

Lewis Acid-Catalyzed Carbofluorination Reactions via Fluoride Recycling

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Abstract

Fluorinated compounds are widely employed as pharmaceuticals, agrochemicals, and polymer materials. As a result, there is a strong interest in developing more sustainable ways to make fluorinated molecules, as well as exploring their fundamental reactivity and stability. This dissertation focuses on the development of carbonyl fluorides derivatives—namely carbamoyl fluorides, acyl fluorides, and fluoroformates—as dual-function reagents that serve both as carbonyl fragments and as fluoride sources. These fluorinated building blocks were applied in the intramolecular carbofluorination of π bonds and in fluorine retentive rearrangement reactions under Lewis acid-catalyzed “fluoride shuttling” conditions.

Chapter 1 provides background on fluorination chemistry, introducing common fluorinating reagents and then transitions into strategies that combine fluorine incorporation with carbon–carbon bond formation, namely the fluorinative difunctionalization of π -bonds (carbofluorination), which enables efficient construction of complex organofluorine compounds.

Chapter 2 identifies a range of borane and borate-based catalysis that can activate acyl fluorides to acts as dual-function reagents. Trityl tetrafluoroborate was identified as the optimal catalyst for the synthesis of 1-(fluoromethylene)indan-2-ones from alkyne-tethered acyl fluorides, affording products with exceptional stereoselectivity under mild conditions. This method also enabled access to fluorinated scaffolds that had only been reported previously under harsher, transition metal-catalyzed conditions.

Chapter 3 expands the use of Lewis acid catalyzed carbofluorination reactions to the stereoselective synthesis of 3-fluoromethylene oxindoles and γ -lactams from alkyne-tethered carbamoyl fluorides. Inexpensive, commercially available $\text{BF}_3 \cdot \text{OEt}_2$ identified as the optimal catalyst. Combined experimental and computational studies suggest that the reaction is initiated through oxophilic activation of the carbonyl group. This chapter also demonstrates that fluorinated secondary oxindoles can be accessed directly through a fluorocarbonylative annulation of *o*-alkynyl anilines.

Finally, Chapter 4 details a mild and practical synthesis of fluoroformates from alcohols, employing a commercially available oxidant and a difluorocarbene source as an *in situ* difluorophosgene surrogate. These

reaction conditions can also be applied to the synthesis of fluoro(thio)formates, carbamoyl fluorides, and acyl fluorides, providing a unified strategy for the synthesis of diverse (heteroatom)carbonyl fluoride derivatives. Preliminary studies exploring the use of fluoroformates as dual-function reagents are also presented, focusing on the fluorinative rearrangement of cyclopropylmethyl fluoroformates to fluorinated cyclobutanes.

Dedication

for kiki

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List of Abbreviations

4CzIPN	1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene, 2,4,5,6-Tetrakis(9 <i>H</i> -carbazol-9-yl)isophthalonitrile
act.	activator
Ad	adamantyl
Ar	aryl
atm	atmosphere
BARF ₂₀	tetrakis(pentafluorophenyl)borate
BC	bathocuproine
BDE	bond dissociation energy
BCF	tris(pentafluorophenyl)borane
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
bipy	bipyridine
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BrettPhos	2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
BTMG	2-(<i>tert</i> -butyl)-1,1,3,3-tetramethylguanidine
Bu	butyl
cat.	catalyst
cod	1,5-cyclooctadiene
Cy	cyclohexyl
DABCO	(1,4-diazabicyclo[2.2.2]octane)
DAST	(diethylamino)sulfur trifluoride
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DFC	difluorocarbene
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMPU	<i>N,N'</i> -dimethylpropyleneurea
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppbz	<i>ortho</i> -bis(diphenylphosphino)benzene
dr	diastreomeric ratio
dtbbpy	4,4'-di- <i>tert</i> -butyl-2,2'-dipyridyl
DTBM	3,5-di- <i>tert</i> -butyl-4-methoxyphenyl

EDG	electron-donating group
er	enantiomeric ratio
Et	ethyl
EN	electronegativity
EWG	electron-withdrawing group
F	faraday
FAT	fluoride atom transfer
FLP	frustrated Lewis pair
GC-MS	Gas Chromatography-Mass Spectrometry
H_0	Hammett acidity function
HALEX	halogen-exchange reaction
HBD	hydrogen bond donor
HBGF	hexabutylguanidinium fluoride
HFIP	hexafluoroisopropanol
IR	Infrared spectroscopy
L*	chiral ligand
L	ligand
LA	Lewis acid
LB	Lewis base
LDA	lithium diisopropylamide
LG	leaving group
mes	mesityl, 2,4,6-trimethylphenyl
MI	migratory insertion
MTBE	methyl <i>tert</i> -butyl ether
NA	not applicable
NAS	nucleophilic acyl substitution
NFSI	<i>N</i> -fluorobenzenesulfonimide
NHC	<i>N</i> -heterocyclic carbene
NHPI	<i>N</i> -hydroxyphthalimide
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Nuc or Nu	nucleophile
OA	oxidative addition
OAc	acetate
OTf	trifluoromethanesulfonate, triflate
PG	protecting group
PA-Ar	aryl phosphadmantane
PBS	phosphate-buffered saline
PC	photocatalyst
PDFA	(triphenylphosphonio)difluoroacetate

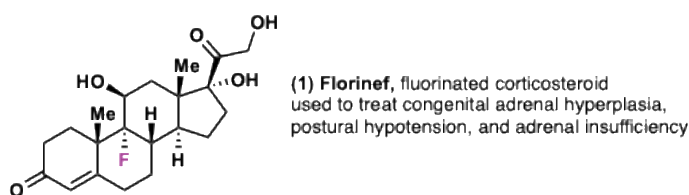
PET	positron emission tomography
pK_a	acid dissociation constant
PMP	<i>para</i> -methoxyphenyl
ppy	2-phenylpyridine
Pr	propyl
PTFE	polytetrafluoroethylene
Pyr	pyridine
r.r.	regiomer ratio
rds	rate determining step
RE	reductive elimination
RPC	radical polar crossover
rt	room temperature
S_EAr	electrophilic aromatic substitution
SET	single electron transfer
S_NAr	nucleophilic aromatic substitution
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBPH	bis(2-ethylhexyl)tetrabromophthalate
TEA	triethylamine
TFA	trifluoroacetic acid
TFDA	trimethylsilyl fluorosulfonyldifluoroacetate
TFE	tetrafluoroethylene
TFP	tetrafluorophenyl
THF	tetrahydrofuran
TIPS	triisopropylsilane
TLC	thin layer chromatography
TLS	turnover limiting step
TM	transmetalation
TMB	1,3,5-trimethoxybenzene
TMS	trimethylsilyl
Tr	tritylium, trityl
TREAT-HF	triethylamine hydrogen fluoride
Tro	tropylium
Ts	toluenesulfonyl, tosyl
w/v	weight/volume
Xantphos	(9,9-dimethyl-9 <i>H</i> -xanthene-4,5-diyl)bis(diphenylphosphane)
Xphos	dicyclohexyl[2',4',6'-tris(propan-2-yl)[1,1'-biphenyl]-2-yl]phosphane

1 Synthesis of Organofluorine Compounds via Carbofluorination

1.1 Properties of fluorine and importance of organofluorine compounds

Fluorine occupies a unique position in the periodic table as the most electronegative element (Pauling EN = 3.98) with a small atomic radius (~50 pm) and extremely low polarizability.¹⁻⁴ These intrinsic features enable the formation of strong bonds to other atoms. Of particular importance is the C–F bond, the strongest type of carbon single bond, which can range anywhere from 105-130 kcal·mol⁻¹ depending on the nature of adjacent substituents.² The strategic incorporation of a fluorine fragment into an organic molecule not only enhances a compound's thermodynamic stability—particularly when replacing an existing hydrogen, alcohol, or carbonyl—but also significantly alter a molecule's physicochemical properties.⁵

Since the approval of the first fluorinated drug, the synthetic 9 α -fluoro-substituted corticosteroid fludrocortisone Florinef in 1955 (Scheme 1.1),⁶ the deliberate incorporation of fluorine to enhance drug potency has become increasingly common. Fluorine substitution can enhance potency and modulate target selectivity by influencing conformational preferences, hydrophobic and other noncovalent interactions, pK_a, and overall lipophilicity, either individually or in combination.⁷ In recent years, approximately 20% of new small molecule drug compounds contained at least one fluorine,⁸ and, in 2024 alone, 11 out of 31 newly FDA approved small molecule drugs were fluorinated.⁹

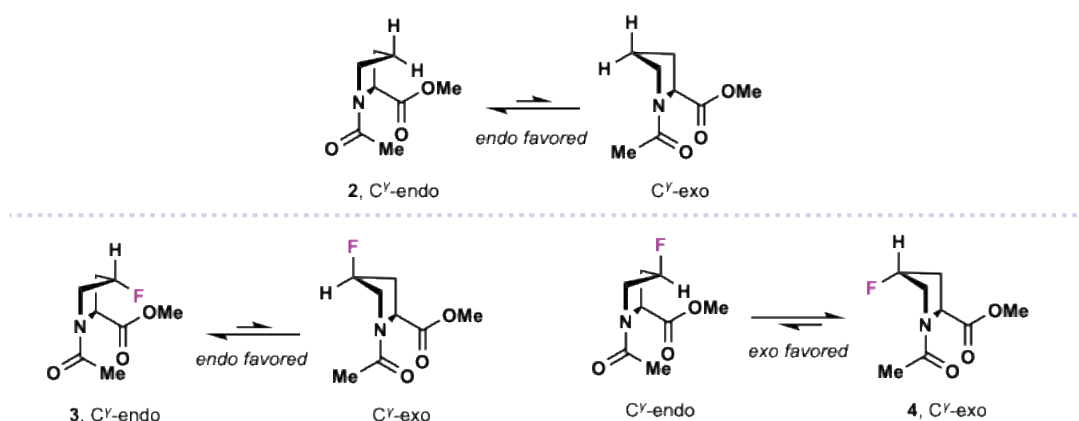


Scheme 1.1 First fluorinated drug compound: Florinef.

The incorporation of fluorine into a molecule can have distinct and significant influence on molecular conformation. From a steric standpoint, its impact is expected to be minimal: fluorine is a small atom with a van der Waals radius of 1.47 Å, comparable to that of hydrogen (1.20 Å).¹⁰ However, fluorine's high electronegativity gives rise to a highly polarized C–F bond characterized by a strong dipole moment (μ C–F = 1.41 D) and a low-lying σ^* orbital capable of accepting electron density through

hyperconjugation. In aliphatic systems, these electronic features combine to generate a pronounced preference for vicinal substituents to adopt a gauche orientation relative to fluorine. The reason for this effect can range from hyperconjugative donation from adjacent C–H bonds into C–F σ^* orbitals, C–F $\cdots$ H–X hydrogen bonding interactions, and dipole–dipole or electrostatic effects,¹¹ all of which have been exploited in the rational design of both pharmaceuticals and organocatalysts.⁷

One of the most straightforward illustrations of fluorine-induced conformational control via the gauche effect is provided by proline-based ligands bearing fluorine substitution at the C-4 position (Scheme 1.2). Unsubstituted *N*-acetyl proline methyl ester **2** preferentially adopts a C $^{\gamma}$ -endo conformation, a bias that is further reinforced upon installation of a 4-(*S*)-fluoro substituent in **3**. In contrast, 4-(*R*)-fluoro **4** has an equilibrium shifted toward the C $^{\gamma}$ -exo conformation, reflecting the energetic preference for a gauche relationship between the C–F bond and the adjacent methylenes.

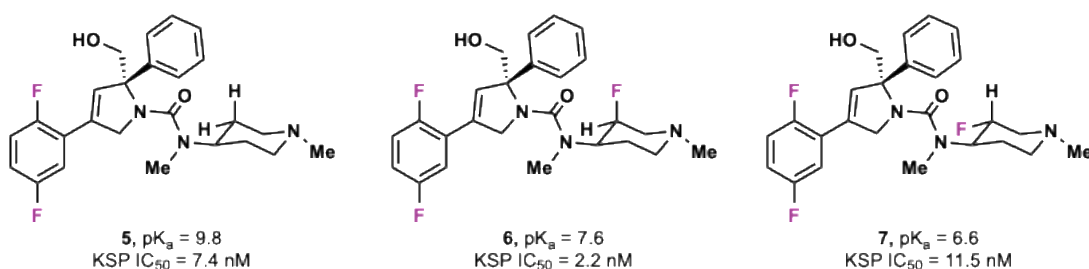


Scheme 1.2 Conformational bias via gauche effect of C-4 fluorinated *N*-acetyl-proline methyl esters.

Fluorine is also a powerful tool for tuning the pK_a of nearby functional groups and modulating the electron density of aromatic and heteroaromatic systems.¹² Fluorine primarily alters the pK_a of neighboring substituents through its strong inductive electron-withdrawing effect, which stabilizes negative charge build-up and destabilizes positive charge build-up, effectively lowering the pK_a of acids. Additional through-space electrostatic effects and limited resonance interactions, particularly in aromatic systems, can modulate the magnitude of this shift depending on distance and substitution pattern. The conformational biases that fluorine can enforce can also indirectly influence pK_a by enforcing specific conformations that affect lone-pair availability, solvation, or intramolecular interactions. The pK_a of an ionizable moiety

directly influences a drug's lipophilicity profile via the pH dependence of its distribution or partition coefficient, thereby affecting solubility, permeability, and protein binding. Consequently, these changes in pK_a can translate into altered potency, selectivity, toxicity, and pharmacokinetic behavior, including absorption, distribution, metabolism, and excretion.¹³

The impact of fluorine on pK_a is illustrated by a series of kinesin spindle protein inhibitors **5-7** in which active site binding was shown to be highly sensitive to the basicity of a central piperidine moiety (Scheme 1.3).¹⁴ Optimal efficacy in a tumor cell line was observed for compounds with pK_a values in the range of 6.5–8.0, corresponding to reduced efflux, or extrusion from the cell. This tuning was achieved through incorporation of a fluorine atom into the piperidine ring, with the resulting pK_a strongly dependent on its stereochemical configuration. The axial compound **6**, which was selected for clinical evaluation, is more basic than the equatorial isomer **7**.

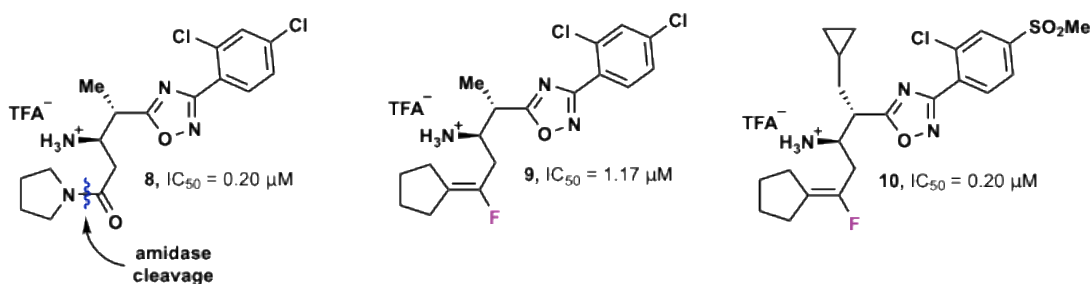


Scheme 1.3 Influence of fluorination induced pK_a changes on IC_{50} of kinesin spindle protein inhibitors.

In addition, fluorine has been widely employed to mitigate liabilities associated with drug metabolism. Direct replacement of metabolically labile hydrogen atoms with fluorine like substitution of an Ar–H for an Ar–F or CH_3 with a CF_3 can attenuate oxidative metabolism, particularly relevant for electron-rich aromatic rings that are often susceptible to biotransformation.¹⁵ Fluorine is also frequently incorporated as a bioisosteric replacement for carbonyl-containing functional groups, given the similarity between bond lengths, van der Waals radii and dipoles of the two functionalities, as well as the electronegativity of oxygen and fluorine when comparing $C=O$ to $C-F$ or CF_2 .

Monofluoroalkene containing **9** was evaluated as a potential amide bioisostere in a series of DPP-4 inhibitors to impart resistance to cleavage by amidases or proteases (Scheme. 1.4).¹⁶ Compound **9** was

approximately fivefold less potent than its matched amide analogue **8**, an effect attributed to the weaker dipole of the fluoro-olefin functionality. Subsequent modification of the aryl ring appended to the oxadiazole as well as a methyl on the backbone resulted in compound **10** as a significantly more potent DPP-4 inhibitor that no longer contains the problematic amide bond. An X-ray co-crystal of **10** complexed with DPP-4 showed a binding mode closely analogous to that of the corresponding amide; the fluorine atom positioned near the side-chain N–H groups of Arg and Asn residues, consistent with a hydrogen-bonding interaction.



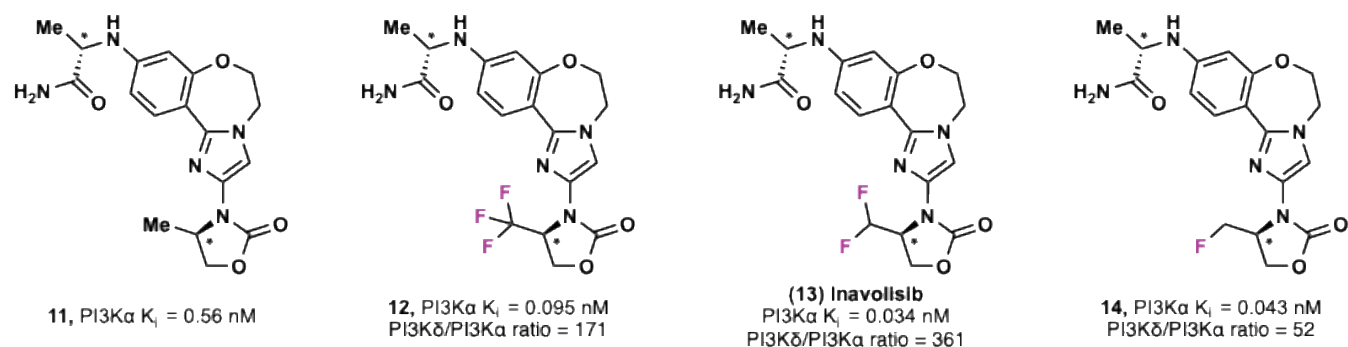
Scheme 1.4 Incorporation of monofluoroalkene in place of amide bonds in drug design.

Despite these advantages, fluorine incorporation is not universally beneficial. In some cases, increased lipophilicity can alter primary pharmacology or unfavorably affect pharmacokinetic properties, resulting in increased side effects or decreased bioavailability. As a result, optimization of pharmacological activity and metabolic stability is typically pursued in parallel to balance these competing effects.

One prime example of this is in the development of Inavolisib (**13**, brand name Itovebi®), which was approved in October 2024 for the treatment of locally advanced or metastatic breast cancer.¹⁷ Inavolisib functions as a selective inhibitor of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) signaling pathway, a key regulator of cellular growth and differentiation. PI3K enzymes are heterodimeric complexes composed of a regulatory (p85) and a catalytic (p110) subunit, and exist as four isoforms (PI3K α , PI3K β , PI3K γ , and PI3K δ).¹⁸ Among these, PI3K α is most strongly implicated in tumorigenesis due to frequent mutations and amplifications in PIK3CA, the gene encoding the p110 α subunit. Dysregulation of this pathway occurs in approximately one-third of breast cancer cases and is associated with poor prognosis. Consequently, the development of PI3K α -selective inhibitors that spare other PI3K isoforms—thereby

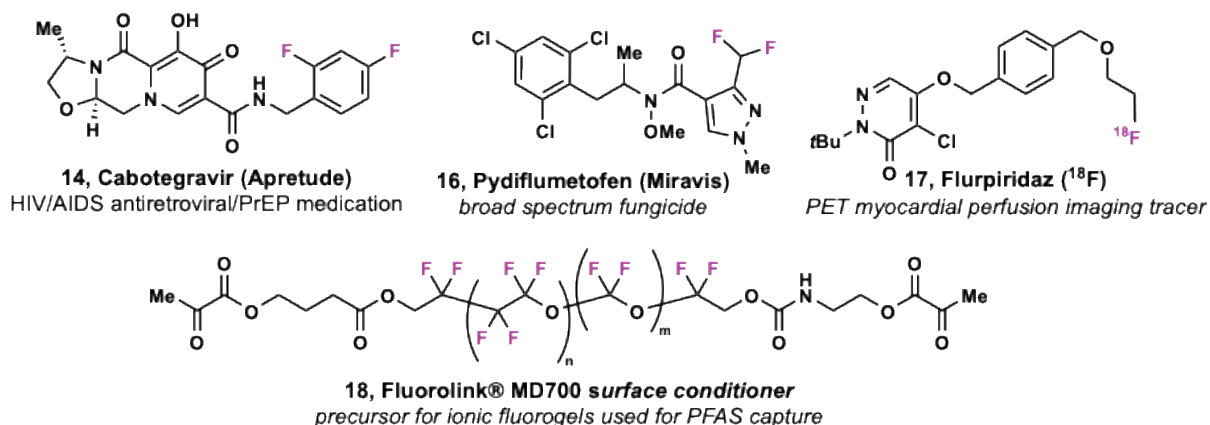
minimizing off-target toxicity—as benchmarked by the K_i ratio between PI3K δ and PI3K α has been a major therapeutic objective.

Inavolisib exhibits an enzyme K_i of 0.034 nmol/L for PI3K α , compared with 100 nmol/L for PI3K β , 18 nmol/L for PI3K γ , and 12 nmol/L for PI3K δ , corresponding to approximately 350-fold selectivity for PI3K α over PI3K δ (Scheme 1.5).¹⁹ The core scaffold of Inavolisib consists of a benzoxazepine–oxazolidinone framework appended with a carboxamide moiety, the latter contributing significantly to isoform selectivity. High-affinity binding arises from a key hydrogen-bonding interaction between the side-chain hydroxyl of a serine residue within the p110 α active site and a fluorine atom of the difluoromethyl substituent, resulting in enhanced potency relative to the corresponding methyl analogue **11**. However, this interaction is highly sensitive to the identity of the fluorinated group. Replacement of the difluoromethyl moiety with a trifluoromethyl group in **12** led to diminished selectivity for the α isoform, while the fluoromethylene analogue **14** displayed a K_i comparable to Inavolisib but substantially reduced α selectivity. These differences are likely attributable to variations in serine positioning between PI3K isoforms. Although a homologous serine residue is present in PI3K δ , its side chain is positioned approximately 3.2 Å farther from the active site relative to PI3K α . This spatial offset may weaken the binding energy derived from interaction with the fluorine atom, consistent with the observation that difluoro- (Inavolisib) and monofluoromethyloxazolidinone **14** enhance potency and selectivity for PI3K α , whereas the trifluoromethyl analogue **12** does not.



Scheme 1.5 Influence of fluorine motif identity on PI3K α inhibitor Inavolisib's potency and selectivity.

Even outside of pharmaceuticals^{20–22} the need for fluorinated compounds has grown significantly over the past five decades—starting with applications as coolants like Freons, which replaced more reactive chlorocarbons—and expanding into the agrochemical^{23–26} and material sectors^{27–29} (Scheme 1.6). This interest, in turn, fuels increased research in new synthetic methods for accessing fluorinated molecules as well as fundamental research on their reactivity, as historically fluorine’s broader incorporation into both drug compounds and functional materials has been limited by synthetic accessibility. Particular effort has been spent on developing conditions that are mild and selective to facilitate the late stage functionalization of complex molecules,³⁰ with recent efforts geared towards developing methods for efficient delivery of ¹⁸F-enriched fluorocarbons for positron emission tomography (or PET) radiotracers.³¹



Scheme 1.6 Organofluorine materials.

Aside from roughly a dozen naturally occurring (primarily monofluoroacetate-based) organofluorine compounds present in a small number of plants located in the southern hemisphere,^{32,33} organofluorine compounds do not occur in nature and, as such, all commercially available organofluorine compounds are synthetic. The reason for the lack of organofluorine molecules is fourfold: First, fluorine’s high electronegativity makes the evolution of C–F bond biosynthesis highly challenging, as it cannot be oxidized by haloperoxidases that generate other halocarbons, requiring fluorinating enzymes to evolve *de novo*. Secondly, unlike Cl, Br, and I, fluoride’s high oxidation potential and strong hydration in water create high energetic barriers necessitating desolvation before C–F bond formation. Handling highly reactive fluorine species also poses toxicity risks, requiring specialized enzyme machinery to protect cellular

components. Consequently, both the formation and degradation of organofluorines are energetically costly, explaining the rarity of fluorine incorporation in natural biochemistry. Given the importance of organofluorine compounds across multiple industries, it is then surprising that relatively few methods are available for general, selective C–F bond formation, when compared to methods for other C–halogen bond formations.

The first part of this introduction will give a general overview on various fluorinating reagents and approaches to the synthesis of C–F bonds. The second part will give an overview of and provide context for methods that use an existing C–F bond as a dual function reagent for the step- and atom-economical fluorinative difunctionalization of π -bonds, referred to herein as carbofluorination reactions, resulting in the streamlined synthesis of complex organofluorine compounds from common building blocks.

1.2 Fluorine Reagents

1.2.1 Electrophilic Fluorine Reagents

Although fluorine is relatively abundant in the Earth's crust (≈ 525 ppm, 13th most abundant element), it is found almost exclusively in the form of minerals such as fluorite (CaF_2), a source of anionic fluoride.³⁴ The simplest form of electrophilic fluorine, elemental fluorine (F_2), occurs naturally in trace amounts, generated as a byproduct of uranium salt decay in fetid fluorite (radioactive fluorite). Industrial synthesis of F_2 from HF/KHF_2 mixtures via low-temperature electrolysis currently makes up roughly 1% of the global fluorochemical industry by production, with roughly 17,000 metric tons produced for industrial applications per year.³⁴ Despite the abundance of elemental fluorine produced, F_2 is largely an impractical electrophilic fluorinating reagent. The low F–F bond energy ($36.6 \text{ kcal}\cdot\text{mol}^{-1}$) resulting from strong repulsion of lone pair electrons, combined with the high energy of bonds formed with other elements, make reactions with F_2 extremely exothermic and often explosive. This high reactivity coupled with lack of selectivity, toxicity, and risk of free radical initiated runaway reactions renders F_2 almost completely incompatible with standard organic substrates and laboratory equipment.³⁵ Moreover, specialized training is required for handling F_2 , limiting its broad use.

As such, the development of alternative electrophilic fluorination reagents has been a central challenge to electrophilic fluorination chemistry. While early efforts employed xenon difluoride (XeF_2)^{36,37} and organic hypofluorites (RO-F),³⁸ their use was ultimately limited by safety concerns and impractical handling requirements, as well as issues with functional group compatibility due to their high oxidation potentials.

Modern electrophilic fluorinating reagents are almost entirely composed of benchtop stable *N*-fluoro reagents (Scheme 1.7). Given the relatively lower electronegativity of nitrogen as well as the greater strength of the N-F bond compared to the O-F bond, these reagents exhibit reduced electrophilicity and oxidation potential, making them safer and easier to handle. *N*-fluoropyridinium salts,^{39–42} DABCO-derived Selectfluor,⁴³ and *N*-fluorosulfonamides like *N*-fluorobenzenesulfonimide (NFSI)⁴⁴ are all examples of *N*-fluoro reagents.



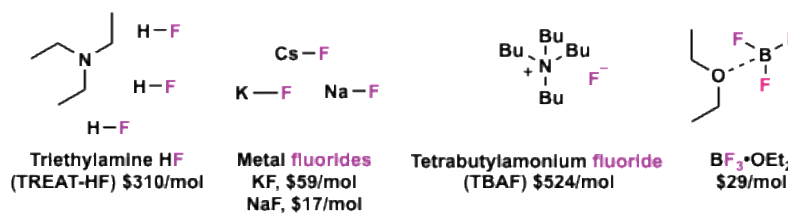
Scheme 1.7 Electrophilic fluorinating reagents.

Electrophilic fluorine reagents are typically used to form C-F bonds via direct electrophilic fluorination of a suitably activated carbon-based nucleophile or as an oxidant to enable C-F bond reductive elimination from high valent metal centres.^{45,46} Additionally, radical fluorination can be achieved using electrophilic fluorine sources, namely N-F reagents given their relatively low N-F BDE.^{47–49}

1.2.2 Nucleophilic Fluoride Reagents

Nucleophilic fluorination is complicated by the inherent properties of the fluoride anion. Fluoride is a hard base with a high charge density, high hydration energy ($117 \text{ kcal}\cdot\text{mol}^{-1}$), and a high oxidation potential (-3 V), which suppress its nucleophilicity. Thus, fluoride often promotes elimination over substitution unless its basicity is regulated by other secondary interactions.^{50–52} While the regulation of fluorides with hydrogen bonding has been demonstrated as a feasible strategy to reduce elimination

reactions, introduction of hydrogen bond donors (HBDs) can also attenuate fluoride nucleophilicity by sequestering it through the formation of hydrogen-bonding networks.

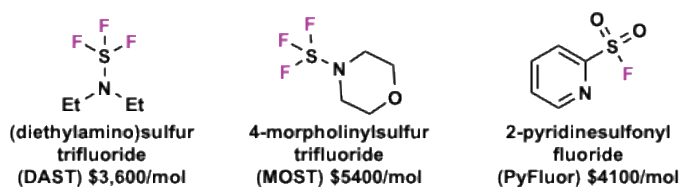


Scheme 1.8 Nucleophilic fluorinating reagents.

The most available and inexpensive nucleophilic fluoride source is hydrogen fluoride (HF), synthesized industrially via the treatment of fluorite with sulfuric acid at high temperatures.⁵³ Pure HF in has a low boiling point (19.6 °C) and is highly corrosive, which leads to logistical complications limiting its use and transformation. Aqueous HF forms a strong hydration shell with water as well as forming the strongly bound ion pair $[\text{H}_3\text{O}^+][\text{F}^-]$ upon dissociation. As a result, aqueous HF solutions typically react as a strong Brønsted acid instead of a fluoride source. For fluorination reactions, stable solutions of amine:HF (e.g., Olah's reagent/pyridine•xHF or TREAT•HF) are highly versatile reagents, as the fluoride is only weakly nucleophilic, allowing for suppression of elimination pathways promoted by fluoride as a base.⁵⁴

Alkali metal fluoride salts (e.g., CsF, KF, NaF) are the most common, inexpensive, and easy to handle forms of nucleophilic fluoride. However, their strong lattice energy leads to low solubility in organic solvents, high hygroscopicity, and strong Brønsted basicity, making them challenging to work with.^{55,56} When they are used, it is typically in combination with crown ethers, or in ionic liquids, buffered HF systems, or in a biphasic system with a fluoride transfer reagent present.⁵⁷ Additionally, aprotic solvents, especially polar aprotic solvents, are preferred both so that the metal fluoride salt is more soluble and so that the nucleophilicity of the fluoride anion is not attenuated by the solvent. Circumventing issues with solubility, ammonium fluoride salts like tetramethylammonium fluoride (TMAF)^{58,59} and tetrabutylammonium fluoride (TBAF)⁶⁰ as well as tetrabutylammonium difluorotriphenylsilicate (TBAT)⁶¹ are readily available and frequently used as more soluble fluoride sources for halogen-exchange reactions (HALEX), for example.

Sulfur(IV) fluorides can serve as nucleophilic fluorination reagents (Scheme 1.9). One of the most versatile fluorinating agents in this class is (diethylamino)sulfur trifluoride (DAST), a less toxic and less volatile analog of sulfur tetrafluoride (SF_4). However, DAST can lead to extremely exothermic reactivity when heated above 90 °C, which ultimately drove the development of more thermally stable SF_4 derivatives with similar reactivity, such as 4-morpholinylsulfur trifluoride (MOST) and the mono-fluoro solid reagent 2-pyridinesulfonyl fluoride (PyFluor)—the latter is a sulfur(VI) fluoride. Large advances in nucleophilic fluorination have come from employment of these sulfur fluorides as deoxyfluorinating reagents, which have enabled the selective and asymmetric fluorination of a range of C–O bonds.⁶²



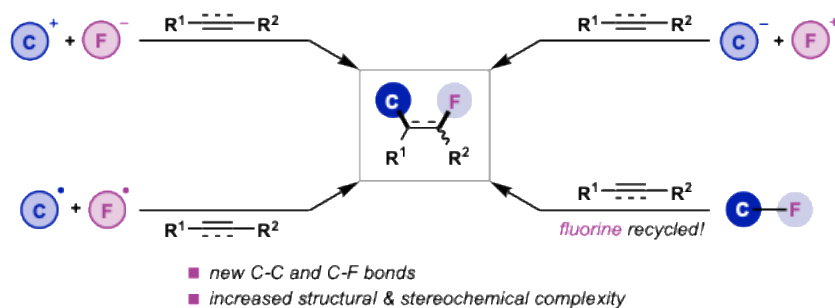
Scheme 1.9 Sulfur-based deoxyfluorinating reagents.

Boron-fluorides, specifically BF_4^- salts and $\text{BF}_3 \cdot \text{OEt}_2$ can also be used as a fluoride source, as highlighted by the synthesis of aryl fluorides via the Balz–Schiemann reaction, though their use as fluoride reagents extends well beyond this example.⁶³ The use of such boron-based fluorinating reagents in “carbofluorination reactions” will be the focus of this thesis.

1.3 Carbofluorination Reactions

A wide range of synthetic methods now enable site-selective and efficient C–F bond formation, supported by the broad commercial availability of fluorinating reagents.^{64–66} The typical formation of a C–F bond involves the 1:1 substitution of a leaving group or other activated functionality with a nucleophilic fluoride source. While valuable, such processes are inherently limited in the molecular complexity they deliver, since only a single reactive site is engaged and a single C–F bond is formed.⁶⁷ An alternative approach to constructing organofluorine compounds is via the difunctionalization of a π -bond, such as an alkene, alkyne or allene. A subset of these reactions, named carbofluorination reactions, involve the addition of a fluorine fragment and a carbon fragment across a π -bond, forming both a C–C and a C–F bond in a single

transformation (Scheme 1.10).^{67,68} Carbofluorination can proceed via intra- or intermolecular pathways and can be accompanied by rearrangements depending on the reaction mechanism. The capacity to forge two strategically significant bonds at once not only improves synthetic efficiency but also grants access to novel fluorinated scaffolds that may be difficult to synthesize using other methods.



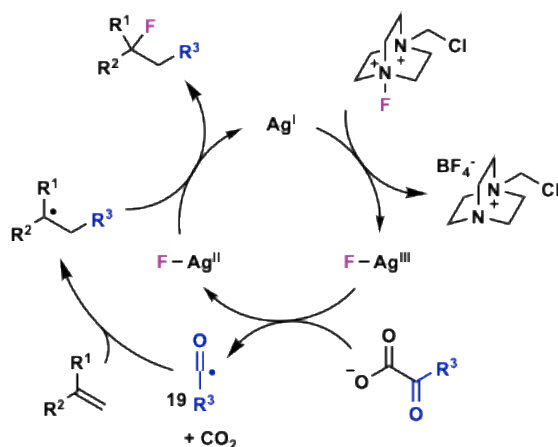
Scheme 1.10. General carbofluorination reaction scheme.

While these reactions have historically used separate reagents to deliver the fluorine and carbon fragments, recent years have shown that it is possible to directly insert a π -bond into a pre-existing C–F bond. In these cases, the fluorinated organic compound acts as a dual function reagent (i.e., as an electrophilic carbon fragment and a nucleophilic fluoride fragment), enabling elaboration of fluorine containing precursors into more structurally complex fluorinated molecules. These reactions can proceed without the need for external fluorinating reagents, and, in principle, achieve perfect atom economy. Despite these advantages, examples of these “atom-economical” carbofluorination reactions remain exceedingly rare. The scarcity arises from the formidable challenge of activating a C–F bond. As noted, fluorine forms the strongest single bond to carbon of any element and cleaving such a C–F bond requires a significant thermodynamic driving force. While the literature is full of reactions that cleave C–F bonds, it is typically achieved at the expense of forming a stronger heteroatom–F bond (i.e., through coordination to a Lewis acidic metal or main-group element). Often, the result of such activation is sequestration of the fluoride anion, rendering reincorporation of the fluoride into the organic substrate or “fluoride recycling” difficult. Nevertheless, over the past five years, a handful of strategies have emerged which promote efficient C–F bond insertions reactions under both catalytic and H-bonding mediated conditions using activated C–F bonds like acyl, propargyl and benzyl fluorides, as well as trifluoromethyl and *gem*-

difluorocyclopropyl moieties.^{67,68} The rest of this introduction aims to give mechanistic context for strategies reported for atom-economic carbofluorination reactions and is organized by the type of carbon fragment (acyl/carbonyl vs alkyl) delivered.

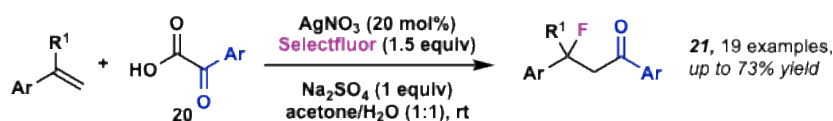
1.3.1 Acylfluorination

For non-atom economical acylfluorination carbofluorination reactions, acyl radical precursors are typically used as the coupling partner. Many of these acyl radicals are generated in the presence of a Ag^{I} catalyst (Scheme 1.11). Using Selectfluor, Ag^{I} is readily oxidized to a $\text{Ag}^{\text{III}}\text{-F}$ species, which is primed to undergo SET with the acyl precursor to produce an acyl radical **19** and a $\text{Ag}^{\text{II}}\text{-F}$ species. Addition of **19** to an alkene acceptor generates a new carbon-based radical which can undergo fluoride atom transfer (FAT) with the $\text{Ag}^{\text{II}}\text{-F}$ intermediate to form the carbofluorination product, while simultaneously regenerating the active Ag^{I} catalyst.



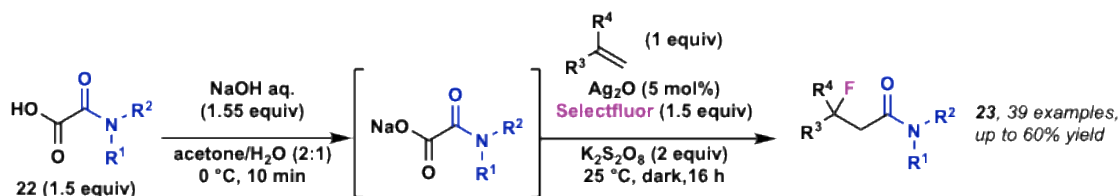
Scheme 1.11. General scheme for Ag^{I} -catalyzed acylfluorination of alkenes via acyl radical generation.

In 2014, Duan and co-workers reported the AgNO_3 -catalyzed decarboxylative acylfluorination of styrenes with α -oxocarboxylic acids **20** and Selectfluor to yield β -fluorinated 3-aryl ketones **21** (Scheme 1.12).⁶⁹ The reaction is exclusive to styrenes as attempts to use aliphatic terminal alkenes led to no product formation. The addition of a Na_2SO_4 promotes the formation of the redox-active carboxylate, leading to enhanced yields.⁷⁰



Scheme 1.12. α -Oxocarboxylic acids as acyl radical precursors in Ag^{I} -catalyzed acylfluorination of styrenes.

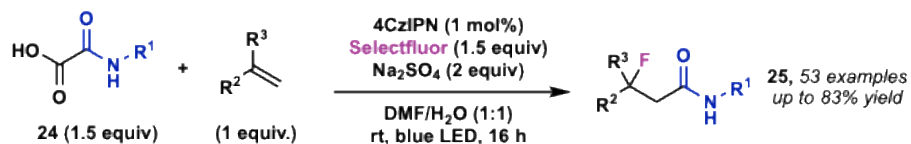
Recently, Vincent and Brioché reported the use of oxamic acids as carbamoyl radical precursors for the synthesis of either β -fluoroamides or β,β -difluoroamides from non-activated olefins or α -fluoroolefins, respectively.⁷¹ The reaction uses in situ generated sodium oxamate salts, which then can, in the presence of Ag^{I} , release carbamoyl radicals, adding to either the olefin acceptor to give the acylfluorination products (Scheme 1.13). While the reaction works well with primary, secondary, and aniline-derived oxamic acids as radical precursors, lowered reactivity was observed with both electron-rich styrenes and aliphatic olefins.



Scheme 1.13. Oxamic acids as acyl radical precursors in Ag^{I} -catalyzed acylfluorination of alkenes.

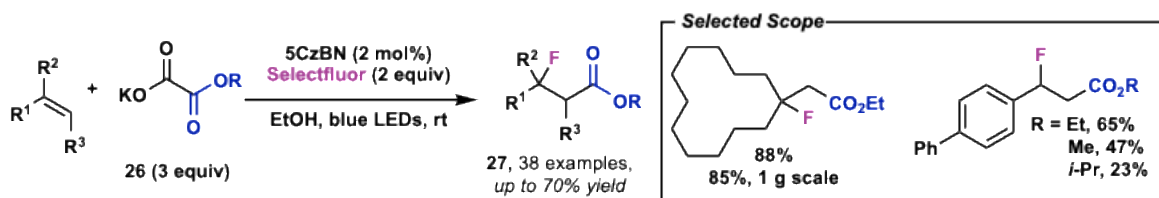
In a complementary study, Jana and co-workers demonstrated that carbamoyl radicals can be generated under milder organophotoredox conditions from amino-acid-derived oxamic acids **24**, circumventing the need for pre-activation of the oxamic acid with NaOH, enabling late-stage *N*-terminal modification of amino acids, peptides, and biomolecules (Scheme 1.15).⁷² Na_2SO_4 was employed as an additive to enhance the solubility of Selectfluor. In contrast to the Brioché report, both styrene derivatives and unactivated alkenes were competent substrates, although electron-rich styrenes failed to afford products under the reaction conditions. When chiral amino-acid derivatives were used, diastereoselectivities were uniformly low. Notably, the transformation did not require blue-light irradiation, as comparable yields were obtained under sunlight irradiation when tested on a subset of substrates. Interestingly, the use of DAST, typically a nucleophilic fluoride source for

deoxyfluorination, afforded product in 23% yield, representing a rare example of a nucleophilic fluoride reagent operating under FAT conditions.



Scheme 1.14. Oxamic acids as acyl radical precursors in organocatalyzed acylfluorination of alkenes.

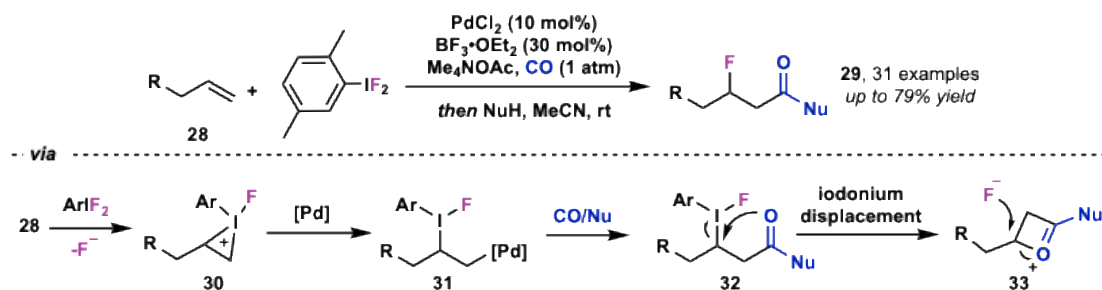
Fluoroacylation can also be achieved using an alkoxycarbonyl radical generated from potassium 2-ethoxy-2-oxoacetates **26** in the presence of the organophotoredox catalyst 5CzBN, Selectfluor, and blue light, as reported by Chen and Wu in 2022 (Scheme 1.15). The reaction is general, working on both styrenes and non-activated olefins with similar efficiencies. While oxalates derived from methanol and isopropanol were productive under the reaction conditions, *t*-butyl and benzyl alcohol derivatives gave no product.



Scheme 1.15 Oxoacetates as acyl radical precursors in Ag^I-catalyzed fluoroacylation of alkenes.

Examples of fluoroacylation of alkenes using nucleophilic fluoride sources are rare. Chen and Liu reported a strategy employing stoichiometric difluoro- λ^3 -aryl iodane, which serves as both an activator and the fluorine source for the reaction (Scheme 1.16).⁷³ The reaction is initiated by the electrophilic addition of the activated iodane across the alkene, generating an iodocyclopropyl cation **30** that is susceptible to oxidative addition with the palladium catalyst to form complex **31**. Subsequent CO insertion and nucleophilic attack on the acyl palladium species generates intermediate **32**. While this intermediate can undergo direct intermolecular S_N2 with a fluoride ion, the authors suggest that instead the neighboring acyl fragment displaces the iodonium species intramolecularly to form oxocarbenium intermediate **33**, which can then undergo nucleophilic fluorination. The reaction can result in a variety of carbonylated products like β -fluoro esters (with alcohol nucleophiles), carboxylic acids (with water), and amides (with amines).

The method tolerates heteroaryl substituents, is exclusive to terminal alkenes, and is selective for electron-rich alkenes over electron-poor alkenes when they are present within the same substrate.

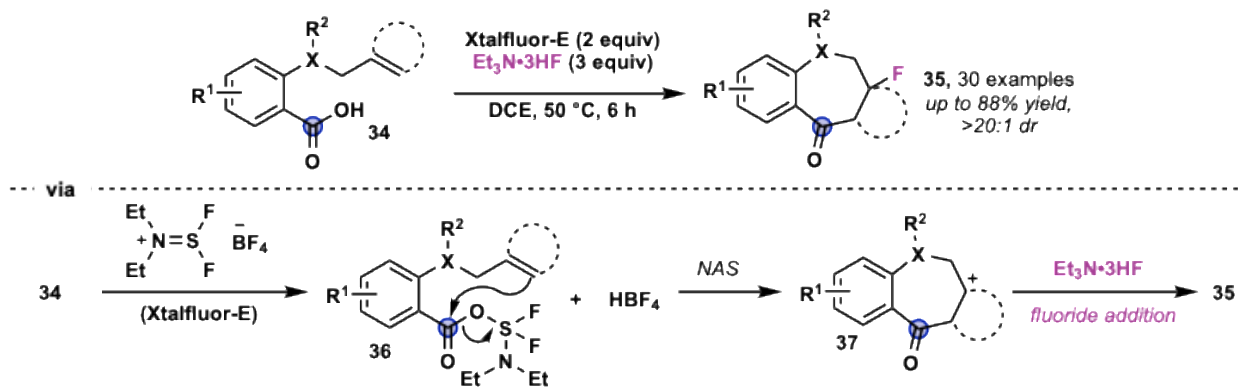


Scheme 1.16 1,2-Fluorocarbonylation of unactivated alkenes using hypervalent iodine and Pd/CO catalysis.

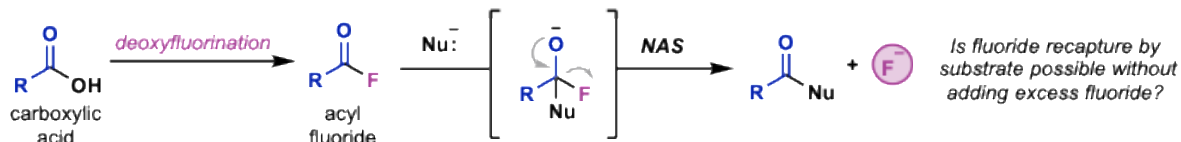
One reaction that is primed for atom-economical acylfluorination is the nucleophilic acyl substitution (NAS) of acyl fluorides. NAS is appealing because it proceeds through a two-step mechanism: first a nucleophile attacks the carbonyl carbon of an acyl derivative, forming a tetrahedral intermediate. Collapse of the tetrahedral intermediate expels a leaving group, yielding the substitution product. Typically, NAS requires a proficient leaving group on the acyl precursor and either a strong nucleophile or an acid activator for the carbonyl oxygen to increase its electrophilicity, making it more susceptible to nucleophilic attack. The acid activator can be either a Lewis acid or a Brønsted acid.

Carboxylic acids can undergo intramolecular fluoroacylation of unactivated alkenes **34** via NAS activation to access benzo[b]azapines **35** (Scheme 1.17.A).⁷⁴ Given the relatively poor leaving group ability of ⁻OH, typical NAS reactions of carboxylic acids involve the use of an activator. In this case, the activator is XtalFluor-E which generates mixed anhydride species **36**, making the carbonyl carbon electrophilic enough to undergo NAS in a 7-*endo-trig* cyclization with the internal alkene. Cyclization results in the formation of carbocation **37** which can then be captured by an equivalent of nucleophilic fluoride.

— A. Intramolecular carbofluorination via NAS and subsequent fluoride transfer, Xu (2023)



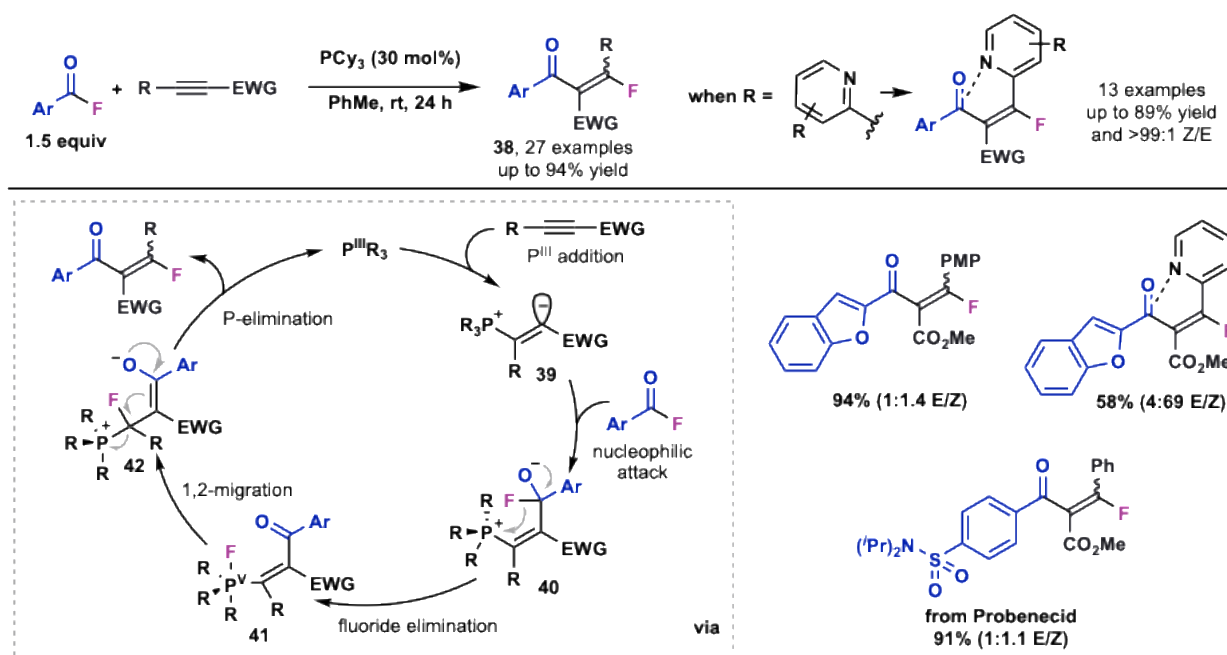
— B. Potential Reactivity: Acyl fluorides as acyl electrophiles in carbofluorinative NAS



Scheme 1.17 NAS for carbofluorination reactions.

Despite their strong C–F bonds, acyl fluorides are known to undergo nucleophilic activation in a manner that is typical to other acyl compounds. When employed as substrates under NAS conditions, the leaving group is a fluoride equivalent, which can in theory be recycled in the reaction to form a new C–F bond (Scheme 1.17.B).

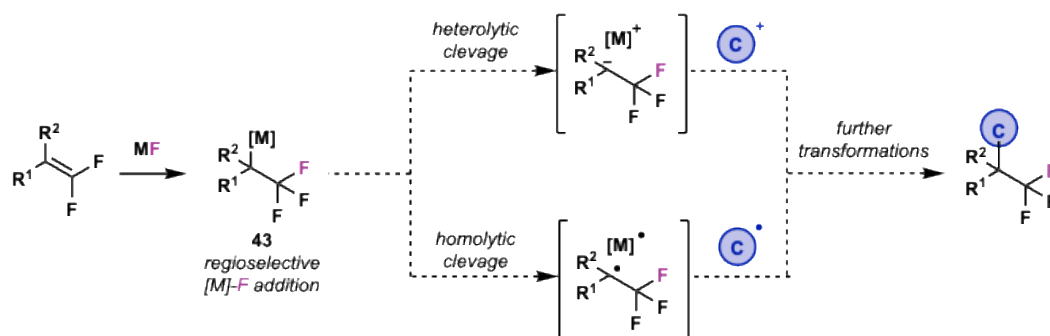
The seminal work for atom-economical carbofluorination reactions takes advantage of NAS reactions of acyl fluorides. In 2020, Tobisu and co-workers reported the first intermolecular 1,2-acylfluorination of alkynoates using aroyl fluorides, proceeding through an unprecedented P^V -ligand coupling mechanism, furnishing β -fluoroenones **38** (Scheme 1.18).⁷⁵ Mechanistically, the reaction is initiated by the addition of the PCy_3 catalyst to the alkynoate, forming the zwitterionic species **39**. Resonance stabilized carbanion **39** is a competent nucleophile for the NAS of the acyl fluoride, and the initial addition generates tetrahedral intermediate **40**. Collapse of **40** leading to fluoride elimination is likely promoted in an intramolecular fashion by the presence of the Lewis acidic cationic P^{III} -species, which can act as a fluoride abstractor leading to fluorophosphorane **41**. Subsequent ligand coupling via a 1,2-fluoride migration from the phosphorus center to the adjacent electrophilic carbon atom affords the zwitterionic species **42**, which then releases the PCy_3 catalyst upon elimination.



Scheme 1.18 P(III)/P(V)-redox catalyzed 1,2-fluoroarylation of electron-deficient alkynes with aroyl fluorides.

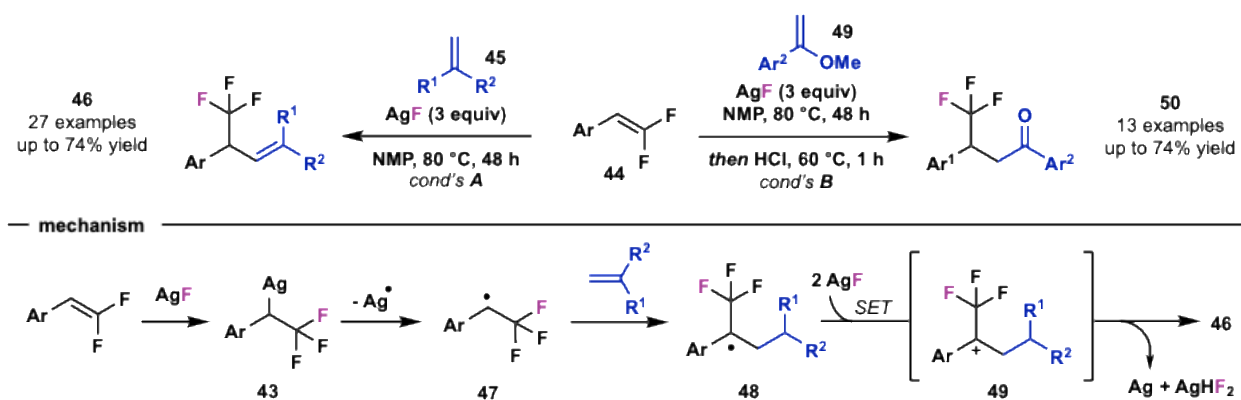
The reaction is exclusive to aryl-alkynoates, which are electron-deficient enough to be activated by the nucleophilic PCy₃-catalyst, and exhibits broad tolerance toward both electron-donating and electron-withdrawing substituents on the aryl ring. Aryl-alkynoates bearing ethyl ester, *tert*-butyl ester, or benzoyl groups as electron-withdrawing substituents also furnished the desired products. Likewise, the transformation accommodates a wide range of electronic and steric variations on the aroyl fluoride fragment. The *E/Z* selectivity is substrate-dependent: apart from alkynoates containing a 2-pyridyl substituent, which afforded the *Z*-isomer with near exclusivity, most substrates displayed modest stereoselectivity (<1:1.6 *E/Z*).⁷⁶

In the Tobisu report, the active nucleophile for NAS is a carbanion, limiting the π -bond acceptors that can be used in this reaction to those that are able to stabilize its formation (i.e., aryl-alkynoates). One way to generate a competent nucleophile for carbofluorination is via the addition of a [M]-F group across an alkene, typically a fluorinated alkene. Mechanistically, the reaction leverages the electron deficient nature of a fluorinated alkene to undergo direct 1,2-addition of the [M]-F species. The resulting [M]-fluoroalkane species **43** can serve as a competent intermediate for further transformation via either homolytic or heterolytic cleavage of the [M]-C bond (Scheme 1.19).



Scheme 1.19. Addition of a [M]-F bond across a fluorinated alkene.

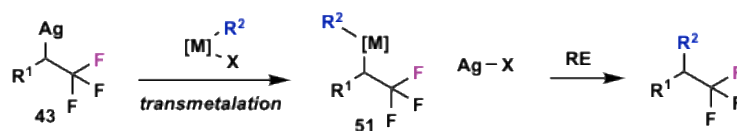
Frequently, AgF is added across *gem*-difluoroalkenes to yield α -CF₃-organosilver intermediate **43**, which then can be intercepted to yield trifluoromethyl-containing products. Building on initial work of the homocoupling of *gem*-difluoroalkenes in the presence an AgF catalyst,⁷⁷ Hu and co-workers found that addition of AgF to β,β -difluorostyrene derivatives **44** in the presence of 1,1-disubstituted ethylenes **45** led to the formation of α -CF₃ alkenes **46** (Scheme 1.20, cond's A).⁷⁸ In this case, the key intermediate **43** can undergo thermal Ag–C bond homolysis to give benzylic α -CF₃ radical **47** that can react with ethylene **45** to give intermediate **48**. Subsequent SET with AgF oxidizes the radical to carbocation **49**, which then undergoes rapid deprotonation to give the desired α -CF₃ alkenes. While the reaction tolerated both electron-rich and electron-deficient β,β -difluorostyrenes, the addition of 0.5 equiv. AgBF₄ was beneficial to suppress the formation of the hydrofluorination by-product for electron-deficient substrates. The reaction could also be used to furnish β -CF₃ ketones **50** when α -methoxystyrenes **49** were used as the olefin: the initially formed α -CF₃ methoxyalkenes were amenable to acid-hydrolysis, forming the desired β -CF₃ ketones **50**. The hydrolysis is mild enough to tolerate ester, tosyl, sulfonyl, nitro, and cyano groups and was successfully scaled up with retention of yield. Additionally, the products can be derivatized into known pest control reagents.



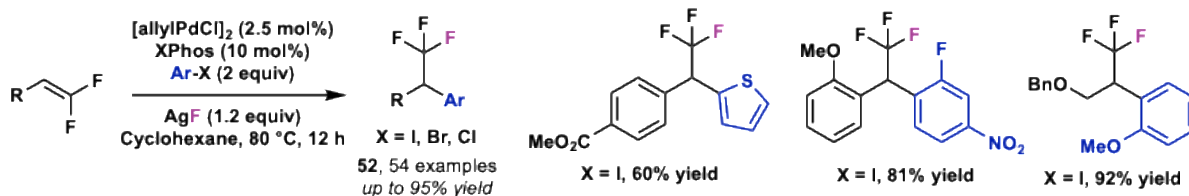
Scheme 1.20. Direct coupling of α -CF₃-Ag intermediates with alkenes via radical propagation.

Aside from direct coupling with alkenes, organo-silver intermediate **43** can also be used as transmetalation reagents in transition metal-redox catalysis (Scheme 1.21.A). Feng and Loh leveraged **43** as a transmetalation agent in a Pd-catalyzed 1,2-fluoroarylation of *gem*-difluoroalkenes using aryl halides as coupling partners and AgF as the fluoride source (Scheme 1.21.B).⁷⁹ Both styrenyl and aliphatic *gem*-difluoroalkenes were shown to be competent substrates. The reaction displayed a broad substrate scope: *gem*-difluorostyrenes bearing methyl, methoxy, or *N,N*-diphenylamino substituents, regardless of substitution pattern, all proved to be productive substrates. The method is exclusive to *gem*-difluoroalkenes, as other alkenes were unreactive. While aryl-iodides were identified as the optimal aryl halide, aryl bromides are also sufficient coupling partners. Further advancement came in 2020, when Li and Zhang developed an enantioselective variant of the fluoroarylation enabled by a chiral sulfinamide–phosphine ligand (Scheme 1.21.C). This asymmetric protocol proved broadly applicable to allyl, aryl, and alkenyl *gem*-difluoroalkenes and was successfully scaled to gram quantities with full retention of yield and enantioselectivity.

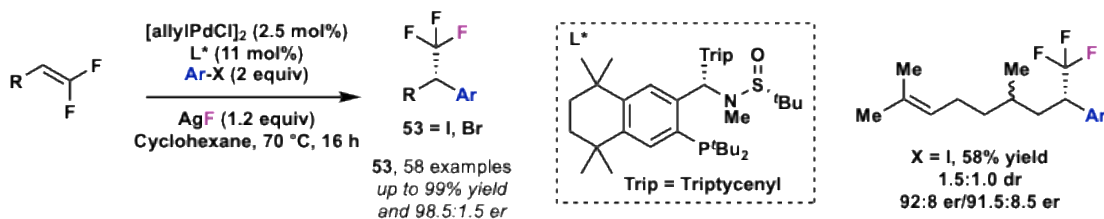
— A. Capture of α -CF₃-Ag by TM



— B. Racemic, Feng and Loh (2017)

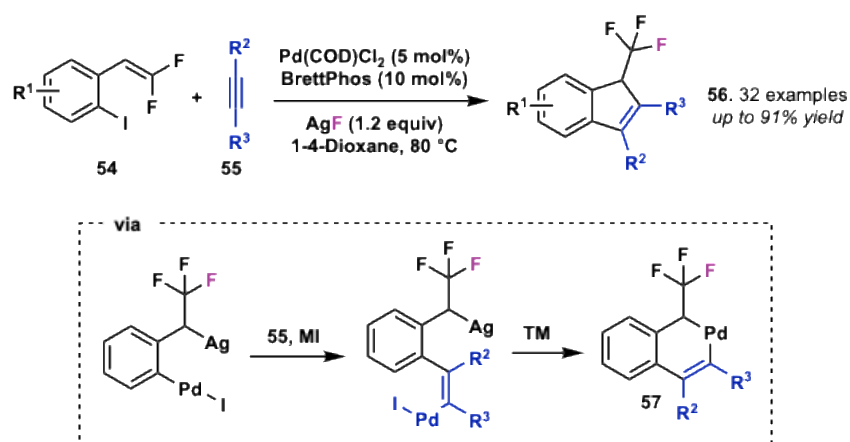


— C. Asymmetric, Li and Zhang (2020)



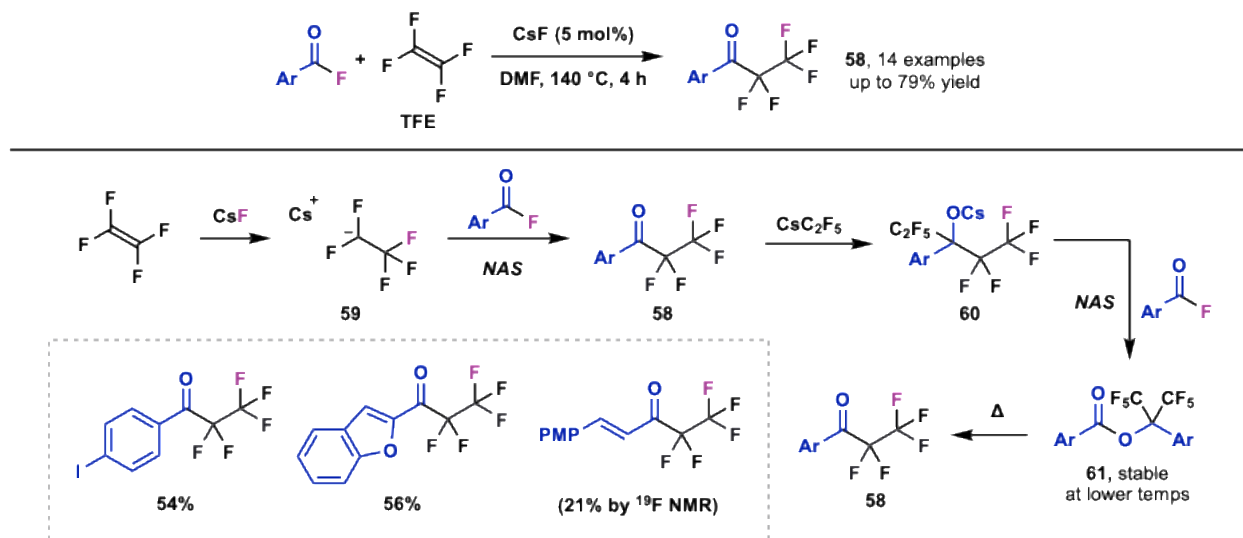
Scheme 1.21. General scheme of transmetalation of α -CF₃-Ag with a transition metal and Pd-catalyzed fluoroarylation of *gem*-difluoroalkenes via an organo-silver intermediate.

The versatility of this method can be underscored by the ability to combine the reactivity of the organo-silver intermediate with other well-defined elementary steps in transition metal catalysis. One example is the formation of CF₃-indenes **56** via the [3 + 2] annulation of 1-(2,2-difluorovinyl)-2-iodobenzene **54** and acetylenes **55** (Scheme 1.22).⁸⁰ The reaction is initiated via dual AgF addition across the *gem*-difluoroalkenes and Pd-aryl iodide oxidative addition. Intramolecular transmetalation is disfavored from this intermediate due to steric constraints so an intermolecular alkyne insertion can occur, releasing the steric constraints on transmetalation and allowing for the formation of Pd-metallacycle **57**, which undergoes C–C bond RE to give the final product.



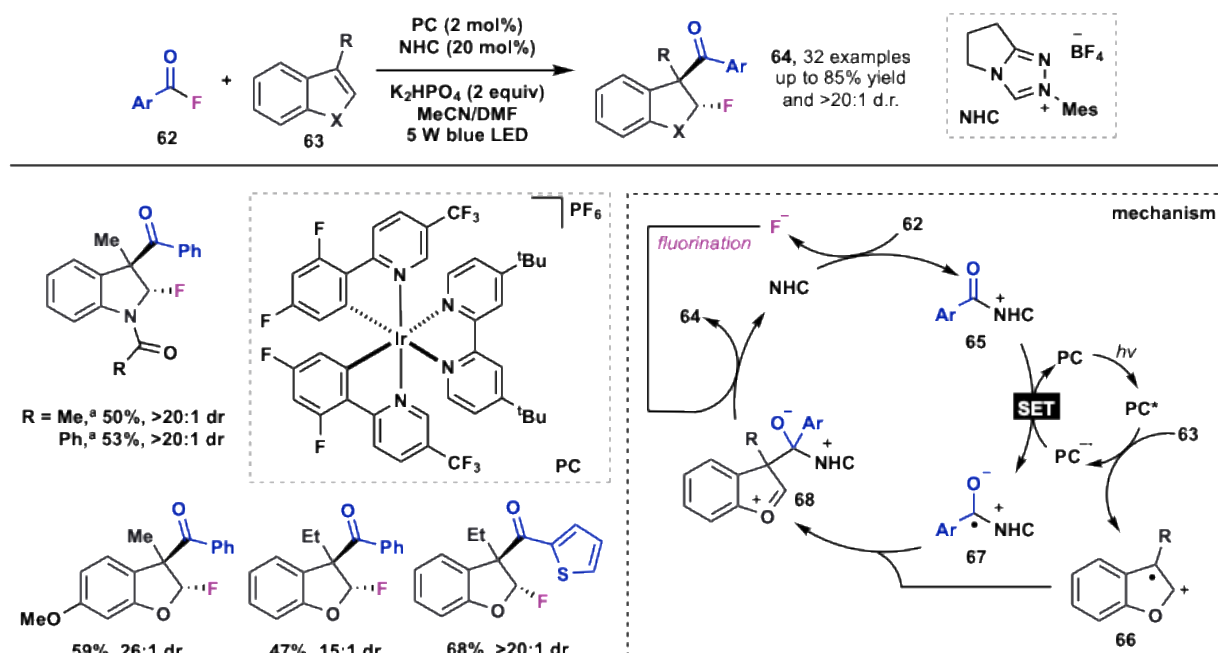
Scheme 1.22. Pd-catalyzed [3 + 2] annulation of *ortho-gem*-difluoro-aryl iodides with acetylenes.

This strategy has also been employed in atom-economical fluoride shuttling catalysis. Shortly after the original Tobisu report, Ogoshi reported the use of aroyl fluorides as C–F bond donor for the 1,2-acylfluorination of tetrafluoroethylene (TFE) via CsF-catalysis to synthesize pentafluoroethyl ketones **58** (Scheme 1.23).⁸¹ The authors postulated that the reaction is initiated by the addition of CsF across TFE, giving intermediate **59** as an ion pair and competent nucleophile for NAS. Subsequent addition and elimination of the pentafluoroethanide anion to the acyl fluoride yields the desired pentafluoroethyl ketone **58** while at the same time regenerating CsF. The pentafluoroethyl ketone **58** is not stable under the reaction conditions and a second addition of **59** can occur at the ketone, resulting in Cs-methoxide **60**. A second NAS reaction with aroyl fluoride results in the formation of by-product perfluorinated ester **61**, which at lower temperatures, is a stable compound. Under the optimized reaction conditions, ester **61** can undergo decomposition back to **58**. The reaction works best with electron-rich and neutral aroyl fluorides, and while it can be extended to electron-rich α,β -unsaturated acyl fluorides, the product is produced in low yield and cannot be isolated.



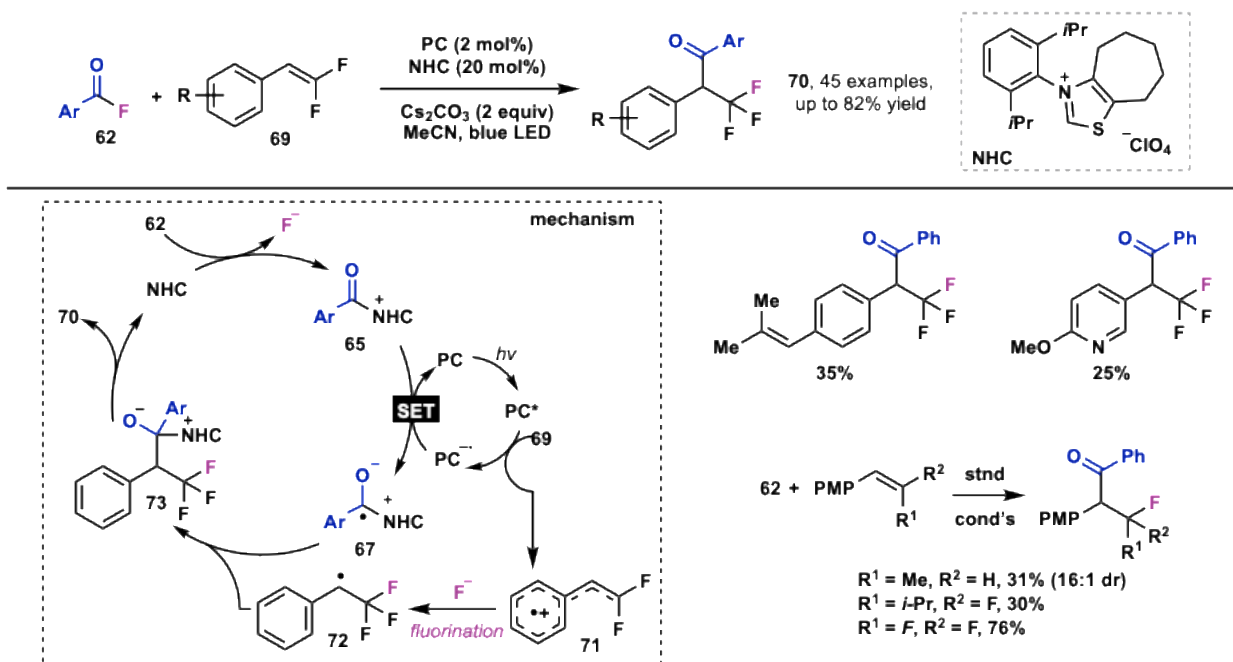
Scheme 1.23 CsF-catalyzed 1,2-acylfluorination of TFE with aryl fluorides.

Aryl fluorides can also be activated under cooperative NHC/photoredox catalysis, building off previously reported acyl fluoride activation via NHC catalysis, as reported by Studer and co-workers, for the 1,2-acylfluorination of benzofurans **63** to yield fluorinated oxabicycles **64** (Scheme 1.24).⁸² In this case, an initial NAS with the aryl fluoride and nucleophilic NHC catalyst induces C–F bond cleavage directly, affording a fluoride ion and the acyl-azolium intermediate **65**. The reaction is largely exclusive to benzofurans because of the following steps: concurrent with formation of **65**, the excitation of the Ir^{III} photocatalyst by blue light provides an excited Ir^{III*} species—a strong oxidant that can accept an electron from the comparatively electron rich benzofuran **63**, generating radical cation **66**. The acyl-azolium salt **65** can then accept an electron from the reduced Ir^{II} species, regenerating the active Ir^{III} catalyst and producing acyl-azolium radical **67**. Radical–radical cation coupling between **66** and **67** then furnishes oxocarbenium intermediate **68**, which undergoes fluoride capture and NHC release to deliver the fluoroacylation product in high diastereoselectivity. Aside from benzofurans, *N*-acetyl and *N*-benzoyl indoles can also give 1,2-acylfluorination products when the photocatalyst is swapped to 4CzIPN.



Scheme 1.24 1,2-Fluoroacylation of benzofurans and indoles with aryl fluorides via cooperative NHC/photoredox catalysis.

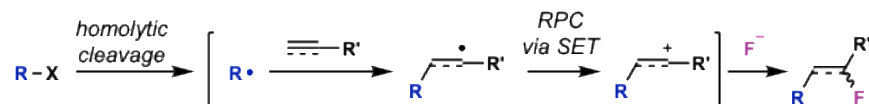
A follow-up publication found that *gem*-difluorostyrenes, β -fluorostyrenes, and styrenes can also be used as coupling partners under the Ir-photocatalyzed conditions with modifications to the NHC catalyst, giving access to α -fluoromethyl ketones (Scheme 1.25).⁸³ With styrenes, a slightly different mechanistic path is followed: SET oxidation of the styrene by photoexcited Ir^{III*} catalyst generates radical cation **71** that undergoes regioselective nucleophilic fluorination, resulting in benzylic radical species **72**. **72** is then the active radical coupling partner for the C–C bond forming step with the acyl-azolium radical **67**, resulting in the formation of tetrahedral intermediate **73**, thus differing from the radical-radical cation coupling pathway exhibited by benzofurans and indoles.



Scheme 1.25. 1,2-Fluoroacylation of fluorinated and non-fluorinated styrenes with aryl fluorides via cooperative NHC/photoredox catalysis.

1.3.2 Fluoroalkylation

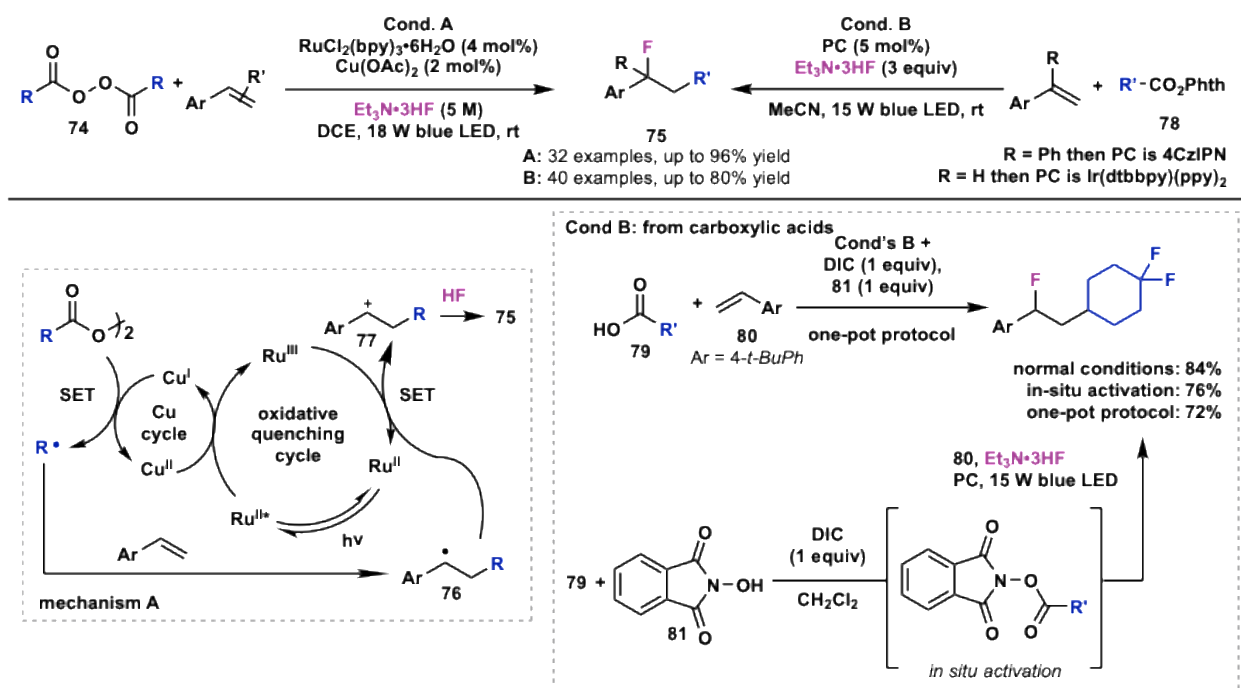
One way that 1,2-fluoroalkylation reactions can occur is via radical polar crossover reactions (RPC) (Scheme 1.26). Typically, carbofluorination via RPC is initiated by the fragmentation of a radical precursor under thermal, photochemical, or electrochemical conditions, generating a carbon-centered radical. This radical then adds to a π -acceptor, forming a new carbon-centered radical intermediate. Subsequent SET oxidation of this species yields a carbocation, which can be trapped by a fluoride ion, affording the desired carbofluorination product.



Scheme 1.26. Radical polar crossover promoted fluoroalkylation of π -acceptors.

In 2018, Bao and co-workers reported a Ru/Cu co-catalyzed 1,2-fluoroalkylation of styrenes under blue-light irradiation, using alkyl diacyl peroxides **74** as alkyl radical precursors and $\text{Et}_3\text{N}\cdot 3\text{HF}$ as the fluoride source in a RPC reaction (Scheme 1.27.A).⁸⁴ The proposed mechanism is initiated by a SET from a photoexcited Ru^{II} catalyst to the Cu^{II} co-catalyst, which generates an oxidized Ru^{III} complex and a reduced

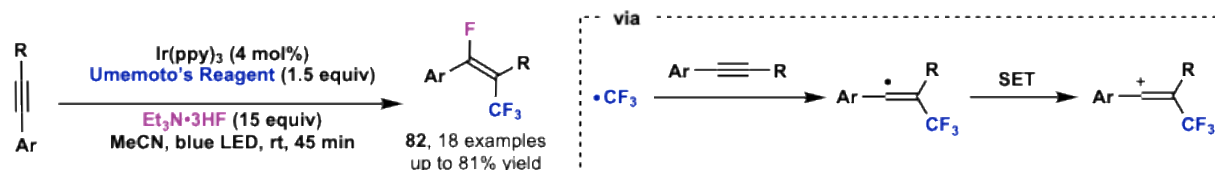
Cu^I species respectively. The Cu^I complex serves to activate the peroxide to generate an alkyl radical that can add to the alkene acceptor. Intermediate **76** can then undergo oxidative RCP with the Ru^{III} species, forming the key carbocation intermediate **77** that can undergo fluoride trapping. One major limitation is that only primary radicals can be used in the reaction. Use of alkyl radicals generated from NHPI esters under Ir/blue light-photocatalyzed conditions, as disclosed by Sim and co-workers, enabled the use of secondary primary, benzylic, and tertiary alkyl and primary α -alkoxyalkyl radicals (Scheme 1.27.B).⁸⁵ By switching the photocatalyst to 4CzIPN the reaction could be extended to use α,α -diphenylethylene as the alkene, though some of the resulting fluorinated products proved unstable, undergoing HF elimination to form trisubstituted alkenes. A practical advantage of Sim's method is that the NHPI esters need not be pre-synthesized: both a sequential *in situ* activation of carboxylic acids followed by photocatalytic carbonyl fluorination, and a true one-pot process, proceed with little erosion in yield.



Scheme 1.27 RCP promoted alkylation of styrenes to yield benzyl fluorides **75**.

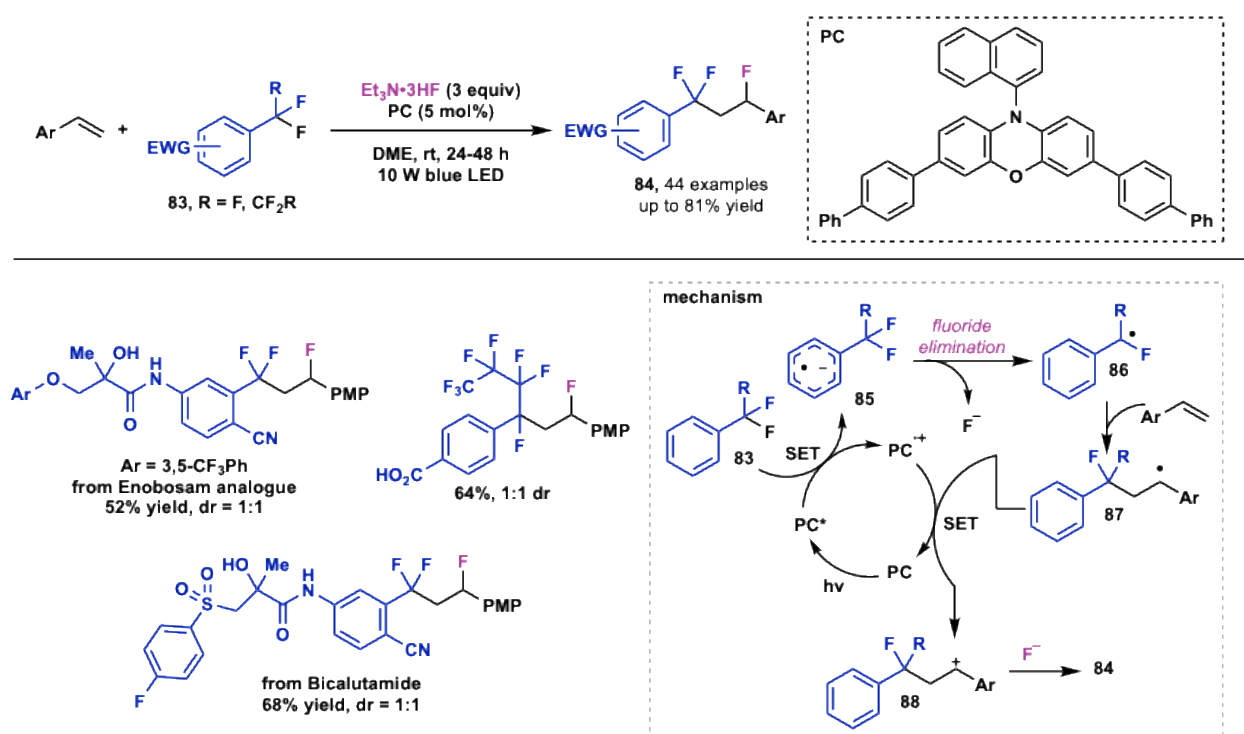
Disubstituted alkynes can also undergo *anti*-fluorotrifluoromethylation reactions as disclosed by Kim and Han in 2020: Umemoto reagent is activated by photoexcited Ir^{III}*, releasing a CF₃ radical that, in combination with Et₃N·3HF adds across an acetylene to yield (*E*)- α -fluoro- β -trifluoromethyl styrenes **82**

in a highly regioselective manner (Scheme 1.28).⁸⁶ The reaction is exclusive to 2-aryl-1-alkyl-disubstituted alkynes and is also shown to be useful for the late-stage functionalization of natural products given its tolerance for secondary amines, esters, and alcohols.



Scheme 1.28 Ir-photocatalyzed *anti*-fluorotrifluoromethylation of disubstituted alkynes.

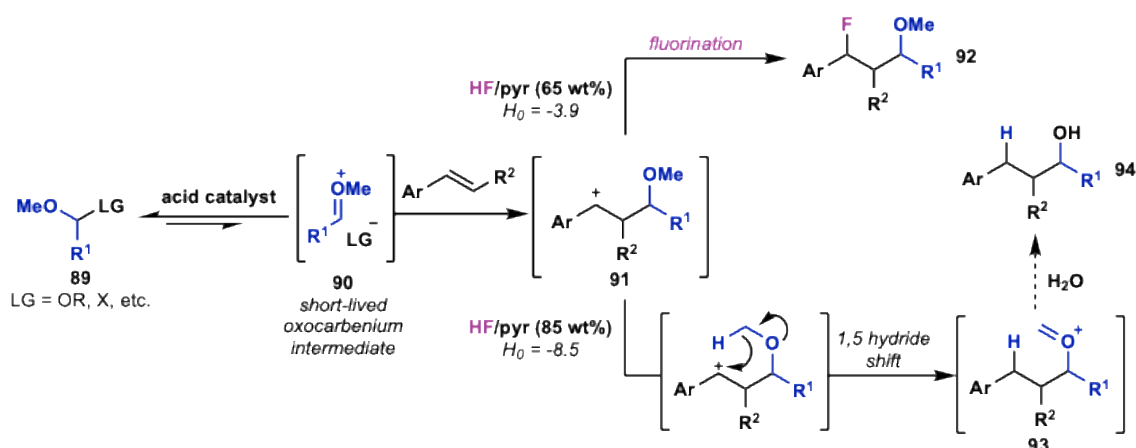
Electron-deficient α,α,α -trifluorotoluene derivatives can be utilized as C–F bond donors for 1,2-fluoro-*gem*-difluoromethylation of electron-poor styrene derivatives **83** under photoredox conditions, as disclosed by Zhang and co-workers (Scheme 1.29). The proposed mechanism is initiated by SET of aryl- CF_3 **83** by an excited photocatalyst forming radical anion species **85**. Rearomatization of **85** provides the driving force for release of a fluoride ion, generating an electrophilic (aryl)difluoromethyl radical **86**. Radical **86** can then undergo radical propagation with an electron-rich alkene generating nucleophilic carbon radical **87**, which is primed for radical polar crossover forming carbocation **88**. Although a fluoride equivalent is released from the starting aryl- CF_3 compound, efficient reaction turnover requires the presence of excess $\text{Et}_3\text{N} \cdot 3\text{HF}$, making this a not-entirely atom-economical process. The conditions are very mild, allowing for coupling in the presence of a wide range of otherwise sensitive functional groups, like nitriles, thiols, heteroaryls, secondary amines and carboxylic acids. Additionally, the conditions enabled late-stage functionalization of complex, biologically relevant molecules bearing an aryl- CF_3 motif. The reaction can also be extended to using perfluoroalkylarenes, with selective singular activation of a benzylic C–F bond occurring.



Scheme 1.29 Organophotoredox enabled 1,2-fluoro-*gem*-difluoromethylation of styrenes with α,α,α -trifluorotoluene derivatives.

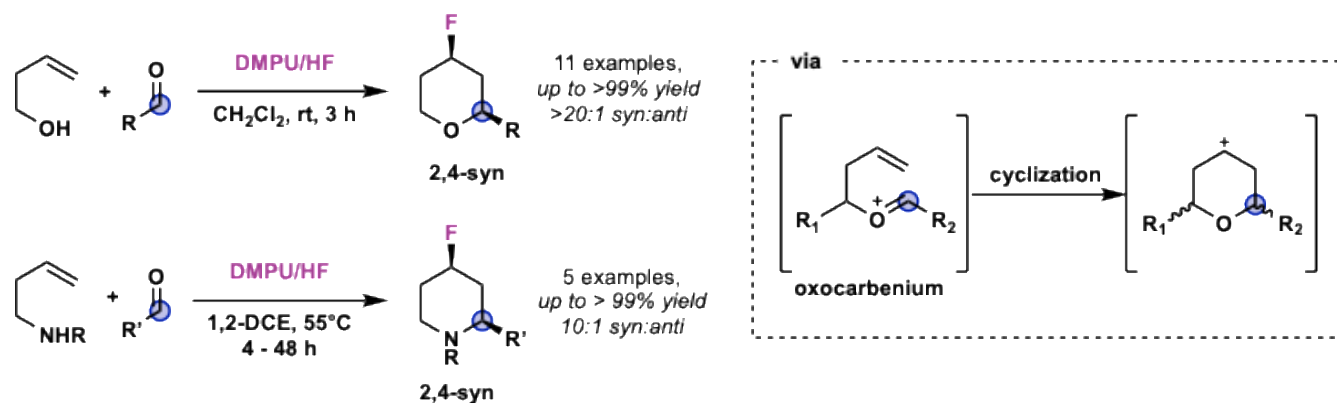
As noted previously, nucleophilic fluorination can be complicated by fluoride's propensity to act as a base, resulting in elimination over substitution unless its basicity is regulated by other secondary interactions. One way that basicity can be regulated is via coordination of the fluoride ion with hydrogen bond donors (HBDs). One stark example of the power of HBD regulation of fluoride reactivity in carbofluorination reactions comes from the work of Guégan, Michelet, and Thibaudeau who reported the chemodivergent fluoro- and hydro-alkoxylation of alkenes using $\text{Pyr}\cdot(\text{HF})_x$ as the fluoride source and an oxocarbenium precursor **89** (Scheme 1.30).⁸⁷ Previous studies by the same group demonstrated that the acidity of $\text{Pyr}\cdot(\text{HF})_x$ solutions can be tuned across approximately eight units of the Hammett acidity function (H_0), ranging from -2 to -10 , by varying the composition of the mixture by weight percent.⁸⁸ The Hammett acidity function provides a measure of acidity in highly concentrated acid systems, including superacids, where simple pH approximations fail due to changes in activity coefficients; the lower the value, the more acidic the solution. Increasing HF weight percent results in a more acidic medium and greater sequestration of fluoride. The accessibility of the fluoride anion as a nucleophile could be seen in

chemodivergent reactivity with carbocation **91**. Generated by the addition of oxocarbenium **90** to a styrene, when a 65 wt% Pyr·(HF)_x solution was used for the reaction ($H_0 = -3.9$, lower fluoride sequestration), **91** was readily trapped by fluoride, yielding the formal fluoroalkoxylation product **92**. When an 85 wt% Pyr·(HF)_x solution was used for the reaction ($H_0 = -8.5$, higher fluoride sequestration) the carbocation is instead quenched via a 1,5-hydride transfer to yield oxocarbenium intermediate **93**, which upon aqueous work up generates formal hydro-hydroxymethylation product **94**.



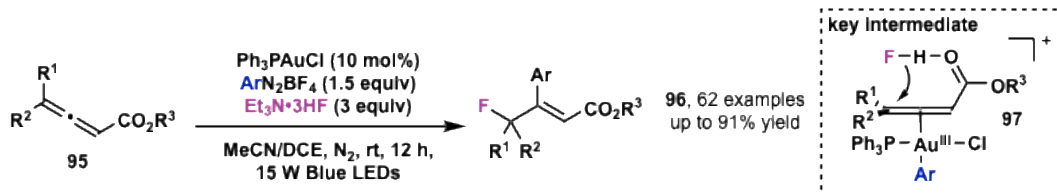
Scheme 1.30 HBD regulation of Pyr·(HF)_x solutions acidity causes chemodivergent reactivity.

Other examples of fluoride HBD regulation via amine coordination for carbofluorination reactions can be found in the literature. In 2015, Hammond and Xu found that a 65 wt% solution of DMPU/HF ($H_0 = -6.0$) was a sufficient fluoride source for the two-component fluorinative Prins cyclization of homoallyl-alcohols and allyl-amines with aldehydes (Scheme 1.31).⁸⁹



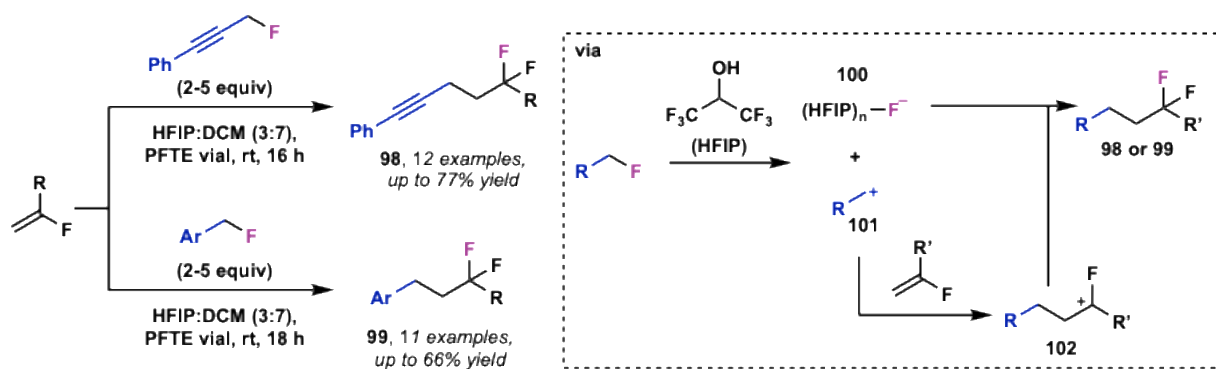
Scheme 1.31. Fluoride HBD regulation in fluorinative Prins reactions.

In 2020, Feng and co-workers reported the intermolecular carbofluorination of allenates **95** under visible light-promoted Au redox catalysis using Et₃N·3HF (*H*₀ >> -2.0) as the fluoride source (Scheme 1.32).⁹⁰ Key C–F bond formation occurs as an intramolecular process via HF coordination to an ester present in the substrate as shown in intermediate **97**. These cases illustrate the need to make an appropriate match between the acidity of the HF/amine solution and the reactive carbon species being captured.



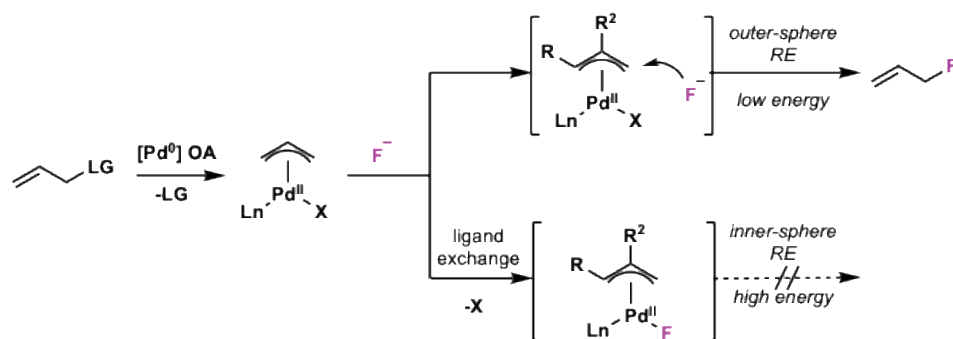
Scheme 1.32. Fluoride HBD regulation in 1,2-fluoroacylation of allenates.

Aside from fluorination reactions, HBDs have been reported in the literature to promote C(*sp*³)–F bond cleavage, creating potential for HBDs to be used as fluoride shuttles under the certain reaction conditions. In 2023, Hopkinson and co-workers reported the fluoroalkylation of mono-fluoroalkenes using activated C(*sp*³)–F bonds (benzyl and propargyl fluorides) as dual function reagents, using HBDs to enable fluoride recycling (Scheme 1.33).⁹¹ The reaction is initiated by direct cleavage of the C(*sp*³)–F bond by hexafluoroisopropanol (HFIP) generating an alkyl carbocation **101** and a hydrogen-bonded fluoride complex **100**. Regioselective trapping of carbocation **101** with the monofluoroalkene results in formation of α-F carbocation **102**, which is then trapped by the hydrogen-bonded fluoride to yield *gem*-difluorinated product **98** or **99**. The reaction proved effective not only with primary benzylic fluorides but also with secondary and tertiary propargylic fluoride substrates, while accommodating a broad scope of α-fluorostyrene coupling partners.



Scheme 1.33. HFIP-promoted fluoride shuttling from C(*sp*³)-F bonds to enable fluoroalkylation of mono-fluoroalkenes.

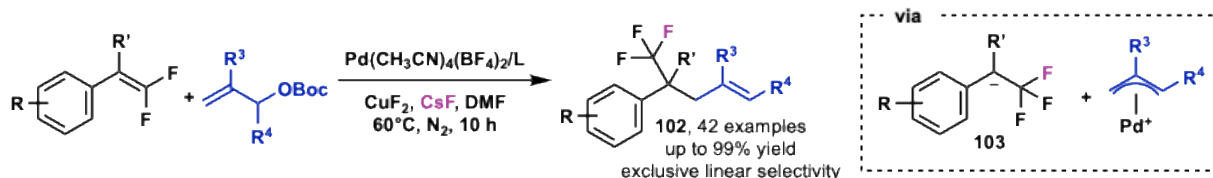
Finally, although numerous Pd(II/IV)-catalyzed carbofluorination reactions utilizing electrophilic fluorine sources have been documented, examples employing nucleophilic fluoride sources remain comparatively rare. This limited reactivity stems from the inherent reluctance of Pd^{II}-F complexes to undergo C-F bond-forming reductive elimination due to the typical endothermicity of this process. However, formal carbofluorination reactions can be facilitated through the generation of a metal- π -allyl intermediate, enabling an outer-sphere C-F bond reductive elimination (Scheme 1.34).



Scheme 1.34. Outer- vs. inner-sphere C-F bond reductive elimination on Pd^{II}-centers.

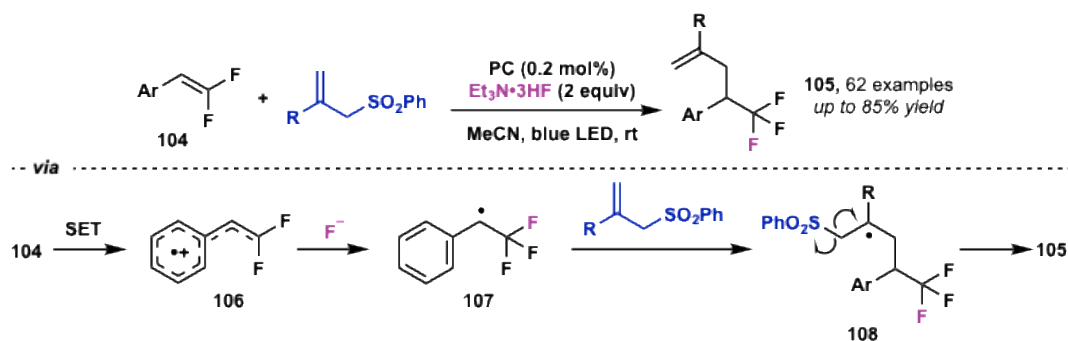
In 2016, Feng and Loh reported the Pd-catalyzed allylic alkylation of styrene-derived *gem*-difluoroalkenes with allyl *tert*-butyl carbonates and CsF resulting in fluoroallylation products **102** with exclusive linear selectivity (Scheme 1.35).⁹² Similar to previously discussed [M]-F additions across *gem*-difluoroalkenes, the addition of CsF across the alkene generates β -trifluorocarbanion species **103**, which is stabilized by electron withdrawing groups on the *gem*-difluorostyrene. This intermediate can undergo outer-sphere reductive elimination from the Pd^{II}- π allyl intermediate generated via oxidative addition of the allylic

carbonate. The addition of CuF_2 was crucial to maintain reactivity and was hypothesized to stabilize the *in situ* generated carbanion. The reaction could also be extended to ketone-derived *gem*-difluoroalkene derivatives as well as a trifluoroacetophenone-derived *gem*-difluoroalkene.



Scheme 1.35. Pd-catalyzed fluorinative allylic alkylation of *gem*-difluorostyrenes.

To access reactivity with electron-rich *gem*-difluoroalkenes, photoredox catalysis was employed by Feng and co-workers in 2019 (Scheme 1.36).⁹³ The key to gaining reactivity is that instead of going through a carbanion intermediate, the reaction goes through SET to generate *gem*-difluoroalkene radical cation **106**, which then undergoes fluoride capture generating a stabilized α - CF_3 benzylic radical **107**. Subsequent capture of the allyl sulfones (**108**) and β -fragmentation yields the desired homoallylic α - CF_3 derivatives **105**. The reaction is chemoselective for styrenyl *gem*-difluoroalkenes and tolerates the presence of allyl ether, terminal alkyne, and indole functional groups. However, substrates with electron-withdrawing substituents such as ester, cyano, nitro, and ketone groups in *para*-position of the phenyl ring gave reduced reactivity, offering a complementary method to the Pd-catalyzed allylic alkylation reaction.



Scheme 1.36. Trapping of α - CF_3 benzylic radical with masked allylic reagent.

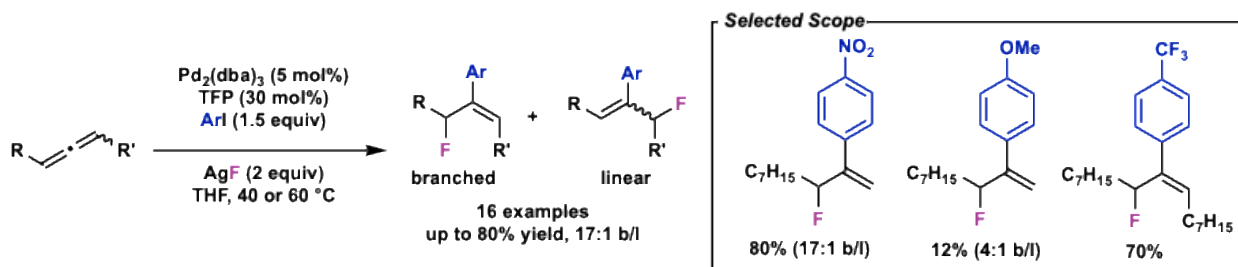
Aside from alkenes, allenes have been used as π -bond acceptors for carbofluorination reactions via the formation of a Pd- π -allyl intermediate. The first use of allenes in carbofluorination-type reactions was reported by Doyle and co-workers, who found success in a Pd-catalyzed Heck-type carbofluorination

A: P(3,5-CF₃-C₆H₄)₃ (20 mol%), DCM, rt, 24 h; used when $n = 0$ and $X = N$
B: XPhos (20 mol%), PhMe, 60 °C, 2-3 h; used when $n = 0$ and $X = O$ or S
C: PPh₃ (30 mol%), PhMe, 40 °C, 24 h; used when $n = 1, 2$

via

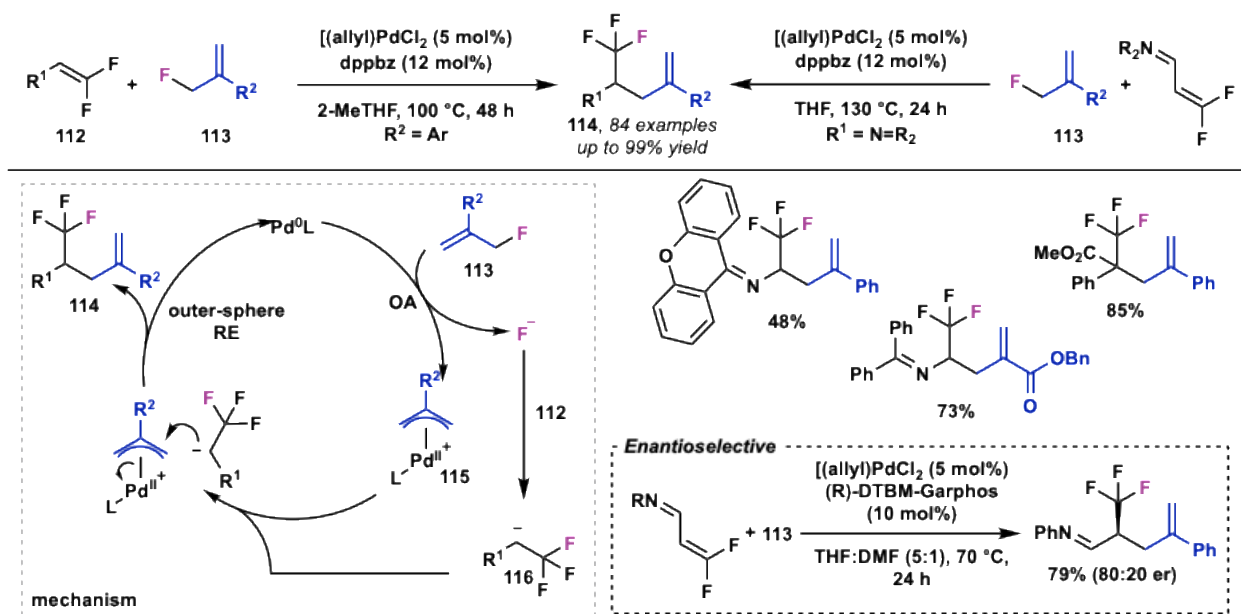
110 $\xrightarrow{\text{MI}}$ **111** $\xrightarrow[\text{outer-sphere RE}]{\text{AgF}}$ **109**

Liu and co-workers later reported an intermolecular version of this reaction that favored the formation of branched allylic fluorides, while also extending reactivity to 1-alkyl-3-aryl allenes and 1,3-diaryl allenes (Scheme 1.38).⁹⁵ The reaction is compatible with both electron-poor and electron-rich aryl iodides, though the use of electron-rich aryl iodides resulted in decreased yields and regioselectivities. Similarly, 1,3-diaryl allenes resulted in lowered regioselectivity.



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The formation metal- π -allyl species can also be leveraged in carbofluorination reactions under fluoride shuttling catalysis. In 2025, Wu and co-workers reported the Pd-catalyzed fluoroallylation of *gem*-difluoroolefins **112** with allyl fluorides **113** to yield homoallylic α -CF₃ derivatives **114** (Scheme 1.39).⁹⁶ The authors propose that initial insertion into the allylic fluoride generates a cationic Pd^{II}- π -allyl intermediate **115** with an equivalent of fluoride as the counterion. Subsequent addition of the fluoride to the *gem*-difluoroalkene generates α -CF₃ carbanion **116**, which can then undergo outer-sphere reductive elimination on the Pd^{II}- π -allyl intermediate, yielding the product and regenerating the active catalyst. Both *gem*-difluorostyrenes and *gem*-difluoroazadienes were competent alkenes in the reaction, and when *gem*-difluoroazadienes were used moderate enantiomeric induction could be achieved using chiral bisphosphine ligand (*R*)-DTBM-Garphos without sacrificing product yield (79% yield, 80:20 er).



Scheme 1.39. Pd⁰-catalyzed fluoroallylation of *gem*-difluoroolefins via fluoride shuttling catalysis.

1.4 Conclusion and research prelude

While the literature on carbofluorination reactions has expanded significantly over the past decade, several important gaps remain. Where alkene carbofluorination reactions are relatively abundant, the use of alkynes in this chemistry to access monofluoroalkenes—valuable motifs in medicinal chemistry and materials science⁹⁷—remains comparatively underdeveloped. This gap is even more pronounced in the

context of atom-economical transformations. Another underexplored direction lies in the use of dual function reagents with stronger C–F bonds (e.g. aryl fluorides, carbamoyl fluorides) in atom-economical carbofluorination reactions. Overcoming these challenges would significantly broaden the scope and synthetic utility of this transformation. This dissertation seeks to address these gaps by developing Lewis acid (LA) driven, atom-economical carbofluorination reactions. Specifically, this body of work initially focuses on coupling alkynes with carbonyl fluorides, beginning with acyl fluorides and later extending to carbamoyl fluorides, to construct a diverse array of fluorinated carbocycles and heterocycles. The latter part of the dissertation will focus on the synthesis of fluoroformates via fluorocarbonylation reactions, as well as initial studies into decarbonylative LA-catalyzed fluoride shuttling reactivity.

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2 Intramolecular Fluoroacylation Enabled by TrBF₄-Catalyzed Fluoride Recycling

2.1 Contributions

This chapter describes the TrBF₄-catalyzed fluoroacylation of alkyne- and alkene-tethered acyl fluorides to yield fluorinated 5- and 6-membered carbocycles and heterocycles. This work was done in collaboration with undergraduate student Yuriko Fujisato, who assisted with starting material preparation and characterization. Dr. Namrata Khanal, a former PhD student at the University of New Mexico, initiated the project and ran a preliminary optimization study on the synthesis of chromanone products. My contributions include the optimization of the reaction conditions, conducting the substrate scope and mechanistic studies. The contributions of each author are noted in the text and labelled as such throughout the chapter. Much of the work in this chapter was published in the journal *Organic Letters*.

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2.2 Introduction

Acyl fluorides are considered relatively stable and versatile reagents. Owing to the strong electrostatic stabilization and low polarizability of the C–F bond,² acyl fluorides exhibit greater resistance to solvolysis than comparable acyl halides, such as chlorides.³ Traditionally, acyl fluorides have been employed as acylating agents under nucleophilic acyl substitution conditions. In particular, their use in peptide synthesis is well established: derivatization of amino acids to the corresponding acyl fluorides facilitates peptide coupling through acyl C–N bond formation.^{4–7} These reactions can even be run *in vivo* where acyl fluorides can be formed via blue light-mediated photodefluorination of *m*-aminotrifluorobenzenes enabling peptide coupling reactions (Figure 2.1).^{8,9} Beyond amide formation, numerous NAS reactions have been reported, encompassing the formation of acyl C–C bonds (via Friedel-Crafts-like reactivity,^{10,11} as well as direct

coupling with organometallic reagents^{12,13} and other carbanions)^{14,15} and C–O bonds, typically with the inclusion of stoichiometric activators to increase the electrophilicity of the carbonyl carbon.^{16–18}

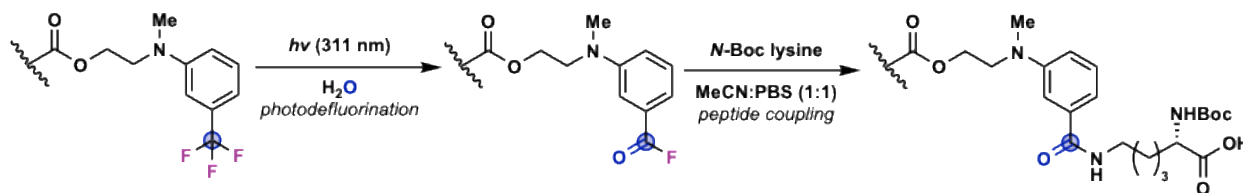


Figure 2.1. *In vivo* peptide coupling of aryl fluoride generated via photodefluorination and N-Boc protected lysine.

Recent interest has shifted toward utilizing acyl fluorides as building blocks under transition metal-catalyzed conditions, as acyl fluorides have the potential to function as four distinct types of synthetic fragments: an “RCO” source, an “R” source, an “F” source, or as a dual acyl and fluoride source, depending on the reaction conditions. Before 2023, all methods that used acyl fluorides as dual function reagents for carbofluorination reactions operated under nucleophilic catalysis—these methods were described previously in Chapter 1 (Tobisu:^{19,20} PCy_3 catalyst, Scheme 1.18; Ogoshi:²¹ CsF catalyst, Scheme 1.23, Studer:^{22,23} NHC/photocatalysis, Scheme 1.24, Scheme 1.25). This introduction instead focuses on using Lewis acids for the direct electrophilic activation of C–F bonds via fluoride abstraction. In the case of acyl fluorides, this activation yields highly reactive acylium ions which can be harnessed for carbofluorination reactions, particularly for the synthesis of monofluoroalkenes—an important and emerging class of amide bond bioisosteres.

2.2.1 Lewis Acid C–F Bond Activation

In recent years, C–F bond activation using main-group Lewis acids has emerged as a promising strategy for the selective activation of C–F bonds.²⁴ Mechanistically, LAs promote heterolytic cleavage of the C–F bond via fluoride abstraction. In contrast, transition metal-mediated C–F bond activation typically proceeds via redox pathways such as OA. This distinction is significant, as fluoride abstraction generally generates carbocation intermediates, providing versatile synthetic handles that can be intercepted by a wide range of nucleophiles. The strength of a given LA is often approximated by its fluoride ion affinity (FIA), a computational metric corresponding to the enthalpy change ($-\Delta H$) associated with fluoride binding; higher

FIA values reflect stronger Lewis acidity and greater stability of the resulting fluoride adduct. While such transformations are well established for more fluorophilic main-group LAs based on silicon, antimony, and aluminum, the resulting strong heteroatom–F bonds often act as thermodynamic sinks, sequestering the fluoride from further reactivity (e.g., AlCl_3 : 505 kJ/mol, SbF_5 : 496 kJ/mol).²⁴

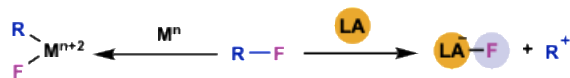


Figure 2.2. Lewis acid activation of C–F bonds vs. TM activation of Lewis acids.

Boron-based Lewis acids (boranes) offer an alternative approach. The electrophilic activation of C–F bonds is well documented for frustrated Lewis pair (FLP) systems, which are composed of a LA and a LB that cannot form a stable Lewis adduct due to steric hinderance. In these systems, the borane LA abstracts fluoride from a C–F bond, while the sterically encumbered LB captures and stabilizes the resulting carbocation through reversible coordination. This cooperative activation enables controlled reactivity of the carbon-centered intermediate.^{25–29} Outside of FLP systems, boranes can also facilitate reactions that directly exploit carbocation intermediates. A seminal example is the Friedel–Crafts alkylation of arenes with alkyl fluorides catalyzed by boron trifluoride (BF_3), as reported by Olah and co-workers (Figure 2.3).³⁰ In this transformation, BF_3 abstracts fluoride to generate a carbocation, which undergoes electrophilic aromatic substitution to form the Wheland intermediate. The resulting tetrafluoroborate anion (BF_4^-) is well documented fluoride source;³¹ however, re-aromatization of the Wheland intermediate outcompetes fluoride rebound, preventing re-incorporation of fluorine into the product.

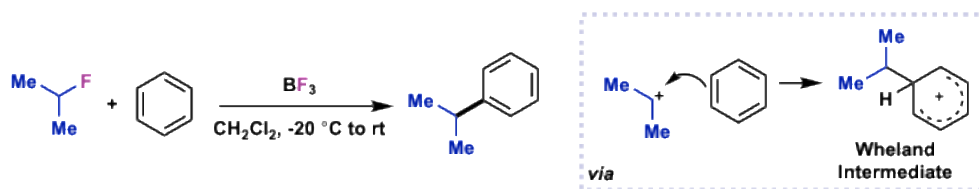


Figure 2.3. Friedel–Crafts type alkylation of arenes with alkyl fluorides and BF_3 .

In 2004, Oshima and co-workers demonstrated that unactivated secondary and tertiary alkyl fluorides can be coupled with silyl enol ethers using $\text{BF}_3 \cdot \text{OEt}_2$ as a catalyst.³² In this system, BF_3 abstracts fluoride to generate an alkyl carbocation and BF_4^- . Nucleophilic addition of the silyl enol ether affords an

oxonium intermediate, which subsequently undergoes desilylation via fluoride transfer from BF_4^- , regenerating the active catalyst and forming the product. Here, while $\text{BF}_3 \cdot \text{OEt}_2$ acts as a fluoride shuttle, the fluoride is ultimately sequestered by the formation of a strong Si–F bond. Notably, BF_3 is effective in these transformations despite its relatively modest FIA (346 kJ/mol) compared to stronger Lewis acids such as AlCl_3 (505 kJ/mol) and SbF_5 (496 kJ/mol), increasing the feasibility of fluoride rebound.

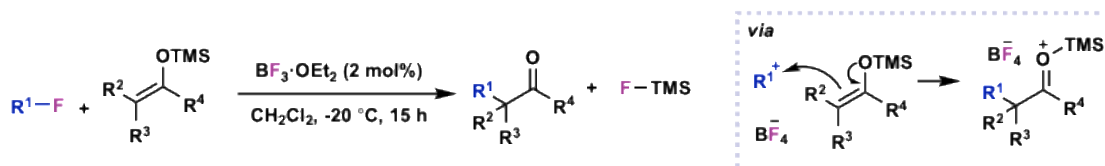


Figure 2.4. Friedel-Crafts type alkylation of arenes with alkyl fluorides and haloboranes.

Like alkyl fluorides, acyl fluorides can also be activated by Lewis acidic boranes, typically forming highly electrophilic acylium cations with a fluoroborate counterion. These acylium tetrafluoroborates were first disclosed by Seel in 1943, who found that when methylacyl fluoride was treated with BF_3 , methylacylium tetrafluoroborate was generated.³³ Building off this initial report, mechanistic studies by Olah in 1962 demonstrated that acylium salts derived from aliphatic acyl fluorides could be isolated and characterized in non-coordinating solvents at low temperatures.³⁰ These isolated acylium BF_4^- salts could then be subsequently trapped by a variety of weak nucleophiles (alcohols and amines) to form C–O and C–N bonds, forming HBF_4 as the by-product. In 1979, Smit and Caple disclosed the first example of fluoride rebound while using acylium BF_4^- salts, finding that they could serve as competent reagents for the acylfluorination of terminal acetylenes. (Figure 2.5).³⁴ When an isolated acylium BF_4^- salt derived from cyclohexyl acyl fluorides was reacted with methyl acetylene, two major fluorinated products were identified: product **118** formed via direct fluorination of the vinylic carbocation **117** and product **120** formed via a 1,5-hydride shift process from carbocation **119** prior to fluoride rebound. Under the reaction conditions, fluoride reincorporation is likely slow and thus not competitive with more facile reaction pathways, such as base-assisted elimination from the rearranged intermediate **119**.

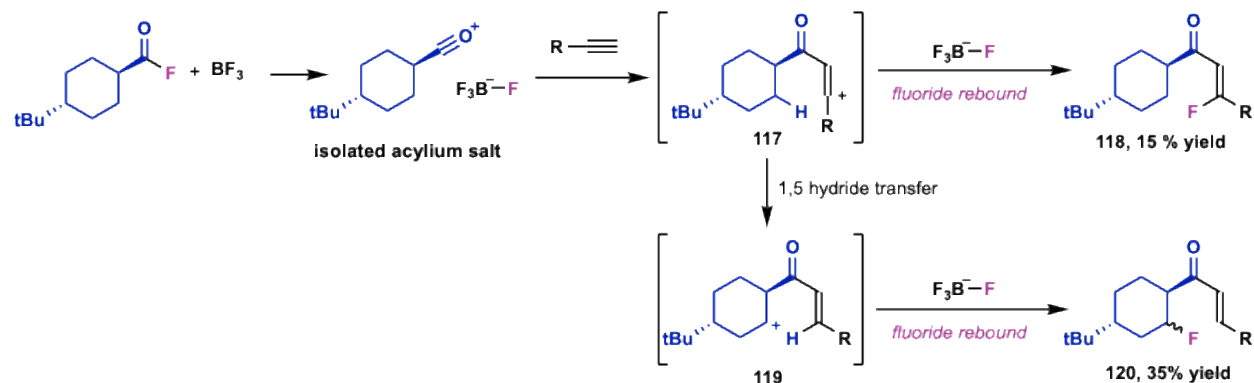


Figure 2.5 Fluorinative Friedel-Crafts acylation of acetylenes.

Equally promising is the use of BF_3 and BF_4^- salts for the formation of acylium intermediates from acyl chlorides (and to a lesser extent acyl fluorides). These acylium tetrafluoroborate salts are frequently isolable, and in scattered reports in the literature methylacylium tetrafluoroborate (**121**) has been shown to be a competent fluoroacylation reagent for alkenes (Figure 2.6). Aside from direct fluoroacylation of both endo and exo alkenes in cyclobutanes to give carbofluorination products **122** and **123**,³⁵ alkenes present in bicyclo-systems can also undergo fluoroacylation in conjunction with ring expansion. In the case of bicyclo[3.1.0]hex-2-ene **124**, a 1,3-sigma bond shift yields fluorinated cyclohexene **125**.³⁶ In the case of bicyclo[6.1.0]non-2-ene **126**, the same conditions yielded the formation of bicyclo[5.2.0]nonane **127**.³⁷

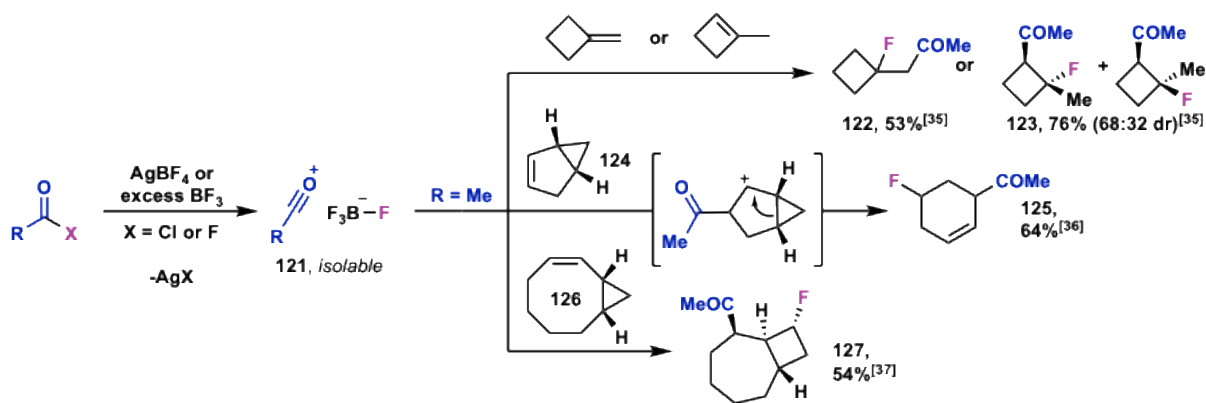


Figure 2.6. Acylium tetrafluoroborate formation and use in fluoroacylation of alkenes.

One potential challenge is that acyl fluorides are extremely reluctant to form the acylium intermediate when R is electron-poor without the presence of excess neat- BF_3 , 2 equivalents of stronger LAs, or by forming an insoluble salt (i.e., formation of AgX upon treatment of RCOX with AgBF_4).³⁰ In

general, more electron-rich acyl substituents (e.g., *t*-Bu) and less coordinating counteranions (e.g., SbF_6^-) favor acylium salt formation, whereas less electron-donating acyl substituents coupled with more coordinating counteranions (e.g., BF_4^-) favor the formation of a Lewis adduct instead, which still increases the electrophilicity of the carbonyl carbon but not to the extent that formation of an acylium ion does.

While acylium tetrafluoroborates can be generated using Lewis acidic boranes, there were no atom-economical carbofluorination reactions where this intermediate was leveraged at the time we initiated these studies. By comparison, there are a few examples of other C–F bonds that have been successfully activated catalytically using Lewis acids. The first example of $\text{BF}_3 \cdot \text{OEt}_2$ operating in this capacity was reported by Nishimoto and Yatsuda in 2020, who disclosed a BF_3 -catalyzed formal C–F bond insertion of diazoesters into secondary benzylic fluorides, affording homobenzylic fluorides with high diastereoselectivity.³⁸ The authors proposed that the reaction is initiated by abstraction of fluoride from the activated benzylic $\text{C}(sp_3)$ –F bond, forming BF_4^- and a benzylic cation. DFT calculations showed that the benzylic cation forms a van der Waals complex with the diazo ester through π – π interactions between the aryl groups (Figure 2.7), enabling an electrophilic addition followed by extrusion of N_2 to afford carbocation **128**. Formation of a thermodynamically favored contact ion pair with BF_4^- precedes diastereoselective nucleophilic fluorination of the carbocation, providing the final product and regenerating the BF_3 catalyst.

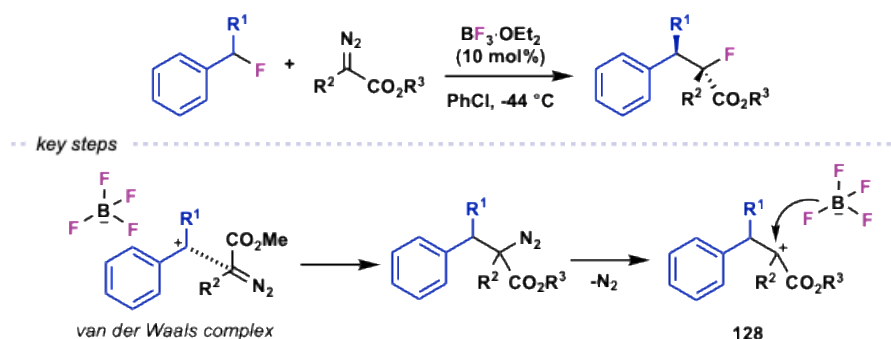


Figure 2.7 BF_3 -catalyzed diastereoselective insertion of diazoesters into secondary benzyl fluorides.

In 2022, Crimmin and co-workers showed that $\text{BF}_3 \cdot \text{OEt}_2$ could be used as a catalytic HF shuttle for the generation of *gem*-difluoroalkanes from alkynes using fluoroalkanes as an HF source (Figure 2.8).³⁹ The reaction is initiated by the dissociation of $\text{BF}_3 \cdot \text{OEt}_2$ into BF_3 and OEt_2 which can then act as a dual

reagent for the simultaneous activation of the fluoroalkane C–F and C–H bonds, generating an alkene, BF_4^- and HOEt_2^+ . HOEt_2^+ then serves to protonate the alkyne, creating a carbocation that then can be trapped by nucleophilic fluoride generated from BF_4^- . In the presence of a second equivalent of fluoroalkane, HF abstraction can occur again and the monofluoroalkene is sufficiently activated to accept another HF equivalent, leading to the formation of *gem*-difluoroalkanes.

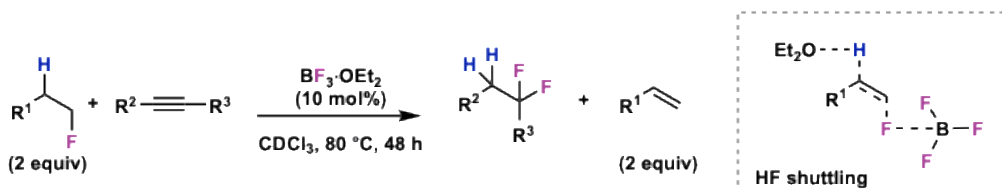


Figure 2.8. BF_3 -catalyzed HF shuttling for the generation of *gem*-difluoroalkanes from alkynes.

In both cases, the nucleophilic fluoride source is generated from BF_3 fluoride abstraction, yielding a nucleophilic BF_4^- species. However, fluoride shuttling is not limited to $\text{BF}_3/\text{BF}_4^-$ mediated systems. Triaryl-fluoroborates have been developed for the phase transfer fluorination of weaker carbon-based electrophiles using fluoride scavenged from an insoluble alkali metal salt (CsF , Figure 2.9).⁴⁰ This method highlights one of the largest advantages of emerging borane/borate fluoride shuttling strategies: namely the ability to modulate the FIA of the borane via substituent changes. Similar to tuning the reactivity of a transition metal complex via modifications to the ligands, the ability to fine tune the B–F BDE could enable the activation of stronger C–F bonds while still allowing for reversible fluoride binding.

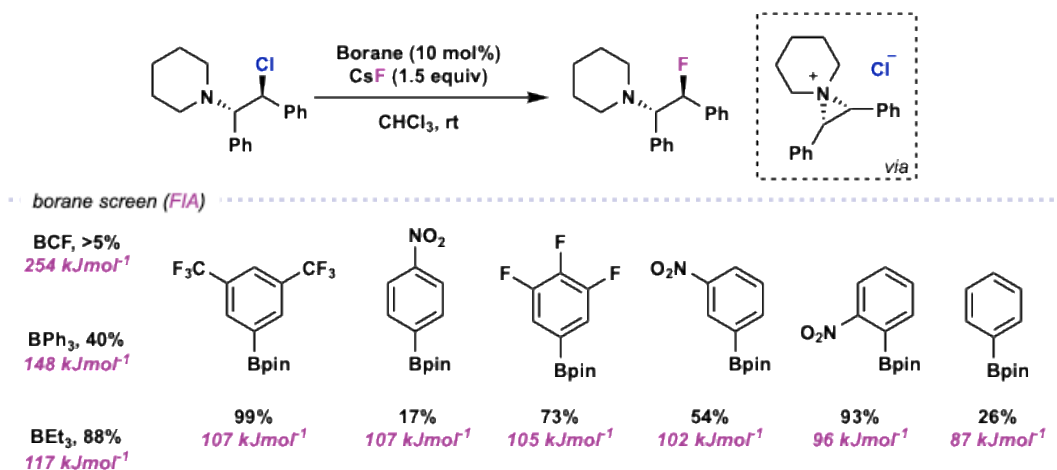
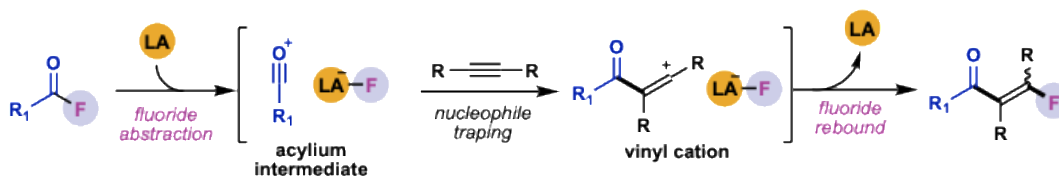


Figure 2.9. Boranes as phase transfer fluorination catalysts, solvent-corrected FIAs reported.

2.3 Methods and Motivation

Ultimately, our primary objective was to develop a general catalytic platform for atom-economical carbofluorination reactions. Guided by literature precedent demonstrating that highly electrophilic acylium intermediates can enable fluorinative capture of both alkynes and alkenes, we selected acyl fluorides as a readily accessible starting material to begin our studies.

Our proposed reaction mechanism (Scheme 2.1) begins with fluoride abstraction from the acyl fluoride by the LA catalyst to generate an acylium ion paired with a fluorinated LA species. Subsequent nucleophilic attack of the alkyne/alkene affords a carbocation intermediate, which undergoes fluoride rebound to form the C–F bond while regenerating the catalyst. Overall, this transformation constitutes an acylfluorination reaction, providing direct access to β -fluoro- α,β -unsaturated ketones from simple acyl fluorides and alkynes. Achieving this “fluoride-shuttling” reactivity requires careful tuning of the LA catalyst. Specifically, the catalyst must reversibly bind fluoride to enable turnover and suppress premature quenching of the vinyl carbocation intermediate via competing pathways such as elimination or trapping by exogenous nucleophiles.



Scheme 2.1. Proposed catalytic cycle for electrophilic Lewis acid activation of acyl fluorides for atom-economical carbofluorination reactions.

In this context, the $\text{BF}_3/\text{BF}_4^-$ manifold represents an attractive catalytic platform, as it enables both fluoride abstraction and delivery. Operating via electrophilic activation, this approach is complementary to existing strategies that rely on nucleophilic catalysis and should be amenable to expansion to other C–F bond donors. Additionally, the use of Lewis acidic boranes offers key advantages in tuning reactivity. Their fluorophilicity—and thus their effective fluoride ion affinity—can be systematically modulated, enabling activation of less electrophilic C–F bonds while expanding the range of compatible π -nucleophiles.

As an initial model, alkynes were selected as reaction partners due to their inherent nucleophilicity and because the resulting monofluoroalkene should be resistant to elimination reactions. Monofluoroalkenes have recently gained considerable interest as amide bond isosteres. Structurally, fluoroalkenes closely mimic amide linkages: for example, the C=O and C–N bond lengths in amides (1.228 Å and 1.368 Å, respectively) are comparable to the C=C and C–F bond lengths in fluoroalkenes (1.333 Å and 1.376 Å, respectively). Additionally, fluorine and oxygen possess similar van der Waals radii (1.47 Å vs 1.52 Å), enabling fluorine to partially replicate the steric profile of the carbonyl oxygen.⁴¹ Beyond geometric similarity, the fluoroalkene motif reproduces key electronic features of the amide bond. The polarized C–F bond imparts a dipole moment (~1.4 D) that, while smaller than that of an amide (~3.6 D), is sufficient to mimic aspects of amide polarity. The alkene unit enforces conformational rigidity, and the fluorine atom can function as a weak hydrogen bond acceptor in both intra- and intermolecular interactions. Notably, stereodefined fluoroalkenes can emulate distinct amide conformations: the (*Z*)-fluoroalkene corresponds to the *s*-trans amide geometry, whereas the (*E*)-fluoroalkene mimics the *s*-cis conformation.

From a physicochemical perspective, fluoroalkenes are more lipophilic than amides and exhibit enhanced resistance to enzymatic hydrolysis, making them attractive bioisosteres in medicinal chemistry. A representative example is Leu-enkephalin (Tyr¹–Gly²–Gly³–Phe⁴–Leu⁵), an endogenous ligand for the δ -opioid receptor whose therapeutic application is limited by poor receptor selectivity and rapid proteolytic degradation. Cleavage occurs readily at the Tyr¹–Gly² bond by aminopeptidases in plasma and at the Gly³–Phe⁴ bond by angiotensin-converting enzyme at the blood–brain barrier.⁴² Replacement of the Tyr¹–Gly² amide linkage with a fluoroalkene dramatically enhances stability, increasing the plasma half-life from <12 minutes to >4 hours.⁴³ This improvement is attributed to the strong σ -withdrawing effect of fluorine, which reduces the basicity of adjacent functional groups, weakens hydrogen-bonding interactions with water and enzyme active sites, and eliminates the scissile amide bond required for proteolysis. Collectively, these features result in improved pharmacokinetic properties, correspond to significantly improved *in vivo* distribution in both plasma and the central nervous system.

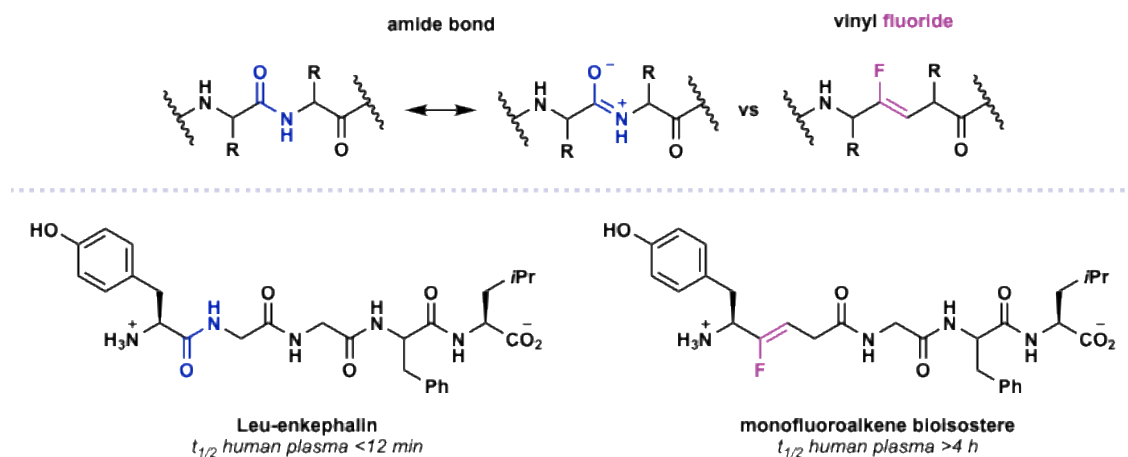


Figure 2.10. Monofluoroalkenes as amide bond isosteres.

Despite their potential utility, general and selective methods for constructing tetrasubstituted fluoroalkenes are limited, especially using carbofluorination reactions, particularly when compared to alkene carbofluorination reactions that afford alkyl fluorides. Beyond Tobisu's acylfluorination of alkynoates, examples of alkenyl fluoride formation via carbofluorination remains rare. Accordingly, the development of catalytic carbofluorination strategies that directly furnish these motifs represents a significant advance in monofluoroalkene synthesis.

To establish proof of principle, we sought to investigate alkyne-tethered aroyl fluorides in an intramolecular carbofluorination reaction catalyzed by borane LAs (Figure 2.11). Tethering the alkyne is expected to enforce regio- and stereoselectivity while enhancing the reaction rate through intramolecular reactivity. Aroyl fluorides were specifically selected to suppress undesired hydride transfer processes, such as the 1,5-hydride shift reported by Smit and Caple for cyclohexyl-derived acyl fluorides (Figure 2.5).



Figure 2.11. Initial substrate design for testing borane LA for atom-economical carbofluorination reactions.

2.4 Results and Discussion

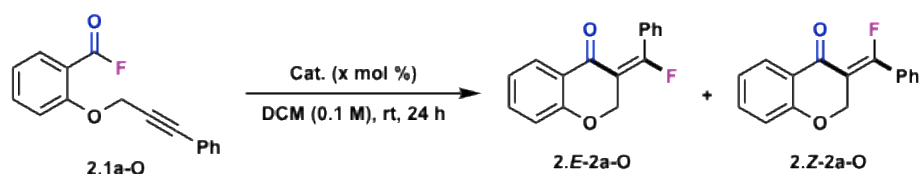
2.4.1 Initial Reaction Optimization on Chromanone System

Initial investigations were conducted using acyl fluoride **2.1a-O** as a model substrate. This standard substrate was synthesized via S_N2 reaction between phenyl propargyl mesylate and methyl salicylate, followed by NaOH promoted ester hydrolysis. The acyl fluoride was formed via a deoxyfluorination reaction using a difluorocarbene source (TFDA) and oxidant system—a modified protocol from one developed by the Le group in 2023 for the synthesis of fluorides.⁴⁴ General details on these reaction conditions can be found in the experimental section of this chapter. The reactions were performed on 0.1 mmol scale, and conversion, yield, and *E/Z*-selectivity were determined by ¹⁹F NMR spectroscopy using α,α,α -trifluorotoluene as internal standard for yield and *p*-toluenesulfonyl fluoride as standard for conversion. Quantitative ¹⁹F NMR spectroscopy was run using a single-scan experiment with a 60 second relaxation delay, which was found to be a sufficient delay to get full spin-lattice relaxation via an inversion recovery experiment.

A proof-of-concept reaction was run with 1 equiv. of BF₃·OEt₂ (Table 2.1, entry 1), which yielded the desired 3-fluoromethylene chromanone product **2.2a-O** in 70% yield with an *E/Z* ratio of 64:37 (Table 2.1, entry 1). The major isomer, which results from a formal *trans* addition, was unambiguously confirmed by single-crystal X-ray crystallography. Decreasing the loading of BF₃·OEt₂ to 10% led to an increase of yield to 80% with retention of *E/Z* stereoselectivity (Table 2.1, entry 2). Given that acyl fluorides are known to be activated by Lewis acids via a direct fluoride abstraction pathway to give a reactive acylium intermediate, we were keen to probe reactivity based on FIA. Using more Lewis acidic boranes B(3,5-CF₃-C₆H₃)₃ (FIA: 471 kJ mol⁻¹)⁴⁵ and B(C₆F₅)₃ (FIA: 448 kJ mol⁻¹)⁴⁶ resulted in a large conversion-to-yield gap and lower yields (Table 2.1, entries 3-4), while the less Lewis acidic BPh₃ (FIA: 320 kJ mol⁻¹, Table 2.1, entry 6)⁴⁶ led to no reactivity. B(4-F-C₆F₄)₃ has a FIA⁴⁷ of 376.7 kJ mol⁻¹ and when implemented as the catalyst, **2.2a-O** was formed in 75% yield which makes it a comparable catalyst to BF₃·OEt₂ (Table 2.1, entry 5).

We also screened Brønsted acid $\text{HBF}_4 \cdot \text{OEt}_2$ which gave **2.2a-O** in 76% yield (Table 2.1, entry 8). Interested in probing the competency of BF_4^- salts as catalysts, we tested $\text{Pd}(\text{MeCN})_4(\text{BF}_4)_2$ which gave **2.2a-O** in 48% yield, but also led to full conversion (Table 2.1, entry 9). Switching to an organic Lewis acid TrBF_4 led to an increase in yield to 78% (Table 2.1, entry 10). Switching the counterion to PF_6 (Table 2.1, entry 12), a worse fluoride donor, or switching the carbocation to TroBF_4 , a weaker Lewis acid (Table 2.1, entry 11), led to reduced reactivity, reinforcing the importance of both Lewis acid identity and the fluoride source are key to high turnover. Interested in probing stronger non-borane Lewis acids in this chemistry, we attempted to use Sc- and Bi-triflates in the chemistry and observed near complete conversion of the starting material but very little product formation (Table 2.1, entries 13-14).

Table 2.1. Preliminary Catalyst Screen for **2.1a-O**.



Entry*	Lewis or Brønsted Acid	Loading	Conv. (%) ^b	Yield (%) ^c	E/Z ratio	FIA (kJ mol ⁻¹) ^c
1	$\text{BF}_3 \cdot \text{OEt}_2$	1 equiv.	100	70	64:36	346.1 ⁴⁷
2	$\text{BF}_3 \cdot \text{OEt}_2$	10 mol%	100	85	64:36	346.1 ⁴⁷
3	$\text{B}(3,5\text{-CF}_3\text{Ph})_3$	10 mol%	73	27	66:34	471 ⁴⁵
4	BCF	10 mol%	84	31	64:36	448.1 ⁴⁶
6	$\text{B}(4\text{-F,Ph})_3$	10 mol%	100	75	66:34	376.7 ⁴⁶
7	BPh_3	10 mol%	0	NA	NA	320.1 ⁴⁶
8	$\text{HBF}_4 \cdot \text{OEt}_2$	10 mol%	100	76	64:36	
9	$\text{Pd}(\text{MeCN})_4(\text{BF}_4)_2$	10 mol%	100	48	64:36	
10	TrBF_4	10 mol%	100	78	66:34	599 ^{d, 48}
11	TroBF_4	10 mol%	50	17	71:29	
12	TrPF_6	10 mol%	61	10	64:36	
13	$\text{Sc}(\text{OTf})_3$	10 mol%	98	4	trace	
14	$\text{Bi}(\text{OTf})_3$	10 mol%	100	9	74:26	

*All reactions run at 0.1 mmol in a sealed 1-dram vial at rt °C for 24 h; ^a *p*-toluenesulfonyl fluoride (δ 65.8) used as internal standard; ^b α,α,α -trifluorotoluene (δ -63.72 ppm) used as internal standard; ^c note FIAs from different sources are calculated at different levels of theory; ^d calculated for Tr^+ .

Based on the preliminary catalyst screening, two divergent mechanistic pathways appear to be operative. For the borane series, a correlation is observed between fluorophilicity (as measured by FIA) and catalytic activity, suggesting that a fluoride-abstraction pathway may be relevant. In contrast, strong

cationic Lewis acids are only competent catalysts when a BF_4^- counterion is present, making it likely that While carbocations possess a low-lying empty p orbital, and are highly potent Lewis acids capable of activating electrophiles, their catalytic applications have largely been confined to carbonyl activation.^{49–56}

This discrepancy suggests an alternative mechanism, potentially driven by fluoride transfer from BF_4^- to the alkyne concurrent with nucleophilic addition to the Lewis acid–activated acyl fluoride, forming the new C–C bond. Fluoride transfer from the substrate to BF_3 would then regenerate the catalyst. Notably, this mechanism does not involve an acylium ion intermediate (Figure 2.12).

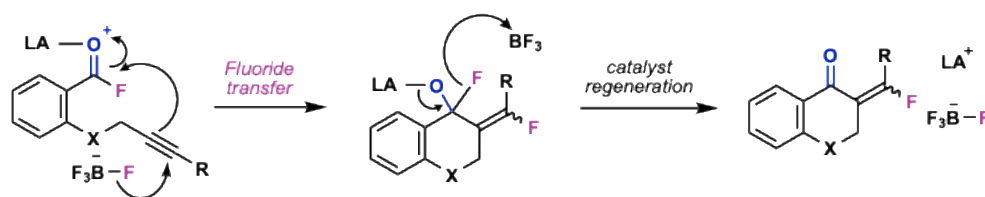


Figure 2.12. Possible divergent mechanism for carbocation- BF_4 salt fluoroacylation reaction.

2.4.2 Investigation into Chromanone Stereoselectivity

Given that the observed stereoselectivity remained consistent across all catalysts tested, with a slight increase in selectivity at lower conversions, we sought to determine whether the product stereoselectivity resulted from *in situ* isomerization of **2.2a-O** or if the *E/Z* ratio was consistent throughout the entire reaction profile. To probe this, substrate **2.1a-O** was subjected at NMR-scale to both $\text{BF}_3 \cdot \text{OEt}_2$ - and TrBF_4 -catalyzed reaction conditions, and the reaction progress was monitored by ^{19}F NMR spectroscopy (see Supplemental Information for experimental details). When $\text{BF}_3 \cdot \text{OEt}_2$ was used as catalyst (Figure 2.13), the product distribution at reaction onset is 75:25 *E/Z* – marginally higher than the *E/Z* ratio observed at the end of our reactions. The TrBF_4 reaction, which is slower all together, initially produces only the *E*-isomer, with the formation of the *Z*-isomer occurring slowly at higher conversions (Figure 2.14). In both cases, an induction period is observed, possibly due to an initial activation step needed to gain the active catalyst.

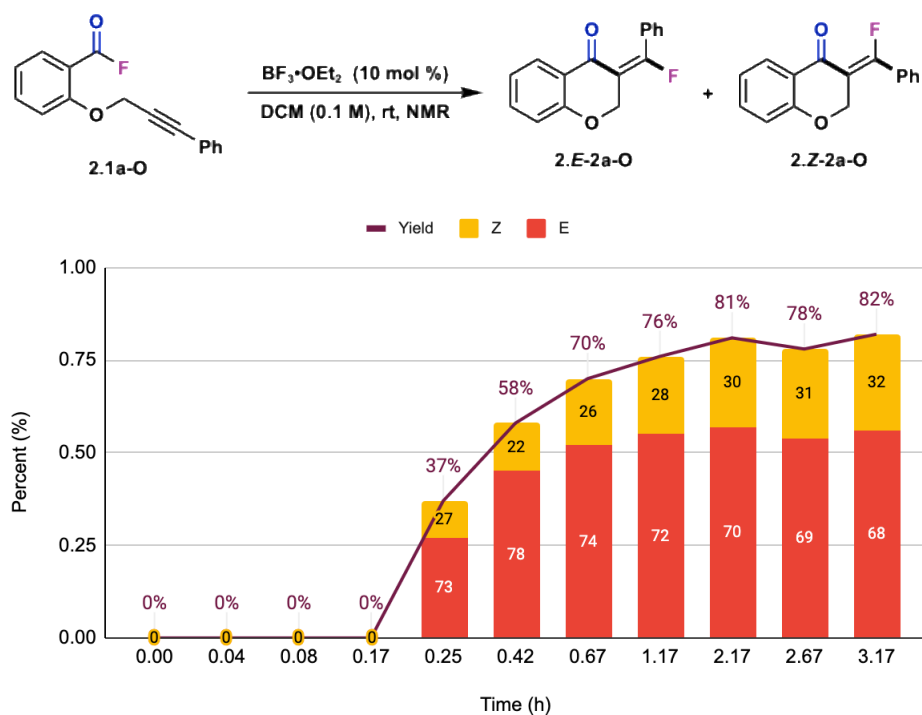


Figure 2.13. E/Z ratio for **2.2a-O** product over the course of the reaction time for the $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed reaction, conversion excluded.

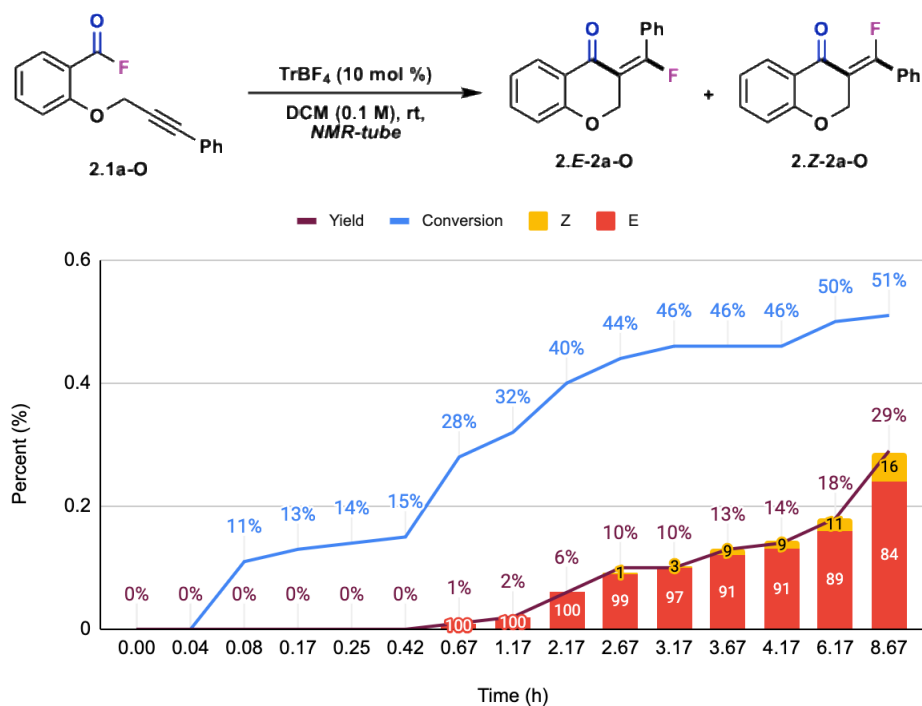


Figure 2.14. E/Z ratio for **2.2a-O** product over the course of the reaction time for the TrBF_4 -catalyzed reaction.

Intrigued by these results we subjected pure **2.E-2a-O** to the TrBF₄-catalyzed reaction conditions present in Table 2.1. We observed isomerization of the product to the 67:33 *E/Z* ratio obtained when **2.1a-O** is subjected to the same conditions, making it likely that under the TrBF₄ reaction conditions, the product **2.E-2a-O** can isomerize *in situ* to a thermodynamic mixture. Interested in looking at potential ways to mitigate this isomerization, we reevaluated the reaction conditions using TrBF₄ as the catalyst.

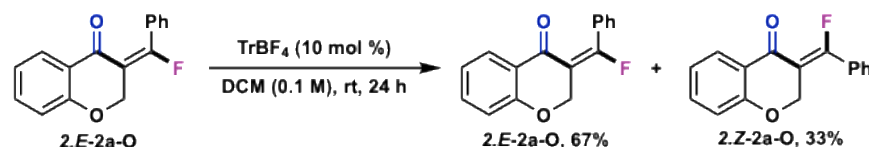
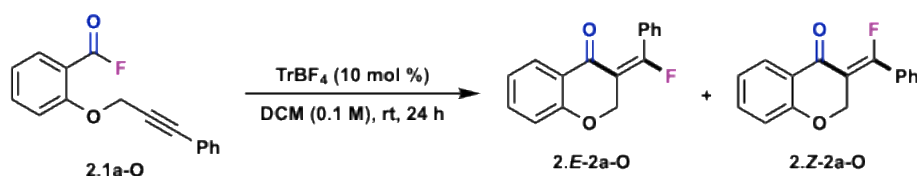


Figure 2.15. Isomerization of **2.E-2a-O** under TrBF₄ catalyzed conditions.

Decreasing the catalyst loading of TrBF₄ to 5 mol% increased the yield to 95%, with no significant change in the *E/Z* ratio (Table 2.2, entry 2). Raising the reaction temperature to 40 °C afforded near-quantitative yields but similarly showed no substantial impact on selectivity. When the 40 °C reaction was quenched after 0.5 h, a marginally higher initial *E/Z* ratio of 71:29 was observed. Further temperature increases required switching the solvent to 1,2-dichloroethane (DCE). A reaction conducted at 50 °C for 0.5 h in DCE provided both higher yields and an improved *E/Z* ratio of 78:22. Increasing the temperature to 75 °C under the same reaction time gave comparable yields with a further slight enhancement in selectivity to 82:18. Finally, extending the 75 °C reaction to 1 h resulted in a yield of 88% and a marginally higher *E/Z* ratio of 85:15. The increase in *E/Z* selectivity at higher temperature, combined with the observation that selectivity is highest at low conversion, and that the isolated product undergoes catalyst-mediated isomerization to a distinct thermodynamic ratio, suggests that alkene stereoselectivity is under kinetic control during initial product formation. Subsequent catalyst-promoted isomerization is a secondary process that erodes the kinetic product distribution.

Table 2.2. TrBF₄ conditions screen for **2.1a-O**.



Entry*	Deviation from Standard Conditions	Conv. (%)	Yield (%)	E/Z ratio
1	none	100	78	66:34
2	5 mol%	98	95	65:35
3	40 °C	100	96	65:35
4	40 °C, 0.5 h	100	42	71:29
5	50 °C, DCE (0.1M), 0.5 h	100	85	78:22
6	75 °C, DCE (0.1M), 0.5 h	98	82	82:18
7	75 °C, DCE (0.1M) 1 h	100	88 (84) ^a	85:15

*All reactions run at 0.1 mmol in NMR tubes; ¹⁹F NMR analysis using α,α,α -trifluorotoluene as internal standard for yield of **2.2a** and *p*-toluenesulfonyl fluoride as standard for conversion of **2.1a**; a. Isolated yield.

2.4.3 Re-evaluation of the Substrate Scope

At this point in our reaction development, Tobisu and co-workers reported a dual Rh^I/BF₄ catalyst system for the intramolecular fluoroacylation of alkene-tethered acyl fluorides **129** (Figure 2.16).⁵⁷ The reaction is mechanistically different from the previously reported atom-economic acylfluorination reactions given that C–F bond activation occurs via fluoride abstraction by a Lewis acidic Rh^I cation, forming an acylium ion and a neutral Rh–F complex, instead of an oxidative addition complex. This circumvents the need for the transition metal catalyst to be proficient at both oxidative addition and reductive elimination. This acylium cation **131** is intercepted by the pendant alkene to generate a tertiary carbocation **132** that can then undergo nucleophilic trapping by BF₄[–] to yield **130** as the carbofluorination product. The resulting BF₃ is sequestered via fluoride abstraction from the neutral Rh–F complex to regenerate the starting Rh^IBF₄ catalyst. The reaction was not limited to alkenes as coupling partners, as employing alkyne-tethered acyl fluorides **133** under slightly modified reaction conditions yielded 6-exo cyclization product **134** with substrate-controlled *E/Z* selectivity.

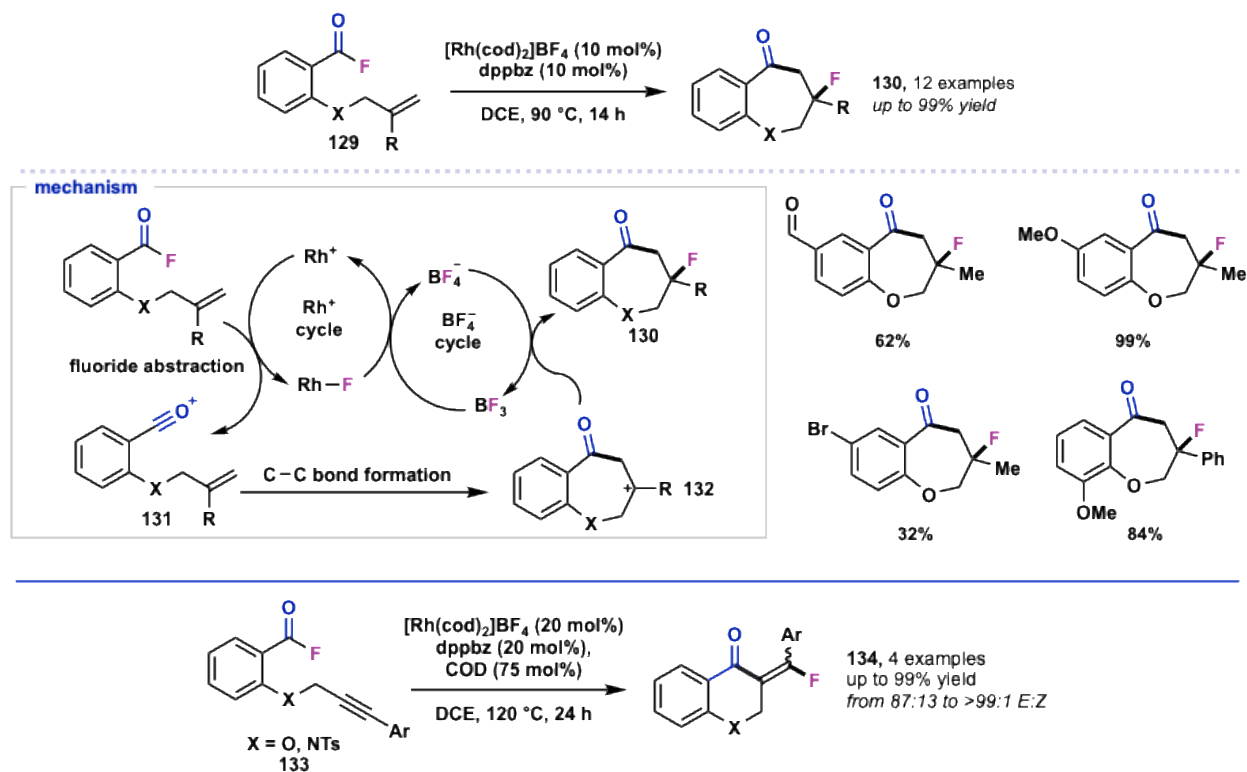


Figure 2.16. 1,2-Fluoroacylation of alkene-tethered acyl fluorides **129** and alkyne tethered acyl fluorides **130** under Rh^I/BF₄-catalysis.

This sequestering of BF₃ by the formation of BF₄⁻ at the end of the reaction was key to product formation. When BF₃·OEt₂ was used as a catalyst for the reaction, full conversion of the starting material was observed, but the only product formed was the formal HF-elimination product **135** instead of the desired product. The same product can be observed when product **130a** was resubjected to even catalytic amounts of BF₃·OEt₂, leading the authors to hypothesize that the product likely arises via fluoride abstraction from **130a** by BF₃ at the end of the reaction.

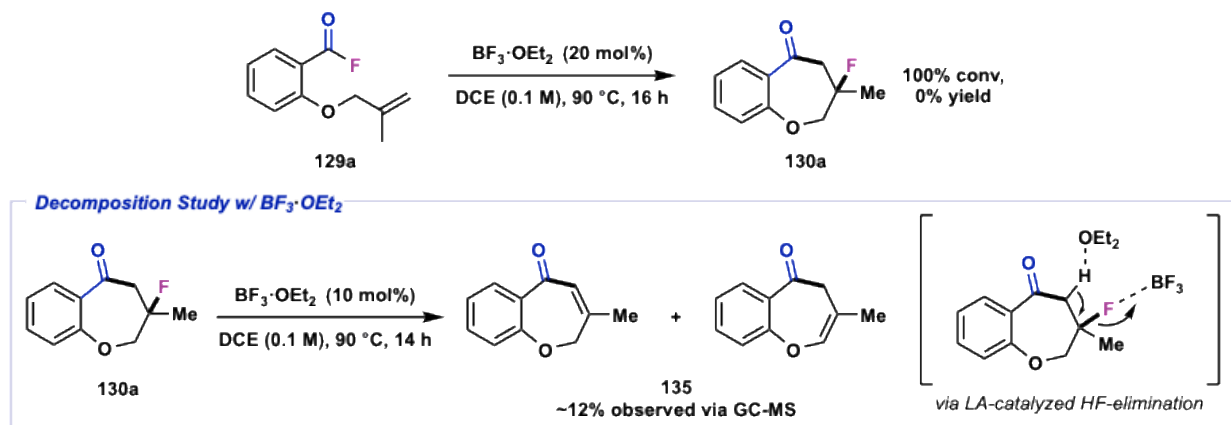
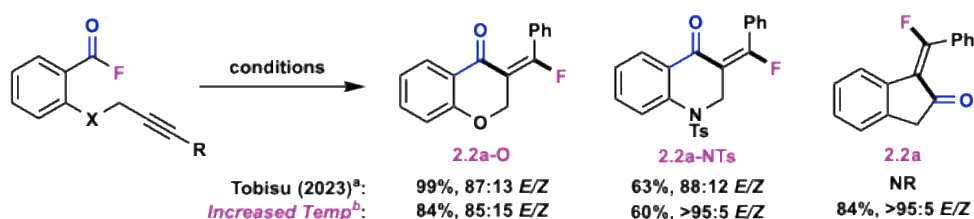


Figure 2.17. Attempts at using $\text{BF}_3 \cdot \text{OEt}_2$ as catalyst and decomposition of **130a** in the presence of $\text{BF}_3 \cdot \text{OEt}_2$.

With this information in hand, we were interested in comparing the reaction conditions that we had developed to the $\text{Rh}^{\text{I}}/\text{BF}_4$ -catalyzed reaction conditions developed by Tobisu. Using the increased temperature conditions reported in Table 2.2, we see comparable results. The increased *E*-selectivity for **2.2a-O** is roughly the same as the *E*-selectivity reported under the $\text{Rh}^{\text{I}}/\text{BF}_4$ catalyzed conditions (Scheme 2.2), though at a slightly decreased yield (88% vs. 99%). Similar yields are observed for amine containing **2.2a-NTs** between Tobisu's report and our developed TrBF_4 conditions, but an increase in *E/Z* selectivity is observed using our method (88:12 to >95:5 *E/Z*). Given that a handful of the chromanone products had been published using $\text{Rh}^{\text{I}}/\text{BF}_4$ catalysis, we turned our focus to the synthesis of the indanone products **2.2** using Lewis acid catalysis at higher temperature conditions.



Scheme 2.2. Comparison of conditions for intramolecular carbofluorination of alkynes; a. TrBF_4 (10 mol%), 40 °C in DCM (0.1 M), 24 h; b. $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (20 mol%), *dppbz* (20 mol%), (COD 75 mol%), DCE, 120 °C, 16 h; c. TrBF_4 (10 mol%), 75 °C in DCE (0.1 M), 1 h.

At present, the use of acyl fluorides as electrophilic coupling partners, in both conventional defluorinative reactions and as dual functional reagents in reactions remains largely confined to aromatic or otherwise activated derivatives. In contrast, aliphatic acyl fluorides, like the benzyl fluoride present in the 1-methylene-indan-2-ones starting material (**2.1**), exhibit low reactivity and poor efficiency. These limitations primarily arise from the instability of aliphatic acyl fluorides, which are harder to access synthetically, coupled with the prevalence of competing side reactions making selectivity difficult to achieve. Ultimately with this information in hand, we were motivated to pursue a Lewis acid-catalyzed alternative, in light of the cost and handling challenges associated with rhodium.⁵⁹

The work presented herein identified tropylium tetrafluoroborate (TrBF_4), a low-cost, carbon-based Lewis acid, as an alternative catalyst capable of promoting atom-economical carbofluorination reaction of

alkyne-tethered acyl fluorides. This system achieves comparable reactivity under milder conditions while reducing the overall reaction cost by more than 66% relative to the Tobisu method. Moreover, the reaction is effective for the activation of aliphatic, benzylic, and aromatic acyl fluorides, enabling access to previously unknown 3-fluoromethylene indan-2-ones **2.2**.

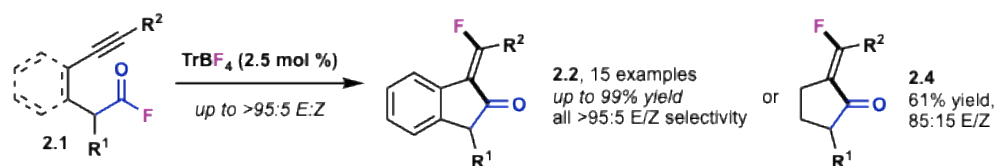


Figure 2.18. TrBF_4 -catalyzed fluoroacylation reaction of alkyne-tethered acyl fluorides.

The synthesis of functionalized 1-methylene-indan-2-ones is sparsely documented, with the most common approach relying on aldol condensations performed under strongly acidic conditions.^{60,61} In 2008, van de Weghe and co-workers reported a multistep route to the 1-methylene indan-2-one core featuring a tandem Pd-catalyzed carbocyclization/Suzuki–Miyaura sequence of *ortho*-alkylalkynyl iodobenzenes **136** with boronic acids. Subsequent desilylation and oxidation of masked alcohol **137** yields the indan-2-one **138**. Extension of the strategy to access fluorinated derivatives under Pd-catalysis would require the use of costly and functional-group-intolerant electrophilic fluorinating reagents. Consequently, efficient synthetic entry to 1-(fluoromethylene)indan-2-ones remains elusive.

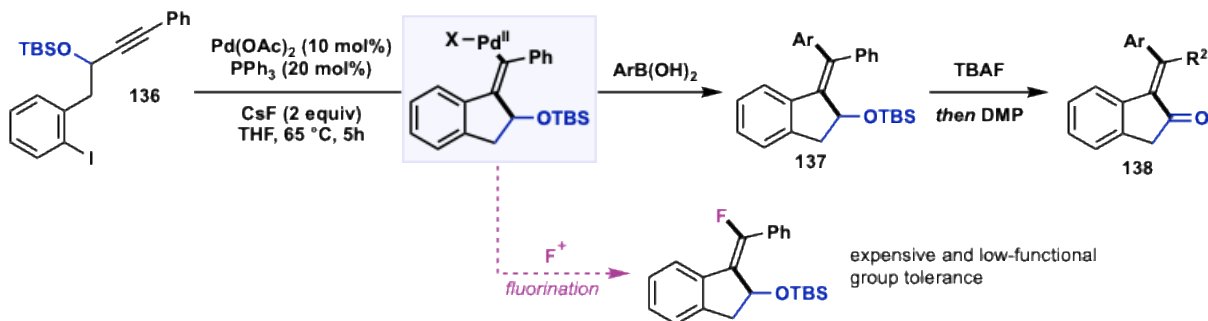


Figure 2.19. Pd-catalyzed carbocyclization/Suzuki–Miyaura sequence to construct 1-methylene indan-2-ones.

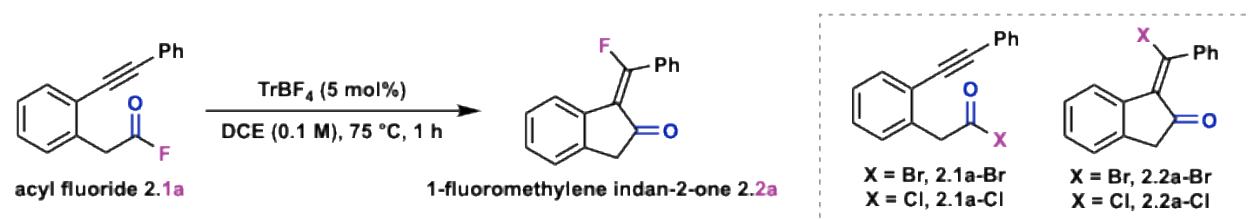
2.4.4 Reaction Optimization on Indanone System

Using the higher temperature conditions, an optimization of the intramolecular fluoroacylation reaction was carried out using **2.1a** as a model substrate. This standard substrate was synthesized via a Sonogashira

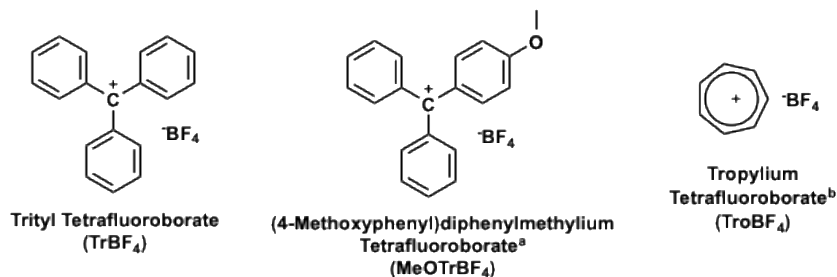
reaction between methyl (2-iodophenyl)acetate and phenylacetylene, followed by the same saponification and deoxyfluorination sequence established previously.⁴⁴

We began our investigation of the fluoroacylation of **2.1a** by decreasing the catalyst loading of TrBF₄ to 5 mol% (Table 2., entry 2).¹⁶ We were pleased to find **2.2a** was formed in 84% yield and with excellent *E*-selectivity (>95:5 *E/Z*). Two carbon-based Lewis acids with a BF₄[−] counterion were screened at this lowered catalyst loading (Table 2., entries 3 and 4), and the yields correlated to the Lewis acidity of the carbocation with TrBF₄ being both the most Lewis acidic and the most reactive (TrBF₄ > MeOTrBF₄ > TroBF₄).⁴⁸ Switching the counterion from BF₄[−] to PF₆[−] (Table 2., entry 5) or BARF₂₀[−] (Table 2., entry 6) led to cessation of catalytic activity, showing the importance of both the fluoride source and the Lewis acid identity for the fluoroacylation reaction. Branching out from carbon-based cationic species, Pd(MeCN)₄BF₄ (Table 2., entry 7) provided **2a** in 45% yield, whereas AgBF₄ (Table 2.1, entry 8) only gave 3% of the desired product. Using Brønsted acidic HBF₄ the reaction proceeded with a decreased yield of 60% yield. Other Brønsted acids and fluoride sources were unable to promote the chemistry (Table 2., entries 10-12).⁶² BF₃·OEt₂ (Table 2., entry 13) gave a similar yield to the use of TrBF₄. Other boron-trihalide species (Table 2., entries 14-15) gave decreased yield in comparison to BF₃·OEt₂ and led to halogen exchange products **2.1a-Br**, **2.2a-Br**, **2.1a-Cl**, and **2.2a-Cl**. Highly Lewis acidic B(C₆F₅)₃ provided **2.2a** in diminished yield, likely due to irreversible fluoride abstraction and subsequent side reactions (Table 2., entry 4). Applying the Rh^I/BF₄ conditions developed by Tobisu provided **2.2a** in only 19% yield, illustrating the efficiency of our method to access the inda-2-one motif (Table 2., entry 17) and revealing an inefficiency in the activation of aliphatic acyl fluorides under their developed conditions.

Table 2.2. Optimization of **2.2a** synthesis



Entry*	Deviation from Standard Conditions	Conv. (%)	Yield (%)
1	10 mol% TrBF ₄	87	84
2	none	97	84
3	TroBF ₄ ^b	18	0
4	MeOTrBF ₄ ^a	85	70
5	TrPF ₆	35	4
6	TrBARF ₂₀ ^c	18	0
7	Pd(MeCN) ₄ (BF ₄) ₂	90	71
8	AgBF ₄	63	3
9	HBF ₄ ·OEt ₂	100	60
10	TREAT·HF	45	0
11	Pyr·(HF) _x	46	0
12	TBAF	35	0
13	BF ₃ ·OEt ₂	100	78
14	BCl ₃ ^d	100	63
15	BBr ₃ ^e	100	67
16	B(C ₆ F ₅) ₃	65	7
17	[Rh(COD) ₂]BF ₄ , dppbz, COD ^f	31	19

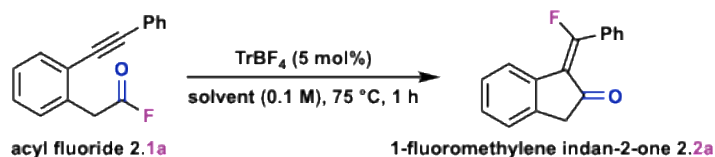


*All reactions run at 0.1 mmol in a sealed 1-dram vial at 75 °C for 1 h, yield, *E/Z* selectivity for all >95:5 *E/Z*; ¹⁹F NMR analysis using *α,α,α*-trifluorotoluene as internal standard for yield of **2.2a** and *p*-toluene sulfonyl fluoride as standard for conversion of **2.1a**; c. Trityl tetrakis(pentafluorophenyl)borate, (TrBARF₂₀); d. **2.2a-Cl** formed in 7% yield (>95:5 *E/Z*), **2.1a-Cl** detected by GC-MS; e. **2.2a-Br** formed in 6% yield (>95:5 *E/Z*), **2.1a-Br** detected by GC-MS; f. Reaction conditions: [Rh(cod)₂]BF₄, dppbz (20 mol%), COD (0.75 equiv.), DCE (0.2 M), in a sealed 1-dram vial at 120 °C for 24 h; g. Isolated yield.

Although TrBF₄ and BF₃·OEt₂ gave comparable yields, our interest in accessing the tertiary alkyl fluoride products **130** reported by Tobisu led us to not to pursue BF₃·OEt₂ further. Having identified TrBF₄ as the most efficient catalyst, we ran an additional screen of different solvents (Table 2.3). Doping DCE

with HFIP as H-bond solvent donor led to near complete cessation of reactivity and similar results were observed with toluene as the solvent (Table 2.3, entries 2-3). The reaction could be run in chloroform with retention of yield (Table 2.3, entry 4) but we opted to continue using DCE due to its higher boiling point.

Table 2.3. Solvent Screen for **2.1a**

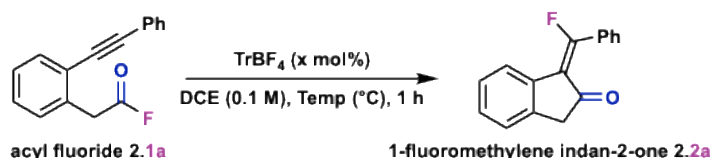


Entry*	Solvent	Conv. (%)	Yield (%)
1	DCE	97	84
2	(1:1) DCE/HFIP	27	0
3	PhMe	45	0
4	CHCl ₃	100	85

*All reactions run at 0.1 mmol in a sealed 1-dram vial at 75 °C for 1 h, yield, *E/Z* selectivity for all >95:5 *E/Z*; ¹⁹F NMR analysis using α,α,α -trifluorotoluene as internal standard for yield of **2.2a** and *p*-toluene sulfonyl fluoride as standard for conversion of **2.1a**;

Lowering the temperature of the reaction to 60 °C reduced the yield of the reaction to 46% (Table 2.4, entry 1) while decreasing the catalyst loading to 2.5 mol % at 75 °C, increased the yield of **2.2a** to 99% by ¹⁹F NMR (97% isolated, Table 2.4, entry 3). However, decreasing the catalyst loading to 1 mol % led to incomplete conversion of **2.1a** (Table 2.4, entry 4).

Table 2.4. Temperature and Catalyst Loading Screen for **2.1a**

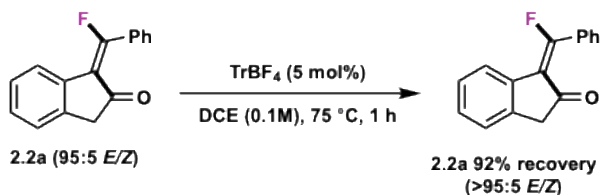


Entry*	Temp (°C)	x (mol%)	Conv. (%)	Yield (%)
1	60	5	77	46
2	75	5	97	84
3	75	2.5	100	>99 (97) ^a
4	75	1	92	82

*All reactions run at 0.1 mmol in a sealed 1-dram vial at indicated temperature for 1 h, yield, *E/Z* selectivity for all >95:5 *E/Z*; ¹⁹F NMR analysis using α,α,α -trifluorotoluene as internal standard for yield of **2.2a** and *p*-toluene sulfonyl fluoride as standard for conversion of **2.1a**; a. Isolated yield.

To understand why the observed yields were lower at higher catalyst loadings, we resubjected purified **2.2a** to reaction conditions with 5% TrBF₄. Clean recovery of **2.2a** in 92% (>95:5 *E/Z*) occurred after standard work-up involving filtration of the crude material through a silica plug (Scheme 2.). During

the filtration, a considerable amount of red residue was left at the top of the silica plug, likely the result of a polar Lewis acid–base adduct between the catalyst and product formed at the end of the reaction. While this would account for ~2.5% of the yield difference between the 5 mol% loading conditions and the 2.5 mol% conditions, there still is a mass balance of ~12% that is unaccounted for between the two reactions.

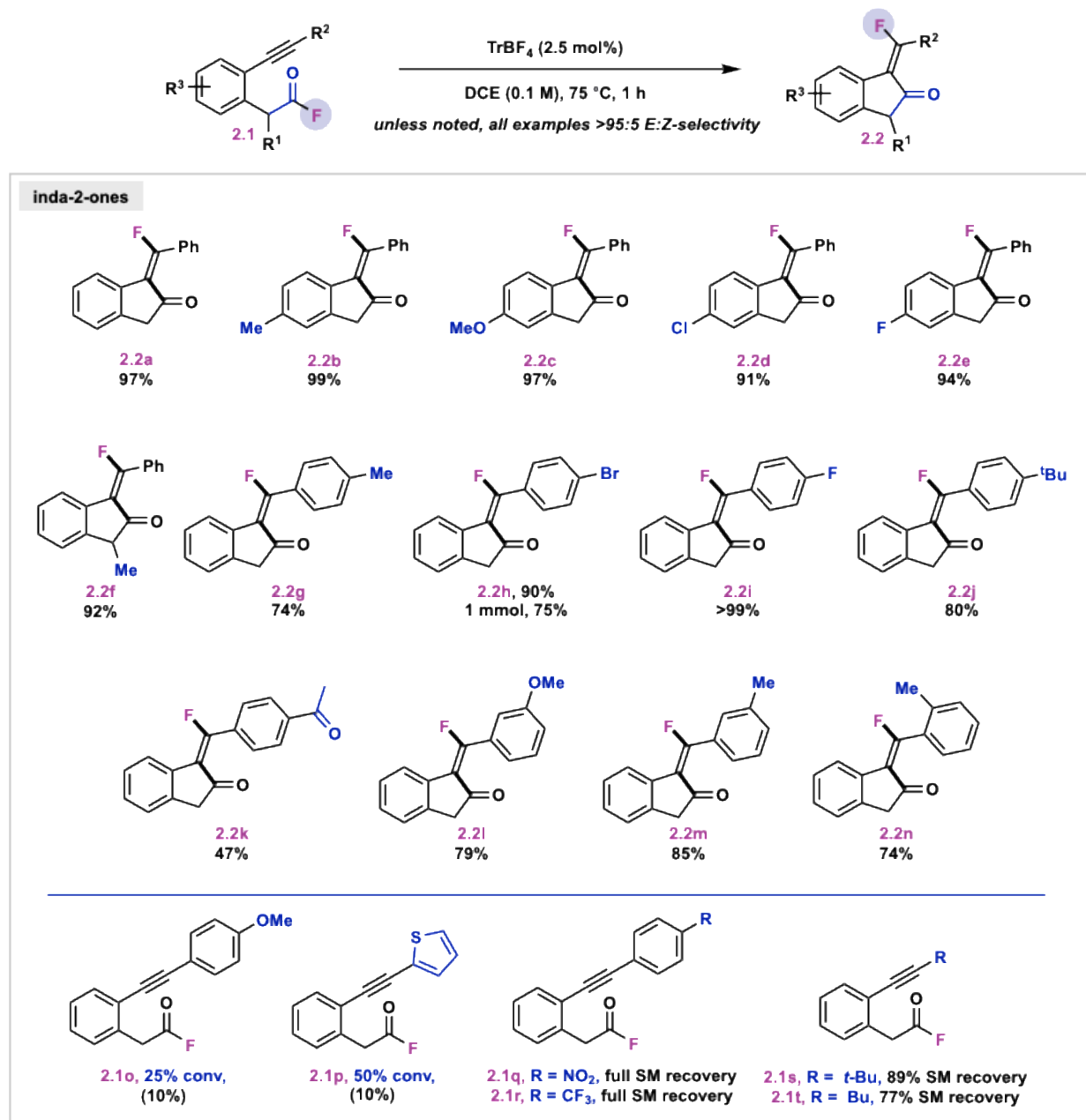


Scheme 2.2. Isomerization study of **2.2a** under reaction conditions.

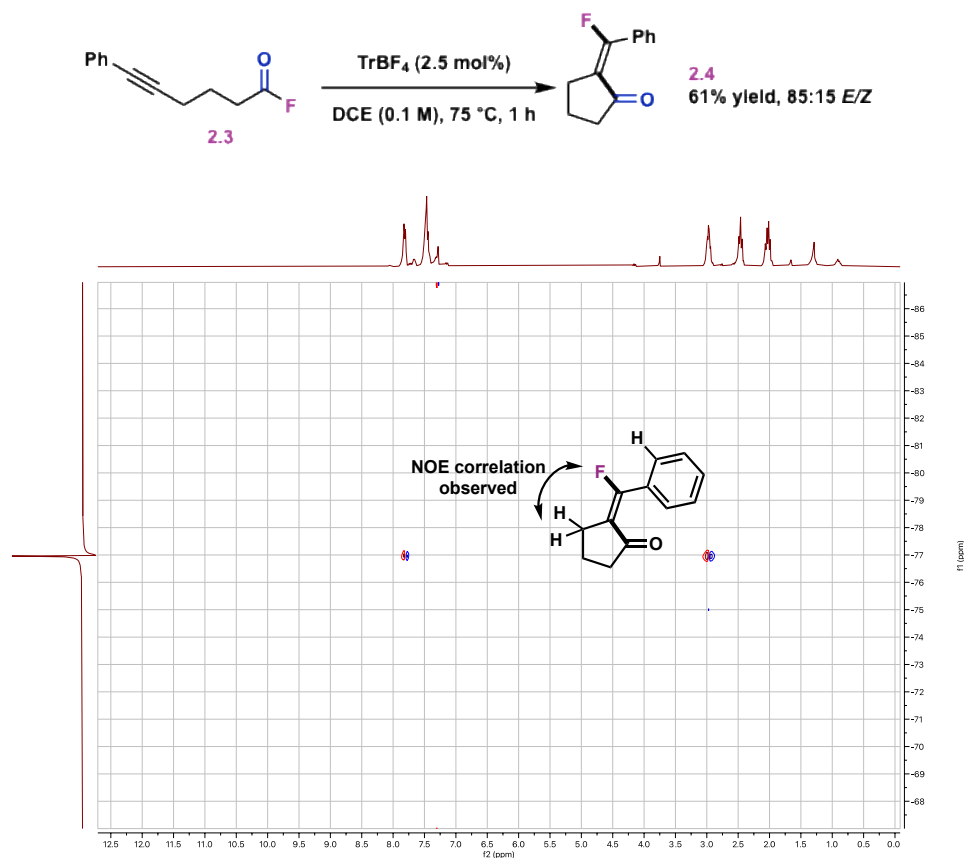
2.4.5 Substrate Scope

With the optimized conditions in hand, we turned to probe the functional group tolerance of the method. In all cases, the desired 3-fluoromethylene indan-2-one products **2.2** were formed with >95:5 *E/Z*-selectivity as determined by ¹⁹F NMR spectroscopy of the crude reaction mixture (Scheme 2.3). The major isomer was unambiguously confirmed by obtaining a single-crystal X-ray structure of **2.2c** and all other substrates were assigned by observation of a ³J_{C-F} coupling constant of ~15 Hz in the ¹³C NMR of the products, which only occurs for the *E*-isomer. The method was amenable to electron-rich groups (**2.2b-c**) as well as halogens (**2.2d-e**) on the aromatic backbone. Substitution at the benzylic position did not hinder the reaction, providing **2.2f** in excellent yield. Modification of the distal aryl ring with mildly electron-donating groups (**2.2g**, **2.2j**, **2.2l**) was well tolerated. Inductively withdrawing halogen atoms at the *para* positions (**2.2h-i**) and a *meta*-OMe group (**2.2l**) provided indanones **2.2** in good yields. However, the presence of a deactivating Lewis basic ketone moiety (**2.2k**) led to reduced reactivity, likely due to competitive binding with the catalyst. Attempts at using electron-rich **2.1o** and **2.1p** led to minimal product formation, while no product formation occurred with aliphatic alkynes **2.1s** and **2.1t**. Use of substrates with distal aryl rings substituted with strongly electron-withdrawing groups at the *para* position (NO₂, **2.1q** and CF₃, **2.1r**) led to full starting material recovery, though it should be noted that nitro-containing **2.1q** was insoluble under the reaction conditions. Additionally, the synthesis of **2.2h** could be

achieved on a 1 mmol scale, providing the product with 75% isolated yield. Cyclopentanone **2.4** could be accessed using this method with 85:15 *E/Z* selectivity, which was confirmed using ^{19}F - ^1H 2D NMR HOSEY experiments (Scheme 2.4).

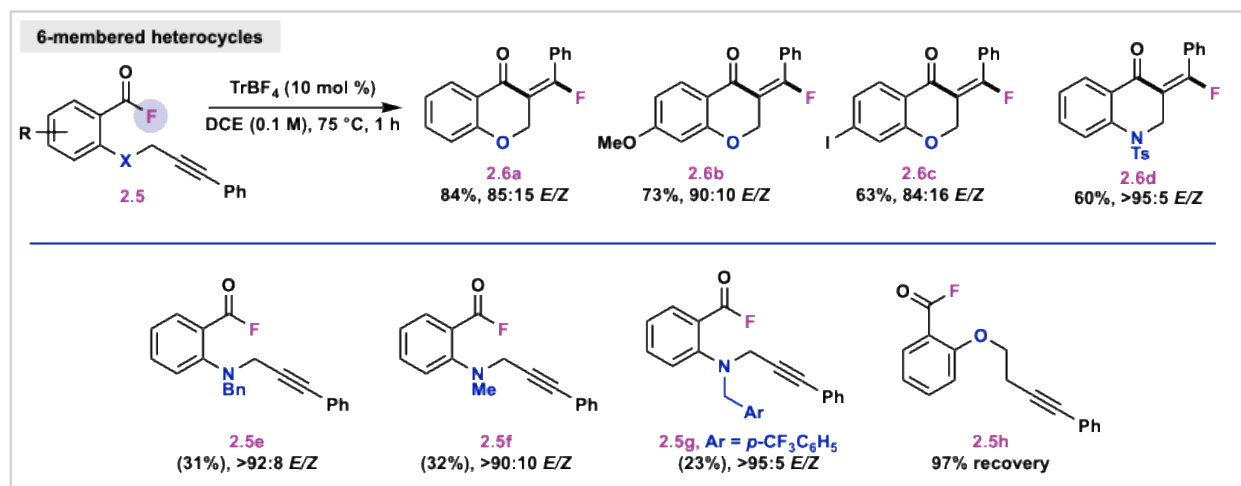


Scheme 2.3. Substrate scope for alkyne tethered acyl fluorides **2.1a** under TrBF₄-catalyzed intramolecular fluoroacylation conditions.



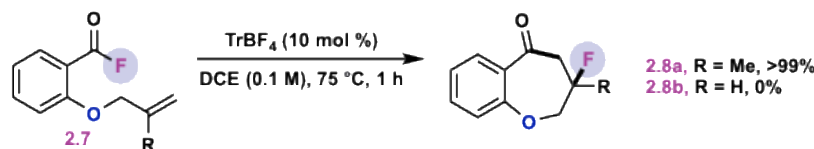
Scheme 2.4. Formation of cyclopentanone **2.4** under TrBF₄-catalyzed intramolecular fluoroacylation conditions and assignment of selectivity via positive ¹⁹F-¹H 2D NMR HOSEY.

Interested in further probing the compatibility of our developed method in the synthesis of six-membered heterocycles **6**, previously accessed by Tobisu under Rh^I/BF₄ catalysis, we tested additional aroyl fluoride-tethered alkynes **2.5** (Scheme 2.5). For those bearing ether linkers, substitution at the 5-position with either an electron-donating OMe group (**2.6b**) or electron-withdrawing iodine atom (**2.6c**) were tolerated, with slightly higher selectivity observed for the former. Attempts at forming a seven-membered heterocycle with compound **2.5h** led to almost complete starting material recovery. To probe the extent the substituents on the amine linker played in the stereochemical outcome of the reaction, we also tested substrates where the amine was substituted with a Bn (**2.5e**), Me (**2.5f**), and an electron-poor benzyl (**2.5g**). These substrates all resulted in lower yields and unstable products. Overall, higher selectivity was observed with the amine-containing substrates regardless of yield.



Scheme 2.5. Formation of six-membered heterocycles **2.6** under TrBF_4 -catalyzed intramolecular fluoroacylation conditions.

Lastly, we were pleased to find that our conditions were also amenable to the fluoroacylation of 1,1-disubstituted alkene **2.7a**, forming tertiary fluoride **2.8a** in quantitative yield (Scheme 2.6). Attempts at using the terminal alkene **2.7b** led to full consumption of starting material but no formation of **2.8b**, in line with yields observed using $\text{Rh}^{\text{I}}/\text{BF}_4$ catalysis. In both cases, it is likely that the resulting product is more susceptible to HF elimination or that fluoride rebound is not occurring, as the secondary carbocation formed is less stable than the tertiary carbocation presumably formed prior to the fluoride addition step.



Scheme 2.6. Formation of tertiary alkyl fluorides **2.8** under TrBF_4 -catalyzed intramolecular fluoroacylation conditions.

2.4.6 Mechanistic Studies

Turning our attention to the mechanism of the TrBF_4 -catalyzed fluoroacylation of **2.1a**, we considered a fluoride-abstraction mechanism analogous to reported Friedel-Crafts-type alkyne additions with acyl fluorides.^{34,58} This pathway results in the formation of acylium intermediate **A'**, which can undergo nucleophilic attack by the pendant alkyne (Figure 2.20). Fluoride rebound from BF_4^- to vinyl cation **A''** generates **2.2a** and regenerates the active Lewis acid catalyst.

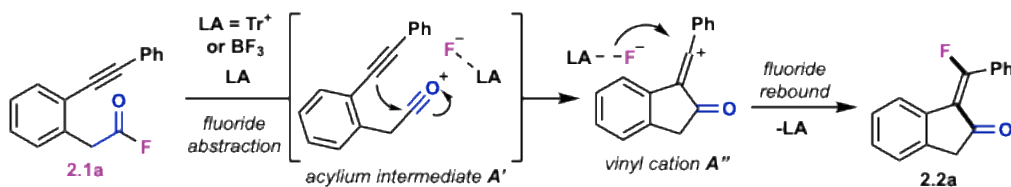


Figure 2.20. Fluoride abstraction pathway for fluoroacylation reaction of **2.1a**.

In this reaction scheme, the identity of the Lewis acid could be either the trityl cation or BF_3 . While it is possible that TrBF_4 could act as a source of BF_3 via either direct fluoride abstraction from BF_4 (Figure 2.21.I) or after the first catalytic turn over (Figure 2.21.II), the possibility of TrBF_4 as a BF_3 reservoir seems unlikely, given that tertiary alkyl fluoride **2.8** is known to degrade in the presence of catalytic $\text{BF}_3 \cdot \text{OEt}_2$.

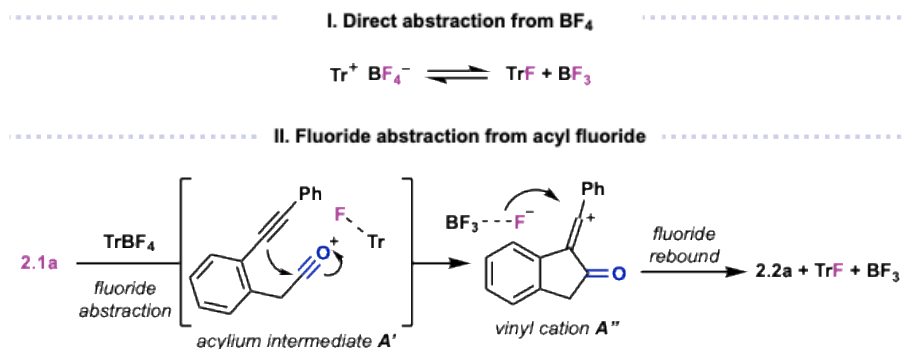
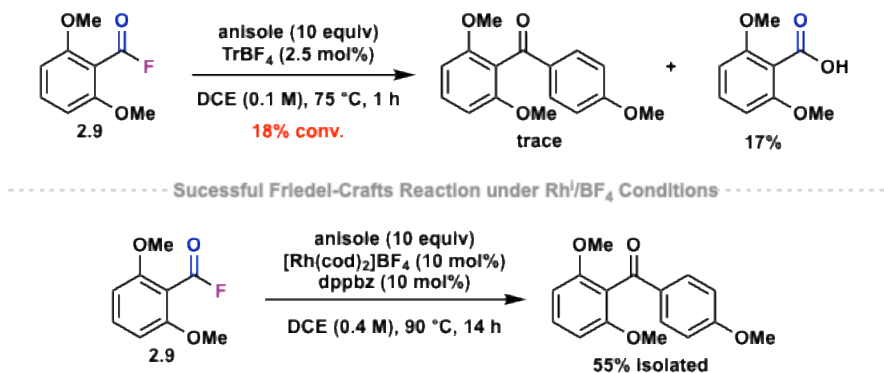


Figure 2.21. Potential pathways for the formation of BF_3 as active catalyst.

While this fluoride abstraction pathway seems to be a viable mode of activation for the borane Lewis acids, it is unclear if it is a viable pathway under the optimized conditions with TrBF_4 as the catalyst. While there is no precedent for Tr species in the activation of C-F bonds in this manner, the trityl cation is a strong Lewis acid (FIA 599 kJ mol^{-1}) and for the aryl fluorides **2.1a-O** reviewed in this study, the optimal FIA for rebound was around 350 kJ mol^{-1} making it a possibility that the trityl cation could abstract a fluoride. Even if fluoride rebound from a trityl-fluoride intermediate is possible, its formation could signal that BF_3 is the active catalyst in the reaction.

To probe the feasibility of fluoride abstraction under our reaction conditions, acyl fluoride **2.9** was subjected to standard Friedel-Crafts conditions in the presence of excess anisole and catalytic TrBF_4 (Scheme 2.7). The reaction provided only trace Friedel-Crafts product **2.10** and 87% recovery of **2.9**. This result is not surprising, as the generation of an acylium ion from an acyl fluoride generally requires more

potent fluorophilic Lewis acids.^{26–28} The remaining mass balance from the crude mixture was the carboxylic acid precursor, which can be formed via hydrolysis of **2.9** with adventitious water. This result is in direct contrast to the Tobisu $\text{Rh}^{\text{I}}/\text{BF}_4$ conditions which were successfully implemented in a Friedel-Crafts reaction of acyl fluoride **2.9**. The success of this reaction was key to their fluoride abstraction mechanistic proposal.



Scheme 2.7. Intramolecular Friedel-Crafts reaction of acyl fluoride **2.9** under TrBF_4 catalysis vs. $\text{Rh}^{\text{I}}/\text{BF}_4$

Additional NMR experiments with acyl fluoride **2.9** in the presence stoichiometric TrBF_4 revealed that the concentration of both **2.9a** and TrBF_4 remained constant throughout the monitoring period (Figure 2.22) and no amount TrF above what is typically present in commercial TrBF_4 (97:3 ratio of TrBF to TrF , Figure 2.) was observed, thus making it unlikely that fluoride abstraction is occurring under catalytically relevant conditions.

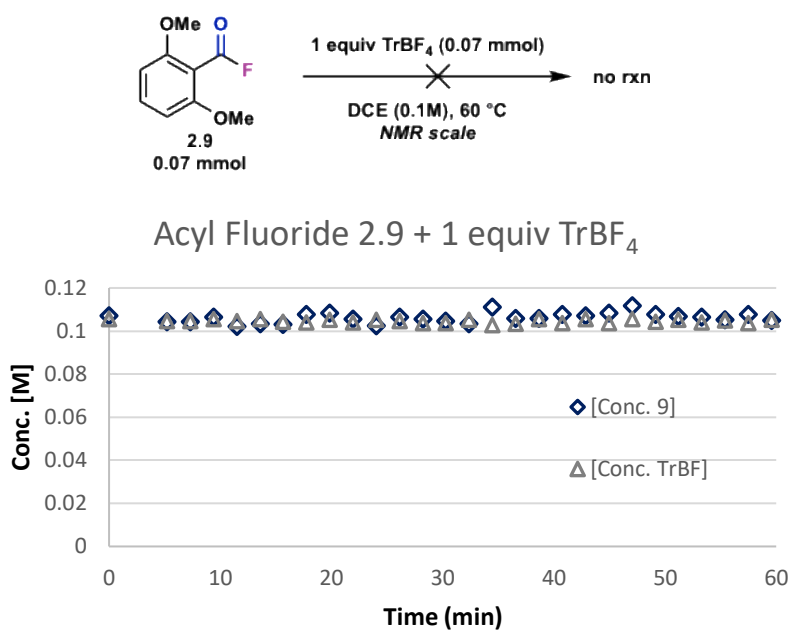


Figure 2.22. Reaction of **2.9** and TrBF₄ over time as monitored by *in situ* ¹⁹F NMR spectroscopy, time vs concentration plot.

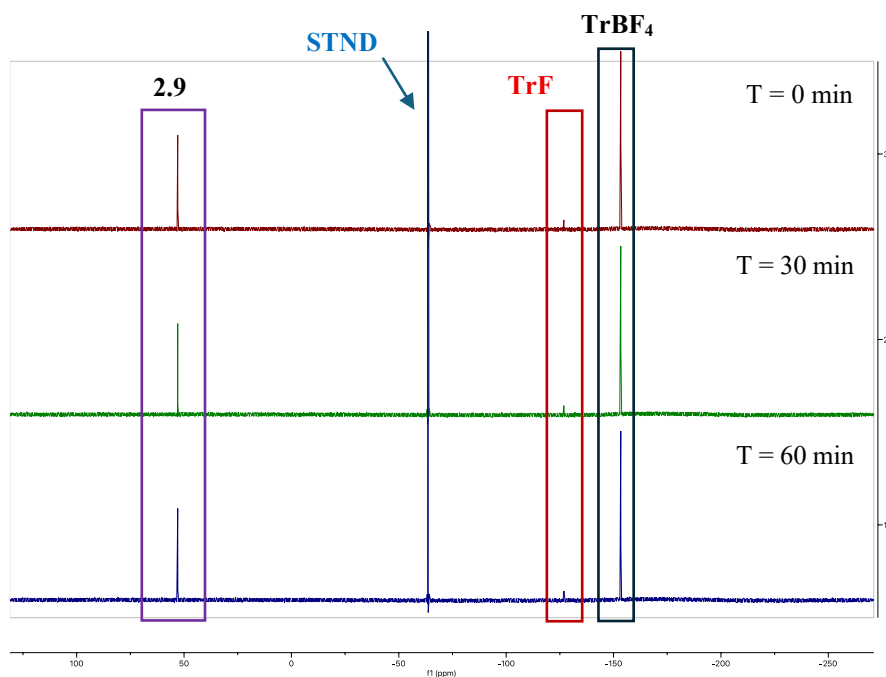


Figure 2.2. Reaction of **2.9** and TrBF₄ over time as monitored by *in situ* ¹⁹F NMR spectroscopy, NMR spectra at time = 0, 30, and 60 minutes.

Given that Friedel-Crafts-type reactivity seems to not be a feasible pathway under our reaction conditions, we instead proposed that the reaction proceeds through a dual activation pathway (Figure

2.23).⁶³ The reaction is initiated by activation of the C=O bond of the acyl fluoride by the trityl cation (intermediate **B'**), increasing the electrophilicity of the carbonyl carbon. This is in line with literature reports of trityl cations acting as a Lewis acid activator for a range of alcohols and carbonyl moieties.^{64,65} The cyclization via C–C bond formation and fluoride addition from BF_4^- may be stepwise or concerted. Collapse of the tetrahedral intermediate **B''** forms the carbonyl moiety and expels a fluoride ion to regenerate the TrBF_4 catalyst. The proposed mechanism is in line with previous studies by Yeh for the carbofluorination of allylic alcohols **211** yielding fluorinated pyrrolizidines **212**.⁶⁶ In this system, the trityl cation acts as a Lewis acid activator, initiating the cationic cyclization by abstracting an OH group, generating a carbocation. The subsequent C–C bond formation occurs concurrently with fluorination by the BF_4^- counterion, yielding the formal carbofluorination product, and highlighting the critical roles of both the carbocation and the counteranion in stoichiometric TrBF_4 -mediated carbofluorination reactions. Similar cyclizations can also occur in carbonyl-ene systems **209** where the Tr-activated carbonyl is electrophilic enough to undergo nucleophilic attack by an alkene in an intramolecular fashion, as demonstrated by Kotsuki.⁶⁷ In our case, the use of an organofluorine compound as the starting reagent enables fluoride recycling, and thus, only a catalytic amount of TrBF_4 is required.

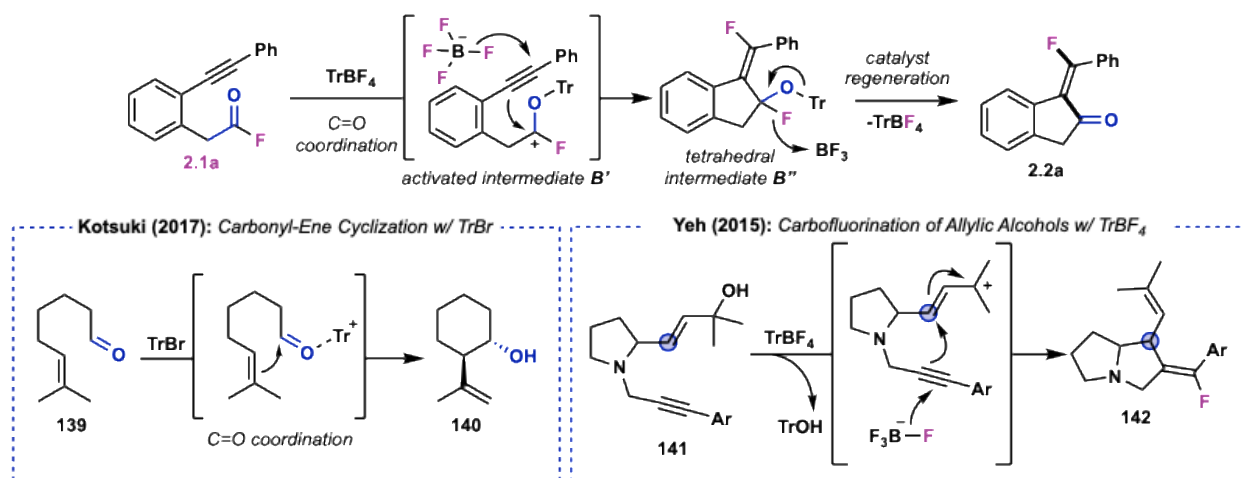


Figure 2.23. Dual-activation pathway for the fluoroacylation of **2.1a** and literature precedent for dual-activation of substrates with TrBF_4 and activation of carbonyls with Tr salts.

In line with the Yeh fluorocyclization reactions of alkynes mediated by $\text{BF}_3/\text{BF}_4^-$, we can rationalize the *E*-selectivity (i.e., *trans*-addition) due to preferential fluoride delivery by BF_4^- from the least hindered side. This conclusion is supported via reaction monitoring. The reaction of **2.1a** was run under standard conditions and monitored by *in situ* ^{19}F NMR spectroscopy using α,α,α -trifluorotoluene as an internal standard (Figure 2.24). Over the course of the reaction no formation of **2.Z-2a** was observed above signal-to-noise ratio.

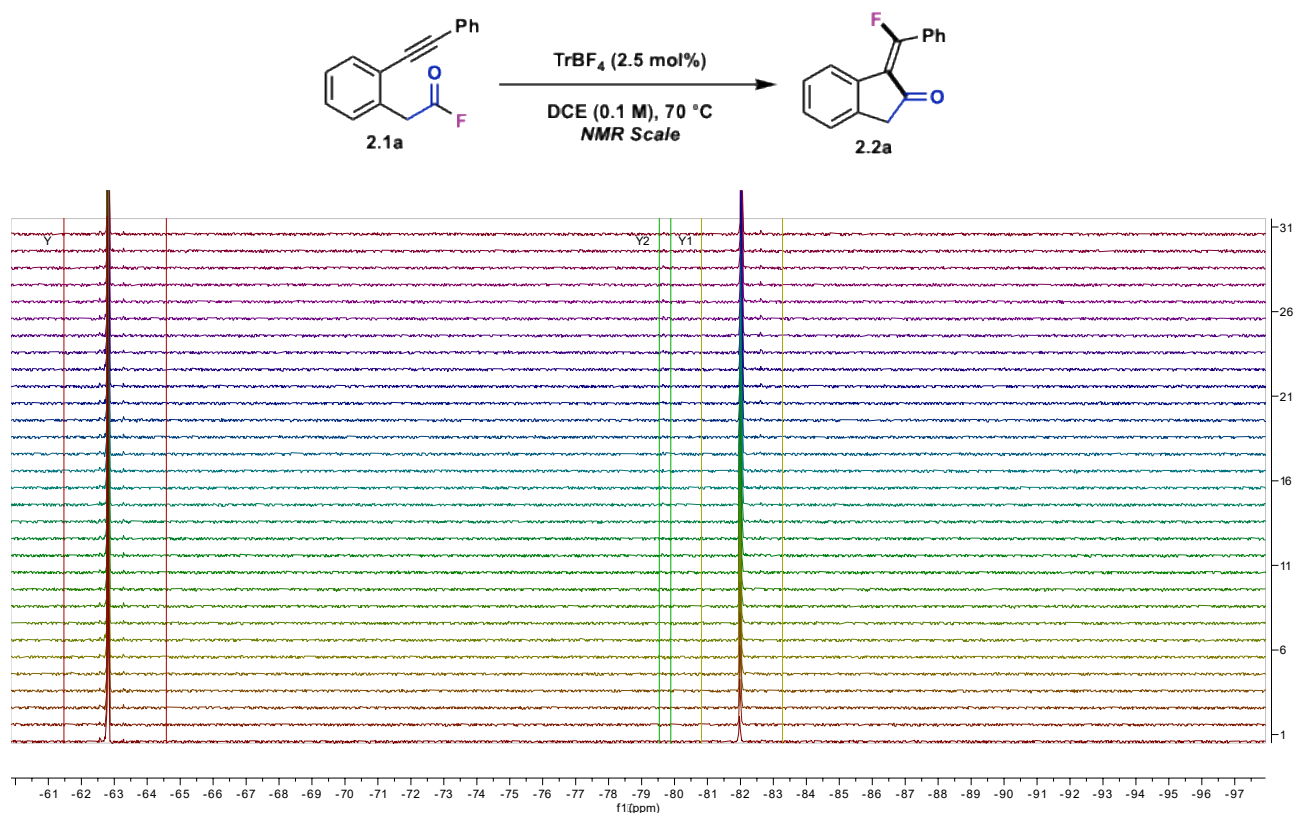


Figure 2.24. Formation of **2.2a** over time as monitored by *in situ* ^{19}F NMR spectroscopy: $t = 3$ minutes for scan 1; Y = α,α,α -trifluorotoluene standard, Y2 = **2.Z-2a**, Y1 = **2.E-2a**.

