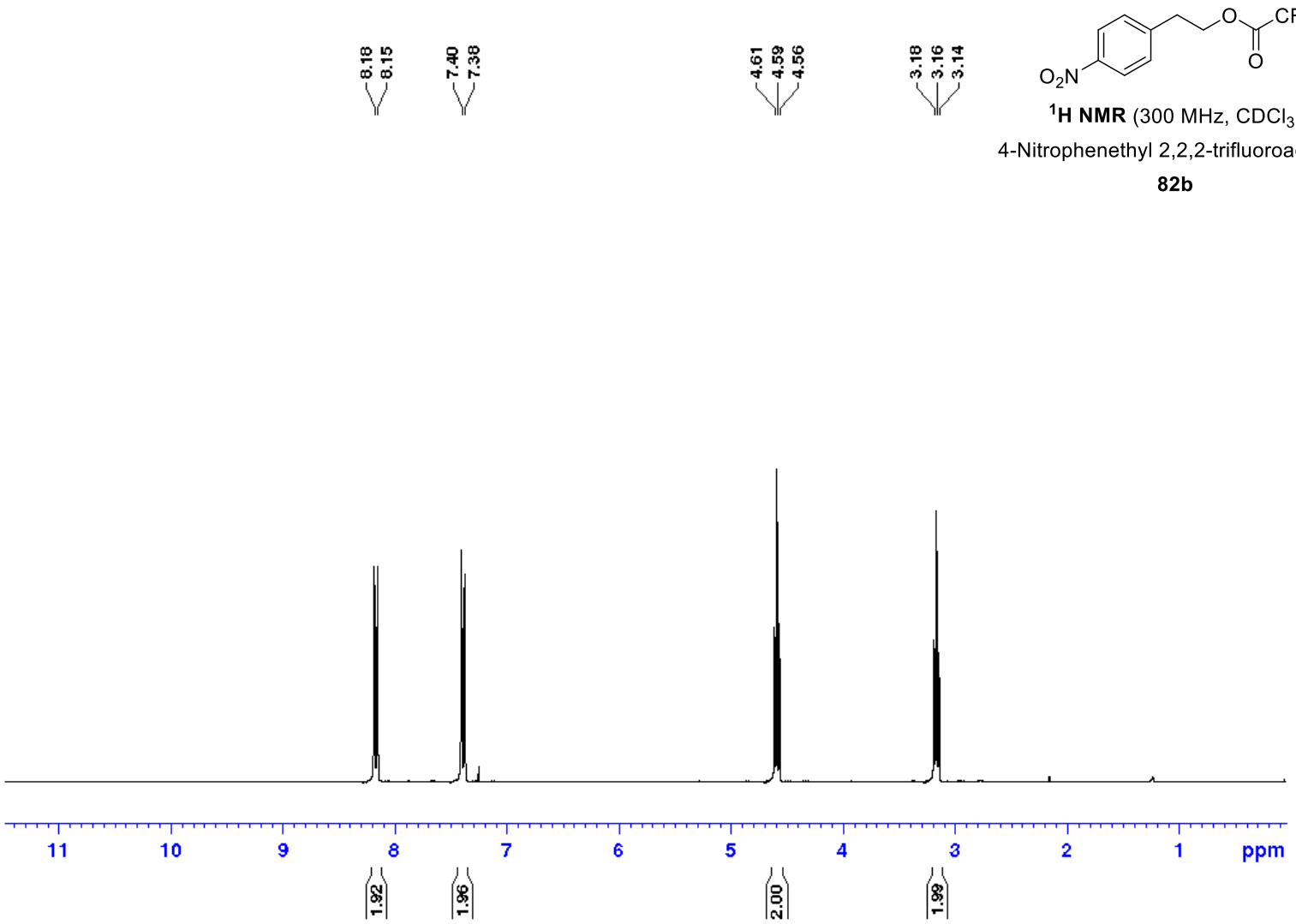




^{19}F NMR (282 MHz, $CDCl_3$)

