Use of Iodoarene Dihalides Reagents in Halogenation Reactions

by

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Author’s Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

I would like to acknowledge the work of Grace Shimokura, who worked on this project with me. She performed the substrate scope of the triphenylphosphine dichloride synthesis project and synthesized compounds **33-55, 58-59** from chapter 2.

Abstract

Halogenation of organic molecules is a fundamental transformation in organic chemistry. Introducing halogens into substrates can be a challenge, since most methods for introducing fluorine or chlorine into molecules include the use of toxic reagents, harsh reaction conditions or expensive reagents. In recent years, hypervalent iodine compounds have garnered much interest due to their reactivity, their ease of synthesis and their mild reaction conditions, and they have been successfully employed in numerous halogenation reactions. My master's thesis has been focused on two projects, deoxygenative chlorination using iodobenzene dichloride ($PhICl_2$) and denitrogenative hydrofluorination using iodotoluene difluoride ($TolIF_2$).

Denitrogenative hydrofluorination of hydrazones using iodotoluene difluoride, where the iodane acts as both an oxidant and a fluorine source in this reaction. By altering the reaction conditions, the monofluorinated product or difluorinated product can be targeted from a single common starting material. Specifically, when 1.7 equivalent of $TolIF_2$ is reacted with the hydrazone, the reaction gives the mono-fluorinated product in 99% yield. When 2.1 equivalents of $TolIF_2$ are reacted with the hydrazone in the presence of a Lewis acid, the *gem*-difluorinated product is currently obtained in 52% optimized yield.

Triphenylphosphine dichloride (Ph_3PCl_2) is a versatile chlorinating agent, commonly used for deoxygenative chlorination, such as the Appel reaction. A novel synthesis of the phosphorane is reported in this thesis, using $PhICl_2$ and triphenylphosphine (PPh_3). This synthesis can be performed in the presence of a carboxylic acid or alcohol to generate acyl- and alkyl chlorides. Addition of nucleophiles results in a mild and easy synthesis of amides and esters.

Acknowledgements

I would like to thank my supervisor, Dr. Graham Murphy, for the opportunity and guidance he has offered me. Similarly, thanks are due to my advisory committee members, Dr. Michael Chong and Dr. Eric Fillion, for their helpful discussion and for lending me chemicals and equipment.

Special thanks to Grace Shimokura, who is a co-author on my publication, for her help in with my triphenylphosphine dichloride research.

I would like to thank my co-workers Richard Tran, for helping me and making sure everything was going right for me as well as, Jasmin Eljo, for being supportive of all my work, Dr. Leanne Racicot for her help and lively discussion and Farhana Abbas for putting up with sharing my fume hood. As well as all other members of the Murphy group: Jason Tao, Tristan Chidley, Zhengsheng Zhao and Ahbinandan Shyamsunder.

Dedication

To my family,

Germain, Lise, Gabriel, Melissa and Sophie

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3c-4e	Three-center-four-electron
Ac	Acetyl
Ar	Aromatic
BINAP	(±)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
DAST	Diethylamino sulfur trifluoride
DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethylsulfoxide
DNA	Deoxyribose nucleic acid
EDG	Electron donating group
equiv.	Equivalent
Et	Ethyl
EWG	Electron withdrawing group
HMDSO	Hexamethyldisiloxane
HOMO	Highest occupied molecular orbital
HTIB	Koser’s reagent

HVI	Hypervalent iodine
IBX	2-Iodoxybenzoic acid
in-situ	In place or in the reaction mixture
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
kCal	Kilocalories
kJ	Kilojoules
Me	Methyl group
MO	Molecular orbital
NBS	*N*-Bromosuccinimide
NFSI	*N*-Fluorobenzenesulfonimide
NMR	Nuclear magnetic resonance
NQR	Nuclear quadrupole resonance
Nu	Nucleophile
p-ABSA	4-Acetamidobenzenesulfonyl azide
PFA	Perfluoroalkoxy
Ph	Phenyl
PIDA	(diacetoxy)iodobenzene
py	Pyridine
R	Any carbon or hydrogen group
r.t.	Room temperature
T	Temperature
TBAF	Tetrabutylammonium fluoride

THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TIPS-EBX	1-[(Triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one
Tol	Toluene
Ts	Tosyl

Chapter 1 – Hypervalent iodine and fluorination reactions

1.0 Introduction to iodine

Iodine is the heaviest non-radioactive halogen as well as the largest and the least electronegative. It has been used in organic chemistry since the mid-1800s. Like the other halogens, organoiodine compounds are most commonly found as monovalent with an oxidation state of -1. However, due to iodine's large atomic radius and the fact that it contains more filled orbitals than the other stable halogens, iodine can form polyvalent compounds known as hypervalent iodine (HVI) molecules. Iodobenzene dichloride ($PhICl_2$) was the first polyvalent iodine molecule to be discovered in 1886 by an experiment in which Willgerodt bubbled chlorine gas through iodobenzene in chloroform.[1] Although polyvalent iodine molecules were discovered over a century ago, the chemistry of hypervalent iodine has only been rapidly developing since the 1980s. HVI molecules are of great interest due to their oxidizing properties, mild reaction conditions and commercial availability.[2] The reactivity profile of HVI reagents is similar to that of transition metals, but they have the advantage of being environmentally benign and relatively inexpensive to make.[2–4] HVI molecules are routinely used in organic synthesis for the oxidation of substrates and ligand transfer.[2,5] Figure 1.1 shows the versatility of HVI reagents and the variety of reaction types that can be accomplished.

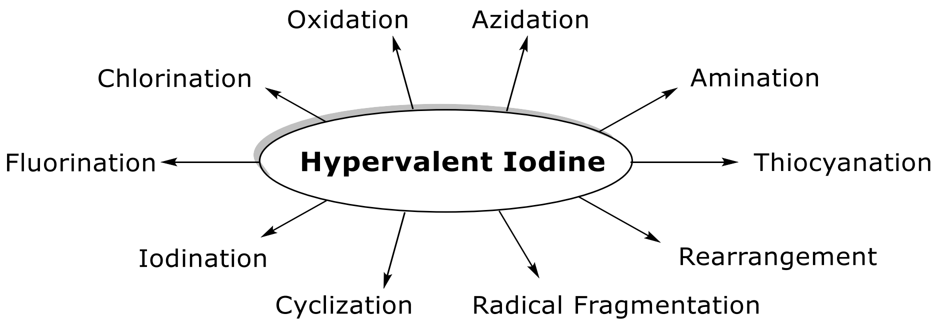


Figure 1.1 – Reactivity profile of hypervalent iodine molecules

1.1 Structure and reactivity of HVI molecules

The International Union of Pure and Applied Chemistry names hypervalent iodine molecules λ^n-iodanes, where n is the oxidation state of the iodine atom.[6] Polyvalent iodine compounds can be generally classified as: a) trivalent iodine molecules, λ^3-iodanes, or b) pentavalent iodine molecules, λ^5-iodanes. The iodine in λ^5-iodanes have an oxidation state of +5 and five bonds to the iodine, while λ^3-iodanes have three bonds to the iodine and an oxidation state of +3.

The HVI reagents shown in Figure 1.2 are commonly used in organic syntheses. λ^5-Iodanes such as 2-iodoxybenzoic acid (IBX, **1**)[7] and Dess-Martin Periodinane (DMP, **2**)[8] are usually used for oxidation reactions. λ^3-Iodanes can be put into 4 different subgroups: a) acyclic λ^3-iodanes, such as $PhCl_2$ (**3**) and (diacetoxy)iodobenzene (PIDA, **4**); b) cyclic λ^3-iodanes, such as fluorobenziodoxoles (**5**) and Togni's reagent (**6**); c) aryliodonium salts (**7**); and d) iodonium ylides (**8** and **9**) (Figure 1.2).

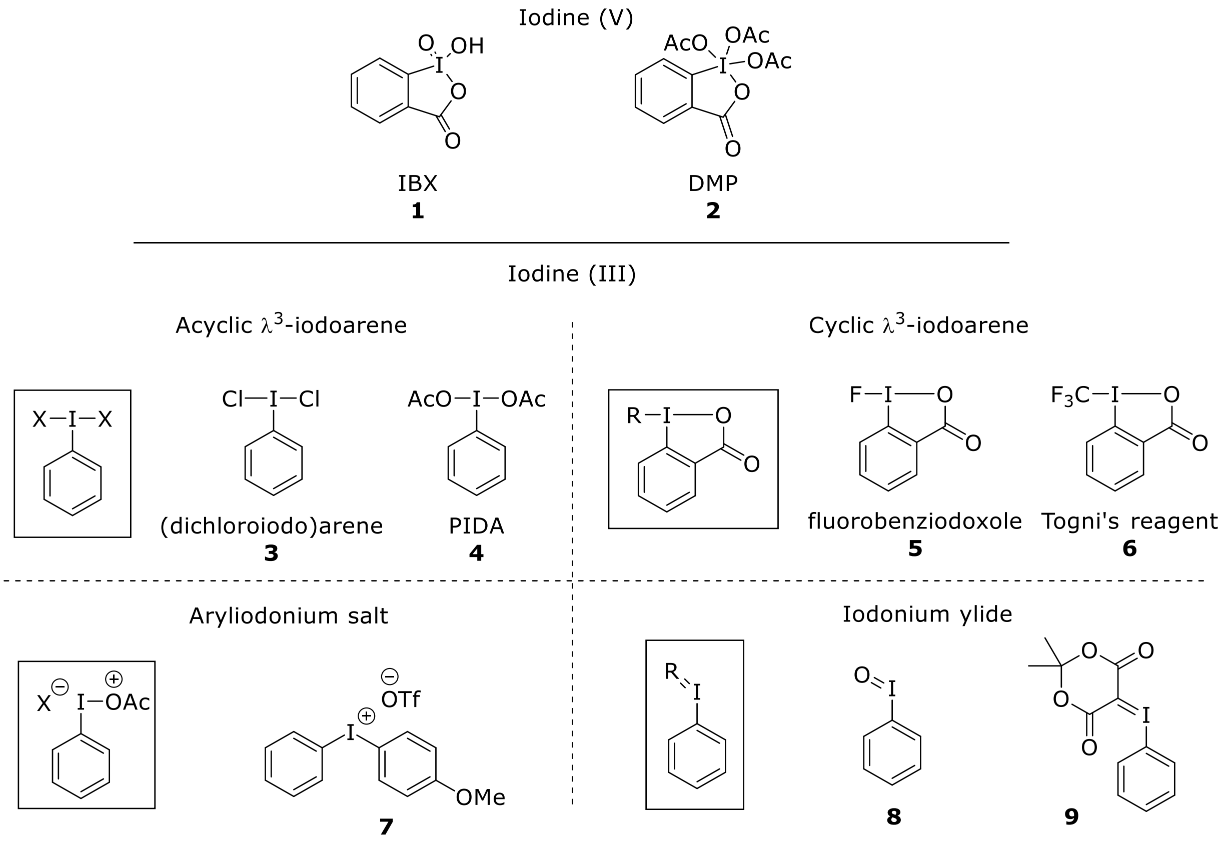


Figure 1.2 – Main classes of HVI reagents

λ^3-Iodanes have 10 electrons around the iodine atom and a trigonal bipyramidal shape, with the least electronegative carbon substituent and two lone pairs of electrons in the equatorial positions and the two most electronegative ligands in the apical position. This gives the λ^3-iodanes a T-shape (Figure 1.3). λ^3-Iodanes in which the R group is an aryl substituent are commonly used because of their relative stability. The reactivity and geometry of hypervalent iodine comes from the three-center-four-electron (3c-4e) hypervalent bond. The iodine and two ligands share four electrons, and the molecular orbital (MO) diagram shows that the highest occupied molecular orbital (HOMO) is the non-bonding MO. This creates a node at the iodine atom and makes the bond highly polarized and weaker, rendering the iodine center highly electrophilic.

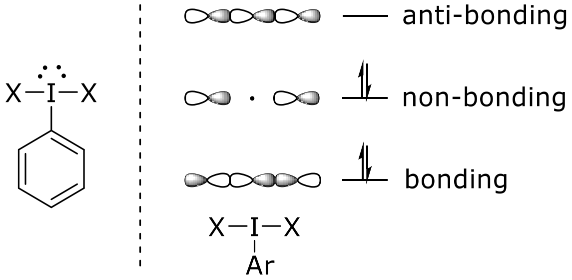
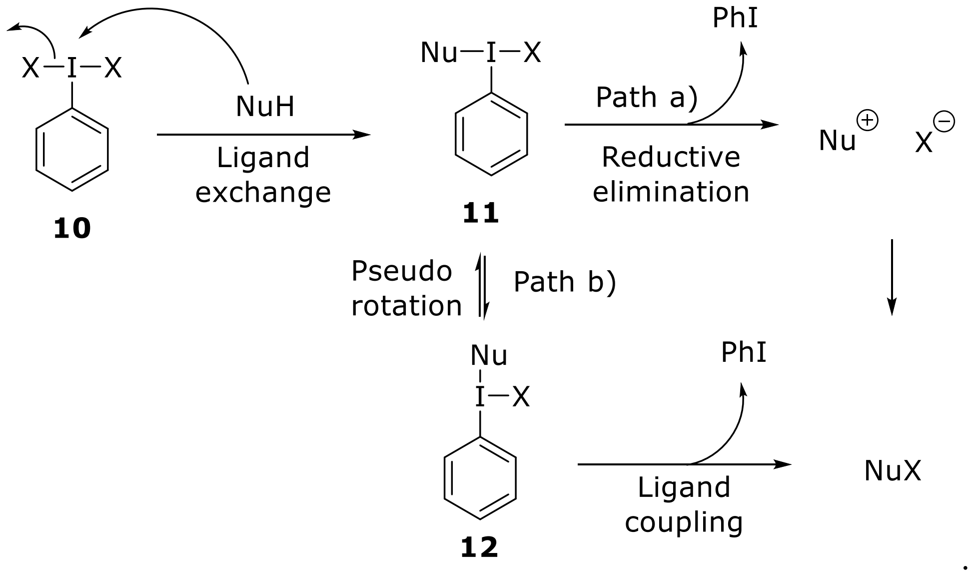


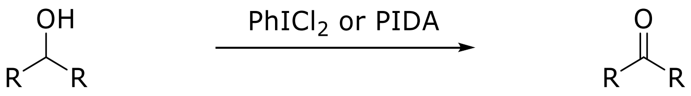
Figure 1.3 – Typical structure and MO diagram of λ^3*-iodanes*

HVI molecules exhibit three types of reactivity patterns typically associated with transition metals: ligand exchange, ligand coupling and reductive elimination. All of these reactivities are present in a ligand transfer reaction, as shown in Scheme 1.1. The electrophilic iodine of a HVI molecule is first attacked by a nucleophile and one of the ligands is replaced by the nucleophile. The resulting intermediate **11** can react according to path a) and reductively eliminate monovalent iodine and its ligands. The nucleophile then shows umpolung reactivity by becoming electrophilic and will react with the ligand to form the product. Path b) is an alternative pathway in which the intermediate **12** undergoes a pseudo-rotation so that the ligands become *cis* to each other and a ligand coupling occurs, yielding the product.[2,3,7–10]



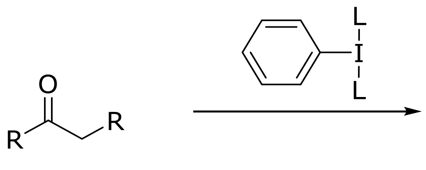
Scheme 1.1 – Typical reactivity of λ^3-iodanes

This reactivity has been exploited in both oxidation and ligand transfer reactions. λ^3-Iodanes are capable of oxidizing alcohols to ketones (Scheme 1.2),[13] aldehydes[14] and esters[15,16] as well as oxidizing a variety of heteroatoms such as sulfur[17,18] and phosphorus.[19,20] These transformations can be done using a variety of different HVI compounds such as iodosobenzene,[21] PIDA[15,16] and $PhICl_2$.[13,14]



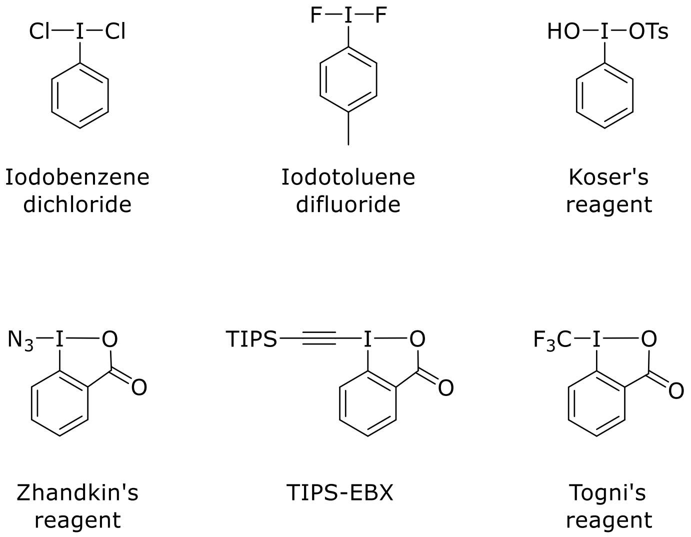
Scheme 1.2 – Oxidation of alcohols using λ^3-iodanes

λ^3-Iodanes have also been exploited by many chemists to facilitate ligand transfer (Scheme 1.3) to nucleophiles,[4] such as enolates[22], alkenes[23], diazo compounds,[24] and aromatic rings.[25] A variety of ligands can be used for these ligand transfer reactions.



Scheme 1.3 – Single ligand transfer using HVI

Many HVI molecules have been developed to transfer different functional groups such as: chlorine using iodobenzene dichloride ($PhICl_2$),[26] trifluoromethyl using Togni's reagent,[27] fluorine using iodotoluene difluoride ($TolIF_2$),[28] tosyloxy with Koser's reagent (HTIB),[29] azide with Zhandkin's reagent,[30] and alkynyl groups with 1-[(Triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX)[31] to name a few examples (Figure 1.4).[4]



Iodobenzene dichloride
Iodotoluene difluoride
Koser's reagent
Zhandkin's reagent
TIPS-EBX
Togni's reagent

Figure 1.4 – λ^3-iodane ligand transfer reagent

1.2 Fluorination

Organofluorine compounds are often desirable targets in the pharmaceutical and agricultural industries.[32–36] The C-F bond is of interest due to its ability to alter a molecule's bioavailability, solubility and metabolic stability compared to its corresponding C-H analogue.[37] Fluorine's van der Waals radius (1.47 Å) lies between that of oxygen (1.57 Å) and hydrogen (1.20 Å) meaning that it can act as a biostere of hydrogen atoms and hydroxyl groups.[33] Since C-F bonds are stronger than C-H bonds and are not easily broken down by oxidative or hydrolytic enzymes in the body, they can increase metabolic stability in drugs.[33] Fluorine can also alter the pK_a values of molecules due to its high electronegativity, and it can modify the lipophilicity of a molecule.[33] Reactions which add fluorine to a molecule have garnered a significant amount of interest in the scientific community,[38–40] and there has been a recent corresponding increase in the development of fluorinating agents.

Fluorine is the 13th most abundant element in the earth and is generally found in minerals as calcium fluoride (fluorite).[41] Fluorite can be treated to yield the two simplest and atom economical fluorinating agents, HF and F_2. HF is a chemical that is often used in industrial and research labs, however, it is very corrosive material that cannot be used with glass and is incompatible with acid sensitive compounds. The other fluorinating agent, F_2, is not commonly used in laboratories due to its high reactivity and corrosiveness, as well as the need for specialized equipment and extensive training.[42,43] As such, the use of these fluorinating agents is often undesirable, and research has been conducted to invent or discover new fluorinating agents that are less toxic and easier to handle (Figure 1.5).

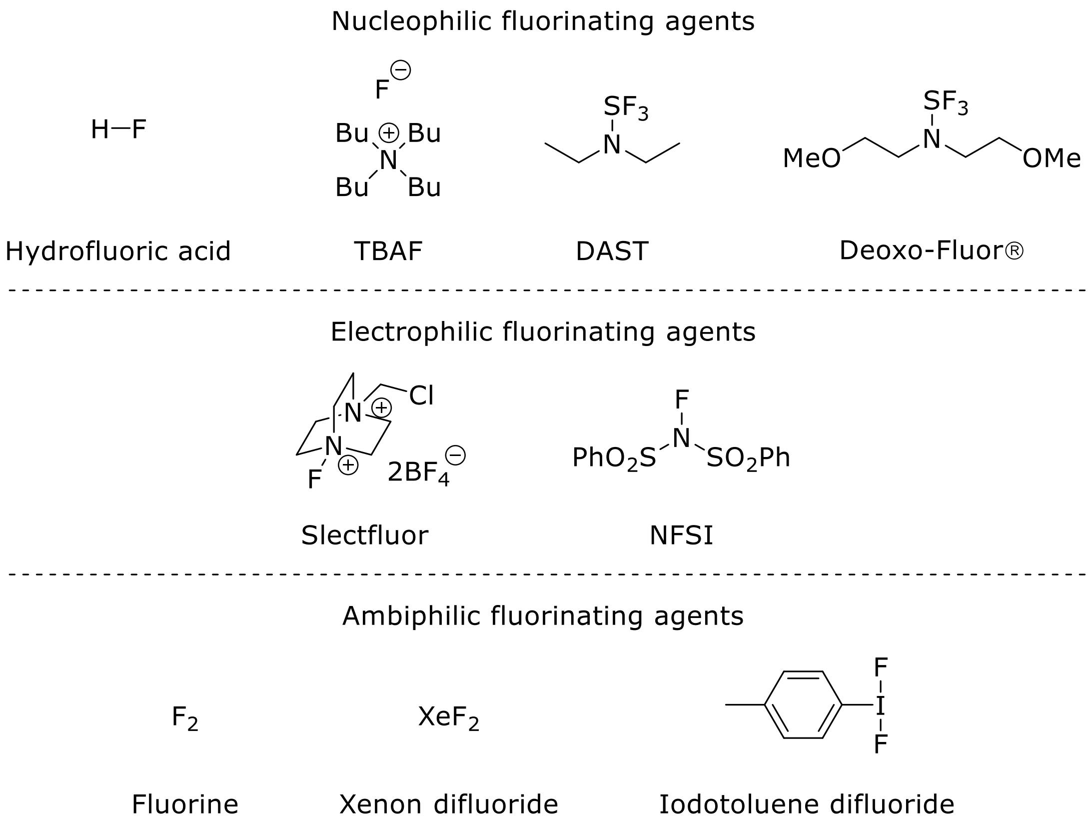
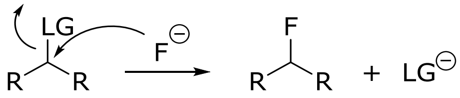


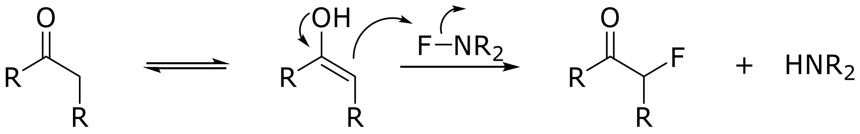
Figure 1.5 – Types of fluorinating agents

Fluoride ions are weak nucleophiles in polar protic solvents due to the formation of hydrogen bonds, but can be very potent nucleophiles in aprotic solvents. New less corrosive reagents have been discovered which release fluoride ions in solution such as tetrabutylammonium fluoride (TBAF), diethylamino sulfur trifluoride (DAST) or Deoxo Fluor®. Unfortunately, those reagents can react violently with water. The biggest disadvantage of DAST and Deoxo Fluor® is that they are synthesized using F_2. These reagents are known as nucleophilic fluorinating agents since they release a fluoride anion that can attack electrophilic centers (Scheme 1.4). These reagents work well with molecules containing a good leaving group that fluoride can displace.



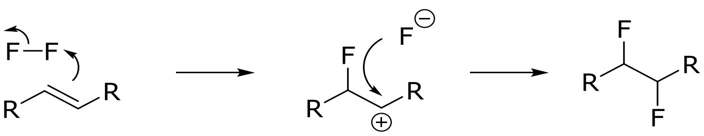
Scheme 1.4 – Nucleophilic fluorination

While nucleophilic fluorinating agents are useful, they will not be effective if the starting material does not have an electrophilic center. Electrophilic fluorination is the opposite of nucleophilic fluorination and requires an electrophilic fluorine source that can be attacked by a nucleophile (Scheme 1.5). Electrophilic fluorination has become more prevalent since the introduction of N-F reagents, such as Selectfluor and N-fluorobenzenesulfonimide (NFSI).[44] These reagents tend to be solid, non-volatile and easy to handle. They are widely used in the scientific community despite their high cost and relatively low “active” fluorine content.



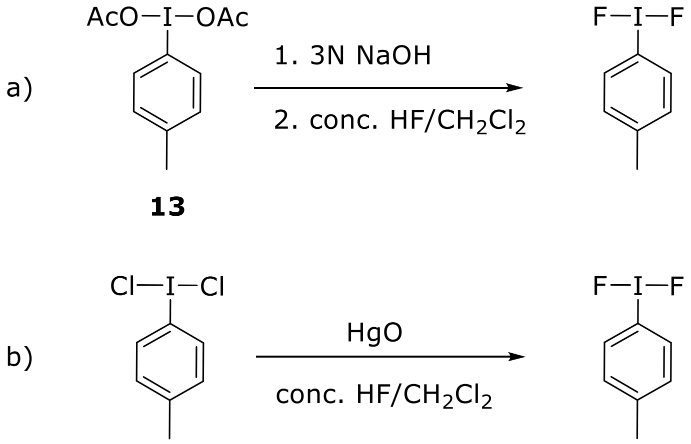
Scheme 1.5 – Electrophilic fluorination using N-F reagents

Fluorine gas is a highly reactive material but it is also the only known amphiphilic fluorine source. Amphiphilic fluorine reagents can deliver both an electrophilic fluorine and a nucleophilic fluoride (Scheme 1.6). While not truly ambiphilic, xenon difluoride (XeF_2, **25**) and iodotoluene difluoride ($TolIF_2$) are considered to be surrogates for F_2 since they can deliver two fluorine atoms and are much safer alternatives to F_2. However, XeF_2 is synthesized by the reaction of xenon with fluorine gas. $TolIF_2$, on the other hand, is synthesized using HF, making it very attractive to the scientific community.



Scheme 1.6 – *Ambiphilic fluorination*

$TolIF_2$ can be easily synthesized from diacetoxyiodotoluene (**13**) by reacting it with NaOH to form iodosobenzene which is then reacted with aq HF to yield $TolIF_2$ (Scheme 1.7, a)).[45,46] It can also be easily synthesized by reacting iodotoluene dichloride (**14**) with HF in the presence of mercuric oxide (Scheme 1.7, b)). [47] Other methods include using dangerous chemicals such as F_2[48] and SF_4,[49] or expensive regents such as XeF_2[50] or Selectfluor.[51]

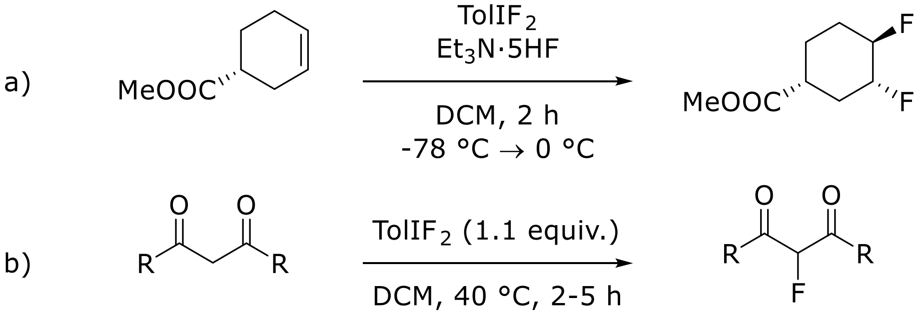


13

14

Scheme 1.7 – Synthesis of $TolIF_2$

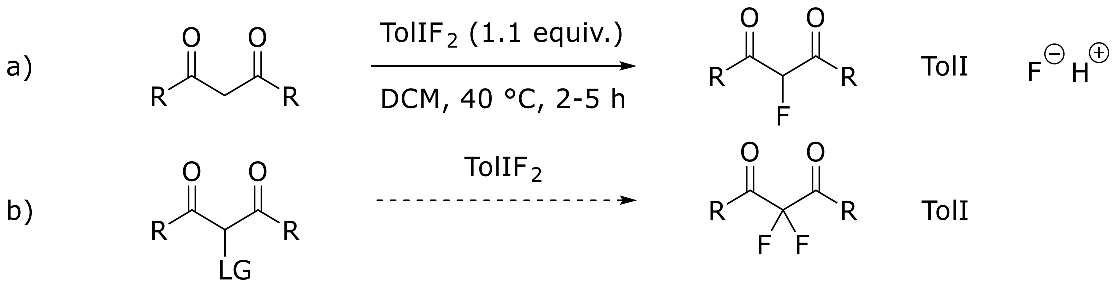
$TolIF_2$ has been used in organic chemistry as a surrogate for fluorine gas. The elemental states of other stable halogens are often used in organic synthesis for halogenation reactions. While Cl_2, Br_2 or I_2 can easily di-halogenate alkenes or halogenate dicarbonyl compounds, F_2 is too reactive to perform these reactions. $TolIF_2$ is capable of delivering two fluorine atoms and difluorinating alkenes (Scheme 1.8, a)).[47,52] The monofluorination of dicarbonyl (Scheme 1.8, b)), in which an electrophilic fluorine atom is delivered,[53] is a reaction that can be done using $TolIF_2$.[24] $TolIF_2$ has a reactivity profile similar to that of elemental fluorine in which it delivers one electrophilic fluorine, followed by a nucleophilic fluoride.



Scheme 1.8 – Fluorination reactions using $TolIF_2$

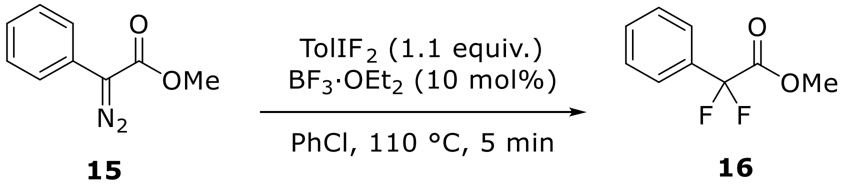
1.3 Fluorination of diazo and hydrazone compounds

In the monofluorination of β-ketoesters using $TolIF_2$, a single fluorine atom is delivered to the substrate and the second fluoride is discarded (Scheme 1.9, a)).[53] Our lab thought to improve on this by placing a leaving group at the α-position, thus allowing for a double ligand transfer using only one equivalent of $TolIF_2$ (Scheme 1.9, b)). This reaction would eliminate the waste of the fluoride anion seen in the monofluorination.