2.5 Conclusions and Future Work

In conclusion, using inexpensive TrBF_4 as the catalyst, we have enabled the synthesis of previously unreported 1-(fluoromethylene)indan-2-ones **2.2** and cyclopentanone **2.4** with exceptional stereoselectivity under mild conditions. Furthermore, this method is amenable to the synthesis of both six-membered heterocycles **2.6** and tertiary fluoride **2.8**, which have previously only been reported under harsher transition metal-catalyzed reaction conditions. Preliminary mechanistic studies reveal that the trityl cation plays a

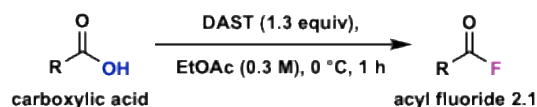
crucial role in substrate activation, paving the way for future investigations into organocatalyzed carbofluorination reactions. Given that the only known intermolecular, atom-economical carbofluorination of alkynes relies on activated alkynoates to achieve reactivity,¹⁹ we sought to determine whether any of the Lewis acids identified as effective catalysts for the intramolecular variant could also promote an intermolecular reaction. While preliminary studies were conducted with both phenylacetylene and diphenylacetylene as alkyne coupling partners, only trace product was formed across all combinations of alkyne and with both the borane catalysis and with TrBF₄.

Ultimately, though the reaction mechanism with TrBF₄ likely is not initiated via a fluoride abstraction, the preliminary studies on the aroyl fluoride system showed that there was a correlation between Lewis acidity (as calculated by FIA) and the relative reactivity of the catalyst, proving our initial hypothesis correct that controlled fluoride shuttling reactions relies on balancing the fluorophilicity of the catalyst. With this knowledge in hand, we aimed to develop the substrate scope further, turning our attention expanding the scope of C–F bond donors to heteroatom-carbonyl fluorides, namely carbamoyl fluorides (Chapter 3) and fluoroformates (Chapter 4).

2.6 Experimental and Spectral Information

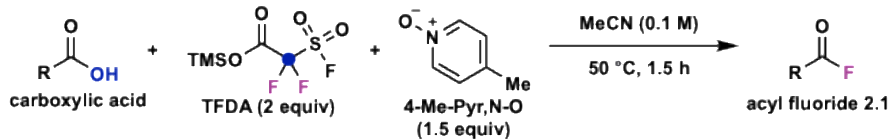
2.6.1 Synthesis and Characterization of Starting Materials

2.6.1.1 General Procedure for Acyl Fluoride Synthesis (*Method A*)



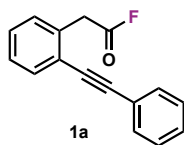
Following a modified literature procedure:¹ A solution of carboxylic acid (1.0 equiv.) in dry EtOAc (0.3 M) was cooled to 0 °C. DAST (1.3 equiv.) was added dropwise under N₂, and the resulting mixture was stirred at 0 °C for 30 min. A saturated aqueous solution of NaHCO₃ was then added and the organic layer was separated and dried using Na₂SO₄. After filtration, volatiles were removed in vacuo, and if necessary, the residue was purified by flash column chromatography to yield acyl fluoride **2.1**.

2.6.1.2 General Procedure for Acyl Fluoride Synthesis (*Method B*)



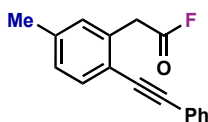
Following a modified literature procedure:² A flame dried vial was charged with carboxylic acid (1.0 equiv.) and 4-methylpyridine-*N*-oxide (1.5 equiv.), then dissolved in MeCN (0.1 M). Trimethylsilyl difluoro(fluorosulfonyl)acetate or (TFDA, 2.0 equiv.) was added neat via syringe under nitrogen atmosphere and the vessel sealed with a Teflon-lined screw cap. The vial was placed into a pre-heated 50 °C oil bath and allowed to stir for 1.5 hours before removing from the oil bath and allowing to cool to room temperature. The solvent was removed under reduced pressure, and the crude mixture was immediately dissolved in minimal CH₂Cl₂ and filtered through a short pad of packed silica (2.5 cm thick x 0.5 cm diameter). The silica pad was further washed with the 10% EtOAc/hexanes (~8 mL). The filtrate was concentrated under reduced pressure to yield acyl fluoride **2.1**.

2-[2-(2-phenylethynyl)phenyl]acetyl fluoride (**2.1a**):



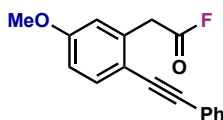
The title compound was prepared using **Method A** from **2-(2-(phenylethynyl)phenyl)acetic acid** (0.400 g, 1.69 mmol). The crude material was purified via flash chromatography (10-20% EtOAc/hexanes) to yield the desired product as a non-crystalline white solid (0.277 g, 1.17 mmol, 69% yield). **¹H NMR** (400 MHz, CDCl₃) δ 7.64 – 7.60 (m, 1H), 7.58 – 7.53 (m, 2H), 7.45 – 7.30 (m, 6H), 4.09 (s, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 161.1 (d, *J* = 361.1 Hz), 133.1 (d, *J* = 3.6 Hz), 132.5, 131.7, 130.0, 128.93, 128.86, 128.6, 128.3, 123.9, 122.8, 95.1, 86.6, 38.1 (d, *J* = 56.4 Hz); **¹⁹F NMR** (277 MHz, CDCl₃) δ 45.43 (s, 1F); **HRMS** (DART-TOF) *m/z*: [M+NH₄]⁺ [C₁₆H₁₅FNO]⁺ Calcd 256.11322, found 256.11287.

2-(5-methyl-2-(2-phenylethynyl)phenyl)acetyl fluoride (2.1b):



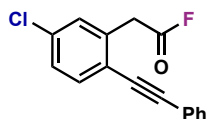
The title compound was prepared using **Method A** from **2-(5-methyl-2-(2-phenylethynyl)phenyl)acetic acid** (0.400 g, 1.60 mmol). The crude material was purified via flash chromatography (10-20% EtOAc/hexanes) to yield the desired product as a white solid (0.130 g, 0.52 mmol, 32% yield). **¹H NMR** (400 MHz, *CDCl*₃) δ 7.59 – 7.54 (m, 2H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.43 – 7.34 (m, 3H), 7.18 – 7.16 (m, 2H), 4.06 (s, 2H), 2.40 (s, 3H); **¹³C NMR** (101 MHz, *CDCl*₃) δ 161.2 (d, *J* = 361.4 Hz), 139.2, 132.9 (d, *J* = 3.3 Hz), 132.3, 131.6, 130.7, 129.0, 128.6, 128.5, 123.0, 120.8, 94.3, 86.8, 38.0 (d, *J* = 56.2 Hz), 21.5; **¹⁹F NMR** (377 MHz, *CDCl*₃) δ 45.45 ppm (s, 1F); **HRMS** (DART-TOF) *m/z*: [M+NH₄]⁺ [C₁₇H₁₇NOF]⁺ Calcd 270.12887, found 270.12930.

2-[5-methoxy-2-(2-phenylethynyl)phenyl]acetyl fluoride (2.1c):



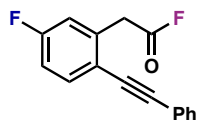
The title compound was prepared according to **Method A** from **2-[5-methoxy-2-(2-phenylethynyl)phenyl]acetic acid** (0.221 g, 0.83 mmol). The crude material was purified via flash chromatography (10-20% EtOAc/hexanes) to yield the desired product as a white solid* (93% purity, 0.126 g, 0.47 mmol, 57% yield, *remaining mass balance is the corresponding carboxylic acid). **¹H NMR** (400 MHz, *CDCl*₃) δ 7.69 – 7.51 (m, 3H), 7.44 – 7.30 (m, 3H), 6.98 – 6.83 (m, 2H), 4.08 (s, 2H), 3.84 (s, 3H); **¹³C NMR** (101 MHz, *CDCl*₃) δ 160.9 (d, *J* = 361.9 Hz), 159.9, 134.6 (d, *J* = 3.8 Hz), 133.7, 131.4, 128.5, 128.4, 123.0, 115.9, 115.8, 113.6, 93.6, 86.6, 55.4, 38.1 (d, *J* = 56.5 Hz); **¹⁹F NMR** (400 MHz, *CDCl*₃) δ 45.56 ppm (s, 1F); **HRMS** (DART-TOF) *m/z*: [M+NH₄]⁺ [C₁₇H₁₇NO₂F]⁺ Calcd 286.12378, found 286.12425.

2-[5-chloro-2-(2-phenylethynyl)phenyl]acetic fluoride (2.1d):



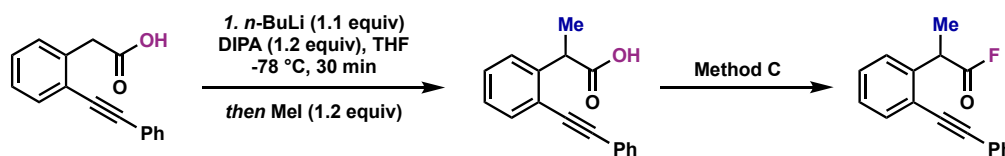
The title compound was prepared according to **Method B** from **2-[5-chloro-2-(2-phenylethynyl)phenyl]acetic acid** (106 mg, 0.39 mmol). The crude material was purified via flash chromatography (10-20% EtOAc/hexanes) to yield the desired product as an orange oil (62 mg, 0.24 mmol, 65% yield). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.57 – 7.49 (m, 3H), 7.41 – 7.30 (m, 5H), 4.05 (s, 2H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 160.4 (d, $J = 361.3$ Hz), 134.6, 134.5 (d, $J = 4.0$ Hz), 133.4, 131.6, 130.1, 129.0, 128.54, 128.52, 122.4, 122.3, 95.9, 85.5, 37.7 (d, $J = 57.4$ Hz); $^{19}\text{F NMR}$ (400 MHz, CDCl_3) δ 45.65 (s, 1F); **HRMS** (DART-TOF) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_{11}\text{ClFO}]^+$ Calcd 273.04770, found 273.04773.

2-[5-fluoro-2-(2-phenylethynyl)phenyl]acetyl fluoride (2.1e):



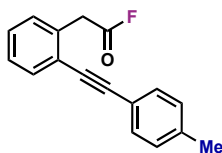
The title compound was prepared according to **Method B** from **2-[5-fluoro-2-(2-phenylethynyl)phenyl]acetic acid** (0.101 g, 0.40 mmol) to yield the desired product as a bright yellow oil (69 mg, 0.27 mmol, 53% yield). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.68 – 7.46 (m, 3H), 7.48 – 7.29 (m, 3H), 7.22 – 6.95 (m, 2H), 4.09 (s, 2H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 163.6 (d, $J = 251.1$ Hz), 158.7 (d, $J = 360.6$ Hz), 135.3 (dd, $J = 8.3, 4.1$ Hz), 134.2 (d, $J = 8.6$ Hz), 131.6, 128.9, 128.6, 122.5, 120.0 (d, $J = 3.6$ Hz), 117.3 (d, $J = 23.2$ Hz), 115.6 (d, $J = 21.8$ Hz), 94.8, 85.6, 37.9 (d, $J = 57.7$ Hz); $^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ 45.66 (s, 1F), -107.77 – -112.13 (m, 1F); **HRMS** (DART-TOF) m/z : $[\text{M}+\text{NH}_4]^+$ $[\text{C}_{16}\text{H}_{14}\text{NOF}_2]^+$ Calcd 274.10380, found 274.10478.

2-[2-(2-phenylethynyl)phenyl]propanoyl fluoride (2.1f)



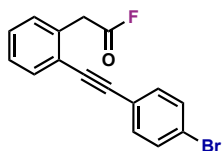
To a solution of (*i*-Pr)₂NH (0.15 mL, 1.20 equiv., 1.01 mmol) in anhydrous THF (3 mL) was added *n*-BuLi (1.00 mL, 1.10 equiv., 2.4 M in THF) at -78 °C under nitrogen. After stirring -78 °C for 15 min, the LDA solution was added dropwise to a solution of **1a** (0.201 g, 1.00 equiv., 0.85 mmol) in THF (2 mL) at -78 °C. The mixture was allowed to stir for 15 minutes at -78 °C before a solution of methyl iodide (66 µL, 1.20 equiv., 1.01 mmol) in THF (2 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for an additional 12 h. The reaction mixture was quenched with 1 M HCl (2 mL), extracted with ethyl acetate (3 x 2 mL), washed with brine, dried over anhydrous MgSO₄, and concentrated in vacuo. The crude carboxylic acid intermediate was carried forward into the next step without any further purification. The title compound was prepared according to **Method A** from the crude carboxylic acid (1.00 equiv., 0.22 mmol, ~55 mg) and was purified via flash chromatography (10-20% EtOAc/hexanes) to yield the product as a yellow oil* (~95% purity, 49 mg, 0.18 mmol, 64% yield, *remaining mass balance is the corresponding carboxylic acid). ¹H NMR (600 MHz, CDCl₃) δ 7.62 – 7.58 (m, 1H), 7.58 – 7.53 (m, 2H), 7.41 – 7.35 (m, 4H), 7.34 – 7.31 (m, 2H), 4.48 (q, *J* = 7.2 Hz, 1H), 1.67 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 164.3 (d, *J* = 365.6 Hz), 139.4, 132.9, 131.7, 129.2, 128.9, 128.6, 128.0, 127.2, 123.0, 122.8, 94.9, 86.6, 42.8 (d, *J* = 50.3 Hz), 17.5; ¹⁹F NMR (377 MHz, CDCl₃) δ 40.22; HRMS (DART-TOF) *m/z*: [M+NH₄]⁺ [C₁₇H₁₇NOF]⁺ Calcd 270.12887, found 270.12891.

2-[2-[2-(p-tolyl)ethynyl]phenyl]acetyl fluoride (2.1g):



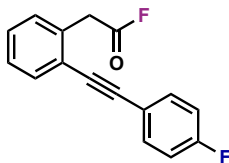
The title compound was prepared according to **Method A** from **2-[2-[2-(p-tolyl)ethynyl]phenyl]acetic acid** (0.414 g, 1.66 mmol). The crude material was purified via flash chromatography (0-10% EtOAc/hexanes) to yield the desired product as a white solid (0.151 g, 0.6 mmol, 36% yield). **¹H NMR** (400 MHz, CDCl₃) δ 7.65 – 7.61 (m, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.39 – 7.32 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 4.11 (s, 2H), 2.42 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 161.1 (d, *J* = 361.5 Hz), 139.0, 132.9 (d, *J* = 3.6 Hz), 132.3, 131.5, 129.9, 129.3, 128.7, 128.2, 124.0, 119.6, 95.3, 86.0, 38.0 (d, *J* = 56.4 Hz), 21.6 ppm; **¹⁹F NMR** (377 MHz, CDCl₃) δ 45.41 ppm (s, 1F); **HRMS** (DART-TOF) *m/z*: [M+NH₄]⁺ [C₁₇H₁₇NOF]⁺ Calcd 270.12887, found 270.12975.

2-[2-[2-[4-bromophenyl)ethynyl]phenyl]acetyl fluoride (2.1h):



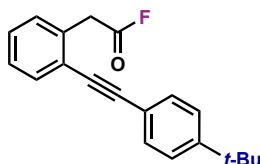
The title compound was prepared using **Method A** from **2-[2-[2-[4-bromophenyl)ethynyl]phenyl]acetic acid** (0.387 g, 1.23 mmol). The crude material was purified via flash chromatography (10-20% EtOAc/hexanes) to yield the desired product as a white solid (0.141 g, 0.453 mmol, 37% yield). **¹H NMR** (400 MHz, CDCl₃) δ 7.63 – 7.60 (m, 1H), 7.54 – 7.51 (m, 2H), 7.46 – 7.40 (m, 2H), 7.41 – 7.34 (m, 3H), 4.08 (s, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 160.9 (d, *J* = 361.5 Hz), 133.0 (2C), 132.4, 131.8, 130.0, 129.1, 128.3, 123.5, 123.1, 121.6, 93.9, 87.7, 38.1 (d, *J* = 56.4 Hz); **¹⁹F NMR** (377 MHz, CDCl₃) δ 45.51 ppm (s, 1F); **HRMS** (DART-TOF) *m/z*: [M+H]⁺ [C₁₆H₁₁BrFO]⁺ Calcd 316.9972, found 316.9989.

2-[2-[2-[4-fluorophenyl]ethynyl]phenyl]acetyl fluoride (2.1i):



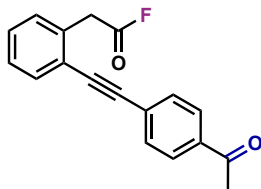
The title compound was prepared according to **Method A** from **2-[2-[2-[4-fluorophenyl]ethynyl]phenyl]acetic acid** (0.153 g, 0.60 mmol). The crude material was purified via flash chromatography (0-10% EtOAc/hexanes) to yield the desired product as a yellow oil (49 mg, 0.19 mmol, 32% yield). **¹H NMR** (400 MHz, *CDCl*₃) δ 7.62 – 7.60 (m, 1H), 7.57 – 7.54 (m, 2H), 7.39 – 7.36 (m, 3H), 7.09 (t, *J* = 8.7 Hz, 2H), 4.09 (s, 2H); **¹³C NMR** (101 MHz, *CDCl*₃) δ 164.2 (d, *J* = 249.0 Hz), 159.2 (d, *J* = 362.6 Hz), 133.6 (d, *J* = 8.4 Hz), 133.0 (d, *J* = 3.4 Hz), 132.4, 130.0, 129.0, 128.3, 123.7, 118.9 (d, *J* = 3.4 Hz), 115.9 (d, *J* = 22.2 Hz), 94.0, 86.4, 38.1 (d, *J* = 56.4 Hz); **¹⁹F NMR** (377 MHz, *CDCl*₃) δ 45.40 (s, 1F), -108.60 – -111.24 (m, 1F); **HRMS** (DART-TOF) *m/z*: [M+NH₄]⁺ [C₁₆H₁₄F₂NO]⁺ Calcd 274.10380, found 274.10478.

2-[2-[2-(4-*tert*-butylphenyl)ethynyl]phenyl]acetyl fluoride (2.1j):



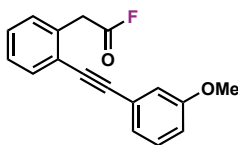
The title compound was prepared according to **Method A** from **2-[2-[2-(4-*tert*-butylphenyl)ethynyl]phenyl]acetic acid** (0.378 g, 1.30 mmol). The crude material was purified via flash chromatography (10-20% EtOAc/hexanes) to yield the desired product as a white solid (0.131 g, 0.472 mmol, 57% yield). **¹H NMR** (400 MHz, *CDCl*₃) δ 7.64 – 7.58 (m, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.38 – 7.31 (m, 3H), 4.09 (s, 2H), 1.36 (s, 9H); **¹³C NMR** (101 MHz, *CDCl*₃) δ 161.1 (d, *J* = 361.5 Hz), 152.2, 133.0 (d, *J* = 3.5 Hz), 132.4, 131.5, 129.9, 128.7, 128.2, 125.6, 124.1, 119.7, 95.3, 86.0, 38.1 (d, *J* = 56.4 Hz), 35.0, 31.3; **¹⁹F NMR** (400 MHz, *CDCl*₃) δ 45.40 (s, 1F); **HRMS** (DART-TOF) *m/z*: [M+NH₄]⁺ [C₂₀H₂₃NOF]⁺ Calcd 312.17582, found 312.17519.

2-[2-[2-(4-acetylphenyl)ethynyl]phenyl]acetyl fluoride (2.1k):



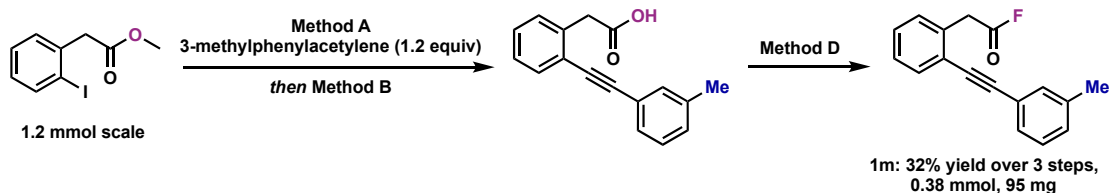
The title compound was prepared according to **Method B** from **2-[2-[2-(4-acetylphenyl)ethynyl]phenyl]acetic acid** (60.7 mg, 0.22 mmol). The crude material was purified via flash chromatography (10-20% EtOAc/hexanes) to yield the desired product as a yellow oil (52 mg, 0.19 mmol, 86% yield). **¹H NMR** (400 MHz, *CDCl*₃) δ 7.94 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 3H), 7.44 – 7.27 (m, 3H), 4.07 (s, 2H), 2.61 (s, 3H); **¹³C NMR** (101 MHz, *CDCl*₃) δ 197.4, 160.9 (d, *J* = 361.4 Hz), 136.7, 133.2 (d, *J* = 3.4 Hz), 132.6, 131.8, 130.1, 129.49, 128.45, 128.38, 127.5, 123.2, 94.1, 89.7, 38.1 (d, *J* = 56.6 Hz), 26.7; **¹⁹F NMR** (400 MHz, *CDCl*₃) δ 45.48 (s, 1F); **HRMS** (DART-TOF) *m/z*: [M+H]⁺ [C₁₈H₁₄O₂F]⁺ Calcd 281.09723, found 281.09666.

2-[2-[2-(3-methoxyphenyl)ethynyl]phenyl]acetyl fluoride (2.1l):



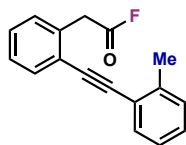
The title compound was prepared according to **Method B** from **2-[2-[2-(3-methoxyphenyl)ethynyl]phenyl]acetic acid** (71 mg, 1.00 equiv., 0.28 mmol). The crude material was purified via flash chromatography (10-20% EtOAc/hexanes) to yield the desired product as a white solid (49 mg, 0.18 mmol, 64% yield). **¹H NMR** (400 MHz, *CDCl*₃) δ 7.67 – 7.58 (m, 1H), 7.43 – 7.34 (m, 3H), 7.32 – 7.26 (m, 1H), 7.22 – 7.14 (m, 1H), 7.11 (s, 1H), 7.01 – 6.88 (m, 1H), 4.10 (s, 2H), 3.86 (s, 3H); **¹³C NMR** (101 MHz, *CDCl*₃) δ 161.1 (d, *J* = 361.5 Hz), 159.5, 133.1 (2C), 132.4, 130.0, 129.7, 129.0, 129.3, 124.2, 123.8 (d, *J* = 8.1 Hz), 116.5, 115.5, 95.0, 86.4, 55.4, 38.1 (d, *J* = 56.4 Hz); **¹⁹F NMR** (400 MHz, *CDCl*₃) δ 45.43 (s, 1F); **HRMS** (DART-TOF) *m/z*: [M+NH₄]⁺ [C₁₇H₁₇NO₂F]⁺ Calcd 286.12378, found 286.12479.

2-[2-[2-(m-tolyl)ethynyl]phenyl]acetyl fluoride (2.1m):



The Sonogashira reaction was conducted using **Method A** from methyl (2-iodophenyl)acetate (0.331 g, 1 equiv., 1.20 mmol) and 3-methylphenylacetylene (0.167 g, 1.20 equiv., 1.44 mmol). The crude material was telescoped through the saponification step (via **Method B**). Purification via flash chromatography (10-20% EtOAc/hexanes) provided the desired product as a yellow oil* (95% pure, 95 mg, 0.38 mmol, 42% yield, *remaining mass balance is the corresponding carboxylic acid). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.60 – 7.57 (m, 1H), 7.37 – 7.33 (m, 5H), 7.29 – 7.14 (m, 2H, overlap with CDCl_3 signal), 4.08 (s, 2H), 2.37 (s, 3H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 164.5 (d, $J = 365.9$ Hz), 139.6, 133.1, 132.7, 131.8, 129.4, 129.0, 128.8, 128.6, 128.1, 127.4, 123.1, 123.0 (d, $J = 2.2$ Hz), 95.1, 86.8, 43.0 (d, $J = 50.3$ Hz), 17.7; $^{19}\text{F NMR}$ (400 MHz, CDCl_3) δ 45.64 (s, 1F); **HRMS** (DART-TOF) m/z : $[\text{M}+\text{NH}_4]^+$ $[\text{C}_{17}\text{H}_{17}\text{NOF}]^+$ Calcd 270.12887, found 270.12795.

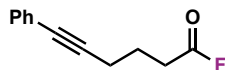
(2-(2-(2-o-tolyl)ethynyl)phenyl)acetyl fluoride (2.1n):



The title compound was prepared according to **Method A** from 2-[2-(2-o-tolyl)ethynyl]phenyl]acetic acid (0.500 g, 2.00 mmol). The crude material was purified via flash chromatography (0-10% EtOAc/hexanes) to yield the desired product as a white solid* (94% pure, 0.290 g, 1.15 mmol, 58% yield, *remaining mass balance is the corresponding carboxylic acid). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.68 – 7.62 (m, 1H), 7.60 – 7.53 (m, 1H), 7.42 – 7.36 (m, 3H), 7.31 – 7.27 (m, 2H), 7.27 – 7.23 (m, 1H), 4.14 (s, 2H), 2.56 (s, 3H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 161.1 (d, $J = 361.4$ Hz), 140.2, 132.7 (d, $J = 3.6$ Hz), 132.6, 132.2, 130.0, 129.7, 128.92, 128.86, 128.3, 125.9, 124.2, 122.6, 93.9, 90.5, 38.0 (d, $J = 56.3$ Hz), 20.9; $^{19}\text{F NMR}$ (377 MHz,

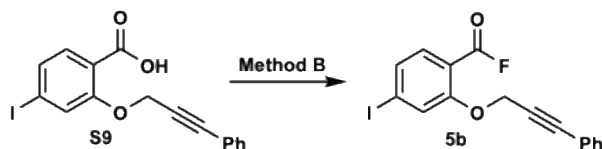
$CDCl_3$) δ 45.37 (s, 1F); **HRMS** (DART-TOF) m/z : $[M+NH_4]^+$ $[C_{17}H_{17}NOF]^+$ Calcd 270.12887, found 270.12952.

6-Phenylhex-5-ynoyl fluoride (2.3):



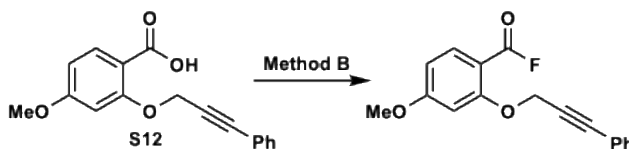
The title compound was prepared according to **Method B** from **6-Phenylhex-5-ynoic acid** (71 mg, 1.00 equiv., 0.28 mmol). The crude material was purified via flash chromatography (0-10% Et₂O/pentanes) to yield the desired product as a clear oil (49 mg, 0.18 mmol, 64% yield). **¹H NMR** (700 MHz, $CDCl_3$) δ 7.47 – 7.36 (m, 2H), 7.35 – 7.27 (m, 3H), 2.77 – 2.69 (m, 2H), 2.60 – 2.53 (m, 2H), 2.01 – 1.96 (m, 2H); **¹³C NMR** (176 MHz, $CDCl_3$) δ 163.3 (d, J = 359.8 Hz), 137.5, 131.6, 128.3, 128.0, 87.7, 82.2, 30.9 (d, J = 51.3 Hz), 22.95 (d, J = 2.5 Hz), 18.4; **¹⁹F NMR** (400 MHz, $CDCl_3$) δ 45.84 (s, 1F); **HRMS** (DART-TOF) m/z : $[M+H]^+$ $[C_{12}H_{13}O_2]^+$ Calcd 189.09131, found 189.09135. (*Note: only carboxylic acid can be detected by HRMS due to hydrolysis under the conditions of the analysis*)

5-iodo-2-((3-phenylprop-2-ynoxy)benzoyl fluoride (2.5b)



Synthesis of 5b: The title compound was prepared according to **Method B** from carboxylic acid **S9** (150 mg, 0.4 mmol). Pure **5b** was isolated without the need for column chromatography as a yellow solid (100 mg, 0.26 mmol, 65% yield). **¹H NMR** (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.46 – 7.44 (m, 3H), 7.37 – 7.30 (m, 3H), 5.07 (s, 2H); **¹³C NMR** (101 MHz, $CDCl_3$) δ 159.2 (d, J = 3.8 Hz), 154.7 (d, J = 342.8 Hz), 134.5 (d, J = 2.9 Hz), 132.1, 130.8, 129.2, 128.5, 124.2 (d, J = 2.8 Hz), 121.8, 113.9 (d, J = 60.3 Hz), 104.0, 89.1, 82.1 (d, J = 4.4 Hz), 57.9; **¹⁹F NMR** (377 MHz, $CDCl_3$) δ 32.46 (s, 1F); **HRMS** (DART-TOF) m/z : $[M+NH_4]^+$ $[C_{16}H_{14}NO_2FI]^+$ Calcd 398.00478, found 398.00486.

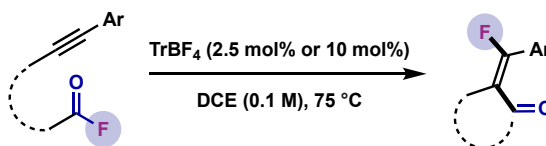
4-methoxy-2-((3-phenylprop-2-ynoxy)benzoyl fluoride (2.5c)



Synthesis of **5c**: The title compound was prepared according to **Method B** from carboxylic acid **S12** (113 mg, 0.4 mmol). Pure **5c** was isolated without the need for column chromatography as a yellow solid (80 mg, 0.28 mmol, 70% yield). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.90 (d, $J = 8.9$ Hz, 1H), 7.42 (dd, $J = 7.7, 1.8$ Hz, 2H), 7.36 – 7.27 (m, 3H), 6.84 – 6.70 (m, 1H), 6.59 (dd, $J = 8.9, 2.3$ Hz, 1H), 5.05 (s, 2H), 3.89 (s, 3H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.5, 161.8 (d, $J = 4.9$ Hz), 154.7 (d, $J = 337.9$ Hz), 135.9 (d, $J = 2.8$ Hz), 131.9, 129.0, 128.4, 122.0, 106.65, 106.1, 100.7 (d, $J = 2.9$ Hz), 88.4, 82.8, 57.5, 55.8; $^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ 28.67 (s, 1F); **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{14}\text{O}_3\text{F}]^+$ Calcd 285.09131, found 285.09215.

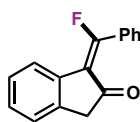
2.6.2 General Procedures and Characterization Data for Cyclized Products

General procedure for the TrBF_4 -catalyzed fluoroacylation (**Method C**)



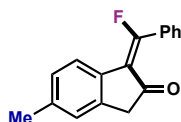
In the glovebox, a 1-dram vial was charged with acyl fluoride **2.1** (1 equiv.), anhydrous DCE (0.1 M) and either 2.5 mol% (50 μL) or 10 mol % (200 μL) TrBF_4 (0.05 M solution in DCE). The vial was capped, removed from the glovebox and placed in a pre-heated oil bath at 75 $^\circ\text{C}$ for 1 h. The reaction was cooled to rt, filtered across a pad of silica gel, eluted with CH_2Cl_2 (3 x 1 mL), and then concentrated in vacuo. If necessary, the crude reaction mixture was purified by flash chromatography using the reported eluent to yield **2.2**. Isomeric ratio was determined from the crude sample by ^{19}F NMR spectroscopy using anhydrous α,α,α -trifluorotoluene (10 μL) as an internal standard. Product **2.2** was taken up in neutralized CDCl_3^* for ^{19}F NMR analysis as trace acid promotes slight *E/Z*-isomerization. A single scan NMR experiment was used to ensure full relaxation of all ^{19}F signals. $^*\text{CDCl}_3$ is stored over solid K_2CO_3 or 4 $\text{\AA}$ mol sieves and filtered through a short plug of basic alumina before use.

(1E)-1-[fluoro(phenyl)methylene]indan-2-one (2.2a)



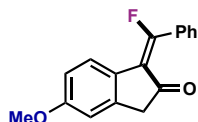
The title compound was prepared according to **Method C** using **2.1a** (23.8 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The desired product was isolated as a yellow solid (32 mg, 0.097 mmol, 97%, >95:5 E/Z); **¹H NMR** (400 MHz, CDCl₃) δ 7.96 (d, *J* = 8.0, 1H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.57 – 7.44 (m, 3H), 7.41 – 7.30 (m, 3H), 3.62 (s, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 201.4 (d, *J* = 15.2 Hz), 164.1 (d, *J* = 279.0 Hz), 138.0 (d, *J* = 3.2 Hz), 136.2, 131.6, 129.4 (d, *J* = 6.9 Hz), 128.6 (d, *J* = 2.5 Hz), 127.9, 127.8, 125.7, 125.5, 124.7, 118.0 (d, *J* = 13.6 Hz), 43.6 (d, *J* = 3.6 Hz); **¹⁹F NMR** (377 MHz, CDCl₃) δ -80.37 (s, 1F); **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₁₆H₁₂FO]⁺ Calcd 239.0867, found 239.0866.

(1E)-1-[fluoro(phenyl)methylene]-5-methyl-indan-2-one (2.2b)



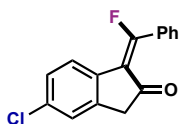
The title compound was prepared according to **Method C** using **2.1b** (25.2 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as a yellow solid (25.2 mg, 0.099 mmol, 99%, >95:5 E/Z). **¹H NMR** (400 MHz, CDCl₃) δ 7.88 – 7.78 (m, 3H), 7.54 – 7.43 (m, 3H), 7.21 – 7.15 (m, 2H), 3.57 (s, 2H), 2.41 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 201.9 (d, *J* = 15.4 Hz), 163.4 (d, *J* = 277.2 Hz), 138.9 (d, *J* = 2.5 Hz), 136.4, 135.4 (d, *J* = 3.3 Hz), 131.5, 129.4 (d, *J* = 6.8 Hz), 128.8, 128.0, 127.5, 125.48, 125.48 (d, *J* = 15.9 Hz), 118.2 (d, *J* = 14.2 Hz), 43.7 (d, *J* = 3.6 Hz), 21.8; **¹⁹F NMR** (377 MHz, CDCl₃) δ -81.93 (s, 1F); **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₁₇H₁₄FO]⁺ Calcd 253.1023, found 253.1025.

(1E)-1-[fluoro(phenyl)methylene]-5-methoxy-indan-2-one (2.2c)



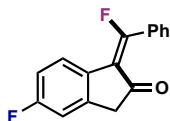
The title compound was prepared according to **Method C** using **2.1c** (32.9 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as a yellow solid (32 mg, 0.097 mmol, 97%, >95:5 E/Z). **¹H NMR** (400 MHz, CDCl₃) δ 7.91 (d, *J* = 8.7 Hz, 1H), 7.83 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.57 – 7.42 (m, 3H), 6.94 (dd, *J* = 8.3, 2.9 Hz, 1H), 6.89 – 6.86 (m, 1H), 3.89 (s, 3H), 3.61 (s, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 201.6 (d, *J* = 15.3 Hz), 162.3 (d, *J* = 275.3 Hz), 160.1 (d, *J* = 2.8 Hz), 138.1, 131.3, 131.0 (d, *J* = 2.9 Hz), 130.4 (d, *J* = 25.9 Hz), 129.3 (d, *J* = 6.9 Hz), 127.9, 126.9 (d, *J* = 15.9 Hz), 117.9 (d, *J* = 14.6 Hz), 114.1, 110.0, 55.5, 43.9 (d, *J* = 3.5 Hz); **¹⁹F NMR** (377 MHz, CDCl₃) δ -84.38 (s, 1F); **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₁₇H₁₄O₂F]⁺ Calcd 269.0972, found 269.0976.

(1E)-1-[fluoro(phenyl)methylene]-5-chloro-indan-2-one (2.2d)



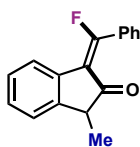
The title compound was prepared according to **Method C** using **2.1d** (27.2 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as a pale-yellow solid* (23.2 mg, 0.091 mmol, 91%, >95:5 E/Z, *93% pure, coeluted with unknown contaminant). **¹H NMR** (600 MHz, CDCl₃) δ 7.89 (d, *J* = 8.3 Hz, 1H), 7.85 – 7.78 (m, 2H), 7.54 – 7.51 (m, 1H), 7.49 – 7.46 (m, 2H), 7.37 – 7.34 (m, 1H), 7.34 – 7.33 (m, 1H), 3.59 (s, 2H); **¹³C NMR** (151 MHz, CDCl₃) δ 200.4 (d, *J* = 14.7 Hz), 164.59 (d, *J* = 279.6 Hz), 137.9, 136.6 (d, *J* = 3.0 Hz), 134.4 (d, *J* = 3.4 Hz), 132.0, 129.55, 129.50, 128.3, 128.12, 126.79 (d, *J* = 16.4 Hz), 125.13, 117.52 (d, *J* = 14.0 Hz), 43.53 (d, *J* = 3.4 Hz); **¹⁹F NMR** (377 MHz, CDCl₃) δ -79.47 (s, 1F); **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₁₆H₁₁ClFO]⁺ Calcd 273.0477, found 273.0480.

(1E)-1-[fluoro(phenyl)methylene]-5-fluoro-indan-2-one (2.2e)



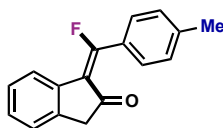
The title compound was prepared according to **Method C** using **2.1e** (25.6 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as a yellow solid (24.1 mg, 0.094 mmol, 94%, >95:5 E/Z). **¹H NMR** (400 MHz, CDCl₃) δ 7.93 (dd, *J* = 8.5, 5.3 Hz, 1H), 7.87 – 7.74 (m, 2H), 7.56 – 7.42 (m, 3H), 7.11 – 6.97 (m, 2H), 3.59 (s, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 200.6 (d, *J* = 15.1 Hz), 165.2 (dd, *J* = 281.9, 2.2 Hz), 164.0 (dd, *J* = 248.9, 3.5 Hz), 138.5 (d, *J* = 8.8 Hz), 134.13, 134.12 (d, *J* = 6.2 Hz), 130.0 (d, *J* = 25.5 Hz), 129.4 (d, *J* = 6.9 Hz), 128.0, 127.3 (dd, *J* = 16.5, 8.4 Hz), 117.4 (d, *J* = 13.6 Hz), 115.2 (d, *J* = 22.2 Hz), 112.1 (d, *J* = 22.7 Hz), 43.7 (d, *J* = 2.5 Hz); **¹⁹F NMR** (377 MHz, CDCl₃) δ -81.51 (s, 1F), -111.01 – -111.12 (m, 1F); **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₁₆H₁₁F₂O]⁺ Calcd 257.0772, found 257.0776.

(1E)-1-[fluoro(phenyl)methylene]-3-methyl-indan-2-one (2.2f)



The title compound was prepared according to **Method C** using **2.1f** (25.2 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as a yellow solid (23.2 mg, 0.092 mmol, 92%, >95:5 E/Z). **¹H NMR** (400 MHz, CDCl₃) δ 8.03 – 7.91 (m, 1H), 7.88 – 7.75 (m, 2H), 7.54 – 7.44 (m, 3H), 7.39 – 7.33 (m, 3H), 3.52 (q, *J* = 7.5 Hz, 1H), 1.44 (d, *J* = 7.5 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 204.9 (d, *J* = 14.5 Hz), 164.1 (d, *J* = 279.1 Hz), 142.1, 136.6, 131.6, 129.4 (d, *J* = 6.9 Hz), 128.8, 128.7, 127.90, 127.87, 125.4 (d, *J* = 15.8 Hz), 124.0, 117.1, 47.4 (d, *J* = 3.3 Hz), 16.2; **¹⁹F NMR** (377 MHz, CDCl₃) δ -80.61; **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₁₇H₁₄FO]⁺ Calcd 253.1023, found 253.1026.

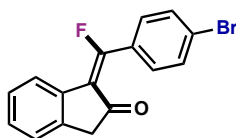
(1E)-1-[fluoro(*p*-tolyl)methylene]indan-2-one (2.2g)



The title compound was prepared according to **Method C** using **2.1g** (25.2 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired

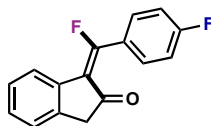
product was isolated as a yellow solid (18.7 mg, 0.074 mmol, 74%, >95:5 E/Z). **¹H NMR** (400 MHz, CDCl₃) δ 7.97 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.39 – 7.28 (m, 5H), 3.61 (s, 2H), 2.45 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 201.5 (d, *J* = 15.3 Hz), 164.6 (d, *J* = 278.5 Hz), 142.4, 138.3 (d, *J* = 3.3 Hz), 136.2, 129.4 (d, *J* = 7.0 Hz), 128.7, 128.42, 128.39, 127.8, 125.5 (d, *J* = 16.3 Hz), 124.7, 117.7 (d, *J* = 13.7 Hz), 43.7 (d, *J* = 3.6 Hz), 21.8; **¹⁹F NMR** (377 MHz, CDCl₃) δ -80.33 (s, 1F); **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₁₇H₁₄FO]⁺ Calcd 253.1023, found 253.1031.

(1E)-1-[(4-bromophenyl)-fluoro-methylene]indan-2-one (2.2h)



The title compound was prepared according to **Method C** using **2.1h** (31.5 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as a yellow solid (28.5 mg, 0.090 mmol, 90%, >95:5 E/Z). **¹H NMR** (400 MHz, CDCl₃) δ 7.95 (d, *J* = 6.8 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.41 – 7.31 (m, 3H), 3.62 (s, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 201.4 (d, *J* = 14.9 Hz), 162.8 (d, *J* = 277.5 Hz), 137.8 (d, *J* = 3.2 Hz), 136.4, 131.3, 130.9 (d, *J* = 6.9 Hz), 129.1, 128.9 (d, *J* = 2.7 Hz), 128.0, 126.3, 125.7 (d, *J* = 16.3 Hz), 124.9, 118.5 (d, *J* = 13.4 Hz), 43.6 (d, *J* = 3.4 Hz); **¹⁹F NMR** (377 MHz, CDCl₃) δ -82.57 (s, 1F); **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ Calcd 316.9972, found 316.9980. *Scale Up to 1.0 mmol*: In the glovebox, a 20 ml scintillation vial was charged with **3.1h** (0.315 g, 1.00 equiv., 1.00 mmol), TrBF₄ (8.2 mg, 2.5 mol%, 0.025 mmol) and DCE (0.1 M, 10 mL). The vial was capped with a Teflon lined cap, sealed with electrical tape, removed from the glovebox and placed in a pre-heated oil bath at 75 °C for 1 h. The reaction was cooled to rt, filtered across a pad of silica gel, eluted with CH₂Cl₂ (3 x 10 mL), and then concentrated in vacuo. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as a light yellow solid (0.236 g, 0.75 mmol, 75%, >95:5 E/Z).

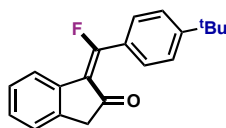
(1E)-1-[(4-fluorophenyl)-fluoro-methylene]indan-2-one (2.2i)



The title compound was prepared according to **Method C** using **2.1i** (25.6 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The desired product was isolated as a yellow solid (25.6 mg, 0.10 mmol, >99% yield, >95:5 E/Z).

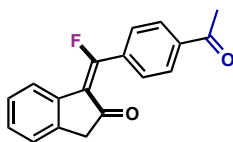
¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, *J* = 7.5 Hz, 1H), 7.88 – 7.82 (m, 2H), 7.40 – 7.31 (m, 3H), 7.16 (t, *J* = 8.4 Hz, 2H), 3.62 (s, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 201.6 (d, *J* = 15.1 Hz), 164.6 (d, *J* = 253.0 Hz), 163.1 (d, *J* = 278.1 Hz), 138.0, 136.3, 132.0 (dd, *J* = 8.9, 6.9 Hz), 128.8 (d, *J* = 2.5 Hz), 128.0, 126.3, 125.7 (d, *J* = 16.2 Hz), 124.9, 118.1 (d, *J* = 13.9 Hz), 115.3 (d, *J* = 22.0 Hz), 43.7 (d, *J* = 3.5 Hz); **¹⁹F NMR** (377 MHz, CDCl₃) δ -80.73 (s, 1F), -106.59 – -106.71 (m, 1F) ; **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₁₆H₁₁F₂O]⁺ Calcd 257.0772, found 257.0776.

(1E)-1-[(4-tert-butylphenyl)-fluoro-methylene]indan-2-one (2.2j)



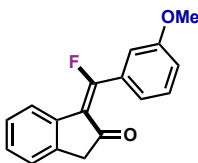
The title compound was prepared according to **Method C** using **2.1j** (29.5 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as a yellow solid (23.5 mg, 0.08 mmol, 80% yield, >95:5 E/Z). **¹H NMR** (400 MHz, CDCl₃) δ 7.97 (d, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.38 – 7.31 (m, 3H), 3.62 (s, 2H), 1.38 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃) δ 201.6 (d, *J* = 15.4 Hz), 164.6 (d, *J* = 278.2 Hz), 155.4, 138.4 (d, *J* = 3.3 Hz), 136.2, 130.5, 129.3 (d, *J* = 7.3 Hz), 128.4 (d, *J* = 2.4 Hz), 127.9, 125.6 (d, *J* = 16.4 Hz), 125.1, 124.8, 117.8 (d, *J* = 14.0 Hz), 43.8 (d, *J* = 3.5 Hz), 35.2, 31.2; **¹⁹F NMR** (377 MHz, CDCl₃) δ -80.59 (s, 1F); **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₂₀H₂₀FO]⁺ Calcd 295.1493, found 295.1496.

(1E)-1-[(4-acetylphenyl)-fluoro-methylene]indan-2-one (2.2k)



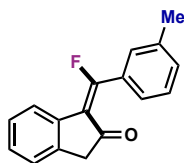
The title compound was prepared according to **Method C** using **2.1k** (28.1 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as a yellow solid (13.2 mg, 0.047 mmol, 47%, >95:5 E/Z crude, 90:10 E/Z isolated). **¹H NMR** (400 MHz, CDCl₃) δ 8.06 – 8.02 (m, 2H), 7.98 (d, *J* = 6.4 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.41 – 7.35 (m, 3H), 3.63 (s, 2H), 2.66 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 201.4 (d, *J* = 14.9 Hz), 197.5, 162.5 (d, *J* = 277.9 Hz), 139.0, 137.7 (d, *J* = 3.0 Hz), 136.7, 134.4 (d, *J* = 26.0 Hz), 129.7 (d, *J* = 6.8 Hz), 129.3 (d, *J* = 2.5 Hz), 128.1, 127.9, 126.0 (d, *J* = 16.2 Hz), 125.0, 119.4 (d, *J* = 13.2 Hz), 43.7 (d, *J* = 3.4 Hz), 26.9; **¹⁹F NMR** (377 MHz, CDCl₃) δ -83.26 (s, 1F); **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₁₈H₁₄FO₂]⁺ Calcd 281.0972, found 281.0973.

(1E)-1-[(3-methoxyphenyl)-fluoro-methylene]indan-2-one (2.2l)



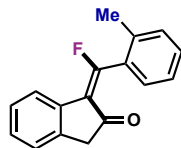
The title compound was prepared according to **Method C** using **2.1l** (28.6 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as a yellow solid (22.6 mg, 0.079 mmol, 79%, >95:5 E/Z). **¹H NMR** (600 MHz, CDCl₃) δ 7.97 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.45 – 7.29 (m, 6H), 7.07 (d, *J* = 7.9 Hz, 1H), 3.87 (s, 3H), 3.62 (s, 2H); **¹³C NMR** (151 MHz, CDCl₃) δ 201.4 (d, *J* = 14.8 Hz), 163.8 (d, *J* = 279.0 Hz), 159.0, 138.0, 136.2, 131.3 (d, *J* = 25.5 Hz), 129.0, 128.6, 127.8, 125.6 (d, *J* = 16.5 Hz), 124.7, 121.8 (d, *J* = 7.2 Hz), 118.2, 118.0, 114.3 (d, *J* = 7.1 Hz), 55.5, 43.7 (d, *J* = 3.6 Hz); **¹⁹F NMR** (377 MHz, CDCl₃) δ -80.49 (s, 1F); **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₁₇H₁₄FO₂]⁺ Calcd 269.0972, found 269.0975.

(1E)-1-[fluoro(*m*-tolyl)methylene]indan-2-one (2.2m)



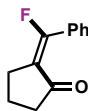
The title compound was prepared according to **Method C** using **2.1m** (25.3 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as a yellow solid (21.4 mg, 0.085 mmol, 85%, >95:5 E/Z). **¹H NMR** (400 MHz, CDCl₃) δ 7.97 (d, *J* = 7.5 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.43 – 7.29 (m, 5H), 3.61 (s, 2H), 2.43 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 201.5 (d, *J* = 15.2 Hz), 164.6 (d, *J* = 279.3 Hz), 138.2 (d, *J* = 3.0 Hz), 137.7, 136.3, 132.6, 129.9 (d, *J* = 6.6 Hz), 128.6 (d, *J* = 2.5 Hz), 128.0, 127.9, 126.8 (d, *J* = 6.9 Hz), 125.7, 125.6, 124.8, 118.1 (d, *J* = 13.4 Hz), 43.7 (d, *J* = 3.5 Hz), 21.5; **¹⁹F NMR** (377 MHz, CDCl₃) δ -79.74 (s, 1F); **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₁₇H₁₄FO]⁺ Calcd 253.1023, found 253.1030.

(1E)-1-[fluoro(*o*-tolyl)methylene]indan-2-one (2.2n)



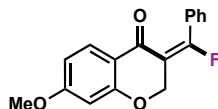
The title compound was prepared according to **Method C** using **2.1n** (25.2 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as a yellow solid (20 mg, 0.074 mmol, 74%, >95:5 E/Z). **¹H NMR** (400 MHz, CDCl₃) δ 8.01 (d, *J* = 7.4 Hz, 1H), 7.48 – 7.29 (m, 7H), 3.59 (s, 2H), 2.40 (d, *J* = 2.9 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 201.5 (d, *J* = 15.1 Hz), 164.8 (d, *J* = 284.6 Hz), 138.0, 137.4 (d, *J* = 4.3 Hz), 136.6, 131.0 (d, *J* = 2.8 Hz), 130.8 (d, *J* = 4.2 Hz), 130.5 (d, *J* = 2.1 Hz), 130.5 (d, *J* = 21.9 Hz), 128.8 (d, *J* = 2.5 Hz), 127.9, 125.7, 125.5, 125.0, 119.0 (d, *J* = 13.4 Hz), 43.5 (d, *J* = 3.7 Hz), 19.8; **¹⁹F NMR** (377 MHz, CDCl₃) δ -73.46 (s, 1F); **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₁₇H₁₄FO]⁺ Calcd 253.1023, found 253.1026.

(2E)-2-[fluoro(phenyl)methylene]cyclopentanone (2.4)



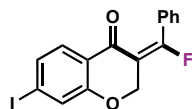
The title compound was prepared according to **Method C** using **2.3** (19.0 mg, 0.10 mmol) using 2.5 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% Ether/Hexanes) and the desired product was isolated as a brown oil (11.6 mg, 0.061 mmol, 61%, 85:15 *E/Z*, major isomer assigned by 2D ¹⁹F-¹H HOSEY). **¹H NMR** (300 MHz, CDCl₃) δ 7.96 – 7.74 (m, 2H), 7.50 – 7.40 (m, 3H), 3.03 – 2.93 (m, 2H), 2.50 – 2.40 (m, 2H), 2.00 (q, *J* = 8.1 Hz, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 204.8 (d, *J* = 14.5 Hz), 162.6 (d, *J* = 268.8 Hz), 131.2, 130.1 (d, *J* = 27.2 Hz), 128.9 (d, *J* = 6.9 Hz), 128.0, 117.4 (d, *J* = 19.6 Hz), 40.9 (d, *J* = 4.3 Hz), 27.8 (d, *J* = 4.0 Hz), 19.6; **¹⁹F NMR** (377 MHz, CDCl₃) δ -76.97 (s, 1F); **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₁₂H₁₂FO]⁺ Calcd 191.0867, found 191.0871.

(3E)-3-[fluoro(phenyl)methylene]-7-methoxy-chroman-4-one (2.6b)



The title compound was prepared according to **Method C** using **2.5b** (28.4 mg, 0.10 mmol) using 10 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as an off-white solid (20.7 mg, 0.073 mmol, 73%, 90:10 *E/Z*). **Major Isomer (6a-E):** **¹H NMR** (400 MHz, CDCl₃) δ 7.86 (d, *J* = 8.9 Hz, 1H), 7.66 (dd, *J* = 7.1, 1.0 Hz, 2H), 7.45 – 7.39 (m, 2H), 7.29 (d, *J* = 4.4 Hz, 1H), 6.60 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 5.23 (d, *J* = 3.3 Hz, 2H), 3.85 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 180.4 (d, *J* = 12.4 Hz), 163.5 (d, *J* = 268.9 Hz), 163.4, 131.4 (d, *J* = 2.0 Hz), 130.6 (d, *J* = 26.3 Hz), 129.5 (d, *J* = 5.9 Hz), 128.8, 128.4, 128.04, 128.02, 116.4 (d, *J* = 5.9 Hz), 111.9 (d, *J* = 17.1 Hz), 110.5, 66.0 (d, *J* = 12.2 Hz), 55.8; **¹⁹F NMR** (377 MHz, CDCl₃) δ -78.26 (*major*, S, 1F), -81.51 (*minor*); **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ [C₁₇H₁₄FO₃]⁺ Calcd 285.0921, found 285.0927.

(3E)-3-[fluoro(phenyl)methylene]-6-iodo-chroman-4-one (2.6c)



The title compound was prepared according to **Method C** using **2.5c** (37.9 mg, 0.10 mmol) using 10 mol% TrBF₄. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as an off-white solid (23.9 mg, 0.063 mmol, 63%, 84:16 *E/Z*). **Major Isomer (6a-E):** ¹H NMR (400 MHz, CDCl₃) δ 7.70 – 7.62 (m, 2H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.52 – 7.48 (m, 1H), 7.46 – 7.43 (m, 2H), 7.39 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.34 – 7.26 (m, 1H), 5.24 (d, *J* = 3.3 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 181.0 (d, *J* = 12.4 Hz), 164.3 (d, *J* = 272.4 Hz), 161.0, 131.6 (d, *J* = 1.9 Hz), 131.3, 129.4 (d, *J* = 6.0 Hz), 128.7, 128.01, 127.95, 127.1, 121.9 (d, *J* = 5.8 Hz), 111.4 (d, *J* = 17.7 Hz), 103.1, 65.8 (d, *J* = 12.1 Hz); ¹⁹F NMR (377 MHz, CDCl₃) δ -75.57 (*major*, s, 1F), -79.45 (*minor*); HRMS (ESI-TOF) *m/z*: [M+H]⁺ [C₁₆H₁₁FO₂]⁺ Calcd 380.9782, found 380.9787.

2.7 References

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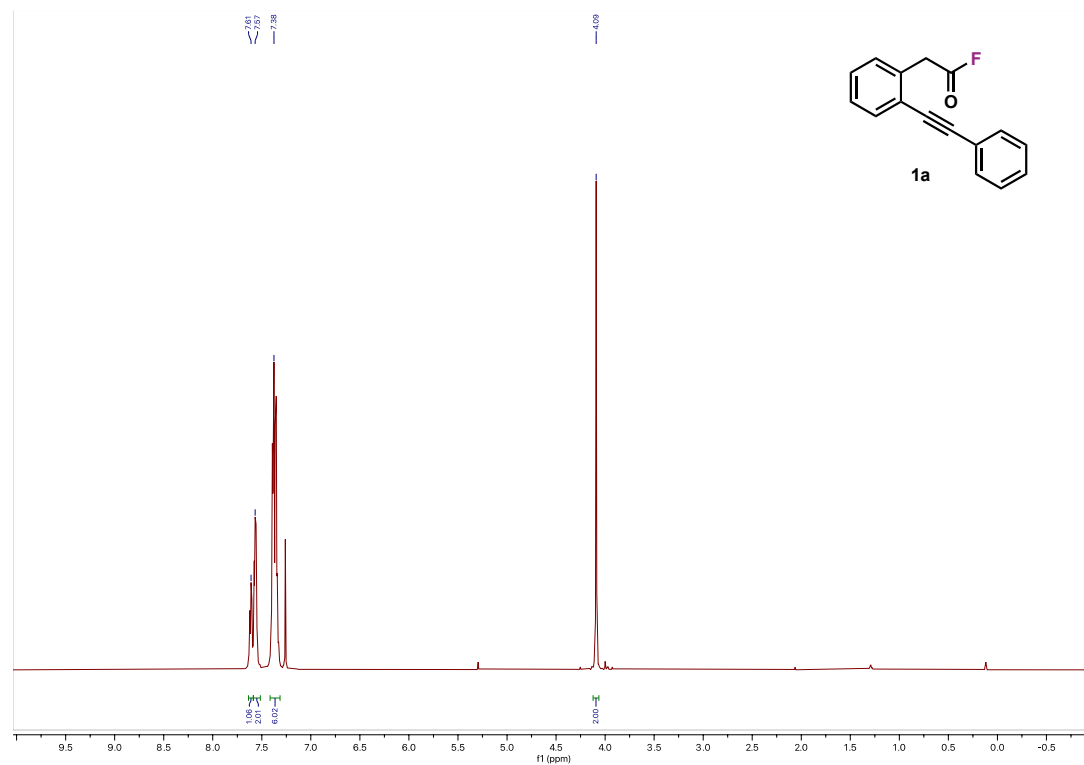
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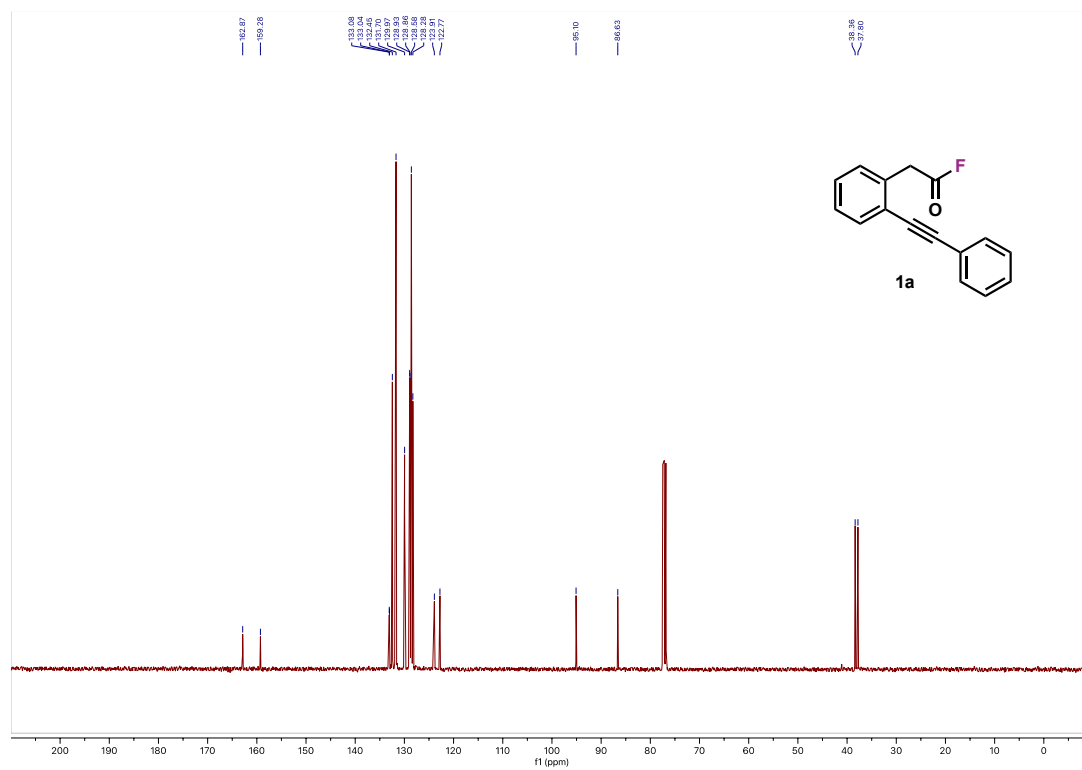
2.8 Appendix

Copies of ^1H , ^{13}C , and ^{19}F NMR Spectra

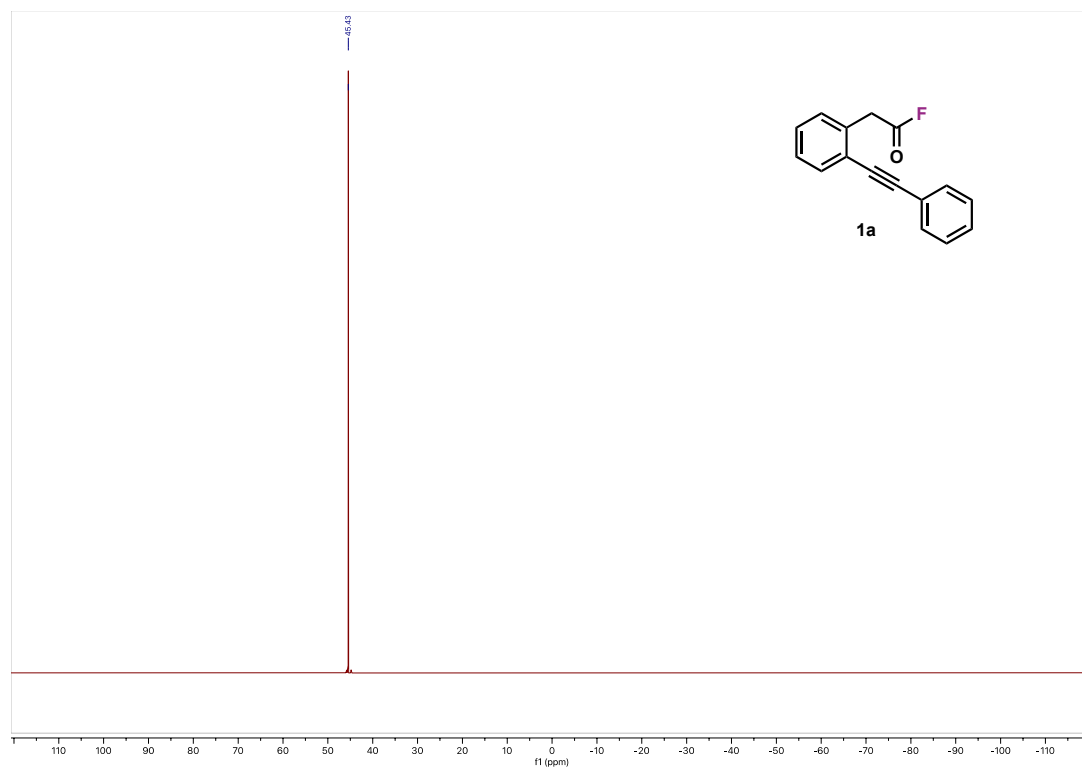
^1H NMR (400 MHz, CDCl_3) of **2.1a**



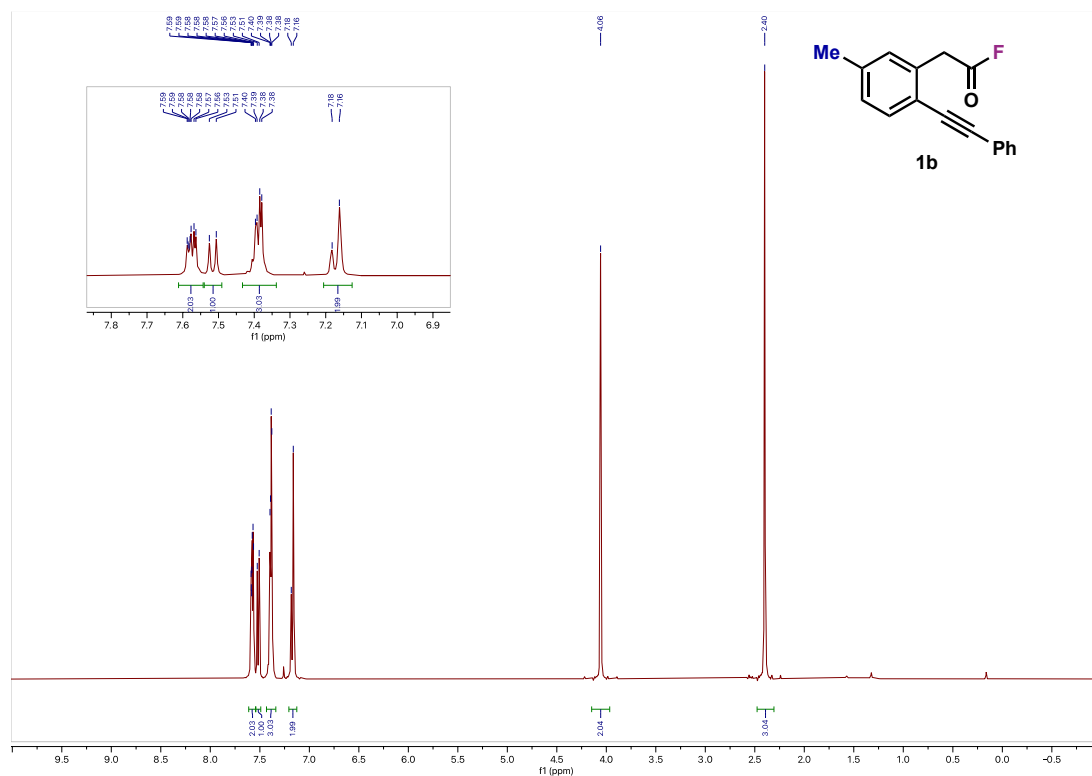
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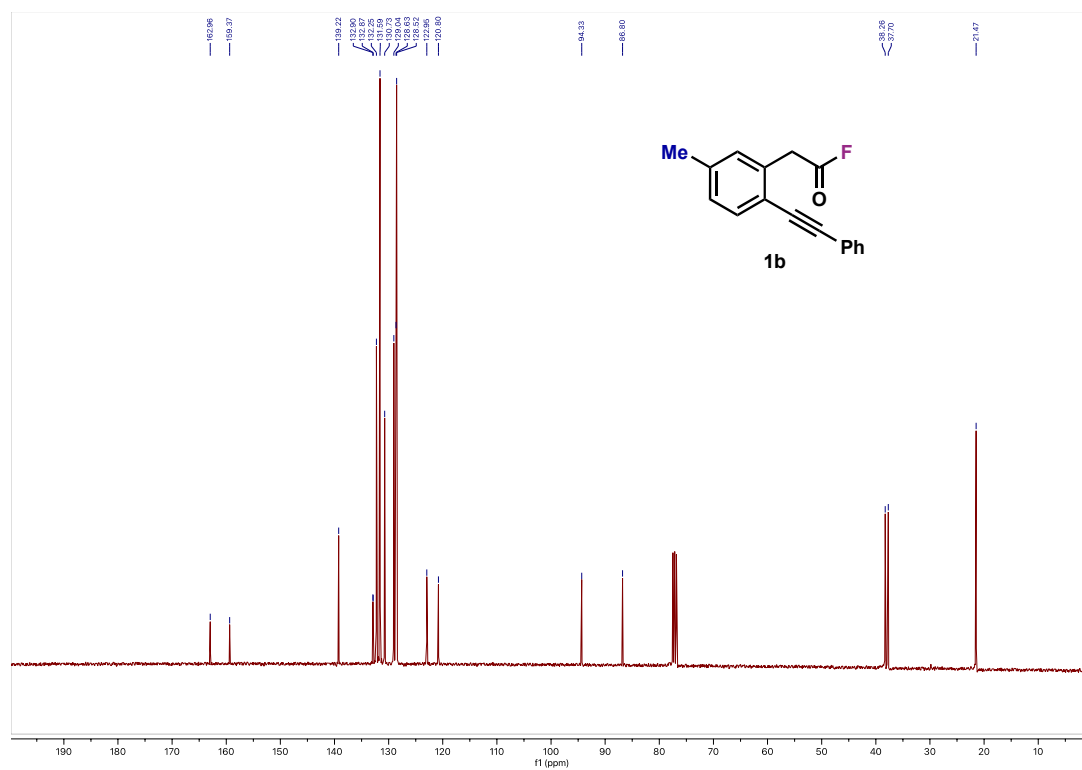
¹⁹F NMR (377 MHz, CDCl₃) of 2.1a



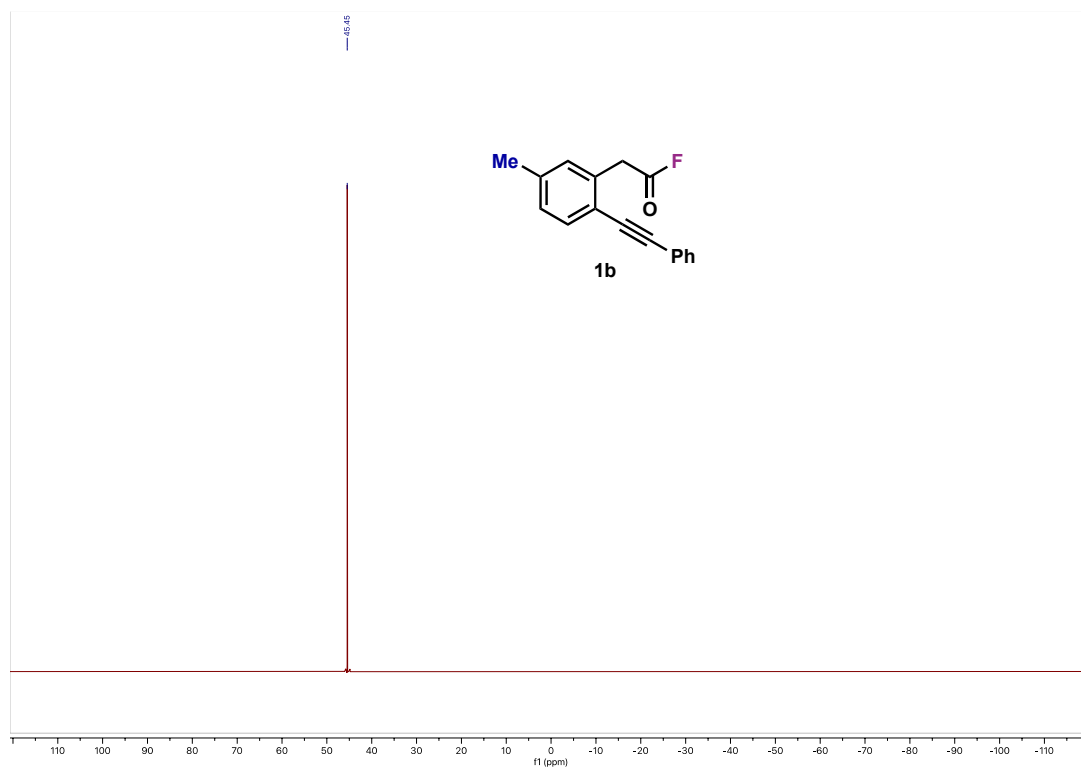
^1H NMR (400 MHz, CDCl_3) of **2.1b**



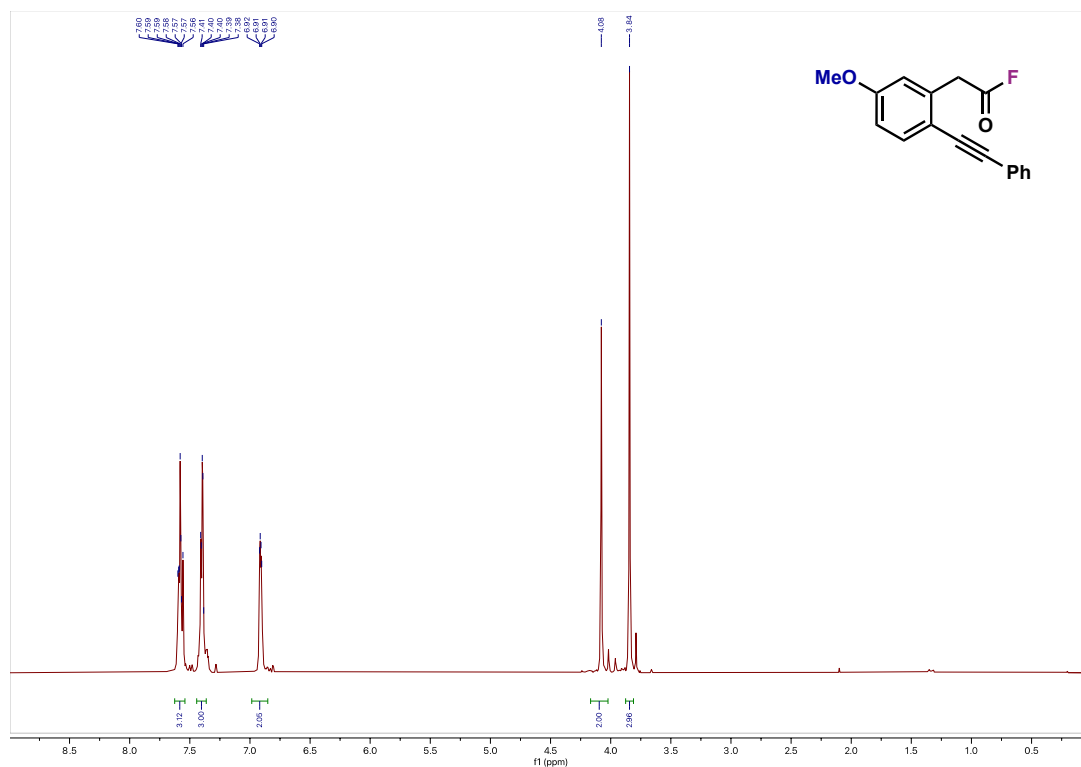
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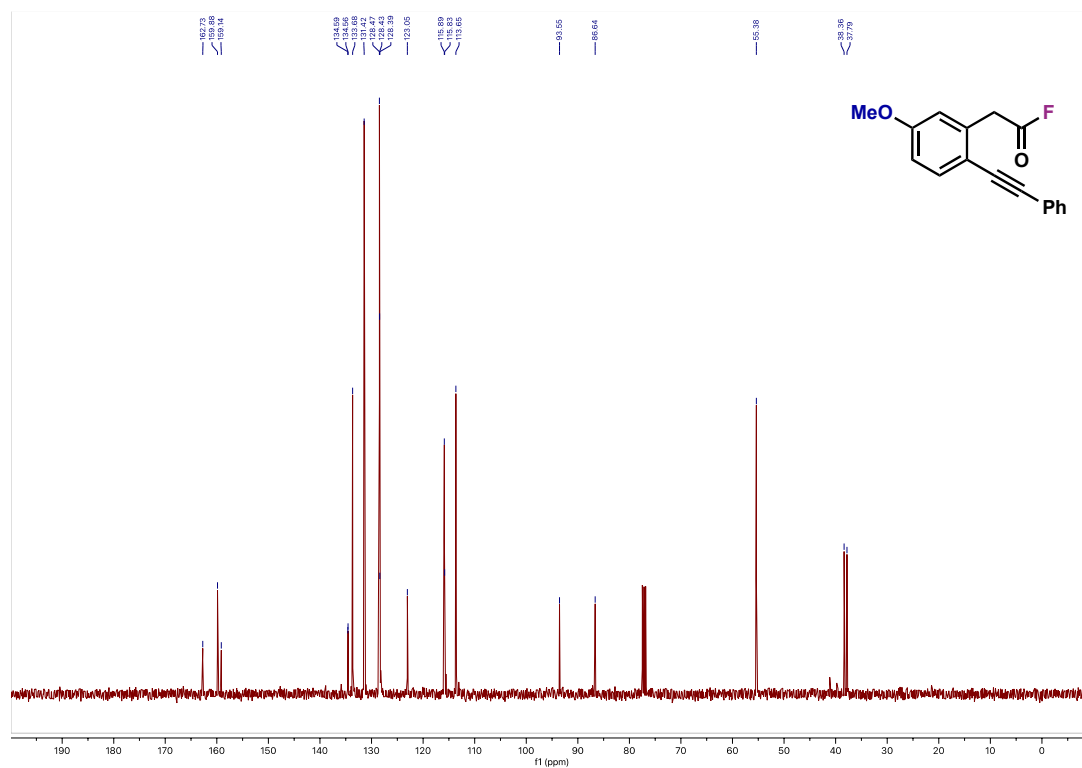
^{19}F NMR (377 MHz, CDCl_3) of **2.1b**



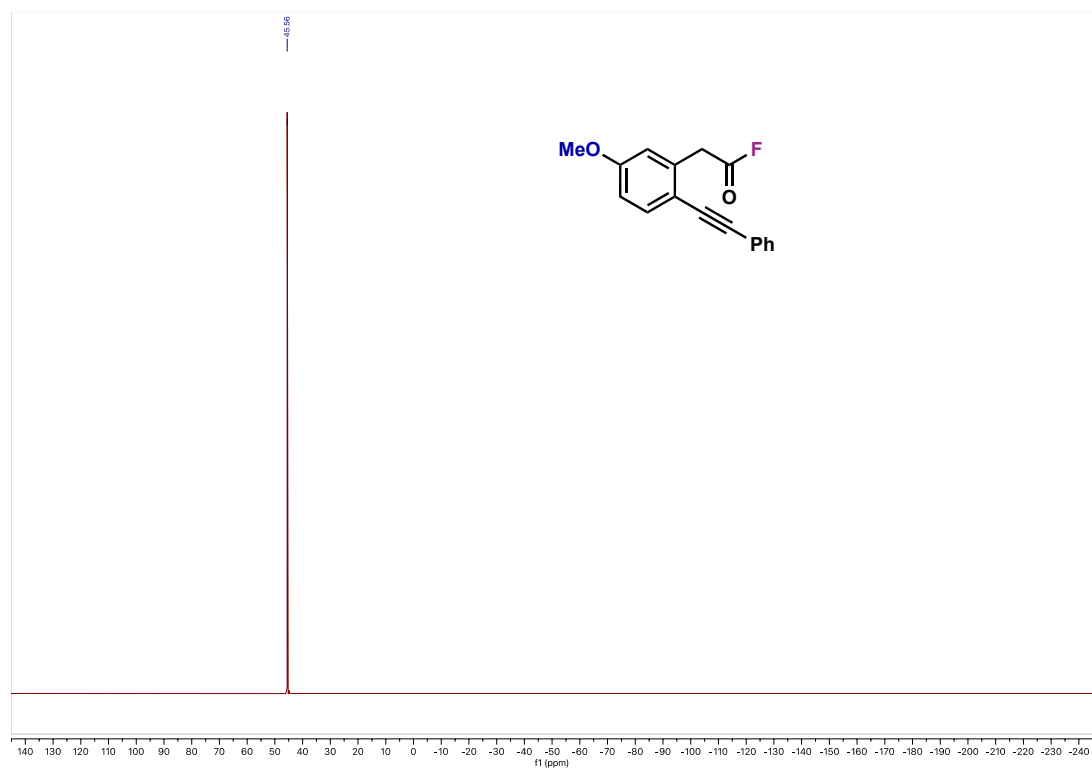
^1H NMR (400 MHz, CDCl_3) of **2.1c**



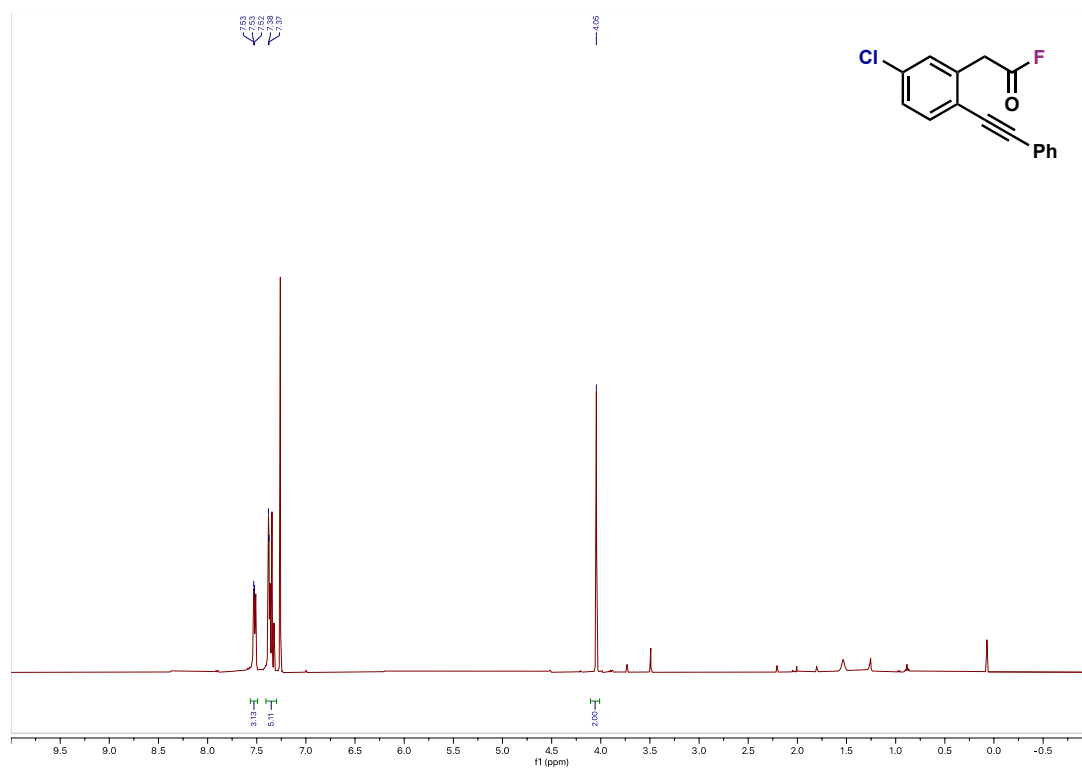
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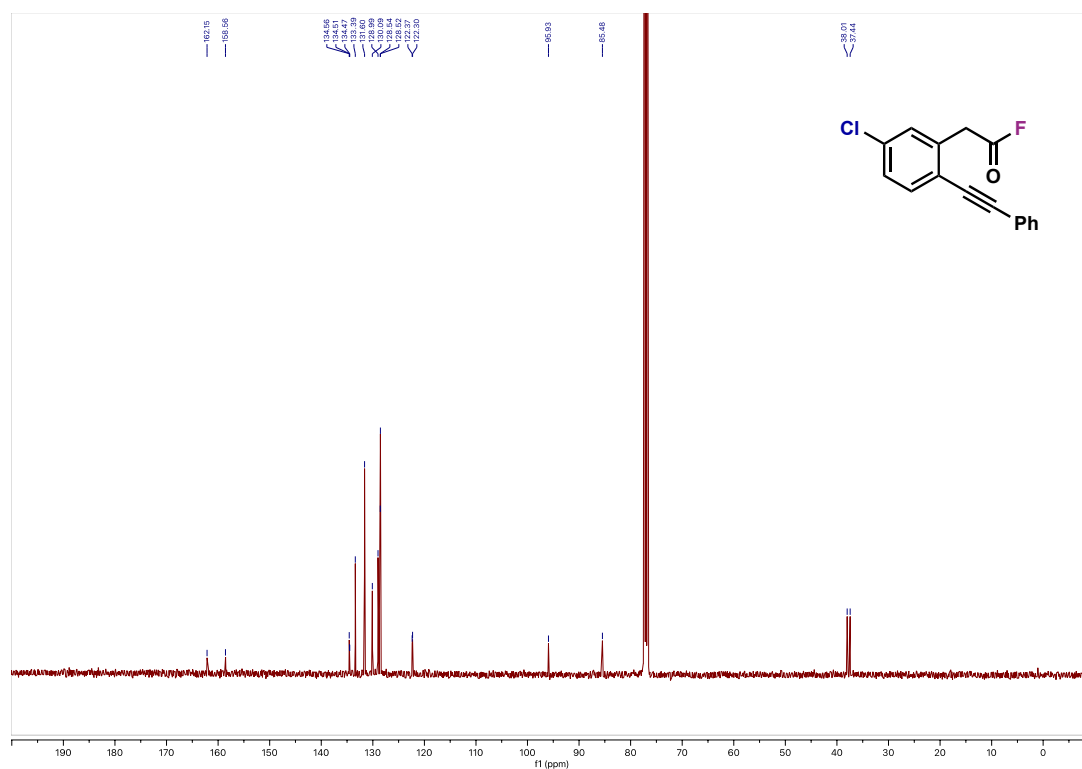
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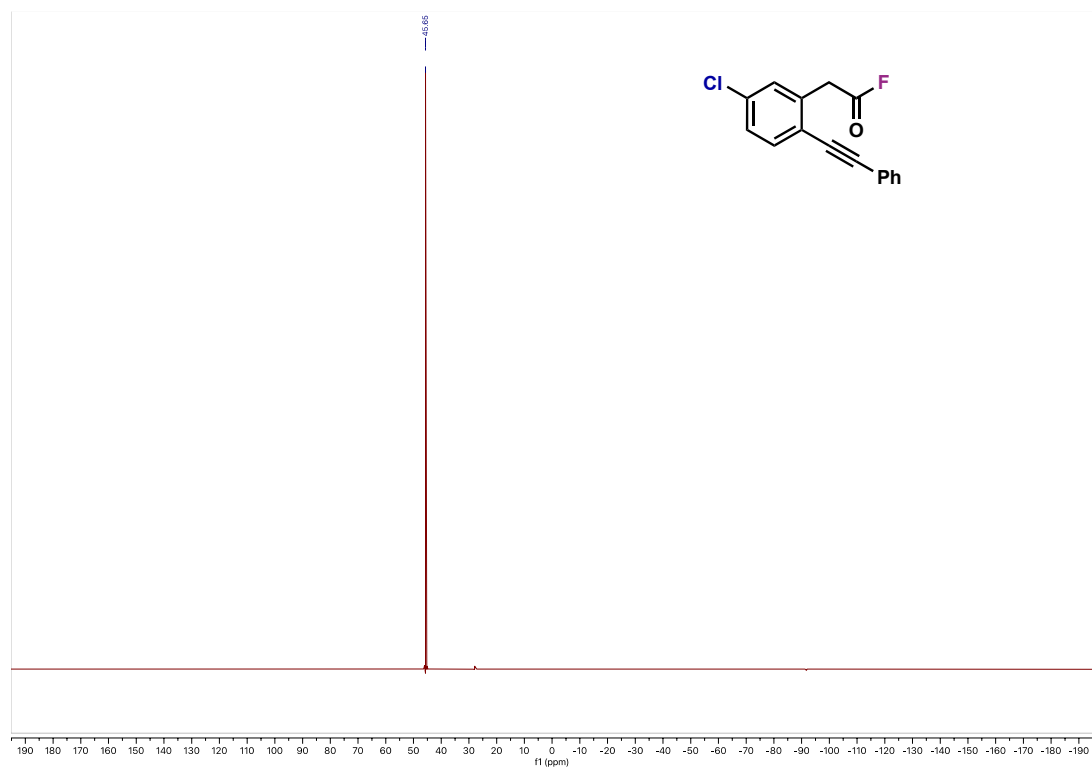
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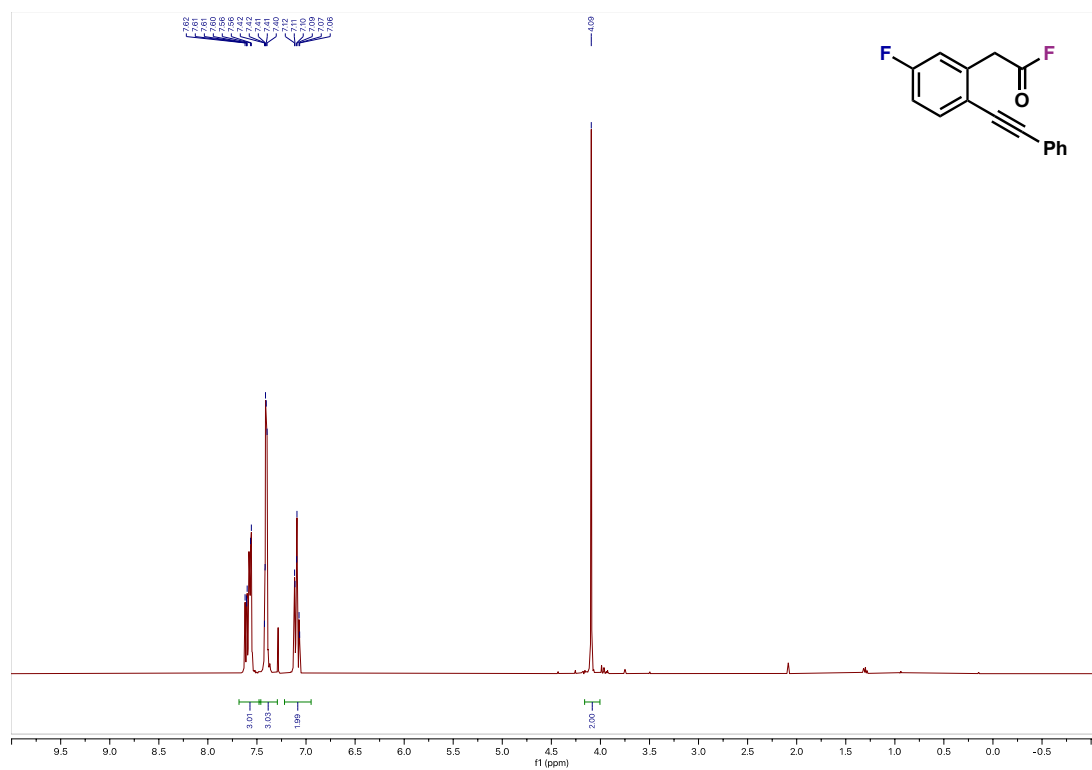
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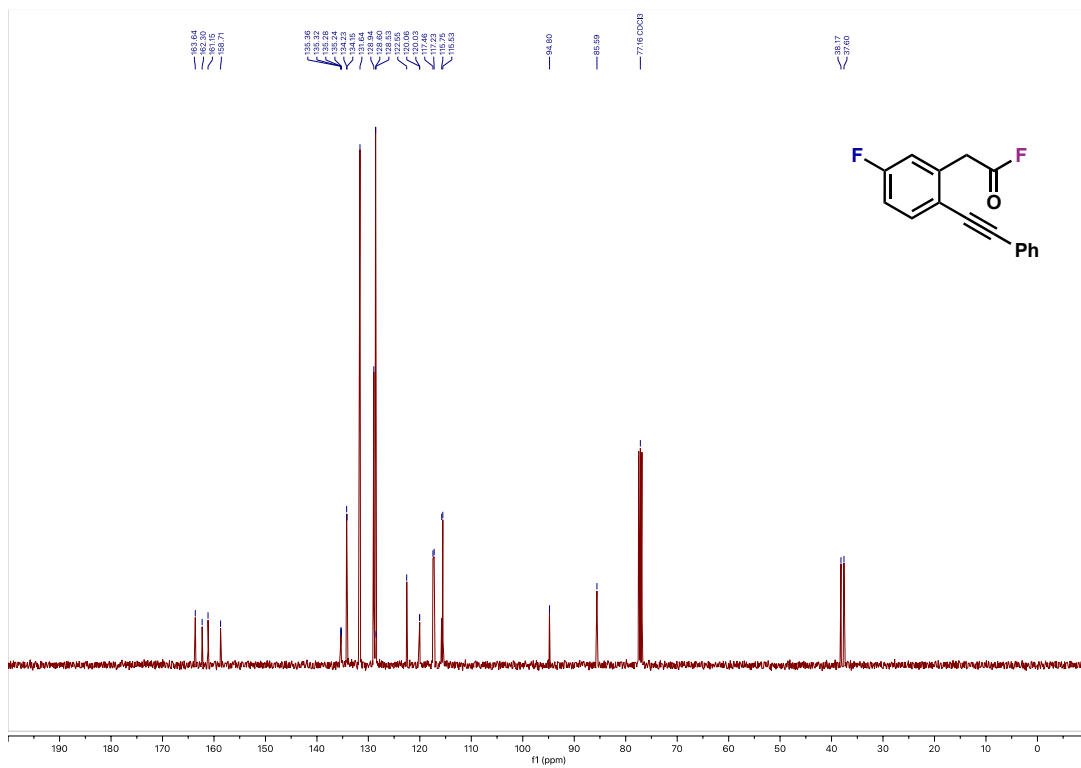
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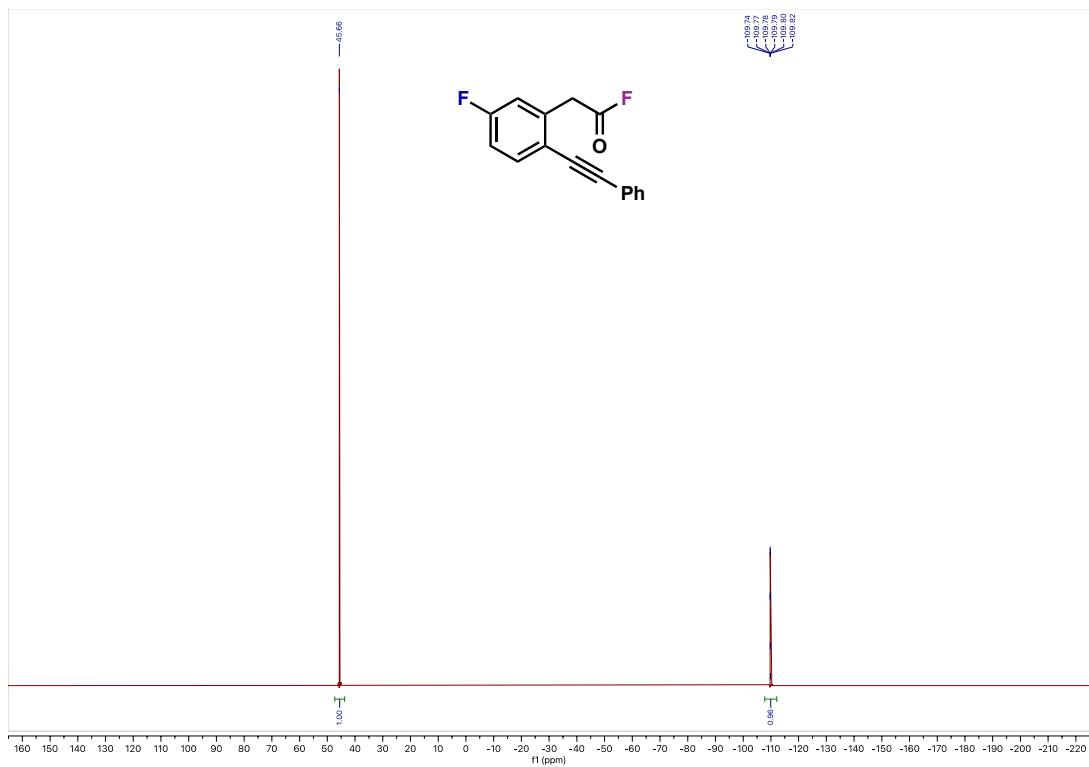
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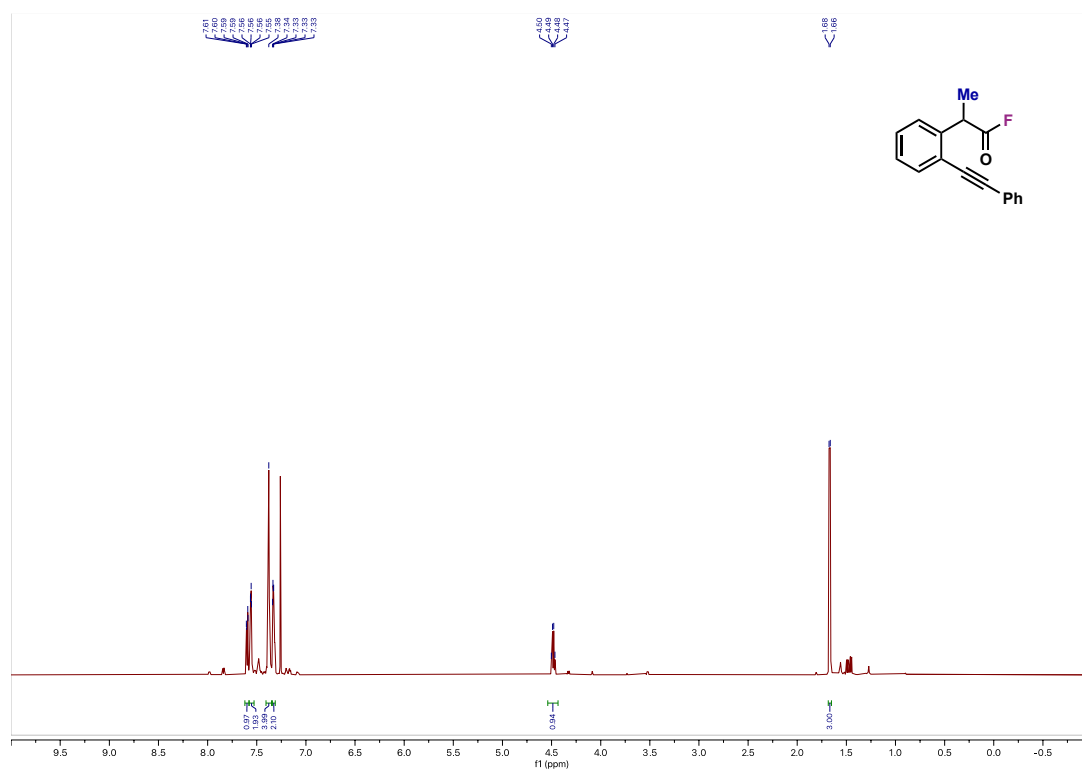
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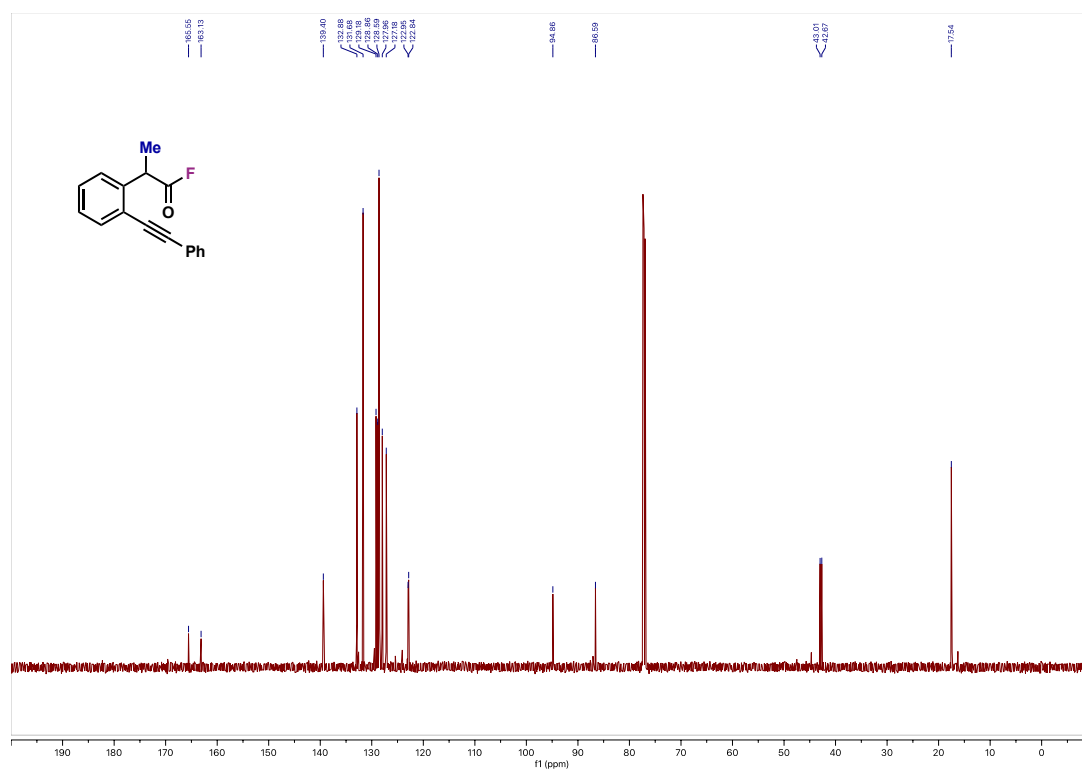
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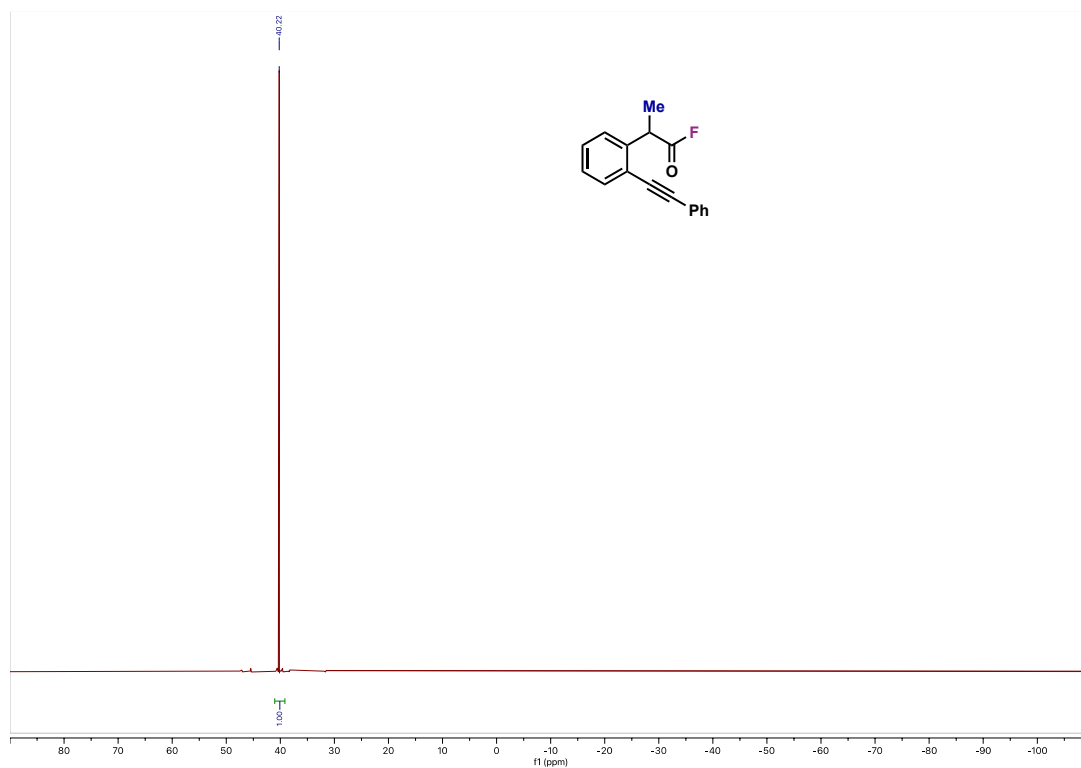
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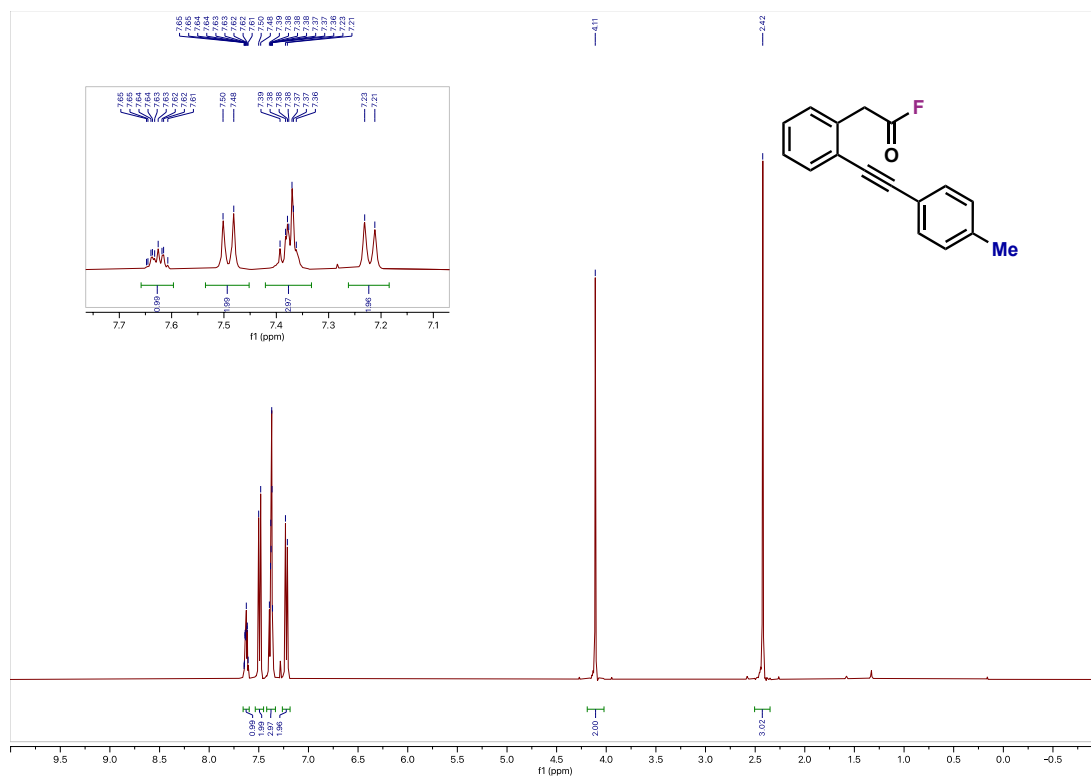
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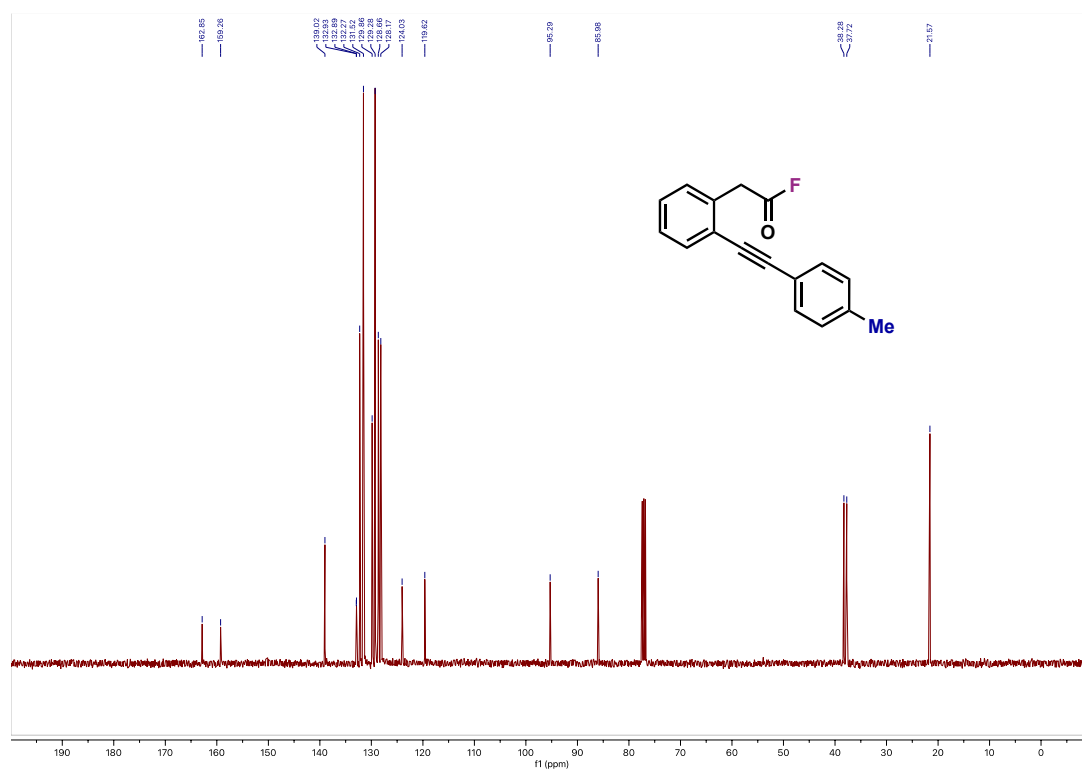
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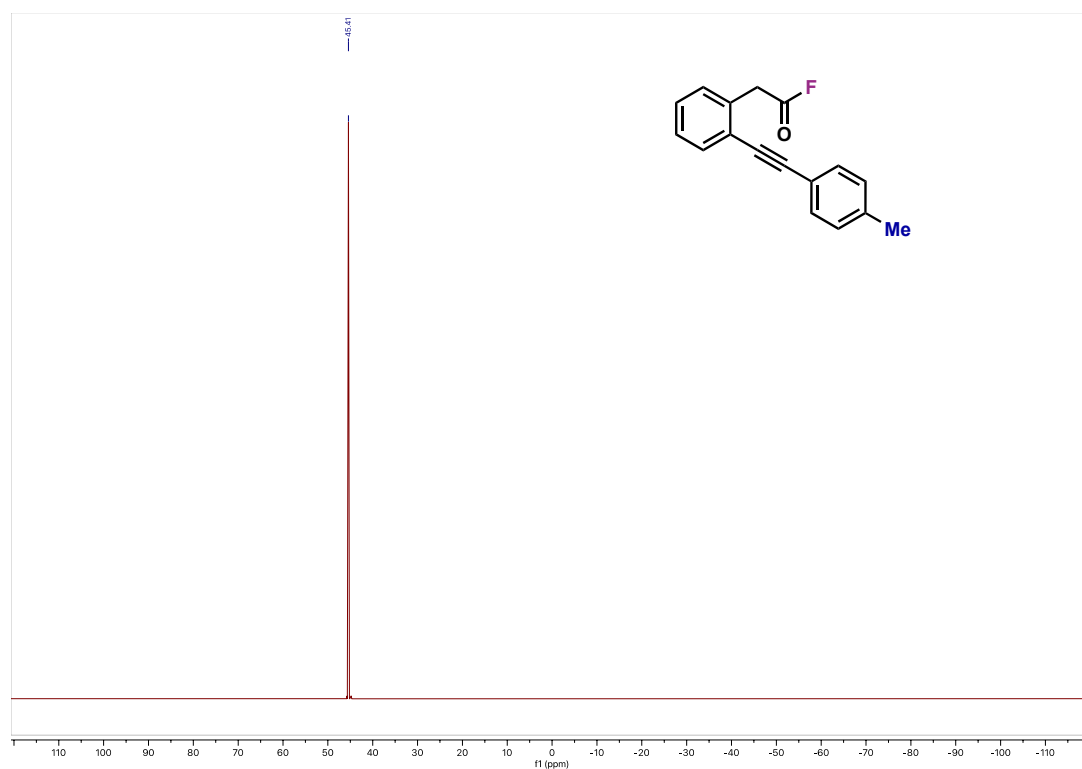
^1H NMR (400 MHz, CDCl_3) of **2.1g**



^{13}C NMR (101 MHz, CDCl_3) of **2.1g**



^{19}F NMR (377 MHz, CDCl_3) of **2.1g**



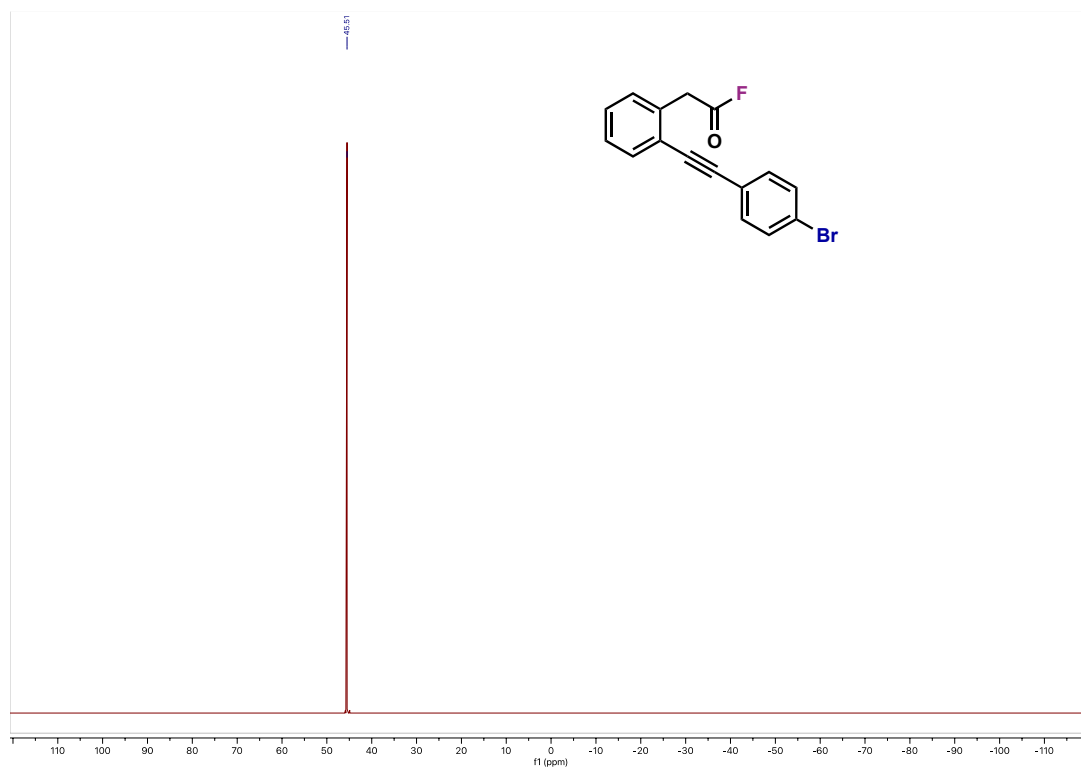
[illegible]

Chemical structure: O=C(C#Cc1ccccc1)Cc2ccccc2 (1-(4-bromophenyl)-2-(2-oxo-2-phenylethynyl)ethan-1-one)

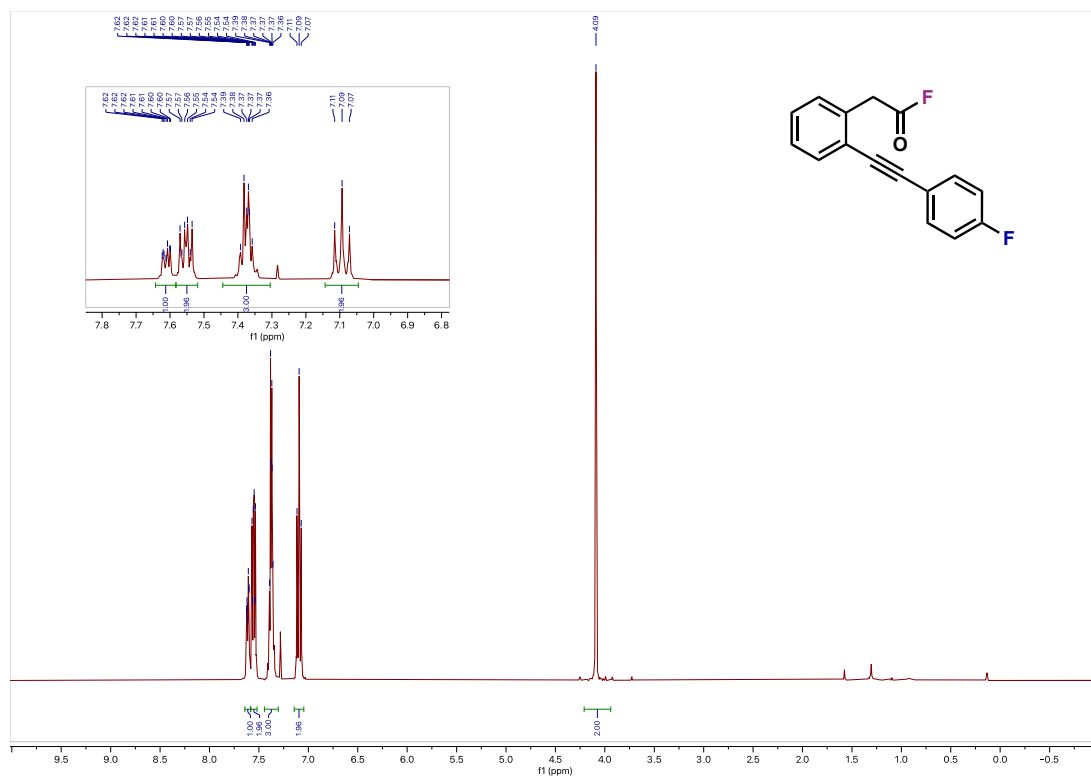
¹³C NMR spectrum (CDCl₃) showing peaks (ppm):

- 162.70
- 159.91
- 133.81
- 133.36
- 132.96
- 132.00
- 131.99
- 131.71
- 131.46
- 131.45
- 131.62
- 93.81
- 87.68
- 77.23
- 77.00
- 76.77

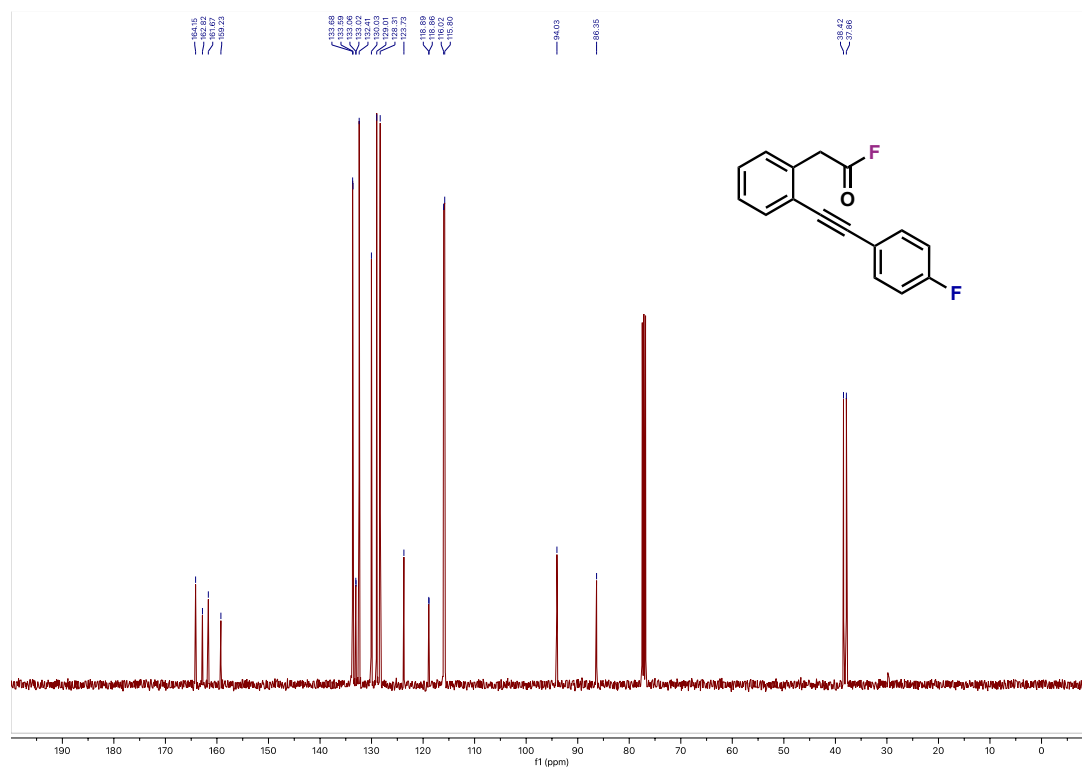
^{19}F NMR (377 MHz, CDCl_3) of **2.1h**



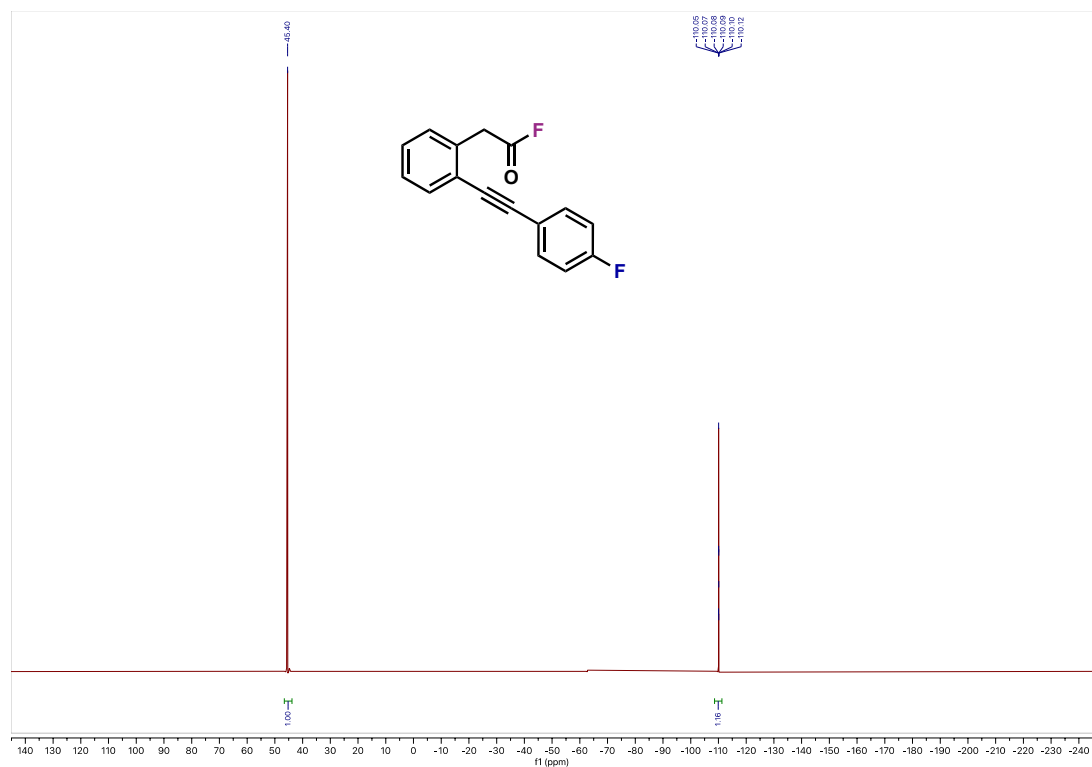
^1H NMR (400 MHz, CDCl_3) of **2.1i**



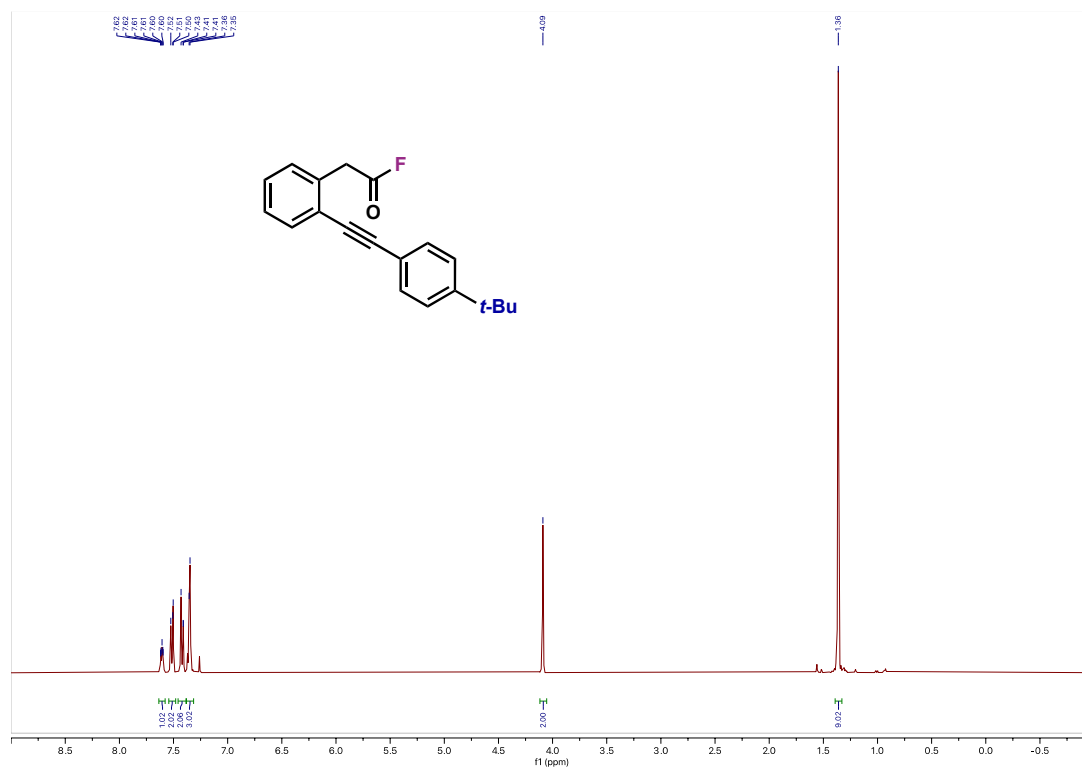
^{13}C NMR (101 MHz, CDCl_3) of **2.1i**



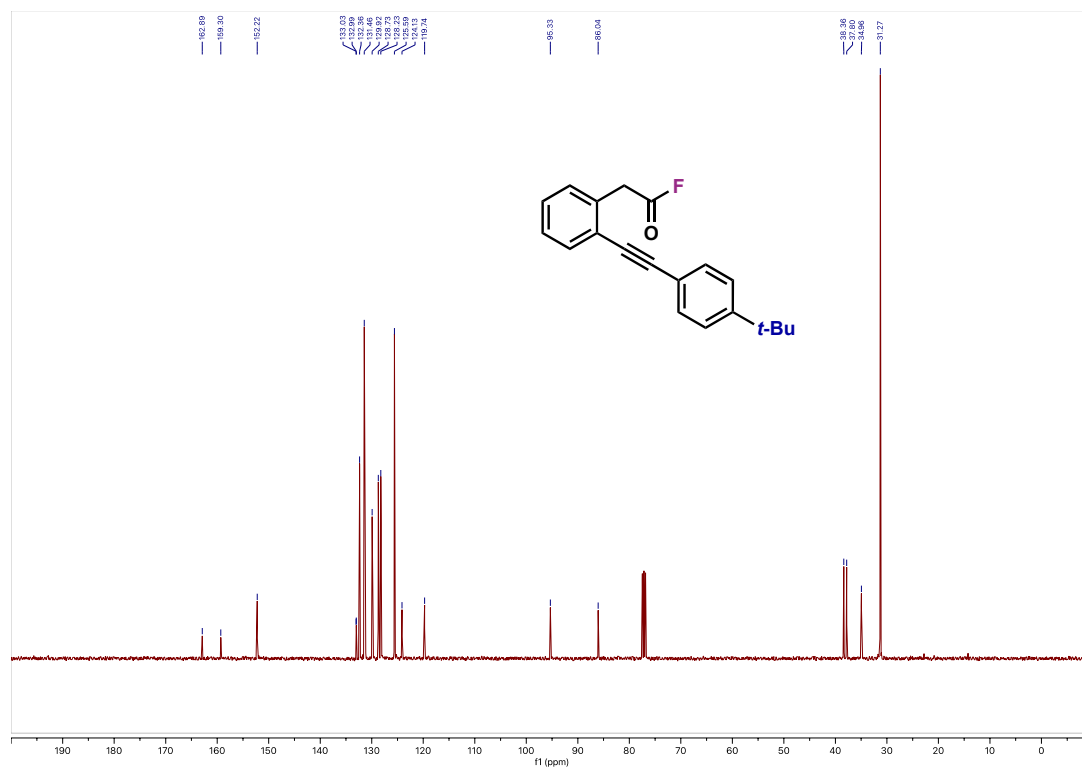
^{19}F NMR (377 MHz, CDCl_3) of **2.1i**



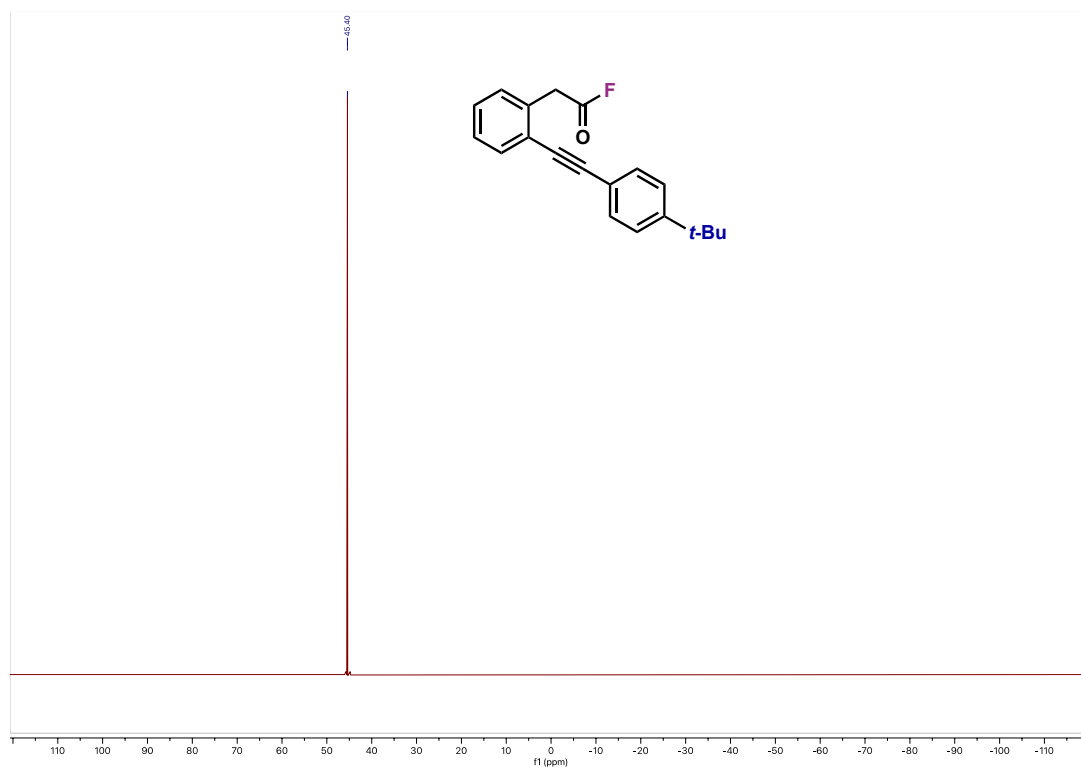
^1H NMR (400 MHz, CDCl_3) of **2.1j**



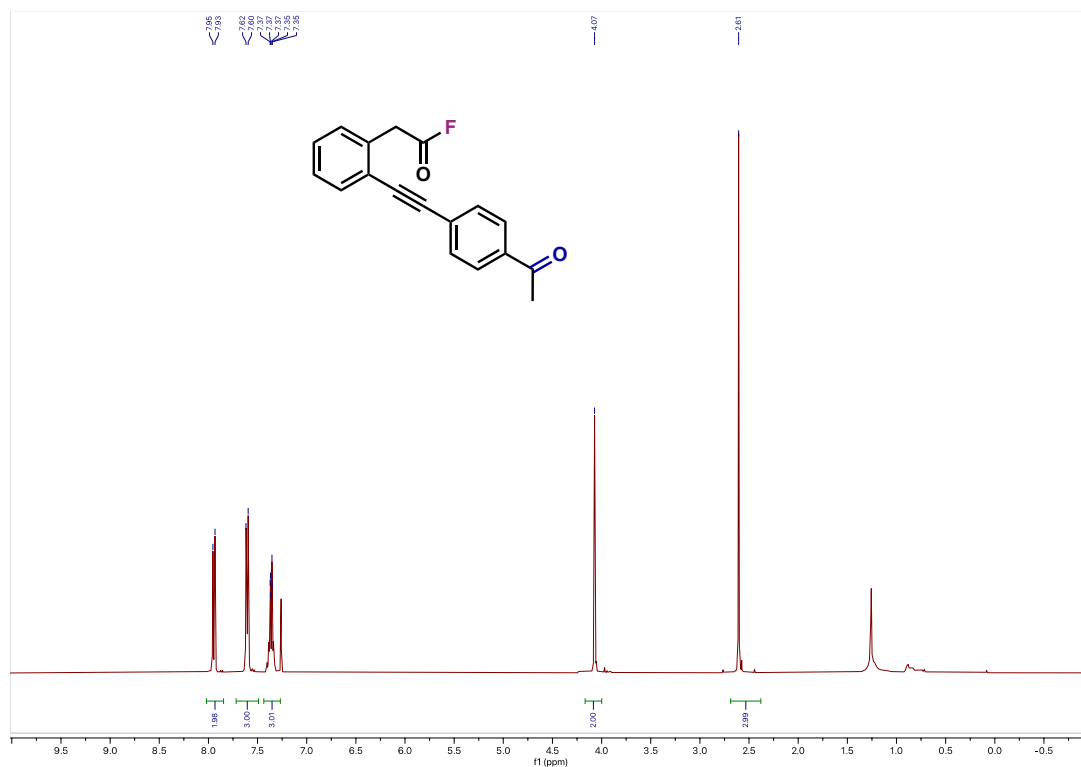
^{13}C NMR (101 MHz, CDCl_3) of **2.1j**



^{19}F NMR (377 MHz, CDCl_3) of **2.1j**



^1H NMR (400 MHz, CDCl_3) of **2.1k**



Chemical structure: CC(=O)CC1=CC=C2C(=C1)C(=C3C(=CC=C2)N4C(=C5C(=CC=C4)N=CN=C5)C(=O)N3C)C(=O)N

¹³C NMR peaks (ppm):

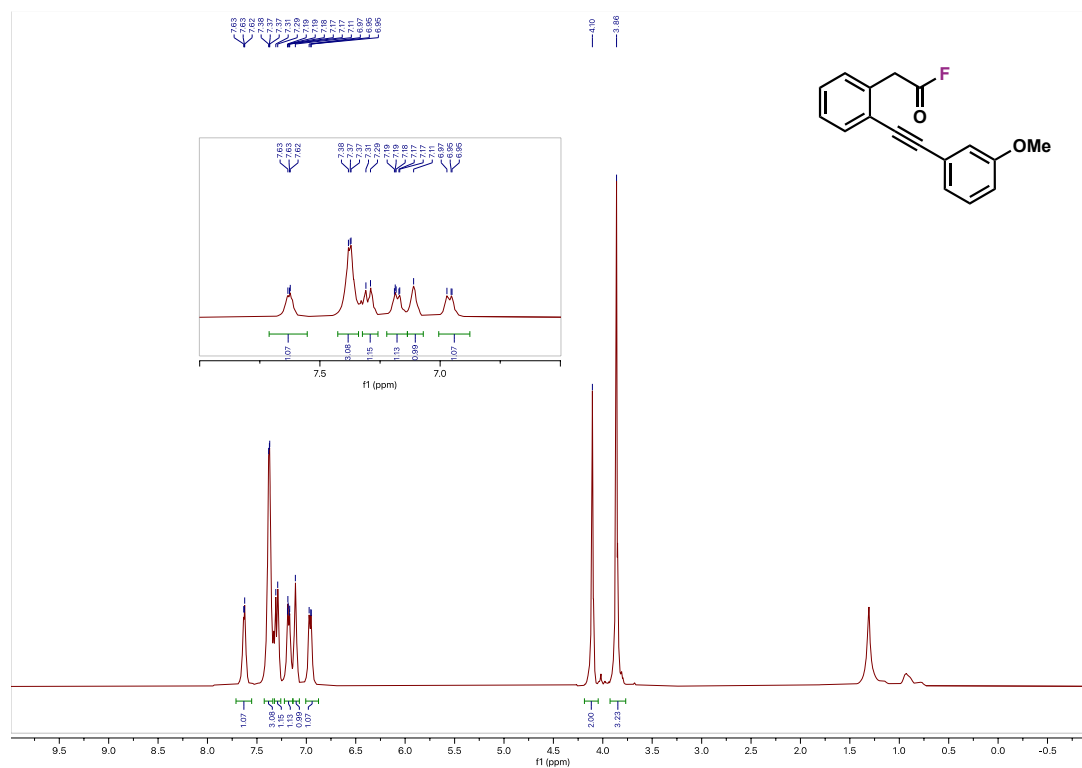
- 197.37
- 162.72
- 159.13
- 139.67
- 138.26
- 137.26
- 136.17
- 135.99
- 135.86
- 132.52
- 132.25
- 94.12
- 89.72
- 38.39
- 37.83
- 26.73

Chemical structure of 1-(4-(4-oxo-4H-chromen-2-yl)-2-butyn-1-yl)pyrrolidine-2-one:

O=C1CCN(C1)C#CC2=CC=CC=C2C(=O)C3=CC=CC=C3

The spectrum shows a single sharp peak at 4.8 ppm, labeled with its chemical shift value.

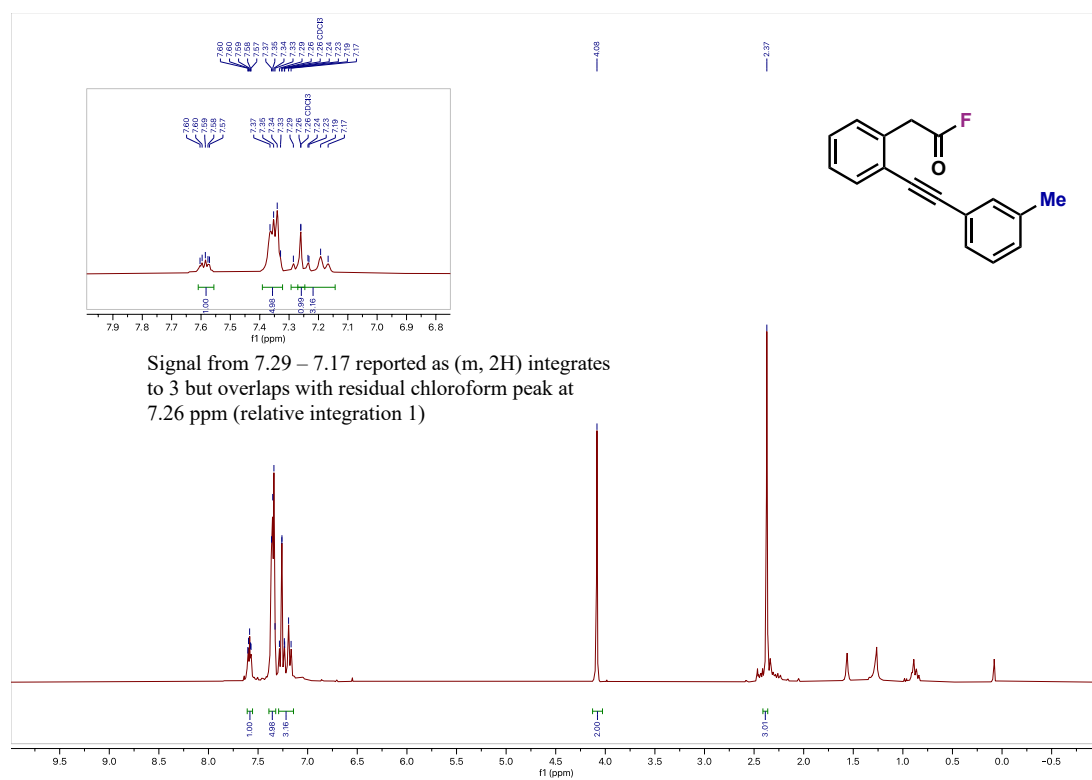
^1H NMR (400 MHz, CDCl_3) of **2.11**



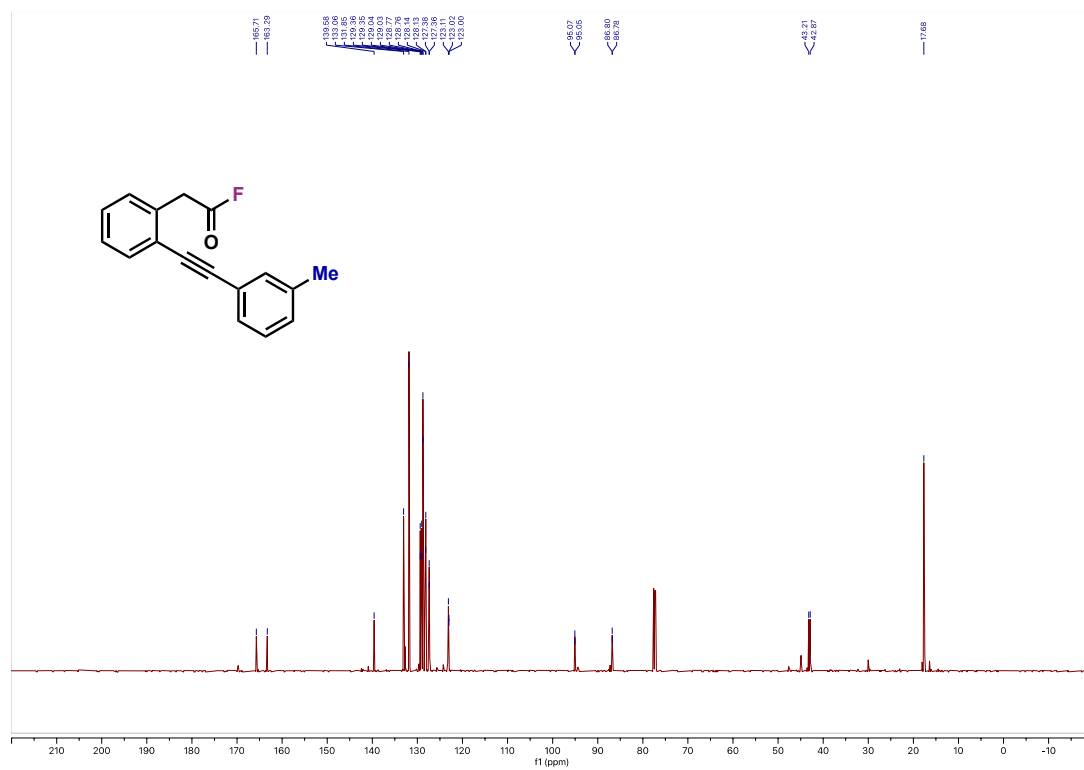
^{19}F NMR (400 MHz, CDCl_3) of **2.1l**



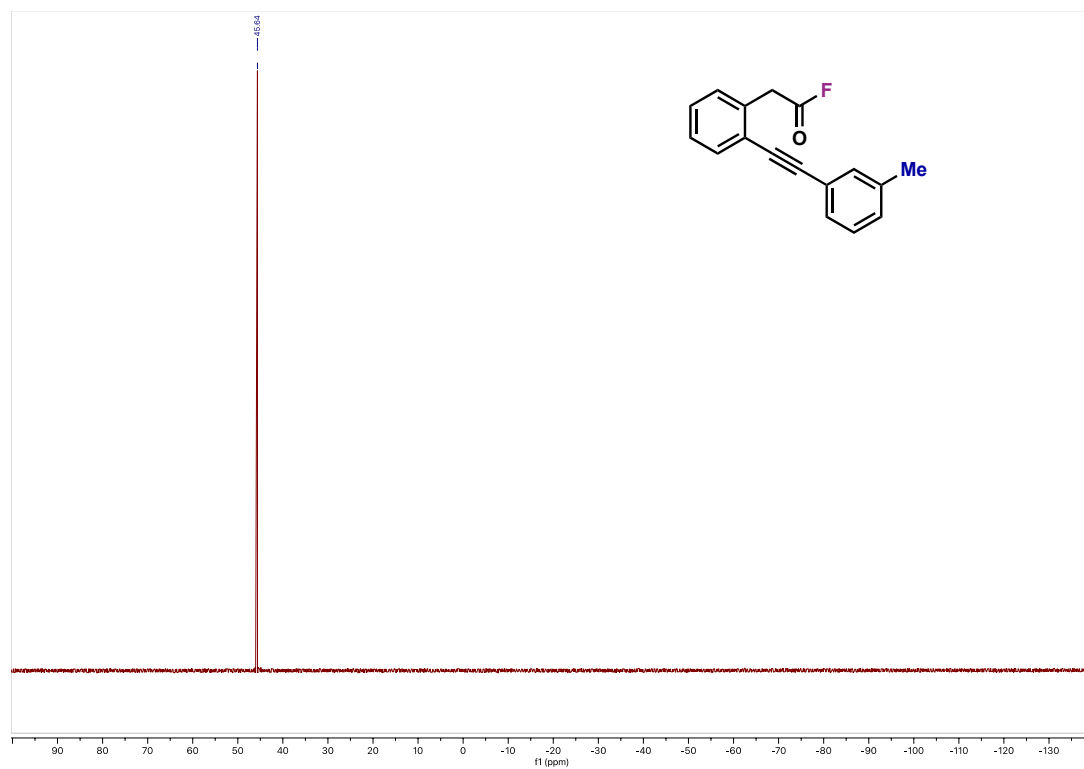
^1H NMR (400 MHz, CDCl_3) of **2.1m**



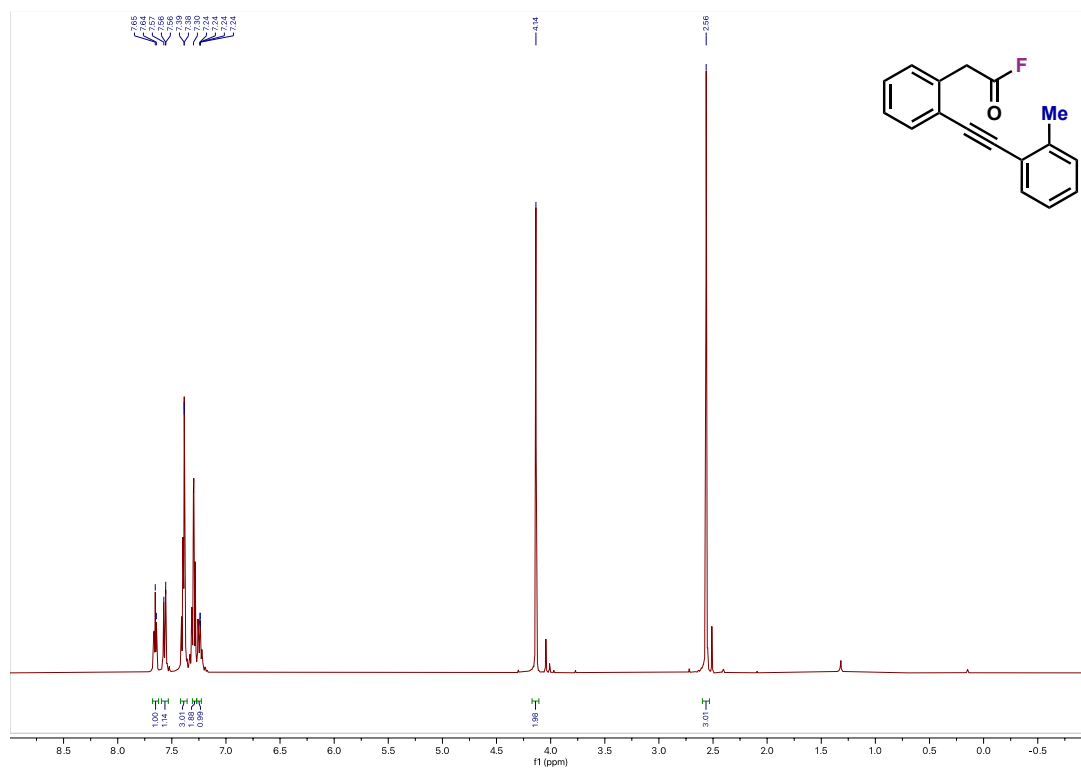
^{13}C NMR (151 MHz, CDCl_3) of 2.1m



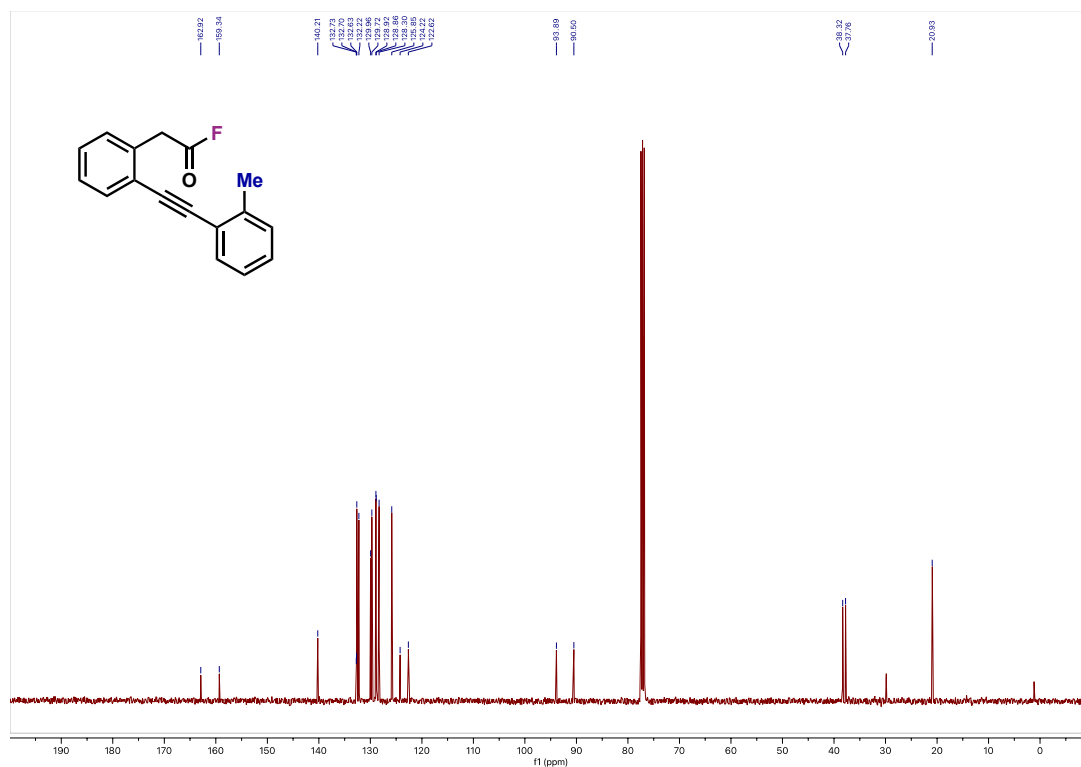
^{19}F NMR (400 MHz, CDCl_3) of 2.1m



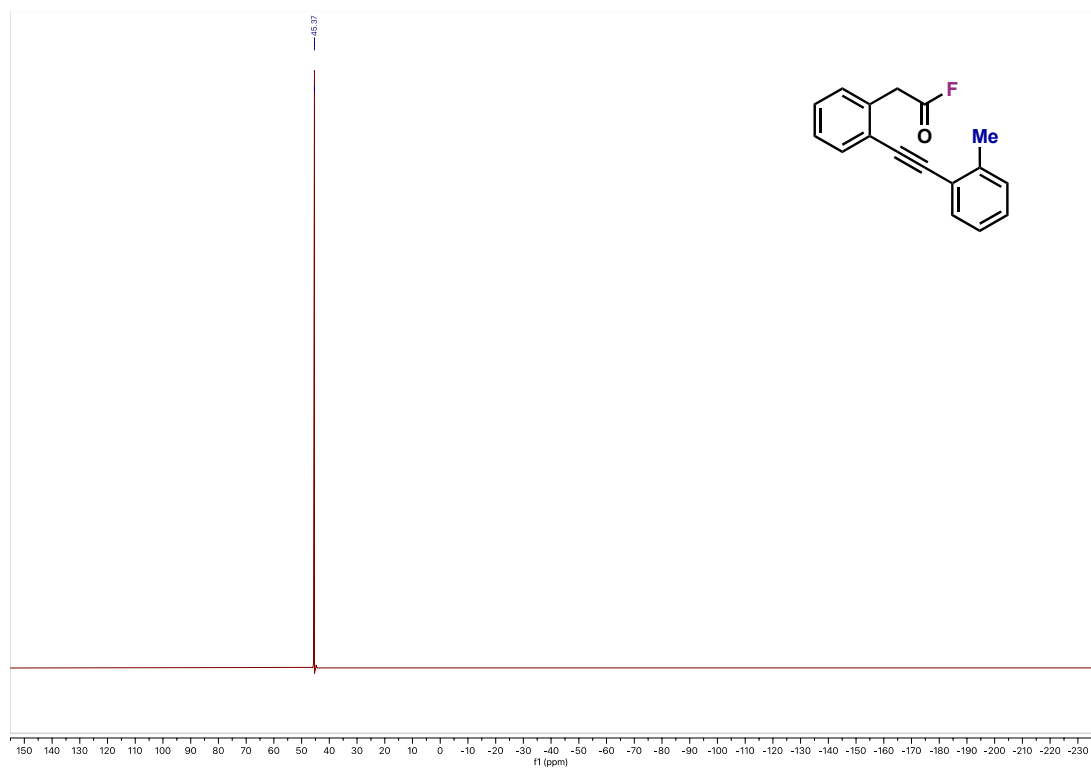
^1H NMR (400 MHz, CDCl_3) of **2.1n**



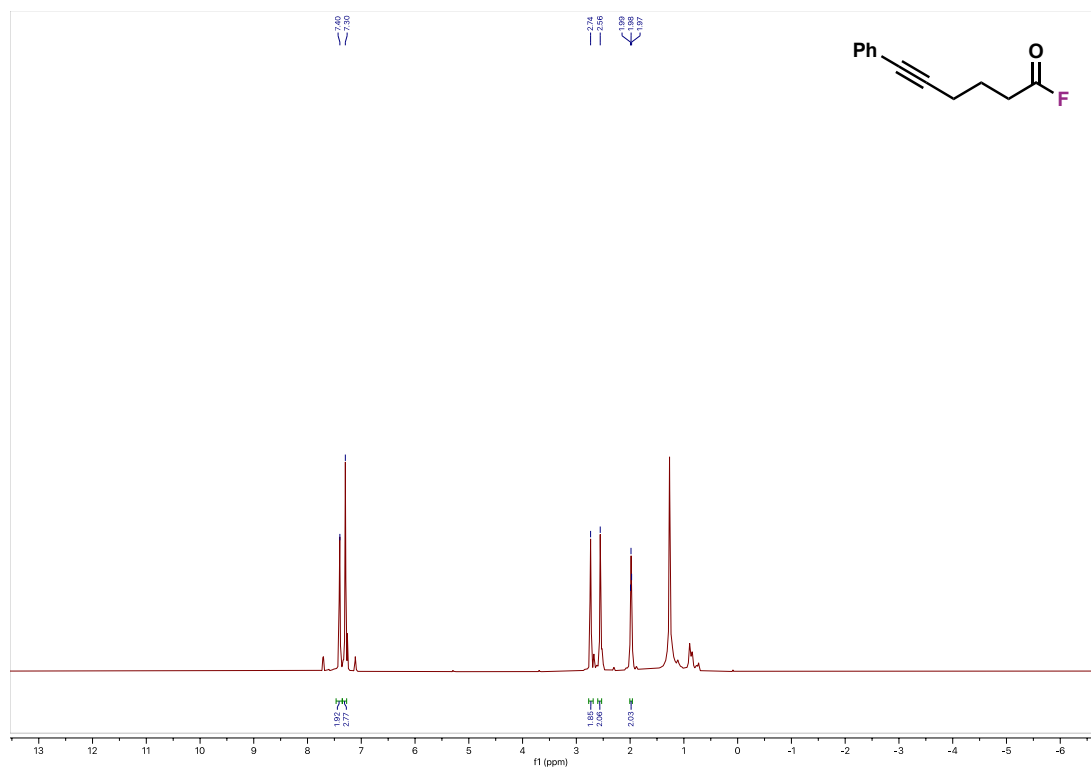
^{13}C NMR (101 MHz, CDCl_3) of **2.1n**



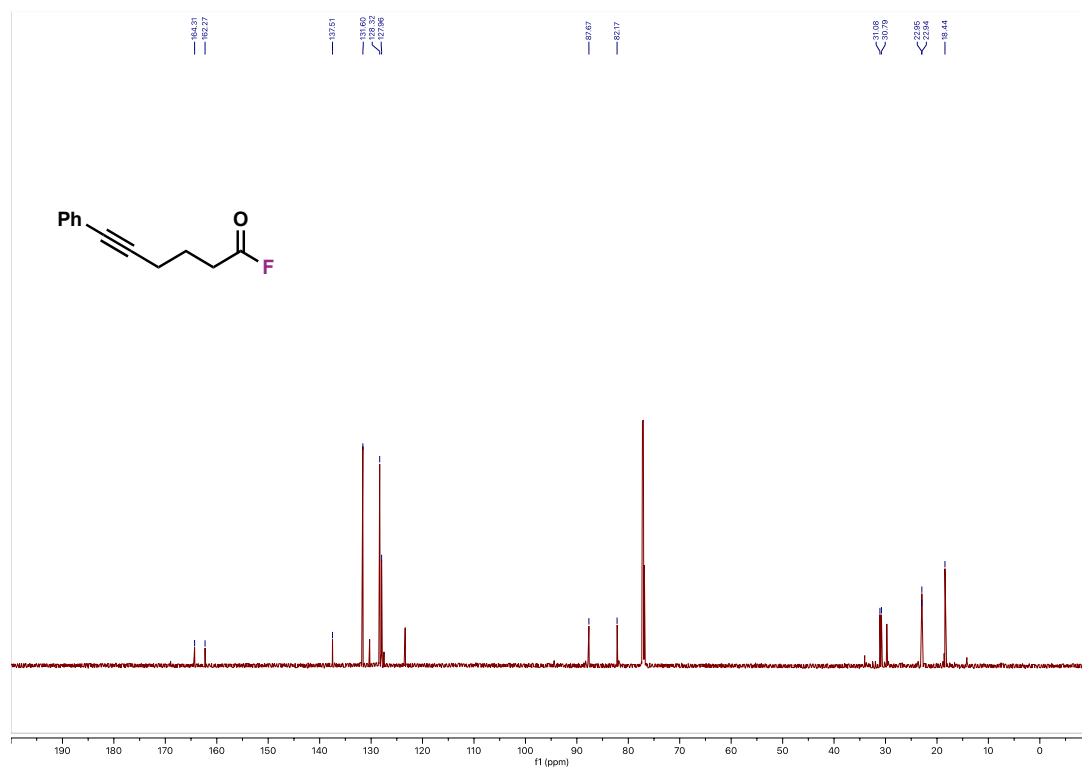
^{19}F NMR (377 MHz, CDCl_3) of **2.1n**



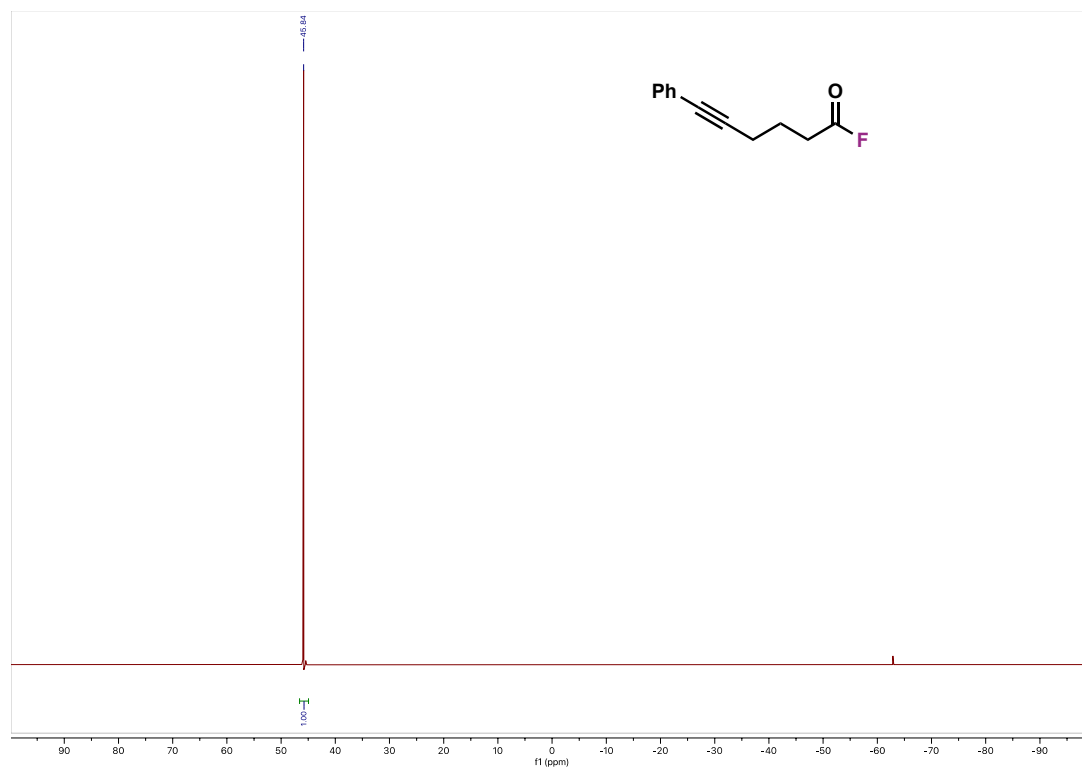
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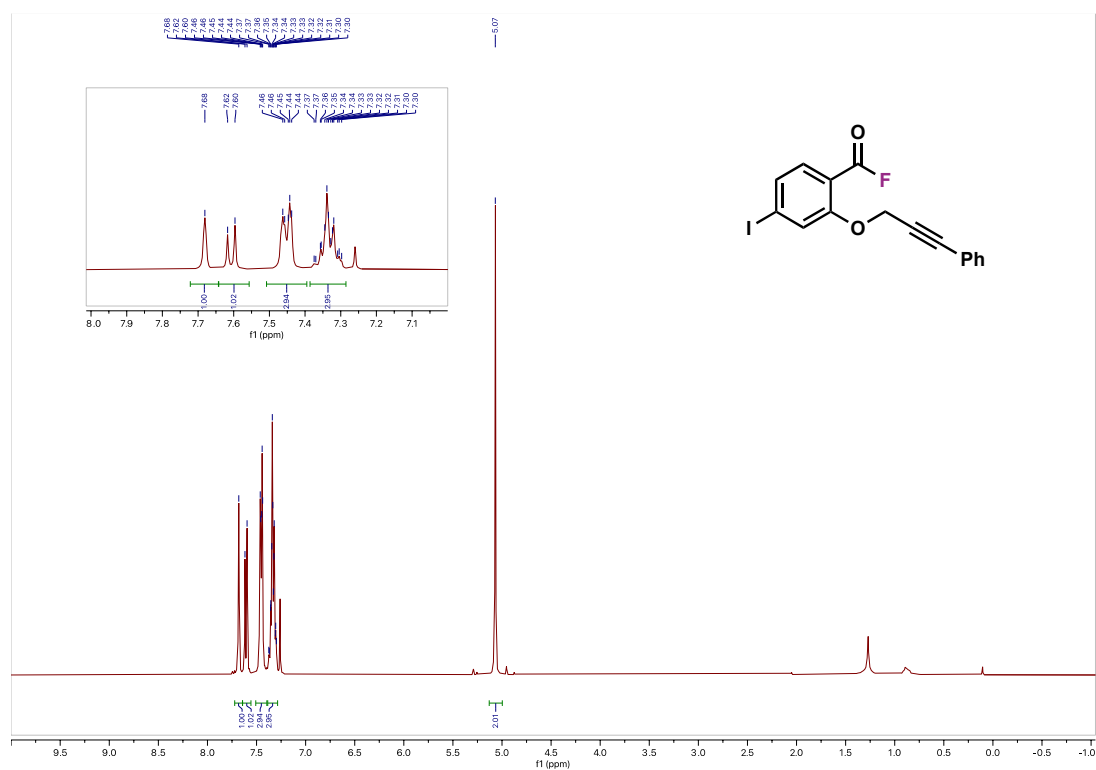
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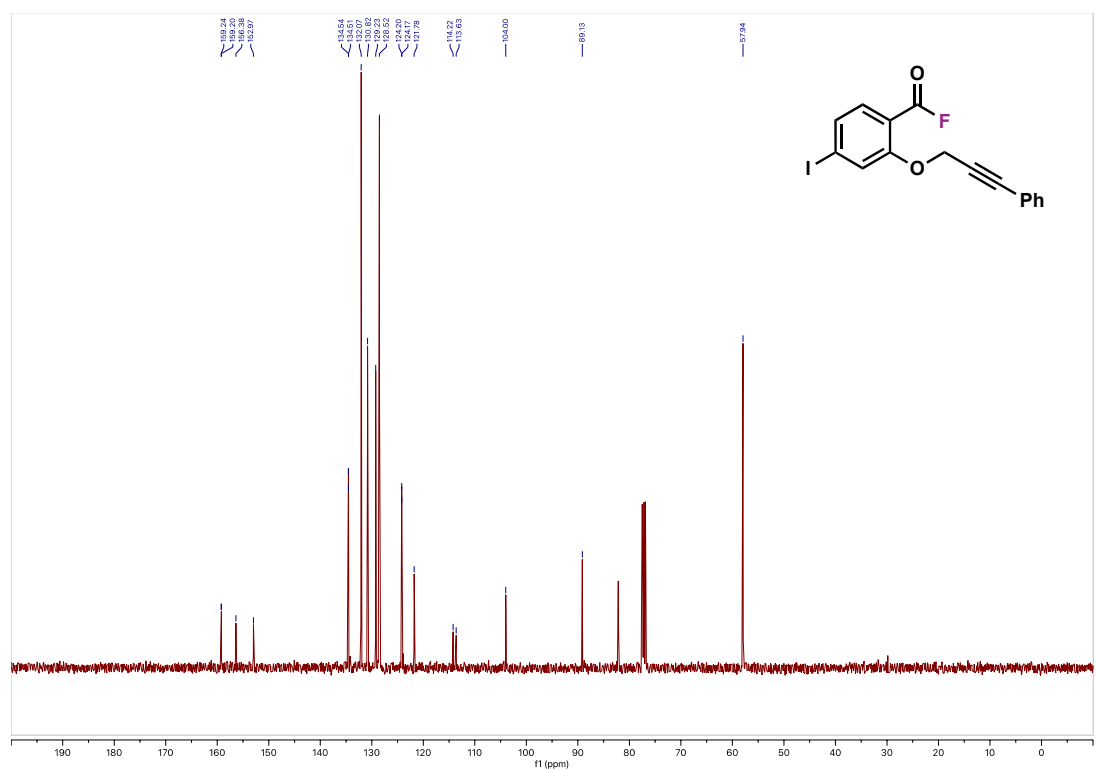
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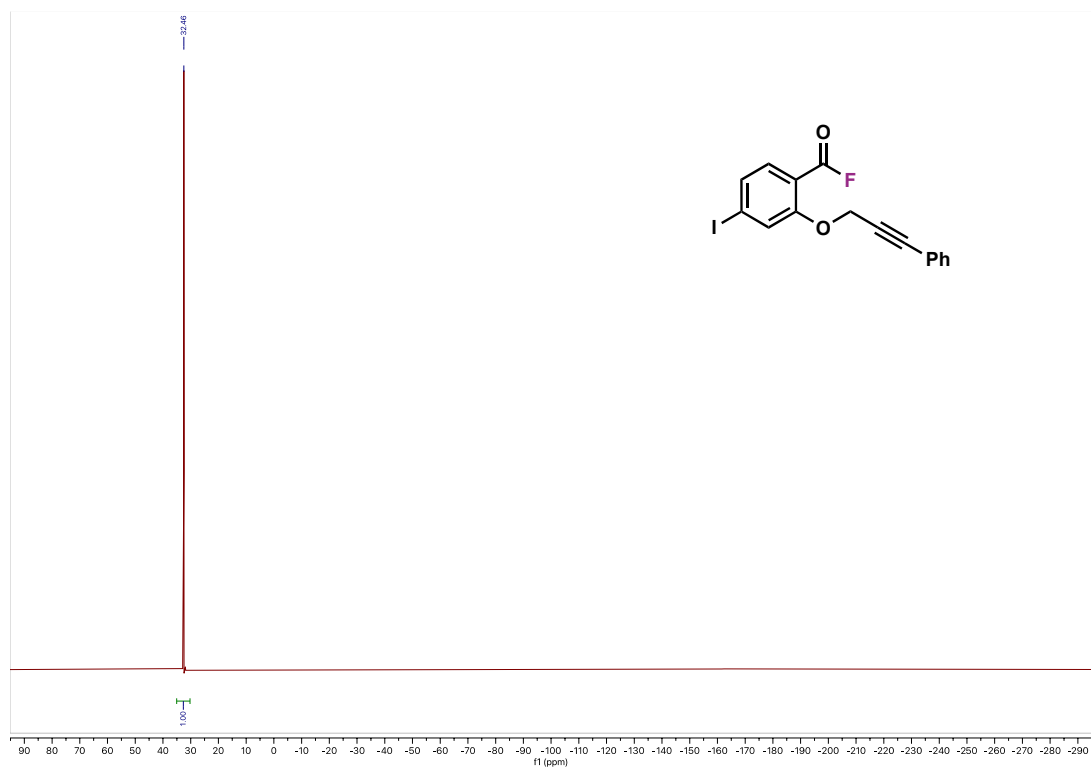
^1H NMR (400 MHz, CDCl_3) of **2.5b**



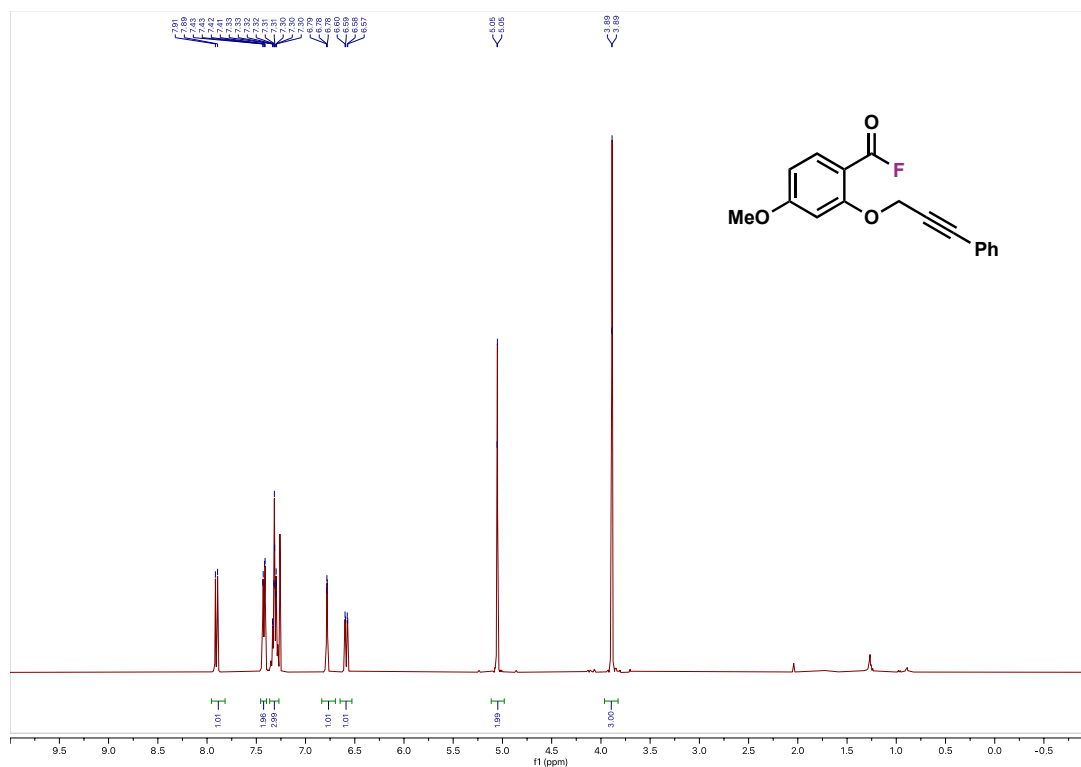
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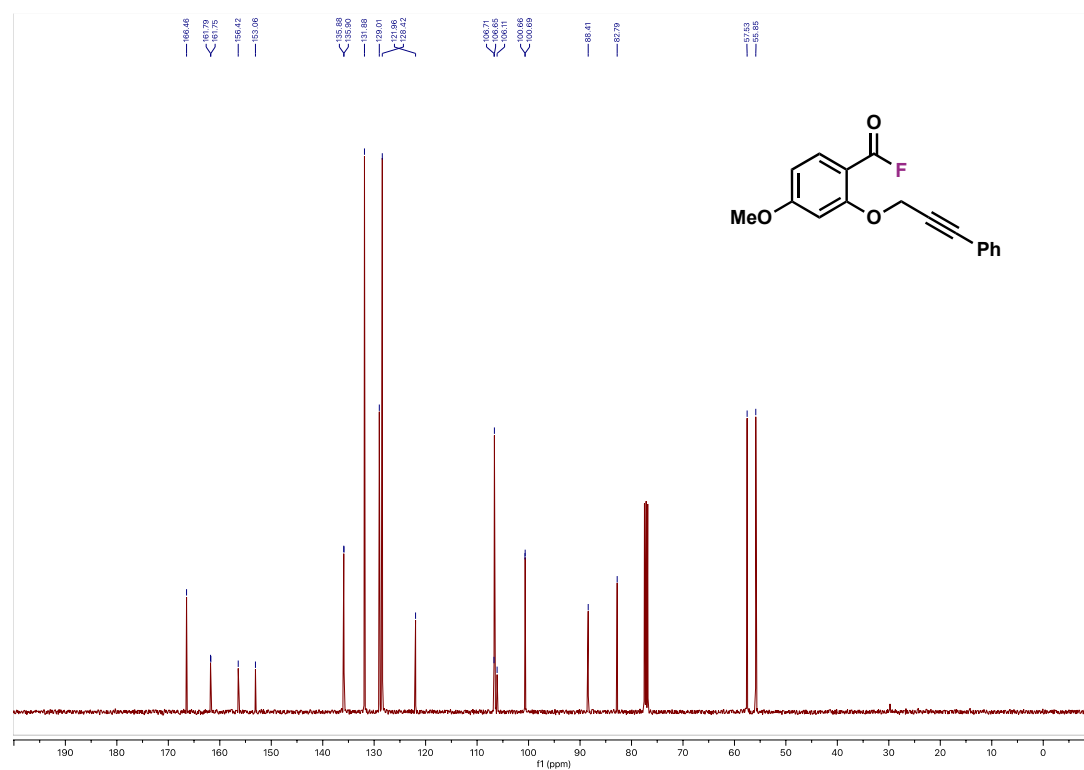
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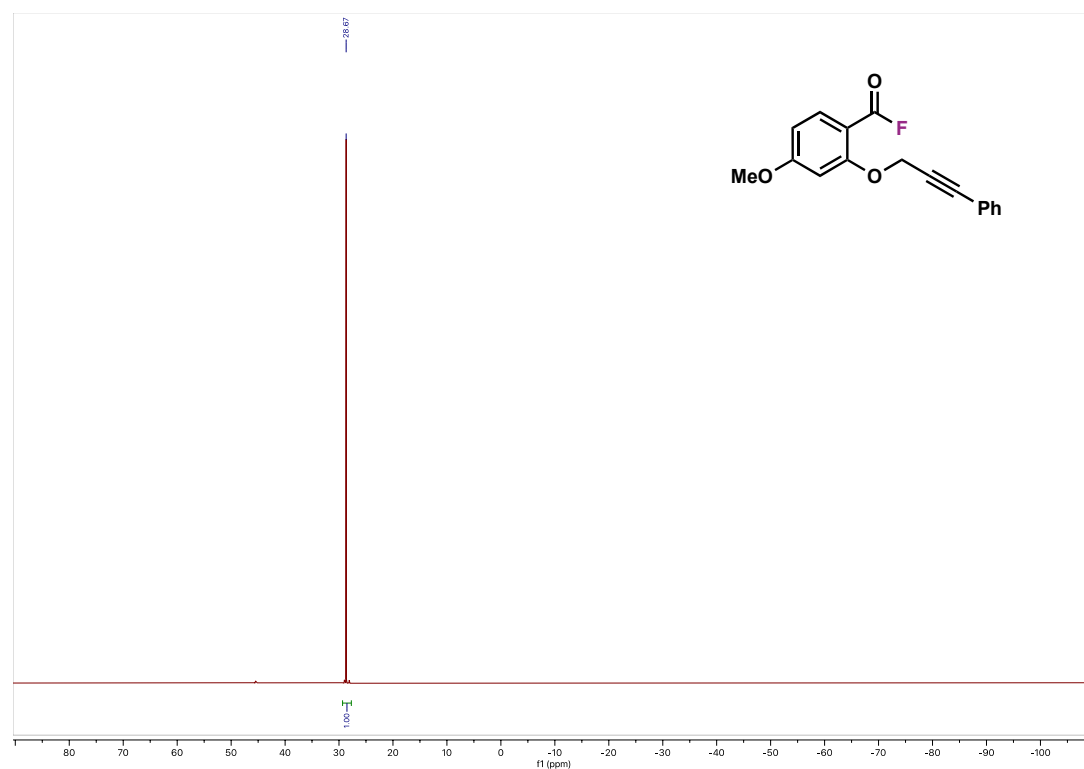
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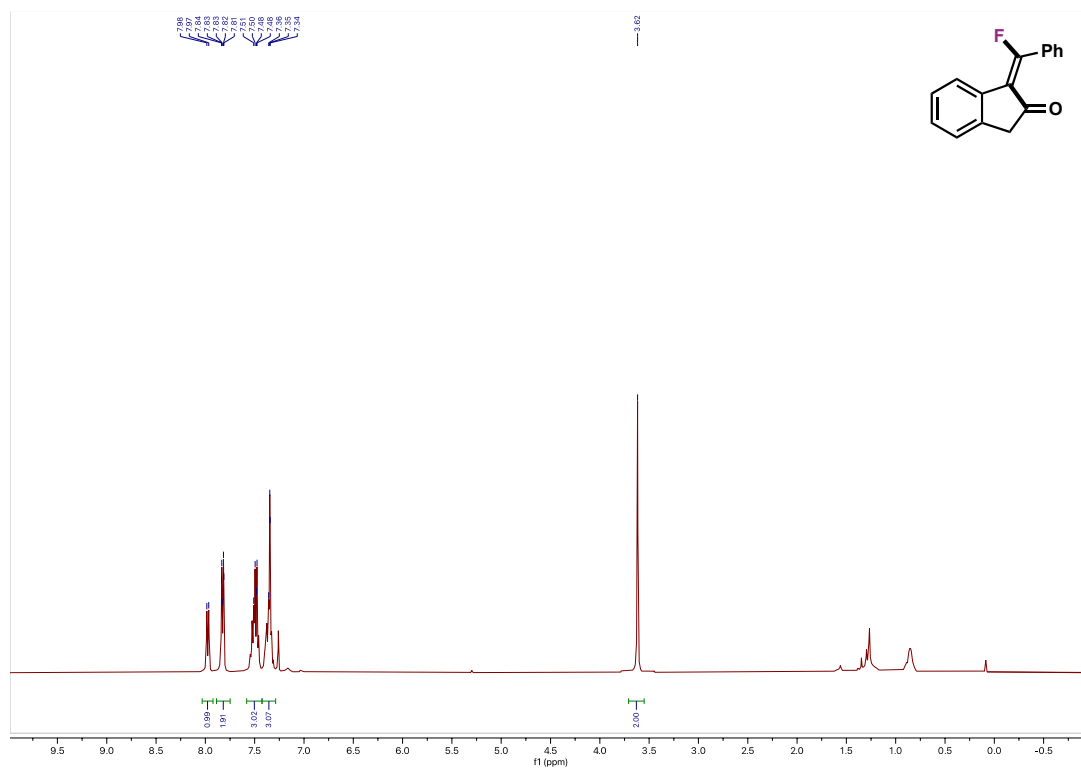
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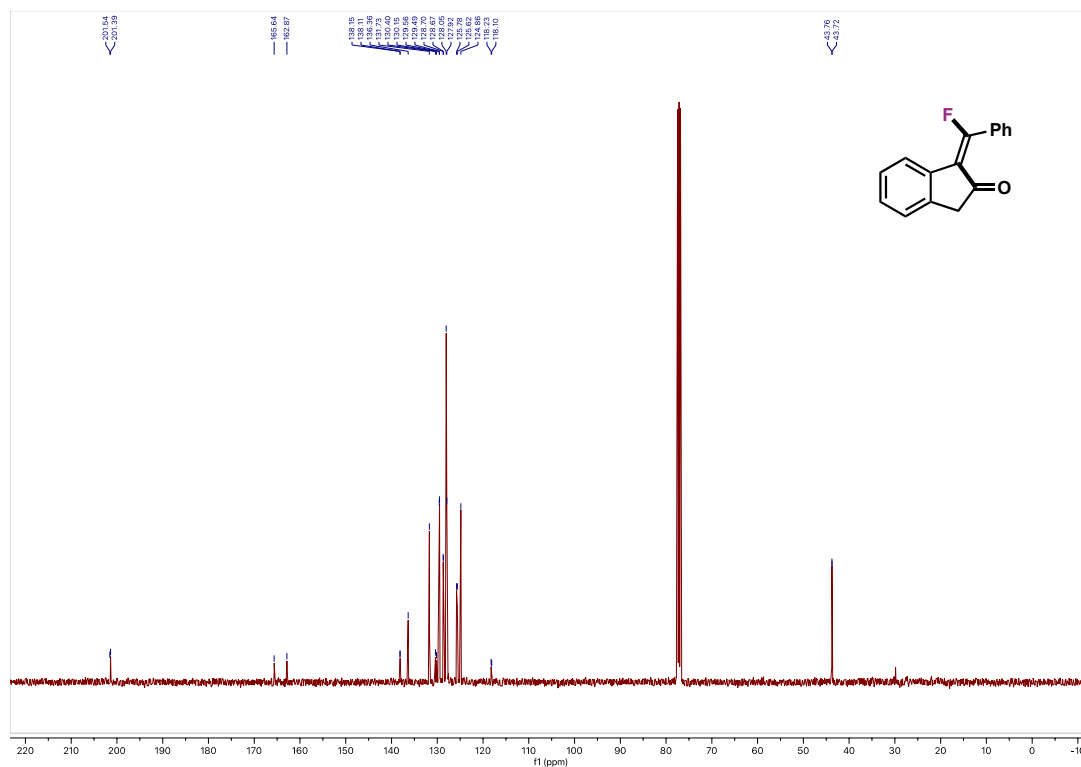
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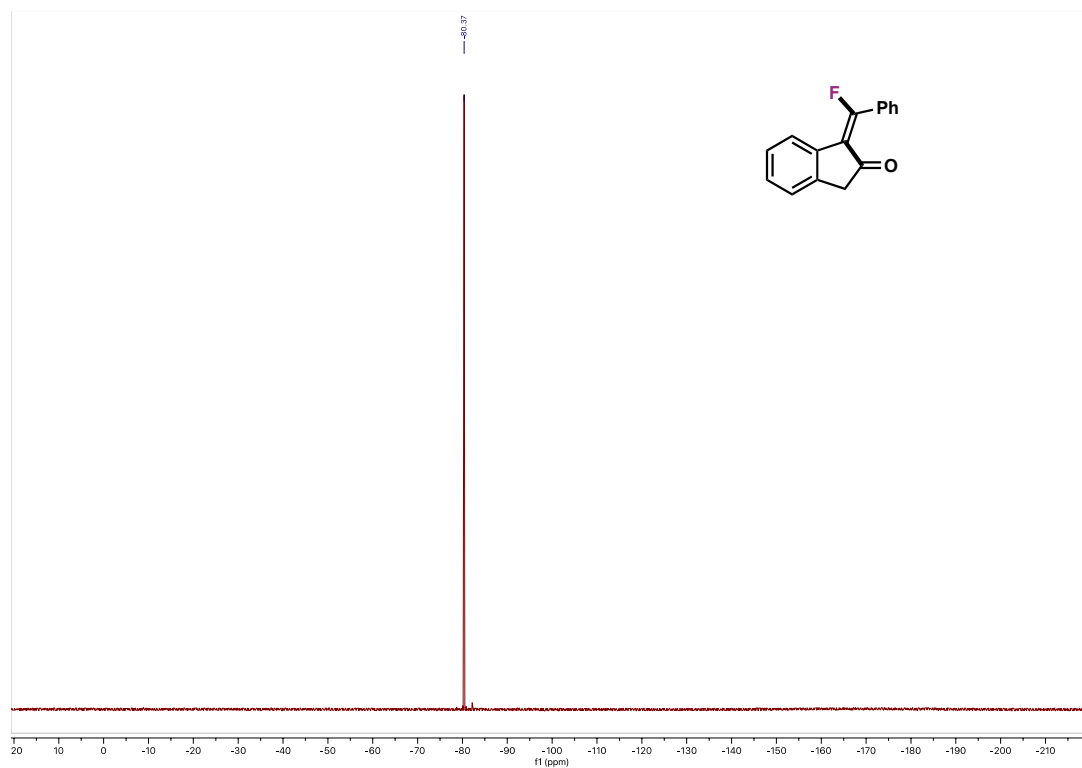
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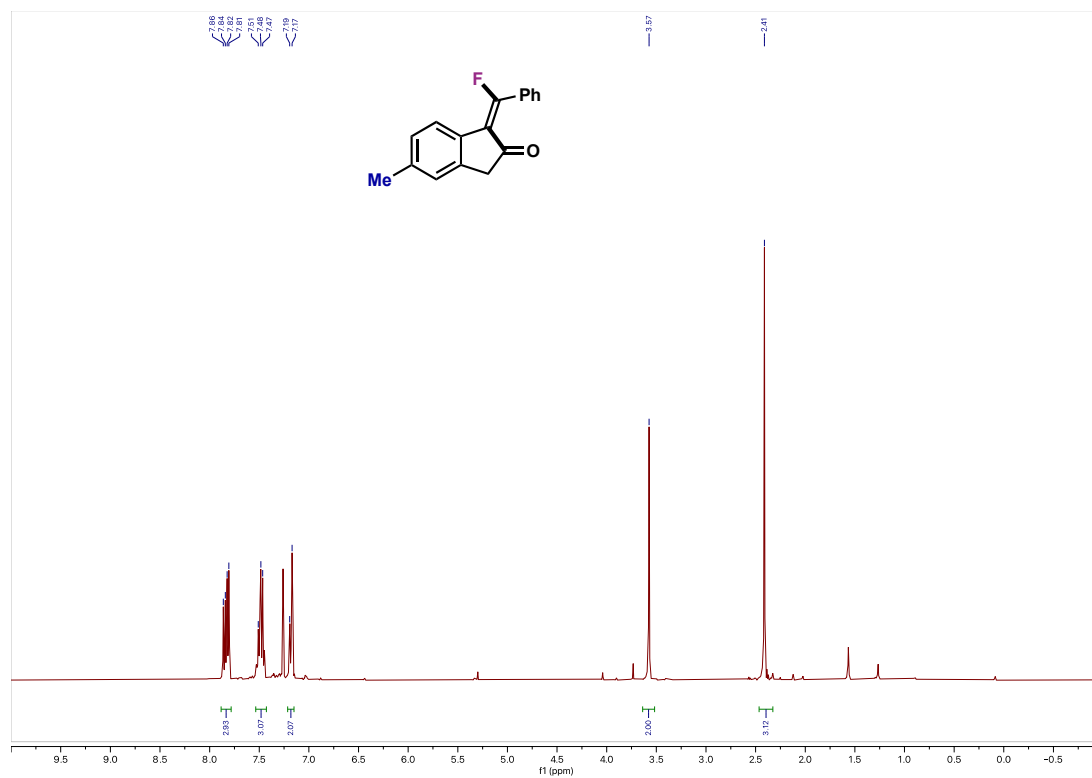
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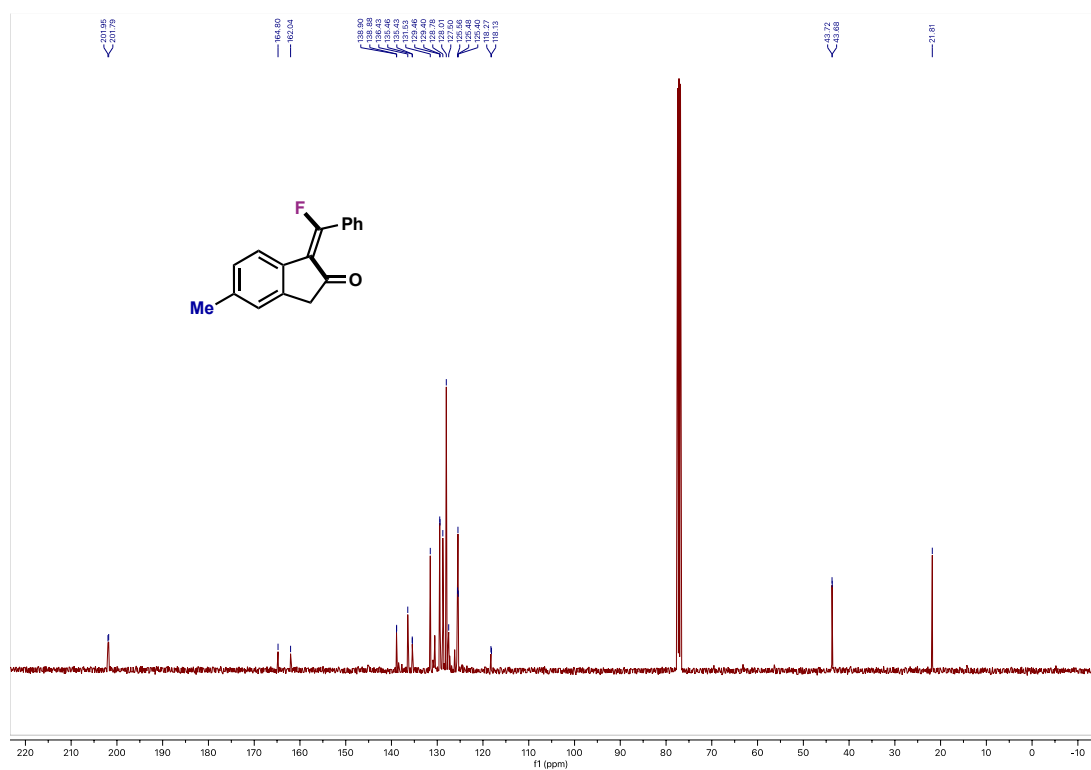
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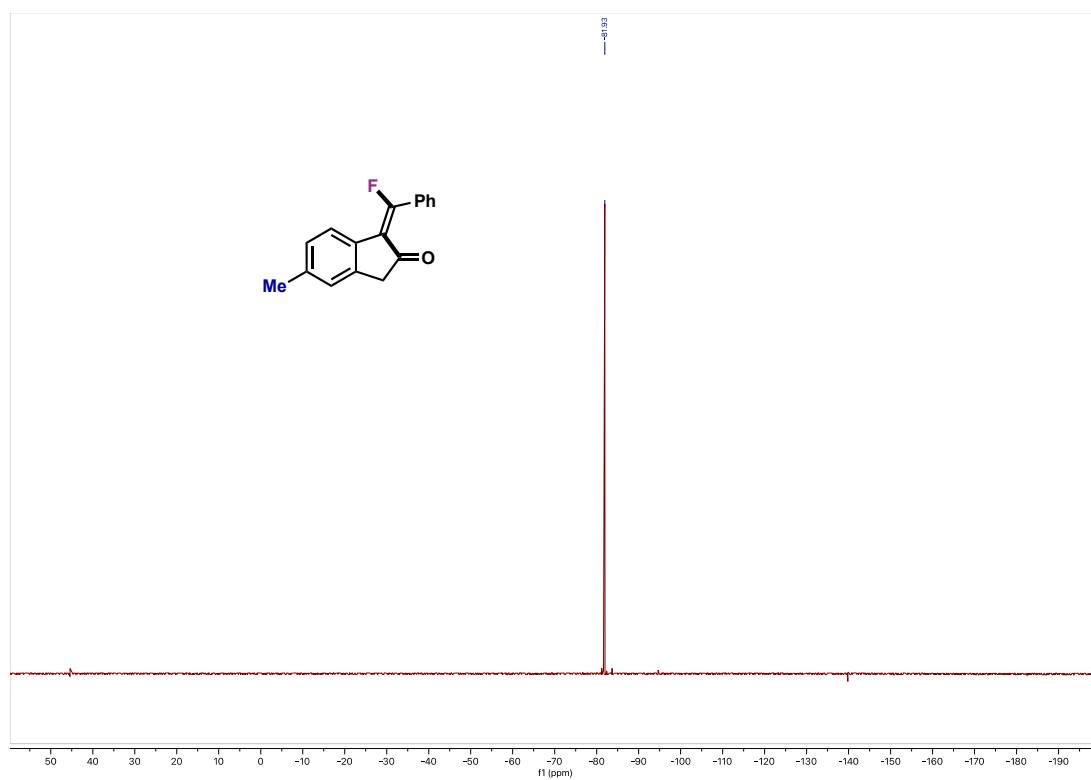
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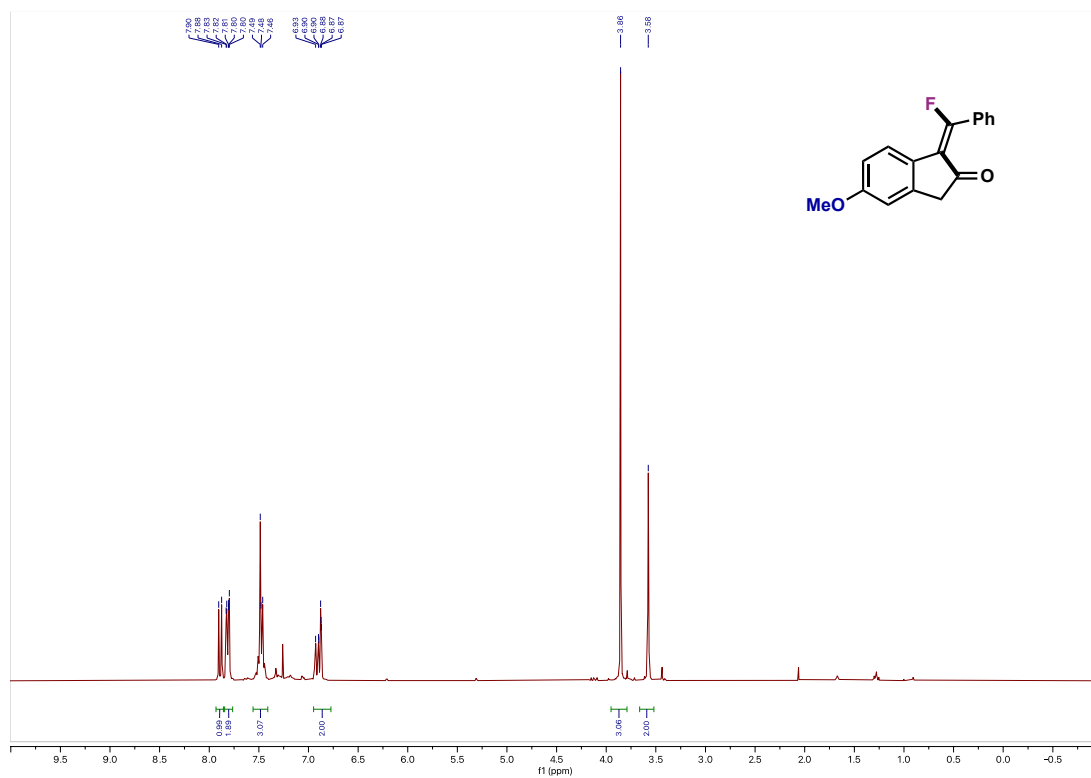
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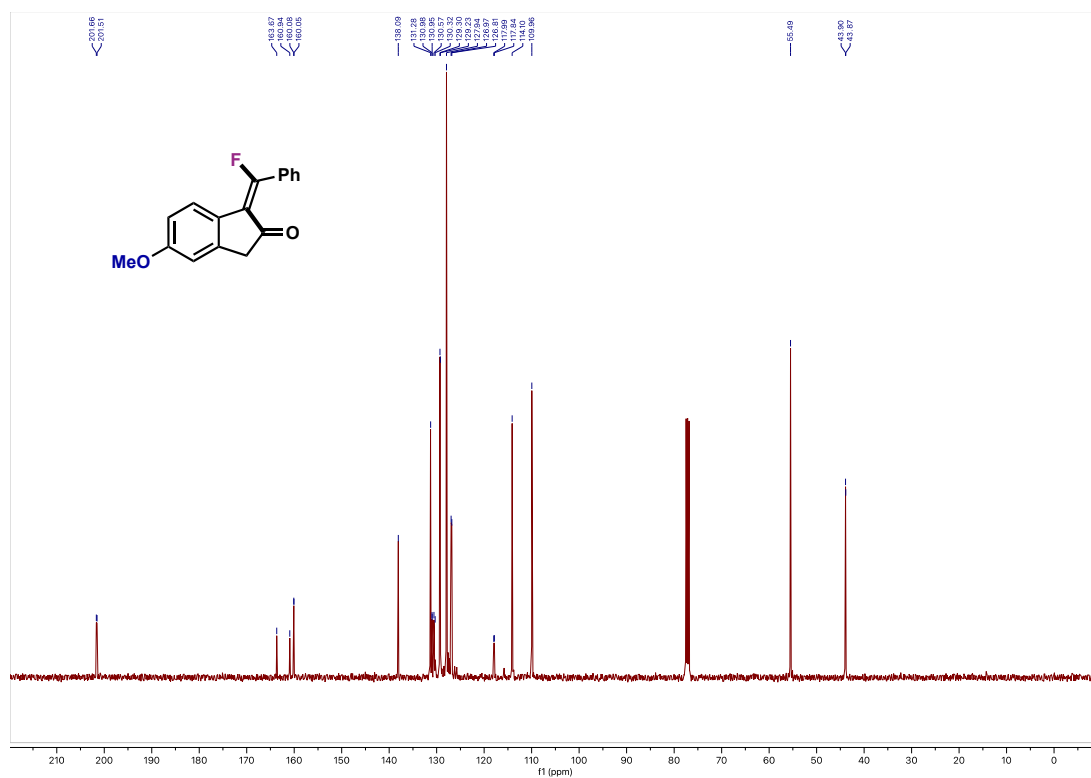
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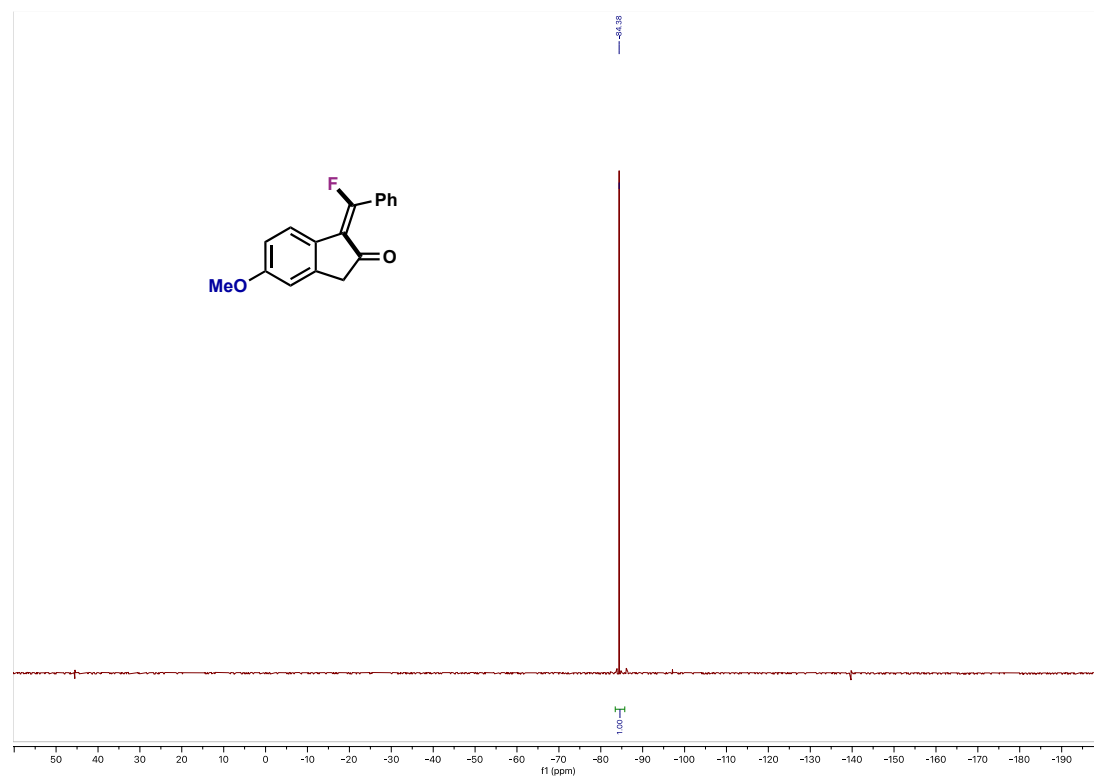
¹H NMR (400 MHz, CDCl₃) of **2.2c**



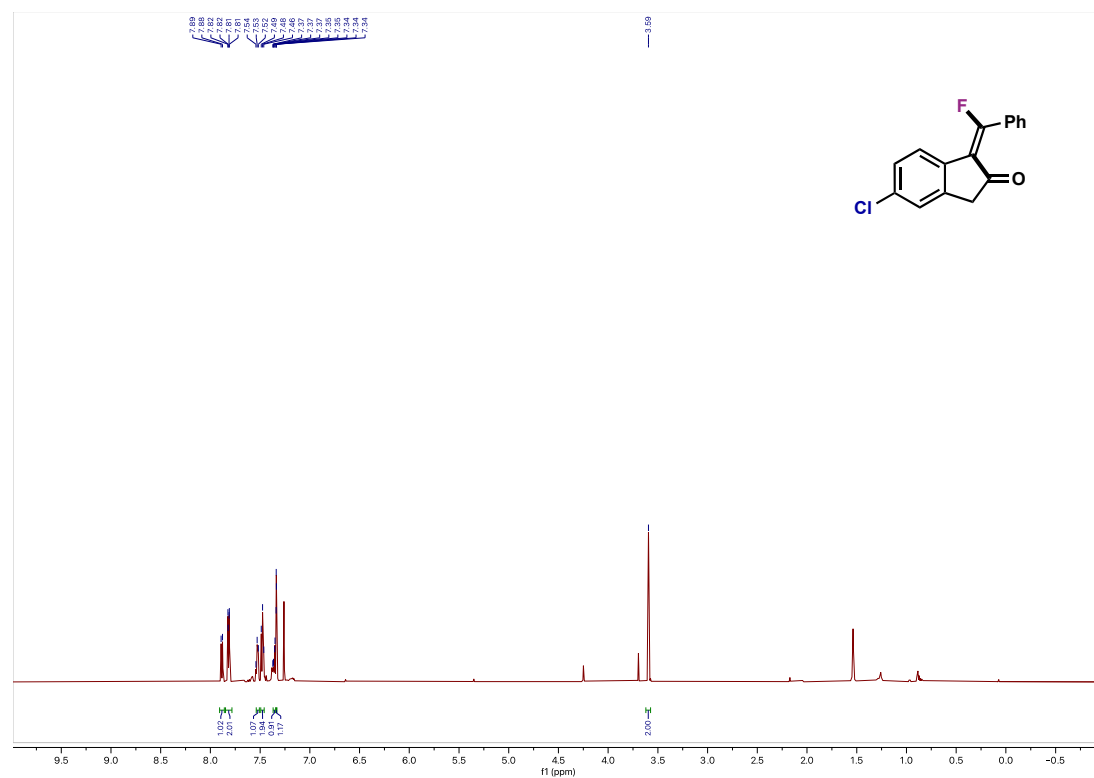
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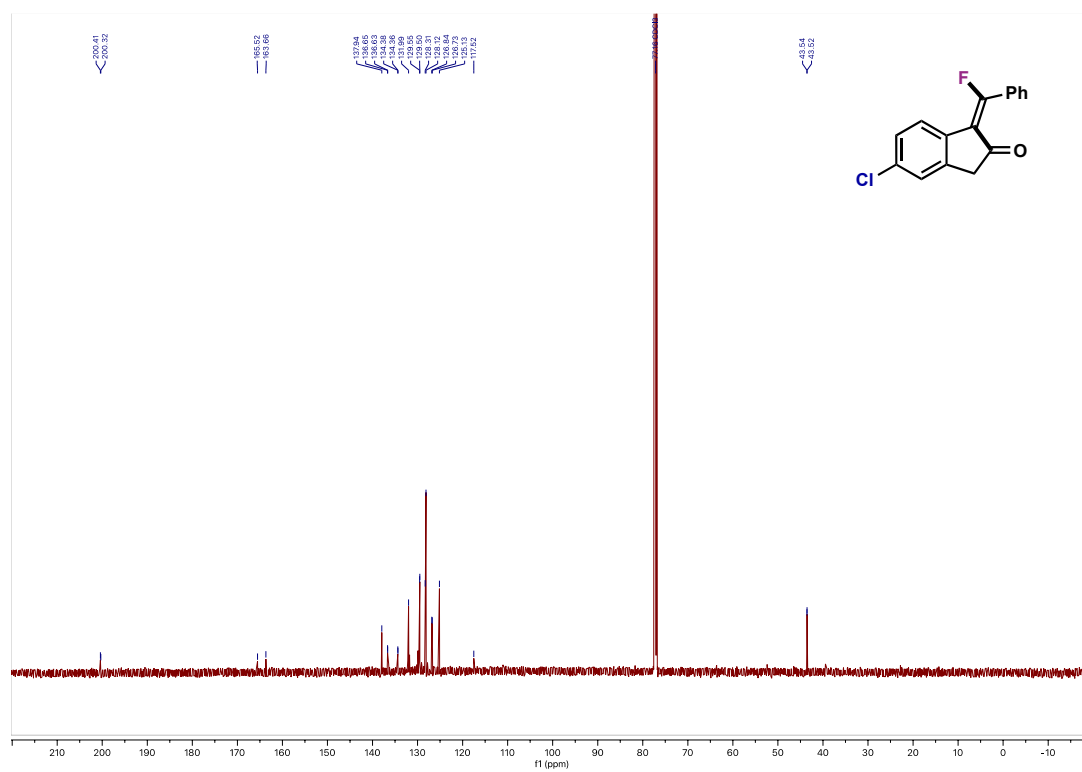
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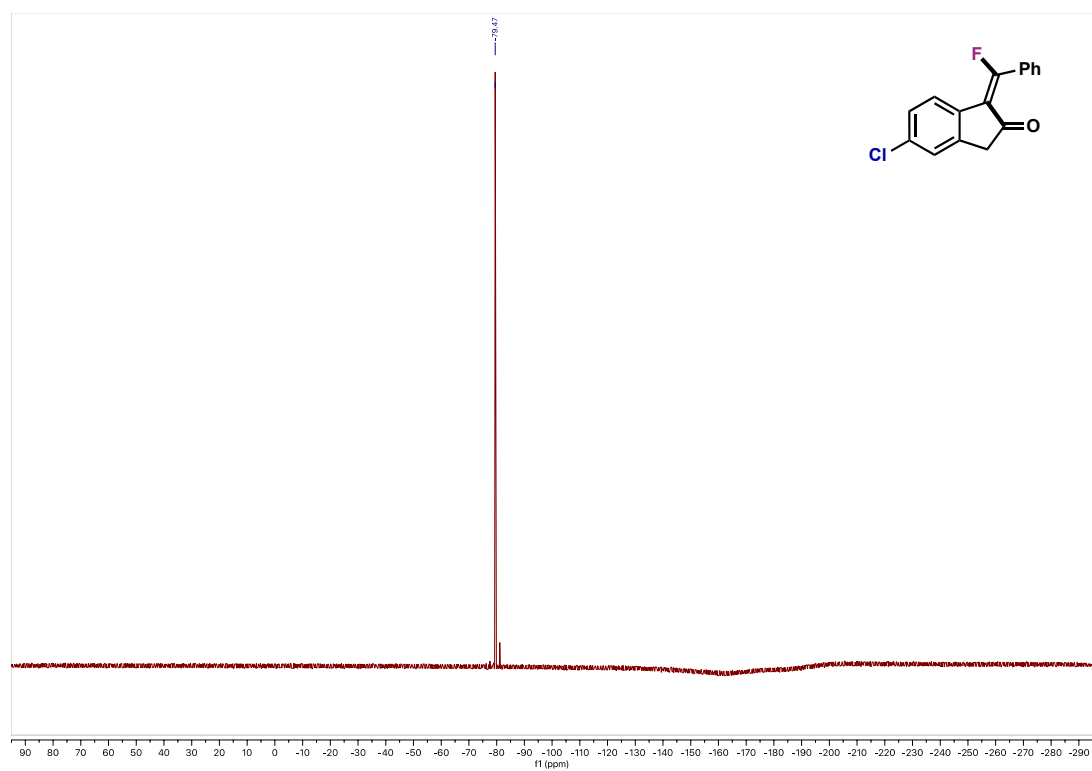
^1H NMR (400 MHz, CDCl_3) of **2.2d**



^{13}C NMR (151 MHz, CDCl_3) of **2.2d**



^{19}F NMR (377 MHz, CDCl_3) of **2.2d**



O=C1C=Cc2cc(F)ccc2C1=Cc3ccccc3

Chemical structure: 2-(2-fluorophenyl)-2-phenyl-1,3-dioxolane-4-one

¹H NMR spectrum (CDCl₃) showing peaks in the aromatic region (7.0-8.0 ppm) and a singlet at 3.59 ppm. Integration values are provided below the peaks.

