Gem-Difluorination of α-Diazo Amides Using (Difluoroiodo)toluene

by

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Author's Declarations

I hereby declare that I am the sole author of this thesis.

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Abstract

Fluorination chemistry is a branch of study that appeals to the pharmaceutical and agricultural industries. Drawbacks of popular methods of forming carbon-fluorine bonds include high cost or hazardous conditions that are often associated with some of these reagents. A less explored route to organofluorine substrates can be achieved through hypervalent iodine compounds, such as (difluoroiodo)toluene ($TolIF_2$). There is large interest in these compounds because of their mild reactivity, relatively inexpensive production, and environmentally benign by-products.

Previously disclosed by the Murphy group is the *α*-carbonyl difluorination of phenyldiazoacetate compounds using (difluoroiodo)toluene to furnish *gem*-difluorinated products. Detailed in this report is an extension of the work established by Murphy *et al*. in the synthesis of 3,3-difluoro-2-oxindole compounds starting from diazo oxindoles. Studies were also performed on tosylhydrazone, hydrazone and dithiane derivatives of oxindole. In addition, the fluorination protocol was used to synthesize *N*,*N*-dimethyl-*p*-nitrophenyldifluoroacetamide from its corresponding α-diazo amide. Finally, strategies towards the synthesis of other phenyldiazoacetamides are discussed in this thesis.

Acknowledgments

I would first like sincerely thank my supervisor, Dr. Graham Murphy, for his continued guidance, support, and advice over the years I have known him. His passion for chemistry can only be matched by his patience to answer every question I have, no matter how grueling or simple they might be. I will fondly remember the interactions I had with him and hope I can one day inspire people like the way he has inspired me.

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List of Abbreviations

Ar	Aromatic Ring
Bn	Benzyl
Bz	Benzoyl
EAS	Electrophilic Aromatic Substitution
et al.	Et alia (and others)
equiv	Molar Equivalent
gem	Geminal
HOMO	Highest Occupied Molecular Orbital
HVI	Hypervalent Iodine
In situ	In Reaction Mixture
iPr	Isopropyl
IR	Infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
L	Ligand
LG	Leaving Group
Me	Methyl
m.p.	Melting Point
MS	Mass Spectrometry
m/z	Mass-to-charge Ratio
ND	Not Determined
NMR	Nuclear Magnetic Resonance
NR	No Reaction
PFA	Perfluoroalkoxy alkanes
PTFE	Polytetrafluoroethylene
R_f	Retention Factor
RT	Room Temperature
sn	Nucleophilic Substitution
TLC	Thin Layer Chromatography
Ts	Tosyl
wt%	Weight Percent

Chapter 1: Introduction

1.1 Fluorination

Fluorine is the lightest halogen and the most electronegative element on the periodic table. Halogens are often incorporated into organic molecules to be used as leaving groups in nucleophilic substitution (S_N) reactions. Amongst the halogens, fluoride is the most inert leaving group (order of leaving group ability I > Br > Cl >> F) given the very strong carbon-fluorine bond as well as the high charge density of the liberated fluoride ion.[1]

Fluorine is also the 13th most abundant element in the Earth's crust owing to its presence in cryolite, fluorite, fluorapatite, and other minerals.[2] Despite fluorine's abundance, organofluorine compounds are scarcely found in nature. Only 13 naturally occurring organofluorine compounds have been identified, 8 of which are analogues of fluoroacetic acid.[3] The formation of carbon-fluorine bonds, however, is highly sought after by synthetic chemists due to the changes in electronic and physical properties fluorine can impart on the given parent compound. Even the introduction of a single fluorine atom or fluorinated group in a key position of a biologically active molecule can have profound pharmacological effects. This is prevalent in medical and agrochemical fields where scientists have replaced carbon-hydrogen bonds with carbon-fluorine bonds to synthesize drug molecules with improved lipophilicity, electrostatic interactions, as well as bioavailability for increased selectivity of target organs.[4] Several fluorine-containing drugs are among the most prescribed and most profitable in the pharmaceutical market.[5]

In the 1970s, about 2% of all drugs on the market contain a fluorine atom in its molecular structure. Currently, this number has grown to approximately 25%.[6] The surge in fluorine's popularity has led to the myriad of methods that have been developed to introduce a fluorine atom

to hydrocarbon scaffolds. These methods can be categorized as using: (i) nucleophilic, (ii) electrophilic, or (iii) ambiphilic sources of fluorine.

Nucleophilic fluorination methods deliver a fluoride ion to an electron-poor carbon atom. One of the simplest sources of nucleophilic fluoride is hydrofluoric acid (HF) (Figure 1.1), a chemical that has found widespread use in industries and research labs. The downside of using hydrofluoric acid is its toxicity and corrosive properties. Aqueous and anhydrous HF can readily penetrate the skin causing deep lesions and necrosis even in small quantities.[7] To circumvent these health issues, scientists have opted to use HF complexed with an amine, such as Olah's reagent (70% HF in pyridine).[8] Although the presence of the amine reduces the nucleophilicity of the fluoride and some reactions may require substrate activation, it also tames the reactive nature of HF and improves ease of handling.

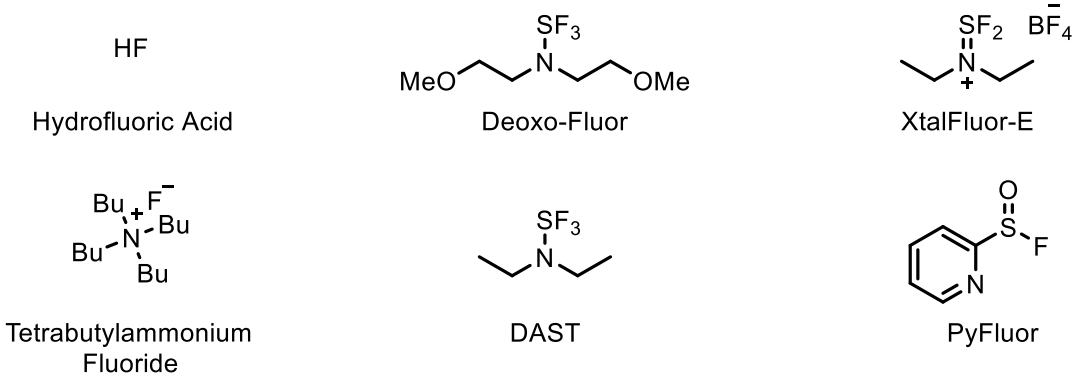
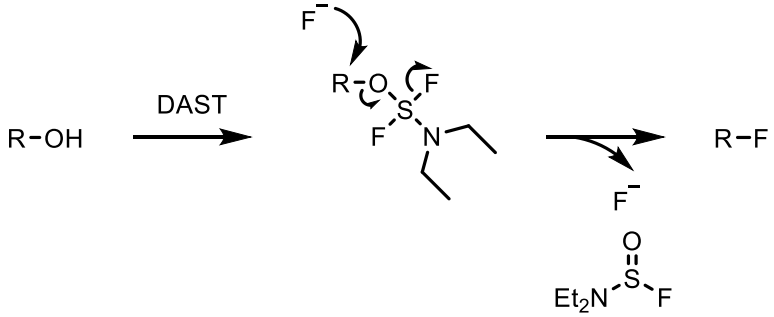


Figure 1.1: Examples of nucleophilic fluorinating reagents

Due to its low polarizability and ability to form strong hydrogen bonds, fluoride ions are relatively weak nucleophiles in protic solvents. Even in aprotic solvents, where there is no potential for hydrogen bonding to occur, fluoride can still be a weak nucleophile because it can form tight ion pairs. To overcome this issue, reagents that utilize a large, sterically demanding cation to

reduce ion pairing have been developed. A well-recognized example illustrating this concept is tetrabutylammonium fluoride (TBAF) (Figure 1.1) which is soluble in aprotic solvents such as THF.[9]

Deoxyfluorination uses a nucleophilic fluoride source to exchange a hydroxyl group for a fluorine atom. "SF"-reagents, such as DAST (Figure 1.1), are typically employed for these transformations and the reaction proceeds via an alkoxyaminosulfur difluoride intermediate that is attacked by a liberated fluoride ion (Scheme 1.1). However, its cost, thermal instability, and potential to form elimination side products makes DAST undesirable for process chemistry. To combat some of these issues, other variants have been developed such as Deoxo-Fluor,[10] and Xtalfluor-E,[11] (Figure 1.1), though these options are generally more expensive. More recently, Doyle *et al*. reported an inexpensive and thermally stable deoxyfluorinating agent, PyFluor (Figure 1.1).[12] In addition to exhibiting high functional group compatibility, PyFluor produces fewer elimination products compared to other deoxyfluorinating reagents.



Scheme 1.1: General deoxfluorination using DAST

On the other side of the polarity spectrum, electrophilic fluorination transfers an "F^+" to an electron rich centre. However, "F^+" cannot exist independently due to the extreme electronegativity of fluorine. Thus, scientists have designed "F^+" equivalents permitting

fluorination of nucleophiles. Typically, these reagents have fluorine bonded to an electron deficient atom. One of the first electrophilic fluorinating reagents with industrial relevance was perchloryl fluoride ($FClO_3$) (Figure 1.2), a gas that is thermally stable up to 500 °C.[13] Although $FClO_3$ enables selective synthesis of complex organic compounds, it poses a constant threat of explosion, and is difficult to work with since it is a gas. Alternative electrophilic fluorinating reagents include hypofluorites, or "OF"-reagents, where fluorine is activated by an oxygen species. The most famous examples in this class of compounds are trifluoroacetyl hypofluorite (CF_3COOF),[14] and trifluoromethyl hypofluorite (CF_3OF) (Figure 1.2).[15] Both of these are highly toxic and tend to detonate upon contact with organic solvents, and therefore are not safe for industrial applications.

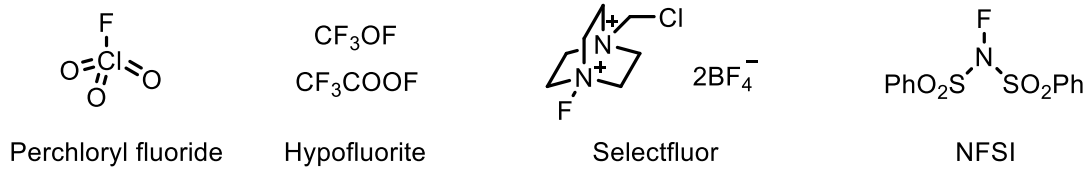


Figure 1.2: Examples of electrophilic fluorinating reagents

In the 1980s the search for safer and controllable electrophilic fluorination strategies led to the discovery of "NF"-reagents, which draw their fluorination reactivity from fluorine bonded to an electron deficient nitrogen atom. Notable examples in this class of reagents include Selectfluor® and *N*-fluorobenzenesulfonimide (NFSI) (Figure 1.2). The lower electronegativity of nitrogen compared to oxygen decreases the electrophilicity of these reagents, but renders them more stable and convenient to handle. Thus, the greatest advantage of "NF"-reagents compared to previous generations of electrophilic fluorinating reagents is that most are solid, non-volatile compounds that are not explosive. A major drawback is their relatively high molecular weight and low content

of "active" fluorine leading to its reduced atom economy. For Selectfluor®, the ratio of active fluorine to the molecular weight is only 5.4%.[16]

Although typically described as an electrophilic fluorination source, elemental fluorine (F_2) (Figure 1.3) can be seen as an example of an ambiphilic fluorinating reagent since it can provide both an "F^+" and "F^-". Under certain conditions, F_2 exhibits reactivity often associated with electrophilic fluorination in presence of a nucleophile. This produces a fluoride ion that can add to an electron deficient site. For example, the reaction between *cis*-stilbene and one equivalent of F_2 produces the 1,2-difluorinated product (Scheme 1.2).[17] Based on the observed selectivity, the mechanism is proposed to proceed via a tight ion pair.

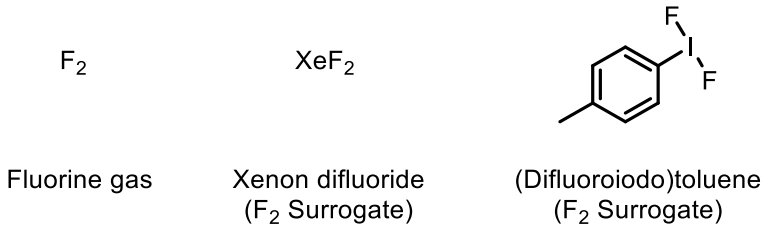
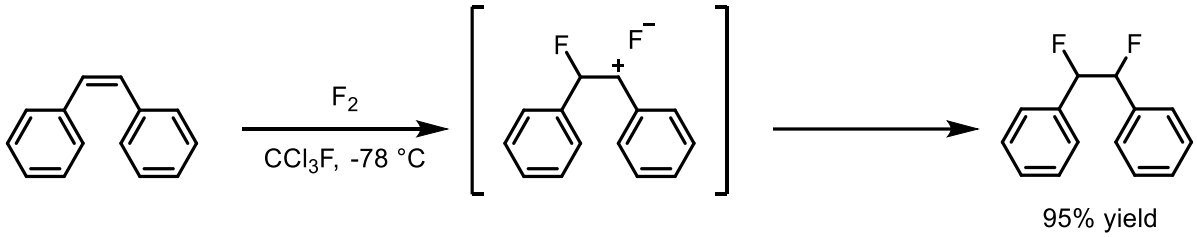


Figure 1.3: Examples of ambiphilic sources of fluorine



Scheme 1.2: Fluorination of *cis*-stilbene using fluorine gas

Unfortunately, F_2 is a violently reactive species, in addition to being toxic and corrosive. Handling fluorine gas can also be challenging, because it requires specialized equipment. As a

result, chemists have sought surrogate reagents to effect the transformations F_2 can perform without having to use the toxic gas. These reagents can be a source of both nucleophilic and electrophilic fluorine, thereby potentially delivering two fluorine atoms with a single reagent molecule. An example is XeF_2 (Figure 1.3), which in the presence of a catalytic amount of HF, produced the vicinal difluoride compound from *cis*-stilbene.[18] The use of XeF_2, however, is limited due to its cost. A second attractive replacement for F_2 is (difluoroiodo)toluene ($TolIF_2$) (Figure 1.3), a hypervalent iodine-based reagent.[19]

1.2 Hypervalent Iodine

The term hypervalency was first coined by Musher in 1969 to denote molecules in Groups 15-18 that are in any valence other than their standard.[20] Today, IUPAC defines hypervalency as the ability of an atom in Groups 15-18 to expand its valence shell beyond the limits of the Lewis octet rule.[21]

There are two possible explanations for this deviation to the octet rule: (i) through the involvement of d orbitals, or (ii) the formation of highly ionic orbitals without involvement of d orbitals. The former, proposed by Pauling, uses an expanded octet model through promotion of electrons into vacant d orbitals leading to sp^3d or sp^3d^2 hybridization.[22] Based on computation studies, it is widely accepted that d orbitals are not required to form hypervalent compounds as the involvement of d orbitals do not offer significant energetic advantages.[23]

Hypervalency is now understood through the 3-center-4-electron bond model (also known as the Pimentel-Rundle model) first proposed by G. C. Pimentel and R. E. Rundle in 1951 based on molecular orbital theory (Figure 1.4). The model depicts the generic hypervalent bond L–X–L as

4 electrons shared between 3 atom centres. The bond is conceptualized as the interaction between the filled p orbital of the central atom and the half-filled orbitals of the two ligands to form three new molecular orbitals: bonding, non-bonding, and anti-bonding. The highest occupied molecular orbital (HOMO) is the nonbonding orbital, which contains a node at the central atom. In the case of HVI compounds where X = iodine, this leads to iodine's electrophilic behaviour and the overall polarized nature of the hypervalent bond.

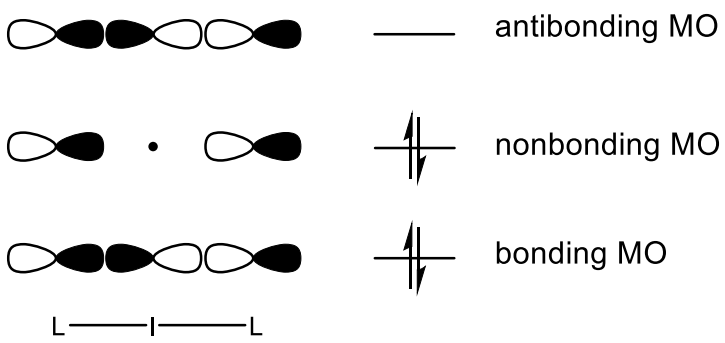


Figure 1.4: Hypervalent bonding depicted by the 3-center-4-electron model

A variation of the 3c-4e model is the valence bond model proposed by Coulson (Figure 1.5).[24] In this model, the electronic structure of a hypervalent molecule, such as XeF_2, is described as a combination of two resonance structures. Each fluorine ligand on the molecule can be drawn as forming an ionic or a covalent bond to the xenon centre. Thus, it can be seen that the electrons between the xenon and fluorine atoms are not equally shared. The resonance structures place a formal +1 charge on the xenon atom and illustrate the electrophilic behaviour of the central atom, while emphasizing the strong electron affinity of the two heteroatom ligands.

Figure 1.5: Hypervalent bonding depicted by valence bond theory

Despite their unique characteristics and the term's absence in introductory textbooks, hypervalent molecules are not uncommon in organic chemistry. They include common molecules such as dimethyl sulfoxide, phosphine oxide, sulfuric acid, as well as perchlorates (Figure 1.6).

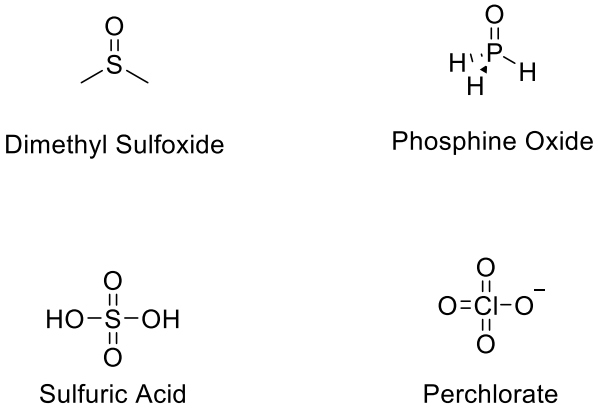


Figure 1.6: Examples of common hypervalent molecules in organic chemistry

Since their discovery by Willgerodt in 1886,[25] hypervalent iodine compounds have garnered wide-spread attention due to their mild reaction conditions, broad reactivity patterns, ease of handling, and the relatively benign by-products associated with their reactions.[26] These polycoordinated species incorporate iodine with an oxidation state of (III), (V), or (VII), and have a rich history in organic synthesis in oxidation reactions. For example, periodates (Figure 1.7) are iodine(VII) compounds that are commonly used in oxidative cleavage of carbon-carbon bonds of 1,2-diol systems to furnish the corresponding carbonyl products. [27] Organoiodine(V) compounds have found applications as efficient oxidants of many functional groups. Well known members in the iodine(V) family of compounds include Dess-Martin periodinane (DMP) and 2-iodoxybenzoic

acid (IBX) (Figure 1.7).[28-29] The iodine(III) class of compounds includes (diacetoxyiodo)benzene and iodosylbenzene (Figure 1.7).

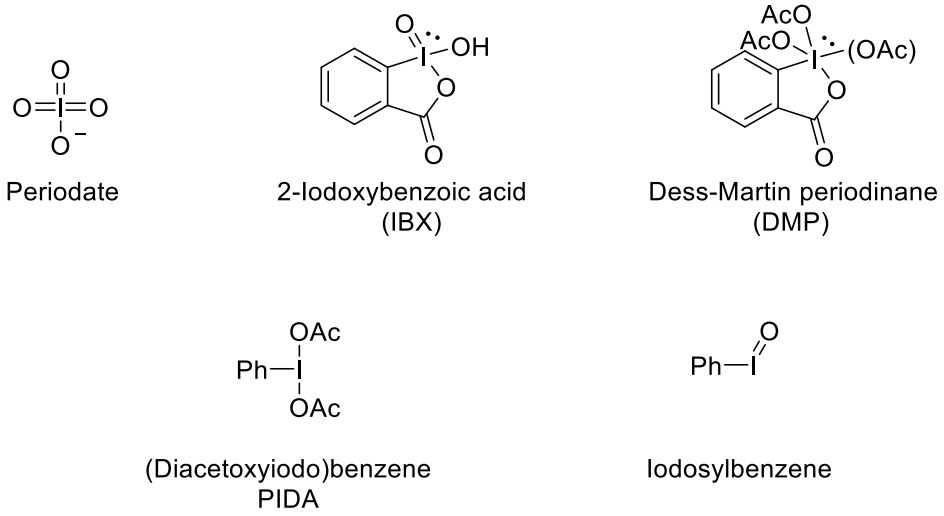


Figure 1.7: Examples of hypervalent iodine compounds

Hypervalent iodine compounds are referred to as iodanes, and use a λ^n notation for naming, where *n* describes the oxidation state of the hypervalent centre. Aryl-λ^3-iodanes ($ArIL_2$) for example, possesses an iodine with an oxidation state (III) bonded to an aromatic ring and two other heteroatom ligands. Aryl-λ^3-iodanes have a T-shaped geometry with the arene and lone pairs occupying the equatorial positions. The two heteroatoms sit in the apical positions to form the collinear hypervalent L–I–L bond (Figure 1.8).

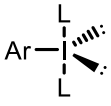
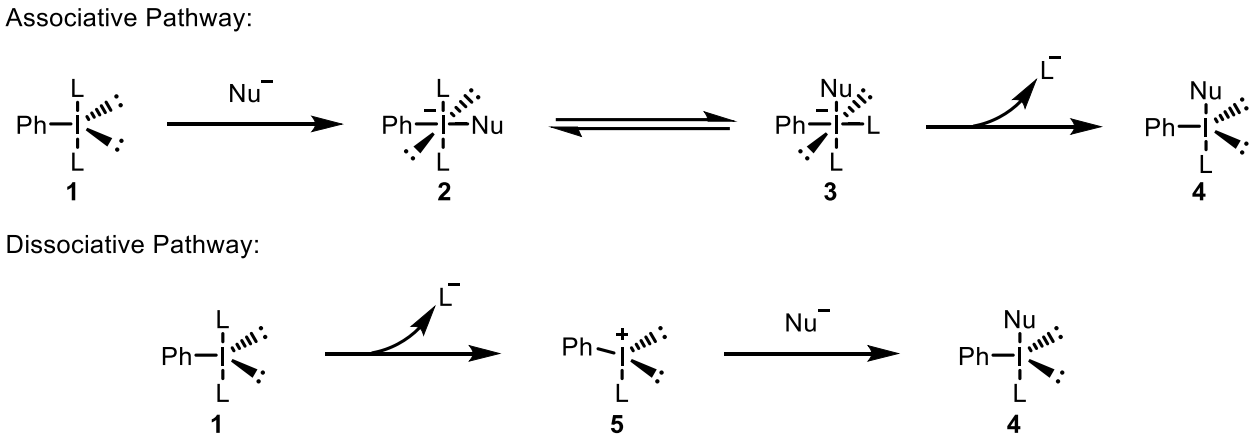


Figure 1.8: T-Shaped geometry of aryl-λ^3-iodanes

There are two fundamental transformations associated with aryl-λ^3-iodanes: (i) ligand exchange, and (ii) reductive elimination. In ligand exchange, the heteroatom ligands on the iodane

centre can be displaced by an external nucleophile. Although the exact mechanism is not certain, two mechanistic pathways are considered: associative and dissociative.



Scheme 1.3: Ligand exchange by associative and dissociative pathways

The associative pathway begins with a nucleophile attacking iodane **1** due to its increased electrophilicity (Scheme 1.3). This produces the square-planar intermediate **2** in which the two ligands are *trans*. Pseudorotation could produce the *cis* intermediate **3**, and elimination of a heteroatom ligand would produce a new aryl-λ^3-iodanes **4**. A second ligand exchange of iodane **4** may occur through a similar sequence to displace the other heteroatom ligand to afford $ArINu_2$. Experimental evidence suggests ligand exchange proceeds through an associative mechanism. Kajigaeshi *et al.* have synthesized the tetracoordinated species benzyltrimethylammonium tetrachloroiodate (BTMA ICl_4) from the reaction between benzyltriammonium chloride with iodine trichloride in dichloromethane.[30] The dissociative pathway begins with the elimination of a heteroatom ligand to produce dicoordinated iodonium ion **5**, which is stabilized due to coordination with solvent molecules. The intermediate can then be intercepted by a nucleophile to reform the aryl-λ^3-iodane **4**. An additional ligand exchange can occur again to afford $ArINu_2$. The

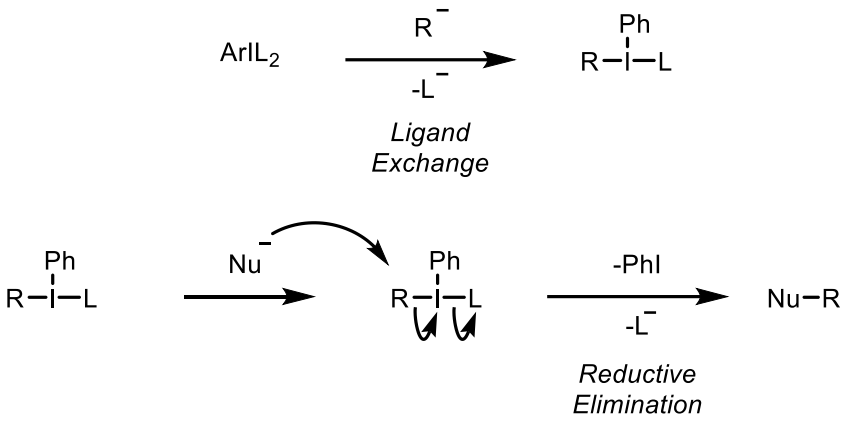
dissociative pathway is believed to be less likely to occur due to the low stability of the iodonium ion(s).

The most common reaction involving λ^3-iodanes is their ability to undergo reduction to produce the univalent iodide, i.e. going from I(III) to I(I). This process is highly energetically favorable because it transforms the hypervalent iodine atom to its standard valence. As proposed by Ochiai, aryl-λ^3-iodanes have been described as hypernucleofuges due to their excellent leaving group capabilities.[31] Hypernucleofugality is used to define hypervalent species with a leaving group ability higher than that of a superleaving group, such as the triflate ion (TfO^-). The reduction of the λ^3-iodane is termed reductive elimination due to the reduction to univalent iodide, and simultaneous elimination of a heteroligand on the iodane centre. Reductive elimination is a term usually reserved to transition metal chemistry to describe a process in which the oxidation state of the metal decreases while a new covalent bond is formed between two ligands. Alternatively, the process is called ligand coupling (or ligand exchange) in reactions without the involvement of transition metals, such as in the case of hypervalent iodine compounds. It is important to note that there are other key reactions associated with hypervalent iodine compounds, such as single-electron transfer, but are beyond the scope of this thesis.[26]

1.3 α-Carbonyl Functionalization Using Aryl-λ^3-iodanes

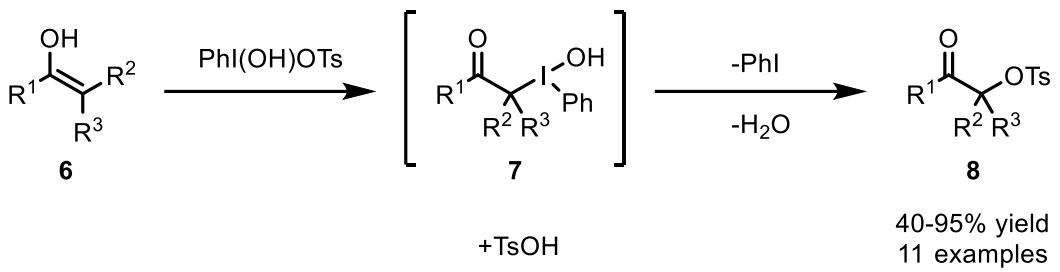
Umpolung reactivity is described as a reversal in polarity of an atom, e.g. having a nucleophile (Nu^-) act like an electrophile (Nu^+). HVI reagents can perform umpolung chemistry through a combination of ligand exchange and reductive elimination to form new carbon-nucleophile (Nu-R) bonds (Scheme 1.4). Ligand exchange first occurs between an aryl-λ^3-iodane ($ArIL_2$) and a

carbon nucleophile (R^-) to produce a new iodane (ArILR). A second nucleophile (Nu^-) can then engage the aryl-λ^3-iodane via nucleophilic substitution to furnish a Nu-R bond with simultaneous production of an aryl iodide.



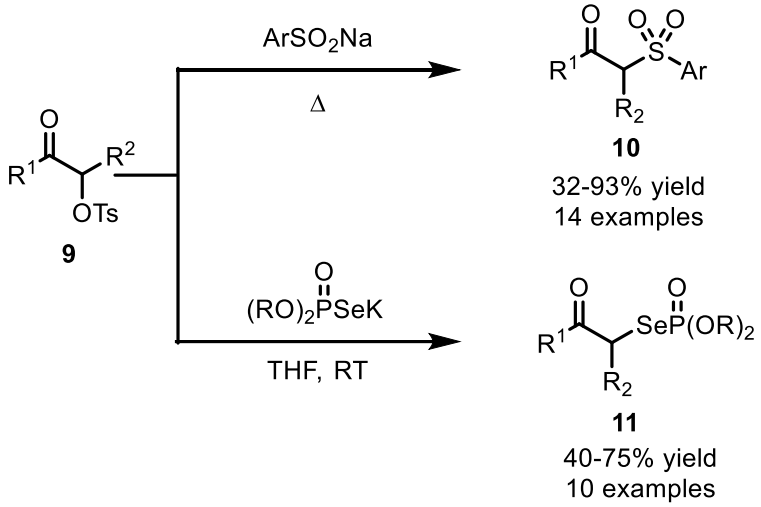
Scheme 1.4: General reaction mechanism for ligand exchange and reductive elimination

The use of HVI reagents for umpolung chemistry is effective for α-carbonyl functionalization. Treating an enolate with an aryl-λ^3-iodane has been used to transfer one of the iodane's ligands onto the α-carbonyl carbon atom. One famous example is [hydroxyl(tosyloxo)iodo]benzene (HTIB, also known as Koser's reagent) in the conversion of ketones to their corresponding α-tosyloxyketones (**8**) (Scheme 1.5).[32] It is proposed that the reaction is initiated by the formation of an α-phenyliodonio ketone (**7**) through a ligand exchange between HTIB and enol **6**. The newly formed aryl-λ^3-iodane, now bearing two carbon ligands, is susceptible towards nucleophilic attack from the displaced tosylate ion, leading to the elimination of iodobenzene. An S_N2 pathway is believed to occur due to the high nucleofugality of the phenyl-λ^3-iodanyl group. This chemistry has also been extended by modifying the ligands on the aryl-λ^3-iodane to allow for α-mesyloxylation[33] or α-phosphoryloxylation,[34] amongst others.[35]



Scheme 1.5: α-Tosylation of ketones using HTIB

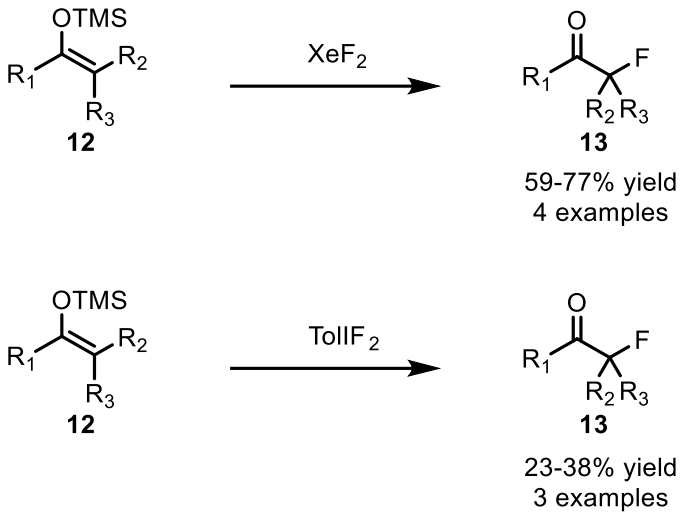
Installment of other heteroatomic groups onto the α-carbon can be achieved through a two-step sequence by introducing an external nucleophile to the α-tosyloxy ketone (**9**) produced using HTIB. For example, introducing sulfur or selenium nucleophiles led to the formation of carbon-sulfur and carbon-selenium bonds in compounds **10** and **11** (Scheme 1.6).[36-37]



Scheme 1.6: Synthesis of β-keto sulfones and β-keto selenophosphates

α-Carbonyl functionalization using aryl-λ^3-iodanes is not exclusive to carbon-oxygen bond formation. For example, α-fluorination can be achieved when the ligands on the iodane are fluorine atoms. The first reported case was by Tsushima *et al.* in 1982 in the synthesis of α-fluoro ketones from steroid silyl enol ethers **12** with XeF_2 and $TolIF_2$ (Scheme 1.7).[38] When the former was used as the fluorinating agent, the transformation was conducted in the absence of any catalyst and

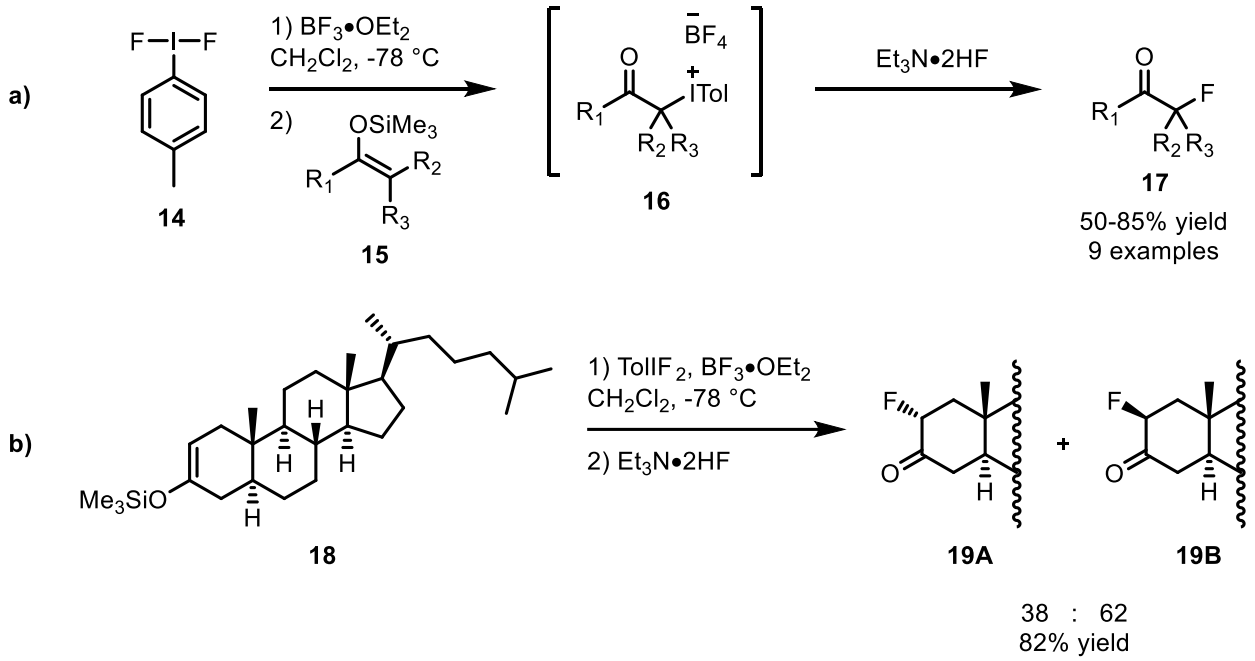
furnished the desired monofluorinated product (**13**) in good yields. In contrast, the use of (difluoro)iodotoluene produced poor yields of **13**.



Scheme 1.7: α-Fluorination of silyl enol ethers using XeF_2 and $TolIF_2$

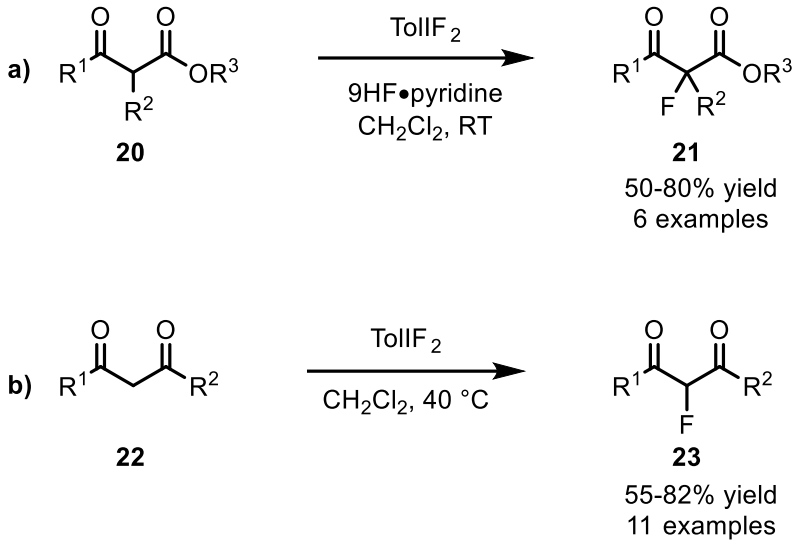
Similarly, in 2005 Hara *et al*. reported the conversion of silyl enol ethers (**15**) to their corresponding monofluorinated species (**17**) using $TolIF_2$ (**14**) (Scheme 1.8a).[39] Unlike the previous example by Tsushima and coworkers, stoichiometric amounts of other additives were added to the reaction mixture in order to improve the yields of **16**. The authors believed that the reaction was proceeding through an iodonium salt intermediate (**16**) which could be stabilized with the addition of BF_3•OEt_2. Furthermore, the addition of nucleophilic fluoride sources were introduced to accelerate the fluorination of the iodonium intermediate, with Et_3N•2HF being the most effective. The authors further applied this methodology in the synthesis of 2-fluorocholestan-3-one (**19A** and **19B**) by treating the silyl enol ether of cholestan-3-one **18** with $TolIF_2$ (Scheme 1.8b). The stereoselectivity was rationalized by the preferential formation of the iodonium

intermediate on the most sterically available face. Inversion of stereochemistry via nucleophilic addition of the fluoride ion produced the desired diastereomer **19B** in a 2:1 ratio.



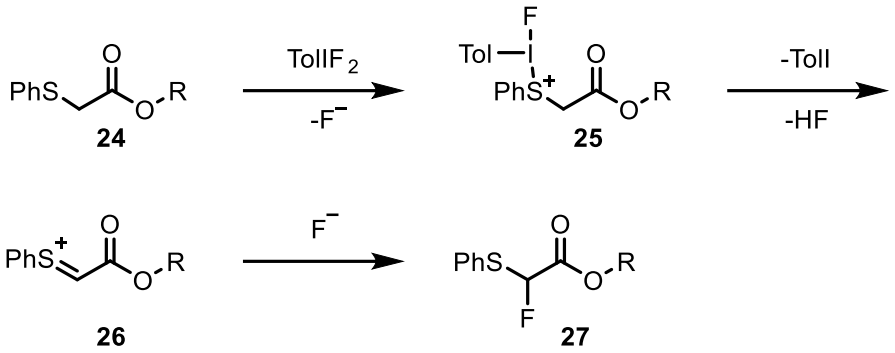
Scheme 1.8: Fluorination of silyl enol ether and the synthesis of 2-fluorocholestan-3-one

α-Carbonyl fluorination was also reported by Yoneda *et al*. on β-ketoesters (**20**) to produce monofluorinated products (**21)** using (difluoro)iodotoluene.[40] Moderate success was achieved by conducting the reaction at room temperature with 1 equivalent of 9HF•pyridine (Scheme 1.9a). Unlike the work reported by Hara and coworkers, the transformation did not require the initial formation of a silyl enol ether. A second iteration of the transformation by the same group expanded the substrate scope to include the monofluorination of ketoamides, diketones, and other β-ketoesters without resorting to external fluoride sources (Scheme 1.9b).[41]



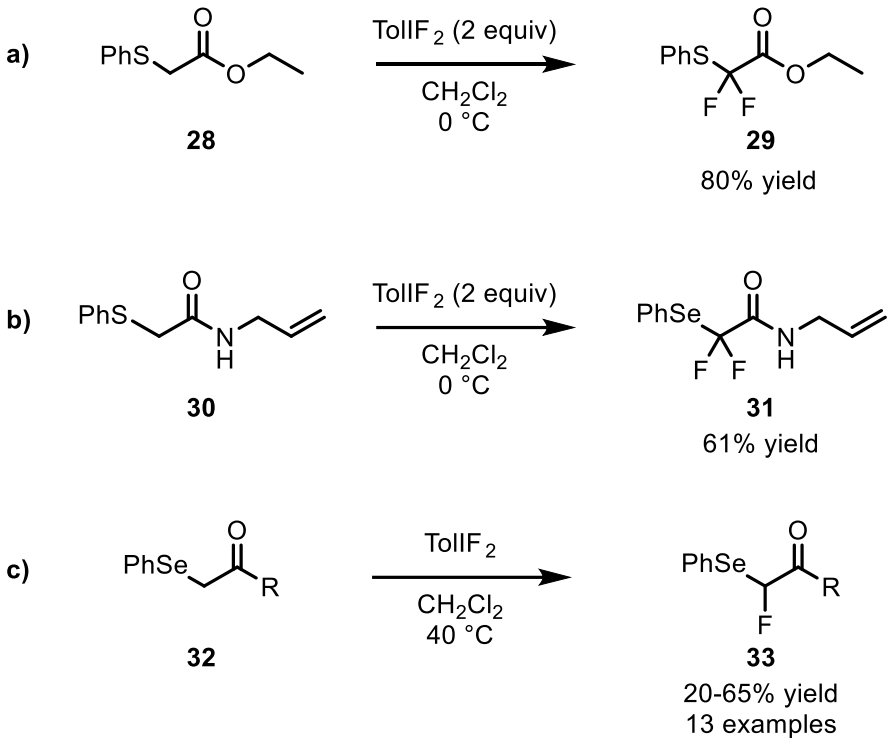
Scheme 1.9: Fluorination of 1,3-dicarbonyl compounds with and without 9HF-pyridine

The reaction between α-phenylsulfanyl esters (**24**) and (difluoro)iodotoluene was reported by Greaney and Motherwell in 2000 (Scheme 1.10).[42] The transformation proceeded through a fluoro-Pummerer sequence to furnish α-fluoro sulfides (**27**). The authors proposed that the reaction is initiated by nucleophilic attack of the sulfur atom onto the iodane to form an iodosulfononium salt (**25**). The liberated fluoride ion would function as a base to deprotonate the α-proton to produce ylide **26**, with simultaneous formation of iodotoluene and a second fluoride ion. Subsequent trapping of **26** with this fluoride ion produced the monofluorinated species (**27**).



