STEREOSELECTIVE SYNTHESIS OF TRISUBSTITUTED (*Z*)-TRIFLUOROMETHYL ALKENES

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAIʻI AT MĀNOA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

IN

CHEMISTRY

FEBURARY 2020

By

Chaolun Liu

Thesis Committee:

Marcus Tius, Chairperson

Jakub Hyvl

Matthew Cain

Acknowledgement

First and foremost, I would like to express my deepest appreciation to my advisor, Professor Marcus A. Tius for his guidance and encouragement during the completion of this work.

I would like to thank my committee members : Professor Jakub Hyvl and Professor Matthew Cain for their assistance and help.

Special thanks to the members of the Tius group: Mr. Jonathan Congmon, who conducted preliminary studies on the Au(I) catalyzed α,β-unsaturated ketone synthesis and gave me help on my project; Mr. Cody Dickinson, who contributed to the study of the mechanism; Mr. Duk Kim, who collected the HRMS data for this project.

Special thanks to Dr. Francisco Lopez-Tapia for his help and contribution to the mechanism study.

Many thanks to Mr. Wesley Yoshida for his help in obtaining NMR data.

I would like to thank my parents for their love and support.

Finally, I would like to thank the chemistry department of University of Hawaii at Manoa for support in the form of teaching assistantships.

Abstract

A stereoselective synthesis of trisubstituted (*Z*)-trifluoromethyl alkenes has been developed. Treating allenes bearing a trifluoromethyl substituent with trifluoroacetic acid leads to the highly stereoselective formation of trisubstituted (*Z*)-trifluoromethyl alkenes. Treating trifluoromethyl allenes with $Hg(OCOCF_3)_2$ or iodine leads to fully substituted dienes.

A novel synthesis of 3-trifluoromethyl-4-isoxazolines has developed. We demonstrated the synthesis of seven trifluoromethyl 4-isoxazolines, one heptafluoro-1-propyl 4-isoxazoline and one example of a non-fluorinated 4-isoxazoline.

List of Abbreviations

Ac	acetyl
Ad	adamantyl
Å	ångstrom
aq.	aqueous
Bn	benzyl
Ipr	1,3-Bis(2,6-di-*i*-propylphenyl)imidazol-2-ylidene
NTf_2	bis(trifluoromethane)sulfonimide
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
n-Bu	*normal*-butyl
t-Bu	*tert*-butyl
calcd.	calculated
δ	chemical shift in parts per million from tetramethylsilane
J	coupling constant
Cy	cyclohexyl
^{o}C	degree Celsius
DCE	1,2-dichloroethane
DCM	dichloromethane
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
DIBAL	diisobutylaluminum hydride
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
d	doublet (NMR)
ESI	electrospray ionization
E	entgegen
equiv.	equivalent(s)
Et	ethyl
g	gram(s)
NHC	*N*-heterocyclic carbene

HFIP	hexafluoroisopropanol
n-C_6H_{13}	*normal*-hexyl
HRMS	high resolution mass spectrometry
h	hour(s)
IR	infrared
i-Pr	isopropyl
L	liter, ligand
mg	milligram(s)
mL	milliliter(s)
M^+	molecular ion
MS	molecular sieves
M	moles per liter
m	multiplet (NMR)
m.p.	melting point
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
mmol	millimole(s)
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
ppm	parts per million
Ph	phenyl
q	quartet(NMR)
rt	room temperature
R_f	retention factor
s	singlet(NMR)
t	triplet(NMR)

TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
Z	zusammen

Table of Contents

1. Introduction

1.1 The Importance of Fluorine Chemistry

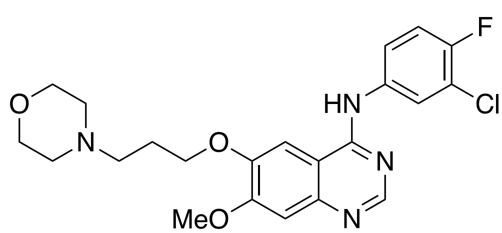
Fluorine was discovered by French chemist Henri Moissan in 1886. Despite being the 13th most abundant element on Earth's crust, the development of fluorine chemistry was slow until the past two decades. Fast progress in this area was accelerated by the development of fluorination processes and new fluorinating reagents as well as the increasing sensitivity of ^{19}F nuclear magnetic resonance (NMR).

Fluorine is a small atom with the highest electronegativity.[1] Due to its chemical properties, a single fluorine atom can impact the structure, reactivity, and function of fluorine-containing compounds.[2] As a result, numerous important fluorine-containing compounds have emerged as pharmaceutical drugs, agrochemicals, catalysts and polymers.[1, 3]

In pharmaceutical chemistry, the benefit of introducing fluorine into drug molecules comes from the unique properties of the fluorine atom or fluoroalkyl groups. Firstly, the CF_3 group is particularly effective at modulating the lipophilicity. Secondly, the substitution of fluorine for hydrogen can drastically change the electrostatic interactions with other functional groups while maintaining relatively similar steric interactions. Finally, introducing fluorine can prevent oxidative metabolic pathways by blocking the potential oxidation sites.[4]

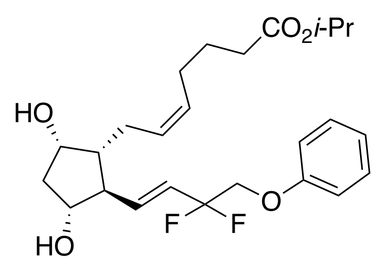
Fifty years ago, only 2% of drugs contained fluorine. Currently, approximately 25% of the drugs on the market contain fluorine. From 2001 to 2011, more than 40 new fluorine-containing drugs were introduced to the market.[4b] There is no doubt that fluorine will be playing a more important role in pharmaceutical development in the future. In what follows some examples of fluorine-containing drugs on the market or in phase II-III clinical trials are discussed.

The first one developed and launched by Astra-Zeneca (formerly Zeneca), is Gefitinib, an oral epidermal growth factor receptor (EGFR) inhibitor used for treatment of certain breast, lung, and other cancers.[4b] Gefitinib contains a quinazoline core with a 3-chloro-4-fluoroaniline moiety. According to X-ray studies, the 3-chloro-4-fluoroaniline moiety extends into the hydrophobic pocket in the back of the ATP binding cleft of EGFR, making a better fit than non-fluorinated aromatic rings (**Figure 1.1A**).[5] The second one is Tafluprost, which belongs to the prostanoid family, and is used as an effective treatment of glaucoma. Adding the difluoro moiety reduces the risk of melanogenesis, a common side effect of other similar drugs (**Figure 1.1B**).[6] The last example, Telotristat, for the treatment of carcinoid syndrome, is in phase III clinical trials under development by Lexicon Pharmaceuticals.[4a] According to their studies, the trifluoromethyl group improves the activity in the cell-based assay compared to non-fluorinated derivatives (**Figure 1.1C**).[7]



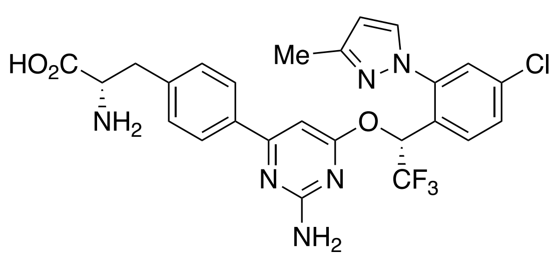
Gefitinib

Figure 1.1A



Tafluprost

Figure 1.1B

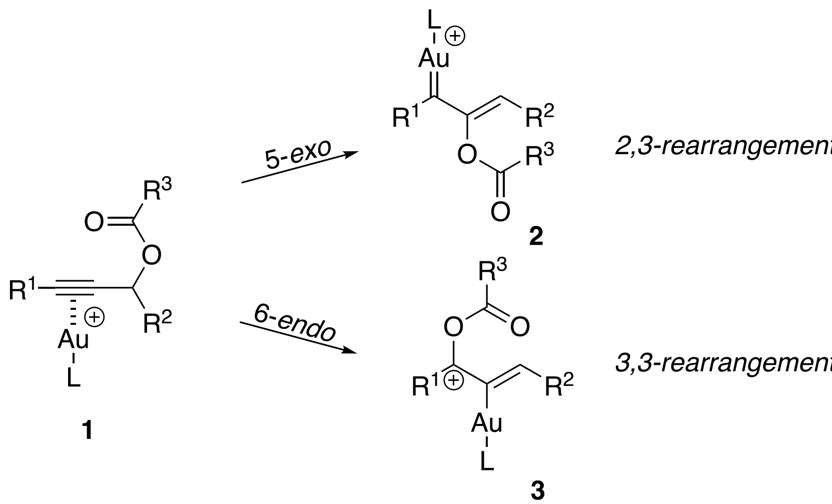


Telotristat

Figure 1.1C

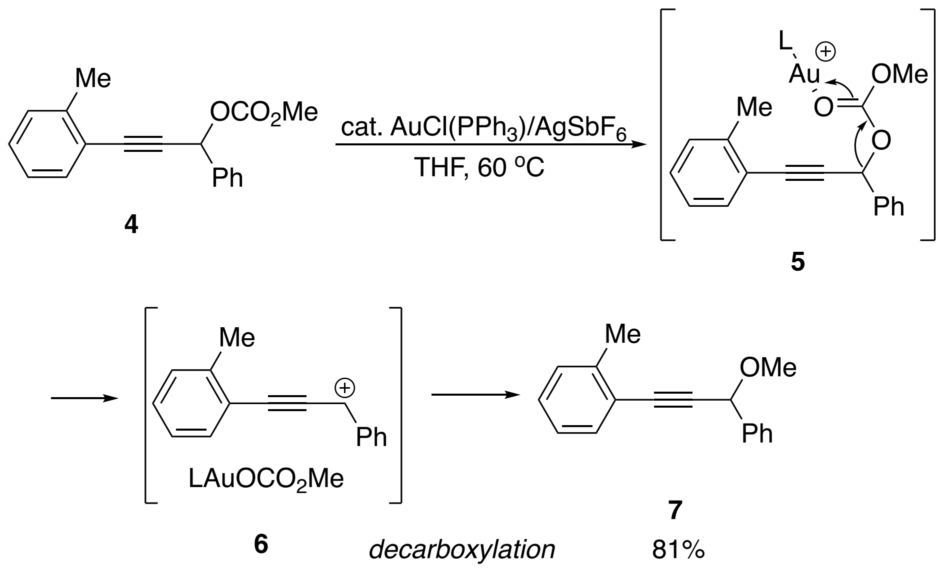
1.2 Gold(I) Catalyzed Rearrangement of Propargyl Carboxylates and Analogues

Au(I) catalysis has drawn a lot of attention over the past couple of decades due to its high π-Lewis acidic reactivity. Activation of alkynes by cationic Au(I) under mild conditions followed by other types of reactions can lead to complex organic molecules.[8] In particular, cationic Au(I) catalyzed rearrangement of propargyl carboxylates has been proven to be a powerful synthetic tool. In terms of mechanism, these reactions start by the activation of an alkyne by cationic Au(I) followed by an intramolecular 5-*exo* or 6-*endo* rearrangement of the carboxylate **1** (**Scheme 1.1**). These active intermediates can undergo various transformations.



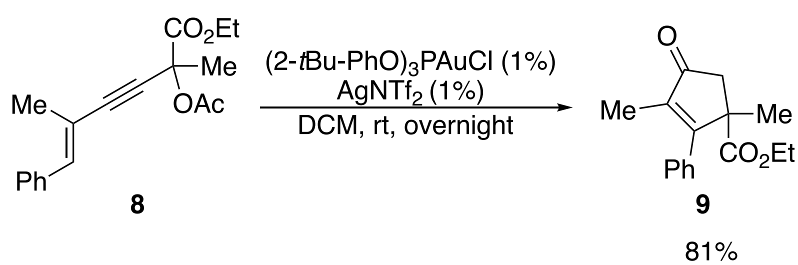
Scheme 1.1

Besides exhibiting strong π-Lewis acidity, cationic Au(I) is also a σ-Lewis acid. For example, Shen and coworkers reported a cationic gold(I) catalyzed decarboxylation of propargyl carbonates **4** followed by intermolecular trapping of the resultant cation **6** (**Scheme 1.2**).[9] This reaction demonstrated the σ-Lewis acidity of the cationic gold catalysts.



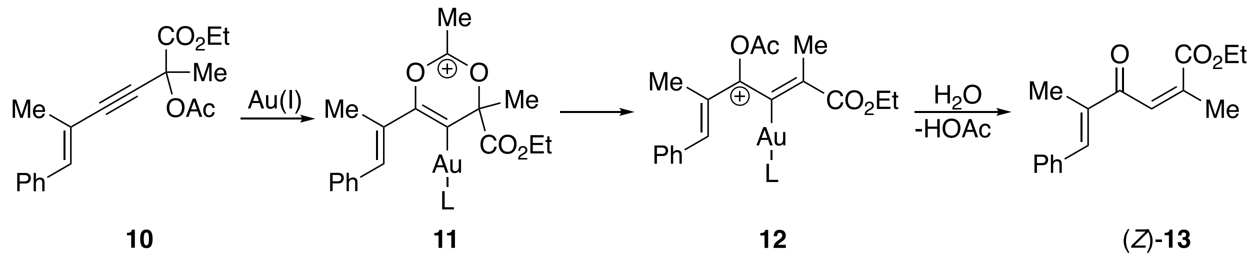
Scheme 1.2

Recently, the Tius group described a cationic Au(I) catalyzed Nazarov cyclization.[10] The electrocyclization was initiated following [3,3]-sigmatropic rearrangement of a propargyl acetate **8** (**Scheme 1.3**). The construction of a quaternary carbon atom in the product **9**, which is considered challenging, is another example of the use of Au(I) catalysis as a powerful tool in forming complex compounds.



Scheme 1.3

During the study of the cyclization, another interesting observation was discovered by accident. Following the presumed formation of the gold vinyl carbenoid species **12** in the presence of water, the reactive intermediate underwent protiodeauration with the loss of acetic acid to give an α,β -unsaturated ketone **13** with excellent *(Z)*-alkene stereoselectivity (**Scheme 1.4**).

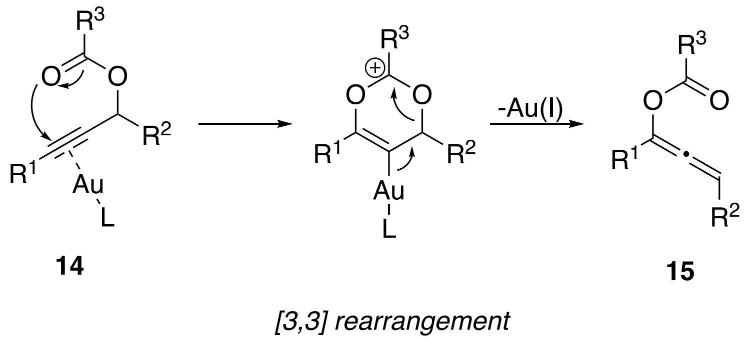


Scheme 1.4

The high selectivity for the *(Z)*-stereoisomer was quite unexpected. We postulated that this observation might be exploited for a stereoselective synthesis of trisubstituted trifluoromethyl alkenes.

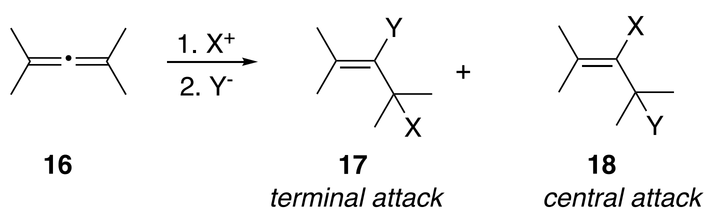
1.3 Electrophilic Addition of Allenes

Allenes are typically isolable and stable compounds, but they also have significant reactivity towards electrophiles which makes them useful intermediates.[11] One common way to generate allenes under mild conditions is through the use of cationic Au(I) catalysis. For example, Au(I) catalyzed rearrangement of propargyl esters will afford allenes (**Scheme 1.5**).



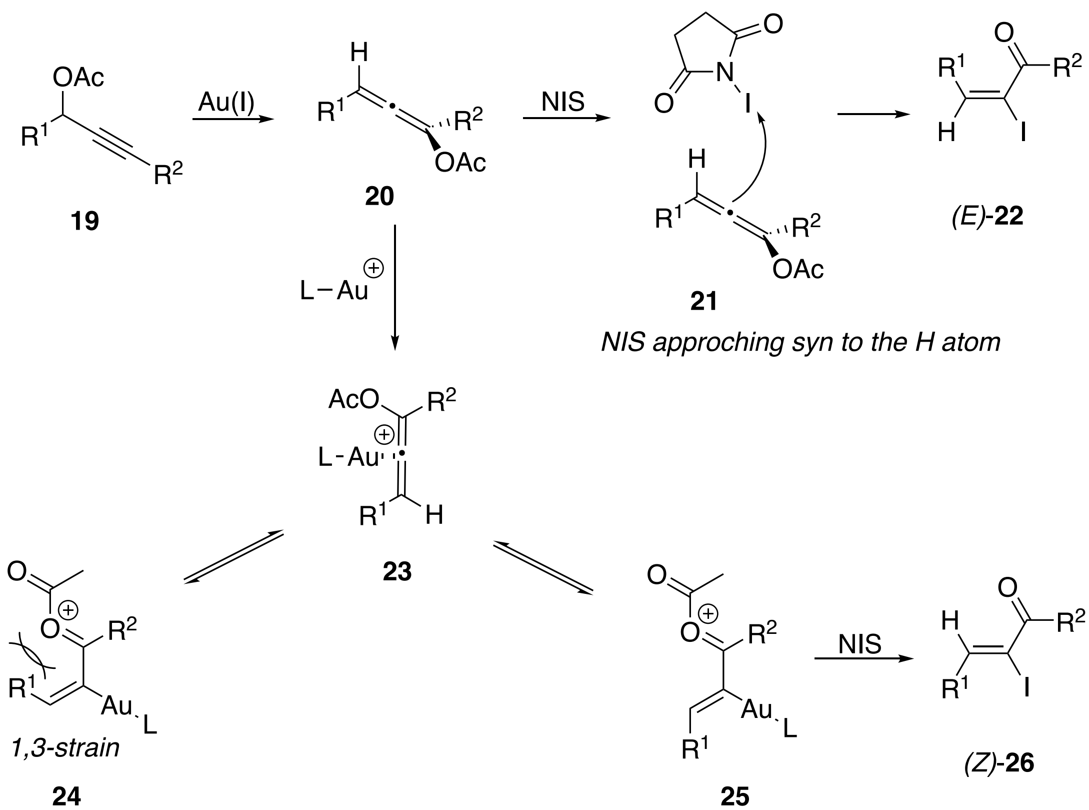
Scheme 1.5

The regio- and stereoselectivity of electrophilic addition to allenes depend on the steric and electronic effects of the substituents on the allene and the nature of the electrophile. Electrophilic addition may afford terminal attack **17** or central attack **18** products, depending on the structures of the allene and the identity of electrophile (**Scheme 1.6**).



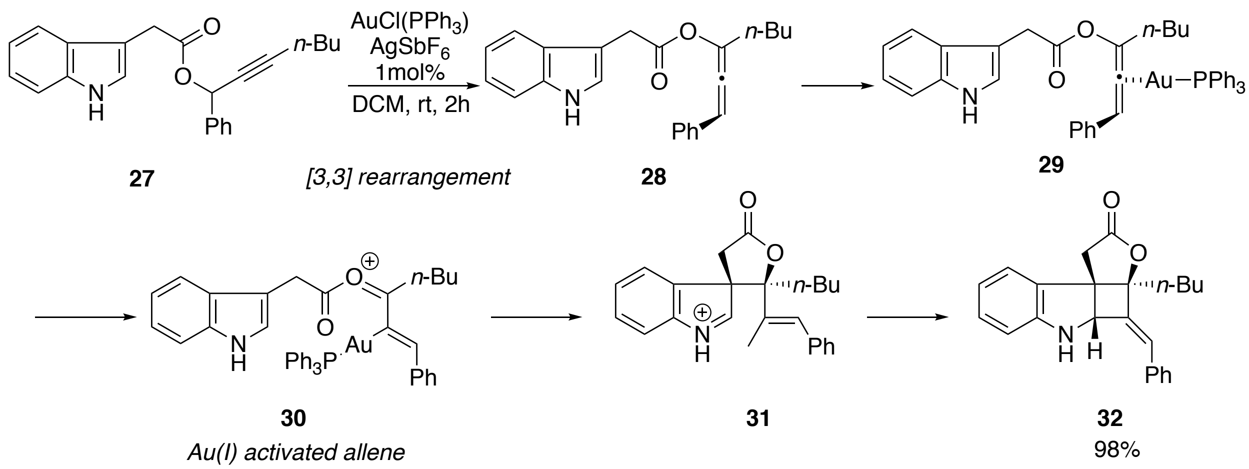
Scheme 1.6

Allenes are also useful to form cyclic and heterocyclic compounds. Similar to other unsaturated systems, allenes can also be activated by various metals, such as gold, copper and palladium. Among these, gold catalysts have excelled owing to their unique reactivity.[12] In 2010Shi reported an example that illustrates the stereoselectivity of electrophilic addition of allene.[13] The acetoxy group from **19** underwent 1,3-migration in the presence of a Au(I) catalyst affording allene ester **20**. When the allene ester was exposed to NIS, *(E)*-**22** was obtained as the major product, due to the bulky R[1] group blocking the approach of the electrophile to one side of the allene. On the other hand, activating the allene with cationic Au(I) resulted in the formation of a vinyl gold intermediate with Au either *anti* (**24**) or *syn* (**25**) to R[1]. While **24** suffers from $A^{1,3}$-strain, **25** experiences 1,2 strain, however, due to longer C(sp^2)-Au bond, the 1,2 strain is not very significant. As a result, the equilibration of **24** and **25** via allene ester **23** favors **25** and thermodynamically favored *(Z)*-**26** is formed (**Scheme 1.7**).



Scheme 1.7

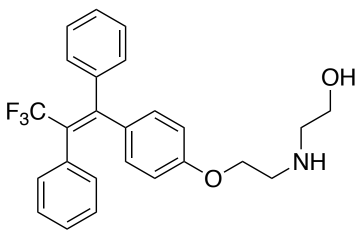
Another interesting demonstration that transformations catalyzed by Au(I) lead to complex products was provided by Zhang in 2005. Zhang reported a tandem Au-catalyzed [3,3]-rearrangement-[2+2] cycloaddition of propargylic esters.[14] The allene intermediate **28**, which was generated by the action of cationic Au(I) as a π-Lewis acid, activated by Au(I), affords the oxonium species **30**. The final product, cyclobutane **32**, was formed by cyclization of oxonium species **31** the to the 3-position of the indole ring, followed by intramolecular trapping of the iminium by the alkenylgold(I) (**Scheme 1.8**).



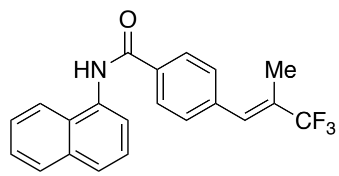
Scheme 1.8

1.4 Stereoselective Construction of Trifluoromethyl Alkene Species

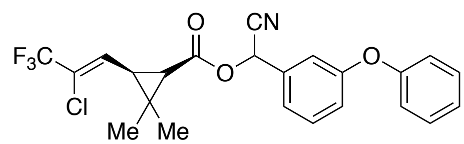
Olefins are one of the most important functional groups used in synthesis. Generating trifluoromethyl alkenes as single geometrical isomer would represent a contribution to organic synthesis. The CF_3 group is important in pharmaceutical chemicals[15] due to its unique electron-withdrawing character, metabolic stability, and lipophilicity.[16] Compounds containing a vinyl trifluoromethyl group have been shown to be useful in drugs and insecticides (**Figure 1.2**).[16a, 17]



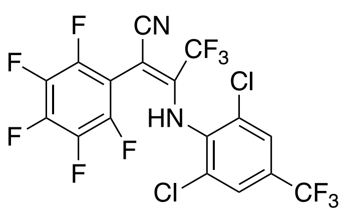
Antiestrogenic agent
(Panomifene)



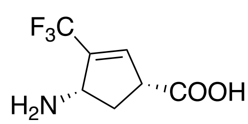
Anti-inflammatory agent



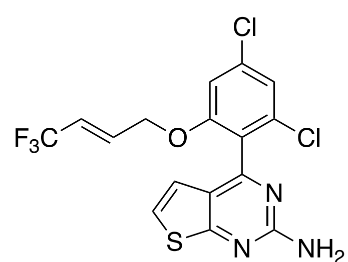
Cyhalothrin pesticide



Insecticide analog



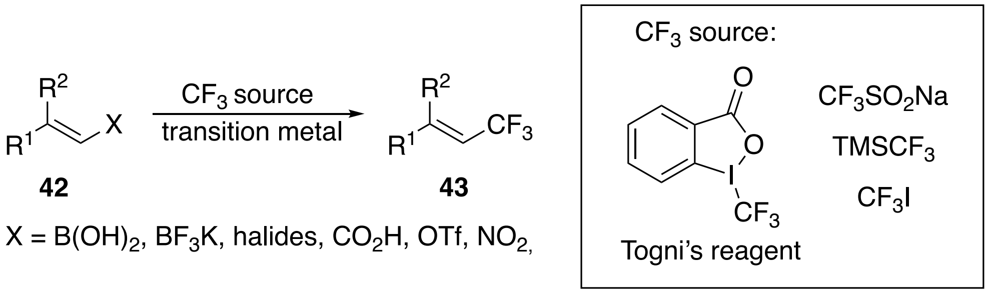
Aminotransferase inhibitor



Anti-cancer agent

Figure 1.2

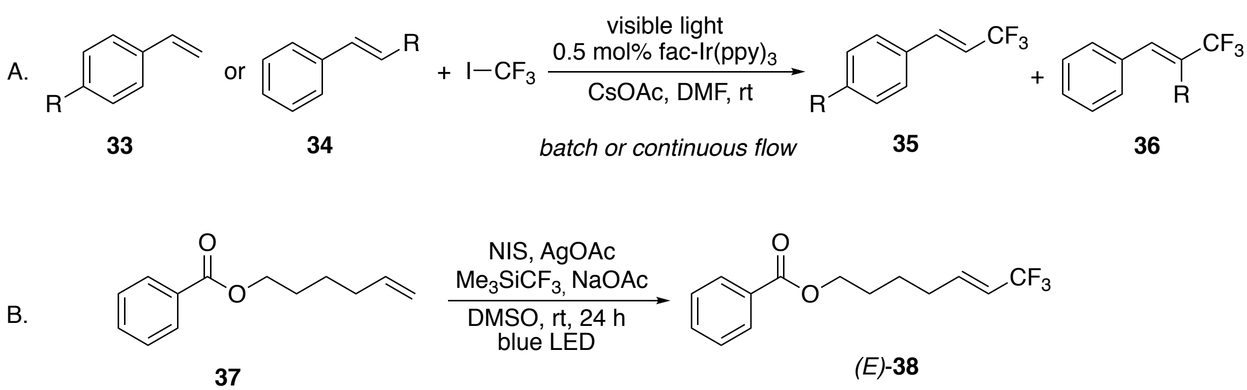
There are no naturally occurring trifluoromethyl alkene compounds that would serve as starting materials, so the design of innovative routes to access trifluoromethylated olefins has generated lots of interest.[18] Cross coupling reactions using pre-functionalized alkenes **42** have been commonly used for the formation of the alkenyl CF_3 bond (**Scheme 1.9**).



Scheme 1.9

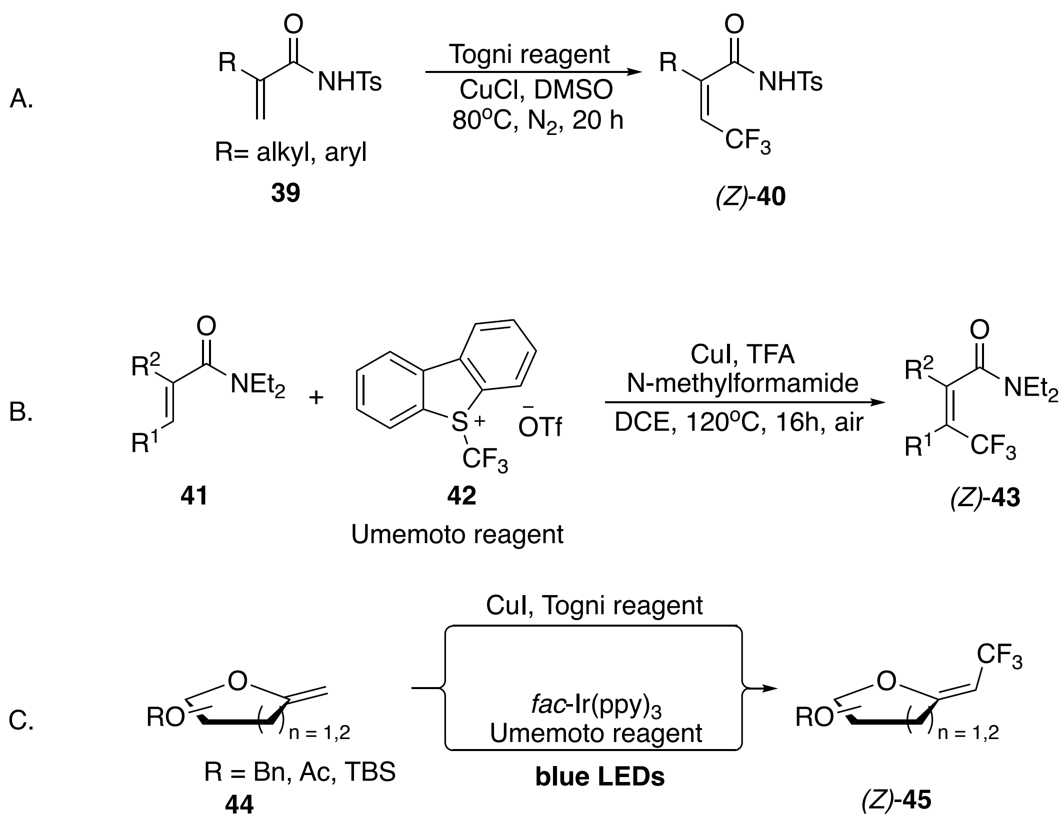
Typically, these pre-functionalized alkenes are tedious to synthesize and these methods suffer from poor atom economy and moderate *E*/*Z* selectivity.

To improve stereoselectivity, other methods have been developed, such as photoredox catalysis and radical-mediated coupling reactions. For example, in 2006, Straathof *et al*. achieved good *(E)*-selectivity for trifluoromethylated styrenes **35** and **36** from a visible light photoredox catalysis reaction using CF_3I as an inexpensive trifluoromethylation reagent (**Scheme 1.10 A**).[16c] In 2019, Tsui and coworkers reported photoredox catalysis that generated a CF_3 radical from the Ruppert-Prakash reagent (Me_3SiCF_3) (**Scheme 1.10 B**).[19] However, most of these methods provided *(E)*-trifluoromethyl olefins primarily due to a steric effect.



Scheme 1.10

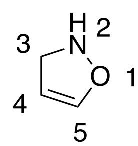
Constructing *(Z)*-trifluoromethyl alkenes is still synthetically challenging and there are only a handful of examples reported. In 2013, Loh *et al.* reported a directing group assisted copper-catalyzed olefinic trifluoromethylation of alkenes.[20] With the amide nitrogen acting as a directing group, the trifluoromethyl group is stereospecifically installed *cis* to the amide group (**Scheme 1.11 A**). In 2014, Pannecoucke *et al*. reported a similar reaction using a different trifluoromethyl and Cu source (**Scheme 1.11 B**).[21] In 2018, Vincent and coworkers described a highly *(Z)*-diastereoselective synthesis of trifluoromethylated *exo*-glycals **45** by copper and photoredox catalysis (**Scheme 1.11 C**).[22] All the methods use either the Togni reagent or the Umemoto reagent, which are both expensive. In addition to the limitations due to the high cost of reagents, a directing group is required in order to achieve high (*Z*)-selectivity. The requirement for these directing groups limits the scope of these methods.



Scheme 1.11

1.5 Synthetic Methods to Prepare 4-Isoxazolines

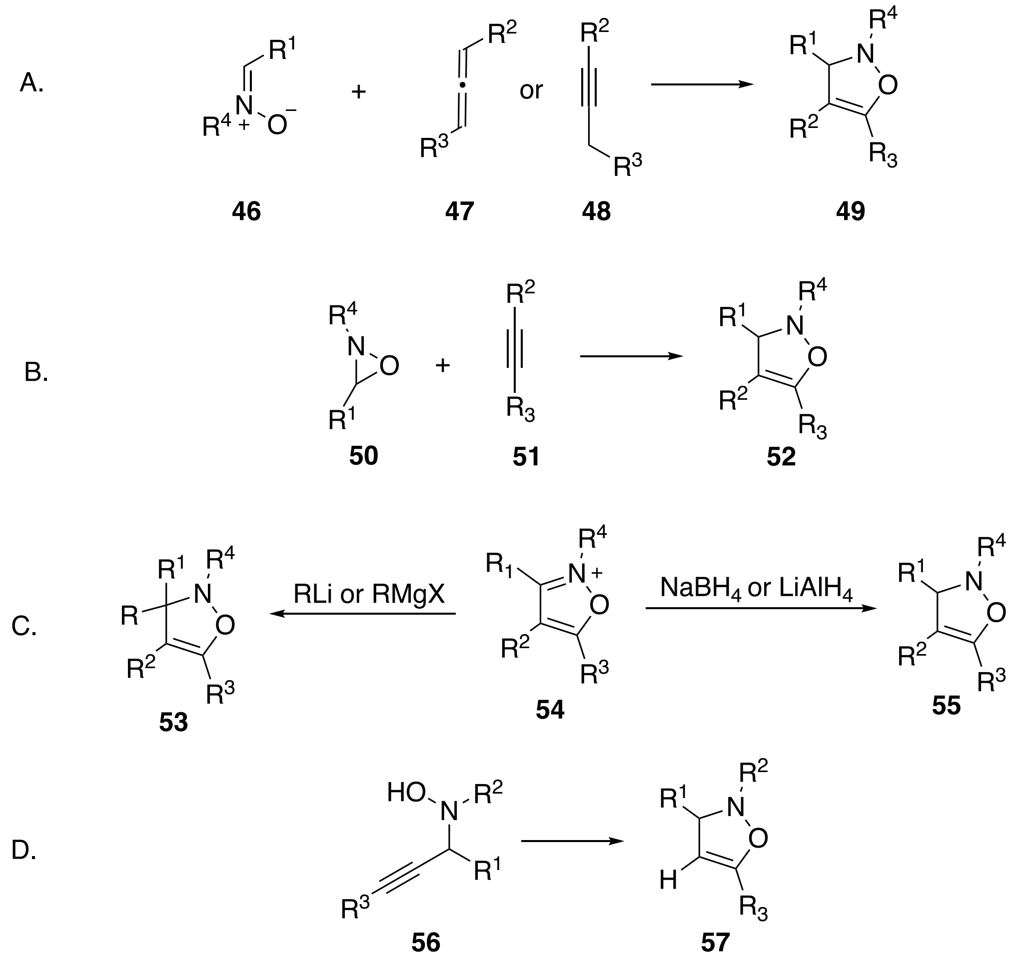
Isoxazolines are five-membered heterocycles incorporating a N-O bond. Due to the labile nature of the N-O bond, isoxazolines provide an access to a diversity of compounds, such as amino acids, β-amino alcohols, β-lactams, alkaloids and other nitrogen containing compounds.[23] Because of the biological importance, many isoxazolines have been of interest in the past couple of decades. This section will mainly discuss 4-isoxazolines of which the structure is shown in **Figure 1.3**.



4-isoxazoline

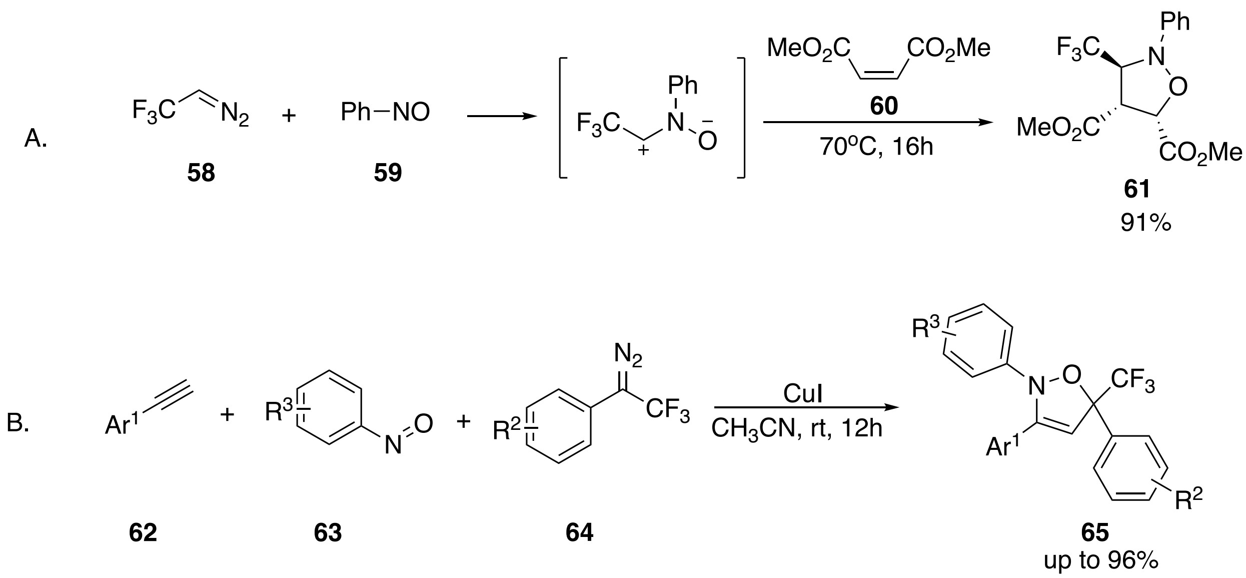
Figure 1.3

The main strategy used to synthesize 4-isoxazolines has been through 1,3-dipolar cycloadditions between nitrones **46** and alkynes **48** or allenes **47** (**Scheme 1.12 A**). Other methods include the cycloaddition of oxaziridines **50** with alkynes **51** (**Scheme 1.12 B**), addition of Grignard reagents or organolithium compounds to isoxazolium salts **54** or their reduction with hydride reagents (**Scheme 1.12 C**), and cyclization of propargylic *N*-hydroxylamines **56** (**Scheme 1.13 D**). [24]



Scheme 1.12

However, the availability of the trifluoromethylated version of isoxazolines is somewhat limited.[25] In 2013, Molander *et al*. reported the 1,3-dipolar cycloaddition of nitrosobenzene **59**, (trifluoromethyl)diazomethane **58** and alkenes **60** afforded trifluoromethylated Isoxazolidines **61**.[26] The reaction proved to be tolerant of a variety of electron-deficient alkenes and nitrosoarenes (**Scheme 1.13 A**). In 2018, a copper(I) catalyzed three-component reaction of diazo compounds **65** with terminal alkyne **63** and nitrosobenzene **64** was reported by Hu's group.[27] This reaction also used trifluoromethyl-containing diazo compounds and afforded trifluoromethyl 3-isoxazolines **66** (**Scheme 1.13 B**). These methods are both limited to multi-component cycloadditions.

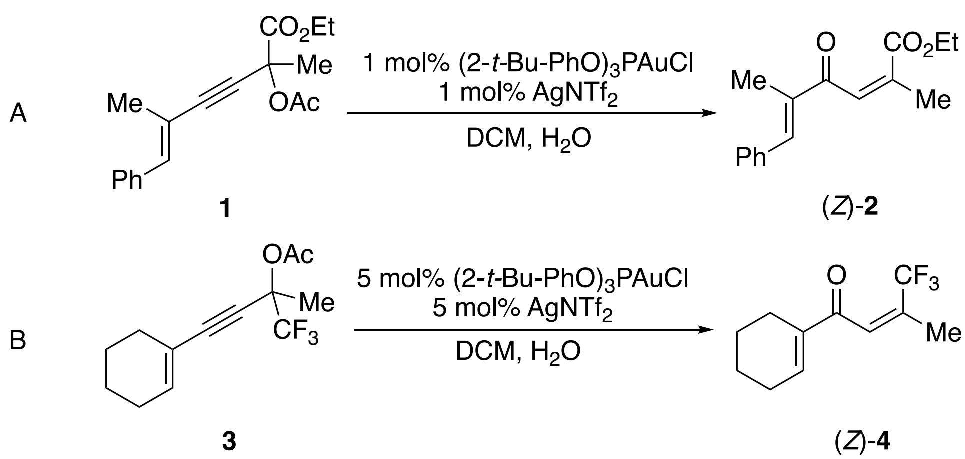

A.
F3C N2
+
Ph−NO
58
59
Ph
F3C N O
60
MeO2C CO2Me
70°C, 16h
Ph
F3C N
O
MeO2C
CO2Me
61
91%
B.
Ar1
+
R3
N O
+
R2
N2
CF3
CuI
CH3CN, rt, 12h
62
63
64
R3
N O CF3
Ar1
R2
65
up to 96%

Scheme 1.13

2. Results and Discussion

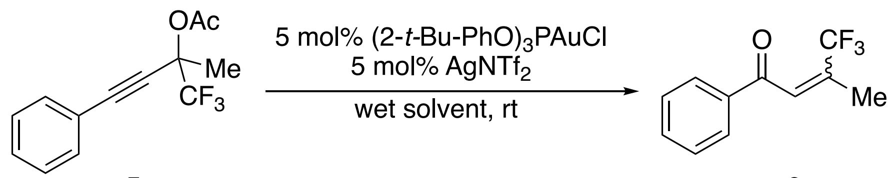
2.1 Preliminary Results

As mentioned in the introduction in 2018 the Tius group reported a (*Z*)-alkene synthesis (**Scheme 2.1 A**).[10] When the propargylic acetate **1** was treated with cationic Au(I) catalyst in the presence of H_2O, an α,β-unsaturated ketone **2** enriched in the (*Z*)-isomer was obtained. Inspired by this reaction, we were interested in whether or not a trifluoromethyl group could be used in place of the ethyl ester group since the stereoselective synthesis of trisubstituted trifluoromethyl alkenes is challenging. Only a handful of examples reported the construction of the *Z* isomer.[20-22] In a preliminary reaction, alkyne **3** was treated with Au(I) in the presence of H_2O and the α,β-unsaturated ketone (*Z*)-**4** was obtained as the major product (**Scheme 2.1 B**).



Scheme 2.1

A series of control experiments were performed in order to optimize the *Z*/*E* selectivity. We started our optimization by investigating the effect of solvents using **5** as model substrate (**Scheme 2.2**). The best solvents that yielded high *Z*/*E* ratios were DCM (entry 2) and DCE (entry 1), providing a 4/1 ratio. Since there was no significant difference in *Z*/*E* selectivity between DCM and DCE, DCE was selected as the optimal solvent for its higher boiling point which allowed us to achieve higher temperatures when we investigated the effect of temperature. The reaction did not proceed in several Lewis basic solvents such as DMSO (entry 6), DMF (entry 7), Et_2O (entry 10) and THF (entry 11). MeCN (entry 3), $MeNO_2$ (entry 4) and PhMe (entry 9) led to lower *Z*/*E* selectivity. The reaction was extremely slow in hexane (entry 8) and cyclohexane (entry 12).

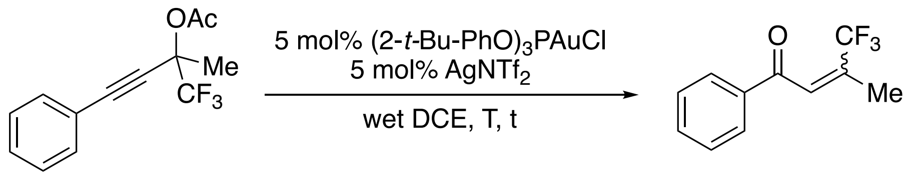


Entry	Solvent	Result (*Z*:*E*)[a]
1	DCE	4:1
2	DCM	4:1
3	MeCN	2:1
4	$MeNO_2$	1:2
5	MeOH	2:1[b]
6	DMSO	No rxn
7	DMF	No rxn
8	hexane	Slow[c]
9	PhMe	2:1
10	Et_2O	No rxn
11	THF	No rxn
12	cyclohexane	Slow[c]

[a] *Z*/*E* ratios determined by ^{19}F NMR analysis of the crude products.
[b] Incomplete reaction after 24h.
[c] Trace amount of **6** detected by ^{19}F NMR after 24h.

Scheme 2.2

Next, the effect of temperature was investigated (**Scheme 2.3**). Higher temperature led to a faster reaction and higher product *Z*/*E* ratio (entry 5). When the reaction was cooled down to 0 °C (entry 1), the reaction was slower and the *Z*/*E* ratio decreased. One possible cause for the poor *Z*/*E* selectivity at lower temperature is isomerization. Although the isomerization rate should decrease at lower temperature, due to a much longer reaction time, the isomerization still proceeded thus led to a lower *Z*/*E* ratio.



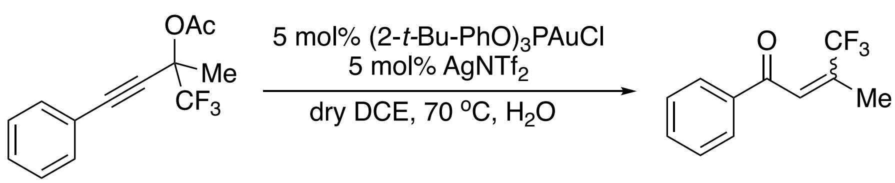
5 **6**

Entry	Temperature (°C)	time (min)	Result (Z:E)[a]
1	0	140	2:1
2	25	60	4:1
3	40	50	5:1
4	60	8	6:1
5	70	5	6:1

[a] Z/E ratios determined by ^{19}F NMR analysis of the crude products.

Scheme 2.3

Next, the effect of water was examined (**Scheme 2.4**). At least one equivalent of water (entries 1-2) is required for the reaction to proceed to completion, since it is necessary to hydrolyze the acetate group. Increasing the amount of water to 4 and 8 equivalents resulted in a heterogenous mixture in the reaction which led to a slight decrease in the *Z*/*E* ratio (entries 4-5).



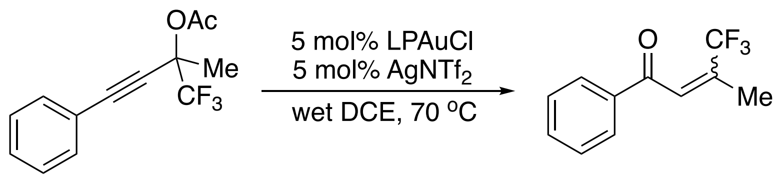
5 **6**

Entry	H_2O (equiv.)	Result (Z:E)[a]
1	0.5	n.d.[b]
2	1	6:1
3	2	6:1
4	4	5:1
5	8	5:1

[a] Z/E ratios determined by ^{19}F NMR analysis of the crude products.
[b] Incomplete reaction after 24h.

Scheme 2.4

Lastly, we screened the ligands on Au. Several ligands were chosen based on their electronic and steric properties (**Scheme 2.5**). The tris(2-*tert*-butylphenyl)phosphite complex (entry 1) provided the highest *Z/E* ratio. The electron deficient ligand, tris(pentafluorophenyl)phosphine, gave a slightly lower *Z/E* ratio (entry 5). The bulky NHC ligands (entries 6-7) gave similar *Z/E* ratios as tris(2-*tert*-butylphenyl)phosphite (entry 1).



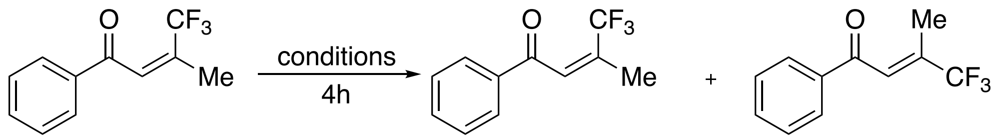
5 **6**

Entry	Ligand	Result (*Z*:*E*)[a]
1	P(O-2-*t*-Bu-Ph)$_3$	6:1
2	P(OPh)$_3$	6:1
3	PAd$_3$	5:1
4	PPh$_3$	3:1[b]
5	P(C$_6$F$_5$)$_3$	5:1
6	IPr	6:1
7	IMes	5:1

[a] *Z*/*E* ratios determined by ^{19}F NMR analysis of the crude products.
[b] Incomplete reaction after 24h.

Scheme 2.5

During the course of the reaction optimization we discovered that if the reaction mixture was exposed to the reaction conditions for extended periods of time (>2h), the *Z/E* ratio of the products decreased. We speculated that the (*Z*)-**6** underwent isomerization during the reaction in the presence of trace amounts of acid. The source of the acid might have come from the hydrolysis of the acetate group, during which one equivalent of acetic acid was generated. Control experiments were carried out that confirmed our hypothesis (**Scheme 2.6**). By dissolving pure (*Z*)-**6** in C_6D_6, no isomerization was detected after 16 h (entry 1). When $CDCl_3$ was used as solvent, the isomerization product (*E*)-**6** was detected after 4h, presumably due to the trace of DCl that was present in aged bottle of chloroform (entry 2). When (*Z*)-**6** was treated with 10% $HNTf_2$ in $CDCl_3$, the isomerization was faster (entry 3).



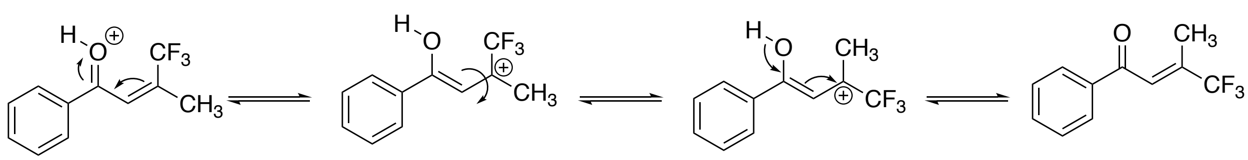
(*Z*)-**6** (*Z*)-**6** (*E*)-**6**

Entry	Conditions	Result (*Z*:*E*)[a]
1	C_6D_6	No isomerization[b]
2	$CDCl_3$	13:1
3	$CDCl_3$, 10% $HNTf_2$	10:1

[a] *Z*/*E* ratios determined by ^{19}F NMR analysis of the crude products.
[b] No isomerization observed after 16h.

Scheme 2.6

The mechanism for enone isomerization under acidic conditions is shown in **Scheme 2.7**. The ketone group of (*Z*)-**6** is activated by a proton or deuteron, to give an allylic cation intermediate **7** and **8.** Even though intermediates **7** and **8** are not favored due to the destabilizing effect of the trifluoromethyl group on the cation, the indicated bond rotation still provides an opportunity for the (*E*)-isomer to form.



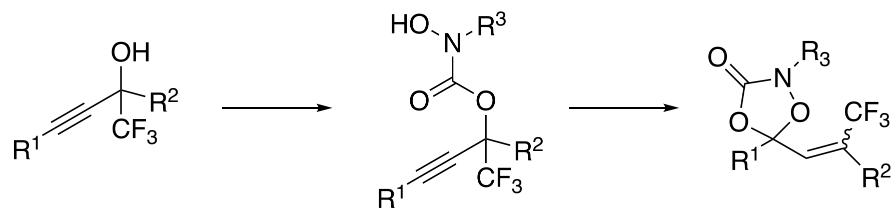
(*Z*)-**6** **7** **8** (*E*)-**6**

Scheme 2.7

At this point we had optimized the reaction conditions for the synthesis of the (*Z*)-trifluoromethyl alkene from propargylic acetate **5**, but because of the isomerization this did not result in a satisfactory method for preparing (*Z*)-trisubstituted trifluoromethyl alkenes.

2.2 Design of the Substrate

In order to suppress isomerization it is necessary to circumvent the formation of the α,β-unsaturated ketone under the reaction conditions. One approach is to form the final product as ketal **11**. We proposed to accomplish this by installing a *N*-hydroxycarbamate group on the propargylic alcohol **9**. By doing this, the *N*-hydroxy group is able to intercept the cationic intermediate that would otherwise lead to the enone (**Scheme 2.8**).

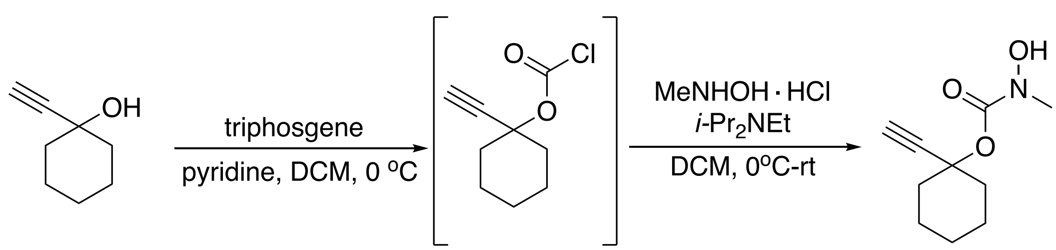


9 **10** **11**

new substrate design

Scheme 2.8

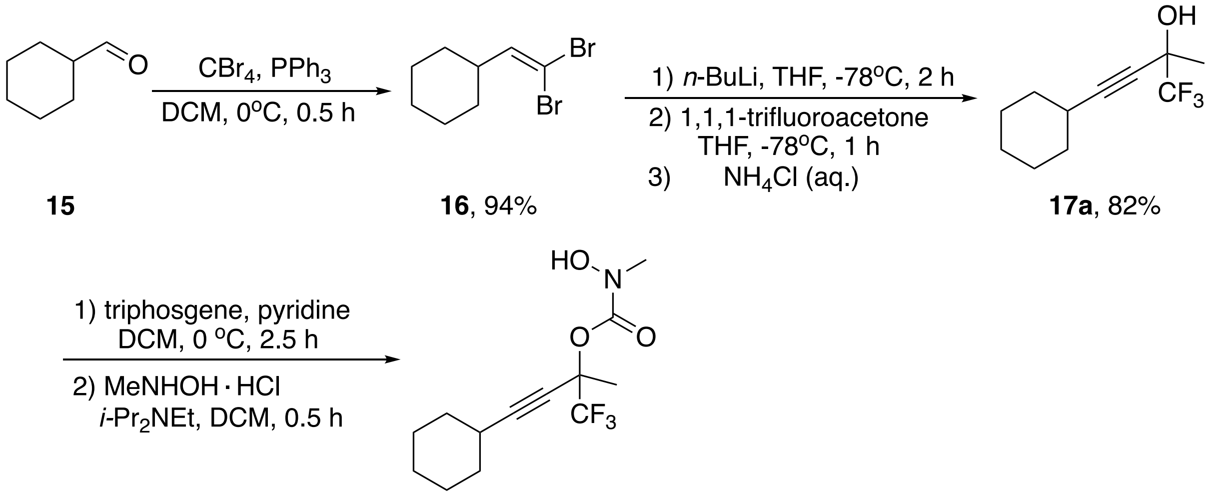
Following the published procedure,[28] using propargyl alcohol **12** as the model starting material, carbamate **14** was prepared in 51% yield by reacting **12** with triphosgene in the presence of pyridine followed by the addition of *N*-methylhydroxylamine (**Scheme 2.9**).



12 **13** **14**, 51%

Scheme 2.9

Having settled on a method to convert a tertiary propargyl alcohol to a *N*-hydroxycarbamate, we proceeded to prepare the first substrate, **18a** (**Scheme 2.10**). Through a Corey-Fuchs reaction.[29] Cyclohexanecarboxaldehyde **15** was exposed to CBr_4 and PPh_3 in DCM at 0 °C for 30 min. The dibromo species **16** was obtained in 94% yield. Treating **16** with two equivalents of *n*-BuLi, followed by the addition of 1,1,1-trifluoromethyl acetone, led to the propargyl alcohol **17a** in 82% yield. By applying the conditions of **Scheme 2.9**, we obtained **18a** in 60% yield.



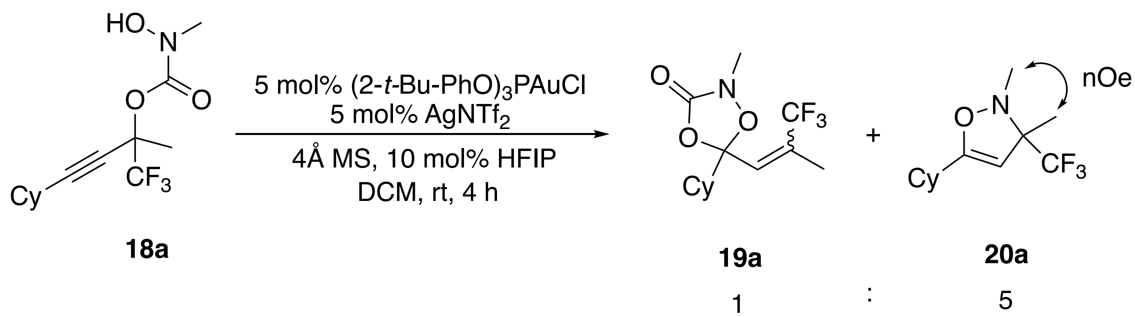
18a, 60%

Scheme 2.10

At this stage, we had designed and synthesized a new substrate that we hoped would lead to the trifluoromethyl alkene with good *Z/E* selectivity.

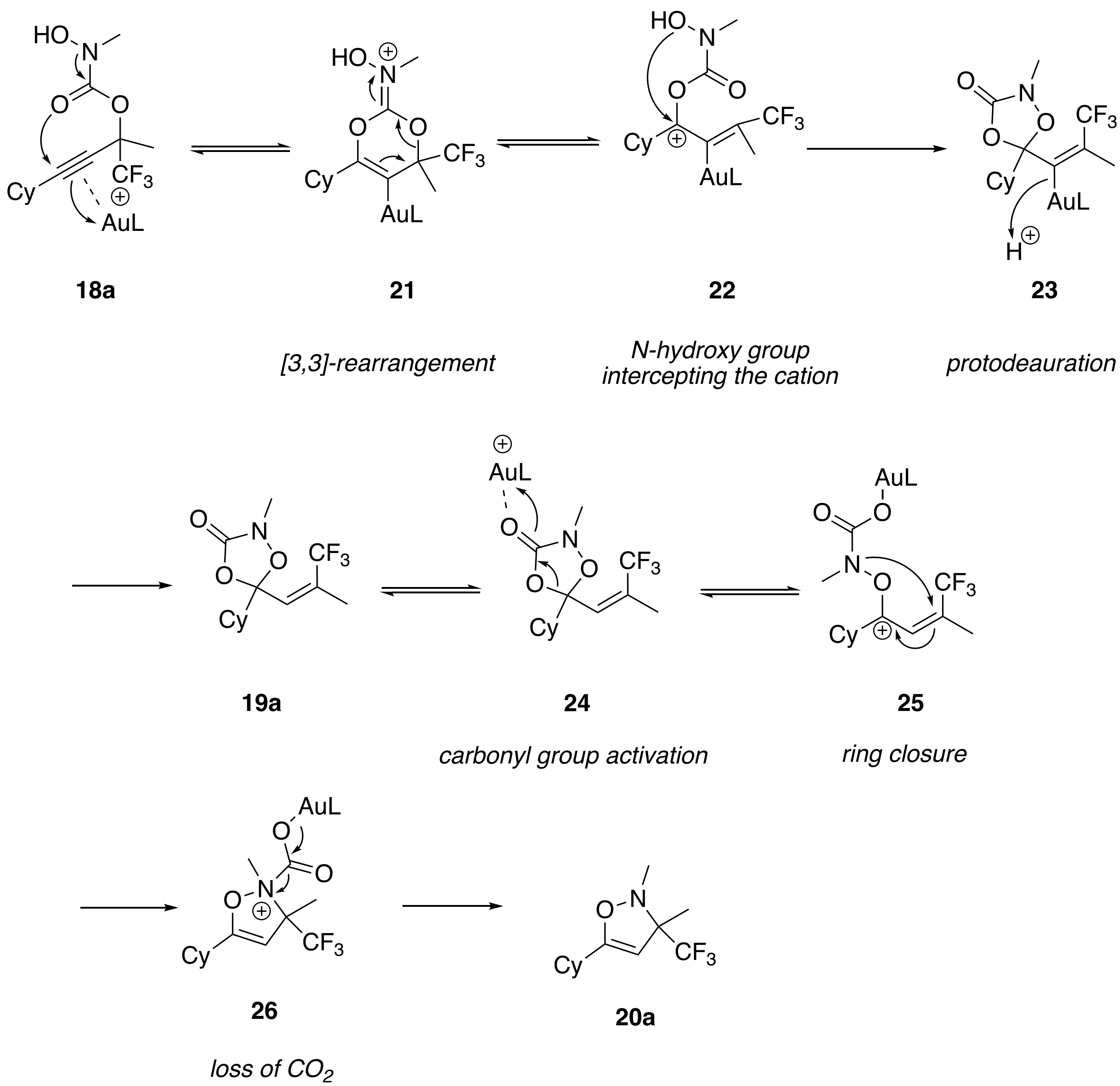
2.3 (*Z*)-Trifluoromethyl Alkene Synthesis

With the modified substrate **18a** on hand, we attempted to synthesize the (*Z*)-trifluoromethyl alkene using Au(I) catalysis. Applying the previously developed Au(I) conditions that led to **6**, using 10% HFIP as an additive due to its cation stabilizing ability, the result was both unexpected and disappointing (**Scheme 2.11**). The reaction provided a mixture of the desired alkene **19a** and an undesired 4-isoxazoline **20a** in a 1:5 ratio after 4h. The relative position of nitrogen and oxygen in **20a** was assigned on the basis of the positive nOe between the *N*-methyl and 3-methyl groups.



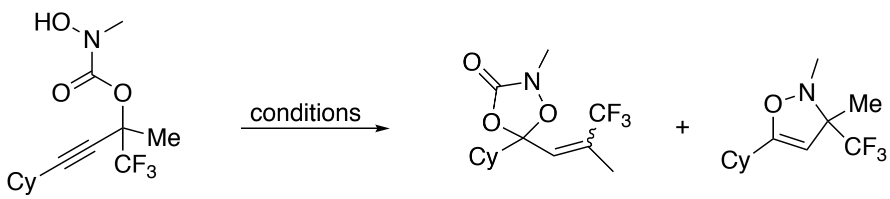
Scheme 2.11

Upon examination of the structure of the two products, it was not hard to see the connection between them. We postulated that the 4-isoxazoline **20a** was the product of decarboxylation of **19a**. We initially proposed what appeared to be a reasonable mechanism (**Scheme 2.12**) that rationalized the formation of **20a** from **19a**. This mechanism turned out to be incorrect (vide infra). The reaction started with the activation of the alkyne group in **18a** by cationic Au(I), followed by intramolecular [3,3]-rearrangement, affording the vinylgold species **22**. The intramolecular trapping of the cation in **22** followed by protodeauration formed **19a**. The carbonyl group in **19a** was further activated by cationic Au(I) which led to intermediate **25**. The 5-membered ring closure of **25** led to **26**, which underwent decarboxylation leading to 4-isoxazoline **20a** as the final product.



Scheme 2.12

In order to support the hypothesis, a series of experiments were carried out. The results are summarized in **Scheme 2.13**. First, we changed the electronic characteristics of the ligand, in an attempt to reduce the Lewis acidity of the Au catalyst thus prevent the activation of the carbonyl group. When SPhos was used as an electron rich ligand, the result was not as we expected, and the ratio of **19a** to **20a** decreased (entry 2). Second, we increased the steric bulk of the ligand, in order to prevent the Au(I) catalyst from approaching the carbonyl group. Tris(1-adamantyl)phosphine (Ad_3P) was chosen for this reason, however, this ligand did not lead to an increase in the **19a**/**20a** ratio, instead **20a** was formed as the only product (entry 4). The final attempt to suppress the decarboxylation was to saturate the solution with CO_2. In one case this led to no improvement (entry 6) and in the other led to a worse result (entry 7). The ratio of **19a** and **20a** was determined by ^{19}F NMR analysis of the crude reaction mixture.



18a **19a** **20a**

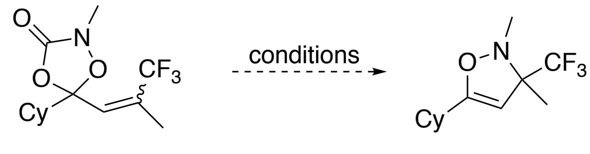
Entry	Catalyst	Conditions	Result (**19a**/**20a**)
1	5 mol% (2-tBu-PhO)$_3$PAuNTf$_2$	4Å MS, 10 mol% HFIP, DCM, rt	1/4
2	5 mol% SPhosAuNTf$_2$	4Å MS, 10 mol% HFIP, DCM, rt	1/5
3	5 mol% PPh$_3$AuNTf$_2$	4Å MS, 10 mol% HFIP, DCM, rt	1/4
4	5 mol% Ad$_3$PAuNTf$_2$	4Å MS, 10 mol% HFIP, DCM, rt	**20a**
5	5 mol% (2-tBu-PhO)$_3$PAuNTf$_2$	3Å MS, 10 mol% HFIP, DCM, rt	1/4
6	5 mol% (2-tBu-PhO)$_3$PAuNTf$_2$	3Å MS, 10 mol% HFIP, saturated with CO_2,[a] DCM, rt	1/4
7	5 mol% (2-tBu-PhO)$_3$PAuNTf$_2$	3Å MS, 10 mol% HFIP, saturated with CO_2,[a] DCM, -78°C-rt	1/7

[a] solvent saturated with CO_2 by bubbling pre-dried CO_2 gas for 5 min.

Scheme 2.13

These results suggested that perhaps **20a** was not derived from **19a** after all. To test this, attempts were made to convert **19a** directly into **20a**. Exposing **19a** to the original reaction condition in the presence of Au(I) would lead to **20a** if **19a** was the precursor of **20a**. In order to find out which reagents in the reaction condition might catalyze the decarboxylation, we started from the simplest condition and added one reagent at a time. The results are summarized in **Scheme 2.14.** First, we dissolved pure **19a** in DCM and no **20a** was detected after 14h (entry 1). Second, we tested the effect of 4Å molecular sieves and HFIP, but no conversion to **20a** was observed in either cases (entries 2-3). Third, we examined the effect of Ag salts that are present in the reaction mixture. Adding $AgNTf_2$ to the reaction did not lead to the formation of **20a** (entry 4). Since AgCl was generated during the ion exchange between $AgNTf_2$ and LAuCl, AgCl was added but no **20a** was detected (entry 5). Next, the (2-*t*Bu-

PhO)3PAuCl catalyst was added, but there was still no formation of **20a** (entry 6). Lastly, pure **19a** was exposed to the original catalysis conditions, and the result was still negative (entry 7).

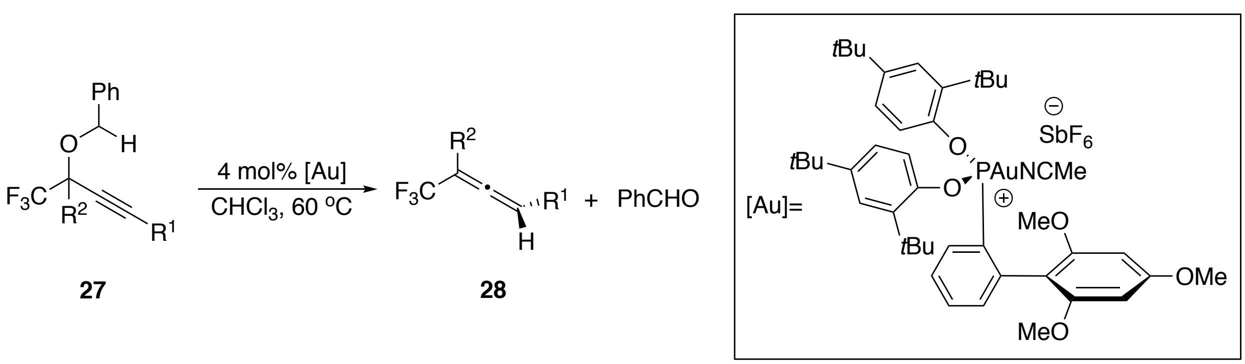


Entry	Conditions	Time	Result
1	DCM	14 h	No rxn
2	4Å MS, DCM, rt	14 h	No rxn
3	4Å MS, 10 mol% HFIP, DCM, rt	14 h	No rxn
4	5 mol% $AgNTf_2$, 4Å MS, 10 mol% HFIP, DCM, rt	14 h	No rxn
5	5 mol% AgCl, 4Å MS, 10 mol% HFIP, DCM, rt	14 h	No rxn
6	5 mol% (2-tBu-PhO)$_3$PAuCl, 4Å MS, 10 mol% HFIP, DCM, rt	14 h	No rxn
7	5 mol% (2-tBu-PhO)$_3$PAuCl, 5 mol% $AgNTf_2$, 4Å MS, 10 mol% HFIP, DCM, rt	14 h	No rxn

Scheme 2.14

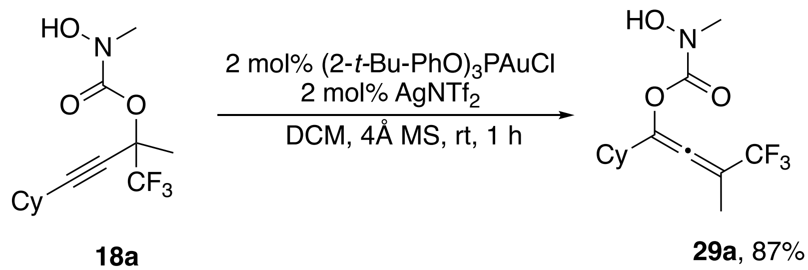
These results strongly suggest that **19a** was not the precursor of **20a**. An alternative mechanism for the formation of both compounds had to be considered.

In 2016, Gagosz *et al.* reported a synthesis of trifluoromethyl allenes by gold catalyzed intramolecular hydride transfer reaction of propargyl benzyl ethers (**Scheme 2.15**).[30] They isolated 23 trifluoromethyl allenes in yields from 43%-99%.



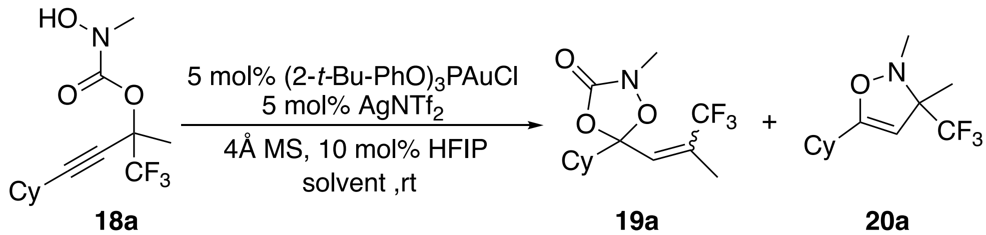
Scheme 2.15

Inspired by this work, we speculated that trifluoromethyl allenes could be a common, isolable intermediate to both trifluoromethyl alkenes and to 4-isoxazolines in our case. Exposing **20a** to Au(I) catalysis in the presence of 4Å molecular sieves without HFIP, we monitored the reaction closely by ^{19}F NMR. After 1 h, the ^{19}F peak of the starting material disappeared and the reaction was stopped. We managed to isolate allene **29a** in 87% (**Scheme 2.16**).



Scheme 2.16

Since the chromatographic mobilities of the starting material **18a** and the allene **29a** were almost identical, the reaction was monitored by ^{19}F NMR by transferring an aliquot of the reaction mixture to an NMR tube and dissolving it in $CDCl_3$. After exposing **18a** to Au(I) catalysis for 1h, allene **29a** was detected. To our surprise, when the same sample was monitored again after three days, **29a** disappeared and the alkene **19a** had formed as the major product. Encouraged by this outcome, a series of experiments were conducted in order to mimic the conditions in the NMR tube that had led to the formation of **19a** (**Scheme 2.17**). We examined the effect of solvents. DCM was used as a control experiment (entry 1), **20a** was formed as the major product. Changing the solvents to $CHCl_3$ (entry 2), DCE (entry 3) and $CDCl_3$ (entry 4) led to the formation **20a**.

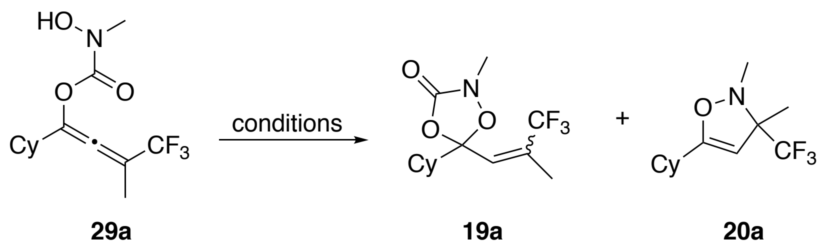


Entry	Solvent	Result[a]
1	DCM	**20a**
2	$CHCl_3$	**20a**
3	DCE	**20a**
4	$CDCl_3$	**20a**

[a] The major product formed.

Scheme 2.17

These control experiments narrowed down the range of important variables to examine for us: the solvent was not the cause of the formation of the alkene. In order to simplify the problem, we isolated the allene **29a** and kept screening the conditions on allene **29a** (**Scheme 2.18**). As expected, there was no reaction when dissolving **29a** in $CHCl_3$ (entry 1). When **29a** was exposed to Au(I) catalyst, **20a** was formed as the major product (entry 2). Allene **29a** did not react with H_2O in $CHCl_3$ (entry 3). An interesting observation was made in entries 4 and 5 : allene **29a** would not react with Au(I) catalyst under strictly anhydrous and proton free conditions, and the presence of H_2O in the reaction mixture was necessary for the formation of **20a**. For entries 6-7, we speculated that a trace amount of DCl present in the $CDCl_3$ might have led to the formation of the alkene **19a**. Indeed, the reaction of **29a** with acid led to the exclusive formation of **19a**.

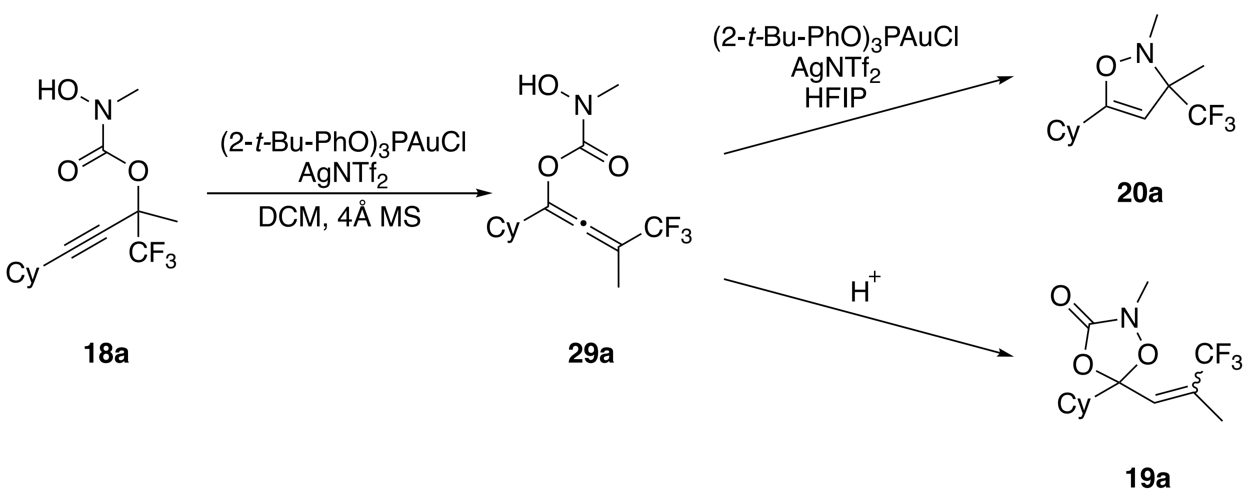


Entry	Conditions[a]	Time	Result
1	$CHCl_3$, rt	14h	No rxn
2	0.5 mol% (2-*t*-Bu-PhO)$_3$PAuCl, 0.5 mol% $AgNTf_2$, $CHCl_3$, rt	14h	**20a**
3	1equiv. H_2O, $CHCl_3$, rt	14h	No rxn
4	0.5 mol% ((2-*t*-Bu-PhO)$_3$PAuCl, 0.5 mol% $AgNTf_2$, 4Å MS, $CHCl_3$, rt	14h	No rxn
5	0.5 mol% (2-*t*-Bu-PhO)$_3$PAuCl, 0.5 mol% $AgNTf_2$, 1 equiv. H_2O, $CHCl_3$, rt	14h	**20a**
6	1 equiv. 1M HCl, $CHCl_3$, rt	14h	**19a**
7	1 equiv. 1M HCl, 0.5 mol% (2-*t*-Bu-PhO)$_3$PAuCl, 0.5 mol% $AgNTf_2$, $CHCl_3$, rt	14h	**19a**

[a] $CHCl_3$ treated with $NaHCO_3$ to remove the trace amount of HCl prior to use.

Scheme 2.18

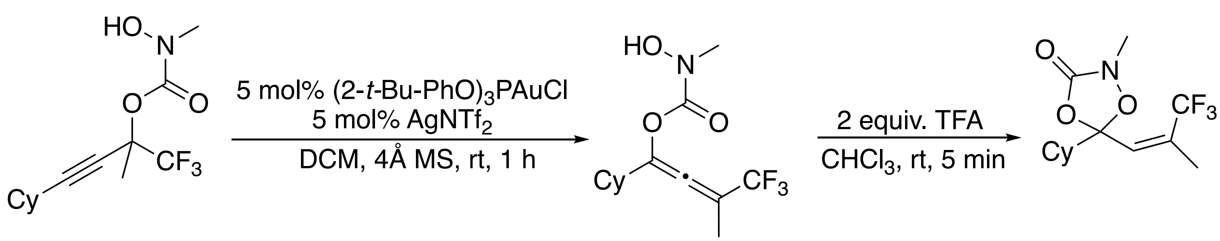
These control experiments confirmed our hypothesis that allene **29a** was the common intermediate both of the 4-isoxazoline **20a** and the alkene **19a**. The formation of **20a** was catalyzed by Au(I) while the formation of **19a** was the result of electrophilic addition of acid to **29a**. The pathways leading to the two products are summarized in **Scheme 2.19**.