4-Nitrophenethyl 2,2,2-trifluoroacetate

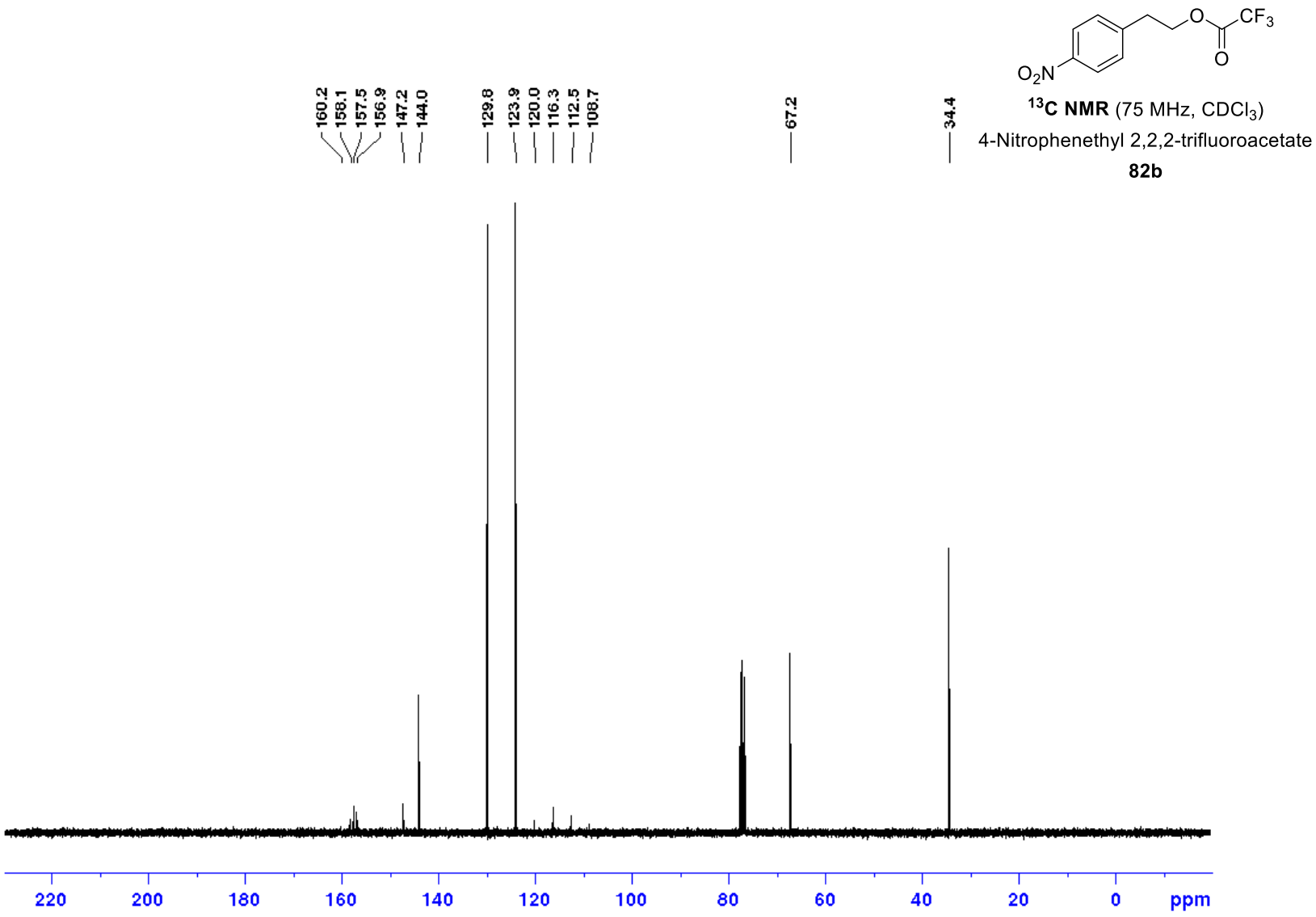
82b



^{1}H NMR (300 MHz, $CDCl_3$)

4-Nitrophenethyl 2,2,2-trifluoroacetate

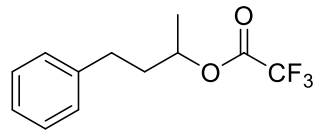
82b



^{13}**C NMR** (75 MHz, $CDCl_3$)

4-Nitrophenethyl 2,2,2-trifluoroacetate

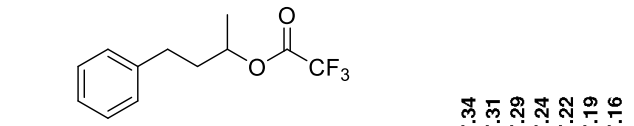
82b



^{19}F NMR (282 MHz, $CDCl_3$)

1-Methyl-3-phenylpropyltrifluoroacetate

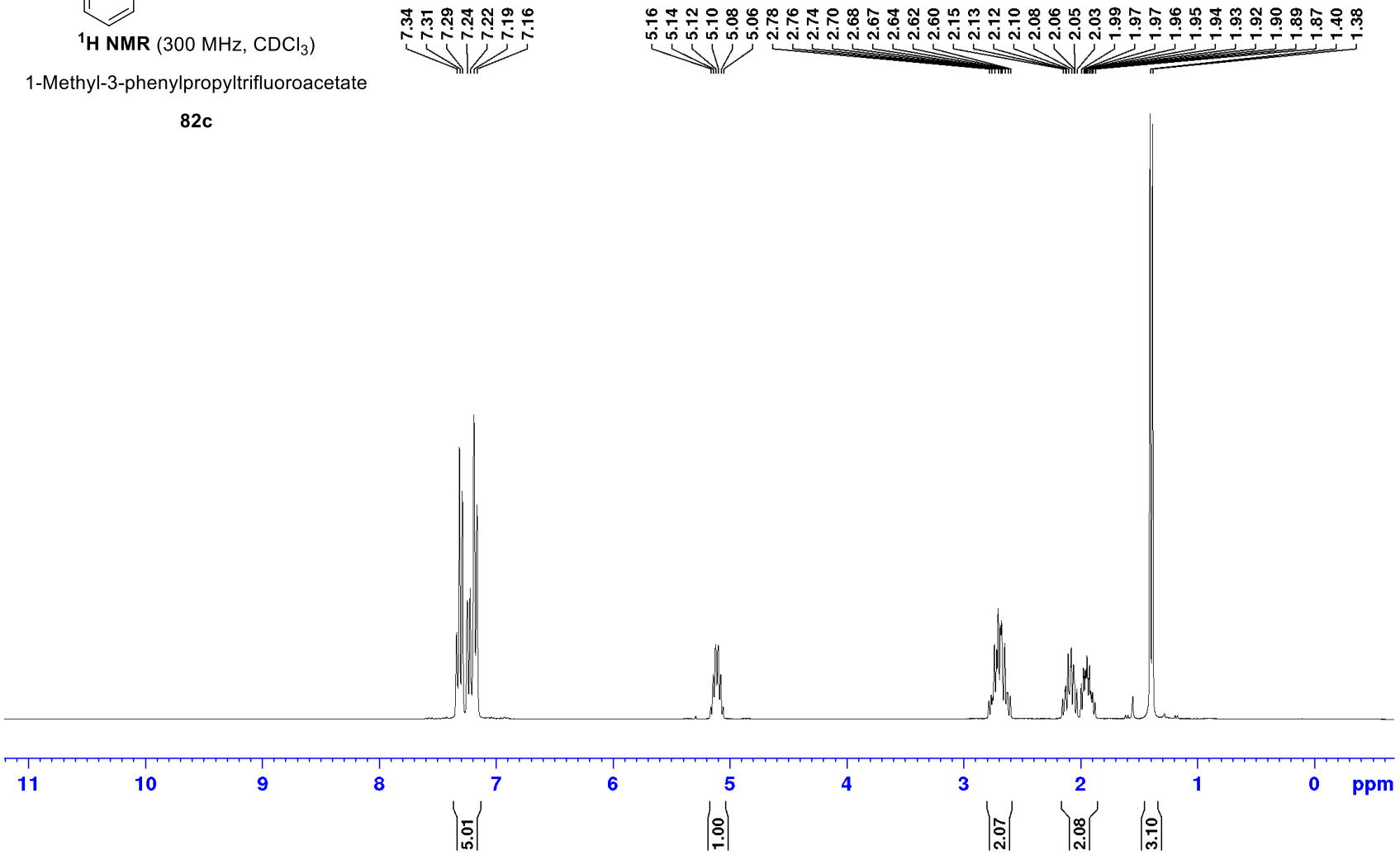
82c

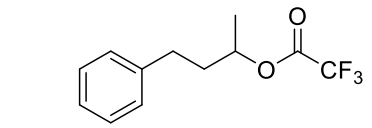


^{1}H NMR (300 MHz, $CDCl_3$)