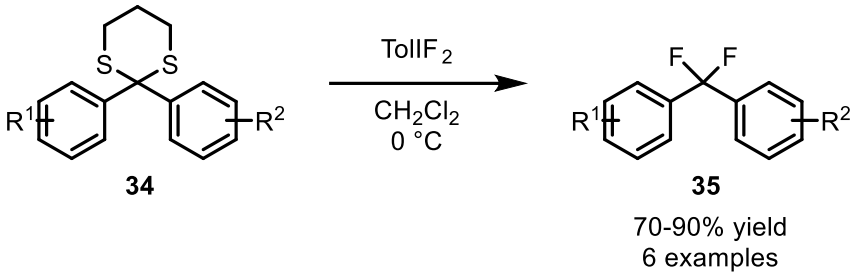
Scheme 1.10: Monofluorination of α-phenylsulfanyl esters using $TolIF_2$

More significantly, it was found that treating the α-phenylsulfanyl ester with two equivalents of $TolIF_2$ furnished the α,α-difluorinated product (**98**) (Scheme 1.11a). Likewise, subjecting α-phenylsulfanylacetamides (**30**) to similar conditions also produced difluorinated products (Scheme 1.11b).[43] Since only one of the two fluorine ligands of the iodane is transferred from each fluoro-Pummerer reaction, two equivalents of $TolIF_2$ are necessary for difluorination of α-phenylsulfanyl carbonyl compounds. Recently, fluorination of α-selenyl carbonyl compounds (**32**) were performed with $TolIF_2$ (Scheme 1.11c).[44] The reaction is proposed to follow a seleno-Pummerer pathway. In contrast to the fluoro-Pummerer reaction, difluorinated products were not observed, and it is believed that the presence of the α-fluorine atom decreased the nucleophilicity of the selenium atom towards a second attack onto $TolIF_2$.



Scheme 1.11: Fluorination of α-carbonyl compounds via fluoro-Pummerer and Seleno-Pummerer reactions

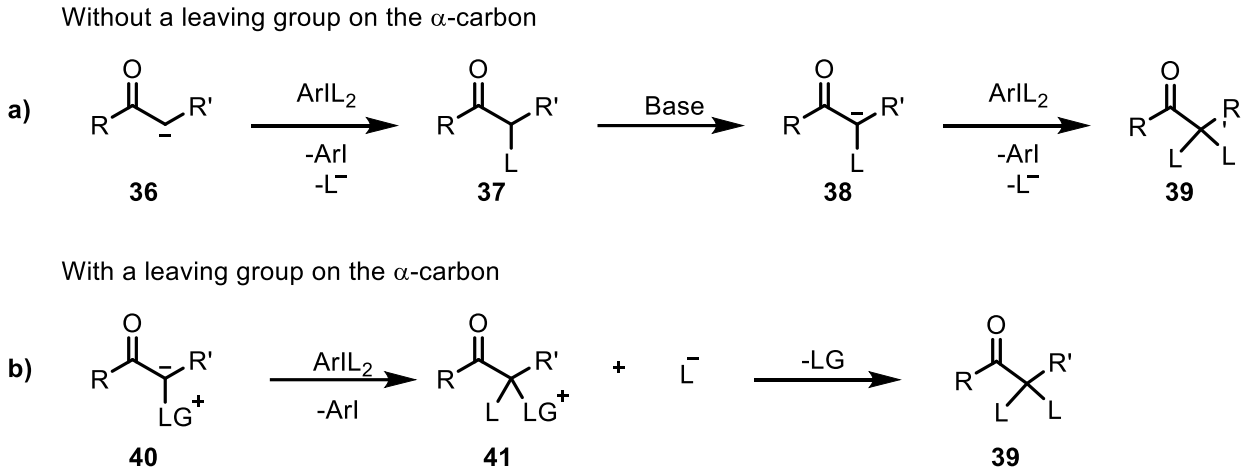
gem-Difluorination using $TolIF_2$ is not exclusive to the fluoro-Pummerer reaction. Thioketals (**34**) were cleaved by $TolIF_2$ to give good yields of the *gem*-difluorinated product (**35**) (Scheme 1.12).[45] The reaction was conducted at 0 °C to furnish diaryldifluoromethanes from their corresponding dithioketal derivatives. Similar to the fluoro-Pummerer method, two equivalents of $TolIF_2$ are necessary to produce the *gem*-difluorinated product.



Scheme 1.12: Geminal difluorination of thioketals using $TolIF_2$

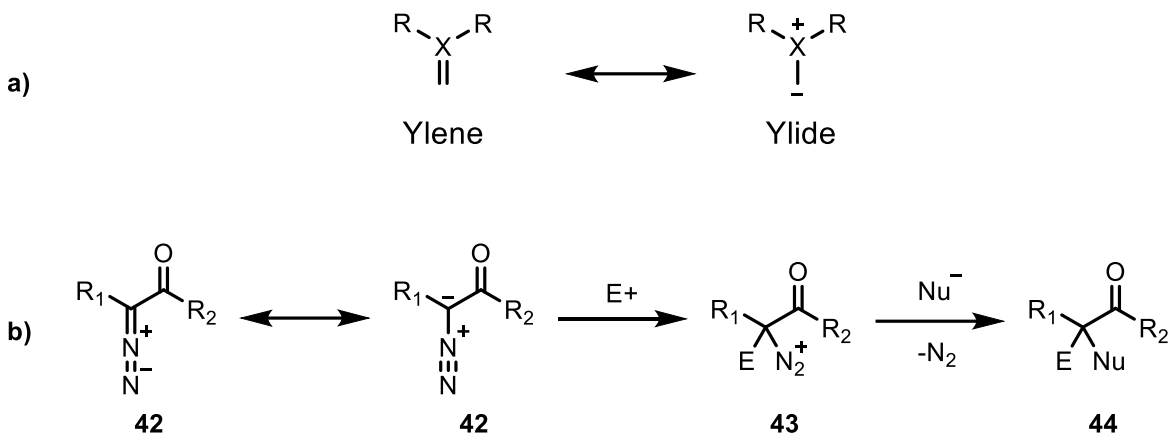
1.4 α-Diazocarbonyl Compounds and Their Synthesis

In all the previously discussed cases, α-functionalization proceeded via a ligand transfer from the iodane to a nucleophilic species through a reductive elimination step. This process simultaneously produced an equivalent of aryl iodide and an anionic ligand (Scheme 1.13a). Following this logic, α-carbonyl difunctionalization would require a second equivalent of the aryl-λ^3-iodane. However, *gem*-difunctionalization can occur using a single equivalent of the aryl-λ^3-iodane if there is a strong leaving group present on the α-carbon of the carbonyl species (**40**) (Scheme 1.13b). Once formed, the anionic ligand byproduct could return and displace the leaving group to allow for delivery of both ligands from the iodane. If the precursor to the leaving group was a positively charged species, molecule **40** bears resemblance to an ylide.



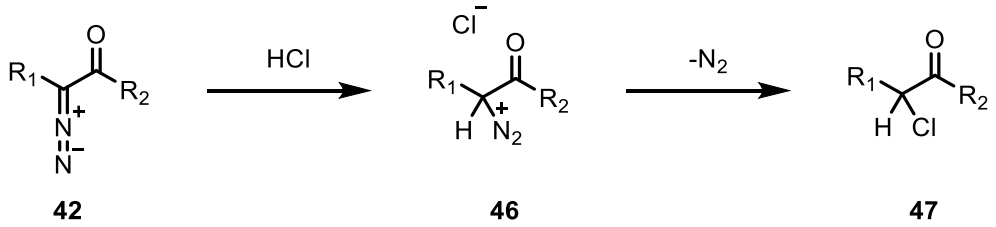
Scheme 1.13: Single and double ligand transfer from HVI reagents

Ylides are defined as neutral compounds containing a formally negative charged atom directly attached to a formally positively charged heteroatom, thus are 1,2-dipolar compounds. Well known examples of ylides include phosphonium ylides (e.g. Wittig reagents),[46] sulfonium ylides (such as ones employed in a Johnson-Corey-Chaykovsky reaction),[47] and titanium ylides (e.g. Tebbe's reagent).[48] Ylides are represented by two resonance structures: the ylene and ylide forms (Scheme 1.14a). Akin to the ylide form are α-diazocarbonyl compounds, whose resonance structure can be drawn to place a negative charge on the α-carbon (**42**) (Scheme 1.14b). Once α-diazocarbonyl compounds react with an electrophile, the diazonium group can be easily displaced by a nucleophile. The latter process is favoured by the expulsion of the neutral leaving group, nitrogen gas.



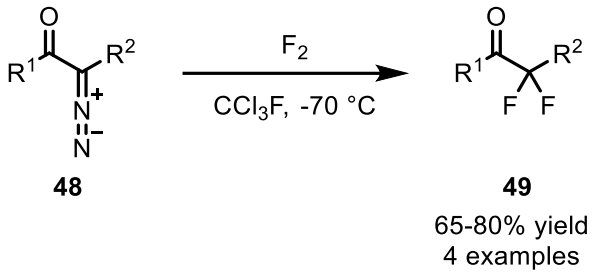
Scheme 1.14: Resonance structures of general ylides and diazo compounds

It should be no surprise that α-diazocarbonyl compounds can undergo *gem*-difunctionalization by replacement of the diazo function with two new substituents, X and Y, in a process called X–Y insertion (Scheme 1.15). One of the simplest X–Y insertions is when X is a proton and Y is a halide, such as in the case of HCl. The mechanism involves a stepwise process starting with initial protonation of the α-diazocarbonyl compound (**42**) followed by expulsion of N_2 through a nucleophilic attack by chloride.[49]



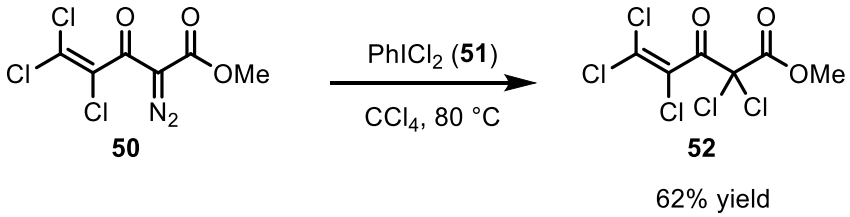
Scheme 1.15: X-Y insertion of HCl onto α-diazocarbonyl compounds

Such insertions are not limited to hydrogen-halide compounds, as they also take place with molecular halogens to furnish *gem*-dihalogenated products. Patrick *et al*. demonstrated the synthesis of geminal difluorinated compounds (**49**) by the reaction between α-diazocarbonyl substrates (**48**) and dilute F_2 in Freon-11 at -70 °C (Scheme 1.16).[50]



Scheme 1.16: X–Y insertion of F_2 onto α-diazocarbonyl compounds

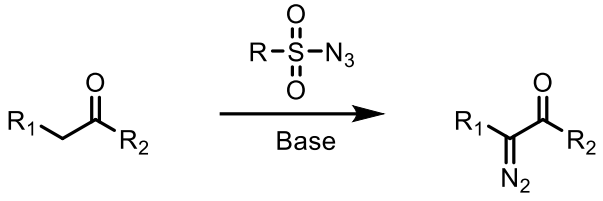
α-Diazocarbonyl compounds also produce *gem*-dihalo products by treatment with reagents surrogate to molecular halogens, such as hypervalent iodine compounds. In 1964, Roedig *et al*. produced the *gem*-dichlorinated product **52** from the α-diazo compound **50** in presence of (dichloroiodo)benzene (**51**) (Scheme 1.17). This is an attractive method for furnishing dichlorinated products without the use of chlorine gas.



Scheme 1.17: *gem*-Dichlorination of an α-diazo-β-dicarbonyl compound using $PhICl_2$

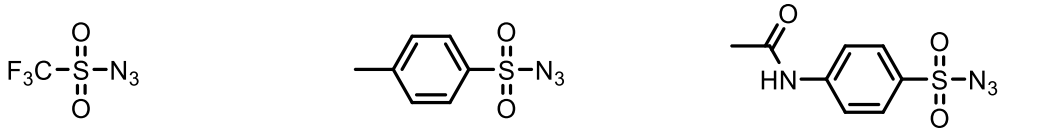
Despite being synthetically useful, diazo compounds have a bad reputation due to their acute toxicity and potential to explode, though these hazards are usually reserved for low molecular weight derivatives like diazomethane. The synthesis of diazo compounds can be dangerous depending on the reagents used, isolation methods, and the scale of the reaction. Through the progression of synthetic organic chemistry, safer methods have been developed to access α-diazocarbonyl compounds.[51]

One of the simplest methods of preparing α-diazo compounds is through a Regitz diazo transfer (Scheme 1.18). This process involves transfer of a diazo group from a donor reagent to an acceptor molecule, which for α-diazocarbonyl products must be derived from a ketone compound bearing acidic α-protons. The reaction is conducted in presence of a base and the diazo donor reagent is most often a sulfonyl azide.



Scheme 1.18: Synthesis of α-diazocarbonyl compounds using a diazo transfer reagent

One of the most commonly employed diazo transfer reagent is trifluoromethanesulfonyl azide (TfN_3), however; its use is often discouraged due to the necessity of expensive and toxic triflic anhydride used in its preparation. Additionally, TfN_3 is notorious as being highly explosive if poorly handled. Safer alternatives to TfN_3 have since been introduced, including tosyl azide (TsN_3) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (Figure 1.9).



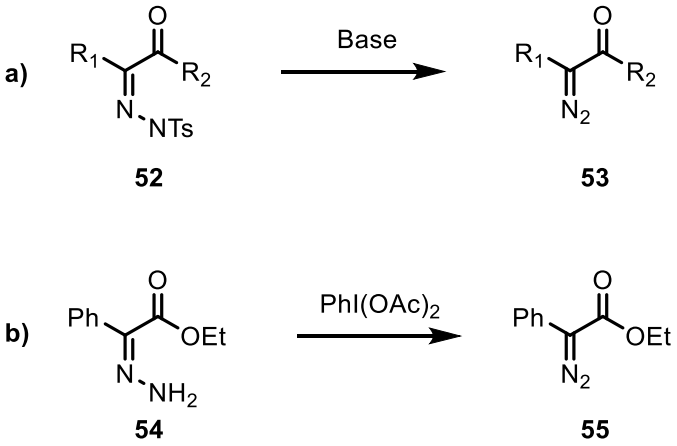
Trifluoromethanesulfonyl Azide (TfN_3)

Tosyl Azide (TsN_3)

p-Acetamidobenzenesulfonyl Azide (*p*-ABSA)

Figure 1.9: Examples of commonly used diazo transfer reagents

In addition to diazo transfer reagents, chemical modifications of tosylhydrazone compounds (**52**) could be employed to produce α-diazocarbonyl products (**53**) (Scheme 1.19a). This method was first discovered by Bamford and Stevens, where they treated tosylhydrazone compounds with a base to produce aryldiazomethanes.[52] Alternatively, it is known that α-diazocarbonyl compounds are formed through oxidation of hydrazone derivatives (**54**) by $PhI(OAc_2)$ (Scheme 1.19b).[53] This protocol provides a safer and more cost-effective alternative to methods that commonly employ manganese dioxide[54] or toxic lead(IV) tetraacetate.[55]

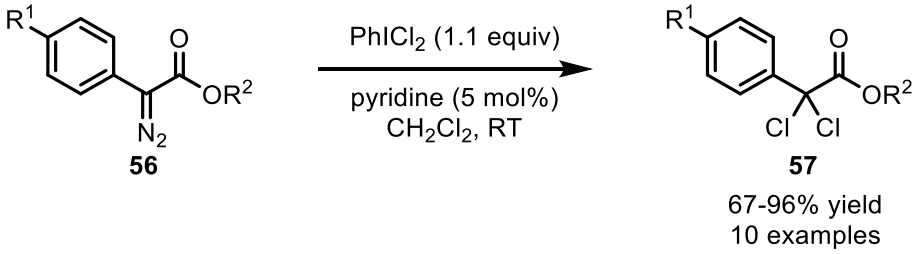


Scheme 1.19: Synthesis of α-diazocarbonyl compounds through chemical modifications

1.5 Halogenation of α-Diazo Compounds Using HVI Reagents

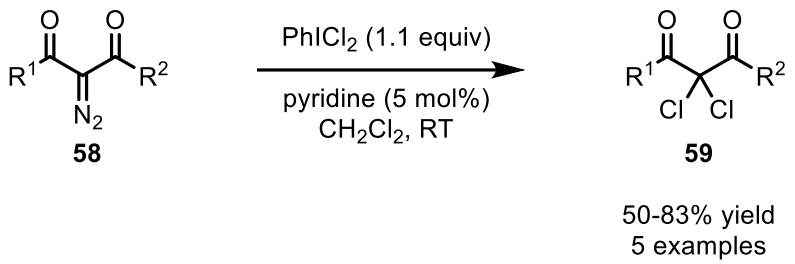
The initial report by Roedig *et al*. on the treatment of α-diazocarbonyl compounds with $PhICl_2$ developed the field for future synthesis of α,α-dihalo compounds using hypervalent iodine reagents. For years this chemistry was left untouched until Murphy *et al*. reported the α,α-dihalogenation of phenyldiazoacetate compounds (**56**). In 2014, the Murphy group reported synthesis of *gem*-dichlorinated and *gem*-difluorinated products using approximately equimolar amounts of the appropriate aryl-λ^3-iodane.[56]

The chlorination reactions were performed with 5 mol% pyridine in CH_2Cl_2 at room temperature and furnished the desired α,α-dichloro product (**57**) in high yields (Scheme 1.20). The group observed that reactions failed in the absence of base and suggested that the pyridine catalyzed the transformation through Lewis base activation of the iodane.



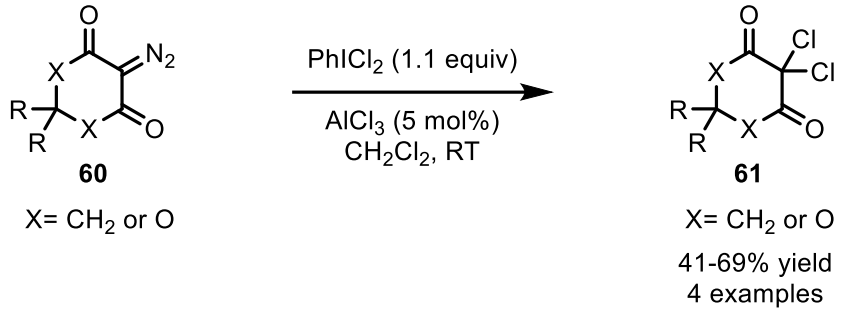
Scheme 1.20: Synthesis of phenyldichloroacetate compounds using $PhICl_2$

Chlorination of α-diazocarbonyl compounds is not limited to monocarbonyl substrates. Murphy *et al*. demonstrated that treating acyclic α-diazo-β-diketones, α-diazo-β-keto esters, and α-diazo-β-diesters compounds (**58**) with $PhICl_2$ furnished the corresponding dichlorinated products (**59**) in good yields (Scheme 1.21).[57]



Scheme 1.21: Synthesis of acyclic dichloro-β-dicarbonyl compounds using $PhICl_2$

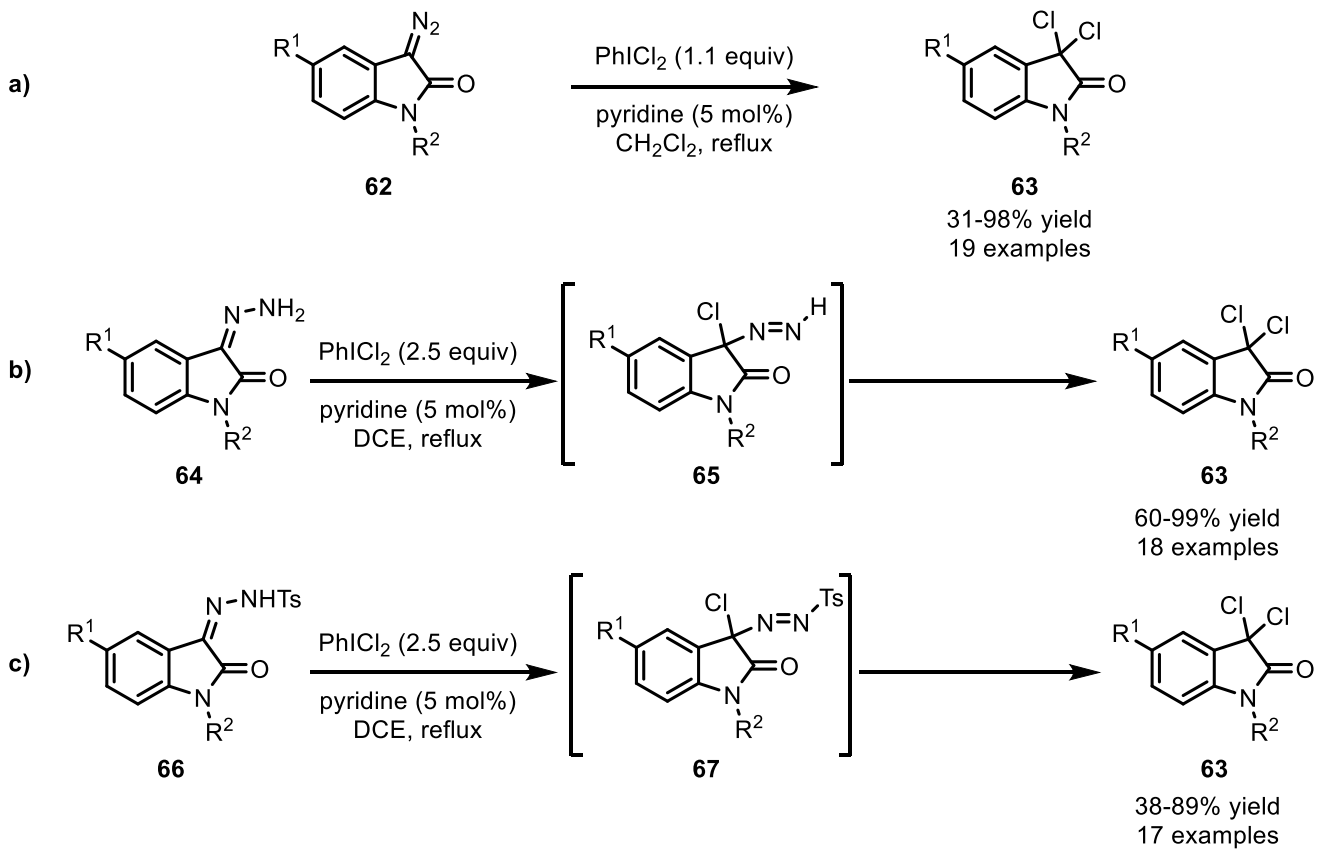
Cyclic α-diazo-β-dicarbonyl compounds were also investigated (Scheme 1.22). Performing the optimized chlorination reactions on acyclic α-diazo-β-dicarbonyl compounds (**60**) furnished poor yields of the desired cyclic *gem*-dichloro β-dicarbonyl products (**61**). Activation of the iodane by $AlCl_3$, however, proved to be effective and produced **61** in good yields.



Scheme 1.22: Synthesis of cyclic dichloro-β-dicarbonyl compounds using $PhICl_2$

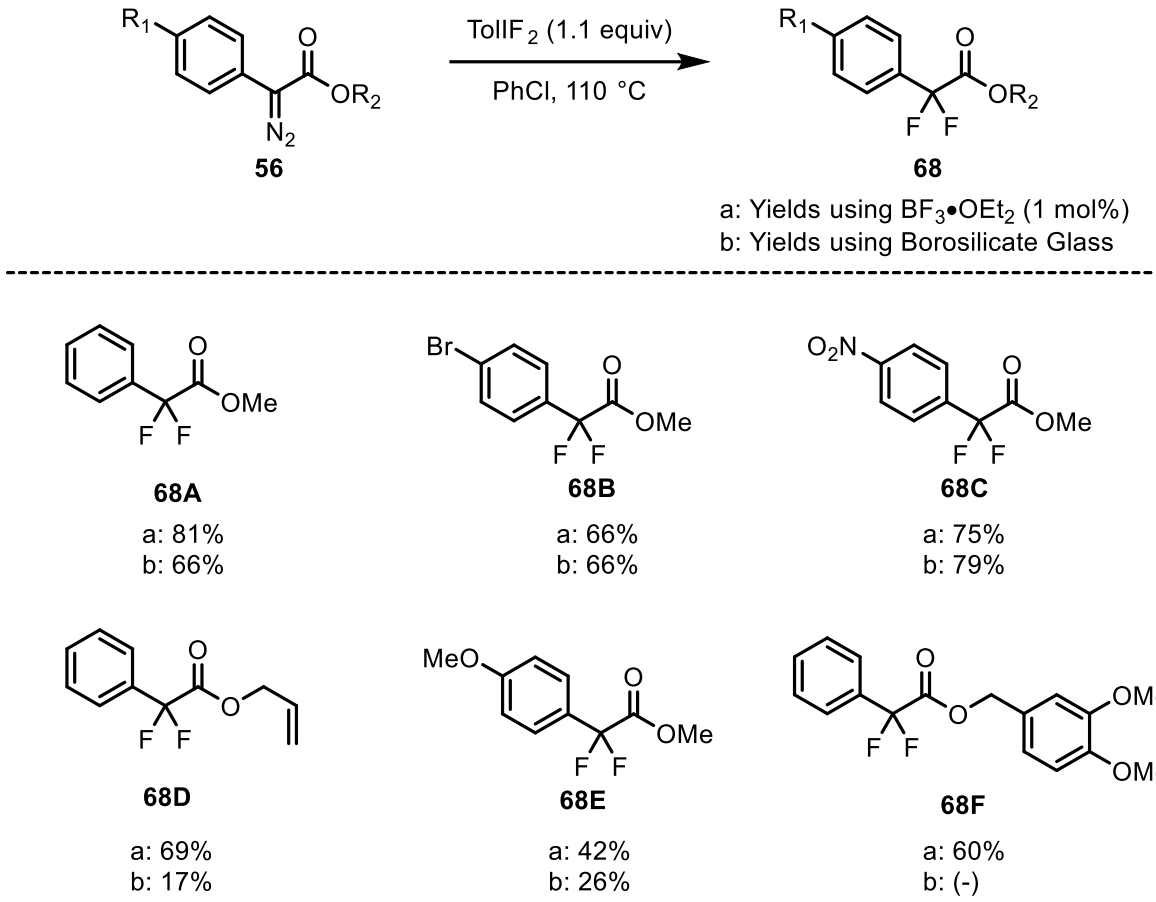
Dichlorination of α-carbonyl compounds using $PhICl_2$ was also expanded to include studies on oxindole derivatives. These substrates were chosen due to the antimicrobial,[58] anticancer,[59] antiviral,[60] and anti-inflammatory[61] characteristics displayed by oxindole compounds and their derivatives. Studies first began on chlorination of 3-diazo-2-oxindoles (**62**) to furnish the 3,3-dichloro-2-oxindole derivatives (**63**) in excellent yields (Scheme 1.23a).[62] The reaction was robust and could be applied to a series of functionalized 3-diazo-2-oxindoles, including a series of *N*-

functionalized and aryl substituted derivatives. In light of the hazardous properties associated with diazo compounds, Murphy *et al*. established methods to synthesize 3,3-dichloro-2-oxindole compounds that circumvents the isolation of the diazo intermediate. Treating the 3-hydrazono-[63] or 3-tosylhydrazono-[64] derivatives of oxindoles, **64** and **61**, with 2 equivalents of $PhICl_2$ furnished the 3,3-dichloro-2-oxindole in good yields, presumably through a successive tandem oxidation and dichlorination reaction (Scheme 1.23b and Scheme 1.23c). Through mechanistic probing, it was deduced that a diazo intermediate is not forming *in situ*, and the reaction instead presumably proceeds through azo-intermediates **65** or **67**.



Scheme 1.23: Synthesis of 3,3-dichloro-2-oxindole compounds using $PhICl_2$

Unfortunately, fluorination of phenyldiazoacetates (**56**) was more difficult. Subjecting the optimized chlorination reaction conditions to the fluorination of phenyldiazoacetate compounds using $TolIF_2$ furnished poor yields of the desired *gem*-difluorinated product (**68**). Murphy and coworkers speculated that the poor yield was due to weak activation of the iodane and accordingly performed screening of other activators to replace pyridine. The Lewis acid BF_3•OEt_2, was investigated because it was known that an electrophilic iodane salt $PhI(F)^+BF_4^-$ was generated by treating $PhIF_2$ with BF_3•OEt_2.[65] Studies with this Lewis acid led to the optimized conditions to produced α,α-difluoro products in moderate yields using 1 mol% BF_3•OEt_2 in PhCl at 110 °C (Scheme 1.24). Variation of the ester moiety and aromatic ring successfully furnished the desired *gem*-difluorinated product, though not as effective as the synthesis of the *gem*-dichlorinated species using $PhICl_2$. Yields were inconsistent with some of the ester variations and overall ineffective when employing an electron donating group on the arene.



Scheme 1.24: Synthesis of phenyldifluoroacetate compounds using $TolIF_2$

In an effort to improve the difluorination methodology, the Murphy group reinvestigated other Lewis acids in replacement of BF_3•OEt_2 to promote the reaction. They sought to find milder Lewis acids, which would be more compatible with electron-rich arenes while still activating $TolIF_2$. Lewis acids that were investigated include AlF_3, GaF_3, FeF_3, TiF_4, and borosilicate glass commonly found in laboratory glassware. Computational studies indicated that borosilicate glass was a better activator of $TolIF_2$ than BF_3•OEt_2. It was proposed that the increase in Lewis acidity displayed by borosilicate glass is due to the dihedral angle between oxygen and boron that results in a less hindered boron centre (Figure 1.10).[66] The group noticed an improvement in yields of the α,α-difluorinated product when borosilicate glass was used in conjunction with high purity and

freshly prepared $TolIF_2$. Using these reaction conditions expanded the substrate scope to include electron-rich arenes and effectively furnished phenyldifluoroaetate compounds (**68**) in good yields (Scheme 1.24).

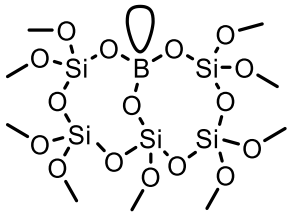
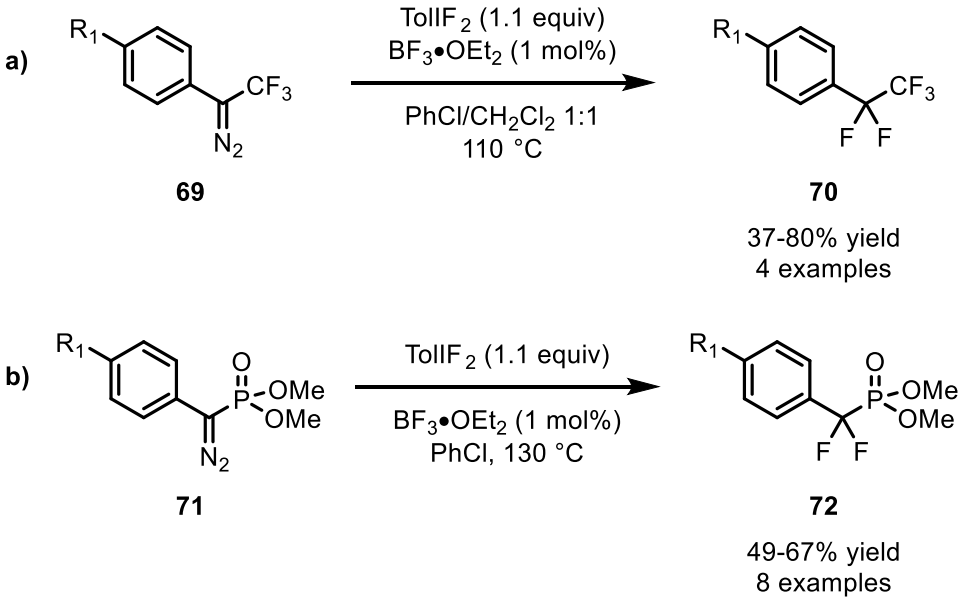


Figure 1.10: Structure of borosilicate found in laboratory glassware

Gouverneur *et al*. has extended this difluorination method to include conversion of trifluoromethyldiazophenylacetates **(69**) to perfluoroethylphenyl compounds (**70**) using BF_3•OEt_2 as the Lewis acid (Scheme 1.25a).[67] Similarly, Wang and coworkers furnished *gem*-difluorinated arylmethyl phosphonates (**72**) from their diazo counterparts (**71**) (Scheme 1.25b).[68]



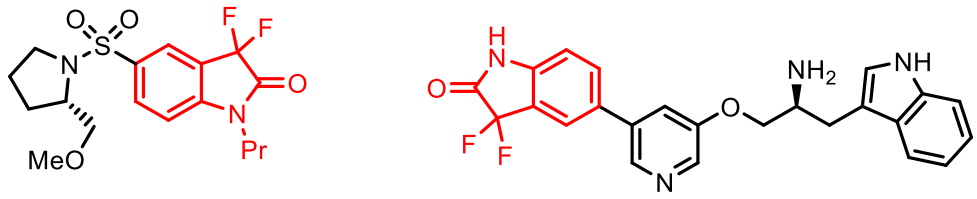
Scheme 1.25: Synthesis of (perfluoroethyl)phenyl compounds using $TolIF_2$

Thus, *gem*-dihalogenation of α-diazocarbonyl compounds or α-diazo precursors were achieved using $PhICl_2$ and $TolIF_2$. The key to these transformations was activation by Lewis acid or Lewis base catalysis. The synthesis of *gem*-dichlorinated products have been constructed from phenyldiazo acetate compounds as well as the diazo, tosylhydrazone and hydrazone derivatives of oxindoles. The synthesis of *gem*-difluorinated products, however, was only strictly performed on phenyldiazoacetate compounds. Extension of the fluorination methodology to produce other *gem*-difluorinated species, such 3,3-difluoro-2-oxindole compounds, is of interest.

Chapter 2: Synthesis of 3,3-Difluoro-2-oxindoles Using TolIF$_2$

2.1 Background

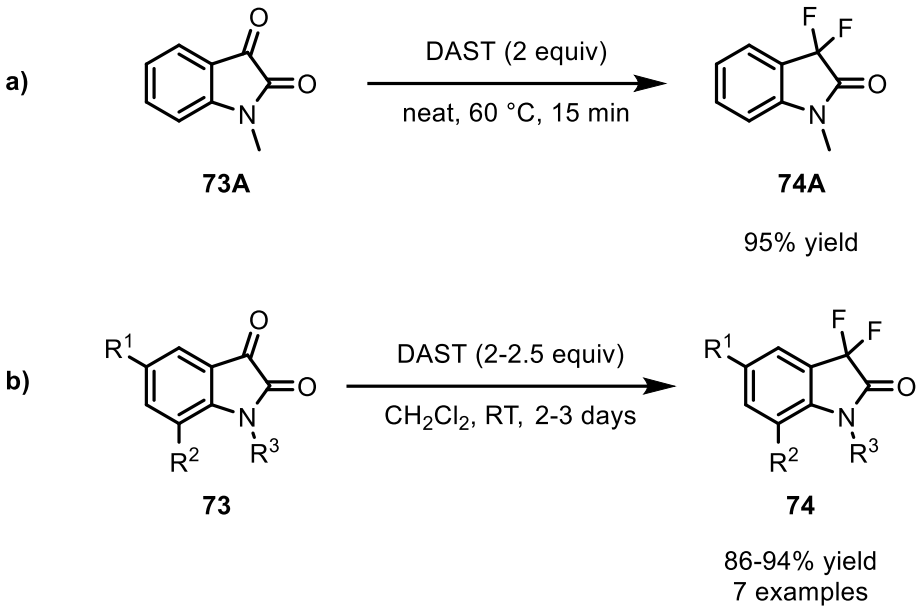
The 3,3-difluoro-2-oxindole motif have been found in specific biological applications. In 2009, Haufe and coworkers designed isatin derivatives in their studies to inhibit caspases-3 and -7. This family of enzymes become activated once apoptosis has been initiated, and have been linked to human degenerative diseases.[69] A series of *N*- and 5-substituted isatin derivatives were synthesized to mimic known inhibitors and their potency towards caspases-3 and -7 were determined. Amongst the ones studied was the 3,3-difluorinated derivative of pyrrolidinylsulfonyl isatins (Figure 2.1). In a similar vein, the 3,3-difluoro-2-oxindole motif was employed by Giranda *et al*. as an inhibitor of Akt through binding of its ATP site.[70] Overexpression of Akt has been found in a variety of human tumours, and as a result, its inhibition has been an attractive target in cancer research. The group previously reported an isoquinoline-pyridine based inhibitor to Akt, but found its drawbacks included short half-life and poor bioavailability in animals. The 3,3-difluoro-2-oxindole motif (Figure 2.1) was chosen as a possible candidate to replace the isoquinoline due to the enhanced stability conferred by the two fluorine atoms. And although the installation of the *gem*-difluorinated motif displayed improved toxicity over the parent compound, it paled in comparison to other candidates that exhibited superior bioavailability.[71]



Caspase-3 and -7 inhibitor Akt inhibitor

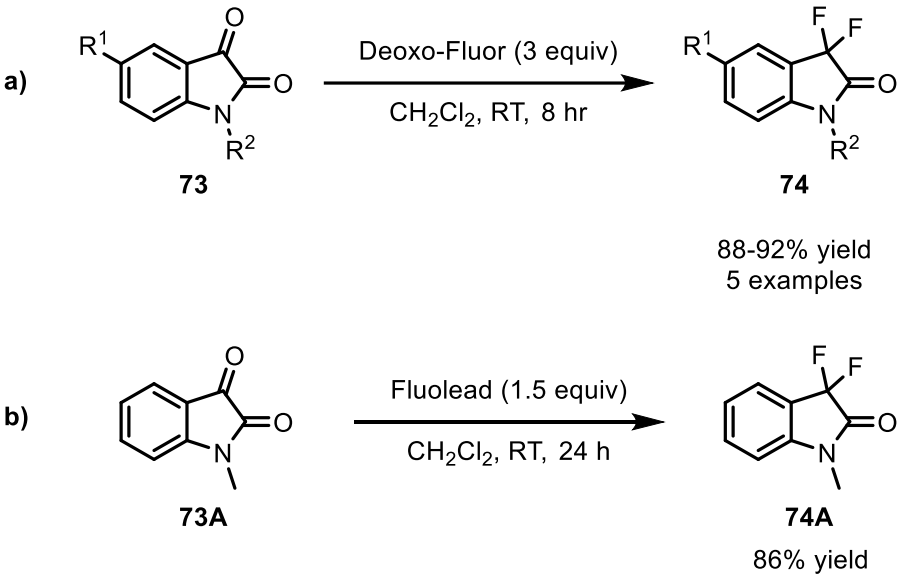
Figure 2.1: Biologically relevant molecules with the 3,3-difluoro-2-oxindole motif

Classical methods of synthesizing 3,3-difluoro-2-oxindole compounds and their derivatives include nucleophilic fluorination using deoxyfluorinating reagents. The first reported case was by Middleton and Bingham through the transformation of *N*-methylisatin (**73A**) to the *gem*-difluorinated species (**74A**) in excellent yields (Scheme 2.1a). Reactions were performed at 60 °C and were completed within 15 minutes.[72] Boechat *et al*. later showed that the synthesis of **74** using DAST could be accomplished at room temperature with longer reaction time (Scheme 2.1b).[73] They also applied this protocol to other *N*-alkyl and aryl-substituted oxindole derivatives (**73**) and produced the corresponding 3,3-difluorinated products in excellent yields. In both cases, at least 2 equivalents of DAST were required to cleanly furnish the difluorinated products.