Scheme 2.19

2.4 Substrate Scope Investigation

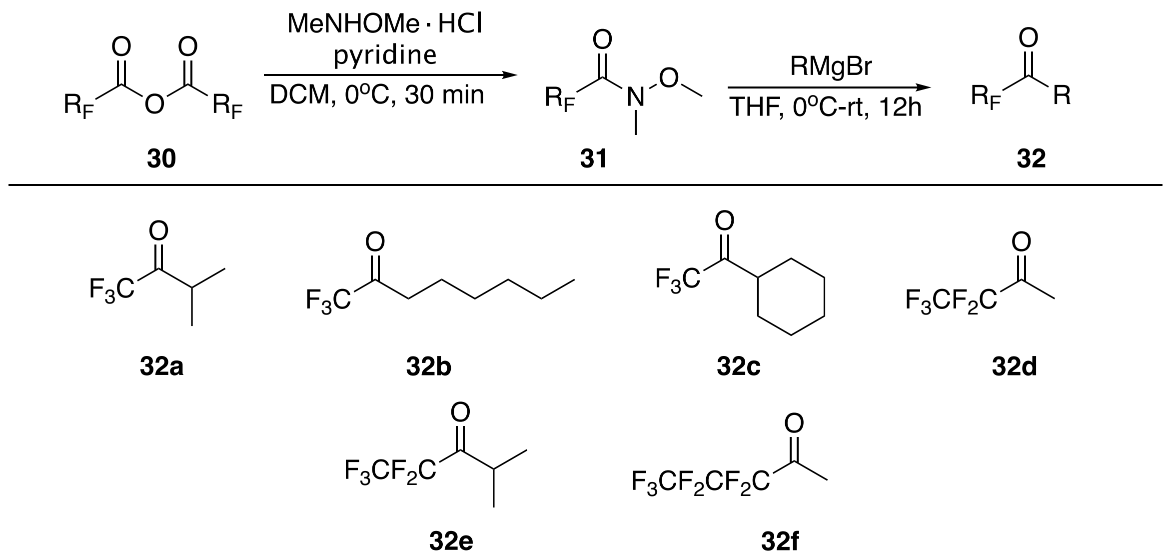
Since adding aqueous HCl to the reaction creates a biphasic mixture which slows down the reaction, TFA was used as the proton source in order to accelerate the reaction. The *Z/E* selectivity of the trifluoromethyl alkene was examined using the conditions represented by entry 6 in **Scheme 2.18**, but substituting 1 equivalent of HCl for 2 equivalents of TFA. Substrate **18a** led to **19a** in high yield and excellent *Z*/*E* selectivity (92/8) (**Scheme 2.20**). Unlike other published methods of (*Z*)-trifluoromethyl alkenes synthesis mentioned in the introduction chapter,[20-22] Which require a nitrogen or an oxygen atom as directing group, there is only trifluoromethyl group as the directing group in our case. The A values of methyl and trifluoromethyl groups are 1.7 and 2.1 respectively, which implies that while there is only a small difference in size between them, that the trifluoromethyl group is the larger of the two. This result is surprising because the marginally larger trifluoromethyl group ends up *cis* to the tertiary group the **19a**. A detailed postulated mechanism will be discussed in the conclusion chapter.



18a **29a**, 87% **19a**, 98% *Z*/*E*=92/8

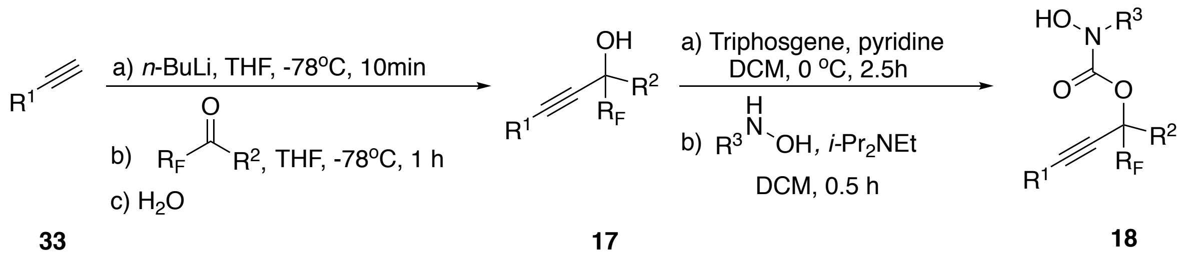
Scheme 2.20

Encouraged by this result, we started investigating the substrate scope. Several fluorine containing ketones were synthesized based on published methods (**Scheme 2.21**).[31] All of the fluorine containing ketones were used directly without purification.



Scheme 2.21

According to the procedure summarized in **Scheme 2.10**, we synthesized 17 fluorine containing *N*-hydroxycarbamates (**Scheme 2.22**, entries 1-17) and one non-fluorine containing *N*-hydroxycarbamate (**Scheme 2.22**, entry 18).

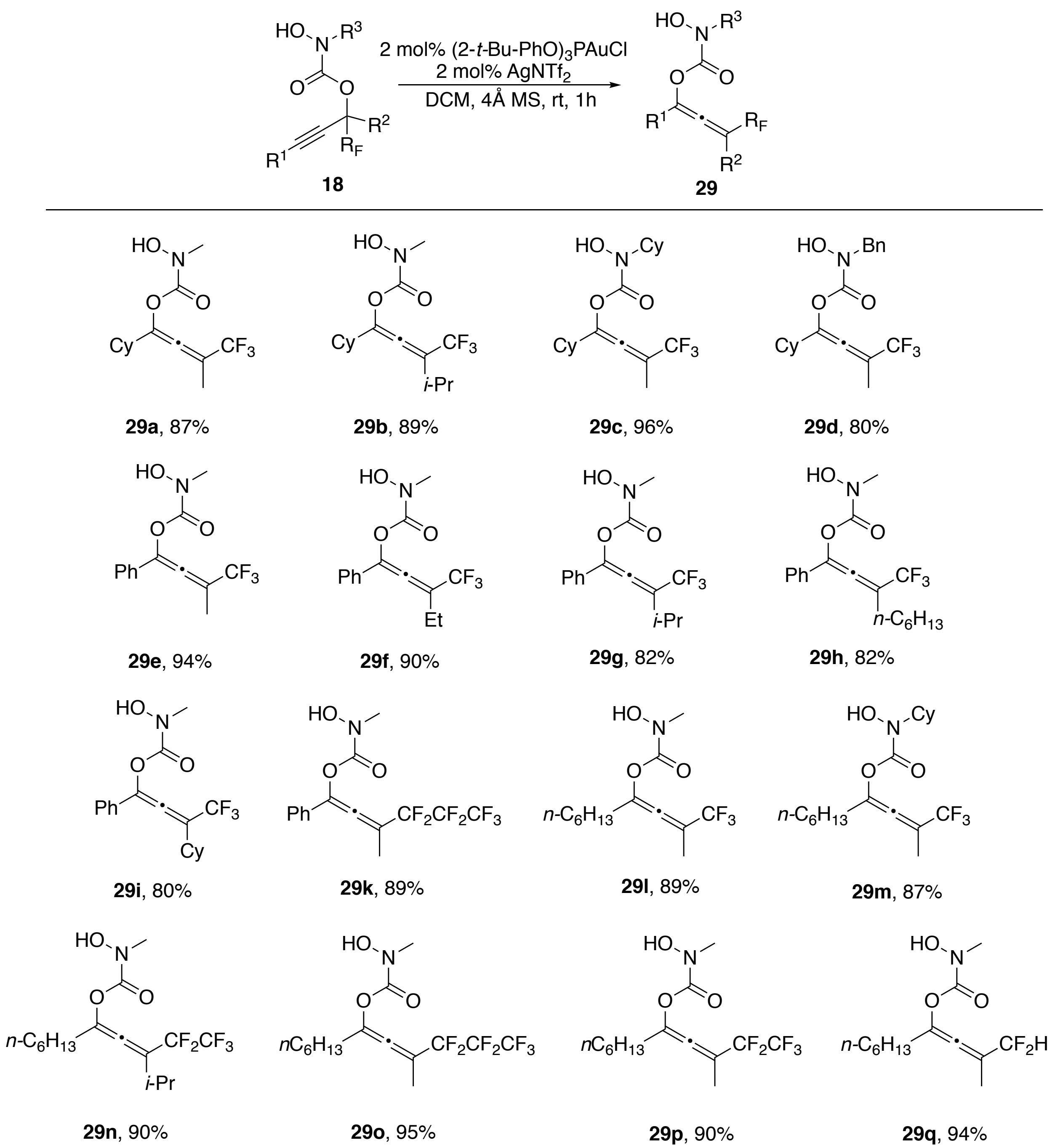


Entry	R_F	R^1	R^2	R^3	**18**	Yield(%)[a]
1	CF_3	Cy	Me	Me	**18a**[b]	60
2	CF_3	Cy	*i*-Pr	Me	**18b**[b]	56
3	CF_3	Cy	Me	Cy	**18c**[b]	56
4	CF_3	Cy	Me	Bn	**18d**[b]	69
5	CF_3	Ph	Me	Me	**18e**	52
6	CF_3	Ph	Et	Me	**18f**	50
7	CF_3	Ph	*i*-Pr	Me	**18g**	57
8	CF_3	Ph	1-hexyl	Me	**18h**	44
9	CF_3	Ph	Cy	Me	**18i**	49
10	CF_3	Ph	Me	Cy	**18j**	61
11	$CF_2CF_2CF_3$	Ph	Me	Me	**18k**	59
12	CF_3	1-hexyl	Me	Me	**18l**	67
13	CF_3	1-hexyl	Me	Cy	**18m**	65
14	CF_2CF_3	1-hexyl	*i*-Pr	Me	**18n**	58
15	$CF_2CF_2CF_3$	1-hexyl	Me	Me	**18o**	54
16	CF_2CF_3	1-hexyl	Me	Me	**18p**	58
17	CF_2H	1-hexyl	Me	Me	**18q**	66
18	— (H)	Ph	*i*-Pr	Me	**18r**	71

[a] The yield of the last step. [b] Substrates synthesized following the method of **Scheme 2.10**.

Scheme 2.22

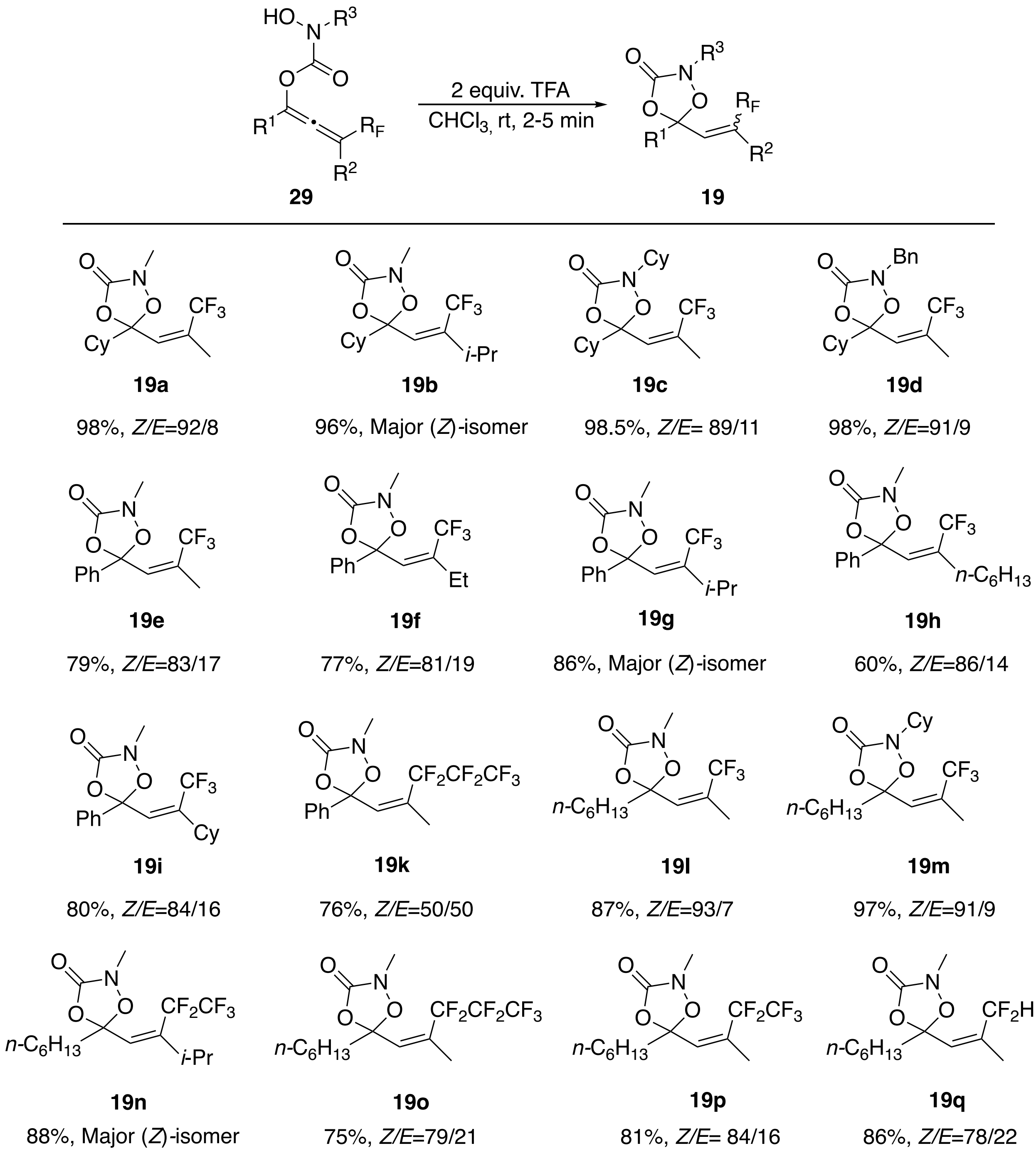
In order to synthesize (*Z*)-trisubstituted alkenes, we isolated 16 fluorine containing allenes by treating carbamates with Au(I) catalyst, except for **18j**. We used **18j** directly to form 4-isoxazloine **20j** in a later experiment. In all cases, the allenes were isolated in high yields (**Scheme 2.23**).



Scheme 2.23

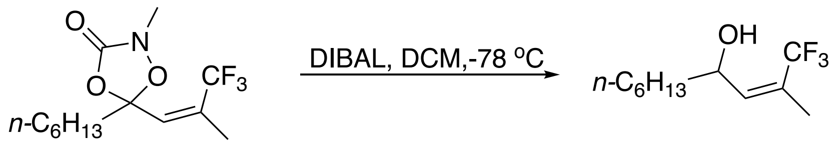
Most of the allenes were stable for months when stored under inert atmosphere at low temperature.

Treatment of the allenes with 2 equivalents of TFA in DCM leads in all cases to fast reactions and affords the alkenes in good yields. The results are shown in **Scheme 2.24**. Alkenes **19a**, **19d**, **19l** and **19m** showed excellent *Z*/*E* selectivity (91/9 to 93/7). Alkenes **19c**, **19e**, **19f**, **19h**, **19i** and **19p** showed good *Z*/*E* selectivity (81/19 to 89/11). Alkenes **19o** and **19q** showed moderate *Z*/*E* selectivity (78/22 to 79/21). In the cases that R^2 is isopropyl (**19b**, **19g**, **19n**), we were not able to identify the (*E*)-isomers from ^{19}F NMR, and we were only able to isolate the major product (*Z*)-isomers. In the case of **19f**, the *Z*/*E* selectivity was poor (50/50). The *Z* stereochemistry was assigned on the basis of the positive nOe between the vinyl proton and the allylic proton(s) on R^2 group. The structure of compound **19c** was confirmed by X-ray crystallography.


HO
N
R3
O
O
R1
RF
R2
29
2 equiv. TFA
CHCl3, rt, 2-5 min
O
N
R3
O
O
RF
R1
R2
19
19a
98%, Z/E=92/8
19b
96%, Major (Z)-isomer
19c
98.5%, Z/E= 89/11
19d
98%, Z/E=91/9
19e
79%, Z/E=83/17
19f
77%, Z/E=81/19
19g
86%, Major (Z)-isomer
19h
60%, Z/E=86/14
19i
80%, Z/E=84/16
19k
76%, Z/E=50/50
19l
87%, Z/E=93/7
19m
97%, Z/E=91/9
19n
88%, Major (Z)-isomer
19o
75%, Z/E=79/21
19p
81%, Z/E= 84/16
19q
86%, Z/E=78/22

Scheme 2.24

To demonstrate that the ketal group can be converted into the generally useful allylic alcohol, we reduced (*Z*)-**19i**. As summarized in **Scheme 2.25**, the ketal group of (*Z*)-**19i** was reduced by DIBAL at -78^{o}C, affording an allylic alcohol (*Z*)-**34** with retention of the alkene geometry.



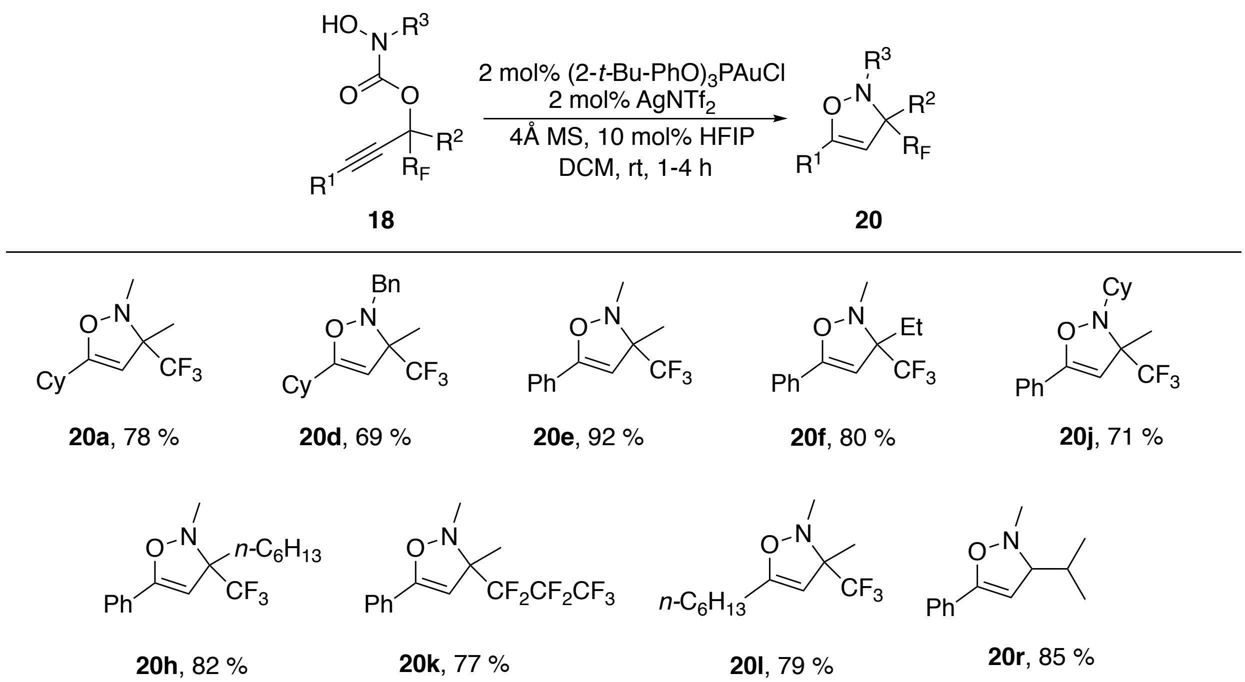
(*Z*)-**19i** (*Z*)-**34**, 82%

Scheme 2.25

To summarize, we successfully prepared 16 fluorine containing allenes and achieved a highly (*Z*)-selective synthesis of trisubstituted trifluoromethyl alkenes with a broad substrate scope. We also illustrated a method to functionalize the alkenes without compromising the (*Z*)-selectivity.

2.5 Trifluoromethyl 4-Isoxazoline Synthesis

We next examined the scope of the reaction that led to the formation of 3-trifluoromethyl 4-isoxazolines. The 4-isoxazolines could be formed in a one-pot reaction without isolating the allenes. We synthesized 8 fluorine containing 4-isoxazolines and 1 non-fluorine 4-isoxazoline in good yields. (**Scheme 2.26**).



Scheme 2.26

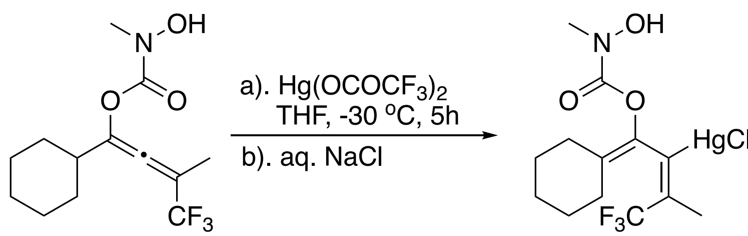
This method is not limited to 3-trifluoromethyl 4-isoxazolines. In the case of **20k**, we achieved good yield (77%) when heptafluoro-1-propyl was used. In the case of **20r**, we demonstrated that this method works for non-fluorine 4-isoxazolines.

We have described an efficient one-pot synthesis of fluorine containing 4-isoxazolines. The reaction is general, it proceeds under mild conditions and in high yield and allows for multiple diversification.

2.6 Tetrasubstituted Trifluoromethyl Alkene Synthesis

In section 2.4, we described an discovery of the electrophilic addition of proton to trifluoromethyl allenes leading to (*Z*)-selective synthesis of trisubstituted trifluoromethyl alkenes. The next objective was to synthesize tetrasubstituted alkenes with specific geometry by utilizing electrophiles other than proton.

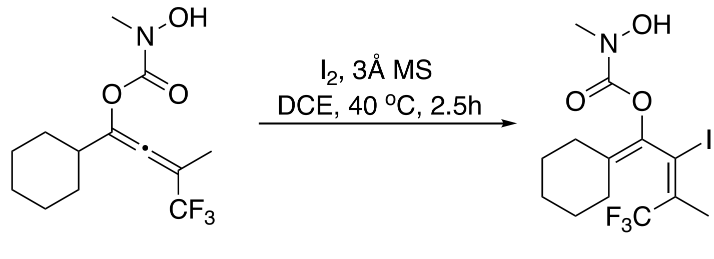
We first treated allene **29a** with $Hg(OAc)_2$. Due to the slowness of the reaction, we changed the mercury source to $Hg(OCOCF_3)_2$. With a more reactive Hg species, the reaction proceeded at -30 ^{o}C. After 5 hours, the reaction was quenched with NaCl, but instead of forming a ketal, as was the case when **29a** was exposed to TFA, loss of a proton from the cyclohexyl group led to the fully substituted diene **35** as a single isomer. The geometry of the diene is shown in **Scheme 2.27**. The structure of **35** was confirmed by X-ray crystallography.



29a **35**, 53%

Scheme 2.27

For the next experiment, we used iodine as the electrophile. However, during the reaction, hydrogen iodide was generated, causing the reaction to be extremely messy. In order to scavenge the acid, 3 Å molecular sieves were added to the reaction mixture. By heating up the reaction to 40 ^{o}C in DCE for 2.5 hours, we obtained the diene **36** as a single isomer in 65% yield. (**Scheme 2.28**).



29a

36, 65%

Scheme 2.28

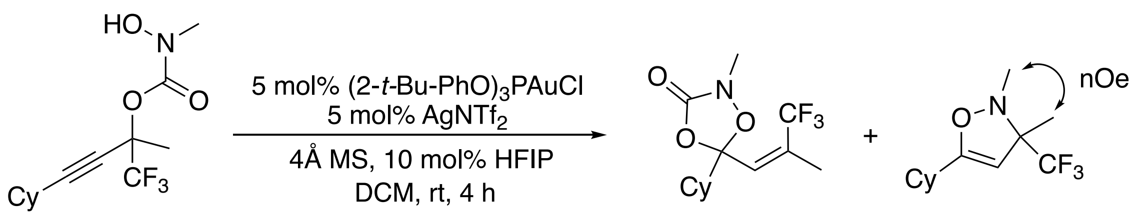
We successfully synthesized two trifluoromethyl fully substituted dienes with defined geometry at both double bonds. Both of these compounds can undergo further transformations such as cross coupling reactions.

3. Conclusion

We have developed a stereoselective synthesis of trisubstituted (*Z*)-trifluoromethyl alkenes in yields ranging from 60% to 98% with up to 93/7 *Z*/*E* selectivity. This reaction is valuable for the stereoselective construction of trifluoromethyl alkenes of the otherwise difficult to access (*Z*)-isomers.

By exposing the substrate **18a** to cationic Au(I) catalysis, we initially obtained two products: 4-isoxazoline **20a** and alkene **19a**. We hypothesized that the 4-isoxazoline was the product of decarboxylation of **19a** (**Scheme 3.1**).

.

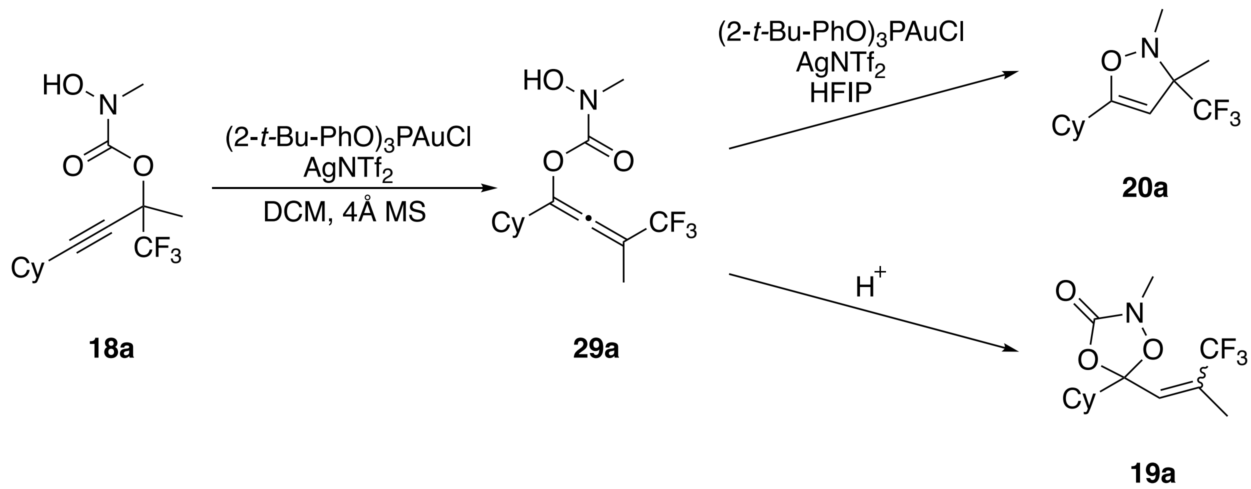


18a **19a** **20a**

1 : 5

Scheme 3.1

However, control experiments proved that the alkenes were not the precursors of the 4-isoxazolines, and that the two compounds are formed from a common intermediate through different pathways. The trifluoromethyl allene **29a** (**Scheme 3.2**) proved to be the common intermediate of both products. The formation of 4-isoxazolines is catalyzed by Au(I) while the alkenes are the products of the electrophilic addition of proton to the allene.

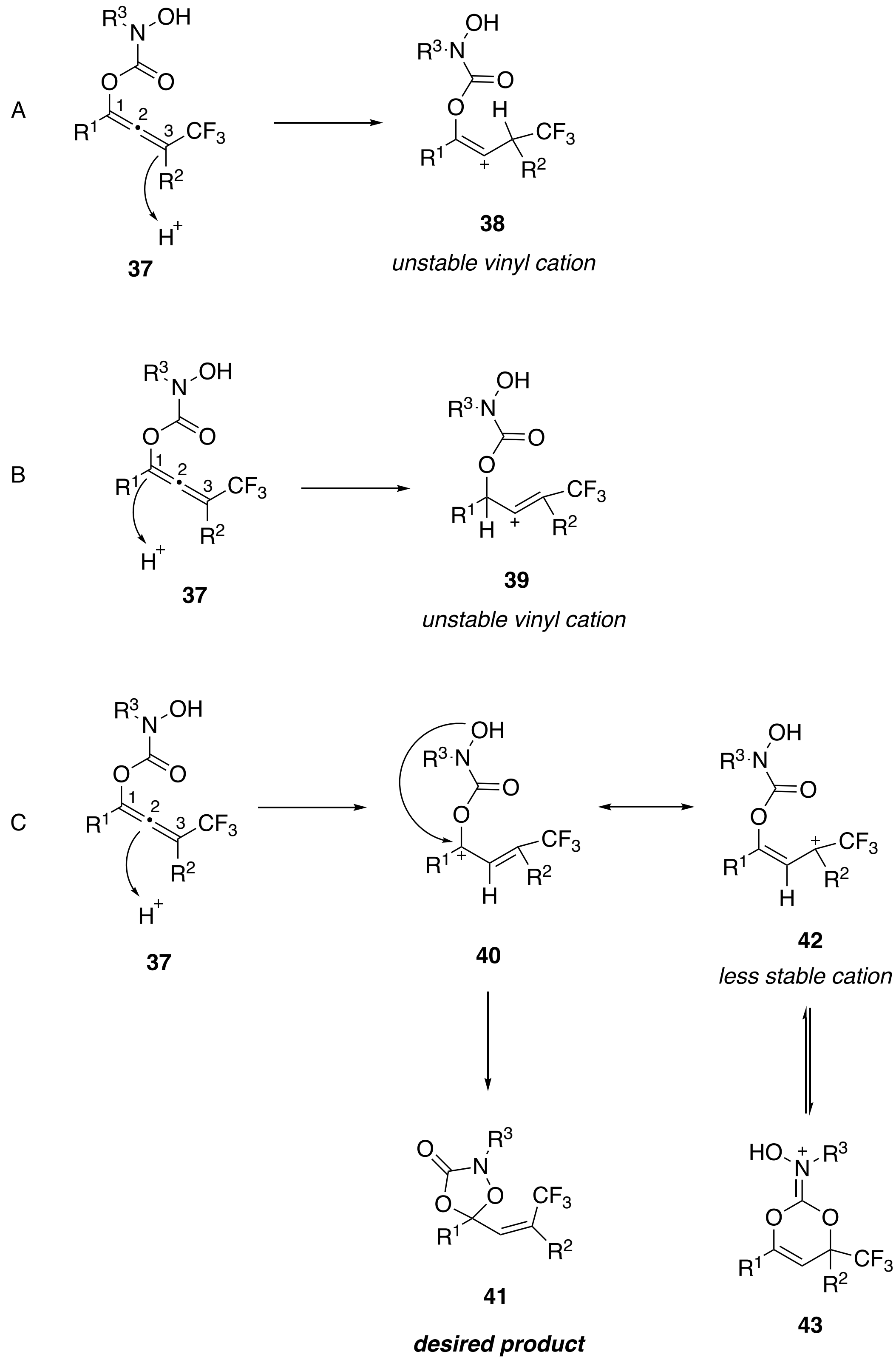


Scheme 3.2

The reaction conditions were subsequently optimized and the substrate scope investigated. We have isolated 16 fluorine containing allenes in good yields. By reacting the allenes with TFA we obtained one trisubstituted difluoromethyl alkene, 11 trisubstituted trifluoromethyl alkenes, two trisubstituted pentafluoroethyl alkenes and 2 trisubstituted heptafluoro-1-propyl alkenes. Most of the alkenes were formed in high yields with good to excellent *Z*/*E* selectivity (78/22 to 93/7). We also demonstrated the reduction of the ketal to form an allylic alcohol. Finally we synthesized two fully substituted trifluoromethyl dienes by exposing the allene to electrophiles other than TFA .

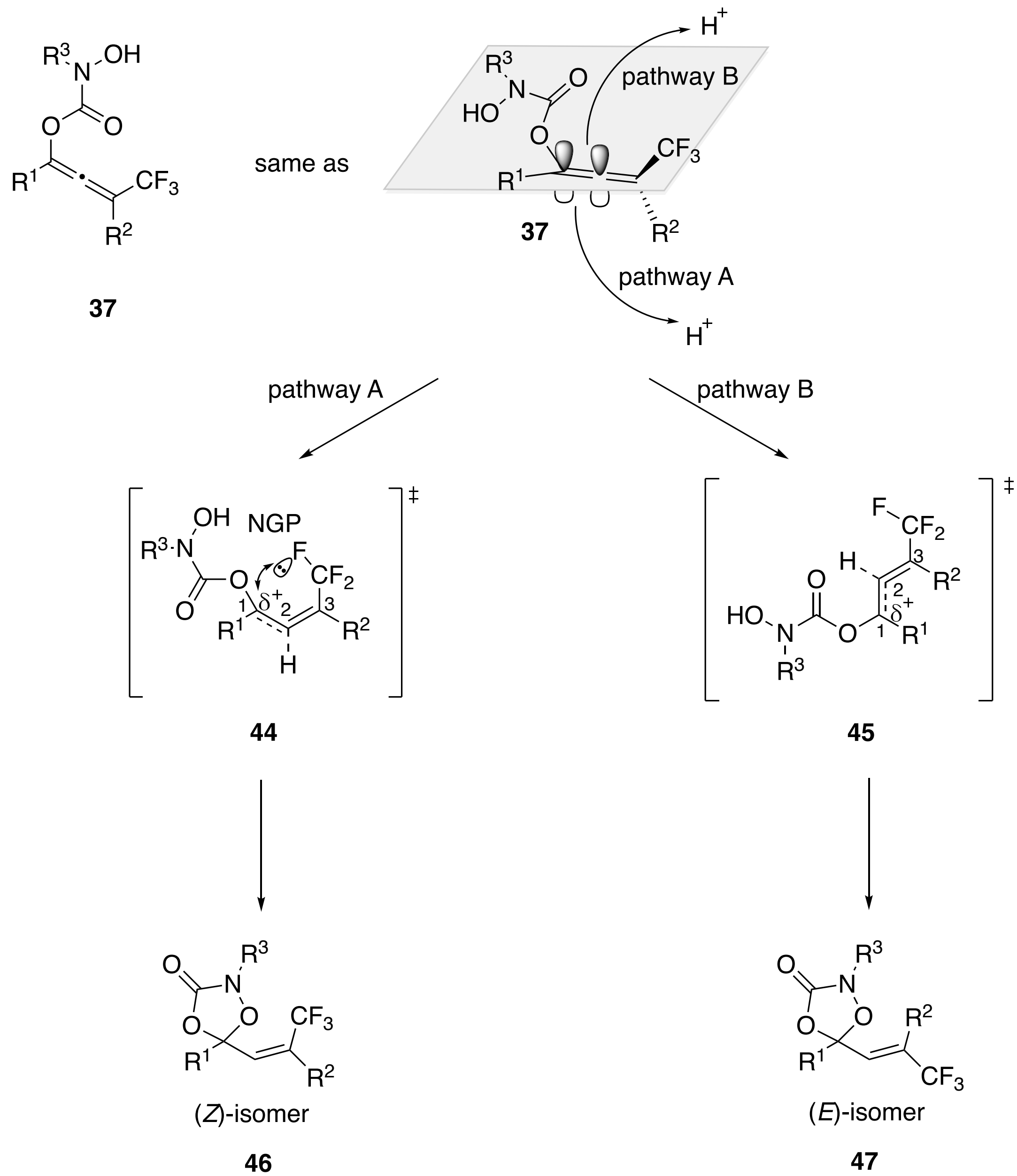
We have also described a one-pot synthesis of fluorine containing 4-isoxazolines which are useful building blocks, as mentioned in the introduction chapter, under mild conditions in 69-92% yield. We demonstrated that this method is not limited to 4-isoxazolines bearing a trifluoromethyl group by preparing 2,3-dimethyl-3-(perfluoropropyl)-5-phenyl-2,3-dihydroisoxazole (**20k**, **Scheme 2.26**) in 77% isolated yield.

In order to rationalize the high *Z* selectivity of the alkenes, one postulated mechanism will be discussed in what follows. First, the regioselectivity of the electrophilic addition of the proton to the allene will be discussed. If one of the terminal carbon atoms from the allene (C2 or C3) is protonated, an unstable vinyl cation **38** or **39** would be generated which makes the terminal attack unlikely (**Scheme 3.3** A and B). The central carbon atom C2, on the other hand, is sp-hybridized, and therefore more reactive. Protonation at C2 leads to an allylic cation which is much more stable than a vinyl cation (hydride ion affinity values are: 256 kcal/mol and 287 kcal/mol respectively) (**Scheme 3.3** C). The allylic cation from intermediate **40** is stabilized by oxygen at C1 and subsequently undergoes further cyclization leading to the desired product **41**. Of the two resonance forms of the allylic cation, **40** and **42**, the latter is destabilized by the electron-withdrawing trifluoromethyl group. This leads to the prediction that **42** represents the minor resonance structure. If **42** is intercepted by the carbonyl oxygen atom, **43** can form reversibly. However, proton loss from **43** does not lead to a stable product.


A
37
38
unstable vinyl cation
B
37
39
unstable vinyl cation
C
37
40
42
less stable cation
41
desired product
43

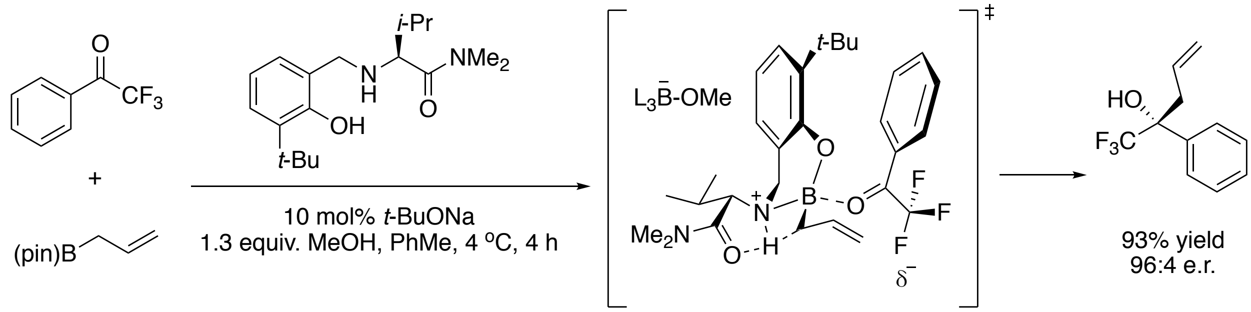
Scheme 3.3

The stereoselectivity will be discussed in what follows. The proton can approach C2 of the allene either according to pathway A or according to pathway B (**Scheme 3.4**) leading in both cases to the development of a partial positive charge on C1 in each of the two transition states **44** and **45**, respectively. We postulate that pathway A is favored over pathway B because of the neighboring group participation (NGP) of a non-bonding electron pair from a fluorine atom as indicated. Because of the greater distance between the fluorine atom and the positively charged C1 in transition state **45** no such NGP is possible thereby raising the energy of **45** relative to **44**. This suggests that pathway A leads to (*Z*)-**46** through favored transition state **44**.



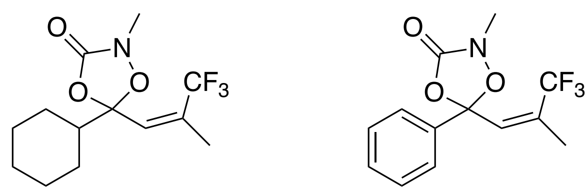
Scheme 3.4

Similar observations have been made several times by others in the past.[32] For example, in 2016, Hoveyda reported a catalytic enantioselective addition of an allyl boronate to trifluoromethyl ketones (**Scheme 3.5**).[32d] The stereochemistry was shown to be controlled by the electrostatic attraction of a non-pair electrons on fluorine to a positively charged ammonium ion as shown in **Scheme 3.5**. This interaction leads to high enantioselectivity (96:4 e.r.).



Scheme 3.5

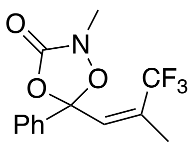
The postulated mechanism also rationalizes some of the trends in selectivity for the *Z* isomer that were observed, for example in alkenes **19a** and **19e** (**Figure 3.1**). In **19a**, the compound bearing a cyclohexyl group at C1, the ratio of isomers was 92/8 in favor of *Z*, whereas in **19e** which has a C1 phenyl group the *Z* selectivity eroded to 83/17. Since the phenyl group can stabilize the partial positive charge on C1 in the transition state, the neighboring group effect of the fluorine atom is attenuated compared to the cyclohexyl case, resulting in diminished selectivity for the *Z* isomer in **19e**.



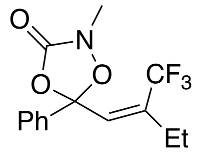
19a, *Z*/*E* = 92/8 **19e**, *Z*/*E* = 83/17

Figure 3.1

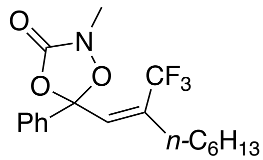
The insensitivity of the isomeric ratio of products to the size of the alkyl group at C3, as indicated by the examples shown in **Figure 3.2**, can also be rationalized according to the postulated mechanism. Because the proton is small, it does not interact strongly with the alkyl group at C3 regardless of the size. As a consequence, the *Z*/*E* ratio depends most strongly on the neighboring group effect of the fluorine atom.



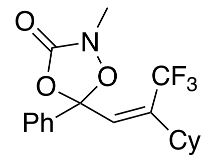
19e, *Z/E* = 83/17



19f, *Z/E* = 81/19



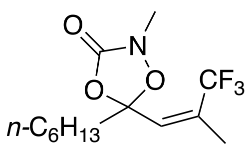
19h, *Z/E* = 86/14



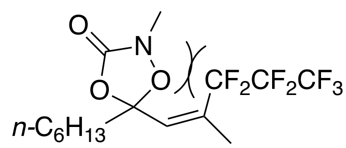
19i, *Z/E* = 84/16

Figure 3.2

While the size of the alkyl group at C3 is of little consequence to the *Z*/*E* ratio of the alkene, the same is not true for the size of the C3 perfluoroalkyl group. As indicated in **Figure 3.3**, the *Z*/*E* ratio for trifluoromethyl alkene **19l** was 93/7 whereas for heptafluoro-*n*-propyl alkene **19o** the ratio of geometric isomers was 79/21. This discrepancy can be explained by noting the larger size of the heptafluoro-*n*-propyl relative to trifluoromethyl, and its larger unfavorable van der Waals interaction with the large tertiary group as indicated in **Figure 3.3**.



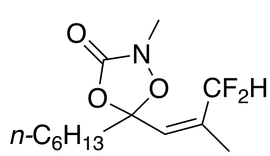
19l, *Z/E* = 93/7



19o, *Z/E* = 79/21

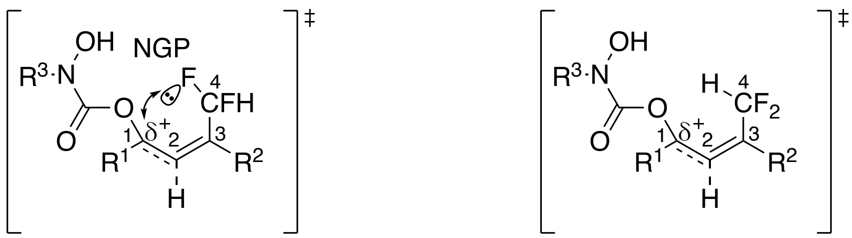
Figure 3.3

We observed a rather poor *Z*/*E* ratio (78/22) in the case of difluoromethyl alkene **19q** (**Figure 3.4**). This may be the result of a statistical effect, which populates the transition state with a fraction of the conformational isomer about C3-C4 in which the hydrogen atom of the CF_2H group, rather than one of the two fluorine atoms, is aligned with C1 (**Y** in **Figure 3.4**).



19q, *Z/E* = 78/22

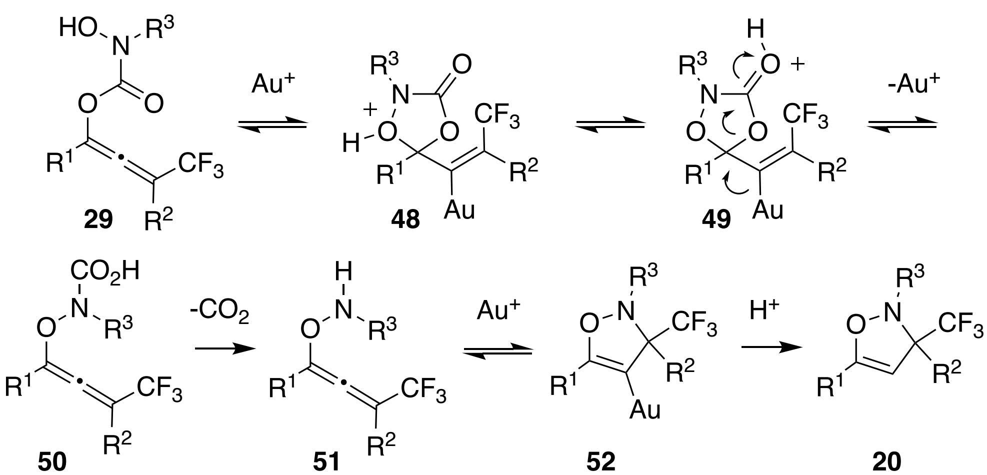
Figure 3.4



X **Y**

Scheme 3.5

Our postulated mechanism that rationalizes the formation of the isoxazolines is summarized in **Scheme 3.6**. Allenes **29** that are formed from the Au(I)-catalyzed isomerization of propargyl carbamates **18** are likely in equilibrium with **48**. In the absence of acid in an aprotic medium this equilibrium is unproductive, however, in the presence of weak acids such as water or HFIP, proton transfers can take place leading to **49** that undergoes rearrangement to carbamic acid **50** with loss of Au(I). Irreversible loss of CO_2 from **50** leads to allenyl ether **51** that undergoes subsequent Au(I)-catalyzed cyclization to **51** with loss of a proton. Protiodeauration converts **51** to isoxazoline **20** thereby completing the catalytic cycle. The isoxazolines are not detected in the presence of strong acids because the conversion of carbamates **18** to alkenes **19** takes place much more rapidly. This mechanism also makes it clear why alkenes **19** cannot be converted to isoxazolines **20**.



Scheme 3.6

In summary, we initially investigated the Au(I) catalyzed (*Z*)-trifluoromethyl alkene synthesis using propargyl acetate. The reaction provided good *Z*/*E* selectivity (up to 6/1). Due to the isomerization of the α,β-unsaturated ketone, the *Z*/*E* ratio drops over time.

To circumvent the isomerization of the α,β-unsaturated ketone, we designed a new substrate by installing a *N*-hydroxycarbamate group on the propargylic alcohol. By doing this, a ketal (**11** in **Scheme 2.8**) is formed instead of the ketone. With the new substrate in hand, we investigated the catalysis conditions. Initially, we obtained the ketal **19a** and the 4-isoxazoline **20a** as products (**Scheme 2.11**) and we postulated that the 4-isoxazoline **20a** was the product of the decarboxylation of the ketal **19a**. Control experiments were conducted that proved this hypothesis to be incorrect. Subsequently, allene **29a** was isolated (**Scheme 2.16**) that turned out to be the common intermediate for both ketal **19a** and 4-isoxazoline **20a**. The formation of the 4-isoxazoline **20a** is catalyzed by Au(I) while the ketal **19a** was the product of the electrophilic addition of proton to allene (**Scheme 2.19**).

Next, the substrate scope was investigated. We are able to obtain 16 fluorine containing alkenes with a Z/E ratio up to 93/7 (**Scheme 2.24**). During the course of this study, 8 fluorine containing 4-isoxazolines one non-fluorine 4-isoxazoline were synthesized in good yield (69-92%) (**Scheme 2.26**).

We also reduced the ketal to an allylic alcohol **34** (**Scheme 2.25**) and synthesized two fully substituted trifluoromethyl dienes **35** and **36** as single geometry isomers (**Scheme 2.27** and **Scheme 2.28**).

Finally, we postulated a mechanism in order to rationalize the high *Z* selectivity. The neighboring group participation (NGP) of a non-bonding pair of electrons on one of the fluorine atom could stabilize the partial positive charge that develops on C1 in the transition state of the protonation of the allene (**Scheme 3.4**). If this were to take place, it would favor the formation of the *Z* alkene.

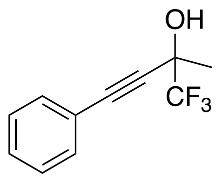
This mechanistic model was used to explain a trend that was observed: the group at C1 is alkyl, the *Z*/*E* ratio is larger than when it is phenyl (**Figure 3.1**). This is what one would predict, since the presence of the phenyl group delocalizes the positive charge on C1, there by attenuating the NGP. The size of the non-fluorinated group at C3 has a minimal effect on the *Z*/*E* ratio (**Figure 3.2**), whereas the size of the fluorinated groups does (**Figure 3.3** and **3.4**) Our results indicate that this method works best for trifluoromethyl.

4. Experimental

4.1 General Experimental

All moisture sensitive reactions were performed under argon atmosphere in oven-dried glassware. Tetrahydrofuran (THF), dimethylformamide (DMF), dichloromethane (DCM) and toluene (PhMe) were dried with a Glass Contour solvent purification system. Acetonitrile (MeCN) was distilled from P_2O_5 followed by CaH_2, and stored over 4 Å molecular sieves. 1,2-dichloroethane (DCE) was distilled and stored over 4 Å molecular sieves. ^{1}H NMR and ^{13}C NMR spectra were measured on Varian Mercury-300 (300 MHz/75MHz) or Varian INOVA-500 (500 MHz/125 MHz) spectrometers at ambient temperature. Chemical shifts are reported in parts per million (ppm or δ) and are referenced to the solvent (δ 7.26 for $CHCl_3$; δ 77.0 for $CDCl_3$). ^{19}F NMR were measured on a Varian Mercury-300 (282 MHz) and reported in ppm relative to TFA (–76.5 ppm). Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), sept (septet) or m (multiplet). Coupling constants (*J*) are reported in Hertz (Hz). Thin layer chromatography (TLC) was performed on SiliCycle glass plates, 250 µm, particle size 5–17 µm, pore size 60 Å. Flash column chromatography was performed on silica-gel (40–63µm, Sorbent Technologies). Infrared (IR) spectra were recorded on a Perkin Elmer 1600 FT-IR spectrophotometer. High-resolution mass spectra (HRMS) were obtained with an Agilent 1100 Agilent 6410 Triple Quad LC/MS. Melting points (m.p.) were recorded on a DigiMelt MPA160 instrument.

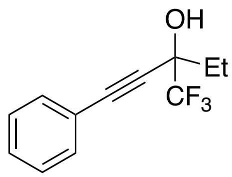
4.2 Synthesis of Tertiary Propargyl Alcohols



1,1,1-trifluoro-2-methyl-4-phenylbut-3-yn-2-ol (17e)

Typical procedure for the synthesis of **17e**, **17f**, **17k**, **17l**, **17o**, **17q**: To a solution of phenyl acetylene (1.3 mL, 12.0 mmol) in THF (20 mL) was added *n*-BuLi (2.5 M in hexanes, 4.8 mL, 12.0 mmol) at −78 °C. After stirring for 10 min at this temperature, 1,1,1-trifluoroacetone (1.0 mL, 12.0 mmol) was added at −78 °C. After stirring for 1 h at −78 °C, the reaction mixture was then quenched by the addition of NH_4Cl (sat. aq.) at −78 °C and allowed to warm to room temperature. The product was extracted with Et_2O (×3) and the combined organic extracts were washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo* and the crude oil was purified by flash column chromatography (hexanes/EtOAc = 10/1) to afford alcohol **17e** (1.86 g, 87 %) as a colorless oil.

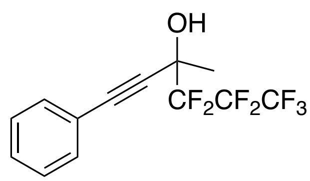
R_f 0.3 (hexanes/EtOAc = 10/1);
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.56 – 7.48 (m, 2H), 7.46 – 7.31 (m, 3H), 3.48 (brs, 1H), 1.80 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 132.0, 129.3, 128.43, 124.2 (q, J_{C-F} = 284.4 Hz), 121.2, 86.2, 84.7, 69.1 (q, J_{C-F} = 32.9 Hz), 23.1. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -82.61.



1-phenyl-3-(trifluoromethyl)pent-1-yn-3-ol (17f)

Colorless oil; Yield (89%); R_f 0.32 (hexanes/EtOAc = 10/1);

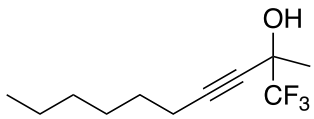
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.62 – 7.50 (m, 2H), 7.48 – 7.32 (m, 3H), 3.54 (s, 1H), 2.20 – 1.84 (m, 2H), 1.32 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 132.0, 129.3, 128.4, 124.4 (q, J_{C-F} = 284.9 Hz), 121.3, 87.5, 83.4 (q, J_{C-F} = 1.3 Hz), 72.9 (q, J_{C-F} = 31.3 Hz), 28.4, 7.7. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -81.20.



4,4,5,5,6,6,6-heptafluoro-3-methyl-1-phenylhex-1-yn-3-ol (17k)

Colorless oil; Yield 79%; R_f 0.29 (hexanes/EtOAc = 10/1);

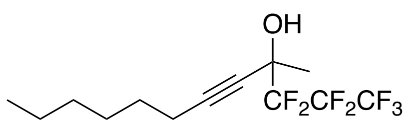
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 – 7.42 (m, 2H), 7.36 (m, 3H), 2.89 (s, 1H), 1.80 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 131.8, 129.3, 128.4, 121.1, 119.8 – 106.6 (m, -$\underline{C}F_2\underline{C}F_2\underline{C}F_3$), 87.3, 84.5, 69.9 (t, J_{C-F} = 26.9 Hz), 23.7. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -81.02 (t, *J* = 10.6 Hz, 3F), -117.69 – -122.41 (m, 2F), -122.88 (m, 2F).



1,1,1-trifluoro-2-methyldec-3-yn-2-ol (17l)

Colorless oil; Yield 89% R_f 0.3 (hexanes/EtOAc = 10/1);

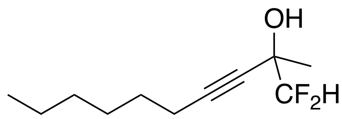
^{1}H NMR (300 MHz, Chloroform-*d*) δ 2.97 (s, 1H), 2.22 (t, *J* = 7.0 Hz, 2H), 1.59 (s, 3H), 1.58 – 1.46 (m, 2H), 1.45 – 1.23 (m, 6H), 0.96 – 0.83 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 124.1 (q, J_{C-F} = 284.1 Hz), 87.5, 76.4 (q, J_{C-F} = 1.2 Hz), 68.5 (q, J_{C-F} = 32.6 Hz), 31.2, 28.3, 28.0, 23.1, 22.4, 18.4, 13.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -83.32.



1,1,1,2,2,3,3-heptafluoro-4-methyldodec-5-yn-4-ol (**17o**)

Colorless oil; Yield 79%; R_f 0.3 (hexanes/EtOAc = 10/1);

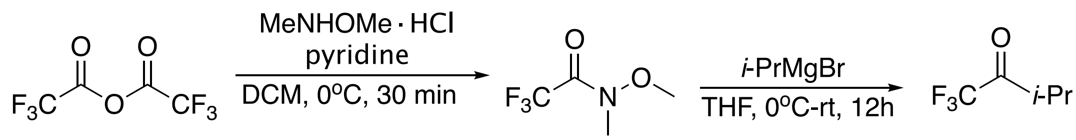
^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.11 (s, 1H), 2.22 (t, *J* = 7.0 Hz, 2H), 1.65 (s, 3H), 1.59 – 1.46 (m, 2H), 1.45 – 1.22 (m, 6H), 0.9 (t, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 124.5 – 103.2 (m, -$\underline{C}F_2\underline{C}F_2\underline{C}F_3$), 88.6, 76.3 (t, J_{C-F} = 3.2 Hz), 69.4 (t, J_{C-F} = 26.7 Hz), 31.1, 28.3, 27.9, 23.8 – 23.7 (m), 22.4, 18.3, 13.7. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -81.54 (t, *J* = 10.6 Hz, 3F), -118.30 – -122.53 (m, 2F), -122.99 – -123.24 (m, 2F).



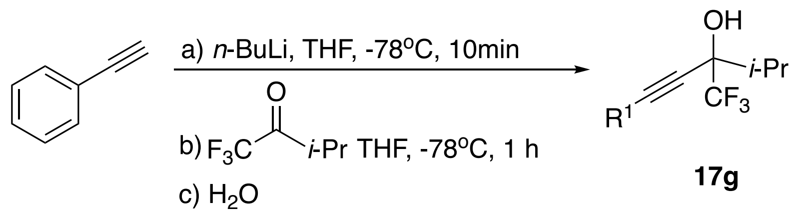
1,1-difluoro-2-methyldec-3-yn-2-ol (**17q**)

Colorless oil; Yield 92%; R_f 0.4 (hexanes/EtOAc = 15/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.55 (t, *J* = 56.6 Hz, 1H), 2.84 (brs, 1H), 2.20 (t, *J* = 7.0 Hz, 2H), 1.60 – 1.44 (m, 5H), 1.44 – 1.17 (m, 6H), 0.88 (t, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 115.3 (t, J_{C-F} = 249.6 Hz), 87.3, 77.6 (t, J_{C-F} = 2.8 Hz), 68.2 (t, J_{C-F} = 23.8 Hz), 31.2, 28.4, 28.2, 22.8, 22.5, 18.5, 13.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -129.50 – -129.99 (m, 2F).



32a

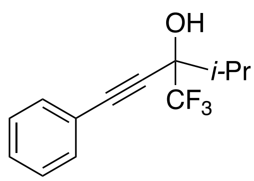


17g

Typical procedure for the synthesis of **17g**, **17h**, **17i**, **17n**, **17p**: Following a published procedure,[31] to a solution of MeNHOMe·HCl (2.15 g, 22 mmol) in DCM (30 mL) was added TFAA (2.9 mL, 20 mmol) and pyridine (3.54 mL, 44 mmol) sequentially at 0 °C. After stirring for 30 min at 0 °C, the reaction was quenched with ice water (50 mL) and washed with 1 M HCl (100 mL). The product was extracted with DCM (x3) and the combined organic extracts were dried over Na_2SO_4. The crude Weinreb amide was obtained after filtration and removal of the solvent *in vacuo*, the crude Weinreb amide was used in the next step without further purification.

To a solution of crude Weinreb amide in THF (20 mL) was added *iso*-propylmagnesium bromide (2.0 M in THF, 11 mL, 22 mmol) at 0 °C. the mixture was stirred at 0 °C for 30 min before allowed to warm to room temperature overnight. The reaction mixture was quenched with NH_4Cl (sat. aq.) and the product was extracted with Et_2O (x3). The organic layers were combined and washed with brine and dried over Na_2SO_4. After filtration, the crude ketone solution was further dried under Ar over activated 4 Å molecular sieves overnight. The ketone was used without further purification.

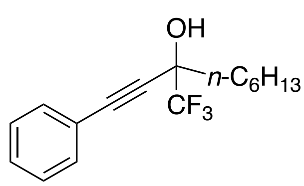
To a solution of phenyl acetylene (2.2 mL, 20 mmol) in THF (40 mL) was added *n*-BuLi (2.5 M in hexanes, 8.0 mL, 20 mmol) at −78 °C. After stirring for 10 min, the ketone solution was added at −78 °C. After stirring for 1 h at −78 °C, the reaction was then quenched by the addition of NH_4Cl (sat. aq.) solution at −78 °C and allowed to warm to room temperature. The product was extracted with Et_2O (×3) and the combined organic extracts were washed with brine, and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (hexanes/EtOAc = 10/1) to afforded alcohol **17g** (3.13 g, 63 % over 3 steps) as a colorless oil.



4-methyl-1-phenyl-3-(trifluoromethyl)pent-1-yn-3-ol(17g)

R_f 0.32 (hexanes/EtOAc = 10/1);

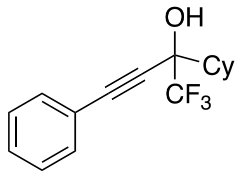
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.61 – 7.50 (m, 2H), 7.47 – 7.32 (m, 3H), 3.07 (brs, 1H), 2.34 (sept, *J* = 6.7 Hz, 1H), 1.27 (dd, *J* = 6.7, 0.9 Hz, 3H), 1.22 (dq, *J* = 6.8, 1.5 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 132.0, 129.3, 128.4, 124.6 (q, J_{C-F} = 286.2 Hz), 121.3, 87.9, 82.7 (q, J_{C-F} = 1.4 Hz), 75.8 (q, J_{C-F} = 29.9 Hz), 33.7, 17.8 (q, J_{C-F} = 2.2 Hz), 17.4 (q, J_{C-F} = 1.4 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -77.02.



1-phenyl-3-(trifluoromethyl)non-1-yn-3-ol (17h)

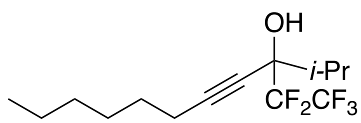
Colorless oil; Yield 45% (over 3 steps); R_f 0.34 (hexanes/EtOAc = 10/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.59 – 7.45 (m, 2H), 7.44 – 7.30 (m, 3H), 2.75 (s, 1H), 2.03 – 1.86 (m, 2H), 1.81 – 1.62 (m, 2H), 1.53 – 1.23 (m, 6H), 1.01 – 0.86 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 132.0, 129.3, 128.4, 124.2 (q, J_{C-F} = 285.0 Hz), 121.2, 87.3, 83.7, 72.3 (q, J_{C-F} = 31.2 Hz), 34.8, 31.7, 29.2, 23.3, 22.6, 14.1. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -81.51.



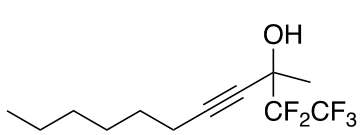
2-cyclohexyl-1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (**17i**)

Colorless oil; Yield 51% (over 3 steps); R_f 0.32 (hexanes/EtOAc = 10/1);
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.52 (m, 2H), 7.45 – 7.33 (m, 3H), 2.80 (brs, 1H), 2.24 – 2.11 (m, 1H), 2.10 – 1.68 (m, 5H), 1.51 – 1.09 (m, 5H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 132.0, 129.3, 128.4, 124.4 (q, $J_{C\text{-}F}$ = 286.5 Hz), 121.3, 87.8, 83.3 (q, $J_{C\text{-}F}$ = 1.5 Hz), 75.2 (q, $J_{C\text{-}F}$ = 30.0 Hz), 43.2, 27.5 (q, $J_{C\text{-}F}$ = 2.0 Hz), 26.8 (q, $J_{C\text{-}F}$ = 1.2 Hz), 26.0, 25.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -76.56.



1,1,1,2,2-pentafluoro-3-isopropylundec-4-yn-3-ol (**17n**)

Colorless oil; Yield 62% (over 3 steps); R_f 0.4 (hexanes/EtOAc = 10/1);
^{1}H NMR (300 MHz, Chloroform-*d*) δ 2.43 (s, 1H), 2.34 – 2.15 (m, 3H), 1.63 – 1.48 (m, 2H), 1.48 – 1.24 (m, 6H), 1.16 – 1.03 (m, 6H), 0.97 – 0.81 (m, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 125.0 – 109.1 (m, -$\underline{C}F_2\underline{C}F_3$), 90.1, 75.4 (t, $J_{C\text{-}F}$ = 24.6 Hz), 73.7, 33.7, 31.2z, 28.3, 28.1, 22.4, 18.5, 17.9 (d, $J_{C\text{-}F}$ = 3.4 Hz), 17.4, 14.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -78.36 (s, 3F), -111.40 – -128.15 (m, 2F).

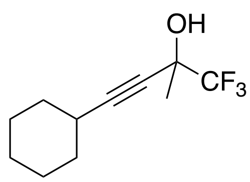


1**,1,1,2,2-pentafluoro-3-methylundec-4-yn-3-ol** (**17p**)

Colorless oil; Yield 43% (over 3 steps); R_f 0.4 (hexanes/EtOAc = 10/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 2.65 (brs, 1H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.66 (s, 3H), 1.61 – 1.46 (m, 2H), 1.45 – 1.20 (m, 6H), 0.98 – 0.83 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 122.4 – 107.8 (m, -$\underline{C}F_2\underline{C}F_3$), 88.7, 76.3, 68.7 (t, J_{C-F} = 26.3 Hz), 31.2, 28.3, 28.0, 23.8 (t, J_{C-F} = 2.0 Hz), 22.5, 18.5, 13.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -78.28 (t, *J* = 4.0 Hz, 3F), -122.12 – -125.90 (m, 2F).

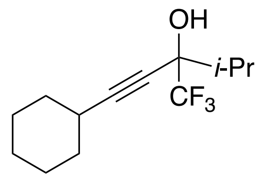
Typical procedure for the synthesis of **17a** and **17b**: (2,2-dibromovinyl)cyclohexanes was prepared according to the published method.[33] To a solution of (2,2-dibromovinyl)cyclohexanes (839 mg, 3.1 mmol) in THF (20 mL) was added *n*-BuLi (2.5 M in hexanes, 2.5 mL, 6.3 mmol) at −78 ^{o}C. After stirring for 1 h at this temperature, 1,1,1-trifluoroacetone (334 µL, 3.1 mmol) was added at -78 ^{o}C. After stirring for 1 h at −78 ^{o}C, the reaction was then quenched by the addition of NH_4Cl (sat. aq.) at −78 ^{o}C. The product was extracted with Et_2O (×3) and the combined extracts were washed by brine, and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo* and the crude oil was purified by flash column chromatography (hexanes/EtOAc = 10/1) to afford alcohol **17a** (564 mg, 82%) as a colorless oil.



4-cyclohexyl-1,1,1-trifluoro-2-methylbut-3-yn-2-ol (**17a**)

R_f 0.33 (hexanes/EtOAc = 10/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 2.62 (brs, 1H), 2.43 (td, *J* = 8.7, 4.5 Hz, 1H), 1.87 – 1.65 (m, 4H), 1.61 (q, *J* = 1.0 Hz, 3H), 1.57 – 1.21 (m, 6H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ = 124.2 (q, $J_{C\text{-}F}$ = 284.2 Hz), 91.4, 76.5, 68.6 (q, $J_{C\text{-}F}$ = 32.7 Hz), 32.0, 28.7, 25.7, 24.5, 23.3. ^{19}F NMR (282 MHz, Chloroform-*d*) δ = -83.28.



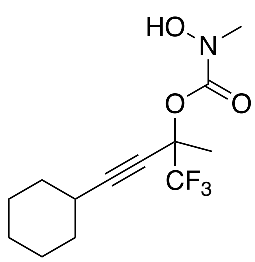
1-cyclohexyl-4-methyl-3-(trifluoromethyl)pent-1-yn-3-ol (17b)

Colorless oil; Yield 31% (over 3 steps); R_f 0.3 (hexanes/EtOAc = 10/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 2.62 (brs, 1H), 2.49 (tt, *J* = 8.4, 3.7 Hz, 1H), 2.15 (sept, *J* = 6.7 Hz, 1H), 1.87 – 1.64 (m, 4H), 1.51 (m, 2H), 1.44 – 1.24 (m, 4H), 1.11 (dd, *J* = 6.7, 0.8 Hz, 3H), 1.07 (dq, *J* = 6.7, 1.5 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 124.5 (q, $J_{C\text{-}F}$ = 285.9 Hz), 93.0, 75.2 (q, $J_{C\text{-}F}$ = 29.8 Hz), 74.2 (q, $J_{C\text{-}F}$ = 1.6 Hz), 33.3, 32.1, 28.7, 25.8, 24.4, 17.7 (q, $J_{C\text{-}F}$ = 2.2 Hz), 17.4 (q, $J_{C\text{-}F}$ = 1.4 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -77.61.

4.3 Synthesis of *N*-hydroxycarbamates

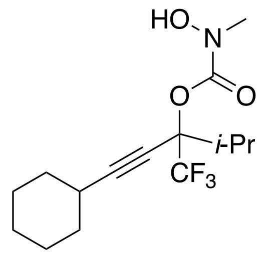
Typical procedure for the synthesis of **18a-18r**: Following a modified procedure from literature,[34] to a solution of triphosgene (565 mg, 1.9 mmol) and pyridine (0.5 mL, 6.0 mmol) in DCM (40 mL) was added propargylic alcohol **17a** (1.20 g, 5.45 mmol) at 0 ^{o}C. After stirring at 0 ^{o}C for 2.5 h, the reaction mixture was transferred via cannula to a separate flask containing MeNHOH·HCl (452 mg, 5.5 mmol) and *i*-Pr_2NEt (1.7 mL, 11.0 mmol) at 0 ^{o}C. The reaction mixture was allowed to stir at 0 ^{o}C for 30 min before being quenched by the addition of NH_4Cl (sat. aq.) at 0 ^{o}C. The product was extracted with DCM (×3) and the combined extracts were washed by brine, and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo* and the crude oil was purified by flash column chromatography (hexanes/EtOAc = 5/1) to afford carbamate **18a** (985 mg, 60%) as a colorless oil.



4-cyclohexyl-1,1,1-trifluoro-2-methylbut-3-yn-2-yl hydroxy(methyl)carbamate (18a)

R_f 0.3 (hexanes/EtOAc = 5/1);

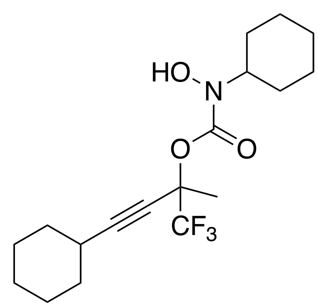
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.41 (brs, 1H), 3.22 (s, 3H), 2.54 – 2.35 (m, 1H), 1.87 (s, 3H), 1.82 – 1.59 (m, 4H), 1.55 – 1.20 (m, 6H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 154.6, 122.9 (q, $J_{C\text{-}F}$ = 283.0 Hz), 93.4, 75.1 (q, $J_{C\text{-}F}$ = 32.6 Hz), 72.8, 38.0, 31.8, 28.7, 25.7, 24.4, 21.3. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -82.05. IR (neat, cm^{-1}) 3287, 2935, 2857, 2253, 1731, 1450, 1379, 1308, 1240, 1183, 1107, 749, 688; HRMS (ESI^{+}) *m/z* calcd for $C_{13}H_{19}F_3NO_3$ [M+H]$^{+}$: 294.1312; found: 294.1312.



1-cyclohexyl-4-methyl-3-(trifluoromethyl)pent-1-yn-3-yl hydroxy(methyl)carbamate (18b)

Colorless oil; yield 56%; R_f 0.35 (hexanes/EtOAc = 5/1);

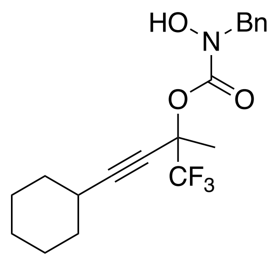
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.26 (brs, 1H), 3.23 (s, 3H), 2.79 – 2.57 (m, 1H), 2.57 – 2.43 (m, 1H), 1.90 – 1.62 (m, 4H), 1.59 – 1.24 (m, 6H), 1.11 (d, *J* = 8.2 Hz, 6H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 154.5, 123.4 (q, J_{C-F} = 286.9 Hz), 95.8, 81.2 (q, J_{C-F} = 30.1 Hz), 71.4, 38.0, 34.3, 31.8, 28.8, 25.8, 24.4, 17.7 (q, J_{C-F} = 1.8 Hz), 17.1 (q, J_{C-F} = 2.2 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -73.34. IR (neat, cm^{-1}) 3257, 2934, 2857, 2244, 1728, 1473, 1450, 1374, 1282, 1195, 1172, 1131, 738, 697; HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{22}F_3NNaO_3$ [M+Na]$^+$: 344.1444; found: 344.1441.



4-cyclohexyl-1,1,1-trifluoro-2-methylbut-3-yn-2-yl cyclohexyl(hydroxy)carbamate (18c)

White foam; yield 56%; R_f 0.34 (hexanes/EtOAc = 7/1)

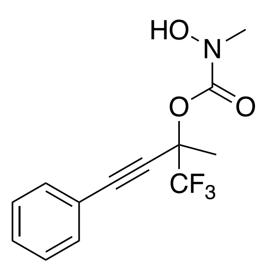
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.28 (brs, 1H), 3.74 (tt, *J* = 11.3, 4.1 Hz, 1H), 2.45 (tt, *J* = 8.4, 3.6 Hz, 1H), 1.89 (s, 3H), 1.86 – 1.57 (m, 10H), 1.56 – 1.20 (m, 10H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 154.0, 123.1 (q, J_{C-F} = 283.0 Hz), 93.2, 74.9 (q, J_{C-F} = 32.5 Hz), 73.1, 58.8, 31.8, 29.2, 28.7, 25.8, 25.5, 25.2, 24.4, 21.4. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -81.98. IR (neat, cm^{-1}) 3380, 2934, 2857, 2251, 1717, 1450, 1378, 1309, 1242, 1179, 1106, 739; HRMS (ESI$^+$) *m/z* calcd for $C_{18}H_{27}F_3NO_3$ [M+H]$^+$: 362.1938; found: 362.1938.



4-cyclohexyl-1,1,1-trifluoro-2-methylbut-3-yn-2-yl benzyl(hydroxy)carbamate (18d)

White solid; yield 69%; R_f 0.3 (hexanes/EtOAc = 7/1); m.p. 77–78 °C;

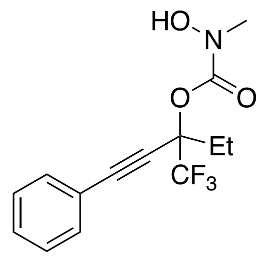
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.92 (brs, 1H), 7.47 – 7.29 (m, 5H), 4.83 – 4.60 (m, 2H), 2.48 (m, 1H), 1.91 (s, 3H), 1.84 – 1.64 (m, 4H), 1.59 – 1.25 (m, 6H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 154.0, 135.8, 128.6, 128.3, 127.9, 123.0 (q, $J_{C\text{-}F}$ = 283.2 Hz), 93.7, 75.4 (q, $J_{C\text{-}F}$ = 32.7 Hz), 72.9, 54.5, 31.8, 28.7, 25.8, 24.4, 21.4. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -81.74. IR (neat, cm^{-1}) 3269, 2933, 2856, 2252, 1719, 1559, 1495, 1378, 1307, 1179, 1105, 802, 729, 701; HRMS (ESI$^+$) *m/z* calcd for $C_{19}H_{22}F_3NNaO_3$ [M+Na]$^+$: 392.1444; found: 392.1437.



1,1,1-trifluoro-2-methyl-4-phenylbut-3-yn-2-yl hydroxy(methyl)carbamate (18e)

Colorless oil; yield 52%; R_f 0.3(hexanes/EtOAc = 5/1);

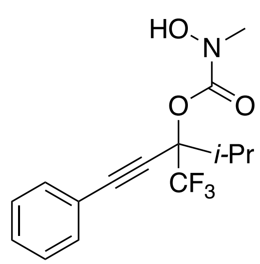
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.53 – 7.47 (m, 2H), 7.40 – 7.30 (m, 3H), 3.18 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 154.6, 132.1, 129.4, 128.3, 123.0 (q, $J_{C\text{-}F}$ = 283.3 Hz), 121.0, 88.0, 81.1, 75.3 (q, $J_{C\text{-}F}$ = 32.8 Hz), 38.1, 21.1. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -81.38. IR (neat, cm^{-1}) 3271, 2951, 2244, 1730, 1491, 1445, 1379, 1276, 1313, 1275, 1197, 1150, 1106, 757, 718, 690; HRMS (ESI$^+$) *m/z* calcd for $C_{13}H_{13}F_3NO_3$ [M+H]$^+$: 288.0842; found: 288.0830.



1-phenyl-3-(trifluoromethyl)pent-1-yn-3-yl hydroxy(methyl)carbamate (**18f**)

Colorless oil; yield 50%; R_f 0.32 (hexanes/EtOAc = 5/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.60 (brs, 1H), 7.58 – 7.46 (m, 2H), 7.41 – 7.30 (m, 3H), 3.18 (s, 3H), 2.51 – 2.27 (m, 2H), 1.16 (td, *J* = 7.6, 1.2 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 154.5, 132.1, 129.4, 128.3, 123.4 (q, J_{C-F} = 286.9 Hz), 121.2, 89.4, 80.4, 78.5 (q, J_{C-F} = 31.3 Hz), 38.1, 28.2, 8.3 (q, J_{C-F} = 1.8 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -77.43. IR (neat, cm^{-1}) 3269, 2948, 2236, 1727, 1491, 1444, 1377, 1251, 1195, 1146, 1119, 757, 690; HRMS (ESI$^+$) *m/z* calcd for $C_{14}H_{15}F_3NO_3$ [M+H]$^+$: 302.0999; found: 302.0999.

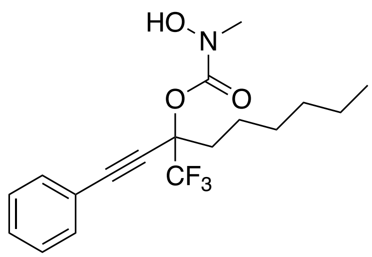


4-methyl-1-phenyl-3-(trifluoromethyl)pent-1-yn-3-yl hydroxy(methyl)carbamate (**18g**)

Colorless oil; yield 57%; R_f 0.34 (hexanes/EtOAc = 7/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.75 (brs, 1H), 7.59 – 7.48 (m, 2H), 7.45 – 7.30 (m, 3H), 3.19 (s, 3H), 2.90 – 2.73 (m, 1H), 1.22 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 154.6, 132.1, 129.4, 128.4, 123.4 (q, J_{C-F} = 286.9 Hz), 121.4, 90.4, 81.3 (q, J_{C-F} = 30.6 Hz), 80.0 (q, J_{C-F} = 1.3 Hz), 38.1, 34.5, 17.7 (q, J_{C-F} = 1.8 Hz), 17.2 (q, J_{C-F} = 2.0 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -

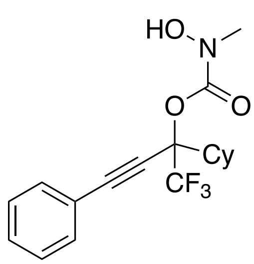
72.85. IR (neat, cm^{-1}) 3260, 2979, 2946, 2237, 1728, 1491, 1444, 1375, 1254, 1197, 1134, 1116, 1049, 757, 691; HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{16}F_3NNaO_3$ [M+Na]$^+$: 338.0974; found: 338.0985.



