

# **Synthesis and Lewis Base-Catalyzed Functionalization of Carbamoyl Fluorides**

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# Abstract

Amides are extremely prevalent in the pharmaceutical, agrochemical and materials industries. Typically, amides are prepared by the combination of amines and carboxylic acids in the presence of an amide-coupling reagent. This dissertation describes the synthesis and reactivity of carbamoyl fluorides, a unique electrophilic class of molecules that form amides when treated with carbon-based nucleophiles.

A synthesis of carbamoyl fluorides directly from secondary amines is described. This method relies on the reaction of difluorocarbene with an oxidant to generate difluorophosgene ( $\text{COF}_2$ ) in-situ. Commercially available 4-methylpyridine *N*-oxide and a stable, easy to prepare source of difluorocarbene were found to be optimal in this reaction. Several carbamoyl fluorides were prepared with this method, and the mechanism was supported by kinetic analysis and nuclear magnetic resonance (NMR) spectroscopy experiments.

To prepare alkynamides, carbamoyl fluorides were paired with alkynyl silanes and the common laboratory reagent tetrabutylammonium fluoride (TBAF) was found to be the optimal catalyst. This reaction proceeded efficiently due to the thermodynamic driving force of forming extremely strong Si-F bonds in the by-products. A selection of alkynamides were synthesized using this method, including those bearing functional groups that may be problematic in other modern alkynamide syntheses.

Using silyl ketene imine nucleophiles,  $\alpha$ -cyanoamides were prepared from carbamoyl fluorides using either fluoride, phenanthrolines or P(V) compounds as catalysts. As the amide produced in this method contains a chiral quaternary carbon centre, this project was focused on identifying a chiral Lewis base for asymmetric catalysis. Much of this effort was committed to the

preparation of chiral P(V) derivatives due to their ease of preparation or modular synthetic routes. Unfortunately, only low enantioselectivity was observed across a broad variety of catalysts. It is suspected that the fluoride released in this reaction acts as the active catalyst, outcompeting the chiral compounds and limiting asymmetric induction.

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# List of Abbreviations

|                |                                               |
|----------------|-----------------------------------------------|
| °C             | degrees celsius                               |
| 2D             | Two dimensional                               |
| acac           | acetylacetone                                 |
| Ad             | adamantly                                     |
| Ar             | Aryl                                          |
| atm            | atmosphere                                    |
| BBN            | 9-borabicyclo(3.3.1)nonane                    |
| BDE            | Bond dissociation energy                      |
| BINAP          | (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) |
| BINOL          | 1,1'-Bi-2-naphthol                            |
| Bipy           | bipyridine                                    |
| Bn             | benzyl                                        |
| BODIPY         | 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene    |
| BQuin          | benzoquinoline                                |
| BTAF           | Benzyltrimethylammonium fluoride              |
| BTC            | Bis(trichloromethyl)carbonate                 |
| Bu             | butyl                                         |
| Bz             | benzoyl                                       |
| cat.           | catalyst                                      |
| C <sub>g</sub> | Glassy carbon                                 |
| COD            | 1,5-cyclooctadiene                            |
| Cy             | cyclohexyl                                    |
| d.r.           | Diastomeric ratio                             |
| DAST           | Diethylaminosulfur trifluoride                |
| dba            | dibenzylideneacetone                          |
| DCC            | Dicyclohexyl dicarboiimide                    |
| DCE            | dichloroethane                                |
| DCPE           | bis(dicyclohexylphosphino)ethane              |
| DCU            | dicyclohexylurea                              |
| DDQ            | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone     |
| DFC            | difluorocarbene                               |
| DIPA           | <i>N,N</i> -diisopropylamine                  |
| DIPEA          | <i>N,N</i> -diisopropylethylamine             |
| DMAP           | 4-dimethylaminopyridine                       |
| DME            | dimethoxyethane                               |
| DMF            | <i>N,N</i> -dimethylformamide                 |
| DMSO           | Dimethylsulfoxide                             |
| DNTFB          | 2,4-dinitrotrifluoromethoxybenzene            |
| DoM            | Directed <i>ortho</i> metalation              |
| DPPP           | 1,3-Bis(diphenylphosphino)propane             |
| dtbbpy         | diterbutylbipyridine                          |
| DTBM           | 3,5-di-tertbutyl-4-methoxyphenyl              |
| e.r.           | Enantiomeric ratio                            |
| EDC            | 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide |

|                   |                                                                  |
|-------------------|------------------------------------------------------------------|
| EOM               | Ethoxymethyl                                                     |
| Et                | Ethyl                                                            |
| F                 | Faraday                                                          |
| Fc                | Ferrocenyl                                                       |
| FDA               | US Food and Drug Administration                                  |
| Fmoc              | 9-fluorenylmethyl                                                |
| GC                | Gas chromatography                                               |
| h                 | Hour                                                             |
| HAT               | Hydrogen atom transfer                                           |
| HMBC              | Heteronuclear multiple bond correlation                          |
| HMPA              | Hexamethylphosphoramide                                          |
| HPLC              | High performance liquid chromatography                           |
| Hz                | Hertz                                                            |
| IMes              | 1,3-Bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene |
| IR                | Infrared spectroscopy                                            |
| L                 | Ligand                                                           |
| LB                | Lewis base                                                       |
| LDA               | Lithium diisopropylamide                                         |
| M                 | Molar                                                            |
| mA                | Milliampere                                                      |
| Me                | Methyl                                                           |
| Mes               | Mesityl, 2,4,6-trimethylphenyl                                   |
| min               | Minute                                                           |
| mmol              | Millimole                                                        |
| MPMN              | 2-methyl-2-phenylmalononitrile                                   |
| MS                | Mass spectrometry                                                |
| NHC               | <i>N</i> -heterocyclic carbene                                   |
| NMR               | Nuclear magnetic resonance                                       |
| Nuc               | Nucleophile                                                      |
| OAc               | acetate                                                          |
| OTf               | Trifluoromethanesulfonate, triflate                              |
| Pc                | phthalocyanine                                                   |
| PDFA              | (triphenylphosphonio)difluoroacetate                             |
| Ph                | phenyl                                                           |
| Phen              | phenanthroline                                                   |
| Pin               | pinacol                                                          |
| PMP               | <i>Para</i> -methoxyphenyl                                       |
| ppm               | Parts per million                                                |
| Pr                | propyl                                                           |
| PyO               | Pyridine <i>N</i> -oxide                                         |
| rt                | Room temperature                                                 |
| s                 | second                                                           |
| SKI               | Silyl ketene imine                                               |
| S <sub>N</sub> Ar | Nucleophilic aromatic substitution                               |
| SS                | Stainless steel                                                  |

|       |                                              |
|-------|----------------------------------------------|
| TBAB  | tetrabutylammonium bromide                   |
| TBAC  | tetrabutylammonium chloride                  |
| TBAF  | tetrabutylammonium fluoride                  |
| TBAI  | tetrabutylammonium iodide                    |
| TBAT  | tetrabutylammonium triphenyldifluorosilicate |
| TBS   | tertbutyldimethyl silyl                      |
| TDAE  | tetrakis(dimethylamino)ethylene              |
| TEMPO | (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl      |
| Tf    | trifluoromethanesulfonyl, trifyl             |
| TFA   | Trifluoroacetic acid                         |
| TFE   | Trifluoroethylene                            |
| TFMT  | Trifluoromethyl triflate                     |
| THF   | Tetrahydrofuran                              |
| TIPS  | Triisopropyl silyl                           |
| TLC   | Thin layer chromatography                    |
| TMB   | 1,3,5-trimethoxybenzene                      |
| TMEDA | <i>N,N,N,N</i> -trimethylethylenediamine     |
| TMG   | 1,1,3,3-tetramethylguanidine                 |
| TMS   | Trimethyl silyl                              |
| TPPO  | Triphenylphosphine oxide                     |
| Ts    | Toluenesulfonyl, tosyl                       |
| XAT   | halogen atom transfer                        |
| XEC   | cross electrophile coupling                  |

# Chapter 1: Introduction

## 1.1. Synthesis of Amides

The amide functional group is ubiquitous in biological systems,<sup>1</sup> as well as in medicinal<sup>2</sup> and materials<sup>3–5</sup> chemistry. Amides are present in countless pharmaceuticals, such as penicillin and atorvastatin, and polymers, such as Kevlar and nylon (Figure 1.1). In biological systems, peptide bond formation is facilitated by enzymatic processes in an extremely efficient manner from carboxylic acids and amines. In a synthetic chemistry lab, direct amide coupling using these starting materials becomes more problematic. In an ideal scenario, amides would be formed by simply combining the two reactants under additive-free conditions, producing one equivalent of water as the sole by-product. However, the hydroxyl group of carboxylic acids are not effective leaving groups for such a substitution to take place, thus making pre-activation with stoichiometric activating reagents and/or harsh conditions essential to amide bond formation. The development of alternative methods for the synthesis of amides is listed as a major goal in green chemistry by the American Chemical Society, and therefore, remains an ongoing research endeavor.<sup>6</sup> This introductory chapter will focus on a brief overview of the various methods to access amide-containing molecules. Traditional amide coupling reagents will be briefly discussed with a heavier focus placed on halogenated carbonyl electrophiles. The chapter will culminate in the application of fluorinated electrophiles in amide-bond forming reactions, with a discussion of the unique reactivity they enable, despite traditionally being labelled as unreactive.

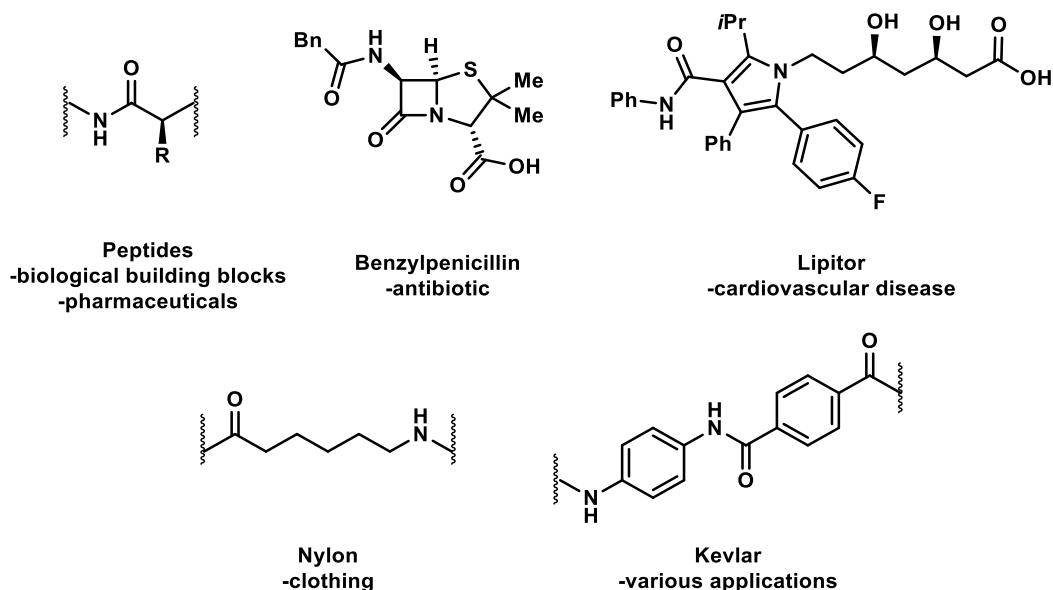
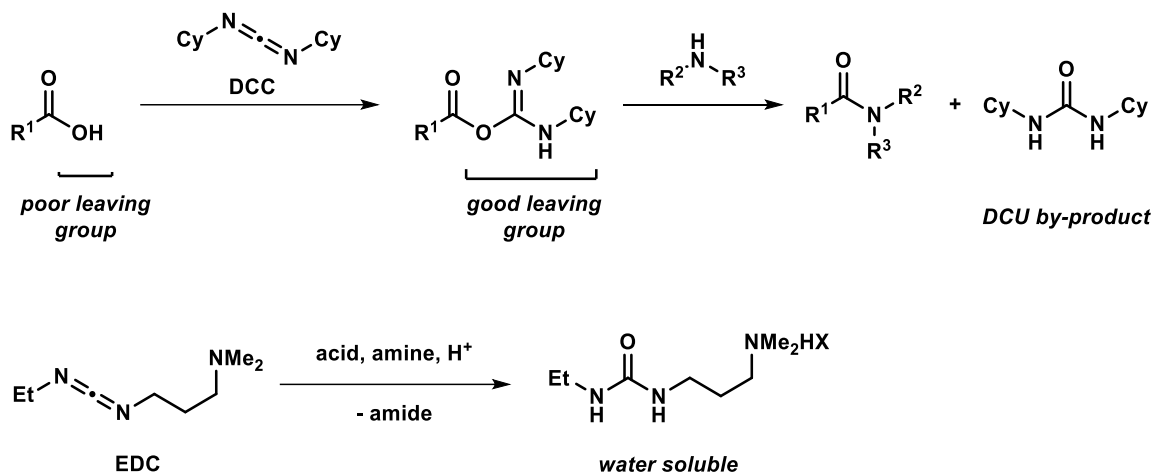


Figure 1. 1: Various Amides Useful to Society

### 1.1.1 Traditional Synthesis of Amides

Amides are typically prepared from amines and carboxylic acids using a variety of coupling reagents.<sup>7,8</sup> In general, these reagents react with the carboxylic acid, transforming the poor hydroxide leaving group into a functionality that is easily displaced by the amine nucleophile under mild conditions. Several classes of coupling reagents have become popularized for amide synthesis—the most common of which arguably being carbodiimides, such as dicyclohexyl carbodiimide (DCC). Upon deprotonation of the acid by DCC, reaction of the carboxylate with the protonated coupling reagent leads to an *O*-isourea (Scheme 1.1). This intermediate is now sufficiently electrophilic to undergo nucleophilic attack by the amine, producing the desired amide and dicyclohexylurea (DCU) as a stoichiometric by-product. In addition to producing significant waste, it is notoriously difficult to separate DCU from the amide product using silica gel chromatography. Alternatively, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) can be

used for amide coupling. Upon acidic work-up, the EDC-derived urea is protonated at the tertiary amine and can be crashed out of solution or extracted into aqueous media. A full discussion of the plethora of other amide coupling reagents is outside the scope of this dissertation.



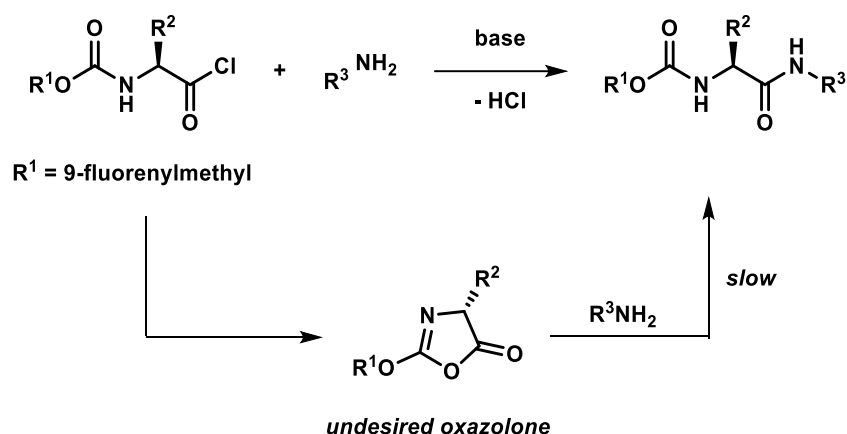
## Representative Amide Coupling Reaction with DCC

### 1.1.2 Halogenated Electrophiles for Amide Synthesis

#### 1.1.2.1 Acyl Halides

A common pre-activation strategy for amide synthesis is the conversion of unreactive carboxylic acids to highly electrophilic acyl halides. This transformation is typically achieved using deoxyhalogenation reagents, which operate similarly to amide coupling reagents. After activation of the carboxylic acid, nucleophilic attack by a halide anion provides the highly reactive acyl halide intermediate. Subsequent treatment of the acyl halide with an amine partner produces the desired amide with one equivalent of a mineral acid ( $HX$ ) as the by-product. Interestingly, the use of acyl chlorides outnumbers that of acyl fluorides by greater than 200:1, indicating a clear preference by synthetic chemists.<sup>9</sup>

The first example describing the use of acyl chlorides in amide-coupling reactions was reported by Fischer in 1903.<sup>10</sup> Since then, these electrophiles have become ubiquitous in amide synthesis and the broader field of synthetic chemistry.<sup>7,9</sup> However, the use of these amide precursors can be problematic, as their high electrophilicity can lead to unwanted side reactions and they are often prone to loss of stereochemical configuration of the  $\alpha$ -carbon via ketene formation. For example, an Fmoc-protected amino acid chloride can cyclize on the acyl chloride moiety to form an undesired oxazolone in the presence of base (Scheme 1.2).<sup>11</sup> Although the oxazolone can react with the amine to reach the desired amide product, this is a slow process and requires an exogenous activating reagent to produce the coupled product in high yield.



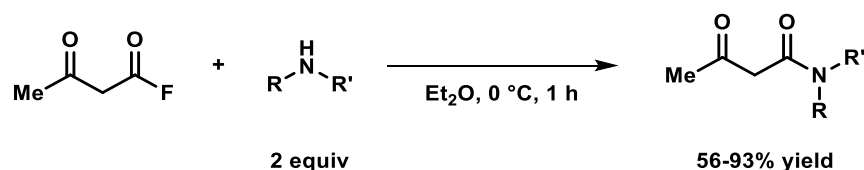
Scheme 1. 1: Oxazolone Formation Hinders Amide Formation from Acylated Amino Acid Chlorides

Acyl chlorides are the most common intermediate for this transformation, but acyl fluorides have also gained significant traction for their ease of synthesis, handling, and isolation.<sup>8,12,13</sup> While acyl fluorides have found use in transition metal catalysis for forming C-C bonds,<sup>14</sup> they are primarily used for amide preparation to circumvent several issues inherent to acyl chlorides. The high electronegativity and low polarizability of fluoride makes it a significantly worse leaving group than chloride, thus increasing the stability of the compound. This effect leads to fewer



unwanted side reactions, slower hydrolysis of the acyl fluoride and increased configurational stability of chiral analogs. Acyl fluorides can be synthesized from carboxylic acids using a number of deoxyfluorination reagents,<sup>15</sup> with some modern examples involving the fluorocarbonylation of aryl and alkyl halides<sup>16</sup> or the radical dehydrofluorination of aldehydes.<sup>17</sup>

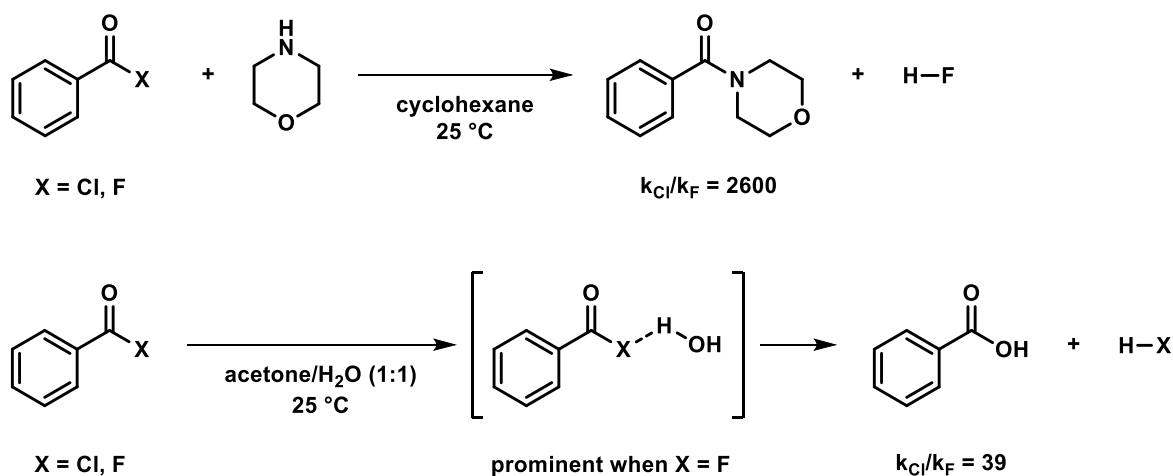
An early example of amide synthesis from acyl fluorides was reported by the Olah group in 1961, where acetoacetyl fluoride was subjected to various primary and secondary amines.<sup>18</sup> An additional equivalent of the reactant amine was used to quench HF produced in this reaction. However, an exogenous tertiary amine base, such as NEt<sub>3</sub>, is often used as a more economically viable alternative. These results indicate that acyl fluorides are competent amide precursors in place of acyl chlorides.



Scheme 1. 2: Synthesis of Amides from Acetoacetyl Fluoride

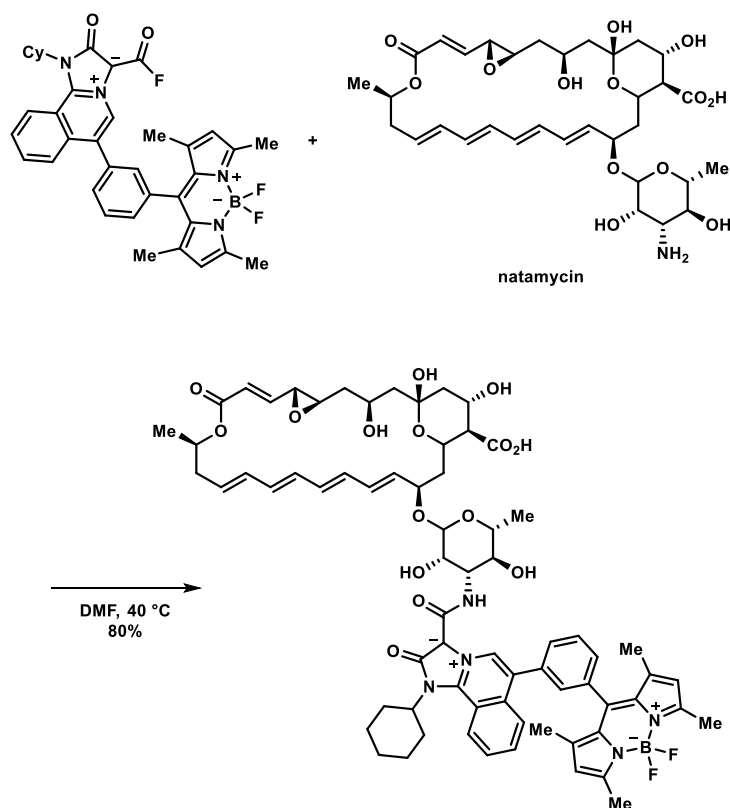
The following year, Bender and co-workers studied the relative rates of nucleophilic acyl substitution reactions with benzoyl fluoride and related acyl halides (Scheme 1.4, top).<sup>19</sup> The authors found the rate of amide formation from benzoyl fluoride with morpholine to be 2600 times slower than the same reaction with benzoyl chloride in cyclohexane at 25 °C. This result suggests that acyl fluorides are indeed more reluctant to react with nucleophiles than the analogous chlorides. Interestingly, however, the rate of hydrolysis of benzoyl fluoride in a 1:1 acetone-water mixture is only 39 times slower than with benzoyl chloride (Scheme 1.4, bottom). The increased hydrogen bond accepting ability of fluoride compared to chloride is likely responsible for this

unproportional change of rates with different nucleophiles. It should also be taken as a precaution that while acyl fluorides are less reactive than acyl chlorides, hydrogen bond donors will greatly increase their reactivity.<sup>20</sup>



Scheme 1. 3: Rate Comparison of Aminolysis (top) and Hydrolysis (bottom) of Benzoyl Halides

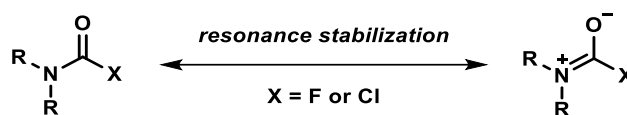
The higher stability of acyl fluorides allows for their incorporation into more complex structures, providing greater freedom of design for more specific applications. An example of this strategy was reported by Kielland, Vendrell and Lavilla, where an acyl fluoride containing a 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) fragment was prepared.<sup>21</sup> BODIPY derivatives are commonly used as fluorescent dyes for cellular imaging. The incorporation of an acyl fluoride moiety in this system allows for rapid conjugation to the antifungal compound natamycin (Scheme 1.5). This molecule was found to be an effective fluorescent staining agent that selectively binds to fungal pathogen cells over bacterial cells *in vitro*.



Scheme 1. 4: Substitution of a BODIPY-Appended Acyl Fluoride

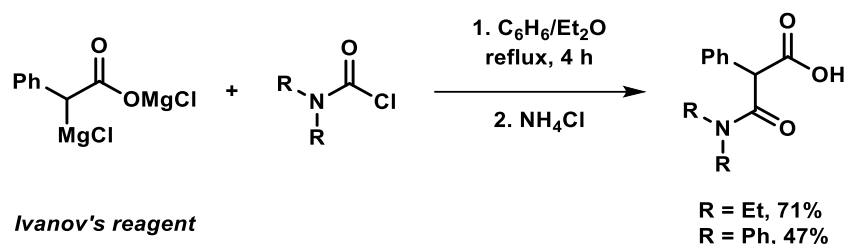
#### 1.1.2.2 Carbamoyl Chlorides

While acyl halides have become commonplace in organic chemistry, their ease of hydrolysis makes them challenging to work with—an issue that persists even when using more stable acyl fluorides. The use of carbamoyl halides ( $R_2NCOX$ ) for amide synthesis via a C-C bond formation offers a complementary route. This transformation may be beneficial when the carboxylic acid required for the targeted amide is difficult to access. Instead, an amine can be converted to a carbamoyl halide and paired with a carbon-based nucleophile. Carbamoyl halides are also significantly more stable than acyl halides. This effect is due to the lone pair of electrons on the nitrogen atom, which decreases the electrophilicity of the carbonyl through resonance stabilization (Scheme 1.6).



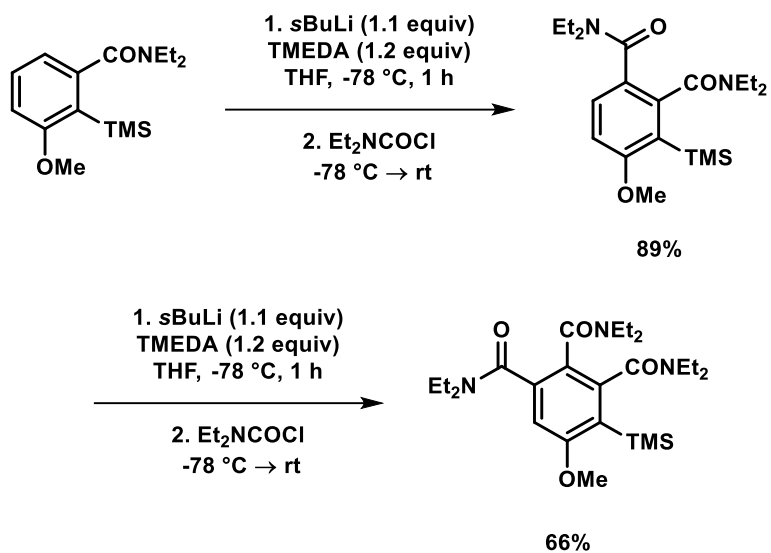
Scheme 1. 5: Structure of Carbamoyl Halides

The treatment of carbamoyl chlorides with organometallic nucleophiles, such as organolithiums (RLi) or Grignard reagents (RMgX, X = Cl, Br, I), is a common route to access amides via a C-C bond formation. One of the earliest observations of this reactivity was reported by Blicke and Zinnes where Ivanov's Grignard reagent was reacted with diethyl or diphenyl carbamoyl chloride to provide  $\alpha$ -phenylmalonamic acids in 71% and 47% yields, respectively (Scheme 1.7).<sup>22</sup>



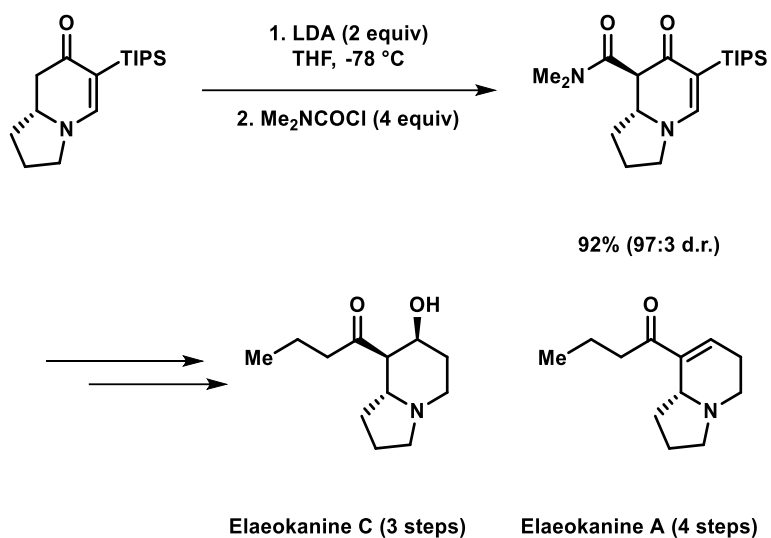
Scheme 1. 6: Reaction of Ivanov's Reagent with Carbamoyl Chlorides

Snieckus and co-workers have used carbamoyl chlorides as electrophiles in directed *ortho*-metalation reactions of benzamides, demonstrating their compatibility with aryl carbanion nucleophiles (Scheme 1.8).<sup>23</sup> A polysubstituted *N,N*-dimethyl benzamide could be selectively deprotonated *ortho* to the amide and quenched with dimethyl carbamoyl chloride to provide the resulting diamide. Repeating the sequence a second time provided access to a pentasubstituted aromatic molecule in moderate yield.



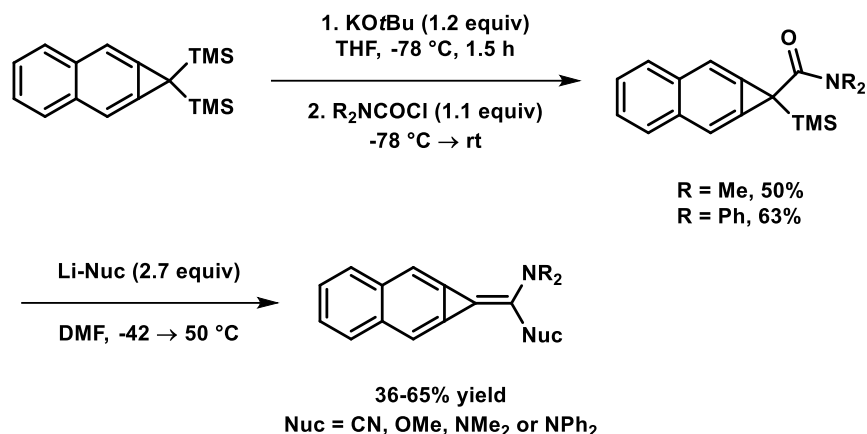
Scheme 1. 7: Directed *ortho*-Metallation and Carbamoylation of Highly Substituted Arenes with Carbamoyl Chlorides

Carbamoyl chlorides have also found use in the total synthesis of natural products. Comins and co-workers used dimethyl carbamoyl chloride to functionalize the enolate of a cyclic ketone to obtain a  $\beta$ -ketoamide with high diastereoselectivity (Scheme 1.9).<sup>24</sup> This intermediate was carried forward to access (+)-Elaeokanine C in three steps and (+)-Elaeokanine A with one additional transformation. This carbamoylation procedure expands upon Zinnes' early work, demonstrating that high yields of amide products can be obtained with ketone enolate nucleophiles.



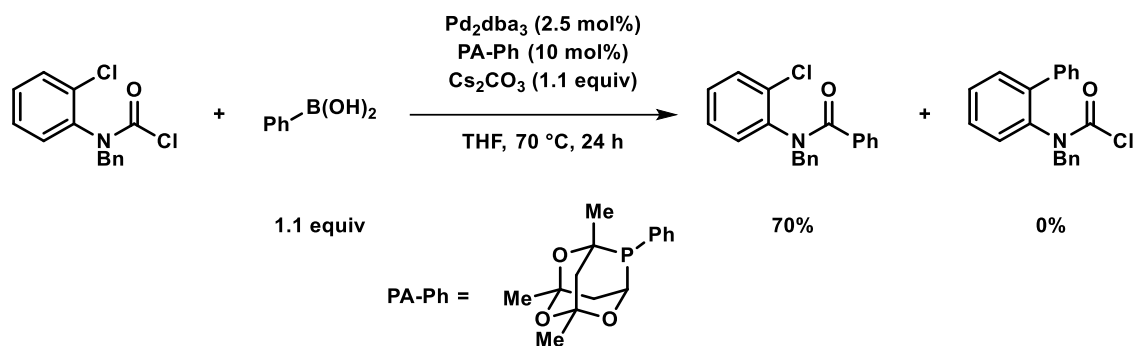
Scheme 1. 8: Enolate Substitution with Carbamoyl Chlorides Towards the Total Synthesis of Elaeokanine C and A

The groups of Stang and Halton also used carbamoyl chlorides for the preparation of a unique class of alkylidenecyclopropanes (Scheme 1.10).<sup>25</sup> Treatment of a disilylated cycloproparene with KOtBu resulted in facile desilylation to obtain an anionic intermediate. This anion reacts with a carbamoyl chloride to produce cyclopropylamides in moderate yields. Carbamoyl electrophiles are essential for the preparation of these intermediates, as it would be challenging to obtain the analogous carboxylic acid for standard amide coupling. Subjecting these compounds to anionic nucleophiles initiates a Peterson olefination reaction to obtain the desired alkylidenecyclopropane.



Scheme 1. 9: Synthesis of Alkylidenecyclopropanes with Carbamoyl Chlorides

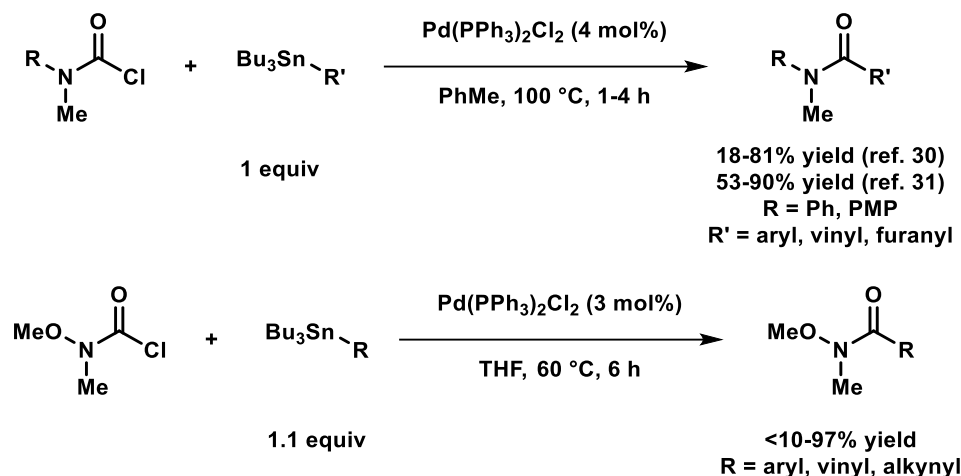
The C-Cl bond of carbamoyl chlorides is relatively weak compared to an aryl chloride (84.7 kcal/mol for ClCONH<sub>2</sub><sup>26</sup> vs 97.6 kcal/mol for chlorobenzene<sup>27</sup>), suggesting that carbamoyl chlorides should be amenable to oxidative addition by a low-valent transition metal. Lautens and Schoenebeck demonstrated this by showing oxidative addition by Pd(0) of a carbamoyl chloride outcompetes an aryl chloride on the same substrate (Scheme 1.11).<sup>28</sup> The same study suggests that oxidative addition of carbamoyl chlorides likely proceeds through an ionic or nucleophilic substitution mechanism rather than a classic three-centred transition state. While significant progress has been made in transition metal-catalyzed reactions of carbamoyl chlorides,<sup>29</sup> most of these reaction involve a cyclization step, with much fewer examples of intermolecular cross couplings reported in the literature.



Scheme 1. 10: Comparing Oxidative Addition of Aryl Chlorides and Carbamoyl Chlorides with Pd(0)

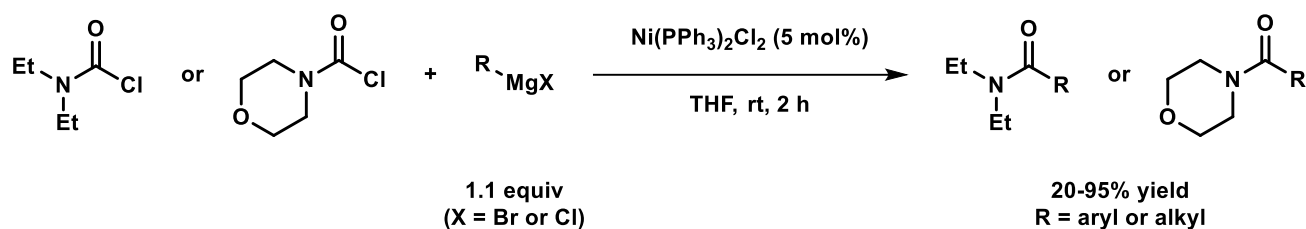
In the early 1990s, Jousseau and co-workers discovered that carbamoyl chlorides can be used as electrophiles in Pd-catalyzed Stille cross-coupling reactions (Scheme 1.12, top).<sup>30,31</sup> Using  $\text{Pd(PPh}_3)_2\text{Cl}_2$  as the catalyst, carbamoyl chlorides could be converted to the corresponding benzamides ( $\text{R}' = \text{aryl}$ ), acrylamides ( $\text{R}' = \text{vinyl}$ ) and furanamides ( $\text{R}' = \text{furan}$ ) in moderate to good yields. This method was further explored by Murakami and Ito, expanding the electrophile scope to *N*-methyl-*N*-methoxycarbamoyl chloride (Scheme 1.12, bottom).<sup>32</sup> This updated method provides access to Weinreb amides, which are extremely useful intermediates for further chemical diversification. This procedure is complementary to typical approaches towards Weinreb amides, which are accessed from a carboxylic acid (derivative) and *N,O*-dimethylhydroxylamine.





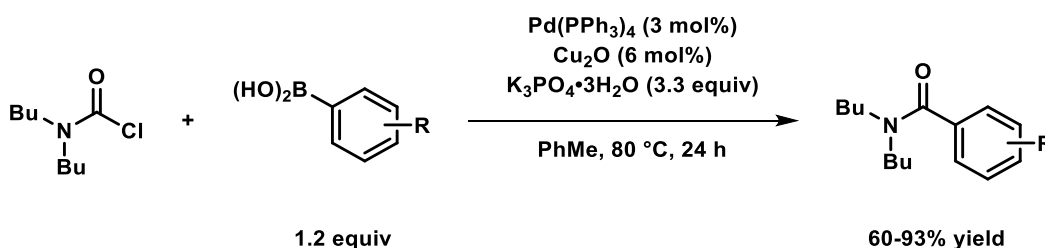
Scheme 1. 11: Pd-Catalyzed Stille Cross-Couplings of Carbamoyl Chlorides

While the Stille cross-coupling is a versatile and reliable method, the use of organotin reagents is undesirable due to their high toxicity. While testing the reaction of carbamoyl chlorides and Grignard reagents at room temperature, Rouden and co-workers found that the transformation was sluggish.<sup>33</sup> The researchers found that adding catalytic amounts of  $\text{Ni(PPh}_3)_2\text{Cl}_2$  to this system—conditions similar to a Kumada coupling—led to amide formation in relatively good yields for both alkyl amides and benzamides (Scheme 1.13). Although the Kumada-like conditions provide a less toxic route to amides from carbamoyl chlorides, the use of strongly basic Grignard reagents can limit functional group tolerance.



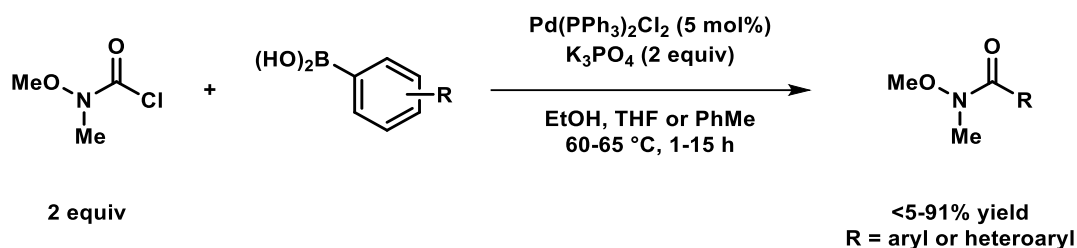
Scheme 1. 12: Ni-Catalyzed Kumada Cross-Coupling of Carbamoyl Chlorides

The Suzuki-Miyaura cross-coupling is the most frequently used catalytic reaction in the pharmaceutical industry.<sup>34</sup> This is due to the stable and relatively non-toxic nature of boronic acid nucleophiles used in the reaction. Boronic acids are also commercially abundant and affordable. Deng and co-workers developed a Pd/Cu co-catalyzed Suzuki-Miyaura coupling of carbamoyl chlorides using several electronically and sterically diverse boronic acids to access benzamides (Scheme 1.14).<sup>35</sup> While this method offers access to amides in a catalytic fashion with less basic and non-toxic nucleophiles, dibutylcarbamoyl chloride was the only electrophile tested in the report and the role of Cu<sub>2</sub>O remains unclear.



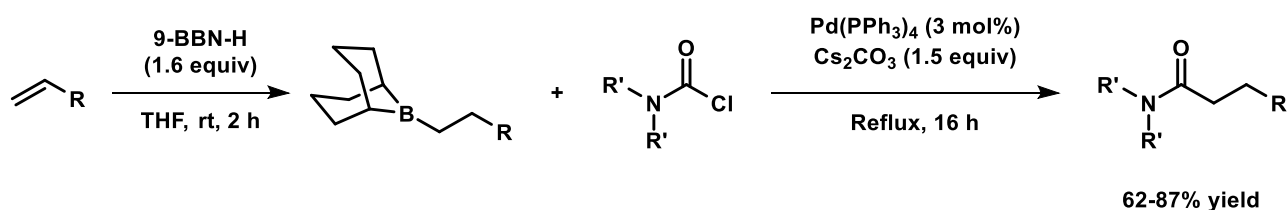
Scheme 1. 13: Pd/Cu Co-Catalyzed Suzuki-Miyaura Coupling of Carbamoyl Chlorides

Similar to earlier studies by Murakami and Ito,<sup>32</sup> Herr and co-workers later developed a Suzuki-Miyaura coupling with *N*-methyl-*N*-methoxycarbamoyl chloride (Scheme 1.15).<sup>36</sup> This reaction can be done in multiple solvents (PhMe, THF and EtOH) at lower reaction temperatures and does not require a Cu co-catalyst. While the resulting Weinreb amides are useful synthons for the synthesis of ketones, expanding the scope of carbamoyl chlorides would be beneficial to expand the reaction toolkit for amide synthesis.



Scheme 1. 14: Synthesis of Weinreb Amides from Carbamoyl Chlorides and Arylboronic Acids

The Takemoto group developed a Csp<sup>2</sup>-Csp<sup>3</sup> Suzuki-Miyaura coupling of carbamoyl chlorides with alkyl borane nucleophiles to access alkyl amide products (Scheme 1.16).<sup>37</sup> Treatment of terminal alkenes with 9-borabicyclo(3.3.1)nonane (9-BBN-H) in THF formed an alkyl-BBN product with anti-Markovnikov selectivity. Upon addition of the Pd catalyst, base and carbamoyl chloride, the desired amide product could be obtained in one pot under refluxing conditions. Simpler alkyl fragments could be coupled with dibenzyl carbamoyl chloride by omitting the hydroboration step and using the commercial borane instead (e.g., triethylborane). Phenylboronic acid and styrylboronic acid were also well tolerated under the developed conditions to obtain benzamides and acrylamides, respectively.



Scheme 1. 15: One-Pot Hydroboration of Alkenes and Subsequent Pd-Catalyzed Suzuki-Miyaura Cross-Coupling of Carbamoyl Chlorides

The Maiti group has developed a Ni/Ir co-catalyzed photochemical cross-electrophile coupling (XEC) reaction of aryl bromides and chlorides with carbamoyl chlorides (Scheme 1.17, top).<sup>38</sup> This reaction proceeds through slightly different mechanisms depending on the halogen of

the aryl electrophile (Scheme 1.17, bottom, mechanism shown for aryl chlorides). Oxidative addition of an aryl chloride by Ni(0) species **A** forms Ni(II) intermediate **B**, which is subsequently oxidized to Ni(III) complex **C** by the excited Ir(III) photocatalyst. Upon visible light excitation, **C** ejects a chlorine radical, leading to Ni(II) species **D**. The chlorine radical promotes hydrogen atom transfer (HAT) from TMS<sub>3</sub>SiH, forming a silyl radical that undergoes halogen atom transfer (XAT) from a carbamoyl chloride. The resulting carbamoyl radical combines with **D** to form Ni(III) intermediate **E**. This species undergoes reductive elimination to produce the desired benzamide product and Ni(I) complex **F**, which is reduced by Ir(II), regenerating both **A** and the Ir(III) photocatalyst. When aryl bromides are used, the photocatalyst undergoes triplet energy transfer with **B**, which ejects a bromide radical from Ni(II). This eventually provides an aryl-carbamoyl-Ni(II) complex (not shown) that produces the product upon reductive elimination and directly regenerates **A**.



fluorides for esterase inhibition.<sup>40</sup> In this study, the authors compared these compounds to their analogous carbamoyl chlorides (Figure 1.2, representative example). Interestingly, the carbamoyl fluorides demonstrated significantly higher rates of inhibition for all enzymes tested. This is likely due to the fluoride leaving group acting as a better hydrogen bond acceptor, as in Bender's substitution study of acyl fluorides (Scheme 1.4), thus leading to higher rates of covalent inhibition in the enzymatic environment.

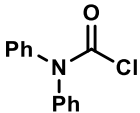
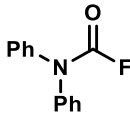
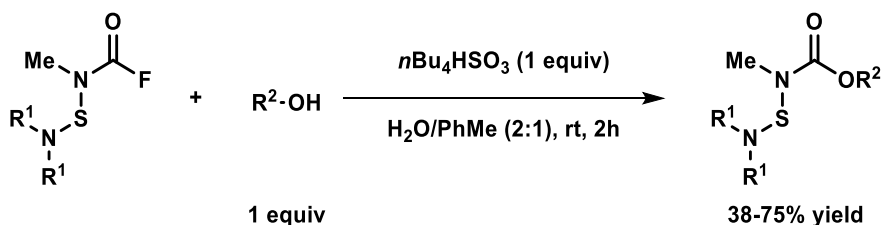
|                             |                                                                                   |                                                                                     |
|-----------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
|                             |  |  |
|                             | Rate Constant of Enzyme Inhibition (L/mol•s)                                      |                                                                                     |
| Enzyme:                     |                                                                                   |                                                                                     |
| acetylcholin esterase       | 2.2                                                                               | 347                                                                                 |
| human serum cholin esterase | 145                                                                               | 12900                                                                               |
| chymotrypsin                | 480                                                                               | 3790                                                                                |
| trypsin                     | 7                                                                                 | 58                                                                                  |

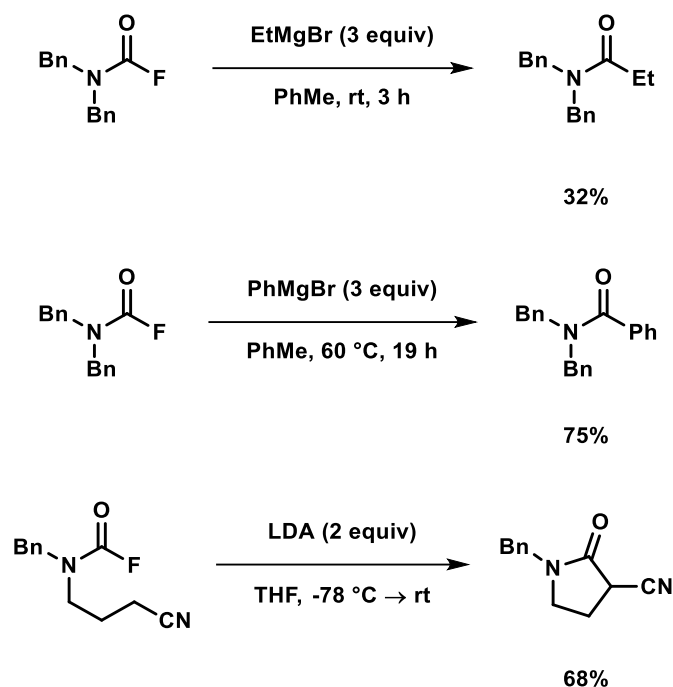
Figure 1. 2: Comparing the Rate of Inhibition of Various Enzymes by Diphenylcarbamoyl Chloride and Fluoride

In 1978, Hatch prepared several potent *N*-sulfenylated carbamate insecticides from carbamoyl fluorides and alcohols under phase-transfer conditions to circumvent certain patent restrictions (Scheme 1.18).<sup>41</sup> Such carbamates are potent insecticides that have low mammalian toxicity, demonstrating another important application of carbamoyl fluorides. This report represents an early example of the applicability of carbamoyl fluorides as useful synthetic intermediates.



Scheme 1. 17: Synthesis of Insecticidal Carbamates from *N*-sulfenylated Carbamoyl Fluorides

While the increased stability of C-F bonds has made acyl fluorides desirable alternatives to their chlorinated analogs, the seemingly sufficient stability of carbamoyl chlorides has led to limited research into the reactivity of carbamoyl fluorides since Hatch's report.<sup>41</sup> With regards to amide preparation via C-C bond formation, the treatment of carbamoyl chlorides with Grignard reagents has already proven to be inefficient at room temperature (Rouden reported a 0.85:1 ratio of amide to unreacted carbamoyl chloride after 21 hours at room temperature).<sup>33</sup> This observation may lead to the assumption that carbamoyl fluorides are not useful in such reactions. However, several groups have demonstrated that the reaction of carbamoyl fluorides with organometallic reagents is possible. Wang, Feng and co-workers reacted dibenzylcarbamoyl fluoride with 3 equivalents of EtMgBr at room temperature to access *N,N*-dibenzylpropanamide in 32% yield (Scheme 1.19, top),<sup>42</sup>. The Min group also subjected this carbamoyl fluoride to PhMgBr, albeit at elevated temperatures, to produce *N,N*-dibenzylbenzamide in 75% yield (Scheme 1.19, middle).<sup>43</sup> Lim and co-workers also found success in lactam formation by treating a nitrile-appended carbamoyl fluoride with LDA (Scheme 1.19, bottom).<sup>44</sup> This led to deprotonation of the  $\alpha$ -proton of the nitrile and subsequent intramolecular substitution of the carbamoyl fluoride.

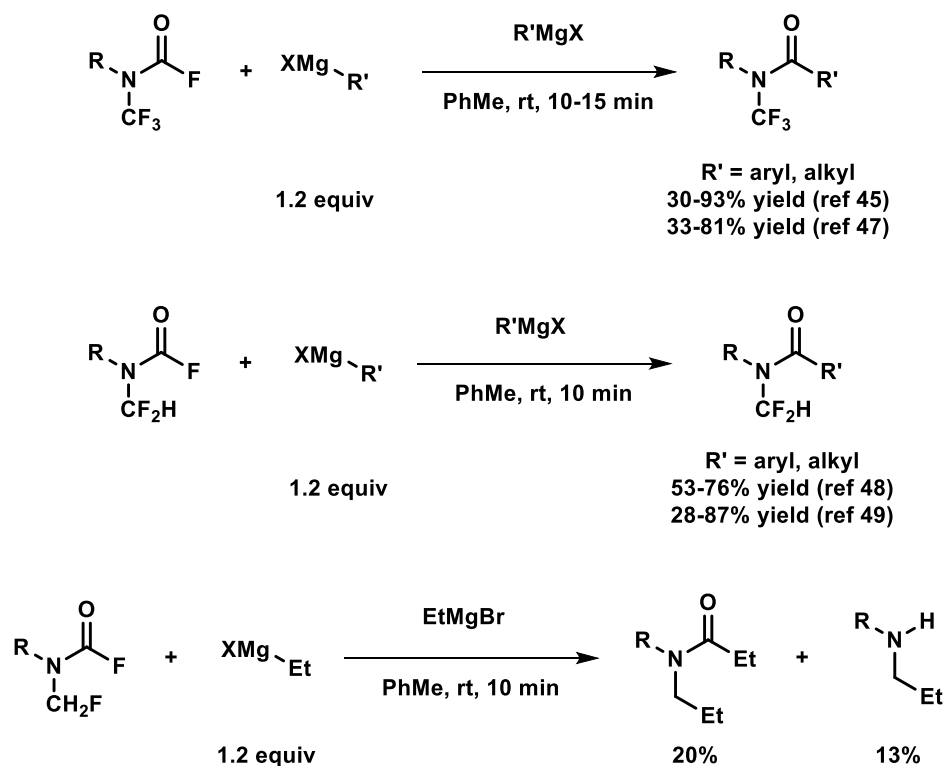


Scheme 1. 18: Substitution of Carbamoyl Fluorides with Carbanion Nucleophiles

More practical applications of carbamoyl fluorides began emerging in the late 2010s and early 2020s. Among these is the isolation of *N*-fluoroalkyl carbamoyl fluorides—pharmaceutically relevant amide precursors. Schoenebeck and co-workers have pioneered this research area, being the first group to synthesize *N*-CF<sub>3</sub> carbamoyl fluorides.<sup>45,46</sup> They found that these compounds reacted smoothly with a variety of aryl and alkyl Grignard reagents at room temperature in just 10 minutes (Scheme 1.20, top). Xu and co-workers found similar reactivity of *N*-CF<sub>3</sub> carbamoyl fluorides prepared by a different method.<sup>47</sup> Both the Schoenebeck and Yi groups found that *N*-CF<sub>2</sub>H carbamoyl fluoride could also be substituted with a variety of Grignard reagents (Scheme 1.20, middle).<sup>48,49</sup> However, when *N*-CH<sub>2</sub>F carbamoyl fluorides were treated with Grignard reagents, defluoroalkylation of the fluoromethyl group occurs, along with substitution of the carbamoyl fluoride or hydrolysis to give a defluorinated amide and amine (Figure 1.20, bottom).<sup>50</sup> These trends in reactivity highlight the challenge with functionalizing carbamoyl fluorides,

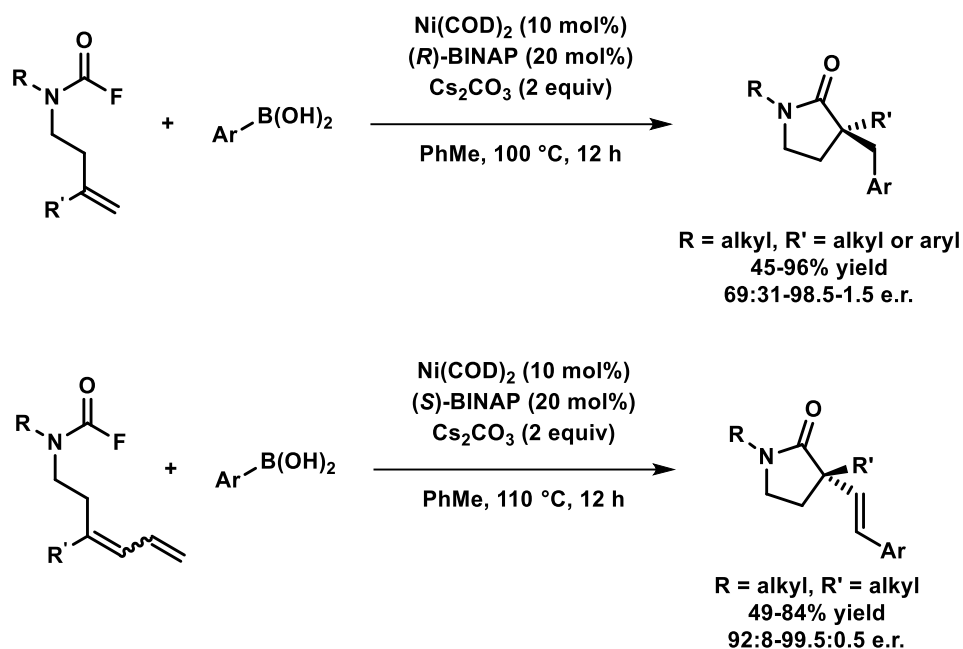


indicating that the use of alternative, catalytic strategies may be required for efficient amide synthesis.



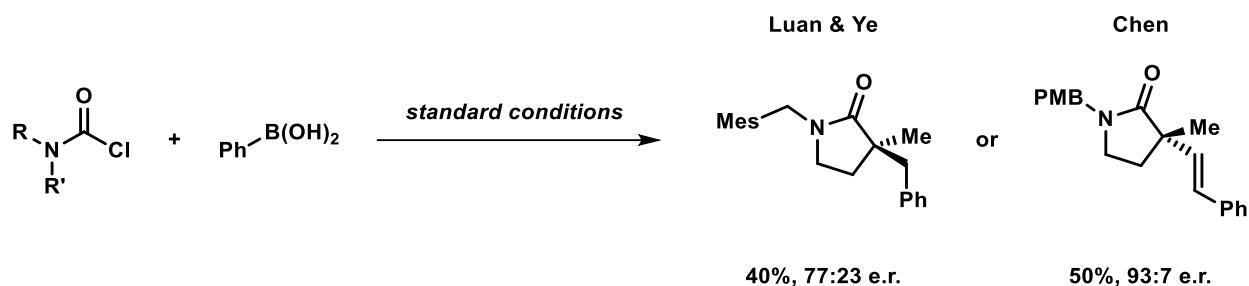
Scheme 1. 19: Reactions of *N*-fluoroalkyl Carbamoyl Fluorides with Grignard Reagents

The carbamoyl fluoride C-F bond is amenable to activation by transition metal catalysis to enable their use in traditional cross-coupling reactions. The first example of such reactivity was published by Luan, Ye and co-workers in 2020.<sup>51</sup> The authors reported an asymmetric intramolecular Suzuki-Miyaura-like reaction of alkene-tethered carbamoyl fluorides with aryl boronic acids to access enantioenriched  $\gamma$ -lactams (Scheme 1.21, top). This method used a Ni catalyst and (*R*)-BINAP as a chiral ligand. A similar reaction was developed by Chen and co-workers using diene-tethered carbamoyl fluorides, giving rise to  $\alpha$ -vinyl- $\gamma$ -lactams (Scheme 1.21, bottom).<sup>52</sup>



Scheme 1. 20: Intramolecular Ni-Catalyzed Asymmetric Carbocarbamoylation of Alkenes with Carbamoyl Fluorides and Arylboronic Acids

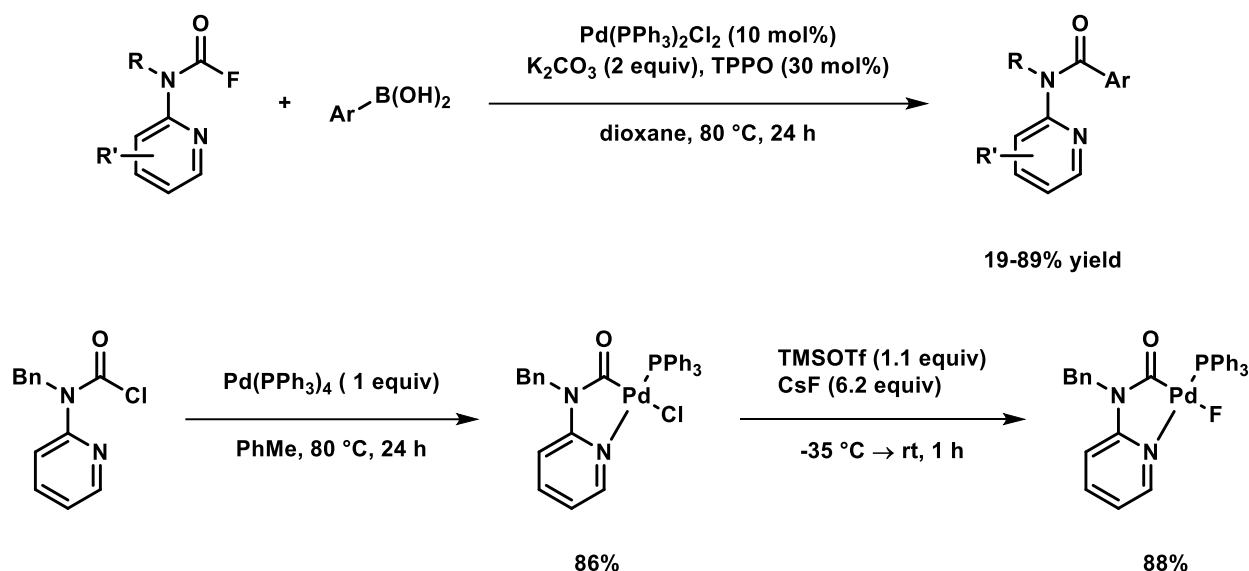
When the analogous carbamoyl chlorides were subjected to the standard reaction conditions for both reactions, the products were obtained in 40% yield with a 77:32 enantiomeric ratio (e.r.) in Luan and Ye's system and 50% yield with 93:7 e.r. in Chen's system (Scheme 1.22). These data indicate that the nature of the carbamoyl halide has a profound effect on both the reactivity and selectivity of catalytic reactions. While the authors have not identified the origins of this halide-dependence, these results should encourage the testing of both carbamoyl chlorides and fluorides in catalytic reaction development, as they may offer complementary reactivity and selectivity profiles.



Scheme 1. 21: Use of Carbamoyl Chlorides Under Ni-Catalyzed Conditions

In both of these reports,<sup>51,52</sup> the direct intermolecular Suzuki-Miyaura cross-coupling product was never observed. When Luan, Ye and co-workers used a carbamoyl fluoride without a tethered alkene with  $PCy_3$  as the ligand, only trace amounts of the benzamide were formed (Scheme 1.23, top). Intriguingly, the intermolecular cross-coupling of carbamoyl fluorides has proven to be a challenging task to date. Even with the seemingly more reactive  $N-CF_3$  carbamoyl fluorides, Suzuki-Miyaura and Negishi couplings failed to yield amide products under Ni catalysis (Scheme 1.23, middle)<sup>53</sup>. The use of  $N-CH_2F$  carbamoyl fluorides also failed to provide an amide under Pd-catalyzed conditions (Scheme 1.23, bottom).<sup>50</sup> These attempts of intermolecular cross coupling led to recovery of the starting material, suggesting that C-F bond activation is challenging. Hiyama-Denmark-type cross coupling of  $N-CF_3$  carbamoyl fluorides has been achieved with alkynyl silanes under Ni catalysis,<sup>53</sup> and discussion of this reaction will be presented in Chapter 3 of this document.





Scheme 1. 23: Pd-Catalyzed Intermolecular Suzuki-Miyaura Coupling of *N*-2-pyridylcarbamoyl Fluorides

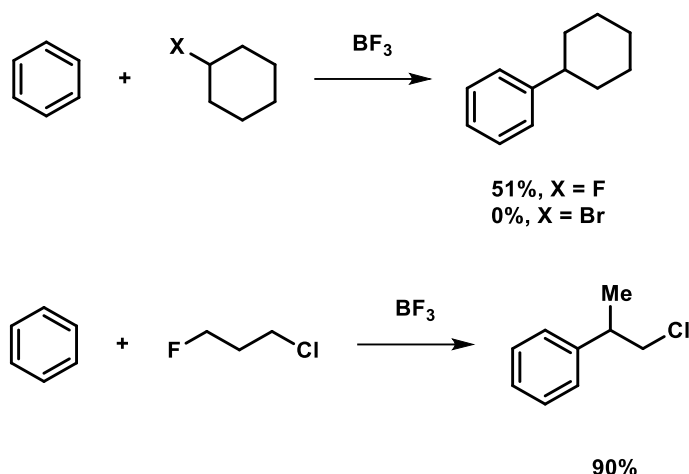
## 1.2 Reactivity of Fluorinated Electrophiles

Fluorine-containing compounds have become prominent in pharmaceutical industry, with roughly 20% of all approved drugs containing at least one fluorine atom.<sup>55</sup> One of the most well-established effects of fluorine substitution in medicinal chemistry is the enhancement of metabolic stability.<sup>56</sup> When a particular site within a drug molecule is susceptible to enzymatic cleavage, medicinal chemists will incorporate a C-F bond in the problematic position to slow down its metabolism and increase its half-life. This effect originates from the high electronegativity of fluorine, leading to incredibly strong C-F bonds. The bond dissociation energy (BDE) of the C-F bond is 105.4 kcal/mol, which is significantly stronger than that of a C-H bond (98.8 kcal/mol). While the high BDE of C-F bonds might appear to pose a significant challenge for its activation in synthetic transformations, it is important to note that these values are reported for direct homolytic bond

cleavage processes—an uncommon mode of activation for organofluorine substrates. In reality, a selection of catalysts can achieve efficient C-F bond activation through polar mechanisms.

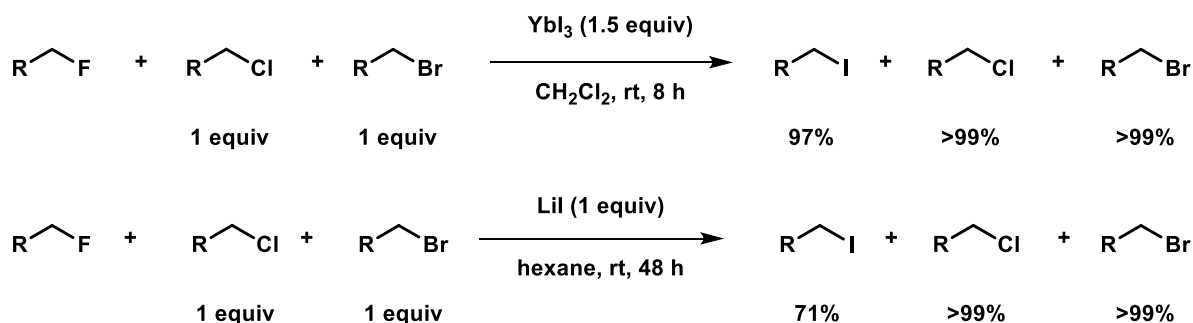
Organofluorine electrophiles have gained significant popularity owing to their increased stability relative to other halide analogs. Despite the fluoride leaving group not being retained in the final product, its presence can be essential for driving the desired chemical reaction. This allows for a high degree of control over chemoselectivity through choice of the appropriate reagents or catalysts. The following examples will highlight this phenomenon, termed *fluoride-enabled reactivity*.

Alkyl fluorides are rarely used as electrophiles in substitution reactions due to their significantly low reactivity compared to alkyl chlorides, bromides and iodides. However, with the correct choice of a Lewis acid catalyst, alkyl fluorides can be rendered more compatible for  $S_N1$ -like reactions. In 1942, Burwell and Archer demonstrated that alkyl fluorides are highly reactive in  $BF_3$ -catalyzed Friedel-Crafts reactions where the other alkyl halides failed (Scheme 1.25, top).<sup>57</sup> Two decades later, Olah and co-workers remarkably found that when 1-chloro-3-fluoropropane in benzene is treated with a stream of  $BF_3$  gas, only the isomerized alkyl chloride product is obtained (Scheme 1.25, bottom).<sup>58</sup>



Scheme 1. 24: F-Selective Friedel-Crafts Alkylation of Benzene

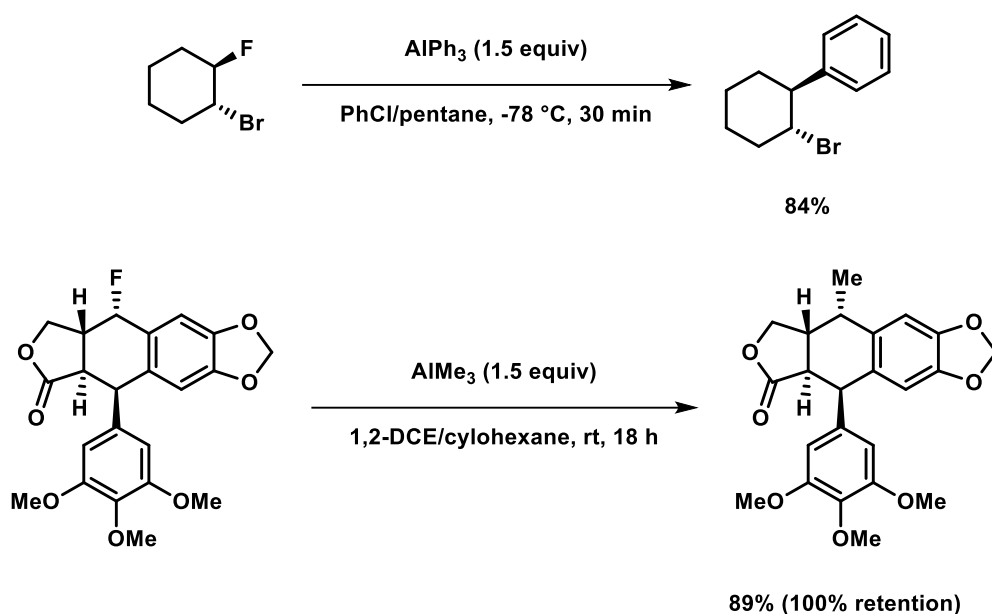
This unexpected result indicates that  $\text{BF}_3$  is selective for fluoride abstraction, even in the presence of a typically more reactive alkyl chloride.<sup>59</sup> More recently, the Hilmersson and Davis groups have achieved the iodo-defluorination of alkyl halides mediated by  $\text{YI}_3$  and  $\text{LiI}$ , respectively (Figure 1.26).<sup>60,61</sup> These methods show selective alkyl iodide formation from the corresponding alkyl fluorides, whereas alkyl chlorides and bromides are unreactive, under Lewis acidic conditions.



Scheme 1. 25: Lewis Acid-Mediated Iodo-defluorination of Alkyl Fluorides in the Presence of Other Alkyl Halides

Wolf and co-workers showed that the use of organoaluminum reagents at low temperature can selectively substitute alkyl fluorides with alkyl, aryl, alkenyl or alkynyl fragments.<sup>62</sup> Selectivity

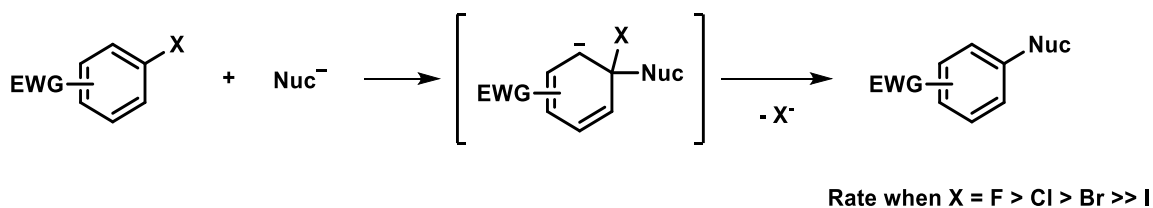
could be achieved in the presence of other alkyl halides (Scheme 1.27, top). Stereochemical configuration is retained when using a sterically congested chiral alkyl fluoride (Scheme 1.27, bottom). These examples demonstrate how fluorine substitution can enable unconventional reactivity and selectivity that can be further exploited in synthesis.



Scheme 1. 26: Selective Substitution of Alkyl Fluorides with Organoaluminum Reagents

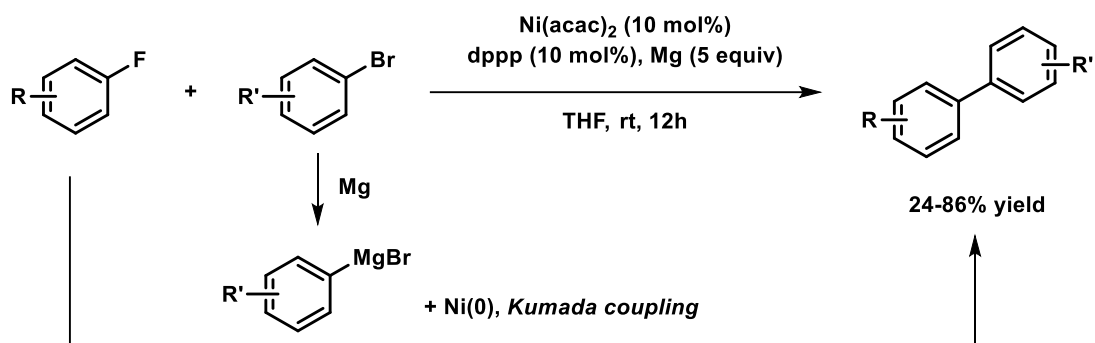
A well-known example of fluoride-enabled reactivity is the nucleophilic aromatic substitution ( $\text{S}_{\text{N}}\text{Ar}$ ) reaction, in which substitution occurs via nucleophile attack of the *ipso* carbon of an electron-deficient aryl halide (Scheme 1.28).<sup>63</sup> Unlike typical substitution reactions,  $\text{S}_{\text{N}}\text{Ar}$  reactions demonstrate a reversed reactivity trend, with aryl fluorides being the most reactive substrates. This observed reactivity is due to the rate-determining step in these reactions being the dearomatization of the aryl halide. Thus, the high electronegativity of fluorine pulls electron density from the *ipso* carbon, making it more electrophilic and susceptible to nucleophilic attack.





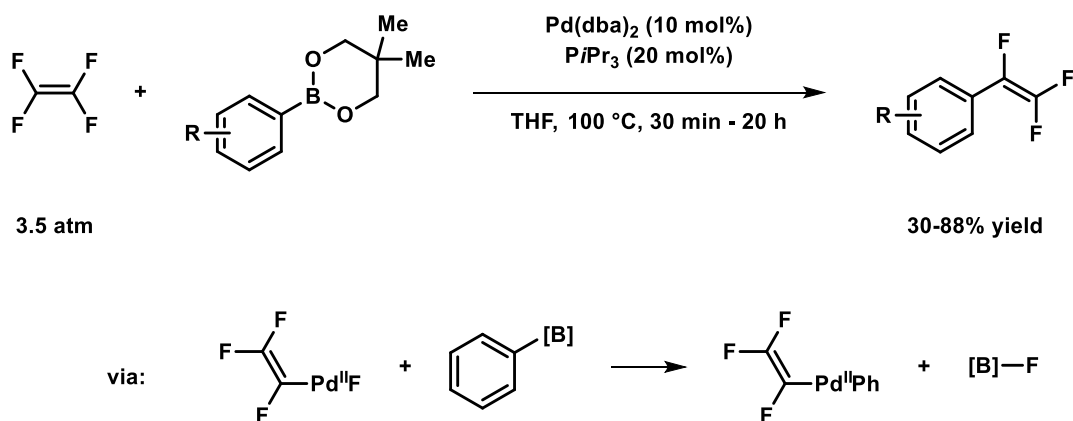
Scheme 1. 27: Mechanism of Nucleophilic Aromatic Substitution of Aryl Fluorides

When engaged in late transition metal-catalyzed cross-coupling reactions, aryl fluorides are typically considered inert due to the challenging oxidative addition of  $Csp^2$ -F bonds. In the limited reports describing the cross-coupling of aryl fluorides, high temperatures, directing groups and/or additives are required for the reaction to proceed, and the presence of other aryl halide moieties is not tolerated.<sup>64-66</sup> However, this sluggish bond cleavage can be beneficial in certain cases. In 2023, a formal XEC reaction of aryl bromides and aryl fluorides was reported under Ni catalysis in the presence of stoichiometric Mg(0) (Scheme 1.29).<sup>67</sup> The authors propose that Mg(0) reacts selectively with aryl bromides to form Grignard reagents in-situ, which participate in a typical Kumada coupling reaction with aryl fluoride electrophiles. In this case, the slow reactivity of aryl fluorides towards insertion with Mg(0) and Ni(0) allows for full conversion of the aryl bromide into their corresponding Grignard reagent before the catalytic cycle begins, leading to complete cross-selectivity.



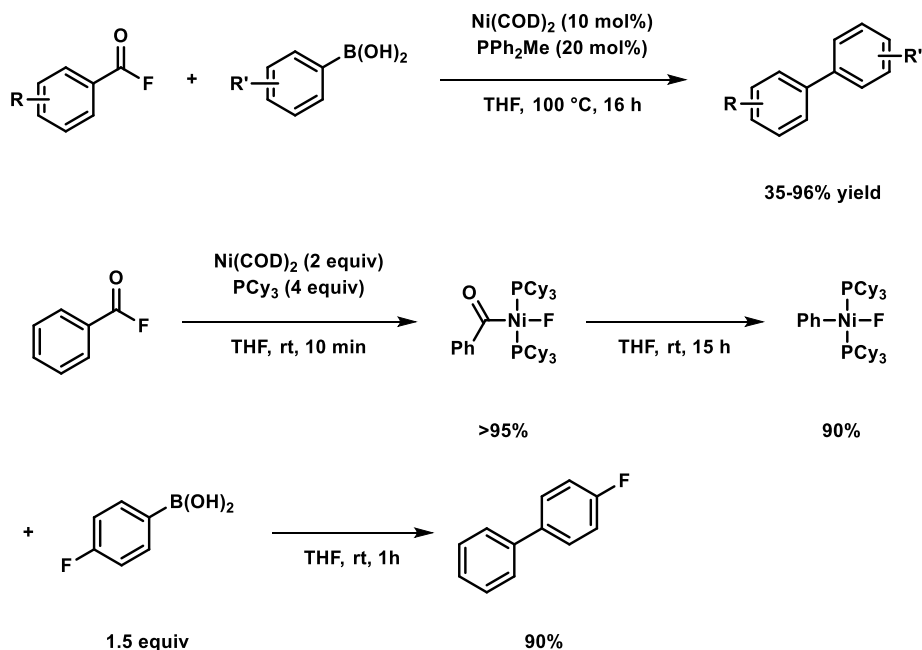
Scheme 1. 28: Ni-Catalyzed XEC of Aryl Fluorides and Aryl Bromides

Another form of fluoride-enabled reactivity is where the fluoride leaving group can participate in the reaction, circumventing the need for additional reagents that may be required with other halides. In 2012, Ogoshi and co-workers reported a Pd-catalyzed Suzuki-Miyaura cross coupling of tetrafluoroethylene (TFE) and similar fluorinated ethylenes with aryl boronic esters (Scheme 1.30).<sup>68</sup> The authors proposed that Pd(0) can undergo C-F bond oxidative addition of TFE to access the vinyl Pd(II)-F complex. As boron is highly fluorophilic, transmetallation of the boronic ester proceeds without the need for exogenous base (Scheme 1.30, bottom) and subsequent reductive elimination provides the vinyl arene product.



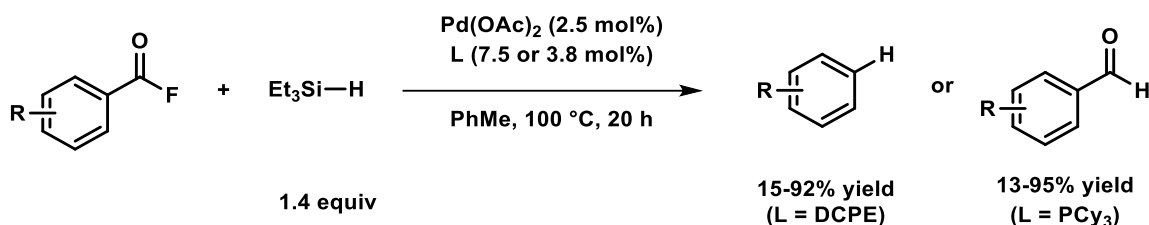
Scheme 1. 29: Pd-Catalyzed Cross-Coupling of TFE and Arylboronic Esters and Proposed Transmetallation Pathway

The principle of using a fluoride leaving group as an internal base for cross-coupling was expanded upon by the Sanford group, who developed a decarbonylative Suzuki-Miyaura coupling of acyl fluorides with aryl boronic acids (Scheme 1.31, top).<sup>69</sup> This report used Ni as the catalyst and conducted detailed stoichiometric studies of the elementary steps (Scheme 1.31, bottom). Treatment of benzoyl fluoride with  $\text{Ni(COD)}_2$  and  $\text{PCy}_3$  provided acyl Ni(II)-F complex in quantitative yield in only 10 minutes, indicating a facile oxidative addition step. Upon stirring in solution overnight, an aryl Ni(II)-F complex is obtained in 90% yield via decarbonylation. Finally, treatment of this complex with an aryl boronic acid provides high yields of the biaryl product in one hour, indicating that transmetalation is highly favourable with a Ni(II)-F species. The catalytic reaction produces biaryl products in moderate to excellent yields, even with electron-deficient boronic acids that are normally prone to protodeborylation in the presence of exogenous base.



Scheme 1. 30: Ni-Catalyzed Decarbonylative Coupling of Acyl Fluoride and Arylboronic Acids

A similar Pd-catalyzed variation of this decarbonylative cross-coupling of acyl fluorides has been reported in the context of a hydrodecarbonylation reaction.<sup>70</sup> In this case, the formation of a Si-F bond as a byproduct provides a thermodynamic driving force for base-free transmetalation with triethylsilane (Scheme 1.32). The authors also found ligand-dependent reactivity in this reaction. The use of DCPE, a bidentate ligand, allows for partial dissociation to open a coordination site, enabling the decarbonylation process to access the arene product. When PCy<sub>3</sub> was used, this dissociation was not favourable and decarbonylation did not occur, thus leading to the aldehyde product.



Scheme 1. 31: Direct and Decarbonylative Cross Coupling of Acyl Fluorides with Tertiary Silanes

## 1.3 Conclusion and Research Prelude

Aside from its use in the pharmaceutical and agrochemical industries, C-F bond electrophiles have gained increasing attention in numerous coupling and substitution reactions, owing to their unique reactivity. The presence of fluoride leaving group can influence these reactions by biasing rates of elementary steps, decreasing the kinetic barrier of certain steps, or undergoing preferential binding to catalysts or other functional handles to create a thermodynamic driving force for C-F bond cleavage. This phenomenon has been observed in the reaction of aryl fluorides, alkyl fluorides and acyl fluorides, giving rise to a variety of diverse products. In the context of fluoride-enabled

reactivity, the carbamoyl fluoride functional group has been scarcely explored.<sup>71</sup> A limited number of C-C bond forming reactions of carbamoyl fluorides have been reported for accessing amides, an extremely important functionality in many fields of chemistry. This dissertation will explore a simple synthetic route for accessing carbamoyl fluorides, as well as their use in catalytic, fluoride-enabled reactions. The primary focus of the latter goal will be the use of organosilicon nucleophiles to provide a thermodynamic driving force in the form of silyl fluoride by-product formation.

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# Chapter 2: Synthesis of Carbamoyl Fluorides

## 2.1 Contributions

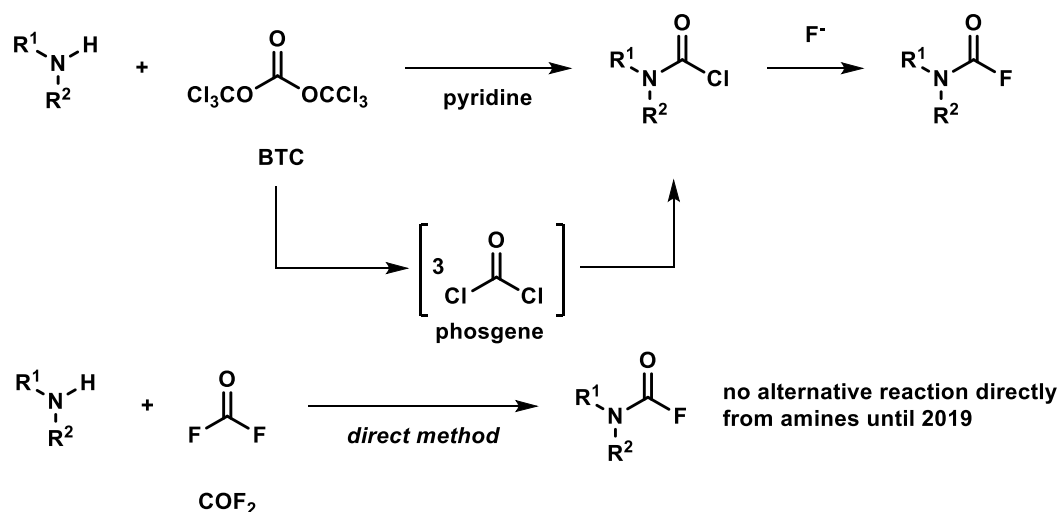
This chapter describes the synthesis of carbamoyl fluorides from secondary amines in combination with 4-methylpyridine *N*-oxide and the difluorocarbene precursor, PDFA. This work was done in collaboration with M.Sc. student Tristan Tiburcio, who synthesized several of the carbamoyl fluoride substrates. Undergraduate student George Cieszynski prepared various starting secondary amines and repeated a handful of the carbamoyl fluoride syntheses for characterization purposes. The author's contributions include the optimization of the reaction conditions, preparing the majority of the substrate scope and performing mechanistic studies. The contributions of each author are noted in the text and labelled as such throughout the chapter. Much of this chapter was published in the *Journal of Organic Chemistry* and was selected as an *ACS Editors' Choice* article and the *2023 Journal of Organic Chemistry Outstanding Publication of the Year*.

Citation: Cadwallader, D.; Tiburcio, T. R.; Cieszynski, G. A.; Le, C. M., *J. Org. Chem.*, **2022**, 87, 11457-11468.<sup>1</sup>

## 2.2 Introduction

In recent years, there has been a reemergence of carbamoyl fluorides as a precursor to amides, carbamates, thiocarbamates and ureas.<sup>2-4</sup> Carbamoyl fluorides are extremely useful in amide bond-forming reactions as an alternative to the coupling of amines and carboxylic acids. However, the chemistry of carbamoyl fluorides has been overshadowed by that of the analogous carbamoyl

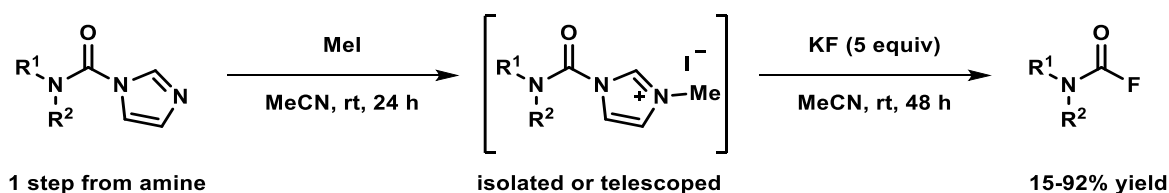
chlorides.<sup>5</sup> The synthesis of carbamoyl chlorides has been heavily adopted due to the invention of triphosgene, or bis(trichloromethyl)carbonate (BTC),<sup>6</sup> a crystalline alternative to gaseous phosgene.<sup>7</sup> At cryogenic temperatures, secondary amines and BTC react in the presence of a nucleophilic base, typically pyridine, to readily form carbamoyl chlorides (Scheme 2.1, top). Researchers have yet to develop a commercially available surrogate for difluorophosgene ( $\text{COF}_2$ ), a slightly less toxic gas that can be used for preparing carbamoyl fluorides (Scheme 2.1, bottom).<sup>8</sup> Typically,  $\text{COF}_2$  is prepared by the reaction of  $\text{CO}$  and  $\text{F}_2$ , two highly toxic and corrosive gasses.<sup>9</sup> This dangerous process, combined with the toxicity of  $\text{COF}_2$  makes alternative fluorocarbonylation methods highly attractive.



Scheme 2. 1: Synthesis of Carbamoyl Chlorides and Fluorides Using Phosgene Derivatives

While efficient and atom-economic, the direct synthesis of carbamoyl fluorides from secondary amines and  $\text{COF}_2$  is highly undesirable due to the toxicity of the gaseous reagent. Alternatively, carbamoyl fluorides can be prepared from a carbamoyl chloride when treated with a fluoride salt (Scheme 2.1, top).<sup>10,11</sup> Recently, Gobec and co-workers developed a method to access carbamoyl fluorides from carbamoyl imidazoles (Scheme 2.2).<sup>12</sup> This protocol first required

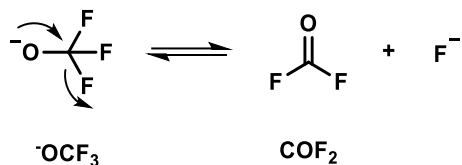
imidazole *N*-methylation with MeI to obtain a more electrophilic imidazolium salt. This salt was then treated with KF to form a carbamoyl fluoride, producing *N*-methyl imidazole as a byproduct. While this reaction is three steps from the parent secondary amine, the reagents used are extremely common and the use of phosgene or COF<sub>2</sub> is avoided completely. However, the multi-step nature of these routes has proven to deter the synthetic chemistry community from realizing the full potential of carbamoyl fluorides. The introductory section of this chapter will highlight modern methods to access carbamoyl fluorides directly from secondary amines or other simple building blocks.<sup>13</sup>



Scheme 2. 2: Synthesis of Carbamoyl Fluorides from Carbamoyl Imidazoles

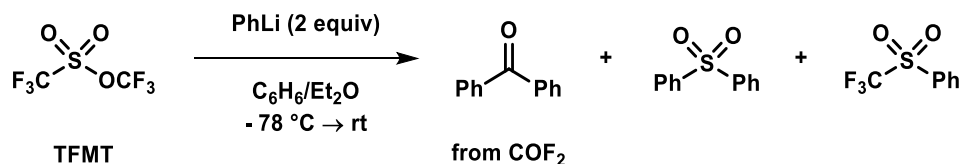
### 2.2.1 Synthesis of Carbamoyl Fluorides via Trifluoromethoxide Anions

To avoid the use of highly toxic COF<sub>2</sub>, surrogates that form the reagent in-situ are highly desirable fluorocarbonylation reagents. The trifluoromethoxide anion has been identified as a useful surrogate for such reactions due to its ability to reversibly eliminate fluoride and form COF<sub>2</sub> (Scheme 2.3).<sup>14,15</sup> Early studies show that smaller cations, or those with high charge-to-size ratio, favour COF<sub>2</sub> at equilibrium.



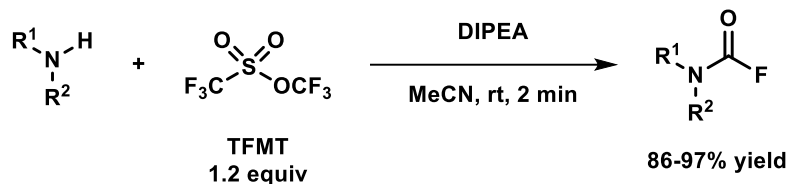
Scheme 2. 3: Conversion of Trifluoromethoxide into Difluorophosgene

In 1987, Martin and co-workers explored the synthesis and reactivity of trifluoromethyl triflate (TFMT) and identified it as a useful sulfonylating reagent.<sup>16</sup> In this study, it was found that when TFMT was treated with a nucleophile, trifluoromethoxide was released as a by-product. The authors demonstrated that treating TFMT with phenyl lithium led to a complex mixture of products, including benzophenone, diphenylsulfone and phenyl trifluoromethyl sulfone (Scheme 2.4). The observation of benzophenone confirms the presence of  $\text{COF}_2$  in the reaction.



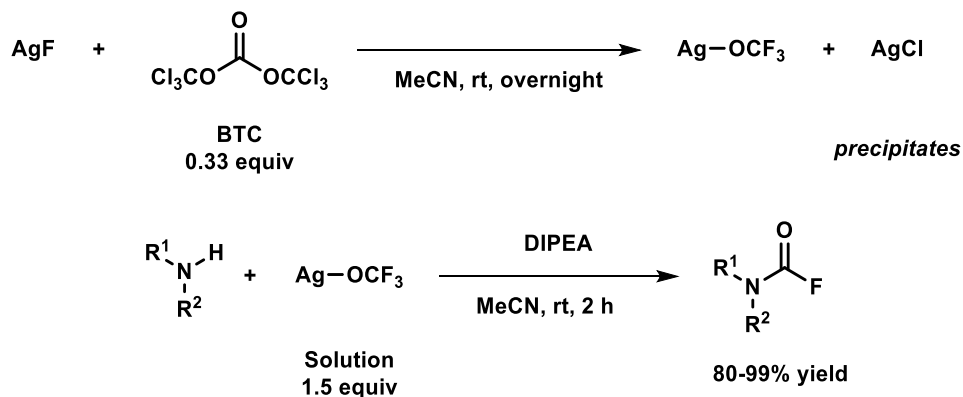
Scheme 2. 4: Reaction of TFMT with PhLi

In 2019, Zhang and co-workers investigated the use of TFMT as a surrogate for  $\text{COF}_2$ .<sup>17</sup> Along with the synthesis of ureas, carbamates and heterocycles, TFMT was found to be extremely effective at preparing carbamoyl fluorides secondary amines (Scheme 2.5). This method boasts high yields and an extremely short reaction time of two minutes. However, one drawback is that TFMT is a volatile liquid that is difficult to handle and store.



Scheme 2. 5: Synthesis of Carbamoyl Fluorides from TFMT and Secondary Amines

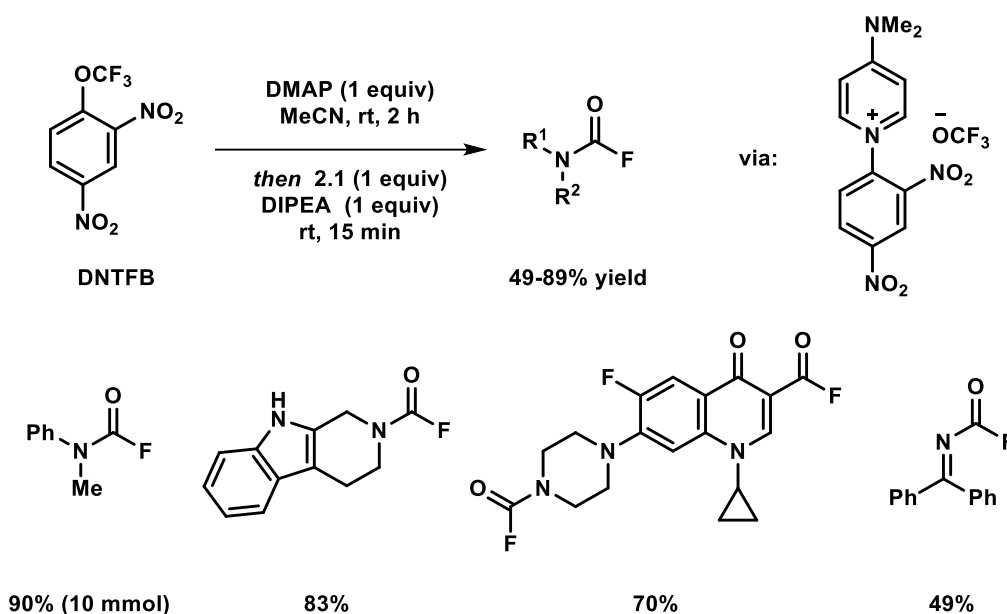
Shortly after, Schoenebeck developed a method to prepare a stable solution of  $\text{AgOCF}_3$  in MeCN that can be stored for up to three months.<sup>18</sup> This solution is obtained by mixing  $\text{AgF}$  with BTC in MeCN, followed by filtration of insoluble  $\text{AgCl}$ . Aside from its use in trifluoromethoxylation of alkyl halides, the  $\text{AgOCF}_3$  solution efficiently converted secondary amines to carbamoyl fluorides with excellent yields and relatively short reaction times (Scheme 2.6).



Scheme 2. 6: Preparation of  $\text{AgOCF}_3$  and its Use in Carbamoyl Fluoride Synthesis

Recently, the groups of Toulgoat and Billard demonstrated that 2,4-dinitrotrifluoromethoxybenzene (DNTFB) can be treated with DMAP to generate a uniquely stable pyridinium trifluoromethoxide salt via an  $\text{S}_{\text{N}}\text{Ar}$  reaction.<sup>19</sup> The same researchers later used this salt to obtain carbamoyl fluorides from secondary amines (Scheme 2.7).<sup>20</sup> While the yields are modest compared to other methods, the authors highlight the scalability of their method by preparing a

carbamoyl fluoride from *N*-methylaniline on a 10 mmol scale. It is also worth noting the successful reaction of several drug-like amines, with many containing other acidic N-H bonds that are untouched under the optimal conditions. To the best of our knowledge, this report also provides the only example of a carbamoyl fluoride prepared from a  $sp^2$ -hybridized nitrogen nucleophile.

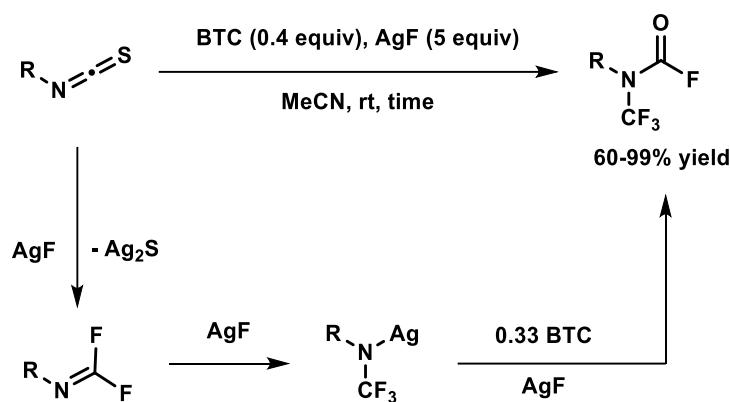


Scheme 2. 7: DNTFB as a  $COF_2$  Source for Carbamoyl Fluoride Synthesis

### 2.2.2 Synthesis of *N*-fluoroalkyl Carbamoyl Fluorides

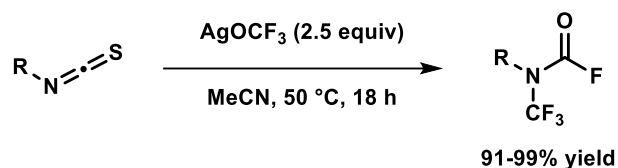
For most of chemical history, the preparation and use of *N*-fluoroalkyl amides has been essentially non-existent. This is due to the challenging nature of their synthesis, which likely arises from the lack of suitable fluoroalkyl electrophiles for amide alkylation, as well as the low nucleophilicity of *N*-fluoroalkyl amines in amide bond-forming reactions. Recently, Schoenebeck and co-workers developed an alternative route to *N*-trifluoromethyl amides from *N*-trifluoromethyl carbamoyl fluorides (Scheme 2.8).<sup>21</sup> Synthesis of these unique carbamoyl fluorides was achieved by reaction of isothiocyanates with BTC and AgF. This reaction proceeds via a fluorodesulfurization of the

isothiocyanate to yield a difluoroimine, which subsequently reacts with another equivalent of fluoride to reach the Ag-trifluoromethylamide intermediate. This species reacts with BTC and excess AgF to furnish the desired carbamoyl fluoride product.



Scheme 2. 8: Synthesis of *N*-CF<sub>3</sub> Carbamoyl Fluorides from Isothiocyanates

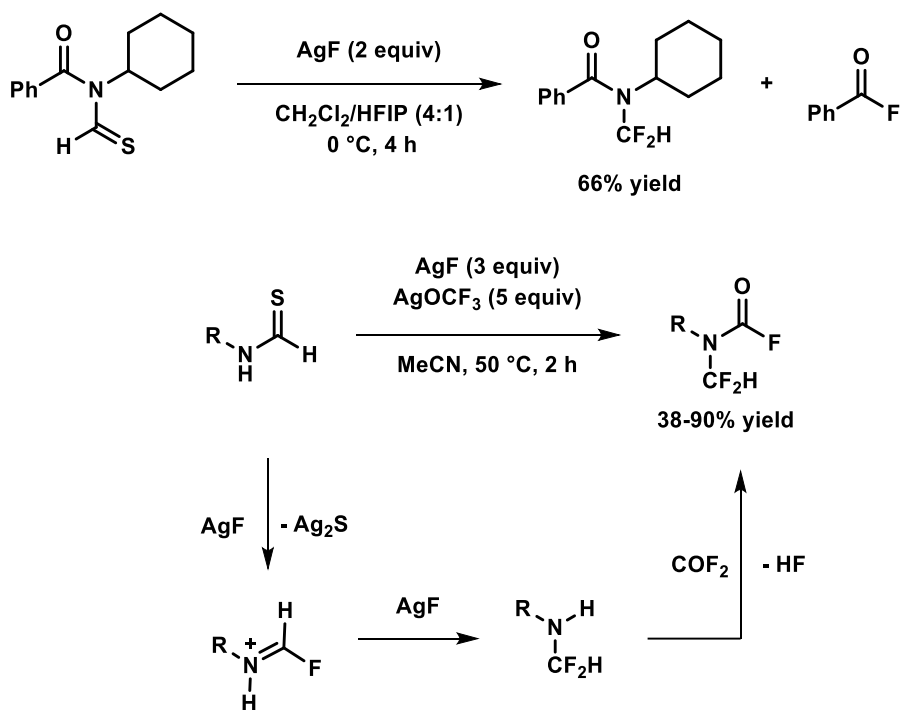
This reaction proceeds well with *N*-aryl and *N*-alkyl isothiocyanates and is tolerant of numerous electron-rich and electron-deficient substituents. The preparation of *N*-CF<sub>3</sub> carbamoyl fluorides from isothiocyanates can be simplified by using a prepared solution of AgOCF<sub>3</sub>, providing a more convenient route to such compounds (Scheme 2.9).<sup>18</sup> In-situ ReactIR monitoring of the AgOCF<sub>3</sub>-mediated reaction suggests a similar mechanism to the original report.<sup>21</sup> These methods represent a significant advance in the synthesis of amides and related compounds. Numerous *N*-trifluoromethyl amides, ureas and (thio)carbamates are readily prepared from the parent carbamoyl fluorides.



Scheme 2. 9: Synthesis of *N*-CF<sub>3</sub> Carbamoyl Fluorides Using a AgOCF<sub>3</sub> Solution

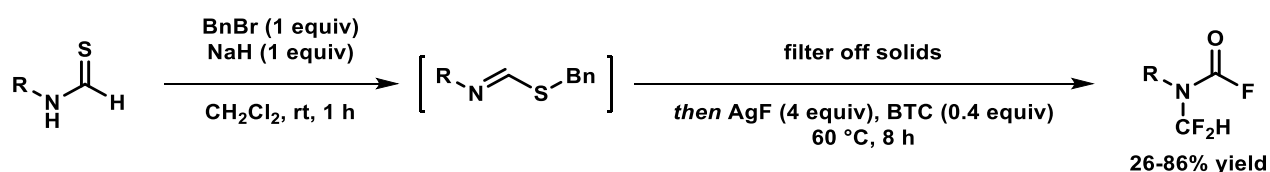


Schoenebeck later reported the reaction of  $\text{AgOCF}_3$  and  $\text{AgF}$  with *N*-benzoyl thioformamide yielding a *N*-difluoromethyl amide directly, as well as benzoyl fluoride as a by-product (Scheme 2.10, top).<sup>22</sup> A similar approach was applied to secondary thioformamides to access *N*- $\text{CF}_2\text{H}$  carbamoyl fluorides, thus allowing a more modular preparation of this unique amide scaffold (Scheme 2.10, bottom). Fluorodesulfurization of the thioformamides was promoted by  $\text{AgF}$ . In this case, the resulting iminium reacts with another equivalent of  $\text{AgF}$  to form a difluoromethylamine intermediate that can be trapped by  $\text{COF}_2$ , furnishing the desired carbamoyl fluoride. A broad substrate scope was reported, and several *N*-difluoromethyl amides, ureas and (thio)carbamates were prepared.



Scheme 2. 10: Synthesis of *N*- $\text{CF}_2\text{H}$  Carbamoyl Fluorides

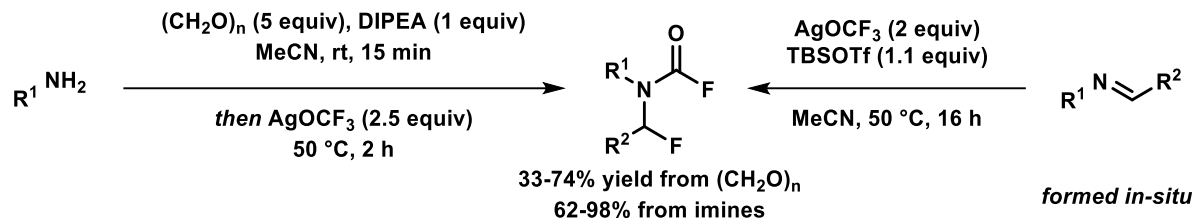
Shortly after, Yi and co-workers disclosed a similar route to *N*-CF<sub>2</sub>H carbamoyl fluorides (Scheme 2.11).<sup>23</sup> This reaction was facilitated by *S*-alkylation of a thioformamide in the presence of NaH. Following filtration, the resulting thioformimidate was treated with AgF and BTC to enable fluorodesulfurization and carbamoylation to obtain the carbamoyl fluoride.



Scheme 2. 11: Yi's Synthesis of *N*-CF<sub>2</sub> Carbamoyl Fluorides

Rounding out the scope of *N*-fluoroalkyl carbamoyl fluorides, Schoenebeck published a report showcasing the synthesis of *N*-monofluoromethyl carbamoyl fluorides from primary amines, paraformaldehyde and AgOCF<sub>3</sub> (Scheme 2.12, left, R<sup>2</sup> = H).<sup>24</sup> Using imines, derived from aldehydes and primary amines, combined with the addition of TBSOTf, *N*-fluoroalkyl carbamoyl fluorides (R<sup>2</sup> ≠ H) could also be prepared (Scheme 2.12, right). The starting materials used in this report represent a significant step forward to access *N*-fluoroalkyl carbamoyl fluorides. Moreover, the use of aldehyde-derived imines introduces another vector of modularity not seen in previous reports. The reaction is initiated by condensation of the amine and aldehyde (when R<sup>2</sup> = H) to provide an imine in-situ. This reaction is followed by the addition of AgOCF<sub>3</sub>, which collapses into AgF and COF<sub>2</sub>. Fluorination of the imine and fluorocarbonylation of the resulting Ag-amido

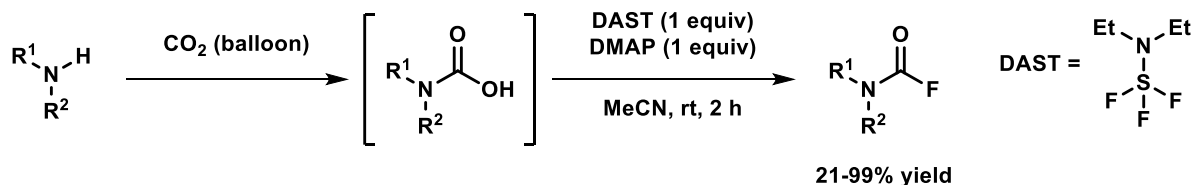
salt provides a variety of *N*-monofluoromethyl and *N*-monofluoroalkyl carbamoyl fluorides.



Scheme 2. 12: Synthesis of *N*-CH<sub>2</sub>F and *N*-fluoroalkyl Carbamoyl Fluorides

### 2.2.3. Synthesis of Carbamoyl Fluoride via Deoxyfluorination

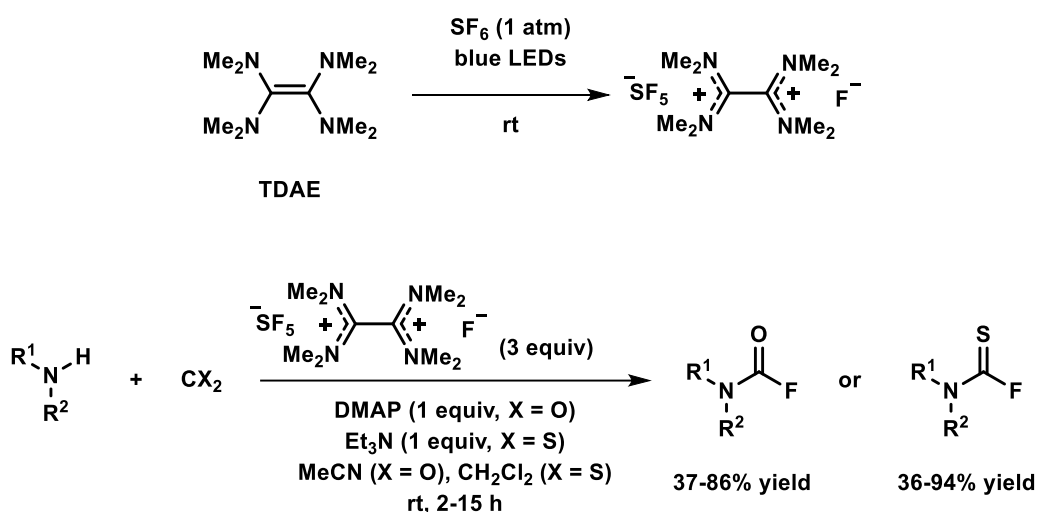
Tlili and co-workers have developed a synthesis of carbamoyl fluorides from carbamic acids generated in-situ from the treatment of secondary amines with CO<sub>2</sub> (Scheme 2.13).<sup>25</sup> This method proceeds by deoxyfluorination of the carbamic acid with DAST, similar to well-known reactions of alcohols. This three-component reaction tolerates a wide range of amines with short reaction times. The authors are also able to use [<sup>13</sup>C]CO<sub>2</sub> to isotopically label the product. While this operationally simple method provides carbamoyl fluorides in good yields, the use of DAST can be problematic on scale, as it is a costly reagent and is prone to detonation at elevated temperatures.<sup>26</sup>



Scheme 2. 13: Synthesis of Carbamoyl Fluorides via Deoxyfluorination of Carbamic Acids

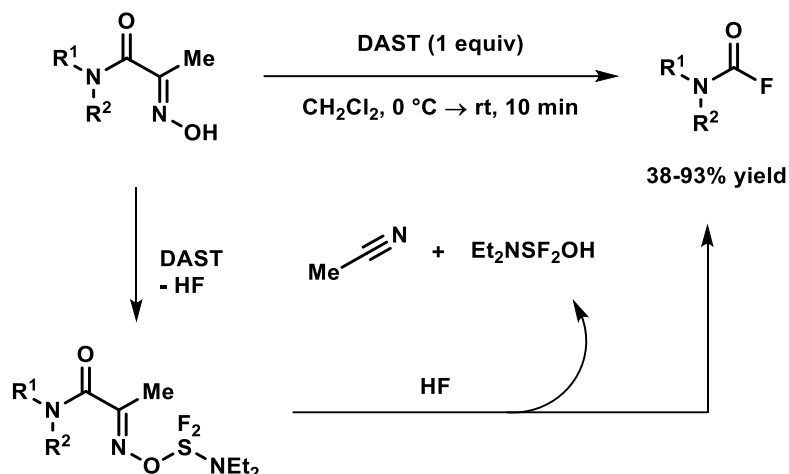
As an alternative protocol, the same group developed a deoxyfluorination reagent derived from SF<sub>6</sub>.<sup>27</sup> Photolysis of tetrakis(dimethylamino)ethylene (TDAE) under an atmosphere of SF<sub>6</sub> leads to the dicationic reagent with one fluoride and one pentafluorosulfide anion (Scheme 2.14, top).

The authors use this compound in combination with CO<sub>2</sub> to prepare a similar array of carbamoyl fluoride products, or with CS<sub>2</sub> to obtain thiocarbamoyl fluorides (Scheme 2.14, bottom). The use of this unique reagent is an a notable improvement to the previous procedure,<sup>25</sup> as it replaces potentially explosive DAST with a reagent derived from SF<sub>6</sub>, which is a potent greenhouse gas.



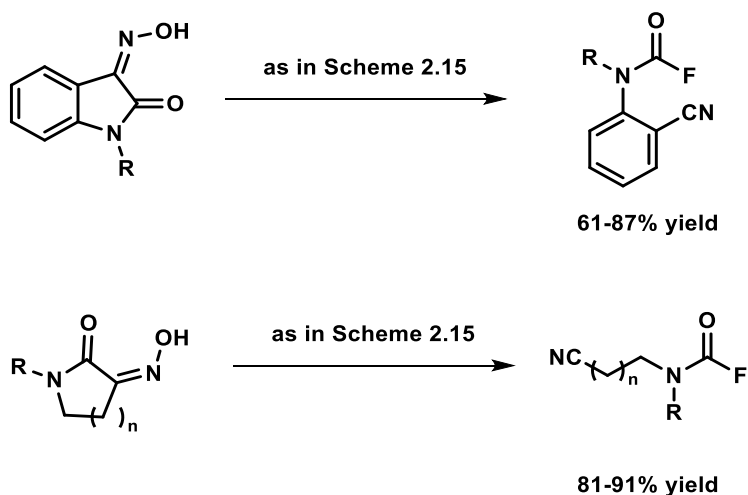
Scheme 2. 14: Deoxyfluorination of Carbamic Acids with a SF<sub>6</sub>-Derived Reagent

The Lim group reported the preparation of carbamoyl fluorides from  $\alpha$ -oximinoamides and DAST, which proceeds via a deoxyfluorination-Beckmann fragmentation mechanism (Scheme 2.15).<sup>28</sup> This unique fragmentation is triggered by the activation of the oxime moiety of the  $\alpha$ -oximinoamide, likely giving rise to a sulfur-bound intermediate. This step is followed by nucleophilic attack of the amide carbonyl by a fluoride anion and subsequent collapse of the tetrahedral intermediate, yielding a carbamoyl fluoride and MeCN by-product. Carbamoyl fluorides were prepared in moderate to good yields from linear  $\alpha$ -oximinoamides, wherein volatile MeCN can be easily removed upon work-up.



Scheme 2. 15: Synthesis of Carbamoyl Fluorides from  $\alpha$ -Oximinoamides

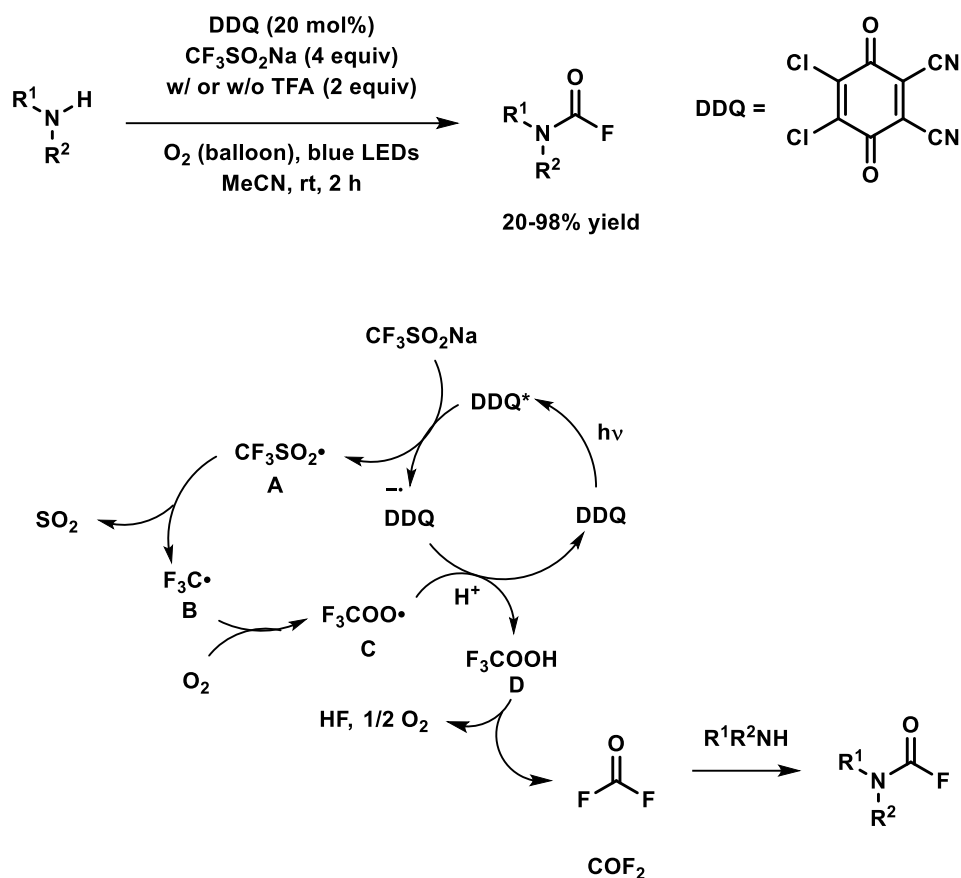
This reaction was also applied to cyclic  $\alpha$ -oximinoamides, prepared from  $\alpha$ -ketolactams and isatin derivatives, which provided carbamoyl fluorides bearing alkyl nitrile or *ortho*-benzonitrile substituents, respectively (Scheme 2.16). Secondary  $\alpha$ -oximinoamides were also compatible with these conditions, forming isocyanates in-situ after HF elimination from the intermediate secondary carbamoyl fluoride.



Scheme 2. 16: Synthesis of Carbamoyl Fluorides from Isatin Derivatives and Cyclic  $\alpha$ -oximinoamides

### 2.2.3 Synthesis of Carbamoyl Fluorides via Radical Methods

In modern synthetic chemistry, the use of photo- and/or electrochemistry has recently become the predominant way for introducing single-electron reactivity.<sup>29</sup> It would be highly valuable to prepare carbamoyl fluorides using mild radical methods, as they tend to have higher functional group tolerance and produce small amounts of waste when photo- or electrochemistry is applied. To this end, Min and co-workers were able to synthesize carbamoyl fluorides from secondary amines, using  $\text{CF}_3\text{SO}_2\text{Na}$ , molecular oxygen and DDQ as a commercially available photocatalyst (Scheme 2.17, top). Upon excitation of DDQ with blue light, single-electron oxidation of  $\text{CF}_3\text{SO}_2\text{Na}$  occurs to form sulfonyl radical **A** (Scheme 2.17, bottom). This leads to the release of  $\text{SO}_2$  and a trifluoromethyl radical **B**, which reacts with triplet oxygen and the resulting trifluoromethylperoxy radical **C** is reduced by DDQ and protonated by acid in the reaction. Decomposition of the newly formed peroxide **D** gave rise to  $\text{COF}_2$  in-situ, which reacts with an amine to provide a carbamoyl fluoride. While exploring the substrate scope of this reaction, the authors found that certain low-yielding reactions could be improved by the addition of TFA. The enhancement from acidic conditions is not well understood, but the authors suggest that TFA may be accelerating the decomposition of **D**.