Scheme 1.9 – Fluorination of β-ketoesters

The diazo group stood out as a substrate since it contains a very good leaving group, N_2. Our lab has shown that diazo compounds can be difluorinated using $TolIF_2$ (Scheme 1.10).[24] α-Diazo methyl phenylacetate **15** was reacted with the iodane to give the difluorinated product **16**, in good yields. Both fluorine atoms from $TolIF_2$ are transferred to the substrate, making nitrogen gas and iodotoluene the only by-products of this reaction.

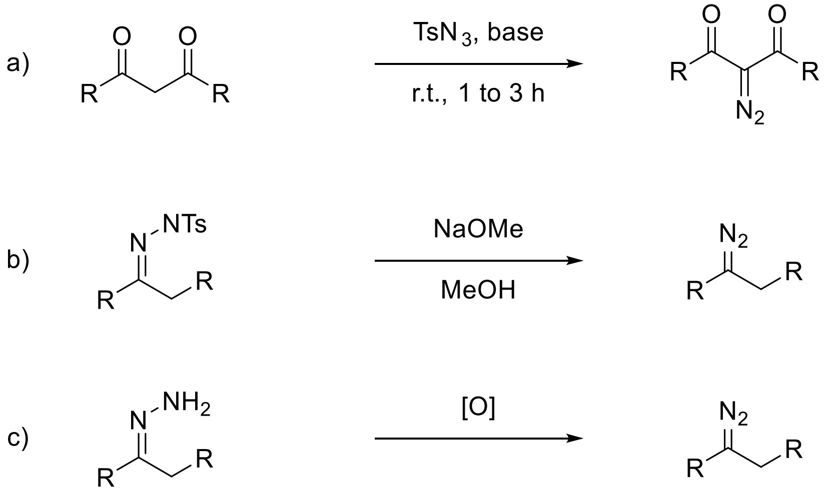


15 **16**

Scheme 1.10 – Difluorination of diazo compounds

Diazos can be synthesized with relative ease using a variety of methods. For example, diazo transfer reagents such as *p*-toluenesulfonyl azide (TsN_3)[54] and 4-acetamidobenzenesulfonyl azide (*p*-ABSA)[55] are often used to introduce the functional group into molecules (Scheme 1.11, a)). However, these reagents are mainly used to transfer the diazo group to a methylene adjacent an EWG, typically a carbonyl. Diazos can also be synthesized via the Bamford-Stevens reaction, in which a tosylhydrazone is subjected to a base (Scheme 1.11, b)).[56,57] Using the

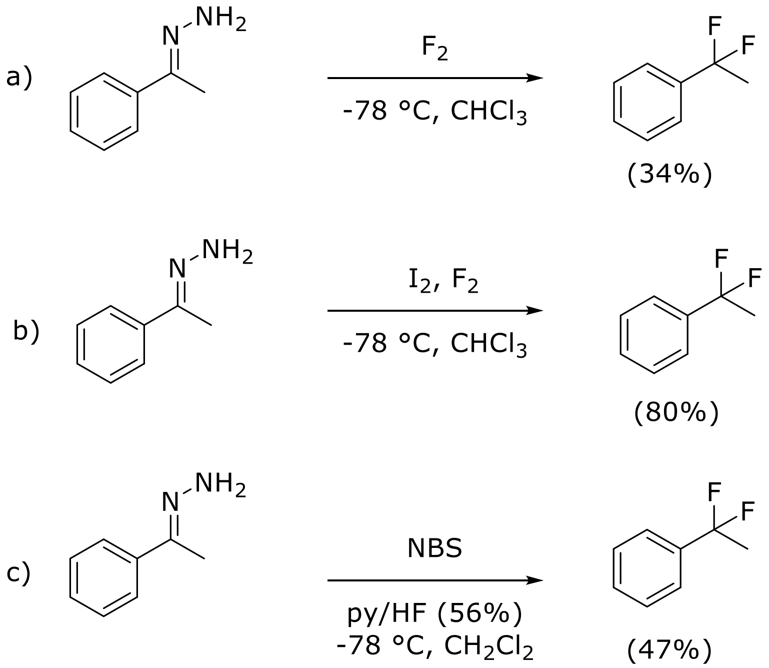
Bamford-Stevens preparative method, diazos can be obtained from ketones or aldehydes. Hydrazones can also be used as diazo precursors via oxidation with various oxidizing agents such as activated dimethyl sulfoxide (DMSO),[58] lead tetraacetate,[59] F_2,[60] and I_2 (Scheme 1.11, c)).[61]



Scheme 1.11 – Synthesis of diazo compounds

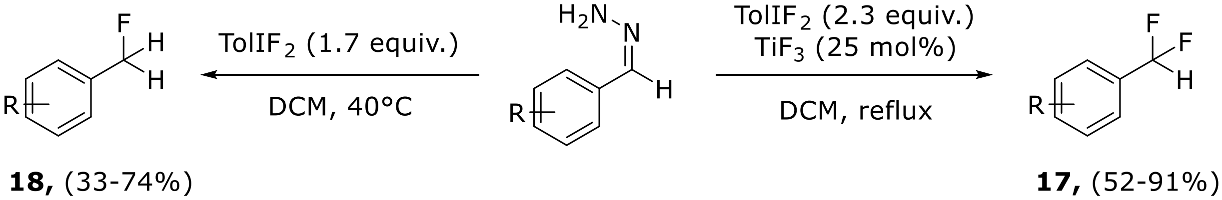
While the difluorination of diazos has been shown to be successful, there are limitations due to the stability of diazo compounds. Diazo molecules will react, sometimes violently, with acids to yield a highly electrophilic molecule, which will react with any nucleophile. This means that diazos are highly reactive and toxic.[62] For example, diazomethane is commonly used as a methylating agent and will alter deoxyribose nucleic acid (DNA).[63] Diazocarbonyls are more stable due to the resonance between the diazo and the carbonyl moiety. Diazocarbonyls are therefore often used and isolated in organic chemistry[64,65], while non-stabilized diazo molecules such as diazomethane are typically formed *in-situ*.[57–59]

Fluorine gas can oxidize hydrazones to diazo compounds, as shown by Flory and Patrick's difluorination of acetophenone hydrazone using F_2 (Scheme 1.12, a)).[60] However, their reaction had rather low yield of 34% for the product. To improve the yield, IF can be synthesized *in-situ* through the reaction of fluorine and iodine and used as the oxidizing and fluorinating agent to give a yield of 80% (Scheme 1.12, b)).[66] This technique still requires the use of fluorine gas, which is the major drawback of this reaction. Recently, hydrazones were reacted with *N*-bromosuccinimide (NBS) and pyridine/HF, yielding the *gem*-difluorinated product (Scheme 1.12, (c)) via the *in-situ* synthesis of BrF.[67] While this technique gives low yields of 47%, it offers the advantage of avoiding F_2.



Scheme 1.12 – Fluorination of hydrazones

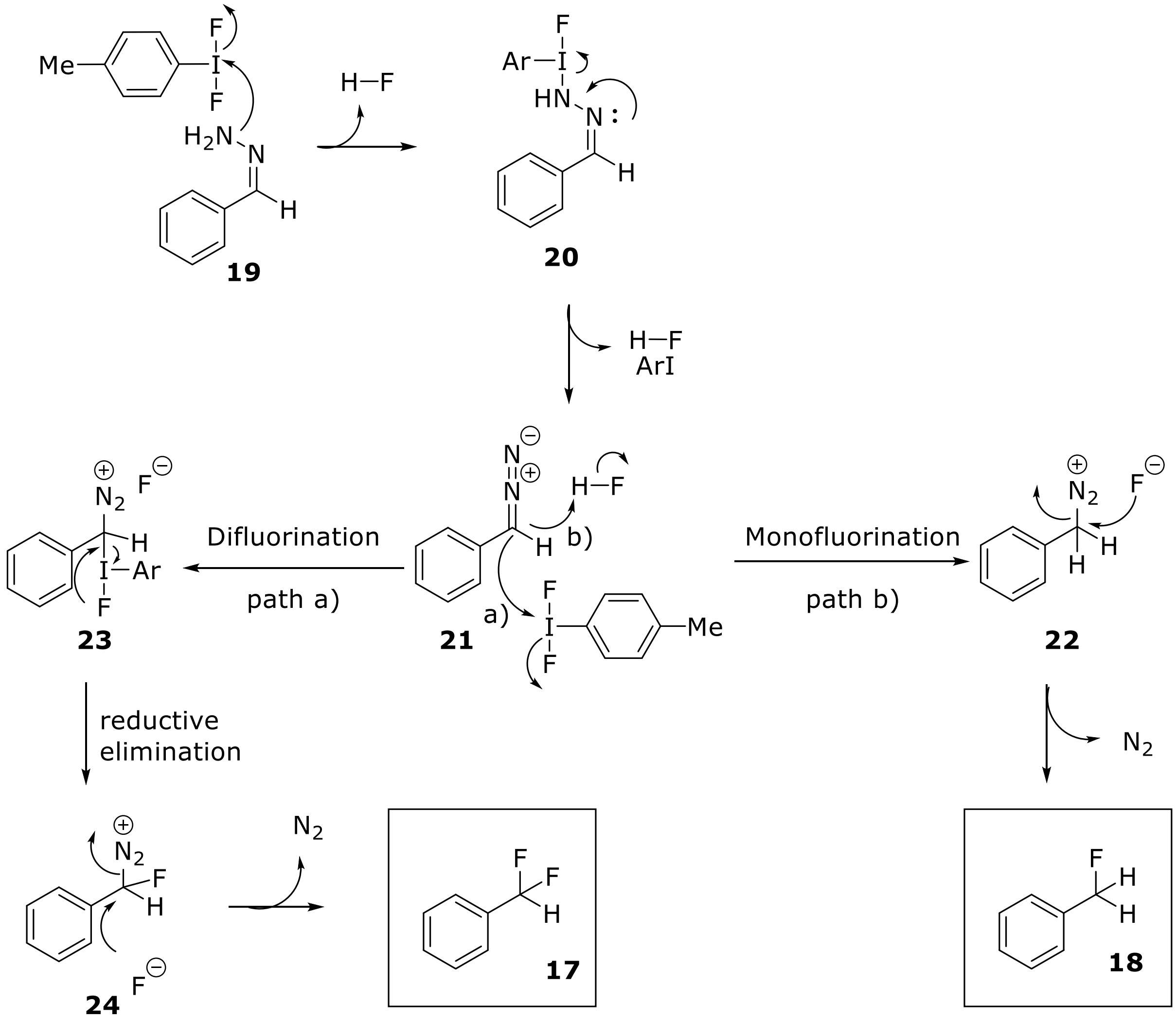
HVI molecules are well known oxidizing agents and have been used in the synthesis of diazo compounds from hydrazones. Many HVI reagents have been tested in this reaction, such as aryliodonium salts,[68] iodosobenzene,[69] IBX,[70] and TolIF$_2$[71]. Given the precedent for the oxidation of hydrazones to diazos with TolIF$_2$ and the *gem*-difluorination of diazo compounds with the same reagent, our group investigated the possibility of combining those two ideas into one reaction. We investigated the reaction of hydrazones derived from aldehydes to synthesize the *gem*-difluorinated products **17** and mono-fluorinated compounds **18** (Scheme 1.13).[72,73] We have successfully demonstrated that both products can be synthesized from the same hydrazone starting material by altering the reaction conditions.



Scheme 1.13 – Difluorination and hydrofluorination of benzylic aldehyde hydrazones

These reactions work well with a variety of substrates and give high yields. We think that both the mono-fluorination (Scheme 1.14, path a)) and the di-fluorination reactions (Scheme 1.14, path b)) start with the oxidation of the hydrazone to the diazo compound **21.** The oxidation yields two equivalent of HF and iodotoluene as a by-product. The HF produced can be attacked by the diazo compound to yield intermediate **22** (Scheme 1.14, path b)) which can undergo a nucleophilic attack from the fluoride anion to yield the monofluorinated product **18**. The addition of a Lewis acid activates TolIF$_2$, making the iodine more electrophilic and susceptible to a nucleophile. Therefore, the addition of the Lewis acid promotes the synthesis of the intermediate

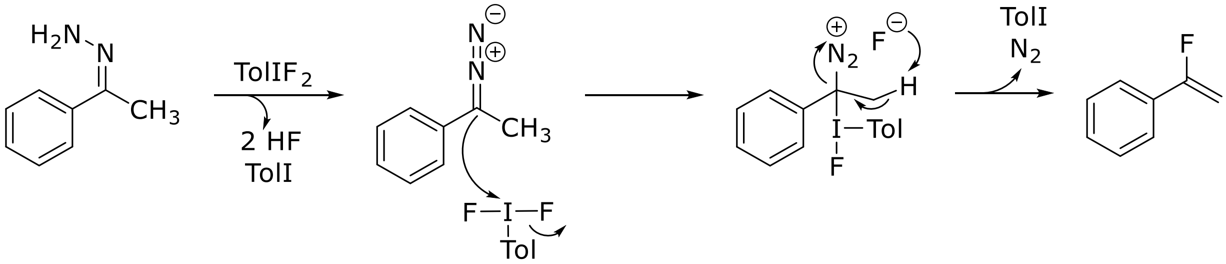
23 (Scheme 1.14, path a)). Intermediate **23** then undergoes sequential fluorinations and loss of N_2 and iodotoluene to yield the difluorinated product **17**.



Scheme 1.14 – Mechanism of the hydrofluorination and difluorination of hydrazones

1.4 Proposal

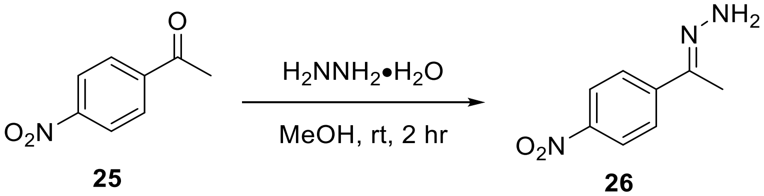
The substrate scope of the reaction is currently limited to hydrazone derived from benzylic aldehydes in which no α-proton is present. The presence of those protons could induce an elimination reaction, leading to loss of product (Scheme 1.15). The goal of this project is to further expand the substrate scope of the hydrofluorination and difluorination of hydrazones derived from ketones using $TolIF_2$.



Scheme 1.15 – Possible elimination side reaction

1.5 Optimization of the reaction conditions

p-Nitroacetophenone (**25**) was chosen as a model substrate since it is similar to *p*-nitrobenzaldehyde, the substrate previously used by our group in the optimization reaction of the aldehyde hydrazones.[72,73] The hydrazones (**26**) are easily synthesized by the reaction of hydrazone mono-hydrate in methanol (Scheme 1.16).



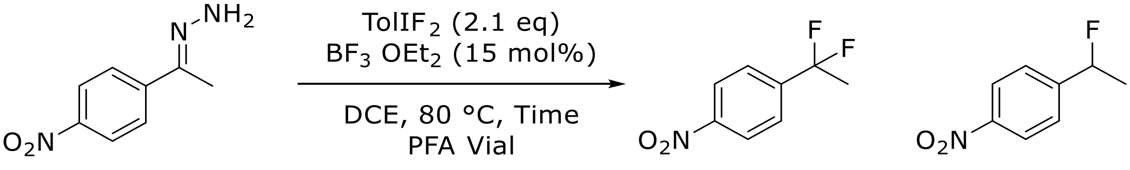
25 **26**

Scheme 1.16 – Synthesis of hydrazones

Using the reaction conditions previously established by our group, we attempted the difluorination of the *p*-nitroacetophenone hydrazone. The reaction was carried out in perfluoroalkoxy (PFA) vials, which are made of an inert polymer, by adding the substrate into

$TolIF_2$ with BF_3•OEt_2 as the Lewis acid in DCE (Table 2.1, entry 1). A trace amount of the difluorinated product **27** was observed as well as a low yield of the monofluorinated product **28**. Along with the product an insoluble substance was observed in the flask. Using infrared (IR) spectroscopy to investigate this solid, it was determined to be the azine. Azines are known to form when working with hydrazones.[74] Since two molecules of the starting material are used during the synthesis of the azine, the low yield of the fluorination reaction could be attributed to the synthesis of this side-product. The synthesis of the azine can be easily avoided by modifying of the addition order of the chemicals.[61]

Table 1.1 – Addition time optimization

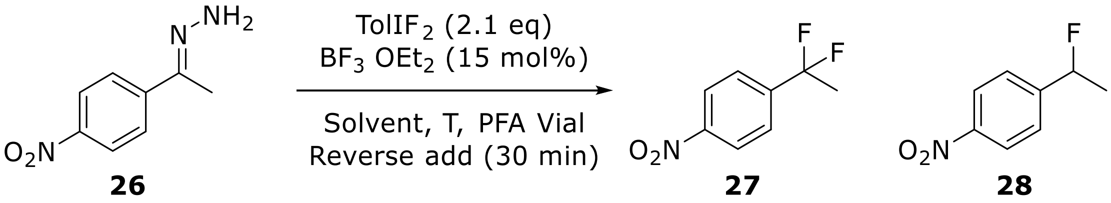


26 **27** **28**

Entry	Time of addition (min)	27 (%)	28 (%)
1	0	<5	21
2	15	12	14
3	30	48	13
4	60	45	20

We believed that a reverse addition would increase the yield by reducing the local concentration of the substrate. A reverse addition is when the substrate is added to the reagent, meaning the substrate would only be present in small amount, it is statistically more likely to come in contact with a molecule of $TolIF_2$ than another hydrazone molecule or a diazo and hence reducing the chances of forming the azine. When the substrate was added to the reagent over 15 min, we observed an increased the production of difluorinated molecules (Table 1.1, entry 2). Increasing the time further to 30 min gave a 48% yield, a small amount of the monofluorinated product, and no detectable azine (Table 1.1, entry 3). There was no improvement in the yield of the difluorinated product when the addition time was increased past 30 min (Table 1.1, entry 4).

Table 1.2 – Solvent optimization

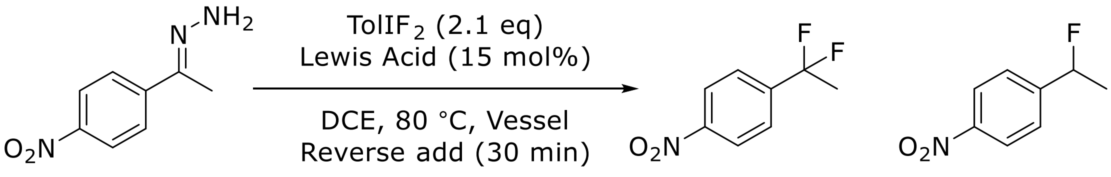


Entry	Solvent	T (˚C)	27 (%)	28 (%)
1	PhCl	80	<5	<5
2	THF	60	0	<5
3	CH_3CN	75	<5	0
4	PhMe	110	0	0
5	DCE	80	48	<5
6	$CHCl_3$	60	50	19
7	DCM	40	14	<5

The optimal solvent to use for the reaction was investigated next. Chlorobenzene gave a poor yield of the desired products which could be attributed to the low solubility of the starting material. Several commonly used organic solvents were tested. Tetrahydrofuran (THF), acetonitrile (CH_3CN) and toluene (PhMe) all gave yields that were below 5% (Table 1.2, entries 2-4). Chloroform and dichloroethane (DCE) (Table 1.2, entries 5-6) were determined to be the best solvents for this reaction. Halogenated solvents (Table 1.2, entries 1 and 5-7) provided the best results, with the exception of chlorobenzene. These results were not surprising, since we believe the reaction to be ionic and polar aprotic solvents tend to promote ionic reactions. While chloroform gave a slightly higher yield for the difluorinated product, it also produced more mono fluorinated molecules than DCE. For this reason, further optimization was done using DCE.

Our group has established that when using TolIF$_2$, the vessel used could greatly affect the reaction.[75] We have shown that borosilicate glass, found in round bottom flasks, can act as a Lewis acid, and could therefore influence the reaction. This parameter was tested by performing the difluorination reaction in the presence of BF_3•OEt_2 in a glass flask. This reaction produced none of the desired products. Next, we performed the reaction in a glass flask but did not add any BF_3•OEt_2 (Table 1.3, entry 2). This reaction yielded only a very small amount of monofluorinated product and trace amount of difluorinated product. These results indicated that the borosilicate glass impeded the desired reaction. When we removed the borosilicate by using a PFA vial and BF_3•OEt_2 we obtained the best result (Table 1.3, entry 3). All subsequent reactions were performed using an inert PFA vessel.

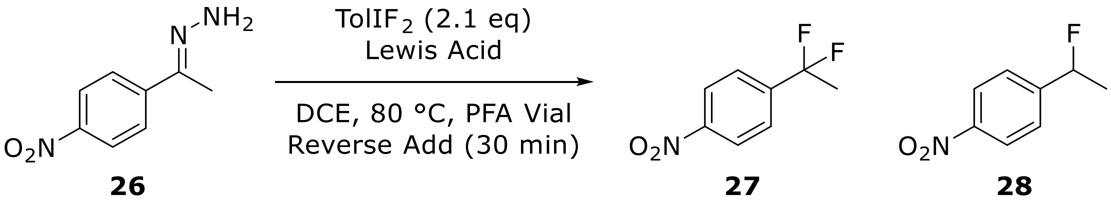
Table 1.3 – Effect of vessel on the reaction



Entry	Vessel	Lewis Acid	27 (%)	28 (%)
1	Glass	BF_3•OEt_2	0	0
2	Glass	None	<5	5
3	PFA	BF_3•OEt_2	48	<5

A control reaction in which the Lewis acid was omitted completely was then carried out (Table 1.4, entry 1). This gave an 87% yield of the monofluorinated product and none of the difluorinated product was observed. This indicated that the Lewis acid is necessary for the difluorination reaction. It acts as a catalyst and activates the iodane in order for it to react with the diazo. To better understand the role of the activator, different catalysts were screened to optimize the reaction.

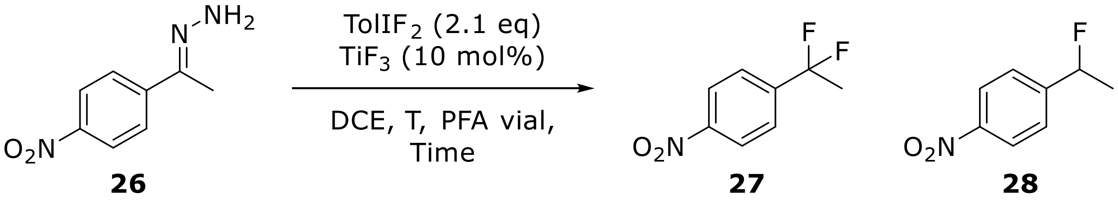
Table 1.4 – Lewis acid optimization



Entry	Lewis Acid	Cat. Loading (mol%)	27 (%)	28 (%)
1	None	N/A	0	87
2	BF_3•OEt_2	10	45	20
3	BF_3•OEt_2	20	29	19
4	BF_3•THF	10	38	20
5	TiF_4	10	42	11
6	GaF_3	10	0	68
7	SbF_3	10	25	7
8	SnF_2	10	46	27
9	TiF_3	10	42	12
10	TiF_3	15	54	<5
11	TiF_3	20	38	<5

First the concentration of the Lewis acid was explored. Increasing the concentration of BF_3•OEt_2 to 20 mol% saw a decrease in yield (Table 1.4, entry 2). A different etherate of boron was tested, BF_3•THF (Table 1.4, entry 3) since it is a weaker Lewis acid due to a stronger Lewis pair complex, but no significant change was observed compared to the BF_3•OEt_2 result. The resulting reaction was not selective, indicating that BF_3•OEt_2 could potentially be too strong of an activator and that other fluorinated metal Lewis acids should be tested (Table 1.4, entries 5-8). The majority of these did not improve the reaction. The yield decreased with the addition of GaF_3 (Table 1.4, entry 6). TiF_3 was then tested and while it yielded similar results to BF_3•OEt_2 at 10 mol% (Table 1.4, entry 9), almost no mono-fluorinated product was observed when the concentration was increased to 15 mol% (Table 1.4, entry 10). It is unclear why this catalyst would affect the fluorination reaction so that the difluorinated pathway is promoted. TiF_3 is not a commonly used as a Lewis acid, it is more commonly used in dehydrogenation reactions involving magnesium borohydride.[76] Even in the dehydrogenation reaction, the role of TiF_3 is not fully understood but it has been shown to improve the hydrogen absorption.[76–78] Raising the concentration of the Lewis acid TiF_3 to 20 mol% decreased the yield of the difluorinated product (Table 1.4, entry 11). Further work is required to fully elucidate the role of TiF_3 in this reaction.

Table 1.5 – Re-optimization of the difluorination reaction using TiF_3

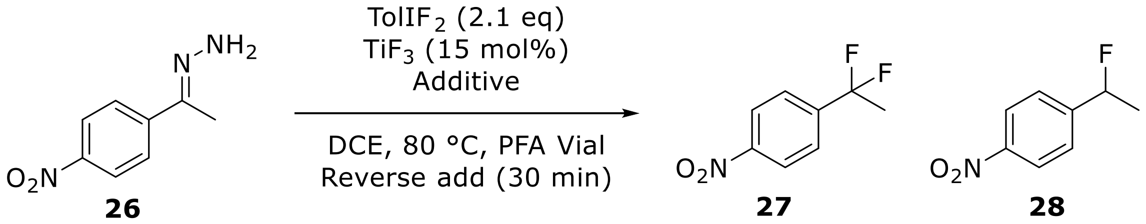


Entry	Temperature (˚C)	Addition	27 (%)	28 (%)
1	80	Reverse (30 min)	55	<5
2	80	Normal (1 portion)	0	71
3	80	Reverse (1 portion)	0	51
4	60	Reverse (30 min)	34	14
5	r.t.	Reverse (30 min)	27	24
6	0	Reverse (30 min)	22	20

Using 15 mol% of TiF_3, we revisited the addition time and temperature parameters of the reaction. The reagents, $TolIF_2$ and TiF_3 in DCE, were slowly added in one portion to the substrate (Table 1.5, entry 2), and only the mono-fluorinated product and the azine were observed. When the substrate was added in one portion to the reagents (Table 1.5, entry 3), the same result was found. This indicated that the slow addition of the substrate is necessary to avoid formation of the azine. Lowering the temperature from 60 ˚C to 0 ˚C resulted in an increase in the formation of the mono-fluorinated product and a decrease in the formation of the difluorinated product (Table 1.5, entries 5-6).

Next, the influence of different additives on the reaction were tested. Since the monofluorination reaction favors the diazo attacking HF, scavenging the HF produced should promote the difluorinated reaction. Limiting the amount of HF present in the reaction would be expected to improve the difluorination yield. Several bases were tested (Table 1.6, entries 1-6) and an increase in the monofluorinated product was observed. Since we had expected an increase in the difluorinated product, these results were explored further to promote the monofluorination reaction (Section 1.6). Acids were then tested to determine how they would affect the difluorination reaction (Table 1.6, entries 7-8). We believed that increasing the concentration of HF would lead to higher chances of hydrofluorination occurring, which was not the case. There was no increase in monofluorination when HF was added as an additive in the reaction mixture. There was also no increase in the monofluorination reaction when using acetic acid.

Table 1.6 – Acid and base testing

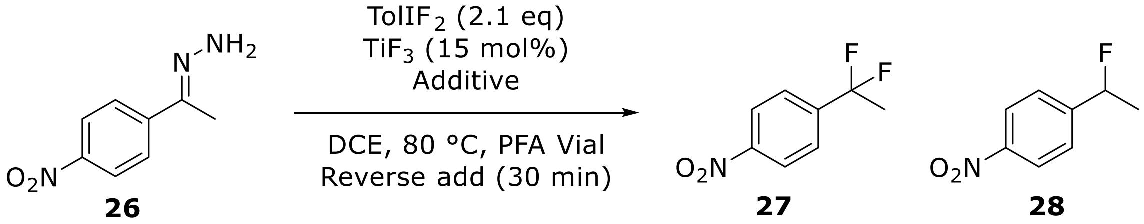


Entry	Additive	27 (%)	28 (%)
1	Cs_2CO_3 (5 mol%)	17	63
2	Na_2CO_3 (10 mol%)	20	13
3	Na_2CO_3 (1 equiv.)	27	17
4	NaOAc (1 equiv.)	23	43
5	2,6-lutidine (10 mol%)	3	70
6	Pyridine (10 mol%)	28	32
7	KOH (xs)	30	37
8	Acetic Acid (20 mol%)	34	11

9	HF (aq) (1 equiv.)	22	38

Since the reaction mechanism involves two steps, we wished to test whether the formation of the diazo would affect the reaction. We tested this by adding Oxone®, a monopersulfate oxidizing agent, which can oxidize hydrazones to diazos. No improvement was observed in the yield when Oxone® was added to the reaction mixture, (Table 1.7, entries 1-2). PIDA, another oxidizing agent, was also tested as an additive and did not improve the reaction yield either (Table 1.7, entry 3). This showed us that the synthesis of the diazo compound was not the issue with the difluorination reaction since oxidants did not improve the yield of the reaction.