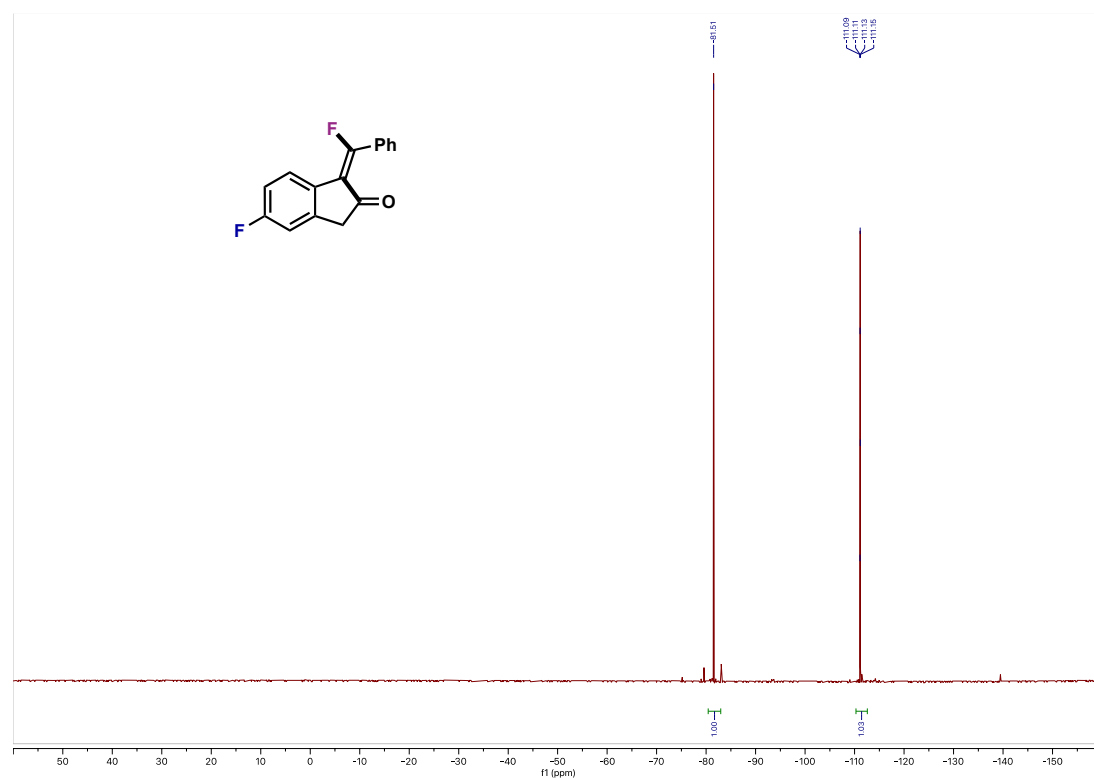
Chemical Shift (ppm)	Integration
7.95, 7.94, 7.93, 7.92, 7.91, 7.90, 7.89, 7.87, 7.86, 7.85, 7.84, 7.83, 7.82, 7.81, 7.80, 7.79, 7.77, 7.76, 7.75, 7.74, 7.73	1.02, 1.95, 3.05, 1.99, 2.00

O=C1Cc2cc(F)ccc2C(=C(F)C3=CC=CC=C3)C1

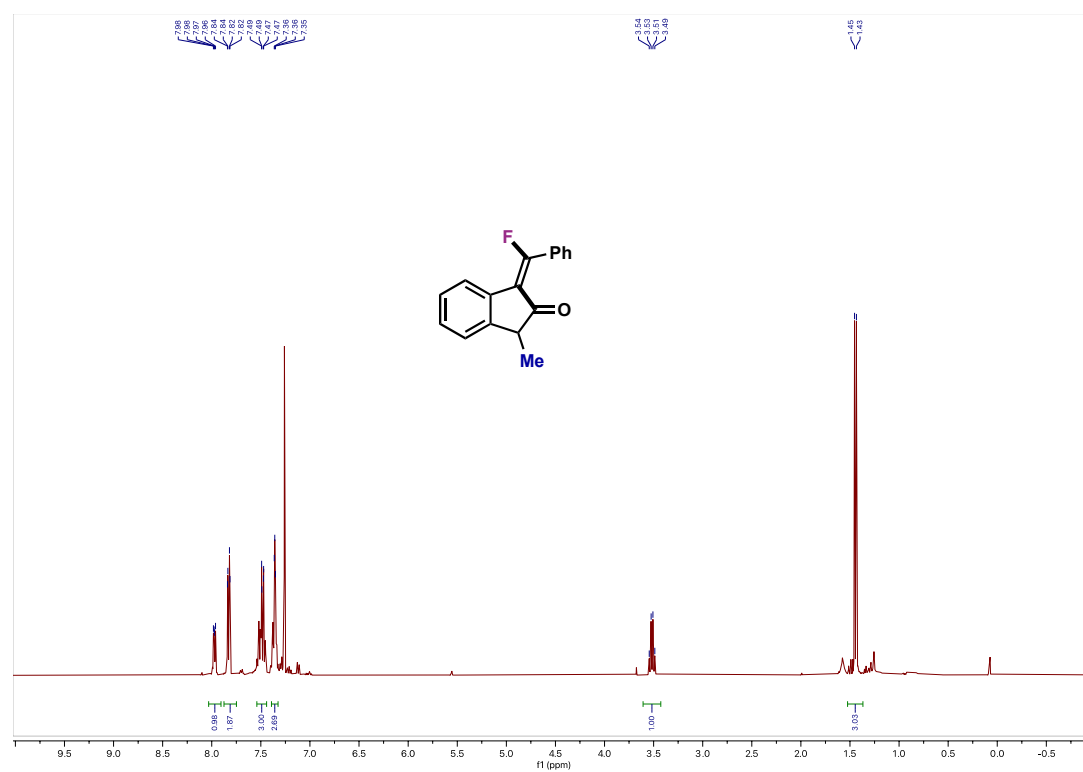
13C NMR spectrum (CDCl₃) of 2-fluoro-1-phenyl-3,4-dihydro-1H-benzo[b]pyran-5(1H)-one. The spectrum shows peaks from 43.30 to 200.51 ppm. The chemical structure is shown in the top right corner.

Chemical Shift (ppm)
200.51
200.46
165.59
163.95
163.55
163.51
161.48
138.46
134.46
134.40
134.33
133.75
129.40
129.37
127.43
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127.24
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117.28
115.69
111.56
111.50
78.30
77.23
43.30

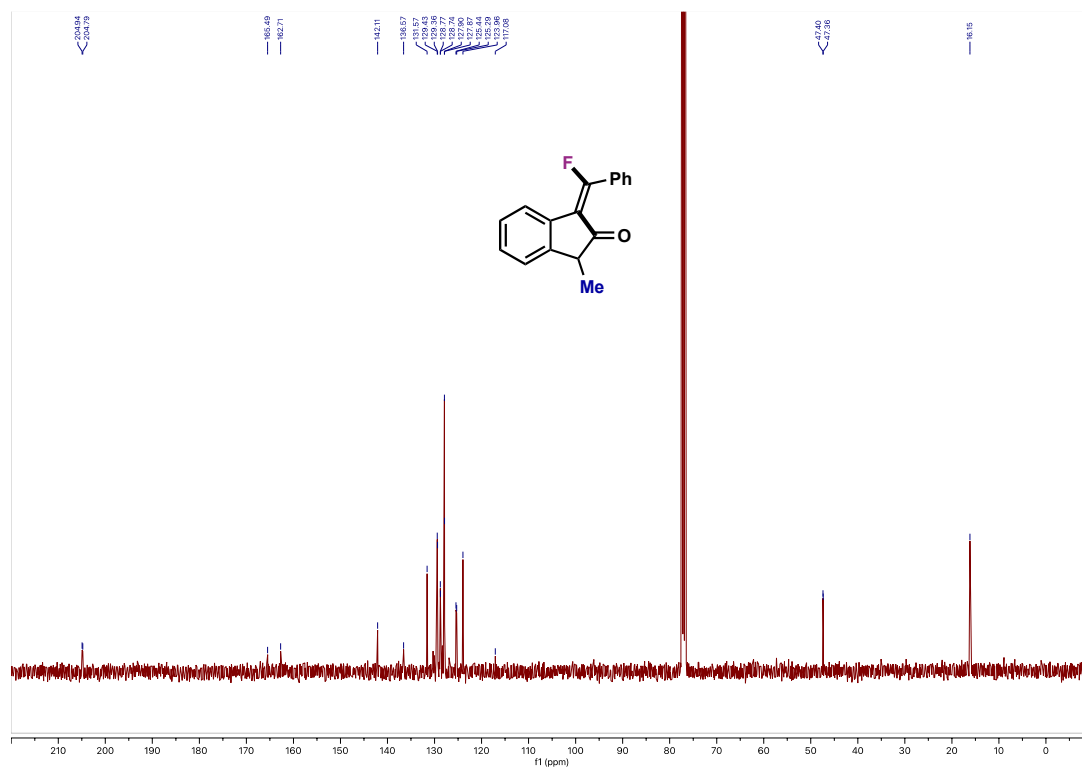
^{19}F NMR (377 MHz, CDCl_3) of **2.2e**



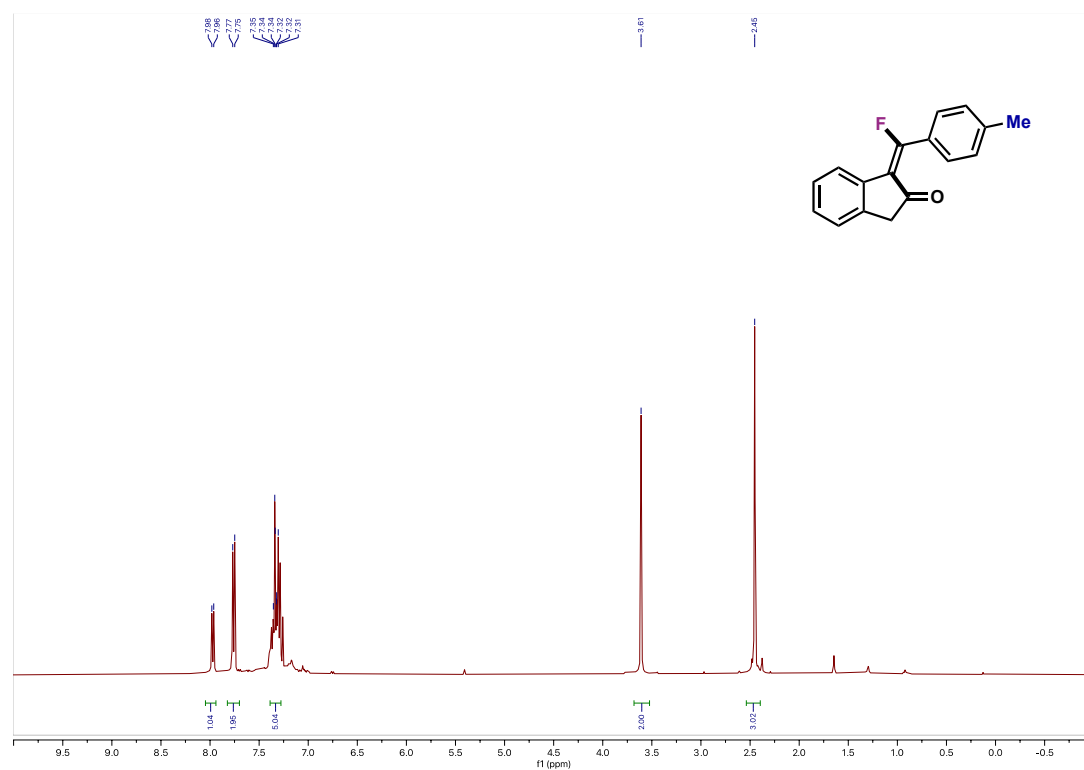
^1H NMR (400 MHz, CDCl_3) of **2.2f**



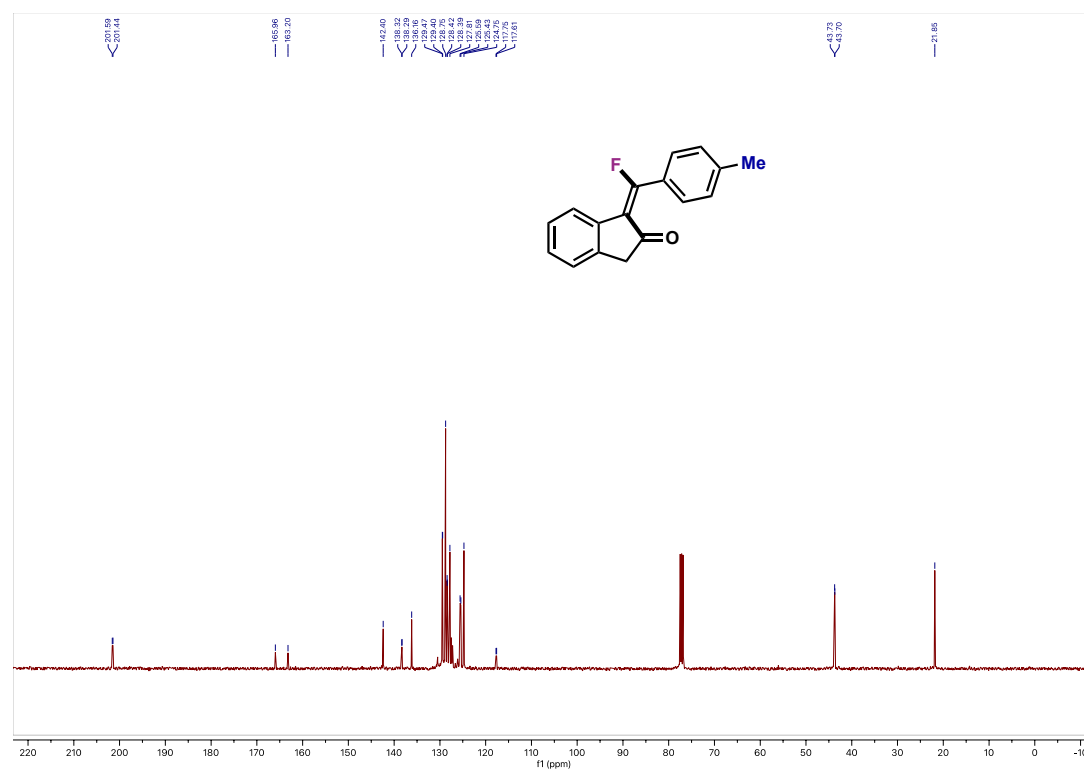
^{13}C NMR (101 MHz, CDCl_3) of **2.2f**



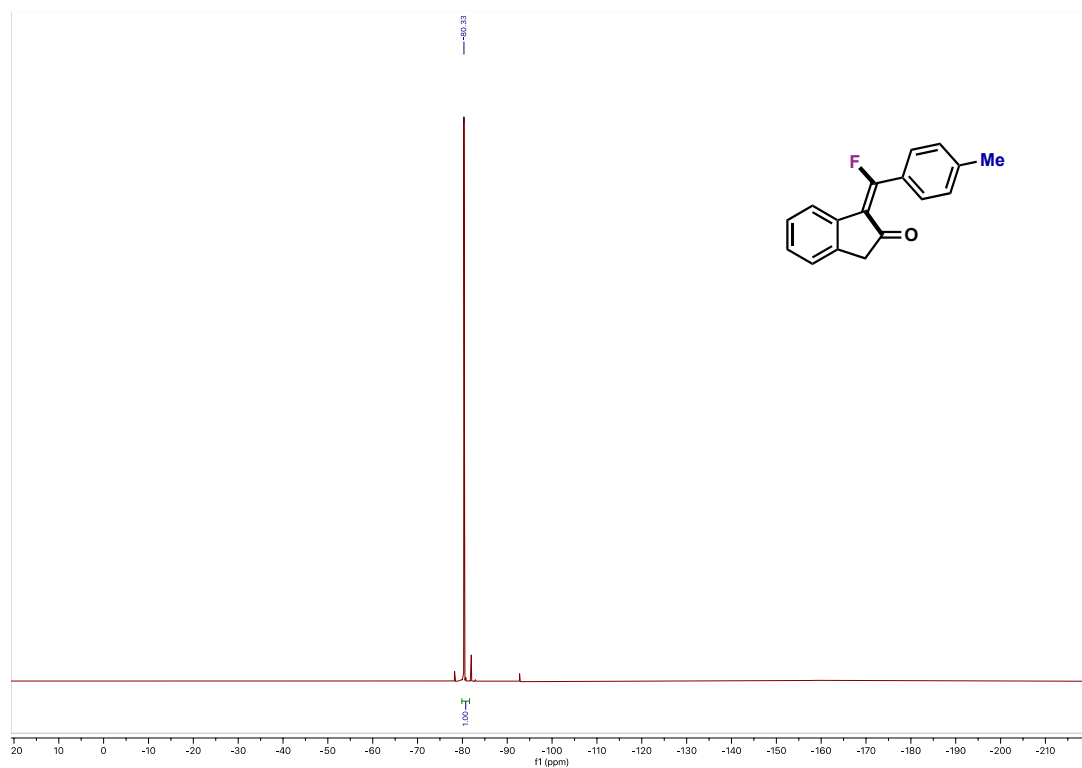
^1H NMR (400 MHz, CDCl_3) of **2.2g**



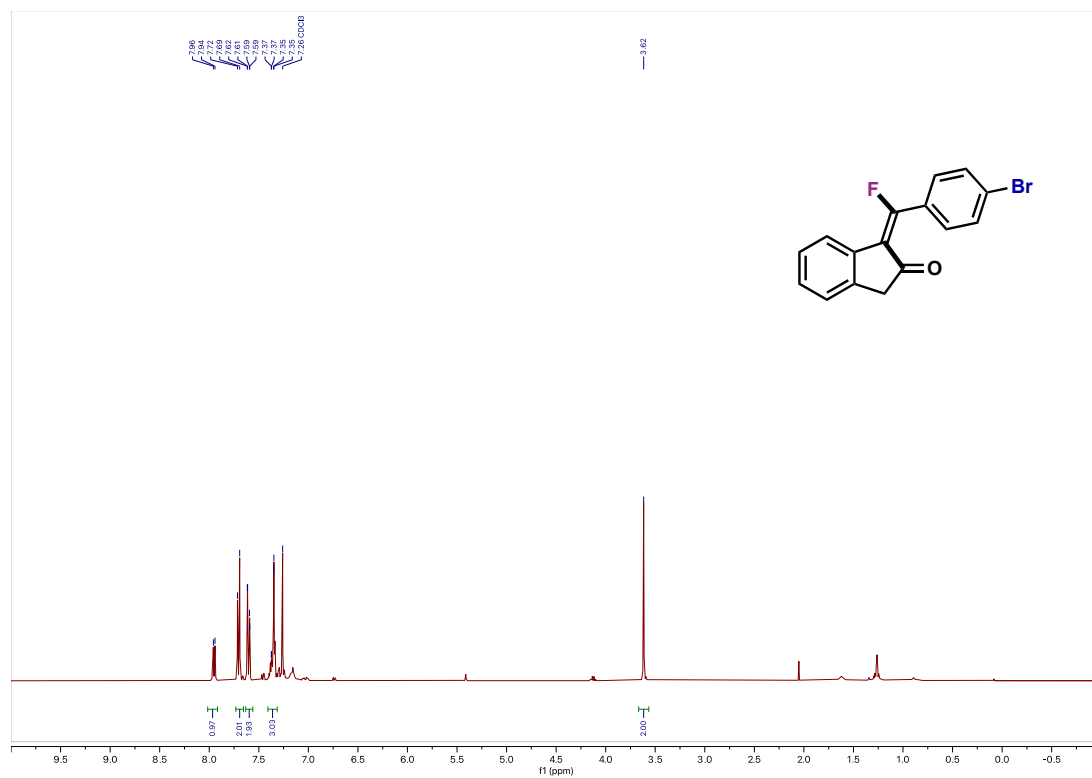
^{13}C NMR (101 MHz, CDCl_3) of **2.2g**

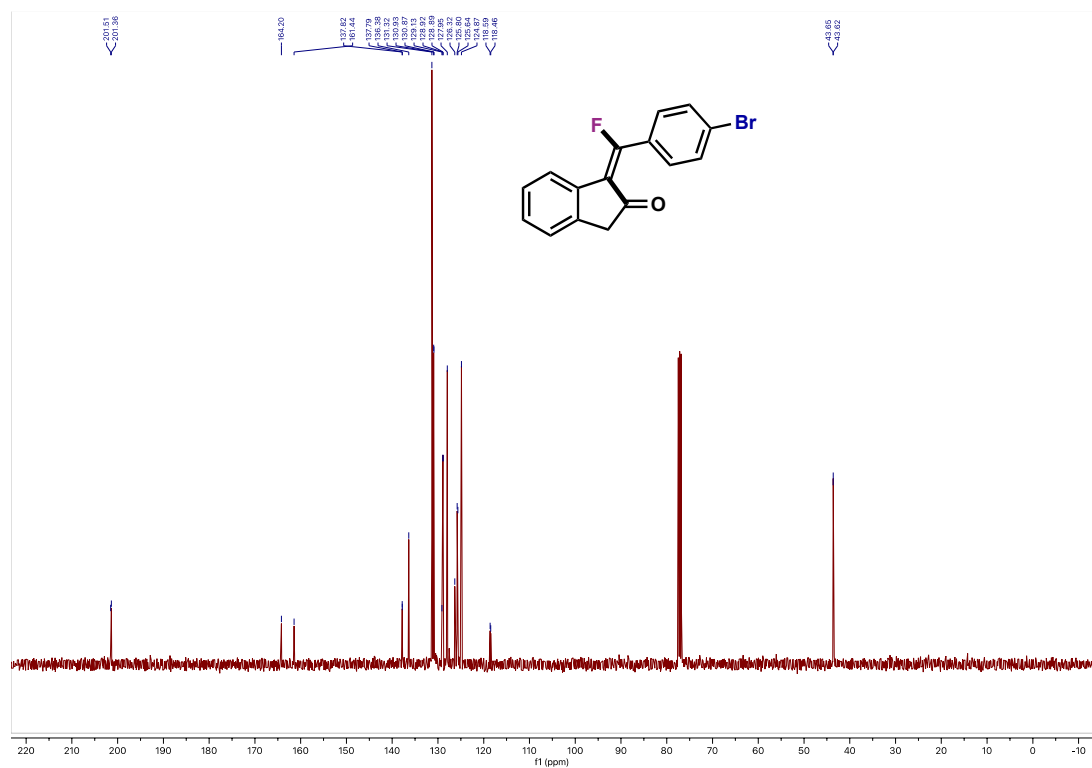


^{19}F NMR (377 MHz, CDCl_3) of **2.2g**

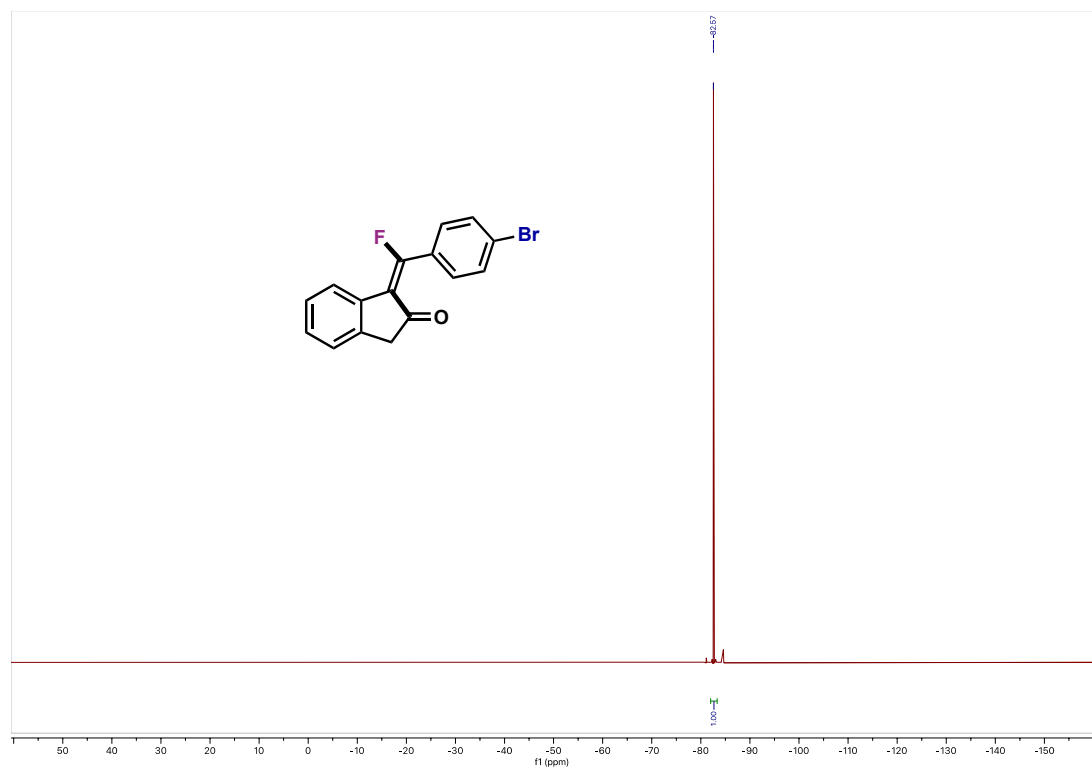


^1H NMR (400 MHz, CDCl_3) of **2.2h**

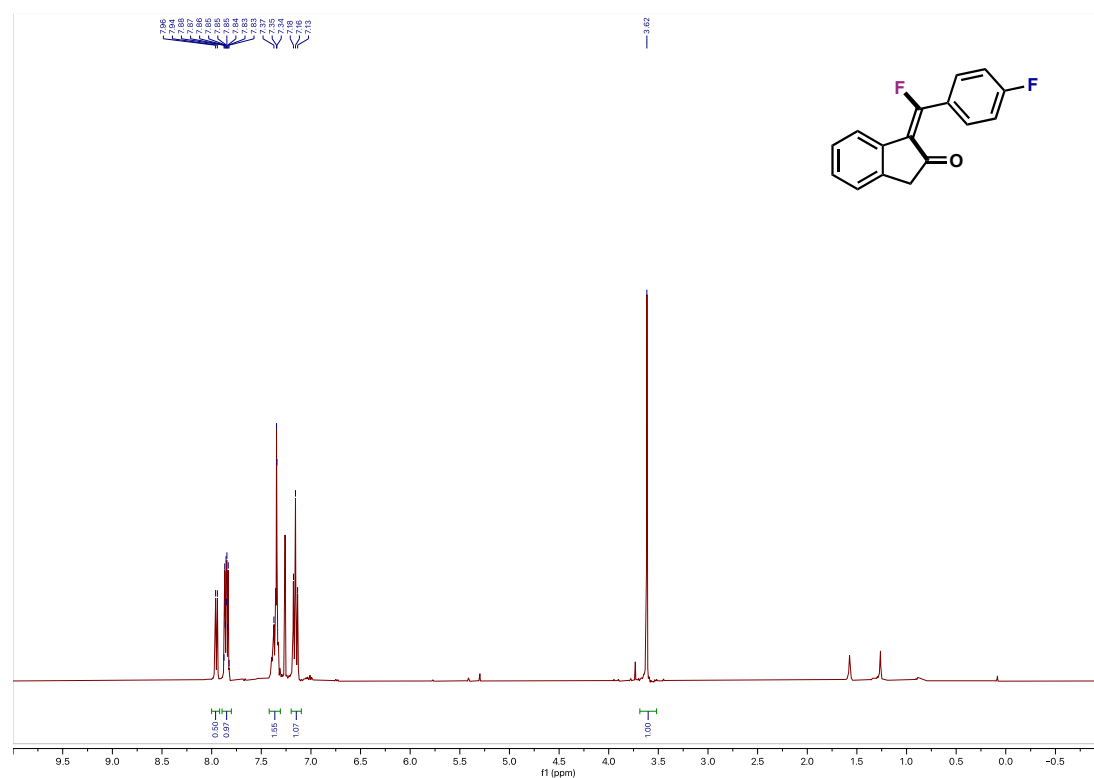


¹³C NMR (101 MHz, CDCl₃) of **2.2h**

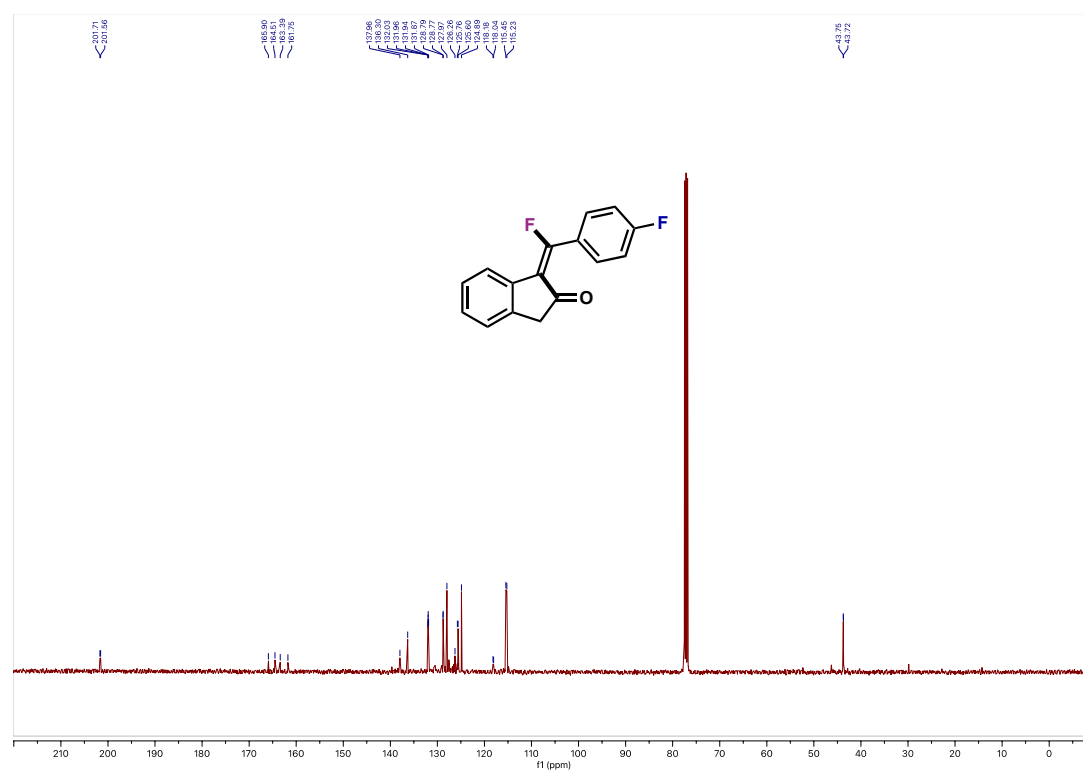
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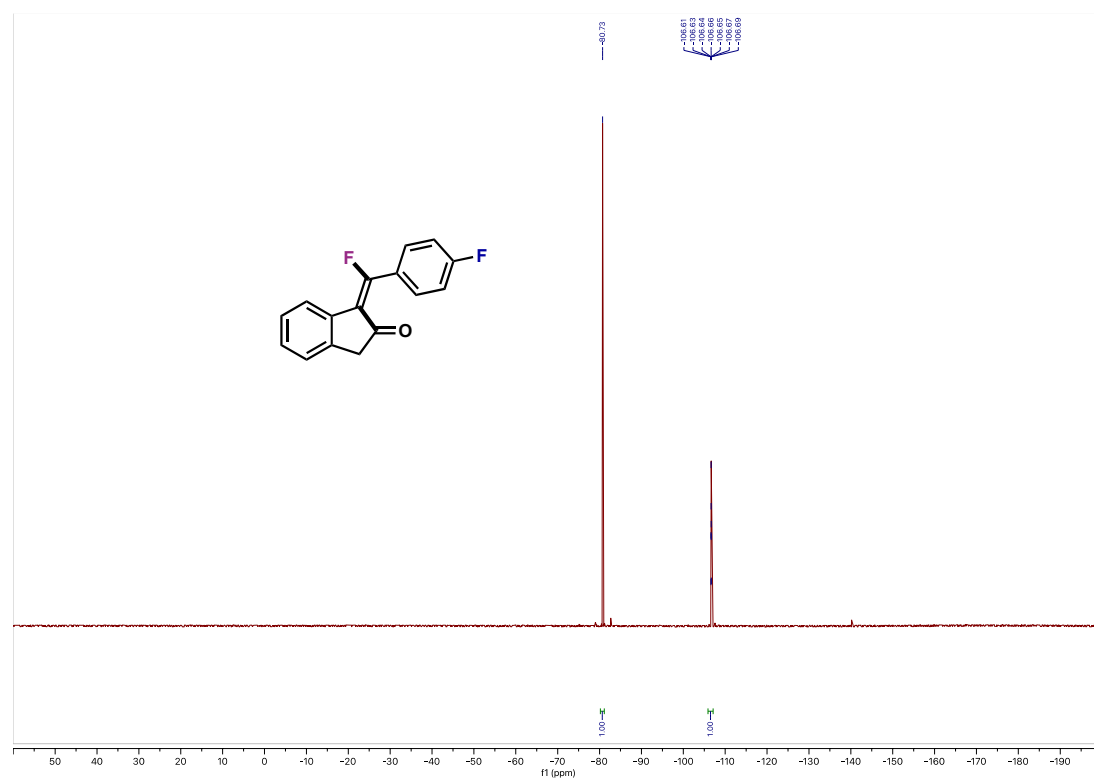
¹H NMR (400 MHz, CDCl₃) of 2.2i



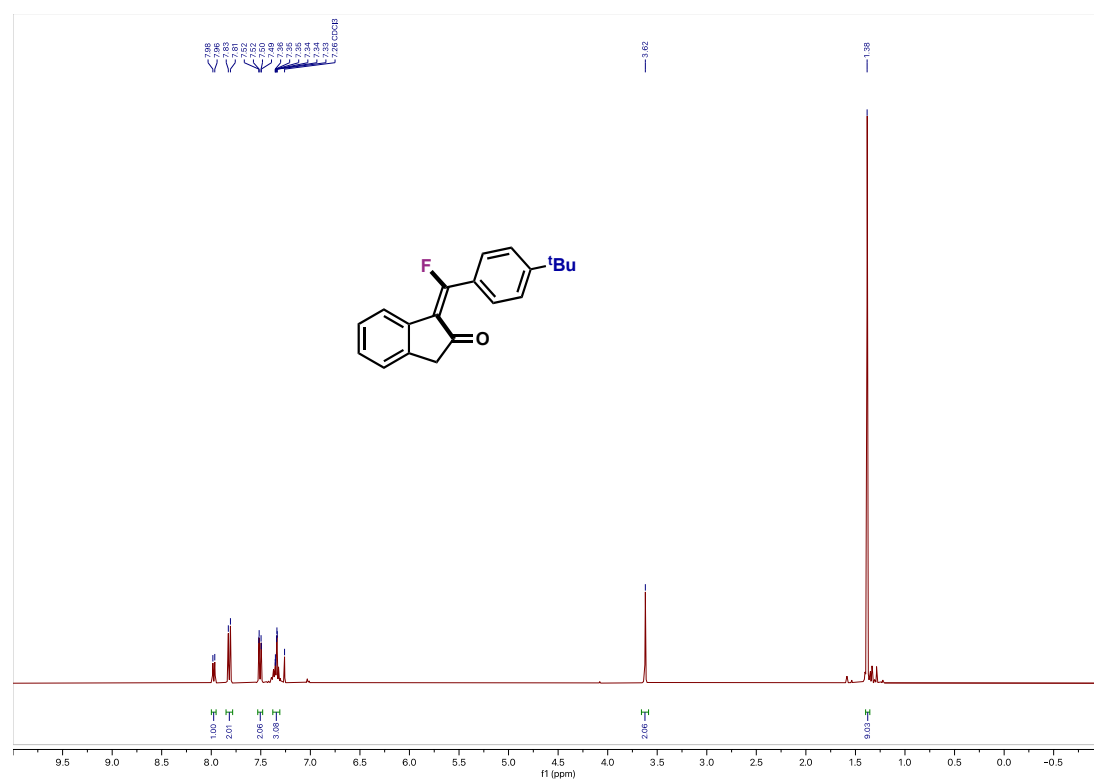
¹³C NMR (101 MHz, CDCl₃) of 2.2i



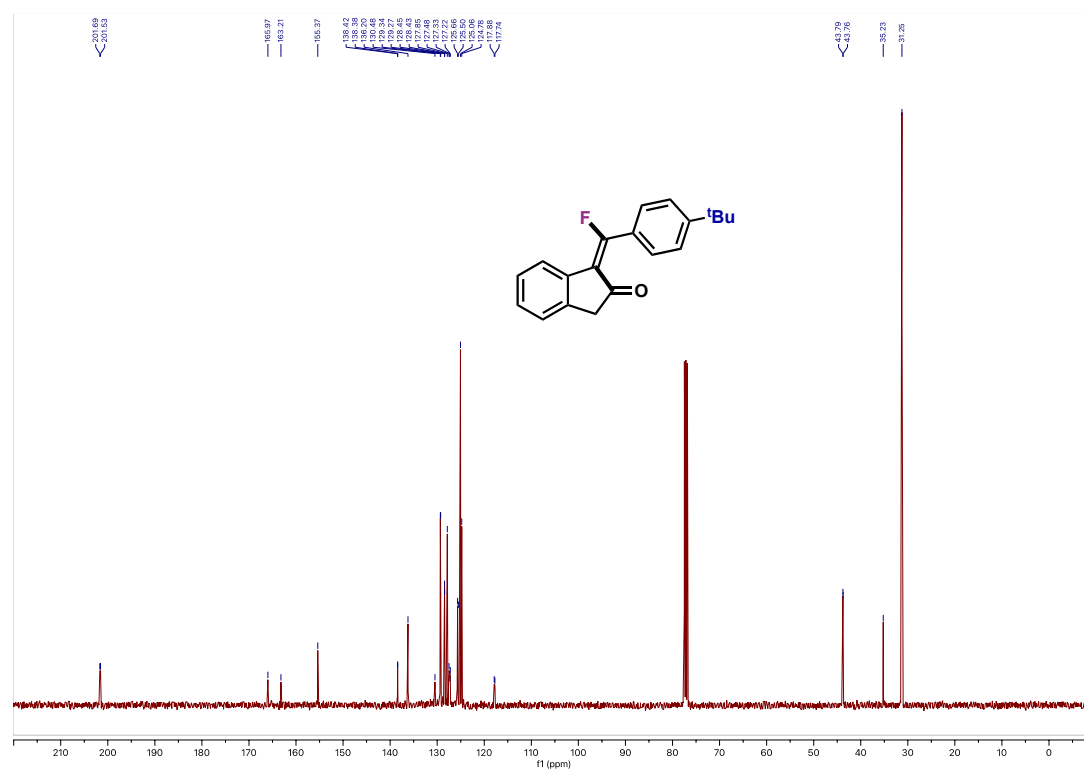
^{19}F NMR (377 MHz, CDCl_3) of **2.2i**



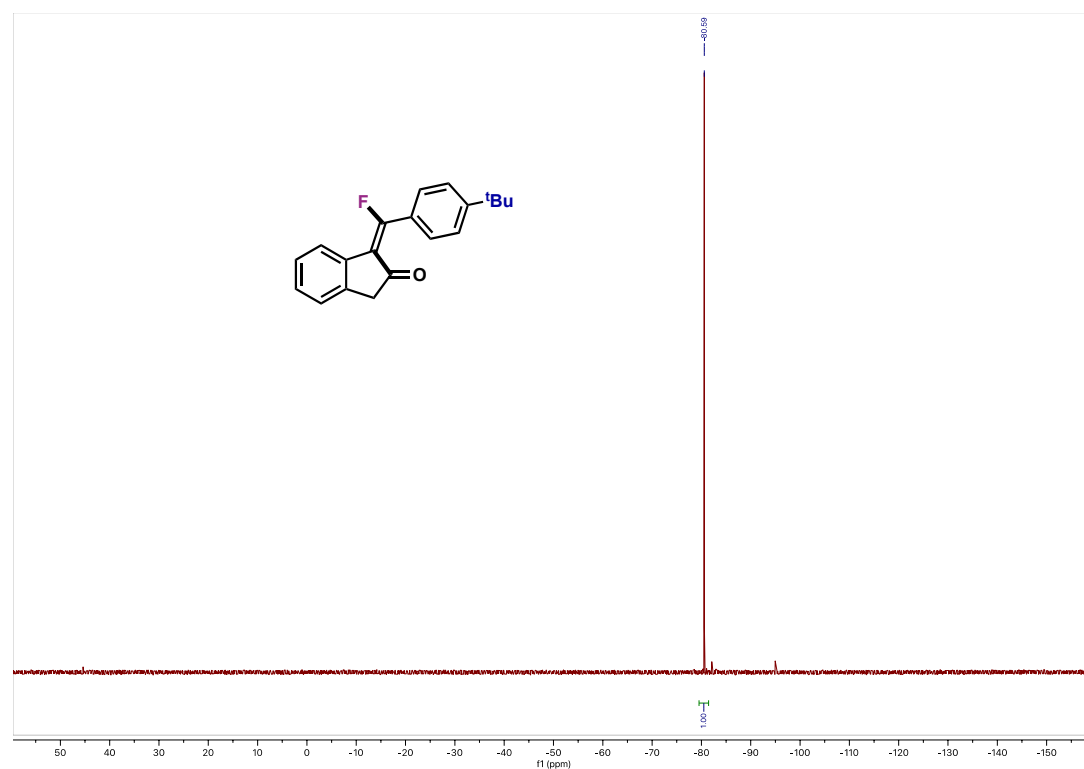
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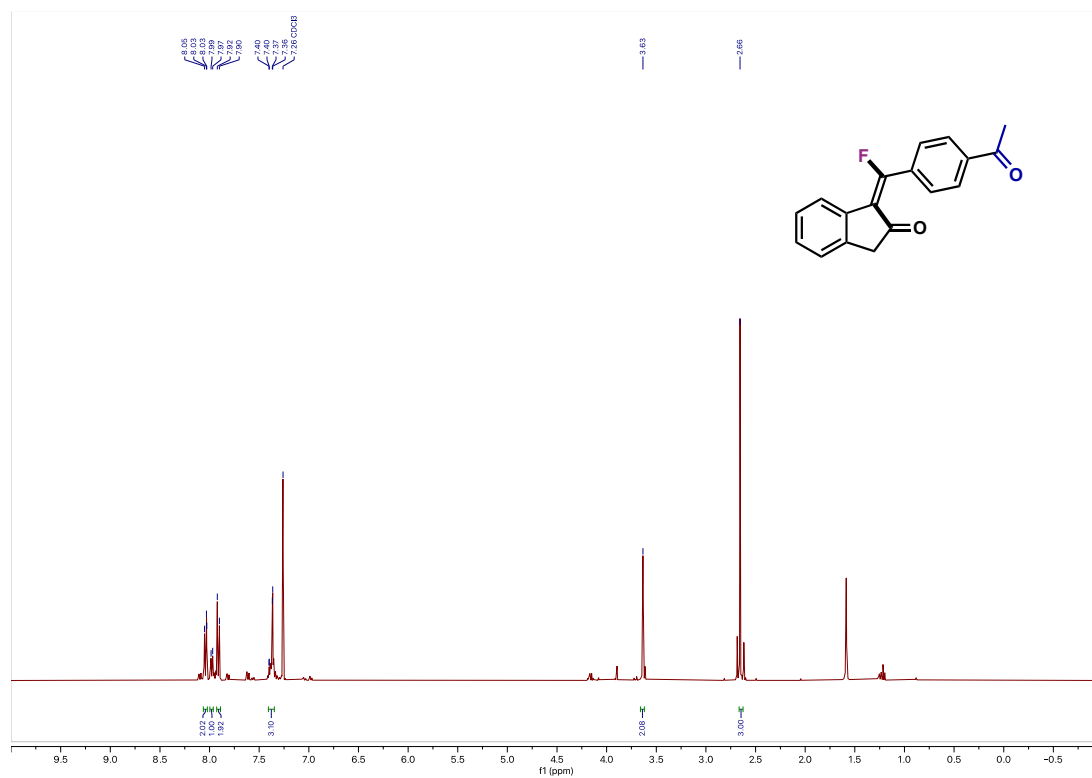
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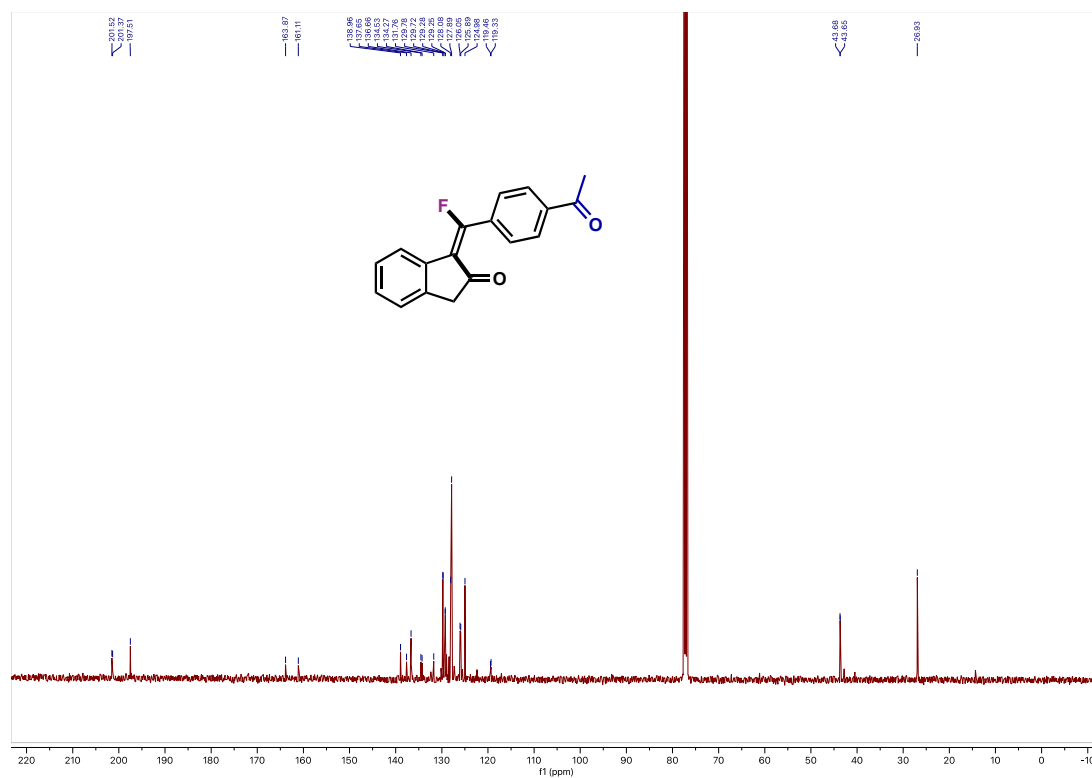
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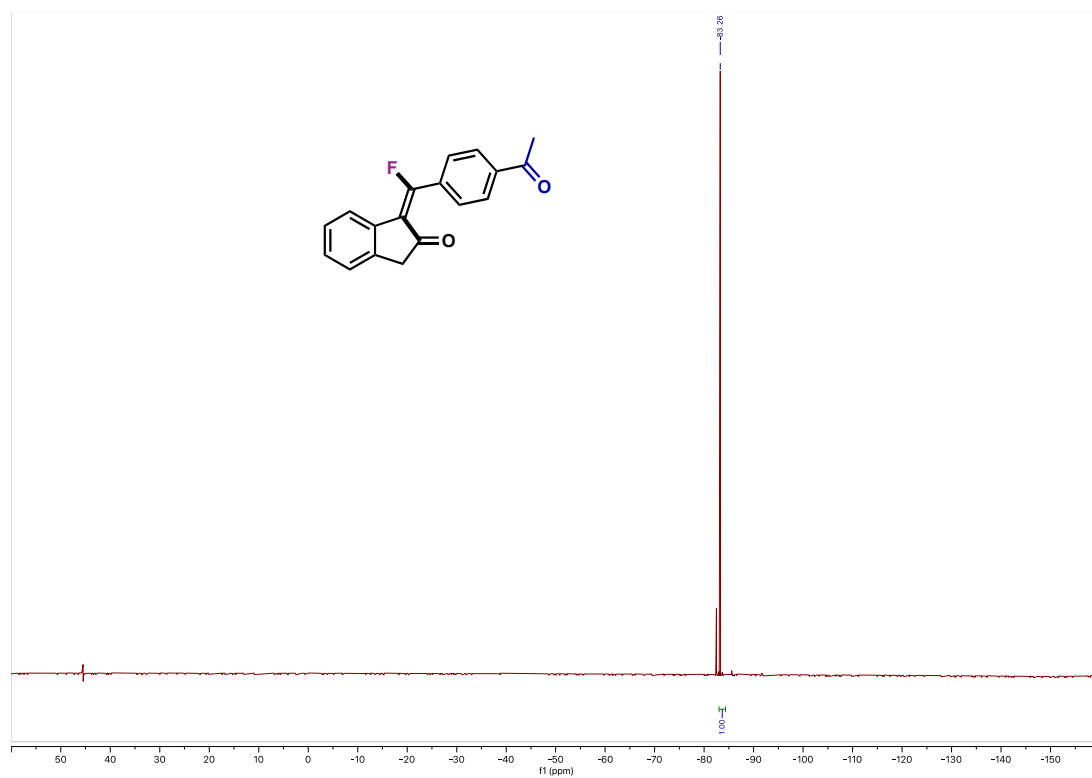
¹H NMR (400 MHz, CDCl₃) of **2.2k**



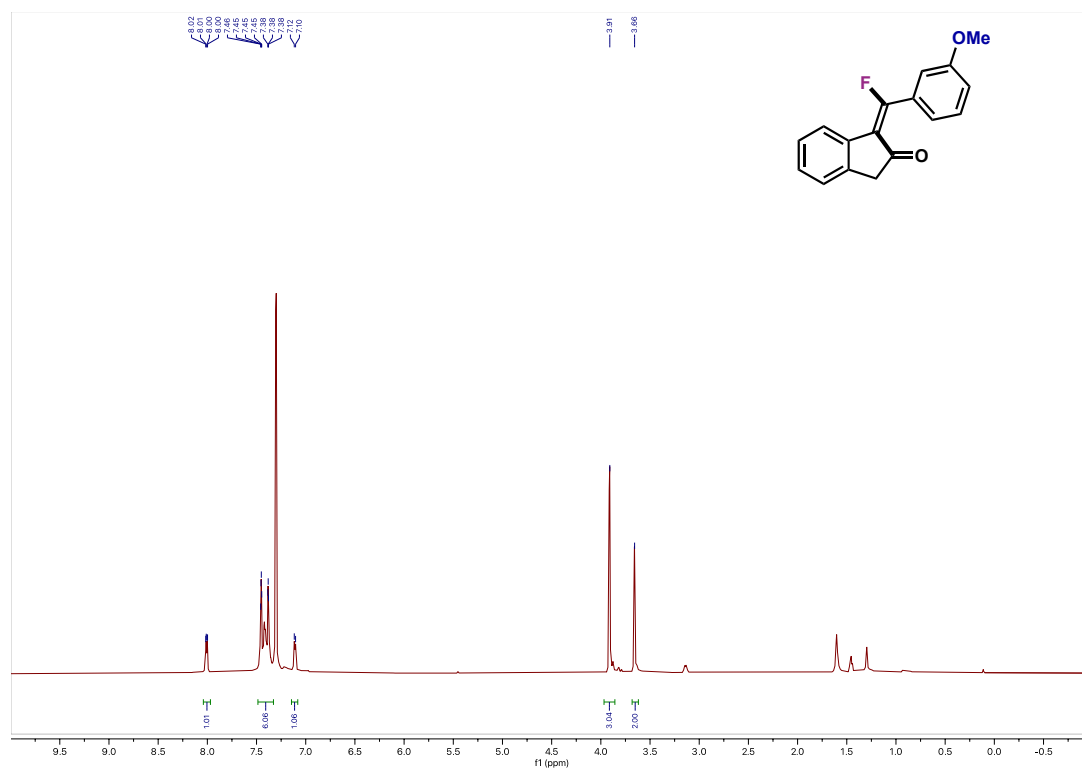
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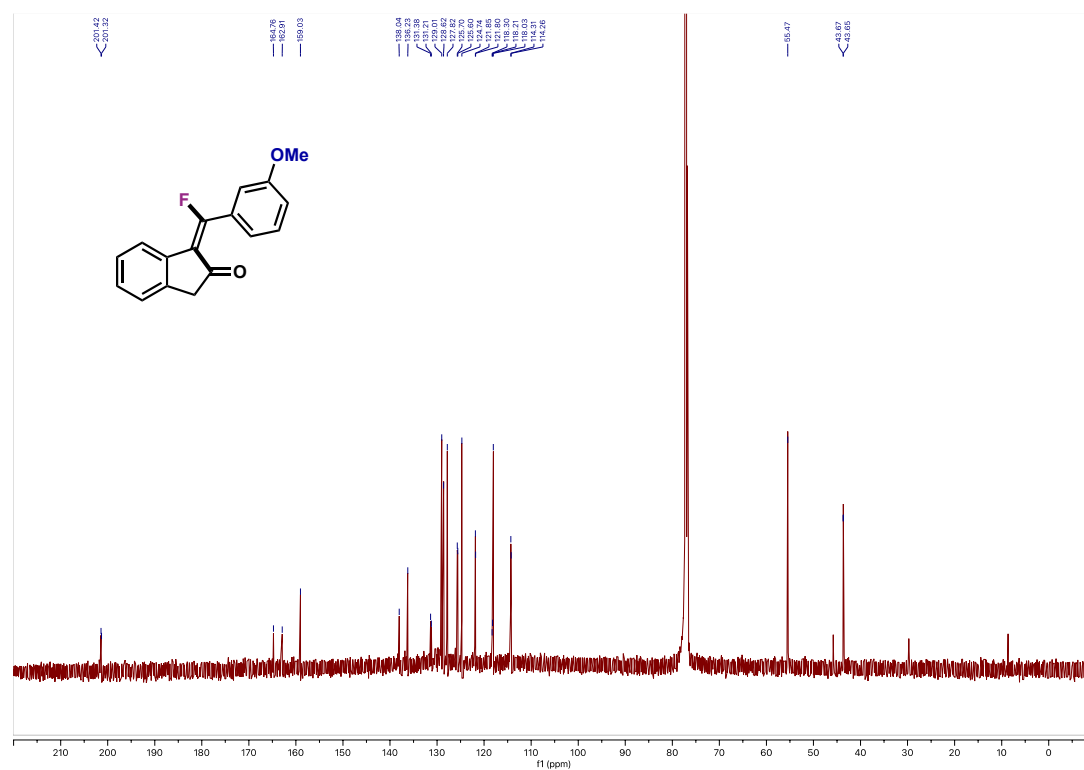
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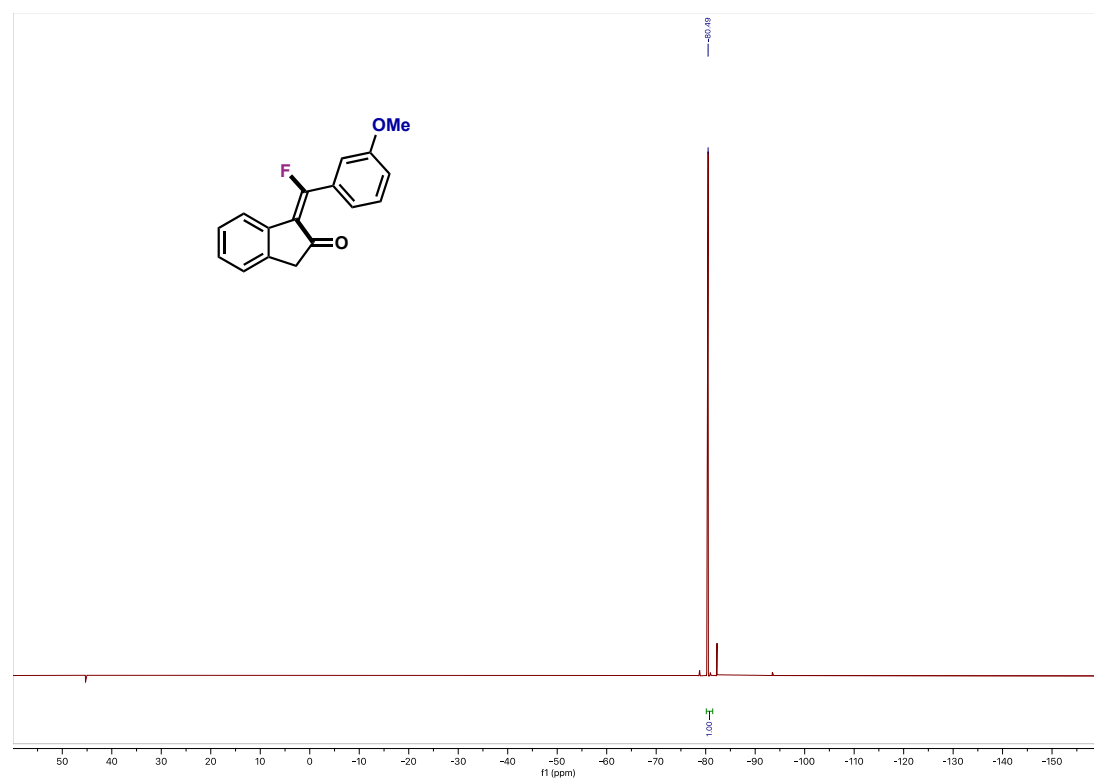
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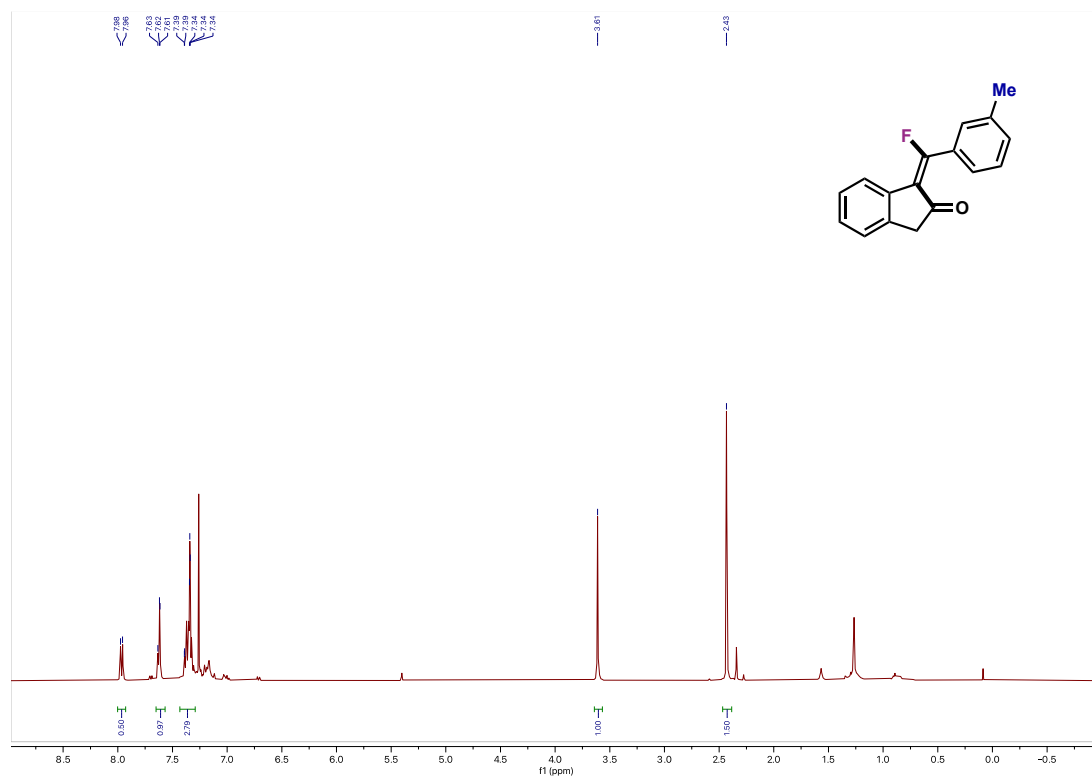
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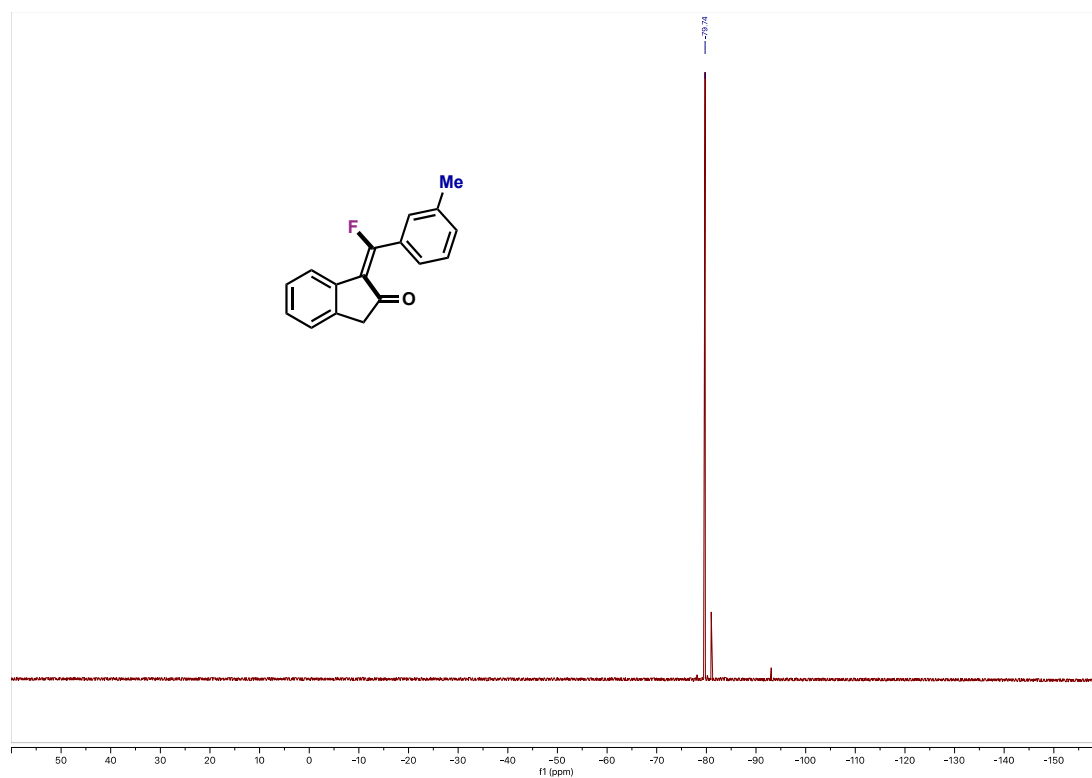
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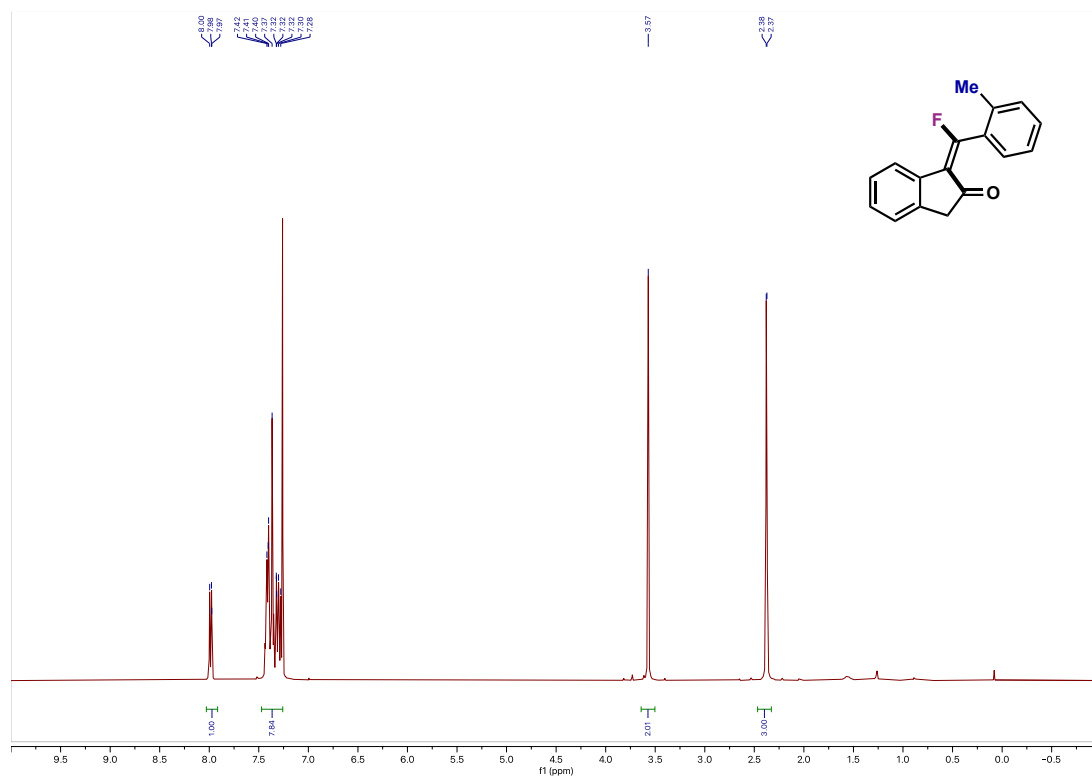
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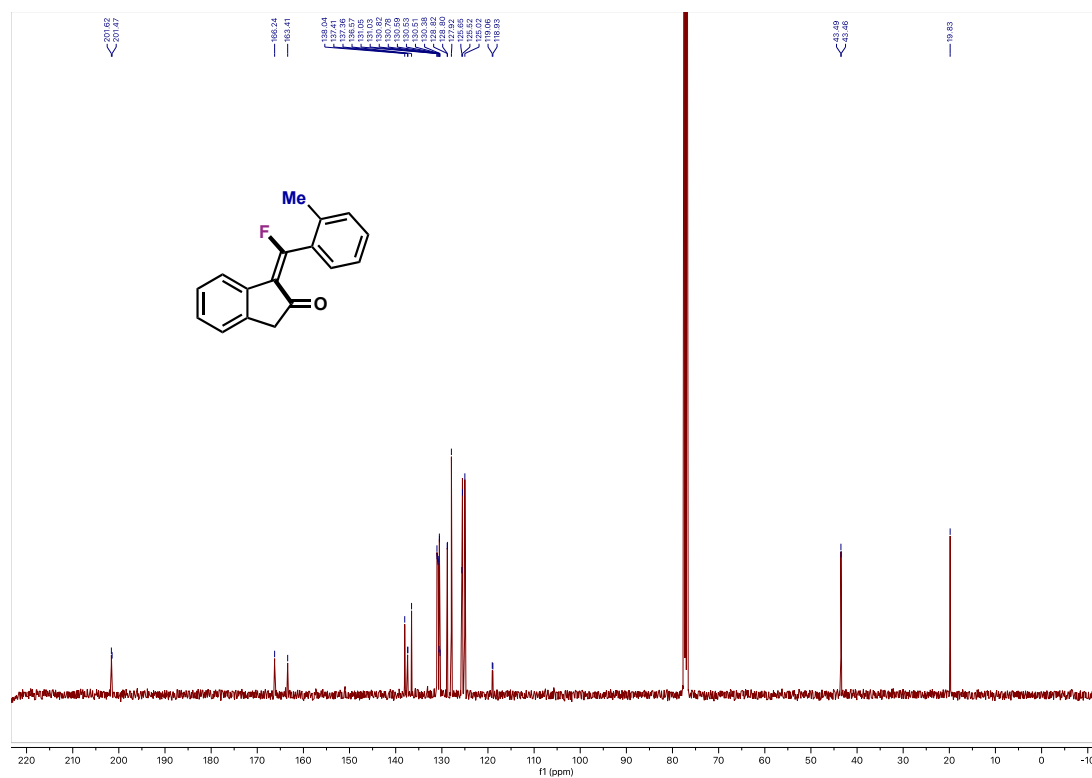
^{19}F NMR (377 MHz, CDCl_3) of **2.2m**



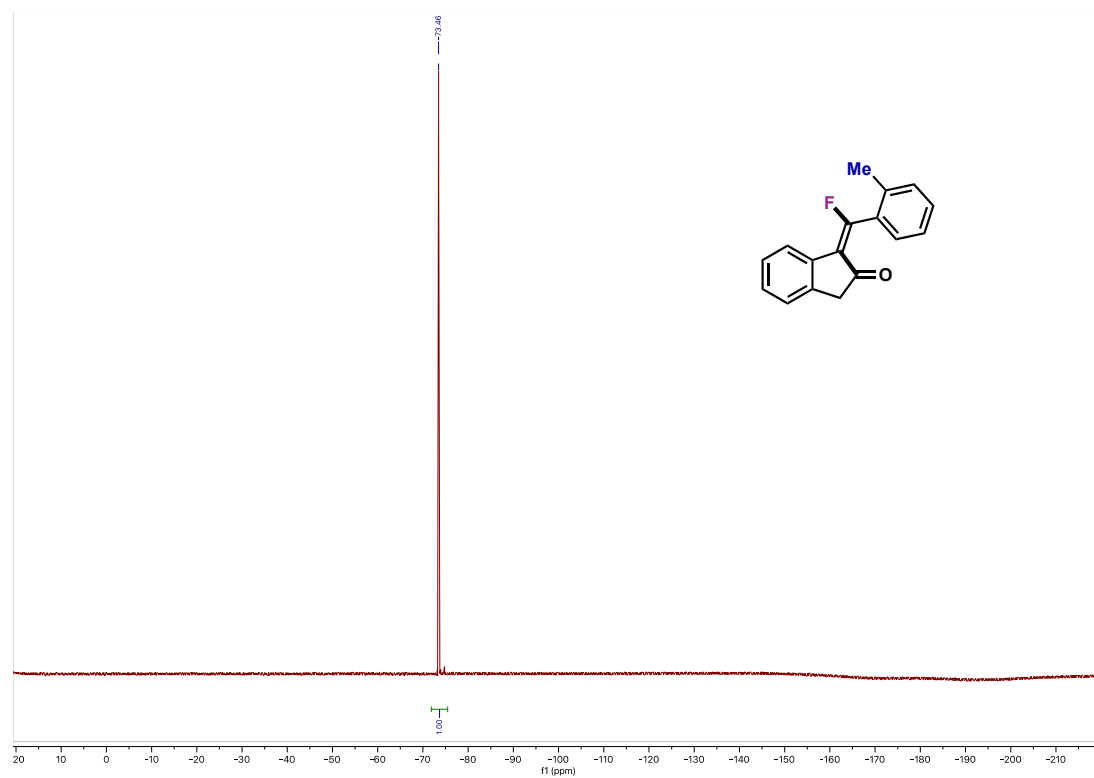
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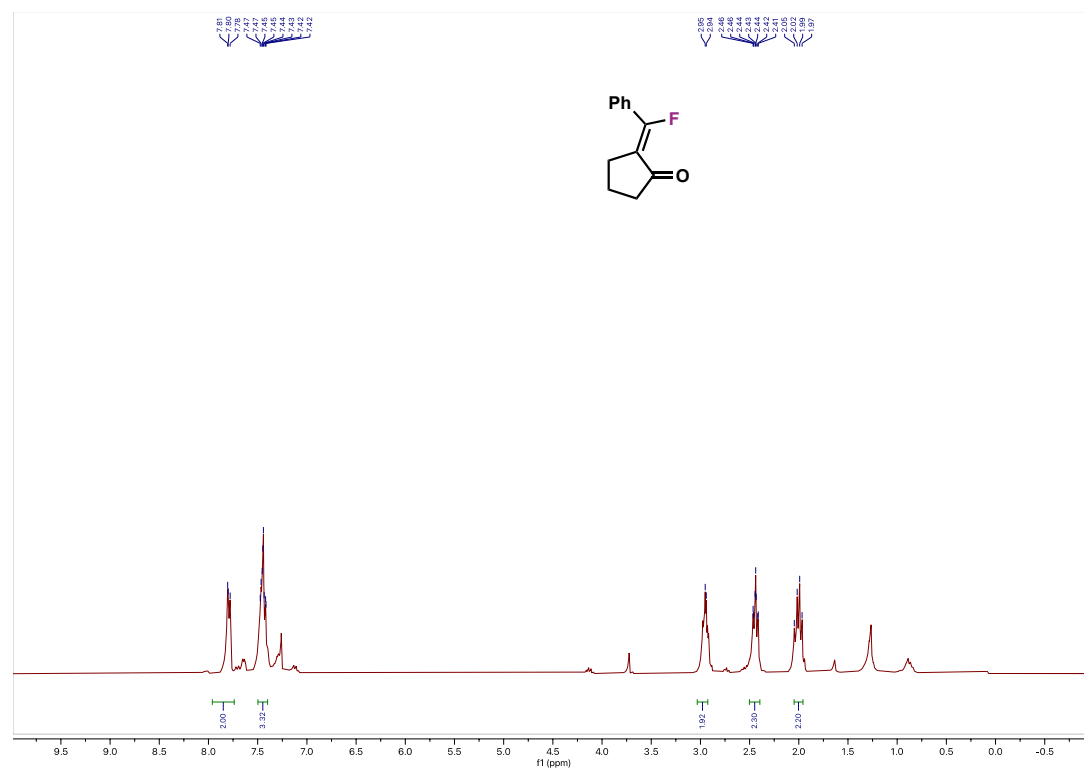
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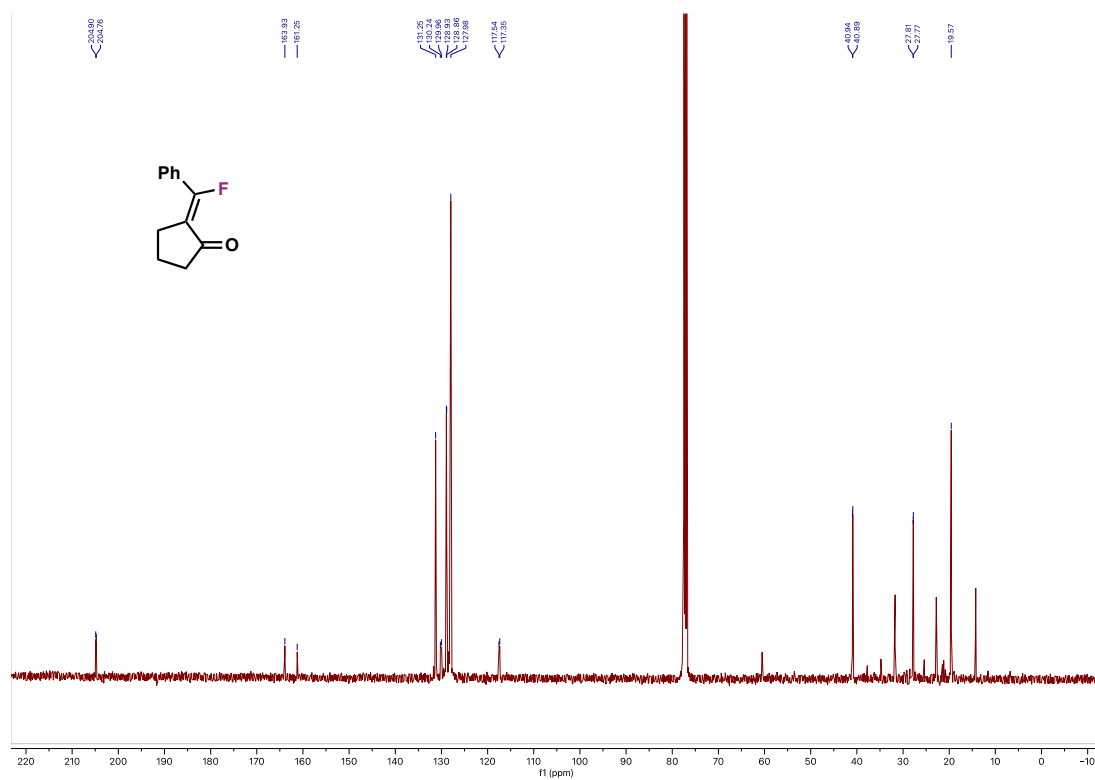
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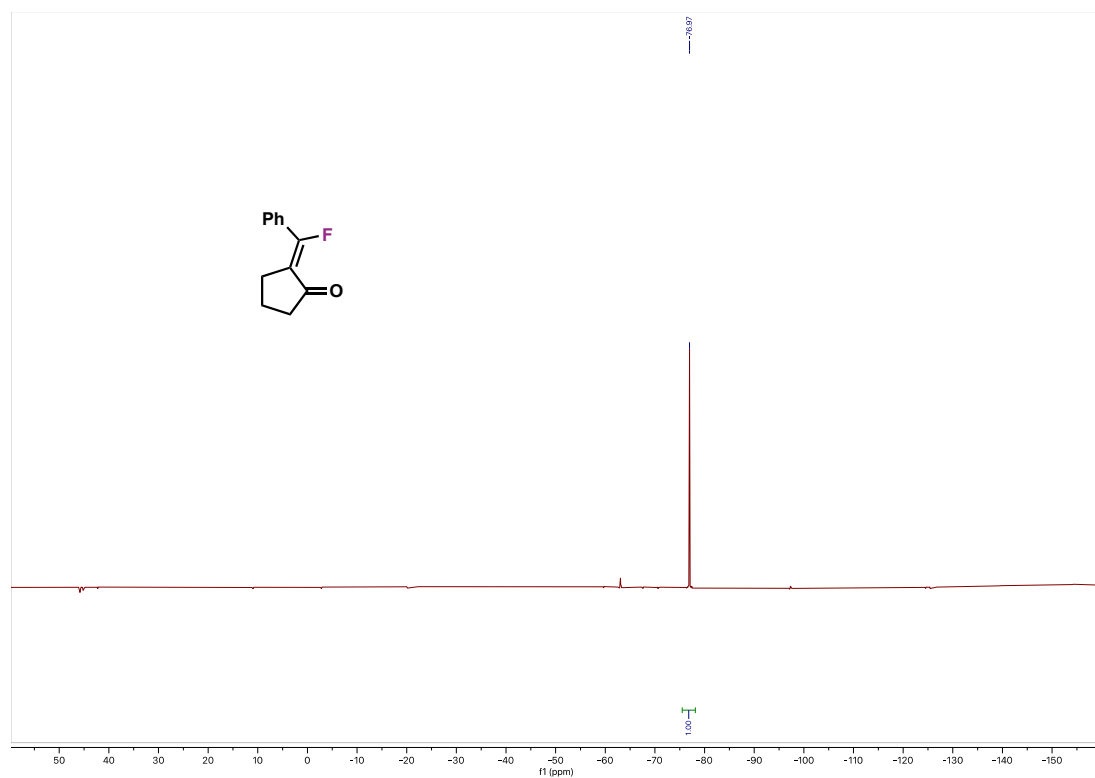
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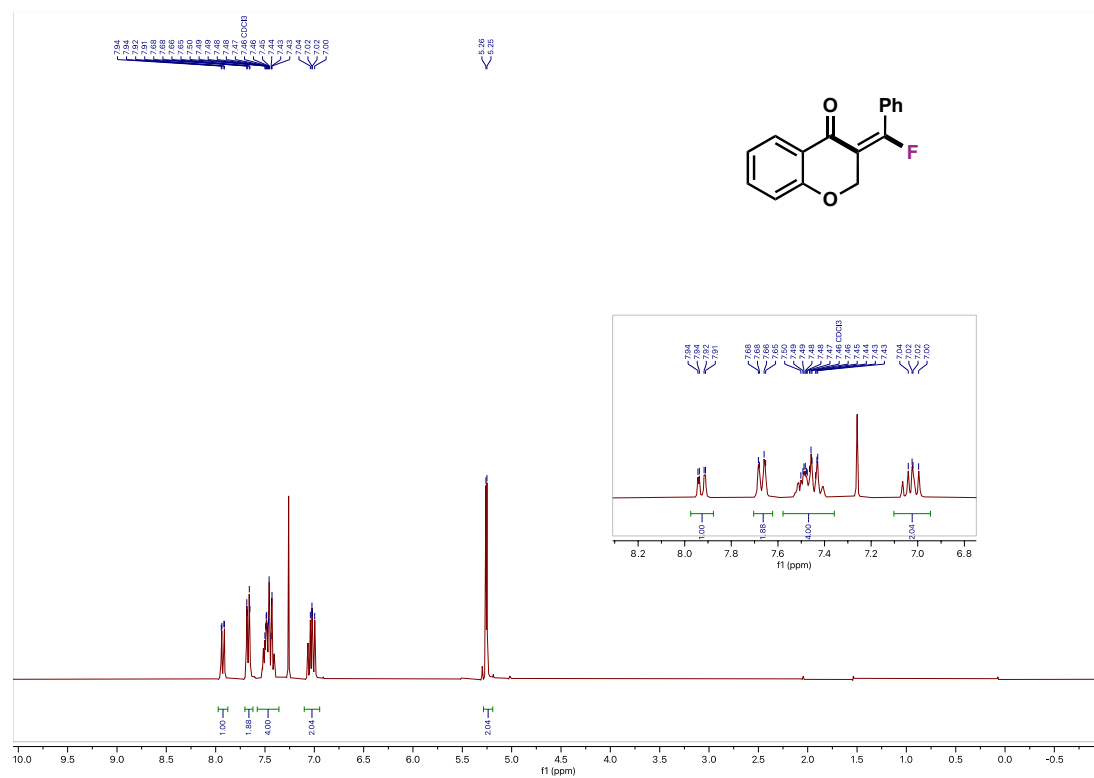
^{13}C NMR (101 MHz, CDCl_3) of 2.4



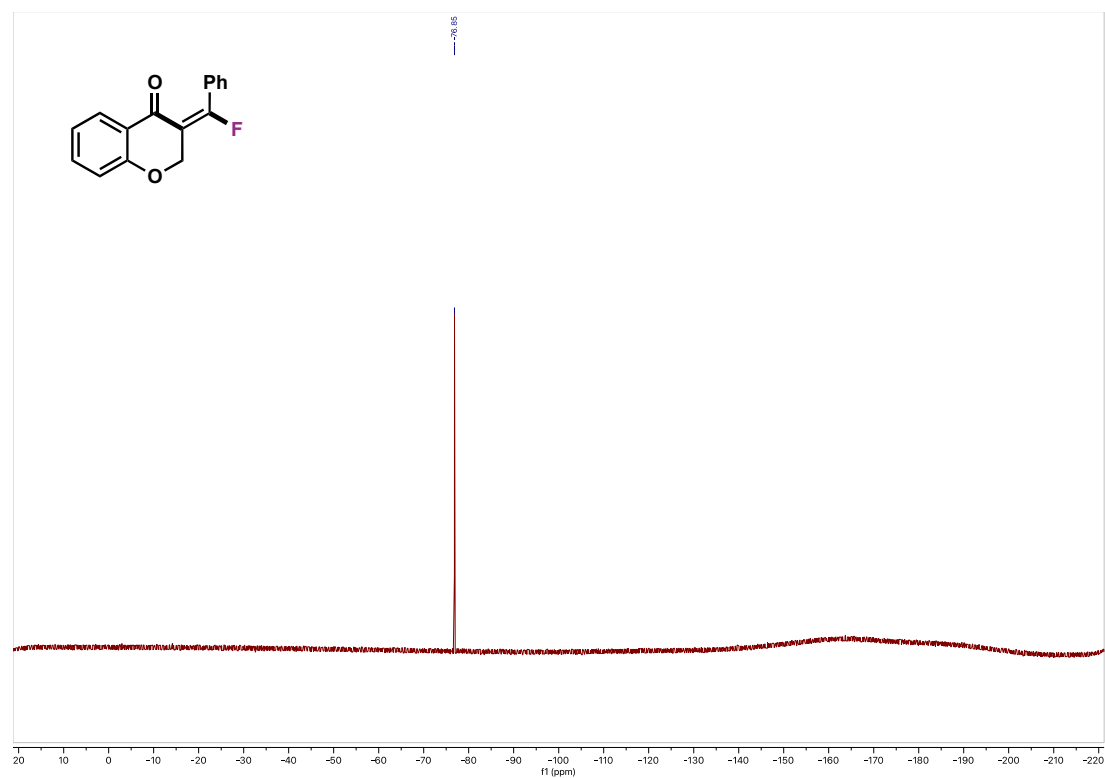
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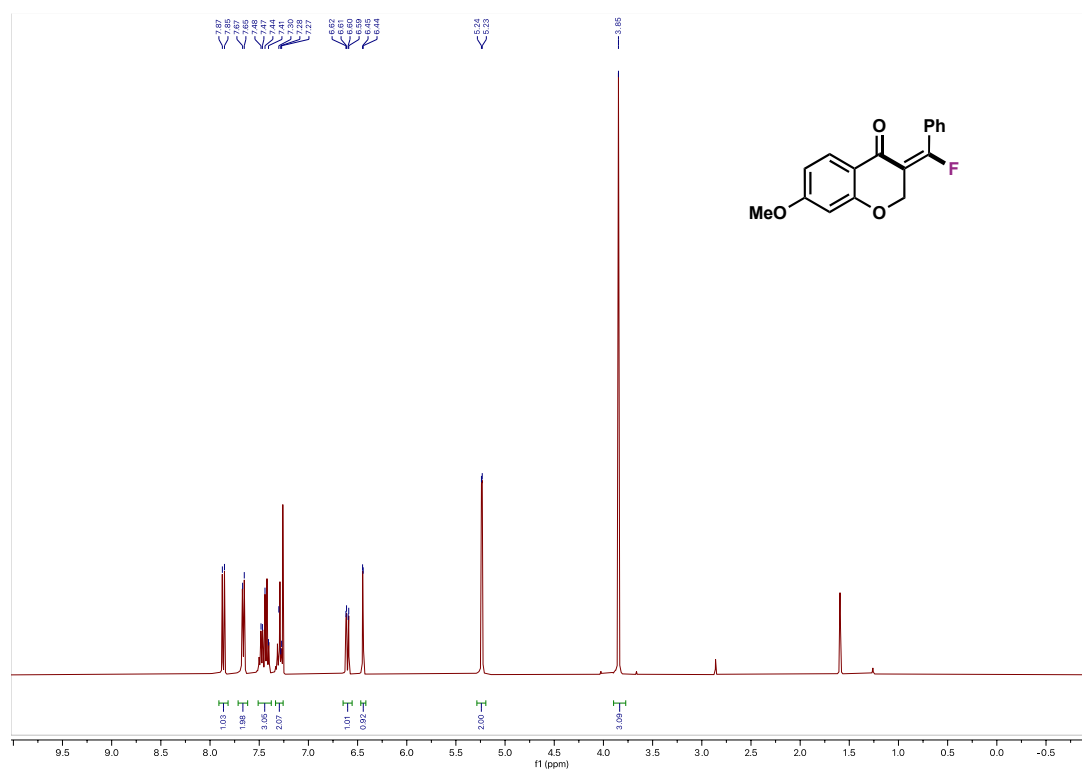
^1H NMR (400 MHz, CDCl_3) of **2.6a**



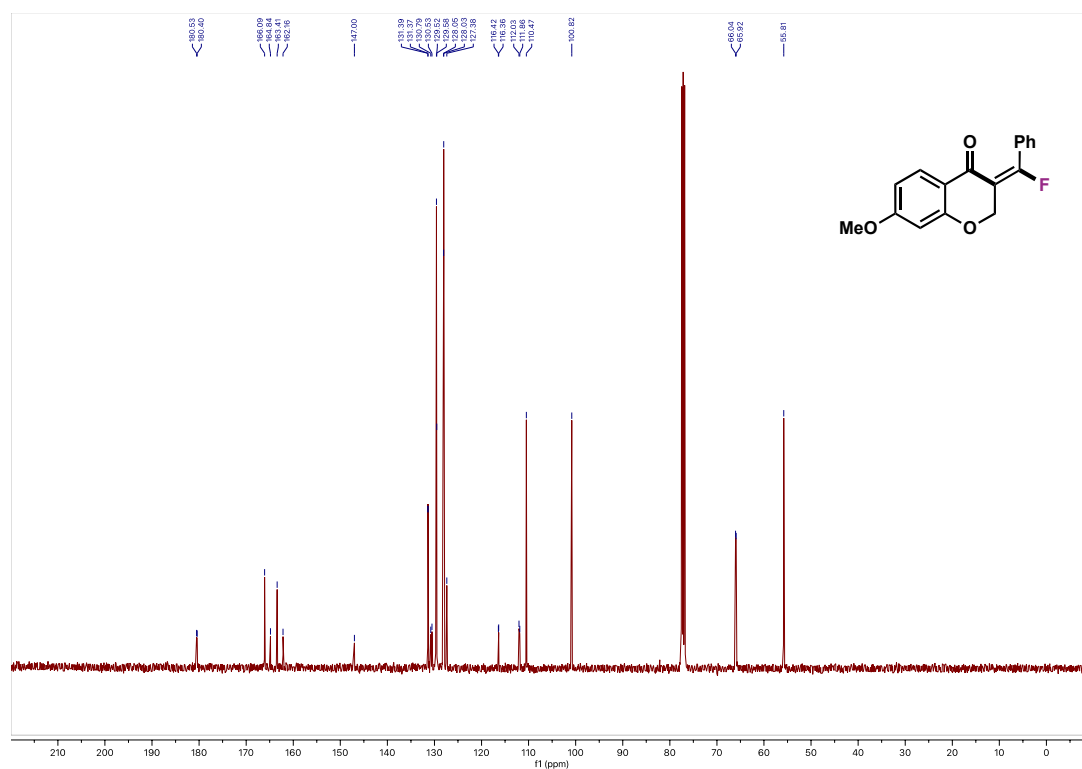
^{19}F NMR (377 MHz, CDCl_3) of **2.6a**



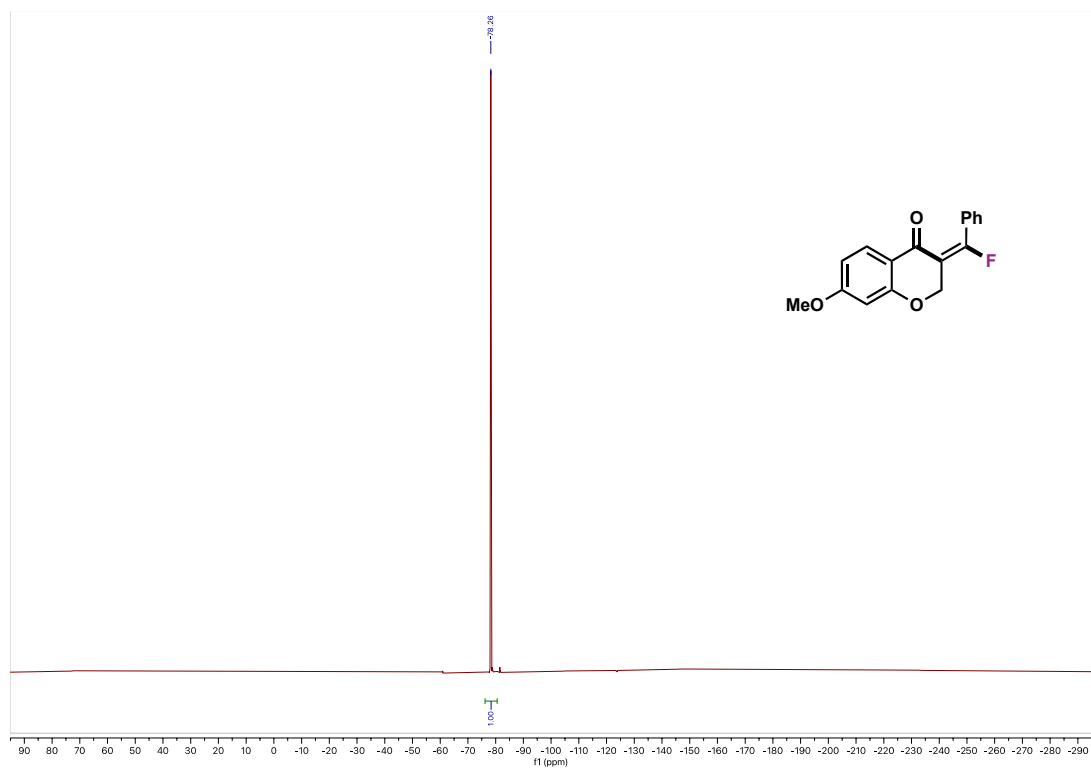
¹H NMR (400 MHz, CDCl₃) of **2.6b**



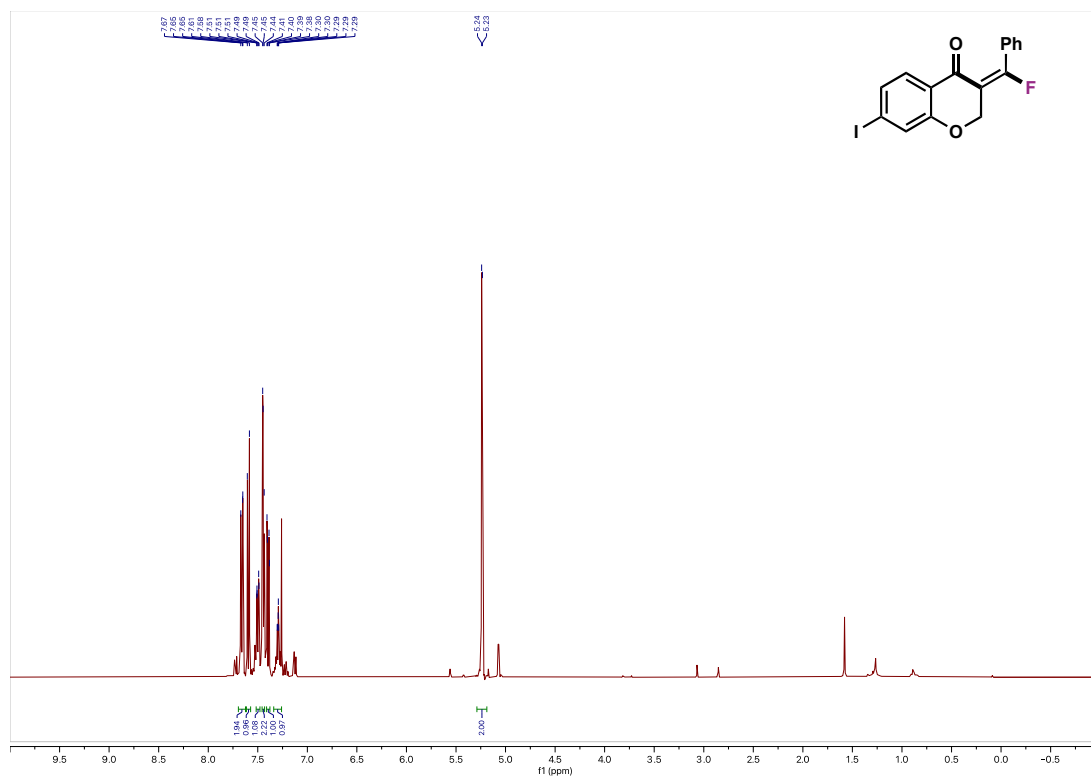
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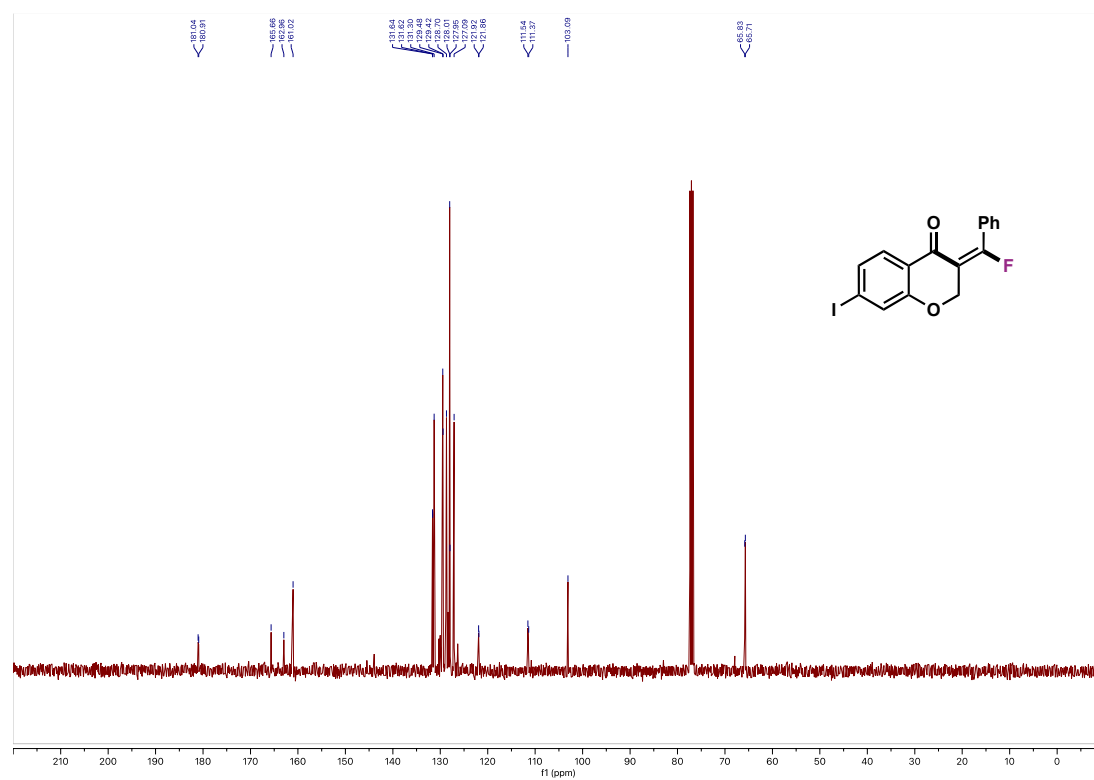
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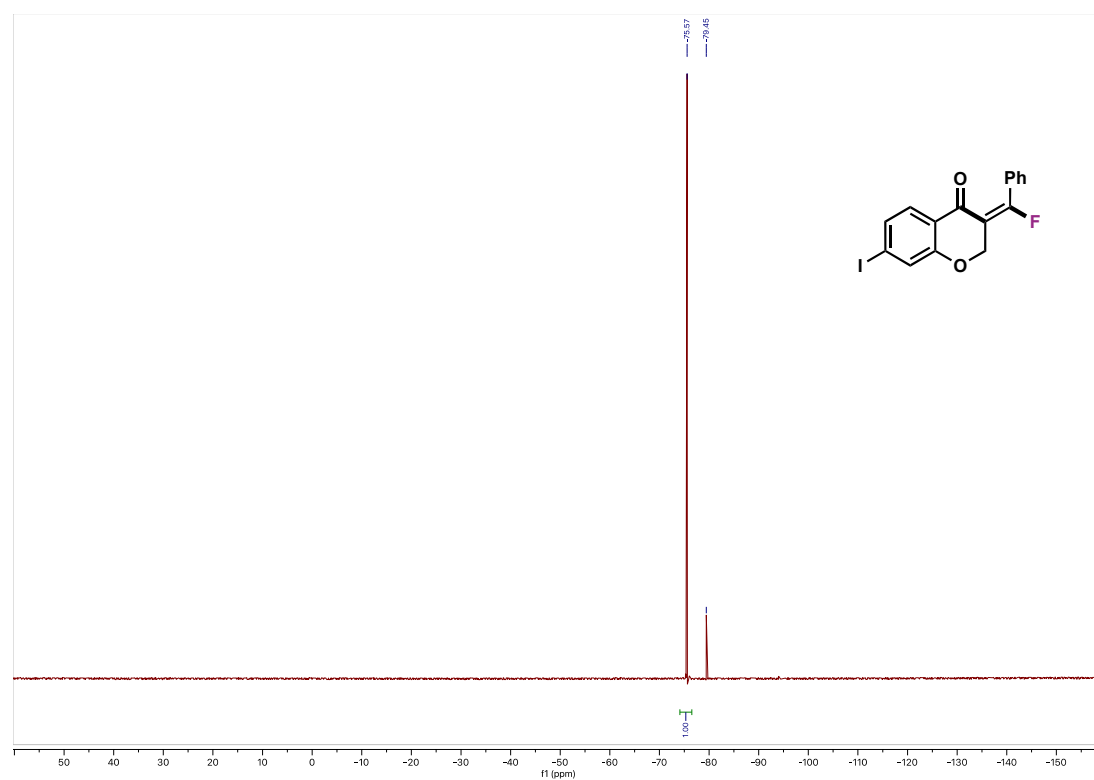
^1H NMR (400 MHz, CDCl_3) of **2.6c**



^{13}C NMR (101 MHz, CDCl_3) of **2.6c**



^{19}F NMR (377 MHz, CDCl_3) of **2.6c**



3 Lewis Acid-Catalyzed Fluorocarbamoylation

3.1 Contributions

This chapter describes the $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed fluorocarbamoylation of alkyne-tethered carbamoyl fluorides to yield 3-fluoromethylene oxindoles. This work was done in collaboration with undergraduate students, Ayonitemi J. Ajayi and Yuriko Fujisato who, along with PhD student Ramon Arora from the Lautens lab at the University of Toronto, assisted with starting material preparation and characterization. Ramon Arora also ran initial studies on a Pd-catalyzed version of this reaction. Dr. Mark Lautens offered discussion and consultation on mechanistic challenges and substrate design. DFT calculations were done by Dr. Ekdashi Prahan and Dr. Tao Zhang at York University. Undergraduate student Sarah Rough did preliminary studies on the synthesis and stability of free NH oxindoles from isocyanates. My contributions include the optimization of the reaction conditions, conducting the substrate scope and experimental mechanistic studies. The contributions of each author are noted in the text and labelled as such throughout the chapter. Much of the work in this chapter was published in the *Journal of the American Chemical Society*.

Citation: McKnight, E. A.; Arora, R.; Pradhan, E.; Fujisato, Y. H.; Ajayi, A. J.; Lautens, M.; Zeng, T.; Le, C. M., *J. Am. Chem. Soc.* **2023**, *145* (20), 11012–11018.¹

3.2 Introduction

Recent advances in atom-economical carbofluorination reactions have shown that π -bond fragments can be formally inserted into the activated C–F bond of acyl fluorides using contemporary catalytic platforms.^{2–5} Applications of these reaction manifolds to less activated C–F bonds, like the related carbamoyl fluorides, would be challenging given the reduced electrophilicity of the carbonyl. Operating under nucleophilic catalysis to drive a NAS reaction would require the formation of a strong nucleophile, while operating under electrophilic catalysis for a fluoride abstraction requires a high FIA, potentially disfavoring the reformation of a C–F bond. In fact, while there is a large library of synthetic applications for acyl fluorides as potent electrophiles,^{6,7} the reactivity of related carbamoyl fluoride electrophiles has been scarcely examined, likely due to the noted decrease in electrophilicity in comparison to acyl fluorides combined with limited user-friendly methods available for their synthesis.⁸ Recent advances in

methods to access carbamoyl fluorides under mild conditions have enabled studies into their reactivity, yet there is no literature precedent for their use as a dual function reagent (i.e., as a carbamoyl electrophile and fluoride source). This introduction will cover synthetic methods using carbamoyl fluorides as electrophiles and then transition into potential strategies that could be used to activate them towards carbofluorination-type reactivity.

3.2.1 Carbamoyl Fluorides as Electrophiles

Activation of the C–F bond in carbamoyl fluorides for simple acyl substitution reactions require the use of strong nucleophiles like alkoxides, azides, or Grignard reagents as reported by Schoenebeck (Figure 3.1).⁹ Additionally, these reactions typically require the use of an *N*-CF₃ carbamoyl fluoride, which are generally more electrophilic than a typical carbamoyl fluoride given the electron-withdrawing nature of the fluoroalkyl moiety.

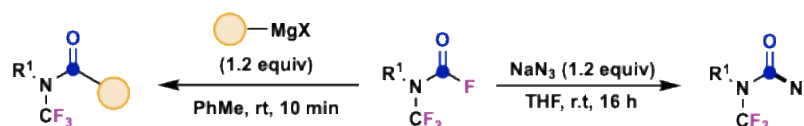


Figure 3.1. Use of strong nucleophiles for acyl substitution reactions of carbamoyl fluorides.

In the context of transition metal-catalyzed reactions, cross-couplings of carbamoyl fluoride electrophiles require either a low-valent Ni⁰-catalyst to facilitate the challenging C–F bond OA step or a chelating moiety on the carbamoyl fluoride to enable OA at a less nucleophilic Pd⁰ center. The first report of carbamoyl fluorides in a transition metal-catalyzed reaction came in 2020 from Luan, Ye, and co-workers who developed an enantioselective synthesis of γ -lactams through a Ni-catalyzed intramolecular carbocarbamylation of unactivated alkenes (Figure 3.2). The reaction is initiated by OA of the Ni⁰ catalyst to the carbamoyl fluoride C–F bond followed by alkene migratory insertion forming the key C–C bond prior to transmetalation with an aryl boronic acid. A second C(sp³)–C(sp²) bond is formed via RE, regenerating the active Ni catalyst.

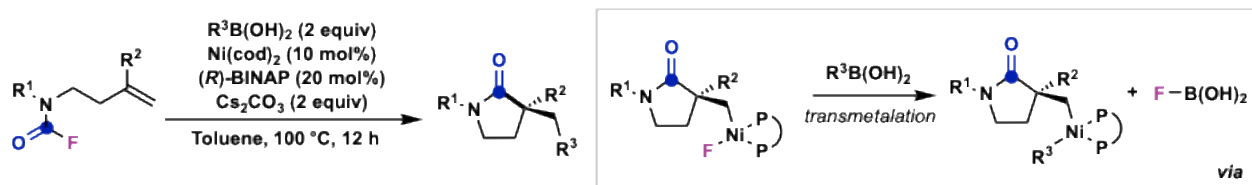


Figure 3.2 Ni-catalyzed intramolecular carbocarbamylation of unactivated alkenes.

Building on these findings, Chen and co-workers in 2022 reported a Ni-catalyzed enantioselective 1,4-arylcaramoylation of 1,3-dienes with aryl boronic acids, affording α -alkenylated γ -lactams (Figure 3.3).¹⁰ Mechanistic studies supported a sequence involving OA of the C–F bond by Ni⁰ followed by alkene migratory insertion forming an η^3 - π -allyl intermediate. Transmetalation with the boronic acid, and RE yielded the 1,4-addition product efficiently.

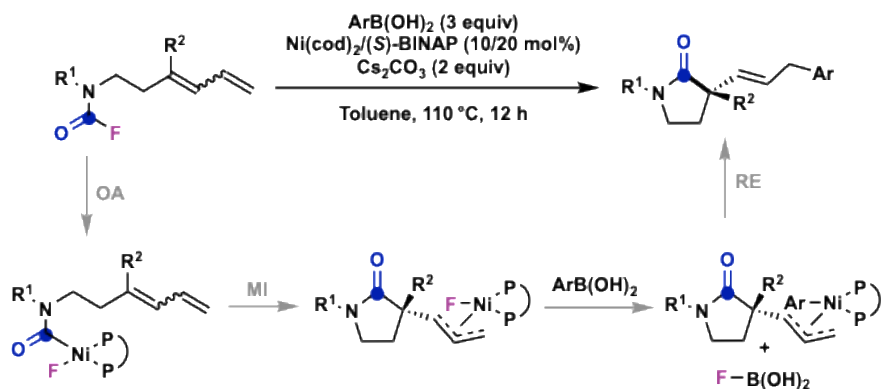


Figure 3.3 Ni-catalyzed enantioselective 1,4-arylcaramoylation of 1,3-dienes with boronic acids.

Ni⁰-catalysis could also be employed for the alkynylation of *N*-CF₃ carbamoyl fluorides as reported by Schoenebeck and co-workers in 2021.¹¹ Computational and experimental studies indicated that the Ni(COD)₂/dtbbpy catalyst selectively undergoes OA at the C–F bond (outcompeting potential C–N bond OA) followed by transmetalation with the alkynyl silane coupling partner. Subsequent C–C bond RE forms the desired *N*-CF₃ alkynamide. In 2023, Le and co-workers reported that alkynyl silanes could also be used for the alkynylation of non-*N*-CF₃ carbamoyl fluorides under fluoride-catalyzed conditions using catalytic TBAF.¹² A recent disclosure from the Schoenebeck group has also shown that with small modifications to the TBAF-catalyzed method, *N*-CFH₂ carbamoyl fluorides can also be used in alkynylation reactions.¹³

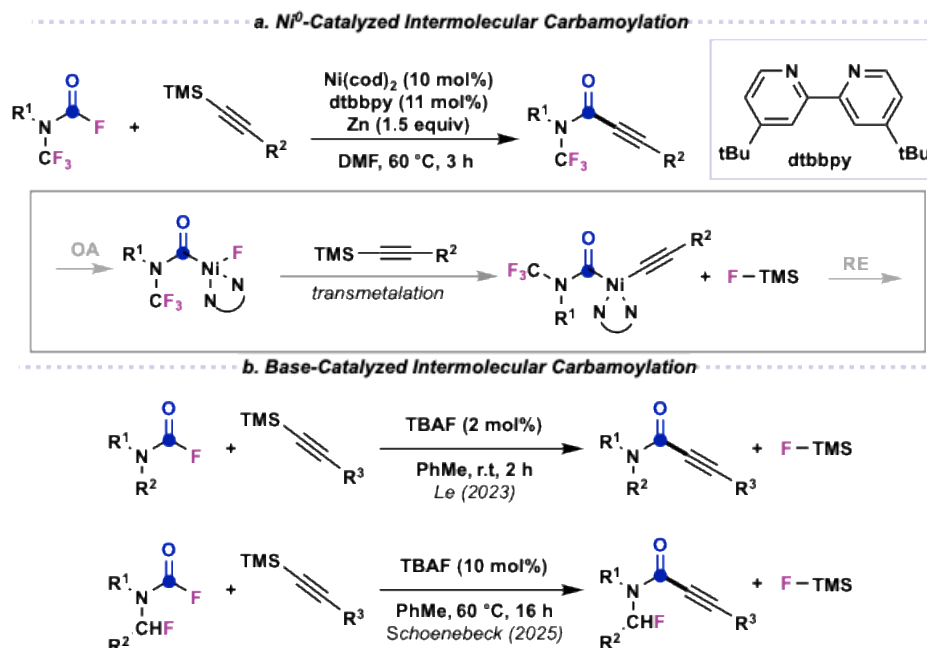


Figure 3.4. Strategies for intermolecular alkynylation of carbamoyl fluorides using TMS-acetylenes.

In 2024, the Le group reported an intermolecular Pd-catalyzed Suzuki-type cross-coupling of carbamoyl fluorides with a 2-pyridyl directing group.¹⁴ The proposed mechanism involves OA of Pd^0 into the C–F bond, facilitated by pyridyl coordination to form a five-membered palladacycle. This coordination is hypothesized to stabilize the intermediate and prevents decomposition to amine via decarbonylation. Subsequent transmetalation with a boronic acid followed by RE resulted in the formation of the desired *N*-2-pyridyl amides. The 2-pyridyl directing group can be removed by switching from Pd-catalysis to Ni-catalysis as shown by Amgoune and Tlili in 2025.¹⁵

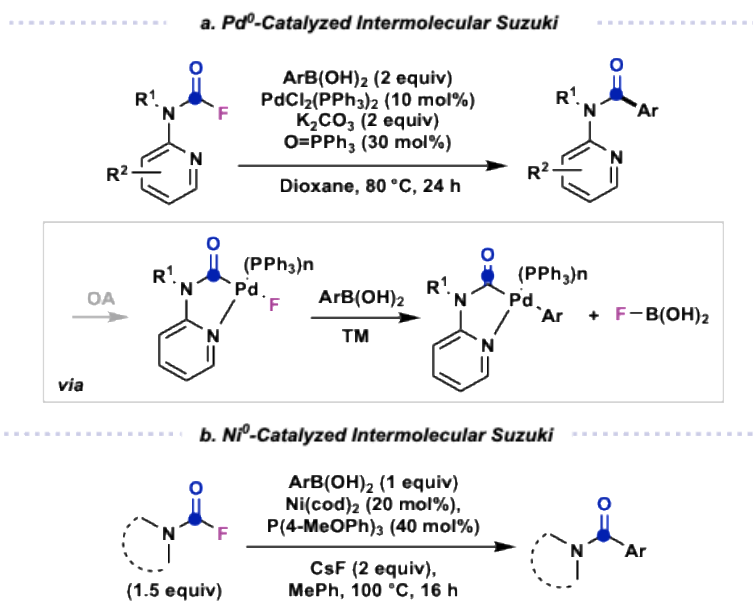


Figure 3.5. Strategies for Suzuki-type cross-coupling of carbamoyl fluorides with aryl boronic acids.

In all cases, the carbamoyl fluoride was uniquely suited to enable the cross-coupling reaction, as employment of the analogous carbamoyl chloride led to lower yields, no reactivity, or reduced enantioselectivities. Despite the enhanced reactivity brought about by using carbamoyl fluorides, all reported transformations sequester the fluoride via the formation of a strong heteroatom–F bond (i.e., Si–F, B–F) either during transmetalation or during activation of the nucleophilic coupling partner, which acts as a thermodynamic sink to drive catalyst turnover. Therefore, the development of reactions that preserve both the carbamoyl fragment and fluoride fragment remains an as-yet-unrealized goal.

3.2.2 Atom-economical Chlorocarbamoylation Reactions

Unlike the elusive fluorocarbamoylation reaction, the analogous chlorocarbamoylation reactions of carbamoyl chlorides are known. The seminal report came from Lautens and co-workers in 2015, who disclosed the chlorocarbamoylation of aryl carbamoyl chlorides with a pendant TIPS alkyne to yield (*E*)-3-chloromethylene oxindole derivatives under a *trans*-selective Pd(0/II)-redox manifold (Figure 3.6).¹⁶ This reaction notably required the use of aryl phosphadamantane (PA-Ar) ligands which help facilitate the rate-determining alkyne insertion step. Meanwhile, the exclusive *trans* selectivity can be attributed to a rapid *cis*→*trans* isomerization following

alkyne insertion which is promoted by the destabilization of the vinyl Pd intermediate by the presence of the TIPS group.¹⁷

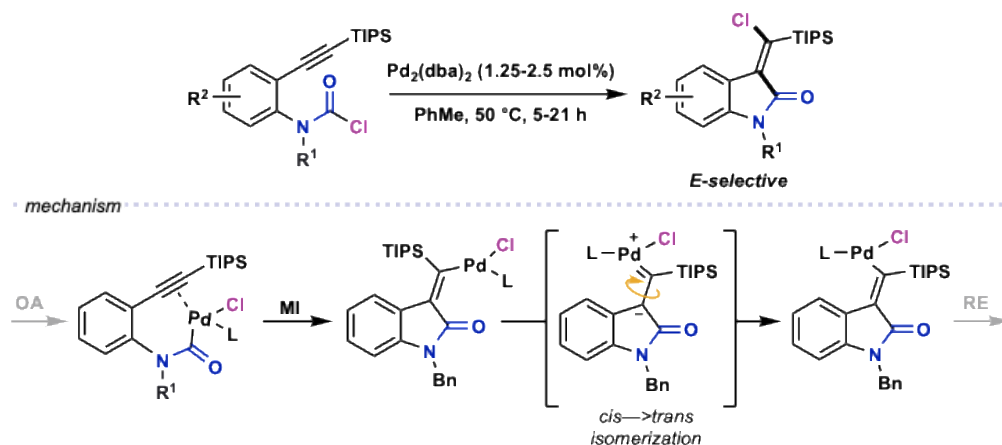


Figure 3.6. $\text{Pd}^{0/\text{II}}$ -catalyzed chlorocarbamylation of carbamoyl chlorides containing a pendant TIPS alkyne.

While this reaction was exclusive to silylated-alkyne substrates, a later report in 2020 showed that subjecting carbamoyl chlorides with a pendant alkyl-alkynes to excess HFIP enabled a Brønsted-acid mediated *trans*-selective chlorocarbamylation reaction to yield (*E*)-3-chloro-3-alkylmethylene oxindoles (Figure 3.7).¹⁸ The authors proposed that the reaction proceeds via hydrogen bond promoted chloride abstraction to form an isocyanate cation. Subsequent cyclization and *trans*-chlorination of the alkyne gave the desired product.

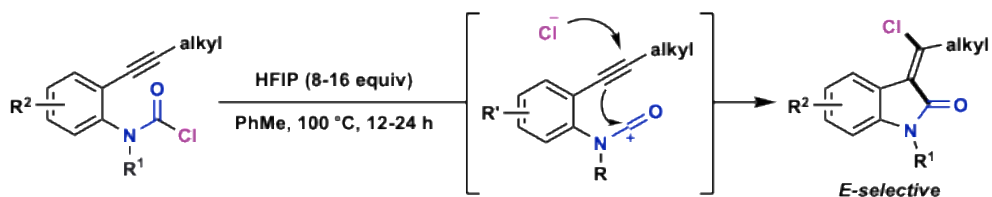


Figure 3.7. HFIP-mediated chlorocarbamylation of carbamoyl chlorides containing a pendant alkyl alkyne.

Access to (*Z*)-3-chloromethylene oxindoles can also be achieved via chlorocarbamylation reactions of carbamoyl chlorides with a pendant aryl-alkyne under high valent Pd-catalysis (Figure 3.8).¹⁹ Instead of OA, the reaction is initiated via an initial chloropalladation step with a Pd^{II} species, followed by OA to the carbamoyl chloride bond to yield a high-valent Pd^{IV} -palladacycle. This intermediate undergoes efficient C–C bond forming RE to give the product.

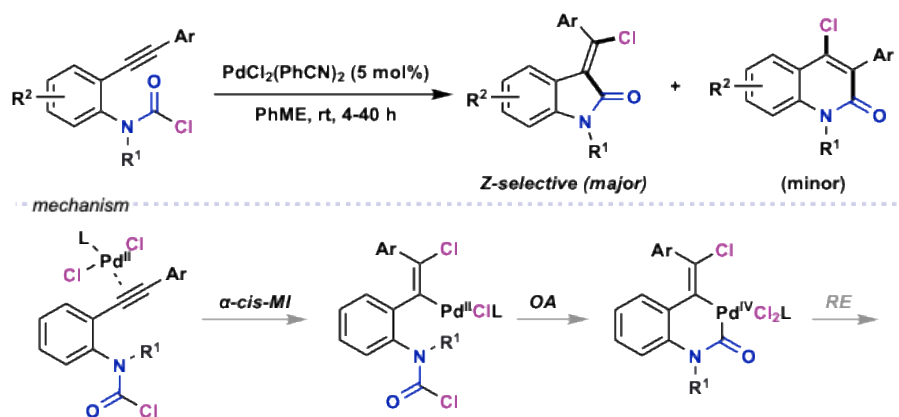


Figure 3.8. $\text{Pd}^{\text{II/IV}}$ -catalyzed chlorocarbamylation of carbamoyl chlorides containing a pendant TIPS alkyne.

3.3 Motivation and Research Plans

Given our success of using boron trifluoride/ BF_4^- as a driver for catalytic fluoride shuttling of acyl fluorides, we were curious if similar reactivity would be seen with carbamoyl fluorides, which have a stronger C–F bond and are generally less electrophilic than acyl fluorides given their resonance stabilization. To target the activation of strong carbamoyl fluoride C–F bonds in atom-economical carbofluorination reactions, we once again initially envisioned exploring an intramolecular system to bias the regioselectivity of the insertion step. Given the precedent of alkyne-tethered carbamoyl chlorides in chlorocarbamylation reactions, and our work on alkyne tethered-acyl fluorides, we opted to pursue a similar substrate for this initial study. This reaction also gives the added benefit of producing 3-fluoromethylene oxindoles and lactams as the product of the reaction, which have medicinal value.

Oxindoles, a class of amide-containing heterocycles, represent a privileged scaffold in medicinal chemistry, with numerous FDA-approved drugs incorporating an oxindole core.²⁰ Within this family, 3-alkenyl oxindoles are particularly well developed: more than 3,900 compounds containing this motif have been reported, many of which display potent biological activities, including anticancer, antibacterial, antifungal, antiviral, and antiangiogenic effects.²¹ A prominent example is Sunitinib, an orally active receptor tyrosine kinase (RTK) inhibitor marketed by Pfizer as Sutent.²² Sunitinib was approved by the FDA in 2006 for the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumors, becoming the first anticancer agent to receive simultaneous approval for two distinct indications. Its therapeutic efficacy arises from the inhibition of multiple RTKs, including all platelet-derived growth factor receptors and vascular endothelial growth factor receptors, which are key regulators of tumor

angiogenesis and tumor cell proliferation. Concurrent inhibition of these signaling pathways reduces tumor vascularization and induces cancer cell apoptosis, ultimately leading to tumor regression.

Reflecting its clinical impact, Sunitinib generated approximately \$847 million in global sales in 2008 alone.²¹ Since its discovery, numerous structurally related oxindole derivatives have been developed for pharmaceutical applications, including Nintedanib, marketed under the brand names Ofev and Vargatef. Nintedanib is an orally administered tyrosine kinase inhibitor approved for the treatment of idiopathic pulmonary fibrosis and, in combination with other therapies, for certain types of non-small-cell lung cancer.^{23,24} Aside from accessing 3-alkenyl oxindoles, our proposed reaction would give access to tetrasubstituted monofluoroalkenes, an emerging peptide bond isosteres,^{25–27} for which general and efficient synthetic methods remain limited. In particular access to tetrasubstituted monofluoroalkenes of potential biological relevance in high stereo- and regio-selectivity remains challenging.²⁸

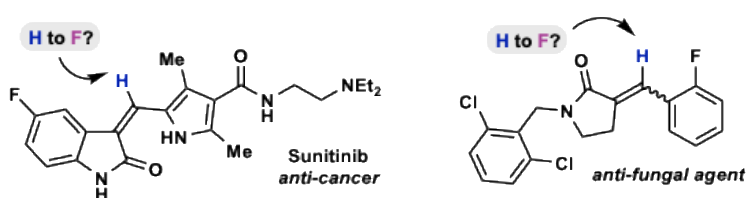


Figure 3.9. Known bioactive oxindole and lactams with a 3-methylene moiety primed for 3-monofluoromethylation.

Typical installation of a 3-methylene fragment on an oxindole scaffold involves the condensation of 2-oxindole derivatives with different aromatic aldehydes. This method precludes the installation of a fluoromethylene group, given that the fluorine-containing precursor (an acyl fluoride) would not be amenable to the reaction conditions (refluxing in MeOH). While 3-fluoromethylene derivatives of methylene oxindoles are known, methods to access them in a general manner are limited.

In 2016, Xu and co-workers found that (triphenylphosphonio)difluoroacetate (PDFA), a difluorocarbene source, reacts with indoline-2,3-dione **128** to form dimerized product **129** containing a 3-fluoromethylene oxindole fragment on one side (Figure 3.10).²⁹ Initially targeting the formation of 3-*gem*-difluoromethylene oxindoles, they found that the reaction yielded 3-fluoroalkenyl-3-trifluoromethyl-2-oxindoles likely via homocoupling of the

intermediate 3-*gem*-difluoromethylene oxindoles. While the reaction gives products in good to excellent yields, the applicability of this method is limited given that only homocoupling products are made.

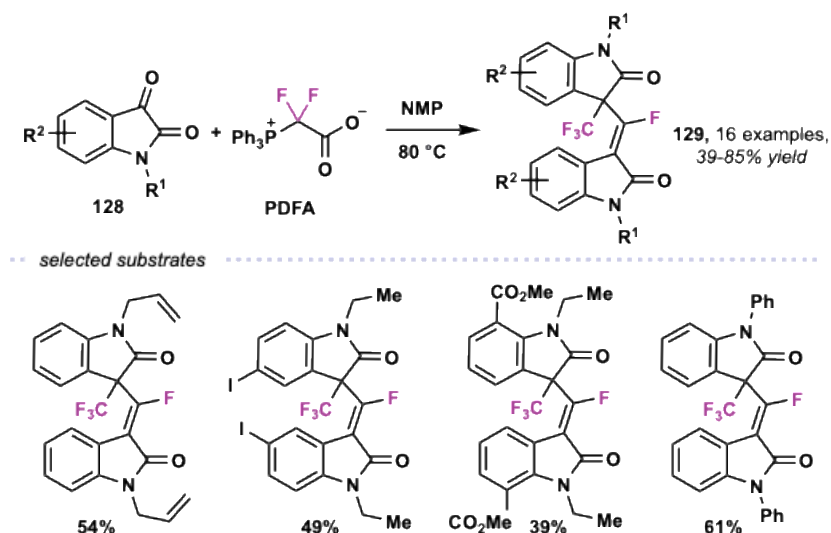


Figure 3.10. Homocoupling of 3-*gem*-difluoromethylene oxindoles generated *in situ* from indoline-2,3-dione and difluorocarbene.

In 2017, Zhou and co-workers disclosed the synthesis of 3-fluoro-3-methylene oxindoles **147** from diazo oxindoles **145** and fluorinated silyl enol ethers **146** under cationic Au^I-catalysis.³⁰ The reaction proceeds via the formation of a Au-carbene via N₂ displacement, which can then react with a *gem*-difluorinated silyl enol ethers to give a tetrasubstituted monofluoroalkene product after fluoride elimination. While the reaction gives access to a versatile product, it does require an expensive transition metal-catalyst and pre-formation of both coupling partners.

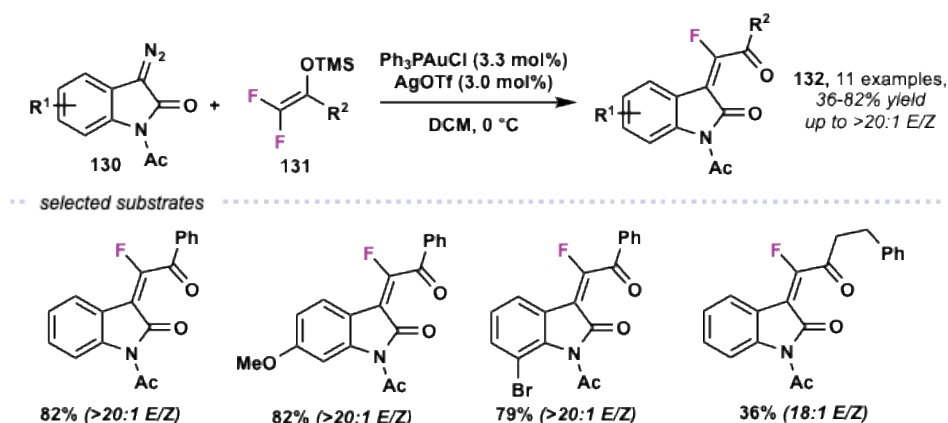


Figure 3.11 Cationic Au^I-catalyzed carbene insertion into *gem*-difluorinated enol silyl ethers.

Finally, Arseniyadis and coworkers reported the synthesis of heterocycles containing a 3-fluoromethylene amide moiety via the Krapcho decarboxylation of α -alkoxycarbonyl-3-difluoromethylated cyclic amides (e.g.,

lactams, oxindoles, and succinimides).³¹ The reaction proceeds quickly and with high stereoselectivity, giving only the *E*-isomer of the monofluoroalkene. Fluorinated lactams of varying ring sizes are accessible, but the reaction is limited to terminal monofluoroalkenes and requires preinstallation of a CHF₂ fragment derived from Hu's reagent (134).

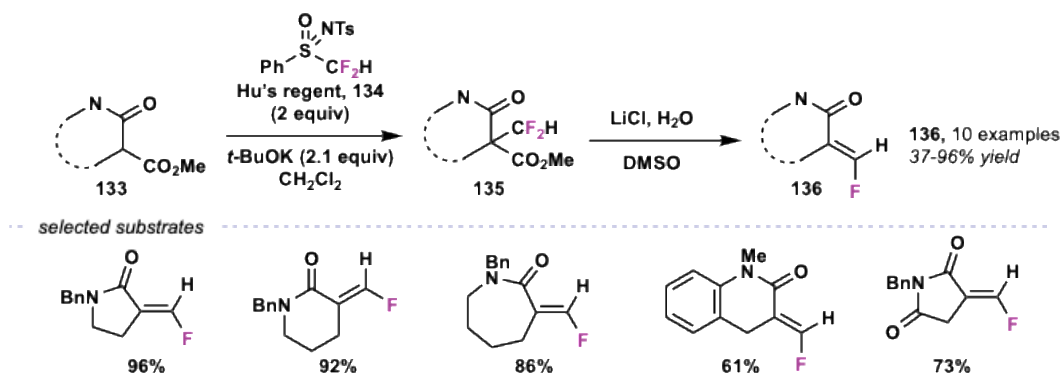


Figure 3.12 Krapcho decarboxylation of α -alkoxycarbonyl-3-difluoromethylated lactams, oxindoles, and succinimides.

One clear gap that exists in the current literature is access to 3-fluoro-3-aryl-methylene oxindoles and lactams. We hypothesized that under a LA-catalyzed system, aryl-alkyne tethered carbamoyl fluorides could be converted into 3-fluoromethylene oxindoles and lactams. The development of a BF₃-catalyzed atom-economical carbofluorination of carbamoyl fluoride C–F bonds is detailed herein, including the reaction development and optimization, substrate scope and mechanistic studies.

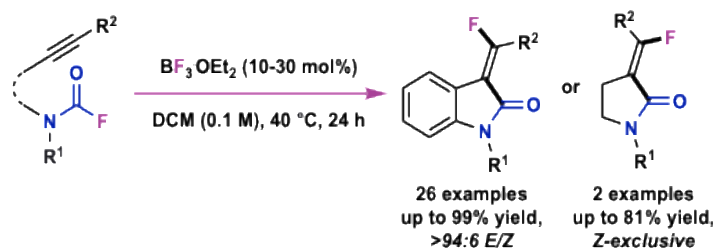
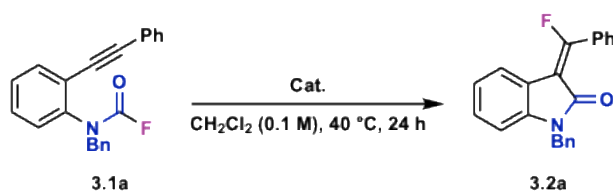


Figure 3.13 BF₃-catalyzed fluorocarbonylation reaction of alkyne-tethered carbamoyl fluorides.

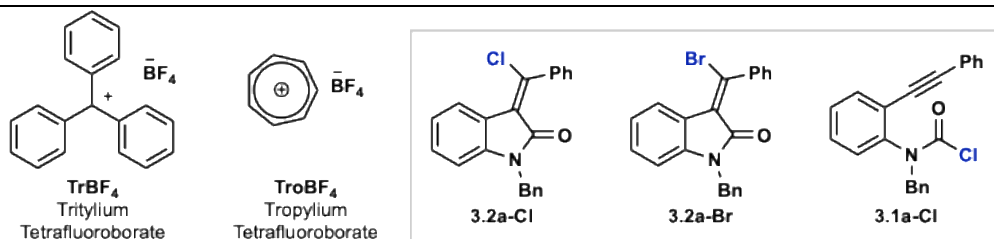
3.4 Results and Discussion

3.4.1 Reaction Optimization

Our study of intramolecular fluorocarbonylation reactions was carried out using **3.1a** as a model substrate. This standard substrate was synthesized via a Sonogashira reaction between 2-iodoaniline and phenylacetylene, followed by formation of the carbamoyl fluoride using a difluorocarbene source (PDFA) and oxidant system, a protocol developed by the Le group in 2023.³² General details on these reaction conditions can be found in the experimental section of this chapter. The reactions were performed on 0.1 mmol scale, and conversion, yield, and E/Z-selectivity were determined by ¹⁹F NMR spectroscopy using α,α,α -trifluorotoluene as internal standard. Quantitative ¹⁹F NMR was run using a single-scan experiment with a 30 second relaxation delay, which was found to be a sufficient delay to get full spin-lattice relaxation via an inversion recovery experiment. An initial proof of concept experiment was conducted using 1 equiv. of BF₃·OEt₂ (Table 3.1, entry 1) given its proficiency in acting as a fluoride abstractor for activated C–F bonds (FIA: 346 kJ mol⁻¹) and its potential for fluoride shuttling as demonstrated by Nishimoto and Yatsuda.³³ The reaction proceeded cleanly under these conditions to give 3-fluoromethylene oxindole **3.2a** in 89% yield with full conversion of starting material. Decreasing the loading of BF₃·OEt₂ to 20 mol% led to a 68% yield (Table 3.1, entry 2), revealing that BF₃·OEt₂ can enable catalytic turnover for the formal cleavage of the harder to activate carbamoyl fluoride C–F bond. Increasing the temperature to 40 °C but keeping the catalyst loading at 20 mol% led to almost complete conversion of the starting material and a 92% yield (Table 3.1, entry 3). Decreasing the catalyst loading to 10 mol% increased yields to >99% by NMR and **3.2a** was isolated via flash column chromatography in 99% yield as a single isomer (Table 3.1, entry 4). The major isomer, which results from a formal *trans* addition, was unambiguously confirmed by single-crystal X-ray crystallography. The reaction conditions of 10 mol% catalyst loading at 40 °C for 24 h were the standard reaction conditions for the rest of the catalyst screen.

Table 3.1. Catalyst screen for the synthesis of **3.2a**.

Entry ^a	Lewis or Brønsted Acid	Loading	Conv. (%)	Yield (%)	E/Z ratio	FIA (kJ mol ⁻¹) ^g
1^b	BF ₃ ·OEt ₂	1 equiv.	>99	89	ND	346 ³⁴
2^b	BF ₃ ·OEt ₂	20 mol%	79	68	>95:5	346 ³⁴
3	BF ₃ ·OEt ₂	20 mol%	100	92	>95:5	346 ³⁴
4	BF ₃ ·OEt ₂	10 mol %	100	>99 (99) ^c	>95:5	346 ³⁴
5	B(4-F-C ₆ H ₄) ₃	10 mol %	3	0	NA	377 ³⁹
6	BCl ₃	10 mol %	100	90 ^d	>95:5	404 ³⁴
7	BBr ₃	10 mol %	100	81 ^e	>95:5	428 ³⁴
8	B(C ₆ F ₅) ₃	10 mol %	30	5	95:5	448 ³⁴
9	HBf ₄ ·OEt ₂	10 mol %	99	67	>95:5	
10	TREAT·HF	10 mol%	0	0	NA	
11	Pyridine·(HF) _x	10 mol%	9	0	NA	
12^f	HFIP	8 equiv	3	0	NA	
13	TrBF ₄	10 mol %	55	55	>95:5	599 ⁴⁰
14	TroBF ₄	10 mol %	1	0	NA	
15	TrPF ₆	10 mol %	5	0	NA	
16	Pd(MeCN) ₄ (BF ₄) ₂	10 mol %	60	45	>95:5	
17	AgBF ₄	10 mol %	5	5	>95:5	
18	AgF	10 mol %	<1	0	NA	



NA = Not applicable; ^a Reactions preformed on 0.1 mmol scale, conversion and yield calculated by ¹⁹F NMR spectroscopy with α,α,α -trifluorotoluene as internal standard; ^b Reaction run at rt instead of 40 °C; ^c Isolated Yield; ^d **3.2a-Cl** formed in 9% yield (>99:1 E/Z) along with trace amounts of **3.1a-Cl** as determined by reference to literature reported data; ^e **3.2a-Br** formed in 8% yield (>99:1 E/Z) as determined by reference to isolated material; ^f Reaction run in PhMe [0.2 M] at 100 °C for 12 h; ^g Note: FIA values from different sources are calculated at different levels of theory in the gas phase.

Given our initial success with using BF₃·OEt₂ we then screened boranes with a range of FIAs to determine if there was a correlation between FIA and catalyst reactivity (Table 3.1, entry 4-8). Both BCl₃ (FIA: 404 kJ mol⁻¹) and BBr₃ (FIA: 428 kJ mol⁻¹) demonstrated good reactivity giving **3.2a** in 90 and 81% yield respectively. The expected fluorinated product was not the only product formed, as both catalysts also yielded approximately catalytic

amounts of halogen exchange products **3.2a-Cl** and **3.2a-Br**, respectively (Table 3.1, entry 5-6). In comparison, triaryl boranes $B(C_6F_5)_3$ (FIA: 448 kJ mol⁻¹) and $B(4-F-C_6H_4)_3$ (FIA: 377 kJ mol⁻¹), were ineffective catalysts (Table 3.1, entry 7-8), even though their Lewis acidities are comparable to BBr_3 and BF_3 , respectively, based on reported FIAs,³⁴⁻³⁶ contradictory to our hypothesis that Lewis acidity should be predictive of catalytic activity. Instead, from this initial screen, it seemed like it was likely that 1. FIA would not be a good predictor for catalyst activity for the carbamoyl fluorides, and 2. that the boron trihalide species were possibly acting as halogen donors to a vinyl carbocation before C–F bond cleavage occurs, giving one catalytic cycle where, in the case of BCl_3 and BBr_3 , only the halogen exchange product can form.

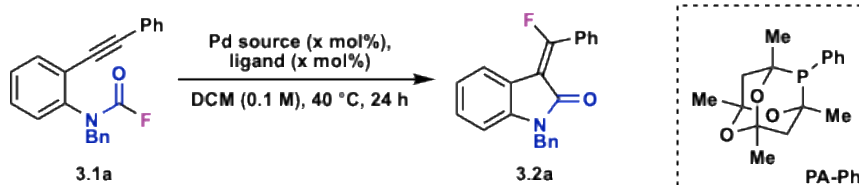
If C–F bond cleavage does occur, a tetrafluoroborate species should be the active fluoride donor. As such, we turned our attention to the applications of BF_4^- sources as potential catalysts. We first evaluated $HBF_4 \cdot OEt_2$ which is frequently concurrently screened as a nucleophilic fluoride source with $BF_3 \cdot OEt_2$,³⁷ and found it to be an effective catalyst for the reaction, giving **3.2a** in 67% yield (Table 3.1, entry 9). Other Brønsted acids containing a potential nucleophilic fluoride source in the form of HF-amine solutions were unable to promote the chemistry (Table 3.1, entries 10-11). Attempts at using HFIP as a Brønsted acid mediator for the reaction, which had previously been reported for the intramolecular chlorocarbamylation of alkynes by Lautens (Figure 3.7),¹⁸ resulted in no appreciable conversion of the starting material (Table 3.1, entry 12).

Given that the boron trihalide species can act as both a Lewis acid and a potential nucleophilic fluoride source we turned our attention to LA/ BF_4^- salts. Trityl tetrafluoroborate ($TrBF_4$) had been previously employed as a stoichiometric fluoride donor and LA activator for fluoride-initiated alkyne cyclization.³⁸ As a catalysts for the carbofluorination of **3.1a**, $TrBF_4$ gave a 55% yield (Table 3.1, entry 13). Switching the counterion to PF_6^- (Table 3.1, entry 14) led to no product formation. PF_6^- is a weaker fluoride donor than BF_4^- given the larger delocalization of the negative charge, thus this result demonstrates the necessity of an effective nucleophilic fluoride source in the reaction. No product was formed with tropylium (Tro) BF_4^- , a weaker LA compared to $TrBF_4$ given the aromatic delocalization of the carbocation (Table 3.1, entry 15), revealing that both the LA identity and the fluoride source are essential for the fluorocarbamylation reaction to proceed. Swapping from a carbon-based LA to a transition

metal-based LA like Pd(MeCN)₄(BF₄)₂ (Table 3.1, entry 16) provided **3.2a** in 45% yield, whereas AgBF₄ only gave 5% of the desired product (Table 3.1, entry 17). Additionally, simple metal fluorides such as AgF resulted in no product formation (Table 3.1, entry 18). It is important to note that across the entire catalyst screen, the *E/Z* selectivity for the product remained consistent at ≥95:5, suggesting a substrate controlled high thermodynamic preference for the *E*-isomer.

Intrigued by the applicability of Pd(MeCN)₄(BF₄)₂ as a catalyst and interested in probing further applicability of Pd-catalysis for fluorocarbamoylation reactions, Ramon Arora conducted a screen using the Pd-catalyst systems previously reported for the analogous chlorocarbamoylation reactions (Table 3.2).^{16,19} As expected, none of the previously reported Pd⁰ or Pd^{II} systems were applicable to the transformation, underscoring the importance of the BF₄ counteranion for catalytic activity.

Table 3.2. Pd-catalyst screen for the synthesis of **3.2a** (Ramon Arora)



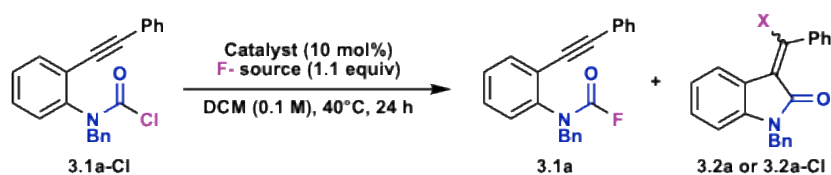
Entry ^a	Pd catalyst	Loading	Ligand	Loading	Conv. (%)	Yield (%)	E/Z ratio
1	Pd(TFA) ₂	5 mol%	NA	NA	0	NA	NA
2	PdCl ₂ (PPh ₃) ₂	5 mol%	NA	NA	0	NA	NA
3	Pd(PPh ₃) ₄	5 mol%	NA	NA	20	0	NA
4	Pd(dba) ₂	5 mol%	PA-Ph	10 mol%	25	0	NA
5	Pd(dba) ₂	5 mol%	PCy ₃	10 mol%	24	0	NA
6 ^b	Pd(dba) ₂	5 mol%	P ^t Bu ₃ ·HBF ₄	10 mol%	14	0	NA
7	Pd(MeCN) ₄ (BF ₄) ₂	10 mol%	NA	NA	60	45	>95:5

NA = Not applicable; ^aReactions performed on 0.1 mmol scale, conversion and yield calculated by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard; ^b1 equiv of K₂CO₃ added.

As part of our reaction optimization, we also probed the necessity of utilizing carbamoyl fluorides at all. Specifically, we were interested in synthesizing **3.2a** via HALEX reaction from alkyne tethered carbamoyl chlorides **3.1a-Cl**, as similar strategies have been exploited in the halocarbamoylation of alkenes.^{41,42} With stoichiometric amounts of BF₃·OEt₂ and HBF₄·OEt₂ acting as both LA and fluoride source (Table 3.3, entries 1-2), the fluoromethylene oxindole product **3.2a** was not formed. Instead, these reaction conditions only led to low yields of

3-chloromethylene oxindole **3.2a-Cl** with moderate *E*-selectivity. Use of tetrabutylammonium fluoride (TBAF, Table 3.3, entry 3) as a soluble fluoride source led to formation of carbamoyl fluoride **3.1a** as sole product. Although **3.2a** was formed in low yields with AgF and AgBF₄ (Table 3.3, entries 4-5), the product mixture contained significant amounts of **3.2a-Cl**, which cannot be separated from the desired fluoromethylene oxindole **3.2a** by silica gel chromatography. In contrast, use of NaF (Table 3.3, entry 6) led only to the formation of **3.2a-Cl**. The application of exogenous fluoride sources in combination with catalytic amounts of BF₃·OEt₂ as a LA (Table 3.3, entries 6-12) also led to a mixture of the chloro- and fluoro-methylene oxindole products, except in the case of CsF, which led to no reaction.

Table 3.3. Halogen exchange reaction development for synthesis of **3.2a**

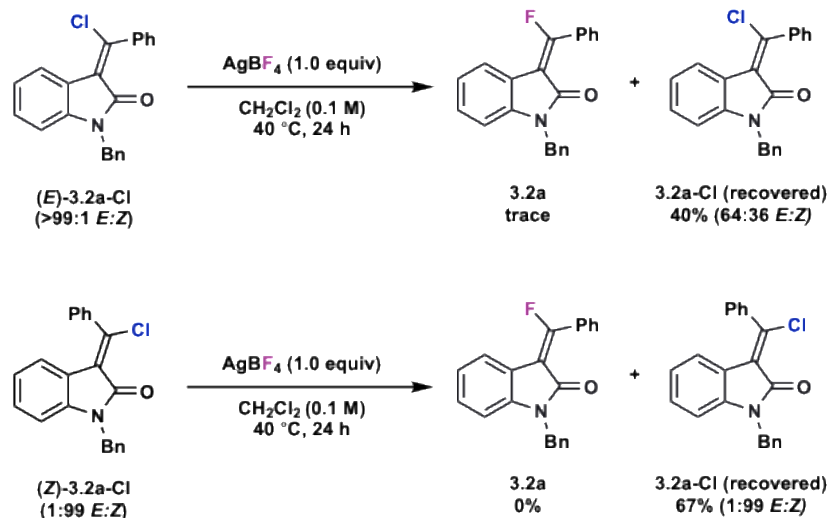


Entry ^a	Catalyst	F-Source	Conv. (%) ^b	1a (%) ^b	2a-Cl (%) (<i>E</i> : <i>Z</i> ratio) ^c	2a (%) (<i>E</i> : <i>Z</i> ratio) ^b	Total Yield (%)
1	NA	HBF ₄ ·OEt ₂	9	0	9 (70:30)	0	9
2	NA	BF ₃ ·OEt ₂	20	0	10 (77:23)	0	10
3	NA	TBAF	91	79	0	0	79
4	NA	AgF	98	19	19 (66:34)	37 (>95:5)	75
5	NA	AgBF ₄	99	0	30 (57:43)	40 (>95:5)	70
6	NA	NaF	27	0	12 (68:32)	0	12
7	BF ₃ ·OEt ₂	TBAF	100	82	18 (>95:5)	0	100
8	BF ₃ ·OEt ₂	AgF	99	7	29 (62:38)	53 (>95:5)	89
9	BF ₃ ·OEt ₂	AgBF ₄	100	0	26 (64:36)	31 (>95:5)	57
10	BF ₃ ·OEt ₂	NaF	24	0	18 (47:53)	53 (>95:5)	72
11	BF ₃ ·OEt ₂	CsF	<1	0	0	0	0
12	BF ₃ ·OEt ₂	NaBF ₄	30	0	15 (>95:5)	0	15

a. Reactions performed on 0.1 mmol scale; b. Calculated using ¹⁹F NMR with α,α,α -trifluorotoluene as internal standard; c. Calculated using ¹H NMR with 1,3,5-trimethoxybenzene as internal standard.

We were curious if the formation of **3.2a** with Ag-salts could occur via a HALEX reaction of **3.2a-Cl**. We subjected isolated *E*- and *Z*-**3.2a-Cl** to stoichiometric AgBF₄ under the standard reaction conditions (Scheme 3.2). In both cases, though a substantial amount of **3.2a-Cl** was consumed, no fluorinated product was formed. While *Z*-**3.2a-Cl** was recovered with same initial isomeric ratio, *E*-**3.2a-Cl** isomerized to a 64:36 *E/Z* ratio, similar to the

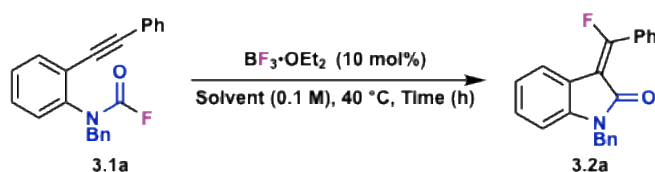
isomeric ratio observed in the original HALEX reactions. Ultimately, these studies revealed that a one-pot mixed HALEX/fluorocarbamoylation reaction using carbamoyl chlorides as the starting material is not an efficient route to 3-fluoromethylene oxindoles, highlighting how carbamoyl fluorides are uniquely suited for this transformation.



Scheme 3.1. Attempts at HALEX reaction of **3.2a-Cl** with AgBF₄.

Finally, having determined that BF₃·OEt₂ was the ideal catalyst with carbamoyl fluoride **3.1a**, we ran an additional screening with different solvents and reaction times (Table 3.4). Poor yields were observed with most other solvents, but the reaction could be run in chloroform with minimal loss of yield (Table 3.4, entry 4). Using DCM as the optimal solvent, 24 h was necessary to achieve full conversion (Table 3.4, entries 7-9).

Table 3.4. Solvent and time screen for the synthesis of **3.2a**.



Entry ^a	Solvent	Time (h)	Conversion (%)	Yield (%)	E/Z ratio
1	DCM	24	100	>99 (99) ^c	>95:5
2	PhMe	24	48	41	94:6
3	DCE	24	44	30	>95:5
4	CHCl ₃	24	97	93	>95:5
5	MeCN	24	39	0	NA
6	1,4-Dioxane	24	43	0	NA
7	DCM	16	94	93	>95:5
8	DCM	6	70	70	>95:5
9	DCM	1	30	28	>95:5

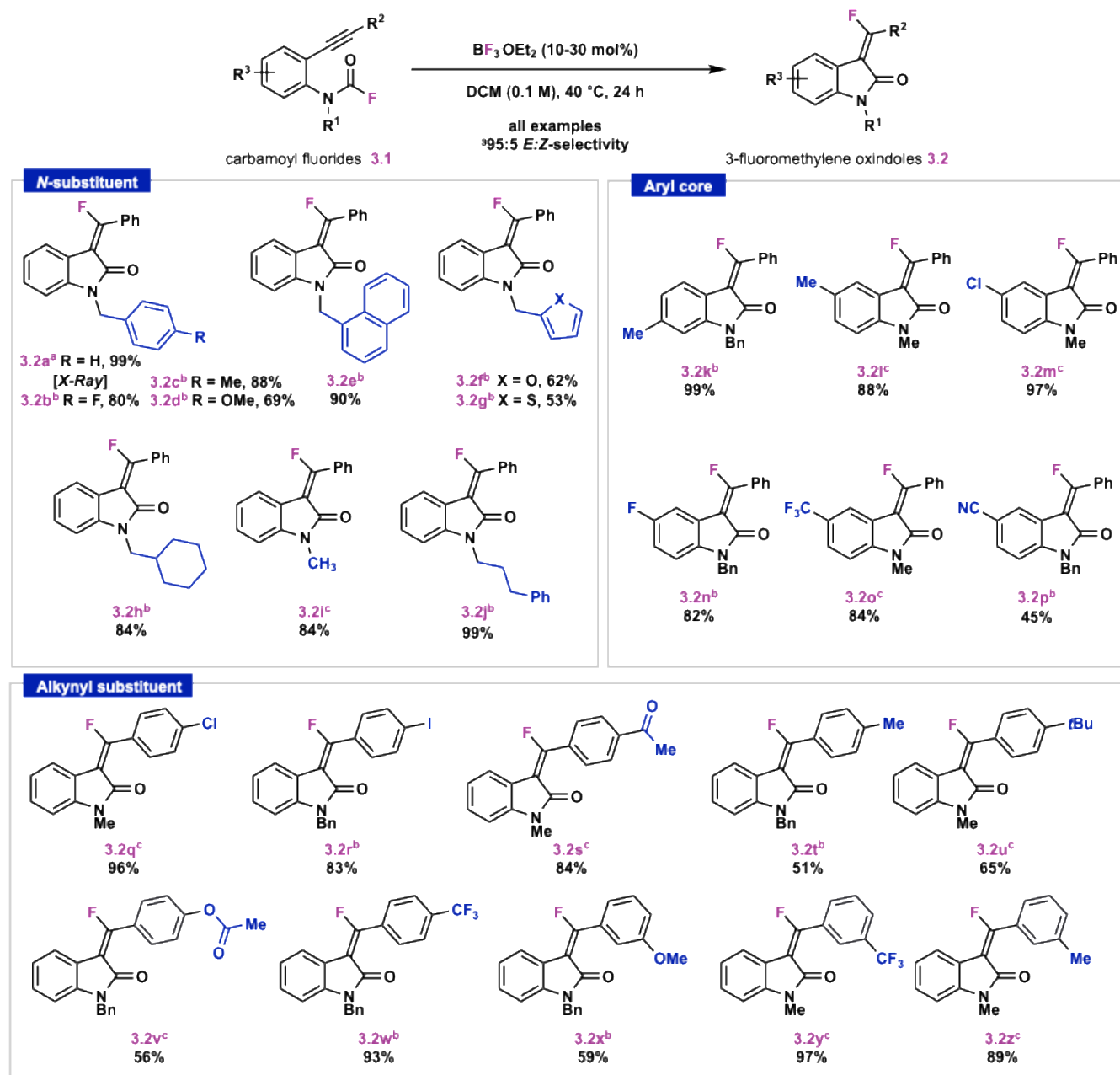
a. Reactions performed on a 0.1 mmol scale, conversion and yield calculated by ¹⁹F NMR with *α,α,α*-trifluorotoluene as internal standard.

3.4.2 Substrate Scope

While complete conversion was observed for the standard substrate **3.2a** with 10 mol% BF₃·OEt₂, we found that increasing the catalyst loading to 20 or 30 mol% allowed most substrates explored in our scope studies to reach full conversion within 24 hours. Any substrates that initially showed lower conversion at 20 mol% were re-run at 30 mol% and the higher yielding conditions are reported in Scheme 3.2. Given the low cost of BF₃·OEt₂, the increased catalyst loading was determined to be acceptable. In all cases, the desired 3-fluoromethylene oxindole products **3.2** were formed with ≥94:6 *E*:*Z*-selectivity (Scheme 3.2) as determined by ¹⁹F-NMR spectroscopy on the crude reaction material. Several of the substrates were prepared by Yuriko Fujisato and are highlighted as such in Scheme 3.3 and Scheme 3.6.

Remote modifications to the *N*-protecting group were well tolerated (**3.2b-j**), although reduced yields were observed for substrates bearing an additional Lewis basic site (**3.2d**, **3.2f**, **3.2g**). The reaction was relatively insensitive to substitution on the core aromatic ring (**3.2k-3.2o**) except for **3.2p**, which bears a coordinating nitrile functionality. The yield of **3.2p** could be improved to 68% by increasing the loading of BF₃·OEt₂ to 1 equiv. Various functionality on the distal aryl ring were tolerated, including halogen atoms (**3.2q**, **3.2r**), moderately donating alkyl groups (**3.2t**, **3.2u**), an acetate derivative (**3.2v**), as well as electron-withdrawing acetyl (**3.2s**) and CF₃ groups

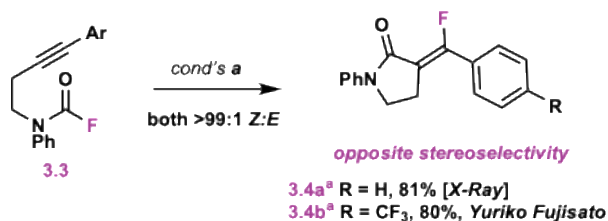
(**3.2w**). Carbamoyl fluorides bearing both mild electron-withdrawing and donating *m*-substituents also underwent the reaction smoothly to give **3.2x**, **3.2y** and **3.2z**. In general, an additional Lewis basic site on the substrate led to lower yields, which we hypothesize is due to competitive coordination of the catalyst to these sites, thus reducing catalytic turnover.



Scheme 3.2. Substrate scope for 3-fluoromethylene oxindoles; ^a10 mol% BF₃·OEt₂; ^b20 mol% BF₃·OEt₂; ^c30 mol% BF₃·OEt₂.

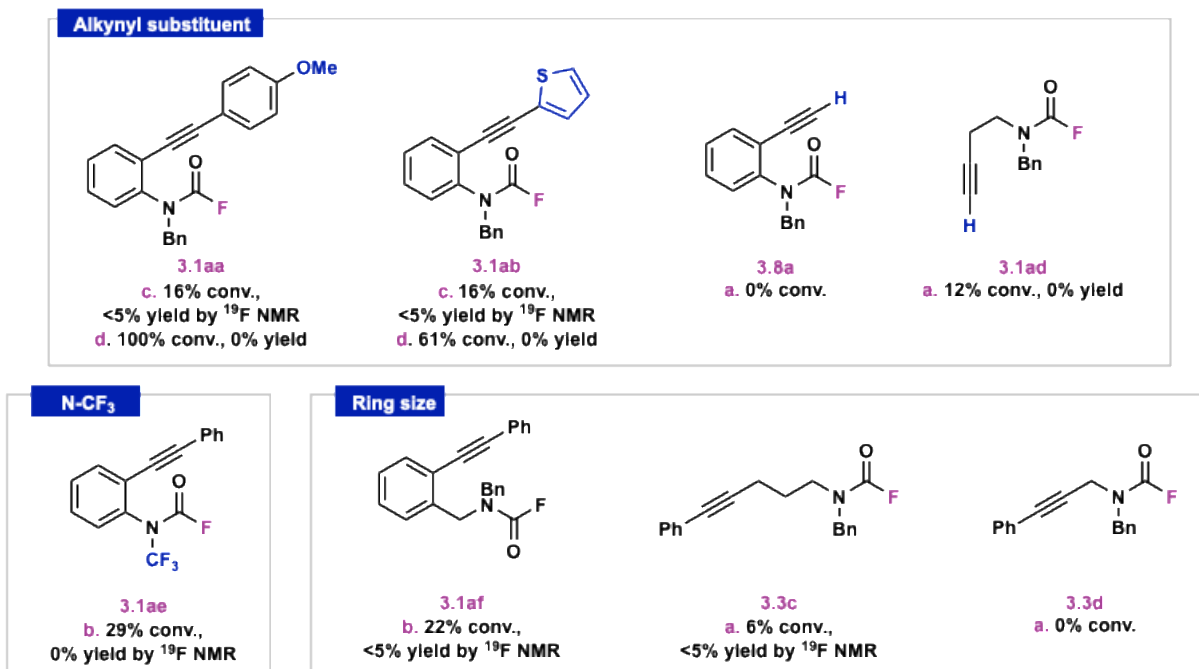
Our method was also applicable towards the synthesis of fluoromethylene γ -lactams **3.4a** and **3.4b**. Interestingly, the reaction furnished the lactam with complete reversal of stereoselectivity, giving the *Z*-3-

fluoromethylene product exclusively, as confirmed by X-ray crystallography for **3.4a**. A similar reversal in selectivity was also observed between oxindole and lactam products in the chlorocarbamoylation of alkyne tethered carbamoyl chlorides under HFIP mediation.¹⁸ Possible explanations for the reversal in stereoselectivity will be discussed in Chapter 3.5.3.



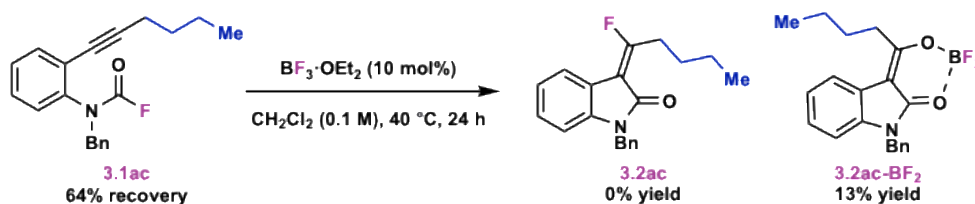
Scheme 3.3 Synthesis of 3-fluoromethylene γ -lactams; ^a 10 mol% BF₃·OEt₂; ^b 20 mol% BF₃·OEt₂

Notably, while the reaction was relatively insensitive to changes of the electronics of the *N*-substituent and on the aryl backbone at the position para to the carbamoyl fluoride, the reaction did not proceed with strong electron-donating moieties on the distal aryl ring like 4-OMe or 2-thiophene (**3.1aa-3.1ab**, Scheme 3.4). Increasing the loading of BF₃·OEt₂ to 1 equiv. increased the conversion of the starting material but ultimately did not lead to any product formation. Similarly, the reaction was not compatible with terminal alkynes (**3.8a**, **3.1ad**), other ring sizes (**3.1af**, **3.3c**, **3.3d**) and *N*-CF₃ carbamoyl fluorides (**3.1ae**).



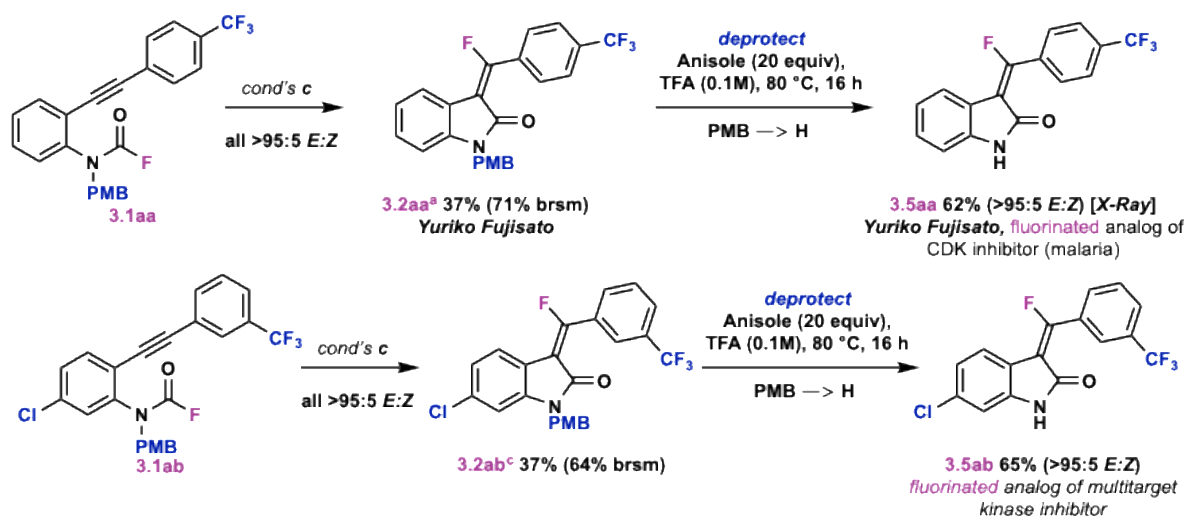
Scheme 3.4. Substrate limitations; ^a Reaction carried out with 10 mol% BF₃·OEt₂; ^b Reaction carried out with 20 mol% BF₃·OEt₂; ^c Reaction carried out with 30 mol% BF₃·OEt₂; ^d Reaction carried out with 1 equiv. BF₃·OEt₂.

Interested in if this reactivity was exclusive to aryl alkynes, we subjected aliphatic alkynyl-substrate **3.1ac** to the optimized conditions (Scheme 3.5). Surprisingly, this reaction resulted in the formation of an unexpected difluoroboron β -diketonate **3.2ac-BF₂** instead of the expected **3.2ac**, initially identified by the unique B–F resonance in the ¹⁹F NMR at –141.18 ppm, which appears as two peaks in a 1:4 ratio corresponding to the natural abundances of ¹⁰B and ¹¹B. The formation of this product was confirmed by isolation. In general, difluoroboron β -diketonates, typically used luminescent probes, are usually accessed via the addition of BF₃·OEt₂ to a 1,3-dione. Given that the yield of **3.2ac-BF₂** matches well with the catalyst loading of BF₃·OEt₂, it is possible that adventitious water can act as a nucleophile to create a 1,3-dione that can be activated by BF₃·OEt₂, or alternatively, form BF₂OH by a reaction with BF₃·OEt₂, which could react with the vinyl carbocation formed after C–C bond formation.



Scheme 3.3.5. Alkyl alkynyl-substrate under standard reaction conditions yields BF₂-adduct.

Finally, the reaction was suitable for the synthesis the 3-fluoro-derivatives (**3.5aa-3.5ab**) of known protein kinase inhibitors which contain a free NH on the oxindole.^{43,44} The free NH is important as it enables participation in hydrogen bonding as a hydrogen bond donor, a key regulating interaction for drug binding. In order to gain access to the free NH oxindoles the starting carbamoyl fluorides were synthesized with PMB protecting groups that could be deprotected using literature-reported conditions (TFA, anisole).⁴⁵



Scheme 3.6. Synthesis of fluorinated isosteres of bioactive compounds; ^a 10 mol% BF₃·OEt₂; ^b 20 mol% BF₃·OEt₂; ^c 30 mol% BF₃·OEt₂.

3.5 Mechanistic Studies

We next turned our attention to the mechanism behind the BF₃-catalyzed fluorocarbamoylation of **3.1a**. Two proposed mechanisms are detailed in Figure 3.14. In **mechanism I**, the reaction is initiated by a fluorophilic BF₃ activating the C–F bond directly, creating cationic isocyanate **I-A** and a nucleophilic fluoride source in the form of the BF₄ anion. Formation of the C–C bond between the alkyne and the electrophilic isocyanate forms vinylic cation **I-B**, which can then undergo fluoride capture to yield product **3.2a**. While drawn stepwise, the reaction can also proceed via a concerted mechanism where C–F and C–C bond formation happens concurrently. Alternatively, the reaction could instead be initiated by an oxophilic BF₃ coordinating to the carbonyl, increasing electrophilicity of the central carbon, concurrent with fluoride addition to the alkyne, prompting cyclization onto the Lewis acid-activated carbamoyl moiety to form intermediate **IIA**. The identity of this initial fluoride source is unknown, but we suspect that it is a Lewis acid-base adduct of BF₃ and **3.1a**. Collapse of the tetrahedral intermediate **II-B** releases a fluoride ion, while regenerating the catalyst. Note that the fluoride ion may bind to BF₃ to form BF₄[−], a nucleophilic fluoride source, which can initiate the second catalytic cycle.

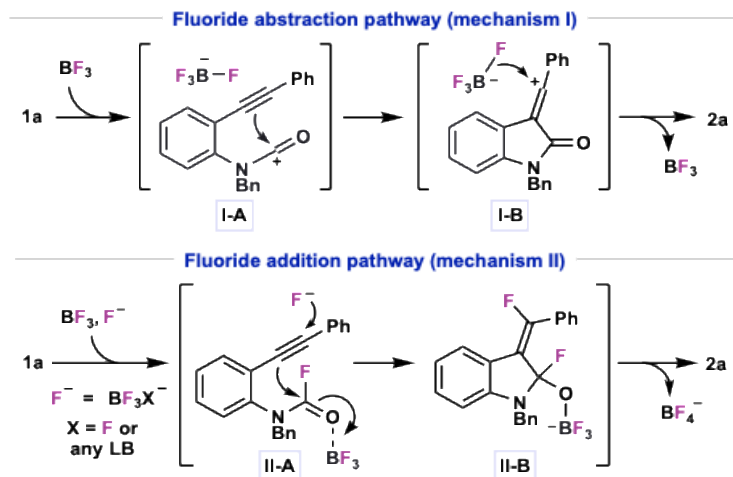


Figure 3.14. Proposed mechanisms for carbofluorination reaction.

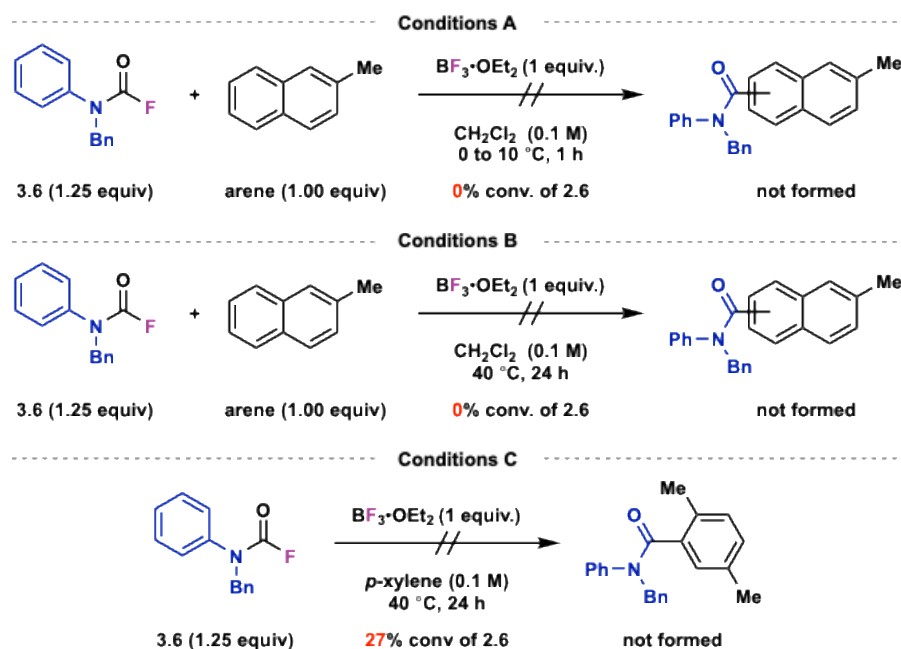
If **mechanism I** were operative, the LA would need to abstract a fluoride ion from the C–F bond of the carbamoyl fluoride. As such, the relative Lewis acidity of the boron catalyst should be predictive of catalytic activity. $\text{B(4-F-C}_6\text{H}_4)_3$ ³⁵ and BF_3 ³⁴ have gas phase FIAs of 366 kJ mol^{-1} and 346 kJ mol^{-1} respectively. Therefore, if the reaction were proceeding via **mechanism I**, both catalysts should have similar fluoride shuttling ability. Yet these catalysts show divergent reactivity: where $\text{BF}_3 \cdot \text{OEt}_2$ is an efficient catalyst, $\text{B(4-F-C}_6\text{H}_4)_3$ is not.

Overall, only catalysts that have the potential to generate a nucleophilic fluoride species work well in the reaction (i.e., $\text{BF}_3 \cdot \text{OEt}_2$,³⁷ $\text{HBF}_4 \cdot \text{OEt}_2$,³⁷ TrBF_4 ,³⁸ and $\text{Pd(MeCN)}_2(\text{BF}_4)_2$), allowing for the fluoride addition step in **mechanism II**. This difference is highlighted when comparing TrBF_4 to TrPF_6 , which have the same carbocation, only differing in their ability to serve as an effective nucleophilic fluoride source. Moreover, Lewis acids without an available nucleophilic fluoride source at the onset of the reaction like $\text{B(C}_6\text{F}_5)_3$ and $\text{B(4-F-C}_6\text{H}_4)_3$ were found to be inefficient catalysts for the reaction. Given that the reaction is exclusively promoted by halide-containing boron-based catalysts and catalytic exogenous halide incorporation is observed with BCl_3 and BBr_3 ,^{46,47} it is likely that $\text{BF}_3 \cdot \text{OEt}_2$ can act as both a fluoride source and a LA activator in the fluorocarbamoylation reaction. While BF_3 on its own cannot act as a nucleophilic fluoride source, Lewis adducts of aldehydes,⁴⁸ epoxides,⁴⁹ imines,⁵⁰ and hypervalent iodine reagents^{50,51} with BF_3 are sufficiently activated to liberate a nucleophilic fluoride. Based on this literature precedent, we reasoned that oxophilic BF_3 coordination to **3.1a** could both activate the carbonyl to be more electrophilic as well as generate a nucleophilic fluoride, facilitating our desired reaction.

Given the literature precedent on the use of $\text{BF}_3 \cdot \text{OEt}_2$ as a fluoride shuttling catalyst, we could not dismiss **mechanism I** entirely.^{33,52} All of the literature precedents proceed via a direct fluoride abstraction by BF_3 from a $\text{C}(sp^3)\text{--F}$ bond. In contrast there is no precedence for Lewis acid-promoted fluoride abstraction from the less reactive $\text{C}(sp^2)\text{--F}$ bond in carbamoyl fluorides. Nevertheless, we wanted to probe the possibility of forming an isocyanate cation.

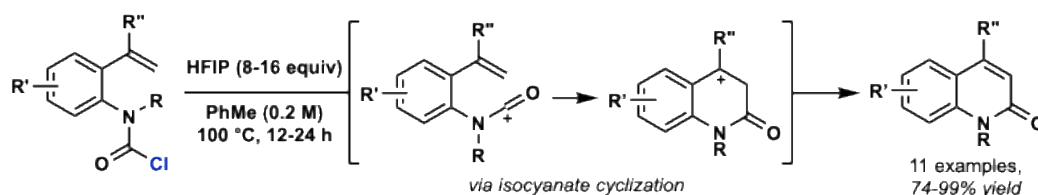
3.5.1 Friedel-Crafts Reactions

To probe the possibility of fluoride abstraction from a carbamoyl fluoride under our conditions, we subjected **3.6** to stoichiometric $\text{BF}_3 \cdot \text{OEt}_2$ in the presence of 2-methylnaphthalene using both the low temperature conditions reported by Hyatt (Scheme 3.7, conditions A), at the slightly elevated temperatures used in our reported reaction (Scheme 3.7, conditions B), and using an alternative arene (*p*-xylene) in excess (Scheme 3.7, conditions C). In all cases, **3.6** was unreactive and no Friedel-Crafts-type carbamoylation products were formed, suggesting that fluoride abstraction to form an isocyanate cation is not favored with BF_3 . These results are in line with Olah's studies demonstrating that carbamoyl fluorides do not form isocyanate cations in the presence of strong Lewis or Brønsted acids, unlike acyl fluorides which readily undergo fluoride abstraction to form acylium ions.⁴⁷ In fact, all reported Friedel-Crafts carbamoylation reactions required the use of highly electrophilic carbamoyl triflates.^{55–57}



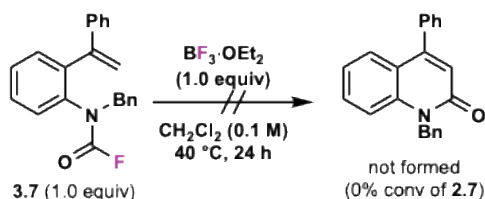
Scheme 3.7. Intermolecular Friedel-Crafts reactions with carbamoyl fluoride.

Interested in probing an analogous intramolecular reaction (i.e., a vinylogous Friedel-Crafts acylation), we turned to alkene-tethered systems. In 2020, Lautens and co-workers reported that alkene-tethered carbamoyl chlorides can undergo cyclization in the presence of HFIP as an activator. The mechanism is proposed to proceed via an intermediate isocyanate cation that undergoes C–C bond formation with an alkene to yield 2-quinolinone products (Scheme 3.8).¹⁸ This reactivity has not been reported for carbamoyl fluorides.



Scheme 3.8. HFIP-promoted intramolecular vinylogous Friedel-Crafts reactions of carbamoyl chlorides.¹⁸

Attempt at using our reaction conditions on alkene-tethered carbamoyl fluoride **3.7** failed as we were unable to produce the vinylogous 2-quinolinone product. In fact, no conversion of the starting material was observed reinforcing the idea that $\text{BF}_3 \cdot \text{OEt}_2$ is not a strong enough Lewis acid to promote C–F bond cleavage in carbamoyl fluorides.

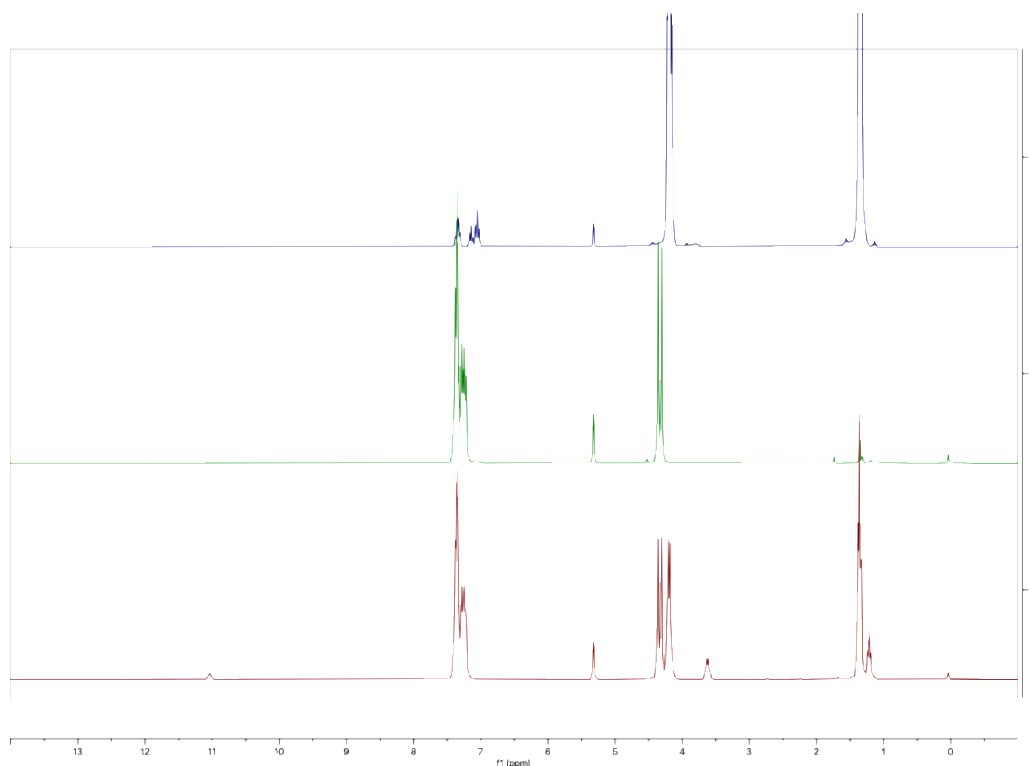


Scheme 3.9. Intramolecular vinylogous Friedel-Crafts reaction with carbamoyl fluoride.

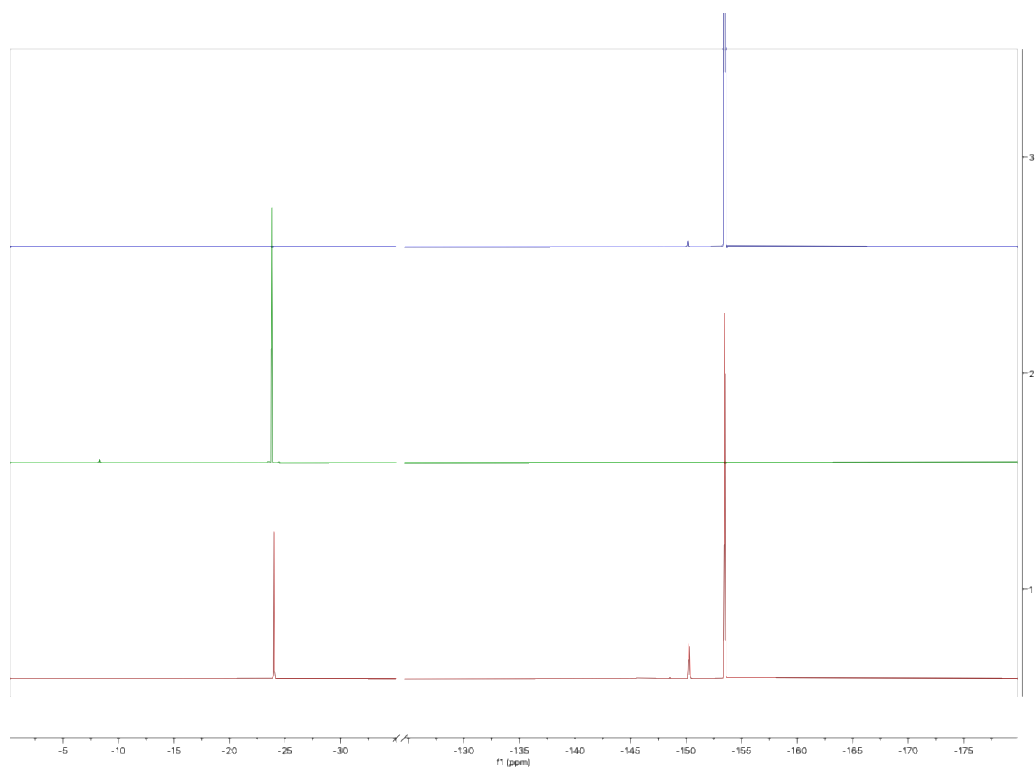
3.5.2 NMR Studies

To see if we could observe a Lewis-adduct forming in our system with low temperature NMR monitoring, we chose *N*-benzyl-*N*-phenyl carbamoyl fluoride **3.6** as a test substrate, which does not contain an alkyne. A 1:1 mixture of $\text{BF}_3 \cdot \text{OEt}_2$:**3.6** was prepared in CD_2Cl_2 then monitored by ^1H (Scheme 3.10), ^{19}F (Scheme 3.11), and ^{11}B (Scheme 3.12) NMR spectroscopy at 233K and compared visually with NMR spectra of $\text{BF}_3 \cdot \text{OEt}_2$ (doped with fluorobenzene as standard) and **3.6** taken separately. In the ^1H NMR spectrum, the 1:1 mixture of $\text{BF}_3 \cdot \text{OEt}_2$:**3.6** revealed an emergence of free OEt_2 , suggesting that there is dissociation of the BF_3 from the OEt_2 . The ^{19}F NMR

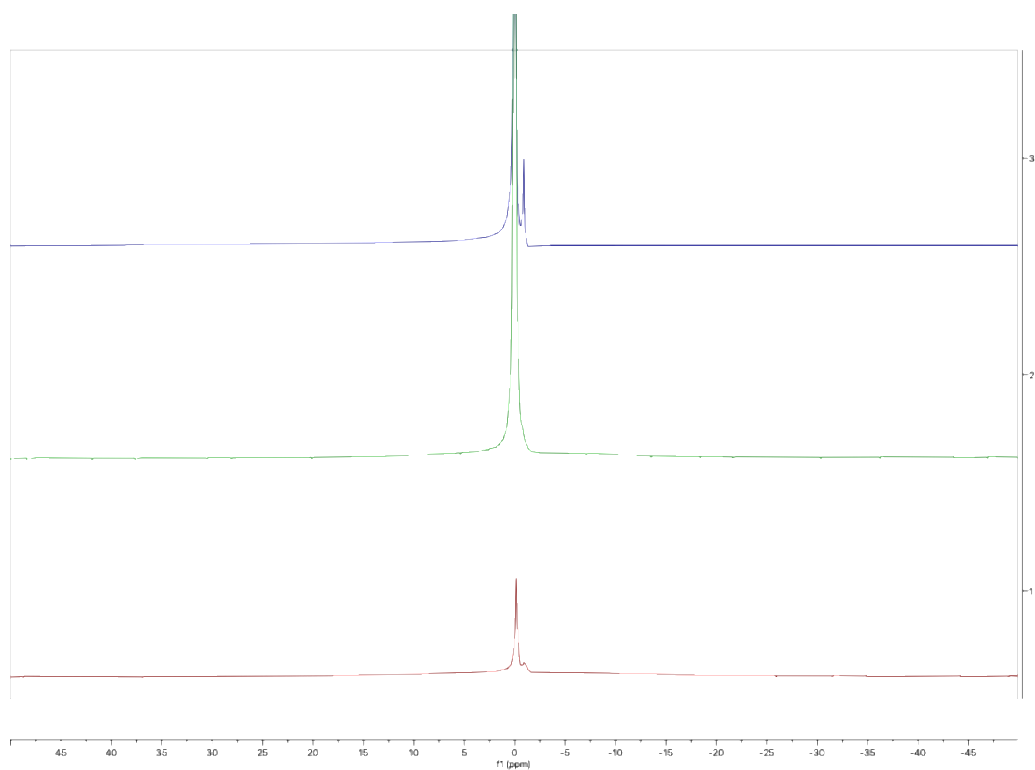
spectrum showed the emergence of a corresponding B–F species at -150.18 ppm as a multiplet, which is deshielded in comparison to the parent $\text{BF}_3\cdot\text{OEt}_2$ peak at -153.44 ppm. The peak itself is not free BF_3 which appears at roughly -131 ppm and corresponds more closely to other tetracoordinate fluoroborates (typically -140 to -160 ppm). Analysis of the ^{11}B signal also supports the formation of a new tetracoordinate fluoroborate species with a new peak emerging at -0.86 ppm.



Scheme 3.10. ^1H NMR (300 MHz, CD_2Cl_2): overlay of $\text{BF}_3\cdot\text{OEt}_2$, doped with fluorobenzene (3), **3.6** (2), and $\text{BF}_3\cdot\text{OEt}_2$:**3.6** 1:1 ratio (1) taken at 233K.



Scheme 3.11. ^{19}F NMR (282 MHz, CD_2Cl_2): overlay of $\text{BF}_3 \cdot \text{OEt}_2$ (3), **3.6** (2), and $\text{BF}_3 \cdot \text{OEt}_2$:**3.6** 1:1 ratio (1) taken at 233K.



Scheme 3.12. ^{11}B NMR (96 MHz, CD_2Cl_2): overlay of $\text{BF}_3 \cdot \text{OEt}_2$: $\text{HBF}_4 \cdot \text{OEt}_2$ 4:1 ratio (3), $\text{BF}_3 \cdot \text{OEt}_2$ (2), and $\text{BF}_3 \cdot \text{OEt}_2$:**3.6** 1:1 ratio (1) taken at 233K.

Despite the observation of this potential fluoroborate species by *in situ* NMR, this new species can only be observed at 233K and any attempts at isolating it or analysis via GC-MS at room temperature resulted in only **3.6** and $\text{BF}_3 \cdot \text{OEt}_2$ being observed. It is likely that the new fluoroborate species being observed is the Lewis adduct formed between BF_3 and the carbonyl, but more conclusive investigations into its formation (^{13}C -NMR, IR) were not perused due to instrument limitations, thus the identity of this species could not be confirmed.

3.5.3 DFT Calculations

Due to the inconclusive data obtained from the low temperature NMR studies, we turned to DFT calculations to probe the possibility of Lewis-adduct formation driving reactivity. All computations were done by our collaborators, Dr. Ekadashi Pradhan and Dr. Tao Zeng, as depicted in Figure 3.15, Figure 3.16, and Figure 3.17. All the stationary points, including intermediates and transition states were optimized using the CAM-B3LYP⁵⁸ functional and the DEF2-SVP (a new hybrid) basis set. The CPCM⁵⁹ model to simulate the solution environment of the DCM solvent to incorporate better experimental conditions in our calculations.

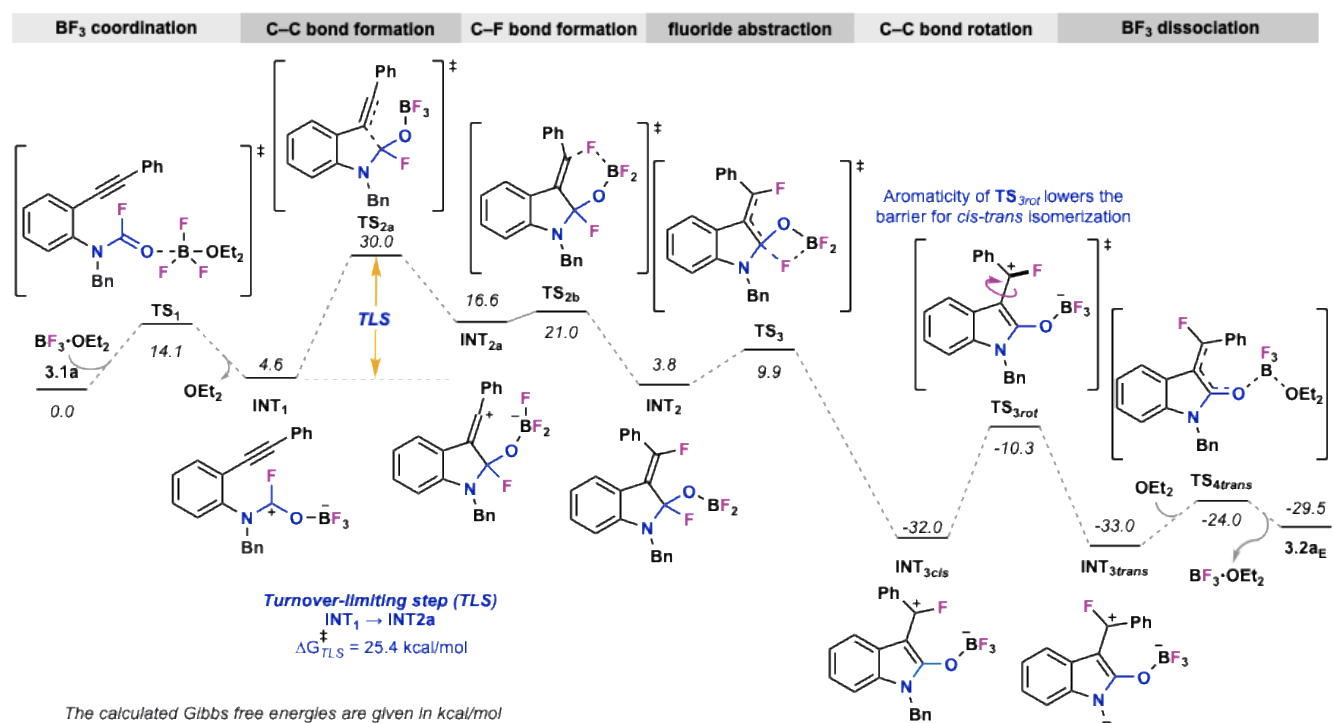


Figure 3.15. Calculated energy profile for the proposed internal fluoride transfer mechanism, calculations performed by Ekadashi Pradhan.

DFT computations showed that the reaction is initiated by migration of BF_3 from OEt_2 to the carbamoyl oxygen of **3.1a**, which comes at a mild energetic cost of 14.1 kcal/mol, generating a zwitterionic intermediate that is more electrophilic at the carbonyl, whilst also creating a nucleophilic fluoride source in the oxygen-bound BF_3 . From **INT**₁, C–C bond formation via cyclization forms the key 5-membered ring. This step was determined to be turnover-limiting with a surmountable barrier of 25.4 kcal/mol, wherein the developing positive charge (δ^+) is stabilized by the conjugated aromatic ring, offering an explanation for why alkyl substituted alkynes are not suitable substrates. The resulting alkenyl cation (**INT**_{2a}) undergoes a facile internal fluoride transfer to forge the key C–F bond. Fluoride migration from the carbamoyl C to B in **INT**_{2b} forms **INT**_{3cis} which can undergo C=C bond rotation to give **INT**_{3trans}. Dissociation of BF_3 can occur from **INT**_{3cis} or **INT**_{3trans} to provide *Z*-**3.2a** or *E*-**2a**, respectively, but these pathways are reversible and therefore the thermodynamically favored *E*-isomer is formed as the major product (Figure 3.16). Overall, the reaction to form *E*-**3.2a** is 29.5 kcal/mol exergonic. The key difference here to our originally proposed mechanism is that fluoride transfer occurs intramolecularly, forming the *Z*-isomer initially before isomerization occurs. A similar formal C=C bond rotation is implicated in the formation of the *E*-3-chloromethylene oxindoles under Pd-catalysis, where the *Z*-isomer is formed initially then isomerized via coordination of the catalyst to the substrate, which lowers the isomerization barrier.

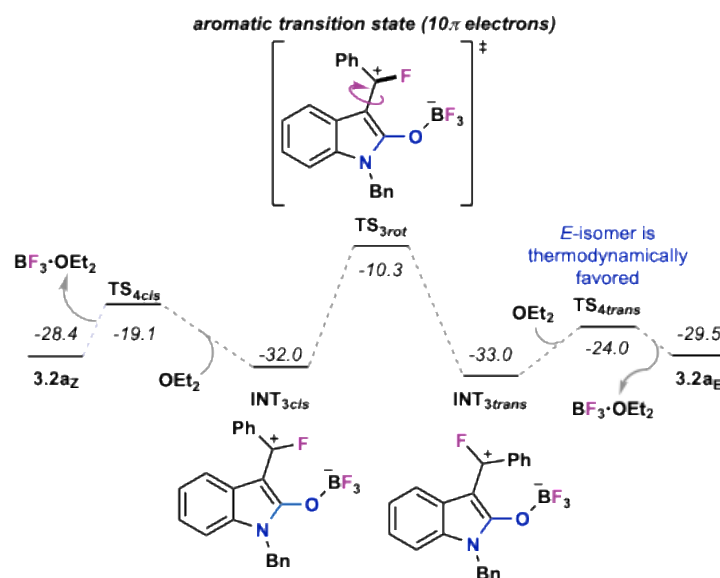


Figure 3.16. Calculated energy profile for methylene oxindole isomerization barrier.

The reversal of stereochemistry can also be probed by DFT calculations. For methylene oxindoles, **TS**_{3rot} possesses significant aromatic character given that it has 10 electrons in the bicyclic framework, which satisfies Hückel's rule for aromaticity. Additional computations via Nucleus Independent Chemical Shift (NICS),^{60,61} which is a computation method for the measurement of magnetic aromaticity, showed a 3x increase in the aromatic character of **TS**_{3rot} in comparison to **INT**_{3cis} and **INT**_{3trans}. This aromatic character decreases the barrier for C=C bond isomerization ($\Delta G^\ddagger_{\text{isom}} = 21.7$ kcal/mol). In contrast, the TS for the isomerization of methylene γ -lactam **3.4a** does not benefit from this aromatic stabilization and the barrier for C=C bond rotation was determined to be significantly higher ($\Delta G^\ddagger_{\text{isom}} = 37.7$ kcal/mol) disfavoring the formation of the *E*-isomer (Figure 3.17). Hence, while both the methylene oxindole and γ -lactam products initially form the *Z*-isomer, only the methylene oxindole results in the *E*-isomer as the major product.

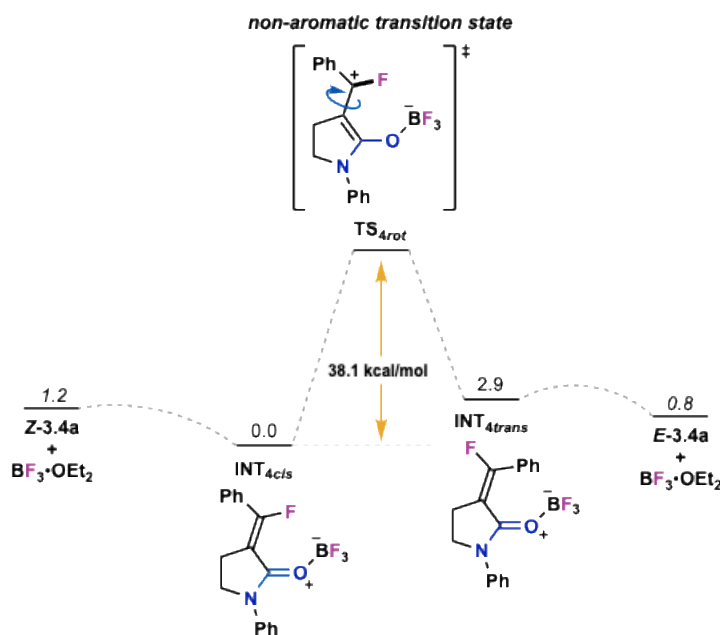


Figure 3.17. Calculated energy profile for γ -lactam isomerization barrier, transition states not calculated for the dissociation of BF_3 from **INT**_{4cis} or **INT**_{4trans}.

3.5.4 Reaction Kinetics via Variable Time Normalization Analysis (VTNA)

The reaction mechanism derived from DFT calculations was further supported by experimental studies, which first included an analysis of the reaction kinetics. Reaction kinetics are typically derived from one of two methodologies: looking at initial rates or rates over the course of an entire reaction profile. Initial rates give insight into the kinetic regime of a reaction before appreciable amounts of product have built-up, and, in the case of catalytic reactions,

before significant catalyst turn-over has occurred. In contrast, kinetic analysis over an entire reaction profile enables the detection of catalyst activation/deactivation pathways, product inhibition and changes of order throughout the reaction, which initial rate kinetics are unable to elucidate. Additionally, unlike initial-rate kinetics, which are laborious to perform and require multiple experiments across a range of concentrations and replicates, analysis of entire reaction profiles minimizes the impact of measurement errors at any single time point and, as a result, requires fewer experiments than traditional initial-rate methods to gain meaningful data. Coupled with the data that we could gain by analyzing the entire reaction profile over initial rates we opted for a kinetic analysis of the entire reaction profile.

There are two common methods for the kinetic analysis of entire reaction profiles: reaction progress kinetic analysis (**RPKA**) which was developed by Blackmond lab⁶² and variable time normalization analysis (**VTNA**) method which was developed by the Burés lab.^{63–65} Both methods use entire reaction profiles to give information about product inhibition or catalyst deactivation, the order in catalyst and the order in any other component of the reaction. While **RPKA** uses reaction rate-against-concentration profiles, **VTNA** uses visual comparison of concentration-against-time profiles. The latter are directly obtained from in situ reaction monitoring, for example, using NMR spectroscopy. The reaction profiles are normalized by time, and then visually inspected for overlay or lack of overlay to gain mechanistic insight.

For each **VTNA** experiment, a 0.20 M stock solution of **3.1a** (0.40 mmol, 131.6 mg) in dry CH_2Cl_2 (2.0 mL) was prepared as well as a stock solution of $\text{BF}_3 \cdot \text{OEt}_2$ in dry CH_2Cl_2 . The details for each run are documented in Table 3.5. Integral measurements were obtained via ^{19}F NMR analysis using α,α,α -trifluorotoluene as internal standard. All scans were taken with $\text{ns} = 1$, $\text{ds} = 0$, and relaxation delay (d1) = 60 s. ^{19}F NMR spectra were analyzed using the fluorine signals from carbamoyl fluoride **3.1a** (δ -14.19 ppm, s, 0.8F and -19.33 ppm, s, 0.2F) relative to the CF_3 signal from α,α,α -trifluorotoluene (δ -63.72 ppm, s, 3F). Similarly, the initial concentration of $\text{BF}_3 \cdot \text{OEt}_2$ (δ -153.13 ppm, s, 3F) was verified by ^{19}F NMR relative to the CF_3 signal from α,α,α -trifluorotoluene. [**3.1a**] was calculated relative to α,α,α -trifluorotoluene and data for all runs can be found in Chapter 3.8.2.1.

Table 3.5. Experimental information for VTNA runs.

Exp #	[3.1a] (M)	[cat] (M)	[3.1a] stock solution (M)	Volume of 3.1a stock solution (μ L)	CH ₂ Cl ₂ (μ L)	[BF ₃ ·OEt ₂] stock solution (M)	Volume of BF ₃ ·OEt ₂ stock solution (μ L)
1	0.10	0.020	0.20	350	330	0.70	20
2	0.055	0.020	0.20	192	488	0.70	20
3^a	0.05	0.030	0.20	175	330	0.70	20
4	0.10	0.034	0.20	350	330	1.05	20
5	0.10	0.013	0.20	350	330	0.35	20

^a. An additional 175 μ L of 0.05 M stock solution of **3.2a** in CH₂Cl₂ was added to the NMR tube.

We started our analysis by identifying if product inhibition or any other catalyst deactivation pathway was occurring in our system via a “same excess” experiment, which involves the visual comparison of the profiles of two reactions where the initial concentration of **3.1a** is varied (Table 3.5, 0.10 M/**Exp. 1** and 0.055 M/**Exp. 2**) with the same initial loading of BF₃·OEt₂ (0.02 M). If there is no catalysts deactivation occurring, upon time adjustment of the two reaction profiles such that ranges of similar concentration during the reaction profile can be directly compared, the effect of product concentrations and number of catalytic turnovers to be assessed. Given that these profiles were plots of concentration over time; in order to facilitate the direct comparison of the reaction profiles, the profile of **Exp. 2** was shifted to the right on the time scale until the first point of the profile overlays with the **Exp. 1** profile (Figure 3.18). Visual analysis of this concentration normalized profile revealed that the reaction profiles for **Exp. 1** and **2** did not overlay, indicating that there was either product inhibition or another catalyst deactivation pathway occurring.

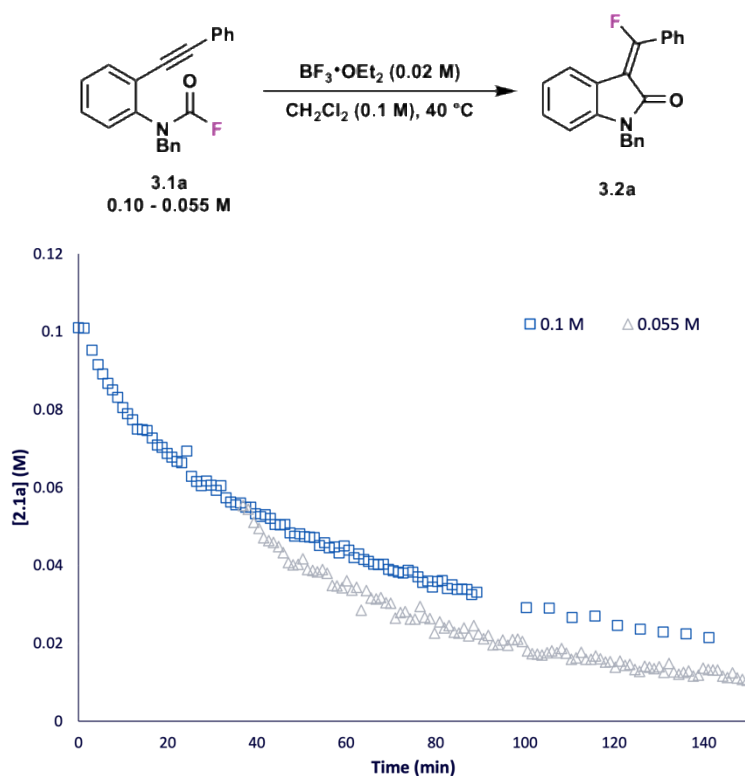


Figure 3.18. Concentration normalized “same excess” experiment.

To differentiate between product inhibition and other catalyst deactivation pathways, a third reaction profile was generated which was initial loaded with 0.05 M of **3.1a**, 0.05 M of **3.2a**, and 0.02 M of $\text{BF}_3 \cdot \text{OEt}_2$ (Table 3.5, **Exp 3**, Figure 3.19). The addition of **3.2a** to the starting conditions is equal to the amount of product that was formed when the concentration of **3.1a** in **Exp. 1** was 0.05 M. If product inhibition was a major off-cycle species, the addition of **3.2a** should reduce the rate of the reaction, giving visual overlay between **Exp 1** and a time adjusted **Exp 3** profile. Instead, upon concentration normalization, there is no overlay between the profiles, making it unlikely that product inhibition is operative under the reaction conditions.

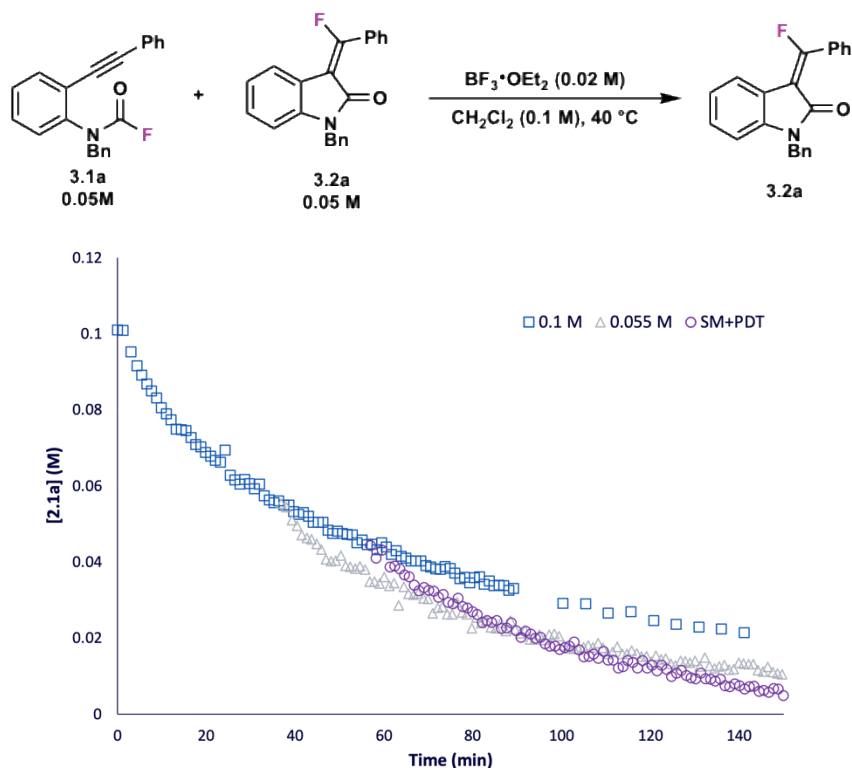


Figure 3.19. Concentration normalized product inhibition; SM + PDT = Exp 3.