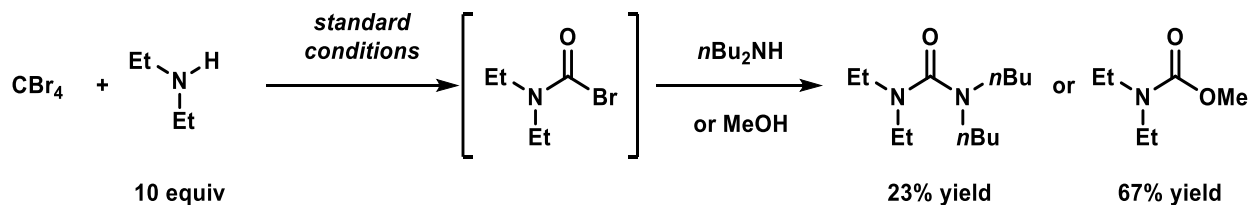


Scheme 2. 17: DDQ-Photocatalyzed Synthesis of Carbamoyl Fluorides

Similarly, the Shimakoshi group prepared carbamoyl fluorides from secondary amines and  $CFBr_3$  under photocatalytic conditions (Scheme 2.18).<sup>30</sup> This method makes use of Co-centred vitamin  $B_{12}$  paired with a Mg ion-modified  $TiO_2$  nanoparticle as the photocatalyst. Through photoexcitation and a series of electron transfers, the  $B_{12}$  catalyst achieves its active state of highly nucleophilic Co(I). This species undergoes either an  $S_N2$ -like or SET reaction with  $CFBr_3$  to access a dibromofluoromethyl radical. Similar Min's work, the radical reacts with oxygen and eventually decomposes to bromofluorophosgene. Nucleophilic acyl substitution by an amine displaces bromide over fluoride, providing carbamoyl fluorides in moderate to excellent yields.

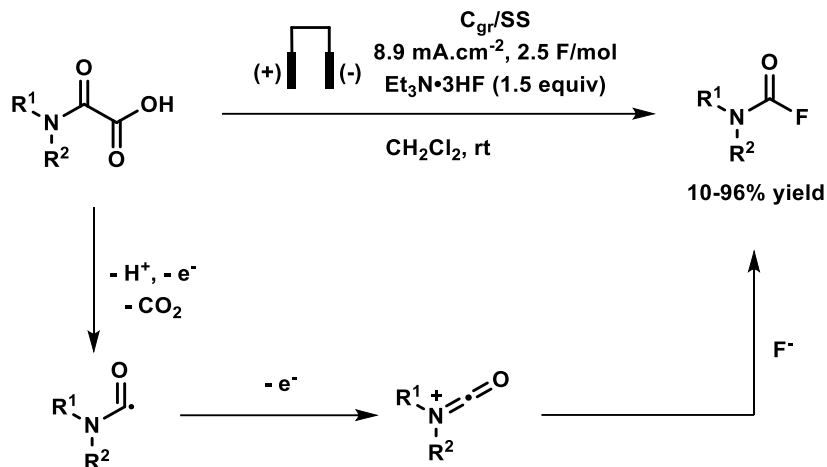






Scheme 2. 19: Synthesis of Ureas and Carbamates from a Transiently Formed Carbamoyl Bromide

A synthesis of carbamoyl fluorides was reported via the electrolysis of oxamic acids in the presence of  $\text{Et}_3\text{N} \cdot 3\text{HF}$  by Lam and co-workers (Scheme 2.20).<sup>34</sup> Deprotonation and anodic oxidation results in the formation of an oxamate radical, which rapidly decarboxylates to the carbamoyl radical. A second anodic oxidation yields an isocyanate cation, which reacts with HF in solution to provide a wide range of carbamoyl fluorides. The authors found that electron-deficient oxamic acids perform poorly under these conditions, likely due to destabilization of the isocyanate. Interestingly, the reaction was amenable to scale-up, producing nearly quantitative yield of carbamoyl fluoride from 1 gram of starting material. The reaction was also efficiently carried out with flow electrochemistry, producing nearly 100 mg of carbamoyl fluoride in one hour. This result highlights that continuous flow chemistry can be used to produce large amounts of material without typical issues associated with increasing the scale of batch reactions.

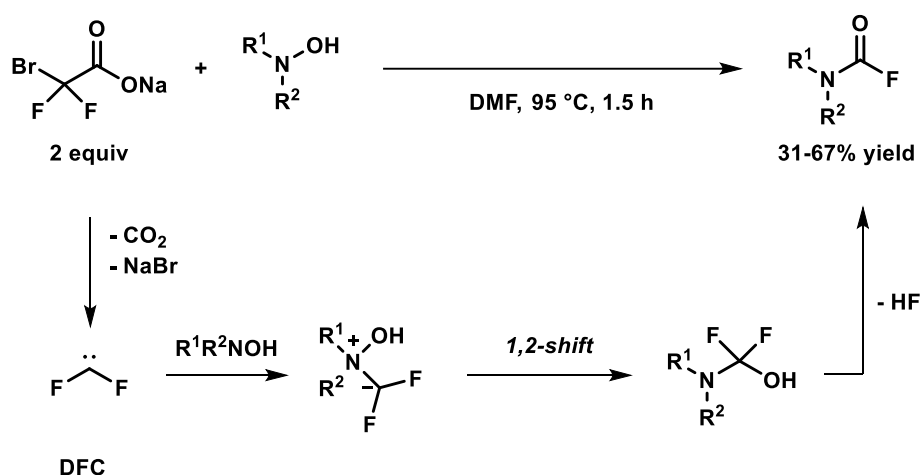


Scheme 2. 20: Electrochemical Synthesis of Carbamoyl Fluorides

## 2.3 Motivation and Research Plans

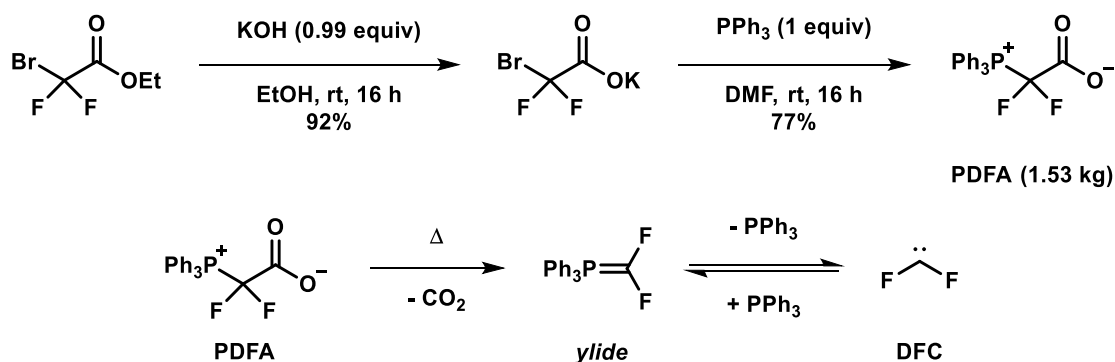
Until recently, the synthesis of carbamoyl fluorides has been limited due to the need for toxic  $\text{COF}_2$ . Chemists have developed a number of safer alternatives to access these compounds through a variety of unique methods.<sup>2,13</sup> However, many of these new preparations require the use of reagents that are hazardous (e.g., DAST) or volatile (e.g., TFMT). Other protocols require designer reagents (e.g.,  $\text{AgOCF}_3$ , DNTFB) or pre-functionalized starting materials (isothiocyanates,  $\alpha$ -oximinoamides, oxamic acids). We were drawn to a 2016 report by Bolm and co-workers using  $\text{BrCF}_2\text{CO}_2\text{Na}$  and hydroxylamines to prepare carbamoyl fluorides (Scheme 2.21). While these starting materials are pre-functionalized and provide carbamoyl fluorides in relatively low yields, the reaction operates by a unique mechanism involving difluorocarbene (DFC). DFC is a highly electrophilic singlet carbene that is commonly used as an ambiphilic  $\text{CF}_2$  source. Although DFC is unstable and prone to dimerization, changing the precursor reagent allows for tuning the rate of DFC release for the desired reaction and several novel reagents have been developed to date.<sup>35–38</sup>

In the Bolm work, after the nitrogen of hydroxylamine attacks the empty p-orbital of DFC, a zwitterionic adduct is formed. Rearrangement to a hemiaminal and subsequent elimination of HF yields the carbamoyl fluoride, with the OH fragment of the hydroxylamine serving as an internal oxidant.



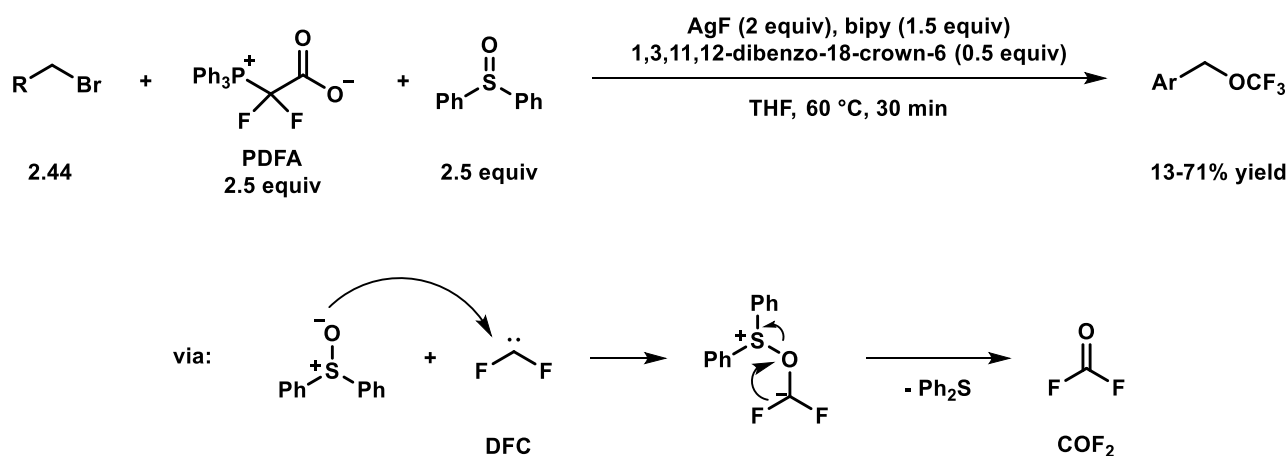
Scheme 2. 21: DFC-Mediated Synthesis of Carbamoyl Fluorides from Hydroxylamines

To provide broad access to carbamoyl fluorides, a method using stable, accessible and easy-to-handle reagents is ideal. In 2013, the Xiao group developed the zwitterionic compound (triphenylphosphonio)difluoroacetate (PDFA), a shelf-stable DFC source that can be synthesized in two steps from commercial starting materials up to a 1 kg scale without column chromatography purification (Scheme 2.22, top)<sup>39</sup>. The synthesis begins with the saponification of BrCF<sub>2</sub>CO<sub>2</sub>Et (an inexpensive building block) with KOH to form BrCF<sub>2</sub>CO<sub>2</sub>K. Displacement of bromide with PPh<sub>3</sub> provides PDFA in good yield. PDFA has been used as a dual purpose reagent that allows access to DFC or a *P*-difluoromethylide under thermal activation (Scheme 2.22, bottom).<sup>40,41</sup>



Scheme 2. 22: Kg-Scale Synthesis of PDFA and its Decomposition to Reactive Intermediates

More recently, the same group utilized PDFA for the synthesis of trifluoromethyl ethers from alkyl halides (Scheme 2.23, top). This is a  $\text{S}_{\text{N}}2$  reaction with nucleophilic  $\text{AgOCF}_3$ , which is formed in situ from the attack of  $\text{COF}_2$  by  $\text{AgF}$ . In the presence of DFC, sulfoxide serves as an oxidant to generate  $\text{COF}_2$ . (Scheme 2.23, bottom).<sup>42</sup>.

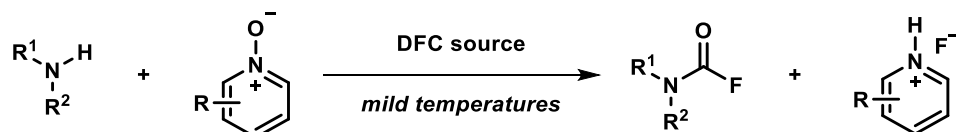


Scheme 2. 23: DFC-Mediated Trifluoromethoxylation of Alkyl Bromides

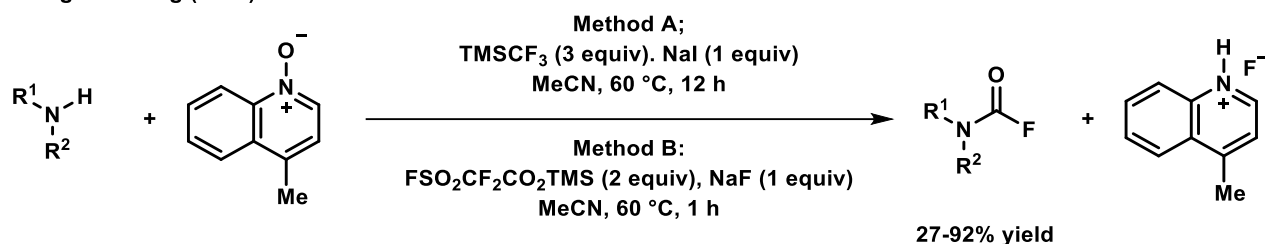
We hypothesized that the DFC/oxidant system would be an efficient route to access carbamoyl fluorides from secondary amines in a modular fashion. In addition to being operationally simple, the protocol would use accessible and relatively safe reagents (Scheme 2.24, top). It was also

postulated that using pyridine *N*-oxide as the oxidant would lead to pyridine as a by-product, which should act as a competent base for the neutralization of the HF by-product during the formation of the carbamoyl fluoride products. It should be noted that nearly a year after the publication our work in JOC, a similar report was published by Wang and Feng, using different DFC sources and 4-methylquinoline *N*-oxide (Scheme 2.24, bottom).<sup>43</sup> The synthesis of carbamoyl fluorides using a DFC/oxidant system is detailed herein, including the reaction development and optimization, substrate scope and mechanistic studies.

Le (2022)



Wang and Feng (2023)



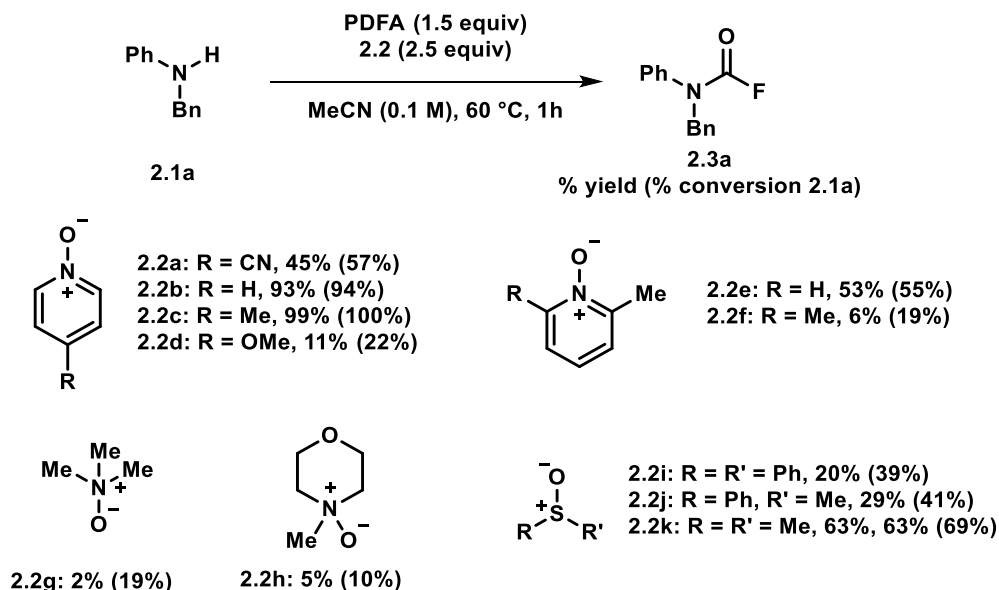
Scheme 2. 24: DFC-Mediated Synthesis of Carbamoyl Fluorides from Secondary Amines and Pyridine *N*-Oxides

## 2.4 Results and Discussion

### 2.4.1. Reaction Optimization

The reaction optimization was carried out using *N*-benzylaniline (**2.1a**) as a model substrate due to its commercial availability, relatively neutral steric and electronic profile. The yields were obtained by quantitative <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxy benzene as an internal standard using the easily distinguishable *N*-Bn methylene group as the reference signal. The DFC precursor PDFa (1.5 equiv) was chosen for its simple preparation, stability, non-hygroscopic nature and its ability to produce DFC without an external activator. The initial screen was done by varying the oxidant **2.2** (2.5 equiv) at 60 °C in anhydrous MeCN.

Initially, pyridine *N*-oxides and trialkylamine *N*-oxides were explored in the reaction (Scheme 2.25). When a pyridine *N*-oxide bearing an electron withdrawing nitrile group (**2.2a**) was used, **2.3a** was obtained in 45% yield. Using unsubstituted pyridine *N*-oxide **2.2b** provided **2.3a** in 93% yield. The use of 4-methyl substituted **2.2c** led to nearly quantitative formation of **2.3a**, emerging as the ideal oxidant for the synthesis of carbamoyl fluorides. Interestingly, electron-rich **2.2d** performed worse than **2.2a**, suggesting a fine electronic balance is required. Steric hinderance around the *N*-oxide moiety hindered reactivity, with **2.2e** and **2.2f** providing **2.3a** in 53% and 6%, respectively. The use of **2.2g** and **2.2h** proved to be ineffective, producing **2.3a** in only trace yields.



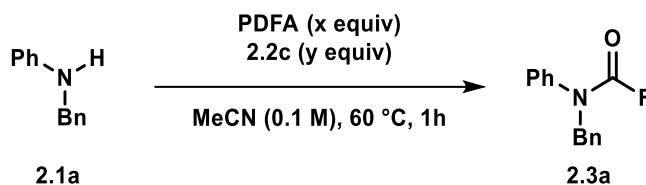
Scheme 2. 25: Oxidant Screen in the DFC-Mediated Synthesis of Carbamoyl Fluorides from Secondary Amines

Testing the compatibility of Xiao's trifluoromethoxylation report, we also investigated sulfoxides as oxidants in the reaction. **2.2i** provided **2.3a**, albeit in low yield. A slight improvement was observed with **2.2j** (29%) but DMSO (**2.2k**) proved to be the highest yielding sulfoxide tested at 63%. We found that using DMSO as solvent led to quantitative yield of carbamoyl fluoride, but these conditions proved to be less general than using **2.2c** in MeCN. This result is likely due to the sulfide by-product not being an effective HF trap, leading to acid-mediated decomposition of more functionalized carbamoyl fluorides

With the optimal reagents in hand, we varied the equivalents of each component to assess its impact on yield. Lowering the amount of **2.2c** and/or PDFFA led to a significant drop in the yield (Table 1, entry 2-5). This trend was consistent, even at longer reaction times (entry 6). However, the loading of **2.2c** could be lowered to 2 equivalents without deterioration of reactivity. Interestingly, we found that regardless of reagent loading, a 1:1 ratio of **2.2c** and PDFFA always

performed poorly (entries 2, 3 and 6). This indicates a requirement for a higher ratio of **2.2c** to PDFA, and both need to be used in excess relative to amine **2.1a**.

**Table 2.1:** Equivalents Screen

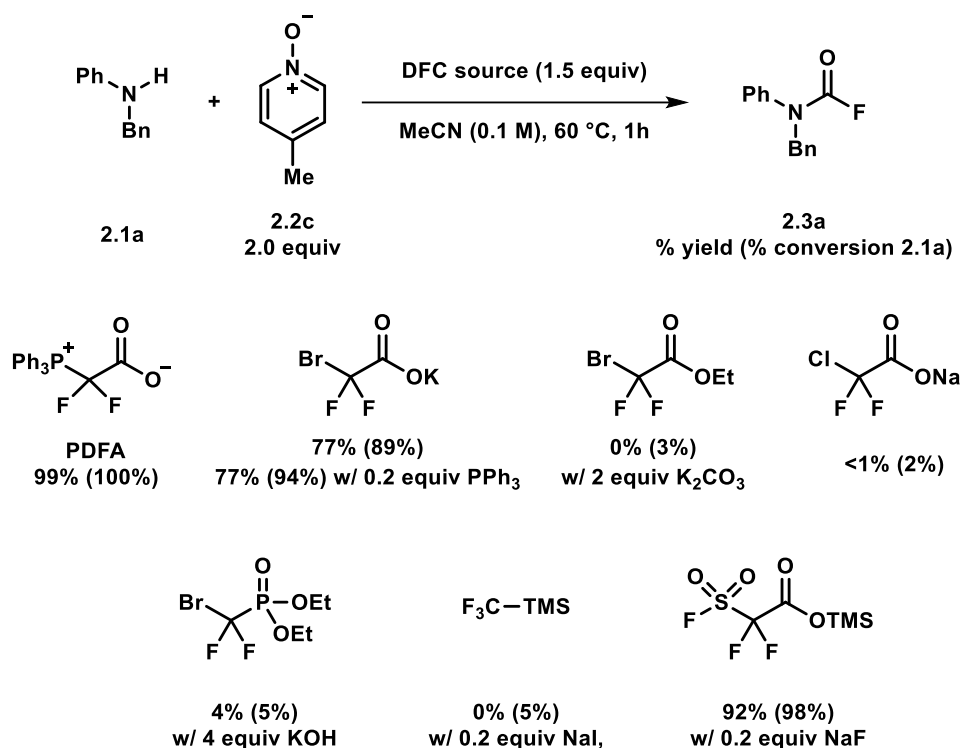


| Entry | 2.2c (equiv) | PDFA (equiv) | Conversion (%) | <sup>1</sup> H NMR Yield (%) |
|-------|--------------|--------------|----------------|------------------------------|
| 1     | 2.5          | 1.5          | 100            | 99                           |
| 2     | 1            | 1            | 67             | 65                           |
| 3     | 1.5          | 1.5          | 72             | 70                           |
| 4     | 1            | 1.5          | 83             | 81                           |
| 5     | 2            | 1            | 76             | 75                           |
| 6     | 1.2          | 1.2          | 79 (after 3 h) | 73                           |
| 7     | 2            | 1.5          | <b>100</b>     | <b>99</b>                    |

While PDFA was found to be an effective DFC source in our reaction, the presence of stoichiometric PPh<sub>3</sub> in the reaction mixture could become problematic during purification. For this reason, we screened several other DFC sources under the conditions from Entry 7 of Table 2.1 (Scheme 2.26). Using BrCF<sub>2</sub>CO<sub>2</sub>K, the precursor to PDFA, **2.3a** was formed in 77% yield. The reactivity was not improved when a catalytic amount of PPh<sub>3</sub> was added to form PDFA in-situ. Although BrCF<sub>2</sub>CO<sub>2</sub>K is a less reactive DFC source, these conditions offer an alternative route to carbamoyl fluorides without preparing PDFA. A combination of BrCF<sub>2</sub>CO<sub>2</sub>Et and base was found to be unproductive in the reaction. Only trace amounts of **2.3a** were observed using ClCF<sub>2</sub>CO<sub>2</sub>Na, which is likely due to the higher temperatures required to decompose this salt. Other common DFC



sources, such as  $\text{TMSCF}_3$  and  $\text{EtO}_2\text{P}(\text{O})\text{CF}_2\text{Br}$  paired with their respective activators, gave insignificant amounts of **2.3a**. Interestingly, the DFC source TFDA did provide **2.3a** in 92% yield, providing another promising alternative to PDFA. However, we chose to move forward with PDFA due to its moisture stability and lower overall cost when compared to TFDA.

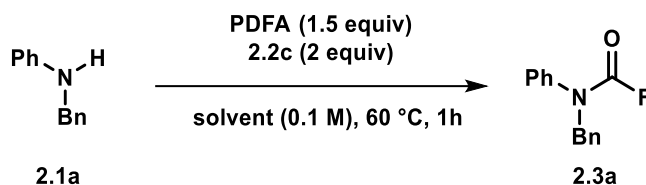


Scheme 2. 26: Screen of DFC Sources in the Synthesis of Carbamoyl Fluorides from Secondary Amines

Solvents selection was also explored in the optimization process (Table 2.2). To test the tolerance of the reaction to ambient conditions, HPLC-grade MeCN was used and **2.3a** was obtained in 57% yield (entry 1). Wet solvent likely hampers reactivity by the reaction of water with  $\text{COF}_2$ . Several other solvents also performed well in the reaction, with >90% yield being observed in THF (entry 3), DCE (entry 5) and PhMe (entry 6). This diverse range of compatible solvents amenable to carbamoyl fluoride synthesis is highly beneficial, as challenging substrates can be

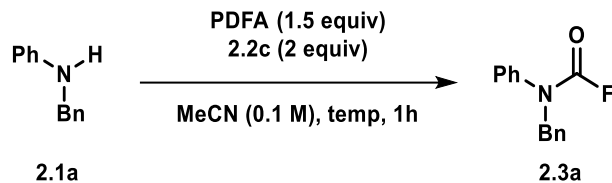
heated more in higher boiling solvents, or lower boiling solvents can be used if the product is volatile.

**Table 2.2:** Solvent Screen



| Entry | Solvent               | Conversion (%) | <sup>1</sup> H NMR Yield (%) |
|-------|-----------------------|----------------|------------------------------|
| 1     | MeCN                  | 100            | 99                           |
| 2     | MeCN (wet HPLC grade) | 63             | 57                           |
| 3     | THF                   | 93             | 92                           |
| 4     | DMF                   | 94             | 75                           |
| 5     | DCE                   | 100            | 94                           |
| 6     | PhMe                  | 100            | 99                           |
| 7     | 1,4-dioxane           | 83             | 78                           |

Finally, the temperature in MeCN was screened (Table 2.3). When the reaction was run at 40 °C the yield of **2.3a** dropped to 37% (entry 1), likely due to slower thermolysis of PDFA. However, 50 °C was found to be the lowest temperature needed for maintaining quantitative yields, with no negative impact upon increasing the temperature up to 70 °C (entry 2-4). A reaction temperature of 60 °C was selected for further studies to ensure efficient reactivity while also keeping the conditions relatively mild.

**Table 2.3:** Temperature Screen

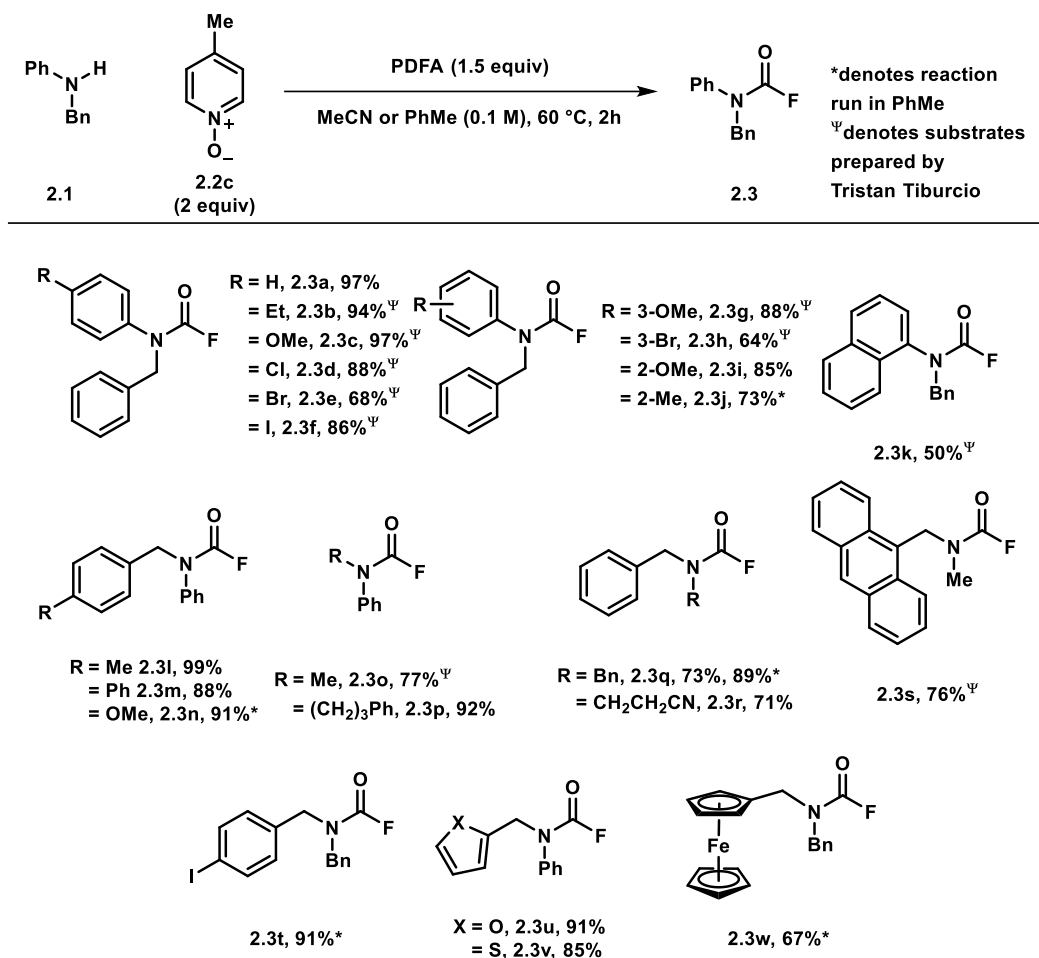
| Entry    | Temperature (°C) | Conversion (%) | <sup>1</sup> H NMR Yield (%) |
|----------|------------------|----------------|------------------------------|
| 1        | 40               | 41             | 37                           |
| 2        | 50               | 99             | 99                           |
| <b>3</b> | <b>60</b>        | <b>100</b>     | <b>99</b>                    |
| 4        | 70               | 100            | 99                           |

## 2.4.2 Substrate Scope

With the ideal conditions in hand, we conducted a substrate scope study of the developed reaction. Several carbamoyl fluorides were prepared by Tristan Tiburcio and are highlighted as such in Scheme 2.27. Several of the substrates were prepared using PhMe as a solvent, as we later noticed these conditions were often more effective at maintaining similar yields upon increasing the scale of the reaction. Details regarding substrates prepared in both MeCN and PhMe are available in the experimental section of this chapter. The model substrate **2.3a** was isolated in 97% yield and effectively scaled to 1 gram (see experimental section). Another graduate student in the group, Jesse LeBlanc, has successfully prepared **2.3a** from 25 mmol of **2.1a**, resulting in over 5 grams of product. Substrates bearing electron-donating groups (**2.3b**, **2.3c**) and halogen atoms (**2.3d-f**) at the *para* position of the aniline backbone were well tolerated. Carbamoyl fluorides derived from *meta*-substituted anilines could also be isolated (**2.3g**, **2.3h**). Electron-rich *ortho*-substituted anilines performed well, despite the increased steric hindrance of the nitrogen atom (**2.3i**, **2.3j**). Increasing the size of the aryl ring from phenyl to naphthyl (**2.3k**) lead to a significant decrease in yield to 50%. Changes to the substituents on the *N*-benzyl aromatic ring were found to have

negligible effect on the yield, with a 4-methyl- (**2.3l**), 4-phenyl- (**2.3m**) and 4-methoxy- (**2.3n**) benzyl group well tolerated. Substrates containing *N*-methyl (**2.3o**) and *N*-propylphenyl (**2.3p**) also worked well under these conditions, providing the carbamoyl fluorides in 77% and 92%, respectively.

Variations of **2.3** containing *N,N*-dialkyl groups as well as several medically relevant functional groups were also prepared. Dibenzyl substituted **2.3q** was obtained in 73% or 89% yield in MeCN and PhMe, respectively. This variation highlights the benefit of having multiple solvents to choose from for this method. A substrate with an appended nitrile (**2.3r**) was isolated in 71% yield while anthracenyl carbamoyl fluoride **2.3s** was obtained in 76% yield. An iodide substituent on one of the benzyl rings (**2.3t**) was well-tolerated. Furan (**2.3u**) and thiophene-containing (**2.3v**) substrates were obtained in 91% and 85% yield, respectively. Ferrocenyl carbamoyl fluoride **2.3w** could be prepared in moderate yield.



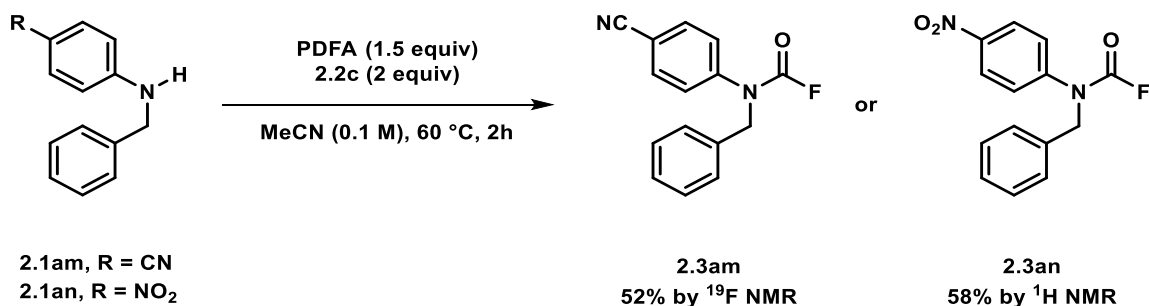
Scheme 2. 27: Substrate Scope of Carbamoyl Fluorides

We then focused on synthesizing carbamoyl fluorides containing heterocyclic functionalities due to their prominence in the pharmaceutical industry (Scheme 2.28). Pyridyl carbamoyl fluorides (**2.3x**, **2.3y**) could be obtained in modest yields, as well as indole-containing **2.3z**. While **2.3z** was obtained in only 54% yield, the free indole NH did not require protection and the structure was confirmed by X-ray crystallography (crystals suitable for X-ray diffraction were grown from a 1:1 mixture of Et<sub>2</sub>O and hexanes, which were then analyzed and processed with the assistance of Jesse LeBlanc). *N*-heterocycles converted into carbamoyl fluorides, including piperazine **2.3aa**, indoline **2.3ab**, and tetrahydroisoquinoline **2.3ac**. The 7-membered amine core of loratadine, an allergy

Scheme 2. 28: Substrate Scope of Carbamoyl Fluorides (continued)



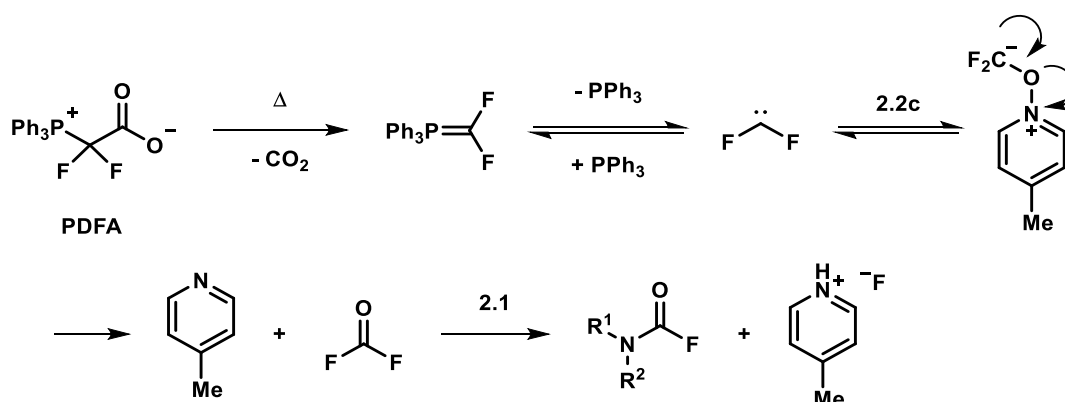
When electron-deficient anilines were tested under the optimized conditions, moderate yields were observed by quantitative  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectroscopy. (Scheme 2.29). However, when **2.4am** and **2.4an** were subjected to column chromatography, decomposition was observed. This is attributed to increased electrophilicity of the carbonyl carbon that arises from the electron withdrawing cyano- and nitro groups on the *N*-bound aromatic ring. It is likely that these compounds hydrolyze on silica, reverting them back to polar secondary amines that were recovered from the column. These substrates were synthesized by Tristan Tiburcio, who also observed their instability and obtained the crude yields by NMR spectroscopy.



Scheme 2. 29: Synthesis and Crude NMR Yields of Carbamoyl Fluorides Bearing Electron Withdrawing Substituents

## 2.5. Mechanistic Studies

To gain insight into the PDFA/oxidant mediated synthesis of **2.3**, a series of mechanistic studies were conducted. The most plausible mechanism mirrors the report by Xiao (Scheme 2.30),<sup>42</sup> where heating of PDFA induces decarboxylation resulting in formation of a difluoromethylide. This ylide exists in equilibrium with free DFC and PPh<sub>3</sub>. Electrophilic DFC undergoes nucleophilic attack by pyridine-*N*-oxide **2.2c** and this intermediate can collapse to form COF<sub>2</sub> and 4-methylpyridine. Further reaction with **2.1** forms the carbamoyl fluoride **2.3a** and 4-methylpyridinium fluoride.



Scheme 2. 30: Proposed Mechanism of Carbamoyl Fluoride Formation

### 2.5.1. Reaction Analysis by NMR Spectroscopy

Examination of the  $^{19}\text{F}$  NMR spectrum of the crude material produced by the reaction of **2.1** under the optimized conditions revealed numerous signals in addition to **2.3a**. Most of these signals are likely related to the pyridinium fluoride salt and other HF-related decomposition products, with many being formed in small amounts and not warranting investigation. However, we were intrigued by two signals close to -40 ppm. To elucidate the identity of this byproduct, several control experiments were conducted in  $\text{MeCN-d}_3$  to allow monitoring by  $^1\text{H}$  NMR spectroscopy. First, the standard conditions were monitored before completion of the reaction (25 minutes). The  $^1\text{H}$  NMR spectrum showed a roughly equimolar amount of amine **2.1a** and carbamoyl fluoride **2.3a**, as well as signals corresponding to pyridine-*N*-oxide **2.2c** and the pyridinium salt (Figure 2.1).



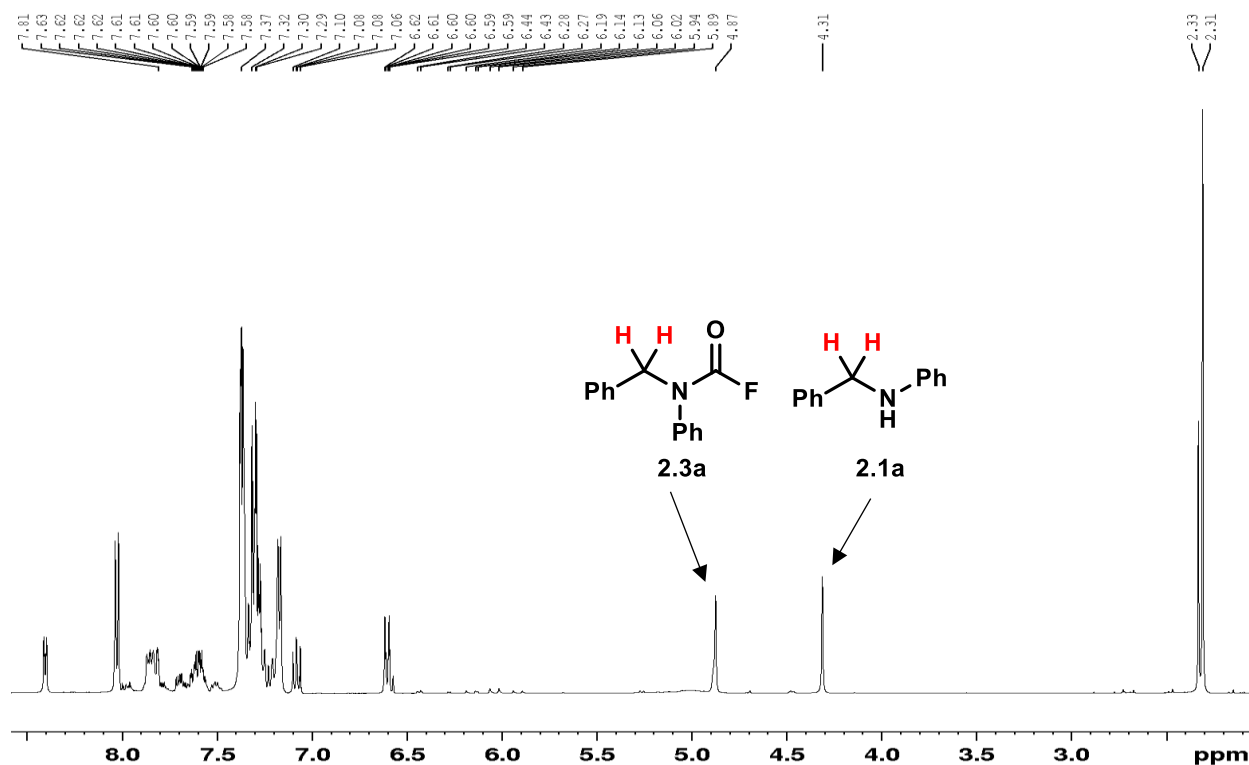


Figure 2. 1:  $^1\text{H}$  NMR Spectrum of the Standard Reaction in  $\text{MeCN-d}_3$  After 25 Minutes at  $60^\circ\text{C}$

Analysis by  $^{19}\text{F}$  NMR spectroscopy shows **2.3a**, unreacted PDFA, and the signals near  $-40$  ppm (Figure 2.2). A closer investigation determined that this signal is a doublet at  $-38.10$  ppm with a coupling constant of  $655.6$  Hz, indicative of  $\text{F-P(V)}$  bonding.<sup>44</sup> A  $^{31}\text{P}$  NMR spectrum was taken of the mixture, which revealed the presence of  $\text{PPh}_3$ , PDFA and triphenylphosphine oxide (TPPO, overlapping signals), and a triplet at  $-53.6$  ppm with a coupling constant matching the doublet observed by  $^{19}\text{F}$  NMR spectroscopy (Figure 2.3).

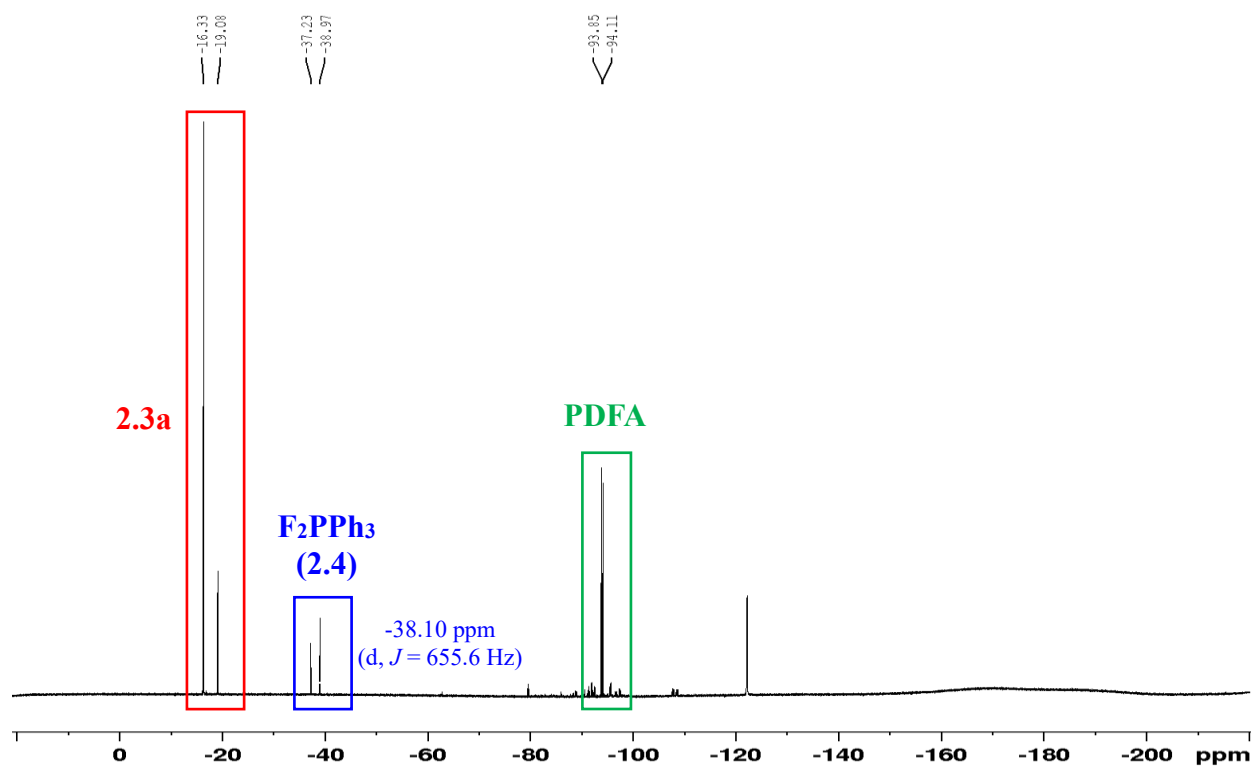


Figure 2. 2:  $^{19}\text{F}$  NMR Spectrum of the Standard Reaction in  $\text{MeCN-d}_3$  after 25 minutes at  $60^\circ\text{C}$

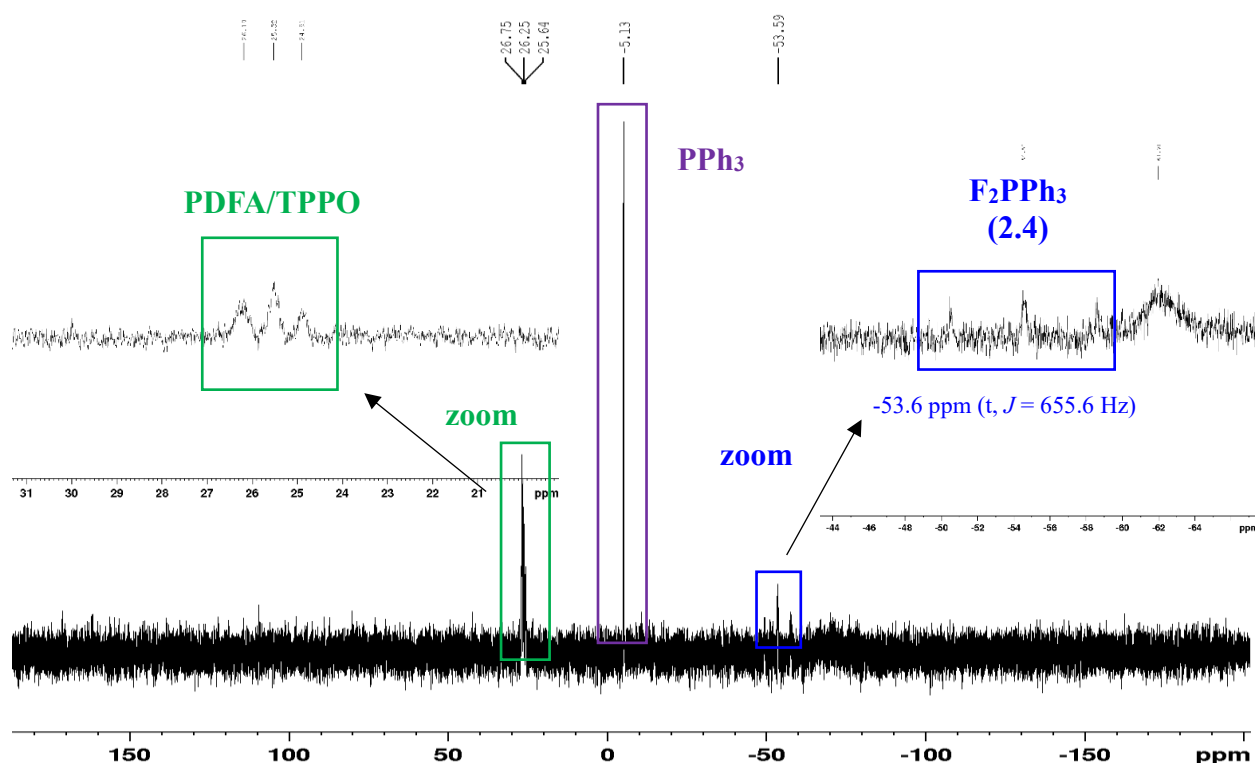


Figure 2. 3:  $^{31}\text{P}$  NMR Spectrum of the Standard Reaction in  $\text{MeCN-d}_3$  after 25 minutes at  $60^\circ\text{C}$

After scouring the literature, this side product was identified as difluorotriphenyl- $\lambda^5$ -phosphorane (**2.4**,  $\text{F}_2\text{PPh}_3$ ) by comparing all of the spectroscopic data in  $\text{MeCN-d}_3$ .<sup>45</sup> Next, PDFA and **2.2c** were heated in  $\text{MeCN-d}_3$  and the reaction was monitored by NMR spectroscopy. After 30 minutes, a  $^1\text{H}$  NMR spectrum was taken but indicative signals were difficult to identify. The  $^{19}\text{F}$  and  $^{31}\text{P}$  NMR spectra, however, showed much stronger signals for **2.4** and nearly complete consumption of PDFA (Figure 2.4 and Figure 2.5).

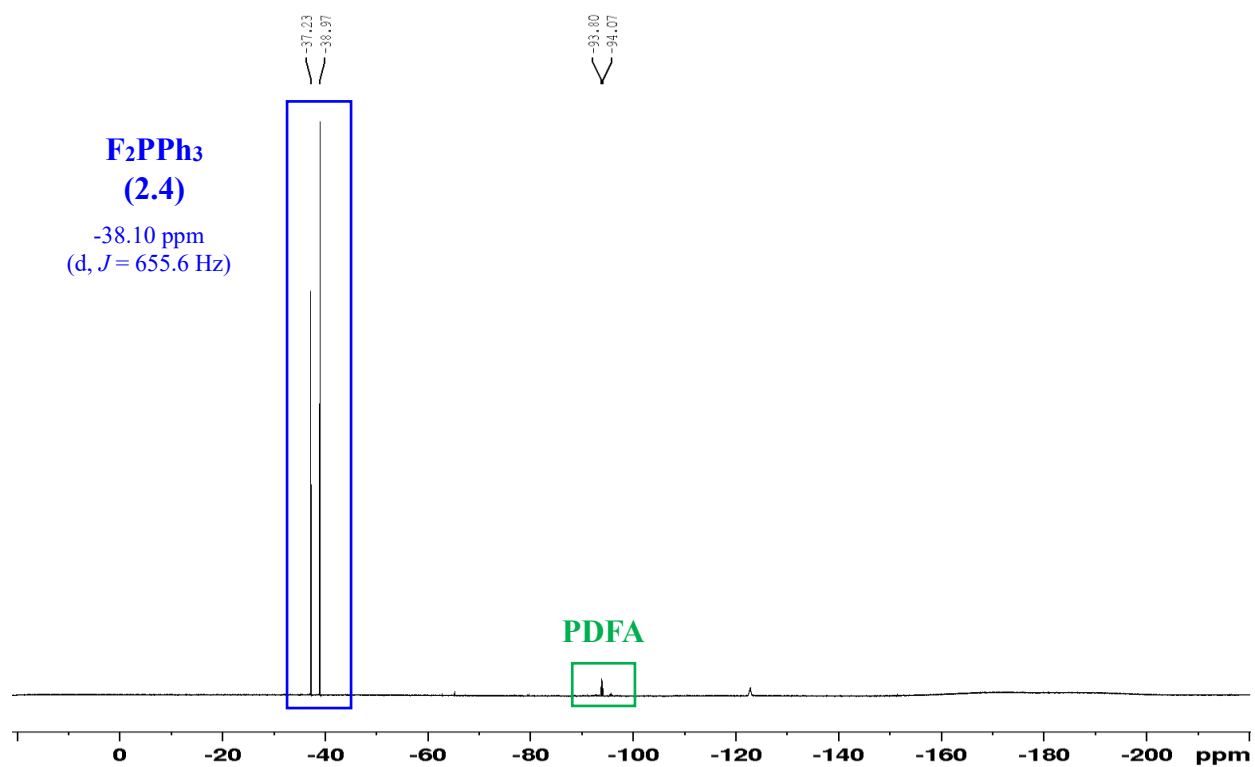


Figure 2. 4:  $^{19}\text{F}$  NMR Spectrum of PDFA and **2.2c** in  $\text{MeCN-d}_3$  for 30 minutes at  $60^\circ\text{C}$

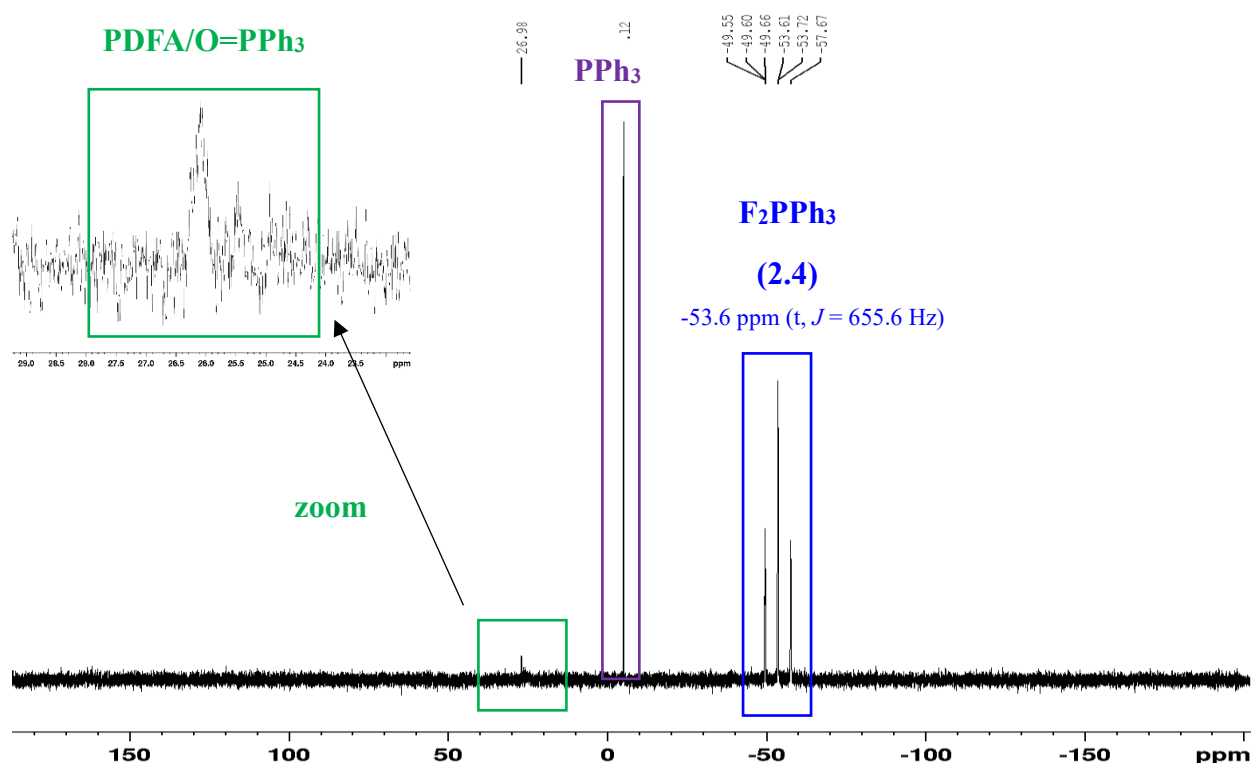
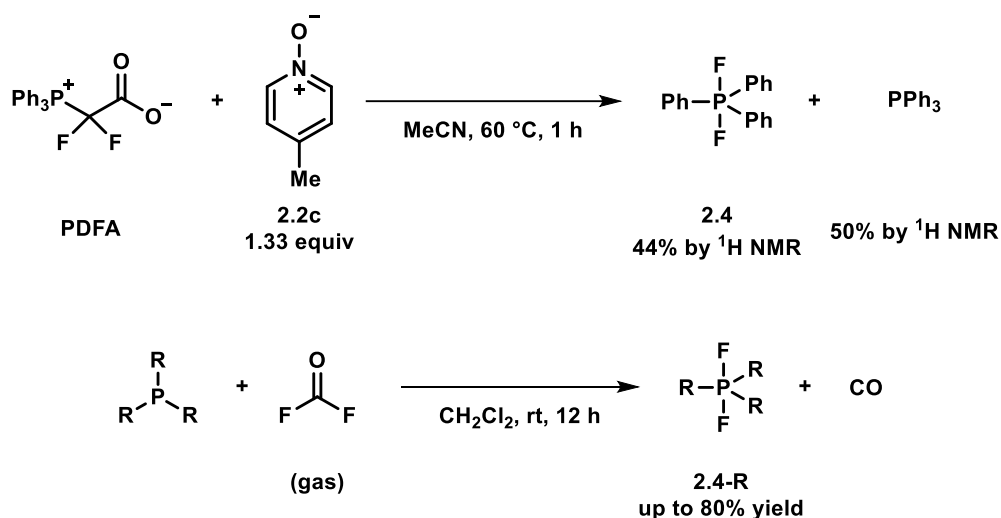


Figure 2. 5:  $^{31}\text{P}$  NMR Spectrum of PDFA and **2.2c** in MeCN- $\text{d}_3$  for 30 Minutes at 60 °C

Allowing the reaction to go to completion, followed by the addition of TMB as an internal standard, allowed for quantitative analysis of the reaction, which revealed a 44% yield of **2.4** and 50% yield of PPh<sub>3</sub> (Scheme 2.31, top). A report from Shreeve suggests that the reaction of P(III) compounds with COF<sub>2</sub> results in difluorinated P(V) products (Scheme 2.31, bottom). This result serves as indirect evidence that COF<sub>2</sub> is present in our reaction conditions,<sup>46</sup> supporting Xiao's mechanism for the oxidation of DFC.



Scheme 2. 31: Synthesis of Difluorophosphoranes from PDFA and **2.2c** or Directly from  $\text{COF}_2$  gas

An NMR experiment was also conducted withholding the oxidant **2.2c** from the reaction. Under these conditions, a new signal at 4.70 ppm was observed in the  $^1\text{H}$  NMR spectrum, likely corresponding to the benzylic methylene protons (Figure 2.6). Additionally, a triplet at 6.93 ppm with a coupling constant of 62.6 Hz was identified. While the most downfield peak of this triplet was hidden beneath the aromatic signals, the observed signals were in a 1:2 ratio with the initially observed signal at 4.70 ppm when correcting for the missing peak (Figure 2.7).

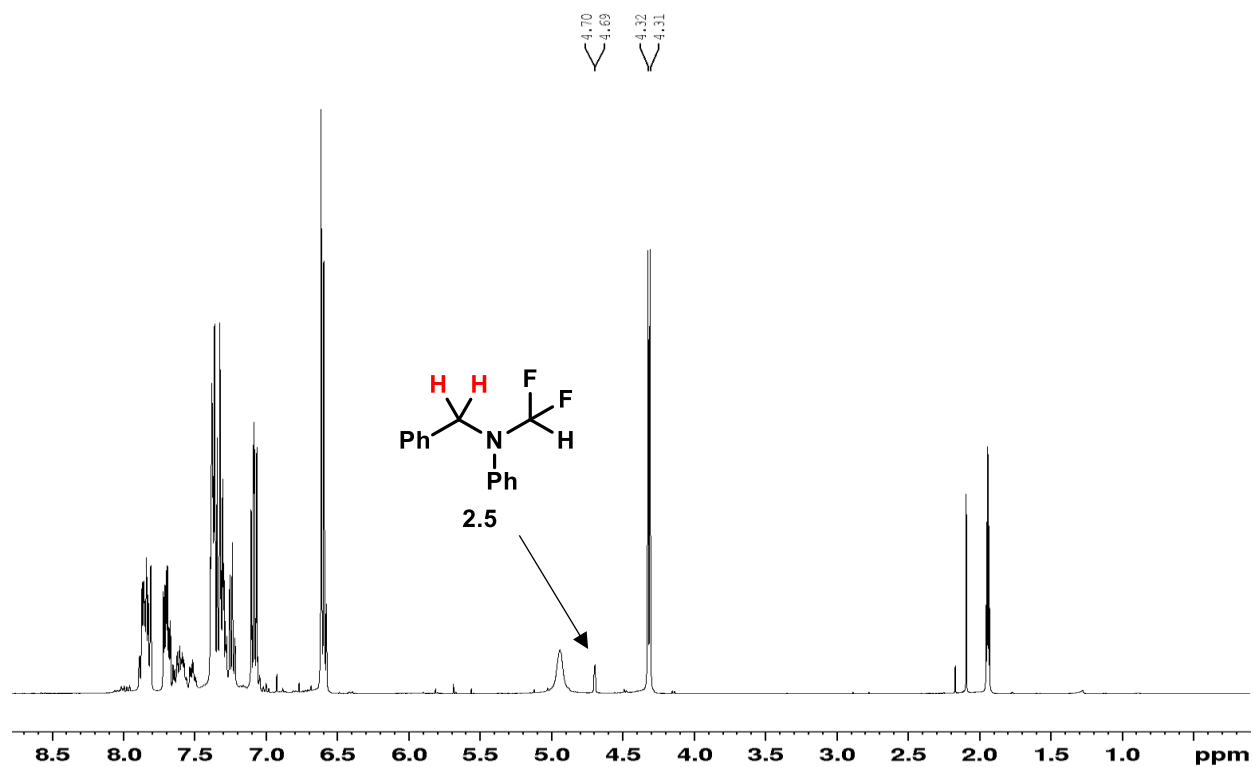


Figure 2. 6:  $^1\text{H}$  NMR Spectrum of **2.1a** and PDFA in  $\text{MeCN-d}_3$  after 30 minutes at 60 °C

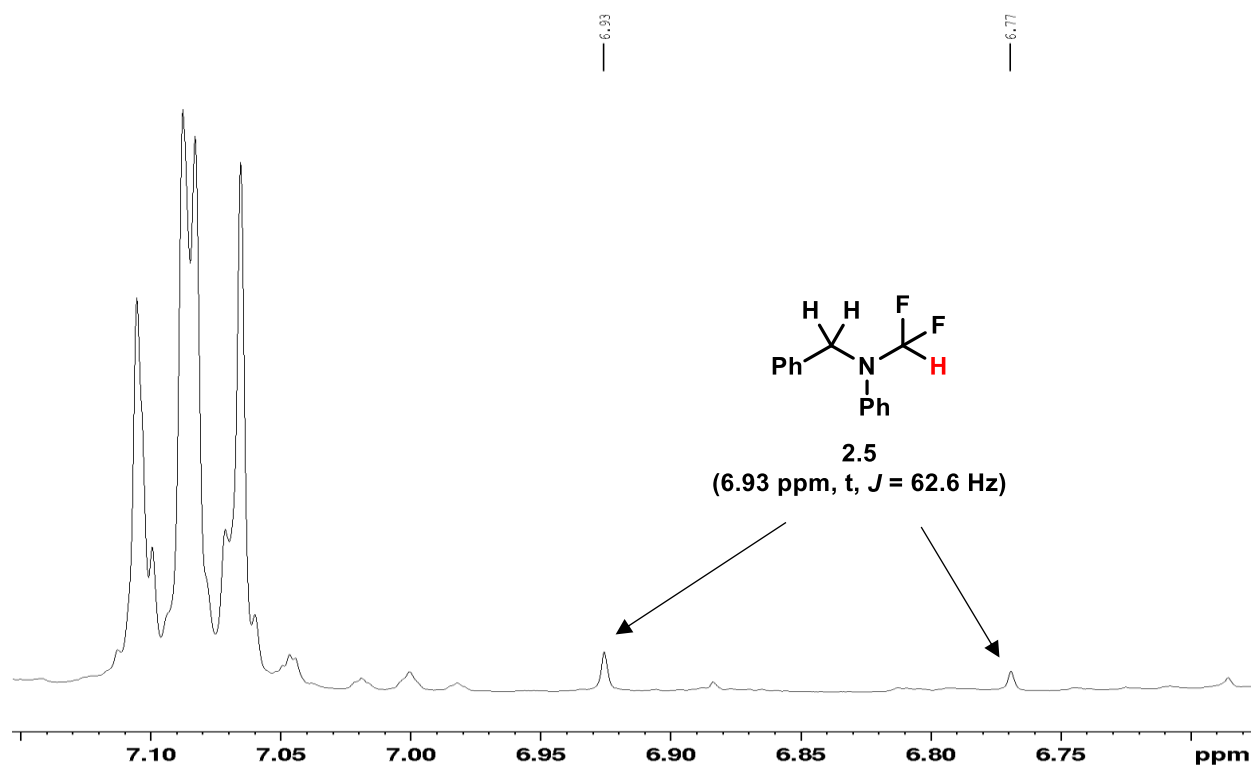


Figure 2. 7: Expanded  $^1\text{H}$  NMR Spectrum from Figure 2.6

In the  $^{19}\text{F}$  NMR spectrum (Figure 2.8), a doublet at -90.9 ppm was found with a matching coupling constant of 62.6 Hz. Such signals are indicative of an unstable difluoromethylamine (Scheme 2.32, **2.5**) and the connectivity was further confirmed by a 2D  $^1\text{H}$ - $^{19}\text{F}$  HMBC experiment (Figure 2.9).



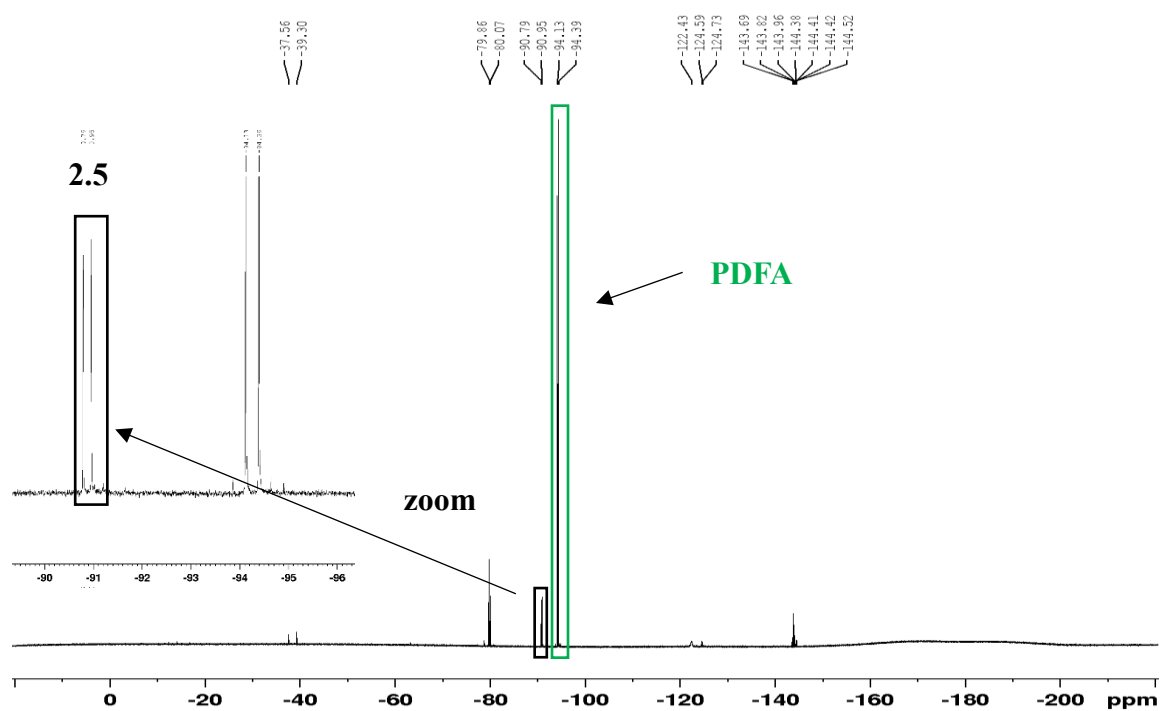


Figure 2. 8:  $^{19}\text{F}$  NMR Spectrum of **2.1a** and PDFA in  $\text{MeCN-d}_3$  After 30 Minutes at  $60^\circ\text{C}$

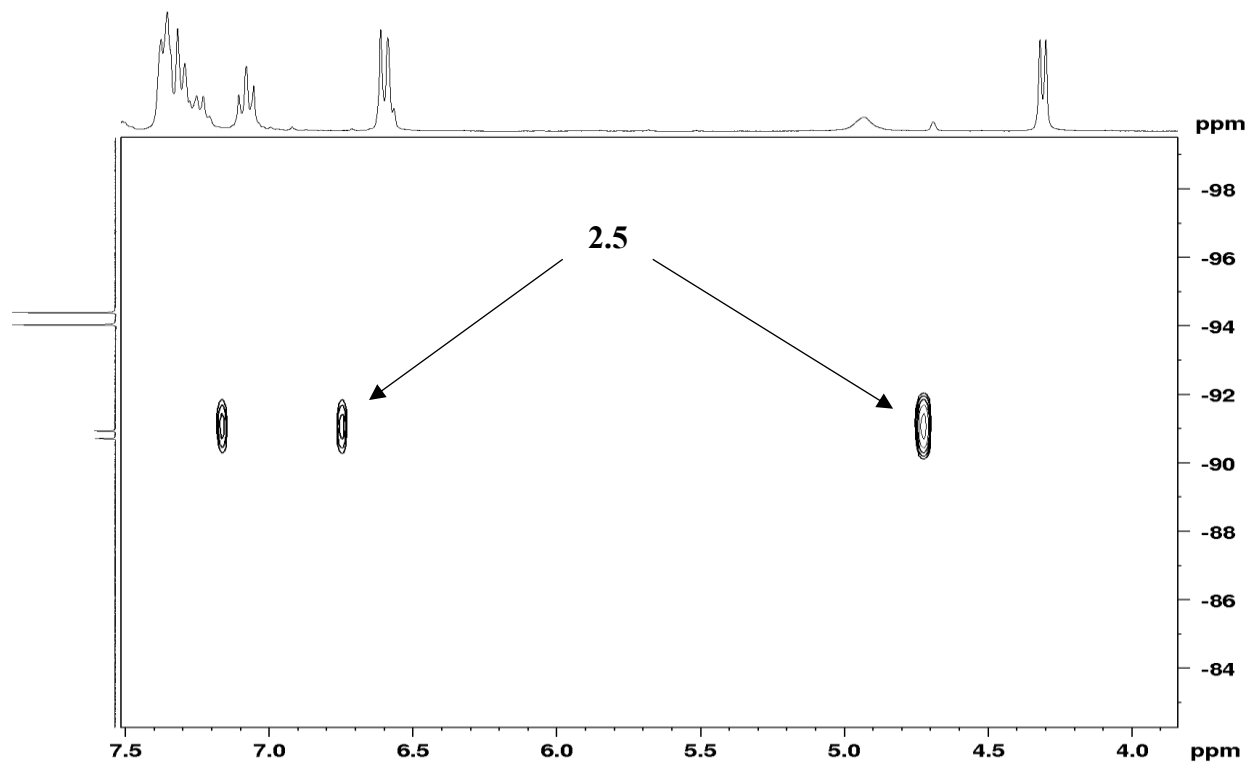
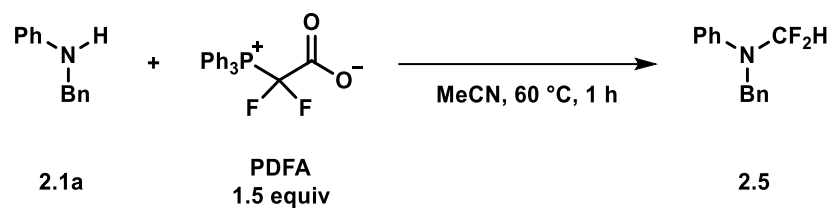


Figure 2. 9:  $2\text{D } ^1\text{H-}^{19}\text{F}$  HMBC Spectrum of **2.1a** and PDFA in  $\text{MeCN-d}_3$  After 30 Minutes at  $60^\circ\text{C}$



Scheme 2. 32: Difluoromethylation of a Secondary Amine with PDFA

Rapid removal of solvent after this reaction and  $^1\text{H}$  NMR analysis in chloroform-*d* led to near complete resolution of the  $\text{CF}_2\text{H}$  triplet (Figure 2.10). These experiments indicate that PDFA is competent in the difluoromethylation of amines. However, this reaction is entirely outcompeted by oxidation when pyridine *N*-oxide is present, as **2.5** is not observed under the standard reaction conditions. A mechanism involving fluoride elimination from **2.5**, then attack of the resulting fluoroiminium by the oxidant was briefly considered, but the identification of P(V) compound **2.4** strongly supports the formation of  $\text{COF}_2$ .

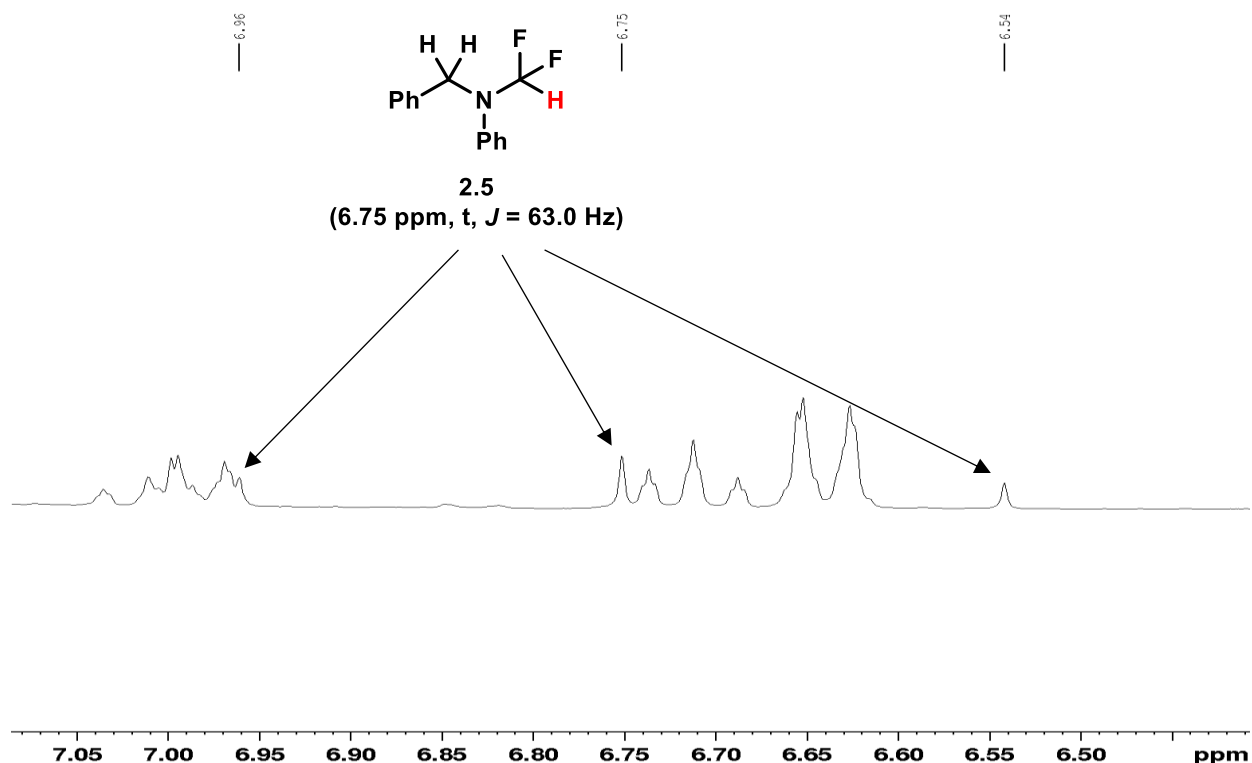


Figure 2. 10:  $^1\text{H}$  NMR Spectrum (6.40-7.10 ppm) of Crude **2.5** in Chloroform- $d$

### 2.5.2. Initial Rates Kinetics

To further understand the reaction mechanism, we conducted kinetic studies using the method of initial rates. The design of these experiments was challenging due to the insolubility of PDFA. Suspended solids make it difficult to take aliquots of the reaction mixture, so typical sampling methods were not applicable. We opted to run reactions in parallel, stopping them at different time points to conduct  $^1\text{H}$  NMR analysis. The reactions were also run at 40 °C, as the typical reaction conditions were too fast to record enough data points within the initial rates regime. The rates were obtained by plotting the yield of **2.3a** against reaction time and determining the slope. Each data point represents an average of two runs. Values deviated significantly in some cases due to reproducibility issues caused by fluctuations in lab humidity, as water was previously shown to

negatively impact the reaction (Table 2.2, Entry 2). While these issues likely render absolute rate values incorrect, the trends hold true and representative plots are shown below.

First, the concentration of **2.1a** was varied and data points were collected at 2.5, 5, 7.5, 10 and 15 minutes. All the slopes from these runs (Table 2.4) were plotted against the concentration of **2.1a**, and a linear correlation with an  $R^2$  value of 0.9648 was obtained (Figure 2.11). These data suggest that the reaction is first order in **2.1a**, meaning that the amine is involved in the rate-determining step. According to our hypothesized mechanism, the rate-determining step is likely the attack of COF<sub>2</sub> by **2.1**.

**Table 2.4:** Initial rates at varying concentrations of **2.1a**

| [ <b>2.1a</b> ] (M) | Initial rate x 10 <sup>-4</sup> (M/min) |              | Average x 10 <sup>-4</sup> (M/min) |
|---------------------|-----------------------------------------|--------------|------------------------------------|
|                     | <i>Run 1</i>                            | <i>Run 2</i> |                                    |
| 0.050               | 8.16                                    | 10.10        | 9.14                               |
| 0.10                | 10.30                                   | 9.92         | 10.10                              |
| 0.15                | 11.80                                   | 10.50        | 11.20                              |
| 0.20                | 14.80                                   | 11.14        | 13.10                              |
| 0.30                | 14.80                                   | 13.70        | 14.43                              |

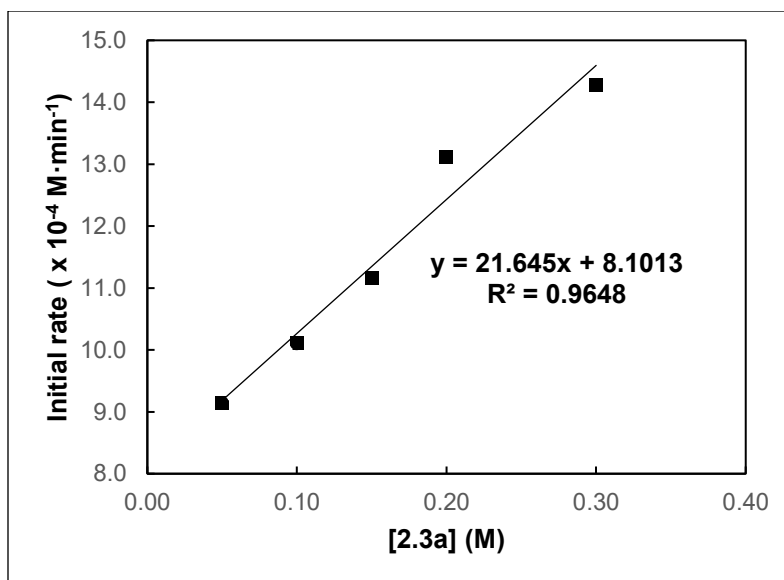


Figure 2. 11: Plot of Initial Rates from Varying **2.1a** vs Concentration of **2.3a**

Next, the concentration of the oxidant **2.2c** was varied for kinetic analysis. Unexpectedly, the rate of the reaction was inversely proportional to the concentration of **2.2c** (Table 2.5, Figure 2.12). We speculate that **2.2c**, a potent nucleophile, can react with electrophilic COF<sub>2</sub> producing the adduct **2.6** (Scheme 2.33). While its formation slows the reaction, **2.6** could be a competent fluorocarbonylation reagent in the conversion of amines to carbamoyl fluorides. These results are also in line with the observed failure of the stronger nucleophile **2.3d** to act as a competent oxidant in this reaction, as it would consume COF<sub>2</sub> faster and yield a less electrophilic analog of **2.6**.

**Table 2.5:** Initial rates at varying concentrations of **2.2c**

| [2.2c] (M)                                                                                                                                                                                           | Initial rate x 10 <sup>-4</sup> (M/min) |            | Average x 10 <sup>-4</sup> (M/min) |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------|------------------------------------|
|                                                                                                                                                                                                      | Run 1                                   | Run 2      |                                    |
| 0.10                                                                                                                                                                                                 | 7.51                                    | 5.47       | 6.49                               |
| 0.15                                                                                                                                                                                                 | 5.68                                    | (see note) | 5.68                               |
| 0.20                                                                                                                                                                                                 | 4.63                                    | 4.19       | 4.41                               |
| 0.30                                                                                                                                                                                                 | 2.72                                    | 3.95       | 3.33                               |
| Note: The initial rate at 0.15 M could not be replicated, as a result of drastic changes in relative humidity in the laboratory within the timeframe of the kinetic study. Nevertheless, this single |                                         |            |                                    |

data point for 0.15 M fits well with the linear correlation observed in Figure 2.12 and running a duplicate experiment would not change the overall interpretation this kinetic study.

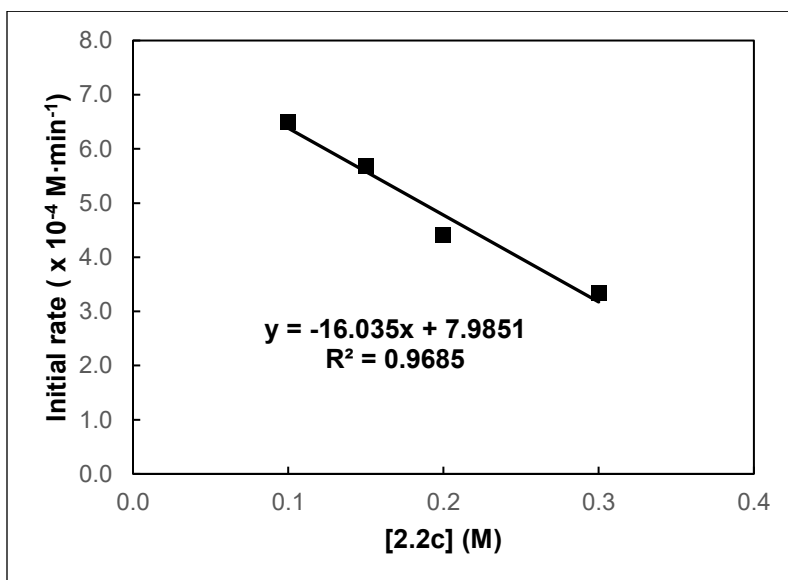
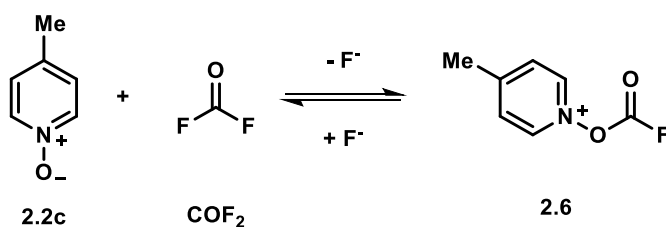


Figure 2. 12: Plot of Initial Rates from Varying **2.2c** vs Concentration of **2.3a**



Scheme 2. 33: Proposed Reaction of **2.2c** with COF<sub>2</sub>

To confirm the role of DFC in the reaction, a kinetic experiment was carried out by adding various amounts of PPh<sub>3</sub> to the reaction. According to La Chatellier's principle, added PPh<sub>3</sub> will push the equilibrium between difluoromethylidene and DFC towards the ylide. If the postulated mechanism is operational, this would indirectly decrease the concentration of COF<sub>2</sub> and lower the rate, if the rate-determining step is the attack of COF<sub>2</sub> by **2.1a**. Additionally, PPh<sub>3</sub> could also react with COF<sub>2</sub> to form **2.4** (F<sub>2</sub>PPh<sub>3</sub>) leading to a scenario similar to that observed with high concentrations of **2.2c**

(Scheme 2.31). As expected, increasing concentration of  $\text{PPh}_3$  led to a decrease in the rate of the reaction, providing further support for the mechanism involving  $\text{COF}_2$ .

**Table 2.6:** Initial rates at varying concentrations of  $\text{PPh}_3$

| Added $[\text{PPh}_3]$ (M) | Initial rate $\times 10^{-4}$ (M/min) |       | Average $\times 10^{-4}$ (M/min) |
|----------------------------|---------------------------------------|-------|----------------------------------|
|                            | Run 1                                 | Run 2 |                                  |
| -                          | 7.74                                  | 8.73  | 8.24                             |
| 0.0099                     | 7.01                                  | 7.87  | 7.44                             |
| 0.030                      | 6.54                                  | 6.49  | 6.51                             |

**Figure S5.** Plot of initial rate vs. added  $[\text{PPh}_3]$

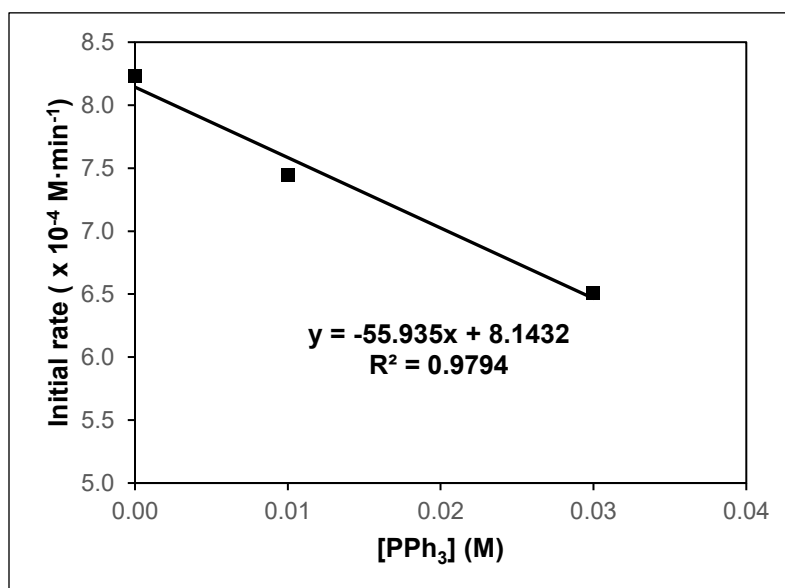
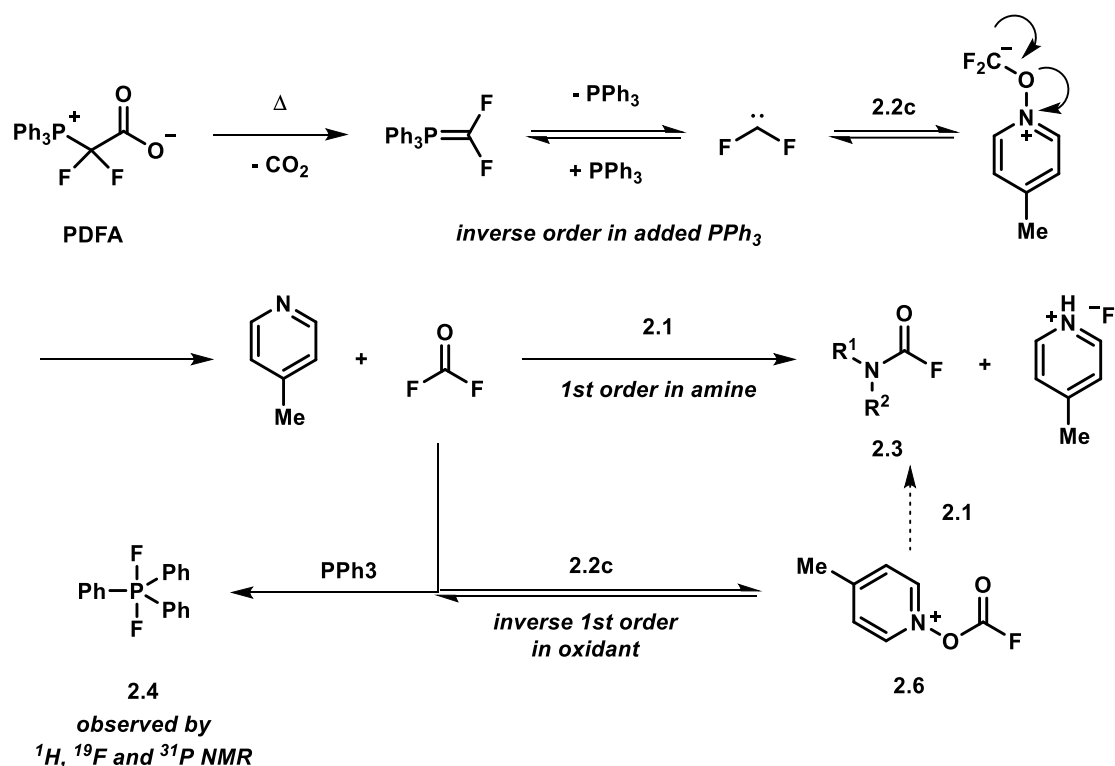


Figure 2. 13: Plot of Initial Rates with added  $\text{PPh}_3$  vs Concentration of **2.3a**

### 2.5.3 Reaction Mechanism

With all the experimental data in hand, the mechanism of the synthesis of carbamoyl fluorides from secondary amines is proposed (Scheme 2.34). Upon heating, PDFa releases  $\text{CO}_2$  to access the equilibrium between difluoromethylide and DFC. The electrophilic carbene is then attacked by the nucleophilic oxidant **2.2c**, leading to the zwitterionic adduct. This intermediate can collapse

to form 4-methylpyridine and  $\text{COF}_2$ . The latter reacts with amine **2.1** to furnish the carbamoyl fluoride product **2.3** and HF, which is neutralized by 4-Me-pyridine to form a pyridinium salt. It is likely that excess **2.2c** can react with  $\text{COF}_2$  to provide the fluoroformate **2.6**. Given that the rate is directly proportional to the concentration of amine and inversely proportional to the concentration of oxidant, we believe that **2.6** is a competent fluorocarbonylation reagent and that attack by the amine is rate-determining. Although **2.6** is less electrophilic than  $\text{COF}_2$ , we believe that its stability leads to the overall higher yields of carbamoyl fluoride we observe with excess oxidant. Additionally,  $\text{PPh}_3$  and  $\text{COF}_2$  can react to form the P(V) compound **2.4**, but little formation of this by-product is observed under the standard conditions.



Scheme 2. 34: Proposed Mechanism of Carbamoyl Fluoride Synthesis

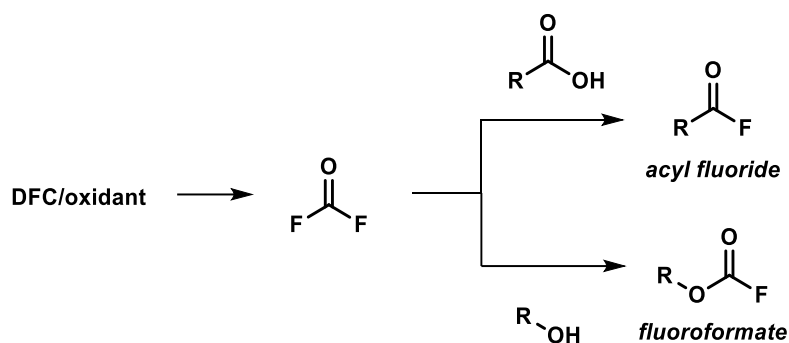


## 2.6. Conclusion and Future Work

A synthesis of carbamoyl fluorides (**2.3**) from secondary amines (**2.1**) using a stable DFC source and a commercial oxidant was developed. After optimization, PDFA and 4-methylpyridine *N*-oxide (**2.2c**) were identified as the optimal reagents for the reaction. Numerous carbamoyl fluorides could be prepared using this method, many of which bear pharmaceutically relevant scaffolds and functional groups. Mechanistic studies were conducted, including analysis by multinuclear NMR spectroscopy and initial rates kinetics. These results suggest a mechanism that involves the in-situ oxidation of DFC to generate difluorophosgene, which reacts with **2.1** to form **2.3**, or with **2.2c** to form a less reactive yet competent fluorocarbonylation reagent **2.6**. This method is user-friendly, uses affordable and stable reagents and requires short reaction times. While we hope that this method will be widely adapted and enable the discovery of unique amide-forming reactions from carbamoyl fluorides, it does suffer from several drawbacks. These include the generation of highly toxic COF<sub>2</sub> and the production of stoichiometric PPh<sub>3</sub> that must be removed by column chromatography. Going forward, methods for by-product removal should be investigated. Towards this goal, Jesse LeBlanc has found that incorporating a reaction work-up with aqueous H<sub>2</sub>O<sub>2</sub> leads to quantitative oxidation of PPh<sub>3</sub> to TPPO. The polar TPPO is easier to separate from the desired products by column chromatography and can likely be precipitated in industrial settings.

The developed DFC/oxidant system for producing COF<sub>2</sub> in-situ should find applications in the preparation of other reactive fluorinated molecules. The synthesis of acyl fluorides from carboxylic acids<sup>47,48</sup> and fluoroformates from alcohols should be attainable under similar systems (Scheme 2.35). With brief re-optimization efforts, graduate student Ali McKnight and former

undergraduate researchers Yuriko Fujisato, Nhu Nguyen and Darnella Devito have found significant success on this front in our group. Mechanistic exploration of these substrates will give further insight into this system and allow for the design of more reactions using  $\text{COF}_2$ .



Scheme 2. 35: Reaction of Other Nucleophiles with  $\text{COF}_2$

## 2.7 Experimental and Spectral Information

### 2.7.1 General Procedure for Reaction Optimization

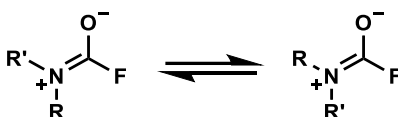
To an oven or flame-dried 1 dram vial was added a stir bar, *N*-benzylaniline (0.018 g, 0.1 mmol), the indicated oxidant and difluorocarbene precursor. The vial was fitted with a septum cap, which was evacuated and backfilled 3x with nitrogen before adding the indicated amount of solvent to the vial. The septum cap was quickly replaced with a Teflon-lined screwcap and the reaction was submerged into a pre-heated 60 °C oil bath. After 1 hour, the vial was removed from the oil bath and upon cooling, the reaction mixture was transferred directly to a scintillation vial containing a known amount of 1,3,5-trimethoxybenzene (internal standard). The solvent was removed under reduced pressure and the residue taken up in CDCl<sub>3</sub> for quantitative <sup>1</sup>H NMR analysis.

### 2.7.2 Synthesis and Characterization Data for Carbamoyl Fluorides

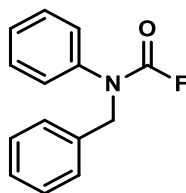
Carbamoyl fluorides were prepared according to our reported procedure<sup>1</sup> using MeCN or PhMe as solvent. It was found that PhMe provided higher yields upon scale-up in most cases. To a pressure tube equipped with a stir bar was added (triphenylphosphonio)difluoroacetate (PDFA) (1.5 equiv) and **2.2c** (2.0 equiv). The tube was fitted with a septum then evacuated and backfilled with nitrogen three times. To the tube was added a 0.1 M solution of a secondary amine **2.1a** (1.0 equiv) in the indicated solvent. The septum was rapidly removed and replaced with a Teflon screw cap before submerging the tube in a pre-heated 60 °C oil bath and stirred for 2 h. After completion of the reaction, the pressure tube was removed from the oil bath and allowed to cool to room temperature before the reaction mixture was transferred directly to a round-bottomed flask. The crude material

was dry loaded on silica gel and was purified by column chromatography to yield the carbamoyl fluoride **2.3**.

**Note:** In line with previous reports, carbamoyl fluorides demonstrate restricted rotation about the N-C<sub>acyl</sub> bond, giving rise to rotamers in solution.<sup>11,25</sup> Distinct resonances for the rotamers are observed for unsymmetrically substituted carbamoyl fluorides ( $R' \neq R$ ) in all  $^{19}\text{F}$  NMR spectra, most  $^{13}\text{C}$  spectra, and some  $^1\text{H}$  spectra. The chemical shifts for both rotamers are listed as they appear in the  $^{13}\text{C}$  NMR data. In instances where the signals for the two rotamers overlap, a “2C” notation is provided in the chemical shift listing.<sup>28</sup>



***N*-benzyl-*N*-phenyl-carbamoyl fluoride (2.3a)**

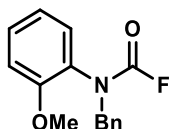


**2.3a**

The title compound was prepared from *N*-benzylaniline (0.073 g, 0.40 mmol) using MeCN as a solvent and isolated as a colorless oil, or a white solid upon standing, (0.089 g, 0.39 mmol 97%, mp = 36-37 °C) after purification by flash column chromatography: 1% EtOAc in hexanes. Scale up: The title compound was synthesized in an oven dried 100 mL Schlenk tube instead of a vial using *N*-benzylaniline for 2 hours (0.500 g, 2.73 mmol) using PhMe as solvent and isolated as a colorless oil, or a white solid upon standing (0.597 g, 2.59 mmol, 95%), flash column chromatography: 1% EtOAc in hexanes.  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ , both rotamers)  $\delta$  7.38-7.27 (m, 6H), 7.25-7.20

(m, 2.5H), 7.06 (d,  $J = 7.3$  Hz, 1.5H), 4.83 (s, 2H).  **$^{13}\text{C}$  NMR** (176 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  146.8 (d,  $J = 287.9$  Hz), 146.6 (d,  $J = 292.2$  Hz), 140.5, 139.2, 135.9, 135.6, 129.3 (2C), 128.8, 128.6, 128.5, 128.1, 127.6, 127.5, 126.9, 125.9, 55.6, 55.0 (2C for minor rotamer overlapping with peaks in the region from 129.3–125.9 ppm).  **$^{19}\text{F}$  NMR** (658 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  -14.63 (s, 1F), -17.06 (s, 0.32F). **HRMS** (DART) Calc'd for  $[\text{C}_{12}\text{H}_{13}\text{NOF}]^+ [\text{M}+\text{H}]^+$  230.09757 found 230.09680. **IR** (ATR, neat,  $\text{cm}^{-1}$ ) 2934, 1784, 1594, 1491, 1215. 731, 692.

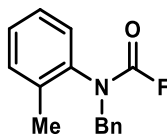
***N*-benzyl-*N*-(2-methoxyphenyl)carbamoyl fluoride (2.3i)**



**2.3i**

The title compound was prepared from *N*-benzyl-2-methoxy-aniline (0.043 g, 0.20 mmol) using MeCN as solvent and isolated as a colorless oil (0.044 g, 0.17 mmol, 85%) after purification by flash column chromatography: 5% EtOAc in hexanes.  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  7.37-7.18 (m, 6H), 7.04-6.79 (m, 3H), 4.99 (bd,  $J = 13.2$  Hz, 0.8H), 4.71 (s, 0.4H), 4.50 (bd,  $J = 13.2$  Hz, 0.8H), 3.81 (bd, 1.7 Hz, 0.5H), 3.76 (bd, 1.8 Hz, 2.5H).  **$^{13}\text{C}$  NMR** (176 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  154.8 (2C), 147.6 (d,  $J = 287.2$  Hz), 146.8 (d,  $J = 291.3$  Hz), 136.1, 136.0, 129.8, 129.8, 129.3, 129.0 (2C), 128.6, 128.4, 128.01, 127.99, 127.7, 120.8, 120.6, 112.3, 111.9, 55.7, 55.6, 54.9, 54.7 (2C overlapping with peaks in the region from 129.8-127.7 ppm).  **$^{19}\text{F}$  NMR** (658.9 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  -16.69 (s, 1F), -20.00 (s, 0.16F). **HRMS** (ESI) calc'd for  $[\text{M}+\text{Na}]^+$  282.0906 found 282.0885. **IR** (ATR,  $\text{CDCl}_3$ ,  $\text{cm}^{-1}$ ) 3065, 3032, 2932, 1783, 1501, 1393, 1266, 1250, 747, 697.

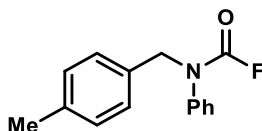
***N*-Benzyl-*N*-(*o*-tolyl)carbamoyl Fluoride (2.3j)**



2.3j

The title compound was prepared from *N*-benzyl-2-methylaniline (0.118 g, 0.60 mmol) using MeCN as solvent. The crude material was purified by flash chromatography (2% EtOAc in hexanes) and the desired product was isolated as colourless oil (0.107 g, 0.44 mmol, 73%) after purification by flash column chromatography: 2% EtOAc in hexanes. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>, *both rotamers*): δ 7.39–7.31 (m, 3H), 7.30–7.14 (m, 5H), 7.03 (d, *J* = 7.7 Hz, 0.2H), 6.92 (d, *J* = 7.9 Hz, 0.8H), 4.94 (d, *J* = 14.2 Hz, <sup>1</sup>H), 4.61 (d, *J* = 14.2 Hz, <sup>1</sup>H), 2.11 (s, 0.6H), 2.08 (s, 2.4H). **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>, *both rotamers*): δ 147.1 (d, *J* = 286.6 Hz), 146.1 (d, *J* = 291.7 Hz), 138.7, 137.8, 135.8, 135.7, 135.52, 135.47, 131.5, 131.3, 129.4, 128.9, 128.83, 128.76, 128.74, 128.70, 128.42, 128.40, 128.0, 127.8, 127.1, 127.0, 55.40, 55.37, 17.44, 17.36. **<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>, *both rotamers*): δ –16.49 (s, 1F), –20.66 (s, 0.25F). **HRMS** (ESI) *m/z*: [M + H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>15</sub>FNO, 244.1132; found, 244.1129. **IR** (ATR, CDCl<sub>3</sub>, cm<sup>–1</sup>) 3065, 3033, 2928, 2857, 1779, 1493, 1455, 1393, 1258, 1082, 1006, 749, 716, 698, 637, 575, 455.

#### **N-phenyl-N-(p-tolylmethyl)carbamoyl fluoride (2.3l)**

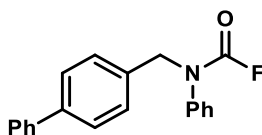


2.3l

The title compound was prepared from *N*-(p-tolylmethyl)aniline (0.039 g, 0.20 mmol) using MeCN as solvent and isolated as a colorless oil (0.048 g, 0.20 mmol, >99%) after purification by flash column chromatography: 1→2% EtOAc in hexanes. **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>, *both*

*rotamers*)  $\delta$  7.38-7.31 (m, 2H), 7.31-7.27 (m, 1H), 7.23 (bd,  $J = 7.4$  Hz, 0.5H), 7.16-7.08 (m, 4H), 7.05 (d,  $J = 7.6$  Hz, 1.5H), 4.79 (s, 2H), 2.33 (s, 3H).  $^{13}\text{C}$  NMR (176 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  147.0 (d,  $J = 287.7$  Hz), 146.9 (d,  $J = 292.0$  Hz), 140.6, 139.4, 138.0 (2C), 133.0, 132.8, 129.6, 129.4 (2C), 128.7, 128.2 (2C), 127.72, 127.66, 127.1, 126.2, 55.5, 55.0, 21.3 (2C).  $^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  -14.57 (s, 1F), -17.23 (s, 0.33F). HRMS (ESI) Calc'd for  $[\text{C}_{15}\text{H}_{14}\text{NOF}]^+ [\text{M}+\text{H}]^+$  244.1138 found 244.1129. IR (ATR, neat,  $\text{cm}^{-1}$ ) 3026, 1779, 1391, 695.

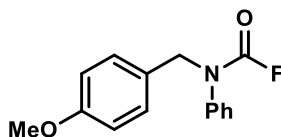
#### N-phenyl-N-[(4-phenylphenyl)methyl]carbamoyl fluoride (2.4m)



2.3m

The title compound was prepared from *N*-[(4-phenylphenyl)methyl]aniline (0.052 g, 0.20 mmol) using MeCN as solvent and isolated as a white solid (0.054 g, 0.18 mmol, 88%, mp = 53-54 °C) after purification by flash column chromatography: 2% EtOAc in hexanes.  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  7.58 (d,  $J = 7.3$  Hz, 2.5H), 7.55 (d,  $J = 8.0$  Hz, 1.5H), 7.44 (t,  $J = 7.6$  Hz, 2H), 7.40-7.34 (m, 3H), 7.33-7.27 (m, 3.5H), 7.11 (d,  $J = 7.6$  Hz, 1.5H), 4.87 (s, 2H).  $^{13}\text{C}$  NMR (176 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  147.0 (d,  $J = 288.0$  Hz), 146.8 (d,  $J = 291.5$  Hz), 141.1 (2C), 140.62, 140.55, 140.5, 139.4, 135.0, 134.8, 129.5, 129.1, 128.9, 128.2, 128.1, 127.8, 127.63, 127.59, 127.5, 127.1, 127.0, 126.1, 55.4, 54.9 (4C for minor rotamer overlapping with peaks in the region from 129.1-126.1 ppm).  $^{19}\text{F}$  NMR (659 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  -14.53 (s, 1F), -16.90 (s, 0.3F). HRMS (ESI) Calc'd for  $[\text{C}_{20}\text{H}_{16}\text{NOF}]^+ [\text{M}+\text{H}]^+$  306.1294 found 306.1291. IR (ATR, neat,  $\text{cm}^{-1}$ ) 2988, 1779, 1391, 745, 694.

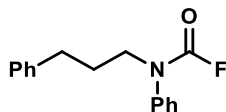
#### *N*-[(4-methoxyphenyl)methyl]-*N*-phenyl-carbamoyl fluoride (2.3n)



**2.3n**

The title compound was prepared from *N*-[(4-methoxyphenyl)methyl]aniline (0.213 g, 1.00 mmol) using PhMe as solvent. The crude material was purified by flash chromatography (5% EtOAc in hexanes) and the desired product was isolated as colourless solid (0.237 g, 0.91 mmol, 91%, *rotamer ratio* = 4:1). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *both rotamers*) δ 7.41-7.26 (m, 3H), 7.26-7.08 (m, 2.5H), 7.04 (d, *J* = 7.1 Hz, 1.5H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.77 (s, 2H), 3.79 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *both rotamers*) δ 159.6, 146.9 (d, *J* = 287.7 Hz), 140.5, 139.3, 132.1, 130.2, 129.4, 129.2, 128.2, 128.1, 127.9, 127.8, 127.2, 126.4, 114.2, 114.1, 55.7, 55.3, 55.2, 54.7. **<sup>19</sup>F NMR** (377 MHz, CDCl<sub>3</sub>, *both rotamers*) δ -14.49 (0.8F), -17.9 (0.2F). **HRMS** (DART) *m/z*: Calc'd for [C<sub>15</sub>H<sub>15</sub>FNO<sub>2</sub>]<sup>+</sup> [M+H]<sup>+</sup> 260.1081 found 260.1081. **IR** (ATR, neat, cm<sup>-1</sup>) 3064, 2960, 2903, 2838, 1778, 1512, 1391.

**N-phenyl-N-(3-phenylpropyl)carbamoyl fluoride (2.3p)**



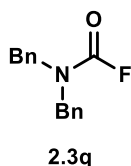
**2.3p**

The title compound was prepared from *N*-(3-phenylpropyl)aniline (0.042 g, 0.20 mmol) and isolated as a colorless oil (0.048 g, 0.18 mmol, 92%) after purification by flash column chromatography: 3% EtOAc in hexanes. **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>, *both rotamers*) δ 7.45-7.40 (m, 2H), 7.38-7.33 (m, 1H), 7.32-7.25 (m, 2.5H), 7.20 (d, *J* = 7.6 Hz, 2.5H), 7.13 (d, *J* = 7.3 Hz, 2H), 3.74 (t, *J* = 7.5 Hz, 1.5H), 3.71 (t, *J* = 7.2 Hz, 0.5H), 2.68-2.63 (m, 2H), 1.94 (p, *J* = 7.6 Hz, 2H). **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>, *both rotamers*) δ 147.0 (d, *J* = 290.7 Hz), 146.5 (d, *J* = 287.6



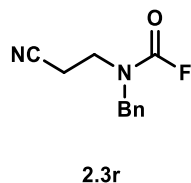
Hz), 141.0, 140.7, 140.3, 139.3, 129.6 (2C), 128.62, 128.57, 128.4, 128.3, 128.2, 127.8, 126.9, 126.3 (2C), 126.2, 51.4, 50.9, 32.9, 32.8, 30.2, 29.2. <sup>19</sup>F NMR (659 MHz, CDCl<sub>3</sub>, *both rotamers*) δ -13.72 (s, 1F), -18.75 (s, 0.25F). HRMS (ESI) Calc'd for [C<sub>16</sub>H<sub>16</sub>NOF]<sup>+</sup> [M+H]<sup>+</sup> 258.1294 found 258.1285. IR (ATR, neat, cm<sup>-1</sup>) 2941, 1779, 1495, 1396, 1265, 746, 695.

***N,N*-dibenzylcarbamoyl fluoride (2.4q)**



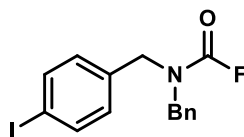
The title compound was prepared from dibenzylamine (0.079 g, 0.40 mmol) using PhMe as a solvent and isolated as a colorless oil (0.081 g, 0.36 mmol, 89%) after purification by flash column chromatography: 2% EtOAc in hexanes. The spectral data are consistent with literature values.<sup>25</sup>

***N*-phenyl-*N*-(3-phenylpropyl)carbamoyl fluoride (2.3r)**



The title compound was prepared from 3-(benzylamino)propanenitrile (0.042 g, 0.20 mmol) using MeCN as solvent and isolated as a colorless oil (0.048 g, 0.18 mmol, 92%) after purification by flash column chromatography: 3% EtOAc in hexanes. The spectral data are consistent with literature values.<sup>28,49</sup>

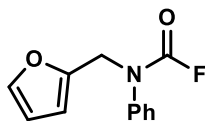
***N*-benzyl-*N*-[(4-iodophenyl)methyl]carbamoyl fluoride (2.3t)**



**2.3t**

The title compound was prepared from *N*-[(4-iodophenyl)methyl]-1-phenyl-methanamine (0.100 g, 0.309 mmol) using PhMe as solvent. After purification by flash chromatography: (5% EtOAc in hexanes) and the desired product was isolated as a colourless oil (0.104 g, 0.28 mmol, 91%). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *both rotamers*) 7.70 (dd, *J* = 8.3 Hz, 2.6 Hz, 2H), 7.44-7.31 (m, 3H), 7.30-7.23 (m, 1H), 7.20 (d, *J* = 6.3 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 4.42 (s, 1H), 4.35 (s, 1H), 4.34 (s, 1H), 4.28 (s, 1H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *both rotamers*) δ 148.2 (d, *J* = 288.8 Hz) 148.1 (d, *J* = 288.8 Hz), 138.2, 138.1, 135.2, 135.1, 130.4, 129.7, 129.2, 129.1, 128.5, 128.43, 128.41, 127.9, 93.9, 93.8, 50.8, 50.1, 50.0 (d, *J* = 3.4 Hz), 49.3 (d, *J* = 3.3 Hz) (Note: not all rotamer peaks are resolved). **<sup>19</sup>F NMR** (377 MHz, CDCl<sub>3</sub>, *both rotamers*) δ -22.2 (s, 0.5F), -22.6 (s, 0.5F). **HRMS** (ESI) Calc'd for [C<sub>15</sub>H<sub>14</sub>FINO]<sup>+</sup> [M+H]<sup>+</sup> 370.0099 found 370.0100.

*N*-(2-furylmethyl)-*N*-phenyl-carbamoyl fluoride (**2.3u**)

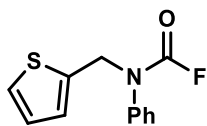


**2.3u**

The title compound was prepared from *N*-(2-furylmethyl)aniline (0.035 g, 0.20 mmol) using MeCN as solvent and isolated as a colorless oil (0.040 g, 0.18 mmol, 91%) after purification by flash column chromatography: 3% EtOAc in hexanes. **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>, *both rotamers*) δ 7.42-7.35 (m, 3H), 7.33 (t = 7.5 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 0.5H), 7.13 (d, *J* = 7.7 Hz, 1.5H),

6.33 (bs, 0.25H), 6.31 (t,  $J = 2.2$  Hz, 0.75H), 6.25 (d,  $J = 3.0$  Hz, 0.75H), 6.23 (bd,  $J = 3.0$  Hz), 4.80 (s, 1.5H), 4.77 (s, 0.5H).  **$^{13}\text{C}$  NMR** (176 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  149.3, 149.0, 146.7 (d,  $J = 292.6$  Hz), 146.5 (d,  $J = 288.7$  Hz), 143.0, 142.9 (d,  $J = 2.6$  Hz), 140.4, 139.2, 129.52, 129.49, 128.4, 128.0, 126.9, 126.2, 110.6 (2C), 110.0, 109.4, 48.3, 48.1.  **$^{19}\text{F}$  NMR** (659 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  -14.13 (s, 1F), -17.07 (s, 0.3F). **HRMS** (ESI) Calc'd for  $[\text{C}_{12}\text{H}_{10}\text{NO}_2\text{F}]^+ [\text{M}+\text{H}]^+$  220.0774 found 220.0770. **IR** (ATR, neat,  $\text{cm}^{-1}$ ) 2988, 1781, 1597, 1494, 743, 694, 595.

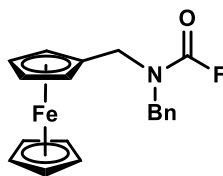
N-phenyl-N-(2-thienylmethyl)carbamoyl fluoride (**2.3v**)



**2.3v**

The title compound was prepared from *N*-(2-thienylmethyl)aniline (0.038 g, 0.20 mmol) using MeCN as solvent and isolated as a yellow solid (0.040 g, 0.17 mmol, 85%, mp = 43-44 °C) after purification by flash column chromatography: 1→2% EtOAc in hexanes.  **$^1\text{H}$  NMR** (700 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  7.41-7.31 (m, 3H), 7.26 (m, 1.5H), 7.12 (d,  $J = 7.6$  Hz, 1.5H), 6.96-6.92 (m, 1H), 6.96-6.94 (m, 0.2H), 6.93-6.91 (m, 0.8H), 6.91-6.90 (m, 1H), 4.97 (bs, 2H).  **$^{13}\text{C}$  NMR** (176 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  146.6 (d,  $J = 289.0$  Hz), 146.4 (d,  $J = 292.6$  Hz), 140.1, 139.0, 138.1, 137.4, 129.61, 129.56, 128.5, 128.1 (2C), 127.4, 127.1 (2C), 126.9, 126.5, 126.4, 126.2, 50.3, 50.1.  **$^{19}\text{F}$  NMR** (659 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  -14.61 (s, 1F), -16.99 (s, 0.25F). **HRMS** (ESI) Calc'd for  $[\text{C}_{12}\text{H}_{10}\text{NOFS}]^+ [\text{M}+\text{H}]^+$  236.0545 found 236.0538. **IR** (ATR, neat,  $\text{cm}^{-1}$ ) 2988, 1777, 1597, 1493, 1394, 693.

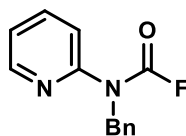
*N*-benzyl-*N*-ferrocenylmethyl-carbamoyl fluoride (**2.3w**)



2.3w

The title compound was prepared from *N*-benzyl-*N*-ferrocenylmethyl amine (0.305 g, 1.00 mmol) using PhMe as solvent. The crude material was purified by flash chromatography (5% EtOAc in hexanes) and the desired product was isolated as a red-orange oil (0.235 g, 0.67 mmol, 67%, *rotamer ratio* = 1:1). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *both rotamers*) 7.43-7.30 (m, 3H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 7.0 Hz, 1H), 4.41 (s, 1H), 4.34 (s, 1H), 4.23 (bs, 1H), 4.19 (s, 1H), 4.17 (bm, 3H), 4.13 (s, 2.5H), 4.12 (s, 2.5H), 4.10 (s, 1H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *both rotamers*) 148.9 (d, *J* = 288.1 Hz), 147.8 (d, *J* = 288.0 Hz), 135.64, 135.62, 128.9, 128.8, 128.03, 127.98, 127.9, 127.4, 81.5, 81.1, 69.6, 69.2, 68.6, 50.2, 49.4 (d, *J* = 3.2 Hz), 46.7, 45.9 (d, *J* = 3.7 Hz) (Note: not all rotamer peaks are resolved). **<sup>19</sup>F NMR** (377 MHz, CDCl<sub>3</sub>, *both rotamers*) δ) -22.1 (0.5F), -22.6 (0.5F). **HRMS** (ESI) Calc'd for [C<sub>19</sub>H<sub>19</sub>FFeNO]<sup>+</sup> [M+H]<sup>+</sup> 352.0795 found 352.0751.

*N*-benzyl-*N*-(2-pyridyl)carbamoyl fluoride (**2.3x**)

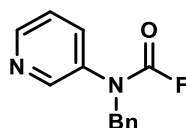


2.3x

The title compound was prepared from 2-benzylaminopyridine (0.074 g, 0.40 mmol) using MeCN as solvent and isolated as a yellow oil (0.041 g, 0.18 mmol, 45%) after purification by flash column chromatography: 10% EtOAc in Hexanes. When reaction time was increased to 3 hours, the yield was found to increase significantly (0.058 g, 0.25 mmol, 63%). **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>, *both rotamers*) δ 8.44 (d, *J* = 4.8 Hz, 1H), 7.74-7.64 (m, 1.2H), 7.61-7.37 (m, 0.5H), 7.35-7.19 (m,

5.3H), 7.14 (dd,  $J = 8.1$  Hz, 4.9 Hz, 1H), 5.22 (s, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  151.9, 148.3, 146.1 (d,  $J = 292.6$  Hz), 138.1, 136.6, 128.6 (2C), 127.7, 121.6, 119.1, 51.0.  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  -7.71 (bs, 1F), -15.21 (bs, 0.81F). HRMS (DART) calc'd for  $[\text{M}+\text{H}]^+$  231.0934 found 231.0928. IR (ATR,  $\text{CDCl}_3$ ,  $\text{cm}^{-1}$ ) 1789, 1590, 1472, 1435, 1392, 1305, 1274, 1223, 779, 697.