1-phenyl-3-(trifluoromethyl)non-1-yn-3-yl hydroxy(methyl)carbamate (18h)

White solid; yield 44%; R_f 0.35 (hexanes/EtOAc = 7/1); m.p. 70 – 72 °C;

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.32 (brs, 1H), 7.57 – 7.45 (m, 2H), 7.43 – 7.31 (m, 3H), 3.18 (s, 3H), 2.44 – 2.21 (m, 2H), 1.77 – 1.47 (m, 2H), 1.42 – 1.28 (m, 6H), 0.92 (t, *J* = 2.0 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 154.5, 132.1, 129.3, 128.3, 123.4 (q, $J_{C\text{-}F}$ = 286.9 Hz), 121.2, 89.3, 80.6, 78.2 (q, $J_{C\text{-}F}$ = 31.5 Hz), 38.0, 34.9, 31.5, 29.2, 23.6, 22.6, 14.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -77.54. IR (neat, cm^{-1}) 3269, 2933, 2856, 2252, 1720, 1449, 1378, 1307, 1234, 1180, 1105, 729, 701, 654; HRMS (ESI$^+$) *m/z* calcd for $C_{18}H_{23}F_3NO_3$ [M+H]$^+$: 358.1625; found: 358.1620.

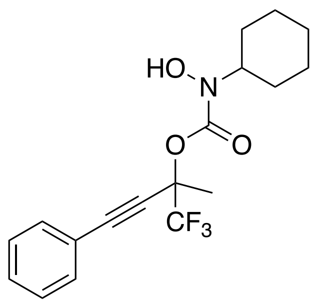


2-cyclohexyl-1,1,1-trifluoro-4-phenylbut-3-yn-2-yl hydroxy(methyl)carbamate (18i)

Colorless oil; yield 49%; R_f 0.35 (hexanes/EtOAc = 7/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.44 (brs, 1H), 7.62 – 7.47 (m, 2H), 7.44 – 7.30 (m, 3H), 3.20 (s, 3H), 2.48 (t, *J* = 11.3 Hz, 1H), 2.21 – 1.64 (m, 5H), 1.33 (s, 5H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 154.6, 132.1, 129.3, 128.3, 123.4 (q, $J_{C\text{-}F}$ = 286.9 Hz), 121.4, 90.3, 81.1 (q, $J_{C\text{-}F}$ = 30.5 Hz), 80.3

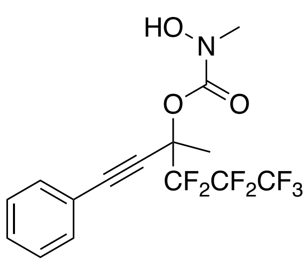
(q, J = 1.2 Hz), 44.2, 38.1, 27.7 (d, J = 1.8 Hz), 27.2 (d, J = 1.8 Hz), 26.5, 26.4, 26.1. ^{19}F NMR (282 MHz, Chloroform-d) δ -72.75. IR (neat, cm^{-1}) 3338, 2934, 2856, 2237, 1727, 1492, 1449, 1375, 1259, 1233, 1182, 1143, 757, 691; HRMS (ESI$^+$) m/z calcd for $C_{18}H_{21}F_3NO_3$ [M+H]$^+$: 356.1468; found: 356.1452.



1,1,1-trifluoro-2-methyl-4-phenylbut-3-yn-2-yl cyclohexyl(hydroxy)carbamate (18j)

Colorless oil; yield 61%; R_f 0.3 (hexanes/EtOAc = 7/1);

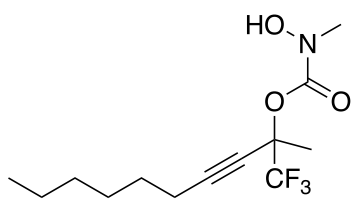
^{1}H NMR (500 MHz, Benzene-d_6) δ 7.44 – 7.31 (m, 2H), 6.96 – 6.75 (m, 3H), 3.85 (tt, J = 11.6, 4.0 Hz, 1H), 1.96 (s, 3H), 1.83 – 1.38 (m, 6H), 1.29 (dt, J = 12.9, 3.4 Hz, 1H), 1.06 – 0.67 (m, 3H). ^{13}C NMR (125 MHz, Benzene-d_6) δ 154.0, 132.0, 129.1, 128.2, 123.6 (q, $J_{C\text{-}F}$ = 283.0 Hz), 121.1, 88.2, 81.7, 75.2 (q, $J_{C\text{-}F}$ = 32.4 Hz), 58.9, 29.2, 25.3, 25.2, 25.0, 20.9. ^{19}F NMR (470 MHz, Benzene-d_6) δ -81.04. IR (neat, cm^{-1}) 3368, 2929, 2856, 2243, 1718, 1450, 1377, 1305, 1199, 1152, 1106, 757, 713, 690, 665; HRMS (ESI$^+$) m/z calcd for $C_{18}H_{21}F_3NO_3$ [M+H]$^+$: 356.1468; found: 356.1461.



4,4,5,5,6,6,6-heptafluoro-3-methyl-1-phenylhex-1-yn-3-yl hydroxy(methyl)carbamate (18k)

Colorless oil; yield 59%; R_f 0.29 (hexanes/EtOAc = 5/1);

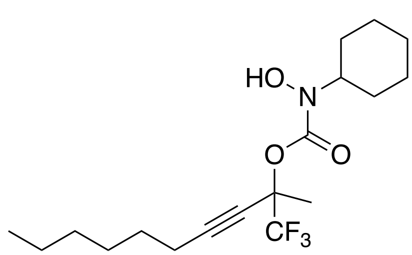
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.21 (brs, 1H), 7.53 – 7.45 (m, 2H), 7.42 – 7.29 (m, 3H), 3.17 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 154.2, 132.0, 129.5, 128.3, 121.1, 120.7 – 105.5 (m, -$\underline{C}F_2\underline{C}F_2\underline{C}F_3$), 89.4, 80.9 (d, *J* = 4.4 Hz), 76.2 (t, $J_{C\text{-}F}$ = 29.2 Hz), 37.8, 21.2. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -81.22 (t, *J* = 10.8 Hz, 3F), -116.16 – -120.78 (m, 2F), -122.36 (t, *J* = 5.0 Hz, 2F). IR (neat, cm^{-1}) 3269, 2953, 2237, 1731, 1491, 1445, 1378, 1344, 1232, 1203, 1126, 757, 732, 690; HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{13}F_7NO_3$ [M+H]$^+$: 388.0778; found: 388.0776.



1,1,1-trifluoro-2-methyldec-3-yn-2-yl hydroxy(methyl)carbamate (**18l**)

Colorless oil; yield 67%; R_f 0.3 (hexanes/EtOAc = 5/1);

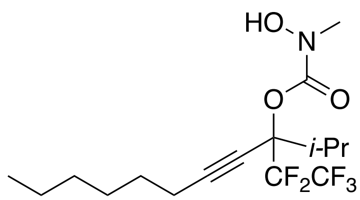
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.46 (brs, 1H), 3.20 (s, 3H), 2.20 (t, *J* = 7.0 Hz, 2H), 1.84 (s, 3H), 1.57 – 1.42 (m, 2H), 1.41 – 1.18 (m, 6H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 154.6, 122.9 (q, $J_{C\text{-}F}$ = 282.9 Hz), 89.6, 75.0 (q, $J_{C\text{-}F}$ = 32.6 Hz), 72.6, 38.0, 31.1, 28.2, 27.8, 22.4, 21.1, 18.4, 13.8. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -82.14. IR (neat, cm^{-1}) 3395, 2933, 2861, 2249, 1728, 1447, 1378, 1308, 1241, 1180, 1105, 716, 680; HRMS (ESI$^+$) *m/z* calcd for $C_{13}H_{21}F_3NO_3$ [M+H]$^+$: 296.1468; found: 296.1469.



1,1,1-trifluoro-2-methyldec-3-yn-2-yl cyclohexyl(hydroxy)carbamate (18m)

White solid; yield 65%; R_f 0.3(hexanes/EtOAc = 6/1); m.p. 85 – 87 °C;

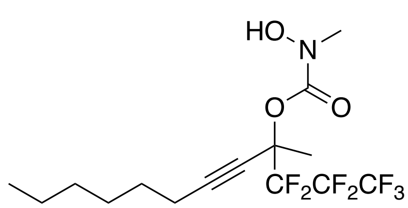
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.64 (brs, 1H), 3.74 (tt, *J* = 11.2, 4.1 Hz, 1H), 2.22 (t, *J* = 7.0 Hz, 2H), 1.88 (d, *J* = 1.1 Hz, 3H), 1.86 – 1.57 (m, 6H), 1.57 – 1.45 (m, 2H), 1.44 – 1.20 (m, 9H), 1.13 (dd, *J* = 14.3, 11.0 Hz, 1H), 0.94 – 0.83 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 154.0, 123.0 (q, J_{C-F} = 283.0 Hz), 89.5, 74.9 (q, J_{C-F} = 32.6 Hz), 72.8, 58.8, 29.2, 29.2, 28.3, 27.9, 25.5, 25.2, 22.5, 21.3, 18.6, 13.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -81.98. IR (neat, cm^{-1}) 3245, 2935, 2859, 2248, 1717, 1453, 1377, 1310, 1241, 1180, 1106, 739, 666; HRMS (ESI$^+$) *m/z* calcd for $C_{18}H_{29}F_3NO_3$ $[M+H]^+$: 364.2094; found: 364.2098.



1,1,1,2,2-pentafluoro-3-isopropylundec-4-yn-3-yl hydroxy(methyl)carbamate (18n)

Colorless oil; yield 58%; R_f 0.32 (hexanes/EtOAc = 7/1);

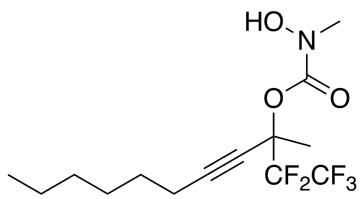
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.11 (brs, 1H), 3.21 (s, 3H), 2.92 (sept, *J* = 6.9 Hz, 1H), 2.27 (t, *J* = 6.9 Hz, 2H), 1.60 – 1.47 (m, 2H), 1.46 – 1.21 (m, 6H), 1.14 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 154.3, 133.5 – 106.0 (m, -$\underline{C}F_2\underline{C}F_3$), 92.9, 81.5 (t, J_{C-F} = 27.0 Hz), 71.0 (d, J_{C-F} = 7.1 Hz), 37.8, 34.4, 31.2, 28.3, 28.0, 22.5, 18.7, 17.8 – 17.5 (m, -$CH\underline{C}H_3\underline{C}H_3$), 13.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -78.61 (s, 3F), -108.62 – -125.69 (m, 2F). IR (neat, cm^{-1}) 3267, 2935, 2862, 2247, 1729, 1468, 1429, 1377, 1331, 1220, 1191, 1160, 1129, 818, 742; HRMS (ESI$^+$) *m/z* calcd for $C_{16}H_{25}F_5NO_3$ $[M+H]^+$: 374.1749; found: 374.1741.



1,1,1,2,2,3,3-heptafluoro-4-methyldodec-5-yn-4-yl hydroxy(methyl)carbamate (18o)

Colorless oil; yield 54%; R_f 0.3 (hexanes/EtOAc = 5/1);

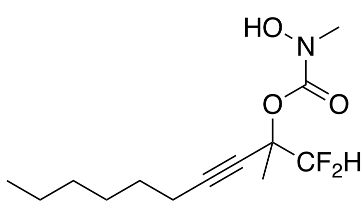
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.87 (brs, 1H), 3.19 (s, 3H), 2.22 (t, *J* = 7.1 Hz, 2H), 1.93 (s, 3H), 1.49 (m, 2H), 1.40 – 1.18 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 154.2, 122.4 – 105.6 (m, -$\underline{C}F_2\underline{C}F_2\underline{C}F_3$), 91.3, 76.3 (t, $J_{C\text{-}F}$ = 28.8 Hz), 72.4 (d, $J_{C\text{-}F}$ = 4.3 Hz), 37.7, 31.2, 28.3, 27.8, 22.4, 21.3, 18.6, 13.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -80.23 – -82.43 (m, 3F), -115.61 – -121.30 (m, 2F), -122.35 (t, *J* = 4.9 Hz, 2F). IR (neat, cm^{-1}) 3269, 2935, 2862, 2250, 1734, 1378, 1344, 1229, 1197, 1163, 1128, 736; HRMS (ESI^{+}) m/z calcd for $C_{15}H_{20}F_7NNaO_3$ $[M+Na]^{+}$: 418.1224; found: 418.1209.



1,1,1,2,2-pentafluoro-3-methylundec-4-yn-3-yl hydroxy(methyl)carbamate (18p)

Colorless oil; yield 58%; R_f 0.3 (hexanes/EtOAc = 5/1);

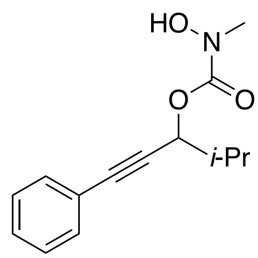
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.90 (brs, 1H), 3.21 (s, 3H), 2.23 (t, *J* = 7.1 Hz, 2H), 1.96 – 1.92 (m, 3H), 1.59 – 1.44 (m, 2H), 1.43 – 1.19 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 154.2, 125.0 – 106.6 (m, -$\underline{C}F_2\underline{C}F_3$), 91.1, 75.5 (t, $J_{C\text{-}F}$ = 28.1 Hz), 72.4, 37.6, 31.2, 28.3, 27.8, 22., 21.24, 18.6, 13.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -77.85 (t, *J* = 4.4 Hz, 3F), -120.29 – -125.08 (m, 2F). IR (neat, cm^{-1}) 3271, 2935, 2862, 2247, 1731, 1469, 1446, 1430, 1379, 1341, 1199, 1165, 1125, 1096, 1009, 792, 740, 681; HRMS (ESI^{+}) *m/z* calcd for $C_{14}H_{21}F_5NO_3$ $[M+H]^{+}$: 346.1436; found: 346.1422.



1,1-difluoro-2-methyldec-3-yn-2-yl hydroxy(methyl)carbamate (18q)

Colorless oil; yield 66%; R_f 0.3 (hexanes/EtOAc = 7/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.41 (brs, 1H), 6.39 – 5.76 (t, J = 57 Hz, 1H), 3.18(s, 3H), 2.18 (t, *J* = 7.0 Hz, 2H), 1.64 (s, 3H), 1.57 – 1.39 (m, 2H), 1.39 – 1.17 (m, 6H), 0.89 – 0.81 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 155.4, 112.9 (dd, $J_{C\text{-}F}$ = 252.4, 248.4 Hz), 89.4 (d, $J_{C\text{-}F}$ = 1.5 Hz), 75.0 (t, $J_{C\text{-}F}$ = 26.3 Hz), 74.8 (d, $J_{C\text{-}F}$ = 5.7 Hz), 38.0, 31.1, 28.3, 28.0, 22.4, 20.0, 18.5, 13.8. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -126.85 – -134.85 (m, 2F). IR (neat, cm^{-1}) 3269, 2932, 2860, 2242, 1719, 1430, 1383, 1168, 1080, 847, 751. HRMS (ESI^{+}) *m/z* calcd for $C_{26}H_{40}F_{4}N_{2}NaO_{5}$ $[2M+Na]^{+}$ [-$H_{2}O$]: 559.2764; found: 559.2755.



4-methyl-1-phenylpent-1-yn-3-yl hydroxy(methyl)carbamate (18r)

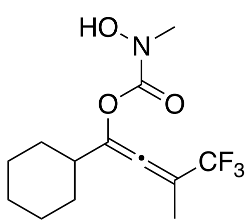
Colorless oil; yield 71%; R_f 0.4 (hexanes/EtOAc = 3/1).

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.44 – 7.29 (m, 2H), 6.96 – 6.85 (m, 3H), 5.61 (d, *J* = 5.5 Hz, 1H), 2.92 (s, 3H), 1.94 (sept, *J* = 6.8 Hz, 1H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, Benzene-d_6) δ 157.3, 131.8, 128.3, 128.2, 122.6, 86.5, 85.7, 71.5, 37.4, 32.8, 17.9, 17.4. IR (neat, cm^{-1}) 3269, 2966, 2931, 2875, 2228, 1704, 1490, 1443, 1386, 1353, 1326, 1167, 1035, 954, 757, 691, 640; HRMS (ESI^{+}) *m/z* calcd for $C_{14}H_{18}NO_{3}$ $[M+H]^{+}$: 248.1281; found: 248.1274.

4.4 Synthesis of Fluorine Containing Allenes

Preparation of a standard solution of the active gold catalyst:[10] A mixture of (2-*t*-Bu-PhO)$_3$PAuCl (35 mg, 0.05 mmol, 5 mol%) and AgNTf$_2$ (19 mg, 0.05 mmol, 5 mol%) in DCM (2 mL) was stirred at room temperature for 30 min.

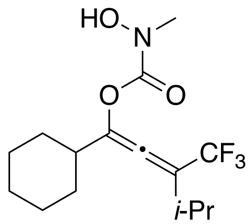
Typical procedure for the synthesis of **29a-29i**, **29k-29q**: Carbamate **18a** (162 mg, 0.55 mmol) was dissolved in DCM (2 mL) and 4 Å MS (1.1 g, 2 g/mmol) was added. The standard solution of the active gold catalyst (1 mL) was added. The reaction mixture was allowed to stir at room temperature for an hour. The volatiles were removed *in vacuo* and the product was purified by flash column chromatography (hexanes/EtOAc = 5/1) to provide allene **29a** (141 mg, 87 %) as a colorless oil.



1-cyclohexyl-4,4,4-trifluoro-3-methylbuta-1,2-dien-1-yl hydroxy(methyl)carbamate (**29a**)

R$_f$ 0.3 (hexanes/EtOAc = 5/1);

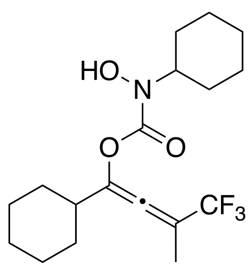
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.56 (brs, 1H), 3.26 (s, 3H), 2.21 (tt, *J* = 11.1, 3.3 Hz, 1H), 1.93 (s, 3H), 1.90 – 1.59 (m, 5H), 1.39 – 1.01 (m, 5H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 194.9 (q, J_{C-F} = 4.2 Hz), 154.7, 132.4, 122.4 (q, J_{C-F} = 274.1 Hz), 103.9 (q, J_{C-F} = 35.1 Hz), 39.6, 38.2, 29.9 (d, *J* = 2.6 Hz), 25.9, 25.6 (d, *J* = 1.2 Hz), 14.1. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -66.79. IR (neat, cm^{-1}) 3362, 2932, 2857, 1990, 1728, 1453, 1377, 1305, 1172, 1124, 1092, 1039, 743.



1-cyclohexyl-4-methyl-3-(trifluoromethyl)penta-1,2-dien-1-yl hydroxy(methyl)carbamate (29b)

Colorless oil; yield 89%; R_f 0.35(hexanes/EtOAc = 5/1);

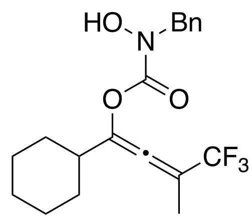
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.72 (brs, 1H), 3.26 (s, 3H), 2.63 – 2.47 (m, 1H), 2.21 (tt, *J* = 11.3, 3.4 Hz, 1H), 1.92 – 1.63 (m, 5H), 1.39 – 1.00 (m, 11H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 193.9 (q, $J_{C\text{-}F}$ = 4.5 Hz), 154.9, 134.8, 122.8 (q, $J_{C\text{-}F}$ = 275.4 Hz), 114.9 (q, $J_{C\text{-}F}$ = 32.2 Hz), 39.9, 38.2, 30.3, 30.1, 27.9, 25.9, 25.7, 21.9, 21.8. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -63.40. IR (neat, cm^{-1}) 3248, 2968, 2933, 2856, 1978, 1728, 1469, 1451, 1417, 1375, 1276, 1154, 1025, 1000, 743, 730, 676.



1-cyclohexyl-4,4,4-trifluoro-3-methylbuta-1,2-dien-1-yl cyclohexyl(hydroxy)carbamate (29c)

White solid; yield 82%; R_f 0.34 (hexanes/EtOAc = 7/1);

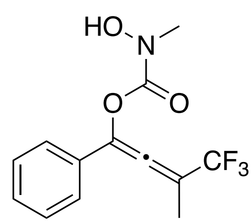
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.83 (brs, 1H), 3.83 (tt, *J* = 10.9, 4.5 Hz, 1H), 2.39 – 2.14 (m, 1H), 1.94 (s, 3H), 1.90 – 1.58 (m, 10H), 1.50 – 0.96 (m, 10H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 195.0 (q, $J_{C\text{-}F}$ = 4.3 Hz), 154.1, 132.3, 122.5 (q, $J_{C\text{-}F}$ = 274.3 Hz), 103.8 (q, $J_{C\text{-}F}$ = 35.2 Hz), 58.8, 39.7, 31.5, 30.0, 29.9, 29.2, 28.3, 26.0, 25.6, 25.6, 25.4, 25.2, 14.2. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -66.71. IR (neat, cm^{-1}) 3264, 2933, 2857, 1990, 1717, 1453, 1392, 1360, 1306, 1244, 1175, 1126, 1061, 740.



1-cyclohexyl-4,4,4-trifluoro-3-methylbuta-1,2-dien-1-yl benzyl(hydroxy)carbamate (29d)

White solid; yield 80%; R_f 0.3 (hexanes/EtOAc = 7/1);

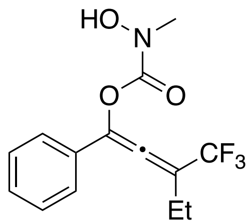
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.89 (brs, 1H), 7.47 – 7.30 (m, 5H), 4.75 (s, 2H), 2.23 (tt, *J* = 11.6, 3.7 Hz, 1H), 1.96 (s, 3H), 1.92 – 1.65 (m, 4H), 1.40 – 1.04 (m, 6H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 195.0 (q, $J_{C\text{-}F}$ = 4.2 Hz), 154.3, 135.8, 132.6, 128.6, 128.1, 127.9, 122.5 (q, $J_{C\text{-}F}$ = 274.2 Hz), 104.3 (q, $J_{C\text{-}F}$ = 35.2 Hz), 54.8, 39.7, 29.9, 29.8, 25.9, 25.6 (d, *J* = 1.3 Hz), 14.2. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -66.62. IR (neat, cm^{-1}) 3284, 2932, 2856, 1990, 1720, 1455, 1395, 1304, 1232, 1173, 1128, 1145, 755, 732, 699.



4,4,4-trifluoro-3-methyl-1-phenylbuta-1,2-dien-1-yl hydroxy(methyl)carbamate (29e)

Colorless oil; yield 94%; R_f 0.3 (hexanes/EtOAc = 5/1);

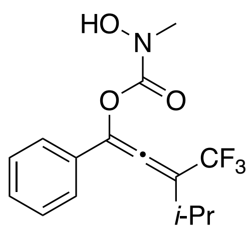
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.92 (brs, 1H), 7.34 – 7.22 (m, 5H), 3.27 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 197.4 (q, $J_{C\text{-}F}$ = 4.2 Hz), 154.3, 130.6, 130.2, 129.1, 128.7, 125.0, 122.1 (q, $J_{C\text{-}F}$ = 275.0 Hz), 106.5 (q, $J_{C\text{-}F}$ = 35.4 Hz), 38.1, 14.1. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -66.36. IR (neat, cm^{-1}) 3272, 2930, 1976, 1731, 1497, 1459, 1377, 1299, 1246, 1175, 1130, 1092, 763, 743, 692.



1-phenyl-3-(trifluoromethyl)penta-1,2-dien-1-yl hydroxy(methyl)carbamate (29f)

Colorless oil; yield 90%; R_f 0.3 (hexanes/EtOAc = 5/1);

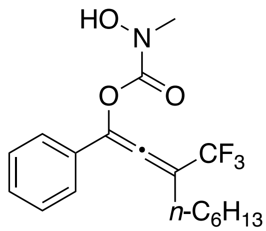
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.27 (brs, 1H), 7.47 – 7.30 (m, 5H), 3.36 (s, 3H), 2.60 – 2.36 (m, 2H), 1.21 (tt, *J*=7.4, 0.7, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 196.8 (q, J_{C-F} =4.1 Hz), 154.5, 130.9, 129.6, 129.1, 128.8, 124.8, 122.3 (q, J_{C-F}=273.8 Hz), 113.2 (q, J_{C-F} =33.9 Hz), 38.2, 21.6, 11.3. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -64.85. IR (neat, cm^{-1}) 3263, 2976, 2940, 1971, 1731, 1496, 1455, 1281, 1244, 1175, 1128, 763, 691.



4-methyl-1-phenyl-3-(trifluoromethyl)penta-1,2-dien-1-yl hydroxy(methyl)carbamate (**29g**)

Colorless oil; yield 82%; R_f 0.34 (hexanes/EtOAc = 5/1);

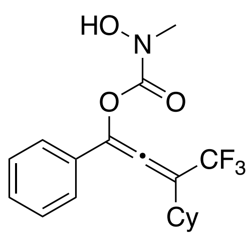
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.65 (brs, 1H), 7.50 – 7.30 (m, 5H), 3.43 – 3.32 (m, 3H), 2.76 (tt, *J* = 6.8 Hz, 1H), 1.27 (d, *J*=6.7, 6H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 196.7 (q, J_{C-F} = 4.4 Hz), 154.6, 130.8, 129.8, 129.1, 128.8, 124.7, 122.5 (q, J_{C-F} = 276.2 Hz), 117.6 (q, J_{C-F} = 32.5 Hz), 38.3, 29.1, 21.9, 21.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ = -62.84. IR (neat, cm^{-1}) 3253, 2971, 2936, 1963, 1731, 1453, 1404, 1377, 1274, 1244, 1130, 1048, 762, 691.



1-phenyl-3-(trifluoromethyl)nona-1,2-dien-1-yl hydroxy(methyl)carbamate (29h)

Colorless oil; yield 82%; R_f 0.3 (hexanes/EtOAc = 7/1);

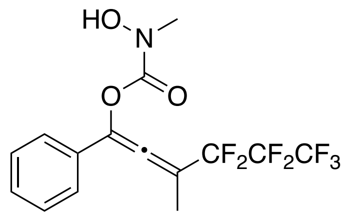
^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.40 (brs, 1H), 7.49 – 7.30 (m, 5H), 3.36 (s, 3H), 2.50 – 2.35 (m, 2H), 1.77 – 1.51 (m, 2H), 1.45 – 1.20 (m, 6H), 0.91 – 0.80 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ = 197.2 (q, $J_{C\text{-}F}$ = 4.1 Hz), 154.6, 130.8, 129.1, 129.1, 128.7, 124.9, 122.3 (q, $J_{C\text{-}F}$ = 275.6 Hz), 111.7 (q, $J_{C\text{-}F}$ = 33.8 Hz), 38.3, 31.5, 28.8, 28.2, 26.9, 22.6, 14.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ = -64.75. IR (neat, cm^{-1}) 3272, 2931, 2856, 1990, 1722, 1454, 1395, 1304, 1232, 1173, 1128, 1084, 734, 698.



3-cyclohexyl-4,4,4-trifluoro-1-phenylbuta-1,2-dien-1-yl hydroxy(methyl)carbamate (29i)

Colorless oil; yield 80%; R_f 0.3 (hexanes/EtOAc = 7/1);

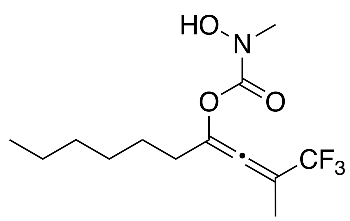
^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.61 (brs, 1H), 7.50 – 7.30 (m, 5H), 3.37 (s, 3H), 2.39 (tt, *J*=11.4, 3.4, 1H), 2.11 – 1.97 (m, 2H), 1.86 – 1.63 (m, 3H), 1.51 – 1.15 (m, 5H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ = 197.2 (q, $J_{C\text{-}F}$ = 4.3 Hz), 154.6, 130.8, 129.6, 129.0, 128.8, 124.7, 122.6 (q, $J_{C\text{-}F}$ = 276.2 Hz), 116.8 (q, $J_{C\text{-}F}$ = 32.4 Hz), 38.4, 32.3, 26.2, 26.2, 25.6. ^{19}F NMR (282 MHz, Chloroform-*d*) δ = -62.90. IR (neat, cm^{-1}) 3273, 2931, 2855, 1961, 1732, 1486, 1451, 1375, 1277, 1230, 1171, 1124, 761, 705, 690.



1,1,1,2,2,3,3-heptafluoro-4-methyldodeca-4,5-dien-6-yl hydroxy(methyl)carbamate (29k)

Colorless oil; yield 89%; R_f 0.3 (hexanes/EtOAc = 5/1);

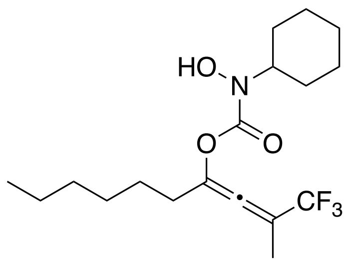
^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.24 (brs, 1H), 7.50 – 7.32 (m, 5H), 3.36 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 200.4 (t, $J_{C\text{-}F}$ = 6.7 Hz), 154.5, 130.5, 129.2, 128.7, 128.2, 125.0, 121.4 – 102.7 (m, $-\underline{C}F_2\underline{C}F_2\underline{C}F_3$), 113.4 (t, $J_{C\text{-}F}$ = 28.0 Hz), 38.2, 15.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ = -80.44 (t, *J* = 9.9 Hz, 3F), -110.66 (qd, *J* = 9.8 Hz, 4.0, 2F), -125.82 (s, 2F). IR (neat, cm^{-1}) 3292, 2936, 1969, 1728, 1497, 1458, 1378, 1346, 1230, 1116, 1058, 762, 739, 691.



1,1,1-trifluoro-2-methyldeca-2,3-dien-4-yl hydroxy(methyl)carbamate (29l)

colorless oil; yield 89%; R_f 0.34 (hexanes/EtOAc = 5/1);

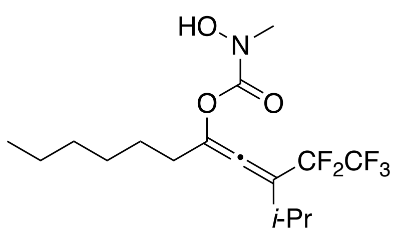
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.28 (brs, 1H), 3.27 (s, 3H), 2.29 (t, *J* = 7.1 Hz, 2H), 1.94 (s, 3H), 1.62 – 1.19 (m, 8H), 1.05 – 0.77 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 195.5 (q, $J_{C\text{-}F}$ = 4.3 Hz), 154.6, 128.6, 122.4 (q, $J_{C\text{-}F}$ = 274.3 Hz), 103.2 (q, $J_{C\text{-}F}$ = 35.2 Hz), 38.1, 31.5, 31.4, 28.4, 25.6, 22.5, 14.1, 14.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -66.80. IR (neat, cm^{-1}) 3269, 2932, 2861, 1993, 1735, 1460, 1378, 1302, 1158, 1025, 746.



1,1,1-trifluoro-2-methyldeca-2,3-dien-4-yl cyclohexyl(hydroxy)carbamate (29m)

colorless oil; yield 87%; R_f 0.3 (hexanes/EtOAc = 7/1);

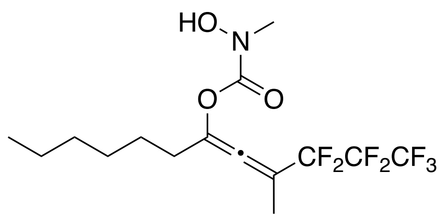
^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.85 (tt, *J* = 11.1, 4.3 Hz, 1H), 2.30 (t, *J* = 7.1 Hz, 2H), 1.95 (s, 3H), 1.90 – 1.58 (m, 8H), 1.45 – 1.23 (m, 10H), 0.93 – 0.86 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 195.5 (q, *J* = 4.2 Hz), 153.8, 128.5, 122.4 (q, *J* = 274.4 Hz), 103.1 (q, *J* = 35.2 Hz), 77.2, 58.7, 31.5, 31.5, 29.2, 29.2, 28.4, 25.7, 25.4, 25.2, 22.5, 14.2, 14.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -66.73. IR (neat, cm^{-1}) 3269, 2933, 2858, 1991, 1717, 1454, 1394, 1304, 1173, 1127, 1093, 739.



2-methyl-3-(trifluoromethyl)undeca-3,4-dien-5-yl hydroxy(methyl)carbamate (29n)

colorless oil; yield 90%; R_f 0.3 (hexanes/EtOAc = 5/1);

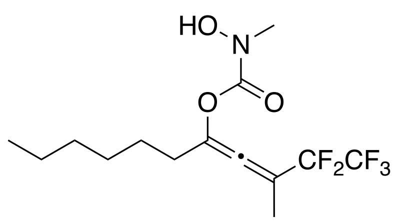
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.46 (brs, 1H), 3.26 (s, 3H), 2.58 (sept, *J* = 6.7 Hz, 1H), 2.30 (dd, *J* = 8.2, 6.6 Hz, 2H), 1.56 – 1.23 (m, 8H), 1.15 (dd, *J* = 6.7, 1.2 Hz, 6H), 0.97 – 0.81 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 196.4 (t, $J_{C\text{-}F}$ = 8.0 Hz), 154.7, 131.5, 122.7 – 107.1 (m, -$\underline{C}F_2\underline{C}F_3$), 112.7 (t, *J* = 24.8 Hz) 38.1, 31.7, 31.5, 28.7, 28.0, 25.9, 22.5, 22.5, 22.4, 14.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -83.28 (t, *J* = 2.0 Hz, 3F), -112.09(s, 2F). IR (neat, cm^{-1}) 3245, 2933, 2875, 1980, 1735, 1467, 1420, 1378, 1330, 1199, 1153, 742.



1,1,1,2,2,3,3-heptafluoro-4-methyldodeca-4,5-dien-6-yl hydroxy(methyl)carbamate (29o)

colorless oil; yield 95%; R_f 0.3 (hexanes/EtOAc = 6/1);

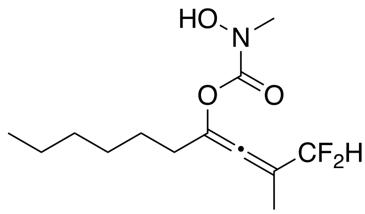
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.39 (brs, 1H), 3.26 (s, 3H), 2.49 – 2.17 (m, 2H), 1.97 (t, *J* = 0.9 Hz, 3H), 1.63 – 1.19 (m, 8H), 1.08 – 0.84 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 198.4 (t, J_{C-F} = 7.0 Hz), 154.6, 128.9, 124.2 – 105.0 (m, -$\underline{C}F_2\underline{C}F_2\underline{C}F_3$), 102.3 (t, J_{C-F} = 26.7 Hz), 38.0, 31.5, 31.4, 28.4, 25.6, 22.5, 14.9 (t, *J* = 2.3 Hz), 13.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -80.68 (t, *J* = 9.8 Hz, 3F), -111.19 (q, *J* = 9.8 Hz, 2F), -126.13 (d, *J* = 3.5 Hz, 2F). IR (neat, cm^{-1}) 3256, 2934, 2862, 1987, 1734, 1459, 1378, 1346, 1229, 1155, 1116, 740, 691.



1,1,1-trifluoro-2-methyldeca-2,3-dien-4-yl hydroxy(methyl)carbamate (29p)

colorless oil; yield 90%; R_f 0.33 (hexanes/EtOAc = 6/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.91 (brs, 1H), 3.27 (s, 3H), 2.29 (td, *J* = 7.1, 1.8 Hz, 2H), 1.97 (t, *J* = 0.7 Hz, 3H), 1.51 – 1.20 (m, 8H), 1.02 – 0.74 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 197.8 (t, J_{C-F} = 6.8 Hz), 154.5, 128.9, 123.7 – 103.1 (m, -$\underline{C}F_2\underline{C}F_3$), 101.9 (t, J_{C-F} = 26.9 Hz), 38.0, 31.5, 31.5, 28.5, 25.6, 22.5**,** 14.6 (q, *J* = 1.4 Hz), 14.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -83.24 (t, *J* = 2.2 Hz, 3F), -114.07 (q, *J* = 2.3 Hz, 2F). IR (neat, cm^{-1}) 3256, 2933, 2862, 1988, 1734, 1459, 1377, 1331, 1204, 1150, 1104, 742.



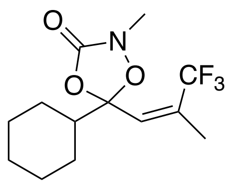
1,1-difluoro-2-methyldeca-2,3-dien-4-yl hydroxy(methyl)carbamate (29q)

colorless oil; yield 94%; R_f 0.4 (hexanes/EtOAc = 7/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.33 (brs, 1H), 6.08 (t, *J* = 56.5 Hz, 1H), 3.25 (s, 3H), 2.24 (t, *J* = 5.8 Hz, 2H), 1.86 (s, 3H), 1.55 – 1.21 (m, 8H), 1.00 – 0.77 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 196.2 (t, J_{C-F} = 9.9 Hz), 155.1, 127.0, 114.3 (t, J_{C-F} = 242.4 Hz), 106.6 (t, J_{C-F} = 26.2 Hz), 38.1, 31.5, 31.5, 28.4, 25.8, 22.5, 14.0, 12.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -115.20 (dd, *J* = 122.8, 56.5 Hz). IR (neat, cm^{-1}) 3268, 2933, 2857, 1990, 1731,1453, 1377, 1305, 1172, 1092, 1039, 745, 704.

2.5 Synthesis of (*Z*)-Trifluoromethyl Alkenes

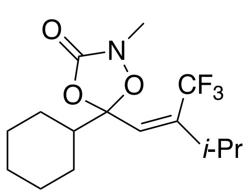
Typical procedure for the synthesis of **19a-19i**, **19k-19q**: Allene **29a** (141 mg, 0.5 mmol) was dissolved in DCM (2 mL) and TFA(100 µL, 1mmol) was added. The reaction mixture was allowed to stir at room temperature and monitored by TLC. The volatiles were removed *in vacuo* and the product was purified by flash column chromatography (EtOAc/hexanes= 15/1) to provide ketal 19a (139 mg, 98%, 92/8 *Z/E*) as a colorless oil.



(*Z*)-5-cyclohexyl-2-methyl-5-(3,3,3-trifluoro-2-methylprop-1-en-1-yl)-1,4,2-dioxazolidin-3-one (19a)

R_f 0.32 (hexanes/EtOAc = 12/1);

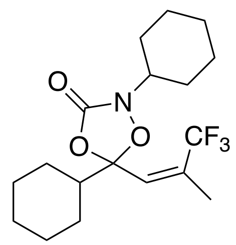
^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.84 (s, 1H), 3.08 (s, 3H), 1.95 (m, 4H), 1.87 – 1.62 (m, 5H), 1.18 (m, 5H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 157.4, 133.5, 130.8 (q, J_{C-F} = 32.3 Hz), 122.5 (q, J_{C-F} = 275.3 Hz), 108.9, 43.9, 35.5, 26.3, 25.8, 25.7, 25.6, 19.7 (d, *J* = 3.5 Hz). ^{19}F NMR (471 MHz, Chloroform-*d*) δ -61.63. IR (neat, cm^{-1}) 2936, 2858, 1792, 1454, 1381, 1336, 1169, 1135, 1013, 751, 727; HRMS (ESI$^+$) *m/z* calcd for $C_{13}H_{18}F_3NNaO_3$ [M+Na]$^+$: 316.1131; found: 316.1127.



(*Z*)-5-cyclohexyl-2-methyl-5-(3-methyl-2-(trifluoromethyl)but-1-en-1-yl)-1,4,2-dioxazolidin-3-one (19b)

Colorless oil; yield 96%; *Z* isomer; R_f 0.3 (hexanes/EtOAc = 12/1);

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.77 (s, 1H), 3.09 (s, 3H), 2.73 – 2.59 (m, 1H), 1.97 (m, 1H), 1.90 – 1.59 (m, 6H), 1.28 – 1.14 (m, 4H), 1.12 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.5, 140.9 (q, $J_{C\text{-}F}$ = 29.3 Hz), 131.1 (d, $J_{C\text{-}F}$ = 3.4 Hz), 123.1 (q, $J_{C\text{-}F}$ = 276.5 Hz), 109.6, 44.1, 35.6, 30.5, 26.4, 25.8, 25.8, 25.8, 25.6, 22.2, 21.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -58.87. IR (neat, cm^{-1}) 2936, 2858, 1793, 1453, 1395, 1340, 1164, 1137, 1021, 751, 719. HRMS (ESI^{+}) *m/z* calcd for $C_{15}H_{22}F_{3}NNaO_{3}$ $[M+Na]^{+}$: 344.1444; found: 344.1453.

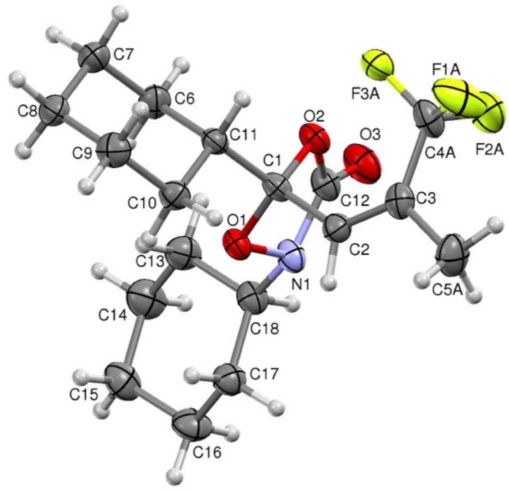


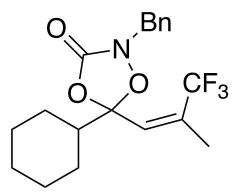
(*Z*)-2,5-dicyclohexyl-5-(3,3,3-trifluoro-2-methylprop-1-en-1-yl)-1,4,2-dioxazolidin-3-one (19c)

White solid; yield 98%; *Z/E* = 89/11; R_f 0.3 (hexanes/EtOAc = 15/1); m.p. 107 – 110 ^{o}C;

^{1}H NMR (300 MHz, Chloroform-*d*) δ = 5.85 (s, 1H), 3.62 (tt, *J* = 11.6, 3.7 Hz, 1H), 1.97 (d, *J*=1.7, 3H), 1.94 – 1.43 (m, 12H), 1.43 – 1.02 (m, 9H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ = 156.5, 134.4 (d, $J_{C\text{-}F}$ = 3.2 Hz), 130.3 (q, $J_{C\text{-}F}$ = 32.5 Hz), 122.5 (q, $J_{C\text{-}F}$ = 275.3 Hz), 108.7, 59.1, 44.3, 29.8, 28.1, 26.6, 25.9, 25.6, 25.5, 25.3, 25.1, 19.7. ^{19}F NMR (282 MHz, Chloroform-*d*) δ = -61.46. IR (neat, cm^{-1}) 2936, 2857, 1782, 1453, 1386, 1282, 1164, 1131, 1102, 753; HRMS (ESI^{+}) *m/z* calcd for $C_{18}H_{26}F_{3}NNaO_{3}$ $[M+Na]^{+}$: 362.1938; found: 362.1938.

Structure of **19c** was confirmed by X-ray.

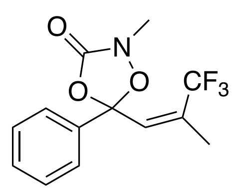




(*Z*)-2-benzyl-5-cyclohexyl-5-(3,3,3-trifluoro-2-methylprop-1-en-1-yl)-1,4,2-dioxazolidin-3-one (**19d**)

White foam; yield 98%; *Z/E* = 91/9; R_f 0.4 (hexanes/EtOAc = 10/1);

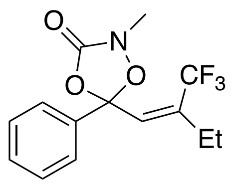
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.35 (m, 5H), 5.83 (q, *J* = 1.7 Hz, 1H), 4.60 (s, 2H), 1.96 (d, *J* = 1.6 Hz, 4H), 1.81 – 1.56 (m, 5H), 1.26 – 0.93 (m, 5H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 156.8, 134.2, 133.8, 130.9 (q, J_{C-F} = 32.7 Hz), 128.9, 128.4, 128.2, 122.4 (q, J_{C-F} = 274.7 Hz), 109.2, 63.8, 53.1, 44.1, 26.2, 25.7 (d, *J* = 8.4 Hz), 25.5 (d, *J* = 10.1 Hz), 19.8, 15.8. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -61.86. IR (neat, cm^{-1}) 2935, 2857, 1787, 1454, 1388, 1230, 1199, 1167, 1082, 1010, 753, 698; HRMS (ESI$^+$) *m/z* calcd for $C_{19}H_{22}F_3NNaO_3$ [M+Na]$^+$: 392.1444; found: 392.1446.



(*Z*)-2-methyl-5-phenyl-5-(3,3,3-trifluoro-2-methylprop-1-en-1-yl)-1,4,2-dioxazolidin-3-one (19e)

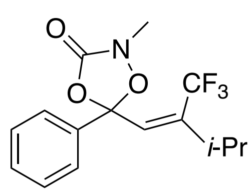
Colorless oil; yield 79%; *Z/E* = 83/17; R_f 0.3 (hexanes/EtOAc = 10/1);

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.56 – 7.50 (m, 2H), 7.49 – 7.39 (m, 3H), 6.25 (q, *J* = 1.7 Hz, 1H), 3.20 (s, 3H), 2.03 (d, *J* = 1.7 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.3, 135.5, 132.5 (q, $J_{C\text{-}F}$ = 36.5 Hz), 132.4, 130.3, 128.5, 126.1, 122.3 (q, $J_{C\text{-}F}$ = 275.1 Hz), 105.6, 36.0, 19.5. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -62.17. IR (neat, cm^{-1}) 3065, 2995, 2930, 1794, 1452, 1379, 1331, 1170, 1136, 1105, 1020, 765, 725, 696; HRMS (ESI^{+}) *m/z* calcd for $C_{13}H_{13}F_3NO_3$ $[M+H]^{+}$: 288.0842; found: 288.0839.



(*Z*)-2-methyl-5-phenyl-5-(2-(trifluoromethyl)but-1-en-1-yl)-1,4,2-dioxazolidin-3-one (19f)

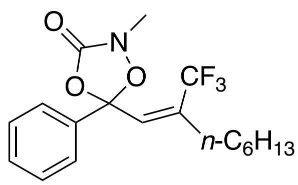
Colorless oil; yield 77%; *Z/E* = 81/19; R_f 0.3 (hexanes/EtOAc = 10/1);
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.56 – 7.51 (m, 2H), 7.48 – 7.39 (m, 3H), 6.18 (t, *J* = 1.6 Hz, 1H), 3.20 (s, 3H), 2.36 (qd, *J* = 7.4, 1.6 Hz, 2H), 1.17 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 157.3, 138.0 (q, $J_{C\text{-}F}$ = 31.2 Hz), 135.6, 131.0, 130.2, 128.4, 126.1, 122.6 (q, $J_{C\text{-}F}$ = 276.1 Hz), 106.0, 36.0, 25.8, 12.4. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -61.32. IR (neat, cm^{-1}) 2979, 2943, 1793, 1452, 1336, 1245, 1169, 1137, 1048, 1011, 764, 696; HRMS (ESI^{+}) *m/z* calcd for $C_{14}H_{15}F_3NO_3$ $[M+H]^{+}$: 302.0999; found: 302.0990.



(*Z*)-2-methyl-5-(3-methyl-2-(trifluoromethyl)but-1-en-1-yl)-5-phenyl-1,4,2-dioxazolidin-3-one (19g)

Colorless oil; yield 86%; Major *Z* isomer; R_f 0.34 (hexanes/EtOAc = 5/1)

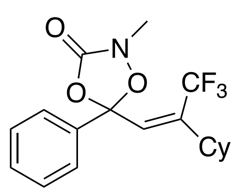
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.55 – 7.50 (m, 2H), 7.48 – 7.40 (m, 3H), 6.20 (d, *J* = 1.0 Hz, 1H), 3.20 (s, 3H), 2.70 (tt, *J* = 6.8, 1.0 Hz, 1H), 1.19 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 157.4, 142.6 (q, J_{C-F} = 29.9 Hz), 135.6, 130.3, 130.0 (d, J_{C-F} = 3.6 Hz), 128.5, 126.1, 122.9 (q, J_{C-F} = 276.6 Hz), 106.4, 36.0, 30.4, 22.1, 22.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -59.81. IR (neat, cm^{-1}) 2973, 1793, 1352, 1243, 1166, 1135, 1010, 764, 696; HRMS (ESI+) *m/z* calcd for $C_{15}H_{17}F_3NO_3$ [M+H]$^{+}$: 316.1155; found: 316.1155.



(*Z*)-2-methyl-5-phenyl-5-(2-(trifluoromethyl)oct-1-en-1-yl)-1,4,2-dioxazolidin-3-one (19h)

Colorless oil; yield 60%; *Z/E* = 86/14; R_f 0.35 (hexanes/EtOAc = 15/1);

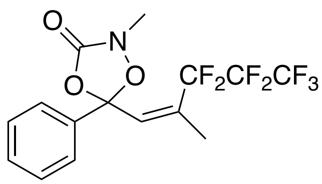
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.56 – 7.50 (m, 2H), 7.48 – 7.39 (m, 3H), 6.19 (d, *J* = 1.4 Hz, 1H), 3.20 (s, 3H), 2.30 (t, *J* = 7.3, Hz, 2H), 1.58 – 1.46 (m, 2H), 1.42 – 1.24 (m, 6H), 0.96 – 0.86 (m, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.3, 136.7 (q, J_{C-F} = 31.2 Hz), 135.5, 131.9, 130.3, 128.5, 126.1, 122.6 (q, J_{C-F} = 275.7 Hz), 106.0, 36.0, 33.0, 31.4, 28.6, 28.0, 22.5, 14.0. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -61.04. IR (neat, cm^{-1}) 2931, 2859, 1793, 1452, 1330, 1167, 1137, 764, 696; HRMS (ESI^{+}) *m/z* calcd for $C_{18}H_{23}F_3NO_3$ [M+H]$^{+}$: 358.1625; found: 358.1632.



(*Z*)-5-(2-cyclohexyl-3,3,3-trifluoroprop-1-en-1-yl)-2-methyl-5-phenyl-1,4,2-dioxazolidin-3-one (19i)

Colorless oil; yield 80%; *Z/E* = 84/16; R_f 0.35 (hexanes/EtOAc = 15/1);

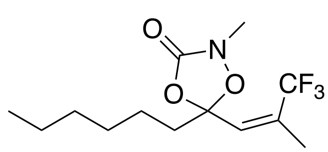
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.57 – 7.48 (m, 2H), 7.48 – 7.35 (m, 3H), 6.17 (d, *J* = 0.9 Hz, 1H), 3.19 (s, 3H), 2.29 (tt, *J* = 11.9, 2.9 Hz, 1H), 1.96 – 1.64 (m, 5H), 1.40 – 1.15 (m, 5H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 157.4, 141.9 (q, $J_{C\text{-}F}$ = 29.9 Hz), 135.7, 130.6 (d, $J_{C\text{-}F}$ = 3.5 Hz), 130.2, 128.4, 126.2, 122.8 (d, $J_{C\text{-}F}$ = 276.9 Hz), 106.4, 40.1, 36.1, 32.9, 32.7, 26.4, 26.4, 25.7. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -60.52. IR (neat, cm^{-1}) 2932, 2856, 1793, 1451, 1359, 1330, 1164, 1132, 1012, 764, 696; HRMS (ESI$^+$) *m/z* calcd for $C_{18}H_{21}F_3NO_3$ [M+H]$^+$: 356.1468; found: 356.1466.



(*Z*)-5-(3,3,4,4,5,5,5-heptafluoro-2-methylpent-1-en-1-yl)-2-methyl-5-phenyl-1,4,2-dioxazolidin-3-one (19k)

Colorless oil; yield 76%; *Z/E* = 50:50; R_f 0.3 (hexanes/EtOAc = 5/1);

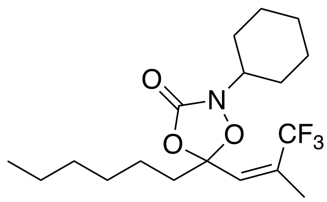
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.56 – 7.49 (m, 2H), 7.47 – 7.37 (m, 3H), 6.48 (q, *J* = 1.6 Hz, 1H), 3.18 (s, 3H), 2.06 (q, *J* = 1.3 Hz, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 157.2, 136.1, 136.0, 131.0 (t, $J_{C\text{-}F}$ = 23.6 Hz), 130.2, 128.4, 126.0, 123.3 – 107.8 (m, -$\underline{C}F_2\underline{C}F_2\underline{C}F_3$), 105.7, 36.0, 20.0. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -81.11 (t, *J* = 10.0 Hz, 3F), -109.30 (m, 2F), -123.02 – -124.74 (m, 2F). IR (neat, cm^{-1}) 2924, 1794, 1452, 1339, 1230, 1195, 1136, 1116, 749. 726, 695; HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{13}F_7NO_3$ [M+H]$^+$: 388.0778; found: 388.0769.



(*Z*)-5-hexyl-2-methyl-5-(3,3,3-trifluoro-2-methylprop-1-en-1-yl)-1,4,2-dioxazolidin-3-one (19l)

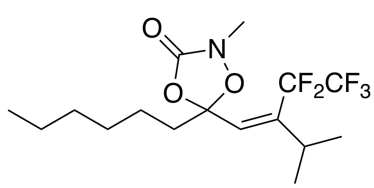
colorless oil; yield 87%; *Z/E* = 93/7; R_f 0.34 (hexanes/EtOAc = 12/1);

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.87 (q, *J* = 1.7 Hz, 1H), 3.11 (s, 3H), 2.05 – 1.97 (m, 1H), 1.95 (d, *J* = 1.6 Hz, 3H), 1.49 – 1.39 (m, 2H), 1.36 – 1.21 (m, 7H), 0.91 – 0.85 (m, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 157.6, 133.8 (d, J_{C-F} = 3.5 Hz), 130.9 (q, J_{C-F} = 32.5 Hz), 122.6 (q, J_{C-F} = 274.7 Hz), 107.6, 36.1, 35.7, 31.5, 28.9, 22.5, 22.4, 19.5, 14.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -61.60. IR (neat, cm^{-1}) 2957, 2933, 1794, 1454, 1378, 1336, 1169, 1136, 1104, 750; HRMS (ESI^{+}) *m/z* calcd for $C_{13}H_{20}F_3NNaO_3$ [M+Na]$^{+}$: 318.1287; found: 318.1279.



(*Z*)-2-cyclohexyl-5-hexyl-5-(3,3,3-trifluoro-2-methylprop-1-en-1-yl)-1,4,2-dioxazolidin-3-one (19m)

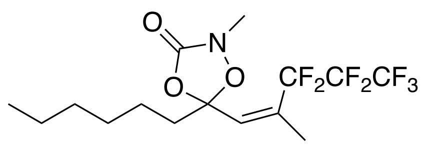
White solid; yield 97%; *Z/E* = 91/9; R_f 0.4 (hexanes/EtOAc = 15/1); m.p. 85 – 87 ^{o}C;
^{1}H NMR (500 MHz, Benzene-d_6) δ 5.54 (d, *J* = 4.6, Hz, 1H), 3.66 (tq, *J* = 11.8, 4.0 Hz, 1H), 1.92 – 1.76 (m, 5H), 1.72 – 1.47 (m, 3H), 1.46 – 1.37 (m, 5H), 1.33 – 1.24 (m, 2H), 1.23 – 1.13 (m, 2H), 1.12 – 1.02 (m, 2H), 1.01 – 0.86 (m, 4H), 0.85 – 0.77 (m, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 156.4, 134.4 (q, J_{C-F} = 9.3 Hz), 130.4 (q, J_{C-F} = 32.8 Hz), 122.5 (q, J_{C-F} = 273.8 Hz), 108.7, 59.0, 44.2, 36.1, 31.5, 29.6, 28.9, 28.1, 26.6, 25.8, 22.5, 22.4, 19.7, 14.0. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -62.38. IR (neat, cm^{-1}) HRMS (ESI^{+}) 2936, 2858, 1783, 1454, 1380, 1280, 1243, 1165, 1132, 1007, 752; *m/z* calcd for $C_{18}H_{29}F_3NO_3$ [M+H]$^{+}$: 364.2094; found: 364.2083.



(*Z*)-5-hexyl-2-methyl-5-(3,3,4,4,4-pentafluoro-2-isopropylbut-1-en-1-yl)-1,4,2-dioxazolidin-3-one (19n)

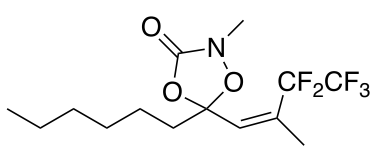
colorless oil; yield 88%; Major *Z* isomer; R_f 0.35 (hexanes/EtOAc = 10/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.09 (t, *J* = 1.4 Hz, 1H), 3.10 (s, 3H), 2.72 – 2.49 (m, 1H), 2.12 – 1.95 (m, 2H), 1.50 – 1.40 (m, 2H), 1.37 – 1.25 (m, 6H), 1.14 (dd, *J* = 6.8, 2.6 Hz, 6H), 0.94 – 0.85 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 157.8, 140.9 (t, J_{C-F} = 20.9 Hz), 135.8 (t, J_{C-F} = 3.7 Hz), 123.1 – 109.2 (m, -<u>C</u>F$_2$<u>C</u>F$_3$, -O<u>C</u>O-), 108.4 (t J_{C-F} = 1.7 Hz), 37.2 (t, *J* = 3.8 Hz), 35.9, 31.5, 28.9, 24.4, 24.0, 22.7, 22.4, 14.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -82.37 (t, *J* = 2.6 Hz, 3F), -111.87 – -112.17 (m, 2F). IR (neat, cm^{-1}) 2960, 2935, 2874, 1798, 1466, 1326, 1192, 1130, 1105, 1060, 982, 751, 713; HRMS (ESI$^+$) *m/z* calcd for $C_{16}H_{25}F_5NO_3$ [M+H]$^+$: 374.1749; found: 374.1740.



(*Z*)-5-(3,3,4,4,5,5,5-heptafluoro-2-methylpent-1-en-1-yl)-5-hexyl-2-methyl-1,4,2-dioxazolidin-3-one (19o)

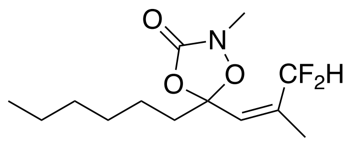
colorless oil; yield 75%; *Z/E* = 79/21; R$_f$ 0.3 (hexanes/EtOAc = 10/1);
^{1}H NMR (500 MHz, Chloroform-*d*) δ 6..08 (s, 1H), 3.08 (s, 3H), 2.03 – 1.94 (m, 5H), 1.50 – 1.39 (m, 2H), 1.34 – 1.21 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 157.6, 137.7, 129.4 (t, J_{C-F} = 23.8 Hz), 120.1 – 108.8 (m, -<u>C</u>F$_2$<u>C</u>F$_2$<u>C</u>F$_3$), 107.7, 37.0, 35.8, 31.5, 28.9, 22.6, 22.4, 20.0, 14.0. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -81.09 (t, *J* = 10.3 Hz, 3F), -106.70 – -110.98 (m, 2F), -124.05 (m, 2F). IR (neat, cm^{-1}) 2946, 2861, 1794, 1458, 1375, 1340, 1230, 1183, 1114, 956, 914, 750, 702; HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{21}F_7NO_3$ [M+H]$^+$: 396.1404; found: 396.1396.



(*Z*)-5-hexyl-2-methyl-5-(3,3,4,4,4-pentafluoro-2-methylbut-1-en-1-yl)-1,4,2-dioxazolidin-3-one (19p)

colorless oil; yield 81%; *Z/E* = 84/16; R$_f$ 0.3 (hexanes/EtOAc = 10/1);
^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.07 (q, *J* = 1.4 Hz, 1H), 3.09 (s, 3H), 2.10 – 1.95 (m, 5H), 1.50 – 1.39 (m, 2H), 1.37 – 1.20 (m, 6H), 0.98 – 0.81 (m, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 157.7,

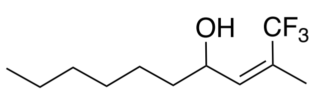
137.7, 129.3 (t, J_{C-F} = 23.1 Hz), 123.3 – 109.9 (m, -$\underline{C}F_2\underline{C}F_3$), 107.7, 36.9 (t, *J* = 3.6 Hz), 35.8, 31.5, 28.9, 22.6, 22.4, 20.0, 14.0. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -82.63(s, 3F), -112.06 (d, *J* = 64.3 Hz, 2F). IR (neat, cm^{-1}) 2958, 2935, 2860, 1795, 1457, 1374, 1328, 1196, 1131, 1109, 1010, 751, 684; HRMS (ESI$^+$) *m/z* calcd for $C_{14}H_{21}F_5NO_3$ [M+H]$^+$: 346.1436; found: 346.1426.



(*Z*)-5-(3,3-difluoro-2-methylprop-1-en-1-yl)-5-hexyl-2-methyl-1,4,2-dioxazolidin-3-one (19q)

colorless oil; yield 86%; *Z/E* = 78/22; R_f 0.4 (hexanes/EtOAc = 10/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.75 (t, *J* = 55.5 Hz, 1H), 5.70 (ddq, *J* = 2.3, 1.5, 0.8 Hz, 1H), 3.20 – 3.10 (m, 3H), 2.01 – 1.88 (m, 5H), 1.51 – 1.24 (m, 8H), 0.95 – 0.86 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 157.4, 135.3, 130.3 (t, J_{C-F} = 8.9 Hz), 110.8 (t, J_{C-F} = 234.0 Hz), 107.7, 37.5, 36.1, 31.5, 28.9, 22.5, 15.7 (t, *J* = 3.3 Hz), 14.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -118.42 (d, *J* = 55.7 Hz). IR (neat, cm^{-1}) 2957, 2933, 1794, 1455, 1334, 1173, 1096, 1026, 960, 769; HRMS (ESI$^+$) *m/z* calcd for $C_{13}H_{22}F_2NO_3$ [M+Na]$^+$: 300.1382; found: 300.1375.



(Z)-1,1,1-trifluoro-2-methyldec-2-en-4-ol (**34**)

To a solution of ketal (*Z*)-**19i** (221 mg, 0.75 mmol) in DCM (10 mL) was added DIBAL (0.27 mL, 1.5 mmol) at -78 °C. After stirring at -78 °C for 1 h, the reaction mixture was quenched by the addition of NH_4Cl (sat. aq.) at −78 °C and allowed to warm to room temperature. The product was extracted with DCM (×3) and the combined organic extracts were washed with brine, and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo* and the crude oil was purified by flash column chromatography (hexanes/EtOAc = 10/1) afforded the allylic alcohol (*Z*)-**34** (138 mg, 82%) as a colorless oil.

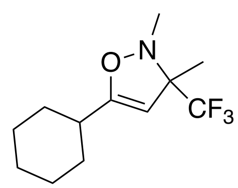
R_f 0.4 (hexanes/EtOAc = 10/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.70 – 5.67 (m, 1H), 4.33 – 4.25 (m, 1H), 1.90 (d, *J* = 1.5 Hz, 3H), 1.86 – 1.52 (m, 6H), 1.43 – 0.84 (m, 7H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 138.1 (q, J_{C-F} = 3.0 Hz), 126.7 (q, J_{C-F} = 29.9 Hz), 123.9 (q, J_{C-F} = 275.5 Hz), 71.7 (d, J_{C-F} = 2.3 Hz), 43.7, 28.6, 28.4, 26.4, 26.0, 25.9, 18.5 (q, J_{C-F} = 2.7 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -60.76.

4.6 Synthesis of Fluorine Containing 4-Isoxazolines

Preparation of a standard solution of the active gold catalyst:[10] A mixture of (2-*t*-Bu-PhO)$_3$PAuCl (35 mg, 0.05 mmol, 5 mol%) and AgNTf$_2$ (19 mg, 0.05 mmol, 5 mol%) in DCM (2 mL) was stirred at room temperature for 30 min.

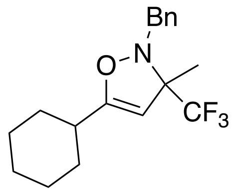
Typical procedure for the synthesis of **20a**, **20d-20h**, **20j-20l**, **20r**: A mixture of active gold catalyst and activated 4 Å MS (2g, 2 g/mmol) was stirred for 10 min at room temperature under argon. To this mixture was added a solution of carbamate **18a** (293 mg, 1 mmol) in DCM (2 mL), followed by HFIP (42 μL, 40 mol%). The reaction was monitored by TLC. After the completion of the reaction, the volatiles were removed *in vacuo* and the product was purified by flash column chromatography (hexanes/EtOAc = 30/1) to provide 4-isoxazoline **20a** (209 mg, 87%) as a colorless oil.



5-cyclohexyl-2,3-dimethyl-3-(trifluoromethyl)-2,3-dihydroisoxazole (20a)

R_f 0.35 (hexanes/EtOAc = 25/1);

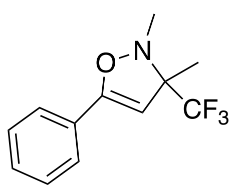
^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.32 (s, 1H), 2.70 (s, 3H), 2.24 – 2.06 (m, 1H), 1.95 – 1.59 (m, 5H), 1.38 (s, 3H), 1.34 – 1.12 (m, 5H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 163.4, 125.8 (q, J_{C-F} = 283.9 Hz), 90.0, 73.6 (q, J_{C-F} = 28.4 Hz), 40.4, 35.2, 30.4, 30.3, 26.0, 25.6, 14.6 (q, J_{C-F} = 1.4 Hz). ^{19}F NMR (282 MHz, Chloroform-*d*) δ = -82.25. IR (neat, cm^{-1}) 2932, 2857, 1670, 1452, 1303, 1172, 1148, 1133, 1105, 1009, 717; HRMS (ESI$^+$) *m/z* calcd for $C_{12}H_{19}F_{23}NO$ [M+H]$^+$: 250.1413; found: 250.1407.



2-benzyl-5-cyclohexyl-3-methyl-3-(trifluoromethyl)-2,3-dihydroisoxazole (20d)

Colorless oil; yield 69%; R_f 0.3 (hexanes/EtOAc = 30/1);

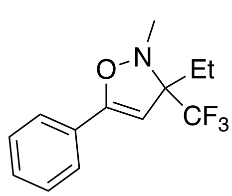
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.58 – 7.28 (m, 5H), 4.45 (d, *J* = 1.1 Hz, 1H), 4.18 – 3.88 (m, 2H), 2.25 – 2.02 (m, 1H), 1.99 – 1.62 (m, 5H), 1.53 (s, 3H), 1.37 – 1.15 (m, 5H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 163.5, 137.4, 128.8, 128.4, 127.3, 125.8 (q, $J_{C\text{-}F}$ = 282.8 Hz) 90.7, 73.6 (q, $J_{C\text{-}F}$ = 28.5 Hz), 57.4, 35.2, 30.7, 30.3, 26.0, 25.7, 25.7, 15.7, 15.6. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -81.78. IR (neat, cm^{-1}) 2932, 2855, 1670, 1497, 1453, 1299, 1205, 1172, 1149, 1109, 944, 729, 717, 696; HRMS (ESI^{+}) *m/z* calcd for $C_{18}H_{23}F_3NO$ $[M+H]^+$: 326.1726; found: 326.1719.



2,3-dimethyl-5-phenyl-3-(trifluoromethyl)-2,3-dihydroisoxazole (20e)

White soild; yield 92%; R_f 0.3 (hexanes/EtOAc = 25/1); m.p. 57 – 60 ^{o}C;

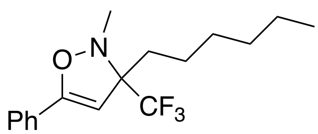
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 (m, 2H), 7.37 (m, 3H), 5.07 (s, 1H), 2.86 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 155.8, 129.8, 128.4, 125.9, 125.7 (q, $J_{C\text{-}F}$ = 284.8 Hz), 125.2, 92.1, 74.4 (q, $J_{C\text{-}F}$ = 28.5 Hz), 40.6, 14.7. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -81.45. IR (neat, cm^{-1}) 3055, 2987, 1655, 1494, 1449, 1301, 1265, 1170, 1104, 1015, 739, 704; HRMS (ESI^{+}) *m/z* calcd for $C_{12}H_{13}F_3NO$ $[M+H]^+$: 244.0944; found: 244.0943.



3-ethyl-2-methyl-5-phenyl-3-(trifluoromethyl)-2,3-dihydroisoxazole (20f)

Colorless oil; yield 80%; R_f 0.32 (hexanes/EtOAc = 25/1);

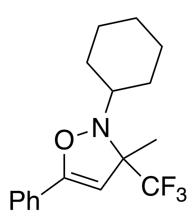
^{1}H NMR (500 MHz, Benzene-d_6) δ 7.50 – 7.31 (m, 2H), 7.08 – 6.93 (m, 3H), 4.82 (s, 1H), 2.71 (s, 3H), 1.64 – 1.45 (m, 2H), 0.85 (t, J = 7.5, 3H). ^{13}C NMR (125 MHz, Benzene-d_6) δ 156.3, 129.4, 128.2, 128.0, 125.8, 124.1 (d, J_{C-F} = 289.8 Hz), 90.8, 77.0 (q, J_{C-F} = 26.3 Hz), 38.7, 22.5, 8.7. ^{19}F NMR (470 MHz, Benzene-d_6) δ -75.90. IR (neat, cm^{-1}) 2977, 2945, 2904, 1655, 1494, 1449, 1251, 1175, 1143, 1114, 739, 721, 689; HRMS (ESI$^+$) m/z calcd for $C_{13}H_{15}F_3NO$ [M+H]$^+$: 258.1100; found: 258.1098.



3-hexyl-2-methyl-5-phenyl-3-(trifluoromethyl)-2,3-dihydroisoxazole (20h)

Colorless oil; yield 82%; R_f 0.3 (hexanes/EtOAc = 30/1);

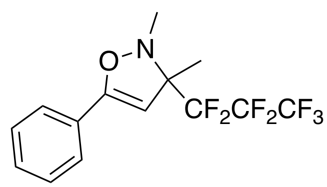
^{1}H NMR (300 MHz, Chloroform-d) δ 7.78 – 7.52 (m, 2H), 7.40 (m, 3H), 5.15 (s, 1H), 3.02 (s, 3H), 2.03 – 1.73 (m, 2H), 1.60 – 1.47 (m, 2H), 1.44 – 1.24 (m, 6H), 1.04 – 0.81 (m, 3H). ^{13}C NMR (75 MHz, Chloroform-d) δ 155.9, 129.7, 128.5, 127.7, 125.9 (q, J_{C-F} = 286.5 Hz), 125.8, 91.3 (q, J_{C-F} = 1.3 Hz), 76.8 (q, J_{C-F} = 26.3 Hz), 39.5, 31.6, 29.9, 29.8, 24.6, 22.6, 14.1. ^{19}F NMR (282 MHz, Chloroform-d) δ -76.61. IR (neat, cm^{-1}) 2956, 2930, 2858, 1655, 1449, 1329, 1265, 1170, 1133, 771, 725, 689; HRMS (ESI$^+$) m/z calcd for $C_{17}H_{23}F_3NO$ [M+H]$^+$: 314.1726; found: 314.1716.



2-cyclohexyl-3-methyl-5-phenyl-3-(trifluoromethyl)-2,3-dihydroisoxazole (20j)

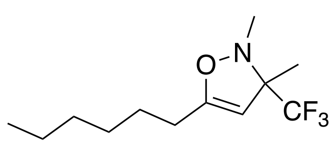
Colorless oil; yield 71%; R_f 0.3 (hexanes/EtOAc = 30/1);

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.52 – 7.38 (m, 2H), 7.09 – 6.96 (m, 3H), 4.81 (s, 1H), 2.65 (tt, *J* = 10.9, 3.3 Hz, 1H), 2.18 – 2.06 (m, 1H), 1.82 (m, 1H), 1.72 – 1.63 (m, 2H), 1.53 – 1.34 (m, 3H), 1.28 (d, *J* = 1.2 Hz, 3H), 1.11 (qt, *J* = 13.1, 3.7 Hz, 1H), 1.04 – 0.85 (m, 2H). ^{13}C NMR (150 MHz, Chloroform-*d*) δ 157.1, 129.6, 128.5, 127.3, 125.9, 125.7 (q, $J_{C\text{-}F}$ = 285.4 Hz), 93.5, 73.9 (q, $J_{C\text{-}F}$ = 28.4 Hz), 62.6, 32.8, 27.7, 26.1, 25.7, 25.2, 14.6. ^{19}F NMR (470 MHz, Benzene-d_6) δ -82.91. IR (neat, cm^{-1}) 2938, 2856, 1654, 1494, 1449, 1277, 1181, 1146, 1107, 771, 723; HRMS (ESI$^+$) *m/z* calcd for $C_{17}H_{21}F_3NO$ [M+H]$^+$: 312.1570; found: 312.1571.



2,3-dimethyl-3-(perfluoropropyl)-5-phenyl-2,3-dihydroisoxazole (20k)

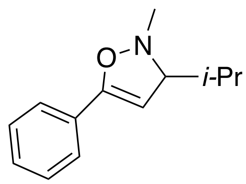
White solid; yield 77%; R$_f$ 0.3 (hexanes/EtOAc = 25/1); m.p. 66 – 68 ^{o}C;
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.61 – 7.51 (m, 2H), 7.41 – 7.34 (m, 3H), 5.08 (d, *J* = 1.6 Hz, 1H), 2.87 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 155.5, 129.8, 128.5, 127.5, 125.9, 121.4 – 106.6 (m, -$\underline{C}F_2\underline{C}F_2\underline{C}F_3$), 92.5, 76.2 (t, $J_{C\text{-}F}$ = 23.3 Hz), 40.4, 15.4. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -81.02 (t, *J* = 10.8 Hz, 3F), -119.80 – -121.30 (m, 2F), -123.48 (dd, *J* = 88.2, 7.9 Hz, 2F). IR (neat, cm^{-1}) 3063, 3004, 2925, 1657, 1449, 1346, 1227, 1196, 1176, 1115, 1101, 748, 728, 689; HRMS (ESI$^+$) *m/z* calcd for $C_{14}H_{13}F_7NO$ [M+H]$^+$: 344.0880; found: 344.0878.



5-hexyl-2,3-dimethyl-3-(trifluoromethyl)-2,3-dihydroisoxazole (20l)

Colorless oil; yield 79%; R$_f$ 0.34 (hexanes/EtOAc = 25/1);
^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.37 (s, 1H), 2.73 (s, 3H), 2.20 – 2.07 (m, 2H), 1.50 (sept, *J* = 6.9 Hz, 2H), 1.41 – 1.36 (m, 3H), 1.36 – 1.22 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz,

Chloroform-*d*) δ 159.1, 125.7 (q, J_{C-F} = 284.0 Hz), 92.0, 73.7 (q, J_{C-F} = 28.5 Hz), 40.5, 31.4, 28.6, 26.4, 25.7, 22.5, 14.7, 14.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -82.03. IR (neat, cm^{-1}) 2957, 2932, 2861, 1676, 1469, 1437, 1379, 1304, 1175, 1132, 1104, 720; HRMS (ESI$^+$) *m/z* calcd for $C_{12}H_{21}F_3NO$ [M+H]$^+$: 252.1570; found: 252.1564.

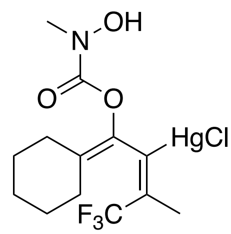


3-isopropyl-2-methyl-5-phenyl-2,3-dihydroisoxazole (20r)

Colorless oil; yield 85%; R_f 0.3 (hexanes/EtOAc = 25/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.69 – 7.52 (m, 2H), 7.49 – 7.30 (m, 3H), 5.24 (d, *J* = 2.7 Hz, 1H), 3.51 (dd, *J* = 6.4, 2.7 Hz, 1H), 2.85 (s, 3H), 1.92 – 1.62 (m, *J* = 6.7 Hz, 1H), 0.98 (t, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 152.1, 129.2, 128.8, 128.3, 125.6, 93.0, 79.8, 48.1, 33.8, 18.6, 18.3. IR (neat, cm^{-1}) 2957, 2928, 2869, 1653, 1493, 1448, 1275, 1047, 1023, 767, 720, 690; HRMS (ESI$^+$) *m/z* calcd for $C_{13}H_{18}NO$ [M+H]$^+$: 204.1383; found: 204.1378.

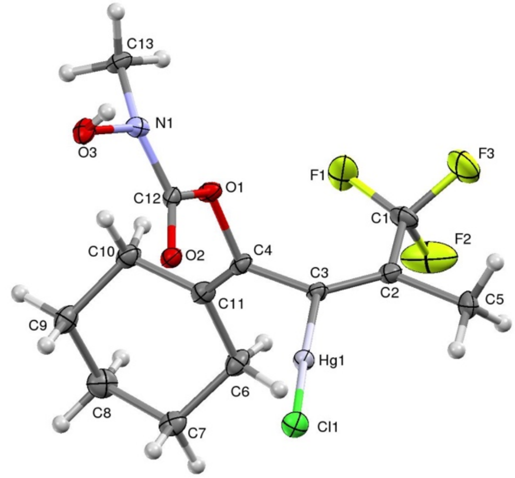
4.7 Synthesis of Trifluoromethyl Dienes

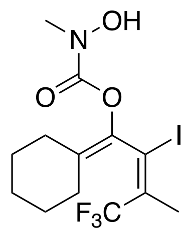


(E)-(1-cyclohexylidene-4,4,4-trifluoro-1-((hydroxy(methyl)carbamoyl)oxy)-3-methylbut-2-en-2-yl)mercury(II) chloride (**35**)

To a solution of allene **29a** (210 mg, 0.72 mmol) in THF (7 mL) was added $Hg(OCOCF_3)_2$ (305 mg, 0.72 mmol) at -30 ^oC. After stirring at -30 ^oC for 5 h, the reaction mixture was quenched with NaCl (sat. aq.). The product was extracted with Et_2O (x3) and the combined extracts were washed with brine, and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo* and the crude oil was purified by flash column chromatography (hexanes/EtOAc = 5/1) to afford **35** (200 mg, 53%) as a white solid.