Order in **3.1a** was determined by comparing two reaction profiles with differing initial concentration of **3.1a** (Table 3.5, 0.10 M/Exp. 1 and 0.055 M/Exp. 2). The concentration of **3.1a** was and plotted against the normalized time scale $\Sigma[3.1a]^\beta \Delta t$ (equation 1). To facilitate visual comparison of the two profiles, the reaction using an initial concentration of 0.055 M for **3.1a** (Exp 2) was shifted up on the y-axis until the first point of the profile overlaid with the first point on the second reaction profile (Figure 3.20). The exponent β corresponds to the order in **3.1a** and the value was varied until the two concentration-time profiles were visually overlayed. In this case, the order of **3.1a** was found to be 1.

$$\sum [3.1a]^\beta \Delta t = \sum_{i=1}^n \left(\frac{[3.1a]_i + [3.1a]_{i-1}}{2} \right)^\beta (t_i - t_{i-1}) \text{ (equation 1)}$$

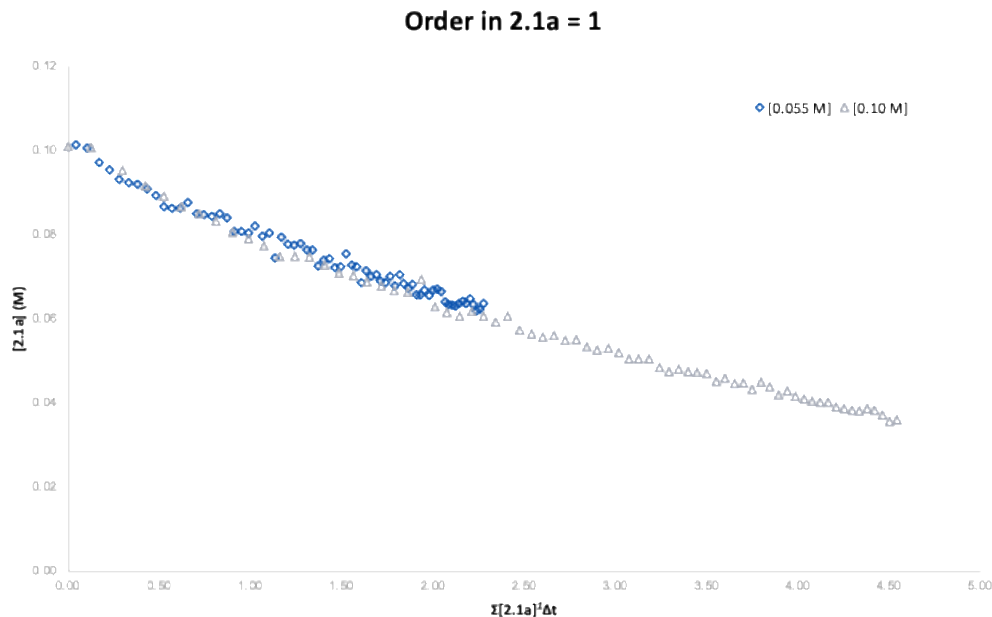


Figure 3.20. Order in **3.1a** as determined by VTNA.

To determine the order in catalyst,⁶⁴ three reaction profiles were generated with various catalyst loadings (13-34%) with a constant concentration of **3.1a** (0.1 M) (Table 3.5, Exp 1, 4 and 5). The reaction was monitored by ¹⁹F NMR spectroscopy using *α,α,α*-trifluorotoluene as the internal standard. The raw integration data were converted into a plot of $\Sigma[\text{cat}]^\gamma \Delta t$ (equation 2) versus concentration of **3.1a**. The exponent γ was varied until the best visual overlay between the three reaction profiles was obtained. The order in catalyst was found to be 0.9, or approximately 1. These kinetic experiments revealed that the reaction was first-order in both **3.1a** and catalyst, suggesting that a single boron species is involved in the turnover limiting step.

$$\sum [\text{cay}]^\gamma \Delta t = \sum_{i=1}^n \left(\frac{[\text{cat}]_i + [\text{cat}]_{i-1}}{2} \right)^\gamma (t_i - t_{i-1}) \text{ (equation 2)}$$

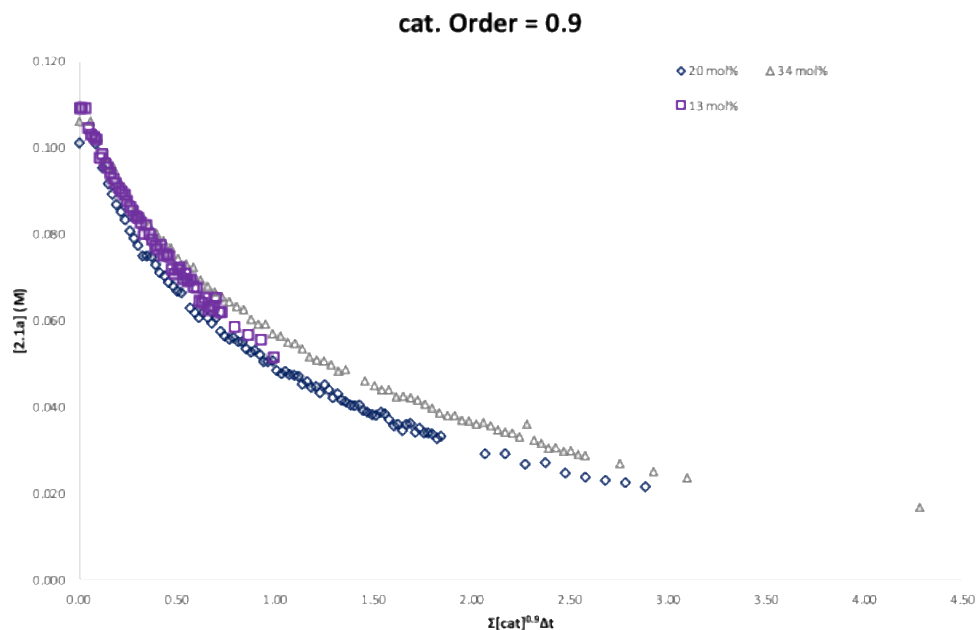


Figure 3.21. Order in $\text{BF}_3 \cdot \text{OEt}_2$ as determined by VTNA.

3.5.5 Hammett Studies

To determine the extent of charge development during the turnover-limiting cyclization step (as determined by computations), a competitive Hammett study was conducted with carbamoyl fluorides bearing different *p*-substituted aryl alkynes **3.1t-w** (Table 3.6).

The Hammett equation ($\log[k_X/k_H] = \rho\sigma$) is a free energy relationship that relates substituent effects to reaction rates and equilibrium constants, giving the ability to probe charge build up in rate determining steps by varying the substituents on an aromatic ring. k_X is the rate for a substituted aromatic substrate while k_H is the rate for an unsubstituted aromatic substrate. σ is a substituent constant, dependent on the electron withdrawing or donating effect of a specific substitution on an aromatic ring, and ρ is the reaction constant, which can give information about potential charge build up in the rate determining step of a reaction.⁶⁶ By plotting $\log[k_X/k_H]$ vs σ , the slope of the linear curve is denoted by ρ . Typically, initial reaction rates are determined for various *para*-substitutions on an aromatic ring, but in our case, we opted to do a competitive Hammett study. Instead of taking relative rates, unsubstituted substrate (**3.1a**) is reacted in a competitive reaction with the *para*-substituted substrate (**3.1t-w**).⁶⁷ The ratio of products formed is then taken as k_X/k_H and plotted against the appropriate σ value for each

substituent. Each competitive Hammett experiment was run in triplicate, and the average was calculated and plotted in Figure 3.22. The standard deviation was calculated at the 95% confidence interval. σ_p values were taken from Hansch et al.⁶⁶

Analysis of the resulting plot showed that electron-donating groups accelerated the rate of the reaction ($\rho = -0.55$), implying the development of δ^+ in the turnover-limiting C–C bond formation step prior to fluoride addition, in line the DFT computed mechanism (Figure 3.15). Interestingly, the ρ derived from the Hammett plot (-0.55) is relatively shallow for discrete carbocation formation. This observation can be explained by donation of electron density from the fluorine atoms in the BF_3 adduct to the developing carbocation during this step, thus attenuating the charge buildup.

Table 3.6. Averaged data from competitive Hammett study.

R	σ_p	k_X/k_H	$\log(k_X/k_H)$	STDEV
<i>p</i> - <i>t</i> Bu (2.1u)	-0.20	1.06	0.023	0.0041
<i>p</i> -Me (2.1t)	-0.17	1.08	0.034	0.0094
<i>p</i> -H (2.1a)	0.00	1.00	0.00	0.00
<i>p</i> -OCOMe (2.1v)	0.31	0.56	-0.26	0.037
<i>p</i> -CF ₃ (2.1w)	0.54	0.45	-0.35	0.023

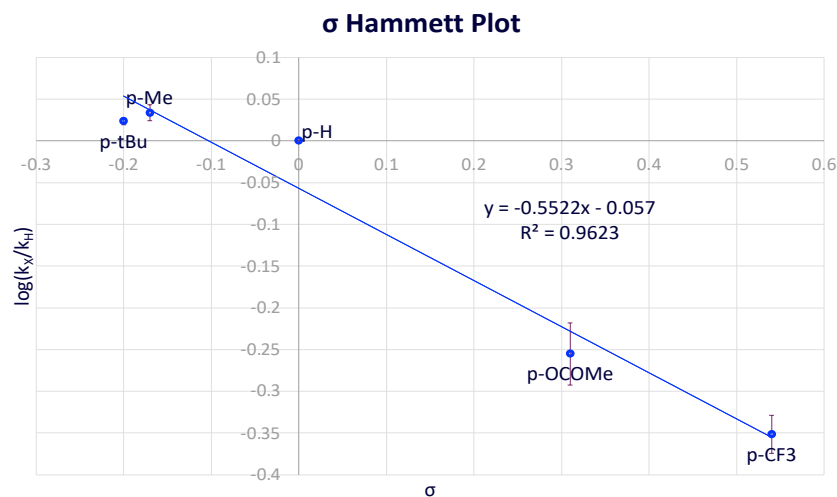


Figure 3.22. Hammett plot.

3.6 Direct Synthesis of Free Oxindole Products

Considering the biological importance of the free oxindole products **3.5** and given both the low step-economy and low overall yield of the free NH 3-fluoromethylene oxindoles using our reported methodology, we were curious if they could be synthesized in an alternative, more direct manner. Looking into the literature we found that free NH 3-chloromethylene oxindoles **138** can be synthesized when alkyne-tethered isocyanates **137** are treated with FeCl_3 (Figure 3.23).⁶⁸ The authors postulate that the reaction proceeds via coordination of FeCl_3 to the isocyanate, yielding imidoyl cation **139** which is primed for C–C bond formation, as well as subsequent or concurrent capture by a nucleophilic chloride.

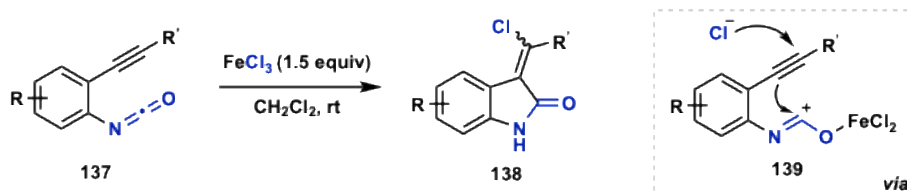


Figure 3.23. Formation of free NH 3-chloromethylene oxindoles from

Given that both $\text{HBF}_4 \cdot \text{OEt}_2$ and $\text{BF}_3 \cdot \text{OEt}_2$ are LAs that can act as fluoride sources and promote fluorinative cyclization, we were curious if they could promote similar reactivity with alkyne-tethered isocyanates **3.8**. If so, given that the isocyanate can be formed directly from the alkynyl aniline via carbonylation, this method would be a reduction to 3 steps from the 5 of the current methodology (Figure 3.24).

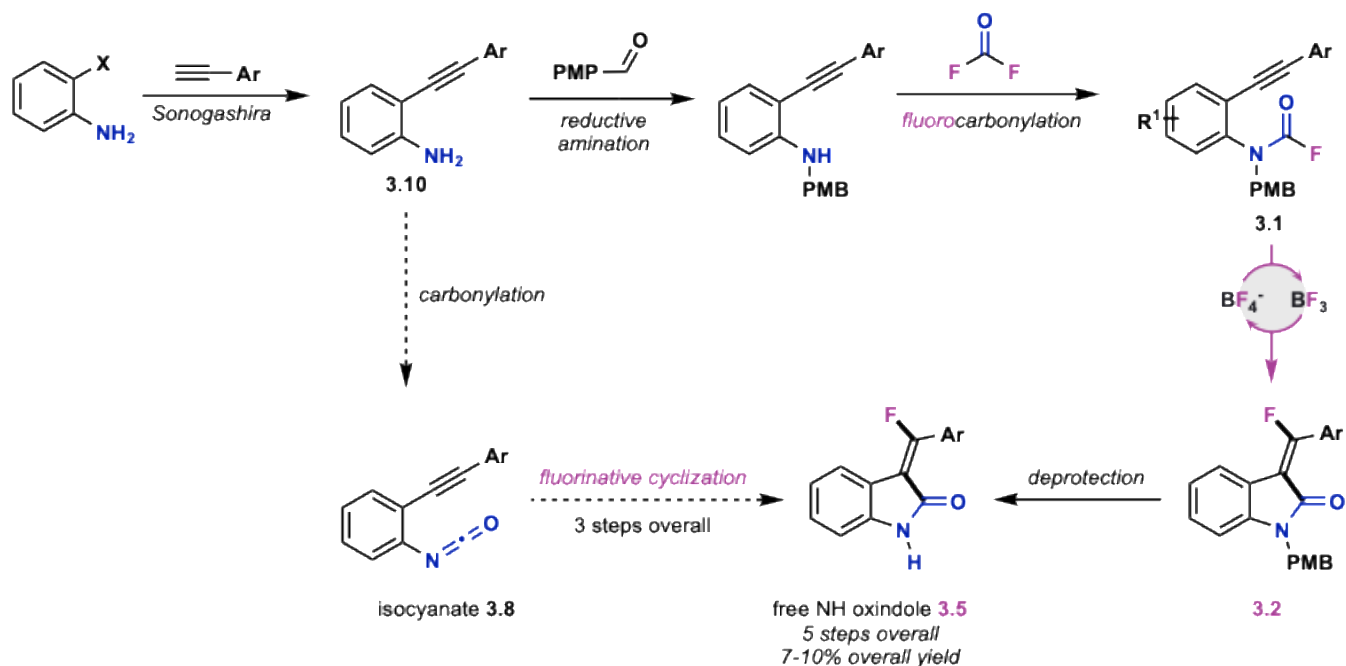
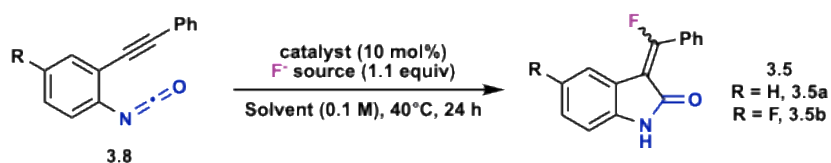


Figure 3.24. Current methodology to access free NH oxindoles **3.5** via carbamoyl fluorides vs proposed strategy from isocyanates **3.8**.

Initial screening of both $\text{HBF}_4 \cdot \text{OEt}_2$ and $\text{BF}_3 \cdot \text{OEt}_2$ on isocyanate **3.8** showed that while both can promote the reaction, $\text{HBF}_4 \cdot \text{OEt}_2$ is superior, yielding the free oxindole **3.5a** in 25% yield isolated with a 96:4 *E/Z* ratio (Table 3.7, entry 1). Attempts at using another cheap tetrafluoroborate salt, NaBF_4 , gave no product, even in the presence of catalytic $\text{HBF}_4 \cdot \text{OEt}_2$ and $\text{BF}_3 \cdot \text{OEt}_2$ as activators (Table 3.7, entries 3-4). Attempts at using TBAF as a more soluble fluoride source in the presence of catalytic $\text{HBF}_4 \cdot \text{OEt}_2$ and $\text{BF}_3 \cdot \text{OEt}_2$ as activators also failed to yield any product (Table 3.7, entries 5-6).

Table 3.7. Fluoride source screen for fluorinative cyclization of isocyanate **3.8**.



Entry*	R	Cat. (10 mol%)	F- Source	Solvent	Conv. (%)	Yield (%)	E/Z ratio
1	H	NA	BF ₃ ·OEt ₂	CH ₂ Cl ₂	11	5	>99:1
2	H	NA	HBf ₄ ·OEt ₂	CH ₂ Cl ₂	50	25 ^a	96:4
3	H	BF ₃ ·OEt ₂	NaBF ₄	CH ₂ Cl ₂	12	>1	--
4	H	HBf ₄ ·OEt ₂	NaBF ₄	CH ₂ Cl ₂	18	1	--
5	H	BF ₃ ·OEt ₂	TBAF ^b	CH ₂ Cl ₂	31	0	--
6	H	HBf ₄ ·OEt ₂	TBAF ^b	CH ₂ Cl ₂	31	0	--
7	F	NA	HBf ₄ ·OEt ₂ ^c	CH ₂ Cl ₂	95	34	>99:1
8	F	NA	HBf ₄ ·OEt ₂ ^d	CH ₂ Cl ₂	100	19	>99:1
9	F	NA	HBf ₄ ·OEt ₂ ^e	CH ₂ Cl ₂	68	38	>99:1

* All reactions run in a flame dried 1-dram vial at a 0.1 mmol scale under the conditions specified, conversion and yield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as internal standard; a. isolated yield; b. TBAF solution was dried before use; c. 1.5 equiv of HBf₄·OEt₂ used; d. 2 equiv of HBf₄·OEt₂ used; e. reaction run at -78 °C instead of 40 °C for 3 hours.

Further optimization of this transformation was carried out by undergraduate thesis student Sara Rough, who ultimately found that increasing the equivalents of HBf₄·OEt₂ to 1.5 equivalents increased the yield to 34% (Table 3.7, entry 7), but the use of 2 equivalents (Table 3.7, entry 12) resulted in a decreased yield of 19%. Interestingly, if the reaction temperature was brought down to -78 °C and run for only 3 hours, more **3.5a** was present at the end of the reaction, leading us to suspect that the oxindole was not stable under the reaction conditions (Table 3.7, entry 13). Sarah found that re-subjecting product **3.5a** to the reaction conditions resulted in substantial decomposition with both HBf₄·OEt₂ and BF₃·OEt₂ (60-70% conversion at 50 min, Figure 3.25).

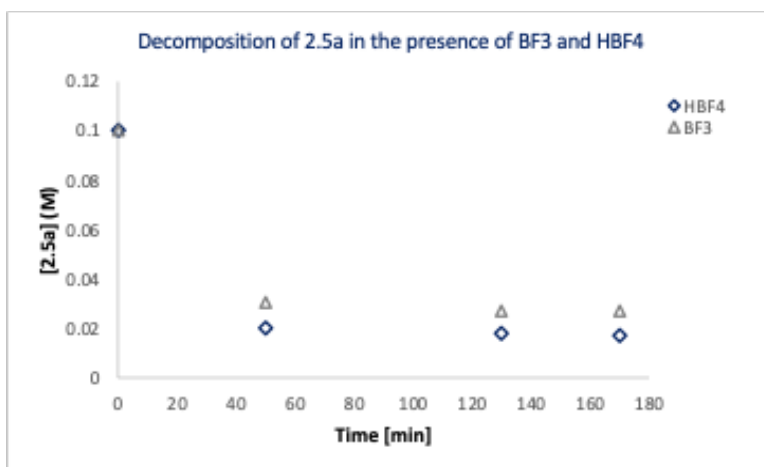


Figure 3.25. Decomposition of **3.5a** in the presence of $\text{HBF}_4 \cdot \text{OEt}_2$ and $\text{BF}_3 \cdot \text{OEt}_2$.

Given the apparent decomposition of **3.5a** under LA conditions, we opted to not continue with the optimization of isocyanate fluorocyclizations. Instead, we turned to looking at potentially using alkenyl anilines **3.10** as starting materials for a fluorocarbonylative annulation reaction. In 2007, Li and co-workers reported the Pd-catalyzed carbonylative annulation of alkenyl anilines for the synthesis of both 3-bromo and 3-chloro methylene oxindoles (Figure 3.26).⁶⁹ The reaction is initiated by a migratory insertion of the $\text{Pd}^{\text{II}}\text{X}_2$ to the alkyne yielding alkene **140**. Subsequent CO coordination and insertion forms palladacycle **141**, which upon RE gives the free NH halogenated oxindole. Similar to previously discussed Pd-catalyzed reactions, incorporating fluorine into this reaction manifold would be difficult due to the poor reactivity of Pd^{II} fluorides.

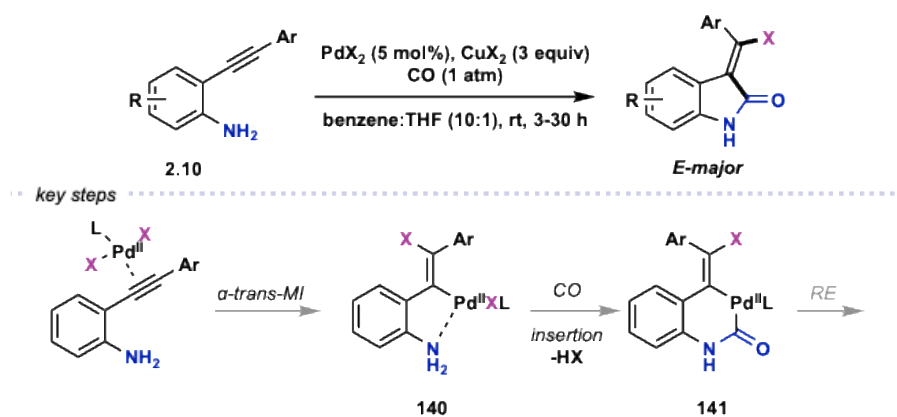


Figure 3.26. Pd-catalyzed carbonylative annulation of alkenyl anilines to make 3-halo methylene oxindoles.

In 2023, Xiao and Lin reported the synthesis of imidazolidine-, oxazolidine- and thiazolidine-2-thiones via the thiocarbonylation of secondary amines (Figure 3.27).⁷⁰ The reaction relies upon the formation of difluorocarbene

(DFC) from the thermal decomposition of PDFA and its subsequent oxidation to thiocarbonyl fluoride (**144**) which is a potent electrophile. NAS with the secondary amine leads to the formation of either thiocarbamoyl fluoride **145** or (thio)isocyanate **146** which are both still electrophilic at the thiocarbonyl carbon. Intramolecular nucleophilic attack of the vicinal X-H functional group and loss of HF forms the desired heterocycle. Over the course of this reaction, 2 equivalents of fluoride are released, likely as HF.

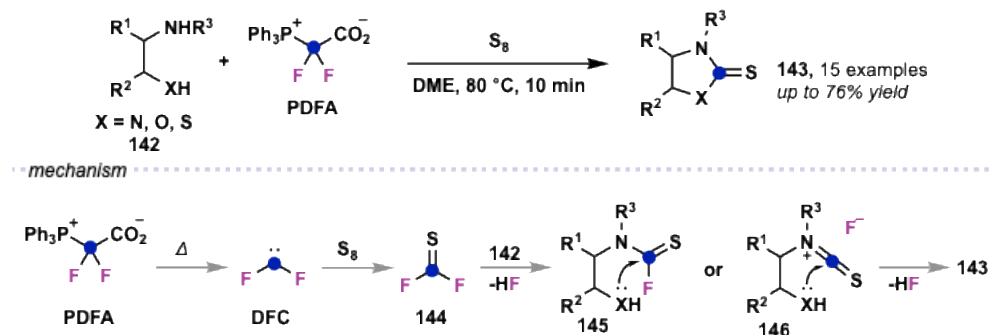


Figure 3.27. Thiocarbonylative annulation of vicinal X-H substituted amines with thiocarbonyl fluoride.

Aside from oxidation to thiocarbonyl fluoride, DFC can also be oxidized to difluorophosgene (COF_2) in the presence of a range of *O*-oxidants. The generation of COF_2 from DFCs has been leveraged for the synthesis of a range of compounds, namely carbamoyl fluorides when reacted with secondary amines.^{32,71-73} Under these conditions, the use of primary amines as nucleophiles results in the formation of ureas **149**. Secondary carbamoyl fluorides **147** are prone to HF elimination, resulting in the formation of isocyanates **148** which are then trapped by a second equivalent of primary amine to form **149** (Figure 3.28). We envisioned that in the case of alkynyl-anilines **3.10**, we could divert the isocyanate into a fluorinative cyclization instead of urea formation because two equivalents of fluoride are released in the reaction, potentially enabling fluoride recycling.

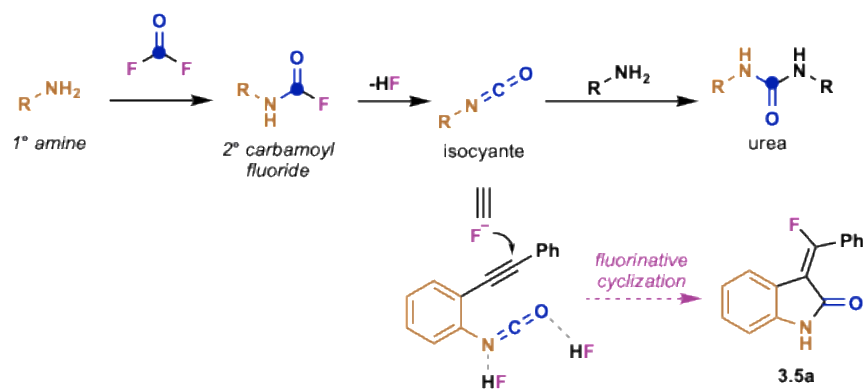
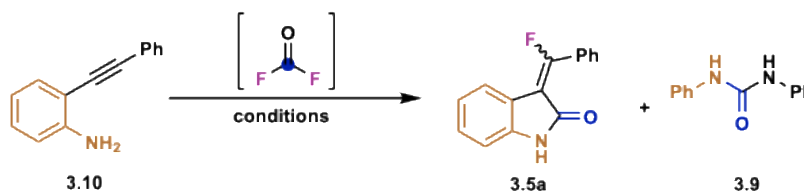


Figure 3.28. Primary amine reaction with COF_2 to yield ureas and potential diversion to fluorinated-oxindole product from common isocyanate intermediate.

To test this hypothesis, we subjected **3.10** to an initial screen of reported and in-house developed DFC-precursors/oxidant pairs as well as other COF_2 releasing reagents (Table 3.8). PDFA/4-MePyr-*N*-oxide, a DFC/oxidant pair developed by the Le group for the synthesis of carbamoyl fluorides, resulted in the exclusive formation of urea **3.9a** in 32% yield (Table 3.8, entry 1).³² Swapping the DFC source for TMSCF_3 resulted in formation of both the urea and the desired oxindole in low yields, with the oxindole as the major product (Table 3.8, entry 2). Use of $\text{BrCF}_2\text{CO}_2\text{Et}$ and increasing the temperature to 80 °C resulted in the formation of **3.5a** in 27% yield by ¹H NMR as a 4:1 ratio of *E/Z*-isomers with minimal production of urea **3.9a**, resulting in a 20% isolated yield of the major isomer (Table 3.8, entry 3). Use of AgCF_3 under conditions reported by the Schoenebeck group for the formation of carbamoyl fluorides⁷⁴ resulted in exclusive urea formation as well (Table 3.8, entry 4). Finally increasing the equivalents of all the reagents in the $\text{BrCF}_2\text{CO}_2\text{Et}$ reaction to 3 equivalents resulted in the formation of oxindole **3.5a** in 54% yield as a 5:1 ratio of *E/Z*-isomers, with an isolated yield of 45% of oxindole **E-3.5a** (Table 3.8, entry 5). This data, while preliminary, reveals that it is possible to form secondary 3-fluoromethylene oxindoles via a DFC/oxidant driven fluorocarbonylative annulation reaction, reducing the steps needed to reach oxindoles **3.5** from 5 to 2, and even un optimized, increasing the overall yield from 7-10% to 42%.

Table 3.8. Initial screen of COF₂ reagents for fluorocarbonylative annulation of **3.10**.



Entry*	Conditions	Conv. (%)	3.5a (%)	3.9a (%)
1	PDFA (1.5 equiv.), 4-MePyr-N,O (2 equiv.), MeCN (0.1 M), 60 °C, 1 h	45	0	32
2	TMSCF ₃ (2 equiv.), NaI (0.2 equiv), 4-MePyr-N,O (2 equiv.), MeCN (0.1 M), 60 °C, 1 h	28	18	5
3	BrCF ₂ CO ₂ Et (2 equiv.), K ₂ CO ₃ (2 equiv), 4-MePyr-N,O (2 equiv.), MeCN (0.1 M), 80 °C, o/n	33	27 (20) ^a	>2
4	AgOCF ₃ (2 equiv), DIPEA (2 equiv), rt, 2h	45	0	25
5 ^b	BrCF ₂ CO ₂ Et (3 equiv.), K ₂ CO ₃ (3 equiv), 4-MePyr-N,O (3 equiv.), MeCN (0.1 M), 80 °C, o/n	71	54 (45) ^a	10

* All reactions run in a flame dried 2-dram vial at a 0.2 mmol scale under the conditions specified, conversion and yield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as internal standard; a. isolated yield of major isomer (*E*-**3.5a**); b. reaction run in pressure tube instead of 2-dram vial.

3.7 Conclusions and Future Work

The synthesis of 3-fluoromethylene oxindoles (**3.2**) and γ -lactams (**3.4**) under mild BF₃-catalyzed fluorocarbamoylation reactions of carbamoyl fluorides (**3.1** and **3.3**) was developed. This method was amenable to the synthesis of a variety 3-aryl-3-fluoromethylene-containing heterocycles in good to excellent yields, using a cheap, commercially available BF₃·OEt₂ as the catalyst. Yields for substrates bearing a competitive Lewis base functionality can often be increased by using stoichiometric amounts of BF₃·OEt₂, enabling a wider range of substrates to be applied. Overall, the combined computational and experimental evidence points towards a formal C–F bond activation pathway: oxophilic BF₃ coordination to the carbamoyl fluoride serves to both increase the electrophilicity of the carbonyl carbon enabling key C–C bond formation. At the same time, the tetracoordinated BF₃ species is primed for intramolecular fluoride transfer and C–F bond formation. Additionally, the reaction can be applied to the synthesis of biologically relevant analogues of secondary oxindole protein kinase inhibitors (**3.5aa** and **3.5ab**) following PMB-deprotection of the tertiary oxindole. This work demonstrates the capacity of boron-trihalides, specifically BF₃·OEt₂, in fluoride recycling reactions, and is the only example in the literature thus far of carbamoyl fluorides being applied as a C–F bond donor in any fluoride shuttling reactions.

Since the publication of this report, boron-trihalides have been shown to be efficient catalysts for other carbohalogenation reactions. Notably, Kong and Yang in 2024 found that BCl₃ could be used as an effective catalyst for the stereoselective intramolecular chlorocarbamoylation of alkynes/allenes, yielding chlorinated methylene lactams or tetrahydroisoquinolinones with exclusive *Z*-geometry at the double bond, directly building off of the halogen shuttling protocol provided here.⁷⁵

Other pathways for the synthesis of biologically relevant secondary oxindoles were also explored. Further investigations by former undergraduate researcher Sara Rough found that carbohalogenation reactions of alkyne-tethered isocyanates with HBF₄·OEt₂ can furnish 3-fluoromethylene oxindoles **3.5a** and **3.5b** (containing a free NH moiety), though the product is not stable under the reaction conditions. Alternatively, the same products can be formed via the fluorocarbonylative annulation of *o*-alkynyl anilines **3.10** using difluorophosgene generated *in situ* by a difluorocarbene surrogate and oxidant.

3.8 Experimental and Spectral Information

3.8.1 Reaction optimization

Carbamoyl fluoride **3.1** (1 equiv) was weighed directly into an oven-dried 1-dram vial equipped with a stir bar. The vial was evacuated and backfilled with N₂ three times before anhydrous CH₂Cl₂ (1.0 mL) was added. If the catalyst was a solid it was weighed directly into the vial, otherwise a stock solution of it was prepped and the correct amount was transferred to the reaction vessel. The vial was sealed with a Teflon-lined cap and placed in a pre-heated oil bath at 40 °C for 24 h. The reaction was cooled to rt and filtered across a pad of silica gel, eluted with CH₂Cl₂ (3 x 1 mL), then concentrated in vacuo. The conversion, yield, and isomeric ratio was determined from the crude sample by ¹⁹F NMR spectroscopy using anhydrous α,α,α-trifluorotoluene (10 μL) as an internal standard. A single scan NMR experiment (T₁ = 30 seconds) was used to ensure full relaxation of all ¹⁹F signals. CDCl₃ is stored over solid K₂CO₃ or 4Å mol sieves and filtered through a short plug of basic alumina before use.

3.8.2 Kinetic Studies

3.8.2.1 Variable Time Normalization Analysis (VTNA)

Kinetic studies were run with **3.1a** and $\text{BF}_3 \cdot \text{OEt}_2$ using CH_2Cl_2 as solvent and monitored by in situ ^{19}F NMR spectroscopy using α,α,α -trifluorotoluene as an internal standard. The data was analyzed using the VTNA method.^{205–207} For each VTNA experiment, a 0.20 M stock solution of **3.1a** (0.40 mmol, 131.6 mg) in dry CH_2Cl_2 (2.0 mL) was prepared. An oven dried NMR tube (Wilmaad-LabGlass 669995700) equipped with rubber septum (MilliporeSigma Z553891) was sealed with electrical tape and evacuated and backfilled with N_2 three times. The NMR tube was charged with α,α,α -trifluorotoluene (8.5 mg, 7.1 μL) via microsyringe and an appropriate amount of **3.1a** stock solution. The contents of the NMR tube were then diluted such that the total volume of CH_2Cl_2 in the NMR tube was 0.68 mL (see Table 3.5). The NMR tube was inserted into a pre-heated (40 $^\circ\text{C}$) Bruker ARX 400 MHz NMR spectrometer. Using the software TopSpin 4.2, “nucloc” was turned off and the probe was tuned. An initial NMR was taken ($t = 0$), then 20 μL of an appropriate stock solution of $\text{BF}_3 \cdot \text{OEt}_2$ in CH_2Cl_2 was added to the NMR tube. The NMR tube shaken vigorously for 30 s before being inserted back into the 400 MHz spectrometer and further scans were taken.

Integral data was obtained via ^{19}F NMR analysis using α,α,α -trifluorotoluene as internal standard. All scans were taken with $\text{ns} = 1$, $\text{ds} = 0$, and relaxation delay (d1) = 60 s. ^{19}F NMR spectra were analyzed using the fluorine signals from carbamoyl fluoride **3.1a** (δ -14.19 ppm, s, 0.8F and -19.33 ppm, s, 0.2F) relative to the CF_3 signal from α,α,α -trifluorotoluene (δ -63.72 ppm, s, 3F). Similarly, the initial concentration of $\text{BF}_3 \cdot \text{OEt}_2$ (δ -153.13 ppm, s, 3F) was confirmed by ^{19}F NMR relative to the CF_3 signal from α,α,α -trifluorotoluene. [**3.1a**] was calculated relative to α,α,α -trifluorotoluene and data for all runs can be found in Table 3.9.

Table 3.9. Concentration of **3.1a** based on raw integral data measured by ¹⁹F NMR spectroscopy.

[3.1a] 0.10 M [cat] 0.02 M		[3.1a] 0.10 M [cat] 0.02 M		[3.1a] 0.10 M [cat] 0.02 M		[3.1a] 0.055 M [cat] 0.02 M		
t (min)	[3.1a] (M)	t (min)	[3.1a] (M)	t (min)	[3.1a] (M)	t (min)	[2.1a] (M)	[3.1a+0.045] (M)
0.000	0.101	44.713	0.053	85.430	0.034	0.000	0.055	0.101
4.113	0.101	45.813	0.052	86.530	0.035	1.583	0.055	0.101
5.880	0.095	46.930	0.050	87.630	0.034	2.717	0.055	0.101
7.247	0.092	48.013	0.050	88.730	0.034	4.017	0.051	0.097
8.347	0.089	49.113	0.050	89.830	0.034	5.117	0.050	0.096
9.447	0.087	50.230	0.048	90.930	0.033	6.200	0.047	0.093
10.547	0.085	51.313	0.048	92.030	0.033	7.300	0.046	0.092
11.663	0.083	52.413	0.048	103.163	0.029	8.383	0.046	0.092
12.763	0.081	53.513	0.047	108.247	0.029	9.500	0.045	0.091
13.863	0.079	54.613	0.047	113.347	0.027	10.583	0.043	0.089
14.963	0.077	55.713	0.047	118.447	0.027	11.683	0.041	0.087
16.063	0.075	56.813	0.045	123.547	0.025	12.767	0.040	0.086
17.180	0.075	57.913	0.046	128.647	0.024	13.867	0.040	0.086
18.280	0.075	59.030	0.044	133.747	0.023	14.950	0.042	0.088
19.397	0.073	60.130	0.045	138.847	0.022	16.050	0.039	0.085
20.497	0.071	61.230	0.043	143.963	0.021	17.150	0.039	0.085
21.597	0.070	62.330	0.045			18.233	0.038	0.084
22.697	0.069	63.413	0.044			19.333	0.039	0.085
23.797	0.068	64.530	0.042			20.417	0.038	0.084
24.897	0.067	65.630	0.043			21.517	0.035	0.081
25.997	0.066	66.730	0.042			22.600	0.035	0.081
27.097	0.069	67.813	0.041			23.700	0.034	0.080
28.197	0.063	68.913	0.040			24.783	0.036	0.082
29.297	0.062	70.030	0.040			25.883	0.034	0.080
30.397	0.061	71.130	0.040			26.967	0.034	0.080
31.480	0.062	72.247	0.039			28.050	0.029	0.075
32.580	0.061	73.347	0.039			29.150	0.034	0.080
33.680	0.059	74.447	0.038			30.233	0.032	0.078
34.797	0.060	75.547	0.038			31.333	0.031	0.077
35.897	0.057	76.630	0.039			32.417	0.032	0.078
36.997	0.056	77.730	0.038			33.517	0.030	0.076
38.097	0.056	78.830	0.037			34.600	0.030	0.076
39.197	0.056	79.930	0.036			35.700	0.027	0.073
40.297	0.055	81.030	0.036			36.800	0.028	0.074
41.413	0.055	82.130	0.034			37.883	0.028	0.074
42.513	0.053	83.230	0.036			38.967	0.026	0.072
43.613	0.053	84.313	0.036			40.067	0.026	0.072

[3.1a] 0.055 M [cat] 0.02 M			[3.1a] 0.055 M [cat] 0.02 M			[3.1a] 0.055 M [cat] 0.02 M		
t (m)	[3.1a] (M)	[3.1a+0.045] (M)	t (m)	[3.1a] (M)	[3.1a+0.045] (M)	t (m)	[3.1a] (M)	[3.1a+0.045] (M)
41.167	0.030	0.076	81.600	0.016	0.062	122.033	0.010	0.056
42.250	0.027	0.073	82.683	0.015	0.061	123.133	0.010	0.056
43.350	0.026	0.072	83.783	0.015	0.061	124.217	0.010	0.056
44.433	0.023	0.069	84.867	0.014	0.060	125.300	0.010	0.056
45.533	0.025	0.071	85.950	0.015	0.061	126.400	0.011	0.057
46.617	0.024	0.070	87.050	0.014	0.060	127.483	0.010	0.056
47.717	0.025	0.071	88.133	0.015	0.061	128.583	0.011	0.057
48.800	0.023	0.069	89.250	0.013	0.059	129.667	0.010	0.056
49.900	0.023	0.069	90.333	0.013	0.059	130.750	0.009	0.055
50.983	0.024	0.070	91.433	0.014	0.060	131.850	0.008	0.054
52.083	0.022	0.068	92.517	0.014	0.060	132.933	0.009	0.055
53.183	0.025	0.071	93.617	0.014	0.060	134.033	0.009	0.055
54.283	0.022	0.068	94.700	0.014	0.060	135.117	0.009	0.055
55.367	0.021	0.067	95.800	0.013	0.059	136.217	0.010	0.056
56.450	0.022	0.068	96.900	0.015	0.061	137.300	0.009	0.055
57.550	0.020	0.066	98.000	0.013	0.059	138.383	0.009	0.055
58.633	0.020	0.066	99.083	0.012	0.058	139.483	0.008	0.054
59.733	0.021	0.067	100.183	0.013	0.059	140.567	0.008	0.054
60.833	0.020	0.066	101.283	0.013	0.059	141.667	0.007	0.053
61.933	0.021	0.067	102.367	0.012	0.058	142.750	0.009	0.055
63.017	0.021	0.067	103.467	0.012	0.058	143.850	0.008	0.054
64.117	0.021	0.067	104.550	0.014	0.060	144.950	0.007	0.053
65.200	0.018	0.064	105.650	0.013	0.059	146.033	0.008	0.054
66.300	0.017	0.063	106.750	0.013	0.059	147.150	0.008	0.054
67.400	0.017	0.063	107.833	0.013	0.059	148.233	0.007	0.053
68.483	0.017	0.063	108.933	0.012	0.058	149.333	0.009	0.055
69.600	0.018	0.064	110.033	0.011	0.057	150.417	0.008	0.054
70.683	0.018	0.064	111.117	0.012	0.058	151.500	0.008	0.054
71.783	0.018	0.064	112.200	0.011	0.057	152.600	0.007	0.053
72.867	0.019	0.065	113.300	0.011	0.057	153.683	0.008	0.054
73.950	0.017	0.063	114.383	0.011	0.057	154.783	0.007	0.053
75.050	0.016	0.062	115.467	0.011	0.057	155.867	0.006	0.052
76.133	0.016	0.062	116.567	0.009	0.055	156.967	0.007	0.053
77.233	0.018	0.064	117.650	0.010	0.056	158.050	0.008	0.054
78.317	0.016	0.062	118.750	0.011	0.057	159.133	0.006	0.052
79.417	0.016	0.062	119.850	0.011	0.057	160.233	0.005	0.051
80.500	0.017	0.063	120.950	0.010	0.056	161.317	0.007	0.053

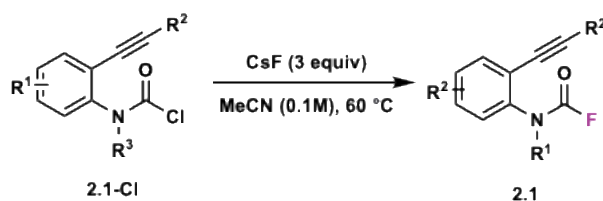
[3.1a] 0.10 M [cat] 0.034 M		[3.1a] 0.10 M [cat] 0.034 M		[3.1a] 0.10 M [cat] 0.013 M		[3.1a] 0.10 M [cat] 0.013 M	
t (min)	[3.1a] (M)	t (min)	[3.1a] (M)	t (min)	[3.1a] (M)	t (min)	[3.1a] (M)
0.000	0.106	42.681	0.046	0.000	0.109	40.512	0.069
1.730	0.106	44.131	0.045	0.861	0.109	41.595	0.071
2.847	0.102	45.214	0.044	2.444	0.109	42.678	0.069
3.930	0.098	46.298	0.044	3.528	0.104	43.762	0.069
5.030	0.095	47.398	0.042	4.611	0.103	44.878	0.068
6.113	0.092	48.481	0.042	5.694	0.102	45.962	0.068
7.197	0.089	49.564	0.042	6.778	0.102	47.045	0.064
8.297	0.086	50.664	0.042	7.878	0.098	48.128	0.064
9.380	0.084	51.748	0.041	8.961	0.099	49.212	0.065
10.480	0.082	52.848	0.040	10.044	0.096	50.295	0.062
11.563	0.080	53.931	0.039	11.128	0.095	51.395	0.063
12.647	0.078	55.031	0.038	12.211	0.094	52.478	0.063
13.730	0.077	56.114	0.038	13.295	0.093	53.562	0.065
14.814	0.074	57.214	0.037	14.395	0.092	54.662	0.062
15.914	0.073	58.298	0.037	15.478	0.090	55.745	0.062
16.998	0.072	59.381	0.036	16.562	0.090	60.862	0.059
18.081	0.069	60.481	0.036	17.645	0.089	65.962	0.057
19.164	0.068	61.564	0.035	18.728	0.088	71.045	0.055
20.248	0.067	62.648	0.035	19.828	0.086	76.128	0.051
21.348	0.065	63.731	0.034	20.912	0.085		
22.431	0.064	64.831	0.034	21.995	0.084		
23.531	0.063	65.914	0.033	23.078	0.084		
24.614	0.062	66.981	0.036	24.162	0.083		
25.714	0.060	68.064	0.032	25.262	0.080		
26.798	0.059	69.164	0.032	26.345	0.082		
27.898	0.059	70.264	0.030	27.445	0.080		
28.981	0.057	71.348	0.031	28.528	0.079		
30.064	0.056	72.431	0.030	29.612	0.077		
31.164	0.055	73.514	0.030	30.695	0.076		
32.264	0.055	74.598	0.029	31.795	0.077		
33.364	0.053	75.681	0.029	32.878	0.075		
34.448	0.052	80.848	0.027	33.962	0.075		
35.548	0.051	85.931	0.025	35.045	0.075		
36.631	0.050	91.031	0.024	36.145	0.072		
37.714	0.050	125.831	0.017	37.228	0.071		
38.798	0.048			38.328	0.072		
39.898	0.08			39.428	0.072		

3.8.3 Competitive Hammett study for *para*-substituted alkynes **3.1t-3.1w**

For each of the competition experiments, a combined stock solution of **3.1a** (1.0 equiv, 0.4 mmol, 131.6 mg) and the desired *para*-substituted carbamoyl fluoride **3.1t-3.1w** (1.0 equiv, 0.4 mmol) in CH₂Cl₂ (4.0 mL) was prepared. 1.0 mL of the stock solution was transferred to an oven-dried 1-dram vial equipped with a stir bar under N₂. A 0.39 M stock solution of BF₃·OEt₂ in CH₂Cl₂ was prepared under N₂ and 50.7 μL (20 mol%) was transferred to the reaction vessel. The vial was sealed with a Teflon-lined cap and placed in a pre-heated oil bath at 40 °C for 1 h. The reaction was cooled to RT and filtered across a pad of silica gel, eluted with CH₂Cl₂ (3 x 1 mL), then concentrated in vacuo. Relative yields of the products were analyzed by ¹⁹F-NMR spectroscopy using anhydrous α,α,α-trifluorotoluene (2.5 μL) as ¹⁹F-NMR reference, except in the case of **3.2w** (*p*-CF₃) where 2-fluoro-4-nitrotoluene (3.0 mg) was used instead to avoid issues with referencing due to overlap with already present CF₃ peaks.

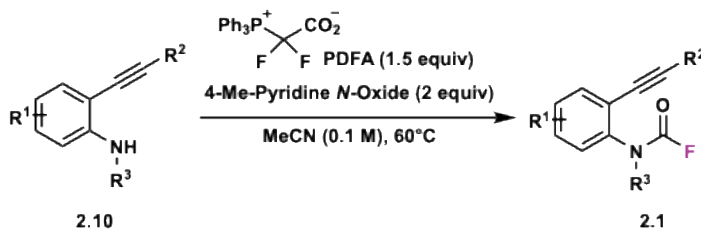
3.8.4 Synthesis and Characterization Data for Starting Materials

General procedure for synthesis of carbamoyl fluorides via carbamoyl chlorides (Method A)



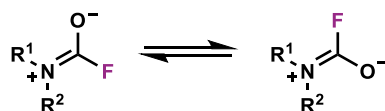
Following a modified literature procedure:⁷⁶ A flame dried flask charged with carbamoyl chloride **1-Cl** (1 mmol, 1.0 equiv), cesium fluoride (1.2 mmol, 1.2 equiv) and MeCN (0.1 M) was stirred at 60 °C until full consumption of the starting material as indicated by TLC (typically 16-48 hours). The reaction was diluted with pentane, flushed through a pad of silica, and concentrated in vacuo. The crude mixture was purified by flash column silica gel chromatography using the indicated eluent.

General procedure for synthesis of carbamoyl fluorides from secondary amines (Method B)

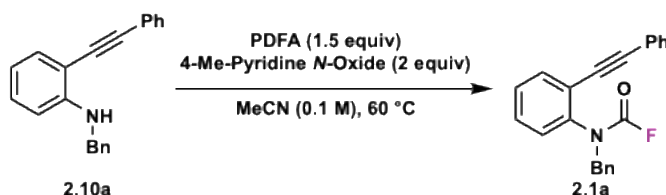


Following a modified literature procedure:³² To a pressure tube charged with PDFA (1.5 mmol, 1.5 equiv) and 4-methylpyridine *N*-oxide (2 mmol, 2 equiv), secondary aniline (1 mmol, 1.0 equiv) in either PhMe or MeCN (10 mL) was added. The pressure tube was capped and submerged in a preheated 60 °C oil bath for 1.5 h, after which the solution was transferred to directly into a round bottom flask and dry loaded onto silica gel. The crude mixture was purified by flash chromatography using the indicated eluent.

Note: In line with previous reports,^{32,77–79} carbamoyl fluorides demonstrate restricted rotation about the N-C_{acyl} bond, giving rise to rotamers in solution. Distinct resonances for the two rotamers are observed in the NMR spectra for unsymmetrically substituted carbamoyl fluorides ($R' \neq R$), although not all peaks may be fully resolved. Where appropriate, fractional integrations have been reported in the ¹H and ¹⁹F NMR data. The chemical shifts for both rotamers are listed as they appear in the ¹³C NMR data.



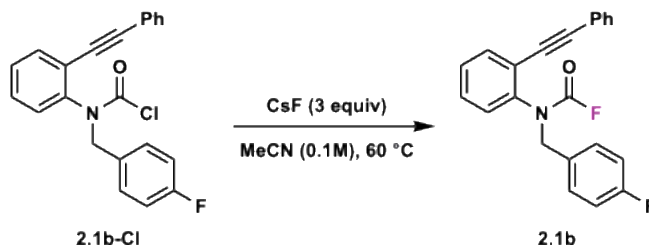
Benzyl(2-(phenylethynyl)phenyl)carbamic fluoride (3.1a)



The title compound was prepared according to **Method B** from **3.10a** (0.988 g, 3.00 mmol). The crude material was purified by flash chromatography (0-10 mol% EtOAc/hexanes) and the desired product was isolated as a light-yellow oil (0.376 g, 1.1 mmol, 57% yield, *rotamer ratio by ¹⁹F NMR*: 85:15). **¹H NMR** (400 MHz, CDCl₃) δ 7.69 (d, J = 7.3 Hz, 0.2H), 7.66 – 7.58 (m, 2.8H), 7.48 – 7.40 (m, 3H), 7.40 – 7.31 (m, 7H), 7.12 (d, J = 7.7 Hz, 0.2H), 7.00 (d, J = 7.9 Hz, 0.8H), 5.23 (d, 0.8H), 4.95 (s, 0.4H), 4.73 (bd, 0.8H); **¹³C {¹H} NMR** (101 MHz, CDCl₃) δ 147.0 (d, J = 288.0 Hz), 146.5 (d, J = 292.1 Hz), 141.1, 140.3, 135.6, 135.5, 133.3, 132.9, 131.8, 131.7, 129.3, 129.2, 129.1, 129.0, 128.8, 128.6, 128.53, 128.49, 128.3, 128.2, 122.7, 122.51, 122.49, 122.2, 95.35, 95.30, 85.1, 84.8, 55.2, 55.0; **¹⁹F NMR** (377 MHz, CDCl₃) δ -14.19 (0.8F, *major*), -19.33 (0.2F, *minor*); **HRMS** (ESI) m/z :

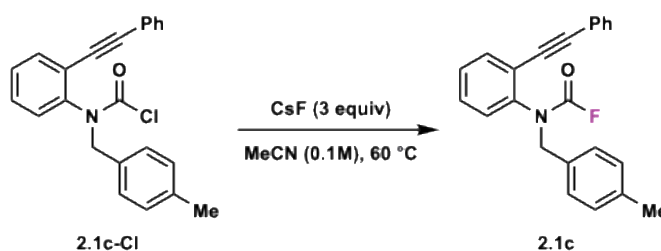
$[M+H]^+ [C_{22}H_{17}FNO]^+$ Calcd for 330.1289; Found 330.1287; **IR** (ATR, $CDCl_3$, cm^{-1}) 1786, 1513, 1250, 1034, 836, 696, 631, 628, 592, 571.

(4-fluorobenzyl)(2-(phenylethynyl)phenyl)carbamic fluoride (3.1b)



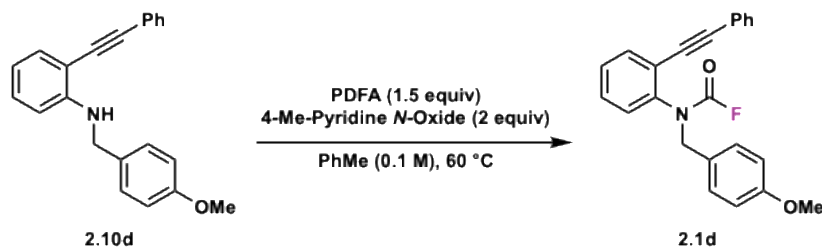
The title compound was prepared according to **Method A** from carbamoyl chloride **3.1b-Cl** (0.226 g, 0.65 mmol), which was synthesized using a known literature procedure.⁸¹ The crude material was purified by flash chromatography (0-10% EtOAc/pentane) and the desired product was isolated as a light yellow crystalline solid (211 mg, 0.61 mmol, 94%, *rotamer ratio by ^{19}F NMR: 90:10*). **1H NMR** (400 MHz, $CDCl_3$) δ 7.62 (dd, $J = 7.5, 1.7$ Hz, 0.2H), 7.58 (dd, $J = 7.6, 1.6$ Hz, 0.8H), 7.55 – 7.46 (m, 2H), 7.43 – 7.15 (m, 7H), 7.04 (d, $J = 7.6$ Hz, 0.2H), 7.00 – 6.88 (m, 2.8H), 5.05 (bd, 0.8H), 4.85 (s, 0.4H), 4.68 (bd, 0.8H); **^{13}C { 1H } NMR** (100 MHz, $CDCl_3$) δ 162.7 (d, $J = 246.9$ Hz), 147.0 (d, $J = 288.5$ Hz), 140.1 (d, $J = 1.9$ Hz), 133.4, 133.0, 131.81, 131.75, 131.3 (d, $J = 3.3$ Hz), 131.1 (d, $J = 8.3$ Hz), 130.6 (dd, $J = 8.1, 1.1$ Hz), 129.4, 129.2, 129.05, 129.01, 128.6, 128.6, 128.3, 122.7, 122.4, 115.7 (d, $J = 21.5$ Hz), 115.6 (d, $J = 21.5$ Hz), 95.4, 84.7, 54.5 (d, $J = 1.3$ Hz), 54.3; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -14.19 (s, 0.9F, *major*), -19.41 (s, 0.1F, *minor*), -113.50 – -113.66 (m, 0.1F, *minor*), -113.69 – -113.80 (m, 0.9F, *major*); **HRMS** (ESI) m/z : $[M+H]^+ [C_{22}H_{16}F_2NO]^+$ Calcd for 348.11946, found 348.11999; **IR** (ATR, $CDCl_3$, cm^{-1}) 1777, 1603, 1519, 1387, 1255, 1219, 1161, 906, 835, 764.

(4-methylbenzyl)(2-(phenylethynyl)phenyl)carbamic fluoride (3.1c)



The title compound was prepared according to **Method A** from carbamoyl chloride **3.1c-Cl** (171 mg, 0.5 mmol), which was synthesized using known literature procedures.¹⁹ The crude material was purified by flash chromatography (0-10% EtOAc/pentane) and the desired product was isolated as a white crystalline solid (136 mg, 0.39 mmol, 78%, *rotamer ratio by ¹⁹F NMR*: 85:15). **¹H NMR** (400 MHz, CDCl₃) δ 7.62 (dd, *J* = 7.5, 1.7 Hz, 0.2H), 7.58 (dd, *J* = 7.6, 1.6 Hz, 0.8H), 7.54 – 7.47 (m, 2H), 7.42 – 7.35 (m, 3H), 7.32 (td, *J* = 7.6, 1.3 Hz, 1H), 7.26 (qd, *J* = 7.3, 1.7 Hz, 1H), 7.18 – 7.01 (m, *J* = 25.3, 6.8 Hz, 4.2H), 6.93 (dd, *J* = 7.8, 0.9 Hz, 0.8H), 5.11 (d, *J* = 12.4 Hz, 0.8H), 4.84 (s, 0.4H), 4.60 (d, *J* = 12.6 Hz, 0.8H), 2.31 (s, 0.6H), 2.29 (s, 2.4H); **¹³C NMR** (101 MHz, CDCl₃) δ 147.1 (d, *J* = 288.1 Hz), 141.2, 140.4, 138.1, 138.0, 133.4, 132.9, 132.7, 132.6, 131.9, 131.8, 129.5, 129.4, 129.2, 129.1, 129.0, 128.8, 128.7, 128.6, 128.5, 122.6, 95.3, 85.1, 84.8, 55.0, 54.8, 21.3; **¹⁹F NMR** (377 MHz, CDCl₃) δ -14.17 (s, 0.85F, *major*), -19.59 (s, 0.15F, *minor*); **HRMS** (ESI) *m/z*: [M+H]⁺ [C₂₃H₁₉FNO]⁺ Calcd for 344.14453, found 344.14423; **IR** (ATR, CDCl₃, cm⁻¹) 1785, 1595, 1482, 1391, 1356, 1183, 1069, 947, 755, 628.

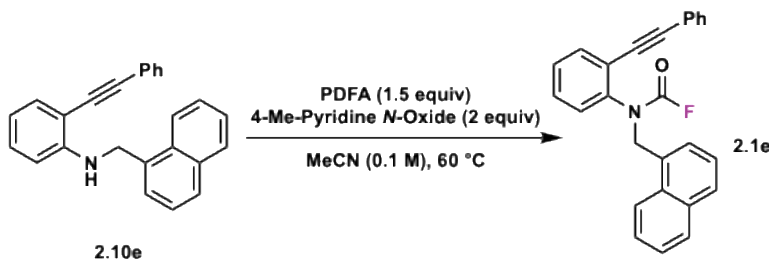
(4-methoxybenzyl)(2-(phenylethynyl)phenyl)carbamic fluoride (3.1d)



The title compound was prepared according to **Method B** from **3.10d** (144 mg, 0.40 mmol), which was synthesized using known literature procedures.⁸¹ The crude material was purified by flash chromatography (0-5% EtOAc/Hexanes) and the desired product was isolated as a clear oil (67 mg, 0.19 mmol, 47%, *rotamer ratio by ¹⁹F NMR*: 85:15). **¹H NMR** (400 MHz, CDCl₃) δ 7.62 (dd, *J* = 7.6, 1.7 Hz, 0.2H), 7.57 (dd, *J* = 7.7, 1.6 Hz, 0.8H), 7.54 – 7.48 (m, 2H), 7.40 – 7.34 (m, 3H), 7.32 (td, *J* = 7.6, 1.4 Hz, 1H), 7.25 (td, *J* = 7.7, 1.7 Hz, 1H), 7.19 – 7.14 (m, 1.7H), 7.12 (d, *J* = 8.6 Hz, 0.3H), 7.02 (dd, *J* = 7.6, 1.5 Hz, 0.2H), 6.92 (dd, *J* = 7.9, 1.2 Hz, 0.8H), 6.82 – 6.73 (m, 2H), 5.06 (bd, 0.8H), 4.82 (s, 0.4H), 4.61 (bd, 0.8H), 3.66 (s, 0.6 H), 3.64 (s, 2.4H); **¹³C {¹H} NMR** (101 MHz, CDCl₃) δ 159.6, 147.0 (d, *J* = 288.1 Hz), 146.5 (d, *J* = 291.9 Hz), 141.1, 140.2 (d, *J* = 1.7 Hz), 133.4, 132.9, 131.9, 131.8, 130.7, 130.2, 129.3, 129.1, 129.0, 128.9, 128.8, 128.51, 128.54, 128.48, 127.8, 127.7, 122.8, 122.7, 122.6, 122.4, 114.1, 114.0, 95.25, 95.22, 85.1, 84.9, 55.34, 55.30, 54.7 (d, *J* = 1.9 Hz), 54.5 (d, *J* = 2.2 Hz); **¹⁹F NMR** (377

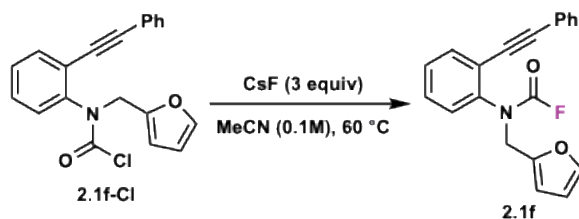
MHz, CDCl₃) δ -14.02 (s, 0.85F, *major*), -19.55 (s, 0.15F, *minor*); **HRMS** (ESI) m/z : [M+Na]⁺ [C₂₃H₁₈FNO₂Na]⁺ Calcd 382.1214, found 382.1205; **IR** (ATR, CDCl₃, cm⁻¹) 1787, 1613, 1514, 1392, 1247, 1177, 1034, 845, 756, 690.

(Naphtha-1-ylmethyl)(2-(phenylethynyl)phenyl)carbamic fluoride (3.1e)



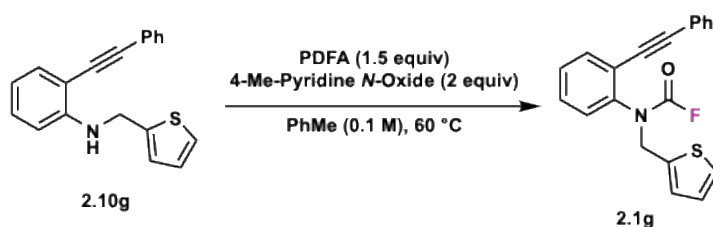
The title compound was prepared according to **Method B** from **3.10e** (380 mg, 1.14 mmol). The crude material was purified by flash chromatography (0-10% EtOAc/pentane) and the desired product was isolated as a light-yellow solid (277 mg, 0.60 mmol, 64%, *rotamer ratio by* ¹⁹F NMR: 90:10). **¹H NMR** (700 MHz, CDCl₃) δ 8.16 (d, J = 8.3 Hz, 0.9H), 7.93 (d, J = 5.5 Hz, 0.1H), 7.88 – 7.81 (m, 1H), 7.81 – 7.73 (m, 1H), 7.59 (d, J = 7.6 Hz, 0.1H), 7.59 – 7.47 (m, 4.9H), 7.42 – 7.35 (m, 3H), 7.32 (d, J = 5.1 Hz, 0.2H), 7.26 – 7.22 (m, 1.9H), 7.15 (d, J = 6.9 Hz, 0.9H), 7.09 (t, J = 7.2 Hz, 0.1H), 7.03 (td, J = 7.8, 1.4 Hz, 0.9H), 6.78 (d, J = 8.0 Hz, 0.1H), 6.52 (d, J = 8.0 Hz, 0.9H), 5.76 (bs, 0.8H), 5.43 (s, 0.2H), 5.10 (bs, 0.8H). **¹³C {¹H} NMR** (176 MHz, CDCl₃) δ 147.0 (d, J = 287.9 Hz), 146.6 (d, J = 292.5 Hz), 140.7, 139.4, 133.9, 133.3, 132.8, 131.9, 131.9, 131.8, 131.5, 130.9, 130.8, 129.4, 129.3, 129.2, 129.0, 128.9, 128.8, 128.7, 128.61, 128.57, 127.9, 127.0, 126.8, 126.1, 125.3, 125.1, 123.9, 123.0, 122.7, 122.6, 122.5, 122.3, 95.4, 95.4, 85.1, 84.7, 52.3, 52.1; **¹⁹F NMR** (659 MHz, CDCl₃) δ -13.51 (s, 0.9F, *major*), -19.47 (s, 0.1F, *minor*); **HRMS** (DART) m/z : [M+ NH₄]⁺ [C₂₆H₂₂FN₂O]⁺ Calcd 397.17107, found 397.17107; **IR** (ATR, CDCl₃, cm⁻¹) 1781, 1598, 1570, 1496, 1482, 1392, 1264, 1104, 1046, 1006, 781; **mp** (°C) 54.0-55.5.

(Furoan-2-ylmethyl)(2-(phenylethynyl)phenyl)carbamic fluoride (3.1f)



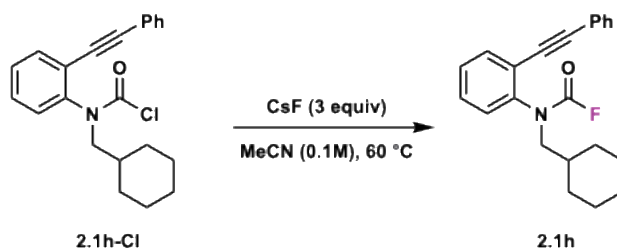
The title compound was prepared according to **Method A** from carbamoyl chloride **3.1f-Cl** (562 mg, 1.76 mmol). The crude material was purified by flash chromatography (0-5% EtOAc/pentane) and the desired product was isolated as a yellow oil (440 mg, 1.38 mmol, 78%, *rotamer ratio by ^{19}F NMR: 85:15*). **^1H NMR** (400 MHz, CDCl_3) δ 7.66 – 7.51 (m, 3H), 7.43 – 7.28 (m, 6H), 7.20 – 7.14 (m, 0.2H), 7.08 (dd, J = 7.4, 1.8 Hz, 0.8H), 6.29 – 6.17 (m, 2H), 5.09 (bd, 0.8H), 4.86 (s, 0.4H), 4.72 (bd, 0.8H); **^{13}C { ^1H } NMR** (101 MHz, CDCl_3) δ 149.0, 148.8, 146.7 (d, J = 288.6 Hz), 143.1, 143.0, 140.9, 140.1 (d, J = 1.9 Hz), 133.2, 132.8, 131.9, 131.8, 129.5, 129.3, 129.01, 128.96, 128.74, 128.72, 128.6, 128.2, 122.70, 122.67, 122.5, 122.4, 110.6, 110.6, 110.2, 109.8, 95.2, 84.8, 84.5, 47.6 (d, J = 1.8 Hz), 47.6; **^{19}F NMR** (377 MHz, CDCl_3) δ -14.02 (s, 0.85F, *major*), -19.47 (s, 0.15F, *minor*); **HRMS** (DART) m/z : $[\text{M}+\text{NH}_4]^+$ $[\text{C}_{20}\text{H}_{18}\text{FN}_2\text{O}_2]^+$ Calcd 337.13468, found 337.13401; **IR** (ATR, CDCl_3 , cm^{-1}) 1786, 1733, 1596, 1570, 1497, 1379, 1264, 1148, 1037, 1016.

(Thiophen-2-ylmethyl)(2-(phenylethynyl)phenyl)carbamic fluoride (3.1g)



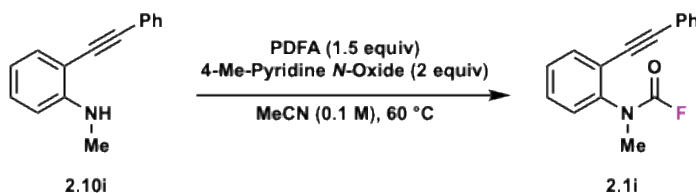
The title compound was prepared according to **Method A** from **3.10g** (217 mg, 0.75 mmol). The crude material was purified by flash chromatography (0-10% EtOAc/hexanes) and the desired product was isolated as a light-yellow oil (114 mg, 0.34 mmol, 45%, *rotamer ratio by ^{19}F NMR: 87:13*). **^1H NMR** (400 MHz, CDCl_3) δ 7.65 (dd, J = 7.5, 1.8 Hz, 0.15H), 7.64 – 7.59 (m, 0.85H), 7.58 – 7.51 (m, 2H), 7.42 – 7.22 (m, 6H), 7.20 – 7.13 (m, 0.2H), 7.09 – 7.04 (m, 0.8H), 6.97 – 6.87 (m, 2H), 5.29 (bd, 0.8H), 5.06 (s, 0.4H), 4.88 (bd, 0.8H); **^{13}C { ^1H } NMR** { ^1H } (100 MHz, CDCl_3) δ 146.6 (d, J = 289.0 Hz), 146.1 (d, J = 292.7 Hz), 140.7, 139.9 (d, J = 1.9 Hz), 137.6, 137.1, 133.3, 132.9, 131.8, 131.8, 129.4, 129.2, 128.98, 128.95, 128.8 (d, J = 1.0 Hz), 128.7, 128.53, 128.52, 128.43, 128.38, 127.9 (d, J = 0.6 Hz), 127.0, 126.9, 126.5, 126.4, 122.6, 122.4, 95.40, 95.36, 84.9, 84.6, 49.4 (d, J = 1.7 Hz), 49.3 (d, J = 3.0 Hz); **^{19}F NMR** (377 MHz, CDCl_3) δ -14.22 (s, 0.87F, *major*), -18.84 (s, 0.13F, *minor*); **HRMS** (DART) m/z : $[\text{M}+\text{NH}_4]^+$ $[\text{C}_{20}\text{H}_{18}\text{FN}_2\text{OS}]^+$ Calcd 353.11184, found 353.11184; **IR** (ATR, CDCl_3 , cm^{-1}): 1786, 1569, 1497, 1432, 1361, 1263, 1155, 1104, 1001, 908.

(Cyclohexylmethyl)(2-(phenylethynyl)phenyl)carbamic fluoride (3.1h)



The title compound was prepared according to **Method A** from carbamoyl chloride **3.1h-Cl** (168 mg, 0.5 mmol), which was synthesized using known literature procedures.⁸¹ The crude material was purified by flash chromatography (0-5% EtOAc/pentane) and the desired product was isolated as viscous white oil (136 mg, 0.41 mmol, 82%, *rotamer ratio by ¹⁹F NMR*: 83:17). **¹H NMR** (400 MHz, CDCl₃) δ 7.69 – 7.62 (m, 1H), 7.60 – 7.52 (m, 2H), 7.47 – 7.33 (m, 5H), 7.31 – 7.25 (m, 1H), 3.79 – 3.64 (m, 0.8H), 3.61 – 3.43 (m, 1.2H), 1.94 – 1.54 (m, 6H), 1.31 – 0.92 (m, 5H); **¹³C {¹H} NMR** (176 MHz, CDCl₃) δ 147.1 (d, *J* = 287.3 Hz), 141.9, 141.3, 133.6, 133.2, 131.84, 131.76, 129.5, 129.3, 129.0, 128.9, 128.60, 128.58, 128.4, 128.3, 127.95, 122.80, 122.7, 122.6, 122.5, 95.3, 95.3, 85.3, 85.0, 58.0, 57.7, 36.9, 36.5, 31.1, 30.8, 26.41, 26.38, 25.83, 25.82; **¹⁹F NMR** (377 MHz, CDCl₃) δ -12.94 (s, 0.83F, *major*), -20.04 (s, 0.17F, *minor*); **HRMS** (DART) *m/z*: [M+H]⁺ [C₂₂H₂₃FNO]⁺ Calcd 336.17583, found 336.17654; **IR** (ATR, CDCl₃, cm⁻¹) 2924, 2219, 1783, 1596, 1497, 1449, 1342, 1209, 1069, 907.

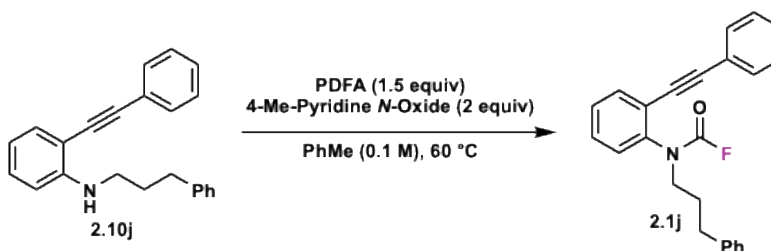
Methyl(2-(phenylethynyl)phenyl)carbamic fluoride (3.1i)



The title compound was prepared according to **Method B** from **3.10i** (129 mg, 0.51 mmol scale), which was synthesized using known literature procedures.¹⁹ The crude material was purified by flash chromatography (0-10% EtOAc/hexanes) and the desired product was isolated as an opaque yellow oil (78 mg, 0.32 mmol, 62%, *rotamer ratio by ¹⁹F NMR*: 84:16). **¹H NMR** (400 MHz, CDCl₃) δ 7.65 – 7.59 (m, 1H), 7.57 – 7.51 (m, 2H), 7.42 – 7.34 (m, 5.2H), 7.30 – 7.26 (m, 0.8H), 3.40 (bd, 0.6H), 3.38 (s, 2.4H); **¹³C {¹H} NMR** (101 MHz, CDCl₃) δ 146.8 (d, *J* = 286.4 Hz), 142.8 (d, *J* = 1.2 Hz), 142.0 (d, *J* = 2.1 Hz), 133.4, 133.0, 131.9, 131.8, 129.7, 129.6, 129.0, 129.0,

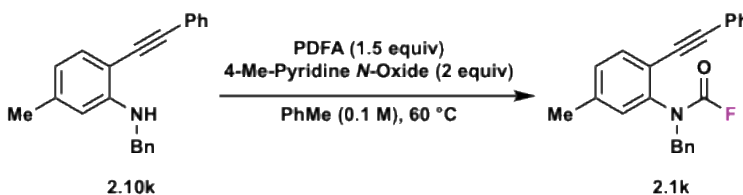
128.61, 128.57, 128.53, 127.5 (d, $J = 1.3$ Hz), 127.3, 122.7, 122.5, 122.1, 121.8, 95.2, 95.2, 84.8, 84.5, 38.6 (d, $J = 2.1$ Hz), 38.3 (d, $J = 2.7$ Hz); ^{19}F NMR (377 MHz, CDCl_3) δ -14.88 (s, 0.84F, *major*), -19.30 (s, 0.16F, *minor*); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_{13}\text{FNO}]^+$ Calcd 354.0976, found 354.0975; IR (ATR, MeCN, cm^{-1}) 3011, 2920, 1786, 1590, 1487, 1350, 1210, 860, 652.

(3-phenylpropyl)(2-(phenylethynyl)phenyl)carbamic fluoride (3.1j)



The title compound was prepared according to **Method A** from **3.10j** (193 mg, 0.93 mmol). The crude material was purified by flash chromatography (0-10% EtOAc/hexanes) and the desired product was isolated as a light-yellow oil (168 mg, 0.47 mmol, 51%, *rotamer ratio by ^{19}F NMR*: 92:8). ^1H NMR (400 MHz, CDCl_3) δ 7.74 – 7.66 (m, 1H), 7.66 – 7.56 (m, 2H), 7.49 – 7.37 (m, 5H), 7.36 – 7.28 (m, 3H), 7.28 – 7.16 (m, 3H), 4.03 – 3.77 (m, 2H), 2.85 – 2.67 (m, 2H), 2.08 (p, $J = 7.6$ Hz, 2H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 146.6 (d, $J = 287.8$ Hz), 141.3, 141.0, 140.8, 140.6 (d, $J = 2.0$ Hz), 133.4, 133.0, 131.8, 131.7, 129.5, 129.4, 129.0, 128.9, 128.55, 128.53, 128.47, 128.42, 128.32, 128.28, 128.22, 127.8, 126.2, 126.1, 122.7, 122.6, 122.5, 122.4, 95.4, 95.3, 85.2, 85.0, 51.4 (d, $J = 2.2$ Hz), 51.1 (d, $J = 2.0$ Hz), 33.0, 32.9, 30.2, 29.2; ^{19}F NMR (377 MHz, CDCl_3) δ -13.03 (s, 0.92F, *major*), -20.30 (s, 0.08F, *minor*); HRMS (DART) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{24}\text{H}_{21}\text{FNO}]^+$ Calcd 358.16018, found 358.15930; IR (ATR, MeCN, cm^{-1}) 2940, 1788, 1496, 1452, 1396, 1288, 964, 755, 690.

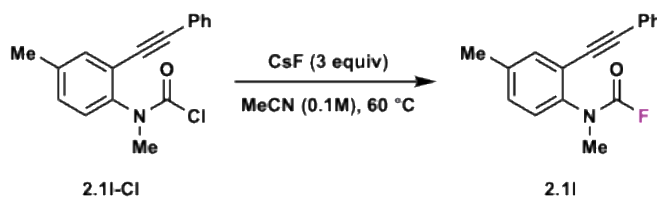
Benzyl(2-(phenylethynyl)-5-methylphenyl)carbamic fluoride (3.1k)



The title compound was prepared according to **Method B** from **3.10k** (171 mg, 0.50 mmol), which was synthesized using known literature procedures.¹⁹ The crude material was purified by flash chromatography (5-10%

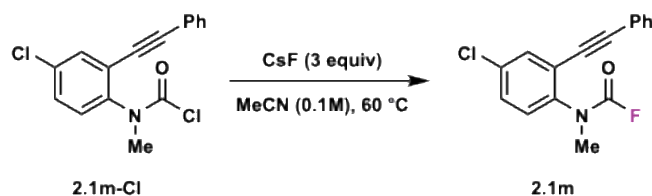
EtOAc/hexanes) and the desired product was isolated as a light-yellow oil (137 mg, 0.40 mmol, 80%, *rotamer ratio* by ^{19}F NMR: 85:15). ^1H NMR (400 MHz, CDCl_3) δ 7.54 – 7.48 (m, 2.15H), 7.46 (d, J = 7.9 Hz, 0.85H), 7.40 – 7.34 (m, 3H), 7.33 – 7.21 (m, 5H), 7.17 – 7.09 (m, 1H), 6.89 (s, 0.15H), 6.77 (s, 0.85H), 5.12 (bd, 0.8H), 4.88 (s, 0.4H), 4.67 (bd, 0.8H), 2.30 (s, 0.6H), 2.29 (s, 2.4H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 147.1 (d, J = 287.9 Hz), 141.1, 140.2 (d, J = 1.7 Hz), 140.0, 139.7, 135.8, 135.6, 133.1, 132.6, 131.8, 131.7, 129.4, 129.3, 129.2, 129.0, 128.78, 128.77, 128.6, 128.5, 128.3, 128.2, 122.9, 122.8, 119.4, 119.1, 94.65, 94.58, 85.2, 85.0, 55.3 (d, J = 1.7 Hz), 55.1 (d, J = 2.0 Hz), 21.5, 21.4; ^{19}F NMR (377 MHz, CDCl_3) δ -14.33 (s, 0.85F, *major*), -19.26 (s, 0.15F, *minor*); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{23}\text{H}_{19}\text{FNO}]^+$ Calcd 344.1445, found 344.1443; IR (ATR, CDCl_3 , cm^{-1}) 1789, 1503, 1384, 1289, 1029, 824, 756, 691.

Methyl(2-(phenylethynyl)-4-methylphenyl)carbamate fluoride (3.11)



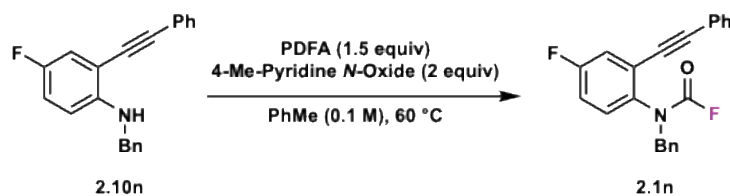
The title compound was prepared according to **Method A** from carbamoyl chloride **3.11-Cl** (267 mg, 1.0 mmol), which was synthesized using known literature procedures.⁸¹ The crude material was purified by flash chromatography (0-10% EtOAc/pentane) and the desired product was isolated as white crystalline solid (130 mg, 0.49 mmol, 49%, *rotamer ratio* by ^{19}F NMR: 82:18). ^1H NMR (400 MHz, CDCl_3) δ 7.57 – 7.48 (m, 2H), 7.44 (bs, 0.2H), 7.42 (bs, 0.8H), 7.39 – 7.33 (m, 3H), 7.25 – 7.13 (m, 2H), 3.37 (d, J = 1.0 Hz, 0.6H), 3.36 (d, J = 0.6 Hz, 2.4H), 2.37 (d, J = 2.4 Hz, 3H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 146.9 (d, J = 285.9 Hz) 140.24, 139.51, 138.60, 138.55, 133.70, 133.31, 133.30, 131.81, 131.78, 131.69, 130.48, 130.33, 128.91, 128.85, 128.55, 127.13, 126.90, 122.76, 122.57, 121.58, 121.33, 94.68, 94.65, 84.98, 84.64, 38.61, 38.3 (d, J = 2.4 Hz) 20.98; ^{19}F NMR (377 MHz, CDCl_3) δ -15.26 (s, 0.82F, *major*), -19.44 (s, 0.18F, *minor*); HRMS (DART) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{15}\text{FNO}]^+$ Calcd 268.11323, found 268.11307; IR (ATR, CDCl_3 , cm^{-1}) 1781, 1741, 1597, 1572, 1492, 1424, 1376, 1287, 1107, 920; mp ($^\circ\text{C}$) 47.7-50.2.

Methyl(2-(phenylethynyl)-4-chlorophenyl)carbamic fluoride (3.1m)



The title compound was prepared according to **Method A** from carbamoyl chloride **3.1m-Cl** (288 mg, 1.0 mmol), which was synthesized using known literature procedures.⁸¹ The crude material was purified by flash chromatography (0-5% EtOAc/pentane) and the desired product was isolated as white solid (187 mg, 0.65 mmol, 64%, *rotamer ratio by ¹⁹F NMR 85:15*). **¹H NMR** (700 MHz, CDCl₃) δ 7.60 (d, *J* = 2.4 Hz, 0.2H), 7.59 (d, *J* = 2.4 Hz, 0.8H), 7.55 – 7.51 (m, 2H), 7.40 – 7.34 (m, 4H), 7.29 (d, *J* = 6.9 Hz, 0.2H), 7.21 (d, *J* = 8.5 Hz, 0.8H), 3.38 (s, 0.6H), 3.36 (s, 2.4H); **¹³C {¹H} NMR** (176 MHz, CDCl₃) δ 146.6 (d, *J* = 291.7 Hz), 146.5 (d, *J* = 286.8 Hz), 141.2, 140.5, 134.3, 134.2, 133.0, 132.6, 131.9, 131.8, 129.8, 129.7, 129.42, 129.35, 128.8, 128.7, 128.5, 123.7, 123.4, 122.2, 122.0, 96.40, 96.37, 83.6, 83.3, 38.6, 38.2 (d, *J* = 2.4 Hz); **¹⁹F NMR** (659 MHz, CDCl₃) δ -14.49 (s, 0.85F, *major*), -18.99 (s, 0.15F, *minor*); **HRMS** (DART) *m/z*: [M+H]⁺ [C₁₆H₁₂ClFNO]⁺ Calcd 288.05861, found 288.05953; **IR** (ATR, CDCl₃, cm⁻¹) 1788, 1596, 1569, 1486, 1420, 1367, 1303, 1132, 1092, 1025, 885, 690; **mp** (°C) 41.5-43.0.

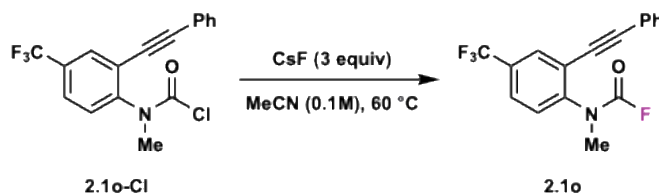
Benzyl(2-(phenylethynyl)-4-fluorophenyl)carbamic fluoride (3.1n)



The title compound was prepared according to **Method B** from **3.10n** (695 mg, 2.00 mmol), which was synthesized using known literature procedures.¹⁹ The crude material was purified by flash chromatography (0-15% EtOAc/Hexanes) and the desired product was isolated as a clear oil (0.527 mg, 1.52 mmol, 76%, *rotamer ratio by ¹⁹F NMR 84:16*). **¹H NMR** (400 MHz, CDCl₃) δ 7.57 – 7.49 (m, 2H), 7.44 – 7.35 (m, 3H), 7.32 – 7.23 (m, 6H), 6.99 – 6.90 (m, 1.2H), 6.89 – 6.84 (m, 0.8H), 5.15 (bd, 0.8H), 4.85 (s, 0.4H), 4.59 (bd, 0.8H); **¹³C {¹H} NMR** (101 MHz, CDCl₃) δ 161.7 (d, *J* = 249.5 Hz), 147.0 (d, *J* = 288.2 Hz), 146.5 (d, *J* = 293.0 Hz), 137.2 (d, *J* = 3.2 Hz),

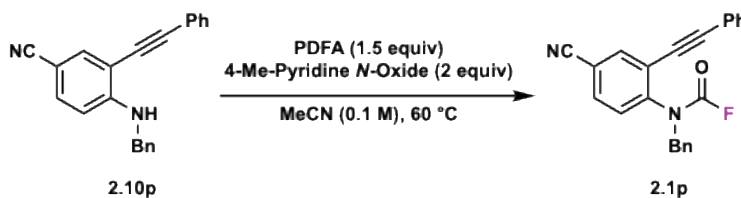
136.4 (dd, $J = 3.1, 1.9$ Hz), 135.4, 135.3, 132.0, 131.9, 130.5 (d, $J = 8.4$ Hz), 130.1 (d, $J = 9.4$ Hz), 129.39, 129.35, 129.30, 128.9, 128.8, 128.6, 128.5, 128.4, 124.5 (d, $J = 10.5$ Hz), 122.2, 122.0, 119.9 (d, $J = 24.3$ Hz), 119.4 (d, $J = 24.3$ Hz), 116.5 (d, $J = 23.1$ Hz), 116.3 (d, $J = 22.8$ Hz), 96.3, 84.0 (d, $J = 3.0$ Hz), 83.8 (d, $J = 2.9$ Hz), 55.3 (d, $J = 1.6$ Hz), 55.1 (d, $J = 1.7$ Hz); ^{19}F NMR (377 MHz, CDCl_3) δ -14.18 (s, 0.85F, *major*), -19.64 (s, 0.15F, *minor*), -112.11 – -112.26 (m, 1F, *major and minor*); HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+ [\text{C}_{22}\text{H}_{15}\text{F}_2\text{NONa}]^+$ Calcd 370.1014, found 370.1007; IR (ATR, MeCN, cm^{-1}) 1789, 1579, 1499, 1392, 1265, 1194, 756, 690.

Methyl(2-(phenylethynyl)-4-trifluoromethylphenyl)carbamate fluoride (3.1o)



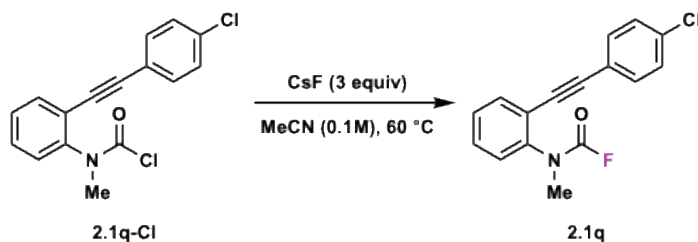
The title compound was prepared according to **Method A** from carbamoyl chloride **3.1o-Cl** (321 mg, 1.0 mmol), which was synthesized using known literature procedures.⁸¹ The crude material was purified by flash chromatography (0-10% EtOAc/pentane) and the desired product was isolated as a white solid (186 mg, 0.58 mmol, 58%, *rotamer ratio by ^{19}F NMR 80:20*). ^1H NMR (700 MHz, CDCl_3) δ 7.90 (d, $J = 2.2$ Hz, 0.2H), 7.88 (d, $J = 2.2$ Hz, 0.8H), 7.67 – 7.62 (m, 1H), 7.58 – 7.52 (m, 2H), 7.50 (d, $J = 8.3$ Hz, 0.2H), 7.44 – 7.37 (m, 3.8H), 3.43 (s, 0.6H), 3.40 (s, 2.4H); ^{13}C $\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) δ 146.5 (d, $J = 292.2$ Hz), 146.2 (d, $J = 287.9$ Hz), 144.7, 132.0, 131.9, 131.0 (q, $J = 33.3$ Hz), 130.6 (q, $J = 2.8$ Hz), 130.1 (q, $J = 3.7$ Hz), 129.6, 129.5, 128.7, 128.3, 128.0, 126.3 (bq), 126.23 (q, $J = 3.3$ Hz), 123.3 (q, $J = 272.8$ Hz), 123.2, 122.8, 122.0, 121.8, 97.0, 83.6, 83.2, 38.5, 38.2; ^{19}F NMR (377 MHz, CDCl_3) δ -13.82 (s, 0.80F, *major*), -18.56 (s, 0.20F, *minor*), -62.92 (m, 3F, *major and minor*); HRMS (DART) m/z : $[\text{M}+\text{H}]^+ [\text{C}_{17}\text{H}_{12}\text{F}_4\text{NO}]^+$ 322.08496, found 322.08440; IR (ATR, CDCl_3 , cm^{-1}) 1791, 1611, 1597, 1503, 1373, 1336, 1277, 1166, 1111, 896, 764; mp ($^{\circ}\text{C}$) 51.2-53.0.

Benzyl(2-(phenylethynyl)-4-cyanophenyl)carbamate fluoride (3.1p)



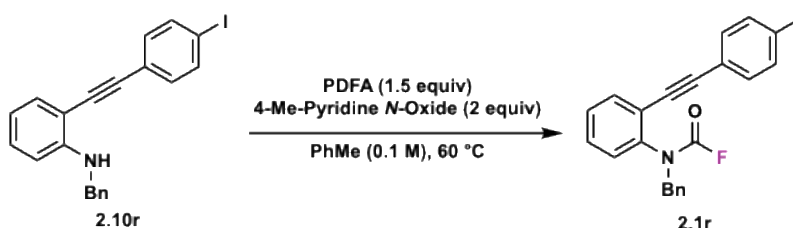
The title compound was prepared according to **Method B** from **3.10p** (425 mg, 1.20 mmol), which was synthesized using known literature procedures.¹⁹ The crude material was purified by flash chromatography (5-10% EtOAc/hexanes) and the desired product was isolated as a light-yellow solid (253 mg, 0.73 mmol, 61%, *rotamer ratio by ¹⁹F NMR*: 80:20). **¹H NMR** (400 MHz, CDCl₃) δ 7.90 (d, *J* = 1.9 Hz, 0.2H), 7.85 (d, *J* = 1.9 Hz, 0.8H), 7.57 – 7.48 (m, 3H), 7.46 – 7.35 (m, 3H), 7.33 – 7.14 (m, 5.2H), 7.05 (d, *J* = 8.2 Hz, 0.8H), 5.07 (bs, 0.8H), 4.90 (bs, 0.4H), 4.76 (bs, 0.8H); **¹³C {¹H} NMR** (101 MHz, CDCl₃) δ 146.2 (d, *J* = 289.8 Hz), 145.9 (d, *J* = 283.3 Hz), 143.7 (d, *J* = 1.7 Hz), 137.0, 136.4, 134.9, 134.7, 132.3, 132.2, 132.04, 131.96, 129.9, 129.8, 129.4, 129.2, 129.1, 128.9, 128.73, 128.71, 128.6, 124.5, 121.5, 117.32, 117.26, 113.0, 113.0, 98.1, 98.0, 83.0, 82.7, 55.1 (d, *J* = 1.6 Hz), 54.8; **¹⁹F NMR** (377 MHz, CDCl₃) δ -12.63 (s, 0.80F, *major*), -18.74 (s, 0.20F, *minor*); **HRMS** (ESI) *m/z*: [M+H]⁺ [C₂₃H₁₆FN₂O]⁺ Calcd 355.1241, found 355.1238; **IR** (ATR, MeCN, cm⁻¹) 2232, 1793, 1497, 1387, 1265, 1082, 745, 690, 636; **mp** (°C) 67.4-70.1.

(2-((4-chlorophenyl)ethynyl)phenyl)(methyl)carbamic fluoride (3.1q)



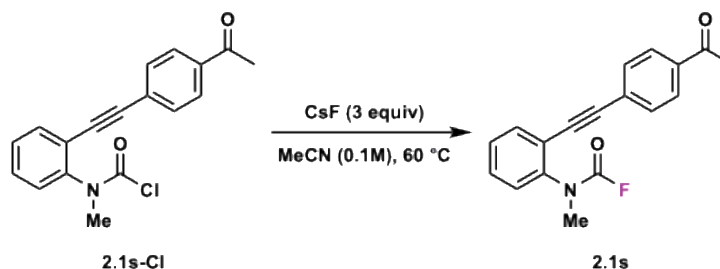
The title compound was prepared according to **Method A** from carbamoyl chloride **3.1q-Cl** (144 mg, 0.50 mmol), which was synthesized using known literature procedures.¹⁸ The crude material was purified by flash chromatography (0-10% EtOAc/pentane) and the desired product was isolated as a white crystalline solid (125 mg, 0.43 mmol, 86%, *rotamer ratio by ¹⁹F NMR*: 82:18). **¹H NMR** (400 MHz, CDCl₃) δ 7.64 – 7.57 (m, 1H), 7.49 – 7.31 (m, 6.2H), 7.28 (dd, *J* = 7.7, 1.5 Hz, 0.8H), 3.38 (bd, 0.6H), 3.37 (bs, 2.4H); **¹³C {¹H} NMR** (176 MHz, CDCl₃) δ 146.8 (d, *J* = 286.5 Hz), 142.7, 142.0 (d, *J* = 1.5 Hz), 135.1, 135.0, 133.4, 133.0, 132.9, 123.0, 129.8, 129.0, 128.6, 128.5, 127.4, 127.2, 121.7, 121.5, 121.2, 121.0, 93.94, 93.90, 85.8, 85.4, 38.6 (d, *J* = 1.0 Hz), 38.3 (d, *J* = 2.2 Hz); **¹⁹F NMR** (377 MHz, CDCl₃) δ -14.72 (s, 0.82F, *major*), -19.20 (s, 0.18F, *minor*); **HRMS** (DART) *m/z*: [M+H]⁺ [C₁₆H₁₂ClFNO]⁺ Calcd 288.05861, found 288.05933; **IR** (ATR, CDCl₃, cm⁻¹) 1787, 1596, 1496, 1485, 1401, 1367, 1303, 1177, 1080, 885; **mp** (°C) 40.0-43.5.

2-((4-iodophenyl)ethynyl)phenyl(benzyl)carbamic fluoride (3.1r)



The title compound was prepared according to **Method B** from **3.10r** (524 mg, 1.15 mmol). The crude material was purified by flash chromatography (0-10% EtOAc/hexanes) and the desired product was isolated as a light-orange oil (235 mg, 0.92 mmol, 45%, *rotamer ratio by ^{19}F NMR: 81:19*). ^1H NMR (400 MHz, CDCl_3) δ 7.74 – 7.71 (m, 1H), 7.70 (m, 1H), 7.60 (dd, J = 7.4, 1.9 Hz, 0.2H), 7.56 (dd, J = 7.6, 1.6 Hz, 0.8H), 7.35 – 7.18 (m, 9H), 7.11 – 7.04 (m, 0.2H), 6.95 (dd, J = 7.7, 1.5 Hz, 0.8H), 5.07 (bs, 0.8H), 4.85 (bs, 0.4H), 4.66 (bs, 0.8H); ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ 147.0 (d, J = 288.4 Hz), 141.2, 140.4 (d, J = 1.9 Hz), 137.8, 135.6, 135.4, 134.0, 133.8, 133.4, 133.3, 133.2, 132.9, 132.3, 132.2, 129.7, 129.4, 129.3, 128.8, 128.7, 128.7, 128.6, 128.4, 128.4, 122.4, 122.2, 122.0, 95.1, 95.0, 94.3, 94.3, 86.5, 86.2, 55.4 (d, J = 1.7 Hz), 55.2 (d, J = 2.1 Hz); ^{19}F NMR (377 MHz, CDCl_3) δ -14.07 (s, 0.81F, *major*), -19.30 (s, 0.19F, *minor*); HRMS (ESI) m/z : $[\text{M}]^+$ $[\text{C}_{22}\text{H}_{15}\text{FINO}]^+$ 455.0177, found 455.0163; IR (ATR, MeCN, cm^{-1}) 1789, 1495, 1451, 1392, 1112, 1005, 863, 747, 670.

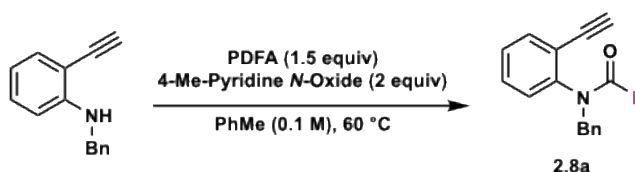
2-((4-acetylphenyl)ethynyl)phenyl(methyl)carbamic fluoride (3.1s)



The title compound was prepared according to **Method A** from carbamoyl chloride **3.1s-Cl** (295 mg, 1.00 mmol), which was synthesized using known literature procedures.¹⁸ The crude material was purified by flash chromatography (0-10% EtOAc/pentane) and the desired product was isolated as a clear oil (161 mg, 0.55 mmol, 55%, *rotamer ratio by ^{19}F NMR: 82:18*). ^1H NMR (700 MHz, CDCl_3) δ 7.96 – 7.92 (m, 2H), 7.65 – 7.57 (m, 3H), 7.43 (td, J = 7.7, 1.7 Hz, 1H), 7.40 – 7.35 (m, 1.2H), 7.30 (dd, J = 7.8, 1.3 Hz, 0.8H), 3.39 (s, 0.6H), 3.38 (s, 2.4H),

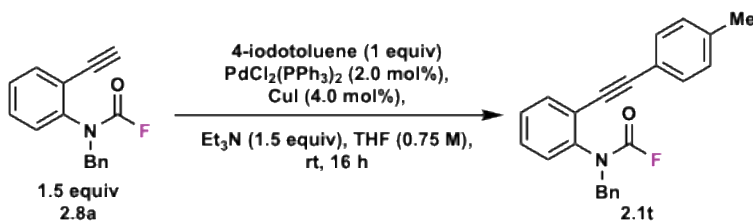
2.61 (bs, 3H); ^{13}C { ^1H } NMR (176 MHz, CDCl_3) δ 197.3, 197.3, 146.7 (d, $J = 286.6$ Hz), 142.9, 142.2 (d, $J = 1.2$ Hz), 136.82, 136.78, 133.6, 133.2, 132.0, 131.9, 130.3, 130.2, 128.65, 138.60, 128.5, 127.5, 127.4, 127.3, 121.5, 121.2, 94.12, 94.10, 87.9, 87.5, 38.7 (d, $J = 1.1$ Hz), 38.4 (d, $J = 2.3$ Hz), 26.78; ^{19}F NMR (377 MHz, CDCl_3) δ -14.61 (s, 0.82F, *major*), -19.13 (s, 0.18F, *minor*); HRMS (DART) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{18}\text{H}_{15}\text{FNO}_2]^+$ 296.10814, found 296.10770; IR (ATR, CDCl_3 , cm^{-1}) 1786, 1681, 1600, 1486, 1359, 1261, 1181, 1069, 945, 835; mp ($^\circ\text{C}$) 92.0-94.5.

Benzyl(2-ethynylphenyl)carbamic fluoride (3.8a)



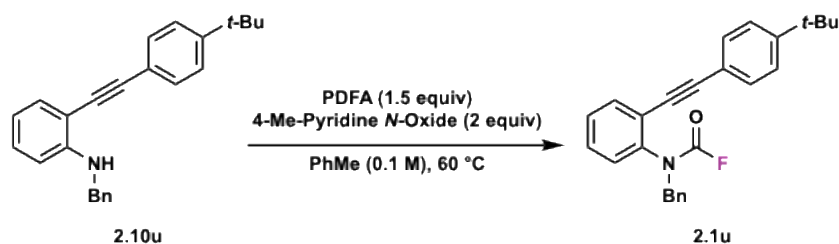
The title compound was prepared according to **Method B** from *N*-(benzyl)-2-(phenylethynyl)aniline (481 mg, 1.90 mmol), which was synthesized using known literature procedures.¹⁹ The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as a colorless oil (0.175 g, 1.31 mmol, 69% yield, *rotamer ratio by* ^{19}F NMR: 85:15). ^1H NMR (400 MHz, CDCl_3) δ 7.61 – 7.57 (m, 0.2H), 7.55 (dd, $J = 7.3, 2.0$ Hz, 0.8H), 7.37 – 7.18 (m, 7H), 7.03 – 6.99 (m, 0.2H), 6.88 (dd, $J = 7.7, 1.4$ Hz, 0.8H), 5.17 (bd, 0.8H), 4.84 (s, 0.4H), 4.57 (bd, 0.8H), 3.36 (s, 0.2H), 3.32 (s, 0.8H); ^{13}C { ^1H } NMR (176 MHz, CDCl_3) δ 146.8 (d, $J = 287.7$ Hz), 146.5 (d, $J = 292.3$ Hz), 141.7, 140.8 (d, $J = 1.7$ Hz), 135.6, 135.5, 134.2, 133.8, 129.9, 129.7, 129.2, 128.8, 128.7, 128.63, 128.60, 128.5, 128.32, 128.30, 121.3, 121.1, 83.2, 83.1, 79.3, 79.1, 55.0 (d, $J = 1.9$ Hz), 54.9 (d, $J = 2.0$ Hz); ^{19}F NMR (377 MHz, CDCl_3) δ -14.07 (s, 0.85F, *major*), -19.51 (s, 0.15F, *minor*); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_{13}\text{FNO}]^+$ Calcd 254.0976, found 254.0975; IR (ATR, CDCl_3 , cm^{-1}) 3293, 2930, 1786, 1513, 1250, 1034, 836, 696, 631, 628, 592, 571.

(2-((4-methylphenyl)ethynyl)phenyl)(benzyl)carbamic fluoride (3.1t)



To solution of 4-iodotoluene (1.0 equiv, 0.60 mmol, 131 mg), PdCl₂(PPh₃)₂ (2.0 mol%, 0.012 mmol, 8.4 mg) and CuI (4.0 mol%, 0.024 mmol, 4.6 mg) in anhydrous THF (0.25 M, 2.4 mL) was added NEt₃ (1.5 equiv, 0.9 mmol, 125 μ L) dropwise at rt under argon. After stirring for 5 minutes, terminal alkyne **3.8a** (1.5 equiv, 0.9 mmol, 309 mg) was added neat and dropwise to the reaction mixture (slightly exothermic). Upon full consumption of the starting material, the reaction mixture was filtered through a pad of celite, eluting with EtOAc (3x). The combined organics were sequentially washed with H₂O (2x) and brine (1x), dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by flash chromatography (0-10% EtOAc/pentane) and the desired product was isolated as a yellow oil (223 mg, 0.65 mmol, 61%, *rotamer ratio by* ¹⁹F NMR: 87:13). ¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, *J* = 7.6, 1.7 Hz, 0.2H), 7.60 (dd, *J* = 7.7, 1.6 Hz, 0.8H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.37 – 7.18 (m, 9H), 7.07 (dd, *J* = 7.8, 1.4 Hz, 0.2H), 6.95 (d, *J* = 7.9 Hz, 0.8H), 5.19 (bd, 0.8H), 4.91 (s, 0.4H), 4.67 (bd, 0.8H), 2.42 (s, 3H); ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 147.1 (d, *J* = 288.1 Hz), 146.6 (d, *J* = 290.4 Hz), 141.0, 140.2 (d, *J* = 1.6 Hz), 139.3, 139.2, 135.7, 135.6, 133.3, 132.8, 132.4 (d, *J* = 10.6 Hz), 131.8, 131.7, 129.3 (d, *J* = 11.1 Hz), 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 122.7, 122.4, 119.6, 119.4, 95.7, 95.6, 84.5, 84.2, 55.1 (d, *J* = 1.7 Hz), 55.0 (d, *J* = 2.0 Hz), 21.7; ¹⁹F NMR (377 MHz, CDCl₃) δ -14.25 (s, 0.87F), -19.48 (s, 0.13F); HRMS (ESI) [M+H]⁺ [C₂₃H₁₉FNO]⁺ Calcd 344.1445, found 344.1446; IR (ATR, MeCN, cm⁻¹) 2216, 1785, 1596, 1512, 1390, 1267, 1252, 1209, 816, 635.

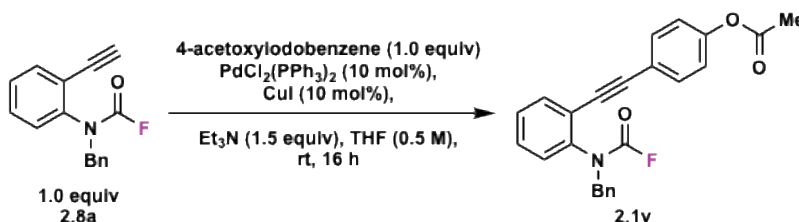
(2-((4-tertbutylphenyl)ethynyl)phenyl)(methyl)carbamic fluoride (3.1u)



The title compound was prepared according to **Method B** from **3.10u** (323 mg, 1.60 mmol), which was synthesized using known literature procedures.⁸² The crude material was purified by flash chromatography (0-10% EtOAc/pentane) and the desired product was isolated as a white solid (285 mg, 0.74 mmol, 46% yield, *rotamer ratio by* ¹⁹F NMR: 85:15). ¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, *J* = 7.6, 1.7 Hz, 0.2H), 7.60 (dd, *J* = 7.7, 1.6 Hz, 0.8H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.36 – 7.21 (m, 7H), 7.08 (dd, *J* = 7.9, 1.4 Hz, 0.2H),

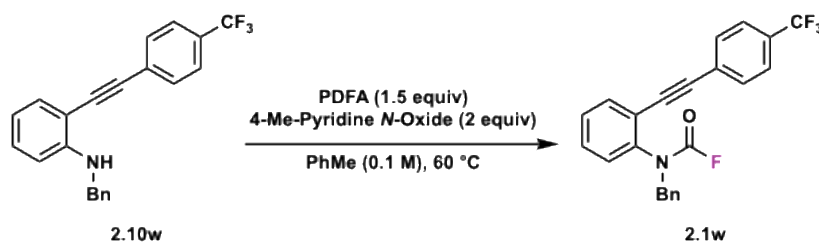
6.95 (dd, $J = 8.0, 1.3$ Hz, 0.8H), 5.22 (bd, 0.8H), 4.92 (s, 0.4H), 4.66 (bd, 0.8H), 1.38 (s, 9H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 152.4, 152.3, 147.1 (d, $J = 288.0$ Hz), 146.5 (d, $J = 292.1$ Hz), 141.1, 140.2 (d, $J = 1.8$ Hz), 135.7, 135.6, 133.3, 132.8, 131.6, 131.5, 129.2, 129.1, 128.9, 128.8, 128.7, 128.63, 128.60, 128.5, 128.4, 128.3, 128.2, 125.6, 122.7, 122.4, 119.7, 119.5, 95.7, 84.5, 84.2, 55.1 (d, $J = 2.1$ Hz), 54.9 (d, $J = 2.2$ Hz), 35.0, 31.3; ^{19}F NMR (377 MHz, CDCl_3) δ -14.17 (s, 0.85F, *major*), -19.42 (s, 0.15F, *minor*); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{26}\text{H}_{25}\text{FNO}]^+$ Calcd 386.19147, found 386.19159; IR (ATR, CDCl_3 , cm^{-1}) 2963, 1783, 1453, 1267, 1267, 1083, 907, 834, 730, 697, 639, 563; mp ($^{\circ}\text{C}$) 86.2-89.0.

Benzyl(2-((4-acetoxy)(phenyl)ethynyl)phenyl)carbamic fluoride (3.1v)



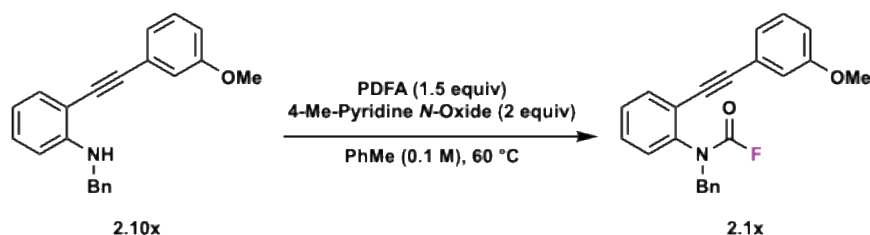
A flame-dried 2-dram vial charged with $\text{PdCl}_2(\text{PPh}_3)_2$ (10 mol%, 0.02 mmol, 14.0 mg), CuI (10 mol%, 0.02 mmol, 3.8 mg), and 4-acetoxyiodobenzene (1 equiv, 0.2 mmol, 52.4 mg). The vial was purged with N_2 before THF (0.5 M, 0.4 mL) and NEt_3 (3 equiv, 0.6 mmol, 80 μL) were added. While stirring, terminal alkyne **3.8a** (1 equiv, 0.20 mmol, 77.5 mg) in minimal amount of THF (50 μL) was added dropwise, and the reaction was stirred at rt for 16 h. When the reaction was complete, the crude mixture was dry loaded on to silica gel then purified by flash chromatography (15% EtOAc/hexanes). The desired product was isolated as an orange oil (64 mg, 1.66 mmol, 83% yield, *rotamer ratio by* ^{19}F NMR: 87:13). ^1H NMR (700 MHz, C_6D_6) δ 7.55 (dd, $J = 7.6, 1.4$ Hz, 0.2H), 7.51 (dd, $J = 7.7, 1.4$ Hz, 0.8H), 7.43 – 7.41 (m, 2H), 7.29 – 7.22 (m, 1.6H), 7.18 – 7.14 (m, 5.4H), 7.08 – 7.03 (m, 2H), 7.00 (d, $J = 7.9$ Hz, 0.2H), 6.84 (dd, $J = 7.9, 0.8$ Hz, 0.8H), 5.07 (bd, 0.8H), 4.80 (s, 0.4H), 4.58 (bd, 0.8H), 2.27 (bs, 3H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 169.2, 151.1, 151.0, 147.1 (d, $J = 288.2$ Hz), 141.2, 140.4 (d, $J = 1.7$ Hz), 135.7, 135.5, 133.4, 133.1, 133.0, 132.9, 129.4, 129.3, 129.2, 128.8, 128.7, 128.6, 128.4, 128.3, 122.5, 122.0, 120.2, 94.5, 85.2, 84.9, 55.3 (d, $J = 1.7$ Hz), 55.1 (d, $J = 1.9$ Hz), 29.8, 21.3; ^{19}F NMR (377 MHz, CDCl_3) δ -14.19 (s, 0.87F, *major*), -19.33 (s, 0.13F, *minor*); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{24}\text{H}_{19}\text{FNO}_2]^+$ Calcd 388.1344, found 388.1335; IR (ATR, CDCl_3 , cm^{-1}) 1789, 1508, 1392, 1195, 909, 746, 699, 617.

Benzyl(2-((4-trifluoromethylphenyl)ethynyl)phenyl)carbamic fluoride (3.1w)



The title compound was prepared according to **Method B** from **3.10w** (656 mg, 1.87 mmol), which was synthesized using known literature procedures.⁸² The crude material was purified by flash chromatography (0-10% EtOAc/pentane) and the desired product was isolated as a clear oil (96 mg, 0.45 mmol, 24% yield, *rotamer ratio by* ¹⁹F NMR: 87:13). ¹H NMR (400 MHz, CDCl₃) δ 7.74 – 7.54 (m, 5H), 7.44 – 7.23 (m, 7H), 7.20 – 7.10 (m, 0.15H), 7.03 (dd, *J* = 7.6, 1.5 Hz, 0.85H), 5.09 (bs, 0.8H), 4.90 (s, 0.4H), 4.73 (bs, 0.8H); ¹³C {¹H} NMR (176 MHz, CDCl₃) 147.0 (d, *J* = 288.3 Hz), 146.4 (d, *J* = 292.0 Hz), 141.4, 140.6, 135.5, 135.4, 133.6, 133.1, 132.1, 132.0, 130.6 (q, *J* = 32.5 Hz), 130.0, 129.8, 129.3, 128.9, 128.73, 128.71, 128.6, 128.5, 128.40, 128.35, 126.5, 126.3, 125.5 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.4 Hz), 122.1, 121.9, 93.63, 93.59, 87.4, 87.1, 55.5, 55.3; ¹⁹F NMR (377 MHz, CDCl₃) δ -13.94 (s, 0.87F, *major*), -19.22 (s, 0.13F, *minor*), -62.87 (s, 3F, *major and minor*); HRMS (ESI) *m/z*: [M+H]⁺ [C₂₃H₁₆F₄NO]⁺ Calcd 398.11625, found 398.11694; IR (ATR, CDCl₃, cm⁻¹) 2965, 1784, 1487, 1452, 1391, 1320, 1124, 1064, 839, 745, 698, 638.

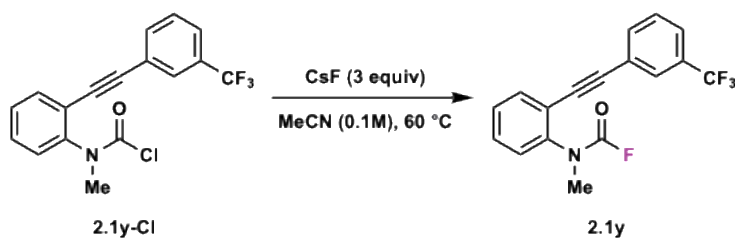
(2-((3-methoxyphenyl)ethynyl)phenyl)(benzyl)carbamic fluoride (3.1x)



The title compound was prepared according to **Method B** from **3.10x** (323 mg, 0.90 mmol), which was synthesized using known literature procedures.⁸² The crude material was purified by flash chromatography (0-10% EtOAc/pentane) and the desired product was isolated as a yellow oil (223 mg, 0.65 mmol, 61%; *rotamer ratio by* ¹⁹F NMR: 87:13). ¹H NMR (400 MHz, CDCl₃) δ 7.65 (dd, *J* = 7.5, 1.7 Hz, 0.2H), 7.61 (dd, *J* = 7.6, 1.6 Hz, 0.8H), 7.39 – 7.24 (m, 8H), 7.18 – 7.16 (m, 1H), 7.12 – 7.06 (m, 1.2H), 6.97 (dd, *J* = 8.1, 1.4 Hz, 1.8H), 5.17 (bd, 0.8H),

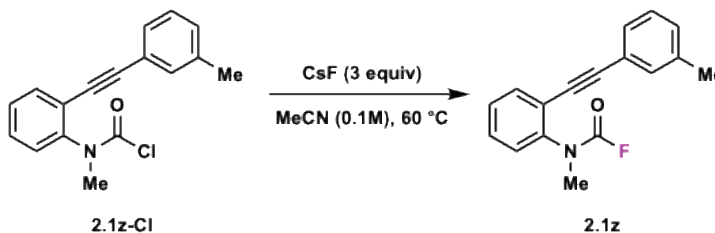
4.91 (s, 0.4H), 4.69 (bd, 0.8H), 3.87 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 159.5, 147.1 (d, J = 288.1 Hz), 146.5 (d, J = 292.1 Hz), 141.2, 140.3 (d, J = 1.7 Hz), 135.7, 135.5, 133.4, 132.9, 131.8, 129.6, 129.4, 129.2, 129.1, 128.8, 128.6, 128.5, 128.4, 128.30, 128.26, 128.0, 124.4, 124.3, 123.7, 123.5, 122.5, 122.2, 116.6, 116.5, 115.7, 115.4, 95.3, 84.9, 84.6, 55.4, 55.2 (d, J = 1.7 Hz), 55.0 (d, J = 2.0 Hz); ^{19}F NMR (377 MHz, CDCl_3) δ -14.10 (s, 0.87F, *major*), -1.39 (s, 0.13F, *minor*); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{23}\text{H}_{19}\text{FNO}_2]^+$ Calcd 360.1394, found 360.1390; IR (ATR, MeCN, cm^{-1}) 3065, 2836, 1789, 1596, 1495, 1392, 1283, 1230, 1040, 747, 699.

(2-((3-trifluoromethylphenyl)ethynyl)phenyl)(methyl)carbamic fluoride (3.1y)



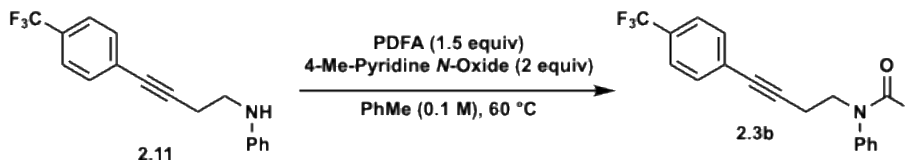
The title compound was prepared according to **Method A** from carbamoyl chloride **3.1y-Cl** (160 mg, 0.50 mmol), which was synthesized using known literature procedures.¹⁸ The crude material was purified by flash chromatography (0-10% EtOAc/pentane) and the desired product was isolated as a yellow oil (123 mg, 0.38 mmol, 77%, *rotamer ratio by* ^{19}F NMR: 83:17). ^1H NMR (400 MHz, CDCl_3) δ 7.77 (m, 1H), 7.73 – 7.46 (m, 1H), 7.66 – 7.59 (m, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.46 – 7.35 (m, 2.2H), 7.30 (dd, J = 7.5, 1.6 Hz, 0.8H), 3.40 (d, J = 1.0 Hz, 0.6H), 3.39 (s, 2.4H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 146.7 (d, J = 286.6 Hz), 142.9 (d, J = 1.2 Hz), 142.2 (d, J = 2.1 Hz), 135.1 (d, J = 0.9 Hz), 134.9, 133.6, 133.1, 131.2 (q, J = 32.7 Hz), 130.3, 130.1, 129.2, 128.64, 128.59, 128.4 (q, J = 3.9 Hz), 127.49 (d, J = 1.3 Hz), 127.3, 125.63 – 125.35 (m), 123.8 (q, J = 272.5 Hz), 123.6, 123.4, 121.4, 121.1, 93.3, 86.3, 85.9, 38.7 (d, J = 2.0 Hz), 38.4 (d, J = 2.6 Hz); ^{19}F NMR (377 MHz, CDCl_3) δ -14.61 (s, 0.83F), -19.14 (s, 0.17F), -62.94 (s, 3F); HRMS (DART) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{12}\text{F}_4\text{NO}]^+$ Calcd 322.08495, found 322.08575; IR (ATR, CDCl_3 , cm^{-1}) 1789, 1726, 1599, 1494, 1452, 1372, 1338, 1068, 1032, 910, 795; mp ($^\circ\text{C}$) 44.5-45.6.

(2-((3-methylphenyl)ethynyl)phenyl)(methyl)carbamic fluoride (3.1z)



The title compound was prepared according to **Method A** from carbamoyl chloride **3.1z-Cl** (134 mg, 0.50 mmol), which was synthesized using known literature procedures.¹⁸ The crude material was purified by flash chromatography (0-10% EtOAc/pentane) and the desired product was isolated as a white crystalline solid (111 mg, 0.41 mmol, 83%, *rotamer ratio by ¹⁹F NMR*: 82:18). **¹H NMR** (400 MHz, CDCl₃) δ 7.63 – 7.57 (m, 1H), 7.41 – 7.31 (m, 4H), 7.29 – 7.22 (m, 2H), 7.20 – 7.15 (m, 1H), 3.39 (d, *J* = 1.1 Hz, 0.6H), 3.38 (d, *J* = 0.6 Hz, 2.4H), 2.36 (s, 3H); **¹³C {¹H} NMR** (176 MHz, CDCl₃) δ 146.82 (d, *J* = 291.2 Hz), 146.76 (d, *J* = 286.4 Hz), 142.7, 141.9, 139.0, 138.3, 133.4, 133.0, 132.3, 132.2, 129.94, 129.87, 129.6, 129.4, 129.0, 128.8, 128.52, 128.47, 127.4, 127.2, 122.4, 122.3, 122.1, 121.8, 95.38, 95.36, 84.4, 84.1, 38.6, 38.3 (d, *J* = 2.0 Hz), 21.3; **¹⁹F NMR** (377 MHz, CDCl₃) δ -14.92 (s, 0.82F), -19.29 (s, 0.18F); **HRMS** (DART) *m/z*: [M+H]⁺ [C₁₇H₁₅FNO]⁺ Calcd 268.11322, found 268.11327; **IR** (ATR, CDCl₃, cm⁻¹) 1787, 1596, 1579, 1493, 1373, 1292, 1103, 945, 746; **mp** (°C) 66.5-71.0.

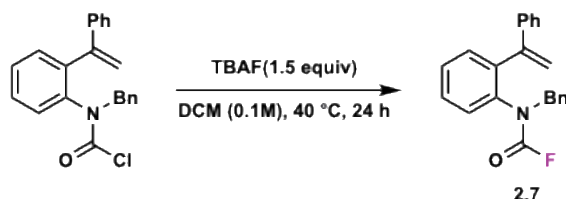
***N*-phenyl-*N*-(4-(4-trifluoromethyl)phenyl)but-3-ynyl)carbamic fluoride (3.3b)**



The title compound was prepared according to **Method B** from **3.11** (188 mg, 0.56 mmol). The crude material was purified by flash chromatography (5-10% EtOAc/hexanes) and the desired product was isolated as a clear oil (129 mg, 0.36 mmol, 64%, *rotamer ratio by ¹⁹F NMR*: 75:25). **¹H NMR** (400 MHz, CDCl₃) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.50 – 7.27 (m, 7H), 4.05 – 3.88 (m, 2H), 2.76 (t, *J* = 6.9 Hz, 1.5H), 2.71 (t, *J* = 6.8 Hz, 0.5H); **¹³C {¹H} NMR** (101 MHz, CDCl₃) δ 146.8 (d, *J* = 291.7 Hz), 146.5 (d, *J* = 288.6 Hz), 139.8, 139.1, 137.3 (d, *J* = 10.7 Hz), 133.84 (d, *J* = 19.4 Hz), 131.9, 130.0, 129.7, 128.8, 128.64, 128.57, 128.46, 128.2, 127.1, 127.0, 126.7, 125.3 (bq, *J* = 3.7 Hz),

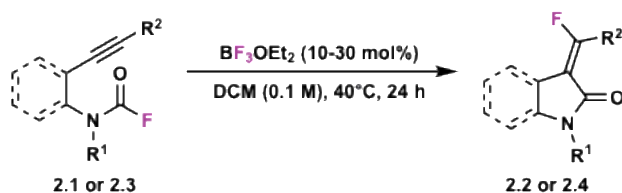
124.0 (q, $J = 272.1$ Hz), 88.6, 88.0, 82.1, 81.7, 50.3, 49.7, 19.7, 18.7; **^{19}F NMR** (377 MHz, CDCl_3) δ -13.57 (s, 0.8F), -18.39 (s, 0.2F), -62.79 (s, 3F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{18}\text{H}_{14}\text{F}_4\text{NO}]^+$ Calcd 336.1006, found 336.1004; **IR** (ATR, CDCl_3 , cm^{-1}) 2940, 2252, 1784, 1618, 1560, 1403, 1323, 1168, 1126, 1061, 843, 748, 700.

Benzyl(2-(1-phenylvinyl)phenyl)carbamic fluoride (3.7)



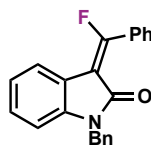
An oven dried 2 dr vial charged with benzyl(2-(1-phenylvinyl)phenyl)carbamic chloride⁸³ (1 equiv, 0.50 mmol, 174 mg), TBAF (1 M in DCM, 1.5 equiv, 1.5 mL), and CH_2Cl_2 (0.1 M, 5 mL). The vial was sealed with a Teflon-lined cap and placed in a pre-heated oil bath at 40 °C for 24 h. The reaction was cooled to rt and was filtered through a silica pad, eluted with CH_2Cl_2 , and then concentrated *in vacuo*. The crude material was purified by flash chromatography (0-5% EtOAc/hexanes) and the desired product was isolated as a light-yellow solid (151 mg, 0.45 mmol, 91% yield). **^1H NMR** (400 MHz, CDCl_3) δ 7.52 – 7.46 (m, 1H), 7.44 – 7.22 (m, 10H), 7.15 (dd, $J = 6.3, 3.2$ Hz, 1.6H), 7.11 (dd, $J = 6.5, 2.8$ Hz, 0.4H), 6.99 (d, $J = 7.9$ Hz, 0.2H), 6.78 (d, $J = 7.9$ Hz, 0.8H), 5.80 (d, $J = 1.1$ Hz, 1H), 5.47 (d, $J = 1.0$ Hz, 0.2H), 5.42 (d, $J = 1.0$ Hz, 0.8H), 4.76 (dd, $J = 14.8, 2.5$ Hz, 0.8H), 4.30 (bm, 0.4H), 3.86 (dd, $J = 14.8, 2.9$ Hz, 0.8H); **^{13}C { ^1H } NMR** (101 MHz, CDCl_3) δ 147.5, 147.4, 146.6 (d, $J = 287.1$ Hz), 140.2, 140.1, 139.7, 139.5 (d, $J = 1.3$ Hz), 137.9, 136.9 (d, $J = 1.5$ Hz), 136.0, 135.9, 131.8, 131.7, 129.7, 129.0, 128.8, 128.71, 128.69, 128.65, 128.63, 128.5, 128.4, 128.3, 128.2, 128.1, 126.7, 117.5, 117.4, 54.2 (d, $J = 2.4$ Hz), 54.1 (d, $J = 2.0$ Hz); **^{19}F NMR** (377 MHz, CDCl_3) δ -13.02 (s, 0.8F), -20.25 (s, 0.2F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{22}\text{H}_{19}\text{FNO}]^+$ Calcd 332.1445, found 332.1433; **IR** (ATR, MeCN, cm^{-1}) 3062, 1788, 1494, 1451, 1392, 1212, 1082, 910, 768, 746, 703, 640; **mp** (°C) 85.4-87.1.

3.8.5 General Procedures and Characterization Data for the Products (Method C)



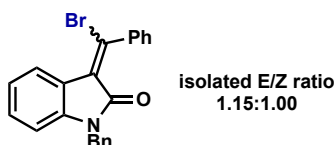
Carbamoyl fluoride **3.1** (1 equiv) was weighed directly into an oven-dried 1-dram vial equipped with a stir bar. The vial was evacuated and backfilled with N₂ three times before anhydrous CH₂Cl₂ (1.0 mL) was added. A stock solution of BF₃·OEt₂ (50 µL) in CH₂Cl₂ (1.0 mL) was prepared under N₂ and the indicated amount was transferred to the reaction vessel. The vial was sealed with a Teflon-lined cap and placed in a pre-heated oil bath at 40 °C for 24 h. The reaction was cooled to rt and filtered across a pad of silica gel, eluted with CH₂Cl₂ (3 x 1 mL), then concentrated in vacuo. If necessary, the crude reaction mixture was either purified by flash chromatography using the reported eluent to yield **3.2**. Some substrates isomerized upon flash chromatography, leading to an isolated product with differing E/Z selectivity compared to crude sample. These substrates are noted in the text. Isomeric ratio was determined from the crude sample by ¹⁹F NMR spectroscopy using anhydrous α,α,α-trifluorotoluene (10 µL) as an internal standard. The product mixture was taken up in neutralized CDCl₃ for ¹⁹F NMR analysis, as trace acid promotes slight E/Z-isomerization of the products **3.2**. A single scan NMR experiment was used to ensure full relaxation of all ¹⁹F signals. CDCl₃ is stored over solid K₂CO₃ or 4Å mol sieves and filtered through a short plug of basic alumina before use.

(E)-1-benzyl-3-(fluoro(phenyl)methylene)indolin-2-one (3.2a)



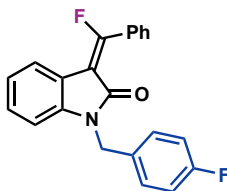
The title compound was prepared according from **3.1a** (32.9 mg, 0.10 mmol) using 10 mol% BF₃·OEt₂. The crude material was purified by flash chromatography (0-10% EtOAc/hexanes) and the desired product was isolated as a bright yellow solid (32 mg, 0.099 mmol, 99%, >95:5 E/Z). ¹H NMR (400 MHz, CDCl₃) δ 8.16 – 8.08 (m, 2H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.61 – 7.48 (m, 3H), 7.40 – 7.25 (m, 5H), 7.23 (td, *J* = 7.8, 1.3 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 4.99 (s, 2H); ¹³C {¹H} NMR (101 MHz, CDCl₃) δ 166.6 (d, *J* = 275.7 Hz), 166.5 (d, *J* = 20.4 Hz), 141.0, 136.2, 132.2, 129.8, 129.6 (d, *J* = 7.7 Hz), 128.92 (d, *J* = 2.5 Hz), 128.87, 128.1, 127.7, 127.4, 125.0 (d, *J* = 14.5 Hz), 122.6, 121.8 (d, *J* = 1.5 Hz), 110.4 (d, *J* = 20.1 Hz), 108.8, 43.8; ¹⁹F NMR (377 MHz, CDCl₃) δ -76.04 (s, 1F); HRMS (ESI) *m/z*: [M+H]⁺ [C₂₂H₁₇FNO]⁺ Calcd 330.1280, found 330.1293; IR (ATR, MeCN, cm⁻¹) 1702, 1604, 1468, 1346, 1177, 1105, 1076, 766, 747, 697; mp (°C) 119.9-122.1.

1-benzyl-3-(bromo(phenyl)methylene)indolin-2-one (3.2a-Br)



(*E*)-isomer: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.50 (d, $J = 6.7$ Hz, 1H), 7.62 – 7.22 (m, 10H), 7.17 – 7.07 (m, $J = 7.5$, 1.2 Hz, 2H), 6.74 (d, $J = 7.9$ Hz, 1H), 4.89 (s, 2H); (*Z*)-isomer: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.61 – 7.24 (m, 11H), 6.74 (d, $J = 7.9$ Hz, 1H), 6.66 (td, $J = 7.7$, 1.1 Hz, 1H), 6.27 (dd, $J = 7.7$, 1.2 Hz, 1H), 5.05 (s, 2H); *E:Z*-mixture: $^{13}\text{C} \{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 165.8, 164.6, 143.1, 141.0, 141.0, 140.5, 138.2, 136.0, 135.9, 133.2, 130.3, 130.1, 129.9, 129.6, 129.4, 128.9, 128.8, 128.7, 128.3, 127.9, 127.8, 127.7, 127.6, 127.4, 127.1, 126.6, 125.0, 123.2, 122.8, 122.4, 122.1, 121.9, 109.1, 108.8, 44.0, 43.6; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{22}\text{H}_{17}\text{BrNO}]^+$ Calcd 390.0488, found 390.0478; IR (ATR, MeCN, cm^{-1}) 3054, 1707, 1600, 1467, 1345, 1174, 1105, 1080, 964, 783, 747, 697; mp ($^{\circ}\text{C}$) 128.6-130.0.

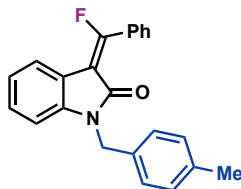
(*E*)-1-(4-fluorobenzyl)-3-(fluoro(phenyl)methylene)indolin-2-one (3.2b)



The title compound was prepared according to **Method C** from **3.1b** (34.7 mg, 0.10 mmol) using 20 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-10% EtOAc/Hexanes) and the desired product was isolated as a bright yellow solid (28 mg, 0.080 mmol, 80%, 94:6 *E/Z* crude, 92:8 *E/Z* after isolation). $^1\text{H NMR}$ (700 MHz, CDCl_3) δ 8.12 – 8.04 (m, 2H), 7.83 (d, $J = 7.6$ Hz, 1H), 7.58 – 7.48 (m, 3H), 7.29 (dd, $J = 8.5$, 5.3 Hz, 2H), 7.21 (td, $J = 7.7$, 0.9 Hz, 1H), 7.08 (t, $J = 7.6$ Hz, 1H), 7.02 – 6.95 (m, 2H), 6.74 (d, $J = 7.7$ Hz, 1H), 4.92 (s, 2H); $^{13}\text{C} \{^1\text{H}\}$ NMR (176 MHz, CDCl_3) δ 166.7 (d, $J = 276.0$ Hz), 166.5 (d, $J = 20.4$ Hz), 162.4 (d, $J = 246.0$ Hz), 140.7, 132.3, 132.0 (d, $J = 3.6$ Hz), 129.64 (d, $J = 25.4$ Hz), 129.61 (d, $J = 7.5$ Hz), 129.2 (d, $J = 8.1$ Hz), 128.9, 128.2, 125.2 (d, $J = 14.5$ Hz), 122.8, 121.9, 115.8 (d, $J = 21.6$ Hz), 110.3 (d, $J = 20.2$ Hz), 108.6, 43.1. $^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ -74.70 (s, 1F), -114.81 (tt, $J = 9.0$, 5.0 Hz, 1F); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$

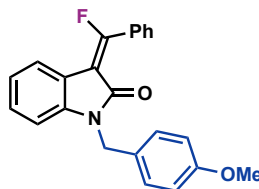
$[\text{C}_{22}\text{H}_{16}\text{F}_2\text{NO}]^+$ Calcd 348.1194, found 348.1180; **IR** (ATR, MeCN, cm^{-1}) 2928, 1690, 1604, 1509, 1468, 1346, 1219, 1177, 1094, 875, 745, 689, 599; **mp** ($^{\circ}\text{C}$) 73.5-76.1.

(E)-1-(4-methylbenzyl)-3-(fluoro(phenyl)methylene)indolin-2-one (3.2c)



The title compound was prepared according to **Method C** from **3.1c** (34.3 mg, 0.10 mmol) using 20 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-10% EtOAc/hexanes) and the desired product was isolated as an orange powder (30 mg, 0.088 mmol, 88%, >95:5 *E:Z*). **^1H NMR** (400 MHz, CDCl_3) δ 8.14 – 8.08 (m, 2H), 7.84 (d, $J = 7.6$, 1H), 7.57 – 7.49 (m, 3H), 7.22 (m, 3H), 7.12 (d, $J = 7.8$ Hz, 2H), 7.07 (t, $J = 7.6$, 1H), 6.78 (d, $J = 7.8$ Hz, 1H), 4.93 (s, 2H), 2.32 (s, 3H); **^{13}C { ^1H } NMR** (101 MHz, CDCl_3) δ 166.5 (d, $J = 275.6$ Hz), 166.4 (d, $J = 20.3$ Hz), 141.0, 137.3, 133.2, 132.2, 129.7 (d, $J = 25.4$ Hz), 129.6 (d, $J = 7.6$ Hz), 129.5, 128.9 (d, $J = 2.5$ Hz), 128.1, 127.5, 125.0 (d, $J = 14.5$ Hz), 122.5, 121.8 (d, $J = 1.5$ Hz), 110.4 (d, $J = 20.0$ Hz), 108.8, 43.5, 21.2; **^{19}F NMR** (377 MHz, CDCl_3) δ -76.32 (s, 1F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{23}\text{H}_{19}\text{FNO}]^+$ Calcd 344.1445, found 344.1432; **IR** (ATR, MeCN, cm^{-1}) 2944, 2253, 1703, 1605, 1468, 1377, 1349, 1177, 1105, 1038, 919, 782, 602; **mp** ($^{\circ}\text{C}$) 107.1-110.0.

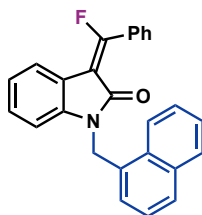
(E)-1-(4-methoxybenzyl)-3-(fluoro(phenyl)methylene)indolin-2-one (3.2d)



The title compound was prepared according to **Method C** from **3.1d** (35.9 mg, 0.10 mmol) using 20 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The desired product was isolated as an orange powder after filtration and concentration *in vacuo* (25 mg, 0.069 mmol, 69%, >95:5 *E:Z* crude, 94:6 *E:Z* after isolation). **^1H NMR** (400 MHz, CDCl_3) δ 8.14 – 8.09 (m, 2H), 7.85 (d, $J = 7.6$ Hz, 1H), 7.59 – 7.50 (m, 3H), 7.33 – 7.26 (m, 2H), 7.23 (td, $J = 7.6$, 1.3 Hz, 1H), 7.09 (t, $J = 7.6$, 1H), 6.89 – 6.84 (m, 2H), 6.81 (d, $J = 7.6$ Hz, 1H), 4.92 (s, 2H), 3.79 (s, 3H); **^{13}C { ^1H } NMR** (101 MHz, CDCl_3) δ

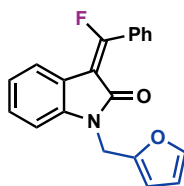
166.5 (d, $J = 275.6$ Hz), 166.4 (d, $J = 20.4$ Hz), 159.1, 140.9, 132.2, 129.8, 129.6 (d, $J = 7.5$ Hz), 128.9 (2C), 128.3, 128.1, 125.0 (d, $J = 14.6$ Hz), 122.5, 121.8, 114.2, 110.4 (d, $J = 20.1$ Hz), 108.8, 55.3, 43.2; ^{19}F NMR (377 MHz, CDCl_3) δ -75.16 (s, 1F); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{23}\text{H}_{19}\text{FNO}_2]^+$ Calcd 360.1394, found 360.1378; IR (ATR, CDCl_3 , cm^{-1}) 2928, 1706, 1609, 1513, 1468, 1348, 1248, 1177, 1104, 1034, 756, 692, 602; mp ($^{\circ}\text{C}$) 117.8-120.2.

(E)-1-(naphtha-1-ylmethyl)-3-(fluoro(phenyl)methylene)indolin-2-one (3.2e)



The title compound was prepared according to **Method C** from **3.1e** (37.9 mg, 0.10 mmol) using 20 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-10% EtOAc/hexanes) and the desired product was isolated as a bright orange solid (34 mg, 0.090 mmol, 90%, 95:5 *E:Z*). ^1H NMR (400 MHz, CDCl_3) δ 8.18 – 8.12 (m, 3H), 7.93 – 7.87 (m, 2H), 7.79 (d, $J = 8.1$ Hz, 1H), 7.63 – 7.51 (m, 5H), 7.42 – 7.35 (m, 1H), 7.28 (dd, $J = 7.1$, 1.3 Hz, 1H), 7.15 (td, $J = 7.7$, 1.4 Hz, 1H), 7.09 (td, $J = 7.6$, 1.2 Hz, 1H), 6.69 (dd, $J = 7.7$, 1.2 Hz, 1H), 5.47 (s, 2H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.7 (d, $J = 275.8$ Hz), 166.6 (d, $J = 20.4$ Hz), 141.2, 133.9, 132.2, 131.1, 130.8, 129.64 (d, $J = 25.1$ Hz), 129.62 (d, $J = 7.6$ Hz), 129.02, 128.96 (d, $J = 2.5$ Hz), 128.2, 128.1, 126.6, 126.0, 125.5, 125.0 (d, $J = 14.5$ Hz), 124.2, 122.9, 122.6, 121.8 (d, $J = 1.7$ Hz), 110.4 (d, $J = 20.2$ Hz), 109.2, 41.8; ^{19}F NMR (377 MHz, CDCl_3) δ -75.97 (s, 1F); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{26}\text{H}_{19}\text{FNO}]^+$ Calcd 380.1445, found 380.1439; IR (ATR, CDCl_3 , cm^{-1}) 2922, 1707, 1605, 1469, 1354, 1219, 1180, 1106, 767, 691, 575; mp ($^{\circ}\text{C}$) 55.2-59.8.

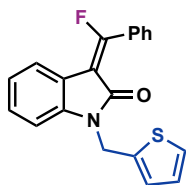
(E)-1-(furoan-2-ylmethyl)-3-(phenylmethylene)indolin-2-one (3.2f)



The title compound was prepared according to **Method C** from **3.1f** (31.9 mg, 0.10 mmol) using 20 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-15% EtOAc/hexanes) and the desired product was

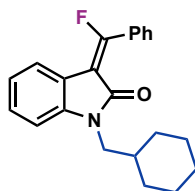
isolated as a dark orange powder (20 mg, 0.062 mmol, 62%, 95:5 *E:Z*). **¹H NMR** (400 MHz, CDCl₃) δ 8.09 – 8.03 (m, 2H), 7.82 (d, *J* = 7.6, 1H), 7.55 – 7.46 (m, 3H), 7.35 – 7.27 (m, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.32 – 6.28 (m, 2H), 4.93 (s, 2H); **¹³C {¹H} NMR** (101 MHz, CDCl₃) δ 166.6 (d, *J* = 275.8 Hz), 166.1 (d, *J* = 20.6 Hz), 149.7, 142.5, 140.7, 132.2, 129.8, 129.6 (d, *J* = 7.6 Hz), 129.0 (d, *J* = 2.5 Hz), 128.1, 125.0 (d, *J* = 14.5 Hz), 122.7, 121.8, 110.6, 110.3 (d, *J* = 21.4 Hz), 108.7, 108.6, 36.8; **¹⁹F NMR** (377 MHz, CDCl₃) δ -74.97 (s, 1F); **HRMS** (ESI) *m/z*: [M+Na]⁺ [C₂₀H₁₅FNO₂]⁺ Calcd 320.1081, found 320.1089; **IR** (ATR, MeCN, cm⁻¹) 1710, 1606, 1469, 1386, 1348, 1173, 1105, 1015, 782, 697; **mp** (°C) 84.2-88.6.

(*E*)-1-(thiophen-2-ylmethyl)-3-(phenylmethylene)indolin-2-one (3.2g)



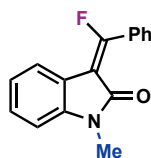
The title compound was prepared according to **Method C** from **3.1g** (33.5 mg, 0.10 mmol) using 20 mol% BF₃·OEt₂. The crude material was purified by flash chromatography (0-5% EtOAc/hexanes) and the desired product was isolated as a yellow solid (18 mg, 0.053 mmol, 53%, >95:5 *E:Z*). **¹H NMR** (700 MHz, CDCl₃) δ 8.08 (d, *J* = 7.0 Hz, 2H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.28 – 7.26 (m, 1H), 7.19 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.11 – 7.03 (m, 2H), 6.97 – 6.89 (m, 2H), 5.11 (s, 2H); **¹³C {¹H} NMR** (176 MHz, CDCl₃) δ 166.6 (d, *J* = 275.9 Hz), 166.0 (d, *J* = 20.5 Hz), 140.4, 138.6, 132.3, 129.7 (d, *J* = 25.0 Hz), 129.58 (d, *J* = 7.6 Hz), 128.9 (d, *J* = 2.5 Hz), 128.1, 127.0, 126.7, 125.4, 125.2 (d, *J* = 14.5 Hz), 122.7, 121.9 (d, *J* = 1.3 Hz), 110.2 (d, *J* = 20.3 Hz), 108.5, 38.6; **¹⁹F NMR** (377 MHz, CDCl₃) δ -74.88 (s, 1F); **HRMS** (ESI) *m/z*: [M+H]⁺ [C₂₀H₁₅FNOS]⁺ Calcd 336.0853, found 336.0845; **IR** (ATR, MeCN, cm⁻¹) 1706, 1606, 1468, 1344, 1180, 1104, 767, 748, 697, 566; **mp** (°C) 80.0-91.5.

(E)-1-(cyclohexylmethyl)-3-(fluoro(phenyl)methylene)indolin-2-one (3.2h)



The title compound was prepared according to **Method C** from **3.1h** (33.5 mg, 0.10 mmol) using 20 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-2.5% EtOAc/hexanes) and the desired product was isolated as an orange powder (28 mg, 0.084 mmol, 84%, 95:5 *E:Z*). **^1H NMR** (400 MHz, CDCl_3) δ 8.06 (m, 2H), 7.82 (d, $J = 7.5$, 1H), 7.55 – 7.45 (m, 3H), 7.29 – 7.25 (m, 1H), 7.07 (t, $J = 7.6$, 1H), 6.85 (d, $J = 7.9$ Hz, 1H), 3.57 (d, $J = 7.3$ Hz, 2H), 1.95 – 1.55 (m, 6H), 1.36 – 0.96 (m, 5H); **^{13}C { ^1H } NMR** (101 MHz, CDCl_3) δ 166.6 (d, $J = 20.2$ Hz), 166.2 (d, $J = 275.0$ Hz), 141.8, 132.1, 129.9, 129.6 (d, $J = 7.7$ Hz), 128.8 (d, $J = 2.5$ Hz), 128.1, 125.0 (d, $J = 14.6$ Hz), 122.2, 121.8 (d, $J = 1.4$ Hz), 110.5 (d, $J = 19.7$ Hz), 108.4, 46.6, 36.7, 31.2, 26.4, 25.9; **^{19}F NMR** (377 MHz, CDCl_3) δ -76.93 (s, 1F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{22}\text{H}_{23}\text{FNO}]^+$ Calcd 336.1758 found 336.1747; **IR** (ATR, MeCN, cm^{-1}) 2924, 2852, 1699, 1607, 1469, 1447, 1356, 1275, 1192, 1103, 748, 698, 595; **mp** ($^\circ\text{C}$) 69.5-73.4.

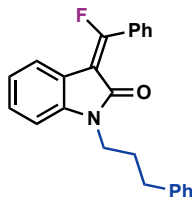
(E)-1-methyl-3-(fluoro(phenyl)methylene)indolin-2-one (3.2i)



The title compound was prepared according to **Method C** from **3.1i** (25.3 mg, 0.10 mmol) using 30 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-15% EtOAc/hexanes) and the desired product was isolated as a yellow solid (21 mg, 0.084 mmol, 84%, 95:5 *E:Z*). **^1H NMR** (400 MHz, CDCl_3) δ 8.08 – 8.01 (m, 2H), 7.81 (d, $J = 7.6$ Hz, 1H), 7.57 – 7.46 (m, 3H), 7.30 (td, $J = 7.7$, 1.2 Hz, 1H), 7.09 (t, $J = 7.6$ Hz, 1H), 6.83 (d, $J = 7.7$ Hz, 1H), 3.24 (s, 3H); **^{13}C { ^1H } NMR** (101 MHz, CDCl_3) δ 166.4 (d, $J = 20.3$ Hz), 166.3 (d, $J = 275.2$ Hz), 141.7, 132.1 (d, $J = 0.7$ Hz), 129.8, 129.5 (d, $J = 7.6$ Hz), 128.9 (d, $J = 2.5$ Hz), 128.0, 124.9 (d, $J = 14.3$ Hz), 122.5, 121.7 (d, $J = 1.4$ Hz), 110.5 (d, $J = 20.0$ Hz), 107.8, 26.2; **^{19}F NMR** (377 MHz, CDCl_3) δ -76.79 (s, 1F); **HRMS**

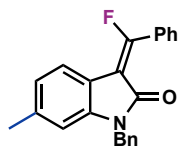
(ESI) m/z : $[M+H]^+$ $[C_{16}H_{13}FNO]^+$ Calcd 254.0976, found 254.0971; **IR** (ATR, MeCN, cm^{-1}) 1708, 1608, 1471, 1374, 1339, 1262, 1207, 1090, 766, 747, 697, 546; **mp** ($^{\circ}C$) 91.6-93.0.

(E)-1-(3-phenylpropyl)-3-(fluoro(phenyl)methylene)indolin-2-one (3.2j)



The title compound was prepared according to **Method C** from **3.1j** (35.7 mg, 0.10 mmol) using 20 mol% $BF_3 \cdot OEt_2$. The desired product was isolated as a yellow solid after filtration and concentration *in vacuo* (35 mg, 0.099 mmol, 99%, >95:5 *E:Z*). **1H NMR** (400 MHz, $CDCl_3$) δ 8.12 – 8.06 (m, 2H), 7.85 (d, $J = 7.6$, 1H), 7.58 – 7.49 (m, 3H), 7.36 – 7.26 (m, 3H), 7.26 – 7.18 (m, 3H), 7.11 (t, $J = 7.6$, 1H), 6.78 (d, $J = 7.9$ Hz, 1H), 3.91 – 3.76 (m, 2H), 2.81 – 2.69 (m, 2H), 2.17 – 1.99 (m, 2H); **^{13}C { 1H } NMR** (101 MHz, $CDCl_3$) δ 166.4 (d, $J = 20.2$ Hz), 166.3 (d, $J = 275.5$ Hz), 141.3, 141.1, 132.1 (d, $J = 1.1$ Hz), 129.7 (d, $J = 25.2$ Hz), 129.6 (d, $J = 7.6$ Hz), 128.9 (d, $J = 2.6$ Hz), 128.6, 128.4, 128.1, 126.2, 125.1 (d, $J = 14.4$ Hz), 122.4, 121.9 (d, $J = 1.7$ Hz), 110.5 (d, $J = 19.7$ Hz), 108.0, 39.8, 33.4, 29.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -76.62 (s, 1F); **HRMS** (ESI) m/z : $[M+H]^+$ $[C_{24}H_{21}FNO]^+$ Calcd 358.1602, found 358.1589; **IR** (ATR, MeCN, cm^{-1}) 2929, 1707, 1606, 1468, 1355, 1168, 1106, 748, 698; **mp** ($^{\circ}C$) 64.2-68.5.

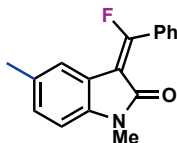
(E)-1-benzyl-3-(fluoro(phenyl)methylene)-5-methylindolin-2-one (3.2k)



The title compound was prepared according to **Method C** from **3.1k** (34.3 mg, 0.10 mmol) using 20 mol% $BF_3 \cdot OEt_2$. The desired product was isolated as a yellow solid after filtration and concentration *in vacuo* (34 mg, 0.099 mmol, 99%, 95:5 *E:Z*). **1H NMR** (400 MHz, $CDCl_3$) δ 8.08 (dd, $J = 7.4$, 1.9 Hz, 2H), 7.71 (d, $J = 7.7$ Hz, 1H), 7.57 – 7.46 (m, 3H), 7.36 – 7.22 (m, 5H), 6.88 (d, $J = 7.8$ Hz, 1H), 6.58 (s, 1H), 4.95 (s, 2H), 2.33 (s, 3H); **^{13}C { 1H } NMR** (101 MHz, $CDCl_3$) δ 166.8 (d, $J = 20.6$ Hz), 165.7 (d, $J = 274.3$ Hz), 141.1, 139.3 (d, $J = 2.7$ Hz), 136.3, 131.9, 129.7 (d, $J = 25.2$ Hz), 129.4 (d, $J = 7.6$ Hz), 128.8, 128.0, 127.5, 127.2, 124.7 (d, $J = 14.1$ Hz), 123.2, 119.1

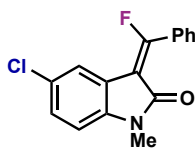
(d, $J = 1.5$ Hz), 110.3 (d, $J = 20.6$ Hz), 109.5, 43.6, 22.1; ^{19}F NMR (377 MHz, CDCl_3) δ -77.69 (s, 1F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{23}\text{H}_{19}\text{FNO}]^+$ Calcd 344.1445, found 344.1435; **IR** (ATR, MeCN, cm^{-1}) 2924, 1709, 1617, 1454, 1378, 1275, 1123, 814, 698, 626; **mp** ($^{\circ}\text{C}$) 113.7-116.6.

(*E*)-1-methyl-3-(fluoro(phenyl)methylene)-4-methylindolin-2-one (3.2l)



The title compound was prepared according to **Method C** from **3.1l** (26.7 mg, 0.10 mmol) using 30 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-5% EtOAc/hexanes) and the desired product was isolated as an orange powder (23 mg, 0.088 mmol, 88%, >95:5 *E:Z*). ^1H NMR (400 MHz, CDCl_3) δ 8.07 – 8.01 (m, 2H), 7.64 (s, 1H), 7.54 – 7.46 (m, 3H), 7.11 (d, $J = 7.9$ Hz, 1H), 6.72 (d, $J = 7.9$ Hz, 1H), 3.22 (s, 3H), 2.39 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.4 (d, $J = 20.3$ Hz), 166.0 (d, $J = 274.8$ Hz), 139.6, 132.0 (d, $J = 9.5$ Hz), 129.8 (d, $J = 25.3$ Hz), 129.5 (d, $J = 7.5$ Hz), 129.3 (d, $J = 2.5$ Hz), 128.6 (d, $J = 15.1$ Hz), 128.0, 125.7 (d, $J = 14.1$ Hz), 121.7 (d, $J = 1.5$ Hz), 110.7 (d, $J = 20.0$ Hz), 107.6, 26.2, 21.4; ^{19}F NMR (377 MHz, CDCl_3) δ -77.15 (s, 1F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{15}\text{FNO}]^+$ Calcd 268.1132, found 268.1125; **IR** (ATR, MeCN, cm^{-1}) 2925, 1705, 1633, 1447, 1340, 1262, 1096, 761, 689, 653, 559; **mp** ($^{\circ}\text{C}$) 59.8 – 63.2.

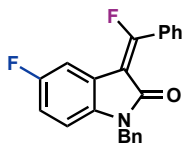
(*E*)-1-methyl-5-chloro-3-(fluoro(phenyl)methylene)indolin-2-one (3.2m)



The title compound was prepared according to **Method C** from **3.1m** (28.8 mg, 0.10 mmol scale) using 30 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-10% EtOAc/hexanes) and the desired product was isolated as a crystalline yellow solid (28 mg, 0.097 mmol, 97%, 94:6 *E:Z*). ^1H NMR (400 MHz, CDCl_3) δ 8.12 – 8.00 (m, 2H), 7.77 (d, $J = 2.1$ Hz, 1H), 7.59 – 7.46 (m, 3H), 7.26 (dd, $J = 8.3, 2.1$ Hz, 1H), 6.74 (d, $J = 8.3$ Hz, 1H), 3.22 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 167.1 (d, $J = 276.9$ Hz), 166.0 (d, $J = 19.9$ Hz), 140.1, 132.5, 129.6 (d, $J = 7.9$ Hz), 129.2 (d, $J = 25.0$ Hz), 128.6 (d, $J = 2.2$ Hz), 128.1, 127.8, 125.0 (d, $J = 15.0$ Hz),

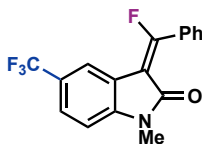
123.0, 109.8 (d, $J = 19.7$ Hz), 108.6, 26.3; ^{19}F NMR (377 MHz, CDCl_3) δ -76.10 (s, 1F); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_{12}\text{ClFNO}]^+$ Calcd 288.0586, found 288.0582; IR (ATR, MeCN, cm^{-1}) 2931, 1710, 1600, 1495, 1396, 1329, 1122, 843, 169, 748, 697; mp ($^{\circ}\text{C}$) 114.7-117.3.

(*E*)-1-benzyl-5-fluoro-3-(fluoro(phenyl)methylene)indolin-2-one (3.2n)



The title compound was prepared according to **Method C** from **3.1n** (34.7 mg, 0.10 mmol) using 20 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-10% EtOAc/hexanes) and the desired product was isolated as a yellow powder (29 mg, 0.082 mmol, 82%, >95:5 *E:Z*). ^1H NMR (400 MHz, CDCl_3) δ 8.17 – 8.08 (m, 2H), 7.60 – 7.49 (m, 4H), 7.36 – 7.24 (m, 5H), 6.90 (td, $J = 8.9, 2.6$ Hz, 1H), 6.64 (dd, $J = 8.6, 4.3$ Hz, 1H), 4.95 (s, 2H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 167.2 (d, $J = 277.7$ Hz), 166.2 (d, $J = 19.7$ Hz), 159.0 (d, $J = 238.6$ Hz), 136.8 (d, $J = 1.4$ Hz), 135.8, 132.5, 129.6 (d, $J = 7.9$ Hz), 129.2 (d, $J = 25.1$ Hz), 128.8, 128.1, 127.7, 127.3, 122.7 (d, $J = 9.6$ Hz), 115.0 (dd, $J = 24.0, 2.2$ Hz), 112.6 (dd, $J = 26.5, 14.7$ Hz), 110.3 (dd, $J = 19.5, 2.8$ Hz), 109.0 (d, $J = 8.3$ Hz), 43.8; ^{19}F NMR (377 MHz, CDCl_3) δ -73.73 (s, 1F), -120.98 (tdd, $J = 9.0, 4.4, 1.6$ Hz, 1F); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{22}\text{H}_{16}\text{F}_2\text{NO}]^+$ 348.1195, found 348.1201; IR (ATR, Acetone, cm^{-1}) 1709, 1579, 1482, 1387, 1346, 1168, 1105, 802, 781, 697, 637, 613; mp ($^{\circ}\text{C}$) 119.9-122.1

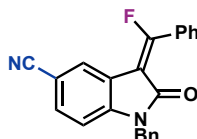
(*E*)-1-methyl-5-trifluoromethyl-3-(fluoro(phenyl)methylene)indolin-2-one (3.2o)



The title compound was prepared according to **Method C** from **3.1o** (32.1 mg, 0.10 mmol) using 30 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-7.5% EtOAc/hexanes) and the desired product was isolated as a yellow solid (27 mg, 0.084 mmol, 84%, >95:5 *E:Z*). ^1H NMR (700 MHz, CDCl_3) δ 8.08 – 8.04 (m, 3H), 7.57 (t, $J = 7.6$ Hz, 2H), 7.51 (t, $J = 7.6$ Hz, 2H), 6.90 (d, $J = 8.2$ Hz, 1H), 3.28 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) δ 167.7 (d, $J = 277.4$ Hz), 166.3 (d, $J = 20.1$ Hz), 144.1, 132.7, 129.6 (d, $J = 7.7$ Hz),

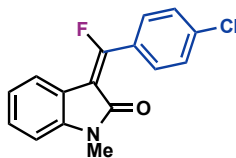
129.1 (d, $J = 24.8$ Hz), 128.4, 126.5 – 126.0 (m), 124.8 (q, $J = 32.4$ Hz), 124.6 (q, $J = 271.5$ Hz), 122.0, 121.9 (dq, $J = 14.6, 3.8$ Hz), 109.5 (d, $J = 19.7$ Hz), 107.6, 26.4 (d, $J = 3.0$ Hz); ^{19}F NMR (659 MHz, CDCl_3) δ -61.47 (s, 3F), -72.94 (s, 1F); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{12}\text{F}_4\text{NO}]^+$ Calcd 322.0850, found 322.0844; IR (ATR, MeCN, cm^{-1}) 3068, 2952, 1791, 1716, 1618, 1454, 1328, 1288, 1118 756, 686, 636; mp ($^{\circ}\text{C}$) 83.9-85.5.

(*E*)-1-benzyl-5-cyano-3-(chloro(phenyl)methylene)indolin-2-one (3.2p)



The title compound was prepared according to **Method C** from **3.1p** (35.4 mg, 0.10 mmol) using 20 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-7.5% EtOAc/hexanes) and the desired product was isolated as a yellow solid (16 mg, 0.045 mmol, 45%, >95:5 *E:Z*). Using 1.0 equiv of $\text{BF}_3 \cdot \text{OEt}_2$, **1p** was formed in 68% yield (24 mg, 0.068 mmol, >95:5 *E:Z*). ^1H NMR (400 MHz, CDCl_3) δ 8.16 – 8.10 (m, 2H), 8.07 (d, $J = 1.6$ Hz, 1H), 7.64 – 7.51 (m, 3H), 7.49 (dd, $J = 8.2, 1.6$ Hz, 1H), 7.37 – 7.25 (m, 5H), 6.82 (d, $J = 8.2$ Hz, 1H), 4.99 (s, 2H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 168.5 (d, $J = 279.0$ Hz), 166.0 (d, $J = 19.7$ Hz), 143.9, 135.2, 133.3 (d, $J = 1.4$ Hz), 133.1, 129.7 (d, $J = 8.2$ Hz), 129.1, 128.8 (d, $J = 24.7$ Hz), 128.3, 128.2, 128.1, 127.4, 122.5, 119.4, 109.2, 108.6 (d, $J = 19.9$ Hz), 105.8, 44.0; ^{19}F NMR (282 MHz, CDCl_3) δ -72.11 (s, 1F); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{23}\text{H}_{16}\text{FN}_2\text{O}]^+$ Calcd 355.1241, found 355.1233; IR (ATR, MeCN, cm^{-1}) 1705, 1686, 1606, 1470, 1339, 1262, 1110, 781, 747, 696, 647, 416; mp ($^{\circ}\text{C}$) 95.7-97.1.

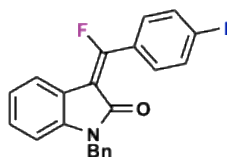
(*E*)-1-methyl-3-(fluoro(4-chlorophenyl)methylene)indolin-2-one (3.2q)



The title compound was prepared according to **Method C** from **3.1q** (28.8 mg, 0.10 mmol) using 30 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-5% EtOAc/hexanes) and the desired product was isolated as yellow solid (28 mg, 0.096 mmol, 96%, >95:5 *E:Z*). ^1H NMR (400 MHz, CDCl_3) δ 8.07 – 7.98 (m, 2H), 7.79 (d, $J = 7.7$ Hz, 1H), 7.46 (d, $J = 8.4$ Hz, 2H), 7.31 (td, $J = 7.7, 1.2$ Hz, 1H), 7.09 (t, $J = 7.8$ Hz, 1H), 6.83

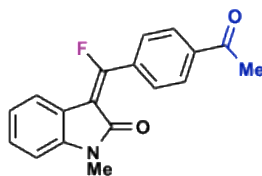
(d, $J = 7.8$ Hz, 1H), 3.24 (s, 3H); ^{13}C { ^1H } **NMR** (101 MHz, CDCl_3) δ 166.3 (d, $J = 20.1$ Hz), 164.9 (d, $J = 274.0$ Hz), 141.8, 138.2, 130.8 (d, $J = 7.7$ Hz), 129.2 (d, $J = 2.6$ Hz), 128.5, 128.1 (d, $J = 25.9$ Hz), 125.1 (d, $J = 14.4$ Hz), 122.7, 121.5 (d, $J = 1.4$ Hz), 111.0 (d, $J = 20.0$ Hz), 108.0, 26.2; ^{19}F **NMR** (377 MHz, CDCl_3) δ -78.92 (s, 1F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_{12}\text{ClFNO}]^+$ Calcd 288.0586, found 288.0576; **IR** (ATR, CDCl_3 , cm^{-1}) 1710, 1644, 1470, 1373, 1260, 1089, 1013, 827, 779, 743, 661, 548; **mp** ($^{\circ}\text{C}$) 147.6-149.3.

(*E*)-1-benzyl-3-fluoro(4-iodophenyl)methylene)indolin-2-one (3.2r)



The title compound was prepared according to **Method C** from **3.1r** (45.5 mg, 0.10 mmol) using 20 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-2.5% EtOAc/hexanes) and the desired product was isolated as an orange-yellow solid (0.038 g, 0.083 mmol, 83% yield, >95:5 *E:Z*). ^1H **NMR** (700 MHz, CDCl_3) δ 7.87 – 7.82 (m, 4H), 7.81 (d, $J = 7.6$ Hz, 1H), 7.32 – 7.28 (m, 4H), 7.28 – 7.23 (m, 1H), 7.21 (t, $J = 7.8$ Hz, 1H), 7.06 (t, $J = 7.6$ Hz, 1H), 6.76 (d, $J = 7.8$ Hz, 1H), 4.95 (s, 2H); ^{13}C { ^1H } **NMR** (176 MHz, CDCl_3) δ 166.3 (d, $J = 20.2$ Hz), 165.4 (d, $J = 274.7$ Hz), 141.0, 137.4, 136.1, 130.9 (d, $J = 7.6$ Hz), 129.2 (d, $J = 2.4$ Hz), 129.1 (d, $J = 26.0$ Hz), 128.9, 127.8, 127.5, 125.2 (d, $J = 14.4$ Hz), 122.7, 121.6, 111.0 (d, $J = 19.8$ Hz), 108.9, 99.5, 43.8; ^{19}F **NMR** (659 MHz, CDCl_3) δ -78.06 (s, 1F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{22}\text{H}_{16}\text{FNOI}]^+$ Calcd 456.0255, found 456.0249; **IR** (ATR, CDCl_3 , cm^{-1}) 1704, 1605, 1468, 1348, 1178. 1105, 1006, 873, 824, 781. 747, 701; **mp** ($^{\circ}\text{C}$) 125.3-128.7.

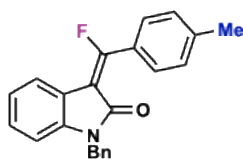
(*E*)-1-methyl-3-(fluoro(4-acetylphenyl)methylene)indolin-2-one (3.2s)



The title compound was prepared according to **Method C** from **3.1s** (29.5 mg, 0.10 mmol) using 30 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-10% EtOAc/hexanes) and the desired product was isolated as an orange solid (25 mg, 0.084 mmol, 84%, >95:5 *E:Z*). ^1H **NMR** (400 MHz, CDCl_3) δ 8.19 – 8.11 (m,

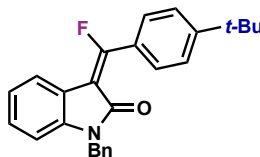
2H), 8.05 (d, $J = 8.3$ Hz, 2H), 7.81 (d, $J = 7.6$ Hz, 1H), 7.33 (td, $J = 7.8, 1.2$ Hz, 1H), 7.10 (t, $J = 7.6$ Hz, 1H), 6.84 (d, $J = 7.8$ Hz, 1H), 3.24 (s, 3H), 2.65 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 197.5, 166.2 (d, $J = 20.1$ Hz), 164.6 (d, $J = 274.6$ Hz), 142.1, 139.2, 133.8 (d, $J = 25.6$ Hz), 129.8 (d, $J = 7.3$ Hz), 129.6 (d, $J = 2.6$ Hz), 127.9, 125.3 (d, $J = 14.1$ Hz), 122.8, 121.3 (d, $J = 1.6$ Hz), 112.0 (d, $J = 19.5$ Hz), 108.1, 26.9, 26.2; ^{19}F NMR (377 MHz, CDCl_3) δ -79.56 (s, 1F); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{18}\text{H}_{15}\text{FNO}_2]^+$ Calcd 296.1081, found 296.1076; IR (ATR, MeCN, cm^{-1}) 1691, 1684, 1605, 1471, 1406, 1338, 1260, 1090, 781, 746, 697, 546; mp ($^\circ\text{C}$) 139.4-144.2.

(*E*)-1-benzyl-3-fluoro(((4-methylphenyl)ethynyl)methylene)indolin-2-one (3.2t)



The title compound was prepared according to **Method C** from **3.1t** (34.3 mg, 0.10 mmol) using 20 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The desired product was isolated as an orange solid (17.5 mg, 0.051 mmol, 51%, 95:5 *E:Z*). ^1H NMR (400 MHz, CDCl_3) δ 8.01 (d, $J = 8.3$ Hz, 2H), 7.83 (d, $J = 7.6$ Hz, 1H), 7.36 – 7.22 (m, 7H), 7.19 (td, $J = 7.8, 1.3$ Hz, 1H), 7.06 (t, $J = 7.6, 1.0$ Hz, 1H), 6.75 (d, $J = 7.8$ Hz, 1H), 4.97 (s, 2H), 2.45 (s, 3H); ^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 167.0 (d, $J = 275.7$ Hz), 166.6 (d, $J = 20.3$ Hz), 143.0, 140.8, 136.3, 129.6 (d, $J = 7.8$ Hz), 128.9, 128.8, 128.6 (d, $J = 1.8$ Hz), 127.6, 127.5, 126.8 (d, $J = 25.3$ Hz), 124.9 (d, $J = 14.5$ Hz), 122.5, 122.0, 109.8 (d, $J = 20.2$ Hz), 108.7, 43.8, 21.9; ^{19}F NMR (377 MHz, CDCl_3) δ -76.20 (s, 1F); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{23}\text{H}_{19}\text{FNO}]^+$ Calcd 344.1445, found 344.1437; IR (ATR, MeCN, cm^{-1}) 2925, 1709, 1607, 1470, 1373, 1338, 1260, 1090, 961, 747, 696; mp ($^\circ\text{C}$) 97.4-100.2.

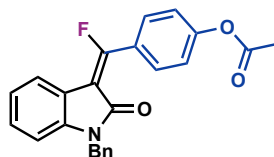
(*E*)-1-benzyl-3-fluoro(((4-tertbutylphenyl)ethynyl)methylene)indolin-2-one (3.2u)



The title compound was prepared according to **Method C** from **3.1u** (38.7 mg, 0.10 mmol) using 20 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-5% EtOAc/hexanes) and the desired product was isolated as a yellow solid (21 mg, 0.065 mmol, 65%, >95:5 *E:Z*). ^1H NMR (400 MHz, CDCl_3) δ 8.08 (d, $J =$

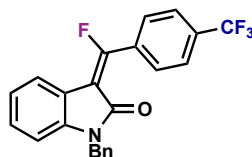
8.5 Hz, 2H), 7.86 (d, $J = 7.6$ Hz, 1H), 7.56 (d, $J = 8.5$ Hz, 2H), 7.37 – 7.26 (m, 5H), 7.21 (td, $J = 7.8, 1.3$ Hz, 1H), 7.08 (td, $J = 7.6, 1.1$ Hz, 1H), 6.78 (d, $J = 7.8$ Hz, 1H), 5.00 (s, 2H), 1.39 (s, 9H); ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ 167.0 (d, $J = 275.0$ Hz), 166.7 (d, $J = 20.4$ Hz), 156.0, 140.8, 136.3, 129.5 (d, $J = 7.8$ Hz), 128.9, 128.7 (d, $J = 2.5$ Hz), 127.7, 126.8 (d, $J = 25.3$ Hz), 126.0, 125.2, 124.9 (d, $J = 14.5$ Hz), 122.5, 122.1 (d, $J = 1.4$ Hz), 109.8 (d, $J = 20.3$ Hz), 108.7, 43.8, 35.3, 31.2; ^{19}F NMR (377 MHz, CDCl_3) δ -75.22 (s, 1F); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{26}\text{H}_{25}\text{FNO}]^+$ Calcd 386.19147, found 386.19159; IR (ATR, CDCl_3 , cm^{-1}) 2963, 1699, 1606, 1468, 1347, 1271, 1177, 1102, 953, 876, 731, 697; mp ($^{\circ}\text{C}$) 113.5-114.7.

(*E*)-1-benzyl-3-fluoro(((4-acetoxyphenyl)ethynyl)methylene)indolin-2-one (3.2v)



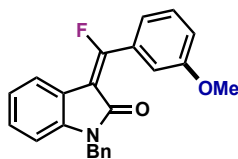
The title compound was prepared according to **Method C** from **3.1v** (38.7 mg, 0.10 mmol) using 30 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-5% EtOAc/hexanes) and the desired product was isolated as an orange-red solid (21 mg, 0.056 mmol, 56%, 95:5 *E:Z*). ^1H NMR (400 MHz, CDCl_3) δ 8.21 – 8.15 (m, 2H), 7.82 (d, $J = 7.7$ Hz, 1H), 7.31 (d, $J = 4.3$ Hz, 4H), 7.27 – 7.23 (m, 3H), 7.20 (td, $J = 7.7, 1.2$ Hz, 1H), 7.06 (td, $J = 7.7, 0.8$ Hz, 1H), 6.76 (d, $J = 7.7$ Hz, 1H), 4.97 (s, 2H), 2.34 (s, 3H); ^{13}C { ^1H } NMR (101 MHz, CDCl_3) δ 169.0, 166.5 (d, $J = 20.3$ Hz), 165.6 (d, $J = 274.6$ Hz), 153.5 (d, $J = 1.2$ Hz), 140.9, 136.1, 131.1 (d, $J = 8.0$ Hz), 129.0 (d, $J = 2.6$ Hz), 128.9, 127.7, 127.4, 125.1 (d, $J = 14.7$ Hz), 122.7, 122.5, 121.8 (d, $J = 1.5$ Hz), 121.4 (d, $J = 0.8$ Hz), 110.5 (d, $J = 20.2$ Hz), 108.8 (d, $J = 0.6$ Hz), 43.8, 21.3; ^{19}F NMR (377 MHz, CDCl_3) δ -76.11 (s, 1F); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{24}\text{H}_{19}\text{FNO}_3]^+$ Calcd 388.1343, found 388.1345; IR (ATR, MeCN, cm^{-1}) 2955, 1706, 1603, 1505, 1468, 1347, 1195, 1167, 1011, 911, 747, 699; mp ($^{\circ}\text{C}$) 106.2-109.5.

(*E*)-1-benzyl-3-fluoro(4-trifluoromethylphenyl)ethynyl)methylene)indolin-2-one (3.2w)



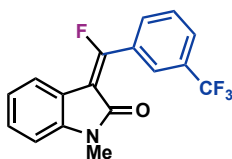
The title compound was prepared according to **Method C** from **3.1w** (39.7 mg, 0.10 mmol) using 20 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-5% EtOAc/hexanes) and the desired product was isolated as a yellow solid (37 mg, 0.093 mmol, 93%, 95:5 *E:Z*). **^1H NMR** (400 MHz, CDCl_3) δ 8.11 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.18 (s, 6H), 7.00 (td, J = 7.7, 1.0 Hz, 1H), 6.69 (d, J = 7.5 Hz, 1H), 4.87 (s, 2H); **^{13}C { ^1H } NMR** (101 MHz, CDCl_3) δ 166.2 (d, J = 20.0 Hz), 164.4 (d, J = 275.0 Hz), 141.3, 136.0, 133.4 (q, J = 33.2 Hz), 133.0 (d, J = 27.1 Hz), 130.0 (d, J = 7.4 Hz), 129.6 (d, J = 2.6 Hz), 128.9, 127.8, 127.5, 125.4 (d, J = 14.3 Hz), 125.1 (q, J = 3.9), 122.8, 121.3 (d, J = 1.7 Hz), 123.8 (q, J = 272.7 Hz), 111.9 (d, J = 19.4 Hz), 109.0, 43.9; **^{19}F NMR** (377 MHz, CDCl_3) δ -63.14 (s, 3F), -77.77 (s, 1F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{23}\text{H}_{16}\text{F}_4\text{NO}]^+$ Calcd 398.11625, found 398.11610; **IR** (ATR, CDCl_3 , cm^{-1}) 1703, 1604, 1469, 1323, 1127, 1107, 1016, 843, 746, 699; **mp** ($^\circ\text{C}$) 112.9-113.5.

(*E*)-1-benzyl-3-fluoro(3-methoxy)(phenyl)ethynyl)methylene)indolin-2-one (3.2x)



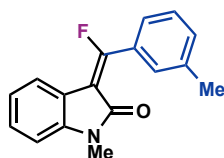
The title compound was prepared according to **Method C** (35.9 mg, 0.10 mmol) from **3.1x** using 30 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-2.5% EtOAc/hexanes) and the desired product was isolated as an orange-red solid (21.1 mg, 0.059 mmol, 59%, 95:5 *E:Z*). **^1H NMR** (400 MHz, CDCl_3) δ 7.83 (d, J = 7.6 Hz, 1H), 7.75 – 7.72 (m, 1H), 7.69 (ddd, J = 7.8, 1.6, 1.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.33 – 7.29 (m, 4H), 7.29 – 7.23 (m, 1H), 7.20 (td, J = 7.7, 1.2 Hz, 1H), 7.12 – 7.03 (m, 2H), 6.75 (d, J = 7.8 Hz, 1H), 4.97 (s, 2H), 3.89 (s, 3H); **^{13}C { ^1H } NMR** (101 MHz, CDCl_3) δ 166.4 (d, J = 20.3 Hz), 166.3 (d, J = 275.4 Hz), 159.2, 140.9, 136.2, 130.8 (d, J = 25.6 Hz), 129.2 (d, J = 0.6 Hz), 129.0 (d, J = 2.6 Hz), 128.9, 127.7, 127.4, 125.1 (d, J = 14.9 Hz), 122.6, 122.0 (d, J = 8.0 Hz), 121.9 (d, J = 1.5 Hz), 118.6 (d, J = 1.1 Hz), 114.5 (d, J = 8.0 Hz), 110.6 (d, J = 20.3 Hz), 108.8 (d, J = 1.0 Hz), 55.6, 43.8; **^{19}F NMR** (377 MHz, CDCl_3) δ -75.3 (s, 1F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{23}\text{H}_{19}\text{FNO}_2]^+$ Calcd 360.1394, found 360.1386; **IR** (ATR, MeCN, cm^{-1}) 3000, 1707, 1642, 1468, 1468, 1348, 1292, 1177, 780, 748, 699; **mp** ($^\circ\text{C}$) 95.2-97.4.

(*E*)-1-methyl-3-fluoro(3-trifluoromethylphenyl)methylene)indolin-2-one (3.2y)



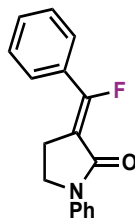
The title compound was prepared according to **Method C** from **3.1y** (32.1 mg, 0.10 mmol) using 30 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The desired product was isolated as a yellow powder (31 mg, 0.097 mmol, 97%, >95:5 *E:Z*). **^1H NMR** (400 MHz, CDCl_3) δ 8.33 (s, 1H), 8.29 (d, $J = 8.0$ Hz, 1H), 7.84 – 7.75 (m, 2H), 7.62 (t, $J = 7.9$ Hz, 1H), 7.33 (td, $J = 7.8, 1.2$ Hz, 1H), 7.10 (t, $J = 7.8$ Hz, 1H), 6.84 (d, $J = 7.8$ Hz, 1H), 3.25 (s, 3H); **^{13}C { ^1H } NMR** (101 MHz, CDCl_3) δ 166.1 (d, $J = 20.0$ Hz), 164.0 (d, $J = 274.2$ Hz), 142.0, 132.8 (d, $J = 7.5$ Hz), 131.1 (q, $J = 32.8$ Hz), 130.6, 130.3, 129.6 (d, $J = 2.6$ Hz), 128.4 (q, $J = 3.7$ Hz), 126.2 (dq, $J = 7.9, 4.0$ Hz), 125.2 (d, $J = 14.3$ Hz), 122.8, 122.6 (q, $J = 273.2$ Hz), 121.2 (d, $J = 1.4$ Hz), 111.8 (d, $J = 19.4$ Hz), 108.0, 26.3; **^{19}F NMR** (377 MHz, CDCl_3) δ -62.79 (s, 3F), -78.93 (s, 1F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{12}\text{F}_4\text{NO}]^+$ Calcd 322.0849, found 322.0838; **IR** (ATR, MeCN, cm^{-1}) 2932, 1705, 1608, 1435, 1334, 1252, 1125, 998, 863, 748, 688, 533; **mp** ($^\circ\text{C}$) 93.5-95.2.

(*E*)-1-methyl-3-fluoro(3-methylphenyl)methylene)indolin-2-one (3.2z)



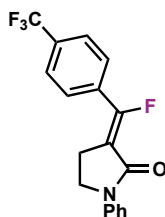
The title compound was prepared according to **Method C** from **3.1z** (26.7 mg, 0.10 mmol) using 30 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-10% EtOAc/hexanes) and the desired product was isolated as an orange powder (24 mg, 0.089 mmol, 89%, >95:5 *E:Z*). **^1H NMR** (400 MHz, CDCl_3) δ 7.88 – 7.83 (m, 2H), 7.80 (d, $J = 7.7$, 1H), 7.41 – 7.33 (m, 2H), 7.30 (td, $J = 7.7, 1.1$ Hz, 1H), 7.09 (t, $J = 7.7$, 1H), 6.83 (d, $J = 7.7$ Hz, 1H), 3.25 (s, 3H), 2.44 (s, 3H); **^{13}C { ^1H } NMR** (101 MHz, CDCl_3) δ 166.5 (d, $J = 275.4$ Hz), 166.4 (d, $J = 20.3$ Hz), 141.6, 137.7, 132.8 (d, $J = 1.3$ Hz), 129.7 (d, $J = 7.2$ Hz), 129.5 (d, $J = 25.0$ Hz), 128.8 (d, $J = 2.5$ Hz), 127.9, 126.7 (d, $J = 7.7$ Hz), 124.8 (d, $J = 14.3$ Hz), 122.4, 121.7 (d, $J = 1.5$ Hz), 110.3 (d, $J = 20.1$ Hz), 107.7, 26.1, 21.4; **^{19}F NMR** (377 MHz, CDCl_3) δ -75.94 (s, 1F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{15}\text{FNO}]^+$ Calcd 268.1132, found 268.1125; **IR** (ATR, MeCN, cm^{-1}) 2925, 1709, 1607, 1470, 1373, 1339, 1090, 781, 747, 695, 545; **mp** ($^\circ\text{C}$) 139.4-144.5.

(3Z)-3-(fluoro(phenyl)methylene)-1-phenyl-pyrrolidin-2-one (3.4a)



The title compound was prepared according to **Method C** from **3.3a** (26.7 mg, 0.10 mmol) using 10 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The desired product was isolated as a white crystalline solid upon workup (22 mg, 0.081 mmol, 81%, >99:1 *Z:E*). **^1H NMR** (400 MHz, CDCl_3) δ 7.86 (dd, $J = 6.9, 2.5$ Hz, 2H), 7.67 (d, $J = 8.0$ Hz, 2H), 7.46 – 7.41 (m, 3H), 7.37 (t, $J = 8.0$ Hz, 2H), 7.16 (t, $J = 7.4$ Hz, 1H), 3.92 (t, $J = 7.0$ Hz, 2H), 3.11 (td, $J = 7.0, 3.3$ Hz, 2H); **^{13}C { ^1H } NMR** (101 MHz, CDCl_3) δ 165.7 (d, $J = 17.0$ Hz), 161.8 (d, $J = 257.3$ Hz), 139.7, 130.7 (d, $J = 1.2$ Hz), 130.0 (d, $J = 26.7$ Hz), 129.2 (d, $J = 6.5$ Hz), 128.9, 127.9, 124.8, 120.2, 113.0 (d, $J = 26.2$ Hz), 45.1 (d, $J = 0.9$ Hz), 21.9 (d, $J = 5.9$ Hz); **^{19}F NMR** (377 MHz, CDCl_3) δ -81.2 (s, 1F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{15}\text{FNO}]^+$ Calcd 268.1132, found 268.1127; **IR** (ATR, MeCN, cm^{-1}) 3065, 1691, 1596, 1486, 1445, 1389, 1300, 1220, 1043, 757, 715, 689, 624, 515; **mp** ($^\circ\text{C}$) 96.1-97.3.

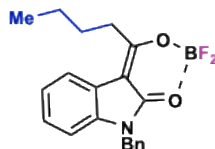
(3Z)-3-(fluoro(4-trifluoromethyl)phenyl)methylene)-1-phenyl-pyrrolidin-2-one (3.4b)



The title compound was prepared according to **Method C** from **3.3b** (33.5 mg, 0.10 mmol) using 10 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The desired product was isolated as a white crystalline solid upon workup (28 mg, 0.080 mmol, 80%, >99:1 *Z:E*). **^1H NMR** 400 MHz, CDCl_3) δ 7.98 (d, $J = 8.3$ Hz, 2H), 7.73 – 7.62 (m, 4H), 7.42 – 7.35 (m, 2H), 7.23 – 7.15 (m, 1H), 4.00 – 3.91 (m, 2H), 3.15 (td, $J = 6.9, 3.3$ Hz, 2H); **^{13}C { ^1H } NMR** (101 MHz, CDCl_3) δ 165.2 (d, $J = 16.6$ Hz), 160.0 (d, $J = 256.8$ Hz), 139.5, 133.3 (d, $J = 27.5$ Hz), 132.1 (q, $J = 32.6$ Hz), 129.6 (d, $J = 6.5$ Hz), 129.0, 125.2, 124.8 (q, $J = 3.7$ Hz), 123.9 (q, $J = 272.4$ Hz), 120.3, 115.0 (d, $J = 25.4$ Hz), 45.2 (d, $J = 1.4$ Hz), 22.0 (d, $J = 5.6$ Hz); **^{19}F NMR** (659 MHz, CDCl_3) δ -62.99 (s, 3F), -83.64 (s, 1F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$

$[\text{C}_{18}\text{H}_{14}\text{F}_4\text{NO}]^+$ Calcd 336.1006, found 336.1007; **IR** (ATR, MeCN, cm^{-1}) 2958, 1686, 1598, 1494, 1324, 1169, 846, 760, 691; **mp** ($^{\circ}\text{C}$) 109.5-110.5.

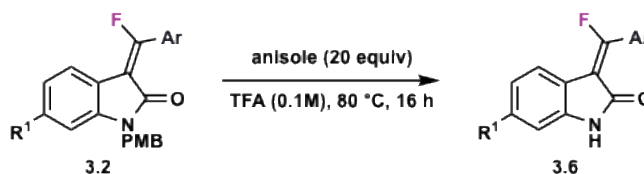
3.2ac-BF₂



The title compound was prepared according to **Method C** from **3.3ac** (30.9 mg, 0.10 mmol) using 10 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The desired product was isolated as a white crystalline solid upon workup (4.0 mg, 0.013 mmol, 13%, >99:1 *Z:E*). **¹H NMR** (500 MHz, CDCl_3) δ 7.49 – 7.65 (m, 1H), 7.00 – 7.35 (m, 7H), 5.19 (s, 2H), 2.83 – 3.03 (m, 2H), 2.31 (s, 3H), 1.77 – 1.96 (m, 2H), 1.52 (h, $J = 7.4$ Hz, 2H), 1.15 – 1.36 (m, 2H), 0.99 (t, $J = 7.3$ Hz, 3H); **¹³C** {**¹H} **NMR** (126 MHz, CDCl_3) δ 184.4, 165.4, 138.3, 135.8, 130.8, 129.8, 127.6, 125.4, 124.4, 121.4, 120.1, 111.5, 99.6, 45.1, 35.3, 27.7, 22.5, 21.1, 13.8; **¹⁹F NMR** (375 MHz, CDCl_3) δ -141.18 (m, 2F).**

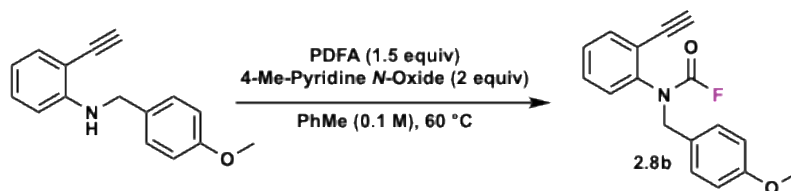
3.8.6 Synthesis of Medicinally Relevant Methylene Oxindoles

3.8.6.1 General Procedure for PMB Deprotection (Method D)



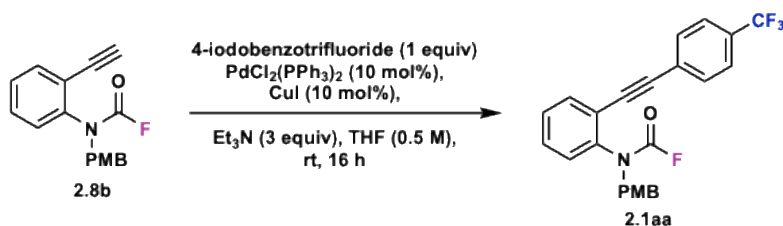
A 1 dr vial equipped with a stir bar was charged with 3-fluoromethylene oxindole **3.2** (1 equiv, 0.1 mmol), TFA (0.1 M, 1 mL) and anisole (20 equiv, 2 mmol, 0.22 mL). The vial was sealed with a Teflon-lined cap, which was wrapped with electrical tape and placed in a pre-heated oil bath at 80 $^{\circ}\text{C}$ for 16 h. The reaction was cooled to rt and quenched with NEt_3 until pH = 8. The reaction mixture was extracted with DCM (3x), washed with water (1x) and brine (1x), and then concentrated *in vacuo*. The crude mixture was filtered through silica, eluted with 25% EtOAc/hexanes, and purified by flash chromatography using the reported eluent.

(4-methoxybenzyl)2-ethynylphenylcarbamic fluoride (3.8b)



The title compound was prepared according to **Method B** using 2-ethynyl-*N*-(4-methoxybenzyl)aniline²²⁶ (4 mmol, 0.933 g). The crude material was purified by flash chromatography (0-3% EtOAc/hexanes) and the desired product was isolated as a colorless oil (0.784 g, 2.77 mmol, 69% yield, *rotamer ratio* by ¹⁹F NMR: 88:12). ¹H NMR (700 MHz, CDCl₃) δ 7.58 (d, *J* = 6.7 Hz, 0.2H), 7.55 (d, *J* = 7.4 Hz, 0.8H), 7.29 (t, *J* = 7.4 Hz, 1.2H), 7.26 – 7.21 (m, 0.8H), 7.14 (d, *J* = 7.9 Hz, 1.6H), 7.09 (d, *J* = 7.9 Hz, 0.4H), 6.94 (d, *J* = 7.0 Hz, 0.2H), 6.87 – 6.76 (m, 2.8H), 5.09 (bd, 0.85H), 4.76 (bs, 0.3H), 4.47 (bd, 0.85H), 3.79 (s, 3H), 3.33 (s, 0.2H), 3.29 (s, 0.8H); ¹³C {¹H} NMR (176 MHz, CDCl₃) δ 159.6, 146.8 (d, *J* = 288.0 Hz), 141.7, 140.8, 134.2, 133.8, 130.7, 130.2, 129.9, 129.7, 129.0, 128.8, 128.5, 127.73, 127.66, 121.4, 121.2, 114.2, 114.0, 83.11 (d, *J* = 3.3 Hz), 83.06 (d, *J* = 4.2 Hz), 79.4, 79.2, 55.4 (d, *J* = 7.5 Hz), 54.5, 54.4; ¹⁹F NMR (659 MHz, CDCl₃) δ -14.07 (s, 0.88F, *major*), -19.90 (s, 0.12F, *minor*); HRMS (ESI) *m/z*: [C₁₇H₁₄FN₂O]⁺ [M+Na]⁺ Calcd 306.0901, found 306.0901; IR (ATR, MeCN, cm⁻¹) 3283, 1940, 2842, 1786, 1613, 1514, 1488, 1392, 1247, 1177, 1034, 752, 625.

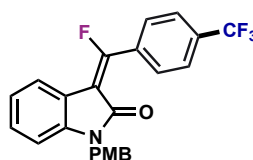
(4-methoxybenzyl)(2-((4-trifluoromethylphenyl)ethynyl)phenyl)carbamic fluoride (3.1aa)



A flame-dried round-bottom flask was charged with 3-iodobenzotrifluoride (1.00 equiv, 1.60 mmol, 240 μL), PdCl₂(PPh₃)₂ (10 mol%, 0.16 mmol, 28 mg), CuI (10 mol%, 0.16 mmol, 15 mg), THF (0.5 M, 0.7 mL) and NEt₃ (3 equiv, 4.80 mmol, 0.64 mL). While stirring, **3.8b** (1.00 equiv, 1.60 mmol, 0.453 g) in minimal amount of THF (0.10 mL) was added dropwise, and the reaction was stirred at rt for 16 h. The reaction was diluted with Et₂O and passed through a silica plug. The crude material was purified by flash chromatography (0-3% EtOAc/hexanes) and the

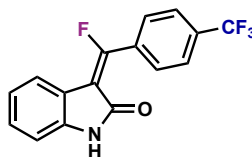
desired product was isolated as a colorless oil (0.497 g, 1.16 mmol, 73% yield, *rotamer ratio by ^{19}F NMR*: 88:12). ^1H NMR (400 MHz, CDCl_3) δ 7.65 – 7.54 (m, 5H), 7.39 – 7.28 (m, 2H), 7.19 – 7.09 (m, 2H), 7.09 – 7.03 (m, 0.2H), 6.98 (m, 0.8H), 6.82 – 6.72 (m, 2H), 4.98 (bd, 0.8H), 4.79 (bs, 0.4H), 4.65 (bd, 0.8H), 3.75 (s, 0.6H), 3.72 (s, 2.4H); ^{13}C { ^1H } NMR (176 MHz, CDCl_3) δ 159.6, 146.8 (d, J = 288.1 Hz), 146.3 (d, J = 291.9 Hz), 141.3, 140.5, 133.4, 132.9, 132.0, 131.9, 130.7, 130.3, 130.2, 129.9, 129.8, 128.6, 128.52, 128.51, 128.3, 127.5, 127.4, 126.5, 126.3, 125.4 (q, J = 3.6 Hz), 124.0 (q, J = 272.2 Hz), 122.0, 121.8, 114.1, 113.9, 93.4, 93.3, 87.5, 87.2, 55.2, 55.1, 54.9, 54.7; ^{19}F NMR (377 MHz, CDCl_3) δ -13.89 (s, 0.88F, *major*), -19.47 (s, 0.12F, *minor*), -62.9 (s, 3F, *major and minor*); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{24}\text{H}_{18}\text{F}_4\text{NO}]^+$ Calcd 428.1268, found 428.1263; IR (ATR, MeCN, cm^{-1}) 2805, 1784, 1613, 1514, 1488, 1392, 1320, 1247, 1124, 1065, 1034, 842, 751, 625.

(*E*)-1-(4-methoxybenzyl)-3-((fluoro(4-trifluoromethyl)(phenyl)ethynyl)methylene)indolin-2-one (3.2aa)



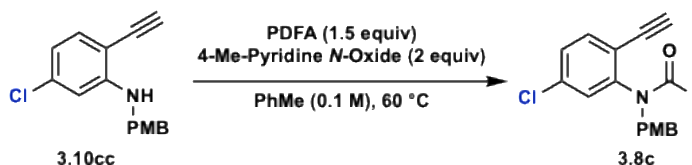
The title compound was prepared according to **Method C** from **3.1aa** (42.7 mg, 0.10 mmol) using 30 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-2% EtOAc/hexanes) and the title compound was isolated as an orange solid (15.8 mg, 0.037 mmol, 37%, >95:5 *E:Z*). ^1H NMR (400 MHz, CDCl_3) δ 8.19 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 8.6 Hz, 2H), 7.29 – 7.19 (m, 3H), 7.07 (t, J = 7.7 Hz, 1H), 6.83 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 7.7 Hz, 1H), 4.88 (s, 2H), 3.77 (s, 3H); ^{13}C { ^1H } NMR (176 MHz, CDCl_3) δ 166.0 (d, J = 20.0 Hz), 164.2 (d, J = 275.0 Hz), 159.1, 141.2, 133.2 (q, J = 32.7 Hz), 132.9 (d, J = 26.0 Hz), 129.8 (d, J = 7.2 Hz), 129.5 (d, J = 2.2 Hz), 128.8, 127.9, 125.3 (d, J = 14.3 Hz), 125.0 (q, J = 3.6 Hz), 123.7 (d, J = 272.6 Hz), 122.6, 121.2, 114.2, 111.8 (d, J = 19.3 Hz), 108.9, 55.3, 43.2; ^{19}F NMR (377 MHz, CDCl_3) δ -63.14 (3F), -77.85 (1F); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{24}\text{H}_{18}\text{F}_4\text{NO}]^+$ Calcd 428.1268, found 428.1267; IR (ATR, MeCN, cm^{-1}) 2930, 1703, 1607, 1513, 1469, 1324, 1248, 1176, 1130, 1071, 845, 745; mp ($^{\circ}\text{C}$) 115.8-118.2.

(E)-3-(fluoro-(4-(trifluoromethyl)phenyl)methylene)indolin-2-one (3.5aa)



The title compound was prepared according to **Method D** from **3.2aa** (42.7 mg, 0.10 mmol). The crude material was purified by flash chromatography (10-20% EtOAc/hexanes) and the title compound was isolated as a yellow-orange solid (26.4 mg, 0.062 mmol, 62%, >95:5 *E:Z*). **¹H NMR** (400 MHz, DMSO-*d*₆) δ 10.74 (s, 1H), 8.19 (d, *J* = 8.1 Hz, 2H), 7.90 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H); **¹³C {¹H} NMR** (101 MHz, DMSO-*d*₆) δ 166.5 (d, *J* = 19.5 Hz), 162.7 (d, *J* = 272.5 Hz), 140.7, 132.9 (d, *J* = 26.2 Hz), 131.3 (q, *J* = 32.3 Hz), 130.2 (d, *J* = 6.8 Hz), 129.9 (d, *J* = 2.2 Hz), 124.9 (q, *J* = 3.4 Hz), 124.8, 123.8 (q, *J* = 272.6 Hz), 121.8, 121.0 (d, *J* = 1.4 Hz), 112.4 (d, *J* = 17.6 Hz), 109.7; **¹⁹F NMR** (377 MHz, DMSO-*d*₆) δ -61.56 (s, 3F), -79.75 (s, 1F); **HRMS** (ESI) *m/z*: [M+H]⁺ [C₁₆H₁₀F₄NO]⁺ Calcd 308.06930, found 308.06203; **IR** (ATR, MeCN, cm⁻¹) 3205, 1709, 1646, 1615, 1468, 1325, 1169, 1127, 1066, 847, 789, 747; **mp** (°C) 193.6-198.0.

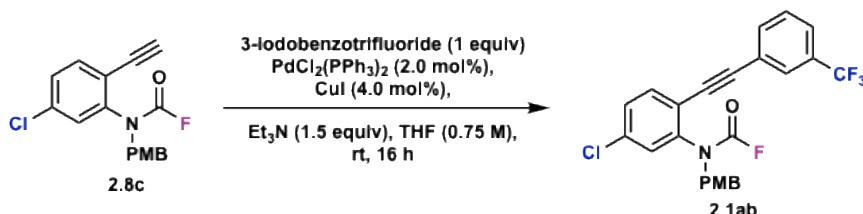
(4-methoxybenzyl)(2-ethynyl)(5-chlorophenyl)carbamic fluoride (3.8c)



The title compound was prepared according to **Method B** from **3.10cc** (381 mg, 1.20 mmol). The crude material was purified by flash chromatography (0-10% EtOAc/hexanes) and the desired product was isolated as a colorless oil (0.190 g, 0.60 mmol, 50% yield, *rotamer ratio by ¹⁹F NMR*: 80:20). **¹H NMR** (400 MHz, CDCl₃) δ 7.50 (d, *J* = 8.4 Hz, 0.2H), 7.47 (d, *J* = 8.4 Hz, 0.8H), 7.34 – 7.32 (m, 0.2H), 7.28 (dd, *J* = 8.4, 2.1 Hz, 0.8H), 7.14 (d, *J* = 8.7 Hz, 1.6H), 7.10 (d, *J* = 8.6 Hz, 0.4H), 6.98 (d, *J* = 1.9 Hz, 0.2H), 6.88 (d, *J* = 2.1 Hz, 0.8H), 6.87 – 6.78 (m, 2H), 5.14 – 4.92 (bd, 0.8H), 4.75 (s, 0.4H), 4.51 (bd, 0.8H), 3.80 (s, 3H), 3.36 (s, 0.2H), 3.32 (s, 0.8H); **¹³C {¹H} NMR** (101 MHz, CDCl₃) δ 159.8, 146.3 (d, *J* = 289.0 Hz), 141.7 (d, *J* = 1.1 Hz), 135.2, 134.9, 134.5, 130.6, 130.1, 129.4, 129.0, 128.9, 128.65, 128.58, 127.2, 127.1, 120.1, 119.9, 114.3, 114.2, 84.1, 84.0, 78.5, 78.2, 55.4, 54.5, 54.4; **¹⁹F**

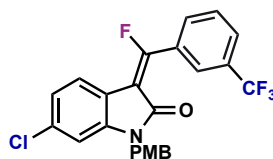
NMR (377 MHz, CDCl₃) δ -14.35 (s, 0.80F, *major*), -20.39 (s, 0.20F, *minor*); **HRMS** (ESI) m/z : [M+H]⁺ [C₁₇H₁₄ClFNO₂]⁺ Calcd 318.0692, found 318.0693; **IR** (ATR, MeCN, cm⁻¹) 3280, 2837, 2083, 1793, 1612, 1514, 1248, 1177, 1030, 827.

(4-methoxybenzyl)(2-(3-trifluoromethylphenyl)ethynyl)(5-chlorophenyl)carbamic fluoride (3.1ab)



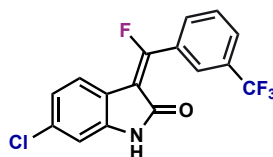
A flame-dried round-bottom flask was charged with 3-iodobenzotrifluoride (1.00 equiv, 0.50 mmol, 73 μ L), PdCl₂(PPh₃)₂ (2 mol%, 0.04 mmol, 0.028 g), CuI (4 mol%, 0.08 mmol, 0.015 g), THF (0.75 M, 0.7 mL) and NEt₃ (1.5 equiv, 6 mL) under N₂. While stirring, **2.8c** (1.00 equiv, 2.4 mmol, 0.34 mL) was added dropwise, and the reaction was stirred at rt for 16 h. The reaction was diluted with Et₂O and passed through a silica plug. The crude material was purified by flash chromatography (0-5% EtOAc/hexanes) and the desired product was isolated as a colorless oil (0.180 g, 0.42 mmol, 84% yield, *rotamer ratio by* ¹⁹F NMR: 84:16). **¹H NMR** (400 MHz, CDCl₃) δ 7.69 (bs, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.56 – 7.45 (m, 2H), 7.33 (dd, J = 8.4, 2.1 Hz, 1H), 7.20 – 7.09 (m, 2.2H), 7.05 (d, J = 2.1 Hz, 0.8H), 6.82 – 6.73 (m, 2H), 4.87 (bs, 0.8H), 4.79 (bs, 0.4H), 4.75 (bs, 0.8H), 3.74 (s, 0.5H), 3.72 (s, 2.5H); **¹³C {¹H} NMR** (101 MHz, CDCl₃) δ 159.8, 146.4 (d, J = 289.4 Hz), 146.0 (d, J = 292.7 Hz), 142.2, 141.4, 135.3, 135.1, 135.0, 134.9, 134.2, 133.7, 131.6, 131.3, 131.0, 130.7, 130.2, 129.1, 129.0, 128.7, 128.4 (q, J = 3.6 Hz), 127.1, 127.0, 125.6 (q, J = 3.6 Hz), 123.7 (q, J = 272.6 Hz), 123.4, 123.2, 121.0, 120.7, 114.2, 114.1, 94.2, 94.1, 85.7, 85.4, 55.2, 55.1, 54.9; **¹⁹F NMR** (377 MHz, CDCl₃) δ -13.27 (s, 0.84F, *major*), -18.96 (s, 0.16F, *minor*), -62.88 – -62.9 (two overlapping singlets, 3F); **HRMS** (ESI) m/z : [M+H]⁺ [C₂₄H₁₇ClF₄NO₂]⁺ Calcd 462.0878, found 462.0872; **IR** (ATR, MeCN, cm⁻¹) 3070, 1793, 1612, 1514, 1340, 1250, 1176, 1130, 826, 696.

(E)-1-(4-methoxybenzyl)-3-((fluoro(3-trifluoromethyl)(phenyl)ethynyl)methylene)-5-chloroindolin-2-one
(3.2ab)



The title compound was prepared according to **Method C** (46.1 mg, 0.10 mmol scale) from **3.1ab** using 30 mol% $\text{BF}_3 \cdot \text{OEt}_2$. The crude material was purified by flash chromatography (0-5% EtOAc/hexanes) and the desired product was isolated as a crystalline yellow solid (17.1 mg, 0.037 mmol, 37%, >95:5 *E:Z*). **^1H NMR** (400 MHz, CDCl_3) δ 8.36 – 8.30 (m, 2H), 7.80 (d, $J = 7.9$ Hz, 1H), 7.71 (d, $J = 8.1$ Hz, 1H), 7.64 (t, $J = 8.1$ Hz, 1H), 7.22 (d, $J = 8.6$ Hz, 2H), 7.04 (dd, $J = 8.1, 2.0$ Hz, 1H), 6.85 (d, $J = 8.6$ Hz, 2H), 6.78 (d, $J = 1.9$ Hz, 1H), 4.87 (s, 2H), 3.78 (s, 3H); **^{13}C { ^1H } NMR** (101 MHz, CDCl_3) δ 166.1 (d, $J = 19.8$ Hz), 164.5 (d, $J = 275.3$ Hz), 159.4, 142.2, 135.2 (d, $J = 3.4$ Hz), 132.9 (d, $J = 7.7$ Hz), 131.0, 130.7, 130.2 (d, $J = 26.2$ Hz), 128.8, 128.7, 127.5, 126.38 – 126.18 (m), 126.1 (d, $J = 14.6$ Hz), 123.8 (d, $J = 272.6$ Hz), 122.7, 119.8, 114.4, 111.0 (d, $J = 19.5$ Hz), 109.6, 55.4, 43.4; **^{19}F NMR** (377 MHz, CDCl_3) δ -62.78 (s, 3F), -77.33 (s, 1F); **HRMS** (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{24}\text{H}_{17}\text{ClF}_4\text{NO}_2]^+$ Calcd 462.0878, found 462.0875; **IR** (ATR, MeCN, cm^{-1}) 2928, 1711, 1605, 1513, 1335, 1250, 1218, 1129, 1078, 810, 721; **mp** ($^\circ\text{C}$) 113.8–117.2.

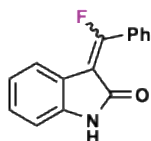
(E)-6-chloro-3-(fluoro-(3-trifluoromethyl)phenyl)methylene)indolin-2-one (3.5ab)



The title compound was prepared according to **Method D** (42.7 mg, 0.10 mmol scale) from **3.2ab**. The desired product was isolated as a yellow-orange solid (22.2 mg, 0.065 mmol, 65%, >95:5 *E:Z*). **^1H NMR** (400 MHz, $\text{DMSO}-d_6$) δ 10.87 (s, 1H), 8.44 (s, 1H), 8.23 (d, $J = 7.9$ Hz, 1H), 7.97 (d, $J = 7.9$ Hz, 1H), 7.78 (t, $J = 7.9$ Hz, 1H), 7.66 (d, $J = 8.2$ Hz, 1H), 7.09 (dd, $J = 8.2, 1.9$ Hz, 1H), 6.90 (d, $J = 1.9$ Hz, 1H); **^{13}C { ^1H } NMR** (101 MHz, $\text{DMSO}-d_6$) δ 166.5 (d, $J = 19.3$ Hz), 163.1 (d, $J = 273.5$ Hz), 141.9, 133.8 (d, $J = 3.3$ Hz), 133.0 (d, $J = 7.1$ Hz), 129.7 (d, $J = 26.4$ Hz), 129.4, 128.8 (d, $J = 32.3$ Hz), 128.59 – 128.44 (m), 126.2 (dq, $J = 7.8, 3.7$ Hz), 125.9 (d, $J = 13.6$ Hz),

123.8 (q, $J = 272.6$ Hz), 121.6, 120.0, 111.3 (d, $J = 17.9$ Hz), 109.7; ^{19}F NMR (377 MHz, CDCl_3) δ -61.29 (s, 3F), -78.52 (s, 1F); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_9\text{ClF}_4\text{NO}]^+$ Calcd 342.0303, found 342.0300; IR (ATR, MeCN, cm^{-1}) 3369, 1673, 1509, 1455, 1200, 1130, 834, 720; mp ($^{\circ}\text{C}$) 195.4-197.