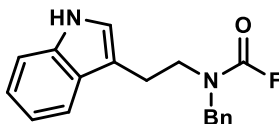
N-benzyl-N-(3-pyridyl)carbamoyl fluoride (**2.3y**)



**2.3y**

The title compound was prepared from *N*-benzyl-3-aminopyridine (0.037 g, 0.20 mmol) using MeCN as solvent and isolated as a yellow oil (0.020 g, 0.09 mmol, 43%) after purification by flash column chromatography: 40% EtOAc in hexanes. Unlike with structurally similar **2.3x**, increased reaction time does not provide an increase in the yield of **2.3y**.  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ , *both rotamers*) 8.57-8.50 (m, 1.25H), 8.38 (bs, 0.75H), 7.57 (bd,  $J = 6.6$  Hz, 0.25H), 7.38-7.26 (m, 4.75H), 7.25-7.18 (m, 2H), 4.87 and 4.85 (overlapping singlets, 2H total).  $^{13}\text{C}$  NMR (176 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  149.3, 148.7, 148.4, 147.4, 146.5 (d, 289.5 Hz, 2C), 137.2, 135.9, 135.2, 135.0, 134.6, 133.7, 129.2, 129.1, 128.7, 128.64, 128.57, 127.6, 124.0, 123.9, 55.7, 55.1.  $^{19}\text{F}$  NMR (659 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  -13.85 (s, 1F), -16.79 (s, 0.30F). HRMS (DART) Calc'd for  $[\text{C}_{13}\text{H}_{11}\text{N}_2\text{OF}]^+ [\text{M}+\text{H}]^+$  231.09367 found 231.09282. IR (ATR, neat,  $\text{cm}^{-1}$ ) 3064, 2987, 1779, 1391, 1266, 695.

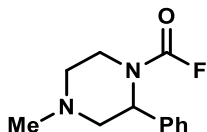
N-benzyl-N-[2-(1H-indol-3-yl)ethyl]carbamoyl fluoride (**2.3z**)



**2.3z**

The title compound was prepared from *N*-benzyl-2-(1H-indol-3-yl)ethanamine (0.202 g, 0.81 mmol) using MeCN as solvent and isolated as a orange-yellow solid (0.128 g, 0.44 mmol, 54%, mp = 72-74 °C) after purification by flash column chromatography: 20% EtOAc in hexanes. Single crystals suitable for X-ray crystallography were grown via slow evaporation of a saturated solution of **2.3z** in 1:1 diethyl ether/hexanes. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *both rotamers*) δ 8.04 (bs, 1H), 7.54 (d, *J* = 7.8 Hz, 0.5H), 7.48 (d, *J* = 7.8 Hz, 0.5H), 7.40-7.29 (m, 4H), 7.26-7.10 (m, 4H), 7.02 (d, *J* = 2.2 Hz, 0.5H), 6.98 (d, *J* = 2.2 Hz, 0.5H), 4.39 (s, 1.1H), 4.32 (s, 0.9H), 3.55 (t, *J* = 7.6 Hz, 0.9H), 3.47 (t, *J* = 7.6, 1.1H), 3.07 (t, *J* = 7.6 Hz, 0.9H), 2.99 (t, *J* = 7.6 Hz, 1.1H). **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) δ 148.7 (d, *J* = 287.46 Hz), 147.7 (d, *J* = 288.78 Hz), 136.43, 136.41, 136.0, 135.9, 129.02, 128.97, 128.32, 128.25, 128.2, 127.7, 127.3, 127.1, 122.4, 122.32 (2C), 122.30, 119.71, 119.67, 118.6, 118.5, 112.2, 112.0, 111.5, 111.4, 52.3, 51.8 (d, *J* = 2.61 Hz), 48.7, 47.7, 24.7, 23.2. **<sup>19</sup>F NMR** (659 MHz, CDCl<sub>3</sub>) δ -21.50 (s, 0.86F), -21.95 (s, 1F). **HRMS** (ESI) calc'd for [M+Na]<sup>+</sup> 319.1223 found 319.1194. **IR** (ATR, neat, cm<sup>-1</sup>) 3356, 3083, 2924, 2858, 1757, 1422, 741, 556.

4-methyl-2-phenyl-piperazine-1-carbonyl fluoride (**2.3aa**)

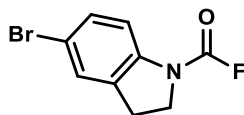


**2.3ab**

The title compound was prepared from 1-methyl-3-phenylpiperazine (0.071 g, 0.40 mmol) using PhMe as solvent and isolated as a colorless oil (0.076 g, 0.34 mmol, 86%) after purification by

flash column chromatography: 30% EtOAc in hexanes. **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) δ 7.61-7.54 (bm, 1H), 7.49 (bs, 1H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 5.21 (bs, 0.5H), 5.07 (bs, 0.5H), 3.86 (bd, *J* = 10.9 Hz, 0.5H), 3.73 (br, *J* = 11.8 Hz, 0.5H), 3.33 (bd, *J* = 10.9 Hz, 1H), 3.21 (dt, *J* = 12.8, 3.2 Hz, 1H), 2.81 (bs, 1H), 2.49 (dd, *J* = 12.0, 3.6 Hz, 1H), 2.32 (s, 3H), 2.21-2.12 (m, 1H). **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) δ 147.1 (d, *J* = 286.9 Hz), 146.9 (d, *J* = 282.9 Hz), 138.5 (2C), 128.8, 128.7, 128.0, 127.8 (2C), 127.4, 57.3, 56.8, 55.0, 54.8 (2C), 54.4, 46.3 (2C), 41.5, 41.3. **<sup>19</sup>F NMR** (657 MHz, CDCl<sub>3</sub>) δ -23.69 (s, 0.9F), -24.16 (s, 1F). **HRMS** (DART) Calc'd for [C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>OF]<sup>+</sup> [M+H]<sup>+</sup> 223.12412 found 223.12359. **IR** (ATR, neat, cm<sup>-1</sup>) 2796, 1777, 1401, 693.

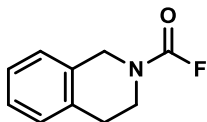
5-bromoindoline-1-carbonyl fluoride (**2.3ab**)



**2.3ac**

The title compound was prepared from using 5-bromoindoline (0.079 g, 0.40 mmol) using MeCN as solvent and isolated as a white solid (0.091 g, 0.37 mmol, 93%, mp = 115-117 °C) after purification by flash column chromatography: 5% EtOAc in hexanes. **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) δ 7.63 (dd, *J* = 8.4, 1.4 Hz, 0.75H), 7.38-7.29 (m, 2H), 7.16 (dd, *J* = 9.2, 4.1 Hz, 0.25H), 4.16-4.05 (m, 2H), 3.19 (t, *J* = 8.60 Hz, 2H). **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) δ 143.7 (d, *J* = 294.8 Hz), 143.0 (d, *J* = 289.8 Hz), 139.6, 138.9 (d, *J* = 5.1 Hz), 133.9, 133.5 (d, *J* = 4.5 Hz), 130.9 (d, *J* = 2.3 Hz), 130.8, 128.6, 128.1, 117.2, 117.1, 116.42, 116.35, 48.5, 47.9, 27.2, 27.1. **<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -5.74 (s, 1F), -13.48 (s, 0.3F). **HRMS** (ESI) calc'd for [M]<sup>+</sup> 242.9695 found 242.9684. **IR** (ATR, CDCl<sub>3</sub>, cm<sup>-1</sup>) 2924, 2861, 1780, 1513, 1426, 1396, 1338, 953.

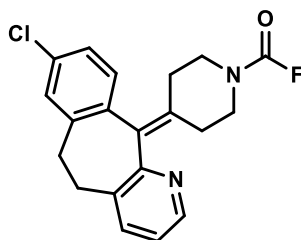
3,4-dihydro-1H-isoquinoline-2-carbonyl fluoride (**2.3ac**)



**2.3ad**

The title compound was prepared from 1,2,3,4-tetrahydroisoquinoline (0.025 mL, 0.20 mmol) using MeCN as solvent and isolated as a colorless oil (0.024 g, 0.13 mmol, 66%) after purification by flash column chromatography: 5% EtOAc in hexanes. The spectral data are consistent with literature values.

4-(13-chloro-4-azatricyclo[9.4.0.0<sup>3,8</sup>]pentadeca-1(11),3(8),4,6,12,14-hexaen-2-ylidene)piperidine-1-carbonyl fluoride (**2.3ad**)

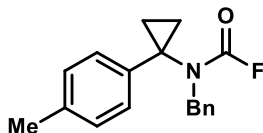


**2.3ae**

The title compound was prepared from desloratadine (0.311 g, 1.00 mmol) using PhMe as solvent and isolated as a yellow solid (0.235 g, 0.66 mmol, 66%) after purification by flash column chromatography: 40% EtOAc in hexanes. The spectral data are consistent with literature values (This compound was not included in our JOC report and appeared in the literature before it was synthesized in our lab).<sup>43</sup>

N-benzyl-N-[1-(p-tolyl)cyclopropyl]carbamoyl fluoride (**2.3ae**)

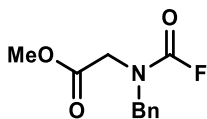




**2.3af**

The title compound was prepared from *N*-benzyl-1-(*p*-tolyl)cyclopropanamine (0.048 g, 0.20 mmol) using MeCN as solvent and isolated as a colorless oil (0.047 g, 0.17 mmol, 83%) after purification by flash column chromatography: 5% EtOAc in hexanes. **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) δ 7.30 (t, *J* = 7.3 Hz, 2H), 7.28-7.25 (m, 1H), 7.24-7.21 (m, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 7.5 Hz, 0.75H), 7.04 (d, *J* = 8.1 Hz, 1.25H), 4.63 (s, 1.25H), 4.57 (s, 0.75H), 2.34 (s, 3H), 1.38-1.33 (m, 2H), 1.23-1.19 (m, 2H). **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) δ 149.5 (d, *J* = 293.7 Hz), 147.8 (d, *J* = 292.7 Hz), 137.8, 137.28, 137.27, 137.11, 137.07, 136.9, 129.4, 129.3, 128.72, 128.68, 127.62, 127.56, 127.3, 126.8, 126.6, 125.3, 53.3, 52.7, 44.1, 43.3, 21.0, 20.9, 17.8, 16.7. **<sup>19</sup>F NMR** (659 MHz, CDCl<sub>3</sub>) δ -13.21 (s, 0.6H), -13.92 (s, 1F). **HRMS** (DART) Calc'd for [C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>OF]<sup>+</sup> [M+NH<sub>4</sub>]<sup>+</sup> 301.17107 found 301.17119. **IR** (ATR, neat, cm<sup>-1</sup>) 2988, 1778, 1392, 697.

methyl 2-[benzyl(fluorocarbonyl)amino]acetate (**2.3ag**)

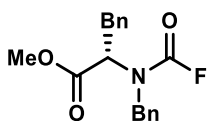


**2.3ag**

The title compound was prepared from methyl 2-(benzylamino)acetate (0.179 g, 1.00 mmol) using PhMe as solvent. The crude material was purified by flash chromatography (15% EtOAc in hexanes) and the desired product was isolated as a colourless oil (0.153 g, 0.68 mmol, 68%, *rotamer ratio* = 1:1). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *both rotamers*) δ 7.41-7.29 (m, 3H), 7.29-7.25

(m, 1H), 7.23 (d,  $J = 7.13$  Hz), 1H), 4.56 (s, 1H), 4.53 (s, 1H), 3.93 (s, 1H), 3.85 (s, 1H), 3.72 (s, 1.5 H), 3.71 (s, 1.5 H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ , both rotamers)  $\delta$  168.6, 168.5, 147.9 (d,  $J = 288.9$  Hz), 147.8 (d,  $J = 290.1$  Hz), 134.7, 129.1, 129.0, 128.5, 128.0, 52.7, 52.6, 52.5, 52.0 (d,  $J = 3.4$  Hz), 48.1, 47.5 (d,  $J = 2.3$  Hz) (Note: not all rotamer peaks are resolved).  $^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ , both rotamers)  $\delta$  -20.6 (0.5F), -23.6 (0.5F). HRMS (ESI) Calc'd for  $[\text{C}_{11}\text{H}_{13}\text{FN}_2\text{O}_3]^+$   $[\text{M}+\text{H}]^+$  226.0874 found 226.0876.

methyl (2S)-2-[benzyl(fluorocarbonyl)amino]-3-phenyl-propanoate (**2.3ag**)

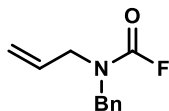


**2.3ah**

The title compound was prepared from (2S)-2-(benzylamino)-3-phenyl-propanoate (0.054 g, 0.20 mmol) using MeCN as solvent and isolated as a colorless oil (0.053 g, 0.17 mmol, 84%,  $[\alpha]_D^{19} +82$  (c 0.34, acetone) after purification by flash column chromatography: 3% to 5% EtOAc in hexanes.  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34-7.25 (m, 6H), 7.16-7.14 (m, 1H), 7.13 (d,  $J = 7.0$  Hz, 1H), 7.10 (d,  $J = 7.0$  Hz), 7.08-7.06 (m, 1H), 4.52 (d,  $J = 15.1$  Hz, 0.4H), 4.41 (d,  $J = 15.6$  Hz, 0.6H), 4.23 (dd,  $J = 10.1, 5.5$  Hz, 0.6H), 4.11 (dd,  $J = 9.9, 5.6$  Hz, 0.4H), 3.91 (d,  $J = 15.7$  Hz, 0.6H), 3.88 (d,  $J = 15.1$  Hz, 0.4H), 3.67 (s, 1.8H), 3.65 (s, 1.2H), 3.39 (dt,  $J = 14.7, 5.5$  Hz, 1H), 3.30 (d,  $J = 10.1$  Hz, 0.4H), 3.28 (d,  $J = 10.2$  Hz, 0.2H), 3.10-3.05 (m, 0.4H).  $^{13}\text{C}$  NMR  $\delta$  169.7, 169.6, 148.0 (d,  $J = 291.2$  Hz), 147.1 (d,  $J = 292.3$  Hz), 136.9, 136.6, 134.8, 129.17, 129.15, 129.0, 128.9, 128.73, 128.70, 128.3, 128.2, 127.3, 127.1, 62.1 (d,  $J = 5.8$  Hz), 61.6 (d,  $J = 6.4$  Hz), 53.4 (d,  $J = 6.4$  Hz, 2C), 52.8 (d,  $J = 4.1$  Hz), 52.7 (d,  $J = 4.9$  Hz), 36.6 (2C), 34.8 (2C) (2C for  $-\text{OCH}_3$  overlapping with peaks for both rotamers in region from 52.8-52.7 ppm).  $^{19}\text{F}$  NMR (659 MHz,  $\text{CDCl}_3$ )  $\delta$  -15.23 (s, 0.9F), -18.06 (s, 1F). HRMS (ESI) Calc'd for

$[\text{C}_{20}\text{H}_{18}\text{NO}_3\text{F}]^+ [\text{M}+\text{Na}]^+ 338.1168$  found  $338.1166$ . **IR** (ATR, neat,  $\text{cm}^{-1}$ ) 2971, 1782, 1741, 1219, 748, 697.

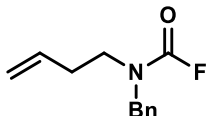
N-allyl-N-benzyl-carbamoyl fluoride (**2.3ah**)



**2.3ai**

The title compound was prepared from N-allyl-N-benzylamine (0.029 g, 0.20 mmol) using MeCN as solvent and isolated as a colorless oil (0.036 g, 0.19 mmol, 92%) after purification by flash column chromatography: 1% EtOAc in hexanes.  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40-7.27 (m, 4H), 7.24 (m, 1H), 5.84-5.68 (m, 1H), 5.28-5.16 (m, 2H), 4.48 (s, 1H), 4.42 (s, 1H), 3.86 (d,  $J = 6.0$  Hz, 1H), 3.77 (d,  $J = 5.7$  Hz, 1H).  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  148.3 (d,  $J = 288.3$  Hz), 147.6 (d,  $J = 288.4$  Hz), 135.70, 135.65, 131.7, 131.4, 129.04, 128.96, 128.4, 128.3, 128.2, 127.8, 119.3, 118.5, 51.0, 50.1 (d,  $J = 3.2$  Hz), 49.9, 49.0 (d,  $J = 3.2$  Hz).  **$^{19}\text{F}$  NMR** (659 MHz,  $\text{CDCl}_3$ )  $\delta$  -22.12 (s, 0.9F), -22.66 (s, 1F). **HRMS** (DART) Calc'd for  $[\text{C}_{11}\text{H}_{13}\text{NOF}]^+ [\text{M}+\text{H}]^+ 194.09757$  found 194.09757. **IR** (ATR, neat,  $\text{cm}^{-1}$ ) 3067, 1777, 1415, 1225, 698.

N-benzyl-N-but-3-enyl-carbamoyl fluoride (**2.3aj**)

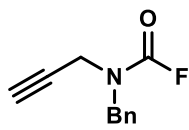


**2.3aj**

The title compound was prepared from N-benzylbut-3-en-1-amine (0.032 g, 0.20 mmol) using MeCN as solvent and isolated as a colorless oil (0.033 g, 0.16 mmol, 80%) after purification by flash column chromatography: 3% EtOAc in hexanes.  **$^1\text{H}$  NMR** (700 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39-7.35

(m, 2H), 7.34-7.31 (m, 1H), 7.30 (d,  $J = 7.2$  Hz, 1H), 7.24 (d,  $J = 7.4$  Hz, 1H), 5.77-5.68 (m, 1H), 5.10-5.05 (m, 2H), 4.49 (s, 1H), 4.44 (s, 1H), 3.32 (t,  $J = 7.3$  Hz, 1H), 3.24 (t,  $J = 7.3$  Hz, 1H), 2.34 (dt,  $J = 7.2, 7.2$ , 1H), 2.27 (dt,  $J = 7.2, 7.2$ , 1H).  $^{13}\text{C}$  NMR (176 MHz,  $\text{CDCl}_3$ )  $\delta$  148.5 (d,  $J = 287.5$  Hz), 147.6 (d,  $J = 288.3$  Hz), 135.88, 135.86, 134.3, 134.0, 129.1, 129.0, 128.25, 128.22, 127.6 (2C), 118.0, 117.7, 51.8, 51.3, 47.4, 46.4, 32.7, 31.6.  $^{19}\text{F}$  NMR (659 MHz,  $\text{CDCl}_3$ )  $\delta$  -21.56(s, 0.9F), -22.04 (s, 1F). HRMS (ESI) Calc'd for  $[\text{C}_{12}\text{H}_{14}\text{NOF}]^+ [\text{M}+\text{H}]^+$  208.1138 found 208.1134. IR (ATR, neat,  $\text{cm}^{-1}$ ) 3067, 2981, 1778, 1419, 698.

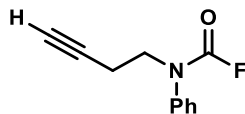
N-benzyl-N-prop-2-ynyl-carbamoyl fluoride (**2.3aj**)



**2.3ak**

The title compound was prepared from *N*-benzylprop-2-yn-1-amine (0.029 g, 0.20 mmol) using MeCN as solvent and isolated as a pale-yellow oil (0.036 g, 0.19 mmol, 95%) after purification by flash column chromatography: 3% EtOAc in hexanes.  $^1\text{H}$  NMR (700 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39-7.28 (m, 4H), 7.27-7.21 (m, 1H), 4.59 (s, 1H), 4.56 (s, 1H), 4.02 (s, 1H), 3.91 (s, 1H), 2.32 (s, 1H).  $^{13}\text{C}$  NMR (176 MHz,  $\text{CDCl}_3$ )  $\delta$  147.25 (d,  $J = 290.0$  Hz), 147.18 (d,  $J = 288.6$  Hz), 134.84, 134.82, 129.13, 129.06, 128.6, 128.5, 128.1 (2C), 76.93, 76.88, 74.0 (d,  $J = 2.5$  Hz), 73.7 (d,  $J = 2.5$  Hz), 50.7 (2C), 50.0 (d,  $J = 2.6$  Hz, 2C), 36.7, 35.9.  $^{19}\text{F}$  NMR (659 MHz,  $\text{CDCl}_3$ )  $\delta$  -21.62 (s, 1F), -22.38 (s, 1F). HRMS (ESI) Calc'd for  $[\text{C}_{11}\text{H}_{10}\text{NOF}]^+ [\text{M}+\text{H}]^+$  192.0825 found 192.0818. IR (ATR, neat,  $\text{cm}^{-1}$ ) 3290, 3034, 1779, 1416, 1223, 697.

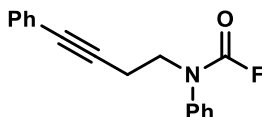
N-but-3-ynyl-N-phenyl-carbamoyl fluoride (**2.3ak**)



**2.3al**

The title compound was prepared from N-but-3-ynylaniline (0.029 g, 0.20 mmol) using MeCN as solvent and isolated as a colorless oil (0.035 g, 0.18 mmol, 92%), flash column chromatography: 3% EtOAc in hexanes. **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) δ 7.45-7.40 (m, 2H), 7.38-7.33 (m, 1.5 H), 7.28-7.25 (m, 1.5 H), 3.85 (t, J = 7.08 Hz, 2H, overlapping with signal at 3.84 ppm), 3.84 (t, J = 7.19 Hz, overlapping with signal at 3.85 ppm), 2.49 (td, J = 7.05, 2.54 Hz, 1.5 H), 2.45 (td, J = 6.93, 2.20 Hz, 0.5 H), 2.06 (t, J = 2.79 Hz, 0.25 H), 2.02 (t, J = 2.52 Hz, 0.75 H) **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) δ 146.6 (d, J = 291.4 Hz), 146.3 (d, J = 288.5), 139.4, 138.7, 129.6, 129.5, 128.3, 128.1, 126.9, 126.5, 80.0, 79.6, 71.1, 70.6 (d, J = 3.5 Hz), 50.0 (t\*, J = 6.1 Hz, 2C), 49.4 (bt\*, 2C), 18.4, 17.4. Note: \*t = apparent triplet, likely two overlapping doublets for the two rotamers. **<sup>19</sup>F NMR** (659 MHz, CDCl<sub>3</sub>) δ -13.59 (s, 1F), -18.62 (s, 0.25F). **HRMS** (ESI) Calc'd for [C<sub>11</sub>H<sub>10</sub>NOF]<sup>+</sup> [M+H]<sup>+</sup> 192.0825 found 192.0817. **IR** (ATR, neat, cm<sup>-1</sup>) 3295, 3063, 1779, 1496, 1396, 1270, 694.

N-phenyl-N-(4-phenylbut-3-ynyl)carbamoyl fluoride (**2.3al**)



**2.3am**

The title compound was prepared from N-(4-phenylbut-3-ynyl)aniline (0.044 g, 0.20 mmol) using MeCN as solvent and isolated as a colorless oil (0.049 g, 0.18 mmol, 93%) after purification by flash column chromatography: 2% EtOAc in hexanes. **<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) δ 7.46-7.33

(m, 5H), 7.32-7.24 (m, 5H), 3.96-3.91 (m, 2H), 2.74 (t, J = 6.7 Hz, 1.5H), 2.69 (t, J = 6.4 Hz, 0.5H). **<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) δ 146.9 (d, J = 291.4 Hz), 146.5 (d, J = 288.5 Hz), 139.8, 139.2, 131.7 (2C), 129.71, 129.65, 128.4 (2C), 128.23, 128.17, 128.1, 127.1, 126.7, 123.3, 123.1, 85.8, 85.2, 83.3, 82.8, 50.5 (2C), 49.9 (2C), 19.7, 18.6 (1C for minor rotamer overlapping with peaks in the region from 129.7-128.1 ppm). **<sup>19</sup>F NMR** (659 MHz, CDCl<sub>3</sub>) δ -13.56 (s, 1F), -18.51 (s, 0.25F). **HRMS** (ESI) Calc'd for [C<sub>17</sub>H<sub>15</sub>NOF]<sup>+</sup> [M+H]<sup>+</sup> 268.1138 found 268.1130. **IR** (ATR, neat, cm<sup>-1</sup>) 3063, 1780, 1491, 1395, 1271, 753, 690.

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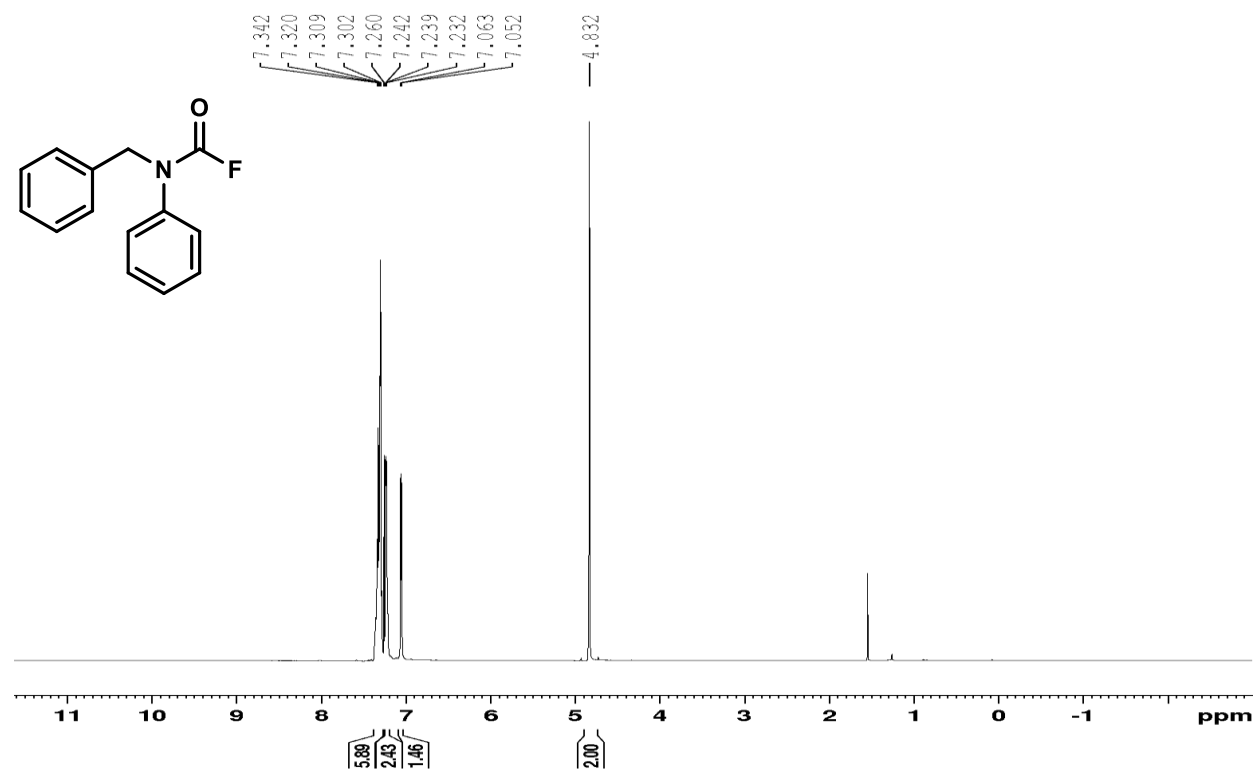


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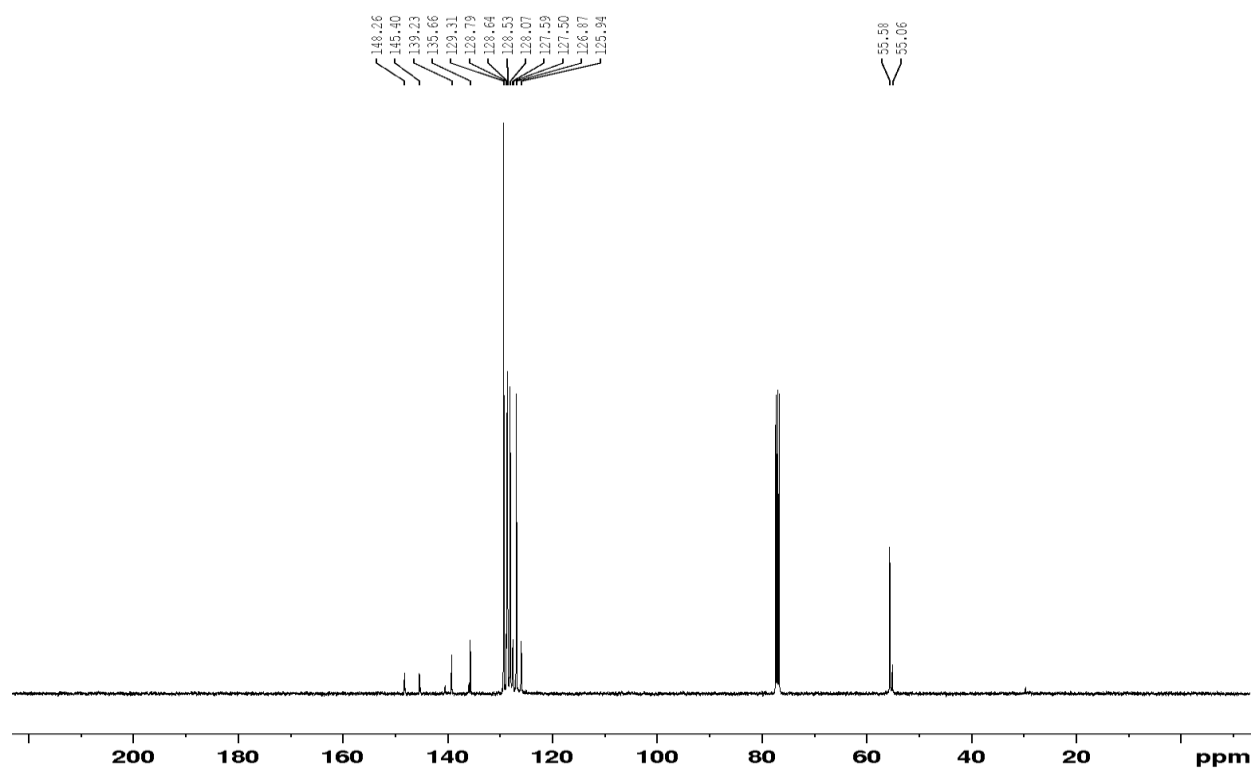
## 2.9 Appendix

### *N*-benzyl-*N*-phenyl-carbamoyl fluoride (**2.3a**)

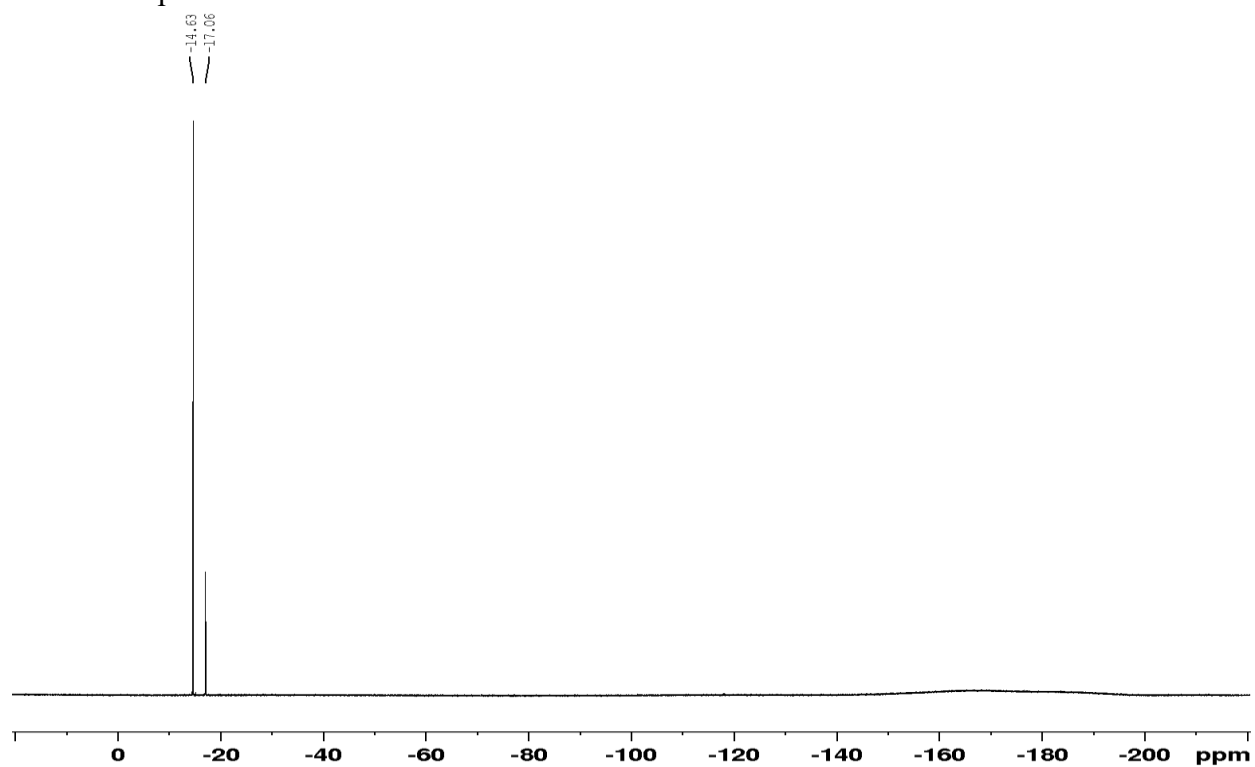
<sup>1</sup>H NMR Spectrum



$^{13}\text{C}$  NMR Spectrum

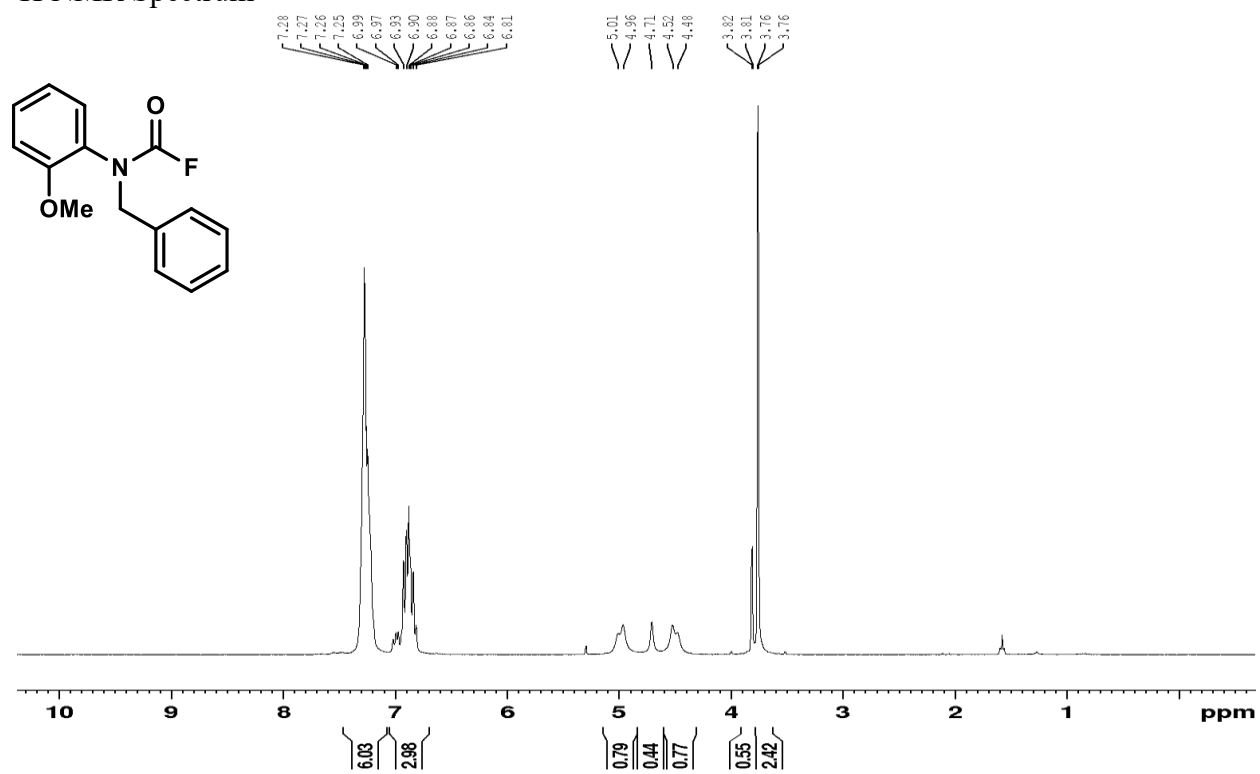


$^{19}\text{F}$  NMR Spectrum

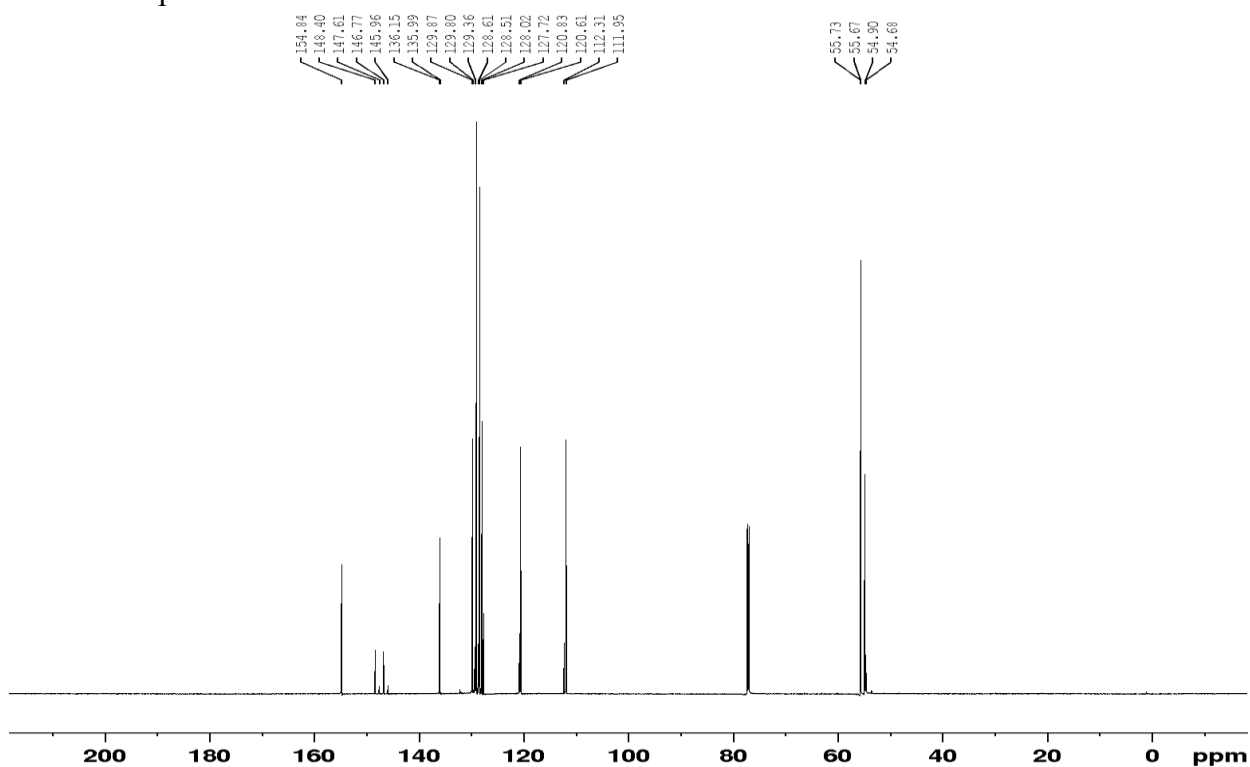


*N*-benzyl-*N*-(2-methoxyphenyl)carbamoyl fluoride (**2.3j**)

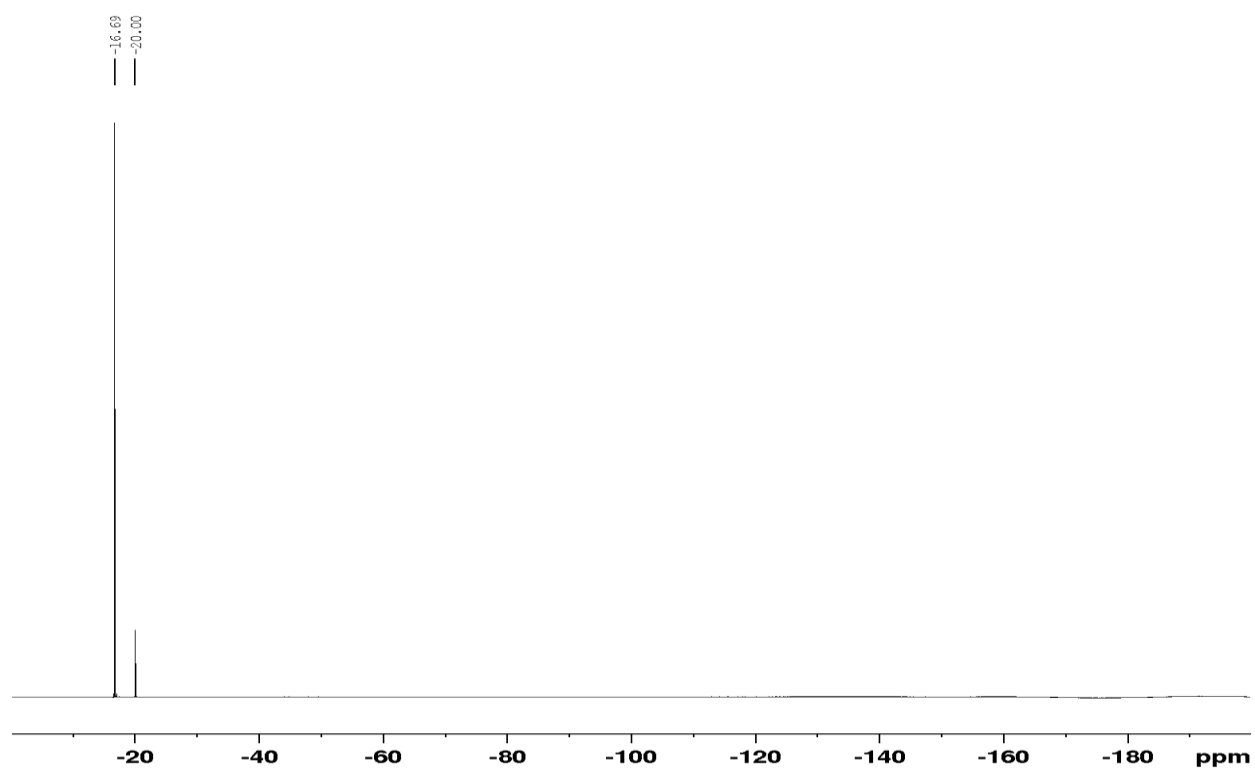
<sup>1</sup>H NMR Spectrum



<sup>13</sup>C NMR Spectrum

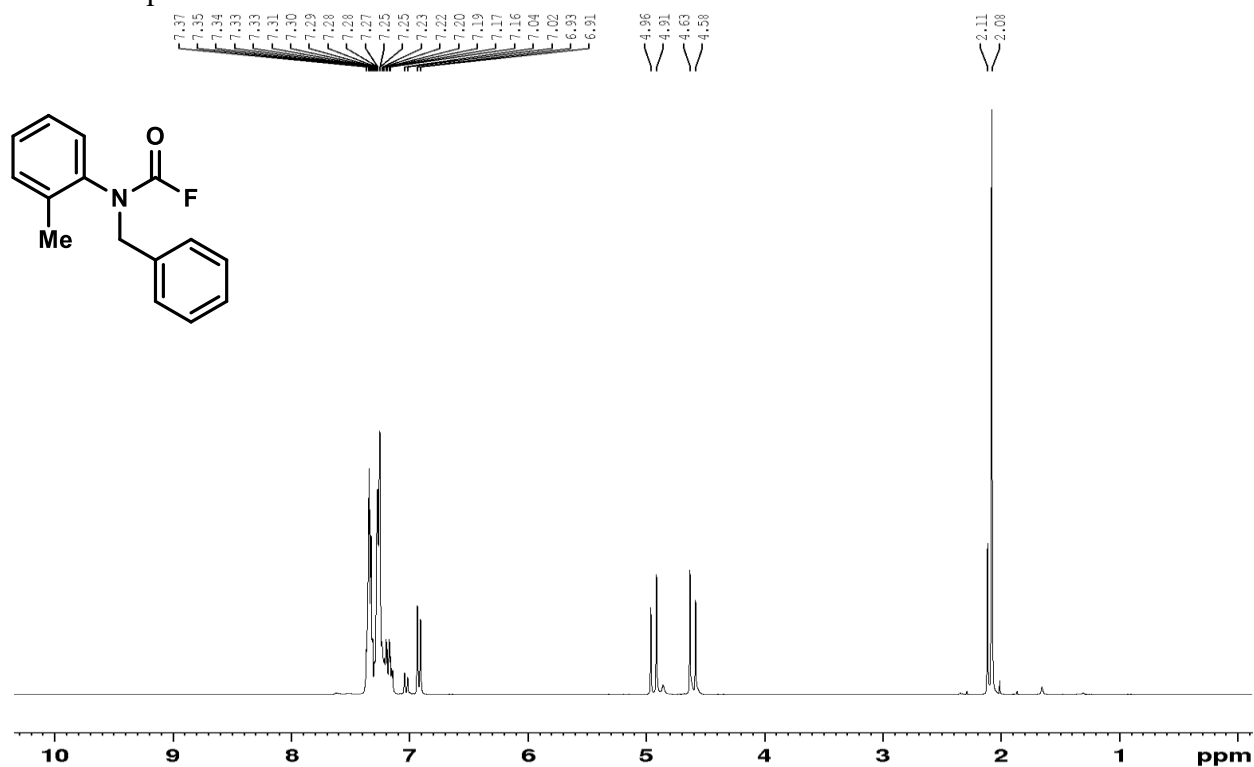


$^{19}\text{F}$  NMR Spectrum

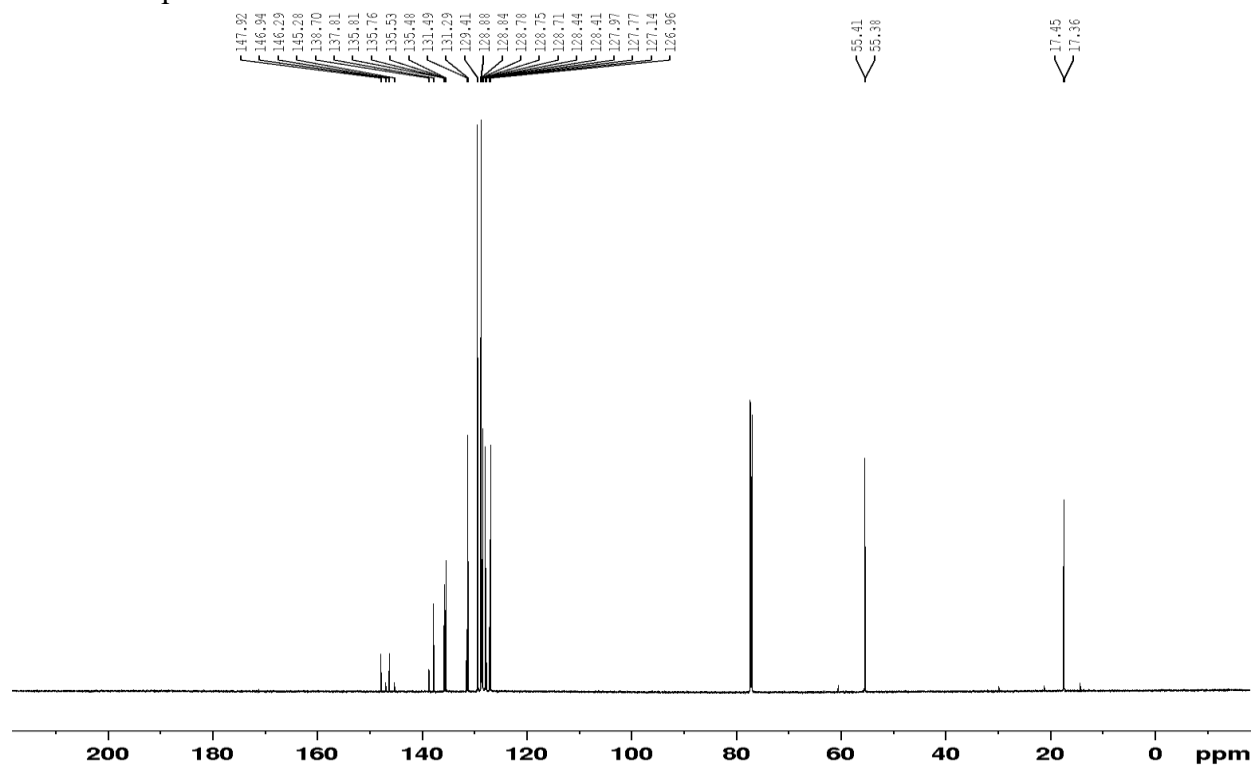


*N*-benzyl-*N*-(*o*-tolyl)carbamoyl fluoride (2.3j)

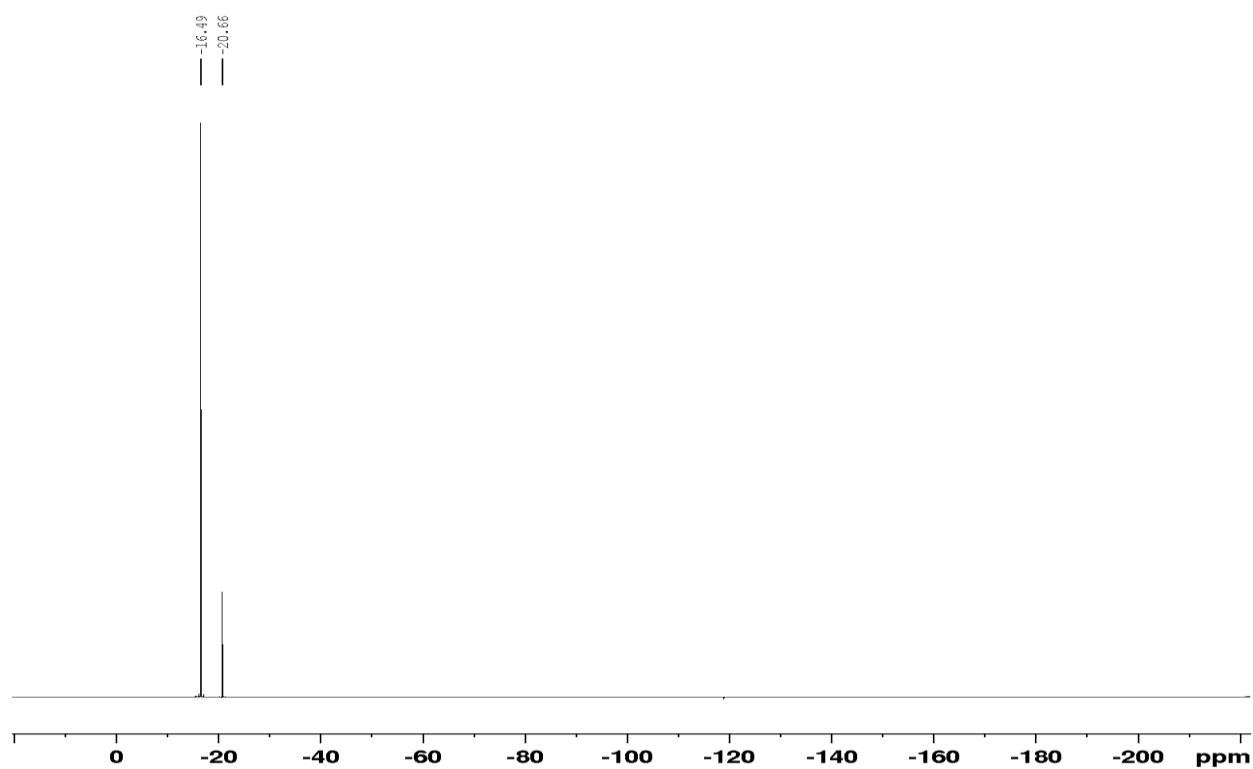
<sup>1</sup>H NMR Spectrum



<sup>13</sup>C NMR Spectrum

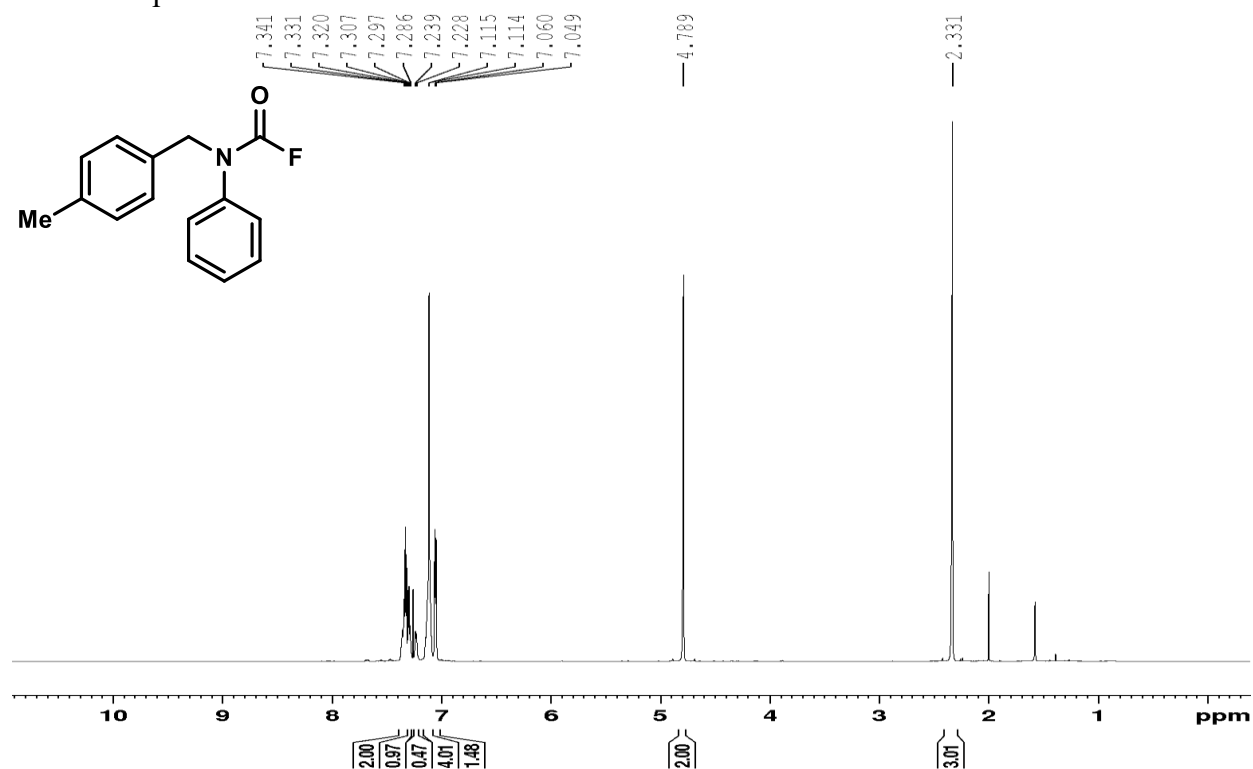


<sup>19</sup>F NMR Spectrum

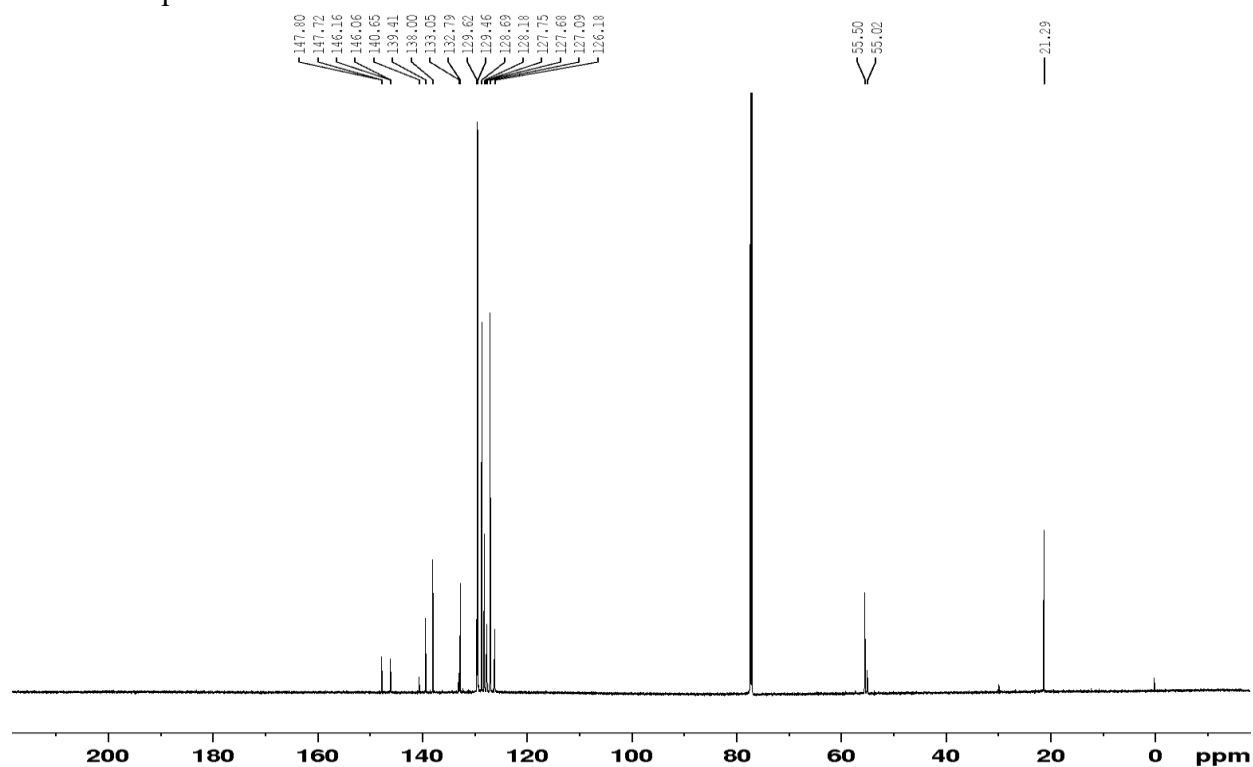


*N*-phenyl-*N*-(*p*-tolylmethyl)carbamoyl fluoride (2.3I)

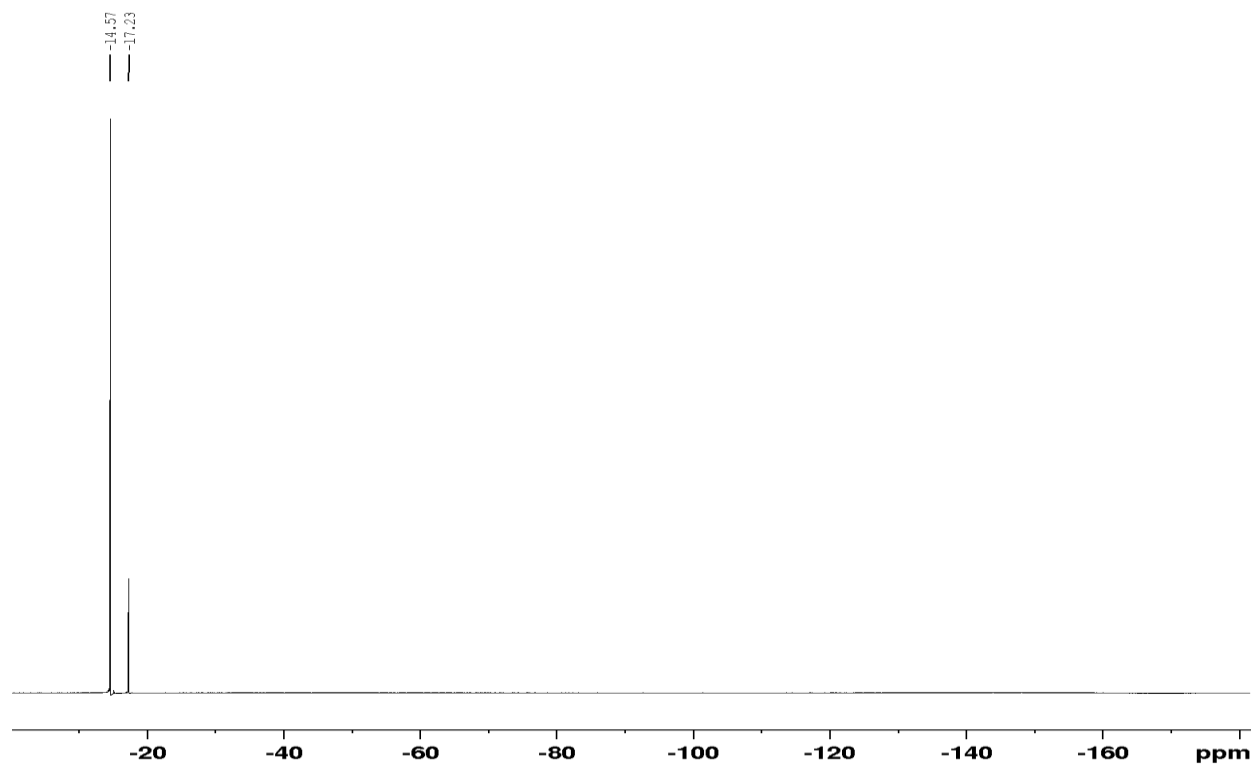
<sup>1</sup>H NMR Spectrum



<sup>13</sup>C NMR Spectrum



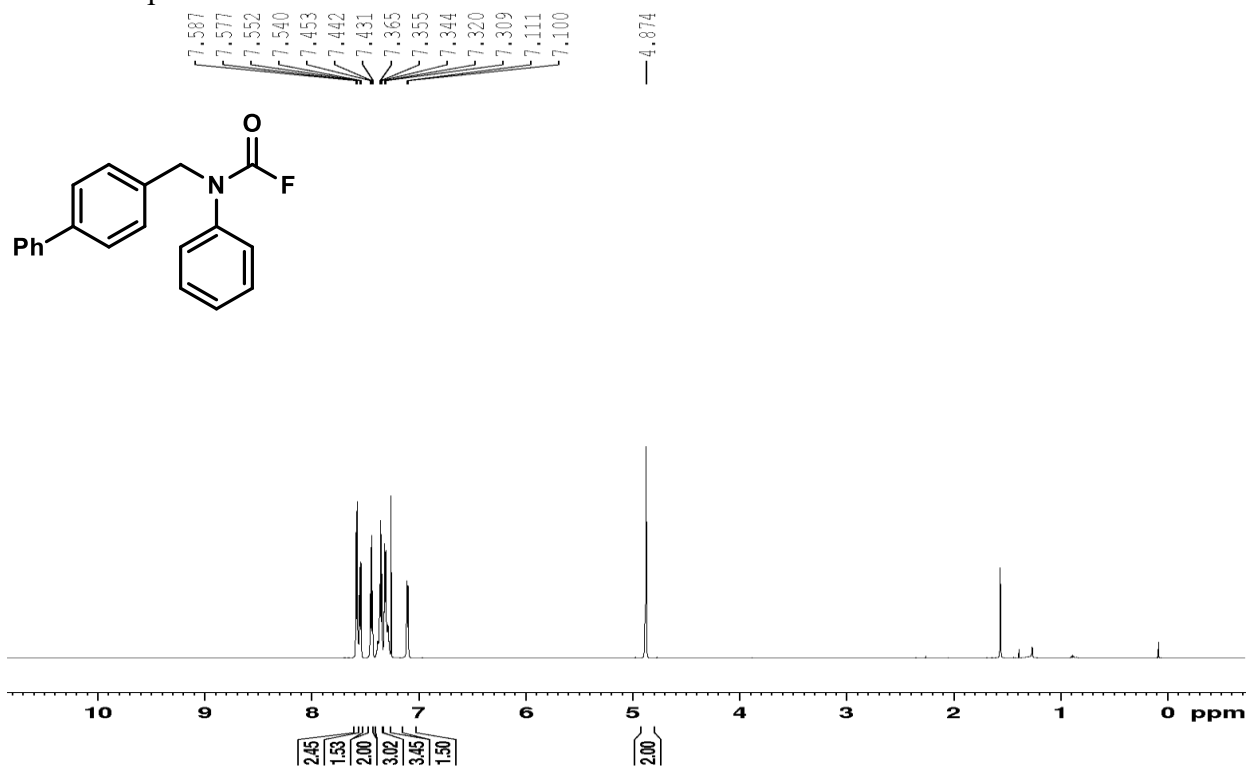
<sup>19</sup>F NMR Spectrum



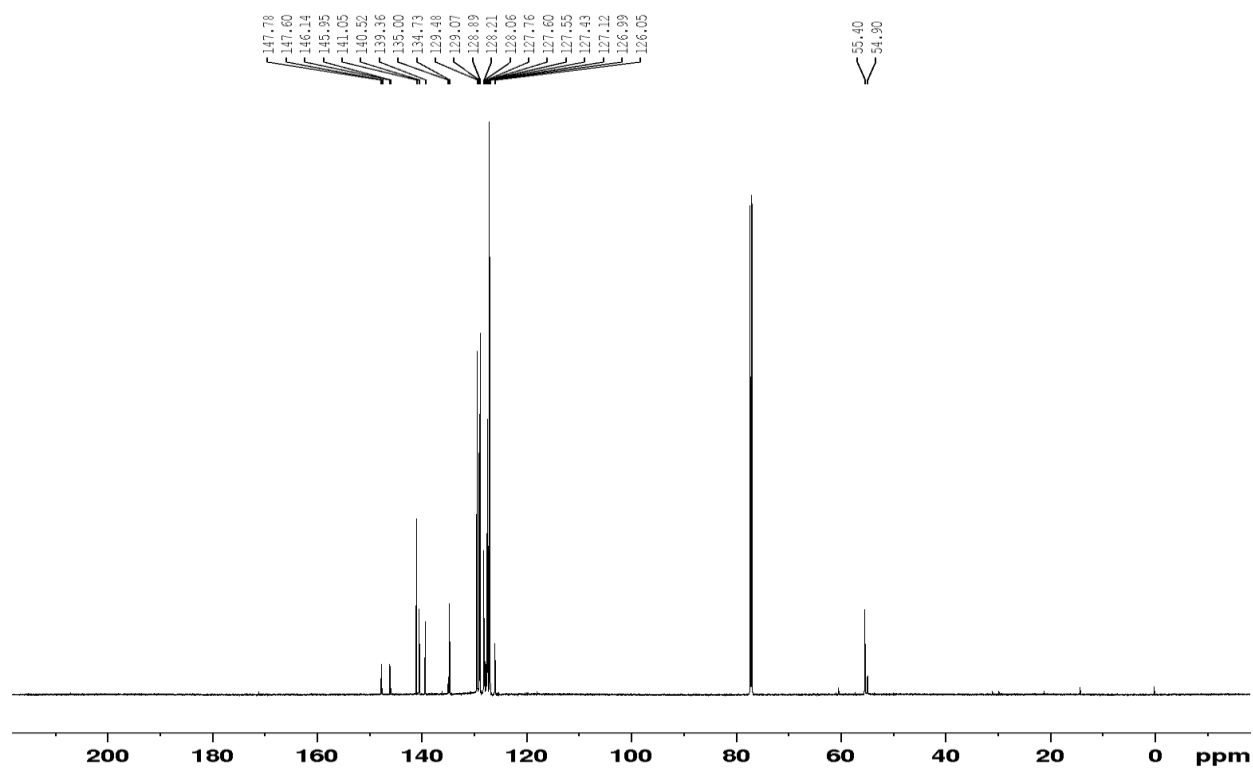
*N*-phenyl-*N*-[(4-phenylphenyl)methyl]carbamoyl fluoride (2.3m)



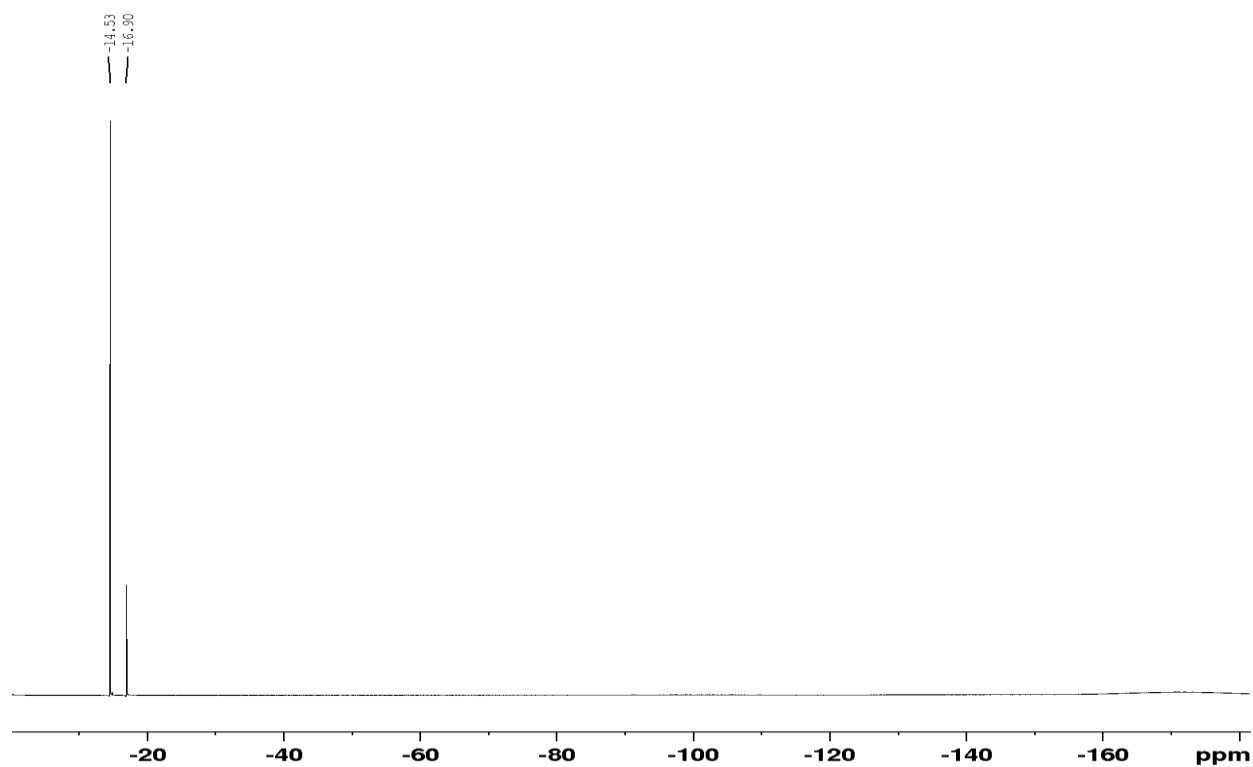
<sup>1</sup>H NMR Spectrum



<sup>13</sup>C NMR Spectrum

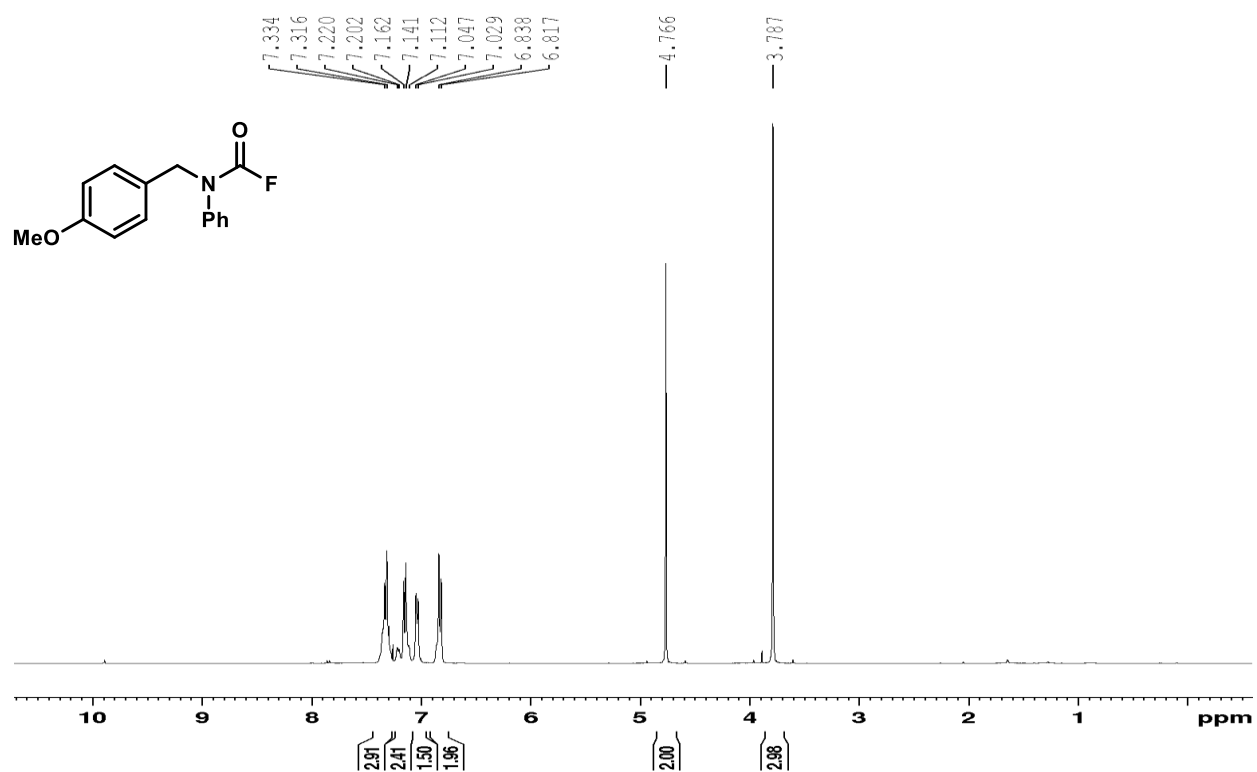


<sup>19</sup>F NMR Spectrum

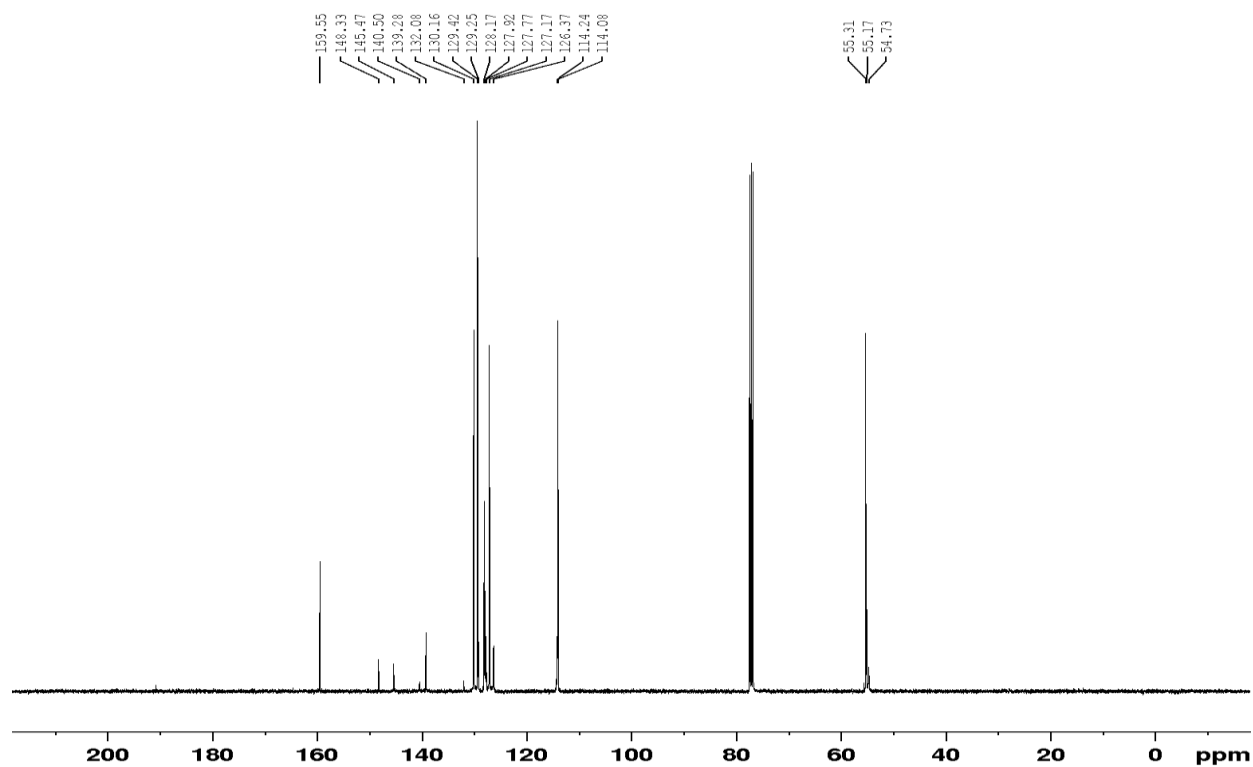


N-[(4-methoxyphenyl)methyl]-N-phenyl-carbamoyl fluoride (2.3n)

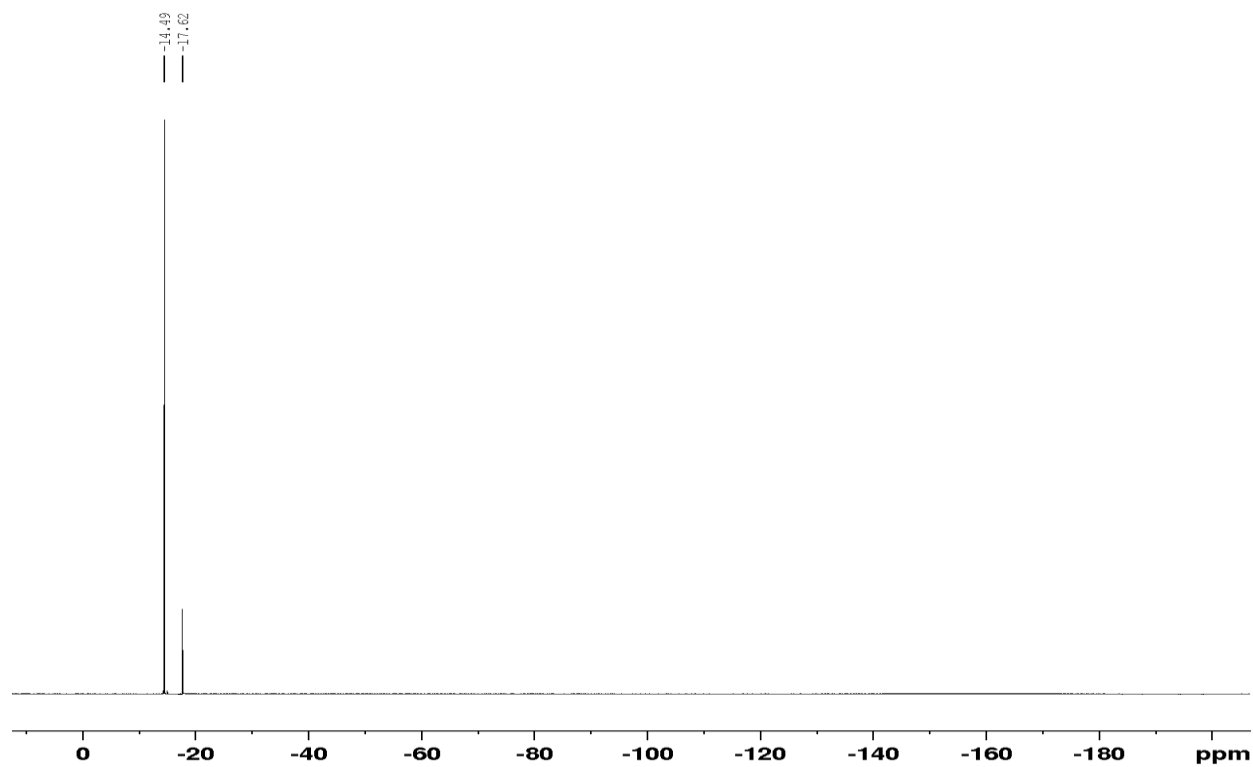
<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (400 MHz)



$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (101 MHz)

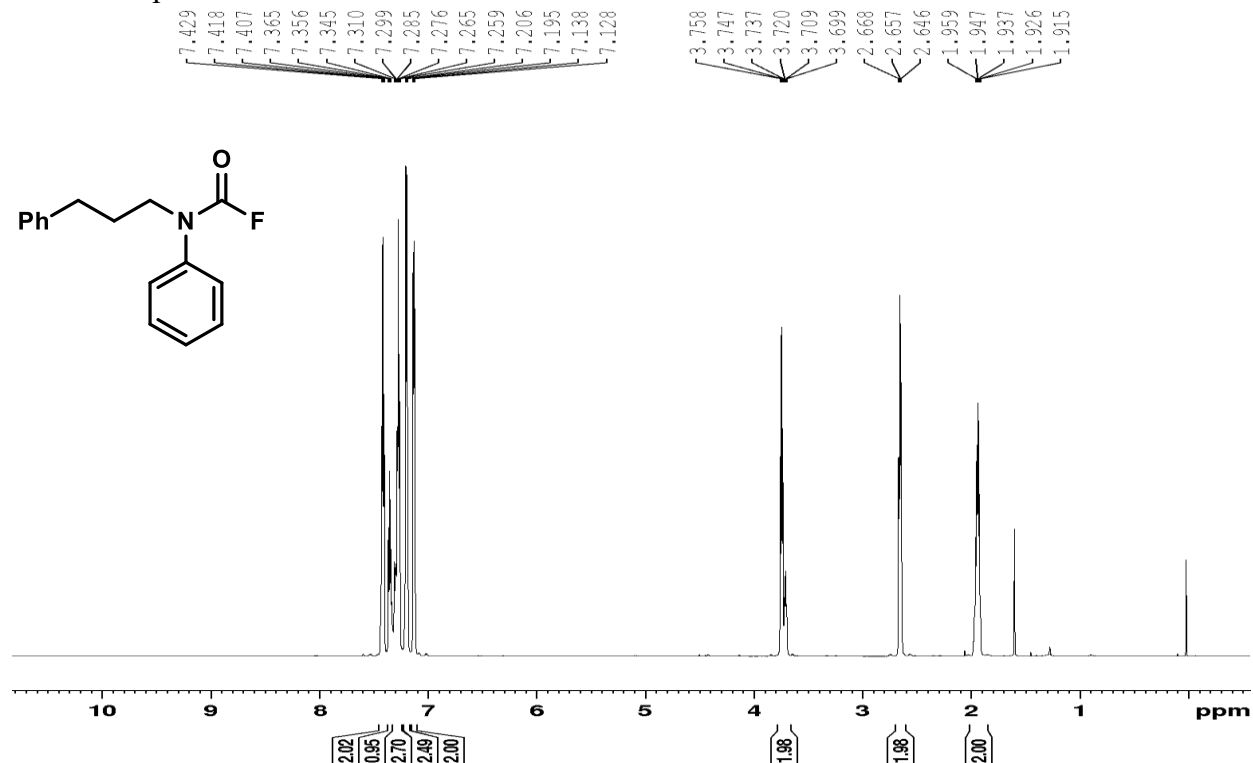


$^{19}\text{F}$  NMR Spectrum  $\text{CDCl}_3$  (377 MHz)

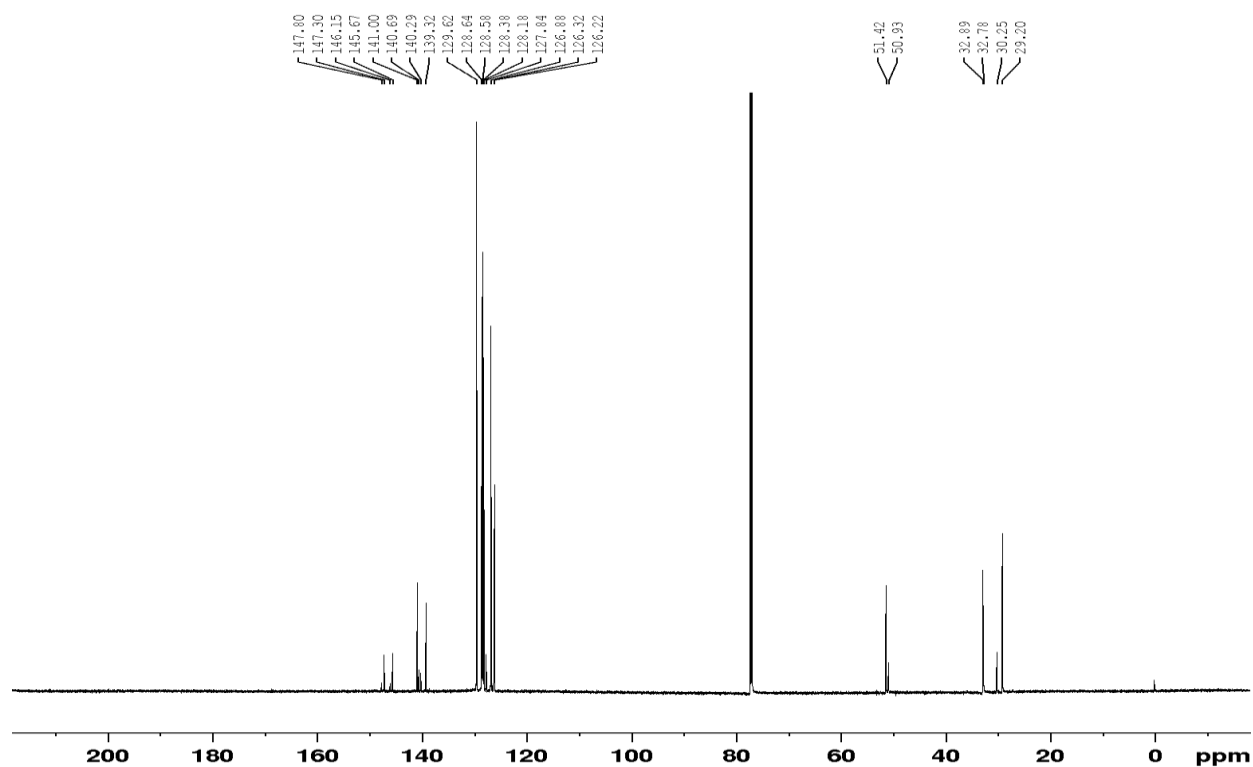


*N*-phenyl-*N*-(3-phenylpropyl)carbamoyl fluoride (2.3p)

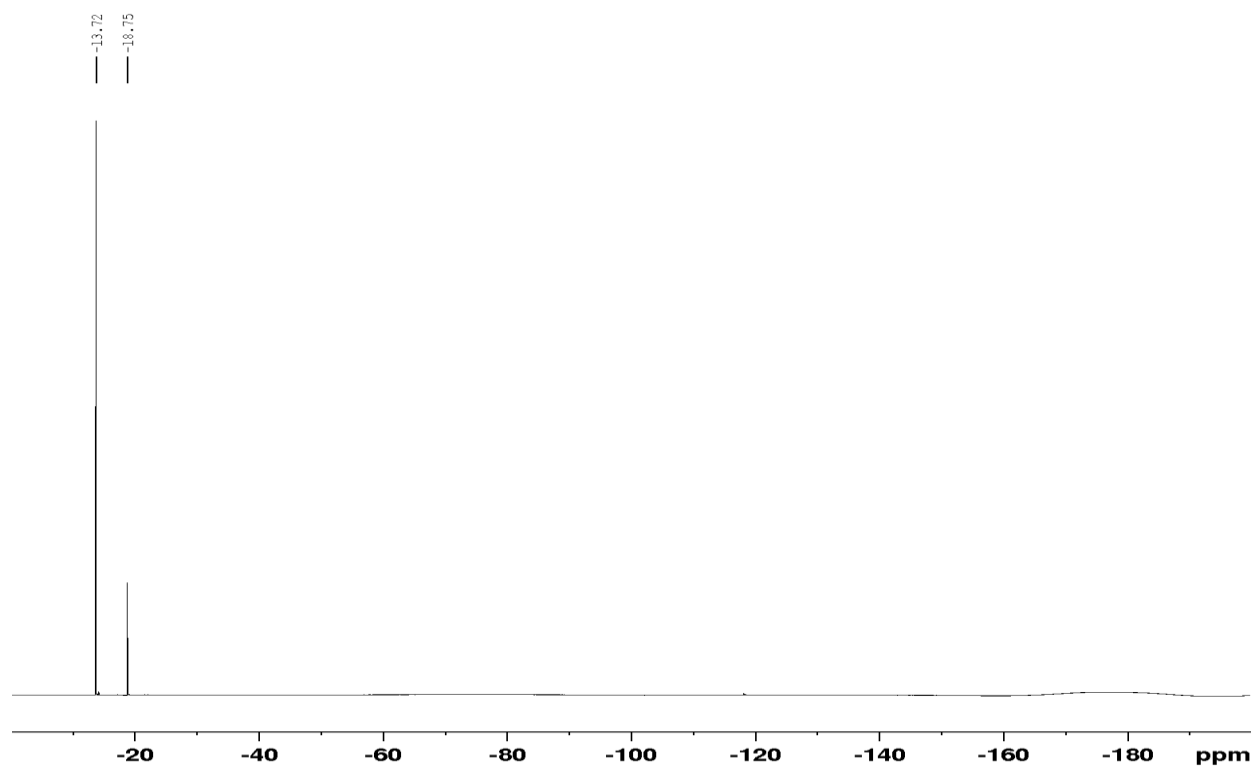
<sup>1</sup>H NMR Spectrum



<sup>13</sup>C NMR Spectrum

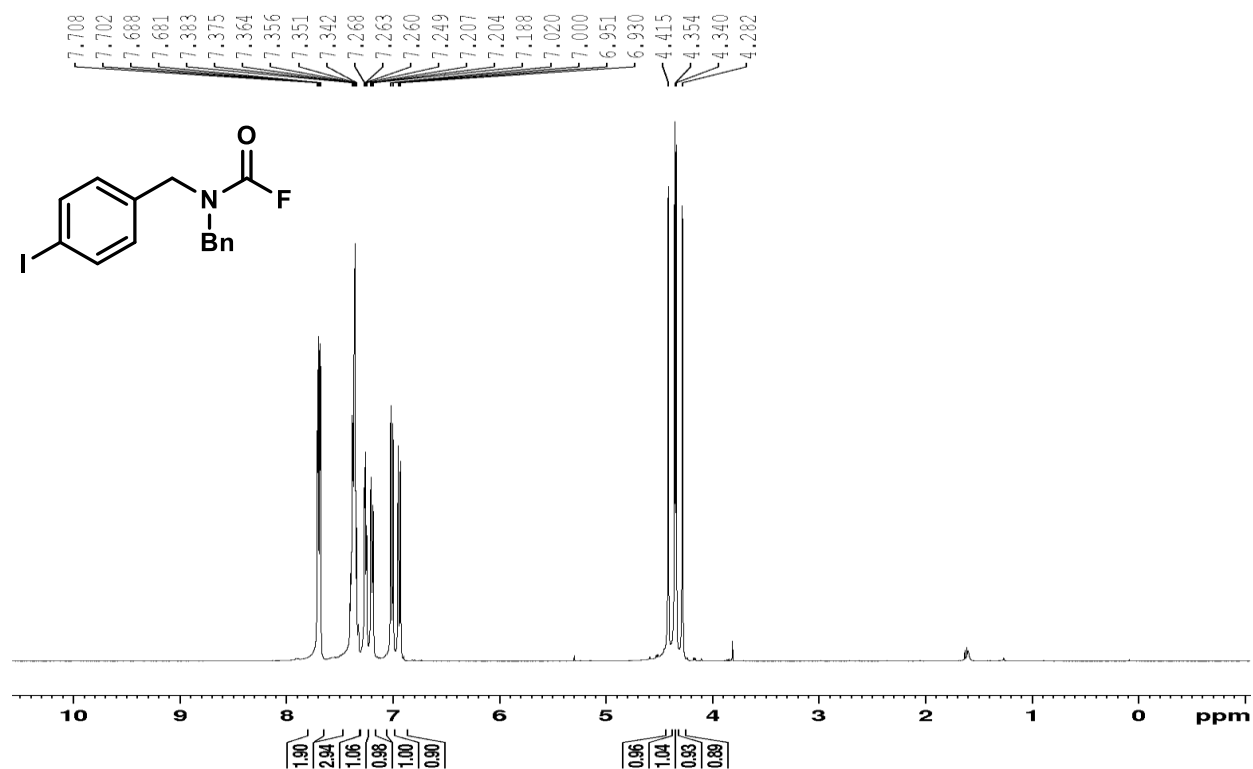


$^{19}\text{F}$  NMR Spectrum

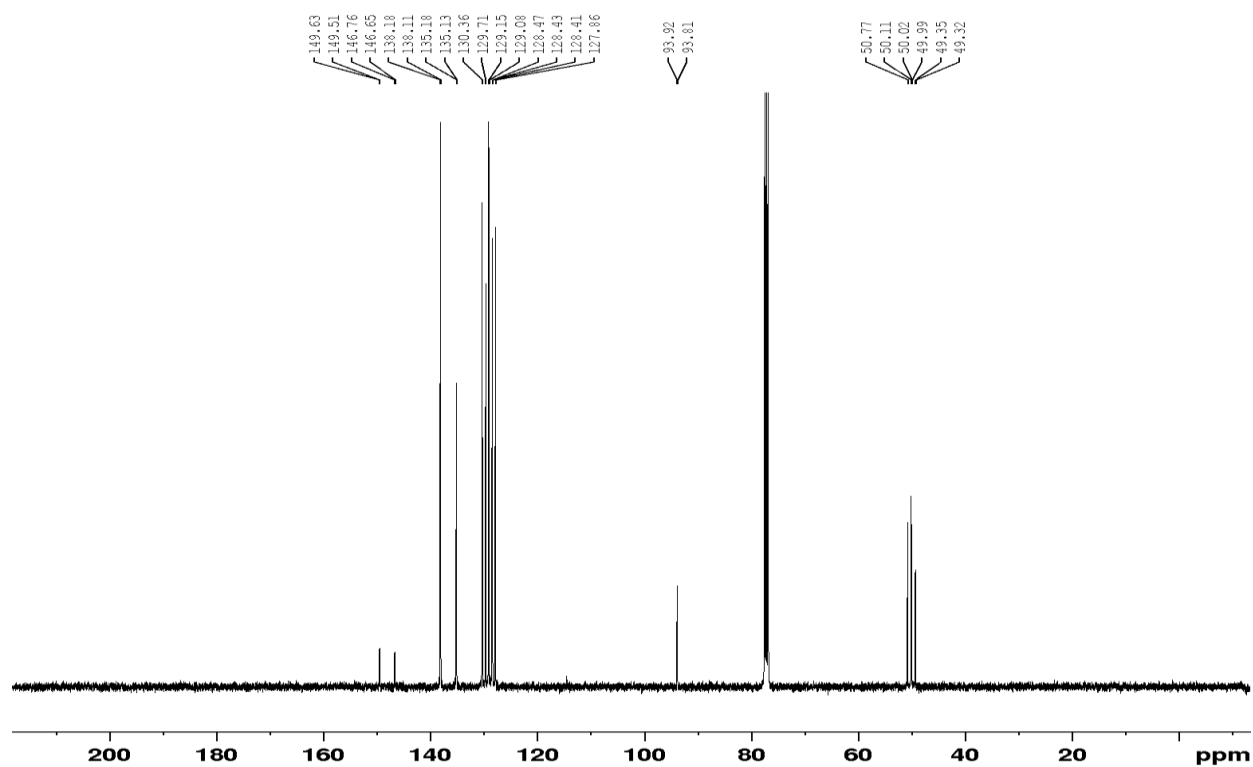


*N*-benzyl-*N*-[(4-iodophenyl)methyl]carbamoyl fluoride (2.3t)

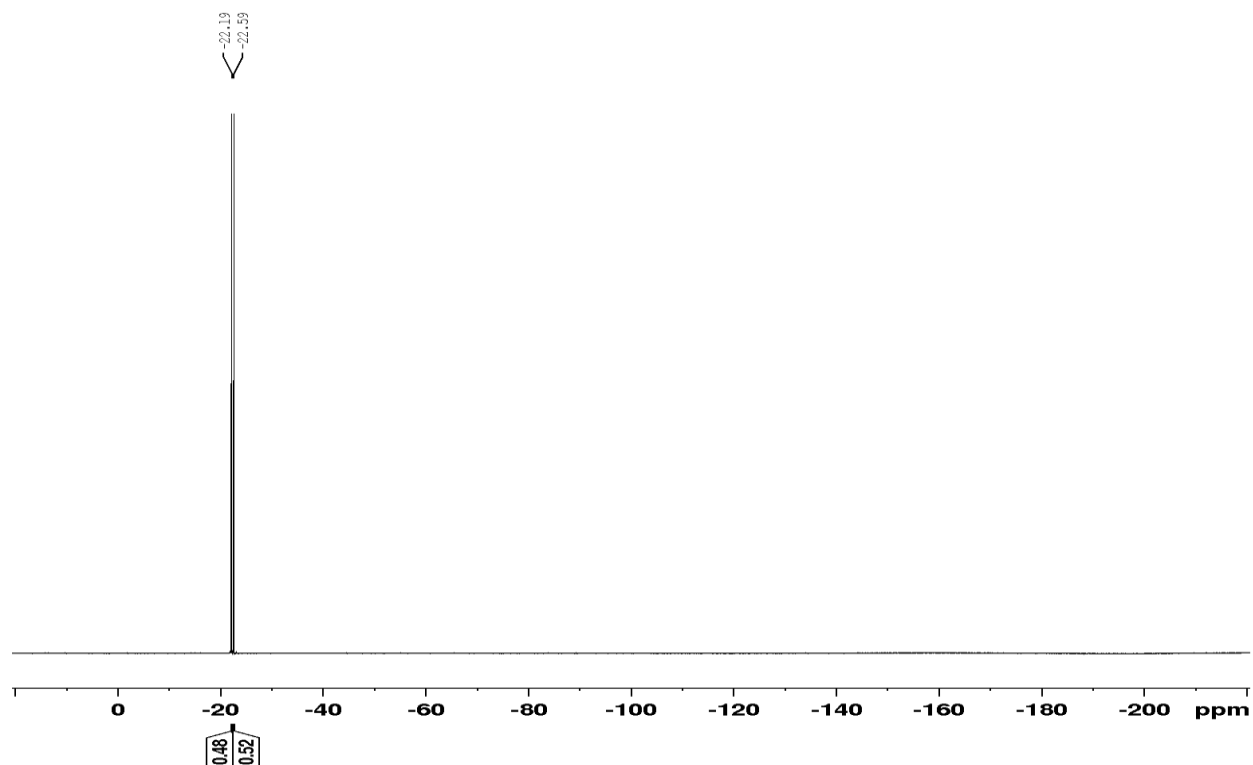
$^1\text{H}$  NMR Spectrum  $\text{CDCl}_3$  (400 MHz)



$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (101 MHz)

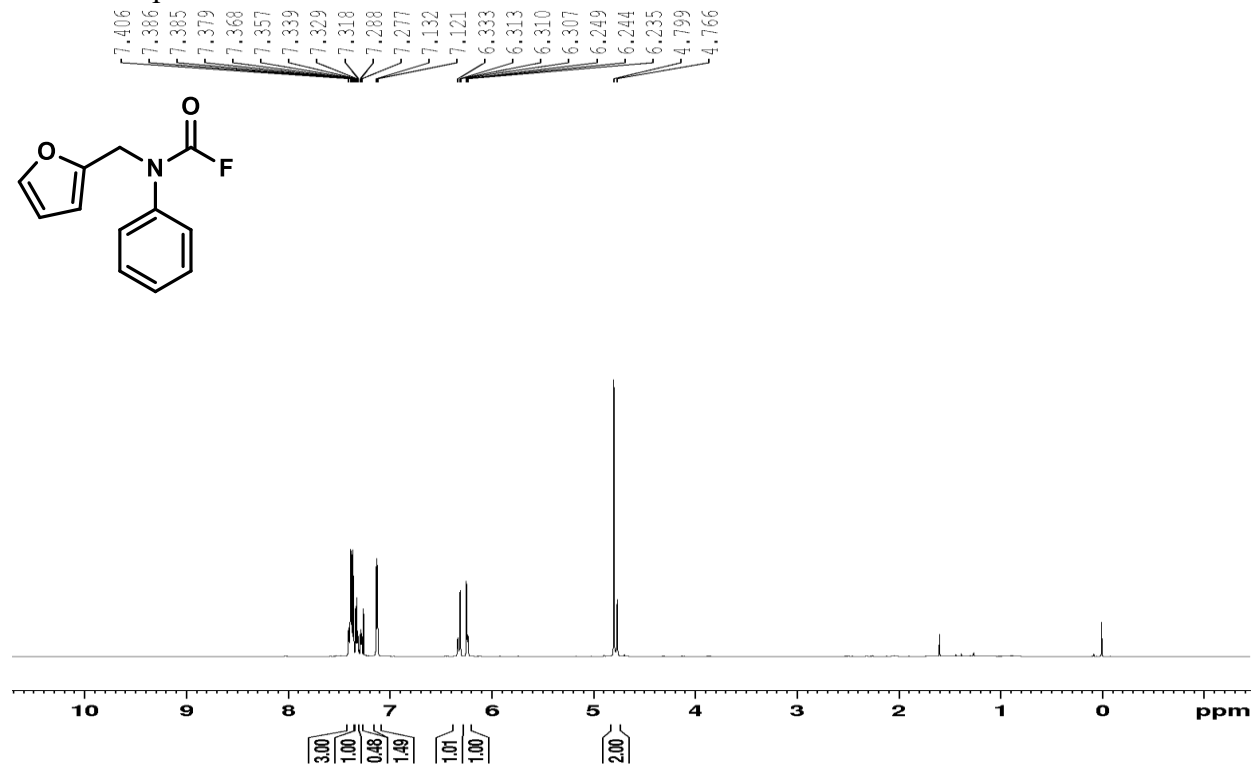


$^{19}\text{F}$  NMR Spectrum  $\text{CDCl}_3$  (377 MHz)

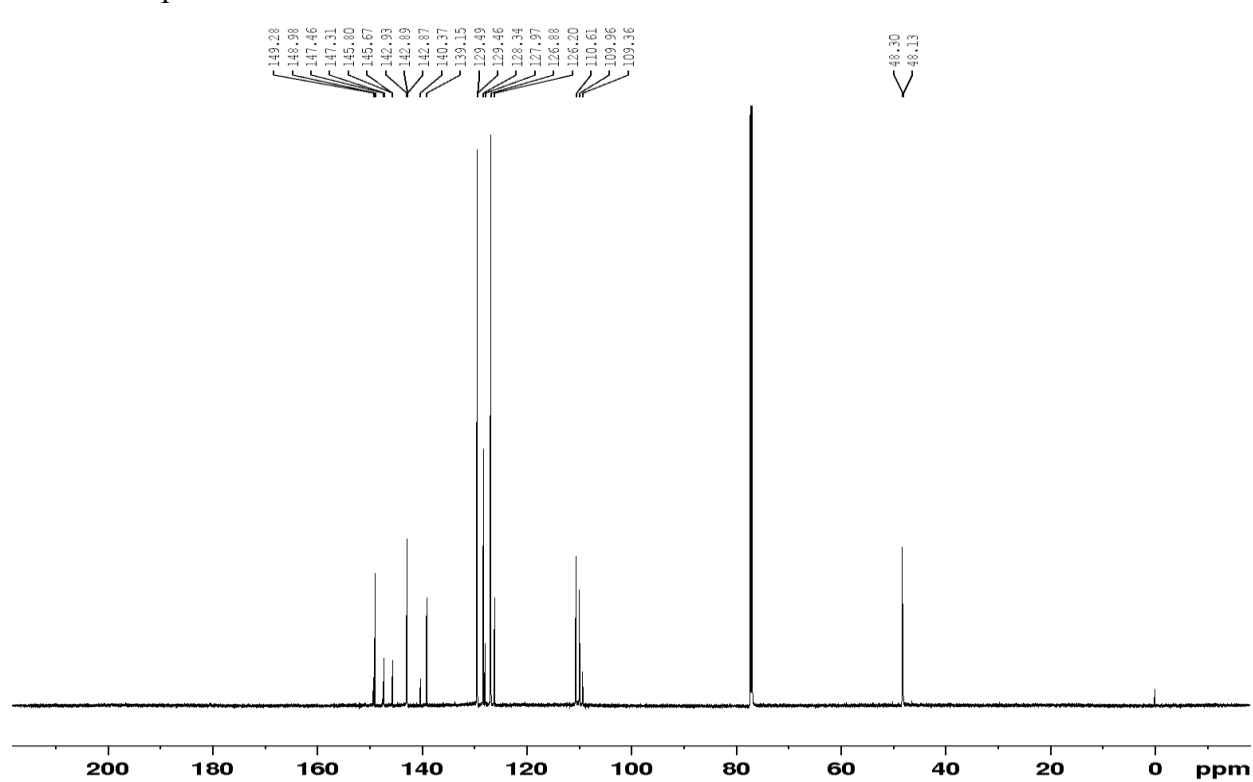


*N*-(2-furylmethyl)-*N*-phenyl-carbamoyl fluoride (**2.3u**)

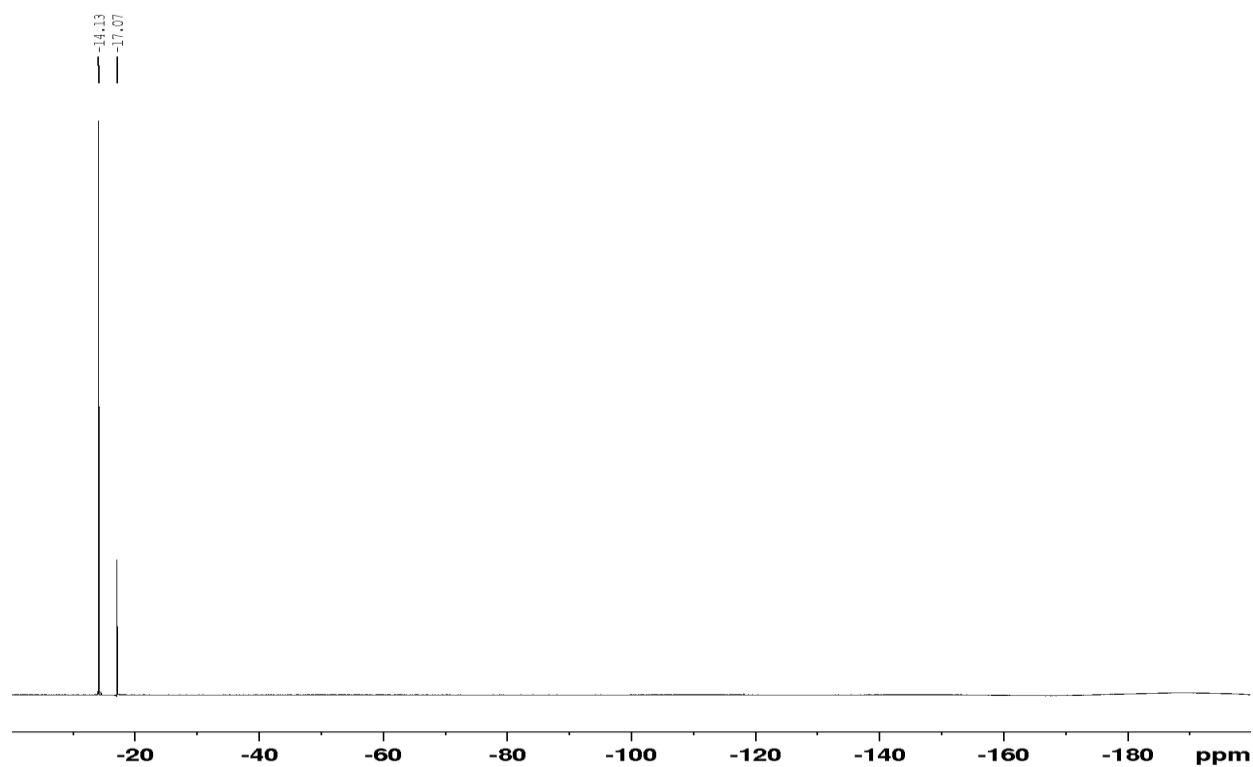
# <sup>1</sup>H NMR Spectrum



# <sup>13</sup>C NMR Spectrum

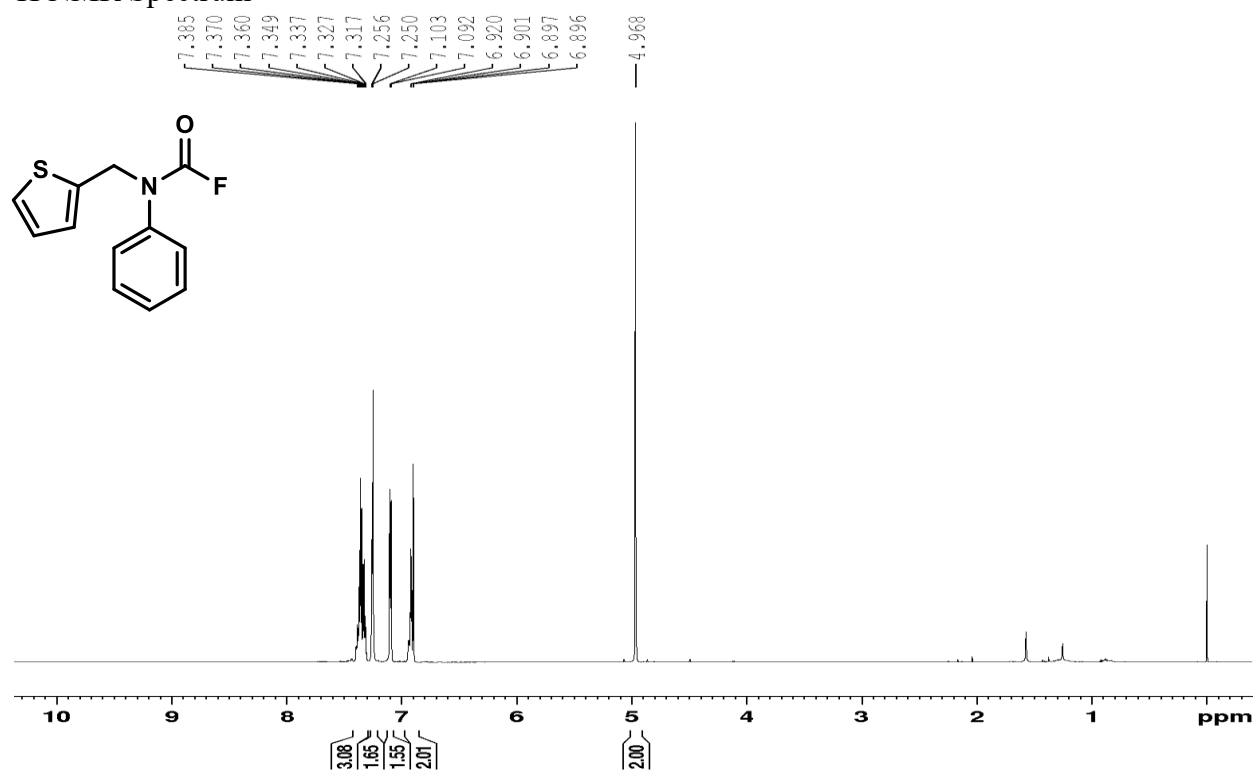


<sup>19</sup>F NMR Spectrum



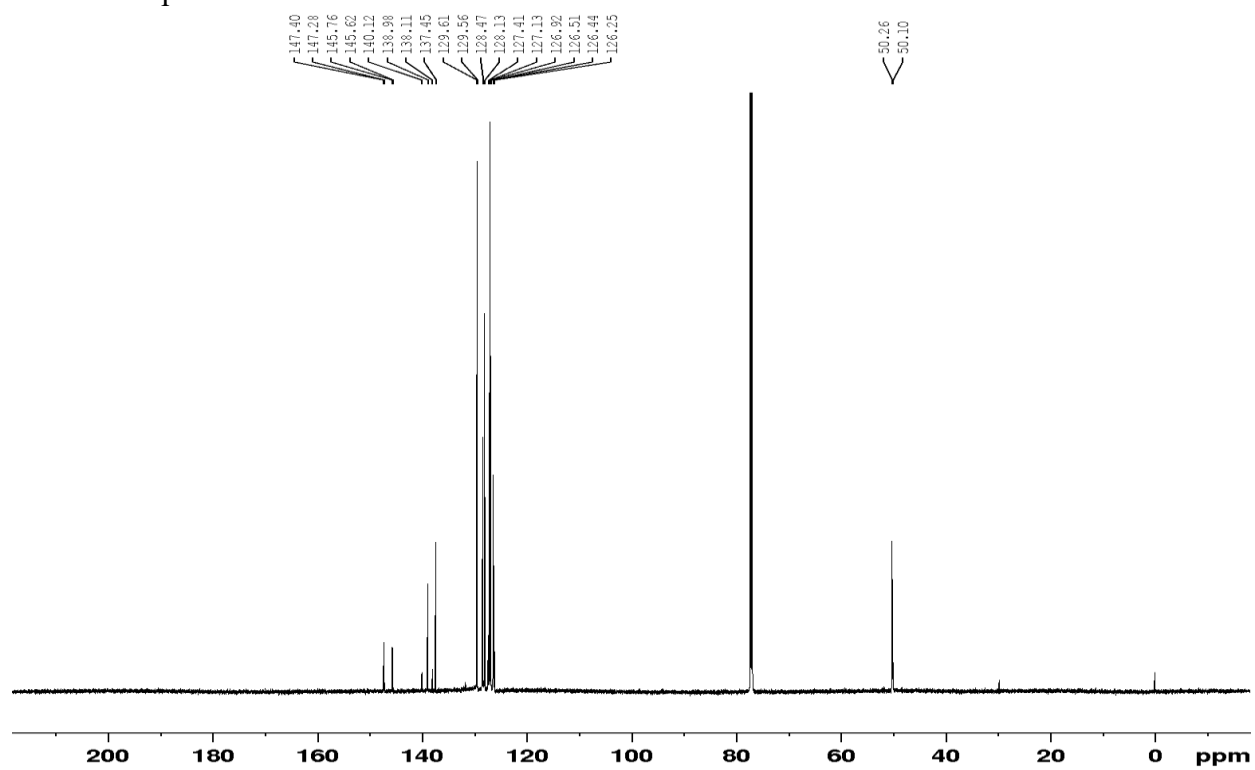
*N*-phenyl-*N*-(2-thienylmethyl)carbamoyl fluoride (2.3v)