R_f 0.3 (hexanes/EtOAc = 5/1); m.p. 137 – 138 ^oC;
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.39 (brs, 1H), 3.33 (s, 3H), 2.35 – 1.97 (m, 7H), 1.55 (d, *J* = 9.9 Hz, 6H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 156.3, 153.0, 135.1 (q, $J_{C\text{-}F}$ = 27.8 Hz), 135.0, 128.9, 123.2 (q, $J_{C\text{-}F}$ = 279.2 Hz), 37.9, 29.6, 27.0, 26.6, 26.3, 26.0, 23.1. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -62.77.
The structure of **35** was confirmed by X-ray.





(E)-1-cyclohexylidene-4,4,4-trifluoro-2-iodo-3-methylbut-2-en-1-yl hydroxy(methyl)carbamate (**36**)

To a solution of allene **29a** (141 mg, 0.5 mmol) in DCE (5 mL) was added 4 Å MS (2 g/mmol) at 45 ^{o}C. After stirring for 10 min, I_2 was added (127 mg, 0.5 mmol). The reaction was monitored by ^{19}F NMR. After 2.5 h, the reaction mixture was quenched with $Na_2S_2O_3$ (sat. aq.). The product was extracted with DCM (×3) and the combined extracts were washed by brine, and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo* and the crude oil was purified by flash column chromatography (hexanes/EtOAc = 5/1) afforded **36** (136 mg, 65%) as a white foam.

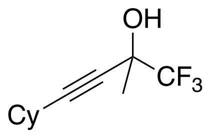
R_f 0.3 (hexanes/EtOAc = 5/1);

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.38 (brs, 1H), 3.31 (s, 3H), 2.17 (s, 3H), 2.12 (q, *J* = 5.7 Hz, 3H), 1.74 – 1.41 (m, 7H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 155.1, 135.4, 135.0 (q, J_{C-F} = 29.2 Hz), 132.4, 120.7 (q, J_{C-F} = 277.5 Hz), 104.1, 38.0 (q, J_{C-F} = 4.9 Hz), 30.3, 28.1, 26.3, 26.0, 25.9, 24.6.

^{19}F NMR (282 MHz, Chloroform-*d*) δ -62.69. HRMS (ESI$^+$) *m/z* calcd for $C_{13}H_{18}INO_3$ $[M+H]^+$: 420.0278; found: 420.0271.

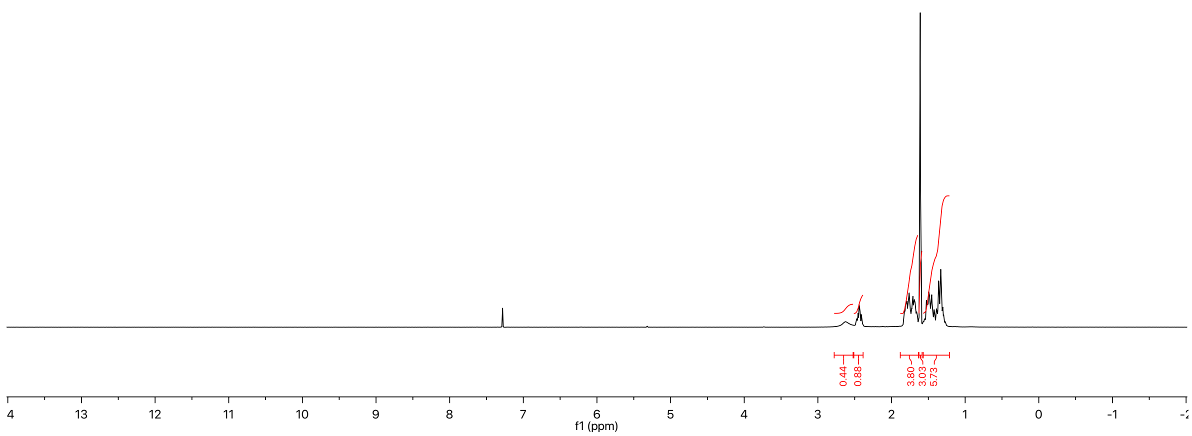
Appendix: NMR Spectra

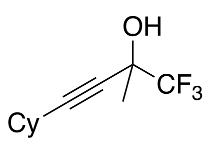
NMR spectrums for tertiary propargyl alcohols (**17a**, **17b**, **17e**-**17i**, **17k**, **17l**, **17n**-**17q**).



17a

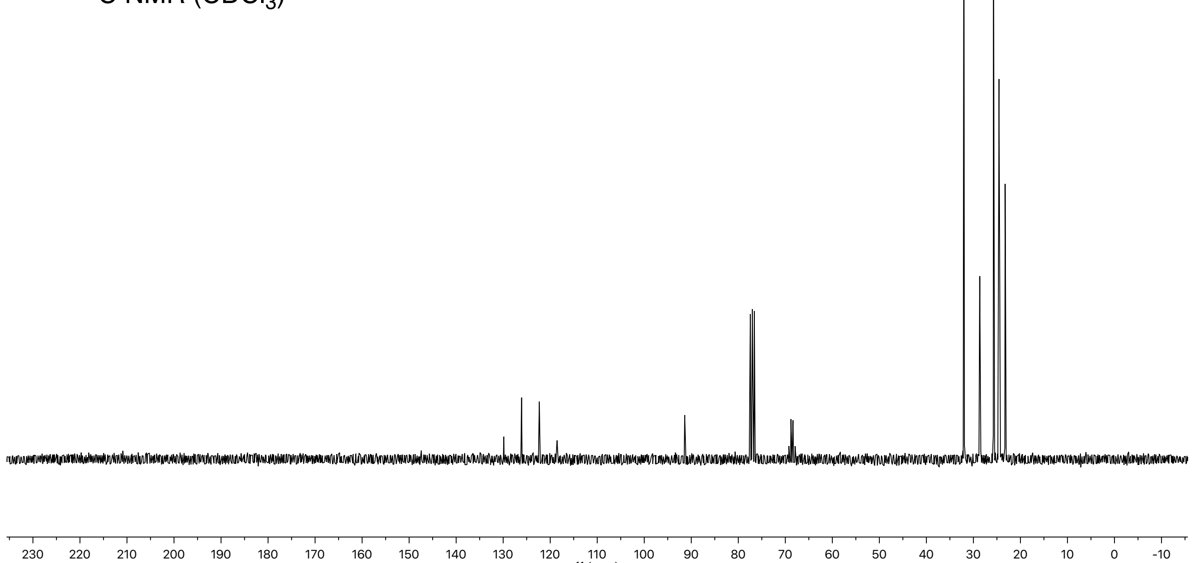
^{1}H NMR ($CDCl_3$)

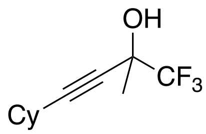




17a

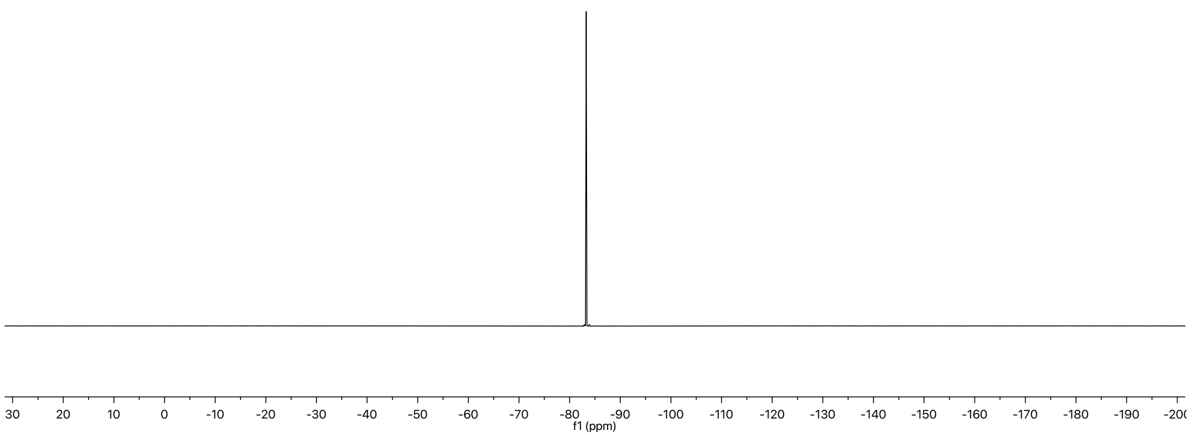
^{13}C NMR ($CDCl_3$)



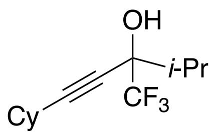


17a

^{19}F NMR ($CDCl_3$)

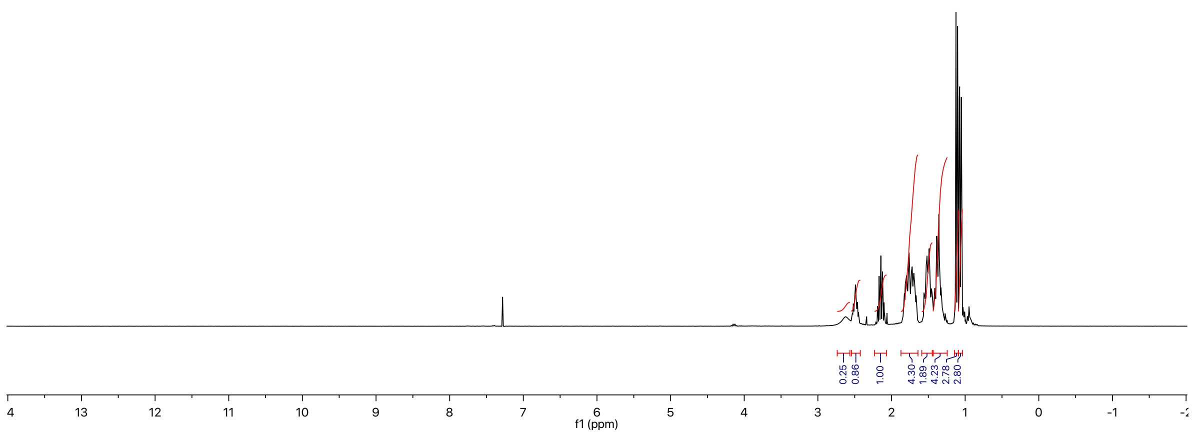


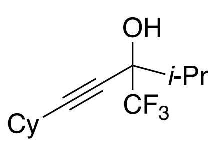
1029



17b

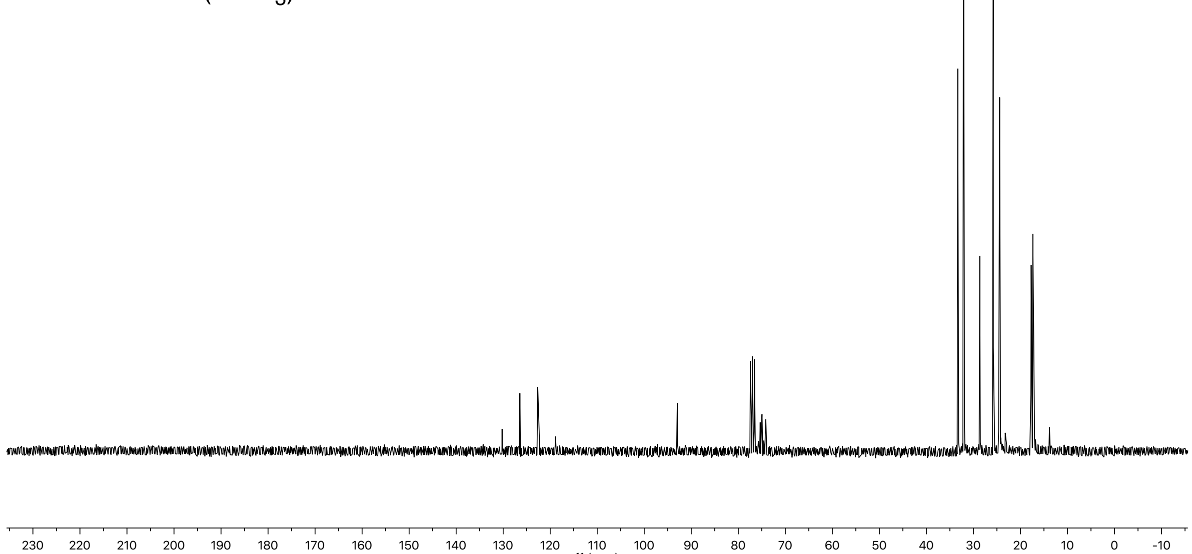
^{1}H NMR ($CDCl_3$)

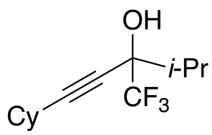




17b

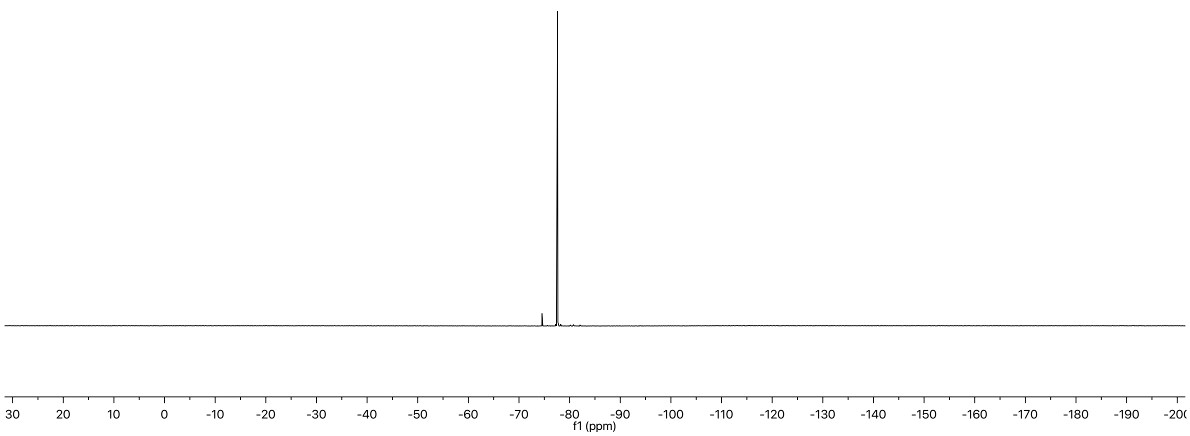
^{13}C NMR ($CDCl_3$)



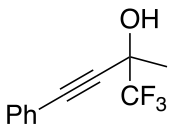


17b

^{19}F NMR ($CDCl_3$)

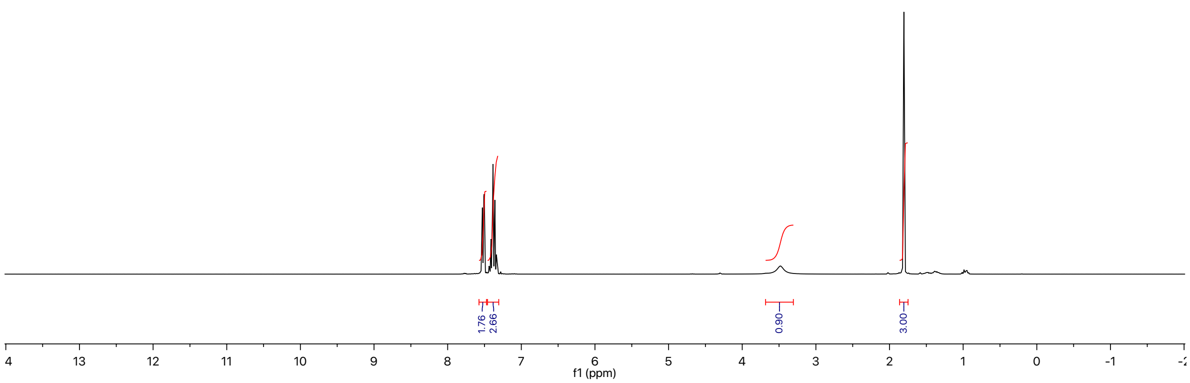


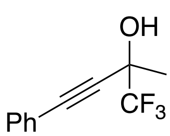
1035



17e

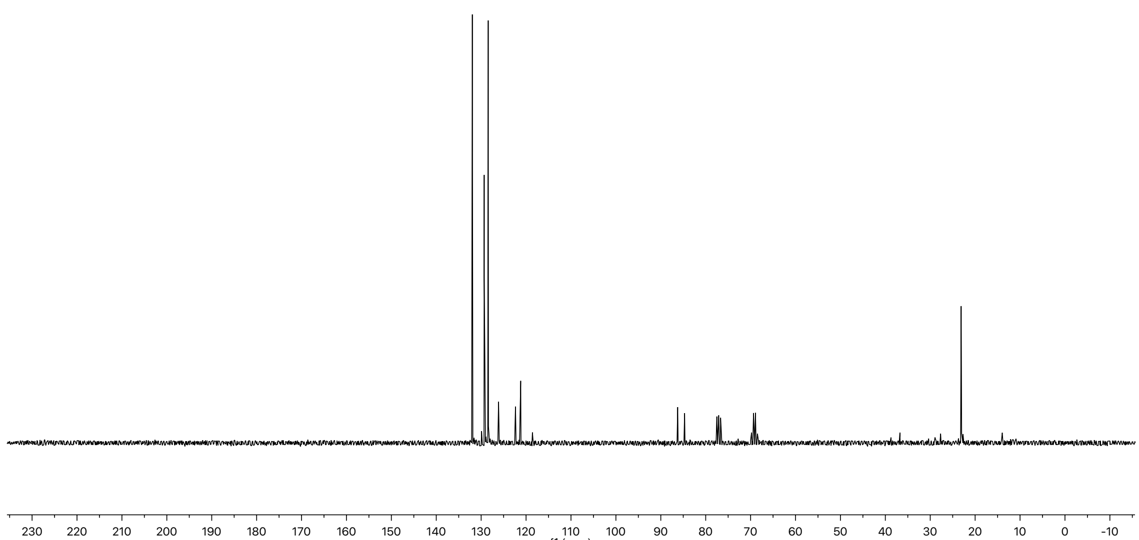
^{1}H NMR ($CDCl_3$)

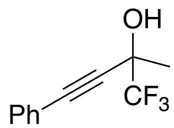




17e

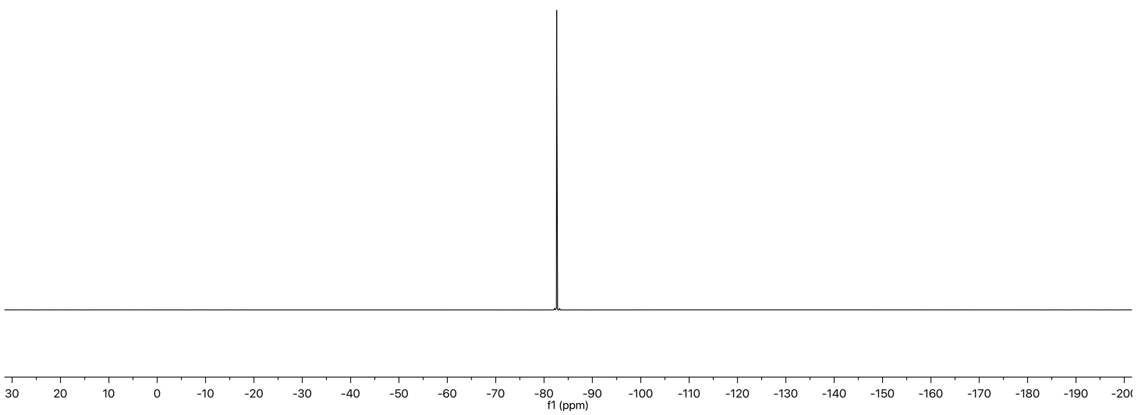
^{13}C NMR ($CDCl_3$)



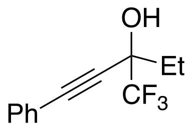


17e

^{19}F NMR ($CDCl_3$)

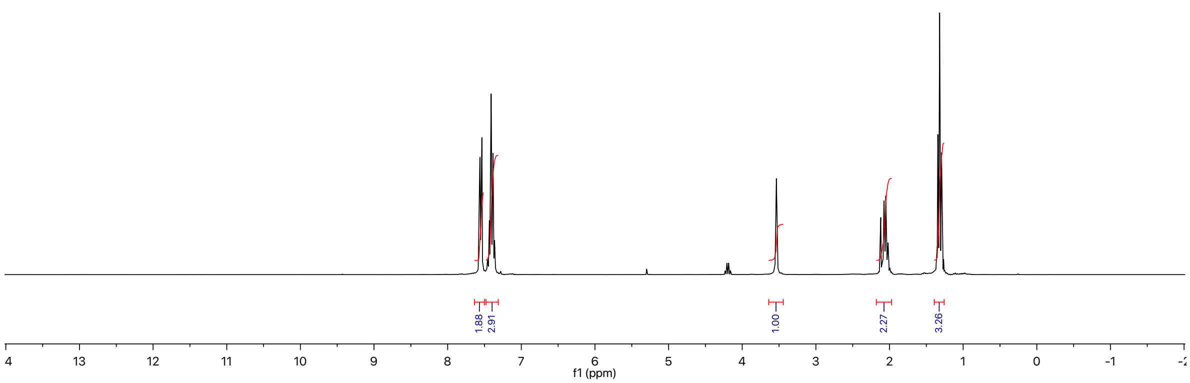


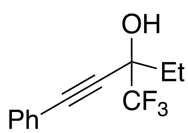
1006



17f

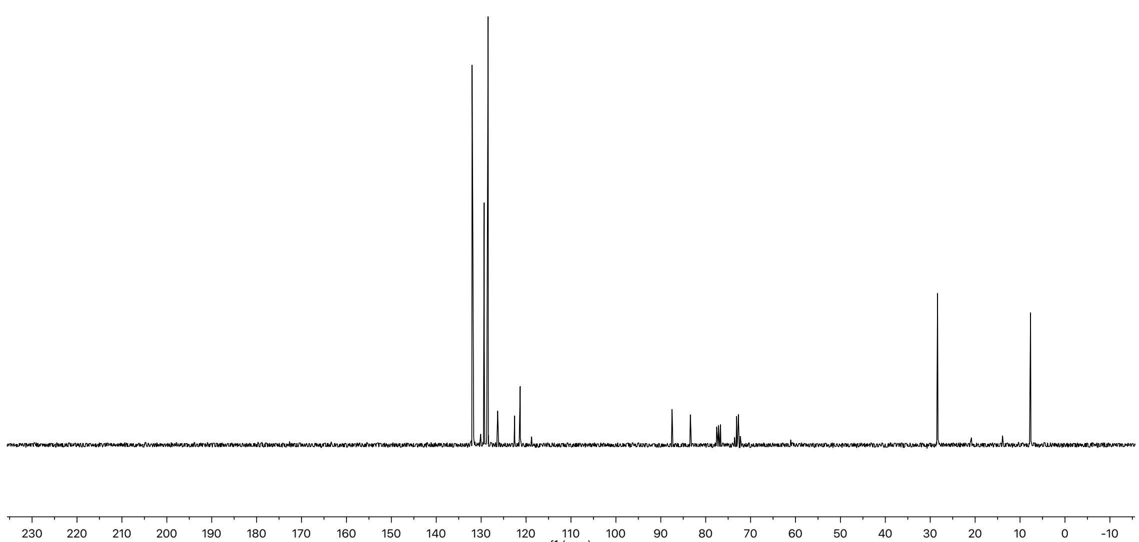
^{1}H NMR ($CDCl_3$)

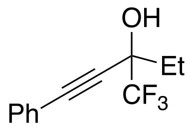




17f

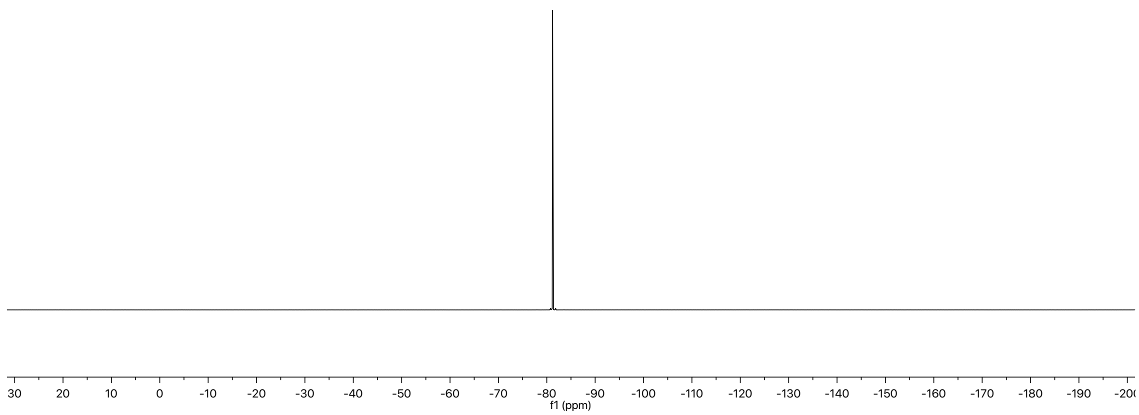
^{13}C NMR ($CDCl_3$)



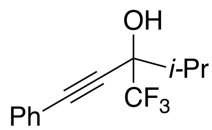


17f

^{19}F NMR ($CDCl_3$)

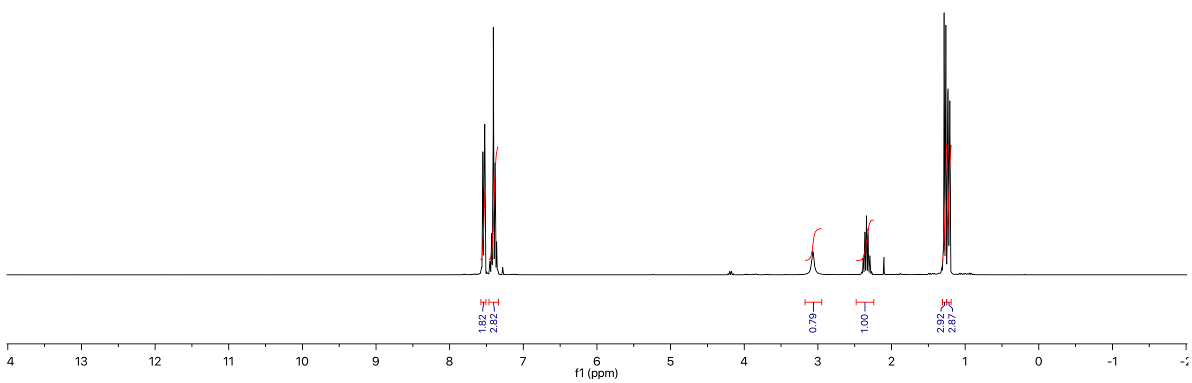


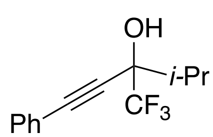
1007



17g

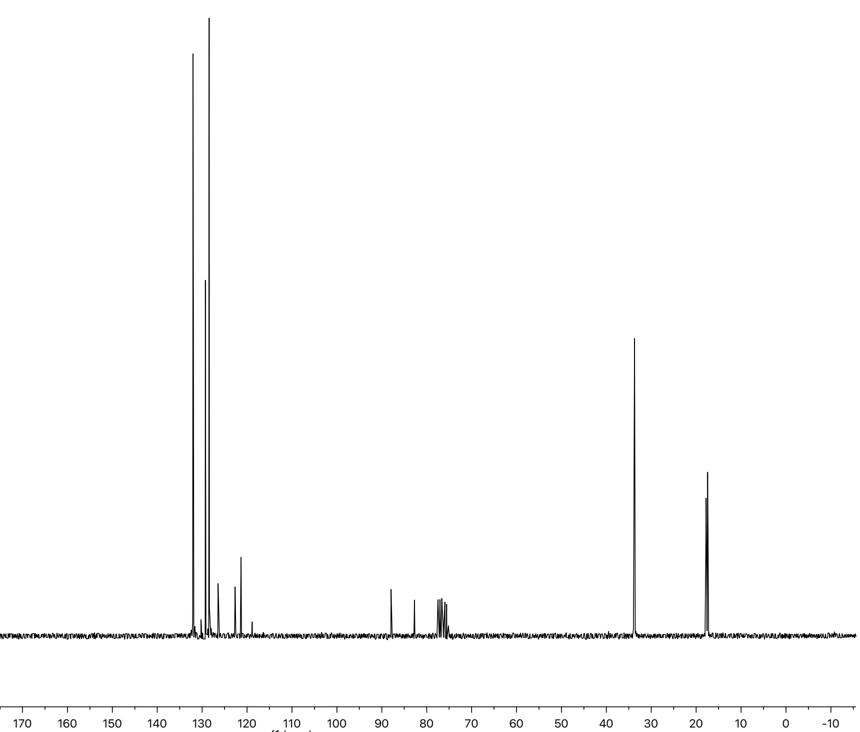
^{1}H NMR ($CDCl_3$)

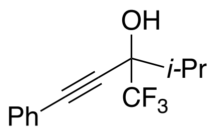




17g

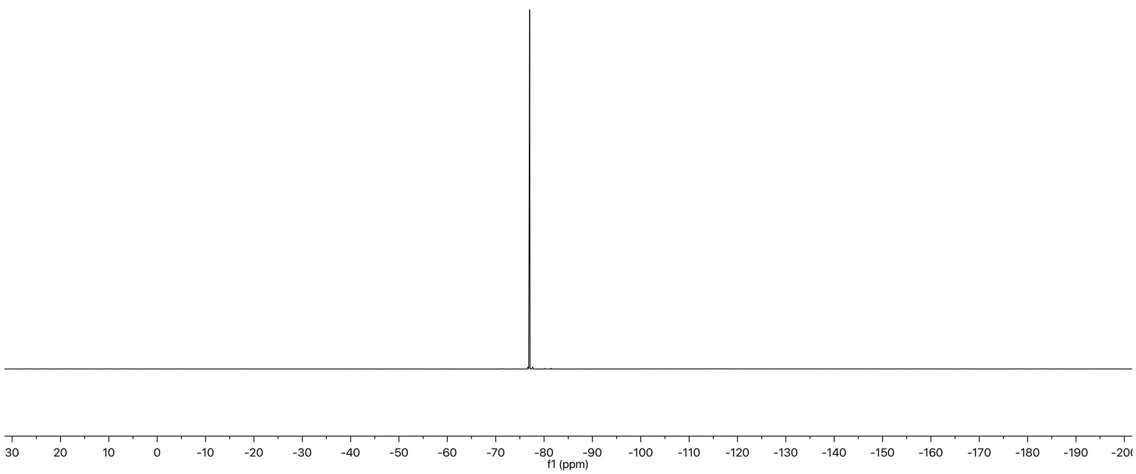
^{13}C NMR ($CDCl_3$)



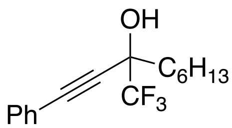


17g

^{19}F NMR ($CDCl_3$)

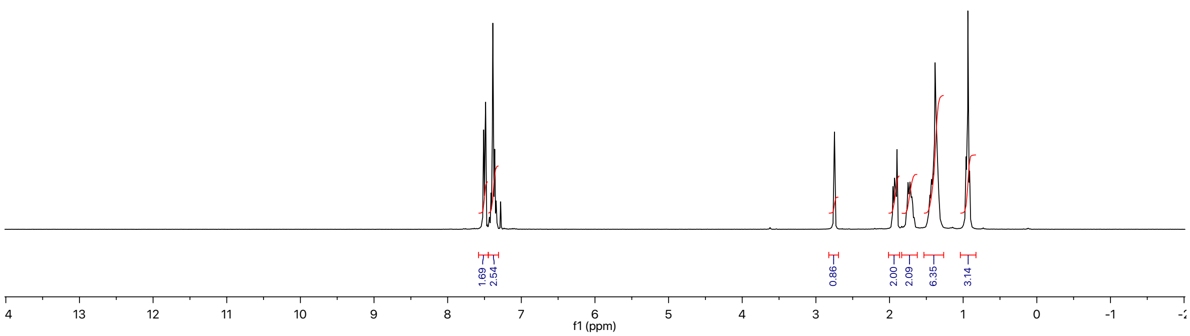


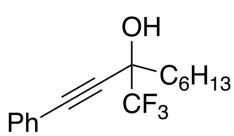
809



17h

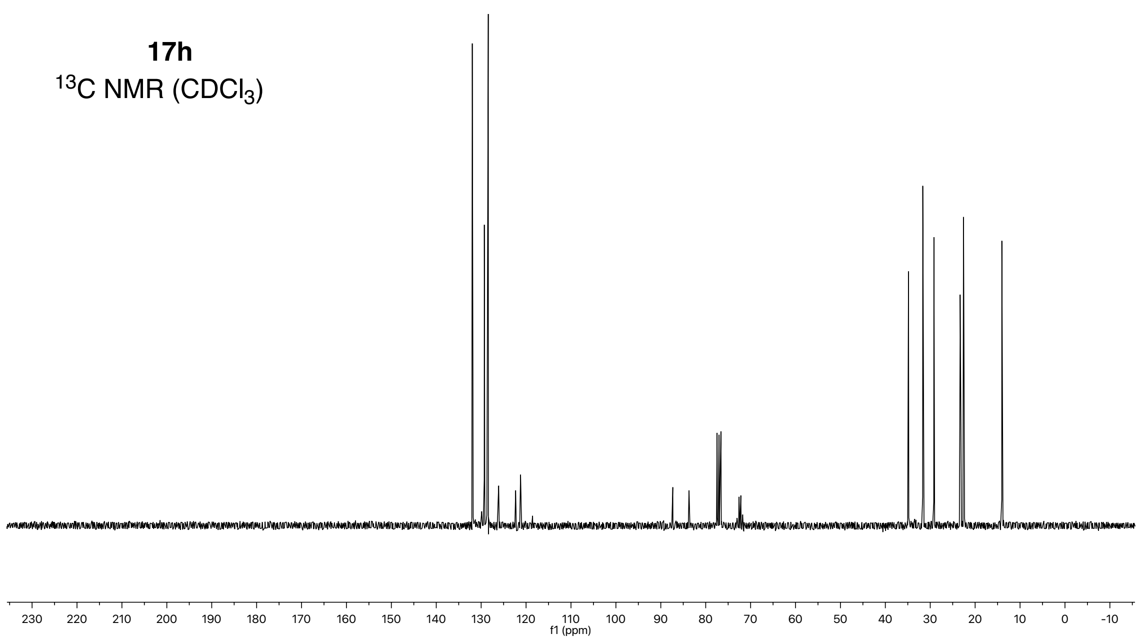
^{1}H NMR ($CDCl_3$)

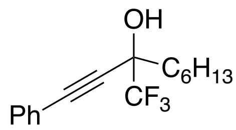




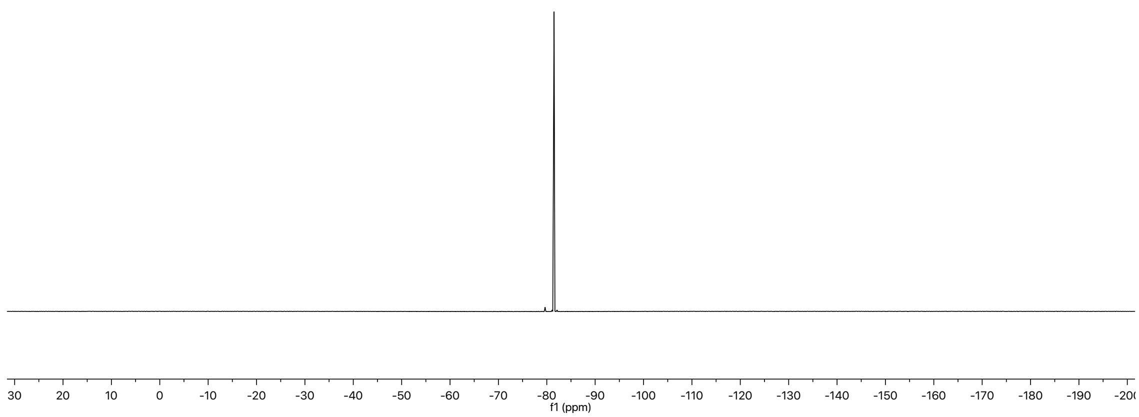
17h

^{13}C NMR ($CDCl_3$)

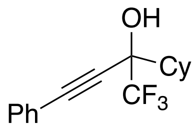




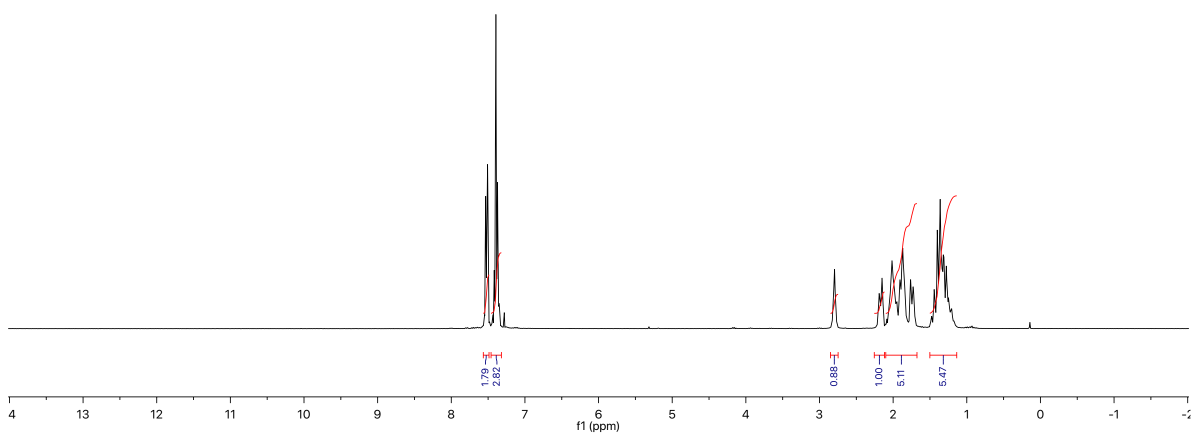
17h
^{19}F NMR ($CDCl_3$)

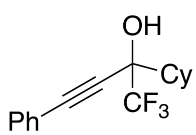


1059

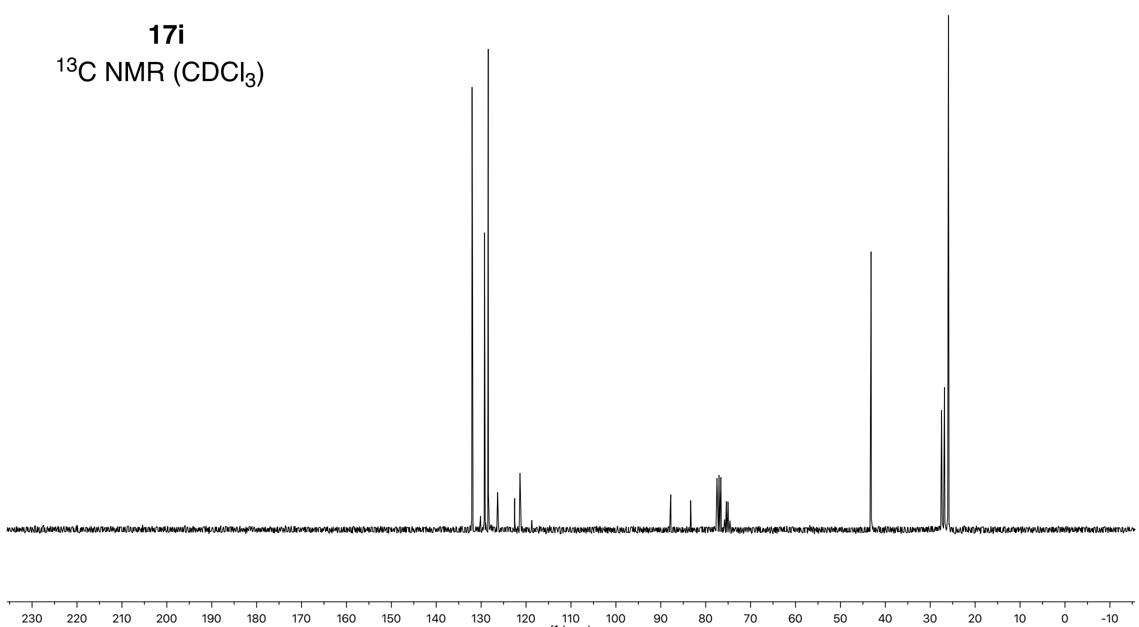


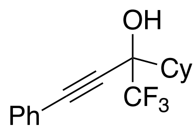
17i
^{1}H NMR ($CDCl_3$)





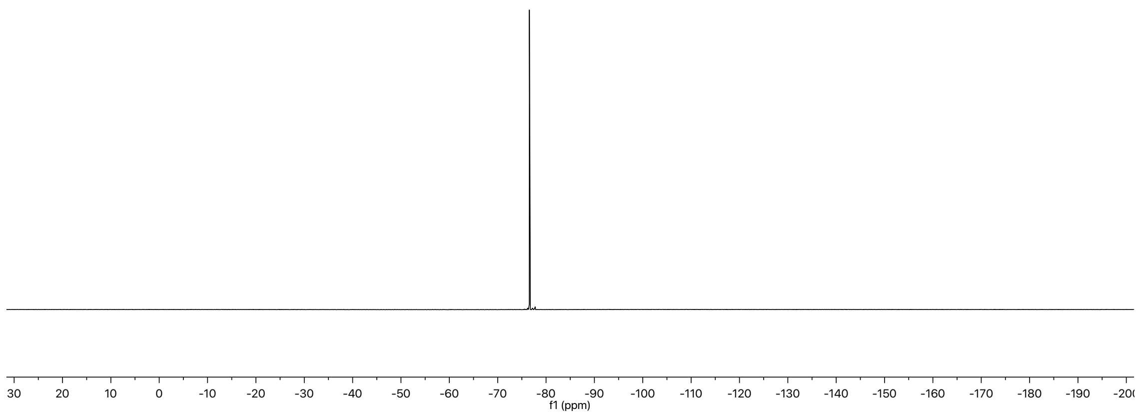
17i
^{13}C NMR ($CDCl_3$)



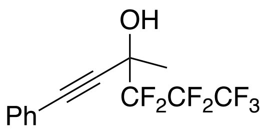


17i

^{19}F NMR ($CDCl_3$)

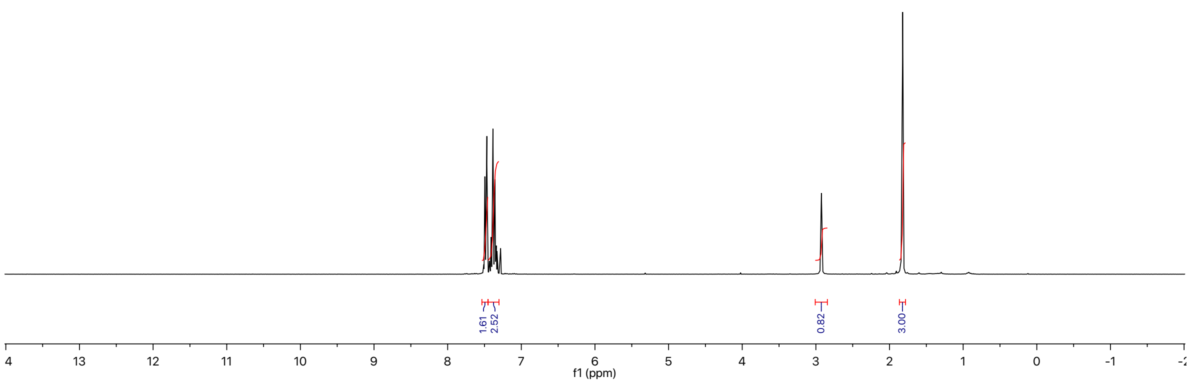


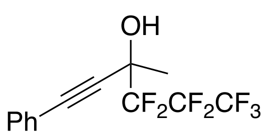
920



17k

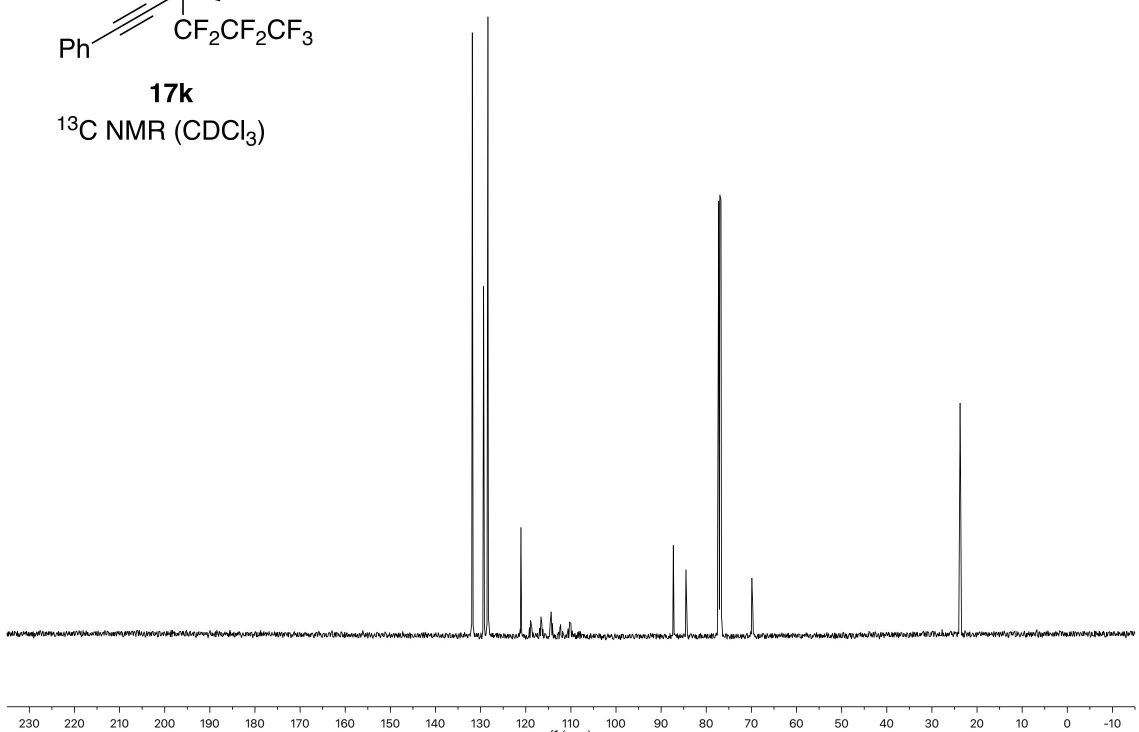
^{1}H NMR ($CDCl_3$)

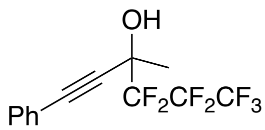




17k

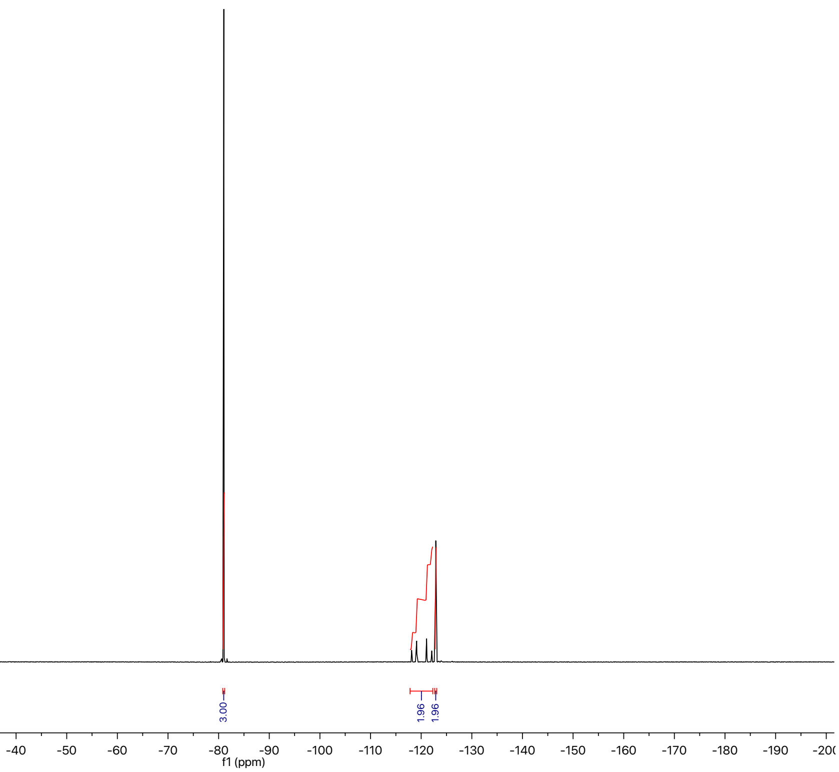
^{13}C NMR ($CDCl_3$)



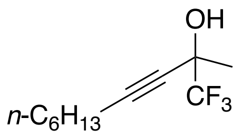


17k

^{19}F NMR ($CDCl_3$)

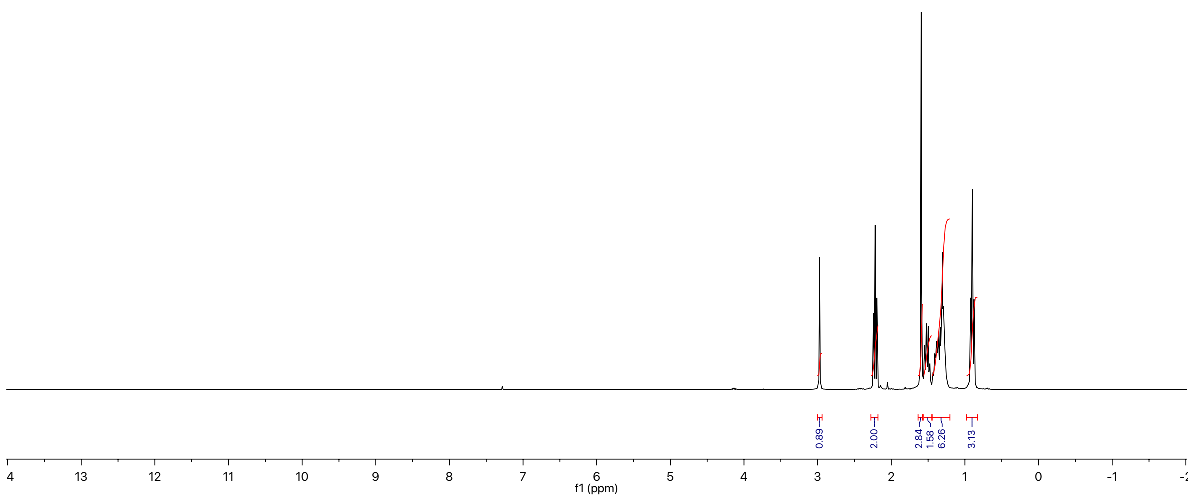


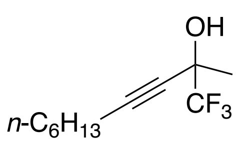
1044



17l

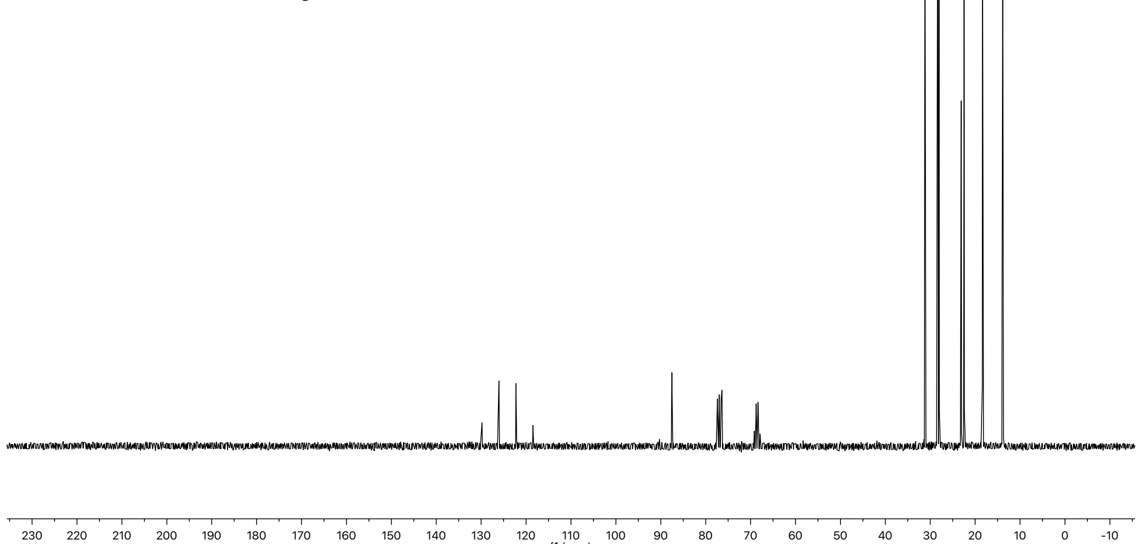
^{1}H NMR ($CDCl_3$)

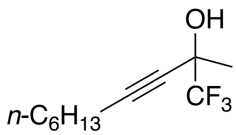




17l

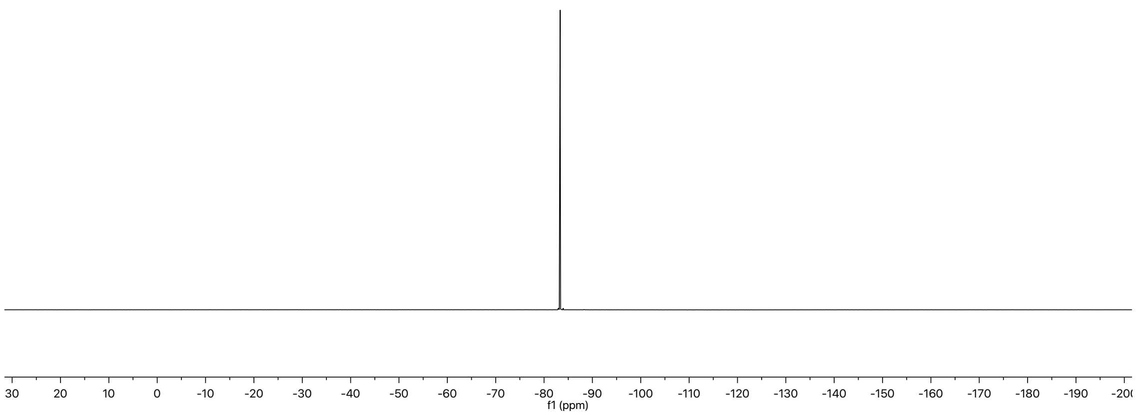
^{13}C NMR ($CDCl_3$)



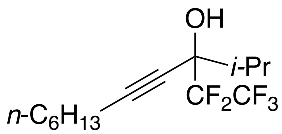


17l

^{19}F NMR ($CDCl_3$)

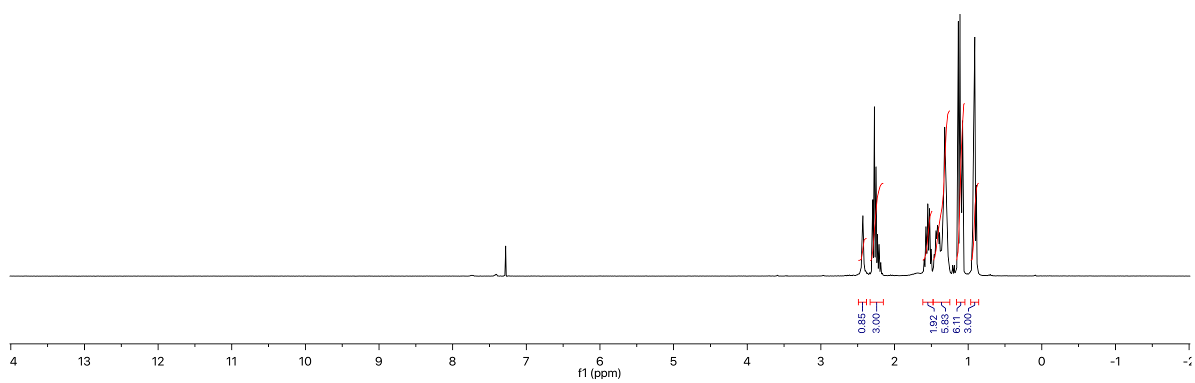


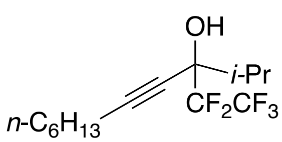
1038



17n

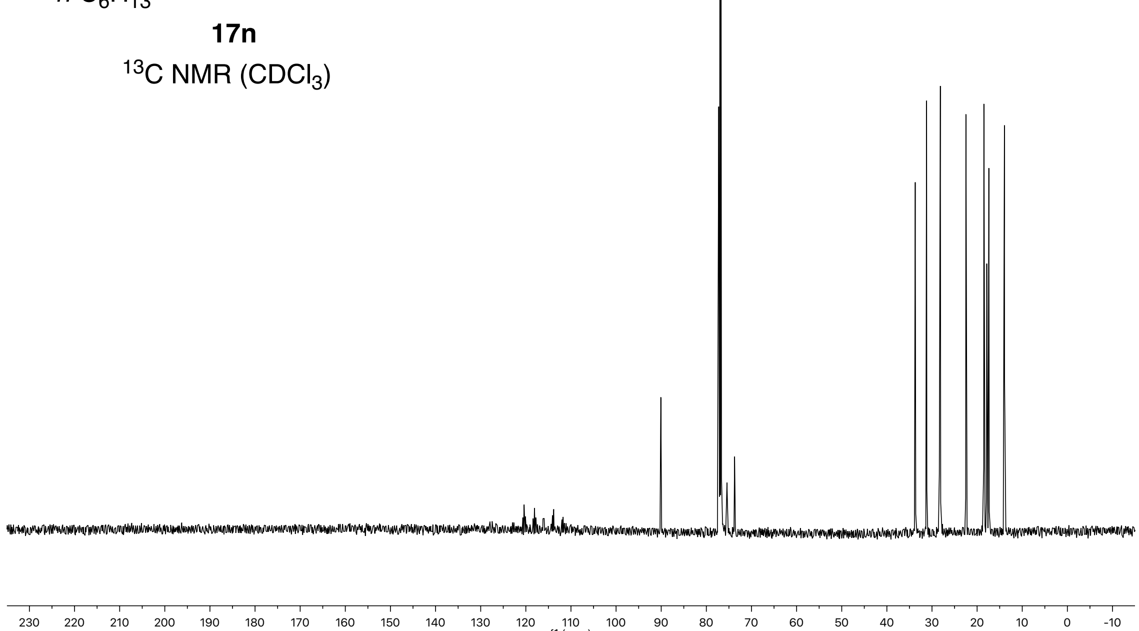
^{1}H NMR ($CDCl_3$)

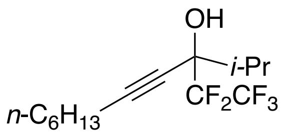




17n

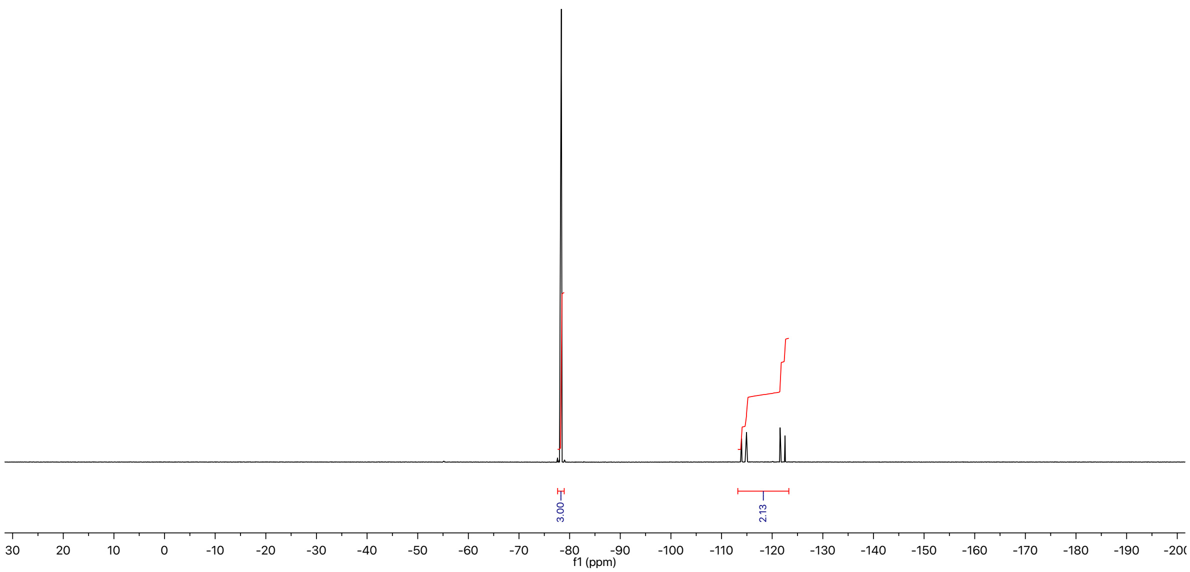
^{13}C NMR ($CDCl_3$)



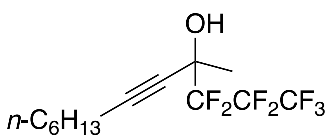


17n

^{19}F NMR ($CDCl_3$)

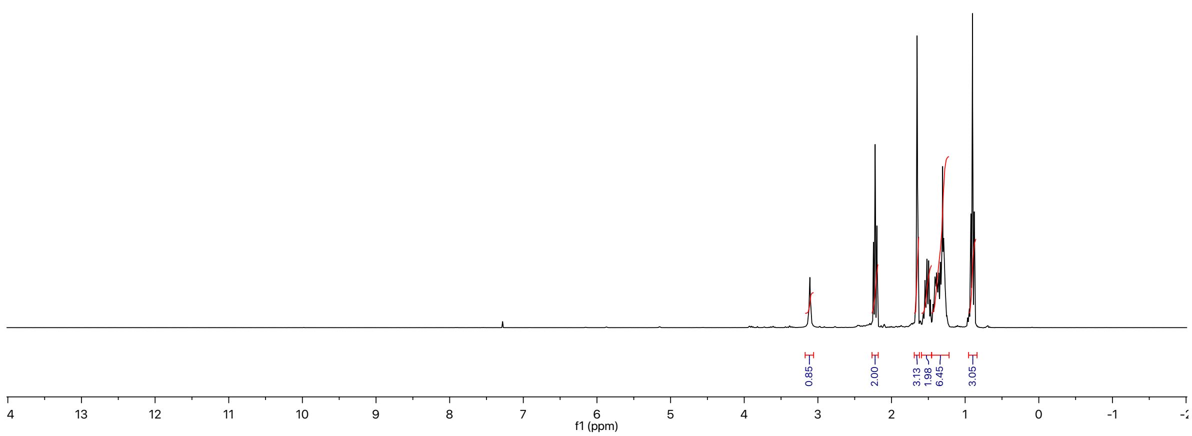


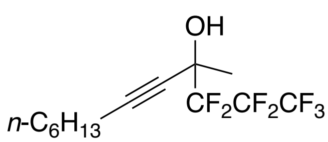
932



17o

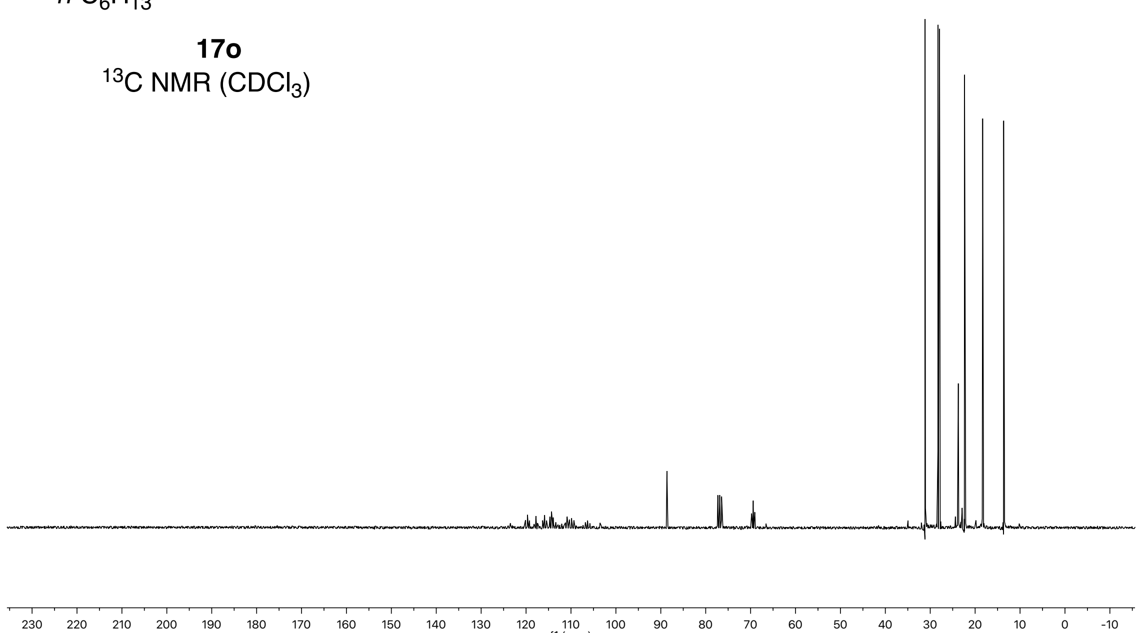
^{1}H NMR ($CDCl_3$)

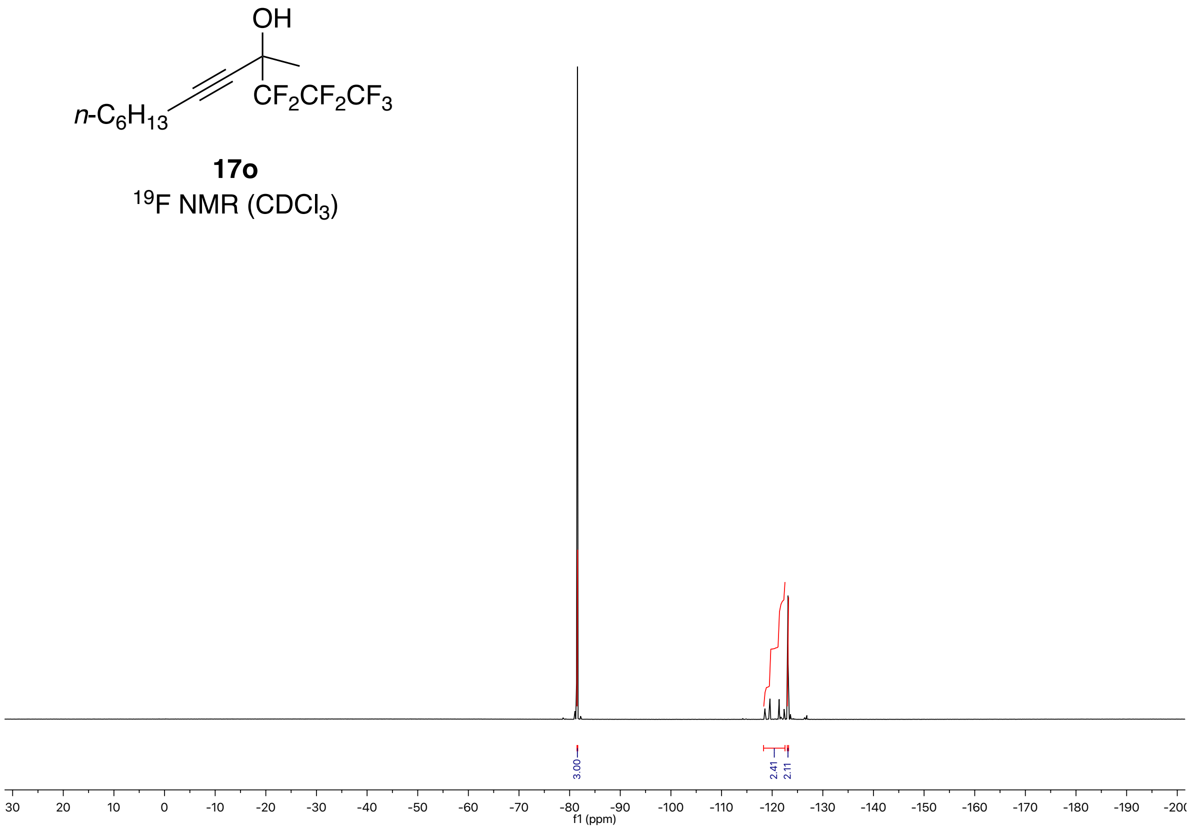




17o

^{13}C NMR ($CDCl_3$)

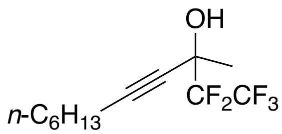




17o

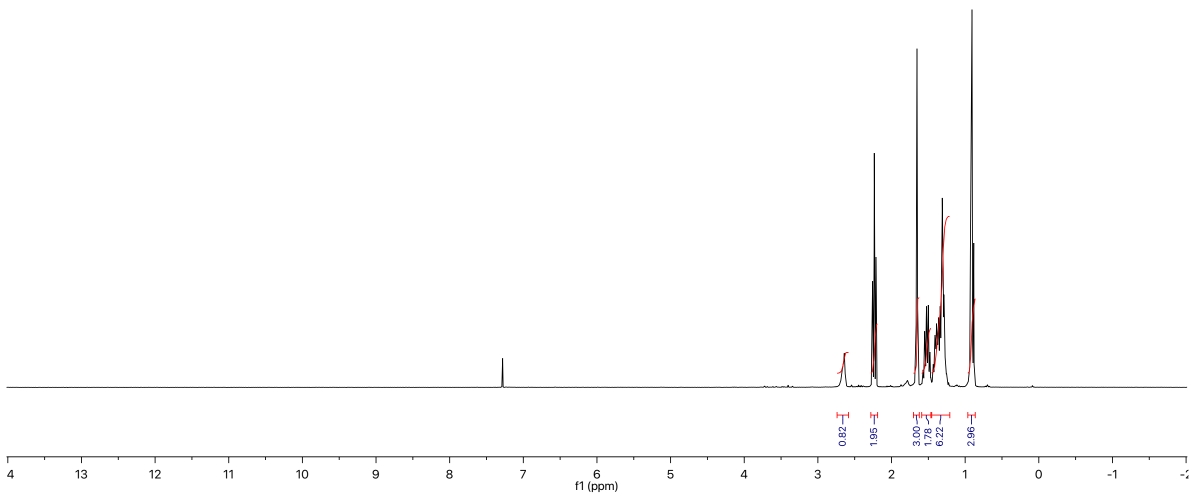
^{19}F NMR ($CDCl_3$)

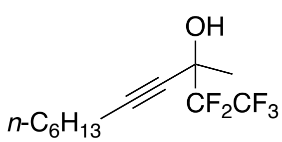
945



17p

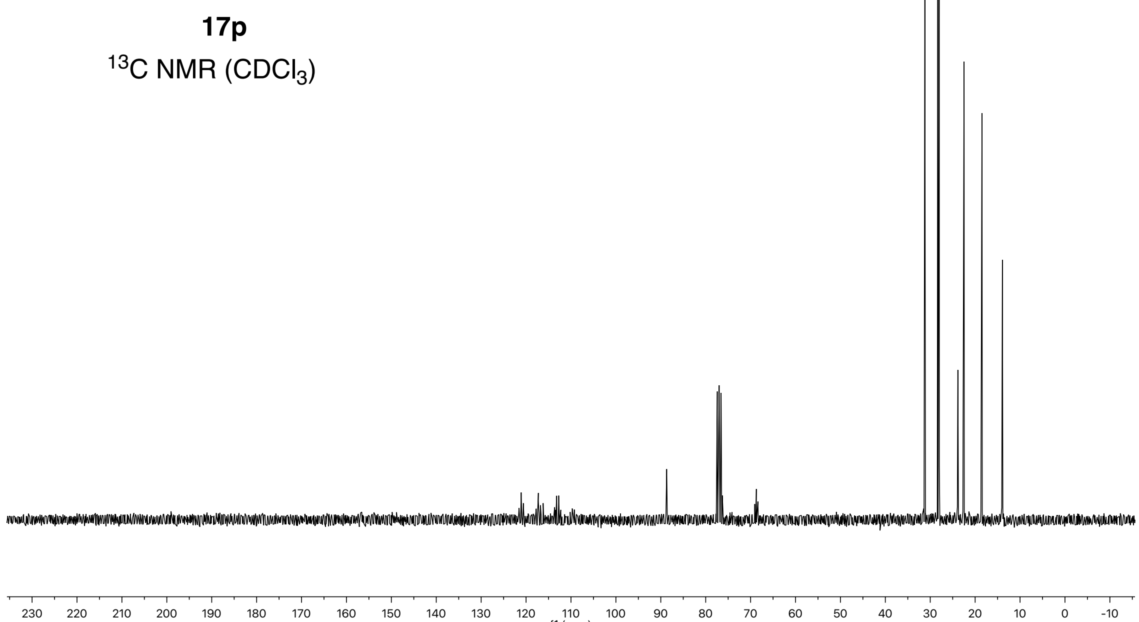
^{1}H NMR ($CDCl_3$)

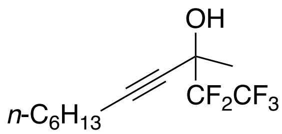




17p

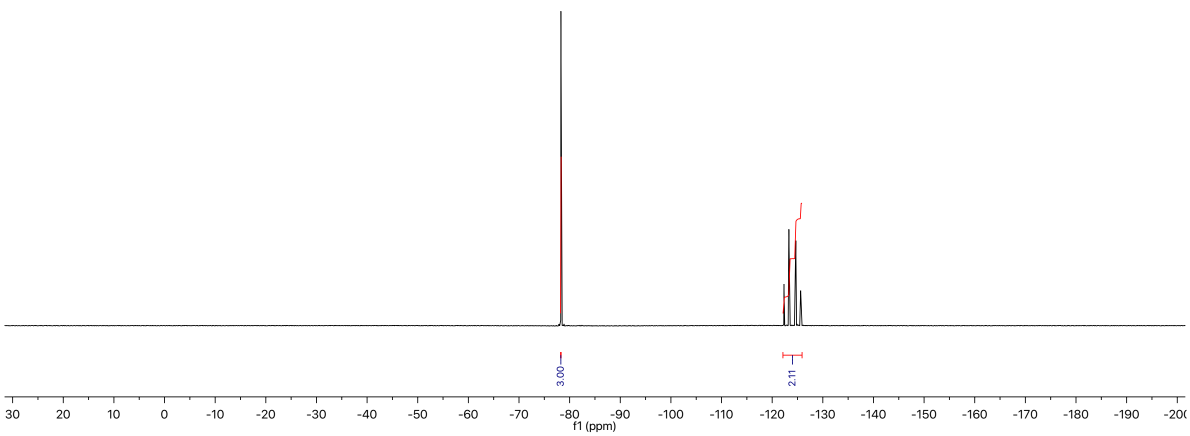
^{13}C NMR ($CDCl_3$)



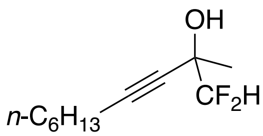


17p

^{19}F NMR ($CDCl_3$)

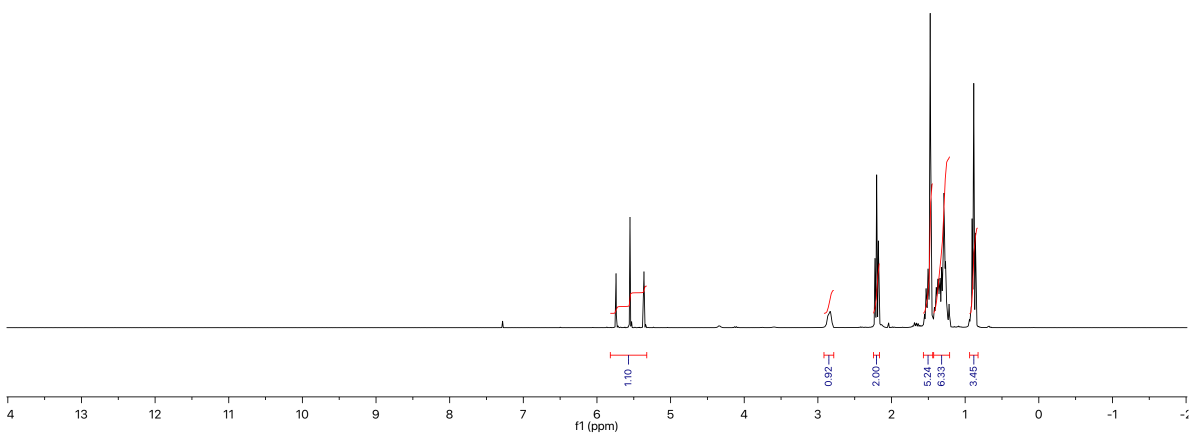


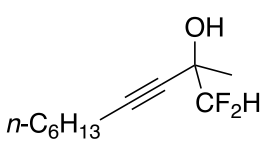
1083



17q

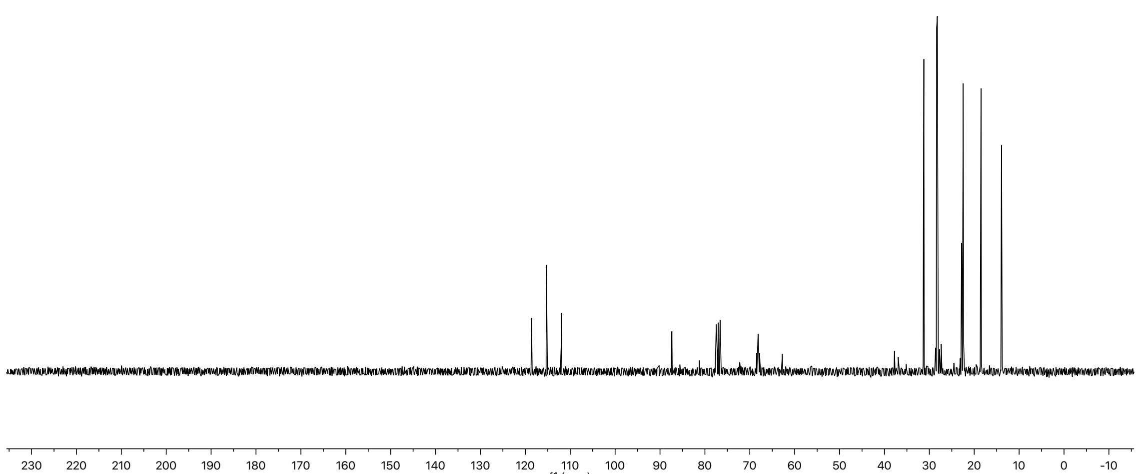
^{1}H NMR ($CDCl_3$)

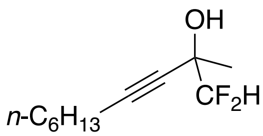




17q

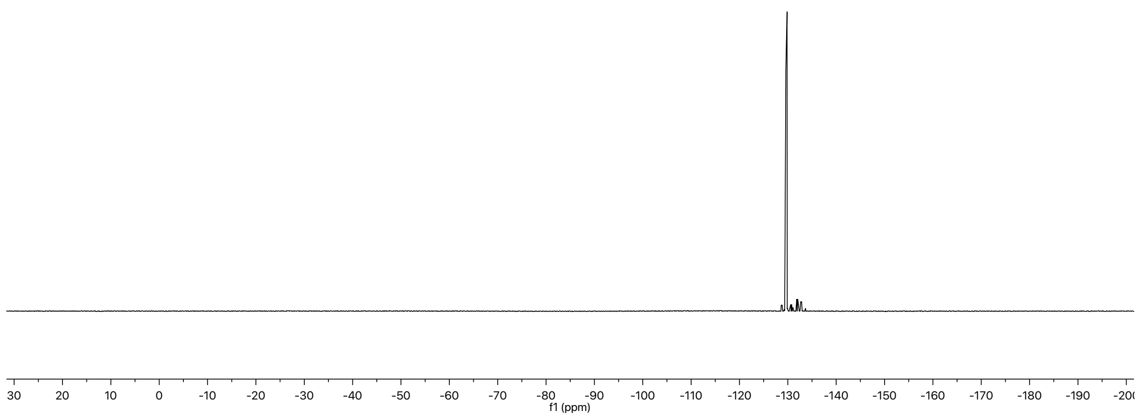
^{13}C NMR ($CDCl_3$)





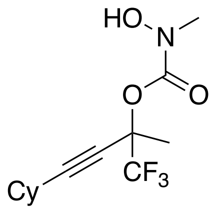
17q

^{19}F NMR ($CDCl_3$)



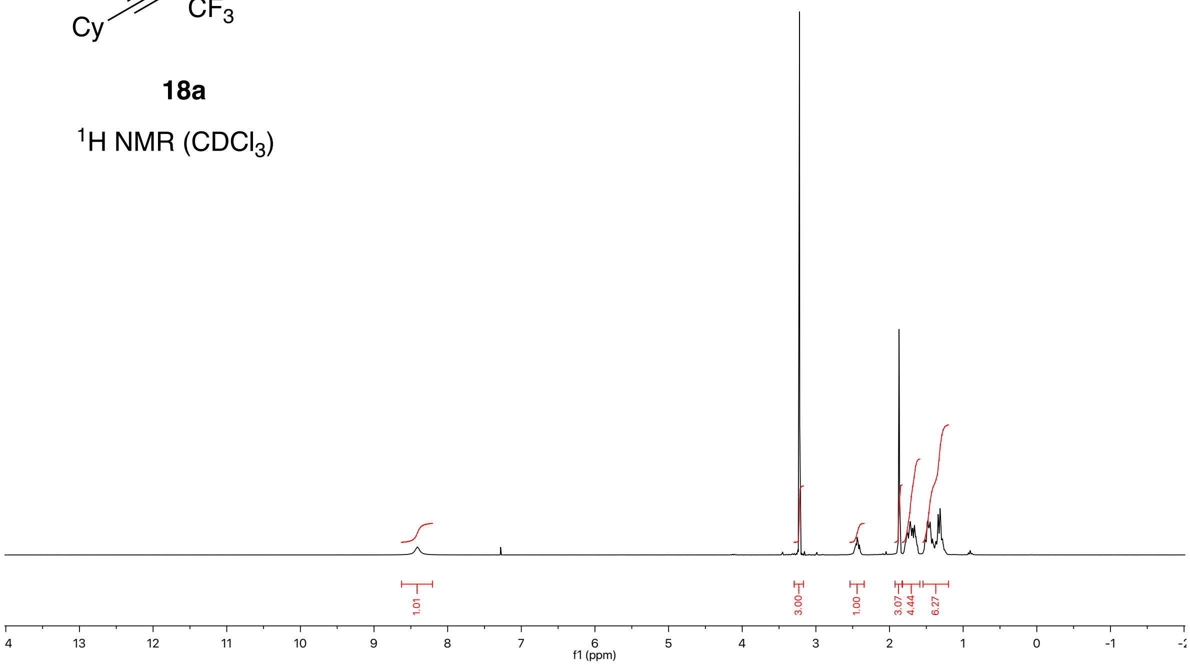
1085

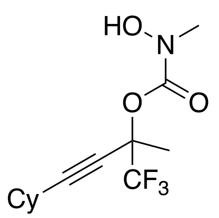
NMR spectrums for *N*-hydroxycarbamates (**18a**-**18r**).