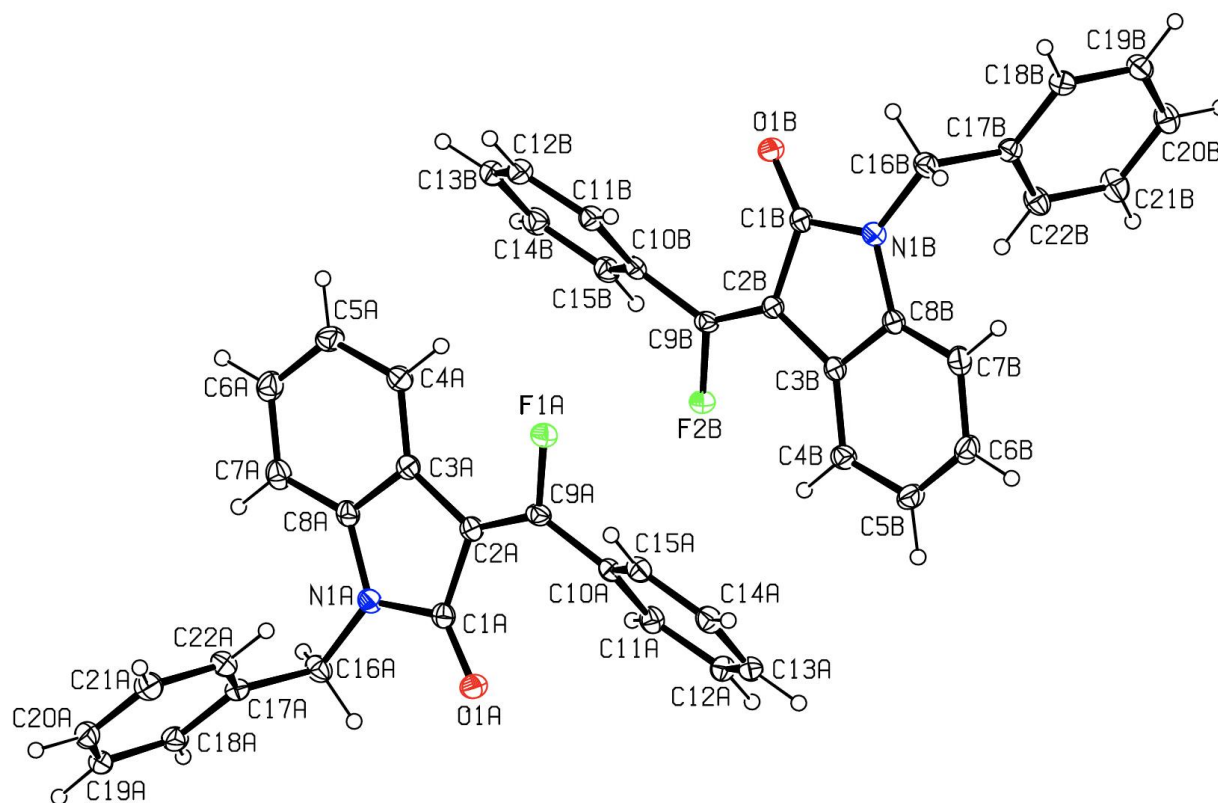
(*E*)-3-(fluoro-(3-phenyl)methylene)indolin-2-one (3.5a)



A 10 mL Schlenk tube equipped with a stir bar was charged with *o*-alkynylaniline **3.10** (0.20 mmol, 1.0 equiv), ethyl bromodifluoroacetate (0.122g, 0.60 mmol, 3.0 equiv), K_2CO_3 (0.083g, 0.60 mmol, 3.0 equiv) and MeCN (0.1 M, 2.0 mL). The reaction vessel was capped and sealed then submerged into an 80 $^{\circ}\text{C}$ oil bath and heated for 24 h. After cooling to rt, the reaction mixture was diluted with DCM, filtered through celite and concentrated under reduced pressure. The crude material was purified by column chromatography (1% MeOH:DCM) to yield the title compound as a yellow solid (23.9 mg, 0.1 mmol, 50% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.07 – 8.02 (m, 2H), 7.80 (d, $J = 7.7$ Hz, 1H), 7.59 – 7.46 (m, 3H), 7.26 – 7.20 (m, 1H), 7.07 (t, $J = 7.8$ Hz, 1H), 6.87 – 6.80 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.9 (d, $J = 8.1$ Hz), 166.5 (d, $J = 263.7$ Hz), 138.8, 132.1, 129.6, 129.4 (d, $J = 7.6$ Hz), 129.4, 129.0, 128.9 (d, $J = 2.5$ Hz), 128.0, 125.2 (d, $J = 14.4$ Hz), 122.5, 122.4, 110.6 (d, $J = 20.3$ Hz), 109.3; ^{19}F NMR (377 MHz, CDCl_3) δ -74.74 (major).

3.9 Crystallographic Data

3.9.1 Crystal Structure of **2a**

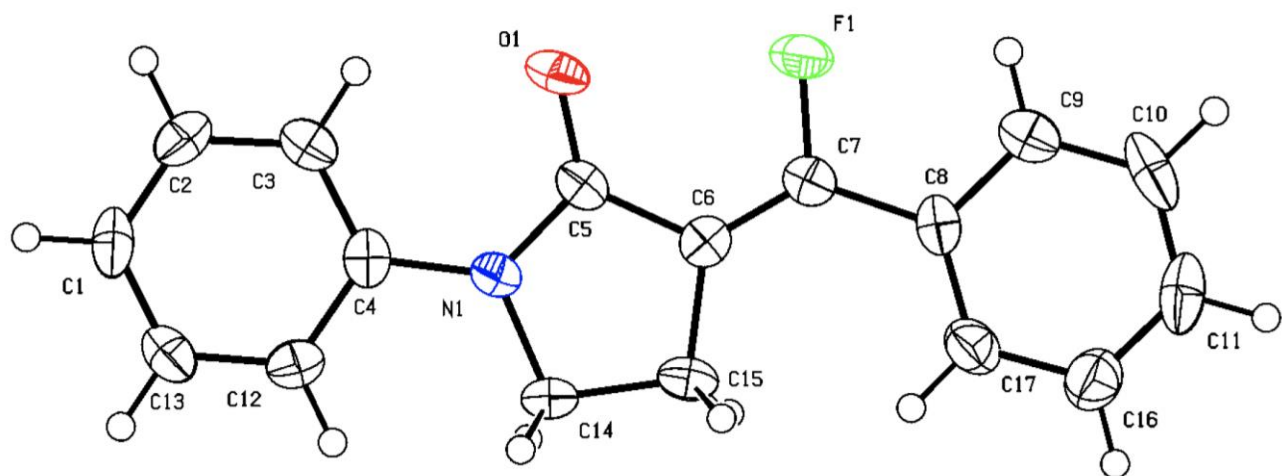


Crystal data and structure refinement for **2a**

Identification code	d2218_a
Empirical formula	C ₂₂ H ₁₆ NOF
Formula weight	329.36
Temperature/K	150(2)
Crystal system	monoclinic
Space group	P2 ₁
a/Å	6.1509(3)
b/Å	19.0134(11)
c/Å	13.8544(8)
α /°	90
β /°	93.892(3)
γ /°	90
Volume/Å ³	1616.53(15)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.353
μ/mm^{-1}	0.733

F(000)	688.0
Crystal size/mm ³	0.38 × 0.23 × 0.1
Radiation	CuK α (λ = 1.54178)
2 θ range for data collection/°	6.394 to 132.912
Index ranges	-7 ≤ h ≤ 7, -22 ≤ k ≤ 22, -16 ≤ l ≤ 16
Reflections collected	38033
Independent reflections	5579 [R_{int} = 0.0392, R_{sigma} = 0.0253]
Data/restraints/parameters	5579/1/451
Goodness-of-fit on F ²	1.067
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0293, wR_2 = 0.0787
Final R indexes [all data]	R_1 = 0.0310, wR_2 = 0.0798
Largest diff. peak/hole / e Å ⁻³	0.14/-0.16
Flack parameter	0.41(4)

3.9.2 Crystal Structure of 4a

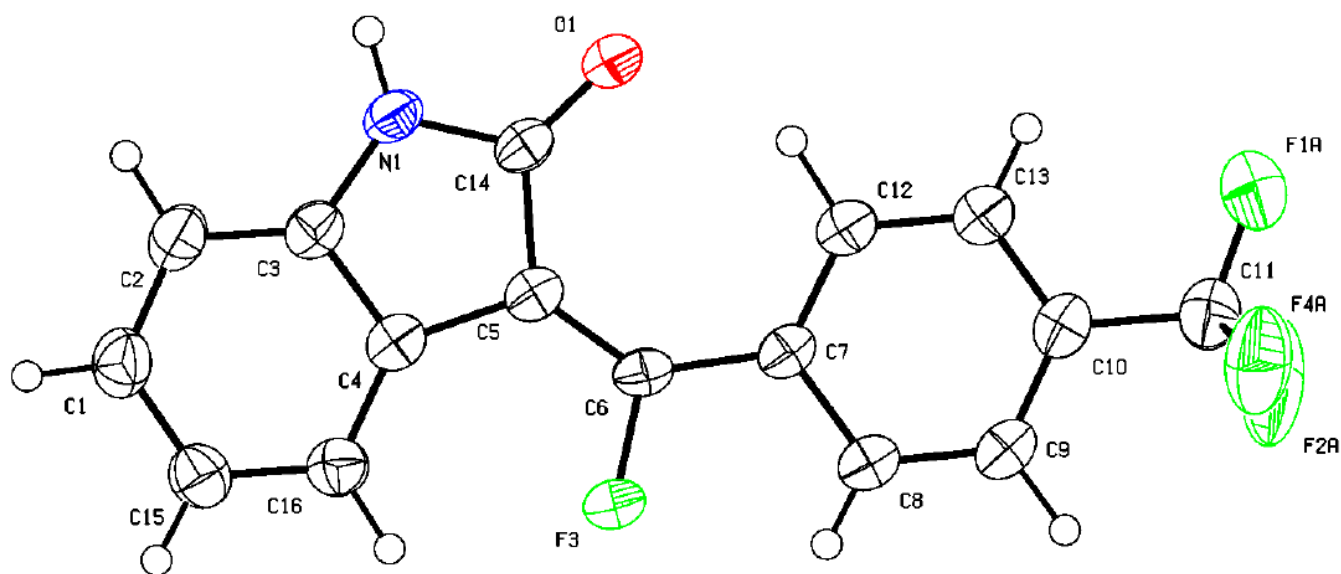


Crystal data and structure refinement for **4a**.

Identification code	EAM02_49_4_b
Empirical formula	C ₁₇ H ₁₄ FNO
Formula weight	267.29
Temperature/K	173.0
Crystal system	monoclinic
Space group	P2 ₁ /c
a/Å	13.8558(12)
b/Å	8.3051(7)
c/Å	10.8661(9)
α /°	90
β /°	92.028(4)
γ /°	90
Volume/Å ³	1249.62(18)
Z	4

$\rho_{\text{calc}}/\text{cm}^3$	1.421
μ/mm^{-1}	0.099
F(000)	560.0
Crystal size/ mm^3	$0.3 \times 0.2 \times 0.05$
Radiation	MoK α ($\lambda = 0.71073$)
2 θ range for data collection/ $^\circ$	5.72 to 55.578
Index ranges	$-18 \leq h \leq 18, -10 \leq k \leq 10, -14 \leq l \leq 14$
Reflections collected	24225
Independent reflections	2908 [$R_{\text{int}} = 0.0812, R_{\text{sigma}} = 0.0452$]
Data/restraints/parameters	2908/0/181
Goodness-of-fit on F^2	1.112
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.1087, wR_2 = 0.2537$
Final R indexes [all data]	$R_1 = 0.1412, wR_2 = 0.2712$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.85/-0.36

3.9.3 Crystal Structure of **5aa**



Crystal data and structure refinement for **5aa**.

Identification code	YF02_21_0m_a
Empirical formula	$\text{C}_{16}\text{H}_9\text{F}_4\text{NO}$
Formula weight	307.24
Temperature/K	173.0
Crystal system	monoclinic
Space group	$C2/c$
$a/\text{\AA}$	28.6033(11)
$b/\text{\AA}$	5.1793(2)
$c/\text{\AA}$	19.1352(7)
$\alpha/^\circ$	90
$\beta/^\circ$	111.9310(10)
$\gamma/^\circ$	90

Volume/Å ³	2629.64(17)
Z	8
ρ _{calc} /cm ³	1.552
μ/mm ⁻¹	0.136
F(000)	1248.0
Crystal size/mm ³	0.4 × 0.1 × 0.075
Radiation	MoKα (λ = 0.71073)
2θ range for data collection/°	4.468 to 55.002
Index ranges	-36 ≤ h ≤ 36, -6 ≤ k ≤ 6, -24 ≤ l ≤ 24
Reflections collected	27214
Independent reflections	2934 [R _{int} = 0.0384, R _{sigma} = 0.0269]
Data/restraints/parameters	2934/0/235
Goodness-of-fit on F ²	1.045
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0644, wR ₂ = 0.1734
Final R indexes [all data]	R ₁ = 0.0845, wR ₂ = 0.1963
Largest diff. peak/hole / e Å ⁻³	0.77/-0.58

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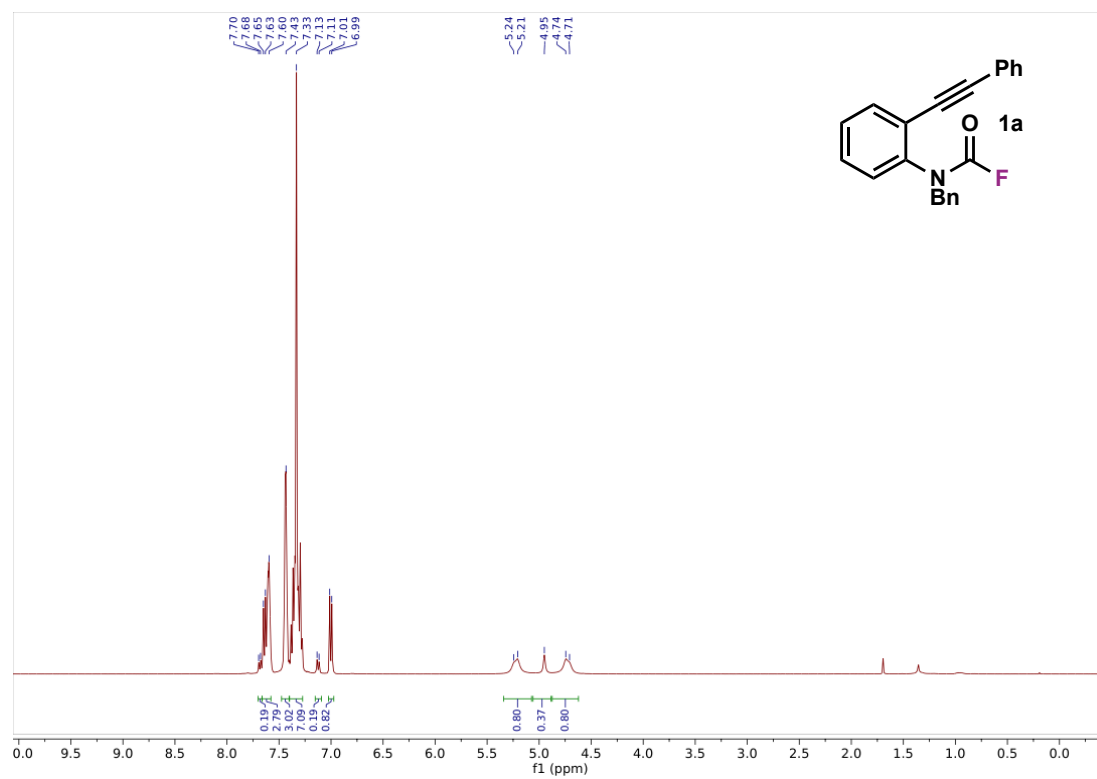
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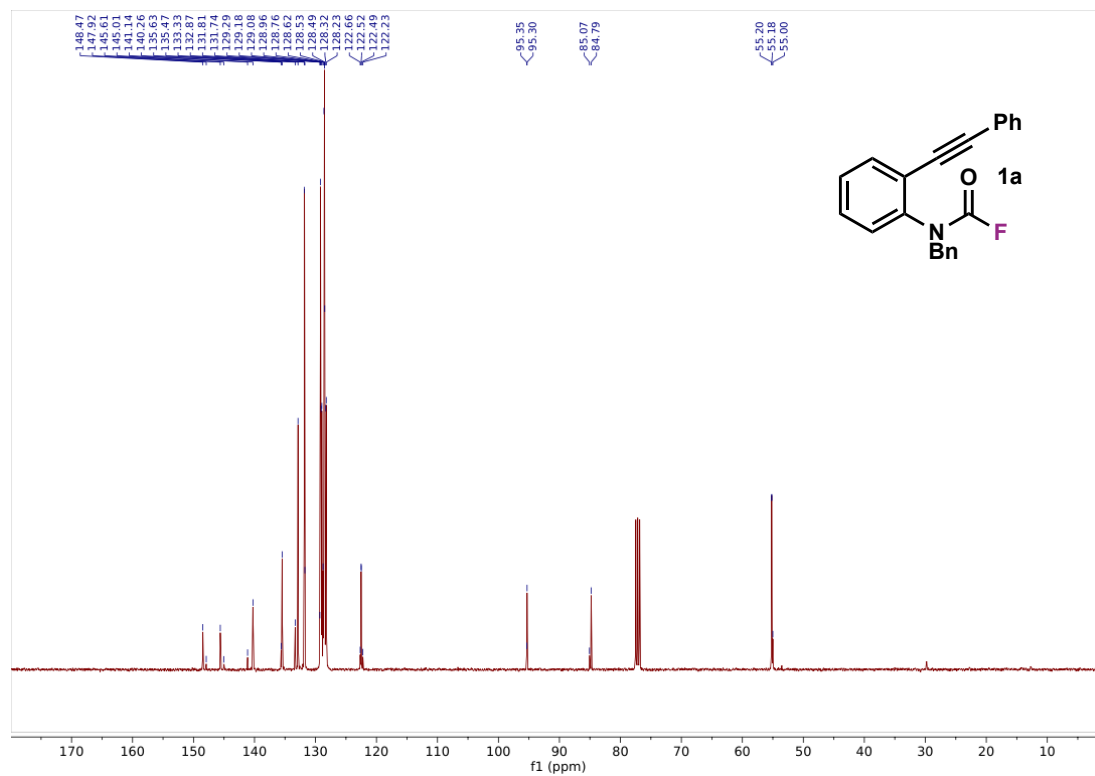
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3.11 Appendix

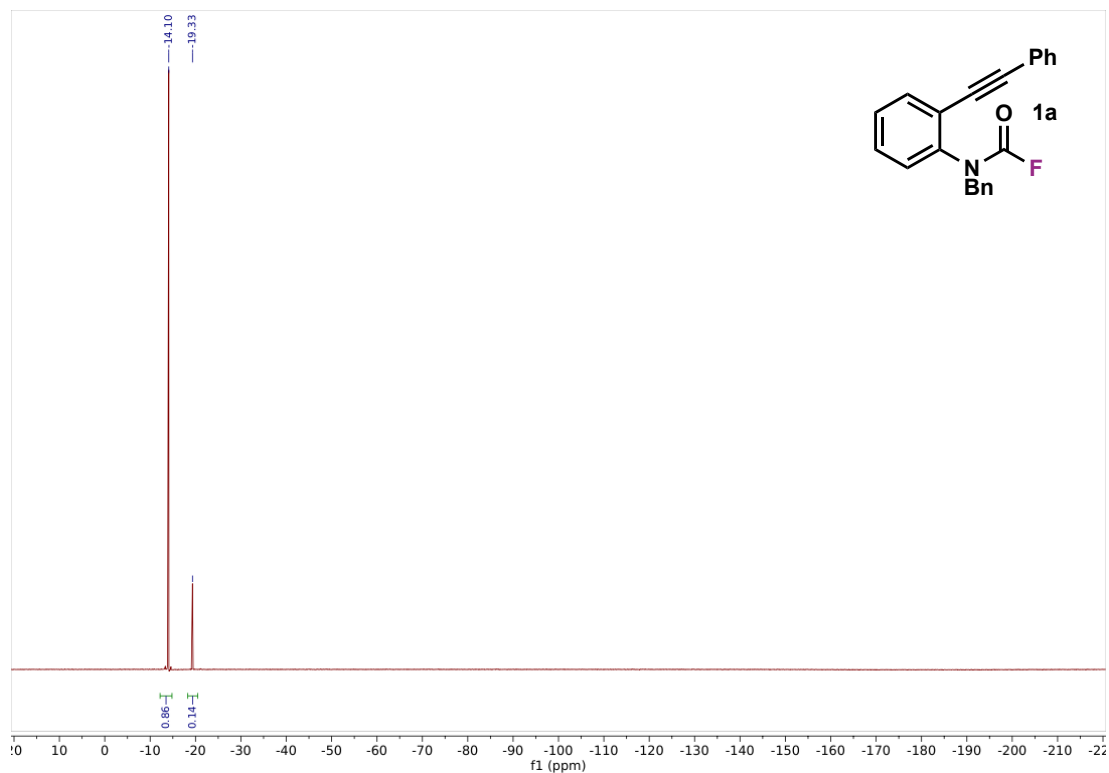
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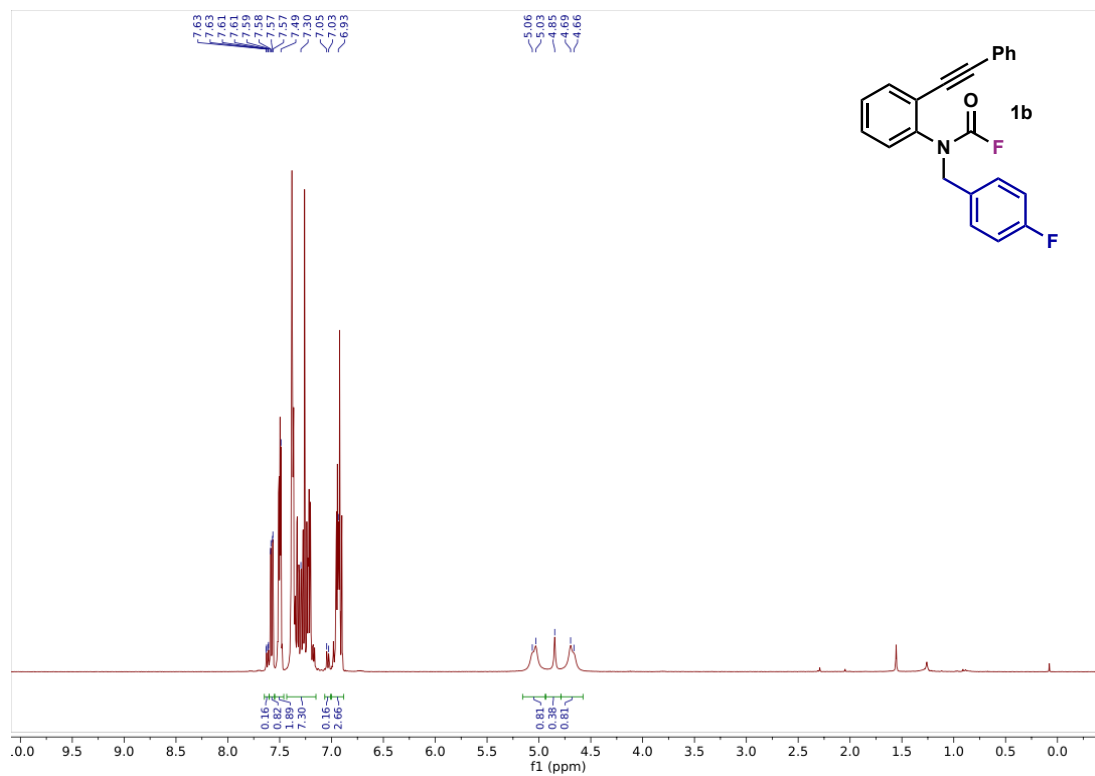
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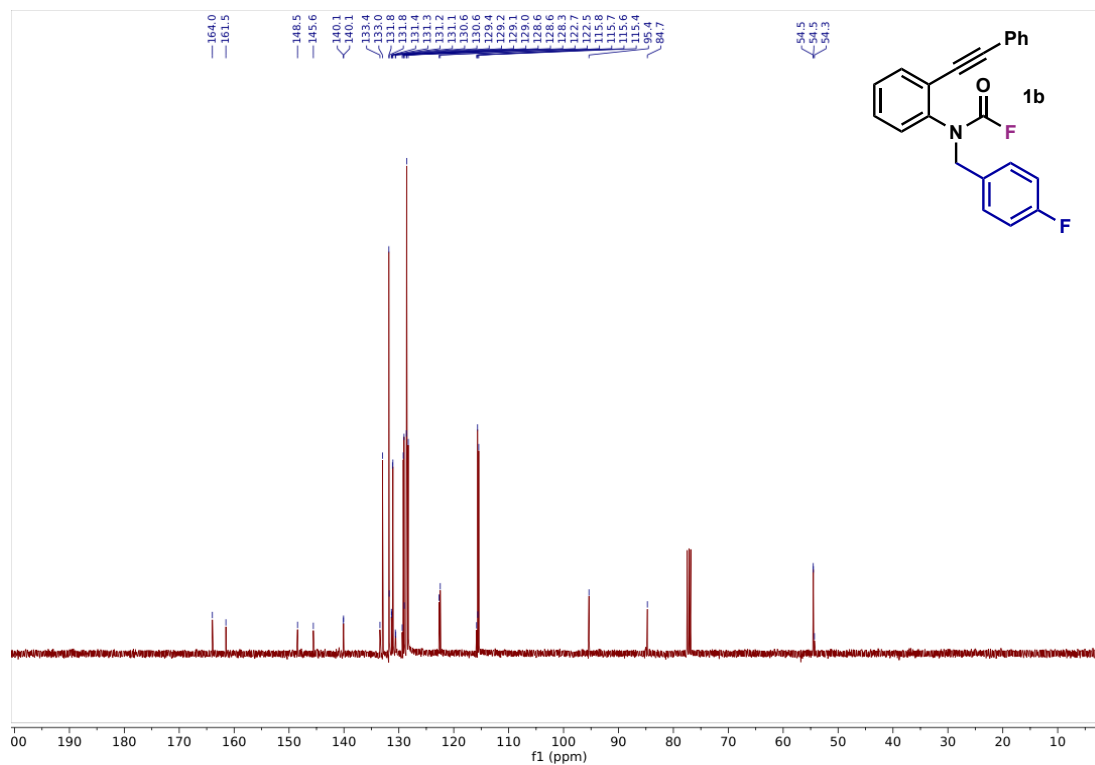
^{19}F NMR (377MHz, CDCl_3) of **3.1a**



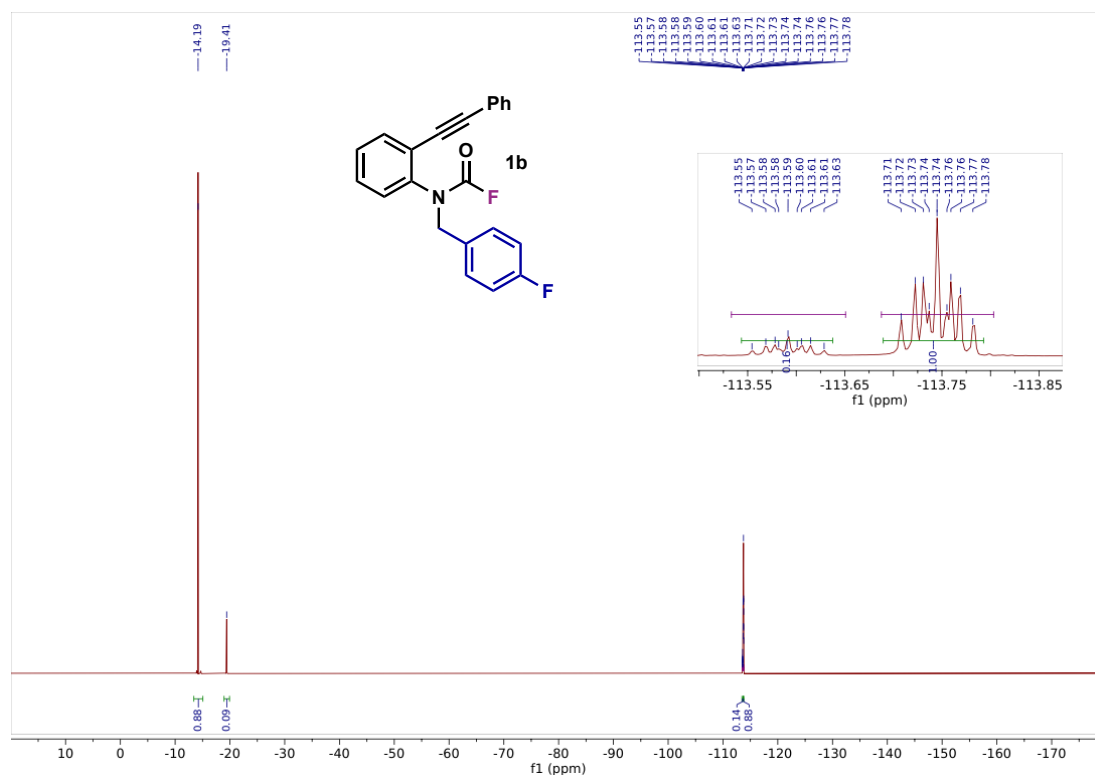
^1H NMR (400 MHz, CDCl_3) of **3.1b**



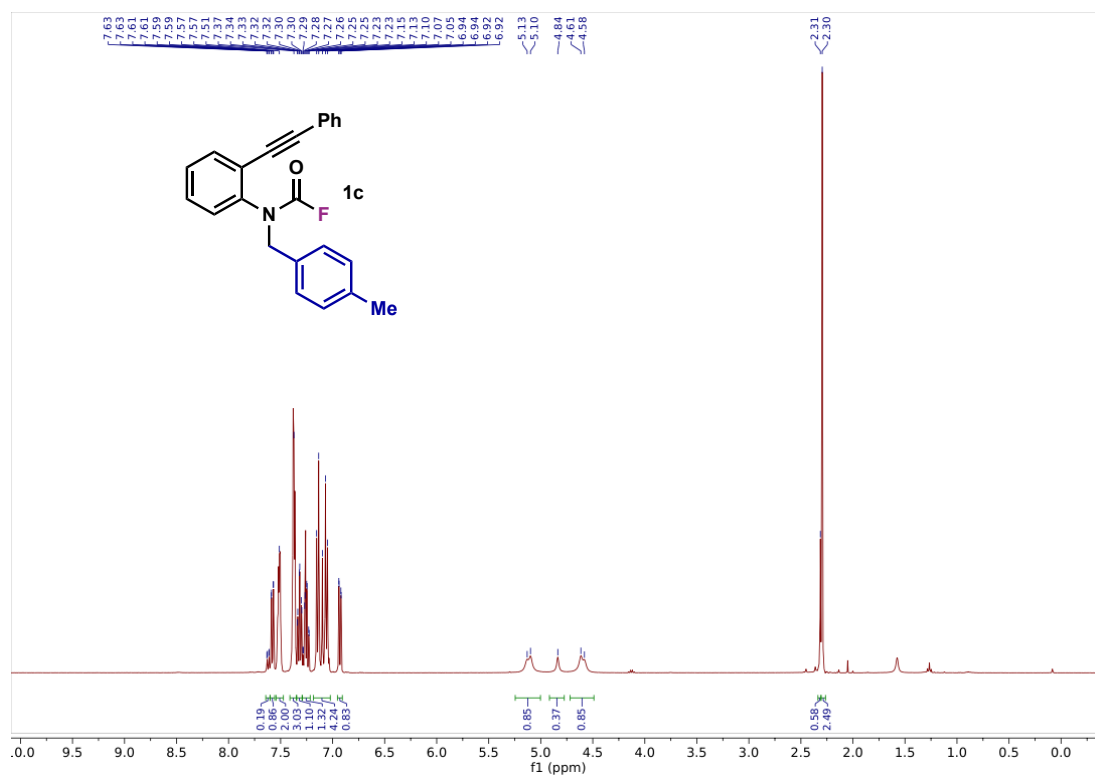
^{13}C { ^1H } NMR (101 MHz, CDCl_3) of **3.1b**



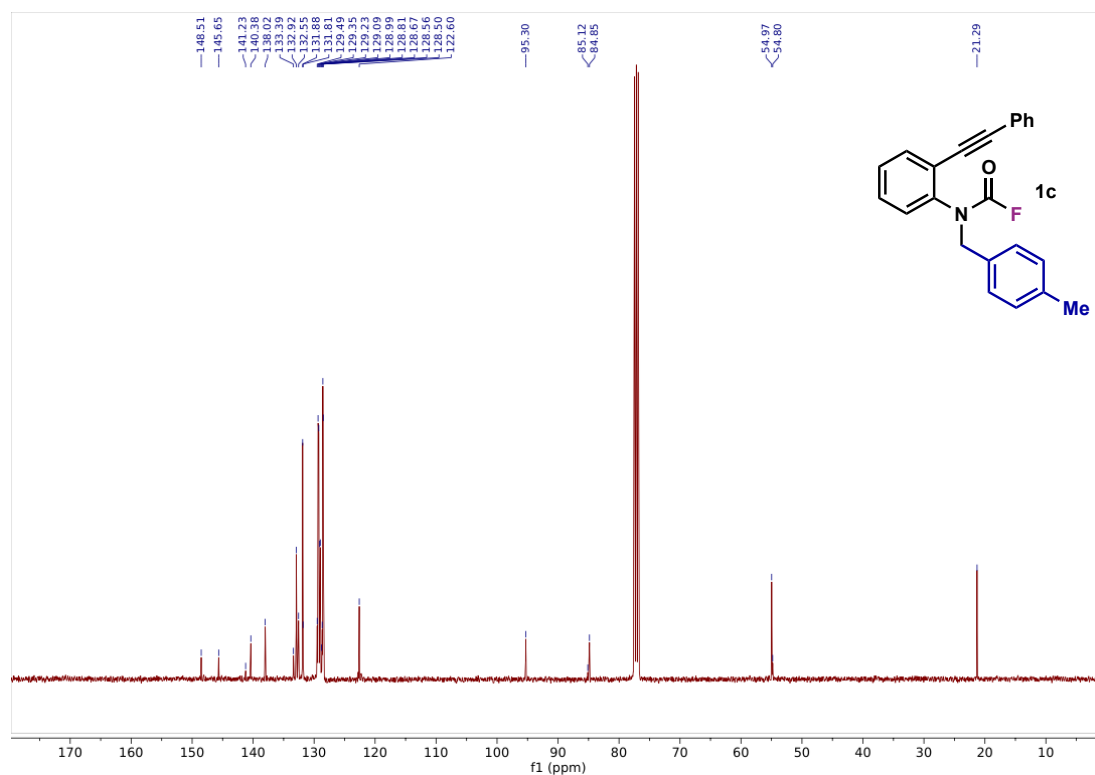
^{19}F NMR (377 MHz, CDCl_3) of **3.1b**



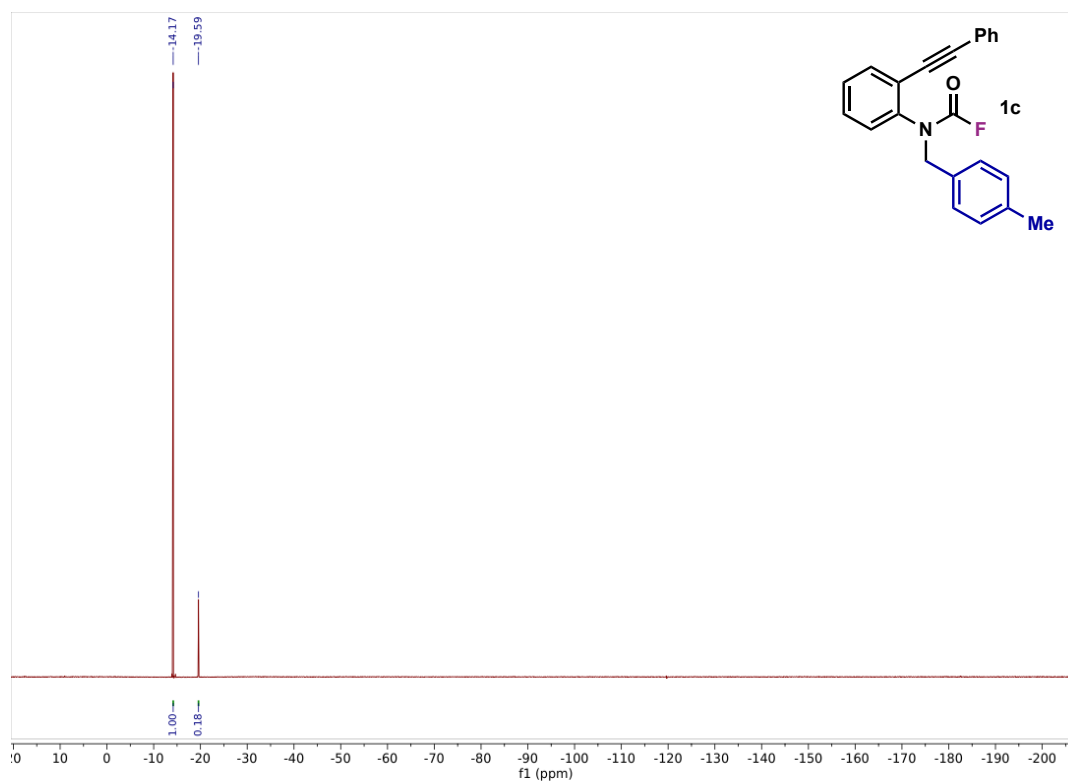
^1H NMR (400 MHz, CDCl_3) of **3.1c**



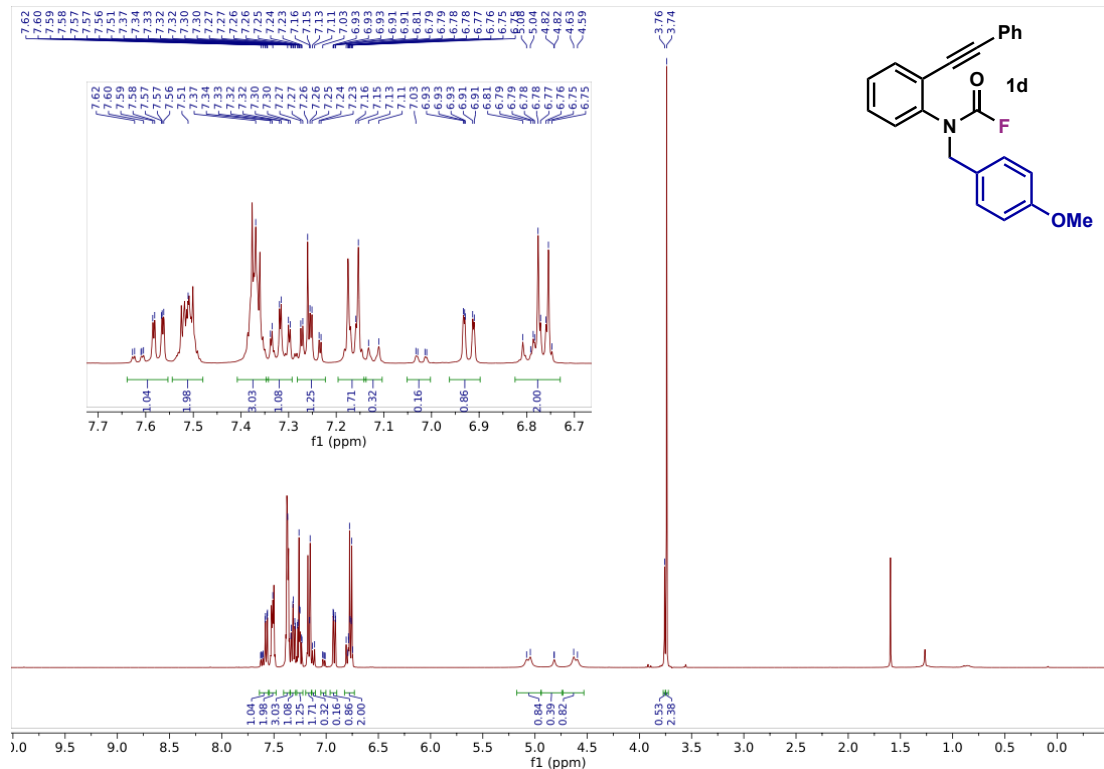
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.1c**



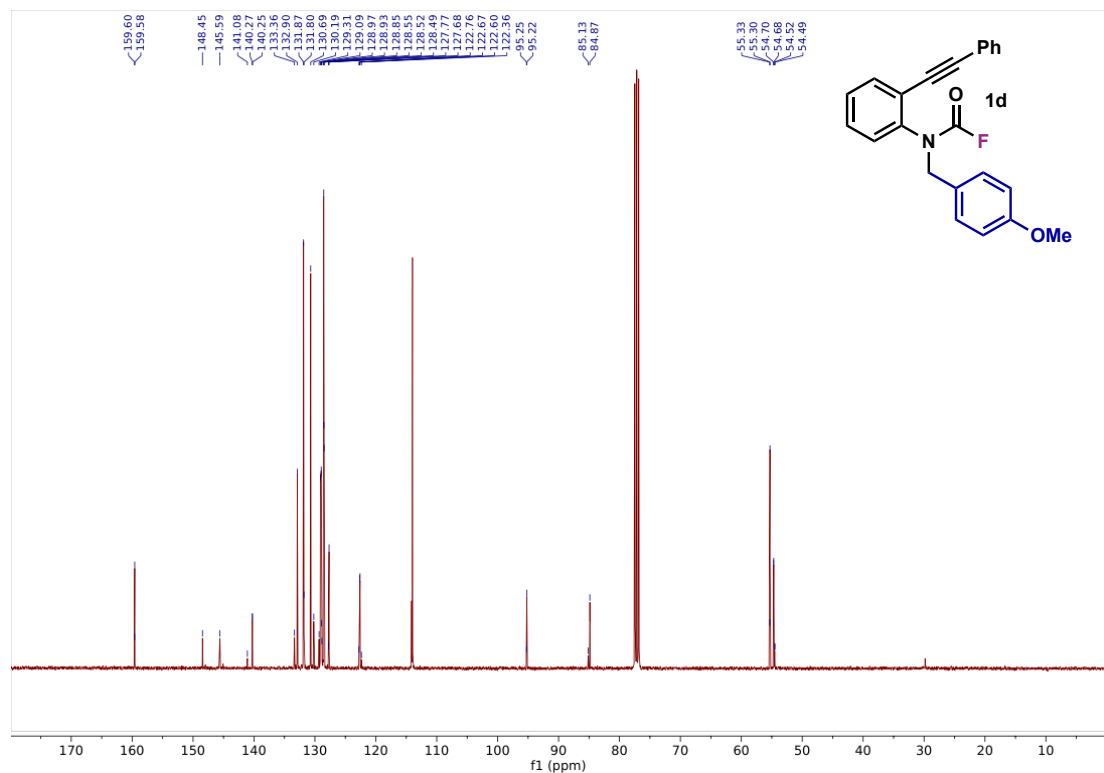
^{19}F NMR (377 MHz, CDCl_3) of **3.1c**



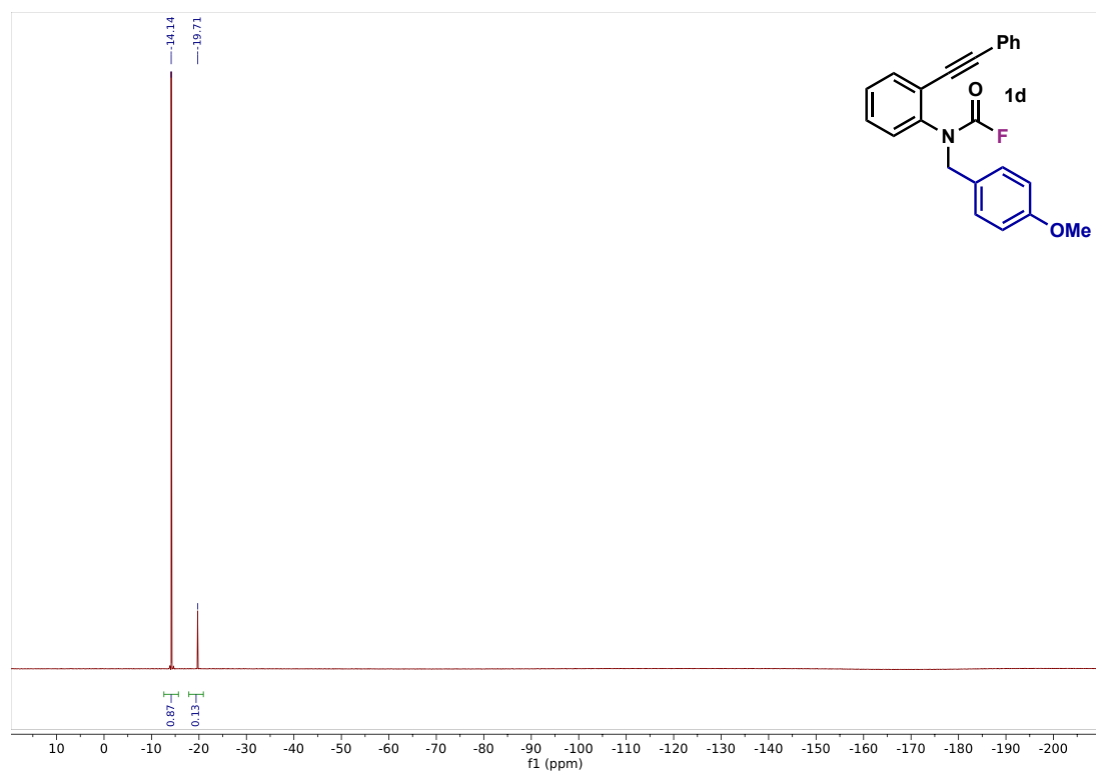
^1H NMR (400 MHz, CDCl_3) of **3.1d**



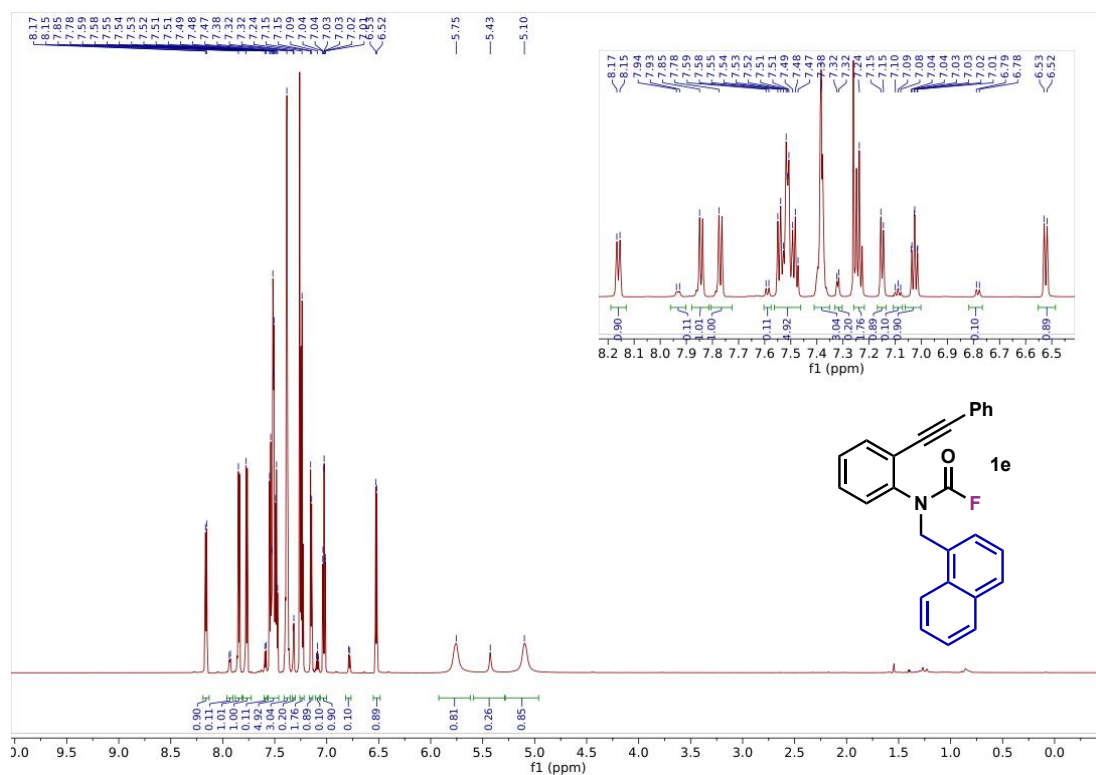
^{13}C { ^1H } NMR (101 MHz, CDCl_3) of **3.1d**



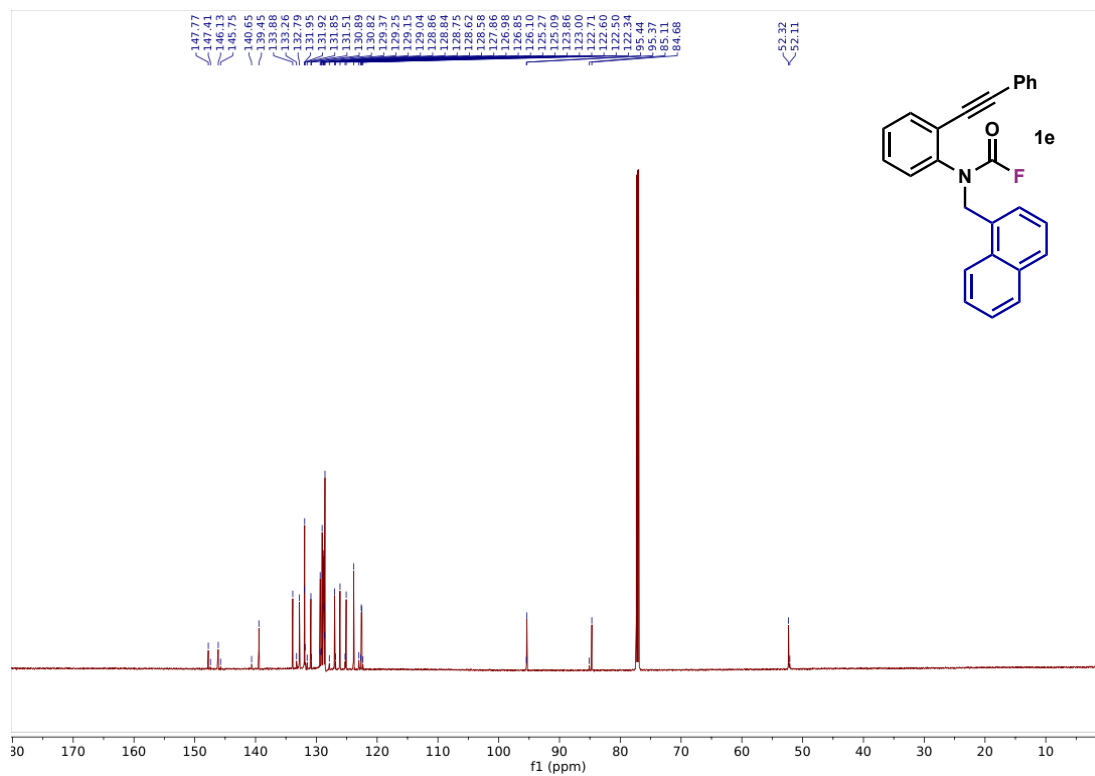
¹⁹F NMR (377 MHz, CDCl₃) of **3.1d**



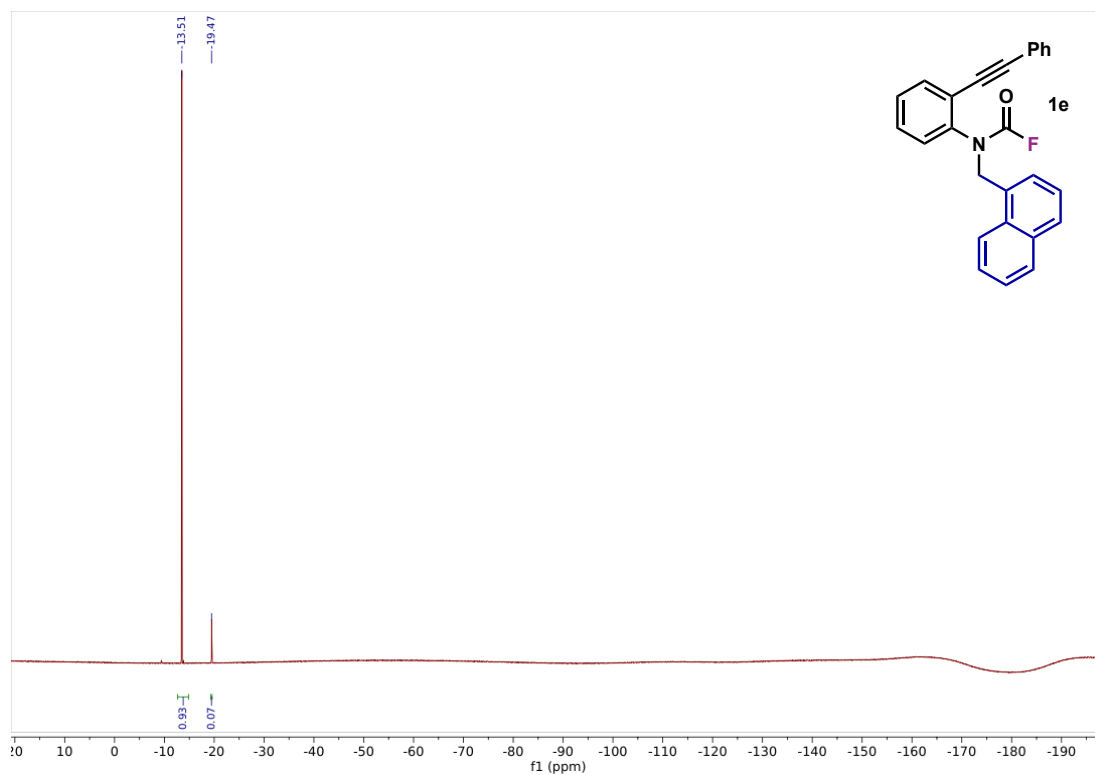
¹H NMR (700 MHz, CDCl₃) of **3.1e**



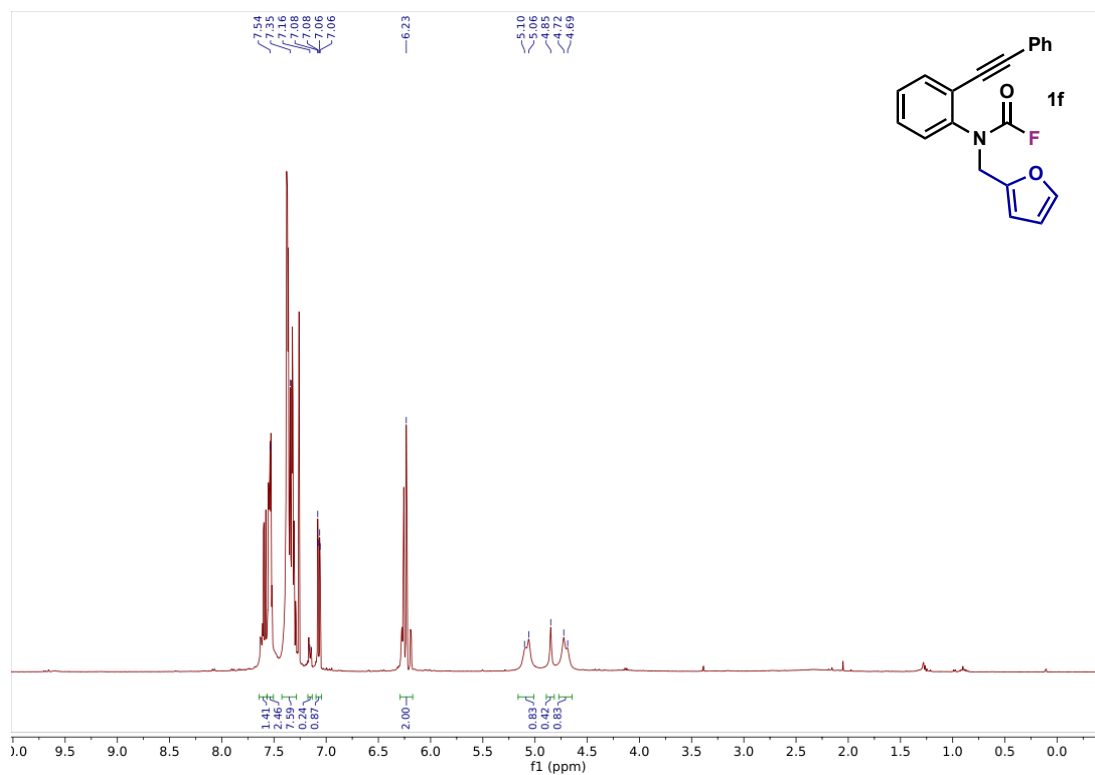
^{13}C { ^1H } NMR (176 MHz, CDCl_3) of **3.1e**



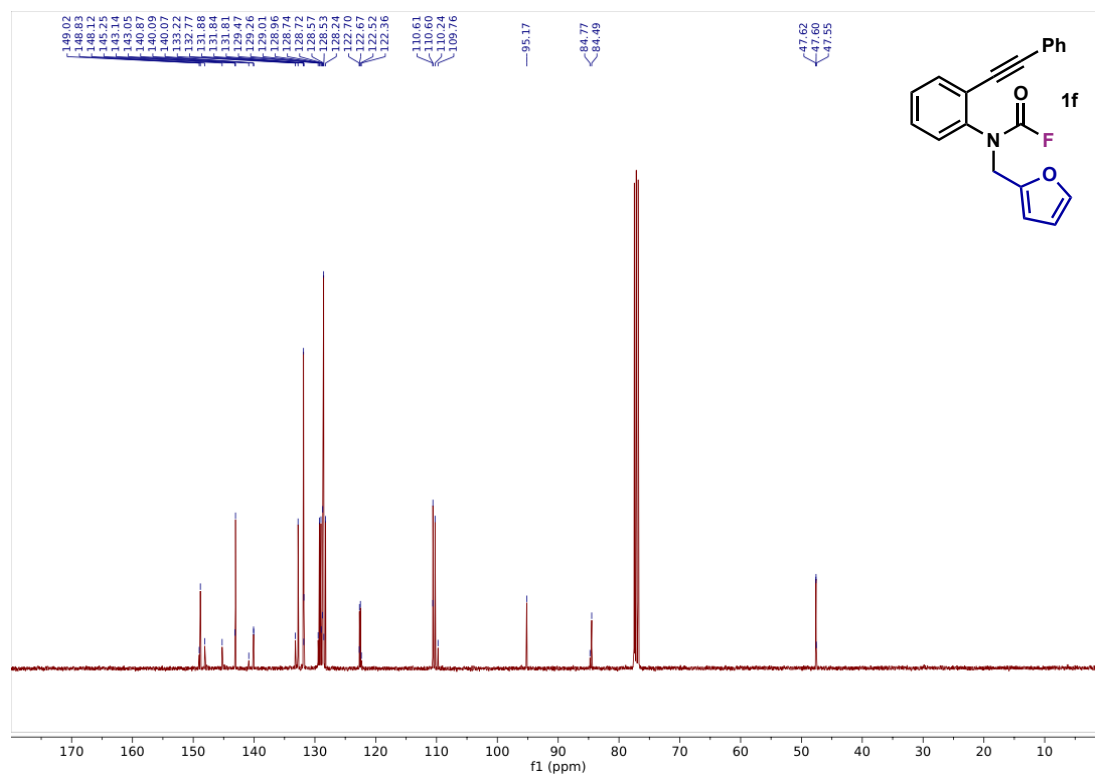
^{19}F NMR (659 MHz, CDCl_3) of **3.1e**



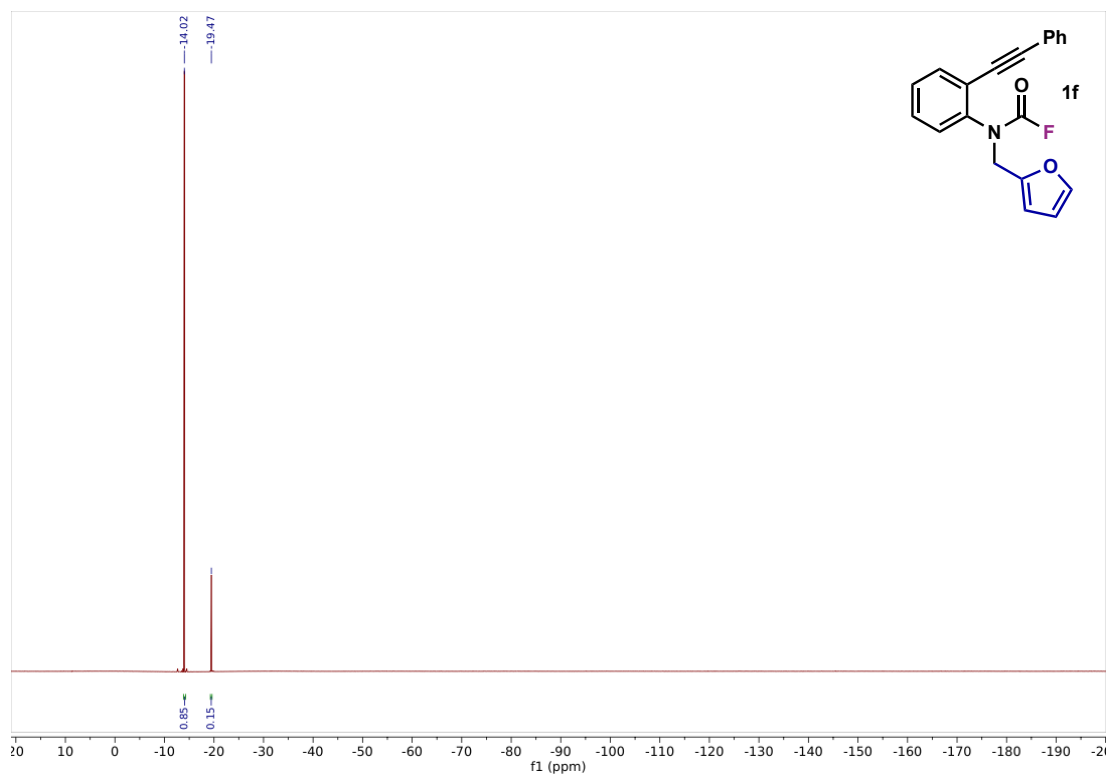
^1H NMR (400 MHz, CDCl_3) of **3.1f**



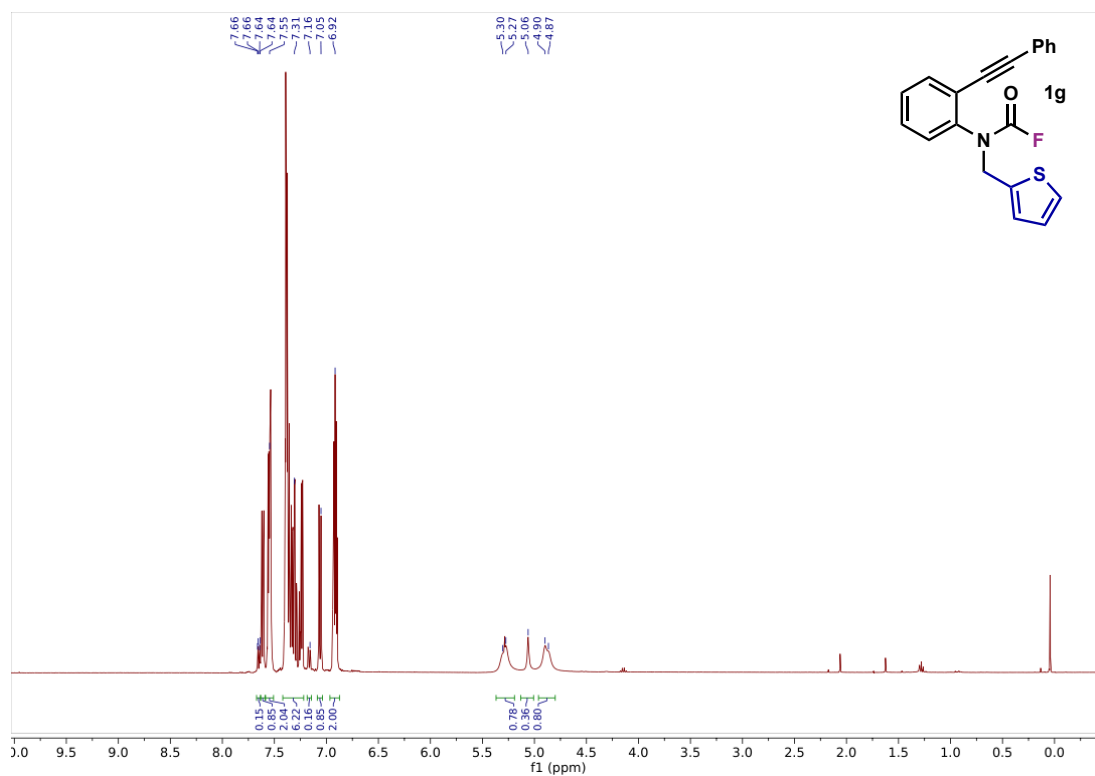
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.1f**



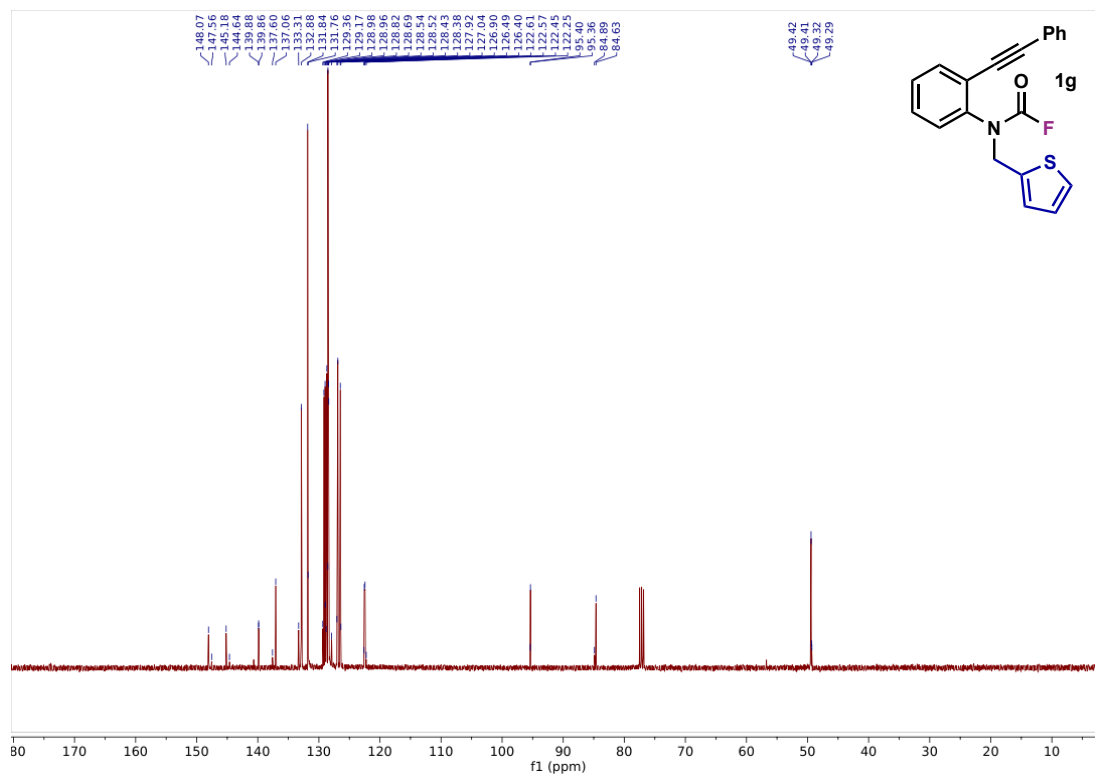
^{19}F NMR (377 MHz, CDCl_3) of **3.1f**



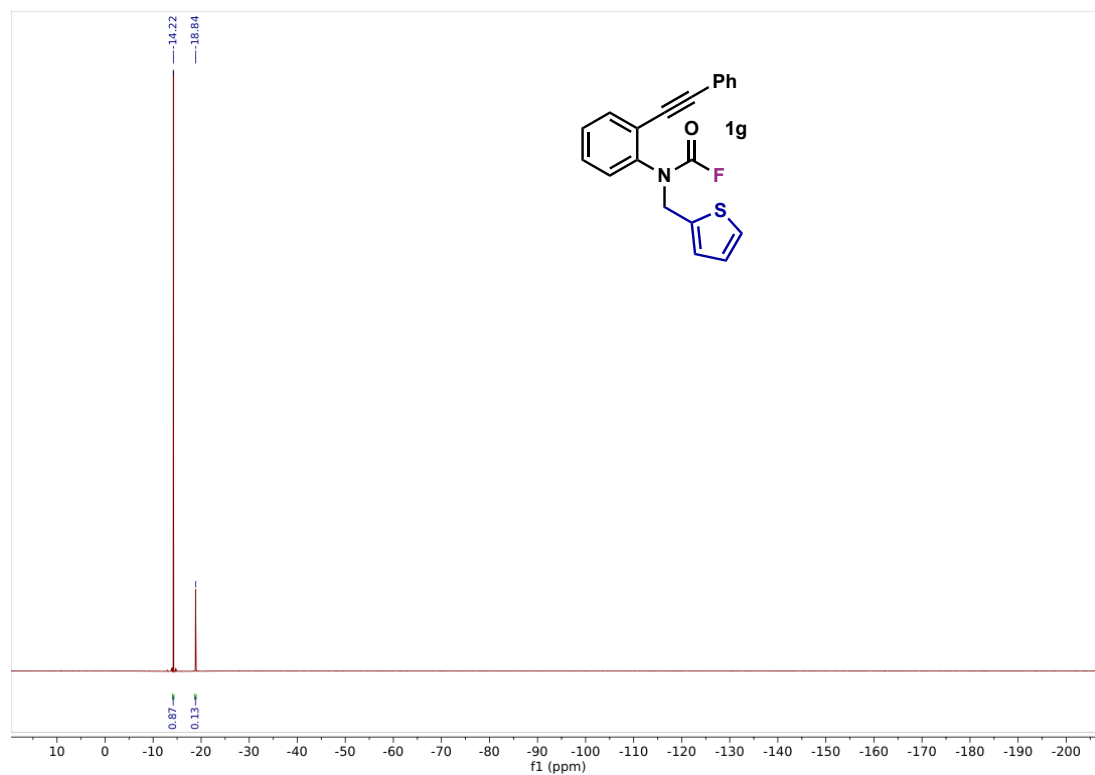
^1H NMR (400 MHz, CDCl_3) of **3.1g**



^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.1g**



^{19}F NMR (377 MHz, CDCl_3) of **3.1g**



Chemical structure of compound **1h** is shown above the spectrum. The structure is a benzimidazole derivative with a phenylethynyl group and a cyclohexylmethyl group.

¹H NMR spectrum (CDCl₃) of compound **1h**. The x-axis represents the chemical shift in ppm (f1), ranging from 0.0 to 10.0. The spectrum shows several peaks corresponding to the protons in the molecule.

Peak list (ppm):

- 7.63
- 7.39
- 7.38
- 7.28
- 3.72
- 3.60
- 3.58
- 3.55
- 3.53
- 1.83
- 1.66
- 1.17
- 1.04

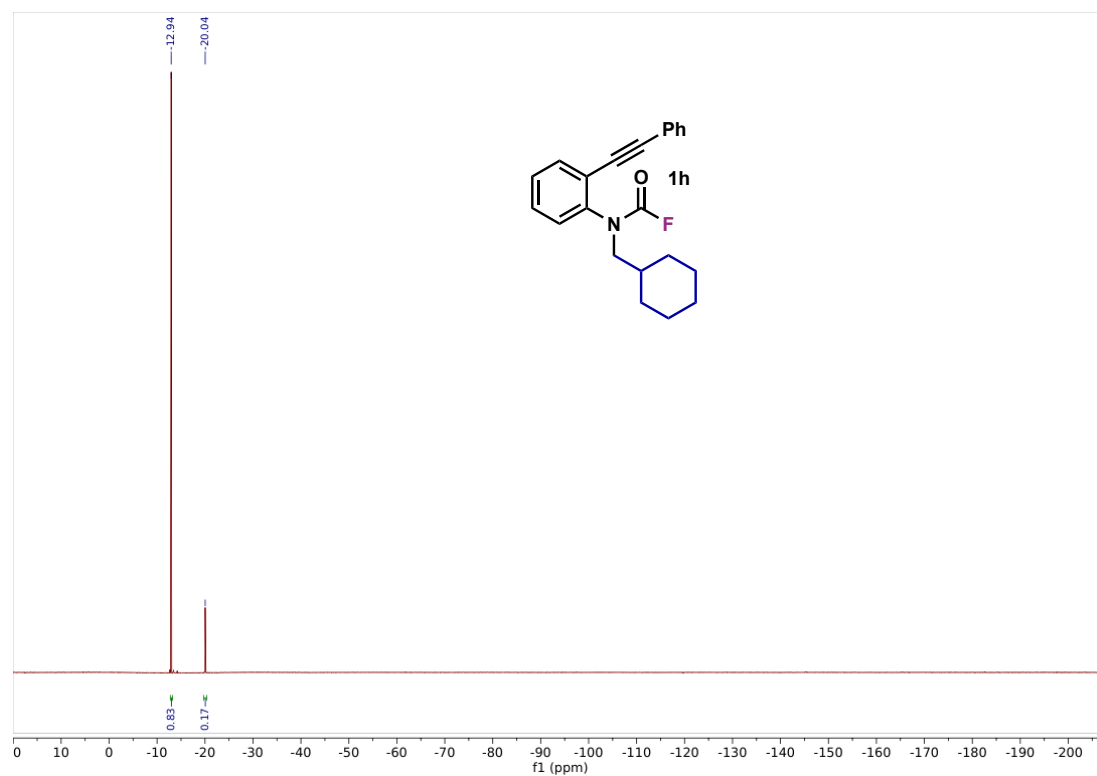
Integration values (from left to right):

- 1.00
- 0.95
- 0.97
- 1.21
- 0.83
- 0.37
- 0.81
- 6.52
- 5.52

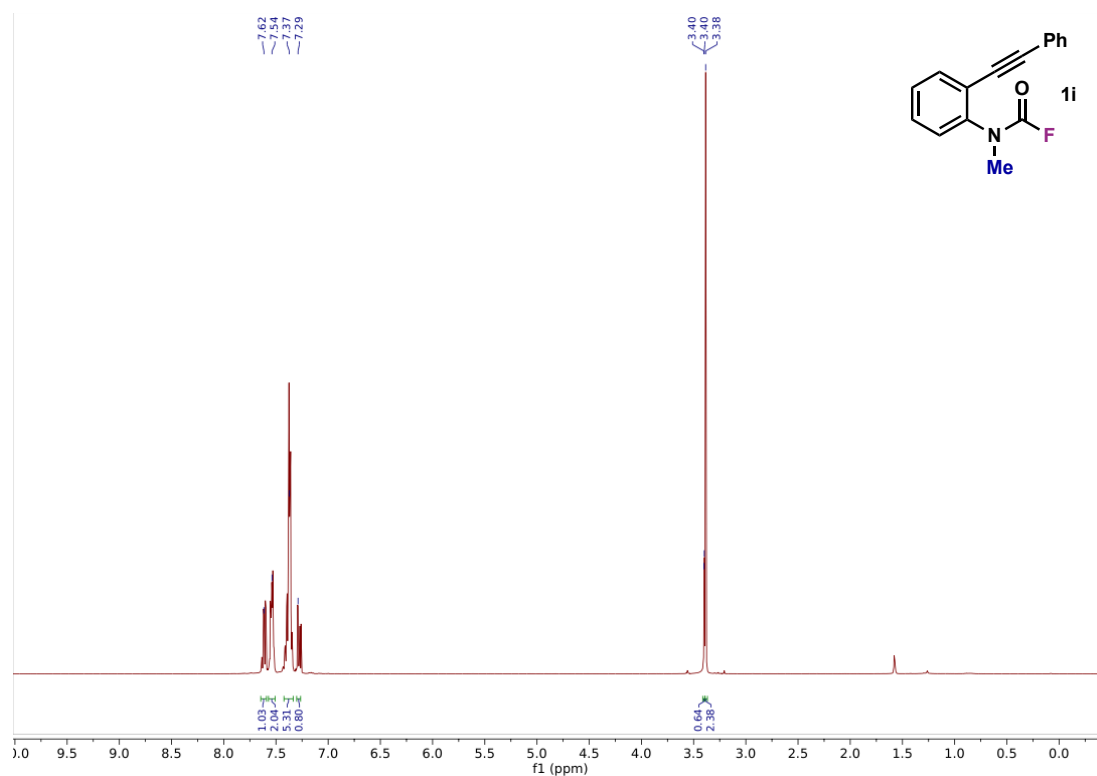
Chemical structure of compound 1h is shown above the spectrum. The structure is a 2-(cyclohexylmethyl)-1-(phenylethynyl)benzamide derivative, labeled 1h. The spectrum displays the ¹³C NMR peaks for this compound, with chemical shifts (ppm) labeled above the peaks:

143.91, 143.27, 141.67, 141.33, 141.19, 139.19, 138.91, 138.76, 138.60, 138.50, 138.39, 138.33, 137.86, 137.80, 137.60, 137.59, 137.45, 137.40, 137.34, 137.28, 137.22, 137.16, 137.10, 137.04, 136.98, 136.92, 136.86, 136.80, 136.74, 136.68, 136.62, 136.56, 136.50, 136.44, 136.38, 136.32, 136.26, 136.20, 136.14, 136.08, 136.02, 135.96, 135.90, 135.84, 135.78, 135.72, 135.66, 135.60, 135.54, 135.48, 135.42, 135.36, 135.30, 135.24, 135.18, 135.12, 135.06, 135.00, 134.94, 134.88, 134.82, 134.76, 134.70, 134.64, 134.58, 134.52, 134.46, 134.40, 134.34, 134.28, 134.22, 134.16, 134.10, 134.04, 133.98, 133.92, 133.86, 133.80, 133.74, 133.68, 133.62, 133.56, 133.50, 133.44, 133.38, 133.32, 133.26, 133.20, 133.14, 133.08, 133.02, 132.96, 132.90, 132.84, 132.78, 132.72, 132.66, 132.60, 132.54, 132.48, 132.42, 132.36, 132.30, 132.24, 132.18, 132.12, 132.06, 132.00, 131.94, 131.88, 131.82, 131.76, 131.70, 131.64, 131.58, 131.52, 131.46, 131.40, 131.34, 131.28, 131.22, 131.16, 131.10, 131.04, 130.98, 130.92, 130.86, 130.80, 130.74, 130.68, 130.62, 130.56, 130.50, 130.44, 130.38, 130.32, 130.26, 130.20, 130.14, 130.08, 130.02, 129.96, 129.90, 129.84, 129.78, 129.72, 129.66, 129.60, 129.54, 129.48, 129.42, 129.36, 129.30, 129.24, 129.18, 129.12, 129.06, 129.00, 128.94, 128.88, 128.82, 128.76, 128.70, 128.64, 128.58, 128.52, 128.46, 128.40, 128.34, 128.28, 128.22, 128.16, 128.10, 128.04, 127.98, 127.92, 127.86, 127.80, 127.74, 127.68, 127.62, 127.56, 127.50, 127.44, 127.38, 127.32, 127.26, 127.20, 127.14, 127.08, 127.02, 126.96, 126.90, 126.84, 126.78, 126.72, 126.66, 126.60, 126.54, 126.48, 126.42, 126.36, 126.30, 126.24, 126.18, 126.12, 126.06, 126.00, 125.94, 125.88, 125.82, 125.76, 125.70, 125.64, 125.58, 125.52, 125.46, 125.40, 125.34, 125.28, 125.22, 125.16, 125.10, 125.04, 124.98, 124.92, 124.86, 124.80, 124.74, 124.68, 124.62, 124.56, 124.50, 124.44, 124.38, 124.32, 124.26, 124.20, 124.14, 124.08, 124.02, 123.96, 123.90, 123.84, 123.78, 123.72, 123.66, 123.60, 123.54, 123.48, 123.42, 123.36, 123.30, 123.24, 123.18, 123.12, 123.06, 123.00, 122.94, 122.88, 122.82, 122.76, 122.70, 122.64, 122.58, 122.52, 122.46, 122.40, 122.34, 122.28, 122.22, 122.16, 122.10, 122.04, 121.98, 121.92, 121.86, 121.80, 121.74, 121.68, 121.62, 121.56, 121.50, 121.44, 121.38, 121.32, 121.26, 121.20, 121.14, 121.08, 121.02, 120.96, 120.90, 120.84, 120.78, 120.72, 120.66, 120.60, 120.54, 120.48, 120.42, 120.36, 120.30, 120.24, 120.18, 120.12, 120.06, 120.00, 119.94, 119.88, 119.82, 119.76, 119.70, 119.64, 119.58, 119.52, 119.46, 119.40, 119.34, 119.28, 119.22, 119.16, 119.10, 119.04, 118.98, 118.92, 118.86, 118.80, 118.74, 118.68, 118.62, 118.56, 118.50, 118.44, 118.38, 118.32, 118.26, 118.20, 118.14, 118.08, 118.02, 117.96, 117.90, 117.84, 117.78, 117.72, 117.66, 117.60, 117.54, 117.48, 117.42, 117.36, 117.30, 117.24, 117.18, 117.12, 117.06, 117.00, 116.94, 116.88, 116.82, 116.76, 116.70, 116.64, 116.58, 116.52, 116.46, 116.40, 116.34, 116.28, 116.22, 116.16, 116.10, 116.04, 115.98, 115.92, 115.86, 115.80, 115.74, 115.68, 115.62, 115.56, 115.50, 115.44, 115.38, 115.32, 115.26, 115.20, 115.14, 115.08, 115.02, 114.96, 114.90, 114.84, 114.78, 114.72, 114.66, 114.60, 114.54, 114.48, 114.42, 114.36, 114.30, 114.24, 114.18, 114.12, 114.06, 114.00, 113.94, 113.88, 113.82, 113.76, 113.70, 113.64, 113.58, 113.52, 113.46, 113.40, 113.34, 113.28, 113.22, 113.16, 113.10, 113.04, 112.98, 112.92, 112.86, 112.80, 112.74, 112.68, 112.62, 112.56, 112.50, 112.44, 112.38, 112.32, 112.26, 112.20, 112.14, 112.08, 112.02, 111.96, 111.90, 111.84, 111.78, 111.72, 111.66, 111.60, 111.54, 111.48, 111.42, 111.36, 111.30, 111.24, 111.18, 111.12, 111.06, 111.00, 110.94, 110.88, 110.82, 110.76, 110.70, 110.64, 110.58, 110.52, 110.46, 110.40, 110.34, 110.28, 110.22, 110.16, 110.10, 110.04, 109.98, 109.92, 109.86, 109.80, 109.74, 109.68, 109.62, 109.56, 109.50, 109.44, 109.38, 109.32, 109.26, 109.20, 109.14, 109.08, 109.02, 108.96, 108.90, 108.84, 108.78, 108.72, 108.66, 108.60, 108.54, 108.48, 108.42, 108.

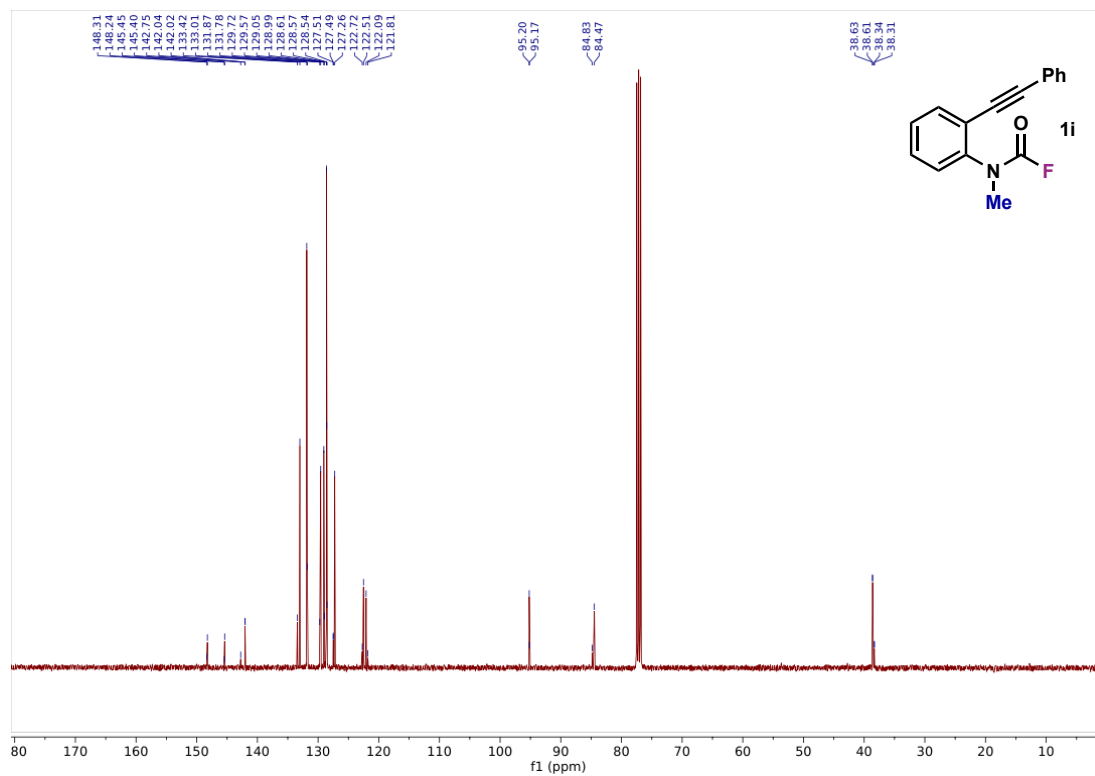
^{19}F NMR (377 MHz, CDCl_3) of **3.1h**



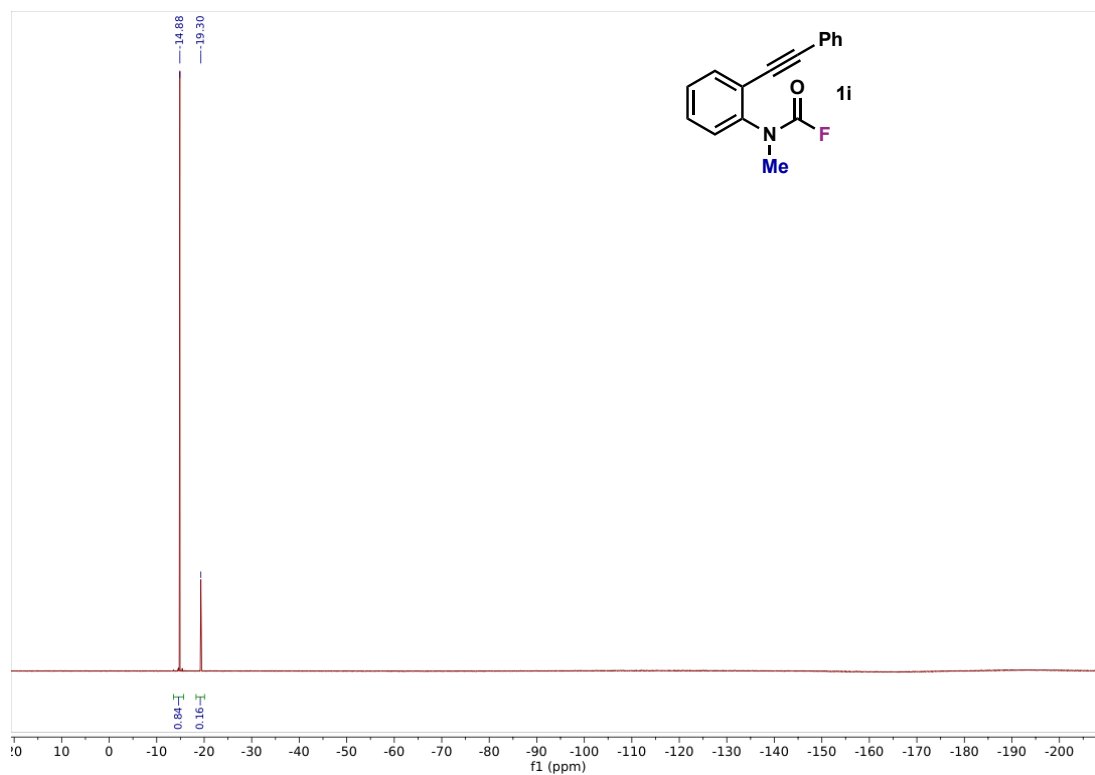
^1H NMR (400 MHz, CDCl_3) of **3.1i**



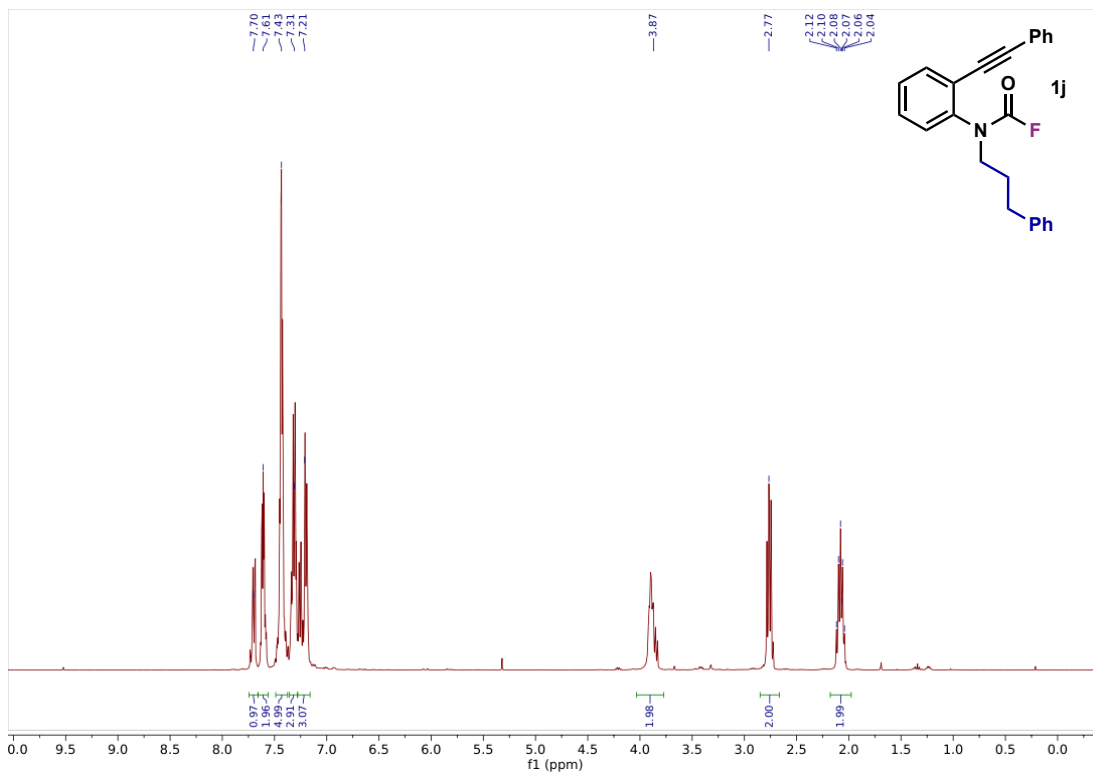
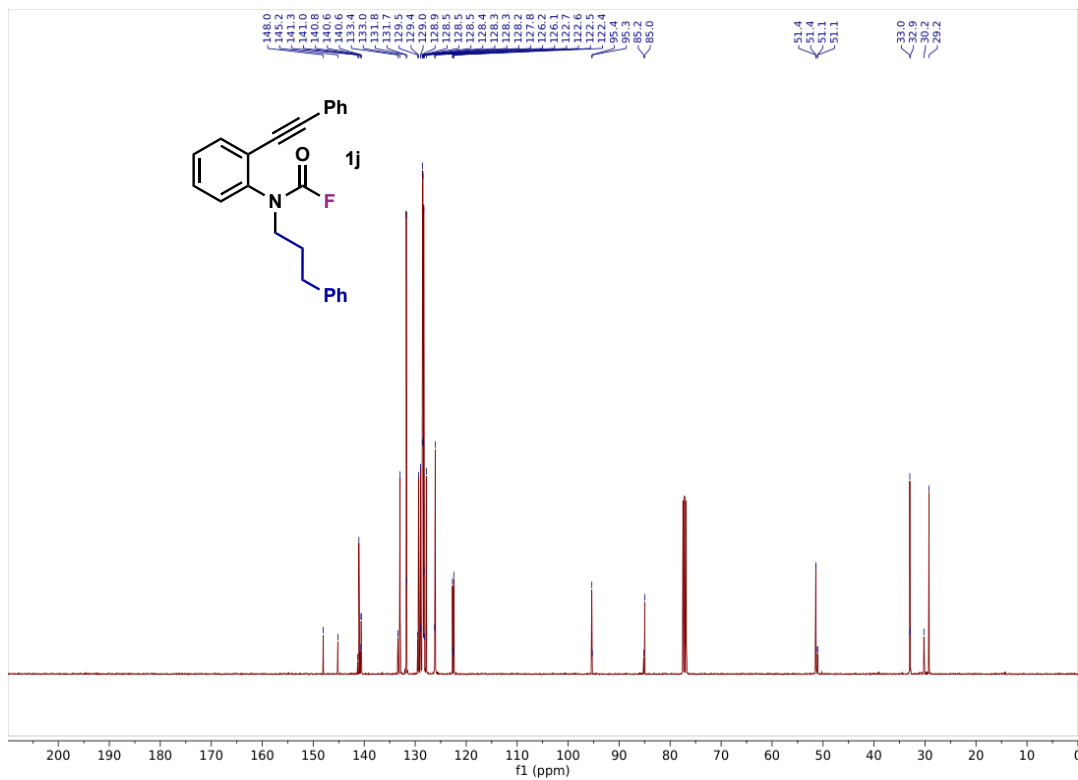
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.1i**



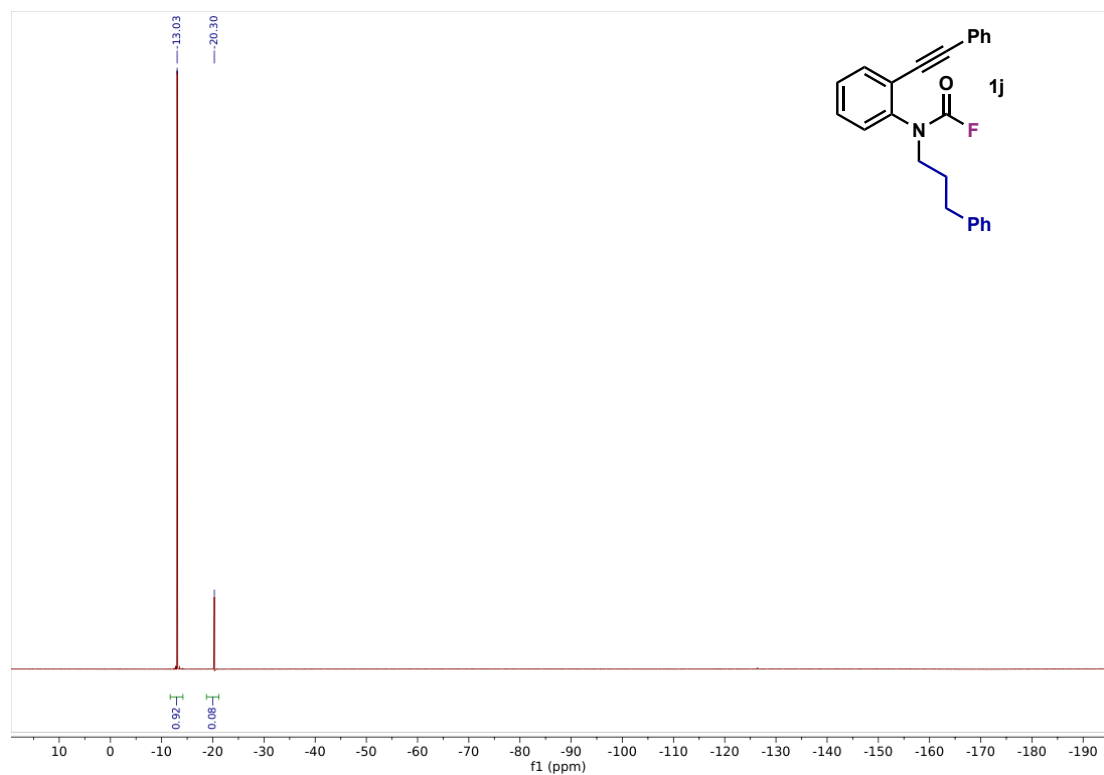
^{19}F NMR (377 MHz, CDCl_3) of **3.1i**



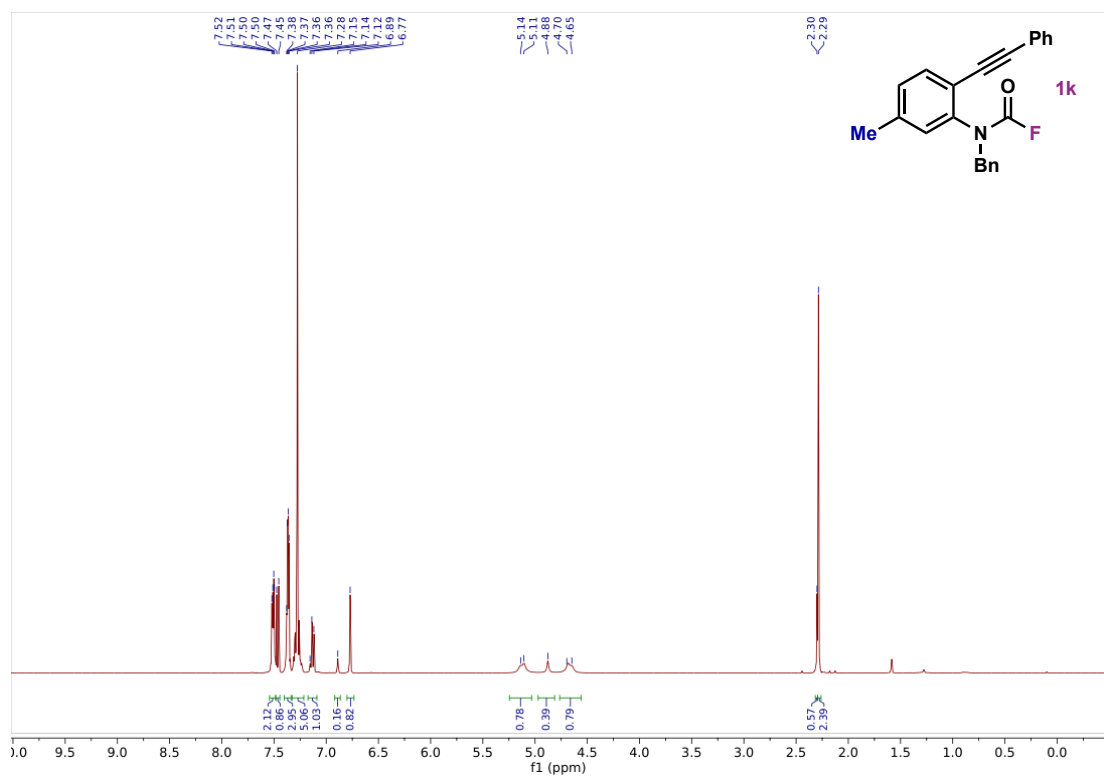
¹H NMR (400 MHz, CDCl₃) of **3.1j**

 $^{13}\text{C} \{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.1j**

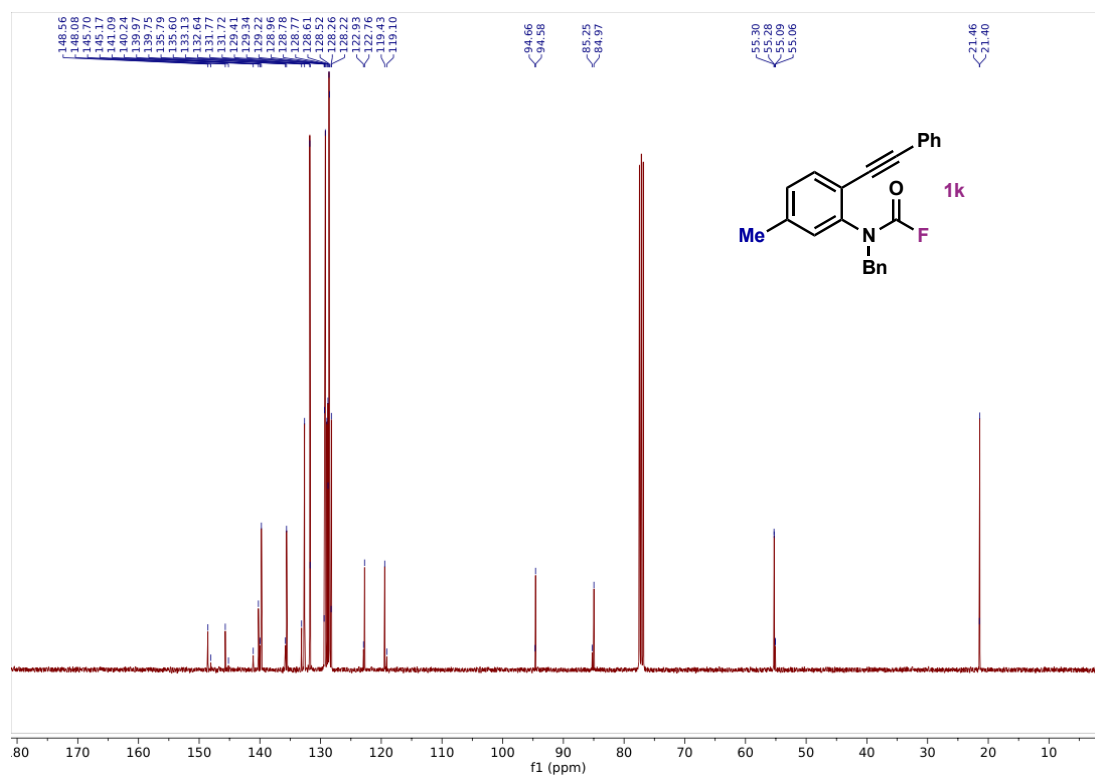
^{19}F NMR (377 MHz, CDCl_3) of **3.1j**



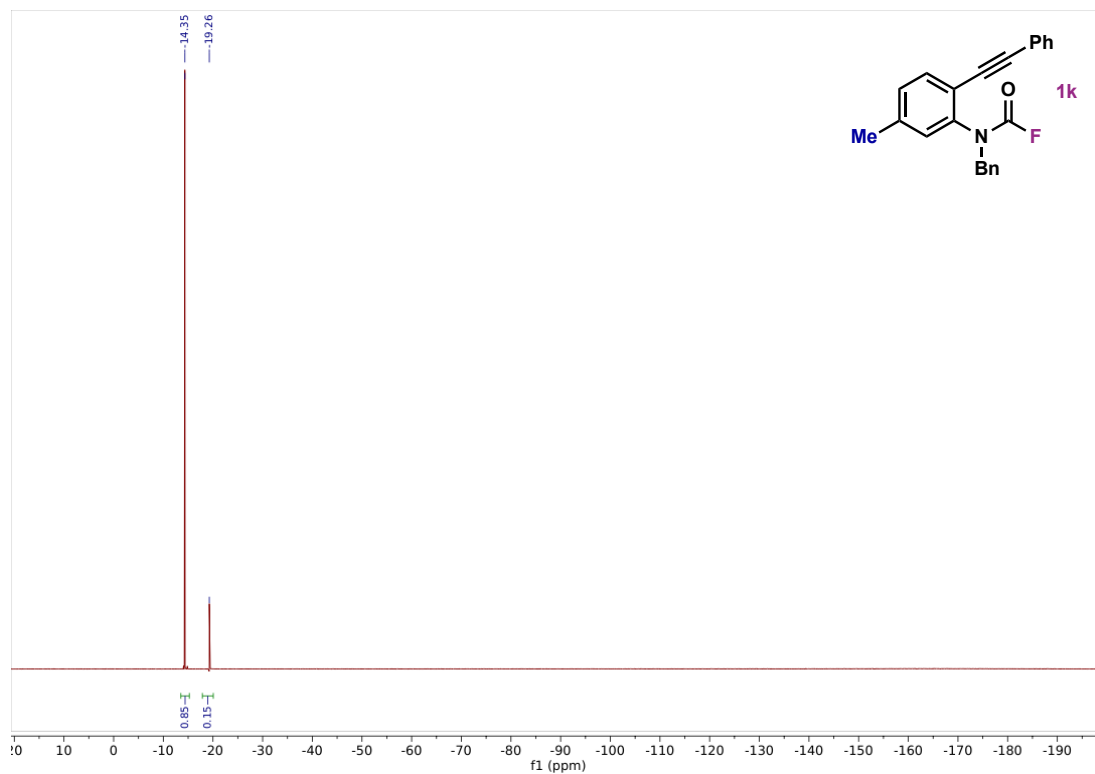
^1H NMR (400 MHz, CDCl_3) of **3.1k**



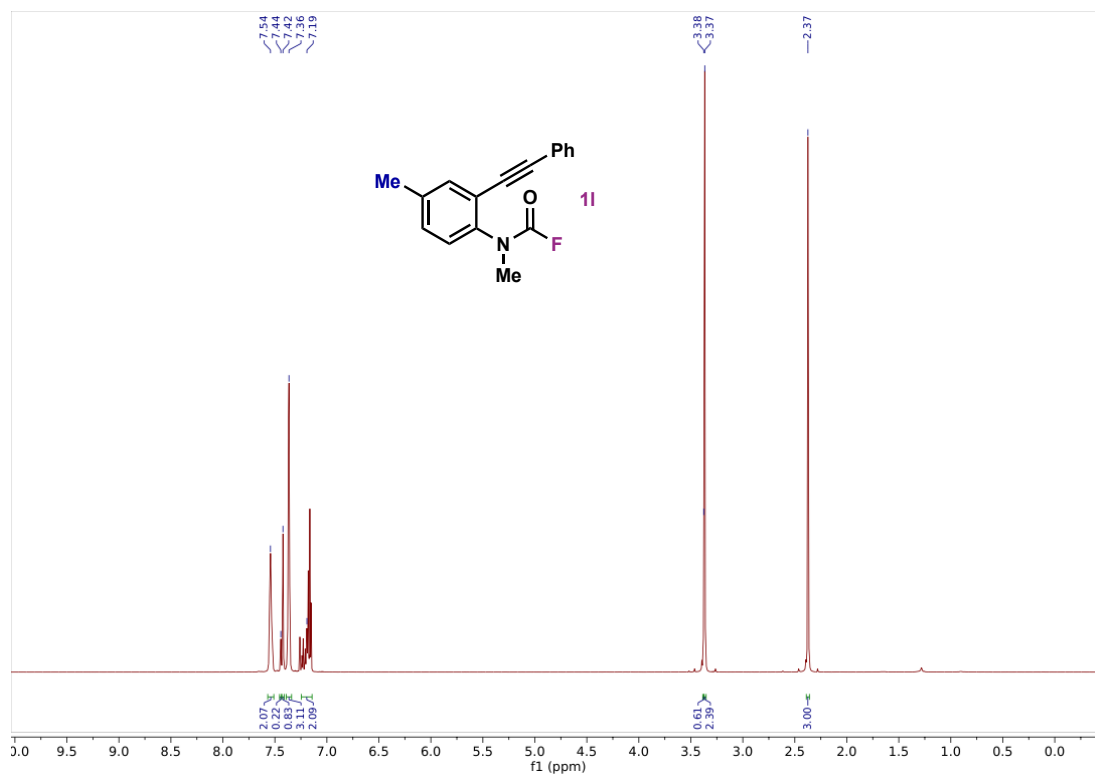
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.1k**



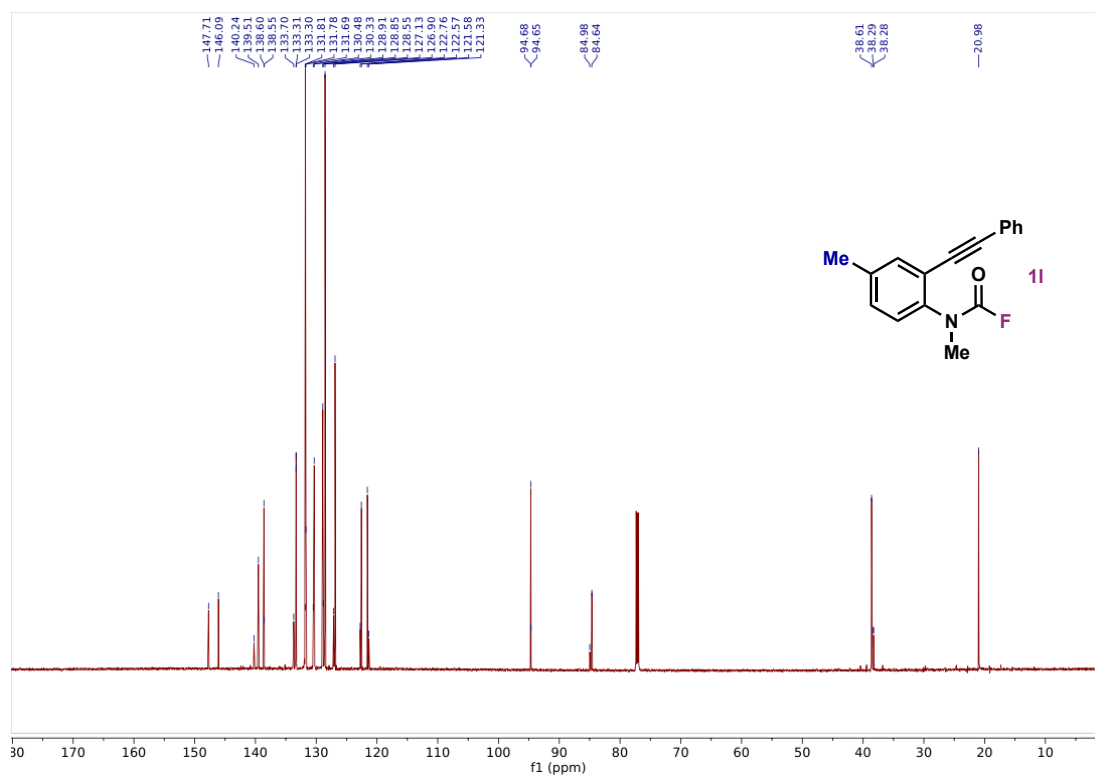
^{19}F NMR (377 MHz, CDCl_3) of **3.1j**



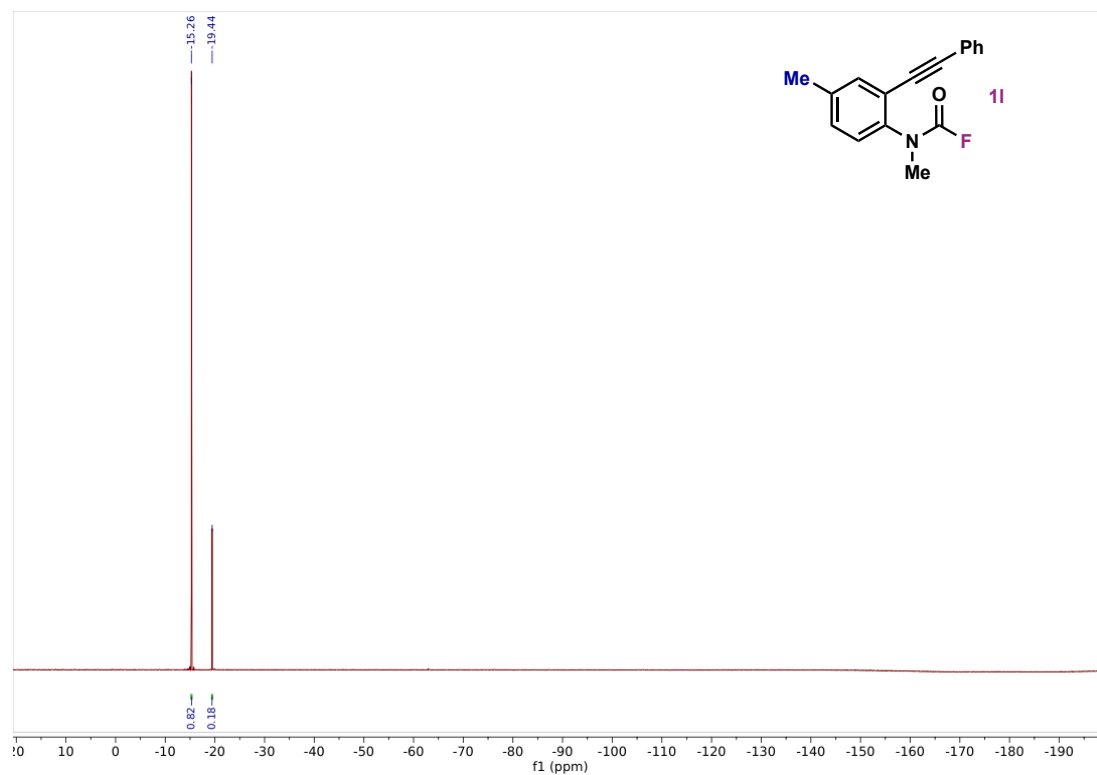
^1H NMR (400 MHz, CDCl_3) of **3.11**



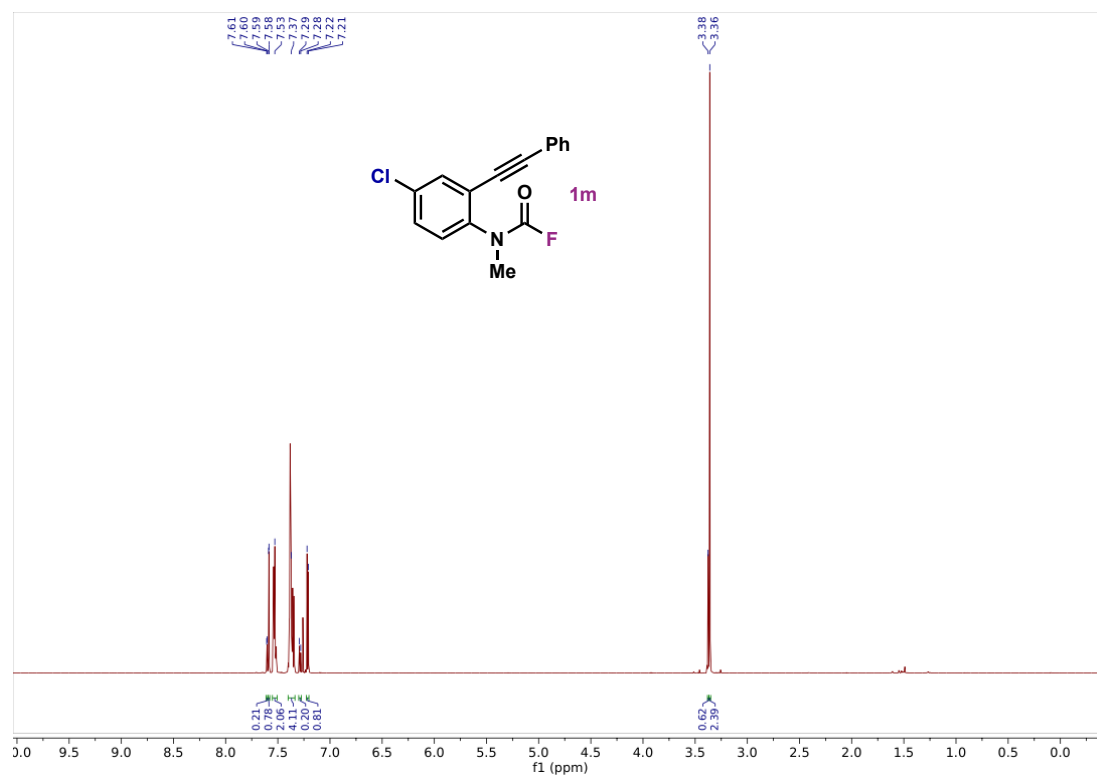
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.11**



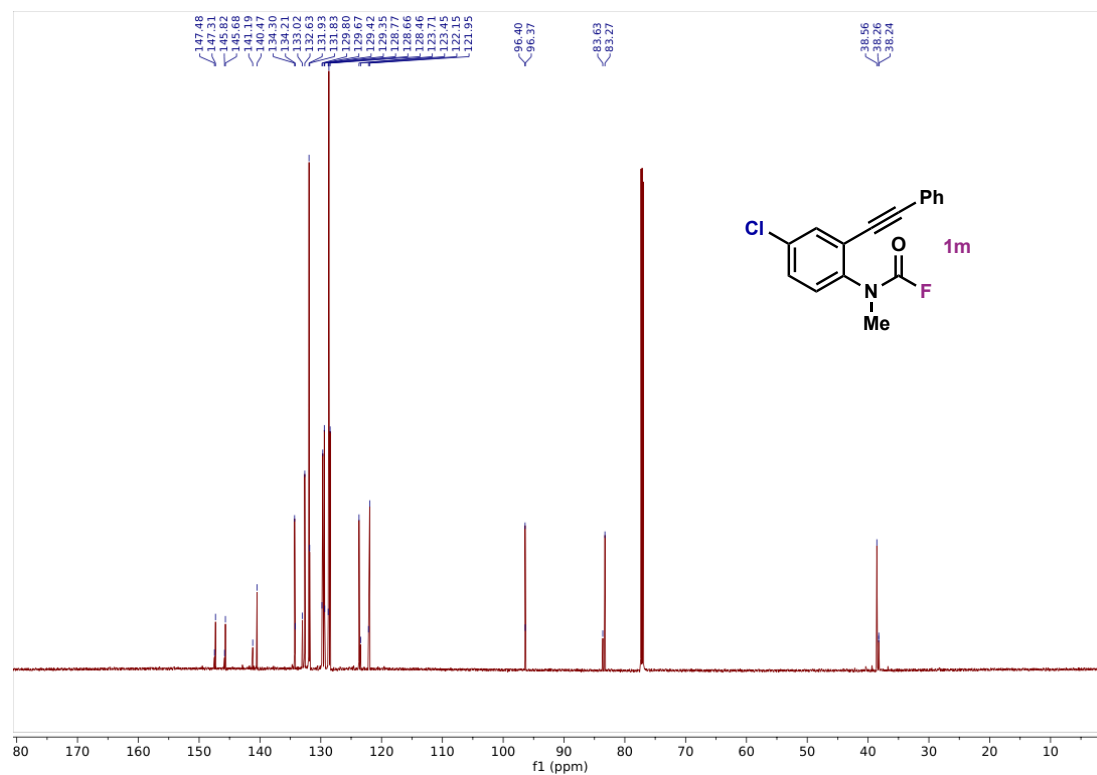
^{19}F NMR (377 MHz, CDCl_3) of **3.1l**



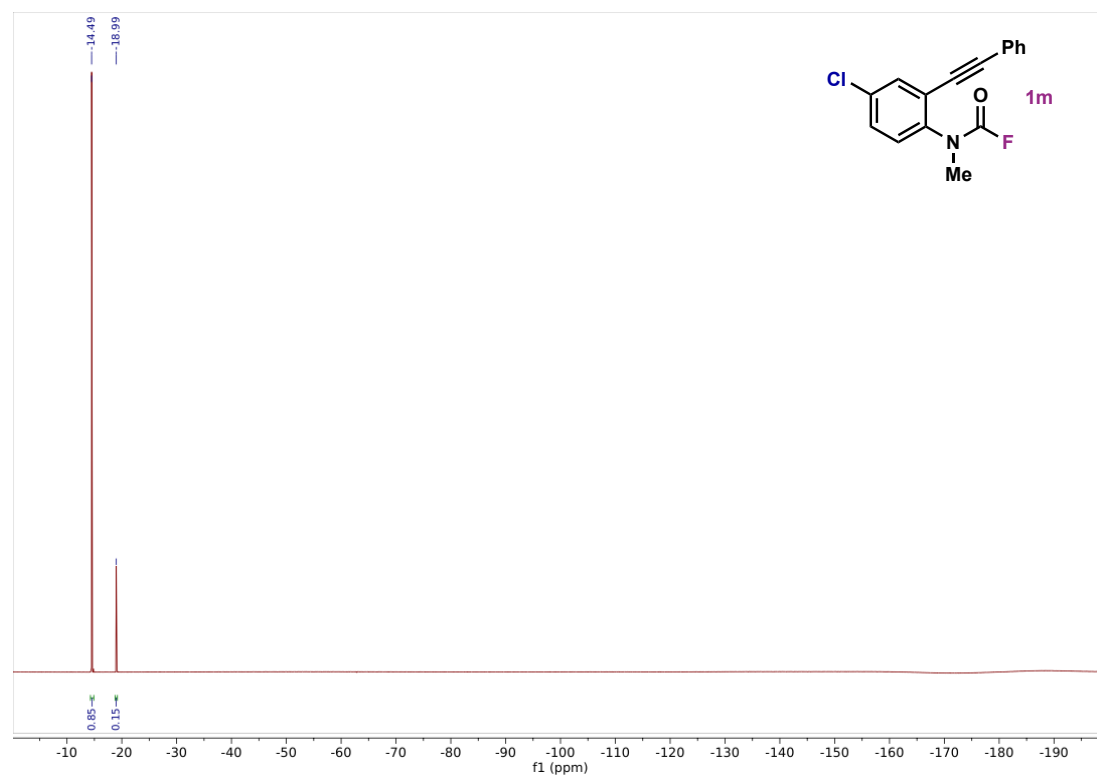
^1H NMR (700 MHz, CDCl_3) of **3.1m**



^{13}C $\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) of **3.1m**



^{19}F NMR (659 MHz, CDCl_3) of **3.1m**



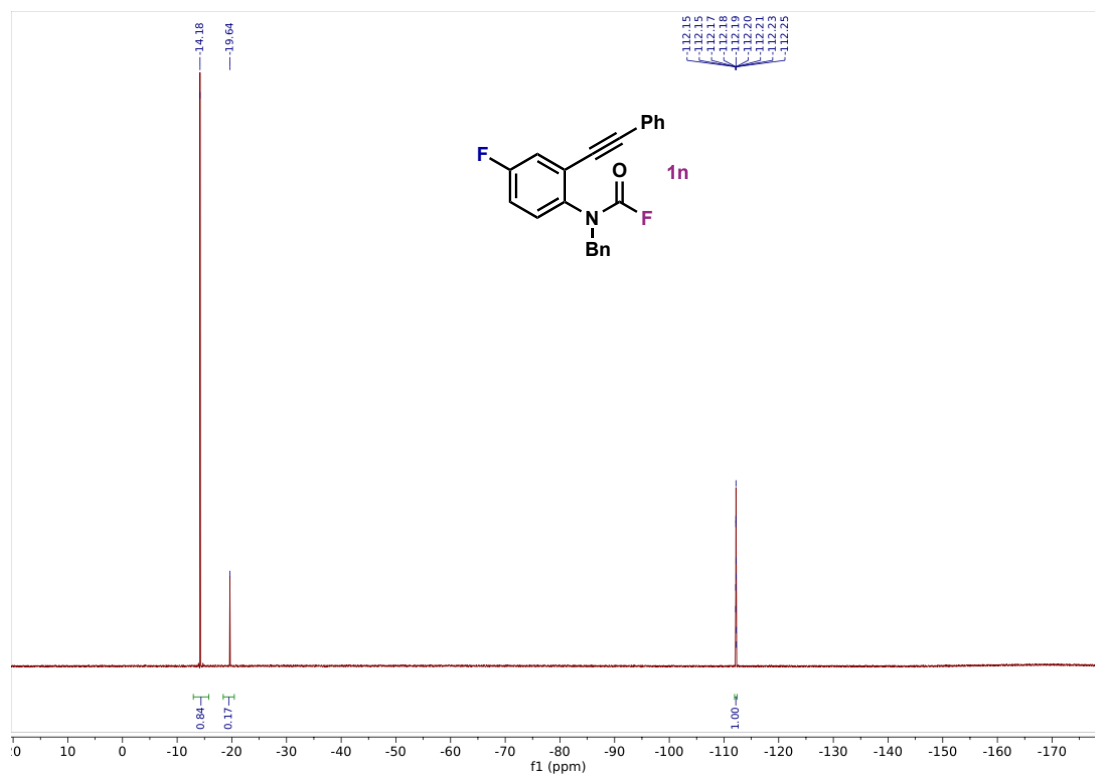
Chemical structure of 1n: c1ccc(cc1)C#CC2=CC=C(C=C2)N(C(=O)F)CC3=CC=CC=C3

¹H NMR spectrum (CDCl₃):

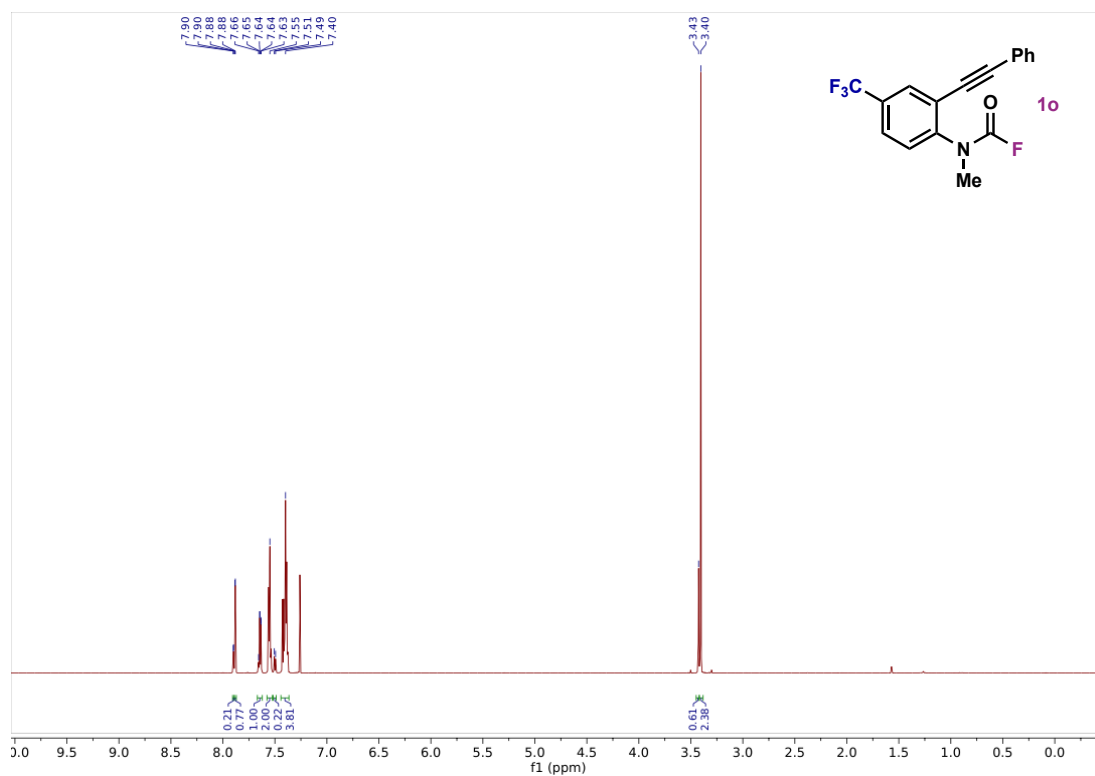
Chemical Shift (ppm)	Integration
7.53	2.00
7.39	3.02
7.26	5.84
7.08	0.48
6.98	0.68
6.96	0.50
6.94	0.23
6.92	
6.91	
6.88	
6.86	
6.84	
5.17	0.82
5.14	
4.85	0.43
4.61	
4.57	0.79

[illegible]

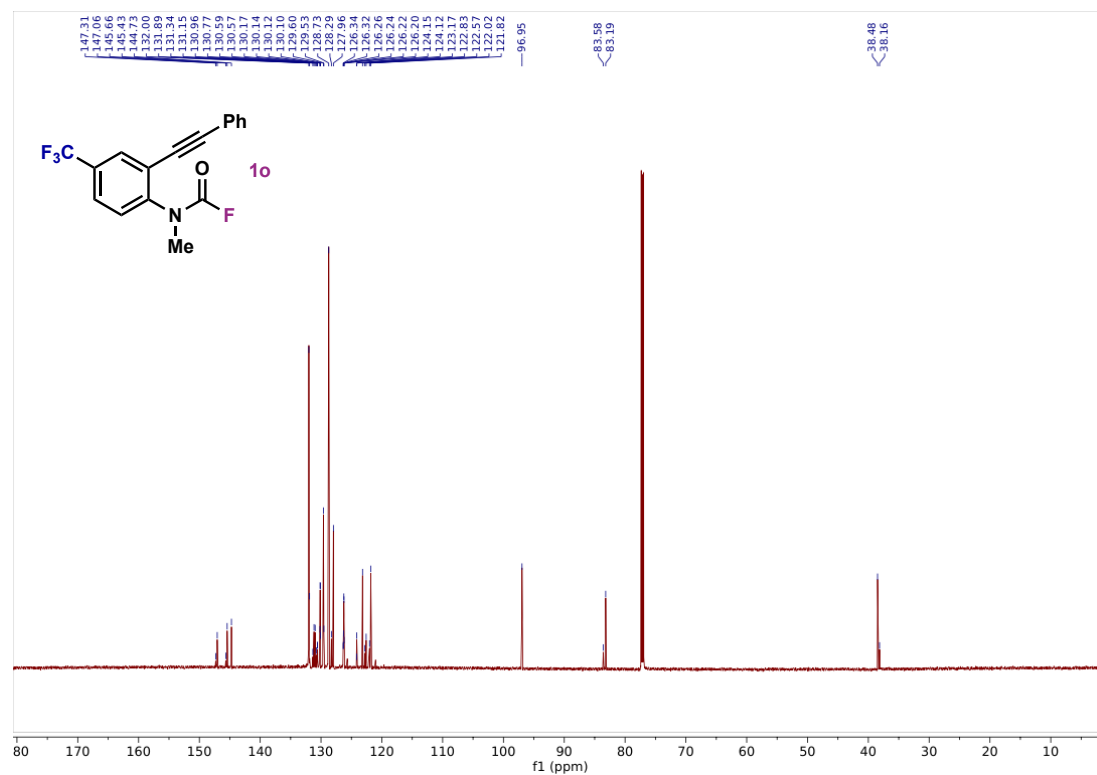
¹⁹F NMR (377 MHz, CDCl₃) of 3.1n



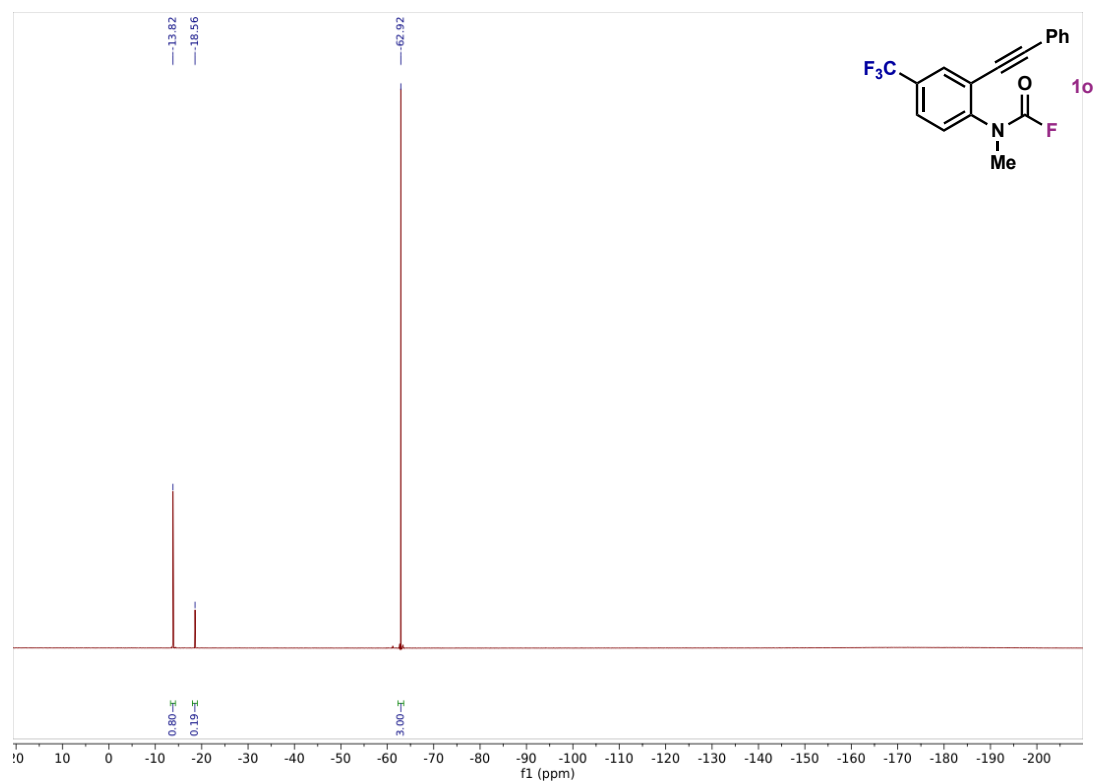
¹H NMR (700 MHz, CDCl₃) of **3.10**



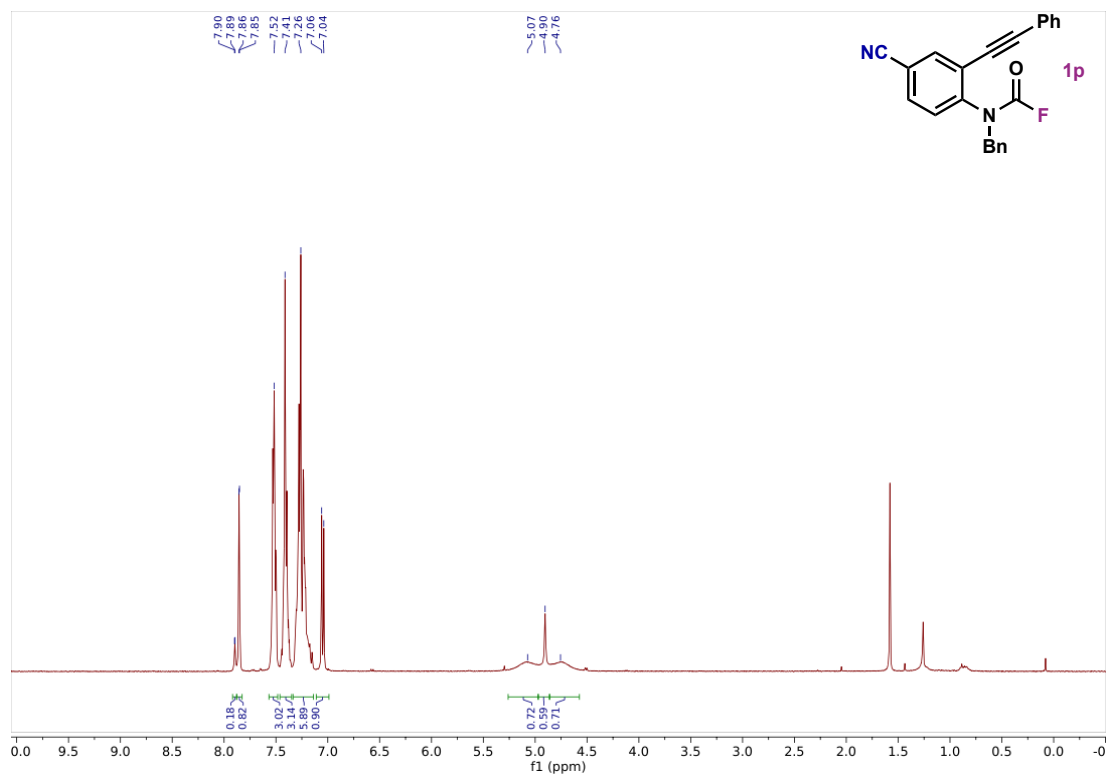
^{13}C { ^1H } NMR (101 MHz, CDCl_3) of **3.1o**



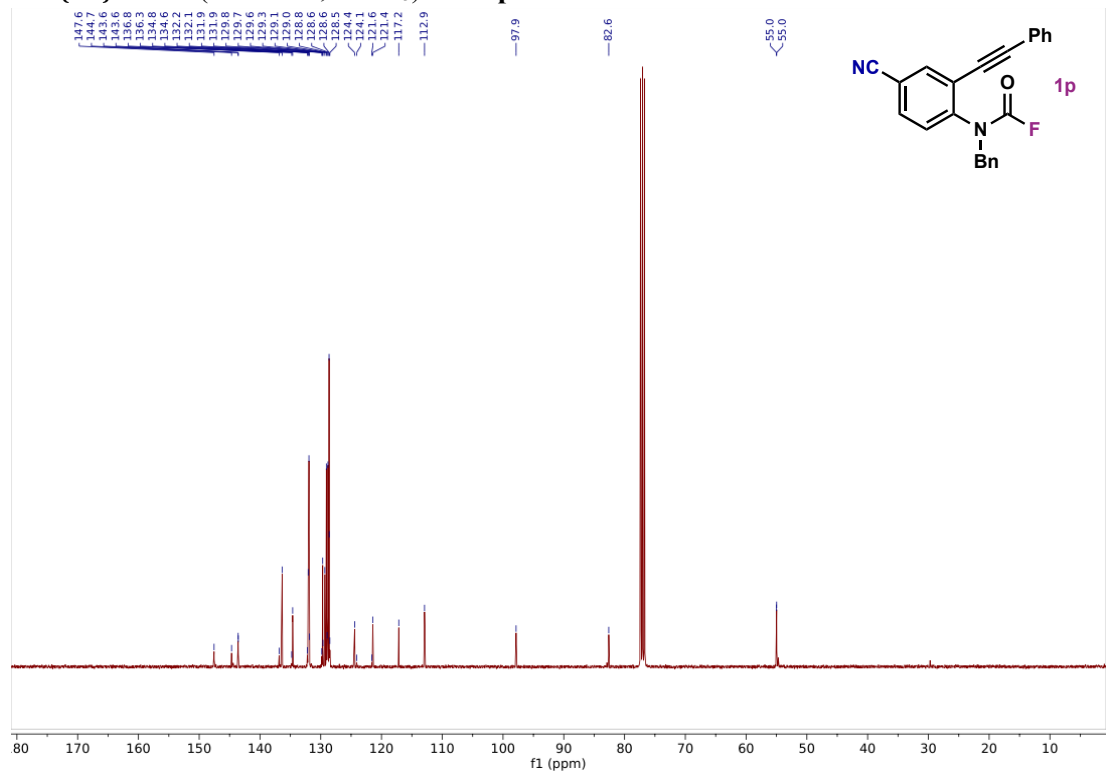
^{19}F NMR (377 MHz, CDCl_3) of **3.1o**



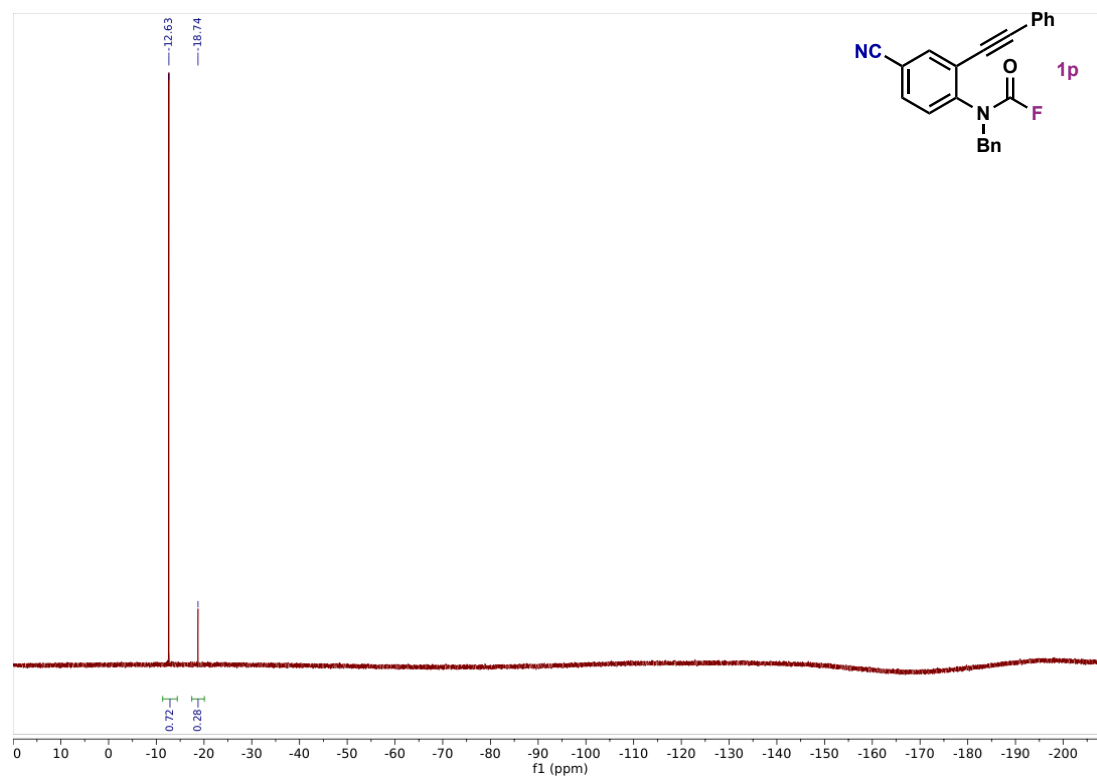
^1H NMR (400 MHz, CDCl_3) of **3.1p**



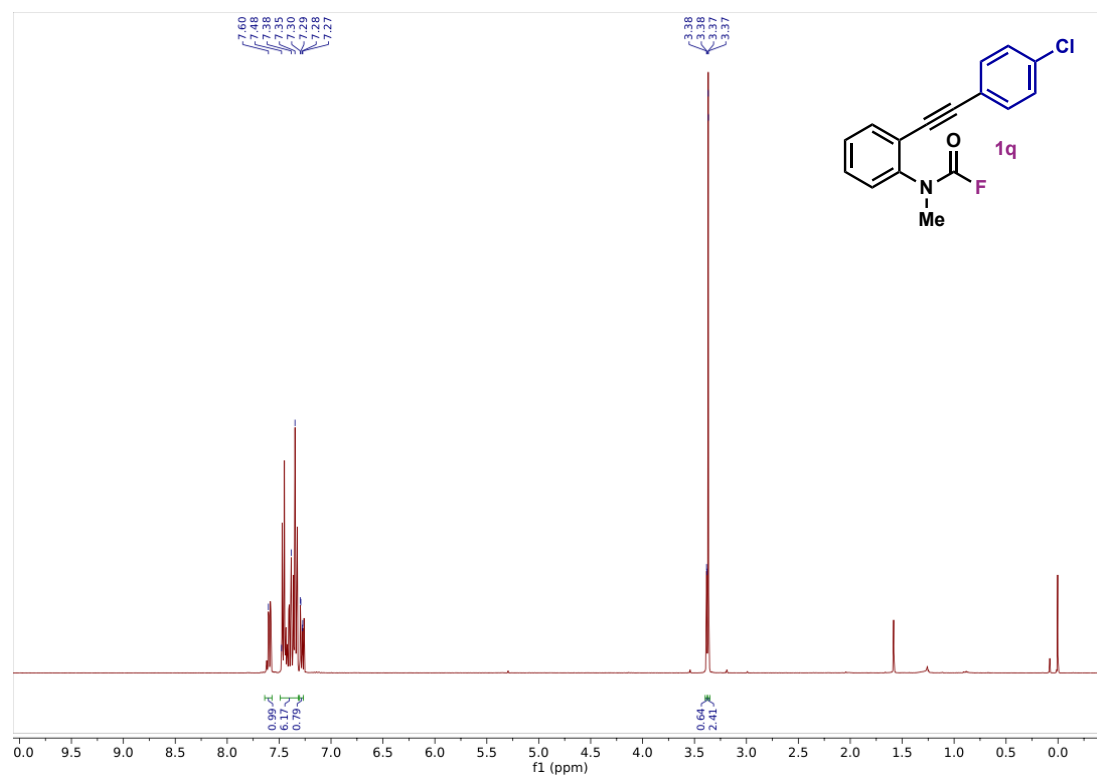
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.1p**



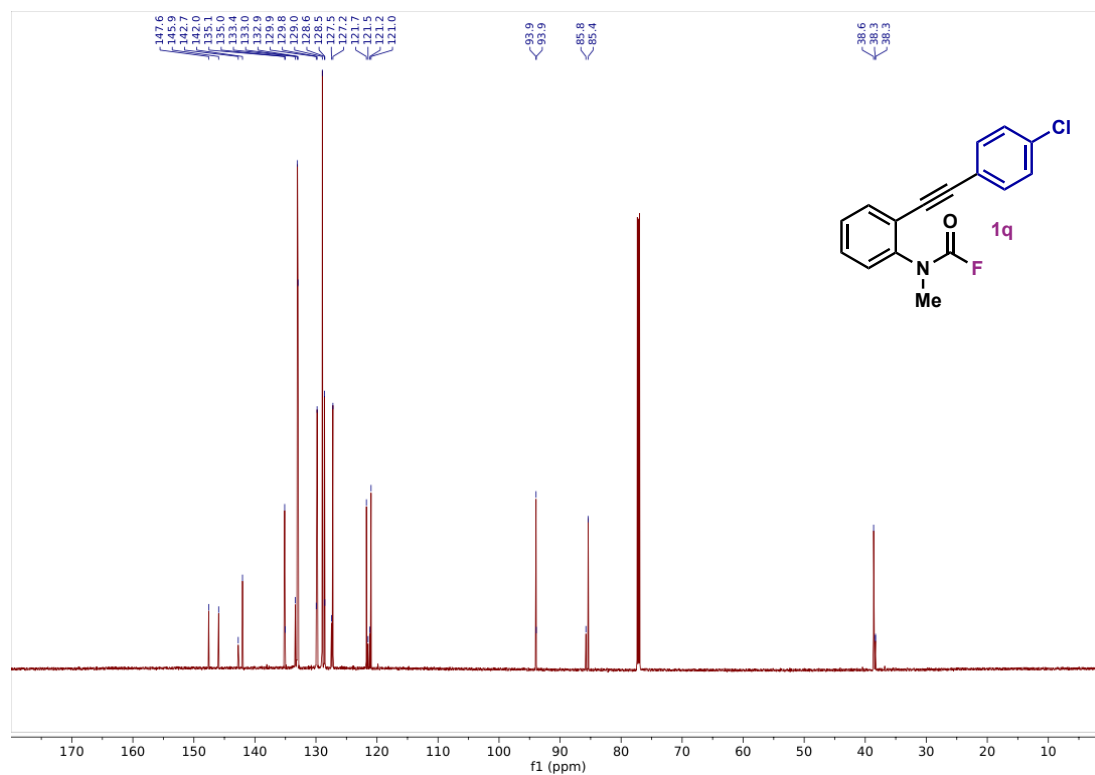
^{19}F NMR (377 MHz, CDCl_3) of **3.1p**



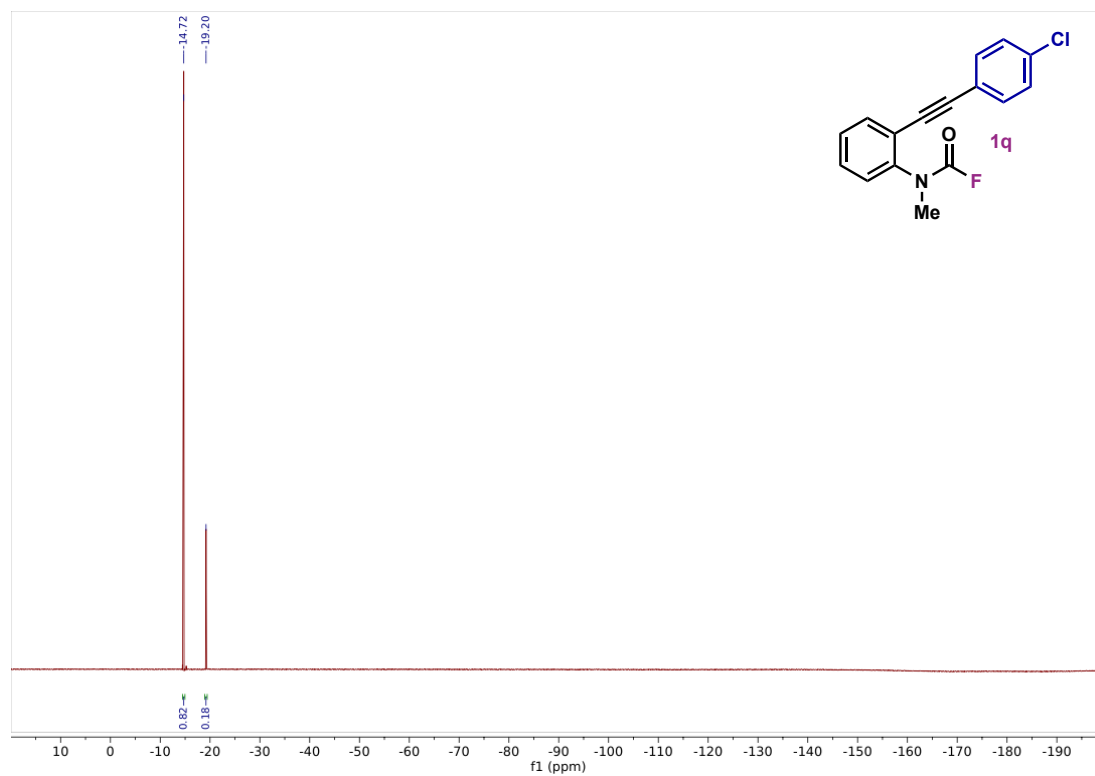
^1H NMR (400 MHz, CDCl_3) of **3.1q**



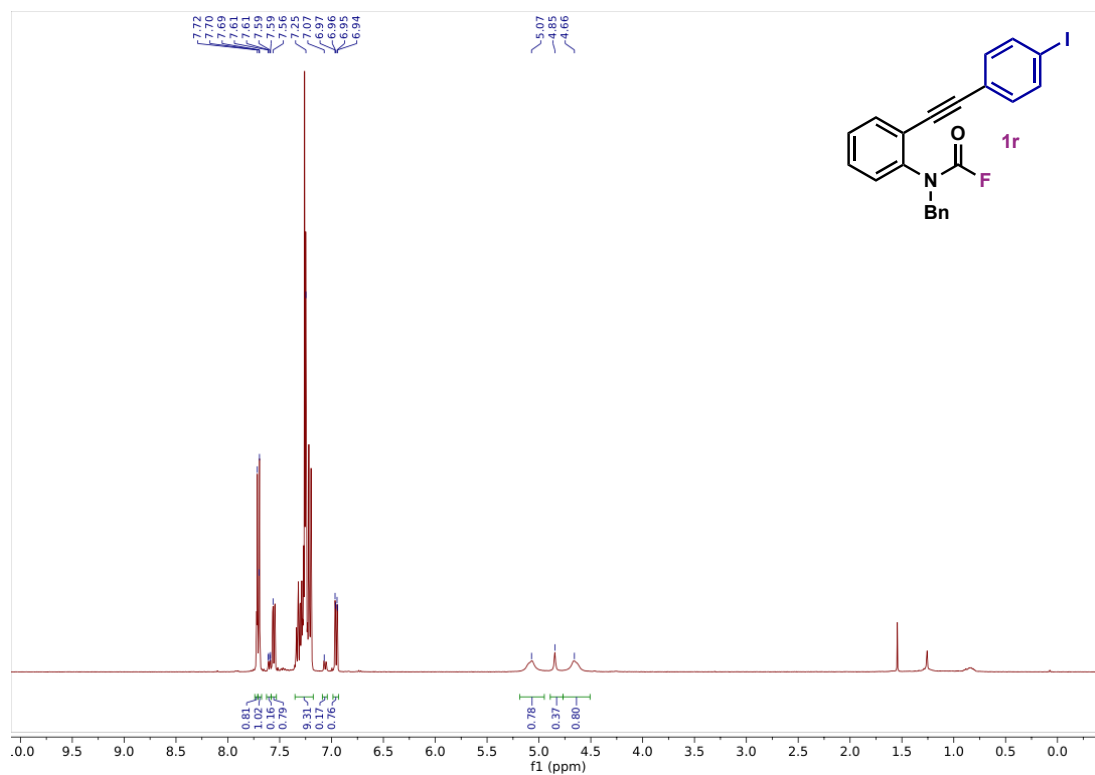
^{13}C { ^1H } NMR (101 MHz, CDCl_3) of **3.1q**



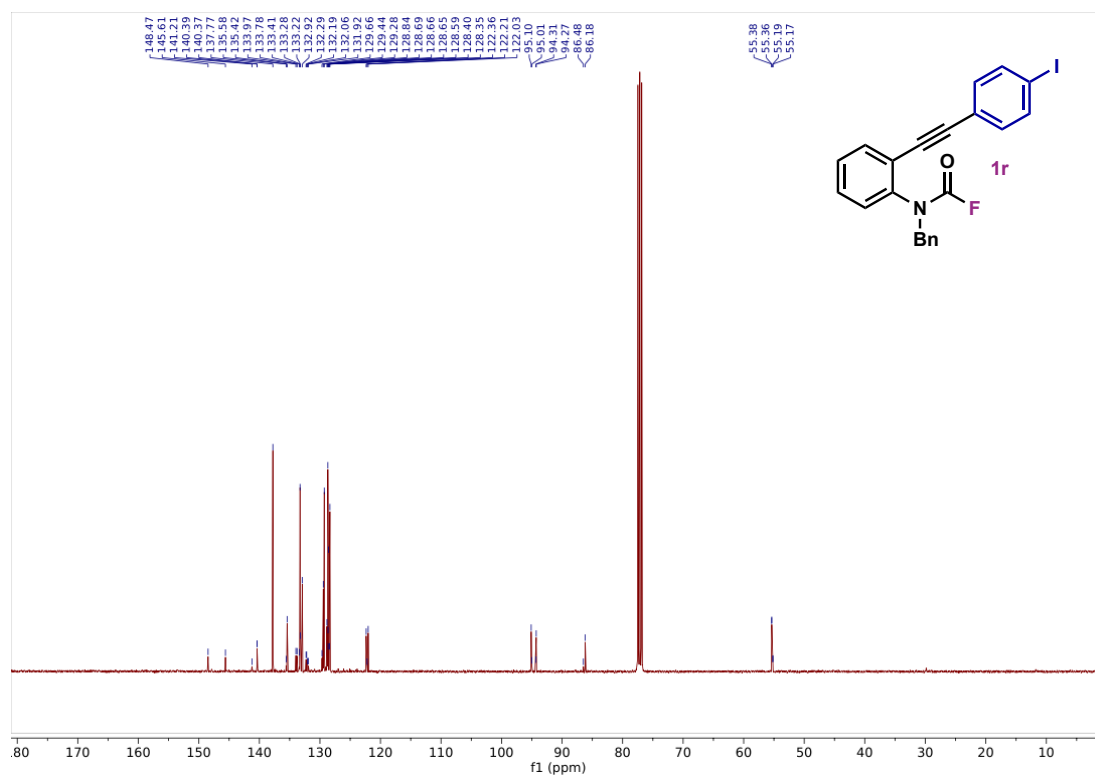
^{19}F NMR (377 MHz, CDCl_3) of **3.1q**



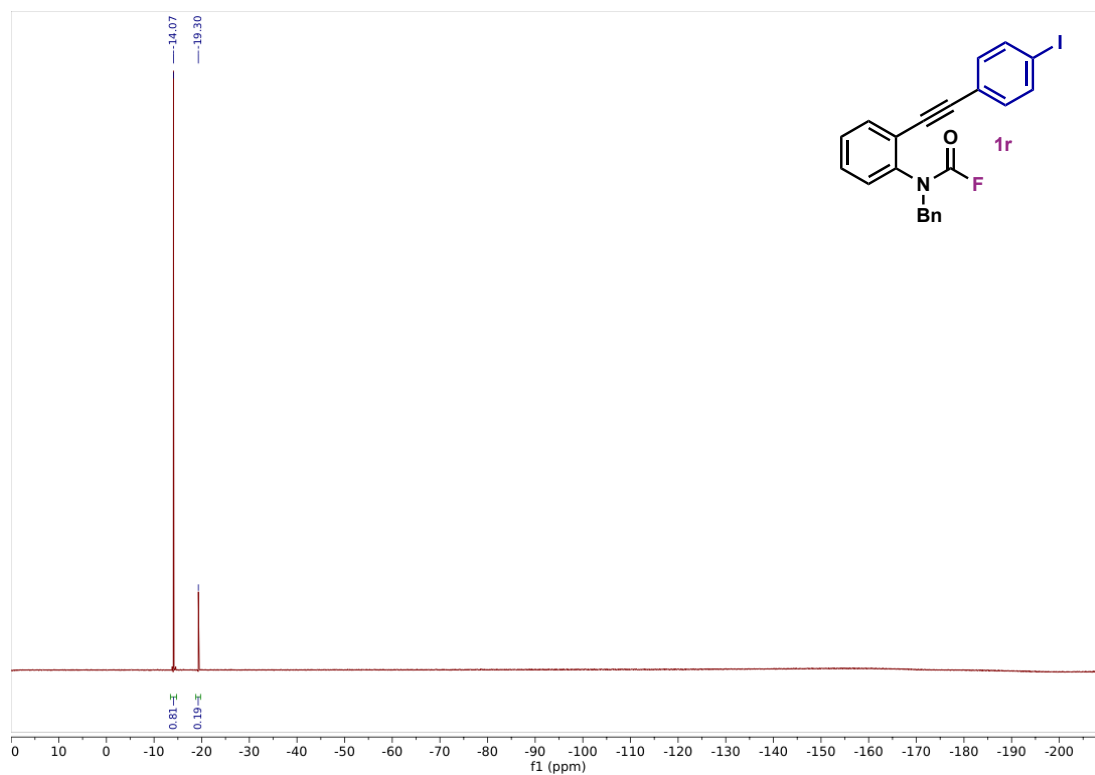
^1H NMR (400 MHz, CDCl_3) of **3.1r**



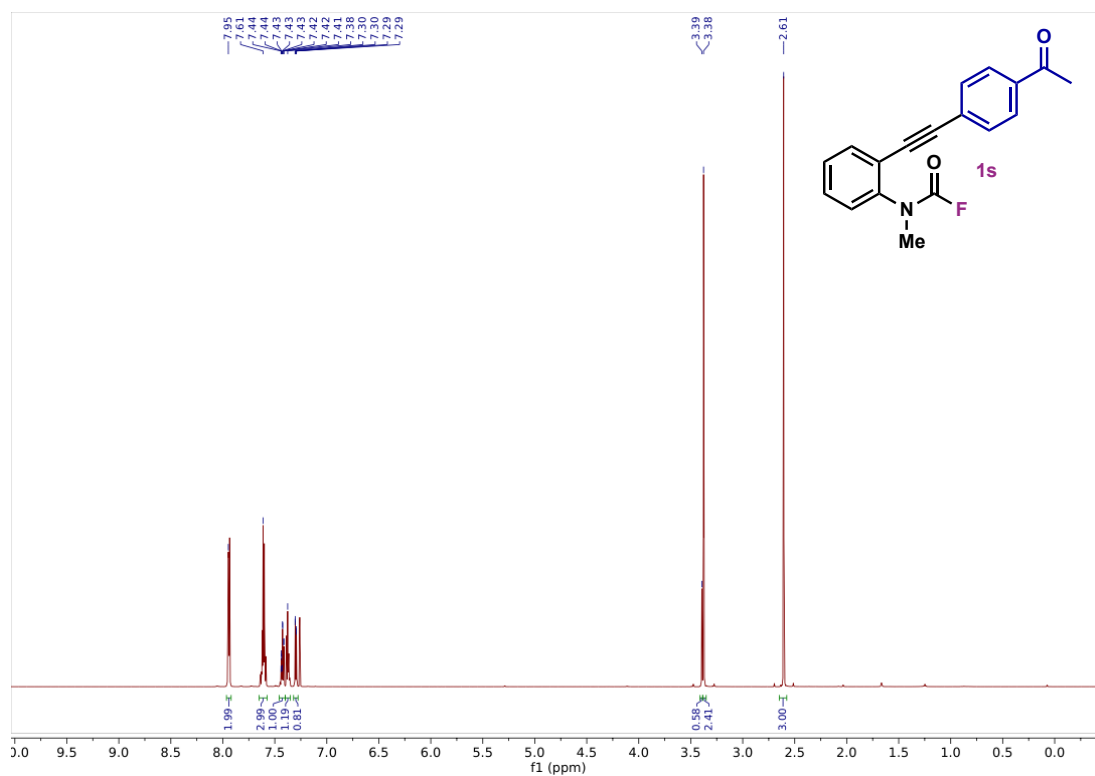
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.1r**



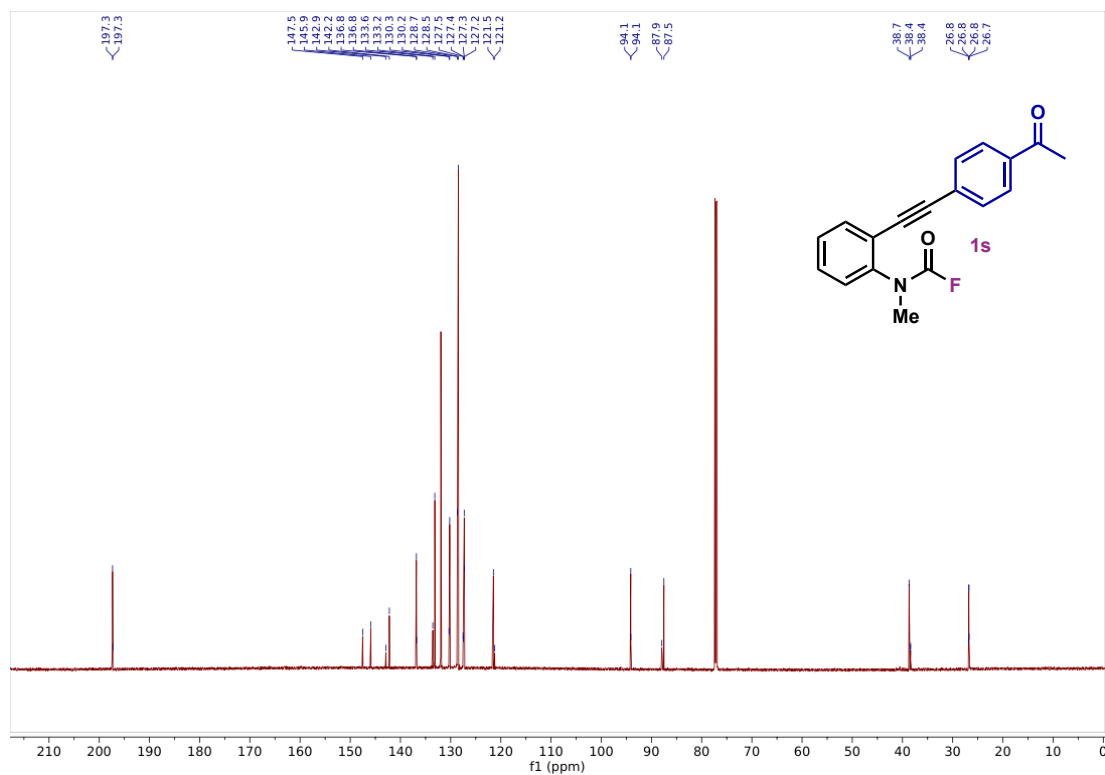
^{19}F NMR (377 MHz, CDCl_3) of **3.1q**



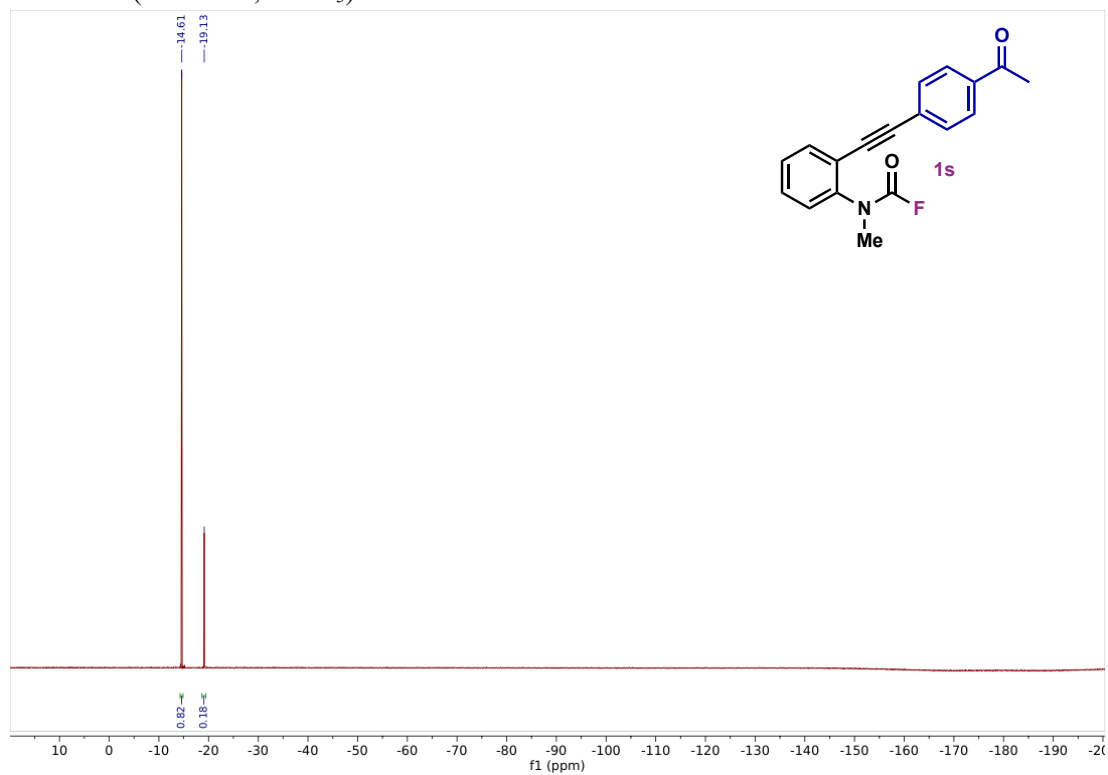
^1H NMR (700 MHz, CDCl_3) of **3.1s**



^{13}C $\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) of **3.1s**



^{19}F NMR (377 MHz, CDCl_3) of **3.1s**



Chemical structure of 1t: Cc1ccc(cc1)C#CC2=CC=CC=C2N(C2)C(=O)F

¹H NMR spectrum (CDCl₃):

Chemical Shift (ppm)	Integration
7.65, 7.65, 7.63, 7.63, 7.61, 7.61, 7.59, 7.59	0.20, 0.81, 0.05, 0.81
7.45, 7.45, 7.43, 7.43, 7.41, 7.41, 7.39, 7.39	0.22, 0.81
7.26 (solvent)	3.00
5.21, 5.18	0.79
4.91, 4.69, 4.66	0.36, 0.78
2.42	3.00

148.55
148.11
145.69
141.05
140.18
139.56
139.36
139.22
135.72
135.56
132.42
132.32
132.22
131.68
129.33
129.22
128.70
128.87
128.79
128.69
128.44
128.56
128.50
128.39
128.26
128.24
122.73
122.42
119.92
119.62
95.67
84.46
84.21

55.16
52.16
54.97

21.69

Me

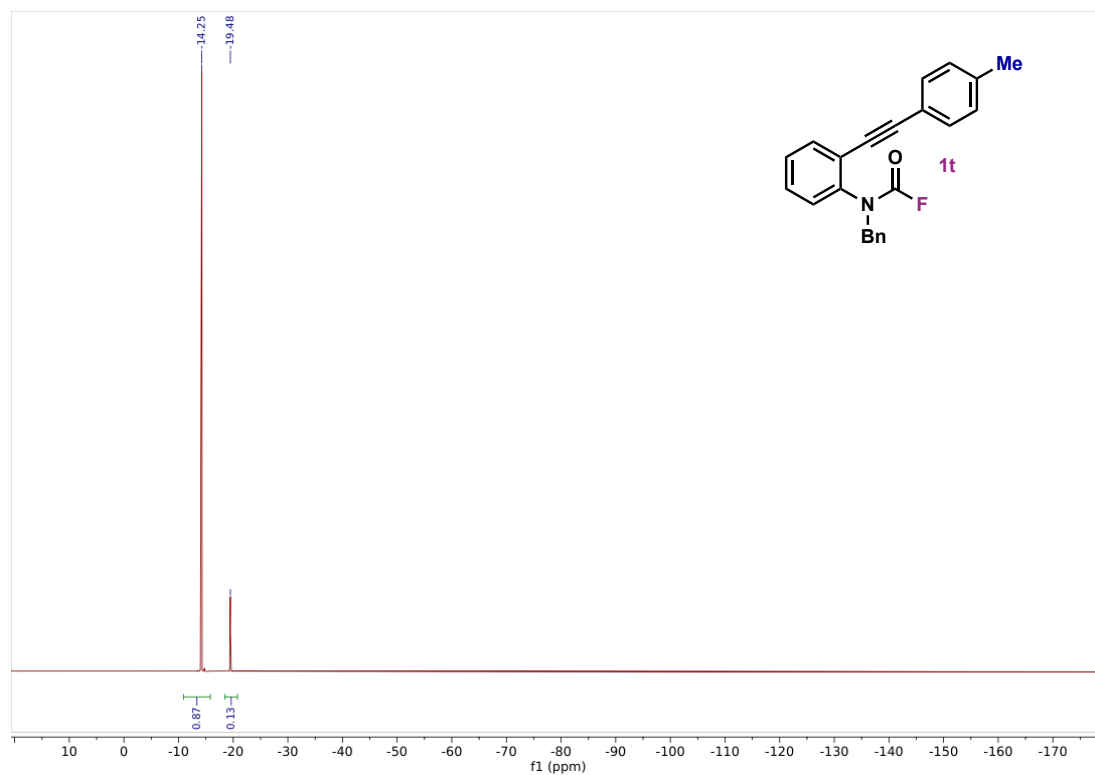
1t

F

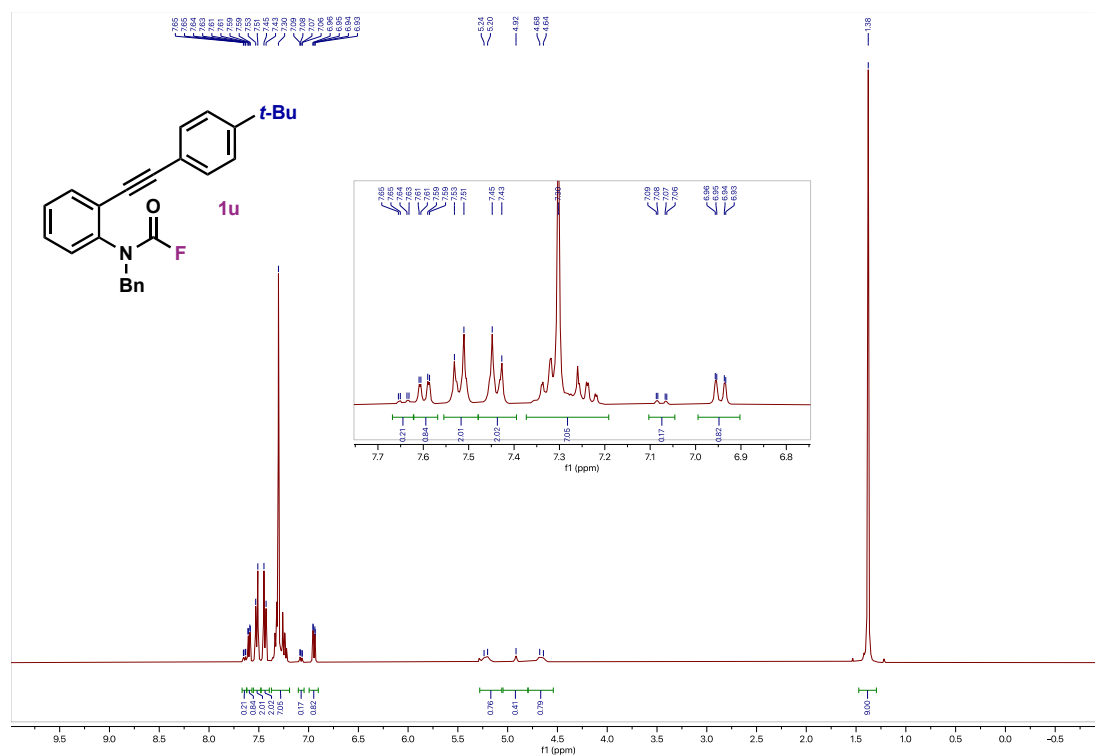
Bn

f1 (ppm)

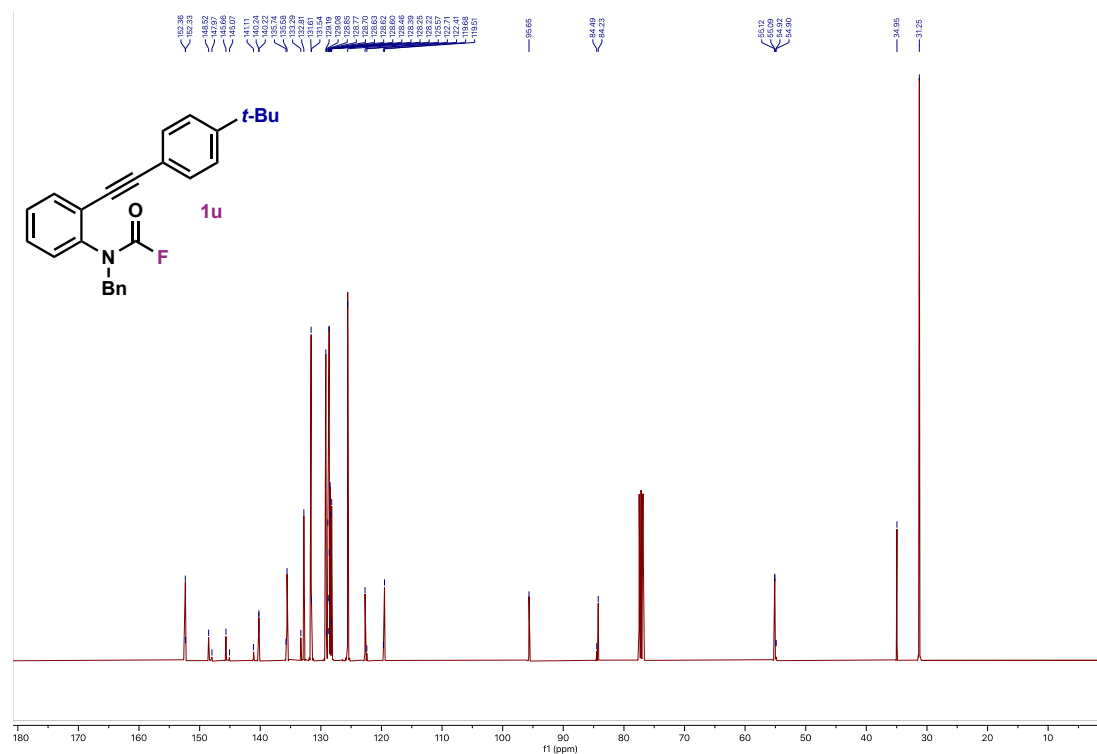
^{19}F NMR (377 MHz, CDCl_3) of **3.1t**



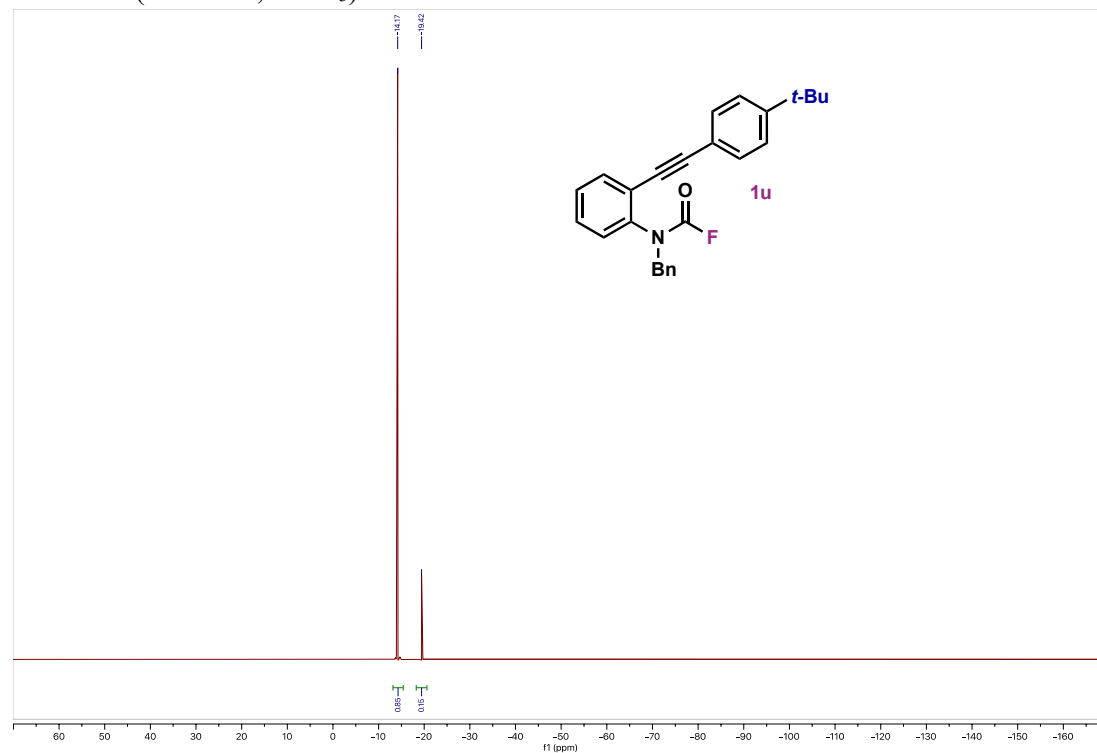
¹H NMR (400 MHz, CDCl₃) of **3.1u**



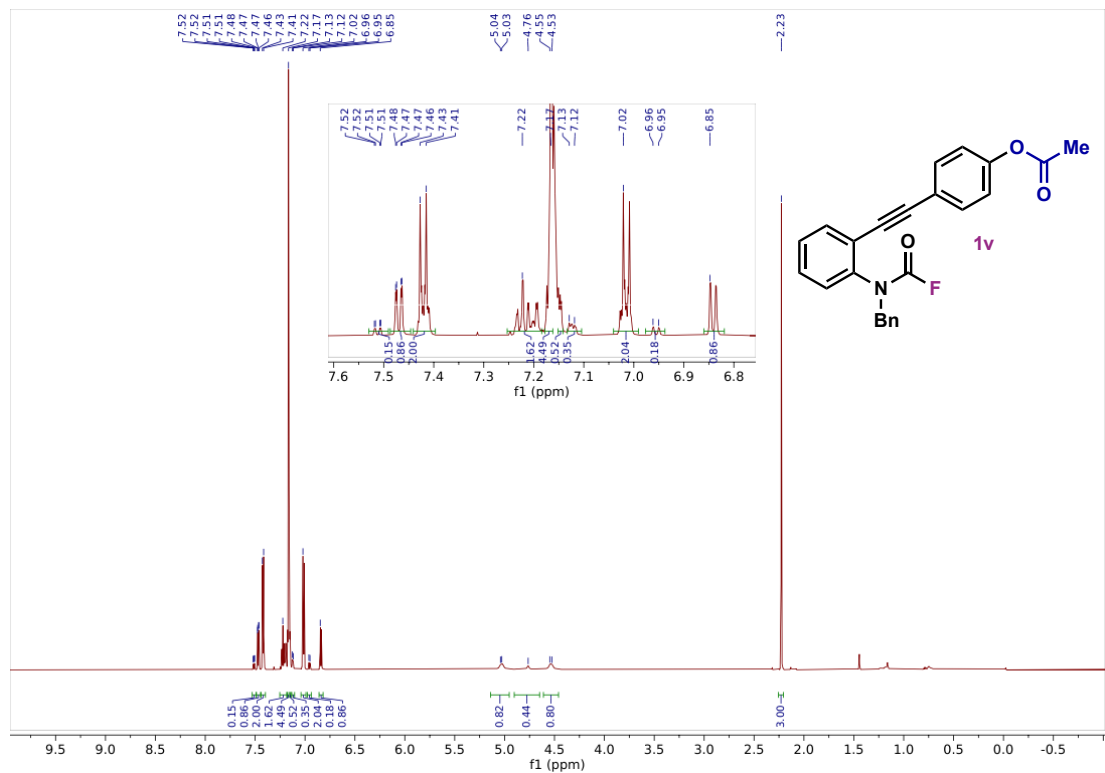
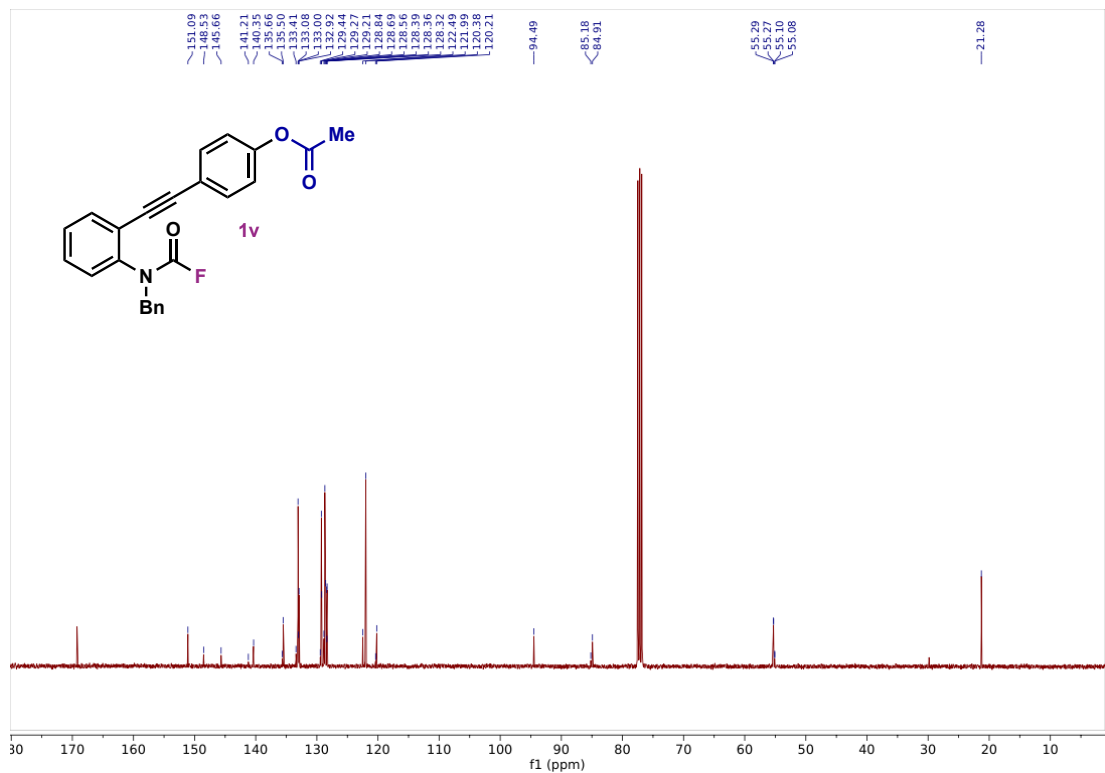
^{13}C { ^1H } NMR (101 MHz, CDCl_3) of **3.1u**



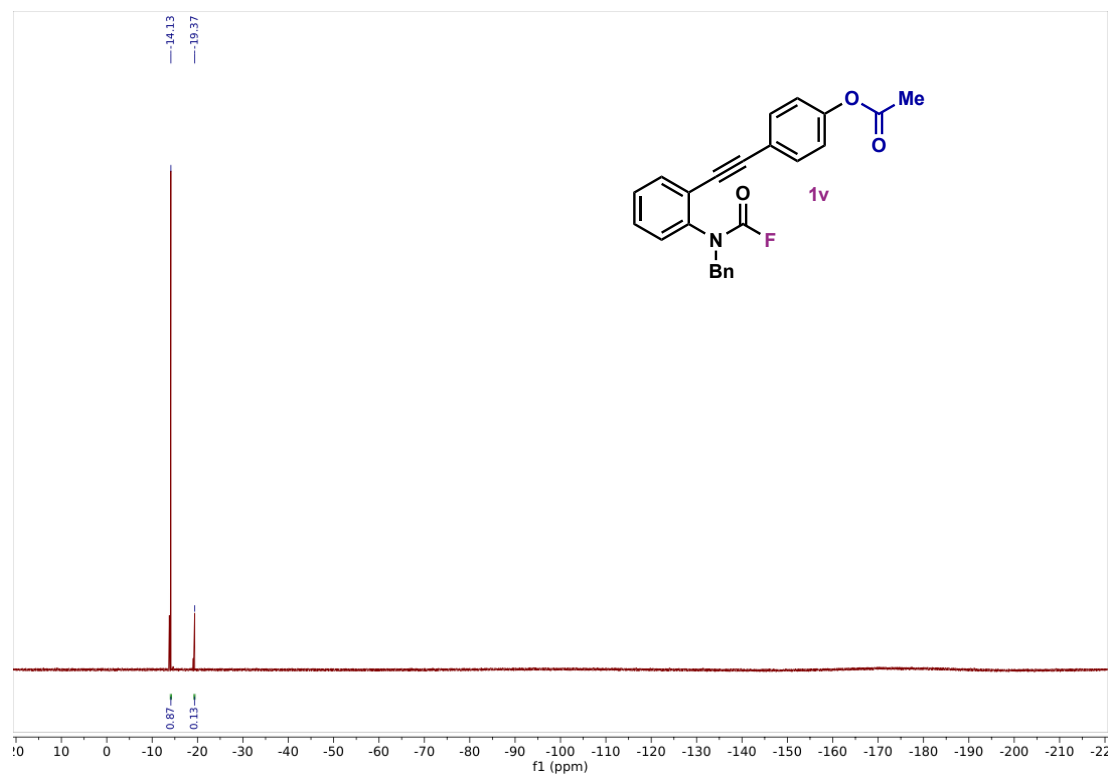
^{19}F NMR (377 MHz, CDCl_3) of **3.1u**



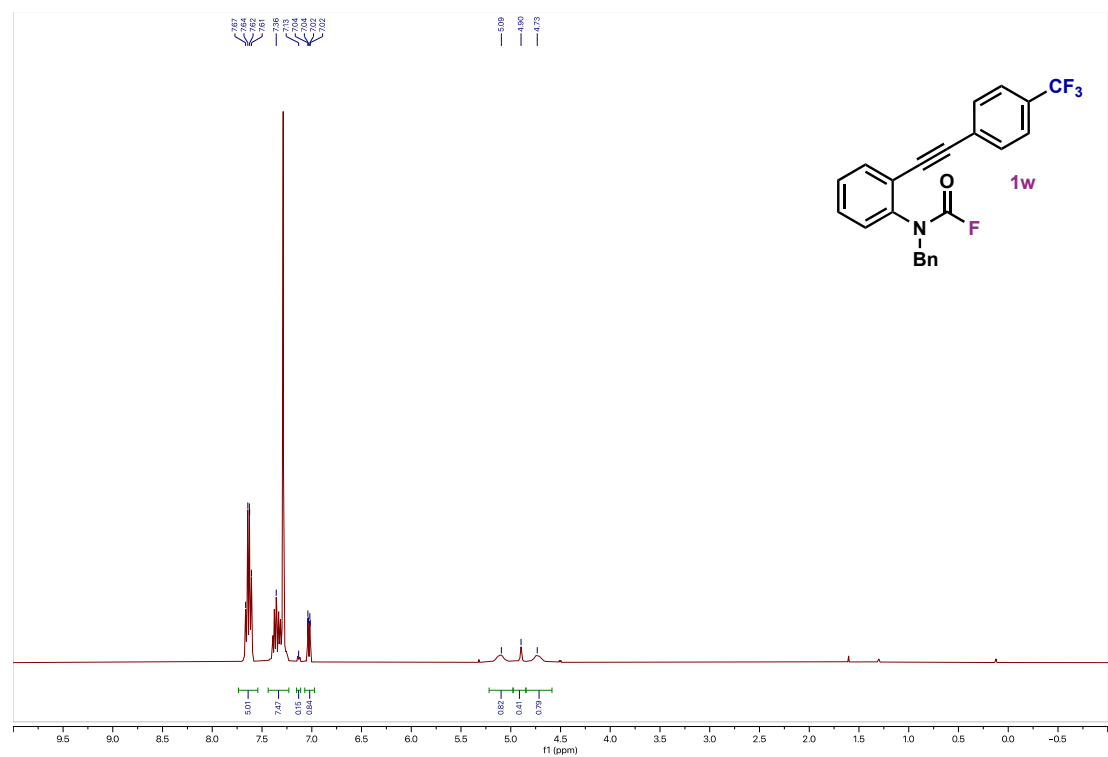
¹H NMR (700 MHz, Benzene-*d*₆) of **3.1v**

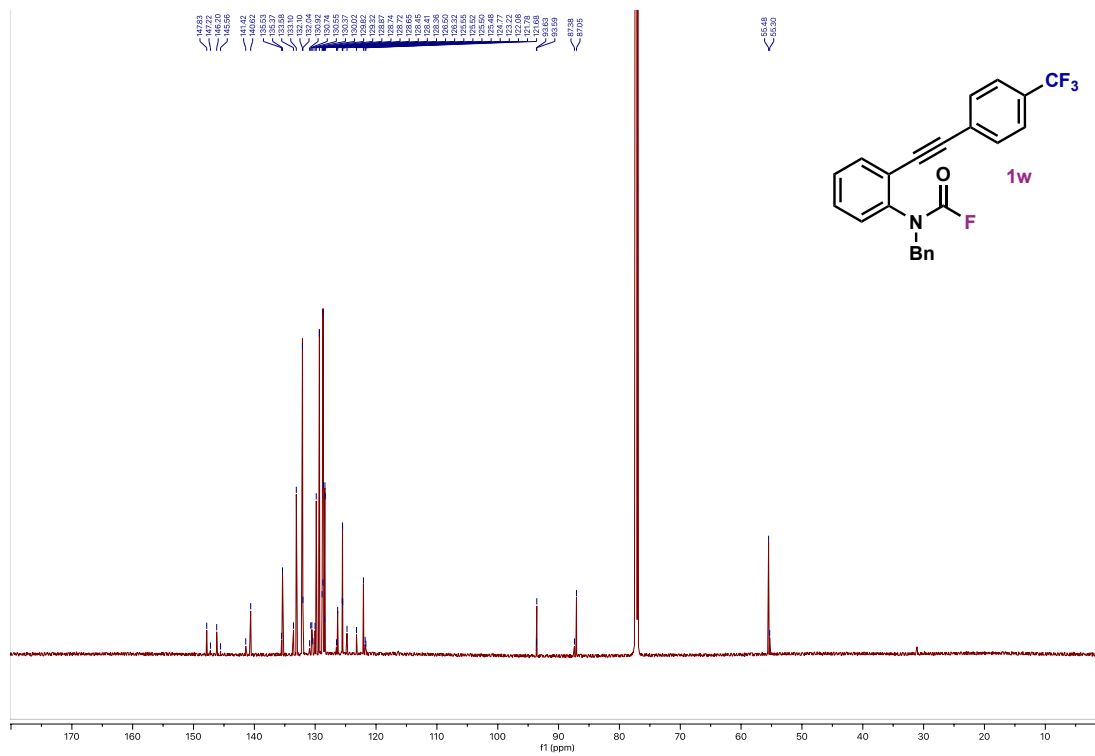
 $^{13}\text{C} \{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.1v**

^{19}F NMR (377 MHz, CDCl_3) of **3.1v**

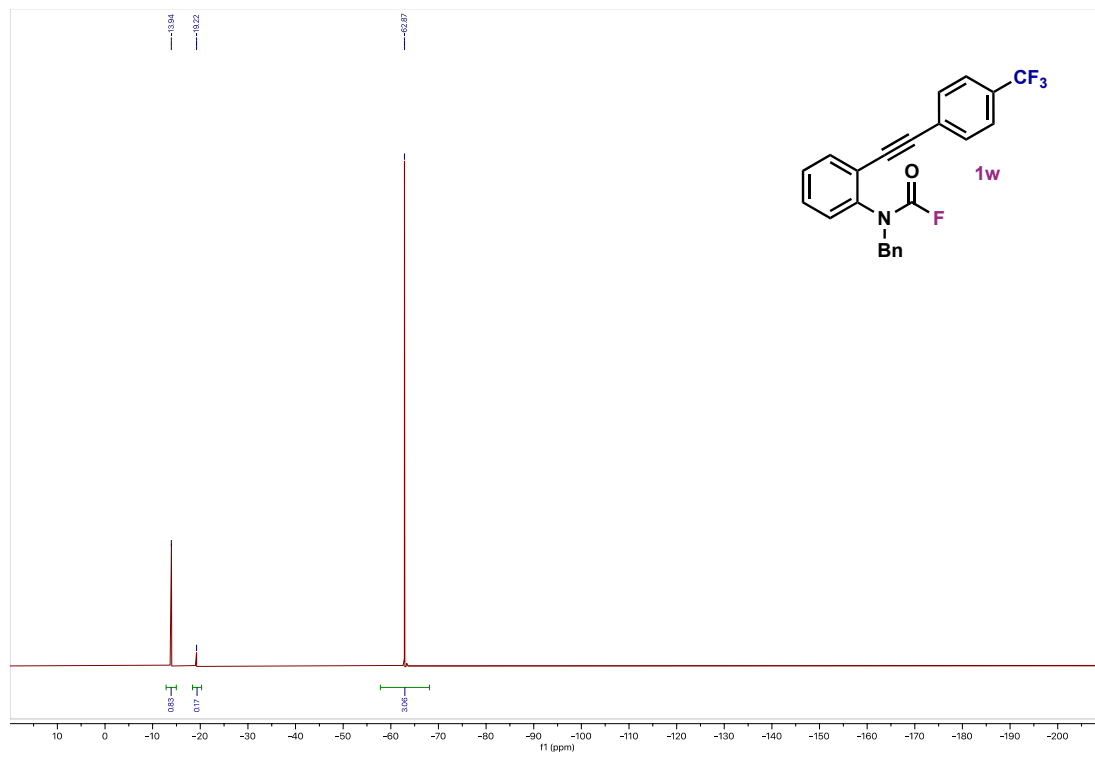


^1H NMR (400 MHz, CDCl_3) of **3.1w**

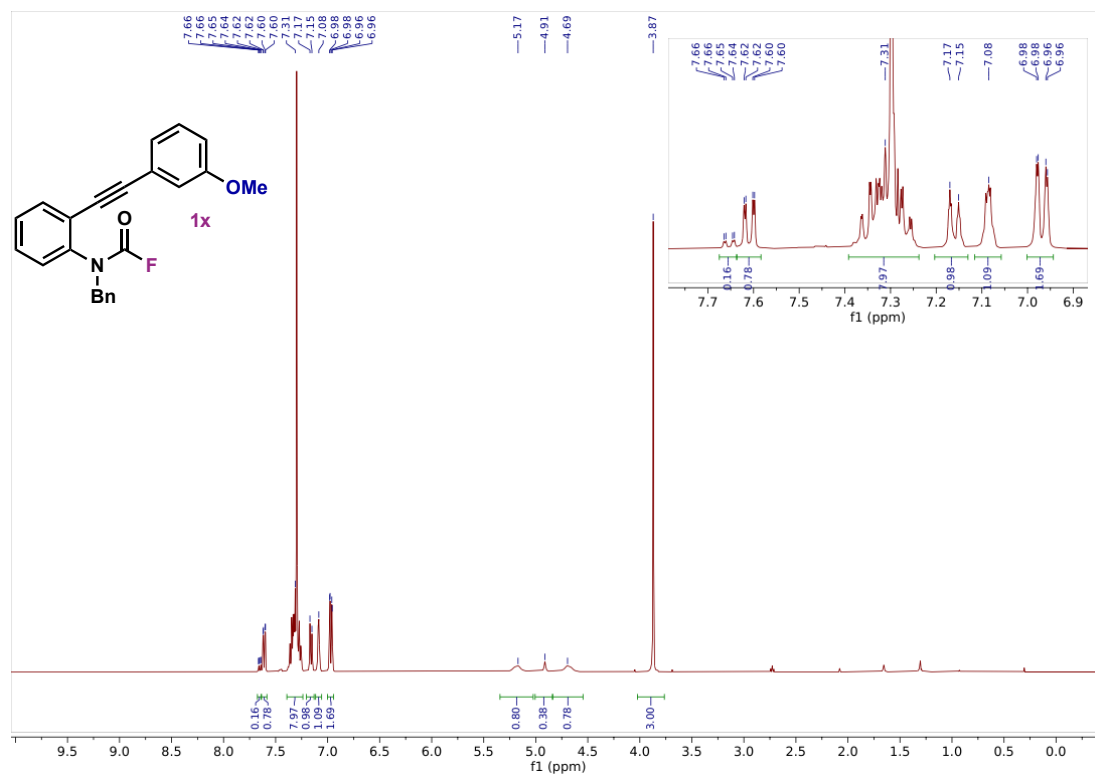


$^{13}\text{C} \{^1\text{H}\}$ NMR (176 MHz, CDCl_3) of **3.1w**

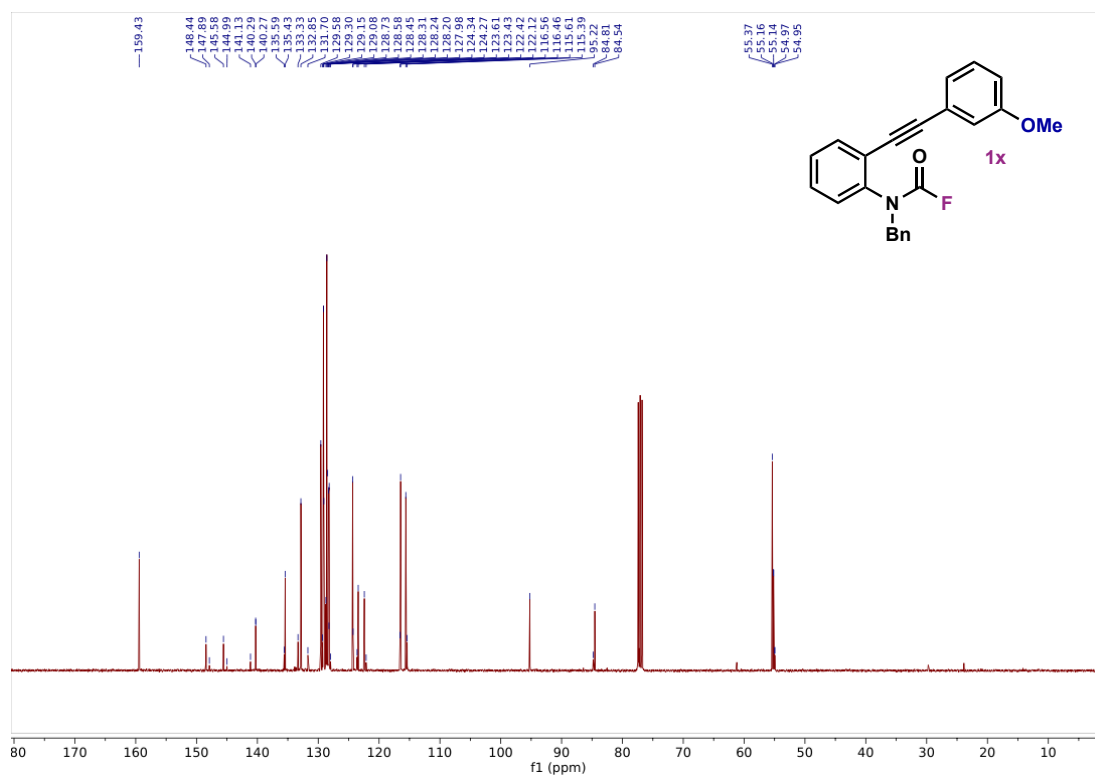
¹⁹F NMR (377 MHz, CDCl₃) of 3.1w



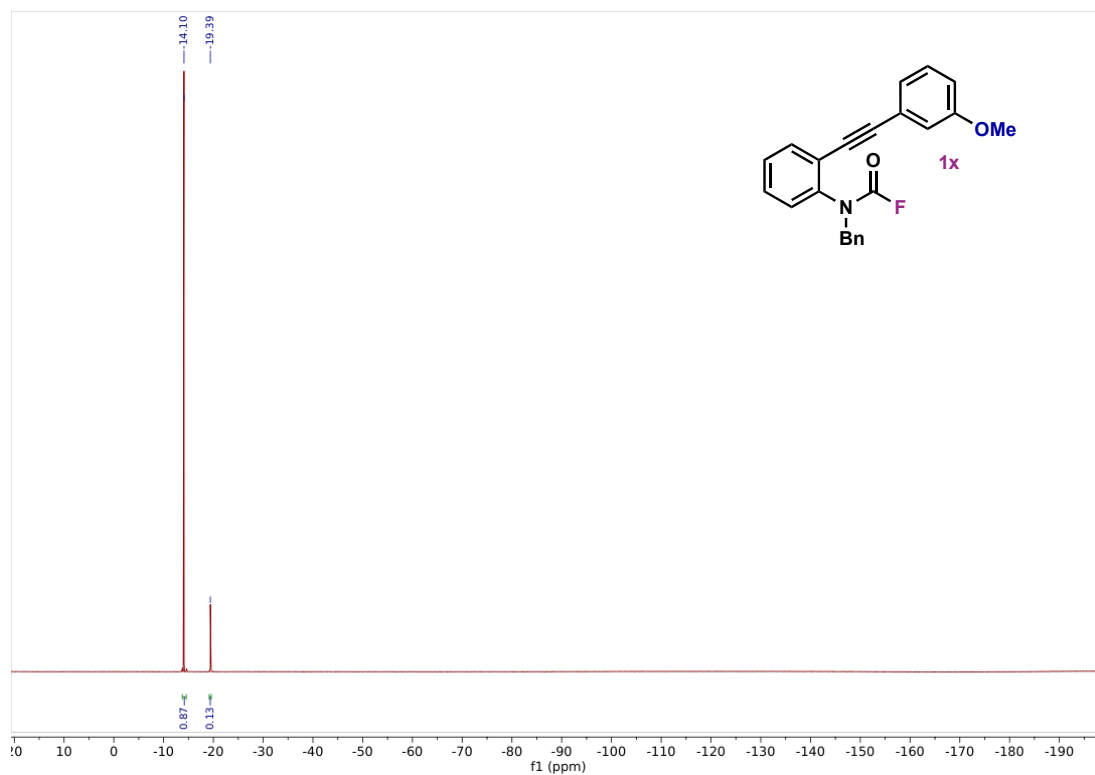
^1H NMR (400 MHz, CDCl_3) of **3.1x**



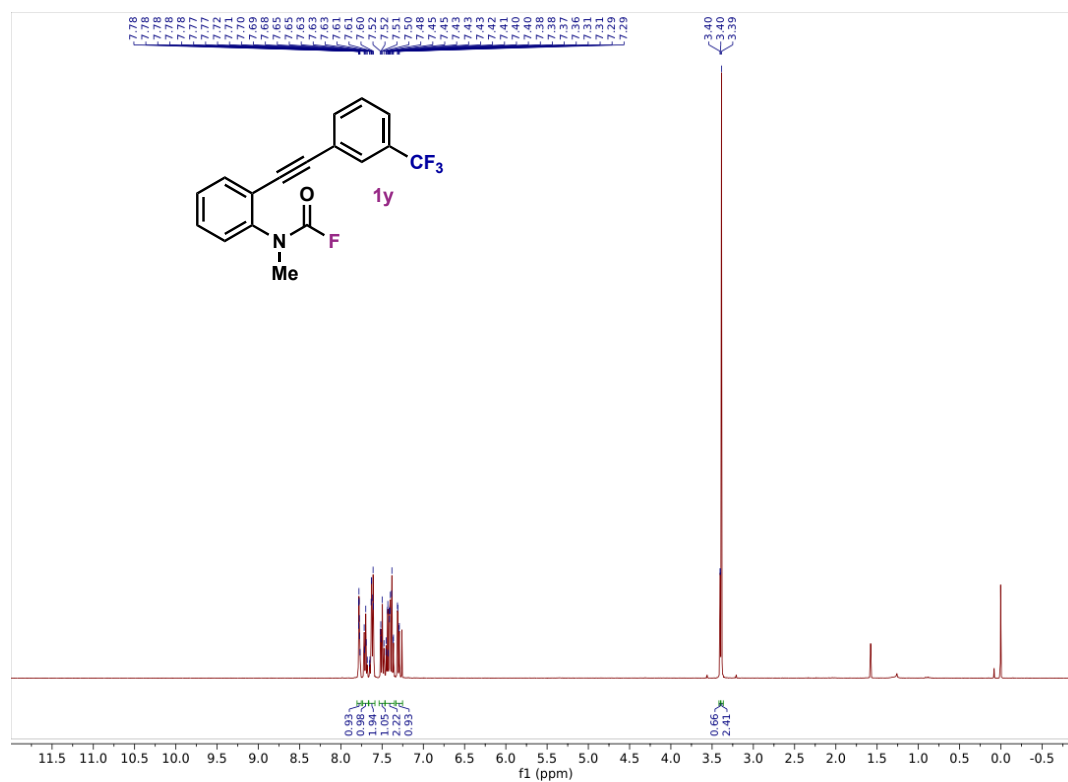
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.1x**