Scheme 2.1: Synthesis of 3,3-difluoro-2-oxindole compounds using DAST

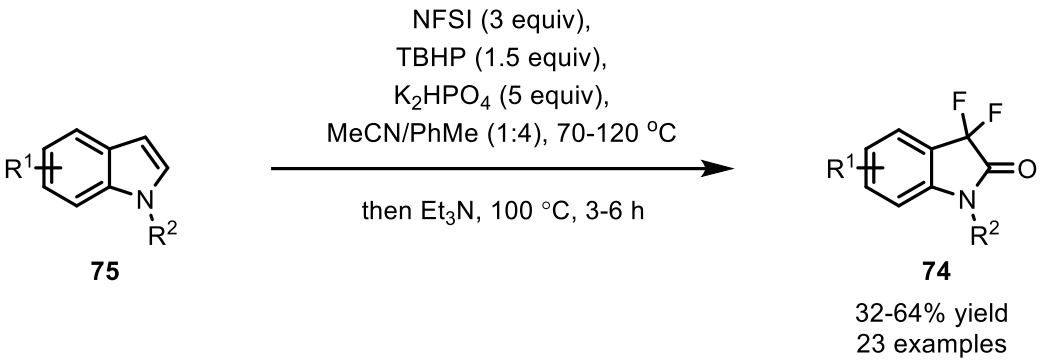
Shreeve and colleagues later disclosed the nucleophilic di- and tetrafluorination of dicarbonyl compounds using Deoxo-Fluor.[74] In their report, 3,3-difluoro-2-oxindole compounds were synthesized from their isatin derivatives in excellent yields (Scheme 2.2a). Similar to DAST, more than 2 equivalents of the nucleophilic fluorinating agent was required to furnish the *gem*-difluorinated product.



Scheme 2.2: Synthesis of 3,3-difluoro-2-oxindoles using Deoxo-Fluor and Fluolead

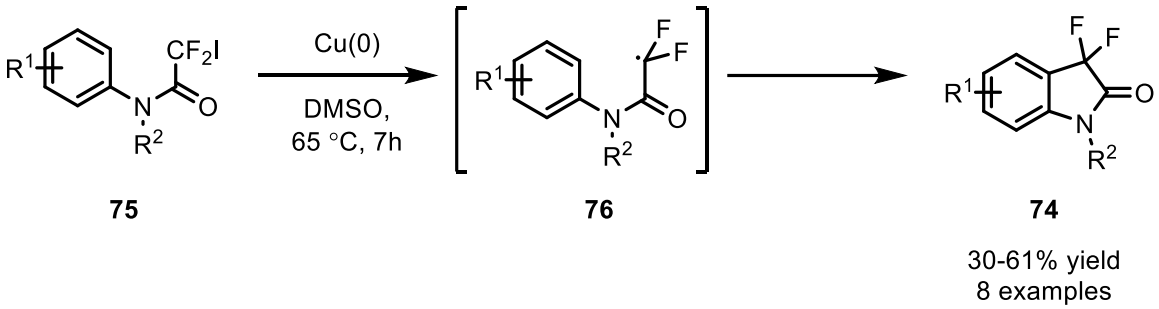
Similarly, Saito *et al*. disclosed the synthesis of 3,3-difluoro-2-oxindole (**74A**) in their original discovery of the nucleophilic fluorinating reagent, Fluolead.[75] *N*-Methyl isatin (**73A**) was treated with 1.5 equivalents of Fluolead at room temperature to furnish the 3,3-difluorinated product in excellent yields (Scheme 2.2b). Although Fluolead is a safer alternative to DAST and Deoxo-Fluor, the reagent is expensive and not cost effective for large scale syntheses.

Electrophilic fluorination has been previously utilized to produce 3,3-difluoro-2-oxindole compounds by Johannes *et al*.[76] Contrary to previous nucleophilic fluorination methods, indole compounds **(75**) were used instead of isatin derivatives. A series of *N*-alkyl and aryl-substituted indoles were treated with 3 equivalents of NFSI, as well as varying amounts of *tert*-butyl hydroperoxide (TBHP) and potassium hydrogenphosphate (K_2HPO_4) to produce the corresponding 3,3-difluoro-2-oxindole product in decent yields (Scheme 2.3). It was observed that when NFSI was substituted with Selectfluor®, only trace amounts of the *gem*-difluorinated product was produced.



Scheme 2.3: Synthesis of 3,3-difluoro-2-oxindole compounds using NFSI

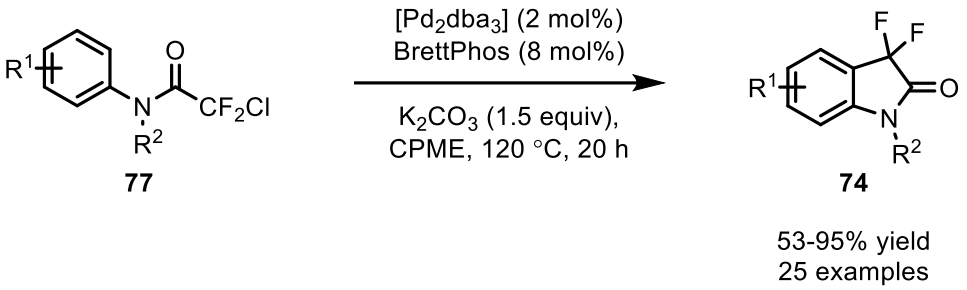
Aside from fluorinating reagents, metal catalyzed reactions have been reported to synthesize 3,3-difluoro-2-oxindole compounds. Such case was first reported by Hu and coworkers through a copper-mediated intermolecular cyclization of iododifluoroacetamides (**75**) (Scheme 2.4).[77] To explain the chemical outcome, they proposed a mechanism involving a *gem*-difluoromethyl radical (**76**) formed through a single electron transfer between iododifluoroacetamide and Cu^0.



Scheme 2.4: Synthesis of 3,3-difluoro-2-oxindole compounds by Hu

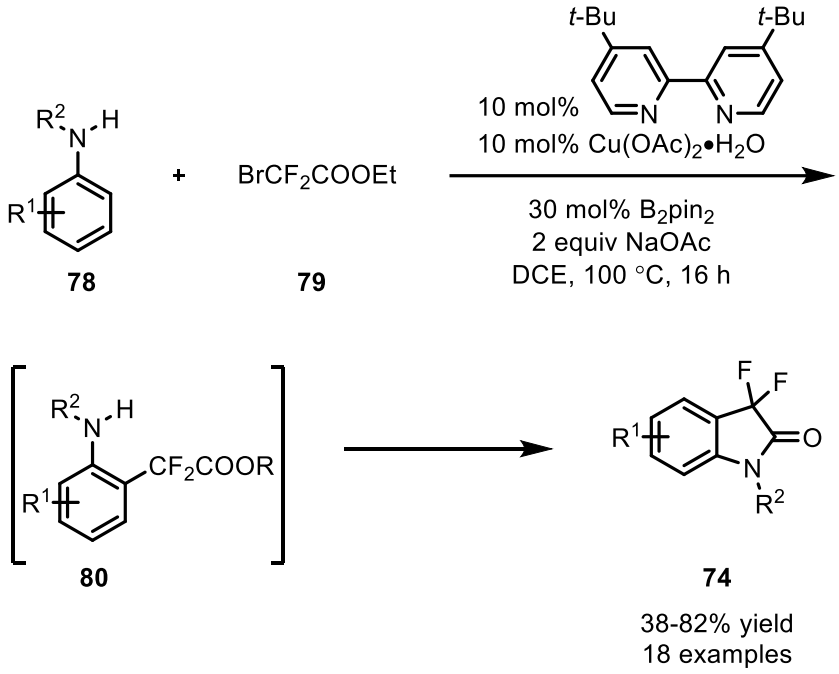
Similarly, a palladium-catalyzed synthesis of substituted 3,3-difluoro-2-oxindoles was reported by Shi and Buchwald starting from chlorodifluoroacetanilides (**77**).[78] The reaction proceeded via an intramolecular C-H difluoroalkylation under cyclopentyl methyl ether (CPME) at 120 °C to furnish compound **74** in good yields (Scheme 2.5). The authors noted that the use of

the bulky biarylphosphine ligand, BrettPhos, was found to be the only phosphine ligand capable of efficiently catalyzing this reaction.



Scheme 2.5: Synthesis of 3,3-difluoro-2-oxindole compounds by Shi and Buchwald

More recently, Ke and Song reported the synthesis of 3,3-difluoro-2-oxindole derivatives via a copper/B_2pin_2-catalyzed difluoroacetylation of aniline derivatives (**78**) through a C-H activation followed by an intramolecular amidation (Scheme 2.6).[79] The reaction proceeded via a one-pot synthesis and furnished the difluorinated oxindole derivatives in poor to excellent yields.



Scheme 2.6: Synthesis of 3,3-difluoro-2-oxindole compounds by Ke and Song

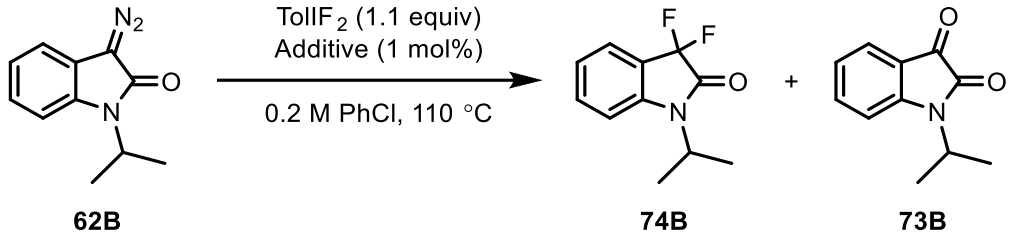
2.2 Proposal

The multitude of methods available to synthesize 3,3-difluoro-2-oxindole derivatives demonstrates their importance in medicinal studies. While significant progress has been made in their syntheses, there are still limitations to accessing these biologically useful molecules. Earlier protocols to producing 3,3-difluoro-2-oxindole compounds employ reagents dangerous for large scale applications,[72] exhibit poor fluorine economy,[72-74] expensive metals and ligands,[78-79] or stoichiometric amounts of transition metal which leads to high cost and pollution.[77] A route to accessing the 3,3-difluoro-2-oxindole motif is envisioned through HVI reagents. Previous work by Murphy *et al.* has shown that the synthesis of 3,3-dichloro-2-oxindole compounds were achieved by treating diazo, tosylhydrazone, or hydrazone derivatives of oxindole with $PhICl_2$.[62-64] Given the success of this work, it is believed the corresponding fluorination transformation is attainable using $TolIF_2$. This pathway provides a metal-free approach that employs a stable and

readily made reagent. Furthermore, the iodotoluene byproduct could be recycled to reform $TolIF_2$, thereby reducing its costs and environmental pollution. Finally, $TolIF_2$ displays excellent fluorine economy in the syntheses of *gem*-difluorinated products as each reagent molecule carries two active fluorine atoms that can be transferred.

2.3 Synthesis of 3,3-Difluoro-2-oxindoles from 3-Diazo-2-oxindoles

N-Isopropyl-3-diazo-2-oxindole (**62B**) was chosen as the model substrate to investigate reaction parameters due to its ease of synthesis, smooth purification, and its high yield in previous dichlorination studies using $PhICl_2$.[62] The Murphy group disclosed poor compatibility between BF_3•OEt_2 and electron-rich functional groups in their report regarding the *gem*-difluorination of phenyldiazoacetates.[56] It was speculated that poor compatibility would also exist between BF_3•OEt_2 and 3-diazo-2-oxindole compounds due to the presence of the nitrogen on the amide that can donate electrons into the arene. Thus, the fluorination of **62B** closely followed the fluorination method established by Murphy *et al* with the substitution of BF_3•OEt_2 with milder Lewis acids. In particular, fluorinated Lewis acids were investigated as opposed to other halide-containing analogues in order to avoid cross-halogenation.



62B **74B** **73B**

Entry	Additive	Yield of **74B**	Yield of **73B**
1	FeF_3	16%	9%
2	GaF_3	19%	10%
3	InF_3	14%	15%
4	AlF_3	13%	10%
5	TiF_3	19%	15%
6	TiF_4	12%	7%
7[a]	Pyridine	0	5%
8[a]	2,6-Lutidine	0	8%

[a]The starting material was not fully consumed and the reaction was stopped after 6 hours.
Table 2.1: Screening of catalysts for the fluorination of *N*-isopropyl-3-diazo-2-oxindole

Thus, diazo compound **62B** was dissolved in PhCl and treated with 1.1 equivalents of $TolIF_2$ and 1 mol% of Lewis acid at 110 ºC in a glass round bottom flask. Following this procedure using FeF_3 as the Lewis acid furnished the corresponding 3,3-difluoro-2-oxindole (**74B**), but in disappointingly low yields (Table 2.1, entry 1). Screening of other Lewis acids was conducted, but similar yields were produced (Table 2.1, entries 2-6). Screening of Lewis bases that were effective in *gem*-dichlorination reactions using $PhICl_2$ failed to produce any of the *gem*-difluorinated product, possibly due to poor activation of the iodane (Table 2.1, entries 7-8).

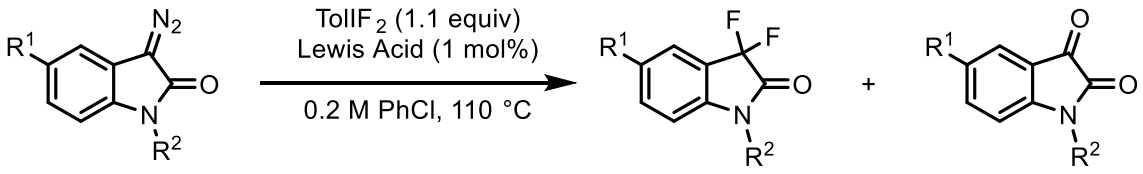
It appeared as though the fluorination of 3-diazo-2-oxindoles produced poorer yields of the *gem*-difluorinated product than the phenyldiazoacetates. A possible explanation for this phenomenon is that **62B** is an aromatic compound and therefore synthesis of *gem*-difluorinated products requires aromaticity to be broken. Breaking aromaticity would produce highly reactive intermediates that may decompose rather than produce *gem*-difluorinated products.

In all of these reactions, *N*-isopropyl isatin (**73B**) was isolated as a side product. This was expected since HVI reagents are well known for their oxidizing capabilities and a similar oxygenated byproduct formed in the fluorination of phenyldiazoacetates.[56] Initially, it was believed the source of oxygen was from atmospheric H_2O, but conducting the fluorination reaction in inert atmosphere or with dry glassware and solvents produced the oxygenated byproduct in similar yields. Studies by the Murphy group to identify the source of oxygen in fluorinations of α-diazocarbonyl compounds remain inconclusive and are still under investigation.

Despite monitoring reactions by TLC and ensuring the complete consumption of starting material, poor mass balance was observed. The only components detectable on ^{1}H NMR were the difluorinated product **74B** and oxygenated product **73B**, roughly accountable for 25-35% of the starting material. It is hypothesized that the remaining mass may be loss through decomposition of the diazo starting material or reaction intermediate(s) formed in solution.

To expand on the substrate scope of difluorination reaction, a series of *N*-alkyl and aryl substituted 3-diazo-2-oxindole species were studied along with the application of various Lewis acids. Amongst the substituted oxindoles that were studied, *N*-benzyl oxindole (**62C**) was chosen due to the presence of the additional phenyl ring to improve detection of potential by-products on TLC. Conversely, the 5-fluoro and 5-chloro derivatives were selected due to their high yielding synthesis in the analogous chlorination studies. The *N*-benzyl substrate produced the corresponding *gem*-difluorinated product in yields similar to the *N*-isopropyl compound (Table 2.2, entries 1-4), the highest yields of **74C** was achieved when **62C** was treated with InF_3 (Table 2.2, entry 3). However, this entry appears to be an outlier since previous tests using InF_3 produced poor yields of the *gem*-difluorinated product (Table 2.1, entry 3). It is interesting to note that fluorination of aryl-substituted systems **62D** and **62E** produced trace amounts of their *gem*-

difluorinated products (Table 2.2, entries 7-8) when their respective chlorination products using $PhICl_2$ were furnished in ~80% yield.[62] It is postulated that the presence of the free N-H in **62D** and **62E** led to wanted deprotonation of the oxindole substrate to produce reactive intermediates that resulted in its decomposition. If that is the case, then the decomposition of the oxindole substrate was avoided in the corresponding chlorination transformation because it was conducted under milder reaction conditions (refluxing CH_2Cl_2). Alternatively, the free N-H may engage with fluoride ions through hydrogen bonding to stabilize transition states (thereby decreasing the activation energy barrier) in pathways that lead to the decomposition of the diazo substrate.



62 **74** **73**

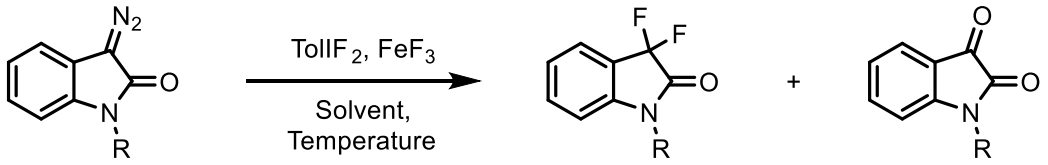
Entry	Substrate	R^1	R^2	Lewis Acid	Yield of **74**	Yield of **73**
1	**62C**	H	Benzyl	FeF_3	20%	25%
2				GaF_3	26%	17%
3				InF_3	34%	15%
4				TiF_3	20%	<5%
7	**62D**	Cl	H	FeF_3	<5%	<5%
8	**62E**	F	H	FeF_3	<5%	<5%

Table 2.2: Screening of other 3-diazo-2-oxindole compounds and Lewis acids

Since it was believed that low yields of the 3,3-difluoro-2-oxindole product was due to decomposition of the diazo substrate, a series of experiments were conducted under milder reaction conditions. It became apparent, however, that higher temperatures were necessary to produce better yields of the difluorinated product. It is postulated that higher temperatures is required to supply the 3-diazo-2-oxindole substrate with enough energy to break aromaticity and form the 3,3-

difluoro-2-oxindole product. This became evident in cases where the reaction was conducted at lower temperatures and little to no difluorinated product was formed (Table 2.3, entries 1-2). Instead, oxygenated side product **73** was largely produced at 40 °C and 80 °C, perhaps because HVI reagents can readily oxidized organic compounds without the use of Lewis acids.[80]

Additionally, more $TolIF_2$ was added in hopes that increasing the concentration of available iodane in solution would improve the yields of the *gem*-difluorinated product (Table 2.3, entry 3). The yield of the *gem*-difluorinated product unfortunately did not significantly increase. A possible explanation for the unaffected yields of **74B** in entry 3 is that FeF_3 is not effectively activating $TolIF_2$ and a stronger Lewis acid is required. It was also believed that a larger percentage of Lewis acid in solution would lead to more activated $TolIF_2$ and promote fluorination activity. However, increasing the catalytic loading of FeF_3 produced similar yields of **74B** as with lower loading (Table 2.3, entries 4,5).

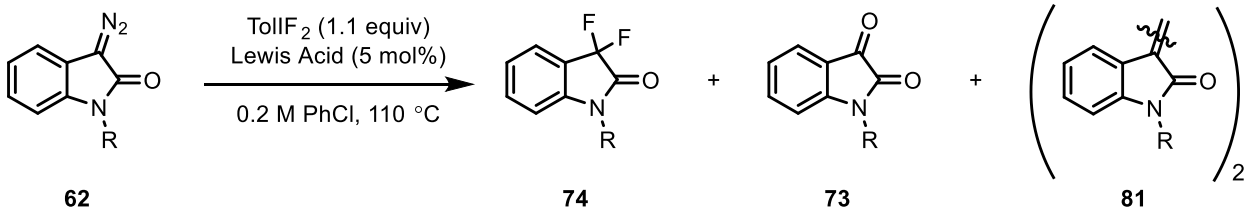


62 **74** **73**

Entry	Substrate	R	Solvent	Tempe-rature	$TolIF_2$ Equiv	FeF_3 Equiv	Yield of **74**	Yield of **73**
1	**62C**	Benzyl	PhCl	40 °C	1.1	1 mol%	0	19%
2[a]			PhCl	80 °C	1.1	1 mol%	8 %	20%
3[a]			PhCl	110 °C	2.0	1 mol%	26%	19%
4	**62B**	*i*Pr	PhCl	110 °C	1.1	1 mol%	16%	9%
5			PhCl	110 °C	1.1	20 mol%	23%	20%

[a]The starting material was not completely consumed and the reaction was stopped after 8 hours.
Table 2.3: Screening of other reaction conditions

Since it was known that the fluorination of phenyldiazoacetate compounds was effected by borosilicate glassware,[81] control reactions were performed on the 3-diazo-2-oxindole substrates in different reaction vessels. Diazo substrate **62B** was treated with $TolIF_2$ in PhCl at 110 °C in PFA vials in the absence of any Lewis acids and compared to a similar fluorination reaction in borosilicate glass. After 24 hours, the reaction in PFA vial was incomplete and only starting material was observed by TLC. Upon addition of 5 mg of borosilicate glass obtained from grounding a round bottom flask, the reaction was complete within minutes. TLC analysis of the crude mixture indicated only two spots: isatin **73B** and a new compound that was identified via ^1H NMR and mass spectrometry as a homodimer of the oxindole compound (**81B**). Given that diazo compounds are known to produce carbenes, it is plausible that the formation of the homodimer could have arisen through such intermediates.



62 **74** **73** **81**

Entry	Substrate	R	Lewis Acid	Yield of **74**	Yield of **73**	Yield of **81**
1	**62B**	*i*Pr	FeF_3	0	10%	0
2			$BF_3{\cdot}OEt_2$	45%	5%	Trace
3	**62C**	Bn	$BF_3{\cdot}OEt_2$	45%	5%	Trace

Reactions were conducted by performing a dropwise addition of diazo to $TolIF_2$ in a PFA vial.
Table 2.4: Fluorination of 3-diazo-2-oxindole compounds in PFA vials

It was hypothesized that decreasing the concentration of the starting material would reduce dimerization by virtue of lowering collision rate between two molecules of 3-diazo-2-oxindole. Accordingly, a dropwise addition of the diazo substrate was added to the reaction mixture containing $TolIF_2$ via a syringe pump in a PFA vial. It was observed that through the reverse

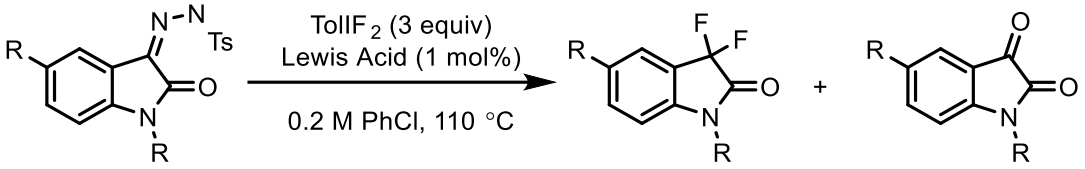
addition, the formation of dimer was nearly abolished and was only detectable in trace amounts. Screening of Lewis acids were performed for this protocol and FeF_3 was found to be ineffective (Table 2.4, entry 1). But substitution of FeF_3 with BF_3•OEt_2 furnished the *gem*-difluorinated product in improved yields with minor production of the isatin and dimer side product (Table 2.4, entry 2). Performing this reaction with the alternative *N*-benzyl substrate coincidentally produced identical yields (Table 2.4, entry 3).

2.4 Synthesis of 3,3-Difluoro-2-oxindoles from Tosylhydrazone and Hydrazone Oxindoles

It became apparent that changing the substituents, Lewis acids, and reaction conditions had minimal impact on enhancing the production of the desired difluoro-2-oxindole compounds from the 3-diazo-2-oxindole. It was believed that the low yields of the *gem*-difluorinated product were due to decomposition of the diazo intermediate in solution. An alternative route to the *gem*-difluoroxindole was envisioned from a tosylhydrazone derivative. Previous work in the Murphy group has shown direct conversion of tosylhydrazone oxindoles to their *gem*-dichlorinated products using $PhICl_2$ through a two-step deoxygenative dichlorination reaction that circumvents that formation of a diazo intermediate.[64] This strategy, however, requires 2.5 equivalent of $PhICl_2$ because the reaction produces *p*-toluenesulfinate as a byproduct that oxidizes and consumes an equivalent of the HVI reagent. It was believed that pursuing the fluorination through a tosylhydrazone derivative would produce the 3,3-difluoro-2-oxindole compound with better yields than the diazo derivatives.

Studies began on the *N*-isopropyl tosylhydrazone compound (**66B**) under the same reaction conditions of the fluorination of 3-diazo-2-oxindole. Reactions were incomplete when performed

with 1.1 equivalents of $TolIF_2$; in addition, a new spot was observed on TLC. Isolation and characterization of this new spot by ^1H NMR revealed the compound to be tosylfluoride, which formed from the sulfinate anion formed *in situ* consuming a molecule of $TolIF_2$. A similar reaction was observed in the chlorination reaction using $PhICl_2$.[64] To combat this issue, $TolIF_2$ loading was increased to 3.0 equivalents with all other reaction parameters remaining the same. Conducting the fluorination reaction with varying tosylhydrazone compounds and Lewis acids disappointingly produced the *gem*-difluorinated product (**74**) in yields ranging from 5-15% (Table 2.5). Similar to the fluorination studies conducted on the 3-diazo-2-oxindole substrate, isatin compound **73** was isolated as a side product. Overall, the tosylhydrazone substrate produced slightly lower yields of the *gem*-difluorinated product. This was expected because chlorination of 3-diazo-2-oxindole compounds using $PhICl_2$ produced higher yields of the corresponding *gem*-dichlorinated products than through the tosylhydrazone derivatives.[62] A possible explanation for this observed reactivity is that the *gem*-dichlorination and difluorination of 3-tosylhydrazono-2-oxindole compounds proceeds through a different mechanism than the analogous 3-diazo-2-oxindoles, and may produce intermediates that are more susceptible to decomposition or oxidation in producing the oxygenated side product **73**. Fluorination of tosylhydrazone derivatives offered no significant advantages over the diazo substrate, and hence, was not further studied.



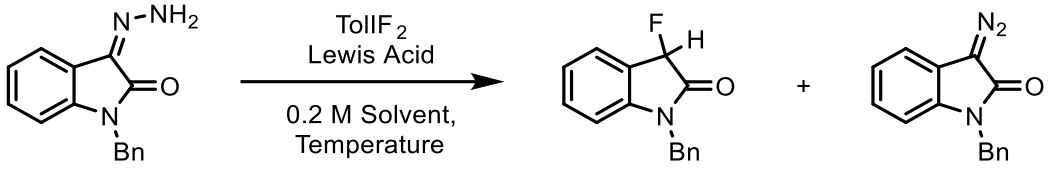
66 **74** **73**

Entry	Substrate	R	Lewis Acid	Yield of **74**	Yield of **73**
1	**66B**	*i*Pr	FeF_3	8%	30%
2			GaF_3	13%	26%
3			TiF_3	5%	30%
4			TiF_4	8%	25%
5	**66A**	CH_3	FeF_3	14%	28%
6	**66C**	Bn	FeF_3	<5%	17%

Table 2.5: Fluorination of 3-tosylhydrazono-2-oxindole compounds

Alternatively, the fluorination of hydrazones derived from oxindoles can access 3,3-difluoro-2-oxindole compounds. Precedents for this work include the one-pot chlorination of such compounds using $PhICl_2$ through a tandem oxidation/chlorination reaction.[57] Other members in the Murphy group reported the tandem oxidation/*gem*-chlorination and oxidation/*gem*-fluorination of benzaldehyde hydrazones to furnish *gem*-dichloro- and *gem*-difluoromethylarenes.[82] Since iodanes can oxidize hydrazones,[53] at least 2 equivalents of the HVI reagent were required to promote the above tandem oxidation/*gem*-dihalogenation. The reaction conditions in both cases were mild and avoided the isolation of a diazo intermediate. Because harsh conditions were speculated to cause the decomposition of the 3-diazo-2-oxindole compounds, the fluorination of hydrazone oxindoles provided an attractive alternative. The following work on the fluorination of hydrazone derivatives of oxindole compounds were conducted by Boris Miokovic under supervision.

N-Benzyl-3-hydrazono-2-oxindole (**64C**) was chosen as the model substrate for optimization studies due to the presence of benzylic protons that can be integrated to obtain NMR yields of the crude reaction mixture. Subjecting *N*-benzyloxindole hydrazone **64C** to 2 equivalents of $TolIF_2$ in CH_2Cl_2 at room temperature (Table 2.6, entry 1) and stirring for 8 hours, the hydrazone was completely consumed and only the oxidized diazo product was recovered. Similar results were observed after switching solvents and increasing the reaction temperature to 40 °C and 80 °C (Table 2.6, entries 2-3). Increasing the temperature to 110 °C produced trace amounts of the monofluorinated species detectable only by a singlet in ^{19}F NMR (Table 2.6, entry 4), suggesting the oxidation readily proceeds under mild reaction conditions, but require harsher circumstances to promote fluorination. The observed monofluoride compound produced could be due to the hydrofluorination of the diazo intermediate by HF generated from the oxidation of **64C**. Addition of Lewis acids $BF_3•OEt_2$ and TiF_3 produced detectable amounts of the monofluorinated species in ^1H NMR, with more produced with the latter (Table 2.6, entries 5-6). Surprisingly, the diazo formed *in situ* was not consumed after stirring for several hours, despite being in similar reaction conditions used in the fluorination of 3-diazo-2-oxindole compounds. This issue was overcome by increasing the reagent loading to 3 equivalents (Table 2.6, entry 7). Switching the solvent to *ortho*-dichlorobenzene at 130 °C led to complete consumption of the diazo intermediate, and only 21% of the monofluoride **82C** was produced (Table 2.6, entry 9). Throughout these trials, the desired 3,3-difluoro-2-oxindole compound was not produced, possibly due to hydrofluorination pathway outcompeting the difluorination. Thus, fluorination through the hydrazone route was discontinued.



64C **82C** **62C**

Entry	Lewis Acid	$TolIF_2$ Equiv	Solvent	Temperature	NMR Yield of **82C**	NMR Yield of **62C**
1	-	2	CH_2Cl_2	0 °C	NR	>90%
2	-	2	CH_2Cl_2	reflux	NR	
3	-	2	PhCl	80 °C	NR	
4	-	2	PhCl	110 °C	Trace	
5	BF_3•OEt_2	2	PhCl	110 °C	5%	80%
6	TiF_3	2	PhCl	110 °C	7%	70%
7	TiF_3	3	PhCl	110 °C	15%	30%
8	TiF_3	3	*o*-DCB	130 °C	25%	-
9	TiF_3	3	*o*-DCB	130 °C	21%[a]	-

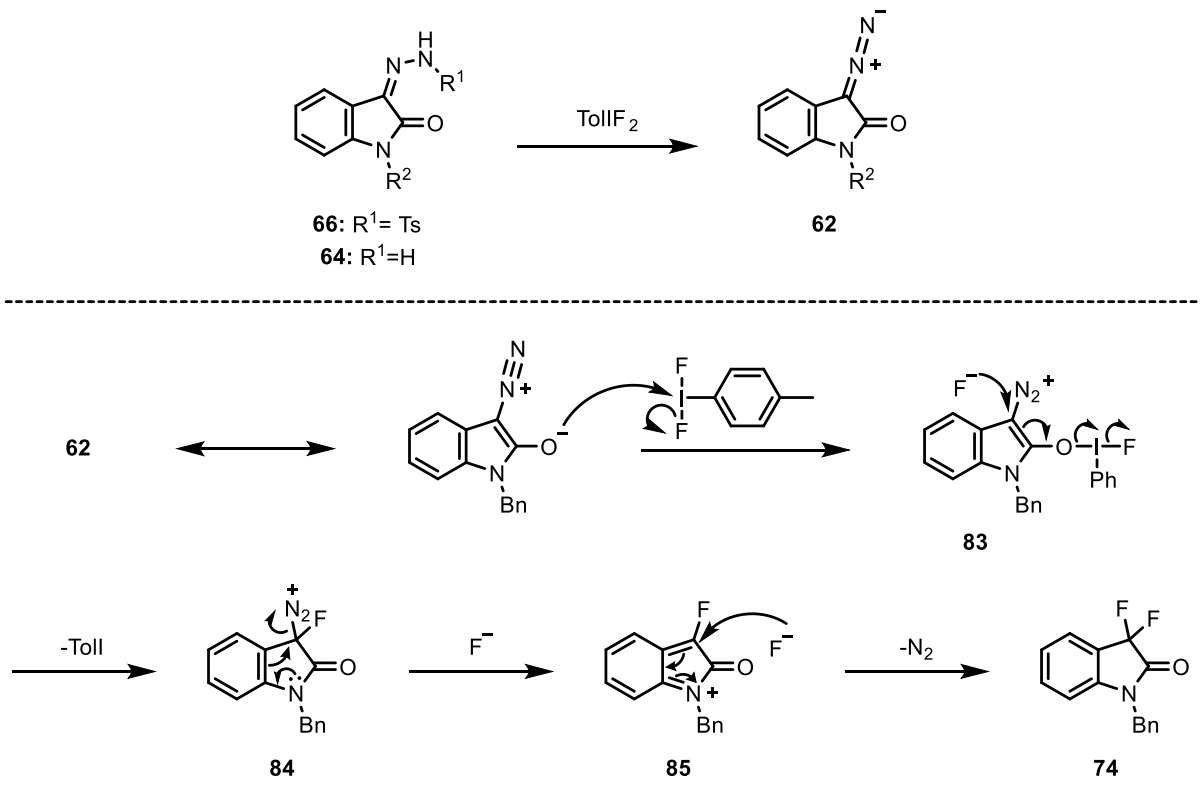
Table 2.6: Fluorination of *N*-benzyl-3-hydrazono-2-oxindole

2.5 Proposed Mechanism

Although a mechanism has been proposed by Murphy *et al*. in the chlorination of oxindole derivatives using $PhICl_2$, experimental results in the fluorination studies suggests that a few adjustments are required. Given the differences in electrophilicity between $PhICl_2$ and $TolIF_2$, the use of Lewis acid for activation of the latter, and the contrasting di-halogenated product distribution, it is proposed that the mechanisms for the fluorination and chlorination reactions are not the same. Murphy *et al*. proposed that the chlorination of tosylhydrazone and hydrazone oxindole species did not proceed via a diazo intermediate.[57,83] However, the observed formation of the 3,3-diazo-2-oxindole compounds in the fluorination of the tosylhydrazone derivative suggests that the *gem*-difluorination of these compounds is achieved through a diazo intermediate. Additionally, Szpilman and coworkers identified enolonium species (iodo(III)enolates) of

carbonyl compounds as intermediates in hypervalent iodine induced α-functionalization.[84] This suggests that the fluorination of 3-diazo-2-oxindole compounds proceeds through an enolate-oxygen-bound hypervalent iodine intermediate as opposed to the α-carbon-bound hypervalent iodine intermediate proposed in literature previously discussed in Chapter 1 of this thesis.

A proposed mechanism for the synthesis of 3,3-difluoro-2-oxindole compounds is outlined below (Scheme 2.7). First, oxidation of the tosylhydrazone **66** or hydrazone **64** produces the diazo oxindole (**62**) *in situ* by an equivalent of $TolIF_2$. Activation of $TolIF_2$ by a Lewis acid allows for attack by the enolate oxygen of diazo. Ligand exchange produces enolonium species **83** and a fluoride ligand, which returns to perform a nucleophilic attack on the α-carbonyl carbon resulting in intermediate **84**. This process proceeds with simultaneous formation of iodotoluene and a second fluoride ion. Donation from the nitrogen atom on the amide could assist in the expulsion of nitrogen gas to produce compound **85**. Finally, nucleophilic attack by the second fluoride ion furnishes the 3,3-difluoro-2-oxindole product (**74**).



Scheme 2.7: Proposed mechanism for the *gem*-difluorination of 3-diazo-2-oxindoles

Prior work in the Murphy group demonstrated that the synthesis of 3,3-dichloro-2-oxindole products were obtained in excellent yields (~90%) by treating the parent diazo, tosylhydrazone, or hydrazone derivatives with $PhICl_2$.[62-64] When these compounds were reacted with $TolIF_2$ however, poor yields of the *gem*-difluorinated product were obtained. These results were unanticipated since the fluorination of phenyldiazoacetate compounds using $TolIF_2$ furnished the *gem*-difluorinated products almost as well as the corresponding *gem*-dichlorinated products with $PhICl_2$.[56,81]

Since fluorides are better nucleophiles in polar aprotic solvents than chlorides,[85] it was believed that the halide addition onto intermediates **83** and **85** would occur more readily in the fluorination reaction than the chlorination. As well, fluorine's 2p orbital is known to exhibit better overlap with the p orbital on a carbon atom than chlorine due to its similarity in size.[85] This increased in orbital

overlap should allow for fluorine atoms to better stabilize adjacent carbocations and lead to faster expulsion of nitrogen gas on intermediate **84**. By these considerations, it was believed that the synthesis of *gem*-difluorinated products would be higher yielding than the respective *gem*-dichlorinated product using $PhICl_2$. From the results gathered from the fluorination of diazo, hydrazone and tosylhydrazone oxindoles, however, it appeared as though this is not the case. The reason for the poor synthesis of the 3,3-difluoro-2-oxindoles compared to the 3,3-dichloro-2-oxindole compounds is not fully understood, though several factors may be taken into account for the observed reactivity.

The first step in the proposed mechanism is ligand exchange between the enolate of diazo oxindole **62** and the iodane. Since chloride is a better leaving group than fluoride, the exchange with $PhICl_2$ occurs readily under mild reaction conditions through Lewis base catalysis, while activation of $TolIF_2$ require strong Lewis acid catalysis at elevated temperatures. It is believed that heating the reaction promotes ligand exchange by increasing the ground state energy of the diazo substrate and decreasing the activation energy barrier. Elevated reaction temperatures however, also come at the cost of decreasing the activation barrier for decomposition to occur.

Another reason for the observed discrepancy in yields of the *gem*-dihalo products is that formation of competing side products. The oxygenated side product was not formed during the chlorination of α-diazocarbonlyl compounds using $PhICl_2$.[56] On the contrary, the oxygenated product is formed in 10-20% yield in the fluorination studies of oxindole compounds, which may indicate that $TolIF_2$ is a stronger oxidant than $PhICl_2$. Under the conducted reaction conditions, the diazo oxindole may engage $TolIF_2$ as an oxidant rather than as a fluorine source. It is also possible that $TolIF_2$ is more hygroscopic than $PhICl_2$ and so the trace amounts of water molecules present in solution would bolster the formation of the oxygenated product.

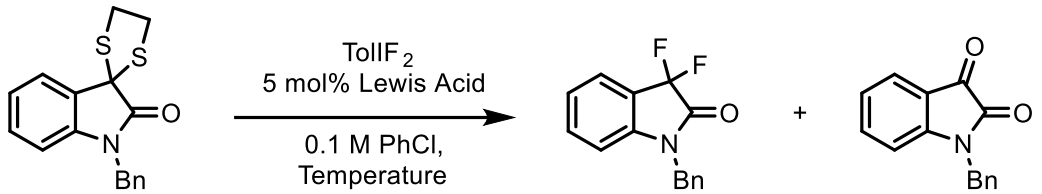
It is possible that the most effective Lewis acid to catalyze the formation of 3,3-difluoro-2-oxindole compounds has yet to be identified. The synthesis of phenyldifluoroacetates significantly improved on electron-rich arenes when BF_3•OEt_2 was substituted with the milder borosilicate glass.[81] Since oxindole compounds contain a nitrogen atom that can donate electron density into the arene, catalysis by BF_3•OEt_2 may not be fitting for this system and may require an alternative Lewis acid. Unfortunately, fluorination of oxindole compounds conducted in the presence of borosilicate glass as the Lewis acid produced poor yields of the 3,3-difluoro-2-oxindole compound. High yielding synthesis of the *gem*-difluorinated species may be achieved once a Lewis acid that is milder than BF_3•OEt_2 but stronger than borosilicate glass has been identified.