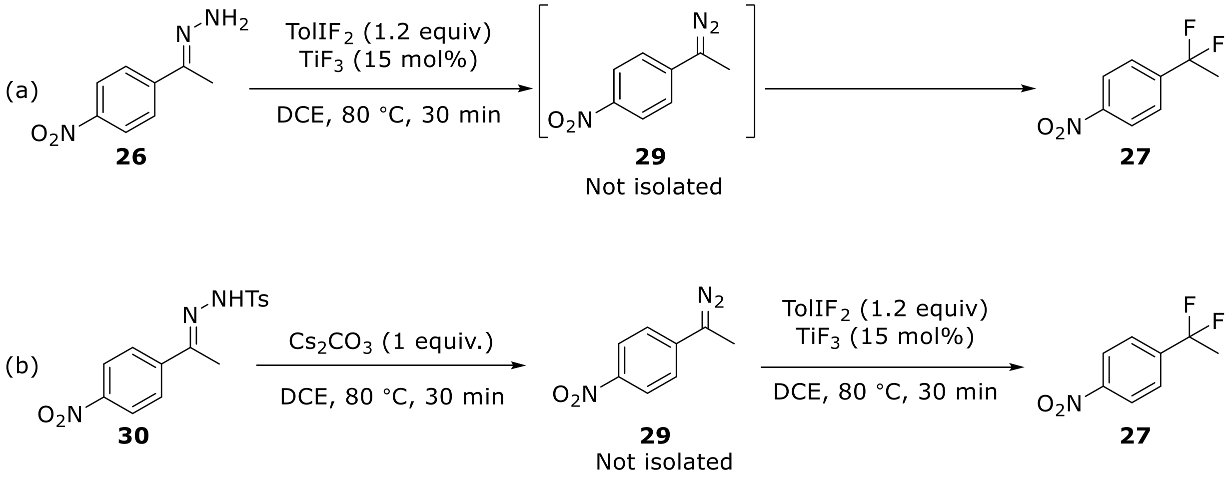
Table 1.7 – Oxidant screen



Entry	Additive	27 (%)	28 (%)
1	Oxone® (1 equiv.)	21	4
2	Oxone® (3 equiv.)	0	55
3	PIDA (1 equiv.)	34	5

1.6 Investigation into the diazo intermediate

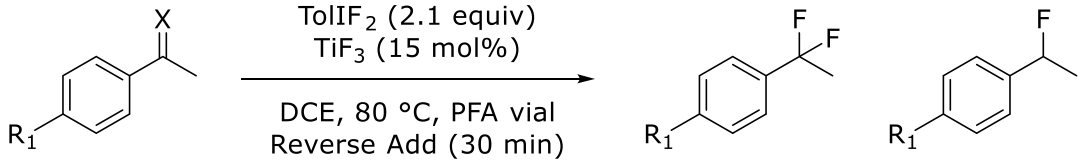
We proposed that the reaction would proceed according to the equation outlined in Scheme 1.17 part (a). We believe that the synthesis of the diazo compound is not the issue with our reaction and that the low yield is attributed to the fluorination. To test this, we attempted the reaction starting from the diazo compound **29**. It was synthesized *in-situ* via a Bamford-Stevens reaction[56] through the reaction of tosylhydrazone **30** with Cs_2CO_3 (Scheme 1.17, part (b)). To our surprise the diazo was not soluble in DCE, the solvent used for the reaction. During a typical reaction some solid would precipitate from the reaction, which could be the diazo compounds and hence reduce the yield of the reaction. We then reacted the diazo with TolIF$_2$ and no product was observed. It is unclear whether this a solubility issue or if our proposed mechanism is wrong. Since the diazo compound did not yield any difluorinated product when reacted with TolIF$_2$, we believe it is unlikely that the diazo is formed *in-situ* when the hydrazone is reacted with TolIF$_2$.



Scheme 1.17 – Testing for the diazo intermediate

Since nitro groups are extremely electron withdrawing, the nucleophilicity of the diazo compound is affected. We synthesized the hydrazone of *p*-methoxyacetophenone (**31**), which contains an electron donating group (EDG), and tested it in the reaction conditions we had already established, yielding no product (Table 1.8, entry 4). To determine whether the diazo compounds would be reactive in the established reaction conditions, we synthesized the diazo compound of *p*-methoxyacetophenone (**32**) *in-situ* and again no product was observed (Table 1.8, entry 5). It is notable that the diazo compound **32** was soluble in DCE and that there was still no product observed. This means that the reason *p*-methoxyacetophenone diazo compound does not react is not solubility. In previous work with the aldehyde derivatives hydrazones, the presence of a methoxy group at the *para* position gave some of the lowest yields, and therefore our results were not surprising.[72,73] The tosyl hydrazones (**30** and **26**) were also tested in the hope that they would undergo fluorination, similar to the work done by Yadav and co-worker[79]. They reported the fluorination of tosylhydrazone derivatives of aromatic aldehyde using a base along with $Et_3N•3HF$. However, when the tosyl hydrazones were treated with our reaction conditions no product was observed.

Table 1.8 – Electronic effect



26, R_1 = NO_2, X = NNH_2
29, R_1 = NO_2, X = N_2
30, R_1 = NO_2, X = NNHTs
31, R_1 = OMe, X = NNH_2
32, R_1 = OMe, X = N_2
33, R_1 = OMe, X = NNHTs

27, R_1 = NO_2
34, R_1 = OMe

28, R_1 = NO_2
35, R_1 = OMe

Entries	Substrate	Difluorinated yield (%)	Monofluorinated yield (%)
1	**26**	**27,** 27%	**28**, 24%
2[a]	**29**	**27**, 0%	**28**, 0%
3	**30**	**27**, 0%	**28**, 0%
4	**31**	**34**, 0%	**35**, 0%
5[a]	**32**	**34**, 0%	**35**, 0%
6	**33**	**34**, 0%	**35**, 0%

[a] The diazo compound was synthesized *in-situ* from the reaction of tosylhydrazone reacting with Cs_2CO_3

We believe that the reaction with the hydrazone **26** does not have a diazo intermediate because the diazo of *p*-nitroacetophenone is insoluble in the reaction solvent and would therefore precipitate once formed during the reaction. We also saw no product formation when the diazo was reacted with $TolIF_2$ indicating that it is unlikely to have reacted to form the product. In the case of the diazo of *p*-methoxyacetophenone no product was formed but the diazo is soluble in DCE, meaning that the reason it is not reacting is not due to solubility. However, the *p*-methoxyacetophenone hydrazone also did not yield any product, and previous work done by our group showed that the para methoxy group gave the worst yields.[72,73]

More experiments, such as nuclear magnetic resonance (NMR) studies to identify the diazo or key intermediates to probe the mechanism, are necessary to fully understand the mechanism of this reaction.

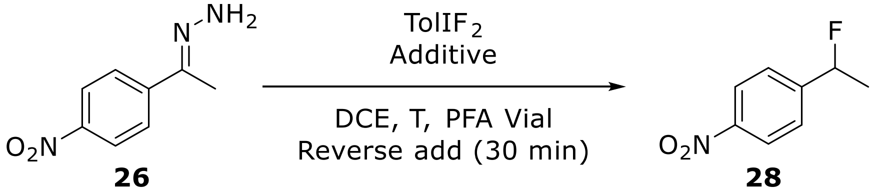
The hydrazone **26** is the only substrate that produced a difluorinated product. This could indicate that the reaction requires a EWG. Other substrates containing EWG should be tested, such as *p*-trifluoro- or *p*-chloro-acetophenone hydrazone derivatives, to determine if this is the case. Neutral substrates, such as acetophenone of biphenylacetophenone hydrazone derivative, should also be tested.

1.7 Optimization of the hydrofluorination reaction

The control reaction in which no Lewis acid was added gave a high yield of the monofluorinated product (Table 1.9, entry 1). Because of this result, the idea of promoting selective monofluorination was investigated. Beginning from the control reaction of 2.1 equivalents of

$TolIF_2$, we explored a decrease in the amount of $TolIF_2$ since only one equivalent would be required for the mechanism. Testing this hypothesis, we added 1.0 equivalent (Table 1.9, entry 2) and a decrease in the yield was observed. Adding a slight excess of the reagent raised the yield to 77% (Table 1.9, entry 3). It had been previously observed that the addition of a base increased the formation of the mono-fluorinated products (Table 1.9, entries 1-6). The addition of a base, in the absence of a Lewis acid, with 1.1 equivalent of $TolIF_2$ resulted in increased yields (Table 1.9, entries 5-8). Adding 5 mol% of 2,6-lutidine gave the best yield of 99%. A lower temperature reaction was attempted in order to have milder reaction conditions (Table 1.9, entry 8), but significantly lower yields were observed.

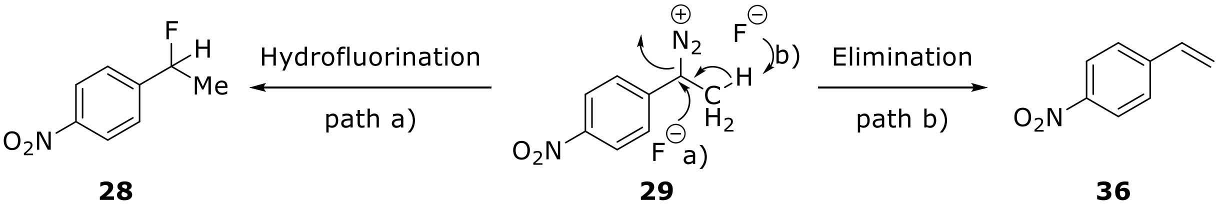
Table 1.9 – Monofluorination optimization



Entry	$TolIF_2$ (equiv.)	Additive	T (˚C)	Yield (%)
1	2.1	None	80	87
2	1.0	None	80	44
4	1.2	None	80	77
5	1.1	Cs_2CO_3 (5 mol%)	80	82
6	1.1	2,6-lutidine (5 mol%)	80	85
7	1.1	2,6-lutidine (10 mol%)	80	99
8	1.1	2,6-lutidine (10 mol%)	60	26

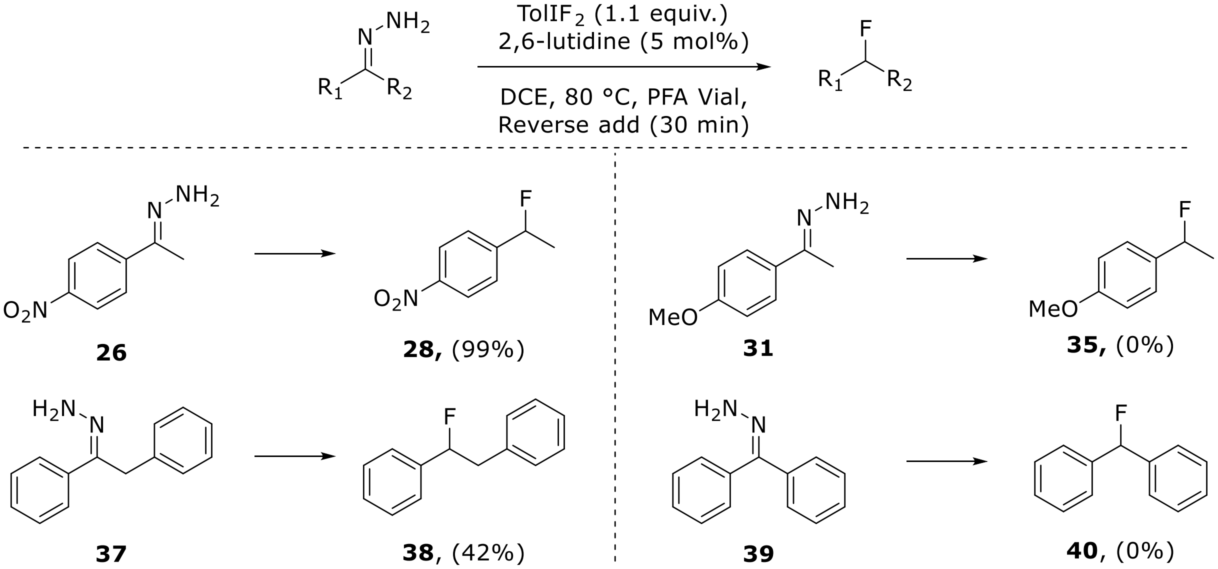
In all of the mono-fluorination reactions, a small amount of a styrene side-product (**36**) was observed. We believe this side-product is synthesized via the elimination reaction shown in

Scheme 1.18. This side product could never be fully removed and there were always trace amounts present.



Scheme 1.18 – Mechanism of the formation of styrene

This is a very promising start for hydrofluorination although other substrates were less successful. Phenyl acetophenone hydrazone derivative (**37**) yielded 42% of the monofluorinated product **38** (Scheme 1.19). When the reaction was attempted on other hydrazone derivative such as *p*-methoxyacetophenone (**31**) and benzophenone (**39**) no mono-fluorinated product was observed.



Scheme 1.19 – Hydrofluorination of various hydrazones

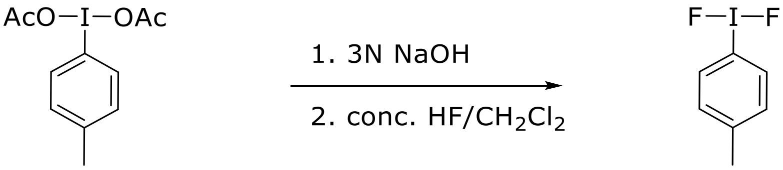
1.8 Conclusions and future work

The reactions involving the aldehyde hydrazones all proved highly successful both in monofluorination and difluorination. When we tried to expand the reaction to ketones, we expected to have complications stemming from the addition of the α-proton. While the addition of the proton did not interfere with the reaction, the reaction did not work as well as with the aldehydes. After some investigation we cannot come to a conclusion as to why it is not working as expected. It could be due to the methyl group lowering the stability of the diazo compound by inductively donating electron density or due to the fact that the diazo is more sterically hindered. However, we think that the acetophenone derivative simply goes through a different mechanism which does not involve a diazo compound. Studies such as real-time IR which could potentially detect the diazo or another type of reactive intermediate should be performed to fully understand the mechanism of the reaction. The reaction could be going through a carbene intermediate and have a decreased yield as a result of nonspecific reactivity. This could be tested by adding an alkene to the reaction and observing whether any cyclopropanation occurs. Similarly, a radical mechanism could be at play in this reaction, which could easily be tested by the addition of a radical inhibitor. To fully optimize this reaction, further studies into the mechanism are required.

1.9 Experimental Procedures

Reactions were carried out in oven-dried glassware unless otherwise stated. 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) or dimethylsulfoxide peak (2.50 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. ppm) or the center line of the septet of dimethylsulfoxide-d_6 (39.52 ppm). Fluorine NMR spectra (^{19}F NMR) were recorded at 470 MHz and are reported (ppm) relative to TFA (-76.53 ppm).

1.9.1 Synthesis of iodotoluene difluoride

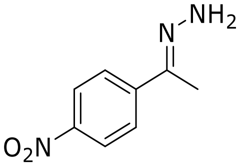


Aqueous 5M sodium hydroxide (28.6 mL, 143 mmol) was added to TolI(OAc)$_2$ (8.4 g, 25 mmol) and stirred for 4 hours. The resulting yellow slurry was filtered through a fritted glass funnel and washed with water (2x100 mL) then chloroform (100 mL), and suction dried to give a yellow solid. The wet TolIO was immediately transferred to a Teflon bottle equipped with a magnetic stir-bar and was suspended in CH_2Cl_2 (40 mL) at room temperature. The mixture was carefully stirred as conc. aq. HF added dropwise via a polyethylene pipette until all of the solid disappeared (typically ~ 9 mL). The aqueous layer was decanted and the organic layer was concentrated to dryness under a stream of nitrogen to obtain a yellow-white solid. The crude solid was recrystallized using a mixture of hexanes and $CHCl_3$ to yield the title compound as white needles (4.1 g, 64%). m.p. 98 – 102 °C. ^{1}H, ^{13}C and ^{19}F NMR data were consistent with the reported values.[80,81]

1.9.2 General procedure A: hydrazone synthesis

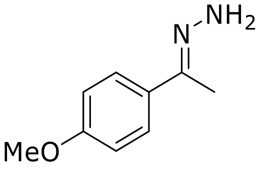
Ketone precursor (1 equiv.) was added to a solution of $NH_2NH_2 \bullet H_2O$ (10 equiv.) in ethanol (20 mL), and the reaction mixture was stirred at room temperature for 16 h. The resulting mixture was poured over ice to obtain a precipitate which was filtered using vacuum suction and dried to obtain hydrazone. These hydrazones were used in difluorination reactions without any further purification.

(1-(4-nitrophenyl)ethylidene)hydrazine (26)



p-Nitroacetophenone (1.07 g, 8.9 mmol, 1.0 equiv.) was subjected to General Procedure A to yield *p*-nitroacetophenone hydrazone (**26**) (1.43 g, 89%) as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 5.64 (br s, 2H), 7.79 (d, *J* = 8.9 Hz, 2H), 8.18 (d, *J* = 8.9 Hz, 2H). Spectral data were consistent with literature values.[82]

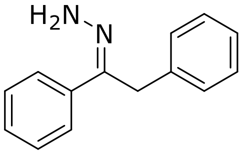
(1-(4-methoxyphenyl)ethylidene)hydrazine (31):



p-Methoxyacetophenone (707 mg, 4.7 mmol, 1.0 equiv.) was subjected to General Procedure A to yield *p*-methoxyacetophenone hydrazone (**31**) (354 g, 45%) as a yellow solid. ^{1}H NMR (300

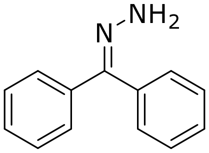
MHz, $CDCl_3$) δ 2.11 (s, 3H), 3.81 (s, 3H), 5.24 (br s, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 7.57 (d, *J* = 8.9 Hz, 2H). Spectral data were consistent with literature values.[82]

(1,2-diphenylethylidene)hydrazine (37)



Phenylacetophenone (986 mg, 5.01 mmol, 1 equiv.) was subjected to General Procedure A to yield phenylacetophenone hydrazone (**37**) (831 g, 79%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (s, 2H), 5.38 (s, 2H), 7.23-7.35 (m, 8H), 7.67-7.70 (m, 2H). Spectral data were consistent with literature values.[83]

(diphenylmethylene)hydrazine (39)

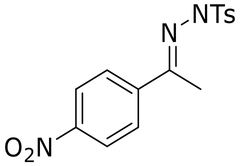


Benzophenone (692 mg, 3.80 mmol, 1 equiv.) was subjected to General Procedure A to yield benzophenone hydrazone (**39**) (663 g, 89%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (s br, 2H) 7.27-7.301 (m, 5H), 7.45-7.52 (m, 5H). Spectral data were consistent with literature values.[84]

1.9.3 General procedure B: tosyl hydrazone synthesis

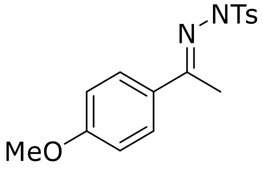
Ketone precursors (1 equiv.) were dissolved in absolute methanol (0.3 M) and stirred vigorously. To this solution was added p-toluenesulfonyl hydrazide (1.05 equiv.) in one portion, and the solution was stirred at reflux for 16 hours. The mixture was cooled to rt and then filtered to afford product. These tosylhydrazones were used in difluorination reactions without any further purification.

(1-(4-nitrophenyl)ethylidene)-2-tosyldiazane (30)



p-Nitroacetophenone (528 g, 3.2 mmol, 1 equiv.) was subjected to General Procedure B to yield *p*-nitroacetophenone hydrazone (**30**) (923 g, 86%) as a pale yellow solid .^{1}H NMR (300 MHz, CDCl$_3$) δ 2.18 (s, 3H), 2.42 (s, 3H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.70 (br s, 1H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 2H), 8.19 (d, *J* = 8.6 Hz, 2H). Spectral data were consistent with literature values.[85]

(1-(4-methoxyphenyl)ethylidene)-2-tosyldiazane (33)

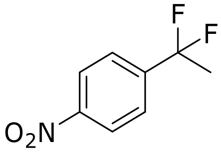


Pp-Methoxyacetophenone (513 mg, 3.42 mmol, 1 equiv.) was subjected to General Procedure B to yield *p*-methoxyacetophenone hydrazone (**33**) (938 g, 86%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11 (s, 3H), 2.40 (s, 3H), 3.80 (s, 3H), 6.83 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.70 (br s, 1H), 7.91 (d, *J* = 8.2 Hz, 2H). Spectral data were consistent with literature values.[85]

1.9.4 General procedure C: *gem*-difluorination reaction

The precursor (1 equiv.) in 2 mL of DCE is added dropwise over 30 mins to a PFA vial containing $TolIF_2$ (2.1 equiv.) and BF_3•OEt_2 (15 mol%) in DCE, heated in an oil bath at 75˚C. After the addition was completed the reaction was allowed to stir for another 10 mins. The crude reaction mixtures were concentrated by rotary evaporation and purified by column chromatography.

1-(1,1-difluoroethyl)-4-nitrobenzene (27)

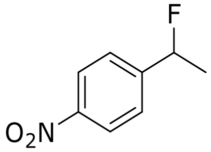


p-Nitroacetophenone hydrazone (**26**) (2 mL, 0.0 8M, 0.16 mmol, 1.0 equiv.) was subjected to General Procedure C to yield a crude reaction mixture that was purified via column chromatography (100% hexanes to 10% EtOAc in hexanes gradient, UV active) to give **27** (27 mg, 99%) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (t, *J* = 18.1 Hz, 3H), 7.68 (d, *J* = 8.4 Hz, 2h), 8.28 (d, *J* = 8.4 Hz, 2H). ^{19}F (470 MHz, $CDCl_3$) δ -89.29. Spectral data were consistent with literature values.[86]

2.5.5 General procedure D: hydrofluorination

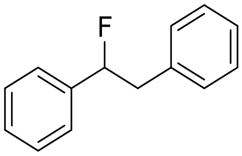
The precursor (1 equiv.) in 2 mL of DCE is added dropwise over 30 mins to a PFA vial containing $TolIF_2$ (2.1 equiv.) and 2,6-lutidine (5 mol%) in DCE, heated in an oil bath at 75˚C. After the addition was completed the reaction was allowed to stir for another 10 mins. The crude reaction mixtures were concentrated by rotary evaporation and purified by column chromatography

1-(1-fluoroethyl)-4-nitrobenzene (28)



p-Nitroacetophenone hydrazone (**26**) (2 mL, 0.08 M, 0.16 mmol, 1.0 eq) was subjected to General Procedure D to yield a crude reaction mixture that was purified via column chromatography (10% EtOAc in hexanes, UV active) to give **28** (27 mg, 99%) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (dd, *J* = 6.5 Hz, 3H), 5.71 (dq, *J* = 6.5 Hz, 2H), 7.49 (d, *J* = 8.6 Hz, 2H), 8.23 (d, *J* = 7.4 Hz, 2H). ^{19}F (470 MHz, $CDCl_3$) δ -172.99. Spectral data were consistent with literature values.[86]

(1-fluoroethane-1,2-diyl)dibenzene (38)



Phenylacetophenone hydrazone **37** (1 mL, 0.1 mmol, 1.0 eq) was subjected to General Procedure D to yield a crude reaction mixture that was purified via column chromatography (10% EtOAc in hexanes, UV active) to give **38** (6 mg, 30%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.06-3.39 (m, 3H), 5.51-5.71 (m, 1H), 7.16-7.58 (m, 10H). ^{19}F (470 MHz, $CDCl_3$) δ -173.46. Spectral data were consistent with literature values.[87]

1.9.7 General procedure E: fluorination via Bamford-Stevens diazo synthesis

The tosylhydrazone precursor (1 equiv.) was dissolved in DCM (2 mL) at 40 ˚C in a PFA vial. Cs_2CO_3 (1.1 eq) was added. After being stirred for 30 min $TolIF_2$ (1.2 equiv.) was added and stirred for another 30 min. The crude reaction mixtures were concentrated by rotary evaporation and purified by column chromatography.

Chapter 2 – Synthesis of triphenylphosphine dichloride using iodobenzene dichloride

2.1 Introduction to organophosphorus compounds

Phosphorus was discovered in 1669 by the alchemist Hennig Brand in Hamburg, Germany. Like many scientists at the time, he was seeking the “philosopher’s stone”, a substance that could transform common metals into gold. In an attempt to create this “philosopher’s stone”, he boiled over 5500 liters of urine to dryness, leaving behind a liquid which would solidify to phosphorus.[88]

Phosphorus is a group 15 element in the periodic table and has 5 valence electrons. Organophosphorus compounds are chemicals which contain at least one C-P bond. The phosphorus atom can have an oxidation state ranging from -3 to +5 (Figure 2.1). It will typically form either 3 covalent bonds, leaving one non-bonding pair of electrons, or five covalent bonds in which all valence electrons form a bond. The oxidation states relevant to this research are trivalent phosphorus compounds (+3) and pentavalent phosphorus compounds (+5).

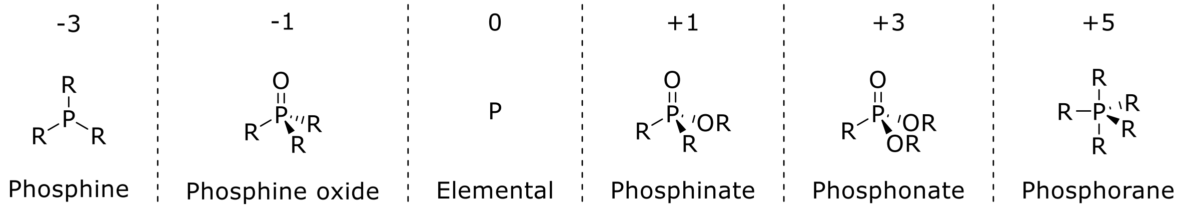
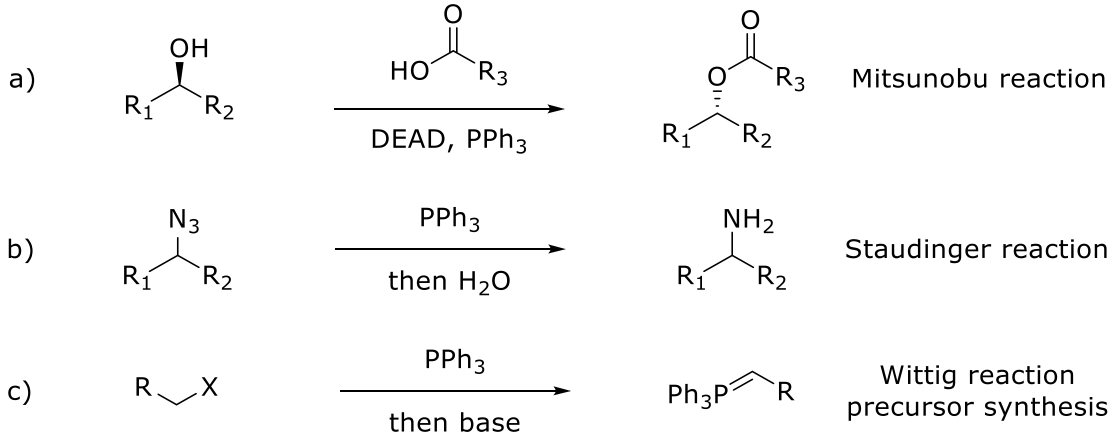


Figure 2.1 – Oxidation states of common organophosphorus compounds

2.2 Phosphorus(III) compounds

Phosphines have an oxidation state of -3. These compounds form 3 covalent bonds with other atoms, have a lone pair of electrons on the phosphorus atom, and have a trigonal pyramidal geometry. The lone pair of electrons on the phosphorus renders the molecule nucleophilic.[89–91] Phosphines are classified as either primary (RPH_2), secondary (R_2PH) or tertiary (R_3P) and are generally used as nucleophiles or reducing agents.[92] Named reactions which use a phosphine include the Mitsunobu (Scheme 2.1, a))[93] or Staudinger reactions (Scheme 2.1, b))[94] and phosphines are also used to synthesize Wittig reaction precursors (Scheme 2.1, c)). It is fairly common for phosphines or phosphites to be used in reactions which synthesize pentavalent organophosphorus compounds such as the Arbuzov reaction.[95] Since phosphines and phosphites are good nucleophiles and HVI reagents are good electrophiles, it is unsurprising that reactions between the two have been explored.

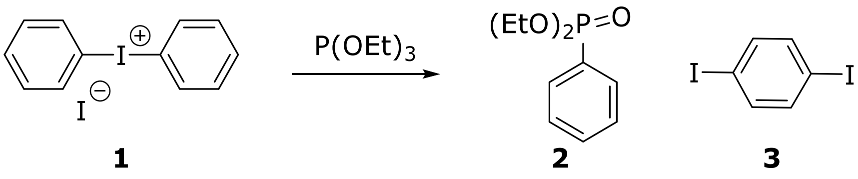


Scheme 2.1 – Named organic reactions using triphenylphosphine

2.3 Oxidation of phosphorus(III) compounds using HVI reagents

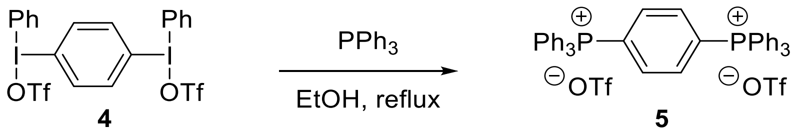
In 1972, Varvoglis reported the reaction of triethyl phosphite and diphenyliodoium salt (**1**) which resulted in the synthesis of diethyl phenyl-phosphonate (**2**) and 1,4-diiodobenzene (**3**) (Scheme

2.2) in low yields.[96] Liu et al. demonstrated that changing from triethylphosphite to a dialkyl phosphite salt increased the yield significantly and gave an effective method for the synthesis of arylphosphonates.[97]



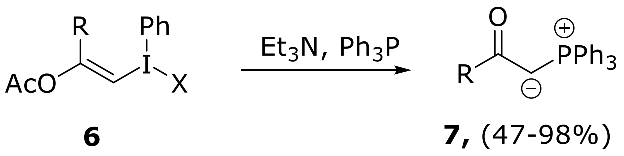
Scheme 2.2 – Formation of C-P bond to form a phosphonate

Kitamura and colleagues worked on the synthesis of (*p*-phenylene)bis(aryliodonium) ditriflates (**4**) and the reaction of this HVI species with various nucleophiles including triphenylphosphine, which yielded the (*p*-phenylene)bis(triphenylphosphonium) salt (**5**) quantitatively (Scheme 2.3).[98]



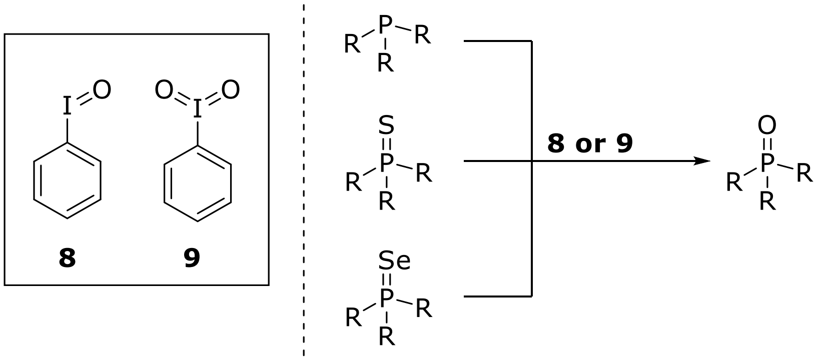
Scheme 2.3 – Synthesis of (p-phenylene)bis(triphenylphosphonium) salt

Ochiai et al. have demonstrated the synthesis of β-keto phosphonium ylides (**6**), which are used in the Wittig olefination, via the reaction of α-λ^3-iodanyl ketones (**7**) with a phosphorus nucleophile (Scheme 2.4).[99]



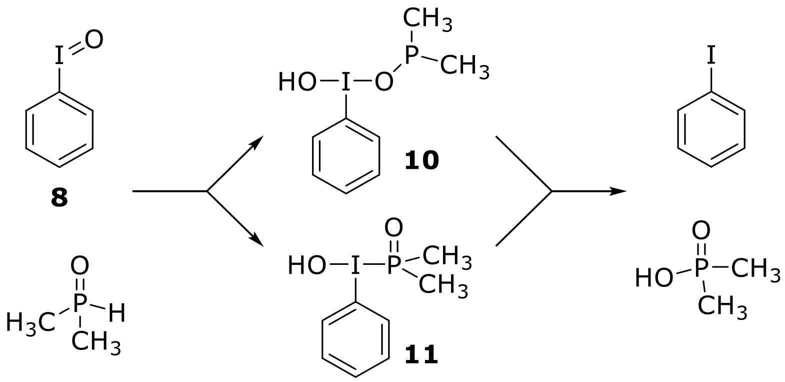
Scheme 2.4 – Synthesis of β-keto phosphonium ylides from α-λ^3-iodanyl ketones

HVI reagents are well known oxidizing agents that can be used in the oxidation of phosphorus(III) species. Mielniczak and Łopusiński studied the use of iodosobenzene (**8**) and iodoxybenzene (**9**) as reagents for oxygen transfer to phosphorus compounds (Scheme 2.5).[100] They studied the oxidation of phosphine and observed high yields for the reaction. However, the oxidation of phosphites was very slow, even in the presence of activators. They further studied the oxidation of thionophosphorus and phosphine selenide compounds and observed the desired phosphorous oxide in good yields.