1-Methyl-3-phenylpropyltrifluoroacetate

82c

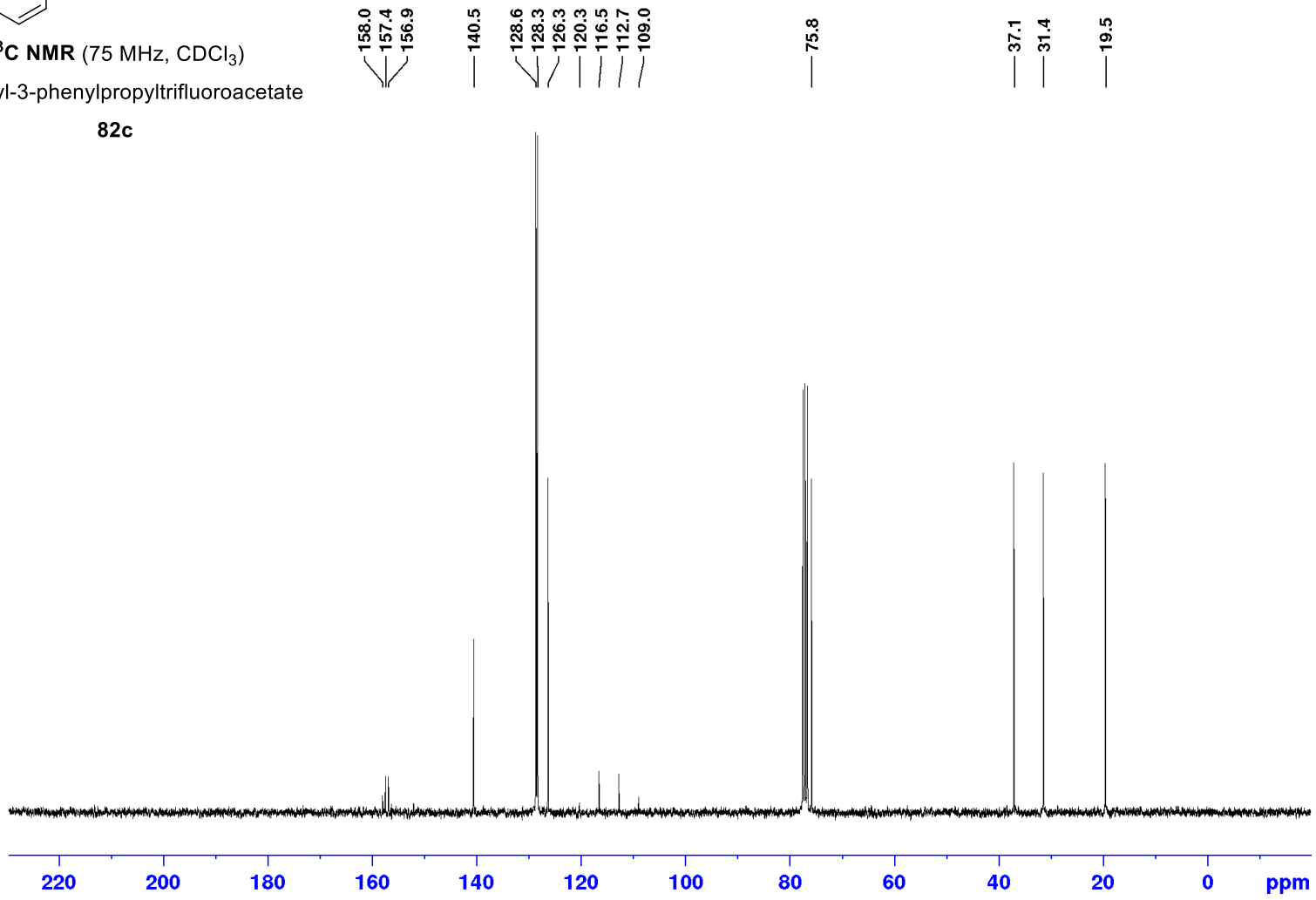


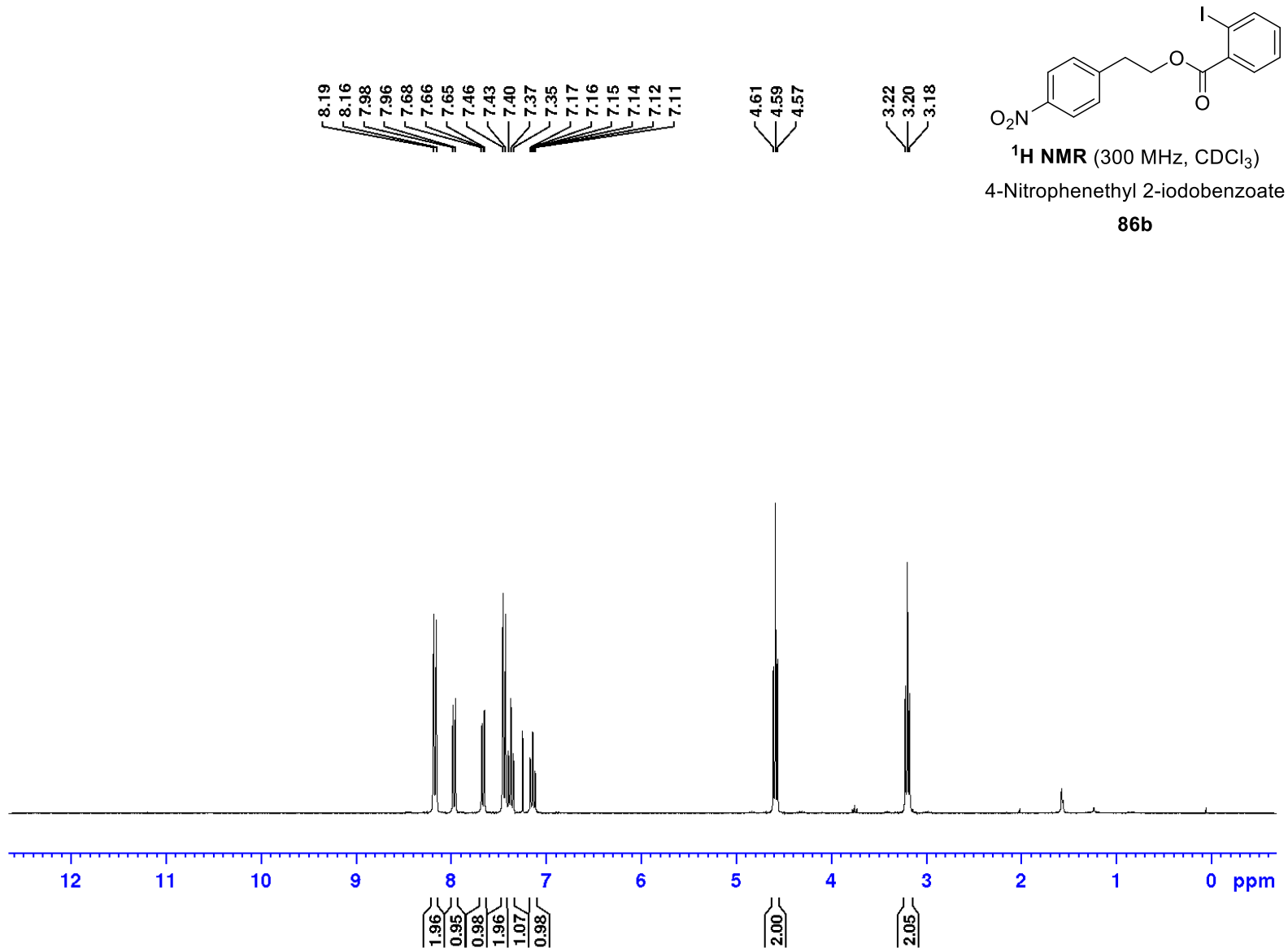


^{13}C NMR (75 MHz, $CDCl_3$)

1-Methyl-3-phenylpropyltrifluoroacetate

82c

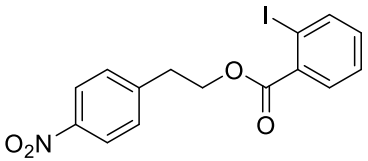