<sup>1</sup>H NMR Spectrum

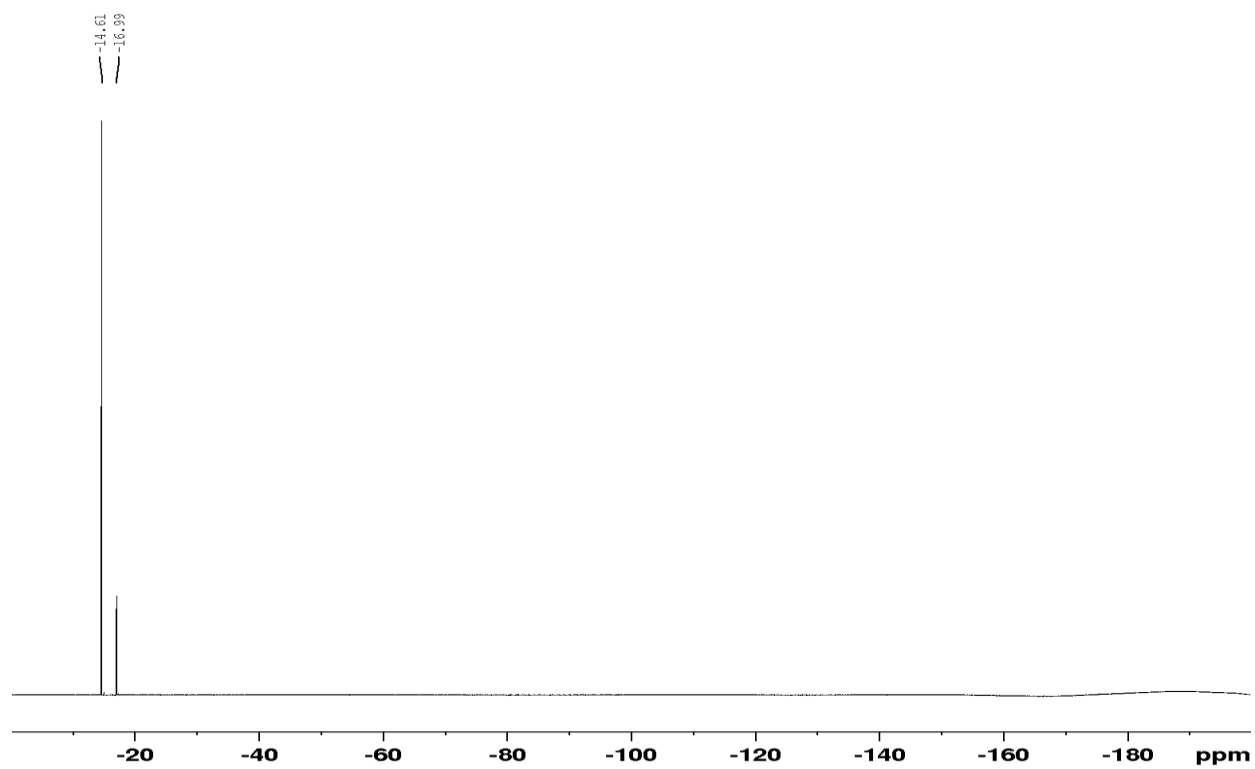




$^{13}\text{C}$  NMR Spectrum

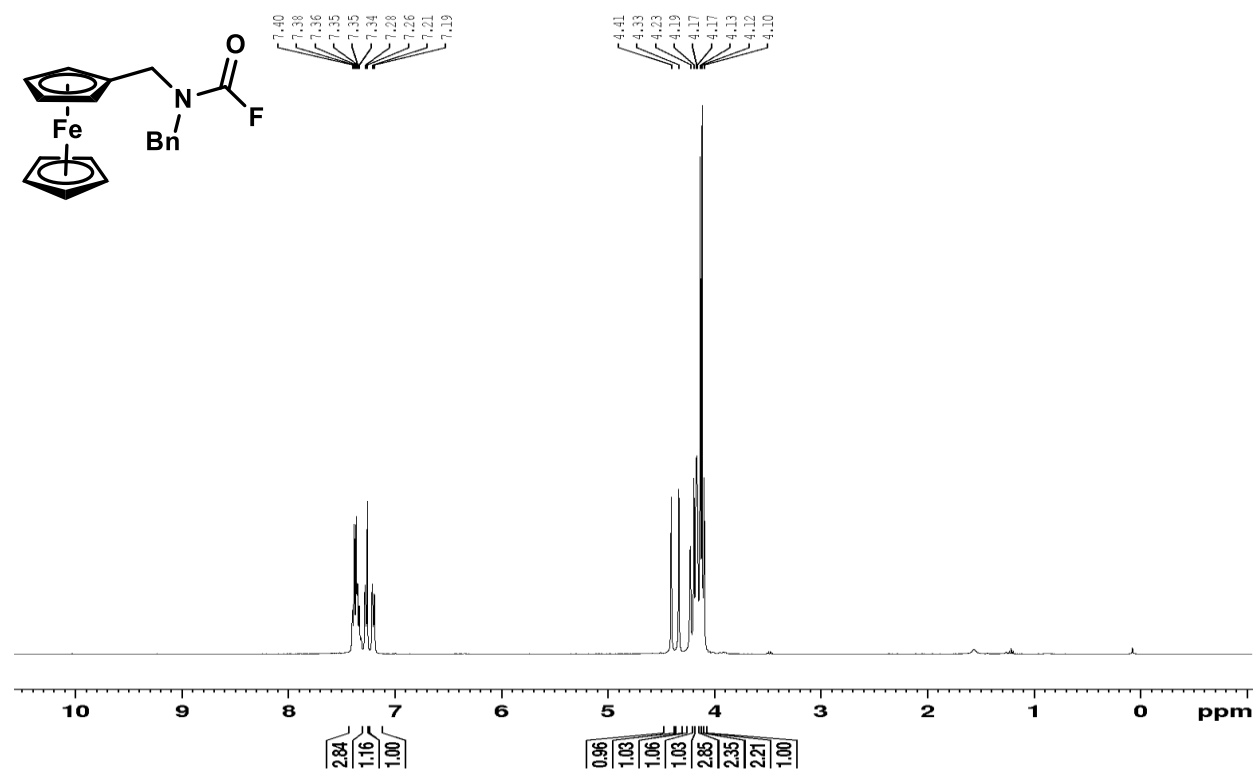


$^{19}\text{F}$  NMR Spectrum

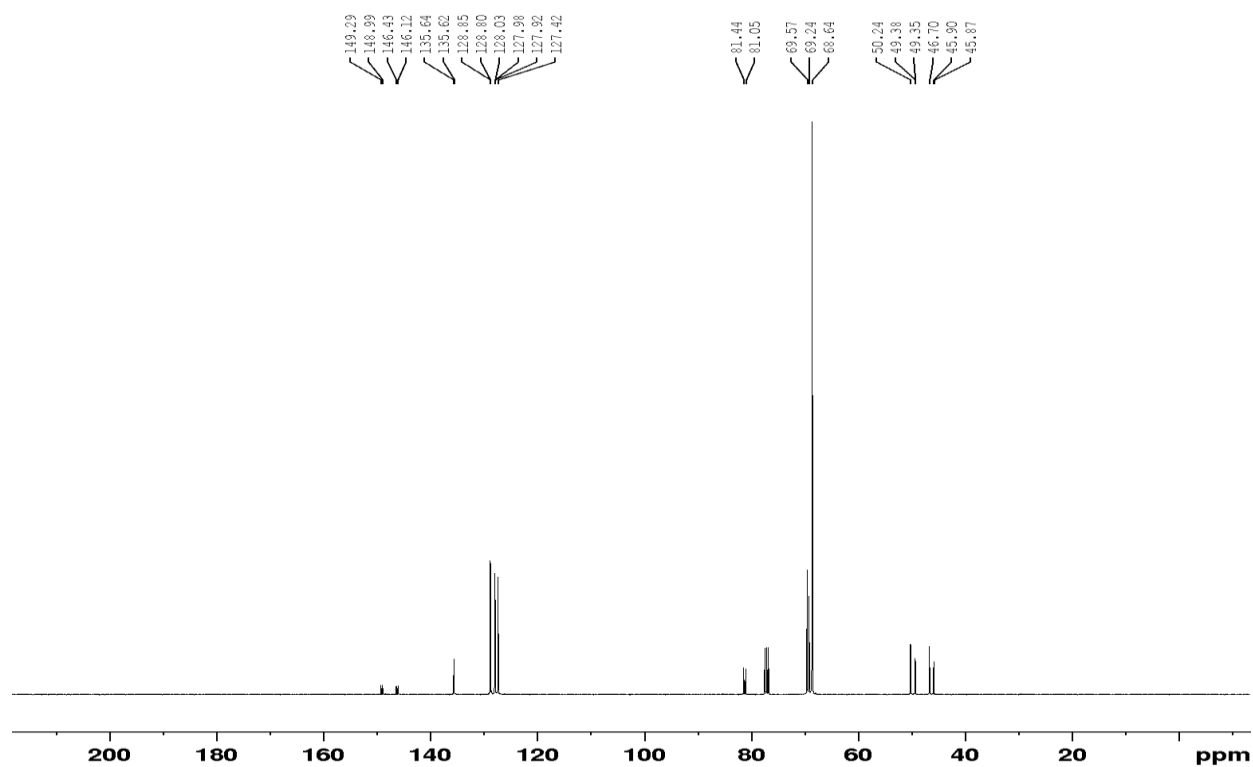


*N*-benzyl-*N*-ferrocenylmethyl-carbamoyl fluoride (**2.3w**)

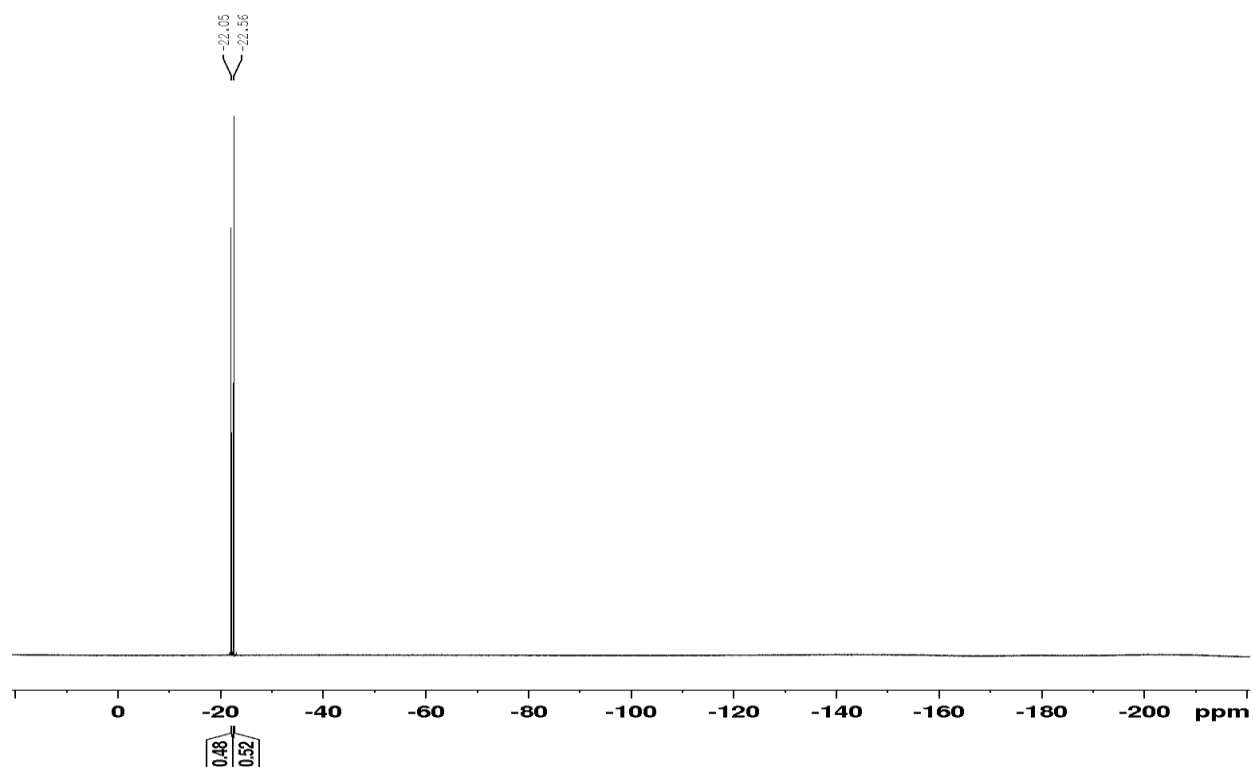
<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (400 MHz)



$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (101 MHz)

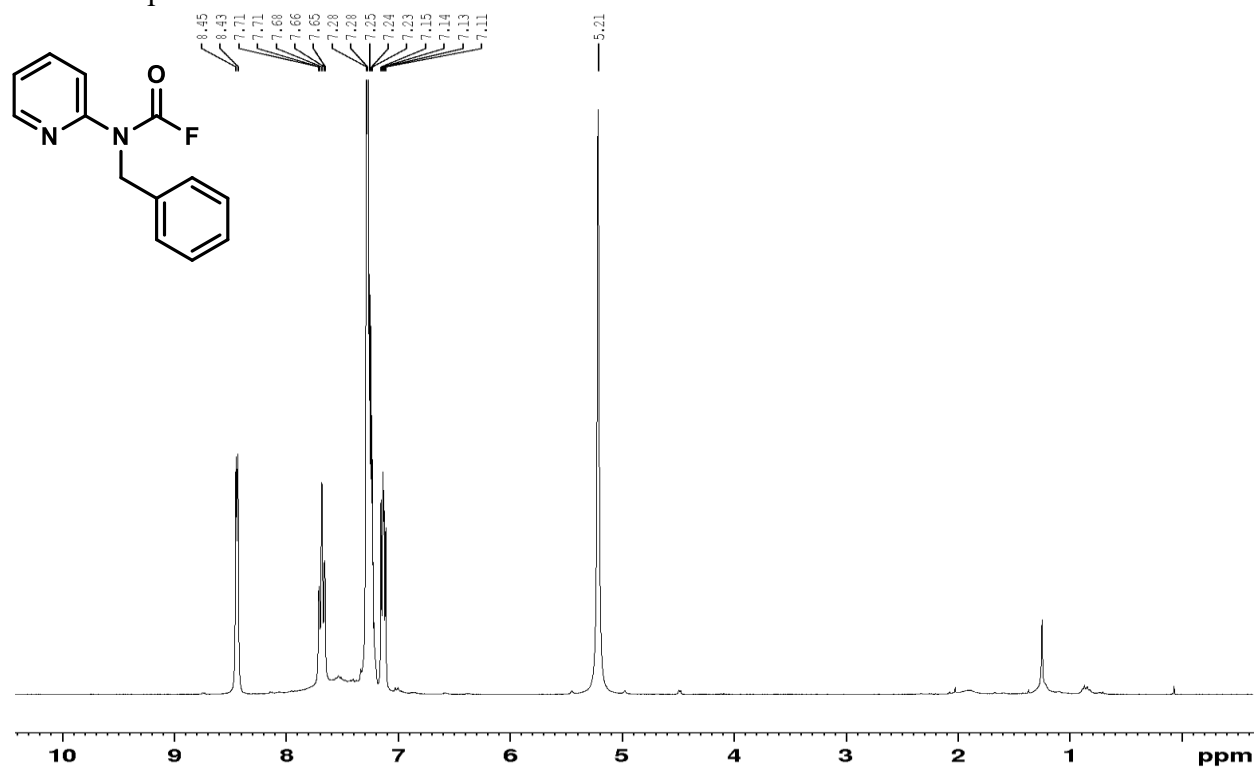


$^{19}\text{F}$  NMR Spectrum  $\text{CDCl}_3$  (377 MHz)

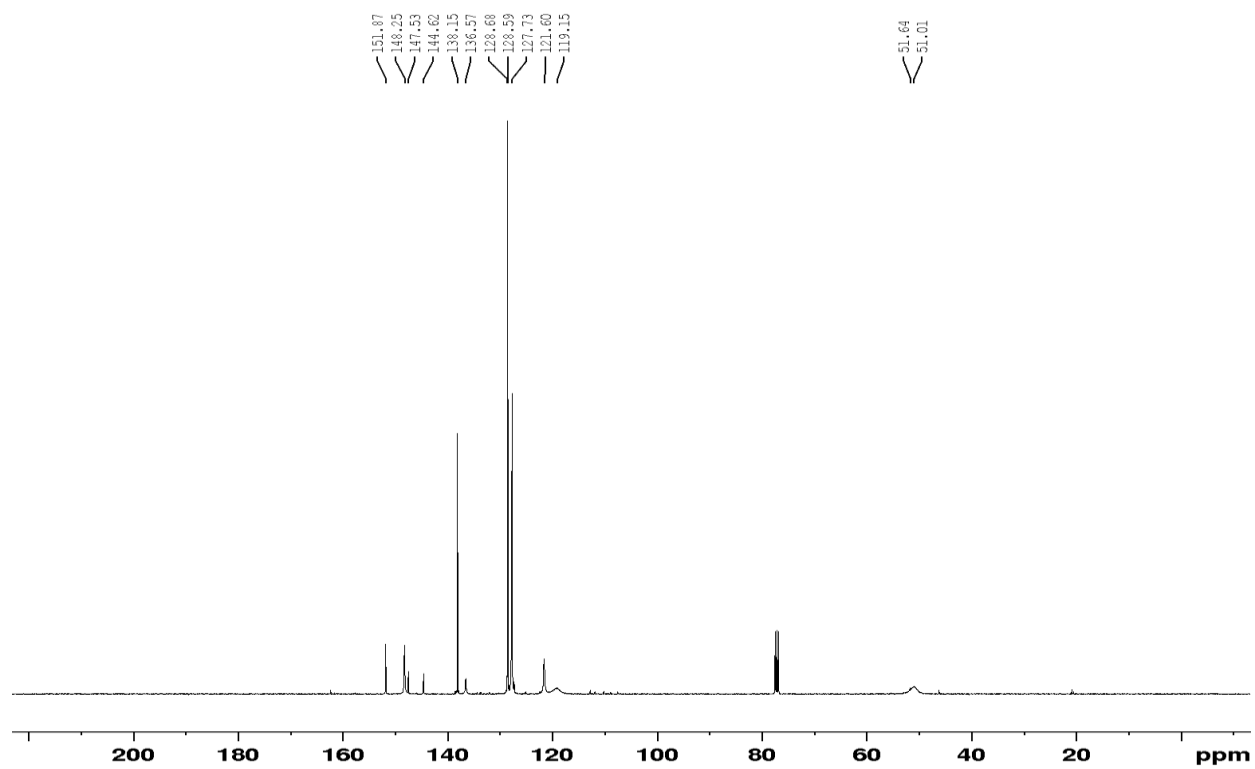


*N*-benzyl-*N*-(2-pyridyl)carbamoyl fluoride (2.3x)

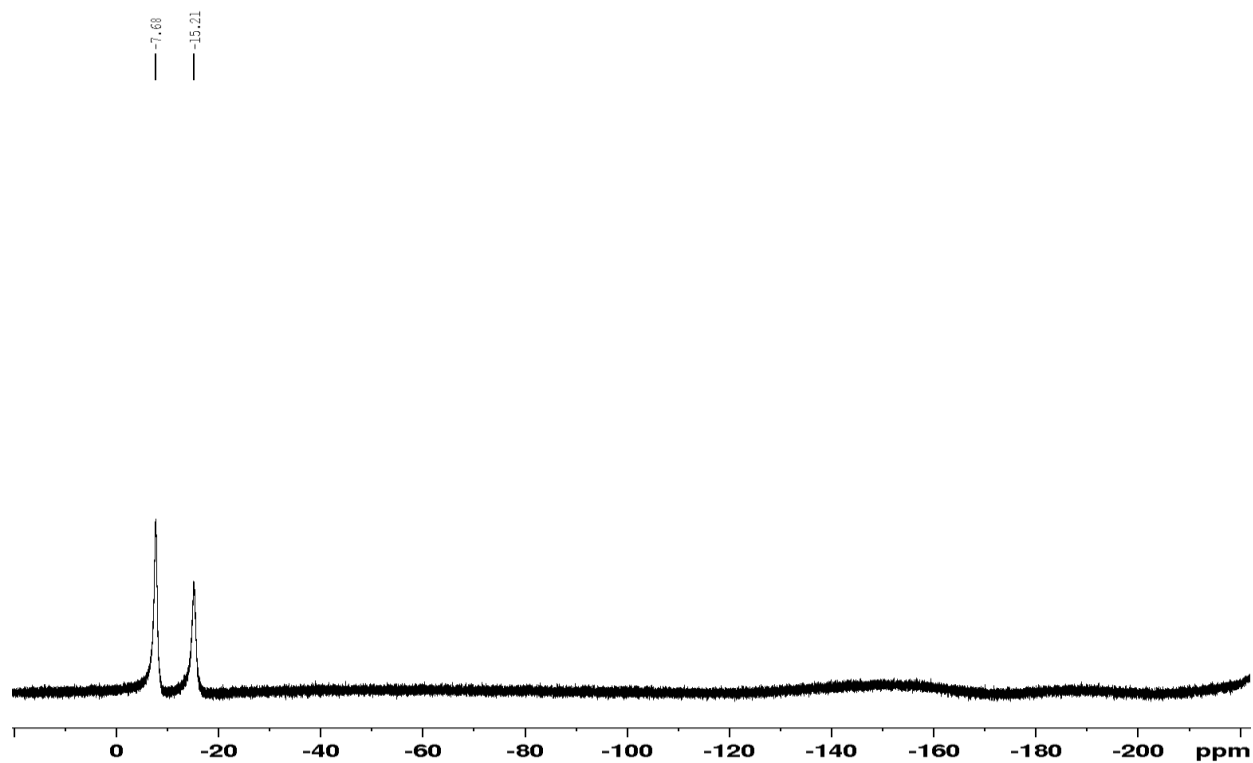
<sup>1</sup>H NMR Spectrum



<sup>13</sup>C NMR Spectrum

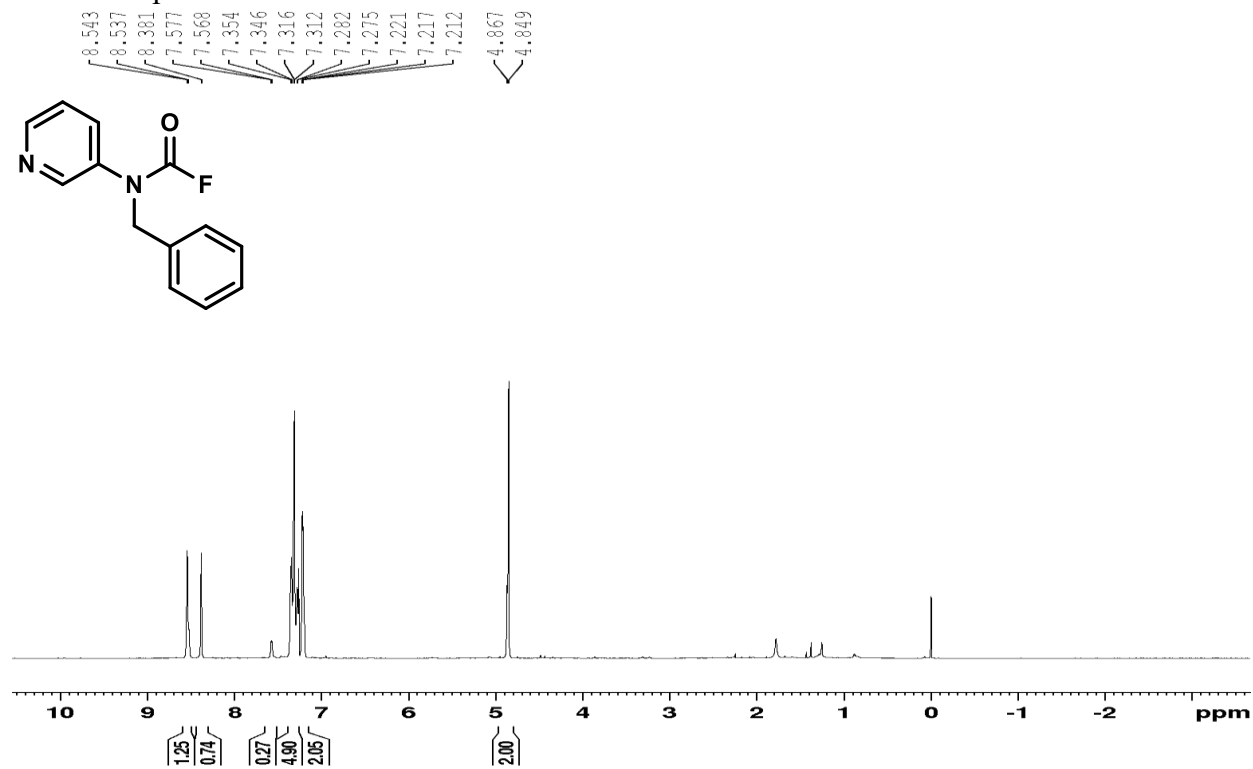


<sup>19</sup>F NMR Spectrum

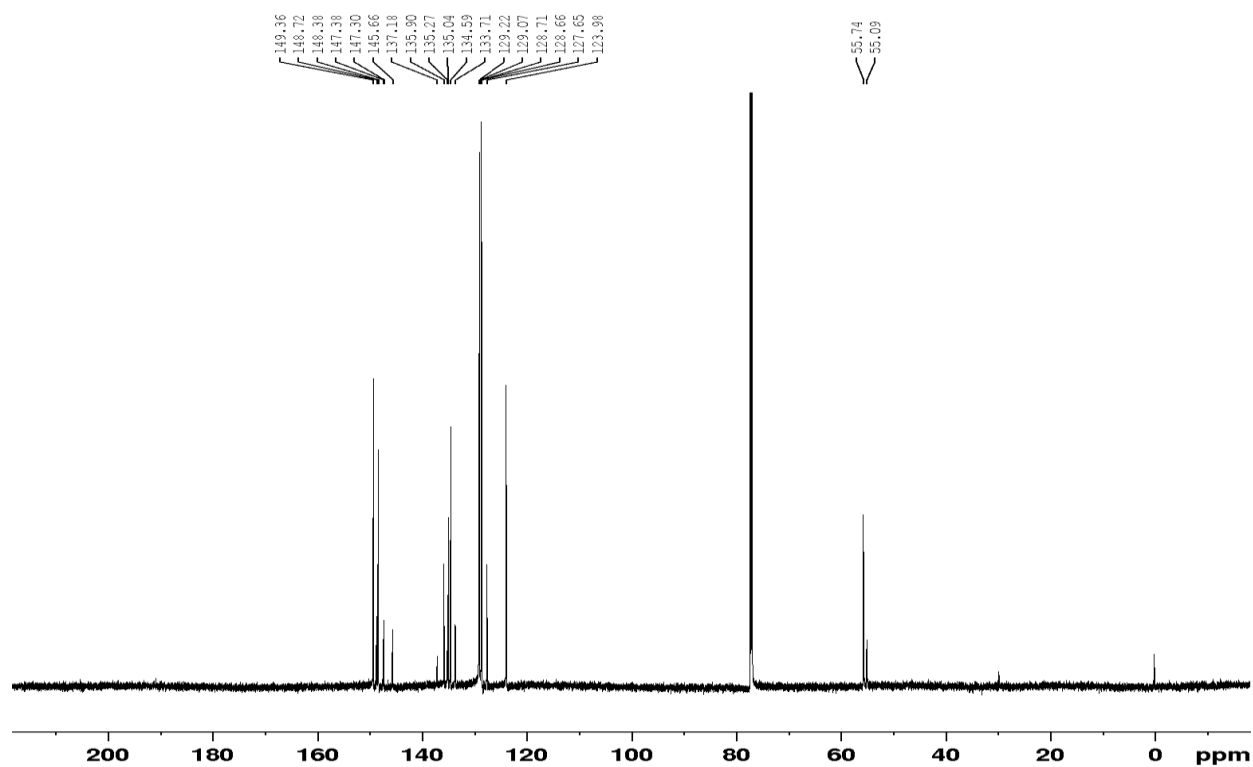


*N*-benzyl-*N*-(3-pyridyl)carbamoyl fluoride (2.3y)

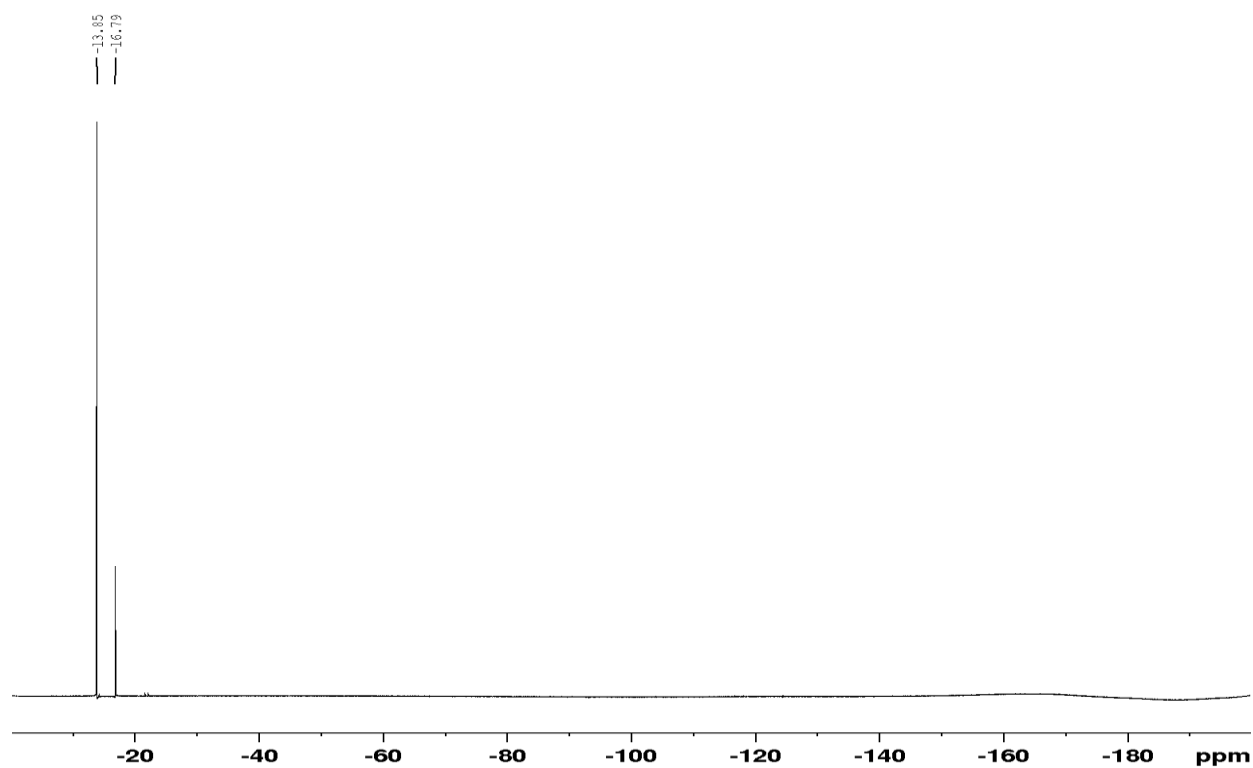
<sup>1</sup>H NMR Spectrum



<sup>13</sup>C NMR Spectrum

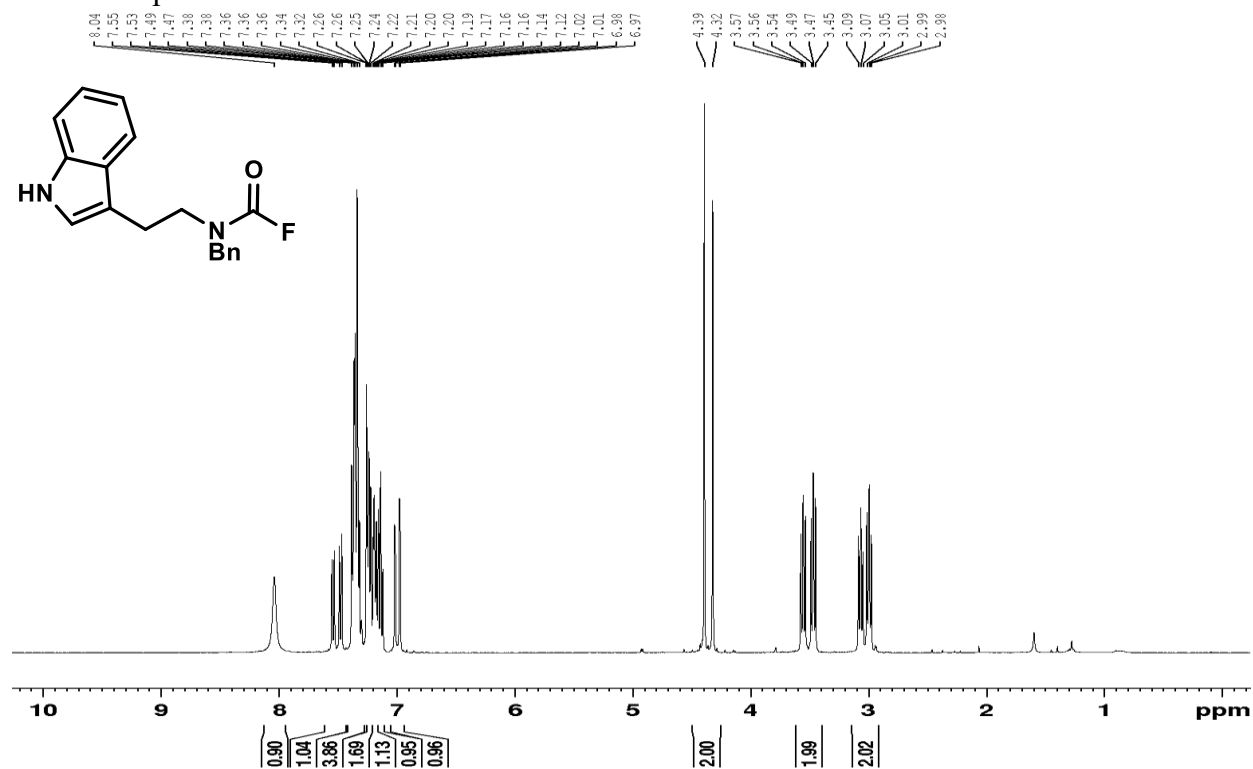


$^{19}\text{F}$  NMR Spectrum

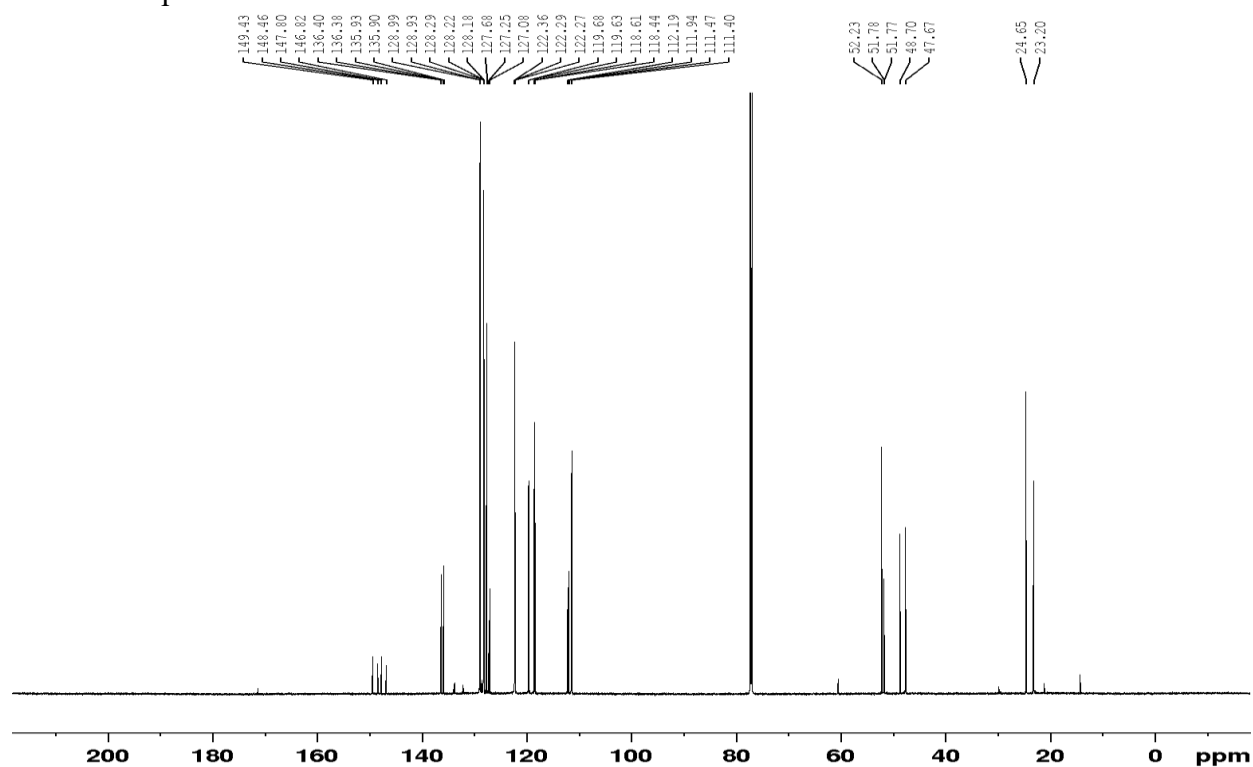


*N*-benzyl-*N*-[2-(1*H*-indol-3-yl)ethyl]carbamoyl fluoride (**2.3z**)

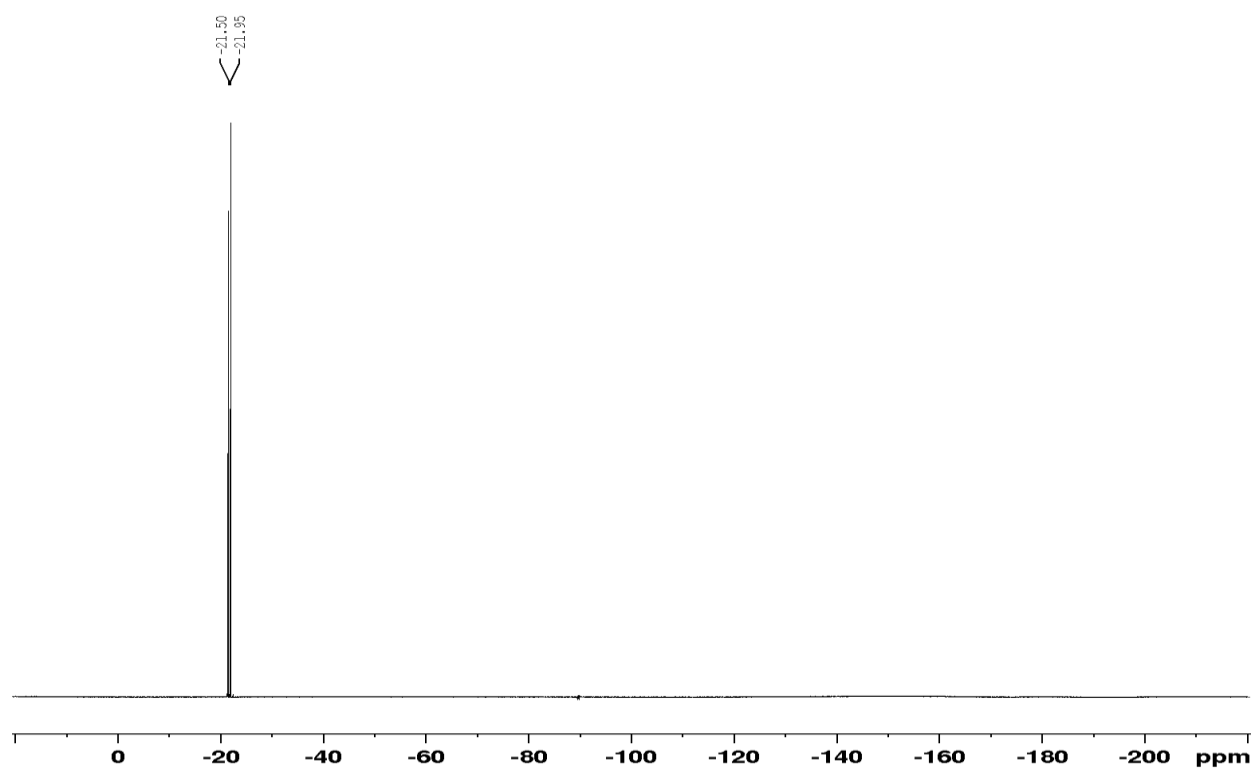
<sup>1</sup>H NMR Spectrum



<sup>13</sup>C NMR Spectrum

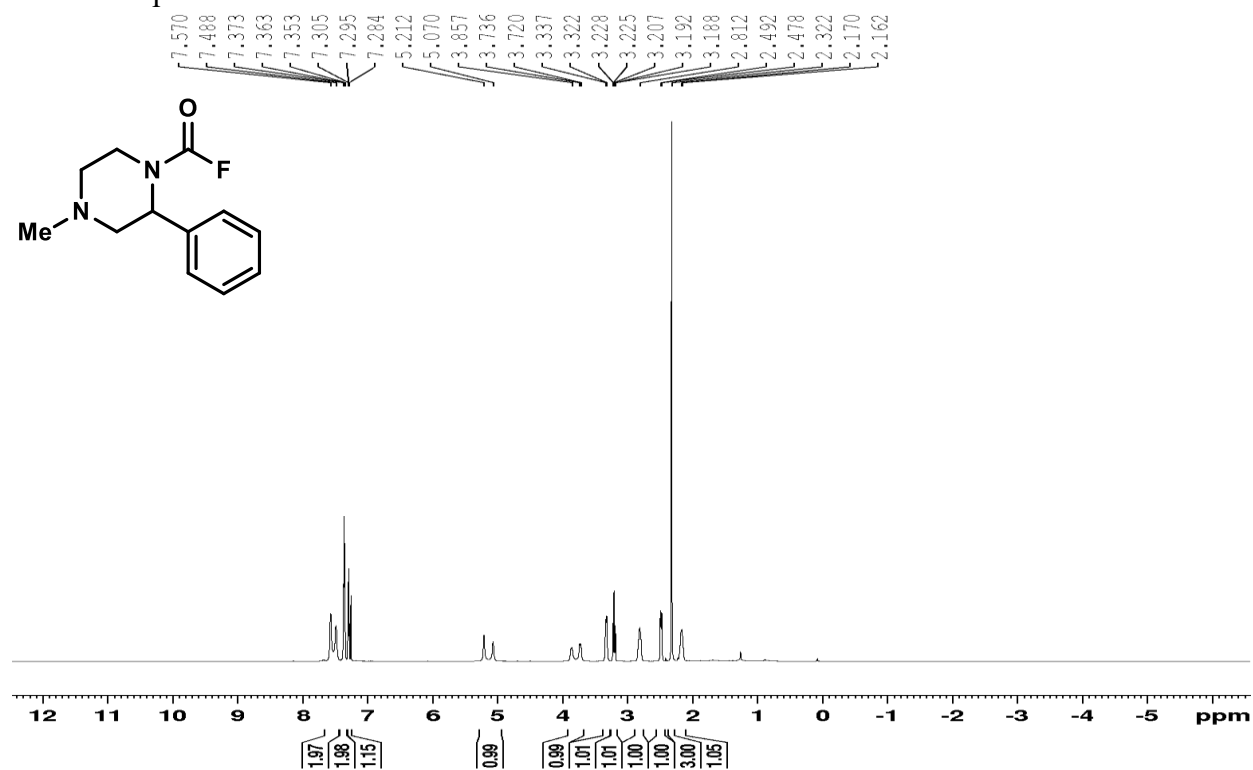


<sup>19</sup>F NMR Spectrum



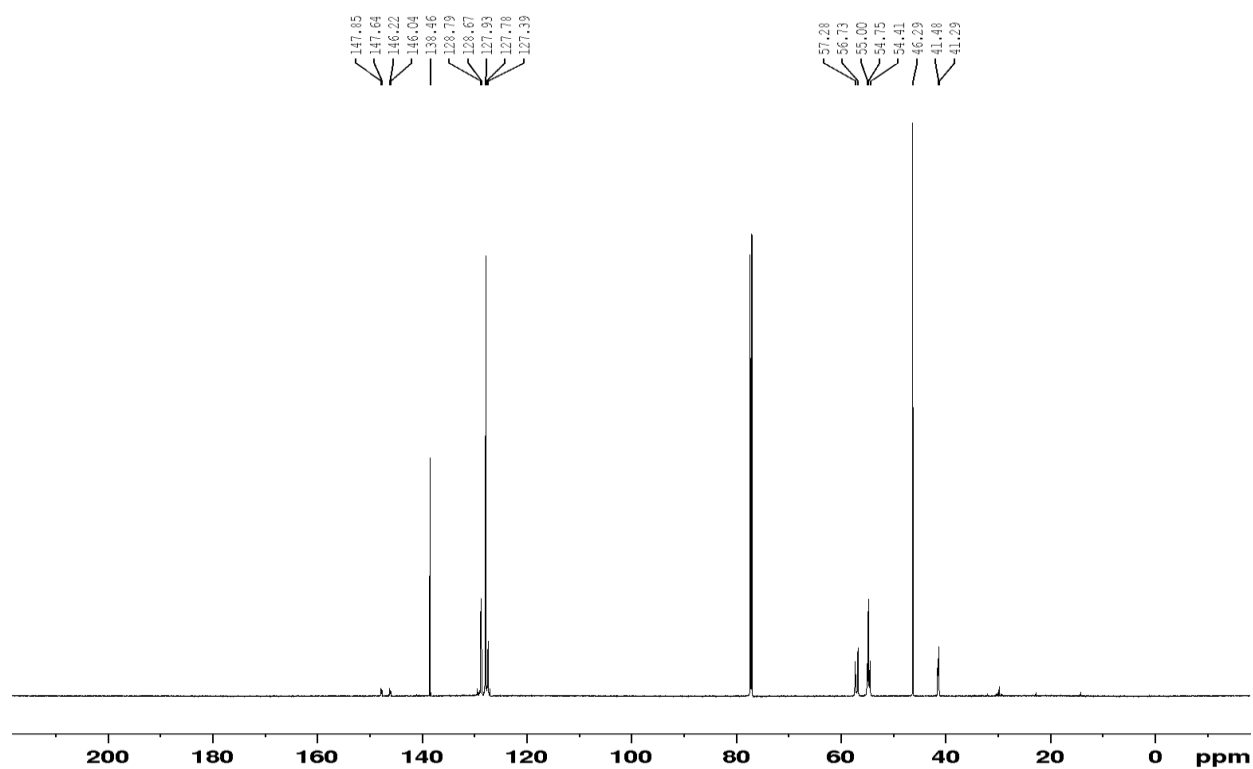
4-methyl-2-phenylpiperazine-1-carbonyl fluoride (2.3aa)

<sup>1</sup>H NMR Spectrum

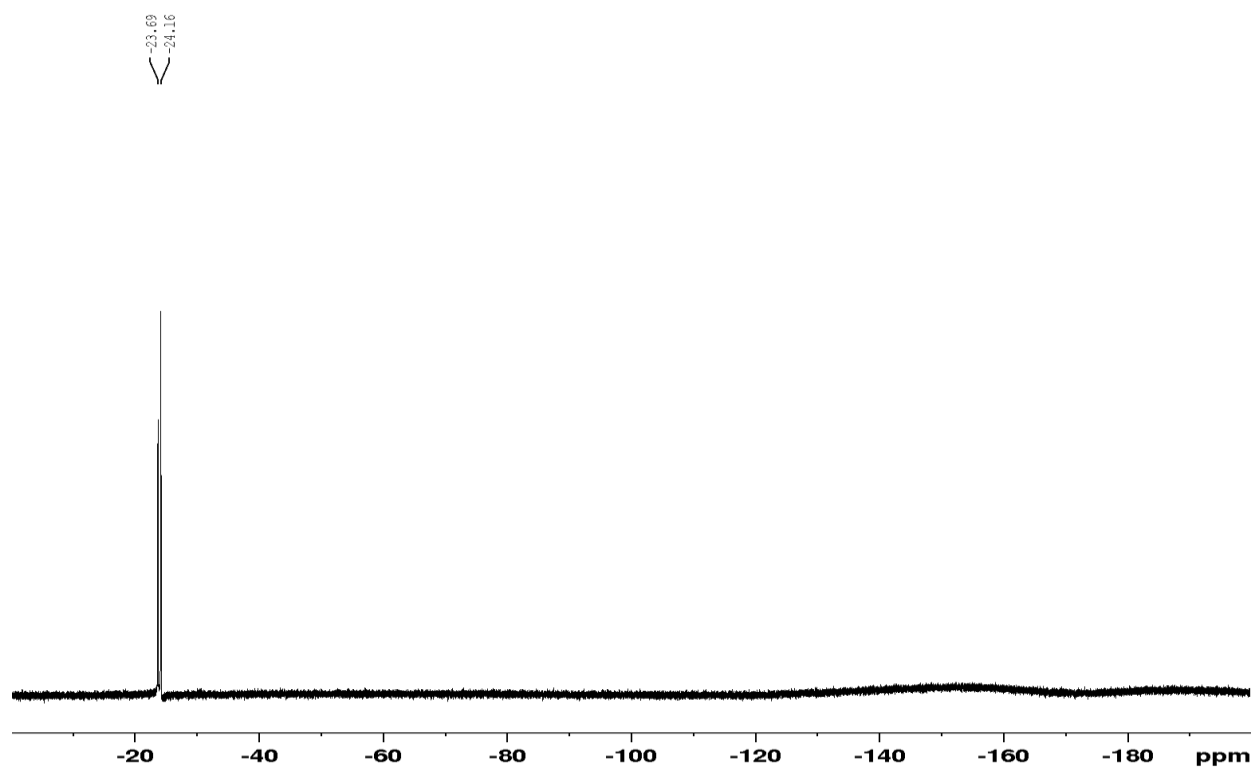




$^{13}\text{C}$  NMR Spectrum

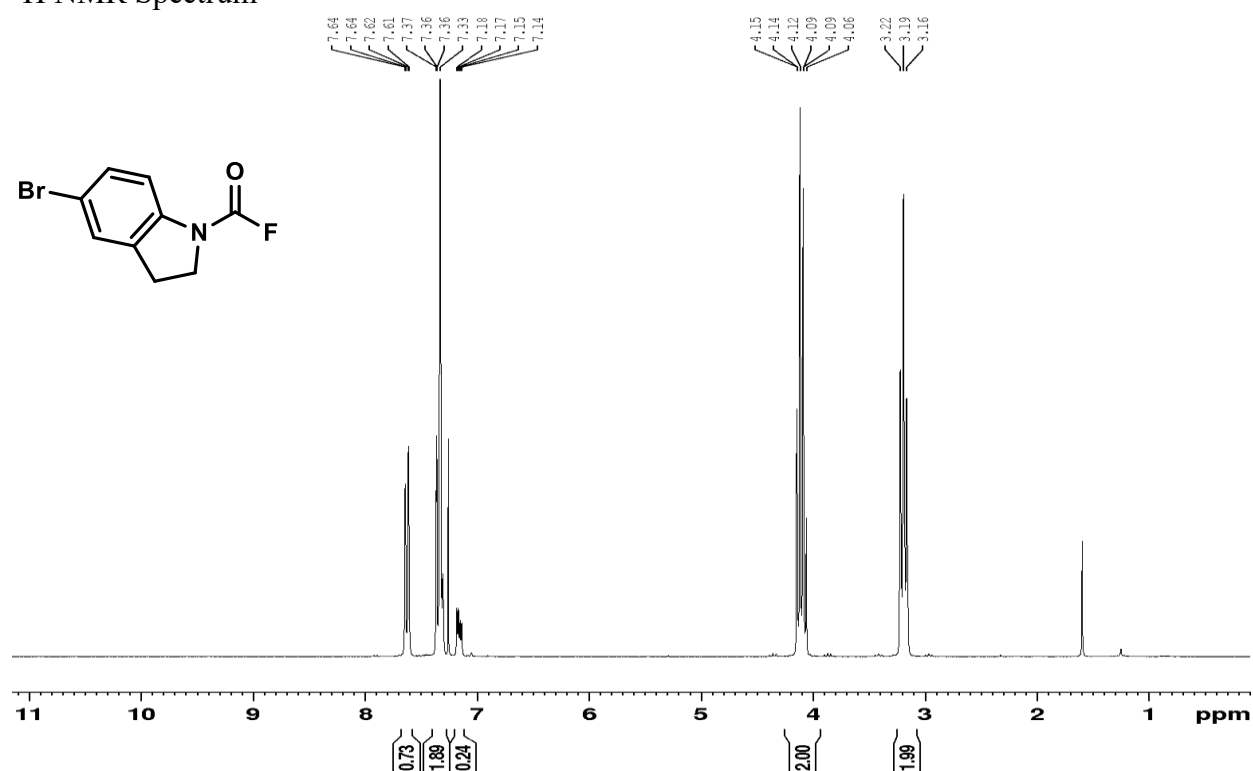


$^{19}\text{F}$  NMR Spectrum

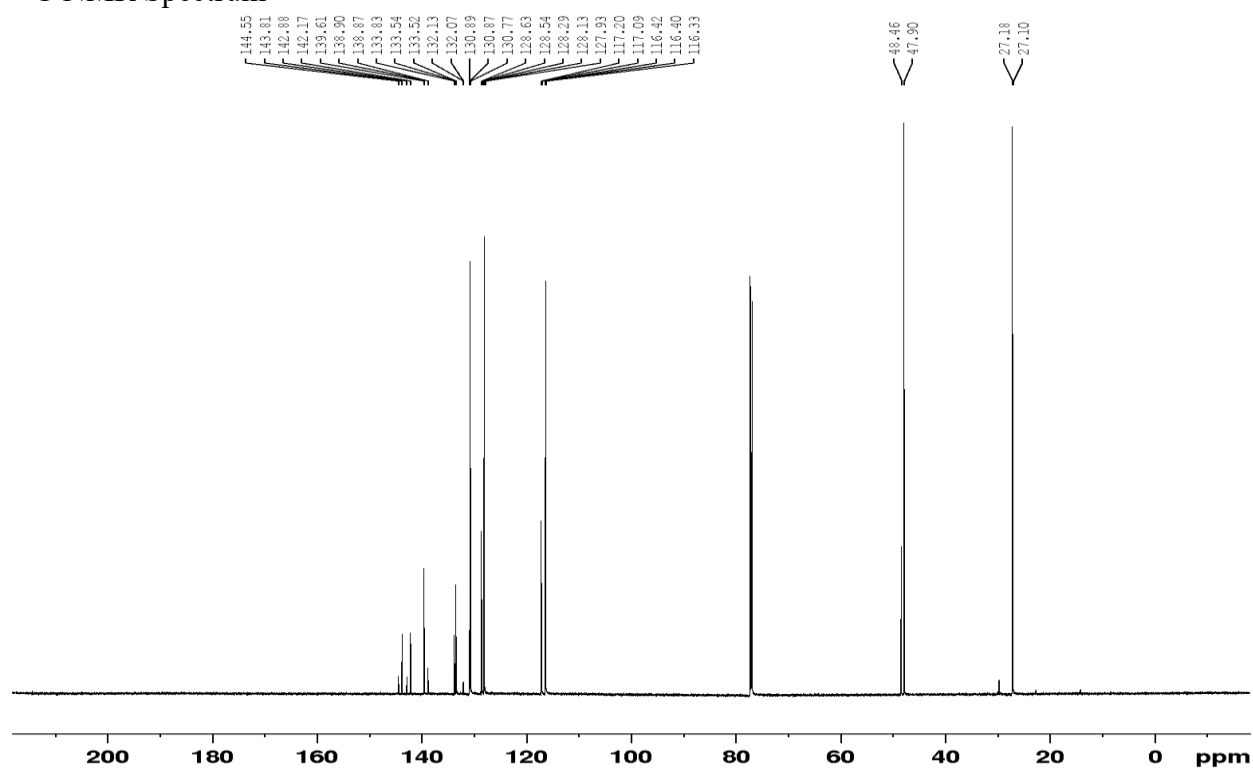


5-bromoindoline-1-carbonyl fluoride (2.3ab)

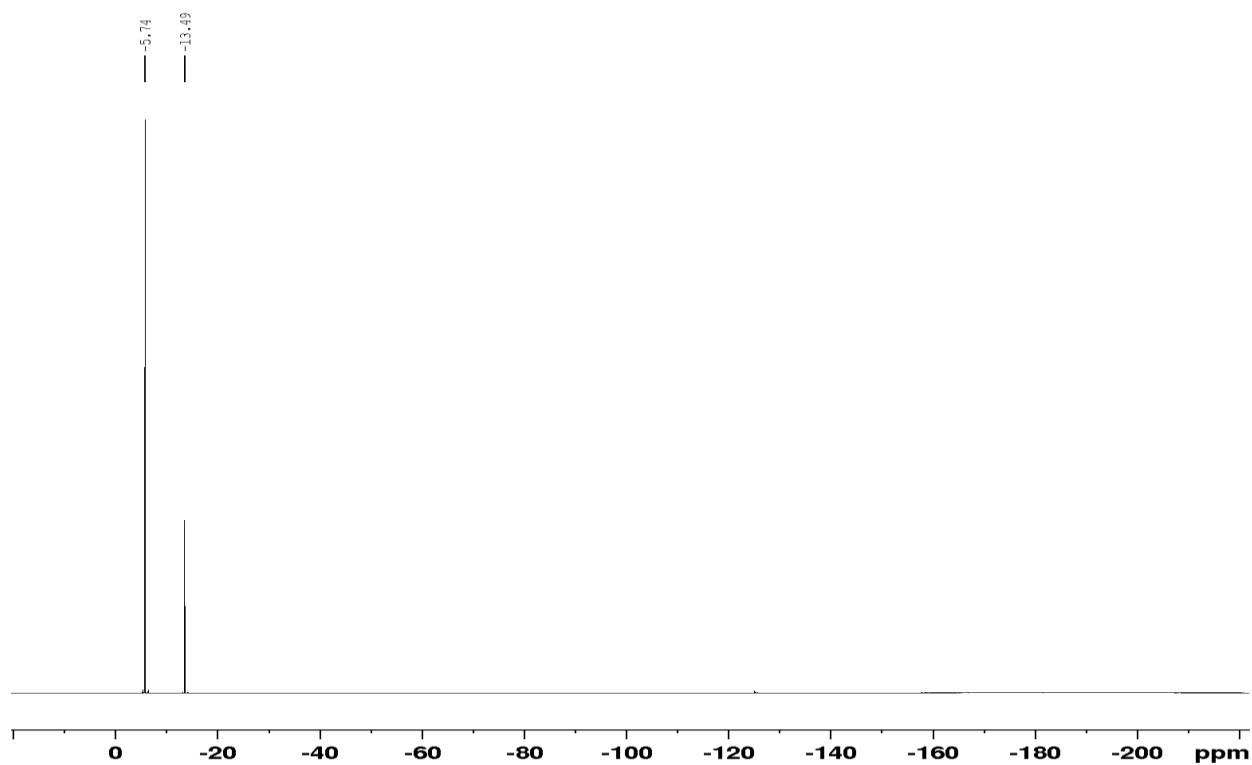
<sup>1</sup>H NMR Spectrum



<sup>13</sup>C NMR Spectrum

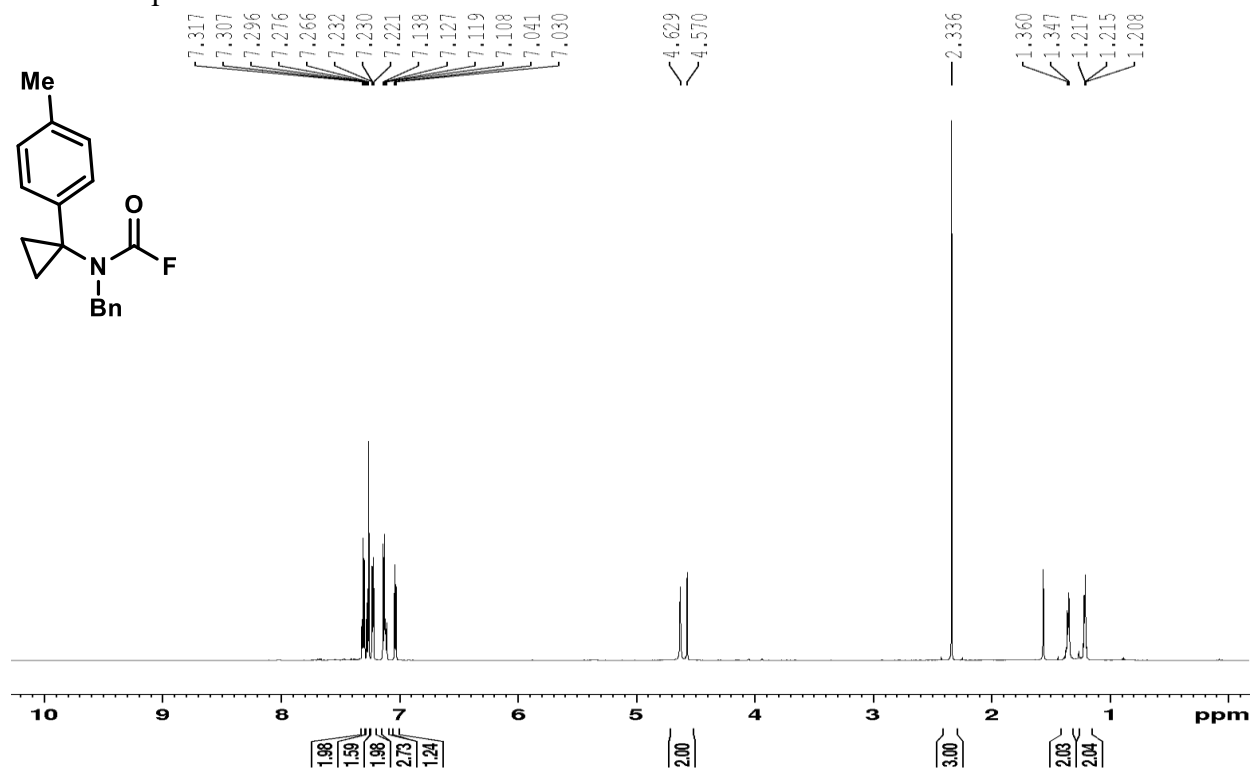


<sup>19</sup>F NMR Spectrum

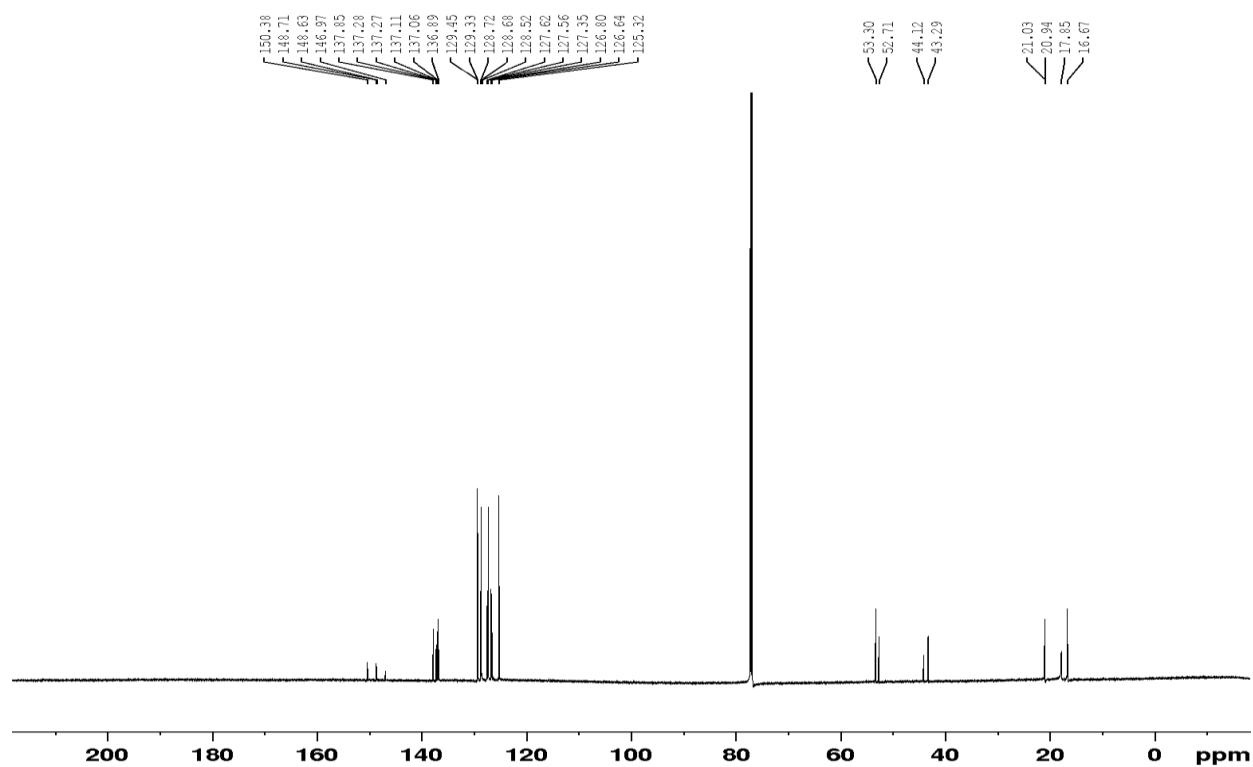


*N*-benzyl-*N*-[1-(*p*-tolyl)cyclopropyl]carbamoyl fluoride (**2.3ae**)

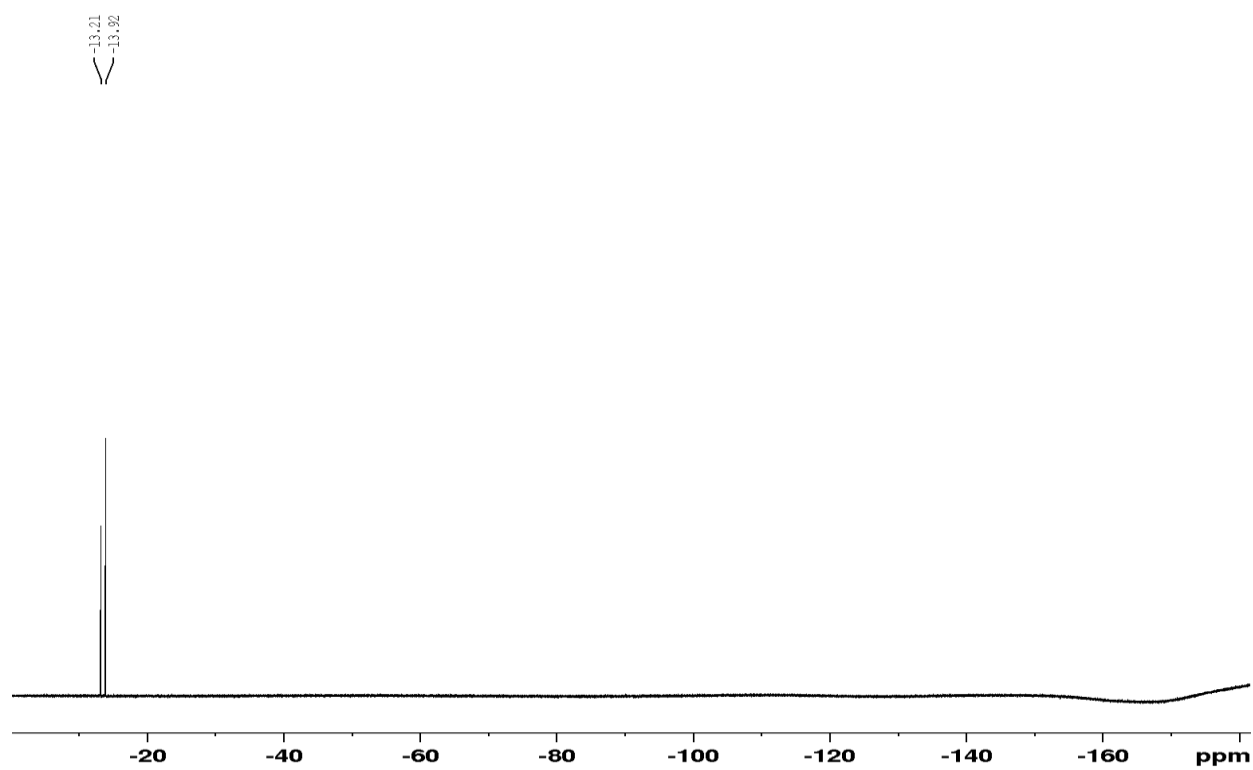
<sup>1</sup>H NMR Spectrum



<sup>13</sup>C NMR Spectrum

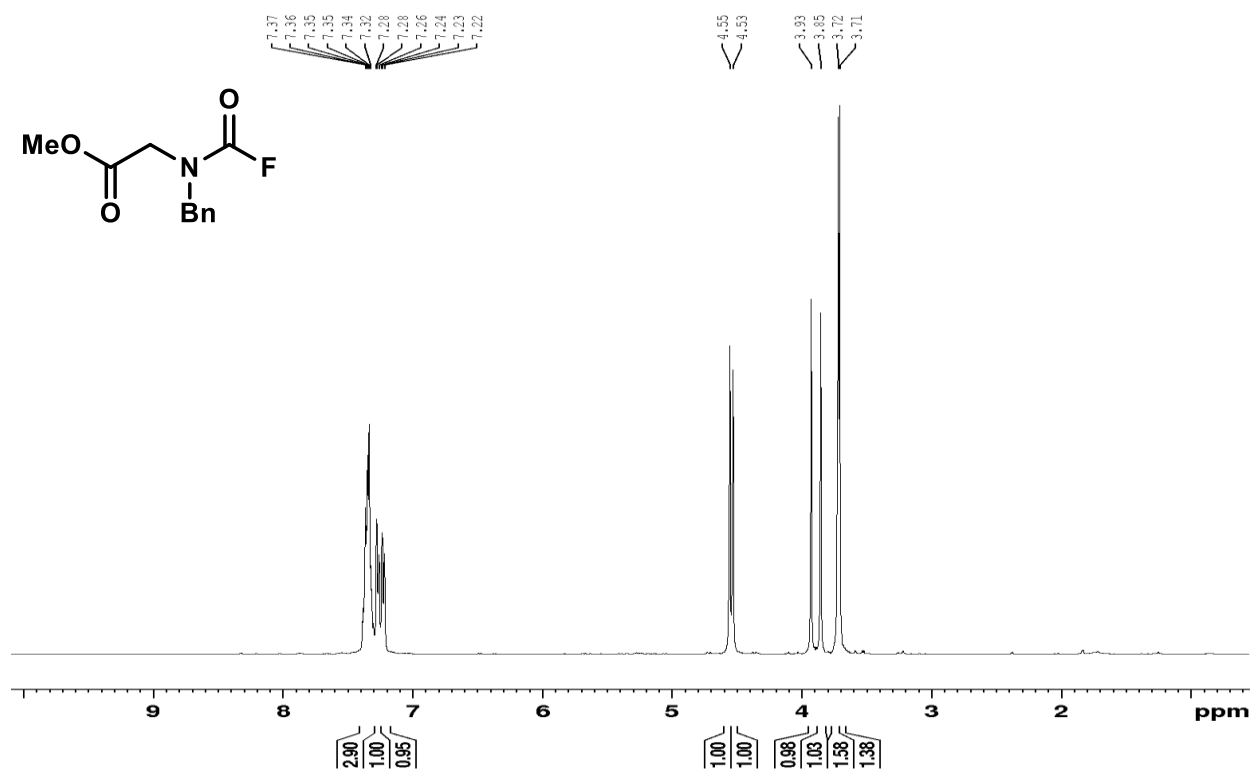


<sup>19</sup>F NMR Spectrum

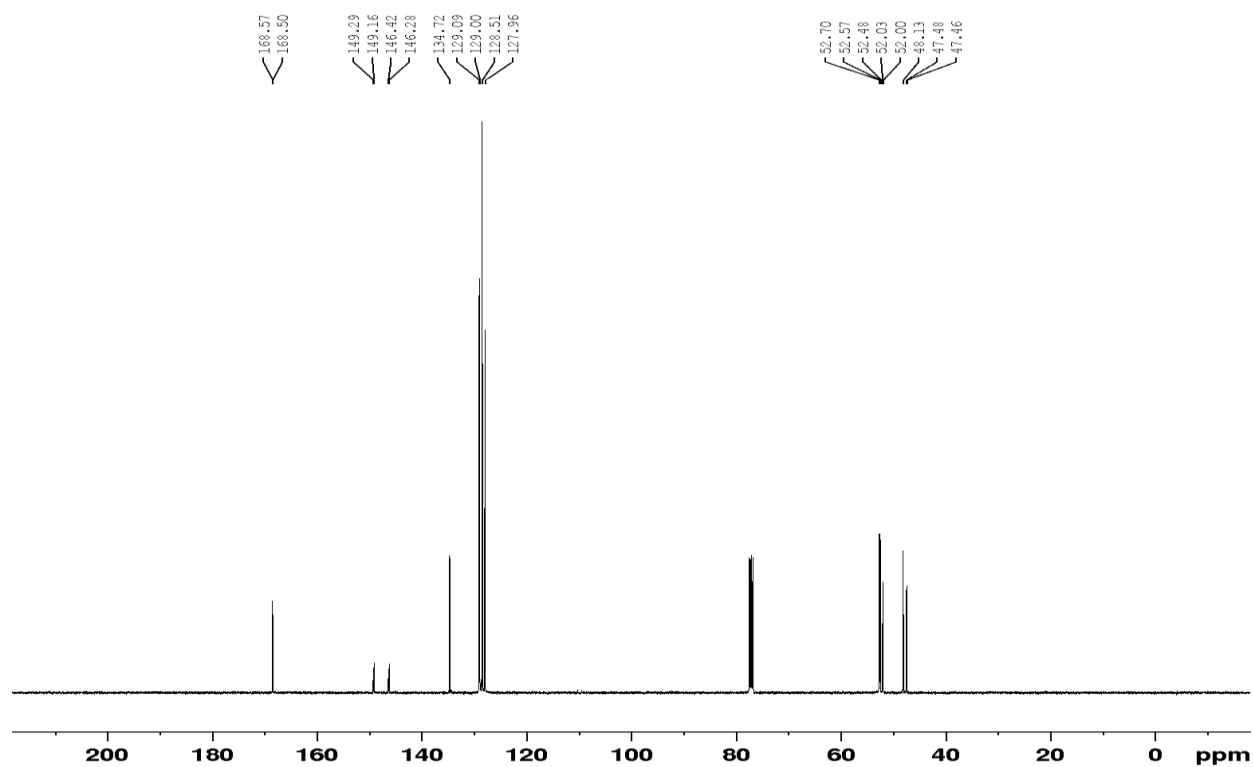


methyl 2-[benzyl(fluorocarbonyl)amino]acetate (2.3af)

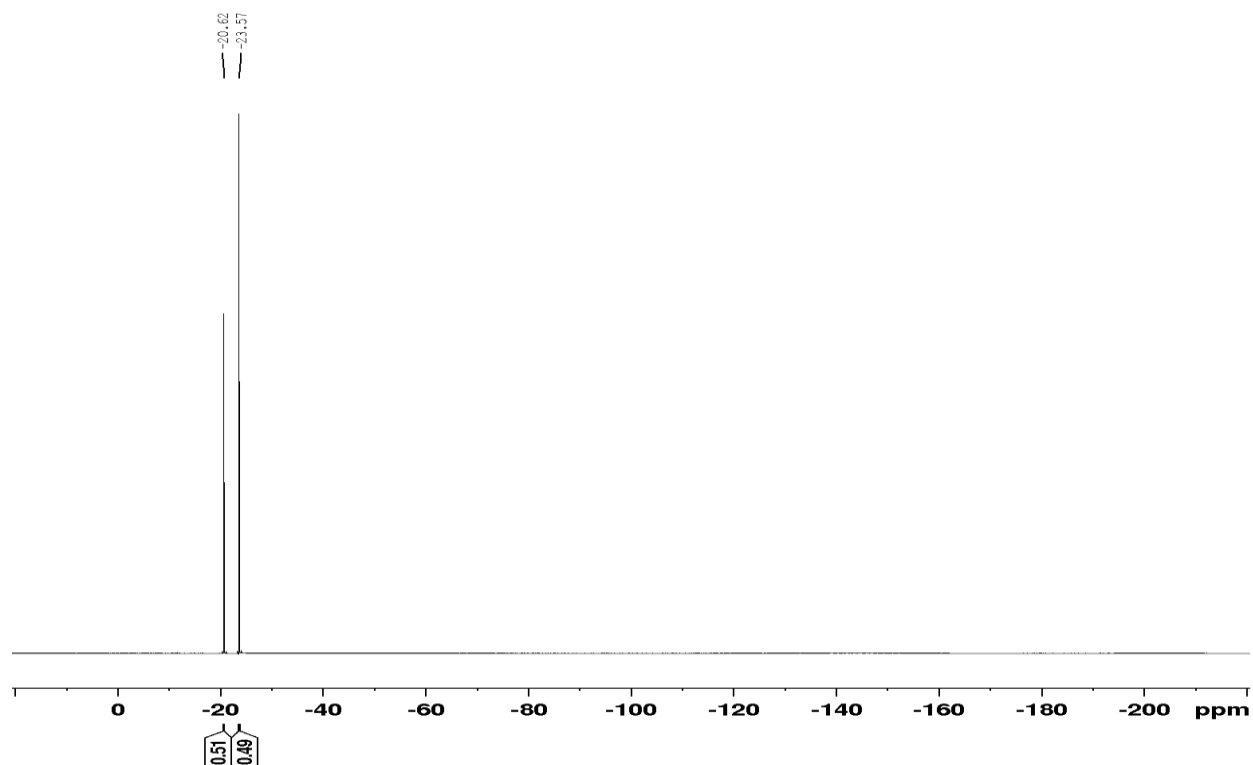
<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (400 MHz)



$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (101 MHz)

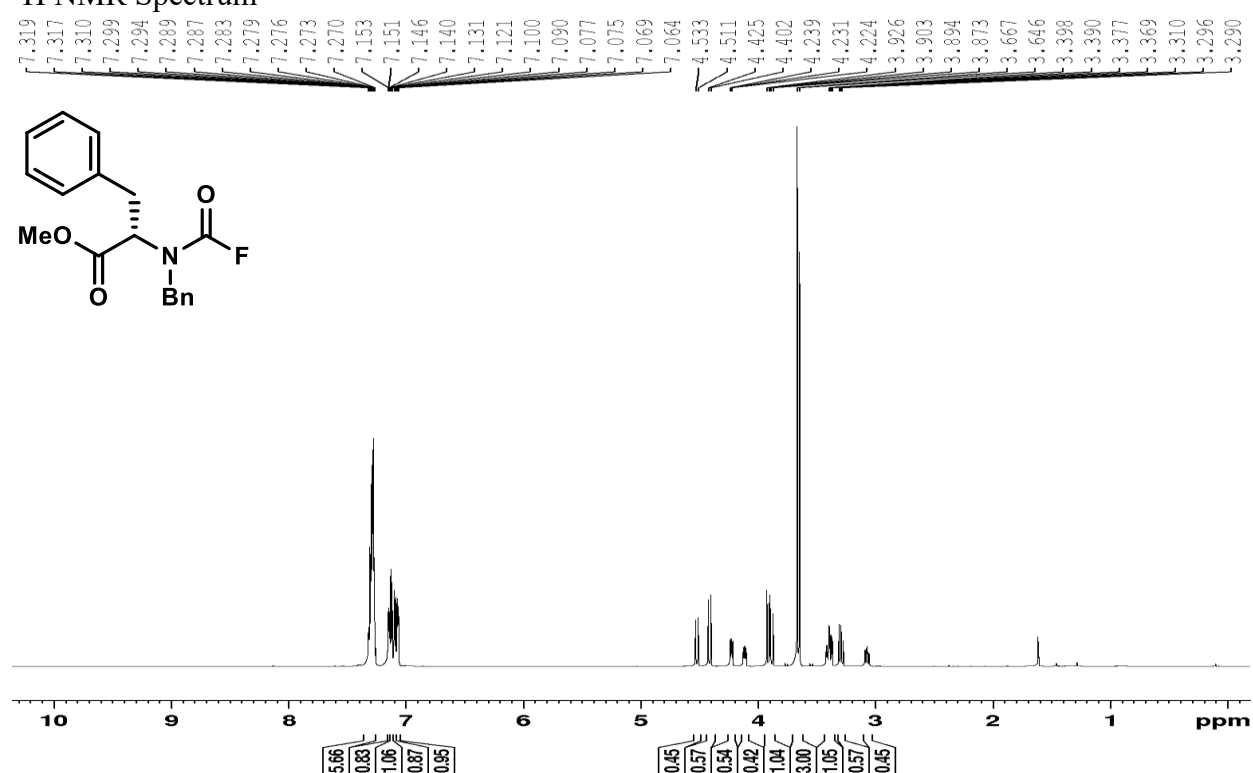


$^{19}\text{F}$  NMR Spectrum  $\text{CDCl}_3$  (377 MHz)

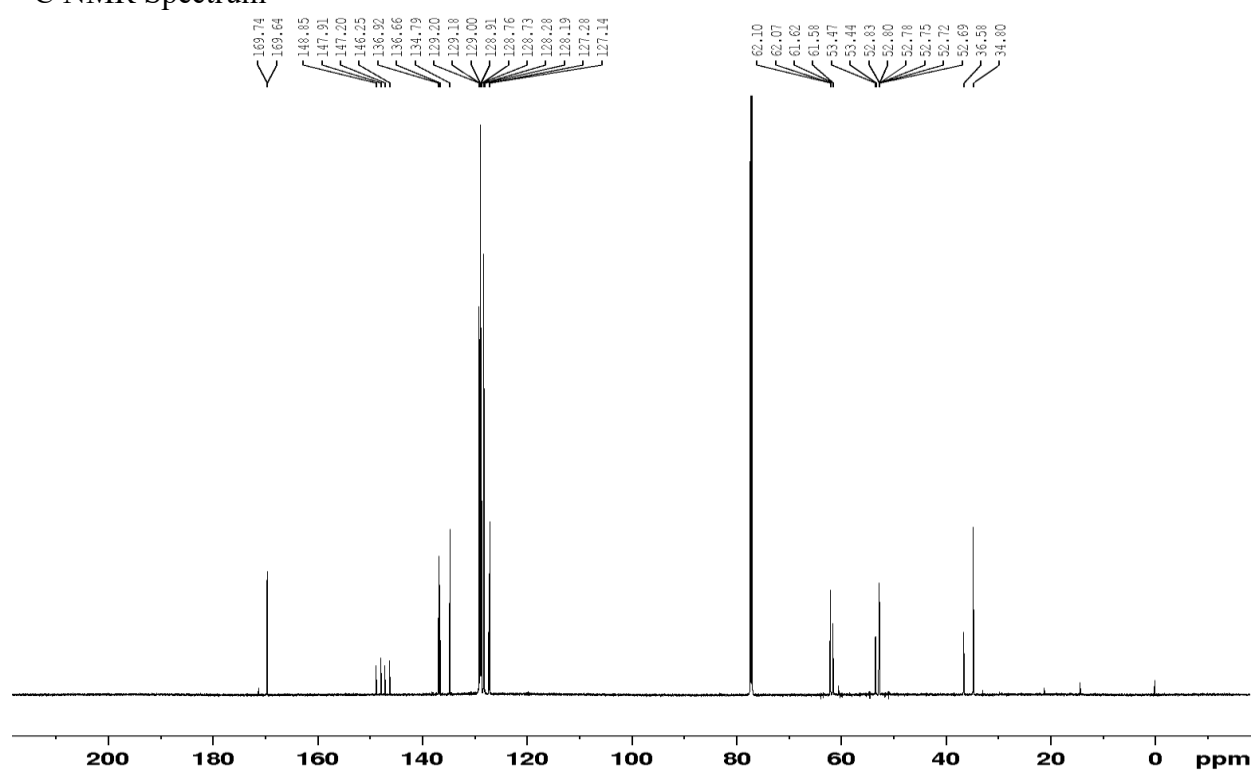


methyl (2S)-2-[benzyl(fluorocarbonyl)amino]-3-phenyl-propanoate (2.3ag)

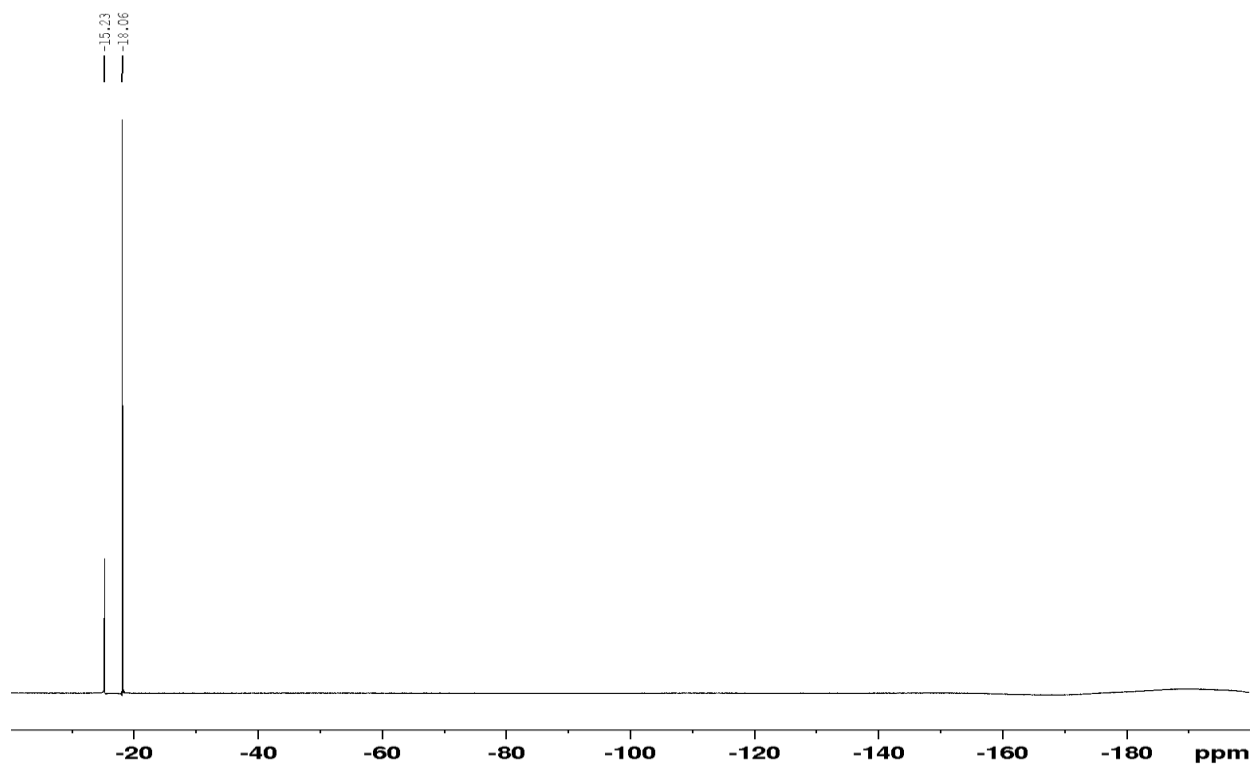
# <sup>1</sup>H NMR Spectrum



# <sup>13</sup>C NMR Spectrum

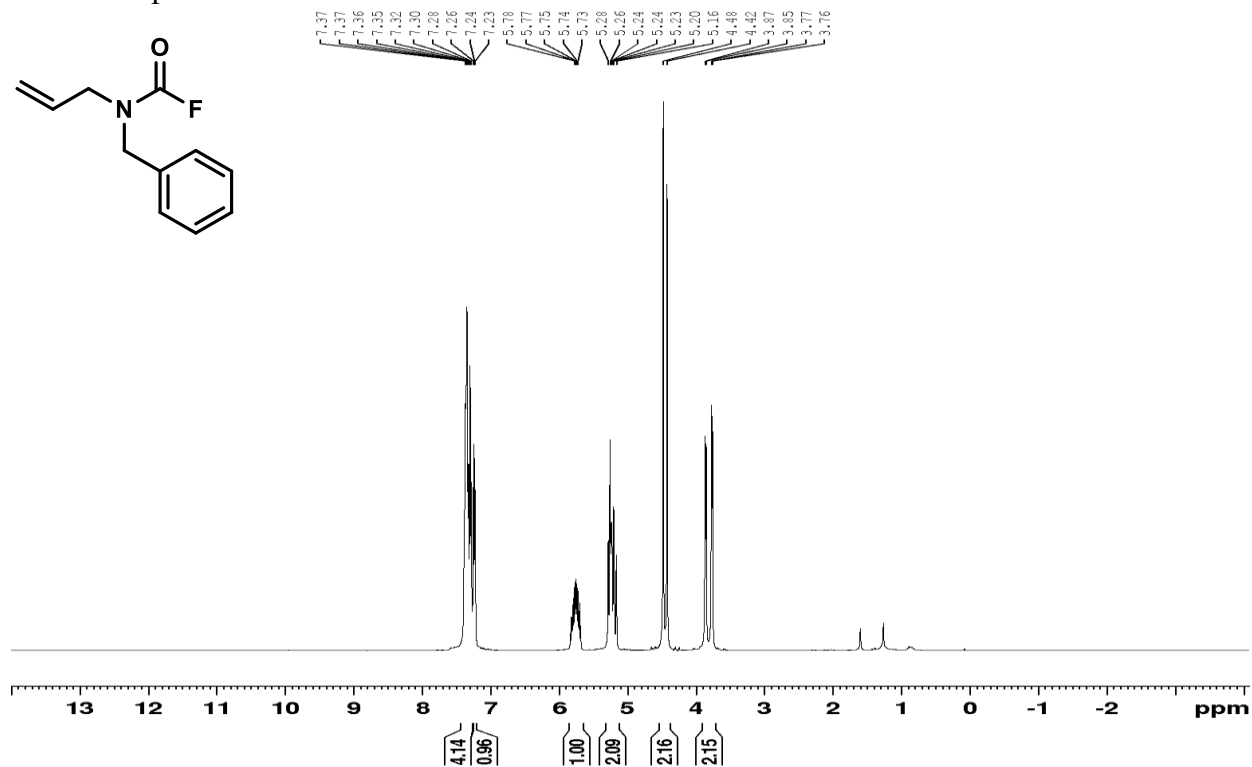


# <sup>19</sup>F NMR Spectrum



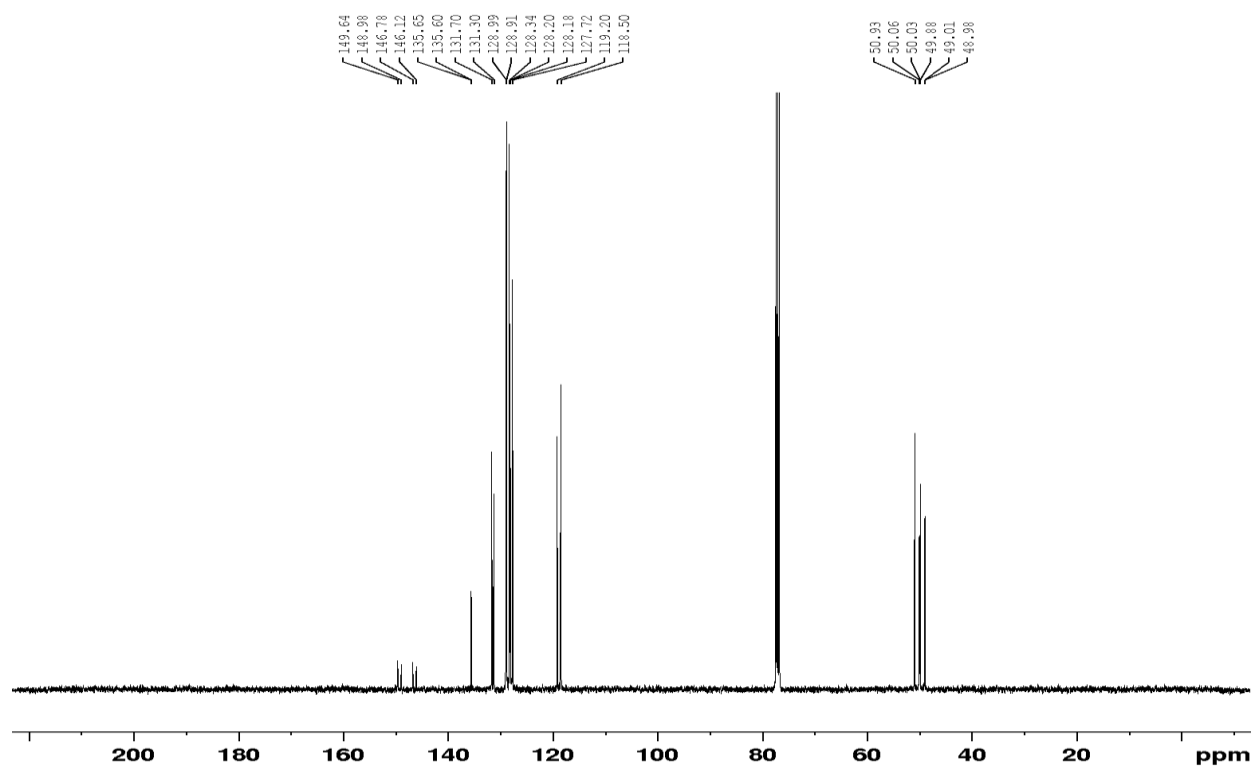
*N*-allyl-*N*-benzyl-carbamoyl fluoride (2.3ah)

<sup>1</sup>H NMR Spectrum

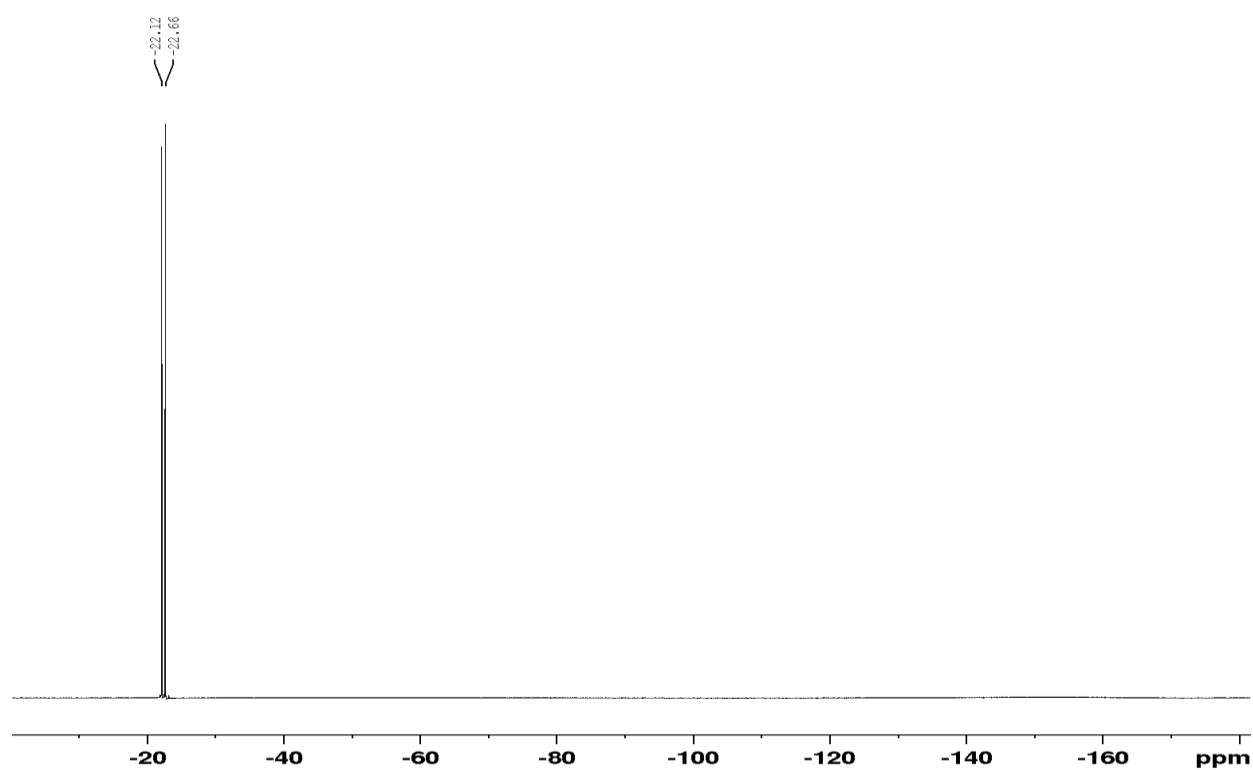


<sup>13</sup>C NMR Spectrum



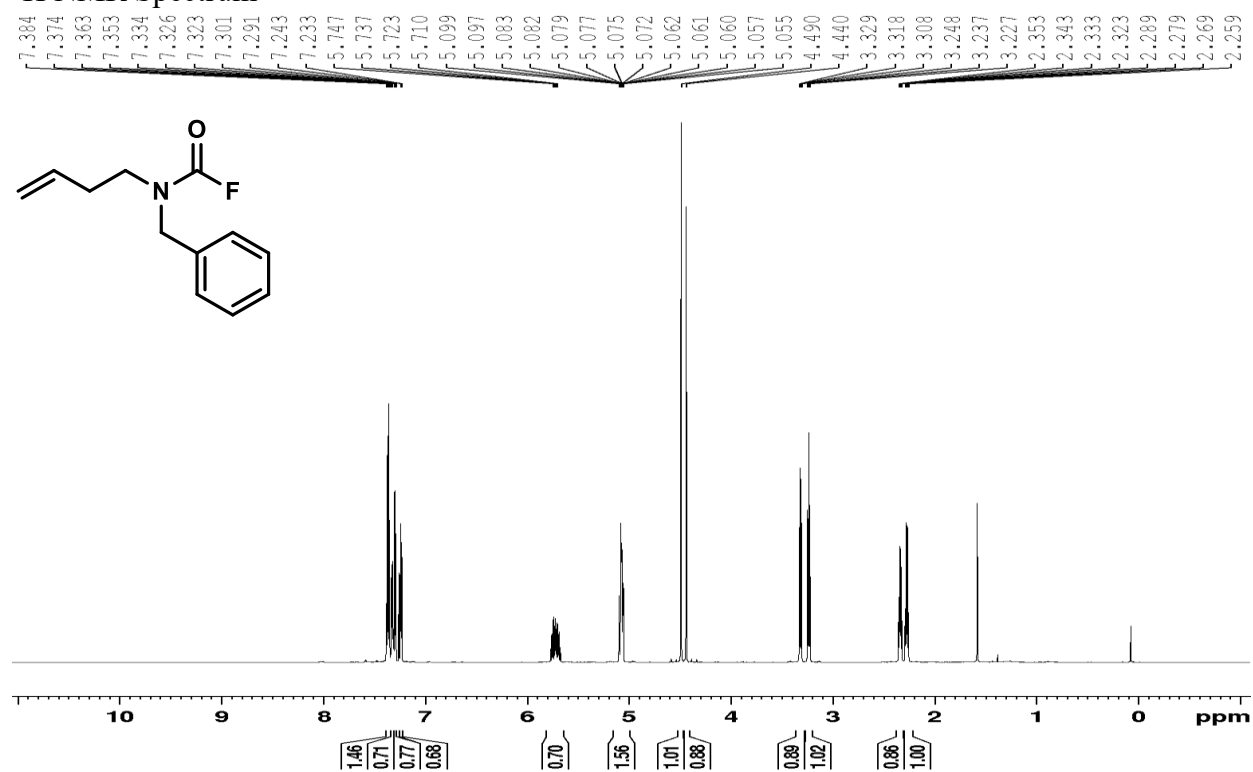


<sup>19</sup>F NMR Spectrum

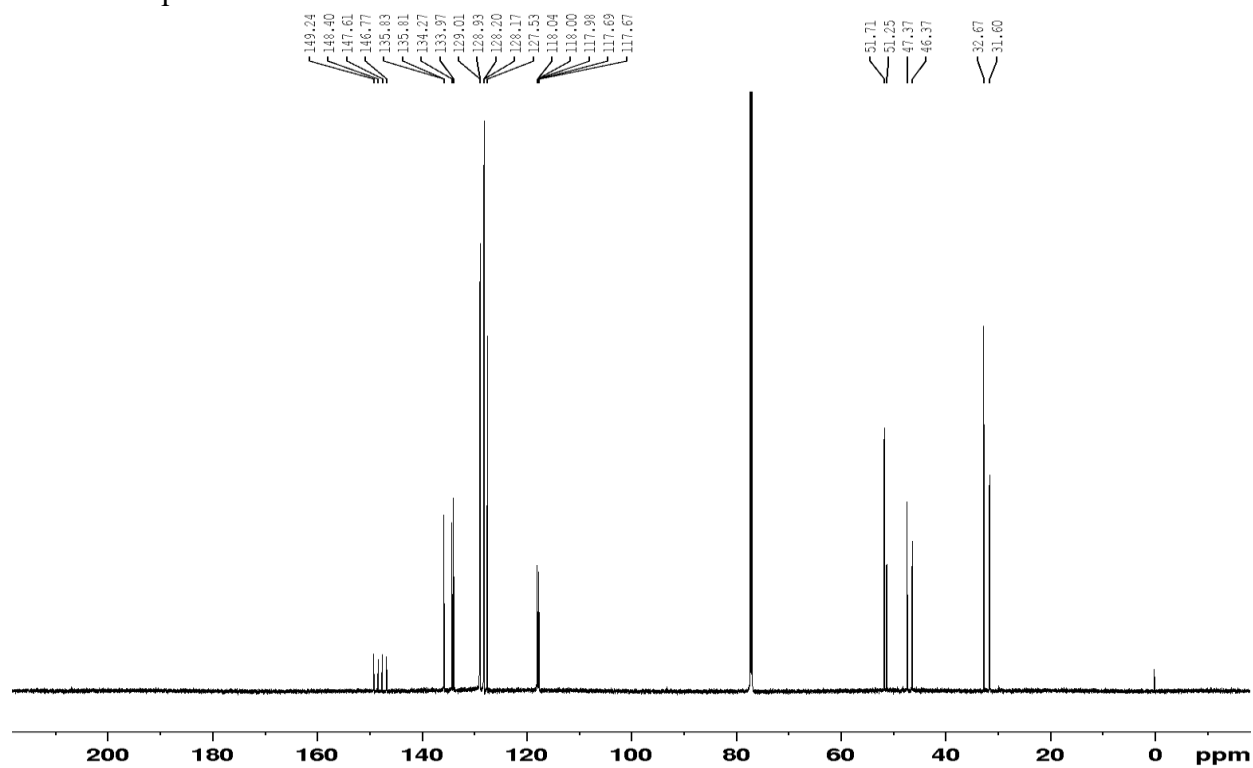


*N*-benzyl-*N*-but-3-enyl-carbamoyl fluoride (2.3ai)

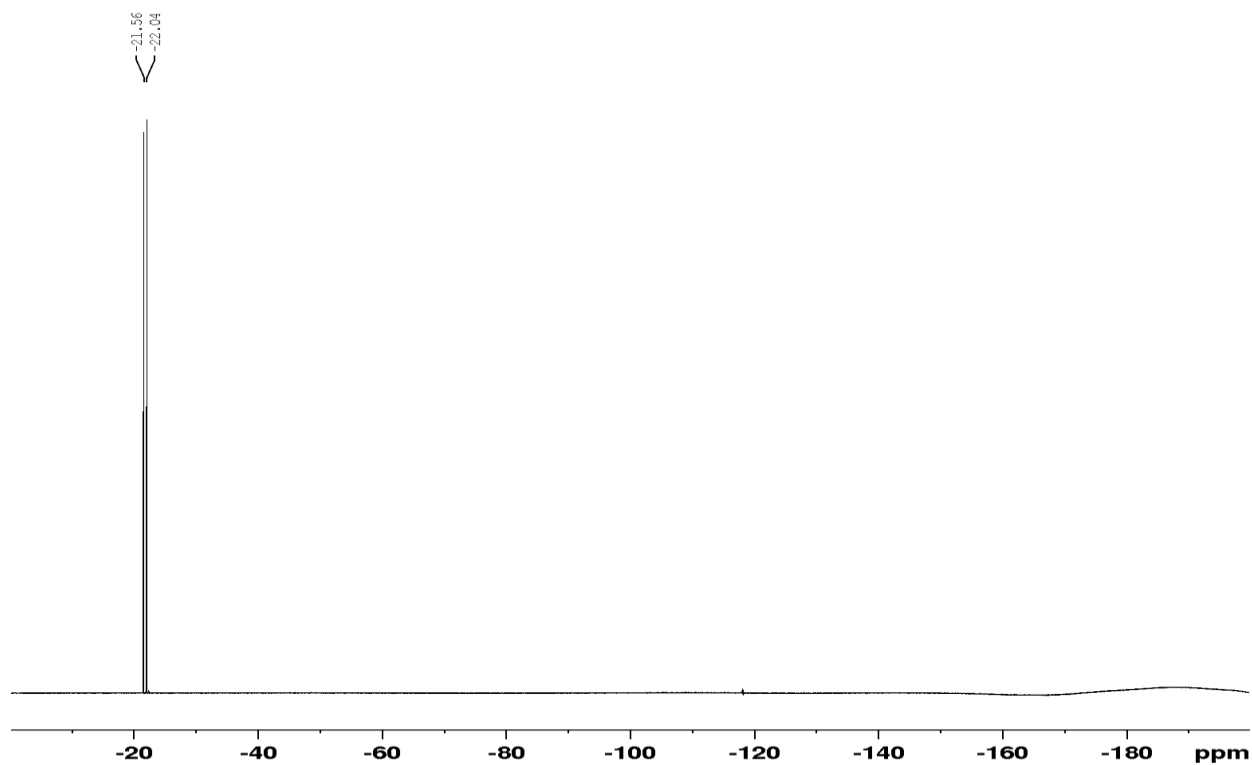
# <sup>1</sup>H NMR Spectrum



# <sup>13</sup>C NMR Spectrum

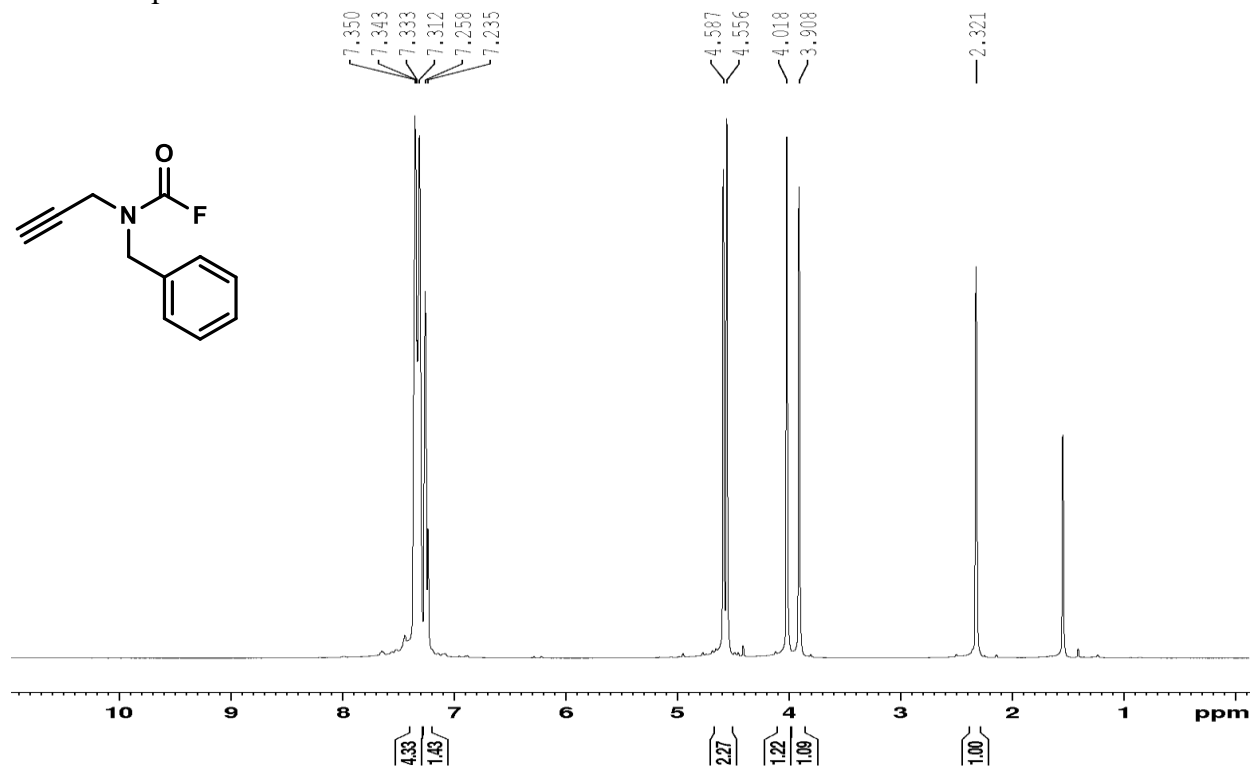


# <sup>19</sup>F NMR Spectrum

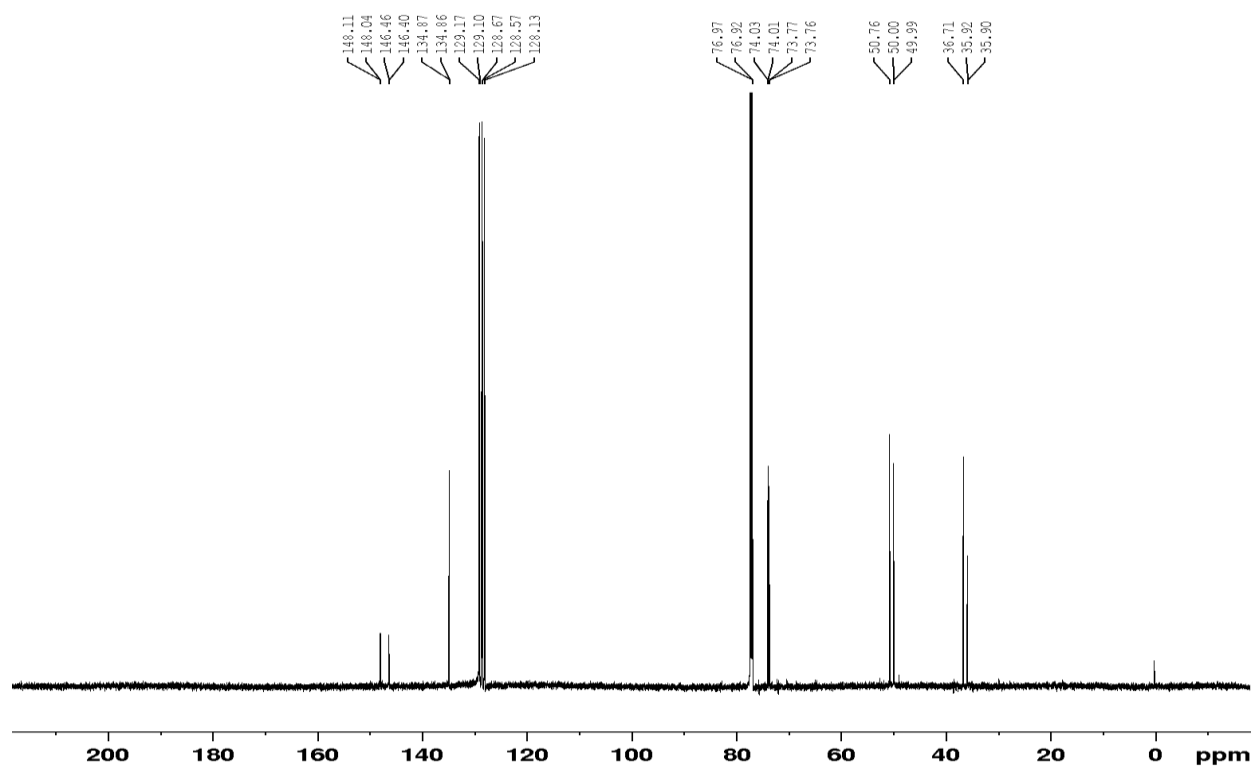


*N*-benzyl-*N*-prop-2-ynyl-carbamoyl fluoride (2.3aj)

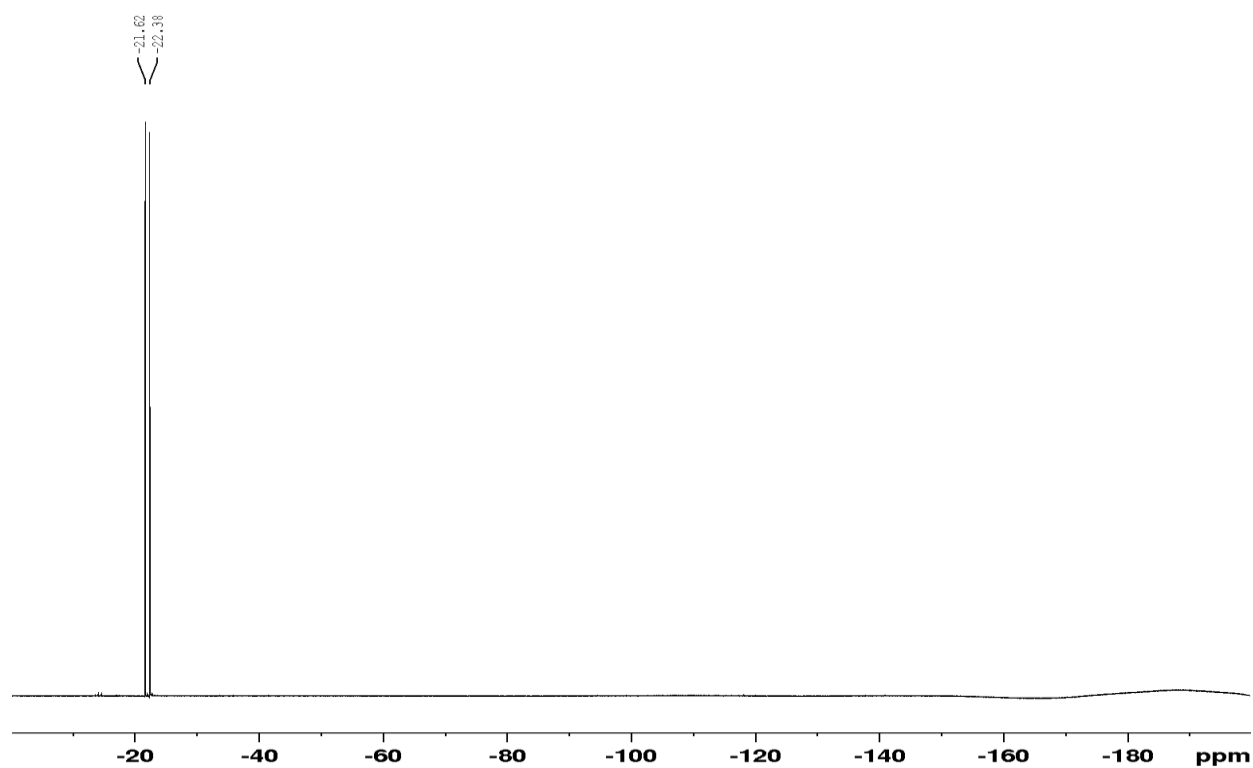
<sup>1</sup>H NMR Spectrum



<sup>13</sup>C NMR Spectrum

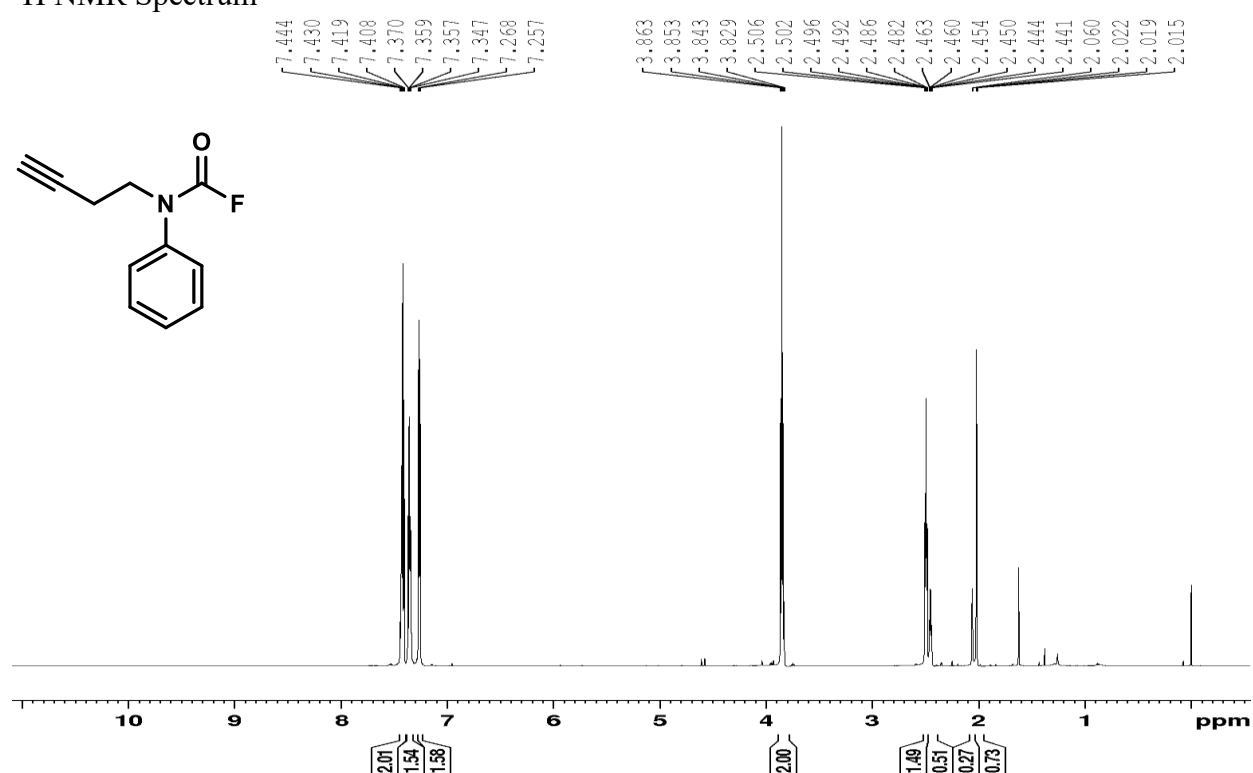


<sup>19</sup>F NMR Spectrum

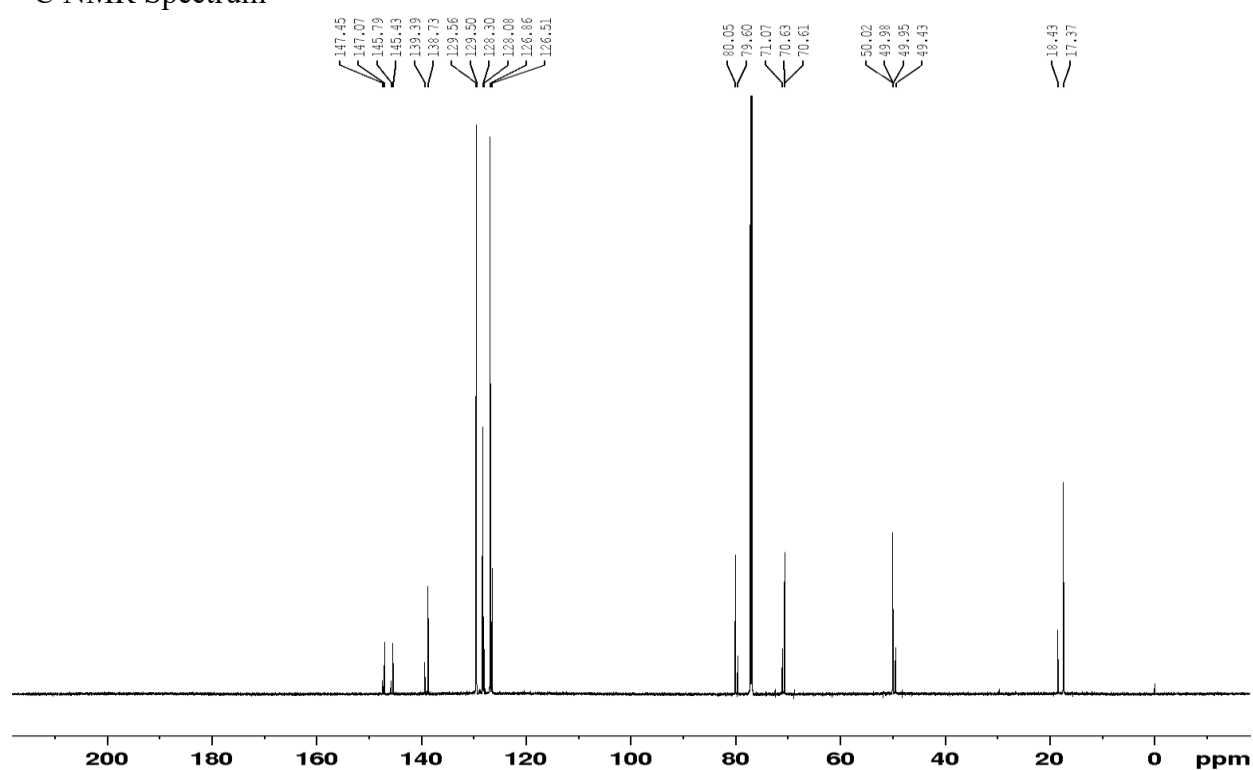


N-but-3-ynyl-N-phenyl-carbamoyl fluoride (2.3ak)

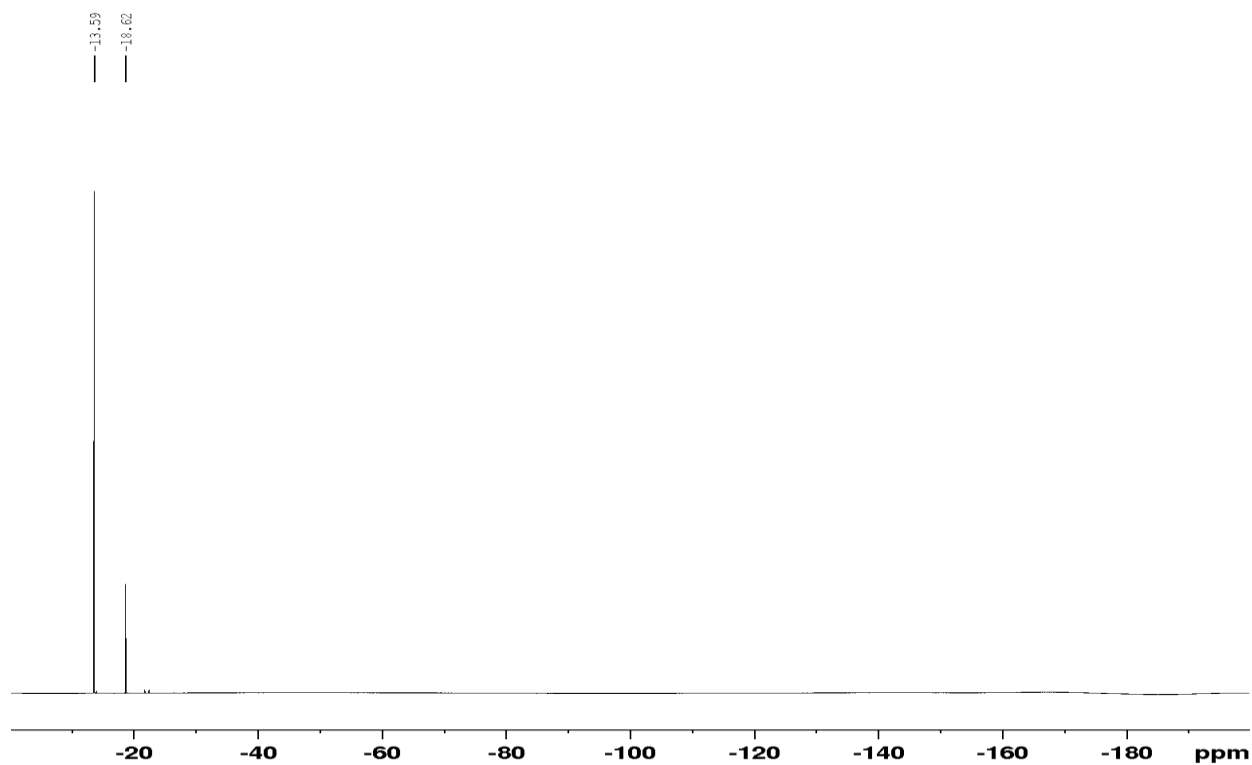
<sup>1</sup>H NMR Spectrum



<sup>13</sup>C NMR Spectrum

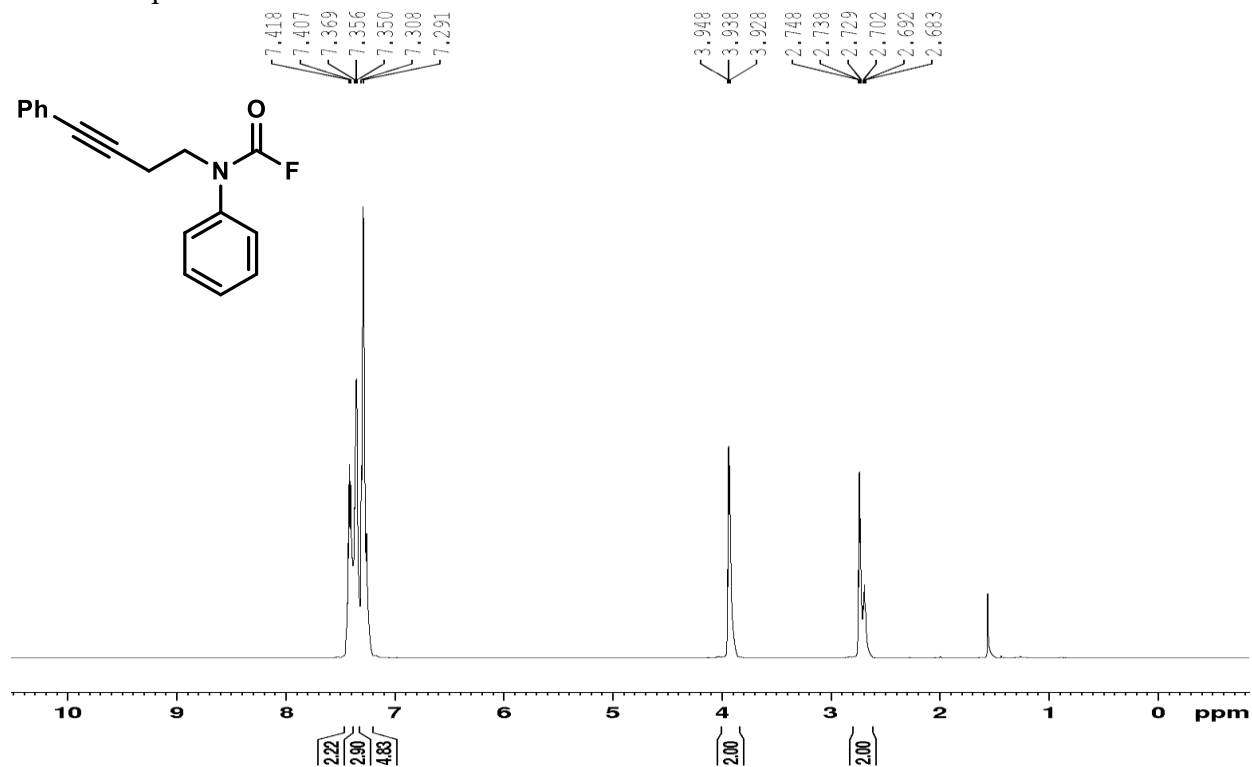


<sup>19</sup>F NMR Spectrum

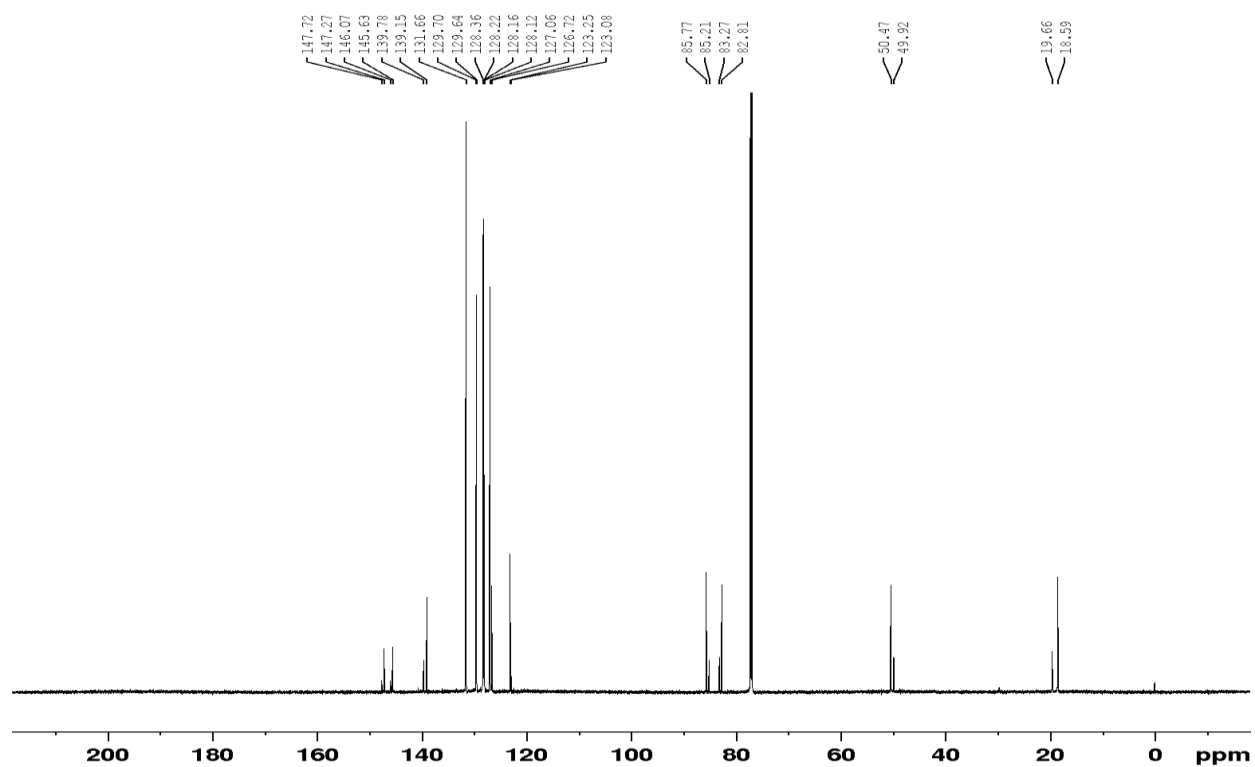


*N*-phenyl-*N*-(4-phenylbut-3-ynyl)carbamoyl fluoride (2.3al)

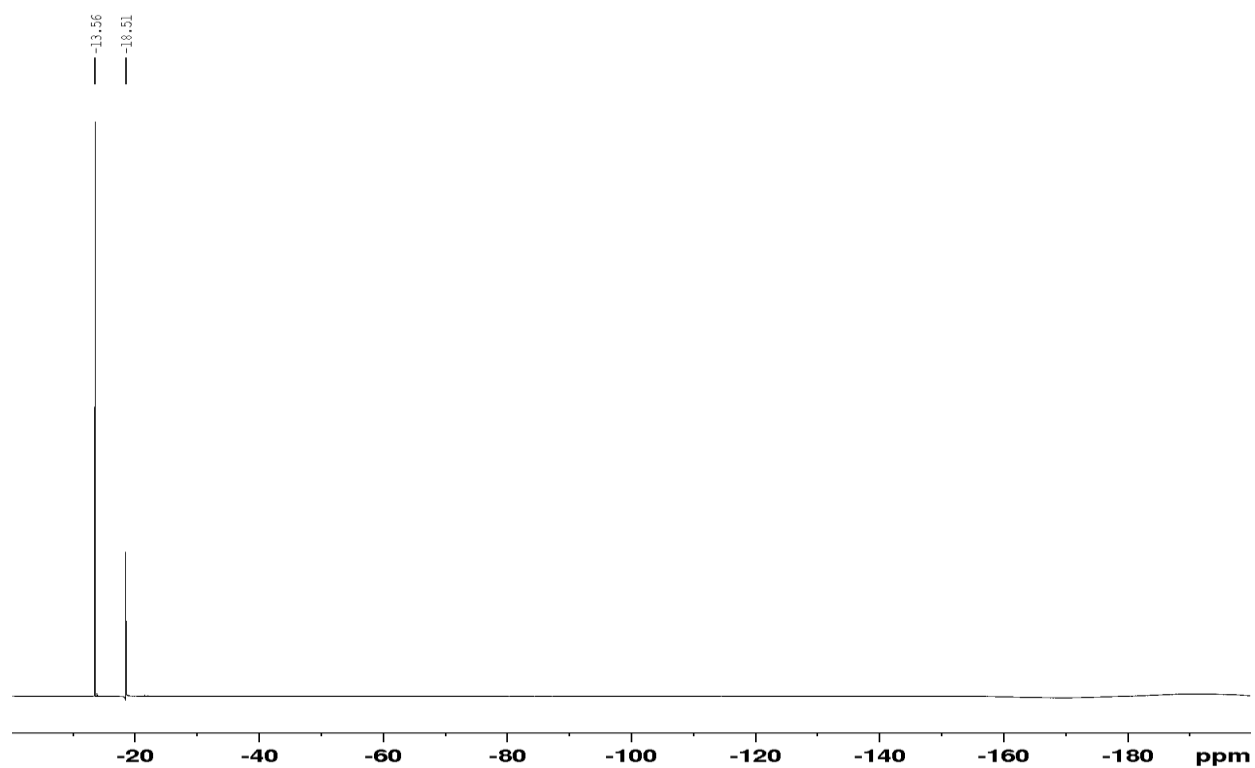
<sup>1</sup>H NMR Spectrum



<sup>13</sup>C NMR Spectrum



$^{19}\text{F}$  NMR Spectrum



# Chapter 3: Fluoride-Catalyzed Alkynylation of Carbamoyl Fluorides

## 3.1 Contributions

This chapter details the catalytic synthesis of alkynamides from carbamoyl fluorides and alkynyl silanes. This reaction was enabled by using tetrabutylammonium fluoride (TBAF), a common laboratory reagent, as the catalyst. This work was done in collaboration with an undergraduate intern, Dmytro Shevchuk, who prepared several alkynamide substrates and developed the scale-up procedure for this method. M.Sc. student, Tristan Tiburcio, conducted initial reactivity tests with Ni catalysts before discovering that TBAF was an effective additive in the reaction. The author's contributions include determining that TBAF was the active catalyst, optimization of the reaction conditions, preparation most of the substrates and carrying out mechanistic investigations. The contributions of each author are stated within the text or labelled in the schemes throughout the chapter. Most of the contents within this chapter were published in the journal *Organic Letters*.