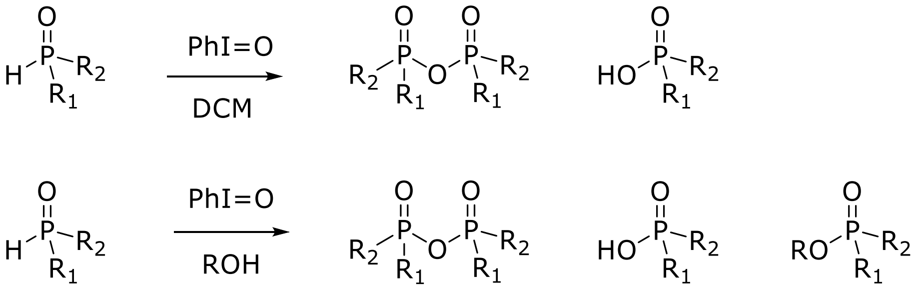
Scheme 2.5 – Oxidation of phosphine, thiophosphine and phosphine seledine using HVI

Makowiec and Rachon also investigated the use of iodoxybenzene in the presence of phosphites to create a new HVI phosphorylating agent (Scheme 2.6). Theoretically, phosphoric acids can add to iodoxybenzene to form either a tetra-coordinate (**10**) or a tri-coordinate phosphorus intermediate (**11**).[19] Both intermediates then collapse to yield iodobenzene and phosphonic acid.



Scheme 2.6 – Reaction of dimethyl phosphine oxide with iodosobenzene

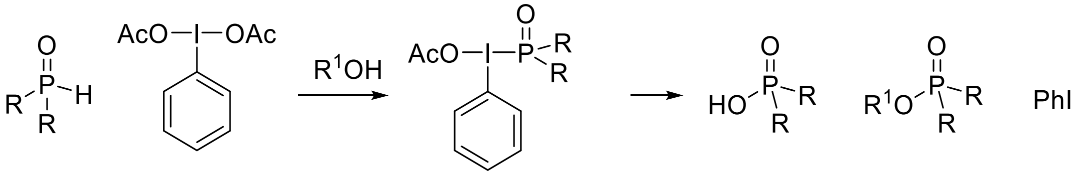
To investigate the synthesis of this phosphorylating agent, Makowiec and Rachon performed the reaction in both aprotic and protic solvents (Scheme 2.7). In aprotic solvents, the phosphonic acid was formed. When the reaction was performed with alcohol as the solvent in the presence of the alcoholate, a phosphonic ester was formed.



Scheme 2.7 – Reaction of phosphine reagents with iodosobenzene

Makoweic and Rachon further investigated the reactivity of phosphine by reacting it with PIDA (Scheme 2.8).[20] The reaction of PIDA with phosphines that have the general formula

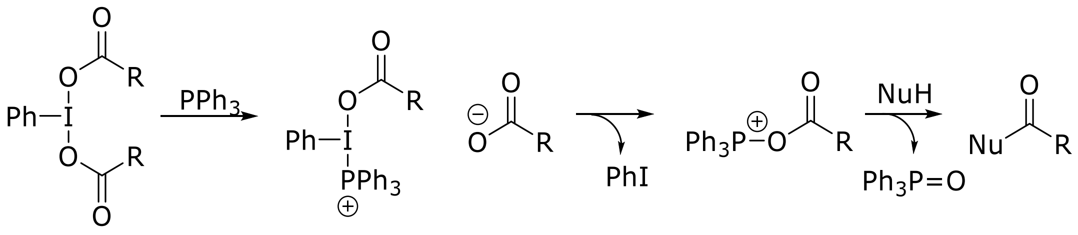
$R^1R^2P(O)H$ in a protic solvent and in the presence of a sodium alcoholate (with the same R group as the alcohol) produced the phosphinate and phosphinic acid. The reaction likely involves the hypervalent iodine intermediate **12.**



12

Scheme 2.8 – Reaction of phosphine with PIDA

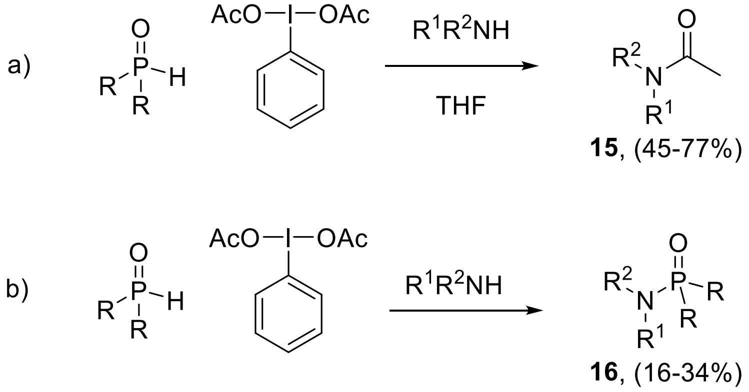
The reaction between diacyloxybenzene, an alcohol and triphenylphosphine or trialkyl phosphite was also investigated as a potential condensation reaction (Scheme 2.9). Phosphine attacks the iodane to yield **13**, followed by a ligand coupling to give the acyloxyphosphonium intermediate **14**. A nucleophilic attack of the **14** will yield the desired product along with triphenylphosphine oxide. The condensation works well and gave high yields for a variety of substrates. The main side product observed is the anhydride formed when a carboxylate ion attacks the acyloxyphosphonium **14**.



13 **14**

Scheme 2.9 – Reaction of PPh_3 with diacyloxyiodobenzene

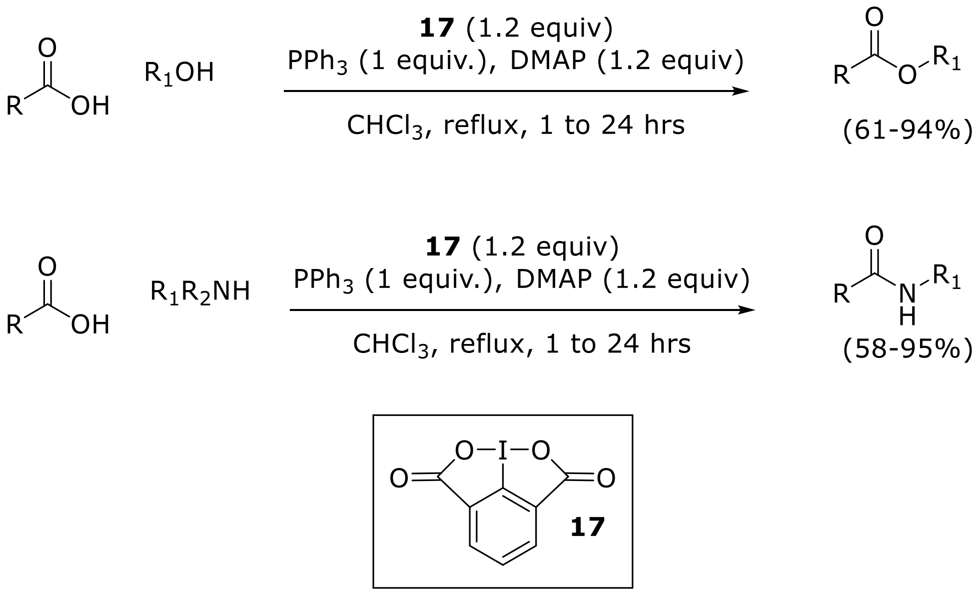
Makoweic and co-workers also examined the acylating properties of PIDA with $R^1R^2P(O)H$ toward acylation of aliphatic amines to obtain the carboxylic amide **15**, as an alternative for the Todd–Atherton reaction (Scheme 2.10, a)).[101] They also performed the reaction with an amine as the solvent and obtained the phosphonic acid amide (**16**) in low yields (Scheme 2.10, b)).



Scheme 2.10 – Coupling reactions using the HVI/phosphorus system

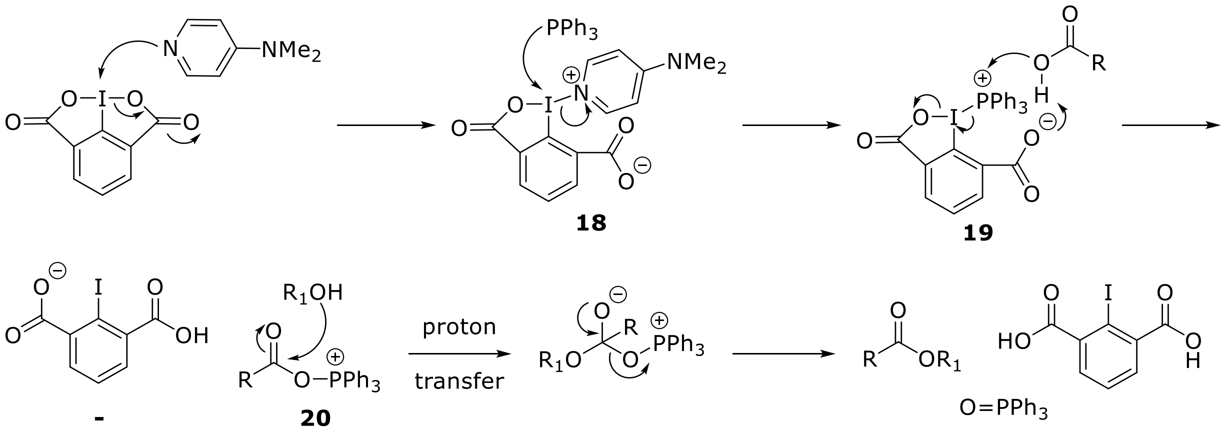
2.4 Ligand transfers from HVI reagents to phosphorus atoms

HVI molecules are well known to perform ligand transfers to nucleophilic species such as enolates and alkenes.[4] Tian et al. recently used the HVI reagent iodosodilactone **17** in conjunction with triphenylphosphine as an efficient coupling reagent for esterification and amidation (Scheme 2.12).[102] The esterification reaction between a carboxylic acid and alcohol proceeds easily and in high yields. This method can also be applied effectively to peptide synthesis, as demonstrated by Zhang et al.[103]



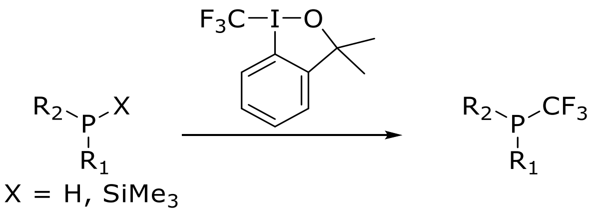
Scheme 2.11 – Esterification and amidation using iodosodilactone

The mechanism shown in Scheme 2.12 is one of the first examples of phosphorus attacking the hypervalent center. The iodine is first activated with 4-dimethylaminopyridine (DMAP), to give intermediate **18**. This facilitates the triphenylphosphine attack, yielding intermediate **19**. The phosphorus atom in intermediate **19** has a formal positive charge and is therefore susceptible to a nucleophilic attack. The carboxylic acid then attacks the phosphorus, which oxidizes the iodine and renders it univalent, the acyloxyphosphonium intermediate **20**. Intermediate **20** is then attacked by a nucleophile and the collapse of the tetrahedral intermediate yields triphenylphosphine oxide and the product.



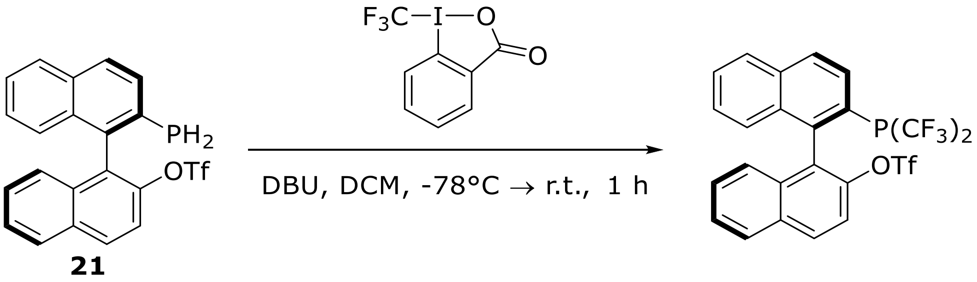
Scheme 2.12 – Proposed mechanism for esterification using iodosolactone

Togni’s reagent, a well-known HVI molecule used for the transfer of trifluoromethyl moieties, has been used in conjunction with phosphorus compounds[104] for reactions such as the monotrifluoromethylation of primary and secondary phosphines (Scheme 2.13).[105]



Scheme 2.13 – Monotrifluoromethlation of phosphines using Togni’s reagent

The monotrifluoromethylation reaction has a broad scope and can react with both aryl and akyl phosphines as well as primary and secondary phosphines**.** Further studies by the Togni group showed the trifluoromethylation of different phosphorus ligands such as BINAP derivative **21** (Scheme 2.14).[106,107]



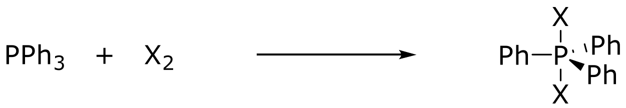
Scheme 2.14 – Monotrifluoromethylation of BINAP derivative

2.5 Phosphorus(V) reagents

Phosphates play an important role in many physiological processes[108] and are important for drug discovery[109–111] and organic synthesis.[112,113] Phosphorus can become hypervalent and form 5 bonds, as was proven in 1948 when Ph_5P was synthesized.[114] Phosphorus(V) molecules have a trigonal bipyramidal geometry in which the most electronegative ligands sit at the apical positions.[89] The L–P–L bond is a 3c-4e hypervalent bond, similar to that of λ^3-iodanes.[115] Therefore, the phosphorus atom is electrophilic and is susceptible to nucleophilic attack. Our main interest lies in synthesizing phosphoranes with the general formula R_3PX_2, where X is a halogen, which were discovered over 100 years ago.[116]

2.6 Triphenylphosphine dihalides

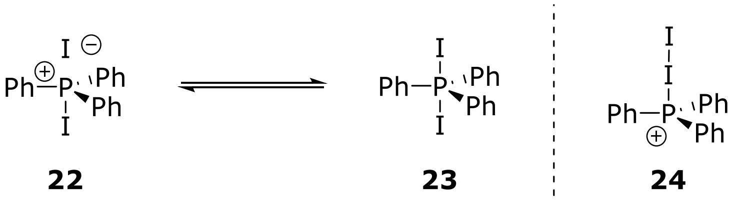
Triphenylphosphine dihalides have typically been synthesized from elemental halogens (Scheme 2.15).[117] Due to the hygroscopic nature of these chemicals, care is usually taken to exclude moisture from their synthesis and storage. These reagents are generally synthesized *in-situ* to avoid degradation.



Scheme 2.15 – Original synthesis of Ph_3PX_2

2.6.1 Triphenylphosphine diiodine

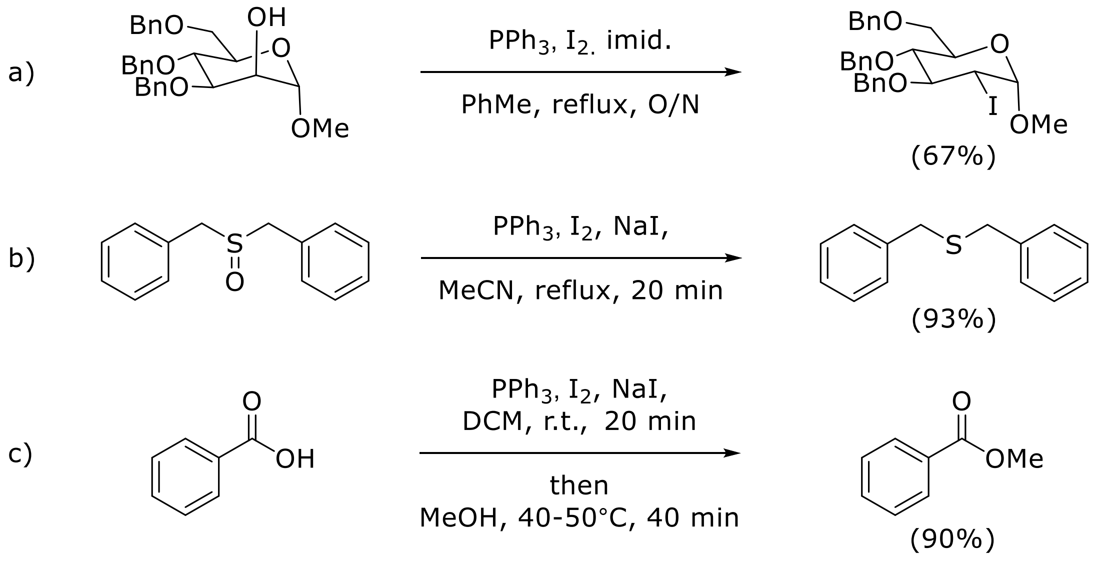
Ph_3PI_2 is generally prepared via the reaction of PPh_3 and I_2 in various solvents.[118] It has been suggested that an equilibrium (Figure 2.2) exists between the ionic **22** and covalent **23** forms of Ph_3PI_2.[119] However, du Mont et al. have obtained the crystal structure of $^{t}Bu_3PI_2$, and observed a linear P–I–I structure.[120] The crystal structure of Ph_3PI_2 was obtained by Godfrey et al. and proved the presence of the elongated P–I–I bond (Figure 2.2, **24**).[121,122]



22 **23** **24**

Figure 2.2 – Structure of Ph_3PI_2

Ph_3PI_2 has been used extensively in organic synthesis and is typically used to convert alcohols to alkyl iodides.[123–125] This reaction undergoes a S_N2 mechanism and goes through an inversion of configuration (Scheme 2.16, a)).[125] Ph_3PI_2 is often used in the reduction of sulfur to sulfides or thiols (Scheme 2.16, b))[126] and can also be used to reduce epoxides[127] and diols[128] to alkenes. Ph_3PI_2 has been used as a coupling agents for carboxylic acids and various nucleophiles (Scheme 2.16, c)).[129,130]

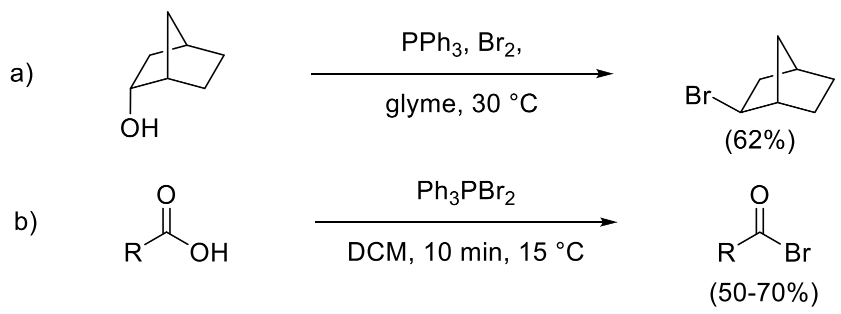


Scheme 2.16 – Reactions involving Ph$_3$PI$_2$

2.6.2 Triphenylphosphine dibromide

Triphenylphosphine dibromide is also commonly used in organic chemistry. It is usually synthesized via the addition of bromine and triphenylphosphine in a dry solvent. The structure of Ph$_3$PBr$_2$ is similar to that of Ph$_3$PI$_2$. It has been reported to have a P–Br–Br structure with a ^{31}P NMR shift of 45 ppm.[131]

Ph$_3$PBr$_2$ has mainly been used to convert alcohols to alkyl bromides, with an inversion of stereochemistry (Scheme 2.17, a)).[132] It may also be used for the synthesis of acyl bromides from carboxylic acids, anhydrides or esters (Scheme 2.17, b)).



Scheme 2.17 – Reaction involving Ph_3PBr_2

2.6.4 Triphenylphosphine dichloride

Triphenylphosphine dichloride is not used as commonly as Ph_3PBr_2 and Ph_3PI_2. This is because its synthesis typically involves toxic chemicals such as gases that are hard to handle (Figure 2.3). The original synthesis of triphenylphosphine dichloride uses chlorine gas (**92**) as a reagent.[117] The most common reaction to produce Ph_3PCl_2 is performed with carbon tetrachloride and three equivalents of triphenylphosphine.[133]

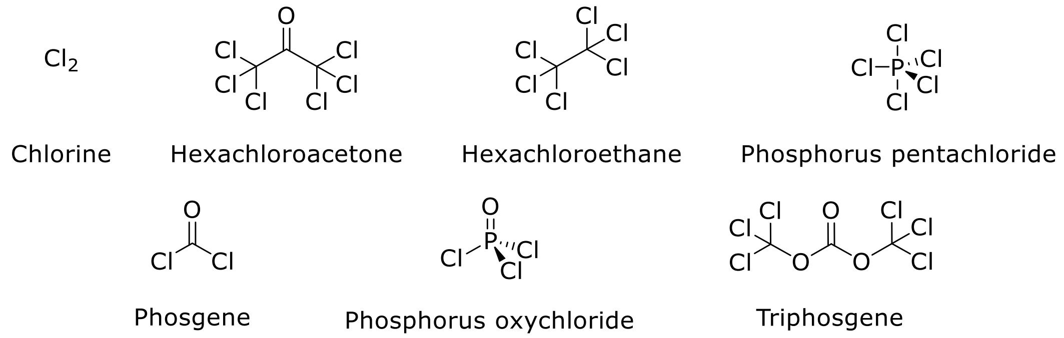
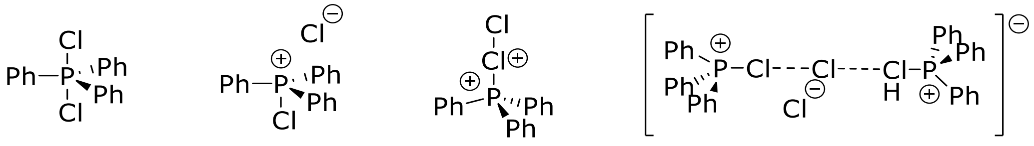


Figure 2.3 – Chlorinating agents used in syntheses of Ph_3PCl_2

Other methods have been explored such as the reaction between PPh_3 and hexachloroacetone.[134] Unfortunately, hexachloroacetone is a toxic chemical that, when heated, can decompose to yield phosgene and chlorine gas.[135] Hexachloroethane is also commonly used for this reaction[136] but, like some of the other reagents used, it is toxic and a carcinogen. Researchers have also tried to mix triphenylphosphine oxide or triphenylphosphine with phosphorus pentachloride.[137] This produced a mixture of species including Ph_3PCl^+, PCl_6^-, PCl_3 and only a small amount of triphenylphosphine dichloride, the desired product.[137] Other techniques for the synthesis of Ph_3PCl_2 use phosgene, phosphorus oxychloride and triphosgene. [123,138] Following this, many scientists have tried to develop a more efficient and less toxic method. One such method is the reaction of triphenylphosphine oxide with oxalyl chloride.[139] The waste products for this reaction are carbon dioxide, carbon monoxide and hydrochloric acid. A catalytic amount of triphenylphosphine oxide facilitates this reaction since oxalyl chloride reacts with triphenylphosphine oxide to yield triphenylphosphine dichloride.

Dillon and Waddington concluded through ^{31}P NMR and nuclear quadrupole spectroscopy (NQR) that Ph_3PCl_2 possesses an ionic form in the solid state.[137] Gates and co-workers also used Raman spectroscopy to propose an ionic species.[140] However, different conformations are observed for Ph_3PCl_2 in solution. Wiley and Stine first observed a difference in ^{31}P NMR for Ph_3PCl_2 in varying solvents such as CH_3CN and DCM.[141] Denney et al. also observed that varying the amount of the chlorinating agent alters the chemical shift in ^{31}P NMR of Ph_3PCl_2.[142]

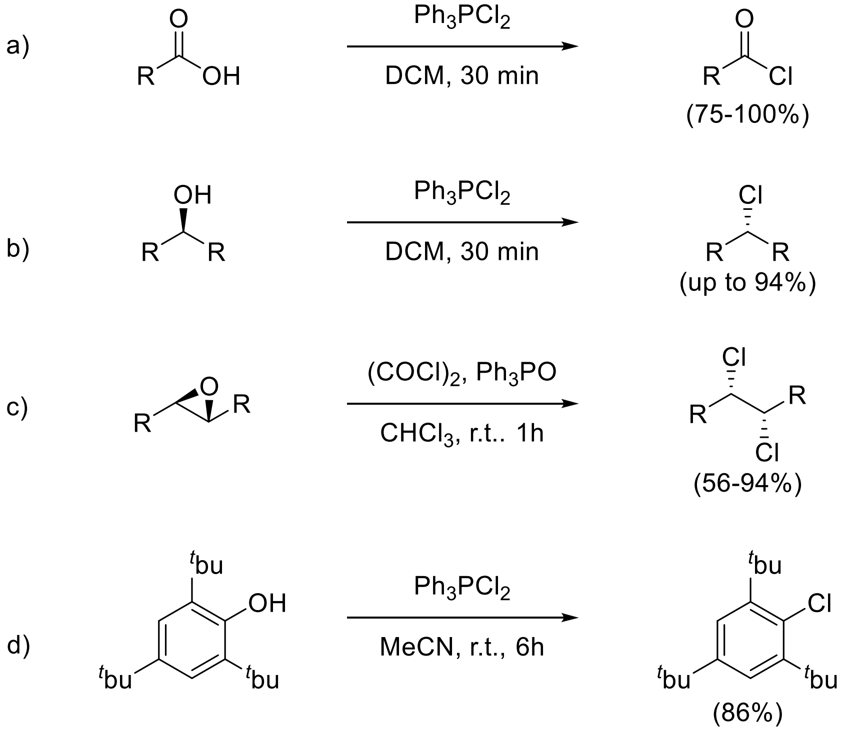


25 **26** **27** **28**

Figure 2.4 – Proposed structures of Ph_3PCl_2

Several structures have been proposed for Ph_3PCl_2, such as **25**, **26** or **27**. Godfrey et al. have shown that Ph_3PCl_2 in DCM does not adopt any of those species but rather an unusual dinuclear ionic species **28** (Figure 2.4).[143,144] They confirmed this structure by obtaining a crystal structure of Ph_3PCl_2 in DCM. When the crystals were obtained from diethyl ether, a trigonal bipyramidal structure was reported.[145] This result prompted several studies to determine the structure of Ph_3PCl_2 in solution.[141,146] Research suggested that there is an equilibrium between an ionic species (**26, 27** or **28**) and the trigonal bipyramidal species **25**. Yin et al. studied the effect of the solvent on the structure by monitoring the formation of Ph_3PCl_2 via ^{31}P NMR. In solvents such as DCM and $CHCl_3$ an ionic tetra-coordinated structure was created with a ^{31}P NMR chemical shift of approximately 60 ppm in ^{31}P NMR, while solvents like benzene and toluene showed a penta-coordinated structure with a shift of -50 ppm.[146] Yin et al. concluded that polar solvents such as acetonitrile, dichloroethane, dichloromethane and chloroform gave ^{31}P NMR chemical shifts of around 55-65 ppm, which is consistent with the more ionic form of Ph_3PCl_2 (Figure 2.4, **26**). Less polar solvents such as THF, benzene and toluene gave a shift of around -35ppm, which would indicate a covalently bound form of Ph_3PCl_2 (Figure 2.4, **25**).

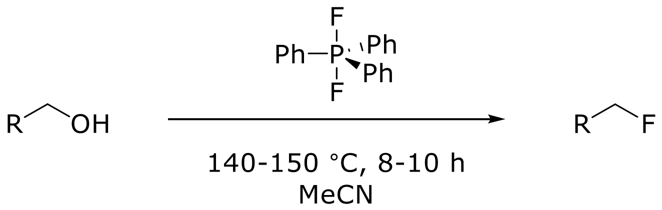
Ph_3PCl_2 has been popularized by the Appel reaction in which an alcohol is converted to an alkyl chloride with inversion of stereochemistry (Scheme 2.18, a)).[147,148] Ph_3PCl_2 can also promote the conversion of carboxylic acids to acyl chlorides (Scheme 2.18, b)).[149] It has been reported to open up epoxides to yield a dechlorinated molecule (Scheme 2.18, c)).[150] Ph_3PCl_2 can also be used to synthesize aryl chlorides from phenols (Scheme 2.18, d)).[151]



Scheme 2.18 – Reactions using Ph_3PCl_2

2.6.3 Triphenylphosphine difluoride

Triphenylphosphine difluoride is the least studied of the Ph_3PX_2 reagents due to the extreme reactivity of F_2. The use of F_2 has been circumvented by using fluorinating agents which include mercuric salts (HgF_2)[152], tetrafluorohydrazine (N_2F_4),[153] and iodine pentafluoride (IF_5).[154] The structure of Ph_3PF_2 has been reported as trigonal bipyramidal in the solid state with a ^{31}P chemical shift of -55 ppm.[155,156] There have been limited reports on the uses of Ph_3PF_2 as a fluorinating agent. Kobayashi and Akash used Ph_3PF_2 in the conversion of alcohols to alkyl fluorides (Scheme 2.19).[157]



Scheme 2.19 – Deoxygenative fluorination using Ph_3PF_2

2.7 Deoxygenative chlorination

A reaction in which oxygen is removed from a molecule is referred to as a deoxygenative reaction. When a chlorine atom is simultaneously added, the reaction is a deoxygenative chlorination. This type of transformation is usually achieved using oxalyl ($(COCl)_2$) or thionyl chloride ($SOCl_2$). Both of these reagents have the disadvantage of being somewhat volatile, as well as reacting violently, sometimes explosively, with water and releasing toxic gas. In the case of $(COCl)_2$, carbon monoxide (CO), carbon dioxide (CO_2) and hydrogen chloride are released and $SOCl_2$ releases sulfur dioxide (SO_2) and HCl. Phosphorus based reagents such as PCl_5 and Ph_3PCl_2 are also capable of deoxygenative chlorination, , with the latter commonly being used in the Appel reaction.[133,149,151,158]

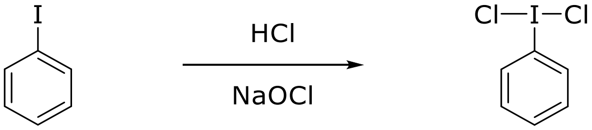
The formation of a strong heteroatom-oxygen bond such as S-O or P=O is typically the driving force behind deoxygenative chlorination. This is the reason why iodobenzene dichloride is not capable of performing this transformation. The resulting I-O bond is unstable, making the reaction unfavorable. The phosphorous oxygen bond is very strong and can therefore drive many reactions such as the Wittig olefination. Looking at the energies of the bonds that are formed and broken[159] (Table 2.1), we can see that the reactions are both energetically favorable. As with many reactions that include triphenylphosphine, such as the Wittig reaction, the synthesis of the P=O bond is the driving force.