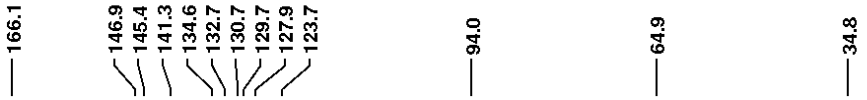


^{1}H NMR (300 MHz, $CDCl_3$)

4-Nitrophenethyl 2-iodobenzoate

86b

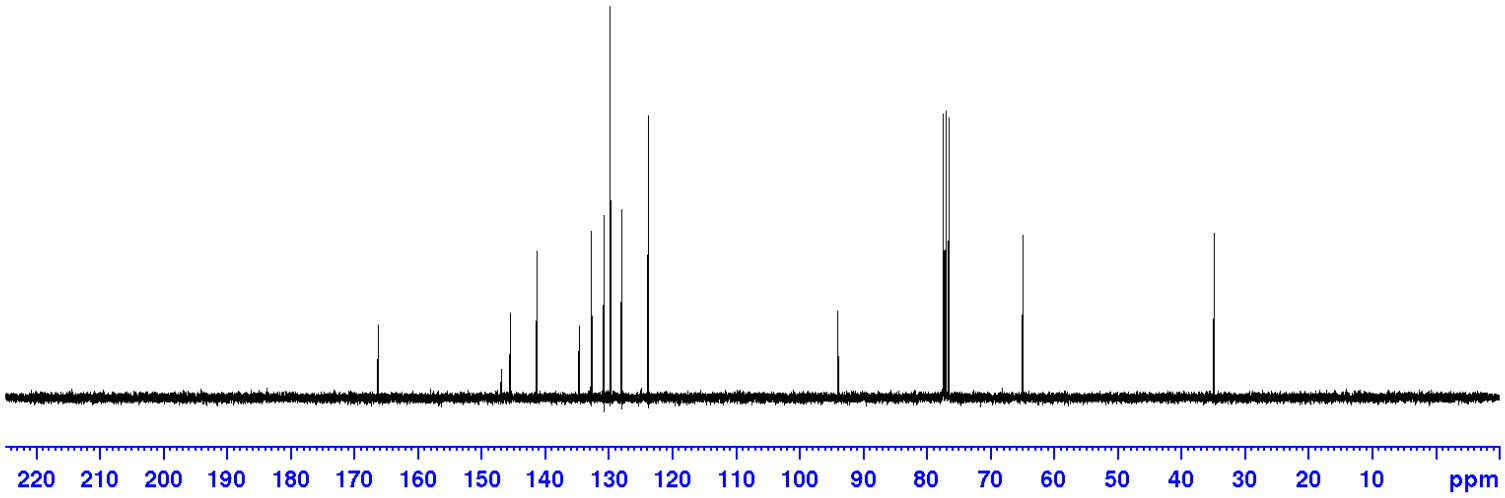


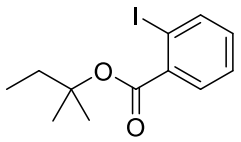


^{13}C NMR (75 MHz, $CDCl_3$)