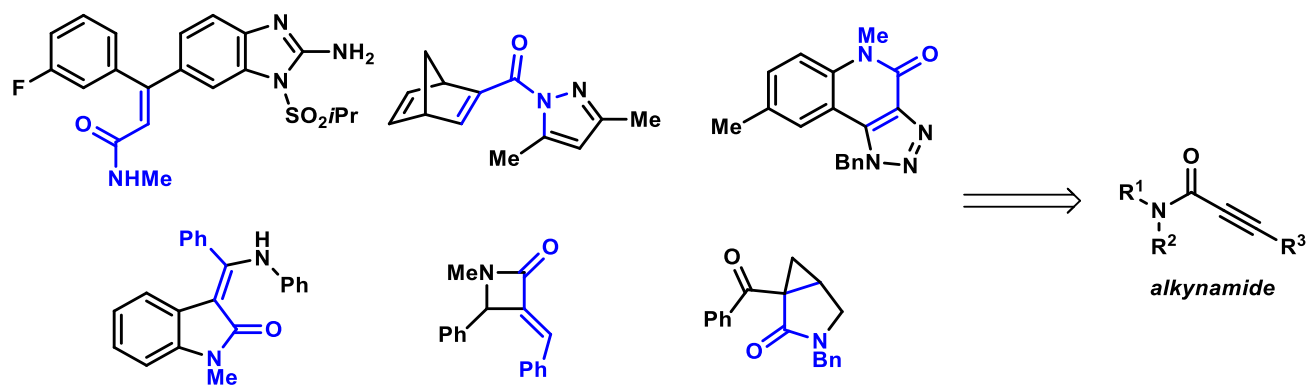
Citation: Cadwallader, D; Shevchuk, D.; Tiburcio, T. R.; Le, C. M., *Org. Lett.*, **2023**, 25, 7369-7373.<sup>1</sup>



## 3.2. Introduction

In the previous chapter, we developed an efficient method for the synthesis of carbamoyl fluorides.

The next step in this research was exploring ways to transform them into useful amides. The first class of amides we targeted was the alkynamide, an  $\alpha,\beta$ -unsaturated carbonyl compound that has gained significant attention in synthetic and medicinal chemistry (Scheme 3.1).<sup>2,3</sup> Examples of some alkynamide transformations include intermolecular hydroarylation,<sup>4</sup> cycloadditions,<sup>5</sup> click-type cascade reactions,<sup>6-8</sup> and cyclizations.<sup>9-16</sup>



Scheme 3. 1: Selected Scaffolds Accessible from Alkynamides

Alkynamides have also gained traction as a pharmacophore in medicinal chemistry. Such compounds have been exploited for targeting enzymes associated with a variety of diseases (Figure 3.1).<sup>17-19</sup>

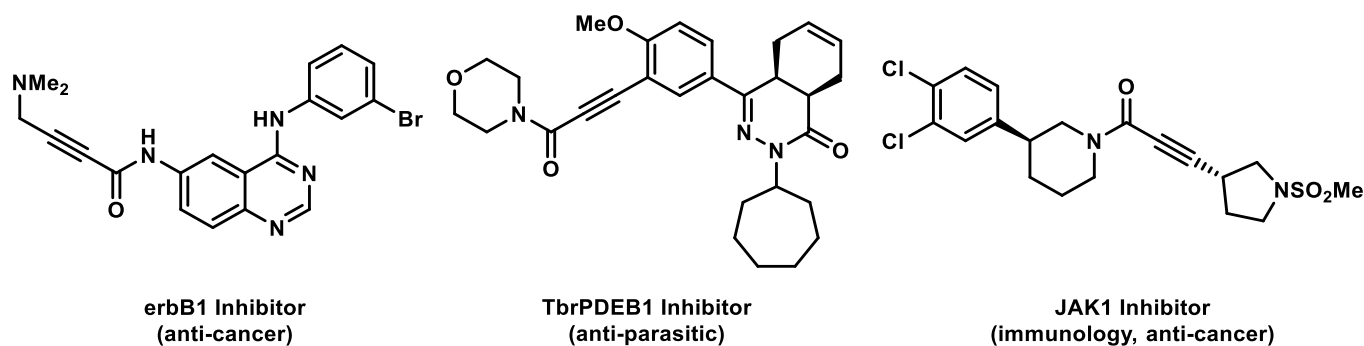


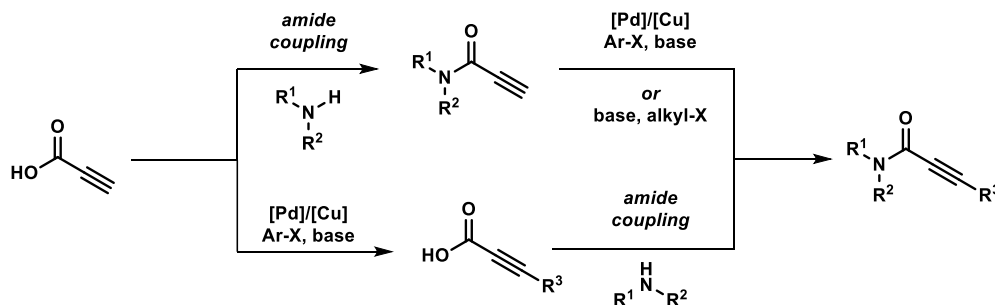
Figure 3. 1: Alkynamide-Based Hit Compounds in Medicinal Chemistry

After analyzing the literature, we determined that a metal-free cross-coupling of carbamoyl fluorides and alkynyl nucleophiles would be a beneficial addition to the reaction space for alkyne synthesis. The introductory section of this chapter will review methods for alkyne synthesis and disclose our development of a fluoride-catalyzed alkynylation reaction of carbamoyl fluorides.

### 3.2.1 Synthesis of Alkynamides

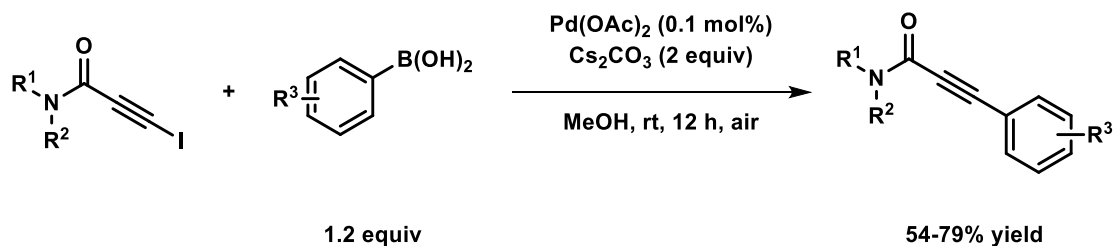
The most common route to access alkyne amides involves the use of traditional amide coupling reagents to directly react carboxylic acids and amines. Aside from the typical pitfalls of this method (i.e., purification issues and stoichiometric waste), the commercial availability of substituted alkynoic acids is limited compared to simple carboxylic acids. This limitation requires functionalization of unsubstituted propionic acid derivatives before or after the key amidation step (Scheme 3.2). This functionalization can be achieved via Sonogashira cross-coupling of the terminal alkyne with an aryl halide, or by deprotonation of the alkyne with a strong base followed by an electrophilic quench. Sonogashira coupling is typically quite robust and numerous reports

of alkynoic acid arylations have been reported.<sup>20</sup> With either approach, the synthetic route to the targeted amide is typically two or more steps from commercial materials.



Scheme 3. 2: Typical Synthesis of Internal Alkynamides

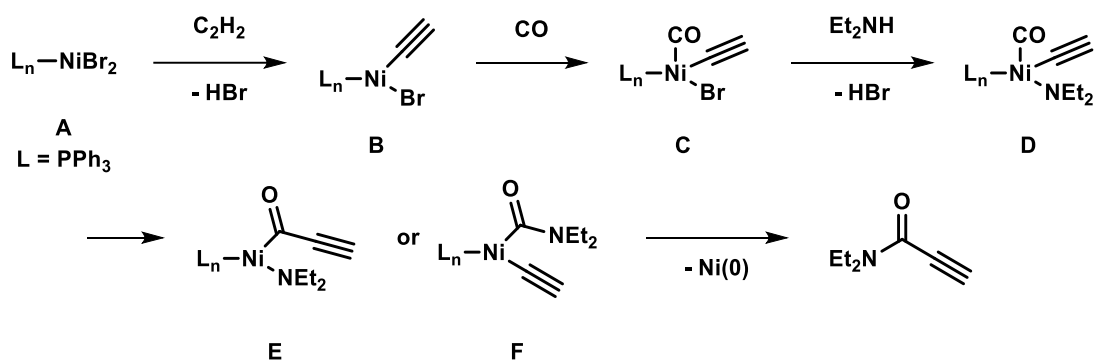
When preparing various alkynamides, Li and co-workers observed that terminal propynamide derivatives only provided moderate yields in the Sonogashira coupling.<sup>21</sup> This is due to the electron deficient nature of the alkyne fragment, making it a poor nucleophile in the coupling reaction. To overcome this inherent reactivity challenge, the authors developed a unique approach using an iodoalkyne in a Pd-catalyzed Suzuki-Miyaura cross-coupling reaction (Scheme 3.3).<sup>21</sup> This umpolung approach, where the alkyne fragment is now the electrophile and an arylboronic acid serves as the nucleophile, led to relatively good yields at room temperature with short reaction times. While this strategy demonstrates promising reactivity, it requires the preparation of iodoalkynes, increasing the overall step count to access the desired products.



Scheme 3. 3: Suzuki-Miyaura Cross-Coupling of Iodoalkynamides and Arylboronic Acids

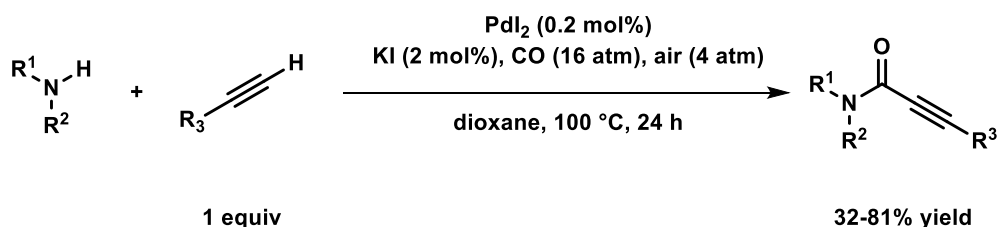
### 3.2.1.1 Alkynamides via Metal-Catalyzed Oxidative Aminocarbonylation

The transition metal-catalyzed aminocarbonylation of alkynes provides an alternative method to access alkynamides. This transformation involves a three-component coupling reaction, typically involving a terminal alkyne, an amine, and carbon monoxide (CO) gas, in the presence of an oxidant and a transition metal catalyst to obtain the amide product. This reaction was initially discovered by Hobert and Reigel, who found that treatment of stoichiometric NiBr<sub>2</sub> with diethylamine, acetylene and 1 bar of CO led to the formation of diethylpropynamide (Scheme 3.4).<sup>22</sup> The authors proposed that the Ni(II) **A** salt can undergo alkynylation with loss of HBr to provide **B**. Under these conditions, CO binds to **B** to access carbonyl complex **C**, which is followed by amine coordination and loss of another equivalent of HBr. From this intermediate **D**, either the amido or acetylide ligand undergoes 1,1-migratory insertion with CO to provide **E** or **F**, and subsequent reductive elimination provides the amide product while forming Ni(0). Unfortunately, no catalytic turnover is observed, as Ni(II) is required for further reactivity and Ni(0) is prone to forming stable complexes in the presence of CO. This report represents a significant advance in the synthesis of alkynamides, enabling their preparation in a single step from commercial materials.



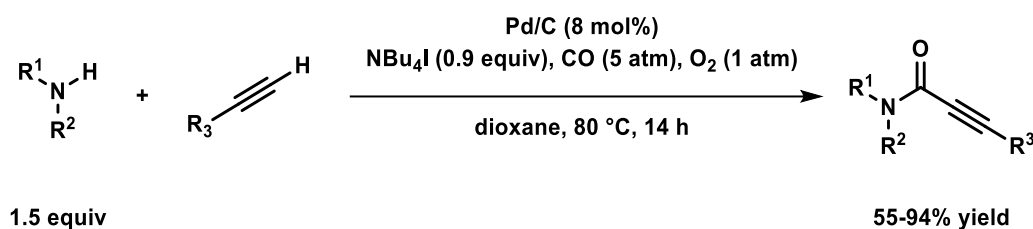
Scheme 3. 4: Ni-Mediated Aminocarbonylation of Acetylene

Years after Hoberg's seminal report, Gabriele and co-workers demonstrated that a Pd catalyst could be used for the aminocarbonylation of alkynes in the presence of air (Scheme 3.5).<sup>23</sup> In this case, the mechanism likely proceeds similarly to Hoberg's initial study but O<sub>2</sub> in air serves to oxidize the generated Pd(0) to catalytically active Pd(II) after the reductive elimination step, thus removing the need for stoichiometric metal in the reaction. This work expands the scope of aminocarbonylation to include substituted alkynes and a variety of dialkylamines. It is also extremely efficient, featuring a low Pd catalyst loading without the requirement of an ancillary ligand. However, the high pressures of multiple gases requires specialized equipment. Other examples of the Pd-catalyzed oxidative aminocarbonylation of alkynes have been reported, but they are limited to a single substrate<sup>24</sup> or require higher catalyst loadings and added ligands.<sup>25</sup>



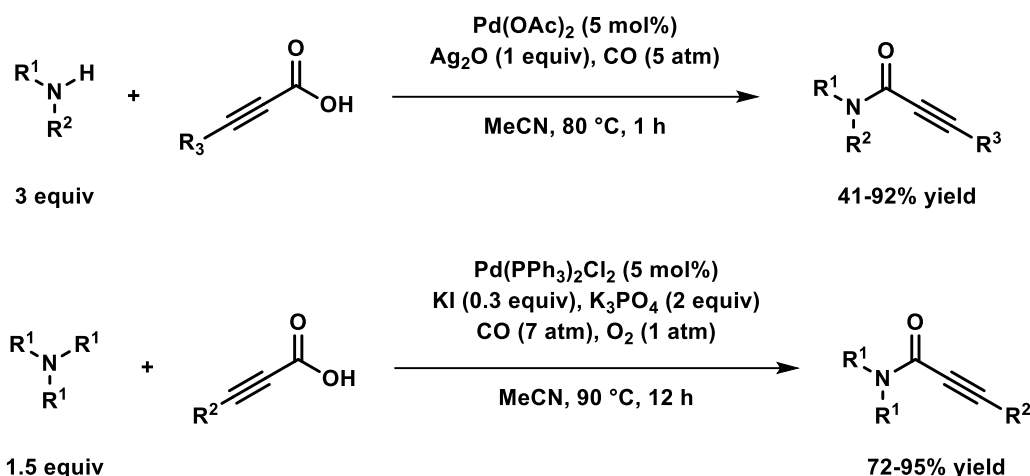
Scheme 3. 5: Pd-Catalyzed Oxidative Aminocarbonylation of Alkynes

A significant advance in aminocarbonylation for alkynamide synthesis was presented by Bhanage in 2012, where a heterogeneous Pd catalyst was used.<sup>26</sup> After screening several Pd sources, the authors found that Pd/C with tetrabutylammonium iodide (TBAI) as an additive led to the highest yields (Scheme 3.6). This method may be especially attractive in industrial settings due to the use of an inexpensive heterogeneous catalyst that can be filtered off and recycled after the reaction.



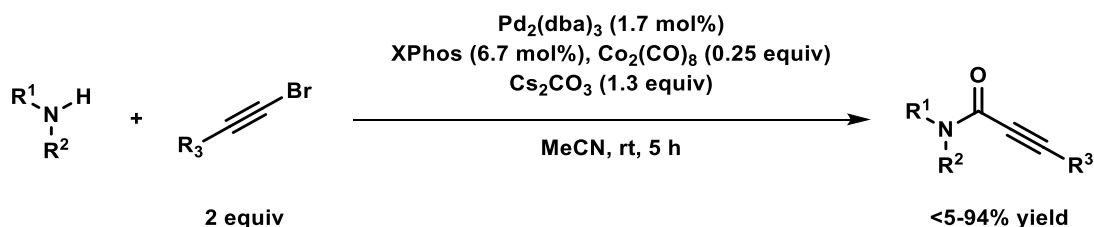
Scheme 3. 6: Aminocarbonylation of Alkynes with a Heterogeneous Pd Catalyst

Using a slightly different approach, Lee and co-workers reported a decarboxylative aminocarbonylation reaction of alkynoic acids (Scheme 3.7, top).<sup>27</sup> This method proceeds without the use of ancillary ligands but does require higher loadings of Pd than previous reports. It also differs in the use of Ag<sub>2</sub>O as the oxidant. The use of precious metal oxidants is more costly than air or O<sub>2</sub>, but its application allowed the reaction to be conducted at lower pressures of a single gas, which simplifies the reaction set-up. Later, the same group demonstrated that similar reactivity could be achieved in the dealkylation process using tertiary amines in the presence of base with O<sub>2</sub> as the oxidant (Scheme 3.7, bottom).<sup>28</sup> Both methods use substituted alkynoic acids which, as previously stated, require preparation from propiolic acid in an additional synthetic step.



Scheme 3. 7: Decarboxylative Aminocarbonylation of Alkynoic Acids with Secondary and Tertiary Amines

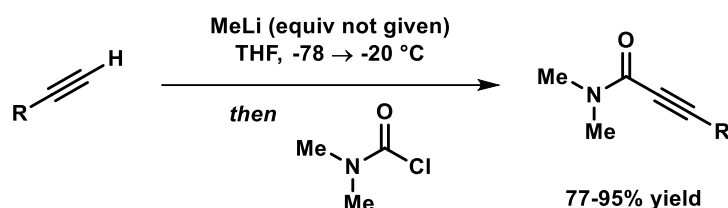
One major drawback of aminocarbonylation is the use of highly toxic CO. To avoid handling this dangerous gas, Yang, Wu, Wu and co-workers developed an alternative route to alkynamides using  $\text{Co}_2(\text{CO})_8$  as a solid surrogate for CO (Scheme 3.8).<sup>29</sup> This reaction also differs in the use of bromoalkynes instead of terminal alkynes, leading to an increase in the total number of steps. However, this slight change in starting material allows the catalytic cycle to begin at Pd(0), thus allowing the reaction to be conducted without oxidants. This work also represents the first example of aniline derivatives and primary amines undergoing aminocarbonylation.



Scheme 3. 8: Oxidant-Free Aminocarbonylation of Bromoalkynes with a CO Surrogate

### 3.2.1.2 Alkynamides via Coupling of Alkynes and Carbamoyl Halides

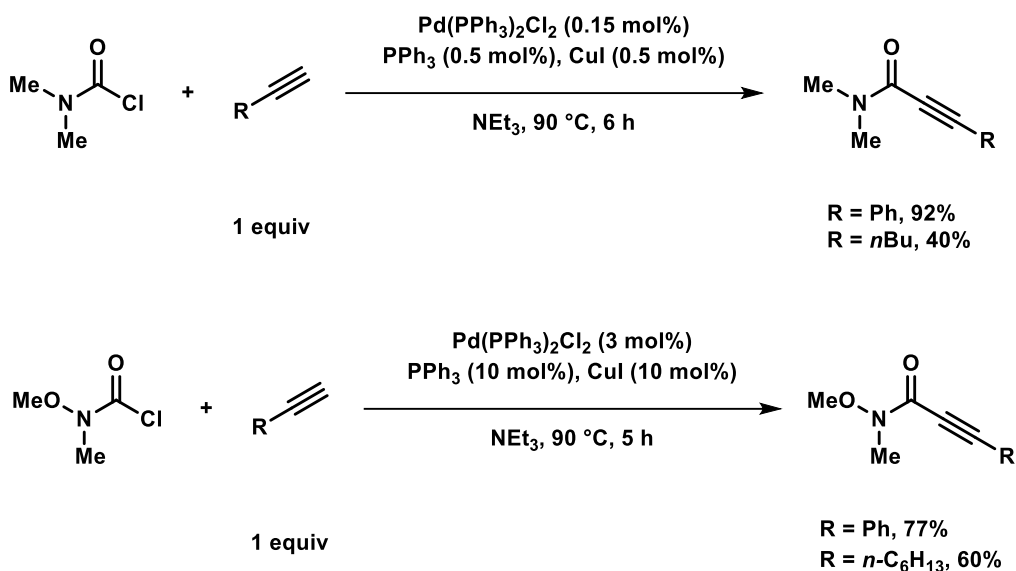
The carbamoyl halide functional group has found use in the preparation of alkynamides. As mentioned in Chapter 1, carbamoyl chlorides are common electrophiles for amidation reactions with carbanion nucleophiles. Earlier reports show that deprotonation of a terminal alkyne with MeLi and treatment with dimethyl carbamoyl chloride provides the corresponding alkynamide (Scheme 3.9).<sup>30</sup> However, this deprotonation requires the use of a relatively strong base, leading to limited functional group tolerance.



Scheme 3. 9: Alkynylation of Carbamoyl Chlorides with in-situ Formed Li-Acetylide

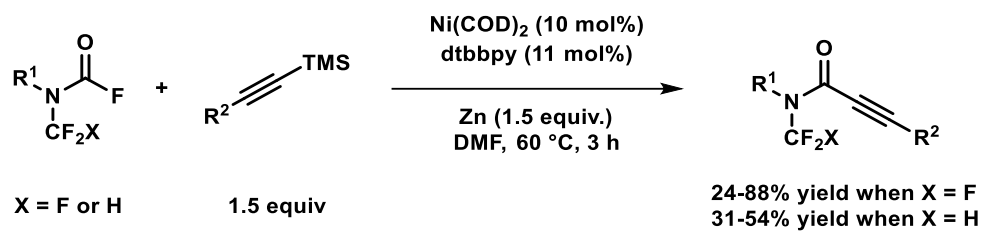
During early studies expanding the scope of what would be colloquially known as the Sonogashira coupling, Hagihara and co-workers applied Pd/Cu co-catalyzed conditions to *N,N*-dimethyl carbamoyl chloride (Scheme 3.10, top). In the same report, the authors found that alkynylation of acyl chlorides proceeded smoothly at room temperature, but carbamoyl chlorides required elevated temperatures. Decades later, Ito adapted this procedure to *N*-methoxy-*N*-methylcarbamoyl chloride to access Weinreb-type alkynamides (Scheme 3.10, bottom).<sup>31</sup> While these products are highly versatile for further derivatization, the reaction also required elevated temperatures and the authors presented only two examples.





Scheme 3. 10: Sonogashira Cross-Coupling Reaction of Carbamoyl Chlorides

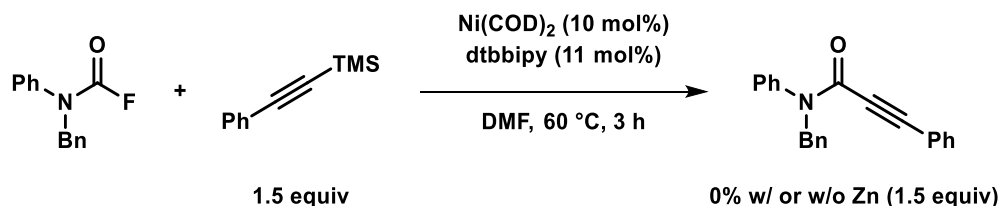
In 2021, Schoenebeck and co-workers expanded this Sonogashira-type chemistry to *N*-trifluoromethyl carbamoyl fluorides under Ni catalysis (Scheme 3.11, X = F).<sup>32</sup> Aside from the Ni catalyst, this method also differs from previous reports in the use of alkynyl silane nucleophiles. The pairing of these coupling partners offers unique reactivity, where after oxidative addition of the carbamoyl fluoride, transmetalation of the alkynyl silane proceeds without a base or additive. This is due to the thermodynamically favourable formation of silyl fluoride by-products. This reaction provides entry to previously unreported *N*-trifluoromethyl alkynamides that can be transformed into a variety of *N*-CF<sub>3</sub>-containing scaffolds. Although the procedure does not require base, the addition of stoichiometric Zn powder is required to suppress undesired homocoupling of the alkynyl silane. The same group was also applied these conditions to *N*-difluoromethyl carbamoyl fluorides (Scheme 3.11, X = H),<sup>33</sup> increasing the diversity of chemically accessible alkynamides and downstream derivatives.



Scheme 3. 11: Ni-Catalyzed Alkynylation of *N*-fluoroalkyl Carbamoyl Fluorides

### 3.3 Motivation and Research Plans

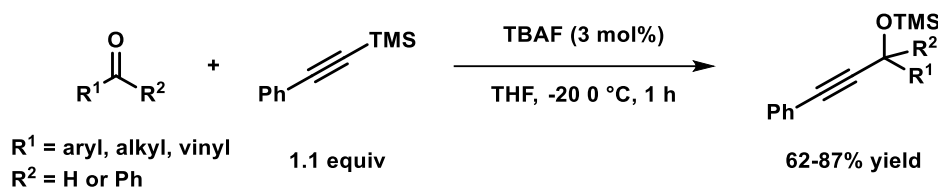
As reviewed in earlier chapters of this dissertation, there are significant reactivity differences between simple carbamoyl fluorides and their *N*-fluoroalkyl analogs. For this reason, we were inspired to adapt Schoenebeck's report of carbamoyl fluoride alkynylation to provide a more general substrate scope. After subjecting *N*-benzyl-*N*-phenyl carbamoyl fluoride to the Ni-catalyzed alkynylation conditions, no alkynamide was formed, thus underscoring the differences in reactivity between *N*-alkyl and *N*-CF<sub>3</sub> carbamoyl fluorides (Scheme 3.12). This result inspired us to explore alternative methods to access alkynamides from these coupling partners, specifically under metal-free conditions, as the thermodynamic driving force of Si-F bond formation alone may be sufficient to drive the cross-coupling reaction.



Scheme 3. 12: Attempted Ni-Catalyzed Alkynylation of Carbamoyl Fluorides

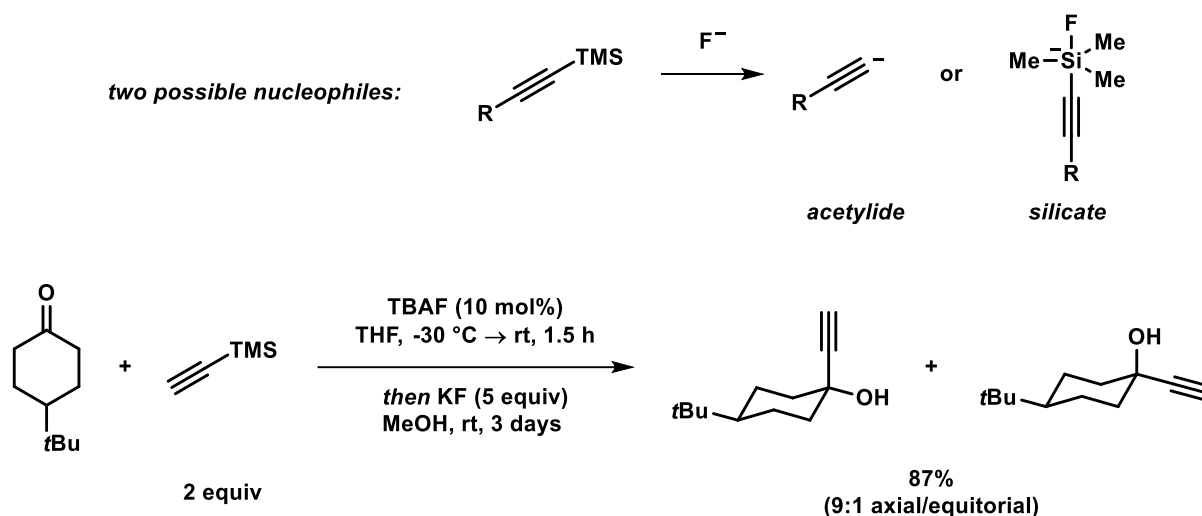
Regarding alkynyl silanes, there are several examples reporting their use as nucleophiles in the presence of fluoride initiators. In 1976, Kuwajima and co-workers developed a fluoride-catalyzed alkynylation of aldehydes and ketones with phenyl(trimethylsilyl)acetylene and TBAF (Scheme 3.13).<sup>34</sup> This method provided access to several silylated secondary and tertiary alcohols in moderate to excellent yields without the use of strong base to access the acetylide intermediate. While report only features one alkynyl silane and a small number of carbonyl compounds, this method offers a unique alternative to using strong bases that may limit functional group tolerance

(for example, by deprotonating ketones with acidic  $\alpha$ -protons). It should be noted that a later report by Verkade and co-workers expanded the scope of alkynyl silane nucleophiles in this reaction, although their conditions are similar to the original reports.<sup>35</sup>



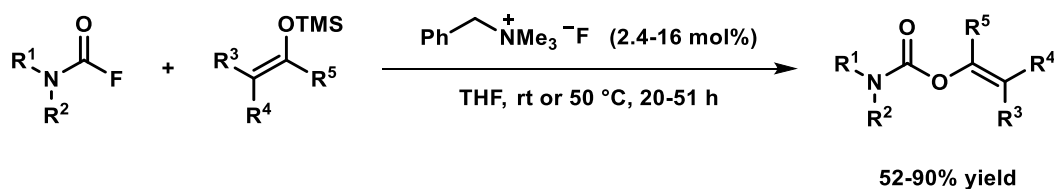
Scheme 3. 13: Fluoride-Catalyzed Alkyne Addition to Carbonyl Compounds

Several years later, the same group conducted a mechanistic study on the related reaction of trimethylsilyl acetylene to determine the nature of the alkynyl nucleophile: an ammonium acetylide versus a pentavalent fluorosilicate intermediate that does not undergo immediate desilylation (Figure 3.14, top).<sup>36</sup> To distinguish between the two possibilities, the authors suggested that the use of 4-tertbutylcyclohexanone could provide mechanistic insight via the distribution of diastereomeric products. In detail, they proposed that if the small ammonium acetylide is present, axial attack should be prominent. However, the larger silicate species should undergo preferential equatorial attack. After subjecting the ketone and alkynyl silane to the reaction conditions, the resulting cyclohexanol was obtained in 87% yield after subsequent desilylation as a 9:1 mixture of diastereomers (Scheme 3.14, bottom). This result indicates that axial attack is favoured, suggesting that the ammonium acetylide species is likely the active nucleophile.



Scheme 3. 14: Fluoride-Catalyzed Addition of an Alkyne to a Chiral Ketone

In terms of fluoride-catalyzed reactions of carbamoyl fluorides, a sole report from Olofson and co-workers uses benzyltrimethylammonium fluoride (BTAF) and silyl enol ethers to prepare enol carbamates (Scheme 3.15).<sup>37</sup> This method follows the template of Schoenebeck's alkynylation reaction, where the silylated nucleophile is necessary to drive the reaction forward via Si-F bond formation. In this report, the fluoride catalyst is used to initiate the reaction by generating the active nucleophilic enolate, likely via desilylation to form a naked anion. Nucleophilic acyl substitution of the carbamoyl fluoride forms the final product and regenerates the fluoride catalyst. These conditions were applied to only a handful of carbamoyl fluorides, with the focus of the report being on carbonate formation from fluoroformates (ROCOF).



Scheme 3. 15: Fluoride-Catalyzed Synthesis of Enol Carbamates from Carbamoyl Fluorides and Silyl Enol Ethers

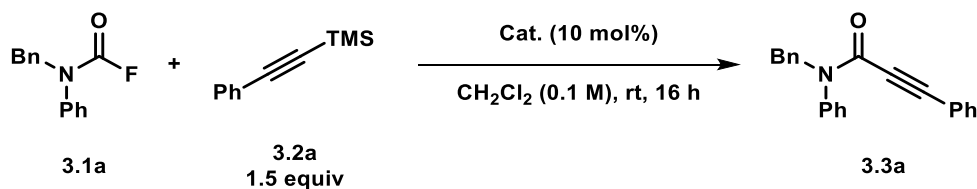
We suspect that by combining the concepts of the methods listed above, alkynamides should be accessible from carbamoyl fluorides and alkynyl silanes using a simple fluoride catalyst. Like Kuwajima's reports, fluoride should effectively desilylate the alkyne to provide an acetylide nucleophile. This intermediate can then attack the carbamoyl fluoride to provide the alkynamide product, releasing the fluoride leaving group to continue the catalytic cycle as in Olofson's reaction. The remainder of this chapter describes our approach to fluoride-catalyzed alkynylation of carbamoyl fluorides with alkynyl silanes using TBAF as a catalyst.

## 3.4 Results and Discussion

### 3.4.1. Reaction Optimization

To initiate this project, carbamoyl fluoride **3.1a** and phenyl(trimethylsilyl)acetylene **3.2a** were treated with 10 mol% of a fluoride catalyst in dichloromethane at room temperature for 16 hours (Table 3.1). Initially, TBAF was used, leading to an excellent 84% yield of alkynamide **3.3a** (Entry 1). Switching the fluoride source to tetrabutylammonium triphenyldifluorosilicate (TBAT) provided **3.3a** in 70% yield, offering comparable reactivity to TBAF (Entry 2). Interestingly, the use of metal fluoride salts resulted in no product formation (Entry 3-7). While this lack of reactivity may be due to the low solubility of these salts in dichloromethane, it is worthwhile to note that the use of KF in the presence of 18-crown-6 in a coordinating solvent (1,4-dioxane) at elevated temperature still did not yield **3.3a** (Entry 5). Ammonium salts of other halides and KO $t$ Bu also proved to be ineffective in this reaction (Entry 8-10). Lewis acids, such as BF<sub>3</sub>·OEt<sub>2</sub> and Ph<sub>3</sub>CBF<sub>4</sub>, as well as the Brønsted acid HBF<sub>4</sub>·OEt<sub>2</sub> were also tested under the reaction conditions but they were all catalytically inactive in this reaction (Entry 11-13). These catalysts were screened to probe alternate fluoride delivery mechanisms, similar to our group's previous report on the Lewis acid-catalyzed activation of carbamoyl fluorides.<sup>38</sup>

**Table 3.1:** Catalyst Screen

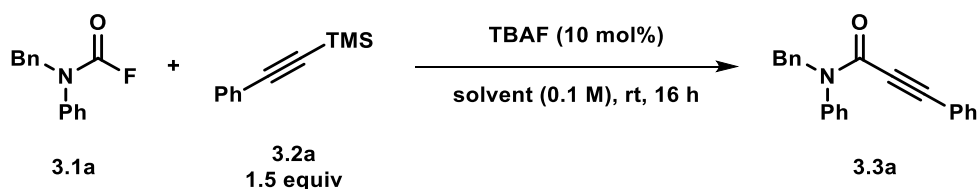


| Entry | Catalyst | Conversion (%) | <sup>1</sup> H NMR Yield (%) |
|-------|----------|----------------|------------------------------|
|-------|----------|----------------|------------------------------|

|    |                                     |    |    |
|----|-------------------------------------|----|----|
| 1  | TBAF (1 M in THF)                   | 91 | 84 |
| 2  | TBAT                                | 82 | 70 |
| 3  | NaF <sup>a</sup>                    | 0  | 0  |
| 4  | KF/18-crown-6                       | 6  | 0  |
| 5  | KF/18-crown-6 (50 °C in dioxane)    | 3  | 0  |
| 6  | CsF <sup>a</sup>                    | 0  | 0  |
| 7  | AgF                                 | 0  | 0  |
| 8  | TBAC                                | 0  | 0  |
| 9  | TBAB                                | 0  | 0  |
| 10 | KO <sup>t</sup> Bu                  | 2  | 0  |
| 11 | BF <sub>3</sub> •Et <sub>2</sub> O  | 3  | 0  |
| 12 | HBf <sub>4</sub> •Et <sub>2</sub> O | 6  | 0  |
| 13 | Ph <sub>3</sub> CBF <sub>4</sub>    | 0  | 0  |

Next, the effect of solvent on the efficiency of alkynamide formation was explored. The use of dioxane with TBAF as the catalyst provided **3.3a** in a moderate 64% yield (Table 3.2, Entry 2). However, this promising reactivity did not translate to other coordinating solvents, as THF and MeCN both gave less than 10% yield of **3.3a** (Entry 3, 4). The use of non-polar PhMe led to the formation of **3.3a** in 98% yield (Entry 5), making it our preferred solvent choice for continued optimization.

**Table 3.2:** Solvent Screen



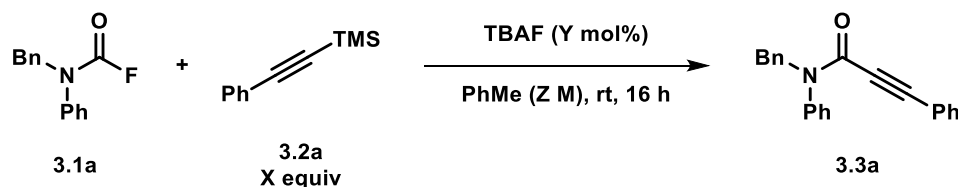
| Entry | Solvent | Conversion (%) | <sup>1</sup> H NMR Yield (%) |
|-------|---------|----------------|------------------------------|
|-------|---------|----------------|------------------------------|



|   |                                 |    |    |
|---|---------------------------------|----|----|
| 1 | CH <sub>2</sub> Cl <sub>2</sub> | 91 | 84 |
| 2 | 1,4-dioxane                     | 79 | 66 |
| 3 | THF                             | 8  | 2  |
| 4 | MeCN                            | 23 | 6  |
| 5 | PhMe                            | 98 | 98 |

We then focused our efforts on optimizing the loading of the TBAF catalyst and alkynyl silane, as well as the concentration of these reagents relative to carbamoyl fluoride **3.1a**. We observed that increasing the loading of **3.2a** to two equivalents led to a significant decrease in the yield (Table 3.3, Entry 2). The reaction remained nearly as efficient when the loading of TBAF was increased to 20 mol% (Entry 3). When the concentration of the reaction was doubled, a slight drop in yield was observed (Entry 4). The amount of alkynyl silane was then screened at this concentration (Entry 5-9) and the optimal loading was found to be 1.6 equivalents (Entry 7), with more or less silane leading to a drop-off in reaction performance. Holding the equivalents of **3.2a** at 1.6, the catalyst loading was screened. We found that high yields could be maintained down to 2 mol% of TBAF (Entry 13). Finally, we found that near-quantitative yield (98%) could be retained at 2 mol% TBAF when the concentration was increased to 0.4 M (Entry 16). This yield was maintained when the conditions from Entry 16 were repeated at 0 °C, and the yield only drops to 91% when the reaction is done under ambient conditions open to air (Entry 17).

**Table S3.** Equivalence, Catalyst Loading and Concentration Screen

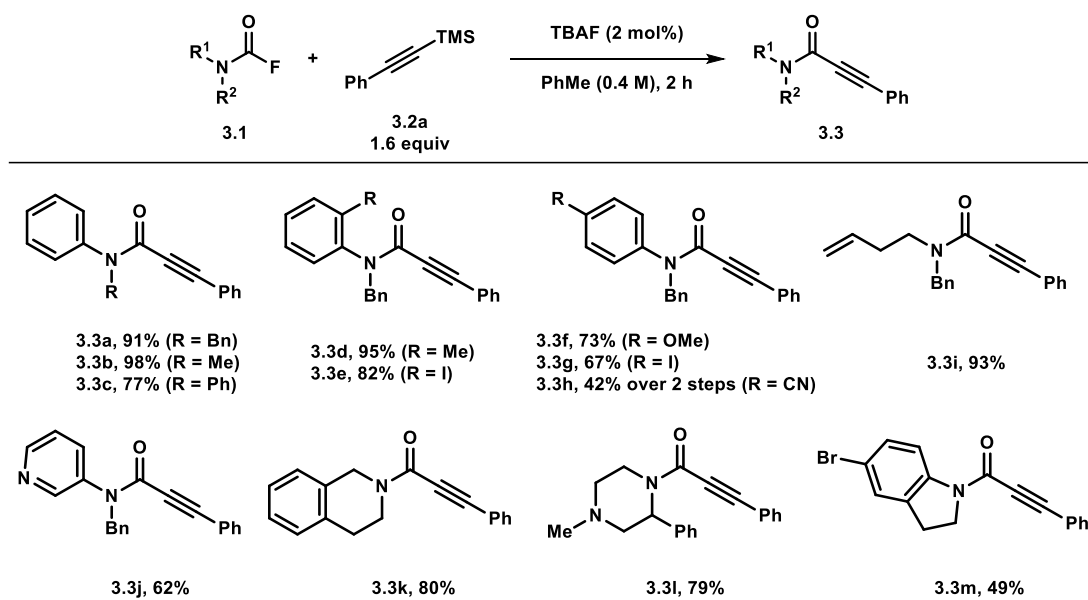


| Entry              | X (equiv) | Y (mol %) | Z (M) | Conversion (%) | <sup>1</sup> H NMR Yield (%) |
|--------------------|-----------|-----------|-------|----------------|------------------------------|
| 1                  | 1.5       | 10        | 0.1   | 98             | 98                           |
| 2                  | 2.0       | 10        | 0.1   | 97             | 61                           |
| 3                  | 1.5       | 20        | 0.1   | 94             | 93                           |
| 4                  | 1.5       | 10        | 0.2   | 99             | 96                           |
| 5                  | 2.0       | 10        | 0.2   | 100            | 75                           |
| 6                  | 1.8       | 10        | 0.2   | 100            | 71                           |
| 7                  | 1.6       | 10        | 0.2   | 100            | 99                           |
| 8                  | 1.4       | 10        | 0.2   | 93             | 89                           |
| 9                  | 1.2       | 10        | 0.2   | 87             | 82                           |
| 10                 | 1.6       | 5         | 0.2   | 100            | 99                           |
| 11                 | 1.6       | 4         | 0.2   | 100            | 95                           |
| 12                 | 1.6       | 3         | 0.2   | 100            | 97                           |
| 13                 | 1.6       | 2         | 0.2   | 100            | 96                           |
| 14                 | 1.6       | 1         | 0.2   | 83             | 83                           |
| 15                 | 1.6       | 5         | 0.4   | 100            | 93                           |
| 16 (rt or 0 °C)    | 1.6       | 2         | 0.4   | 99             | 98                           |
| 17 (under air, rt) | 1.6       | 2         | 0.4   | 100            | 91                           |

### 3.4.2. Substrate Scope

Taking the best conditions from our optimization (1.6 equiv **3.2a**, 2 mol% TBAF, 0.4 M in PhMe), we began exploring the scope of carbamoyl fluorides in the reaction (Scheme 3.16). The model substrate **3.3a** was isolated in 90% yield and the reaction could be conducted on a one-gram scale of carbamoyl fluoride (scale-up was done by Dmytro Shevchuk). Replacing the *N*-benzyl substituent with *N*-methyl (**3.3b**) or *N*-phenyl (**3.3c**) did not significantly hinder the reaction. To probe for steric effects on the carbamoyl fluoride, *ortho*-methyl- and *ortho*-iodoaniline-derived carbamoyl fluorides were tested, resulting in 95% and 82% yields of **3.3d** and **3.3e**, respectively. The use of carbamoyl fluorides bearing electron rich or neutral *N*-aryl groups led to moderate

yields (**3.3f**, **3.3g**), likely due to their reduced electrophilicity. A carbamoyl fluoride bearing an electron withdrawing *para*-benzonitrile was used in the reaction, despite its instability to column chromatography (see Chapter 2). The parent secondary amine was subjected to the typical conditions for carbamoyl fluoride synthesis and the polar by-products were removed by rapid filtration through a short plug of silica gel. After the solvent was removed, the crude residue was subjected to the fluoride-catalyzed conditions with 10 mol% TBAF, leading to an isolated yield of nitrile-containing alkynamide **3.3h**.

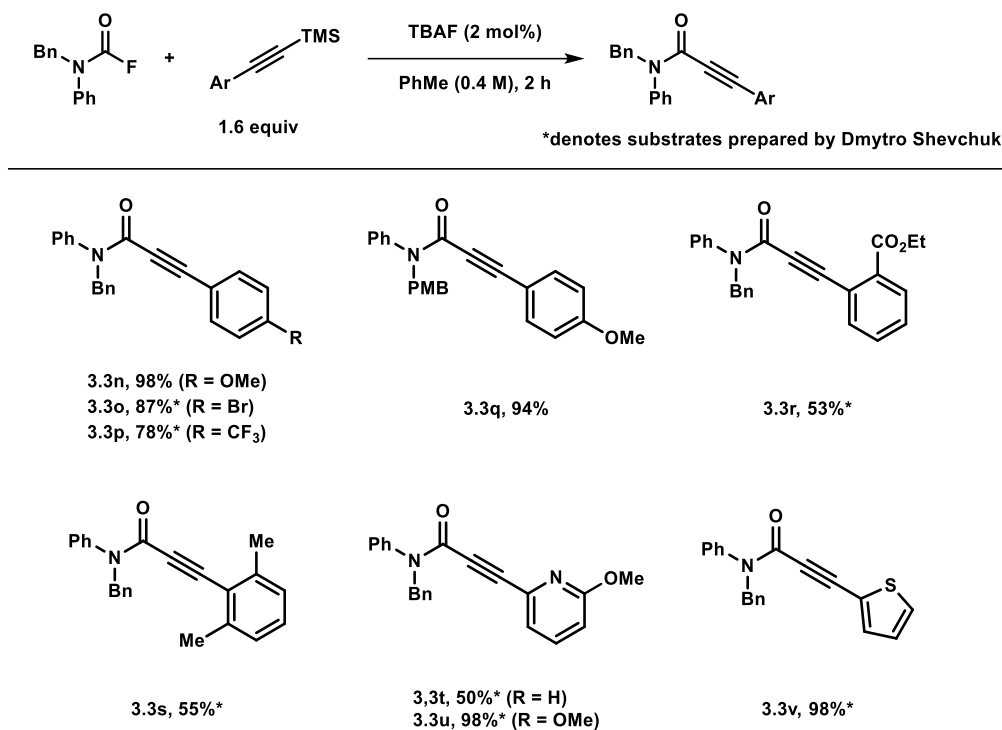


Scheme 3. 16: Scope of Carbamoyl Fluorides

Alkene-tethered alkynamide **3.3i** could be obtained under our conditions and this substrate is of particular interest as it has been used in Au-catalyzed reactions to obtain complex strained bicyclic compounds.<sup>16</sup> Notably, this substrate would likely undergo competitive cyclization in a transition metal-catalyzed reaction of carbamoyl halides, demonstrating an advantage of our fluoride-catalyzed method. Heterocyclic functionalities were also tolerated in the reaction, with pyridyl alkynamide **3.3j** obtained in 62% yield. Isoquinolines, piperazines and indolines were also

competent under the standard conditions providing the corresponding alkynamides in moderate to good yields (**3.3k-m**).

Next, the scope of alkynyl silanes was explored primarily by undergraduate intern, Dmytro Shevchuk (Scheme 3.17). An alkyne bearing an electron donating *para*-methoxy group worked well, providing **3.3n** in 98% yield. An alkyne containing an aryl bromide was also well tolerated (**3.3o**, 87%), but a drop in yield was observed when *para*-trifluoromethylphenyl silyl acetylene was used (**3.3p**, 78%). The carbamoyl fluoride fragment was also modified and paired with this nucleophile, giving access to *N*-*para*-methoxybenzyl alkynamide **3.3q**. In theory, this product could provide entry to a secondary alkynamide, but the literature precedent for alkynamide PMB deprotection is limited and typical procedures were ineffective in our hands. Unfortunately, *ortho*-arylalkynyl silanes led to much lower yields in the reaction (**3.3r**, **3.3s**), indicating steric constraints on the nucleophilic fragment. Heterocycles on the alkyne portion could also be applied, with pyridines **3.3t** and **3.3u** as well as thiophene **3.3v** accessible using our method. While **3.3t** was obtained in modest yield, the *ortho*-substituted pyridyl alkynamide **3.3u** was formed in nearly quantitative yield. This result may suggest that the nucleophilic pyridine may hinder the reaction and blocking the nitrogen with an *ortho* substituent can restore reactivity. Overall, a variety of carbamoyl fluoride and alkynyl silanes were effective under our conditions.

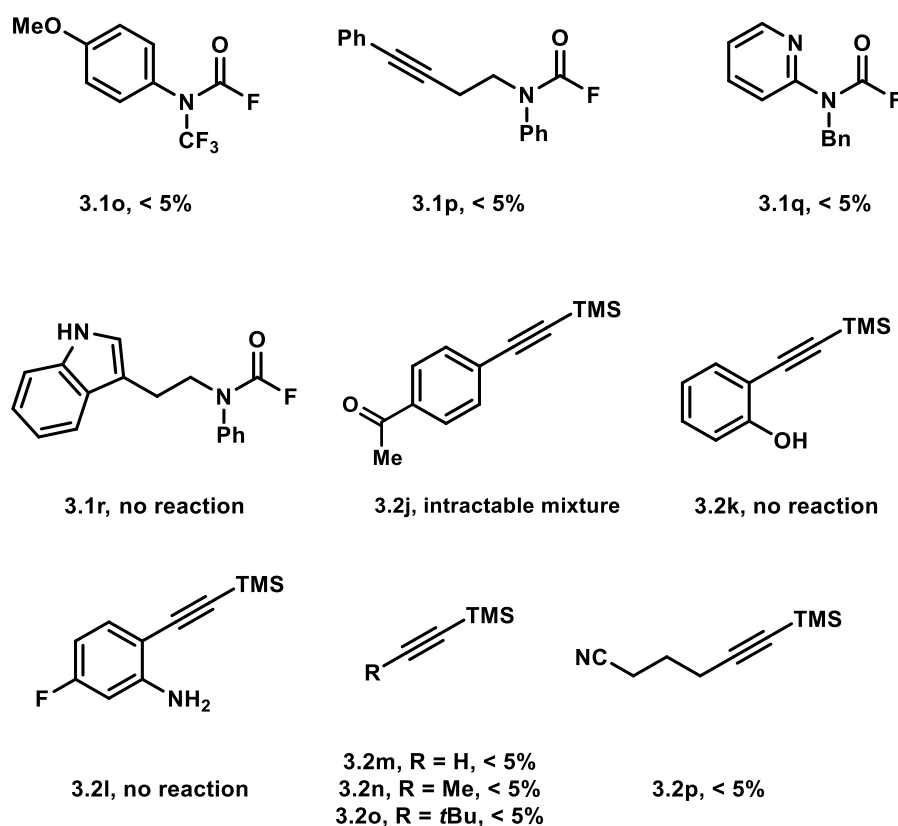


Scheme 3. 17: Scope of Alkynyl Silanes

### 3.4.3. Unsuccessful Substrates

Throughout our study of the substrate scope, we determined several compounds that either did not react or produced less than 5% of the desired alkynamide (Figure 3.18). We subjected one of Schoenebeck's *N*-trifluoromethyl carbamoyl fluorides **3.1o** to our reaction conditions and extremely low conversion was observed. Surprisingly, alkyne-tethered carbamoyl fluoride **3.1p** and *N*-2-pyridyl carbamoyl fluoride **3.1q** both demonstrated low reactivity. To investigate the failing of **3.1p**, the standard reaction of **3.1a** and **3.2a** with 1.6 equivalents of 1-phenyl-1-hexyne. This did not lead to a decrease in yield, indicating that the presence of an internal alkyne was not problematic and that **3.1p** suffers from an unknown reactivity issue. Several carbamoyl fluorides and alkynyl silanes containing relatively acidic protons also failed to produce their corresponding alkynamides (**3.1r**, **3.2j-l**). This was an anticipated limitation, assuming that the active nucleophile

is an ammonium acetylide, such as in Kuwajima's reports,<sup>36</sup> which can deprotonate acidic C-H bonds. Finally, the reaction failed to produce sufficient amounts of alkynamide when unsubstituted or alkyl-substituted alkynyl silanes were used (**3.2m-p**). The origin of this limitation is not yet known; however, these results are consistent with other Lewis base-catalyzed alkynylation reactions<sup>39</sup> where there is a sharp cutoff in reactivity relating to the  $pK_a$  of the parent acetylide.<sup>40</sup>



Scheme 3. 18: Unsuccessful Substrates in Fluoride-Catalyzed Alkynylation of Carbamoyl Fluorides

#### 3.4.4. Complementary Regioselectivity in a Sonogashira Reaction

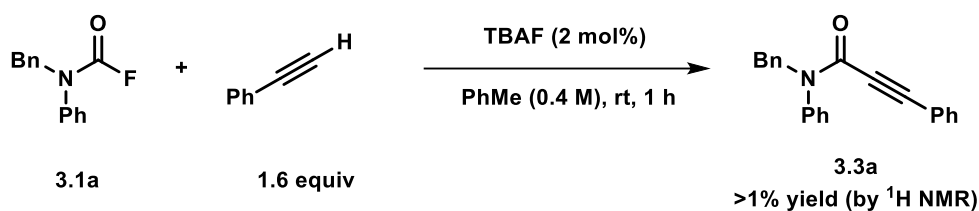
As mentioned in section 3.2.1.2, the Sonogashira reaction of carbamoyl chlorides has been known for several decades and requires elevated temperatures to proceed. This reaction is likely more

challenging with carbamoyl fluorides due to slower oxidative addition with stronger C–F bonds, highlighting an advantage to our TBAF-catalyzed method. When carbamoyl fluoride **3.1a** was subjected to the standard Pd/Cu co-catalyzed Sonogashira conditions, complete recovery of the starting material was observed (Scheme 3.19, top), thus substantiating our claim. However, under similar conditions with an aryl iodide-containing carbamoyl fluoride **3.1g** and 1-hexyne, exclusive alkynylation of the aryl iodide occurs providing **3.5** in 90% yield, with 6% of an alkynylated secondary amine **3.7** present in the crude mixture. Repeating this experiment on the analogous carbamoyl chloride provided similar results, and alkynyl carbamoyl chloride **3.6** was isolated in 94% yield. These results demonstrate the stability of carbamoyl halides to certain conditions, allowing for selective, subsequent alkynylation procedures to be conducted if desired.

Scheme 3. 19: Pd/Cu Co-Catalyzed Sonogashira Coupling of Aryl Iodide-Containing Carbamoyl Halides

### 3.4.5. Comparison to Carbamoyl Chlorides and Mechanistic Insights

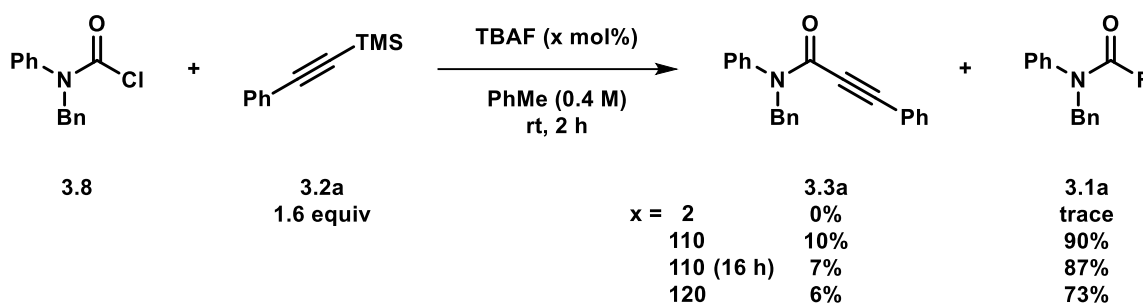
To better understand the reaction, a variety of control experiments and mechanistic studies were done. Initially, we sought to confirm the importance of using fluoride electrophiles and silyl nucleophiles in the reaction. When the reaction was carried out using phenylacetylene instead of **3.2a**, only trace amounts (<1%) of alkynamide **3.3a** were observed by  $^1\text{H}$  NMR spectroscopy (Scheme 3.20). This result confirms the need for an alkynyl silane in the reaction.



Scheme 3. 20: Control Experiment with Phenylacetylene

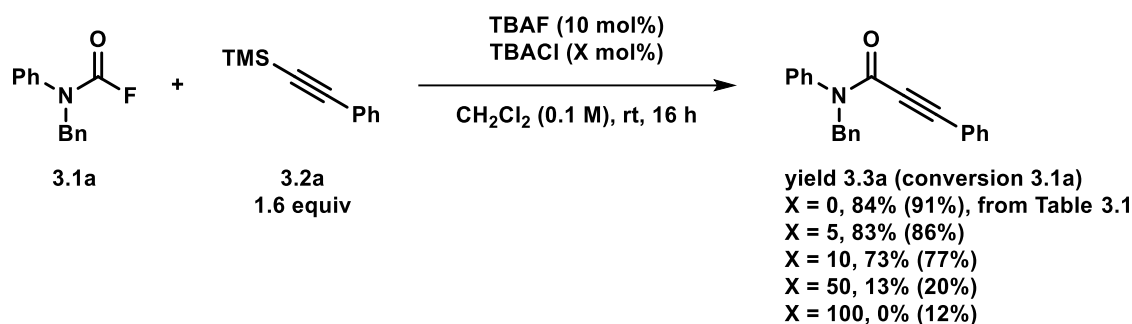
Next, we tested the role of the carbamoyl electrophile in the reaction. When carbamoyl chloride **3.8** was used in the reaction, **3.3a** was not formed and trace amounts of carbamoyl fluoride **3.1a** was observed by  $^{19}\text{F}$  NMR spectroscopy (Scheme 3.21). When the loading of TBAF was increased to 1.1 equivalents, only 10% of alkynamide **3.3a** was observed, with carbamoyl fluoride representing the remaining mass balance. The ratio of **3.3a** to **3.1a** remained essentially the same even with higher loadings of TBAF or letting the reaction proceed for 16 hours.





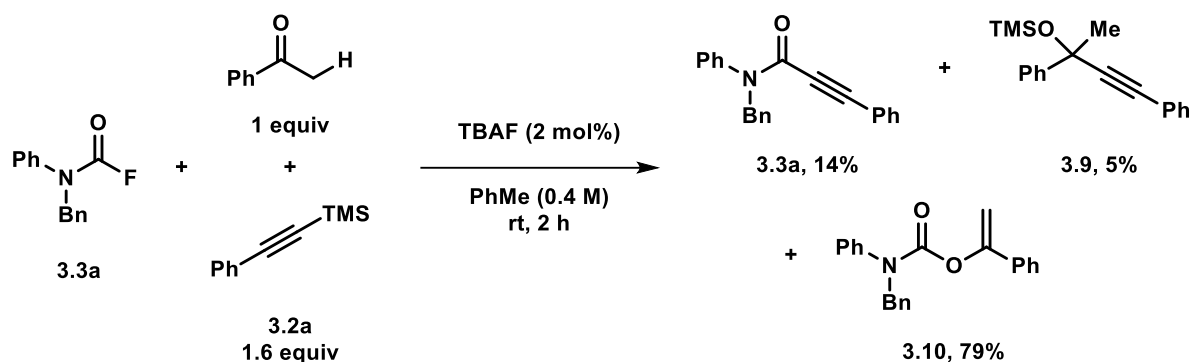
Scheme 3. 21: Attempts at Fluoride-Catalyzed Alkynylation of Carbamoyl Chlorides

In theory, it should be possible to convert the in situ generated carbamoyl fluoride to the alkynamide product with excess fluoride salts. However, we speculate that the lack of reactivity of **3.8** could be due to formation of stoichiometric chloride salts. To explore the effect of chloride, we added various amounts of TBAC to the standard reaction between **3.1a** and **3.2a**. While chloride was clearly detrimental to the reaction yield, TBAC is sparingly soluble in PhMe, leading to a non-linear trend between the TBAC loading and yield of **3.3a**. To avoid this issue, we repeated the poisoning experiment using dichloromethane as solvent (Table 3.1, Entry 1). This experiment undoubtedly demonstrates the negative effects of excess chloride in the reaction (Scheme 3.22). When more than 5 mol% TBAC was added, the yield begins to drop dramatically, with no alkynamide observed with one equivalent of TBAC. We suspect that when chloride attacks the Si atom of **3.2a**, the resulting chlorosilicate species is not sufficiently activated towards electrophilic attack, and thus, not capable of closing the catalytic cycle.



Scheme 3. 22: Chloride Poisoning Experiments

In the fluoride-catalyzed addition of alkynyl silanes to ketones, Kuwajima and co-workers suggested that alkynyl silanes react with TBAF to form ammonium acetylide in-situ by observing the stereochemical outcome of the reaction.<sup>36</sup> Based on the intolerance of our method to substrates bearing acidic protons, we suspect that our transformation likely proceeds by a similar mechanism (i.e., formation of an acetylide anion). To support this hypothesis, we further investigated the outcome of the “failed” reaction of methyl ketone-containing alkynyl silane **3.2j** by designing a competition experiment with 1.0 equiv of acetophenone as an additive (Scheme 3.23). By quantitative <sup>1</sup>H NMR spectroscopy, we were able to identify the desired alkynamide **3.3a** in 14% yield, as well as the silylated propargyl alcohol **3.9** resulting from the addition of **3.2a** to acetophenone. The majority of the materials were converted into enol carbamate **3.10**, similar to Olofson’s work.<sup>37</sup> This study provides evidence that after desilylation of **3.2a**, the ammonium acetylide can deprotonate acetophenone, and the resulting enolate can undergo *O*-substitution with the carbamoyl fluoride. These results strongly suggest a mechanism similar to that described by Kuwajima, thus providing a rationale as to why protic substrates are not tolerated under our conditions.



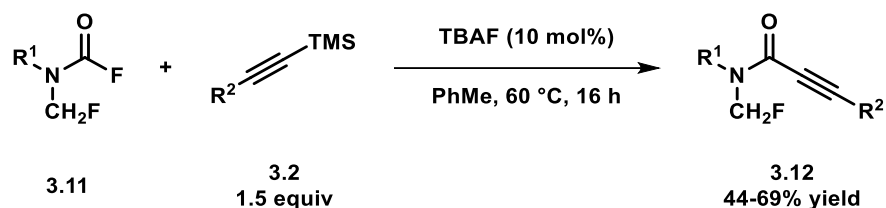
Scheme 3. 23: Protic Additives Lead to Undesired Side Reactions

### 3.5 Conclusion and Future Work

Compared to other catalytic methods for alkynamide synthesis, the fluoride-catalyzed reaction developed in our lab benefits from the use of the common laboratory reagent TBAF in low loadings as the fluoride source. With this method, we can obtain *N*-aryl alkynamides bearing functionality, such as aryl halides or alkenes, that would be problematic in transition metal-catalyzed reactions. In terms of operational simplicity, this reaction does not require stoichiometric additives or high-pressure gas reactors. We also show that typical Pd/Cu co-catalyzed Sonogashira conditions are not effective with carbamoyl fluorides and this chemoselectivity can be used to selectively functionalize aryl iodides. Several control experiments were performed, demonstrating the necessity of both the carbamoyl fluoride and alkynyl silane coupling partners. Mechanistic studies also revealed that the reaction likely proceeds via an ammonium acetylide intermediate.

Since its publication in 2023, our method has been adapted by the Schoenebeck group for the alkynylation of *N*-monofluoromethyl carbamoyl fluorides after their developed Ni-catalyzed conditions failed in the reaction (Scheme 3.24). We anticipate further adoption of this fluoride-catalyzed alkynylation reaction, as it provides the desired product in two steps (longest linear

sequence), or three overall, from commercial materials – comparing well to other methods reported in the literature. We suspect that other silylated nucleophiles should undergo fluoride-catalyzed coupling with carbamoyl fluorides or other fluorinated electrophiles. A former M.Sc. student in our lab (Tristan Tiburcio) found some success using *N*-silylated heterocycles for this purpose and the final chapter of this dissertation will describe our efforts in the cyanoalkylation of carbamoyl fluorides using silyl ketene imines as the nucleophiles.



Scheme 3. 24: Fluoride-Catalyzed Alkynylation of *N*-monofluoromethyl Carbamoyl Fluorides

## 3.6 Experimental and Spectral Information

### 3.6.1 General Procedure for Reaction Optimization

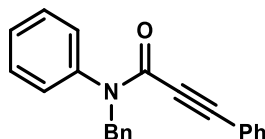
Procedure I (*when fluoride source is a liquid reagent*): To an oven-dried 1 dram vial equipped with a stir bar was added trimethyl(2-phenylethynyl)silane (**2a**) (1.5 equiv, 0.15 mmol) and carbamoyl fluoride **1a** (0.023 g, 0.1 mmol). The vial was fitted with a septum cap, which was evacuated and backfilled with nitrogen (3x) before adding solvent to the vial. The fluoride source was added to the reaction mixture with a micro syringe. After stirring at room temperature for 1 hour, the reaction mixture was filtered through silica gel in a Monstr pipette and flushed with EtOAc into a scintillation vial containing a known amount of 1,3,5-trimethoxybenzene (internal standard). The solvent was removed under reduced pressure and the residue was taken up in CDCl<sub>3</sub> for quantitative <sup>1</sup>H NMR analysis.

Procedure II (*when fluoride source is a solid reagent*): To an oven-dried 1 dram vial equipped with a stir bar was added carbamoyl fluoride **1a** (0.023 g, 0.1 mmol) and the fluoride source (10 mol%, 0.01 mmol). The vial was fitted with a septum cap, which was evacuated and backfilled with nitrogen (3x) before adding 1 mL of a 0.15 M solution of **2a** (1.5 equiv, 0.15 mmol). After stirring at room temperature for 1 hour, the reaction mixture was filtered through silica gel in a Monstr pipette and flushed with EtOAc into a scintillation vial containing a known amount of 1,3,5-trimethoxybenzene (internal standard). The solvent was removed under reduced pressure and the residue was taken up in CDCl<sub>3</sub> for quantitative <sup>1</sup>H NMR analysis.

### 3.6.2 Synthesis and Characterization Data for Alkynamides

Alkynylsilane **3.2** (0.32 mmol, 1.6 equiv) was added to an oven-dried 1 dram vial equipped with a stir bar. The vial was fitted with a septum cap, which was then evacuated and backfilled with nitrogen (3x) before adding a solution of carbamoyl fluoride **3.1** (0.2 mmol, 1 equiv) in PhMe (0.4 M). TBAF (1.0 M in THF, 4.0  $\mu$ L, 2 mol%) was then added to the reaction mixture using a microsyringe. After stirring at room temperature for 2 hours, the reaction was quenched with H<sub>2</sub>O (1 mL) and stirred vigorously for 5 minutes. The organic layer was collected, and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated via rotary evaporation. The crude residue was purified by column chromatography (unless noted otherwise) to yield alkynamides **3.3**.

#### *N*-benzyl-*N*,3-diphenyl-prop-2-ynamide (**3.3a**)



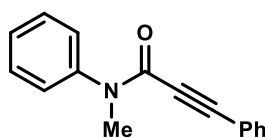
**3.3a**

The title compound was synthesised using **3.1a** (0.046 g, 0.20 mmol) and **3.2a** (0.056 g, 0.032 mmol, 1.6 equiv). Purification by flash chromatography (10% EtOAc in hexanes) provided **3.3a** as a pale-yellow oil (0.056 g, 0.18 mmol, 90%, *rotamer ratio* = 8:1). The spectral data are consistent with literature values.<sup>41</sup> **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *major rotamer*)  $\delta$  7.38-7.13 (m, 13H), 7.09 (m, 2H), 5.00 (s, 2H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *major rotamer*)  $\delta$  154.5, 141.8, 136.8, 132.6, 130.1, 129.1, 128.9, 128.8, 128.6, 128.4, 128.3, 127.7, 120.5, 91.6, 82.7, 52.4.

Scale-up under air: A flame-dried round bottom flask equipped with a stir bar was charged with **3.1a** (1.00 g, 4.36 mmol). To the flask was added a solution of **3.2a** (1.216 g, 6.98 mmol, 1.6 equiv) in 11 mL of PhMe, followed by TBAF (1.0 M in THF, 87  $\mu$ L, 0.09 mmol, 2 mol%). The reaction vessel was capped with a loosely placed septum to block debris and allowed to stir for 3.5 h. At this time, the reaction was quenched with 10 mL of H<sub>2</sub>O and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated by rotary evaporation. The crude residue was purified by column chromatography (10% EtOAc in hexanes) to yield **3.3a** as a pale-yellow oil which solidified after storage in a refrigerator (1.208 g, 3.88 mmol, 89%).

**Safety note:** Upon scale-up, a mild exotherm was observed. If scaled further, we recommend cooling the reaction mixture to 0 °C before the addition of TBAF. This lowered temperature did not change the reaction outcome when previously tested on a 0.1 mmol scale (Table S3).

#### *N*-methyl-*N*,3-diphenyl-prop-2-ynamide (**3.1b**)

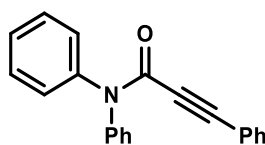


**3.3b**

The title compound was synthesised using **3.1b** (0.031 g, 0.20 mmol, 1.0 equiv) and **3.2a** (0.056 g, 0.032 mmol, 1.6 equiv). Purification by flash column chromatography (10% EtOAc in hexanes) provided **3.3c** as a yellow solid (0.046 g, 0.20 mmol, 98%, *rotamer ratio* = 8:1). The spectral data are consistent with literature values.<sup>42</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, *major rotamer*)  $\delta$  7.50-7.42

(m, 2H), 7.42-7.38 (m, 1H), 7.38-7.33 (m, 2H), 7.33-7.29 (m, 1H), 7.26-7.19 (m, 2H), 7.16-7.10 (m, 2H), 3.39 (s, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ , *major rotamer*)  $\delta$  154.4, 143.4, 132.5, 130.0, 129.3, 128.4, 128.0, 127.5, 120.5, 90.9, 82.7, 36.5.

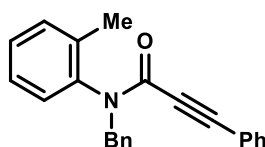
***N,N*,3-triphenylprop-2-ynamide (3.1c)**



**3.3c**

The title compound was synthesised using **3.1a** (0.034 g, 0.20 mmol, 1.0 equiv) and **3.2a** (0.056 g, 0.032 mmol, 1.6 equiv). Purification by flash column chromatography (10→15% EtOAc in hexanes) provided **3.3c** as a yellow solid (0.055 g). A white solid was obtained after trituration with cold  $\text{Et}_2\text{O}$  (0.048 g, 0.16 mmol, 81%). The spectral data are consistent with literature values.<sup>21</sup>  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53-7.30 (m, 10H), 7.29-7.19 (m, 3H), 7.18-7.12 (m, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  153.9, 132.7, 129.3, 129.1, 128.5, 128.3, 126.6, 125.9, 120.4, 92.4, 83.4.

***N*-benzyl-*N*-(*o*-tolyl)-3-phenyl-prop-2-ynamide (3.3d)**

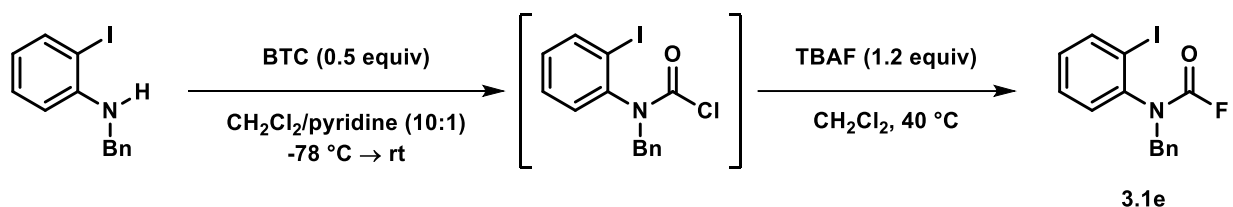


**3.3d**



The title compound was synthesised using **3.1d** (0.049 g, 0.20 mmol, 1.0 equiv) and **2.1a** (0.056 g, 0.032 mmol, 1.6 equiv). Purification by flash column chromatography (10% EtOAc in hexanes) provided **3.3d** as a yellow oil (0.062 g, 0.19 mmol, 95%, *rotamer ratio* = 9:1). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *major rotamer*) δ 7.35-7.24 (m, 8H), 7.24-7.11 (m, 3H), 7.03 (d, *J* = 7.4 Hz, 2H), 6.93 (d, *J* = 7.8 Hz, 1H), 5.25 (d, *J* = 14.0 Hz, 1H), 4.58 (d, *J* = 14.0 Hz, 1H), 2.13 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *major rotamer*) δ 154.8, 140.4, 137.2, 136.6, 132.7, 131.0, 130.03, 129.95, 129.6, 128.7, 128.6, 128.4, 127.9, 126.8, 120.5, 90.4, 82.5, 51.7, 17.7. **IR** (ATR, neat, cm<sup>-1</sup>) 3063, 3030, 2925, 2217, 1631, 1490, 1356, 722. **HRMS** (ESI) *m/z*: Calc'd for [C<sub>23</sub>H<sub>20</sub>NO]<sup>+</sup> [M+H]<sup>+</sup> 326.1539 found 326.1525.

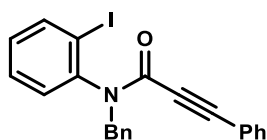
#### *N*-benzyl-*N*-(2-iodophenyl)carbamoyl fluoride (**3.1e**)



Our procedure for the synthesis of carbamoyl fluorides proved to be insufficient for preparing **3.1e** giving only 20% or 38% yield in MeCN or PhMe, respectively, and inseparable impurities were also present. Alternative preparation: An oven-dried 2-dram vial containing a stir bar and triphosgene (0.048 g, 0.16 mmol, 0.5 equiv) was evacuated and backfilled with nitrogen (3x). BTC was dissolved in 0.5 mL DCM and the solution was cooled to -78 °C and pyridine (0.1 mL) was added dropwise and stirred at that temperature for 20 minutes. *N*-benzyl-2-iodo-aniline (0.100 g, 0.33 mmol) as a solution in 0.5 mL of DCM was added slowly and the reaction was stirred for 16 hours, being allowed to slowly reach room temperature. The reaction was quenched with 1 mL of 1 M aqueous HCl and extracted with DCM (3x), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated by rotary

evaporation. A crude  $^1\text{H}$  NMR spectrum revealed complete conversion of *N*-benzyl-2-iodo-aniline to the respective carbamoyl chloride, which was used directly in the next step without purification. The carbamoyl chloride was dissolved in DCM (3 mL, 0.1 M) under nitrogen and treated with TBAF (1.0 M in THF, 0.39 mL, 1.2 equiv.). The solution was heated to 40 °C and stirred for 24 hours. At this time the solution was filtered through a short pad of silica gel, concentrated by rotary evaporation, and purified by flash chromatography (2% EtOAc in hexanes) and the desired product was isolated as a colourless oil (0.094 g, 0.26 mmol, 81%, *rotamer ratio* = 4:1).  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  7.97 – 7.88 (m, 1H), 7.36 – 7.29 (m, 3H), 7.27 – 7.18 (m, 3H), 7.10 – 7.00 (m, 1H), 6.88 (dd,  $J$  = 7.8, 1.6 Hz, 0.2H), 6.76 (dd,  $J$  = 7.9, 1.6 Hz, 0.8H), 5.22 (dd,  $J$  = 14.5, 2.1 Hz, 0.8H), 5.12 (d,  $J$  = 15.1 Hz, 0.2H), 4.32 – 4.22 (m, 1H).  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  146.3 (d,  $J$  = 287.8 Hz), 146.1 (d,  $J$  = 291.9 Hz), 141.9, 141.1 (d,  $J$  = 2.0 Hz), 140.3, 140.1, 135.3, 135.2, 130.40, 130.37, 130.1, 130.0, 129.6, 129.4, 129.2, 129.02, 128.95, 128.8, 128.6, 128.5, 98.8, 98.3, 55.1 (d,  $J$  = 2.0 Hz), 55.0 (d,  $J$  = 2.3 Hz).  **$^{19}\text{F}$  NMR** (377 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  -12.86 (s, 0.8F), -20.03 (s, 0.2F). **IR** (ATR, neat,  $\text{cm}^{-1}$ ) 3064, 3032, 2936, 1783, 1470, 1455, 719. **HRMS** (ESI)  $m/z$ : Calc'd for  $[\text{C}_{14}\text{H}_{12}\text{FINO}]^+$   $[\text{M}+\text{H}]^+$  355.9942 found 355.9935.

***N*-benzyl-*N*-(2-iodophenyl)-3-phenyl-prop-2-ynamide (**3.3e**)**

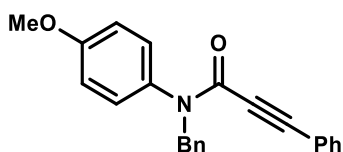


**3.3e**

The title compound was synthesised using **3.1e** (0.071 g, 0.20 mmol) and **3.2a** (0.056 g, 0.032 mmol, 1.6 equiv). Purification by flash column chromatography (10% EtOAc in hexanes) provided **3.3e** as a pale-yellow oil (0.072 g, 0.17 mmol, 82%, *rotamer ratio* = 9:1). The spectral data are

consistent with literature values.<sup>10</sup> **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *major rotamer*) δ 7.95 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.33-7.19 (m, 9H), 7.11-7.02 (m, 3H), 6.83 (dd, *J* = 7.9, 1.4 Hz, 1H), 5.66 (d, *J* = 13.6 Hz, 1H), 4.14 (d, *J* = 14.4 Hz, 1H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *major rotamer*) δ 154.5, 143.6, 139.9, 136.3, 132.6, 131.7, 130.2, 130.1, 129.6, 128.9, 128.6, 128.4, 127.9, 120.3, 100.7, 91.2, 82.6, 51.2.

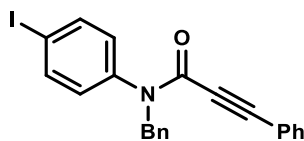
***N*-benzyl-*N*-(4-methoxyphenyl)-3-phenyl-prop-2-ynamide (3.3f)**



**3.3f**

The title compound was synthesised using **3.1f** (0.052 g, 0.20 mmol) and **2.1a** (0.056 g, 0.032 mmol, 1.6 equiv). Purification by flash column chromatography (10% EtOAc in hexanes) provided **3.3f** as a yellow solid (0.050 g, 0.15 mmol, 73%, *rotamer ratio* = 7:1). The spectral data are consistent with literature values.<sup>43</sup> **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *major rotamer*) δ 7.30-7.19 (m, 8H), 7.11 (m, 2H), 7.02 (m, 2H), 6.82 (m, 2H), 4.92 (s, 2H), 3.78 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *major rotamer*) δ 159.3, 156.9, 136.9, 134.6, 132.6, 130.00, 129.96, 129.0, 128.6, 128.4, 127.7, 120.7, 114.3, 91.7, 82.8, 55.6, 52.6.

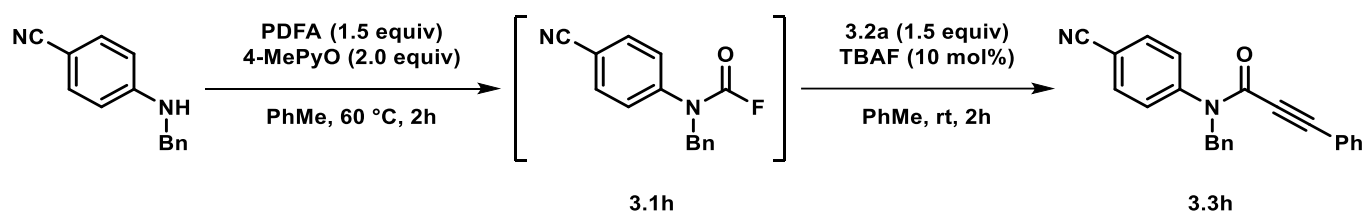
***N*-benzyl-*N*-(4-iodophenyl)-3-phenyl-prop-2-ynamide (3.3g)**



**3.3g**

The title compound was synthesised using **3.1a** (0.070 g, 0.20 mmol) and **3.2a** (0.056 g, 0.032 mmol, 1.6 equiv). Purification by flash column chromatography (10% EtOAc in hexanes) provided **3.3g** as a pale solid (0.059 g, 0.14 mmol, 67%, *rotamer ratio* = 5:1). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *major rotamer*) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.31-7.26 (m, 5H), 7.26-7.19 (m, 3H), 7.13 (d, *J* = 7.6 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 4.97 (s, 2H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *major rotamer*) δ 154.2, 141.6, 138.4, 136.5, 132.6, 130.7, 130.3, 128.9, 128.7, 128.6, 127.9, 120.3, 93.6, 92.1, 82.5, 52.2. **IR** (ATR, neat, cm<sup>-1</sup>) 2988, 2972, 2901, 2215, 1621, 1387. **HRMS** (DART) *m/z*: Calc'd for [C<sub>22</sub>H<sub>17</sub>INO]<sup>+</sup> [M+H]<sup>+</sup> 438.0349 found 438.0354.

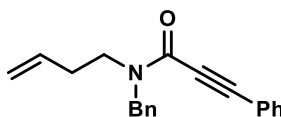
#### *N*-benzyl-*N*-(4-cyanophenyl)-3-phenyl-prop-2-ynamide (**3.3h**)



Due to the instability of electron-deficient carbamoyl fluorides to chromatography,<sup>44</sup> the synthesis of alkynamide **3.3h** was carried out using ‘crude’ **3.1h**: To a 1-dram vial equipped with a stir bar was added 4-(benzylamino)benzonitrile (0.042 g, 0.20 mmol), PDFA (0.107 g, 0.30 mmol, 1.5 equiv), and 4-methylpyridine *N*-oxide (0.044 g, 0.40 mmol, 2.0 equiv). The vial was fitted with a septum then evacuated and backfilled with nitrogen (3x). To the vial was added 2 mL of PhMe. The septum was rapidly removed and replaced with a Teflon screwcap before submerging the vial in a pre-heated 60 °C oil bath and stirred for 2 h. At this time, the vial was removed from the oil bath and the reaction mixture was quickly filtered through a short (~1 cm) plug of silica gel in a Monstr pipette flushed with (9:1 hexanes/EtOAc). In a dry 1-dram vial, the crude material was dried under reduced pressure and redissolved in 2 mL of a PhMe solution of **2.1a** (0.052 g, 0.30

mmol, 1.5 equiv). TBAF (1.0 M in THF, 20.0  $\mu$ L, 10 mol%) was then added to the reaction mixture using a microsyringe. After stirring at room temperature for 2 hours, the reaction was quenched with H<sub>2</sub>O (1 mL) and stirred vigorously for 5 minutes. The organic layer was collected, and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated via rotary evaporation. Purification by flash column chromatography (10→15% EtOAc in hexanes) provided **3.3h** as a yellow oil (0.028 g, 0.08 mmol, 42%, *rotamer ratio* = 3:1). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *both rotamers*)  $\delta$  7.66 (d, *J* = 7.5 Hz, 2H), 7.58-7.27 (bm, 9H), 7.25-7.11 (m, 3H), 5.30 (s, 0.5H), 5.04 (s, 1.5H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *major rotamer*)  $\delta$  153.7, 145.8, 136.1, 133.1, 132.5, 130.6, 129.4, 128.9, 128.7 (2C), 128.1, 119.9, 118.2, 111.9, 92.4, 82.1, 52.1. **IR** (ATR, neat, cm<sup>-1</sup>) 3062, 3031, 2933, 2215, 1635, 1504, 1377, 1197, 688. **HRMS** (DART) *m/z*: Calc'd for [C<sub>23</sub>H<sub>17</sub>N<sub>2</sub>O]<sup>+</sup> [M+H]<sup>+</sup> 337.1335 found 337.1338.

#### ***N*-benzyl-*N*-but-3-enyl-3-phenyl-prop-2-ynamide (3.3i)**

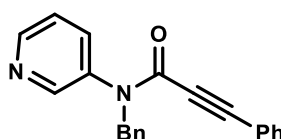


**3.3i**

The title compound was synthesised using **3.1i** (0.042 g, 0.20 mmol) and **3.2a** (0.056 g, 0.032 mmol, 1.6 equiv). Purification by flash column chromatography (8% EtOAc in hexanes) provided **3.3j** as a colourless oil (0.054 g, 0.19 mmol, 93%, *rotamer ratio* = 1:1). The spectral data are consistent with literature values.<sup>16</sup> **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *both rotamers*)  $\delta$  7.54 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.45-7.26 (m, 8H), 5.77 (m, 1H), 5.07 (m, 2H), 4.87 (s, 1H), 4.69 (s, 1H), 3.63 (t, *J* = 7.6 Hz, 1H), 3.43 (t, *J* = 7.6 Hz, 1H), 2.39 (q, *J* = 7.2 Hz, 1H), 2.30 (q, *J* = 7.2 Hz, 1H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *both rotamers*)  $\delta$  155.1, 154.9, 136.8, 136.7, 135.1,

134.5, 132.58, 132.55, 130.3, 130.2, 129.0, 128.9, 128.73, 128.65, 128.3, 128.1, 127.8, 127.7, 120.7, 120.6, 117.7, 117.2, 90.5, 90.3, 82.1, 81.9, 53.2, 48.0, 47.8, 44.0, 33.2, 31.7.

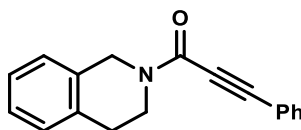
***N*-benzyl-3-phenyl-*N*-(3-pyridyl)prop-2-ynamide (3.3j)**



**3.3j**

The title compound was synthesised using **3.1j** (0.046 g, 0.20 mmol) and **3.2a** (0.056 g, 0.032 mmol, 1.6 equiv). Flash column chromatography (35% EtOAc in hexanes) resulted in co-elution with unreacted carbamoyl fluoride. The resulting orange solid was finely crushed and triturated with hexanes to yield the pure **3.3j** as a white solid (0.039 g, 0.13 mmol, 62%, *rotamer ratio* = 5:1). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *major rotamer*) δ 8.59 (d, *J* = 4.3 Hz, 1H), 8.48 (d, *J* = 2.2 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.34-7.27 (m, 5H), 7.26-7.20 (m, 4H), 7.13 (d, *J* = 7.4 Hz, 2H), 5.02 (s, 2H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *major rotamer*) δ 154.3, 150.2, 149.3, 138.3, 136.1, 136.0, 132.6, 130.4, 128.9 (2C), 128.5, 128.1, 123.7, 120.0, 92.6, 82.2, 52.3. **IR** (ATR, neat, cm<sup>-1</sup>) 3057, 3036, 2218, 1626, 1378, 727. **HRMS** (ESI) *m/z*: Calc'd for [C<sub>21</sub>H<sub>17</sub>N<sub>2</sub>O]<sup>+</sup> [M+H]<sup>+</sup> 313.1335 found 313.1337.

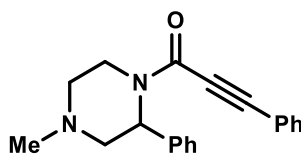
**1-(3,4-dihydro-1H-isoquinolin-2-yl)-3-phenyl-prop-2-yn-1-one (3.3k)**



**3.3k**

The title compound was synthesised using **3.1k** (0.036 g, 0.20 mmol) and **3.2a** (0.056 g, 0.032 mmol, 1.6 equiv). Purification by flash column chromatography (15% EtOAc in hexanes) provided **3.3k** as a pale yellow solid (0.042 g, 0.16 mmol, 80%, *rotamer ratio* = 1.5:1). The spectral data are consistent with literature values.<sup>26</sup> **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *major rotamer*)  $\delta$  7.62-7.55 (m, 2H), 7.46-7.35 (m, 3H), 7.25-7.13 (m, 4H), 4.82 (s, 2H), 4.07 (t, *J* = 6.0 Hz, 2H), 2.98 (t, *J* = 5.8 Hz, 2H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *major rotamer*)  $\delta$  153.8, 133.9, 132.5, 132.3, 130.2, 128.7, 128.6, 127.1, 126.8, 126.7, 120.5, 90.4, 81.4, 48.7, 44.1, 29.6.

**1-(4-methyl-2-phenyl-piperazin-1-yl)-3-phenyl-prop-2-yn-1-one (3.3l)**

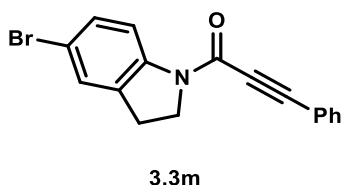


**3.3l**

The title compound was synthesised using **3.1l** (0.045 g, 0.20 mmol) and **3.2a** (0.056 g, 0.032 mmol, 1.6 equiv). Purification by flash column chromatography (40% EtOAc in hexanes) provided **3.3l** as a yellow oil (0.048 g, 0.16 mmol, 79%, *rotamer ratio* = 1.2:1). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *both rotamers*)  $\delta$  7.58-7.48 (m, 4H), 7.45-7.31 (m, 5H), 7.31-7.23 (m, 1H), 5.85 (d, *J* = 3.5 Hz, 0.5H), 4.65 (d, *J* = 2.8 Hz, 0.5H), 4.47 (dt, *J* = 13.4, 1.5 Hz, 0.5H), 4.26 (dt, *J* = 13.4, 1.5 Hz, 0.5H), 3.47 (d, *J* = 11.9 Hz, 0.5H), 3.4-3.3 (m, 1H), 2.98-2.78 (m, 1.5H), 2.50 (dd, *J* = 12.0, 4.2 Hz, 0.5H), 2.39 (dd, *J* = 12.1, 4.3 Hz, 0.5H), 2.34 (s, 1.5H), 2.33 (s, 1.5H), 2.18 (td, *J* = 11.7, 3.2 Hz, 0.5H), 2.10 (td, *J* = 11.8, 3.3 Hz, 0.5H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *both rotamers*)  $\delta$  153.7, 153.6, 139.0, 138.9, 132.5, 132.4, 130.21, 130.18, 128.8, 128.62, 128.60, 127.9, 127.6, 127.4, 127.3, 120.5, 120.45, 91.2, 91.0, 81.4, 81.3, 57.5, 57.1, 56.6, 55.6, 54.8, 50.9, 46.3, 43.7, 38.0.

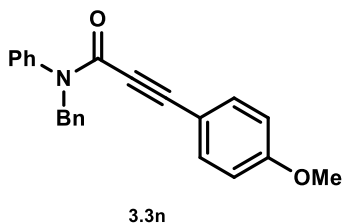
(Note: not all rotamer peaks are resolved). **IR** (ATR, neat,  $\text{cm}^{-1}$ ) 3060, 2939, 2209, 1619, 1445, 689. **HRMS** (ESI)  $m/z$ : Calc'd for  $[\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}]^+ [\text{M}+\text{H}]^+$  305.1648 found 305.1652.

### 1-(5-bromoindolin-1-yl)-3-phenyl-prop-2-yn-1-one (3.3m)



The title compound was synthesised using **3.1m** (0.049 g, 0.20 mmol) and **3.1a** (0.056 g, 0.032 mmol, 1.6 equiv). Purification was achieved by filtering the solids from the reaction mixture and washing with hexanes, which yielded **3.3m** as a colourless solid (0.032 g, 0.1 mmol, 49%, *rotamer ratio* = 6:1). **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ , *major rotamer*)  $\delta$  8.07 (d,  $J$  = 9.2 Hz, 1H), 7.60-7.51 (m, 2H), 7.45-7.36 (m, 3H), 7.36-7.29 (bm, 2H), 4.38 (t,  $J$  = 8.5 Hz, 2H), 3.21 (t,  $J$  = 8.5 Hz, 2H). **<sup>13</sup>C NMR** (101 MHz,  $\text{CDCl}_3$ , *major rotamer*)  $\delta$  151.4, 141.4, 134.5, 132.7, 130.7, 130.5, 128.8, 128.0, 120.2, 118.7, 117.1, 90.6, 82.8, 49.6, 27.5. **IR** (ATR, neat,  $\text{cm}^{-1}$ ) 3059, 3034, 2980, 2205, 1624, 1396, 691. **HRMS** (ESI)  $m/z$ : Calc'd for  $[\text{C}_{17}\text{H}_{13}\text{BrNO}]^+ [\text{M}+\text{H}]^+$  326.0175 found 326.0163.

### *N*-benzyl-3-(4-methoxyphenyl)-*N*-phenyl-prop-2-ynamide (3.3n)

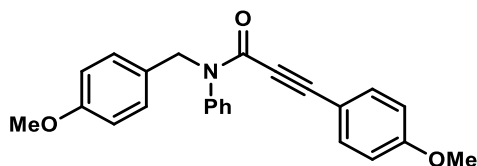


The title compound was synthesised using **3.1a** (0.046 g, 0.20 mmol) and **3.2b** (0.065 g, 0.32 mmol, 1.6 equiv). Purification by flash column chromatography (15% EtOAc in hexanes) provided



**3.3n** as a yellow oil (0.067 g, 0.20 mmol, 98%, *rotamer ratio* = 7:1). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *major rotamer*) δ 7.39-7.32 (m, 3H), 7.28-7.20 (m, 5H), 7.16 (m, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.9 Hz, 2H), 5.00 (s, 2H), 3.76 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *major rotamer*) δ 161.1, 154.8, 142.0, 136.9, 134.4, 129.1, 128.9, 128.8, 128.6, 128.1, 127.6, 114.1, 112.4, 92.3, 82.1, 55.4, 52.3. **IR** (ATR, neat, cm<sup>-1</sup>) 2988, 2972 2901, 2202, 1627, 1406, 1066. **HRMS** (ESI) *m/z*: Calc'd for [C<sub>23</sub>H<sub>20</sub>NO<sub>2</sub>]<sup>+</sup> [M+H]<sup>+</sup> 342.1489 found 342.1491.

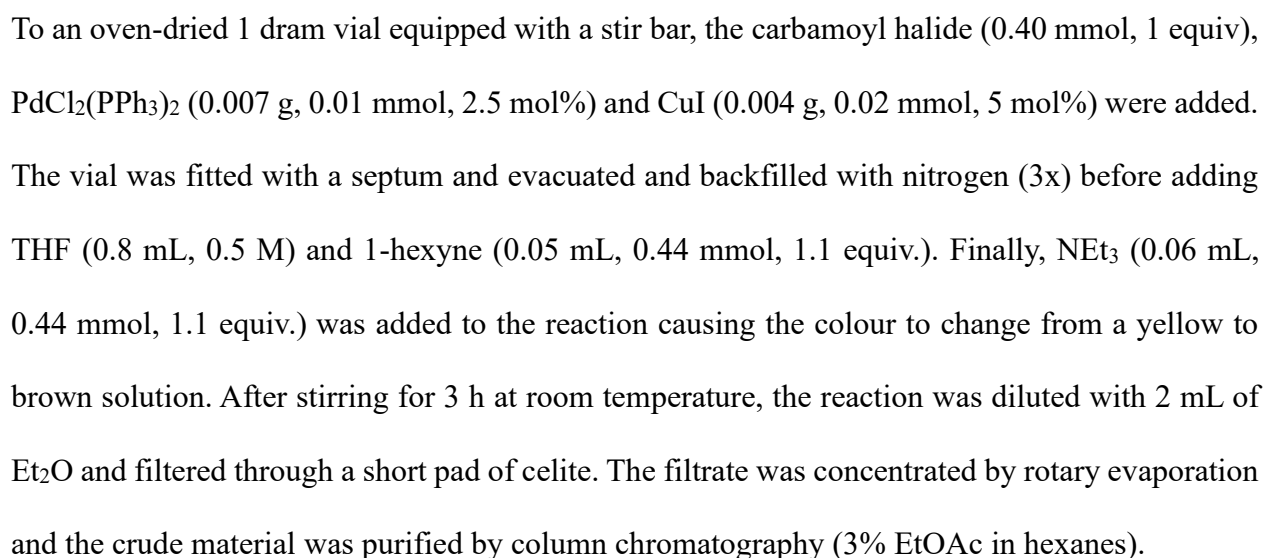
### 3-(4-methoxyphenyl)-*N*-[(4-methoxyphenyl)methyl]-*N*-phenyl-prop-2-ynamide (**3.3q**)



**3.3o**

The title compound was synthesised using **3.1n** (0.104 g, 0.40 mmol) and **3.2b** (0.131 g, 0.64 mmol, 1.6 equiv). Purification by flash column chromatography (25% EtOAc in hexanes) provided **3.3q** as a yellow oil (0.140 g, 0.38 mmol, 94%, *rotamer ratio* = 7:1). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, *major rotamer*) δ 7.35 (m, 3H), 7.18-7.10 (m, 4H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 4.93 (s, 2H), 3.77 (s, 3H), 3.75 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, *major rotamer*) δ 161.0, 159.2, 154.7, 142.0, 134.4, 130.3, 129.1, 129.04, 128.99, 128.1, 114.1, 113.9, 112.4, 92.2, 82.2, 55.4, 55.3, 51.7. **IR** (ATR, neat, cm<sup>-1</sup>) 2959, 2934, 2837, 2207, 1628, 1509, 1244. **HRMS** (DART) *m/z*: Calc'd for [C<sub>24</sub>H<sub>22</sub>NO<sub>3</sub>]<sup>+</sup> [M+H]<sup>+</sup> 372.1594 found 372.1594.

## Coupling Conditions

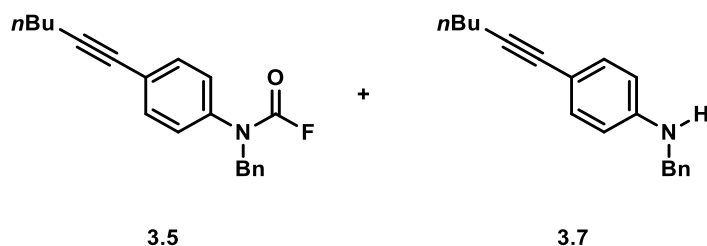


***N*-benzyl-*N*-(4-iodophenyl)carbamoyl chloride (3.4)**



To a solution of triphosgene (0.241 g, 0.81 mmol, 0.5 equiv) in 4.0 mL DCM under N<sub>2</sub>, pyridine (0.5 mL) was added dropwise at -78 °C and reaction was stirred at that temperature for 20 minutes. *N*-benzyl-4-iodo-aniline (0.500 g, 1.62 mmol) was added slowly as a solution in 1.0 mL DCM and the reaction was stirred for 16 hours, being allowed to slowly reach room temperature. The reaction was quenched with 5 mL of 1 M aqueous HCl and extracted with DCM (3x), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated by rotary evaporation. **S11** was isolated as a pale-yellow solid (0.476 g, 1.28 mmol, 79%) after purification by flash column chromatography (5% EtOAc in hexanes). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.67 (m, 2H), 7.36-7.27 (m, 3H), 7.19 (m, 2H), 6.76 (bd, 2H), 4.84 (s, 2H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 149.6, 141.3, 138.8, 135.4, 130.6, 129.1, 128.9, 128.5, 94.4, 56.6. **IR** (ATR, neat, cm<sup>-1</sup>) 3086, 3028, 2937, 1735, 1483, 1378, 639. **HRMS** (ESI) *m/z*: Calc'd for [C<sub>14</sub>H<sub>12</sub>ClINO]<sup>+</sup> 371.9647 [M+H]<sup>+</sup> found 371.9646.

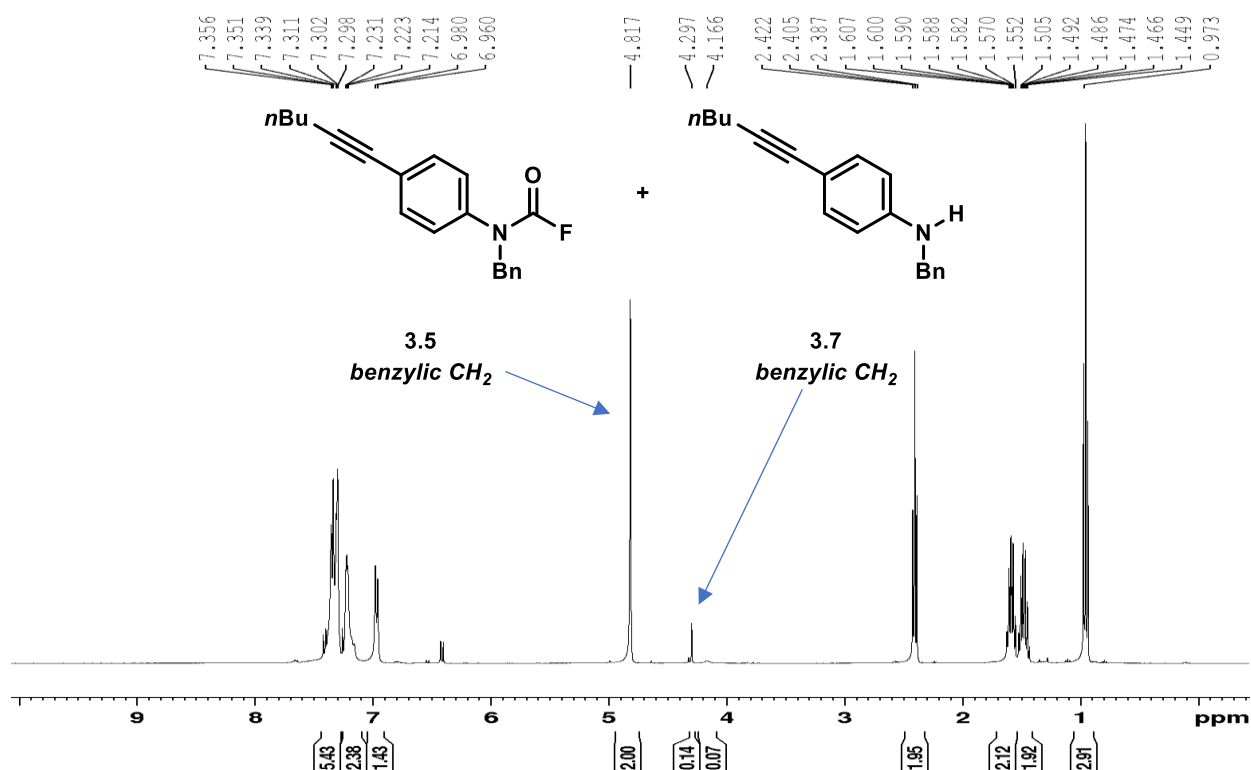
***N*-benzyl-*N*-(4-hex-1-ynylphenyl)carbamoyl fluoride (3.5)**



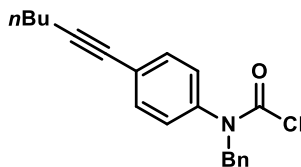
Carbamoyl fluoride **4** was obtained as an orange oil, albeit as a 14:1 mixture with amine **5** (0.118 g **3.5** + **3.7**, calculated 0.111 g, 0.36 mmol, 90% of **3.5**). The mixture of **3.5** and **3.7** were subjected to the typical procedure for carbamoyl fluoride synthesis to obtain clean NMR spectra that could be adequately assigned (colourless oil, 0.072 g, 0.23 mmol, 58%, *rotamer ratio* = 3:1). Copies of NMR spectra for **3.5** are provided in the appendix of this chapter. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, **3.5**, *both rotamers*) δ 7.44-7.27 (m, 5H), 7.25-7.12 (m, 2.5H), 6.97 (d, *J* = 8.1 Hz, 1.5H), 4.81 (s, 2H), 2.40 (t, *J* = 7.1 Hz, 2H), 1.58 (m, 2H), 1.47 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). **<sup>13</sup>C NMR** (101

MHz, CDCl<sub>3</sub>, **4**, *both rotamers*) 146.8 (d,  $J = 288.7$  Hz), 146.6 (d,  $J = 292.9$  Hz), 139.5, 138.2, 135.9, 135.6, 132.6, 129.0, 128.8, 128.7, 128.3, 127.6, 126.8, 125.7, 124.2, 92.1, 91.7, 79.6, 55.6, 55.0, 30.8, 22.1, 19.2, 13.7 (Note: not all rotamer peaks are resolved). **<sup>19</sup>F NMR** (377 MHz, CDCl<sub>3</sub>)  $\delta$  -14.49 (s, 0.75F), -16.47 (s, 0.25F). **IR** (ATR, neat, cm<sup>-1</sup>) 3033, 2957, 2932, 2872, 2230, 1738, 1509, 1386, 731. **HRMS** (ESI)  $m/z$  for **3.5**: Calc'd for [C<sub>20</sub>H<sub>21</sub>FNO]<sup>+</sup> 310.1602 [M+H]<sup>+</sup> found 310.1599.

$^1\text{H}$  NMR Spectrum ( $\text{CDCl}_3$ , 400 MHz) of **3.5** and **3.7** mixture



### *N*-benzyl-*N*-(4-hex-1-ynylphenyl)carbamoyl chloride (**3.6**)



**3.6**

Carbamoyl chloride **3.6** was obtained as an orange oil (0.122 g, 0.37 mmol, 94%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 – 7.33 (m, 2H), 7.33 – 7.27 (m, 3H), 7.24 – 7.15 (m, 2H), 6.93 (bd, 2H), 4.86 (s, 2H), 2.41 (t,  $J$  = 7.1 Hz, 2H), 1.69-1.54 (m, 2H), 1.53-1.43 (m, 2H), 0.95 (t,  $J$  = 7.3 Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  149.7, 140.5, 135.5, 132.6, 129.1, 128.8, 128.5, 128.3, 124.8, 92.4, 79.6, 56.6, 30.8, 22.1, 19.2, 13.7. IR (ATR, neat,  $\text{cm}^{-1}$ ) 3033, 2957, 2932, 2871, 2231, 1790, 1505, 1378, 713. HRMS (ESI)  $m/z$ : Calc'd for  $[\text{C}_{20}\text{H}_{21}\text{ClNO}]^+$  326.1306  $[\text{M}+\text{H}]^+$  found 326.1306.