2.6 Synthesis of 3,3-Difluoro-2-oxindoles from Dithiane Derivatives

Despite numerous trials, high-yielding synthesis of 3,3-difluoro-2-oxindole compounds using HVI reagents did not seem feasible through the diazo, tosylhydrazone, and hydrazone derivatives. As an alternative strategy, 3,3-difluoro-2-oxindoles is envisioned to form by treating dithiane compounds derived from oxindole species with $TolIF_2$. This route was chosen because it is known that dithioketals could be transformed to their *gem*-difluorinated species under mild reaction conditions.[45] Furthermore, by avoiding the diazo functional group, the dithiane oxindole substrate may not produce carbenes or other reaction intermediates that could result in dimerization or decomposition of starting material.

The known dithiane derivative of *N*-benzyloxindole (**86**) was chosen as the model substrate for these reactions.[86] Initial studies began by following the procedure reported by Motherwell and Wilkinson,[45] in particular, compound **86** was subjected to 2 equivalents of $TolIF_2$ in CH_2Cl_2 at 0

°C in a PFA vial with no other additives (Table 2.7, entry 1). TLC and ^{1}H NMR analysis of the crude reaction mixture after 24 hours indicated that no reaction had occurred. Increasing the temperature of the reaction mixture and changing the solvent similarly led to no observed reactivity between the substrate and $TolIF_2$ (Table 2.7, entries 2-4). When catalytic amounts of BF_3•OEt_2 was added to a refluxing mixture in PhCl, the reaction went to completion within one hour and cleanly furnished the 3,3-difluoro-2-oxindole product (**74C**) in 47% yield (Table 2.7, entry 5). Additionally, 31% of isatin (**73C**) was recovered as a byproduct. When the reaction was repeated but with 3 equivalents of $TolIF_2$, the formation of the *gem*-difluorinated product increased to 58% along with minor production of isatin (Table 2.7, entry 6). Although fluorination of **86** was successful and provided the *gem*-difluorinated product in higher yields, this protocol is not significantly advantageous over the 3-diazo-2-oxindole route. Having to use at least 2 equivalents of $TolIF_2$ is a major drawback and eliminates the advantage of using it as an effective ligand transfer reagent in the formation of *gem*-difluorinated species.



86 **74C** **73C**

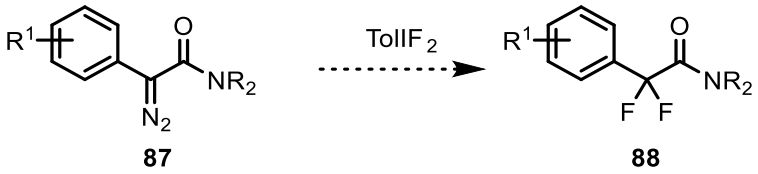
Entry	Lewis Acid	$TolIF_2$ Equiv	Solvent	Temperature	Yield of **74C**	Yield of **73C**
1	-	2	DCM	0 °C	-	-
2	-	2	DCM	reflux	-	-
3	-	2	PhCl	40 °C	-	-
4	-	2	PhCl	110 °C	-	-
5	BF_3•OEt_2	2	PhCl	110 °C	47%	31%
6	BF_3•OEt_2	3	PhCl	110 °C	58%	10%

Table 2.7: Fluorination of *N*-Benzyl-3,3-(ethylenedithio)oxindole

2.7 Conclusions and Future Work

In summary, an unprecedented route to synthesizing 3,3-difluoro-2-oxindole compounds from diazo, tosylhydrazone, hydrazone, and dithiane derivatives of oxindole using the hypervalent iodine reagent $TolIF_2$ has been demonstrated. Unfortunately, yields of the 3,3-difluoro-2-oxindole compound in all cases were poor or non-existent. Two different 3-diazo-2-oxinole derivatives produced the desired difluoro product in 45% yield. The tosylhydrazone derivative produced the difluorinated product in 14% yield, whereas the hydrazone oxindoles failed to produce any. Two equivalents of $TolIF_2$ were necessary in the fluorination of tosylhydrazone and hydrazone oxindoles via a tandem oxidation/fluorination reaction. Dithiane oxindoles furnished the difluoro-2-oxindoles in good yields, but the necessity of using 2 equivalents of $TolIF_2$ solely for fluorination made this route unattractive.

It was interesting to see that the reported fluorination of phenyldiazoacetate,[56] α-diazoarylmethylphosphonates,[77] and trifluoromethyldiazophenylacetate[67] compounds produced good-excellent yields of their corresponding difluorinated species. A possible explanation for the observed difference in yields is that the above substrates are non-aromatic compounds, whereas the oxindole species are aromatic. Aromaticity of the oxindole compounds can be broken by disconnecting the nitrogen-aryl carbon bond to form an acyclic amide. Thus, to investigate whether aromaticity could explain the difference in observed yields, the fluorination of acyclic α-diazo amides will be investigated in the next chapter (Scheme 2.8).



87 **88**

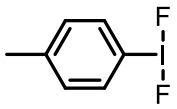
Scheme 2.8: Proposed *gem*-difluorination of acyclic phenyldiazoacetamides

2.8 Experimental Procedures for Chapter 2

2.8.1 General Experimental Details

Reactions were carried out in oven-dried glassware under inert atmosphere unless otherwise stated. Fluorination reactions could be carried out under open atmosphere without adverse effects. PFA vials (4 mL, 14 x 52 mm) were purchased from Elemental Scientific. Chlorobenzene was dried over 4 Å molecule sieves and used without further purifications. Molecular sieves were pre-activated by heating under vacuum. Dichloromethane and tetrahydrofuran were dried and purified using a JC Meyer solvent purification system and were used without further purifications. All other solvents were purchased from Sigma-Aldrich and used without further purifications. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes. Thin layer chromatography was performed on glass plates pre-coated with 0.25 mm Kieselgel 60 F_{254} (Silicycle) and were visualized under UV light. Flash chromatography columns were packed with 230-400 mesh silica gel (Silicycle). Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrum Two with ATR Two. Proton NMR spectra (^{1}H NMR) were recorded at 300 MHz, and are reported (ppm) relative to the residual chloroform peak (7.26 ppm). Carbon NMR spectra (^{13}C NMR) were recorded at 125 or 75 MHz and are reported (ppm) relative to the centre line of the triplet from chloroform-d (77.16 ppm). Coupling constants (*J*) are reported in hertz (Hz). Fluorine NMR spectra (^{19}F NMR) were recorded at 282 MHz and are reported (ppm) relative to the peak of trifluoroacetic acid (-76.53 ppm). Mass spectra were performed on a ThermoFisher Scientific Q-Exactive hybrid mass spectrometer using positive electrospray ionization (ESI). Accurate mass were recorded with a mass resolution of 70,000. ESI samples were infused at 5 µL/min in 1:1 CH_3OH/H_2O+0.1% formic acid. Melting points were determined on a Melt-Temp II.

2.8.2 Synthesis of (Difluoroiodo)toluene ($TolIF_2$) (14)



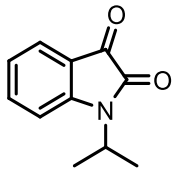
(Diacetoxyiodo)toluene (8.40 g, 25 mmol, 1.0 equiv) was suspended in aqueous 5 M NaOH (28.6 mL, 143 mmol, 5.7 equiv) in an oven-dried flask equipped with magnetic stirring at room temperature for 4 hours. The resulting yellow slurry was then filtered through a fritted glass funnel and washed, sequentially, with H_2O (4 x 100mL) then chloroform (100 mL), and suctioned dry to give a yellow slurry. The slurry was immediately transferred to a Teflon bottle equipped with a stir bar and suspended in CH_2Cl_2 (40 mL) at room temperature. The mixture was carefully stirred as conc. aqueous HF was added dropwise via a polyethylene pipette until all solids have dissolved (approximately 9 mL). The aqueous layer was decanted and the organic layer was concentrated to dryness under a stream of nitrogen to furnish a yellow-white solid. The crude solid was recrystallized using a mixture of hexanes and $CHCl_3$ to yield **14** as a white powder (4.10 g, 64% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.83 (d, *J*=8.6 Hz, 2H, ArH), 7.39 (d, *J*=8.6 Hz, 2H, ArH), 2.46 (s, 3H, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$), δ -177.11. Spectral data is consistent with those found in literature.[87]

2.8.3 General Procedure A: Alkylation of Isatin (73)

Isatin (1.00 g, 6.8 mmol, 1.0 equiv) was dissolved in DMF (6.2 mL, 1.1 M) in an oven-dried flask equipped with magnetic stirring at room temperature. K_2CO_3 (1.13 g, 8.2 mmol, 1.2 equiv) was added in one portion followed by the addition of the corresponding alkyl halide (8.2 mmol, 1.2 equiv). The resulting mixture was then stirred at room temperature for an additional hour after

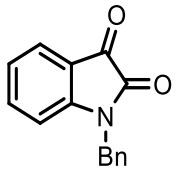
which time TLC analysis showed consumption of starting material. The reaction mixture was then diluted with EtOAc (20 mL) and the aqueous layer was extracted with EtOAc (2 x 20 mL each). The combined organic layer was washed, sequentially, with H_2O and brine (20 mL each). The organic layer was then dried over $MgSO_4$, filtered, and concentrated to dryness *in vacuo*.

2.8.3.1 Synthesis of *N*-Isopropylisatin (73A)



Prepared according to **General Procedure A** with the addition of 2-bromopropane (766 µL) as the alkyl halide to afford **73A** as a bright orange solid (772 mg, 60% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (dd, *J*=7.4 Hz, *J*=1.2 Hz, 1H, ArH), 7.57 (ddd, *J*=7.7 Hz, *J*=7.7 Hz, *J*=1.3 Hz, 1H, ArH), 7.09 (dd, *J*=7.5 Hz, *J*=7.5 Hz, 1H, ArH), 7.03 (d, *J*=8.1Hz, 1H, ArH), 4.54 (sept, *J*=7.1 Hz, 1H, NC<u>H</u>$(CH_3)_2$), 1.52 (d, *J*=7.0 Hz, 6H, NCH$(C\underline{H}_3)_2$). Spectral data is consistent with those found in literature.[88]

2.8.3.2 Synthesis of *N*-Benzylisatin (73C)



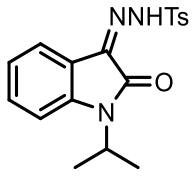
Prepared according to **General Procedure A** with the addition of benzyl bromide (975 µL) as the alkyl halide to afford **73C** as a bright orange solid (1.45 g, 90% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60 (d, *J*=7.4 Hz, 1H, ArH), 7.48 (dd, *J*=7.7 Hz, *J*=7.7 Hz, 1H, ArH), 7.38-7.29 (m, 5H, ArH),

7.08 (dd, *J*=7.5 Hz, *J*= 7.5 Hz, 1H, ArH), 6.77 (d, *J*=8.0 Hz, 1H, ArH), 4.92 (s, 2H, NC$\underline{H}_2$Ph). Spectral data is consistent with those found in literature.[88]

2.8.4 General Procedure B: Synthesis of 3-Tosylhydrazono-2-oxindoles (66)

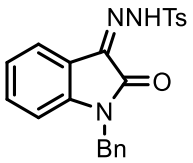
The corresponding derivative of isatin (4.2 mmol, 1.0 equiv) was dissolved in methanol (11 mL, 0.4 M) in an oven dried flask equipped with magnetic stirring at room temperature. *p*-Toluenesulfonyl hydrazide (820 mg, 4.4 mmol, 1.1 equiv) was added in one portion. The resulting mixture was stirred and heated at reflux for an additional hour after which time TLC analysis showed consumption of starting material. After cooling to room temperature, any precipitate formed during this stage was isolated by suction filtration and washed with small quantities of cold methanol.

2.8.4.1 Synthesis of *N*-Isopropyl-3-tosylhydrazono-2-oxindole (66B)



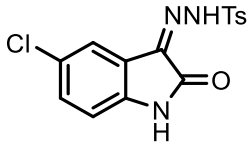
Prepared according to **General Procedure B** starting from *N*-isopropylisatin (795 mg) to afford **66B** as a bright yellow solid (1.22 g, 79% yield) mixture of (*E*) and (*Z*) isomers. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 12.65(br s, 1H, NH), 7.89 (d, *J*=7.9 Hz, 2H, ArH), 7.60 (d, *J*=7.5 Hz, 1H, ArH), 7.33-7.30 (m, 3H, ArH), 7.06 (dd, *J*=8.0 Hz, *J*=8.0 Hz, 1H, ArH), 6.98 (d, *J*=8 Hz, 1H, ArH), 4.52 (sept, *J*=7.1 Hz, 1H, NC$\underline{H}$(CH_3)$_2$), 2.41 (s, 3H, CH_3), 1.48 (d, *J*=7.3 Hz, 6H, NCH(C$\underline{H}_3$)$_2$). Spectral data is consistent with those found in literature.[64]

2.8.4.2 Synthesis of *N*-Benzyl-3-tosylhydrazono-2-oxindole (66C)



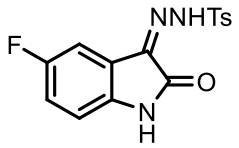
Prepared according to **General Procedure B** starting from *N*-benzylisatin (996 mg) to afford **66C** as a bright yellow solid (1.44 g, 85% yield) mixture of (*E*) and (*Z*) isomers. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 12.62 (br s, 1H, NH), 8.00 (d, *J*=8.3 Hz, 2H, ArH), 7.69 (d, *J*=7.6 Hz, 1H, ArH), 7.42-7.29 (m, 8H, ArH), 7.14 (dd, *J*=7.6 Hz, *J*=7.6 Hz, 1H, ArH), 6.82 (d, *J*=8.0 Hz, 1H, ArH), 4.97 (s, 2H, NC$\underline{H}_2$Ph), 2.40 (s, 3H, CH_3). Spectral data is consistent with those found in literature.[64]

2.8.4.3 Synthesis of 5-Chloro-3-tosylhydrazono-2-oxindole (66D)



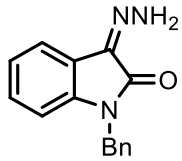
Prepared according to **General Procedure B** starting from *N*-isopropylisatin (762 mg) to afford **66D** as a bright yellow solid (1.47 g, 95% yield) mixture of (*E*) and (*Z*) isomers. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.31 (br s, 1H, NN$\underline{H}$Ts), 7.89 (d, *J*=8.2 Hz, 2H, ArH), 7.44 (d, *J*=8.1 Hz, 2H, ArH), 7.40 (d, *J*=2.3 Hz, 1H, ArH), 7.38 (dd, *J*=8.0 Hz, *J*=2.2 Hz, 1H, ArH), 6.91 (d, *J*=8.3 Hz, 1H, ArH), 2.38 (s, 3H, CH_3). Spectral data is consistent with those found in literature.[64]

2.8.4.4 Synthesis of 5-Fluoro-3-tosylhydrazono-2-oxindole (66E)



Prepared according to **General Procedure B** starting from 5-fluoroisatin (694 mg) to afford **66E** as a bright yellow solid (1.26 g, 90% yield) mixture of (*E*) and (*Z*) isomers. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.98 (br s, 1H, NNHTs), 7.84 (d, *J*=8.2 Hz, 2H, ArH), 7.41 (d, *J*=8.2 Hz, 2H, ArH), 7.26 (d, *J*=2.4 Hz, 1H, ArH), (dd, *J*=9.0 Hz, *J*=3.0 Hz, 1H, ArH), 6.88 (d, *J*=8.8 Hz, 1H, ArH), 2.47 (s, 1H, CH_3). Spectral data is consistent with those found in literature.[64]

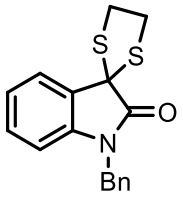
2.8.5 Synthesis of *N*-Benzyl-3-hydrazono-2-oxindole (64C)



N-Benzylisatin (2.00 g, 8.4 mmol, 1.0 equiv) was dissolved in methanol (21 mL, 0.4 M) in an oven dried flask equipped with magnetic stirring at room temperature. Hydrazine monohydrate, reagent grade 98% (830 µL, 16.8 mmol, 2.0 equiv) was added in one portion. The resulting mixture was then stirred and heated at reflux for an additional 30 minutes after which time TLC analysis showed consumption of starting material. After cooling to 0 °C in an ice water bath, any precipitate formed during this stage was isolated by suction filtration and washed with small quantities of cold methanol to furnish **64C** as a bright yellow solid (1.53 g, 73%) as a mixture of (*E*) and (*Z*) isomers. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.52 (d, *J*=7.2 Hz, 1H, ArH), 7.34-7.27 (m, 5H, ArH), 7.16 (ddd, *J*=7.5 Hz, *J*=7.5 Hz, *J*=1.2 Hz, 1H, ArH), 7.05 (ddd, *J*=7.7 Hz, *J*=7.7 Hz, *J*=1.1 Hz, 1H,

ArH), 6.75 (d, *J*=7.8 Hz, 1H, ArH), 4.97 (s, 2H, NC$\underline{H}_2$Ph). Spectral data is consistent with those found in literature.[63]

2.8.6 Synthesis of *N*-Benzyl-3,3-(ethylenedithio)-2-oxindole (86)

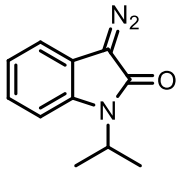


N-Benzylisatin (1.80 g, 7.6 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (38 mL, 0.2 M) in a flame-dried round bottom flask equipped with magnetic stirring at room temperature. Ethane-1,2-dithiol (0.7 mL, 8.4 mmol, 1.1 equiv) was added in one portion followed by dropwise addition of BF_3•OEt_2 (1 mL). The resulting solution was stirred at room temperature for an additional 2 hour after which TLC showed consumption of starting material. The reaction was then quenched with the addition of H_2O (40 mL), and the organic layer was washed, sequentially, with 10% sodium carbonate, H_2O, and brine (40 mL each). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness *in vacuo*. The crude mixture was purified by column chromatography (20% EtOAc in hexanes) to produce **86** as a pink solid (1.43 g, 58%). $\mathbf{R_f}$: 0.35 (20% EtOAc in hexanes, UV Active); ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.55 (dd, *J*=7.4 Hz, *J*=1.0 Hz, 1H, ArH), 7.35-7.23 (m, 5H, ArH), 7.19 (ddd, *J*=7.6 Hz, *J*=7.6 Hz, *J*=1.3 Hz, 1H, ArH), 7.06 (ddd, *J*=7.6 Hz, *J*=7.6 Hz, *J*=0.9 Hz, 1H, ArH), 6.68 (d, *J*=7.8 Hz, 1H, ArH), 4.90 (s, 2H, NC$\underline{H}_2$Ph), 4.02-3.93 (m, 2H, SC$\underline{H}_2$C$\underline{H}_2$S), 3.75 (m, 2H, SC$\underline{H}_2$C$\underline{H}_2$S). Spectral data is consistent with those found in literature.[86]

2.8.7 General Procedure C: Synthesis of 3-Diazo-2-oxindoles (62)

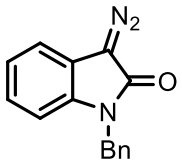
The corresponding derivative of 3-tosylhydrazono-2-oxindole (2.5 mmol, 1.0 equiv) was dissolved in THF (10 mL, 0.25 M) in an oven-dried flask equipped with magnetic stirring. A solution of NaOH (197 mg, 4.9 mmol, 2.0 equiv) dissolved in H_2O (25 mL) was added in one portion and the resulting mixture was stirred at room temperature for 3 hours after which time TLC analysis showed consumption of starting material. The reaction mixture was then diluted with EtOAc (20 mL) and the aqueous layer was extracted with EtOAc (2 x 20 mL each). The combined organic layer was washed, sequentially, with H_2O and brine (20 mL each). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness *in vacuo*. The resulting crude solid was purified by column chromatography.

2.8.7.1 Synthesis of *N*-Isopropyl-3-diazo-2-oxindole (62B)



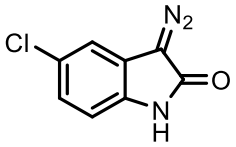
Prepared according to **General Procedure C** starting from *N*-isopropyl-3-tosylhydrazono-2-oxindole (894 mg) to afford **62B** as a red solid (327 mg, 65% yield) after column chromatography (20% EtOAc in hexanes). **R_f**: 0.58 (50% EtOAc in hexanes, UV Active); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.21-7.11 (m, 2H, ArH), 7.10-7.03 (m, 2H, ArH), 4.73 (sept, *J*=7.0 Hz, 1H, NC<u>H</u>$(CH_3)_2$), 1.51 (d, *J*=7.0 Hz, 6H, NC<u>H</u>$(CH_3)_2$). Spectral data is consistent with those found in literature.[62]

2.8.7.2 Synthesis of *N*-Benzyl-3-diazo-2-oxindole (62C)



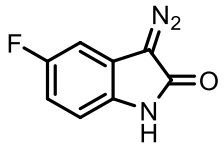
Prepared according to **General Procedure C** starting from *N*-benzyl-3-tosylhydrazono-2-oxindole (1.01 g) to afford **62C** as an orange solid (424 mg, 68% yield) after column chromatography (20% EtOAc in hexanes). **R_f**: 0.30 (20% EtOAc in hexanes, UV Active); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34-7.19 (m, 6H, ArH), 7.12-7.02 (m, 2H, ArH), 6.82 (dd, *J*=6.3 Hz, *J*= 2.0 Hz, 1H, ArH), 5.03 (s, 2H, NC$\underline{H}_2$Ph). Spectral data is consistent with those found in literature.[89]

2.8.7.3 Synthesis of 5-Chloro-3-diazo-2-oxindole (62D)



Prepared according to **General Procedure C** starting from 5-chloro-3-tosylhydrazono-2-oxindole (874 mg) to afford **62D** as an orange solid (392 mg, 81% yield) after column chromatography (40% EtOAc in hexanes). **R_f**: 0.13 (30% EtOAc in hexanes, UV Active); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 10.72 (br s, 1H, NH), 7.52 (d, *J*=1.9 Hz, 1H, ArH), 7.10 (dd, *J*=8.3 Hz, *J*=2.0 Hz, 1H, ArH), 6.87 (d, *J*=8.3 Hz, 1H, ArH). Spectral data is consistent with those found in literature.[62]

2.8.7.4 Synthesis of 5-Fluoro-3-diazo-2-oxindole (62E)

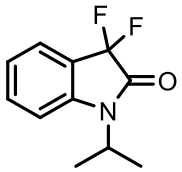


Prepared according to **General Procedure C** starting from 5-fluoro-3-tosylhydrazono-2-oxindole (833 mg) to afford **62E** as a red solid (350 mg, 79% yield) after column chromatography (40% EtOAc in hexanes). **Rf**: 0.13 (30% EtOAc in hexanes, UV Active); ^{1}**H NMR** (300 MHz, DMSO-d_6) δ 10.60 (br s, 1H, NH), 7.35 (dd, *J*=8.8 Hz, *J*=2.2 Hz, 1H, ArH), 6.95-6.82 (m, 2H, ArH). Spectral data is consistent with those found in literature.[62]

2.8.8 General Procedure D: Synthesis of 3,3-Difluoro-2-oxindoles (74)

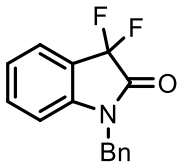
(Difluoroiodo)toluene (60 mg, 0.23 mmol, 1.1 equiv) was dissolved in PhCl (1.1 mL, 0.1 M) in a PFA vial equipped with magnetic stirring at room temperature. The reaction vial was immersed in an oil bath preheated to 110 °C and stirred while BF_3•OEt_2 in CH_2Cl_2 (10% (v/v) solution, 13.0 µL, 10 mol%) was immediately added in one portion. To this, a solution of the corresponding derivative of 3-diazo-2-oxindole (0.21 mmol, 1.0 equiv) dissolved in PhCl (1.0 mL) was added dropwise over 7.5 minutes via a syringe pump and the reaction mixture was stirred for an additional 30 minutes after which time TLC analysis showed consumption of starting material. The reaction mixture was cooled to room temperature and loaded directly onto a flash chromatography column and purified (hexanes (to flush out chlorobenzene), followed by 10% EtOAc, then 20% EtOAc).

2.8.8.1 Synthesis of *N*-Isopropyl-3,3-difluoro-2-oxindole (74B)



Prepared according to **General Procedure D** starting from *N*-isopropyl-3-diazo-2-oxindole (42 mg) to afford **74B** as a red solid (20 mg, 45% yield) after column chromatography. $\mathbf{R_f}$: 0.42 (20% EtOAc in hexanes, UV Active); ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.55 (dd, *J*=7.5 Hz, *J*=1.9 Hz, 1H, ArH), 7.46 (ddd, *J*=7.9 Hz, *J*=7.9 Hz, *J*=1.5 Hz, 1H, ArH), 7.15 (dd, *J*=7.6 Hz, *J*=7.6 Hz, 1H, ArH), 7.02 (d, *J*=8.2 Hz, 1H, ArH), 4.51 (septet, *J*=7.0 Hz, 1H, NC<u>H</u>$(CH_3)_2$), 1.50 (d, *J*=7.1 Hz, 6H, NCH(C<u>H</u>$_3)_2$); ^{19}**F NMR** (282 MHz, $CDCl_3$) δ -112.66. Spectral data is consistent with those found in literature.[76]

2.8.8.2 Synthesis of *N*-Benzyl-3,3-difluoro-2-oxindole (74C)

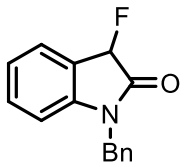


Prepared according to **General Procedure D** starting from *N*-benzyl-3-diazo-2-oxindole (52 mg) to afford **74C** as a red solid (25 mg, 45% yield) after column chromatography. $\mathbf{R_f}$: 0.35 (20% EtOAc in hexanes, UV Active); ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.55 (d, *J*=7.5 Hz, 1H, ArH), 7.40-7.26 (m, 6H, ArH), 7.14 (dd, *J*=7.7 Hz, *J*=7.7 Hz, 1H, ArH), 6.77 (d, *J*=8.1 Hz, 1H, ArH), 4.90 (s, 2H, NC<u>H</u>$_2$Ph); ^{19}**F NMR** (282 MHz, $CDCl_3$) δ -112.01. Spectral data is consistent with those found in literature.[76]

Alternatively, **74C** can be synthesized from *N*-Benzyl-3,3-(ethylenedithio)oxindole using the following procedure:

(Difluoroiodo)toluene (86 mg, 0.33 mmol, 2.0 equiv) was dissolved in PhCl (0.5 mL, 0.1 M) in a PFA vial equipped with magnetic stirring at room temperature. The reaction vial was immersed in an oil bath preheated to 110 °C and stirred while BF_3•OEt_2 in CH_2Cl_2 (10% (v/v) solution, 10 µL, 5.0 mol%) was immediately added in one portion. To this, a solution of *N*-Benzyl-3,3-(ethylenedithio)-2-oxindole (50 mg, 0.16 mmol, 1.0 equiv) dissolved in PhCl (1.0 mL) was added dropwise over 7.5 minutes via a syringe pump and the reaction mixture was stirred for an additional hour after which time TLC analysis showed consumption of starting material. The reaction mixture was cooled to room temperature and loaded directly onto a flash chromatography column and purified (hexanes (to flush out chlorobenzene), followed by 20% EtOAc) to afford **74C** as a red solid (24 mg, 58%).

2.8.9 Synthesis of *N*-Benzyl-3-fluoro-2-oxindole (82C)



(Difluoroiodo)toluene (102 mg, 0.40 mmol, 2.0 equiv) was dissolved in *o*-dichlorobenzene (1.75 mL) in a PFA vial equipped with magnetic stirring at room temperature. TiF_3 (5 mg, 0.05 mol, 25 mol%) was added in one portion and the reaction vial was immersed in an oil bath preheated to 130 °C. To this, a solution of *N*-Benzyl-3-hydrazono-2-oxindole (50 mg, 0.20 mmol, 1.0 equiv) dissolved in *o*-dichlorobenzene (1.25 mL) was added dropwise over 7.5 minutes via a syringe pump and the reaction was stirred for an additional 30 minutes after which time TLC analysis

showed complete consumption of starting material. The reaction mixture was cooled to room temperature and loaded directly onto a flash chromatography column and purified (hexanes (to flush out chlorobenzene), followed by 5% EtOAc in hexanes, 10% EtOAc in hexanes, then 20% EtOAc in hexanes) to afford **82C** as a white solid (10 mg, 21% yield). **R_f**: 0.60 (20% EtOAc in hexanes, UV Active); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 (d, *J*=7.3 Hz, 1H, ArH), 7.33 (m, 6H, ArH), 7.08 (dd, *J*=7.6 Hz, *J*=7.6 Hz, 1H, ArH), 6.72 (d, *J*=8.2 Hz, 1H, ArH), 5.75 (d, *J*=51.0 Hz, 1H, C(=O)CHF), 4.91 (d, *J*=15.7 Hz, 1H, N$\underline{C}H_2$Ph), 4.84 (d, *J*=15.7 Hz, 1H, NC$\underline{H}_2$Ph); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -192.84. Spectral data is consistent with those found in literature.[90]

Chapter 3: Synthesis of Aryldifluoroacetamides Using TolIF$_2$

3.1 Background

The aryldifluoroacetamide structural motif has been found in specific studies regarding enzyme inhibition. Vinitsky *et al*. incorporated aryldifluoroacetamides in their studies concerning the inhibition of binding protein FKBP12 (Figure 3.1).[91] Compounds that have been reported to be effective FKBP12 ligands are α-ketoamides due to the hydrogen bonding between the ketone carbonyl oxygen and nearby tyrosine hydroxyl groups. In their search to discover novel FKBP12 ligands, 2-aryl-2,2-difluoroacetamido-proline was shown to exhibit similar inhibitory activity compared to the corresponding α-ketoamide. Studies of x-ray structures suggested that the fluorine atoms participate in hydrogen bonding with the same tyrosine hydroxyl group.

The *gem*-difluoro motif is also desired in medicinal chemistry because the two fluorine atoms replace labile benzylic protons to make a more stable compound. This strategy is especially useful in enzyme inhibition research to increase the lifespan of biological molecules *in vivo.* For example, in their search for non-acidic EP_1 receptor antagonists, Winyard *et al*. improved the metabolic stability of a potential antagonist molecule by replacing the methylene protons with fluorine atoms (Figure 3.1).[92]

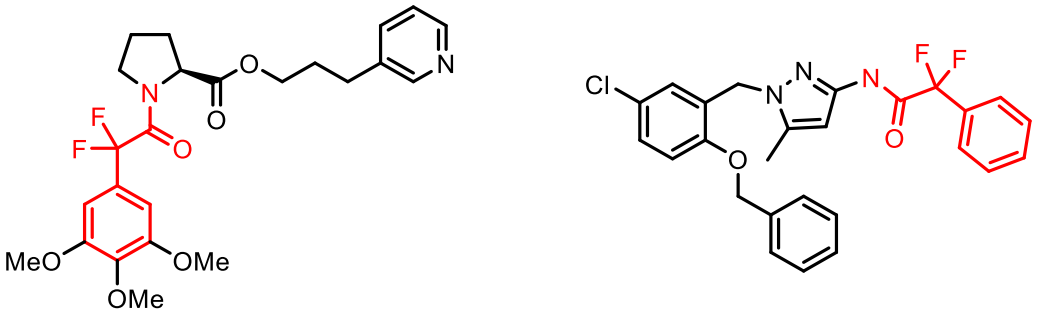
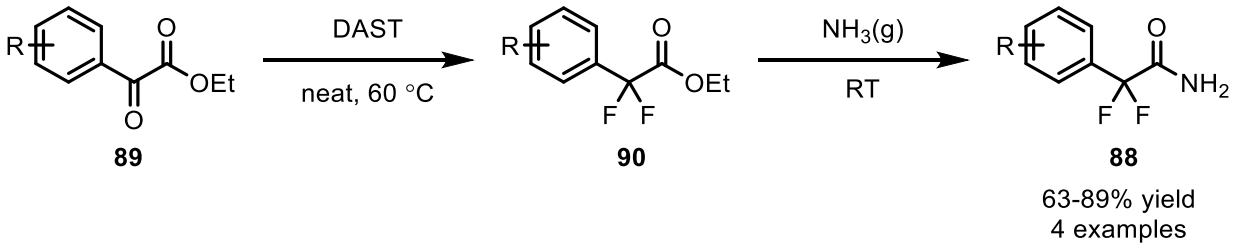


Figure 3.1: Biologically relevant molecules with the aryldifluoroacetamide motif

Aryldifluoroacetamides (**88**) are typically made through nucleophilic deoxyfluorination of the α-keto carbonyl analog. Middleton and Bingham first reported the synthesis of aryldifluoroacetamides by treating esters of α-oxoarylacetic acids (**89**) with DAST, followed by aminolysis of the resulting difluoro ester with ammonia gas (Scheme 3.1).[72] This protocol however, is dangerous because it employs a potentially explosive reagent.



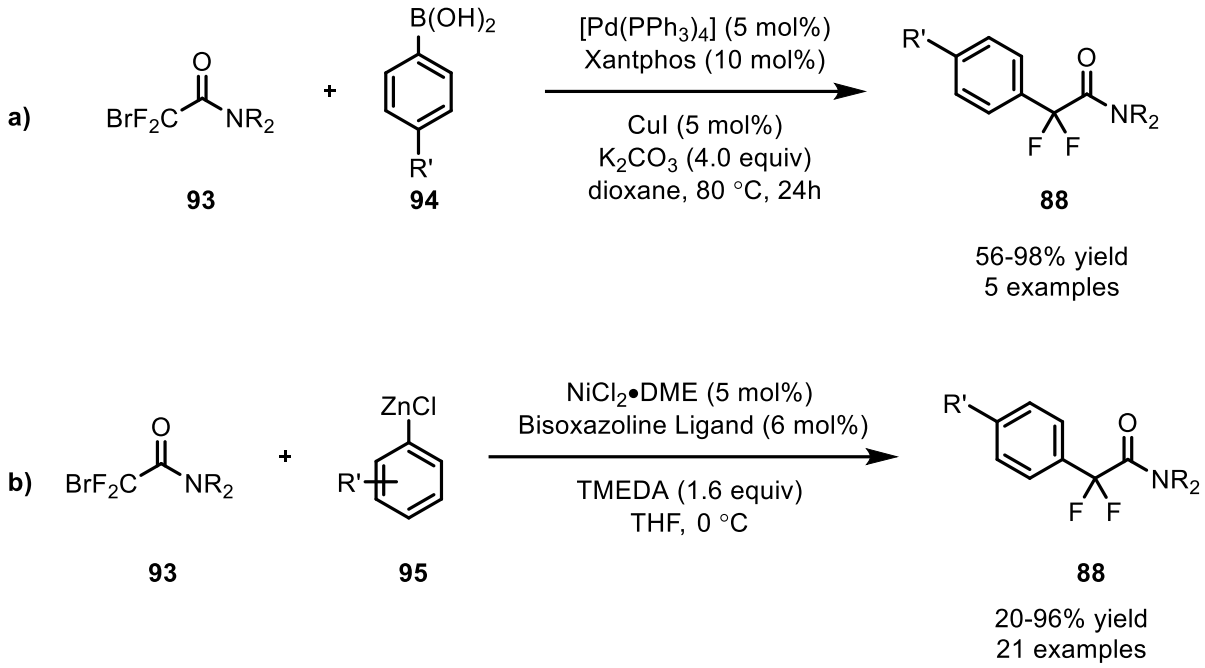
Scheme 3.1: Synthesis of aryldifluoroaceatamides compounds using DAST

In 2011 Lectka *et al*. reported a unique, tricomponent catalytic system for α,α-difluorination starting from acid chlorides **91** using Selectfluor® (Scheme 3.2).[93] The polycatalytic mixture includes the Lewis acid tin(II) triflate, pyridine, to be used as a catalytic nucleophile, and potassium tetrakis-(pentafluorophenyl)borate (KBARF) as an ionic phase transfer catalyst. This

reaction also provided access to other carboxylic acid derivatives by quenching with an appropriate nucleophile, such as aniline, for the synthesis of aryldifluoroacetamides. Unlike the previous protocol, this process produced the aryldifluoroacetamide through a one-pot procedure using a stable fluorinating reagent.

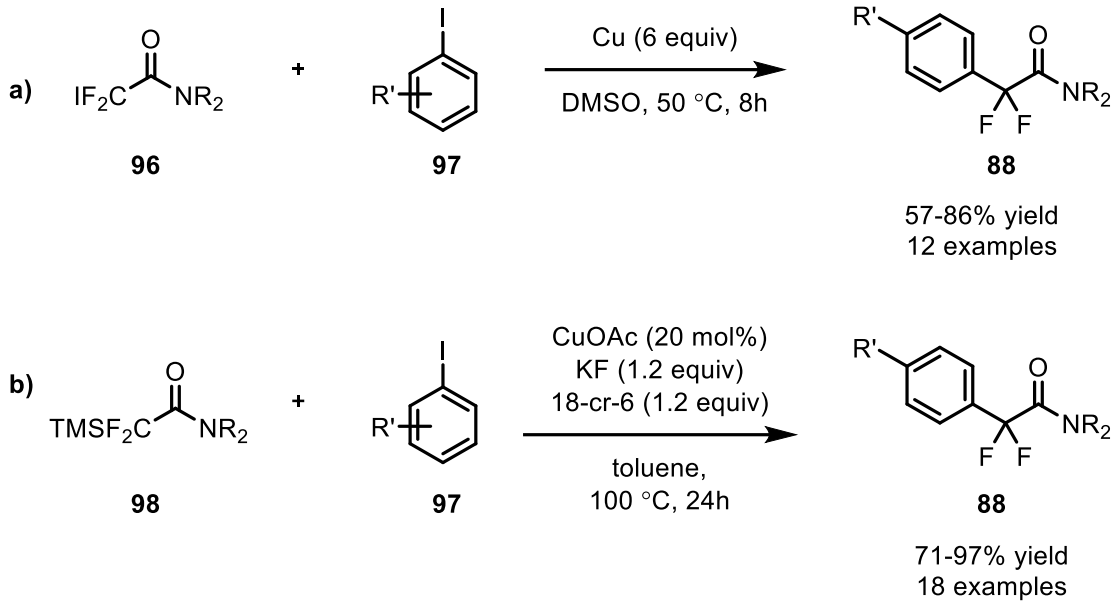
Scheme 3.2: Synthesis of aryldifluoroacetamides using Selectfluor®

Aside from using fluorinating agents, aryldifluoroacetamides were synthesized through cross coupling reactions between bromodifluoroacetamides (**93**) and aryl boronic acids (**94**). Zhang *et al*. reported the palladium catalyzed difluoroalkylation of aryl boronic acids with **93** using a combination of the bidentate ligand Xantphos, K_2CO_3 and dioxane (Scheme 3.3a).[94] Similarly, Ando *et al*. reported a nickel-catalyzed Negishi coupling of bromodifluoroacetamides with arylzinc reagents (**95**) using the ligand bisoxazoline and tetramethylethylenediamine (TMEDA) as an activator (Scheme 3.3b).[95] Yields of difluoroacetamide **88** ranged from good to excellent in both protocols, but they are limited by expensive metals, ligands, and the fact that the bromodifluoroacetamides are not readily available, and have to be synthesized beforehand from ethyl bromodifluoroacetate.



Scheme 3.3: Synthesis of aryldifluoroacetamides via palladium and nickel cross-coupling

Copper-catalyzed coupling was also employed in the synthesis of aryldifluoroacetamides. Notably, in 2010 Hu *et al*. reported the copper-mediated cross coupling between iodofluoroacetamides (**97**) and aryl iodides (**91**) (Scheme 3.4a).[77] Similarly, Arlow and Hartwig disclosed a coupling reaction between aryl iodides and the enolates of α-silyldifluoroacetamides (**98**).[96] While these reactions are improvements to previous protocols by utilizing cheap metals and circumventing the use of ligands, the difluoroacetamide coupling partners are not commercially available and have to be synthesized from chlorodifluoroacetate, or costly iododifluoroacetate.