4-Nitrophenethyl 2-iodobenzoate

86b

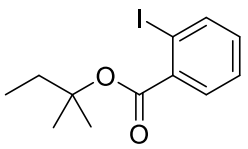




^{1}H NMR (300 MHz, $CDCl_3$)

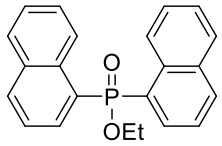
t-Amyl 2-iodobenzoate

86e



^{13}C NMR (75 MHz, $CDCl_3$)
t-Amyl 2-iodobenzoate
86e

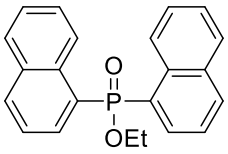
Appendix B: Chapter 2 NMR Spectra

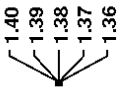


^{31}P NMR (121 MHz, $CDCl_3$)

Ethyl di(naphthalen-1-yl)phosphinate

103f

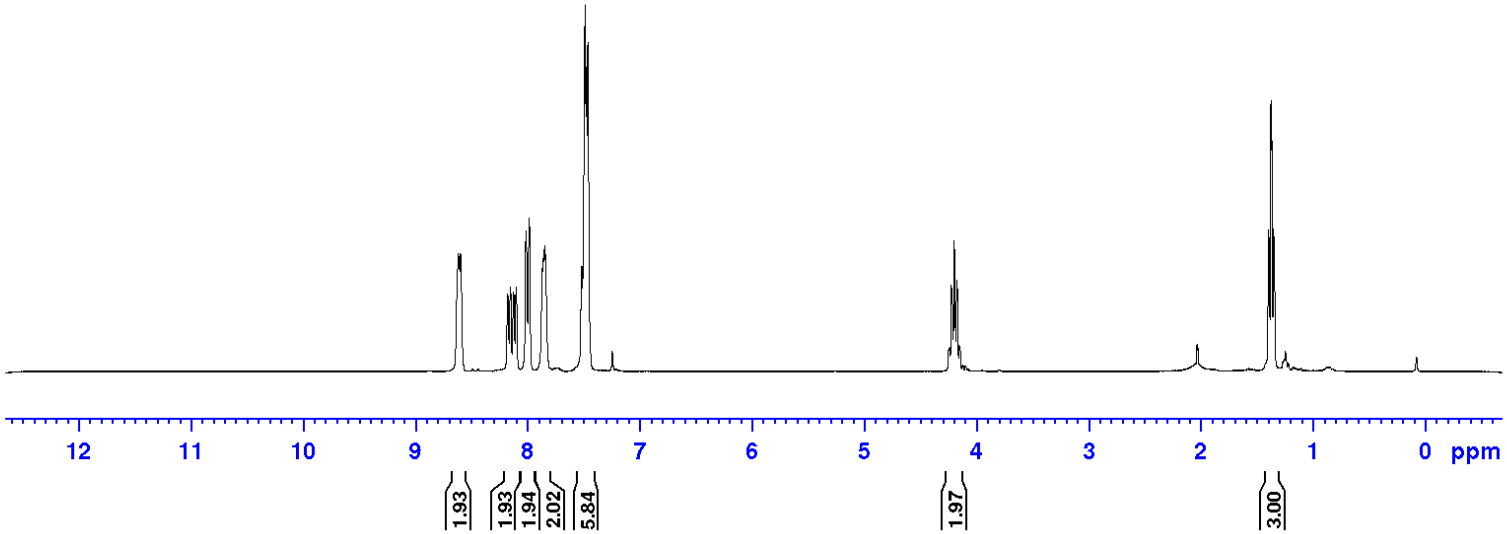


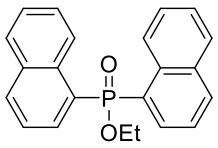


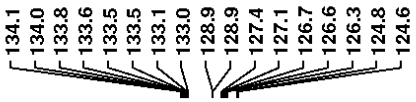
^{1}H NMR (300 MHz, $CDCl_3$)

Ethyl di(naphthalen-1-yl)phosphinate

103f



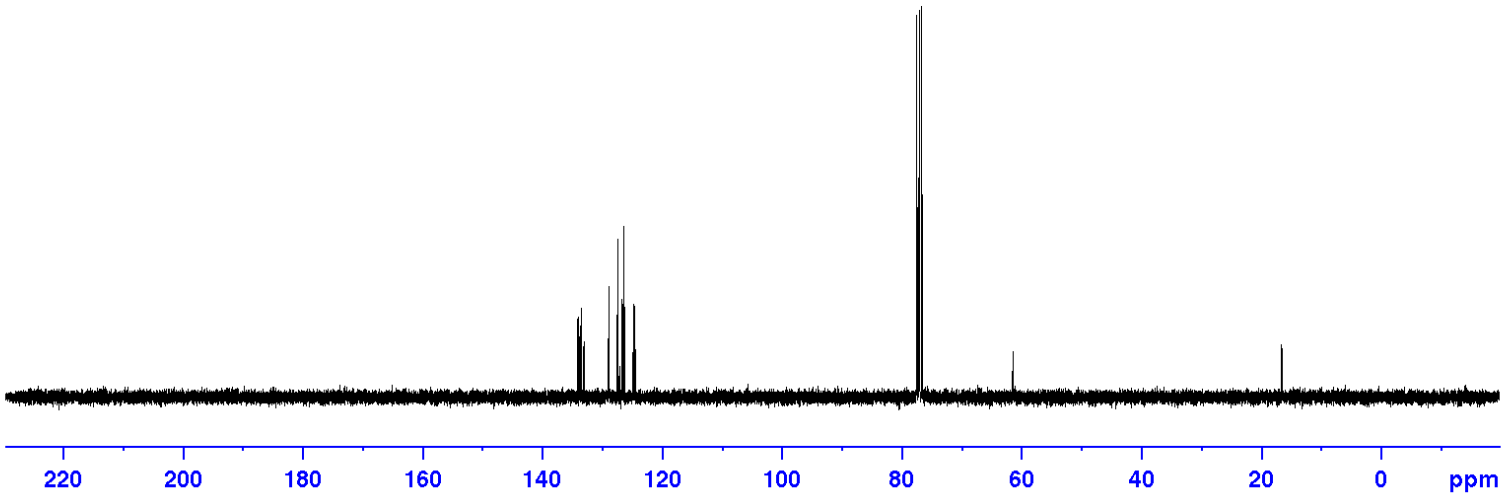


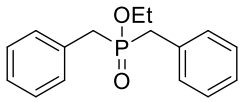


^{13}C NMR (75 MHz, $CDCl_3$)