18a

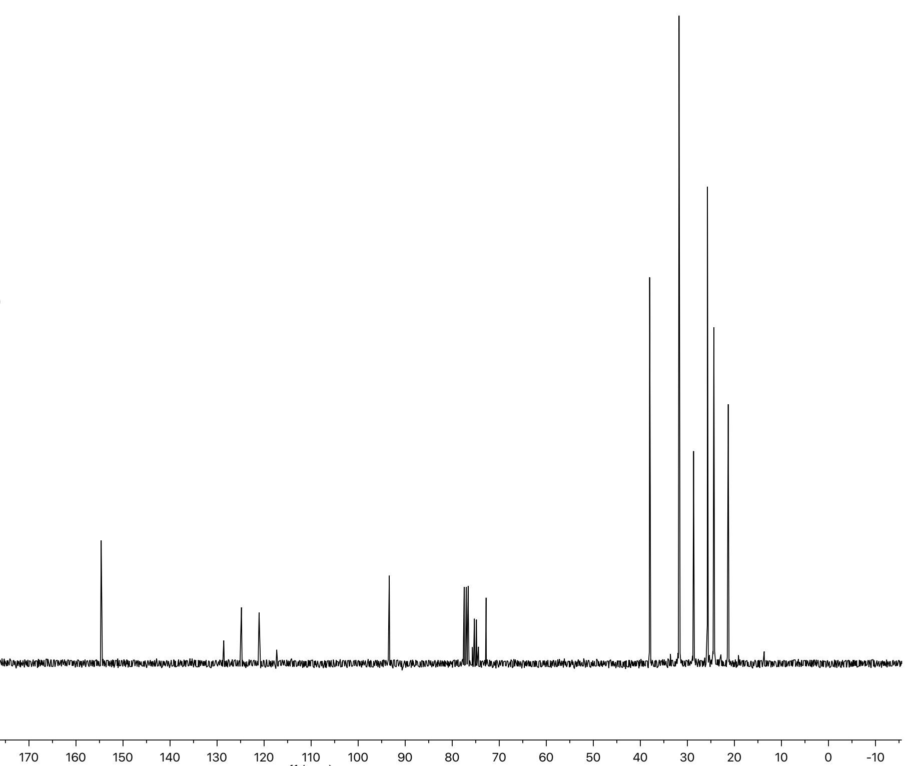
^{1}H NMR ($CDCl_3$)

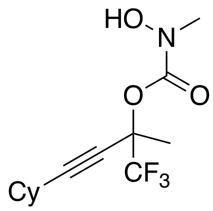




18a

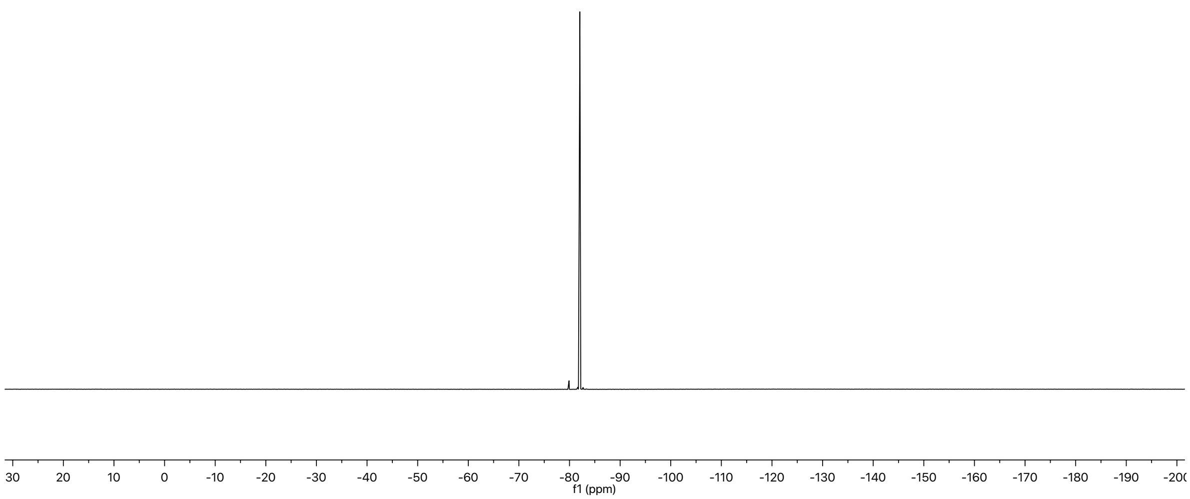
^{13}C NMR ($CDCl_3$)



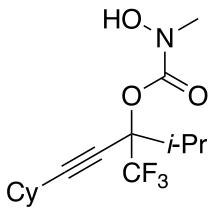


18a

^{19}F NMR ($CDCl_3$)

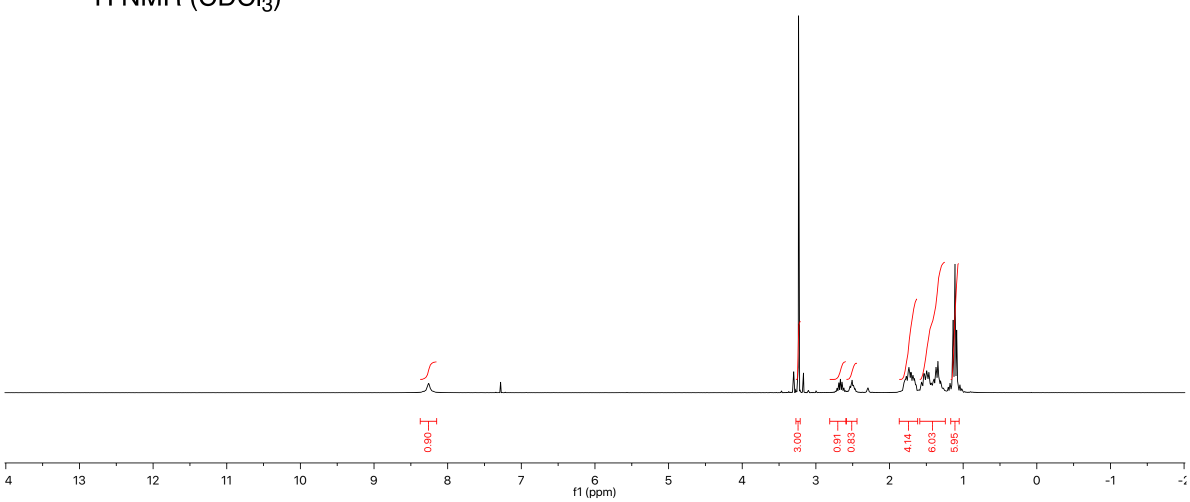


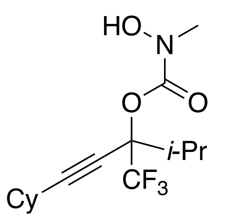
780



18b

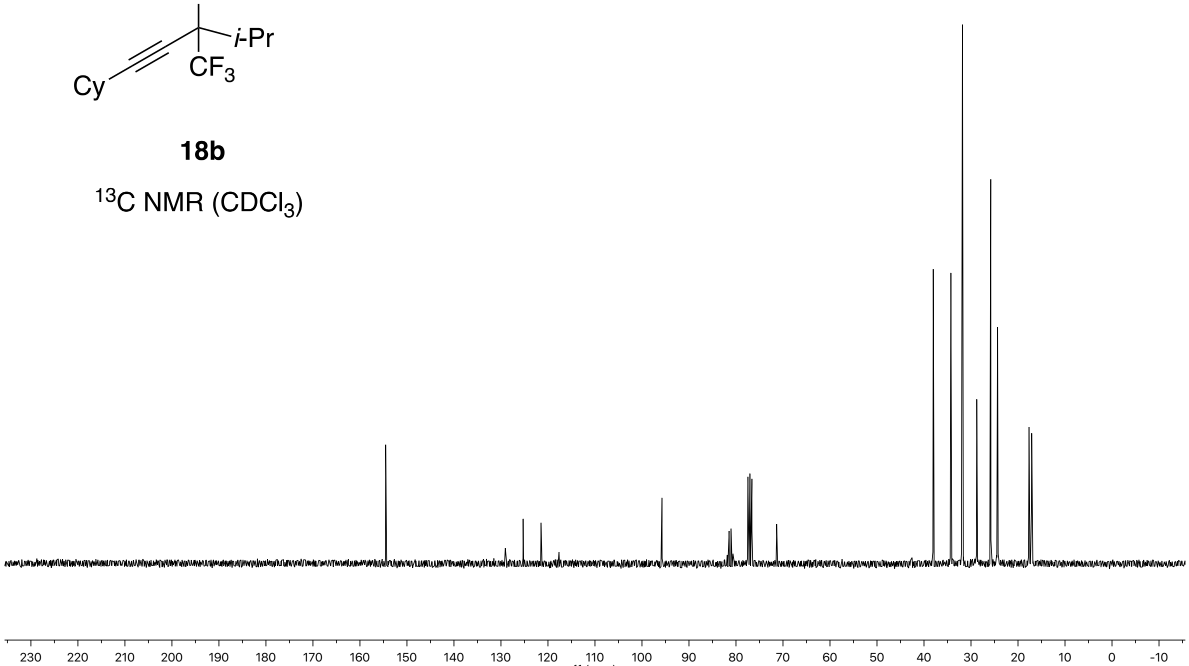
^{1}H NMR ($CDCl_3$)

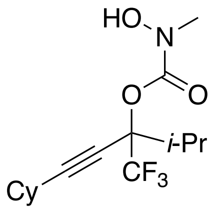




18b

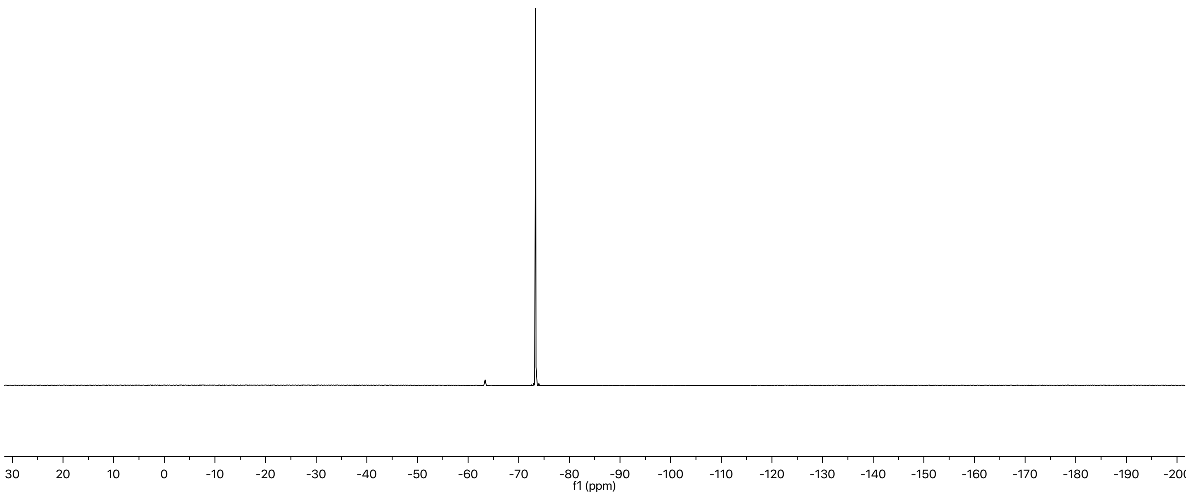
^{13}C NMR ($CDCl_3$)



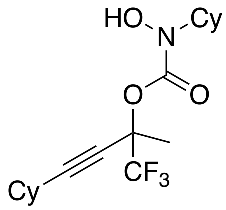


18b

^{19}F NMR ($CDCl_3$)

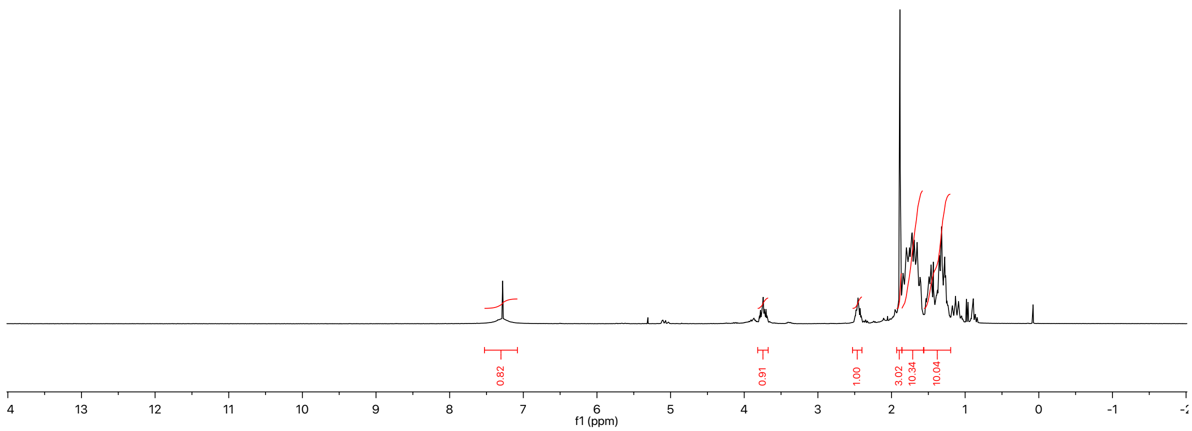


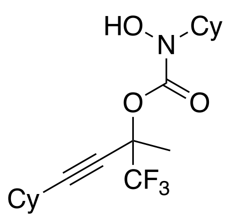
827



18c

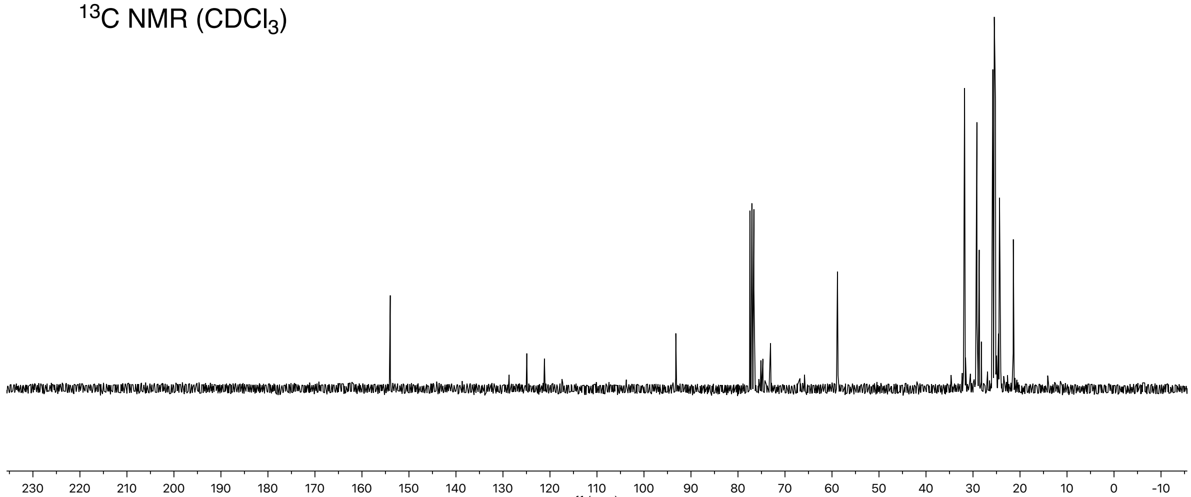
^{1}H NMR ($CDCl_3$)

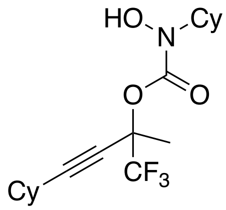




18c

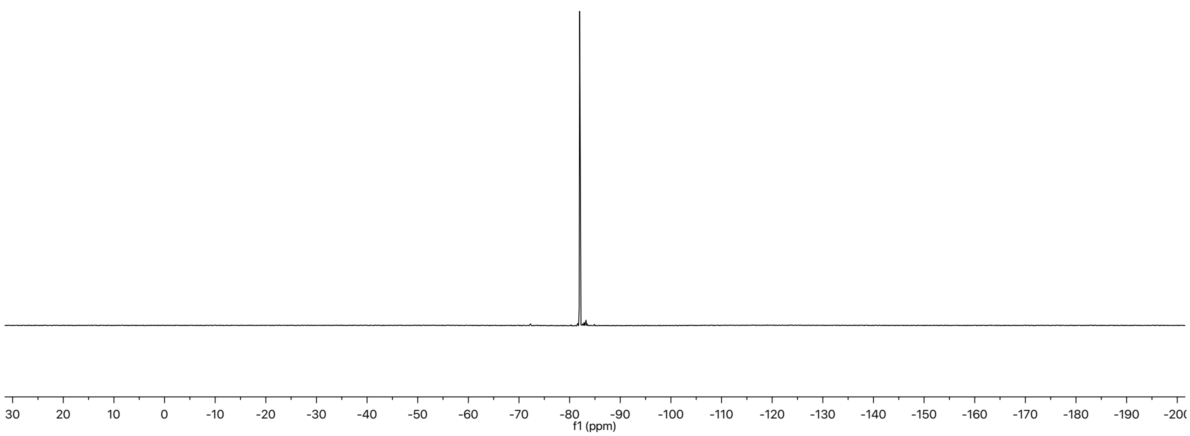
^{13}C NMR ($CDCl_3$)



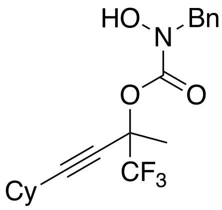


18c

^{19}F NMR ($CDCl_3$)

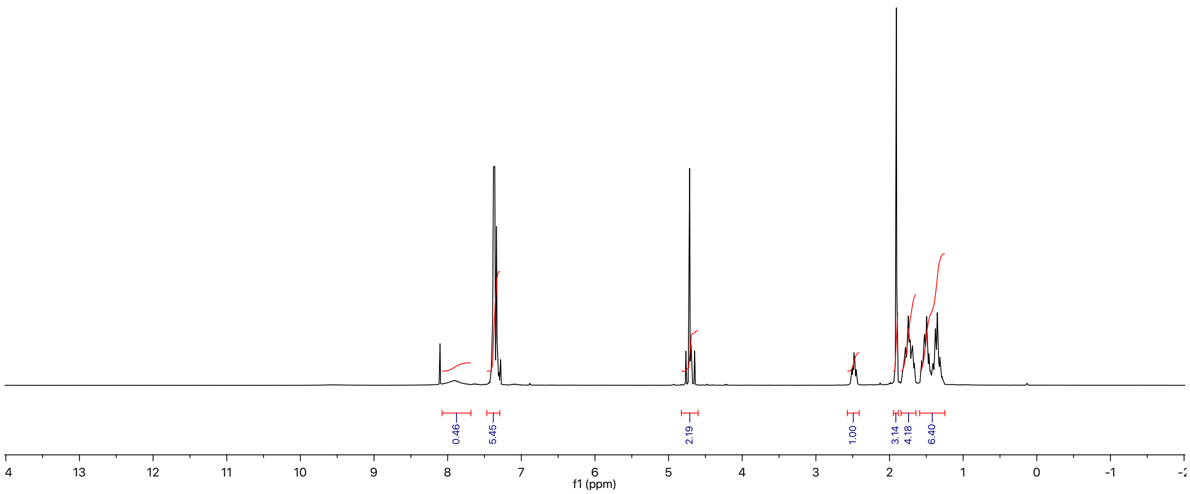


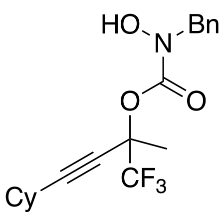
822



18d

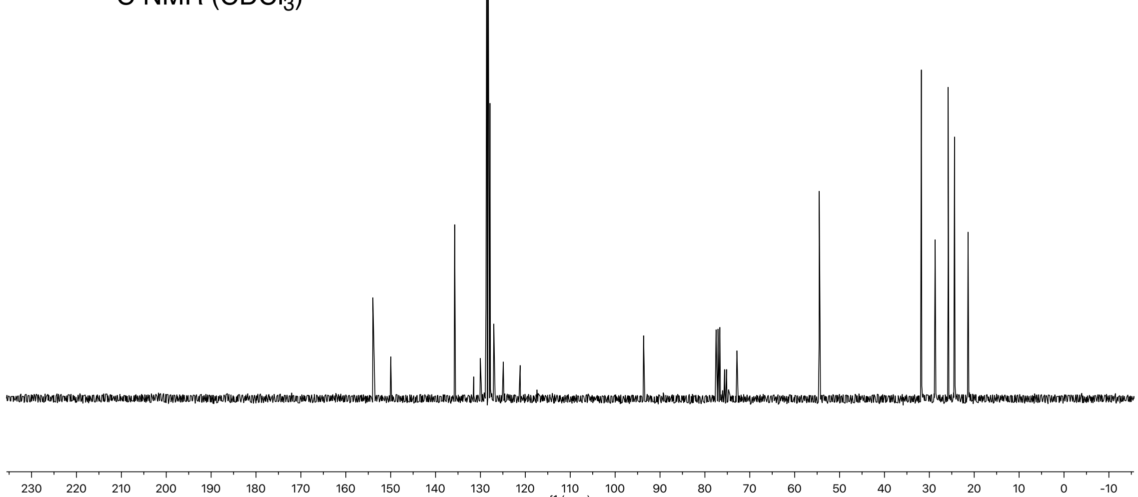
^{1}H NMR ($CDCl_3$)

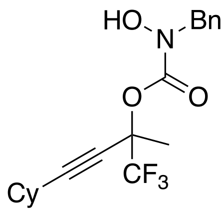




18d

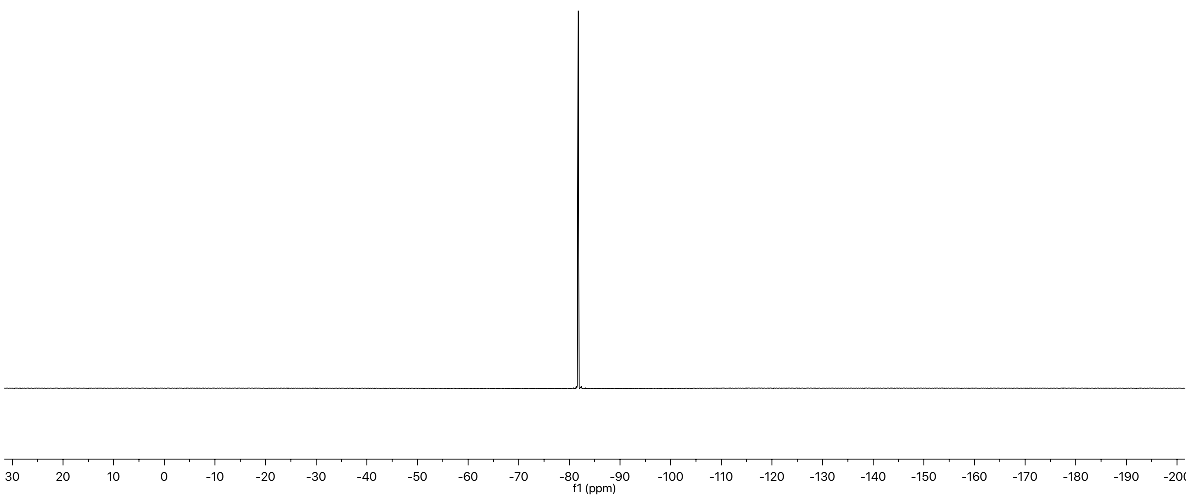
^{13}C NMR ($CDCl_3$)



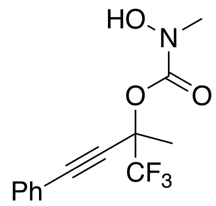


18d

^{19}F NMR ($CDCl_3$)

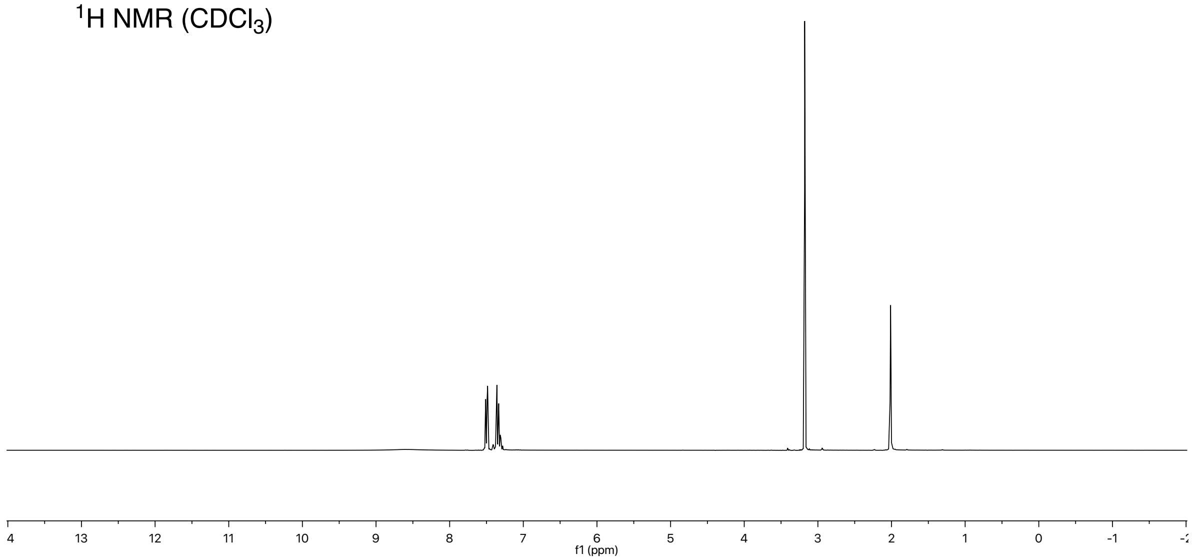


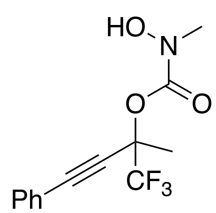
1066



18e

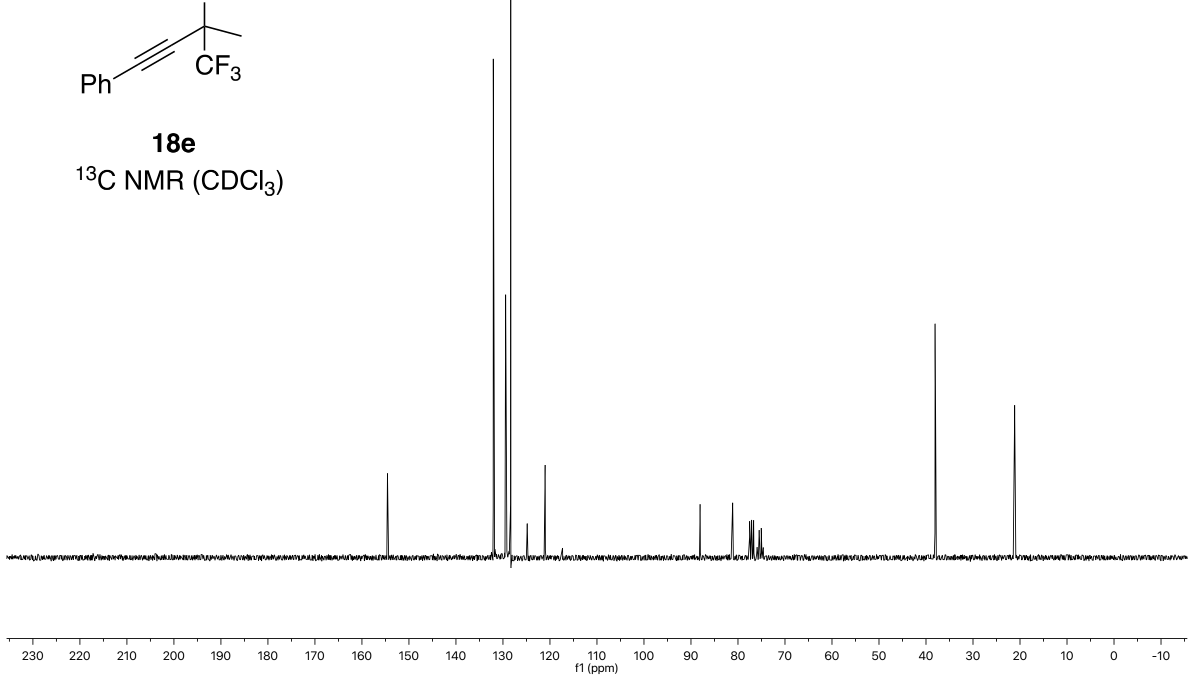
^{1}H NMR ($CDCl_3$)

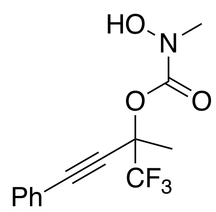




18e

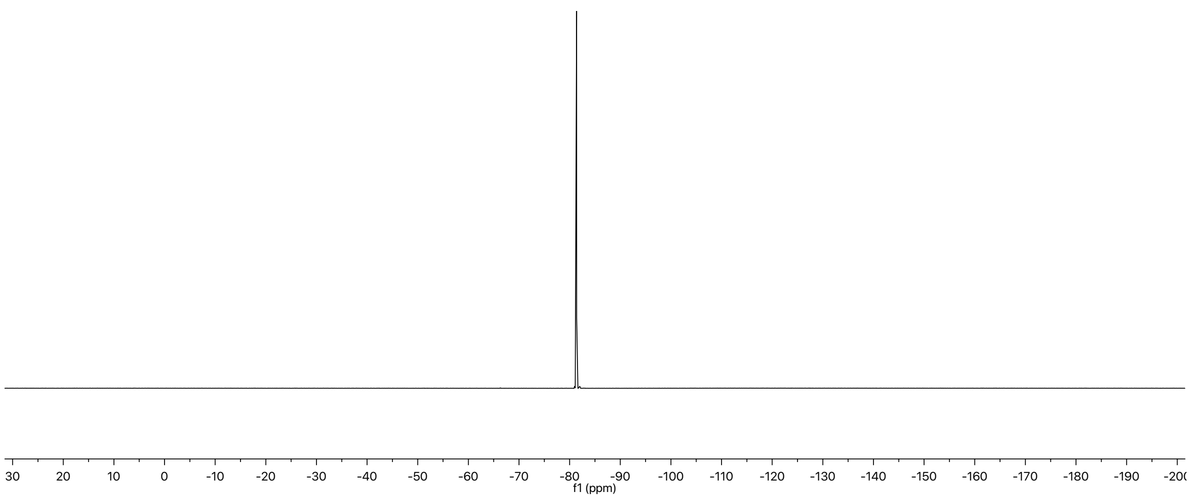
^{13}C NMR ($CDCl_3$)



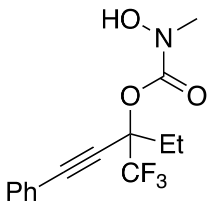


18e

^{19}F NMR ($CDCl_3$)

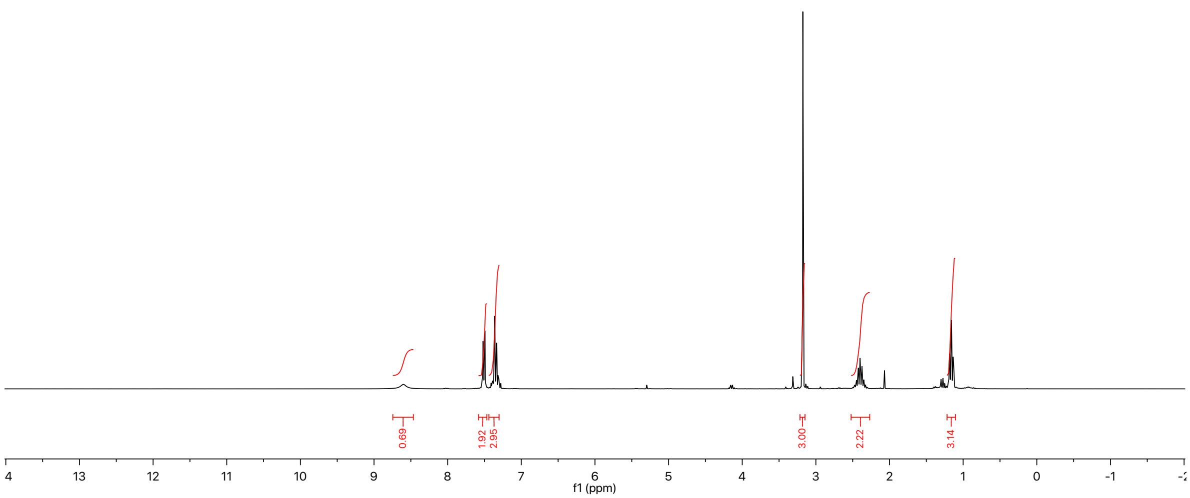


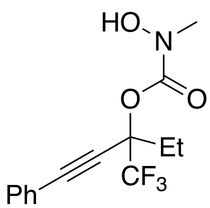
802



18f

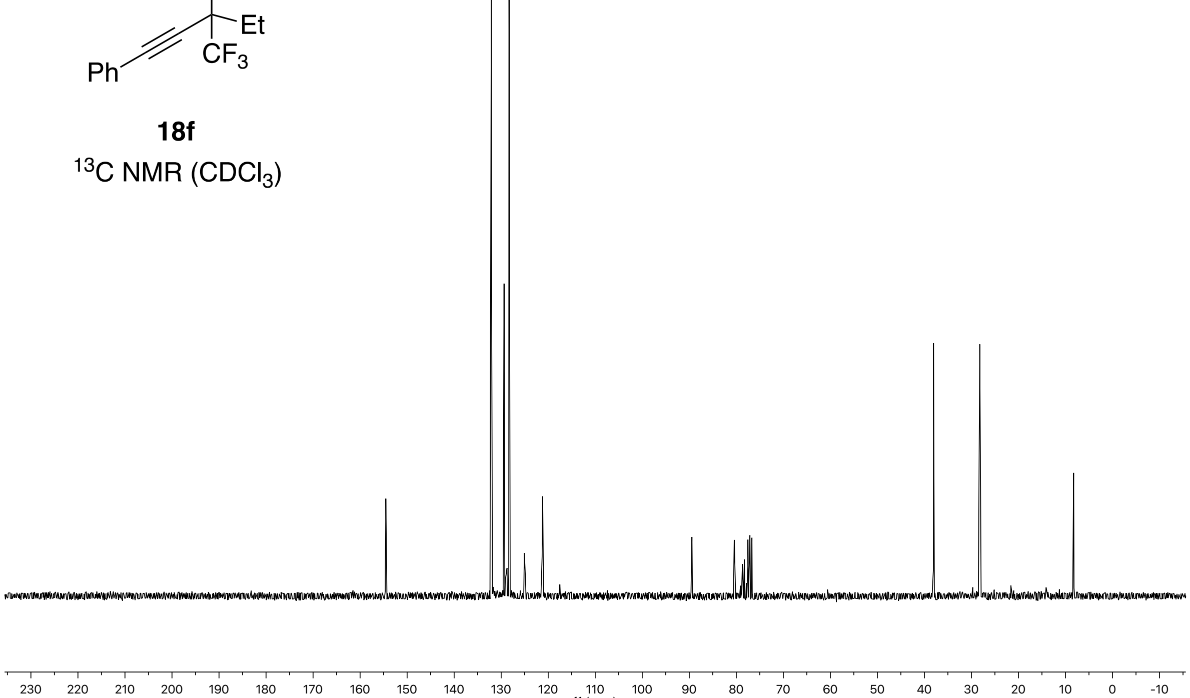
^{1}H NMR ($CDCl_3$)

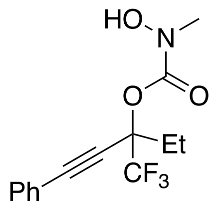




18f

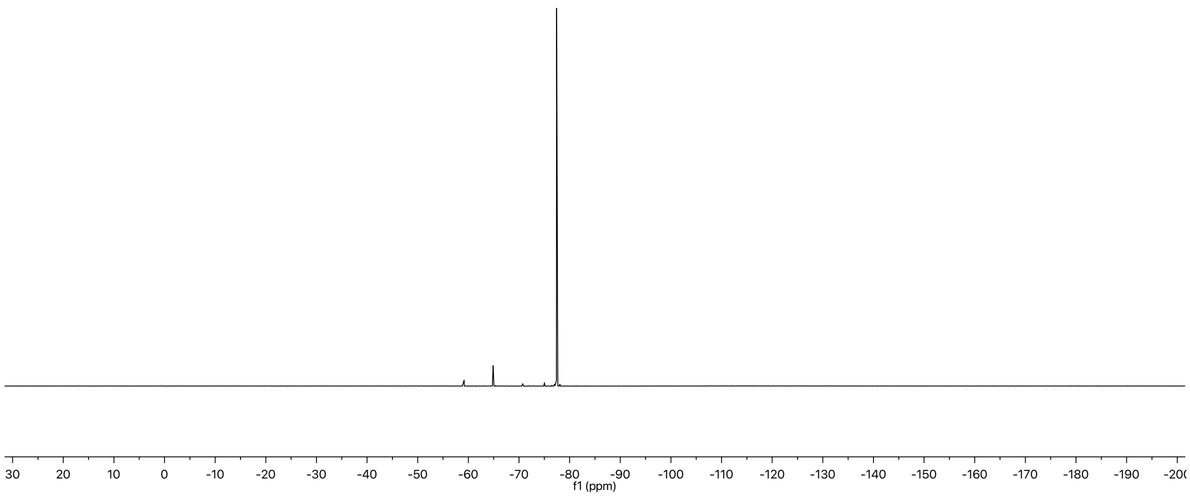
^{13}C NMR ($CDCl_3$)



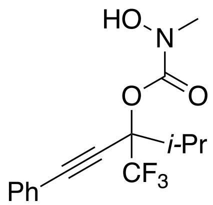


18f

^{19}F NMR ($CDCl_3$)

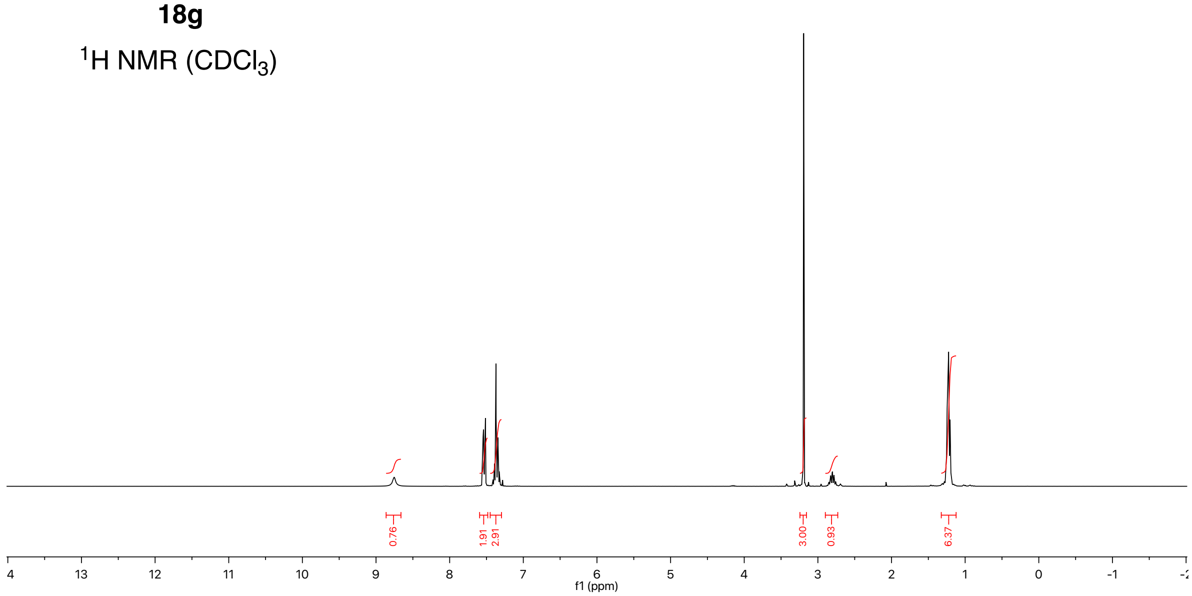


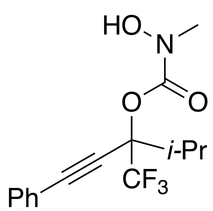
812



18g

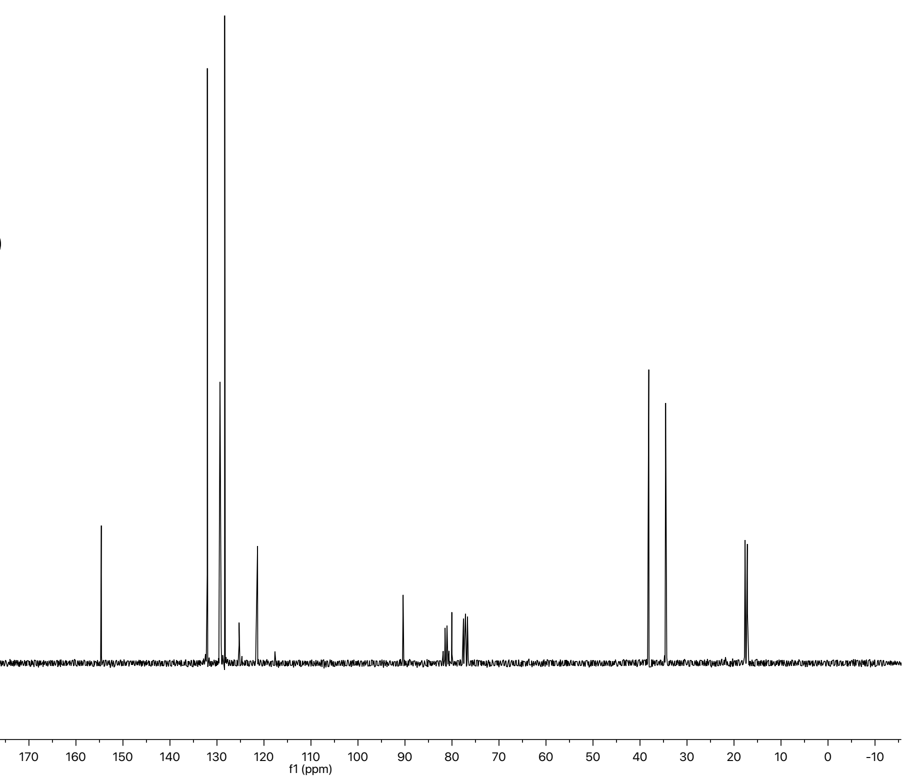
^{1}H NMR ($CDCl_3$)

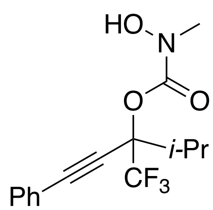




18g

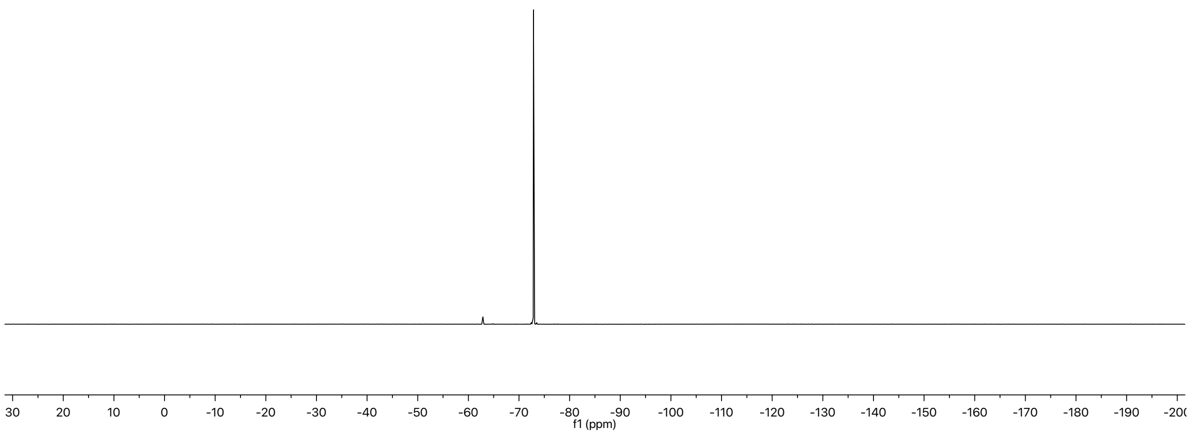
^{13}C NMR ($CDCl_3$)



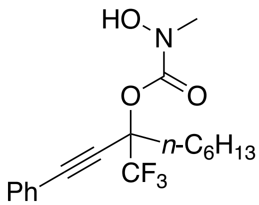


18g

^{19}F NMR ($CDCl_3$)

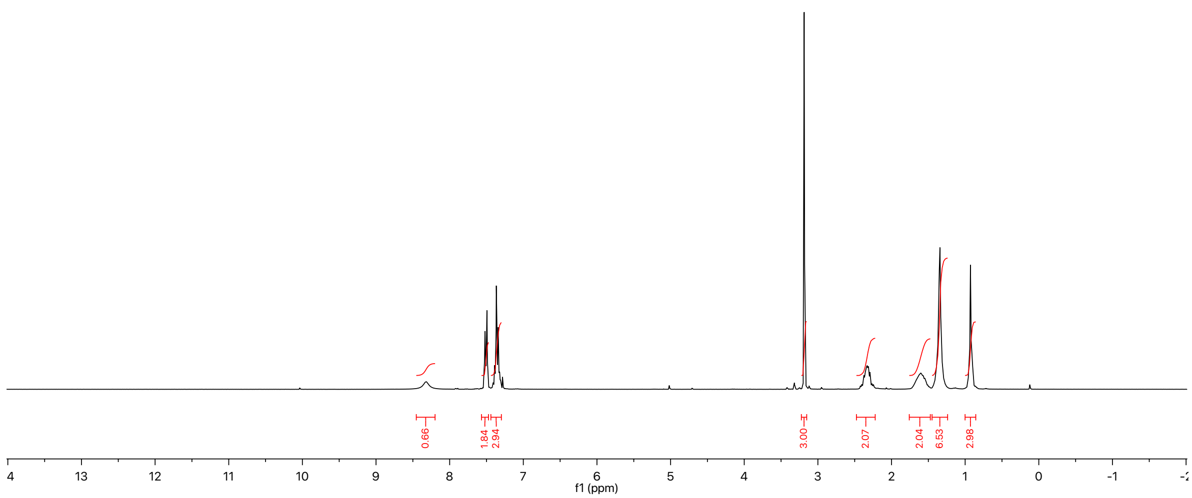


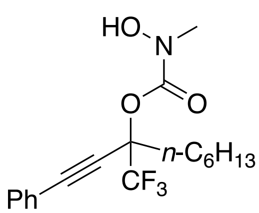
817



18h

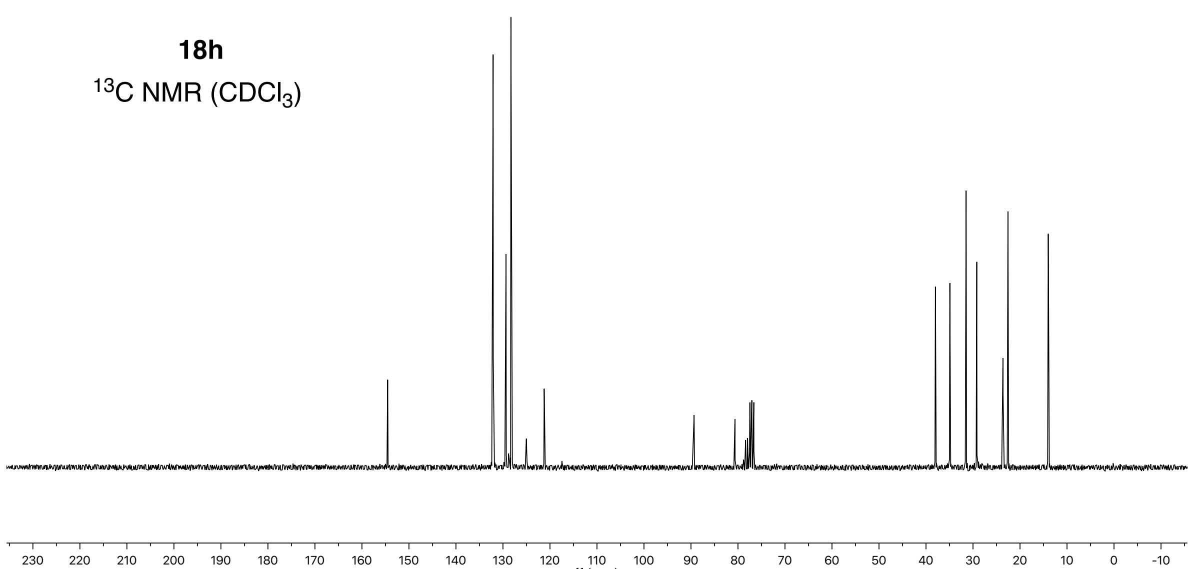
^{1}H NMR ($CDCl_3$)

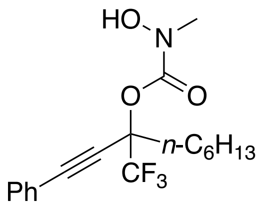




18h

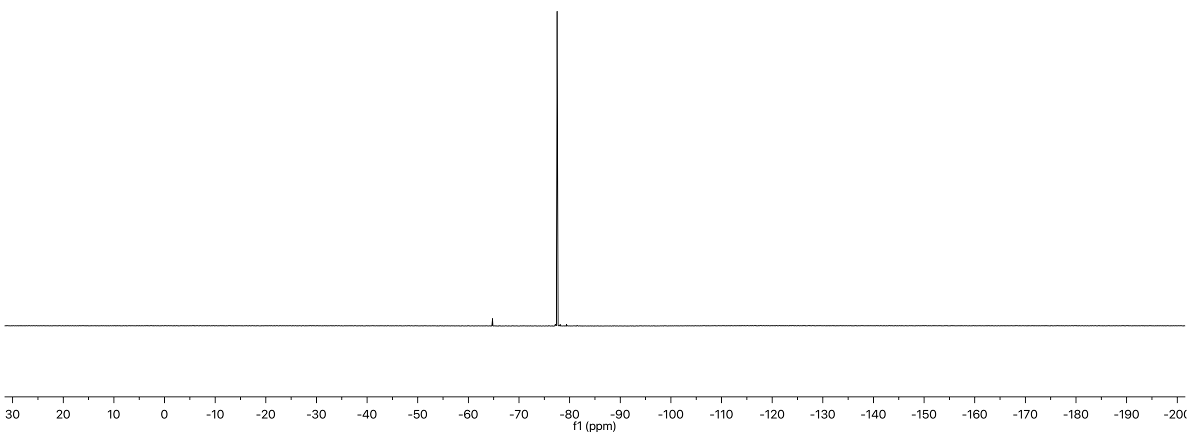
^{13}C NMR ($CDCl_3$)



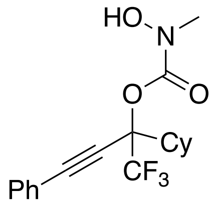


18h

^{19}F NMR ($CDCl_3$)

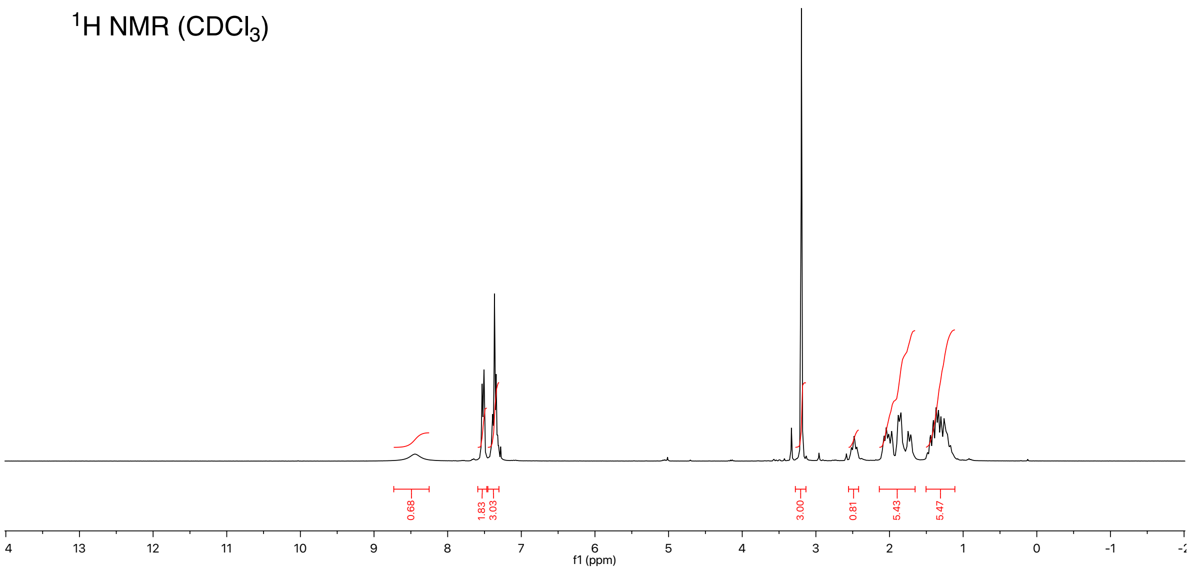


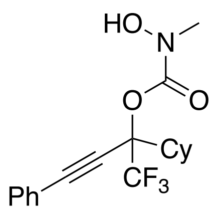
912



18i

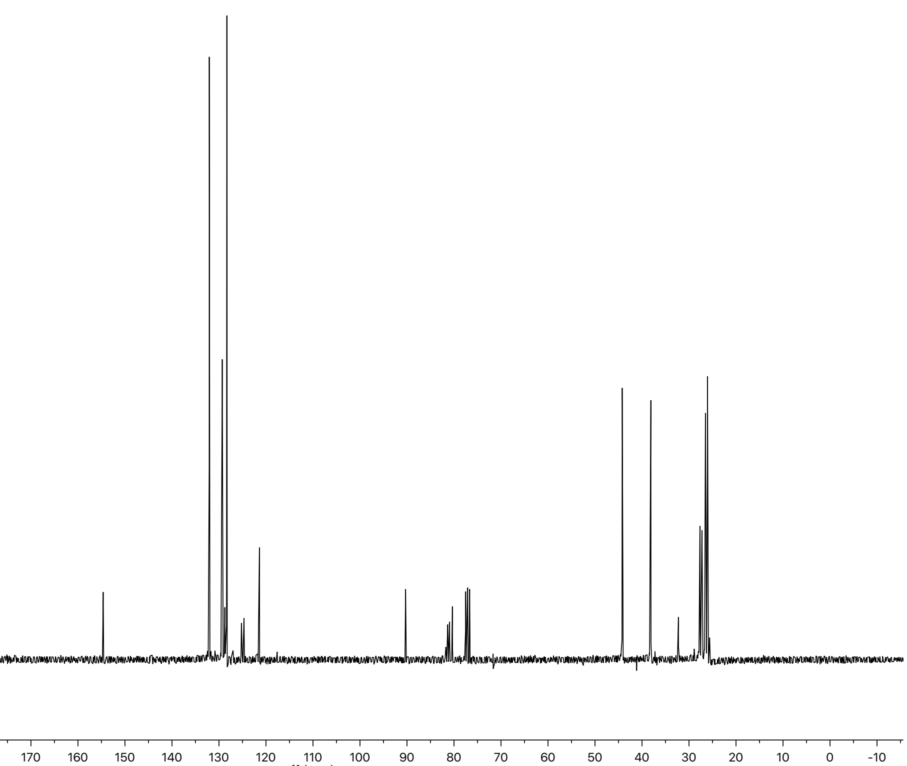
^{1}H NMR ($CDCl_3$)

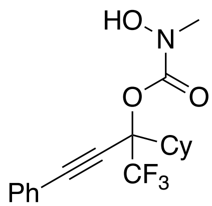




18i

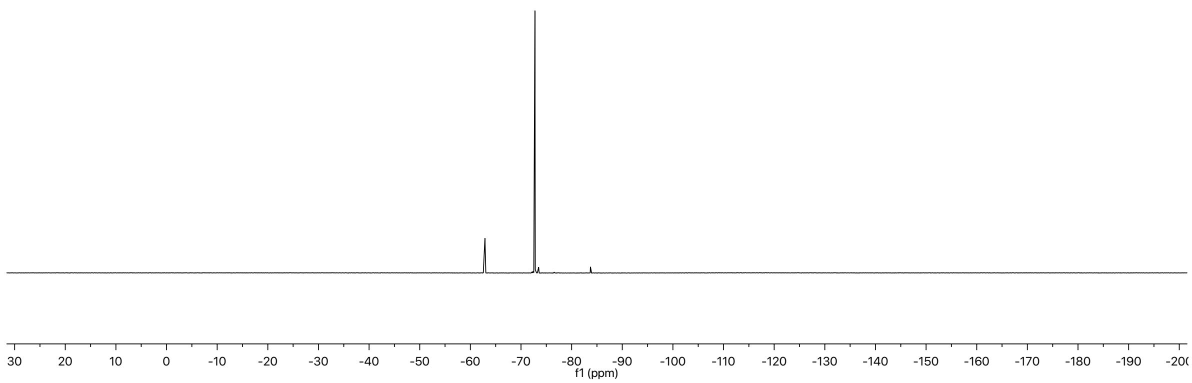
^{13}C NMR ($CDCl_3$)



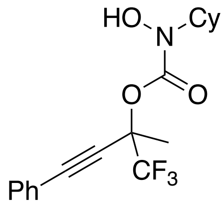


18i

^{19}F NMR ($CDCl_3$)

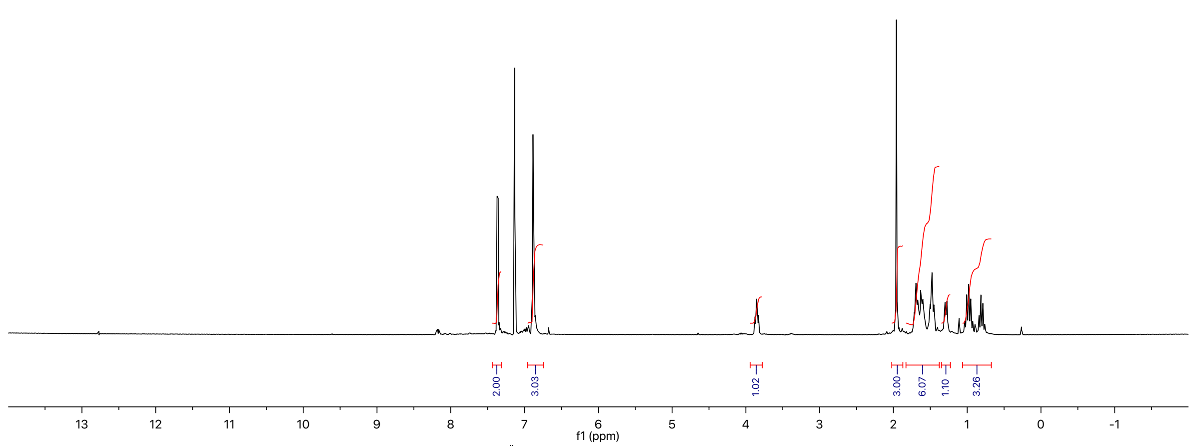


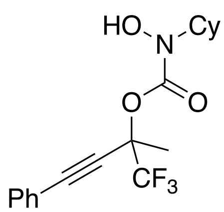
927



18j

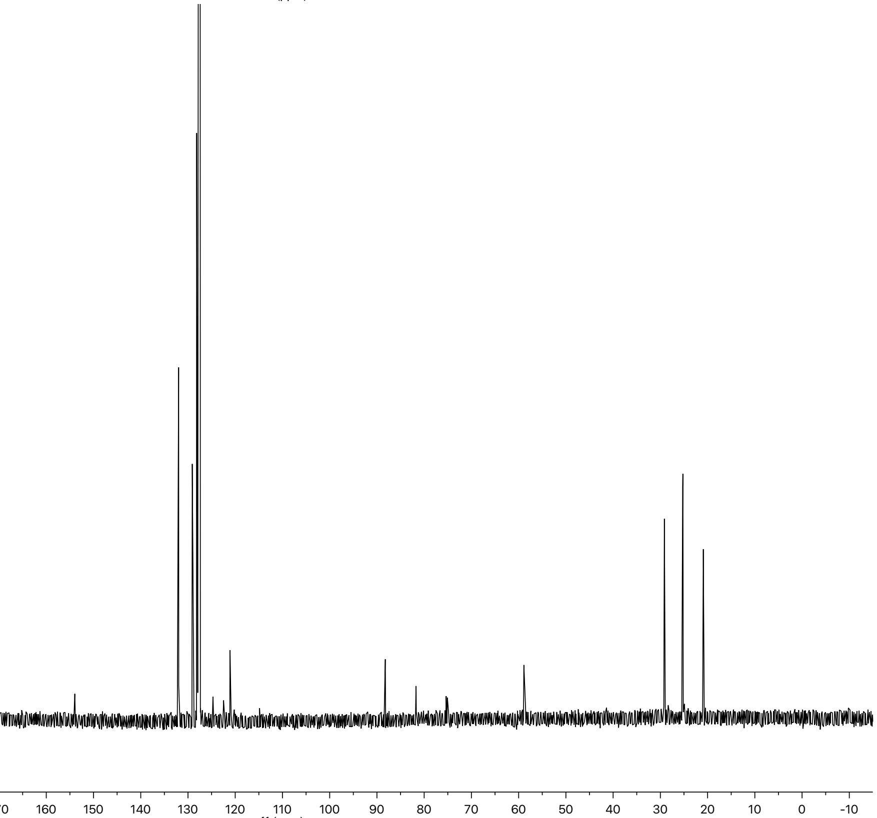
^{1}H NMR (C_6D_6)

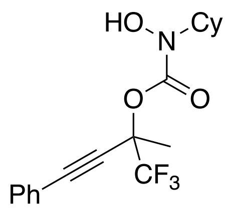




18j

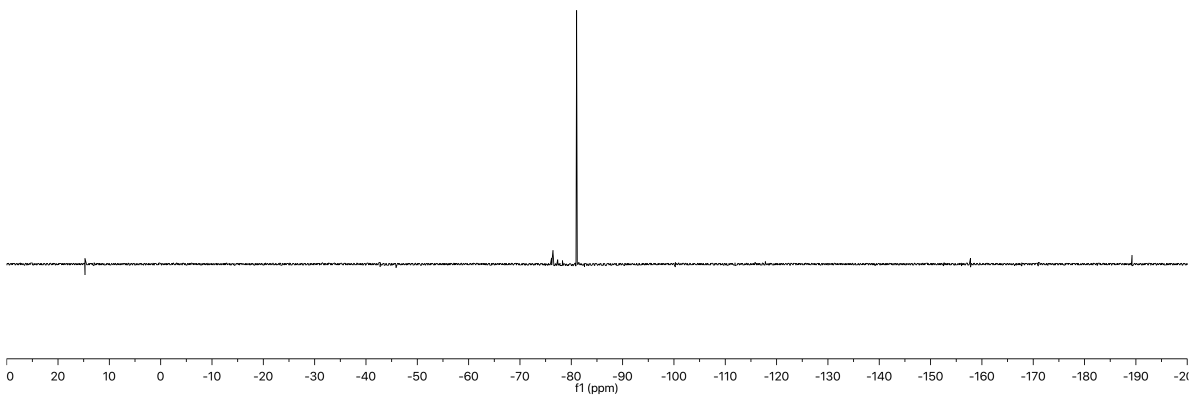
^{13}C NMR (C_6D_6)



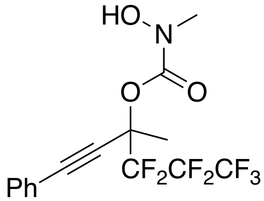


18j

^{19}F NMR (C_6D_6)

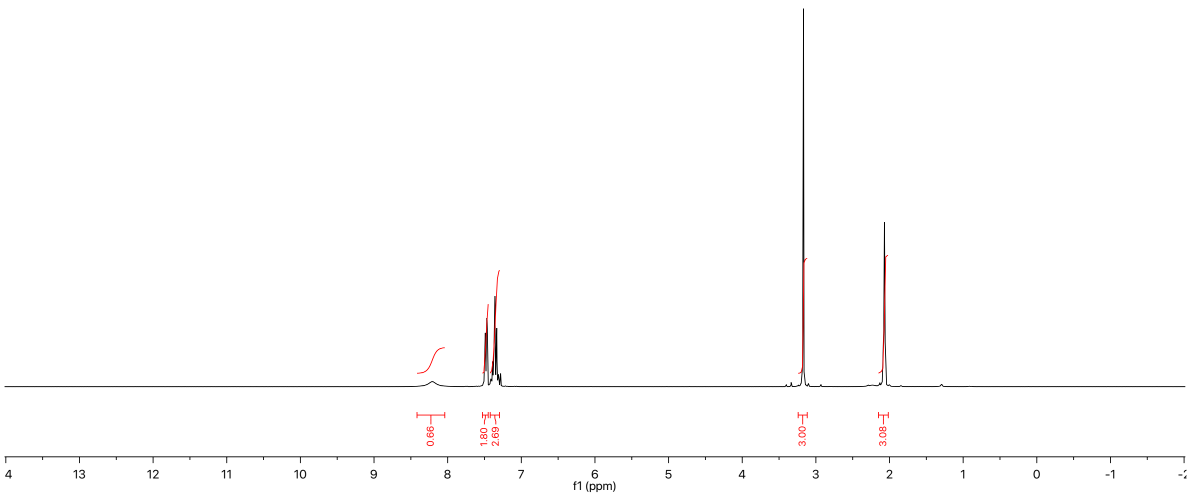


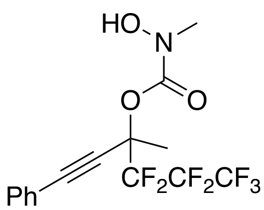
659



18k

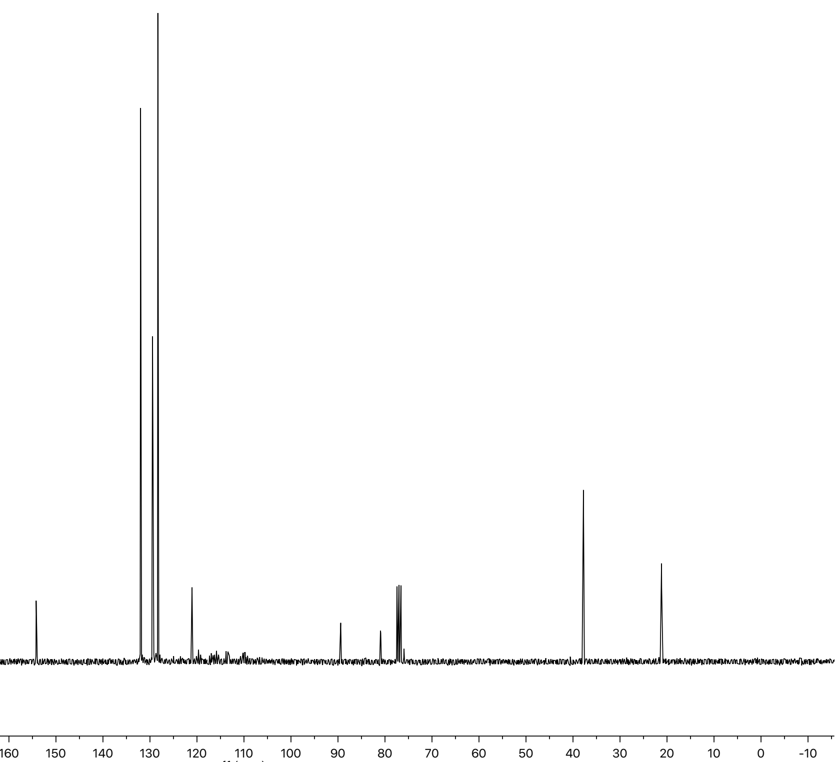
^{1}H NMR ($CDCl_3$)

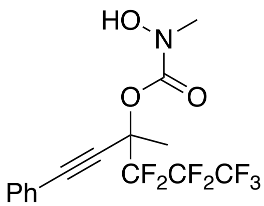




18k

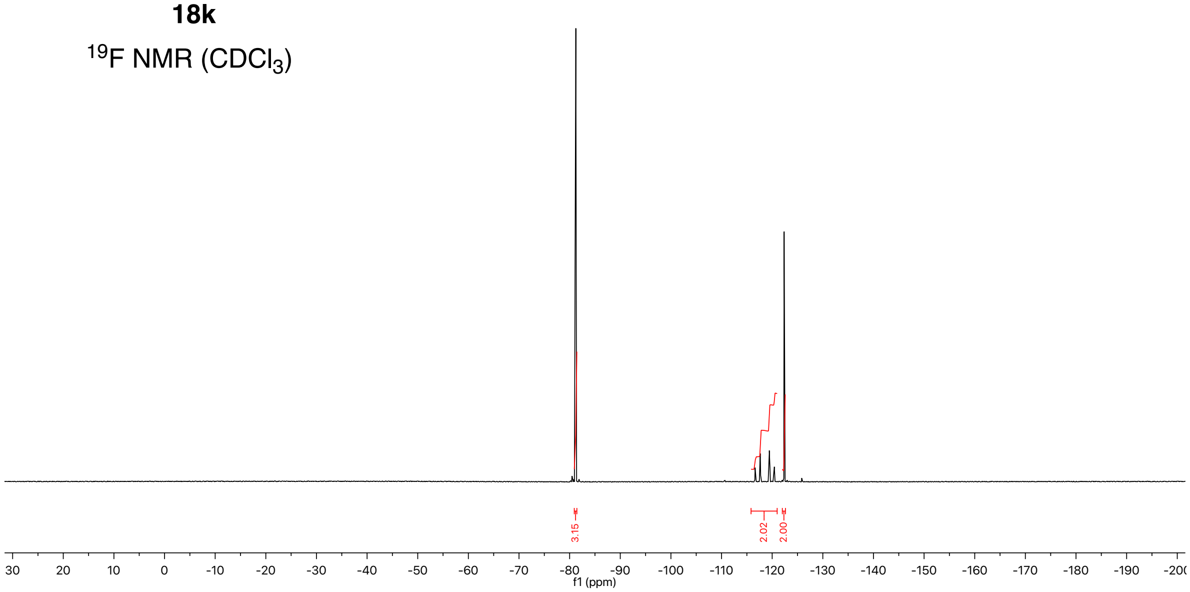
^{13}C NMR ($CDCl_3$)



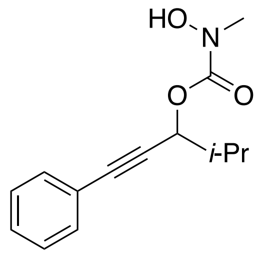


18k

^{19}F NMR ($CDCl_3$)