Table 2.1 – Bond energy of the bonds formed and broken

Bond	**Energy**	
	kcal/mol	**kJ/mol**
C–Cl	83	350
C–O	92	384
P=O	128	544
P–Cl	73	309
I–Cl	50	212

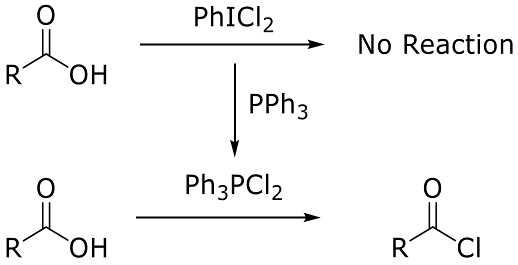
2.8 HVI as deoxygenative chlorination reagent

While Ph_3PCl_2 is used in organic synthesis, chemists tend to veer away from it and utilize different reagents, such as $SOCl_2$ and $(COCl)_2$. We envisioned a new synthesis of Ph_3PCl_2 using $PhICl_2$. The HVI reagent is often considered to be a surrogate for chlorine gas, due to its ability to deliver to chlorine atoms, with the advantages of requiring mild reaction conditions and its overall ease of use. $PhICl_2$ is easily synthesized via the reaction of iodobenzene with bleach and concentrated hydrochloric acid (HCl) (Scheme 2.20)[80].



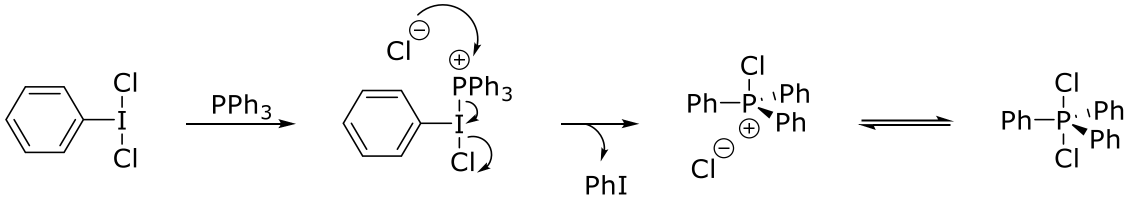
Scheme 2.20 – Synthesis of $PhICl_2$

$PhICl_2$ is a bench stable reagent known to transfer a chlorine to many types of molecules[4] such as enolates[22], alkenes[23], diazo compounds,[24] and aromatic rings.[25] However, the iodane is not capable of deoxygenative chlorination since the resulting I–O bond is unstable. Knowing that Ph_3PCl_2 can perform deoxygenative chlorination, we envisioned the synthesis of the Appel reagent using $PhICl_2$. Once Ph_3PCl_2 is synthesized we hope to effect the deoxygenative chlorination *in-situ* (Scheme 2.21).



Scheme 2.21 – Proposal for the acid chloride synthesis using HVI

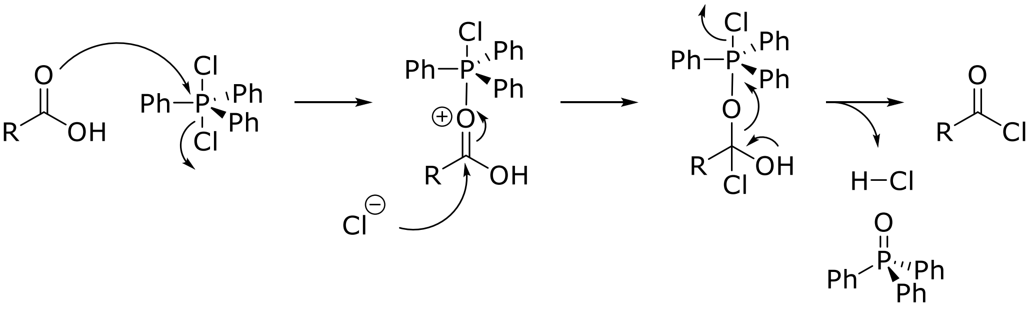
We propose the mechanism outlined in Scheme 2.22 for the synthesis of Ph_3PCl_2. PPh_3 is a good nucleophile when in solution and would therefore attack the electrophilic iodine center to yield intermediate **29**. This intermediate is then attacked by the resulting chloride anion. This attack releases iodobenzene and ionic Ph_3PCl_2 (**26**) which is in equilibrium with the covalently bound form (**25**).



29 **26** **25**

Scheme 2.22 – Mechanism for the synthesis of Ph_3PCl_2

The reaction between Ph_3PCl_2 and a carboxylic acid is documented in the literature[149] and would be expected to proceed as shown in Scheme 2.23. The main side product formed in the synthesis of Ph_3PCl_2, PhI, should not affect the dexoygenative chlorination reaction.



Scheme 2.23 – Mechanism for the deoxygenative chlorination reaction

2.9 Synthesis of Ph_3PCl_2

The synthesis of Ph_3PCl_2 was first attempted in dichloromethane (DCM) by combining triphenylphosphine (PPh_3) in slight excess with $PhICl_2$. ^{31}P NMR testing of the reaction showed that Ph_3P had been fully consumed. However, none of the product had been formed and triphenylphosphine oxide was observed instead at a ^{31}P NMR chemical shift of 30 ppm. This result highlights the hygroscopic nature of Ph_3PCl_2. The reaction was conducted in a nitrogen atmosphere to remedy this problem, and the formation of the product was observed in less than

2 minutes (Figure 2.5). The solvent effect was tested for this synthesis of Ph_3PCl_2 and the results were consistent with those reported by Ying et al.[146] In all of the trials, triphenylphosphine oxide was observed around 25 to 35 ppm. More polar solvents such as acetonitrile, dichloroethane, dichloromethane and chloroform gave ^{31}P NMR chemical shifts of around 55-65 ppm, which is consistent with the more ionic form of Ph_3PCl_2 (Figure 2.5, **26**). Less polar solvents such as THF, benzene and toluene gave a shift of around -35ppm, which would indicate a covalently bound form of Ph_3PCl_2 (Figure 2.5, **25**).

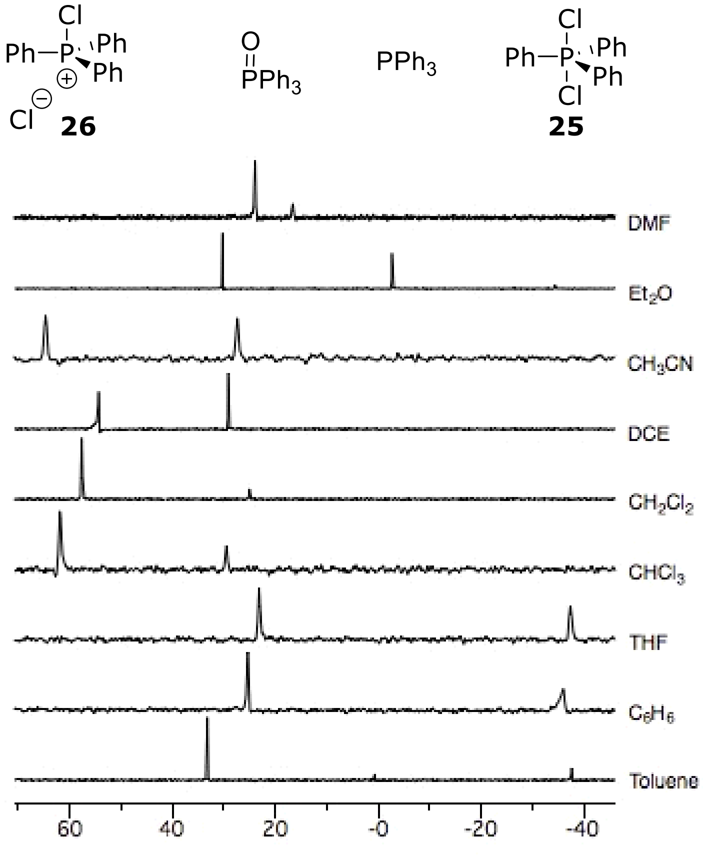


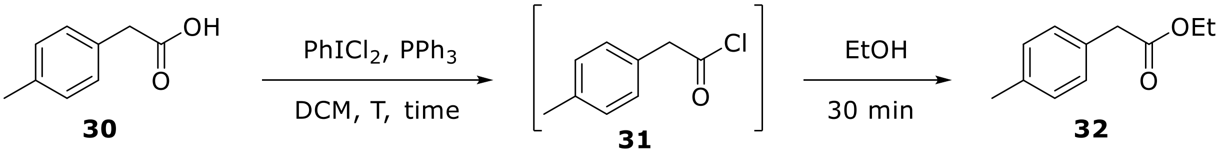
Figure 2.5 – ^{31}P NMR spectra of PPh_3 and $PhICl_2$ in various solvents

When the reaction was performed in diethyl ether (Et_2O), only $Ph_3P=O$ and triphenylphosphine could be seen on the NMR spectrum at 30 ppm and -5 ppm respectively, even after 24 hours. This can be attributed to the insolubility of $PhICl_2$ in Et_2O. Another solvent of interest is dimethylformamide (DMF), which gave two peaks at 16.6 ppm and 23.9 ppm ($Ph_3P=O$). The peak at 16.6 ppm was hypothesized to be the average of a rapid equilibrium between the ionic and covalent forms of Ph_3PCl_2. When the experiment was performed at -35 ˚C, no change in the ^{31}P NMR spectrum was observed. This could indicate that the equilibrium between the two forms is still be occurring at -35 ˚C or that the reagent exists in a dimer, oligomer or possibly a solvent-bound state. Other possibilities include DMF reacting with the reagent to yield a different species, or simply a new form of Ph_3PCl_2.

2.10 Chlorination of carboxylic acids using Ph_3PCl_2

Once Ph_3PCl_2 could be synthesized using $PhICl_2$, the next step was using it to promote deoxygenative chlorination. Isolation of Ph_3PCl_2 is difficult due to its high water sensitivity. The synthesis of Ph_3PCl_2 with $PhICl_2$ is very fast and was attempted in the presence of *p*-tolylacetic acid **30** to form the acid chloride **31**. For ease of isolation, the acid chloride was trapped with EtOH to form ethyl *p*-tolylacetate (**32**). The initial reaction conditions were equimolar amounts of Ph_3P, $PhICl_2$ and the carboxylic acid in DCM at reflux for 30 min before the addition of excess EtOH, which gave the desired product in an 81% yield (Table 2.2, entry 1). Raising the amounts of both PPh_3 and $PhICl_2$ gave an improved yield of 92% (Table 2.2, entry 2). Adding equimolar amounts of PPh_3 and the carboxylic acid and a small excess of $PhICl_2$ gave a 94% yield (Table 2.2, entry 3). When excess $PhICl_2$ is used, the reaction mixture turns yellow. We believe that this is due to the complete conversion of PPh_3 to Ph_3PCl_2 as a result of the excess $PhICl_2$. The increased yield could be attributed to complete conversion of PPh_3 to Ph_3PCl_2. Hoping to promote this reaction with milder reaction conditions, the temperature was lowered to room temperature which showed a decrease in yield (Table 2.2, entry 4). Next, we lowered the reaction time to 10 minutes (Table 2.2, entry 5) and saw no decrease in reaction yield.

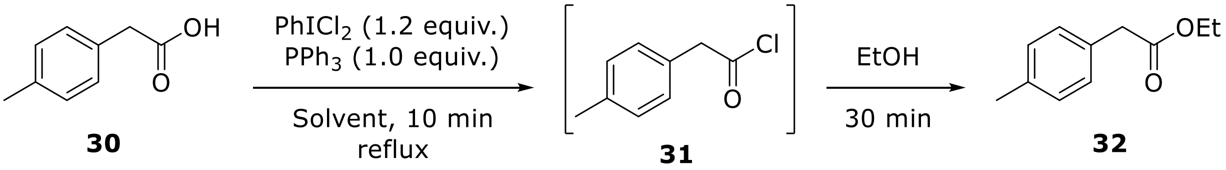
Table 2.2 – Optimization of the acyl chloride synthesis



Entry	PPh_3 (equiv.)	$PhICl_2$ (equiv.)	T (˚C)	Time (min)	Yield (**32**) (%)
1	1	1	40	30	81
2	1.2	1.2	40	30	92
3	1	1.2	40	30	94
4	1	1.2	r.t.	30	84
5	1	1.2	40	10	93

Most of the common organic solvents gave good yields (Table 2.3, entries 1-9) ranging from 77% to 86%. There seemed to be no difference in reactivity between the different configurations of Ph_3PCl_2. When Ph_3PCl_2 is in toluene or THF it has a ^{31}P NMR chemical shift that represents the covalently bonded form. The ionic form was observed to be present in DCM, DCE and chloroform. DMF showed the lowest yield at 49% (Table 2.3, entry 10), which could be related to the fact that a different form of Ph_3PCl_2 is found in DMF.

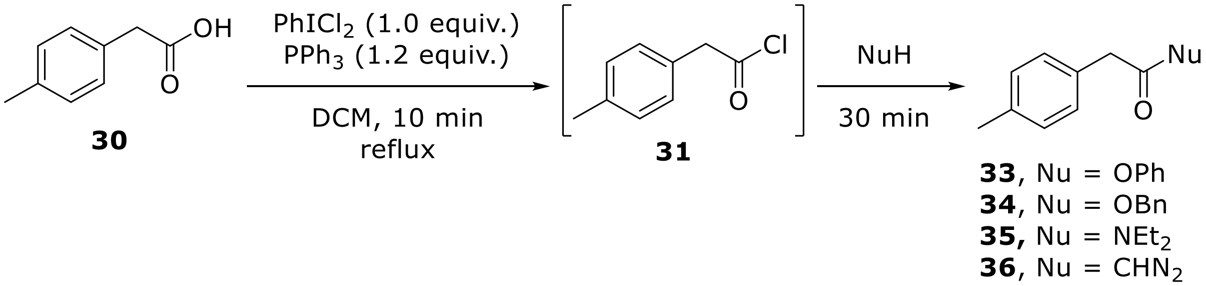
Table 2.3 – Solvent screen



Entry	Solvent	Time (min)	Yield (**32**) (%)
1	Toluene	30	83
2	$CHCl_3$	180	86
3	DCE	120	77
4	THF	30	84
5	DMF	30	48

Next, the nucleophile used for trapping the acyl chloride was investigated. Our intention was to run the reaction with the trapping nucleophile present from the start. We tried running the reaction in ethanol in an effort to decrease its complexity. Given that Ph_3PCl_2 reacts with most alcohols to yield and alkyl chloride, we obtained the desired product in low yield and we believe that ethyl chloride may have been formed in the reaction, proving that two steps are required. Since Ph_3PCl_2 reacts readily with nucleophiles such as alcohol and phenols, we tested a variety of nucleophiles with our model substrates to determine whether the nucleophile would interfere with the reaction conditions. The alcohols (Table 2.4, entries 1,3,4), amines (Table 2.4, entry 2) and diazomethane (Table 2.4, entry 5) we tested gave high yields above 90%.

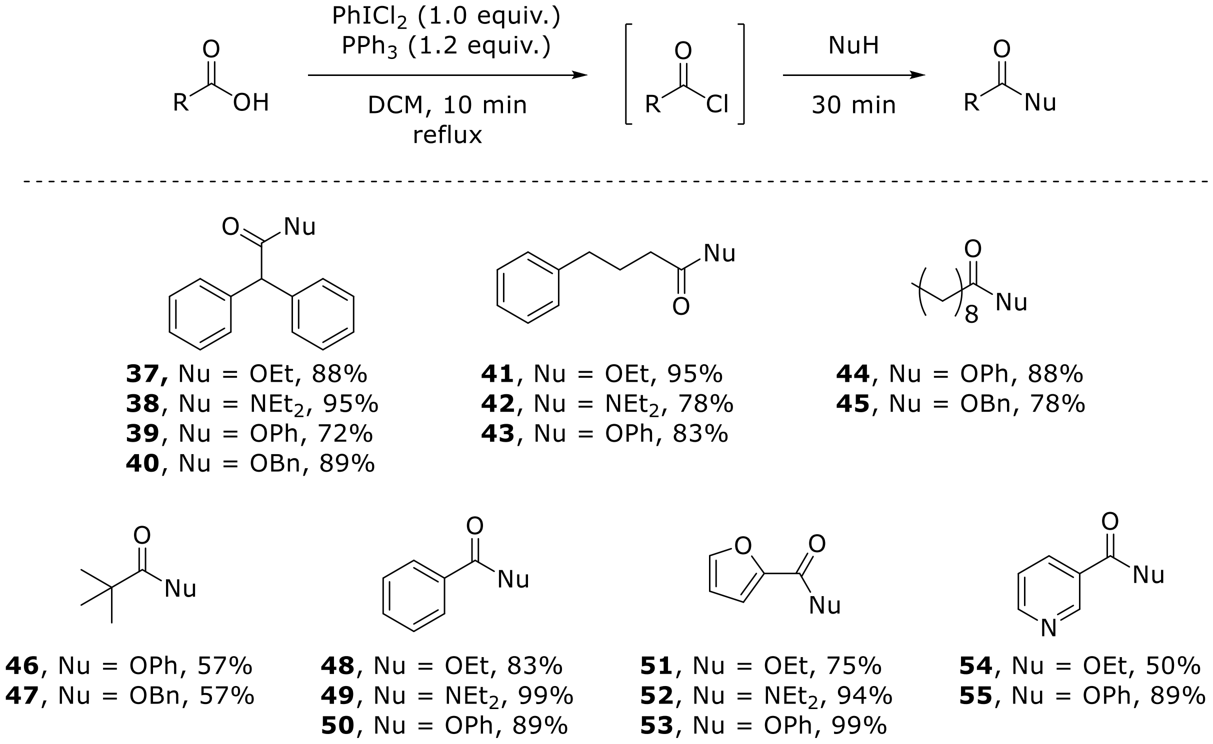
Table 2.4 – Nucleophile scope



Entry	NuH	Yield (%)
1	EtOH	**32**, 95%
2	PhOH	**33**, 90%
3	BnOH	**34**, 92%
4	Et_2NH	**35**, 90%
5	CH_2N_2	**36,** 98%[a]

[a] ^{1}H NMR yield using hexamethyldisiloxane (HMDSO) as an internal standard

Once the reaction was optimized, the substrate scope could be explored (Scheme 2.24). The reaction works very well on most aliphatic and aromatic substrates. Very good yields of 72% to 89% were observed for biphenylacetic acid with all the different nucleophiles attempted. Similar yields of 78% to 95% were obtained with 4-phenylbutyric acid. Decanoic acid also gave good yields of 78% when using benzyl alcohol as the nucleophile and 88% yield when using phenol. The lowest yield of 57% was observed for pivalic acid, which was likely due to steric hindrance. The tetrahedral intermediate of the reaction would have two quaternary centers next to each other due to the *tert*-butyl group adjacent the carboxylic acid, which is unfavorable. Benzylic carboxylic acid also underwent the transformation in high yields. Heteroarene carboxylic acids, such as nicotinic acid and furoic acid, afforded yields ranging from 50% to 99%.



37, Nu = OEt, 88%
38, Nu = NEt_2, 95%
39, Nu = OPh, 72%
40, Nu = OBn, 89%

41, Nu = OEt, 95%
42, Nu = NEt_2, 78%
43, Nu = OPh, 83%

44, Nu = OPh, 88%
45, Nu = OBn, 78%

46, Nu = OPh, 57%
47, Nu = OBn, 57%

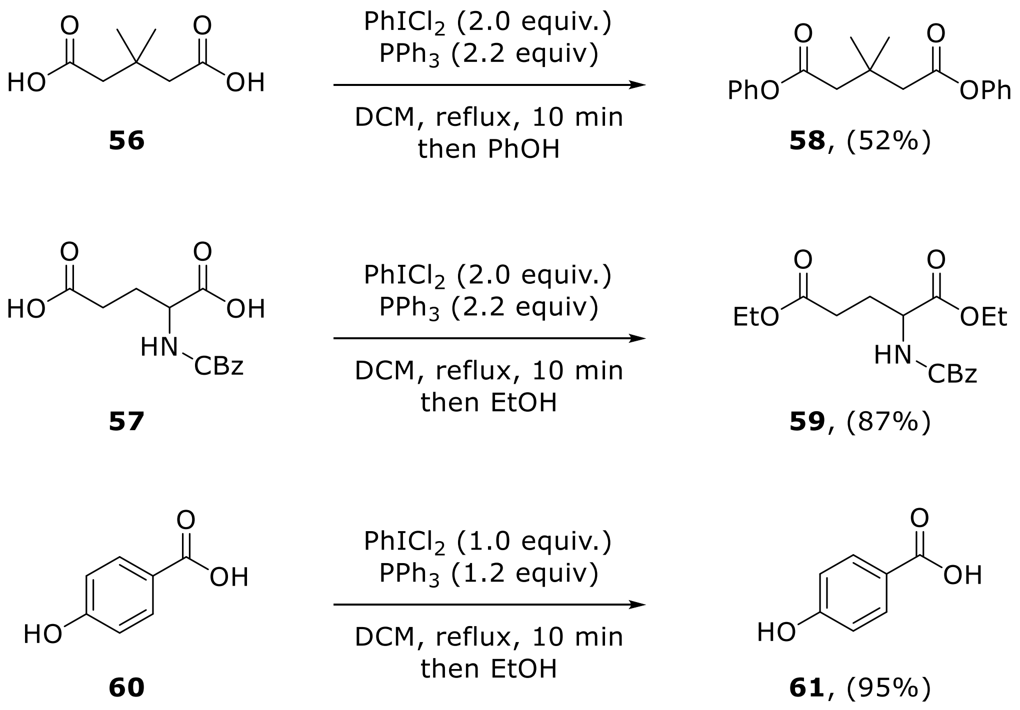
48, Nu = OEt, 83%
49, Nu = NEt_2, 99%
50, Nu = OPh, 89%

51, Nu = OEt, 75%
52, Nu = NEt_2, 94%
53, Nu = OPh, 99%

54, Nu = OEt, 50%
55, Nu = OPh, 89%

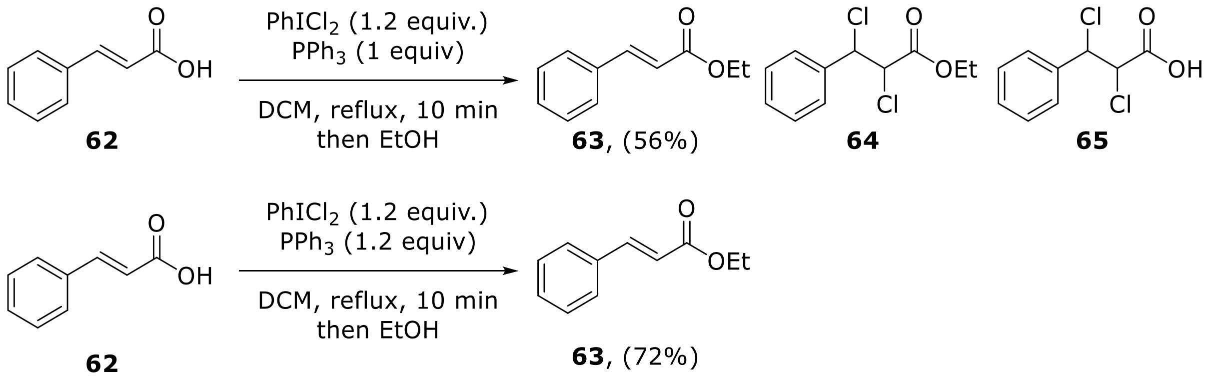
Scheme 2.24 – Substrate scope for the esterification and amidation of carboxylic acids

Some functional group tolerance tests were performed. We also tested whether the reaction would work well in the presence of two carboxylic acids (**56** and **57**). The reagent amounts had to be doubled but the reaction proceeded well and in high yields (**58** and **59**). The reaction conditions seemed to tolerate phenols and secondary amines as shown with N-CBz (*tert*-butyloxycarbonyl) protected aspartic acid (**57**) and *p*-methoxybenzoic acid (**60**). The reaction was attempted on a primary amine, but did not yield the desired product. A mixture of products was obtained, which we believe includes an iminophosphorane species.



Scheme 2.25 – Functional group tolerance

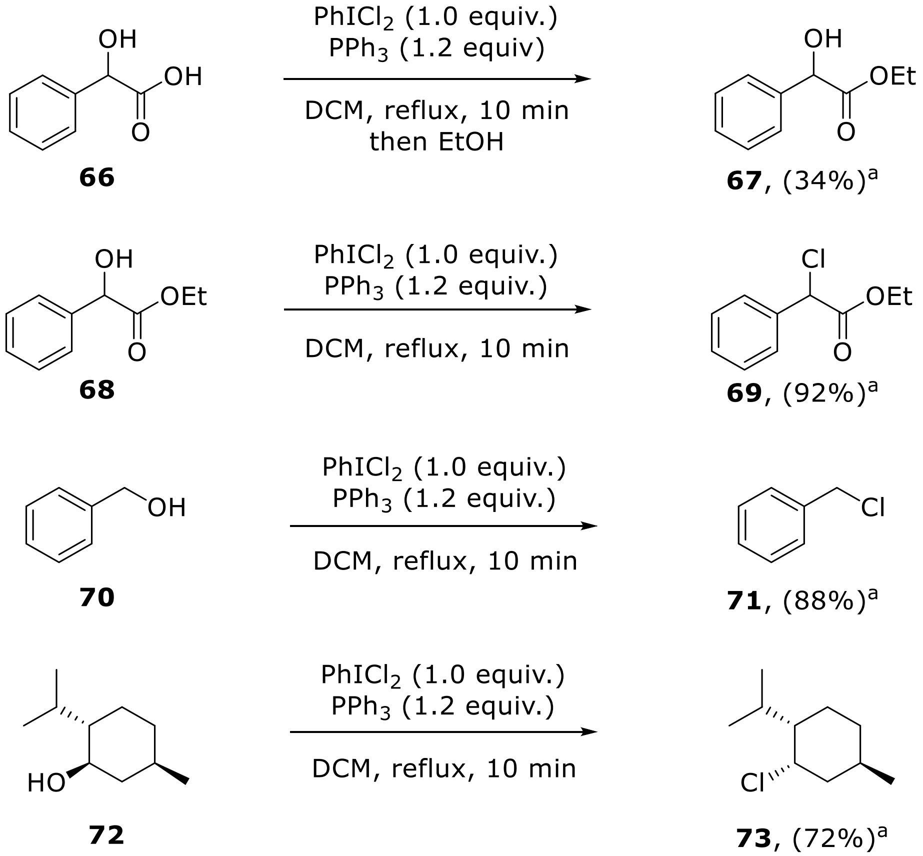
It is commonly known that $PhICl_2$ reacts with alkenes to yield a dichlorinated product.[160] Therefore, the reaction was tested with a substrate containing both a carboxylic acid and an alkene such as *trans*-cinnamic acid (**62**). This reaction was done to investigate which reaction would occur first and whether the double bond would interfere. When we used an equimolar amount of PPh_3 and a slight excess of $PhICl_2$, a mixture of products was formed and a low yield of 56% was obtained for the desired product (**63**) (Scheme 2.26, a)). Chlorinated molecules such as **64** and **65** were also found in the reaction mixture. This indicated that the excess of $PhICl_2$ present chlorinated the product or the starting material. Removing the excess $PhICl_2$ should therefore enhance the yield. We increased the amount of PPh_3 used in the reaction to ensure that all the $PhICl_2$ had reacted. We obtained a 72% yield using these reactions conditions (Scheme 2.26, b)).



Scheme 2.26 – Chlorination of trans-cinnamic acid

2.11 Deoxygenative chlorination of alcohols

The deoxygenation chlorination reaction was also attempted in the presence of a secondary alcohol with mandelic acid (**66**) and a low yield of 31% was obtained for the desired product **67**. Since it is well documented that Ph_3PCl_2 will chlorinate primary and secondary alcohols,[133,147,161] this was evidence of competition between the deoxygenative chlorination of alcohols and carboxylic acids. The reaction could therefore be expanded to the deoxygenative chlorination of alcohols. The reaction between ethyl mandelate (**68**), PPh_3 and $PhICl_2$ in DCM at reflux was performed and a 92% yield of **69** was obtained after 10 min. The substrate scope was expanded further to include a primary alcohol, a benzyl alcohol (**70**) and a secondary alcohol, menthol, (**72**) (Scheme 2.27) which all worked very well. In the reaction with menthol (**72**) we saw an inversion of stereochemistry by NMR, which supports the mechanism of an S_N2 attack from the chloride ion on an oxyphosphonium.



[a] ^{1}H NMR yield using hexamethyldisiloxane (HMDSO) as an internal standard

Scheme 2.27 – Reaction of alcohols with Ph_3PCl_2

2.12 Conclusion

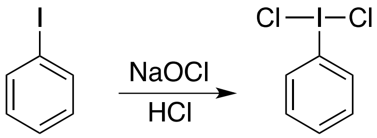
In conclusion, we have developed a novel synthesis for the chlorinating agent Ph_3PCl_2 from PPh_3 and the hypervalent iodine reagent $PhICl_2$. ^{31}P NMR studies have demonstrated the dependence of solvent of the structural form of Ph_3PCl_2 and that the chlorine is easily and rapidly transferred to the phosphorus atom, no matter the solvent or structure of Ph_3PCl_2. We have then used this synthesis of Ph_3PCl_2 *in-situ* to synthesize acid chlorides and alkyl chlorides from carboxylic acids and alcohols respectively.