Scheme 3.4 Synthesis of aryldifluoroacetamides using copper catalyzed cross-coupling

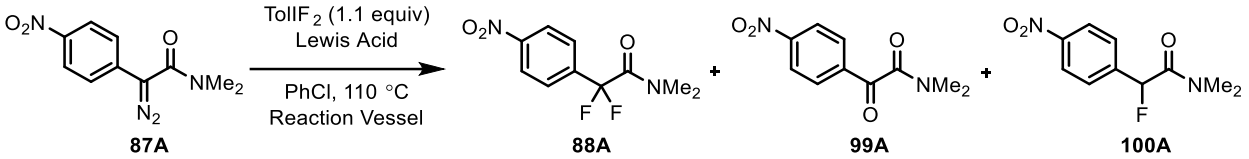
3.2 Proposal

While the syntheses of aryldifluoroacetamides are abundant in the literature, current methods employ hazardous fluorinating agents,[72] exhibit poor fluorine economy,[93] or require the use of expensive metals,[94] ligands,[94-95] or starting materials.[77] Additionally, a large number of these protocols start with fluorinated building blocks, and therefore syntheses are limited to ones that are commercially available. A metal-free, atom economical, and safe alternative to synthesizing aryldifluoroacetamides is envisioned using hypervalent iodine chemistry. Similar to the work previously discussed in Chapter 2, treating diazo derivatives of phenylacetamides with $TolIF_2$ is anticipated to furnish the desired *gem*-difluorinated product. Additionally, $TolIF_2$ has an advantage of being easy to synthesize from commercially available reagents, and would provide a cost-effective method of obtaining the aryldifluoroacetamide motif. Successful synthesis would open up an alternative route to assessing biological useful molecules containing the aryldifluoroacetamide motif, as well as developing an understanding the reaction between α-diazo

amides and $TolIF_2$. Moreover, the synthesis of aryldiazoacetamides presents an opportunity to study the unprecedented *gem*-dichlorination of acyclic α-diazo amides using $PhICl_2$, and other such reaction transformations using aryl-λ^3-iodanes.

3.3 Fluorination of *N*,*N*-Dimethyl-*p*-nitrophenyldiazoacetamide

The model substrate chosen for initial fluorination studies was the known *N*,*N*-dimethyl-*p*-nitrophenyldiazoacetamide (**87A**).[97] Studies began by mimicking the optimized reaction conditions used in the fluorination of phenyldiazoacetate compounds by Murphy *et al*.[81] Thus, the diazoacetamide was dissolved in PhCl in a borosilicate glass (bsg) vial and treated with 1.1 equivalents of $TolIF_2$ (Table 3.1, entry 1). Following this procedure furnished the aryldifluoroacetamide (**87A**) in 30% yield, as well as a mixture of glyoxylamide (**99A**), and arylfluoroacetamide (**100A**), as side products. Similar to the oxygenated side product that was formed in the synthesis of 3,3-difluoro-2-oxindole compounds, the source of the oxygen atom in the glyoxamide is unknown, but it may be due to trace amounts of H_2O in solution. Similarly, H_2O is also speculated to be the source of proton in the formation of **100A**. Because borosilicate glass has been known to activate $TolIF_2$,[81] the reaction was also conducted in a PFA vial in the absence of any other activators (Table 3.1, entry 2). Not surprisingly, fluorination reactivity was decreased significantly, but was restored in presence of ground borosilicate glass (Table 3.1, entry 3). Thus, it appeared an activator is necessary to enable *gem*-difluorination.

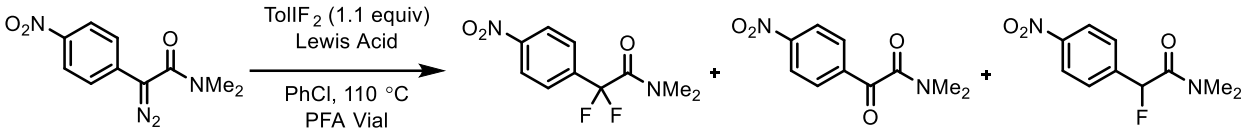


Entry	Reaction Vessel	Additive	Yield of **88A**
1	Bsg	-	30%
2	PFA	-	4%
3	PFA	Bsg (5 wt.-%)	25%

Both **99A** and **100A** were each isolated in 10-20 % yields

Table 3.1: Screening of reaction vessels in the fluorination of **87A**

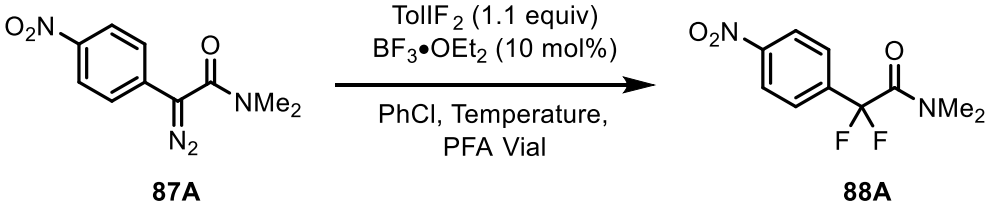
Screening of other activators like BF_3•OEt_2, TiF_4, and FeF_3 were conducted. These were chosen in particular because they performed well in the synthesis of 3,3-difluoro-2-oxindole compounds. Based on the fluorination of phenyldiazoacetate compounds, borosilicate glass (Table 3.1, entry 3) was anticipated to performed just as well or better than BF_3•OEt_2. However, BF_3•OEt_2 provided yields of **88A** equal to or higher than reactions performed with borosilicate glass (Table 3.2, entry 1-4), suggesting that the diazoacetamide **87A** required stronger activation than the diazoacetates. Increasing the loading of BF_3•OEt_2 improved the yield of the difluorinated product and an optimal amount was found at 10 mol% (Table 3.2, entry 2). Reactions conducted with TiF_4 produced yields similar to BF_3•OEt_2, but required a higher catalyst loading (Table 3.2, entries 5-6). On the other hand, FeF_3 performed poorer than borosilicate glass (Table 3.2, entry 7).



Entry	Lewis Acid	Yield of **82A**
1	BF_3•OEt_2 (1 mol%)	24%
2	BF_3•OEt_2 (10 mol%)	40%
3	BF_3•OEt_2 (20 mol%)	37%
4	BF_3•OEt_2 (50 mol%)	32%
5	TiF_4 (10 mol%)	30%
6	TiF_4 (25 mol%)	39%
7	FeF_3 (10 mol%)	10%

Compounds **99A** and **100A** were each recovered in 10-20% yield.
Table 3.2: Screening of Lewis acids in the fluorination of **88A**

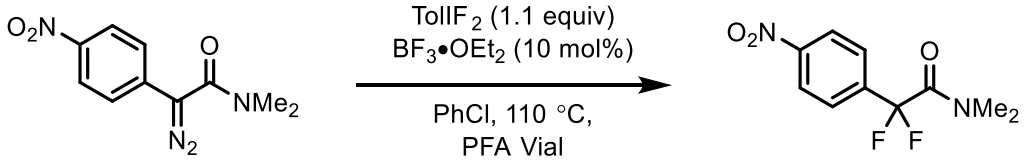
Optimization studies on the reaction temperature were conducted in hopes of improving the selectivity of the aryldifluoroacetamide **88A** over side products **99A** and **100A**. Similar to the fluorination of oxindole compounds, lower temperatures led to no reaction between the diazoacetamide and $TolIF_2$ (Table 3.3, entry 1-3). Conducting the reaction at 80 °C produced low yields of **88A**, and improved when heated to 110 °C and 125 °C (Table 3.3, entries 4-5).



Entry	Temperature	Yield of **88A**
1	0	NR
2	RT	NR
3	40 °C	NR
4	80 °C	24%
5	110 °C	40%
6	125 °C	39%

NR= No reaction.
Table 3.3: Screening of reaction temperatures in the fluorination of **87A**

Precedent for a dropwise addition of the diazo substrate was discussed in Chapter 2. This strategy was previously employed to minimize dimerization of 3-diazo-2-oxindole compounds and led to an increase in the yields of the 3,3-difluoro-2-oxindole products. Although no dimerization was observed in the fluorination of **87A**, performing a dropwise addition of the diazo amide unexpectedly led to an increase in the aryldifluoroacetamide yield with simultaneous decrease in the formation of the glyoxamide and monofluorinated side products. A possible explanation for this observation is that diazo **87A** decomposes in solution and the oxygen amide becomes the ketone oxygen in the glyoxamide. It is believed that by decreasing the concentration of **87A** in solution, there is a smaller probability for two aryldiazoacetamide molecules to collide with one another and form the oxygenated side product. Pleased by these results, a series of optimization experiments were conducted on the dropwise addition by varying the rate of addition.



87A **88A**

Entry	Dropwise Time (mins)	$TolIF_2$ Equiv	Yield of **88A**
1	5	1.1	56
2	7.5	1.1	63
3	15	1.1	52
4	30	1.1	43
5	7.5	1.25	69
6	7.5	1.5	65
7	7.5	2.0	64

Glyoxamide and monofluorinated side products were each isolated in 5-10% yield.
Table 3.4: Screening of other reaction conditions in the fluorination of **87A**

Performing a dropwise addition over 5 minutes produced the arylldifluoroacetamide in 56% yield, while adjusting to 7.5 minutes led to a slight increase in yield (Table 3.4, entries 1-2). When

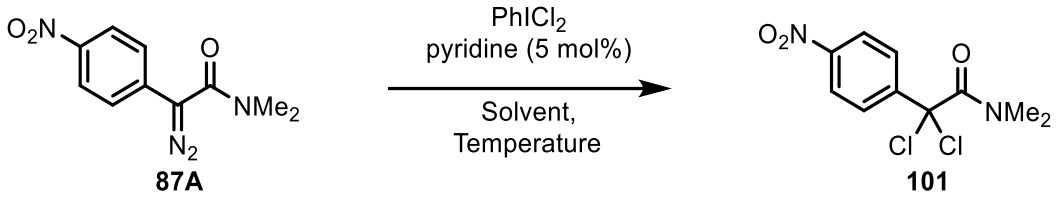
the addition was conducted over a longer period, a decrease in the yield was observed, possibly due to overexposure of $TolIF_2$ to high heat, leading to its decomposition (Table 3.4, entries 3-4). To combat possible decomposition of $TolIF_2$, the reagent loading was modified and an improvement was observed when 1.25 equivalents were used (Table 3.4, entry 5). On the other hand, increasing loading beyond 1.25 equivalents did not have a significant impact on the yield of product **88A** (Table 3.4, entries 6-7).

In brief, a protocol to accessing aryldifluoroacetamide **88A** was achieved by treating aryldiazoacetamide **87A** with $TolIF_2$ through a dropwise addition of the diazo substrate, with activation of the iodane by BF_3•OEt_2. The optimized protocol furnished **88A** in 69% yield (Table 3.4, entry 5), which is a vast improvement to the synthesis of 3,3-difluoro-2-oxindole compounds that were furnished in roughly 45% yields. A possible explanation for this difference is that electron-rich systems exhibit poor compatibility with BF_3•OEt_2, leading to diminished yield of the *gem*-difluorinated product. The nitrogen atom of the oxindole system could donate electrons into the arene. On the other hand, the acyclic α-diazo amide **87A** contains an electron withdrawing group on the phenyl ring, and the nitrogen atom is no longer conjugated to the arene.

3.4 Chlorination of *N*,*N*-Dimethyl-*p*-nitrophenyldiazoacetamide

Having diazoacetamide **87A** available on hand provided an opportunity to understand the reactivity between acyclic α-diazo amides with other aryl-λ^3-iodanes. *Gem*-Dichlorination using $PhICl_2$ was a logical choice given its extensive use as a chlorinating reagent of other α-diazo carbonyl compounds.[56-57] This research was conducted by Iris Wang under supervision.

The chlorination studies were initiated by mimicking the same optimized reaction conditions used to synthesize *gem*-dichlorinated species from phenyldiazoacetate compounds.[56] That is, the diazo substrate **87A** was dissolved in CH_2Cl_2 and treated with $PhICl_2$ at room temperature with pyridine. Doing so produced the corresponding *gem*-dichlorinated product (**101**) in moderate yields (Table 3.5, entry 1). It was not a surprise that the chlorination of **87A** proceeded under milder reaction conditions than the fluorination counterpart, since a similar trend was observed with phenyldiazoacetate compounds.[56] Heating the reaction to 40 °C produced similar yields (Table 3.5, entry 2). Screening of other chlorinated solvents, as well as varying the reaction temperature led to a decrease in yield of **101** (Table 3.5, entries 3-6). An improvement in yields of **101** was observed when the loading of $PhICl_2$ was increased to 1.5 equivalents, with 2.0 equivalents producing near quantitative amount of the phenyldichloroacetamide (Table 3.5, entries 7-8). This was a surprising observation since previous chlorination studies of α-diazo carbonyl compounds required only 1 equivalent of $PhICl_2$ for efficient synthesis of the *gem*-dichlorinated product.[56-57,62] The results suggest that each $PhICl_2$ molecule is only capable of transferring one of its chlorine ligands; however, this is an unlikely scenario because no other species is present in solution that could reduce $PhICl_2$. A more likely explanation is that a higher concentration of $PhICl_2$ is necessary to furnish **101** in high yields.



Entry	Solvent	Temperature	$PhICl_2$ Equiv	Yield of **101**
1	DCM	RT	1.1	53%
2	DCM	reflux	1.1	57%
3	DCE	40	1.1	46%
4	DCE	reflux	1.1	58%
5	PhCl	84	1.1	49%
6	PhCl	130	1.1	44%
7	DCM	reflux	1.5	72%
8	DCM	reflux	2.0	93%

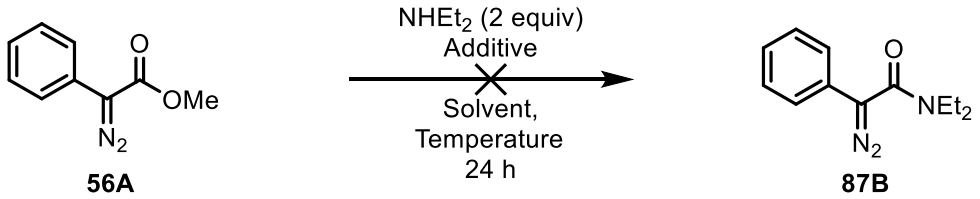
Table 3.5: Screening of reaction conditions in the chlorination of **87A**

Overall, the synthesis of **101** was achieved in excellent yields by treating the corresponding diazo compound with $PhICl_2$. A major disadvantage of this protocol is the requirement of using excess loading of $PhICl_2$ to produce excellent yields of the *gem*-dichlorinated product. Future work for this project includes application of the optimized reaction conditions to other phenyldiazoacetamide derivatives, once they have been synthesized.

3.5 Synthesis and Fluorination of Other Phenyldiazoacetamides

After establishing optimized reaction conditions for the *gem*-difluorination of diazo amide **87A**, efforts were shifted towards synthesizing other acyclic α-diazo amides to be used in further fluorination studies. In particular, phenyldiazoacetamides without substituents on the phenyl ring, such as **87B**, were desired to test the optimized *gem*-difluorination reactions on electron neutral systems. An approach to constructing other phenyldiazoacetamides was envisioned through an aminolysis reaction starting from methyl phenyldiazoacetate. Methyl phenyldiazoacetate (**56A**)

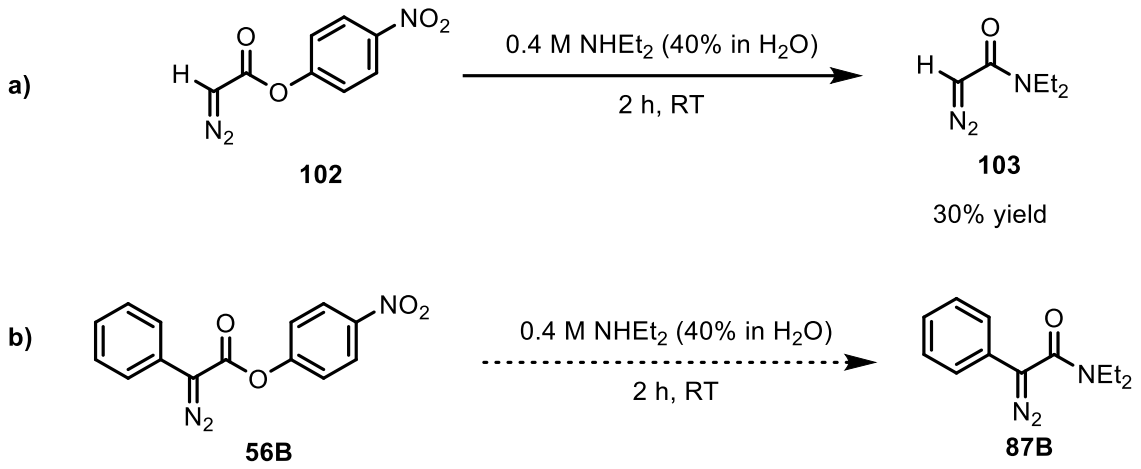
was first subjected to diethylamine at room temperature in an attempt to produce the corresponding diethylamide; unfortunately, no reaction was observed (Table 3.6, entry 1). Similarly, increasing the temperature led to no reaction (Table 3.6, entries 2-3). Typical aminolysis of esters often require the addition of a nucleophilic catalyst,[98] alkali metal catalyst such as $MgBr_2$,[99] or the use of dialkyllithium amides.[100] However, the addition of DMAP and $MgBr_2$ led to no reaction (Table 3.6, entries 4-7), whereas reactions conducted with *n*-BuLi led to decomposition of the diazo substrate (Table 3.6, entry 8). It is believed that the difficulty of effecting the aminolysis of methyl phenyldiazoacetate is attributed to the α-diazo substituent that can donate electron density and deactivate the carbonyl group.



Entry	Solvent	Temperature	Additive
1	DCM	RT	None
2	DCM	reflux	None
3	DCE	reflux	None
4	DCM	RT	DMAP (0.1 equiv)
5	DCE	reflux	DMAP (0.1 equiv)
6	THF	RT	$MgBr_2$ (0.5 equiv)
7	THF	reflux	$MgBr_2$ (0.5 equiv)
8[a]	THF	-41 °C	*n*-BuLi (2 equiv)

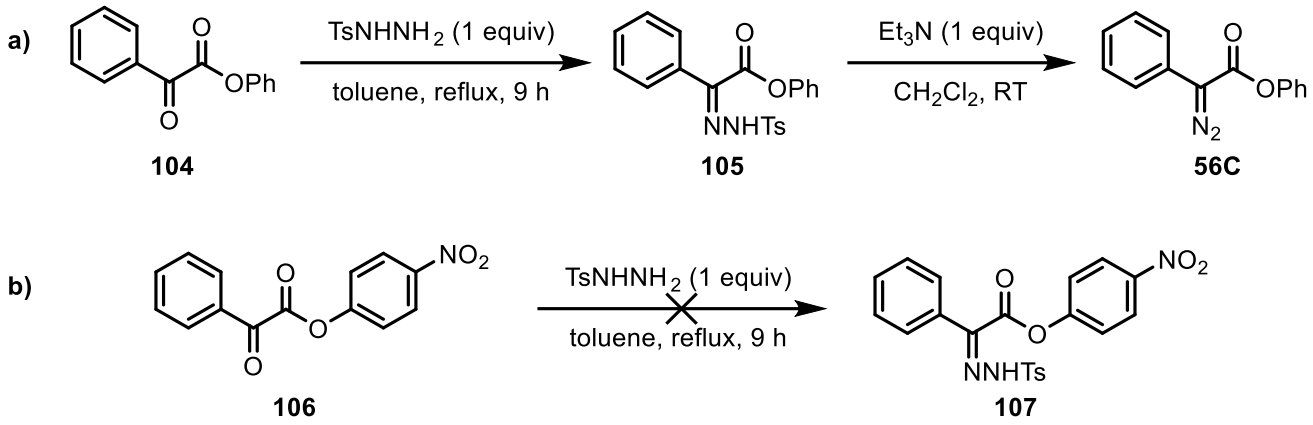
Unless otherwise stated, no reaction between **56A** and diethylamine was observed.
[a]Decomposition of **56A** was observed.
Table 3.6: Attempted synthesis of phenyldiazoacetamide compounds through aminolysis

An alternative approach to synthesizing other phenyldiazoacetamide compounds was inspired by the work by Rando, where *N*,*N*-diethyldiazoacetamide (**96**) was produced through the aminolysis of *p*-nitrophenyl diazoacetate (**95**) with diethylamine at room temperature (Scheme 3.5a).[101]



Scheme 3.5: Rando's synthesis of diazoacetamide **103** and proposed synthsis of **87B**

Modifying Rando's protocol could produce the phenyldiazoacetamide through the aminoloysis of (*p*-nitrophenyl) phenyldiazoacetate (**56B**) with diethylamine (Scheme 3.5b). An initial approach to synthesize ester **56B** was anticipated through a diazo transfer between *p*-ABSA and (*p*-nitrophenyl) phenylacetate, however, no reaction was observed. An alternative method was inspired by Zhou and coworkers where they were able to synthesize phenyl diazophenylacetate compounds (**56C**) from their corresponding tosylhydrazone derivatives (**105**) (Scheme 3.6a).[102]

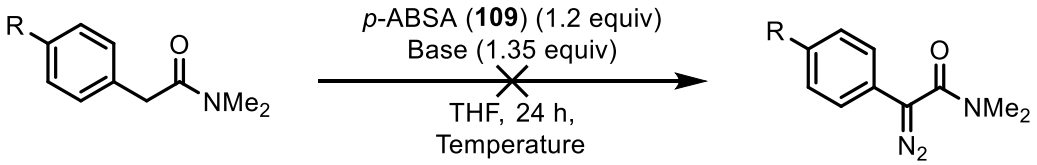


Scheme 3.6 Synthesis of phenyl phenyldiazoacetate compounds

Unfortunately, this strategy could not be pursued because the tosylhydrazone precursor (**107**) could not be made. Mimicking the same conditions that Zhou reported to synthesize the tosylhydrazone compound only led to the decomposition of the glyoxylate (**106**) (Scheme 3.6b). It is believed the *p*-nitro group on compound **106** made the carbonyl ester more electrophilic, by pulling electron density away from the ether oxygen. As a result, the ester is more susceptible to incoming nucleophilic attack, such as by hydrazine, leading to its decomposition. Due to the difficulty of synthesizing tosylhydrazone **107**, Rando's protocol was not further studied.

Another approach to synthesizing other phenyldiazoacetamide compounds was envisioned through a Regitz diazo transfer of amide **108** using *p*-ABSA (**109**). This strategy was previously used to construct diazoacetamide **87A**. Unfortunately, conducting the reaction with amide **108A** under the same conditions led to no reaction (Table 3.7, entry 1). It is postulated that an addition of an electron-withdrawing group on the arene would improve the acidity of the benzylic protons and form the necessary enolate for the diazo transfer reaction. Alternatively, a stronger base could be employ to affect the diazo transfer. However, no reaction was observed with a weakly electron

withdrawing bromine on the arene (**108B**) (Table 3.7, entry 2), and decomposition of **108A** was seen when a stronger base, such as NaOEt or *n*-BuLi, was used (Table 3.7, entries 3-4). It is believed that without a strong electron withdrawing group on the arene to minimize the negative charge on the α-carbon, the diazoacetamide is not stable and readily decomposed in solution.



108 **87B**

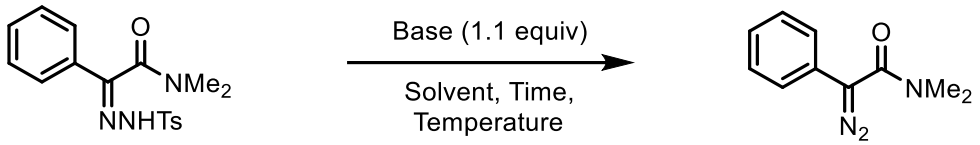
Entry	Substrate	R	Temperature	Base
1	**108C**	H	RT	DBU
2	**108B**	Br	RT	DBU
3	**108C**	H	RT	NaOEt
4	**108C**	H	-78 °C	*n*-BuLi

No reaction between amide **108** and *p*-ABSA was observed.

Table 3.7: Attempted synthesis of phenyldiazoacetamide compounds through a diazo transfer

Another strategy for synthesizing phenyldiazoacetamides was envisioned through a Bamford Stevens reaction by subjecting tosylhydrazone compounds to basic conditions. A screening of bases typically used in a Bamford Stevens reaction was conducted on tosylhydrazone **110** at room temperature over a course of several days, but overall it appeared as though no reaction was observed (Table 3.8, entries 1-7). Similarly, the reaction did not proceed when NaH was used at 60 °C (Table 3.8, entry 8). When *t*-BuOK or DBU were employed, a faint yellow spot on TLC characteristic of α-diazocarbonyl compounds appeared within 30 minutes, but disappeared once the tosylhydrazone was completely consumed (approximately 2 hours) (Table 3.8, entries 9-10). It is postulated that without the presence of an electron withdrawing substituent on the phenyl ring, the phenyldiazoacetamide is unstable to prolonged heating and decomposed in solution. Thus, isolation of this yellow spot was achieved by treating the tosylhydrazone **110** to DBU or *t*-BuOK

for 30 minutes at 60 °C before stopping and working up the reaction. Once isolated, the yellow spot was confirmed to be the desired *N*,*N*-dimethylphenylacetamide (**87C**) through NMR, IR and mass spectrometry analysis.



110 **87C**

Entry	Solvent	Temperature	Base	Yield
1	DCM	RT	Et_3N	NR
2	DCM	RT	NaOH	NR
3	DCM	RT	DBU	NR
4	THF	RT	Et_3N	NR
5	THF	RT	DBU	NR
6	MeOH	RT	KOH	NR
7	H_2O	RT	$NaHCO_3$	NR
8	Toluene	60 °C	NaH	NR
9	Toluene	60 °C	*t*-BuOK	4%
10	Toluene	60 °C	DBU	5%

NR=No reaction.

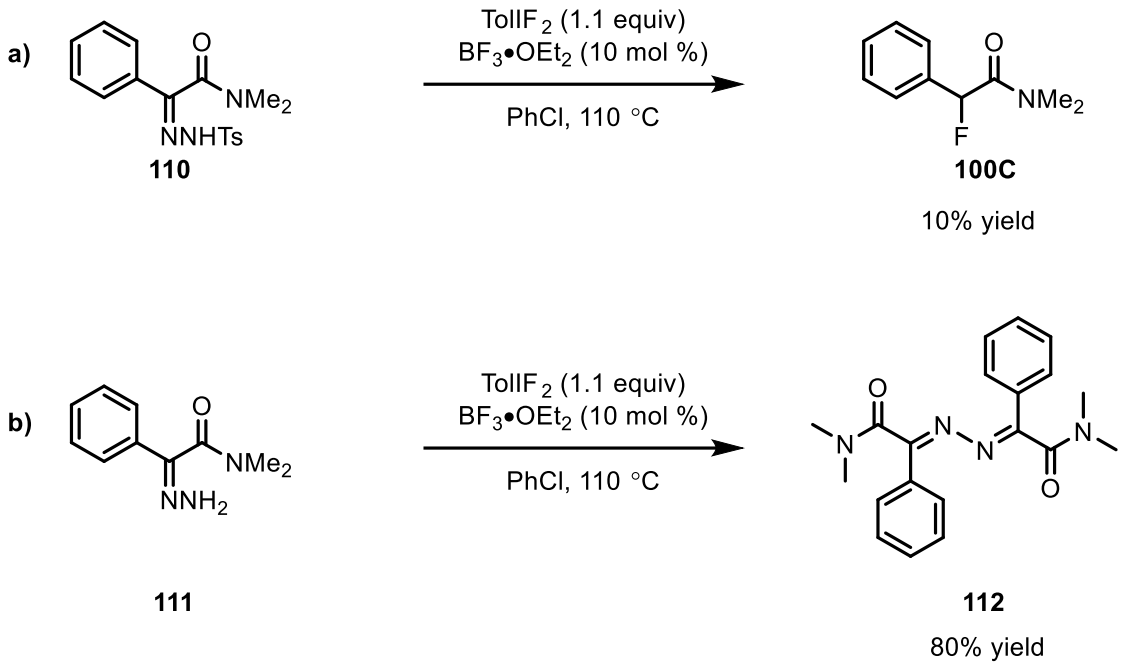
Table 3.8: Screening of reaction conditions for the conversion of **110** to **87C**

With aryldiazoacetamide **87C** finally in hand, studies towards the synthesis of aryldifluoroacetamides resumed. Disappointingly, treating phenyldiazoacetamide **87C** to the optimized conditions developed in the fluorination of *p*-nitrophenyldiazoacetamide **87A** previously discussed in this chapter produced no signals in the ^{19}F NMR corresponding to the *gem*-difluorinated species. Instead, only production of the monofluorinated and ketone products were observed in ^{1}H NMR.

The failed *gem*-difluorination of dimethyl phenyldiazoacetamide was surprising since the methyl phenyldiazoacetate studied by the Murphy group performed well in the fluorination studies.[81] It is postulated that the exchange of the ester with the amide dramatically altered

reactivity of the corresponding α-diazocarbonyl compound. The amide is unable to stabilize the α-diazo group as well as the acetate due to nitrogen's ability to donate electrons to the carbonyl system more readily than oxygen. As a result, the phenyldiazoacetamide is more reactive than the phenyldiazoacetate and may be more prone to side reactions, such as oxidation or hydrofluorination. This is especially true in the case of **87C** where there is no extra stabilization from an electron withdrawing group on the arene.

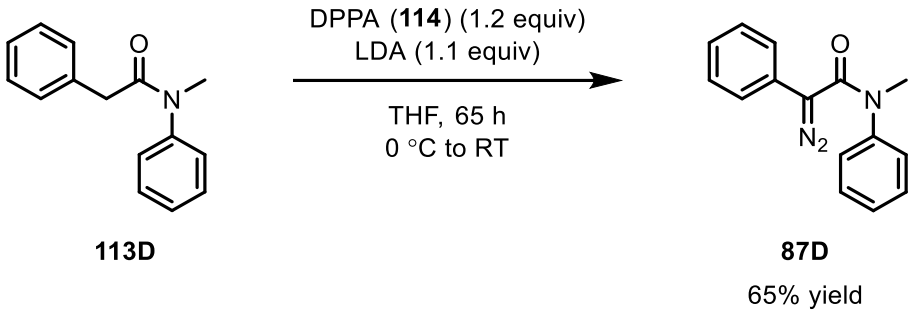
Since the synthesis of phenyldiazoacetamides appeared to be a difficult task, the fluorination reaction was attempted on the hydrazone and tosylhydrazone analogues. Similar to the synthesis of 3,3-difluoro-oxindole compounds, it was believed that treating the hydrazone and tosylhydrazone derivatives would furnish phenyldifluoroacetamides. The benefit of this approach is to circumvent the isolation of the diazo product. However, when tosylhydrazone **110** was treated with $TolIF_2$, only monofluorinated species (**100C**) was recovered (Scheme 3.7a), while the hydrazone derivative (**111**) dimerized and produced only azine (**112**) under the same reaction conditions (Scheme 3.7b).



Scheme 3.7: Attempted difluorination of compounds **110** and **111** using $TolIF_2$

It is unclear at this point if *N*,*N*-dimethylphenyldifluoroacetamide can be synthesized from the diazo, hydrazone, or tosylhydrazone derivatives. Due to its poor yields from the Bamford Stevens reaction, either another method of constructing **87C** or a new model substrate was necessary. Given the numerous methods that failed trying to synthesize **87C**, the latter was chosen.

In 1995, Heimgartner and coworkers presented the synthesis of *N*-methyl-*N*-phenyldiazoacetamide (**87D**) through a diazo transfer using diphenyl phosphorazidate (**114**) (DPPA) as the diazo source (Scheme 3.8). Unfortunately this protocol is limited to the synthesis of *N*-arylphenyldiazoacetamides since the reaction produced low yields of the corresponding diazo compound when *N*,*N*-dialkylamides were used. Given its known synthesis, *gem*-fluorination studies were continued on diazoacetamide **87D**.

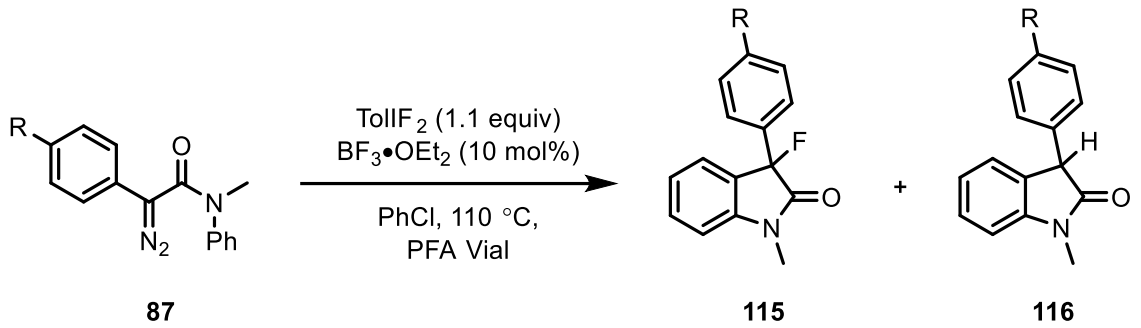


113D **87D**

65% yield

Scheme 3.8 Heimgartner's synthesis of *N*-methyl-*N*-phenylphenyldiazoacetamide

Intriguingly, subjecting diazo amide **87D** to the optimized reaction conditions established in the fluorination of *p*-nitrophenyldiazoacetamide produced a mixture of 3-fluoro- and 3-H-2-oxindole compounds (**115D** and **116D**) with no observed formation of the *gem*-difluorinated product (Table 3.9, entry 1). The 3-H-2-oxindole was anticipated as a side product because Heimgartner *et al*. reported its formation when heating **87D** under reduced pressure at 110 °C. On the other hand, the synthesis of 3-fluoro-2-oxindole **115D** was unexpected and suggested that a successive fluorination and intramolecular ring closure took place. It was postulated that the presence of an electron withdrawing group on the phenyl ring adjacent to the diazo carbon would tune reactivity and produce *gem*-difluorinated products, similar to the previously studied diazo amide **87A**. Subjecting the *N*-phenyl-*p*-nitrophenyldiazoacetamide **87E**, however, produced **115E** and **116E** with no observed formation of the *gem*-difluorinated product (Table 3.9, entry 2). From these studies, it appeared that the formation of the 3-fluoro-2-oxindole product is favoured over the *gem*-difluorination of *N*-phenyldiazoacetamides, presumably because the intramolecular ring closure is faster than the addition of a second fluoride ion.



87 **115** **116**

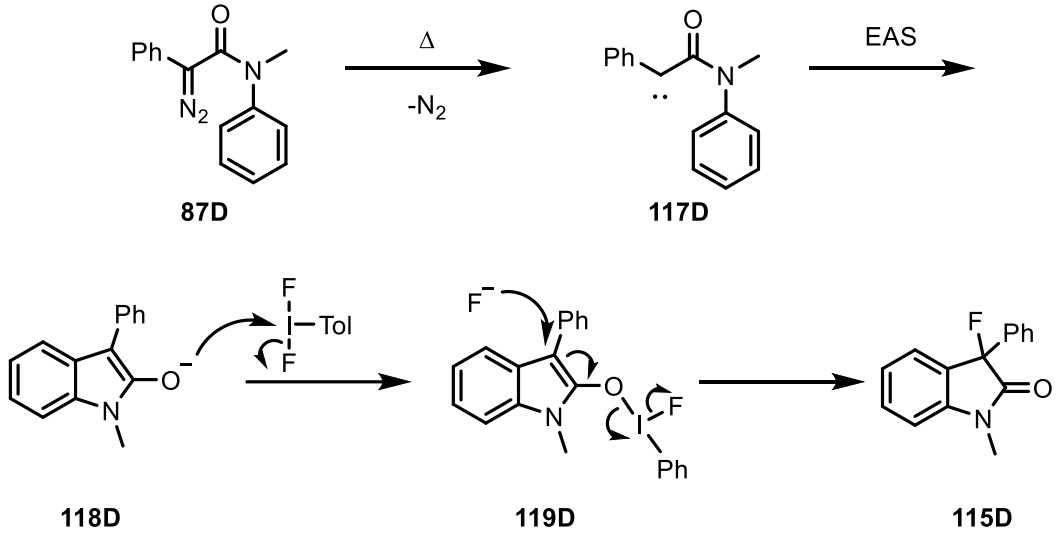
Entry	Substrate	R	Yield of **115**	Yield of **116**
1	**87D**	H	12%	26%
2	**87E**	NO_2	23%	16%

Table 3.9: Fluorination of *N*-methyl-*N*-phenylaryldifluoroacetamides

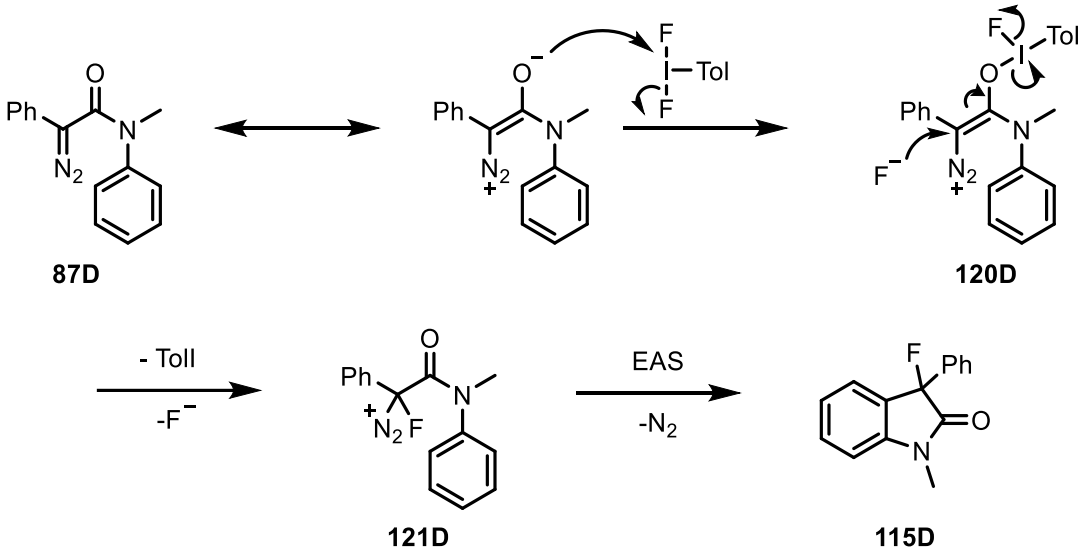
A proposed mechanism for the synthesis of the 3-fluoro-2-oxindole **115D** is outlined below (Scheme 3.9). Based on Heimgartner's report, the diazo amide **87D** could form a carbene in solution at 110 °C. The nitrogen atom of the amide can act as a strong ortho activator to promote electrophilic aromatic substitution (EAS) to produce enolate **118D**. This intermediate would then engage $TolIF_2$ to form an enolate-oxygen-bound hypervalent iodine intermediate **119D** with simultaneous production of a fluoride ion. This fluoride ion could perform a nucleophilic attack on the α-carbon of **119D** with concurrent elimination of iodotoluene and a second fluoride ion. The second fluoride ion could then displace the diazonium group to release N_2 and furnish 3-fluoro-2-oxindole product. This pathway would also explain the formation of 3-H-2-oxindole **116D** by C-H insertion of carbene **117D** onto the *ortho*-carbon of the *N*-phenyl group.

A second pathway similar to the *gem*-difluorination of 3-diazo-2-oxindole is proposed (Scheme 3.10). That is, an enolate-oxygen-bound hypervalent iodine intermediate **120D** is attacked by a fluoride ion to give compound **121D** and iodotoluene. Instead of being expelled by the second fluoride, N_2 is released via electrophilic aromatic substitution of the *ortho*-carbon on the *N*-phenyl group to furnish **115D**. Formation of a five-membered ring compound is believed to be the driving

force of the ring closure. In this reaction pathway, the formation of the 3-H-2-oxindole could arise from protonation of diazo **87D** followed by ring closure via EAS.



Scheme 3.9: Proposed mechanism on the synthesis of **115D** via EAS then fluorination



Scheme 3.10: Proposed mechanism on the synthesis of **107D** via fluorination then EAS

Regardless of mechanism, the 3-fluoro-2-oxindole compound suggests other aryl-λ^3-iodanes could be used instead of $TolIF_2$ to synthesize other 3-functionalized oxindole compounds. For example, $PhICl_2$ could be employed for the synthesis of 3-chloro-2-oxindole compounds.

3.6 Conclusions

In conclusion, an unprecedented route to synthesizing *N*,*N*-dimethyl-*p*-nitrophenyldifluoroacetamide from its diazo equivalent using the hypervalent iodine reagent, $TolIF_2$, was discussed. The key to this reaction was activation of the iodane with the Lewis acid BF_3•OEt_2 and dropwise addition of the diazo substrate. Similarly, the analogous chlorination reaction using $PhICl_2$ produced the *gem*-dichlorinated product in excellent yields under mild reaction conditions. Unfortunately, difficulty in synthesizing other aryldiazoacetamides prevented the substrate scope of these *gem*-dihalogenation reactions to be expanded upon. Strategies that have been attempted to synthesize other phenyldiazoacetamide compounds include aminolysis from phenyldiazoacetate compounds, Regitz diazo transfer, as well as the Bamford-Stevens reaction from the tosylhydrazone phenylacetamide. Finally, preliminary studies show that subjecting the known *N*-aryl-*N*-methylphenyldiazoacetamide to the optimized fluorination reaction conditions produced 3-phenyl-3-fluoro-2-oxindole compounds. Such transformation may potentially open a new route to accessing functionalized 3-aryloxindole compounds by using other aryl-λ^3-iodanes.