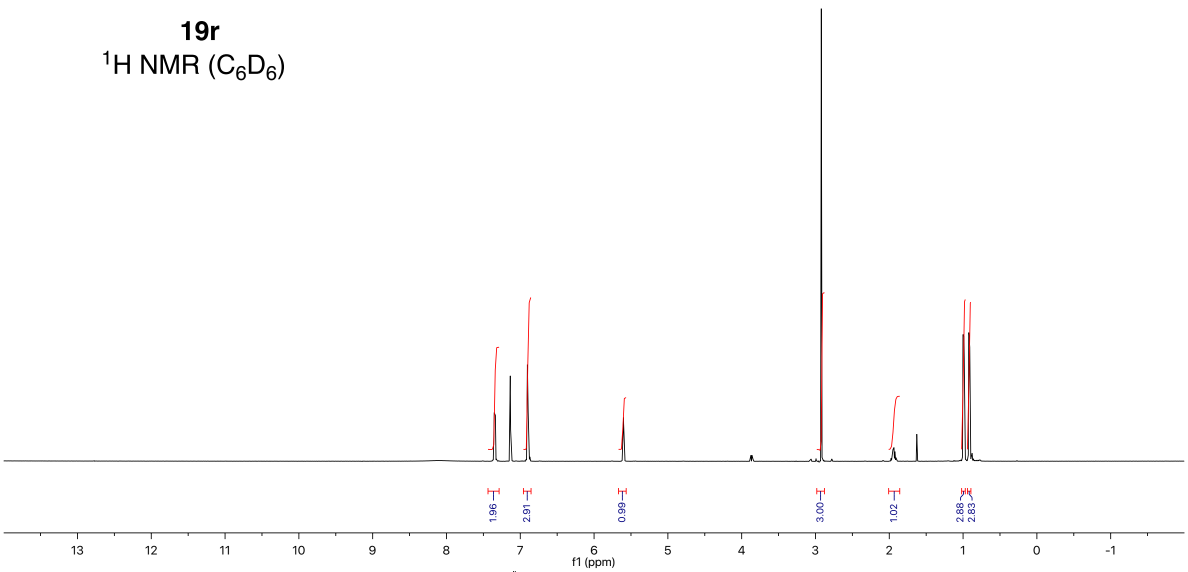


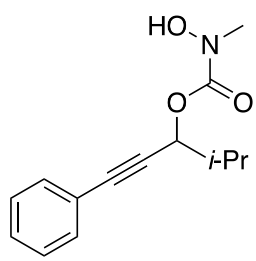
906



19r

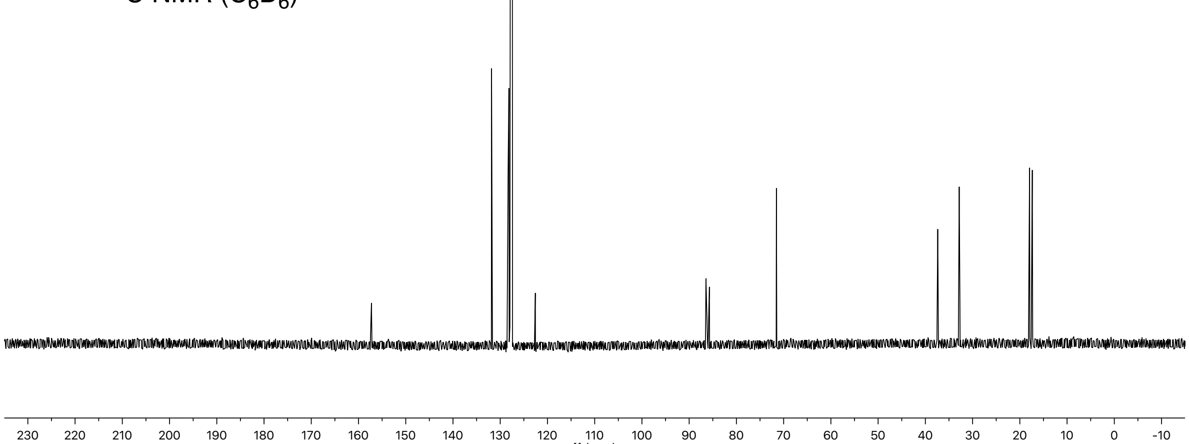
^{1}H NMR (C_6D_6)

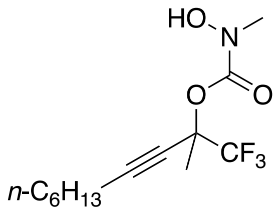




19r

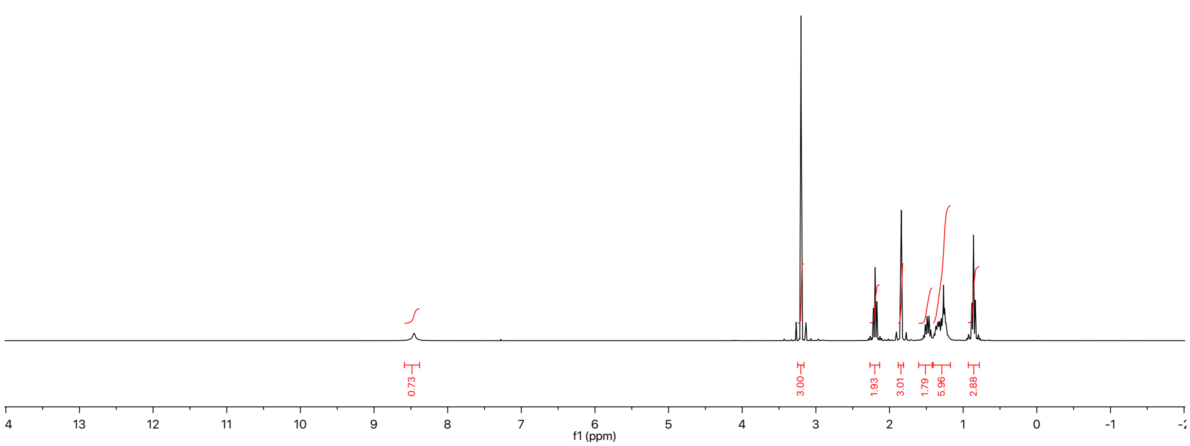
^{13}C NMR (C_6D_6)

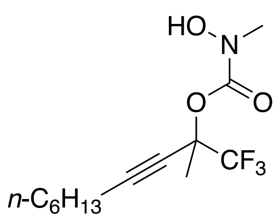




18l

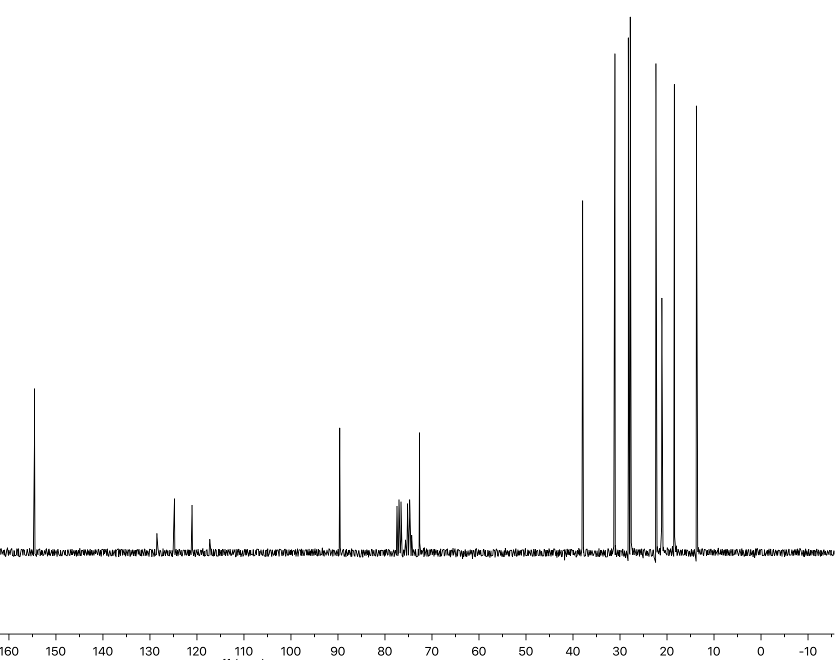
^{1}H NMR ($CDCl_3$)

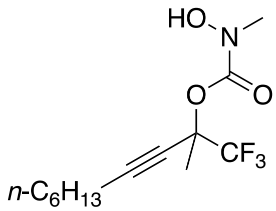




18l

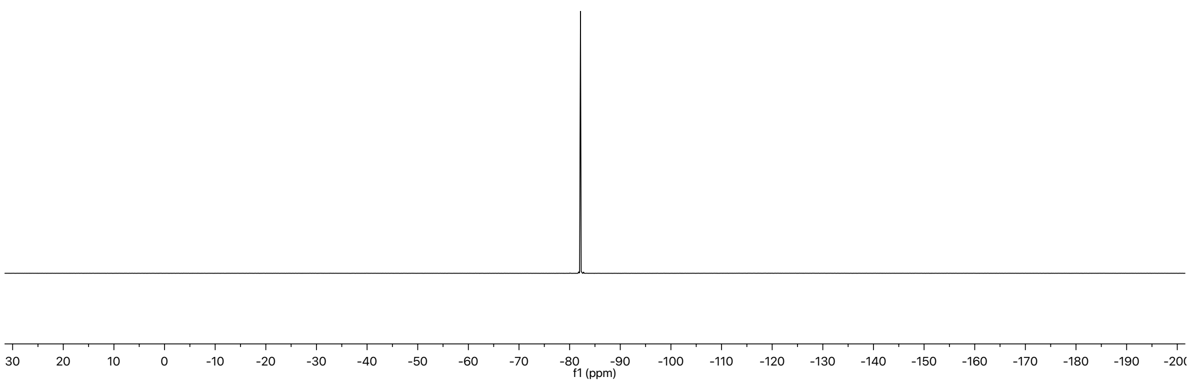
^{13}C NMR ($CDCl_3$)



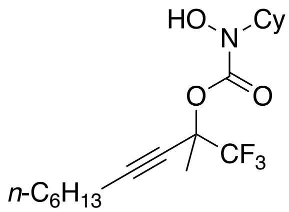


18l

^{19}F NMR ($CDCl_3$)

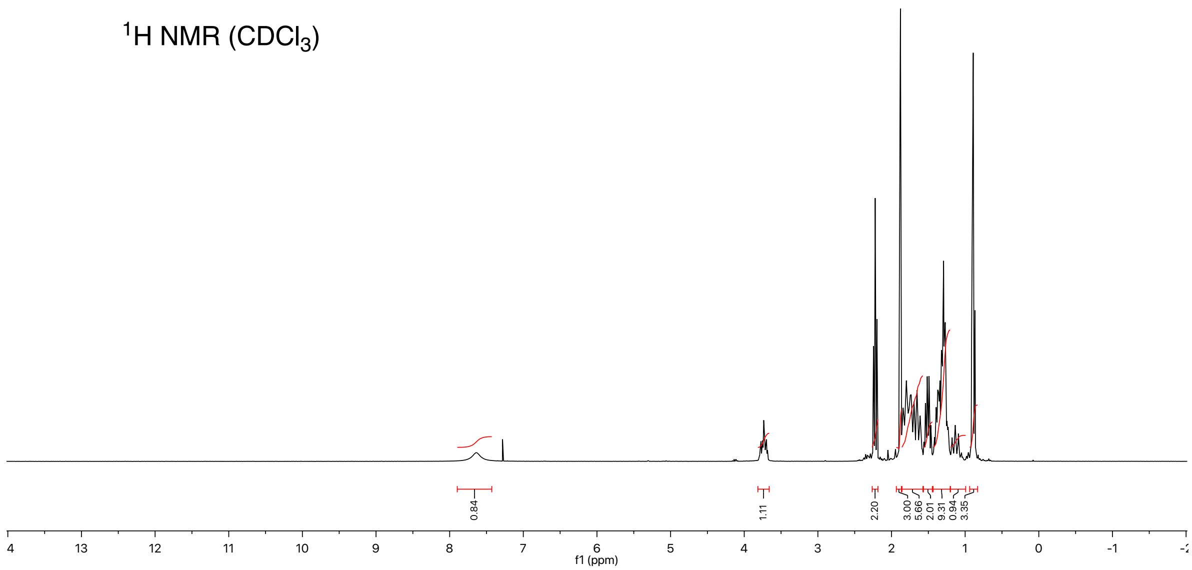


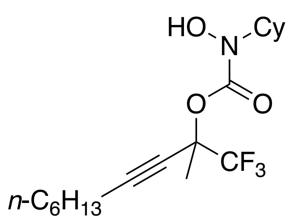
823



18m

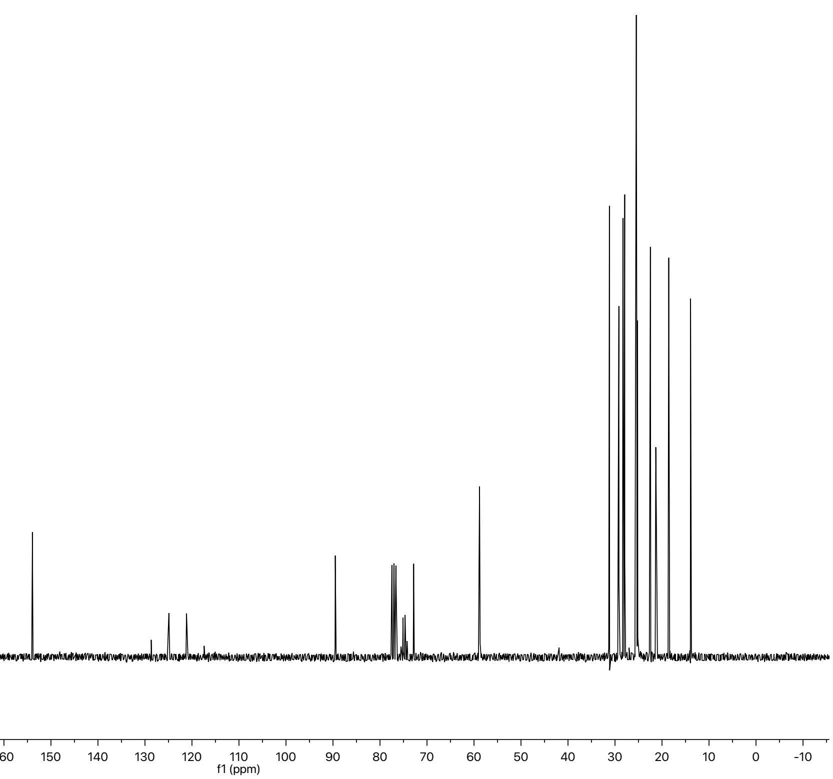
^{1}H NMR ($CDCl_3$)

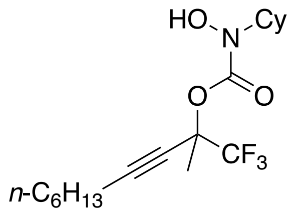




18m

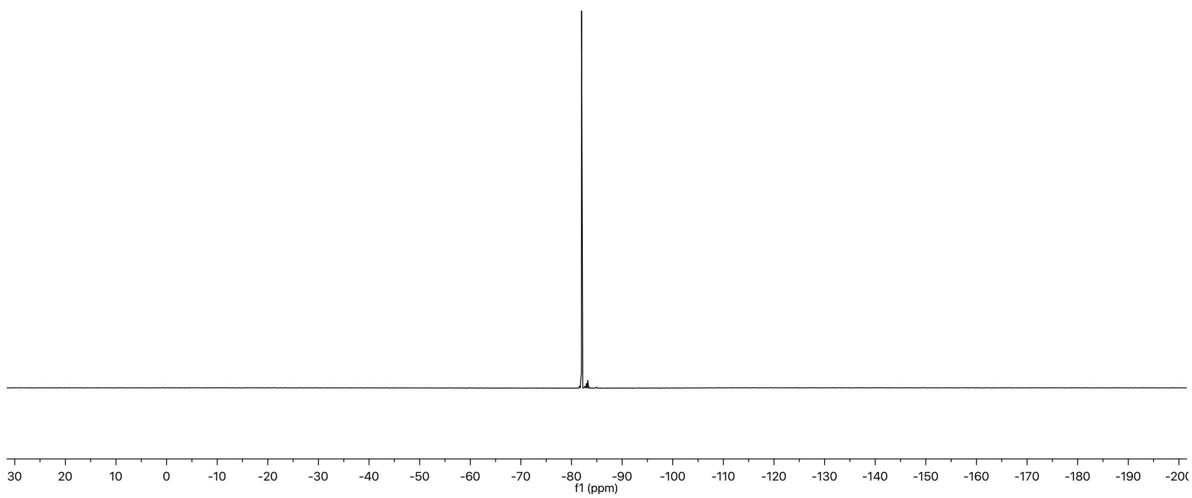
^{13}C NMR ($CDCl_3$)



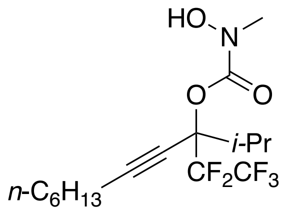


18m

^{19}F NMR ($CDCl_3$)

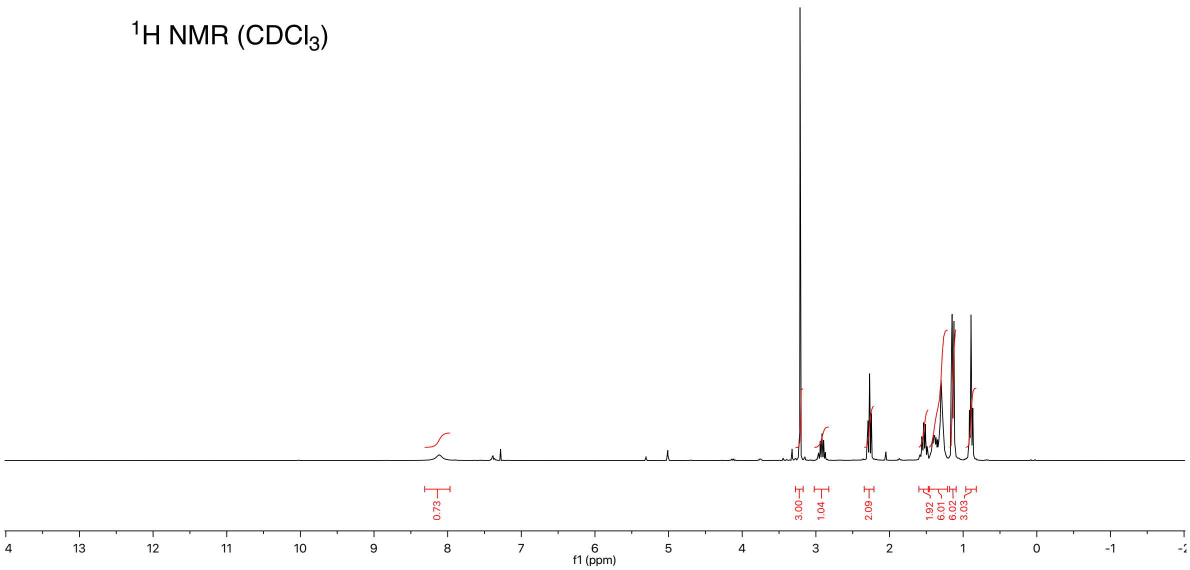


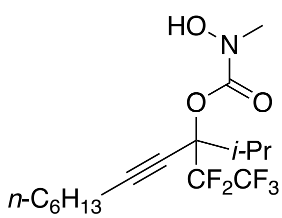
824



18n

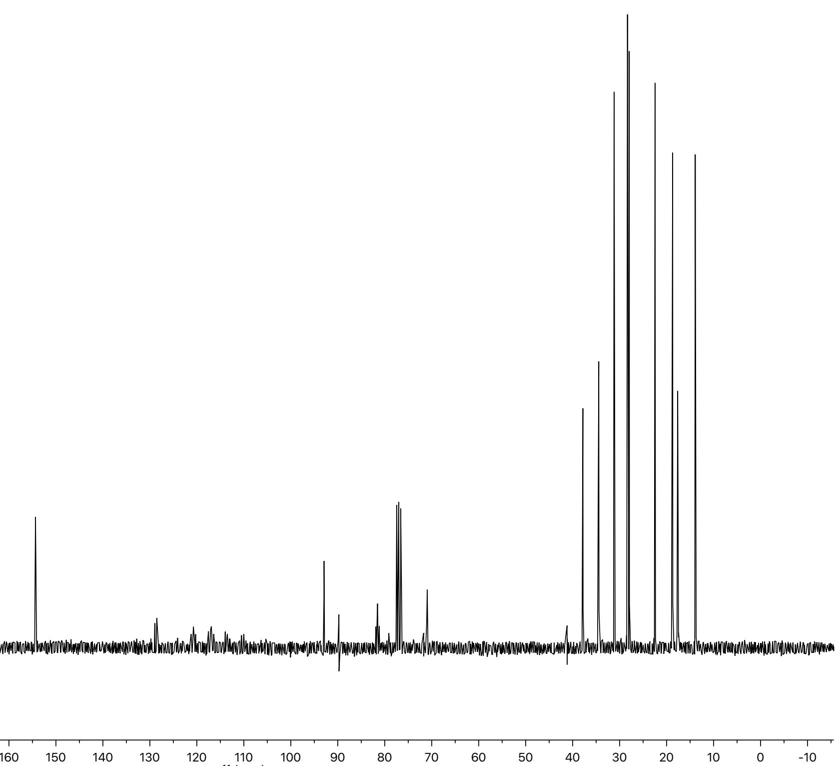
^{1}H NMR ($CDCl_3$)

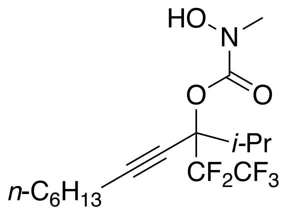




18n

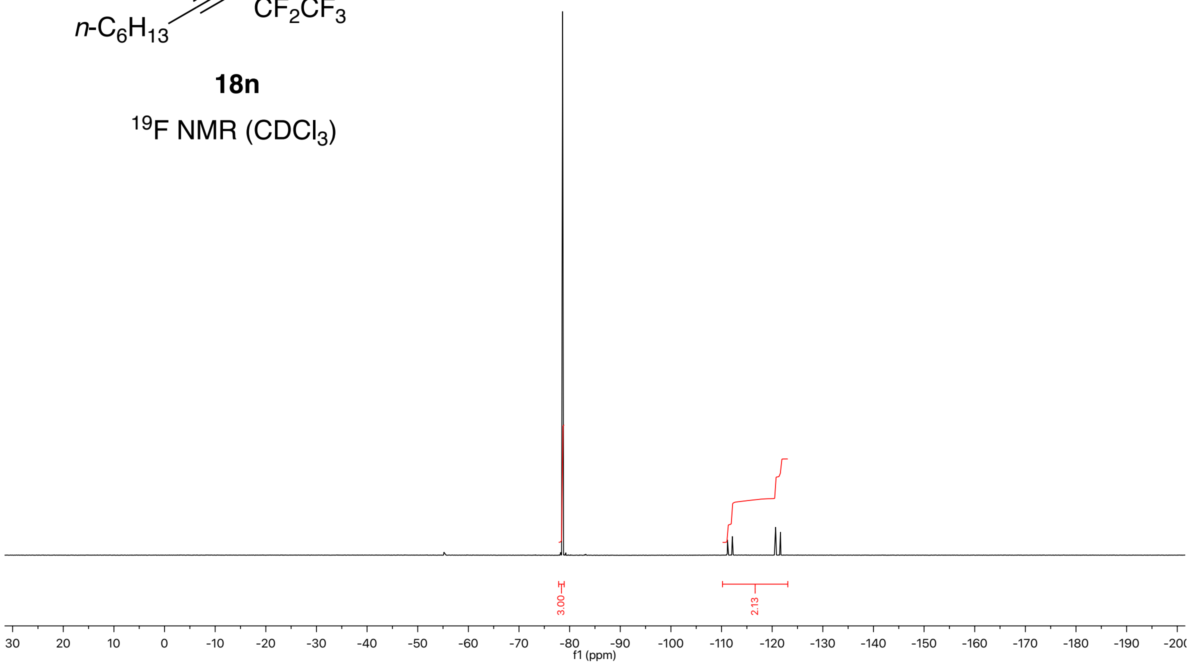
^{13}C NMR ($CDCl_3$)



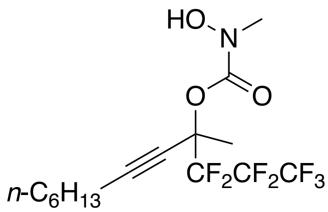


18n

^{19}F NMR ($CDCl_3$)

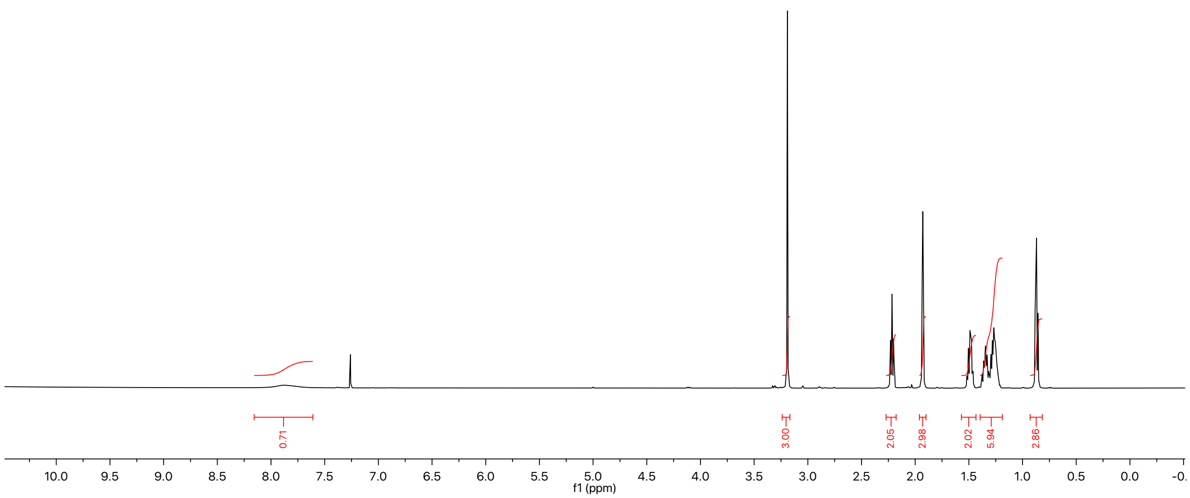


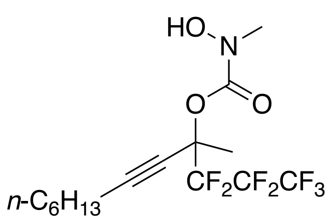
937



19o

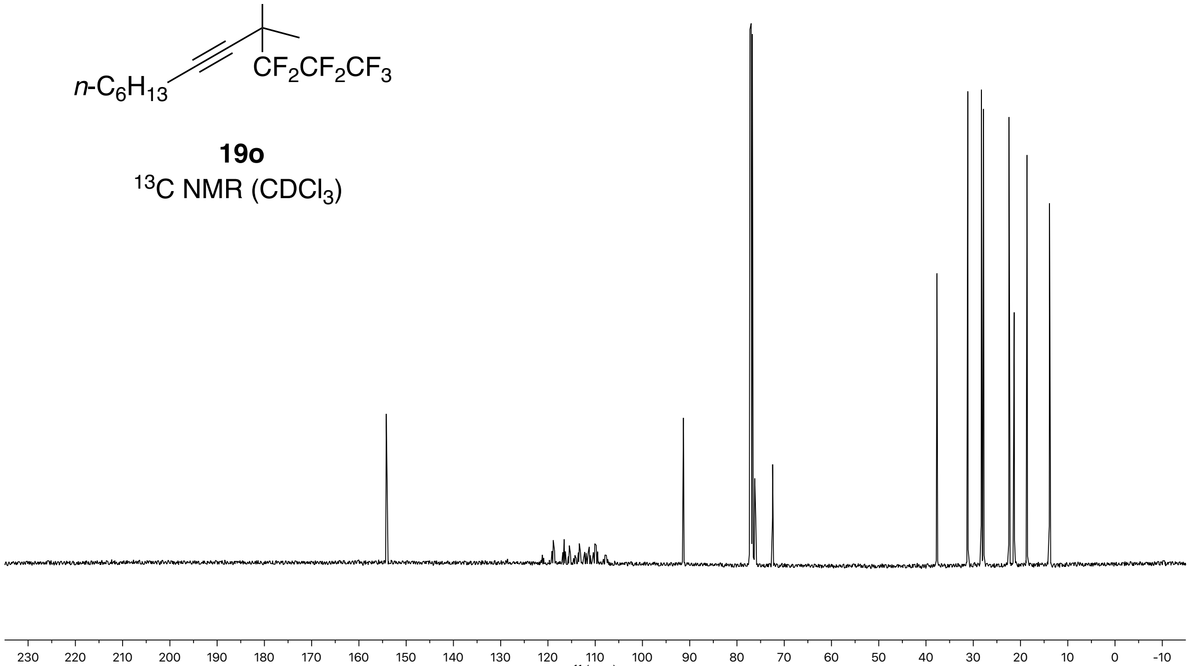
^{1}H NMR ($CDCl_3$)

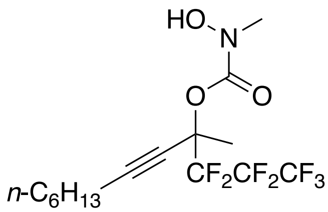




19o

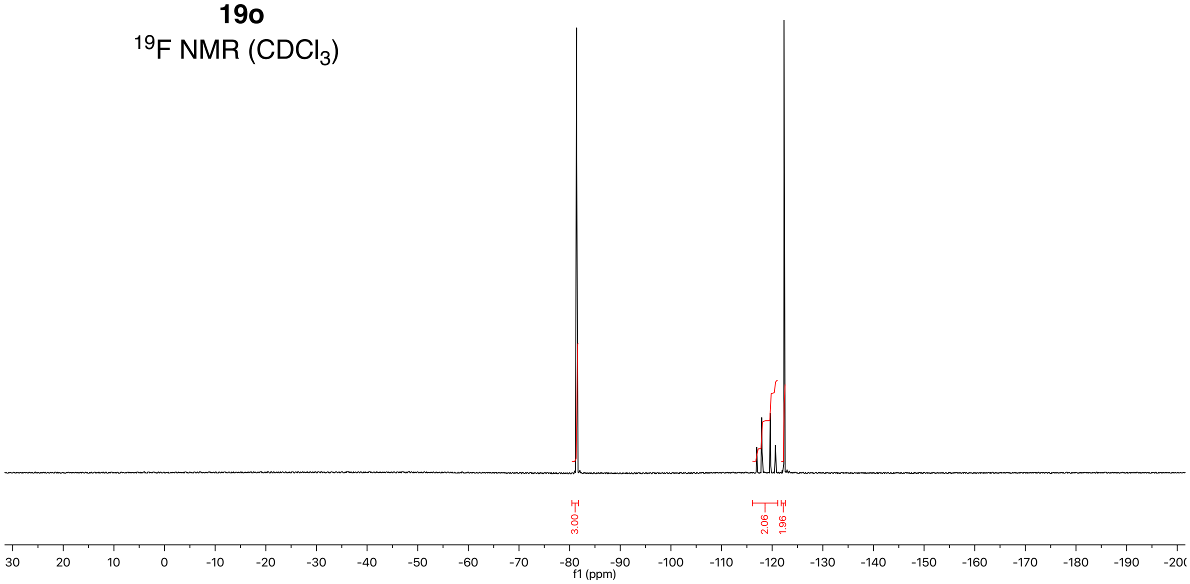
^{13}C NMR ($CDCl_3$)



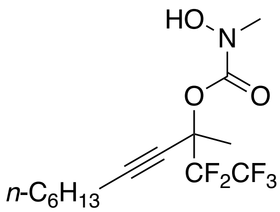


19o

^{19}F NMR ($CDCl_3$)

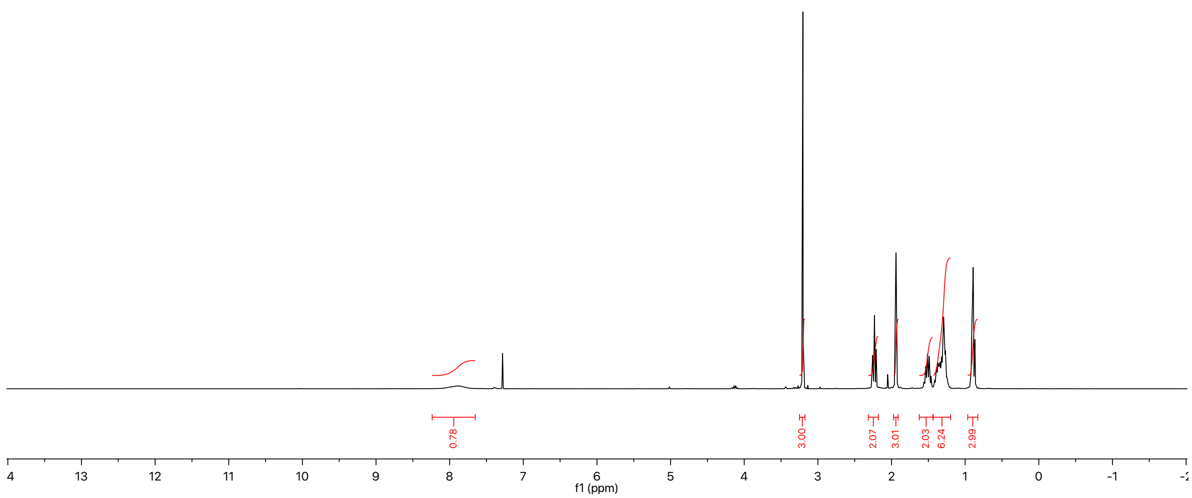


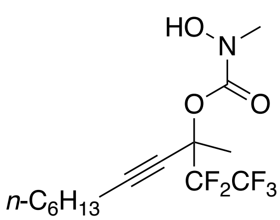
946



19p

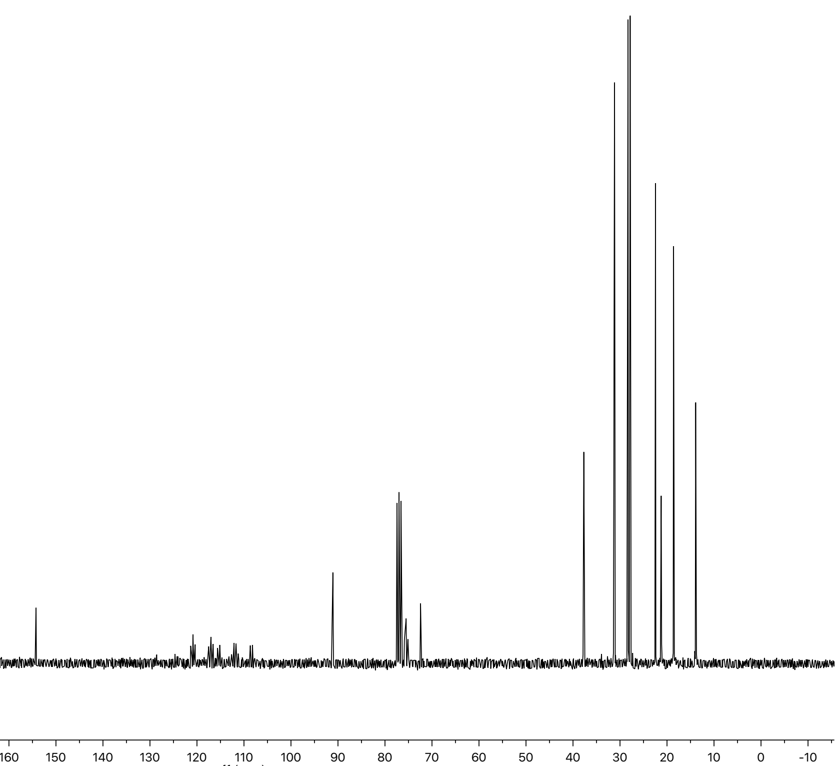
^1H NMR ($CDCl_3$)

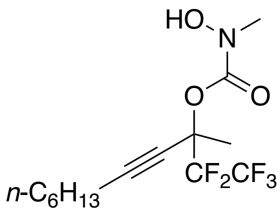




19p

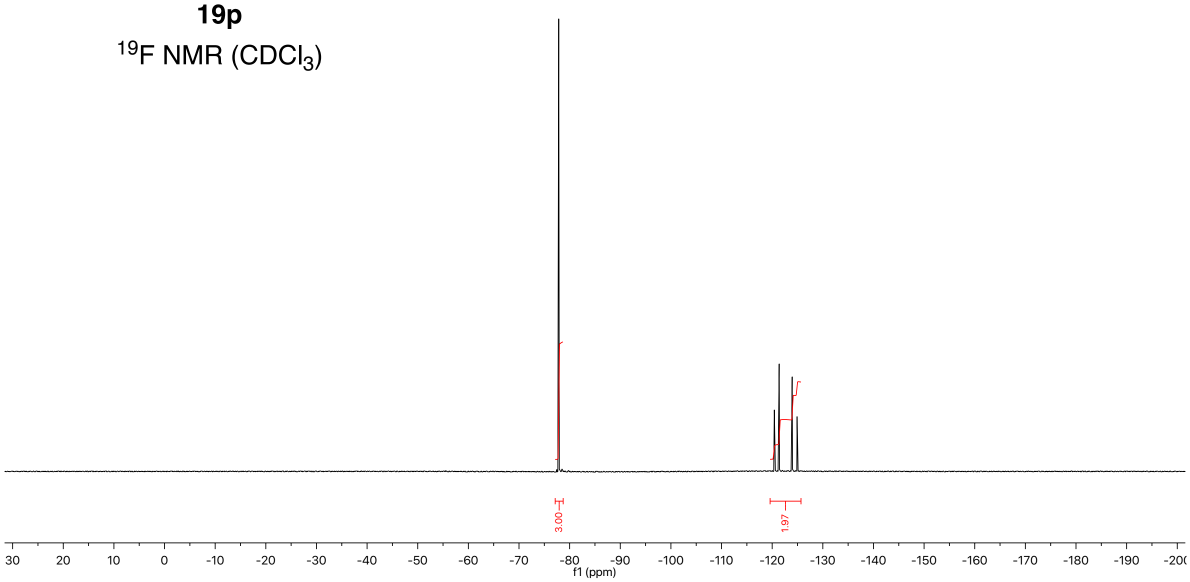
^{13}C NMR ($CDCl_3$)



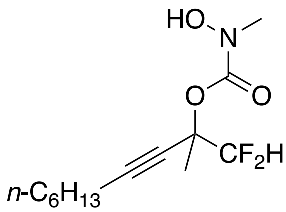


19p

^{19}F NMR ($CDCl_3$)

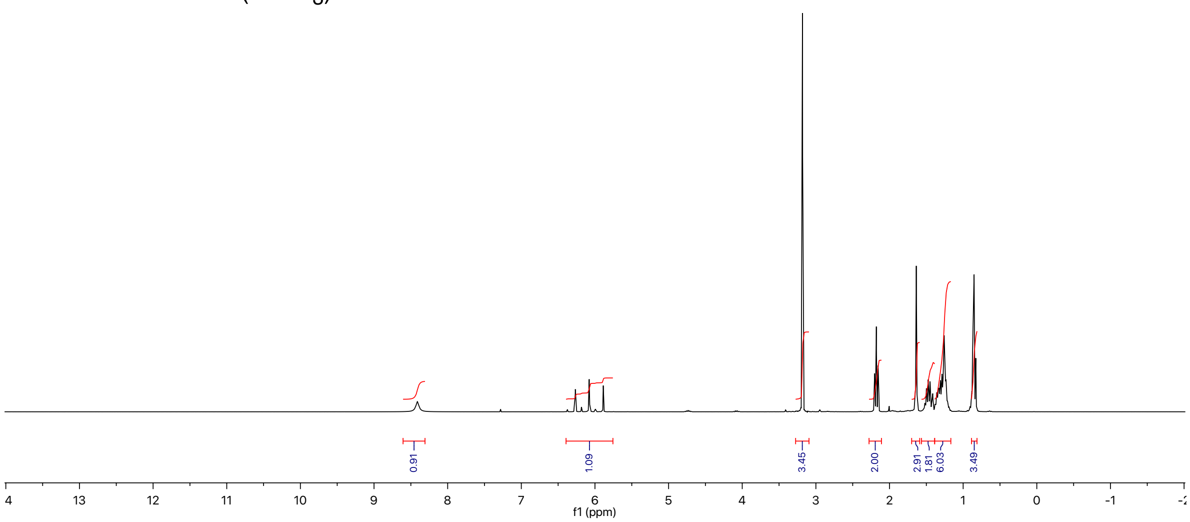


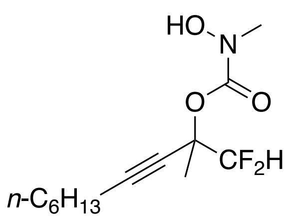
987



19q

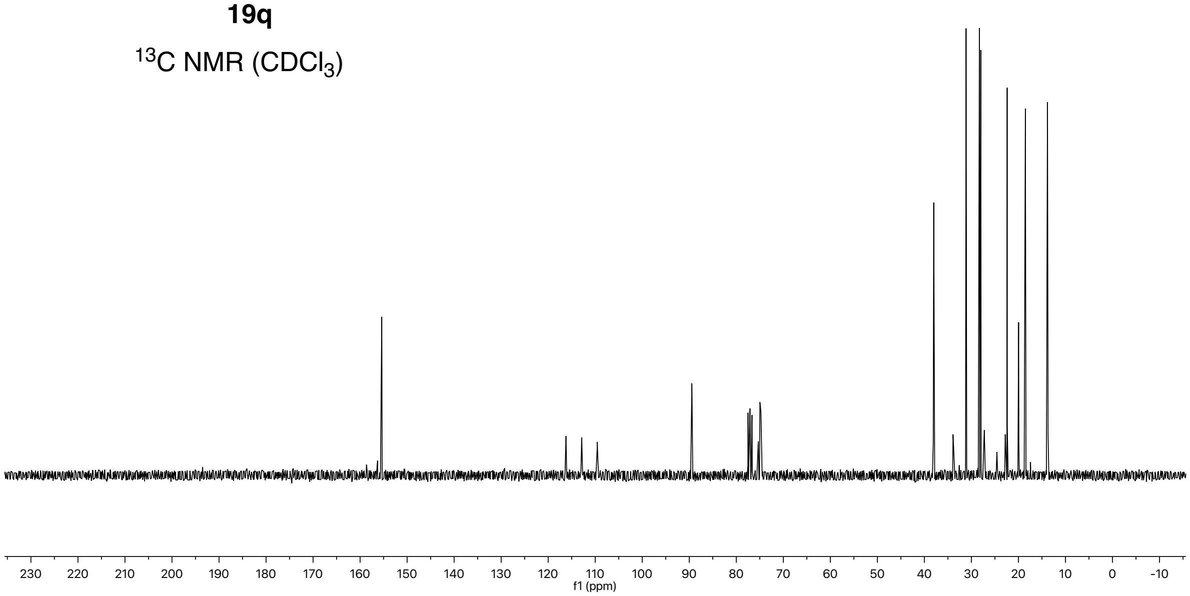
^{1}H NMR ($CDCl_3$)

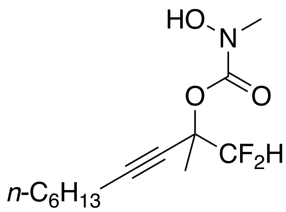




19q

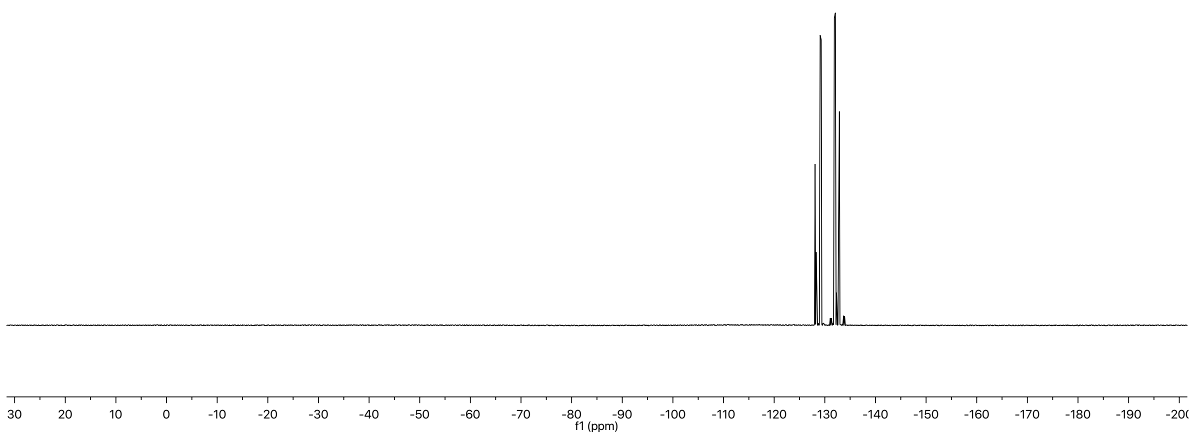
^{13}C NMR ($CDCl_3$)



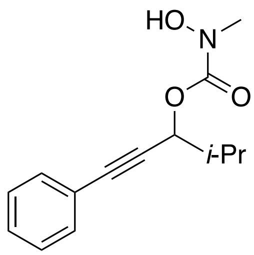


19q

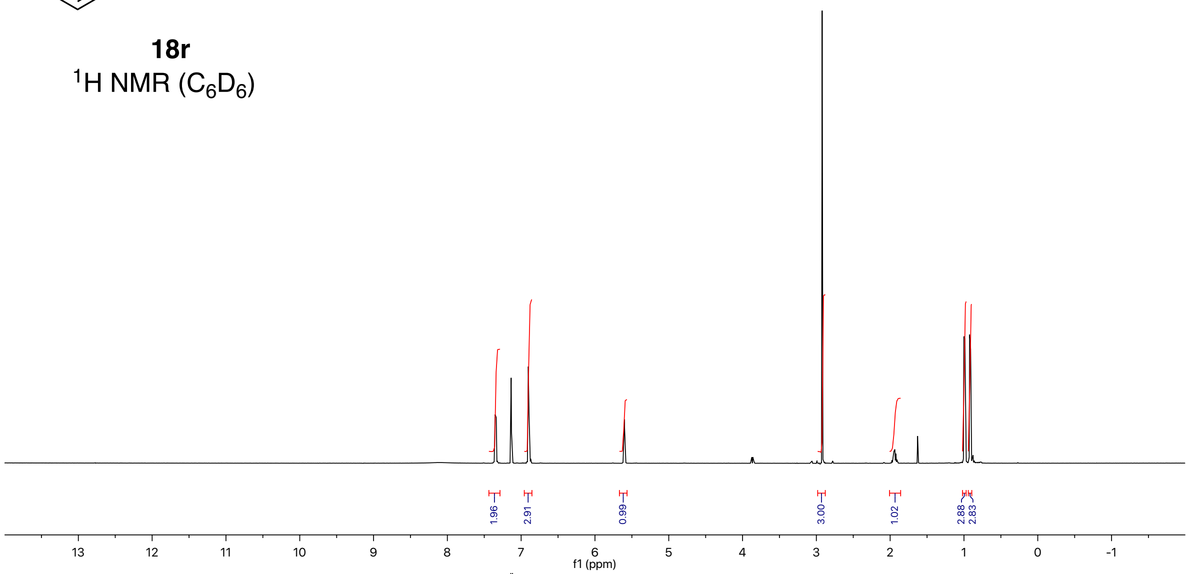
^{19}F NMR ($CDCl_3$)

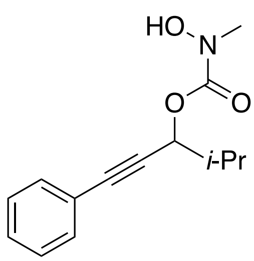


1036

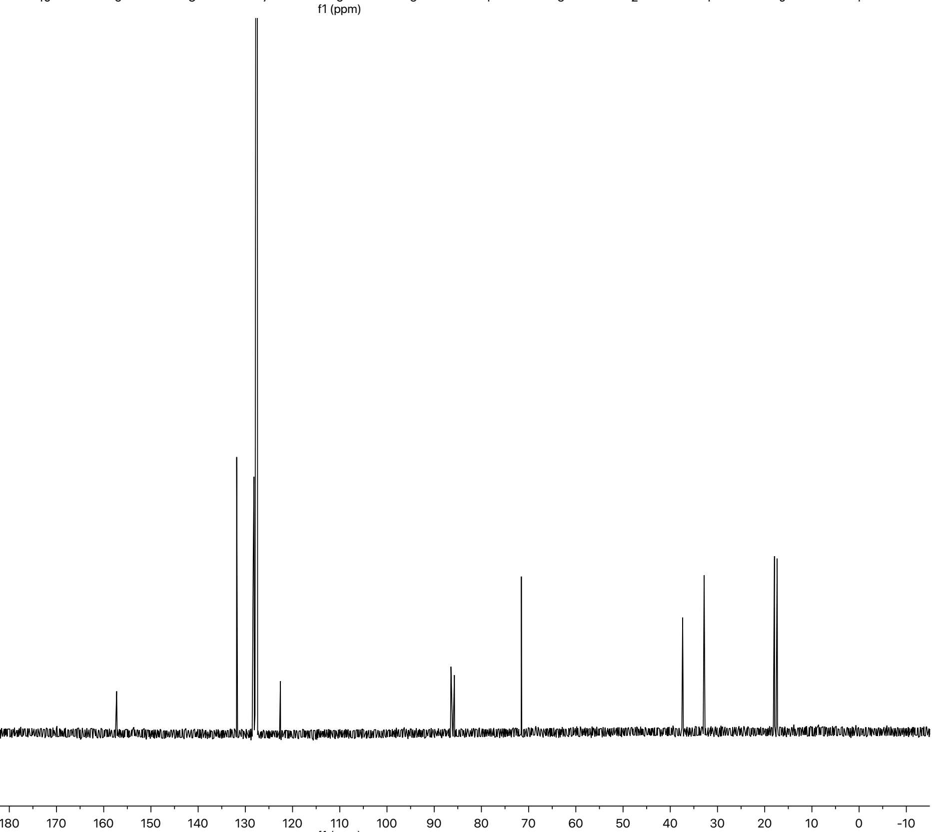


18r
^{1}H NMR (C_6D_6)

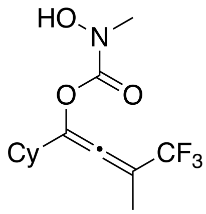




18r
^{13}C NMR (C_6D_6)

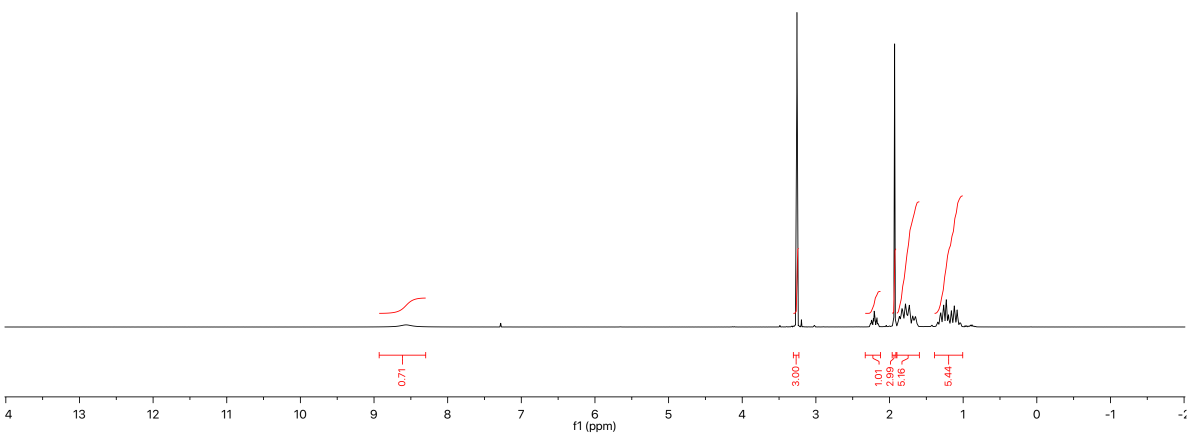


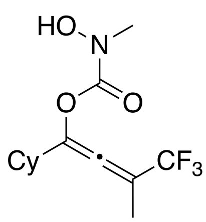
NMR spectrums for allenes (**29a**-**29i**, **29k**-**29q**).



29a

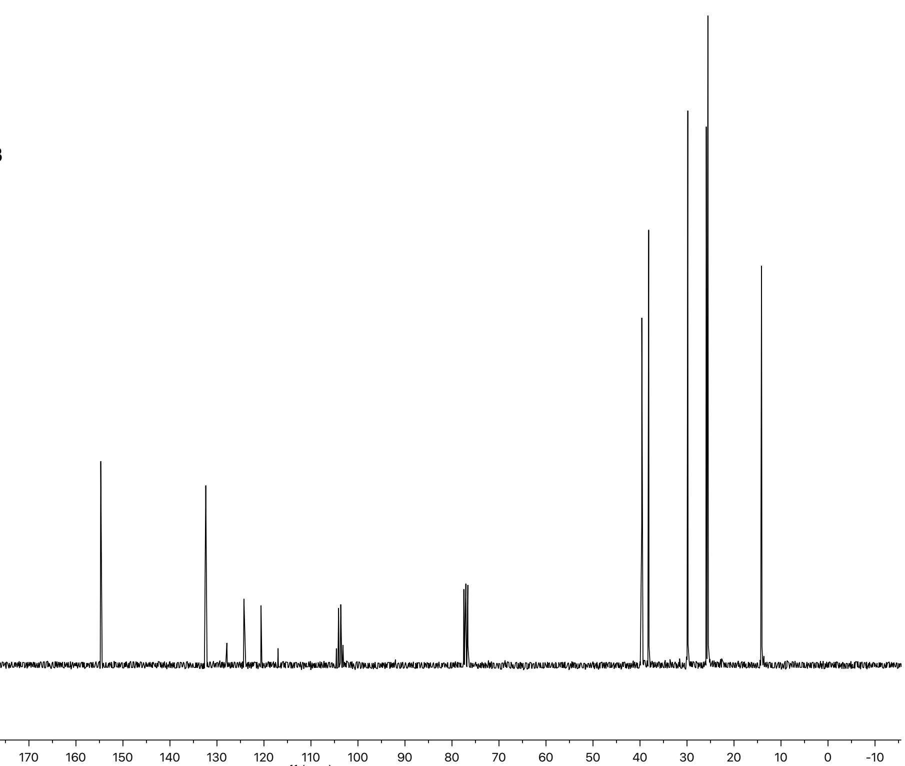
^{1}H NMR ($CDCl_3$)

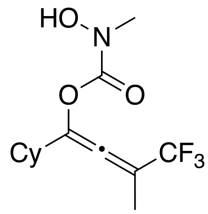




29a

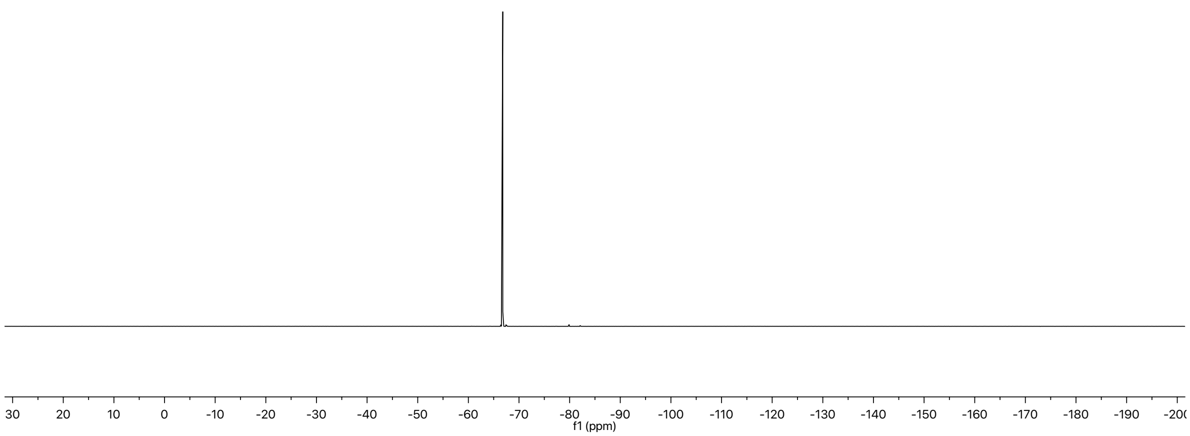
^{13}C NMR ($CDCl_3$)



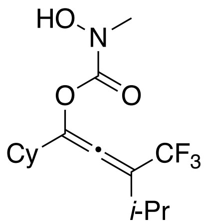


29a

^{19}F NMR ($CDCl_3$)

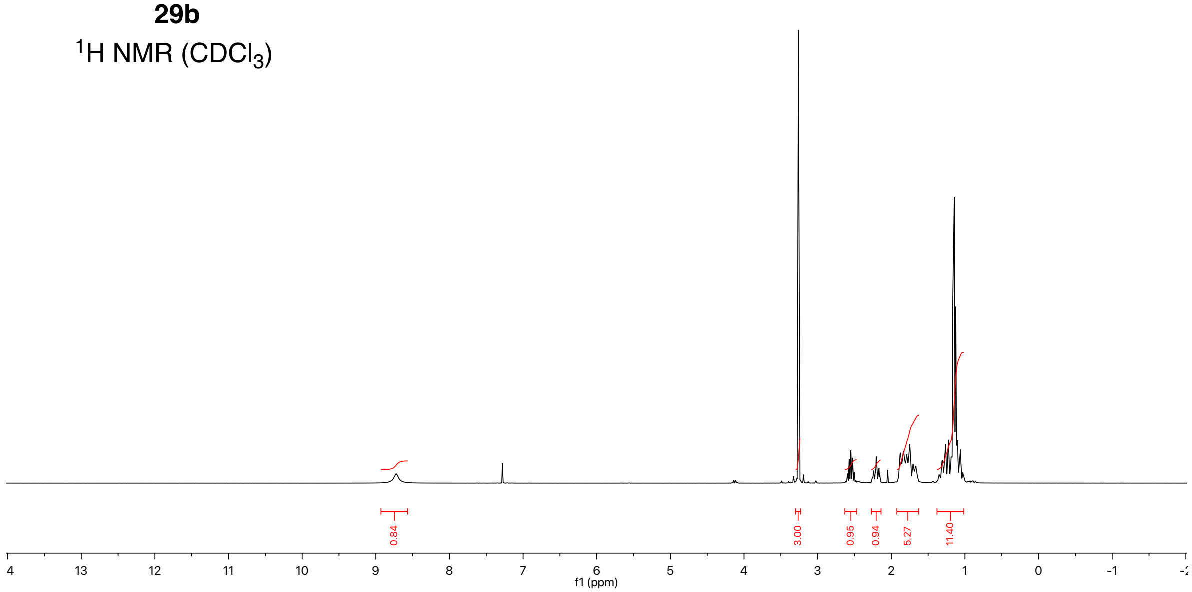


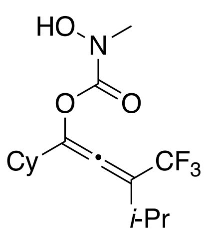
785-allene



29b

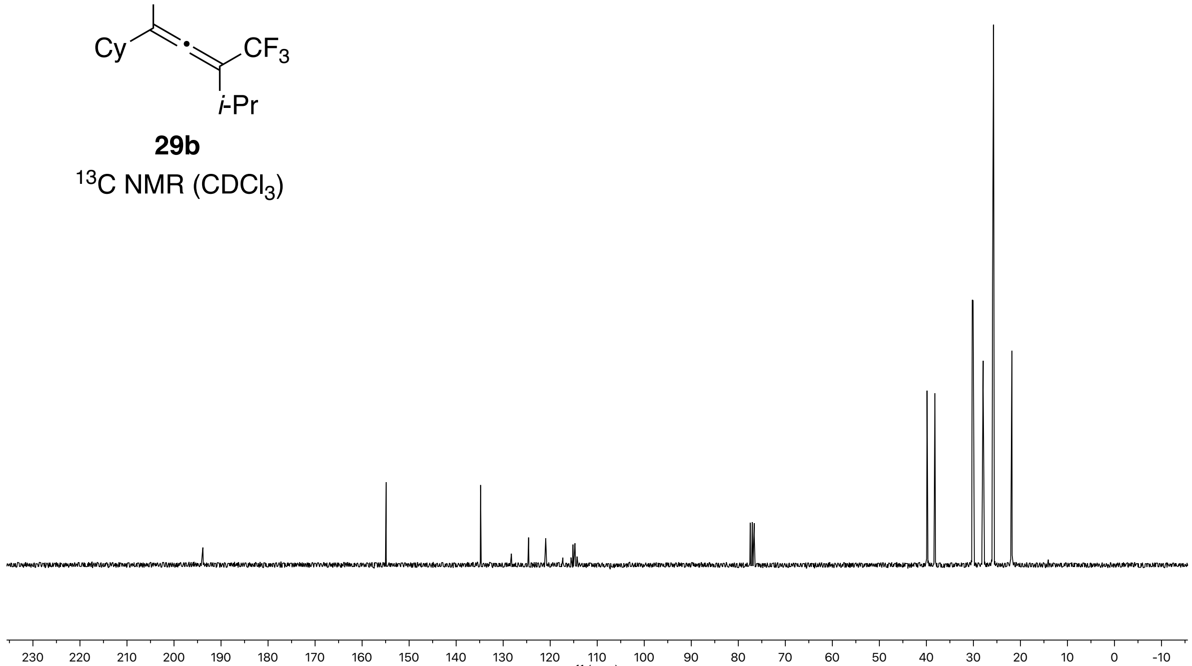
^{1}H NMR ($CDCl_3$)

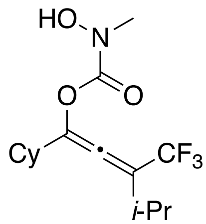




29b

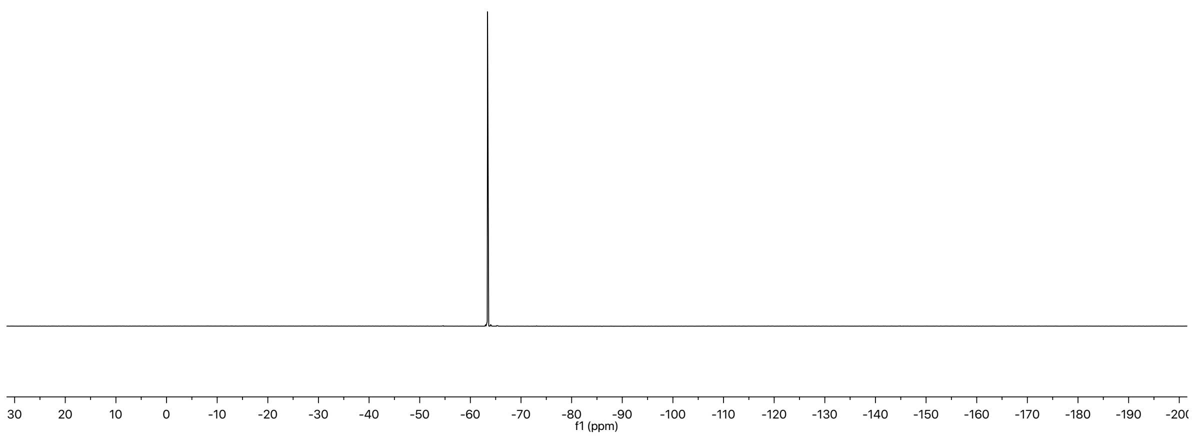
^{13}C NMR ($CDCl_3$)



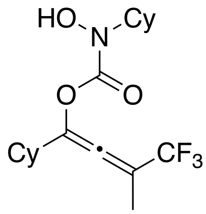


29b

^{19}F NMR ($CDCl_3$)

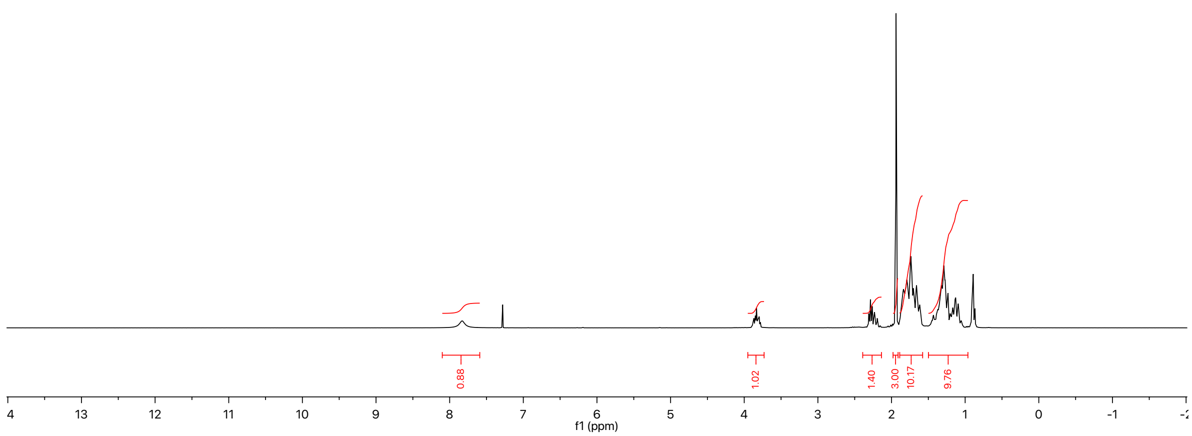


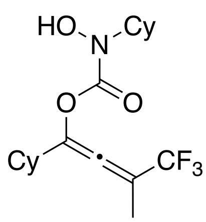
851-allene



29c

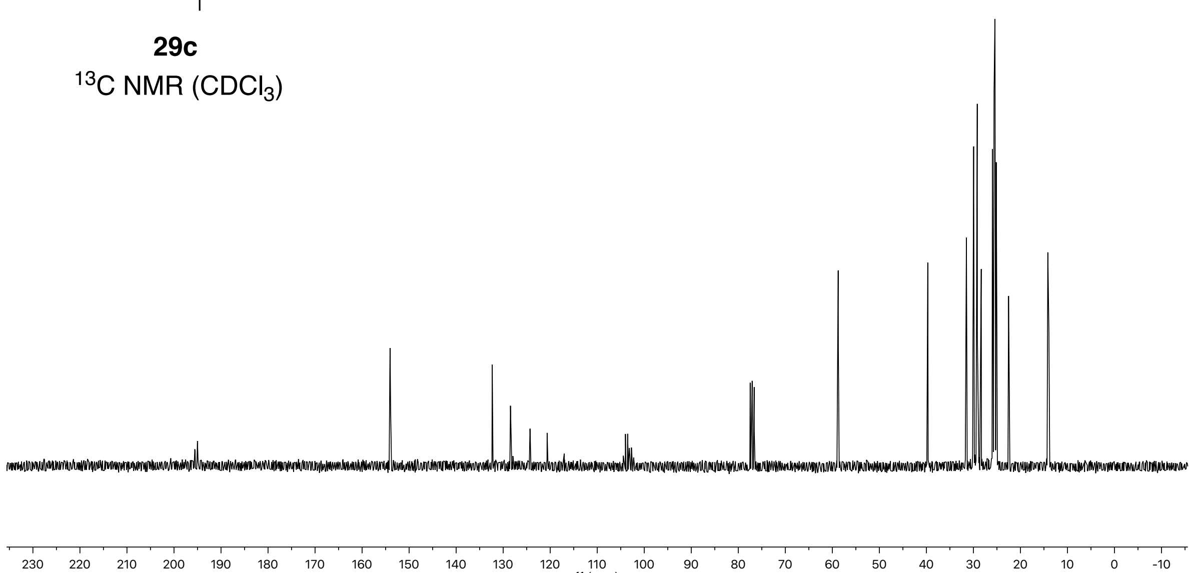
^{1}H NMR ($CDCl_3$)

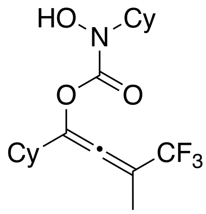




29c

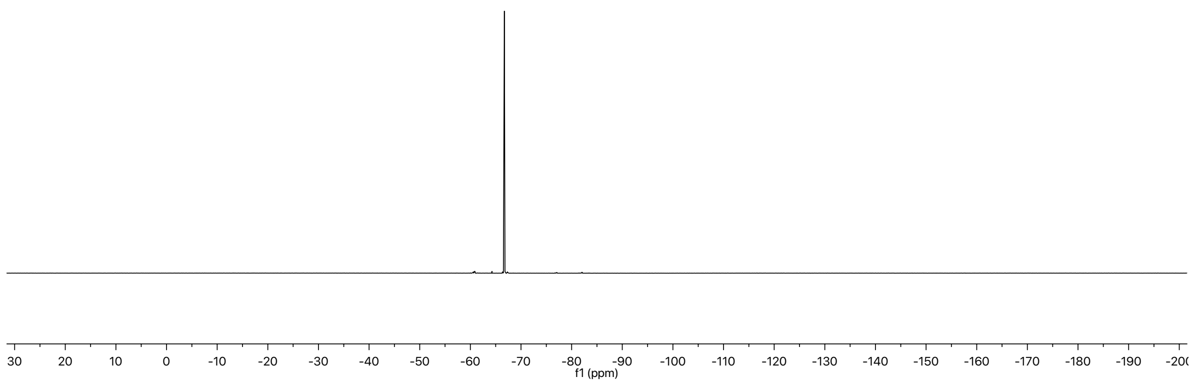
^{13}C NMR ($CDCl_3$)



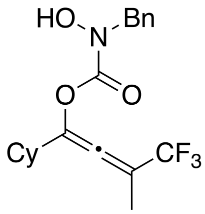


29c

^{19}F NMR ($CDCl_3$)

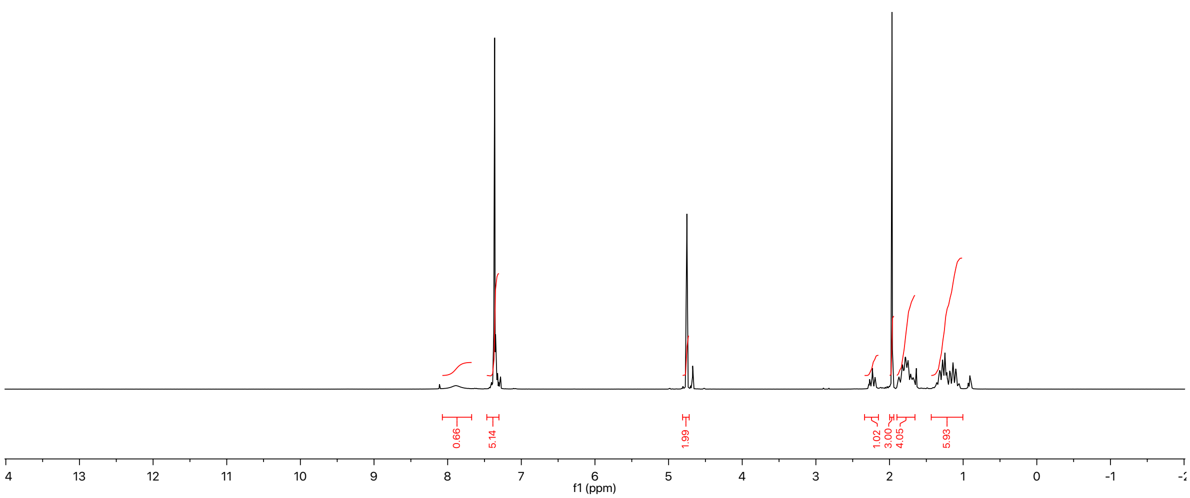


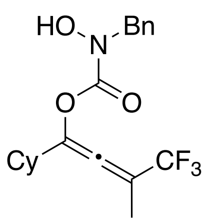
850-allene



29d

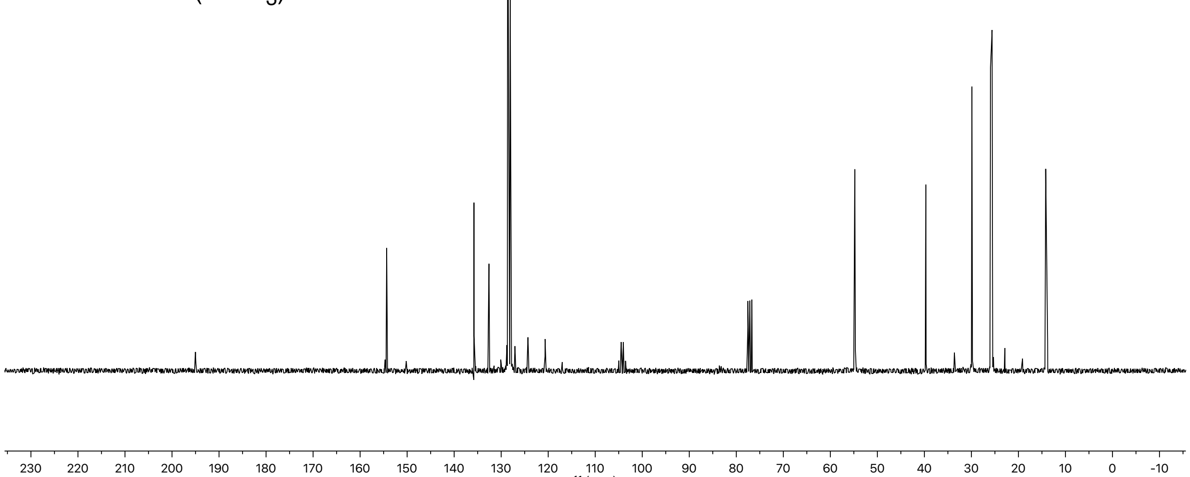
^{1}H NMR ($CDCl_3$)

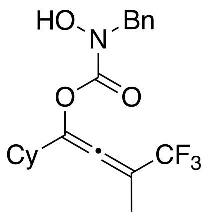




29d

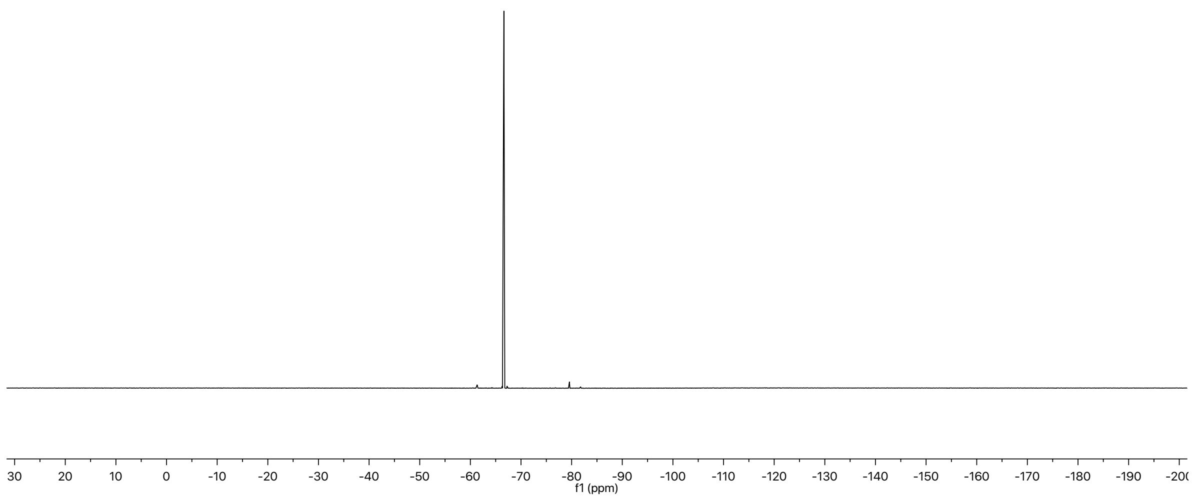
^{13}C NMR ($CDCl_3$)



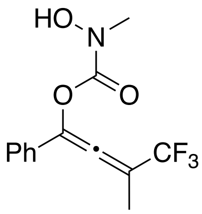


29d

^{19}F NMR ($CDCl_3$)

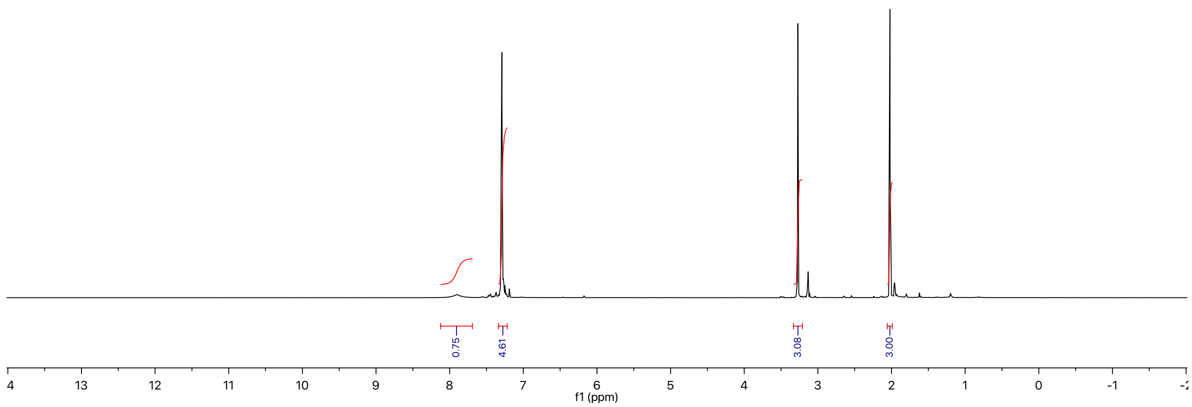


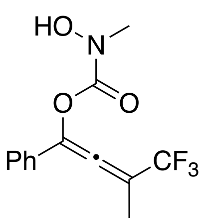
867-allene



29e

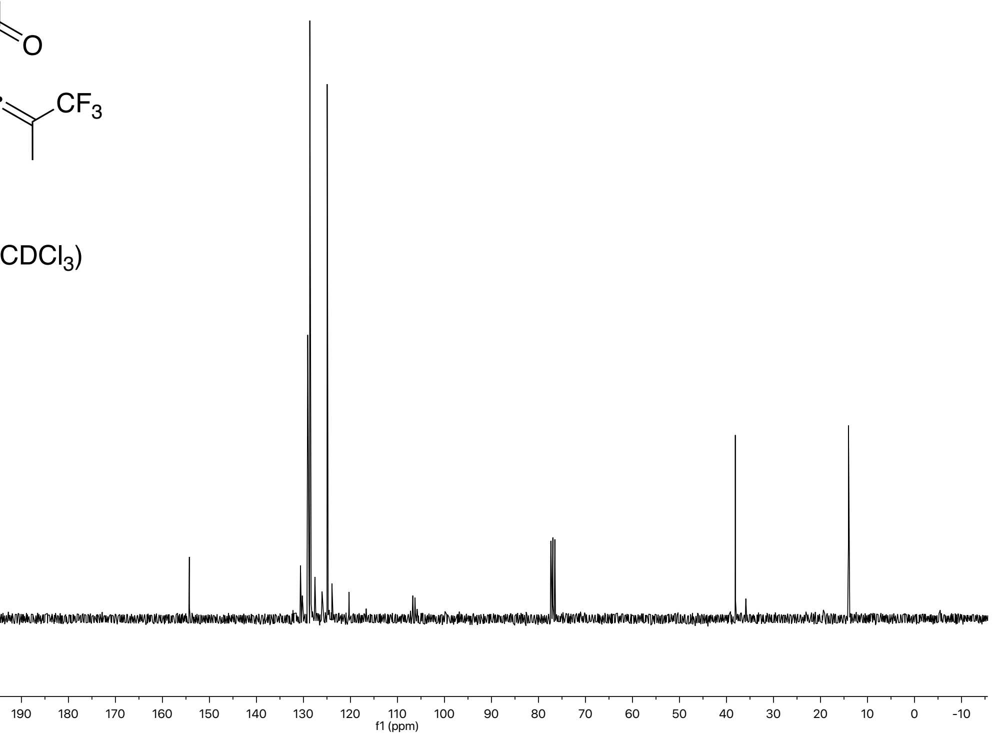
^{1}H NMR ($CDCl_3$)