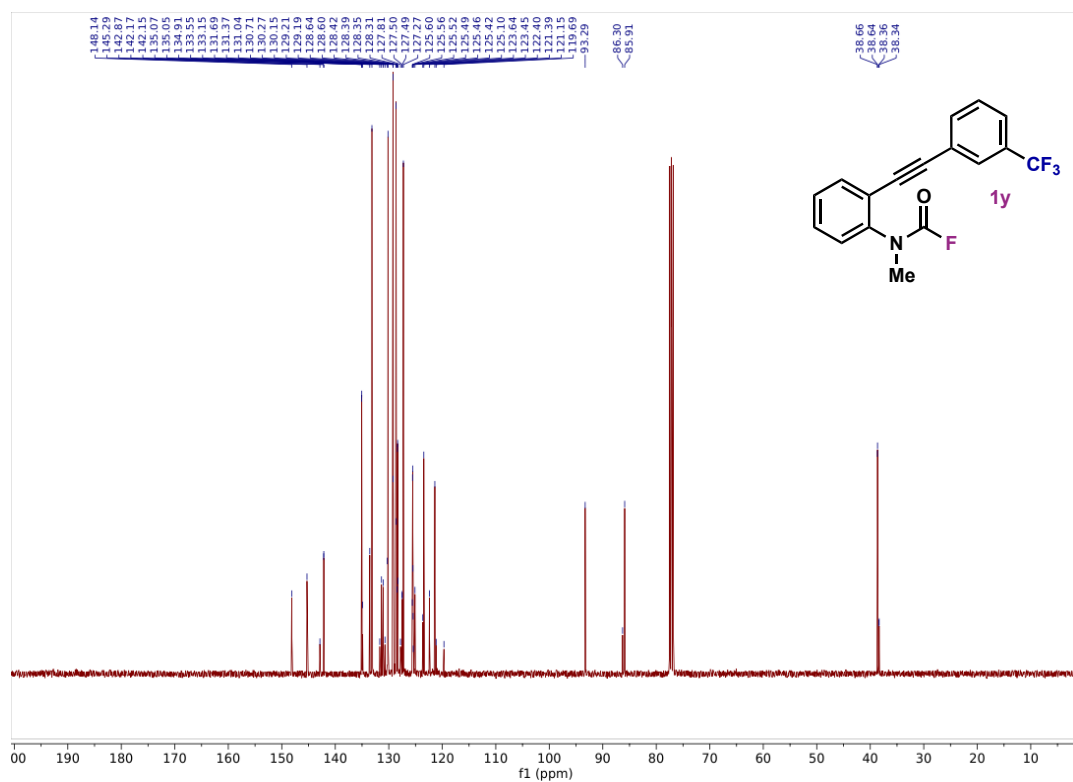
^{19}F NMR (377 MHz, CDCl_3) of **3.1x**



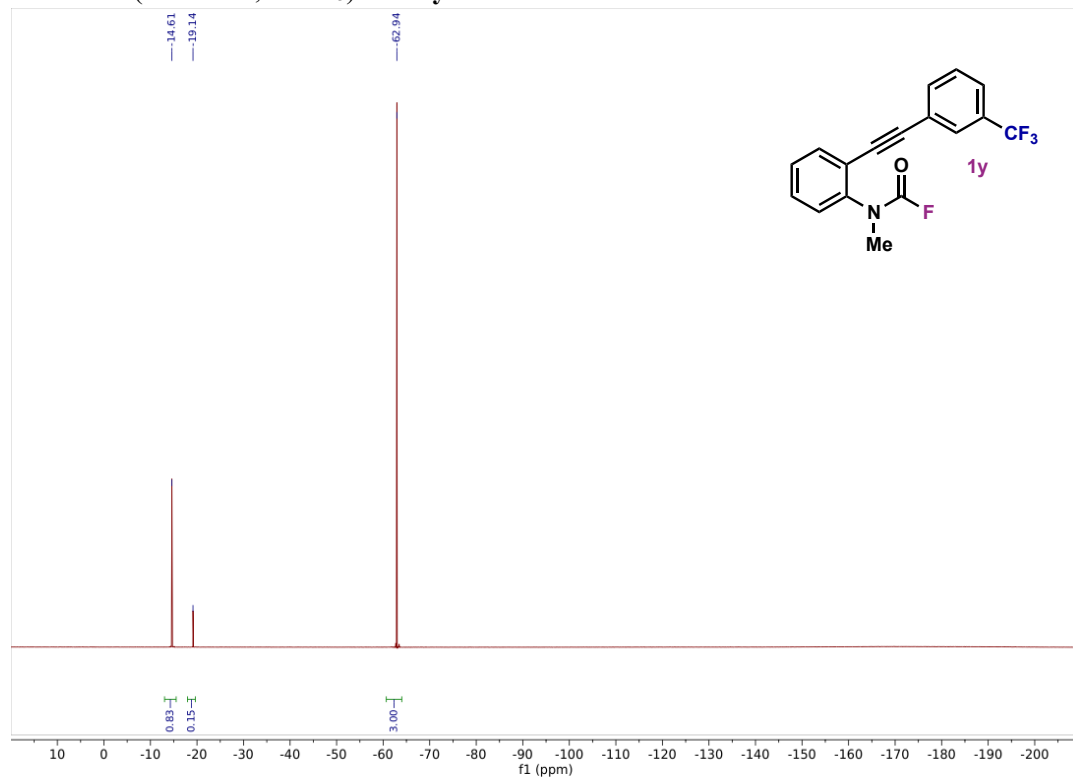
^1H NMR (400 MHz, CDCl_3) of **3.1y**



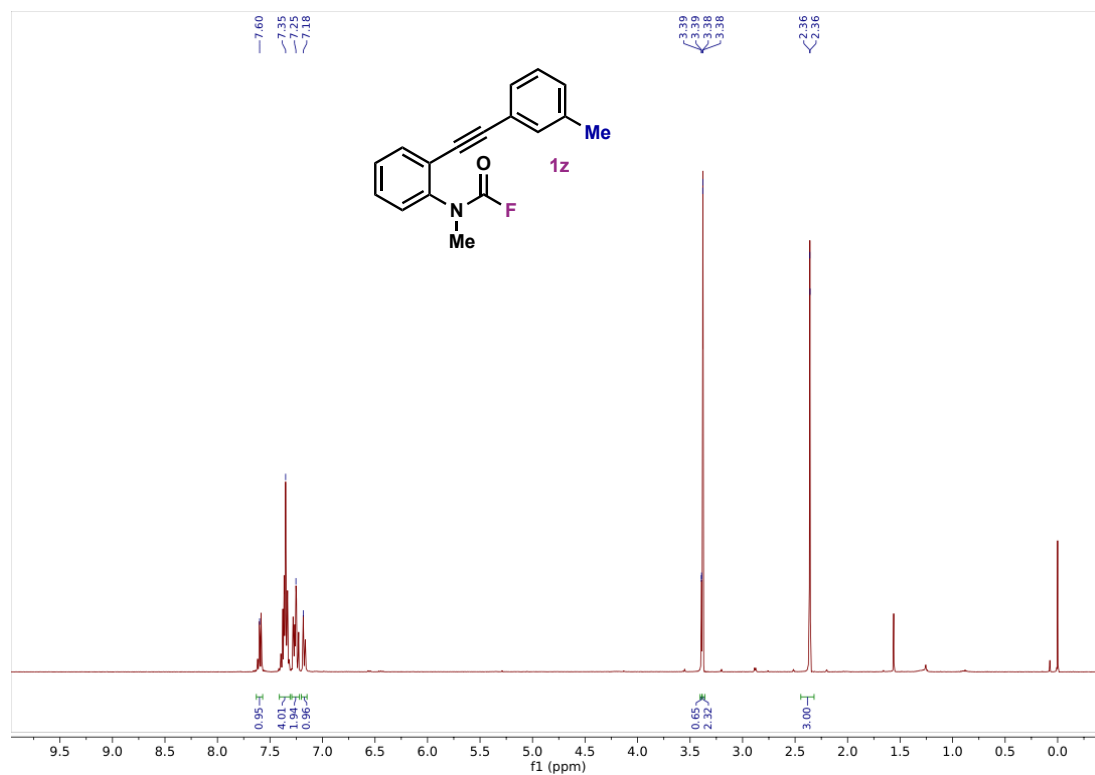
^{13}C { ^1H } NMR (101 MHz, CDCl_3) of **3.1y**



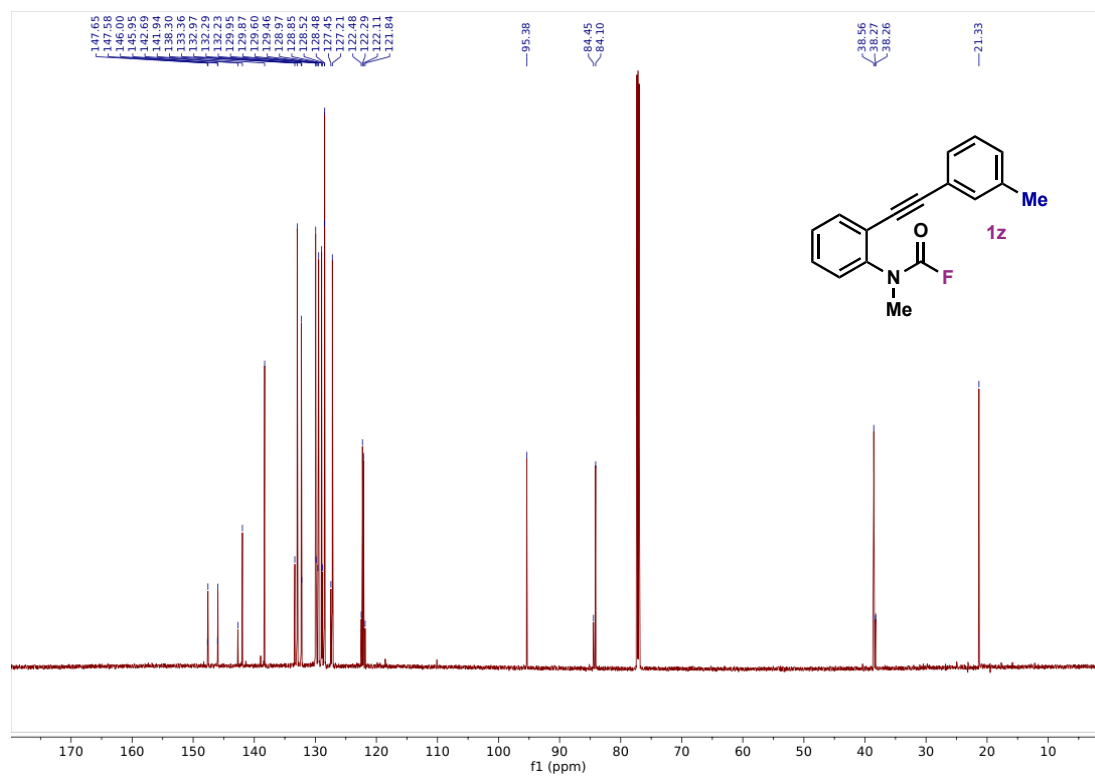
^{19}F NMR (377 MHz, CDCl_3) of **3.1y**



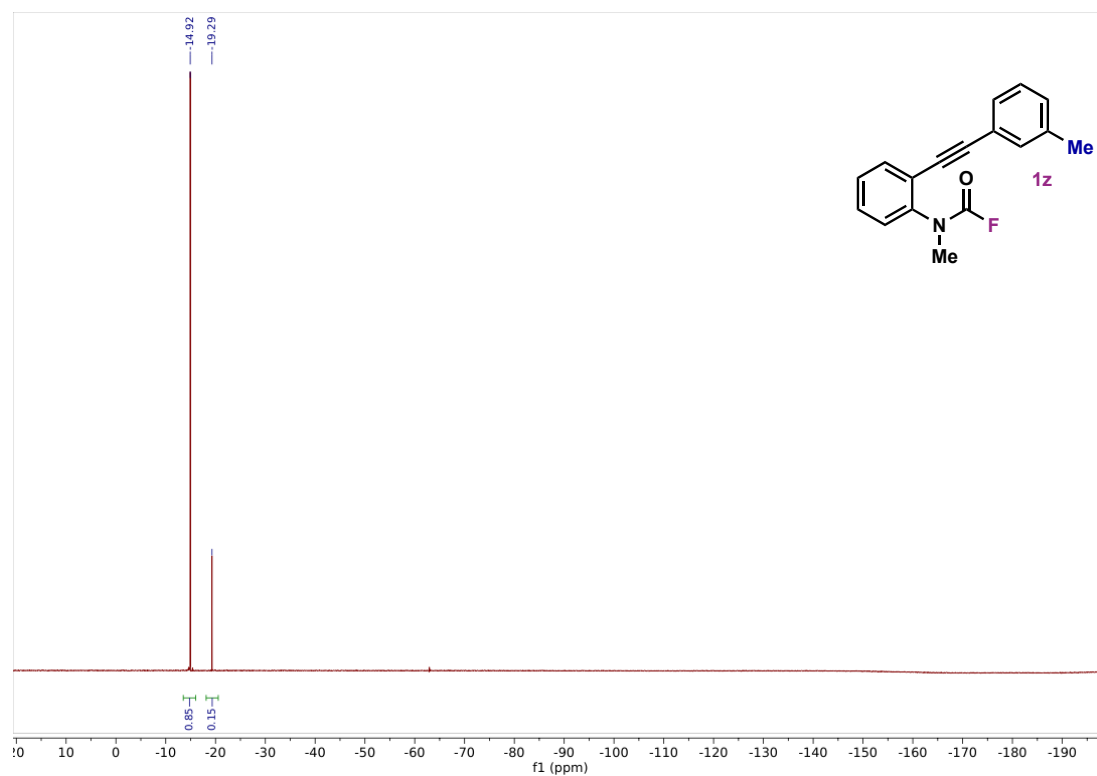
^1H NMR (400 MHz, CDCl_3) of **3.1z**



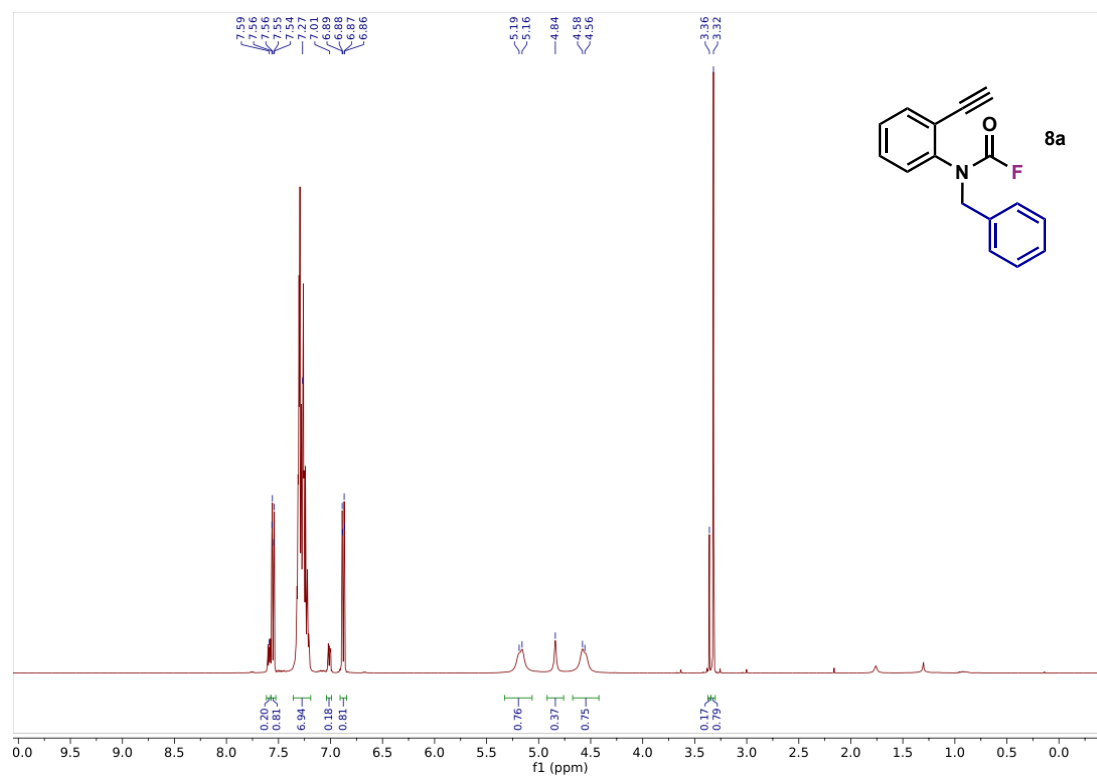
^{13}C $\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) of **3.1z**



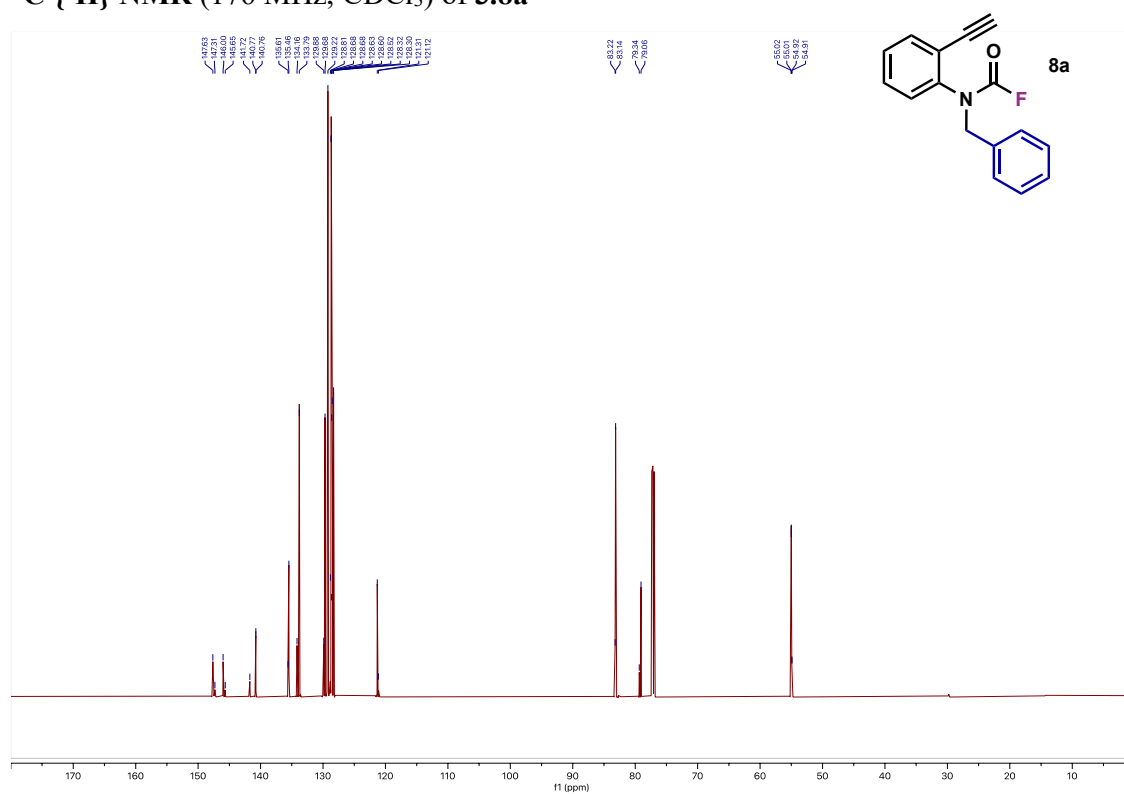
^{19}F NMR (377 MHz, CDCl_3) of **3.1z**



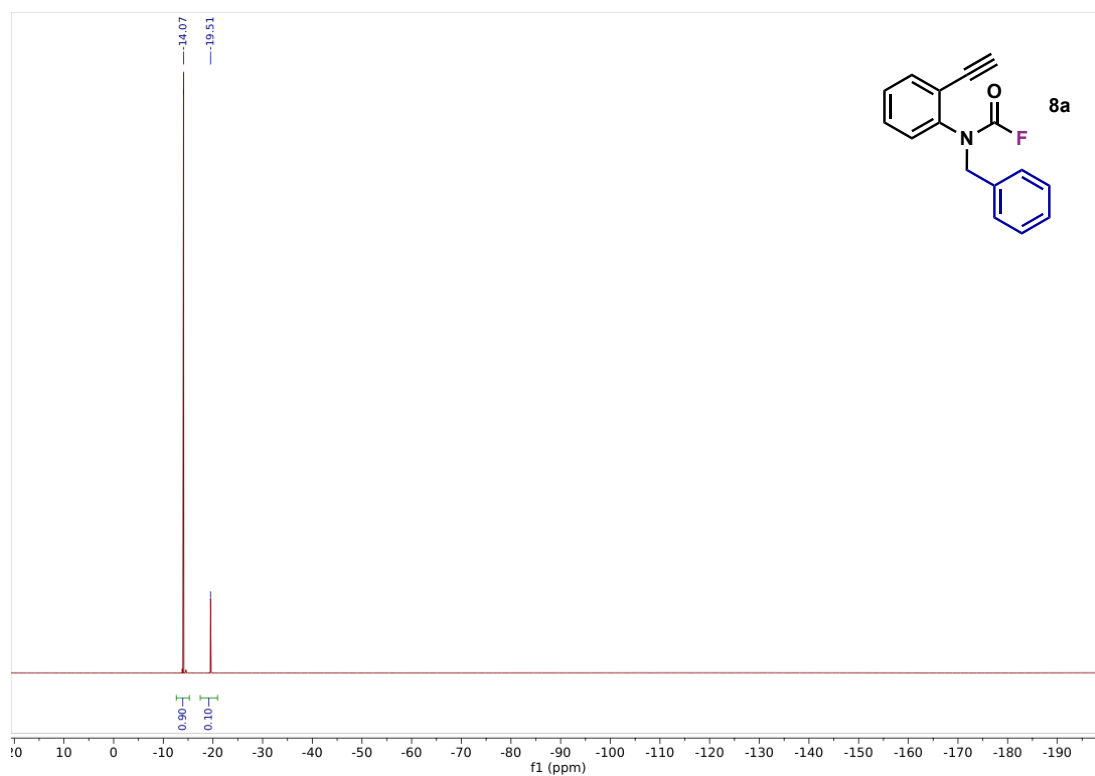
^1H NMR (400 MHz, CDCl_3) of **3.8a**



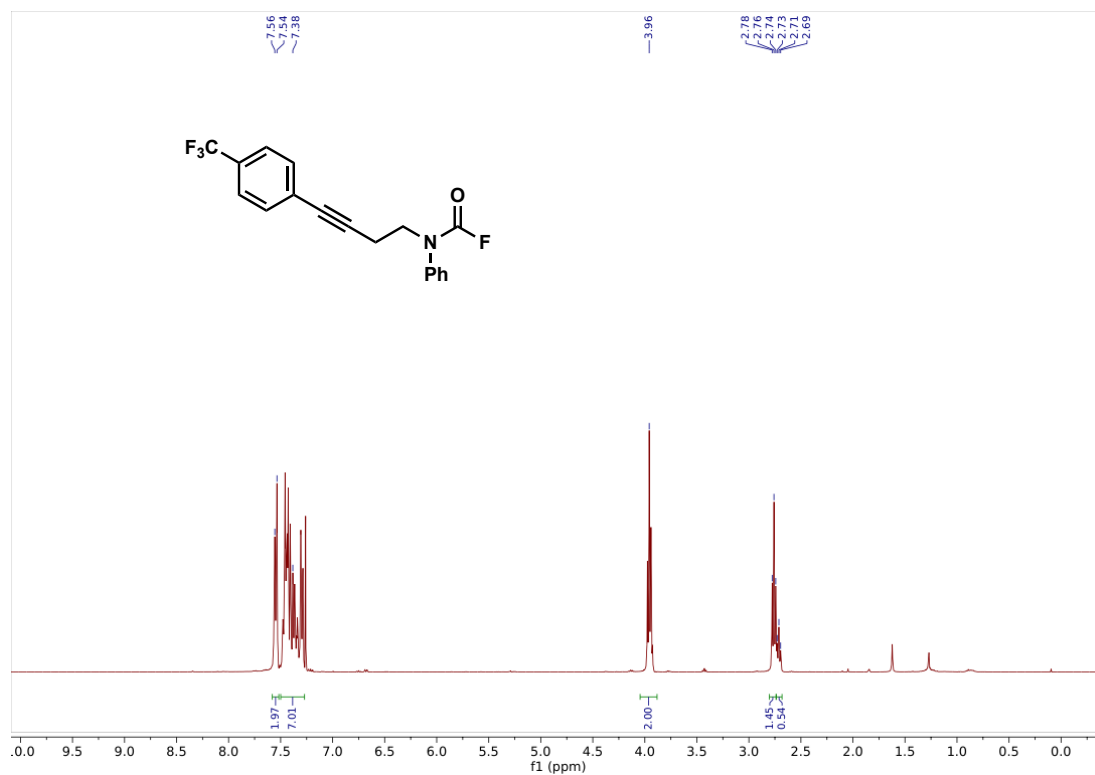
^{13}C $\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) of **3.8a**



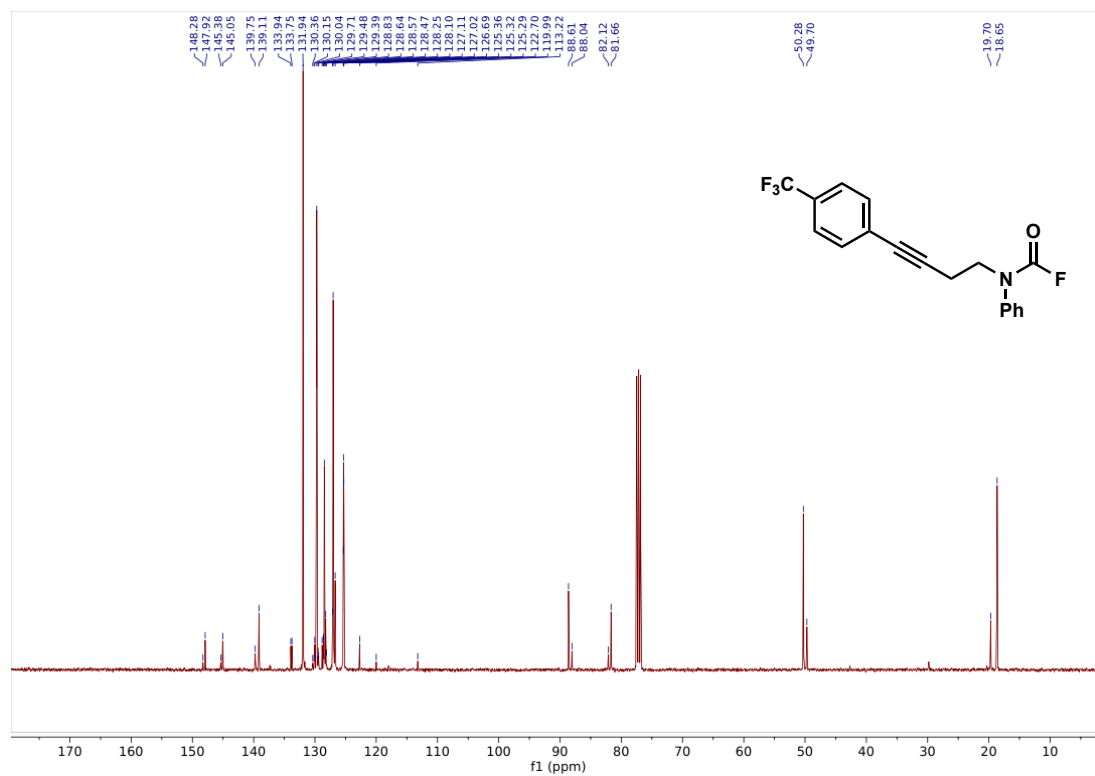
^{19}F NMR (377 MHz, CDCl_3) of **3.8a**



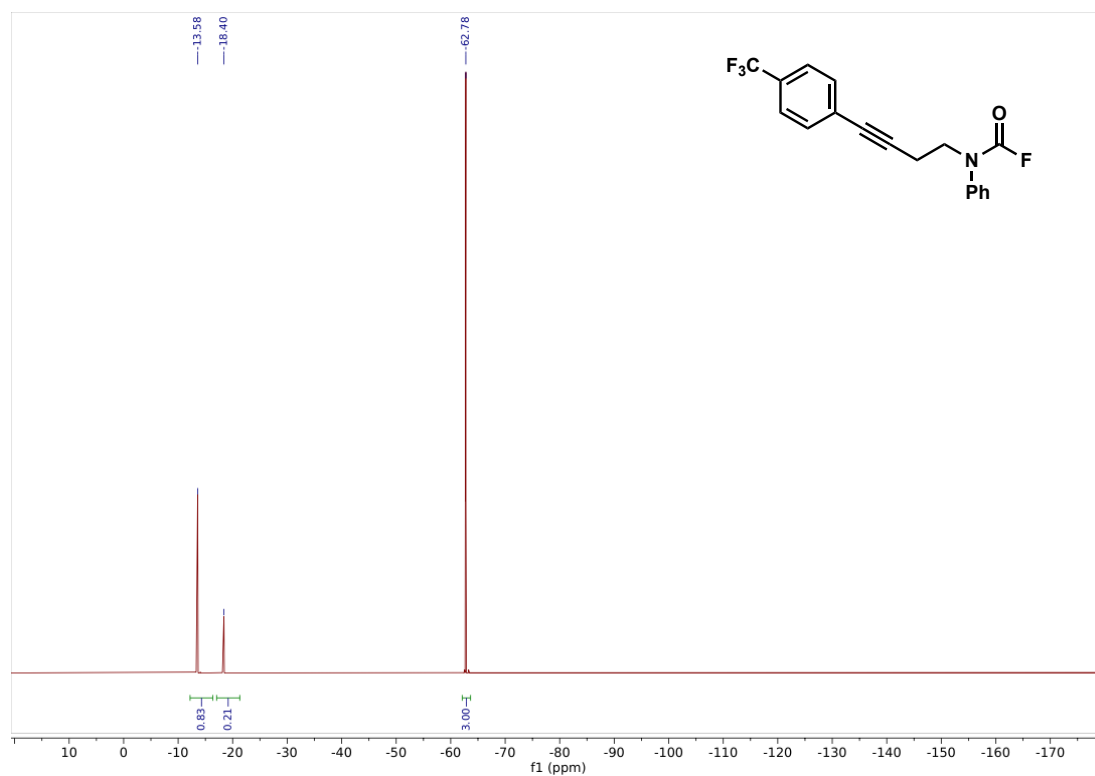
^1H NMR (400 MHz, CDCl_3) of **3.5b**



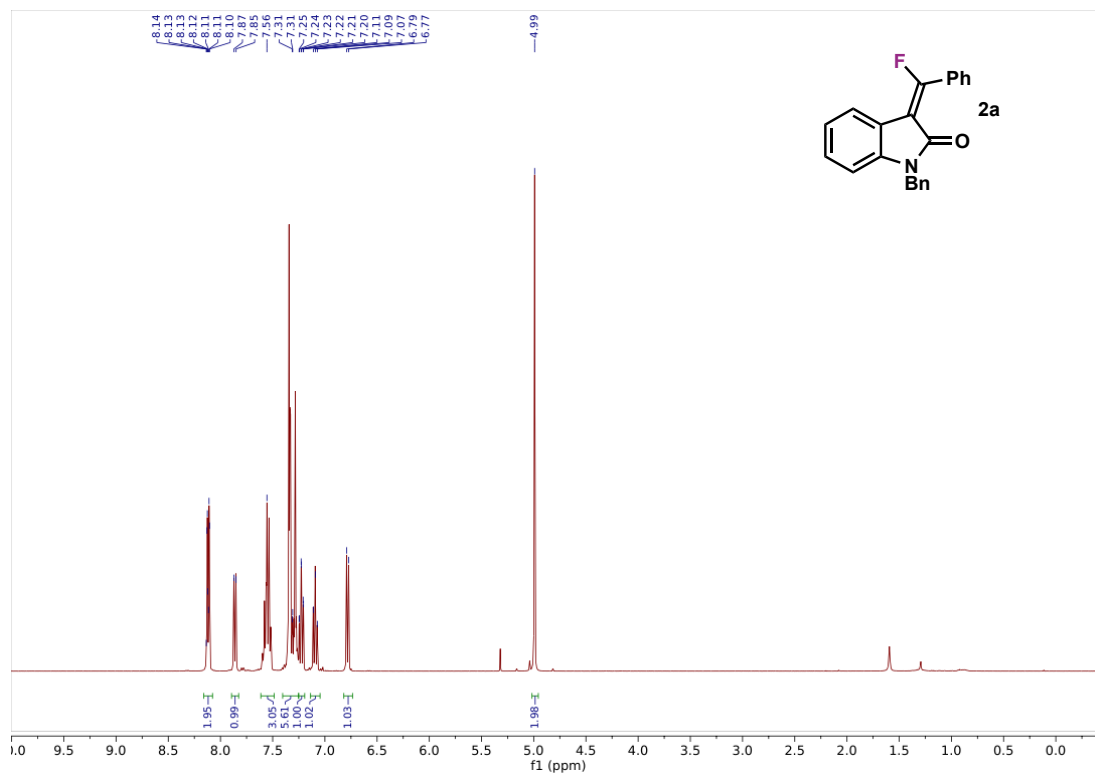
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.5b**



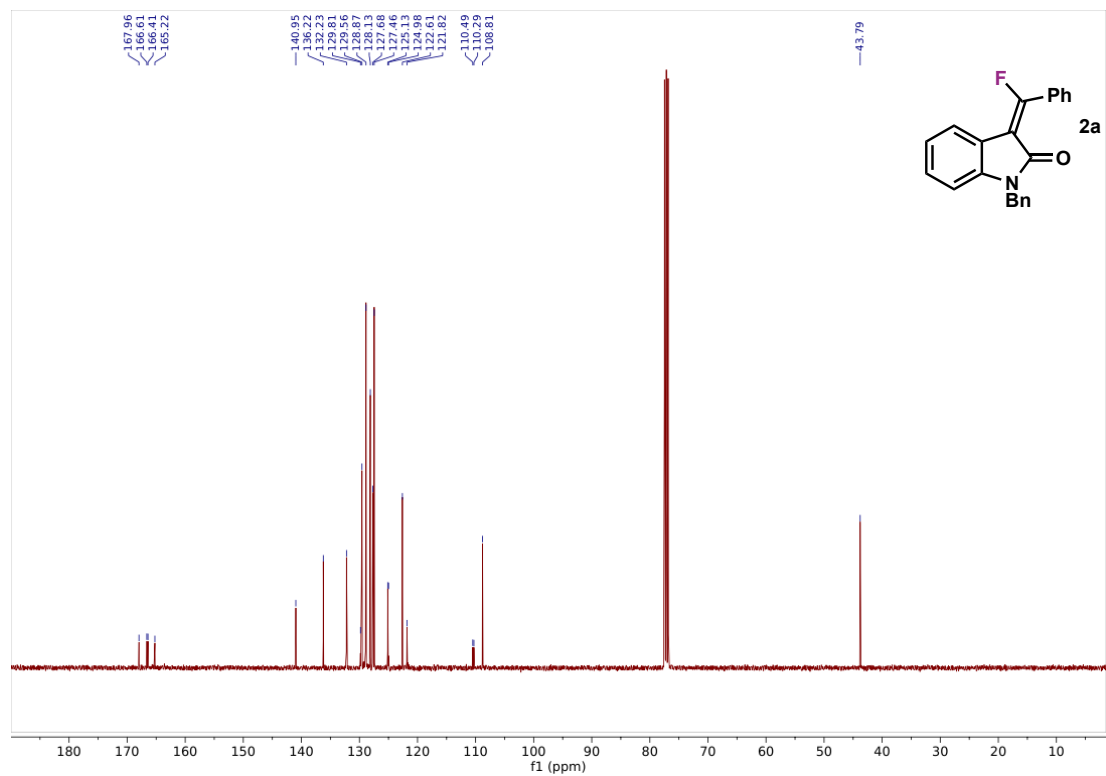
^{19}F NMR (377 MHz, CDCl_3) of **3.5b**



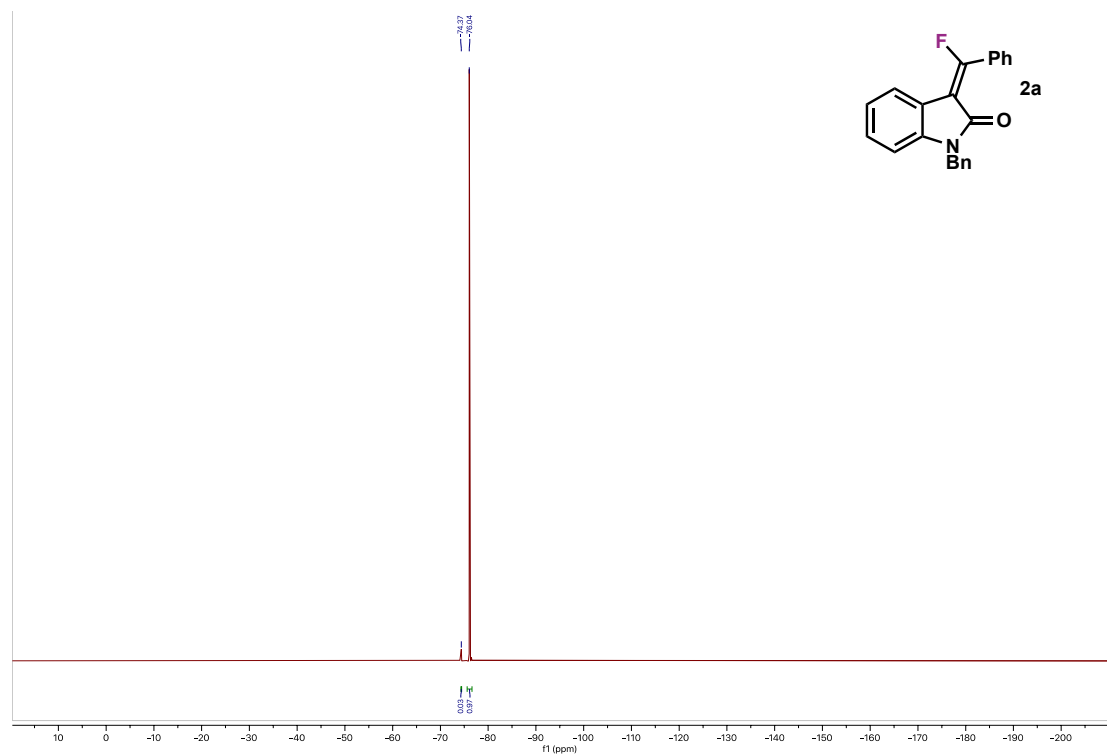
^1H NMR (400 MHz, CDCl_3) of **3.2a**



^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.2a**



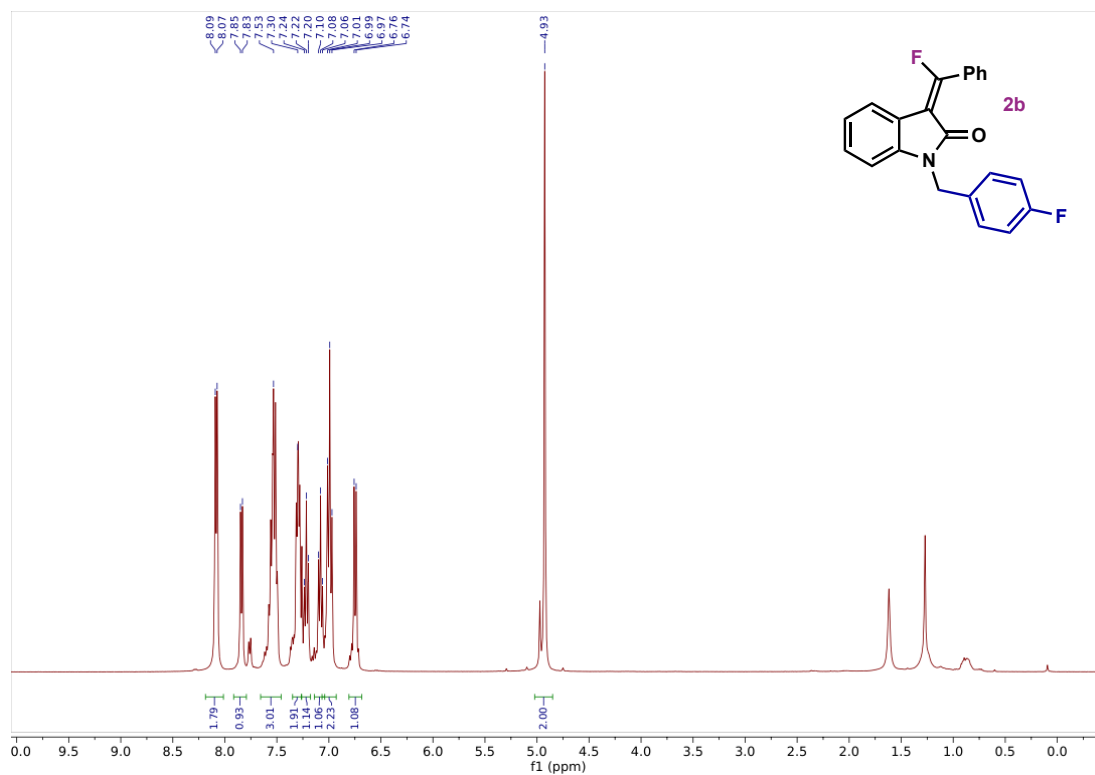
^{19}F NMR (377 MHz, CDCl_3) of **3.2a**



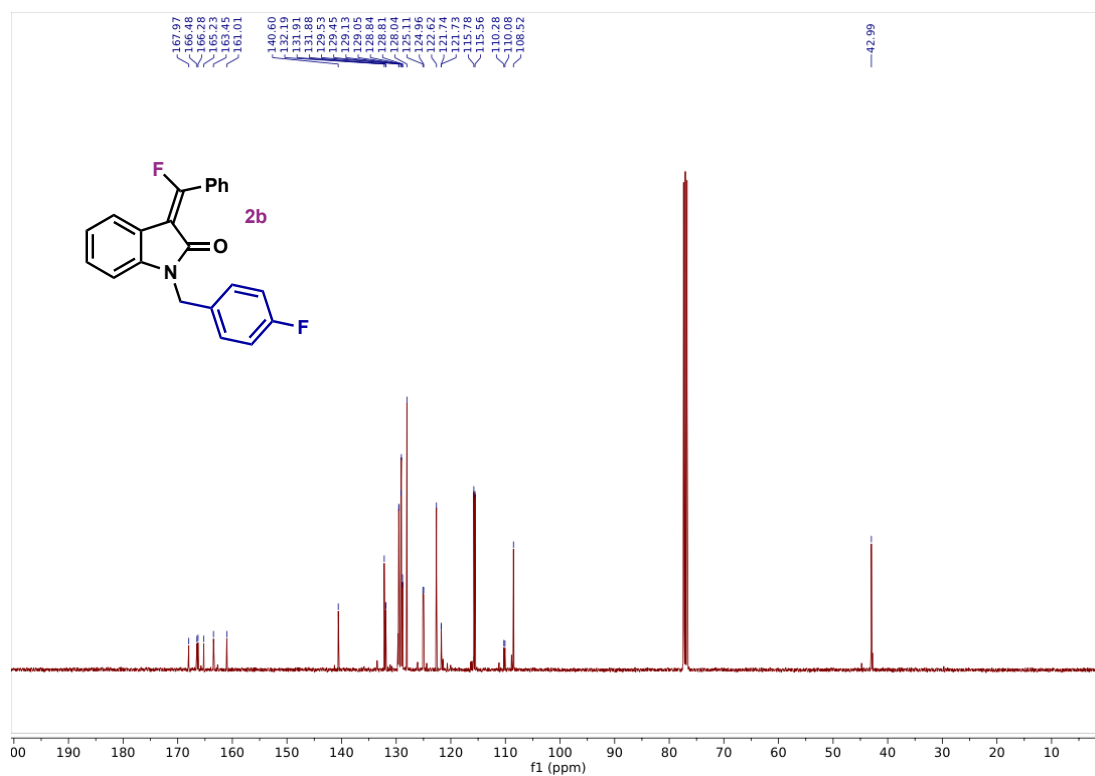
[illegible]

Chemical structure of 2a-Br is shown in the top right corner. The structure is a benzimidazole derivative with a bromophenyl group and a benzyl group on the nitrogen. The $E:Z$ ratio is 1.15:1.

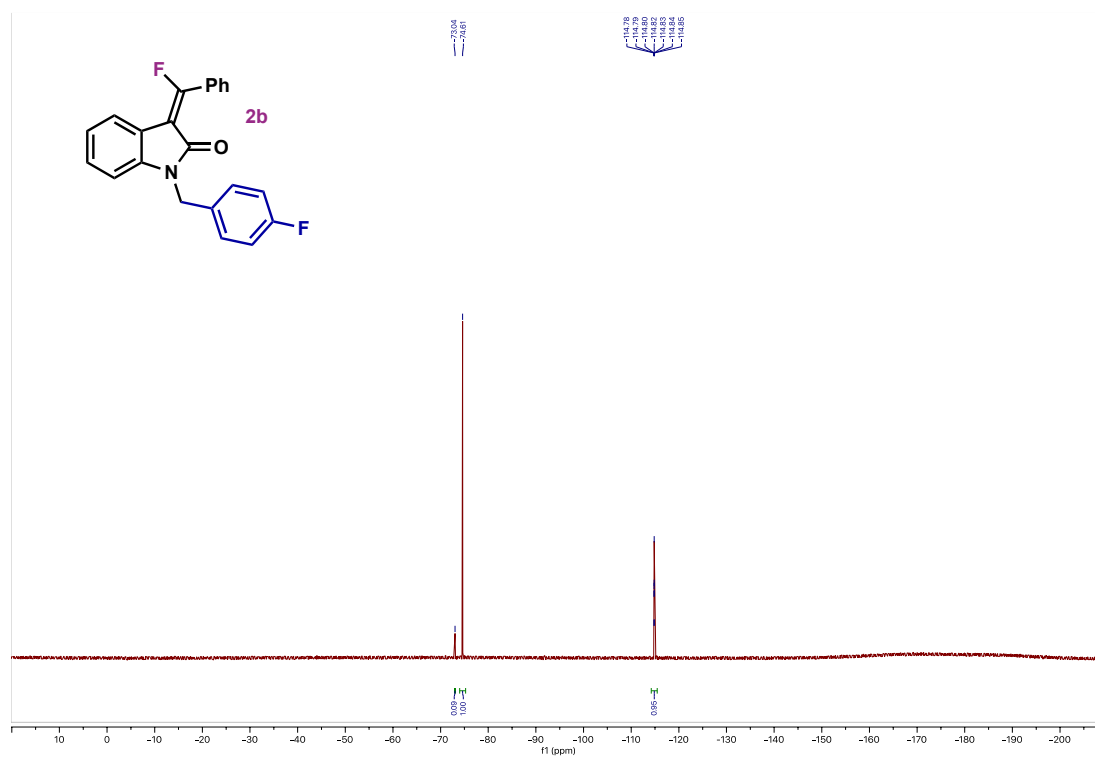
^1H NMR (700 MHz, CDCl_3) of **3.2b**



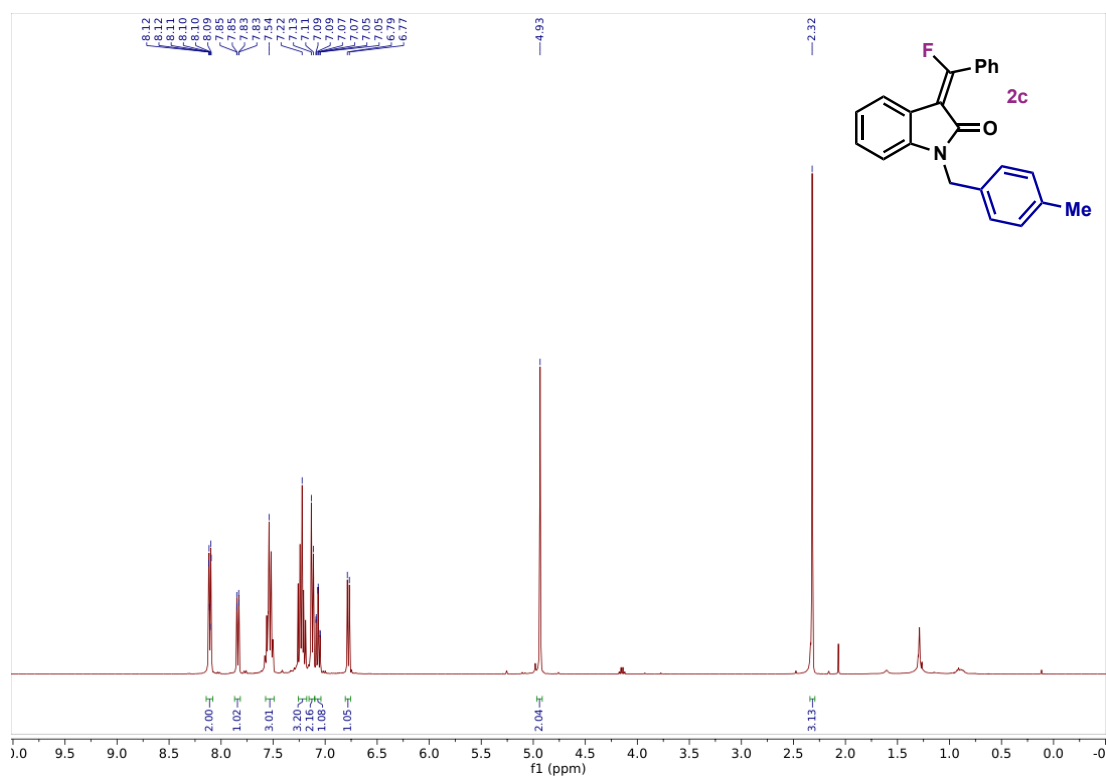
^{13}C { ^1H } NMR (101 MHz, CDCl_3) of **3.2b**



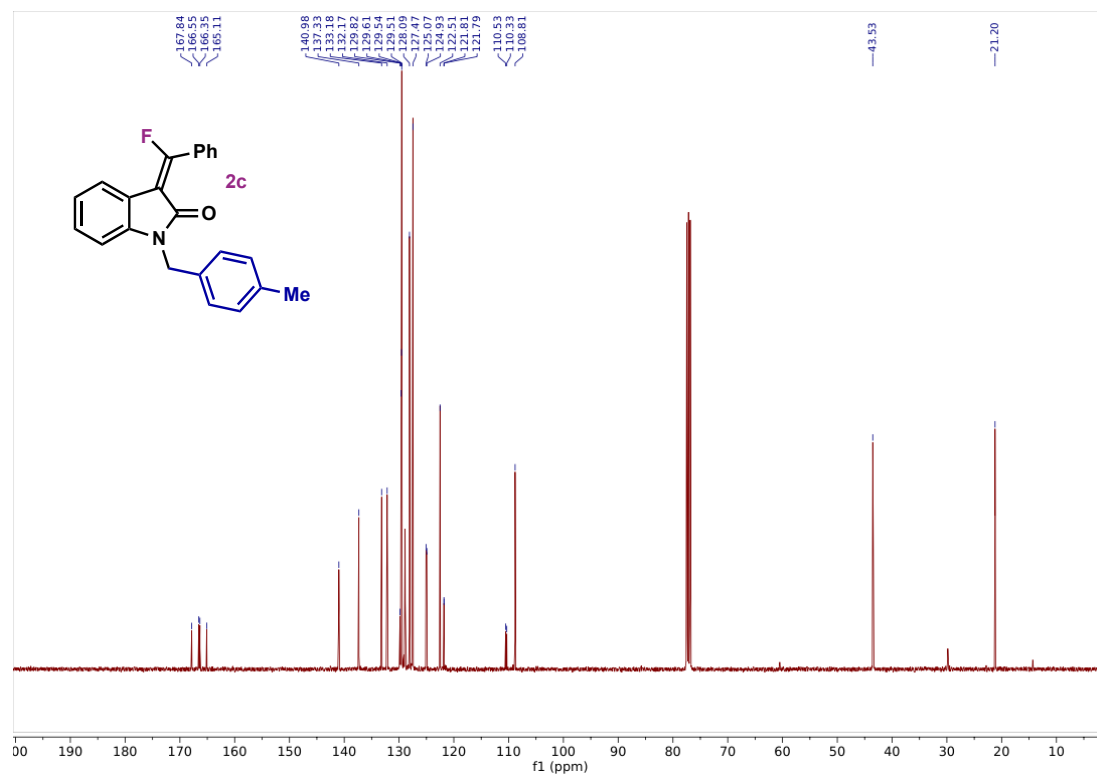
^{19}F NMR (377 MHz, CDCl_3) of **3.2b** (92:8 *E*:*Z* after column)



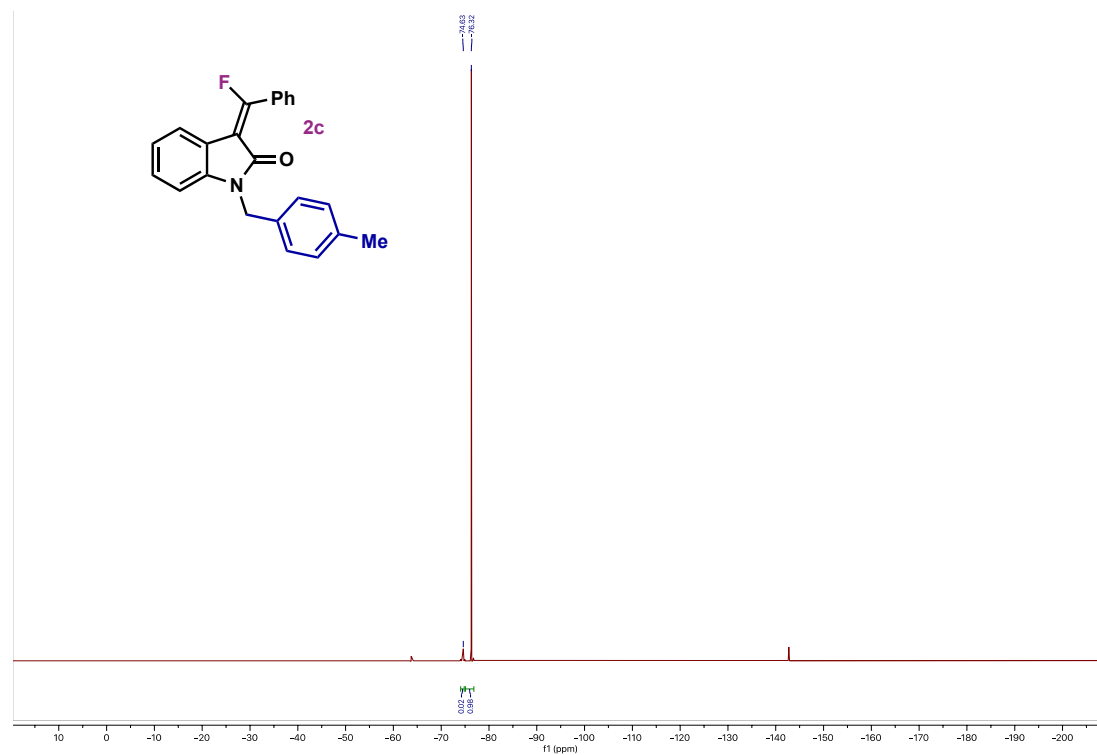
^1H NMR (400 MHz, CDCl_3) of **3.2c**



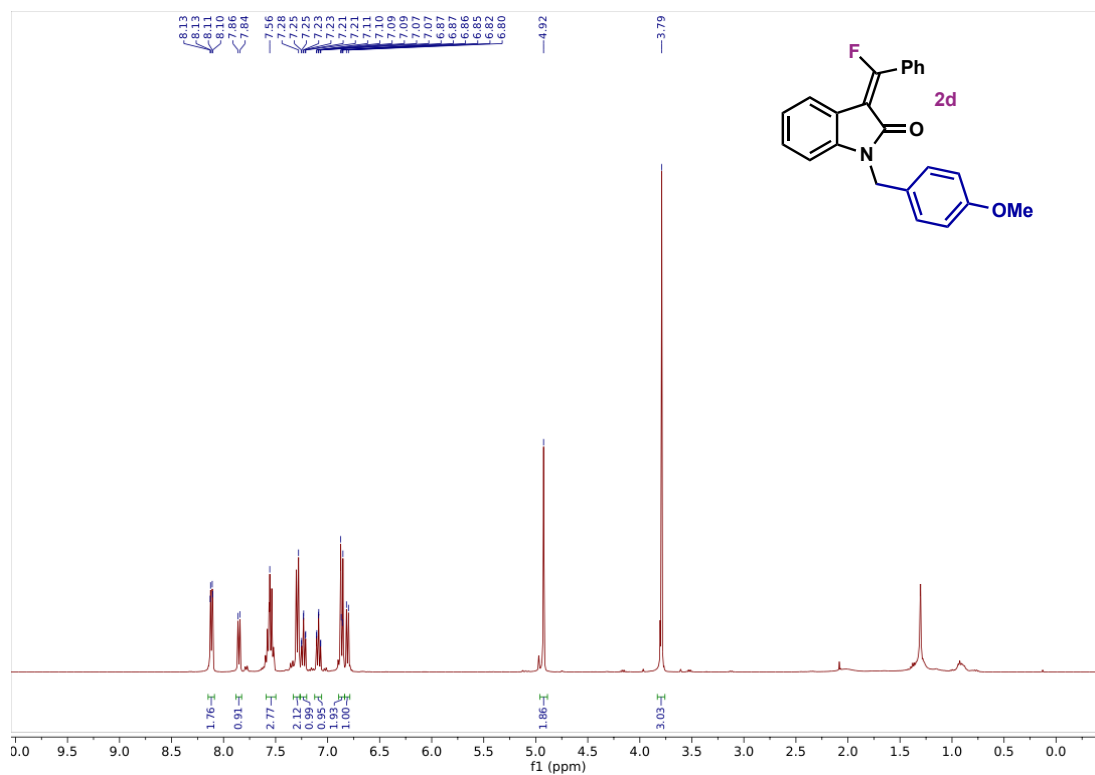
$^{13}\text{C} \{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.2c**



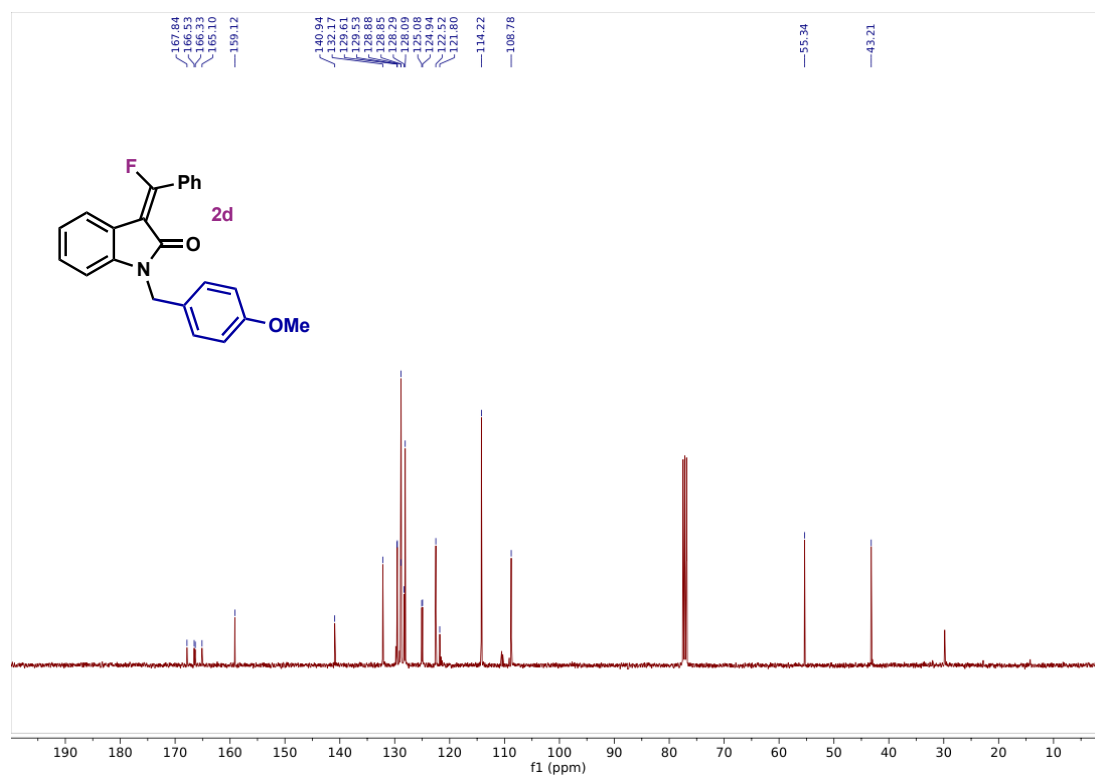
^{19}F NMR (377 MHz, CDCl_3) of **3.2c**



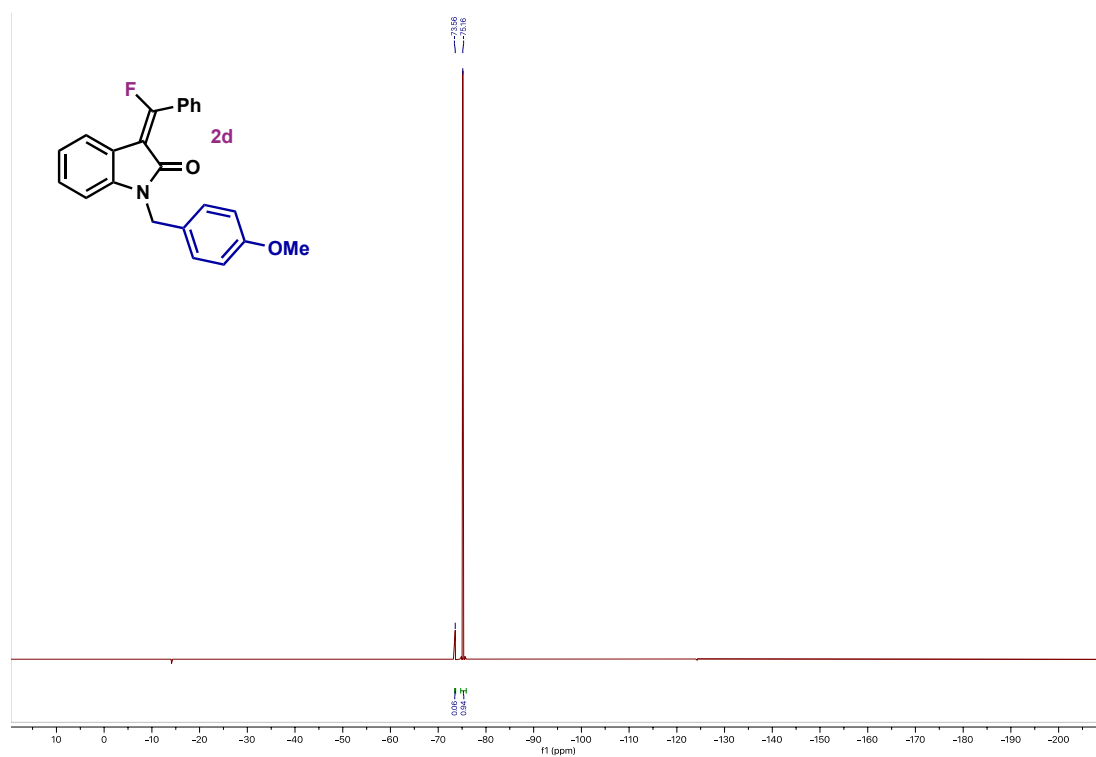
^1H NMR (400 MHz, CDCl_3) of **3.2d**



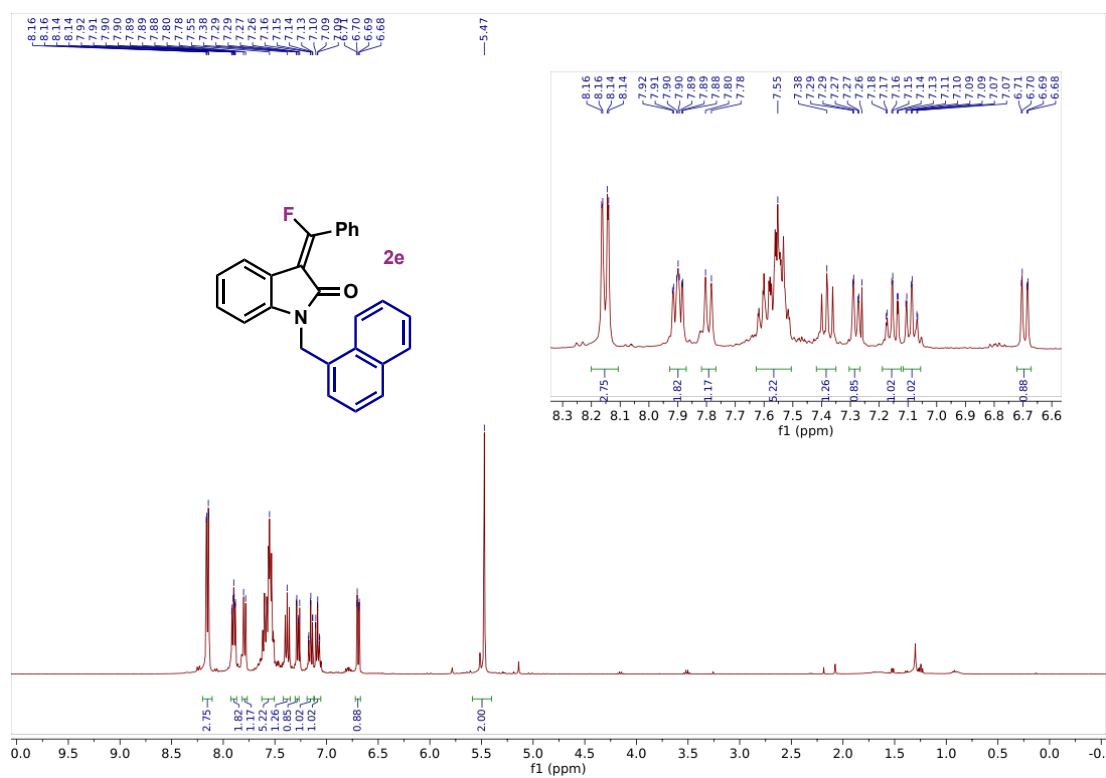
^{13}C { ^1H } NMR (101 MHz, CDCl_3) of **3.2d**



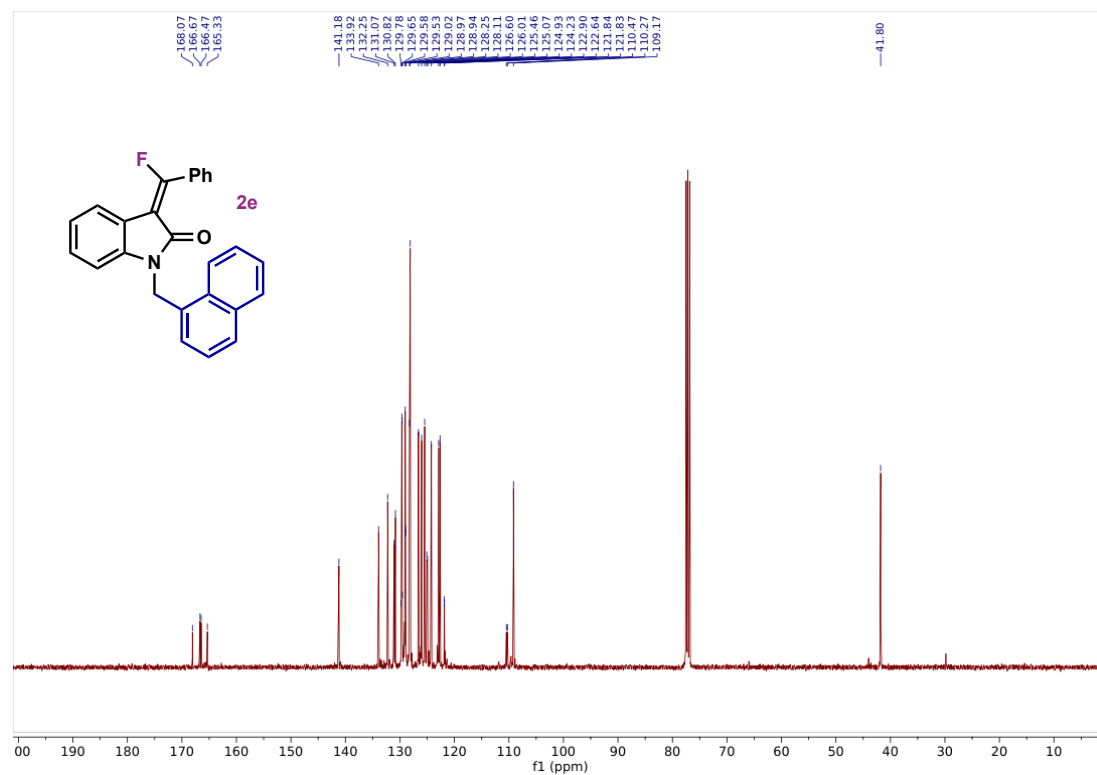
^{19}F NMR (377 MHz, CDCl_3) of **3.2d**



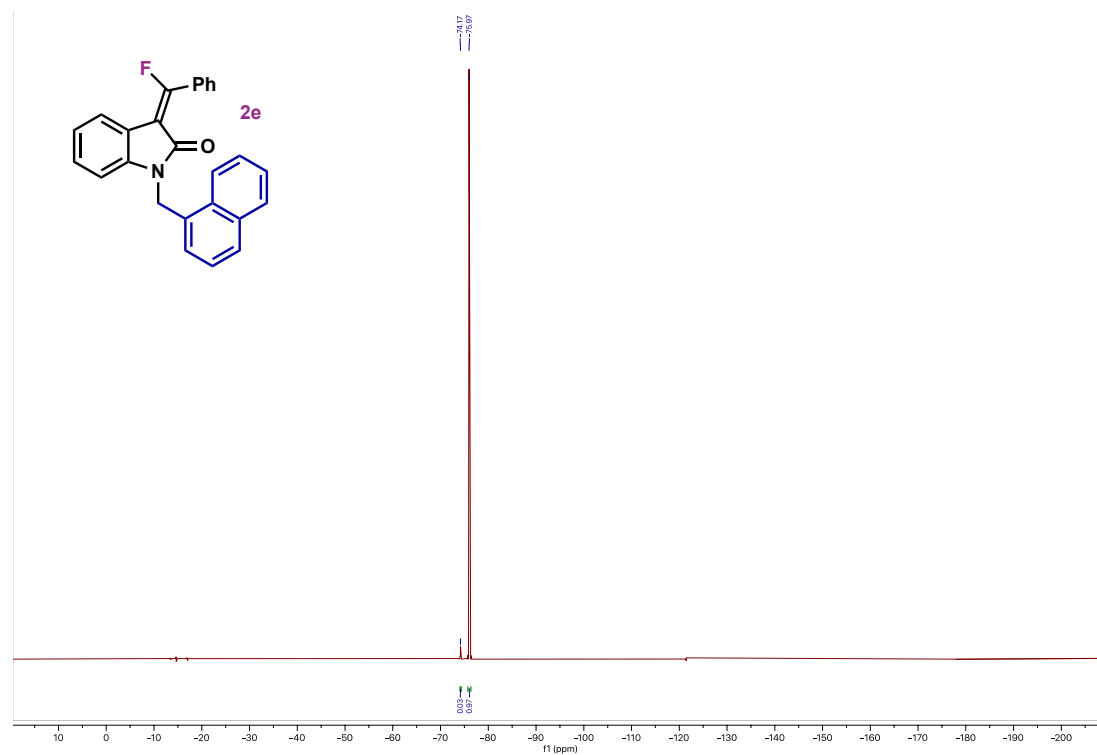
^1H NMR (400 MHz, CDCl_3) of **3.2e**



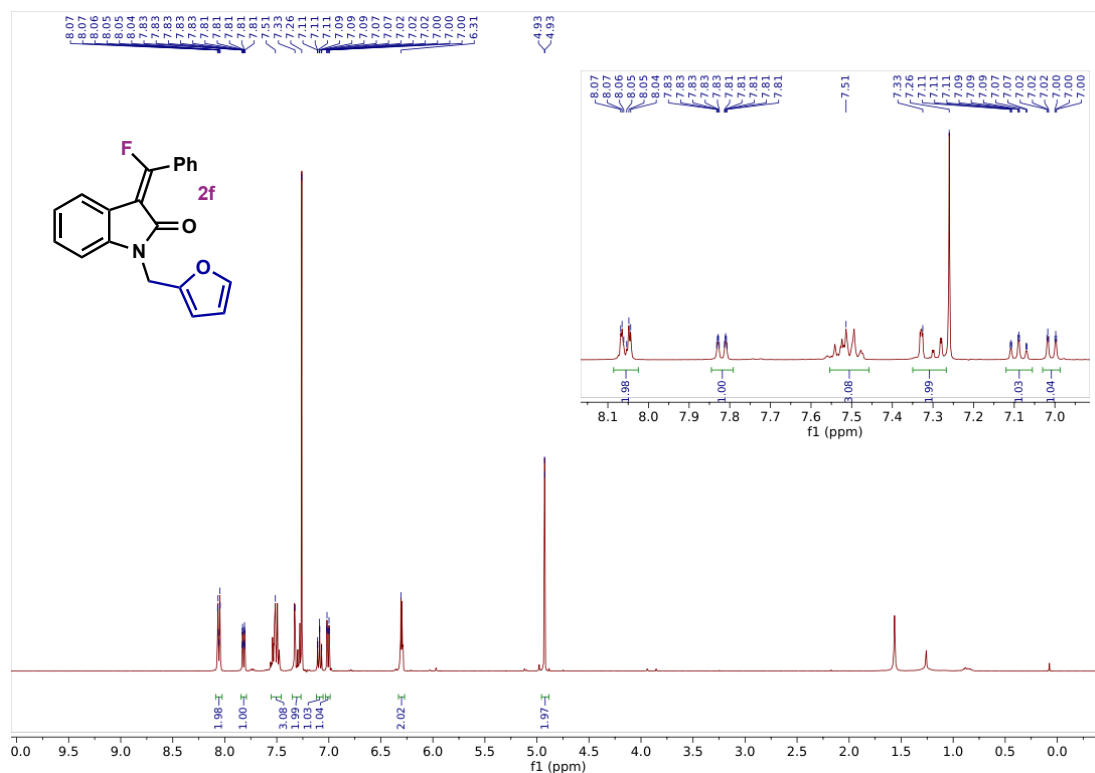
^{13}C { ^1H } NMR (101 MHz, CDCl_3) of **3.2e**



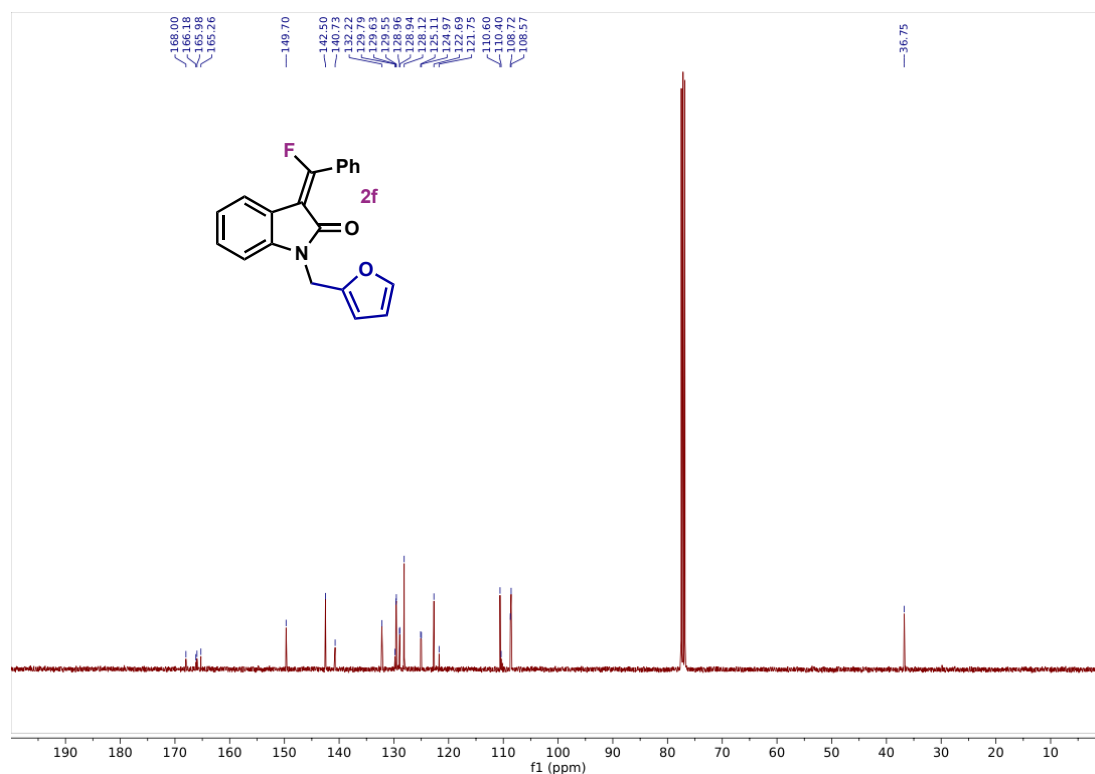
^{19}F NMR (377 MHz, CDCl_3) of **3.2e**



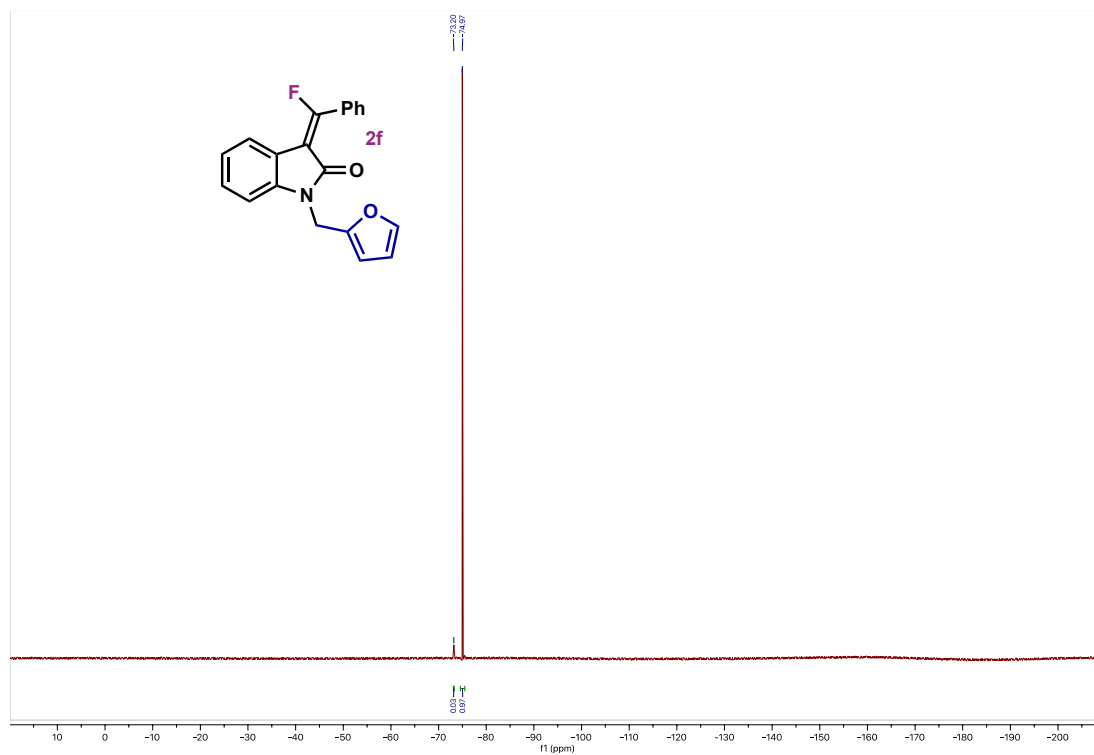
^1H NMR (400 MHz, CDCl_3) of **3.2f**



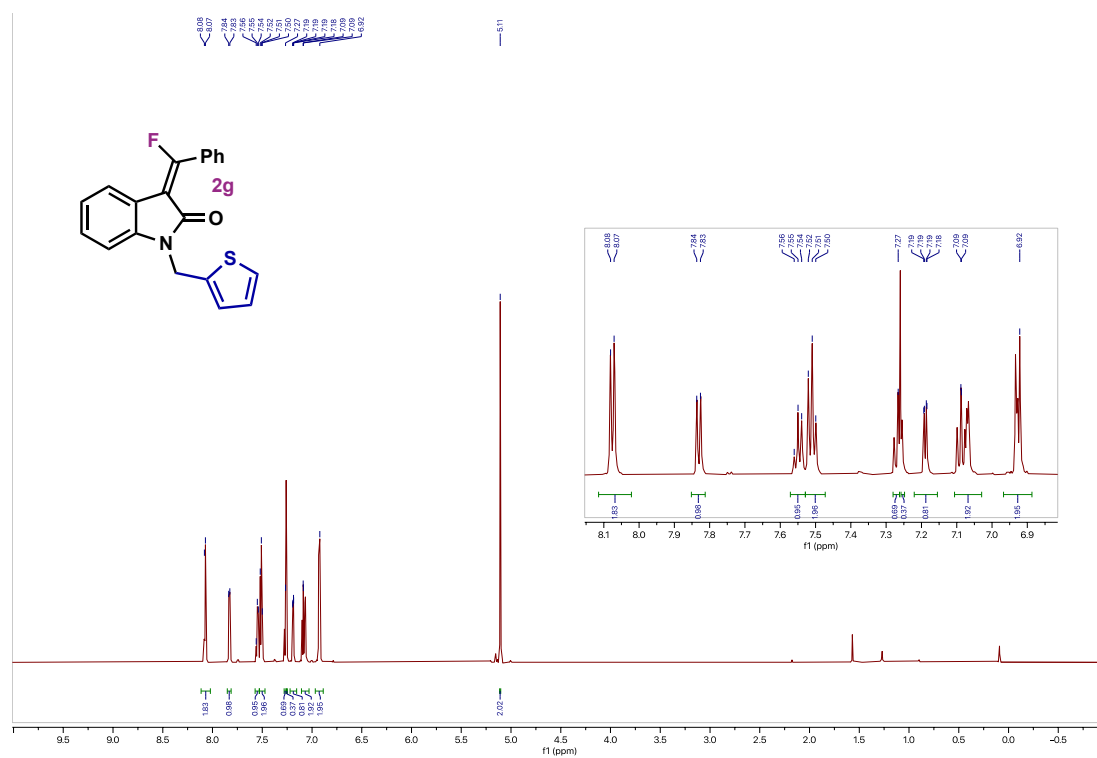
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.2f**



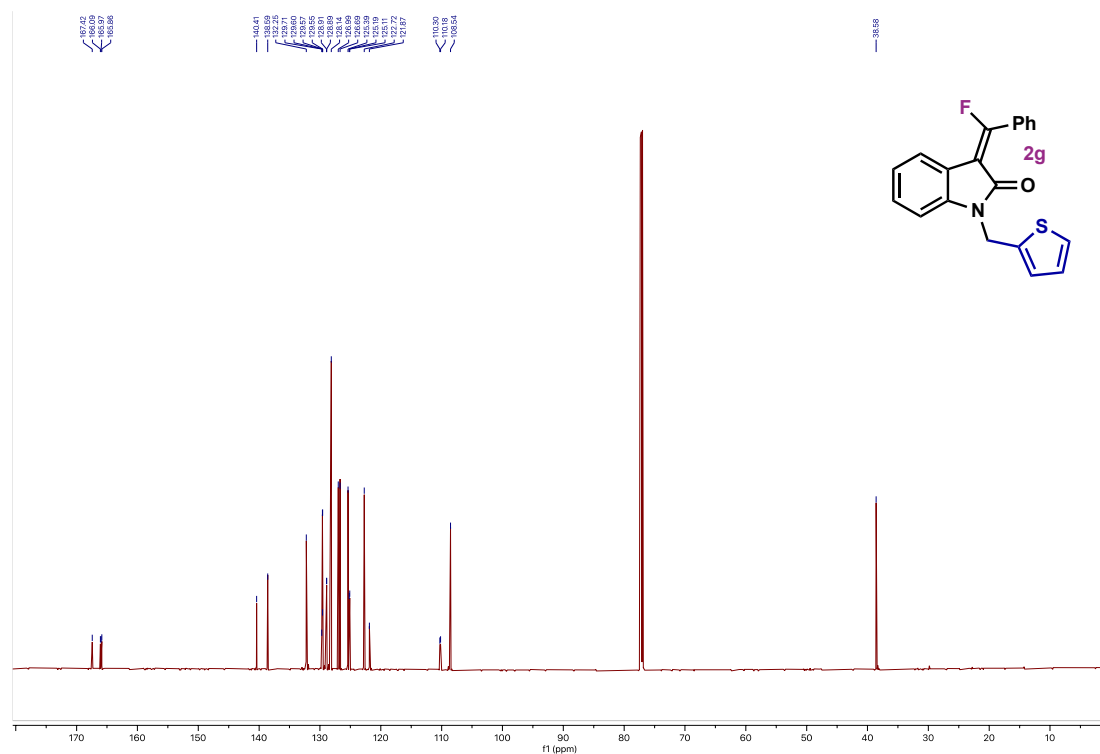
^{19}F NMR (377 MHz, CDCl_3) of **3.2f**



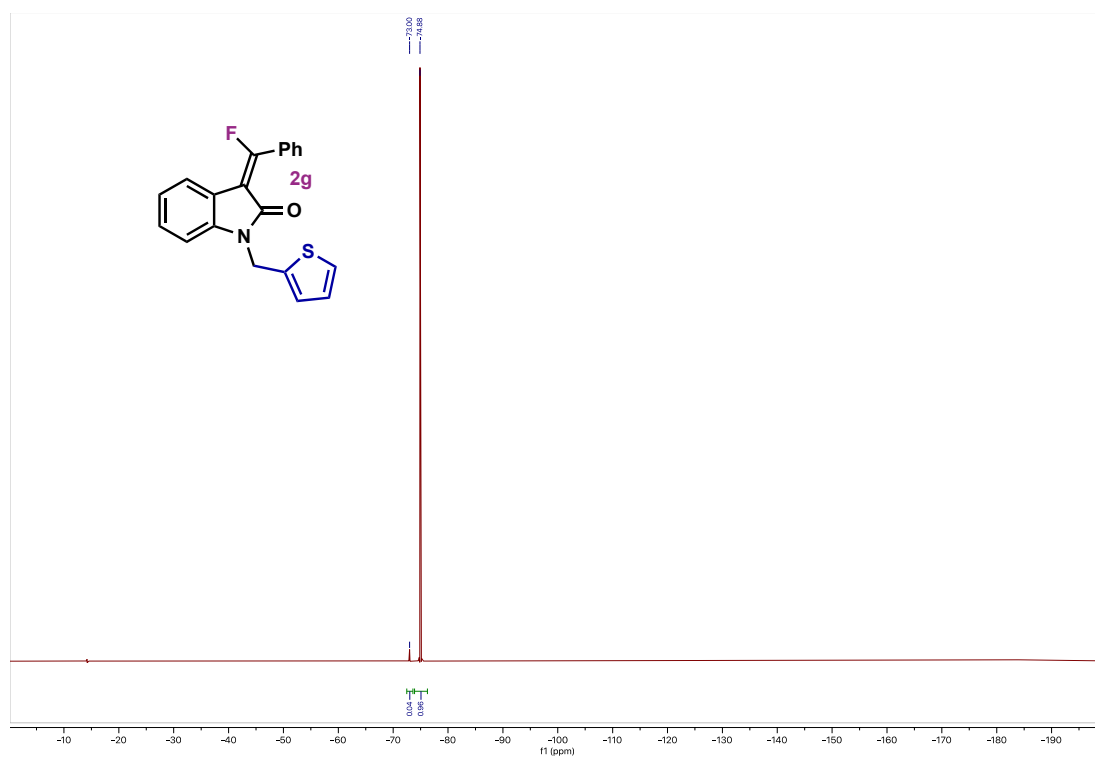
^1H NMR (400 MHz, CDCl_3) of **3.2g**



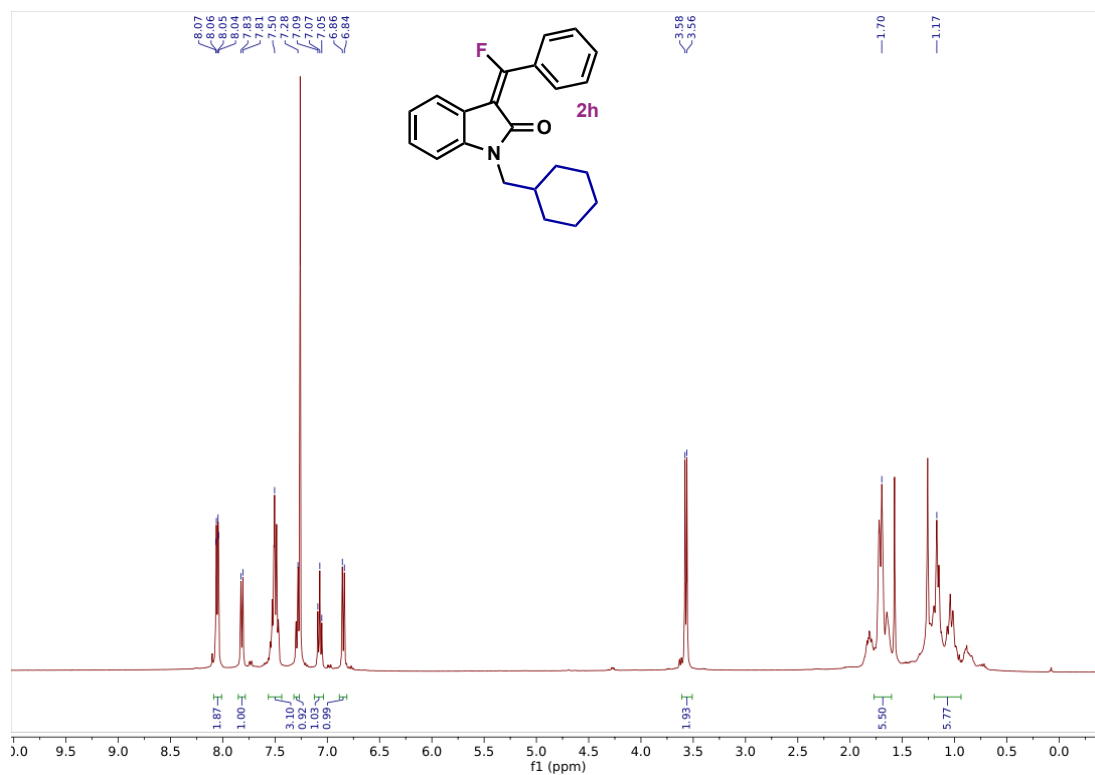
$^{13}\text{C} \{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.2g**



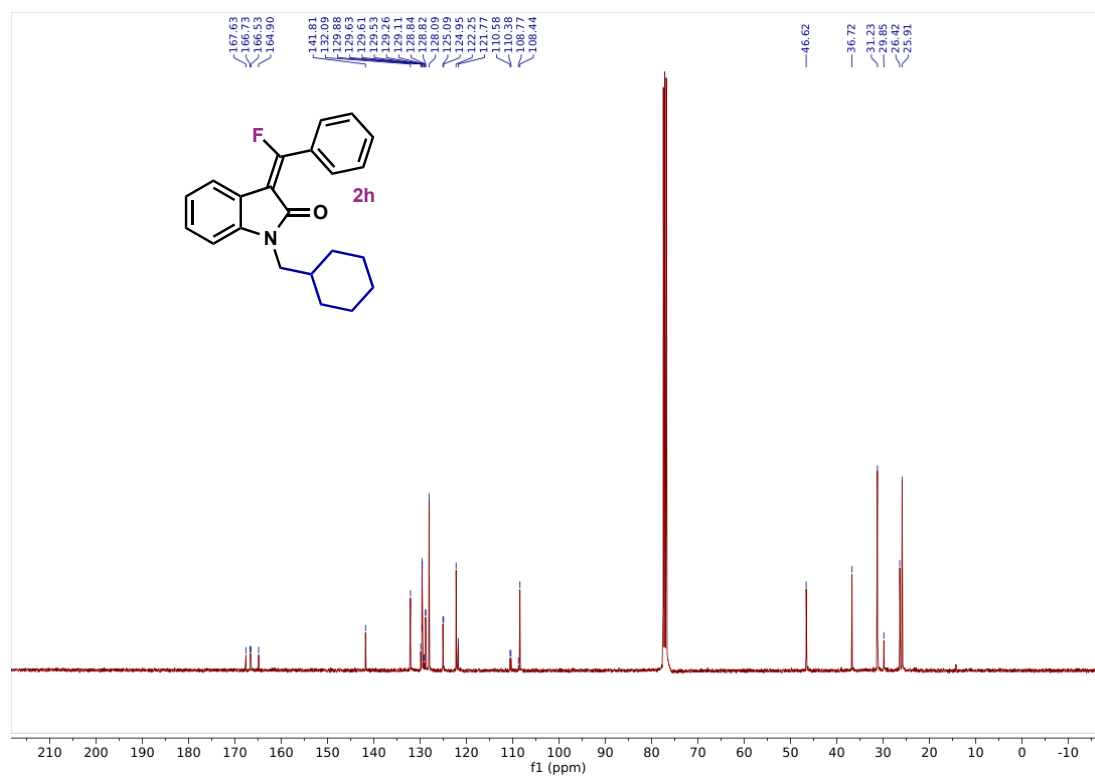
^{19}F NMR (377 MHz, CDCl_3) of **3.2g**



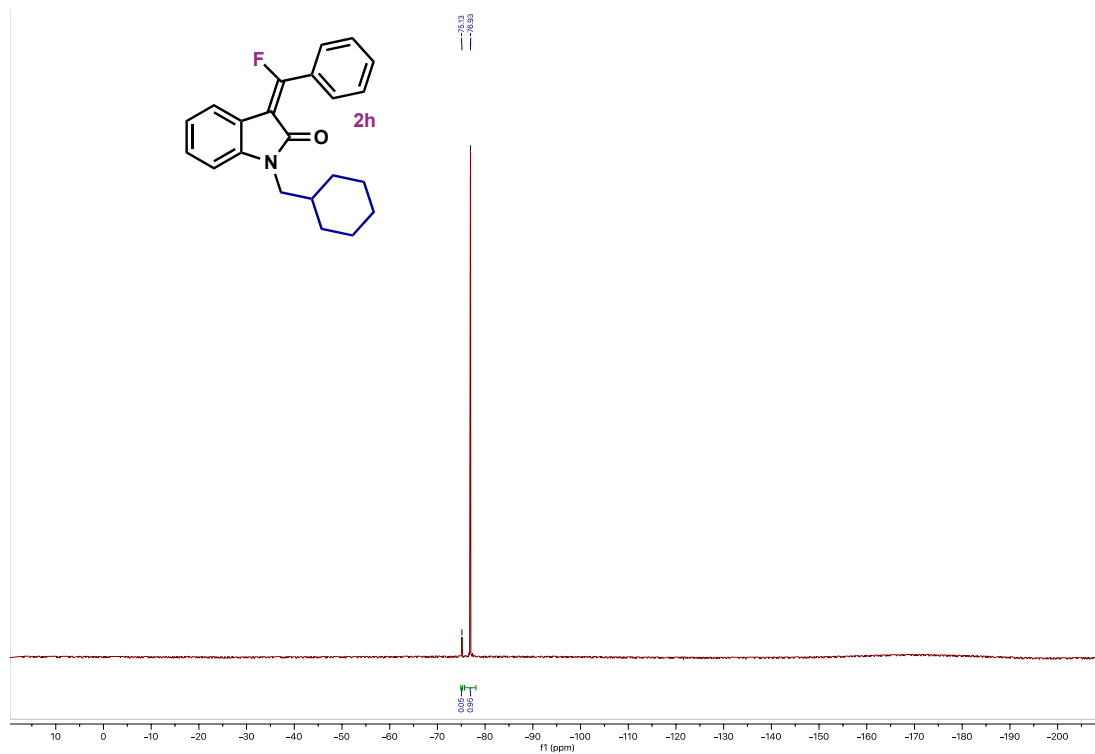
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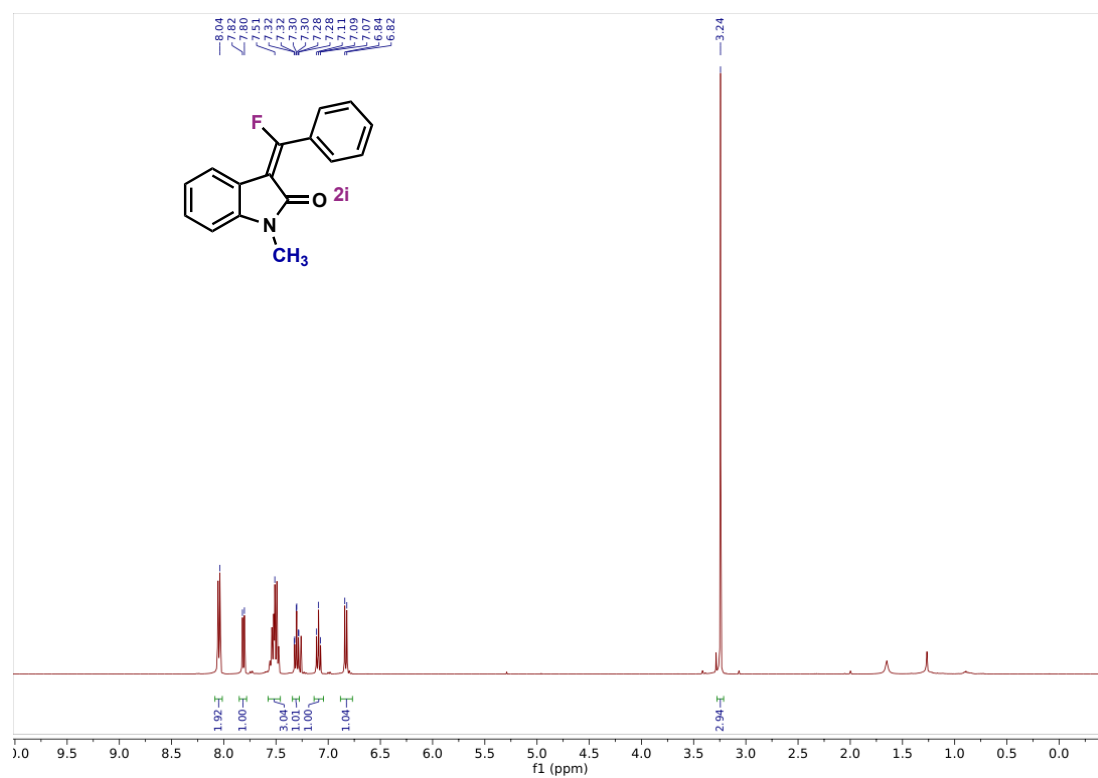
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.2h**



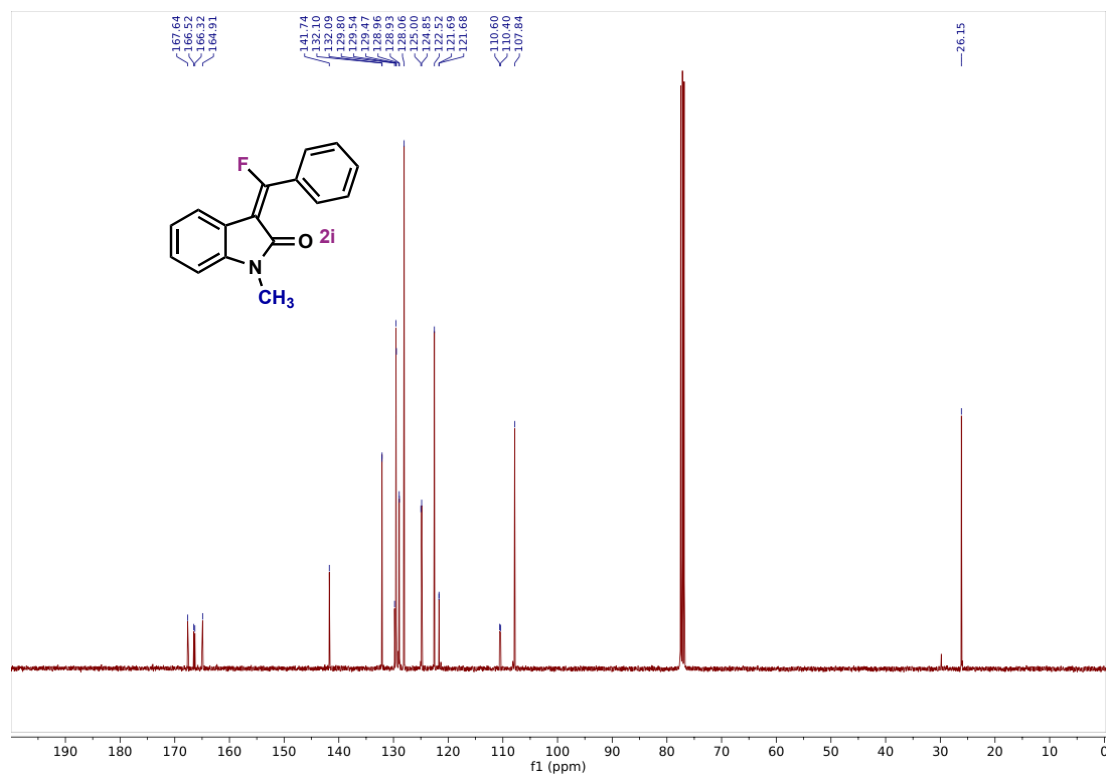
^{19}F NMR (377 MHz, CDCl_3) of **3.2h**



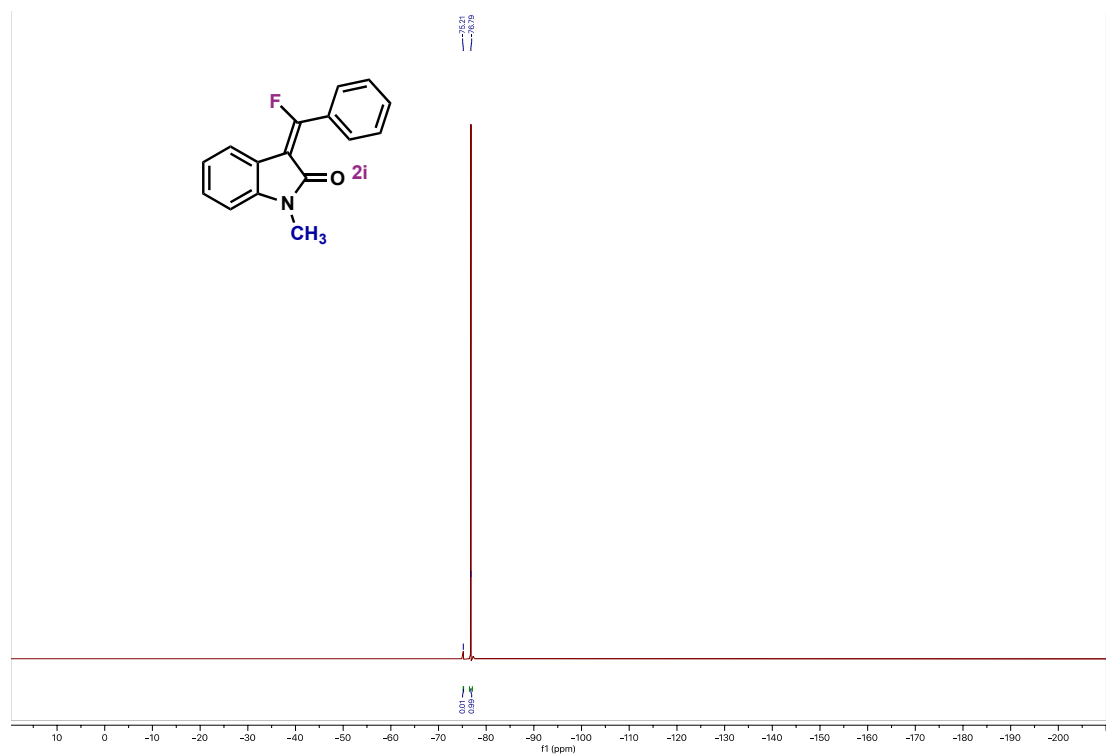
^1H NMR (400 MHz, CDCl_3) of **3.2i**



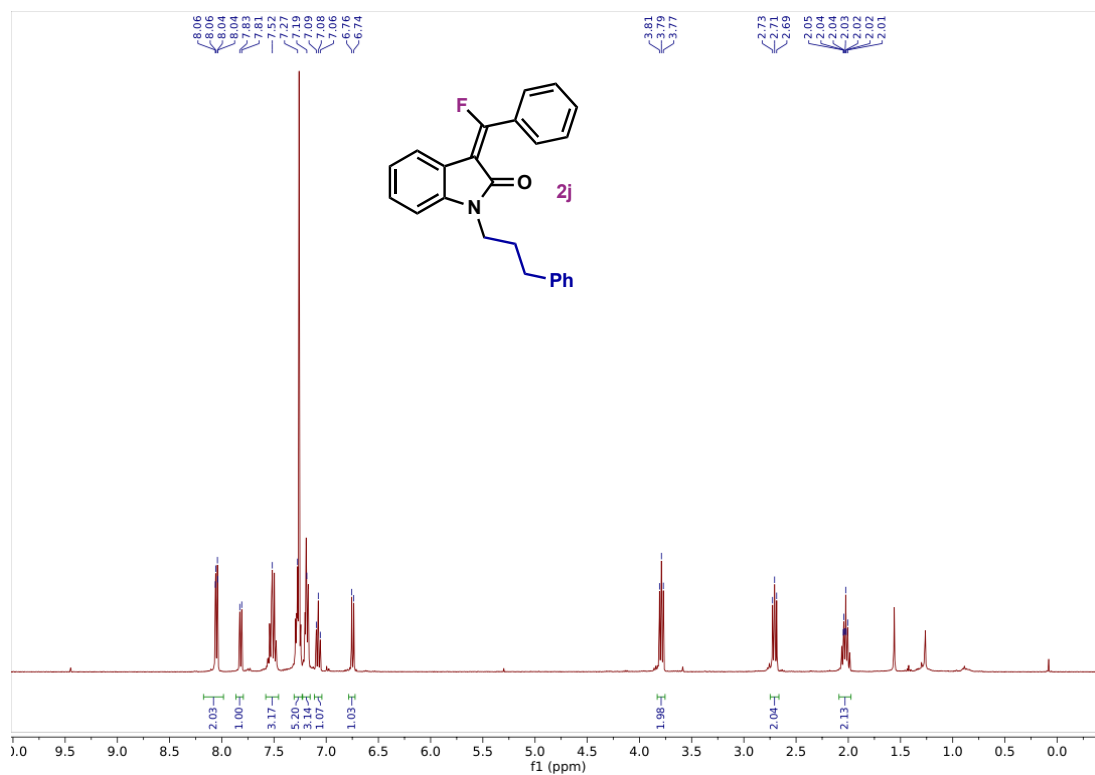
^{13}C { ^1H } NMR (101 MHz, CDCl_3) of **3.2i**



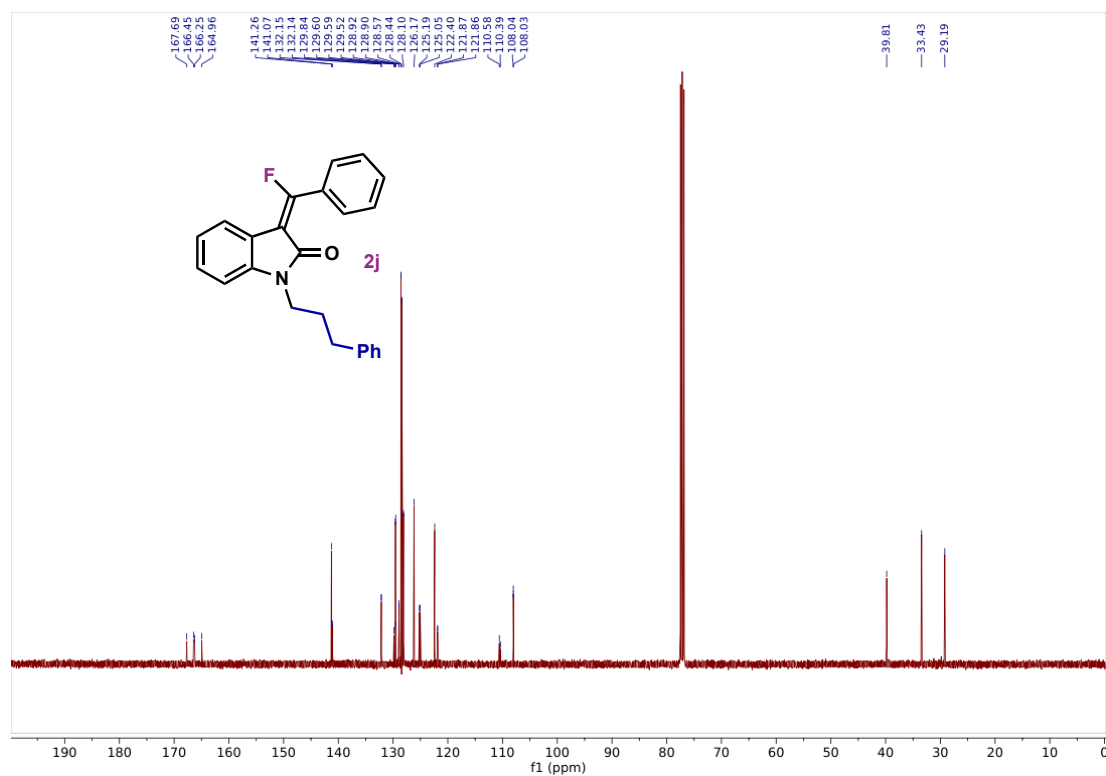
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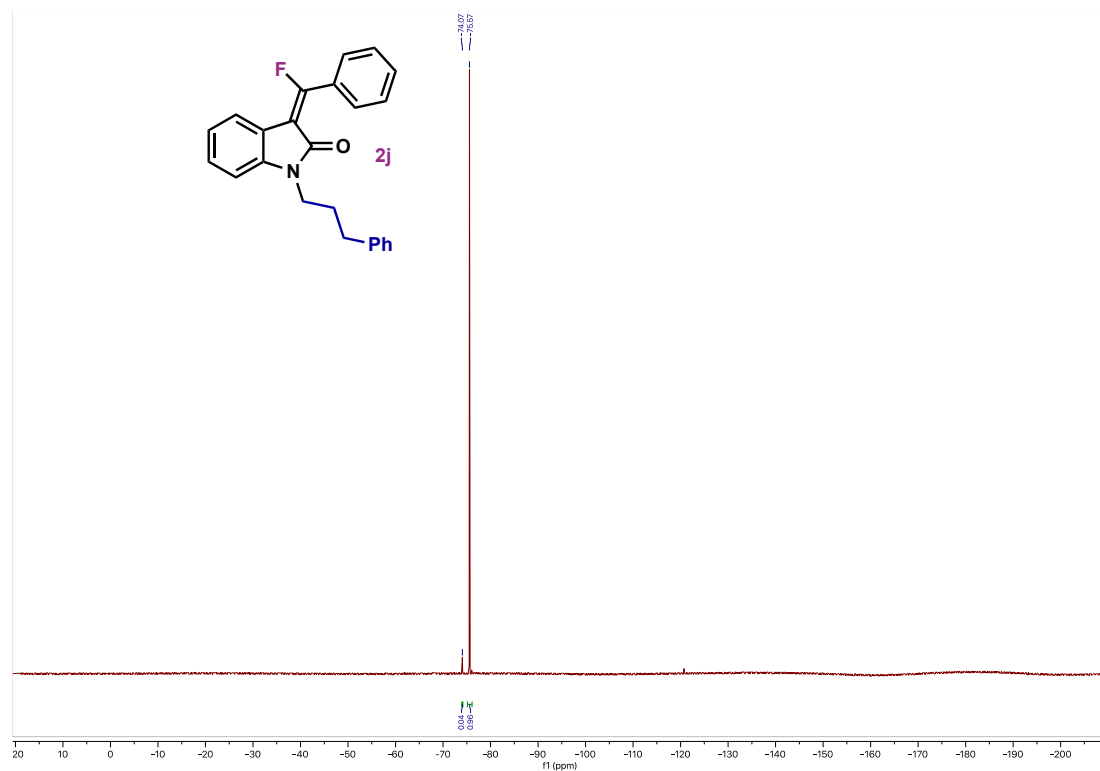
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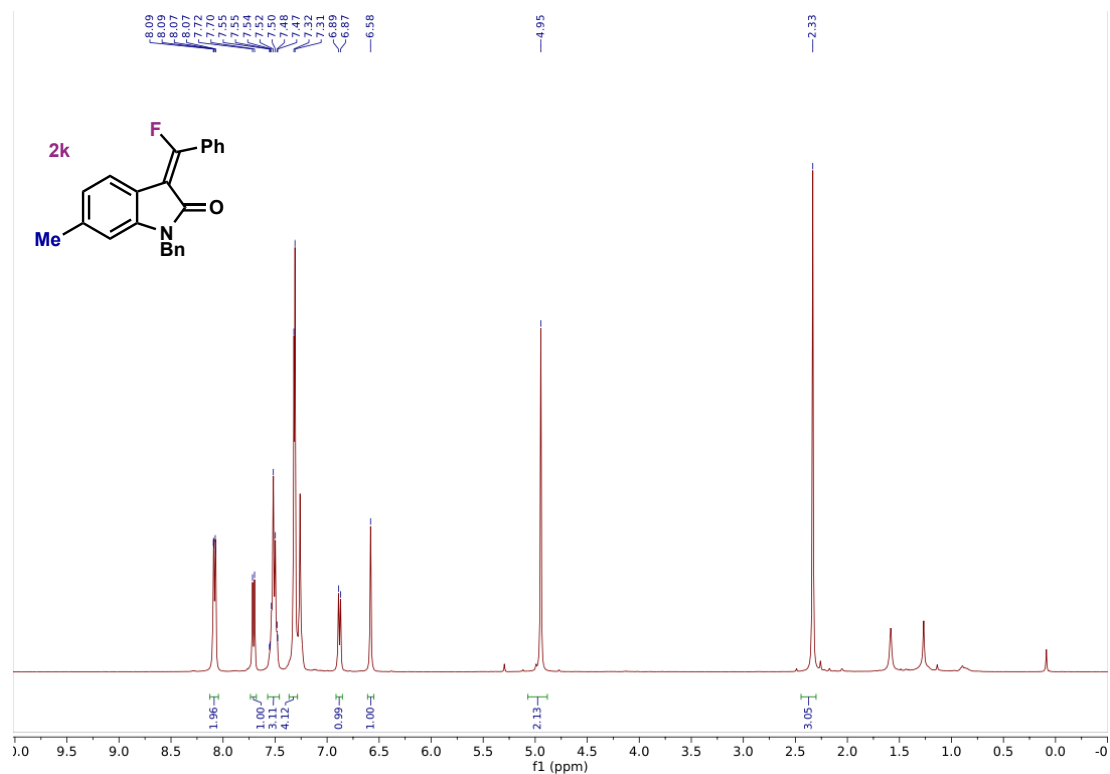
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.2j**



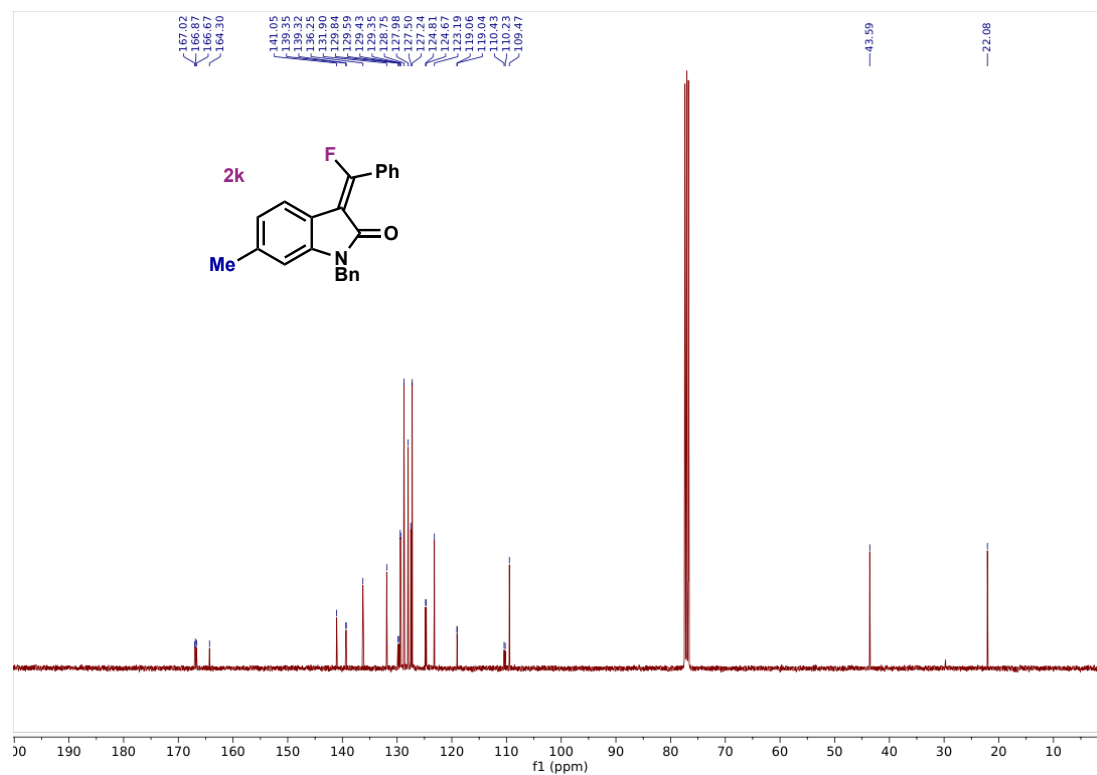
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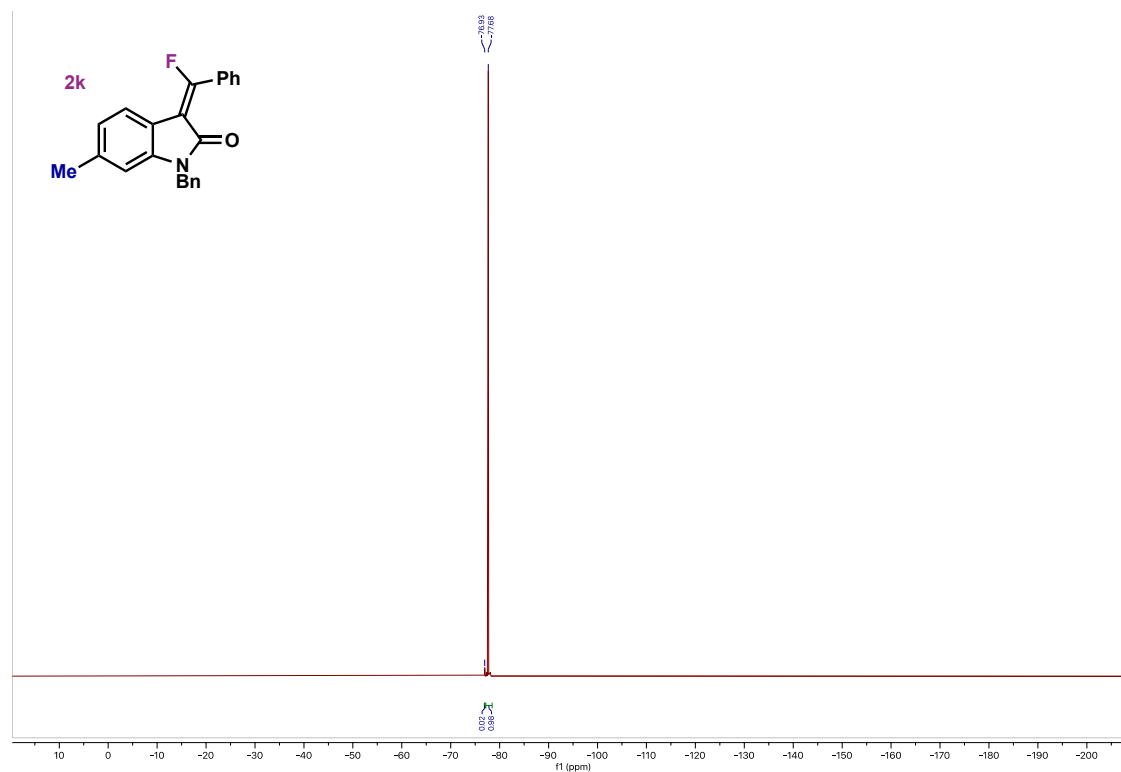
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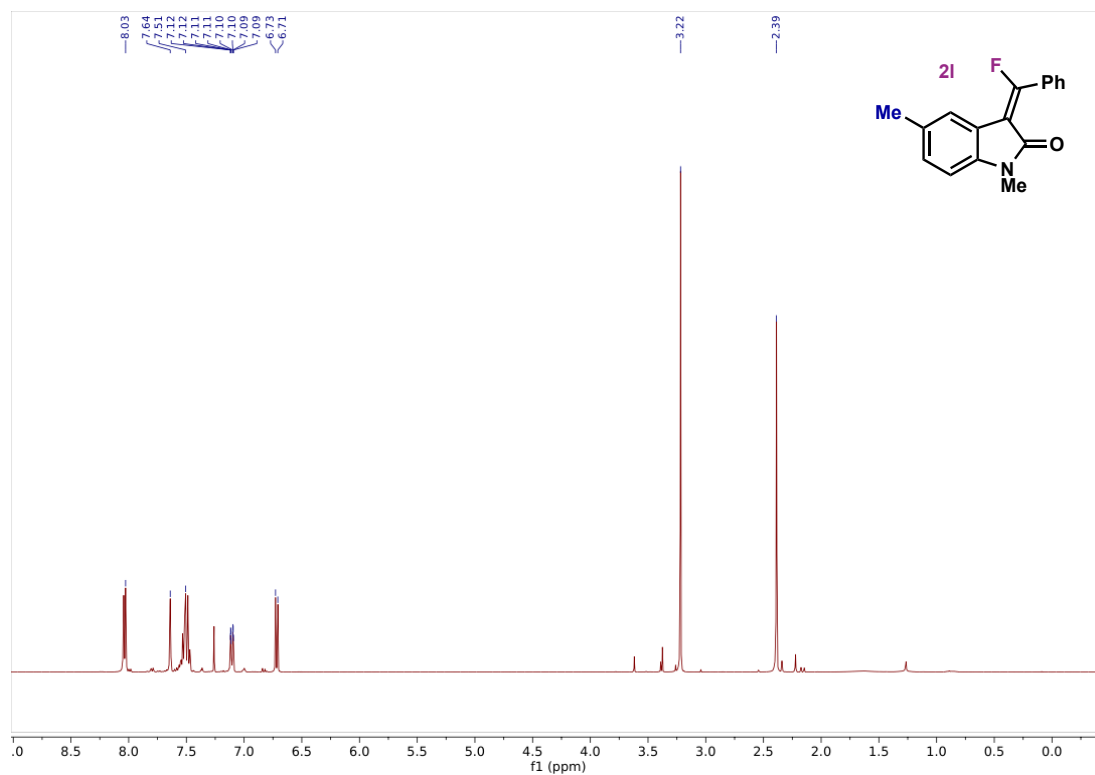
^{13}C { ^1H } NMR (101 MHz, CDCl_3) of **3.2k**



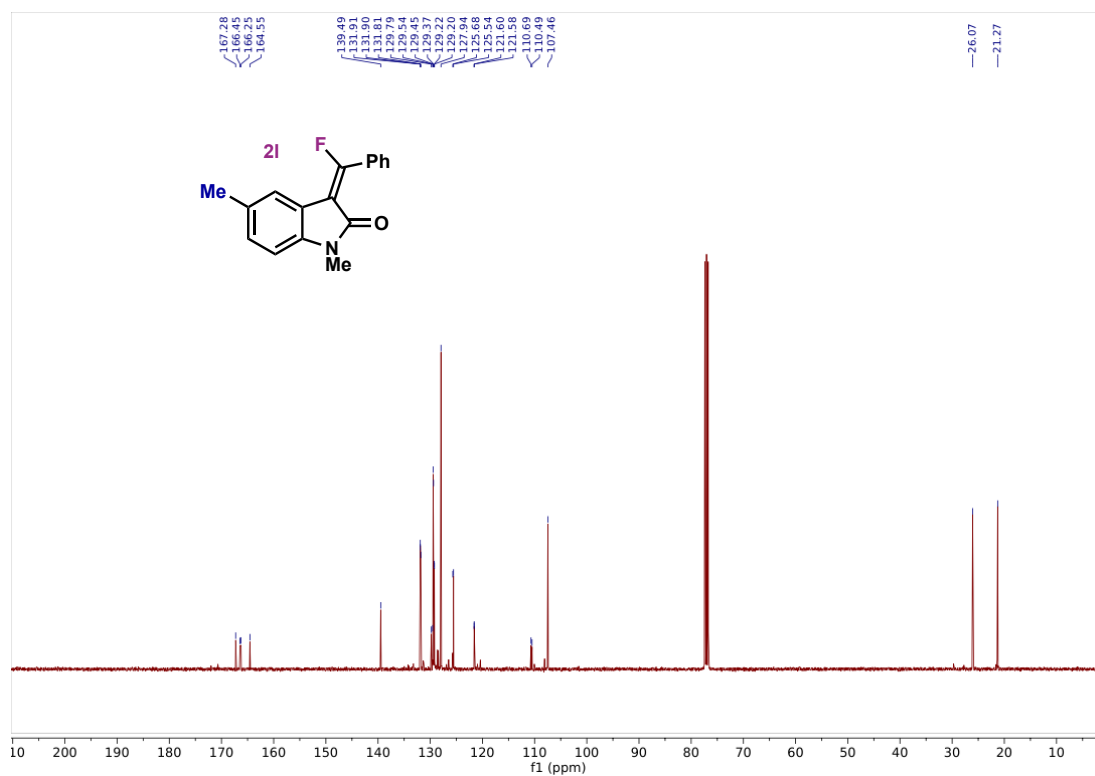
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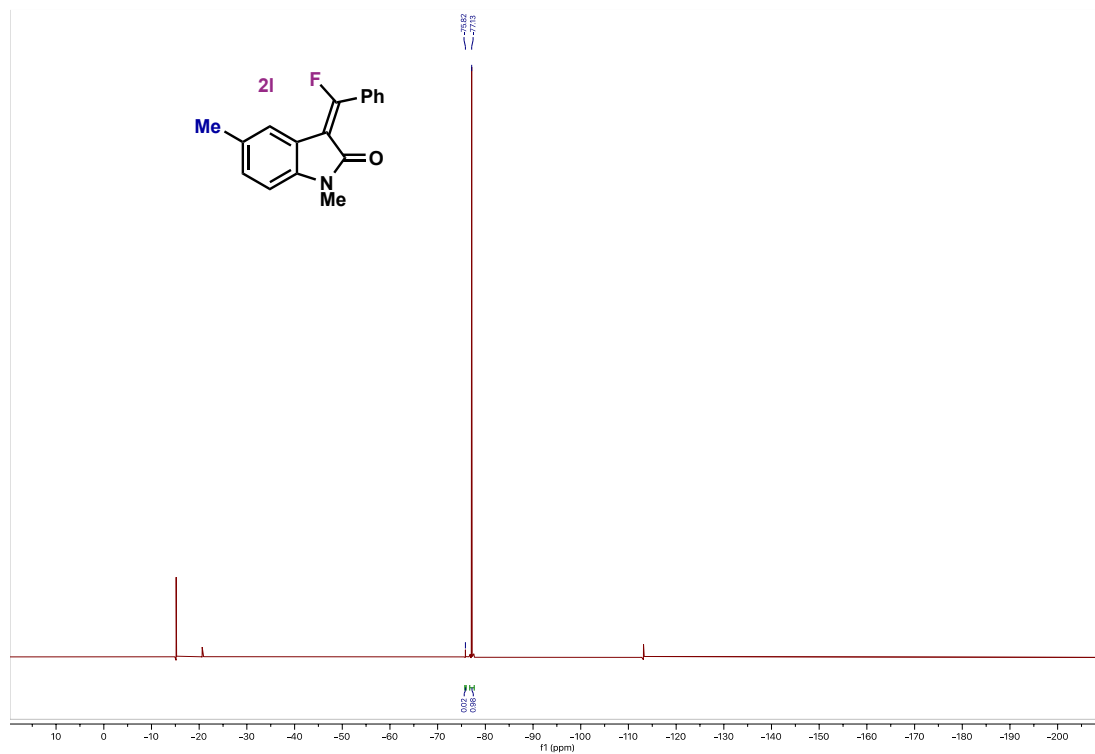
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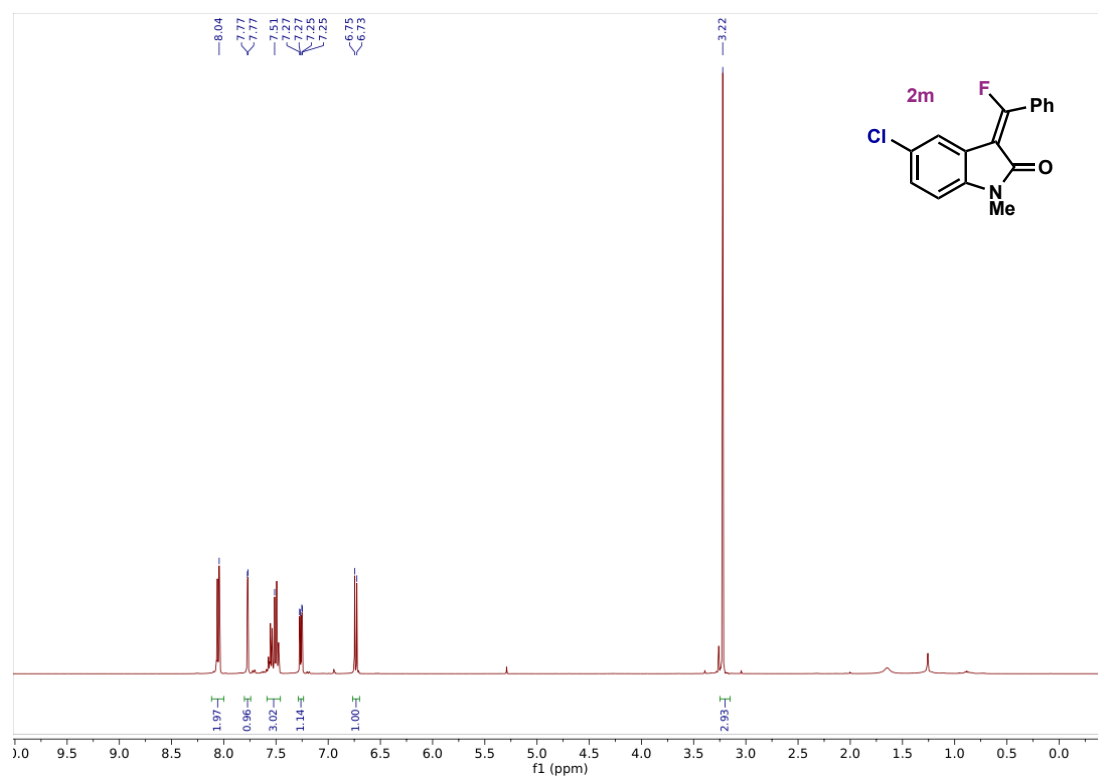
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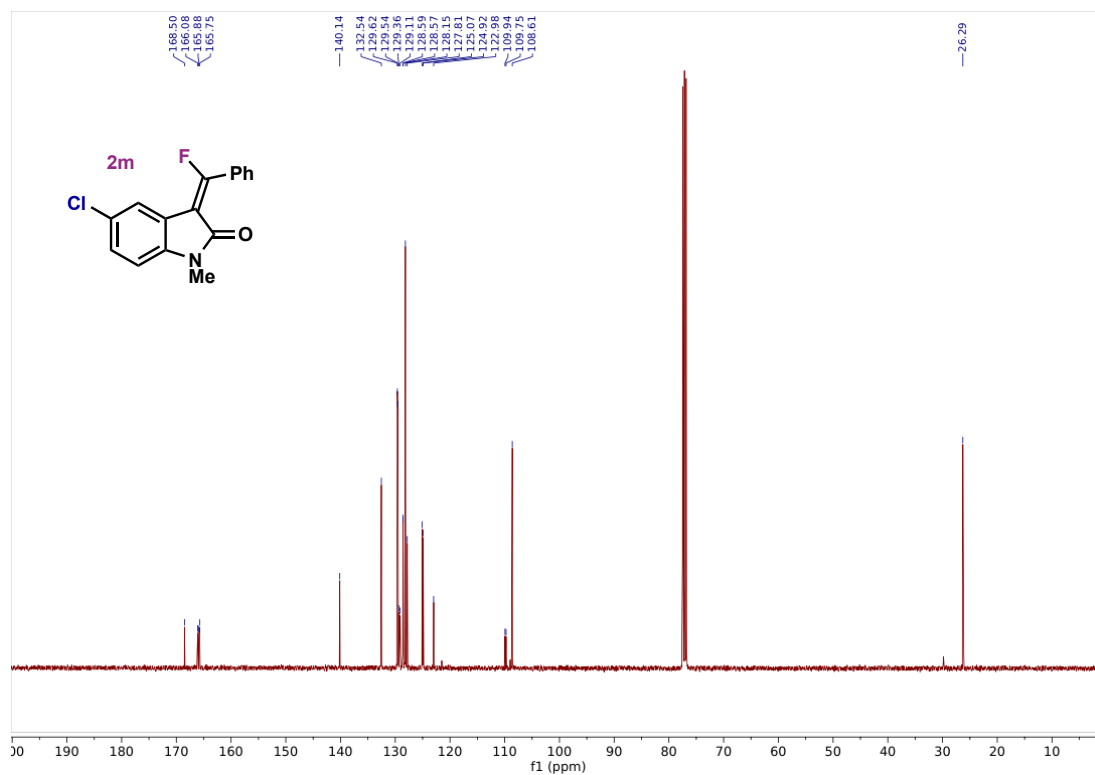
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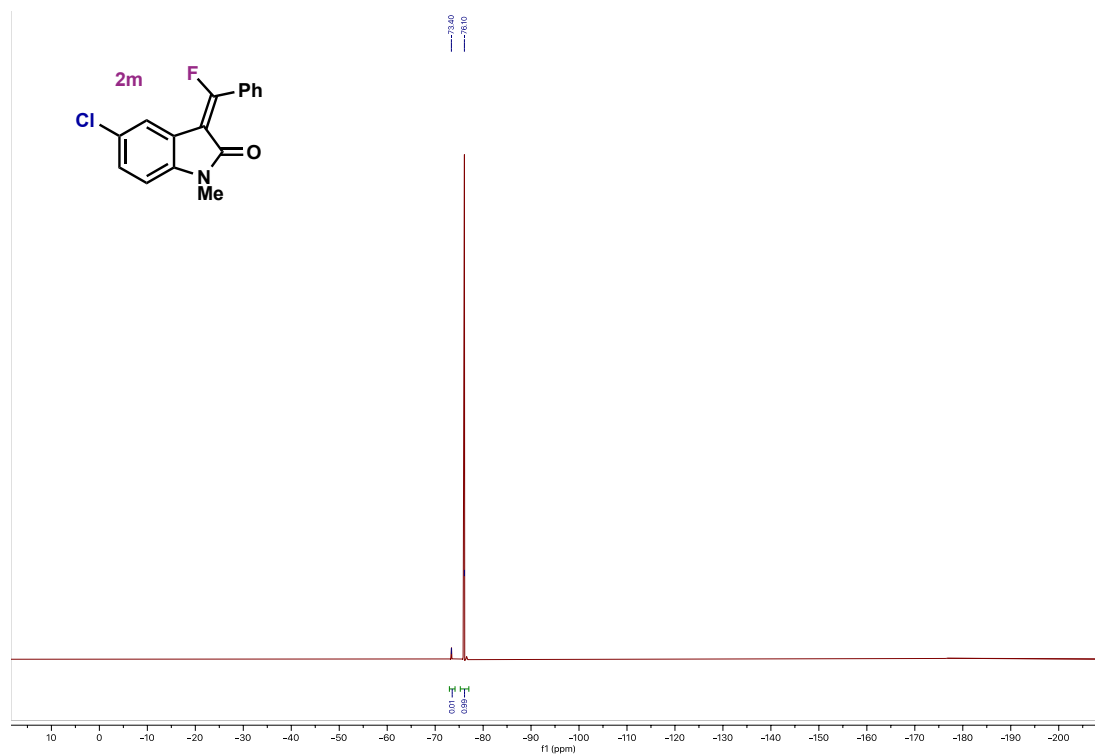
^1H NMR (400 MHz, CDCl_3) of **3.2m**



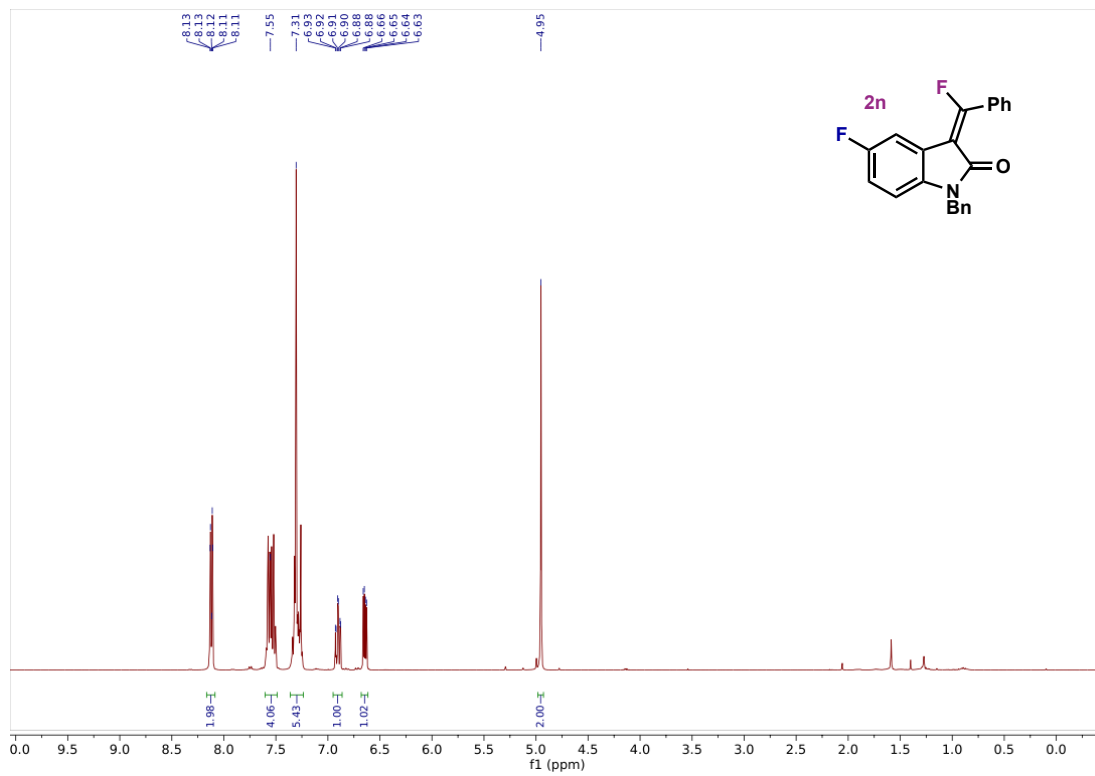
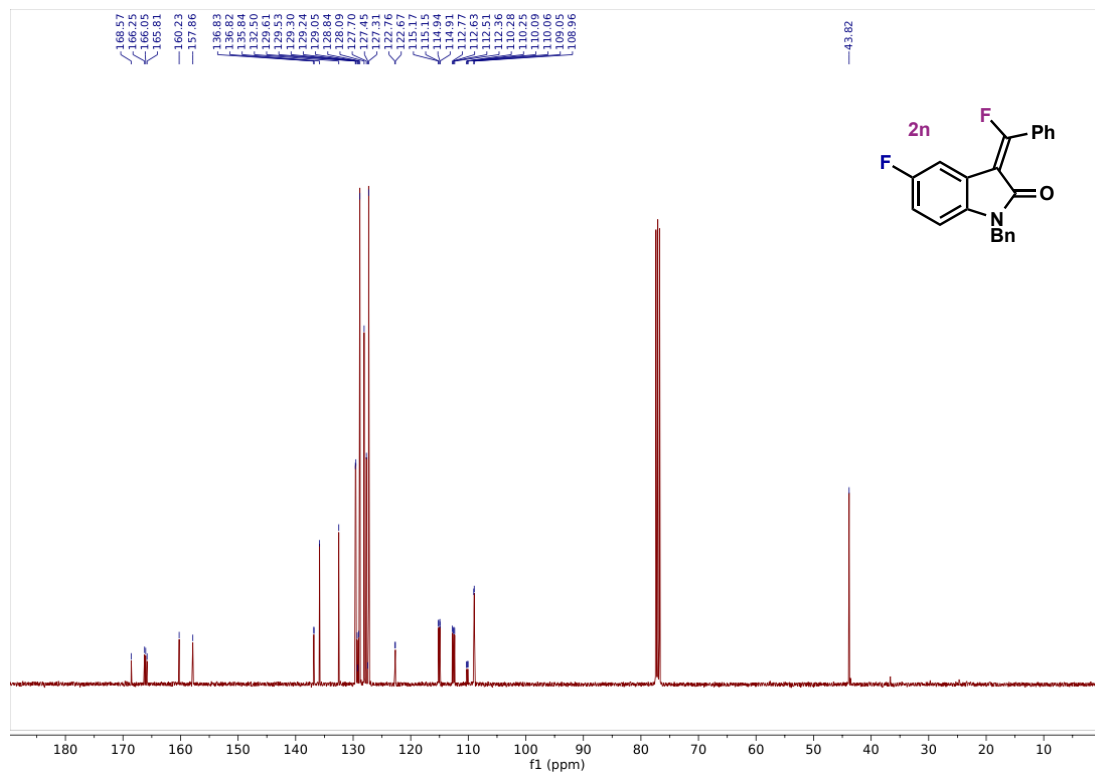
$^{13}\text{C} \{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.2m**



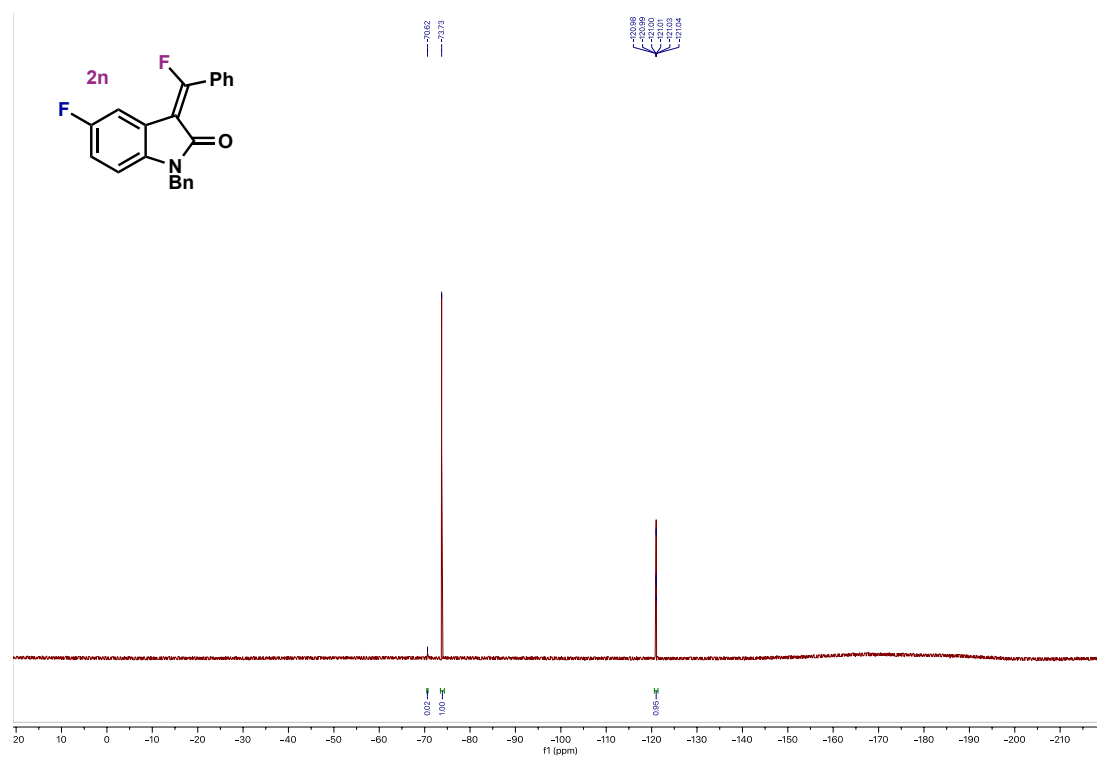
^{19}F NMR (377 MHz, CDCl_3) of **3.2m**



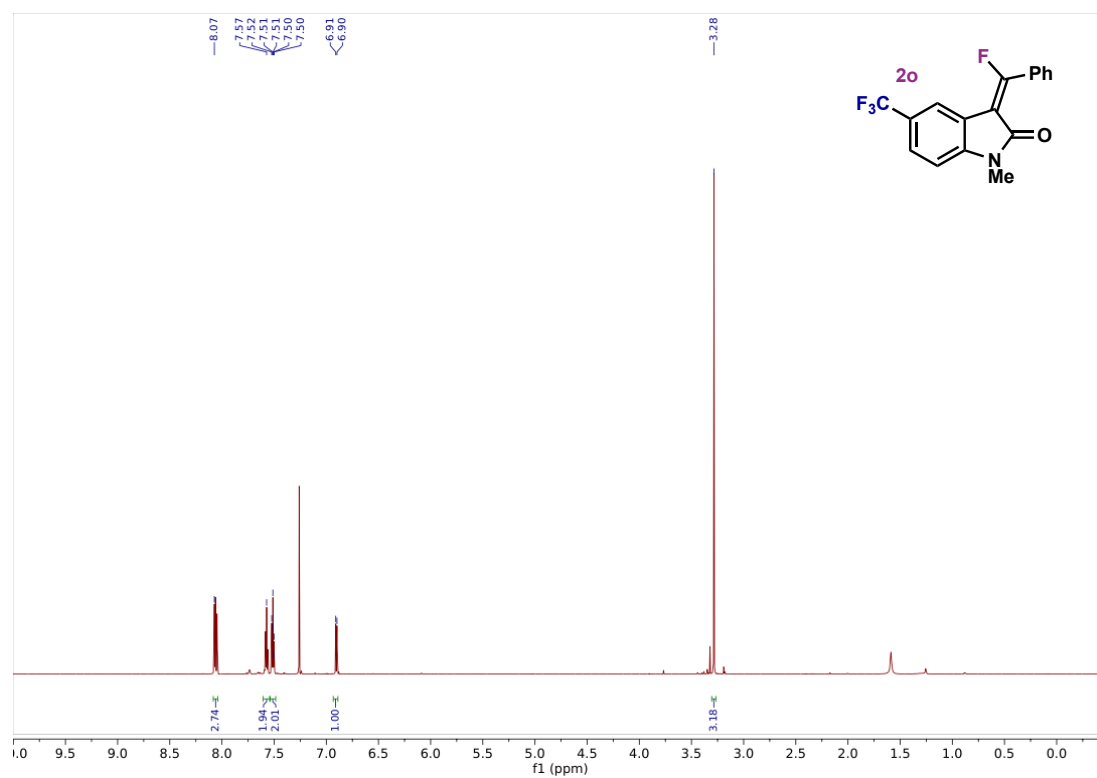
¹H NMR (400 MHz, CDCl₃) of **3.2n**

 $^{13}\text{C} \{^1\text{H}\}$ NMR (176 MHz, CDCl_3) of **3.2n**

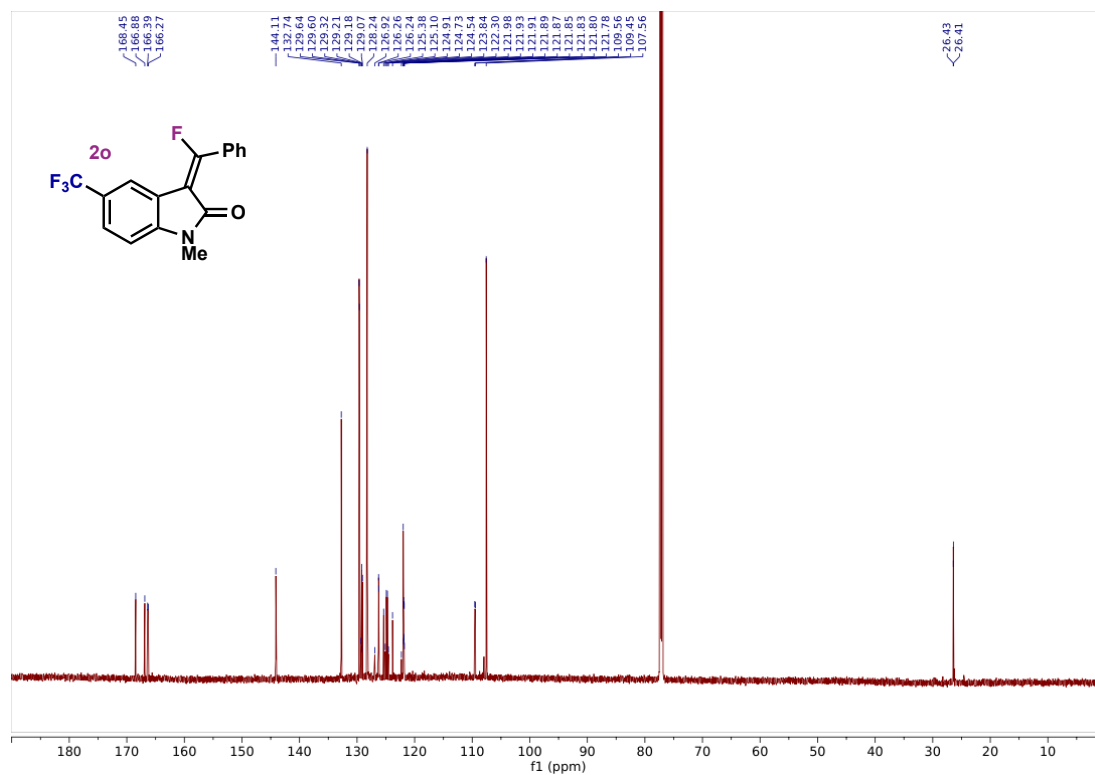
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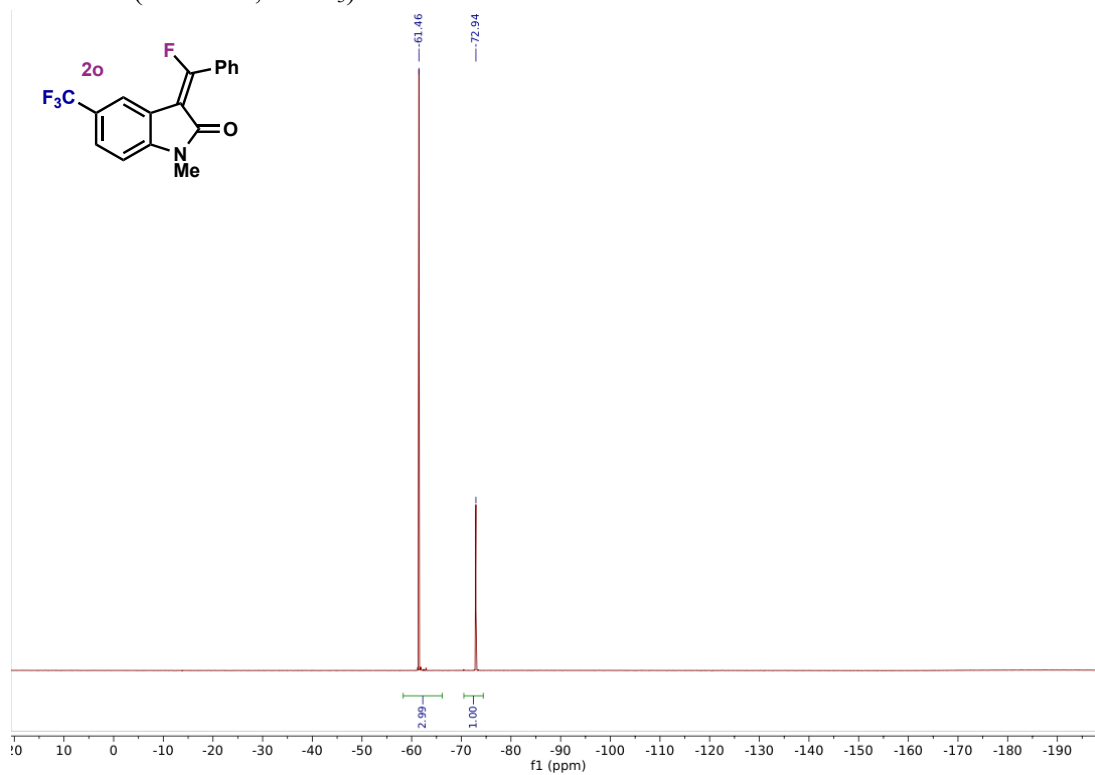
^1H NMR (700 MHz, CDCl_3) of **3.2o**



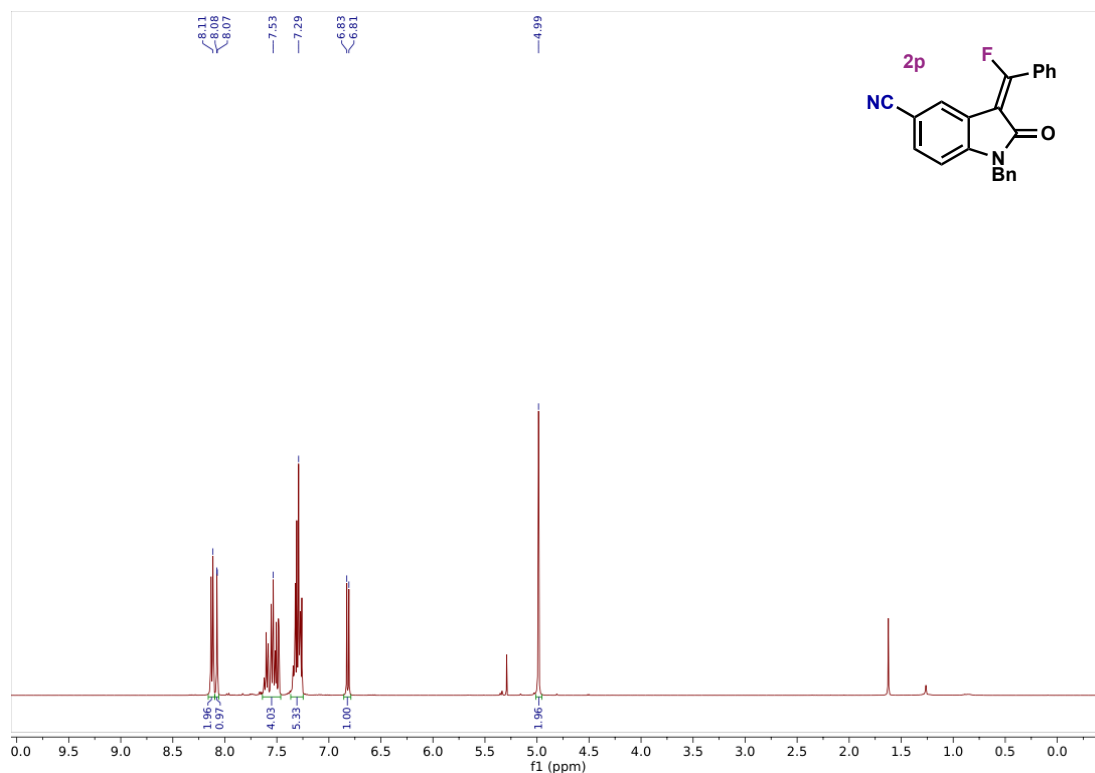
$^{13}\text{C} \{^1\text{H}\}$ NMR (176 MHz, CDCl_3) of **3.2o**



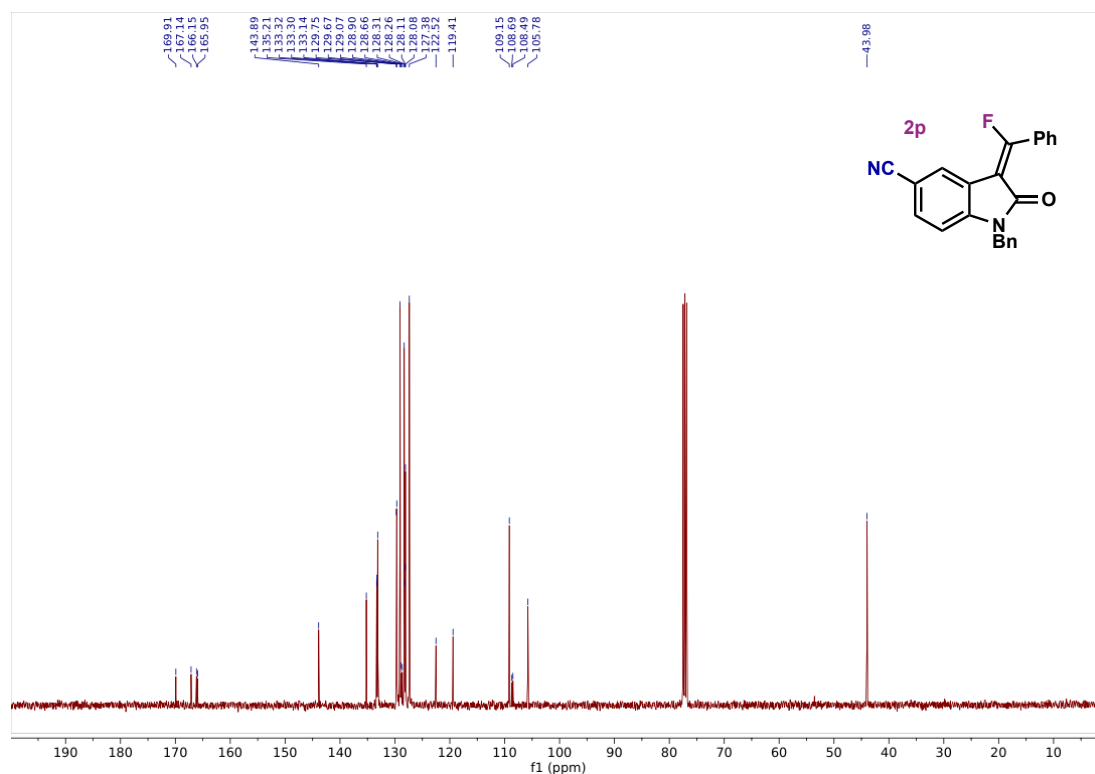
^{19}F NMR (659 MHz, CDCl_3) of **3.2o**



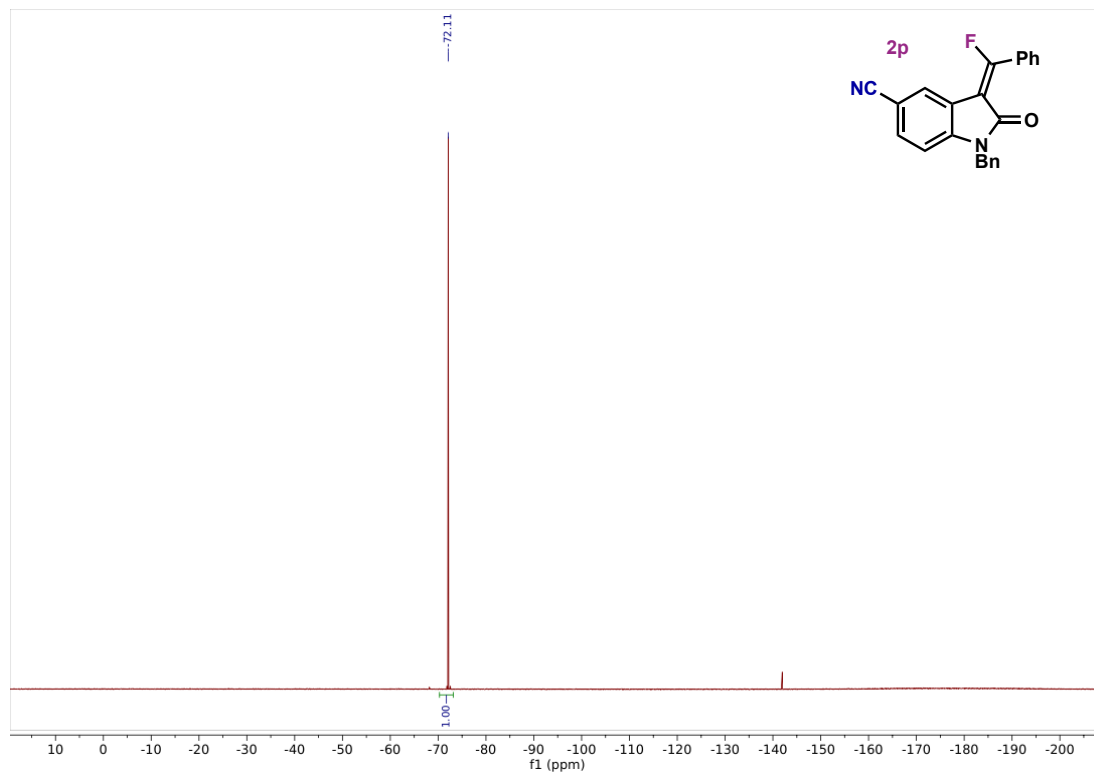
^1H NMR (400 MHz, CDCl_3) of **3.2p**



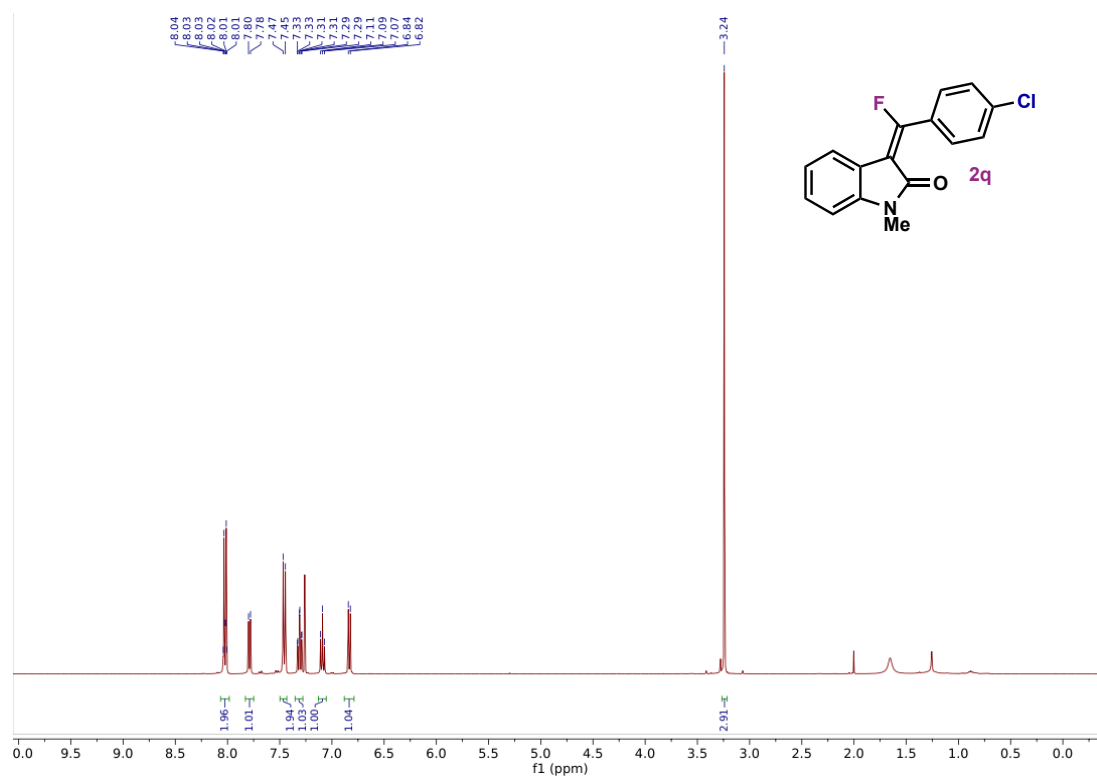
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.2p**



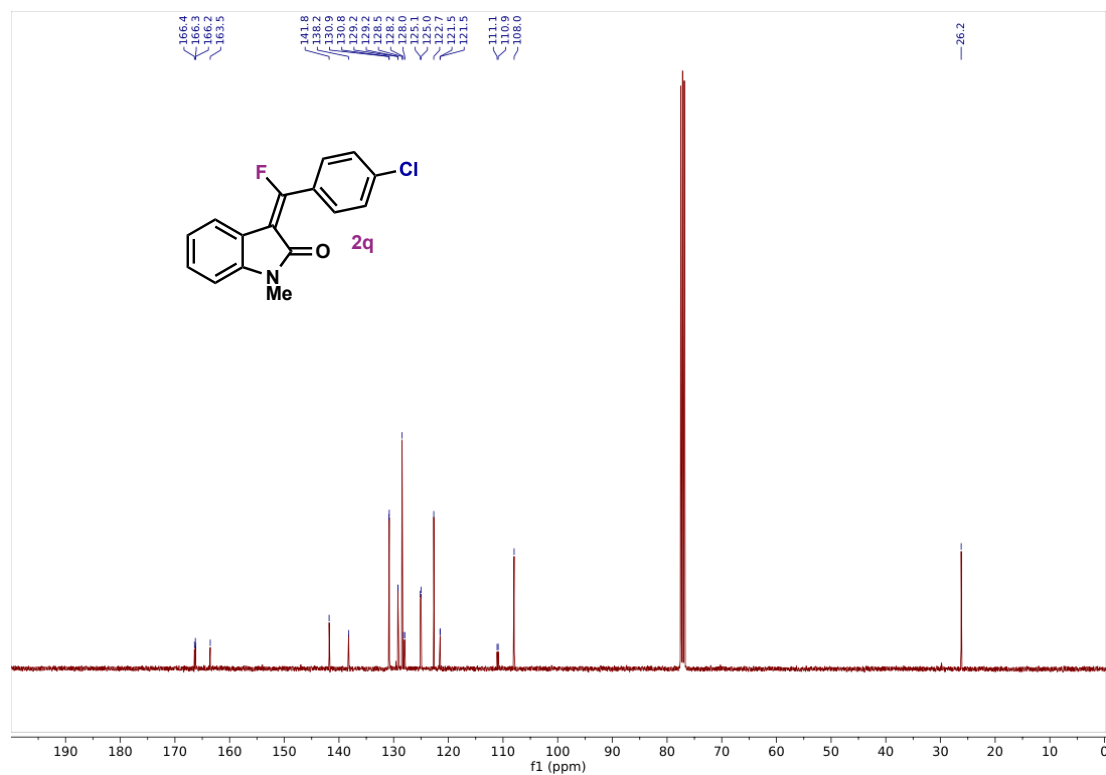
^{19}F NMR (377 MHz, CDCl_3) of **3.2p**



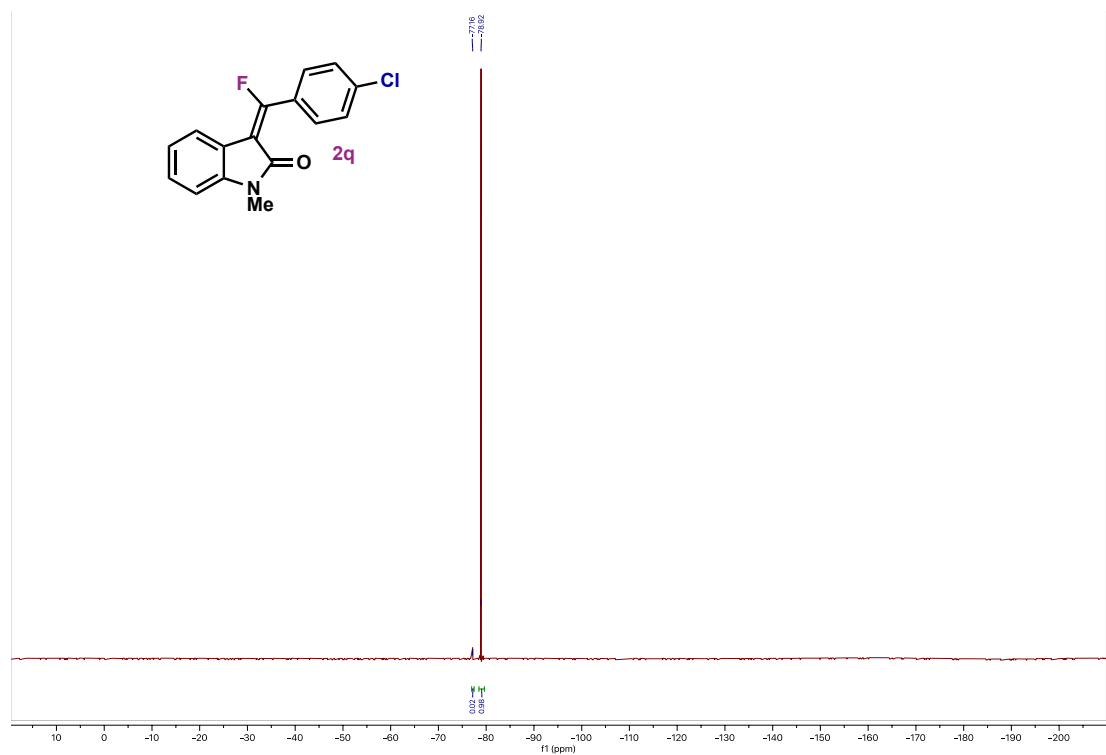
^1H NMR (400 MHz, CDCl_3) of **3.2q**



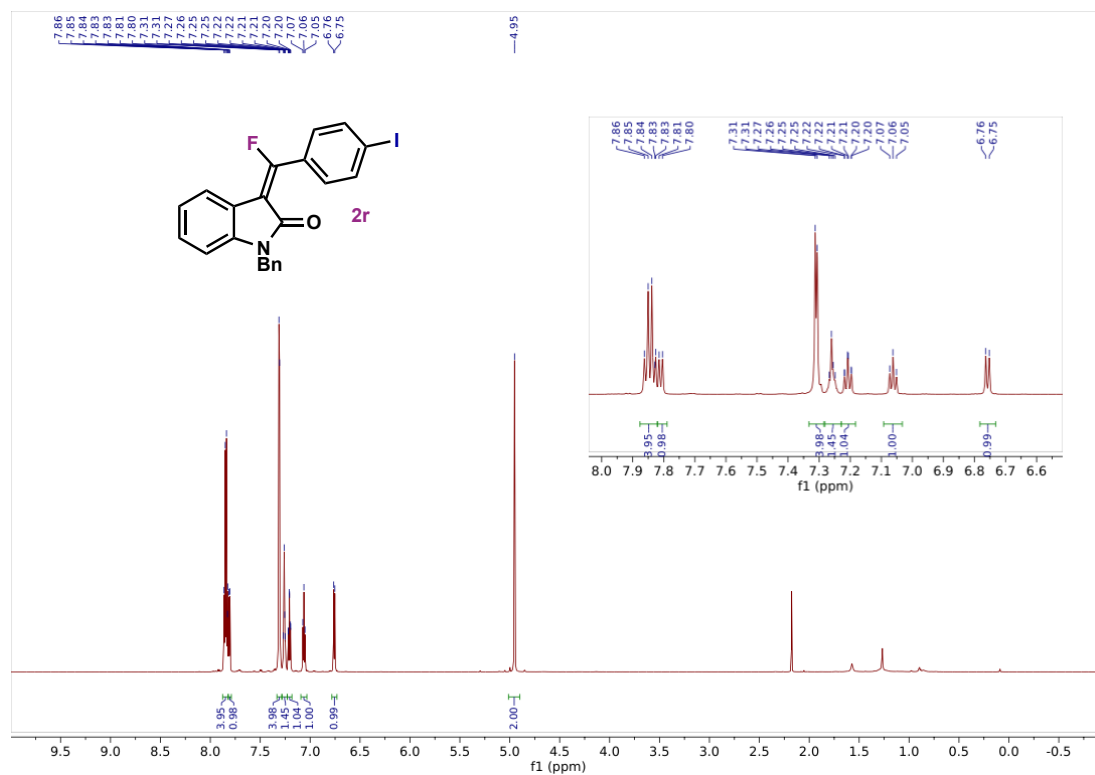
$^{13}\text{C} \{^1\text{H}\}$ NMR (176 MHz, CDCl_3) of **3.2q**



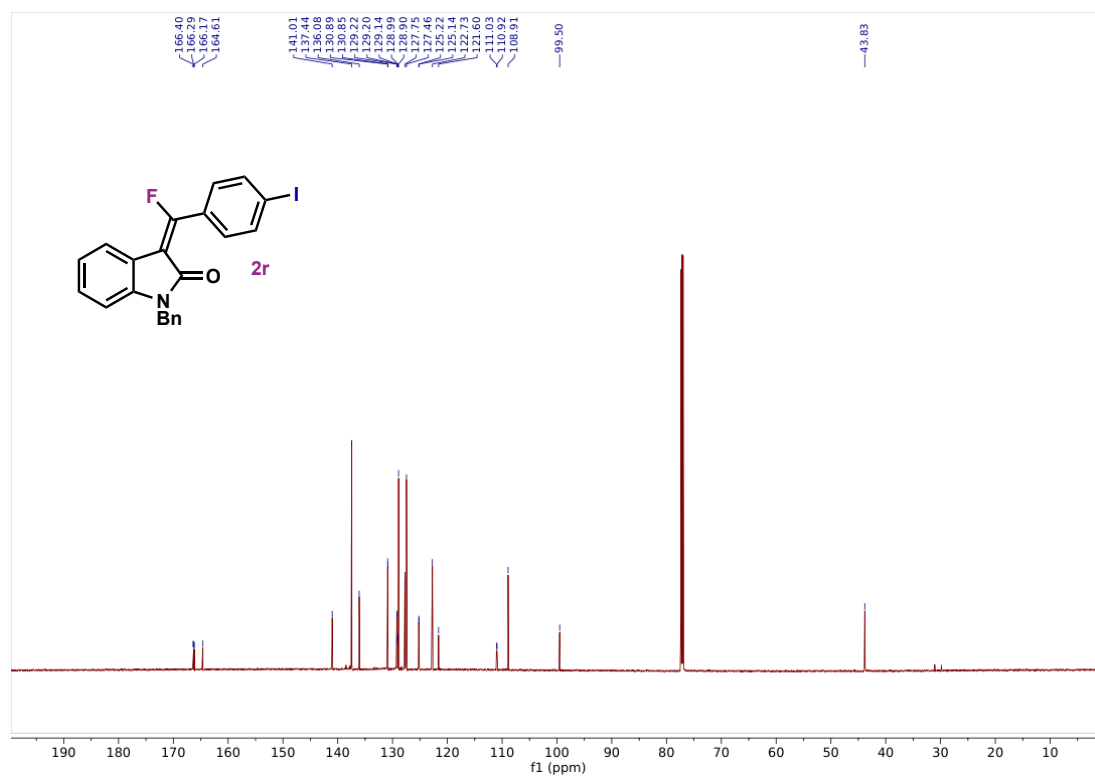
^{19}F NMR (377 MHz, CDCl_3) of **3.2q**



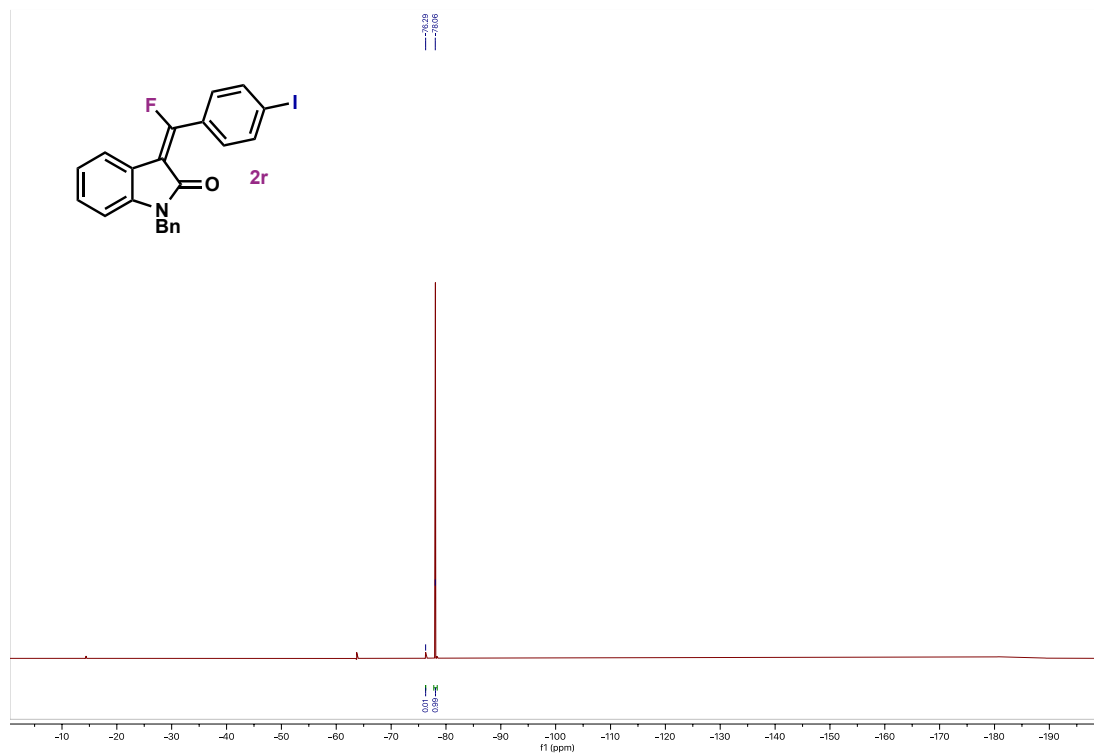
^1H NMR (700 MHz, CDCl_3) of **3.2r**



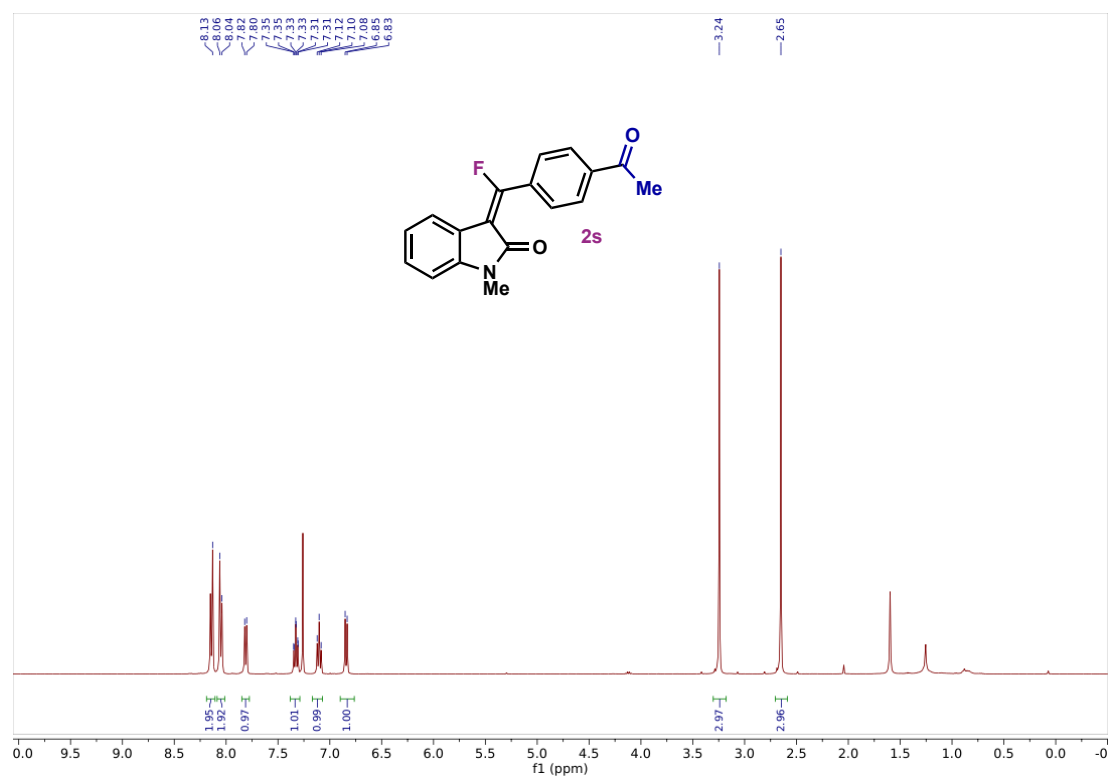
^{13}C $\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) of **3.2r**



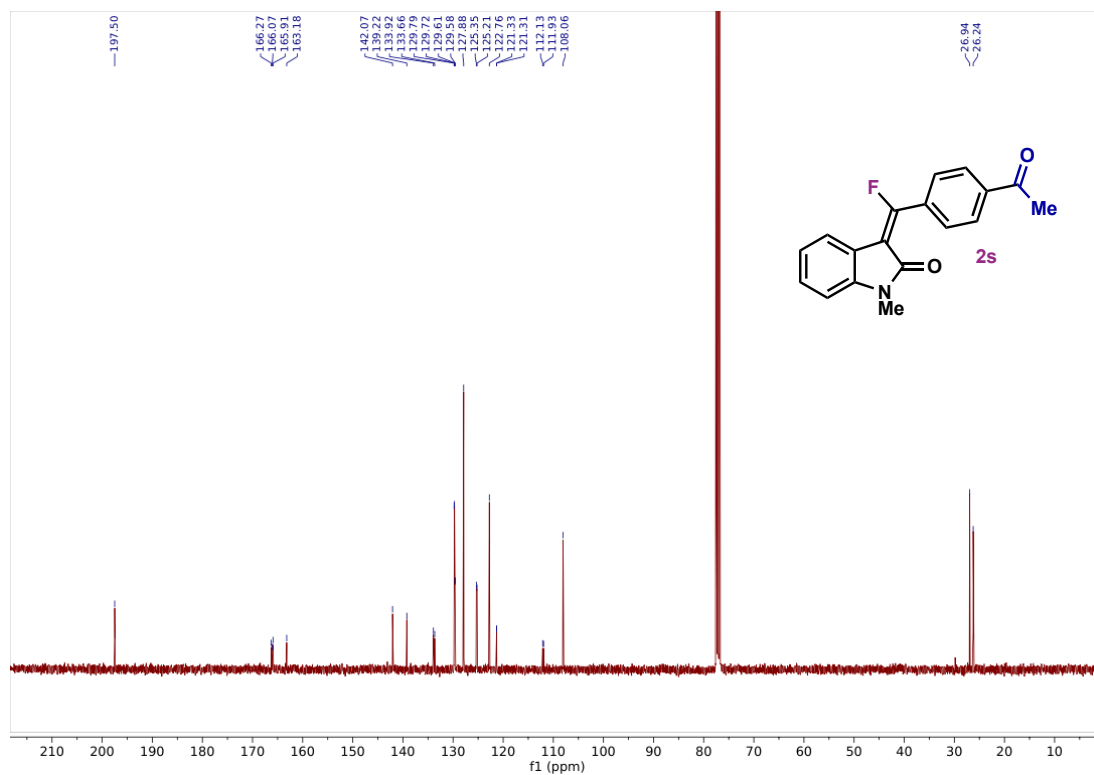
^{19}F NMR (659 MHz, CDCl_3) of **3.2r**



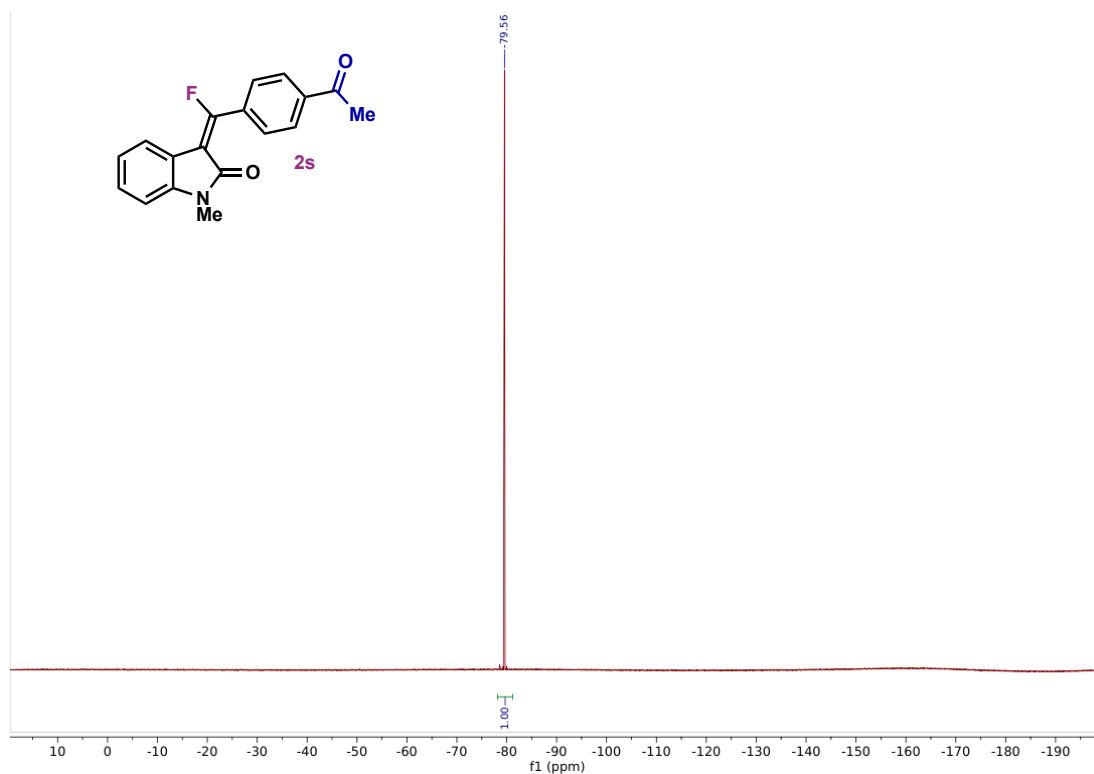
^1H NMR (400 MHz, CDCl_3) of **3.2s**



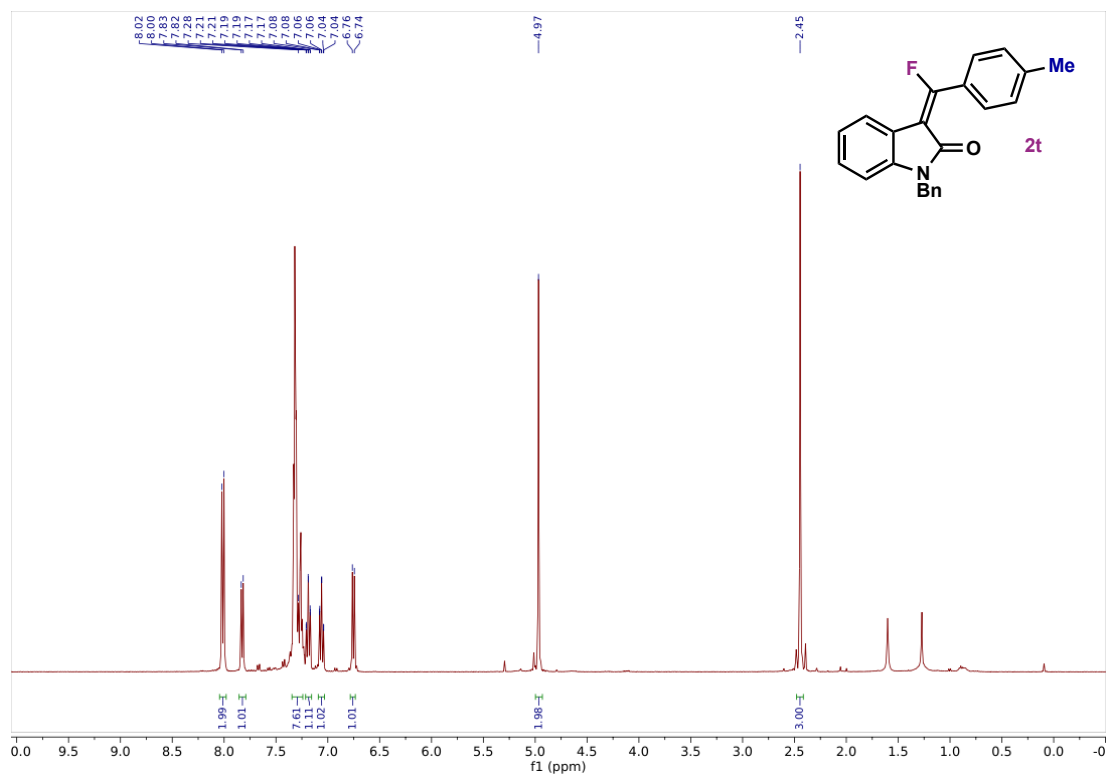
$^{13}\text{C} \{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.2s**



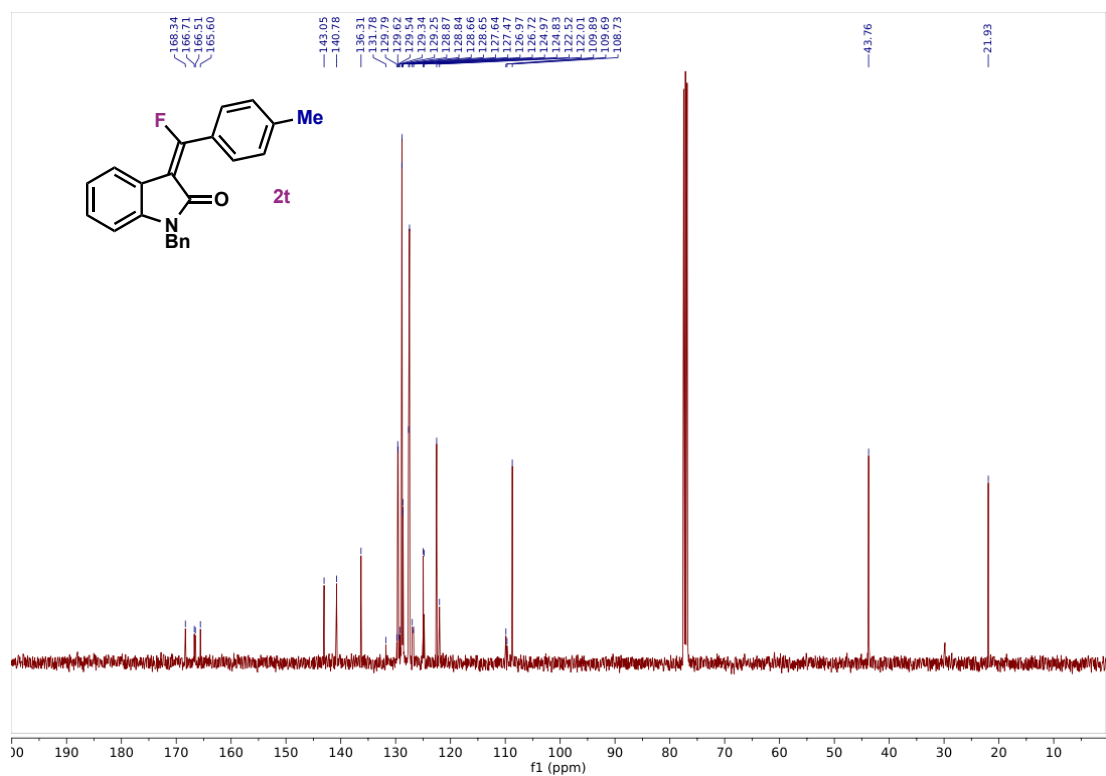
^{19}F NMR (377 MHz, CDCl_3) of **3.2s**



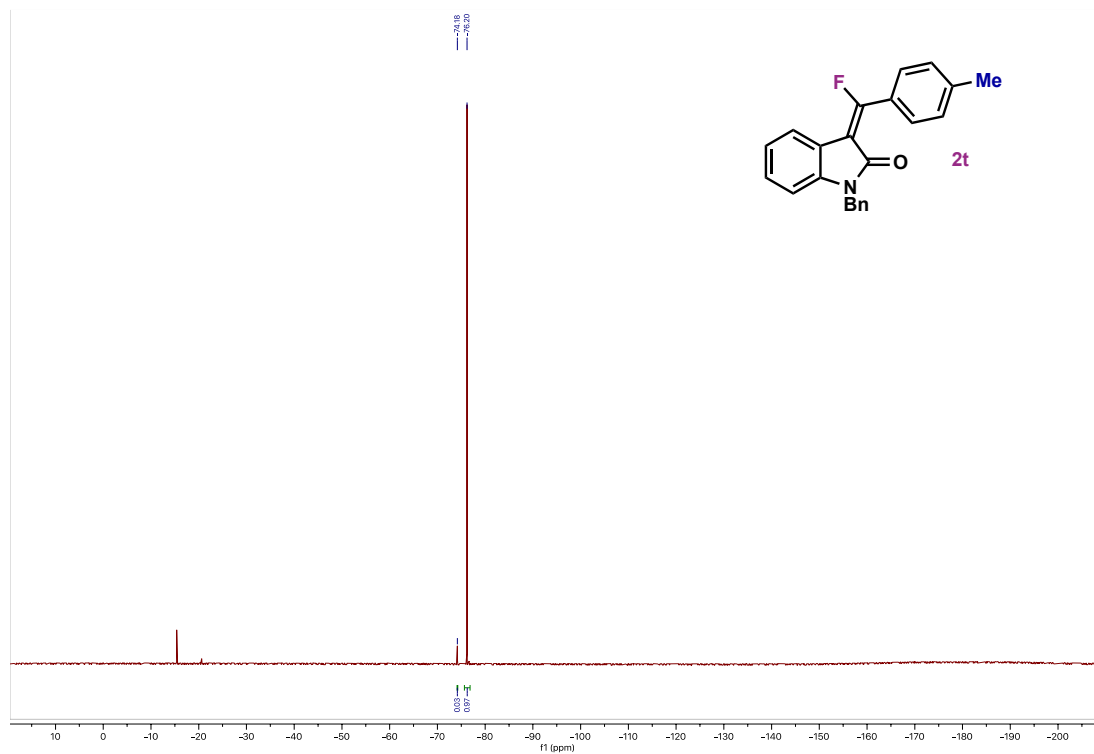
^1H NMR (400 MHz, CDCl_3) of **3.2t**



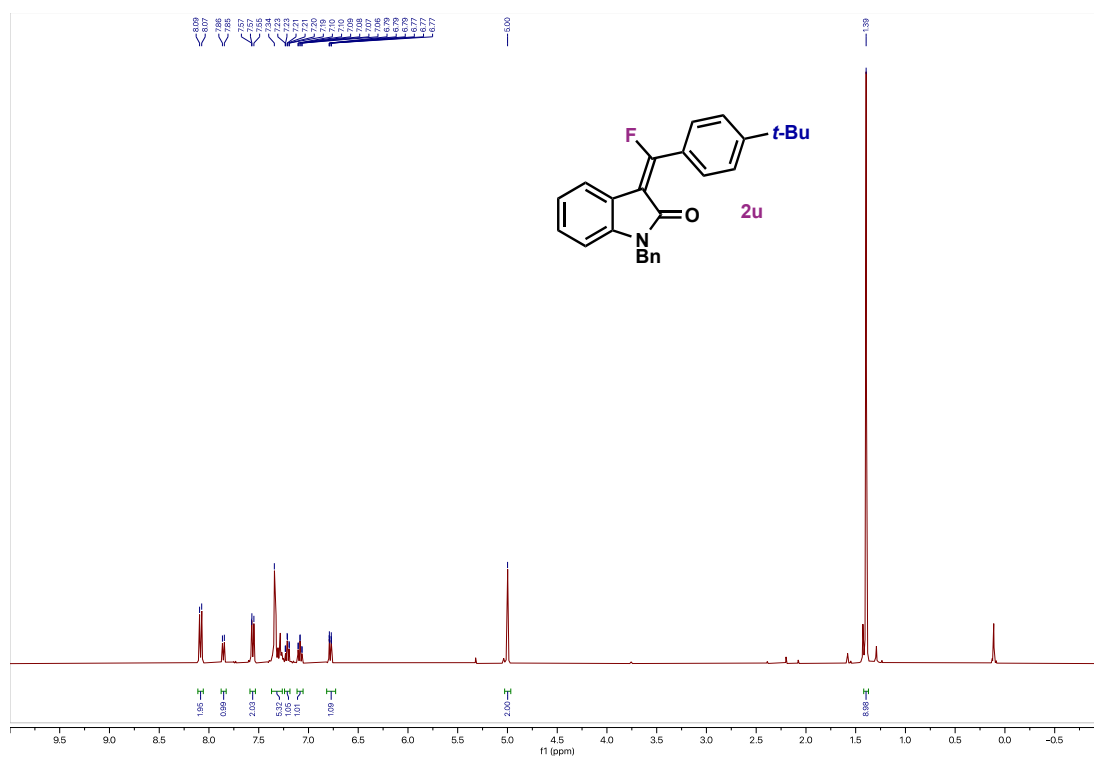
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.2t**



^{19}F NMR (377 MHz, CDCl_3) of **3.2t**



^1H NMR (400 MHz, CDCl_3) of **3.2u**

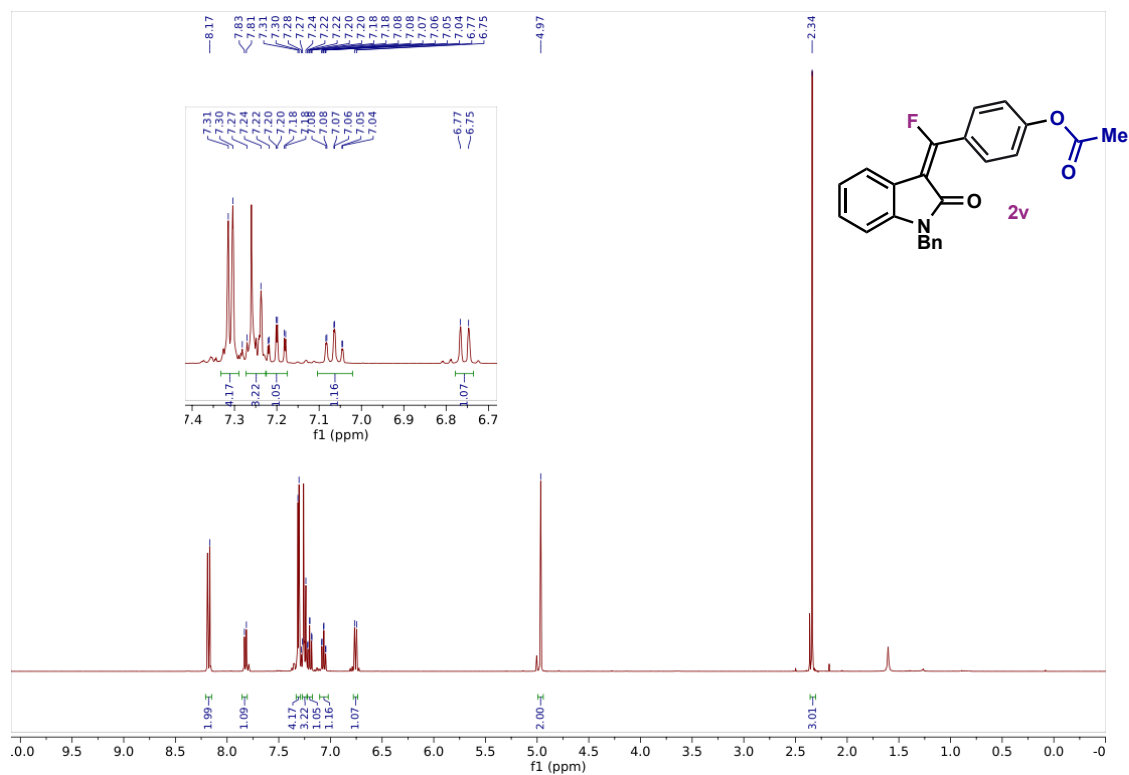


Chemical structure of compound **2u** is shown in the top right corner. The structure is a benzimidazole derivative with a benzyl group on the nitrogen, a carbonyl group at the 2-position, and a 4-tert-butylphenyl group at the 3-position. The structure is labeled **2u** in red.

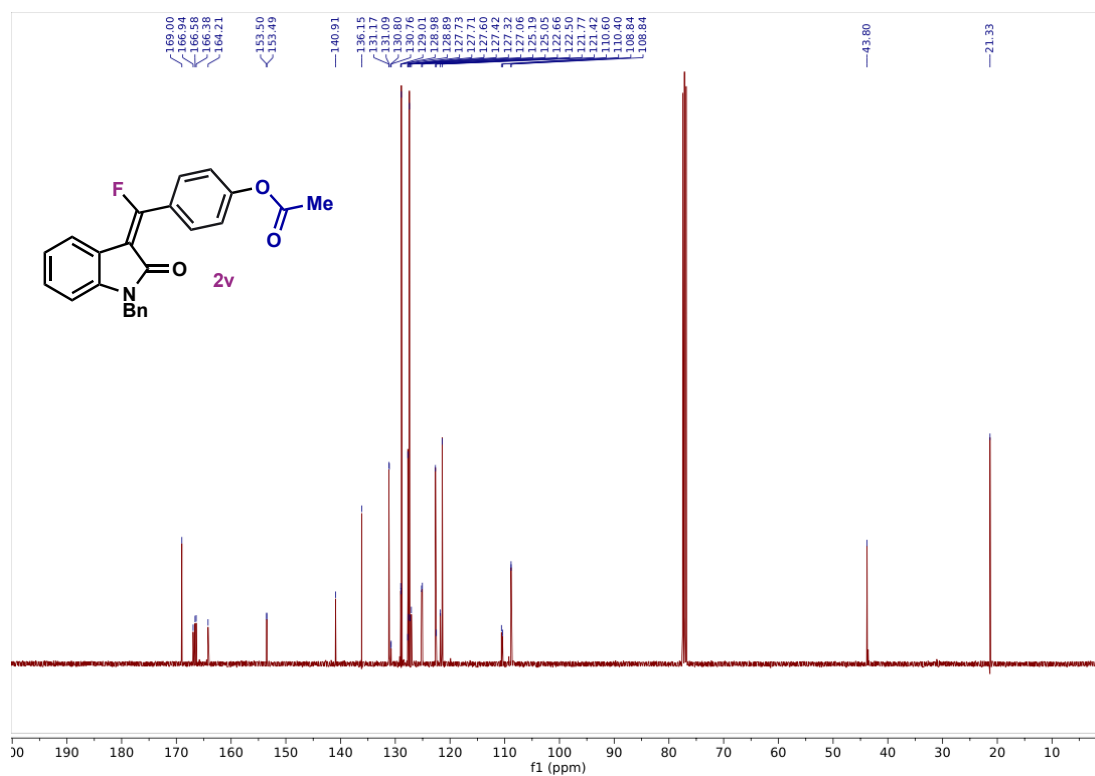
The ^1H NMR spectrum (CDCl₃) shows the following peaks and integrations:

- Aromatic and alkene protons: multiplet, 7.0–7.5 ppm, integration 0.99.
- Benzylic protons: singlet, ~3.0 ppm, integration 1.00.
- Aldehyde proton: singlet, ~9.8 ppm, integration 0.99.