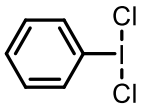
3.7 Experimental Procedures for Chapter 3

3.7.1 General Experimental Details

Reactions were carried out in oven-dried glassware under inert atmosphere unless otherwise stated. Fluorination reactions could be carried out under open atmosphere without adverse effects. PFA vials (4 mL, 14 x 52 mm) were purchased from Elemental Scientific. Chlorobenzene was dried over 4 Å molecule sieves and used without further purifications. Molecular sieves were pre-activated by heating under vacuum. Dichloromethane and tetrahydrofuran were dried and purified using a JC Meyer solvent purification system and were used without further purifications. All other solvents were purchased from Sigma-Aldrich and used without further purifications. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes. Thin layer chromatography was performed on glass plates pre-coated with 0.25 mm Kieselgel 60 F_{254} (Silicycle) and were visualized under UV light. Flash chromatography columns were packed with 230-400 mesh silica gel (Silicycle). Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrum Two with ATR Two. Proton NMR spectra (^{1}H NMR) were recorded at 300 MHz, and are reported (ppm) relative to the residual chloroform peak (7.26 ppm). Carbon NMR spectra (^{13}C NMR) were recorded at 125 or 75 MHz and are reported (ppm) relative to the centre line of the triplet from chloroform-d (77.16 ppm). Coupling constants (*J*) are reported in hertz (Hz). Fluorine NMR spectra (^{19}F NMR) were recorded at 282 MHz and are reported (ppm) relative to the peak of trifluoroacetic acid (-76.53 ppm). Phosphorus NMR spectra (^{31}P NMR) were recorded at 121 MHz and are reported (ppm) relative to the peak of 85% H_3PO_4 (0 ppm). Mass spectra were performed on a ThermoFisher Scientific Q-Exactive hybrid mass spectrometer using positive electrospray ionization (ESI). Accurate mass were recorded with a mass resolution of 70,000. ESI

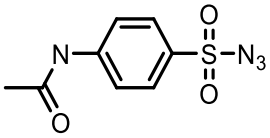
samples were infused at 5 µL/min in 1:1 CH_3OH/H_2O+0.1% formic acid. Melting points were determined on a Melt-Temp II.

3.7.2 Synthesis of (Dichloroiodo)benzene ($PhICl_2$) (51)



Iodobenzene (2.00 g, 9.80 mmol), was suspended in 5.25% sodium hypochlorite (No Name bleach, 60 mL, 0.16 M) in an oven-dried flask and was vigorously stirred at room temperature. Conc. HCl (20 mL) was then added dropwise via an addition funnel over 5 minutes. The yellow suspension was stirred for 5 minutes, then the suspension was filtered, washed, sequentially, with H_2O (200 mL), then petroleum ether (50 mL). The solid was spread thinly on a watch glass with a rubber spatula and air-dried in the dark overnight in a desiccator to furnish **51** as a pale yellow solid (2.51 g, 93% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (dd, *J*=8.5 Hz, 1.2 Hz, 2H, ArH), 7.59 (tt, *J*=6.5 Hz, *J*=1.0 Hz, 1H, ArH), 7.46 (dd, *J*=8.0 Hz, *J*= 7.5Hz, 2H, ArH). Spectral data is consistent with those found in literature.[103]

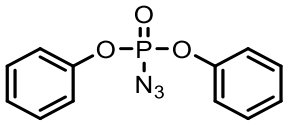
3.7.3 Synthesis of *p*-Acetamidobenzenesulfonyl Azide (*p*-ABSA) (109)



p-Acetamidobenzenesulfonyl chloride (117 g, 0.5 mol, 1.0 equiv) was dissolved in acetone (1 L, 0.5 M) in a flask equipped with magnetic stirring at room temperature. A solution of sodium azide (39 g, 0.60 mol, 1.2 equiv) in H_2O (300 mL) was added and the resulting mixture was left to stir

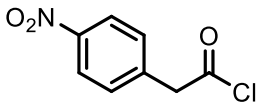
for 12 hours. Three 2L beakers equipped with magnetic stirrers were charged with 1.5 L each of H_2O. The reaction mixture was evenly divided into three portions and poured into the beakers with stirring at room temperature for one hour. The solution was filtered and then washed with cold water to furnish **109** as white crystals (83.2 g, 69% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 (d, *J*=8.9 Hz, 2H, ArH), 7.76 (d, *J*=8.9 Hz, 2H, ArH), 7.53 (br s, 1H, NH), 2.24 (s, 3H, CH_3). Spectral data is consistent with those found in literature.[104]

3.7.4 Synthesis of Diphenylphosphoryl Azide (DPPA) (114)



Sodium azide (0.58 g, 8.9 mmol, 1.2 equiv) was suspended in acetone (4.6 mL, 1.6 M) in an oven-dried flask equipped with magnetic stirring at 0 °C in an ice-water bath. Diphenylphosphoryl chloride (1.5 mL, 7.4 mmol, 1.0 equiv) was then added dropwise over a period of five minutes while the reaction temperature was maintained at 0 °C. The suspension was then warmed to room temperature and stirred for an additional 4 hours. The reaction mixture was then filtered and the filter cake was washed with cold acetone (30 mL). The filtrate was then concentrated to dryness *in vacuo* to produce **114** as a colorless oil (1.93 g, 93%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41-7.36 (m, 4H, ArH), 7.27-7.23 (m, 6H, ArH). **^{31}P NMR** (121 MHz, $CDCl_3$) δ -10.8 (s). Spectral data is consistent with those found in literature.[105]

3.7.5 Synthesis of (*p*-Nitrophenyl)acetyl Chloride (122)

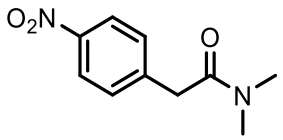


p-Nitrophenylacetic acid (2.00 g, 11.0 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (37 mL, 0.3 M) and DMF (2 drops, cat.) in an oven-dried flask equipped with magnetic stirring at 0 ºC in an ice-water bath. $SOCl_2$ (1.6 mL, 22.0 mmol, 2.0 equiv) was added dropwise over 5 minutes and the resulting solution was heated at reflux for 5 hours. The reaction mixture was cooled to room temperature and concentrated to dryness *in vacuo* to furnish **122** as a yellow oil (2.09 g, 95%) and used without further purifications. ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 8.25 (d, *J*=8.3 Hz, 2H, ArH), 7.47 (d, *J*=7.9 Hz, 2H, ArH), 4.27 (s, 2H, CH_2). Spectral data is consistent with those found in literature.[106]

3.7.6 General Procedure E: Amidation of Acid Chlorides

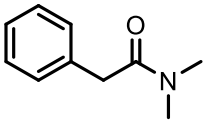
The corresponding acid chloride (10.5 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (35 mL, 0.3 M) in an oven-dried flask equipped with magnetic stirring at room temperature. To this was added the appropriate nucleophile (3.0 equiv) in one portion and the resulting mixture was stirred for an additional hour. The reaction mixture was then diluted with H_2O (40 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layer was washed, sequentially, with sat. NH_4Cl, water, and brine (40 mL each). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness *in vacuo*.

3.7.6.1 Synthesis of *N*,*N*-Dimethyl-*p*-nitrophenylacetamide (108A)



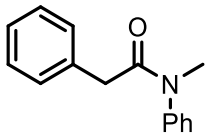
Prepared according to **General Procedure E** starting from *p*-nitrophenylacetyl chloride (**122**) (2.10 g) with the addition of 40 wt% in H_2O dimethylamine (4.2 mL, 33 mmol, 3.0 equiv) as the nucleophile to furnish **108A** as a yellow solid (2.07 g, 95%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.19 (d, *J*=8.7 Hz, 2H, ArH), 7.42 (d, *J*=8.8 Hz, 2H, ArH), 3.80 (s, 2H, CH_2), 3.05 (s, 3H, CH_3), 3.00 (s, 3H, CH_3). Spectral data is consistent with those found in literature.[107]

3.7.6.2 Synthesis of *N*,*N*-Dimethylphenylacetamide (108C)



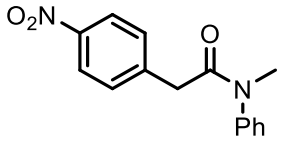
Prepared according to **General Procedure E** starting from phenylacetyl chloride (1.38 mL) with the addition of 40 wt% in H_2O dimethylamine (4.2 mL, 33 mmol, 3.0 equiv) as the nucleophile to furnish **108C** as a yellow oil (1.63 g, 95% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34-7.21 (m, 5H, ArH), 3.71 (s, 2H, CH_3), 3.00 (s, 3H, CH_3), 2.96 (s, 3H, CH_3). Spectral data is consistent with those found in literature.[108]

3.7.6.3 Synthesis of *N*-Methyl-*N*-phenylphenylacetamide (113D)



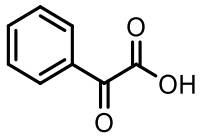
Prepared according to **General Procedure E** starting from phenylacetyl chloride (1.38 mL) with the addition of *N*-methylaniline (3.54 g, 33 mmol, 3.0 equiv) as the nucleophile to furnish **113D** as a yellow solid (2.20 g, 93% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43-7.32 (m, 3H, ArH), 7.25-7.03 (m, 7H, ArH), 3.46 (s, 2H, CH_2), 3.28 (s, 3H, CH_3). Spectral data is consistent with those found in literature.[109]

3.7.6.4 Synthesis of *N*-Methyl-*N*-phenyl-*p*-nitrophenylacetamide (113E)



Prepared according to **General Procedure E** starting from *p*-nitrophenylacetyl chloride (**122**) (2.10 g) with the addition of *N*-methylaniline (3.54 g, 33 mmol, 3.0 equiv) as the nucleophile to furnish **113E** as a yellow solid (2.30 g, 81% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42-7.31 (m, 3H, ArH), 7.25-7.02 (m, 7H, ArH), 3.47 (s, 2H, CH_2), 3.28 (s, 3H, CH_3). Spectral data is consistent with those found in literature.[110]

3.7.7 Synthesis of Phenylglyoxylic Acid (123)



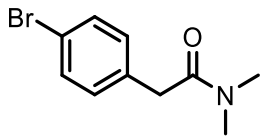
Acetophenone (1.20 g, 10 mmol, 1.0 equiv) was dissolved in pyridine (0.2 M, 5 mL) in a flame-dried flask equipped magnetic stirring at room temperature. SeO_2 (2.22 g, 20 mmol, 2.0 equiv) was added in one portion and the resulting solution was heated at reflux for 18 hours after which time TLC analysis showed consumption of starting material. The reaction mixture was cooled to room temperature, filtered, and the filtrate was concentrated to dryness *in vacuo*. Aqueous 3M NaOH was added to the residue until pH=9-10 and was subsequently washed with EtOAc (2 x 20 mL). Conc. HCl was added to the combined aqueous layer until pH=1-2 and was diluted with EtOAc (40 mL). The organic layer was washed, sequentially, with H_2O then brine (40 mL each). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness *in vacuo* to furnish **123** as a white solid (1.22 g, 81% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.40 (br s, 1H, OH), 8.29 (d, *J*=8.1 Hz, 2H, ArH), 7.69 (d, *J*=7.3 Hz, 1H, ArH), 7.51 (d, *J*=7.7 Hz, 2H, ArH). Spectral data is consistent with those found in literature.[111]

3.7.8 General Procedure F: Amidation and Esterification of Carboxylic Acids

The corresponding carboxylic acid (11 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (37 mL, 0.3 M) and DMF (2 drops, cat.) in an oven-dried flask equipped with magnetic stirring at 0 °C in an ice-water bath. $SOCl_2$ (1.6 mL, 22 mmol, 2.0 equiv) was added dropwise over 5 minutes and the resulting solution was heated at reflux for 5 hours. The reaction mixture was cooled to room

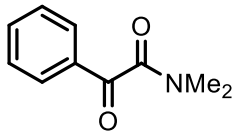
temperature and concentrated to dryness *in vacuo* to furnish the crude acid chloride. The crude acid chloride was then dissolved in CH_2Cl_2 (37 mL, 0.3 M) in an oven-dried flask equipped with magnetic stirring at room temperature. To this was added the appropriate nucleophile (3.0 equiv) in one portion and the resulting mixture was stirred for an additional hour. The reaction mixture was then diluted with H_2O (37 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layer was washed, sequentially, with sat. NH_4Cl, water (6 x), and brine (40 mL each). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness *in vacuo* to furnish generally yellow solids that were used without further purifications.

3.7.8.1 Synthesis of *N*,*N*-Dimethyl-*p*-bromophenylacetamide (108B)



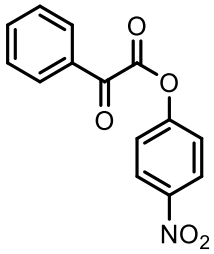
Prepared according to **General Procedure F** starting from *p*-bromophenylacetic acid (2.37 g) with the addition of 40 wt% in H_2O dimethylamine as the nucleophile to furnish **108B** as a light yellow solid (2.47 g, 93%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 (d, *J*=8.3 Hz, 2H, ArH), 7.13 (d, *J*=8.3 Hz, 2H, ArH), 3.66 (s, 2H, CH_2), 3.00 (s, 3H, CH_3), 2.96 (s, 3H, CH_3). Spectral data is consistent with those found in literature.[112]

3.7.8.2 Synthesis of *N,N*-Dimethylphenylglyoxylamide (124)



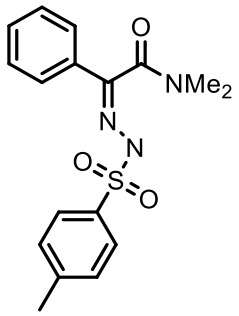
Prepared according to **General Procedure F** starting from phenylglyoxylic acid (**123**) (1.65 g) with the addition of 40 wt% H_2O dimethylamine as the nucleophile to furnish **124** as a yellow solid (1.75 g, 90% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95 (d, *J*=8.1 Hz, 2H, ArH), 7.64 (t, *J*=7.4 Hz, 1H, ArH), 7.50 (dd, *J*=7.7 Hz, *J*=7.7 Hz, 2H, ArH), 3.11 (s, 3H, CH_3), 2.96 (s, 3H, CH_3). Spectral data is consistent with those found in literature.[113]

3.7.8.3 Synthesis of *p*-Nitrophenylphenylglyoxylate (106)



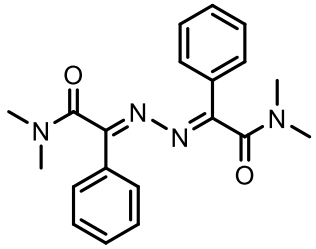
Prepared according to **General Procedure F** starting from phenylglyoxylic acid (1.65 g) with the addition of *p*-nitrophenol as the nucleophile to furnish **106** as an orange solid (2.47 g, 83% yield). **R_f**: 0.63 (20% EtOAc in hexanes, UV Active); **m.p.** 119-121 °C; **IR** (ATR) 3086, 1747, 1685, 1514, 1345, 1157 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.34 (d, *J*=8.8 Hz, 2H, ArH), 8.11 (d, *J*=7.6 Hz, 2H, ArH), 7.73 (t, *J*=7.2 Hz, 1H, ArH), 7.57 (dd, *J*=7.6 Hz, *J*=7.6 Hz, 2H, ArH), 7.48 (d, *J*=8.8 Hz, 2H, ArH). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 184.1 (Ph<u>C</u>(=O)C(=O)O), 160.5 (PhC(=O)<u>C</u>(=O)O), 154.6 (Ar), 146.1 (Ar), 135.8 (Ar), 132.1 (Ar), 130.4 (Ar), 129.3 (Ar), 125.6 (Ar), 122.4 (Ar); **HRMS** (ESI) calcd for $C_{14}H_{10}NO_5$ $(M+H)^+$ 272.05535; found 272.05530.

3.7.8.4 Synthesis of *N*,*N*-Dimethylphenyltosylhydrazonoacetamide (110)



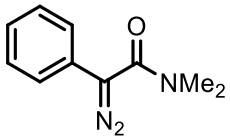
N,*N*-Dimethylphenylglyoxylamide (992mg, 5.6 mmol, 1.0 equiv) was dissolved in EtOH (20 mL, 0.3 M) in an oven-dried flask equipped with magnetic stirring at room temperature. *p*-Toluenesulfonyl hydrazide (1.15 g, 1.1 equiv) was added in one portion followed by conc. H_2SO_4 (1 drop, cat.). The resulting mixture was then stirred and heated at reflux for an additional 6 hours after which time TLC analysis showed consumption of starting material. After cooling the reaction mixture 0 °C in an ice-watch bath, any precipitate formed during this stage was isolated by suction filtration and washed with small quantities of cold ethanol to furnish **110** as a white solid (1.45 g, 75% yield). **R_f**: 0.23 (40% EtOAc in hexanes, UV Active); **m.p.** 169-171 °C; **IR** (ATR) 3051, 1629, 1597, 1495, 1343, 1172 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.14 (br s, 1H, NH), 7.87 (d, *J*=8.1 Hz, 2H, ArH), 7.57-7.54 (m, 2H, ArH), 7.39-7.35 (m, 3H, ArH), 7.29 (d, *J*=8.1 Hz, 2H, ArH), 3.12 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 2.39 (s, 3H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.9 (s, C=O), 150.4 (s, C=N), 144.1 (s, Ar) 135.2 (s, Ar), 132.0 (s, Ar), 130.6 (s, Ar), 129.5 (s, Ar), 128.9 (s, Ar), 128.0 (s, Ar), 126.2 (s, Ar), 37.2 (s, CH_3), 34.2 (s, CH_3), 21.5 (s, CH_3); **HRMS** (ESI) calcd for $C_{17}H_{20}N_3O_3S$ $(M+H)^+$ 346.12199; found 346.12193.

3.7.9 Synthesis of 2,2'-(hydrazine-1,2-diylidene)bis(*N*,*N*-dimethyl phenylacetamide) (112)



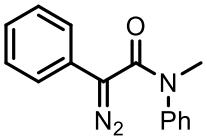
N,*N*-Dimethylphenylglyoxylamide (**124**) (911 mg, 2.6 mmol, 1.0 equiv) was dissolved in ethanol (13 mL, 0.2 M) in an oven dried flask equipped with magnetic stirring at room temperature. Hydrazine monohydrate, reagent grade 98% (260 µL, 5.2 mmol, 2.0 equiv) was added in one portion. The resulting mixture was then stirred and heated at reflux for an additional 12 hours after which time TLC analysis showed consumption of starting material. After cooling to 0 °C in an ice water bath, any precipitate formed during this stage was isolated by suction filtration and washed with small quantities of cold ethanol to furnish **112** as a yellow solid (546 mg, 63%). **Rf**: 0.38 (60% EtOAc in hexanes, UV Active); **m.p.** 228-330 °C; **IR** (ATR) 2929, 1645, 1598, 1499, 1445 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82 (d, *J*=7.2 Hz, 4H, ArH), 7.51-7.39 (m, 6H, ArH), 3.18 (s, 3H, CH_3), 2.90 (s, 6H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.1 (s), 163.4 (s), 131.2 (s, Ar), 130.9 (s, Ar), 128.0 (s, Ar), 127.1 (s, Ar), 36.4 (s, CH_3), 32.8 (s, CH_3); **HRMS** (ESI) calcd for $C_{20}H_{23}N_4O_2$ $(M+H)^+$ 351.18155; found 351.18152.

3.7.10 Synthesis of *N*,*N*-Dimethylphenyldiazoacetamide (87C)



N,*N*-Dimethylphenyltosylhydrazonoacetamide (**110**) (100 mg, 0.3 mmol, 1.0 equiv) was dissolved in toluene (3 mL, 0.1 M) in a flame-dried flask equipped with magnetic stirring at room temperature. DBU (48 µL, 0.33 mmol, 1.1 equiv) was added dropwise and the reaction temperature was heated to 60 °C for 30 min after which time TLC analysis showed partial consumption of starting material. The reaction mixture was concentrated to dryness *in vacuo* and the resulting crude oil was purified by column chromatography (SiO_2, deactivated with 3% triethylamine) (40% EtOAc in hexanes) to furnish **87C** as a red oil (3 mg, 5% yield). **R_f**: 0.31 (40% EtOAc in hexanes, UV Active); **IR** (ATR) 2926, 2055, 1623, 1597, 1496, 1448 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 (dd, *J*=7.6 Hz, *J*=7.6 Hz, 2H, ArH), 7.23-7.14 (m, 3H, ArH), 2.97 (s, 6H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.9 (s, C=O), 129.3 (s, Ar), 127.8 (s, Ar), 125.8 (s, Ar), 124.6 (s, Ar), 37.9 (s, CH_3), (C=N_2 not observed); **HRMS** (ESI) calcd for $C_{10}H_{12}NO$ $(M+H-N_2)^+$ 162.09134; found 162.09136.

3.7.11 Synthesis of *N*-Methyl-*N*-phenylphenyldiazoacetamide (87D)



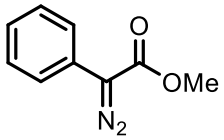
LDA was prepared by adding *n*-BuLi (2.9 mL, 4.6 mmol, 1.6 M in hexanes) to a solution of diisopropylamine (0.7 mL, 5 mmol) in dry THF (9 mL) in a flame-dried flask equipped with magnetic stirring at -78 °C in a dry ice-acetone bath. A solution of *N*-methyl-*N*-phenyl

phenylacetamide (**113**) (946 mg, 4.2 mmol, 1.0 equiv) in dry THF (8.4 mL, 0.5 M) was added dropwise and the reaction mixture was stirred for an additional hour. Diphenylphosphoryl azide (1.27 g, 4.6 mmol, 1.1 equiv) in dry THF (8 mL) was added dropwise and the resulting solution was stirred for 65 hours as the bath expired. After carefully quenching the reaction mixture with aq. NH_4Cl (1 M, 30 mL), the mixture was diluted with EtOAc (30 mL). The organic layer was washed, sequentially, with sat. NH_4Cl, H_2O, and brine (30 mL each). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness *in vacuo*. The crude oil was purified by column chromatography (SiO_2, deactivated with 3% triethylamine) (20% EtOAc in hexanes) to produce **87D** as an orange oil (350 mg, 33% yield). **R_f**: 0.29 (20% EtOAc in hexanes, UV Active); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35-7.08 (m, 10H, ArH), 3.41 (s, 3H, CH_3). Spectral data is consistent with those reported in literature.[114]

3.7.12 General Procedure G: Synthesis of α-Diazocarbonyl Compounds

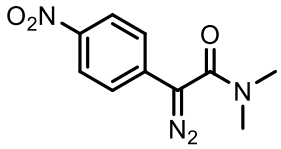
The corresponding carbonyl compound (13.3 mmol, 1.0 equiv), was dissolved in MeCN (40 mL, 0.33 M) in an oven-dried flask equipped with magnetic stirring at room temperature. *p*-Acetamidobenzenesulfonyl azide (3.51 g, 14.6 mmol, 1.1 equiv) was added in one portion and the reaction temperature was reduced to 0 °C in an ice-water bath. DBU (2.69 mL, 18.0 mmol, 1.4 equiv) was added dropwise and the resulting solution was stirred for 14 hours and allowed to warm to room temperature as the bath expired. The reaction mixture was concentrated to dryness *in vacuo*, dissolved in EtOAc and washed, sequentially, with sat. NH_4Cl (3 x), H_2O (3 x), and brine (40 mL each). The organic layer was then dried over $MgSO_4$, filtered, and concentrated to dryness *in vacuo*. The resulting crude oil was purified by column chromatography.

3.7.12.1 Synthesis of Methyl Phenyldiazoacetate (56A)



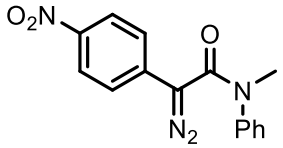
Prepared according to **General Procedure G** starting from methyl phenylacetate (2.00 g) to afford **56A** as a red oil (1.43 g, 60% yield) after column chromatography (5% EtOAc in hexanes). $\mathbf{R_f}$: 0.40 (5% EtOAc in hexanes, UV Active); ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.48 (d, *J*=7.5 Hz, 2H, ArH), 7.38 (dd, *J*=7.7 Hz, *J*=7.7 Hz, 2H, ArH), 7.19 (dd, *J*=7.3 Hz, *J*=7.3 Hz, 1H, ArH), 3.87 (s, 3H, CH_3). Spectral data is consistent with those found in literature.[115]

3.7.12.2 Synthesis of *N*,*N*-Dimethyl-*p*-nitrophenyldiazoacetamide (87A)



Prepared according to **General Procedure G** starting from *N*,*N*-dimethyl-*p*-nitrophenylacetamide (**108A**) (2.77 g) to afford **87A** as a red solid (1.55 g, 50% yield) after column chromatography (40% EtOAc in hexanes). $\mathbf{R_f}$: 0.28 (40% in EtOac in hexanes, UV Active); ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 8.22 (d, *J*=8.8 Hz, 2H, ArH), 7.37 (d, *J*=8.8 Hz, 2H, ArH), 3.05 (s, 6H, CH_3). Spectral data is consistent with those found in literature.[97]

3.7.12.3 Synthesis of *N*-Methyl-*N*-phenyl-*p*-nitrophenyl diazoacetamide (87E)



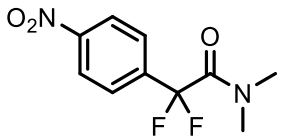
Prepared according to **General Procedure G** starting from *N*-methyl-*N*-phenyl-*p*-nitrophenylacetamide (**113E**) (3.60 g) to afford **87E** as an orange solid (1.06 g, 27% yield) after column chromatography (40% EtOAc in hexanes). **R_f**: 0.15 (20% EtOAc in hexanes, UV Active); **m.p.** 132-134 °C; **IR** (ATR) 2071, 1708, 1633, 1587, 1503, 1490, 1357 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.16 (d, *J*=9.1 Hz, 2H, ArH), 7.44-7.38 (m, 4H, ArH), 7.32-7.26 (m, 1H, ArH), 7.19 (d, *J*=7.7 Hz, 2H, ArH), 3.45 (s, 3H, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) 163.4 (s, C=O), 145.0 (s, Ar), 143.5 (s, Ar), 135.9 (s, Ar), 130.3 (s, Ar), 127.6 (s, Ar), 125.6 (s, Ar), 124.2 (s, Ar), 123.7 (s, Ar), 64.9 (s, $C=N_2$), 38.8 (s, CH_3); **HRMS** (ESI) calcd for $C_{15}H_{13}O_3N_2$ $(M+H-N_2)^+$ 269.09207; found 269.09204.

3.7.13 General Procedure H: Fluorination of Phenyldiazoacetamides

(Difluoroiodo)toluene (67 mg, 0.26 mmol, 1.25 equiv) was dissolved in PhCl (1.1 mL, 0.1 M) in a PFA vial equipped with magnetic stirring at room temperature. The reaction vial was immersed in an oil bath preheated to 110 °C and stirred while BF_3•OEt_2 in CH_2Cl_2 (10% (v/v) solution, 26.0 µL, 10.0 mol%) was immediately added in one portion. To this, a solution of the corresponding phenyldiazoacetamide derivative (0.21 mmol, 1.0 equiv) dissolved in PhCl (1.0 mL) was added dropwise over 7.5 minutes via a syringe pump and the reaction mixture was stirred for an additional 30 minutes after which time TLC analysis showed consumption of starting material. The reaction

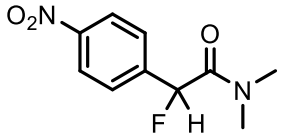
mixture was cooled to room temperature and loaded directly onto a flash chromatography column and purified (hexanes (to flush out chlorobenzene), followed by 20% EtOAc, then 40% EtOAc).

3.7.13.1 Synthesis of *N*,*N*-Dimethyl-*p*-nitrophenyldifluoroacetamide (88A)



Prepared according to **General Procedure H** starting from *N*,*N*-dimethyl-*p*-nitrophenyldiazoacetamide (**87A**) (49 mg) to afford **88A** as an orange solid (36 mg, 69% yield). **R_f**: 0.47 (40% EtOAc in hexanes, UV Active); **m.p.** 57-59 °C; **IR** (ATR) 3077, 2945, 1667, 1523, 1344, 1080 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.26 (d, *J*=8.7 Hz, 2H, ArH), 7.67 (d, *J*=8.8 Hz, 2H, ArH), 3.03 (s, 3H, CH_3), 2.96 (s, 3H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.2 (t, ^2J=30 Hz, C=O), 149.0 (s, Ar), 139.8 (t, ^2J=26 Hz, Ar), 126.8 (t, ^{3}J=6 Hz, Ar), 123.6 (s, Ar), 115.2 (t, ^1J=255 Hz, CF_2), 37.0 (s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -96.73. **HRMS** (ESI) calcd for $C_{10}H_{11}N_2O_3F_2$ $(M+H)^+$ 245.07323; found 227.07329.

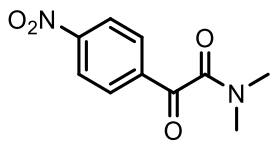
3.7.13.2 Synthesis of *N*,*N*-Dimethyl-*p*-nitrophenylfluoroacetamide (100A)



Recovered as a byproduct in the synthesis of compound **88A** as a white solid (7 mg, 15% yield). **R_f**: 0.18 (40% EtOAc in hexanes, UV Active); **m.p.** 108-110 °C; **IR** (ATR) 3047, 2939, 1646, 1519, 1343 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.26 (d, *J*=8.8 Hz, 2H, ArH), 7.63 (d, *J*=8.8 Hz,

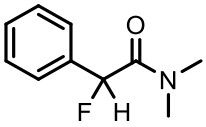
2H, ArH), 6.17 (d, *J*=47.9 Hz, 1H, CHF), 2.99 (s, 6H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.5 (d, ^2J=21 Hz, C=O), 148.4 (s, Ar), 141.5 (d, ^2J=20 Hz, Ar), 127.2 (d, ^3J=7 Hz, Ar), 124.1 (s, Ar), 90.1 (d, ^1J=188 Hz, CHF), 36.7 (d, ^4J=6 Hz, CH_3), 36.5 (s, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -179.28. **HRMS** (ESI) calcd for $C_{10}H_{12}O_3N_2F$ $(M+H)^+$ 227.08265; found 227.08264.

3.7.13.3 Synthesis of *N*,*N*-Dimethyl-*p*-nitrophenylglyoxylamide (99A)



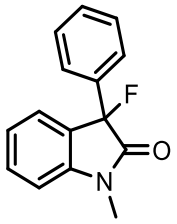
Recovered as a byproduct in the synthesis of compound **88A** as a yellow solid (3 mg, 6% yield). **R_f**: 0.31 (40% EtOAc in hexanes, UV Active); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.35 (d, *J*=9.1 Hz, 2H, ArH), 8.15 (d, *J*=8.9 Hz, 2H, ArH), 3.15 (s, 3H, CH_3), 3.01 (s, 3H, CH_3). Spectral data is consistent with those found in literature.[116]

3.7.13.4 Synthesis of *N*,*N*-Dimethylphenylfluoroacetamide (100C)



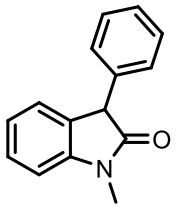
Prepared according to **General Procedure H** starting from *N*,*N*-dimethylphenyldiazoacetamide (**87C**) (40 mg) to afford **100C** as a yellow oil (40% NMR yield). **R_f**: 0.21 (40% EtOAc in hexanes, UV Active); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.44-7.39 (m, 2H, ArH), 7.34-7.28 (m, 3H, ArH), 6.07 (d, *J*=51.2 Hz, 1H, CHF), 2.87 (s, 3H, CH_3), 2.41 (s, 3H, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -173.29. Spectral data is consistent with those found in literature.[117]

3.7.13.5 Synthesis of *N*-Methyl-3-fluoro-3-phenyl-2-oxindole (115D)



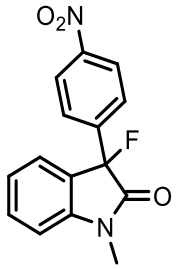
Prepared according to **General Procedure H** starting from *N*-methyl-*N*-phenyl phenyldiazoacetamide (**87A**) (53 mg) to afford **115D** as a yellow solid (6 mg, 12% yield). **R_f**: 0.25 (20% EtOAc in hexanes, UV Active); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48-7.33 (m, 6H, ArH), 7.21 (dd, *J*=7.6 Hz, *J*=7.6 Hz, 1H, ArH), 7.15 (dd, *J*=7.7 Hz, *J*=7.7 Hz, 1H, ArH), 6.93 (d, *J*=7.8 Hz, 1H, ArH), 3.23 (s, 3H, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -153.19. Spectral data is consistent with those found in literature.[90]

3.7.13.6 Synthesis of *N*-Methyl-3-phenyl-2-oxindole (116D)



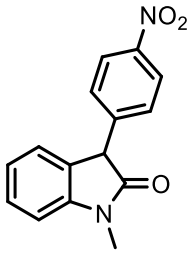
Recovered as a byproduct in the synthesis of compound **115D** as a white solid (13 mg, 27% yield). **R_f**: 0.20 (20% EtOAc in hexanes, UV Active); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.16 (m, 7H, ArH), 7.06 (dd, *J*=7.5Hz, *J*=7.5 Hz, 1H, ArH), 6.90 (d, *J*=7.7 Hz, 1H, ArH), 4.61 (s, 1H, C(=O)C<u>H</u>), 3.26 (s, 3H, CH_3). Spectral data is consistent with those found in literature._ENREF_118[118]

3.7.13.7 Synthesis of *N*-Methyl-3-fluoro-3-*p*-nitrophenyl-2-oxindole (115E)



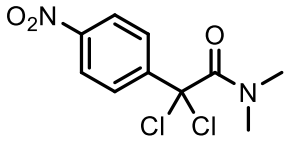
Prepared according to **General Procedure H** starting from *N*-methyl-*N*-*p*-nitrophenyl phenyldiazoacetamide (**87E**) (62 mg) to afford **115E** as a yellow solid (14 mg, 23% yield). **R_f**: 0.41 (40% EtOAc in hexanes, UV Active); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.24 (d, *J*=9.3 Hz, 2H, ArH), 7.55 (d, *J*=9.3 Hz, 2H, ArH), 7.48 (dd, *J*=8.1 Hz, *J*=8.1 Hz, 1H, ArH), 7.30 (d, *J*=8.6 Hz, 7.9 Hz, 1H, ArH), 7.18 (dd, *J*=7.6 Hz, *J*=7.6 Hz, 1H, ArH), 7.00 (d, *J*=7.8 Hz, 1H, ArH), 3.26 (s, 3H, CH_3); **^{19}F NMR** (282 MHz, $CDCl_3$) δ -154.19. Spectral data is consistent with those found in literature.[90]

3.7.13.8 Synthesis of *N*-Methyl-3-*p*-nitrophenyl-2-oxindole (116D)



Recovered as a byproduct in the synthesis of compound **115E** as a yellow solid (9 mg, 16% yield). **R_f**: 0.33 (40% EtOAc in hexanes, UV Active); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.20 (d, *J*=8.7 Hz, 2H, ArH), 7.42-7.37 (m, 3H, ArH), 7.17-7.09 (m, 2H, ArH), 6.94 (d, *J*=7.95, 1H, ArH), 4.73 (s, 1H, C(=O)C<u>H</u>), 3.27 (s, 3H, CH_3). Spectral data is consistent with those found in literature.[119]

3.7.14 Synthesis of *N*,*N*-Dimethyl-*p*-nitrophenyldichloroacetamide (101A)



N,*N*-Dimethyl-*p*-nitrophenyldiazoacetamide (50 mg, 0.21 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.1 mL, 0.19 M) in an oven-dried flask equipped with magnetic stirring at room temperature. Pyridine in CH_2Cl_2 (10% (v/v) solution, 8.5 µL, 5 mol%) was added in one portion followed by the addition of (dichloroiodo)benzene (130 mg, 0.46 mmol, 2.2 equiv) in one portion. The reaction was heated at reflux for hour after which time TLC analysis showed consumption of starting material. The reaction mixture was concentrated to dryness *in vacuo* and the resulting crude oil was purified by column chromatography (40% EtOAc in hexanes) to furnish **101A** as a yellow solid (56 mg, 95% yield). **R_f**: 0.54 (40% EtOAc in hexanes, UV Active); **IR** (ATR) 2923, 1666, 1519, 1346, 845, 740 cm^{-1}; **m.p.** 81-83 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.27 (d, *J*=8.9 Hz, 2H, ArH), 7 (d, *J*=8.9 Hz, 2H, ArH), 3.08 (s, 3H, CH_3), 2.94 (s, 3H, CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.0 (s, C=O), 147.9 (s, Ar), 146.3 (s, Ar), 126.9 (s, Ar), 123.8 (s, Ar), 85.1 (s, CCl_2), 39.4 (s, CH_3), 38.6 (s, CH_3); **HRMS** (ESI) calcd for $C_{10}H_{11}O_3N_2Cl_2$ $(M+H)^+$ 277.01412; found 277.01416.

References

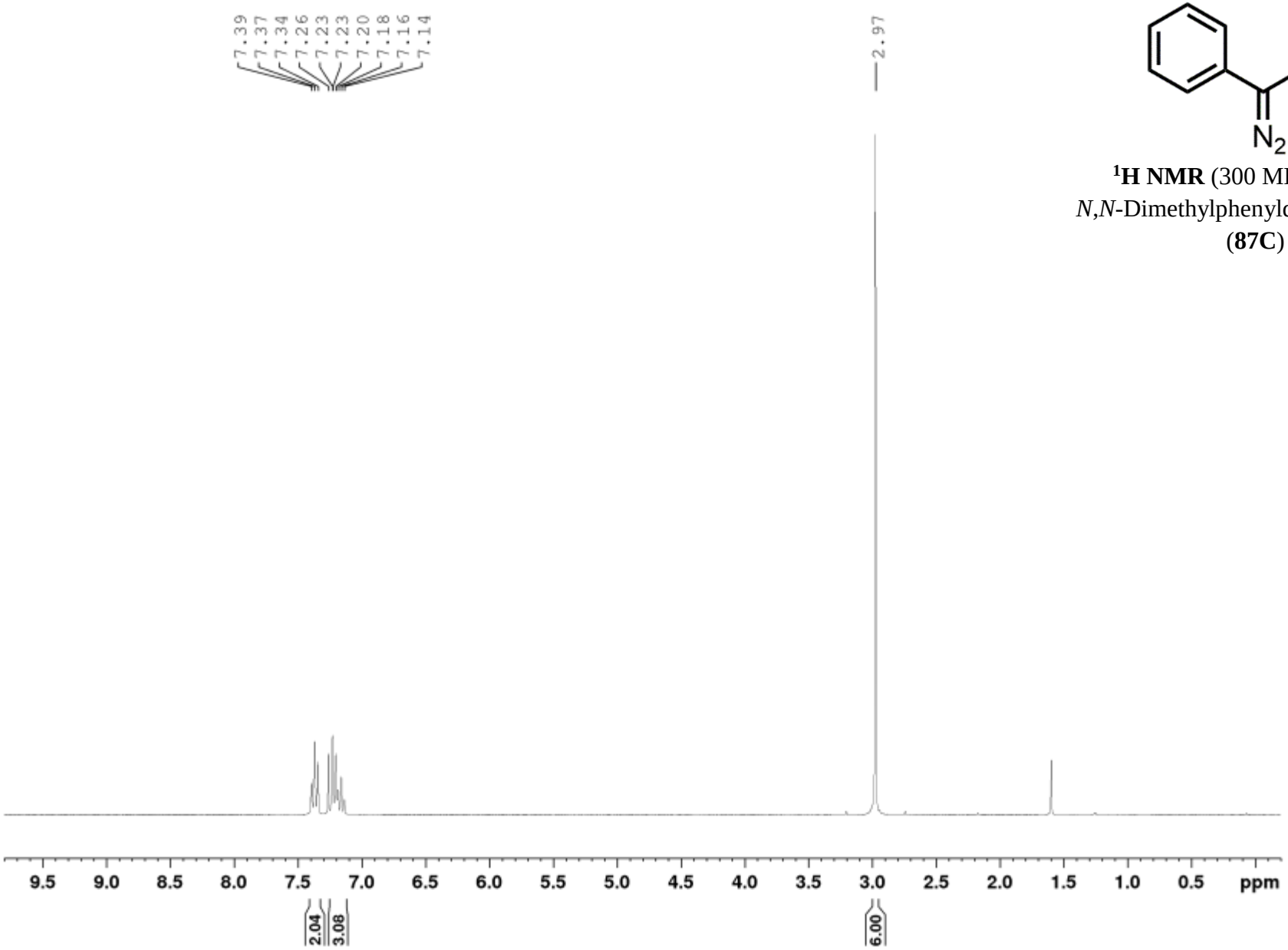
(1) Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*; Oxford Unversity Press: New York, **2000**, p 518.
(2) Ozsvath, D. L. *Rev. Environ. Sci. Biotechnol.* **2009**, *8*, 59.
(3) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305.
(4) Park, B.; Kitteringham, N.; O'Neill, P. *Annu. Rev. Pharmacol. Taxicol.* **2001**, *41*, 443.
(5) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071.
(6) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.
(7) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.
(8) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, *1973*, 779.
(9) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216.
(10) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048.
(11) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. *Org. Lett.* **2009**, *11*, 5050.
(12) Nielsen, M. K.; Ugaz, C. R.; Li, W.; Doyle, A. G. *J. Am. Chem. Soc.* **2015**, *137*, 9571.
(13) Inman, C. E.; Oesterling, R. E.; Tyczkowski, E. A. *J. Am. Chem. Soc.* **1958**, *80*, 5286.
(14) Appelman, E. H.; Mendelsohn, M. H.; Kim, H. *J. Am. Chem. Soc.* **1985**, *107*, 6515.
(15) Rozen, S.; Menahem, Y. *J. Fluorine Chem.* **1980**, *16*, 19.
(16) Lal, S.; Pex, G.; Syvret, R. *Chem. Rev.* **1996**, *96*, 1737.
(17) Merritt, R. F. *J. Org. Chem.* **1966**, *31*, 3871.
(18) Zupan, M.; Pollak, A. *Tetrahedron Lett.* **1974**, *15*, 1015.
(19) Hara, S.; Nakahigashi, J.; Ishi-i, K.; Sawaguchi, M.; Sakai, H.; Fukuhara, T.; Yoneda, N. *Synlett* **1998**, *1998*, 495.
(20) Musher, J. I. *Angew. Chem., Int. Ed.* **1969**, *8*, 54.
(21) Minkin, V. I. *Pur Appl. Chem.* **1999**, *71*, 1919.
(22) Pauling, L. *The Nature of the Chemical Bond and the Structure of Molecules and Crystals*; Cornell University Press: New York, **1940**,145.
(23) Cooper, D. L.; Cunningham, T. P.; Gerratt, J.; Karadakov, P. B.; Raimondi, M. *J. Am. Chem. Soc.* **1994**, *116*, 4414.
(24) Coulson, C. A. *J. Am. Chem. Soc.* **1964**, 1442.
(25) Willgerrodt, C. *J. Prakt. Chem* **1886**, *33*, 154.
(26) Zhdankin, V. *Hypervalent Iodine Chemistry*; Wiley: Chichester, **2014**.
(27) Kristiansen, K.; Potthast, A.; Christensen, B. *Carbohydr. Res.* **2010**, *345*, 1264.
(28) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(29) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.
(30) Kajigaeshi, S.; Kakinami†, T.; Moriwaki, M.; Tanaka, T.; Fujisaki, S. *Tetrahedron Lett.* **1988**, *29*, 5783.
(31) Ochiai, M. *Hypervalent Iodine Chemistry: Modern Developmen in Organic Synthesis*; T., W., Ed.; Springer Verlag: Berlin, **2003**, p 5.
(32) Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1982**, *47*, 2487.
(33) Lodaya, J. S.; Koser, G. F. *J. Org. Chem.* **1988**, *53*, 210.
(34) Koser, G. F.; Lodaya, J. S.; Ray, D. G.; Kokil, P. B. *J. Am. Chem. Soc.* **1988**, *110*, 2987.
(35) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328.
(36) Xie, Y.-Y.; Chen, Z.-C. *Synth. Commun.* **2001**, *31*, 3145.
(37) Xie, Y.-Y. *J. Chem. Res.* **2001**, *2001*, 156.
(38) Tsushima, T.; Kawada, K.; Tsuji, T. *Tetrahedron Lett.* **1982**, *23*, 1165.