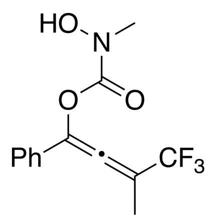




29e

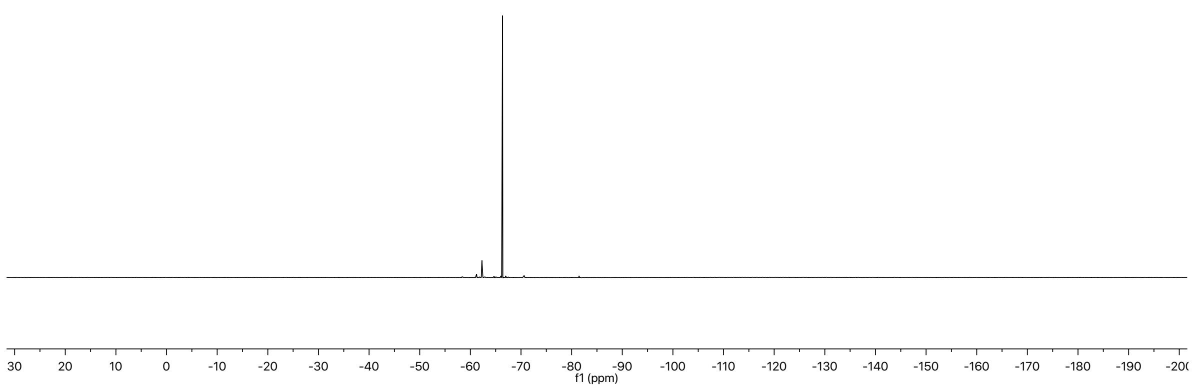
^{13}C NMR ($CDCl_3$)



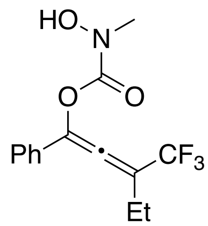


29e

^{19}F NMR ($CDCl_3$)

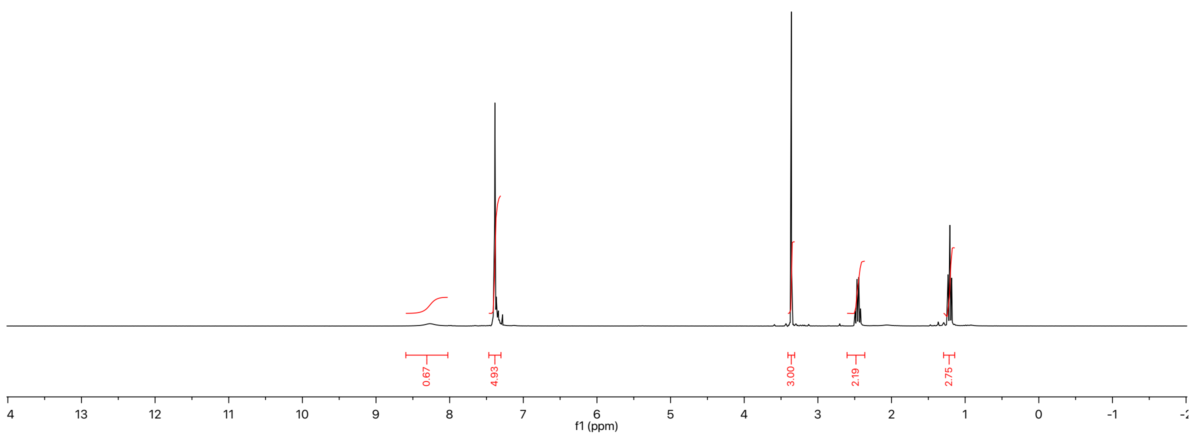


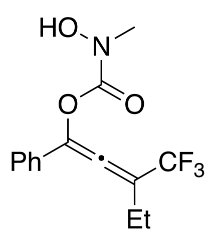
1051-allene



29f

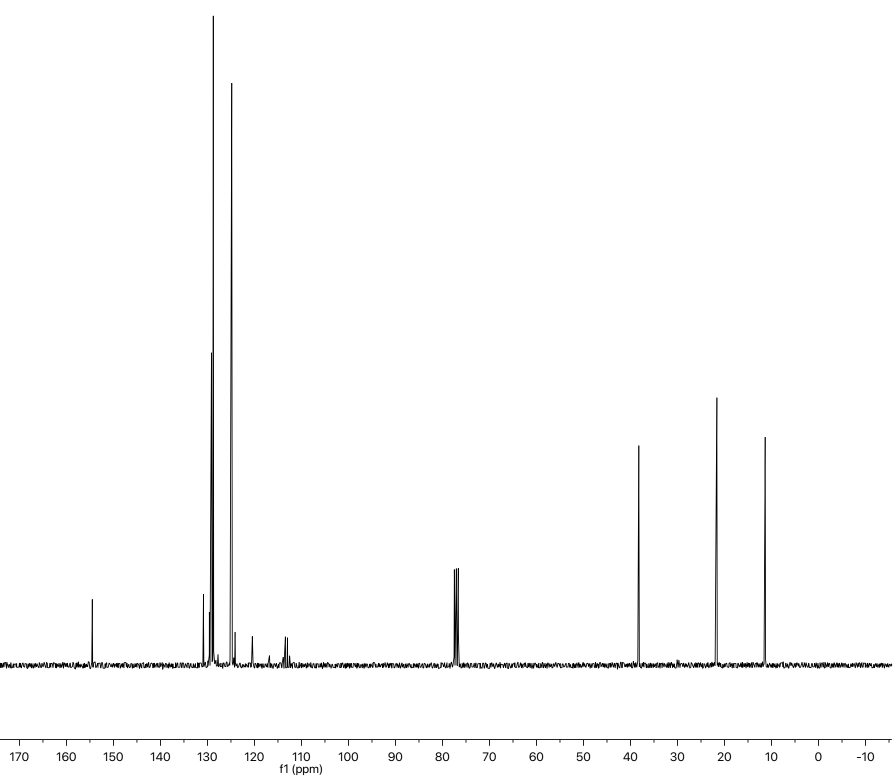
^{1}H NMR ($CDCl_3$)

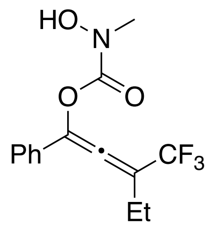




29f

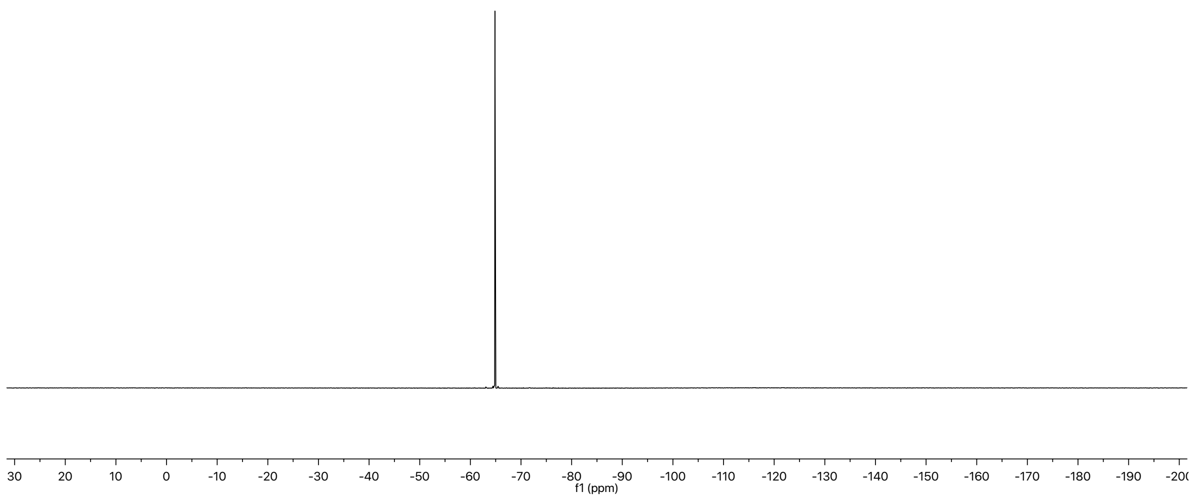
^{13}C NMR ($CDCl_3$)



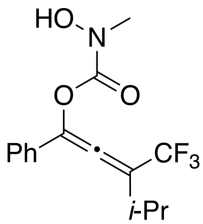


29f

^{19}F NMR (CDCl$_3$)

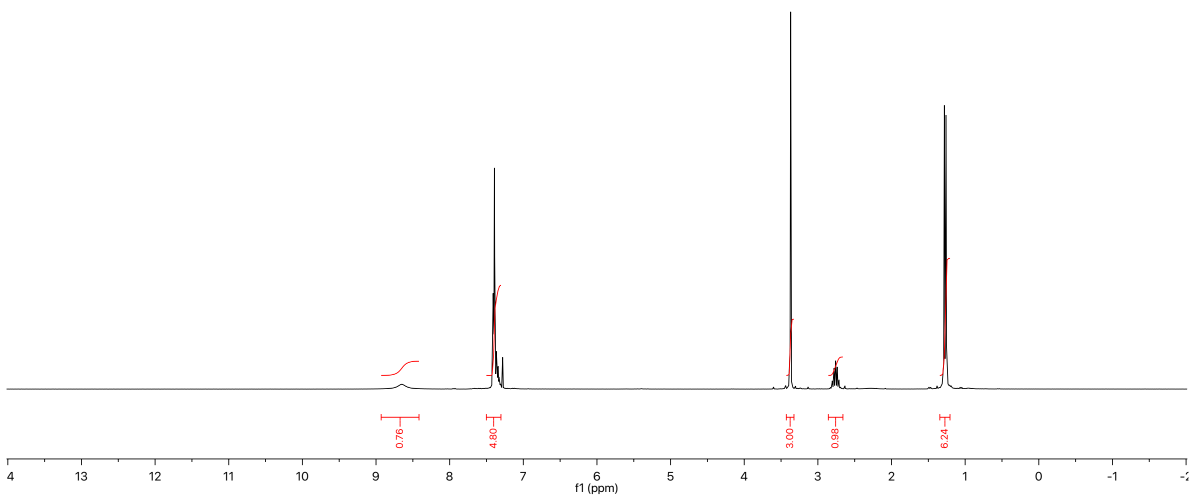


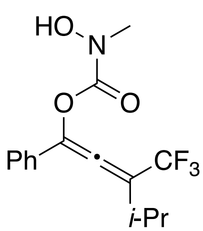
858-allene



29g

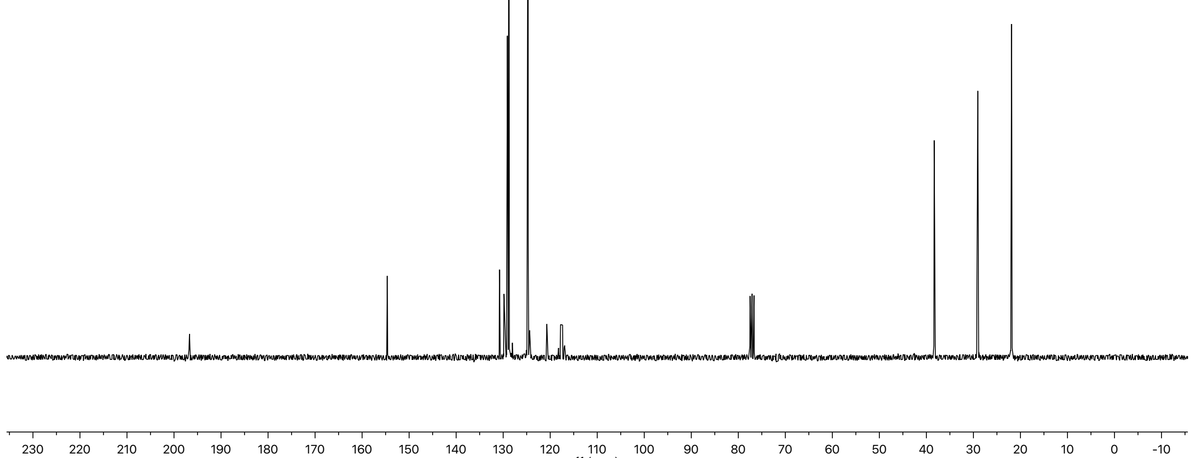
^{1}H NMR ($CDCl_3$)

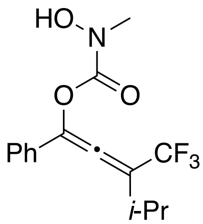




29g

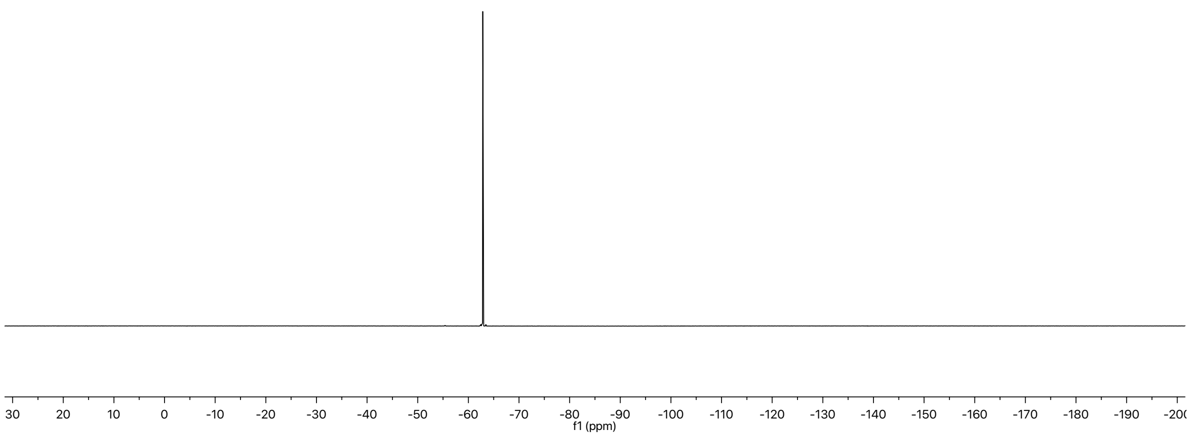
^{13}C NMR ($CDCl_3$)



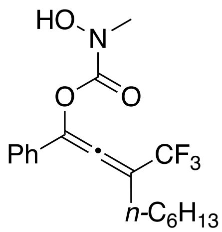


29g

^{19}F NMR ($CDCl_3$)

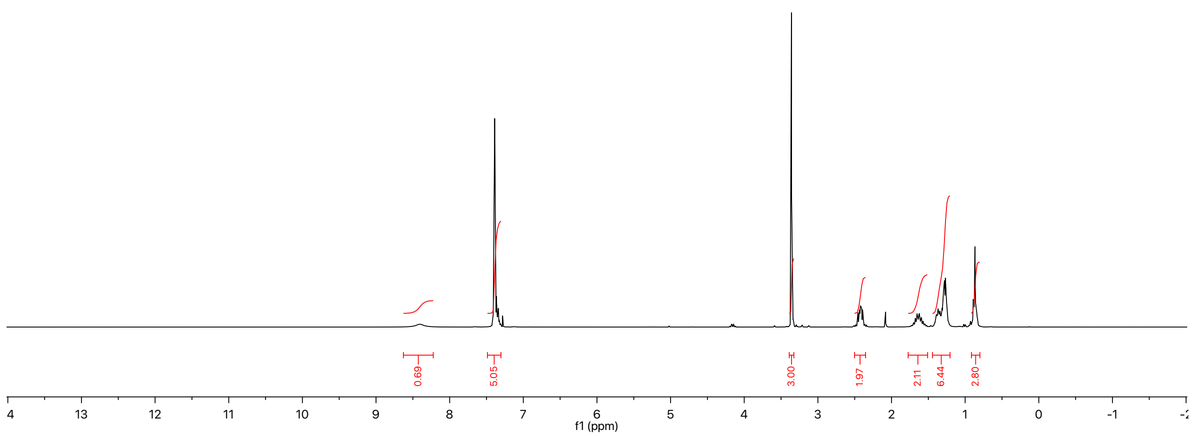


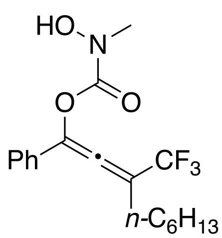
855-allene



29h

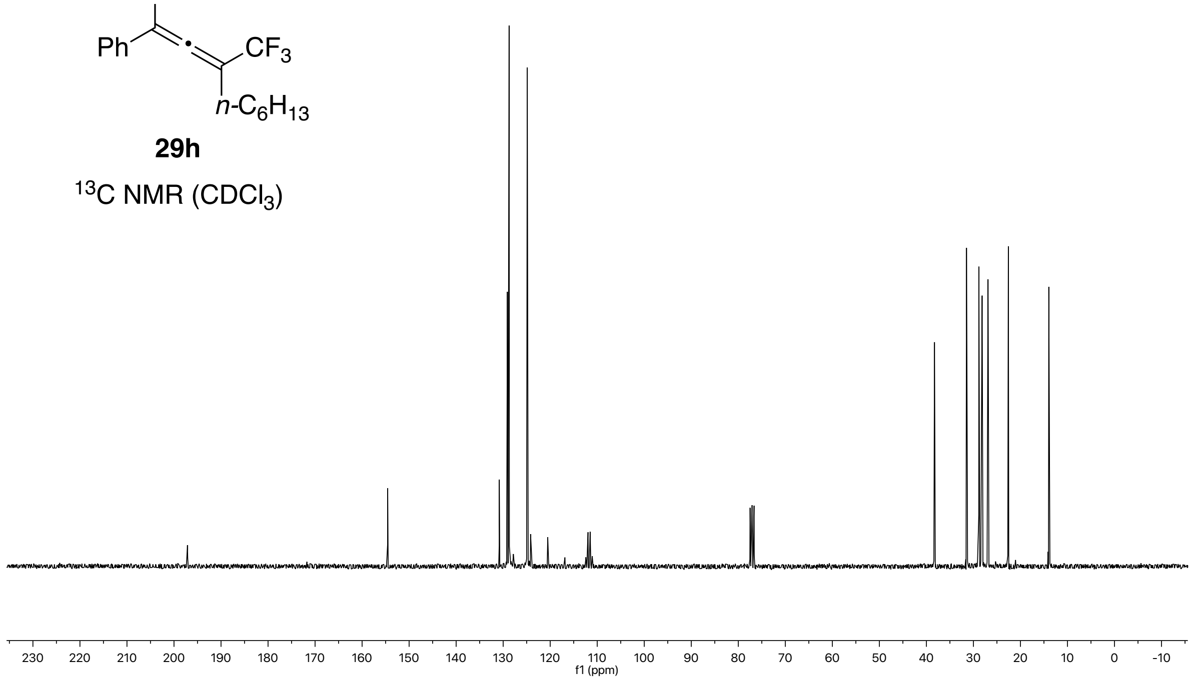
^{1}H NMR ($CDCl_3$)

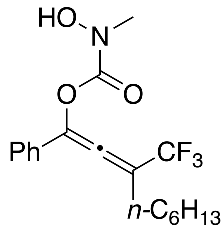




29h

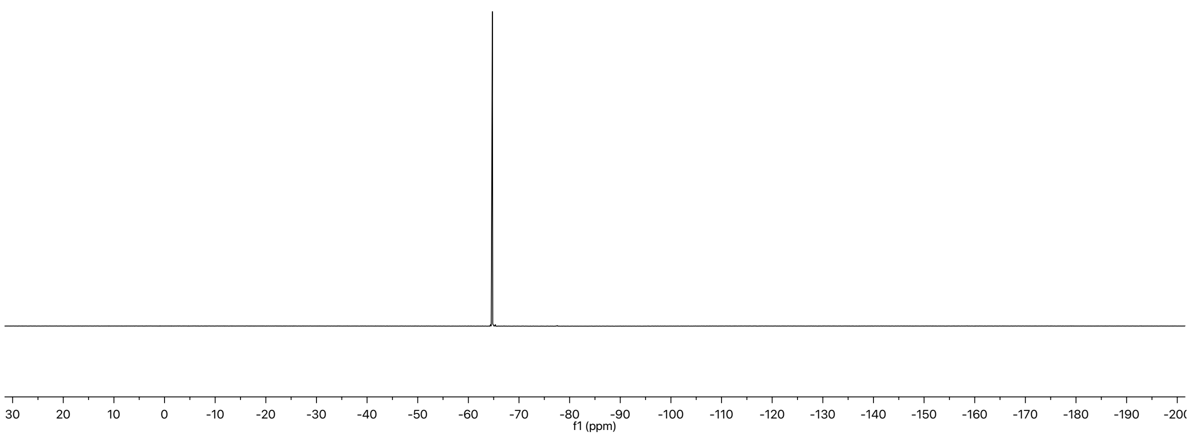
^{13}C NMR ($CDCl_3$)



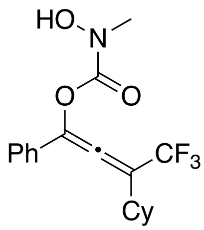


29h

^{19}F NMR ($CDCl_3$)

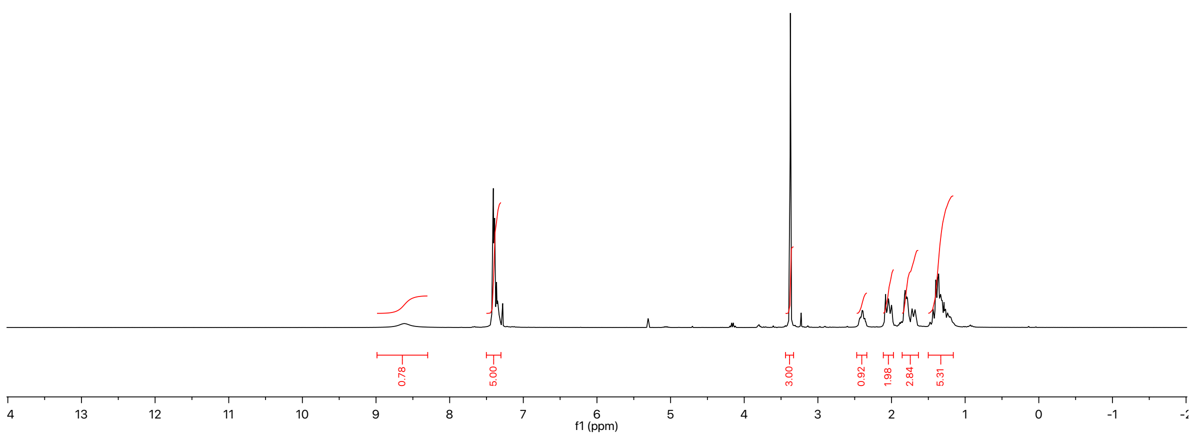


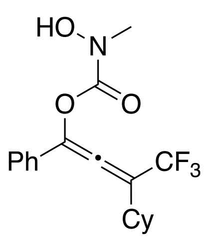
913-allene



29i

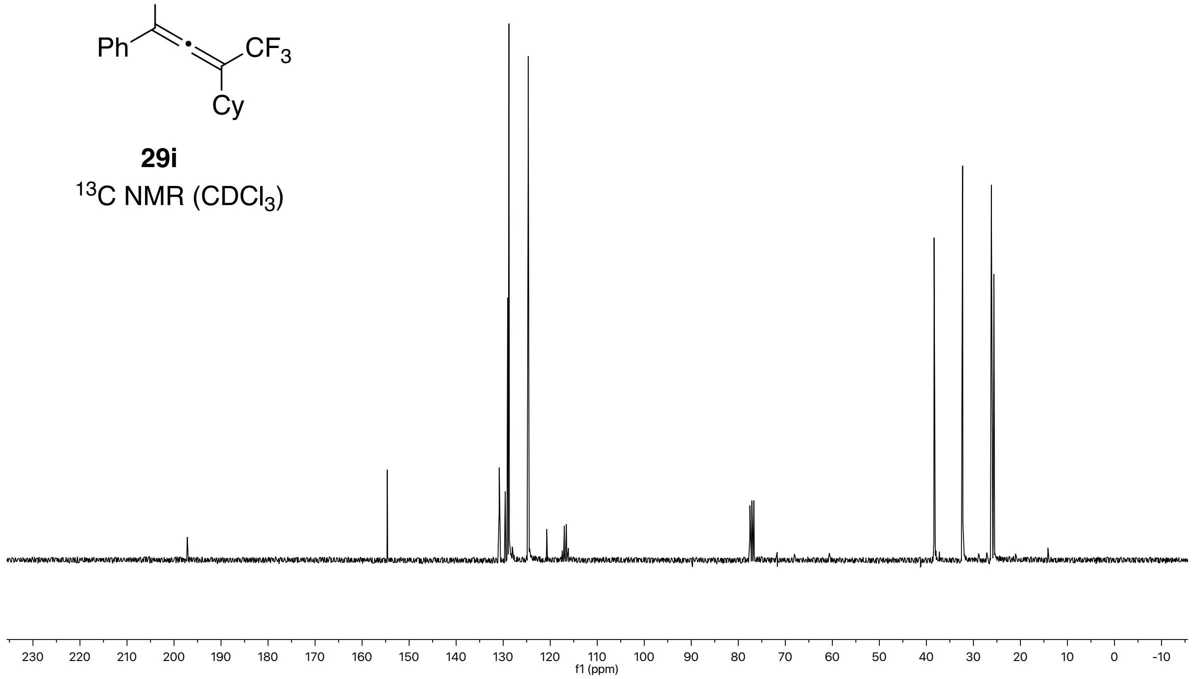
^{1}H NMR ($CDCl_3$)

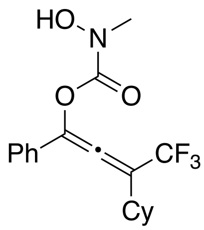




29i

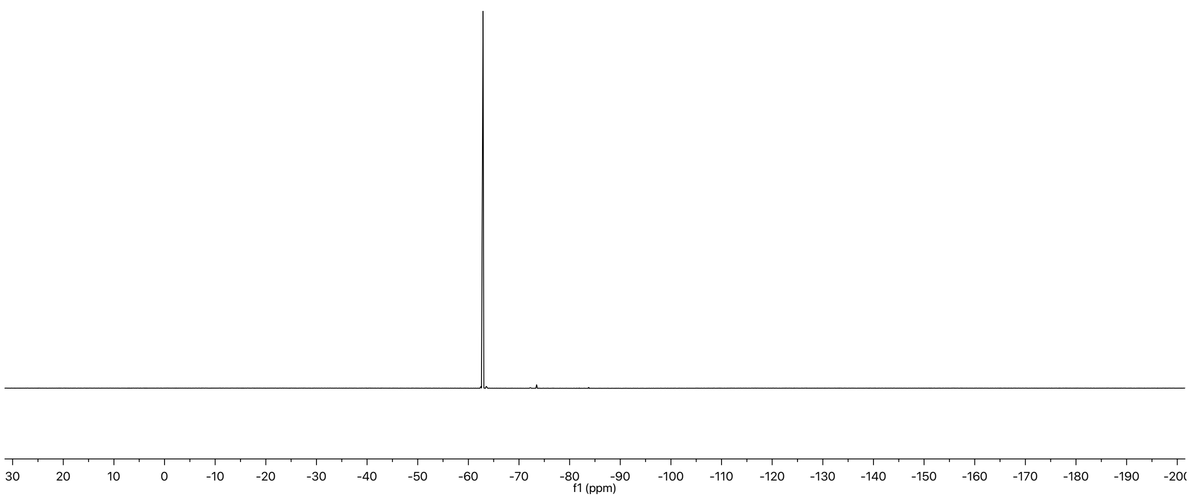
^{13}C NMR ($CDCl_3$)



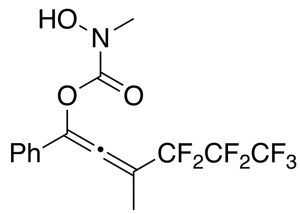


29i

^{19}F NMR ($CDCl_3$)

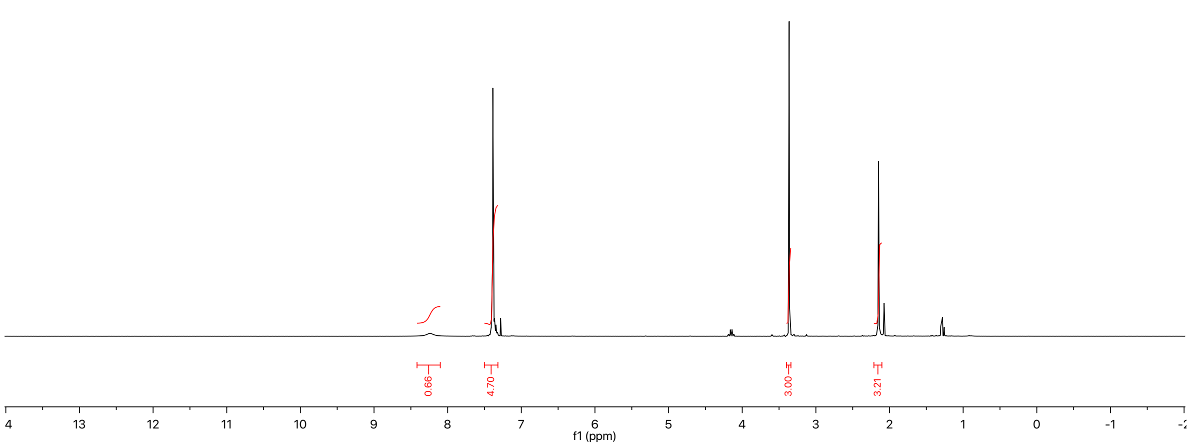


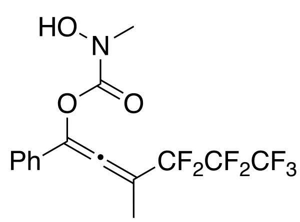
934-allene



29k

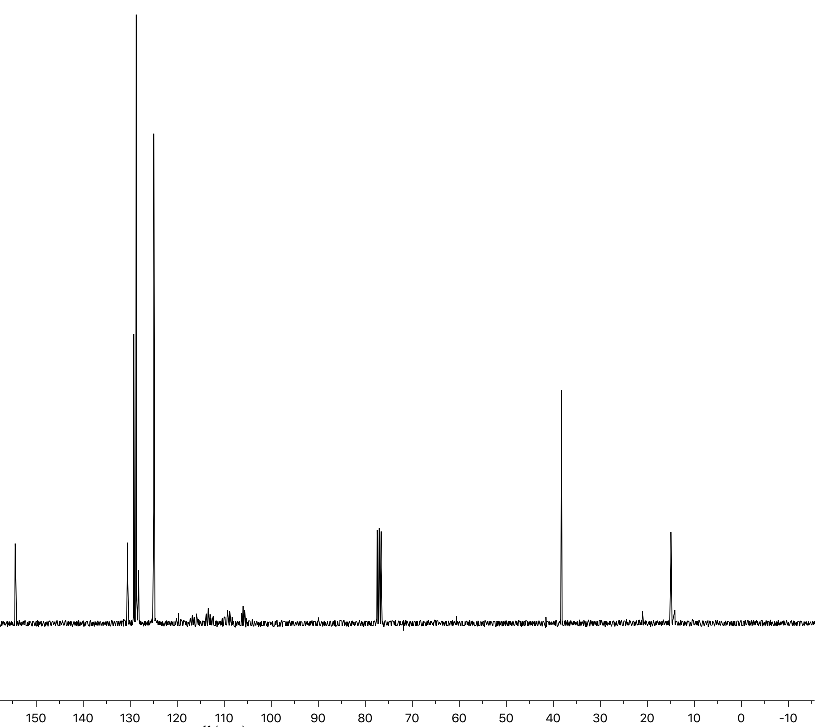
^{1}H NMR ($CDCl_3$)

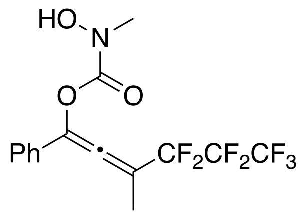




29k

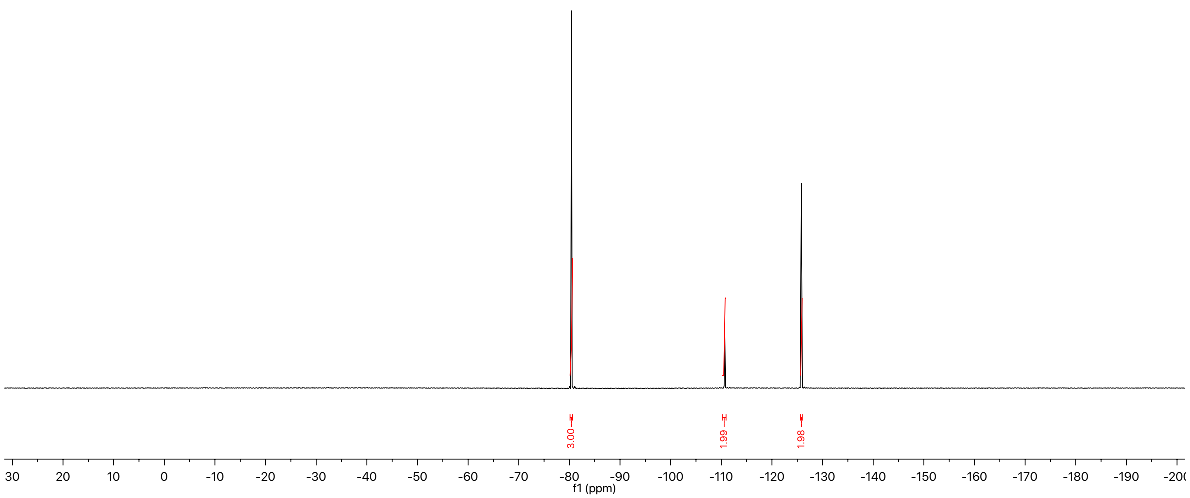
^{13}C NMR ($CDCl_3$)



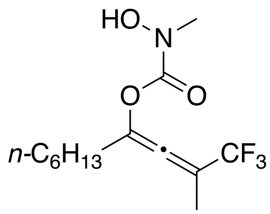


29k

^{19}F NMR ($CDCl_3$)

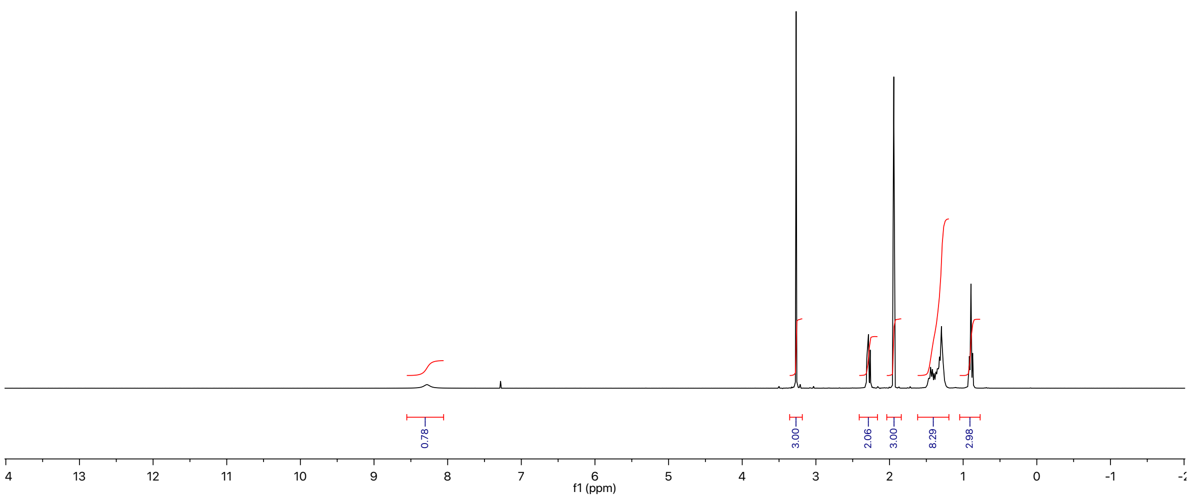


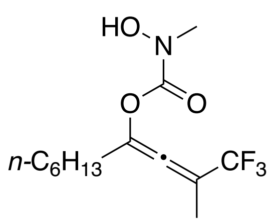
909-allene



29l

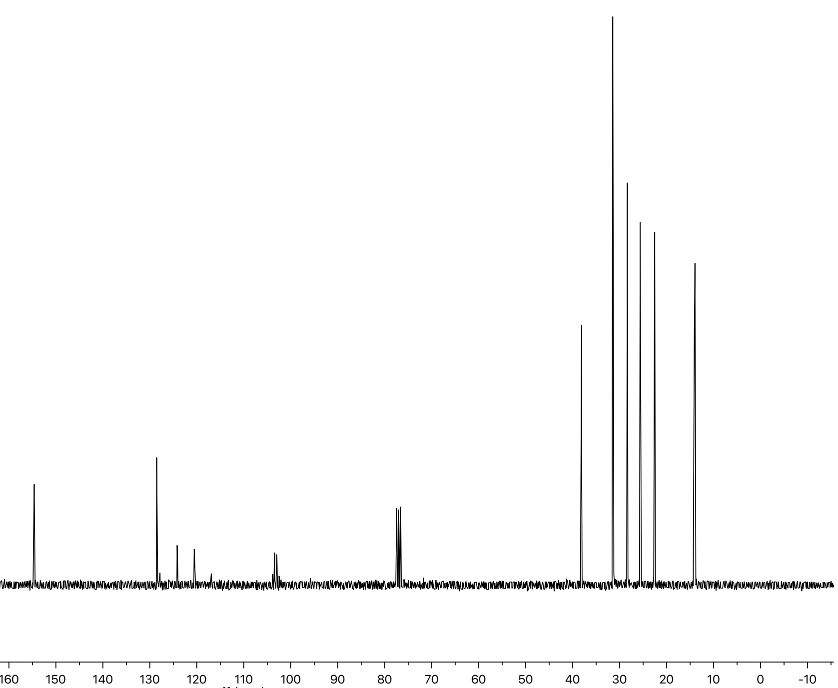
^{1}H NMR ($CDCl_3$)

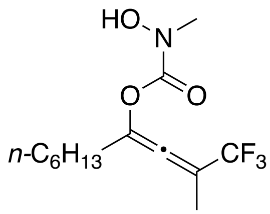




29l

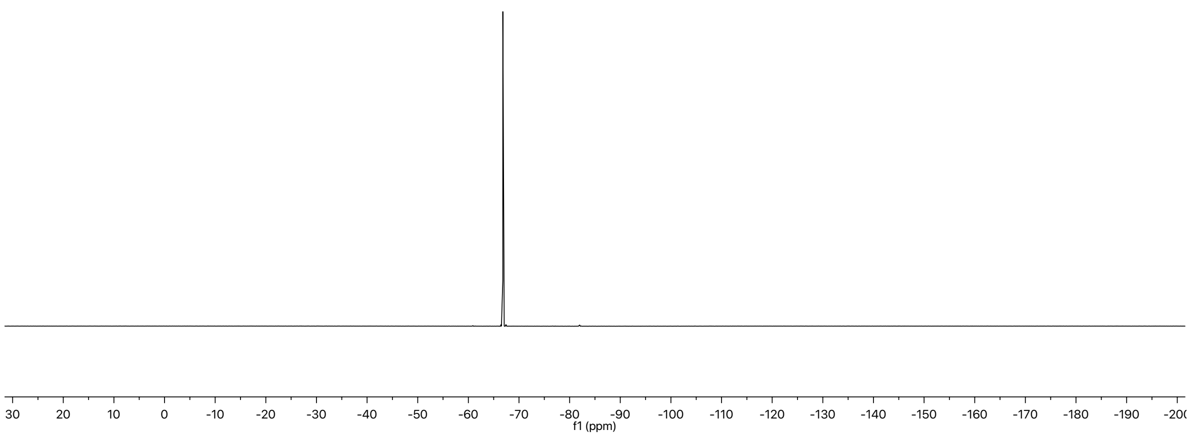
^{13}C NMR ($CDCl_3$)



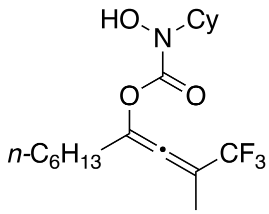


29l

^{19}F NMR ($CDCl_3$)

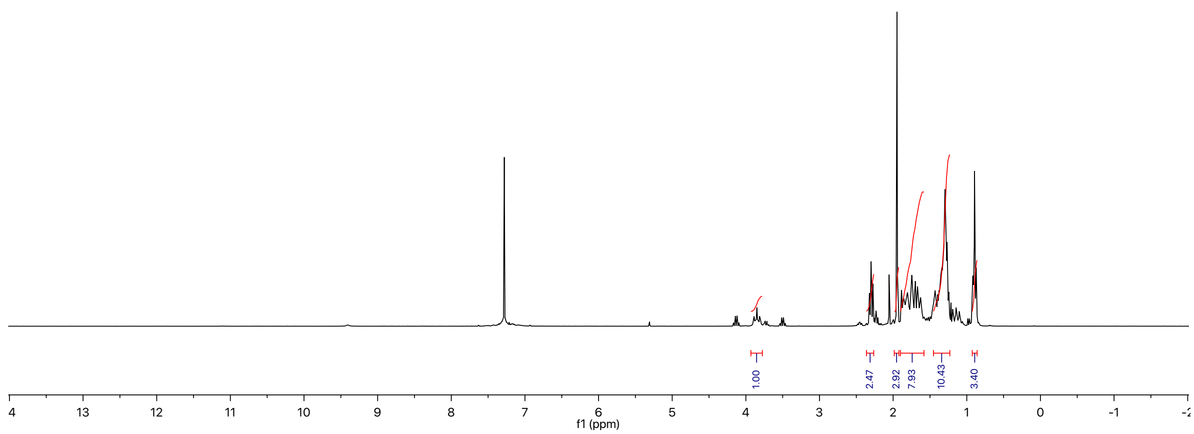


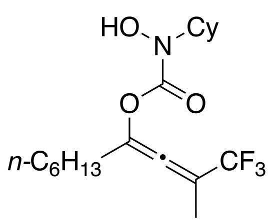
1086-allene



29m

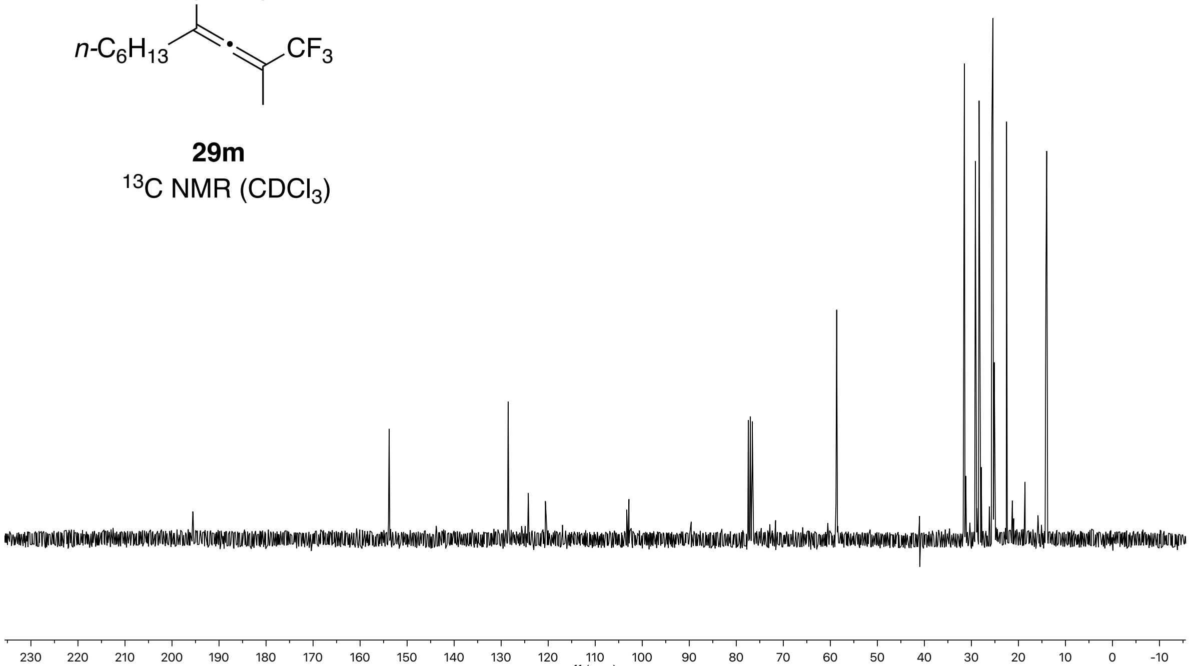
^{1}H NMR ($CDCl_3$)

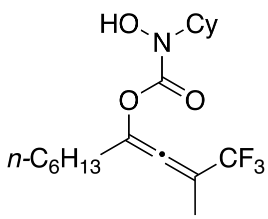




29m

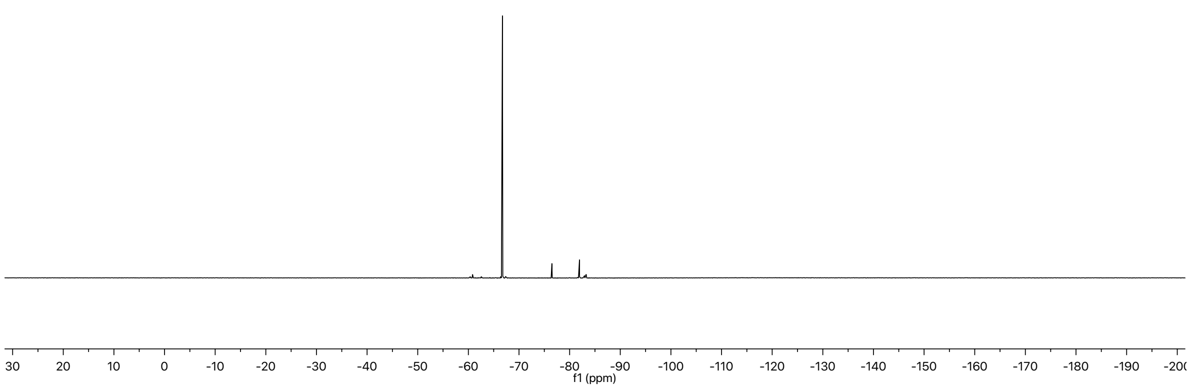
^{13}C NMR ($CDCl_3$)



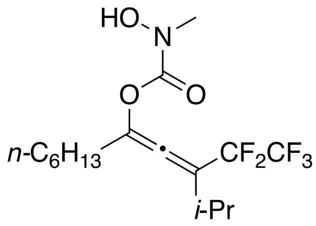


29m

^{19}F NMR ($CDCl_3$)

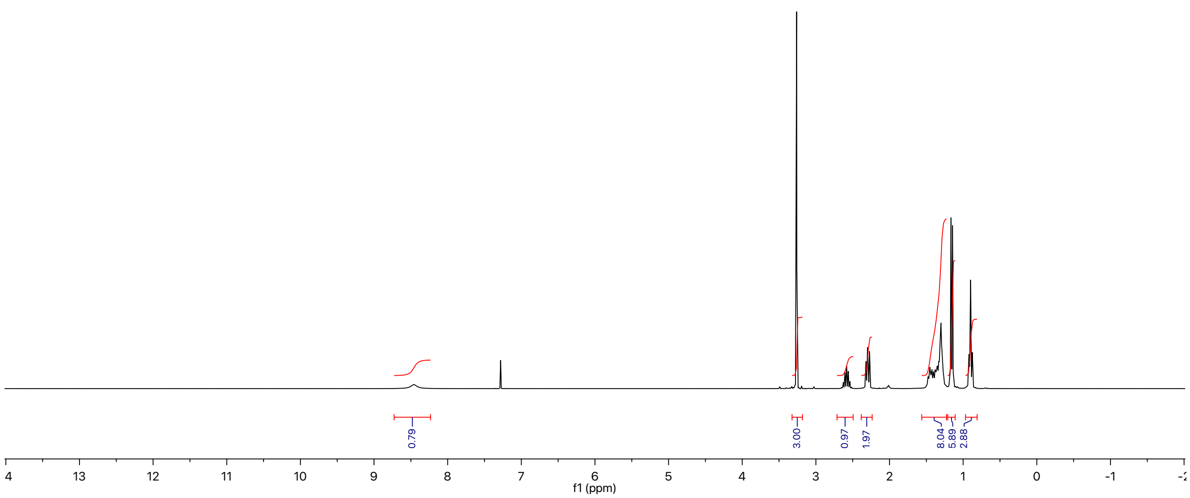


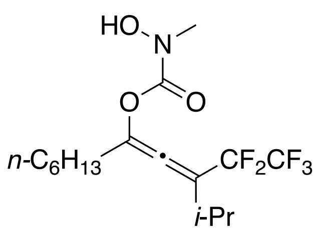
935-allene



29n

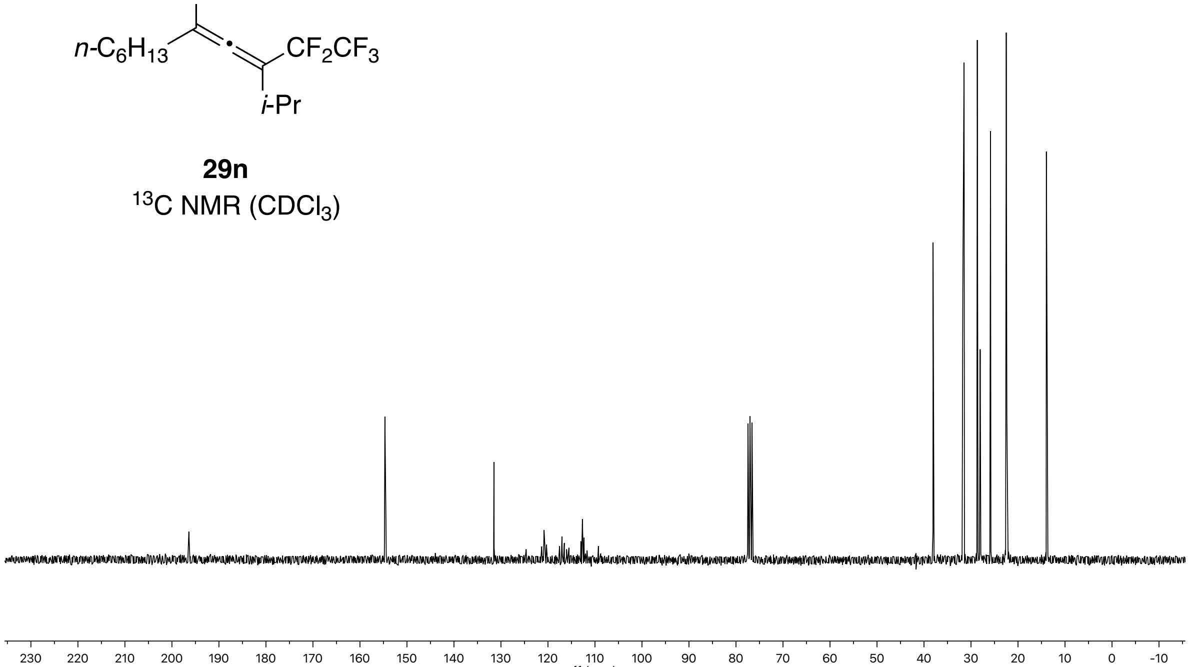
^{1}H NMR ($CDCl_3$)

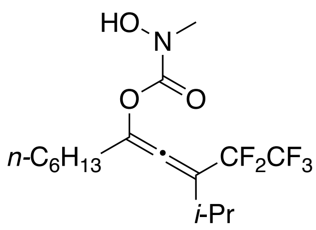




29n

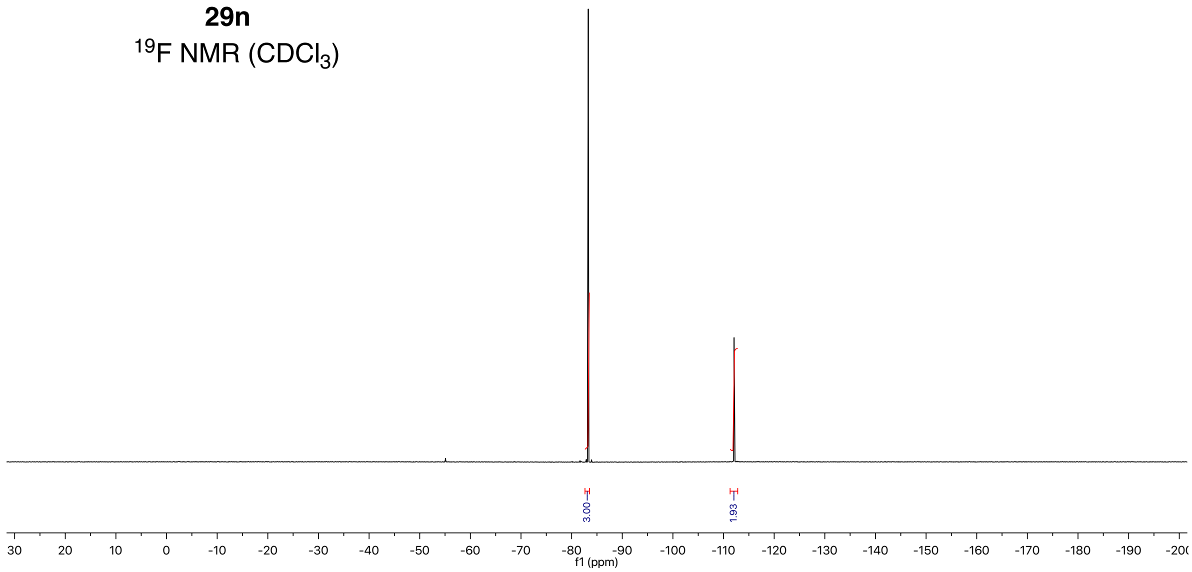
^{13}C NMR ($CDCl_3$)



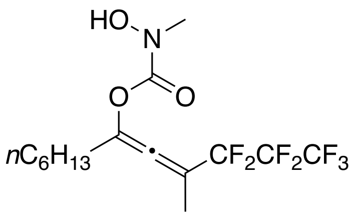


29n

^{19}F NMR ($CDCl_3$)

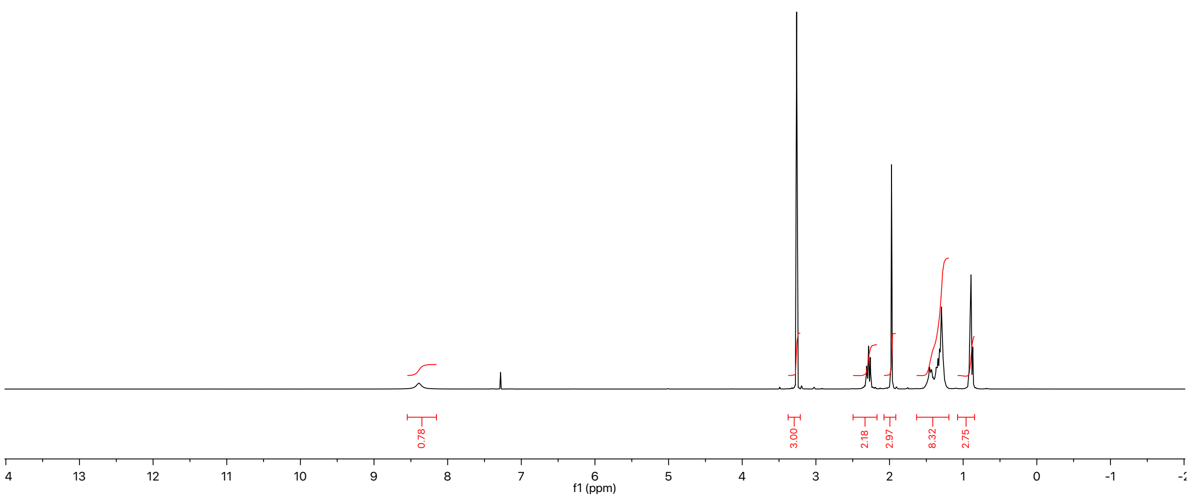


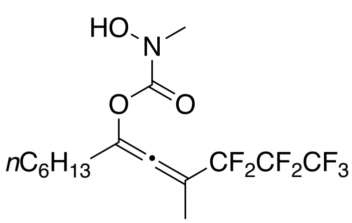
944-allene



29o

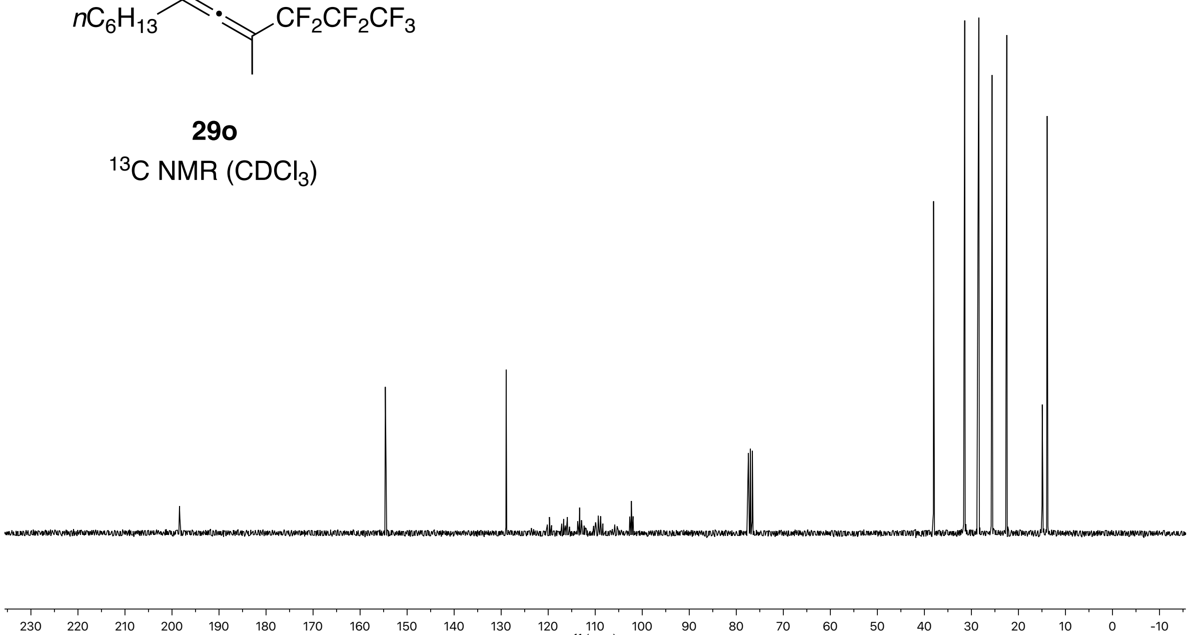
^{1}H NMR ($CDCl_3$)

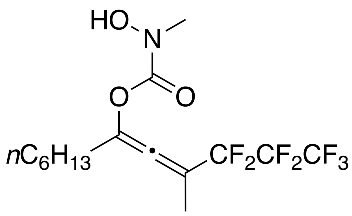




29o

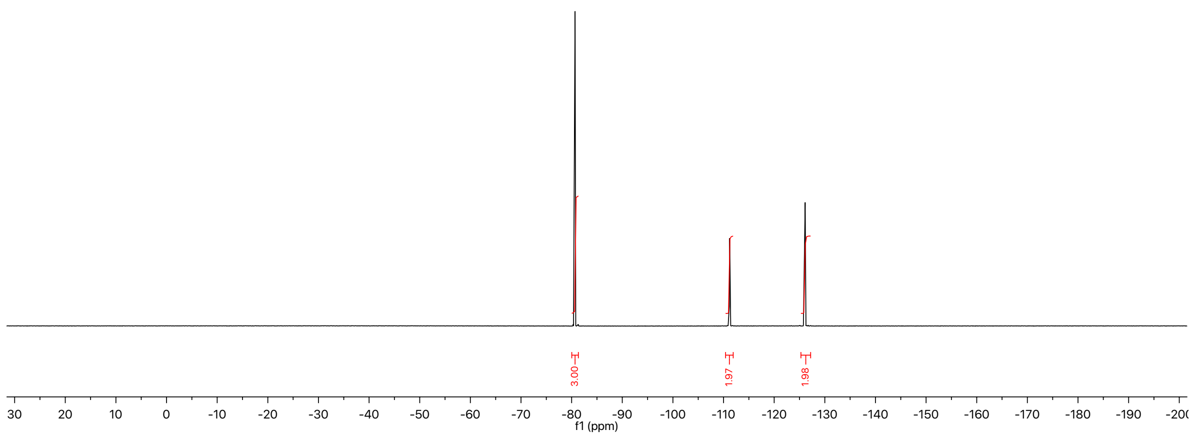
^{13}C NMR ($CDCl_3$)



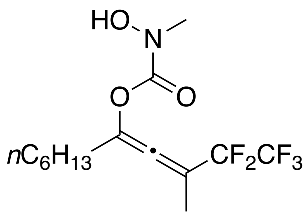


29o

^{19}F NMR ($CDCl_3$)

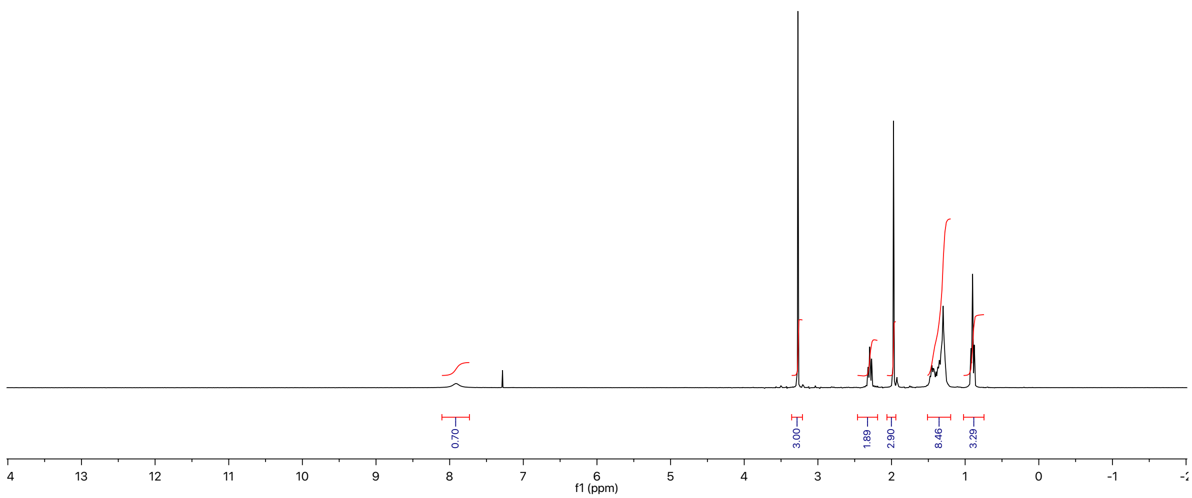


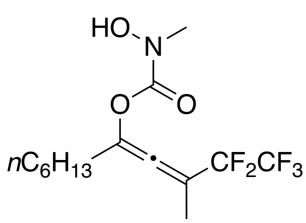
949-allene



29p

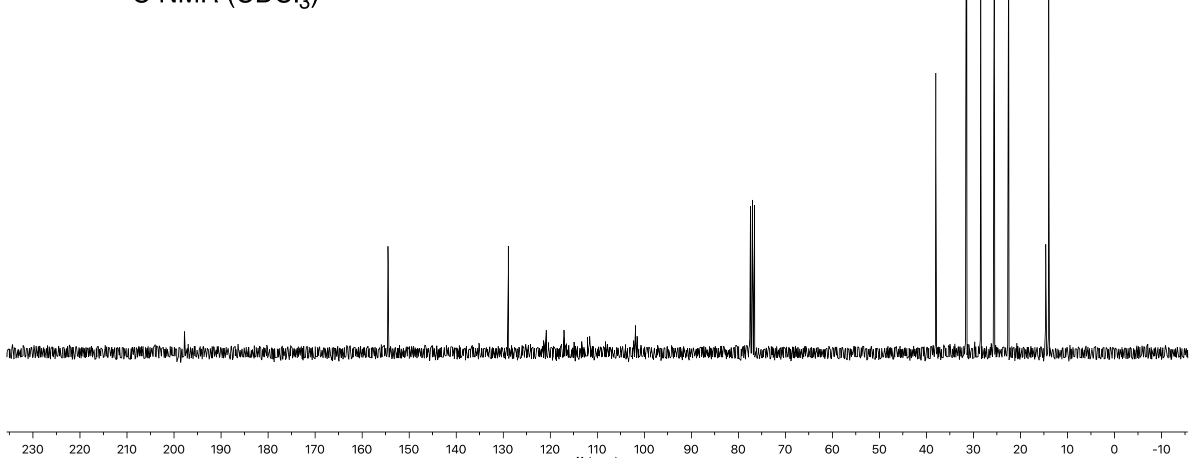
^{1}H NMR ($CDCl_3$)

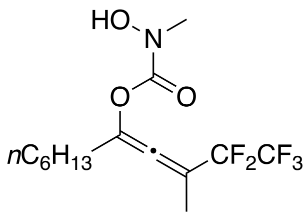




29p

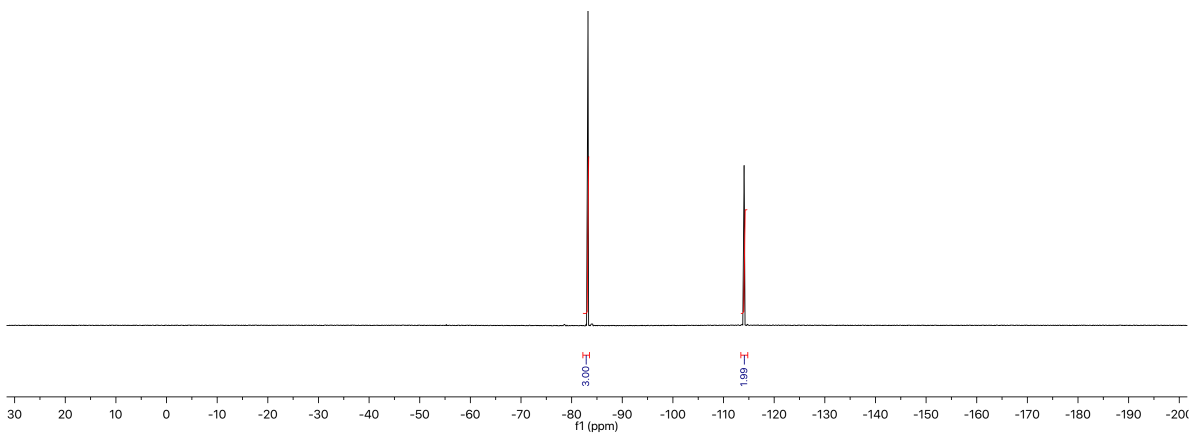
^{13}C NMR ($CDCl_3$)



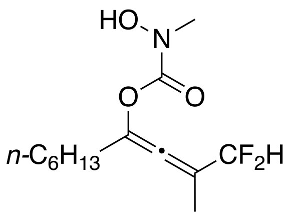


29p

^{19}F NMR ($CDCl_3$)

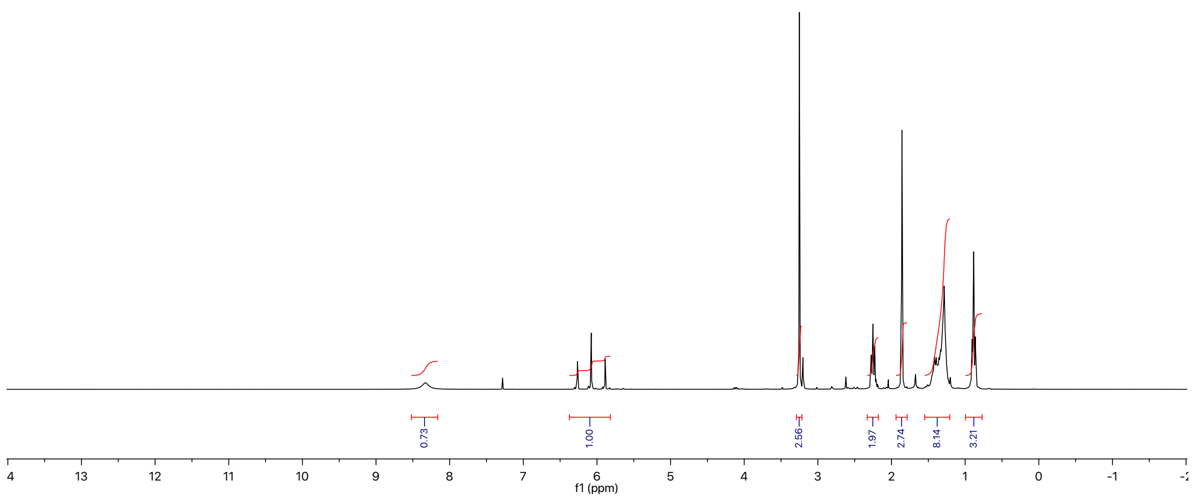


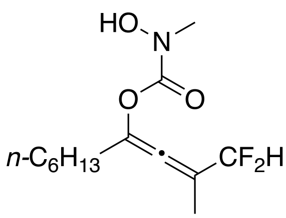
1075-allene



29q

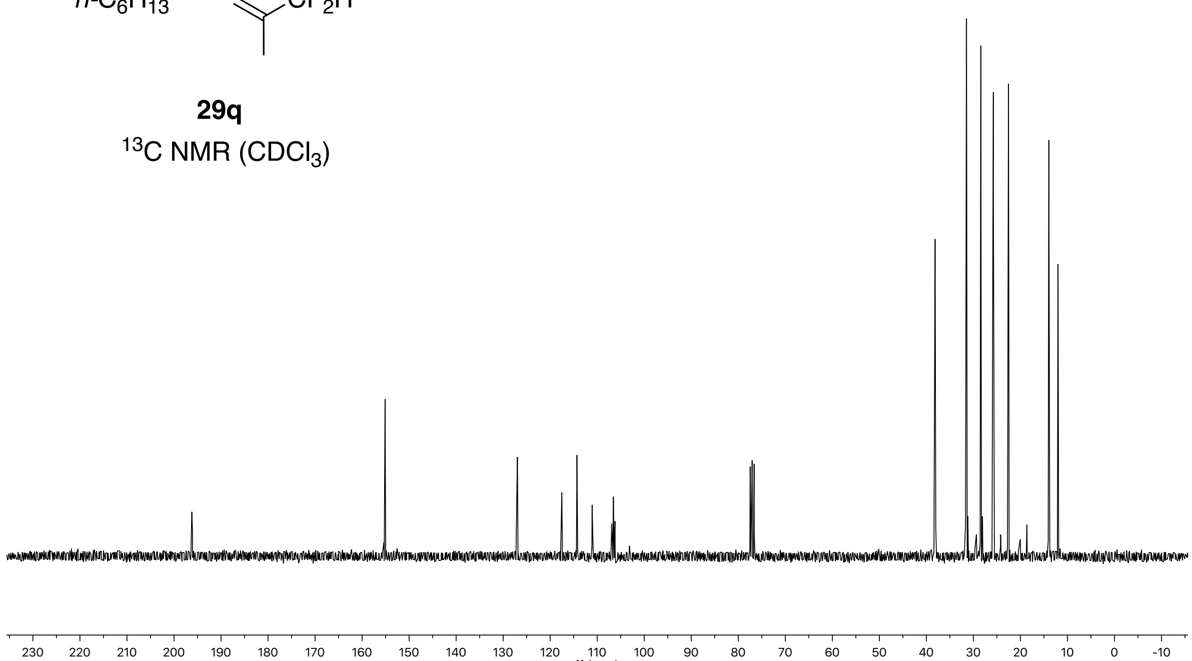
^{1}H NMR ($CDCl_3$)

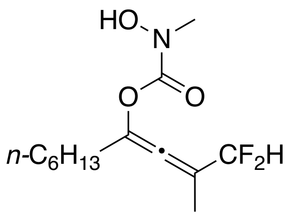




29q

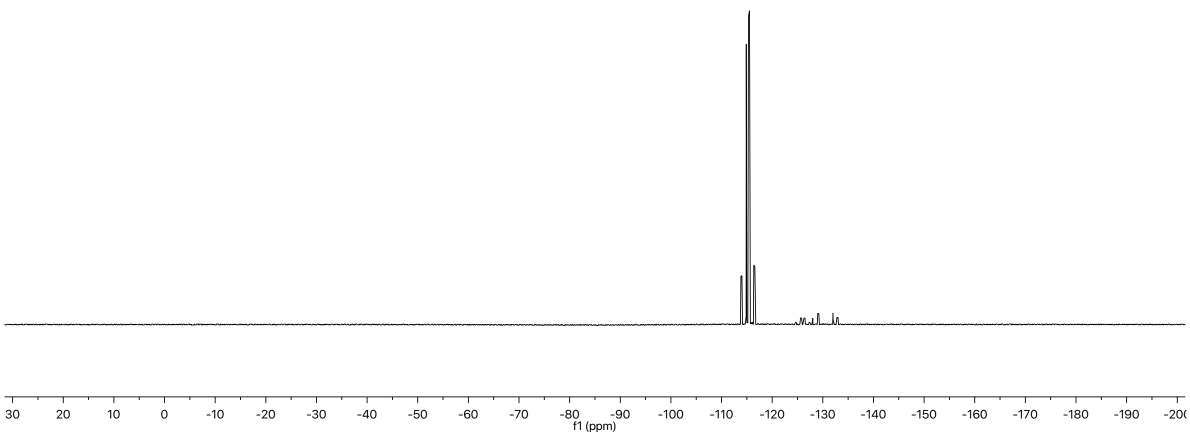
^{13}C NMR ($CDCl_3$)





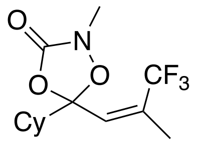
29q

^{19}F NMR ($CDCl_3$)



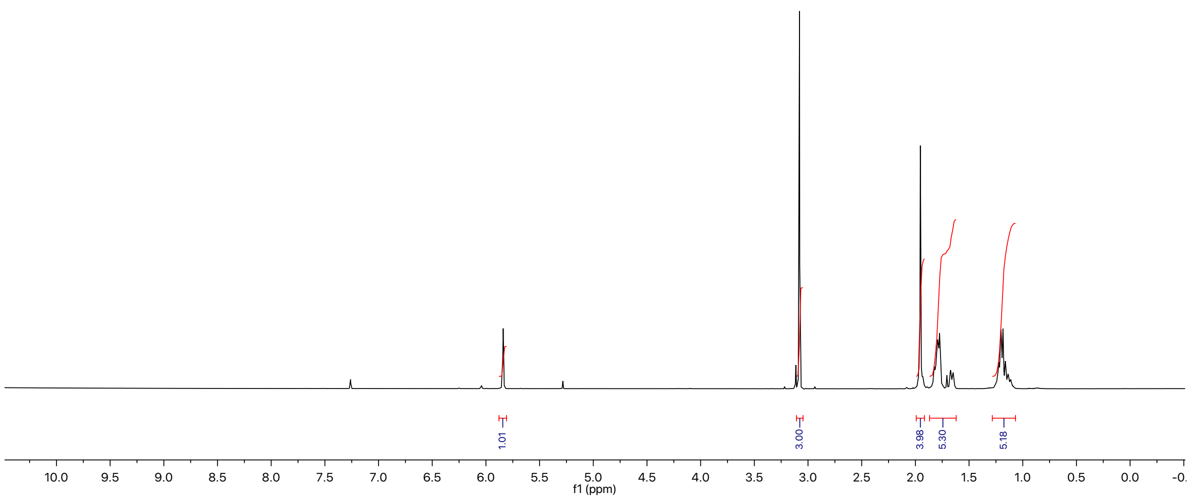
1034-allene

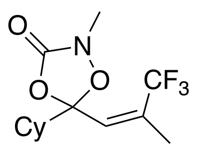
NMR spectrums for alkenes (**19a**-**19i**, **19k**-**19q**, **34**).