Ethyl di(naphthalen-1-yl)phosphinate

103f

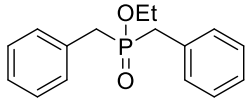




^{31}P NMR (121MHz, $CDCl_3$)

Ethyl dibenzylphosphinate

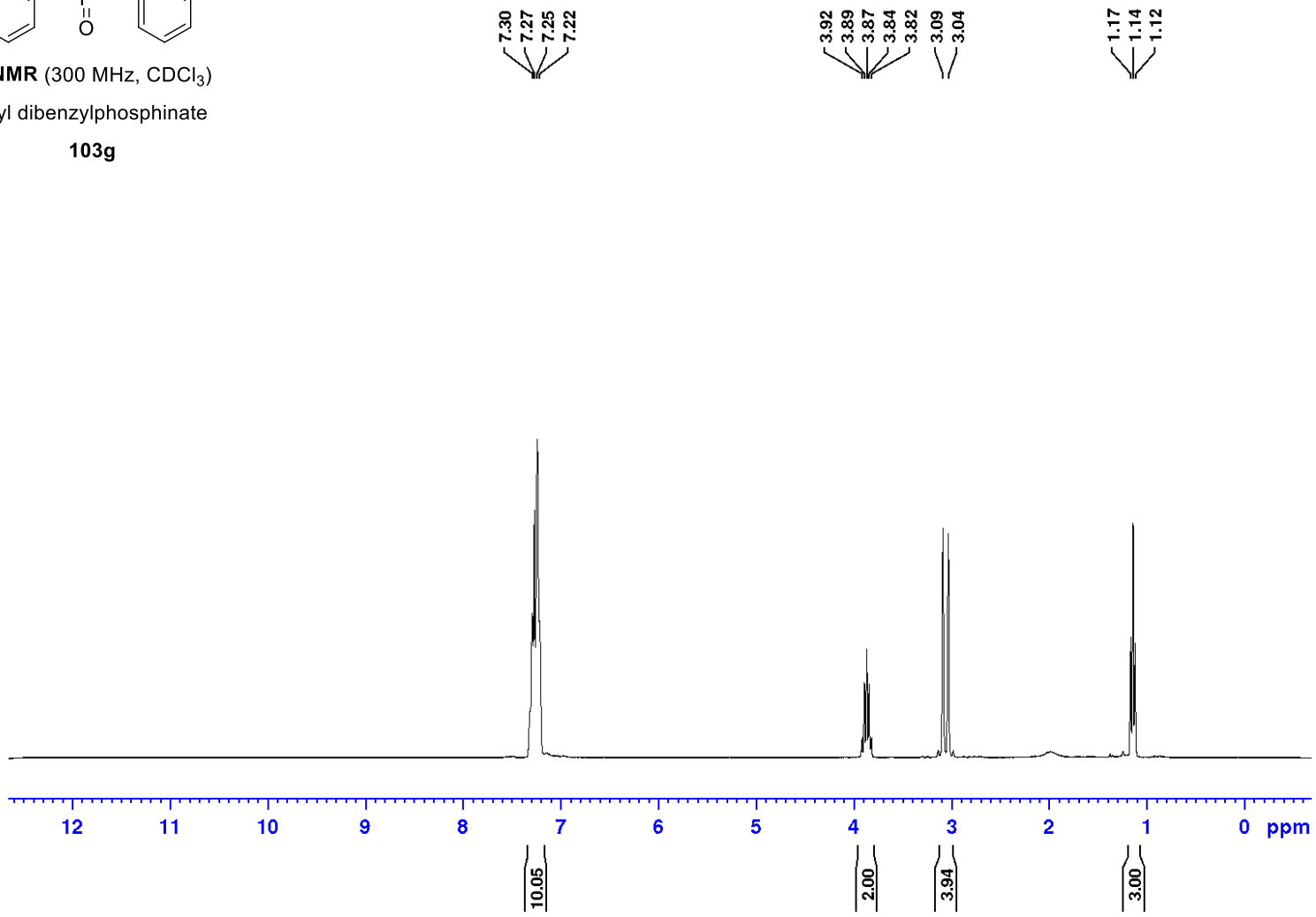
103g

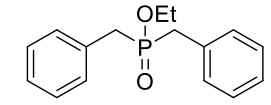


^{1}H NMR (300 MHz, $CDCl_3$)