2.13 Experimental procedures

2.13.1 General procedures

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) or dimethylsulfoxide peak (2.50 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 (77.16 ppm) or the center line of the septet of dimethylsulfoxide-d6 (39.52 ppm). Phosphorus NMR spectra (^{31}P NMR) were recorded at 121 or 202 MHz, and are reported (ppm) relative to the peak of 85% H_3PO_4 (0 ppm). Positive ion electrospray (ESI) experiments were performed with a ThermoFisher Scientific Q-Exactive hybrid mass spectrometer. Accurate mass determinations were performed at a mass resolution of 70,000. For ESI, samples were infused at 5μL/min in 1:1 CH_3OH/H_2O+0.1% formic acid.

2.13.2 Synthesis of iodobenzene dichloride

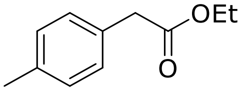


Iodobenzene (2.0 g, 9.8 mmol), was suspended in 5% sodium hypochlorite (commercial household bleach, 60 mL) in a 300 mL round bottom flask equipped with a magnetic stir bar at rt. The mixture was stirred vigorously as conc. HCl (20 mL) was added dropwise over five minutes. The yellow suspension was allowed to stir for 5 minutes, then the suspension was filtered, washed with H_2O (200 mL) then petroleum ether (50 mL). The yellow solid was spread thinly on a watch glass or beaker (with a rubber spatula) and allowed to air-dry in the dark overnight in a desiccator. $PhICl_2$ was recovered as a pale yellow solid (2.5 g, 93% yield). The product with a melting point of 110 – 112 °C was used in the chlorination reactions. Note: The reaction occurred with better reproducibility when bleach formulations that do not contain sodium hydroxide were used.

2.13.3 General procedure A: trapping with EtOH

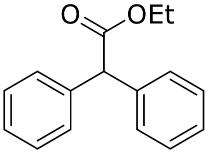
The carboxylic acid (1.0 equiv.) is dissolved in dry DCM (1.5 mL) and heated to reflux under nitrogen. PPh_3 (1.0 equiv.) is added, followed by $PhICl_2$ (1.2 equiv.). The reaction is stirred for 10 minutes at reflux then ethanol (~10 equiv.) is added drop wise over 2 minutes, and the reaction is stirred for 30 minutes, by which time TLC analysis indicates the consumption of the starting materials. The crude reaction mixtures were concentrated by rotary evaporation and purified by column chromatography.

Ethyl *p*-tolylacetate (32)



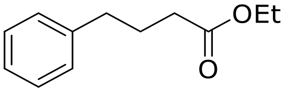
p-Tolylacetic acid (38.5 mg, 0.256 mmol, 1.0 equiv.) was subjected to General Procedure A to give a crude reaction mixture that was purified via column chromatography (5% EtOAc in hexanes, UV active) to give **32** (40.3 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 2.32 (s, 3H), 3.61 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 7.19 (q, *J* = 7.2, 4H). Spectral data were consistent with literature values.[162]

Ethyl diphenylacetate (37)



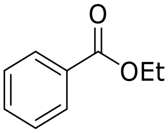
Diphenylacetic acid (50.2 mg, 0.236 mmol, 1.0 equiv.) was subjected to General Procedure A to give a crude reaction mixture that was purified via column chromatography (3% EtOAc in hexanes, UV active) to give **37** (50.0 mg, 88%) as a white solid ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 5.04 (s, 1H), 7.31 (m, 10H). Spectral data were consistent with literature values.[86]

Ethyl 4-phenylbutanoate (41)



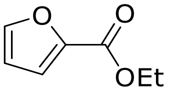
4-Phenylbutyric acid (40.5 mg, 0.247 mmol, 1.0 equiv.) was subjected to General Procedure A to give a crude reaction mixture that was purified via column chromatography (5% EtOAc in hexanes, UV active) to give **41** (45.7 mg, 95%). R_f: 0.46 (5% EtOAc in hexanes, UV active). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1, 3H), 2.00 (q, *J* = 7.5, 2H), 2.34 (t, *J* = 7.4, 2H), 2.68 (t, *J* = 7.6, 2H), 4.15 (q, *J* = 7.1, 2H), 7.21 (m, 3H), 7.31 (m, 2H). Spectral data were consistent with literature values.[163]

Ethyl benzoate (48)



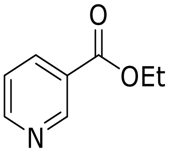
Benzoic acid (30.5 mg, 0.250 mmol, 1.0 equiv.) was subjected to General Procedure A to give a crude reaction mixture that was purified via column chromatography (5% EtOAc in hexanes, UV active) to give **48** (25.4 mg, 83%) as a clear oil after. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.1 Hz, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 7.46 (t, 2H), 7.57 (m, 1H), 8.07 (m, 2H). Spectral data were consistent with literature values.[164]

Ethyl furan-2-carboxylate (51)



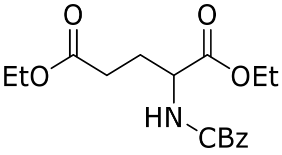
Furoic acid (28 mg, 0.25 mmol, 1.0 equiv.) was subjected to General Procedure A to give a crude reaction mixture that was purified via column chromatography (10% EtOAc in hexanes, UV active) to give **51** (26 mg, 75%) as a clear oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.41 (t, *J* = 7.1 Hz, 3H), 4.39 (q, *J* = 7.1 Hz, 2H), 6.52 (dd, *J* = 3.5, 1.73 Hz, 1H), 7.20 (d, *J* = 3.5 Hz, 1H), 7.60 (d, *J* = 0.7 Hz, 1H). Spectral data were consistent with literature values.[165]

Ethyl nicotinate (54)



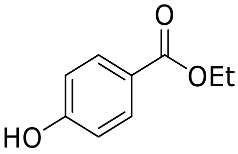
Nicotinic acid (30.5 mg, 0.248 mmol, 1.0 equiv.) was subjected to General Procedure A to give a crude reaction mixture that was purified via column chromatography (50% EtOAc in hexanes, UV active) to give **54** (19.0 mg, 50%) as a clear oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.41 (d, *J* = 14.3, 3H), 4.41 (q, *J* = 7.1, 2H), 7.38 (m, 1H), 8.29 (m, 1H), 8.76 (d, *J* = 4.7, 1H), 9.22 (t, *J* = 1.0 Hz, 1H). Spectral data were consistent with literature values.[166]

Diethyl *N*-Cbz-glutamate (59)



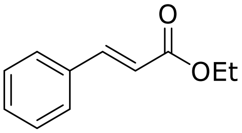
N-Cbz-glutamic acid (70.5 mg, 0.250 mmol, 1.0 equiv.) was subjected to General Procedure A to give a crude reaction mixture that was purified via column chromatography (20% EtOAc in hexanes, UV active) to give **59** (73.0 mg, 87%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (m, 6H), 1.99 (m, 1H), 2.20 (m, 1H), 2.38 (m, 2H), 4.14 (m, 4H), 4.37 (m, 1H), 5.09 (s, 2H), 5.40 (m, 1H), 7.34 (m 5H). Spectral data were consistent with literature values.[167]

Ethyl 4-hydroxybenzoate (61)



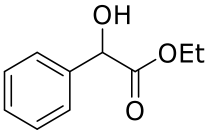
4-Hydroxybenzoic acid (29.4 mg, 0.213 mmol, 1.0 equiv.) was subjected to General Procedure A to give a crude reaction mixture that was purified via column chromatography (20% EtOAc in hexanes, UV active) to give **61** (33.3 mg, 95%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, *J* = 7.5 Hz, 3H), 4.37 (q, *J* = 7.1 Hz , 2H), 6.89 (m, 2H), 7.98 (m, 2H). Spectral data were consistent with literature values.[168]

Ethyl cinnamate (63)



trans-Cinnamic acid (37.1 mg, 0.250 mmol, 1.0 equiv.) was subjected to General Procedure A (with the modification that 1.2 equiv. of PPh_3 was used instead of 1.0 equiv.) to give a crude reaction mixture that was purified via column chromatography (10% EtOAc in hexanes, UV active) to give **63** (31.7 mg, 72%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.1 Hz, 3H), 4.27 (q, *J* = 7.1, 2H), 6.45 (d, *J* = 16.0 Hz, 1H), 7.39 (m, 3H), 7.53 (m, 2H), 7.69 (d, *J* = 16.0 Hz, 1H). Spectral data were consistent with literature values.[167]

Ethyl 2-hydroxyphenylacetate (67)

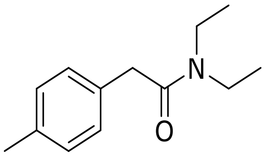


Mandelic acid (39.0 mg, 0.25 mmol, 1.0 equiv.) was subjected to General Procedure A to give a crude reaction mixture that was purified via column chromatography (80% EtOAc in hexanes, UV active) to give **67** (16.1 mg, 34%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (m, 3H), 3.44 (s, 1H), 4.21 (m, 2H), 5.14 (s, 1H), 7.37 (m, 5H). Spectral data were consistent with literature values.[167]

2.12.4 General procedure B: trapping with Et_2NH

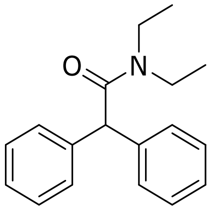
The carboxylic acid (1.0 equiv.) is dissolved in dry DCM (1.5 mL) and heated to reflux under nitrogen. PPh_3 (1.0 equiv.) is added, followed by $PhICl_2$ (1.2 equiv.). The reaction is stirred for 10 minutes at reflux then Et_2NH (~6 equiv.) is added drop wise over 2 minutes, and the reaction is stirred for 30 minutes, by which time TLC analysis indicates the consumption of starting material. The crude reaction mixtures were concentrated by rotary evaporation and purified by column chromatography.

_N,N_-Diethyl-2-(_p_-tolyl)acetamide (35)



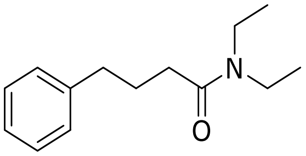
p-Tolylacetic acid (37.6 mg, 0.250 mmol, 1.0 equiv.) was subjected to General Procedure B to give a crude reaction mixture that was purified via column chromatography (20% EtOAc in hexanes, UV active) to give **35** (46.3 mg, 90%) as a clear oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (m, 6H), 2.30 (s, 3H), 3.26 (q, J = 7.1 Hz, 2H), 3.36 (q, J = 7.1 Hz, 2H), 3.63 (s, 2H), 7.11 (m, 4H). Spectral data were consistent with literature values.[169]

N,N-Diethyl-2,2-diphenylacetamide (38)



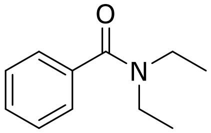
Diphenylacetic acid (50.0 mg, 0.236 mmol, 1.0 equiv.) was subjected to General Procedure B to give a crude reaction mixture that was purified via column chromatography (20% EtOAc in hexanes, UV active) to give **38** (59.9 mg, 95%). R_f: 0.55 (20% EtOAc in hexanes, UV active). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7.1 Hz, 6H), 3.34 (q, *J* = 7.1 Hz, 2H), 3.46 (q, *J* = 7.1 Hz, 2H), 5.19 (s, 1H), 7.30 (m, 10H). Spectral data were consistent with literature values.[170]

N,N-Diethyl-4-phenylbutamide (42)



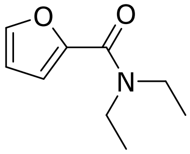
4-Phenylbutyric acid (41.8 mg, 0.255 mmol, 1.0 equiv.) was subjected to General Procedure B to give a crude reaction mixture that was purified via column chromatography (50% EtOAc in hexanes, UV active) to give **42** (43.5 mg, 78%). R_f: 0.57 (50% EtOAc in hexanes, UV active). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.1 Hz, 6H), 2.02 (m, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 3.24 (q, *J* = 7.1 Hz, 2H), 3.38 (q, *J* = 7.1 Hz, 2H), 7.20 (m, 3H), 7.29 (m, 2H). Spectral data were consistent with literature values.[171]

_N,N_-Diethylbenzamide (49):



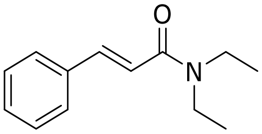
Benzoic acid (30.2 mg, 0.247 mmol, 1.0 equiv.) was subjected to General Procedure B to give a crude reaction mixture that was purified via column chromatography (50% EtOAc in hexanes, UV active) to give **49** (43.8 mg, 99%) as a white solid. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.39 (m, 5H), 3.56 (m, 2H), 3.26 (m, 2H), 1.25 (m, 3H), 1.13 (m, 3H). Spectral data were consistent with literature values.[170]

_N,N_-Diethylfuran-2-carboxamide (52)



Furoic acid (28.5 mg, 0.254 mmol, 1.0 equiv.) was subjected to General Procedure B to give a crude reaction mixture that was purified via column chromatography (100% EtOAc, UV active) to give **52** (40.0 mg, 94%) as a yellow oil. R$_f$: 0.60 (100% EtOAc, UV active). ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.26 (t, *J* = 6.9 Hz, 6H), 3.56 (d, *J* = 5.6, 4H), 6.47 (dd, *J* = 3.4, 1.7 Hz, 1H), 7.01 (dd, *J* = 3.4, 0.6 Hz, 1H), 7.48 (dd, *J* = 1.6, 0.7 Hz, 1H). Spectral data were consistent with literature values.[172]

***N,N*-Diethylcinnamide (74)**



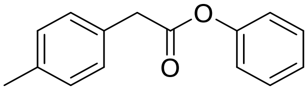
trans-Cinnamic acid (36.9 mg, 0.249 mmol, 1.0 equiv.) was subjected to General Procedure B (with the modification that 1.2 equiv. of PPh_3 was used instead of 1.0 equiv.) to give a crude reaction mixture that was purified via column chromatography (20% EtOAc in hexanes) to give **145** (41.0 mg, 81%) as a cream-colored solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 3.48 (t, *J* = 6.9 Hz, 4H), 6.82 (d, *J* = 15.4 Hz, 1H), 7.35 (m, 3H), 7.52 (m, 2H), 7.71 (d, *J* = 15.42 Hz, 1H). Spectral data were consistent with literature values.[170]

2.12.5 General procedure C: trapping with PhOH

A solution of phenol (4.0 equiv.) in dry DCM (1.5 mL) is heated to reflux under nitrogen, and to this is added distilled Et_3N (3.5 equiv.) before stirring for an additional 20 minutes. The resulting mixture is used to trap the acid chloride.

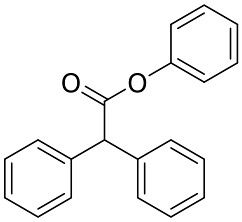
The carboxylic acid (1.0 equiv.) is dissolved in dry DCM (1.5 mL) and heated to reflux under nitrogen. PPh_3 (1.0 equiv.) is added, followed by $PhICl_2$ (1.2 equiv.), and the reaction is stirred for 10 minutes at reflux. The previously prepared mixture of PhOH/Et_3N is then added over 2 minutes via cannula and the reaction is stirred for 30 minutes, by which time TLC analysis indicates the consumption of starting material. The crude reaction mixtures were concentrated by rotary evaporation and purified by column chromatography.

Phenyl 2-(*p*-tolyl)acetate (33)



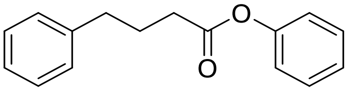
p-Tolylacetic acid (39.6 mg, 0.26 mmol, 1.0 equiv.) was subjected to General Procedure C to give a crude reaction mixture that was purified via column chromatography (10% EtOAc in hexanes, UV active) to give **33** (49.4 mg, 90%). R_f: 0.60 (10% EtOAc in hexanes, UV active). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.82 (s, 2H), 7.04 (m, 2H), 7.28 (m, 7H). Spectral data were consistent with literature values.[173]

Phenyl-2,2-diphenylacetate (39)



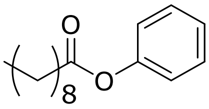
Diphenylacetic acid (53.2 mg, 0.248 mmol, 1.0 equiv.) was subjected to General Procedure C to give a crude reaction mixture that was purified via column chromatography (10% EtOAc in hexanes, UV active) to give **39** (52.0 mg, 72%) as a white. R_f: 0.33 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (s, 1H), 7.10 (m, 2H), 7.36 (m, 13H). Spectral data were consistent with literature values.[174]

Phenyl 4-phenylbutanoate (43)



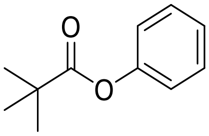
4-Phenylbutyric acid (40.7 mg, 0.248 mmol, 1.0 equiv.) was subjected to General Procedure C to give a crude reaction mixture that was purified via column chromatography (10% EtOAc in hexanes, UV active) to give **43** (49.2 mg, 83%) as a clear oil. R_f: 0.34 (10% EtOAc in hexanes, UV active); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13 (quintet, *J* = 7.5 Hz, 2H), 2.61 (m, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 7.11 (m, 2H), 7.52 (m, 8H). Spectral data were consistent with literature values.[175]

Phenyl decaonate (44)



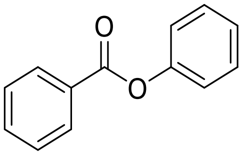
Decanoic acid (43.3 mg, 0.26 mmol, 1.0 equiv.) was subjected to General Procedure C to give a crude reaction mixture that was purified via column chromatography (5% EtOAc in hexanes, UV active) to give **44** (54.6 mg, 88%) as a colorless oil. R_f: 0.55 (5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (m, 3H), 1.36 (m, 12H), 1.76 (m, 2H), 2.56 (dd, J = 7.49 Hz, 2H), 7.08 (d, *J* = 7.7 Hz, 2H), 7.23 (dd, *J* = 13.0 Hz, 5.7 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 2H). Spectral data were consistent with literature values.[176]

Phenyl pivalate (45)



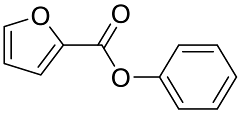
Pivalic acid (25.2 mg, 0.247 mmol, 1.0 equiv.) was subjected to General Procedure C to give a crude reaction mixture that was purified via column chromatography (5% EtOAc in hexanes, UV active) to give **45** (25.3 mg, 57%). R_f: 0.46 (5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H), 7.04 (d, *J* = 7.8 Hz, 2H), 7.22 (m, 1H), 7.36 (t, *J* = 7.7 Hz, 2H). Spectral data were consistent with literature values.[177]

Phenyl benzoate (50)



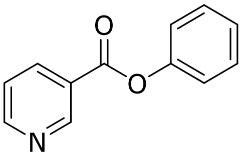
Benzoic acid (30.2 mg, 0.26 mmol, 1.0 equiv.) was subjected to General Procedure C to give a crude reaction mixture that was purified via column chromatography (10% EtOAc in hexanes) to give **50** (43.7 mg, 89%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 3H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.50 (m, 1H), 7.64 (t, *J* = 7.3 Hz, 1H), 8.21 (d, *J* = 7.7 Hz, 1H). Spectral data were consistent with literature values.[174]

Phenyl furan-2-carboxylate (53)



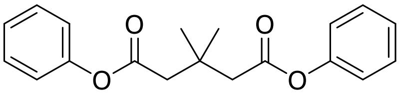
Furoic acid (27.8 mg, 0.248 mmol, 1.0 equiv.) was subjected to General Procedure C to give a crude reaction mixture that was purified via column chromatography (10% EtOAc in hexanes, UV active) to give **53** (46.4 mg, 99%) as a white solid. ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.43 (m, 1H), 7.05 (m, 3H), 7.22 (m, 3H), 7.49 (m, 1H). Spectral data were consistent with literature values.[173]

Phenyl nicotinate (55)



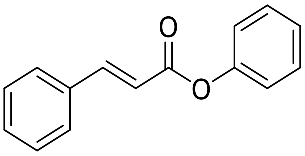
Nicotinic acid (30.2 mg, 0.245 mmol, 1.0 equiv.) was subjected to General Procedure C to give a crude reaction mixture that was purified via column chromatography (50% EtOAc in hexanes, UV active) to give **55** (48.2 mg, 99%) as a white solid after. R$_f$: 0.73 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.25 (m, 3H), 7.43 (m, 2H), 8.43 (m, 1H), 8.85 (m, 1H), 9.38 (d, *J* = 1.2 Hz, 1H). Spectral data were consistent with literature values.[178]

Diphenyl 3,3-dimethylpentanedioate (58)



3,3-Dimethylpentanedioic acid (40.4 mg, 0.252 mmol, 1.0 equiv.) was subjected to General Procedure C to give a crude reaction mixture that was purified via column chromatography (20% EtOAc in hexanes, UV active) to give **58** (40.4 mg, 52%) as a clear oil. IR (ATR) 1750, 1593, 1493, 1456, 1187, 1103 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.34 (s, 6H), 2.81 (m, 4H), 7.12 (m, 4H), 7.26 (m, 2H), 7.41 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 28.3, 33.5, 45.1, 122.0, 126.20, 129.8, 150.9, 170.7. HRMS (DART) calcd for $C_{19}H_{20}O_4$ (M+H)$^+$ 313.1434; found 313.1437.

Phenyl cinnamate (75)



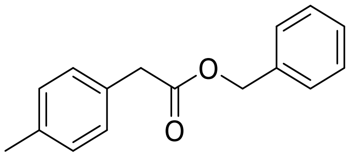
trans-Cinnamic acid (37.0 mg, 0.250 mmol, 1.0 equiv.) was subjected to General Procedure C (with the modification that 1.2 equiv. of PPh$_3$ was used instead of 1.0 equiv.) to give a crude reaction mixture that was purified via column chromatography (20% EtOAc in hexanes) to give **75** (44.2 mg, 80%) as a white solid. ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.66 (d, *J* = 16.0 Hz, 1H), 7.20 (m, 2H), 7.28 (m, 2H), 7.45 (m, 4H), 7.62 (m, 2H), 7.90 (d, *J* = 16.0 Hz, 1H). Spectral data were consistent with literature values.[178]

2.13.6 General procedure D: trapping with BnOH

A solution of benzyl alcohol (4.0 equiv.) in dry DCM (1.5 mL) is heated to reflux under nitrogen, and to this is added distilled Et_3N (3.5 equiv.) before stirring for an additional 20 minutes. The resulting mixture is used to trap the acid chloride.

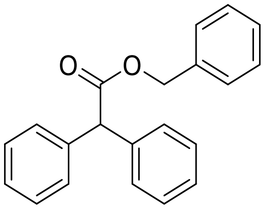
The carboxylic acid (1.0 equiv.) is dissolved in dry DCM (1.5 mL) and heated to reflux under nitrogen. PPh_3 (1.0 equiv.) is added, followed by $PhICl_2$ (1.2 equiv.), and the reaction is stirred for 10 minutes at reflux. The previously prepared mixture of BnOH/Et_3N is then added over 2 minutes via cannula and the reaction is stirred for 30 minutes, by which time TLC analysis indicates the consumption of starting material. The crude reaction mixtures were concentrated by rotary evaporation and purified by column chromatography.

Benzyl-2-(*p*-tolyl)acetate (34)



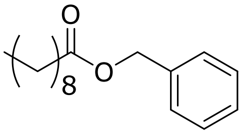
p-Tolylacetic acid (37.8 mg, 0.252 mmol, 1.0 equiv.) was subjected to General Procedure D to give a crude reaction mixture that was purified via column chromatography (10% EtOAc in hexanes, UV active) to give **34** (55.5 mg, 92%) as a clear oil. R_f: 0.68 (10% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.65 (s, 2H), 5.15 (s, 2H), 7.15 (d, *J* = 7.9 Hz, 4H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.35 (m, 5H). Spectral data were consistent with literature values.[179]

Benzyl 2,2-diphenylacetate (40)



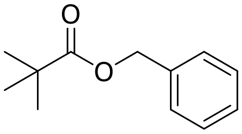
Diphenylacetic acid (53.5 mg, 0.252 mmol, 1.0 equiv.) was subjected to General Procedure D to give a crude reaction mixture that was purified via column chromatography (10% EtOAc in hexanes, UV active) to give **40** (67.5 mg, 89%) as a clear oil. R_f: 0.50 (10% EtOAc in hexanes, UV active); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 15H), 5.22 (s, 2H), 5.11 (s, 1H) Spectral data were consistent with literature values.[180]

Benzyl proprionate (45)



Decanoic acid (42.8 mg, 0.248 mmol, 1.0 equiv.) was subjected to General Procedure D to give a crude reaction mixture that was purified via column chromatography (5% EtOAc in hexanes, UV active) to give **45** (50.5 mg, 78%) as a clear oil. R_f: 0.58 (5% EtOAc in hexanes, UV active); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 6.7 Hz, 3H), 1.28 (m, 13H), 1.67 (s, 2H), 2.38 (t, *J* = 6.5 Hz, 2H), 5.14 (s, 2H), 7.37 (q, *J* = 3.3 Hz, 5H). Spectral data were consistent with literature values.[176]

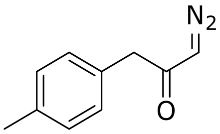
Benzyl pivalate (47)



Pivalic acid (24.5 mg, 0.240 mmol, 1.0 equiv.) was subjected to General Procedure D to give a crude reaction mixture that was purified via column chromatography (5% EtOAc in hexanes, UV active) to give **47** (26.3 mg, 57%). R_f: 0.43 (5% EtOAc in hexanes, UV active); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9H), 5.14 (s, 2H), 7.37 (m, 5H). Spectral data were consistent with literature values.[175]

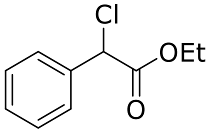
2.13.7 Miscellaneous procedures with NMR yields:

1-Diazo-3-(4-methylphenyl)-2-propanone (36)



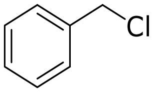
p-Tolylacetic acid (41.6 mg, 0.27 mmol, 1.0 equiv.) was dissolved in dry DCM (1.5 mL) and heated to reflux under nitrogen environment. PPh_3 (71.2 mg, 0.27 mmol, 1.0 equiv.) was added in one portion, followed by $PhICl_2$ (86.0 mg, 0.30 mmol, 1.2 equiv.). The reaction was stirred for 10 mins. A five-fold excess of CH_2N_2 in ether (made from nitrosomethylurea in KOH) was added dropwise until the solution turns a clear yellow. The reaction is then stirred 12 hours then the solvent was evaporated. To this was added HMDSO (3 µL) which was integrated to 1H upon 1 H NMR analysis. Based on HMDSO (1H = 0.254 mmol) the yield of **71** was 98%.

Ethyl 2-chloro-2-phenylaceate (69)



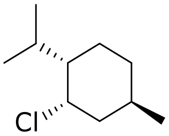
Ethyl mandelate (50.9 mg, 0.28 mmol, 1.0 eq) was dissolved in dry DCM (1.0 mL) and heated to reflux under nitrogen. PPh3 (98.7 mg, 0.37 mmol, 1.3 eq) was added in one portion. PhICl2 was then added until the solution turned yellow, indicating the consumption of Ph3P. The reaction was stirred for 1 hr then the solvent was evaporated. To this was added HMDSO (3 µL) which was integrated to 1H upon 1 H NMR analysis. Based on HMDSO (1H = 0.254 mmol) the yield of **69** was 92%.

Benzyl chloride (71)



Benzyl alcohol (25 µL, 0.245 mmol, 1.0 equiv.) was dissolved in dry DCM (0.5 mL) and heated to reflux under nitrogen. PPh_3 (69.2 mg, 0.26 mmol, 1.05 equiv.) was added in one portion. $PhICl_2$ was then added until the solution turned yellow, indicating the consumption of Ph_3P. The reaction was stirred for 1 hr then solvent was evaporated. To this was added HMDSO (3 µL) which was integrated to 1H upon 1 H NMR analysis. Based on HMDSO (1H = 0.254 mmol) the yield of benzyl chloride was 88%.

Neomenthyl Chloride (73)



(–)-Menthol (36.0 mg, 0.23 mmol, 1.0 eq) was dissolved in dry DCM (1.0 mL) and heated to reflux under nitrogen. PPh_3 (71 mg, 0.25 mmol, 1.05 eq) was added in one portion. PhICl2 was then added until the solution turned yellow, indicating the consumption of Ph3P. The reaction was stirred for 1 hr then the solvent was evaporated. To this was added HMDSO (3 µL) which was integrated to 1H upon ^{1}H NMR analysis. Based on HMDSO (1H = 0.254 mmol) the yield of **73** was 72%.

References

[1] C. Willgerodt, *J. Prakt. Chem.* **1886**, *33*, 154.

[2] V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299–5358.

[3] P. J. Stang, V. V. Zhdankin, *Chem. Rev.* **1996**, *96*, 1123–1178.

[4] A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328–3435.

[5] P. J. Stang, *Chem. Rev.* **2009**, *108*, 5299–5358.

[6] W. H. Powell, *Pure Appl. Chem.* **1984**, *56*, 769–778.

[7] M. Frigerio, M. Santagostino, *Tetrahedron Lett.* **1994**, *35,* 8019–8022.

[8] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156.

[9] V. V. Zhdankin, *Hypervalent Iodine Chemistry*, Wiley, **2014**.

[10] V. V Zhdankin, P. J. Stang, *Chem. Rev.* **2002**, *102*, 2523–2584.

[11] Y. Kita, G. F. Koser, M. Ochai, H. Thoma, A. Varvolglis, T. Wirth, V. V. Zhdankin, *Topics in Current Chemistry: Hypervalent Iodine Chemistry*, **2003**.

[12] V. V. Zhdankin, *Arkivoc* **2009**, *i*, 1–62.

[13] J. Wicha, A. Zarecki, M. Kocór, *Tetrahedron Lett.* **1973**, *14*, 3635–3638.

[14] T. P. Mohandas, A. S. Mamman, P. M. Nair, *Tetrahedron* **1983**, *39*, 1187–1188.

[15] N. N. Karade, V. H. Budhewar, A. N. Katkar, G. B. Tiwari, *Arkivoc* **2006**, *xi*, 162–167.

[16] N. N. Karade, G. B. Tiwari, D. B. Huple, *Synlett* **2005**, *13*, 2039–2042.