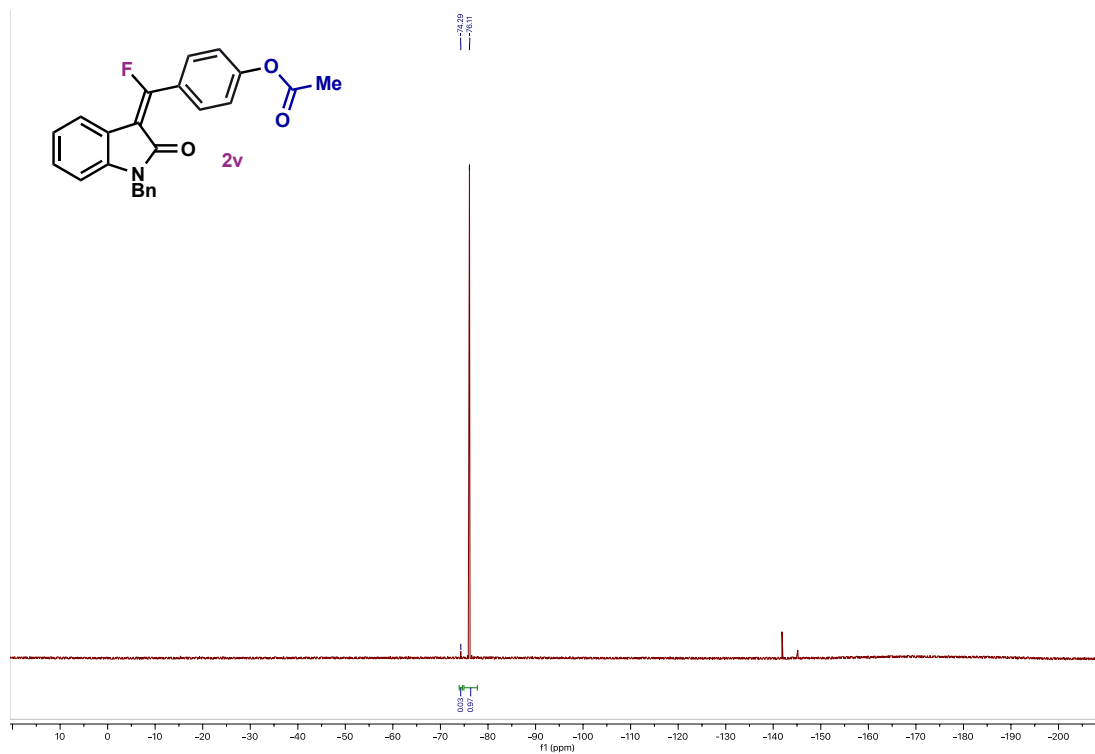
^1H NMR (400 MHz, CDCl_3) of **3.2v**



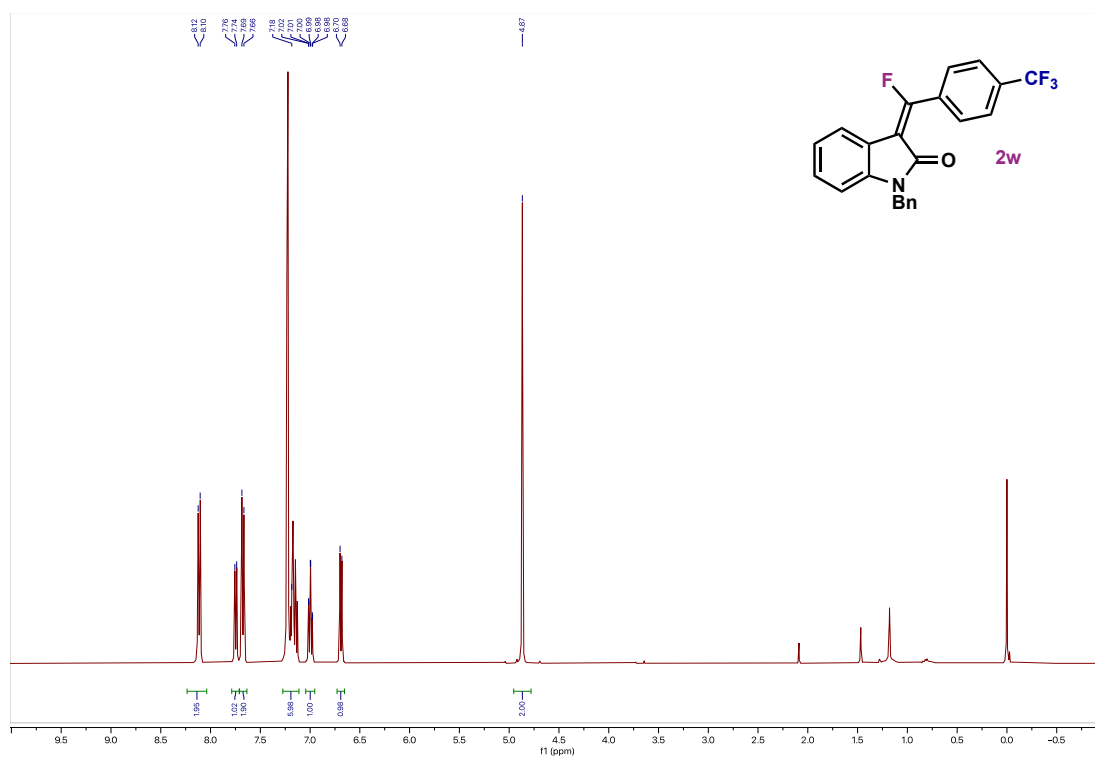
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.2v**



^{19}F NMR (377 MHz, CDCl_3) of **3.2v**



^1H NMR (400 MHz, CDCl_3) of **3.2w**

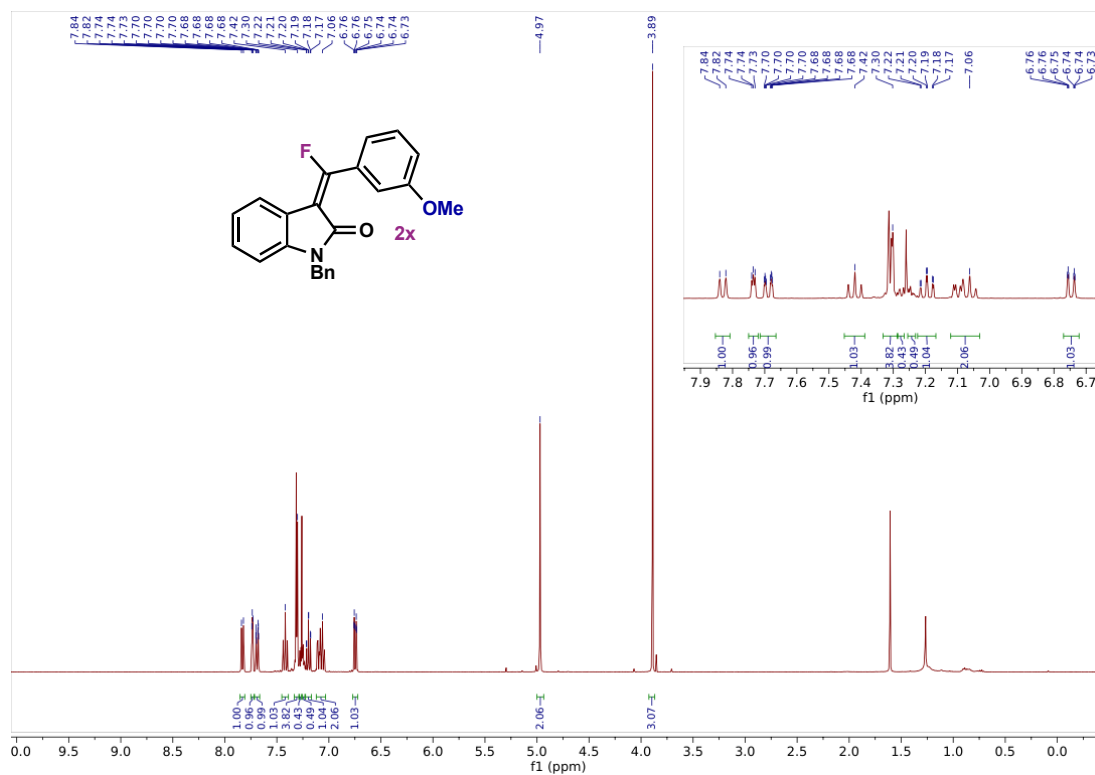


[illegible]

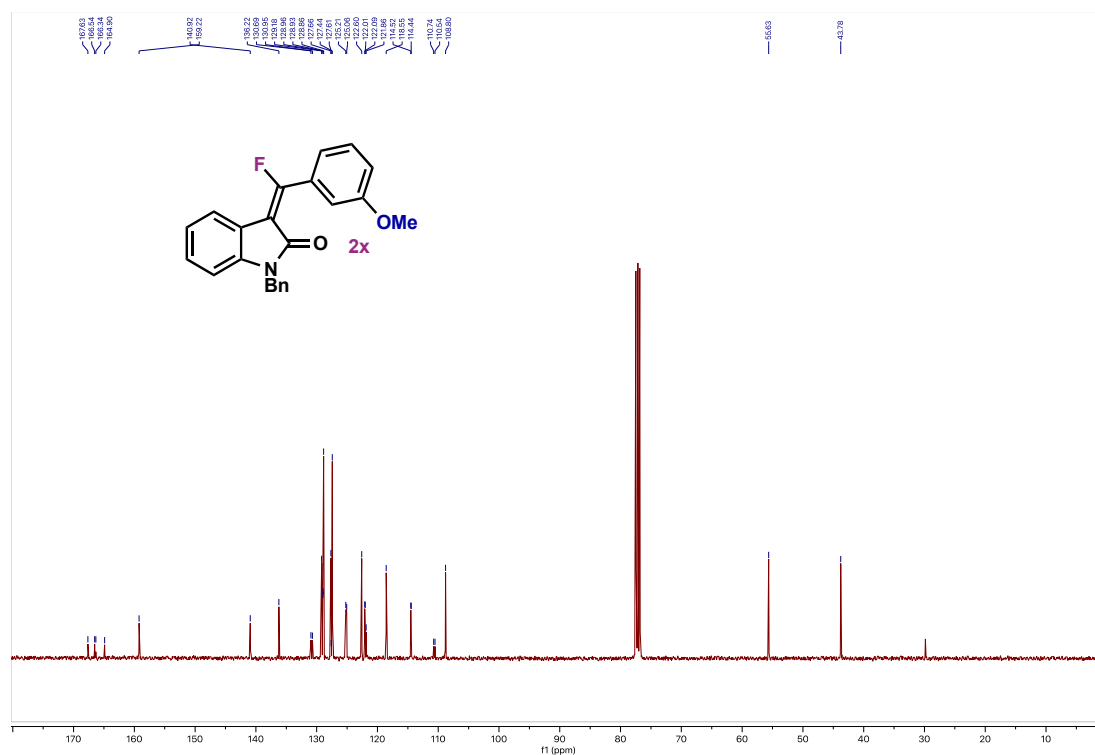
Chemical structure of compound 2w is shown. The structure is a benzimidazole derivative with a benzyl group on the nitrogen and a 4-(trifluoromethyl)phenyl group on the 2-position. The structure is labeled 2w.

¹H NMR spectrum (CDCl₃) of compound 2w. The spectrum shows two main signals: a broad singlet at approximately 7.5 ppm (integration 2.00) and a sharp singlet at approximately 7.8 ppm (integration 0.96). The solvent peak for CDCl₃ is visible at 7.26 ppm.

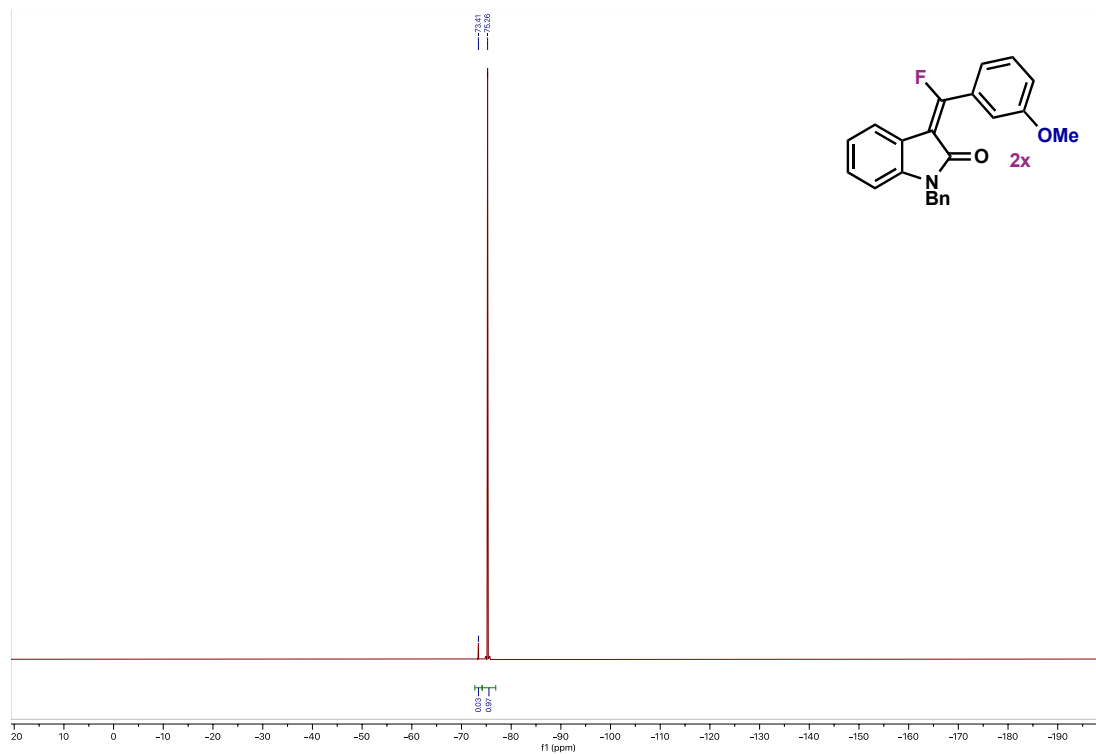
^1H NMR (400 MHz, CDCl_3) of **3.2x**



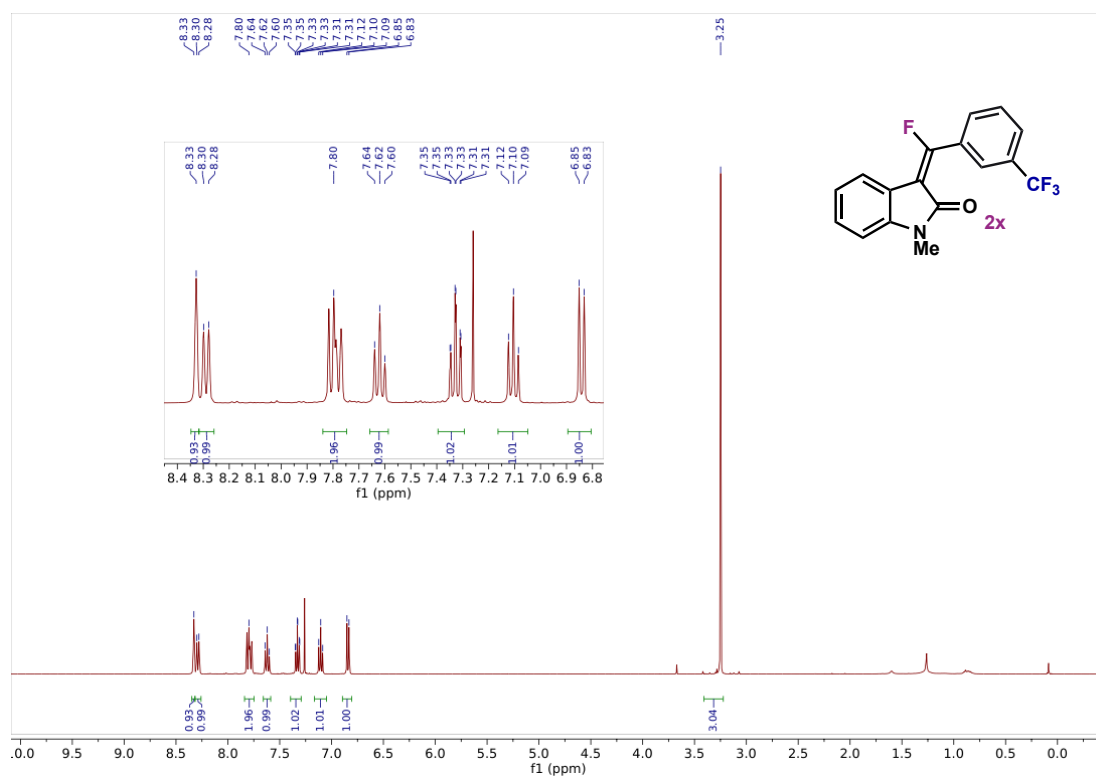
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.2x**



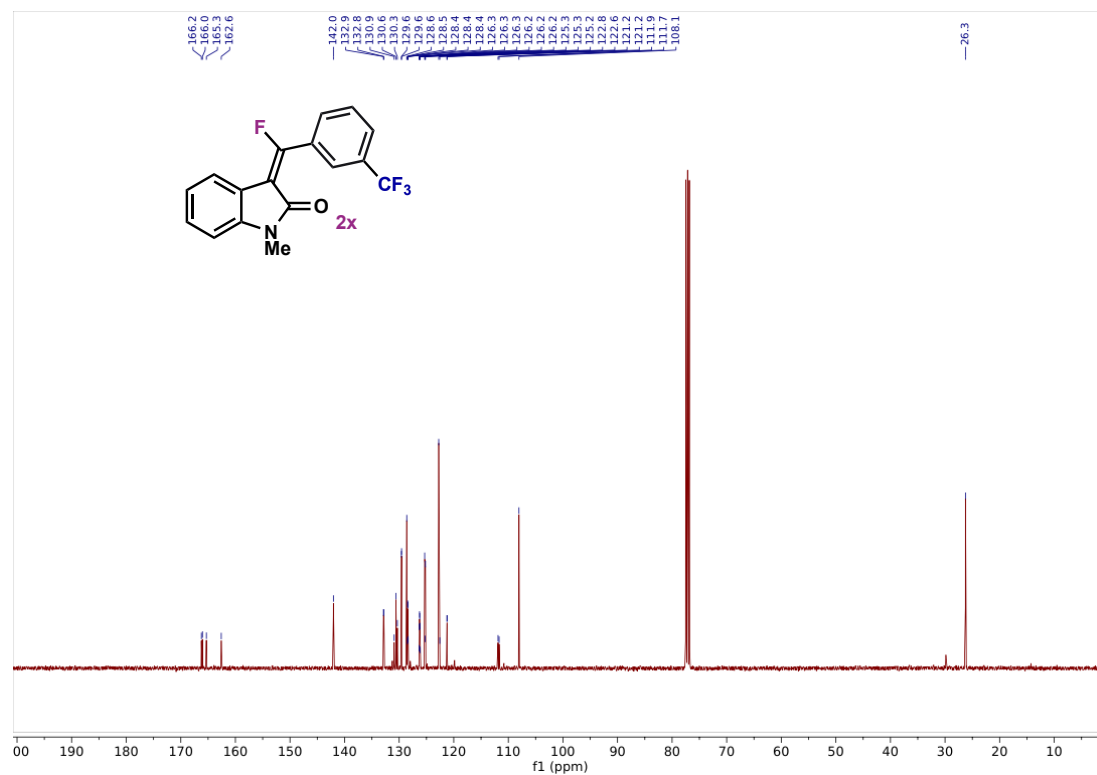
^{19}F NMR (377 MHz, CDCl_3) of **3.2x**



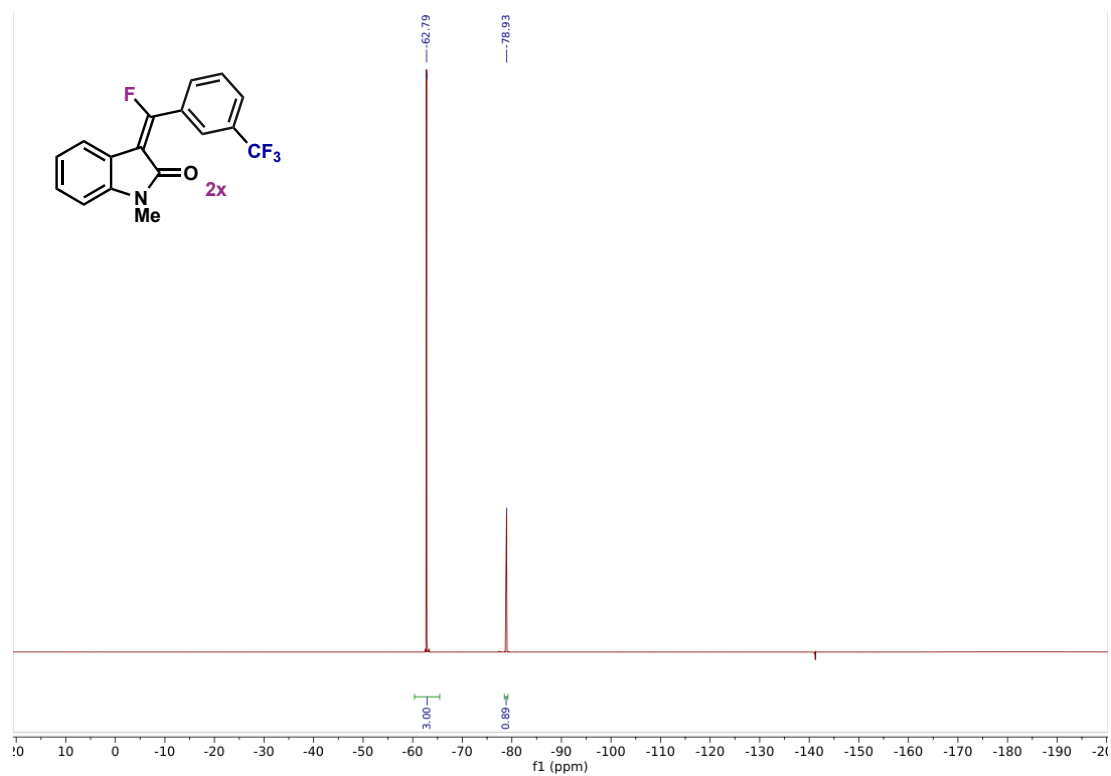
^1H NMR (400 MHz, CDCl_3) of **3.2y**



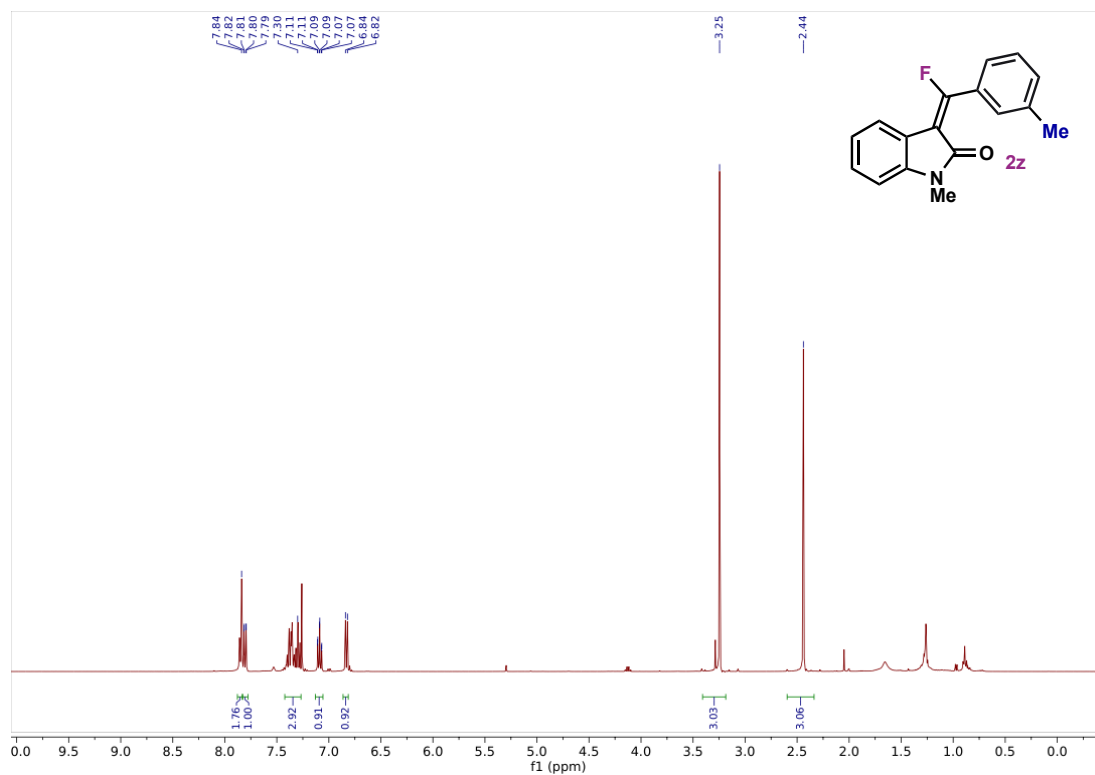
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.2y**



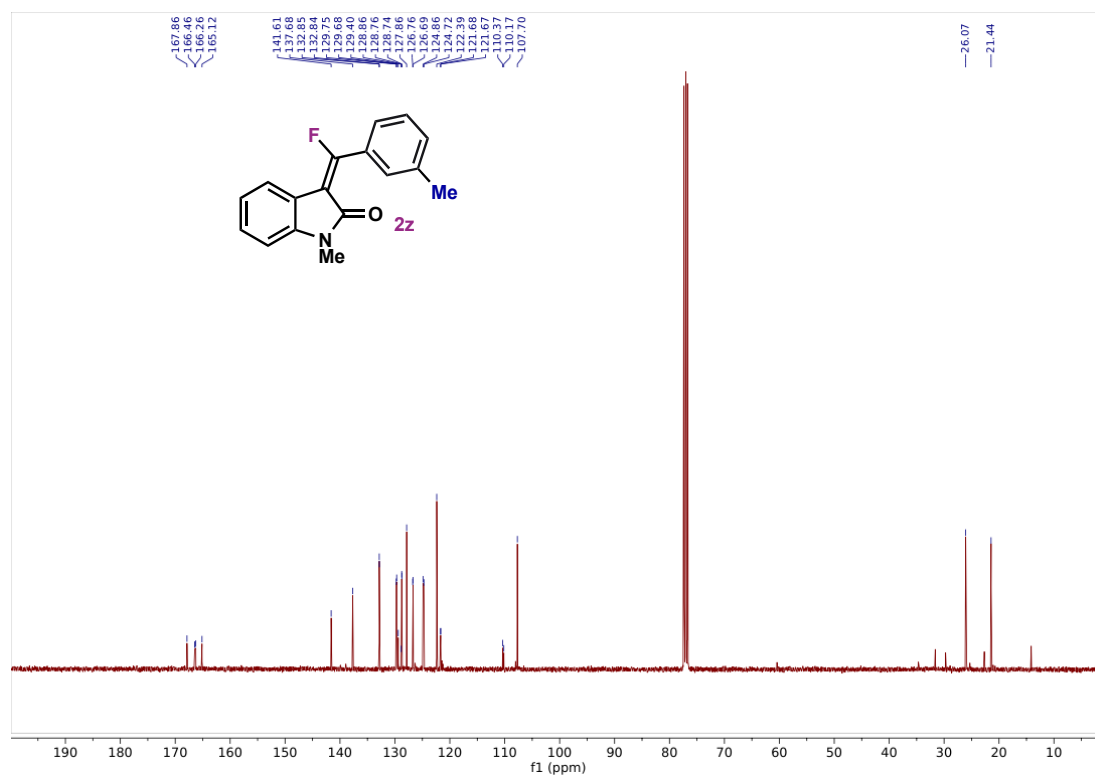
^{19}F NMR (377 MHz, CDCl_3) of **3.2y**



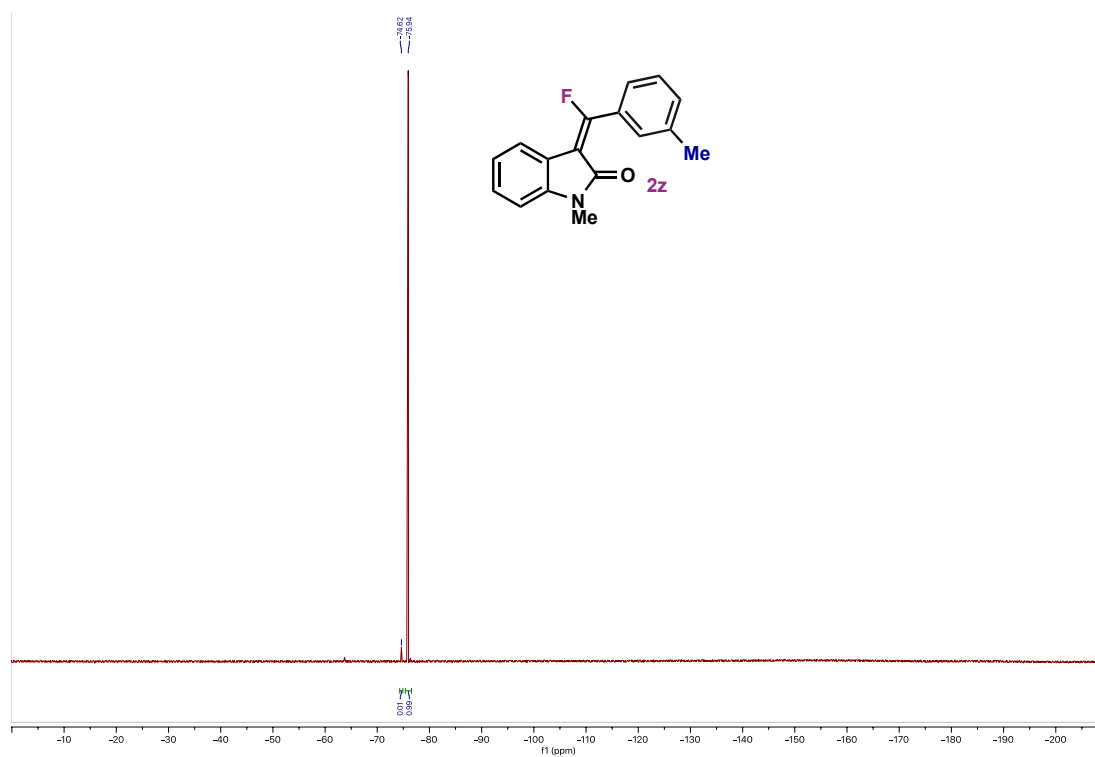
^1H NMR (400 MHz, CDCl_3) of **3.2z**



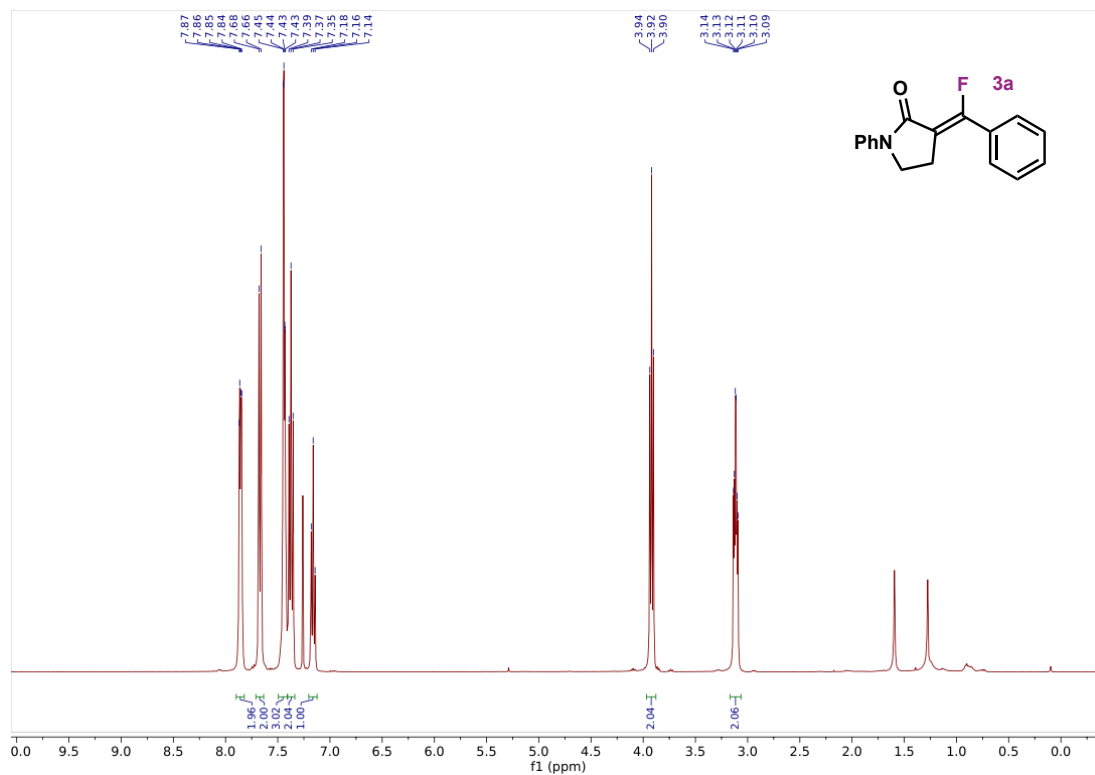
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.2z**



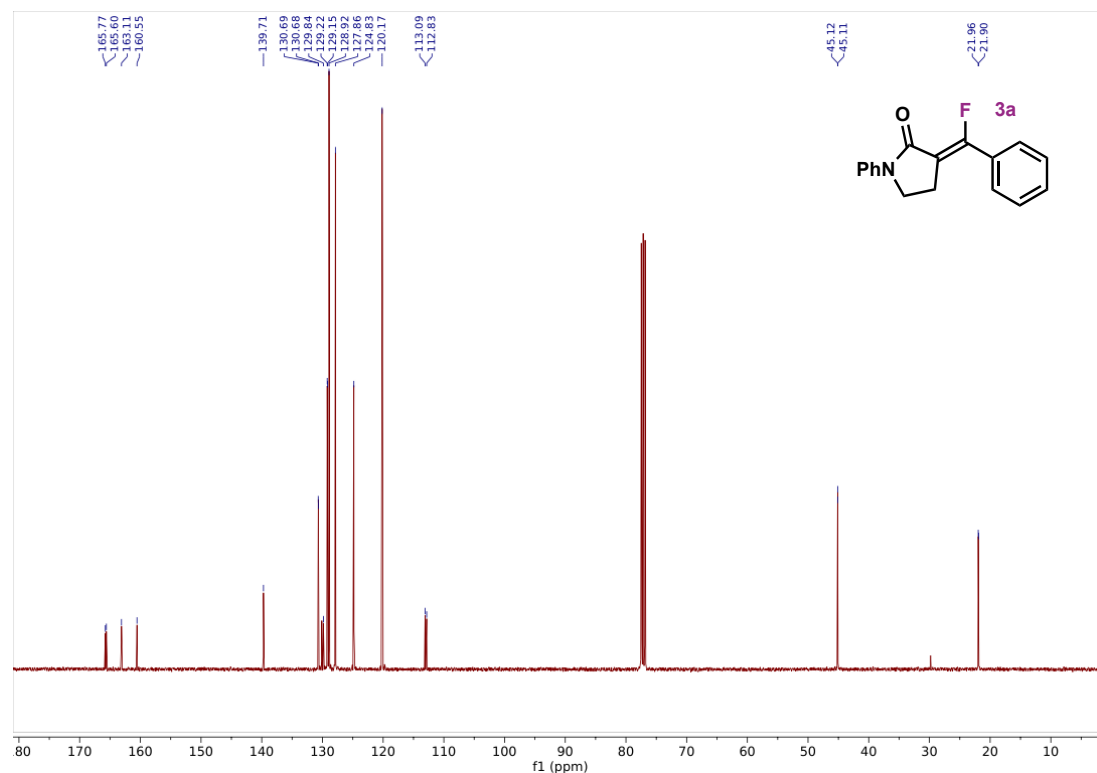
^{19}F NMR (377 MHz, CDCl_3) of **3.2z**



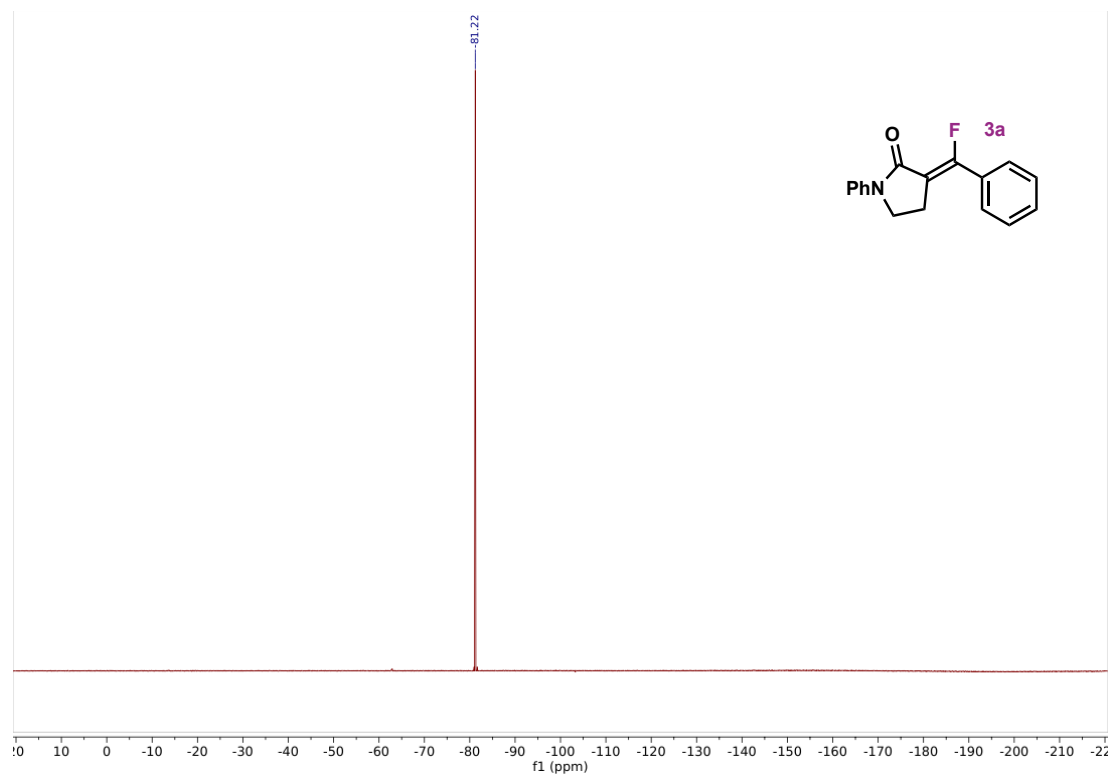
^1H NMR (400 MHz, CDCl_3) of **3.3a**



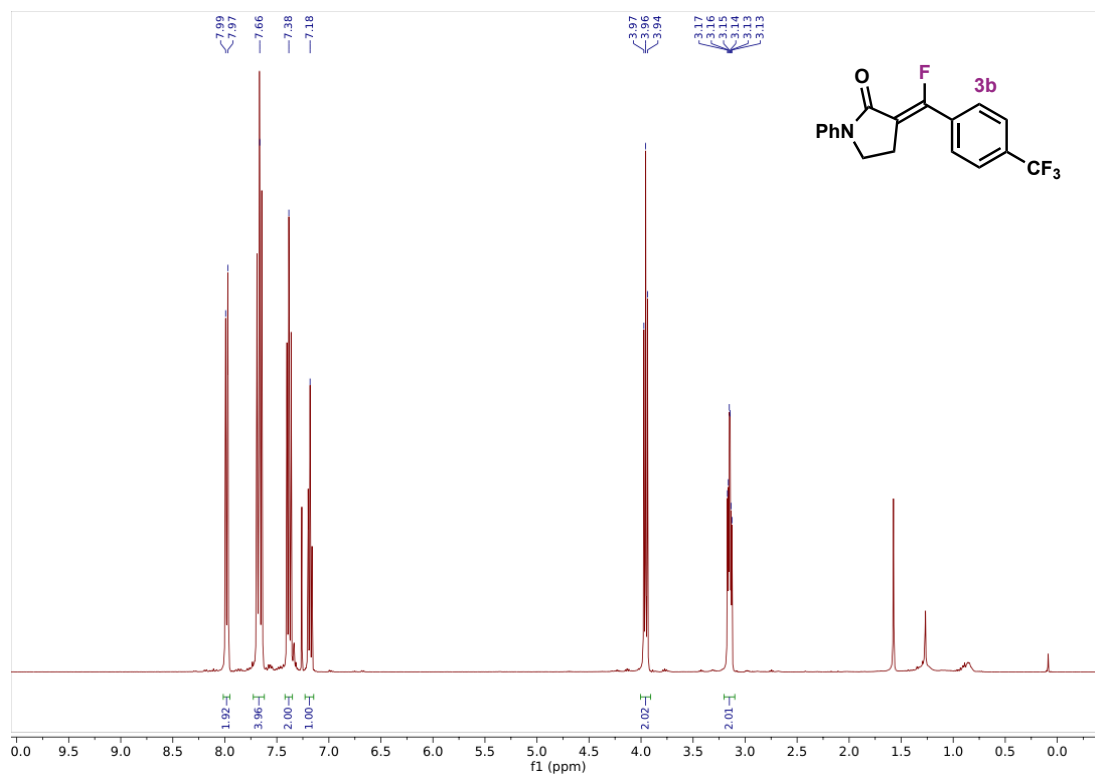
^{13}C { ^1H } NMR (101 MHz, CDCl_3) of **3.3a**



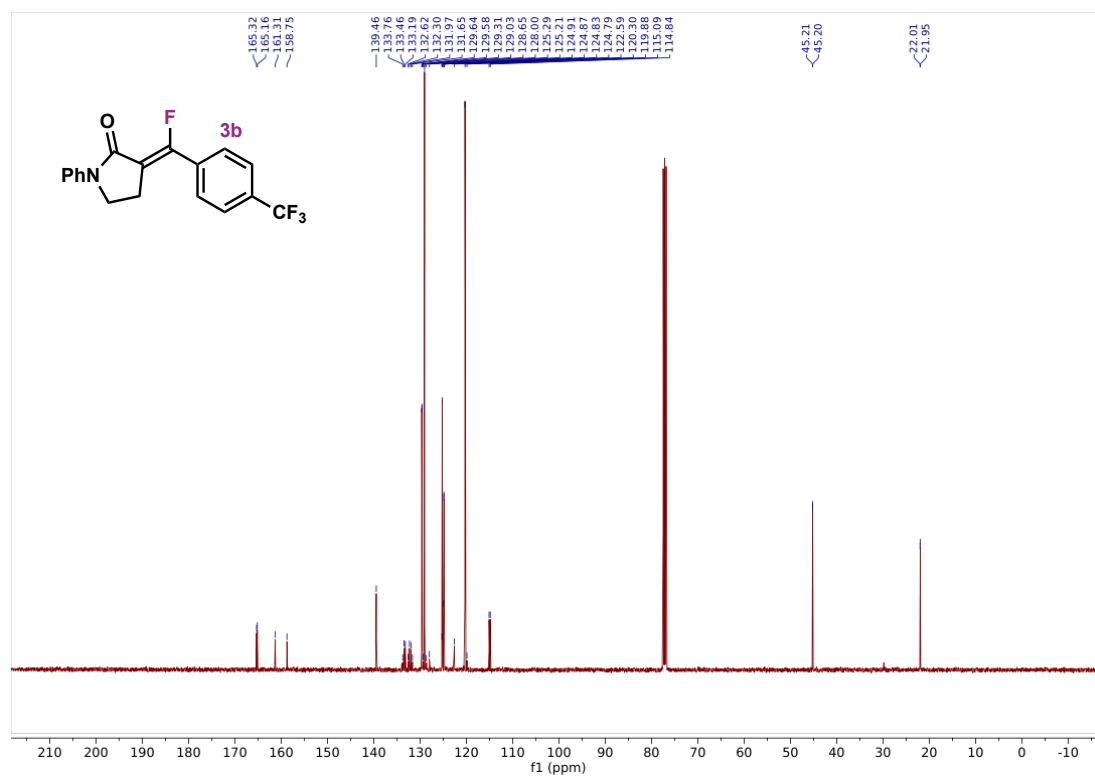
^{19}F NMR (377 MHz, CDCl_3) of **3.3a**



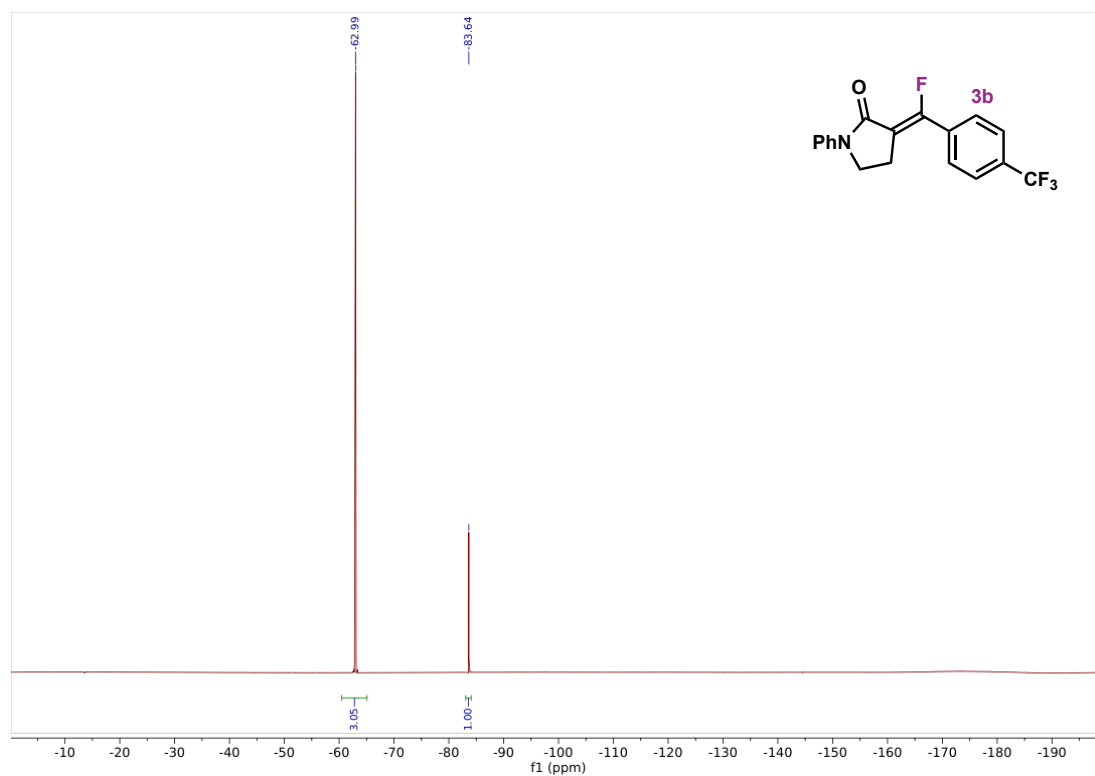
^1H NMR (400 MHz, CDCl_3) of **3.3b**



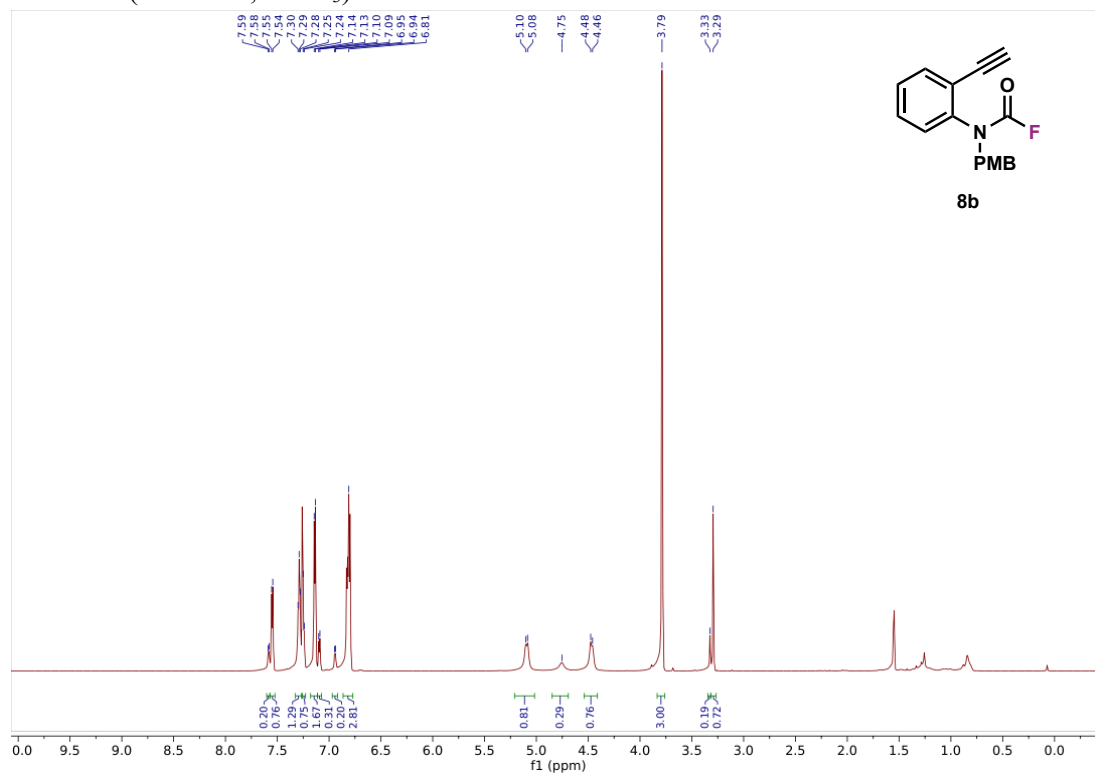
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.3b**



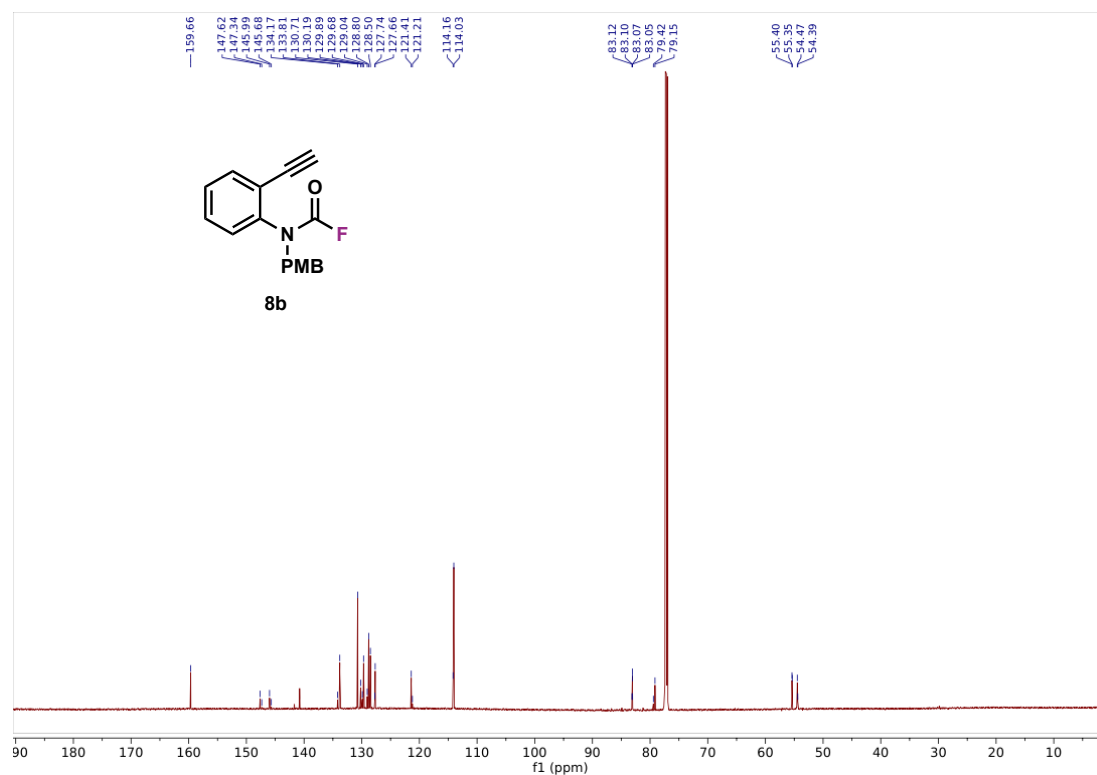
^{19}F NMR (659 MHz, CDCl_3) of **3.3b**



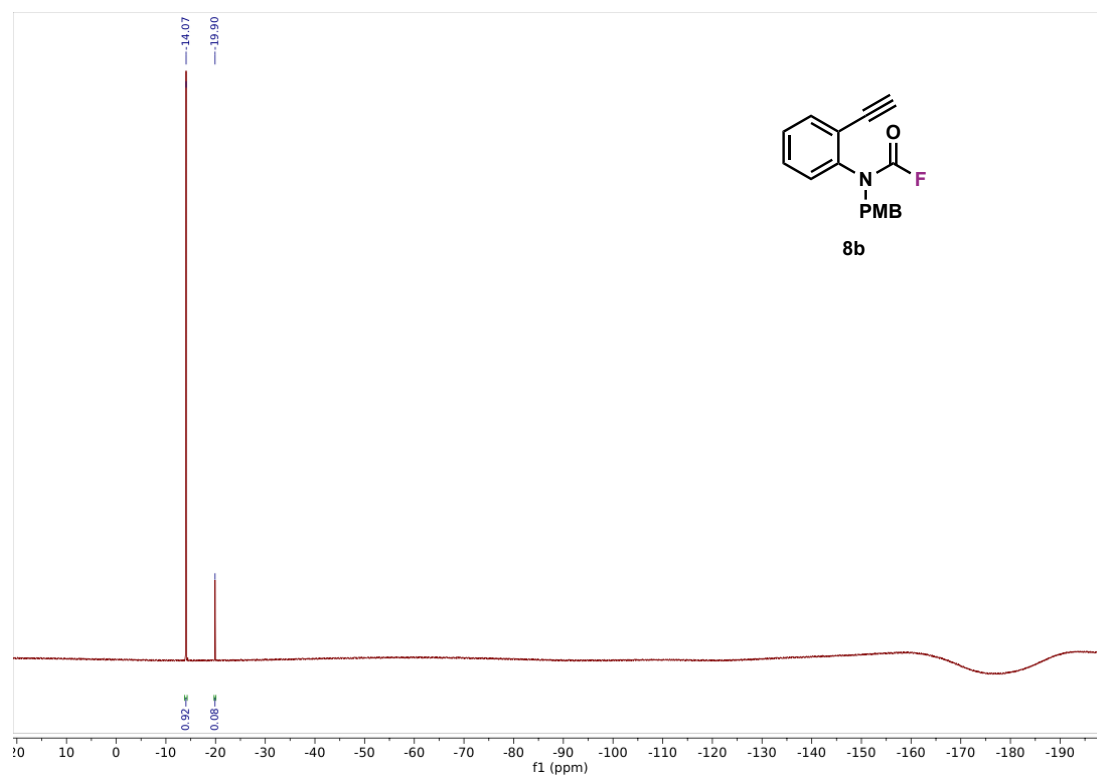
^1H NMR (700 MHz, CDCl_3) of **8b**



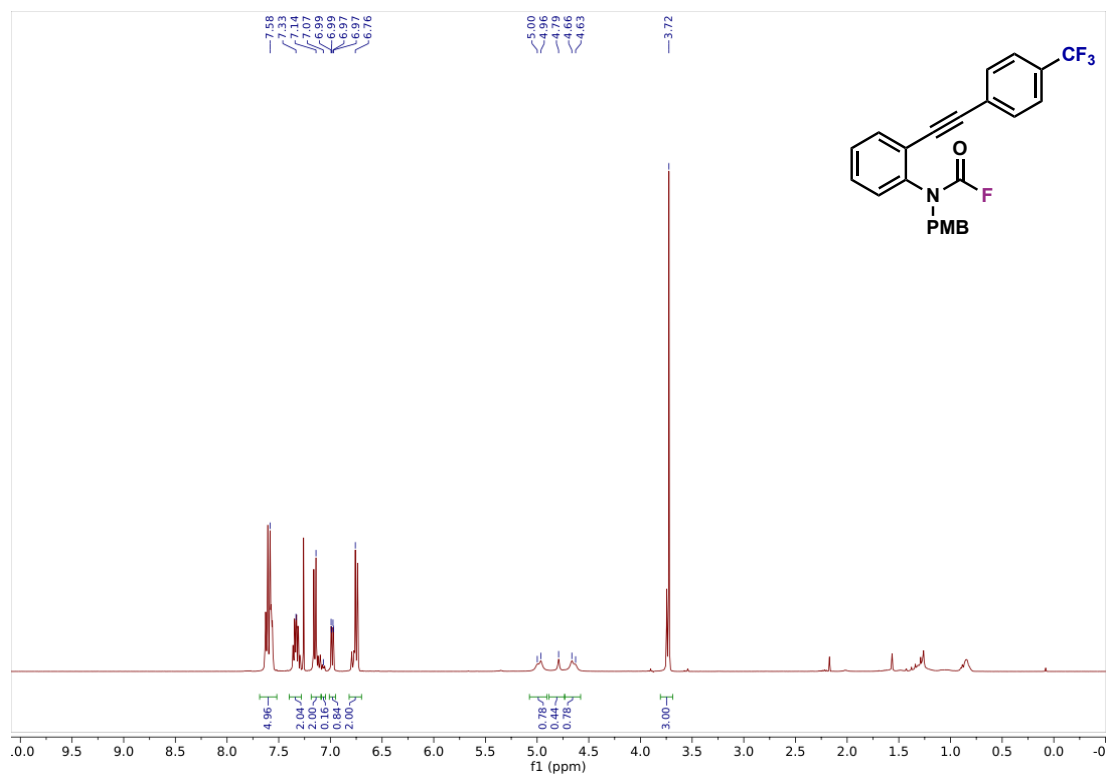
^{13}C $\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) of **3.8b**



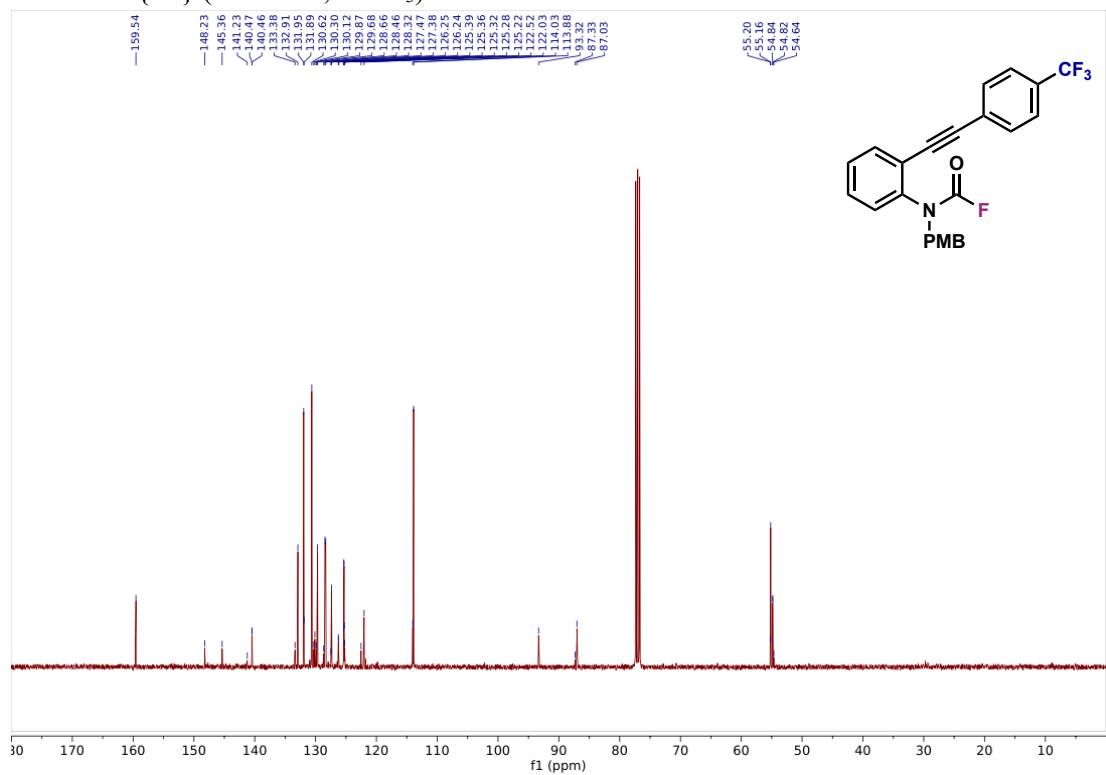
^{19}F NMR (659 MHz, CDCl_3) of **3.8b**



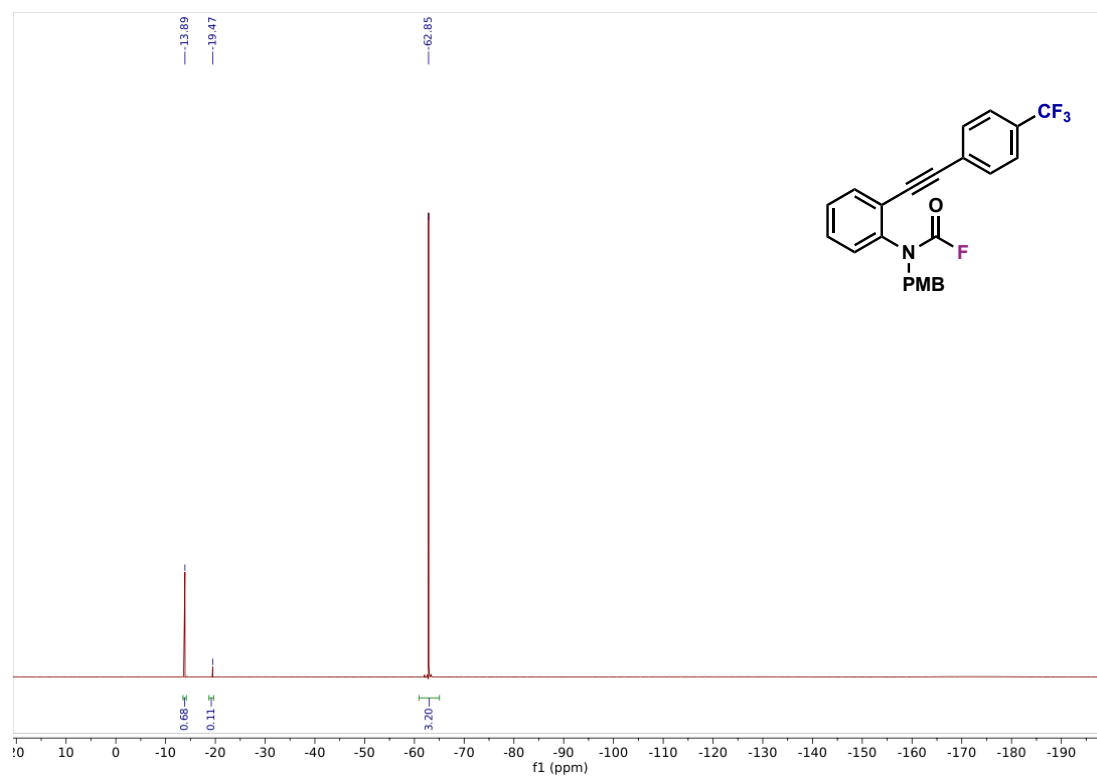
^1H NMR (400 MHz, CDCl_3) of **3.1aa**



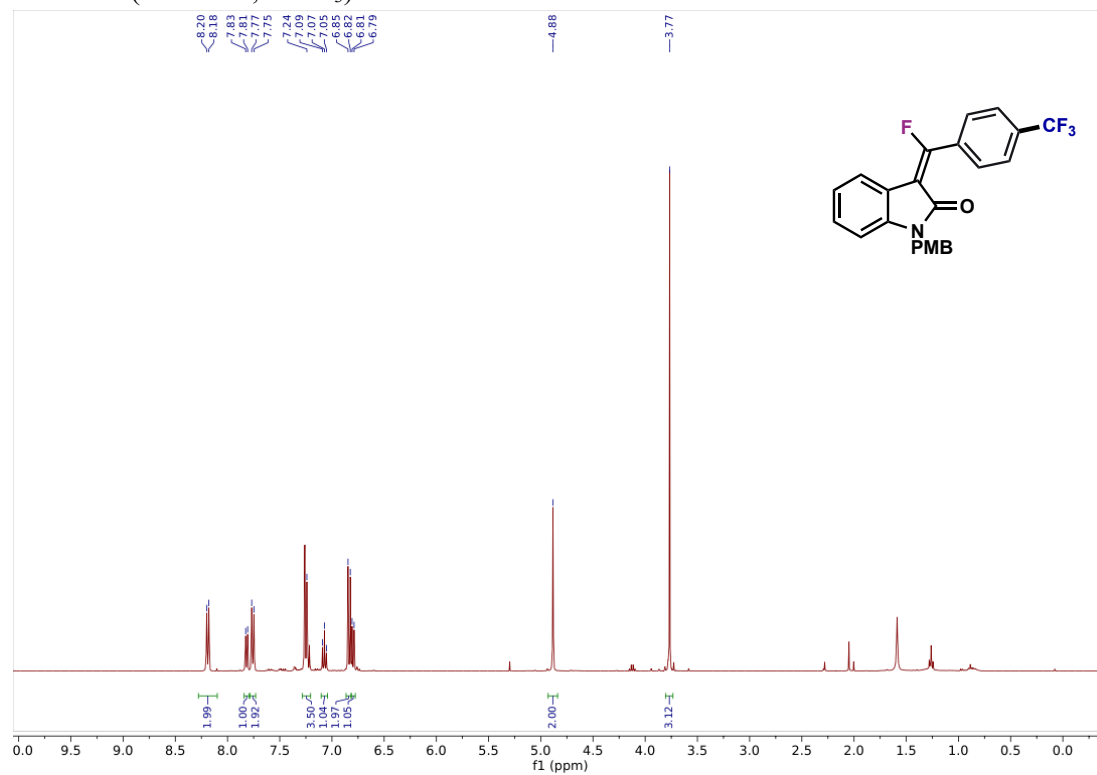
^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3) of **3.1aa**



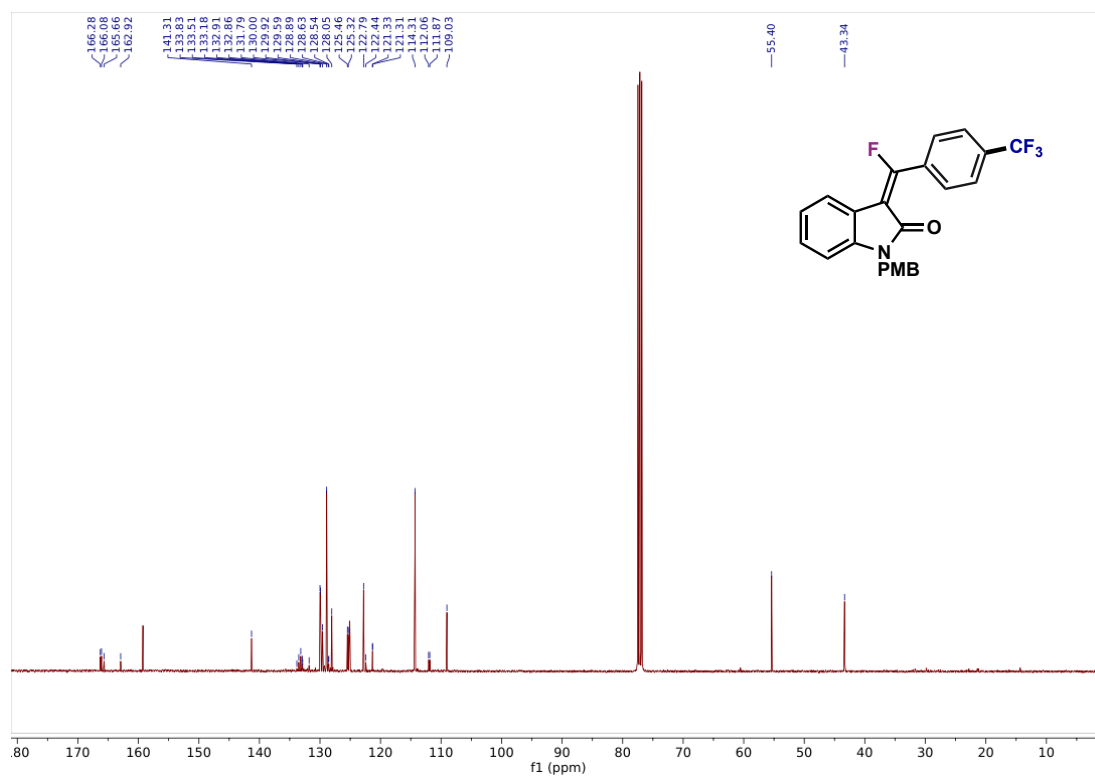
^{19}F NMR (377 MHz, CDCl_3) of **3.1aa**



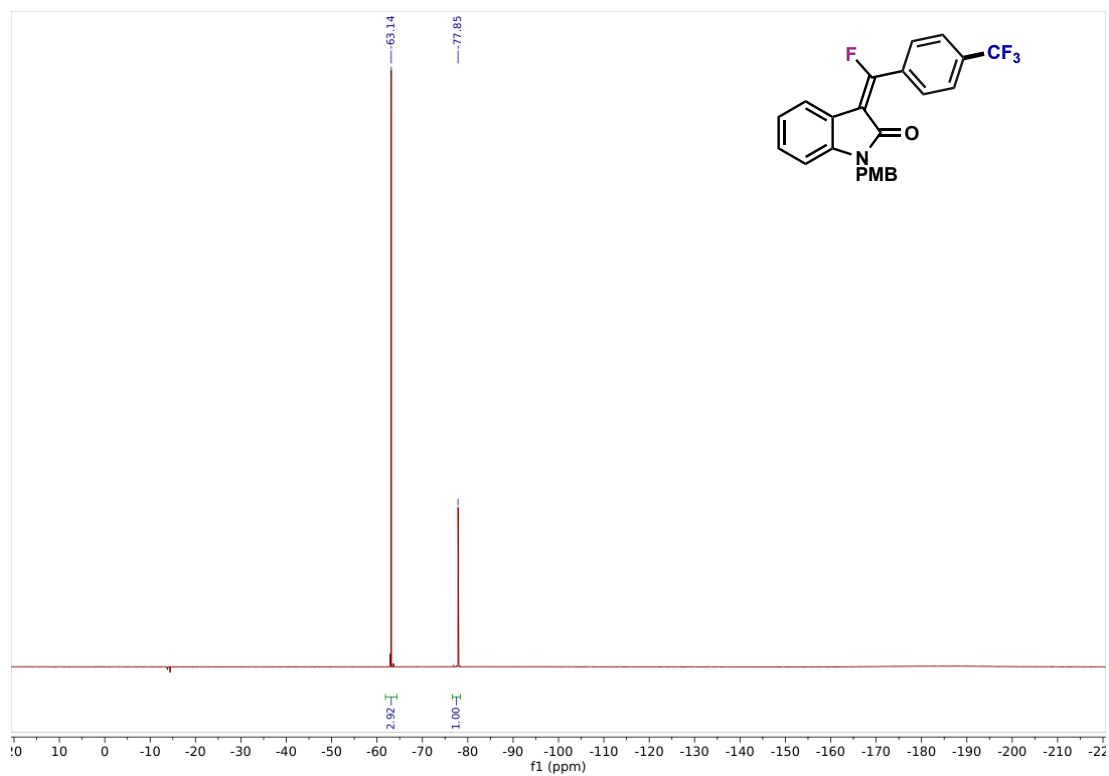
^1H NMR (400 MHz, CDCl_3) of **3.2aa**



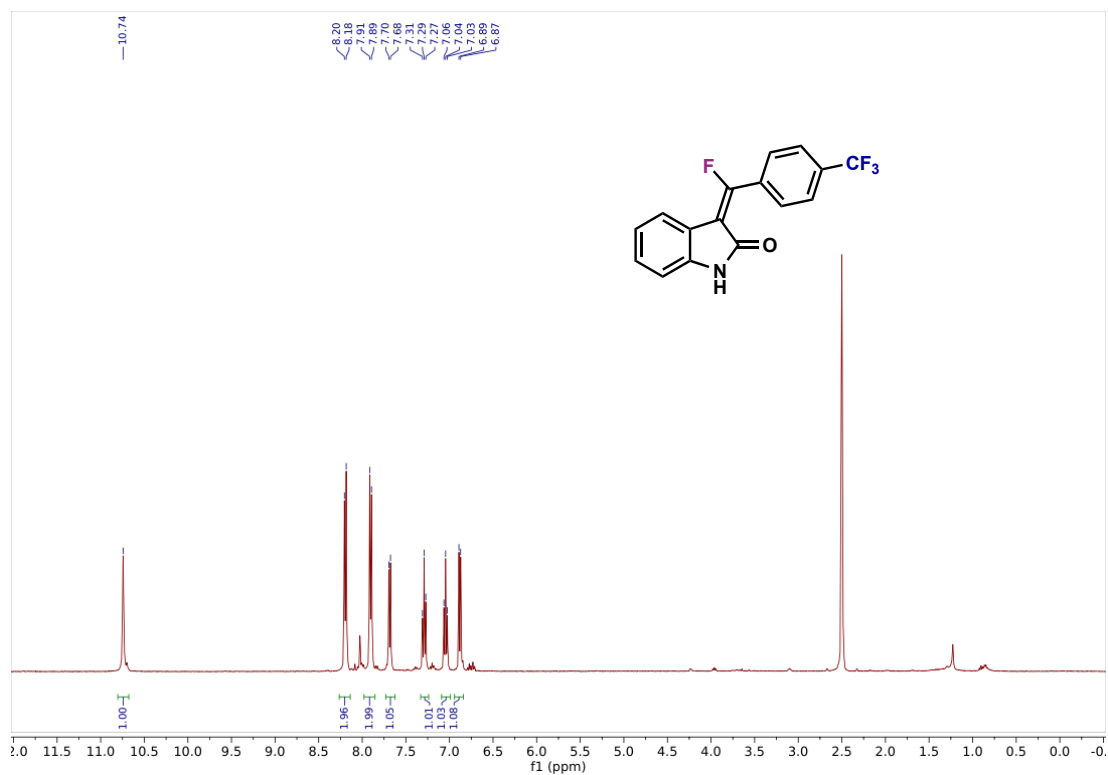
^{13}C NMR $\{^1\text{H}\}$ (101 MHz, CDCl_3) of **3.2aa**



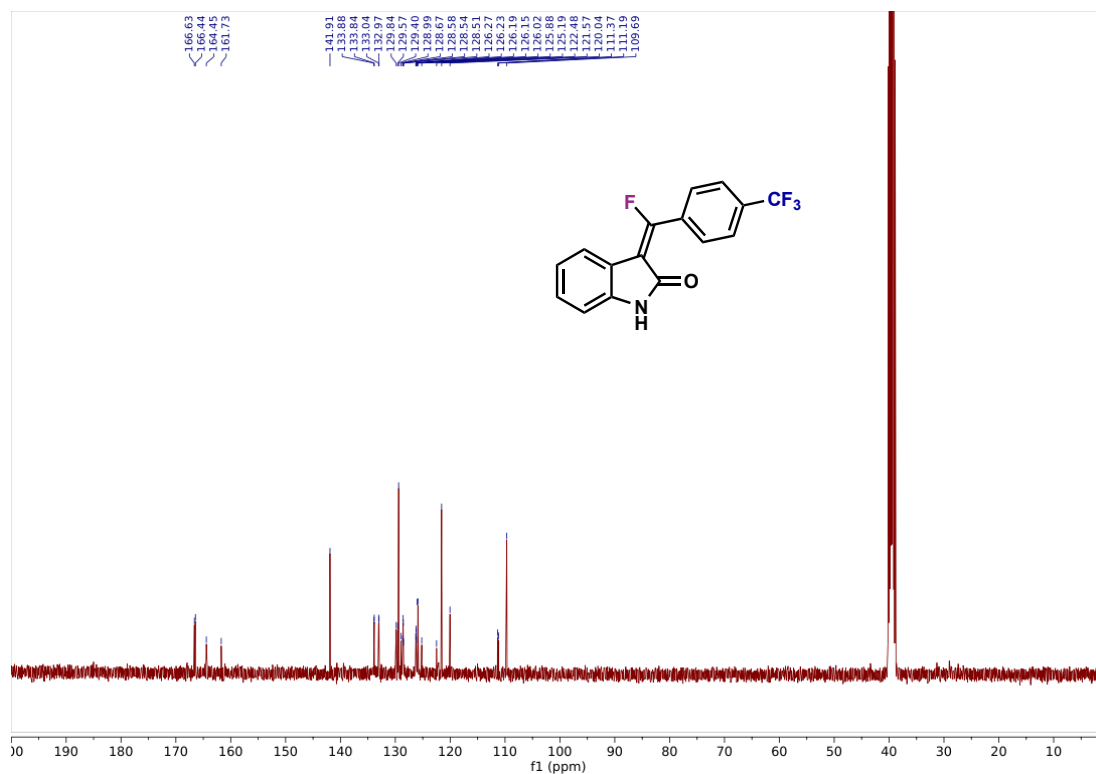
^{19}F NMR (377 MHz, CDCl_3) of **3.2aa**



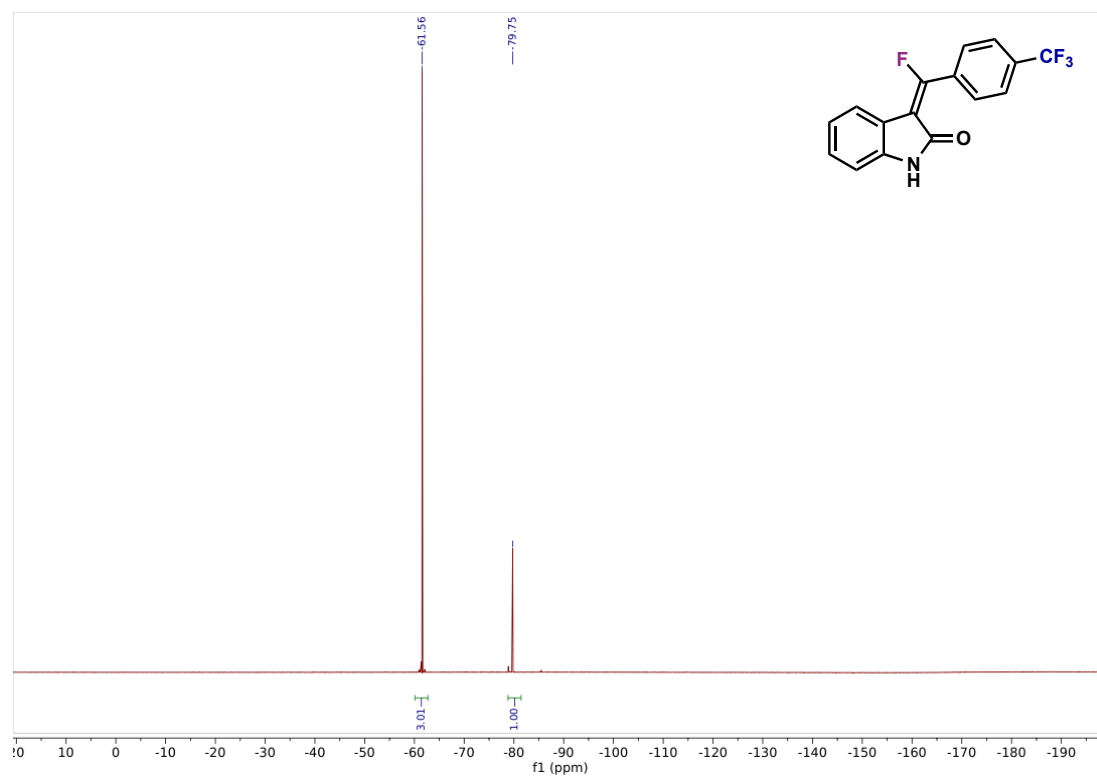
^1H NMR (400 MHz, $\text{DMSO}-d_6$) of **3.5aa**



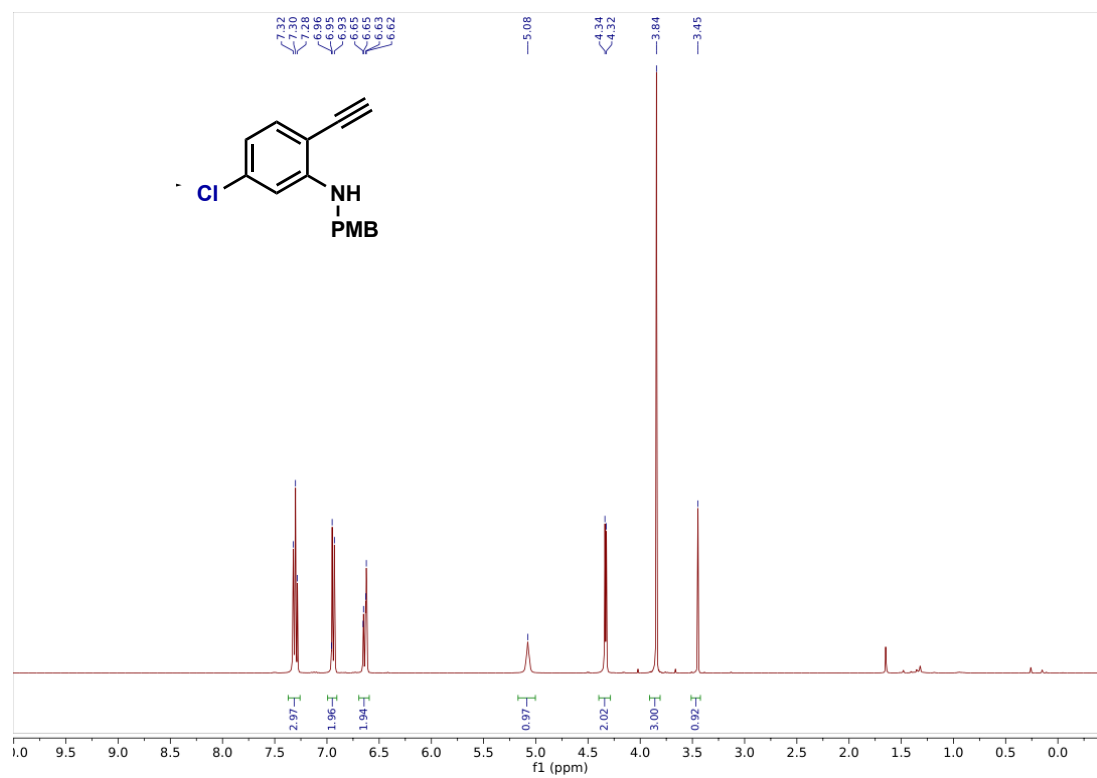
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) of **3.5aa**



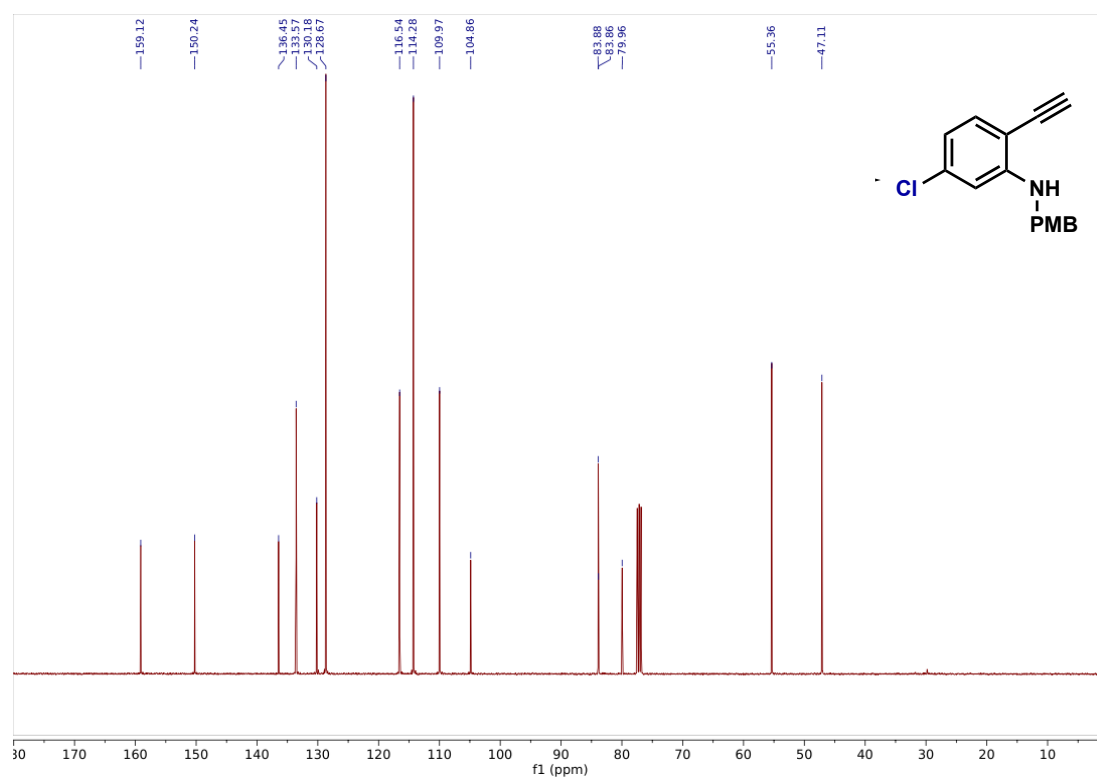
^{19}F NMR (377 MHz, $\text{DMSO}-d_6$) of **3.5aa**



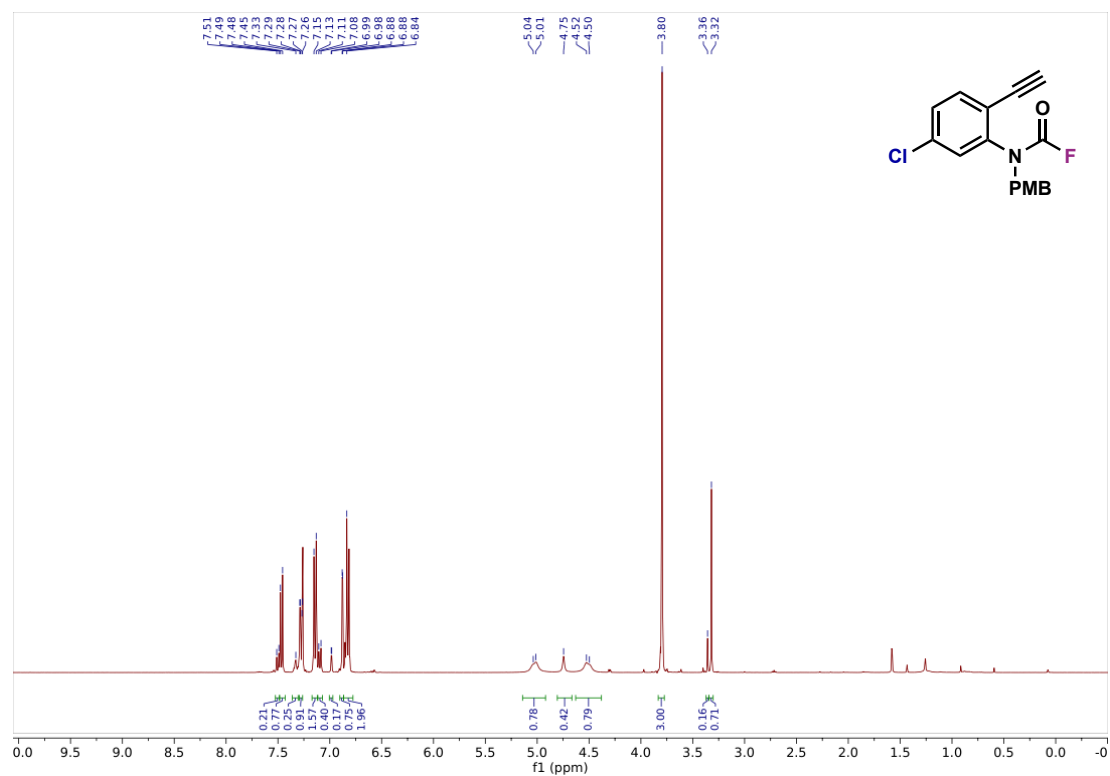
^1H NMR (400 MHz, CDCl_3) of **3.10c**



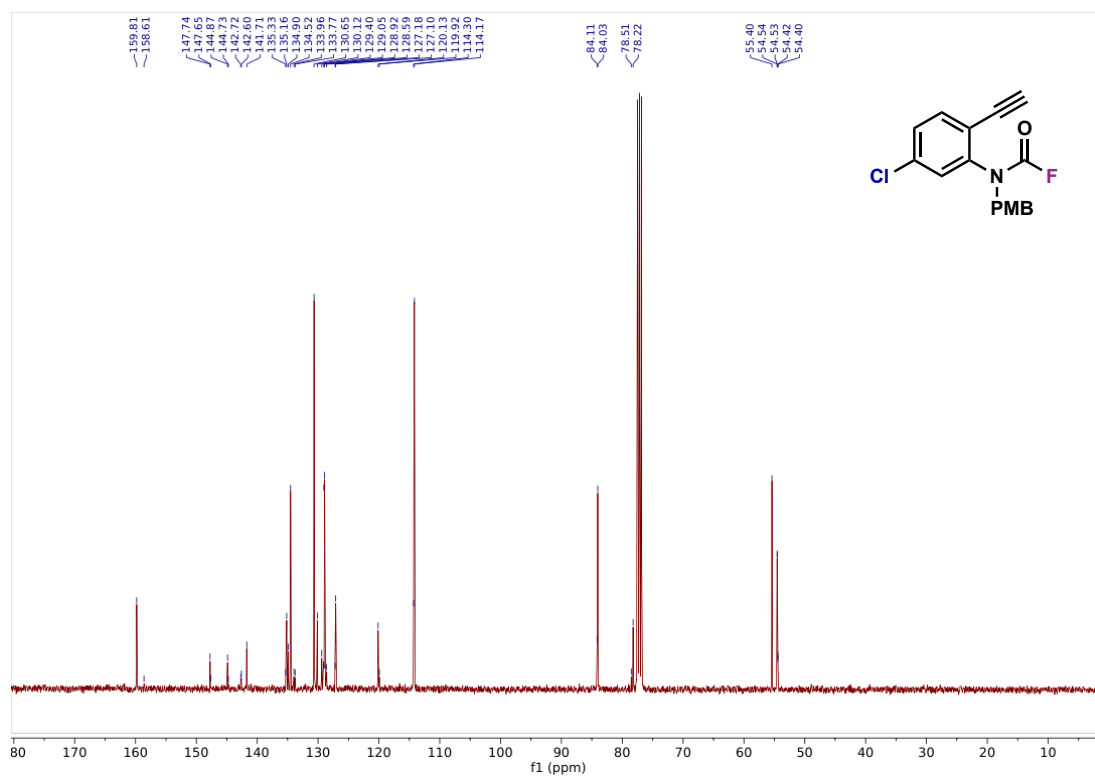
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.10c**



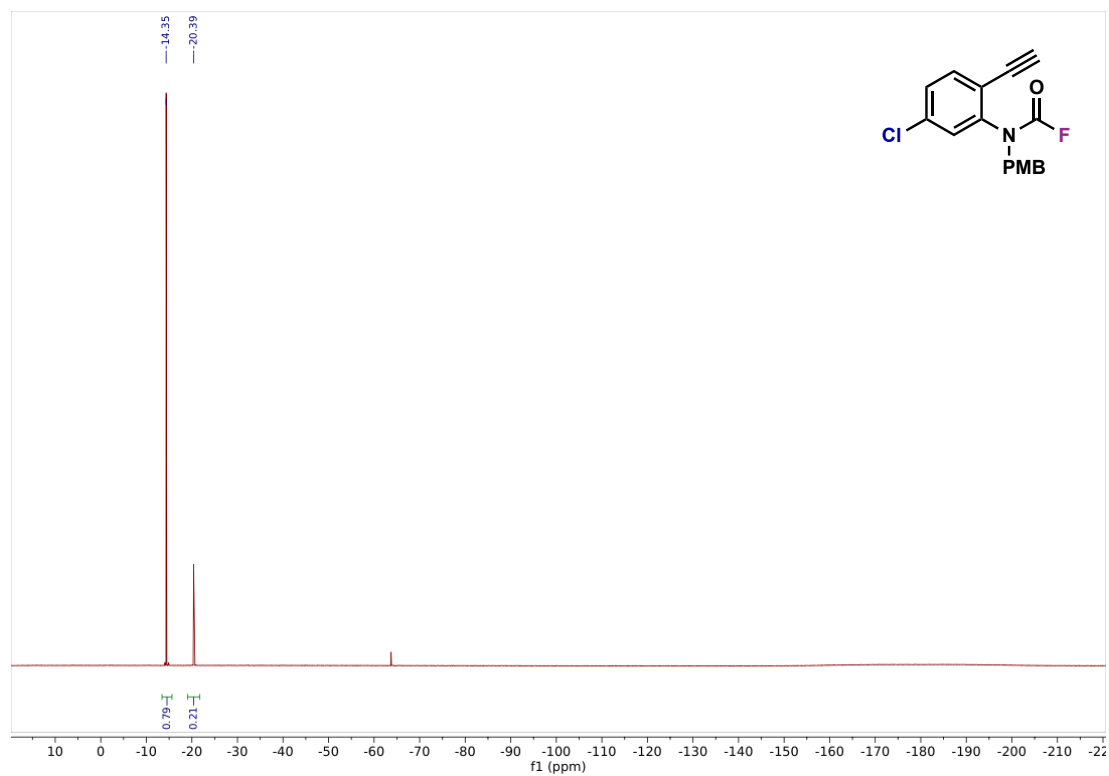
^1H NMR (400 MHz, CDCl_3) of **3.8c**



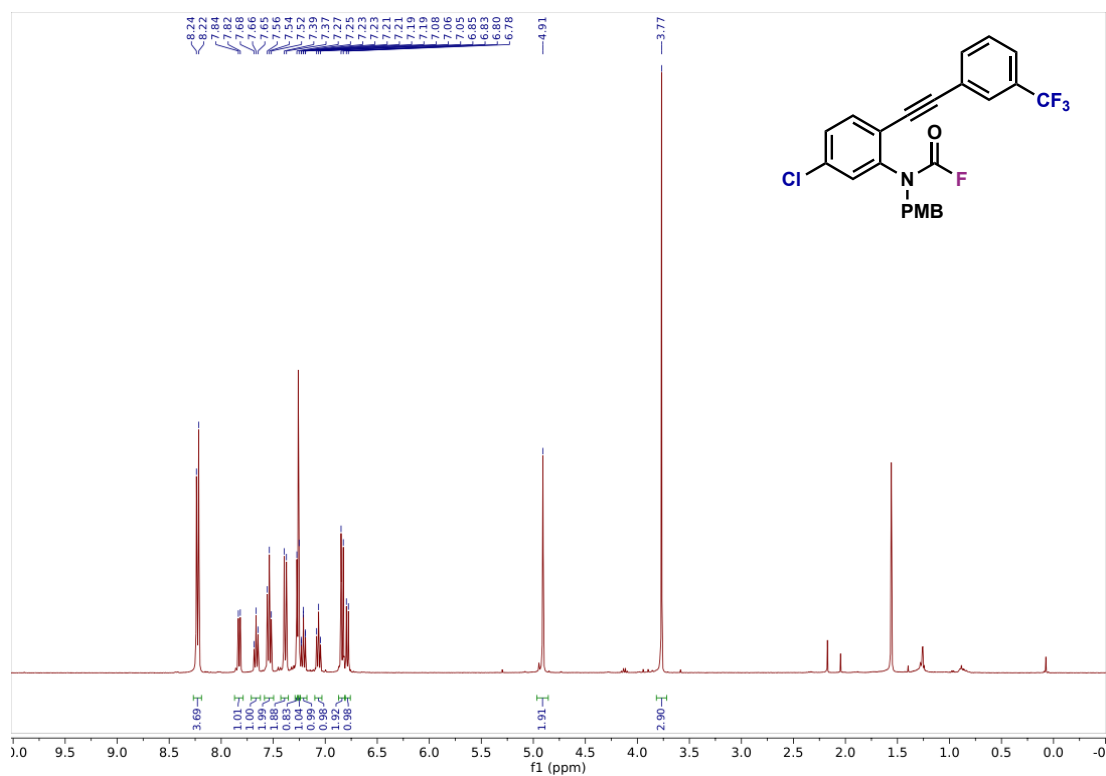
^{13}C { ^1H } NMR (101 MHz, CDCl_3) of **3.8c**



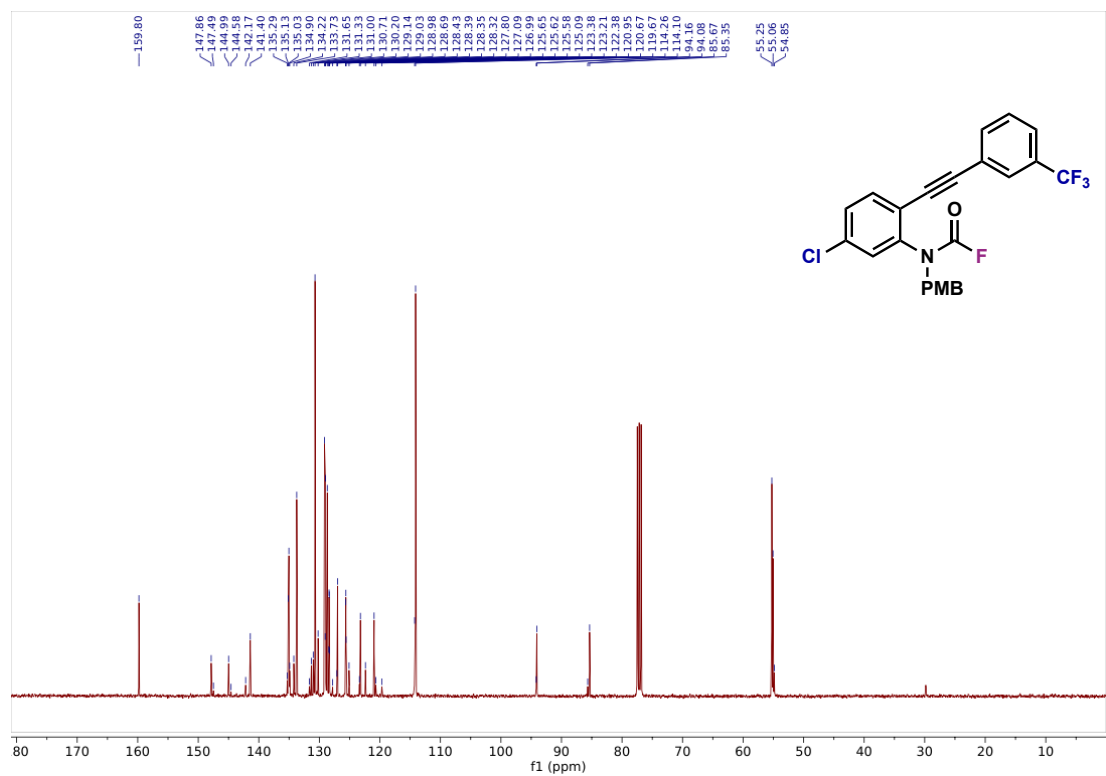
^{19}F NMR (377 MHz, CDCl_3) of **3.8c**



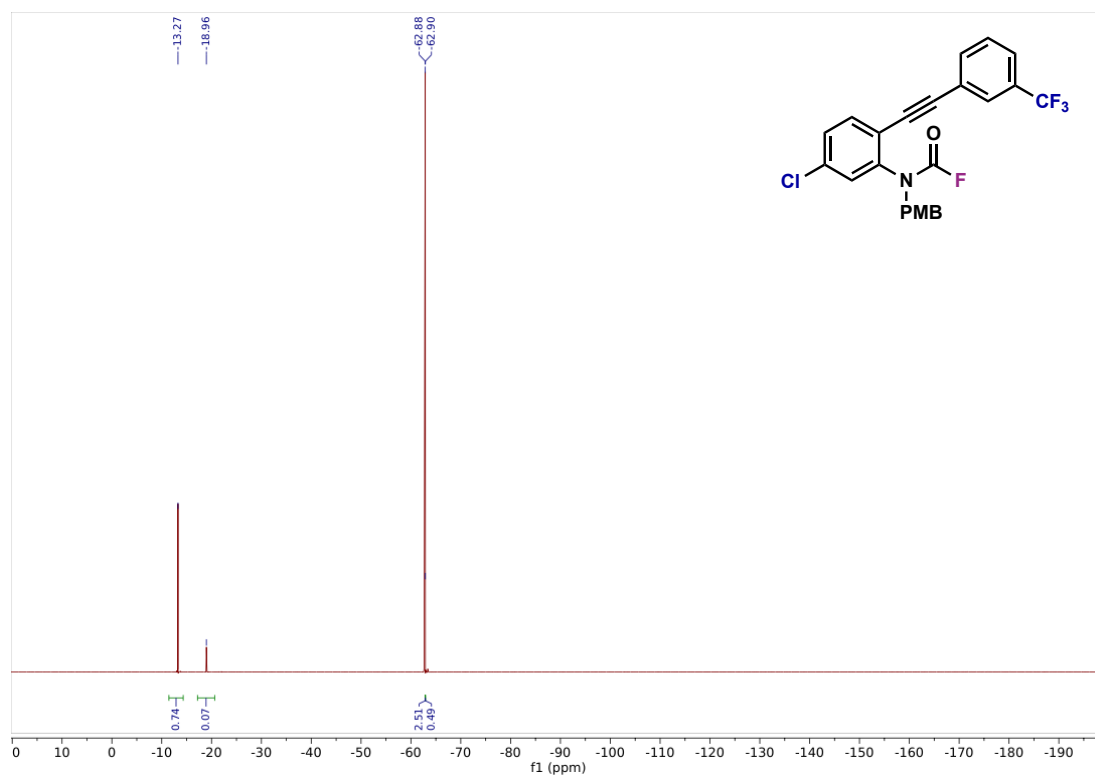
^1H NMR (400 MHz, CDCl_3) of **3.1ab**



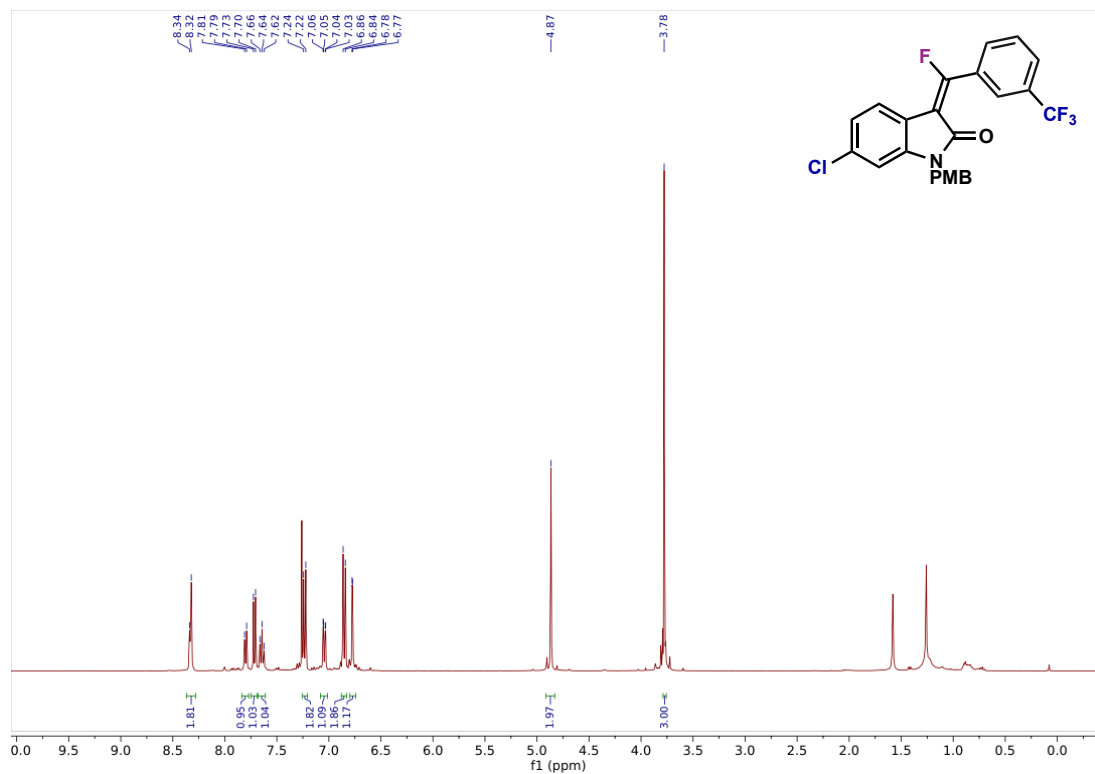
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.1ab**



^{19}F NMR (377 MHz, CDCl_3) of **3.1ab**



^1H NMR (400 MHz, CDCl_3) of **3.2ab**



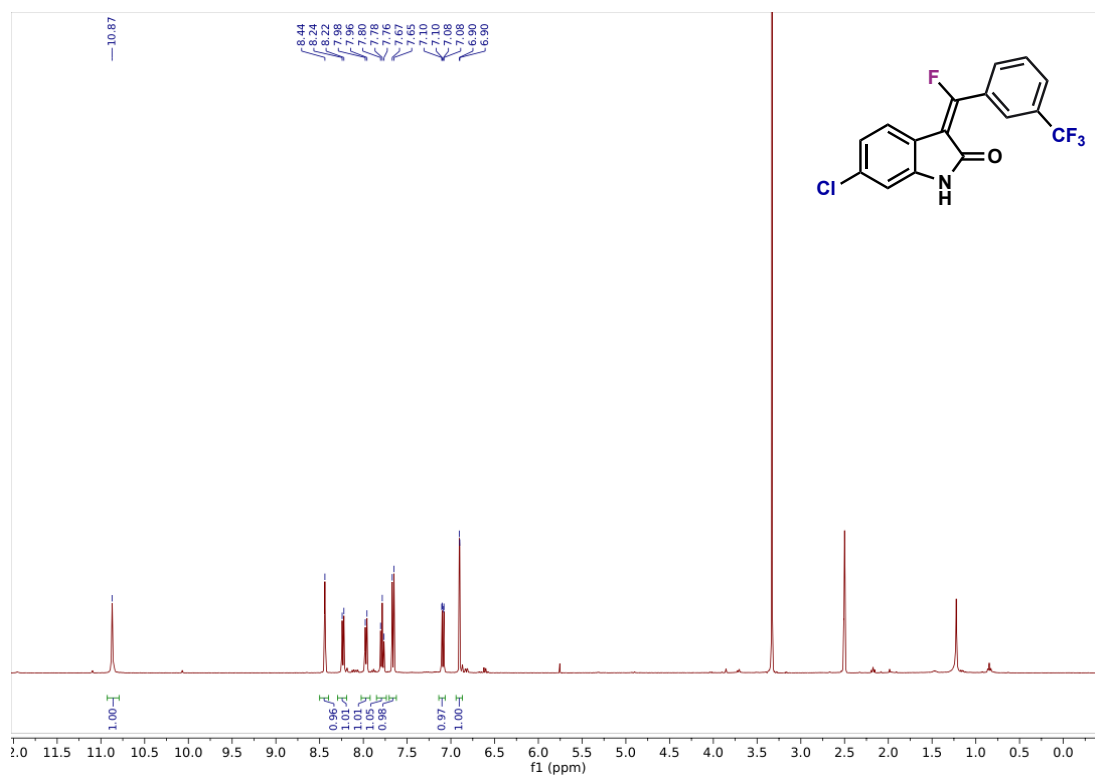
Chemical structure of compound 10: 2-(4-chlorophenyl)-3-(4-(trifluoromethyl)phenyl)-4-fluoro-1-(4-methylphenyl)pyrazole.

¹³C NMR spectrum (ppm):

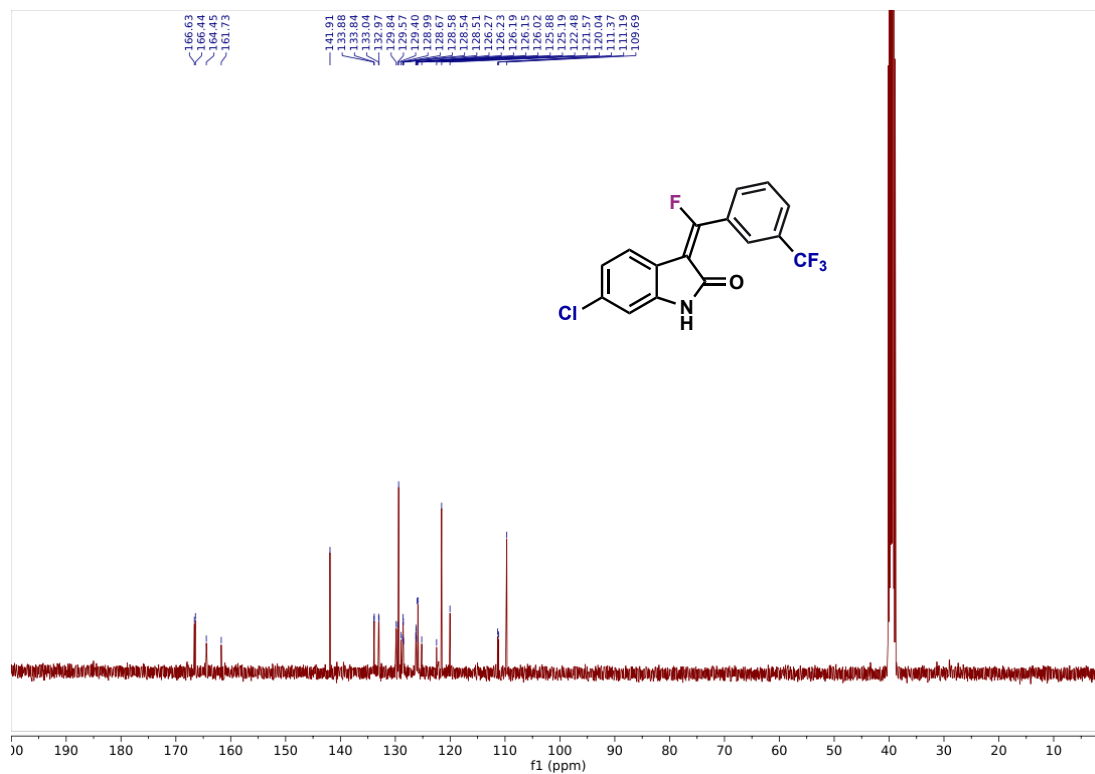
- 166.24, 166.05, 165.86, 163.12, 159.56
- 142.23, 135.27, 132.97, 132.89, 131.38, 130.73, 130.32, 130.06, 128.83, 128.73, 127.51, 126.55, 126.33, 126.28, 126.24, 126.20, 125.99, 125.99, 125.20, 122.72, 122.72, 119.79, 118.40, 114.43, 110.66, 109.58
- 55.40, 43.45

Chemical structure of compound 10 is shown in the top right corner. The structure is a 4-chloro-2-(4-(trifluoromethyl)phenyl)-3-(4-methylphenyl)indolizin-5(1H)-one. The NMR spectrum shows peaks at 62.78 ppm (integral 3.04) and 77.33 ppm (integral 1.00).

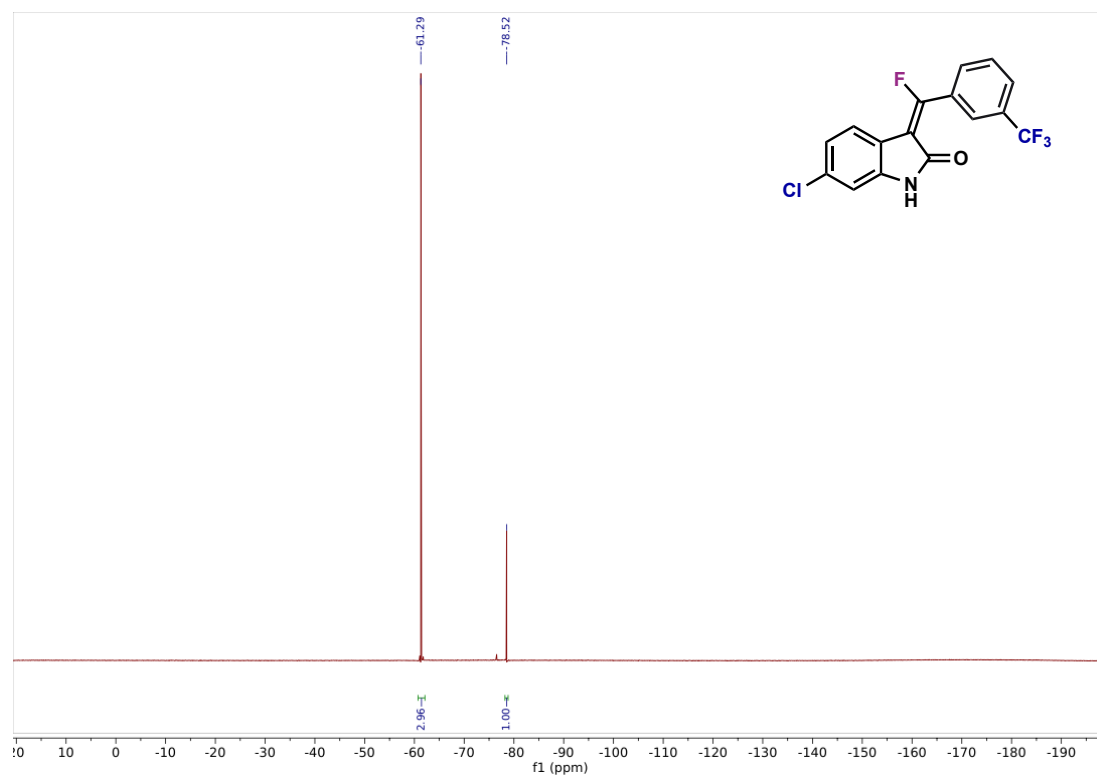
^1H NMR (400 MHz, DMSO- d_6) of **3.5ab**



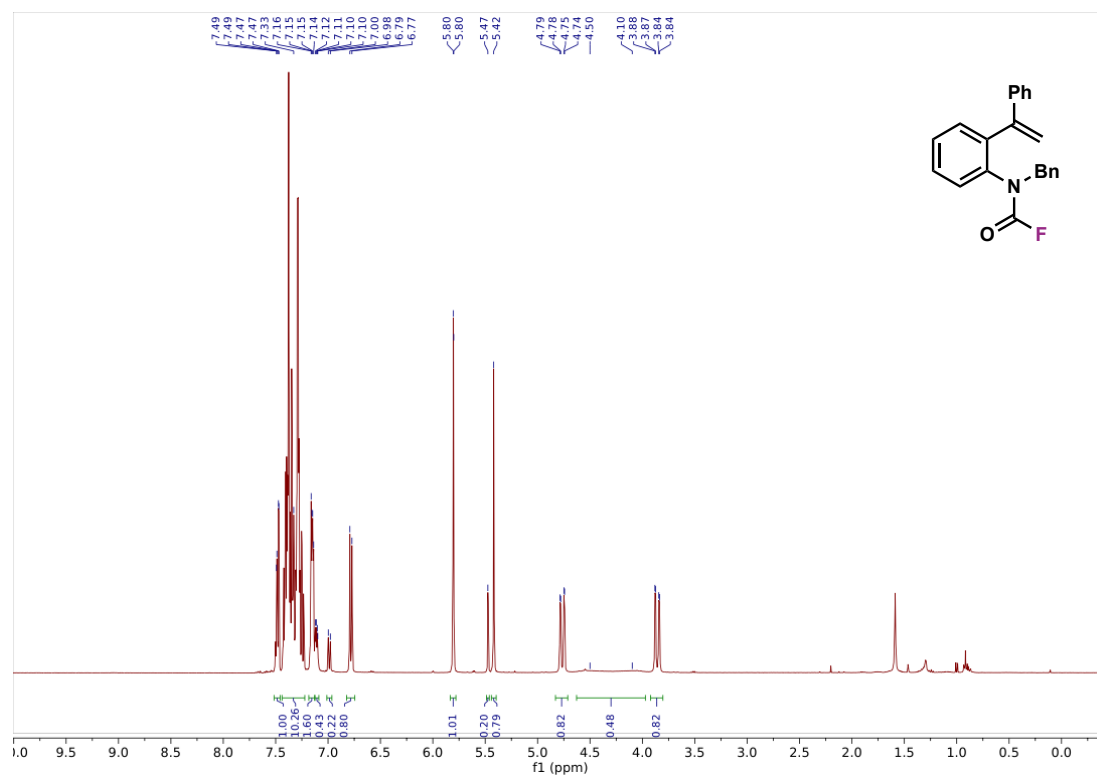
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) **3.5ab**



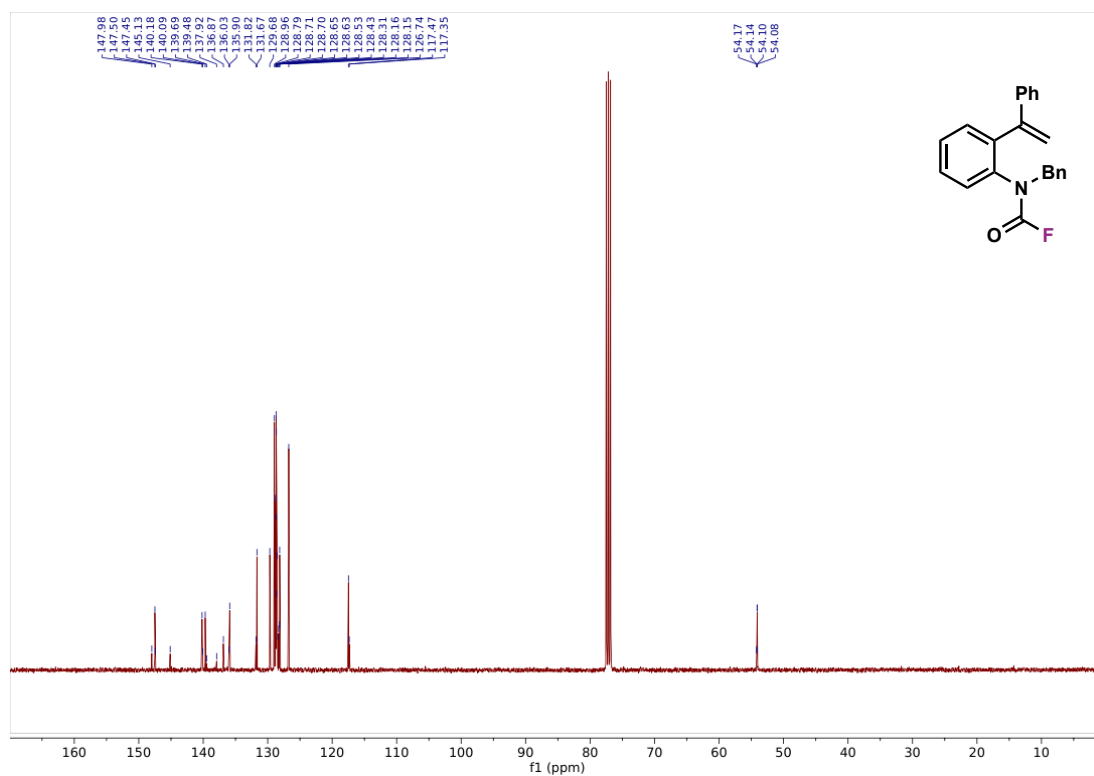
^{19}F NMR (377 MHz, CDCl_3) 3.5ab



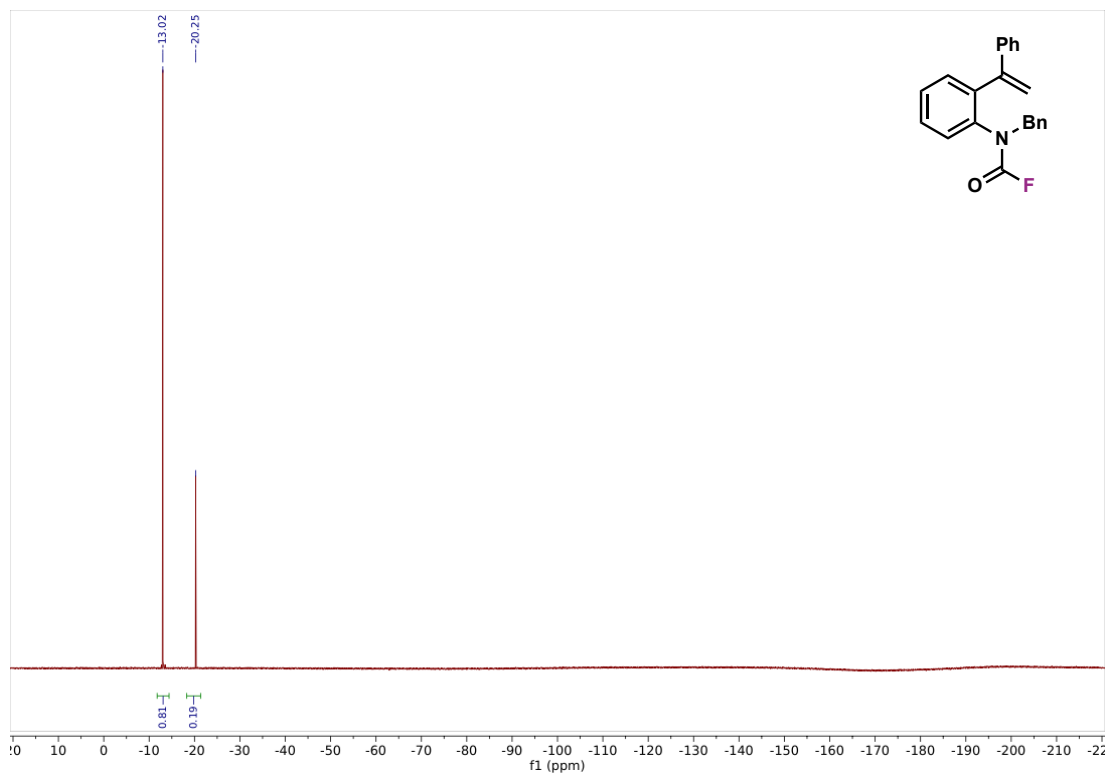
^1H NMR (400 MHz, CDCl_3) of 3.7



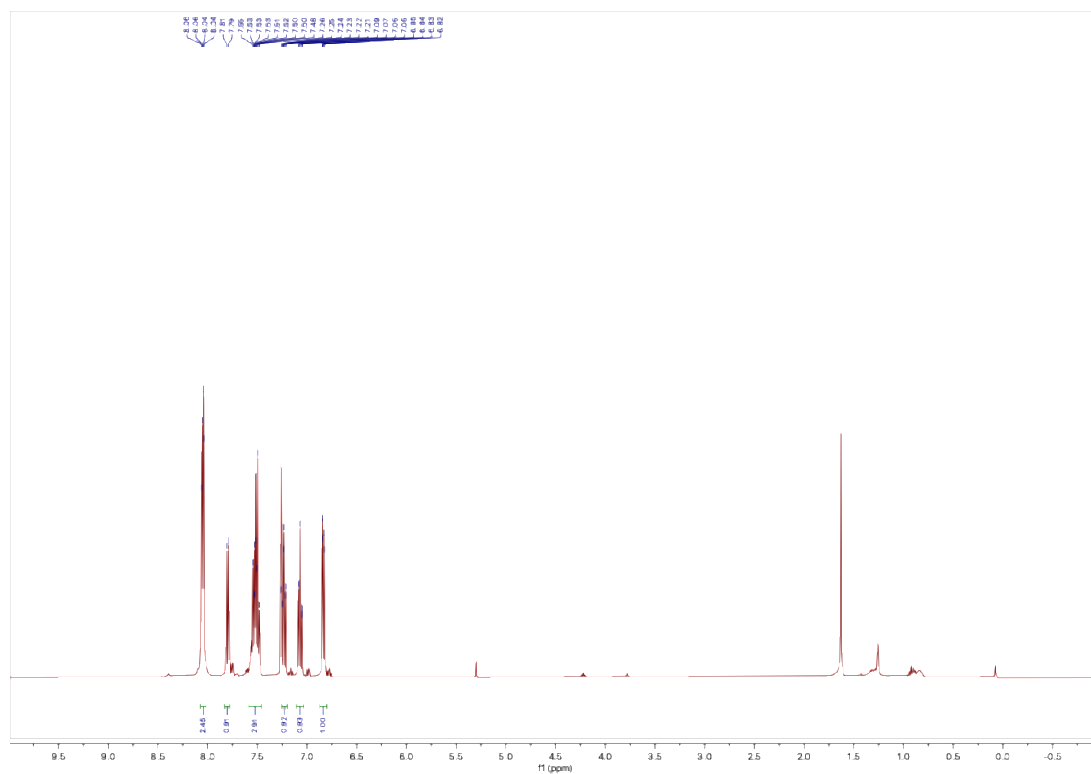
^{13}C $\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) of **3.7**



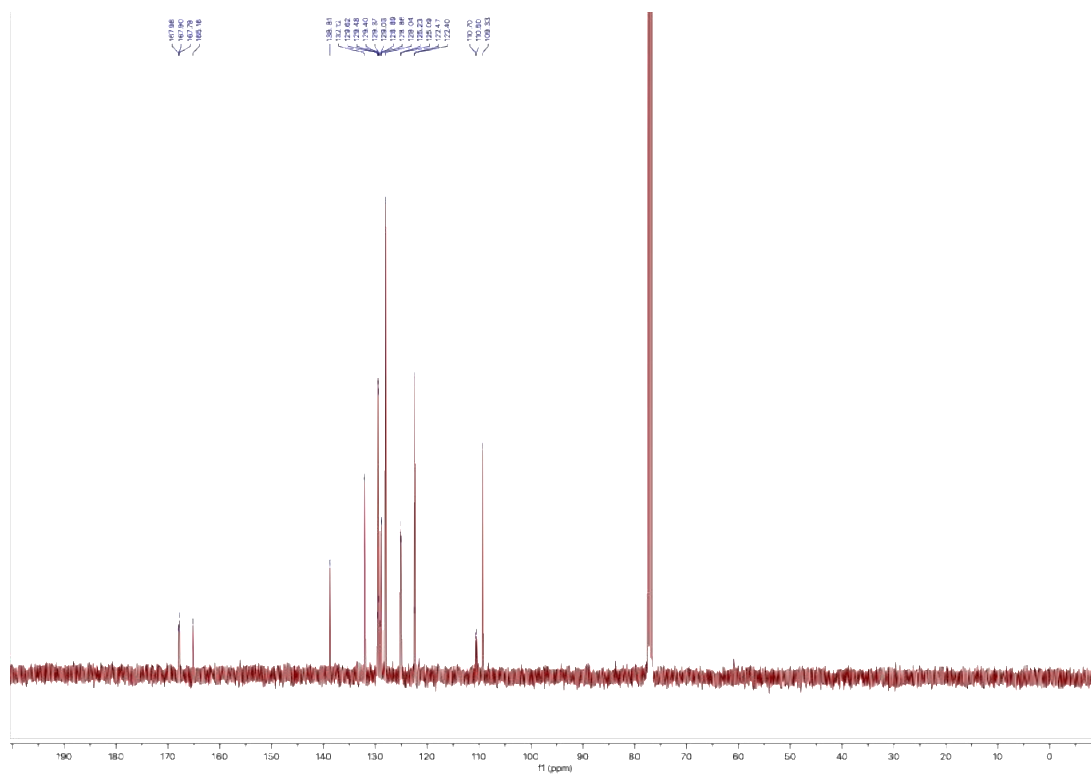
^{19}F NMR (377 MHz, CDCl_3) of **3.7**



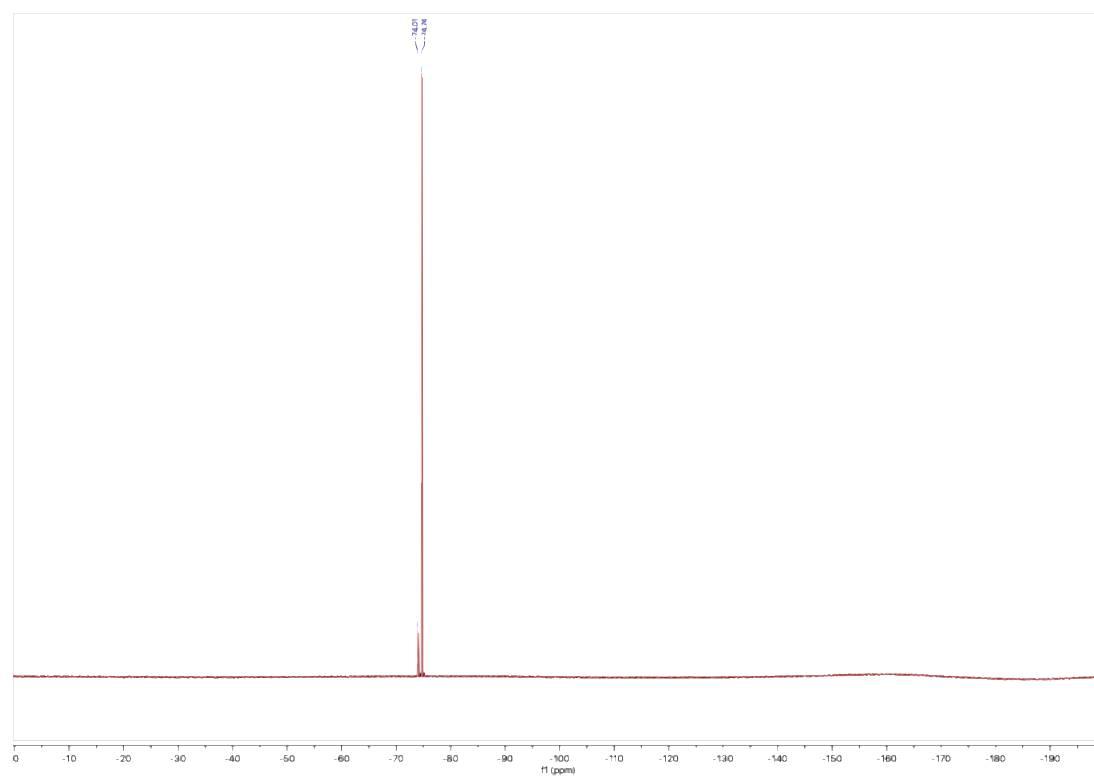
^1H NMR (400 MHz, CDCl_3) of oxindole **3.5a**



^{13}C NMR (101 MHz, CDCl_3) of oxindole **3.5a**



^{19}F NMR (377 MHz, CDCl_3) of oxindole **3.5a**



4 Accessing Fluoroformates via *in situ* Generated Difluorophosgene

4.1 Contributions

The final chapter of this dissertation details work on the synthesis of fluoroformates from alcohols using a difluorocarbene source and oxidant pair, as well as some preliminary investigation into their fluoride recycling reactivity in comparison to the analogous carbamoyl fluorides. Initial screening reactions were done in collaboration with undergraduate student Darnella Devito. My contributions include all other experiments in the chapter.

4.2 Introduction

As previously discussed, among fluorine-containing reagents, heteroatom-carbonyl fluorides like carbamoyl fluorides have found use as carbonyl electrophiles under catalytic conditions. Their use in organic synthesis has been spurred by both their relative stability in comparison to carbonyl chlorides, as well as their unique fluoride-enabled reactivity.¹ Additionally, carbamoyl fluorides can be used as bifunctional reagents (both a carbamoyl source and a fluoride source), enabling the fluorocarbonylation of various π -bonds under select conditions (Chapter 2).² While the chemistry of carbamoyl fluorides has been developed, studies applying the analogous heteroatom-carbonyl fluorides, fluoroformates in particular, remain limited. Fluoroformates have proven advantageous as carboxylation reagents, enabling access to carbonates through fluoride-driven reactivity (*vide infra*). Additionally, they can serve as alkyl sources—or “R” fragments—via decarboxylation.³ This introduction will introduce fluoroformates as a potential synthon for unactivated alkyl fluorides, as well as highlight the limited methods to access them.

4.2.1 Potential Pathways for Fluoroformate Reactivity

Fluoroformates have been documented to function both as “RCO₂” sources in esterification reactions and as “R” sources in alkylation reactions. In esterifications, fluoroformates can be activated via nucleophilic acyl substitution (NAS) by a suitable nucleophile, serving as alkoxycarbonyl donors. While acyl fluorides can undergo decarbonylation under transition-metal catalysis to generate “R” or carbon fragments,⁴ fluoroformates are capable of acting as “R”/alkyl sources without the use of transition metals. Two mechanistic pathways have been proposed

(Figure 4.1): 1. S_N2 -type direct attack on an activated ester intermediate generated from the reaction of the fluoroformate with a suitable activator or 2. via fluoride abstraction followed by CO_2 extrusion from carboxylate **161**, leaving a carbocation that can be attacked in an S_N1 fashion. Alternatively, S_N2 attack of carboxylate **161** can occur, leading to the extrusion of CO_2 .

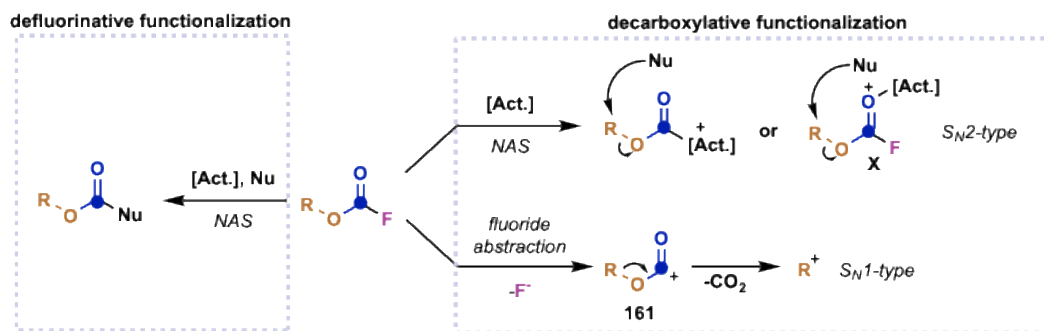


Figure 4.1. Defluorinative functionalization vs. decarboxylative functionalization of fluoroformates.

4.2.2 Fluoroformates in Esterification Reactions (Defluorinative Functionalization)

4.2.2.1 C–O/C–N Bond Forming Reactions

Initial investigations into using fluoroformates as alkoxycarbonyl sources was pioneered by Olofson starting in 1980 with the synthesis of enol carbonates **183** from fluoroformates and silyl enol ethers **182** using a fluoride catalyst (Figure 4.2).⁵ The reaction is initiated by fluorination of the silyl enol ethers with benzyltrimethylammonium fluoride ($BnNMe_3F$) forming either the naked enolate or a pentavalent silicon anion which can also act as an *O*-nucleophile. The fluoroformates are then able to undergo NAS with the nucleophile generating the enol carbonate product. Only a catalytic amount of $BnNMe_3F$ is required for the reaction given that an equivalent of fluoride is generated by the starting material upon NAS.

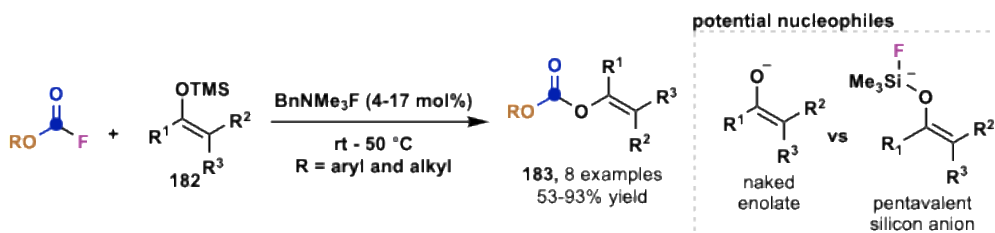


Figure 4.2. Synthesis of enol carbonates **183** from fluoroformates and silyl-enol ethers **182**.

In 1990, Olofson reported that aldehydes could also act as *O*-nucleophiles for the synthesis of 1-alkenyl carbonates **184** in the presence of KF and catalytic crown ether as a phase transfer catalyst (Figure 4.3).⁶ The reaction was more efficient with fluoroformates when compared to the analogous chloroformates, often requiring shorter reaction times. Additionally, when fluoroformates were used, the reaction could be run in DMSO, removing the need for a phase transfer catalyst.

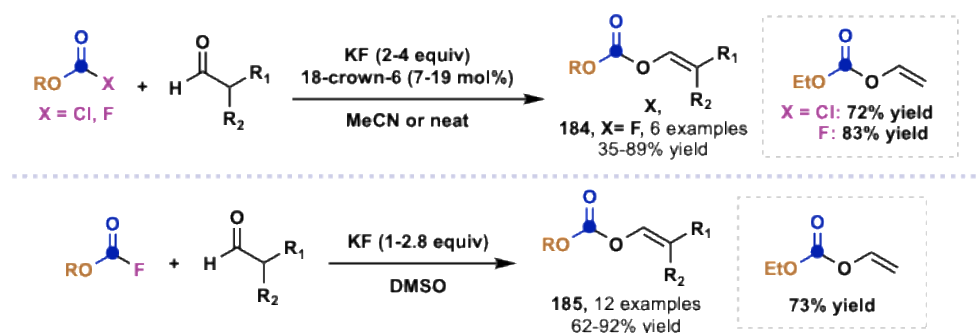


Figure 4.3. Synthesis of 1-alkenyl carbonates **184** from fluoroformates and aldehydes.

The fact that fluoroformates tolerate DMSO as a solvent is notable because chloroformates are not inert in DMSO or other tertiary amide solvents (). Chloroformates readily acylate DMF and related tertiary amides, yielding Vilsmeier intermediates **186** which react with water to give aldehydes.⁷ Similarly, the highly exothermic reaction between DMSO and chloroformates produces adducts **187** that can undergo Pummerer-type rearrangements.⁸ Olofson and Dang first exploited this stability towards the alkoxycarbonylation of polar compounds like glucose (Figure 4.4),⁹ which were not amenable to alkoxycarbonylation with chloroformates in non-polar solvents. The use of fluoroformates as alkoxycarbonyl source has enabled the synthesis of compounds like dextran alkyl carbonates⁷ and polysaccharide carbonates.¹⁰ Similar conditions were also used to form C–N bonds in carbamates using secondary and primary amines as the nucleophile in NAS reactions with fluoroformates.

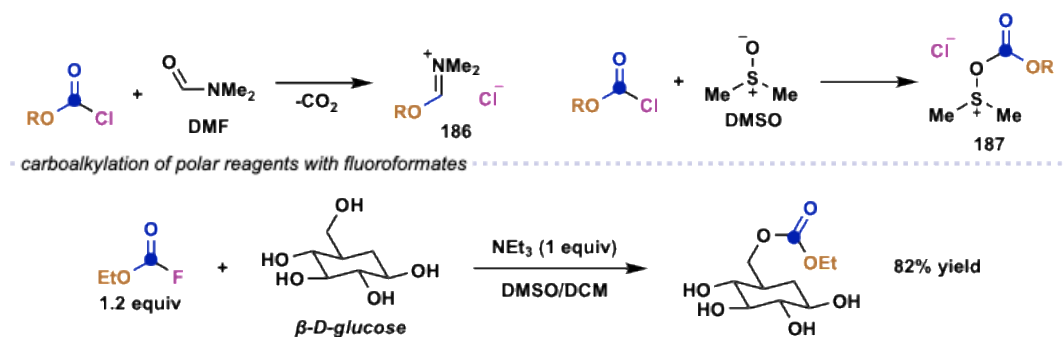


Figure 4.4. Reactions of chloroformates with DMF and DMSO and alkoxycarbonylation of glucose with ethyl fluoroformate.

4.2.2.2 C–C Bond Forming Reactions

While the analogous chloroformates are commonly employed in catalytic esterification and carboxylation reactions for the synthesis of C–C bonds, only two examples exist for fluoroformates. The seminal work was described by Buchwald and co-workers in 2021 on the CuH-catalyzed enantioselective hydroesterification and hydrocarboxylation of allenes **188** (Figure 4.5).¹¹ Notably, the sole fluoroformate explored in that study—adamantyl fluoroformate **189**—is also the only commercially available fluoroformate. Screening experiments indicated that adamantyl fluoroformate exhibits higher reactivity than other carbonyl electrophiles such as diphenyl carbonate, Boc-anhydride, and methyl chloroformate. Initial hydrocupration of the allene gives organocuprate intermediate **192**, which is an effective nucleophile for the NAS of adamantyl fluoroformate. The advantage of fluoroformates for this reaction lies in formation of a Cu^{II}–F species via β -fluoride elimination from intermediate **193**, which reacts rapidly with Si–H to regenerate the active Cu–H catalyst and R₃Si–F. The formation of a strong Si–F bond serves as a key driving force for the reaction and is not as feasible with chloroformates, which require the addition of an exogenous base to achieve turnover. This example contrast underscores the unique potential of fluoride-enabled reactivity for fluoroformates.

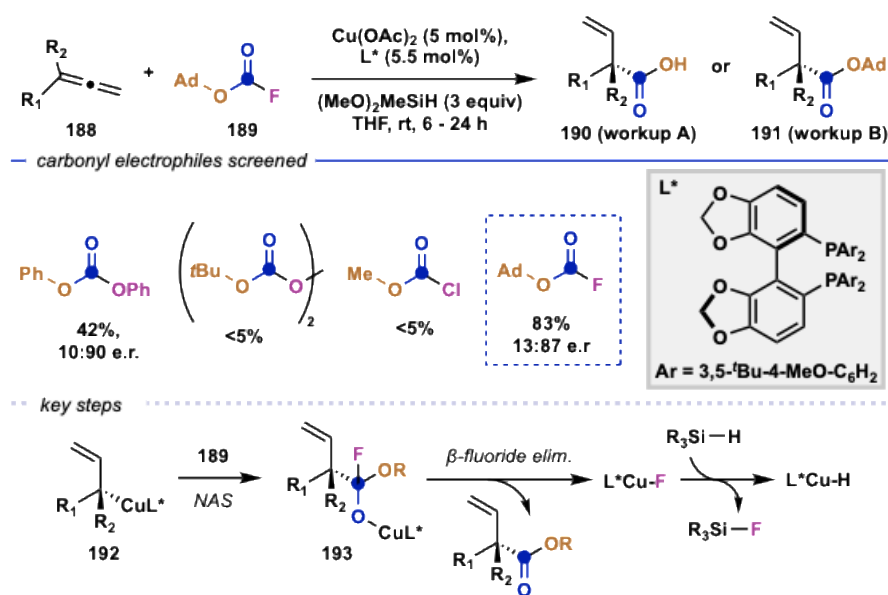


Figure 4.5. CuH-catalyzed enantioselective hydroesterification and hydrocarboxylation of allenes with adamantyl fluoroformate; workup A: NH₄F/MeOH workup followed by hydrolysis using TFA; workup B: NH₄F/MeOH workup.

In 2025, a second report of fluoroformates being used as carboxylation reagents was published by Shin and co-workers; this time for the synthesis of quaternary α -cyano esters (Figure 4.6).¹² In their case, an initial regioselective hydronickelation of α,β -unsaturated nitrile **194** forms organo-Ni-intermediate **196** which is in equilibrium with a rearranged nickel-keteneimine species **197**, an effective nucleophile for NAS with adamantyl fluoroformate. Catalyst turnover is once again promoted by the reaction of the resulting Ni^I-F species with hydrosilane, regenerating the active Ni^I-H species, as well as generating a Si-F byproduct. Co-screening of *t*-butylchloroformate resulted in no product formation. Similar to the earlier Buchwald report, the only fluoroformate employed under the reactions conditions is the commercially available adamantyl fluoroformate. Notably this reaction works well with both acyl and carbamoyl fluorides, one of the few examples of a catalytic system that works well across a range of carbonyl fluoride electrophiles.

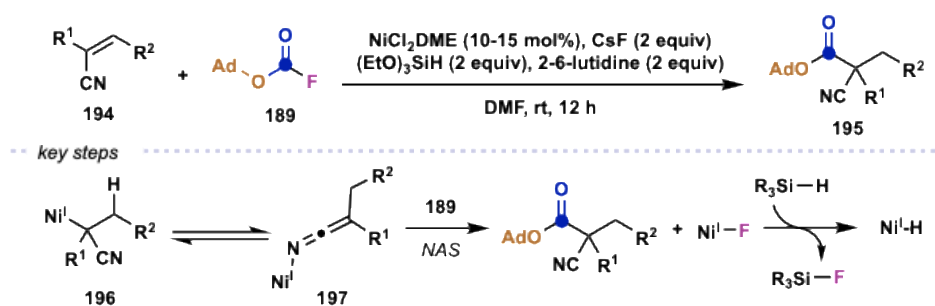


Figure 4.6. NiH-catalyzed hydroesterification of α,β -unsaturated nitriles with adamantyl fluoroformates.

4.2.3 Fluoroformates as Dual Function Reagents

There is one singular example of fluoroformates undergoing carbofluorination reactions. In 2005, Navarrini and coworkers found that in the presence of catalytic CsF, methylfluoroformate will undergo a formal addition across tetrafluoroethylene (TFE) (Figure 4.7).¹³ The reaction similar to the previously discussed class of [M]-F catalyzed carbofluorination reactions with (Chapter 1.3).

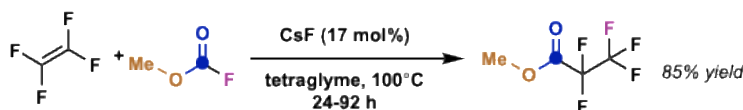


Figure 4.7. Atom-economical carbofluorination of TFE and fluoroformates.

In the same report, Navarrini and co-workers also found that fluoroformates could be used as alkylating reagents for the transformation perfluoroacyl fluorides, perfluoroketones, and fluoroolefins to the respective

hydrofluoroethers and hydrofluoroalkanes in the presence of catalytic KF or CsF.¹³ With carbonyl **198**, the reaction is initiated by the addition of fluoride as a nucleophile to the C=O bond, creating fluorinated alkoxide **200**, which is in equilibrium with the starting carbonyl compound (Figure 4.8). Experimental evidence supports the formation of fluoroether **201** via attack on the α carbon of the fluoroformates from fluorinated alkoxide **200**. The use of tetraglyme as the solvent for this reaction is important to both support the formation of alkoxide **200** as well as the solvation of the metal fluoride salt catalyst. While these reactions do not constitute carbofluorination reactions, the transformation is a fluoride-shuttling reaction, given KF or CsF is present only in catalytic amounts and fluoride is regenerated after the addition of the nucleophile.

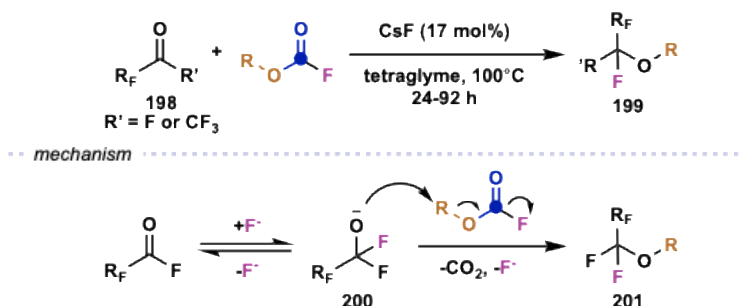


Figure 4.8. Formation of hydrofluoroethers **199** via decarboxylation Lewis-acid catalyzed fluoride shuttling from fluoroformates.

Fluoroformates can also be used as both an “R” source and as a fluoride source to form aryl and alkyl fluorides from the parent fluoroformate via decarboxylation. This reactivity was first explored by Jensen and co-workers, who in a series of communications in 1954 and 1955, showed that isolated alkyl fluoroformates could be activated to form alkyl fluorides in the presence of catalytic BF_3 ¹⁴ or pyridine¹⁵ (Figure 4.9). In the case of pyridine, the authors hypothesize that the fluoroformate undergoes the NAS activation pathway. The α -carbon of the resulting pyridinium acyl salt is rendered electrophilic and susceptible towards S_N2 attack by the liberated fluoride. In contrast, for BF_3 , the authors propose that the reaction may either occur via the S_N2 pathway from a Lewis-adduct between the catalyst and the substrate, or via the S_N1 pathway from a fluoride abstraction. Olofson in 2002 showed that alkyl fluoroformates could be converted to alkyl fluorides in the presence of catalytic hexabutylguanidinium fluoride (HBGF) at high temperatures.¹⁶

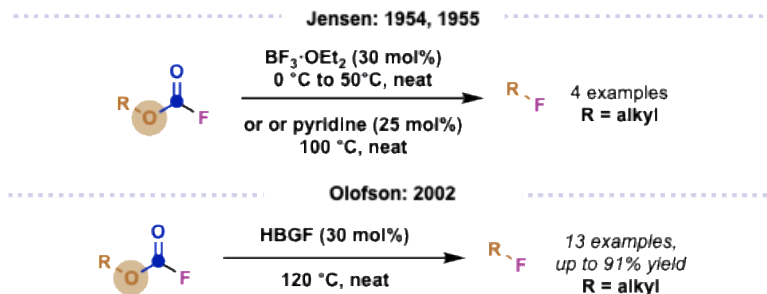
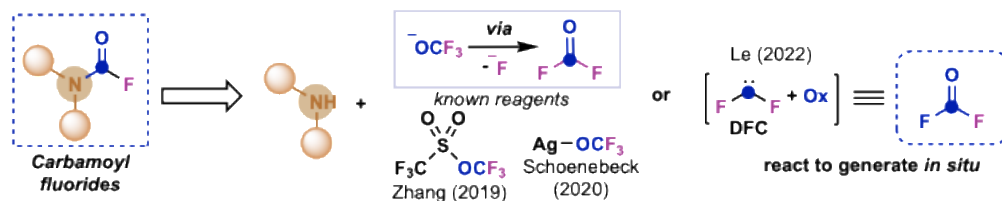


Figure 4.9. Lewis acid and Lewis base catalyzed decarboxylation of fluoroformates to make alkyl fluorides.

The activation of aryl fluoroformates to undergo decarboxylation to yield fluoroarenes requires much more forceful conditions than alkyl fluoroformates. In 1965, Christie and Pavlath reported that fluoroformates could be converted into aryl fluorides under thermal conditions when heated in a quartz flow reactor coated with Pt-gauze.^{17,18} In 1985, Ryan and co-workers showed that aryl-fluoroformates could be transformed to fluoroarenes in flow using alumina or alumina-based catalysts as well.¹⁹ Given the forceful conditions found in both of these reports, both of these methods are scarcely used, especially since the advent of specialized deoxyfluorination reagents which can enable the conversion of phenols to aryl fluorides.

4.2.4 Fluoroformate Synthesis

Interest in carbamoyl fluorides as electrophiles—and, to a lesser extent, as bifunctional reagents—has been fueled over the past decade by the development of new synthetic strategies utilizing easy-to-handle reagents.^{20,21} Prime among these is the development of reagents that liberate difluorophosgene (COF_2) *in situ*, allowing for the direct fluorocarbonylation of secondary amines. Reagents like trifluoromethyl triflate²² and AgOCF_3 ²³ act as direct reservoirs for COF_2 , while difluorocarbene (DFC) surrogates generate COF_2 *in situ* when paired with an appropriate oxidant (Scheme 4.1). In contrast, synthetic methods for the formation of fluoroformates and fluorothioformates via COF_2 fluorocarbonylation are particularly limited.



Scheme 4.1. Modern COF_2 reservoirs used for the synthesis of carbamoyl fluorides.

While fluoroformates can be synthesized from chloroformates via halogen exchange in the presence of excess fluoride,^{24,25} aside from their solvent incompatibilities, alkyl chloroformates are thermally unstable. Primary and secondary chloroformates are known to decompose to alkyl chlorides/alkenes and CO₂ when heated²⁴ and tertiary alkyl chloroformates like *t*-butylchloroformate are known to decompose at room temperature.²⁵ While fluoroformates have been shown to be accessible via direct use of COF₂ or COFCl, these reagents pose their own challenges.³ Namely, COF₂ is similarly toxic to phosgene, and both COF₂ and COFCl are difficult to handle and source commercially. Historically, the limitation on synthesis of fluoroformates primarily stems from the practical inaccessibility of generating COF₂ *in situ* in a manner that does not also promote deoxyfluorination or other fluorinative side reactions.

The first comprehensive study on the synthesis and isolation of fluoroformates from alcohols directly from COF₂ was published by Olofson in 2002 (Figure 4.10).¹⁶ Fluoroformates were obtained in excellent yields from aliphatic alcohols via treatment with COF₂ generated *ex situ* from the phosgene surrogate bis(trichloromethyl) carbonate and KF. COF₂ was condensed and delivered dropwise into a reaction vessel containing the alcohol and excess KF in ether, the latter serving as an acid scavenger. Aside from the safety hazards posed by condensing COF₂, particularly on scale, the method performs poorly with phenols, limiting its applicability for the synthesis of aryl fluoroformates.

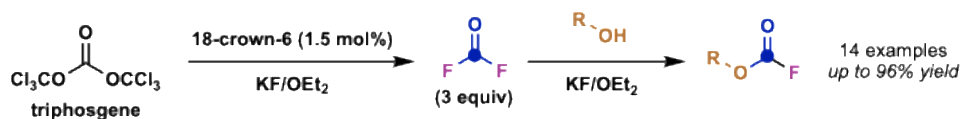


Figure 4.10. Formation of COF₂ *ex situ* for the synthesis of fluoroformates.

While fluoroformates have shown to be synthesized from alcohols in the presence of COF₂ reservoirs, they typically are a transient intermediate in deoxyfluorination reactions. In 2020, Chen and co-workers found that aliphatic alcohols could be converted into alkyl fluorides **203** via deoxyfluorination with COF₂ liberated from perfluoroalkyl ether carboxylic acids (PFECAs) in the presence of tetramethylammonium fluoride (TMAF).²⁶ The authors found that PFECAs can undergo thermal decomposition at >120 °C to generate COF₂ which then reacts with the alcohol to form fluoroformate **202**. While the fluoride additive is not necessary given that an equivalent of

fluoride is liberated in the reaction, its addition helps to outcompete the formation of trifluoromethyl ether by-product **204**.

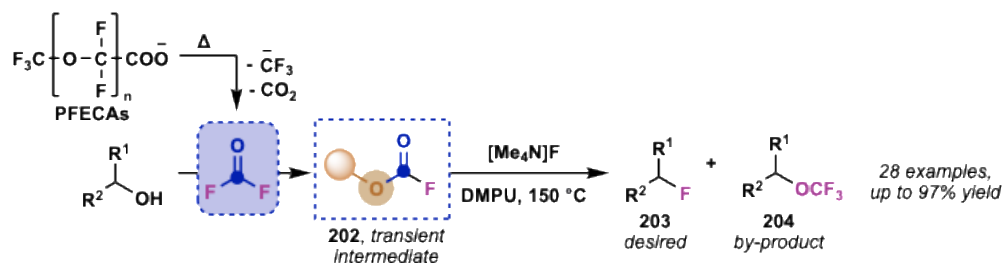


Figure 4.11. PFECAs used for the formal deoxyfluorination of alcohols via a fluoroformate transient intermediate.

In 2023, Zhang and co-workers reported that trifluoromethyl trifluoromethanesulfonate (CF₃SO₂OCF₃, **205**) can also promote the formation of alkyl fluorides in the presence of 2-(*tert*-butyl)-1,1,3,3-tetramethylguanidine (BTMG) via a formal deoxyfluorination pathway involving a transient fluoroformate intermediate (Figure 4.12).²⁷ In this reaction BTMG both activates CF₃SO₂OCF₃ to release COF₂ and promotes fluoroformate activation towards S_N2-type fluoride attack via the formation of the activated *N*-acylammonium **207**, generating the deoxyfluorination product **206**.

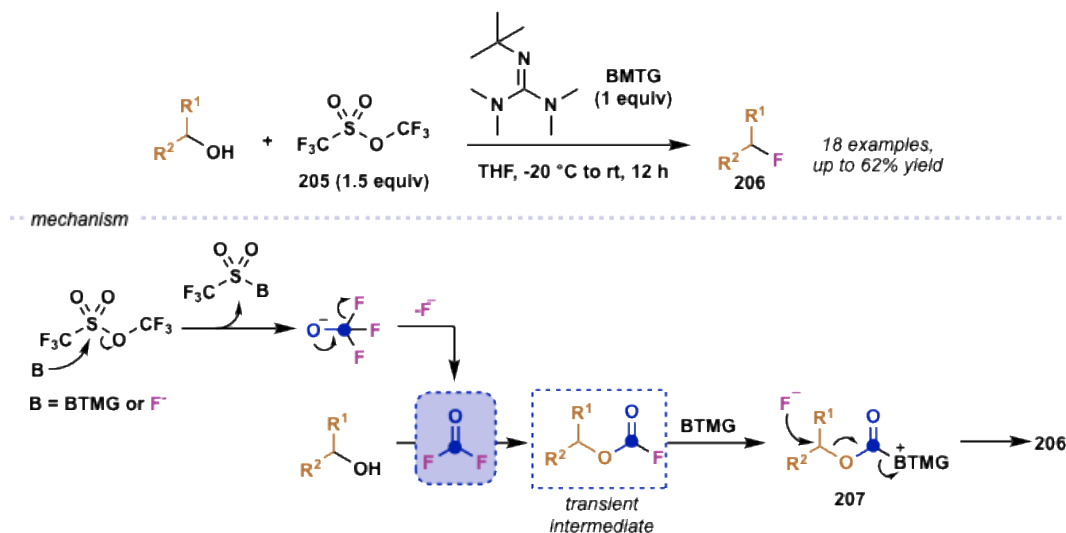


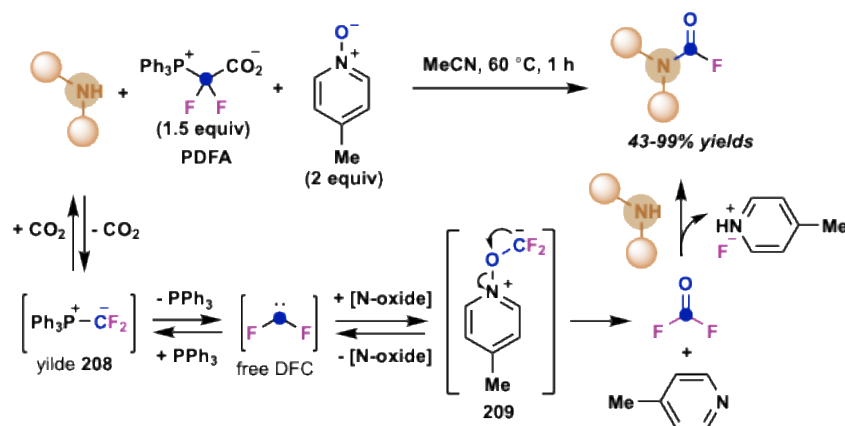
Figure 4.12. CF₃SO₂OCF₃ used for the formal deoxyfluorination of alcohols via a transient fluoroformate intermediate.

4.3 Methods and Motivation

Our interest in fluoroformates stemmed from their potential as a new class of heteroatom-carbonyl fluorides to activate under Lewis acid catalysis for carbofluorination reactions, particularly their use as unactivated alkyl

fluoride synthons. However, we found that literature-reported methods for their preparation were prohibitive towards this goal. Inspired by work previously published by our own lab, we sought to investigate the feasibility of generating fluoroformates from alcohols via COF_2 generated *in situ* from a DFC/oxidant pair under mild reaction conditions. In turn, we hoped that development of a reliable method for their formation under mild conditions would allow us to study their reactivity as bifunctional reagents and assess their general stability and reactivity profiles.

In 2022, the Le group established (triphenylphosphonio)difluoroacetate (PDFA) and pyridine *N*-oxides as a competent DFC/oxidant pair for the *in situ* formation of COF_2 .²⁸ Under the reported reaction conditions, it was proposed that PDFA undergoes thermal decarboxylation to generate an equilibrium mixture of phosphonium ylide **208** and free DFC. The free DFC is then trapped by 4-methylpyridine-*N*-oxide to form zwitterionic species **209**, which subsequently decomposes to release 4-methylpyridine and COF_2 . The generated COF_2 is then captured by the secondary amine to form a carbamoyl fluoride, while the liberated 4-methylpyridine acts as a scavenger for the HF produced during the reaction, resulting in the formation of a pyridinium fluoride salt (Scheme 4.2).



Scheme 4.2. Synthesis of carbamoyl fluoride via difluorocarbene source and oxidant pair.

PDFA was initially selected as the DFC source for carbamoyl fluorides due to its accessibility: it can be synthesized on scale from inexpensive starting materials and is operationally straightforward, being a non-hygroscopic reagent that can be stored and weighed easily on the benchtop. However, a significant drawback of the reaction is the formation of PPh_3 as a byproduct, complicating purification. Removal of PPh_3 is typically done via column chromatography or via reoxidation to O=PPh_3 in the presence of H_2O_2 (30% w/v) which can be removed

via a plug of silica. Fluoroformates, typically isolated by distillation, often decompose to their parent alcohol under standard silica gel chromatography conditions, as well as base-neutralized silica, complicating the use of PDFA.

Seeking to eliminate the formation of PPh_3 as a by-product from the reaction, we turned to other known DFC precursors that can be activated under mild conditions. Of those, trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) appeared particularly attractive. TFDA was developed in 2000 by Dolbier and Chen, who found that under mild conditions and in the presence of catalytic fluoride it forms difluorocarbene, which can then be used in the synthesis of *gem*-difluorocyclopropanes **210** (Figure 4.13).²⁹ In the presence of catalytic NaF, TFDA undergoes fluoride-initiated decomposition releasing TMS-F and carboxylate **211**, which undergoes facile decomposition to release difluorocarbene as well as SO_2 , CO_2 , and fluoride, all byproducts that can be readily removed under reduced pressure by rotary evaporation which was particularly appealing for the synthesis of fluoroformates.²⁹

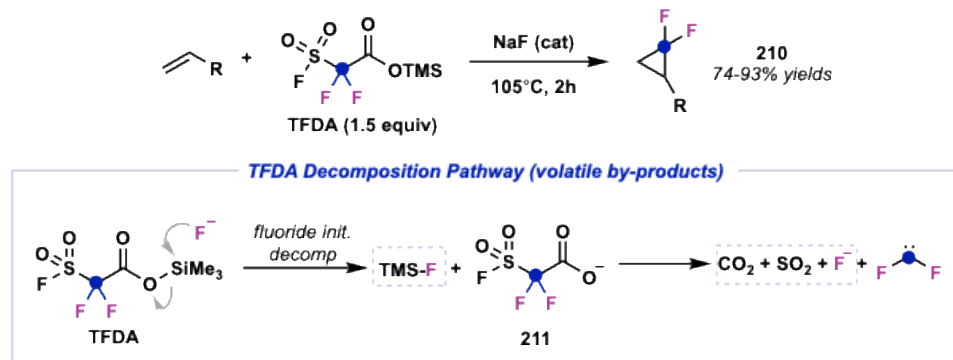


Figure 4.13. TFDA for the synthesis of *gem*-difluorocyclopropanes and decomposition in the presence of catalytic fluoride.

In the years since TFDA's introduction, it has been used for a range of classic *O*-,^{30,31,32} *N*-,³³ and alkene/alkyne *gem*-difluoromethylation reactions.^{34,35} For example, TFDA can be used for the *O*-difluoromethylation of simple ketones containing an α -hydrogen (**212**) as disclosed by Ichikawa and co-workers (Figure 4.14, top).^{30,31} The authors propose that difluorocarbene is captured by the ketone, forming oxocarbenium **213** which then undergoes a 1,4-proton migration to yield the stable difluoromethyl enol ethers **214**. When an NHC is used for the generation of difluorocarbene, difluorocyclopropanation of the final product is suppressed, but when NaF is used as a catalytic initiator for the generation of difluorocarbene, the resulting difluoromethyl enol ethers readily undergo a further [2+1] cycloaddition with difluorocarbene to give difluoromethyl 2,2-difluorocyclopropyl ethers **215** (Figure 4.14, bottom).³²

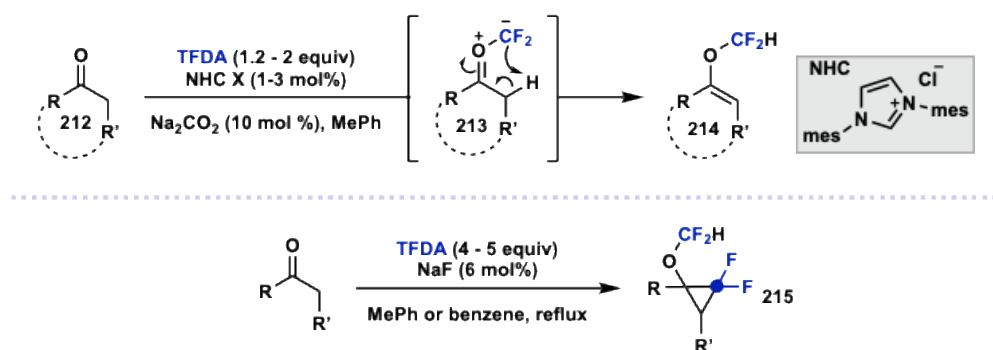
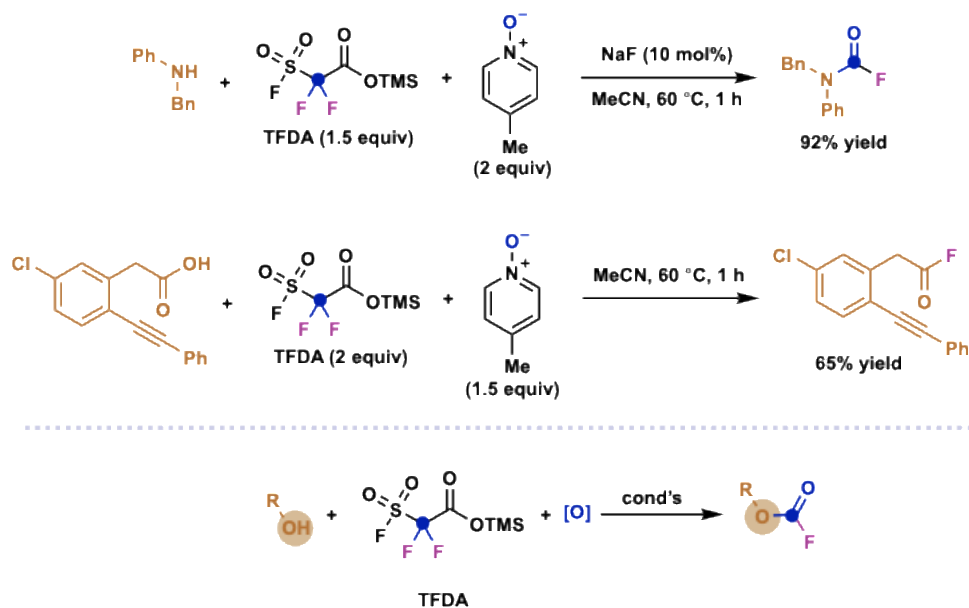


Figure 4.14. *O*-Difluoromethylation of ketones with TFDA.

Additionally, the oxidation of difluorocarbene generated from TFDA to COF_2 is known. While screening of DFC sources for the formation of carbamoyl fluorides with a DFC source, Le and co-workers found that the combination of TFDA and 4-Me-pyridine *N*-oxide gave rise to *N*-benzyl-*N*-phenyl carbamoyl fluoride in 92% yield, comparable to the optimized conditions (99% yield).²⁸ With minor changes to the stoichiometry of the reagents, the combination of TFDA and 4-Me-pyridine *N*-oxide was also used to promote the formal deoxyfluorination reaction of carboxylic acids to acyl fluorides (Scheme 4.3).³⁷ Building off of these results, our initial goal was to find an optimal system for the fluorocarbonylation of alcohols.



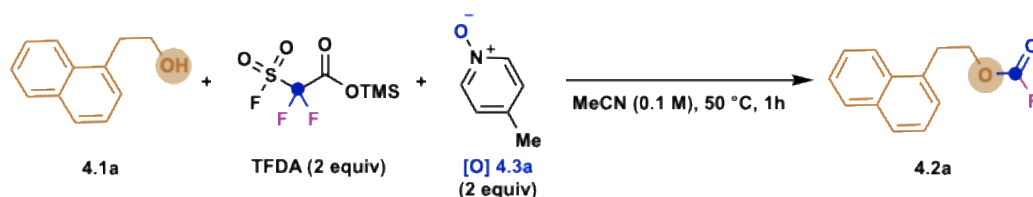
Scheme 4.3. TFDA and oxidant pair for the synthesis of carbamoyl fluorides and for acyl fluorides; as well as the proposed reaction to synthesize fluoroformates.

4.4 Results and Discussion

4.4.1 Optimization of Reaction Conditions

Initial investigations were conducted using commercially available solid primary alcohol **4.1a** as model substrate. The reactions were performed on 0.1 mmol scale. Given the lack of fluoride handle on the starting material, conversion and yield were determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard, which also gave insight into non-fluorinated products of the reaction. Quantitative ^1H NMR spectroscopy was run using a single-scan experiment with a 10 second relaxation delay. We were pleased to find that treatment of **4.1a** with TFDA and catalytic NaF in the presence of 4-methylpyridine *N*-oxide as the oxidant resulted in formation of **4.2a** in 28% yield (Table 4.1, entry 1). Notably, when the same reaction was conducted in the absence of NaF, **4.2a** was still obtained in an improved yield of 34% (Table 4.1, entry 2), indicating that exogenous fluoride is not required under these conditions. One downside of TFDA as the difluorocarbene source for the reaction is that it is a relatively expensive reagent in comparison to PDFA and, as a volatile liquid, requires special handling considerations. To evaluate other DFC sources for fluoroformate synthesis we evaluated the benchtop stable PDFA (Table 4.1, entry 3). Ultimately, no observable product formation occurred, avoiding complications associated with purification of PPh_3 derived from PDFA decomposition. Likewise, attempts to use TMSCF_3 with NaI as an activator resulted in no product formation (Table 4.1, entry 4). Similar results were obtained when $\text{BrCF}_2\text{CO}_2\text{Et}$, which generates difluorocarbene upon treatment with K_2CO_3 , was employed in place of TFDA (Table 4.1, entry 5). Finally, use of AgOCF_3 as a COF_2 reservoir resulted in 53% conversion and 15% yield of **4.2a** (Table 4.1, entry 6).

Table 4.1. Difluorocarbene source screen for synthesis of fluoroformate **4.2a**.



Entry*	Deviation from Standard Conditions	Conv. (%)	Yield (%)
1	Add NaF (10 mol%)	30	28
2	none	41	34
3	PDFA instead of TFDA	32	0
4	TMSCF ₃ (2 equiv) + NaI (0.2 equiv) instead of TFDA	20	0
5	BrCF ₂ CO ₂ Et (2equiv) and K ₂ CO ₃ (2 equiv) instead of TFDA	5	0
6	AgOCF ₃ (2 equiv.) instead of TDFA and 4-Me-Pyr-N,O	53	15

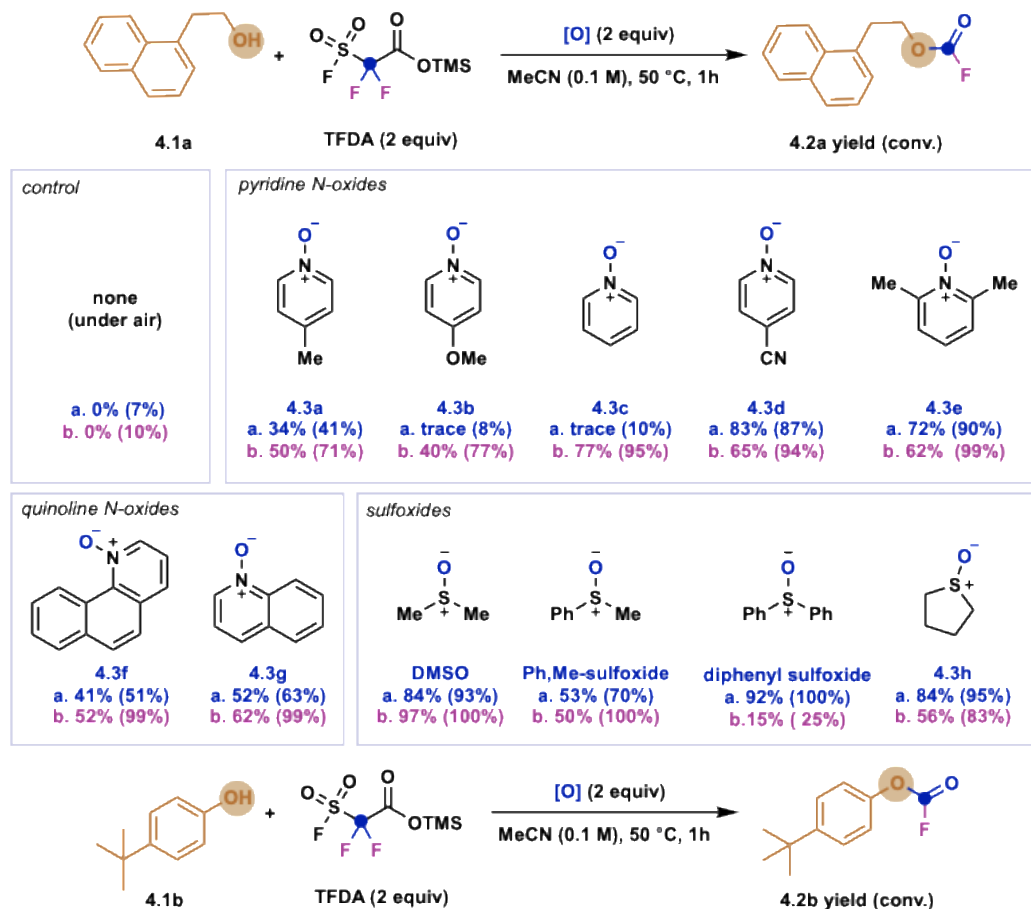
*All reactions run at 0.1 mmol in a sealed 1-dram vial at 50 °C for 1 h, conversion and yield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

Interested in pursuing this initial hit, we turned to exploring other oxidants, as fine-tuning the oxidant pair had proven key for improving carbamoyl fluoride yields (Scheme 4.4). Screening pyridine *N*-oxide derivatives, we found that the electron-deficient 4-cyanopyridine *N*-oxide **4.3d** led to an increased yield of 83%. In contrast, electron-rich 4-methoxypyridine *N*-oxide **4.3b** and the electronically neutral pyridine *N*-oxide **4.3c** both resulted in only trace formation of **4.2a**. In the case of 4-methoxypyridine *N*-oxide **4.3b**, <5% of the alkyl fluoride was also present at the end of the reaction. Increasing the steric demand around the nitrogen by use of 2,6-methylpyridine *N*-oxide **4.3e** or 1,10-phenanthroline *N*-oxide **4.3f** led to moderate yields as well. The trends among the pyridine and quinoline bases show that the generation of a strong or accessible base over the course of the reaction is detrimental to the yield of fluoroformate, which is in line with previous studies where pyridine bases are shown to enable the decomposition of alkyl fluoroformates via NAS reactivity.¹⁵

Interested in getting rid of the pyridine base altogether from the reaction, given the propensity of our substrate to undergo base promoted elimination to form an alkene, we switched to sulfur-based oxidants which had previously been shown to work as effective oxidants for the formation of carbamoyl fluorides with PDFA as the DFC source.²⁸ DMSO was of particular interest, given that upon reduction it forms dimethyl sulfide, which is a volatile by product. When used as the oxidant for TFDA, DMSO gave **4.2a** in 84% yield. Swapping to methylphenyl sulfide gave 53% yield, while diphenyl sulfide afforded full conversion to **4.2a** in 92% yield. Use of cyclic

tetramethylene sulfoxide also led to comparable yields to DMSO (84%), but the resulting sulfide was not as volatile and was not considered in further screening.

Scheme 4.4. Oxidant screen for the fluorocarbonylation of **4.1a** and **4.1b**

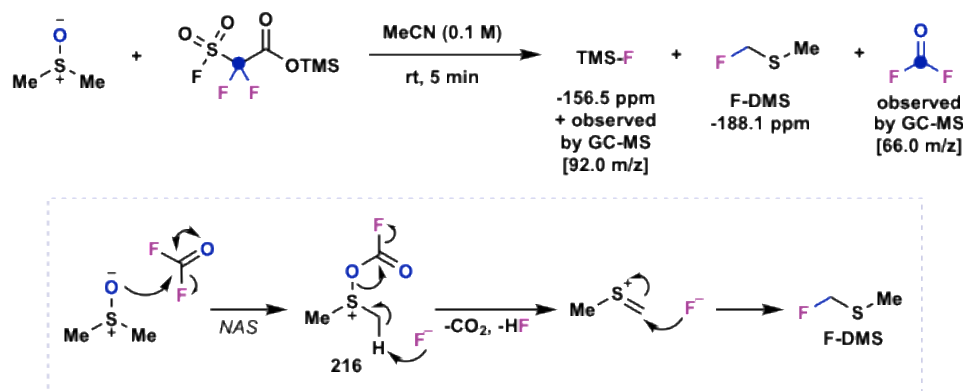


*All reactions run at 0.1 mmol in a sealed 1-dram vial at 50 °C for 1 h, conversion and yield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as internal standard; a. (blue) **4.1a** used as substrate; b. (purple) **4.1b** used as substrate.

To probe the applicability of our conditions for the formation of aryl fluoroformates, we tested 4-*t*-butylphenol **4.1b** with the three best performing oxidants: DMSO, diphenyl sulfoxide, and 4-CN-pyridine *N*-oxide **4.3d**. While DMSO gave the best yield of **4.2b** at 97%, there were major differences in the yields between **4.2b** and **4.2a** for diphenyl sulfoxide, and 4-CN-pyridine *N*-oxide **4.3d** and so we performed a second oxidant screen with 4-*t*-butylphenol **4.1b**. Although we observed markedly different reactivity trends among the pyridine *N*-oxide derivatives where the electronically neutral pyridine *N*-oxide **4.3c** gave the best yields at 77%, we ultimately selected DMSO as the optimal oxidant due to its superior performance with both **4.1a** and **4.1b**. Given the

substantial difference in reactivity between phenols **4.1b** and aliphatic alcohol **4.1a**, all subsequent optimization studies were conducted in parallel on both substrates.

Next, we turned our attention to a temperature screen. Interested in whether our reaction conditions could promote the room temperature generation of COF₂ from TFDA, we first treated TFDA with 1 equivalent of DMSO at room temperature in MeCN (Scheme 4.5). Gas evolution was observed almost immediately, and subsequent ¹⁹F NMR and GC-MS analysis of the reaction mixture at a 5-minute time point revealed that only trace amounts of TFDA remained (>99% conv.). Analysis of the ¹⁹F NMR spectrum revealed signal overlap in the region of the TMS-F resonance (−156.5 ppm), which may indicate the presence of trace amounts of Teflon generated during the reaction, as fluorinated polymers appear in this region as well. In addition to TMS-F, it is likely that F-DMS (−188.1 ppm) is also present in the reaction mixture. Formation of this species is consistent with a Pummerer-type rearrangement of intermediate **216** and aligns with prior studies by Lange and Shreeve on the reactions of COF₂ with DMSO.³⁸ A third fluorinated species was observed in the ¹⁹F NMR spectrum at −58.8 ppm, which falls within the expected chemical shift range for a trifluoromethoxy-containing compound; however, the identity of this species could not be determined. Although COF₂ was not directly observed by ¹⁹F NMR spectroscopy, both TMS-F and COF₂ were detected by GC-MS analysis, confirming the generation of COF₂ under these conditions.



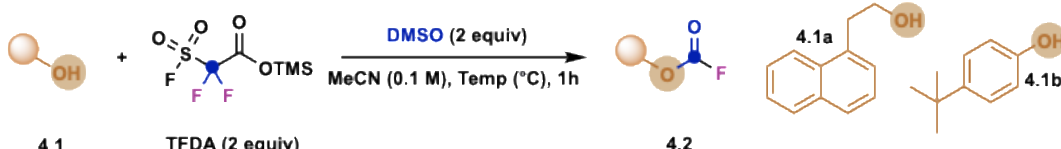
Scheme 4.5. Reaction of DMSO and TDFA at room temperature in MeCN.

With this information in hand, a temperature screen was conducted (Table 4.2). Lowering the reaction temperature to room temperature for aliphatic alcohol **4.1a** afforded yields comparable to those obtained at 50 °C (83%), with a marginally higher conversion of 97% (Table 4.2, entry 1). Overall, alcohol **4.1a** was converted to

fluoroformate **4.2a** in good yields across the entire temperature range examined, although temperatures above 40 °C resulted in slight decreases in both yield and conversion. This behavior is consistent with a low activation barrier for nucleophilic attack of the aliphatic alcohol on COF₂, such that product formation is efficient even at ambient temperature. Elevated temperatures therefore provide minimal benefit while promoting minor decomposition pathways or competing fluoride-mediated processes, resulting in slightly diminished efficiency under the conditions.

The reaction temperature used for the rest of the screening with **4.1a** was 30 °C (Table 4.2, entry 2). In contrast, phenol **4.1b** demonstrated a pronounced sensitivity to temperature. At room temperature, the yield dropped significantly to 25% (Table 4.2, entry 1). Increasing the temperature to 30 °C and then to 40 °C (Table 4.2, entries 2–3) led to substantial improvements in yield. These improvements are consistent with the reduced nucleophilicity of phenols relative to aliphatic alcohols, necessitating higher temperatures to achieve productive reaction with COF₂. Nevertheless, the yields obtained at these intermediate temperatures remained below those obtained at 50 °C (Table 4.2, entry 4), indicating that sufficient thermal activation is required to overcome the higher barrier associated with the phenol vs the aliphatic alcohol. Further increasing the temperature to 60 °C resulted in diminished yields (Table 4.2, entry 5). Consequently, 50 °C was identified as the optimal reaction temperature for phenol **4.1b** and was the temperature used moving forward in the rest of the screening.

Table 4.2. Temperature Screen for **4.1a** and **4.1b**



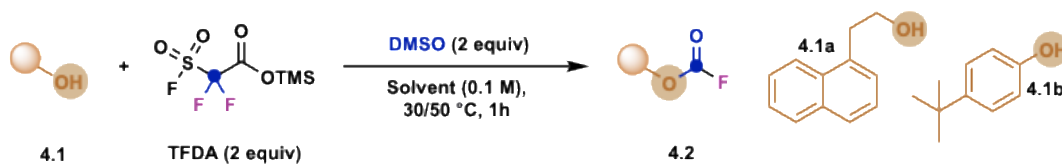
Entry*	Temperature	Conv. 4.1a (%)	Yield 4.2a (%)	Conv. 4.1b (%)	Yield 4.2b (%)
1	rt	97	83	50	25
2	30	100	81(79 ^a)	52	43
3	40	100	78	83	67
4	50	93	84	100	97 (95 ^a)
5	60	80	74	93	86

*All reactions run at 0.1 mmol in a sealed 1-dram vial at temperature given °C for 1 h, conversion and yield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as internal standard; a. isolated yield.

A solvent screen was then conducted. Across both substrates, MeCN gave the best yields (Table 4.3, entry 1), but chlorinated solvents DCM (Table 4.3, entry 2), DCE (Table 4.3, entry 3), and chloroform (Table 4.3, entry

4) all gave the product in moderate yields. Attempts to use ethereal solvent THF resulted in practically no fluoroformate formation (Table 4.3, entry 5). When 10 mol% NaF was added to the THF conditions (Table 4.3, entry 6) fluoroformate could be formed 70% yield, making it likely that THF hinders the formation of COF₂ from TFDA initiated by DMSO. The ability to use CH₂Cl₂ is of interest given that it has a much lower boiling point than MeCN, which could be advantageous for fluoroformates that are challenging to isolate due to their volatility.

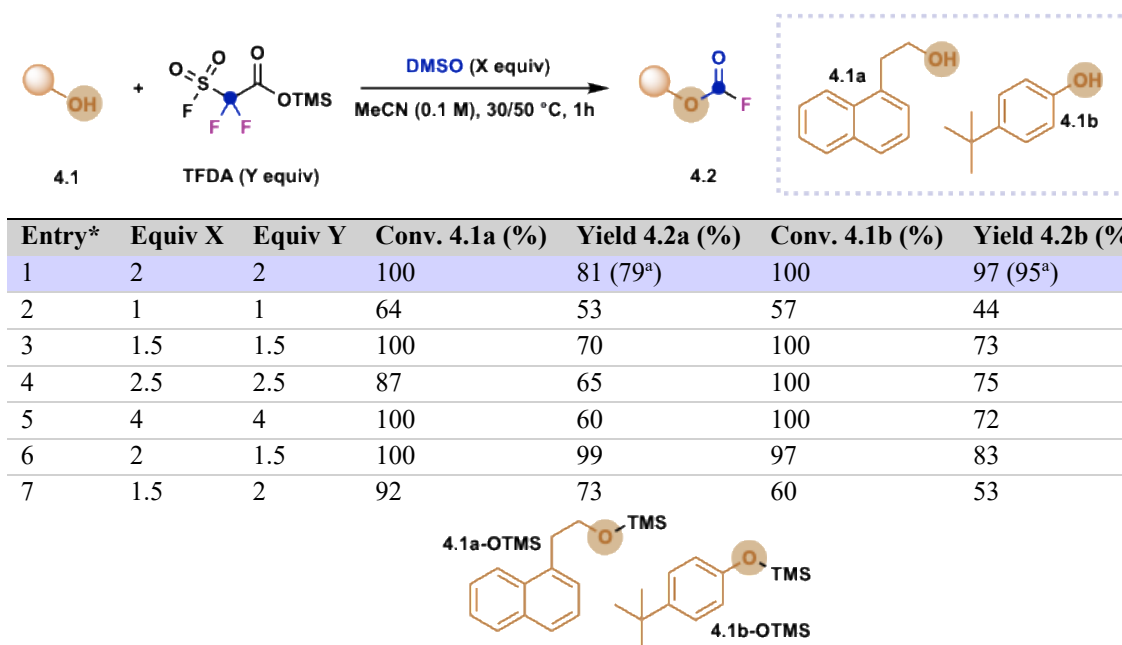
Table 4.3. Solvent Screen for **4.1a** and **4.1b**



Entry*	Solvent	Conv. 4.1a (%)	Yield 4.2a (%)	Conv. 4.1b (%)	Yield 4.2b (%)
1	MeCN	100	81 (79 ^a)	100	97 (95 ^a)
2	CH ₂ Cl ₂	98	63	94	80
3	DCE	96	59	90	69
4	CHCl ₃	97	74	92	82
5	THF	80	<5%	53	<5%
6	THF ^a	93	70	-	-

- = not run; *All reactions run at 0.1 mmol in a sealed 1-dram vial at 30 °C for 1 h, conversion and yield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as internal standard; a. 10 mol% of NaF added.

To probe how the stoichiometry of the reagents affected the reaction, we varied the equivalents of each component to assess its impact on yield. Lowering the loading of DMSO and TFDA to 1 equivalent each led to a significant drop in both yield and conversion for both substrates (Table 4.4, entry 2). Loadings of 1.5, 2.5, and 4 equivalents gave lower yields as well across both substrates (Table 4.4, entries 3-5). Adjusting the ratio between DMSO and TFDA to 2:1.5 increased the yield of alkyl fluoroformate **4.2a** to 99% (Table 4.4, entry 6) but gave worst yields in the case of phenyl fluoroformate **4.2b**. Adjusting the ratio between DMSO and TFDA to 1.5:2 gave decreased yield for both substrates.

Table 4.4. Equivalency Screen for **4.1a** and **4.1b**

*All reactions run at 0.1 mmol in a sealed 1-dram vial at 30/50 °C for 1 h, conversion and yield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

One thing to note about the equivalency screenings was when 4 equivalents of TFDA/DMSO were used, substantial formation of the corresponding silyl ether byproducts **4.1a-OTMS** and **4.1b-OTMS** were observed (ca. 7–10%), with trace amounts (2–5%) detected across nearly all screening conditions. Given the challenges associated with fluoroformate purification, we sought to suppress silyl ether formation through the re-introduction of a fluoride source, leveraging the thermodynamic favorability of Si–F bond formation to sequester TMS.

Fluoride additives were initially screened at a 1:1 molar ratio relative to TFDA using alcohol **4.1a** as the model substrate (Table 4.5, entries 2–7). Both KF and CsF effectively suppressed formation of **4.1a-OTMS** while maintaining yields and conversions comparable to fluoride-free conditions (Table 4.5, entries 2–3). In contrast, NaF led to a marked reduction in yield (45%, Table 4.5, entry 4). Use of TBAF as a 0.1 M solution in THF similarly decreased yields, whereas the dry salt prepared from dehydration of the hexahydrate restored yields to >90%. However, the anhydrous surrogate TBAT, proposed to release TBAF slowly *in situ*, afforded substantially lower yields (33%, Table 4.5, entry 7). Given its low cost, KF was selected for further study. Reducing the KF loading (Table 4.5, entries 8–11) revealed that at 0.5 equivalents both yield and conversion declined from quantitative levels, accompanied by trace reappearance of **4.1a-OTMS** (Table 4.5, entry 11).

Addition of 1 equivalent of KF to the optimized conditions for phenol **4.1b** furnished fluoroformate **4.2b** in 93% yield (Table 4.5, entry 12), while increasing KF to 2 equivalents delivered complete conversion and near-quantitative yield (Table 4.5, entry 13). Under the same conditions, alcohol **4.1a** likewise afforded near-quantitative formation of the corresponding fluoroformate (Table 4.5, entry 14).

Table 4.5. Fluoride additives screen.

Entry*	Substrate	Fluoride Source	Y equiv.	X equiv.	Conv. (%)	Yield (%)
1	4.1a	none	NA	1.5	100	99
2	4.1a	KF	2	1.5	100	98
3	4.1a	CsF	2	1.5	100	>99
4	4.1a	NaF	2	1.5	58	45 ^b
5	4.1a	TBAF (0.1 M in THF)	2	1.5	54	45 ^b
6	4.1a	TBAF (dry)	2	1.5	>99	97
7	4.1a	TBAT	2	1.5	35	3
8	4.1a	KF	1.5	1.5	100	>99
9	4.1a	KF	1.2	1.5	100	>99
10	4.1a	KF	1.0	1.5	100	>99
11	4.1a	KF	0.5	1.5	99	98 ^b
12	4.1b	KF	1	2	>99	93
13	4.1b	KF	2	2	100	95 ^a
14	4.1a	KF	2	2	100	>99 (97) ^a

*All reactions run at 0.1 mmol in a sealed 1-dram vial at 30/50 °C for 1 h, conversion and yield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as internal standard; a. isolated yield; b. 2-5% formation of **4.1a-OTMS**.

Finally, the effect of reaction concentration was examined using phenol **4.1b** as the test substrate (Table 4.6). Increasing the concentration from 0.1 to 0.2 M in a standard 1-dram vial led to a modest decrease in yield, from 98% to 91%. To further explore higher concentrations, the reaction was conducted at 0.4 M in a conical microwave vial, which afforded complete conversion and a near-quantitative yield (Table 4.6, entry 4). Interestingly, performing the reaction at 0.2 M in the same conical vial resulted in a reduced yield of 83% (Table 4.6, entry 3), suggesting that the shape of the reaction vessel and the associated headspace influence reaction

efficiency. One possible way to rationalize this difference is that the conical vial provides greater headspace and the vessels, which are crimp-capped closed with a PTFE/Silicon septa cap and rated for up to 300 PSI, allows COF₂ to build up in the gas phase and maintain a higher effective partial pressure. At higher substrate concentrations, this elevated partial pressure ensures efficient interaction between COF₂ and the substrate, promoting complete conversion. In contrast, the smaller 1-dram vials with limited headspace may allow COF₂ to escape or limit its distribution, reducing the effective reaction rate and yield.

Table 4.6. Concentration Screen for **4.1b**



Entry*	[Conc] (X)	Conv. (%)	Yield (%)
1	0.1	100	98
2	0.2	92	91
3	0.2 ^b	85	83
4	0.4 ^b	100	>99

*All reactions run at 0.2 mmol in a sealed 1-dram vial at 50 °C for 1 h, conversion and yield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as internal standard; a. isolated yield; b. run in a 2 mL conical microwave vial.

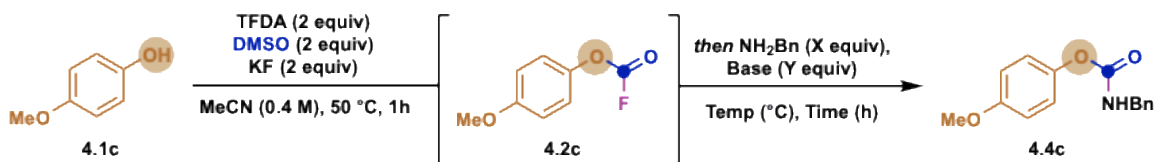
4.4.2 Work-up, Purification, and Isolation

When the reaction goes to full completion, the fluoroformates can be isolated in >90% purity via an extraction of the crude residue with ether (see experimental section for full procedure). In cases where there is starting material still present at the end of the reaction, it is often difficult to separate the starting material from the product unless the starting material is insoluble in ether. While fluoroformate yield can be obtained from *in situ* NMR, we explored methods to trap the fluoroformate *in situ* via a NAS reaction with benzyl amine to form carbamates **4.4**. This is a strategy that is often used in method development for the synthesis of acyl fluorides, which can be similarly challenging to isolate via column chromatography.

To verify the efficacy of the NAS reaction, we tested reaction conditions on 4-methoxyphenyl fluoroformate **4.2c**. The transformation of alcohol to fluoroformate was performed on scale and then at 1 hour the solution was purged with N₂ for 5 minutes. After which an aliquot was taken for *in situ* NMR analysis of fluoroformate formed, and a 0.1 mmol equivalent of the solution was transferred via syringe to a mixture of base

and benzyl amine in 0.5 mL of MeCN and allowed to stir under the conditions described in Table 4.7. At 50 °C for 2 hours, no base in the reaction resulted in low conversion of fluoroformate to carbamate. Amine bases like DIPEA, TEA, pyridine, and DMAP all gave moderate to excellent yields of the carbamate with TEA and DMAP giving above 90% yield (Table 4.7, entries 2-5). Using inorganic base K₂CO₃ resulted in 85% yield. Moving forward with TEA as the optimized base due to its cost, we then tested the reaction at room temperature which gave 83% yield (Table 4.7, entry 7). Increasing the loading of both TEA and benzyl amine at room temperature resulted in the same yield of carbamate to fluoroformate and an isolated yield of 92% (Table 4.7, entry 8). Further increasing the equivalents of TEA and benzyl amine, as well as running the reaction with no KF and running the NAS reaction for a shorter amount of time all resulted in lower carbamate formation (Table 4.7, entries 9-11). Using the TEA as the base the NAS reaction of fluoroformates with benzylamine is rapid and quantitative, and the yield of the resulting carbamate directly reflects the total amount of fluoroformate generated during the reaction.

Table 4.7. Screening of conditions for trapping of fluoroformate with benzyl amine



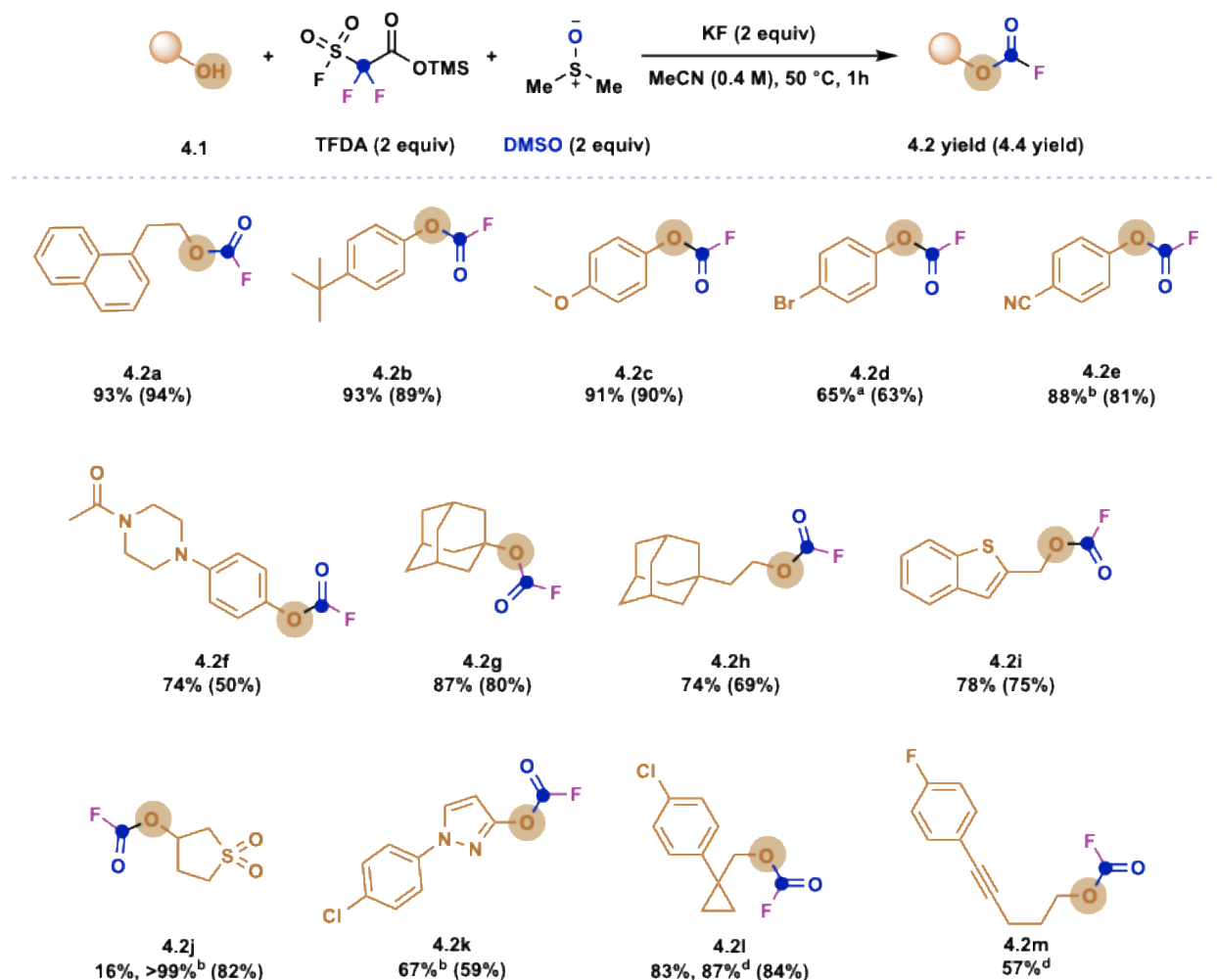
Entry*	Base	Base (equiv)	Amine (equiv)	Time (h)	Temp (C)	4.2c (%)	4.4c (%)
1	none	-	1.2	2	50	97	5
2	DIPEA	1.2	1.2	2	50		67
3	TEA	1.2	1.2	2	50		93
4	Pyridine	1.2	1.2	2	50		75
5	DMAP	1.2	1.2	2	50		90
6	K ₂ CO ₃	1.2	1.2	2	50		85
7	TEA	1.2	1.2	2	rt	98	83
8	TEA	1.5	1.5	2	rt		98 (90) ^a
9	TEA	2	2	2	rt		95
10	TEA (no KF)	1.5	1.5	2	rt		93
11	TEA	1.5	1.5	1	rt		92

* Reactions performed on 0.1 mmol scale; b. Calculated using ¹⁹F NMR with α,α,α -trifluorotoluene as internal standard; c. Calculated using ¹H NMR with 1,3,5-trimethoxybenzene as internal standard; a. Isolated yield.

4.4.3 Substrate Scope

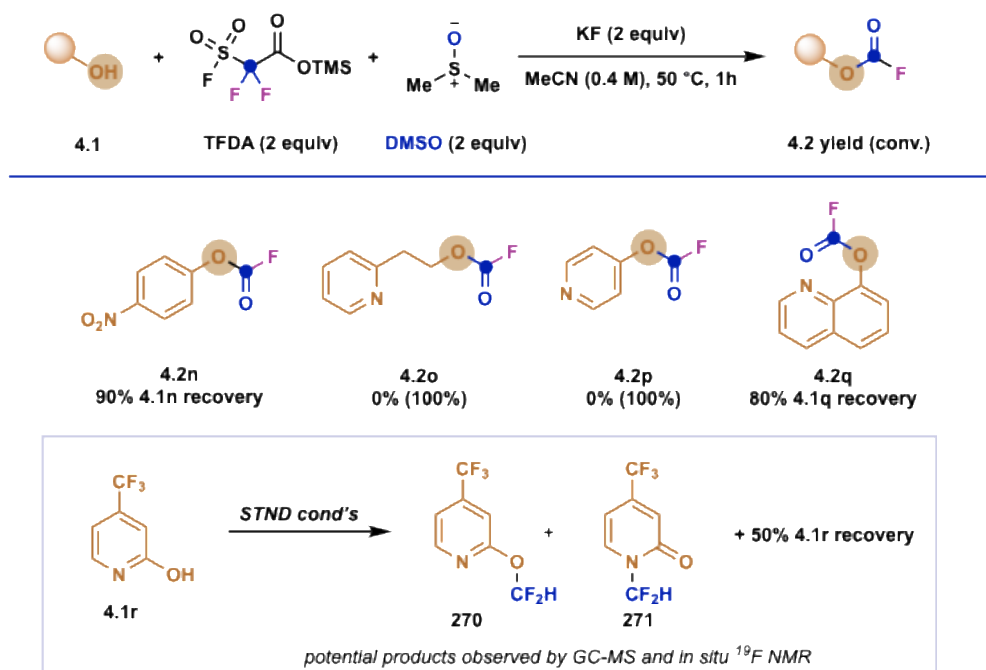
With the optimized reaction conditions in hand, we then turned to exploring the potential functional group tolerance of the reaction (Scheme 4.6, Scheme 4.7). Screening a range of phenols, we found that both electron

donating (**4.2b-c**) and mildly electron withdrawing (**4.2d-e**) phenols were well tolerated by the reaction conditions. Introduction of amides and tertiary amines (**4.2f**) also did not hinder reactivity. Fluoroformates derived from primary alcohols (**4.2h, 4.2i, 4.2l**, and **4.2m**) were formed in moderate to excellent yields. Adamantyl fluoroformate **4.2g**, derived from a tertiary alcohol, could also be obtained with only trace (<5%) formation of the corresponding alkyl fluoride, demonstrating that this method enables access to the only commercially available fluoroformate. Secondary alcohols could also be used as substrates (**4.2j**). Alkynes, like the one present in **4.2m**, did not undergo difluorocyclopropanation under the reaction conditions. Additionally, multiple substrates also contained halogens (**4.2d, 4.2k**, and **4.2l**) that could be used as handles for transition-metal catalyzed derivatization of the products.



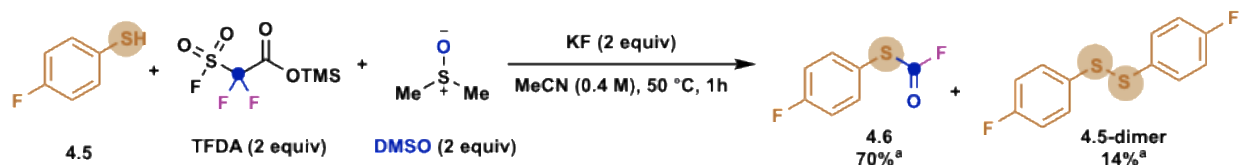
Scheme 4.6. Preliminary scope of fluoroformates; a. co-isolated with 32% **4.1d**; b. *in situ* yield determined by ¹⁹F NMR using α,α,α-trifluorotoluene as internal standard; c. reaction run at 1.0 mmol scale.

para-Nitrophenol **4.1n** did not produce any fluoroformate under the reaction conditions but it was also insoluble under the reaction conditions. Looking to examine the tolerance of heterocycles in the reaction, we screened a host of readily available heterocycles. While alcohols attached to benzothiophene (**4.2i**), cyclic sulfones (**4.2j**), and pyrazole (**4.2k**) were transformed into the desired fluoroformates in moderate to excellent yields, attempts to use substrates containing pyridine or quinoline moieties (**4.2o-q**) resulted in no detectable fluoroformate, even when monitored using *in situ* ^{19}F NMR. This is in contrast to the previously report PDFA conditions, where the presence of pyridines did not hinder the formation of carbamoyl fluorides.²⁸ There is literature precedent for both *O*- and *N*-difluoromethylation of pyridinones via DFC capture by the two pyridinone tautomers.^{30,39} To evaluate if this sequestration of DFC is possible under our reaction conditions, we subjected the electron-poor pyridinone **4.1r**, which is expected to favor the 2-hydroxypyridine tautomer and exhibit reduced nucleophilicity at nitrogen, to the standard conditions. *In situ* analysis of the reaction mixture by ^{19}F NMR and GC–MS indicates that, in addition to the anticipated *O*-difluoromethylation product **270** arising from DFC capture, a second product consistent with *N*-difluoromethylation product **271** (–103.74 ppm) is also formed, which had previously been observed when 2-pyridinones were treated with TMSCF_2Br , a difluorocarbene source, in the absence of oxidant.⁴⁰ Collectively, these observations suggest that competitive DFC capture by pyridinone substrates occurs under the reaction conditions, thereby inhibiting formation of the desired fluoroformate.



Scheme 4.7. Unsuccessful substrates for fluoroformate generation and probing potential DFC sequestration by pyridinones.

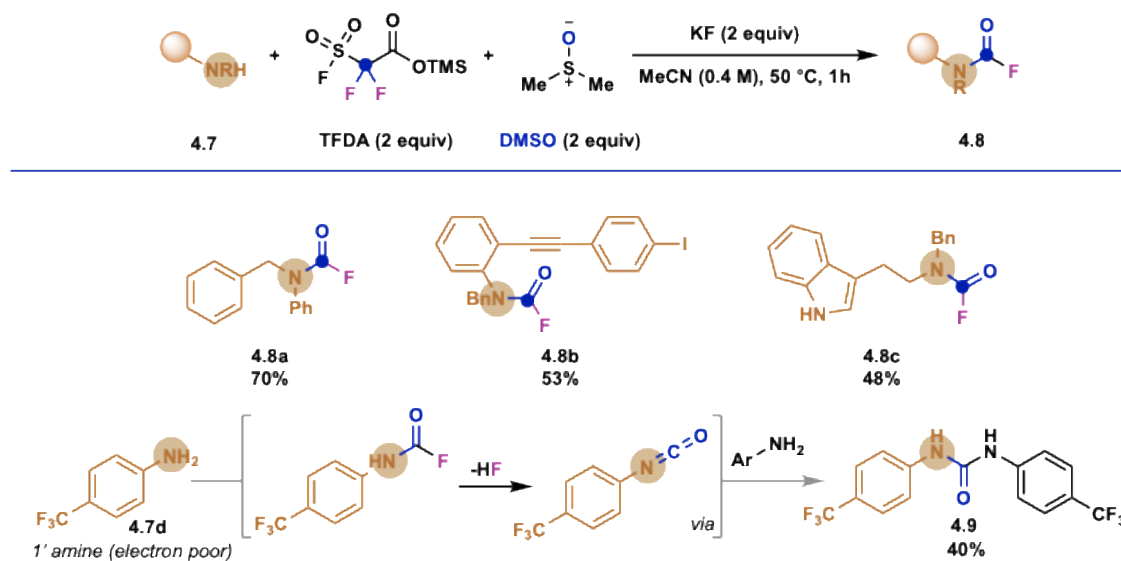
Interested in expanding the substrate scope beyond fluoroformates, we next explored the fluorocarbonylation of thiols to access fluorothioformates (Scheme 4.8). To do so, we subjected thiol **4.5** to the optimized conditions and generated the corresponding fluorothioformate in 70% ^{19}F NMR yield. All attempts at isolation of the thiofluoroformate resulted in its partial decomposition to disulfide **4.5-dimer** which was the major isolated product from the electrochemical method for generating fluorothioformates when thiol **4.5** was used as well.⁴¹



Scheme 4.8. Attempts at synthesizing fluorothioformate from thiol with DFC/oxidant pair; a. *in situ* yield determined by ^{19}F NMR using α,α,α -trifluorotoluene as internal standard.