Ethyl dibenzylphosphinate

103g

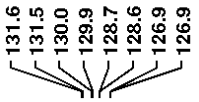


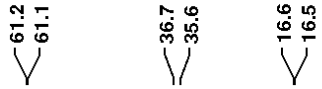


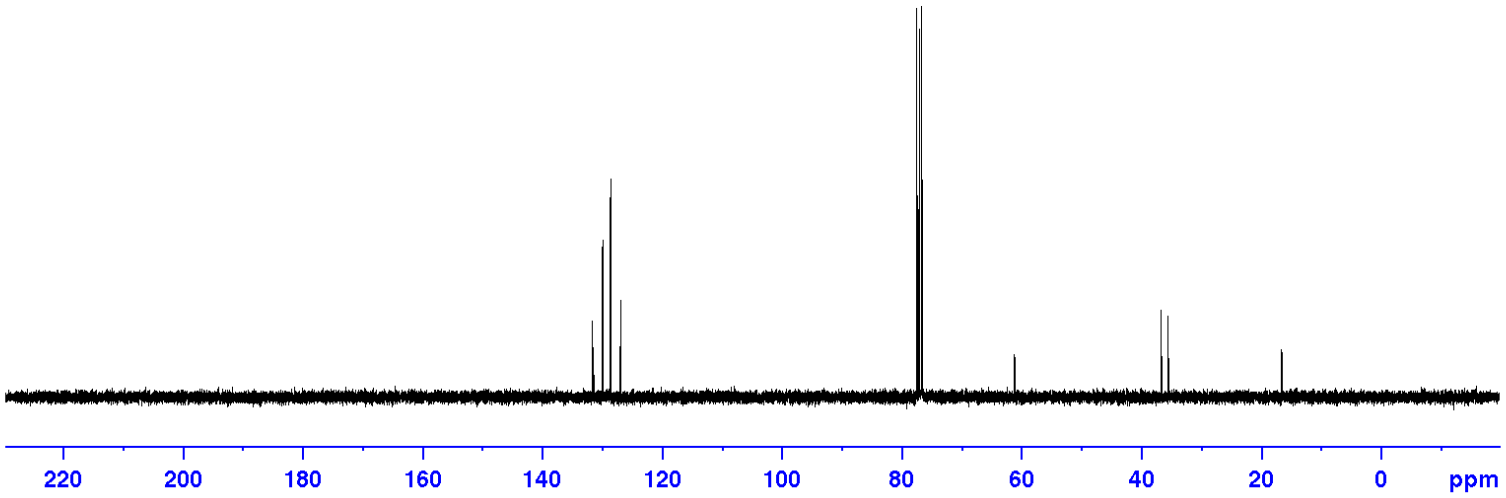
^{13}C NMR ($CDCl_3$, 75 MHz)

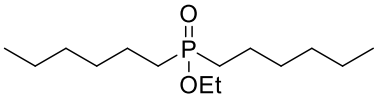
Ethyl dibenzylphosphinate

103g





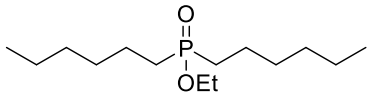




^{31}P NMR (121 MHz, $CDCl_3$)

Ethyl dihexylphosphinate

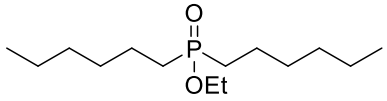
103h



^{1}H NMR (300 MHz, $CDCl_3$)

Ethyl dihexylphosphinate

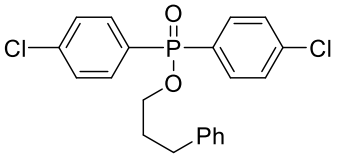
103h



^{13}C NMR (75 MHz, $CDCl_3$)

Ethyl dihexylphosphinate

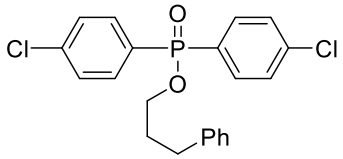
103h



^{31}P NMR (121 MHz, $CDCl_3$)

3-Phenylpropyl bis(4-chlorophenyl)phosphinate

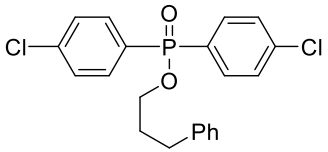
104e

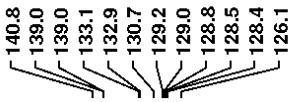


^{1}H NMR (300 MHz, $CDCl_3$)

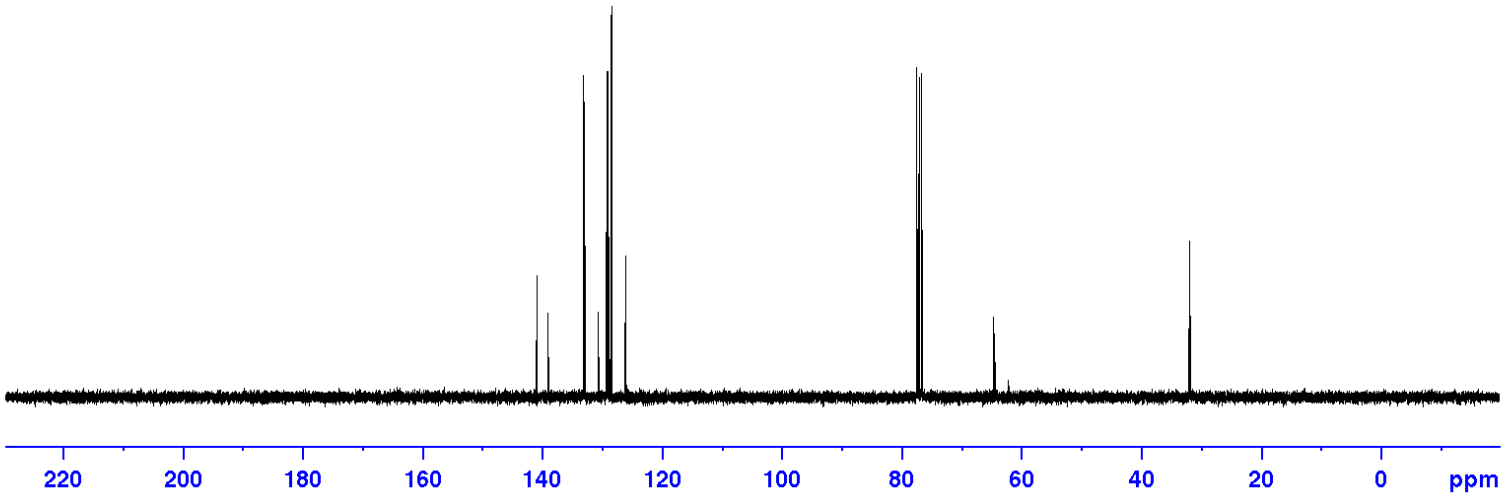
3-Phenylpropyl bis(4-chlorophenyl)phosphinate