[17] A. Y. Koposov, B. C. Netzel, M. S. Yusubov, V. N. Nemykin, A. Y. Nazarenko, V. V. Zhdankin, *Eur. J. Org. Chem.* **2007**, 4475–4478.

[18] M. S. Yusubov, R. Y. Yusubova, T. V. Funk, K. W. Chi, V. V. Zhdankin, *Synthesis* **2009**, *3*, 2505–2508.

[19] S. Makowiec, J. Rachon, *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 941–955.

[20] S. Makowiec, J. Rachon, *Heteroat. Chem.* **2003**, *14*, 352–359.

[21] J. M. Vatèle, *Synlett* **2006**, *13*, 2055–2058.

[22] F. Mizukami, M. Ando, T. Tanaka, J. Imamura, *Bull. Chem. Soc. Jpn.* **1978**, *51*, 335–336.

[23] L. Liu, D. Zhang-Negrerie, Y. Du, K. Zhao, *Org. Lett.* **2014**, *16*, 436–439.

[24] J. Tao, R. Tran, G. K. Murphy, *J. Am. Chem. Soc.* **2013**, *135*, 16312–16315.

[25] A. Zanka, H. Takeuchi, A. Kubota, *Org. Process Res. Dev.* **1998**, *2*, 270–273.

[26] C. Hepples, G. K. Murphy, *Tetrahedron Lett.* **2015**, *56*, 4971–4974.

[27] J. Charpentier, N. Fru, A. Togni, *Chem. Rev.* **2015**, *115*, 650–682.

[28] S. V Kohlhepp, T. Gulder, *Chem. Soc. Rev.* **2016**, *45*, 6270–6288.

[29] G. F. Koser, A. G. Relenyi, A. N. Kalos, L. Rebrovic, R. H. Wettach, *J. Org. Chem.* **1982**, *47*, 2487–2489.

[30] H. Yin, T. Wang, N. Jiao, *Org. Lett.* **2014**, *16*, 2302–2305.

[31] J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2015**, *54*, 8876–8878.

[32] D. O. Hagan, D. Chambers, *Chem. Soc. Rev.* **2008**, *37*, 308–319.

[33] S. Swallow, *Prog. Med. Chem.* **2015**, *54*, 65–133.

[34] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359.

[35] P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589.

[36] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–6.

[37] S. Purser, P. R. Moore, D. O. Hagan, S. Purser, P. R. Moore, *Chem. Soc. Rev.* **2008**, *37*, 320–330.

[38] X. Yang, T. Wu, R. J. Phipps, F. D. Toste, *Chem. Rev.* **2015**, *115*, 826–870.

[39] C. Hollingworth, V. Gouverneur, *Chem. Commun.* **2012**, *48*, 2929–42.

[40] O. Lozano, G. Blessley, T. Martinez Del Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, V. Gouverneur, *Angew. Chem. Int. Ed.* **2011**, *50*, 8105–8109.

[41] M. Jaccaud, R. Faron, D. Devilliers, R. Romano, M. Jaccaud, R. Faron, D. Devilliers, R. Romano, in *Ullmann's Encycl. Ind. Chem.*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2000**.

[42] C. B. Mcpake, G. Sandford, *Org. Process Res. Dev.* **2012**, *16*, 844–851.

[43] R. Landau, R. Rosen, *Ind. Eng. Chem.* **1886**, *39*, 281–286.

[44] E. Differding, R. W. Lang, *Tetrahedron Lett.* **1988**, *29*, 6087–6090.

[45] M. A. Arrica, T. Wirth, *Eur. J. Org. Chem.* **2005**, 395–403.

[46] M. Sawaguchi, S. Ayuba, S. Hara, *Synthesis* **2002**, *2002*, 1802–1803.

[47] W. Carpenter, *J. Org. Chem.* **1966**, *31*, 2688–2689.

[48] I. Ruppert, *J. Fluor. Chem.* **1980**, *15*, 173–178.

[49] V. V. Lyalin, V. V. Orda, L. A. Alekseev, L. M. Yagupols, *Zh. Org. Khim.* **1970**, *6*, 329.

[50] M. Sawaguchi, S. Hara, Y. Nakamura, S. Ayuba, T. Fukuhara, *Tetrahedron* **2001**, *57*, 3315–3319.

[51] C. Ye, B. Twamley, J. M. Shreeve, *Org. Lett.* **2005**, 1802–1803.

[52] S. Hara, J. Nakahigashi, K. Ishi-i, M. Sawaguchi, H. Sakai, T. Fukuhara, N. Yoneda, *Synlett* **1998**, *1998*, 495–496.

[53] M. Yoshida, K. Fujikawa, S. Sato, S. Hara, *Arkivoc* **2003**, *vi*, 36–42.

[54] M. Regitz, *Angew. Chem. Int. Ed.* **1967**, *6*, 733–749.

[55] J. S. Baum, D. A. Shook, H. M. L. Davies, H. D. Smith, *Synth. Commun.* **1987**, *17*, 1709–1716.

[56] W. R. Bamford, T. S. Stevens, *J. Chem. Soc.* **1952**, *0*, 4735–4740.

[57] J. R. Fulton, V. K. Aggarwal, J. De Vicente, *Eur. J. Org. Chem.* **2005**, 1479–1492.

[58] M. I. Javed, M. Brewer, *Org. Lett.* **2007**, *9*, 1789–1792.

[59] T. L. Holton, H. Shechter, *J. Org. Chem.* **1995**, *60*, 4725–4729.

[60] B. Patrick, P. A. Flory, *J. Fluor. Chem.* **1984**, *25*, 157–164.

[61] B. Quiclet-Sire, S. Z. Zard, *Chem. Commun.* **2006**, 1831–2.

[62] M. Regitz, G. Maas, *Diazo Compounds : Properties and Synthesis*, Academic Press, **1986**.

[63] R. L. C. Brimacombe, B. E. Griffin, J. A. Haines, W. J. Haslam, C. B. Reese, *Biochemistry* **1965**, *4*, 2452–2458.

[64] A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981–10080.

[65] K. A. Mix, M. R. Aronoff, R. T. Raines, *ACS Chem. Biol.* **2016**, *11*, 3233–3244.

[66] S. Rozen, M. Brand, D. Zamir, D. Hebel, *J. Am. Chem. Soc.* **1987**, *109*, 896–897.

[67] G. K. S. Prakash, V. P. Reddy, S.-Y. Li, G. A. Olah, *Synlett* **1990**, 594–596.

[68] R. Weiss, J. Seubert, *Angew. Chem. Int. Ed.* **1994**, *33*, 891–893.

[69] H. Liu, Y. Wei, C. Cai, *New J. Chem.* **2016**, *40*, 674–678.

[70] K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *J. Am. Chem. Soc.* **2004**, *126*, 5192–5201.

[71] E. Michael, A. G. Myers, *J. Am. Chem. Soc.* **2004**, *126*, 12222–12223.

[72] Z. Zhao, K. G. Kulkarni, G. K. Murphy, *Adv. Synth. Catal.* **2017**, *359*, 2222–2228.

[73] K. G. Kulkarni, B. Miokovic, M. Sauder, G. K. Murphy, *Org. Biomol. Chem.* **2016**, *14*, 9907–9911.

[74] D. H. R. Barton, R. E. 0'Brien, S. Sternhell, *J. Chem. Soc.* **1962**, 470–476.

[75] G. S. Sinclair, R. Tran, J. Tao, W. S. Hopkins, G. K. Murphy, *Eur. J. Org. Chem.* **2016**, 4603–4606.

[76] C. Paduani, P. Jena, *Int. J. Hydrogen Energy* **2013**, *38*, 2357–2362.

[77] L. P. Ma, P. Wang, H. M. Cheng, *J. Alloys Compd.* **2007**, *432*, 3–6.

[78] N. Juahir, N. S. Mustafa, F. A. Halim Yap, M. Ismail, *Int. J. Hydrogen Energy* **2015**, *40*, 7628–7635.

[79] A. K. Yadav, V. P. Srivastava, L. D. S. Yadav, *Chem. Commun.* **2013**, *49*, 2154.

[80] X. F. Zhao, C. Zhang, *Synthesis* **2007**, 551–557.

[81] S. Sato, M. Yoshida, S. Hara, *Synthesis* **2005**, 2602–2605.

[82] V. Z. Shirinian, L. I. Belen'kii, M. M. Krayushkin, *Russ. Chem. Bull.* **1999**, *48*, 2171–2173.

[83] M. J. López-Gómez, D. Martin, G. Bertrand, *Chem. Commun.* **2013**, *49*, 4483–5.

[84] E. Schmitt, G. Landelle, J. P. Vors, N. Lui, S. Pazenok, F. R. Leroux, *Eur. J. Org. Chem.* **2015**, *2015*, 6052–6060.

[85] S. Ghiya, Y. C. Joshi, *Med. Chem. Res.* **2016**, *25*, 970–976.

[86] J. Ma, W. Yi, G. Lu, C. Cai, T. Furuya, A. E. Strom, T. Ritter, F. Narjes, K. F. Koehler, U. Koch, et al., *Org. Biomol. Chem.* **2015**, *13*, 2890–2894.

[87] X. Huang, W. Liu, H. Ren, R. Neelamegam, J. M. Hooker, J. T. Groves, *J. Am. Chem. Soc.* **2014**, *136*, 6842–5.

[88] M. E. Weeks, *J. Chem. Educ.* **1933**, *10*, 302.

[89] B. J. Walker, *Organophosphorus Chemistry*, Penguin Book Ltd, London, **1972**.

[90] W. A. Henderson Jr, S. A. Buckler, *J. Am. Chem. Soc.* **1960**, *82*, 5794–5800.

[91] J. L. Methot, W. R. Roush, *Adv. Synth. Catal.* **2004**, *346*, 1035–1050.

[92] S. A. Buckler, L. Doll, F. K. Lind, M. Epstein, *J. Org. Chem.* **1962**, *27*, 794–798.

[93] O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382.

[94] H. Staudinger, E. Hauser, *Helv. Chim. Acta* **1919**, 635–646.

[95] A. Michaelis, R. Kaehne, *Berichte der Dtsch. Chem. Gesellschaft* **1898**, *31*, 1048–1055.

[96] A. G. Varvoglis, *Tetrahedron Lett.* **1972**, *13*, 31–32.

[97] Z.-D. Liu, Z.-C. Chen, *Synthesis* **1993**, 373–374.

[98] T. Kitamura, K. Nagata, H. Taniguchi, P. J. Stang, *J. Org. Chem.* **1992**, *57*, 6810–6814.

[99] M. Ochiai, J. Nishitani, Y. Nishi, *J. Org. Chem.* **2002**, *67*, 4407–4413.

[100] G. Mielniczak, A. Lopusinski, *Synlett* **2001**, 505–508.

[101] A. Hubacz, S. Makowiec, *Heteroat. Chem.* **2009**, *20*, 81–86.

[102] J. Tian, W. Gao, D. Zhou, C. Zhang, *Org. Lett.* **2012**, *14*, 3020–3023.

[103] C. Zhang, S.-S. Liu, B. Sun, J. Tian, *Org. Lett.* **2015**, *17*, 4106–4109.

[104] J. Charpentier, N. Fru, A. Togni, *Chem. Rev.* **2015**, *115*, 650–682.

[105] P. Eisenberger, I. Kieltsch, N. Armanino, A. Togni, *Chem. Commun.* **2008**, 1575–1577.

[106] N. Armanino, R. Koller, A. Togni, *Organometallics* **2010**, *29*, 1771–1777.

[107] R. Aardoom, A. Togni, A. Sondenecker, J. Cvengros, *Eur. J. Org. Chem.* **2011**, 78–87.

[108] G. M. Blackburn, M. W. Bowler, M. J. Cliff, P. Waltho, G. M. Blackburn, *New J. Chem.* **2010**, *34*, 769–1028.

[109] S. J. Hecker, M. D. Erion, *J. Med. Chem.* **2008**, *51*, 2328–2345.

[110] C. Schultz, *Bioorg. Med. Chem.* **2003**, 885–898.

[111] C. Ducho, U. Go, *J. Med. Chem.* **2007**, *50*, 1335–1346.

[112] S. Protti, M. Fagnoni, *Chem. Commun.* **2008**, 3611–21.

[113] A. Parra, S. Reboredo, A. M. M. Castro, J. Alemán, *Org. Biomol. Chem.* **2012**, *10*, 4989–

5152.

[114] G. Wittig, M. Rieber, *Liebigs Ann. Chem* **1949**, *562*, 187–192.

[115] R. Engel, *Synthesis of Carbon-Phosphorus Bonds*, CRC Press, Inc. Boca Raton, Florida, **1988**.

[116] A. Michaelis, *Liebigs Ann. Chem* **1875**, *181*, 256.

[117] G. A. Wiley, R. L. Hershkovitz, B. M. Rein, B. C. Chung, *J. Am. Chem. Soc.* **1964**, *86*, 964–965.

[118] J. Dormoy, B. Castro, M. L. Crawley, in *E-EROS*, **2009**.

[119] A. D. Beveridge, G. S. Harris, F. Inglis, *J. Chem. Soc. A* **1966**, 520–528.

[120] W.-W. du Mont, M. Batcher, S. Pohl, W. Saak, *Angew. Chem. Int. Ed.* **1987**, *26*, 912–913.

[121] S. M. Godfrey, D. G. Kelly, C. A. Mcauliffe, A. G. Mackie, R. G. Pritchard, S. M. Watson, *J. Chem. Soc., Chem. Commun.* **1991**, *2*, 1163–1164.

[122] N. Bricklebank, S. M. Godfrey, A. G. Mackie, C. A. McAuliffe, R. G. Pritchard, P. J. Kobryn, *J. Chem. Soc. Dalt. Trans.* **1993**, 101.

[123] E. Piers, I. Nagakura, *Synth. Commun.* **1975**, *5*, 193–199.

[124] A. R. Hajipour, M. Mostafavi, A. E. Ruoho, *Org. Prep. Proced. Int.* **2009**, *41*, 87–91.

[125] P. J. Garegg, R. Johansson, C. Ortega, B. Samuelsson, *J. Chem. Soc. Perkin Trans. 1* **1982**, 681–683.

[126] G. A. Olah, D. G. B. Gupta, S. C. Narang, *Synthesis* **1978**, 137–138.

[127] Z. Paryzek, R. Wydra, *Tetrahedron Lett.* **1984**, *25*, 2601–2604.

[128] P. J. Garegg, B. Samuelsson, *Synthesis* **1979**, 813–814.

[129] R. Caputo, C. Ferreri, G. Palumbo, *Synthesis* **1987**, 386–390.

[130] R. Caputo, E. Corrado, C. Ferreri, G. Palumbo, *Synth. Commun.* **1986**, *16*, 1081–1083.

[131] N. Bricklebank, S. M. Godfrey, A. G. Mackie, C. A. Mcauiiffe, R. G. Pritchard, *J. Chem. Soc. Chem. Commun.* **1992**, 355–356.

[132] J. P. Shaefer, D. S. Weinberd, *J. Org. Chem.* **1965**, *30*, 2635–2639.

[133] R. Appel, *Angew. Chem. Int. Ed.* **1975**, *14*, 801–811.

[134] R. M. Magid, O. S. Fruchey, W. L. Johnson, *Tetrahedron Lett.* **1977**, *18*, 2999–3002.

[135] I. Sunshine, *CRC Handbook of Analatical Toxicology,* **1969**.

[136] J. P. Kilburn, J. Lau, R. C. F. Jones, *Tetrahedron* **2002**, *58*, 1739–1743.

[137] K. B. Dillon, R. N. Reeve, T. C. Waddington, *J. Inorg. Nucl. Chem* **1976**, *38*, 1439–1442.

[138] A. Licea-Claverie, I. A. Rivero, B. L. Garcia, *Polym. Bull.* **1996**, *37*, 415–421.

[139] K. V. Rajendran, L. Kennedy, C. T. O’Connor, E. Bergin, D. G. Gilheany, *Tetrahedron Lett.* **2013**, *54*, 7009–7012.

[140] M. A. H. Al-Juboori, P. N. Gates, A. S. Muir, *J. Chem. Soc., Chem. Commun.* **1991**, 1270–1271.

[141] G. A. Wiley, W. R. Stine, *Tetrahedron Lett.* **1967**, *24*, 2321–2324.

[142] D. B. Denney, D. Z. Denney, B. C. Chang, *J. Am. Chem. Soc.* **1968**, *90*, 6332–6335.

[143] S. M. Godfrey, C. A. McAuliffe, R. G. Pritchard, J. M. Sheffield, *Chem. Commun.* **1996**, *1*, 2521.

[144] S. M. Godfrey, A. Hinchliffe, A. Mkadmh, *J. Mol. Struc: Theochem* **2005**, *719*, 85–88.

[145] S. M. Godfrey, C. A. McAuliffe, J. M. Sheffield, *Chem. Commun.* **1998**, *280*, 921–922.

[146] Q. Yin, Y. Ye, G. Tang, Y.-F. Zhao, *Spectrochim. Acta Mol. Biomol. Spectrosc.* **2006**, *63*, 192–5.

[147] R. Appel, W. Moorbach, *Angew. Chem. Int. Ed.* **1977**, *16*, 180–181.

[148] S. G. Newman, C. S. Bryan, D. Perez, M. Lautens, *Synthesis* **2011**, 342–346.

[149] H. M. Relles, R. W. Schluenz, *J. Am. Chem. Soc.* **1974**, *96*, 6469–6475.

[150] R. M. Denton, X. Tang, A. Przeslak, *Org. Lett.* **2010**, *12*, 4678–4681.

[151] K. Shibata, Y. Itoh, N. Tokitoh, R. Okazaki, N. Inamoto, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3749–3751.

[152] K. M. Doxsee, E. M. Hanawalt, T. J. R. Weakley, *Inorg. Chem.* **1992**, *31*, 4420–4421.

[153] W. C. Firth, S. Frank, M. Garber, V. P. Wystrach, *Inorg. Chem.* **1965**, *4*, 1963–1964.

[154] H. J. Frohn, H. Maurer, *J. Fluor. Chem.* **1986**, *34*, 73–82.

[155] K. M. Doxsee, E. M. Hanawalt, T. J. Weakley, *Acta Crystallogr. Sect. C Cryst. Struct. Commun.* **1992**, *48*, 1990–1992.

[156] F. Weller, D. Nuszhar, K. Dehnicke, *Anorg. Allg. Chem.* **1991**, *602*, 7–16.

[157] Y. Kobayashi, C. Akashi, *Chem. Pharm. Bull.* **1968**, *16*, 1009–1013.

[158] B. S. Burton, H. von Pechmann, *Chem. Ber.* **1887**, *20*, 145.

[159] R. T. Sanderson, *Chemical Bonds and Bond Energy*, Academic Press, **1971**.

[160] M. S. Yusubov, R. J. Yusubova, V. D. Filimonov, K. Chi, *Synth. Commun.* **2004**, *34*, 443–450.

[161] R. M. Magid, S. Fruchey, W. L. Johnson, T. G. Allen, *J. Org. Chem.* **1979**, *44*, 359–262.

[162] L.-G. Xie, Z.-X. Wang, *Angew. Chem. Int. Ed.* **2011**, *50*, 4901–4904.

[163] O. Vechorkin, V. Proust, X. Hu, *J. Am. Chem. Soc.* **2009**, *131*, 9756–9766.

[164] A. Schmidt, T. Habeck, B. Snovydovych, W. Eisfeld, *Org. Lett.* **2007**, *9*, 3515–3518.

[165] W. Fan, S. Ma, *Eur. J. Org. Chem.* **2015**, *16*, 3531–3539.

[166] C. Salomé, H. Kohn, *Tetrahedron* **2009**, *65*, 456–460.

[167] P. Gopinath, S. Nilaya, K. M. Muraleedharan, *Org. Lett.* **2011**, *13*, 1932–1935.

[168] D. González-Calderón, L. J. Benítez-Puebla, C. A. González-González, S. Assad-Hernández, A. Fuentes-Benítez, E. Cuevas-Yáñez, D. Corona-Becerril, C. González-Romero, *Tetrahedron Lett.* **2013**, *54*, 5130–5132.

[169] Z.-W. Chen, H.-F. Jiang, X.-Y. Pan, Z.-J. He, *Tetrahedron* **2001**, *67*, 5920–5927.

[170] B. Xiong, L. Zhu, X. Feng, J. Lei, T. Chen, Y. Zhou, L.-B. Han, C.-T. Au, S.-F. Yin, *Eur. J. Org. Chem.* **2014**, *20*, 4244–4247.

[171] T. Fukuyama, S. Nishitani, T. Inouye, K. Morimoto, I. Ryu, *Org. Lett.* **2006**, *8*, 1383–1386.

[172] Z. Liu, J. Zhang, S. Chen, E. Shi, Y. Xu, X. Wan, *Angew. Chem. Int. Ed.* **2012**, *51*, 3231–3235.

[173] M. Zhang, S. Zhang, G. Zhang, F. Cheng, C. Jiang, *Tetrahedron Lett.* **2011**, *52*, 2480–2483.

[174] J.-E. Won, H.-K. Kim, J.-J. Kim, H.-S. Yim, M.-J. Kim, S.-B. Kang, H.-A. Chung, S.-G. Lee, Y.-J. Yoon, *Tetrahedron* **2007**, *63*, 12720–12730.

[175] T. Satoh, H. Unno, Y. Mizu, Y. Hayashi, *Tetrahedron* **1997**, *53*, 7843–7854.

[176] H. Toledo, E. Pisarevsky, A. Abramovich, A. M. Szpilman, *Chem. Commun.* **2013**, *49*, 4367–4369.

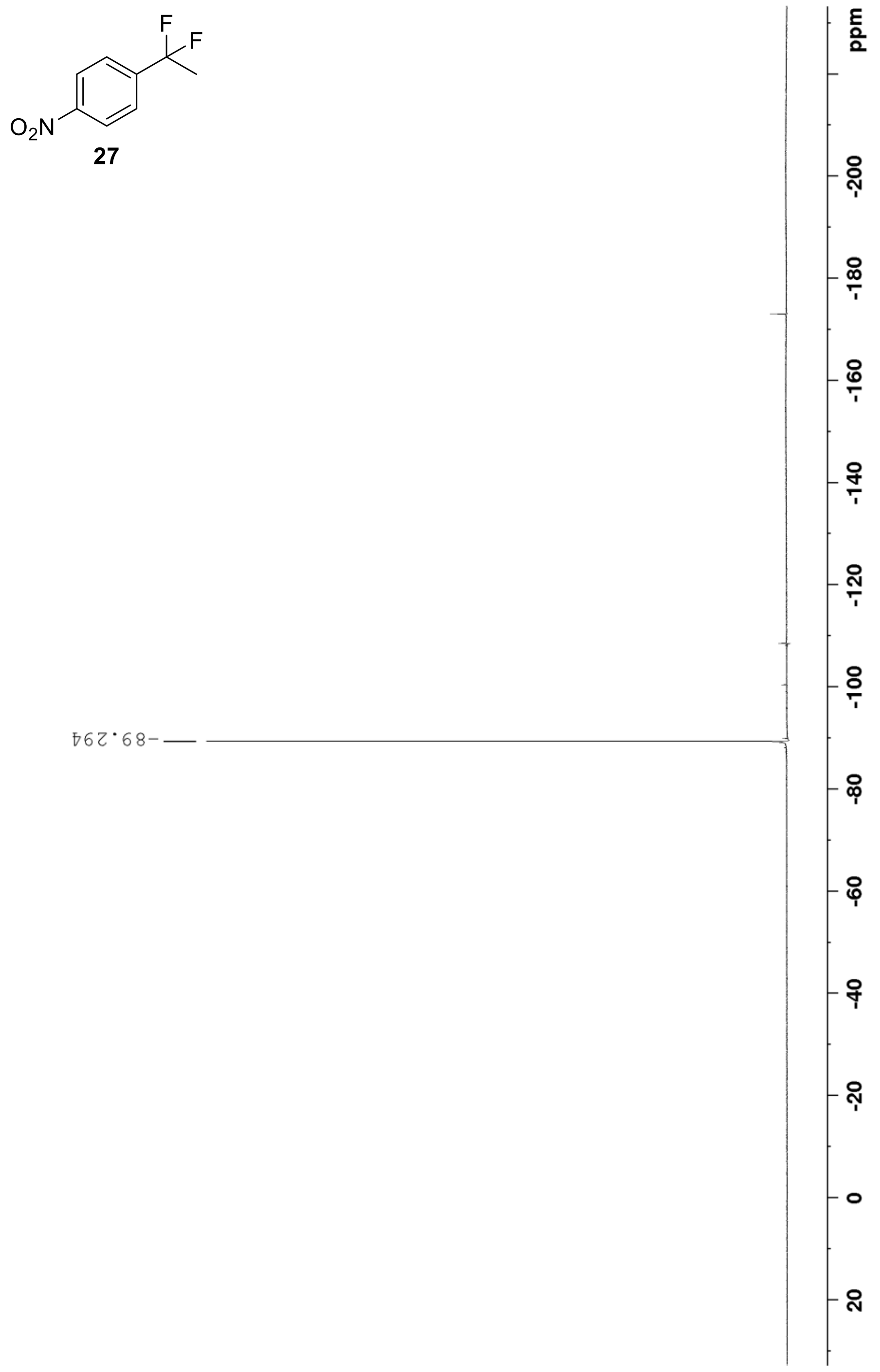
[177] W. M. Czaplik, S. Grupe, M. Mayer, A. Jacobi von Wangelin, *Chem. Commun.* **2010**, *46*, 6350–6352.

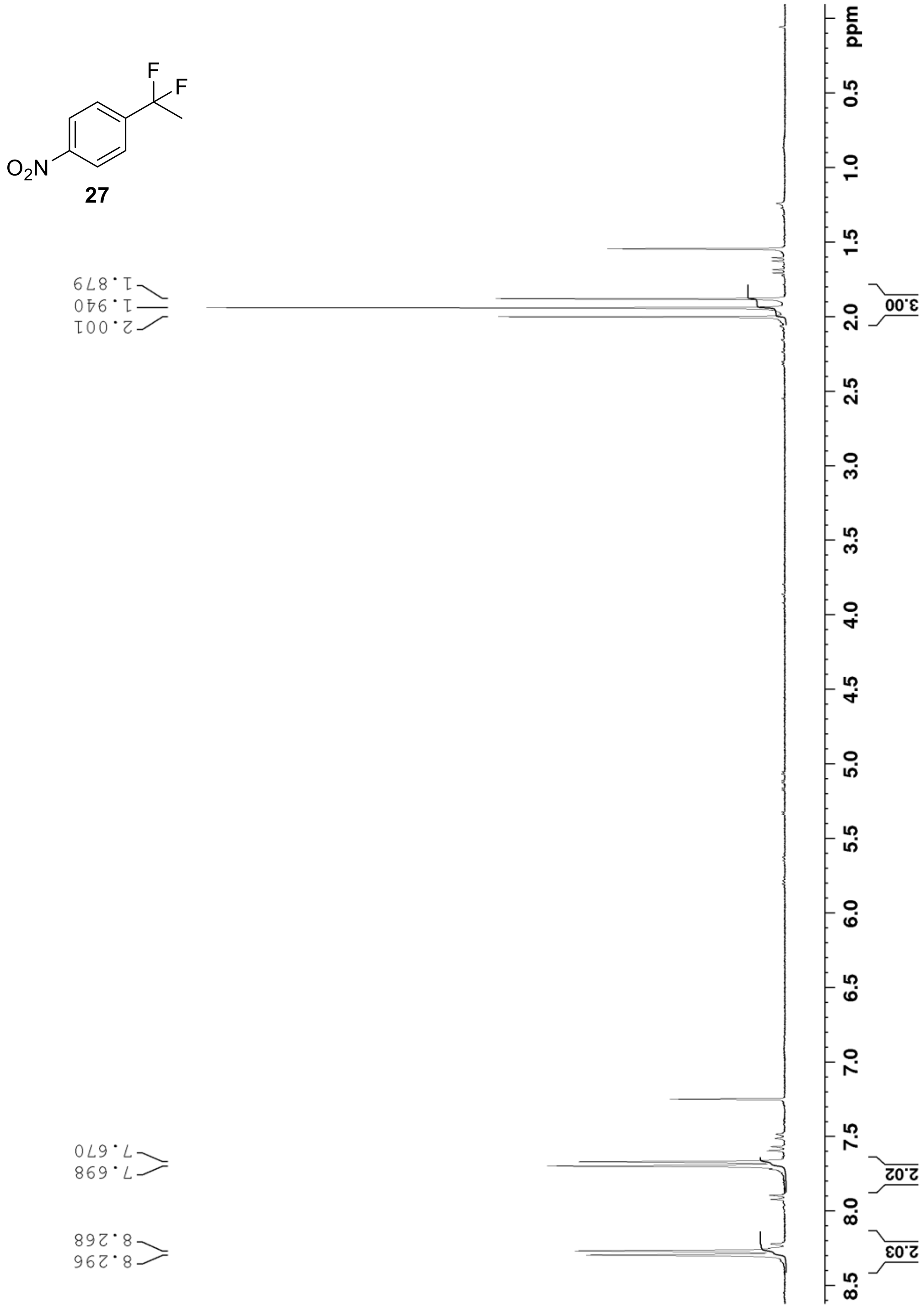
[178] T. Ueda, H. Konishi, K. Manabe, *Org. Lett.* **2012**, *14*, 3100–3103.

[179] O. Roy, A. Riahi, F. Hénin, J. Muzart, *Eur. J. Org. Chem.* **2002**, 3986–3994.

[180] P. Froyen, *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, *91*, 145–151.