## 3.7 References

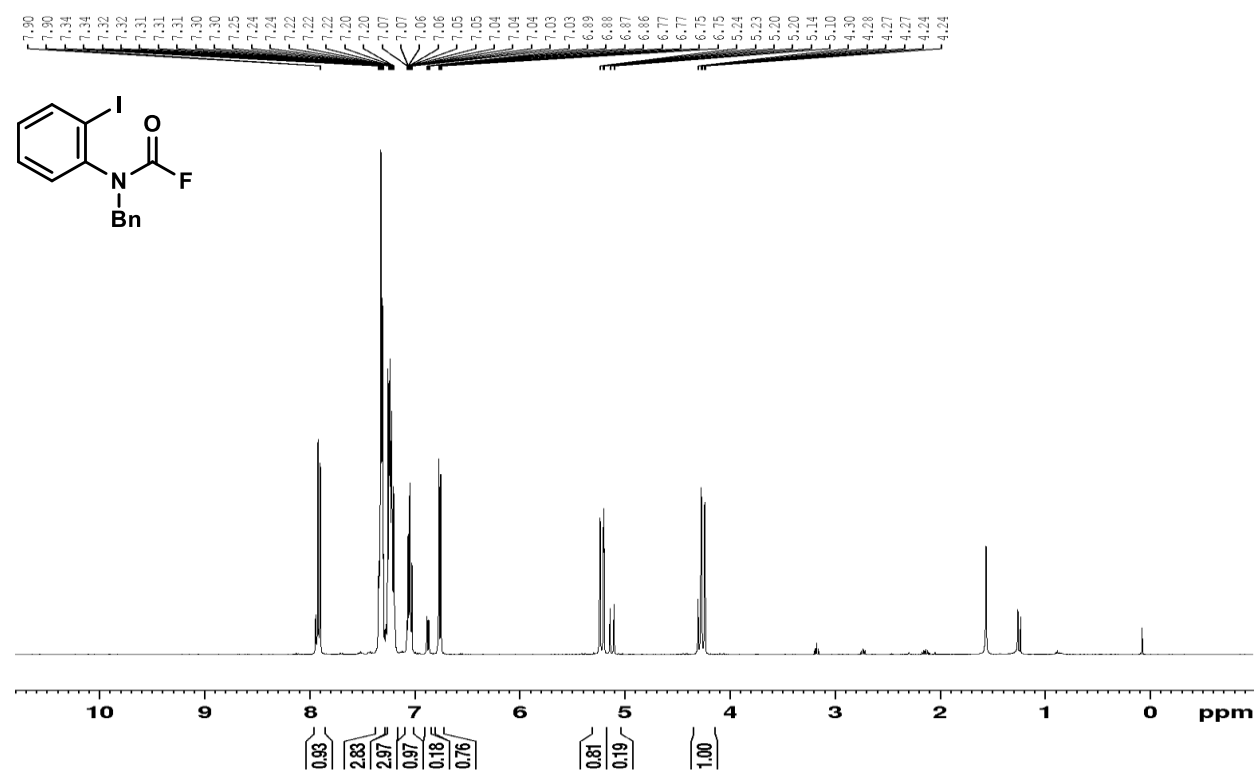
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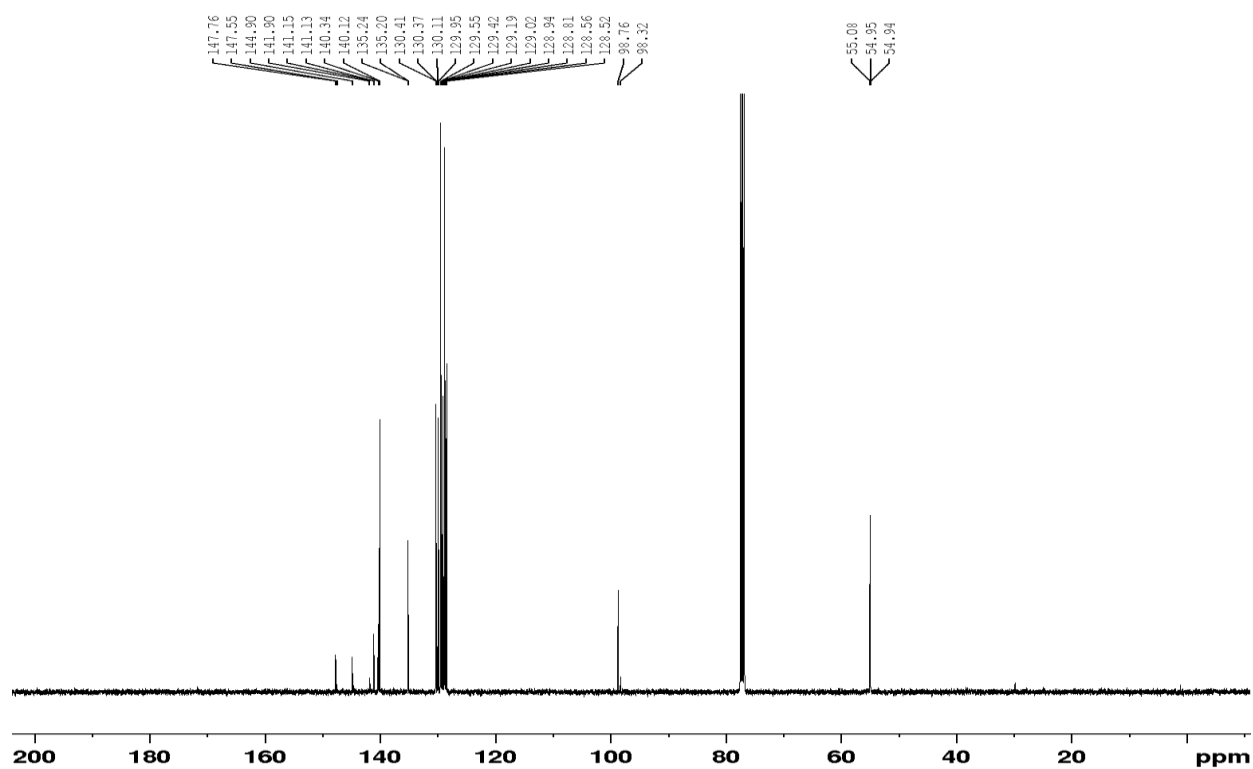
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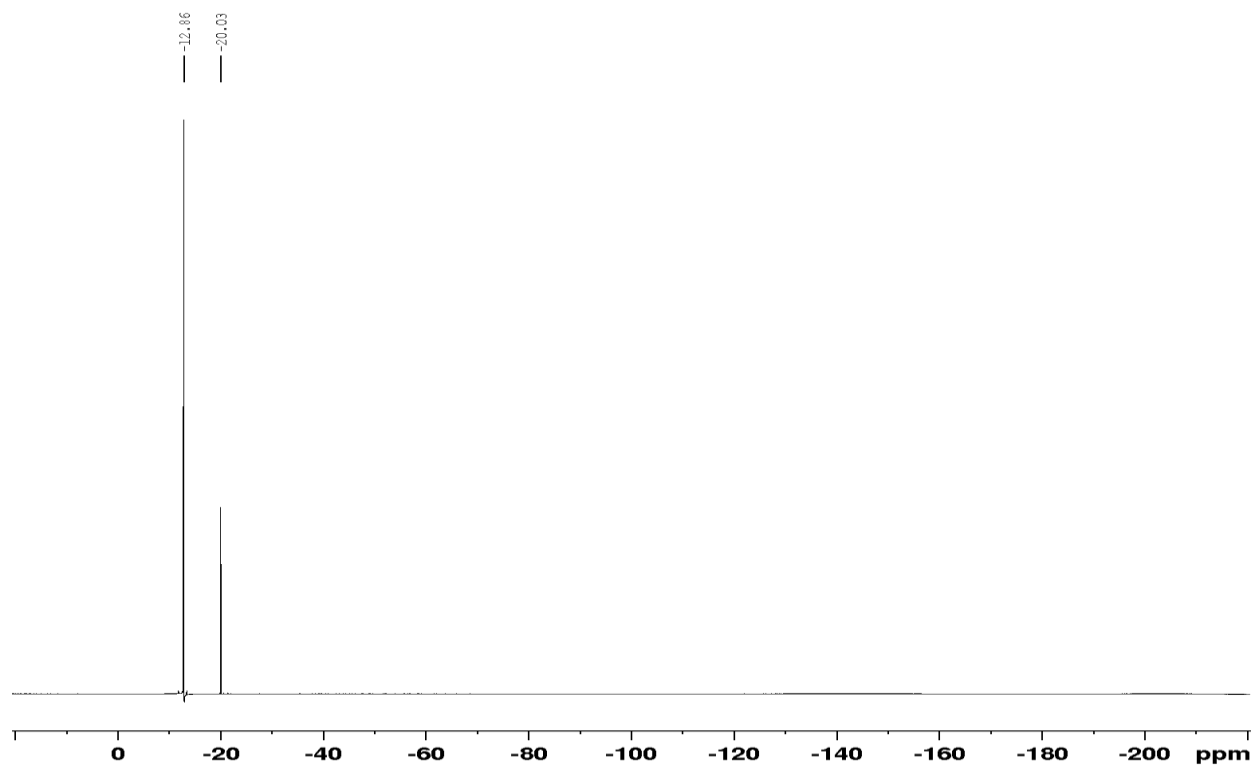
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$^{13}\text{C} \{^1\text{H}\}$  NMR Spectrum  $\text{CDCl}_3$  (101 MHz)

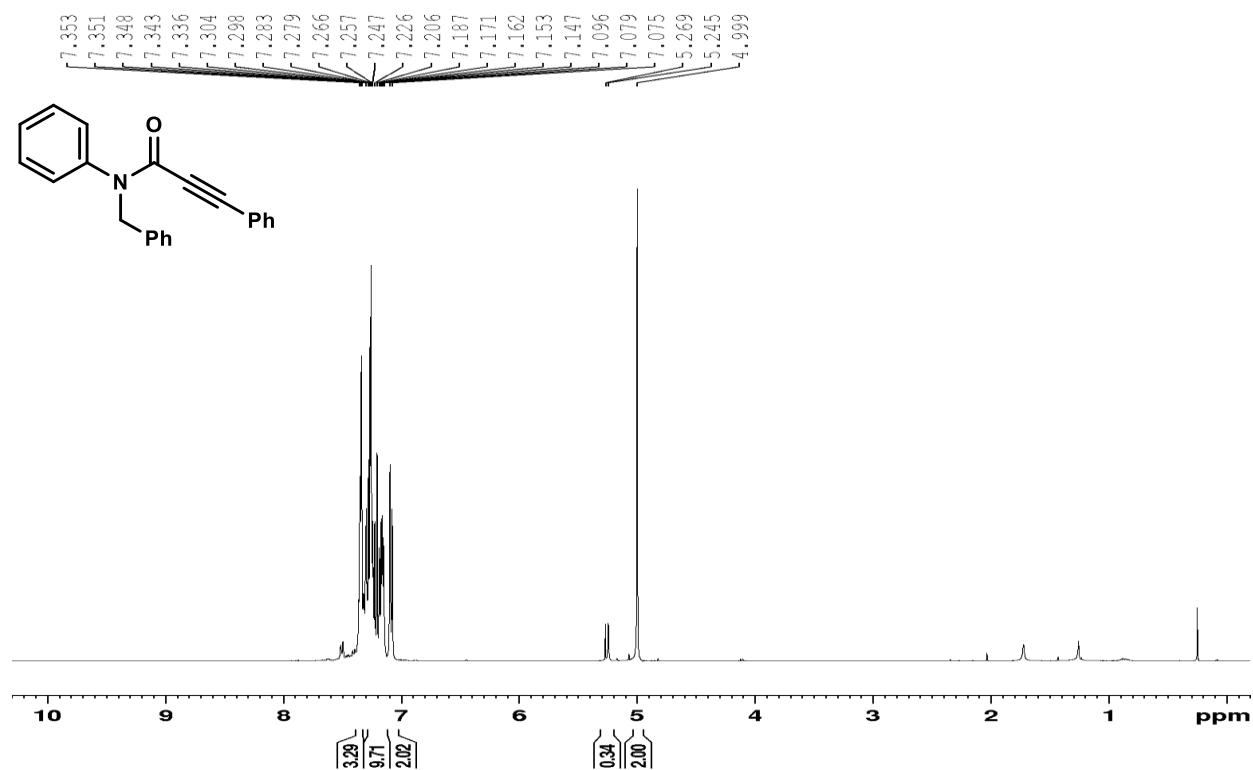


$^{19}\text{F}$  NMR Spectrum  $\text{CDCl}_3$  (377 MHz)



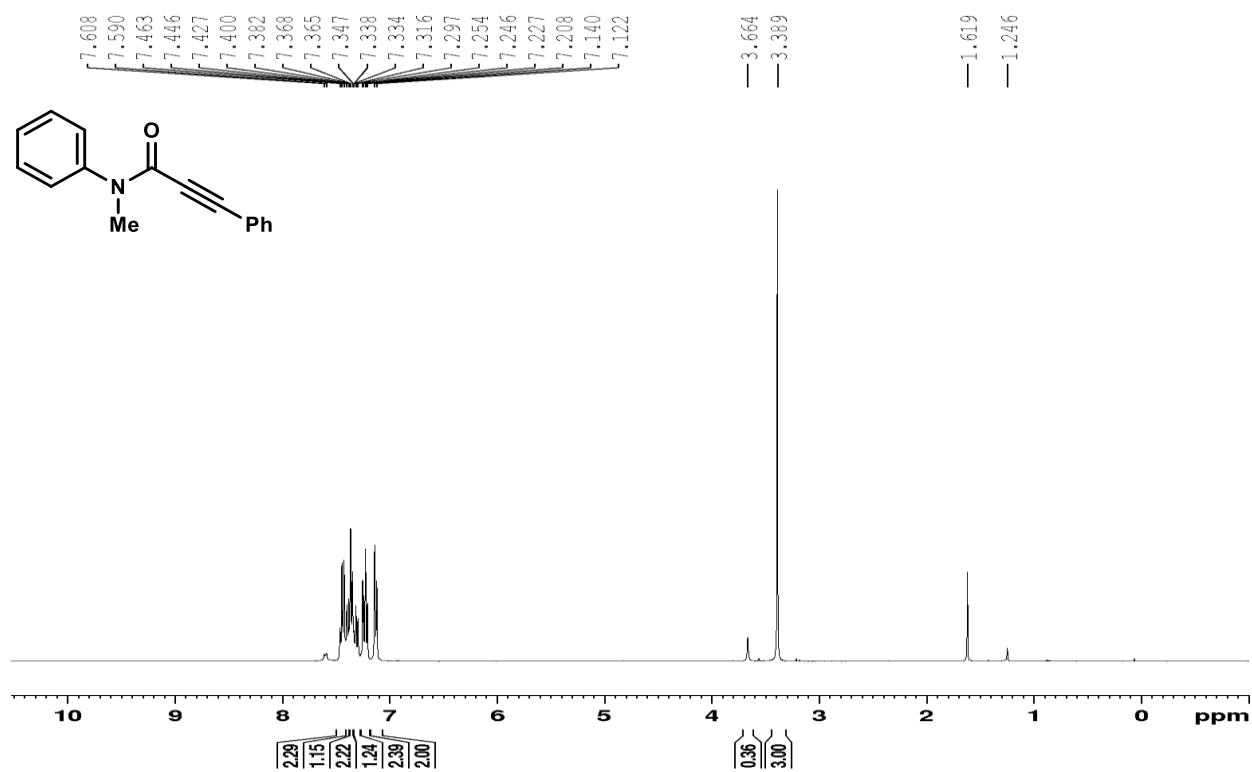
*N*-benzyl-*N*,3-diphenyl-prop-2-ynamide (**3.3a**)

<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (400 MHz)



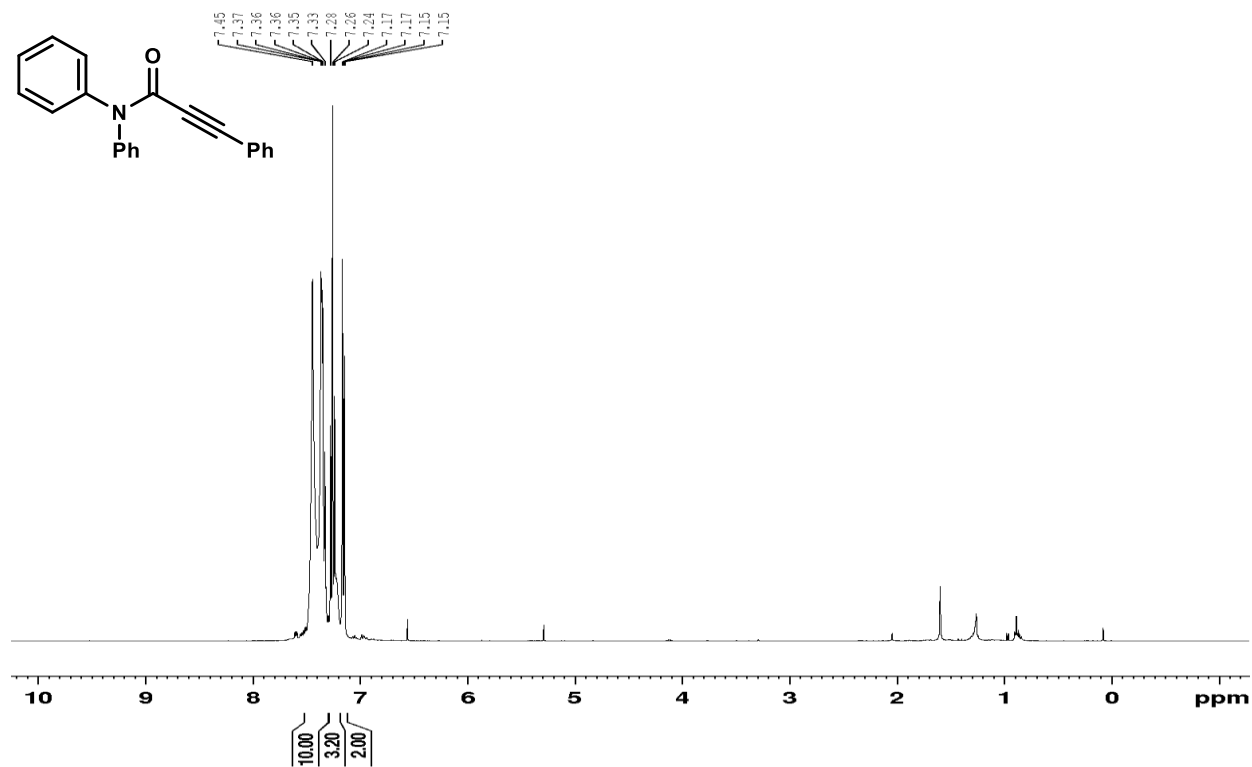
*N*-methyl-*N*,3-diphenyl-prop-2-ynamide (**3.3b**)

<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (400 MHz)



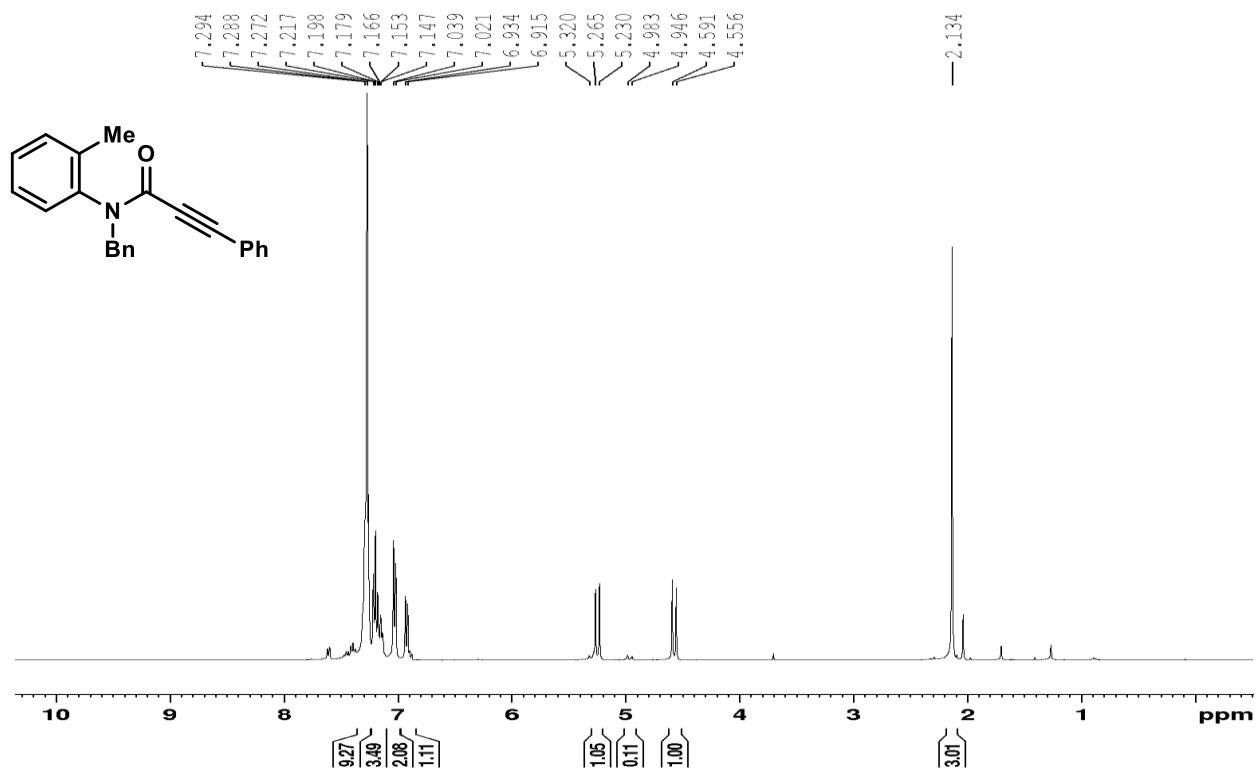
*N,N*,3-triphenylprop-2-ynamide (3.3c)

<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (400 MHz)

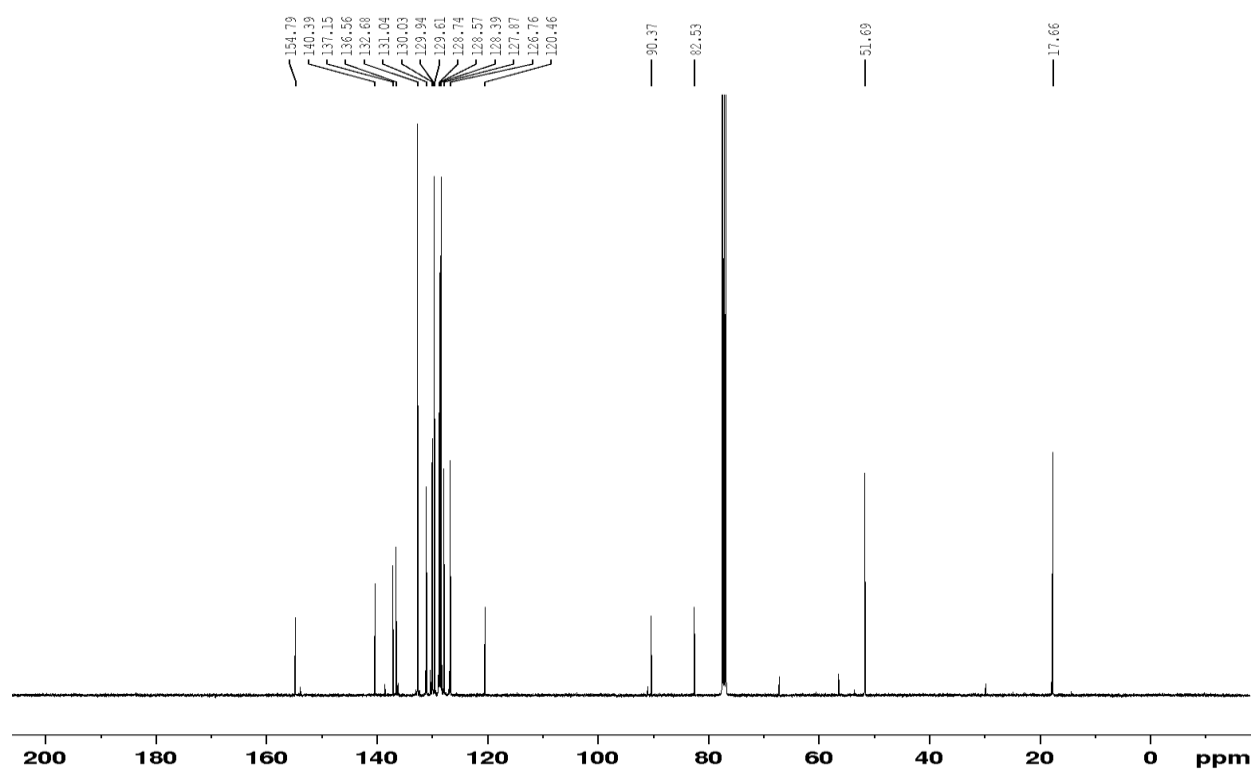


*N*-benzyl-*N*-(*o*-tolyl)-3-phenyl-prop-2-ynamide (**3.3d**)

$^1\text{H}$  NMR Spectrum  $\text{CDCl}_3$  (400 MHz)

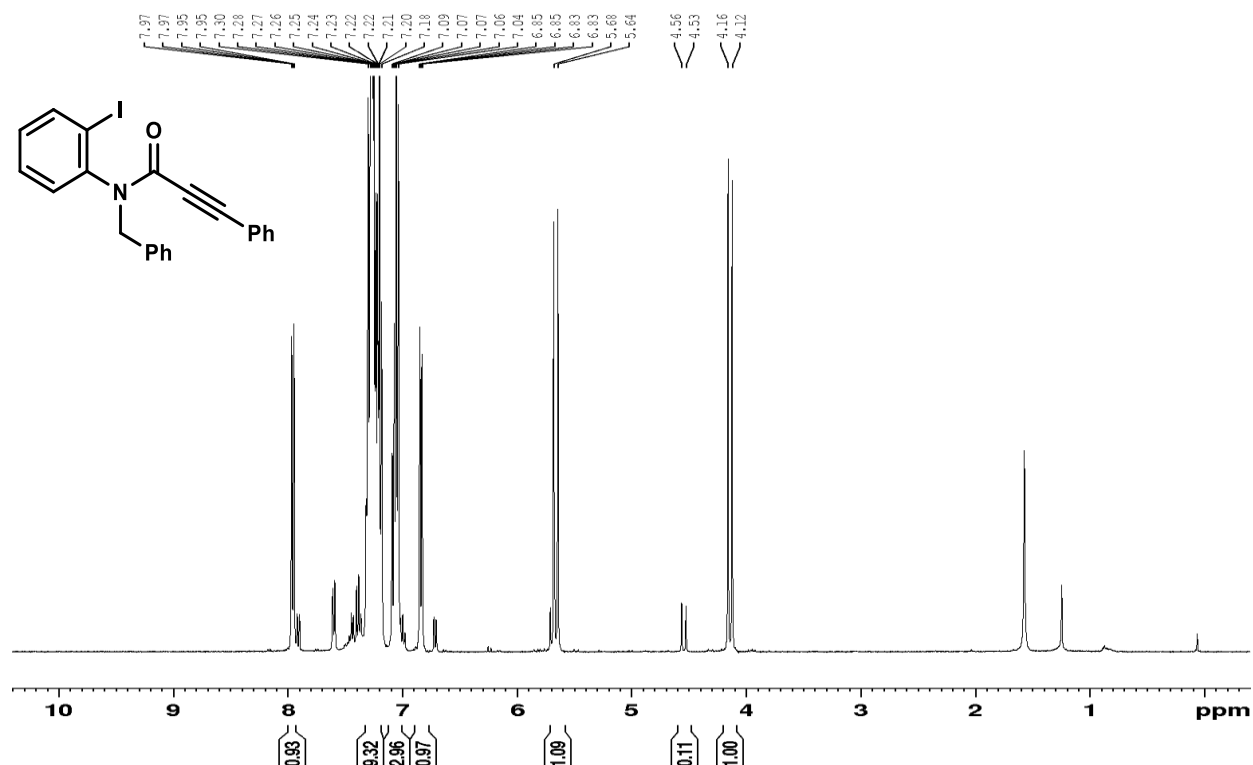


$^{13}\text{C}$  { $^1\text{H}$ } NMR Spectrum  $\text{CDCl}_3$  (101 MHz)



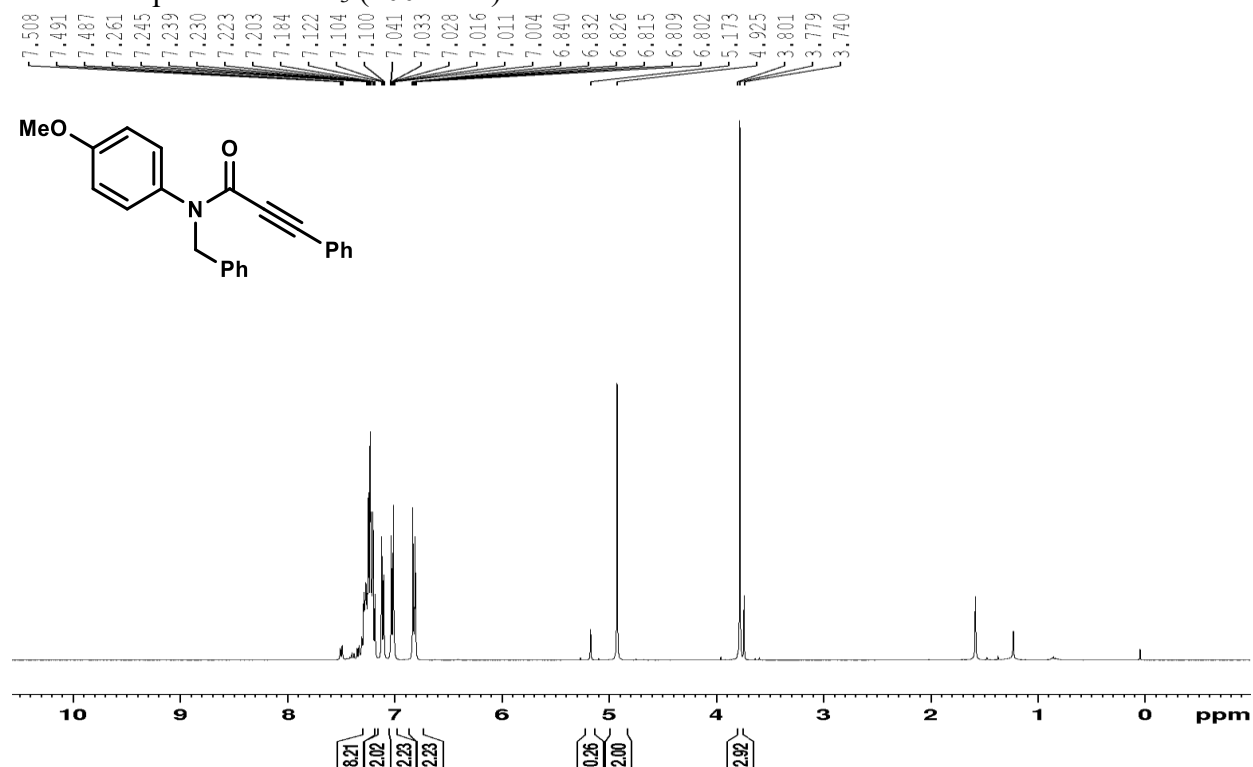
*N*-benzyl-*N*-(2-iodophenyl)-3-phenyl-prop-2-ynamide (**3.3e**)

<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (400 MHz)



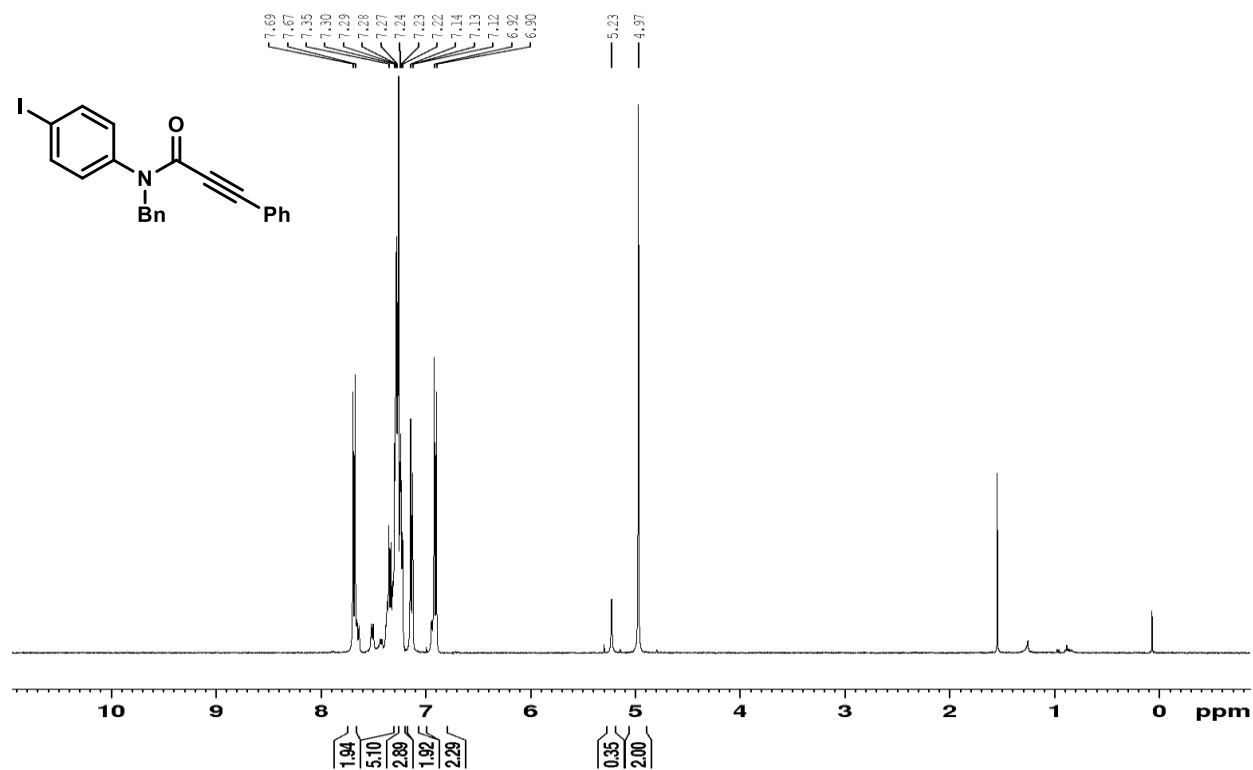
*N*-benzyl-*N*-(4-methoxyphenyl)-3-phenyl-prop-2-ynamide (**3.3f**)

<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (400 MHz)

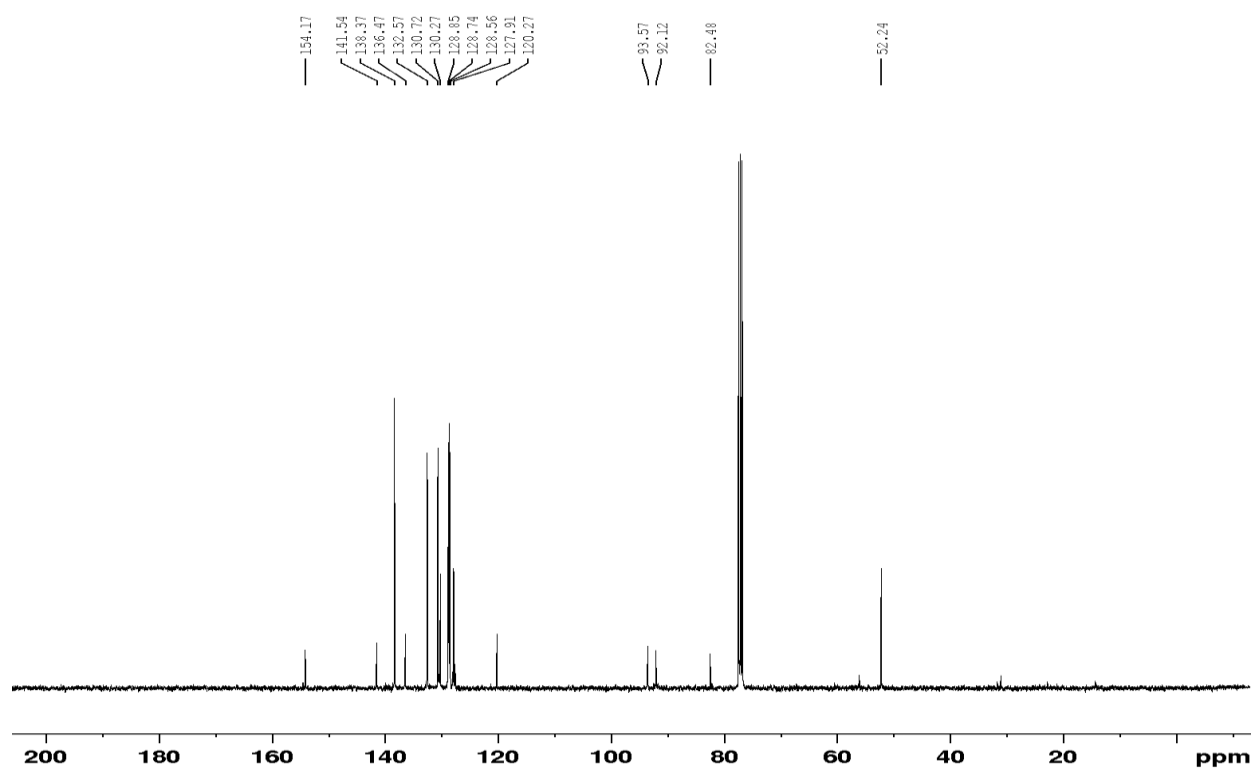


*N*-benzyl-*N*-(4-iodophenyl)-3-phenyl-prop-2-ynamide (**3.3g**)

<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (400 MHz)

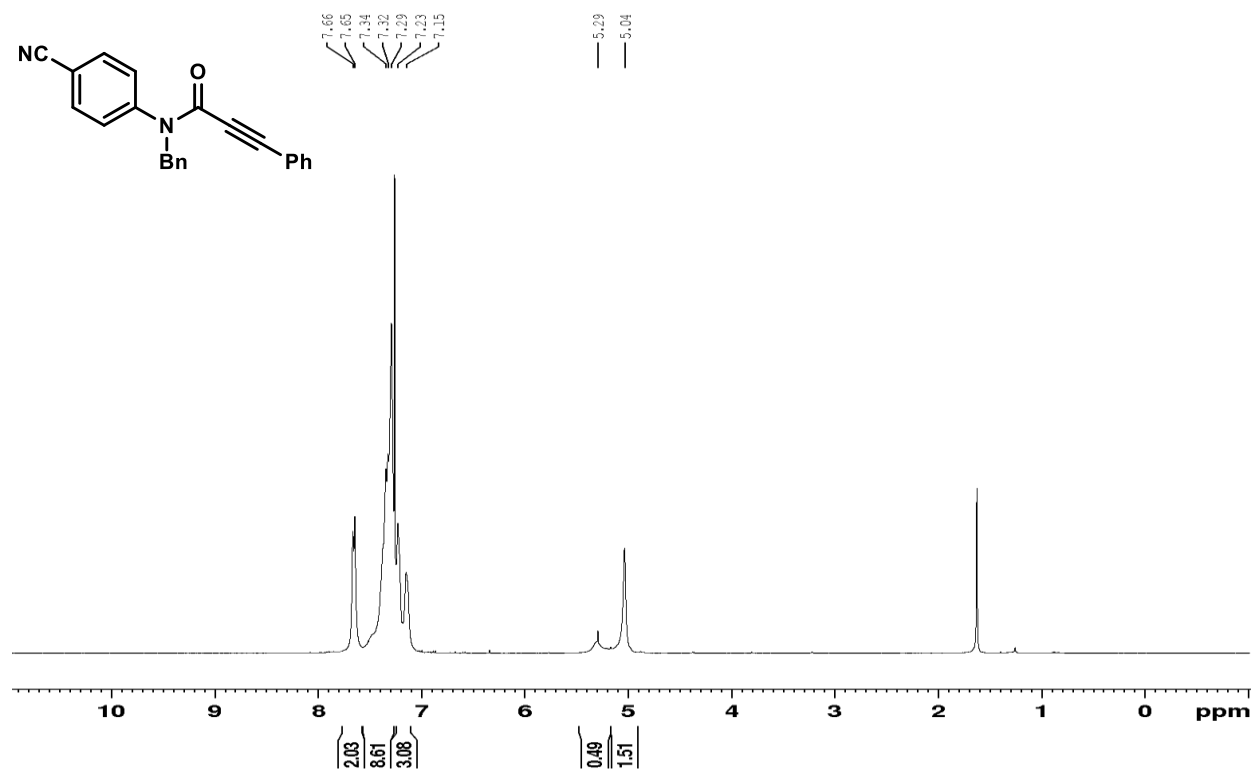


<sup>13</sup>C {<sup>1</sup>H} NMR Spectrum CDCl<sub>3</sub> (101 MHz)

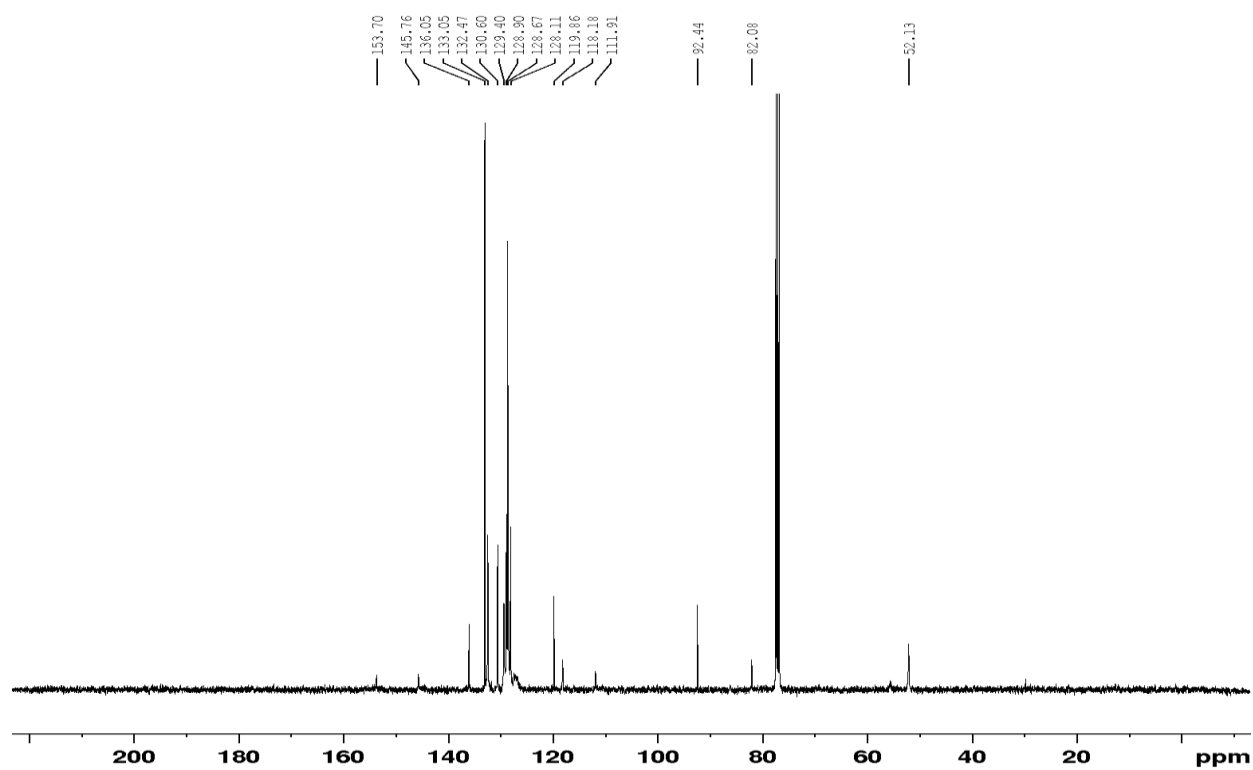


*N*-benzyl-*N*-(4-cyanophenyl)-3-phenyl-prop-2-ynamide (**3.3h**)

$^1\text{H}$  NMR Spectrum  $\text{CDCl}_3$  (400 MHz)



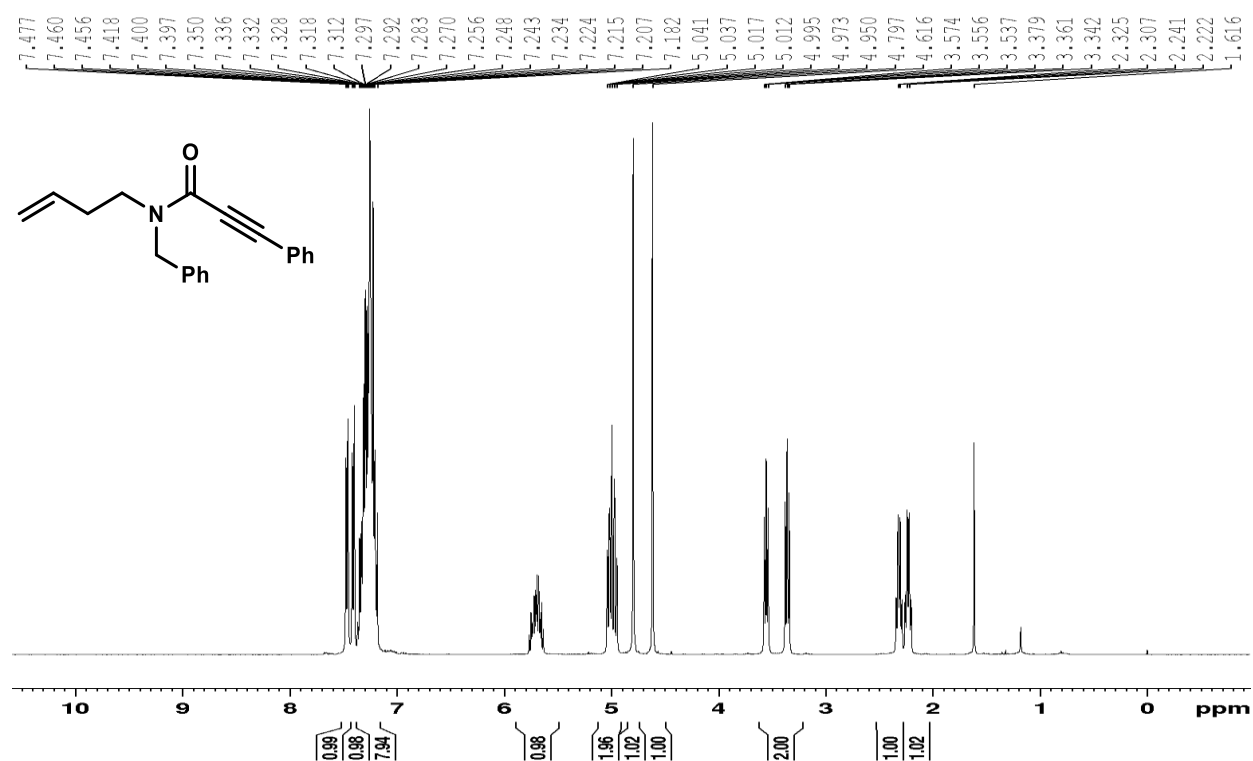
$^{13}\text{C}$  { $^1\text{H}$ } NMR Spectrum  $\text{CDCl}_3$  (101 MHz)





*N*-benzyl-*N*-but-3-enyl-3-phenyl-prop-2-ynamide (**3.3i**)

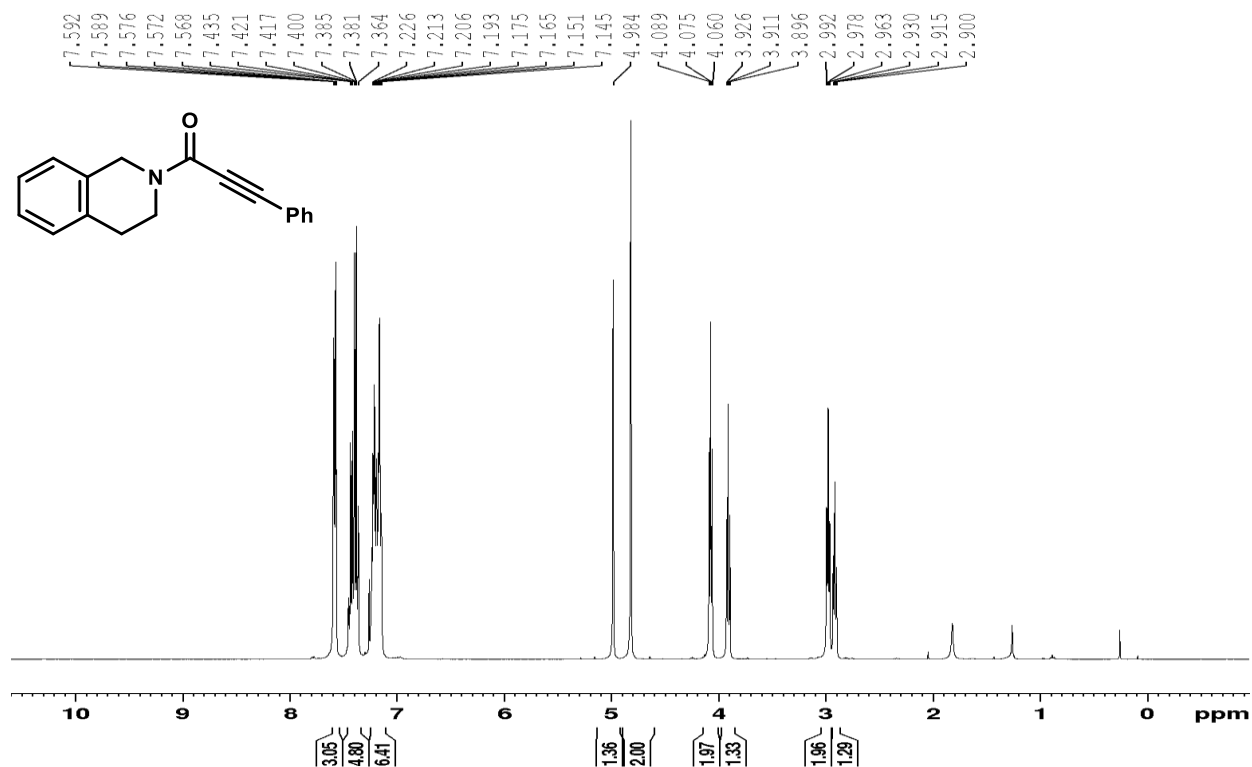
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*N*-benzyl-3-phenyl-*N*-(3-pyridyl)prop-2-ynamide (**3.3j**)

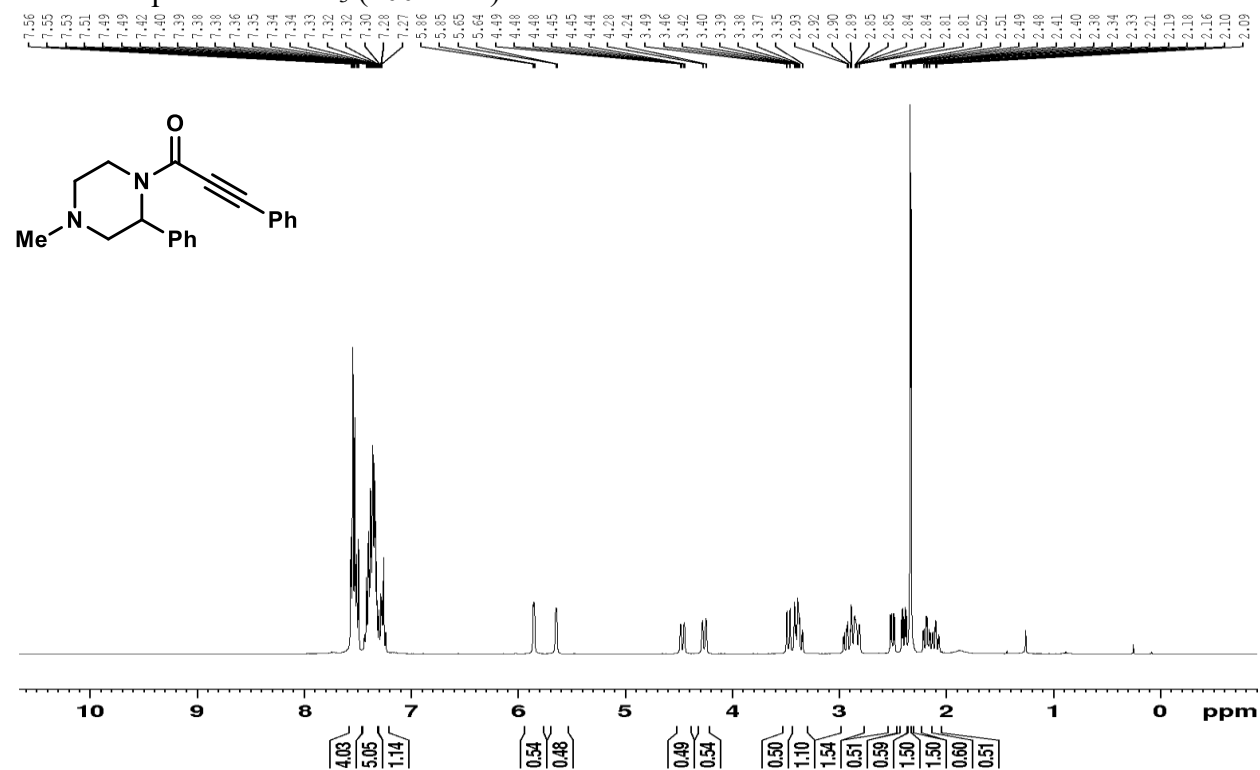
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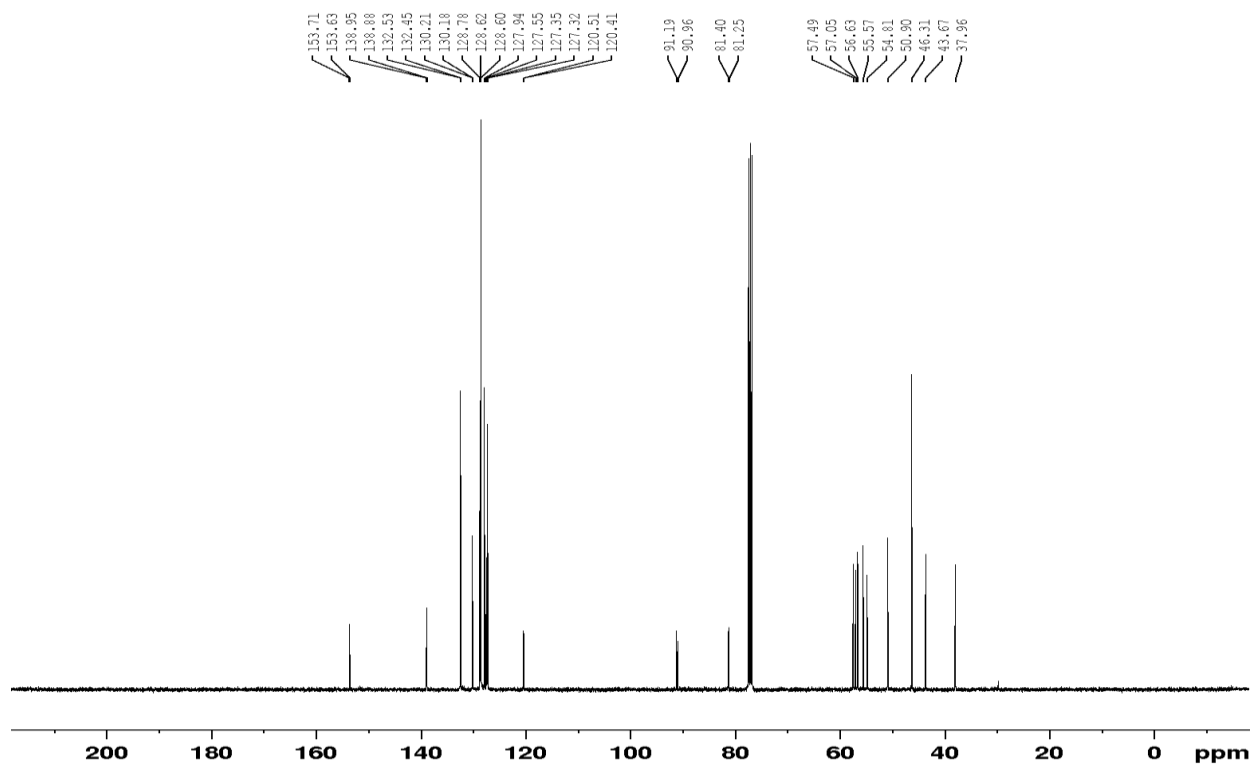


1-(4-methyl-2-phenyl-piperazin-1-yl)-3-phenyl-prop-2-yn-1-one (3.3I)

<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (400 MHz)

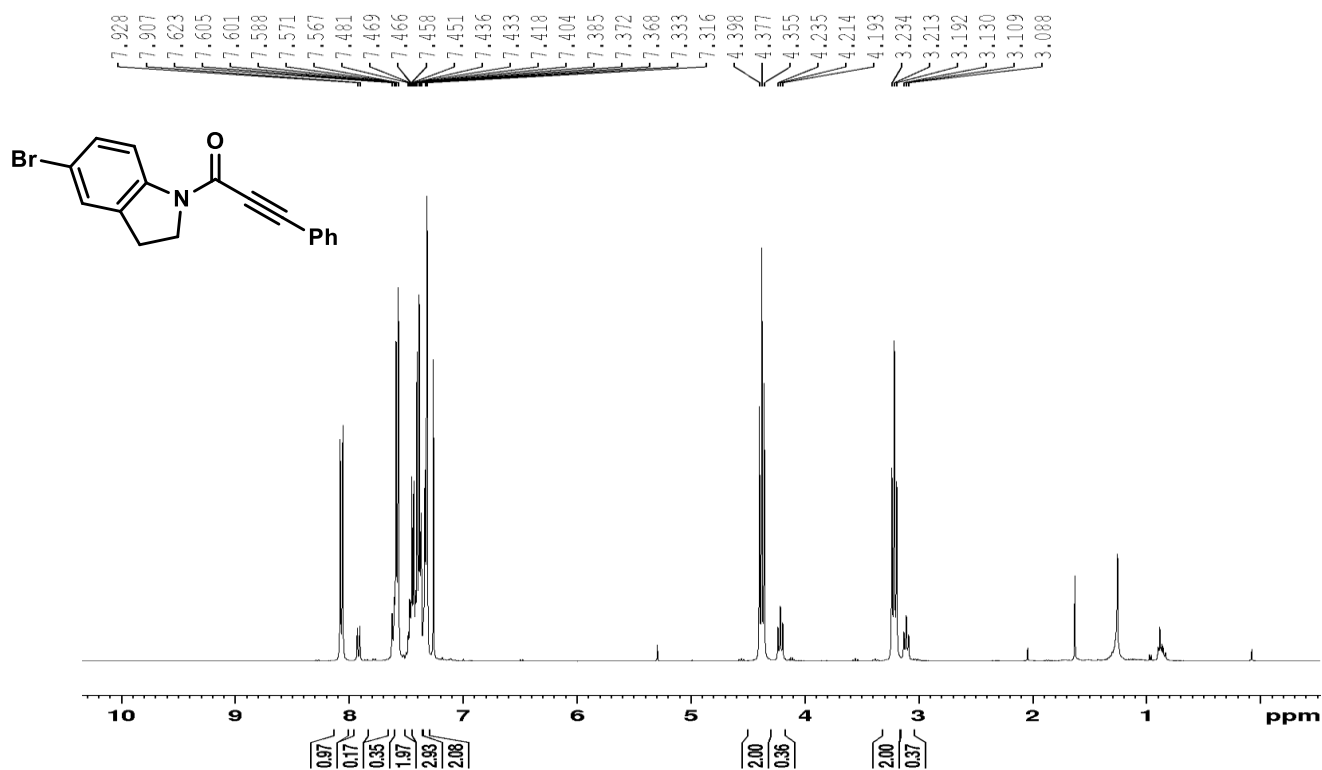


<sup>13</sup>C {<sup>1</sup>H} NMR Spectrum CDCl<sub>3</sub> (101 MHz)

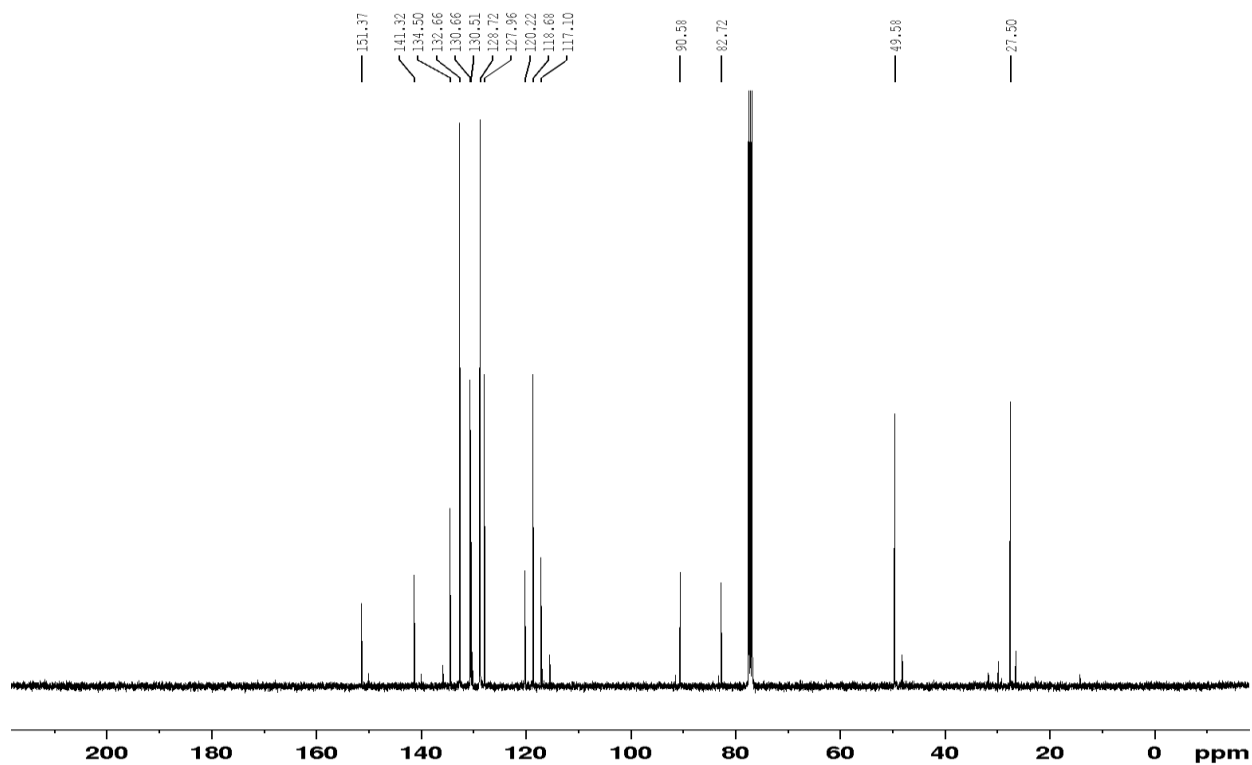


1-(5-bromoindolin-1-yl)-3-phenyl-prop-2-yn-1-one (3.3m)

$^1\text{H}$  NMR Spectrum  $\text{CDCl}_3$  (400 MHz)

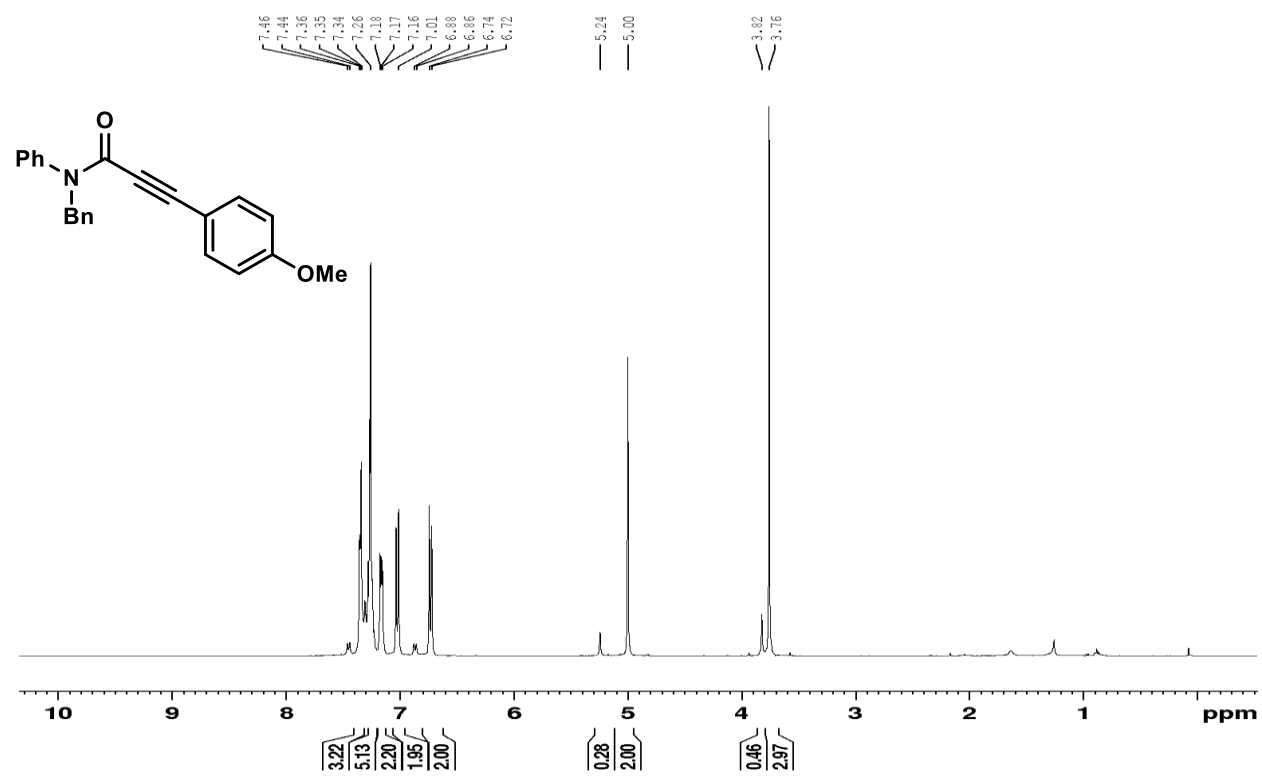


$^{13}\text{C}$   $\{^1\text{H}\}$  NMR Spectrum  $\text{CDCl}_3$  (101 MHz)

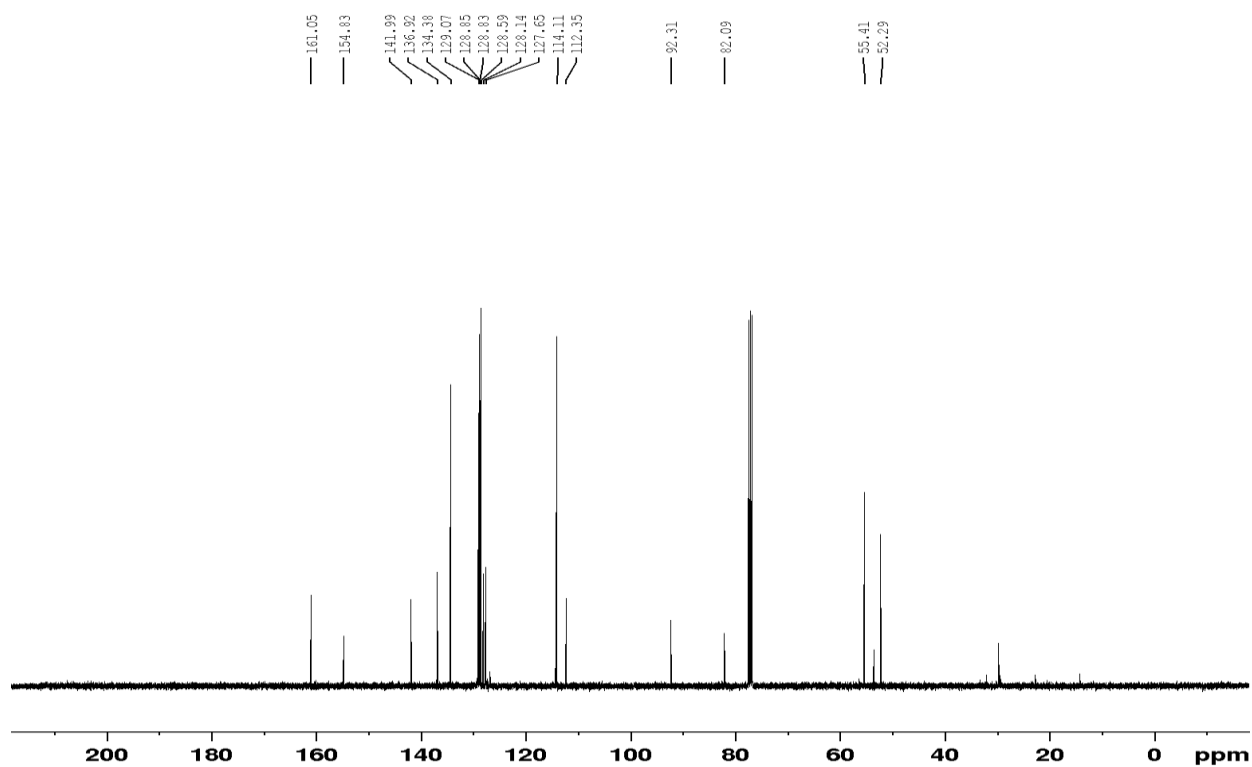


*N*-benzyl-3-(4-methoxyphenyl)-*N*-phenyl-prop-2-ynamide (3.3n)

<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (400 MHz)

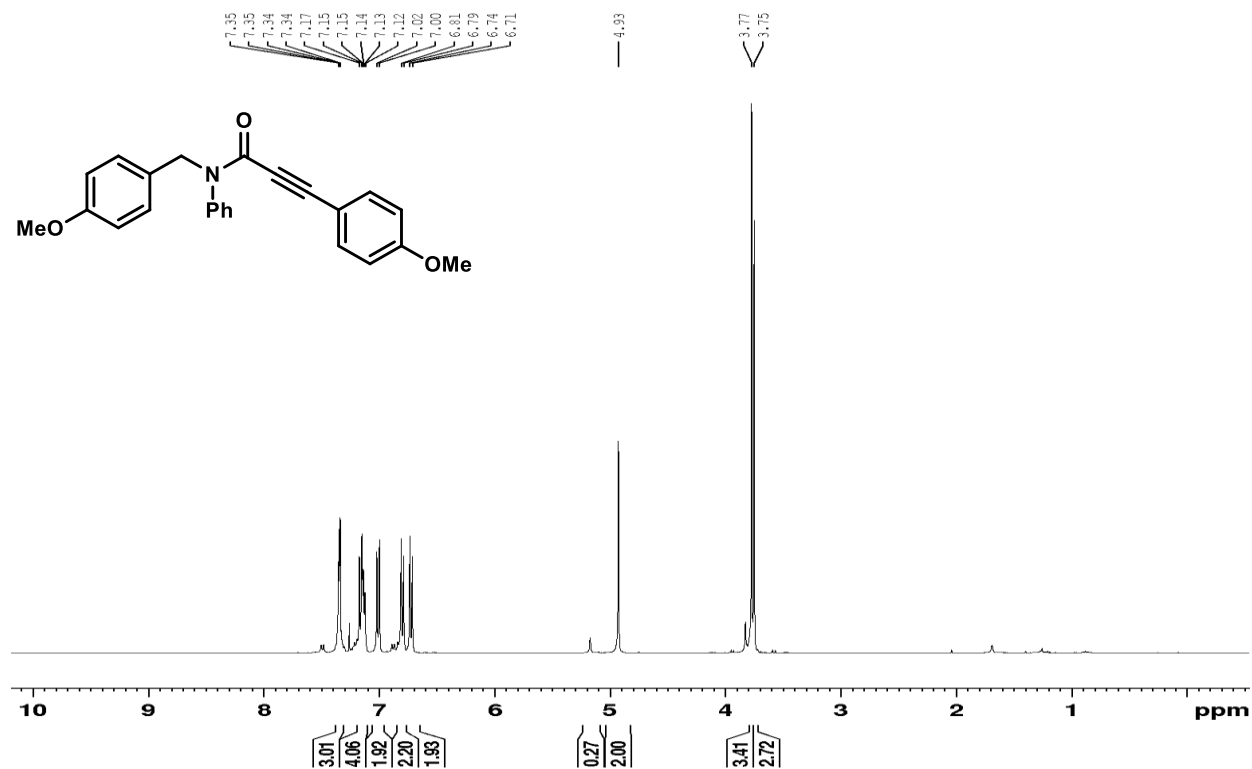


<sup>13</sup>C {<sup>1</sup>H} NMR Spectrum CDCl<sub>3</sub> (101 MHz)

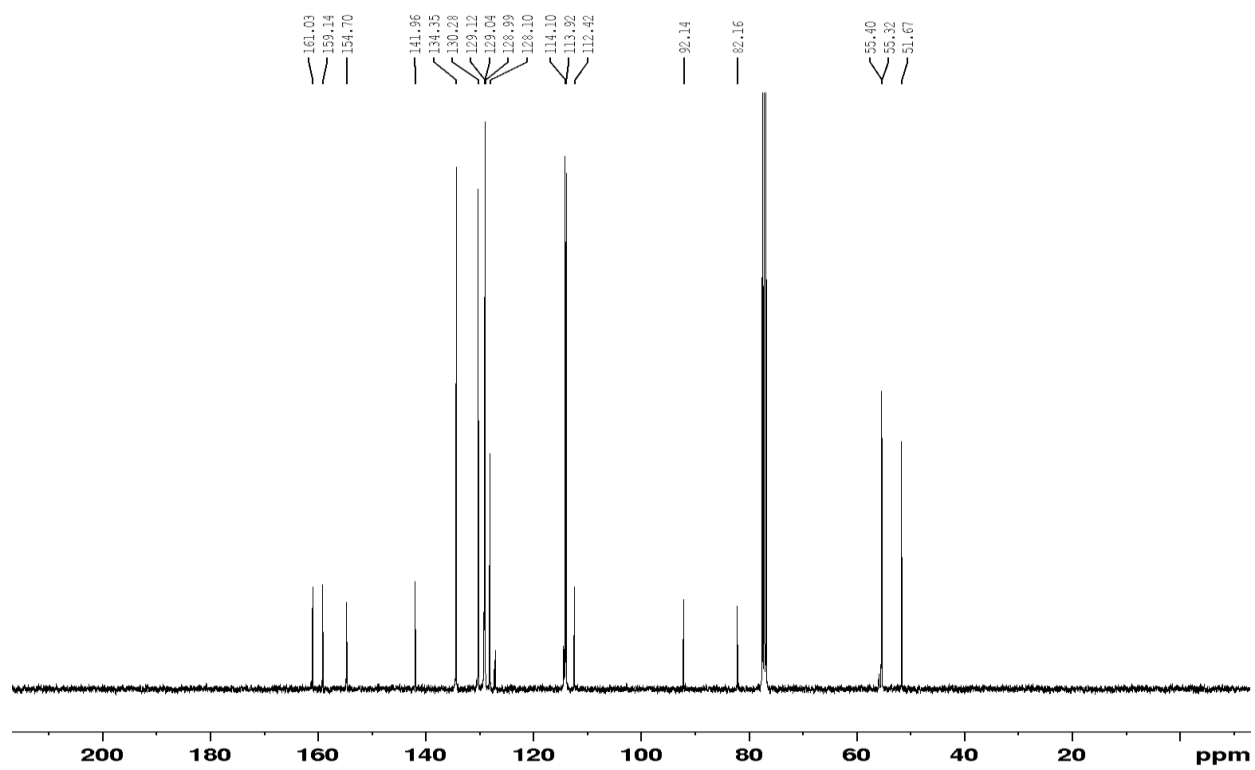


3-(4-methoxyphenyl)-N-[(4-methoxyphenyl)methyl]-N-phenyl-prop-2-ynamide (3.3q)

$^1\text{H}$  NMR Spectrum  $\text{CDCl}_3$  (400 MHz)



$^{13}\text{C}$   $\{^1\text{H}\}$  NMR Spectrum  $\text{CDCl}_3$  (101 MHz)



# Chapter 4: Towards the Asymmetric Cyanoalkylation of Carbamoyl Fluorides

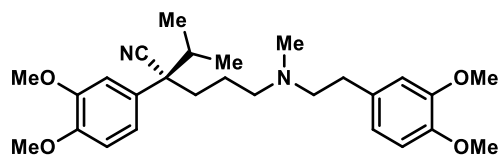
## 4.1. Contributions

The final chapter of this dissertation describes the development of a Lewis base-catalyzed cyanoalkylation of carbamoyl fluorides with silyl ketene imines and our efforts towards an asymmetric variant. Following the previously described alkynylation of carbamoyl fluorides,  $\alpha$ -cyanoamides could be obtained under fluoride catalysis. Phenanthrolines and phosphine oxides were also found to catalyze this reaction, allowing an entry point to asymmetric catalysis. This work was done in collaboration with undergraduate student Xavier Poblete, who prepared various starting materials and conducted a mechanistic study using  $^{31}\text{P}$  NMR spectroscopy. The author's contributions include all other experiments detailed in this chapter.

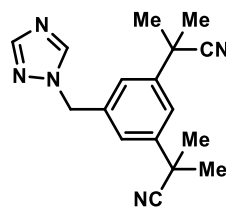
## 4.2. Introduction

In the previous chapter, we developed a method to access alkynamides from carbamoyl fluorides and alkynyl silanes driven by the formation of a strong Si-F bond. To expand this fluoride-enabled reactivity, we identified silyl ketene imines (SKIs) as a unique class of silylated nucleophiles. Coupling SKIs to carbamoyl fluorides would produce  $\alpha$ -cyanoamides—a class of amides containing a nitrile group, which are prominent in medicinal chemistry (Figure 4.1)<sup>1</sup> and can be used as a synthetic handle for further diversification.

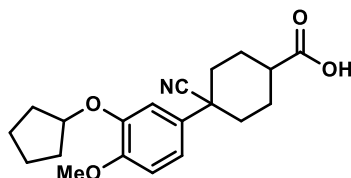




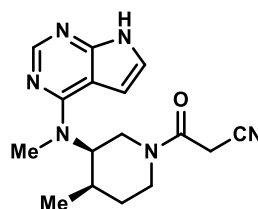
Verapamil (arrhythmia)



Anastrozole (breast cancer)



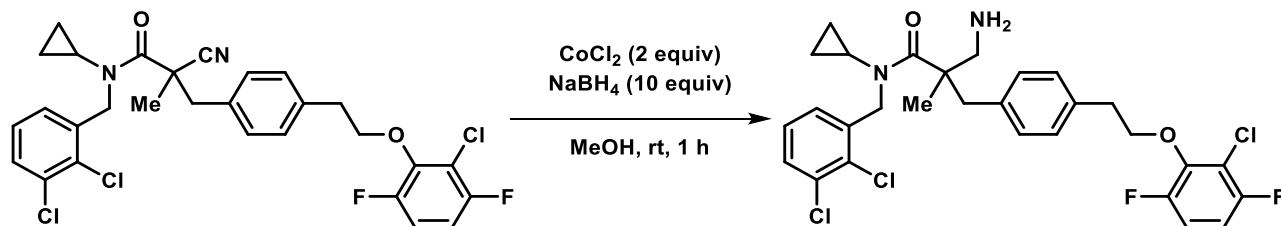
Cilomilast (anti-inflammatory)



Tofacitinib (rheumatoid arthritis)

Figure 4. 1: Selected Examples of Nitrile-Containing Molecules in the Pharmaceutical Industry

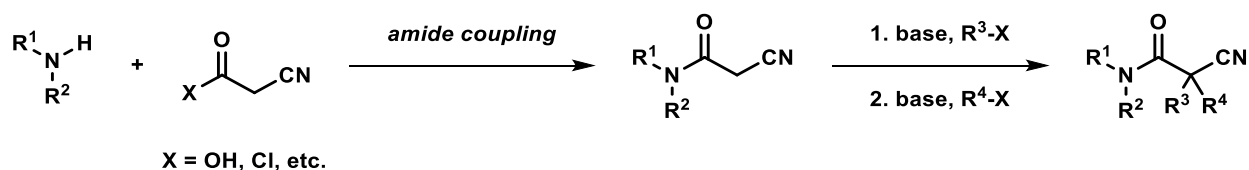
While less common than alkynamides,  $\alpha$ -cyanoamides have found impactful applications in the pharmaceutical industry. This moiety is present in the FDA-approved drug Tofacitinib, a treatment for rheumatoid arthritis (Figure 4.1). Researchers at Merck also used  $\alpha$ -quaternary  $\alpha$ -cyanoamides as intermediates towards  $\beta$ -aminoamides (Scheme 4.1), which were explored as renin inhibitors for blood pressure regulation.<sup>2</sup> These few yet impactful contributions to drug discovery motivated us to pursue a catalytic cyanoalkylation of carbamoyl fluorides. The introduction of this chapter will describe currently available routes for accessing  $\alpha$ -cyanoamides, including typical amide couplings, as well as some unique methods that provide highly substituted  $\alpha$ -cyanoamides from pre-formed amides. Applications of SKIs in asymmetric addition reactions will also be discussed.



Scheme 4. 1: Merck's Reduction of  $\alpha$ -Cyanoamides to  $\beta$ -Aminoamides

### 4.2.1 Synthesis of $\alpha$ -Cyanoamides

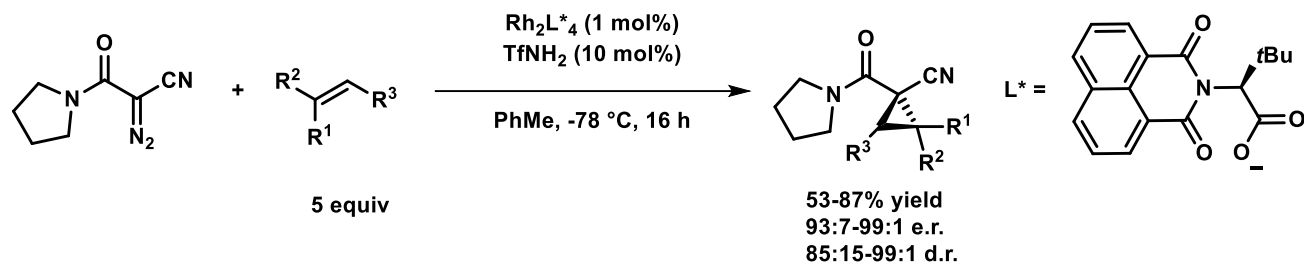
$\alpha$ -Cyanoamides can be prepared by the coupling of an amine with an  $\alpha$ -cyanocarboxylic acid using traditional amidation methods. This route is exemplified in the numerous syntheses of Tofacitinib, where a late-stage coupling of cyanoacetic acid to a highly functionalized amine scaffold is conducted.<sup>3,4</sup> The intermediates reported by Merck were also prepared by this method and amides bearing an  $\alpha$ -quaternary centre are accessed by sequential deprotonation-alkylation reactions after the key amide coupling step (Scheme 4.2).<sup>2</sup> The synthesis of highly substituted  $\alpha$ - $\alpha$ -disubstituted-cyanoamides via the coupling of tertiary carboxylic acids has also been reported.<sup>5-8</sup> Cyanoacetic acid derivatives suffer from limited commercial availability and the challenges of derivatizing cyanoacetic acid in the presence of an acidic carboxylic group can be daunting.



Scheme 4. 2: Typical Synthetic Route to  $\alpha$ -Cyanoamides

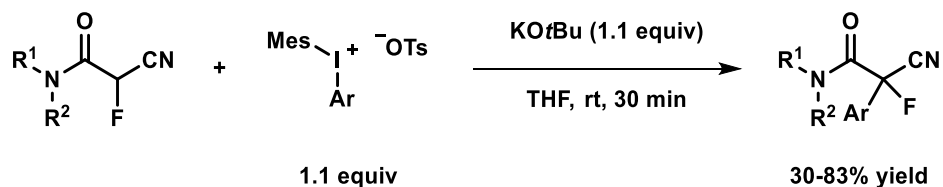
In 2009, Charette and co-workers developed a Rh-catalyzed asymmetric cyclopropanation reaction of alkenes with  $\alpha$ -diazo- $\alpha$ -cyanoamides to produce an all-carbon quaternary centre (Scheme 4.3).<sup>9</sup> During their optimization, the authors found that Brønsted acids had a profound effect on the enantioselectivity of the reaction. They determined that TfNH<sub>2</sub> was the optimal additive, noting that the influence of an achiral hydrogen bond donor on enantioselectivity is an unusual phenomenon. A variety of highly substituted  $\alpha$ -cyanoamides were prepared from terminal

and disubstituted alkenes in a highly enantio- and diastereoselective fashion. However, the scope of this reaction was limited in its diversity due to its exclusive use of pyrrolidine-derived amides.



Scheme 4. 3: Rh-Catalyzed Asymmetric Cyclopropanation of  $\alpha$ -Diazo- $\alpha$ -Cyanoamides

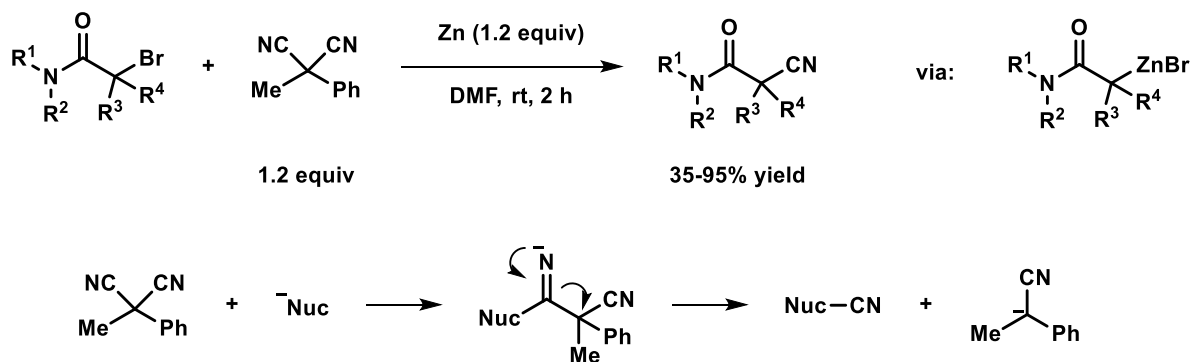
More recently, Mohanan and co-workers developed a nucleophilic arylation of  $\alpha$ -cyano- $\alpha$ -fluoroamides using diaryliodonium salts bearing a mesityl substituent (Scheme 4.4).<sup>10</sup> Deprotonation of the amide occurs with KO $t$ Bu and the resulting enolate coordinates to the cationic I(III) centre. A 1,2-shift of the enolate to the least hindered aryl ligand leads to selective arylation of the amide. This method provides a variety of  $\alpha$ -cyanoamides bearing quaternary  $\alpha$ -carbon centres under weakly basic conditions, although the authors focused their efforts only on fluorine-containing substrates.



Scheme 4. 4: Base-Mediated Arylation of  $\alpha$ -Cyano- $\alpha$ -Fluoroamides

Shortly after, the groups of Tian and Dong disclosed a reductive cyanation of  $\alpha$ -bromoamides using Zn dust and 2-methyl-2-phenylmalononitrile (MPMN) as the nitrile source (Scheme 4.5, top).<sup>11</sup> This reaction represents the only report of a C-CN disconnection to access  $\alpha$ -cyanoamides. This

occurs by the in-situ formation of the organozinc nucleophile, which then attacks MPMN to expel a  $\alpha$ -nitrile anion as a leaving group (Scheme 4.5, bottom). Alternatively, the same disconnection could theoretically be achieved via a substitution reaction of the  $\alpha$ -bromoamide with a highly toxic cyanide salt. The presented approach benefits from the use of a non-toxic, electrophilic cyanide source. While the above methods are useful for accessing highly substituted  $\alpha$ -cyanoamides, they suffer from the requirement of pre-functionalized amide starting materials that are prepared by stoichiometric coupling reactions.

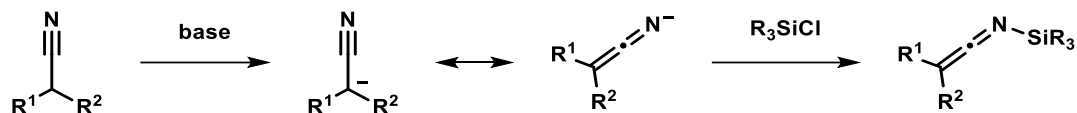


Scheme 4. 5: Zn-Mediated Cyanation of  $\alpha$ -Bromoamides

#### 4.2.2 Silyl Ketene Imines in Asymmetric Addition Reactions

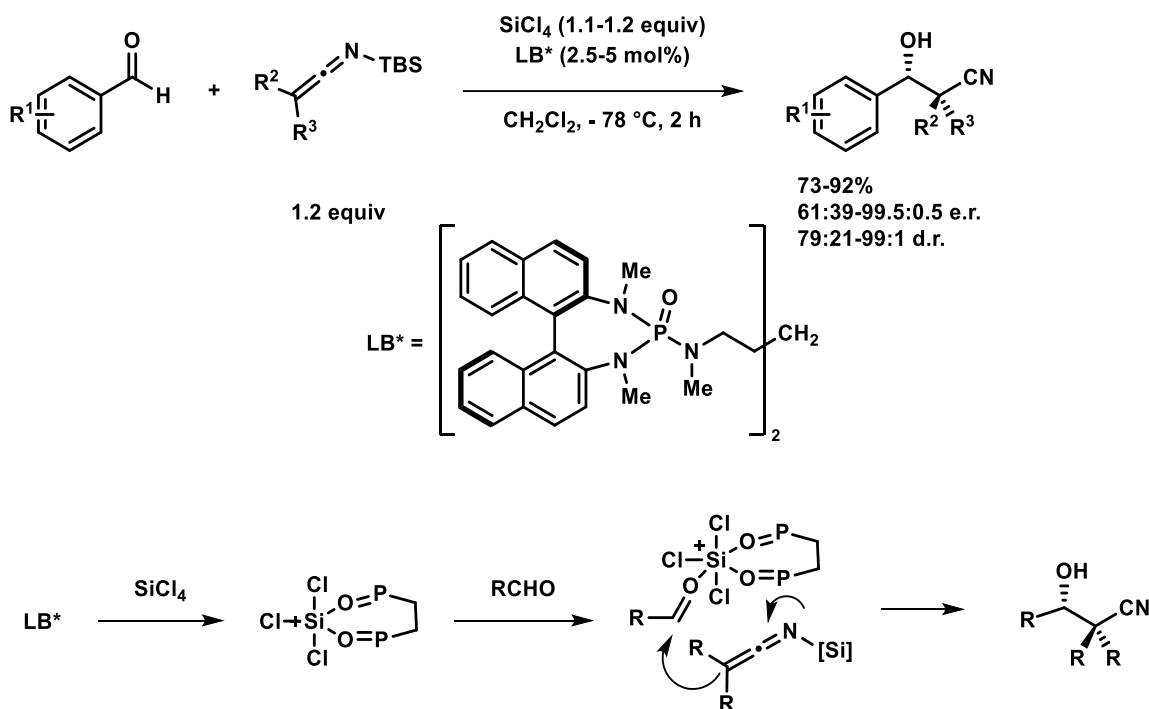
A common way to prepare nitrile-containing molecules is by cyanoalkylation, a process in which an organic fragment containing a nitrile is coupled to another reactive synthon.<sup>12</sup> The most common method for cyanoalkylation is to simply deprotonate the  $\alpha$ -C–H bond of an alkyl nitrile and quench the anion with an electrophile. However, the  $\alpha$ -nitrile anion is in equilibrium with a ketene imide anion which can be trapped with a silyl chloride, leading to isolable SKIs when starting from a secondary nitrile (Scheme 4.6). While SKIs are highly susceptible to hydrolysis, they have found widespread use in asymmetric synthesis and catalysis, as their reaction with various electrophiles provides entry to stereogenic all-carbon quaternary centres.<sup>13</sup> The bulky silyl

groups (TBS or TIPS) are required to form isolable SKIs, but these protecting groups may also enhance asymmetric induction through steric interactions.



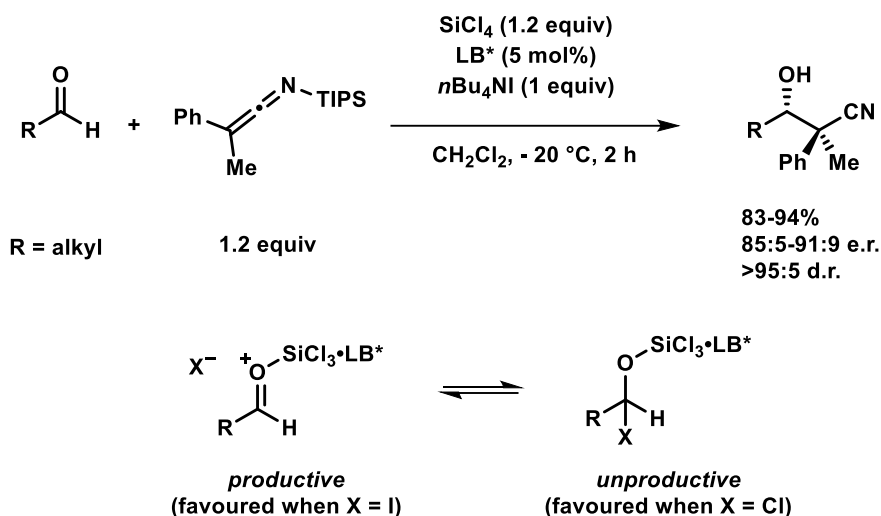
Scheme 4. 6: Preparation of Silyl Ketene Imines

In 2007, Denmark and co-workers developed a Lewis base-catalyzed,  $\text{SiCl}_4$ -mediated cyanoalkylation of benzaldehydes with SKIs in an aldol-type reaction to produce  $\beta$ -hydroxy nitriles (Scheme 4.7, top).<sup>14</sup> The authors found the ideal Lewis base to be a bis-phosphoramidate ( $\text{LB}^*$ ), which maintained high enantio- and diastereoselectivity across a number of substrates. Based on an earlier report,<sup>15</sup> it is speculated that the active catalyst in this reaction is formed by the coordination of both phosphoramidate oxygens to  $\text{SiCl}_4$ , displacing a chloride to form a highly Lewis acidic cationic silane (Scheme 4.7, bottom). The aldehyde then coordinates to the Si atom, increasing its electrophilicity and allowing for attack by the SKI.



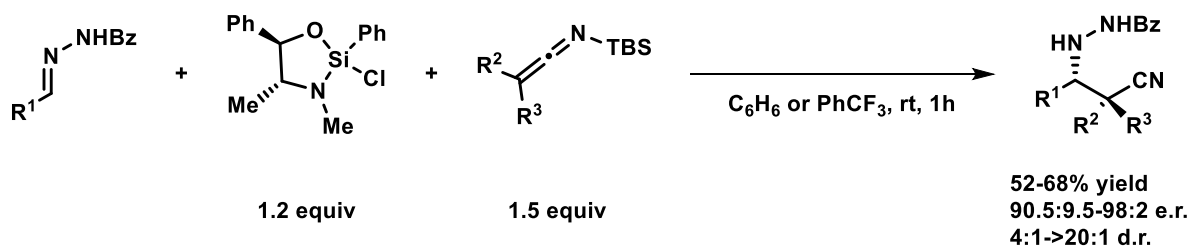
Scheme 4. 7: Lewis Base-Catalyzed Cyanoalkylation of Benzaldehydes with SKIs

In a follow-up report, the same group found that this method could be expanded to aliphatic aldehydes when the silyl group on the SKI was changed to TIPS and stoichiometric tetrabutylammonium iodide (TBAI) was added to the reaction (Scheme 4.8, top).<sup>16</sup> The Lewis acid-activated carbonyl can undergo attack by a chloride anion, a feature that is detrimental to the rate of the reaction with aliphatic aldehydes (Scheme 4.8, bottom). The addition of TBAI shifts this equilibrium to the coordinated aldehyde, allowing the reaction to proceed smoothly. The bulkier TIPS group improved the enantioselectivity with aliphatic aldehydes.



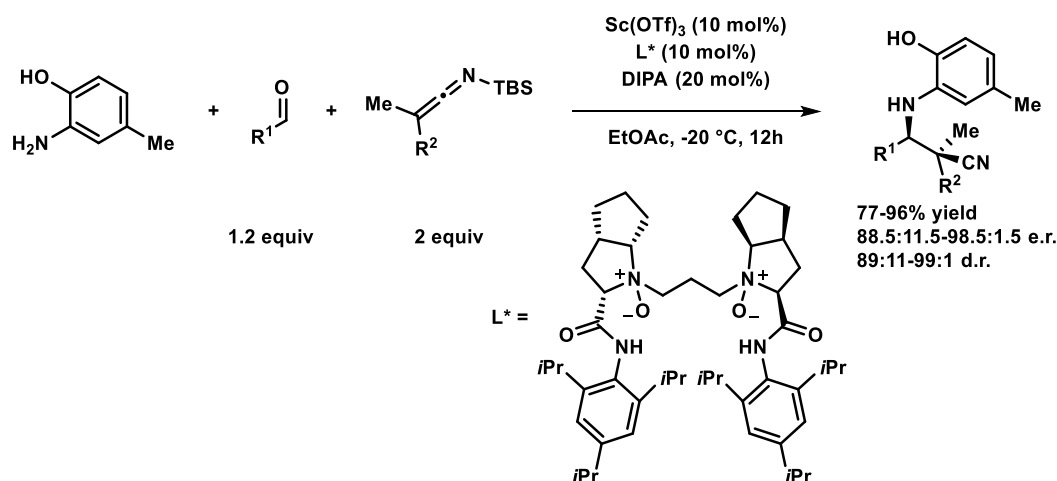
Scheme 4. 8: Cyanoalkylation of Alkyl Aldehydes and Halide-Dependant Equilibrium

Shortly after Denmark's seminal report, Leighton and co-workers developed an asymmetric Mannich-type reaction of aldehyde-derived *N*-benzoyl hydrazones (Scheme 4.9).<sup>17,18</sup> Rather than a catalytic ligand system, this reaction uses a stoichiometric chiral silane to mimic the Denmark approach without using pyrophoric  $\text{SiCl}_4$ . The chiral moiety of the silane is derived from the amino acid alanine, making it more economically viable than Denmark's phosphoramidate. The resulting  $\beta$ -hydrazinyl nitriles were obtained in moderate yields and with good to excellent enantiomeric and diastereomeric ratios.



Scheme 4. 9: Chiral Silane-Mediated Cyanoalkylation of *N*-Benzoyl Hydrazones

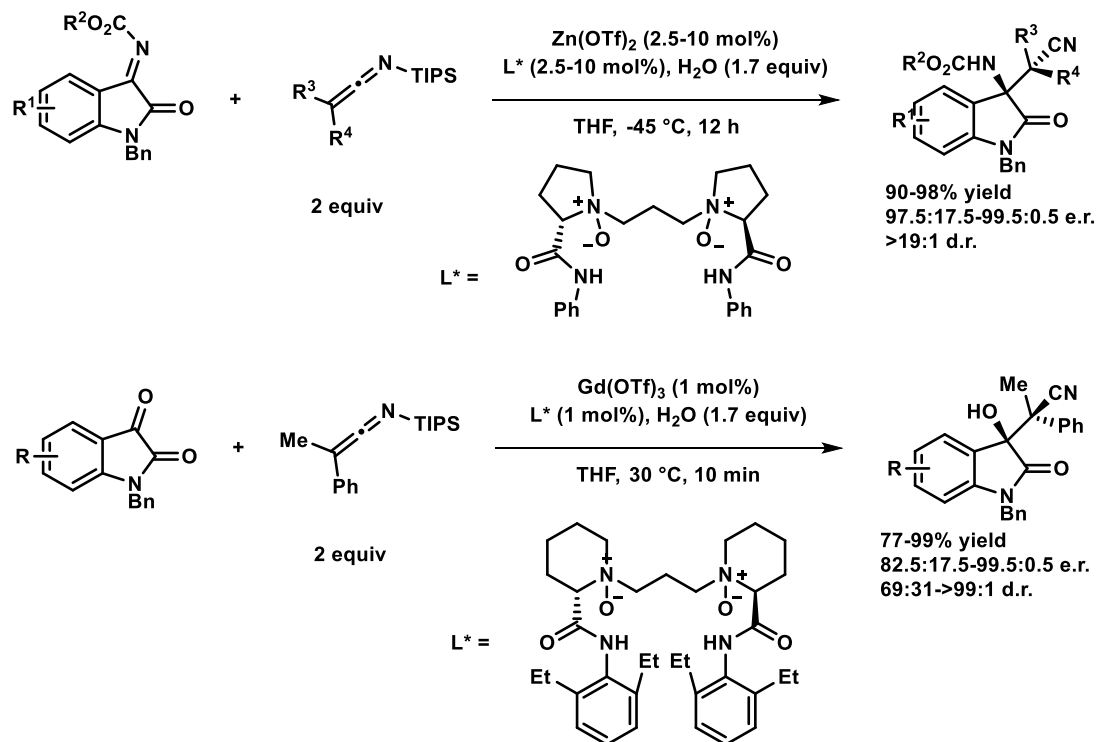
Feng and co-workers have developed several addition reactions of SKIs enabled by metal triflate salts in combination with chiral *N,N*-dioxide ligands developed in their lab.<sup>19</sup> The use of these ligated Lewis acid systems remove the need for stoichiometric additives in the reaction. This group first developed an asymmetric Sc-catalyzed three-component Mannich-type reaction of aldehydes, SKIs and 2-amino-4-methylphenol (Scheme 4.10).<sup>20</sup> After condensation of the aldehyde and the aminophenol, the resulting imine and phenolic oxygen coordinate to the *N,N*-dioxide-bound Sc(OTf)<sub>3</sub> which is sufficiently electrophilic to enable SKI addition.



Scheme 4. 10: Sc/*N,N*-dioxide-Catalyzed Cyanoalkylation of In-Situ-Formed Imines

Another report by the Feng group disclosed the asymmetric addition of SKIs to imines derived from isatin analogs (Scheme 4.11, top).<sup>21</sup> Ligand-bound Zn(OTf)<sub>2</sub> effectively catalyzed this reaction with excellent yields, enantio- and diastereoselectivities. The *N*-carbamate group is also easily deprotected, allowing simple access to primary amines. Switching to a Gd(OTf)<sub>3</sub> catalyst enables the aldol-type addition of parent isatin derivatives (Scheme 4.11, bottom).<sup>22</sup> This advance provides access to functionalized 3-hydroxy-2-oxindole products.



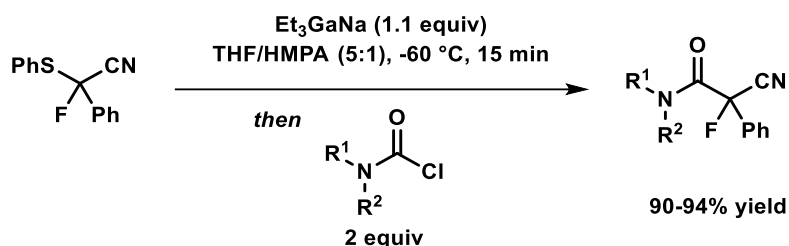


Scheme 4. 11: Zn or Gd/*N,N*-dioxide-Catalyzed Cyanoalkylation of Isatin Derivatives

## 4.3 Motivation and Research Plans

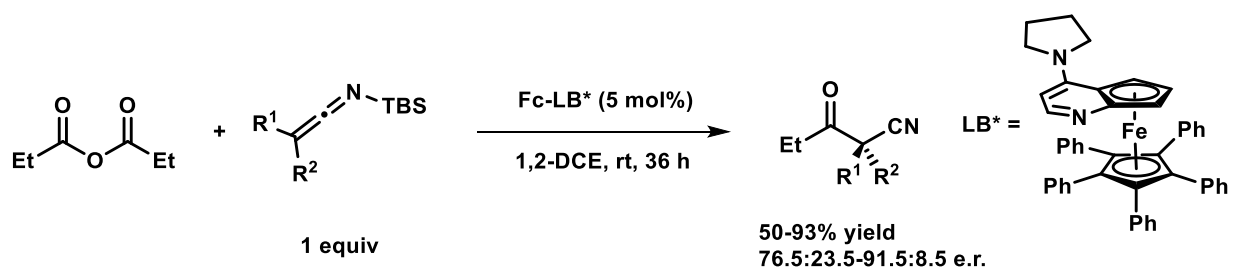
To expand the reactivity of carbamoyl fluorides, we envisioned the cyanoalkylation with SKIs would provide efficient entry to  $\alpha$ -cyanoamides bearing a chiral quaternary carbon centre. This method features a convergent coupling of two functionalized fragments, in contrast to the methods introduced in Section 4.2.1., involving the amidation and subsequent alkylation of cyanoacetic acid.<sup>2-8</sup> We hypothesize that fluoride catalysts should produce the desired products, like our previous study on alkynamide synthesis.<sup>23</sup> While chiral fluoride catalysts have been reported,<sup>24,25</sup> other classes of Lewis bases would likely provide a more accessible avenue for asymmetric catalysis. As SKIs are more reactive than alkynyl silanes, finding a suitable Lewis base for screening chiral variants should be achievable.

The cyanoalkylation of carbamoyl chlorides has previously been reported using 2-fluoro-2-phenylthio-2-phenylacetonitrile and Et<sub>3</sub>GeNa (Scheme 4.12).<sup>26</sup> Treatment of the nitrile precursor with Et<sub>3</sub>GeNa at low temperature initiates a desulfurization, providing the nitrile anion in-situ. Subsequent treatment with carbamoyl chloride leads to the desired fluorine-containing  $\alpha$ -cyanoamide. Despite the use of a limited number of substrates, the desired products were obtained in excellent yield, demonstrating that the cyanoalkylation of carbamoyl electrophiles is possible. While carbamoyl fluorides are less prone to nucleophilic attack than their chloride counterparts, the use of SKIs should provide a thermodynamic driving force in the form of Si-F bond formation.



Scheme 4. 12: Desulfurative Cyanoalkylation of Carbamoyl Chlorides

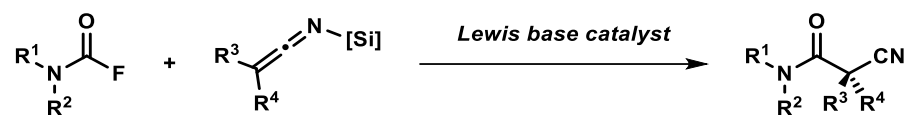
In asymmetric catalysis, SKIs have primarily been used in addition reactions to aldehydes, ketones and imines while operating via Lewis acid activation. In 2005, Fu and co-workers reported a Lewis base-catalyzed cyanoalkylation of anhydrides to access  $\alpha$ -cyanoketones (Scheme 4.13).<sup>27</sup> The nucleophilic catalyst, a planar chiral 4-aminopyridine derivative (Fc-LB\*), attacks the anhydride to form a highly electrophilic acyl pyridinium intermediate without the addition of Lewis acidic additives. Nucleophilic acyl substitution by the SKI forms the desired product with excellent enantioselectivity. Overall, this method demonstrates that SKIs can participate in acylation reactions under an alternative activation mechanism.



Scheme 4. 13: Lewis Base-Catalyzed Cyanoalkylation of Propanoic Anhydride

Considering the body of work on cyanoalkylation,  $\alpha$ -cyanoamides formation from carbamoyl fluorides and SKIs should be viable (Scheme 4.14). Fluoride, or another suitable Lewis base, should activate the SKI via desilylation or silicate formation. Then, the activated nucleophile can attack the carbamoyl fluoride, ejecting the fluoride leaving group which can re-enter the

catalytic cycle or serve to liberate the Si-bound Lewis base. Such reactivity would build upon the work of Olofson and us by expanding the scope of carbamoyl fluoride additions to Csp<sup>3</sup> nucleophiles to provide chiral products.

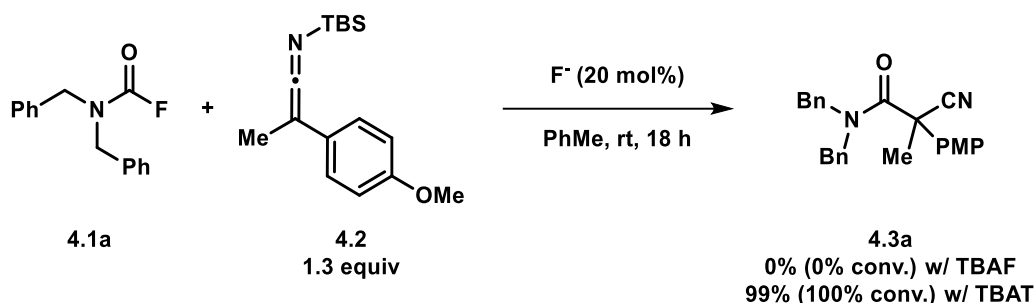


Scheme 4. 14: Proposed Lewis Base-Catalyzed Cyanoalkylation of Carbamoyl Fluorides with SKIs

## 4.4. Results and Discussion

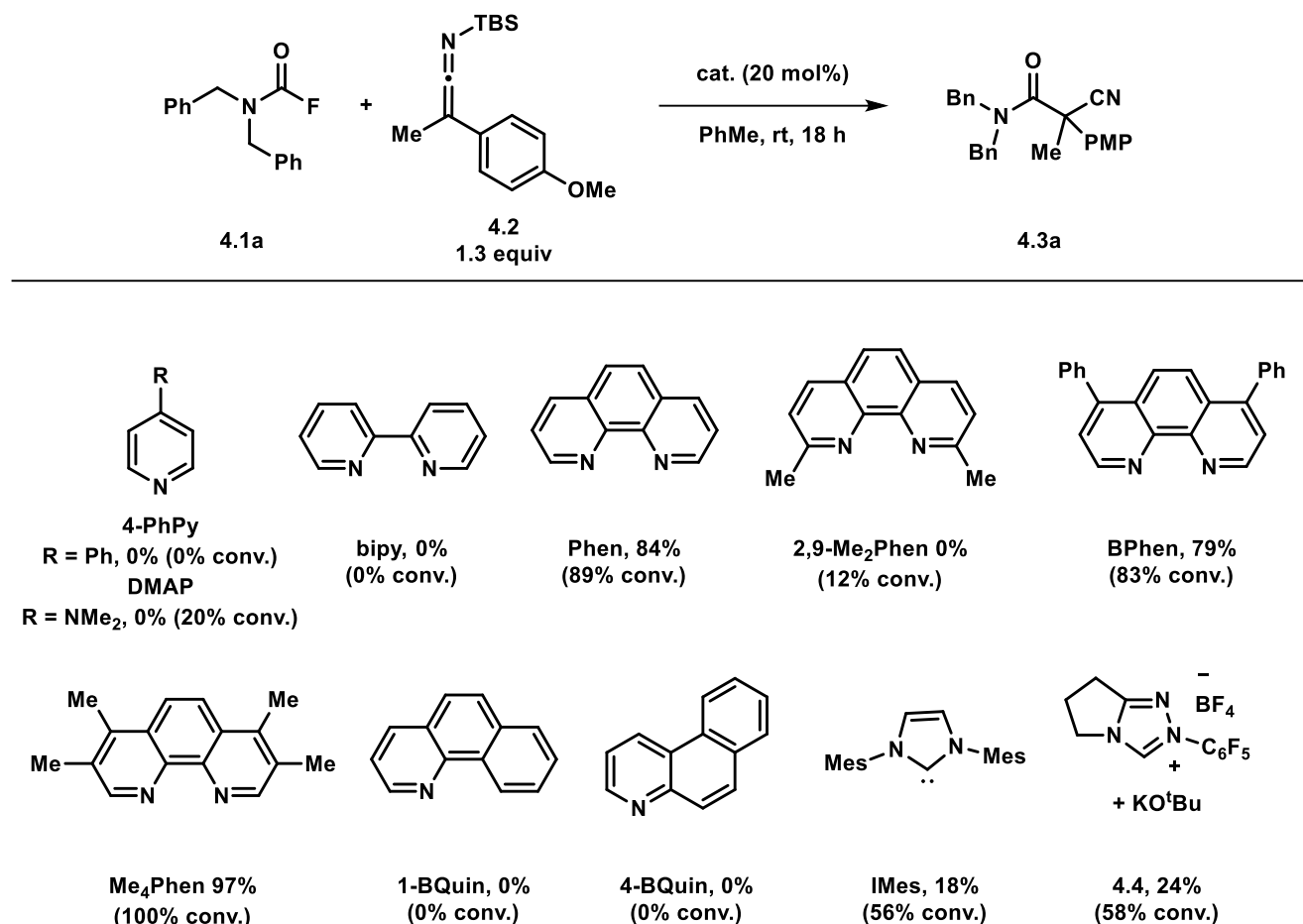
### 4.4.1. Racemic Reaction Optimization

We began this project by identifying an optimal achiral Lewis base catalyst. Dibenzylcarbamoyl fluoride **4.1a** was combined with 1.3 equivalents of SKI **4.2** and 20 mol% of the catalyst in PhMe at room temperature for 18 hours (Scheme 4.15). The yield of **4.3a** and conversion of **4.1a** were determined by quantitative <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. When using TBAF, we observed no formation of α-cyanoamide **4.3a** with complete recovery of **4.1a** and the formation of a secondary nitrile corresponding to hydrolysis of **4.2**. This result is not entirely unsurprising, as TBAF is hygroscopic and SKIs are extremely sensitive to water. Next, we tested TBAT, a less hygroscopic fluoride source, and found that **4.3a** was obtained in near quantitative yield.



Scheme 4. 15: Initial Hit for Fluoride-Catalyzed Cyanoalkylation of Carbamoyl Fluorides

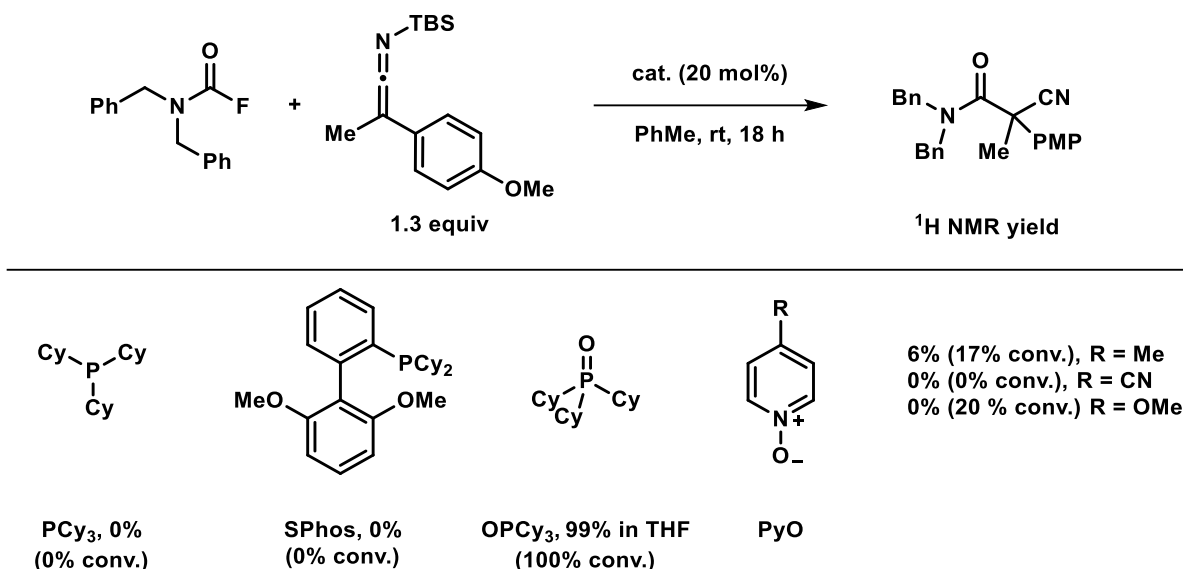
Despite this encouraging result, we opted to continue screening Lewis bases to have multiple entry points to asymmetric catalyst design (Scheme 4.16). Mimicking Fu's report, 4-phenyl pyridine (4-PhPy) and DMAP were both tested in the reaction, but no product was observed from either reaction. Using bipyridine (bipy) as a bis-chelating catalyst also provided no reactivity. Interestingly, when phenanthroline (Phen) was used in the reaction, **4.3a** was obtained in 84% yield. When 2,9-dimethylphenanthroline (2,9-Me<sub>2</sub>Phen) was used, the yield of **4.3a** dropped to 0% with minimal consumption of carbamoyl fluoride, indicating steric hinderance at the nitrogen atoms of the catalyst is detrimental to reactivity. Bathophenanthroline (BPhen) was comparable to the unsubstituted heterocycle, and we found that 2,3,6,7-tetramethylphenanthroline (Me<sub>4</sub>Phen) provided **4.3a** in 97% yield. As bipy was an ineffective catalyst, it is apparent that the rigidity of the phenanthrene core is essential to reactivity. To further explore the impact of the catalyst structure, we tested two benzoquinolines molecules (2-BQuin and 4-BQuin) that contain the correct aromatic structure but only a single nitrogen atom. These were also found to be ineffective catalysts, indicating that both nitrogen atoms are required.



Scheme 4. 16: Screen of Heterocyclic Lewis Base Catalysts for Cyanoalkylation of Carbamoyl Fluorides

Common Lewis base catalysts for asymmetric catalysis are *N*-heterocyclic carbenes (NHCs), a class of neutral ambiphilic molecules. We tested the isolable, bulky and electron-rich NHC, IMes, which led to an 18% yield. A less electron-rich NHC prepared in-situ from triazolium salt **4.4** provided **4.3a** in 24% yield. However, both catalysts consumed significantly more carbamoyl fluoride than the amide produced and the <sup>1</sup>H NMR spectra revealed several unidentified by-products. During the reaction set-up, we observed a slight colour change when the stock solution of carbamoyl fluoride was added to the NHCs, indicating that they may react with both **4.1a** and **4.2a**, leading to unproductive decomposition of both reagents.