(39) Sato, S.; Yoshida, M.; Hara, S. *Synthesis* **2005**, *2005*, 2602.
(40) Hara, S.; Sekiguchi, M.; Ohmori, A.; Fukuhara, T.; Yoneda, N. *Chem. Commun.* **1996**, 1899.
(41) Yoshida, M.; Fujikawa, K.; Sato, S.; Hara, S. *ARKIVOC* **2003**, 36.
(42) Greaney, M. F.; Motherwell, W. B. *Tetrahedron Lett.* **2000**, *41*, 4463.
(43) Greaney, M. F.; Motherwell, W. B. *Tetrahedron Lett.* **2000**, *41*, 4467.
(44) Arrica, M. A.; Wirth, T. *Eur. J. Org. Chem.* **2005**, *2005*, 395.
(45) Motherwell, W.; Wilkinson, J. *Synlett* **1991**, *191*.
(46) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318.
(47) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(48) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.
(49) Doyle, M. P.; Mckervey, M. A.; Tao, Y. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, **1998**, p 16.
(50) Patrick, T. B.; Scheibel, J. J.; Cantrell, G. L. *J. Org. Chem.* **1981**, *46*, 3917.
(51) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981.
(52) Bamford, W. R.; Stevens, T. S. *J. Am. Chem. Soc.* **1952**, 4735.
(53) Barton, D. H. R.; Jaszberenyi, J. C.; Liu, W.; Shinada, T. *Tetrahedron* **1996**, *52*, 14673.
(54) Murray, R. W.; Trozzolo, A. M. *J. Org. Chem.* **1961**, *26*, 3109.
(55) Ciganek, E. *J. Org. Chem.* **1970**, *35*, 862.
(56) Tao, J.; Tran, R.; Murphy, G. *J. Am. Chem. Soc.* **2013**, *135*, 16312.
(57) Coffey, K. E.; Murphy, G. K. *Synlett* **2015**, *26*, 1003.
(58) Bhrigu, B.; Pathak, D. *Int. J. Pharm. Sci. Drug Res.* **2010**, *2*, 229.
(59) Medvedev, A.; Buneeva, O.; Glover, V. *Biologics* **2007**, *1*, 151.
(60) Pandeya, S.; Smitha, S.; Jyoti, M.; Sridhard, S. *Acta Pharm.* **2005**, *55*, 27.
(61) Singh, S.; Desta, Z. *Chem. Rev.* **2012**, *112*, 6104.
(62) Murphy, G. K.; Abbas, F. Z.; Poulton, A. V. *Adv. Synth. Catal.* **2014**, *356*, 2919.
(63) Coffey, K. E.; Moreira, R.; Abbas, F. Z.; Murphy, G. K. *Org. Biomol. Chem.* **2015**, *13*, 682.
(64) Hepples, C.; Murphy, G. K. *Tetrahedron Lett.* **2015**, *56*, 4971.
(65) Zefirov, N. S.; Samsoniya, N. S.; Kutateladze, T. G.; Zhdankin, V. V. *Zh. Org. Khim.* **1991**, *27*, 220.
(66) Yasuda, M.; Yoshioka, S.; Yamasaki, S.; Somyo, T.; Chiba, K.; Baba, A. *Org. Lett.* **2006**, *8*, 761.
(67) Emer, E.; Twilton, J.; Tredwell, M.; Calderwood, S.; Collier, T. L.; Liégault, B.; Taillefer, M.; Gouverneur, V. *Org. Lett.* **2014**, *16*, 6004.
(68) Zhou, Y.; Zhang, Y.; Wang, J. *Org. Biomol. Chem.* **2016**, *14*, 10444.
(69) Podichetty, A. K.; Faust, A.; Kopka, K.; Wagner, S.; Schober, O.; Schäfers, M.; Haufe, G. *Bioorg. Med. Chem.* **2009**, *17*, 2680.
(70) Luo, Y.; Shoemaker, A. R.; Liu, X.; Woods, K. W.; Thomas, S. A.; de Jong, R.; Han, E. K.; Li, T.; Stoll, V. S.; Powlas, J. A.; Oleksijew, A.; Mitten, M. J.; Shi, Y.; Guan, R.; McGonigal, T. P.; Klinghofer, V.; Johnson, E. F.; Leverson, J. D.; Bouska, J. J.; Mamo, M.; Smith, R. A.; Gramling-Evans, E. E.; Zinker, B. A.; Mika, A. K.; Nguyen, P. T.; Oltersdorf, T.; Rosenberg, S. H.; Li, Q.; Giranda, V. L. *Mol. Cancer Ther.* **2005**, *4*, 977.
(71) Zhu, G.-D.; Gandhi, V. B.; Gong, J.; Luo, Y.; Liu, X.; Shi, Y.; Guan, R.; Magnone, S. R.; Klinghofer, V.; Johnson, E. F.; Bouska, J.; Shoemaker, A.; Oleksijew, A.; Jarvis, K.; Park, C.; Jong, R. D.; Oltersdorf, T.; Li, Q.; Rosenberg, S. H.; Giranda, V. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3424.
(72) Middleton, W.; Bingham, E. *J. Org. Chem.* **1980**, *45*, 2883.
(73) Torres, J.; Garden, S. J.; Pinto, A. C.; da Silva, F. S. Q.; Boechat, N. *Tetrahedron* **1999**, *55*, 1881.
(74) Singh, R.; Majumder, U.; Shreeve, J. *J. Org. Chem.* **2001**, *66*, 6263.
(75) Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. *J. Am. Chem. Soc.* **2010**, *132*, 18199.
(76) Lim, Y. H.; Ong, Q.; Duong, H. A.; Nguyen, T. M.; Johannes, C. W. *Org. Lett.* **2012**, *14*, 5676.
(77) Zhu, J.; Zhang, W.; Zhang, L.; Liu, J.; Zheng, J.; Hu, J. *J. Org. Chem.* **2010**, *75*, 5505.

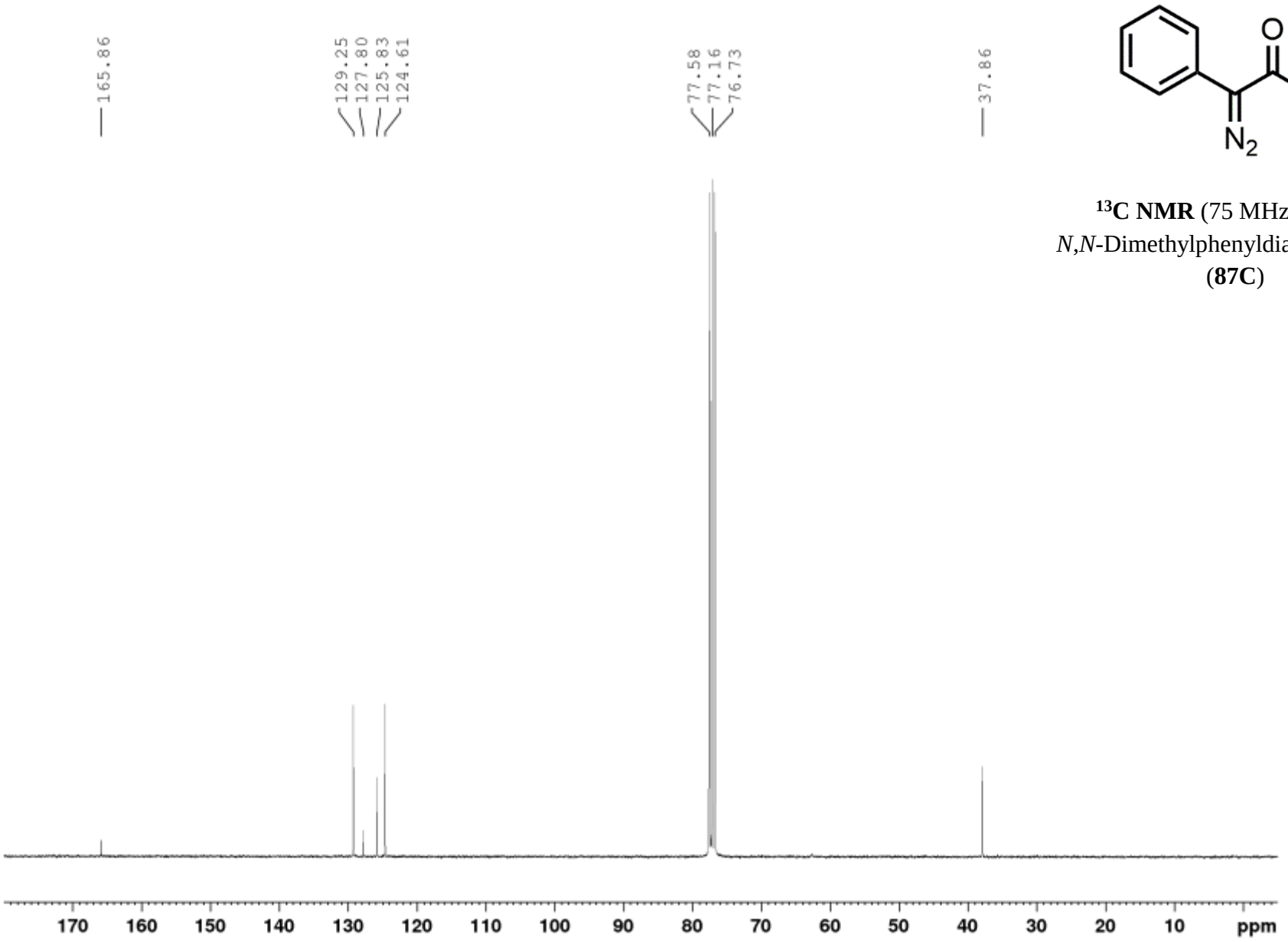
(78) Shi, S.-L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2015**, *54*, 1646.
(79) Ke, M.; Song, Q. *Chem. Commun.* **2017**, *53*, 2222.
(80) Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 12222.
(81) Sinclair, G. S.; Tran, R.; Tao, J.; Hopkins, W. S.; Murphy, G. K. *Eur. J. Org. Chem.* **2016**, *27*, 4603.
(82) Zhao, Z.; Kulkarni, K. G.; Murphy, G. K. *Adv. Synth. Cat.* **2017**, *359*, 2222.
(83) Hepples, C.; Murphy, G. *Tetrahedron Lett.* **2015**, *35*, 4971.
(84) Arava, S.; Kumar, J. N.; Maksymenko, S.; Iron, M. A.; Parida, K. N.; Fristrup, P.; Szpilman, A. M. *Angew. Chem., Int. Ed.* **2017**, *56*, 2599.
(85) Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*; Oxford Unversity Press: New York, **2000**, p 345.
(86) Connolly, T. J.; Durst, T. *Can. J. Chem.* **1997**, *75*, 542.
(87) Sawaguchi, M.; Ayuba, S.; Hara, S. *Synthesis* **2002**, *2002*, 1802.
(88) Ošeka, M.; Kimm, M.; Kaabel, S.; Järving, I.; Rissanen, K.; Kanger, T. *Org. Lett.* **2016**, *18*, 1358.
(89) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505.
(90) Dong, K.; Yan, B.; Chang, S.; Chi, Y.; Qiu, L.; Xu, X. *J. Org. Chem.* **2016**, *81*, 6887.
(91) Dubowchik, G. M.; Vrudhula, V. M.; Dasgupta, B.; Ditta, J.; Chen, T.; Sheriff, S.; Sipman, K.; Witmer, M.; Tredup, J.; Vyas, D. M.; Verdoorn, T. A.; Bollini, S.; Vinitsky, A. *Org. Lett.* **2001**, *3*, 3987.
(92) Hall, A.; Billinton, A.; Brown, S. H.; Clayton, N. M.; Chowdhury, A.; Giblin, G. M. P.; Goldsmith, P.; Hayhow, T. G.; Hurst, D. N.; Kilford, I. R.; Naylor, A.; Passingham, B.; Winyard, L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3392.
(93) Bloom, S.; Scerba, M. T.; Erb, J.; Lectka, T. *Org. Lett.* **2011**, *13*, 5068.
(94) Feng, Z.; Min, Q.-Q.; Xiao, Y.-L.; Zhang, B.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 1669.
(95) Tarui, A.; Shinohara, S.; Sato, K.; Omote, M.; Ando, A. *Org. Lett.* **2016**, *18*, 1128.
(96) Arlow, S. I.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2016**, *55*, 4567.
(97) Shishkov, I. V.; Rominger, F.; Hofmann, P. *Organometallics* **2009**, *28*, 1049.
(98) Yoshioka, E.; Imoto, Y.; Yoshikawa, T.; Kohtani, S.; Miyabe, H. *Synlett* **2017**, *28*, 863.
(99) Guo, Z.; Dowdy, E. D.; Li, W.-S.; Polniaszek, R.; Delaney, E. *Tetrahedron Lett.* **2001**, *42*, 1843.
(100) Rivière-Baudet, M.; Morère, A.; Dias, M. *Tetrahedron Lett.* **1992**, *33*, 6453.
(101) Rando, R. R. *J. Am. Chem. Soc.* **1972**, *94*, 1629.
(102) Cheng, Q.-Q.; Zhu, S.-F.; Zhang, Y.-Z.; Xie, X.-L.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2013**, *135*, 14094.
(103) Powers, D. C.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14092.
(104) Davies, H. M. L.; Cantrell, W. R.; Romines, K. R.; Baum, J. S. *Org. Synth.* **1992**, *70*, 93.
(105) Wolff, O.; Waldvogel, S. R. *Synthesis* **2004**, *2004*, 1303.
(106) Cooper, G. K.; Rapoport, H. *J. Labelled Comp. Radiopharm.* **1985**, *22*, 1201.
(107) Huh, D. H.; Jeong, J. S.; Lee, H. B.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2002**, *58*, 9925.
(108) Smith, L. A.; Wang, W.-B.; Burnell-Curty, C.; Roskamp, E. J. *Synlett* **1993**, *1993*, 850.
(109) Rossi, R. A.; Alonso, R. A. *J. Org. Chem.* **1979**, *45*, 1239.
(110) Mąkosza, M.; Sypniewski, M.; Glinka, T. *Tetrahedron* **1996**, *52*, 3189.
(111) Rai, M. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1979**, *17B*, 169.
(112) Yardley, J. P.; Husbands, G. E. M.; Stack, G.; James, M. N. G.; Sielecki, A. R. *J. Med. Chem.* **1990**, *33*, 2899.
(113) Campaigne, E.; Skowronski, G.; Rogers, R. B. *Synth. Commun.* **1973**, *3*, 325.
(114) Villalgordo, J. M.; Enderli, A.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1995**, *78*, 1983.
(115) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.
(116) Mai, W.-P.; Wang, H.-H.; Li, Z.-C.; Yuan, J.-W.; Xiao, Y.-M.; Yang, L.-R.; Mao, P.; Qu, L.-B. *Chem. Commun.* **2012**, *48*, 10117.
(117) Xu, Y.; Dolbier, W. R.; Rong, X. X. *J. Org. Chem.* **1997**, *62*, 1576.

(118) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308.
(119) Sattar, M.; Rathore, V.; Prasad, C. D.; Kumar, S. *Chem. Asian J.* **2017**, *12*, 734.

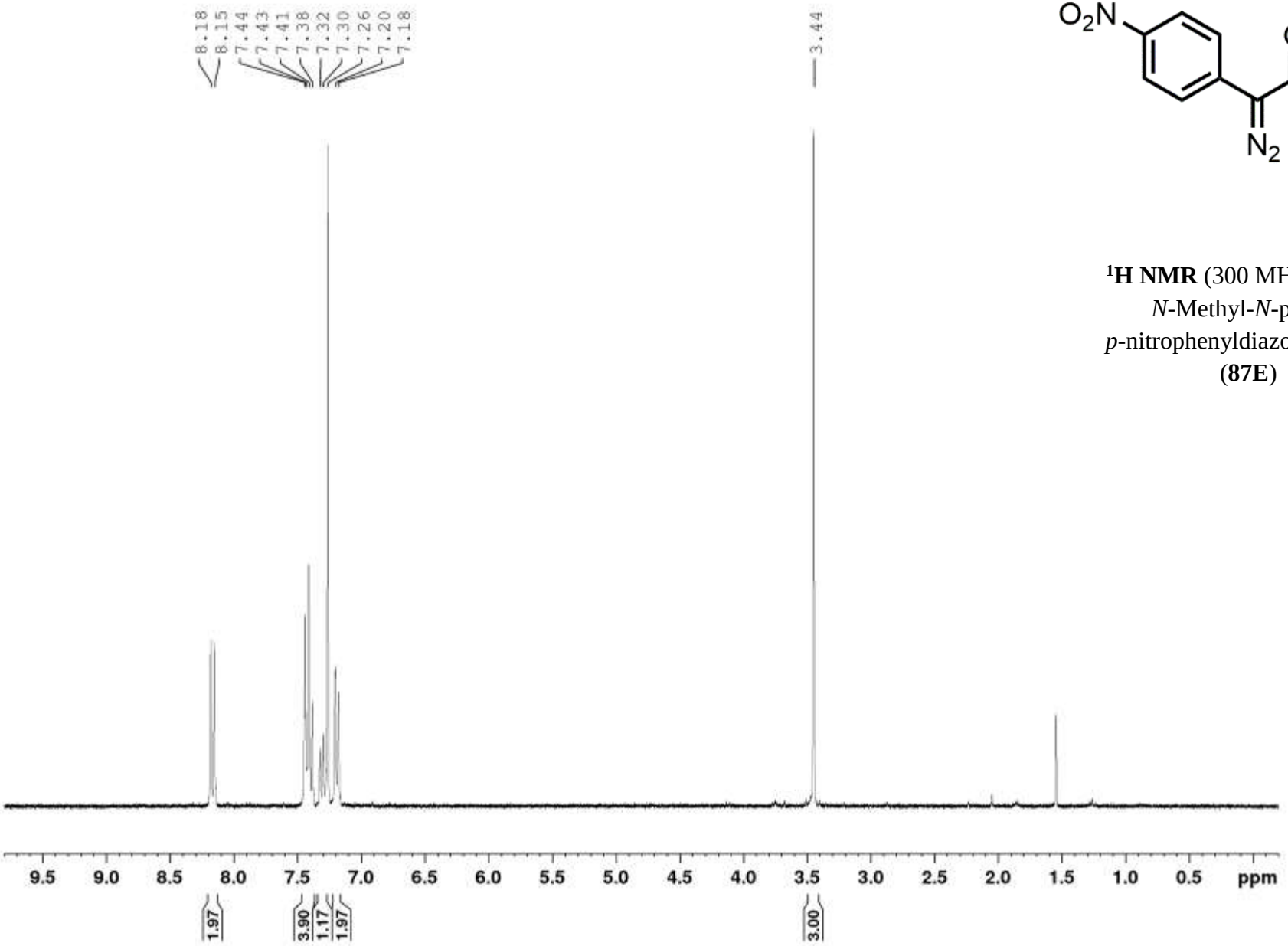
Appendix A: NMR Spectra of New Compounds



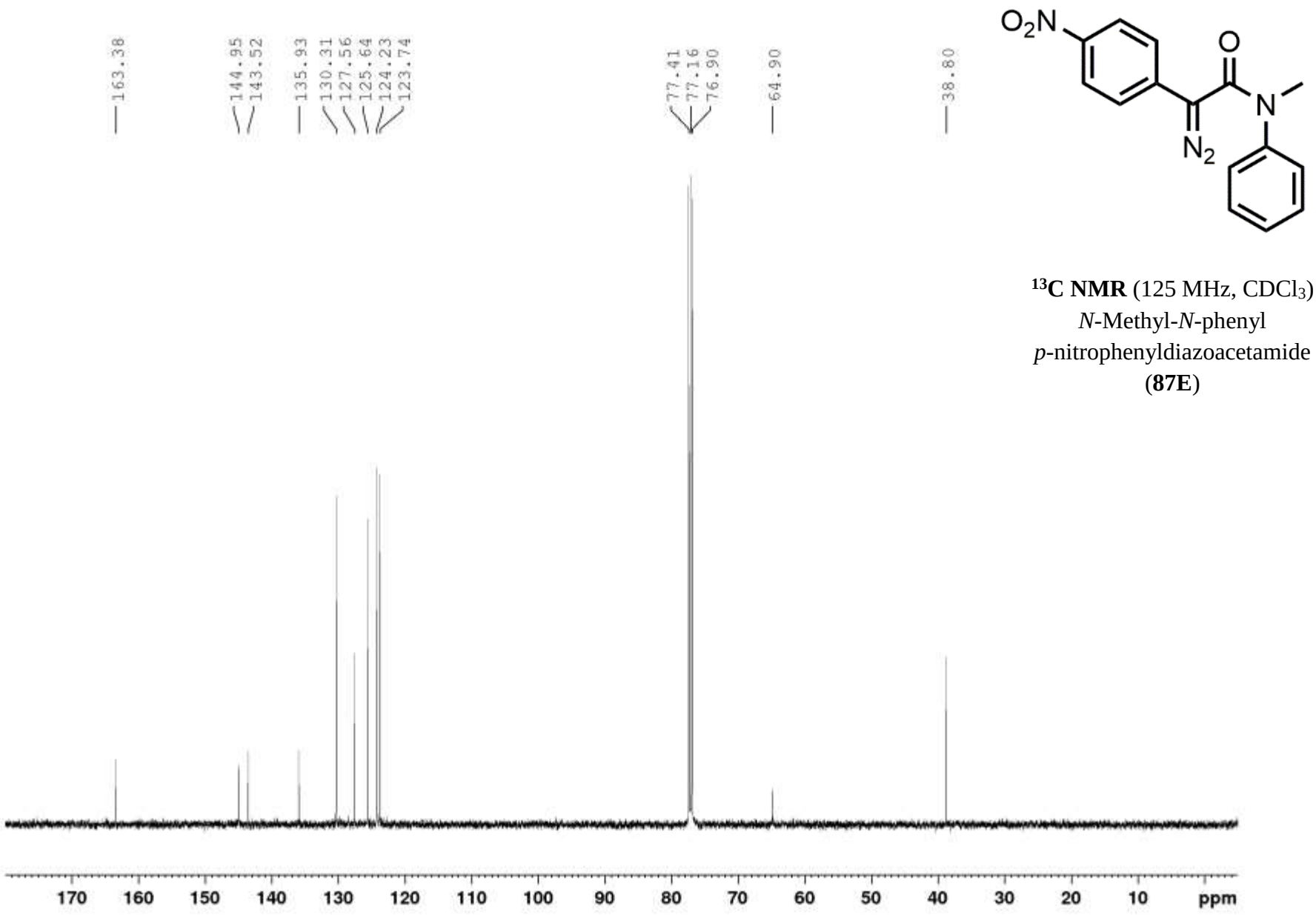
^{1}H NMR (300 MHz, $CDCl_3$)
N,*N*-Dimethylphenyldiazoacetamide
(**87C**)



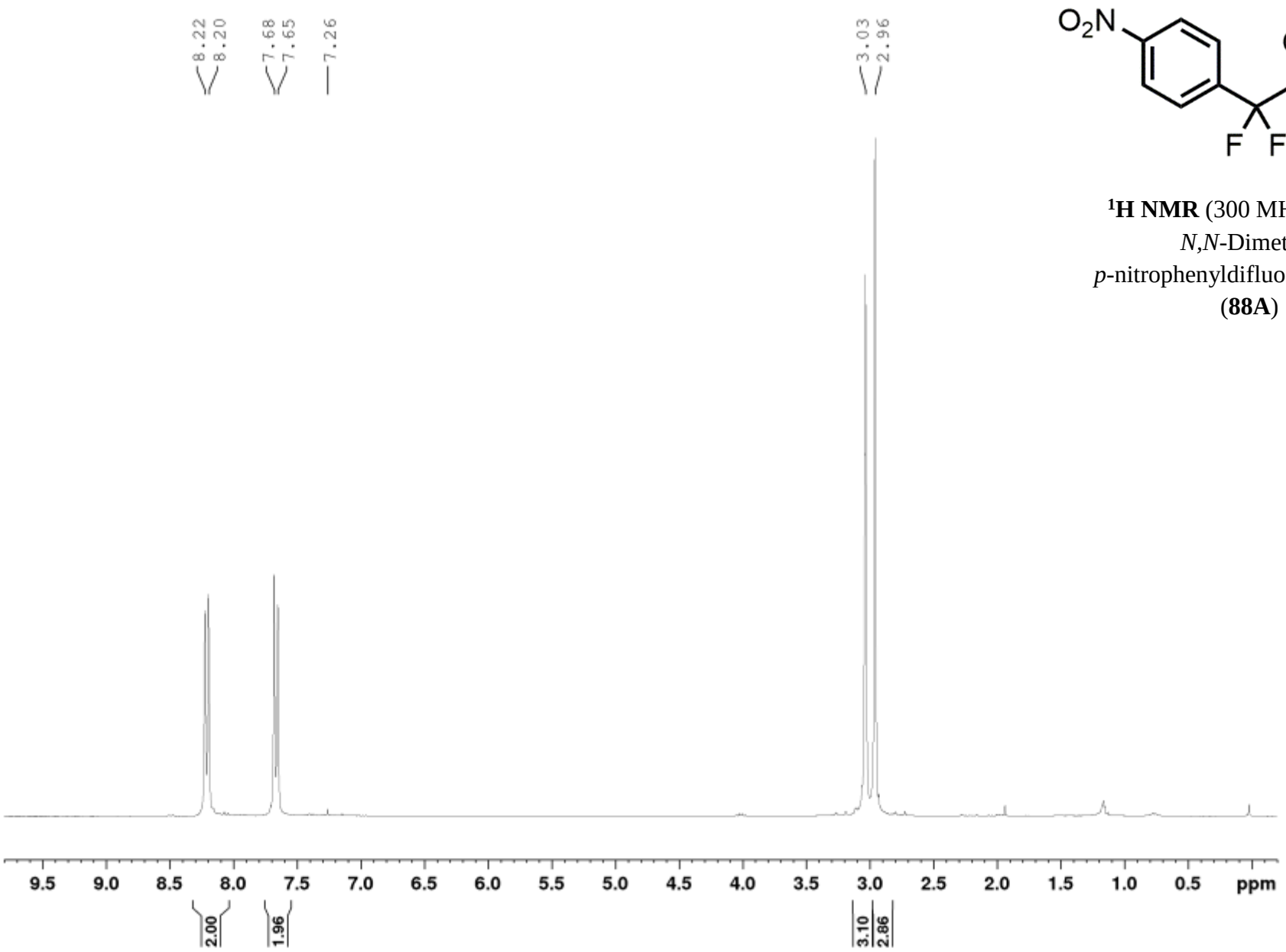
^{13}C NMR (75 MHz, $CDCl_3$)
N,*N*-Dimethylphenyldiazoacetamide
(**87C**)



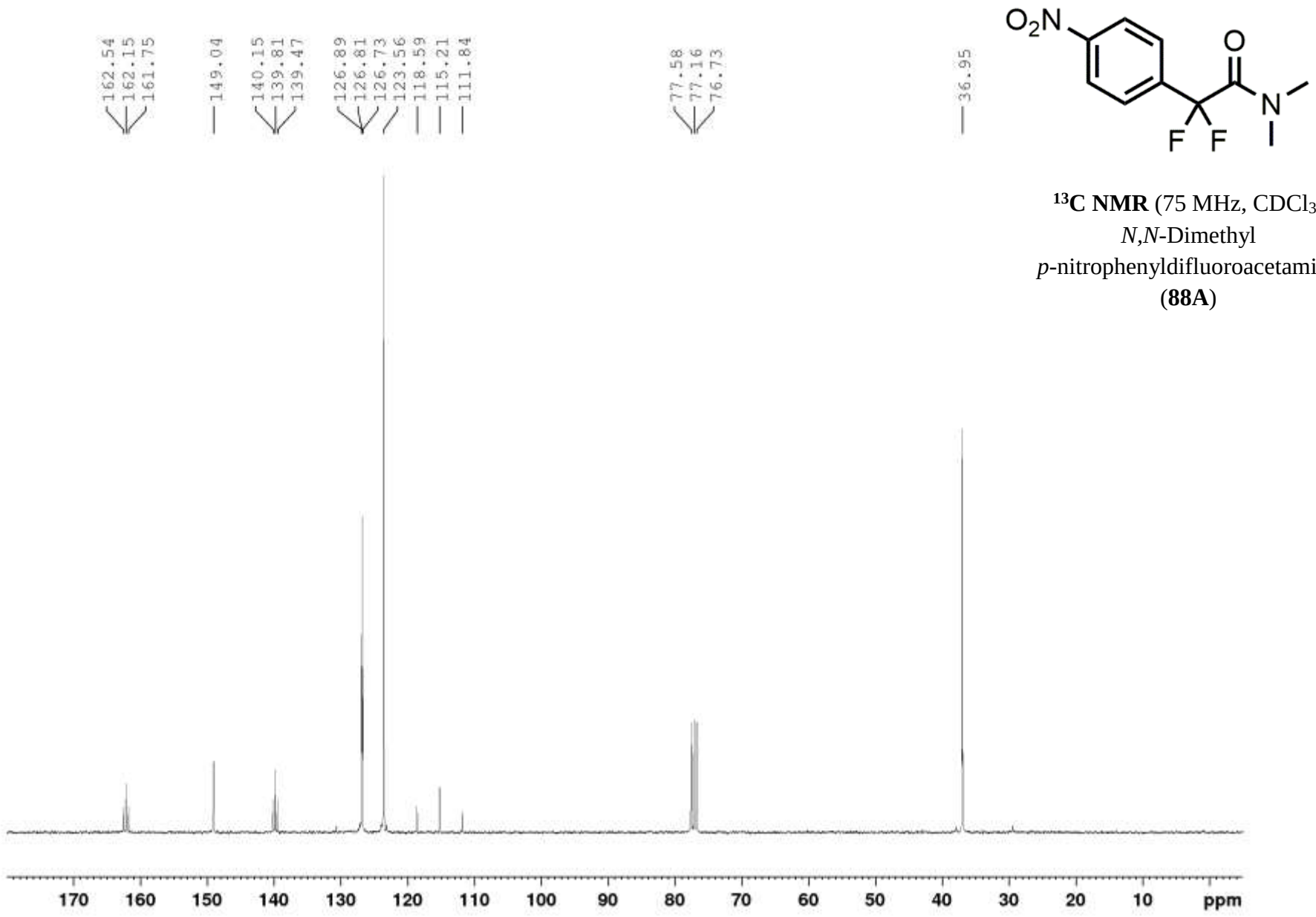
^{1}H NMR (300 MHz, $CDCl_3$)
N-Methyl-*N*-phenyl
p-nitrophenyldiazoacetamide
(**87E**)



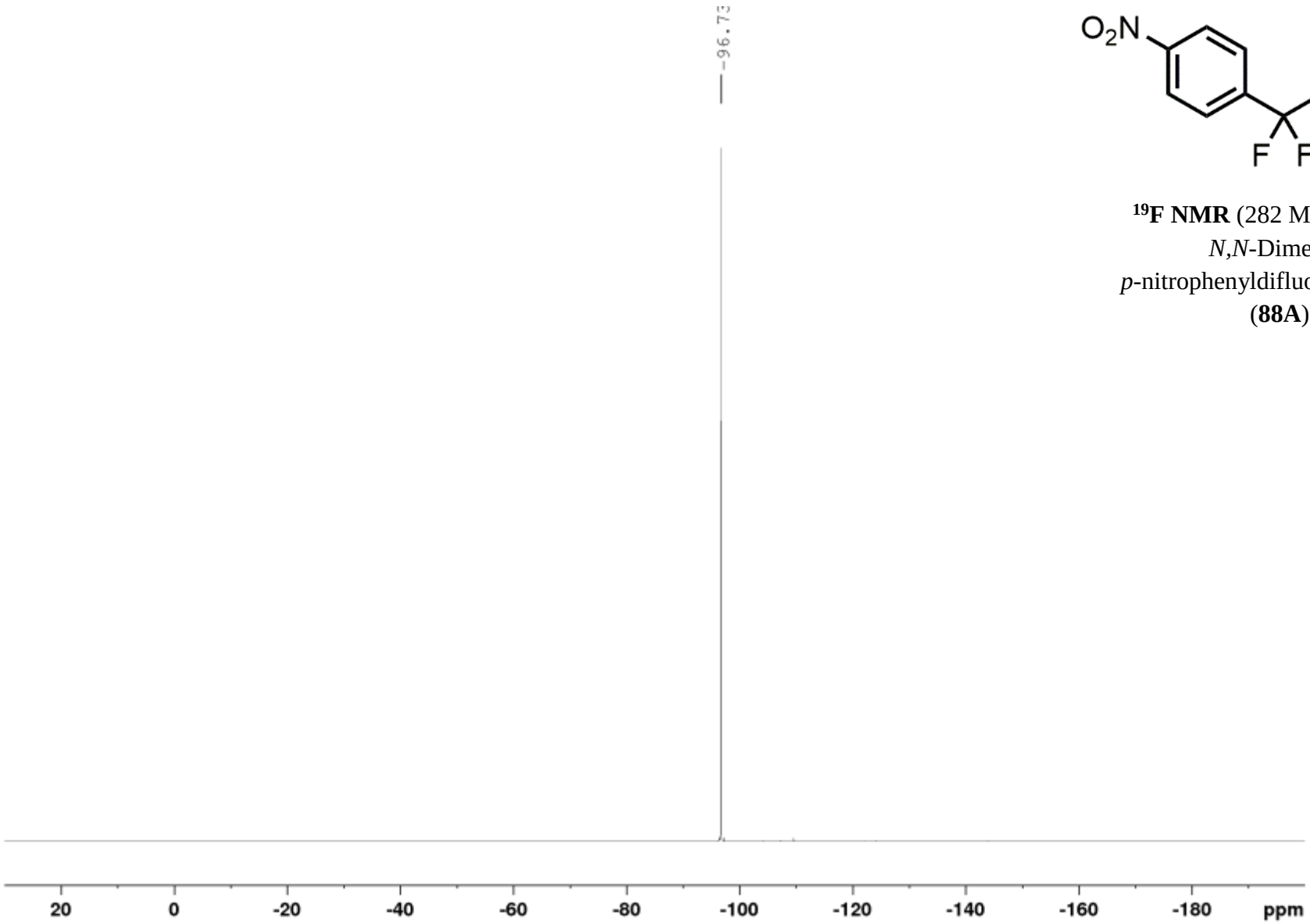
^{13}C NMR (125 MHz, $CDCl_3$)
N-Methyl-*N*-phenyl
p-nitrophenyldiazoacetamide
(**87E**)



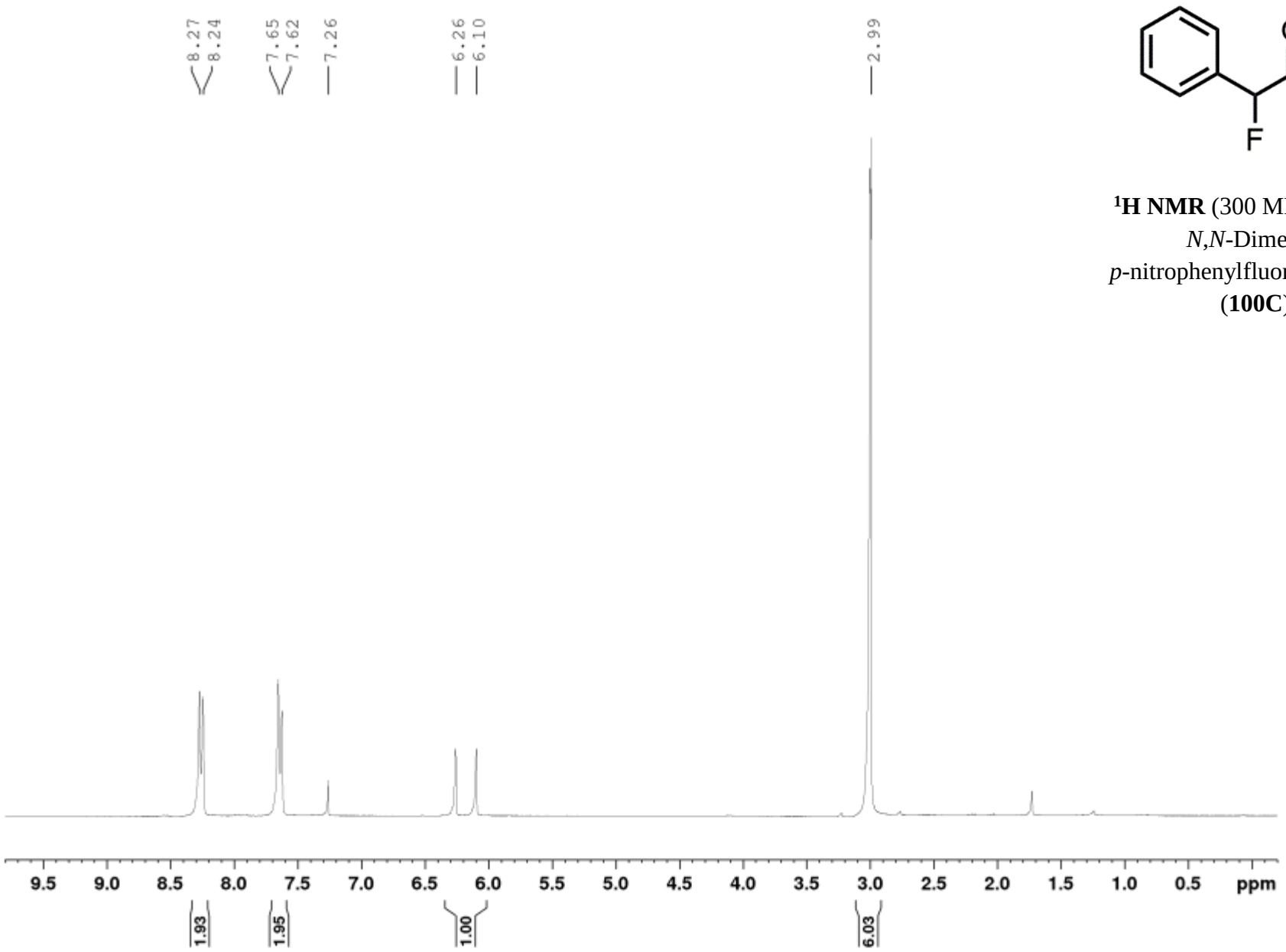
^{1}H NMR (300 MHz, $CDCl_3$)
N,*N*-Dimethyl
p-nitrophenyldifluoroacetamide
(**88A**)