Appendix A – Chapter 1 NMR spectra

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ppm
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1.5
2.0
2.5
3.0
3.5
4.0
4.5
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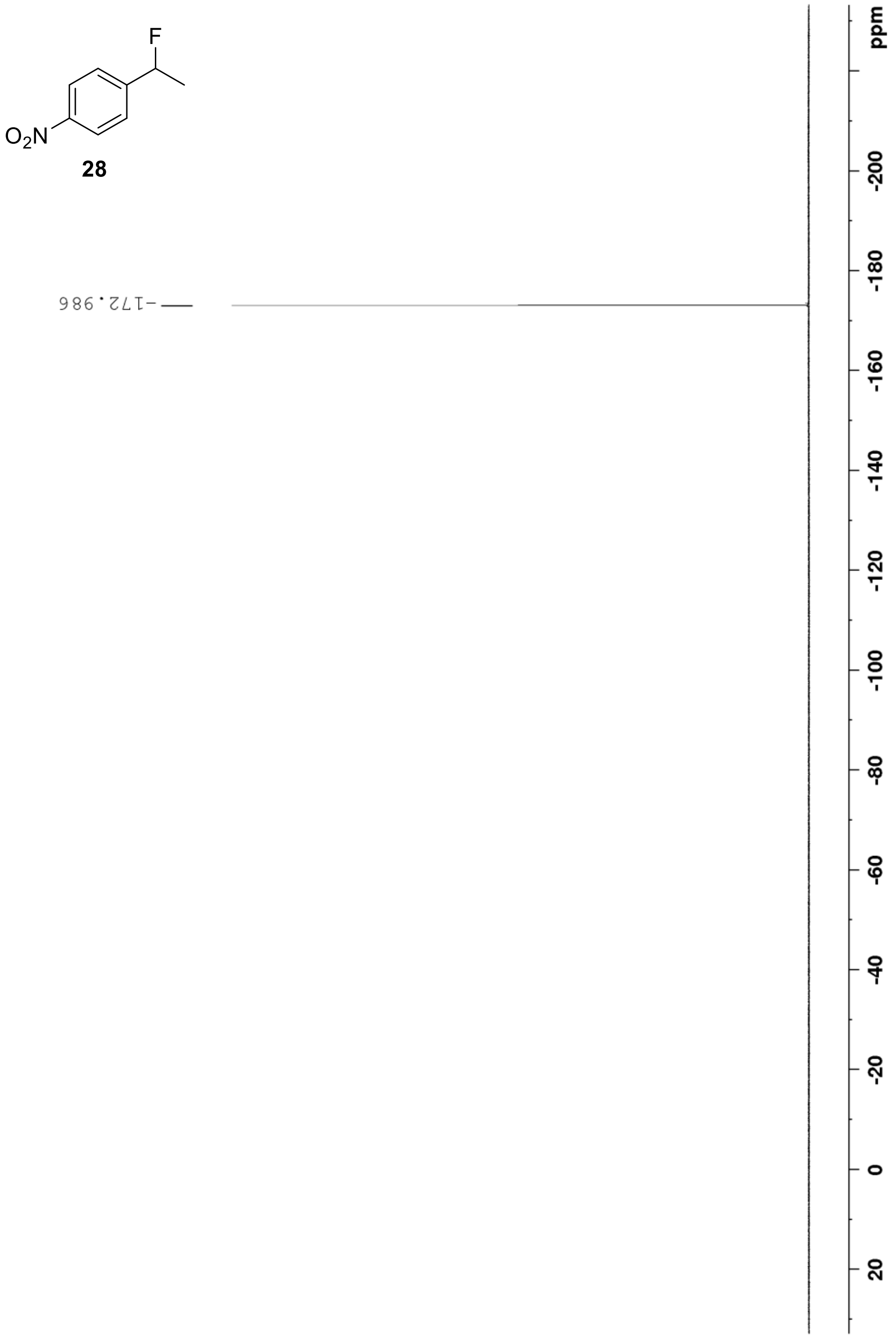
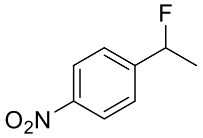
6.0
6.5
7.0
7.5
8.0
8.5
3.00
2.02
2.03

27



28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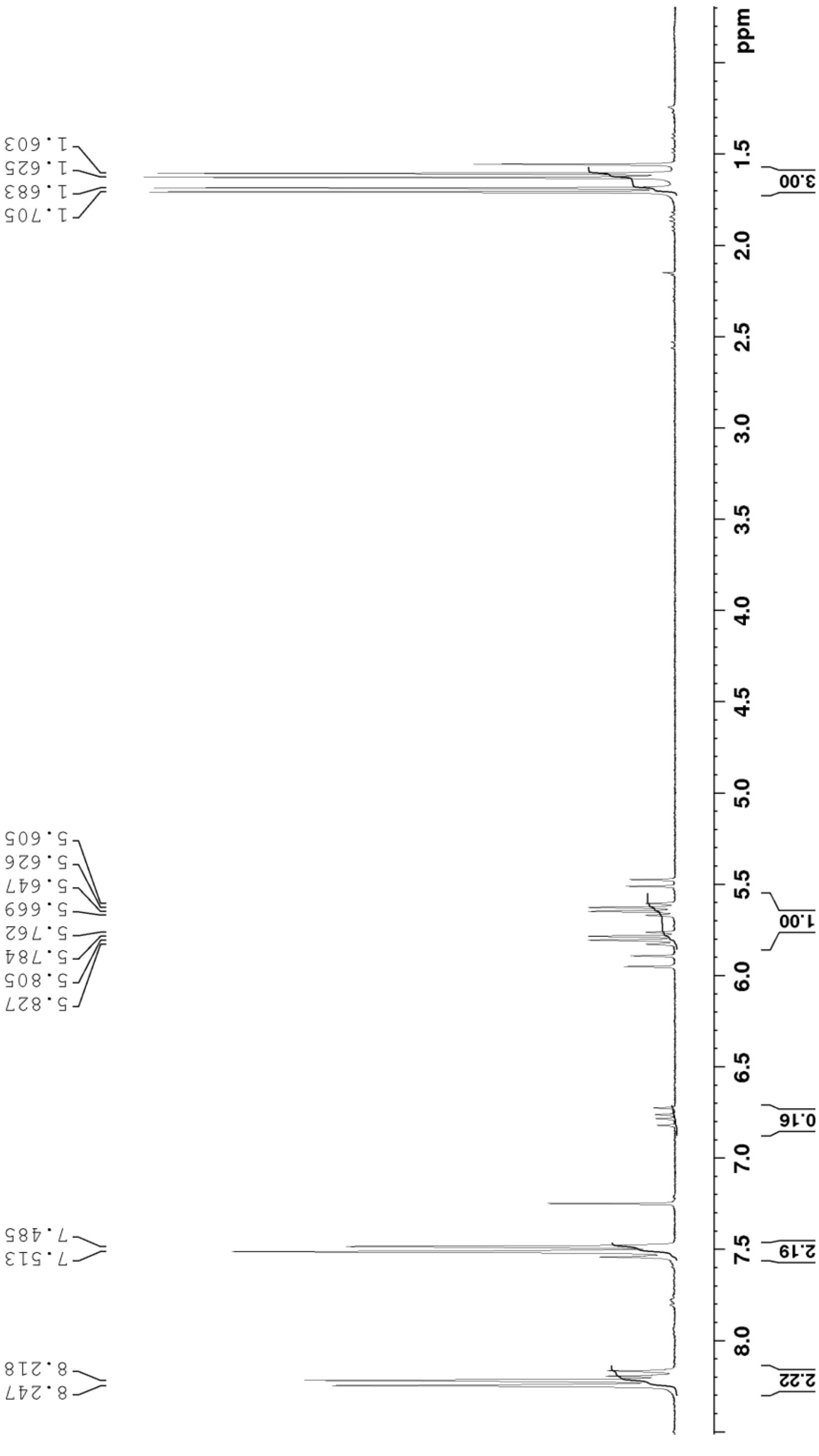
28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5.647
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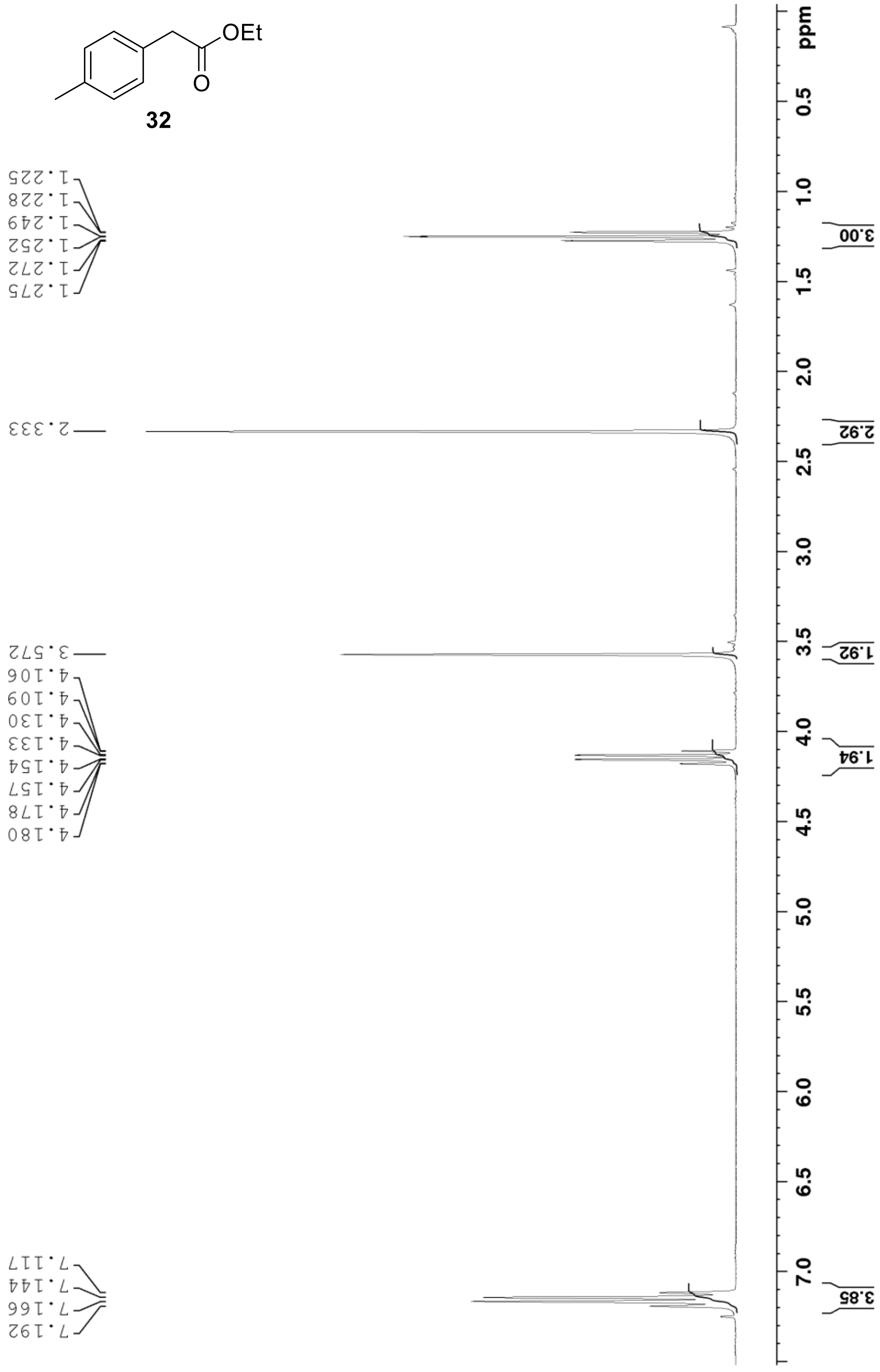
7.485
7.513
8.218
8.247
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
3.00
1.00
0.16
2.19
2.22

Appendix B – Chapter 2 NMR Spectra



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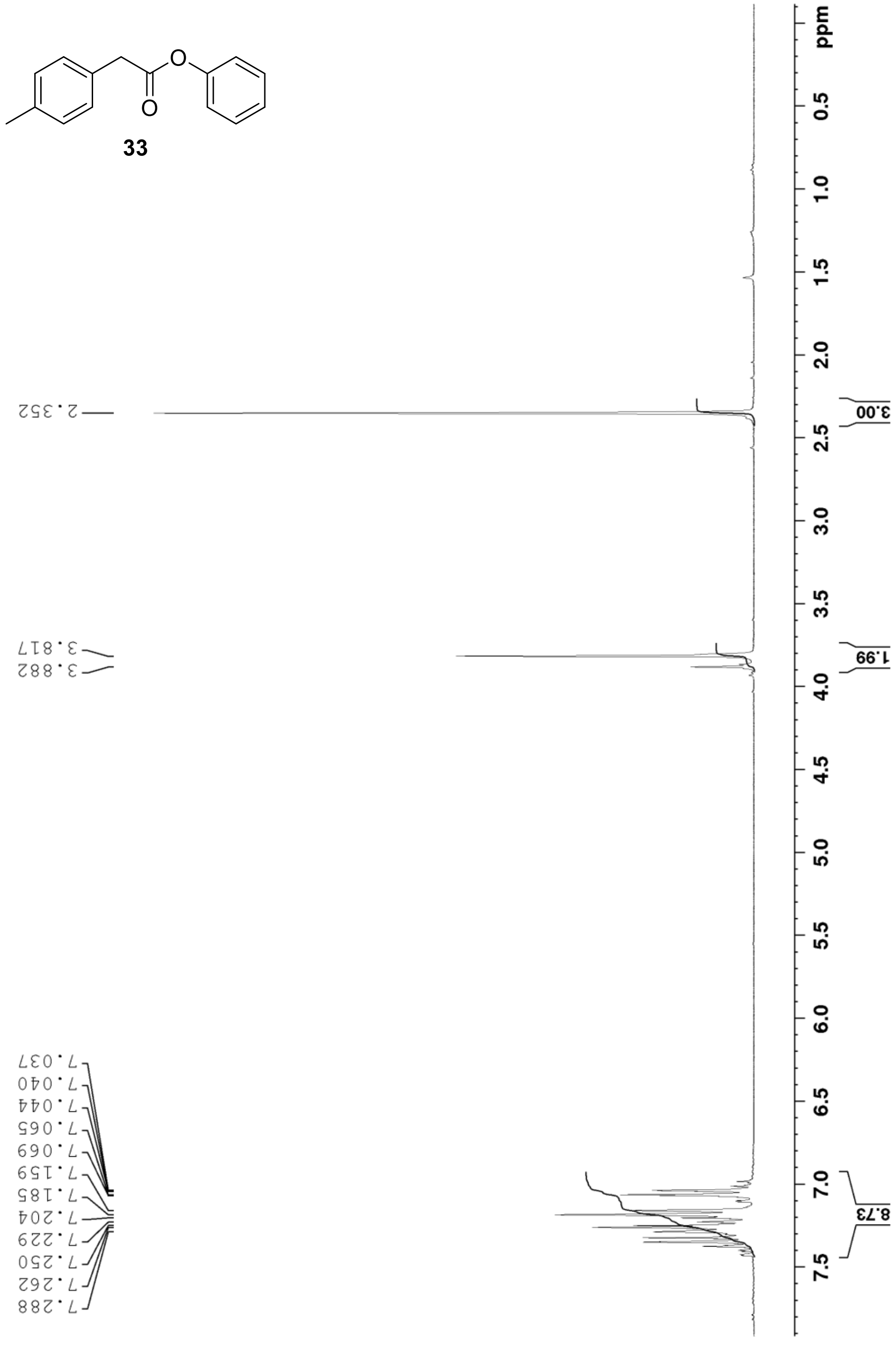

33

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3.817
3.882
7.037
7.040
7.044
7.065
7.069
7.159
7.185
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7.229
7.250
7.262
7.288
3.00
1.99
8.73
ppm
0.5
1.0
1.5
2.0
2.5
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5.0
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6.0
6.5
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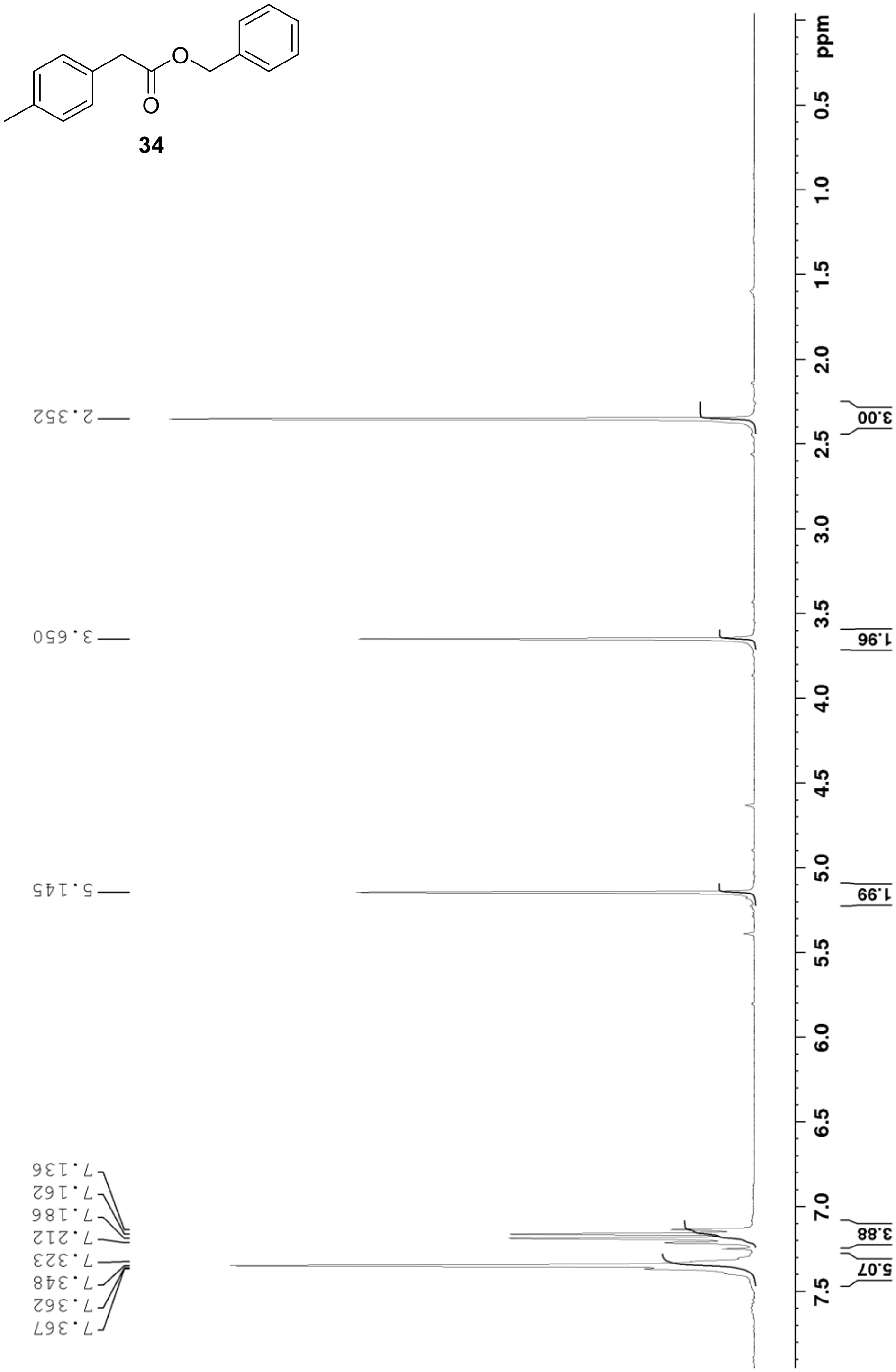
7.5
O
O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3.00
1.96
1.99
3.88
5.07
ppm
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1.0
1.5
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4.5
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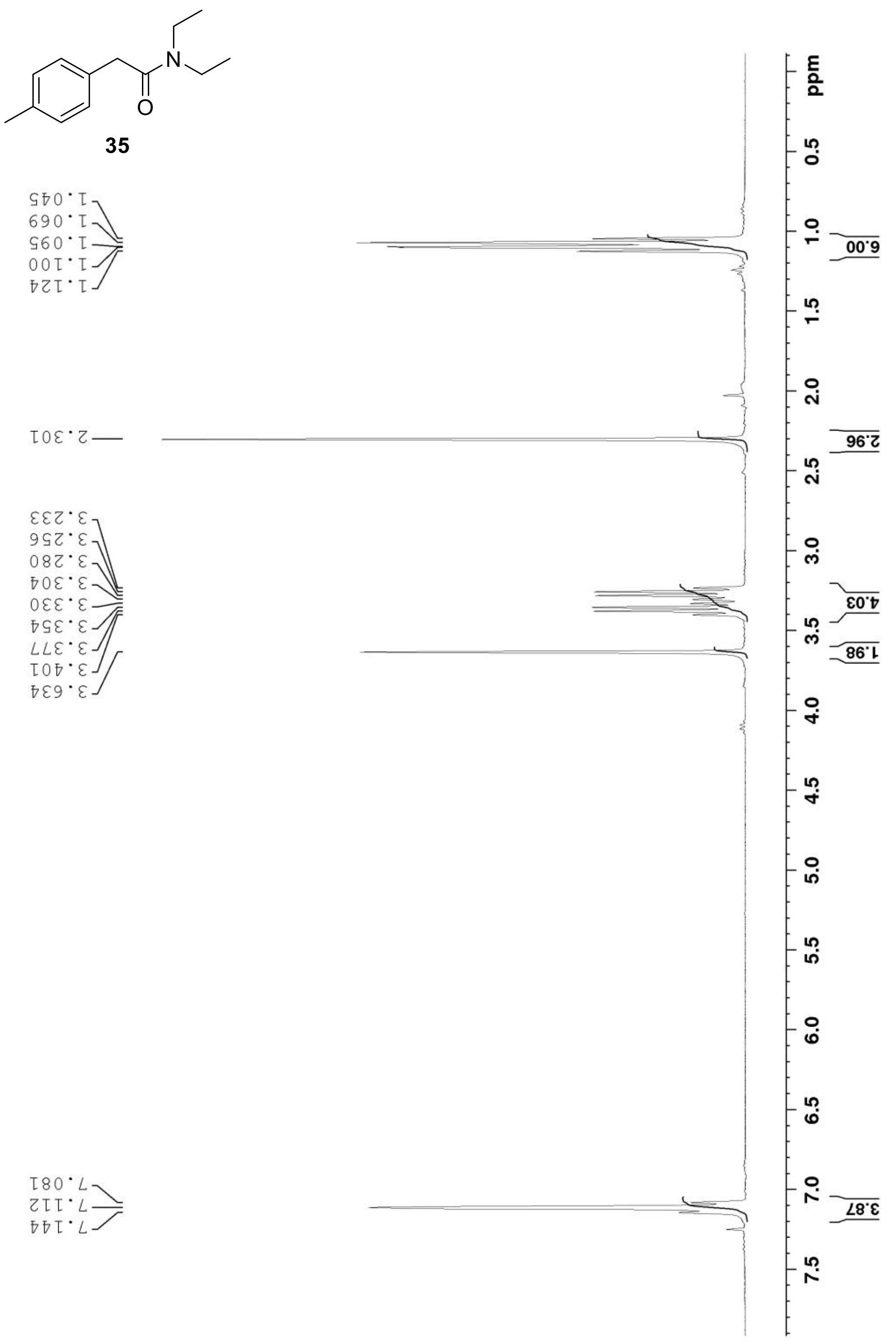
6.0
6.5
7.0
7.5

34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3.354
3.377
3.401
3.634
7.081
7.112
7.144
6.00
2.96
4.03
1.98
3.87
ppm
0.5
1.0
1.5
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6.5
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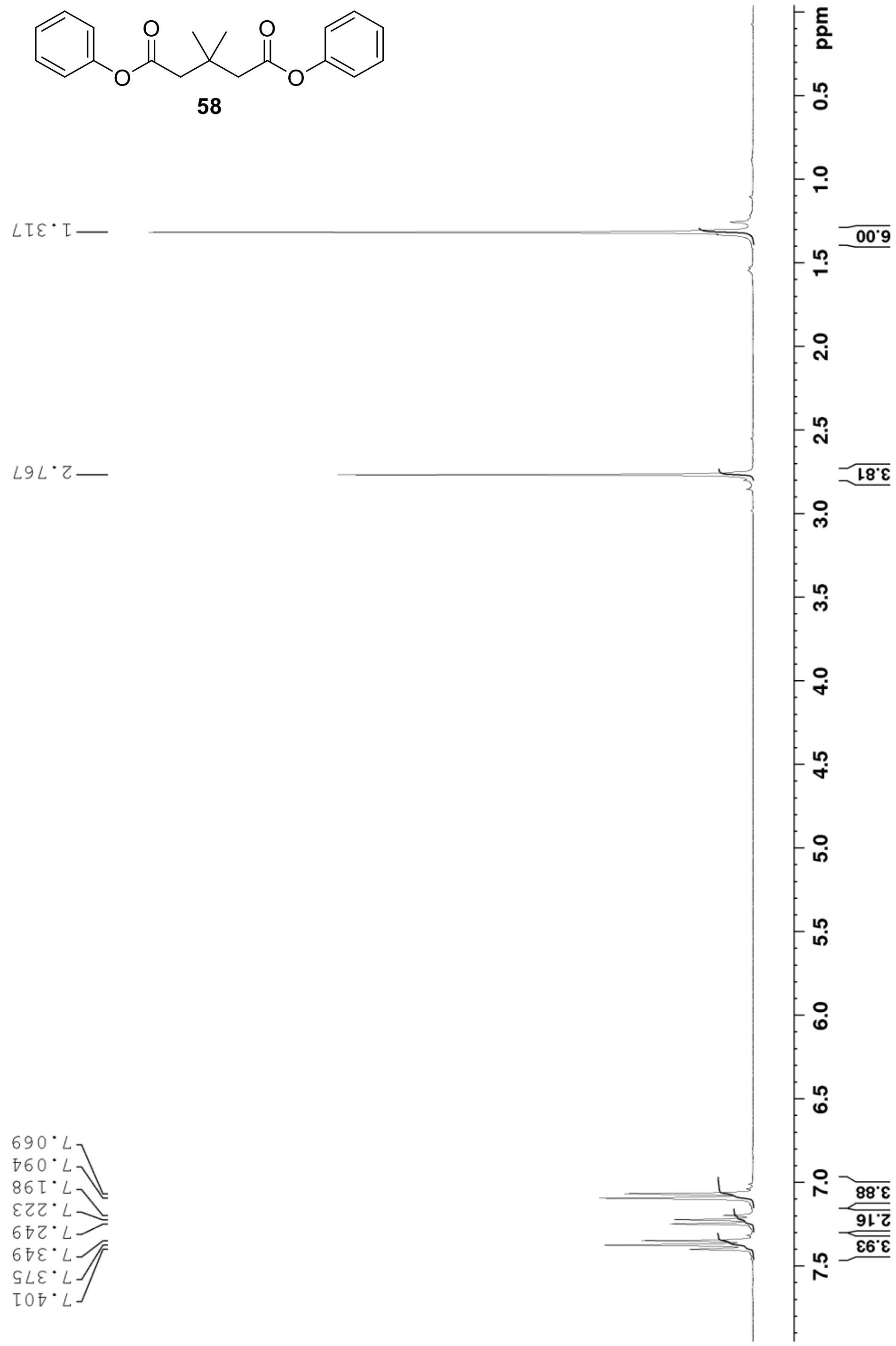
7.5



58

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7.223
7.249
7.349
7.375
7.401
ppm
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1.0
1.5
2.0
2.5
3.0
3.5
4.0
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5.5
6.0
6.5
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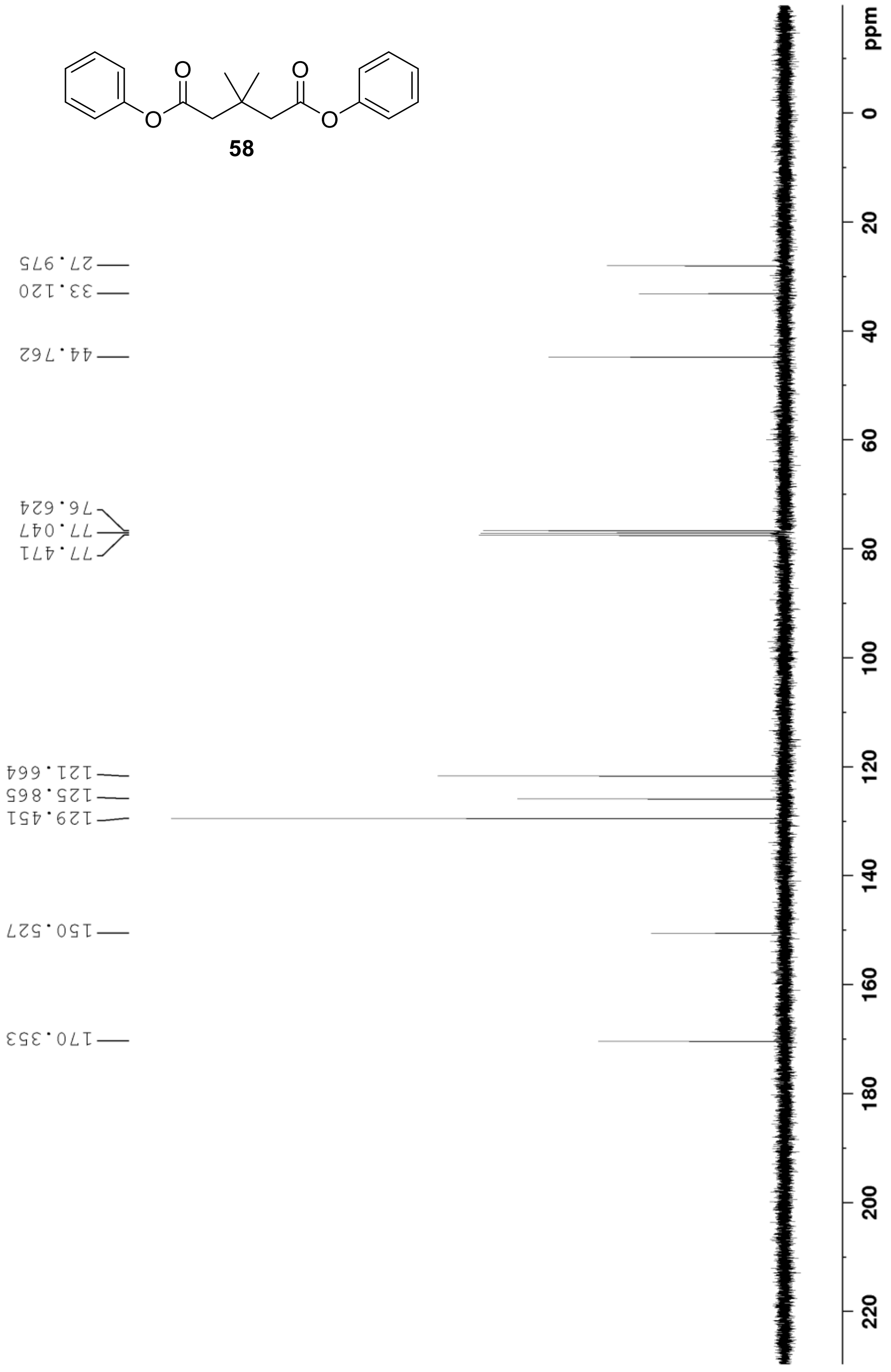
3.88
2.16
3.93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33.120
44.762
76.624
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77.471
121.664
125.865
129.451
150.527
170.353
ppm
0
20
40
60
80
100
120
140
160
180
200
220