Several phosphines were also screened in the hope of adopting widely available ligands as catalysts for this cyanoalkylation reaction. Unfortunately, no reactivity was observed with either PCy<sub>3</sub> or SPhos (Scheme 4.17). Oxidation of phosphines to phosphine oxides is a fast and simple process and the resulting P(V) compounds are also good Lewis bases. When OPCy<sub>3</sub> was used in the reaction, **4.3a** was obtained in quantitative yield. This reaction was conducted in THF, as we were initially concerned about the solubility of the catalyst. Pyridine *N*-oxides (PyO) were also tested as nucleophilic catalysts. However, 4-MePyO provided a low yield of **4.3a**, with other electronically diverse analogs proving to be unreactive.

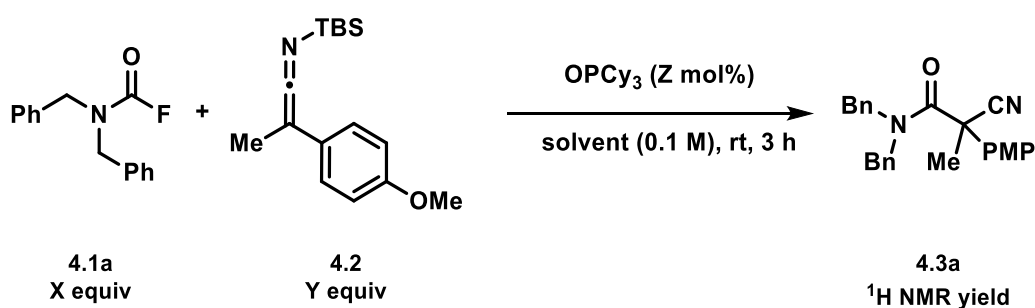


Scheme 4. 17: Screening of Phosphine, Phosphine Oxide and Pyridine *N*-Oxide Catalysts for the Cyanoalkylation of Carbamoyl Fluorides

As phosphine oxides offered the simplest path forward for screening chiral derivatives, the reaction was further optimized with OPCy<sub>3</sub> as the catalyst (Table 4.1). When changing the equivalents of **4.1a** and **4.2a**, we found lowering the equivalents of SKI decreased the yield of the desired amide (Entry 1-3). Switching the SKI to the limiting reagent (Entry 4, 5) provided no

improvement over a 1:1 ratio of **4.1a** and **4.2**. We also found that decreasing the catalyst loading dropped the yield significantly (Entry 6, 7), leading us to keep the initial 20 mol% loading of OPCy<sub>3</sub>. Finally, several solvents were screened, and it was revealed that the reaction proceeds quantitatively in both PhMe (Entry 8) and hexanes (Entry 9). The use of dichloromethane and MeCN led to subpar yields of 10 and 27%, respectively (Entry 9, 10).

Table 4.1: Further Optimization with OPCy<sub>3</sub>

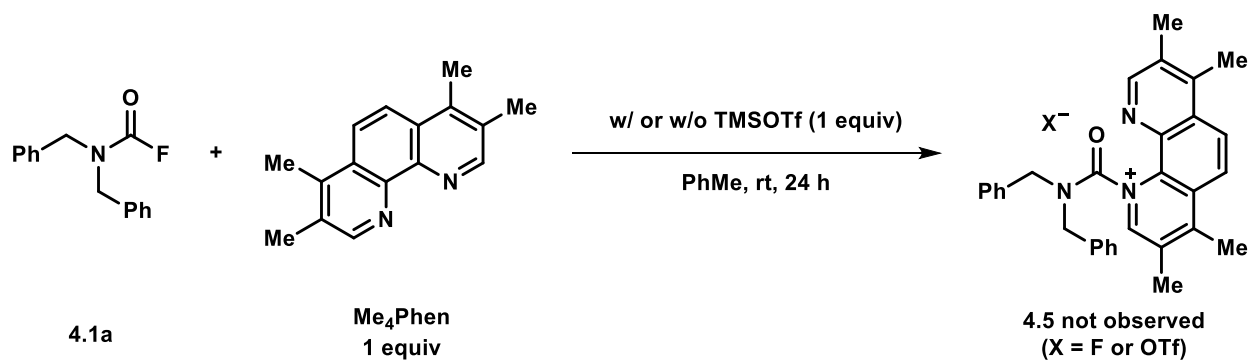


| Entry | X   | Y   | Z  | Solvent                         | Conversion of limiting reagent (%) | <sup>1</sup> H NMR Yield (%) |
|-------|-----|-----|----|---------------------------------|------------------------------------|------------------------------|
| 1     | 1.0 | 1.3 | 20 | THF                             | 100                                | 99                           |
| 2     | 1.0 | 1.1 | 20 | THF                             | 89                                 | 86                           |
| 3     | 1.0 | 1.0 | 20 | THF                             | 80                                 | 79                           |
| 4     | 1.1 | 1.0 | 20 | THF                             | 89                                 | 80                           |
| 5     | 1.3 | 1.0 | 20 | THF                             | 90                                 | 81                           |
| 6     | 1.0 | 1.3 | 10 | THF                             | 53                                 | 49                           |
| 7     | 1.0 | 1.3 | 5  | THF                             | 16                                 | 13                           |
| 8     | 1.0 | 1.3 | 20 | PhMe                            | 100                                | 99                           |
| 9     | 1.3 | 1.3 | 20 | hexanes                         | 100                                | 99                           |
| 10    | 1.0 | 1.3 | 20 | CH <sub>2</sub> Cl <sub>2</sub> | 5                                  | 10                           |
| 11    | 1.0 | 1.3 | 20 | MeCN                            | 18                                 | 27                           |



## 4.4.2 Substrate Compatibility and Mechanistic Studies

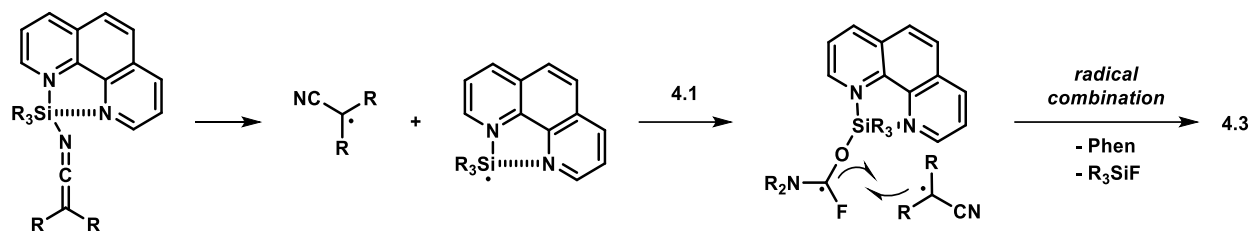
Phenanthrolines represent the most fascinating catalyst discovered for the cyanoalkylation of carbamoyl fluorides with SKIs. They are worse Lewis bases than numerous other failed catalysts and their structural rigidity and two nitrogen atoms seem to be required. Prior examples of phenanthroline catalysis<sup>28</sup> and Fu's work<sup>27</sup> suggest that an aromatic heterocycle can form a pyridinium-type salt with a reactive electrophile. However, when combining **4.1a** and 1 equivalent of Me<sub>4</sub>Phen no evidence of a carbamoyl phenanthroline salt **4.5** was observed by <sup>1</sup>H and <sup>19</sup>F NMR monitoring (Scheme 4.18). We hypothesized that the addition of TMSOTf could trap the fluoride anion to force the formation of a salt, but no reaction was observed, indicating that **4.5** is not a likely intermediate at room temperature. No change in the <sup>1</sup>H or <sup>19</sup>F NMR spectra was observed when SKI **4.2a** was combined with an equivalent of Me<sub>4</sub>Phen, suggesting that all three components must be present for the reaction to occur.



Scheme 4. 18: Attempted Formation of a Postulated Carbamoyl Phenanthroline Salt

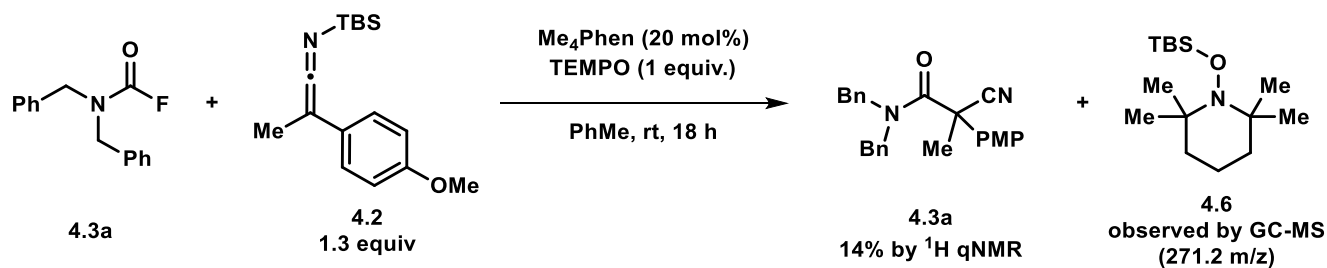
A radical cyanoalkylation mechanism under phenanthroline catalysis was also briefly considered. This may proceed by homolytic cleavage of the Si-N bond upon phenanthroline coordination to Si, followed by radical activation of **4.3** to the Phen-Si complex (Scheme 4.19). The resulting

radical partners could then combine and subsequent loss of silyl fluoride and regeneration of the catalyst could produce **4.3**.



Scheme 4. 19: Possible Radical Cyanoalkylation Mechanism Under Phenanthroline Catalysis

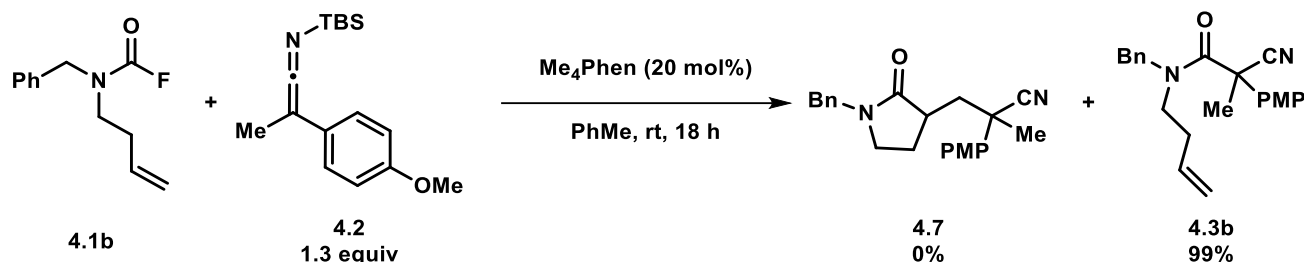
To investigate the plausibility of this radical pathway, one equivalent of TEMPO was added to the reaction (Scheme 4.20). Interestingly, this addition dropped the yield of **4.3a** to 14% and a silane-TEMPO adduct **4.6** was observed by GC-MS. While this may provide evidence for a radical mechanism, the oxophilicity of Si and high reactivity of **4.2** may lead to its decomposition. In fact, when **2.4** is subjected to TEMPO alone, **4.6** is still observed by GC-MS.



Scheme 4. 20: Standard Reaction in the Presence of TEMPO

A radical clock experiment was conducted using alkene-tethered carbamoyl fluoride **3.1b** to probe the formation of a carbamoyl radical (Scheme 4.21). In this case, such a radical should cyclize on the alkene, providing lactam product **4.7**. No cyclization was observed and **4.3b** was obtained in quantitative yield, indicating that a radical mechanism is not likely. No peak broadening was observed when the reaction of **4.1a** and **4.2a** was also monitored by in situ  $^1\text{H}$  and

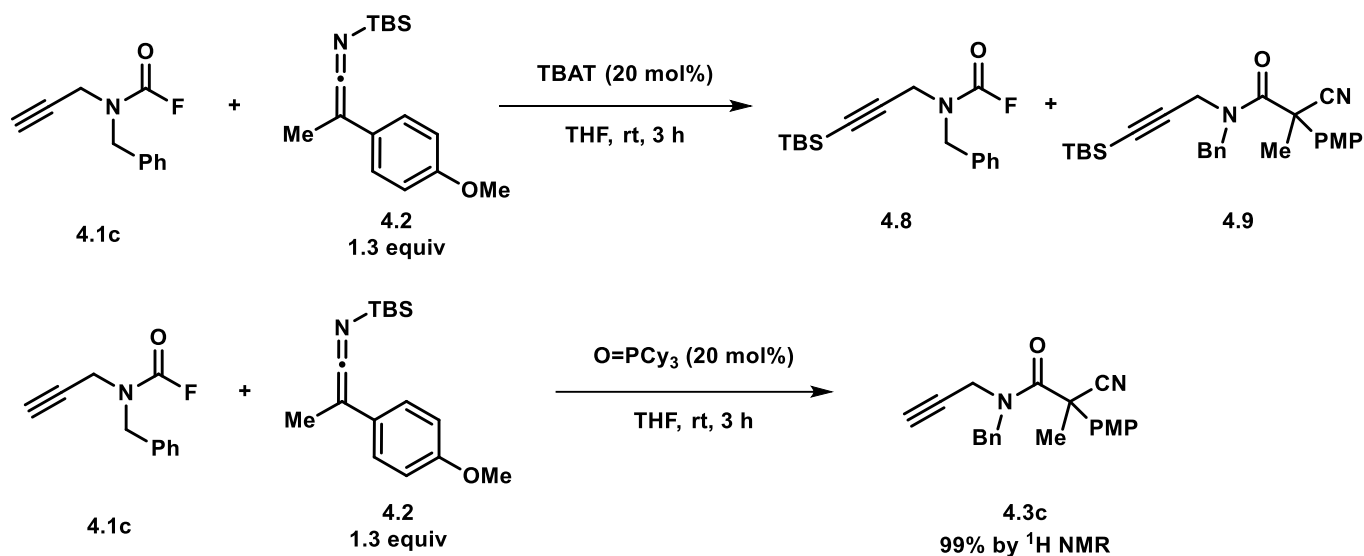
$^{19}\text{F}$  NMR spectroscopy, making the presence of radical intermediates unlikely. At this time, we suspect that the phenanthroline-catalyzed reaction proceeds through activation of the Si atom of **4.2**.



Scheme 4. 21: Radical Clock Experiment with Alkene-Tethered Carbamoyl Fluoride

In our previous study on the alkynylation of carbamoyl fluorides, we determined that substrates bearing relatively acidic protons were incompatible due to the generation of an ammonium acetylide via desilylation. To see if this issue was present in the cyanoalkylation chemistry, we subjected *N*-propargyl carbamoyl fluoride **4.1c** to the standard conditions with TBAT as the catalyst (Scheme 4.22, top). After observing a complex mixture by  $^1\text{H}$  NMR spectroscopy, the materials were partially separated by preparatory thin layer chromatography (TLC). Silylated amide **4.8**, silylated carbamoyl fluoride **4.9** and unreacted **4.1c** were identified in the mixture. This result indicates that in the presence of fluoride, the SKI undergoes desilylation to the ammonium ketene imide, which can deprotonate the acetylenic C–H bond of both **4.1b** and **4.3c** to form **4.8** and **4.9** upon in situ silylation. Remarkably, when  $\text{OPCy}_3$  was used, only the desired product **4.3b** was observed (Scheme 4.22, bottom). This result suggests that when phosphine oxide is used, SKI activation proceeds via a  $\text{P}=\text{O}$ -Si adduct without formation of a highly basic carbanion. Alternatively,  $\text{OPCy}_3$  may be catalyzing the reaction through a different mechanism entirely. We believe this is unlikely, as we have observed a slight downfield shift in

the  $^{31}\text{P}$  NMR spectrum of  $\text{OPCy}_3$  when it is combined with **4.2** in a Gutmann-Beckette-type experiment (Figure 4.2, experiment conducted by Xavier Poblete). This result indicates that **4.2** is behaving as a very weak Lewis acid, likely coordinating to  $\text{OPCy}_3$ . There is also an extremely small upfield change in chemical shift observed from the addition of **4.1a**, but it likely negligible or due to trace water in the carbamoyl fluoride.



Scheme 4. 22: Comparing the Fate of Acetylenic Substrates with TBAT and  $\text{OPCy}_3$  Catalysts

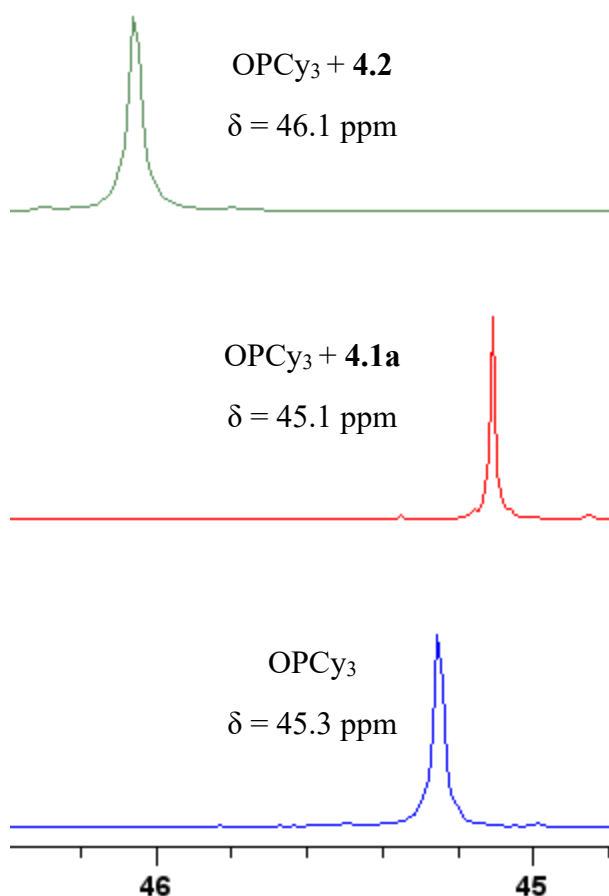
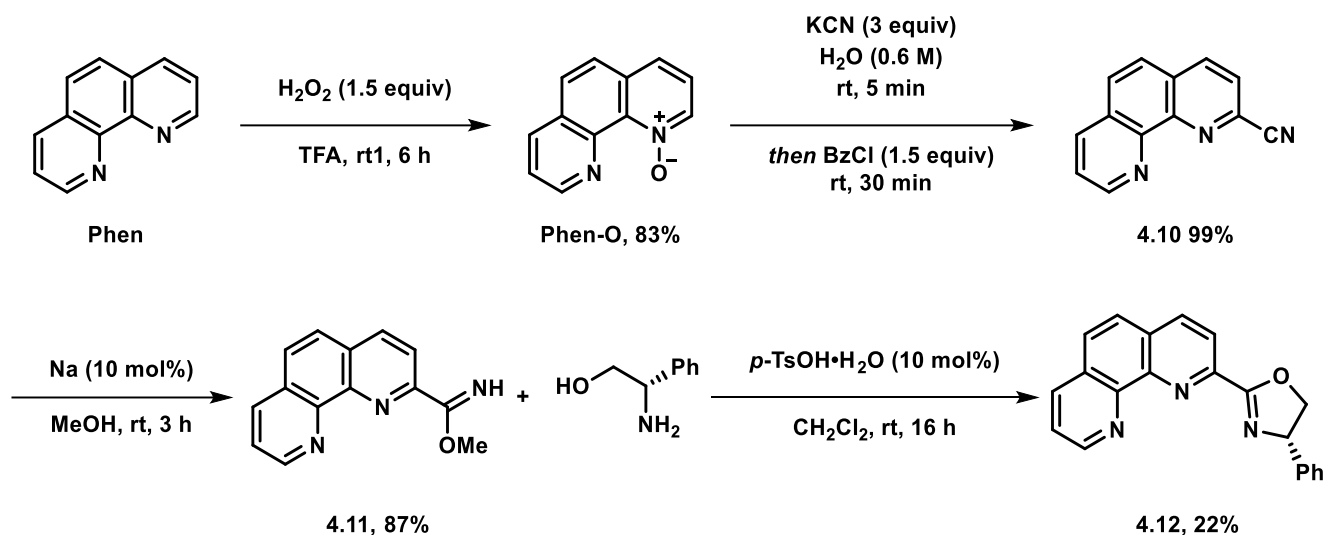


Figure 4. 2: Overlaid <sup>31</sup>P NMR Spectra of OPCy<sub>3</sub> Alone and with **4.1a** and **4.2** (experiment conducted by Xavier Poblete)

#### 4.4.2. Synthesis of Chiral Lewis Base Catalysts

Initial efforts towards an asymmetric reaction involved the synthesis of phenanthroline derivatives containing a chiral oxazoline moiety in the 2-position (Scheme 4.23). Reports suggest that 1,10-phenanthroline can be converted into phenanthroline mono-*N*-oxide (Phen-O) in the presence of acetic acid and hydrogen peroxide; however this reaction was found to be problematic. Despite considerable optimization of equivalents, temperature, and work-up procedure, the purification of Phen-O remained challenging. The reaction also suffered from inconsistent yields. Eventually, Phen-O could be obtained in good yield and high purity by running the reaction in trifluoroacetic

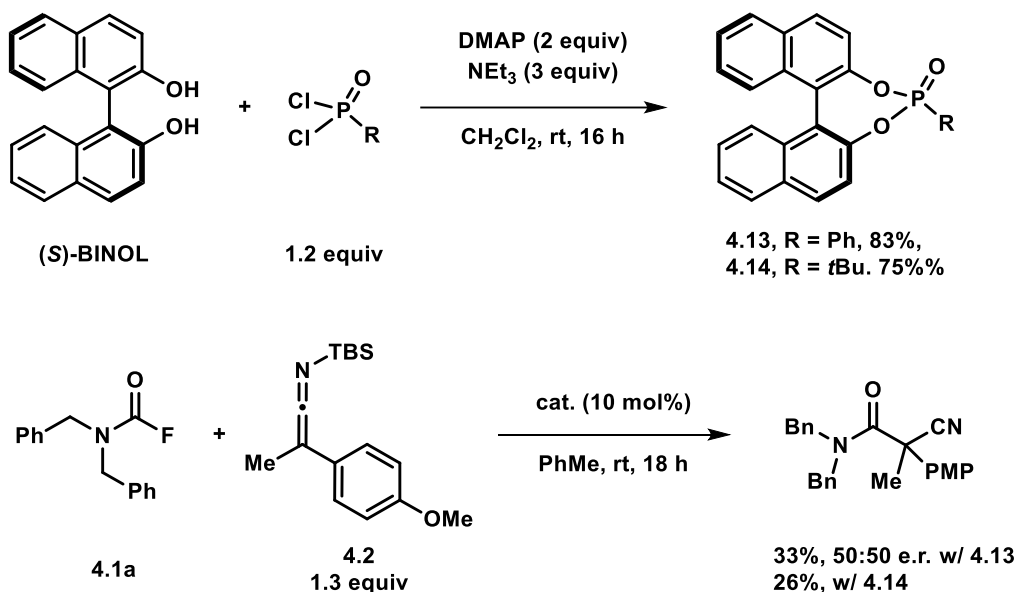
acid.<sup>29</sup> Next, Phen-O was treated with KCN and benzoyl chloride to afford 2-cyanophenanthroline **4.10** in excellent yield.<sup>30</sup> This step was followed by sodium metal-catalyzed methoxide addition to the nitrile to obtain methoxyimide **4.11**.<sup>31</sup> With slight deviation from the reported procedure,<sup>32</sup> phenanthroline bearing a chiral oxazoline group (**4.12**) could be obtained from reacting **4.11** with (*S*)-phenylglycinonl using *p*-toluenesulfonic acid (*p*-TsOH) as a catalyst. While the yield of **4.12** was relatively low, it should be noted that steps from phenanthroline to **4.11** proceed in excellent yield and do not require chromatography or other rigorous purification techniques.



Scheme 4. 23: Synthesis of a Chiral Phenanthroline Derivative

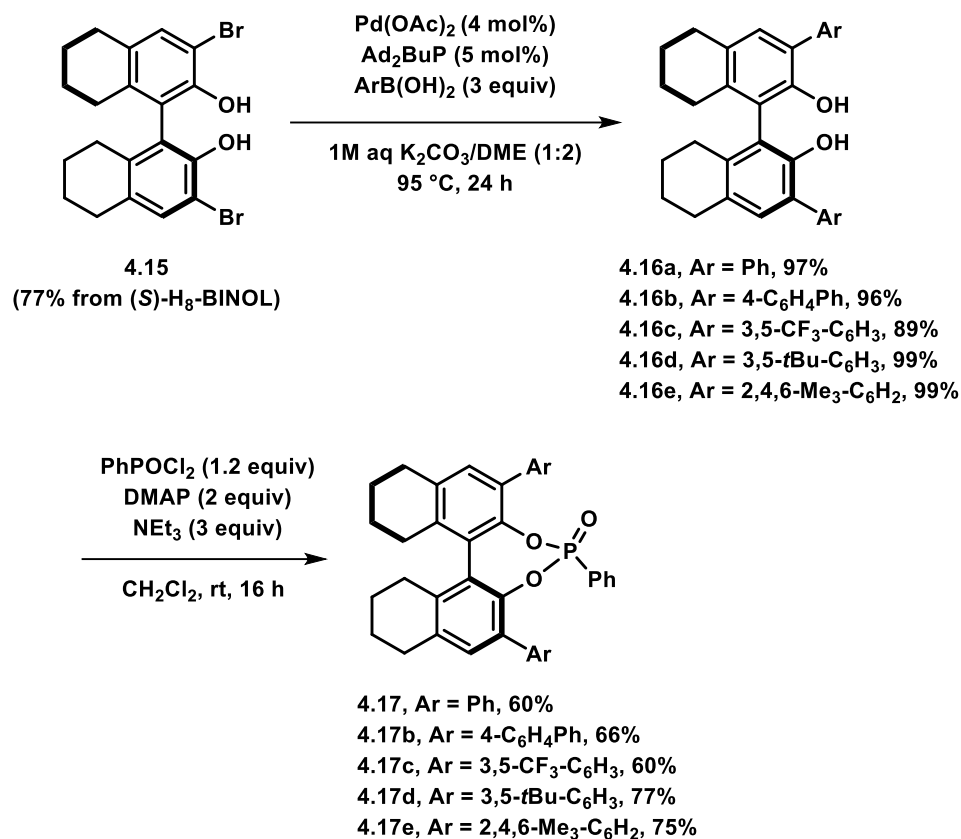
A variety of chiral phosphinates were also prepared, as they were easily accessible from BINOL derivatives. Model compounds **4.13** and **4.14** were synthesized from (*S*)-BINOL with  $\text{PhPOCl}_2$  and  $t\text{BuPOCl}_2$  in the presence of DMAP and  $\text{Et}_3\text{N}$  (Scheme 4.24, top). These compounds were used as catalysts for the standard reaction, with the Ph-substituted **4.13** providing slightly higher yield of **4.3a** than the *t*Bu-substituted **4.14** (Scheme 4.24, bottom). While the yields were low and no enantioselectivity was observed using **4.13** (enantioselectivity was not measured for the reaction with **4.14**), we continued to pursue this class of catalysts, as their synthesis is highly

modular. Phenyl-substituted phosphinates were selected for further exploration, as the phosphinic dichloride was significantly cheaper than the *t*Bu analog.



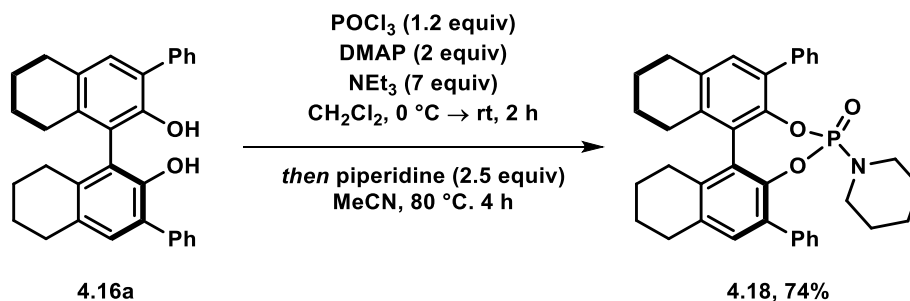
Scheme 4. 24: Synthesis of (*S*)-BINOL-Derived Lewis Bases and their use in Cyanoalkylation

We hypothesized that placing substituents near the Lewis basic oxygen may increase enantioselectivity through steric effects or non-covalent interactions with the substrates. Efforts were focused on (*S*)-H<sub>8</sub>-BINOL derivatives, as they can be brominated selectively without protection and the subsequent arylation is reported in the presence of the free phenols (Scheme 4.25). First, brominated H<sub>8</sub>-BINOL **4.15** was obtained (see experimental) and Suzuki-Miyaura coupling was carried out with a variety of arylboronic acids, generally providing **4.16** in excellent yields.<sup>33</sup> The previously used procedure for chelating the prepared BINOLs to the P(V) centre was employed to prepare the desired Lewis base catalysts **4.17** in moderate yields.



Scheme 4. 25: Synthesis of Chiral Phosphinates

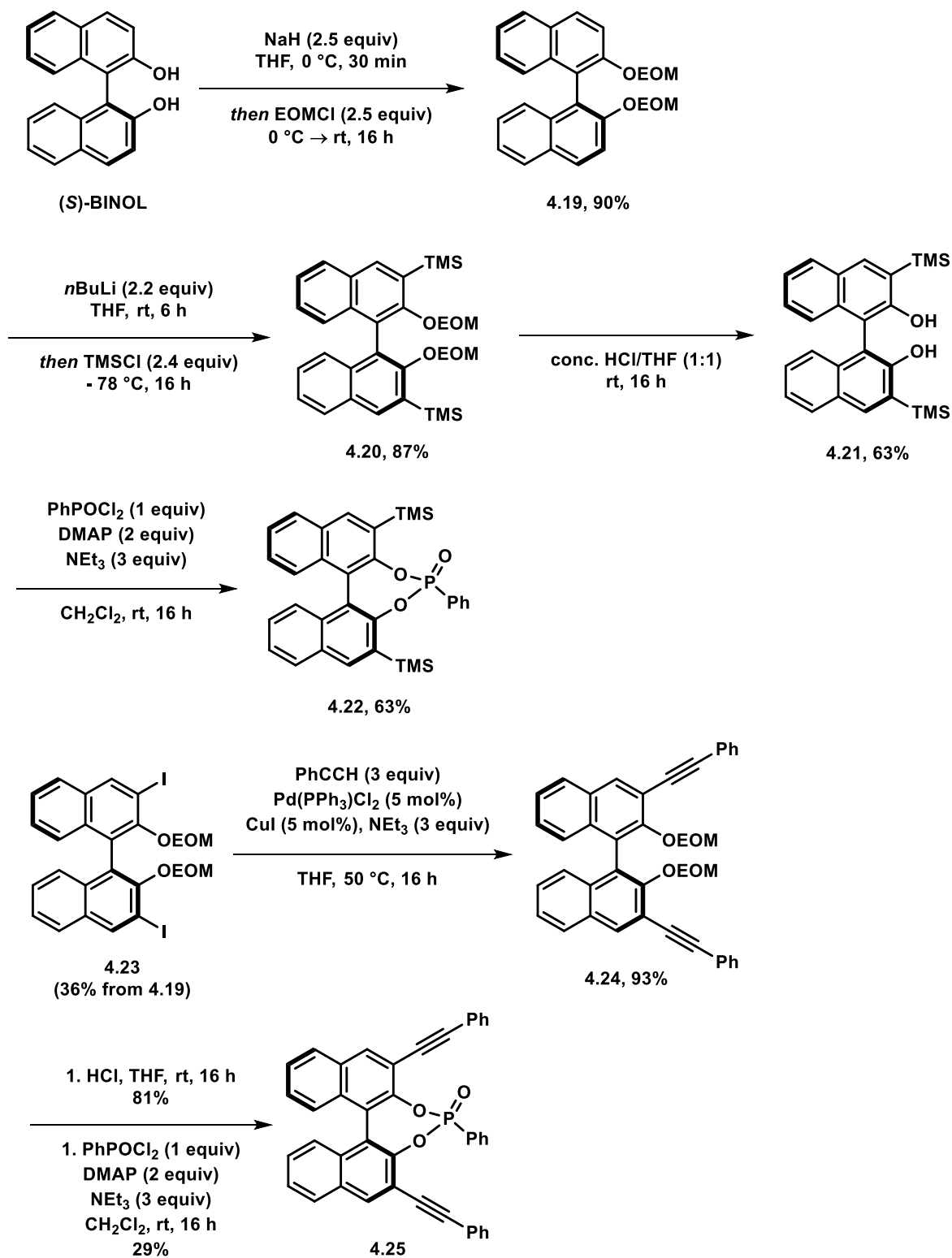
Phosphoramidate catalyst **4.18** was also prepared from BINOL **4.16a**, POCl<sub>3</sub> and piperidine using a modified procedure reported by Rueping and co-workers (Scheme 4.25).<sup>34</sup> This transformation was achieved using a slightly modified procedure for synthesizing triflylamide-based Brønsted acid catalysts, providing the desired compound in 74% yield.



Scheme 4. 26: Synthesis of Chiral Phosphoramidate **4.18**

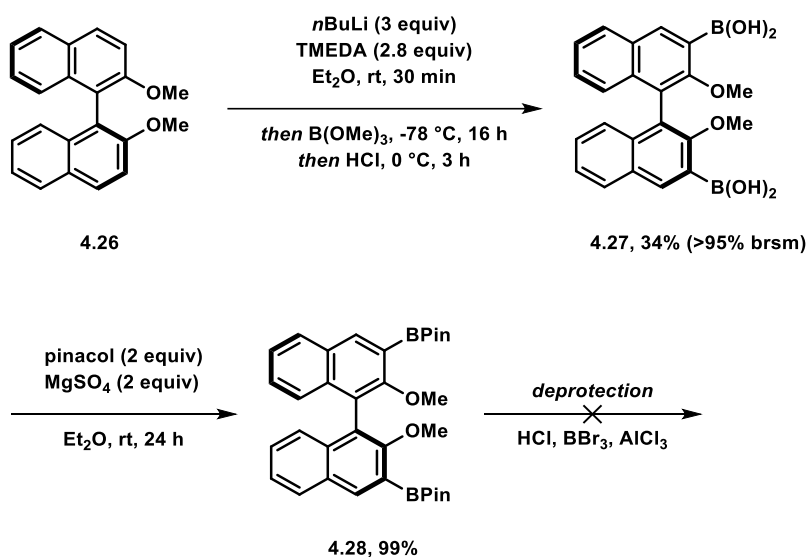


Two unique catalysts were prepared from (*S*)-BINOL with non-aryl substituents at the 3,3'-positions (Scheme 4.27). First, (*S*)-BINOL was protected with ethoxymethyl (EOM) chloride to access **4.19**. From this intermediate, directed *ortho*-metallation (DoM) was carried to functionalize the BINOL scaffold. Quenching with TMSCl provided the silylated product **4.20** in good yield. This compound underwent smooth deprotection to **4.21** and phosphination to obtain the desired catalyst **4.22**. An alkyne-substituted catalyst was also targeted in hopes of providing some steric influence without overcrowding the Lewis basic oxygen. The DoM reaction could also be quenched with I<sub>2</sub> to obtain diiodinated **4.23** (not shown, see experimental). Sonogashira coupling provided access to alkylated BINOL **4.24** in 93% yield, followed by a deprotection-phosphination sequence to access the catalyst **4.25**.



Scheme 4. 27: Synthesis of Unique (*S*)-BINOL-Derived Catalysts

We also attempted to prepare a catalyst bearing additional Lewis acidic substituents (Scheme 4.28). Such a compound should be able to activate the SKI, while also coordinating the carbamoyl fluoride to create a highly ordered system that could increase the enantioselectivity of the reaction. Towards this goal, methoxy ether-protected (*S*)-BINOL **4.26** was subjected to DoM conditions and quenched with trimethylborate to obtain the bis-boronic acid **4.27**.<sup>35</sup> While no starting material could be observed by thin layer chromatography or <sup>1</sup>H NMR spectroscopy, only a 34% yield of **4.27** was isolated. Next, boronic acid **4.27** was quantitatively converted to boronic ester **4.28** using pinacol. Unfortunately, the attempted deprotection of the methyl protecting group to access the free BINOL under acidic conditions was unsuccessful.

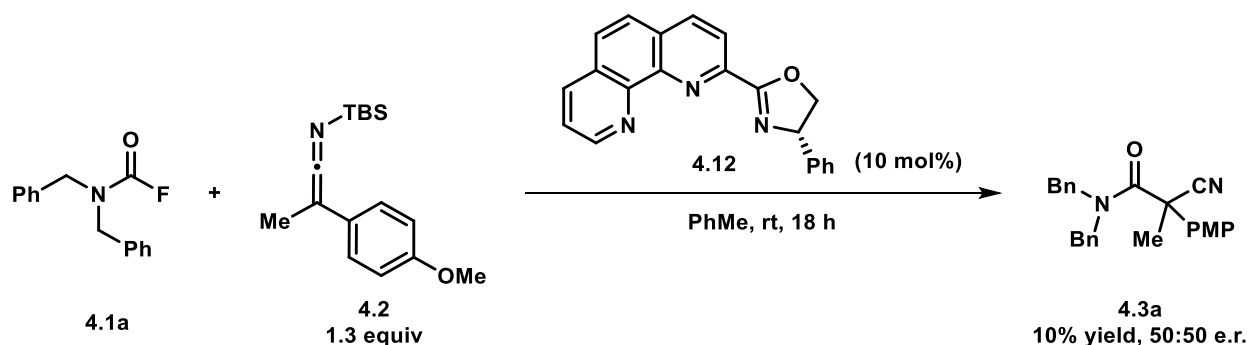


Scheme 4. 28: Attempts Toward a BPIN-Containing BINOL Scaffold

### 4.4.3 Chiral Catalyst Screening

After preparing a variety of chiral Lewis base catalysts, we began screening them in our cyanoalkylation reaction. Due to the increased cost of multistep syntheses and chiral starting materials, chiral catalysts were tested at 10 mol% loading instead of 20%. While this change was

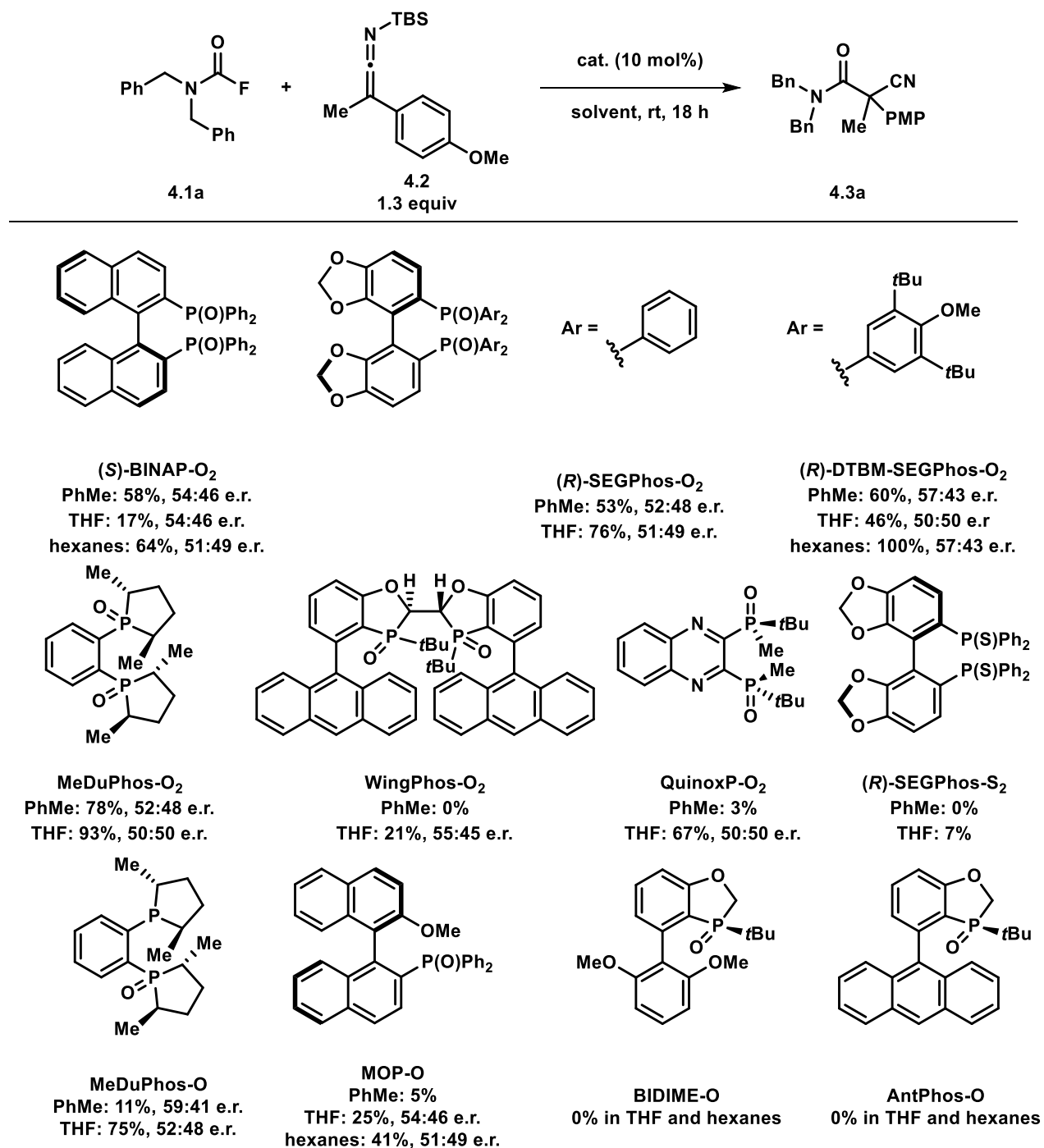
shown to significantly decrease to yield with OPCy<sub>3</sub> (see Table 4.1), we rationalized that we could still obtain enough material to confidently measure the enantiopurity by chiral HPLC. When chiral phenanthroline **4.12** was used as a catalyst, only a 10% yield of **4.3a** was observed with no enantioselectivity (Scheme 4.29). Phenanthrolines as a class of catalysts are problematic, as the intuitive design for a chiral analog would be to incorporate the chirality in the 2- and/or 9-positions (*ortho* to nitrogens) based on a mechanism where they bind to the Si atom of **4.2**. However, as observed in the achiral catalyst screen, even methyl groups in these positions lead to a shutdown of reactivity. A concrete understanding of the reaction pathway under phenanthroline catalysis may provide insight into catalyst design, but our attempts at mechanistic elucidation were inconclusive.



Scheme 4. 29: Chiral Phenanthroline-Catalyzed Cyanoalkylation of **4.1a** with **4.2a**

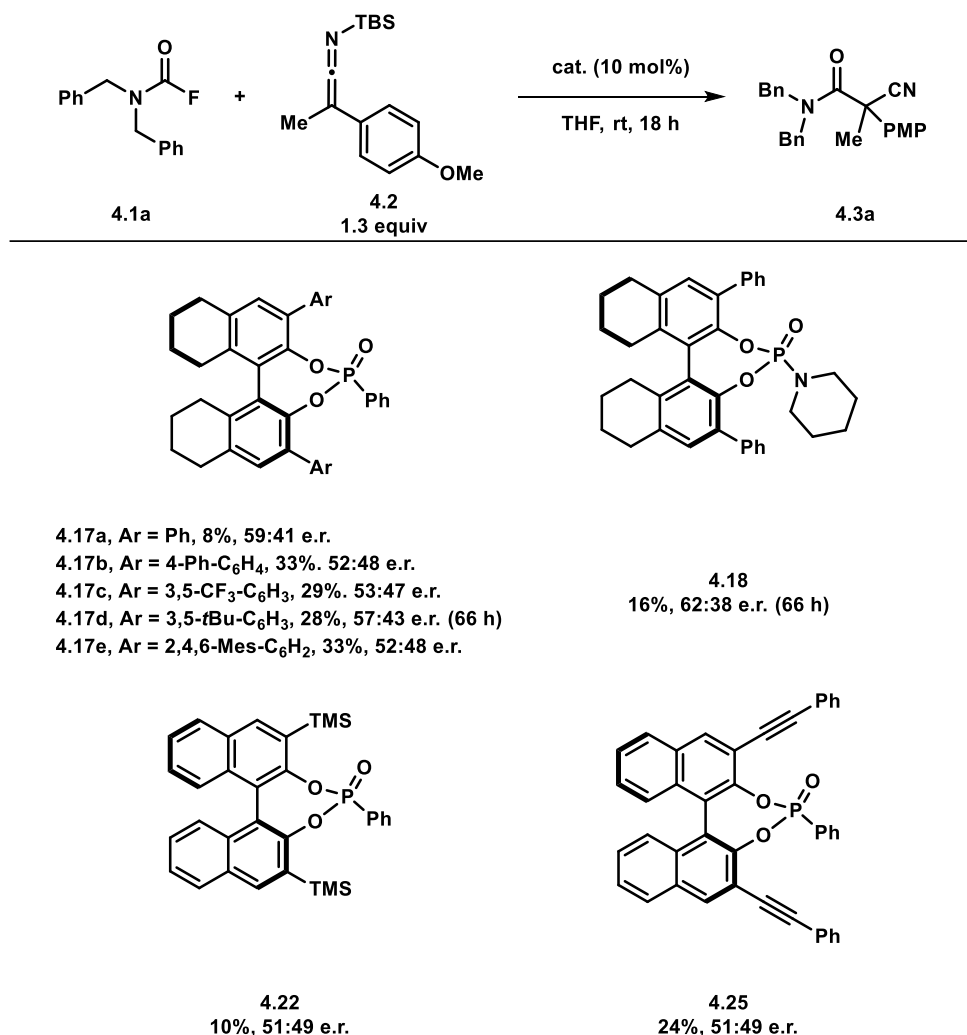
Next, we turned our attention to P(V) compounds derived from commercial chiral phosphines (see experimental). A variety of chiral bisphosphine dioxides were tested under the reaction conditions and produced **4.3a** in moderate to excellent yields in THF, PhMe and hexanes (Scheme 4.30). Low enantioselectivity was observed with (*S*)-BINAP-O<sub>2</sub> in THF or PhMe while (*R*)-SEGPhos-O<sub>2</sub> gave practically racemic product. The use of (*R*)-DTBM-SEGPhos-O<sub>2</sub> provided some interesting solvent-dependent results. A trade-off between reactivity and selectivity was observed with this catalyst, with THF giving higher yield of racemic product and PhMe giving

lower yield of slightly enantioenriched **4.3a**. When hexane was used as solvent, **4.3a** is produced quantitatively and the selectivity is retained from the PhMe reaction. MeDuPhos-O<sub>2</sub> was highly active in the reaction with little selectivity. The use of QuinoxP-O<sub>2</sub> was nearly unreactive in PhMe and completely unselective in THF. The exceptionally bulky catalyst WingPhos-O<sub>2</sub> proceeded with low yield and a 55:45 enantiomeric ratio of **4.3a** in THF. We also tested (*R*)-SEGPHOS-S<sub>2</sub> which was only slightly active in THF and unreactive in PhMe (enantiomeric ratios not determined), indicating that sulfur is a poor base for the reaction. The use of chiral monophosphine oxides MeDuPhos-O and MOP-O provided comparable results to the previously tested catalysts. We also prepared the oxides of chiral dialkylbiaryl phosphines BIDIME and AntPhos. Unfortunately, both of these catalysts failed to produce **4.3a** in either THF or PhMe.



Scheme 4. 30: Chiral P(V) Catalysts Screened for Asymmetric Cyanoalkylation of Carbamoyl Fluorides

Finally, we tested our novel class of (*S*)-BINOL-derived Lewis base catalysts (Scheme 4.31). Unfortunately, all compounds prepared gave very poor yields with very little asymmetric induction. Somewhat notable selectivity could be observed with **4.17a**, (59:41 e.r.) **4.17d** (57:43 e.r.) and **4.18** (62:38 e.r.) at great cost to the reactivity. The reactions of phosphinate **4.17d** and phosphoramidate **4.18** were run over an extended period (66 hours) to improve the yield. Unfortunately, this only led to a slight improvement of the yield compared to other catalysts, indicating an extremely slow process. The observation of poor yield compared to phosphine oxide catalysts is likely due to the inductive withdrawing effect of the oxygen substituents.

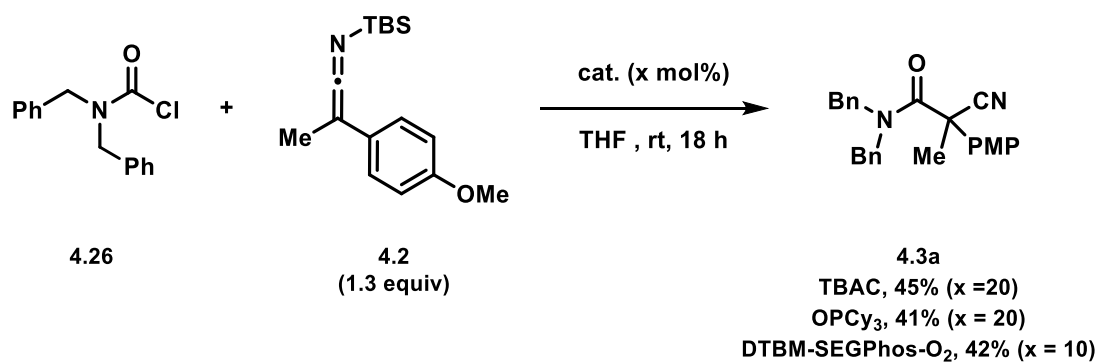


Scheme 4. 31: Screening of BINOL-Derived Catalysts in the Cyanoalkylation of Carbamoyl Fluorides

We decided to test the viability of carbamoyl chlorides in this reaction, as the fluoride released in the reaction may serve catalyze the reaction faster than the P(V) catalysts. This would make asymmetric induction beyond a single turnover extremely challenging. A simple carbamoyl chloride **4.26** was combined with **4.2** in THF to assess several Lewis base catalysts (Scheme 4.32). Using TBAC as the catalyst to avoid the presence of any fluoride, **4.3a** was obtained in 45% yield. The use of OPCy<sub>3</sub> was also effective for the cyanoalkylation of **4.26**, producing the desired product



with similar reactivity. We then used (*R*)-DTBM-SEGPhos in this reaction and **4.3a** was prepared in 42% yield and 59:41 e.r., an improvement over the carbamoyl fluoride (46%, racemic). This result implies that carbamoyl chlorides may be better candidates for this cyanoalkylation reaction, unless an appropriate fluoride-mediator can be identified to slow the reaction of released fluoride with **4.2**.



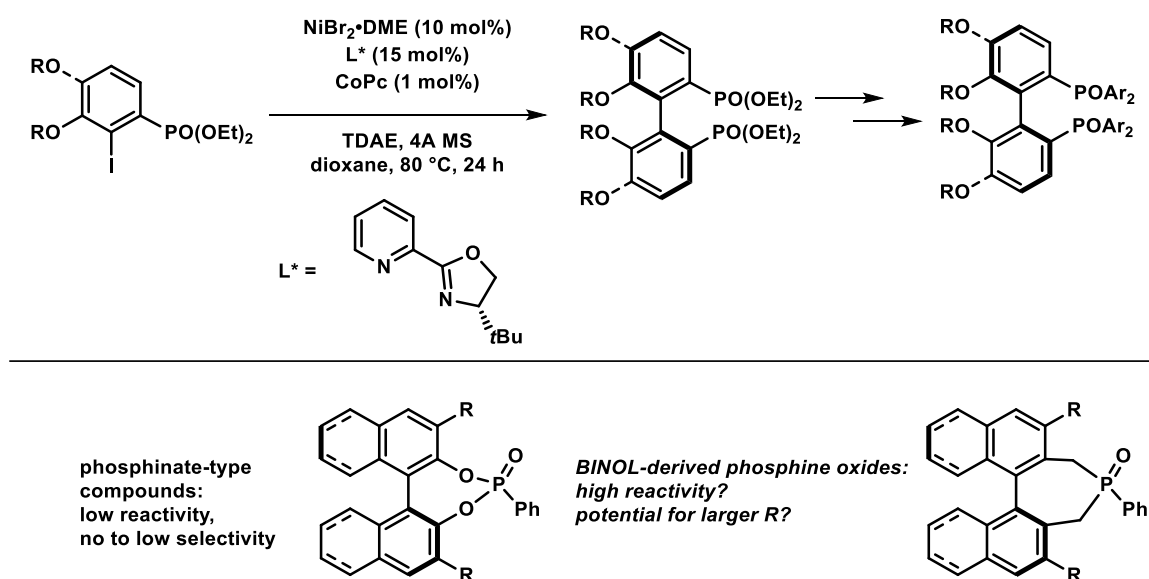
Scheme 4. 32: Lewis Base-Catalyzed Cyanoalkylation of a Carbamoyl Chloride

## 4.5 Conclusion and Future Work

We have developed the first Lewis base-catalyzed cyanoalkylation of carbamoyl fluorides using SKI nucleophiles to access  $\alpha$ -cyanoamides bearing a chiral quaternary carbon centre. Such compounds are of interest to the pharmaceutical industry. Three distinct classes of Lewis bases (fluoride, phenanthroline, and phosphine oxides) were identified that effectively catalyze this reaction. Like our previous work on alkynylation, fluoride is a highly efficient catalyst but leads to intolerance to even mildly acidic substrates. Phenanthroline derivatives were also found to catalyze cyanoalkylation, but the mechanism of this activation remains elusive. Finally, we found that phosphine oxides and related P(V) compounds were competent catalysts in the reaction and likely operate by coordinating the Si atom of the SKI. A  $^{31}\text{P}$  NMR study supports the formation of this adduct and OPCy<sub>3</sub> was found to be more tolerant to acidic protons than TBAT.

A variety of chiral catalysts were prepared with the goal of accessing enantioenriched  $\alpha$ -cyanoamides. These synthetic efforts included an amino acid-derived phenanthroline, numerous phosphine oxides prepared in a single step from commercial chiral phosphines and several (*S*)-BINOL-derived P(V) compounds. Unfortunately, the prepared catalysts failed to provide acceptable enantioselectivity. The bis-phosphine dioxide DTBM-SEGPhos-O<sub>2</sub>, bis-phosphine monoxide MeDuPhos-O and two (*S*)-BINOL-derived P(V) compounds offered the highest enantiomeric ratios of **4.3a**, making them attractive candidates for further optimization. With DTBM-SEGPhos-O<sub>2</sub> being highly active in hexanes while retaining the modest selectivity observed in other solvents, we hope to access other axially chiral bis-phosphine dioxides using a method by Watson and co-workers<sup>36</sup> to see the effect of the bulky 3,5-di-*tert*-butyl-4-methoxyphenyl groups on different axially chiral backbones (Scheme 4.33, top). The high

reactivity of this class of catalysts allows for flexibility in optimization, enabling the introduction of increasingly sterically demanding substituents and use of lower temperatures. The substituted (*S*)-BINOL scaffolds also impart some enantioselectivity but demonstrate low reactivity. This may be remedied by preparing phosphine oxide analogs of these compounds, replacing the oxygens of the BINOL with carbon to obtain higher yields (Scheme 4.33, bottom).



Scheme 4. 33: Watson's Cross-Electrophile Coupling Towards SEGPhos-Type Compounds and Potential BINOL-Derived Phosphine Oxides

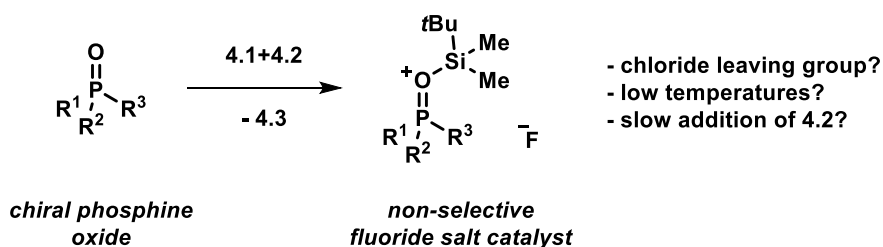
The high fluorophilicity of Si-containing compounds may also serve as a pitfall in the design of an asymmetric cyanoalkylation. In the proposed mechanism, when the Lewis base catalyst attacks the Si atom of **4.2**, leading to product formation, fluoride is released. We initially assumed fluoride would selectively desilylate the P-O-Si adduct (Scheme 4.34) to close the catalytic cycle. However, SKI **4.2** is present in significantly higher concentration than the catalyst, meaning that its attack by fluoride is more likely than the attack of this adduct. As we observed the fluoride-catalyzed reaction to be extremely fast (<30 min to full conversion), any chiral catalyst

$$\begin{array}{ccc}
 \begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1\text{P}-\text{R}^3 \\ | \\ \text{R}^2 \end{array} & \xrightarrow[\text{- 4.3}]{\text{4.1+4.2}} & \begin{array}{c} \text{tBu} \\ | \\ \text{O}-\text{Si}-\text{Me} \\ | \\ \text{Me} \\ \parallel \\ \text{R}^1\text{P}-\text{R}^3 \\ | \\ \text{R}^2 \end{array} \quad \text{F}^-
 \end{array}$$

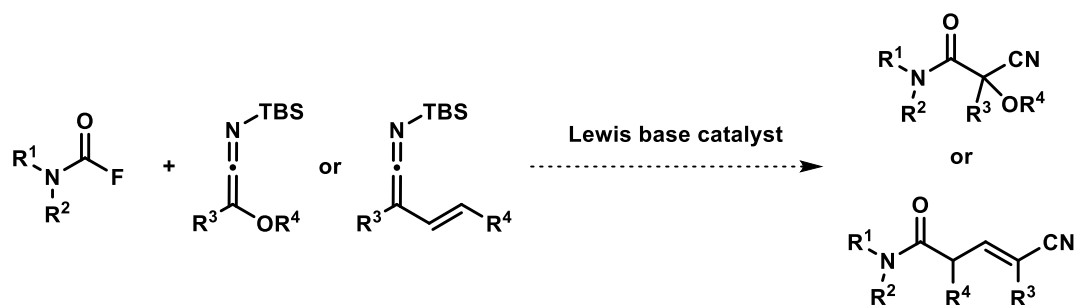
*chiral phosphine oxide*

*non-selective fluoride salt catalyst*

- chloride leaving group?
- low temperatures?
- slow addition of 4.2?



Upon optimization of the asymmetric cyanoalkylation of carbamoyl fluorides, other SKI derivatives may be explored under these conditions. Denmark reported two unique classes of compounds for asymmetric addition reactions: the silyl oxyketene imine<sup>37</sup> and the silyl vinylketene imine.<sup>38</sup> Pairing these nucleophiles with carbamoyl fluorides would provide access to  $\alpha$ -cyano- $\alpha$ -oxyamides and acrylonitrile-substituted amides (Scheme 4.35). Both unexplored compounds should have potential use in medicinal chemistry and contain useful handles for further derivatization into more complex scaffolds.



Scheme 4. 35: Potential Lewis Base-Catalyzed Cyanoalkylation of Carbamoyl Fluorides with Silyl Oxy- or Vinylketene Imines

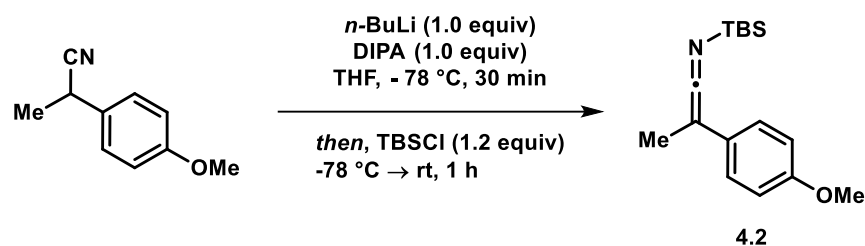
## 4.6 Experimental and Spectral Information

### 4.6.1 Reaction Optimization

In a nitrogen-filled glovebox, a 1-dram vial was charged with a stir bar and a catalyst (20 mol%, 0.020 mmol). To the vial was added a solution of **4.1a** in PhMe, THF or hexanes (0.5 mL, 0.100 mmol) and then a solution of **4.2** in PhMe (0.5 mL, 0.130 mmol). The vial was sealed tightly with a Teflon screwcap, removed from the glovebox, and stirred at room temperature for 18 h. After this time, the reaction mixture was filtered through silica gel in a Monstr pipette (flushed with EtOAc) into a scintillation vial containing a known amount of 1,3,5-trimethoxybenzene (internal standard). The solvent was removed under reduced pressure and the residue was taken up in CDCl<sub>3</sub> for quantitative <sup>1</sup>H NMR analysis to determine the yield of **4.3a**.

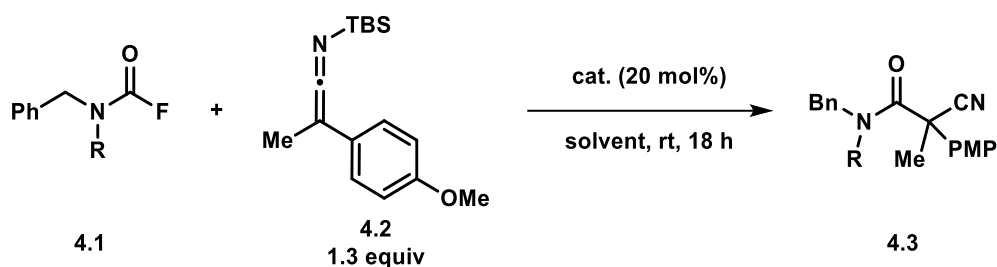
#### Synthesis and Characterization Data

#### Synthesis of SKI **4.2**



In an oven-dried round-bottomed flask, a solution of diisopropyl amine (1 equiv.) in THF was prepared. This solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and  $n\text{BuLi}$  (1 equiv.) was added dropwise and stirred for 5 minutes to generate LDA. To this solution was added a THF solution of 2-(4-methoxyphenyl)propanenitrile and stirred for 10 minutes. A THF solution of *tert*-butyldimethylsilyl chloride (1.2 equiv.) was added to the reaction in a dropwise manner and the solution was warmed to room temperature. After 1 h THF and other volatiles were removed under vacuum on a Schlenk line. The vessel was moved into a nitrogen-filled glovebox and the residue was taken up in pentane. The solution was then filtered into a scintillation vial and the pentane was removed under vacuum giving the desired product **4.2** which was used without further purification.

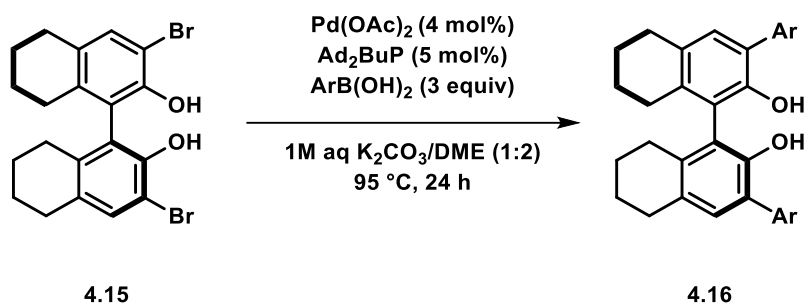
#### Synthesis of $\alpha$ -cyanoamides **4.3** (General Procedure A)



In a nitrogen-filled glovebox, a 2-dram vial was charged with a stir bar and a Lewis base catalyst (20 mol%, 0.04 mmol). To the vial was added a solution of **4.1** in PhMe or THF (1.0 mL, 0.20 mmol) and then a solution of **4.2** in PhMe or THF (1.0 mL, 0.260 mmol). The vial was sealed tightly with a Teflon screwcap, removed from the glovebox, and stirred at room temperature for

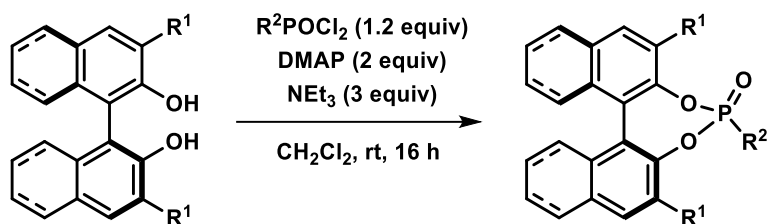
18 h. After this time, the reaction quenched with H<sub>2</sub>O and extracted with EtOAc three times, and the organic layer dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was then evaporated under reduced pressure and the crude material was purified by flash column chromatography to provide pure **4.3**.

#### Suzuki-Miyaura Arylation of H<sub>8</sub>-BINOL Derivatives (General Procedure B)



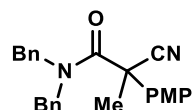
To a 2-dram glass vial was added **4.15** (0.050 g, 0.111 mmol, 1 equiv), arylboronic acid (0.332 mmol, 3 equiv), Pd(OAc)<sub>2</sub> (0.004 mmol, 4 mol%), PdAd<sub>2</sub>nBu (0.006 mmol, 5 mol%) and a Teflon-coated stir bar. The vial was fitted with a septum cap, then evacuated and backfilled with Ar three times. To the vial was added 0.5 mL of a 1M solution of K<sub>2</sub>CO<sub>3</sub> in H<sub>2</sub>O and 1 mL of DME. Both solvents were rigorously degassed with Ar beforehand. The septum cap was quickly replaced with a Teflon screw-cap and the vial was heated to 95 °C for 24 hours. After this time, the organic layer was collected from the biphasic mixture. The aqueous phase was then extracted two times with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic phases were washed with concentrated NH<sub>4</sub>Cl, then dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed via rotary evaporation and **4.16** was purified by column chromatography.

#### Preparation of phosphonate catalysts (General Procedure C)



A flame-dried 2-dram vial was charged with **4.16** (1 equiv), DMAP (g, mmol, 2 equiv) and a Teflon-coated stir bar. The vial was fitted with a septum cap, then evacuated and backfilled with Ar three times. Solids were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (mL). To the vial was added Et<sub>3</sub>N (mL, mmol, 3 equiv) and then PhPOCl<sub>2</sub> or a solution of *t*BuPOCl<sub>2</sub> in 0.5 mL CH<sub>2</sub>Cl<sub>2</sub> (1.2 equiv) was added dropwise. The septum cap was quickly replaced with a Teflon screwcap and the reaction was stirred at room temperature for 16 hours. After this time, the reaction was quenched with H<sub>2</sub>O and extracted two times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were then dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed via rotary evaporation and the phosphonate was purified by column chromatography.

#### ***N,N*-dibenzyl-2-cyano-2-(4-methoxyphenyl)propenamide (4.3a)**

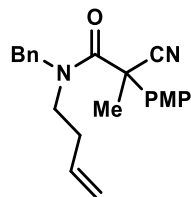


The title compound was prepared according to General Procedure A using **4.1a** (0.048 g, 0.200 mmol), **4.2** (0.072 g, 0.260 mmol, 1.3 equiv) with TBAT (0.022 g, 0.040 mmol, 20 mol%) as the catalyst in PhMe to obtain **4.3a** (0.071 g, 0.184 mmol, 92%) as a colourless oil after purification by flash column chromatography (5% EtOAc in hexanes). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.34 (d, *J* = 8.7 Hz, 2H), 7.32-7.20 (m, 6H), 7.11 (d, *J* = 6.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 4H), 4.55 (d, *J* = 14.8 Hz, 1 H), 4.49 (d, *J* = 15.8 Hz, 1H), 4.39 (d, *J* = 14.8 Hz, 1H), 4.22 (d, *J* = 15.8 Hz, 1H), 3.78 (s, 3H), 1.95 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.6, 159.7, 136.4, 134.7, 129.7, 128.7,



128.4, 128.0, 127.9, 127.7, 126.5, 120.1, 115.1. 55.5, 51.1, 48.4, 46.8, 30.1. **HRMS** (ESI) Calc'd for  $[C_{25}H_{25}N_2O_2]^+ [M+H]^+$  385.1911 found 385.1913.

***N*-benzyl-*N*-but-3-enyl-2-cyano-2-(4-methoxyphenyl)propenamide (4.3b)**

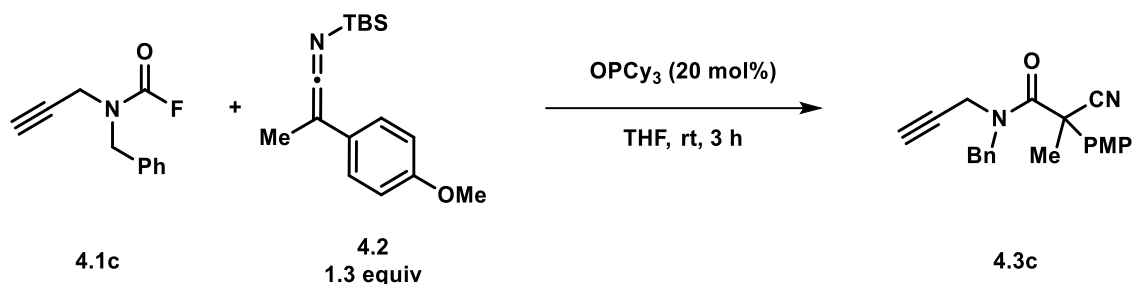


**4.3b**

The title compound was prepared according to General Procedure A using **4.1b** (0.0 g, 0.100 mmol), **4.2** (0.036 g, 0.130 mmol, 1.3 equiv) with **Me<sub>4</sub>Phen** (0.005 g, 0.020 mmol, 20 mol%) as the catalyst in PhMe. **4.3b** (99%) was observed by quantitative  $^1\text{H}$  NMR spectroscopy using 1,3,5-trimethoxy benzene as an internal standard. Using TBAT (0.011 g, 0.020 mmol, 20 mol%) as the catalyst, pure **3.3b** (0.025 g, 0.072 mmol, 72%) was obtained as a colourless oil after purification by flash column chromatography (5% EtOAc in hexanes).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  7.64 (m, 1H), 7.36 (d,  $J$  = 8.6 Hz, 2H), 7.34-7.30 (m, 4H), 7.27 (d,  $J$  = 7.3 Hz), 7.23 (m, 2H), 7.20 (d,  $J$  = 7.4 Hz, 2H), 6.91 (m, 6H), 5.68 (m, 1H), 5.38 (m, 1H), 5.02 (d,  $J$  = 11.8 Hz, 1H), 5.99 (d,  $J$  = 4.4 Hz, 1H), 4.90 (d,  $J$  = 10.11 Hz, 1H), 4.84 (d,  $J$  = 17.7 Hz, 1H), 4.64 (s, 2H), 5.34 (d,  $J$  = 15.7 Hz, 1H), 4.28 (d,  $J$  = 15.7 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.38 (m, 1H), 3.23 (m, 2H), 3.14 (m, 1H), 2.26 (m, 2H), 2.17 (m, 1H), 1.89 (s, 3H), 1.87 (s, 3H), 1.72 (m, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ , *both rotamers*)  $\delta$  166.3, 166.2, 159.6, 136.7, 135.4, 135.12, 135.05, 135.0, 133.9, 130.2, 129.87, 129.85, 128.8, 128.7, 128.0, 127.9, 127.8, 127.6, 126.5, 126.4, 120.1,

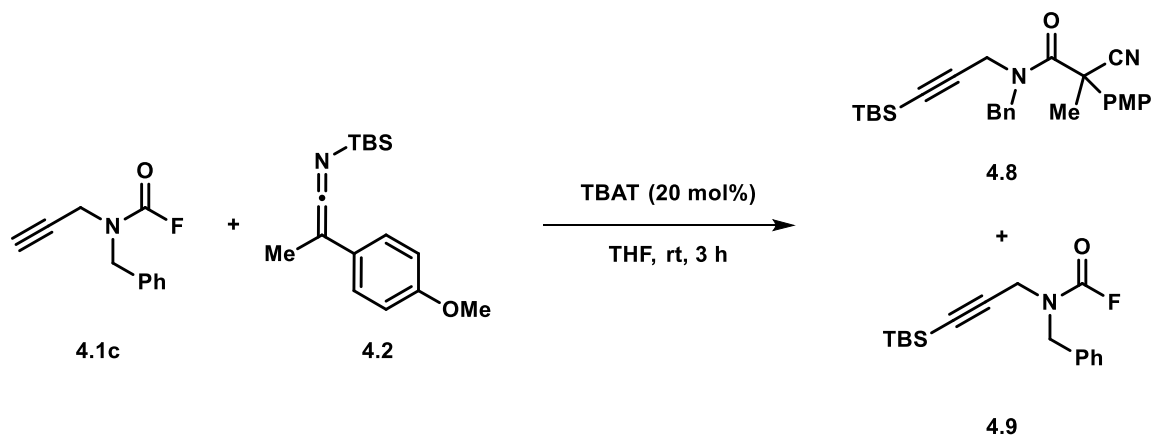
117.4, 117.2, 115.1, 114.9, 55.5, 52.0, 49.2, 47.0, 46.8, 46.7, 45.5, 31.4, 31.2, 30.0, 29.8. **HRMS** (ESI) Calc'd for  $[C_{22}H_{25}N_2O_2]^+$   $[M+H]^+$  349.1911 found 333.1914.

***N*-benzyl-2-cyano-2-(4-methoxyphenyl)-*N*-prop-2-ynyl-propanamide (4.3c)**



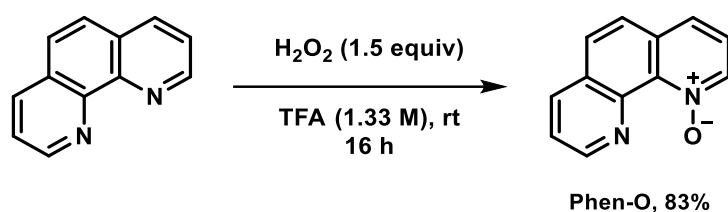
The title compound was prepared according to General Procedure A using **4.1c** (0.033 g, 0.100 mmol), **4.2** (0.036 g, 0.130 mmol, 1.3 equiv) with **OPCy<sub>3</sub>** (0.006 g, 0.020 mmol, 20 mol%) as the catalyst in THF. **4.3c** (99%) was observed by quantitative  $^1\text{H}$  NMR spectroscopy using 1,3,5-trimethoxy benzene as an internal standard. The  $\alpha$ -cyanoamide **4.3c** could not be separated from various other reaction components chromatographically, but its presence was confirmed via mass spectrometry. **HRMS** (ESI) Calc'd for  $[C_{21}H_{21}N_2O_2]^+$   $[M+H]^+$  333.1598 found 333.1598.

***N*-benzyl-*N*-[3-[*tert*-butyl(dimethyl)silyl]prop-2-ynyl]carbamoyl fluoride (4.9)**



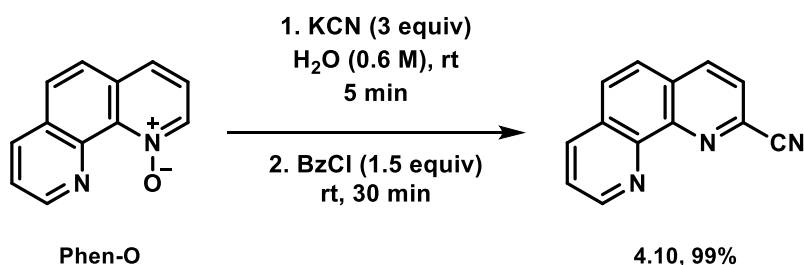
The title compound was prepared according to General Procedure A using **4.1c** (0.033 g, 0.100 mmol), **4.2** (0.036 g, 0.130 mmol, 1.3 equiv) with **TBAT** (0.011 g, 0.020 mmol, 20 mol%) as the catalyst in THF. The complex mixture proved extremely difficult to separate, but **4.8** and **4.9** were identified by  $^1\text{H}$  NMR spectroscopy. The presence of **4.9** was confirmed via mass spectrometry. **HRMS** (ESI) Calc'd for  $[\text{C}_{17}\text{H}_{25}\text{FNOSi}]^+ [\text{M}+\text{H}]^+$  306.1684 found 306.1684.

### 1,10-phenanthroline 1-oxide (Phen-O)



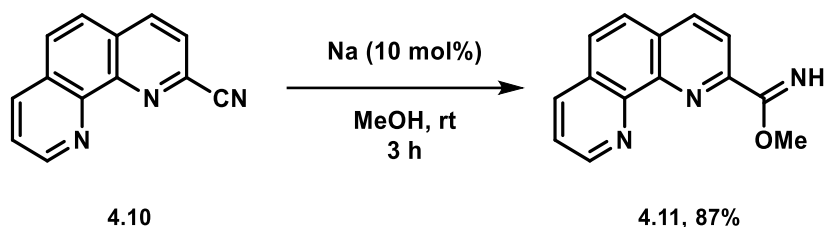
In a round-bottomed flask, 1,10-phenanthroline (0.510 g, 2.80 mmol) was dissolved in trifluoroacetic acid and cooled to 0 °C.  $\text{H}_2\text{O}_2$  (35% aq., 0.6 mL) was added dropwise, then the reaction was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was neutralized with 6M NaOH (~pH 10 by pH paper), then extracted with  $\text{CHCl}_3$  three times. The organic extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered and solvent was removed under reduced pressure to provide **Phen-O** (0.456 g, 2.32 mmol, 83%) as an off-white solid without further purification. Spectral data was consistent with the literature.<sup>29</sup>

### 1,10-phenanthroline-2-carbonitrile (**4.10**)



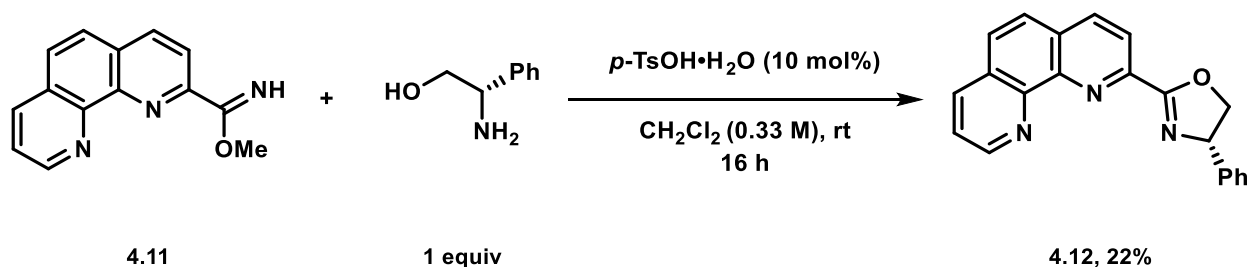
In a 2-dram vial, **Phen-O** (0.250 g, 1.27 mmol) and KCN (0.248 g, 3.81 mmol, 3.0 equiv.) were dissolved in H<sub>2</sub>O (2 mL). The solution was stirred for 5 minutes before adding benzoyl chloride (0.268 g, 1.91 mmol, 1.5 equiv.) which caused precipitation of **4.10**. After 30 minutes, the solid was collected by vacuum filtration, then dissolved in minimal amounts of CH<sub>2</sub>Cl<sub>2</sub>. This solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and solvent was removed under reduced pressure to provide **5** (0.258 g, 1.26 mmol, 99%) as a pink-orange solid without further purification. Spectral data was consistent with the literature.<sup>30</sup>

**methyl 1,10-phenanthroline-2-carboximidate (4.11)**



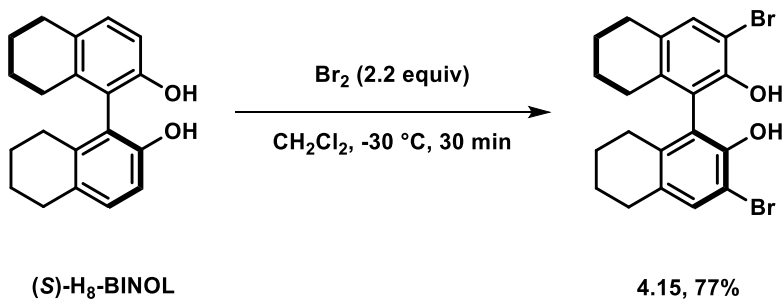
In a 2-dram vial, **4.10** (0.200 g, 0.98 mmol) was suspended in MeOH (2 mL). Na (0.002 g, 0.098 mmol, 10 mol%) was added to the suspension which was stirred at room temperature. During the reaction, the suspension slowly became a homogenous solution. After 3 h, the reaction was quenched with AcOH and methanol was removed via rotary evaporation. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub>, washed with saturated sodium bicarbonate solution and the aqueous phase was extracted 2 times with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and solvent was removed under reduced pressure to provide **4.11** (0.202 g, 0.85 mmol, 87%) as an orange solid without further purification. Spectral data was consistent with the literature.<sup>31</sup>

**(4S)-2-(1,10-phenanthroline-2-yl)-4-phenyl-4,5-dihydrooxazole (4.12)**



In a 1-dram vial, **4.11** (0.050 g, 0.21 mmol), (2*S*)-2-amino-2-phenyl-ethanol (0.029 g, 0.21 mmol, 1 equiv.) and *p*-toluenesulfonic acid monohydrate (0.004 g, 0.02 mmol, 10 mol%) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL) and stirred at room temperature for 16 h. After this time, H<sub>2</sub>O was added to the reaction mixture and extracted 2 times with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and solvent was removed under reduced pressure and purified by flash column chromatography (15% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to afford **4.12** (0.150 g, 0.046 mmol, 22%) as a pale yellow solid. Spectral data was consistent with the literature.<sup>32</sup>

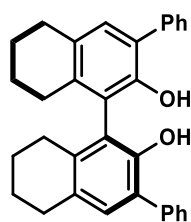
#### Procedure for 4.15 via bromination of (*S*)-H<sub>8</sub>-BINOL



In a flame-dried 100 mL round-bottomed flask, (*S*)-H<sub>8</sub>-BINOL (1.00 g, 3.34 mmol, 1 equiv) was dissolved in 33 mL of CH<sub>2</sub>Cl<sub>2</sub> and cooled to -30 °C. To the reaction was added Br<sub>2</sub> (0.40 mL, 7.81 mmol, 2.3 equiv) in a dropwise manner stirring was continued at this temperature for one hour. At this time, the reaction was quenched with a 1M aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and allowed to slowly reach room temperature. The reaction mixture was extracted three times with CH<sub>2</sub>Cl<sub>2</sub> and the

combined organic phases were washed once with saturated NaHCO<sub>3</sub> and once with water, then dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed via rotary evaporation and the crude material was purified by flash column chromatography (5% EtOAc in hexanes) to obtain **4.15** (1.161 g, 2.57 mmol, 77%) as a colourless solid. Spectral data was consistent with the literature.<sup>33</sup>

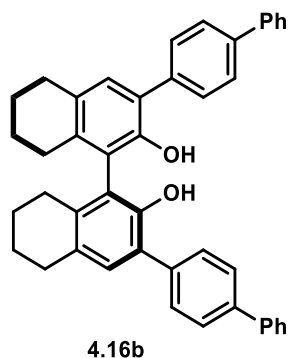
**(*S*)-5-(6-hydroxy-7-phenyl-tetralin-5-yl)-7-phenyl-tetralin-6-ol (4.16a)**



**4.16a**

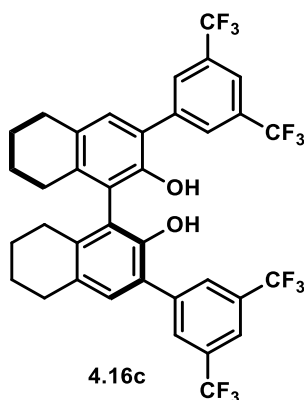
**4.16a** was obtained using General Procedure B using **4.15** (0.200 g, 0.44 mmol), phenylboronic acid (0.162 g, 1.330 mmol, 3 equiv), Pd(OAc)<sub>2</sub> (0.004 g, 0.018 mmol, 4 mol%), and PAd<sub>2</sub>*n*Bu (0.007 g, 0.022 mmol, 5 mol%). The reaction was purified by flash column chromatography (33% CH<sub>2</sub>Cl<sub>2</sub> in hexanes) to obtain the product as a white solid (0.190g, 0.427 mmol, 97%). Spectral data was consistent with the literature.<sup>33</sup>

**(*S*)-5-[6-hydroxy-7-(4-phenylphenyl)tetralin-5-yl]-7-(4-phenylphenyl)tetralin-6-ol (4.16b)**



**4.16b** was obtained using General Procedure B using **4.15** (0.050 g, 0.111 mmol), 4-biphenylboronic acid (0.064 g, 0.332 mmol, 3 equiv), Pd(OAc)<sub>2</sub> (0.001 g, 0.004 mmol, 4 mol%), and PAd<sub>2</sub>*n*Bu (0.002 g, 0.006 mmol, 5 mol%). The reaction was purified by flash column chromatography (30% CH<sub>2</sub>Cl<sub>2</sub> in hexanes) to obtain the product as a white solid (0.064 g, 0.107 mmol, 96%). Spectral data was consistent with the literature.<sup>34</sup>

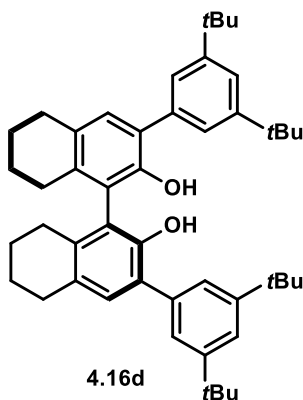
**(S)-7-[3,5-bis(trifluoromethyl)phenyl]-5-[7-[3,5-bis(trifluoromethyl)phenyl]-6-hydroxy-tetralin-5-yl]tetralin-6-ol (4.16c)**



**4.16c** was obtained using General Procedure B using **4.15** (0.050 g, 0.111 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (0.083 g, 0.332 mmol, 3 equiv), Pd(OAc)<sub>2</sub> (0.001 g, 0.004 mmol, 4 mol%), and PAd<sub>2</sub>*n*Bu (0.002 g, 0.006 mmol, 5 mol%). The reaction was purified by flash

column chromatography (10% CH<sub>2</sub>Cl<sub>2</sub> in hexanes) to obtain the product as a white solid (0.071 g, 0.099 mmol, 89%). Spectral data was consistent with the literature.<sup>33</sup>

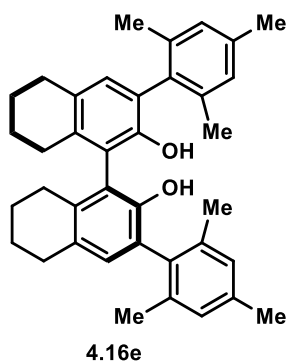
**(*S*)-7-(3,5-ditert-butylphenyl)-5-[7-(3,5-ditert-butylphenyl)-6-hydroxy-tetralin-5-yl]tetralin-6-ol (4.16d)**



**4.16d** was obtained using General Procedure B using **4.15** (0.050 g, 0.111 mmol), 3,5-bis(*tert*-butyl)phenyllboronic acid (0.075 g, 0.332 mmol, 3 equiv), Pd(OAc)<sub>2</sub> (0.001 g, 0.004 mmol, 4 mol%), and PAd<sub>2</sub>*n*Bu (0.002 g, 0.006 mmol, 5 mol%). The reaction was purified by flash column chromatography (10% CH<sub>2</sub>Cl<sub>2</sub> in hexanes) to obtain the product as a white solid (0.079 g, 0.111 mmol, >99%). Spectral data was consistent with the literature.<sup>39</sup>

**(*S*)-5-[6-hydroxy-7-(2,4,6-trimethylphenyl)tetralin-5-yl]-7-(2,4,6-trimethylphenyl)tetralin-6-ol (4.16e)**

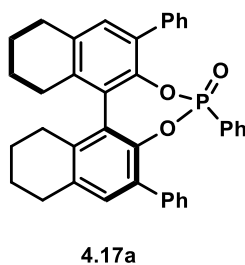




**4.16d** was obtained using General Procedure B using **4.15** (0.050 g, 0.111 mmol), 1,3,5-mesityllboronic acid (0.053 g, 0.332 mmol, 3 equiv), Pd(OAc)<sub>2</sub> (0.001 g, 0.004 mmol, 4 mol%), and PAd<sub>2</sub>nBu (0.002 g, 0.006 mmol, 5 mol%). The reaction was purified by flash column chromatography (10% CH<sub>2</sub>Cl<sub>2</sub> in hexanes) to obtain the product as a white solid (0.060 g, 0.111 mmol, >99%). Spectral data was consistent with the literature.<sup>33</sup>

**(S)-10,13,16-triphenyl-12,14-dioxa-13λ<sup>5</sup>-**

**phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricos-1(23),2(11),3(8),9,15,17-hexaene 13-oxide (4.17a)**

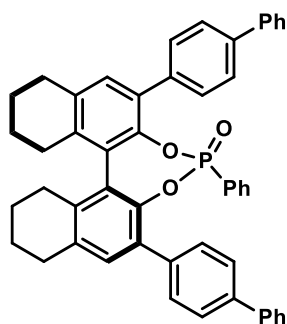


**4.17a** was obtained using General Procedure B using **4.16a** (0.045 g, 0.100 mmol), PhPOCl<sub>2</sub> (0.023 g, 0.120 mmol, 1.2 equiv), DMAP (0.024 g, 0.200 mmol, 2 equiv) and NEt<sub>3</sub> (0.030 g, 0.300 mmol, 3 equiv). The reaction was purified by flash column chromatography (20% EtOAc in hexanes) to obtain the product as a white solid (0.051 g, 0.071 mmol, 66%). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.76 (d, *J* = 7.1 Hz, 2H), 7.39 (m, 3H), 7.30 (m, 2H), 7.20-7.16 (m, 1H), 7.16-7.12 (m, 2H), 7.11-

7.04 (m, 4H), 7.01 (s, 1H), 6.99 (d,  $J = 7.1$  Hz, 2H), 3.02-2.92 (m, 2H), 2.90 (m, 2H), 2.78 (m, 2H), 2.50 (dt,  $J = 16.3$  Hz, 6.3 Hz, 1H), 2.44 (dt,  $J = 16.3$  Hz, 5.9 Hz, 1H), 1.91 (m, 6H), 1.73 (m, 2H)  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  143.1 (d,  $J = 9.9$  Hz), 141.6 (d,  $J = 9.3$  Hz), 137.9, 137.5, 137.3, 136.4, 135.5 (d,  $J = 1.8$  Hz), 135.4 (d,  $J = 1.7$  Hz), 132.6 (d,  $J = 2.8$  Hz), 132.4 (d,  $J = 2.3$  Hz), 132.0 (d,  $J = 10.1$  Hz), 131.9, 131.8, 130.5, 129.8, 129.2, 128.2, 127.93, 127.90 (d,  $J = 1.7$  Hz), 127.8, 127.5, 127.3, 126.8, 124.7 (d,  $J = 188.2$  Hz), 29.4, 28.1, 27.9, 22.9, 22.82, 22.80, 22.7.  $^{31}\text{P}$  NMR (243 MHz,  $\text{CDCl}_3$ ) 22.4. HRMS (ESI) Calc'd for  $[\text{C}_{38}\text{H}_{34}\text{O}_3\text{P}]^+ [\text{M}+\text{H}]^+$  569.2241 found 569.2230.  $[\alpha]_{\text{D}}^{23} + 214.8$  ( $c = 0.017$ ,  $\text{CHCl}_3$ )

**(S)-13-phenyl-10,16-bis(4-phenylphenyl)-12,14-dioxo-13 $\lambda^5$ -**

**phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricoso-1(23),2(11),3(8),9,15,17-hexaene 13-oxide (4.17b)**

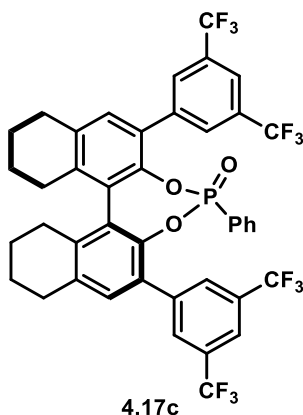


**4.17b**

**4.17b** was obtained using General Procedure C using **4.16b** (0.064 g, 0.107 mmol),  $\text{PhPOCl}_2$  (0.025 g, 0.128 mmol, 1.2 equiv), DMAP (0.026 g, 0.214 mmol, 2 equiv) and  $\text{NEt}_3$  (0.033 g, 0.321 mmol, 3 equiv). The reaction was purified by flash column chromatography (10% EtOAc in hexanes) to obtain the product as a white solid (0.051 g, 0.071 mmol, 66%).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.81 (d,  $J = 8.5$  Hz, 2H), 7.59 (m, 6H), 7.49 (t,  $J = 7.5$  Hz, 2H), 7.42-7.33 (m, 6H), 7.33-7.27 (m, 2H), 7.13-7.00 (m, 7H), 3.00-2.90 (m, 2H), 2.88 (m, 2H), 2.77 (m, 2H), 2.50 (dt,  $J = 16.3$

Hz, 6.1 Hz, 1H), 2.43 (dt,  $J = 16.3$  Hz, 5.4 Hz, 1H), 1.89 (m, 6H), 1.71 (m, 2H).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  143.2 (d,  $J = 10.0$  Hz), 141.7 (d,  $J = 9.5$  Hz), 141.0 (d,  $J = 9.1$  Hz), 140.0, 139.5, 138.0, 137.6, 136.3, 135.7, 135.6, 135.5, 132.7 (d,  $J = 2.4$  Hz), 132.0 (2,  $J = 10.1$  Hz), 131.9, 131.8, 131.5 (d,  $J = 3.5$  Hz), 130.3, 130.2, 129.6, 128.9, 128.8, 128.0, 127.9, 127.6, 127.4, 127.21, 127.18, 127.1, 127.0, 126.6, 124.6 (d,  $J = 187.4$  Hz), 29.4, 28.1, 27.9, 22.9, 22.81, 22.80, 22.7.  $^{31}\text{P}$  NMR (243 MHz,  $\text{CDCl}_3$ ) 22.6. HRMS (ESI) Calc'd for  $[\text{C}_{50}\text{H}_{42}\text{O}_3\text{P}]^+ [\text{M}+\text{H}]^+$  721.2867 found 721.2859.  $[\alpha]_D^{23} + 324.4$  ( $c = 0.011$ ,  $\text{CHCl}_3$ )

**(S)-10,16-bis[3,5-bis(trifluoromethyl)phenyl]-13-phenyl-12,14-dioxo-13 $\lambda^5$ -phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricoso-1(23),2(11),3(8),9,15,17-hexaene 13-oxide (4.17c)**

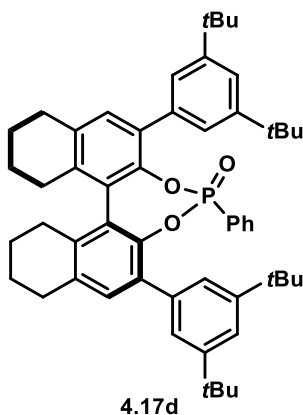


**4.17c** was obtained using General Procedure C using **4.16c** (0.071 g, 0.099 mmol),  $\text{PhPOCl}_2$  (0.023 g, 0.119 mmol, 1.2 equiv), DMAP (0.024 g, 0.198 mmol, 2 equiv) and  $\text{NEt}_3$  (0.030, 0.296 mmol, 3 equiv). The reaction was purified by flash column chromatography (25%  $\text{CH}_2\text{Cl}_2$  in hexanes) to obtain the product as a white solid (0.050 g, 0.059 mmol, 60%).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.19 (s, 2H), 7.78 (s, 1H), 7.65 (s, 1H), 7.41 (s, 2H), 7.34 (t,  $J = 7.6$  Hz, 1H), 7.25 (s, 1H), 7.08 (m, 2H), 7.05-6.99 (m, 2H), 7.01 (s, 1H), 3.00-2.88 (m, 4H), 2.87 (m, 2H), 2.49 (m, 2H), 1.91 (m,

6H), 1.73 (m, 2H). **<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 143.0 (d, *J* = 10.2 Hz), 141.4 (d, *J* = 9.6 Hz), 140.1, 139.6, 139.2, 138.3, 136.7 (d, *J* = 2.3 Hz), 136.6, 133.7 (d, *J* = 3.4 Hz), 131.8, 131.61, 131.55, 131.5 (q, *J* = 33.2 Hz), 131.3 (q, *J* = 33.2 Hz), 130.3, 131.1, 129.8 (d, *J* = 2.2 Hz), 129.1 (d, *J* = 2.9 Hz), 129.0 (d, *J* = 3.1 Hz), 128.1 (d, *J* = 15.2 Hz), 127.9, 127.6, 123.6 (d, *J* = 187.3 Hz), 123.5 (q, *J* = 273.2 Hz), 123.2 (q, *J* = 272.8 Hz), 121.30 (d, *J* = 4.2 Hz), 121.28 (d, *J* = 3.4 Hz), 120.82 (d, *J* = 3.6 Hz) 120.78 (d, *J* = 3.2 Hz) 29.8, 29.30, 29.28, 28.2, 28.1, 22.57, 22.56, 22.54, 22.45. **<sup>31</sup>P NMR** (243 MHz, CDCl<sub>3</sub>) 22.9. **<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -62.7, -62.8. **HRMS** (ESI) Calc'd for [C<sub>42</sub>H<sub>30</sub>F<sub>12</sub>O<sub>3</sub>P]<sup>+</sup> [M+H]<sup>+</sup> 841.1736 found 841. **[α]<sub>D</sub><sup>23</sup>** + 203.9 (*c* = 0.032, CHCl<sub>3</sub>)

**(*S*)-10,16-bis(3,5-ditert-butylphenyl)-13-phenyl-12,14-dioxo-13λ<sup>5</sup>-**

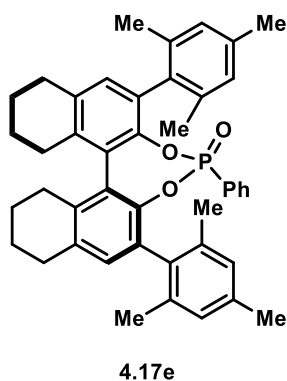
**phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricoso-1(23),2(11),3(8),9,15,17-hexaene 13-oxide (4.17d)**



**4.17d** was obtained using General Procedure C using **4.16d** (0.075 g, 0.111 mmol), PhPOCl<sub>2</sub> (0.026 g, 0.133 mmol, 1.2 equiv), DMAP (0.027 g, 0.222 mmol, 2 equiv) and NEt<sub>3</sub> (0.034 g, 0.333 mmol, 3 equiv). The reaction was purified by flash column chromatography (10% EtOAc in hexanes) to obtain the product as a white solid (0.066 g, 0.083 mmol, 75%). **<sup>1</sup>H NMR** (600 MHz,

CDCl<sub>3</sub>)  $\delta$  7.65 (d,  $J$  = 1.4 Hz, 2H), 7.32 (t,  $J$  = 1.7 Hz, 1H), 7.29 (td,  $J$  = 7.4 Hz, 1.1 Hz, 2H), 7.26 (under CHCl<sub>3</sub>, 1H), 7.21 (t,  $J$  = 1.7 Hz), 7.10 (d,  $J$  = 7.6 Hz, 1H), 7.08(d,  $J$  = 7.6 Hz, 1H), 7.04 (s, 1H), 7.04-6.99 (m, 2H), 6.98 (d,  $J$  = 1.3 Hz, 2H), 3.00-2.92 (m, 1H), 2.88 (m, 3H), 2.75 (m, 2H), 2.51 (dt,  $J$  = 16.7 Hz, 6.1 Hz, 1H), 2.39 (dt,  $J$  = 16.5 Hz, 5.6 Hz, 1H), 1.87 (m, 6H), 1.70 (m, 2H), 1.28 (s, 18 H), 1.26 (s, 18H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  150.3, 150.0, 143.4 (d,  $J$  = 10.0 Hz), 141.7 (d,  $J$  = 9.5 Hz), 137.5, 137.1, 136.2, 135.4, 135.33 (d,  $J$  = 2.4 Hz), 135.28, 133.0 (d,  $J$  = 2.1 Hz), 132.7 (d,  $J$  = 2.3 Hz), 132.5 (d,  $J$  = 3.2 Hz), 132.1, 132.0, 131.8, 130.6, 128.0, 127.6, 127.5, 125.1 (d,  $J$  = 189.9 Hz), 124.4, 123.5, 121.1, 121.0, 35.1, 34.9, 31.6, 29.5, 29.4, 28.1, 27.9, 22.94, 22.88, 22.8. <sup>31</sup>P NMR (243 MHz, CDCl<sub>3</sub>) 21.9. HRMS (ESI) Calc'd for [C<sub>54</sub>H<sub>66</sub>O<sub>3</sub>P]<sup>+</sup> [M+H]<sup>+</sup> 793.4745 found 793.4738. [ $\alpha$ ]<sub>D</sub><sup>23</sup> + 213.1 ( $c$  = 0.019, CHCl<sub>3</sub>)

**(S)-13-phenyl-10,16-bis(2,4,6-trimethylphenyl)-12,14-dioxa-13 $\lambda^5$ -phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricos-1(23),2(11),3(8),9,15,17-hexaene 13-oxide (4.17e)**

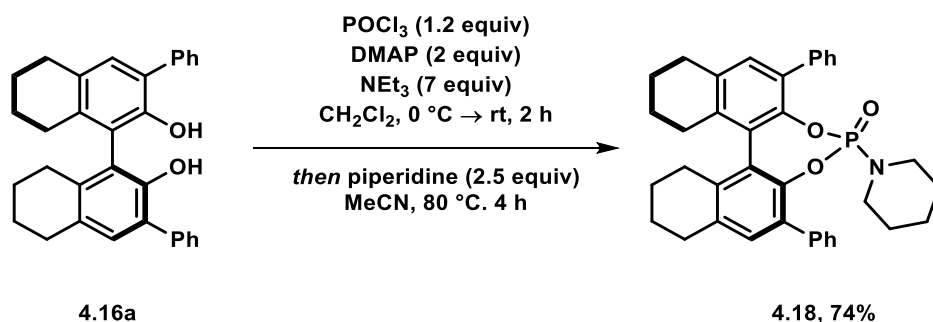


**4.17e** was obtained using General Procedure C using **4.16e** (0.059 g, 0.111 mmol), PhPOCl<sub>2</sub> (0.026 g, 0.133 mmol, 1.2 equiv), DMAP (0.027 g, 0.222 mmol, 2 equiv) and NEt<sub>3</sub> (0.034 g, 0.333 mmol, 3 equiv). The reaction was purified by flash column chromatography (10% EtOAc in hexanes) to obtain the product as a white solid (0.056 g, 0.085 mmol, 77%). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$

7.39 (td,  $J = 7.5$  Hz, 1.4 Hz, 1H), 7.13-7.05 (m, 4H), 7.00 (s, 1H), 6.91 (s, 1H), 6.88 (s, 1H), 6.84 (s, 1H), 6.76 (s, 1H), 6.57 (s, 1H), 2.87 (m, 2H), 2.85-2.70 (m, 4H), 2.38-2.31 (m, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 2.23 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H), 1.85 (m, 6H), 1.70 (m, 2H).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  144.2 (d,  $J = 10.0$  Hz), 142.1 (d,  $J = 8.9$  Hz), 137.7, 137.5, 136.9, 136.79, 136.77, 136.7, 136.6, 136.2, 135.4 (d,  $J = 2.2$  Hz), 134.4, 133.6, 132.9, 132.4 (d,  $J = 3.4$  Hz), 132.0, 131.7, 131.6, 131.2 (d,  $J = 2.3$  Hz), 129.2 (d,  $J = 3.8$  Hz), 129.0, 128.2, 128.1 (d,  $J = 1.8$  Hz), 128.0, 127.6 (d,  $J = 1.6$  Hz), 127.4, 127.2, 126.3 (d,  $J = 187.6$  Hz), 29.4, 29.3, 28.0, 27.9, 22.91, 22.89, 22.8, 21.3, 21.2, 20.5, 20.3, 20.0.  $^{31}\text{P}$  NMR (243 MHz,  $\text{CDCl}_3$ ) 21.7 HRMS (ESI) Calc'd for  $[\text{C}_{44}\text{H}_{46}\text{O}_3\text{P}]^+ [\text{M}+\text{H}]^+$  653.3180 found 653.3175.  $[\alpha]_{\text{D}}^{23} - 43.7$  ( $c = 0.015$ ,  $\text{CHCl}_3$ )

**(S)-10,16-diphenyl-13-(1-piperidyl)-12,14-dioxo-13 $\lambda^5$ -**

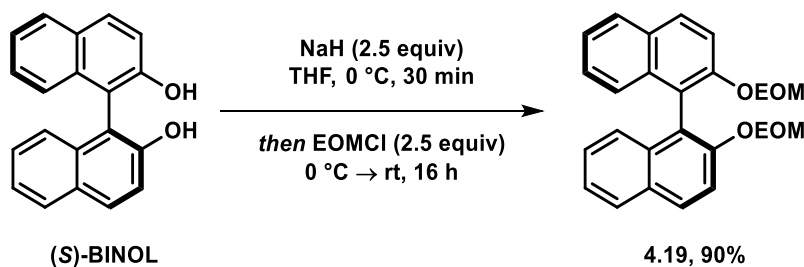
**phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricoso-1(23),2(11),3(8),9,15,17-hexaene 13-oxide (4.18)**



A flame-dried 2-dram vial was charged with **4.16a** (0.050 g, 0.112 mmol, 1 equiv), DMAP (0.027 g, 0.224 mmol, 2 equiv) and a Teflon-coated stir bar. The vial was fitted with a septum cap, then evacuated and backfilled with Ar three times. Solids were dissolved in  $\text{CH}_2\text{Cl}_2$  (1 mL). To the vial was added  $\text{Et}_3\text{N}$  (0.079 g, 0.784 mmol, 7 equiv) and then  $\text{POCl}_3$  was added dropwise. The septum cap was quickly replaced with a Teflon screwcap and the reaction was stirred at room temperature for 2 hours. After this time, piperidine (0.024 g, 0.280 mmol, 2.5 equiv) in 0.5

mL of MeCN was added to the reaction. The vial was then heated to 80 °C for 4 hours, then quenched with H<sub>2</sub>O and extracted two times with EtOAc. The combined organic phases were then dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed via rotary evaporation and the crude was purified by column chromatography (15% EtOAc in hexanes) to provide **4.18** (0.048 g, 0.083 mmol, 74%) as a white solid. **<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.72 (d, *J* = 7.4 Hz, 2H), 7.69 (d, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.32 (m, 2H), 7.24 (s, 1H), 7.17 (s, 1H), 2.96-2.86 (m, 3H), 2.86-2.79 (m, 1H), 2.69 (m, 2H), 2.59 (m, 2H), 2.38 (dt, *J* = 16.5 Hz, 6.0 Hz, 1H), 2.32 (dt, *J* = 16.3 Hz, 6.2 Hz, 1H), 2.06 (m, 2H), 1.83 (m, 6H), 1.63 (m, 2H), 1.27 (m, 2H), 1.13 (m, 4H). **<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 143.9 (d, *J* = 10.2 Hz), 142.8 (d, *J* = 8.0 Hz), 137.9, 137.5, 137.3, 137.1, 135.13 (d, *J* = 1.8 Hz), 135.09 (d, *J* = 2.2 Hz), 132.1 (d, *J* = 3.2 Hz), 131.5, 131.2 (d, *J* = 3.3 Hz), 130.3, 129.9, 129.8, 129.7, 128.4, 128.2, 128.1, 128.0, 127.2, 45.2, 29.4, 29.3, 28.0, 27.9, 26.0, 25.9, 24.2, 22.9, 22.84, 22.80, 22.7. **<sup>31</sup>P NMR** (243 MHz, CDCl<sub>3</sub>) 7.6. **HRMS** (ESI) Calc'd for [C<sub>37</sub>H<sub>38</sub>NO<sub>3</sub>P]<sup>+</sup> [M+H]<sup>+</sup> 576.2663 found 576.2668. [α]<sub>D</sub><sup>23</sup> + 305 (*c* = 0.006, CHCl<sub>3</sub>)

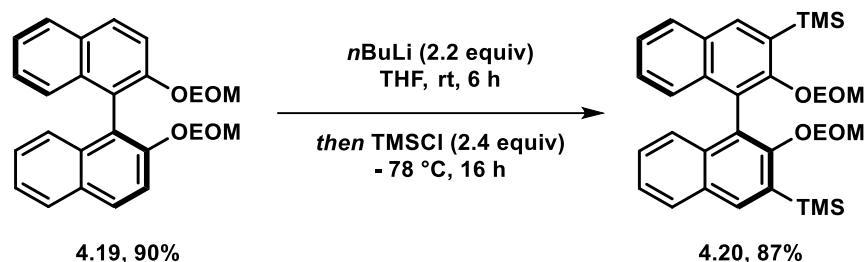
**(S)-2-(ethoxymethoxy)-1-[2-(ethoxymethoxy)-1-naphthyl]naphthalene (4.19)**



In a round-bottomed flask containing (S)-BINOL (4.008 g, 14.00 mmol, 1 equiv) and a Teflon-coated stir bar was fitted with a rubber septum and evacuated and back-filled with argon three times. The solid was dissolved in THF (28 mL) and the reaction was then cooled to 0 °C. The

septum was removed and NaH (0.420 g, 35.00 mmol, 2.5 equiv) was added in portions and the septum was re-fitted. After this addition, ethoxymethyl chloride (3.25 mL, 35.00 mmol, 2.5 equiv) was added dropwise and the reaction was allowed to reach room temperature and stirred for 16 h. After this time, the reaction was quenched with H<sub>2</sub>O and extracted with EtOAc three times. The combined organic layers were then dried over Na<sub>2</sub>SO<sub>4</sub>. The crude residue was purified by flash column chromatography (3% EtOAc in hexanes) and **4.19** (5.094 g, 12.60 mmol, 90%) was obtained as a colourless oil. Spectral data was consistent with the literature.<sup>40</sup>

**(S)-[3-(ethoxymethoxy)-4-[2-(ethoxymethoxy)-3-trimethylsilyl-1-naphthyl]-2-naphthyl]-trimethyl-silane (4.20)**

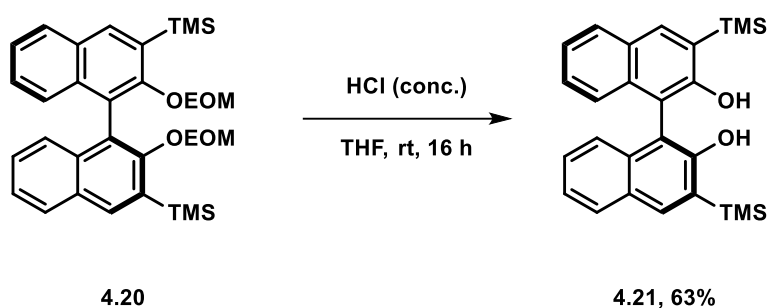


A flame-dried 2-dram vial was charged with **4.19** (0.121 g, 0.30 mmol, 1 equiv) and a Teflon-coated stir bar. The vessel was sealed with a septum cap and evacuated and backfilled with argon three times. **4.19** was dissolved in THF (1 mL) and *n*BuLi (0.39 mL, 2.34 M in hexane, 0.90 mmol, 3 equiv) was added slowly at room temperature. Over the course of 2 hours, a precipitate forms. This suspension was cooled to -78 °C and TMSCl (0.11 mL, 0.90 mmol, 3 equiv) was added dropwise. The reaction was allowed to warm to room temperature and stir for 16 hours. After this time, the reaction was quenched with H<sub>2</sub>O and extracted 2 times with EtOAc. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (1% EtOAc in hexanes) to afford **4.20**



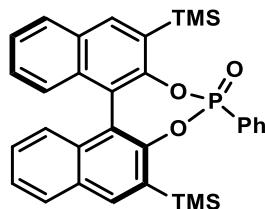
(0.142 g, 0.26 mmol, 87%) as a colourless solid. **<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 8.09 (s, 2H), 7.90 (d, *J* = 8.1 Hz, 2H), 7.40 (m, 2H), 7.31-7.23 (m, 4H), 4.49 (d, *J* = 4.5 Hz, 2H), 4.19 (d, *J* = 4.5 Hz, 2H), 3.41 (m, 2H), 2.93 (m, 2H), 0.93 (t, *J* = 7.1 Hz, 6H), 0.46 (s, 18H). **<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 158.2, 137.1, 135.7, 134.3, 130.3, 128.3, 127.1, 126.1, 124.6, 122.4, 96.5, 64.9, 14.9, -0.3. **HRMS** (ESI) Calc'd for [C<sub>32</sub>H<sub>42</sub>NaO<sub>4</sub>Si<sub>2</sub>]<sup>+</sup> [M+Na]<sup>+</sup> 569.2514 found 569.2516.

**(*S*)-1-(2-hydroxy-3-trimethylsilyl-1-naphthyl)-3-trimethylsilyl-naphthalen-2-ol (4.21)**



In a 1-dram vial, **4.20** (0.085 g, 0.167 mmol, 1 equiv) was dissolved in THF (2 mL). To this solution was added concentrated aqueous HCl (1 mL) and the resulting mixture was stirred at room temperature for 16 hours. At this time the reaction was quenched with saturated NaHCO<sub>3</sub> and extracted three times with EtOAc. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude residue recrystallized in a mixture of CH<sub>2</sub>Cl<sub>2</sub> and hexanes to afford the unprotected BINOL (0.055 g, 0.135 mmol, 81%) as a pale-yellow solid. Spectral data was consistent with the literature.<sup>41</sup>

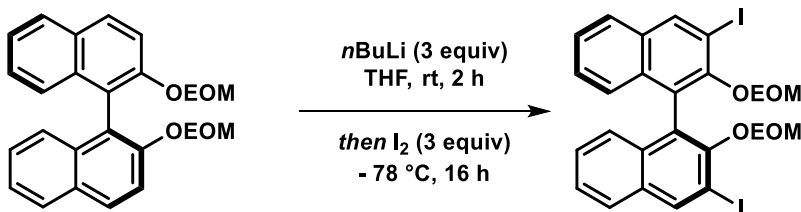
**(*S*)-trimethyl-(13-oxo-13-phenyl-16-trimethylsilyl-12,14-dioxo-13λ<sup>5</sup>-phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricoso-1(23),2(11),3(8),4,6,9,15,17,19,21-decaen-10-yl)silane (4.22)**



**4.22, 63%**

**4.22** was obtained using General Procedure C using **4.21** (0.071 g, 0.170 mmol),  $\text{PhPOCl}_2$  (0.035 g, 0.180 mmol, 1.2 equiv), DMAP (0.042 g, 0.340 mmol, 2 equiv) and  $\text{NEt}_3$  (0.051 g, 0.510 mmol, 3 equiv). The reaction was purified by flash column chromatography (10% EtOAc in hexanes) to obtain the product as a white solid (0.059 g, 0.107 mmol, 63%).  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.15 (s, 1H), 8.01 (s, 1H), 7.94 (d,  $J = 8.3$  Hz, 2H), 7.55 (t,  $J = 7.5$  Hz, 1H), 7.52 (d,  $J = 7.3$  Hz, 1H), 7.51-7.46 (m, 2H), 7.44 (t,  $J = 7.3$  Hz, 1H), 7.34-7.30 (m, 2H), 7.29 (dd,  $J = 6.6$  Hz, 0.9 Hz, 1H), 7.27 (s, 1H), 7.25-7.21 (m, 1H), 7.11 (d,  $J = 8.6$  Hz), 0.45 (s, 9H), 0.05 (s, 9H).  $^{13}\text{C NMR}$  (151 MHz,  $\text{CDCl}_3$ )  $\delta$  151.7 (d,  $J = 10.0$  Hz), 149.8 (d,  $J = 9.5$  Hz), 138.0, 137.8 (d,  $J = 9.3$  Hz), 133.7 (d,  $J = 2.8$  Hz), 133.2 (d,  $J = 9.5$  Hz), 132.5 (d,  $J = 1.8$  Hz), 132.2 (d,  $J = 3.4$  Hz), 131.5, 131.1, 128.6 (d,  $J = 8.3$  Hz), 128.5, 127.3, 127.0, 126.9 (d,  $J = 6.8$  Hz), 126.1 (d,  $J = 187.1$  Hz), 125.5 (d,  $J = 11.5$  Hz), 121.3 (d,  $J = 2.7$  Hz), 120.8 (d,  $J = 1.7$  Hz), 0.0, -0.2.  $^{31}\text{P NMR}$  (243 MHz,  $\text{CDCl}_3$ )  $\delta$  23.6. **HRMS** (ESI) Calc'd for  $[\text{C}_{32}\text{H}_{34}\text{O}_3\text{PSi}_2]^+ [\text{M}+\text{H}]^+$  553.1779 found 553.1776.  $[\alpha]_{\text{D}}^{23} + 342.1$  ( $c = 0.035$ ,  $\text{CHCl}_3$ )

**(S)-2-(ethoxymethoxy)-1-[2-(ethoxymethoxy)-3-iodo-1-naphthyl]-3-iodo-naphthalene (4.23)**

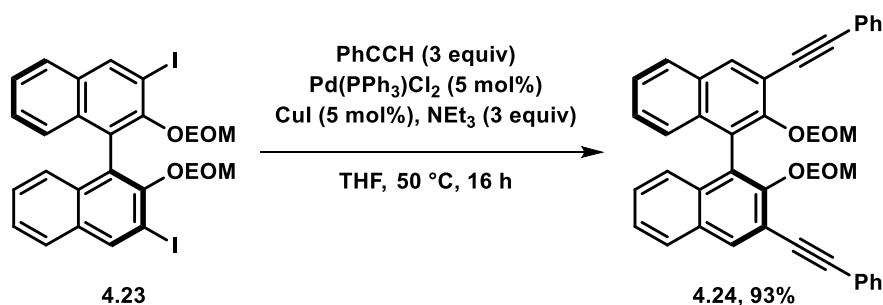


**4.19**

**4.23 (36%)**

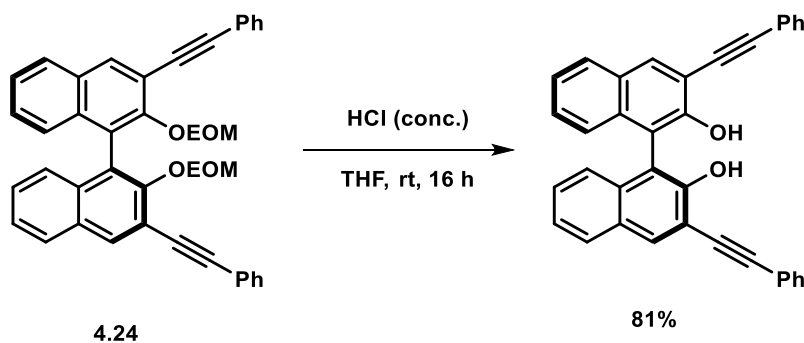
A flame-dried 2-dram vial was charged with **4.19** (0.308 g, 1.00 mmol, 1 equiv) and a Teflon-coated stir bar. The vessel was sealed with a septum cap and evacuated and backfilled with argon three times. **4.19** was dissolved in THF (3 mL) and *n*BuLi (1.26 mL, 2.384 M in hexane, 3.00 mmol, 3 equiv) was added slowly at room temperature. Over the course of 2 hours, a precipitate forms. This suspension was cooled to -78 °C and a solution of I<sub>2</sub> (0.791 g in 0.5 mL THF, 3.00 mmol, 3 equiv) was added dropwise. The reaction was allowed to warm to room temperature and stir for 16 hours. After this time, the reaction was quenched with a 1M aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted 2 times with EtOAc. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (5% EtOAc in hexanes) to afford **4.23** (0.203 g, 0.360 mmol, 36%) as a colourless solid. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.55 (s, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.42 (t, *J* = 7.1 Hz, 2H), 7.30 (t, *J* = 7.1 Hz, 2H), 7.17 (d, *J* = 8.6 Hz), 4.89 (d, *J* = 5.8 Hz, 2H), 4.72 (d, *J* = 5.8 Hz, 2H), 3.06 (m, 2H), 2.60 (m, 2H), 0.61 (t, *J* = 7.1 Hz, 6H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 152.2, 140.1, 133.7, 132.2, 127.3, 126.9, 126.5, 126.2, 125.9, 98.3, 92.7, 65.1, 14.5. HRMS (ESI) Calc'd for [C<sub>26</sub>H<sub>25</sub>I<sub>2</sub>NaO<sub>4</sub>]<sup>+</sup> [M+Na]<sup>+</sup> 676.9657 found 676.9653.