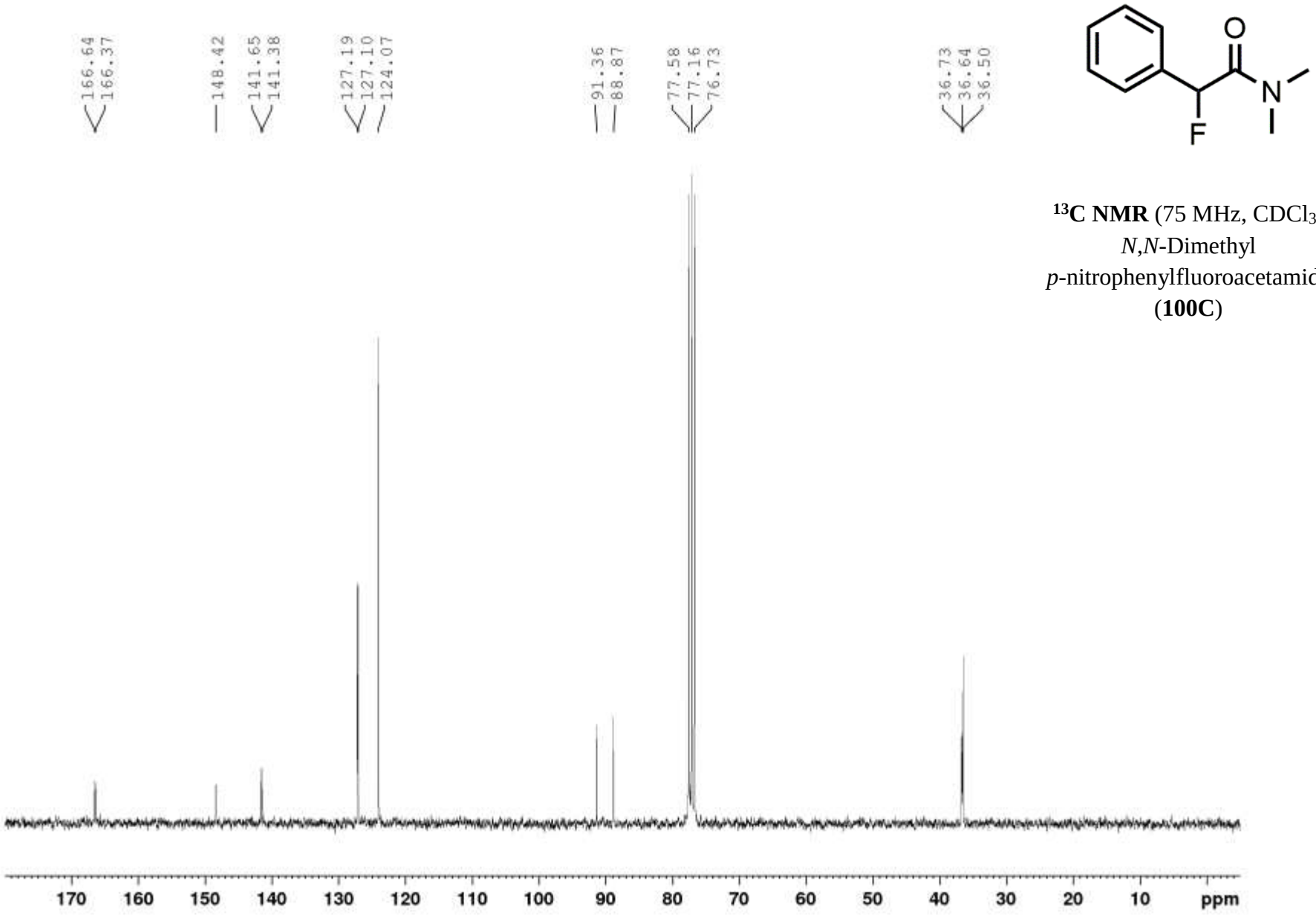
^{13}C NMR (75 MHz, $CDCl_3$)
N,*N*-Dimethyl
p-nitrophenyldifluoroacetamide
(**88A**)



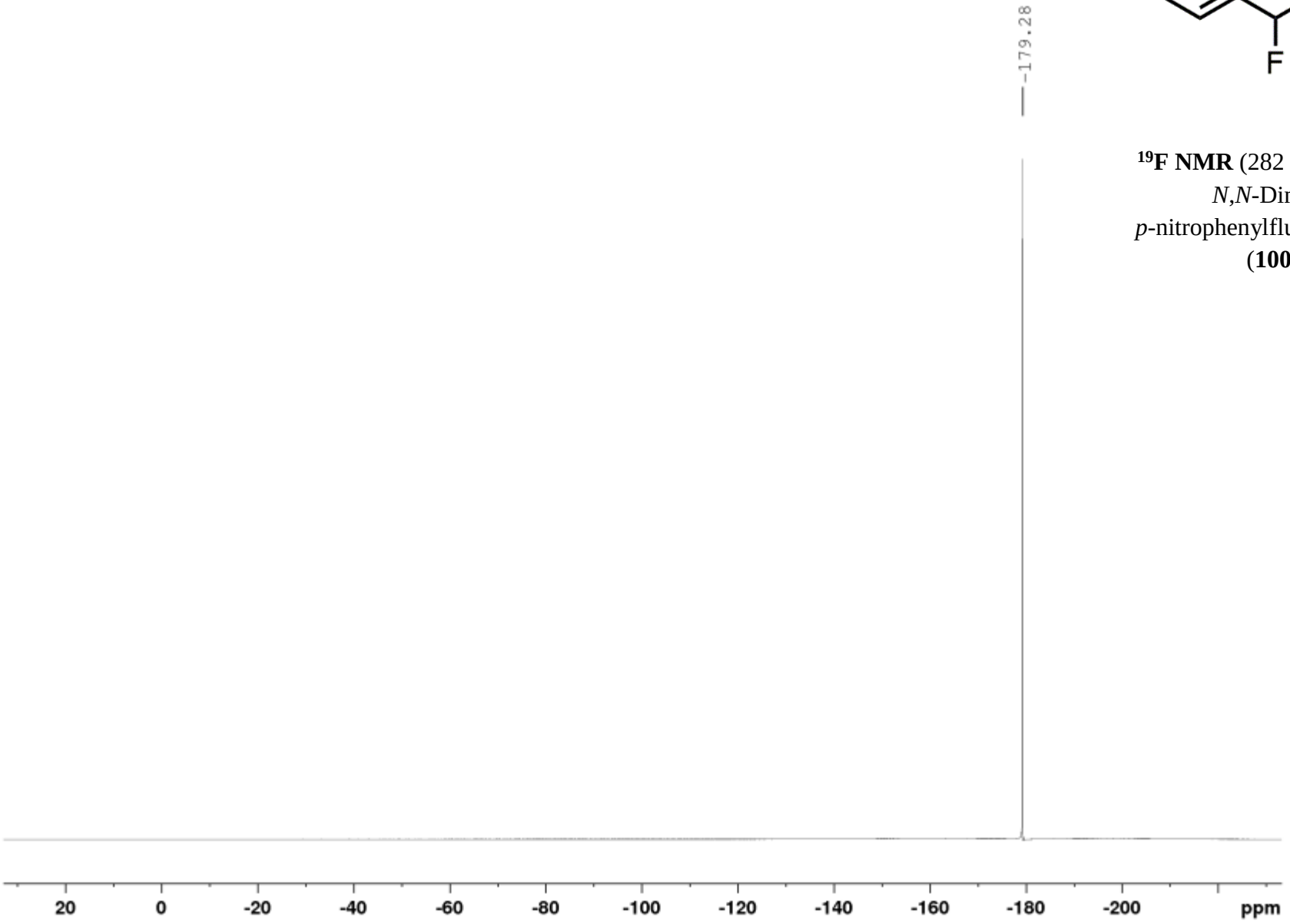
^{19}F NMR (282 MHz, $CDCl_3$)
N,*N*-Dimethyl
p-nitrophenyldifluoroacetamide
(**88A**)



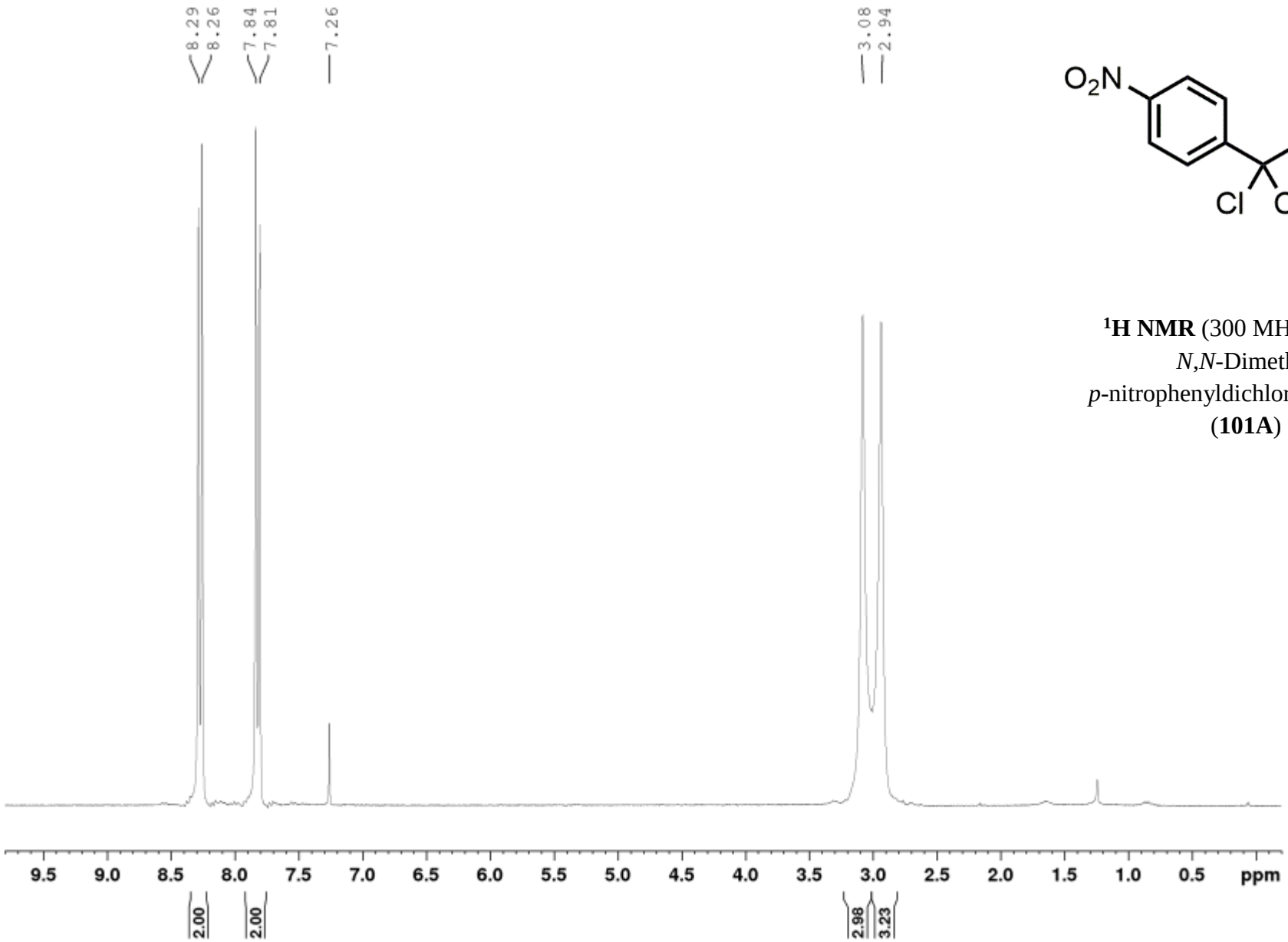
^{1}H NMR (300 MHz, $CDCl_3$)
N,*N*-Dimethyl
p-nitrophenylfluoroacetamide
(**100C**)



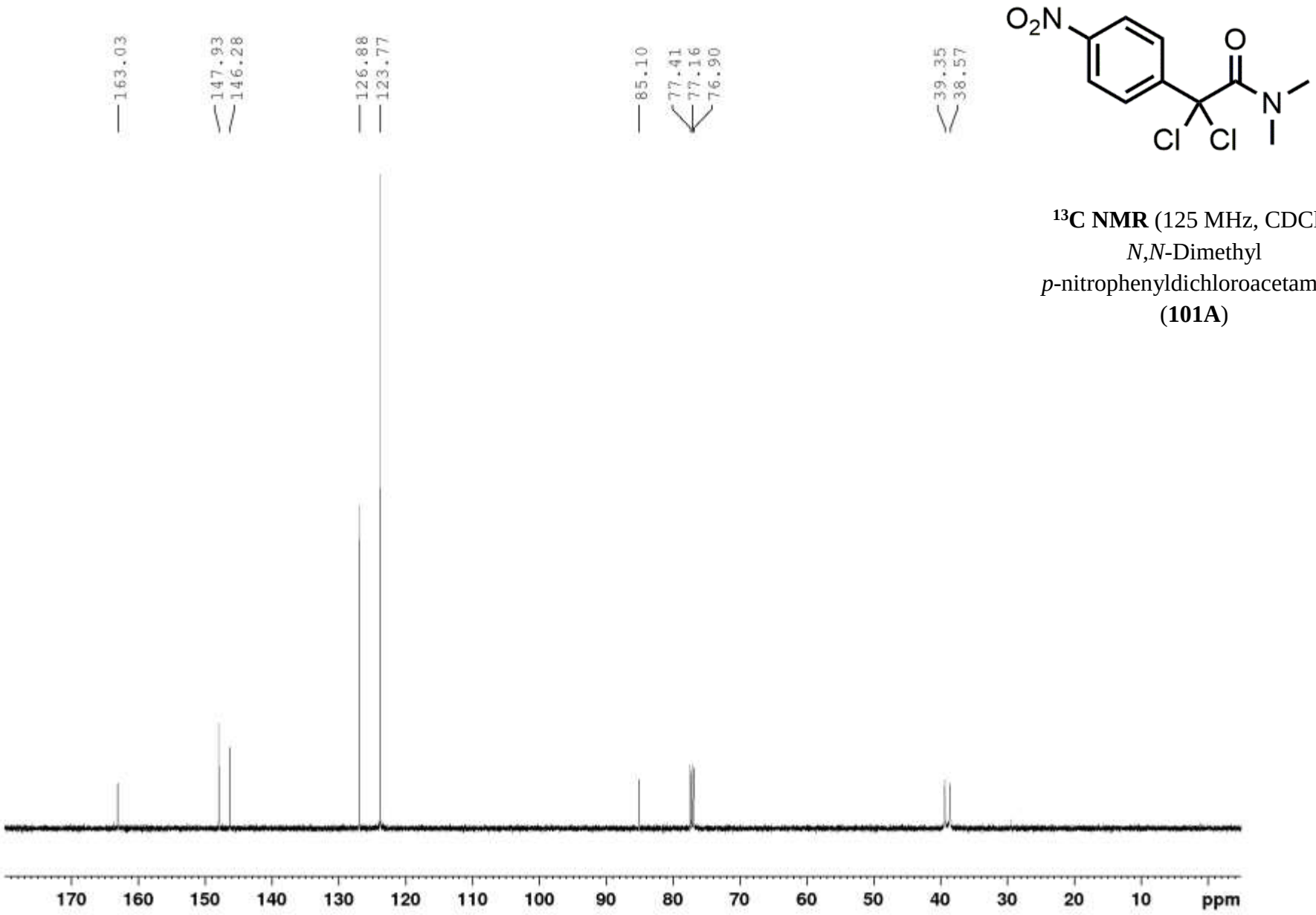
^{13}C NMR (75 MHz, $CDCl_3$)
N,*N*-Dimethyl
p-nitrophenylfluoroacetamide
(**100C**)



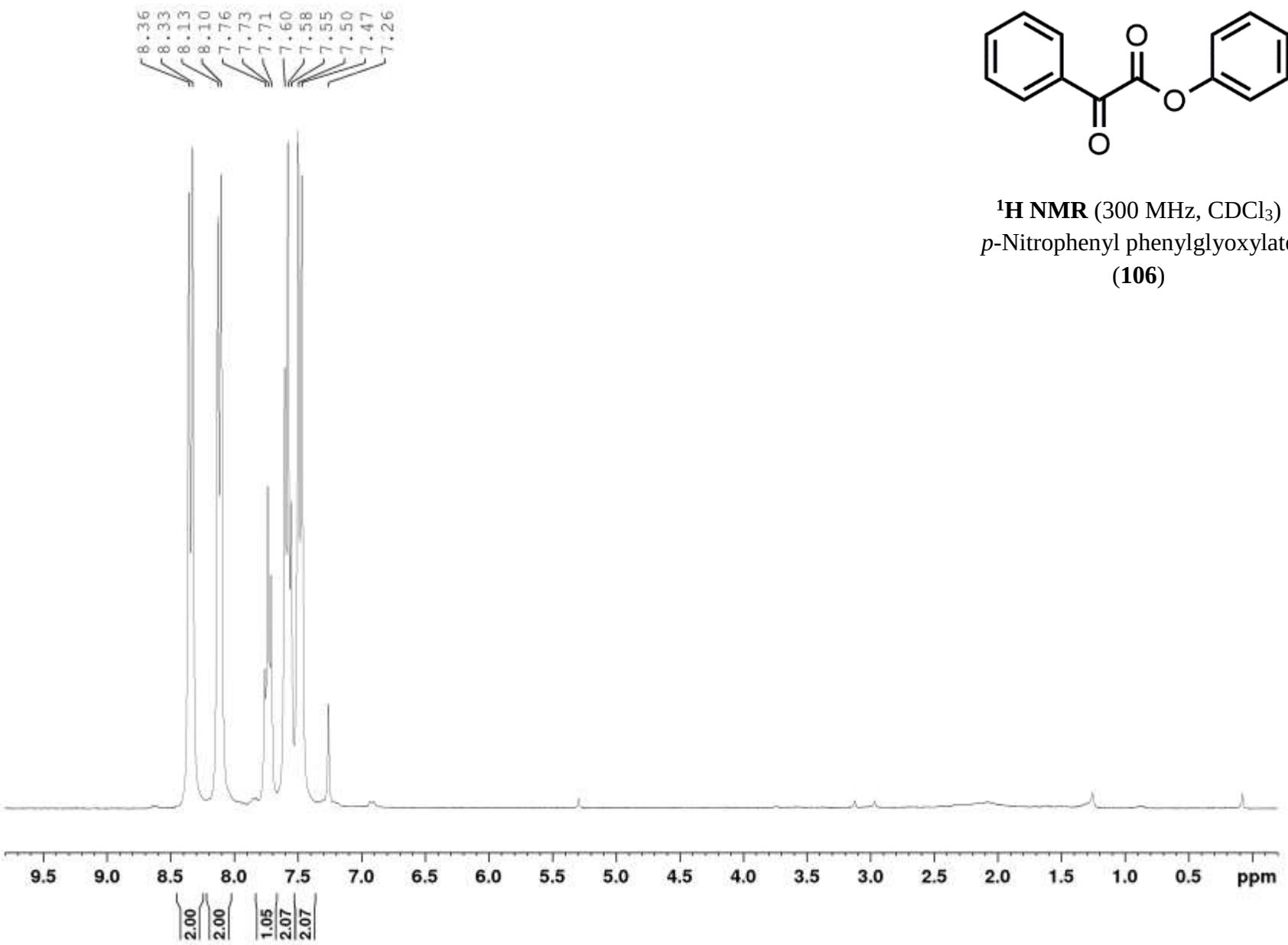
^{19}F NMR (282 MHz, $CDCl_3$)
N,*N*-Dimethyl
p-nitrophenylfluoroacetamide
(**100C**)



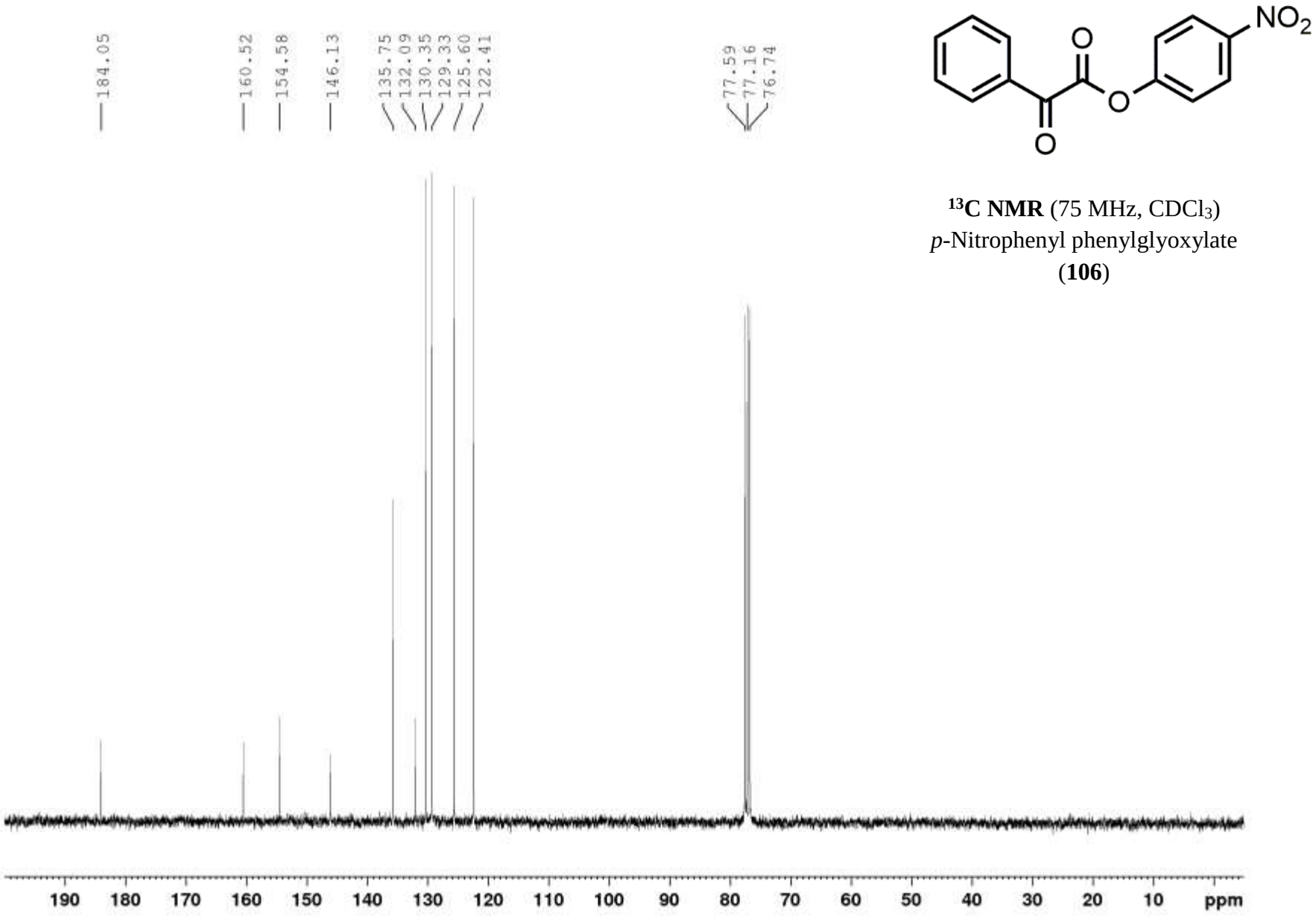
^{1}H NMR (300 MHz, $CDCl_3$)
N,*N*-Dimethyl
p-nitrophenyldichloroacetamide
(**101A**)



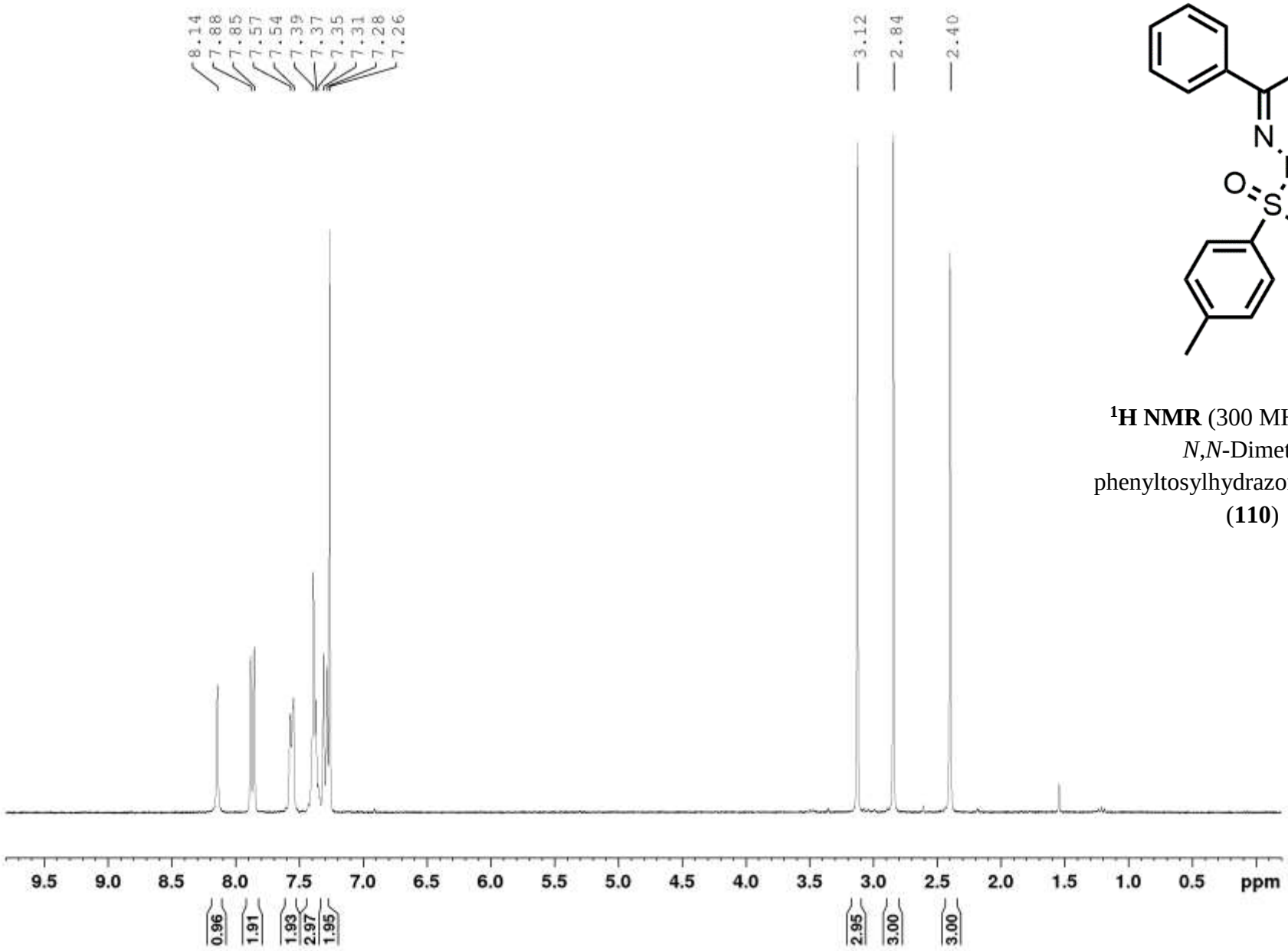
^{13}C NMR (125 MHz, $CDCl_3$)
N,*N*-Dimethyl
p-nitrophenyldichloroacetamide
(**101A**)



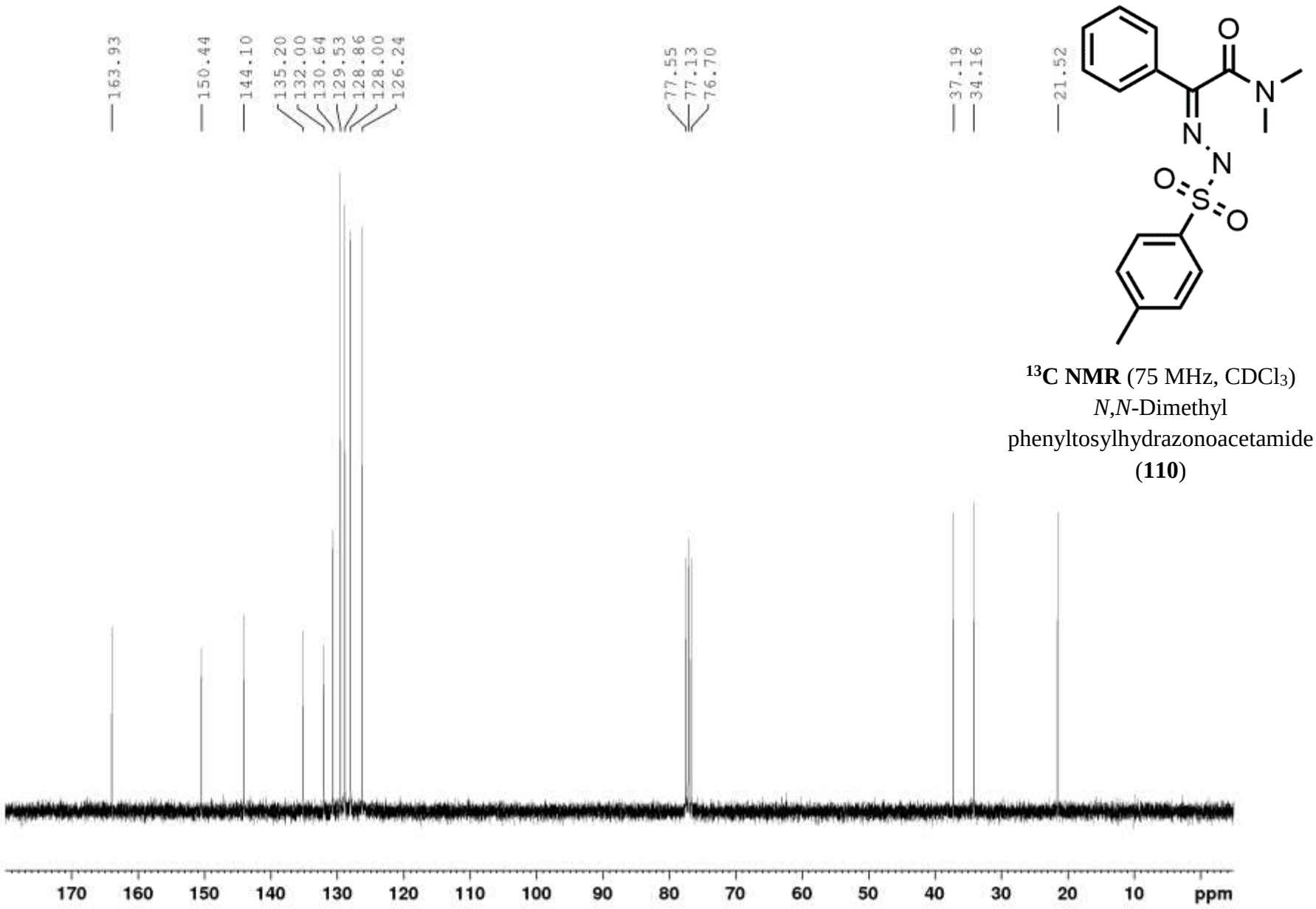
^{1}H NMR (300 MHz, $CDCl_3$)
p-Nitrophenyl phenylglyoxylate
(**106**)



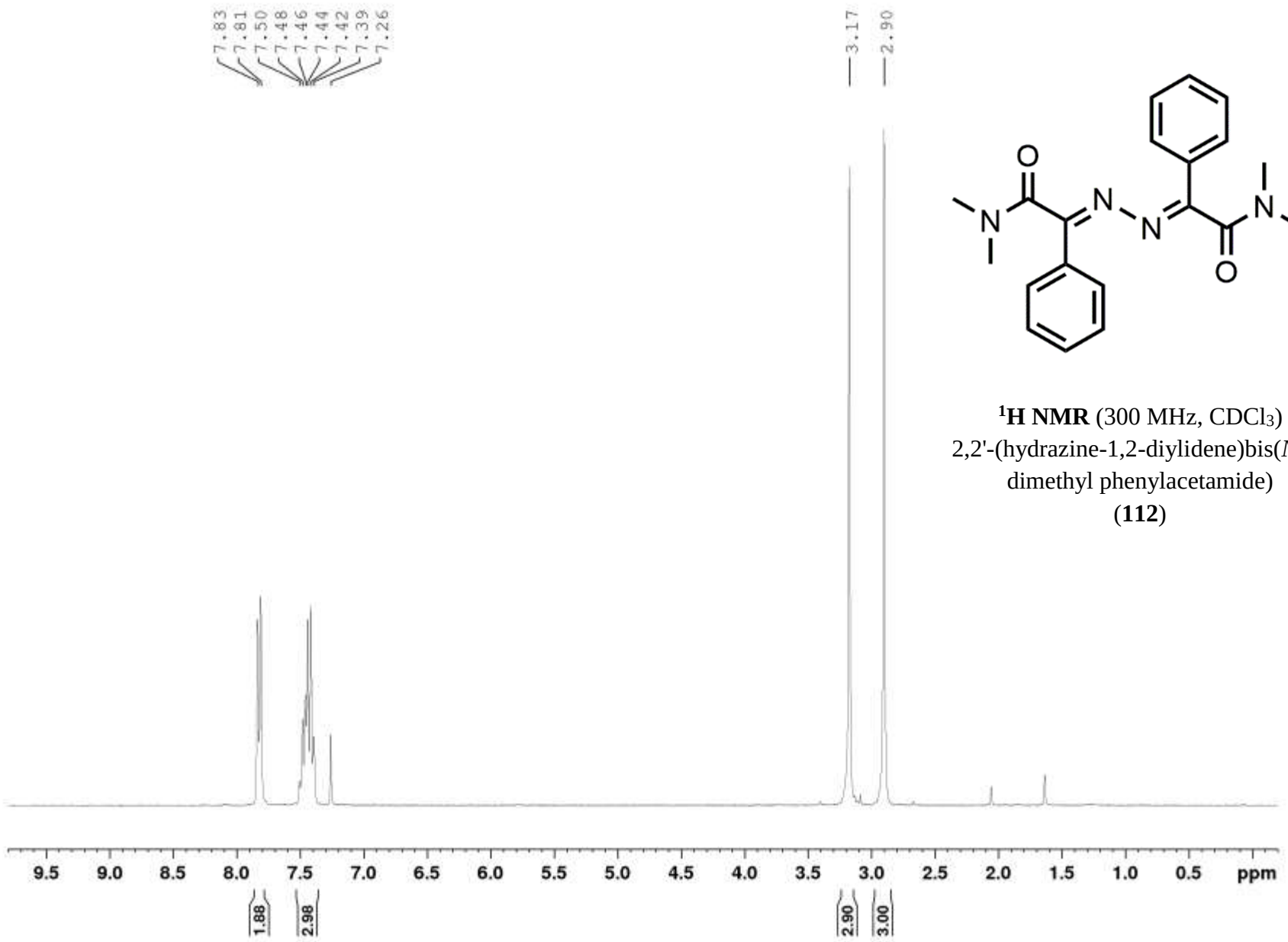
^{13}C NMR (75 MHz, $CDCl_3$)
p-Nitrophenyl phenylglyoxylate
(**106**)



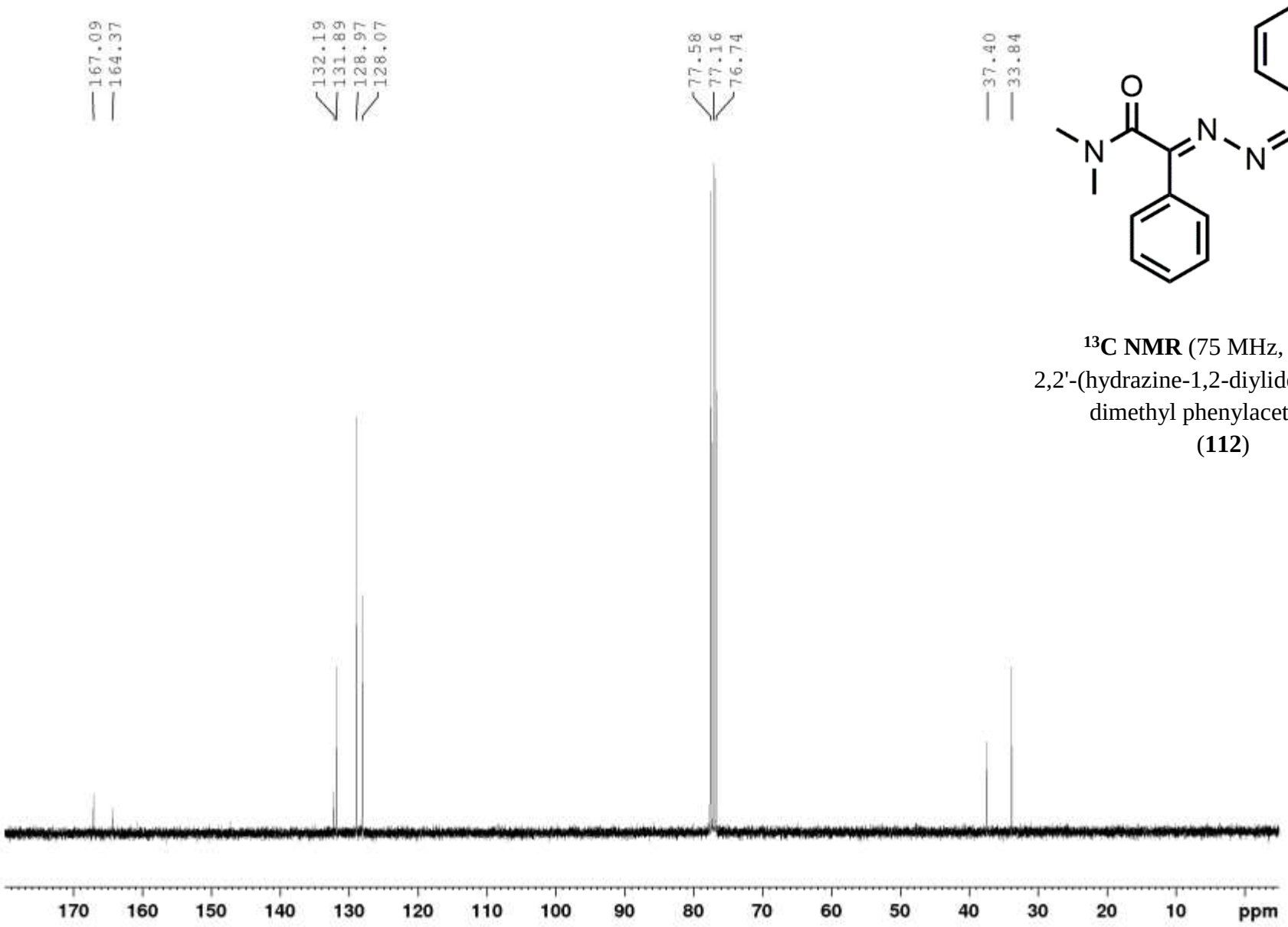
^{1}H NMR (300 MHz, $CDCl_3$)
N,*N*-Dimethyl
phenyltosylhydrazonoacetamide
(**110**)



^{13}C NMR (75 MHz, $CDCl_3$)
N,*N*-Dimethyl
phenyltosylhydrazonoacetamide
(**110**)



^{1}H NMR (300 MHz, $CDCl_3$)
2,2'-(hydrazine-1,2-diylidene)bis(*N*,*N*-dimethyl phenylacetamide)
(**112**)



^{13}C NMR (75 MHz, $CDCl_3$)
2,2'-(hydrazine-1,2-diylidene)bis(*N*,*N*-dimethyl phenylacetamide)
(**112**)