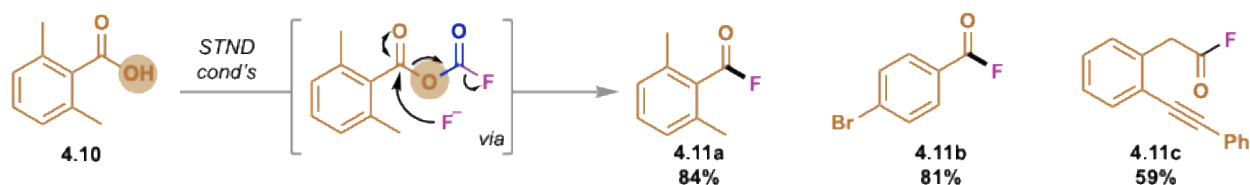
We found that secondary amines (**4.7a-c**) could be successfully converted into the corresponding carbamoyl fluorides in moderate yields, comparable to other known DCF/[oxidant] systems. In contrast to most primary amines, which react with COF_2 to yield ureas through HF elimination from a secondary carbamoyl fluoride intermediate and subsequent isocyanate formation, several literature reports describe electron-poor anilines that

form stable secondary carbamoyl fluorides directly under analogous conditions. Under our conditions, we primarily observed the formation of the urea product **4.9**, suggesting that while the carbamoyl fluoride is initially formed, the reaction conditions, specifically the use of excess fluoride and the presence of silanes, could promote fluoride elimination to generate the isocyanate and subsequent urea.



Scheme 4.9. Scope of carbamoyl fluorides.

Finally, inspired by previous reports of difluorophosgene surrogates being used for the deoxyfluorination of carboxylic acids to afford acyl fluorides,⁴² we applied our optimized conditions to carboxylic acid **4.10a-c**. To our delight, the reaction conditions gave comparable yields to other known methods, demonstrating the broad applicability of this method for the synthesis of diverse carbonyl fluoride derivatives.



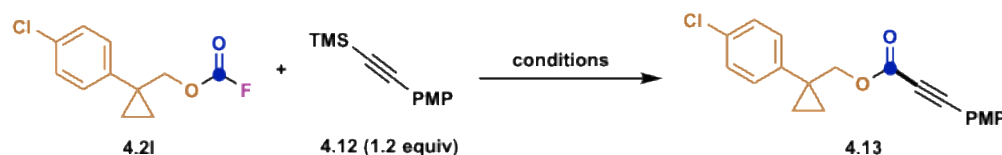
Scheme 4.10. Scope of acyl fluorides, all reactions run at 50 °C.

4.4.4 Alkynylation of Fluoroformates

Interested in expanding the scope of C–C bond-forming reactions enabled by fluoroformates as esterification reagents, we first investigated fluoride-catalyzed alkynylation reactions that had previously been reported for carbamoyl fluorides. Fluoroformate **4.21** and alkynylsilane **4.12** were chosen as the model substrate for

these studies. Initial attempts using the TBAF-catalyzed conditions reported by Le and co-workers in 2023 resulted in complete decomposition of the starting material to the parent alcohol **4.11** (Table 4.8, entry 1).⁴³ This outcome is unsurprising given that Le and co-workers found that any water sensitive functionalities were incompatible with the TBAF solution and instead needed anhydrous TBAT. Applying the same reaction conditions but substituting anhydrous TBAT as the fluoride source led to 66% conversion of the starting material and 7% yield of alkynoate **4.13** (Table 4.8, entry 2). We next evaluated the alkynylation reaction conditions developed for *N*-CF_x carbamoyl fluorides. In 2025, Schoenebeck and co-workers reported modified fluoride-catalyzed conditions involving extended reaction times and elevated temperatures (60 °C).⁴⁴ When these conditions were applied to **4.21** again using TBAT as the catalyst, complete conversion of the starting material was observed. Product formation, however, remained at about a catalytic amount (13%, Table 4.8, entry 3).

Table 4.8. Screening alkynylation reactions developed for carbamoyl fluorides on fluoroformates.



Entry*	Conditions	Conv. 4.21 (%)	Yield 4.13 (%)
1	TBAF (0.1 M in THF, 10 mol%), MePh (0.1 M), rt, 16 h	100	0
2	TBAT (0.1 M in THF, 10 mol%), MePh (0.1 M), rt, 16 h	66	7
3	TBAT (0.1 M in THF, 10 mol%), MePh (0.1 M), 60 °C, 16 h	100	13
4	Ni(cod) ₂ (10 mol%), dtbbpy (11 mol%), Zn (1.5 equiv), DMF (0.5 M), 60 °C, 3 h	91	34 (25) ^a

*All reactions run in a flame dried 2-dram vial at a 0.2 mmol scale under the conditions specified, conversion and yield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as internal standard; a. Isolated yield.

Finally, we examined Ni-catalyzed alkynylation conditions previously developed by Schoenebeck and co-workers for *N*-CF₃ carbamoyl fluorides.⁴⁵ Under these conditions, the desired alkynoate **4.13** was formed in 34% yield as determined by ¹H NMR and was isolated in 25% yield via flash column chromatography (Table 4.8, entry 4). This yield is comparable to the yield reported for the analogous alkynylsilane in the *N*-CF₃ carbamoyl fluoride scope (32% yield). The lack of catalytic reactivity with TBAF and TBAT is interesting given that BnNMe₃F, another ammonium fluoride salt, is used as a catalyst for the formation of enol carbonates from fluoroformates and silyl enol ethers. The difference between the two reactions is likely the nucleophile that is formed over the course of the

reaction. The nucleophile for the silyl enol ether is likely the naked enolate ion, while for the alkynylsilane the nucleophile is the weaker pentavalent silicate and not the naked acetylide.

4.5 Fluoroformates Under Lewis Acid-Catalyzed Fluoride Recycling Conditions

Although scattered examples of fluoroformates acting as dual-function reagents toward polyfluorinated alkenes have been reported (Figure 4.7, Figure 4.8), these transformations generally require harsh reaction conditions. Drawing inspiration from our previous work on Lewis acid-catalyzed fluorocyclizations of alkyne-tethered carbamoyl fluorides and acyl fluorides, as well as from Jensen's seminal report on the synthesis of alkyl fluorides from fluoroformates using $\text{BF}_3 \cdot \text{OEt}_2$ as a catalyst, we sought to evaluate the feasibility of atom-economical carbofluorination reactions enabled by fluoroformates.

Initial studies focused on fluoroformate **4.2m**, which was designed to resemble substrates previously employed in fluorocyclizations of carbamoyl fluorides and acyl fluorides. This substrate contains a three-carbon tether linking the fluoroformate moiety to an alkyne and, upon cyclization, could in principle give three distinct carbofluorination products (Figure 4.15): (i) a 6-*exo* cyclization retaining the ester functionality to afford **4.14**; (ii) 4-*exo* cyclization with CO_2 loss to furnish **4.15**, or (iii) the 5-*endo* cyclization with CO_2 loss to furnish **4.16**. Given the potential for undesired elimination reactions to form an alkene we opted to design substrate **4.2m** with an aryl fluoride to help track both fluorinated and non-fluorinated product formation better.

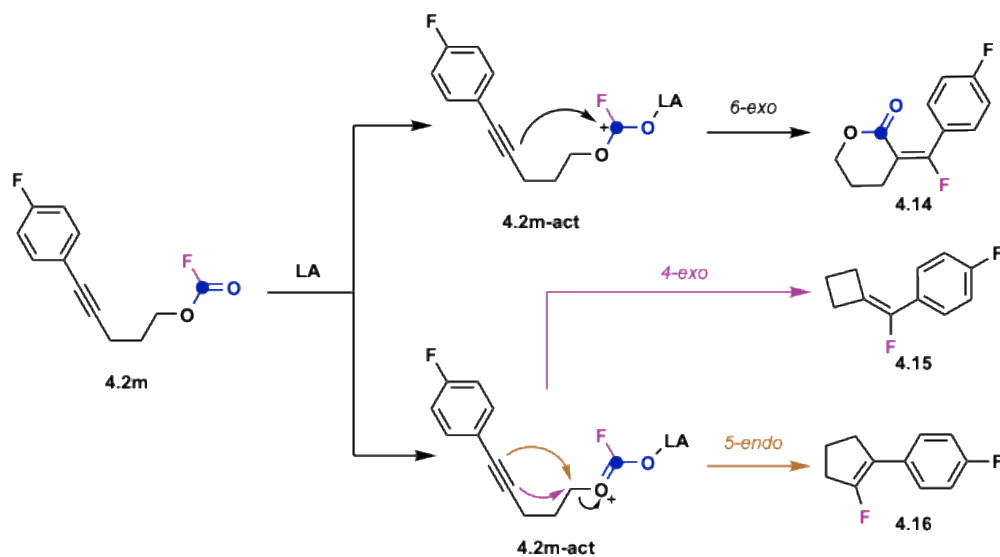


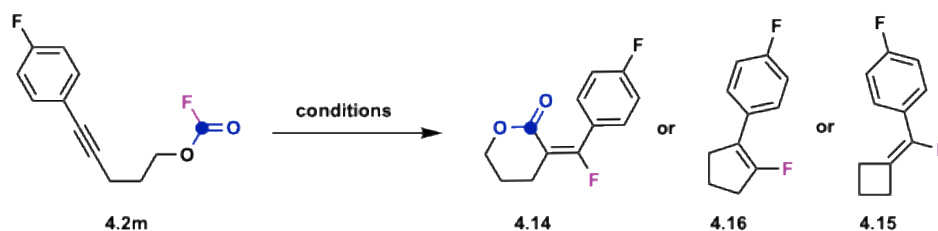
Figure 4.15. Potential fluorinative cyclization modes of fluoroformates **4.2m**.

Given that Jensen reported efficient activation of fluoroformates at room temperature using 30 mol% $\text{BF}_3 \cdot \text{OEt}_2$, we initially evaluated the carbofluorination conditions previously developed for carbamoyl fluorides at room temperature (Table 4.9, entry 1). Under these conditions, only 25% conversion of the starting material was observed, with no detectable carbofluorination products. Increasing the reaction temperature to 40 °C led to a modest increase in conversion but again these conditions did not result in formation of any new carbofluorination products (Table 4.9, entry 2). Swapping $\text{BF}_3 \cdot \text{OEt}_2$ for the more Lewis acidic BCF at 40 °C a trace signal appeared (δ –78.42 ppm, s) which could correspond to a potential carbofluorination product. While spectroscopically observed, we could not isolate this compound, but we assume that it is likely one of the two *exo* products (**4.14** or **4.15**) based on the multiplicity of the signals by ^{19}F NMR (Table 4.9, entry 4).

Further increasing the temperature to 75 °C using $\text{BF}_3 \cdot \text{OEt}_2$ gave an 83% conversion of the starting material, accompanied by the formation of multiple new, fluorinated species as observed by ^{19}F NMR. No fluorinated products, however, could be isolated by preparative TLC (Table 4.9, entry 5). When TrBF_4 , the optimized catalyst for intramolecular acyl fluoride fluorocyclization, was screened at 75 °C, the conversion was lower and there were no new carbofluorination products observed (Table 4.9, entry 6). Use of BCF at 75 °C produced the same tentatively assigned carbofluorination product at δ –78.42 ppm in trace amounts, and analogous results were obtained with $\text{Pd}(\text{MeCN})_4(\text{BF}_4)_2$, which generated the same species in trace amounts (Table 4.9, entry 8).

Given the established role of HFIP in alkyl fluoride activation and fluoride shuttling,⁴⁶ we investigated its use as a fluoride shuttle mediator for fluoroformates at 75 °C. At 8 equivalents 12% of the HFIP carbonate was formed as the sole fluorinated product observed (Table 4.9, entry 9). Interested in screening other conditions that are known to promote fluoride shuttling reactivity, we tested the Rh/BF₄ catalyzed conditions reported by Tobisu for the carbofluorination of alkyne-tethered acyl fluorides (Table 4.9, entry 10). While 50% of the starting material was consumed, no new fluorinated products were formed. Finally, use of TBAT as a fluoride catalyst gave rise to 9% of alkyl fluoride via decarboxylation of the starting fluoroformate.

Table 4.9. Preliminary catalyst screen for fluoroformates as dual-reagents for carbofluorination of alkynes.



Entry*	Conditions (unless otherwise specified 10 mol% of cat added)	Conv. (%)	New Fluorinated Products (¹⁹ F NMR, ppm)
1	BF ₃ ·OEt ₂ , DCM (0.1M) 24h, rt	25	no
2	BF ₃ ·OEt ₂ , DCM (0.1M) 24h, 40 C	32	no
3	BCF, DCM (0.1M) 24h, rt	15	no
4	BCF, DCM (0.1M) 24h, 40 C	32	< 5% @ -78.42 + -117.96 ^a
5	BF ₃ ·OEt ₂ , DCE (0.1 M), 1 h, 75 C	83	Yes, multiple
6	TrBF ₄ , DCE (0.1 M), 1 h, 75 C	45	no
7	BCF, DCE (0.1 M), 1 h, 75 C	75	< 5% @ -78.42 + -117.96 ^a
8	Pd(MeCN) ₄ (BF ₄) ₂ , DCE (0.1 M), 1 h, 75 C	35	< 5% @ -78.42 + -117.96 ^a
9	HFIP (8 equiv.), DCE (0.1 M), 1 h, 75 C	90	12% HFIP carbonate @ -73.38 + -112.12 ^b
10	Tobisu (RhBF ₄ , COD, dppbz, 120 C, 16 h)	50	no
11	TBAT, DCE (0.1 M), 1 h, 75 C	40	9% at -169.7 + -111.97 ^c

*All reactions run at 0.1 mmol in a sealed 1-dram vial under the conditions specified; conversion and yield determined by ¹⁹F NMR analysis using α,α,α -trifluorotoluene as internal standard; a. peak at -117.96 ppm belongs to the aryl fluoride; b. peak at -112.12 ppm belongs to the aryl fluoride; c. peak at -111.97 ppm belongs to the aryl fluoride.

Given the difficulties in isolating potential products from this system, we sought to develop a test substrate for carbofluorination where the products were known or could be generated via an alternative method easily. One potential reaction that caught our eye was the ring opening transformation of cyclopropanes to cyclobutanes. In 1998 Kirihaara and co-workers reported the fluorination of small ring tertiary cyclobutanols **217** with DAST (Figure 4.16).⁴⁷ Under their reaction conditions, they found that three products could be made: fluorocyclobutane **219**,

(fluoromethyl)cyclopropane **221**, or homoallylic fluoride **223**, depending on the electronics of the starting material. The authors propose that after initial elimination of diethylamidofluorine fluoride the carbocation is formed in an equilibrium mixture of three intermediates. With electron-donating substituents at R¹, cyclobutyl cation **218** predominates and the fluorocyclobutane **219** is formed. In the cases of compounds bearing an electron-withdrawing group at R¹, cyclopropylmethyl cation **220** predominated yielding (fluoromethyl)-cyclopropane **221**. Formation of the homoallylic fluoride **223** only occurred in substrates having an electron-withdrawing group at R¹ and electron-donating substituents at R³. Given the interconversion between carbocations demonstrated here, we were interested in exploring if fluoroformates derived from cyclopropylmethanols could be used as an appropriate starting material for a ring-strain release fluorinative rearrangement under catalytic activation with Lewis acids.

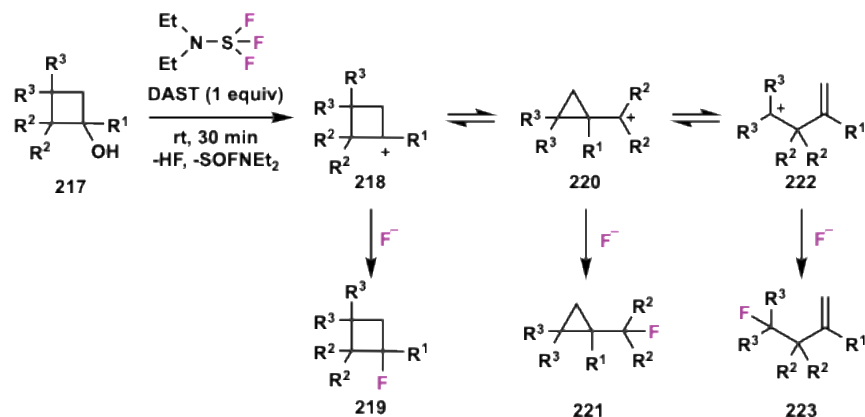


Figure 4.16. DAST deoxyfluorination of tertiary cyclobutanols and rearrangement of carbocation intermediate.

This exact reactivity is illustrated in the patent literature for the conversion of complex cyclopropylmethyl-alcohols **224** to fluorocyclobutanes **227** is often achieved with DAST (Figure 4.17). The reaction likely goes through DAST-alcohol adduct **225** which can either undergo direct deoxyfluorination via an intermolecular fluorination to yield **228** or instead go through an intramolecular 1,2-alkyl shift driven by ring-strain release to give stabilized tertiary carbocation **226** which then can undergo fluorination to yield fluorocyclobutane **227**.

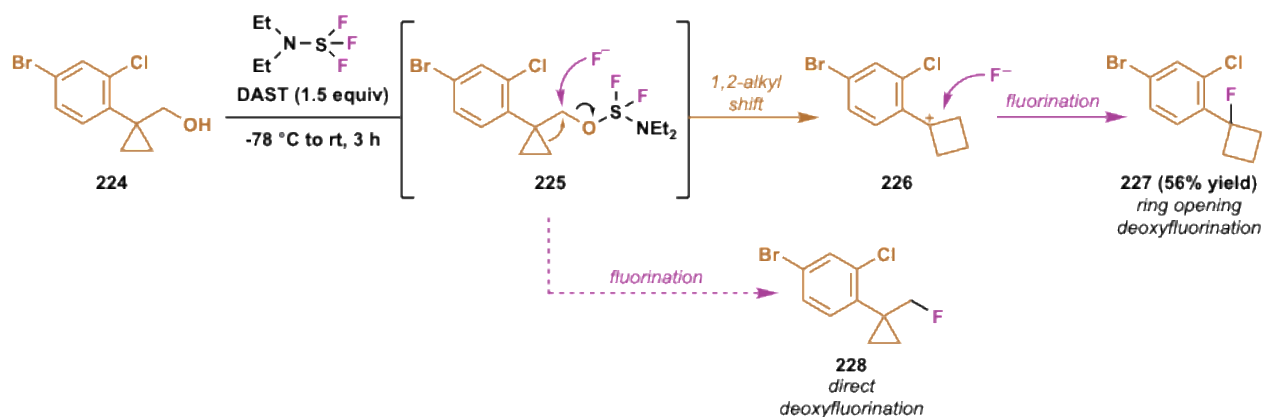


Figure 4.17. Deoxyfluorination of cyclopropylmethanols **4.2mb** to form fluorocyclobutane or cyclopropylmethylfluoride.

Initial investigations into the fluorinative rearrangement were conducted using fluoroformate **4.21** as model substrate (Table 4.10). An authentic standard of fluorocyclobutane **4.17I** was prepared using the DAST deoxyfluorination of **4.11**. Attempts to promote the reaction using BCF (10 mol%) or $\text{BF}_3 \cdot \text{OEt}_2$ (50 mol%) at room temperature resulted in essentially no conversion of the starting material. Increasing the temperature to 40 °C led to modestly higher conversion for both Lewis acids, but still no formation of fluorinated products was observed. At 75 °C, near-complete consumption of the starting material was achieved in both cases: BCF afforded only 18% of **4.17I**, while $\text{BF}_3 \cdot \text{OEt}_2$ gave only trace amounts of this product. Under the same conditions, the use of TrBF_4 and $\text{Pd}(\text{MeCN})_4(\text{BF}_4)_2$ gave low conversions and no detectable fluorinated products. Interested in testing a borane with a FIA in between $\text{BF}_3 \cdot \text{OEt}_2$ and BCF, BCl_3 was evaluated and yielded a 25% mixture of halogen-exchange products **4.17I-Cl** and **4.11-Cl**, along with 10% of the elimination product **4.19**, but no fluorinated products were detected. The preferential chloride transfer observed is consistent with our prior observations of HALEX product formation when using BCl_3 as a LA for fluoride shuttling reactions.

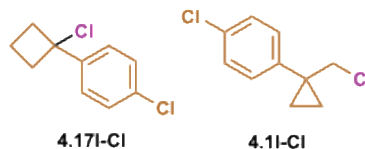
Analogous to carbofluorination attempts on **4.2m**, application of the $\text{Rh(I)}/\text{BF}_4^-$ catalyst system previously developed for acyl fluorides again failed to deliver any fluorinated products (Table 4.10, entry 10). Use of HFIP led to 17% formation of the corresponding HFIP carbonate (Table 4.10, entry 12). Treatment with TBAT gave only trace formation of the alkyl fluoride product (Table 4.10, entry 11). Finally, employing alternative conditions reported by Jensen for the conversion of fluoroformates to alkyl fluorides (Table 4.10, entry 13) resulted in full consumption of the starting material, but no formation of the desired product. The original Jensen report ran the

reaction at a 1 mole scale and attempts at scaling it down to 0.2 mmol in our hands have proven unsuccessful. Ultimately, the only catalyst that showed any appreciable amount of the desired fluorination product was BCF, which likely proceeds via a fluoride abstraction mechanism. In all cases where starting material consumption occurred elimination product **4.19I** was observed via ^1H NMR, which could be formed either from the product via HF-elimination, or from the intermediate carbocation before fluoride rebound occurs.

Table 4.10. Preliminary screen of conditions for decarboxylative fluorinative rearrangement of **4.2I**.



Entry*	Conditions	Conv. (%)	Yield (%)
1	BCF (10 mol%), CH_2Cl_2 (0.1 M), rt, 24 h	9	0
2	$\text{BF}_3 \cdot \text{OEt}_2$ (50 mol%), CH_2Cl_2 (0.1 M), rt C, 24 h	5	0
3	BCF (10 mol%), CH_2Cl_2 (0.1 M), 40 C, 24 h	23	0
4	$\text{BF}_3 \cdot \text{OEt}_2$ (50 mol%), CH_2Cl_2 (0.1 M), 40 C, 24 h	91	0
5	BCF (50 mol%), DCE (0.1 M), 75 C, 1 h	93	18
6	$\text{BF}_3 \cdot \text{OEt}_2$ (50 mol%), DCE (0.1 M), 75 C, 1 h	100	trace
7	TrBF_4 (50 mol%), DCE (0.1 M), 75 C, 1 h	15	0
8	$\text{Pd}(\text{MeCN})_4[\text{BF}_4]_2$ (50 mol%), DCE (0.1 M), 75 C, 1 h	24	0
9	BCl_3 (50 mol%), DCE (0.1 M), 75 C, 1 h	100	0 ^a
10 ¹⁴⁶	RhBF_4 , COD, dppbz, DCE, 120 C, 16 h	44	0
11	TBAT (50 mol%), DCE (0.1 M), 75 C, 1 h	15	trace
12	HFIP (8 equiv), DCE (0.1 M), 75 C, 1 h	47	0 ^b
13 ²⁴⁰	$\text{BF}_3 \cdot \text{OEt}_2$ (50 mol%), Hexanes (0.1 M), 0 C - rt, 1 h	100	0



*All reactions run at 0.1 mmol in a sealed 1-dram vial under the indicated reaction conditions; conversion and yield determined by ^{19}F NMR analysis using α,α,α -trifluorotoluene as internal standard; a. 25% of 4.17Ia-Cl and 4.1I-Cl recovered; b. ~17% HFIP carbonate formed.

4.6 Conclusion

A method for the synthesis of fluoroformates (**4.2**) from alcohols (**4.1**) using commercially available TFDA as a DFC source and DMSO as an oxidant was developed. The reaction can give access to crude derived from primary, secondary and tertiary alcohols as well as phenols fluoroformates in up to 90% purity. Preliminary substrate investigations show a broad tolerance of functional groups with the exception of pyridines, which likely acts as a

poison to the reaction via difluorocarbene capture. The same conditions could also be used for the synthesis of fluorothioformates (**4.6**) from thiols (**4.5**) and carbamoyl fluorides (**4.8**) from secondary amines (**4.7**) as well as enabling the synthesis of acyl fluorides (**4.11**) via deoxyfluorination of carboxylic acids. Preliminary investigations into the derivatization reactions showed that the fluoroformates could be captured via an NAS reaction with secondary amines, enabling an efficient one-pot formation of carbamates (**4.4**). The fluoroformates could also be employed as substrate in the Ni-catalyzed alkynylation reaction developed for *N*-CF₃ carbamoyl fluorides; this reaction remains unoptimized.

Attempts at employing fluoroformates under the previously developed Lewis acid-catalyzed carbofluorination conditions only resulted in trace amount of potential product formation. While attempts at an analogous decarboxylative fluorination transformation of fluoroformates derived from cyclopropylmethanols to fluorocyclobutanes showed promise, the best conditions (10 mol% BCF at 75 °C) only gave 18% yield of the known fluorocyclobutane product. This reaction likely proceeds via a fluoride abstraction mechanism meaning that FIA should be able to be used as a predictor for reactivity of boranes like it was for the aroyl fluorides discussed in Chapter 4. Future work on the development of fluoroformates as a synthon for unactivated alkyl fluorides should involve careful *in situ* analysis of the reaction using BCF to see if fluoride abstraction can be observed via ¹⁹F, ¹⁰B, or ¹³C NMR. If fluoride abstraction to from the carboxylate seems to be a key intermediate then a broader scope of borane catalysis should be explored, geared at probing the effect of FIA on catalyst efficacy. If not, potentially using alternative conditions (higher temperatures, more polar solvents, higher catalyst loading) could be employed. Additionally, investigations into the formation of the elimination product should be conducted to determine how best to suppress its formation. An alternative pathway for this reaction could be activation with a Lewis base instead, given the precedent of fluoroformate activation via Lewis bases like pyridines for decarboxylative fluorination.

4.7 Experimental and Spectral Information

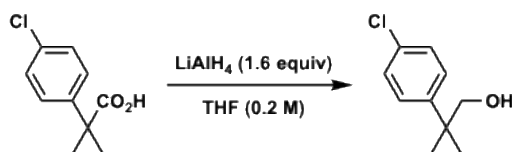
4.7.1 General Procedure for Reaction Optimization

In a glovebox under an N₂ atmosphere, a 1-dram vial equipped with a stir bar was charged with alcohol **4.1a** (15.0 mg, 0.2 mmol, 1.0 equiv.), any necessary additive and anhydrous solvent. The vial was capped with a septa cap and

removed from the glovebox. Anhydrous DMSO (14 μ L, 0.4 mmol, 2.0 equiv.) was added via microsyringe, and the mixture was stirred for 5 min before TFDA (40 μ L, 0.4 mmol, 2.0 equiv.) was added by microsyringe. The vial was placed in a pre-heated oil bath and stirred for the indicated amount of time. The reaction was then removed from the block and allowed to cool to room temperature, after which it was degassed with N₂ then concentrated. NMR yields were obtained by analysis of the crude reaction mixtures by ¹H NMR spectroscopy using a 10 s relaxation delay and 1,3,5-trimethoxybenzene (δ 6.08 ppm) as internal standard.

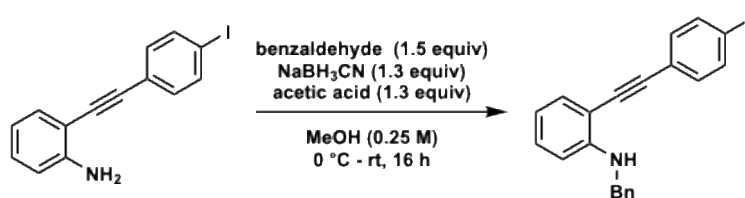
4.7.2 Starting Material Synthesis

(1-(4-Chlorophenyl)cyclopropyl)methanol



To an oven dried 250 mL RBF charged with LiAlH₄ (0.61 g, 16.0 mmol, 1.60 equiv.) in THF (48 mL) at 0 °C under an N₂ atmosphere commercially available 3-(4-chlorophenyl)-1-cyclopropanecarboxylic acid (1.97 g, 10.0 mmol, 1.00 equiv.). The reaction mixture was allowed to warm up to rt then stirred for 2 h. Upon completion the mixture was quenched with H₂O, filtered through celite then washed with hexanes. The obtained mixture was extracted twice with EtOAc then the combined organic phases were washed with H₂O, brine, dried with Na₂SO₄ and concentrated. The obtained crude material was purified via flash column chromatography (10-30% EtOAc/hexanes) to give the title compound as a white crystalline solid (1.60 g, 9.0 mmol, 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.25 (m, 4H), 3.65 (s, 2H), 2.27 (bs, 1H), 0.86 (s, 4H).

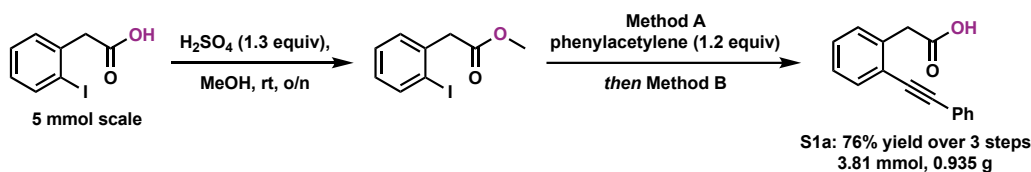
N-(benzyl)-2-((4-iodophenyl)ethynyl)phenyl)-aniline



2-((4-iodophenyl)ethynyl)aniline (1 equiv., 1.21 mmol, 386 mg) was added to a flame dried 2 dr vial charged with benzaldehyde (1.5 equiv., 1.82 mmol, 185 μ L) and glacial acetic acid (1.5 equiv., 1.5 mmol, 86 μ L) in methanol

(3.3 mL, 0.3 M). The resulting mixture was stirred at 0 °C for 1 hour, then sodium cyanoborohydride (1.5 equiv., 1.5 mmol, 92 mg) was added portion-wise. The reaction was quenched with 1 M NaOH until pH 7-8, then extracted with DCM (3x). The combined organic layers were washed with water (1x), brine (1x), then dried over Na₂SO₄. The crude material was purified by flash chromatography (0-10% EtOAc/pentane) and the desired product was isolated as yellow oil (429, 1.05 mmol, 87%). ¹H NMR (400 MHz, CDCl₃) δ 7.71 – 7.63 (m, 2H), 7.41 – 7.33 (m, 5H), 7.31 – 7.27 (m, 1H), 7.22 – 7.15 (m, 3H), 6.67 (td, J = 7.5, 1.1 Hz, 1H), 6.59 (d, J = 8.3 Hz, 1H), 5.07 (bt, 1H), 4.46 (d, J = 5.4 Hz, 2H).

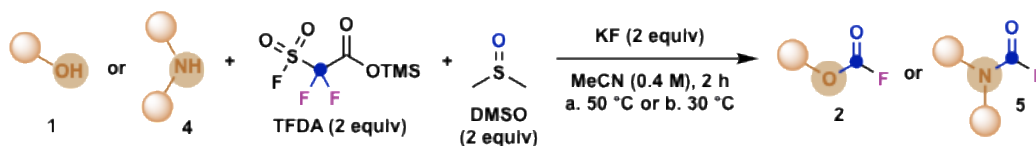
2-(2-(Phenylethynyl)phenyl)acetic acid



The title compound was prepared according to literature procedure at 5.00 mmol scale.³ The crude material was purified via flash chromatography (0-10% EtOAc/hexanes) to isolate the desired product as a white solid (76% yield over 3 steps, 3.81 mmol, 0.925 g). Spectral data are consistent with literature values: ¹H NMR (400 MHz, CDCl₃) δ 11.48 (bs, 1H), 7.69 – 7.45 (m, 3H), 7.40 – 7.21 (m, 6H), 3.94 (s, 2H).

4.7.3 General Procedures and Characterization Data for fluorocarbonylation reaction

General Procedure A: Fluorocarbonylation



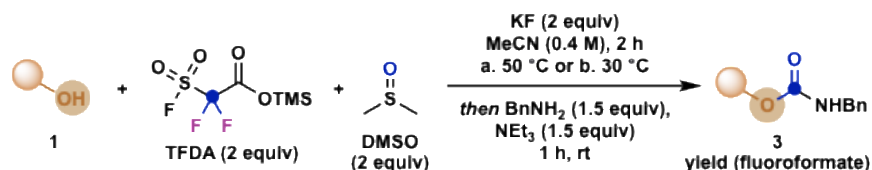
In a glovebox under an N₂ atmosphere, a 2 mL conical microwave vial (ChemGlass: CG-4920-03) equipped with a stir bar was charged with alcohol **4.1** or amine **4.4** (0.2 mmol, 1.0 equiv.), anhydrous KF (0.4 mmol, 2.0 equiv., 23.2 mg), and anhydrous MeCN (0.5 mL). The vial was crimp-capped with a Teflon/PFTE septa cap (ChemGlass: CG-4920-10) and removed from the glovebox. Anhydrous DMSO (28 µL, 0.4 mmol, 2.0 equiv.) was added via microsyringe, and the mixture was stirred for 5 min before TFDA (80 µL, 0.4 mmol, 2.0 equiv.) was added by microsyringe. The vial was placed in a pre-heated 30/50 °C wedge reaction block (ChemGlass: CG-1991-P-23) and

stirred for 2 h. The reaction was then removed from the block and allowed to cool to room temperature, after which it was degassed with N₂ and transferred to a separate vial.

For fluoroformates: The transferred reaction mixture was concentrated. The resulting residue was dissolved in a minimal amount of either DCM or Et₂O, then passed through a 1 cm silica plug and eluted with the same solvent it was dissolved in (DCM or Et₂O, 3 × 1 mL) then concentrated to yield crude fluoroformate **4.2**. For products that were not soluble in either DCM or Et₂O, after degassing α,α,α-trifluorotoluene (10 mg) was added directly to the reaction vial and yield was determined by in-situ ¹⁹F NMR.

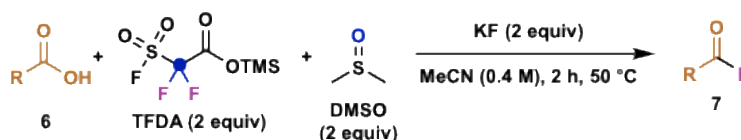
For carbamoyl fluorides: The crude reaction material was concentrated down on to silica and purified by flash column chromatography (see conditions for each substrate) to yield carbamoyl fluoride **4.5**.

General Procedure B: Synthesis of carbamates from alcohols via in situ fluoroformate formation



A flame dried 2 dr vial with stir bar was charged with alcohol 1 (0.2 mmol, 1.0 equiv.) and anhydrous KF (0.4 mmol, 2.0 equiv.). The vial was fitted with a septum and evacuated and backfilled 3x with N₂. To the vial was added anhydrous MeCN (2.0 mL) and distilled DMSO (28 μL, 0.4 mmol, 2 equiv.) and the solution was allowed to stir for 5 minutes before TFDA (80 μL, 0.4 mmol, 2.0 equiv.) was added. The septum was rapidly removed and replaced with a Teflon-lined screw cap then wrapped with electrical tape. The vial was placed into a pre-heated 30/50°C oil bath and allowed to stir for 2 h. After completion of the reaction, the vial was removed from the oil bath and allowed to cool to room temperature before a 0.5 mL of a stock solution of amine (0.30 mmol, 1.50 equiv.) and NEt₃ (0.30 mmol, 1.50 equiv.) in MeCN (0.4 M) was added via syringe and the reactions was allowed to stir at room temperature for 2 h. If solids were present at the end of the reaction, the reaction was then filtered across a 1 cm silica filter and eluted with DCM (3 x 1 mL) and concentrated, otherwise it was just concentrated. The crude material was purified by flash column chromatography (see conditions for each substrate) to yield carbamate **4.3**.

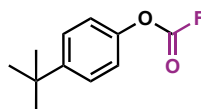
General Procedure C: Deoxyfluorination



In a glovebox under an N₂ atmosphere, a 2 mL conical microwave vial (ChemGlass: CG-4920-03) equipped with a stir bar was charged with carboxylic acid **4.6** (0.2 mmol, 1.0 equiv.), anhydrous KF (0.4 mmol, 2.0 equiv., 23.2 mg), and anhydrous MeCN (0.5 mL). The vial was crimp-capped with a Teflon/PFTE septa cap (ChemGlass: CG-4920-10) and removed from the glovebox. Anhydrous DMSO (28 μ L, 0.4 mmol, 2.0 equiv.) was added via microsyringe, and the mixture was stirred for 5 min before TFDA (80 μ L, 0.4 mmol, 2.0 equiv.) was added by microsyringe. The vial was placed in a pre-heated 50 °C wedge reaction block (ChemGlass: CG-1991-P-23) and stirred for 2 h. The reaction was then removed from the block and allowed to cool to room temperature, after which it was degassed with N₂, transferred to a separate vial, and concentrated down on to silica and purified by flash column chromatography (see conditions for each substrate) to yield acyl fluoride **4.7**.

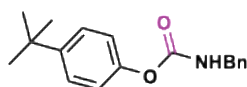
4.7.3.1 Characterization data for Fluoroformates and Carbamates

(4-*tert*-Butylphenyl) carbonofluoridate (**4.2a**)



Commercially available 4-*tert*-butylphenol (30.0 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 50 °C. The title compound was isolated via ether extraction (3 x 1 mL) in technical grade purity (>95:5%, product to SM) as a clear oil (35.3 mg, 1.86 mmol, 93% yield). Spectral data matches literature data:⁵⁰ **¹H NMR** (600 MHz, CDCl₃) δ 7.42 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 1.32 (s, 9H); **¹⁹F NMR** (377 MHz, CDCl₃) δ -15.50.

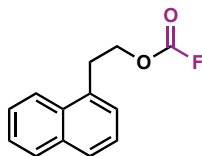
(4-*tert*-Butylphenyl) *N*-benzylcarbamate (**4.3a**)



Commercially available 4-*tert*-butylphenol (30.0 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure B** at 50 °C. The title compound was isolated via flash column chromatography (50% DCM/hexanes) as a white

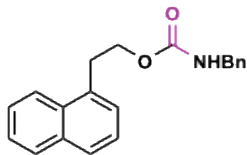
amorphous solid (49.2 mg, 1.78 mmol, 89% yield). **¹H NMR** (600 MHz, *CDCl*₃) δ 7.52 – 7.32 (m, 7H), 7.18 – 7.02 (m, 2H), 5.44 (s, 1H), 4.49 (d, *J* = 5.9 Hz, 2H), 1.37 (d, *J* = 2.4 Hz, 9H). **¹³C NMR** (151 MHz, *CDCl*₃) δ 155.0, 148.8, 148.2, 138.2, 128.9, 127.84, 127.77, 126.3, 121.0, 45.4, 34.5, 31.5.

2-(1-Naphthyl)ethyl carbonofluoridate (4.2b)



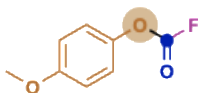
Commercially available 1-naphthaleneethanol (34.0 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 30 °C. The title compound was isolated via an ether extraction (3 x 1 mL) as a clear oil (35.3 mg, 1.80 mmol, 93% yield, >95% pure residual SM present). **¹H NMR** (400 MHz, *CDCl*₃) δ 8.04 (d, *J* = 8.6 Hz, 1H), 7.90 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.61 – 7.49 (m, 2H), 7.47 – 7.40 (m, 1H), 7.41 – 7.36 (m, 1H), 4.61 (t, *J* = 7.5 Hz, 2H), 3.54 (t, *J* = 7.6 Hz, 2H); **¹³C NMR** (101 MHz, *CDCl*₃) δ 145.75 (d, *J* = 284.6 Hz), 134.1, 131.90, 131.87, 129.2, 128.2, 127.5, 126.7, 126.0, 125.7, 123.15, 71.05 (d, *J* = 2.3 Hz), 31.8; **¹⁹F NMR** (377 MHz, *CDCl*₃) δ -16.43 (s, 1F); **HRMS** (DART) *m/z*: [M+NH₄]⁺ [C₁₃H₁₅NO₂F]⁺ Calc'd 236.10813, found 236.10877

2-(1-Naphthyl)ethyl *N*-benzylcarbamate (4.3b)



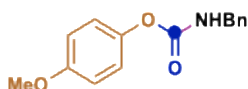
Commercially available 1-naphthaleneethanol (34.0 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure B** at 30 °C. The title compound was isolated via flash column chromatography (50% DCM/hexanes) as a white crystalline solid (57.2 mg, 1.87 mmol, 94% yield); **¹H NMR** (600 MHz, *CDCl*₃) δ 8.13 (d, *J* = 8.4 Hz, 1H), 7.91 – 7.83 (m, 1H), 7.77 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.51 – 7.48 (m, 1H), 7.44 – 7.27 (m, 7H), 5.02 (d, *J* = 6.4 Hz, 1H), 4.46 (t, *J* = 7.3 Hz, 2H), 4.39 (d, *J* = 5.8 Hz, 2H), 3.44 (t, *J* = 7.3 Hz, 2H); **¹³C NMR** (151 MHz, *CDCl*₃) δ 156.7, 138.6, 134.01, 133.96, 132.3, 128.9, 128.8, 127.63, 127.61, 127.5, 127.1, 126.3, 125.8, 125.6, 123.8, 65.1, 45.2, 32.8; **IR** (ATR, neat, cm⁻¹): 3309, 3022, 2924, 1694, 1511, 1246, 775, 697; **mp** (°C): 91.2-94.5.

4-Methoxyphenyl carbonofluoridate (4.2c)



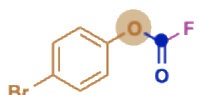
Commercially available 4-methoxyphenol (24.8 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 50 °C. The title compound was isolated via ether extraction (3 x 1 mL) as an oil (30.9 mg, 0.18 mmol, 91% yield, <95:5 purity w/ SM); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.17 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 9.2 Hz, 2H), 3.82 (s, 3H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 158.3, 144.33 (d, J = 285.6 Hz), 144.28 (d, J = 2.2 Hz), 121.1, 114.9, 55.8; $^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ -17.52 (s, 1F).

4-Methoxyphenyl benzylcarbamate (4.3c)



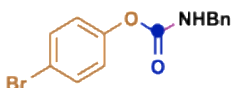
Commercially available 4-methoxyphenol (24.8 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure B** at 50 °C. The title compound was isolated via flash column chromatography (50% DCM/hexanes) as a white solid (46.3 mg, 0.180 mmol, 90% yield). Spectral data matches literature reported data:⁵¹ $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.42 – 7.28 (m, 5H), 7.10 – 6.97 (m, 2H), 6.92 – 6.82 (m, 2H), 5.38 (s, 1H), 4.44 (d, J = 6.0 Hz, 2H), 3.79 (s, 3H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 157.0, 155.2, 144.6, 138.1, 128.8, 127.8, 127.7, 122.5, 114.4, 55.7, 45.4.

4-Bromophenyl carbonofluoridate (4.2d)



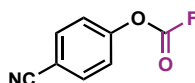
Commercially available 4-bromophenol (34.6 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 50 °C. The title compound had incomplete conversion at 2 h (65% yield) and 18 h (73% yield), and starting material was not easily separated. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.56 – 7.50 (m, 2H), 7.20 – 7.10 (m, 2H); $^{19}\text{F NMR}$ (282 MHz, CDCl_3) δ -17.10 (s, 1F).

4-Bromophenyl benzylcarbamate (4.3d)



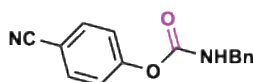
Commercially available 4-bromophenol (34.6 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure B** at 50 °C. The title compound was isolated via flash column chromatography (50% DCM/Hexanes) as a white crystalline solid (38.6 mg, 0.126 mmol, 63% yield). Spectral data matches reported literature data:⁵¹ **¹H NMR** (600 MHz, *CDCl*₃) δ 7.49 – 7.44 (m, 2H), 7.40 – 7.29 (m, 5H), 7.04 (d, *J* = 8.8 Hz, 2H), 5.33 (bs, 1H), 4.45 (d, *J* = 6.0 Hz, 2H); **¹³C NMR** (151 MHz, *CDCl*₃) δ 154.30, 150.23, 137.92, 132.44, 129.0, 128.0, 127.9, 123.5, 118.47, 45.5.

4-Cyanophenyl carbonofluoridate (4.2e)



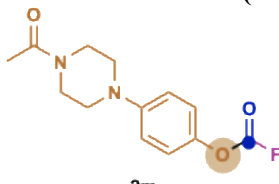
Commercially available 4-cyanophenol (23.8 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 50 °C. The title compound was not soluble in either DCM or Et₂O, so, after degassing α,α,α-trifluorotoluene (10 mg) was added directly to the reaction vial and yield was determined by *in situ* ¹⁹F NMR: **¹⁹F NMR** (376 MHz, *MeCN*) δ -14.18 (s, 1F).

4-Cyanophenyl *N*-benzylcarbamate (4.3e)



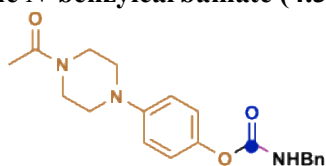
Commercially available 4-cyanophenol (23.8 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure B** at 50 °C. The title compound was isolated via flash column chromatography (1-10% MeOH/DCM) as a white crystalline solid (40.8 mg, 1.62 mmol, 81% yield). **¹H NMR** (600 MHz, *CDCl*₃) δ 8.18 (s, 1H), 7.55 – 7.45 (m, 2H), 7.37 – 7.29 (m, 3H), 7.29 – 7.23 (m, 2H), 6.96 – 6.89 (m, 2H), 5.11 (t, *J* = 5.6 Hz, 1H), 4.39 (d, *J* = 5.8 Hz, 2H); **¹³C NMR** (151 MHz, *CDCl*₃) δ 160.81, 158.80, 138.41, 134.28, 128.89, 127.72, 127.40, 119.69, 116.58, 102.88, 44.83; **IR** (ATR, neat, cm⁻¹): 3317, 2927, 2224, 1607, 1585, 1511, 1285, 1168, 837, 733, 696, 548; **mp** (°C): 69.4–72.9

N-acetyl-*N'*-(4-hydroxyphenyl)piperazine carbonofluoridate (4.2f)



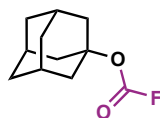
Commercially available N-acetyl-N'-(4-hydroxyphenyl)piperazine (44.0 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 50 °C. The title compound was isolated via DCM extraction (3 x 1 mL) in technical grade purity as a red oil (39.3 mg, 1.48 mmol, 74% yield, SM still present). ¹H NMR (600 MHz, CDCl₃) δ 7.12 (d, *J* = 9.1 Hz, 2H), 6.89 (d, *J* = 9.2 Hz, 2H), 3.72 (t, *J* = 5.3 Hz, 2H), 3.59 (t, *J* = 5.2 Hz, 2H), 3.12 (dt, *J* = 12.6, 5.3 Hz, 4H), 1.96 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 169.09, 150.24, 149.89, 144.21 (d, *J* = 285.6 Hz), 144.02 (d, *J* = 2.6 Hz), 120.90, 120.75, 117.40, 117.28, 49.73, 49.38, 46.13, 41.25, 21.35; ¹⁹F NMR (282 MHz, CDCl₃) δ -15.94 (s, 1F); IR (ATR, CDCl₃, cm⁻¹): 2917, 1833, 1644, 1508, 1435, 1224, 984, 767.

N-Acetyl-N'-(4-hydroxyphenyl)piperazine N-benzylcarbamate (4.3f)



Commercially available N-acetyl-N'-(4-hydroxyphenyl)piperazine (44.0 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure B** at 50 °C. The title compound was isolated via flash column chromatography (1-10% MeOH/DCM) in technical grade purity as a crystalline pale-yellow solid (50.8 mg, 1.44 mmol, 50% yield). ¹H NMR (600 MHz, CDCl₃) δ 7.38 – 7.27 (m, 5H), 7.06 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 5.38 (t, *J* = 6.1 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 2H), 3.80 – 3.72 (m, 2H), 3.64 – 3.56 (m, 2H), 3.12 (dd, *J* = 6.2, 4.1 Hz, 2H), 3.10 – 3.07 (m, 2H), 2.13 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 169.14, 155.19, 148.77, 144.95, 138.21, 128.88, 127.84, 127.81, 122.35, 117.82, 50.47, 50.04, 46.38, 45.46, 41.48, 21.46; IR (ATR, CDCl₃, cm⁻¹): 3329, 2919, 1732, 1627, 1503, 1439, 1206, 1000, 731, 698; mp (°C): 69.4-72.9.

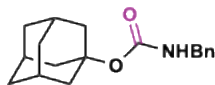
Adamant-1-yl carbonofluoridate (4.2g)



Commercially available 1-adamantanol (30.4 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 50 °C. The title compound was isolated via an ether extraction (3 x 1 mL) in technical grade purity (>95%, alkyl fluoride <5%) as a white solid (34.5 mg, 1.74 mmol, 87% yield). Spectral data matches literature reported data:⁵²

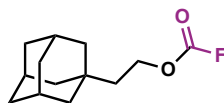
^1H NMR (600 MHz, CDCl_3) δ 2.25 (s, 3H), 2.14 (d, J = 3.1 Hz, 6H), 1.69 (s, 6H); ^{13}C NMR (151 MHz, CDCl_3) δ 142.6 (d, J = 285.9 Hz), 86.6 (d, J = 3.3 Hz), 40.6, 35.9, 31.2; ^{19}F NMR (377 MHz, CDCl_3) δ -5.72 (s, 1F).

Adamant-1-yl *N*-benzylcarbamate (4.3g)



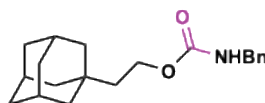
Commercially available 1-adamantanol (30.4 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure B** at 50 °C. The title compound was isolated via flash column chromatography (20% EtOAc/hexanes) as a white amorphous solid (45.6 mg, 1.60 mmol, 80% yield). Spectral data matches literature reported data:⁵³ ^1H NMR (600 MHz, CDCl_3) δ 7.39 – 7.34 (m, 2H), 7.34 – 7.28 (m, 3H), 4.93 (t, J = 6.0 Hz, 1H), 4.35 (d, J = 6.0 Hz, 2H), 2.20 (s, 3H), 2.16 (s, 6H), 1.74 – 1.65 (m, 6H); ^{13}C NMR (151 MHz, CDCl_3) δ 155.6, 139.1, 128.7, 127.6, 127.4, 79.5, 44.8, 41.8, 36.3, 31.0.

2-(Adamant-1-yl) carbonofluoridate (4.2h)



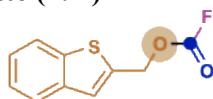
Commercially available 2-(adamant-1-yl)ethanol (36.0 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 30 °C. The title compound was isolated via ether extraction (3 x 1 mL) in technical grade purity (94%, alkyl fluoride 6%) as a clear oil (35.3 mg, 1.80 mmol, 74% yield). ^1H NMR (600 MHz, CDCl_3) δ 4.35 (t, J = 7.1 Hz, 2H), 1.99 – 1.95 (m, 3H), 1.72 (d, J = 11.6 Hz, 3H), 1.65 – 1.62 (m, 3H), 1.54 – 1.50 (m, 8H); ^{13}C NMR (151 MHz, CDCl_3) δ 145.8 (d, J = 283.6 Hz), 68.6 (d, J = 2.3 Hz), 42.5, 42.0, 37.0, 31.8, 28.6; ^{19}F NMR (377 MHz, CDCl_3) δ -16.05 (s, 1F).

2-(Adamant-1-yl) *N*-benzylcarbamate (4.3h)



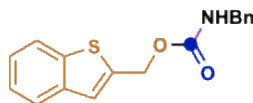
Commercially available 2-(adamant-1-yl)ethanol (36.0 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure B** at 30 °C. The title compound was isolated via flash column chromatography (50% DCM/hexanes) as a white amorphous solid (43.2 mg, 1.38 mmol, 69% yield). **¹H NMR** (600 MHz, *CDCl*₃) δ 7.40 – 7.35 (m, 2H), 7.35 – 7.30 (m, 3H), 4.97 (bs, 1H), 4.41 (d, *J* = 5.9 Hz, 2H), 4.20 (t, *J* = 7.4 Hz, 2H), 1.98 (s, 3H), 1.74 (d, *J* = 12.4 Hz, 3H), 1.67 (d, *J* = 12.2 Hz, 3H), 1.59 – 1.52 (m, 6H), 1.46 (t, *J* = 7.4 Hz, 2H); **¹³C NMR** (151 MHz, *CDCl*₃) δ 156.92, 138.78, 129.39, 128.79, 127.67 (b), 127.59, 61.71, 45.19, 42.95, 42.68, 37.17, 31.90, 28.74. **IR** (ATR, *CDCl*₃, cm⁻¹): 3370, 2900, 2846, 2229, 1698, 1617, 1544, 749, 702; **mp** (°C): 98.7-91.6.

Benzothiophene-2-ylmethyl carbonofluoridate (4.2i)



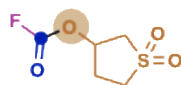
Commercially available benzothiophene-2-methanol (32.8 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 30 °C. The title compound was isolated via ether extraction (3 x 1 mL) in technical grade purity as a light-yellow oil (32.8 mg, 0.156 mmol, 78% yield, trace amounts of alkyl fluoride). **¹H NMR** (600 MHz, *CDCl*₃) δ 7.87 – 7.83 (m, 1H), 7.83 – 7.78 (m, 1H), 7.43 (d, *J* = 0.9 Hz, 1H), 7.42 – 7.36 (m, 2H), 5.52 (d, *J* = 0.8 Hz, 2H); **¹³C NMR** (151 MHz, *CDCl*₃) δ 145.54 (d, *J* = 286.9 Hz), 140.96, 139.00, 135.16, 126.73, 125.57, 124.89, 124.39, 122.63, 67.73; **¹⁹F NMR** (282 MHz, *CDCl*₃) δ -16.60, -196.9 (m, alkyl fluoride); **IR** (ATR, *CDCl*₃, cm⁻¹): 3050, 1827, 1537, 1435, 1374, 1229, 747.

Benzothiophene-2-ylmethyl *N*-benzylcarbamate (4.3i)



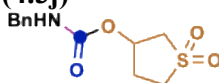
Commercially available benzothiophene-2-methanol (32.8 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure B** at 30 °C. The title compound was isolated via column (0-5% MeOH/DCM) as a white crystalline solid (44.5 mg, 0.150 mmol, 75% yield). **¹H NMR** (600 MHz, *CDCl*₃) δ 7.89 – 7.82 (m, 1H), 7.82 – 7.76 (m, 1H), 7.41 – 7.25 (m, 8H), 5.41 (s, 2H), 5.17 (s, 1H), 4.44 (d, *J* = 6.1 Hz, 2H); **¹³C NMR** (151 MHz, *CDCl*₃) δ 156.13, 140.57, 139.59, 139.38, 138.32, 128.83, 127.71, 127.68, 124.74, 124.51, 124.22, 123.91, 122.52, 62.05, 45.34; **IR** (ATR, neat, cm⁻¹): 3309, 3060, 3030, 2914, 1692, 1494, 1266, 726, 695; **mp** (°C): 125.7-128.3

(1,1-Dioxothiolan-3-yl) carbonofluoridate (4.2j)



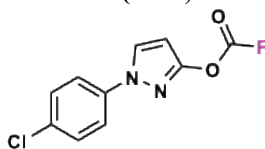
Commercially available 3-hydroxy-sulfolane (27.2 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 50 °C. The title compound was isolated via ether extraction (3 x 1 mL) in technical grade purity as a clear oil (5.8 mg, 0.32 mmol, 16% yield, ^{19}F -NMR yield >99%); ^1H NMR (600 MHz, CDCl_3) δ 5.49 (pd, $J = 4.0$, 1.4 Hz, 1H), 3.51 – 3.46 (m, 1H), 3.37 (d, $J = 14.9$ Hz, 1H), 3.33 – 3.27 (m, 1H), 3.25 – 3.19 (m, 1H), 2.65 – 2.57 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 144.50 (d, $J = 289.5$ Hz), 76.87, 55.90, 48.89, 28.72; ^{19}F NMR (282 MHz, *in MeCN*) δ -18.38 (s, 1F); IR (ATR, CDCl_3 , cm^{-1}): 2959, 1821, 1404, 1252, 1124, 773

(1,1-Dioxothiolan-3-yl) *N*-benzylcarbamate (4.3j)



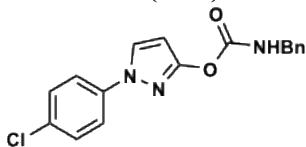
Commercially available 3-hydroxy-sulfolane (27.2 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure B** at 50 °C. The title compound was isolated via flash column chromatography (1-5% MeOH:DCM) as a white solid (44.1 mg, 1.64 mmol, 82% yield). ^1H NMR (600 MHz, CDCl_3) δ 7.37 (t, $J = 7.4$ Hz, 2H), 7.34 – 7.27 (m, 3H), 5.54 – 5.34 (m, 2H), 4.43 – 4.30 (m, 2H), 3.37 (dd, $J = 14.5$, 6.2 Hz, 1H), 3.30 – 3.20 (m, 2H), 3.19 – 3.10 (m, 1H), 2.53 – 2.44 (m, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.92, 137.90, 128.84, 127.80, 127.63, 70.39, 57.13, 49.44, 45.17, 29.31; IR (ATR, neat, cm^{-1}): 3371, 3028, 2961, 1698, 1683, 1525, 1305, 1253, 1123, 697; mp (°C): 87.4-88.3.

1-(4-Chlorophenyl)-pyrazol-3-yl carbonofluoridate (4.2k)



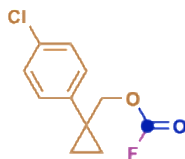
Commercially available 1-(4-chlorophenyl)-pyrazol-3-ol (38.8 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 50 °C. The title compound was not soluble in either DCM or Et₂O, so, after degassing α,α,α -trifluorotoluene (10 mg) was added directly to the reaction vial and yield was determined by *in-situ* ^{19}F NMR. ^{19}F NMR (282 MHz, *in MeCN*) δ -17.93 (s, 1F).

1-(4-Chlorophenyl)-pyrazol-3-yl *N*-benzylcarbamate (4.3k)



Commercially available 1-(4-chlorophenyl)-pyrazol-3-ol (38.8 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure B** at 50 °C. The title compound was isolated via flash column chromatography (50% DCM/hexanes) as a light yellow crystalline solid (38.4 mmol, 0.118 mmol, 59% yield). **¹H NMR** (600 MHz, *CDCl*₃) δ 7.78 (d, *J* = 2.6 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.40 – 7.27 (m, 7H), 6.42 (d, *J* = 2.6 Hz, 1H), 5.64 (s, 1H), 4.45 (d, *J* = 6.0 Hz, 2H); **¹³C NMR** (151 MHz, *CDCl*₃) δ 157.2, 153.0, 138.3, 137.6, 131.8, 129.5, 128.8, 127.8, 127.7, 127.6, 119.7, 99.3, 45.3; **IR** (ATR, neat, cm⁻¹): 3316, 3148, 1718, 1527, 1465, 1252, 831, 742.; **mp** (°C): 137.6 – 139.1.

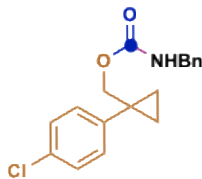
1-(4-Chlorophenyl)cyclopropyl)methyl carbonofluoridate (4.2l)



(1-(4-chlorophenyl)cyclopropyl)methanol (36.4 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 30 °C. The title compound was isolated via ether extraction (3 x 1 mL) in technical grade purity as a clear oil (37.4 mg, 0.166 mmol, 83% yield, >95% pure). **¹H NMR** (400 MHz, *CDCl*₃) δ 7.30 (s, 4H), 4.34 (s, 2H), 1.07 – 1.03 (m, 2H), 1.02 (t, *J* = 1.8 Hz, 2H); **¹³C NMR** (101 MHz, *CDCl*₃) δ 145.61 (d, *J* = 284.6 Hz), 139.68, 132.97, 130.46, 128.70, 79.00 (d, *J* = 2.2 Hz), 24.33, 12.08; **¹⁹F NMR** ((377 MHz, *CDCl*₃) δ -16.33 (s, 1F). *Scale Up to 1.0 mmol*: In the glovebox under N₂ atmosphere a 20 mL Schlenk tube with stir bar was charged with (1-(4-chlorophenyl)cyclopropyl)methanol (0.182 g, 1.00 mmol, 1.00 equiv.), anhydrous KF (0.4 mmol, 0.2 equiv., 23.2 mg) and anhydrous MeCN (2.5 mL, 0.4 M). The tube was capped with a pierceable Teflon lined 2-dr cap (Agilent: 5183-4306) then removed from the glovebox. Anhydrous DMSO (28 μL, 0.4 mmol, 2.0 equiv.) was added using syringe and the solution was allowed to stir for 5 min. before TFDA (80 μL, 0.4 mmol, 2.0 equiv.) was added via syringe and the reaction placed in a 30 °C oil bath. The reaction was allowed to stir for 2 h before the reaction was then removed from the block and allowed to cool to room temperature, after which it was degassed with N₂, transferred to a separate vial and concentrated. The resulting residue was dissolved in a minimal amount of either

Et₂O, then passed through a 1 cm silica plug and eluted with Et₂O (3 × 1 mL) then concentrated to yield the title compound in technical grade purity as a clear oil (0.198 g, 0.87 mmol, 87% yield, >95% pure).

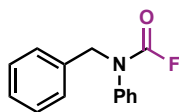
(1-(4-Chlorophenyl)cyclopropyl)methyl benzylcarbamate (4.3l)



(1-(4-chlorophenyl)cyclopropyl)methanol (36.4 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure B** at 50 °C. The title compound was isolated via flash column chromatography (5% MeOH/DCM) as a white solid (52.9 mg, 0.168 mmol, 84% yield). ¹H NMR (600 MHz, CDCl₃) δ 7.51 – 7.06 (m, 9H), 5.04 (bs, *J* = 6.0 Hz, 1H), 4.37 (d, *J* = 6.0 Hz, 2H), 4.22 (s, 2H), 1.04 – 0.89 (m, 4H); ¹³C NMR (151 MHz, CDCl₃) δ 156.60, 141.36, 138.54, 132.31, 130.13, 128.78, 128.47, 127.63, 72.03, 45.17, 24.67, 12.36; IR (ATR, CDCl₃, cm⁻¹): 3324, 2225, 1693, 1512, 1494, 1230, 696, 530; mp (°C): 85.4-88.7.

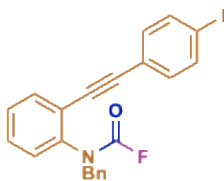
4.7.3.2 Characterization data for carbamoyl fluorides

N-Benzyl-N-phenyl carbamic fluoride (4.5a)

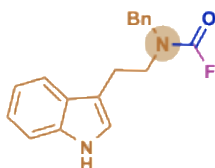


Commercially available *N*-benzylaniline (36.6 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 50 °C. The title compound was isolated via flash column chromatography (10% EtOAc/pentanes) as a white solid (32.1 mg, 1.40 mmol, 70% yield). Spectral data matches literature reported data:³⁸ ¹H NMR (400 MHz, CDCl₃): δ 7.40 – 7.25 (m, 6H), 7.27–7.22 (m, 2.5H), 7.06 (d, *J* = 7.3 Hz, 1.5H), 4.84 (s, 2H); ¹⁹F NMR (377 MHz, CDCl₃, rotamers): δ -14.63 (s, 1F), -17.06 (s, 0.35 F).

2-((4-iodophenyl)ethynyl)phenyl(benzyl)carbamic fluoride (4.5b)



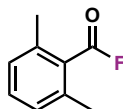
N-(benzyl)-2-((4-iodophenyl)ethynyl)phenyl)-aniline (36.6 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 50 °C. The title compound was isolated via flash column chromatography (5% EtOAc/hexanes) as a yellow oil (48.3 mg, 1.06 mmol, 53% yield). Spectral data matches literature reported data:³ **Rotamer ratio** (1:0.34); ¹H NMR (400 MHz, CDCl₃) δ 7.73 (dd, *J* = 8.6, 2.1 Hz, 2H), 7.65 – 7.52 (m, 1H), 7.38 – 7.18 (m, 9H), 6.97 (d, *J* = 1.4 Hz, 1H), 4.88 (t, *J* = 84.0 Hz, 2H); ¹⁹F NMR (377 MHz, CDCl₃) δ -14.07 (s, 1F), -19.30 (s, 0.34F). ***N*-Benzyl-*N*-[2-(1*H*-indol-3-yl)ethyl] carbamic fluoride (4.5c)**



Commercially available *N*-benzyltryptamine (30.0 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A** at 50 °C. The title compound was isolated via flash column chromatography (10% EtOAc/pentanes) as a white solid (28.4 mg, 0.096 mmol, 48% yield). Spectral data matches literature reported data:³⁸ **Rotamer ratio** (1:0.84); ¹H NMR (600 MHz, CDCl₃) δ 8.23 (bd, *J* = 10.1 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 0.5H), 7.56 (d, *J* = 7.9 Hz, 0.5H), 7.47 – 7.37 (m, 4H), 7.34 – 7.20 (m, 4H), 7.02 (dd, *J* = 19.7, 2.4 Hz, 1H), 4.43 (d, *J* = 46.9 Hz, 2H), 3.66 – 3.51 (m, 2H), 3.10 (ddd, *J* = 44.5, 8.7, 6.5 Hz, 2H); ¹⁹F NMR (377 MHz, CDCl₃) δ -21.32 (d, *J* = 11.8 Hz, 1F), -21.82 (d, *J* = 8.5 Hz, 1F).

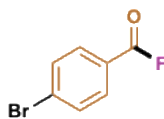
4.7.3.3 Characterization data for acyl fluorides

2,6-Dimethylbenzoyl fluoride (4.7a)



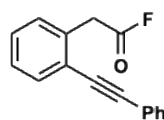
Commercially available 2,6-dimethylbenzoic acid (30.0 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A**. The title compound was isolated via flash column chromatography (10% EtOAc/pentanes) as a white solid (25.5 mg, 0.168 mmol, 84% yield). Spectral data matches literature reported data:⁵⁴ ¹H NMR (400 MHz, CDCl₃) δ 7.41 (t, *J* = 8.5 Hz, 1H), 6.59 (dd, *J* = 8.5, 1.0 Hz, 2H), 3.87 (s, 6H); ¹⁹F NMR (377 MHz, CDCl₃) δ 53.63 (s, 1F).

4-Bromobenzoyl fluoride (4.7b)



Commercially available 4-bromobenzoic acid (40.2 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure A**. The title compound was isolated via flash column chromatography (5% OEt₂/hexanes) as a white solid (32.6 mg, 0.162 mmol, 81% yield). Spectral data matches literature reported data:⁵⁴ ¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H); ¹⁹F NMR (282 MHz, CDCl₃) δ 18.43 (s, 1F).

2-[2-(2-Phenylethynyl)phenyl]acetyl fluoride (4.7c)



2-(2-(phenylethynyl)phenyl)acetic acid (43.2 mg, 0.20 mmol, 1.00 equiv.) was subjected to **general procedure C**. The title compound was isolated via flash column chromatography (0-5% OEt₂/hexanes) as a yellow oil (28.1 mg, 0.118 mmol, 59% yield). Spectral data matches literature reported data: ¹H NMR (300 MHz, CDCl₃) δ 7.56 (dt, *J* = 16.8, 3.0 Hz, 3H), 7.36 (s, 6H), 4.08 (s, 2H); ¹⁹F NMR (282 MHz, CDCl₃) δ 45.40 (s, 1F).

4.8 References

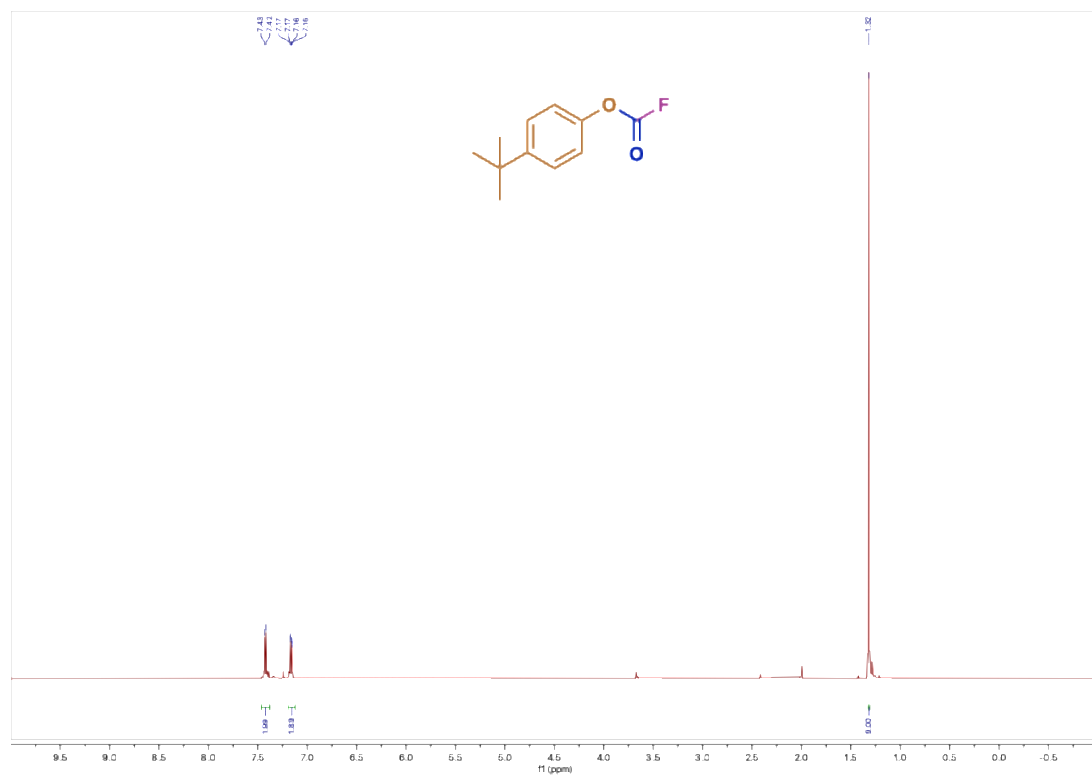
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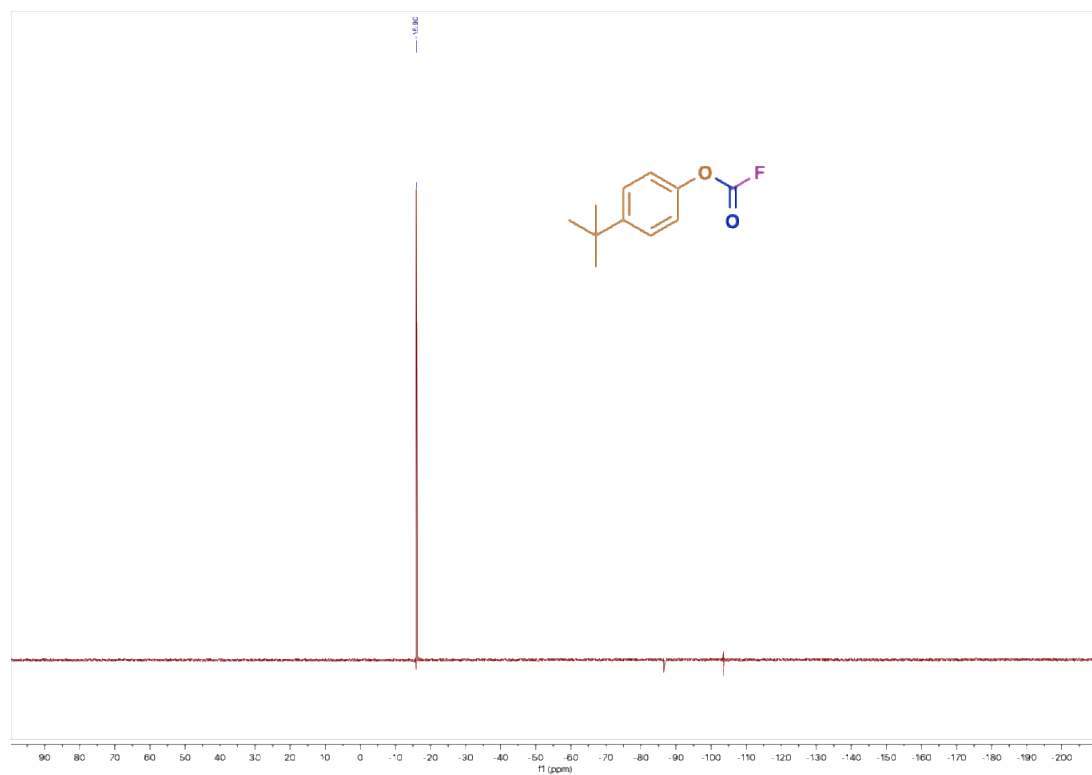
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4.9 Appendix

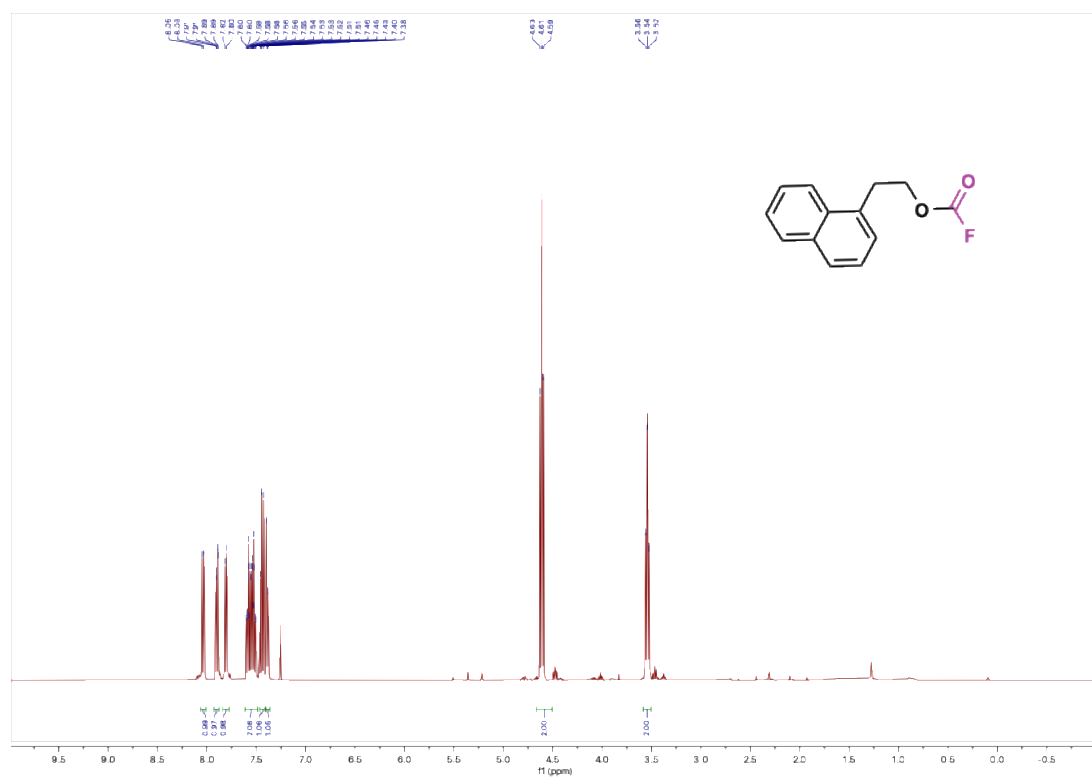
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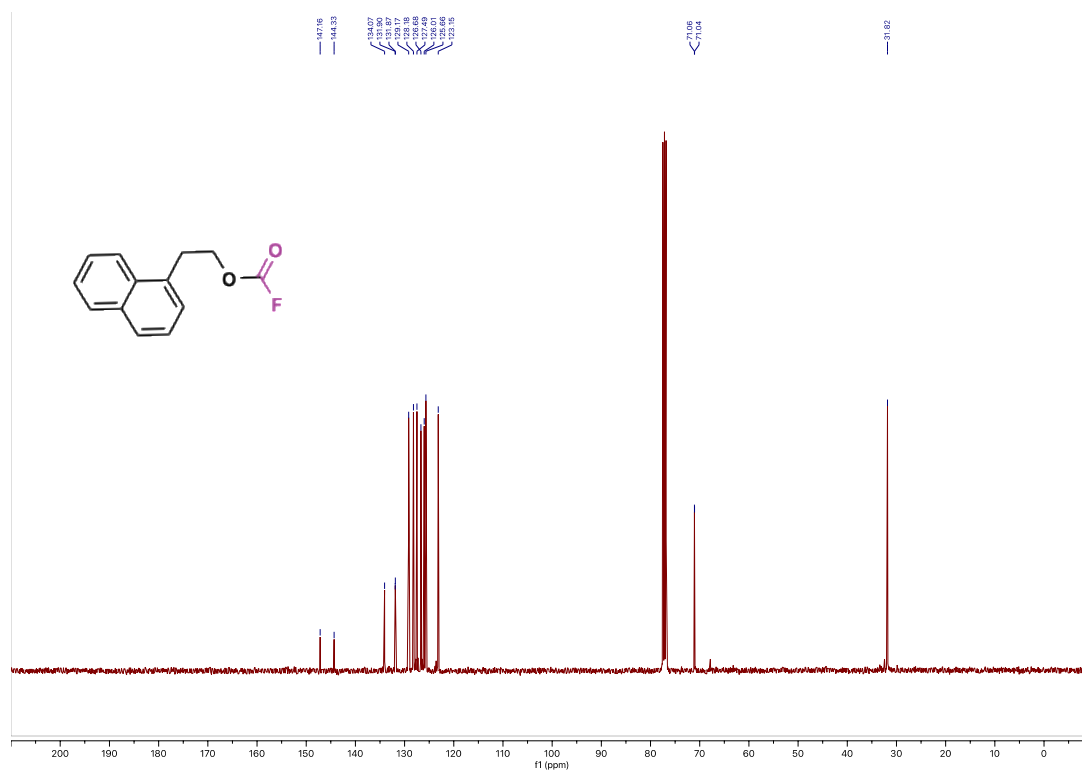
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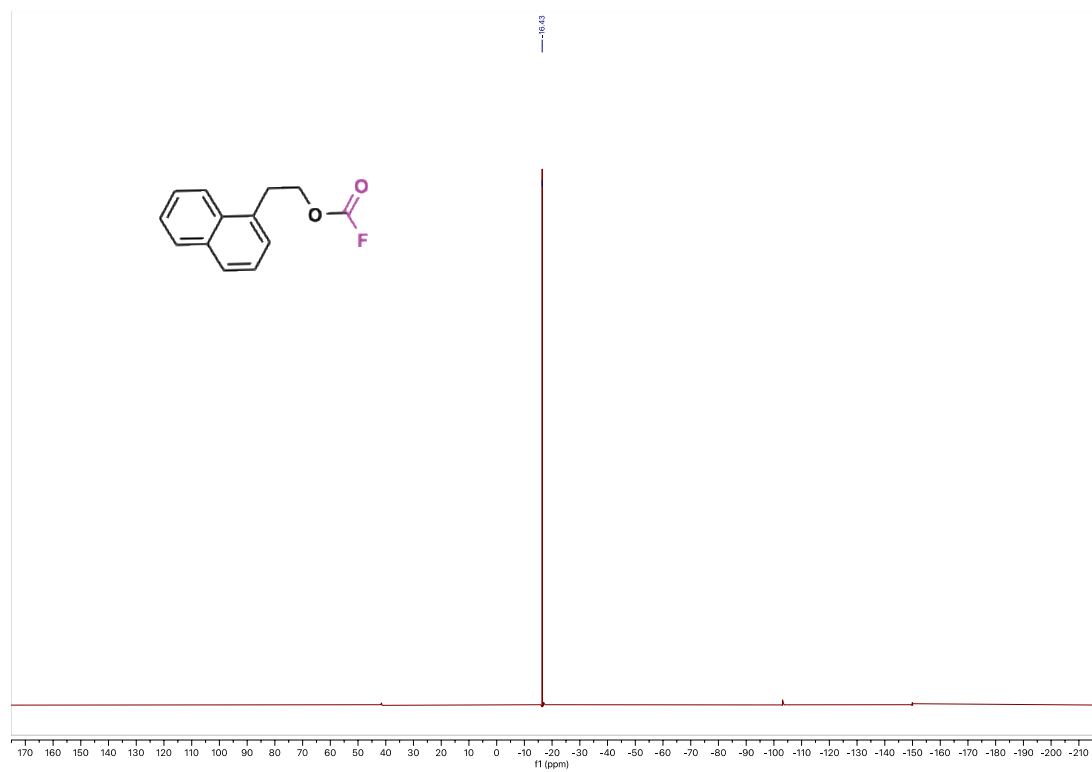
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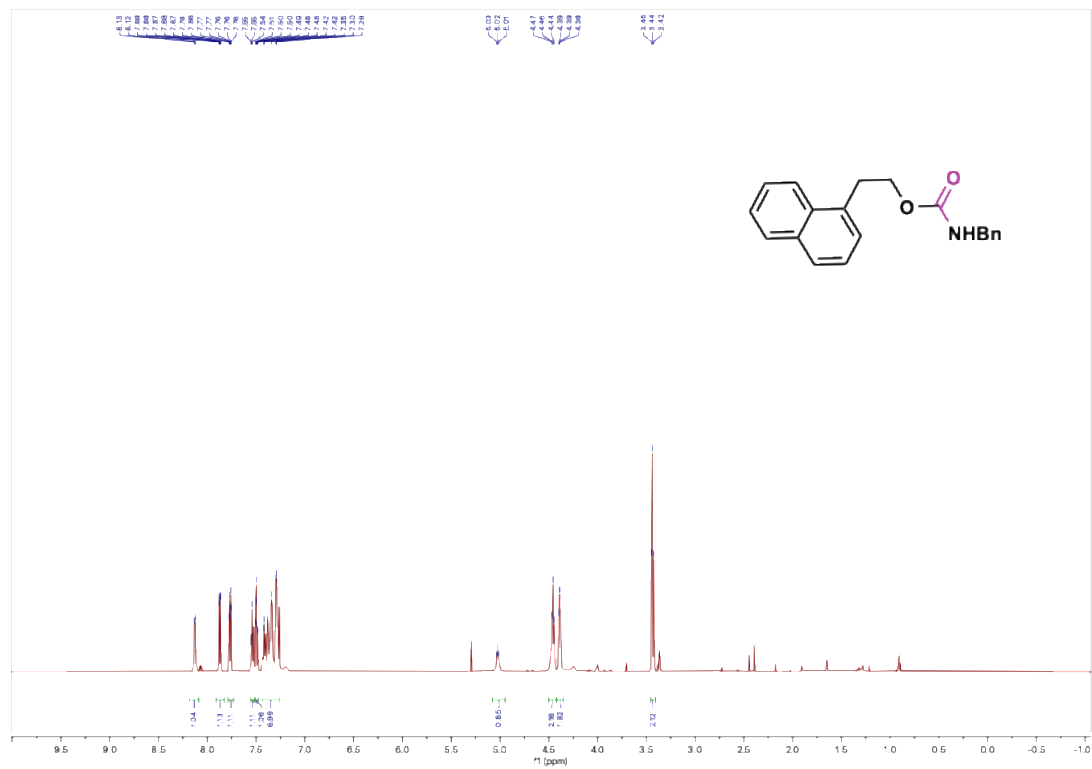
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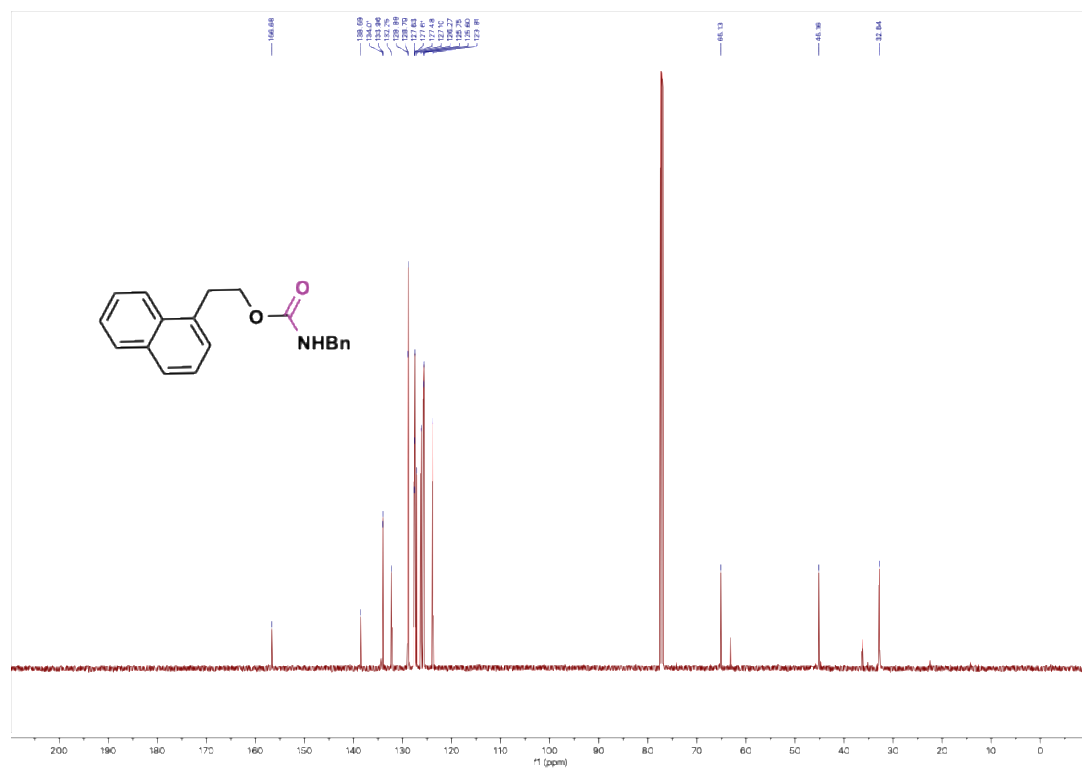
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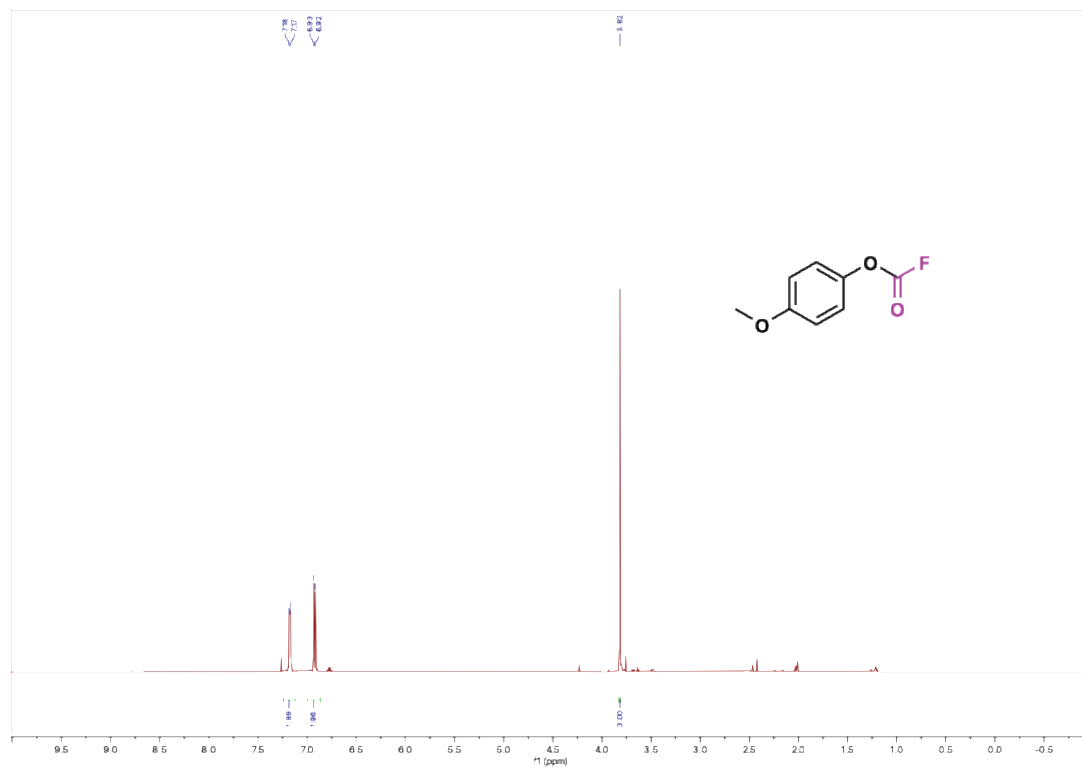
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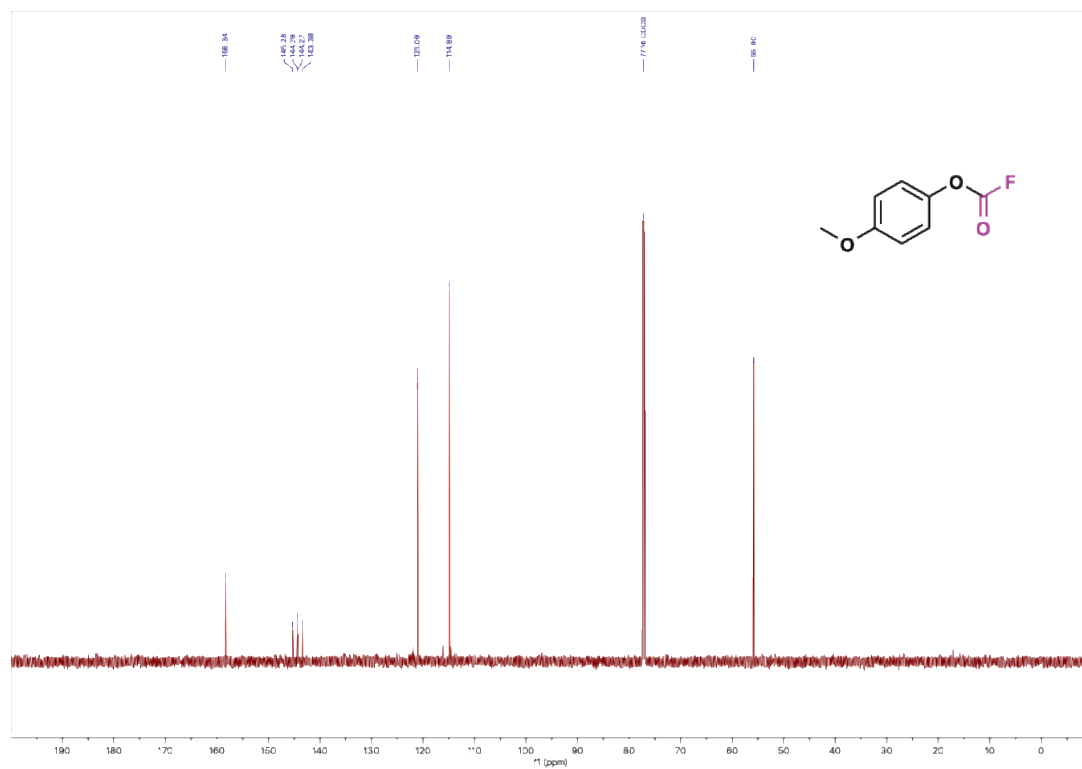
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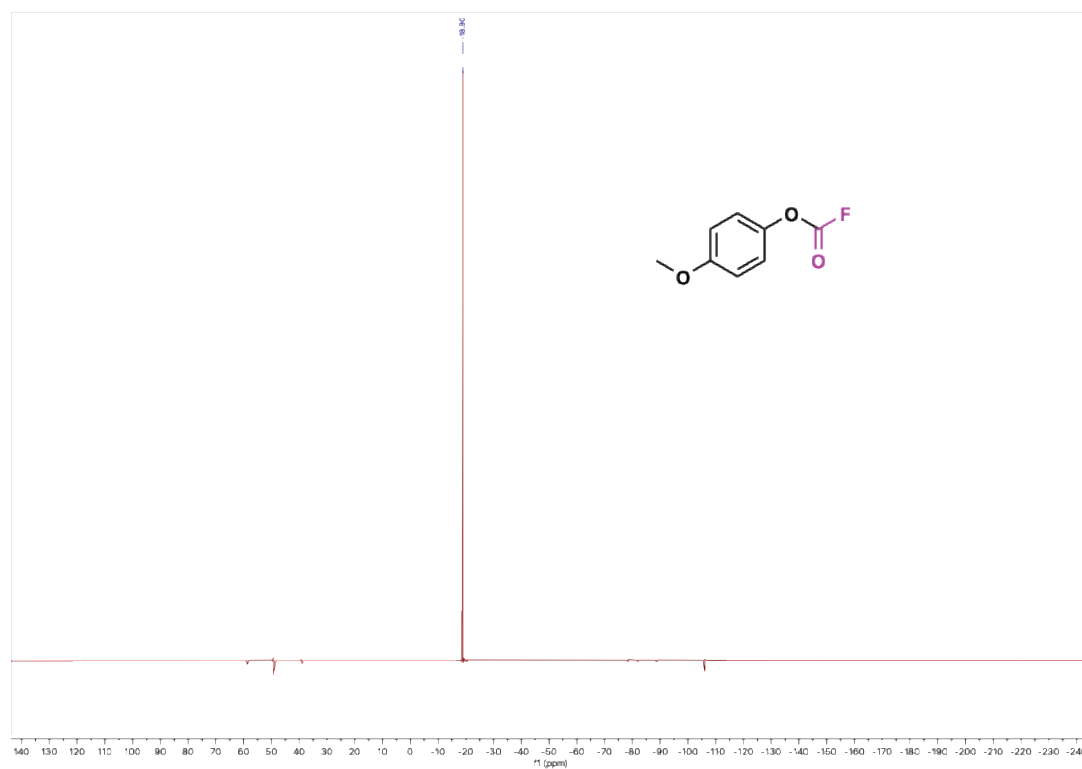
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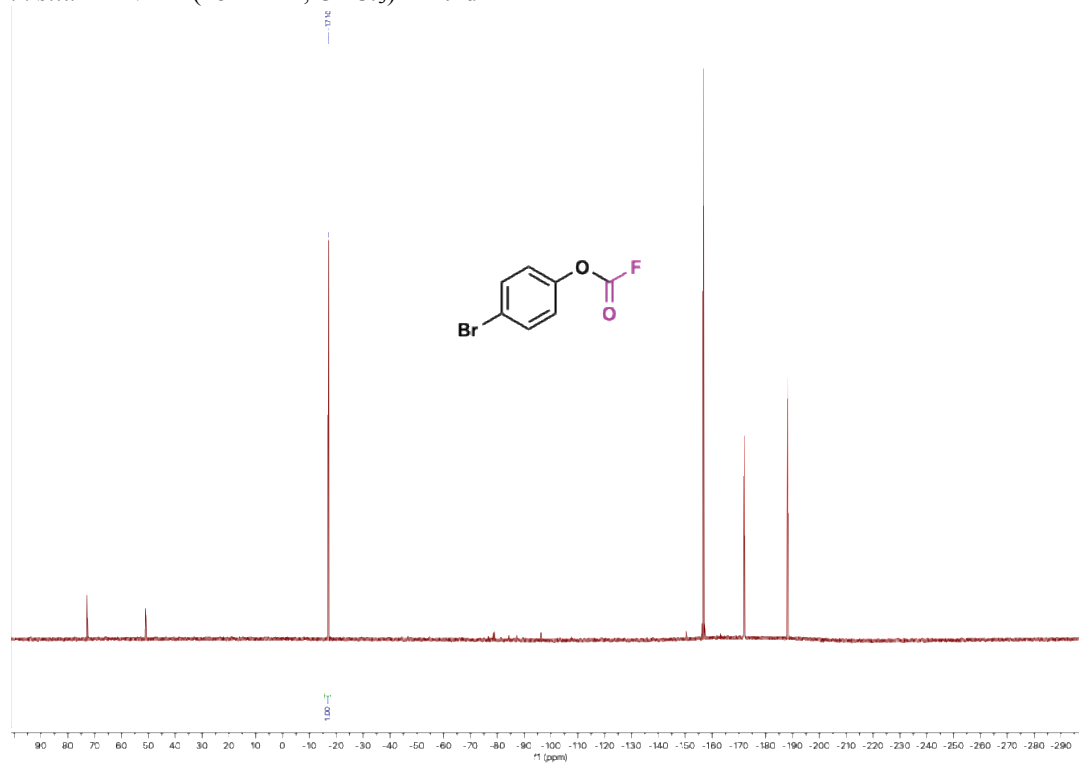
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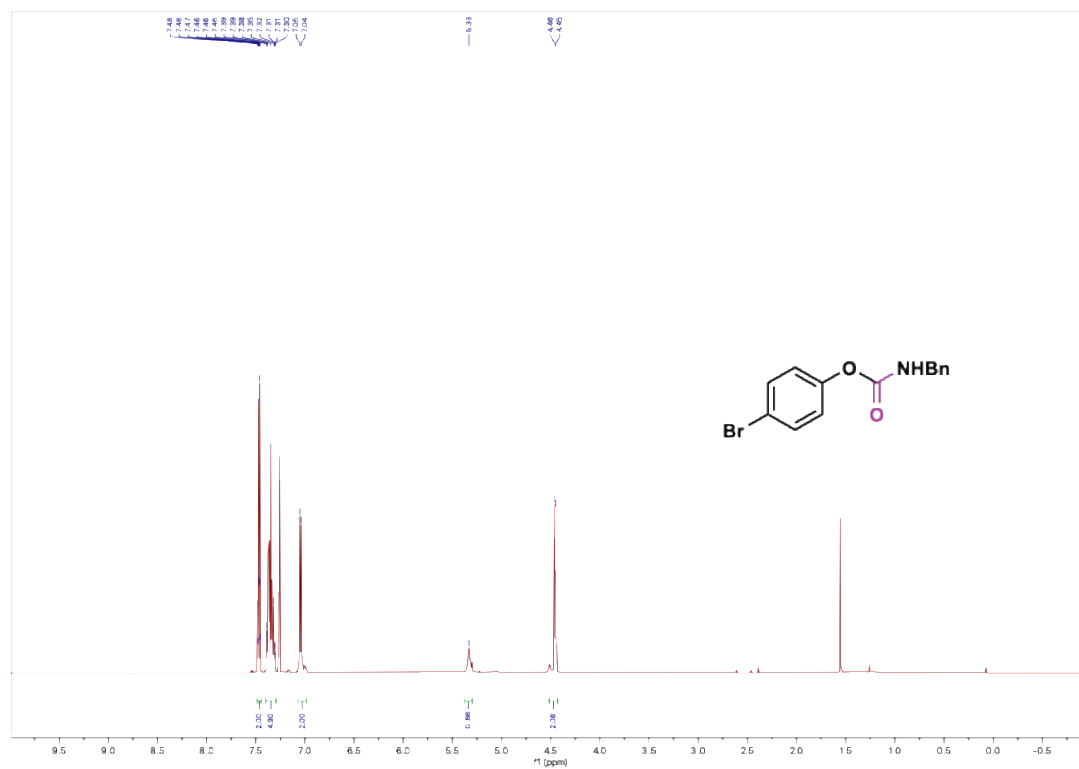
Crude ^1H NMR (600 MHz, CDCl_3) of **4.2d** + starting alcohol



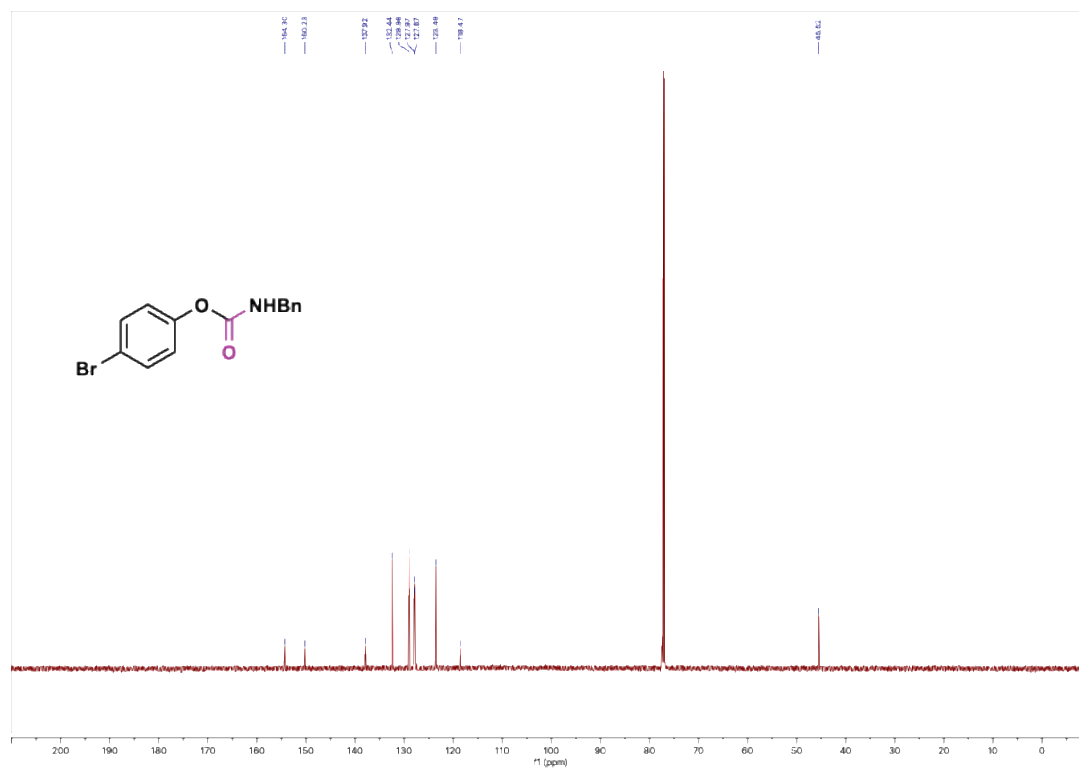
in situ ^{19}F NMR (282 MHz, CDCl_3) of **4.2d**



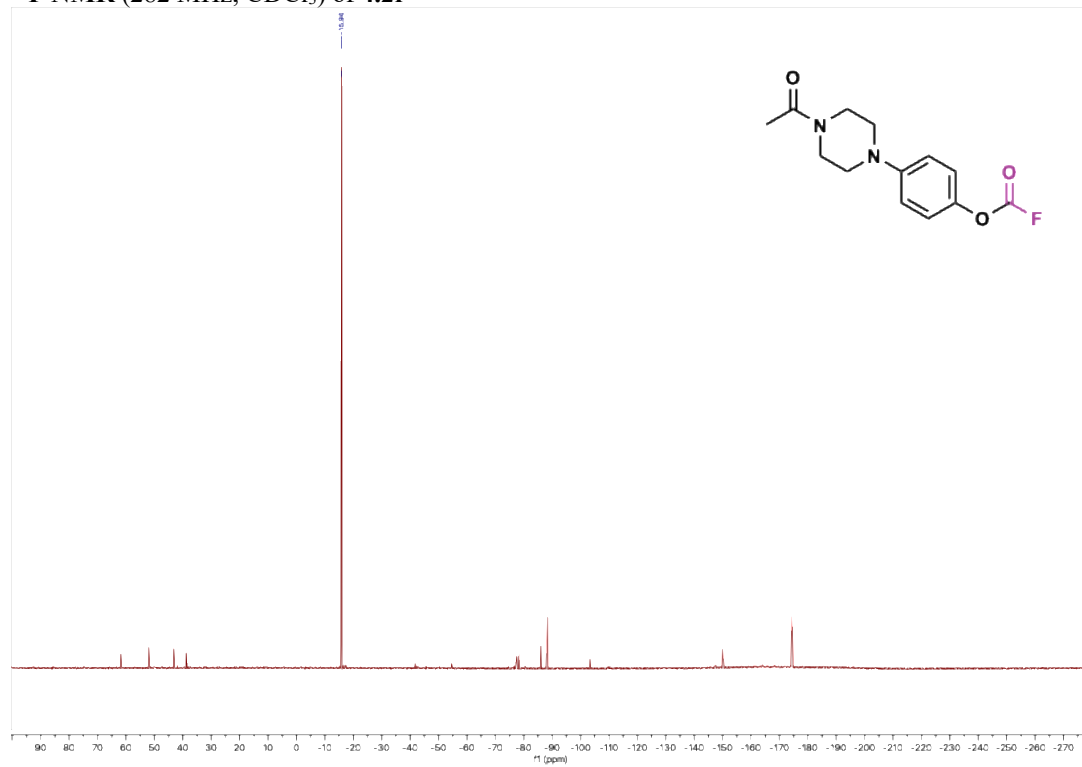
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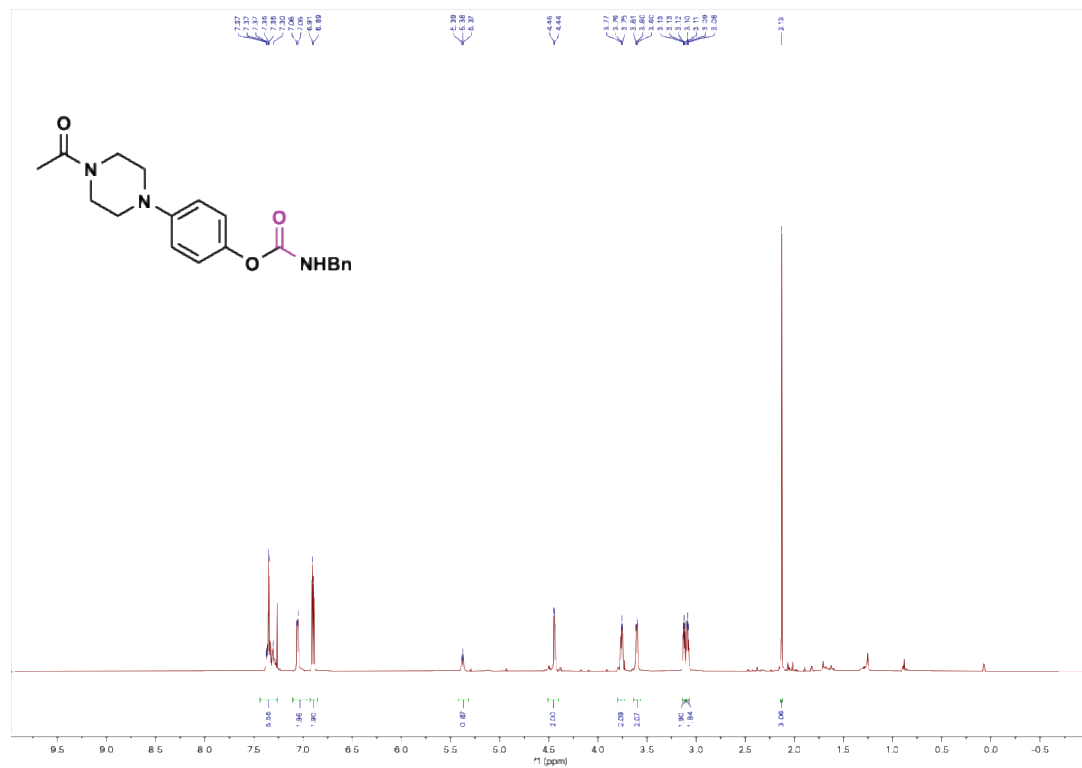
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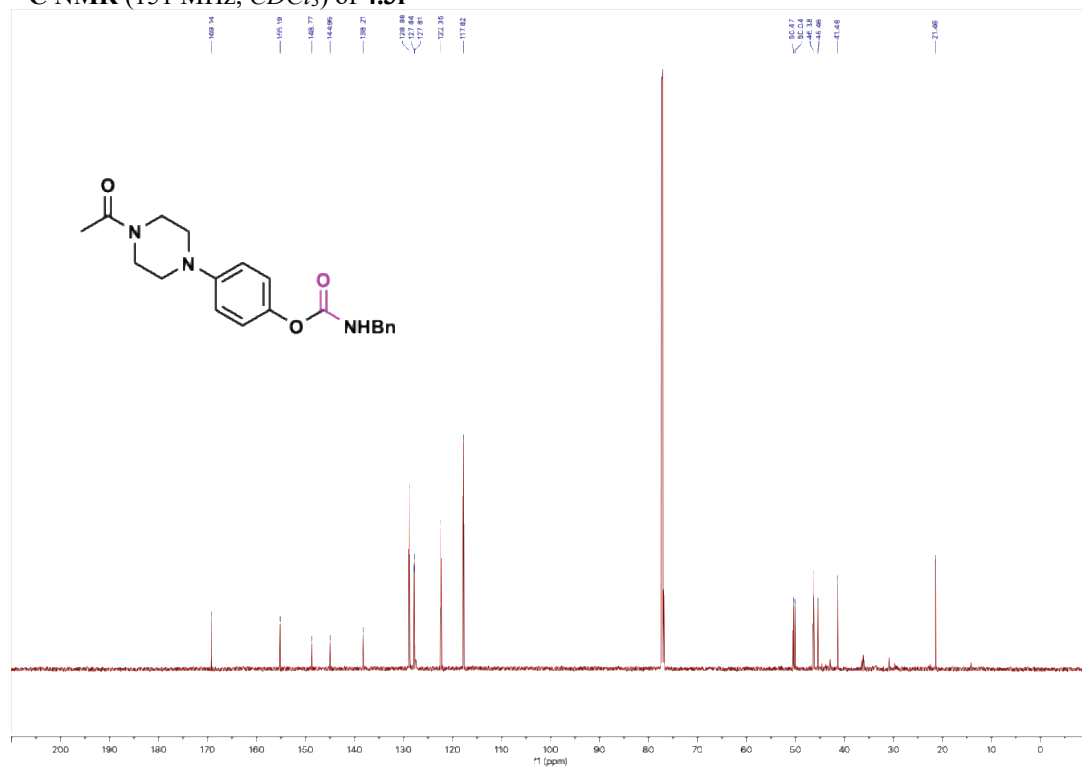
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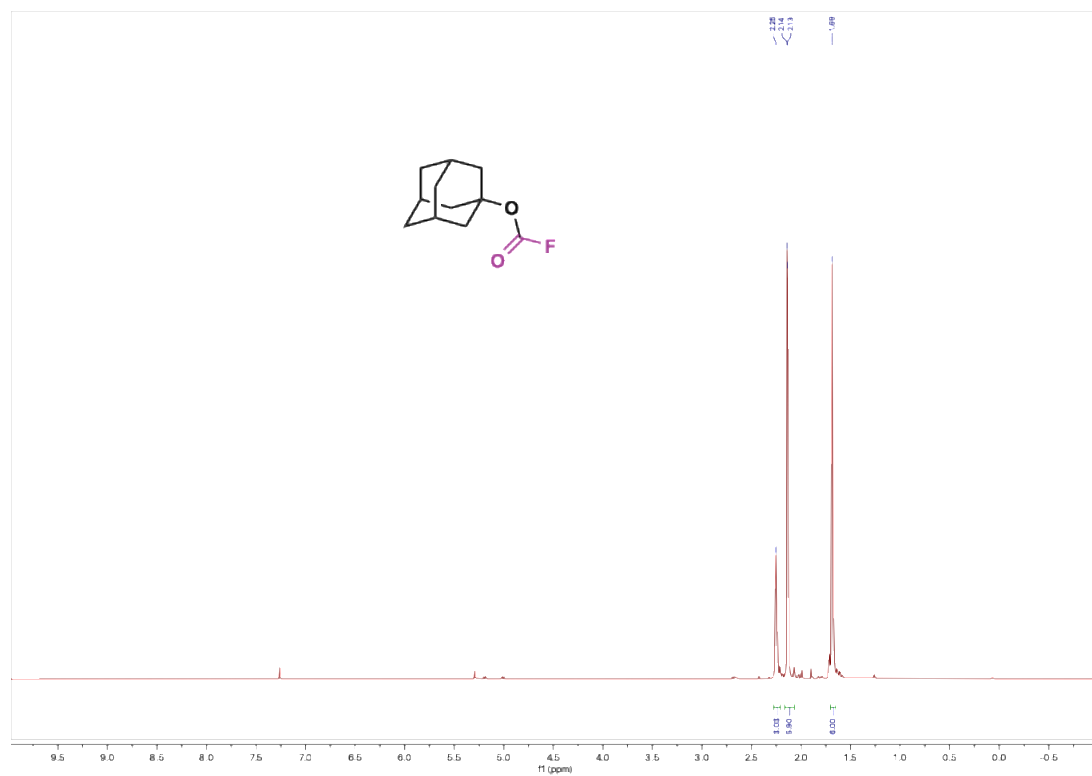
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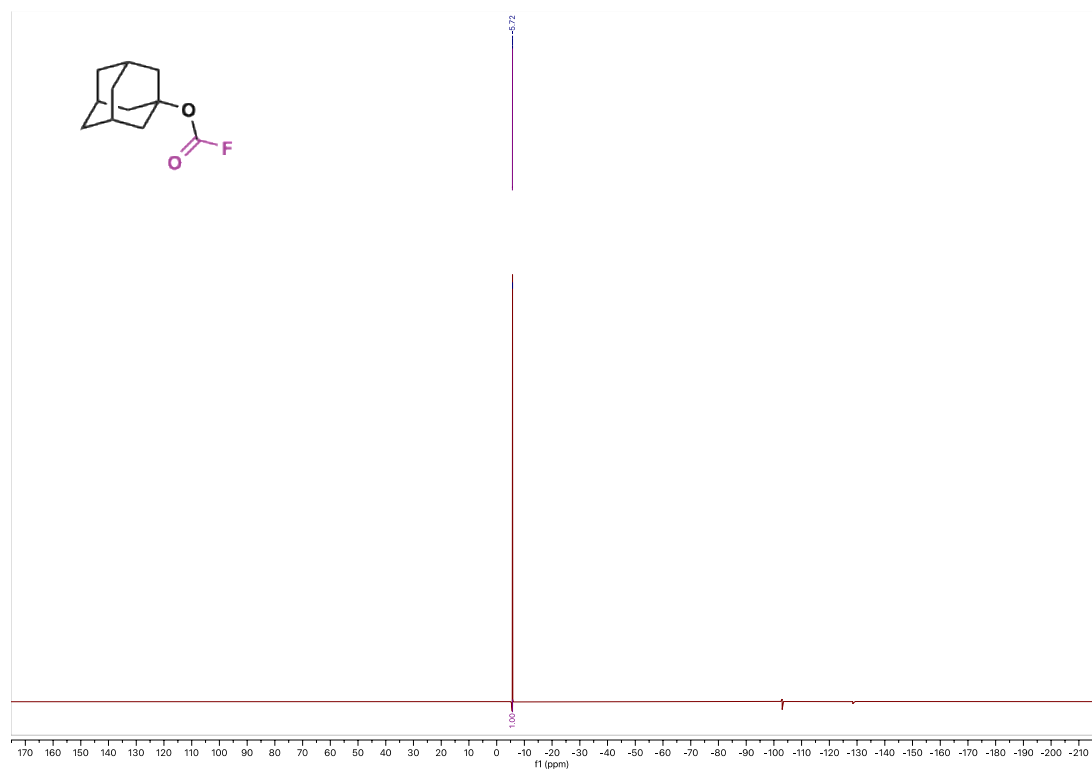
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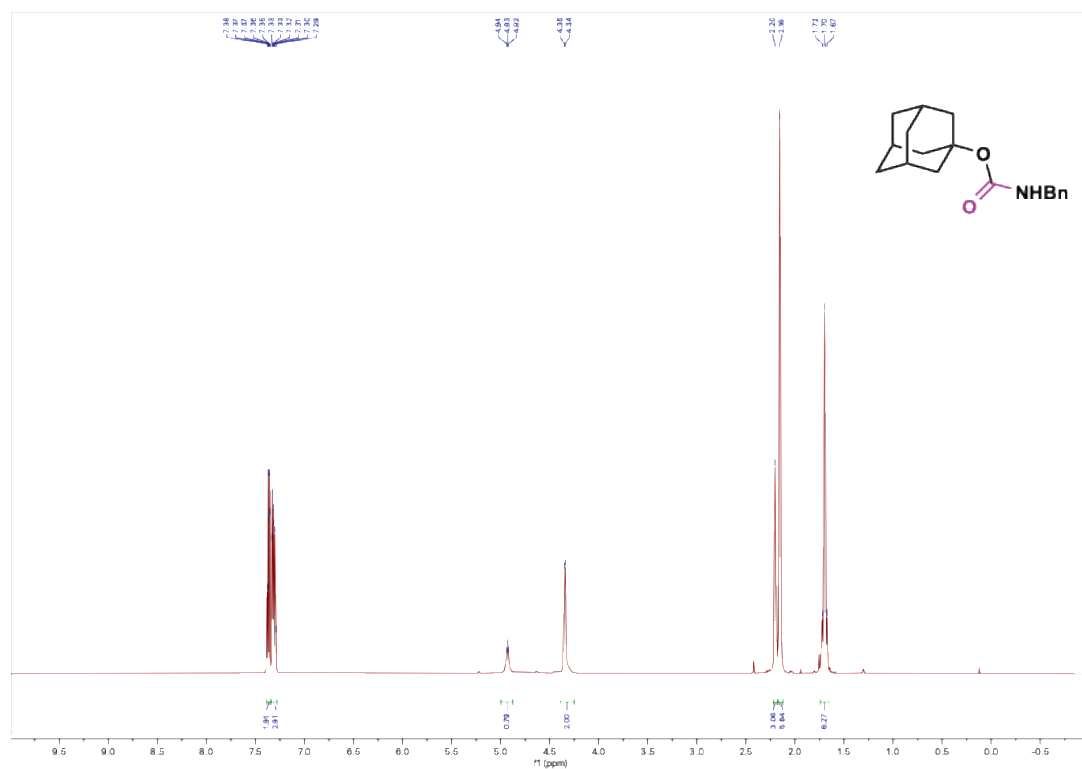
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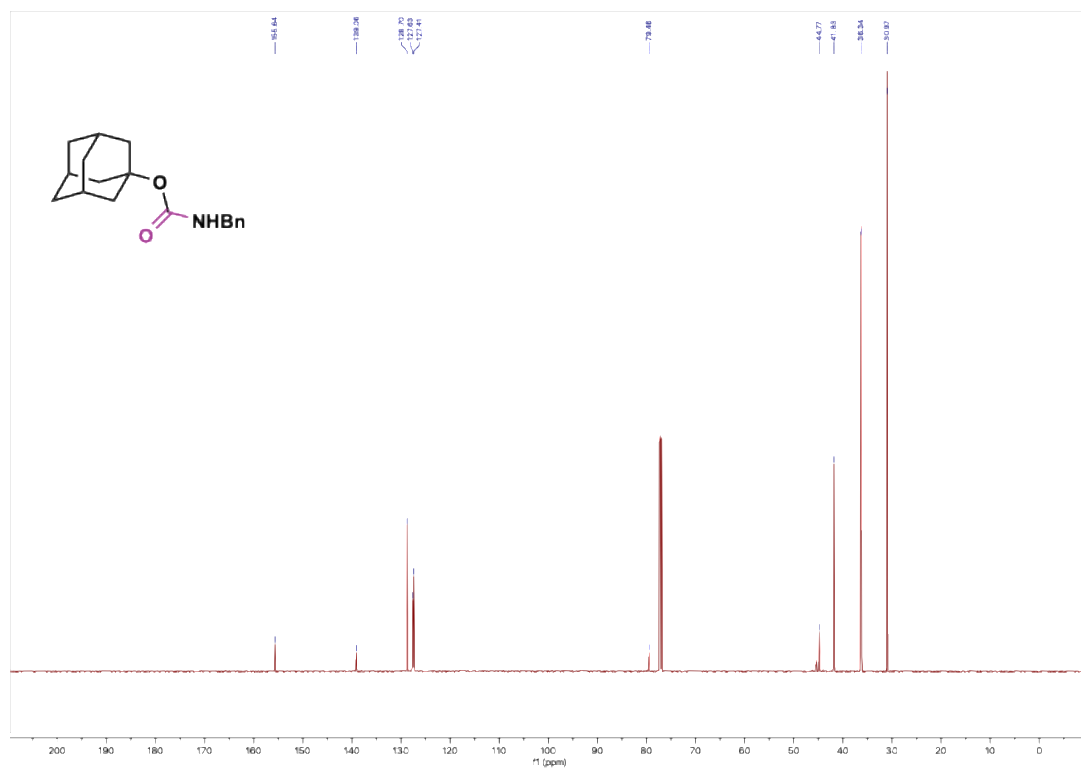
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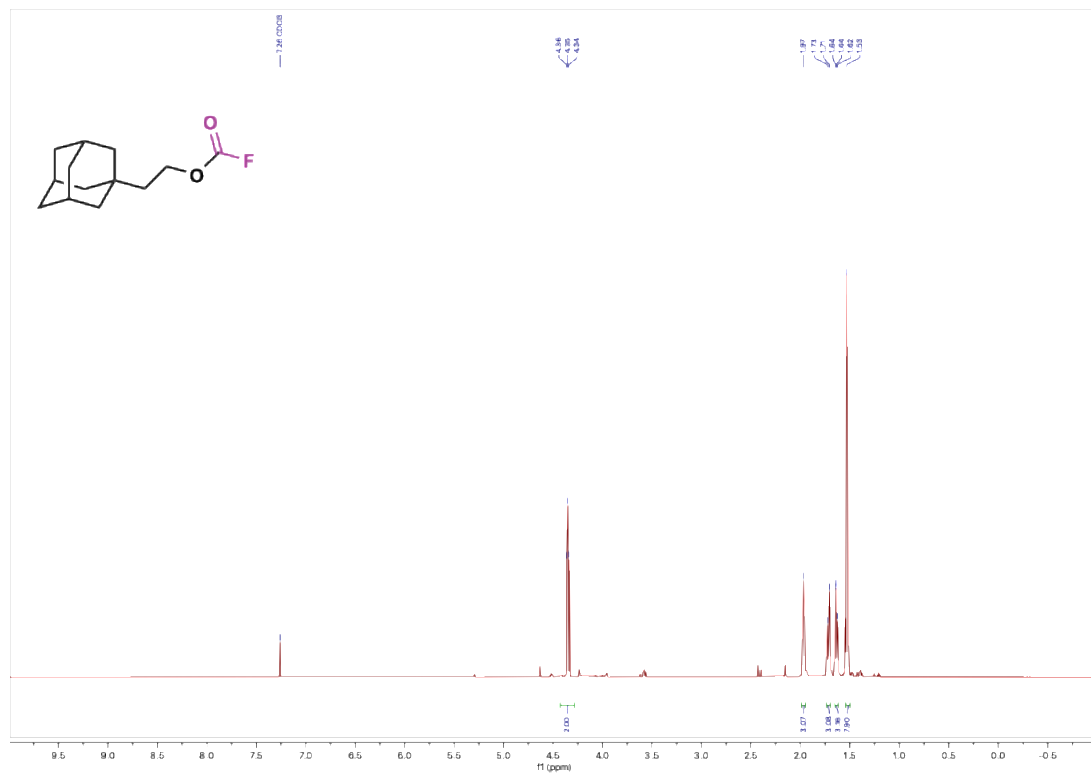
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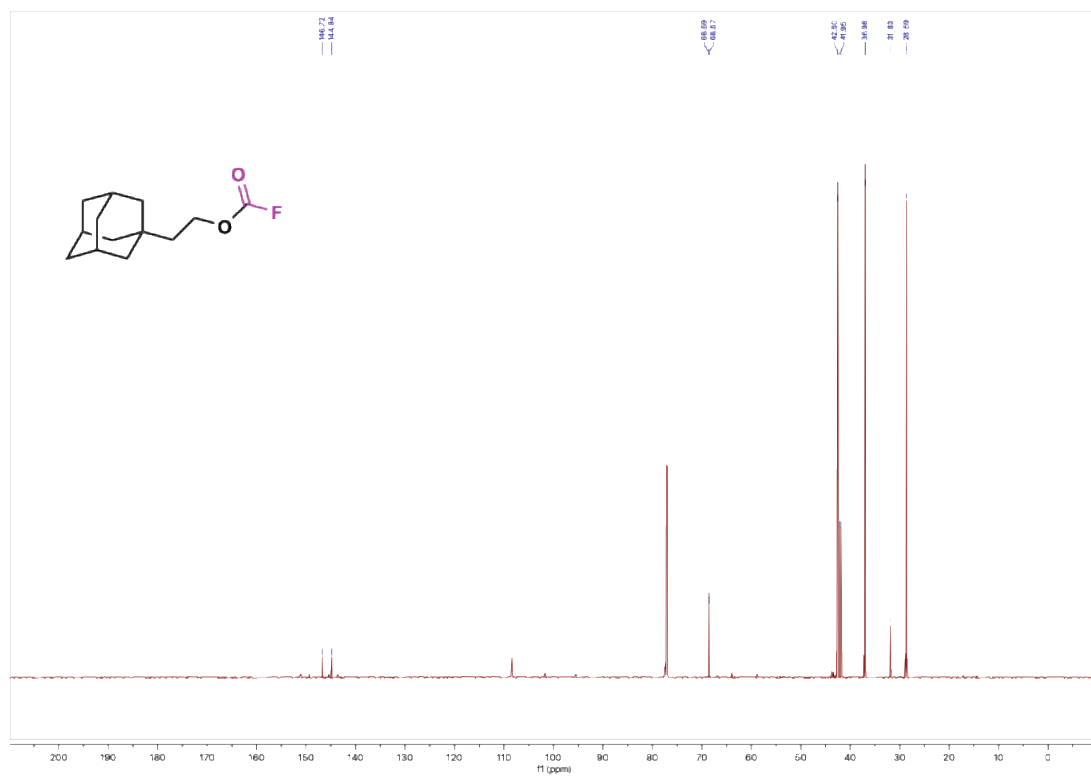
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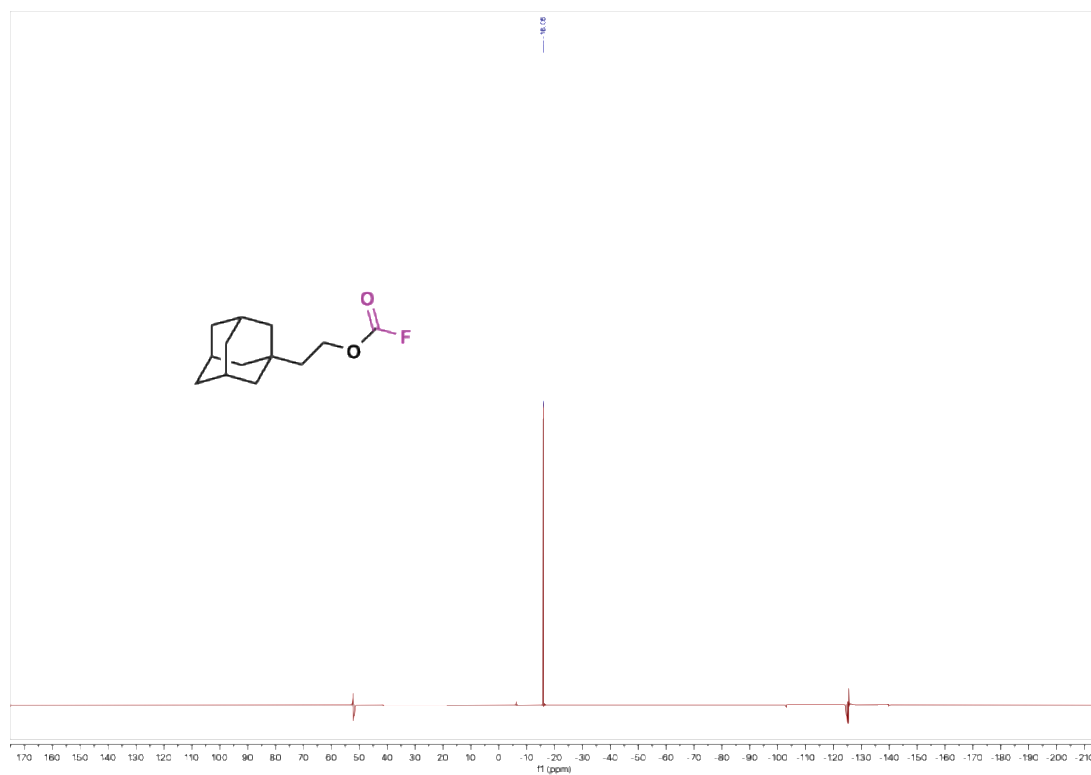
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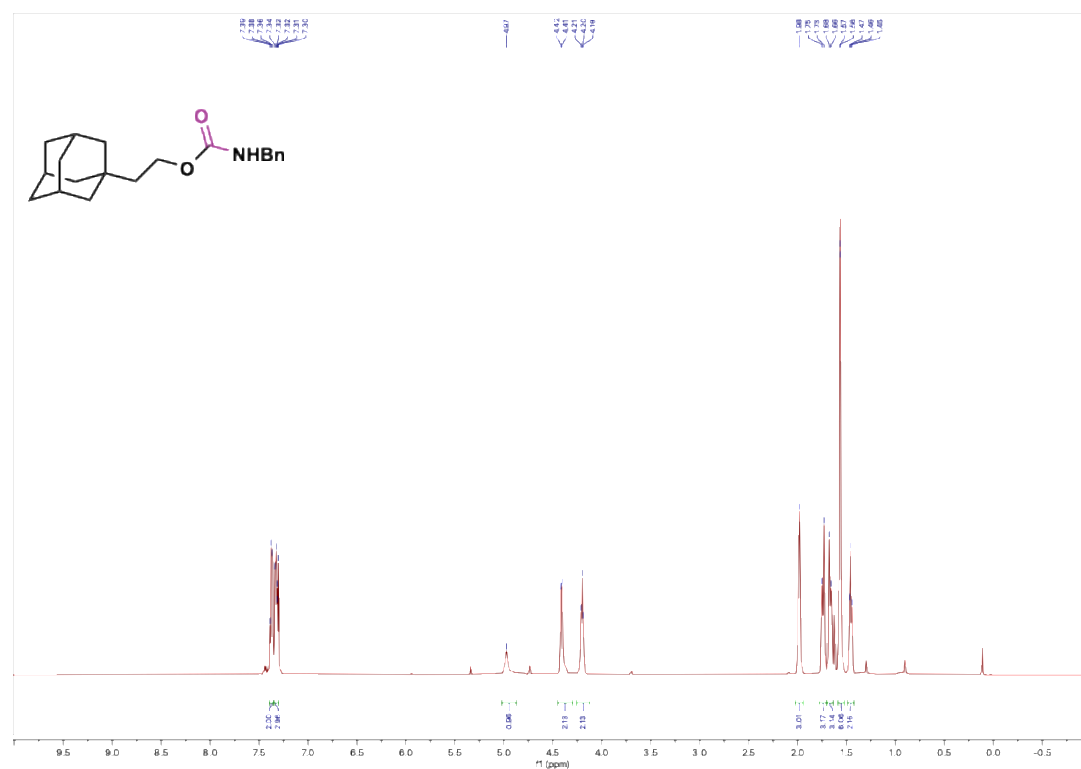
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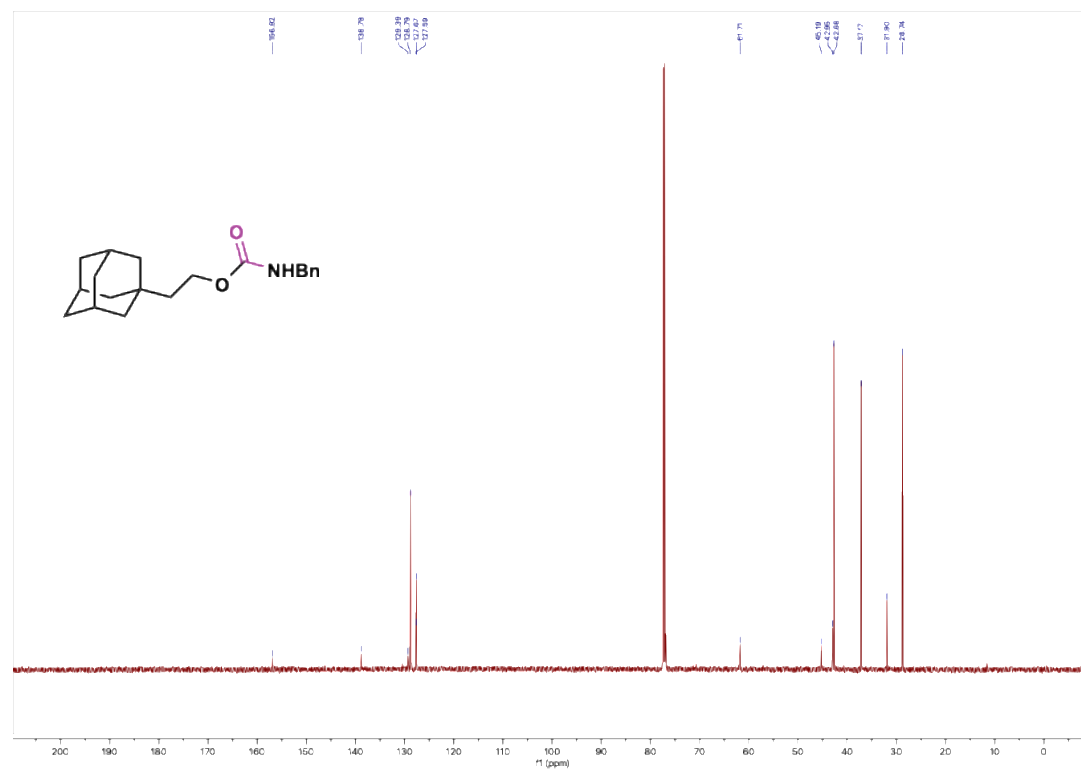
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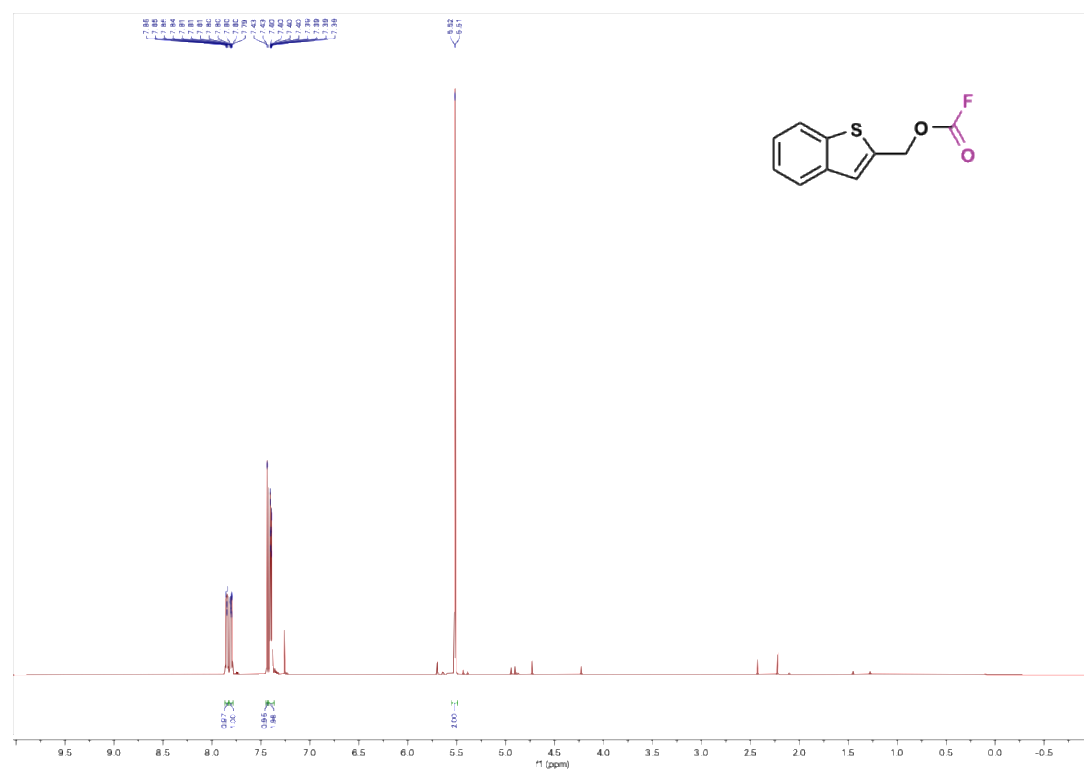
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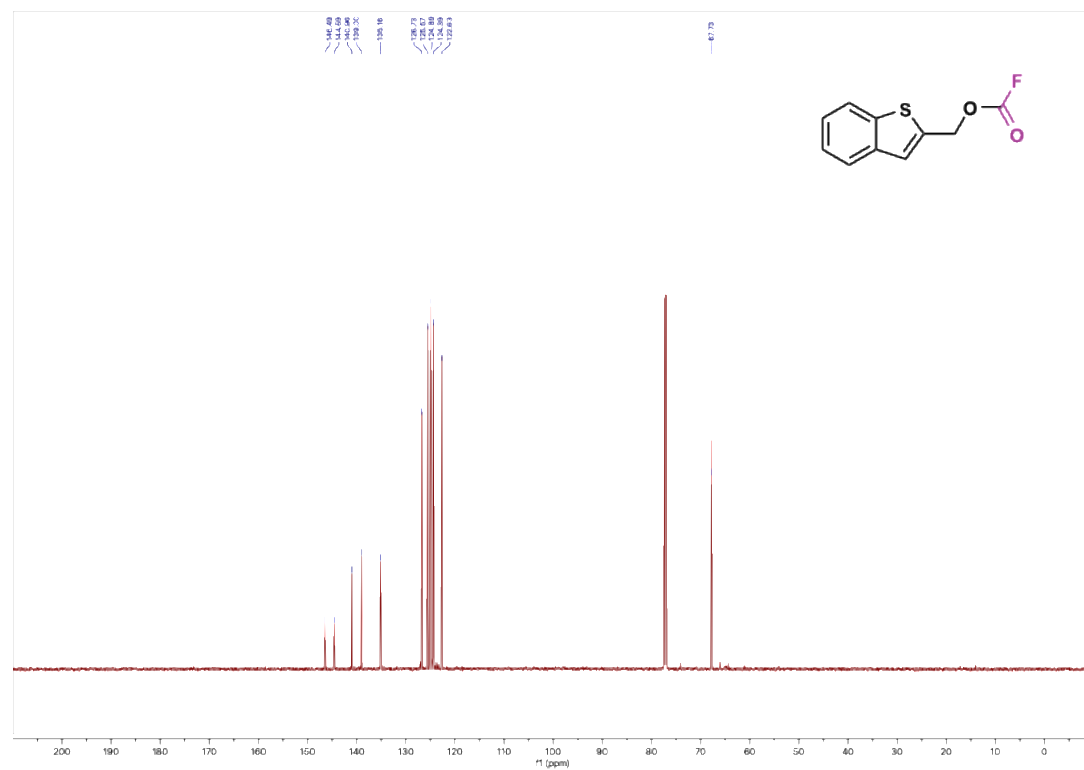
^{13}C NMR (151 MHz, CDCl_3) of **4.3h**



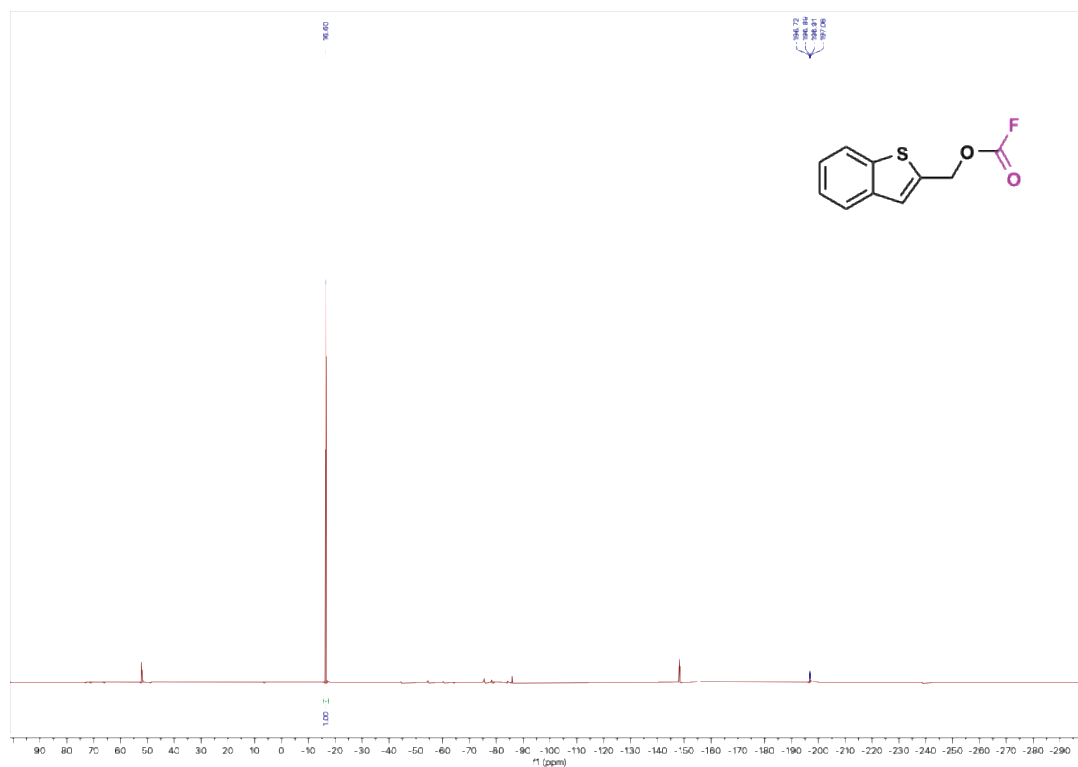
^1H NMR (600 MHz, CDCl_3) of **4.2i**



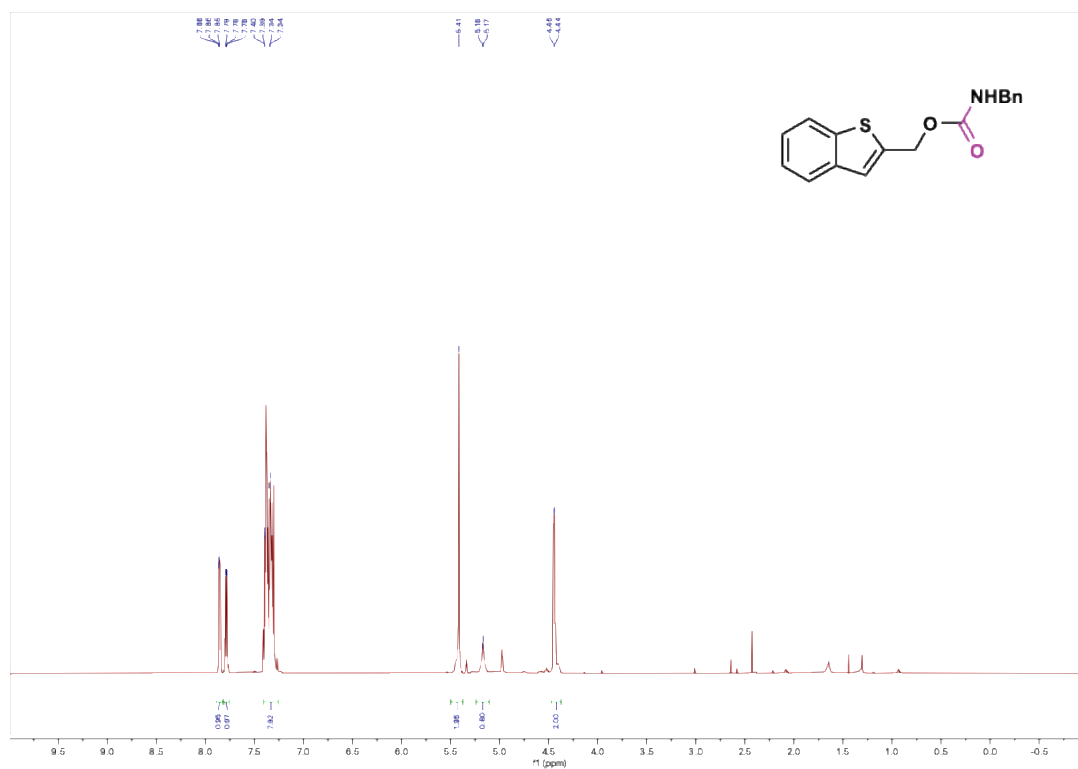
^{13}C NMR (151 MHz, CDCl_3) of **4.2i**



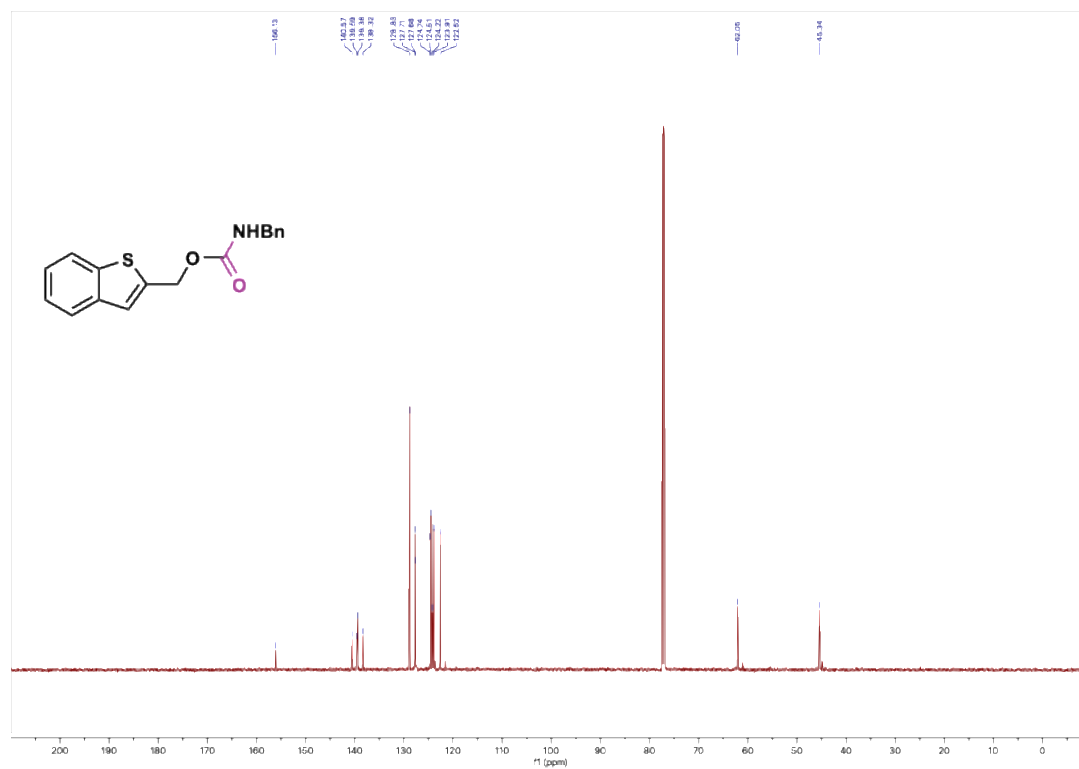
^{19}F NMR (282 MHz, CDCl_3) of **4.2i**



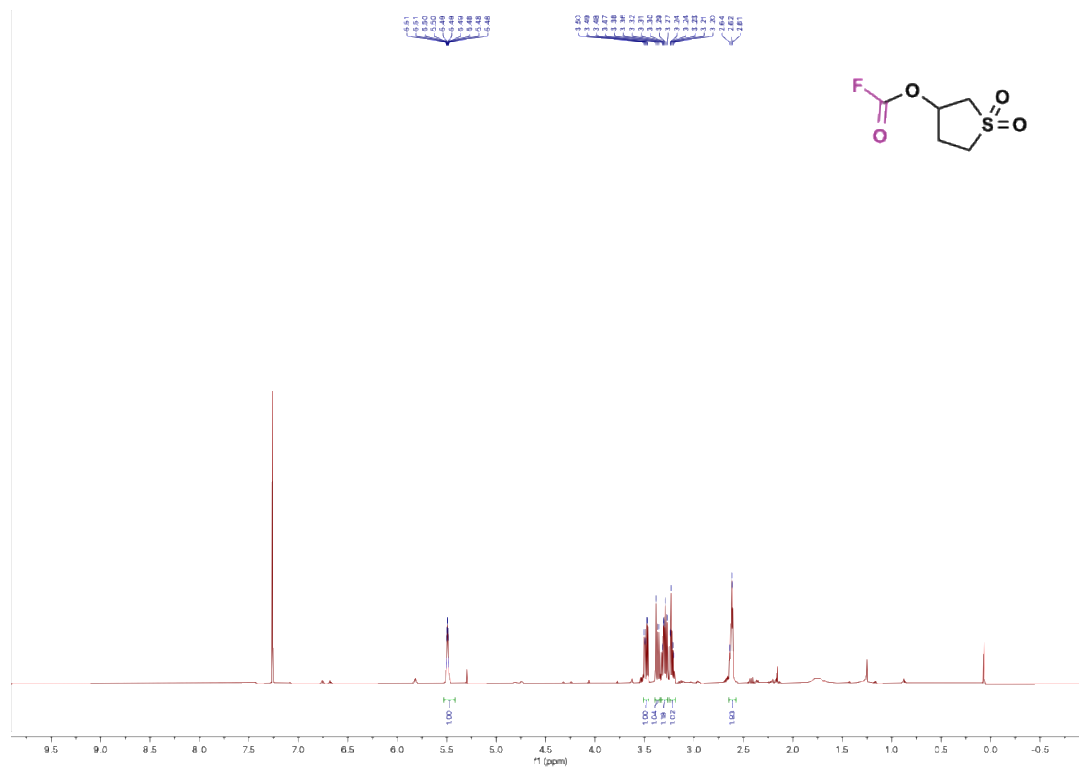
^1H NMR (600 MHz, CDCl_3) of **4.3i**



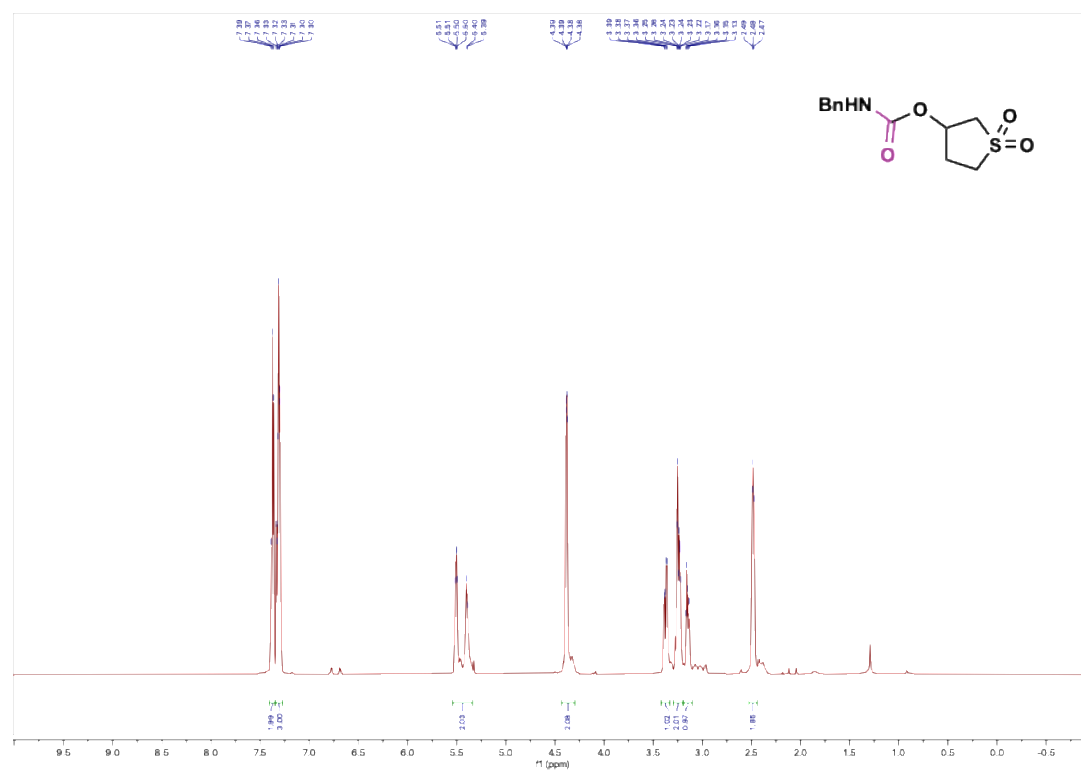
^{13}C NMR (151 MHz, CDCl_3) of **4.3i**



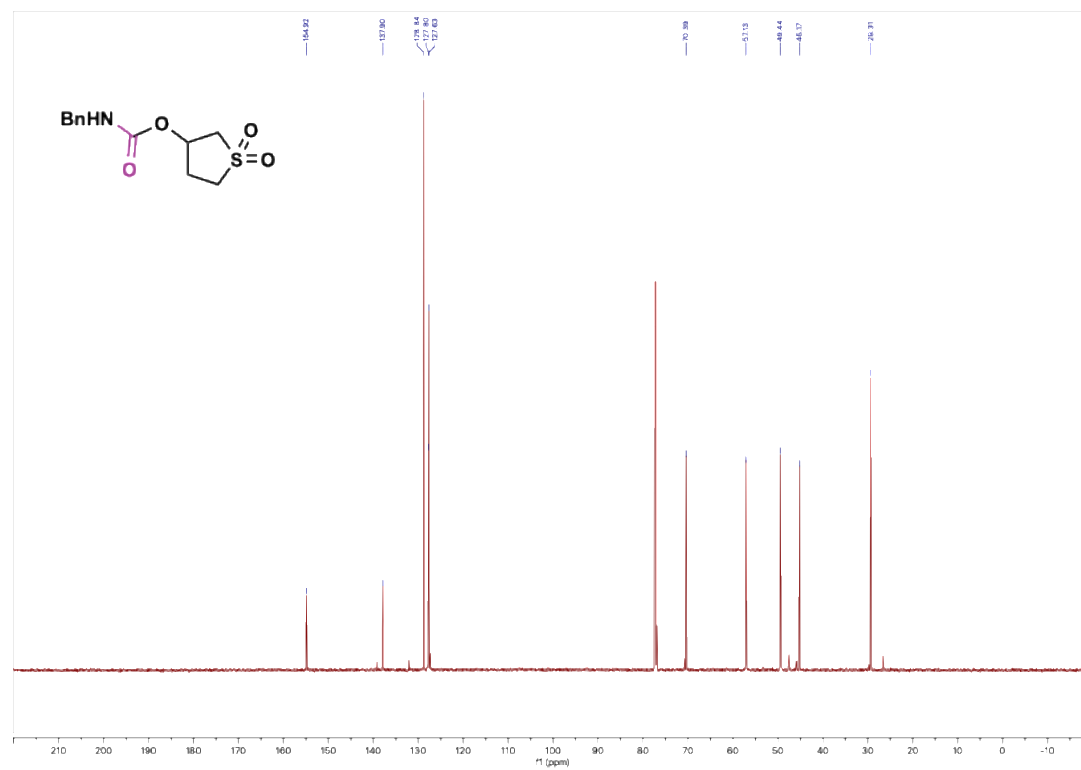
¹H NMR (600 MHz, *CDCl*₃) of **4.2j**



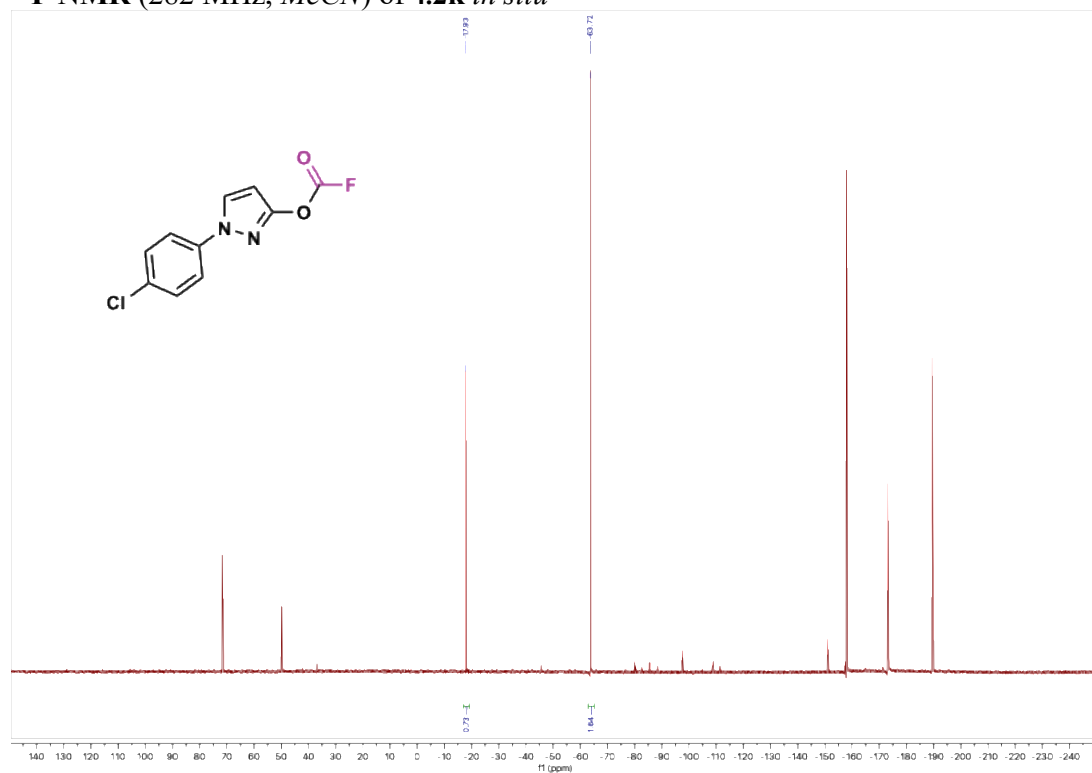
^1H NMR (600 MHz, CDCl_3) of **4.3j**



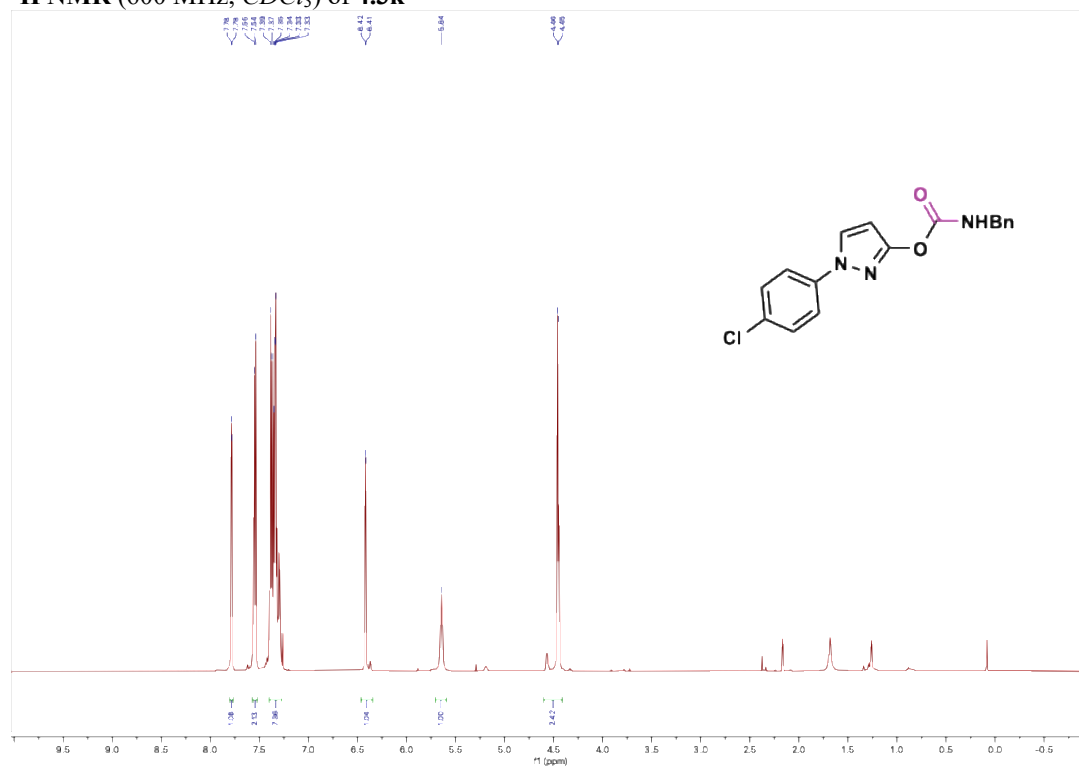
^{13}C NMR (151 MHz, CDCl_3) of **4.3j**



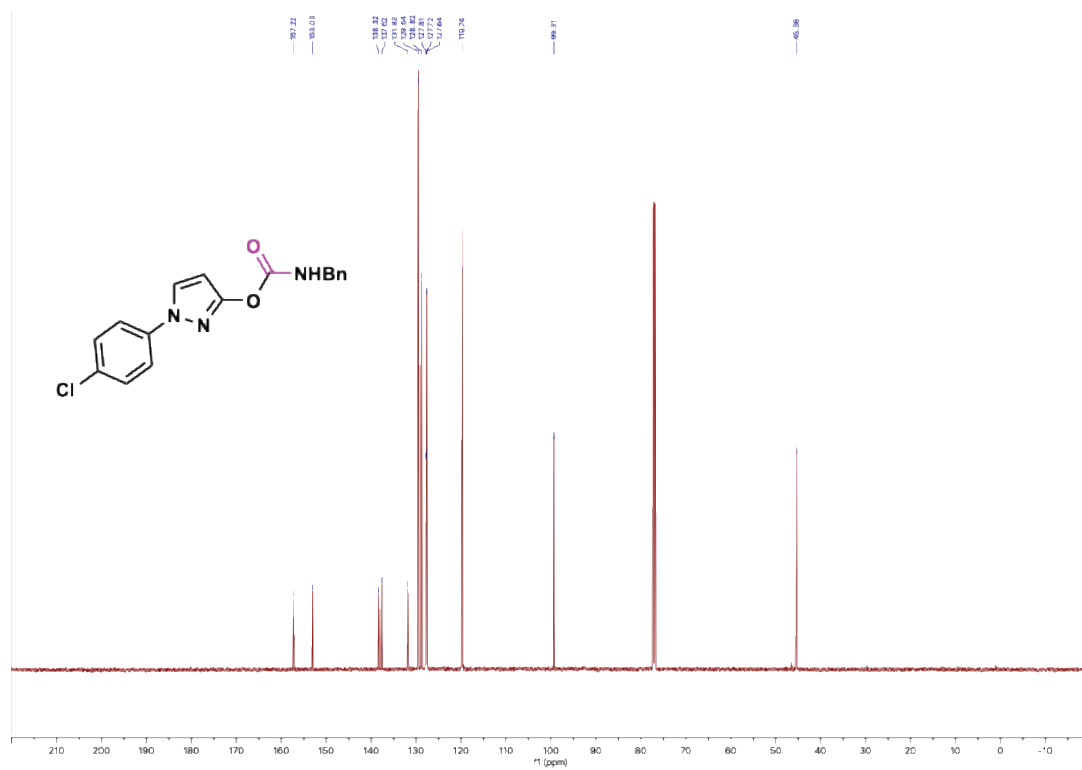
^{19}F NMR (282 MHz, MeCN) of **4.2k *in situ***



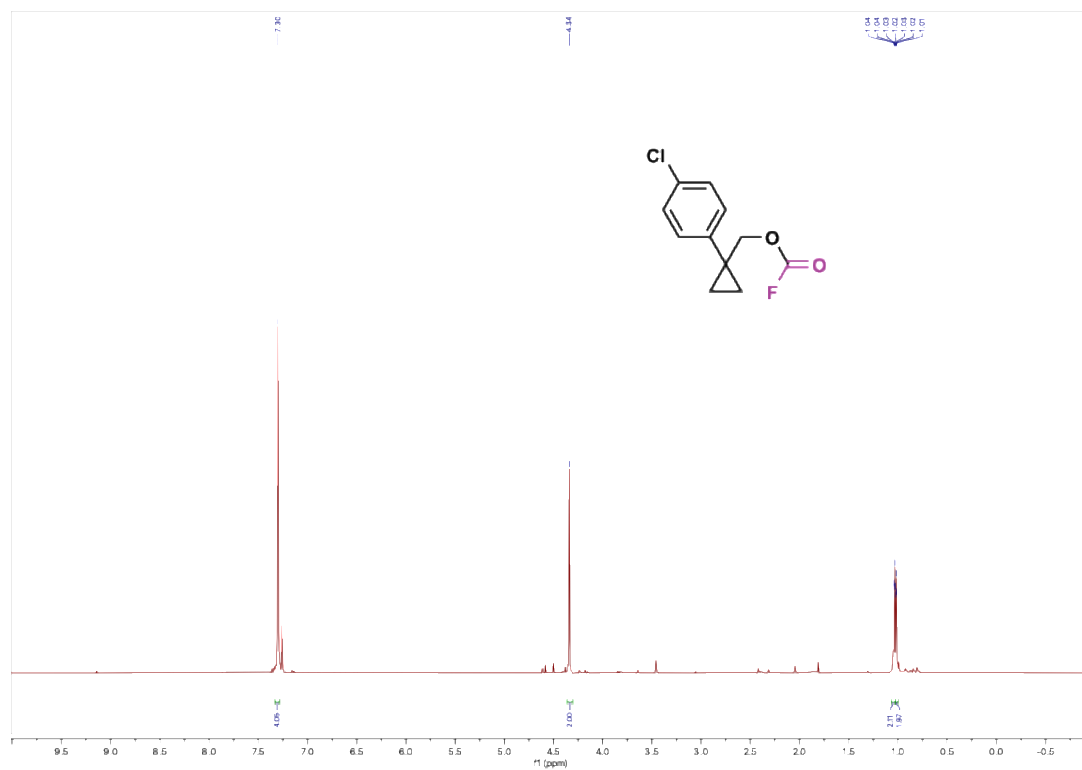
^1H NMR (600 MHz, CDCl_3) of **4.3k**



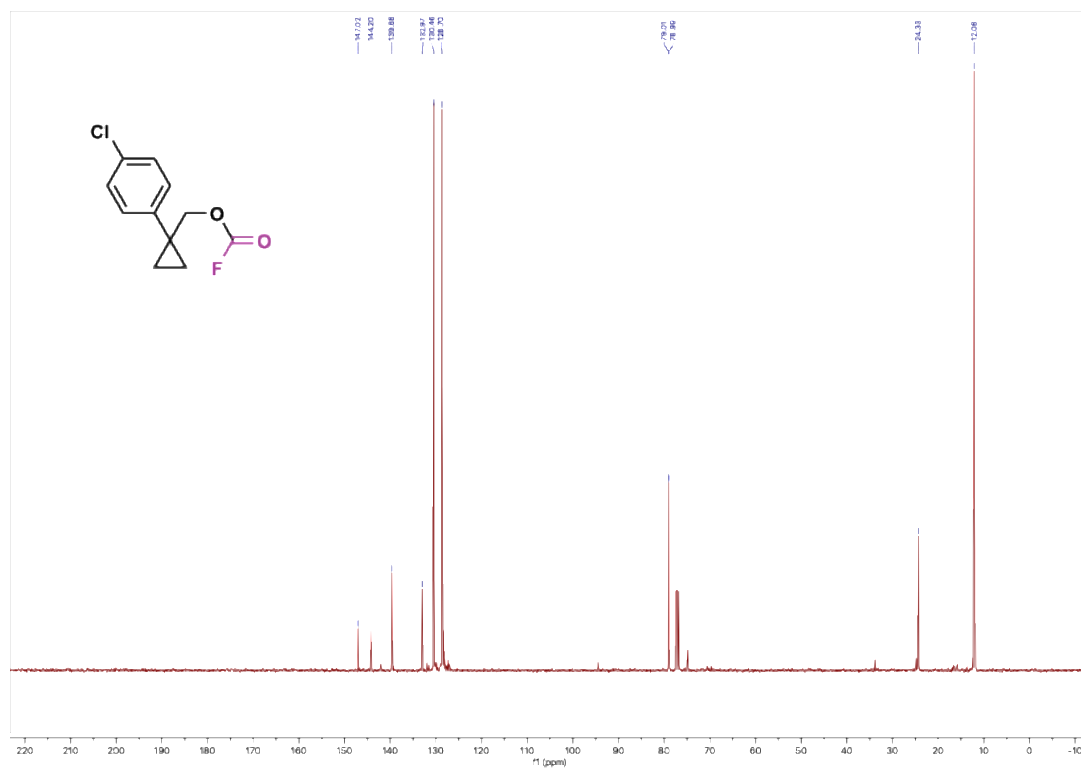
^{13}C NMR (151 MHz, CDCl_3) of **4.3k**



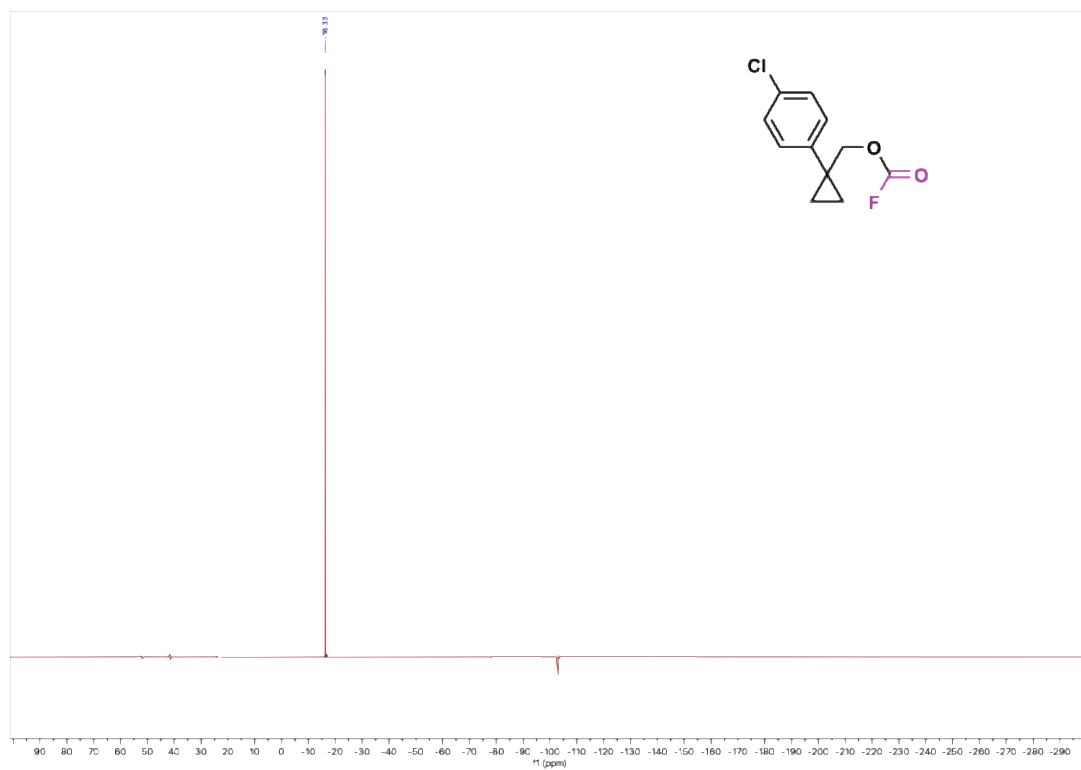
¹H NMR (400 MHz, CDCl₃) of 4.21



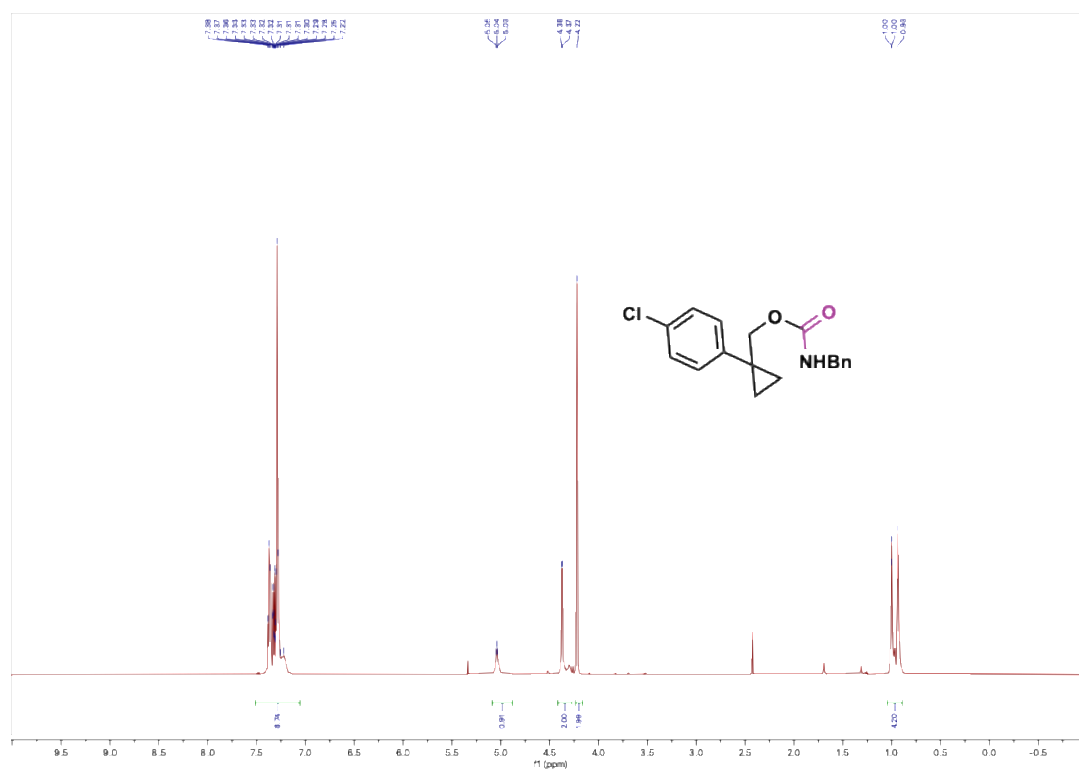
^{13}C NMR (101 MHz, CDCl_3) of 4.2I



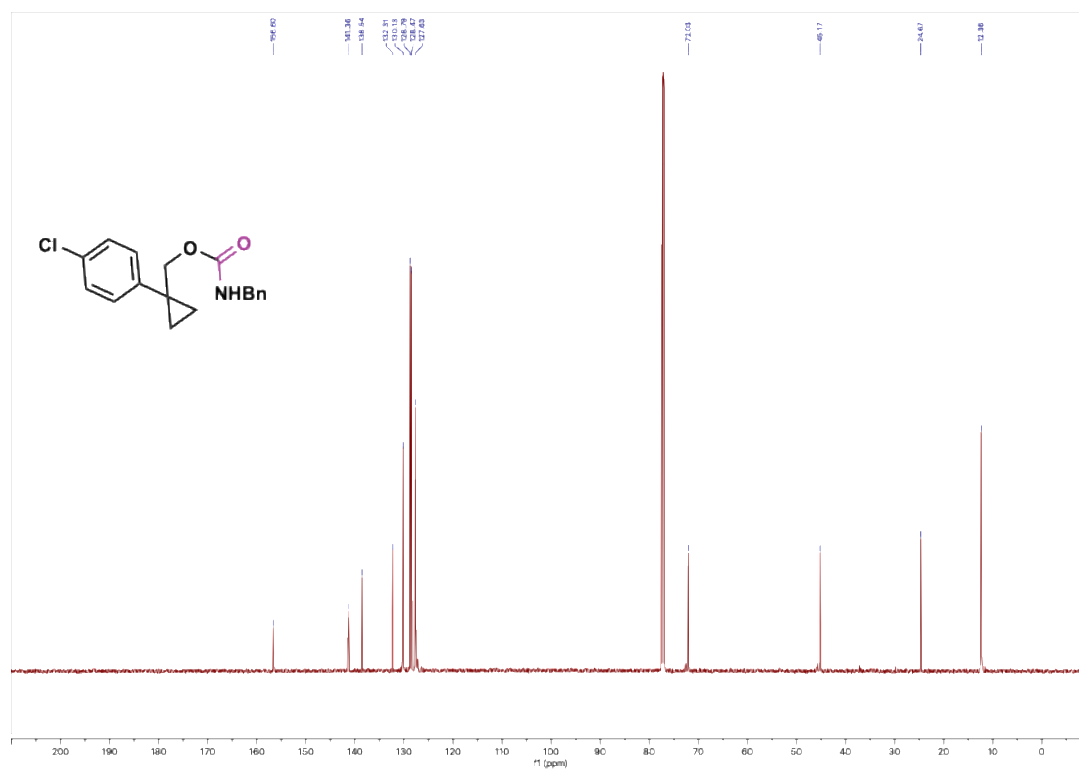
^{19}F NMR ((377 MHz, CDCl_3) of 4.2I



^1H NMR (600 MHz, CDCl_3) of **4.31**



^{13}C NMR (151 MHz, CDCl_3) of **4.31**

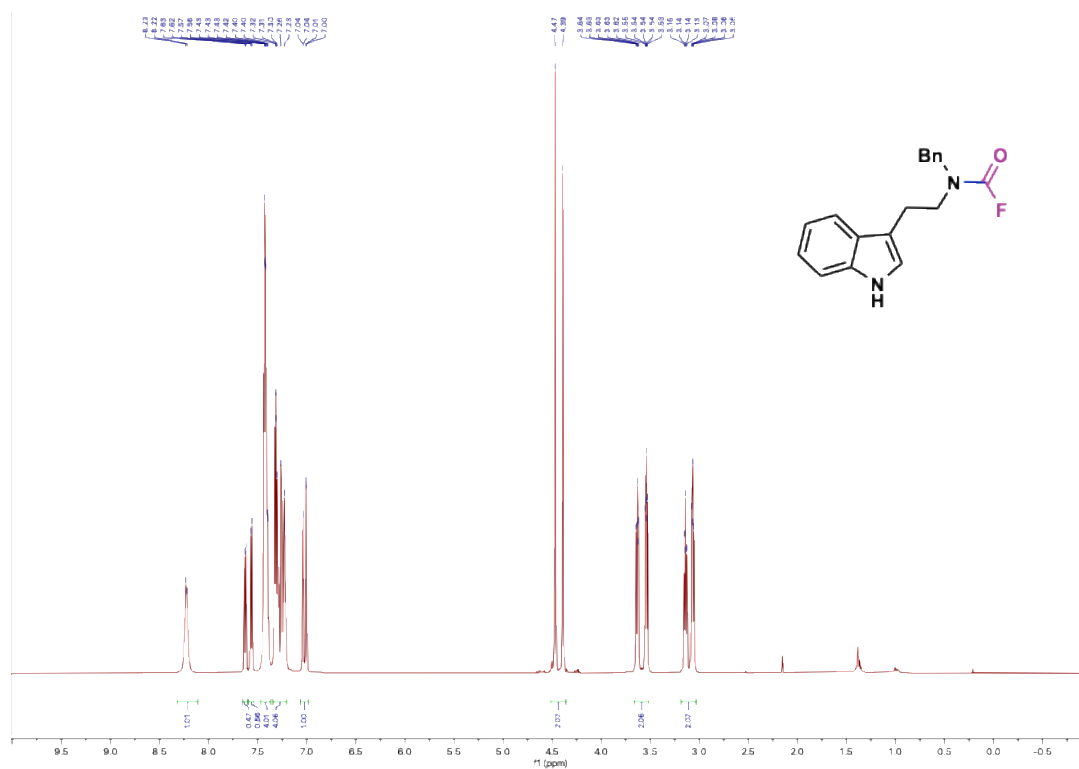
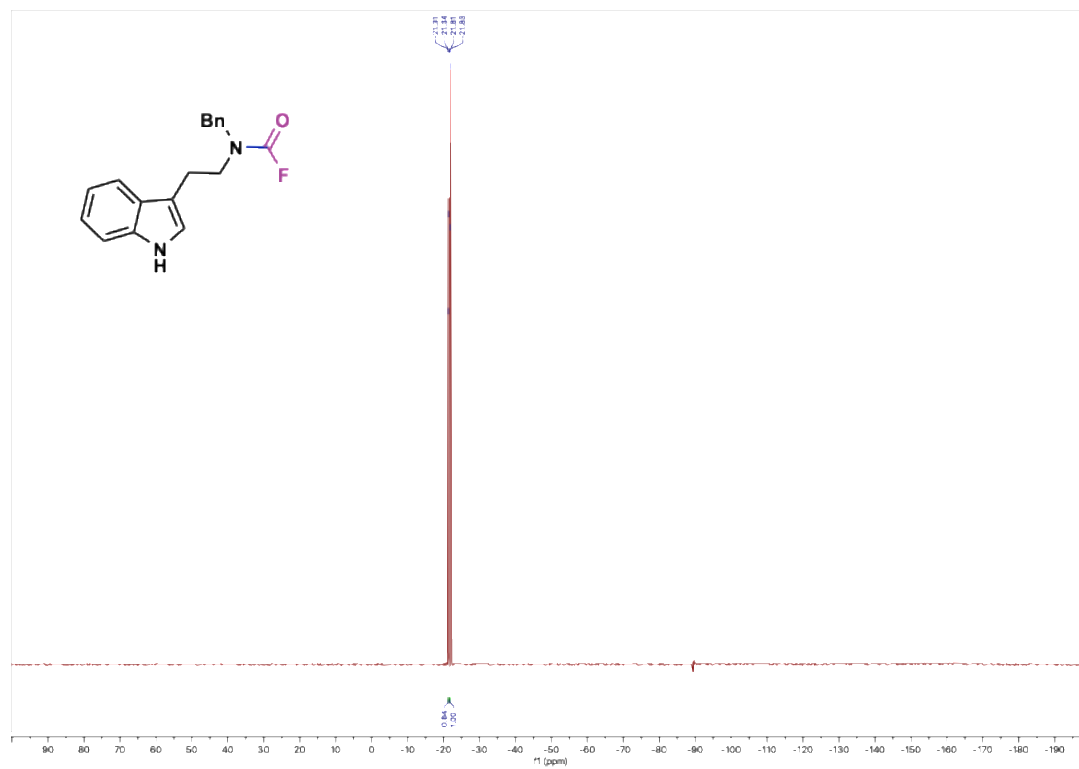


Chemical structure of 1-(4-iodophenyl)-2-(2-(benzylamino)-2-oxoethyl)-1H-benzotriazole (10): O=C(NCc1ccccc1)CCN1C=NC2=CC=CC=C21

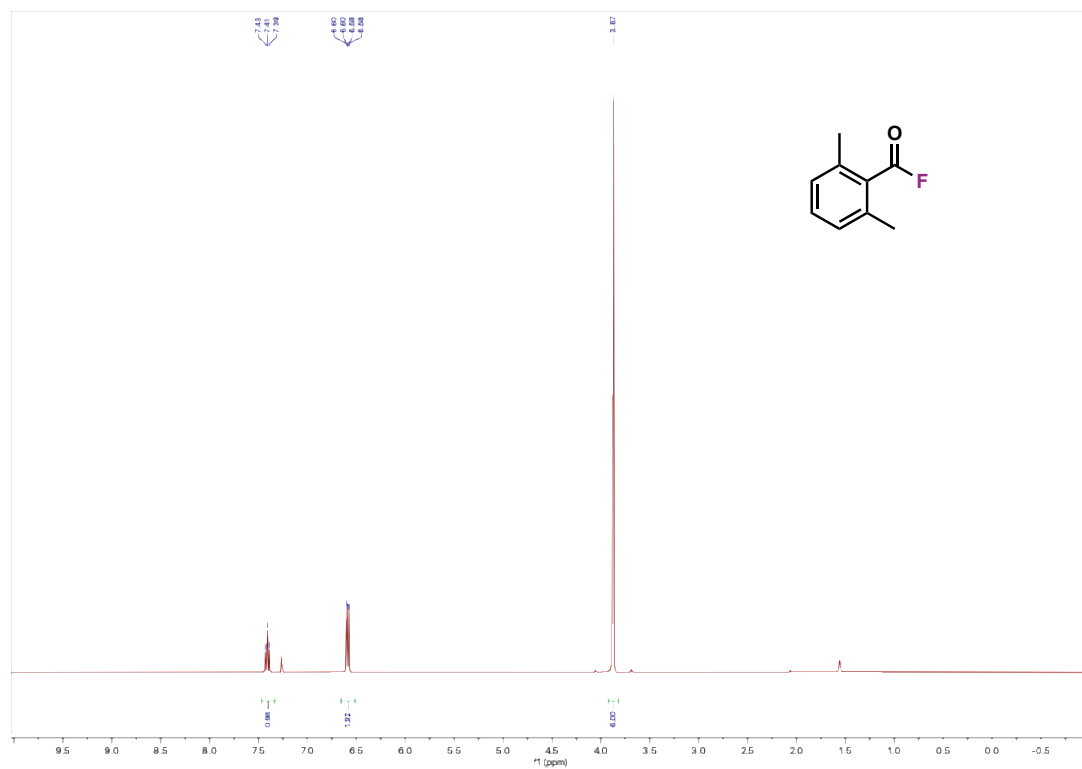
¹H NMR spectrum (CDCl₃) of compound 10. The spectrum shows peaks in the aromatic region (7.0-7.8 ppm) and a broad peak for the NH group (10.0 ppm). Integration values are provided below the peaks.

¹³C NMR spectrum (CDCl₃) of compound 10. The spectrum shows peaks in the aromatic region (118.0-140.0 ppm) and a peak for the carbonyl carbon (166.0 ppm). Integration values are provided below the peaks.

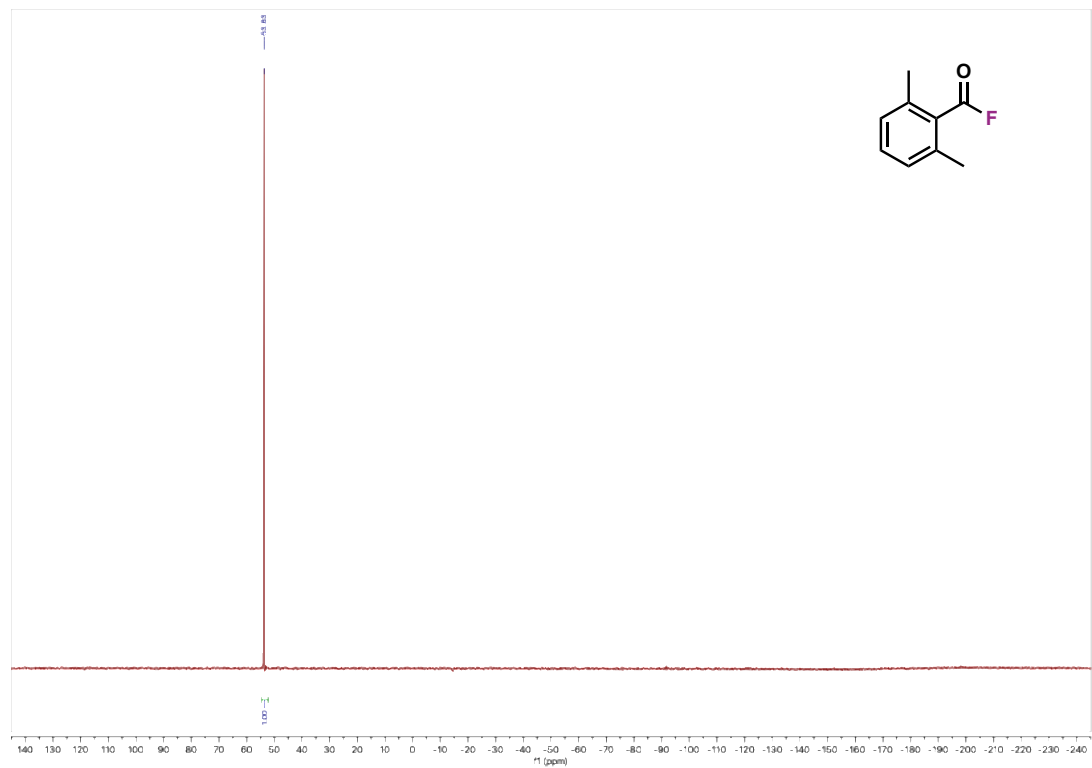
¹H NMR (600 MHz, CDCl₃) of **4.5c**

¹⁹F NMR (377 MHz, CDCl₃) δ of **4.5c**

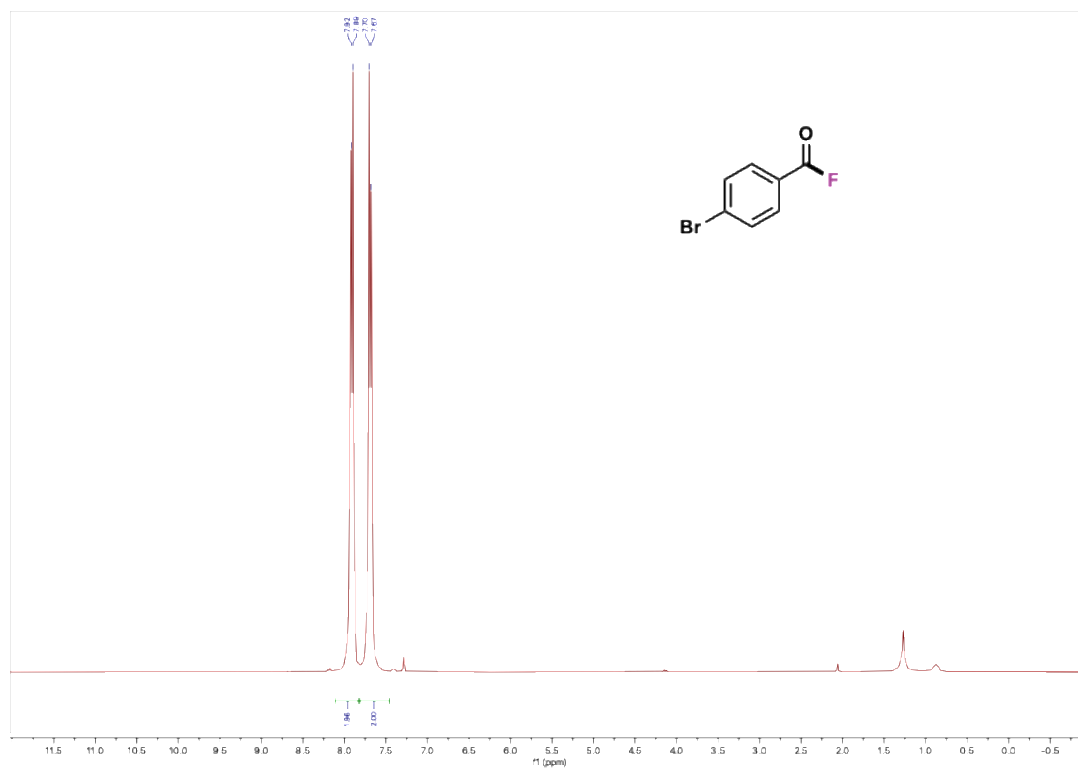
^1H NMR (400 MHz, CDCl_3) of **4.7a**



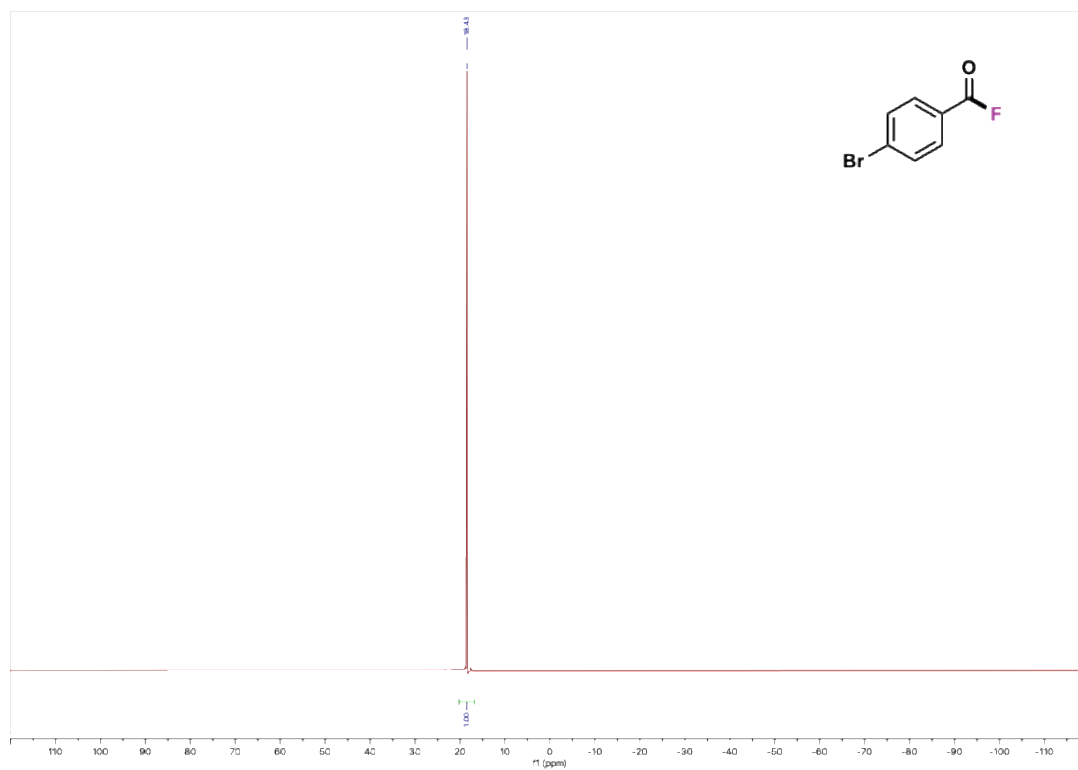
^{19}F NMR (377 MHz, CDCl_3) of **4.7a**



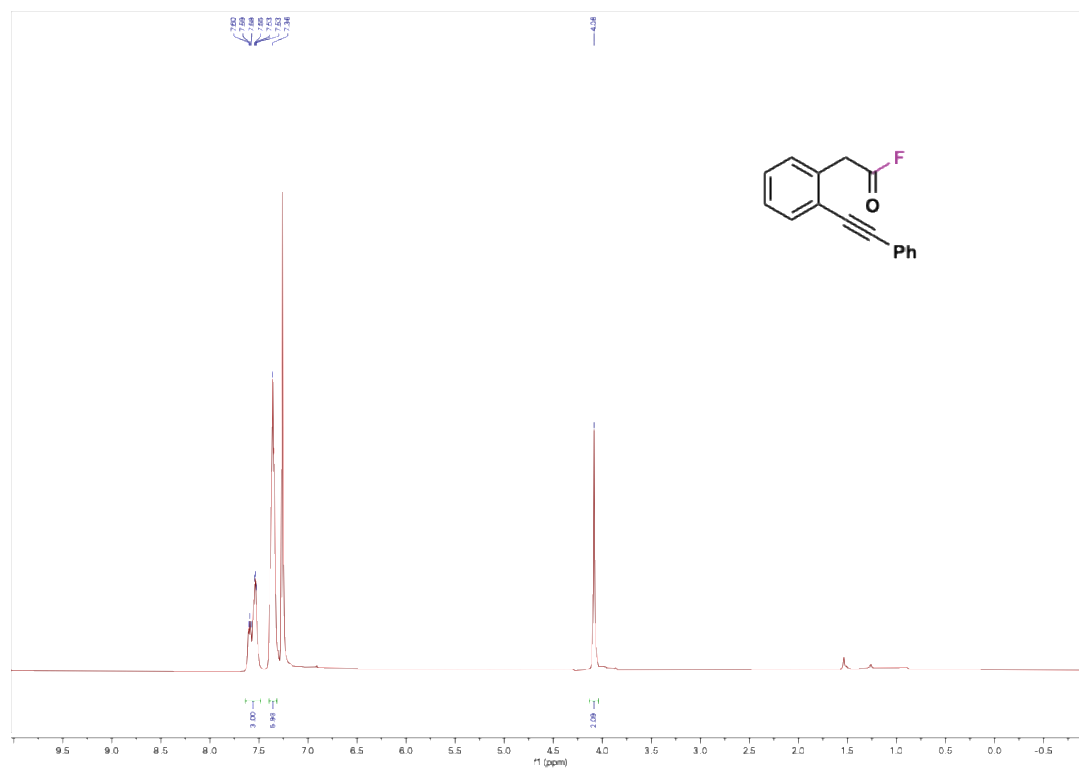
^1H NMR (400 MHz, CDCl_3) of 4.7b



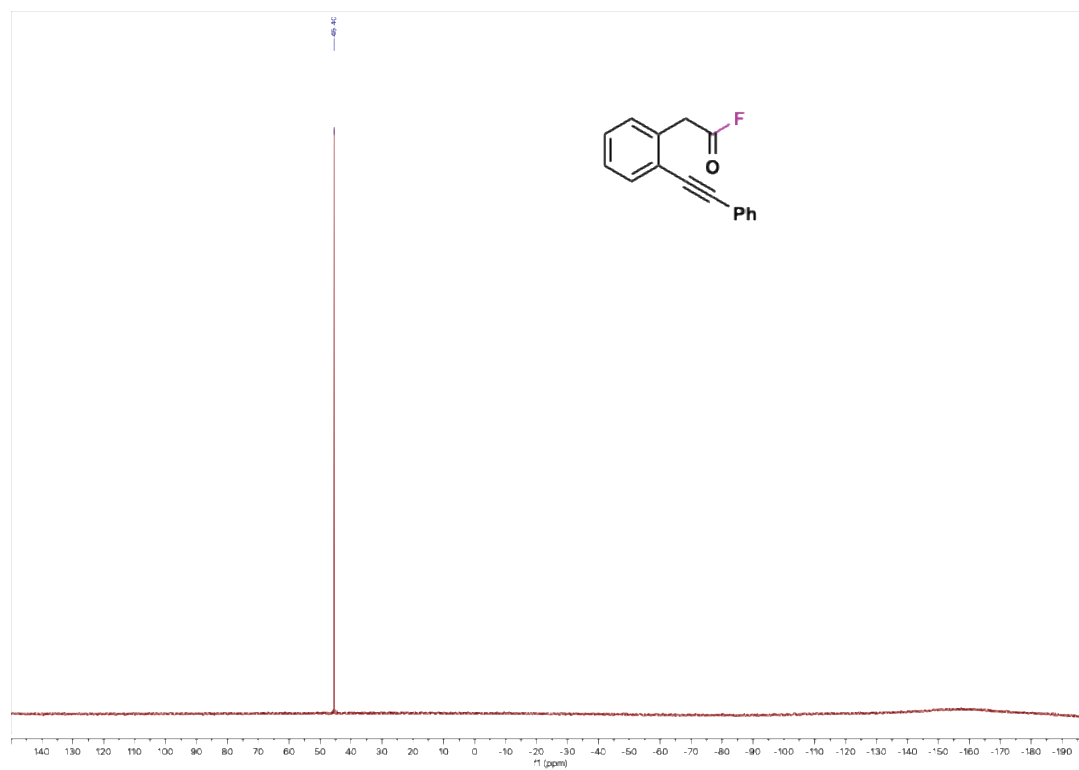
^{19}F NMR (282 MHz, CDCl_3) of 4.7b



^1H NMR (300 MHz, CDCl_3) of **4.7c**



^{19}F NMR (282 MHz, CDCl_3) of **4.7c**



5 Conclusions and Outlook

The work presented in this dissertation sought to harness organofluorine materials as dual function reagents, with a specific eye towards the use of carbonyl fluoride derived materials as both a carbonyl electrophile source and as a fluoride source for the carbofluorination of π bonds under Lewis acid-catalyzed fluoride shuttling reactivity.

Inspired by the activation of acyl fluorides with $\text{BF}_3 \cdot \text{OEt}_2$ and AgBF_4 to form highly electrophilic acylium ions we initially explored borane-based Lewis acids and tetrafluoroborate salts as for the carbofluorination of alkyne and alkene tethered acyl fluorides. The catalyst screen indicated that acyl fluorides can be activated either via a fluoride abstraction or through Lewis adduct formation at the carbonyl; tris(4-fluorophenyl)borane, which has a similar FIA to $\text{BF}_3 \cdot \text{OEt}_2$ but is not a nucleophilic fluoride source, was a competent catalyst for the reaction as well. With TrBF_4 as the optimized catalyst, previously unreported 1-(fluoromethylene)indan-2-ones and cyclopentanones were formed with exceptional stereoselectivity, as well as heterocycles that had previously only been reported using a more expensive Rh/BF_4 catalysts system.

Next, we identified carbamoyl fluorides both as a potentially challenging C–F bond to activate and as a C–F bond donor that had not yet been explored in the literature. Screening of Lewis acids identified a range of boron and based and cation- BF_4 Lewis acids that were competent at furnishing the desired 3-fluoromethylene oxindoles and γ -lactams from alkyne tethered carbamoyl fluorides in high stereoselectivity across all catalysts tested. $\text{BF}_3 \cdot \text{OEt}_2$ was selected as the optimal catalyst, and mechanistic studies pointed towards a formal C–F bond activation pathway instead of fluoride abstraction, BF_3 coordinates to the carbonyl oxygen instead. Computations revealed that C–C bond formation and C–F bond formation are a stepwise process via a vinylic carbocation, explaining why the reaction is limited to aryl groups across the alkyne.

Additionally, the reaction can be used as a key step for the synthesis of analogues of biologically relevant secondary oxindole protein kinase inhibitors following PMB-deprotection of the tertiary oxindole. Further investigations into potential synthetic routes to these free NH oxindoles found that the same products could be formed via the fluorocarbonylative annulation of *o*-alkynyl anilines using an oxidant/DFC strategy, which could potentially overcome the substrate limitations and enabling access to 3-fluoroalkyl methylene oxindoles as well.

Finally, in identifying mild conditions for the formation of fluoroformates using DMSO and TFDA as an oxidant/DFC pair, we had hoped to enable research into both their stability and potential as ester sources, harnessing their potential to act as surrogate for unactivated alkyl fluorides in carbofluorinative transformations. To that end, we showed that the fluoroformates could be employed as substrate in the Ni-catalyzed alkynylation reaction developed for *N*-CF₃ carbamoyl fluorides, showing preferential activation at the C–F bond over an aryl chloride present in the molecule. While attempts at employing alkyne tethered fluoroformates under the previously developed Lewis acid catalyzed carbofluorination conditions were unsuccessful, it was possible to do a fluorinative rearrangement of cyclopropylmethyl fluoroformates to fluorocyclobutanes with BCF.

Ultimately, the research presented in this dissertation represents preliminary work on Lewis acid-catalyzed “fluoride shuttling” reactions, having identified two classes of catalysts (boranes and cation/BF₄[−]) and two potential reaction pathways (fluoride abstraction and Lewis adduct activation) that are able to sufficiently activate a handful of carbonyl electrophiles towards insertion reactions. Ideally further research into these electrophilic catalysts will be able to expand the known coupling partners for carbofluorination reactions as well as atom-economic fluoride-shuttling chemistry in general.

One potential place of expansion is to the activation and extension of S^{VI}–F bonds across π -bonds. While there is a growing number of methods in the literature for the atom-economical carbofluorination of π -bond nucleophiles, there have been no analogous reports for the activation and extension of S^{VI}–F bonds across π -bond nucleophiles. Similar to the activation of carbonyl fluorides the reactivity of S^{VI}–F moieties can be driven via either direct (fluoride abstraction) or indirect (activation of S=O or S=N bond) activation of the S^{VI}–F bond. Direct activation pathways involve the abstraction of the fluoride from the S^{VI}–F bond via either hydrogen bonding (the method most likely prevalent under physiological conditions when sulfonyl fluorides are used as covalent inhibitors) or via abstraction by calcium/barium-based Lewis acids to yield Friedel-Crafts-type products.¹⁻² Indirect activation pathways tend to utilize organic bases like DBU and DABCO to promote nucleophilic substitution of sulfonyl fluorides, likely via coordination to the S=O bond to increase the electrophilic character of the S^{VI}.³

Recent investigations by the groups of Wang, Deng, and Jiang have shown that BF₃ can activate sulfonimidoyl fluoride S^{IV}–F bonds, enabling the SuFEx coupling of sulfonimidoyl fluorides with both silylated

nucleophiles⁴⁻⁵ and unactivated alkenes⁶ for the formation of S^{VI}-C bonds. In the case of silylated nucleophiles the driving force of the reaction is typically the high fluorophilicity of silicon. This is illustrated well by the BF₃-catalyzed divergent linkage of sulfonimidoyl fluorides and TMS-alkynes to generate S^{IV}-C(*sp*) and S^{IV}-C(*sp*²) bonds. The reaction proceeds via a concerted BF₃-bridged 6-membered transition state where the BF₃ mediates fluoride transfer to the silylated carbon nucleophile, and the acetylene is transferred to the S^{IV}. A similar strategy is utilized by Deng and Jiang in their report of a BF₃-mediated SuFEx linkage of allyltrimethylsilanes (allyl-TMS) and sulfonimidoyl fluorides. In this case they hypothesize that the BF₃ acts as a fluoride transfer reagent between the sulfonimidoyl fluoride and the TMS via an 8-membered transition state, enabling the concerted formation of both Si-F and S^{VI}-C bonds and breakage of Si-C and S^{VI}-F bonds. In 2022 Wang and Jiang reported the BF₃-mediated hydrosulfonimidoylation of unactivated alkenes using sulfonimidoyl fluorides. In their proposed mechanism, supported by DFT calculations and experimental studies, BF₃ directly activates the S^{IV}-F of the sulfonimidoyl fluoride to create an ion-pair intermediate, which then undergoes construction of the S-C bond and drives the intermolecular 1,5-hydride transfer via a concerted cyclic transition state with the assistance of water.

In all the aforementioned cases BF₃ is able to activate sulfonimidoyl fluoride S^{IV}-F bonds, but due to either substrate design or reaction design the formed fluoroborate is consumed before it can serve as a sufficient nucleophilic fluoride source. Potentially replacing the coupling partner in these reactions with an alkyne would enable fluorosulfonylative reactivity.

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6 Complete List of References

6.1 Chapter 1

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6.2 Chapter 2

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6.4 Chapter 4

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6.5 Chapter 5:

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