**(*S*)-2-(ethoxymethoxy)-1-[2-(ethoxymethoxy)-3-(2-phenylethynyl)-1-naphthyl]-3-(2-phenylethynyl)naphthalene (**4.24**)**



A flame-dried 2-dram vial was charged with **4.23** (0.100 g, 0.18 mmol, 1 equiv), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (0.012 g, 0.018 mmol, 10 mol%), CuI (0.003 g, 0.018 mmol, 10 mol%) and a Teflon-coated stir bar. The vessel was sealed with a septum cap and evacuated and backfilled with argon three times. The solids were dissolved in THF (3 mL) and phenylacetylene (0.06 mL, 0.54 mmol, 3 equiv) was added, followed by Et<sub>3</sub>N (0.08 mL, 0.54 mmol, 3 equiv). The septum cap was quickly switched out for a Teflon screwcap and the reaction was heated to 50 C for 16 hours. After this time, the reaction was dry-loaded directly onto silica gel and purified by flash column chromatography (5% EtOAc in hexanes) to obtain **4.24** (0.085 g, 0.167 mmol, 93%) as an orange oil. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.23 (s, 2H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.59 (m, 4H), 4.44 (t, *J* = 7.1 Hz, 2H), 7.40-7.34 (m, 6H), 7.32 (m, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 5.30 (d, *J* = 6.4 Hz, 2H), 5.10 (d, *J* = 6.4 Hz, 2H), 3.04 (m, 2H), 2.62 (m, 2H), 0.48 (t, *J* = 7.1 Hz, 6H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 153.4, 134.3, 133.8, 131.7, 130.4, 128.6, 128.5, 127.7, 127.4, 126.7, 125.9, 125.7, 123.4, 117.4, 97.8, 93.8, 86.7, 64.7, 14.2. HRMS (ESI) Calc'd for [C<sub>42</sub>H<sub>34</sub>O<sub>4</sub>]<sup>+</sup> [M+H]<sup>+</sup> 603.2530 found 603.2530.

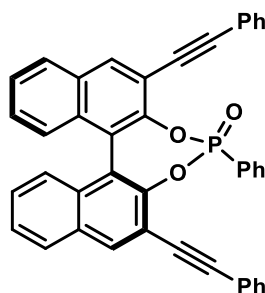
**(S)-1-[2-hydroxy-3-(2-phenylethynyl)-1-naphthyl]-3-(2-phenylethynyl)naphthalen-2-ol** (not shown in text)



In a 1-dram vial, **4.24** (0.085 g, 0.167 mmol, 1 equiv) was dissolved in THF (2 mL). To this solution was added concentrated aqueous HCl (1 mL) and the resulting mixture was stirred at room

temperature for 16 hours. At this time the reaction was quenched with saturated  $\text{NaHCO}_3$  and extracted three times with EtOAc. The combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude residue recrystallized in a mixture of  $\text{CH}_2\text{Cl}_2$  and hexanes to afford the unprotected BINOL (0.055 g, 0.135 mmol, 81%) as a pale-yellow solid. Spectral data was consistent with the literature.<sup>42</sup>

**(*S*)-13-phenyl-10,16-bis(2-phenylethynyl)-12,14-dioxo-13 $\lambda^5$ -phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricoso-1(23),2(11),3(8),4,6,9,15,17,19,21-decaene 13-oxide (4.25)**



**4.25, 29%**

**4.25** was obtained using General Procedure C using (*S*)-1-[2-hydroxy-3-(2-phenylethynyl)-1-naphthyl]-3-(2-phenylethynyl)naphthalen-2-ol (0.055 g, 0.135 mmol),  $\text{PhPOCl}_2$  (0.032 g, 0.162 mmol, 1.2 equiv), DMAP (0.033 g, 0.270 mmol, 2 equiv) and  $\text{NEt}_3$  (0.041 g, 0.404 mmol, 3 equiv). The reaction was purified by flash column chromatography (15% EtOAc in hexanes) to obtain the product as a yellow solid (0.024 g, 0.085 mmol, 63%).  **$^1\text{H}$  NMR** (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.33 (s, 1H), 8.09 (s, 1H), 7.96 (d,  $J = 8.3$  Hz, 1H), 7.90 (d,  $J = 8.2$  Hz), 7.73 (d,  $J = 7.6$  Hz, 1H), 7.71 (d,  $J = 7.6$  Hz, 1H), 7.57 (m, 2H), 7.52 (m, 3H), 7.39-7.25 (m 14H).  **$^{13}\text{C}$  NMR** (151 MHz,  $\text{CDCl}_3$ )  $\delta$  146.8 (d,  $J = 10.6$  Hz), 145.4 (d,  $J = 10.1$  Hz), 134.8, 134.4, 133.7 (d,  $J = 2.9$  Hz), 132.7 (d,  $J = 10.2$  Hz), 132.1, 132.0, 131.8, 131.5, 131.1, 128.7, 128.6, 128.51, 128.47, 128.4, 128.3, 127.5,

127.3, 127.1, 126.5 (d,  $J = 1.7$  Hz), 125.0 (d,  $J = 187.2$  Hz), 123.2, 122.8, 122.4 (d,  $J = 2.7$  Hz), 122.3 (d,  $J = 1.8$  Hz), 117.2 (d,  $J = 1.8$  Hz), 116.7 (d,  $J = 2.9$  Hz) 95.1, 94.4, 84.6, 84.0.  $^{31}\text{P}$  NMR (243 MHz,  $\text{CDCl}_3$ )  $\delta$  26.9. **HRMS** (ESI) Calc'd for  $[\text{C}_{42}\text{H}_{26}\text{O}_3\text{P}]^+$   $[\text{M}+\text{H}]^+$  609.1615 found 609.1614.  $[\alpha]_{\text{D}}^{23} + 143.5$  ( $c = 0.011$ ,  $\text{CHCl}_3$ )

## 4.7 References

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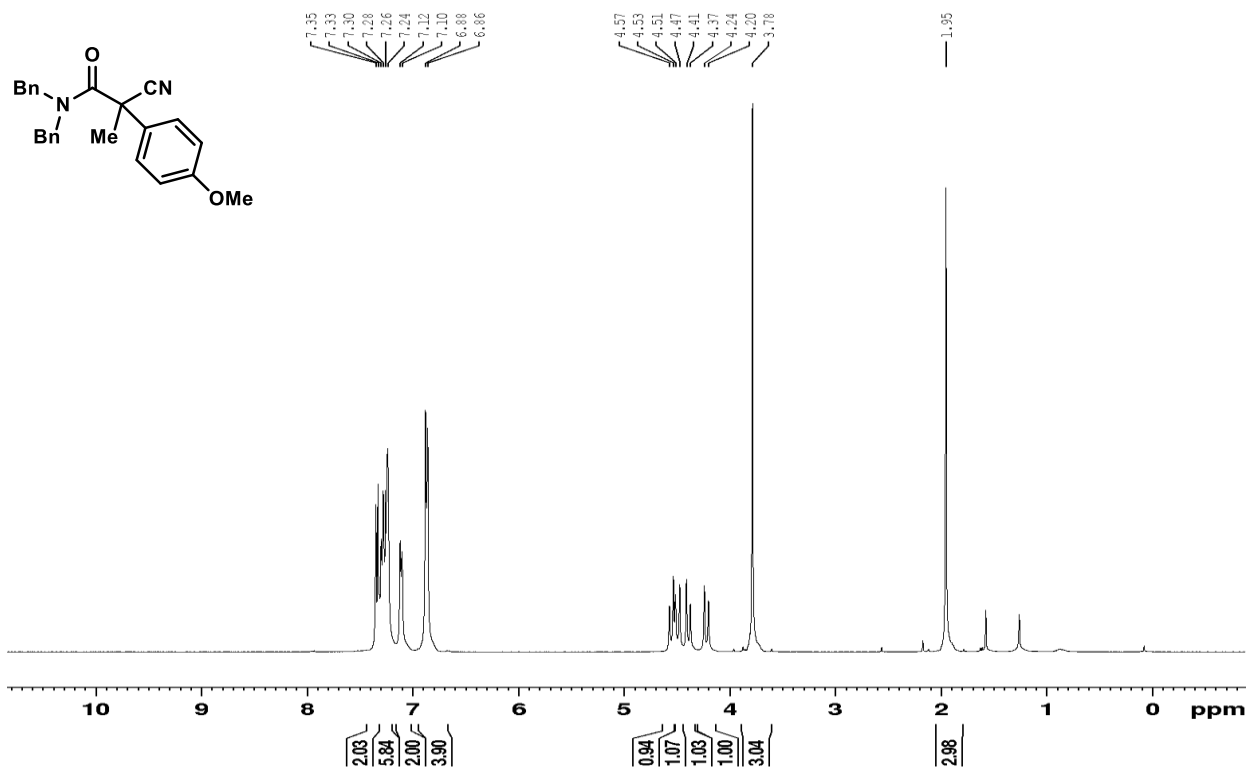
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## 4.8 Appendix

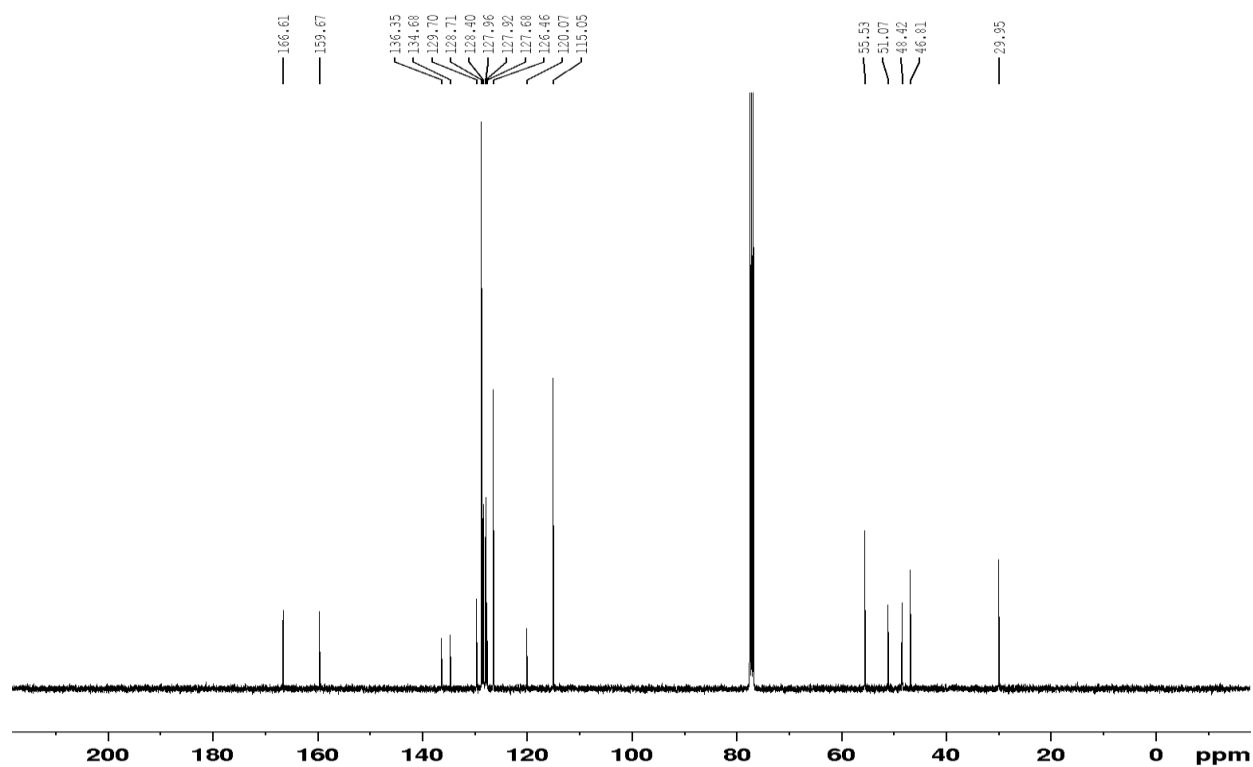
### *N,N*-dibenzyl-2-cyano-2-(4-methoxyphenyl)propenamide (4.3a)

<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (400 MHz)



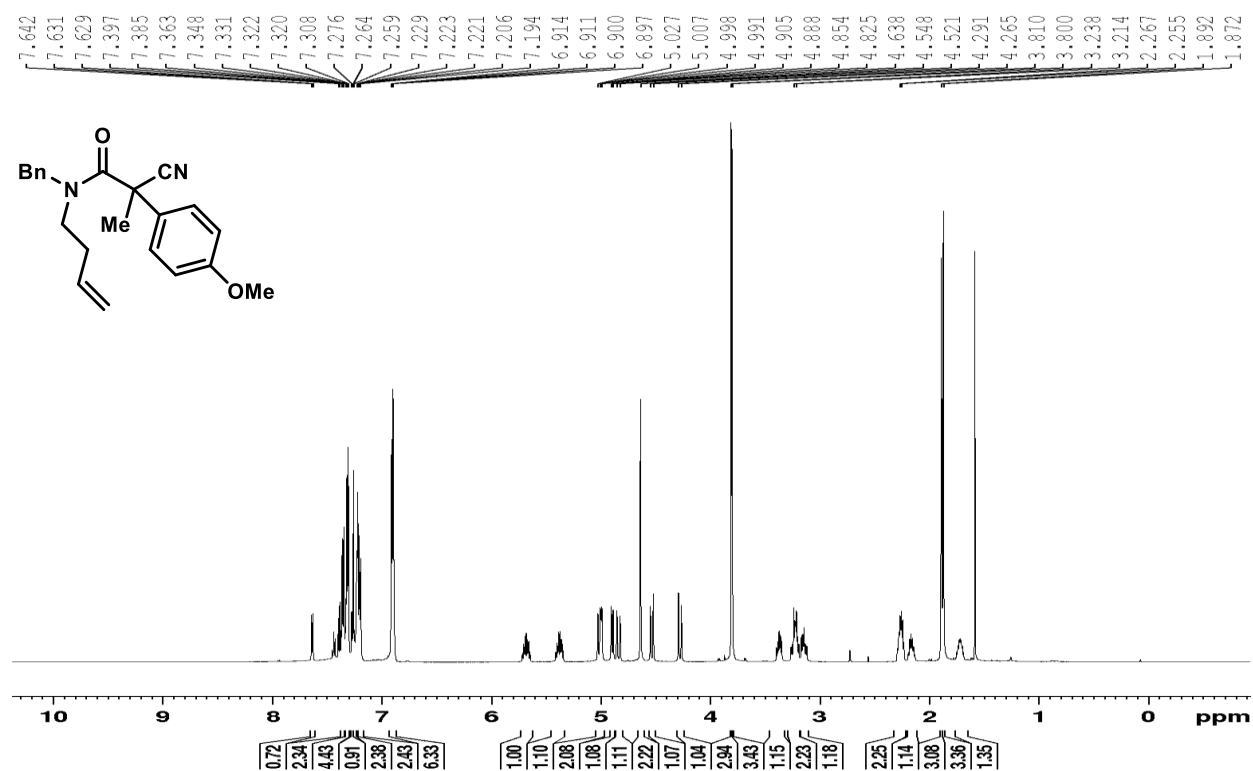


$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (101 MHz)

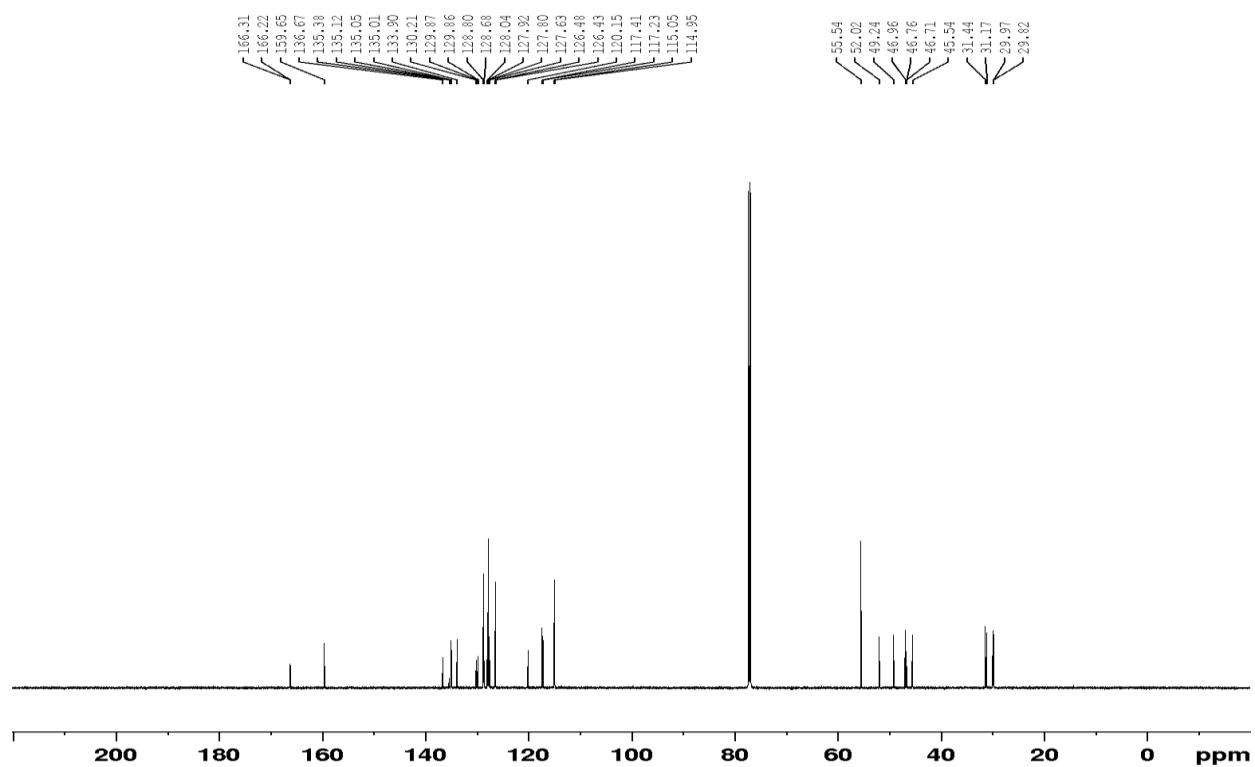


*N*-benzyl-*N*-but-3-enyl-2-cyano-2-(4-methoxyphenyl)propenamide (**4.3b**)

$^1\text{H}$  NMR Spectrum  $\text{CDCl}_3$  (600 MHz)

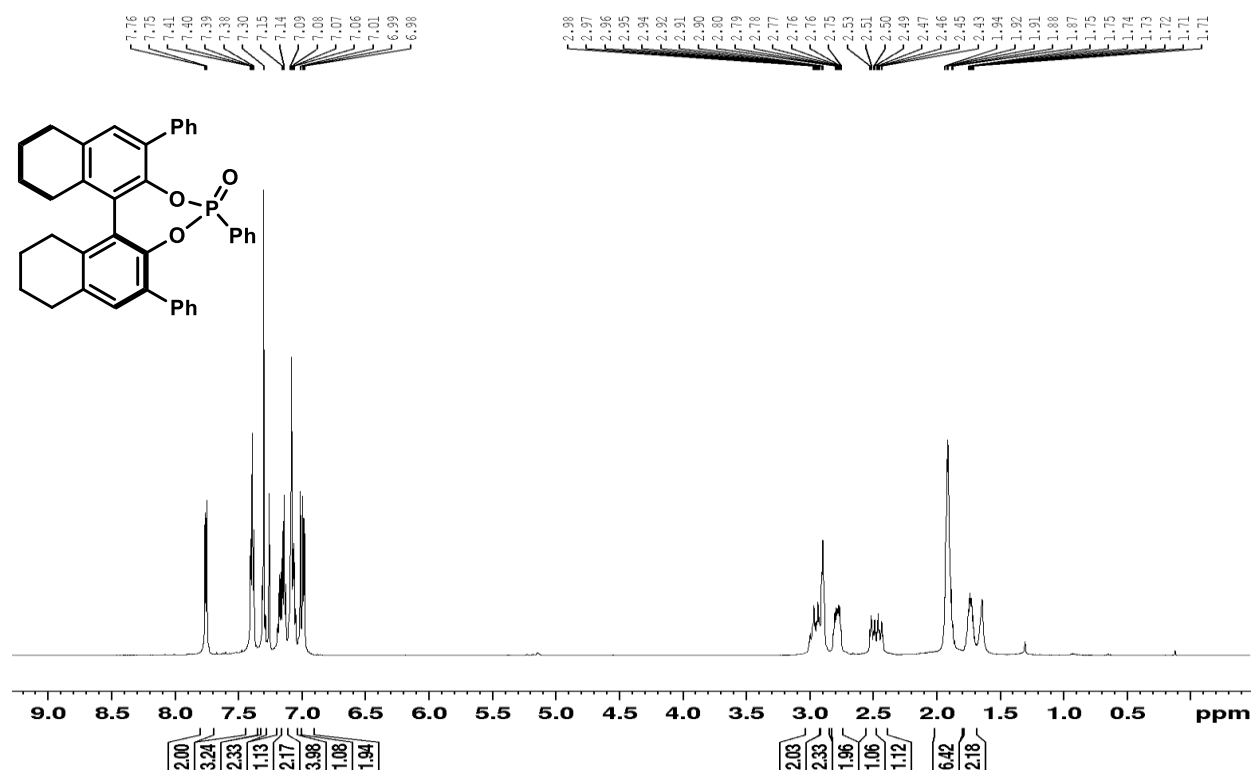


$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (151 MHz)

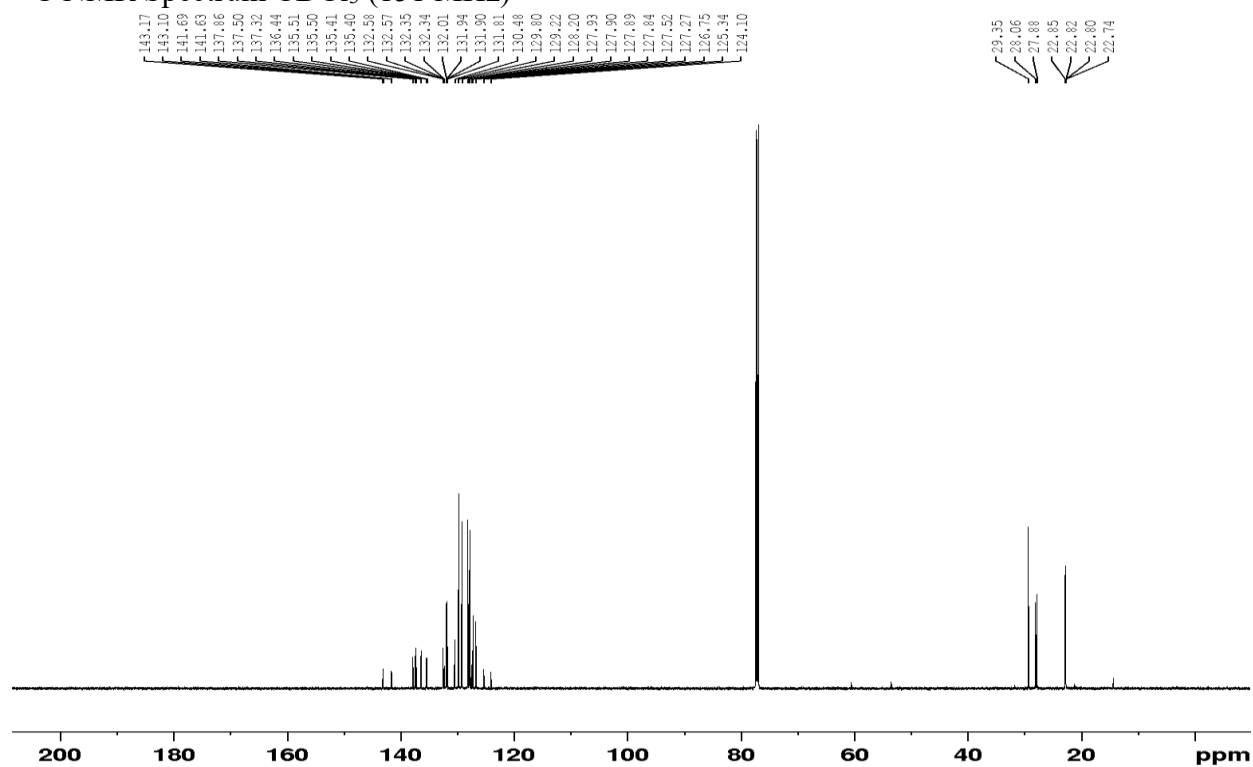


(S)-10,13,16-triphenyl-12,14-dioxo-13 $\lambda^5$ -phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricoso-1(23),2(11),3(8),9,15,17-hexaene 13-oxide (**4.17a**)

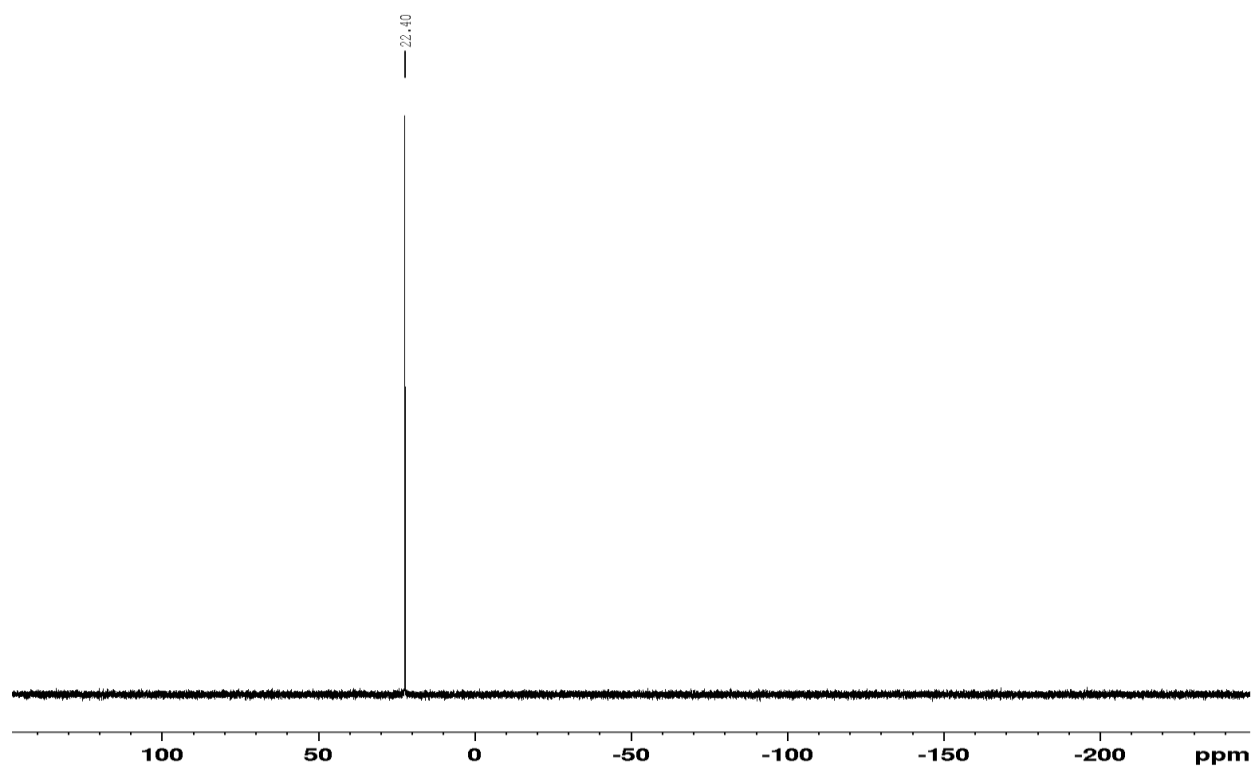
$^1\text{H}$  NMR Spectrum  $\text{CDCl}_3$  (600 MHz)



$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (151 MHz)

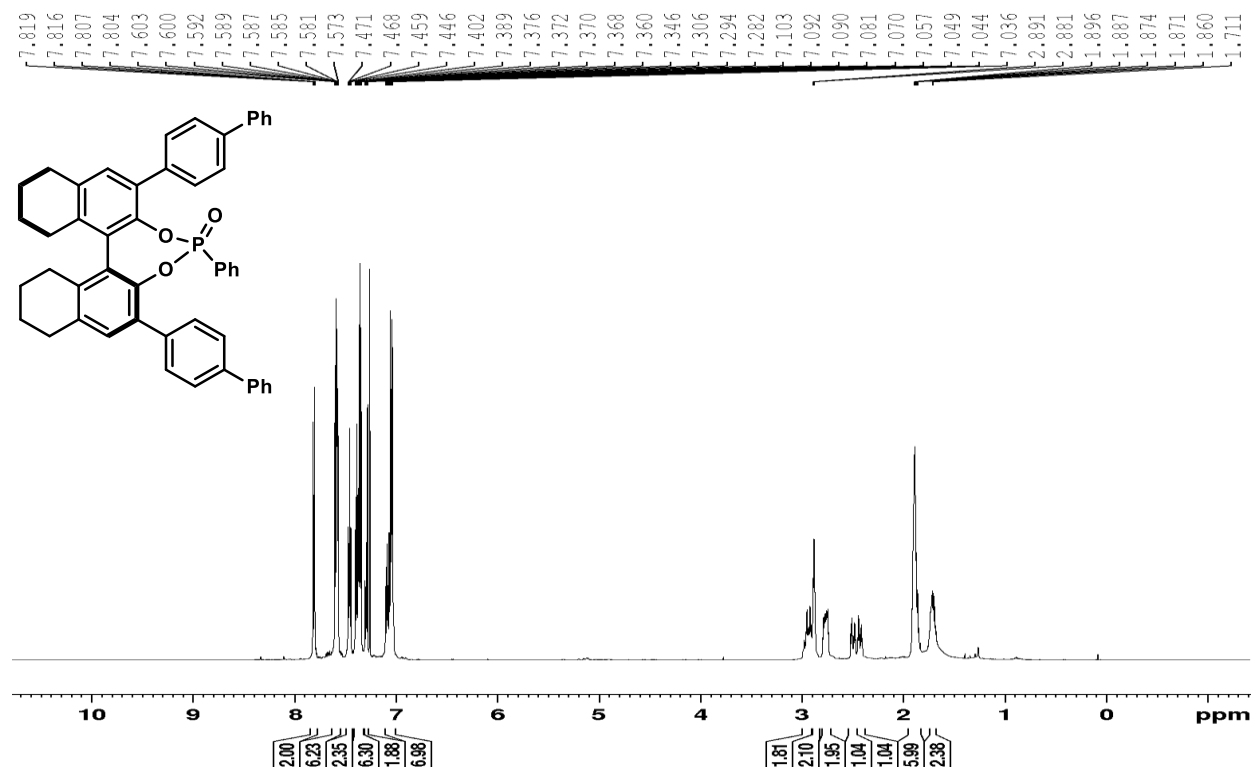


$^{31}\text{P}$  NMR Spectrum  $\text{CDCl}_3$  (243 MHz)

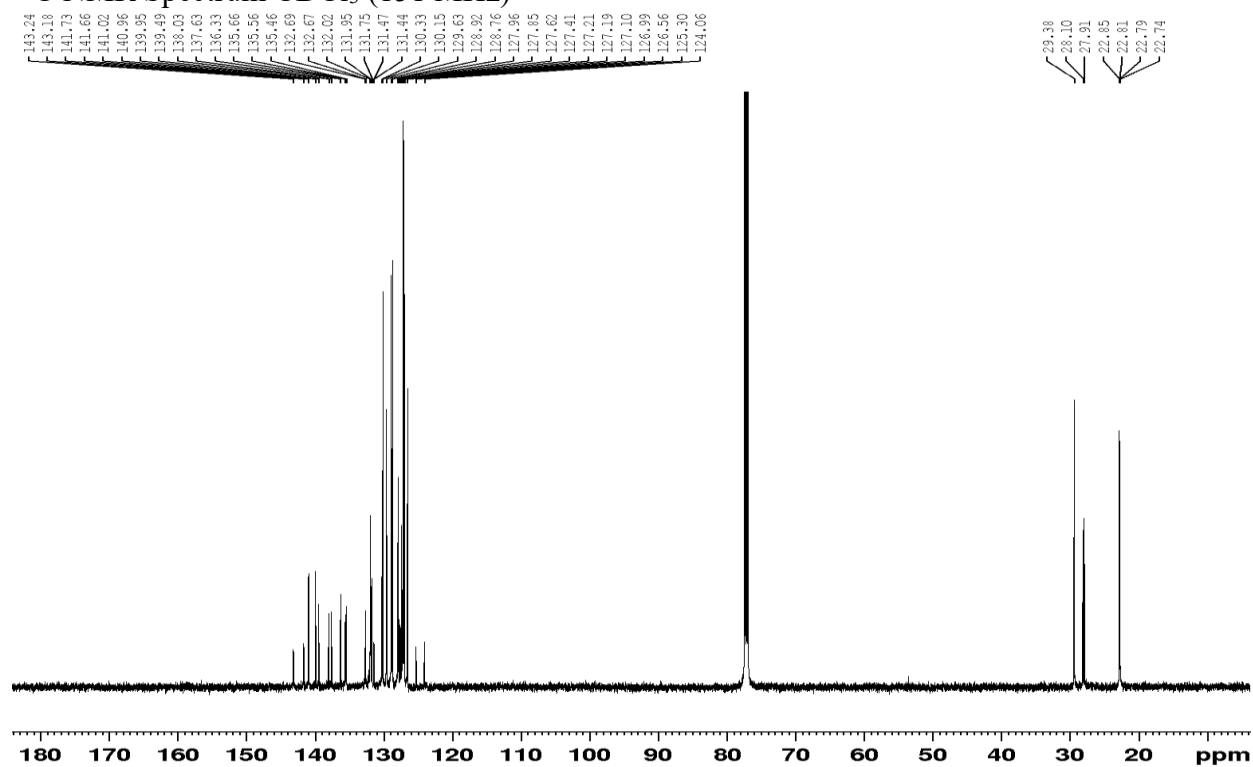


(S)-13-phenyl-10,16-bis(4-phenylphenyl)-12,14-dioxa-13 $\lambda$ <sup>5</sup>-phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricos-1(23),2(11),3(8),9,15,17-hexaene 13-oxide  
**(4.17b)**

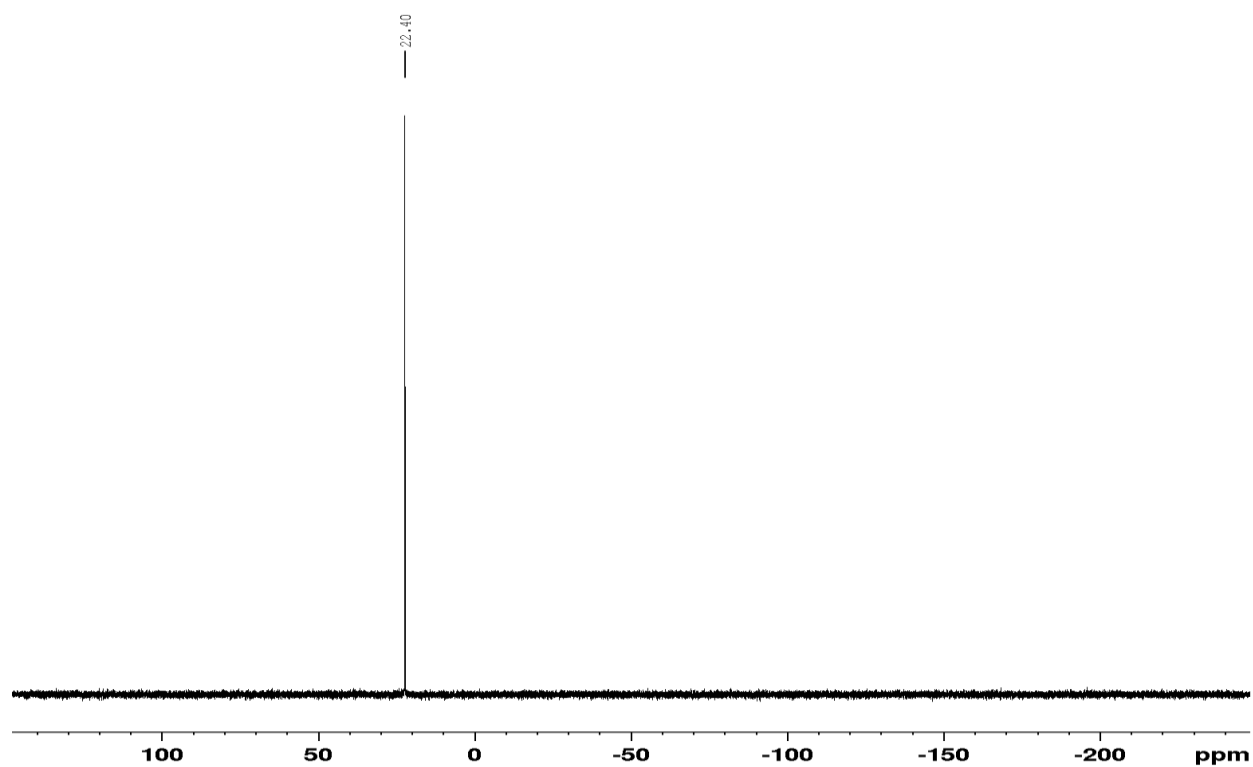
<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (600 MHz)



$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (151 MHz)

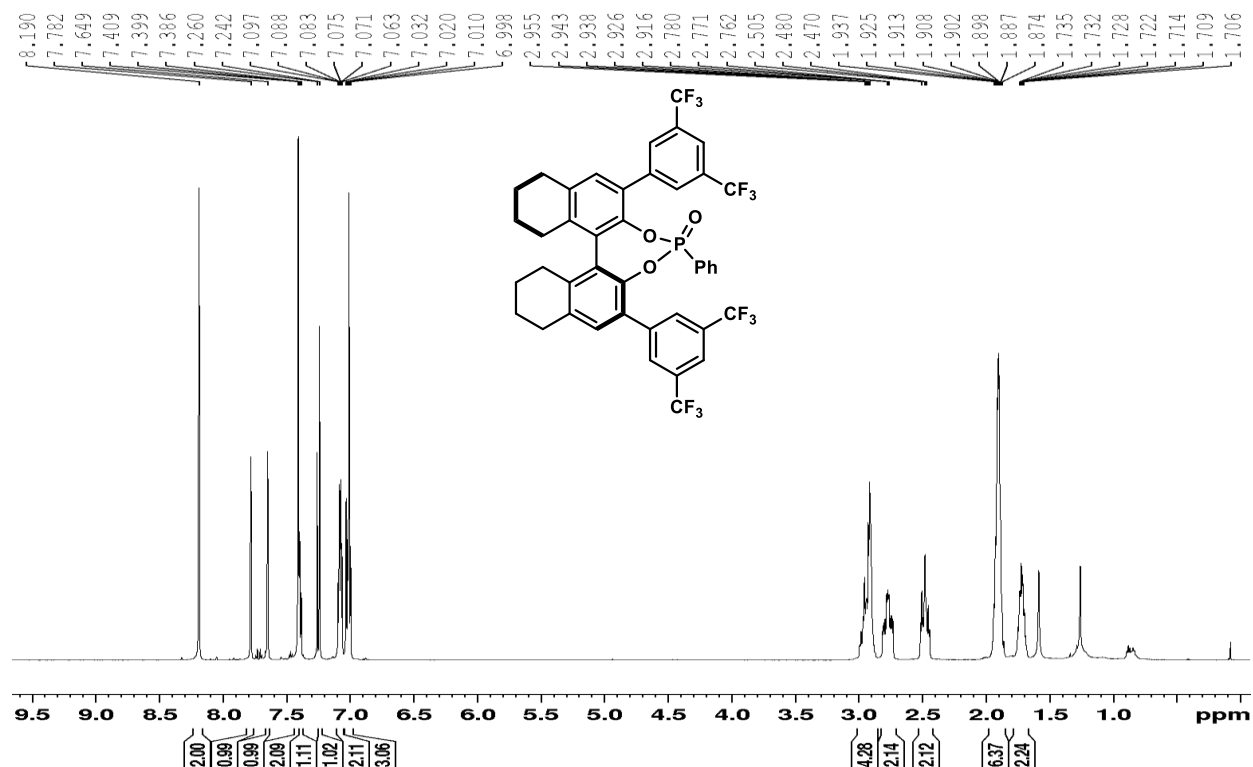


$^{31}\text{P}$  NMR Spectrum  $\text{CDCl}_3$  (243 MHz)



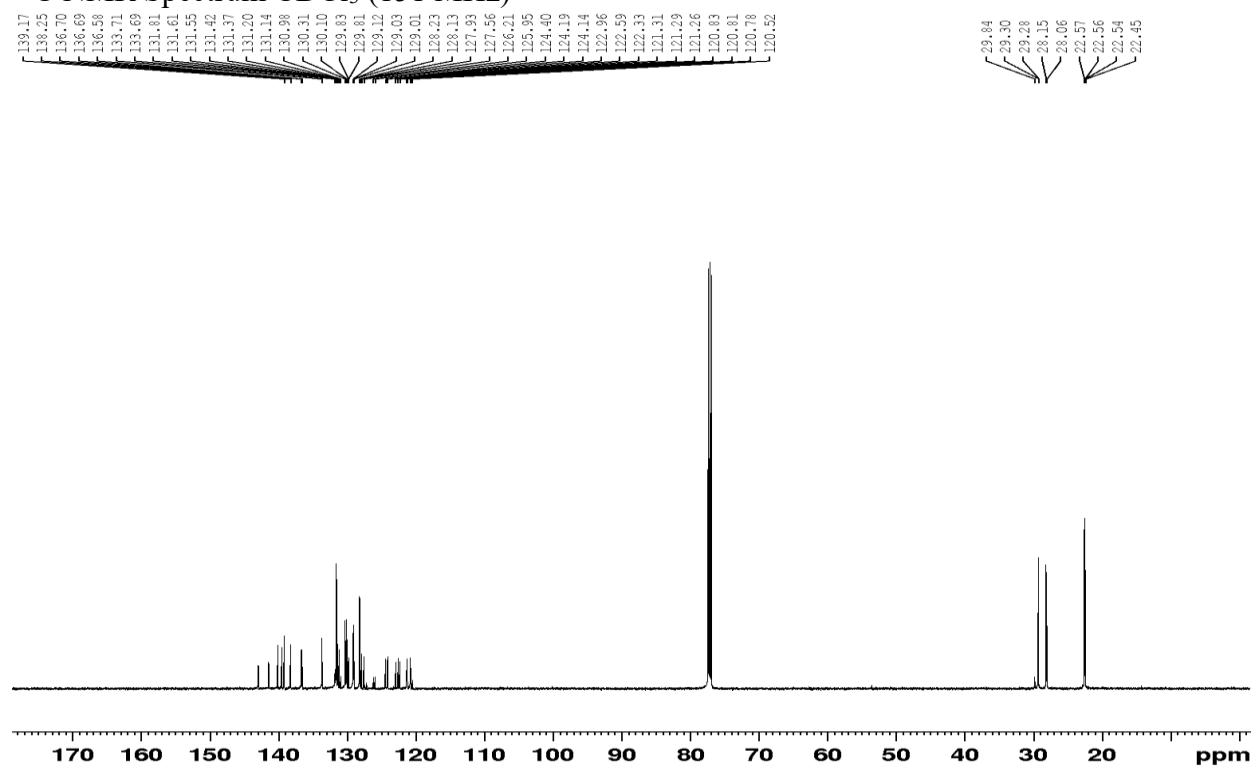
(S)-10,16-bis[3,5-bis(trifluoromethyl)phenyl]-13-phenyl-12,14-dioxo-13 $\lambda^5$ -phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricoso-1(23),2(11),3(8),9,15,17-hexaene 13-oxide  
**(4.17c)**

$^1\text{H}$  NMR Spectrum  $\text{CDCl}_3$  (600 MHz)

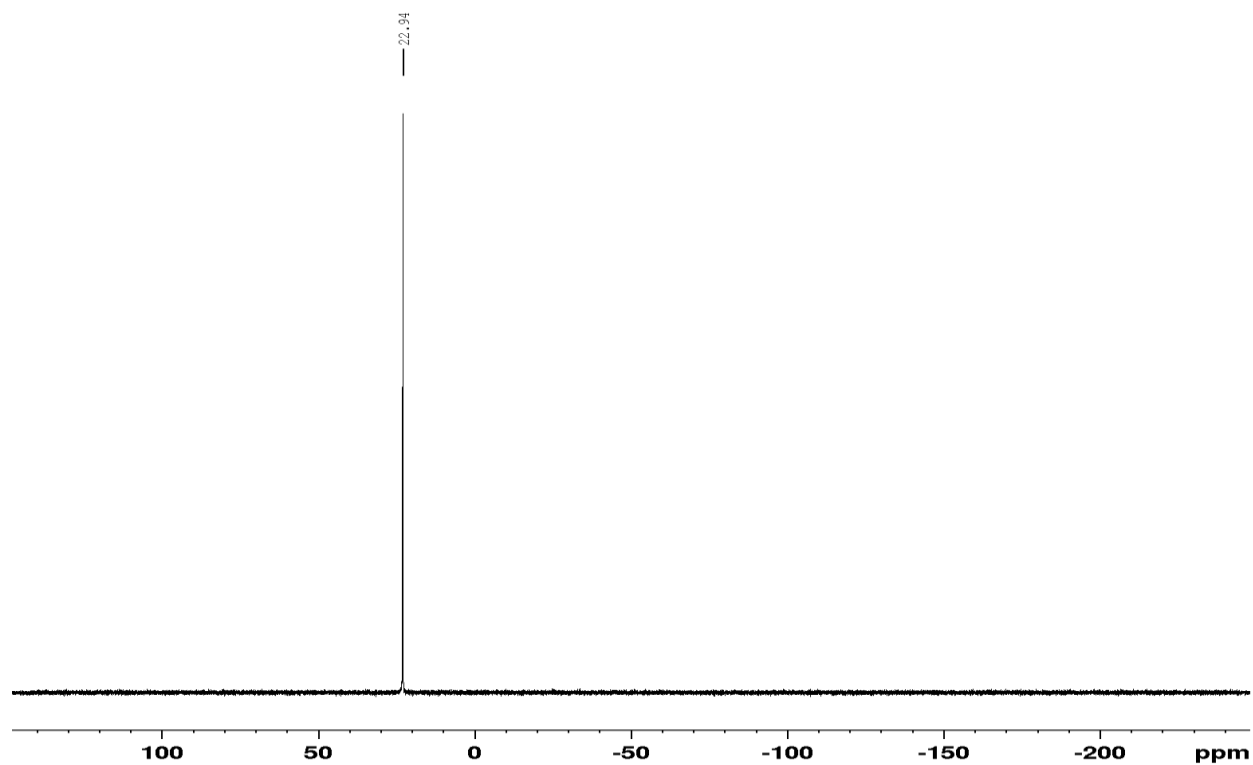




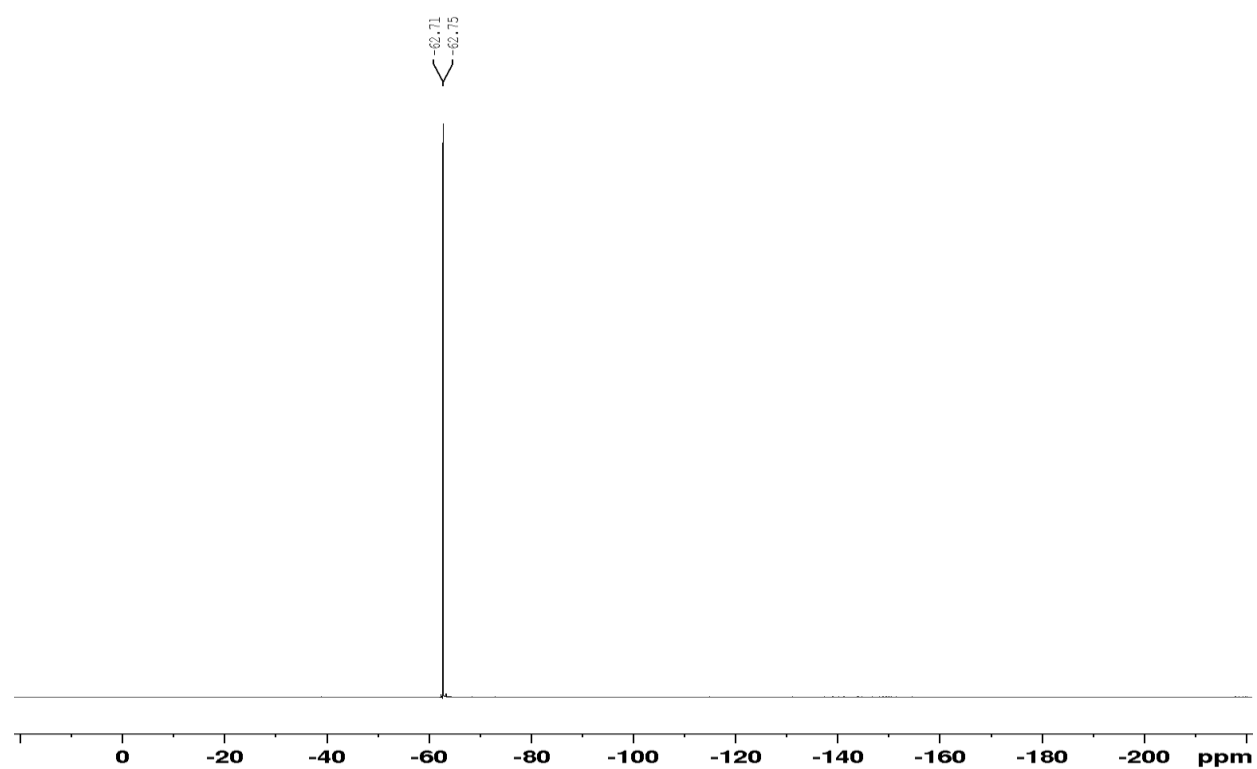
$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (151 MHz)



$^{31}\text{P}$  NMR Spectrum  $\text{CDCl}_3$  (243 MHz)

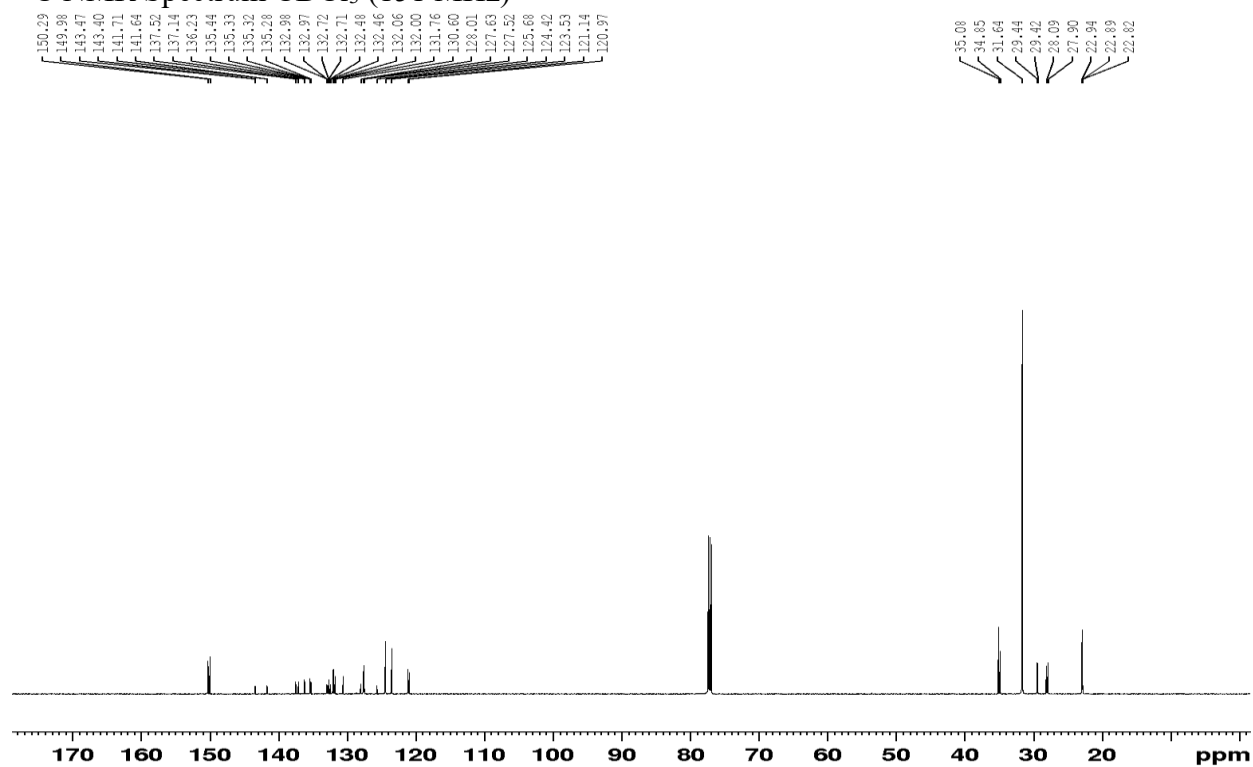


$^{19}\text{F}$  NMR Spectrum  $\text{CDCl}_3$  (282 MHz)

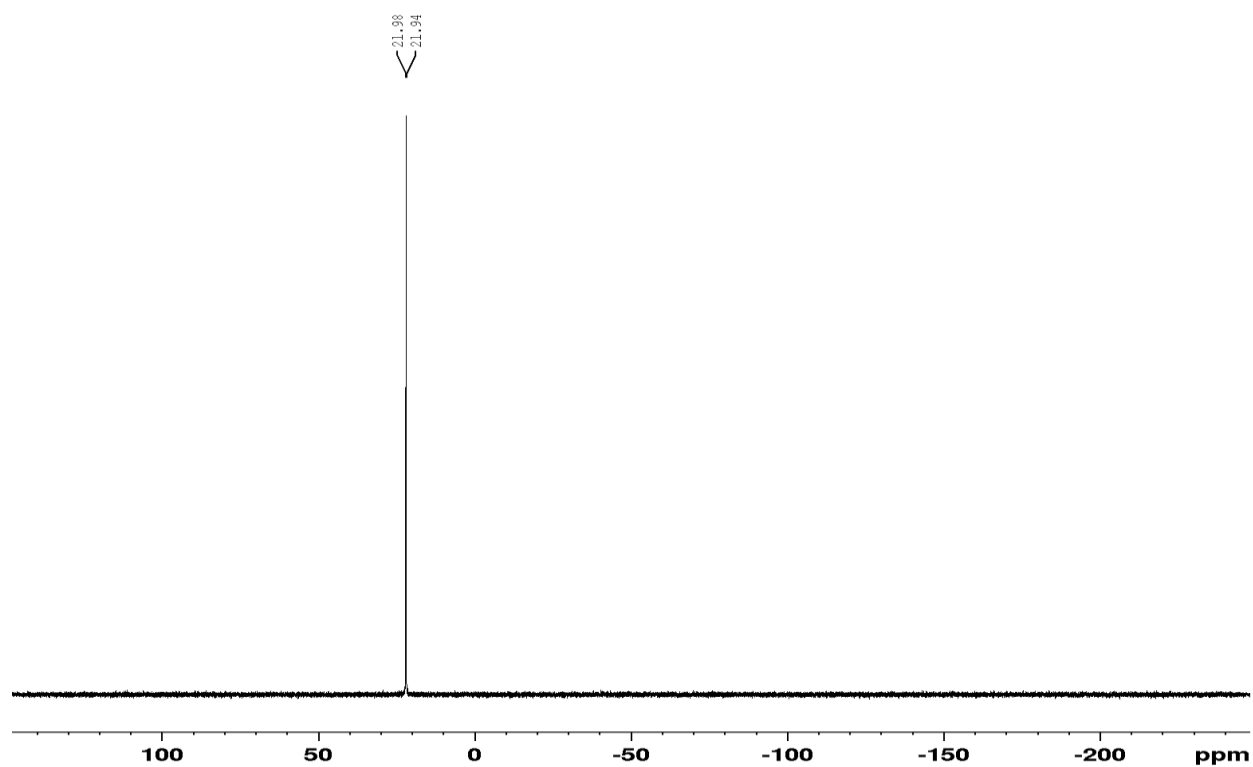


<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (600 MHz)

$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (151 MHz)

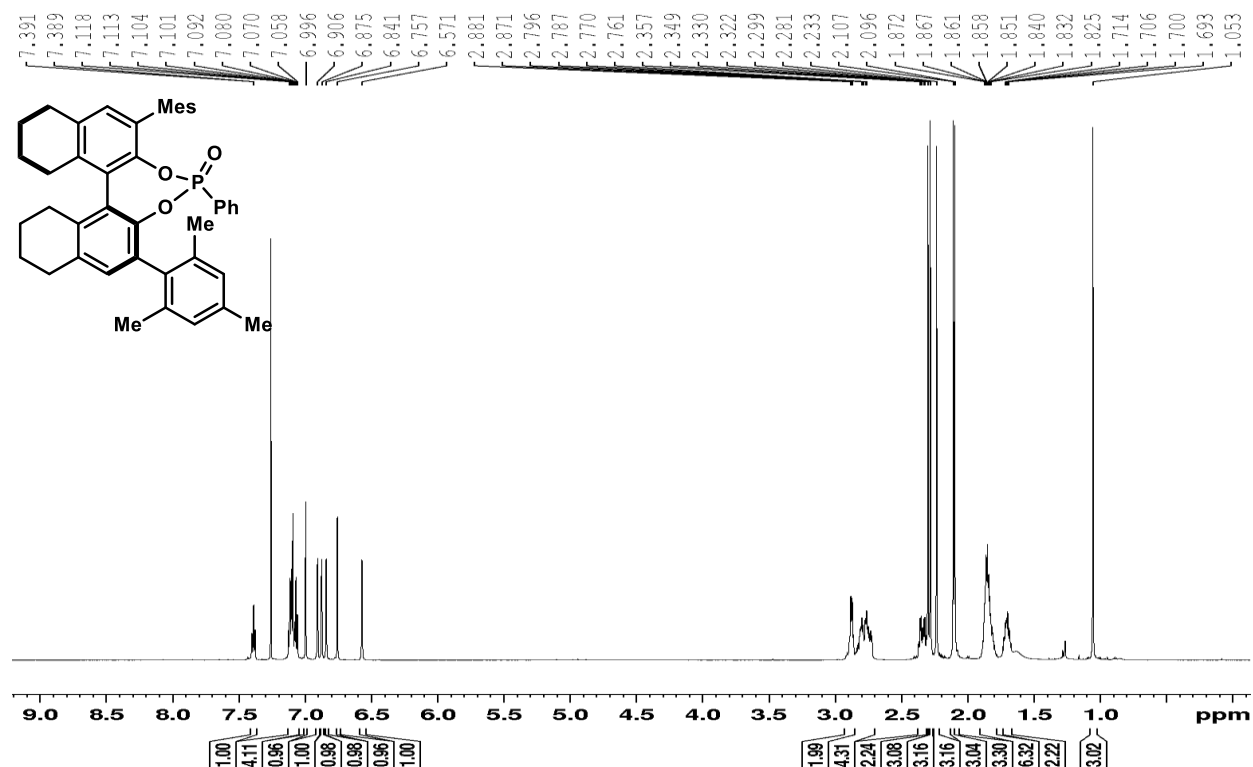


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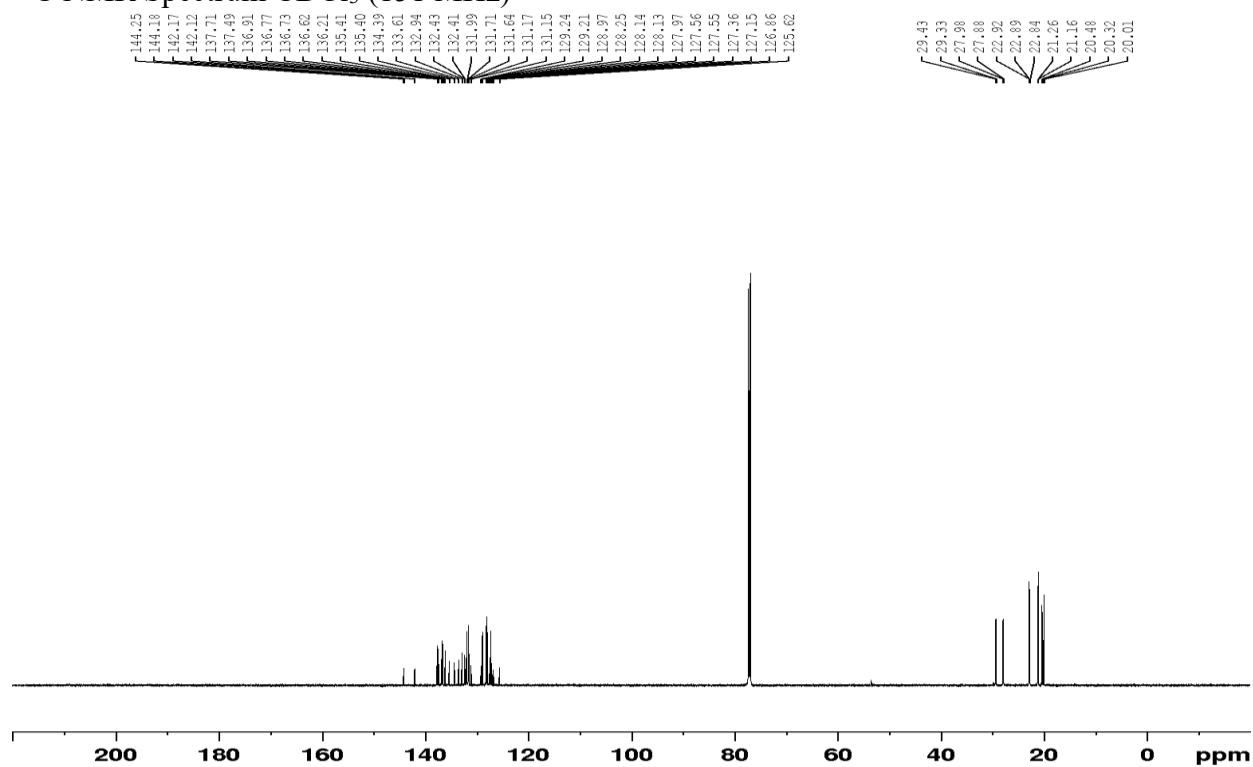


(S)-13-phenyl-10,16-bis(2,4,6-trimethylphenyl)-12,14-dioxa-13 $\lambda^5$ -phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricos-1(23),2(11),3(8),9,15,17-hexaene 13-oxide  
**(4.17e)**

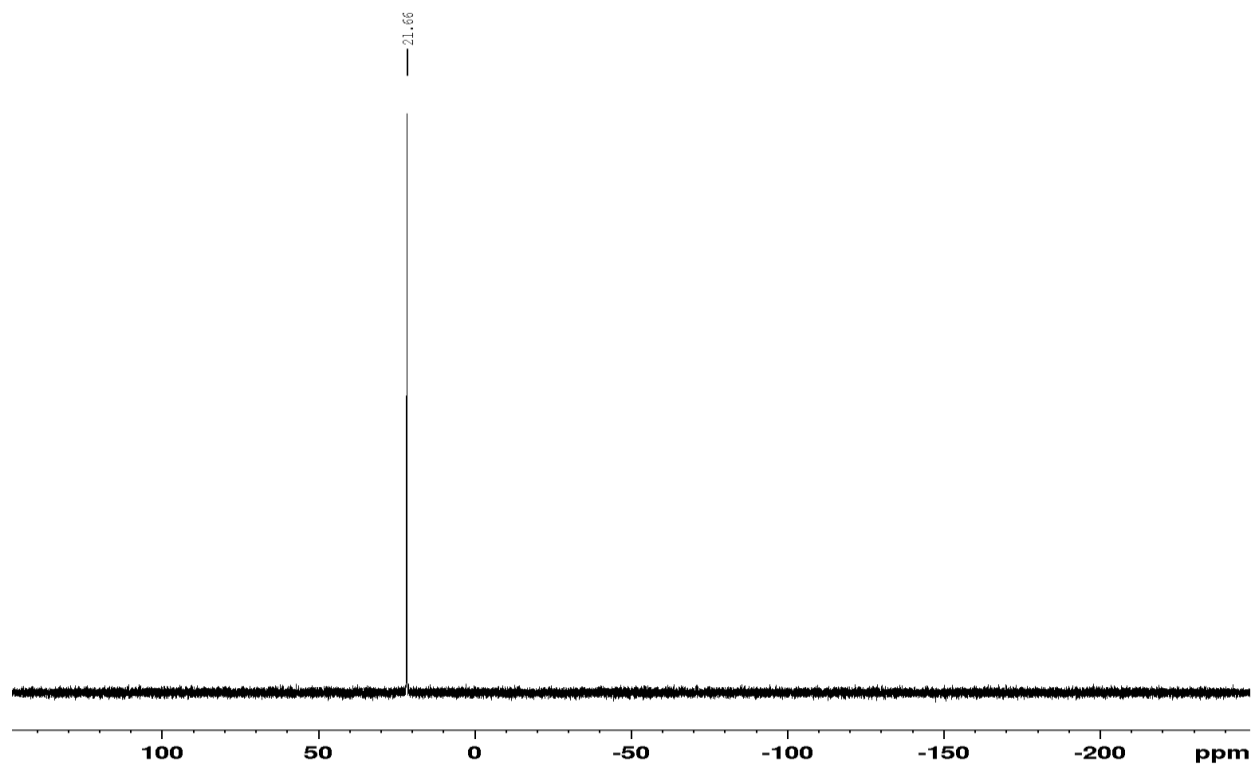
$^1\text{H}$  NMR Spectrum  $\text{CDCl}_3$  (600 MHz)



$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (151 MHz)

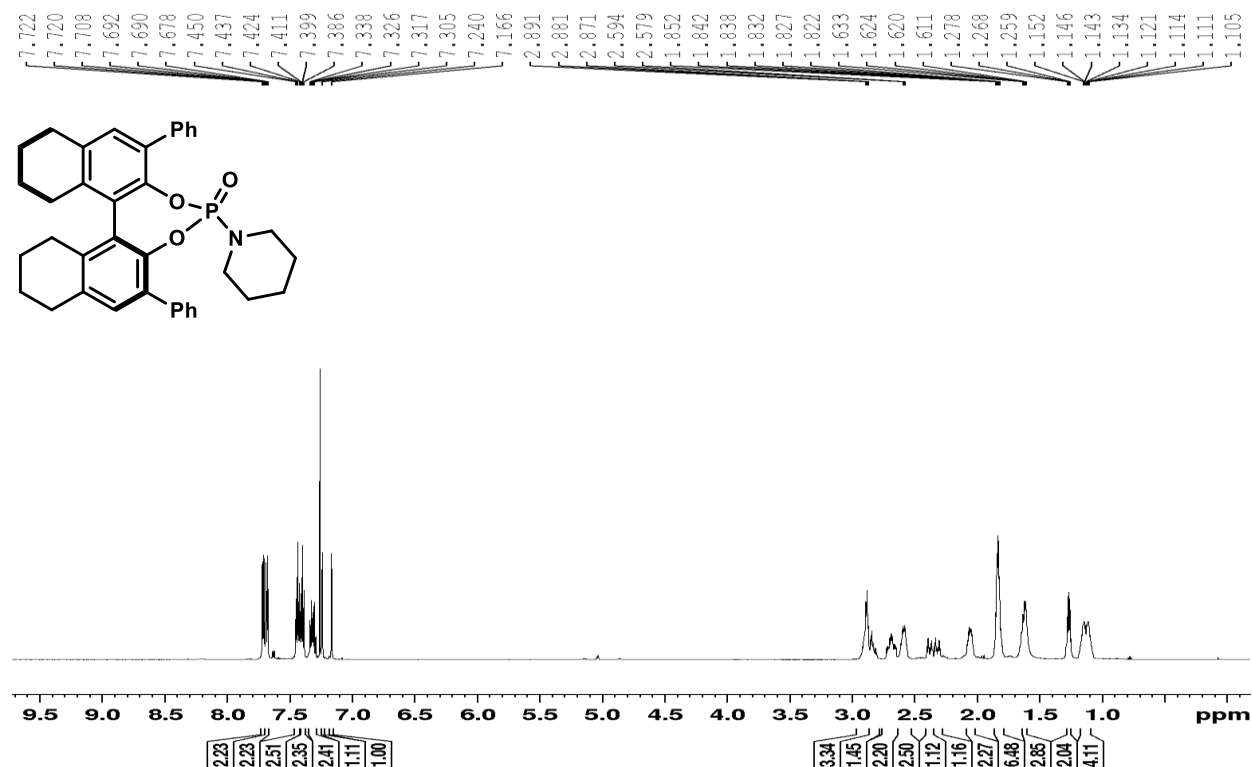


$^{31}\text{P}$  NMR Spectrum  $\text{CDCl}_3$  (243 MHz)

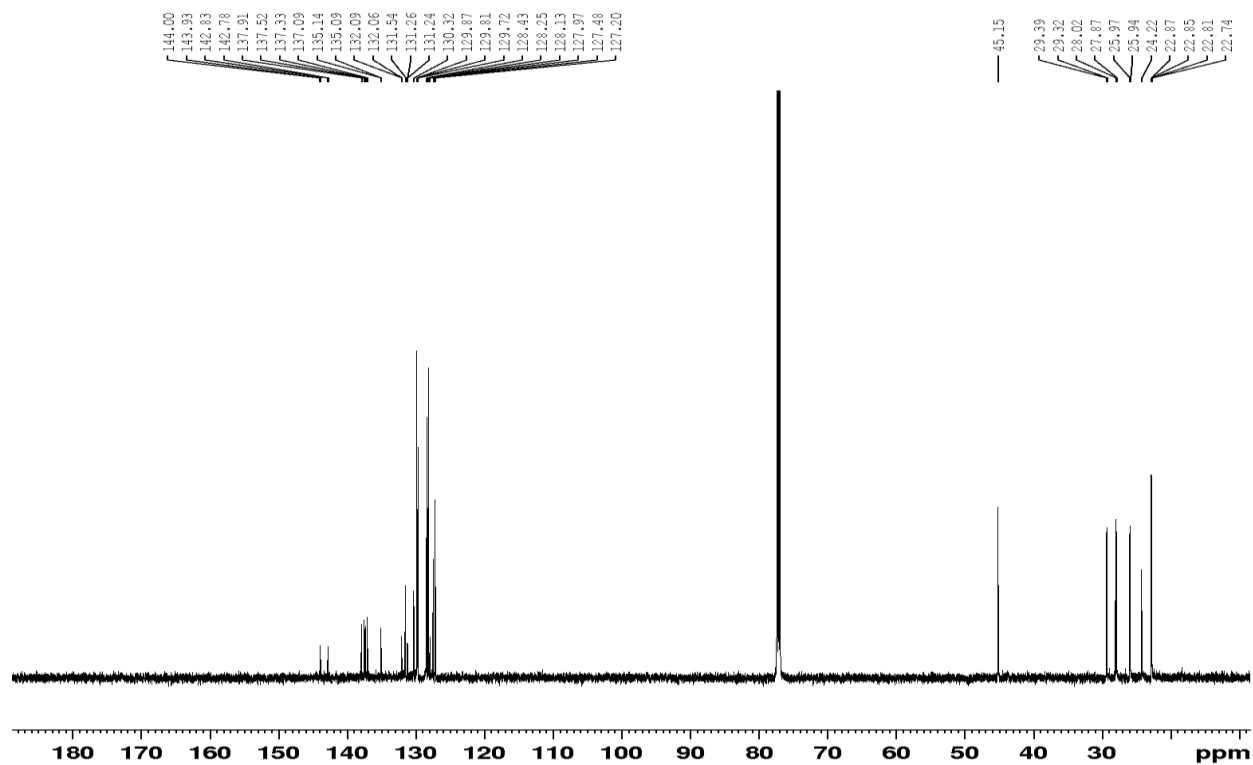


(S)-10,16-diphenyl-13-(1-piperidyl)-12,14-dioxaphosphapentacyclo[13.8.0.02,11.03,8.018,23]tricos-1(23),2(11),3(8),9,15,17-hexaene 13-oxide  
**(4.18)**

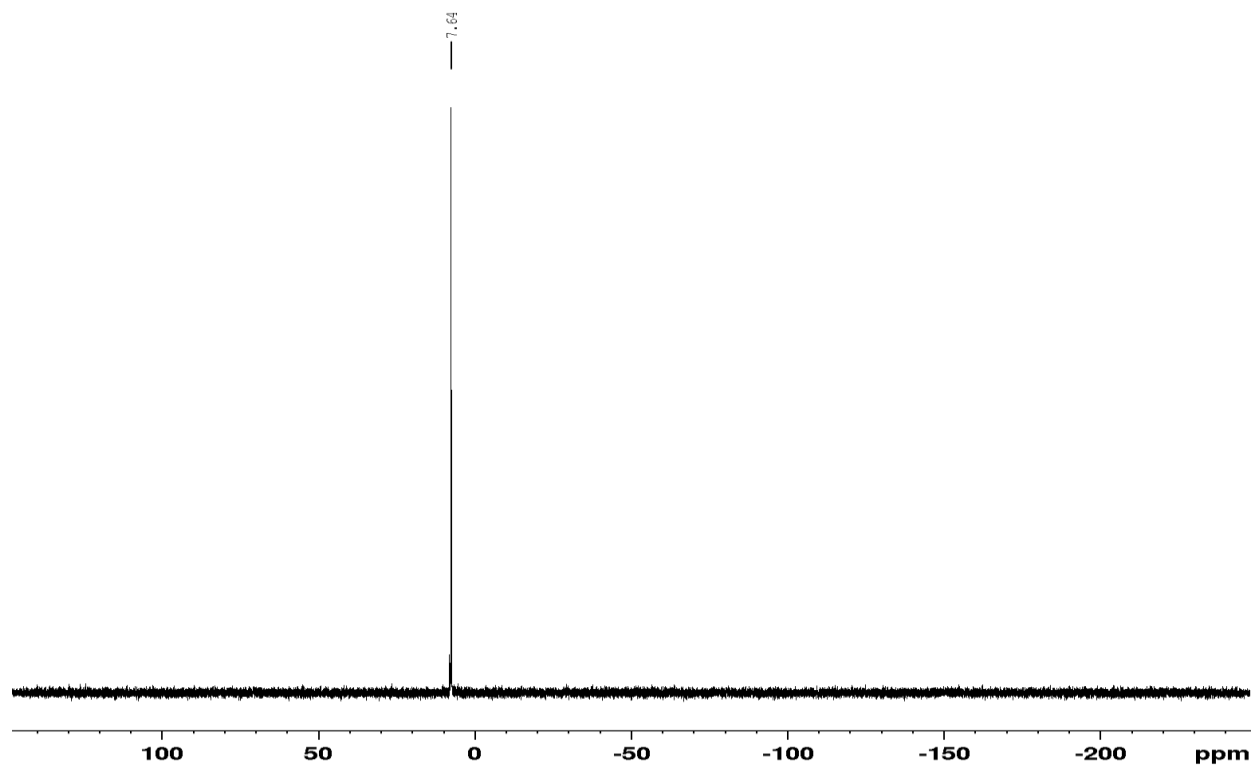
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$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (151 MHz)



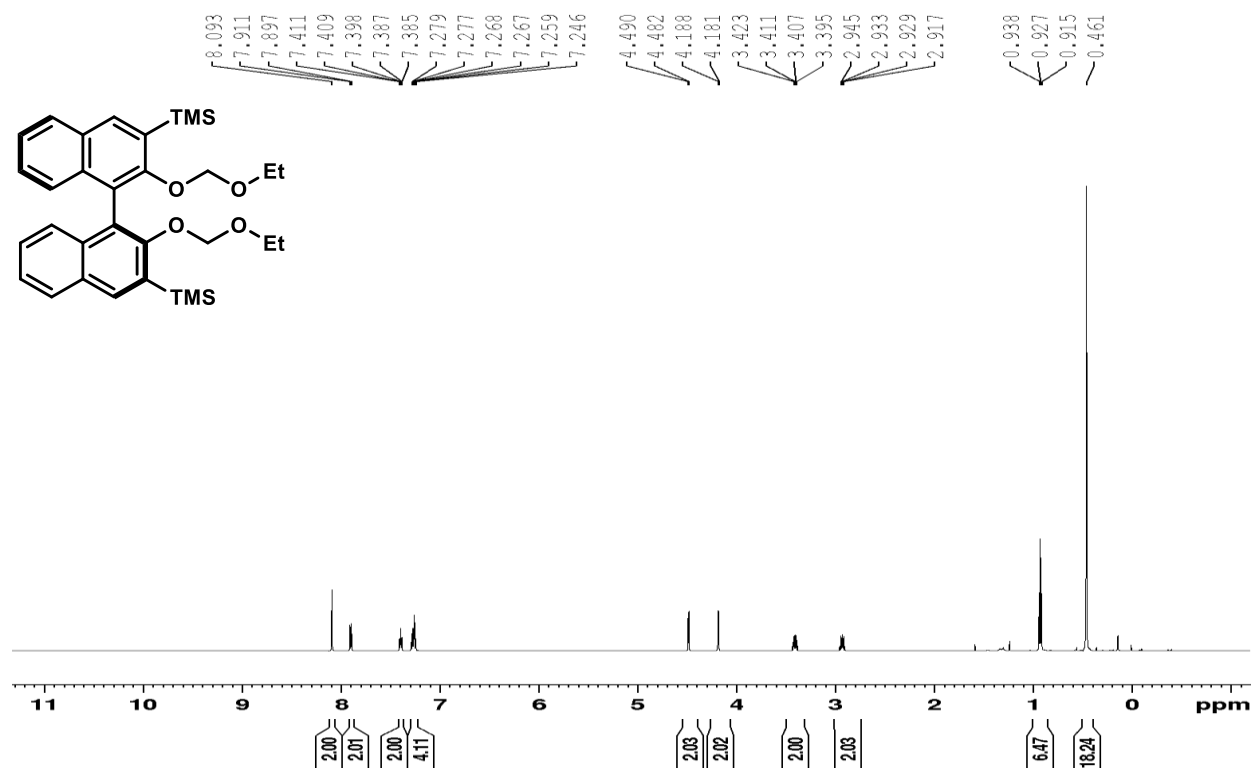
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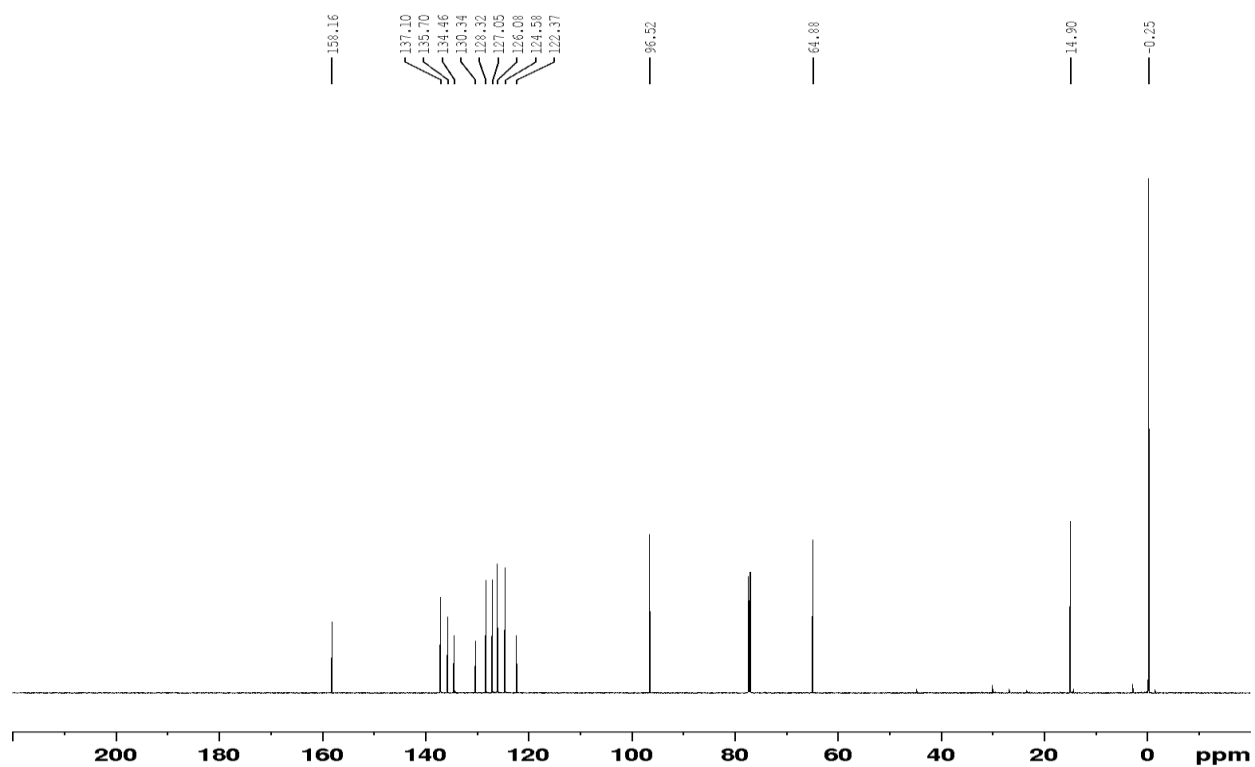


(S)-[3-(ethoxymethoxy)-4-[2-(ethoxymethoxy)-3-trimethylsilyl-1-naphthyl]-2-naphthyl]-trimethyl-silane (4.20)

$^1\text{H}$  NMR Spectrum  $\text{CDCl}_3$  (600 MHz)

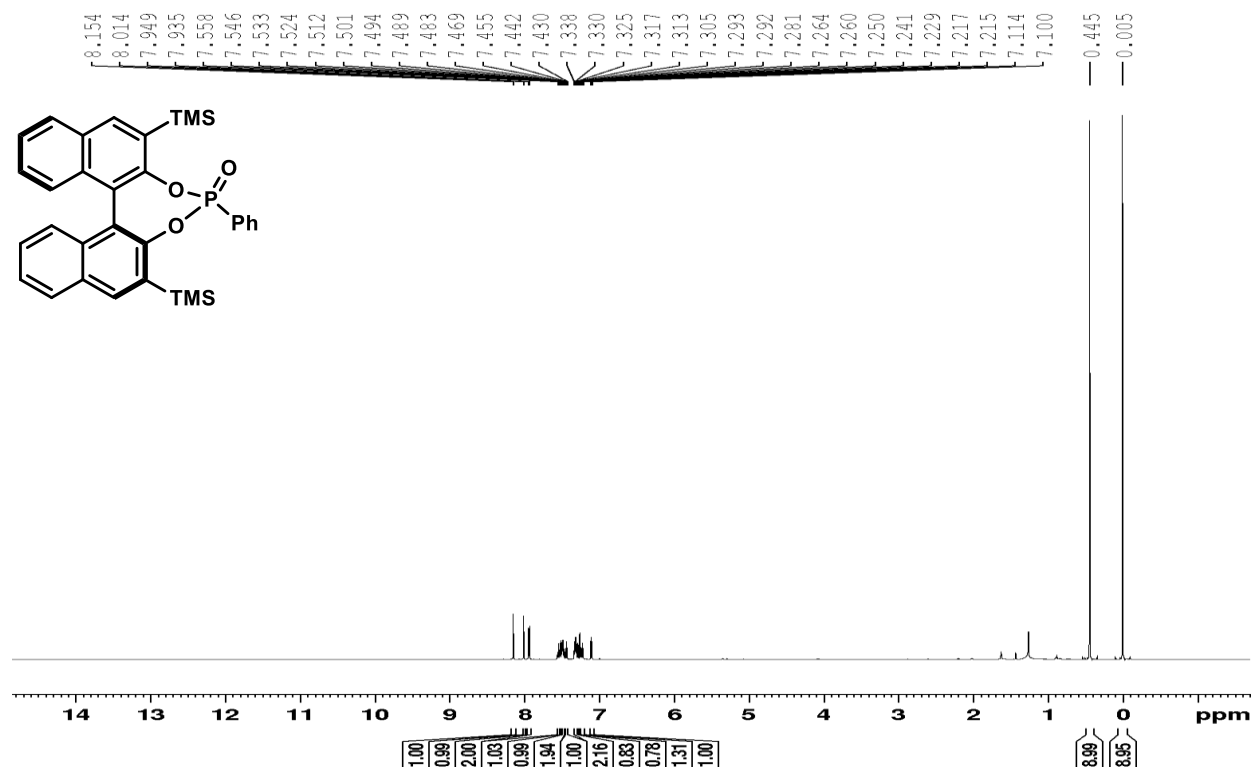


$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (151 MHz)

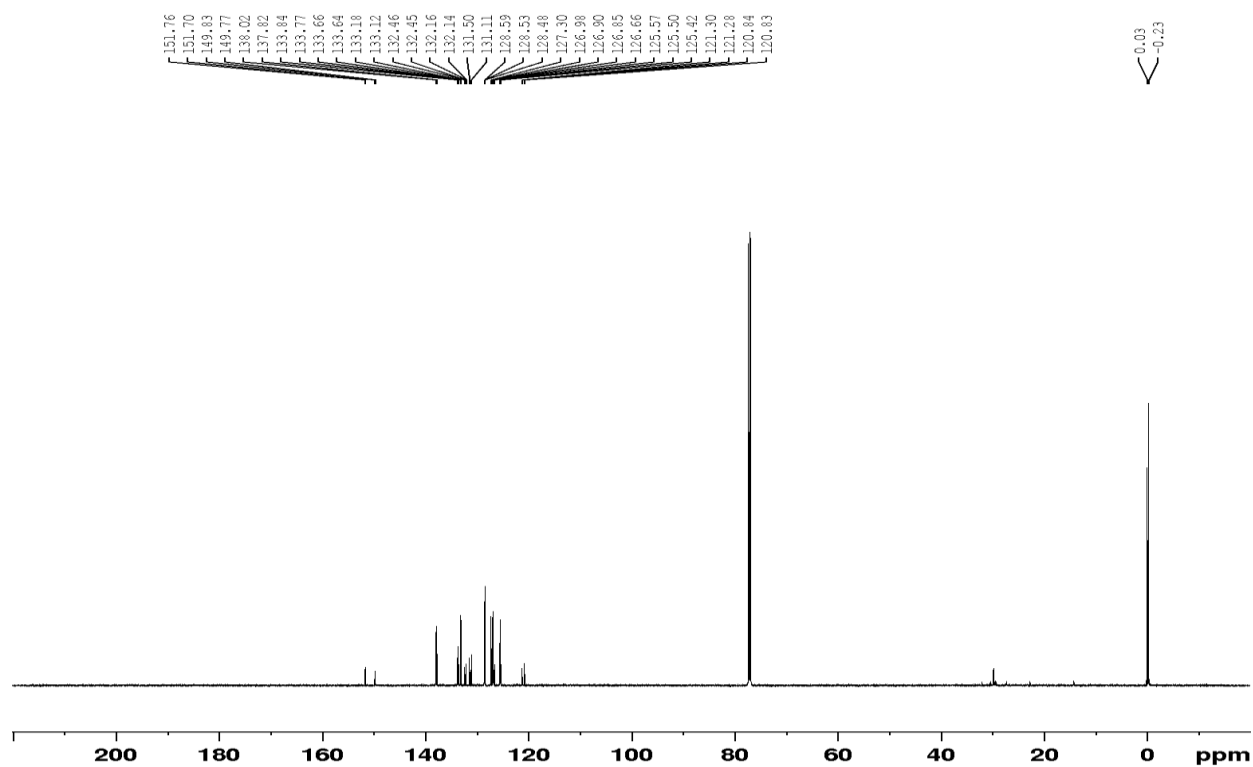


(S)-trimethyl-(13-oxo-13-phenyl-16-trimethylsilyl-12,14-dioxo-13 $\lambda^5$ -phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricoso-1(23),2(11),3(8),4,6,9,15,17,19,21-decaen-10-yl)silane (4.22)

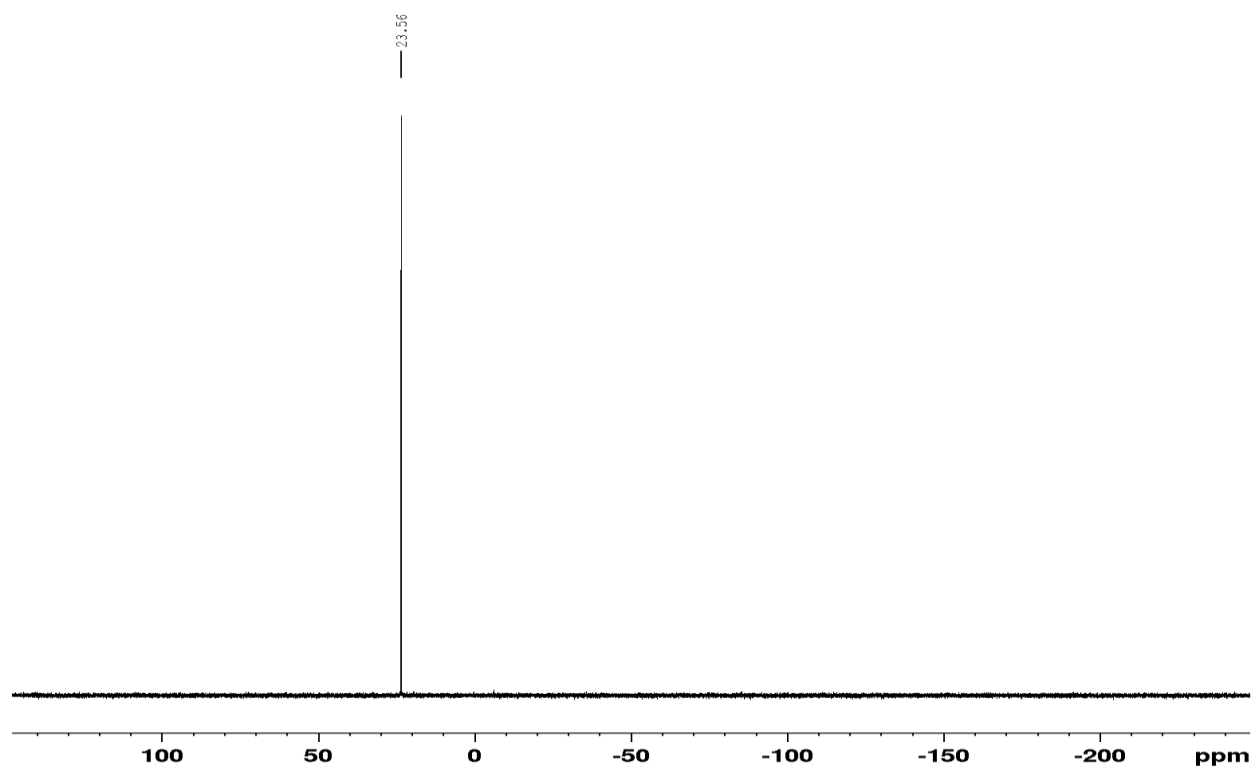
$^1\text{H}$  NMR Spectrum  $\text{CDCl}_3$  (600 MHz)



$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (151 MHz)

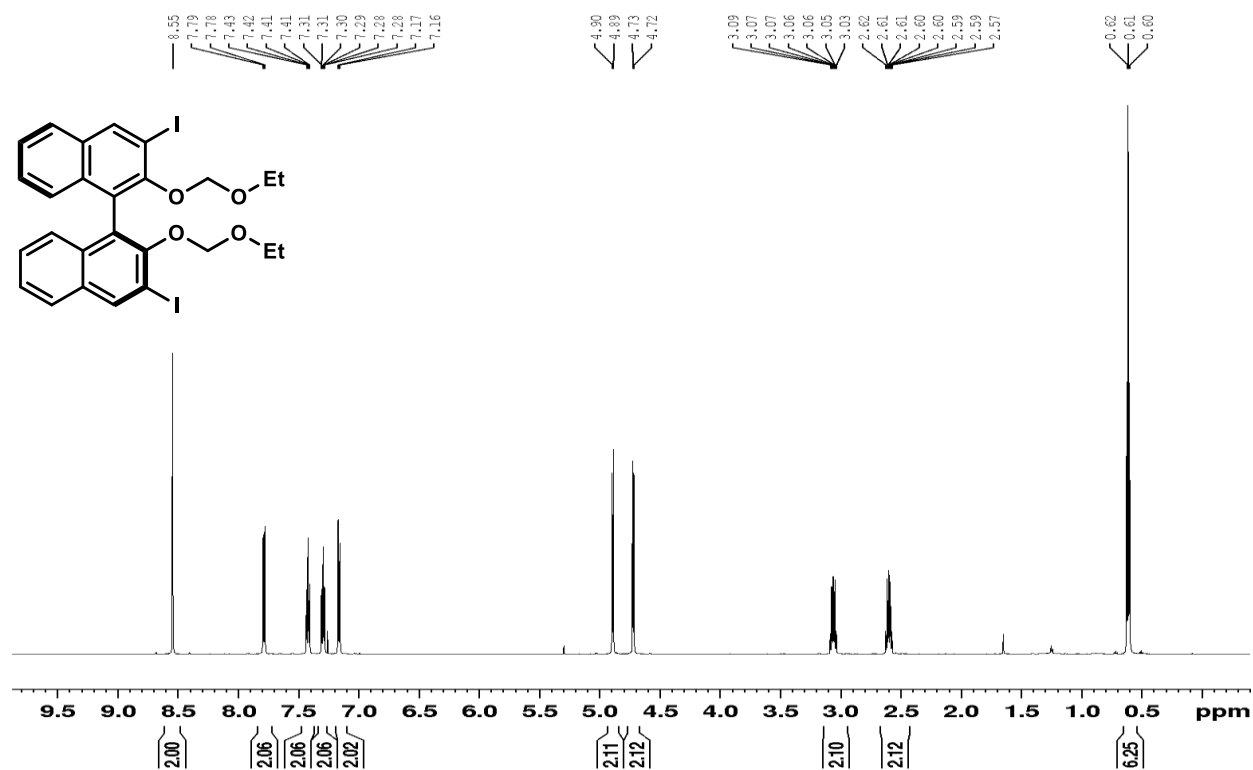


$^{31}\text{P}$  NMR Spectrum  $\text{CDCl}_3$  (243 MHz)

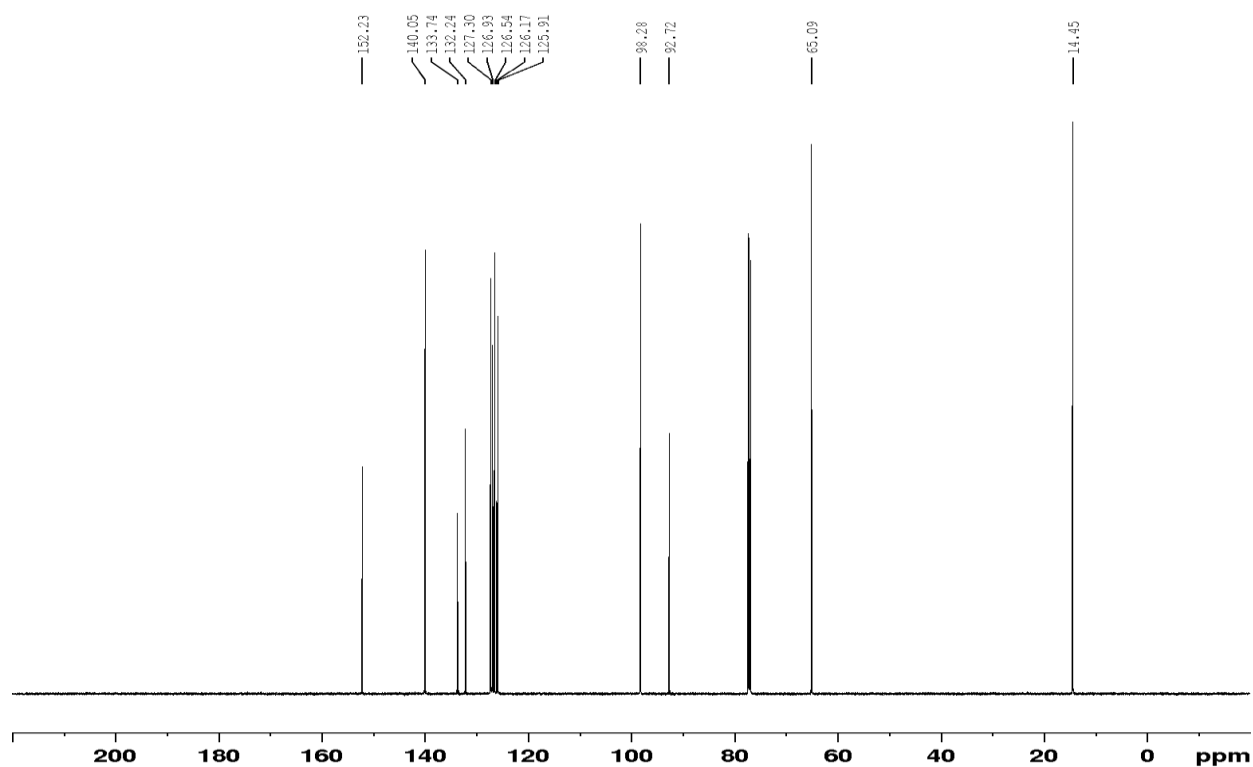


(S)-2-(ethoxymethoxy)-1-[2-(ethoxymethoxy)-3-iodo-1-naphthyl]-3-iodo-naphthalene (4.23)

$^1\text{H}$  NMR Spectrum  $\text{CDCl}_3$  (600 MHz)

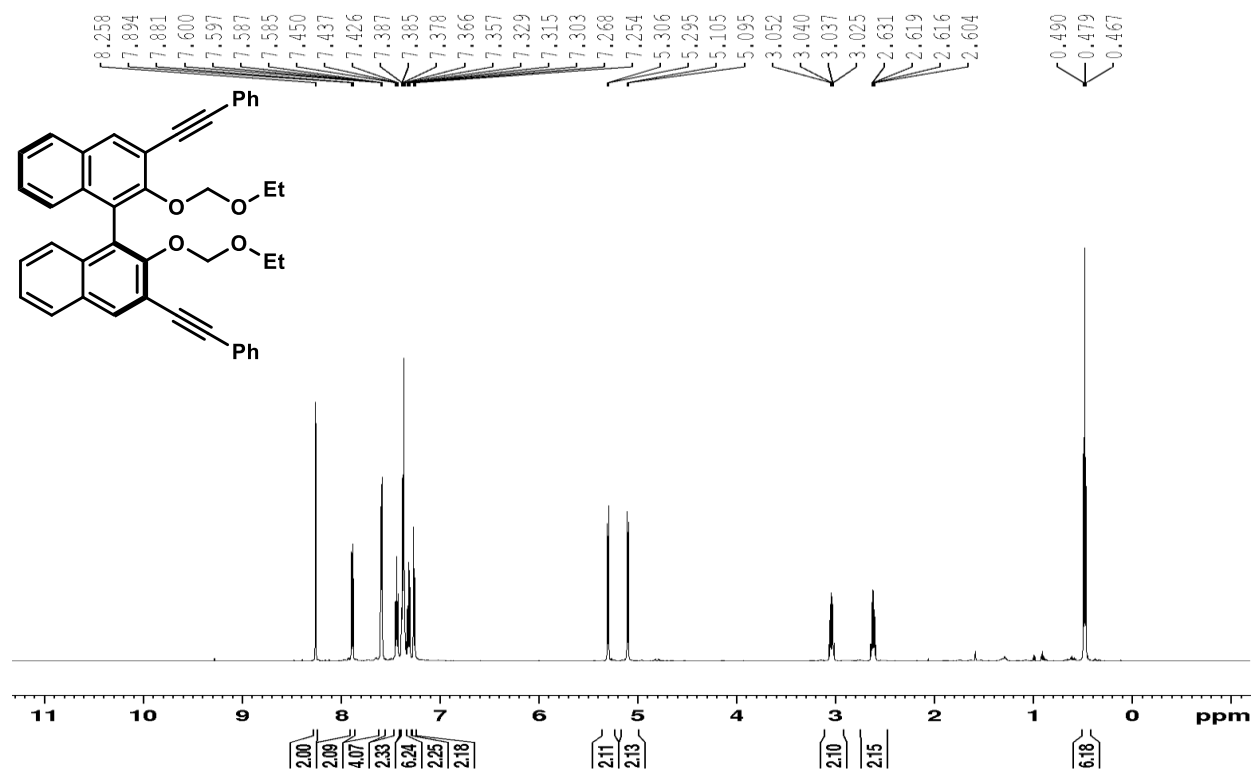


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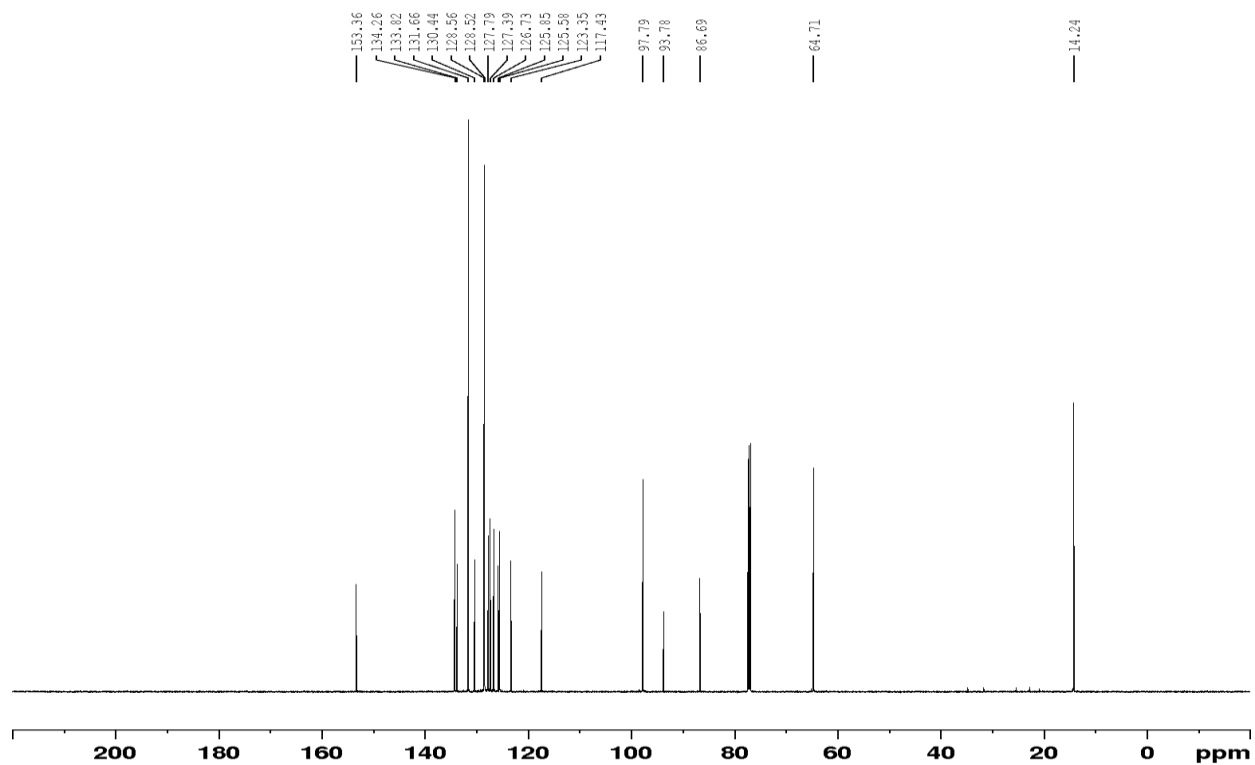


(S)-2-(ethoxymethoxy)-1-[2-(ethoxymethoxy)-3-(2-phenylethynyl)-1-naphthyl]-3-(2-phenylethynyl)naphthalene (4.24)

<sup>1</sup>H NMR Spectrum CDCl<sub>3</sub> (600 MHz)

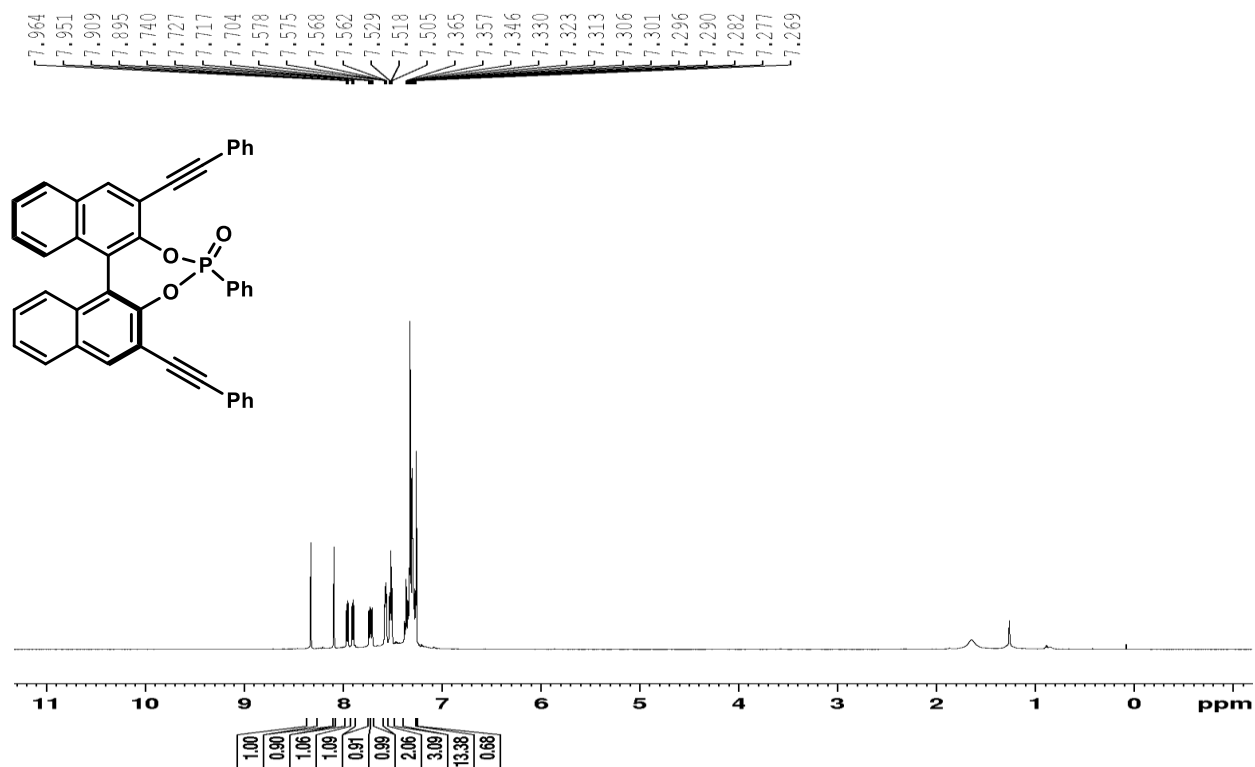


$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (151 MHz)



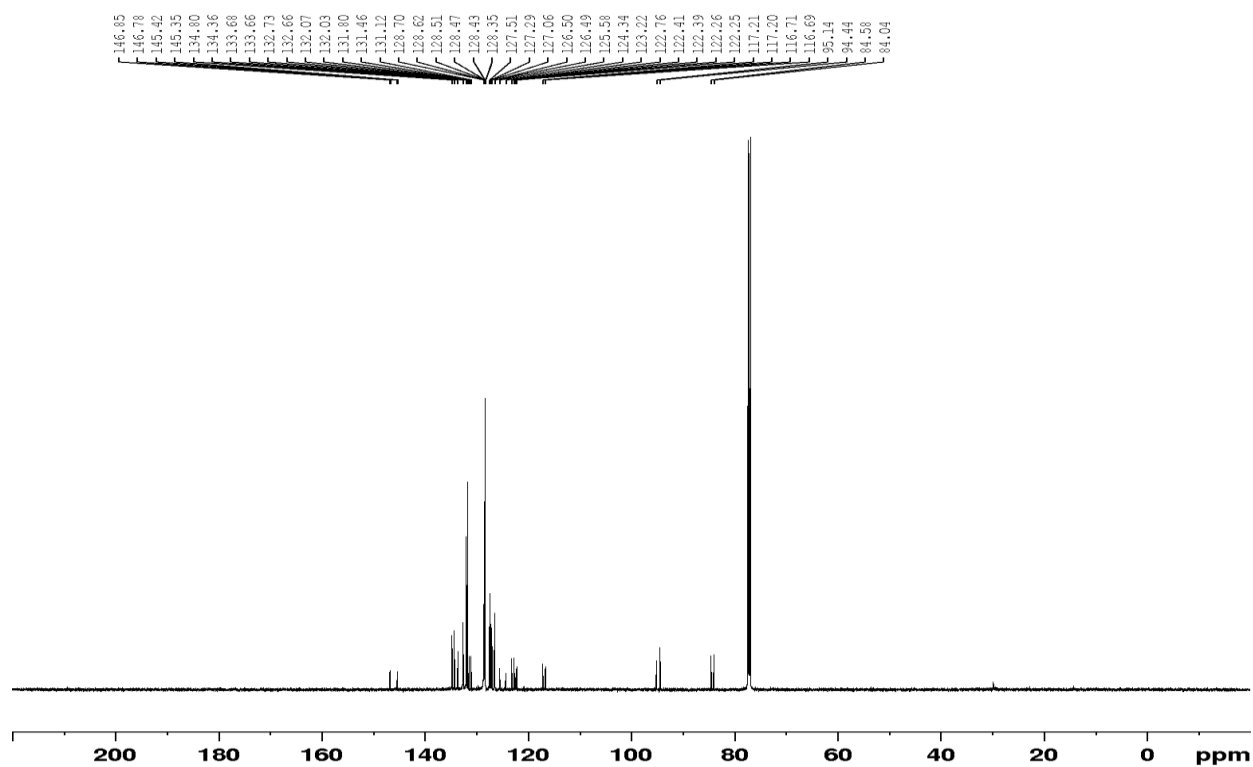
(S)-13-phenyl-10,16-bis(2-phenylethynyl)-12,14-dioxo-13 $\lambda^5$ -phosphapentacyclo[13.8.0.02,11.03,8.018,23]tricoso-1(23),2(11),3(8),4,6,9,15,17,19,21-decaene 13-oxide (4.25)

$^1\text{H}$  NMR Spectrum  $\text{CDCl}_3$  (600 MHz)

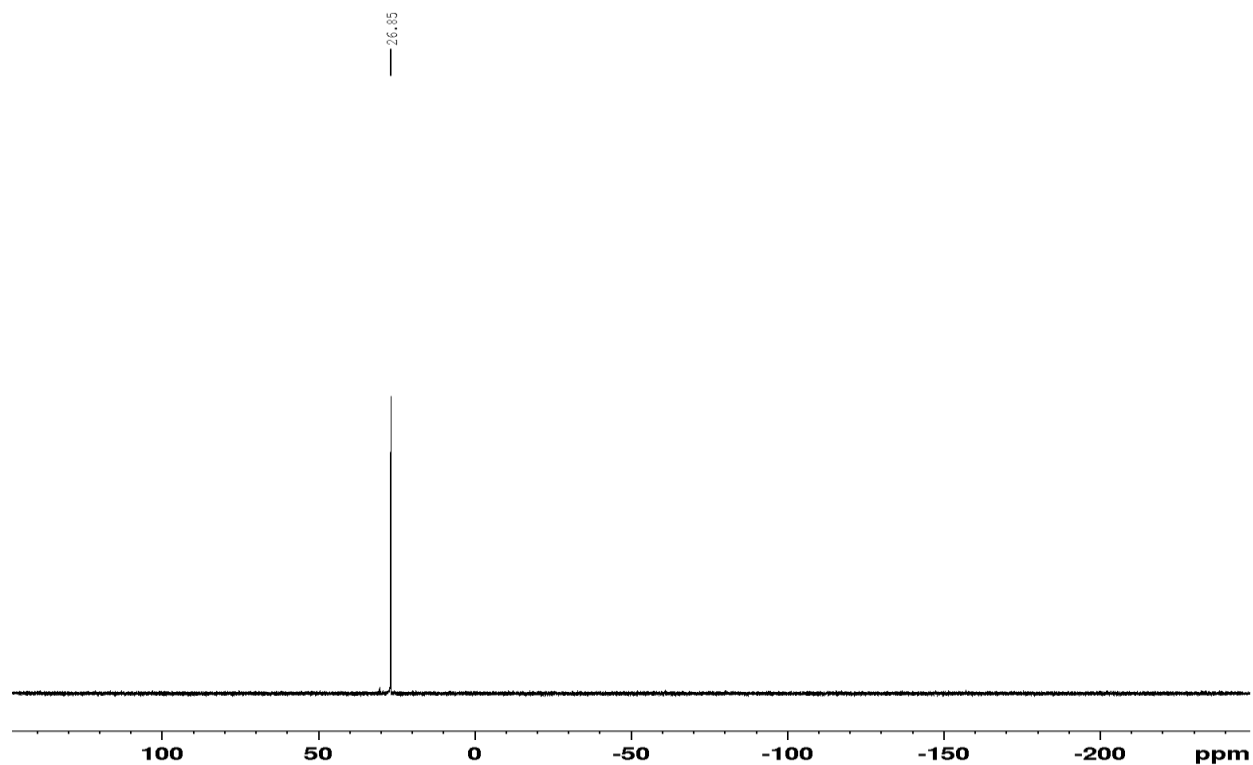




$^{13}\text{C}$  NMR Spectrum  $\text{CDCl}_3$  (151 MHz)



$^{31}\text{P}$  NMR Spectrum  $\text{CDCl}_3$  (243 MHz)



## Chapter 5: Conclusions and Outlook.

This dissertation details research efforts relating to carbamoyl fluorides, an emerging class of fluorinated, electrophilic amide precursors. These compounds are underexplored in the literature compared to the analogous carbamoyl chloride. We sought to fill this knowledge gap by first developing a simple method for their synthesis as previous methods require expensive reagents, pre-functionalized starting materials or multiple steps from amines. We found that carbamoyl fluorides could be prepared directly from secondary amines using a stable and use friendly difluorocarbene source paired with 4-methylpyridine *N*-oxide as an inexpensive oxidant. We explored the scope of this reaction, preparing 38 carbamoyl fluorides for this document, with numerous others being synthesized by other members of our group. Mechanistic studies revealed that  $\text{COF}_2$  is generated in-situ upon combination of difluorocarbene and oxidant. We anticipate that this method will be widely adopted by synthetic chemists, enabling further reaction development with carbamoyl fluorides by other research groups.

We then explored carbamoyl fluorides in the context of fluoride-enabled reactivity, exploiting the fluorine atom to do chemistry that may not be accessible by carbamoyl chlorides. The reaction designs focused on the use of silylated nucleophiles to prepare useful amides by forging new C-C bonds, with the formation of a fluorosilane by-product acts as a thermodynamic driving force. First, we developed the alkynylation of carbamoyl fluorides with alkynyl silanes to access medically relevant alkynamides using TBAF as the catalyst. Through mechanistic studies, we deduced that fluoride can desilylate the nucleophile to generate an ammonium acetylide anion, which goes on to attack the carbamoyl fluoride and regenerating the catalyst. Several alkynamides

were prepared, but the scope was limited due to the strongly basic nature of the reaction intermediate. However, we determined that carbamoyl fluorides are stable to typical Pd/Cu co-catalyzed Sonogashira coupling reactions, allowing site selective alkynylation of an aryl iodide-containing substrate.

Finally, a cyanoalkylation of carbamoyl fluorides with silyl ketene imines was developed, and three classes of Lewis base catalysts were found to be effective: fluorosilicate salts, 1,10-phenanthrolines and phosphine oxides. This reaction gave rise to  $\alpha$ -cyanoamides, an underexplored class of compound that have found limited, yet impactful, applications in the pharmaceutical industry. Significant effort was put into identifying a chiral P(V) compound to do this reaction asymmetrically, as the product amide contains a chiral quaternary carbon centre. Only marginal enantioselectivity was observed in our screening, but future work aims to understand the kinetics and mechanism of this reaction to better inform catalyst design.

Overall, this dissertation presents a synthetic method for the synthesis of carbamoyl fluorides and lays the groundwork for their use as electrophiles in fluoride-enabled reactions. Our hope is that this work serves as starting point for further reaction development and that carbamoyl fluorides can become a staple in the synthetic chemist's "toolbox". This may allow for them to be used for the discovery of more complex reactions, bioconjugation methods or the direct use of carbamoyl fluorides as drug candidates.

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