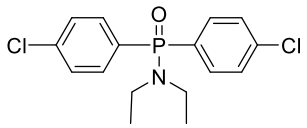
104e





^{13}C NMR (75 MHz, $CDCl_3$)
3-Phenylpropyl bis(4-chlorophenyl)phosphinate
104e



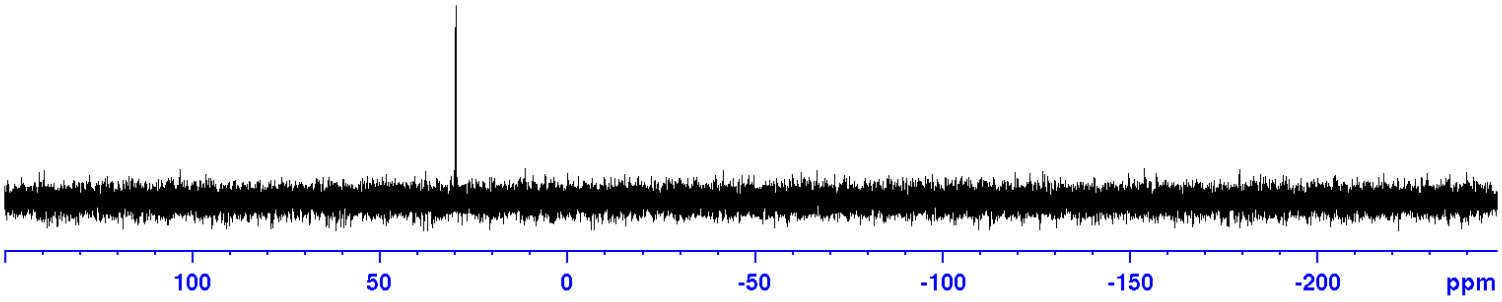


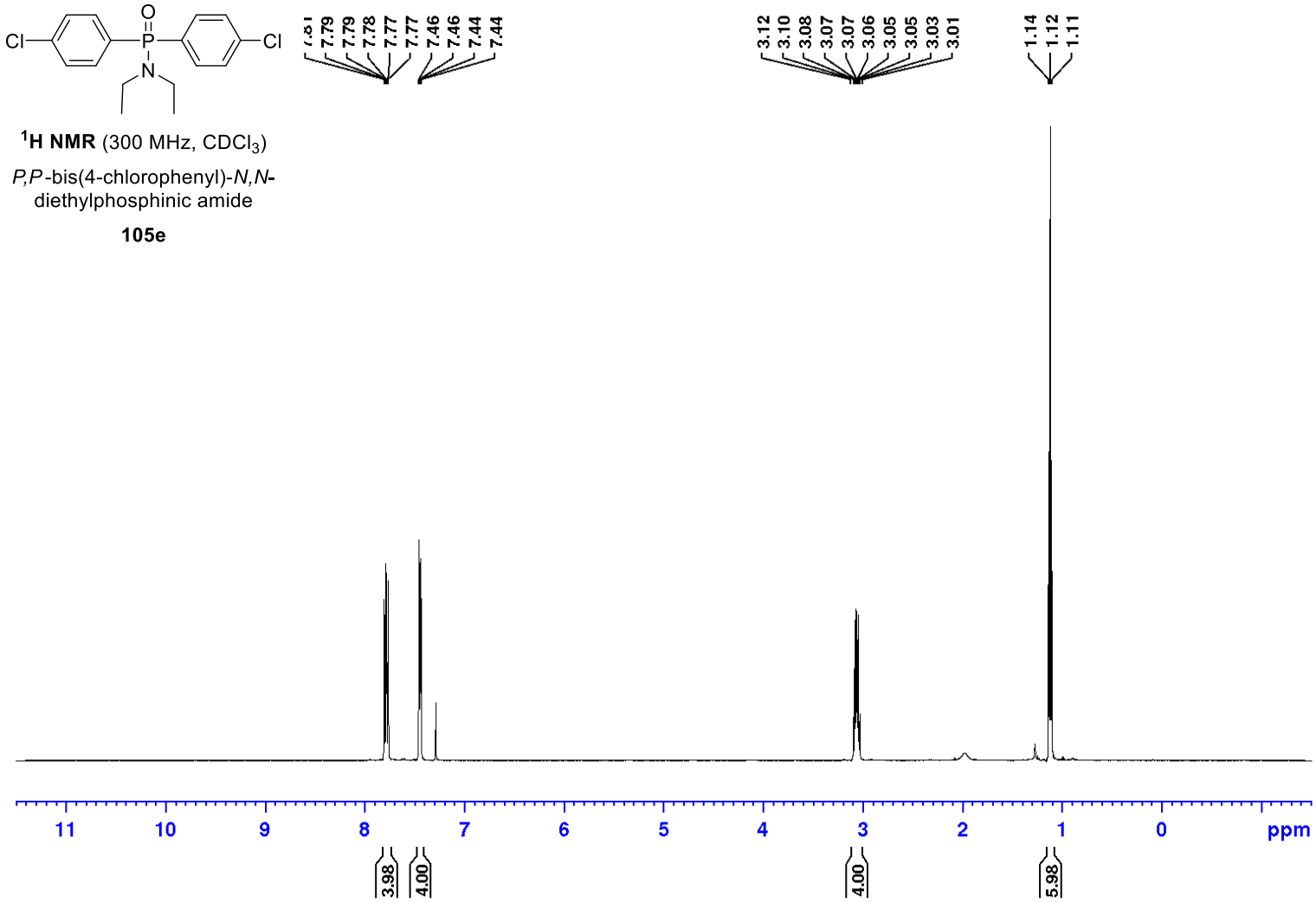
^{31}P NMR (121 MHz, $CDCl_3$)

P,P-bis(4-chlorophenyl)-*N,N*-diethylphosphinic amide

105e

29.81

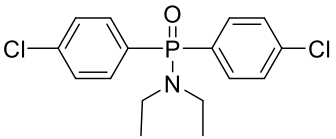




^{1}H NMR (300 MHz, $CDCl_3$)

P,P-bis(4-chlorophenyl)-*N,N*-diethylphosphinic amide

105e



^{13}C NMR (75 MHz, $CDCl_3$)

P,P-bis(4-chlorophenyl)-*N,N*-diethylphosphinic amide

105e