19a

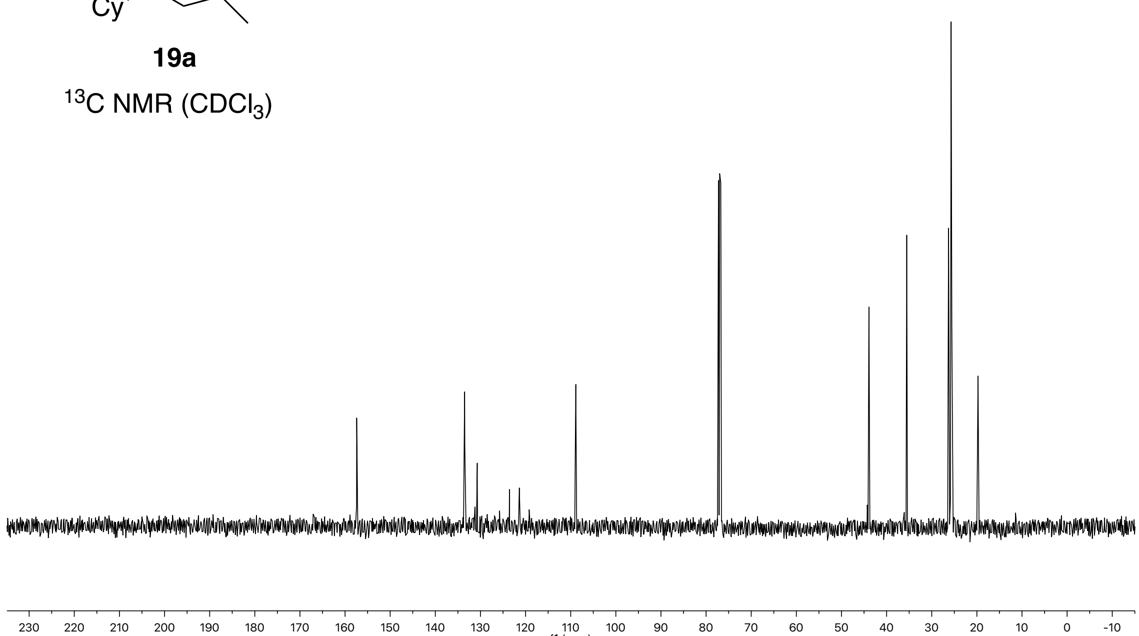
^1H NMR ($CDCl_3$)

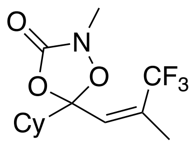




19a

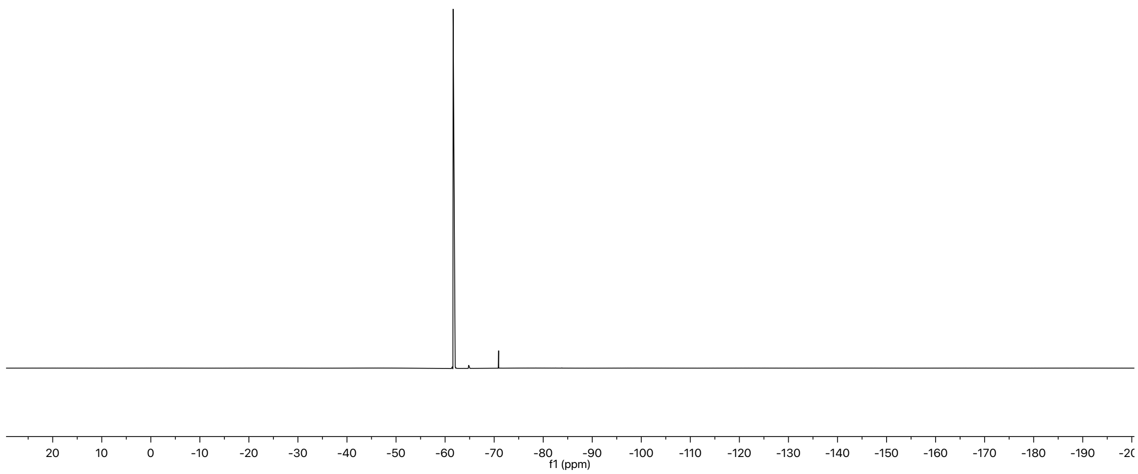
^{13}C NMR ($CDCl_3$)

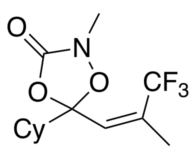




19a

^{19}F NMR ($CDCl_3$)

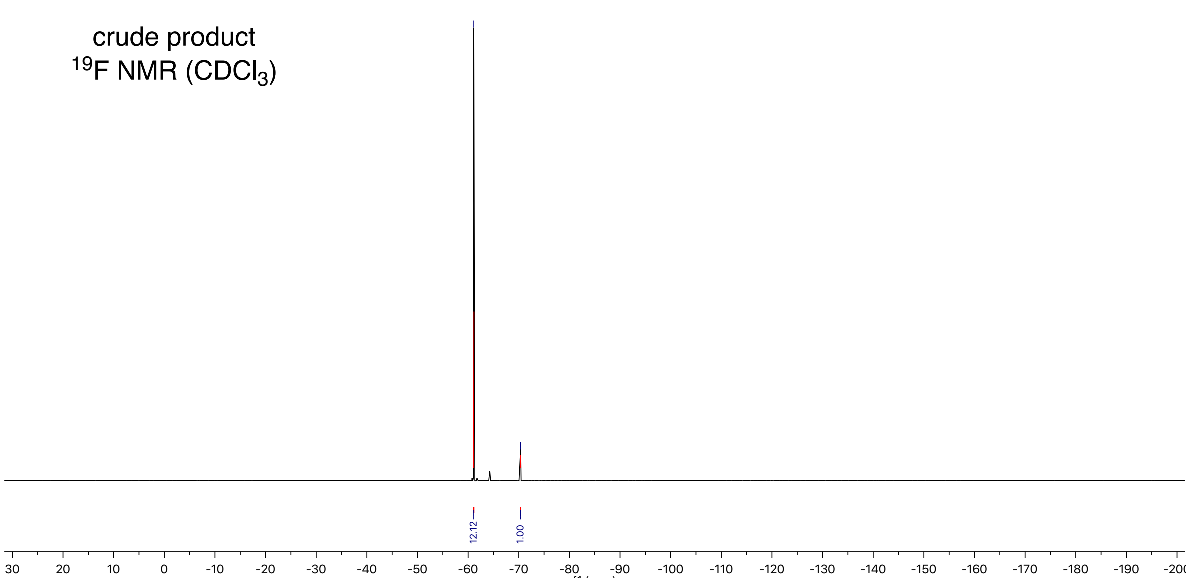




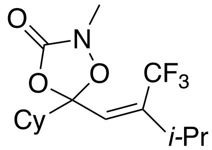
19a

crude product

^{19}F NMR ($CDCl_3$)

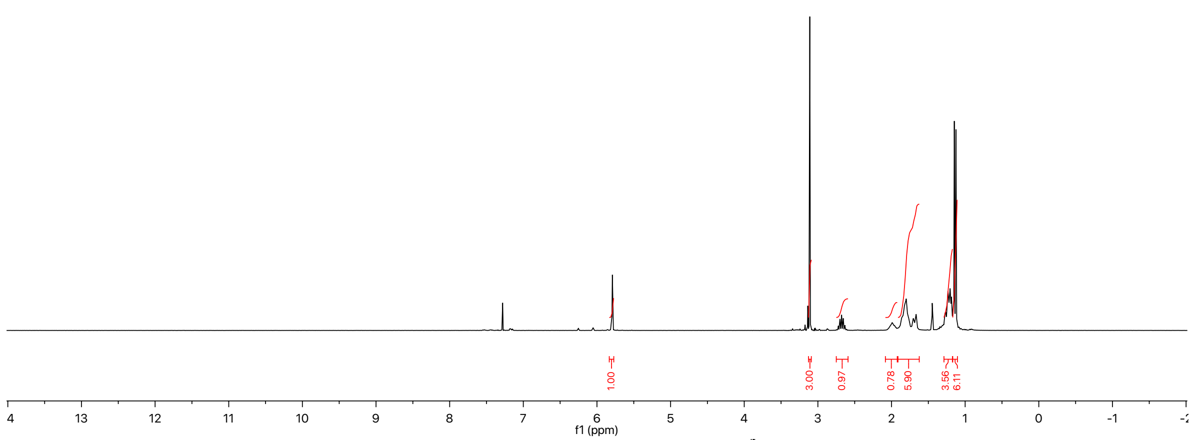


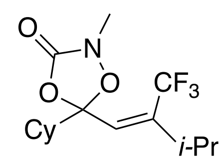
1056



19b

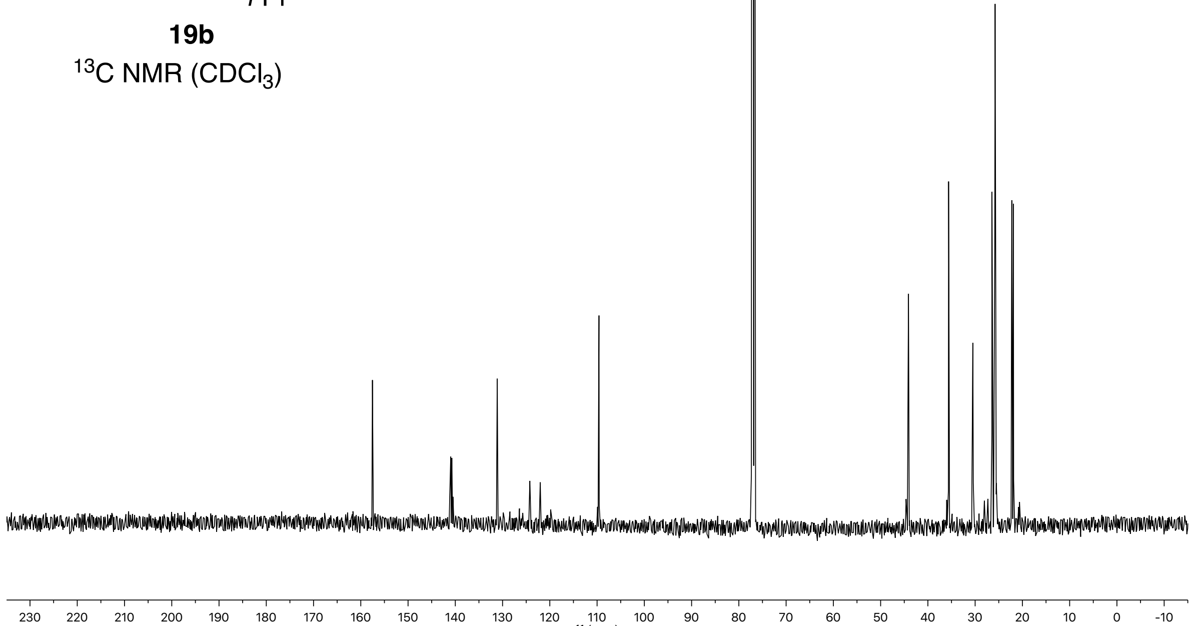
^{1}H NMR ($CDCl_3$)

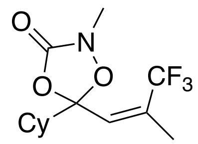




19b

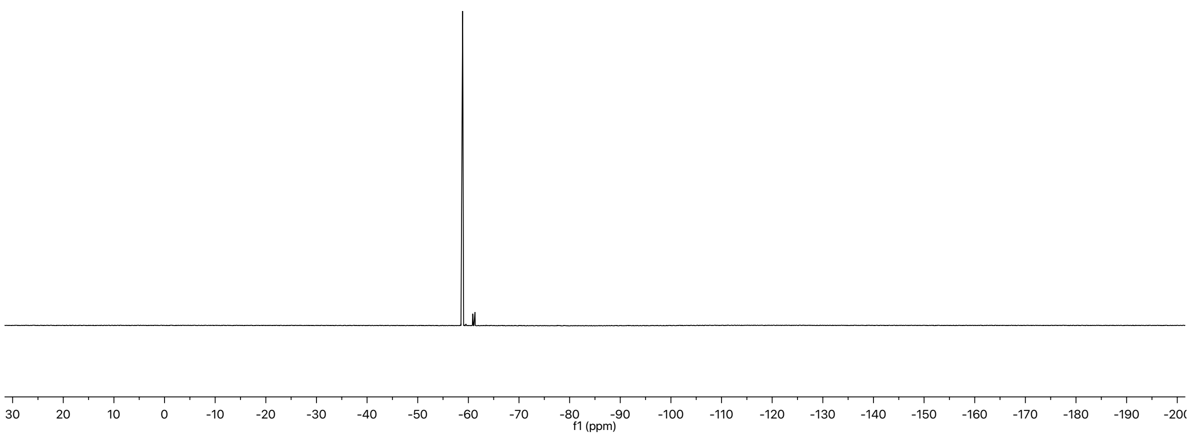
^{13}C NMR ($CDCl_3$)

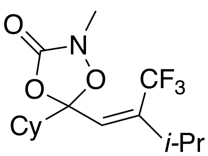




19a

^{19}F NMR ($CDCl_3$)

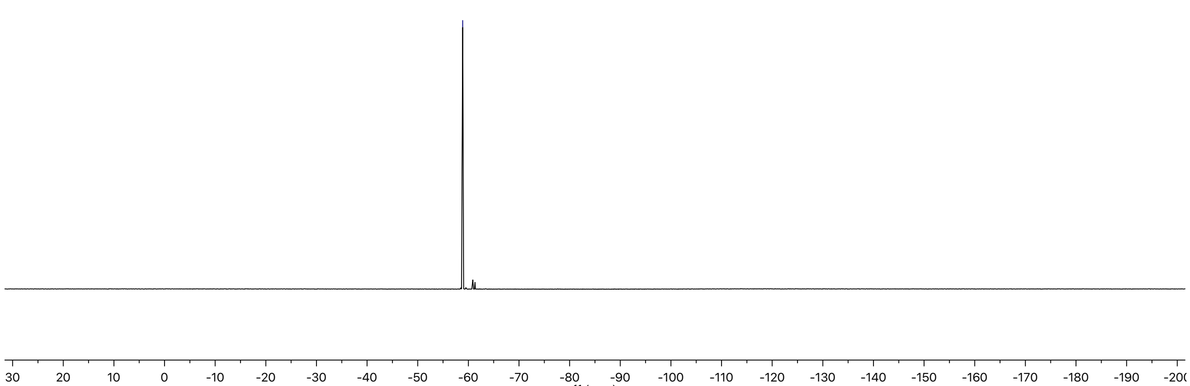


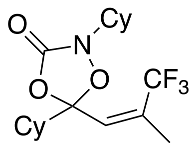


19b

crude product

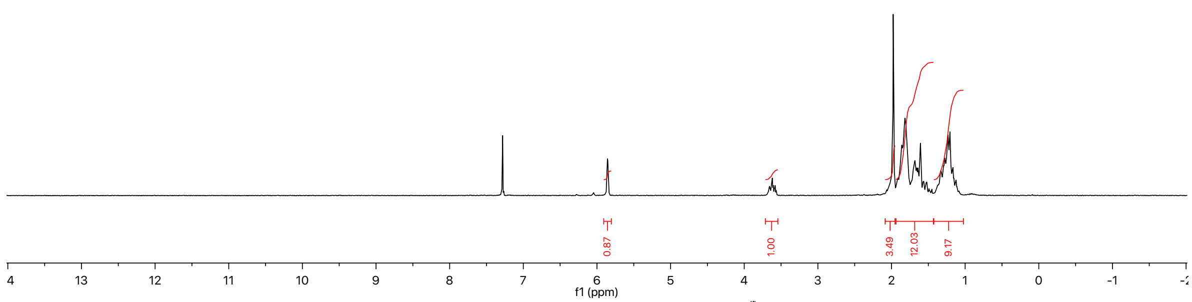
^{19}F NMR ($CDCl_3$)

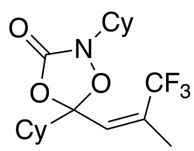




19c

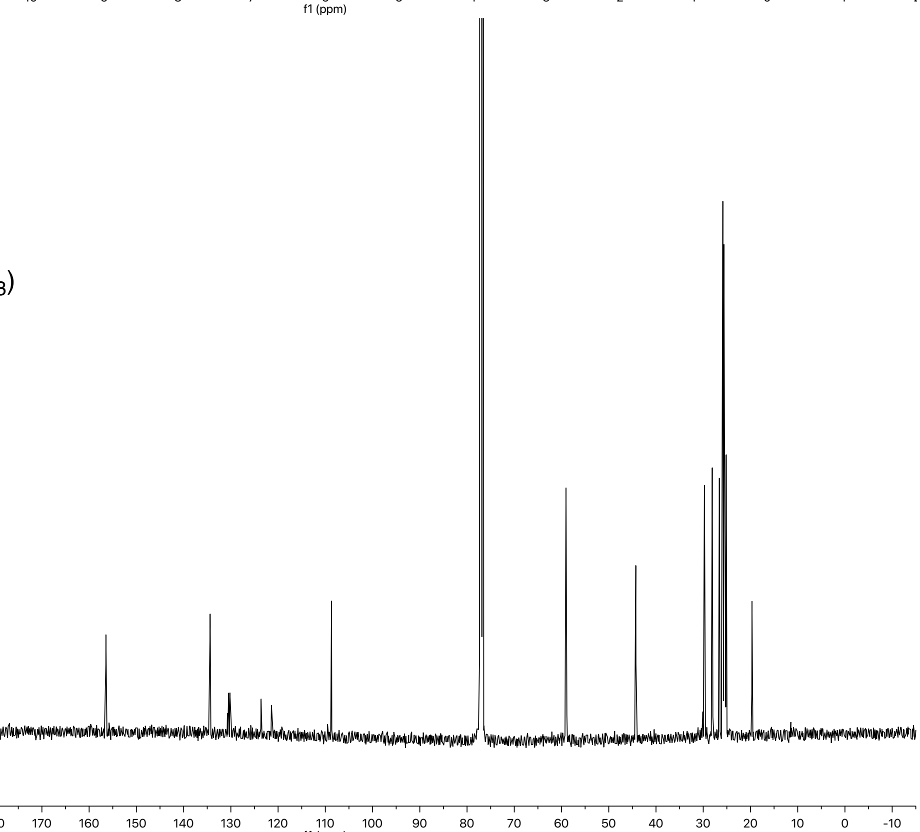
^{1}H NMR ($CDCl_3$)

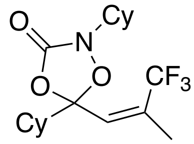




19c

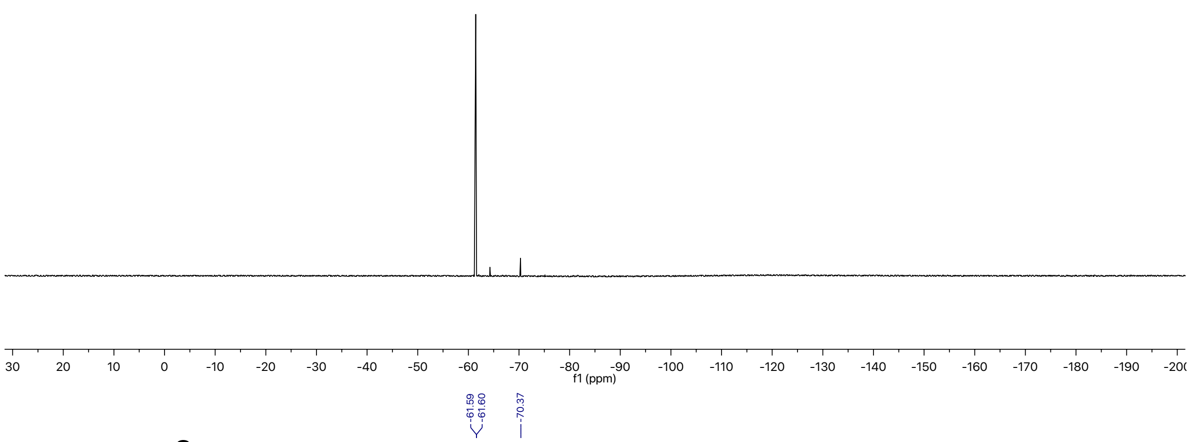
^{13}C NMR ($CDCl_3$)

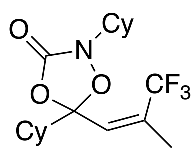




19c

^{19}F NMR ($CDCl_3$)

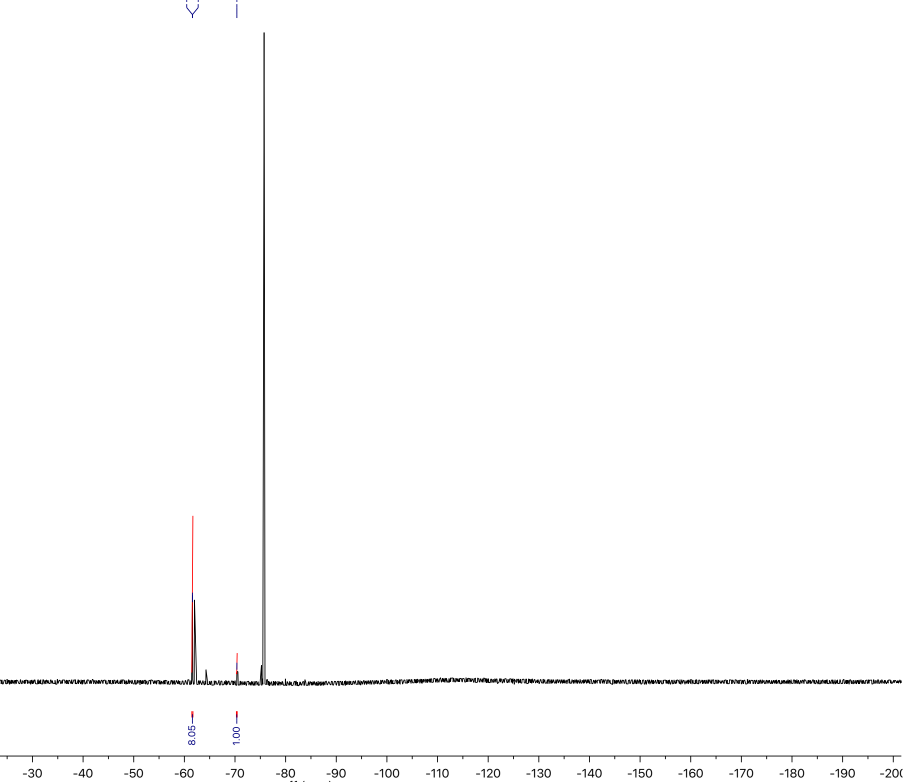


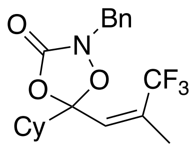


19c

crude product

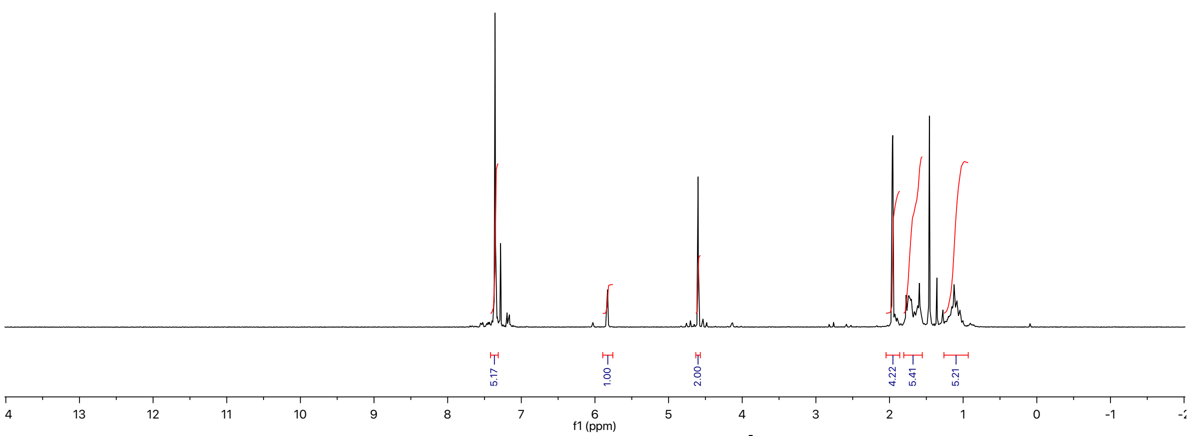
^{19}F NMR ($CDCl_3$)

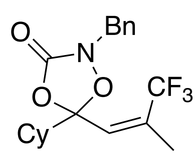




19d

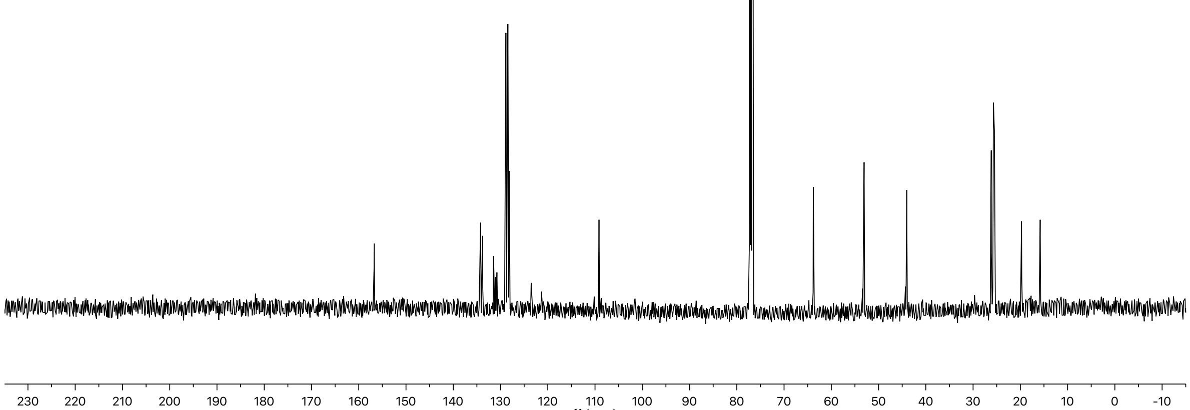
^{1}H NMR ($CDCl_3$)

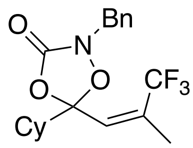




19d

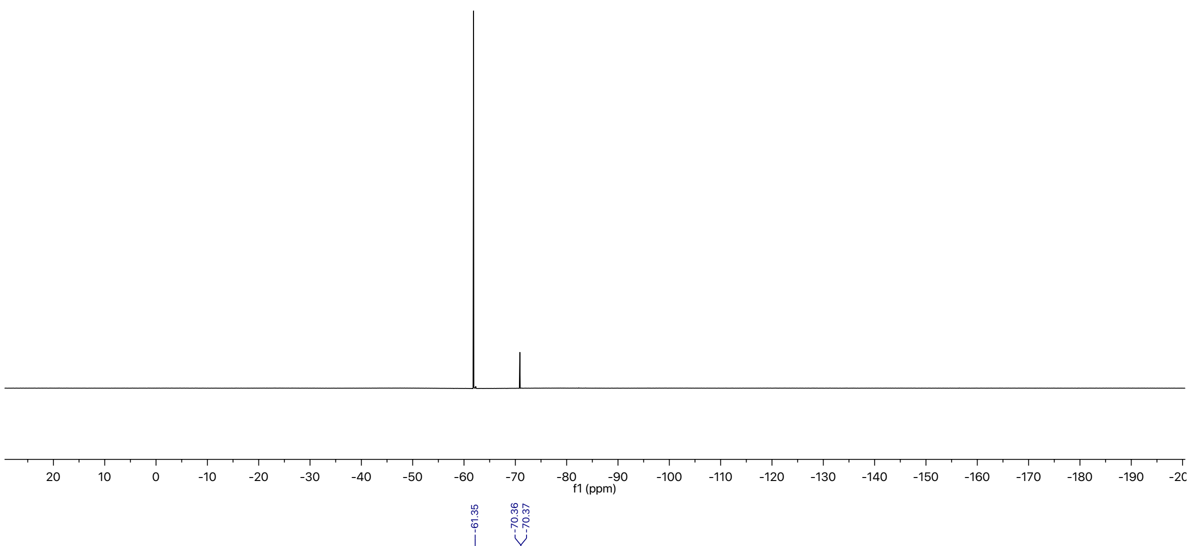
^{13}C NMR ($CDCl_3$)

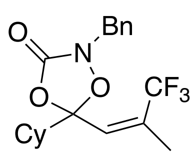




19d

^{19}F NMR ($CDCl_3$)

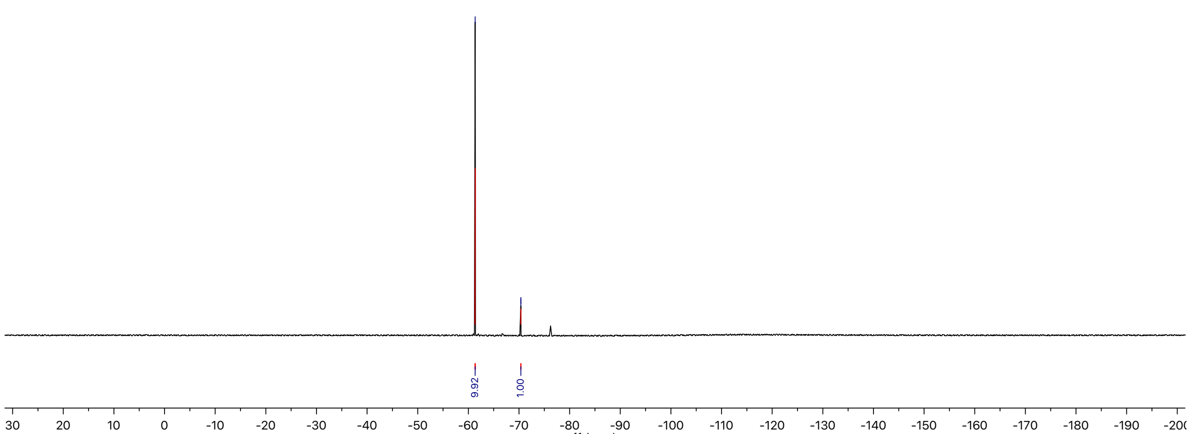




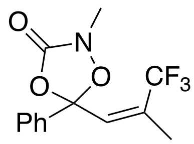
19d

crude product

^{19}F NMR ($CDCl_3$)

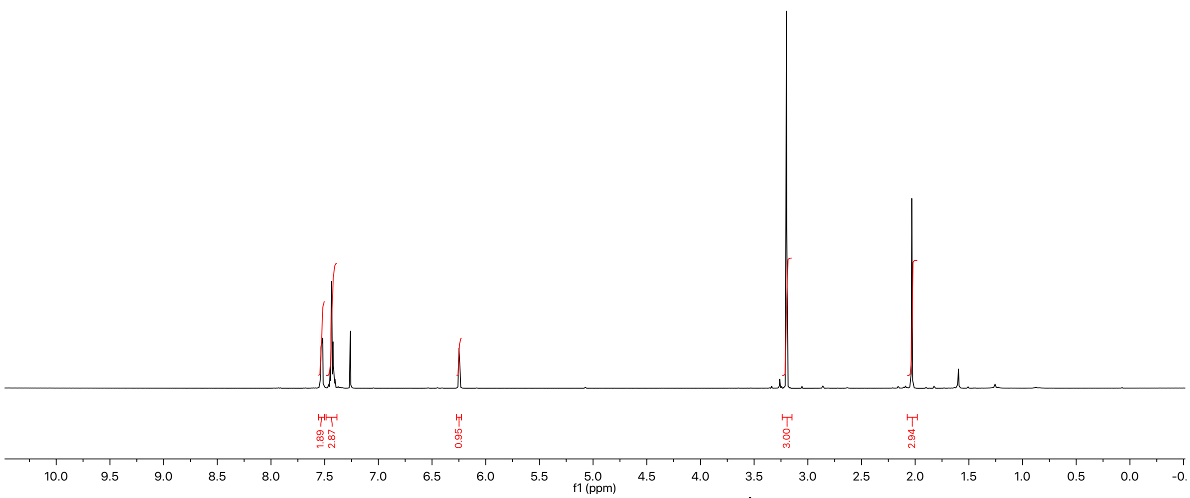


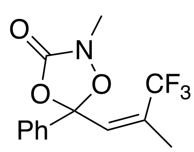
942/1072



19e

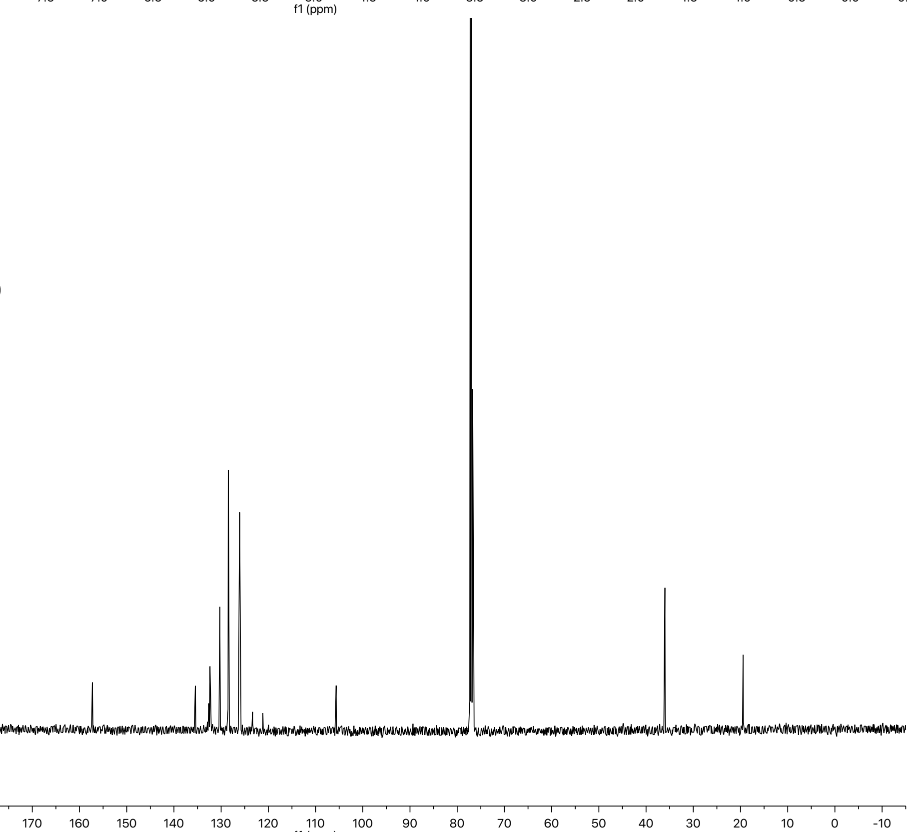
^{1}H NMR ($CDCl_3$)

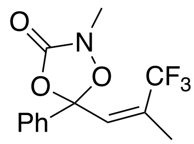




19e

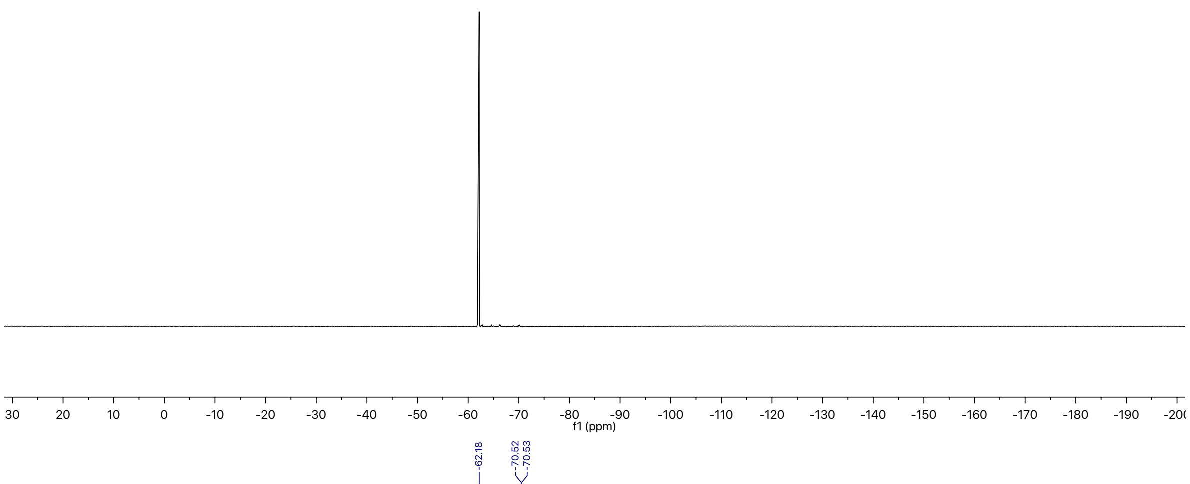
^{13}C NMR ($CDCl_3$)

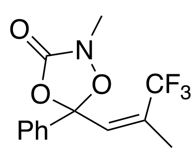




19e

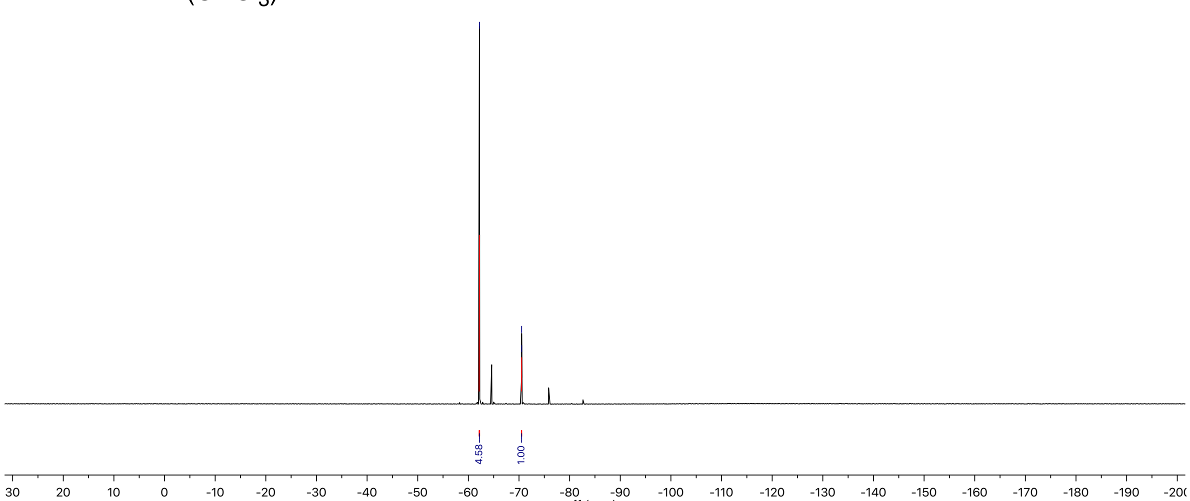
^{19}F NMR ($CDCl_3$)

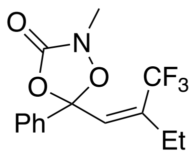




19e

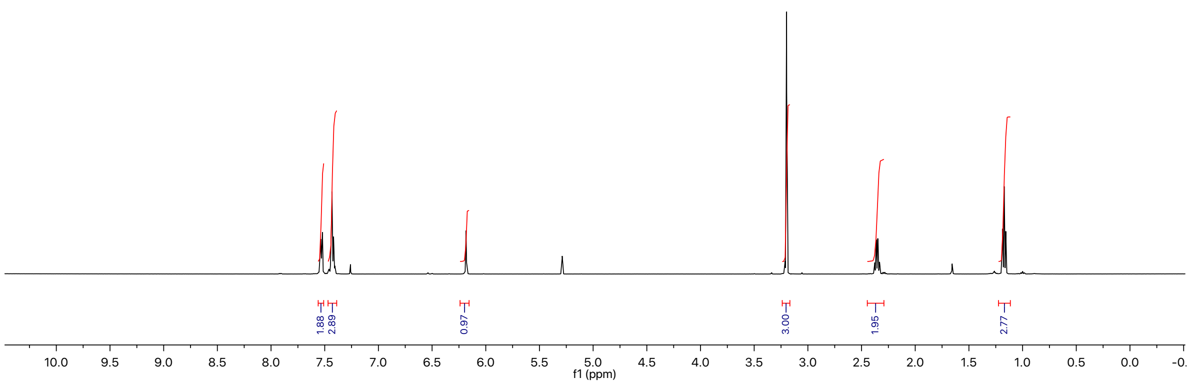
crude product
^{19}F NMR ($CDCl_3$)

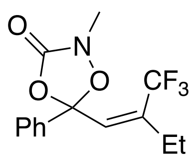




19f

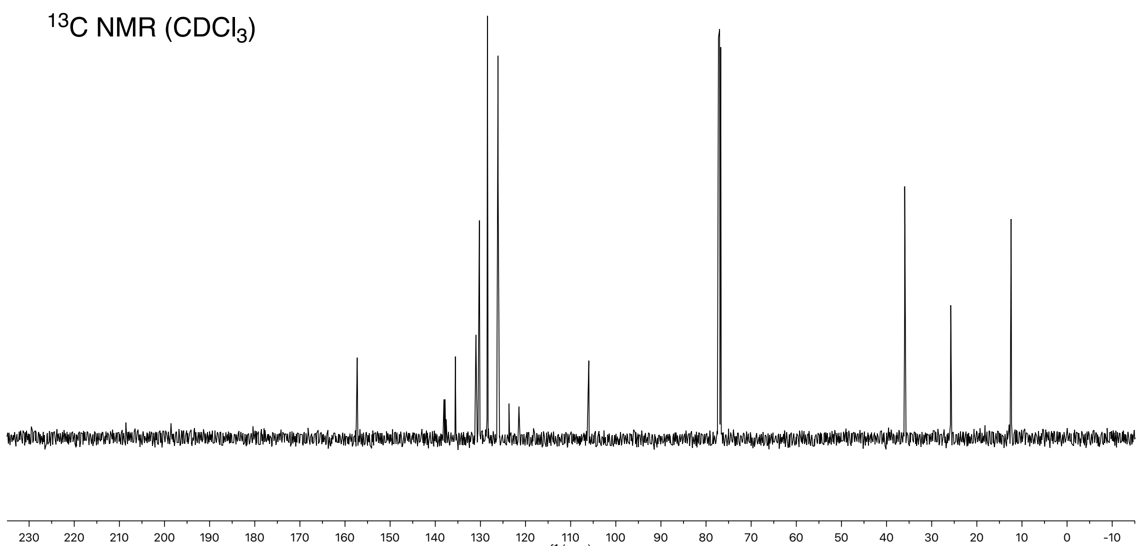
^{1}H NMR ($CDCl_3$)

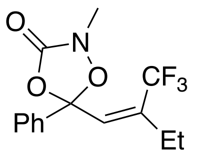




19f

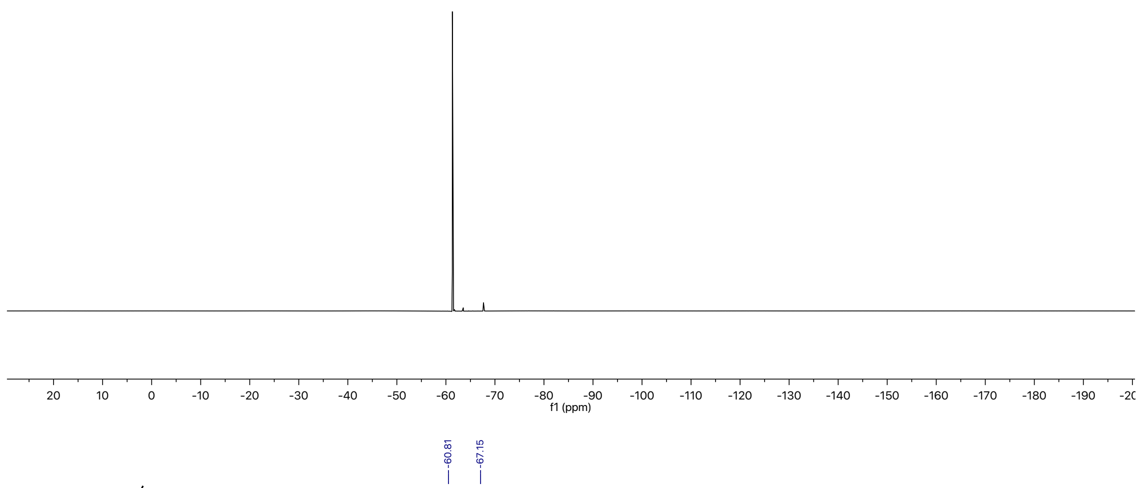
^{13}C NMR ($CDCl_3$)

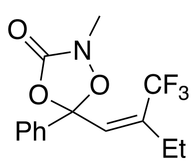




19f

^{19}F NMR (CDCl$_3$)

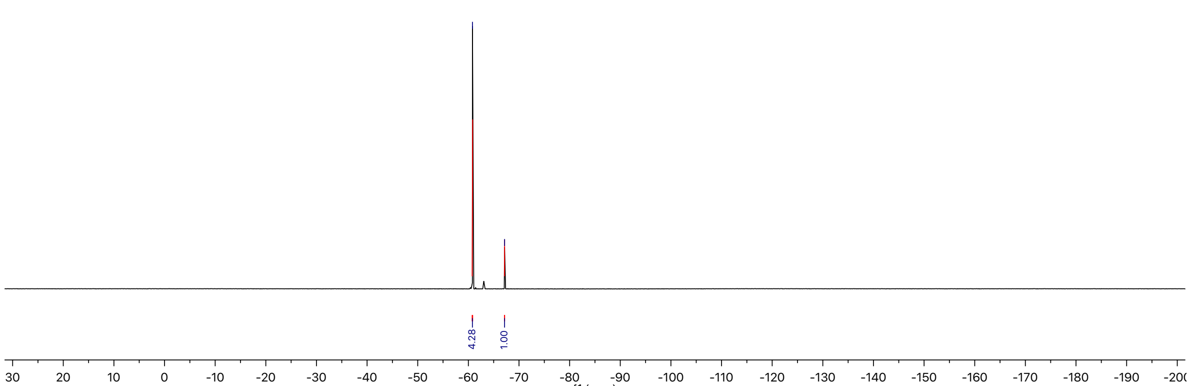


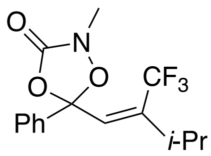


19f

crude product

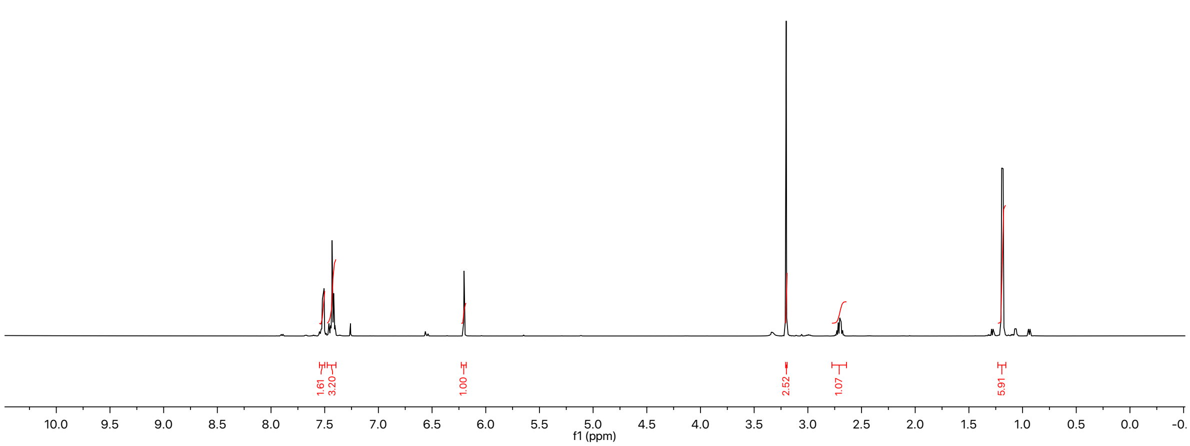
^{19}F NMR (CDCl$_3$)

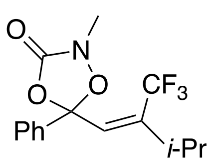




19g

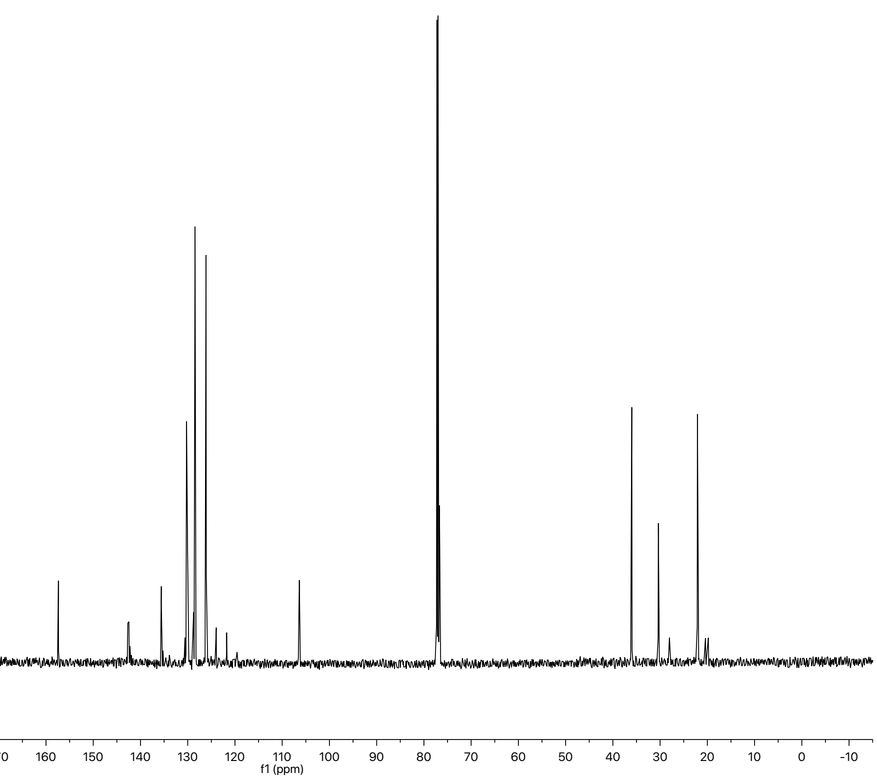
^{1}H NMR ($CDCl_3$)

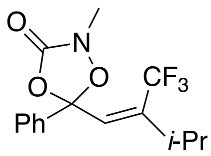




19g

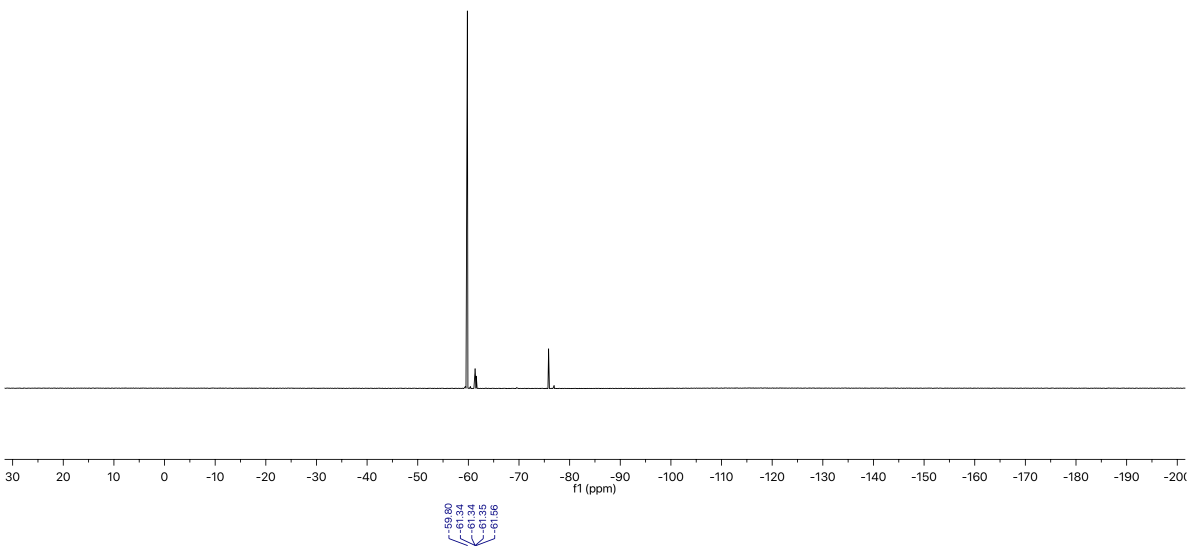
^{13}C NMR ($CDCl_3$)

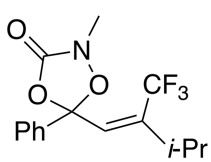




19g

^{19}F NMR ($CDCl_3$)

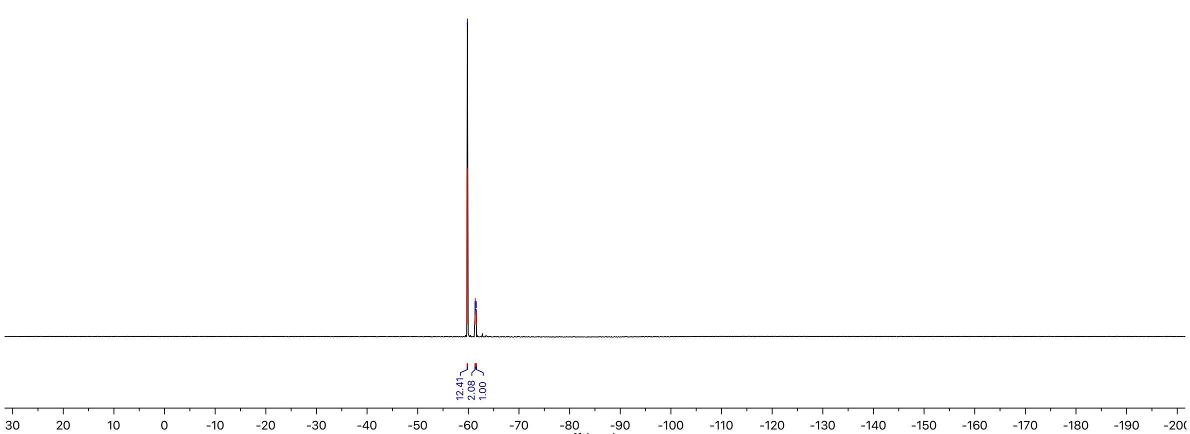




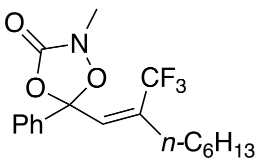
19g

crude product

^{19}F NMR ($CDCl_3$)

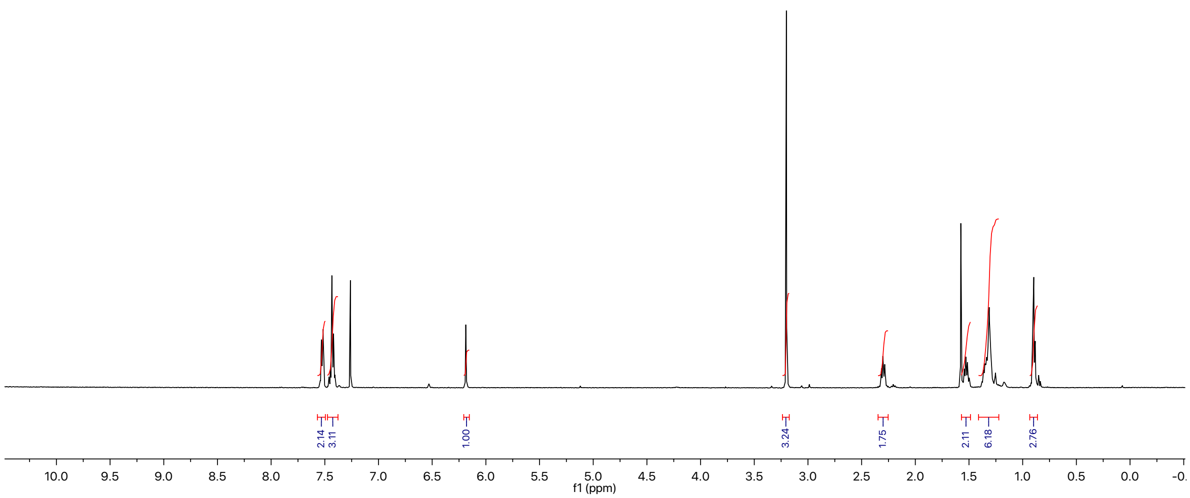


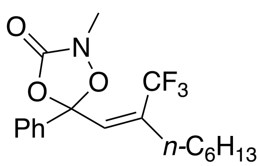
855/1073



19h

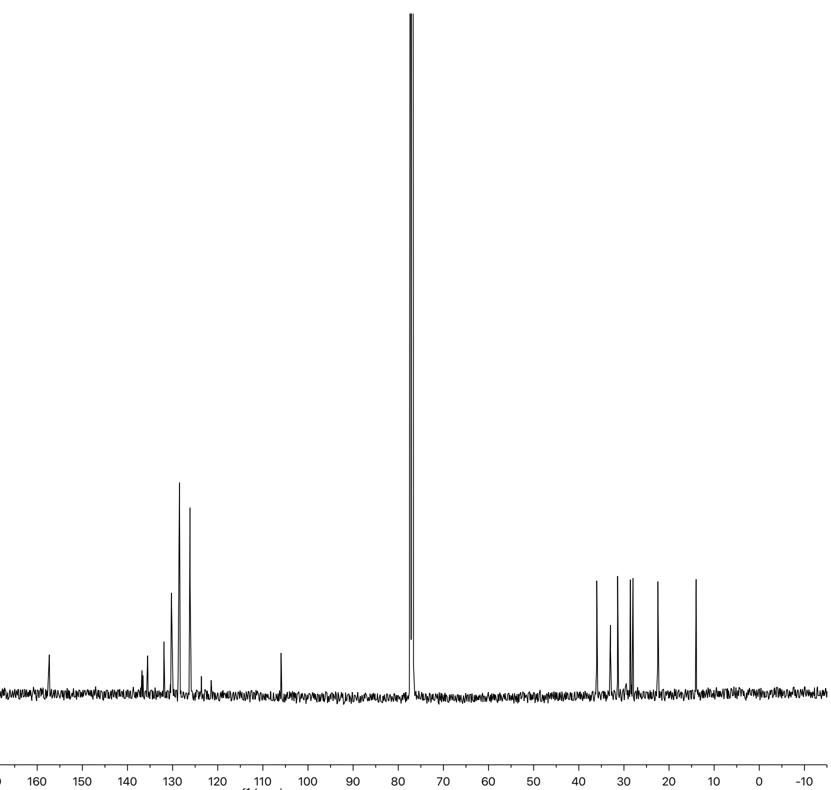
^{1}H NMR ($CDCl_3$)

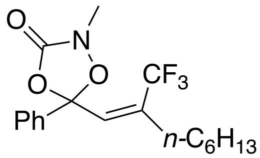




19h

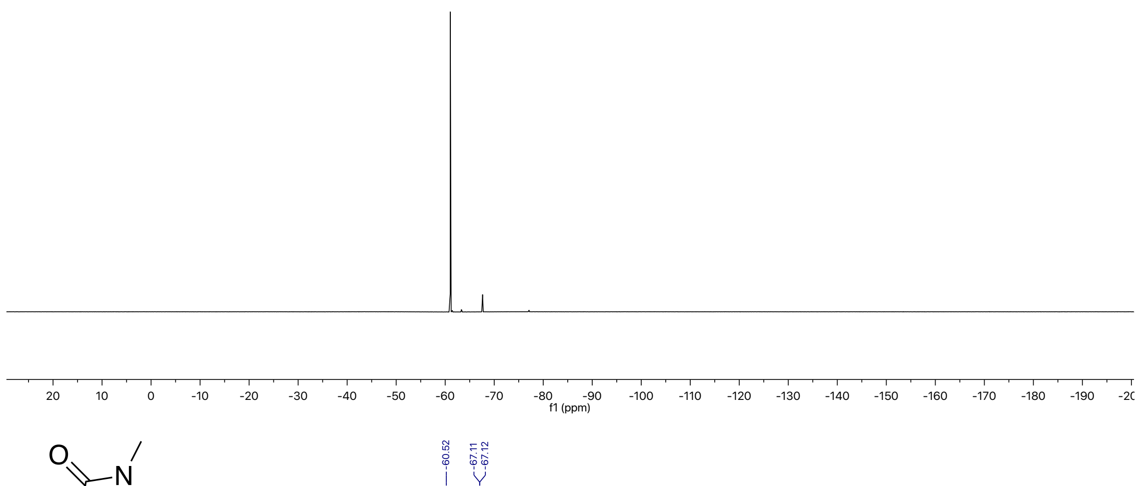
^{13}C NMR ($CDCl_3$)

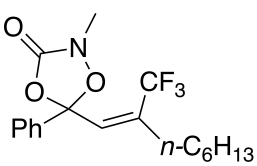




19h

^{19}F NMR ($CDCl_3$)

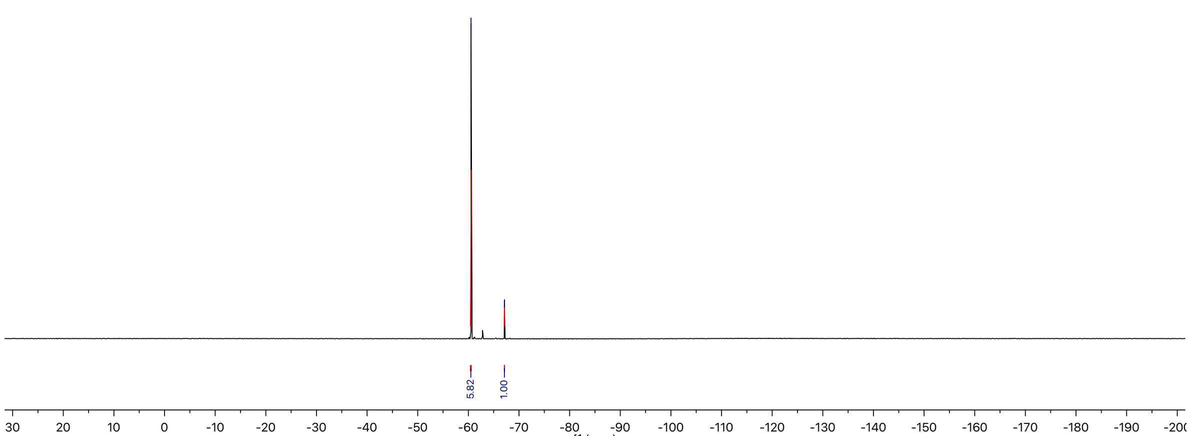


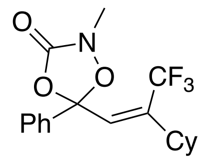


19h

crude product

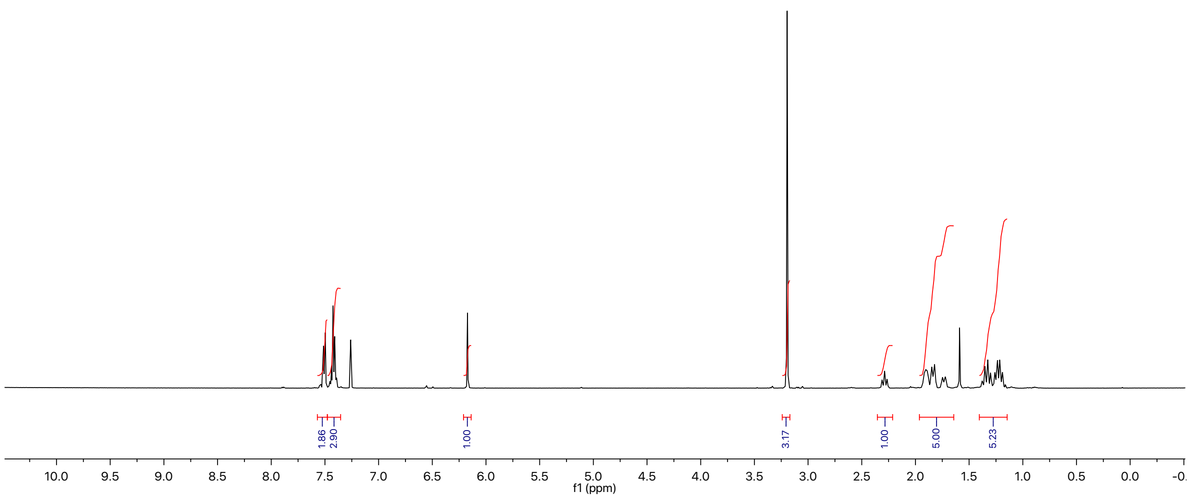
^{19}F NMR ($CDCl_3$)

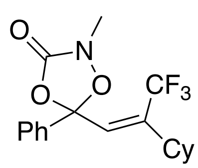




19i

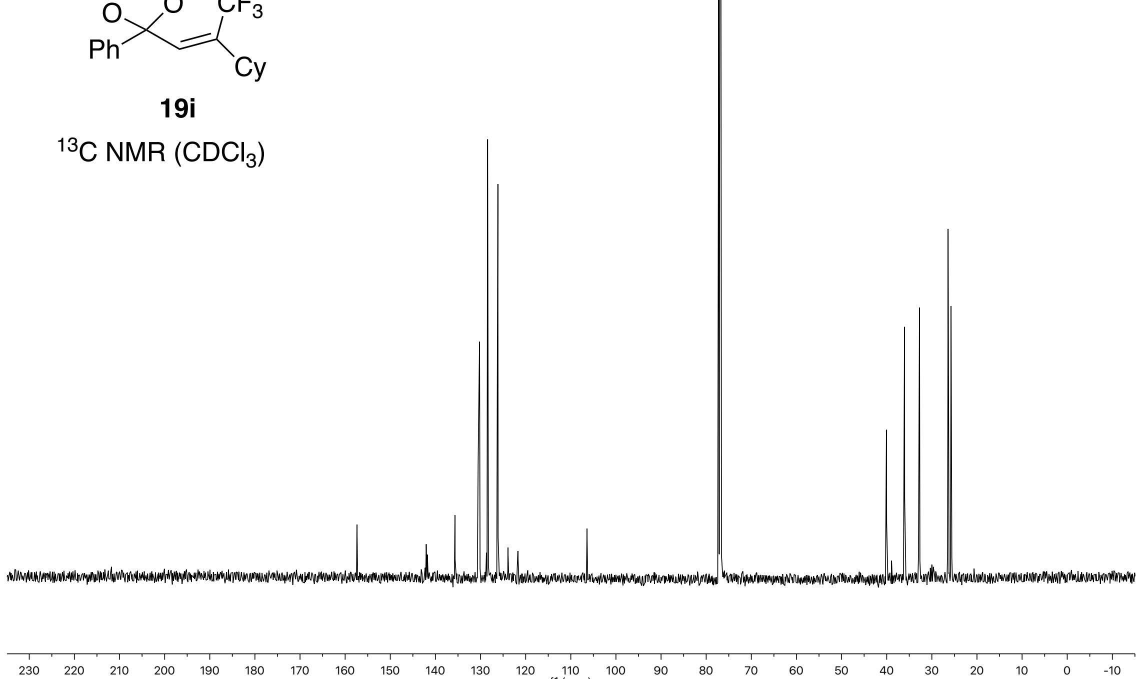
^1H NMR ($CDCl_3$)

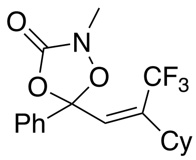




19i

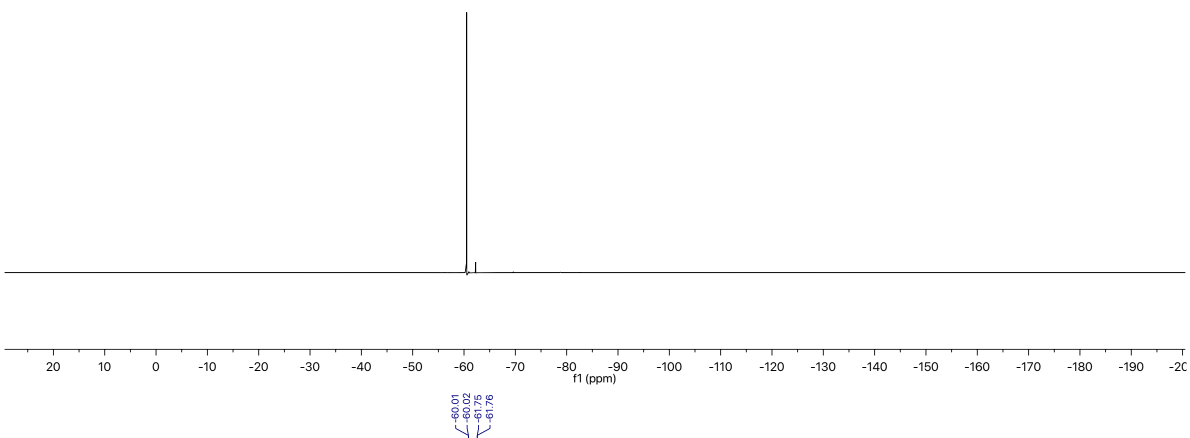
^{13}C NMR ($CDCl_3$)

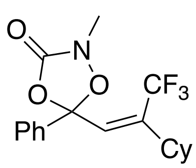




19i

^{19}F NMR ($CDCl_3$)

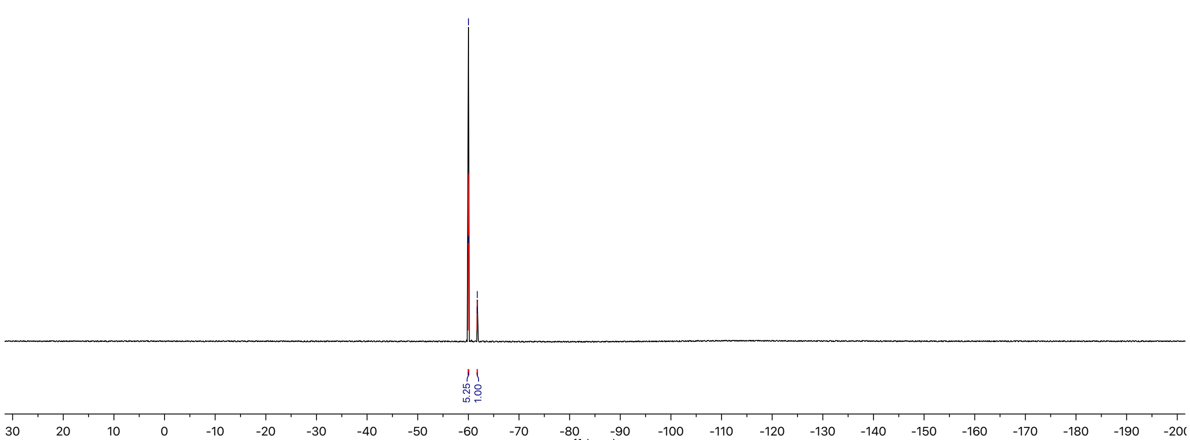


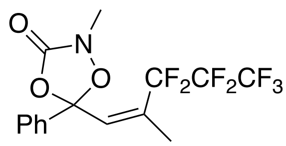


19i

crude product

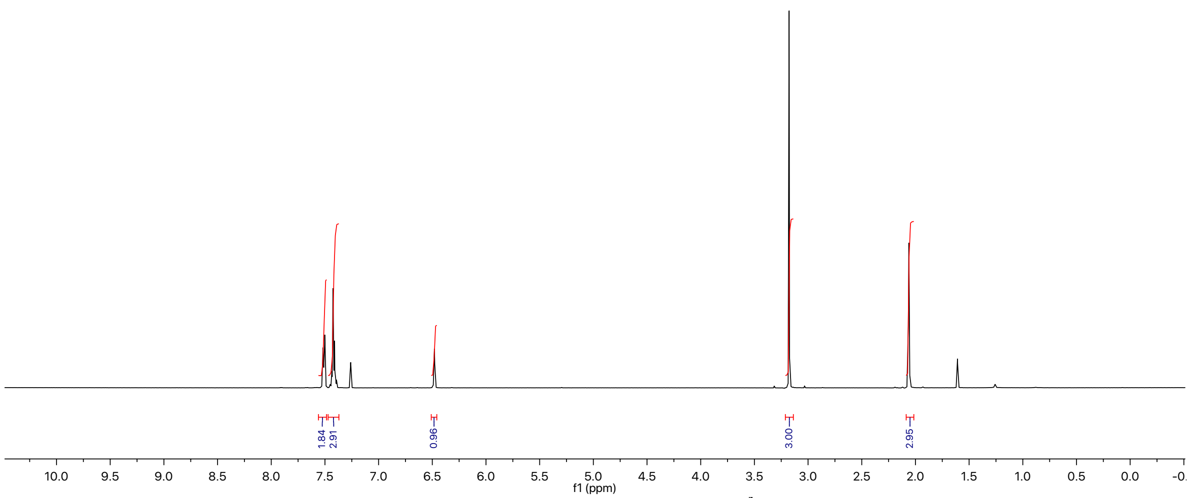
^{19}F NMR ($CDCl_3$)

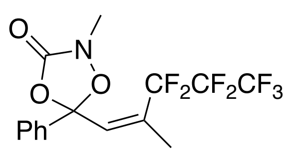




19k

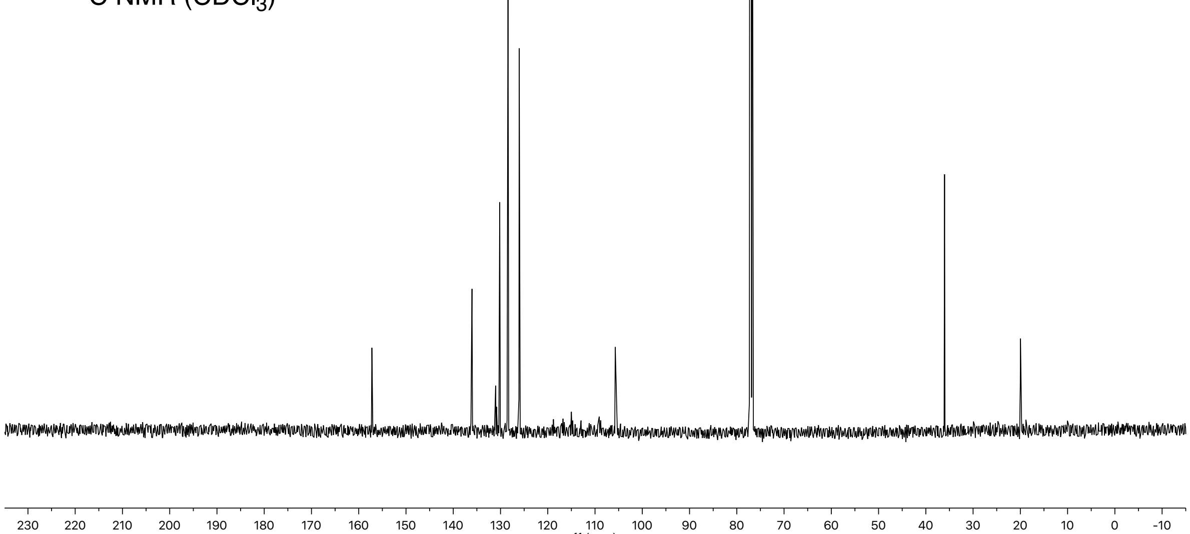
^{1}H NMR ($CDCl_3$)

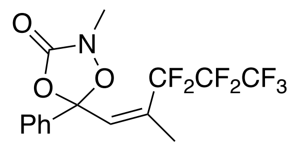




19k

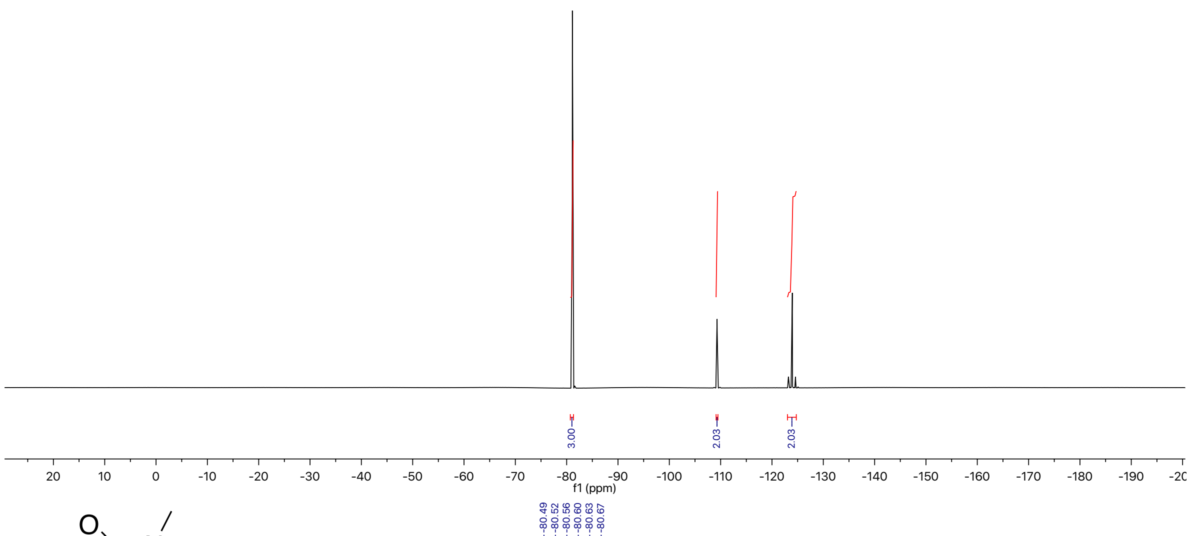
^{13}C NMR ($CDCl_3$)

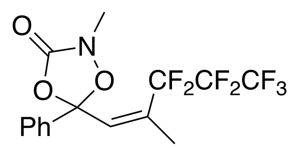




19k

^{19}F NMR (CDCl$_3$)

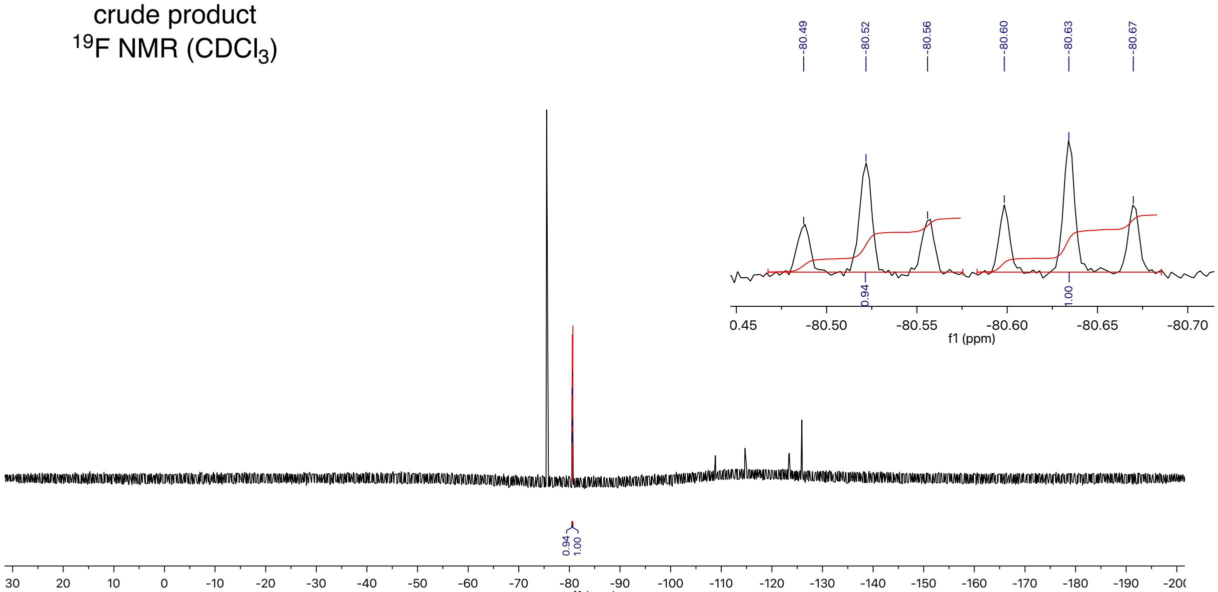


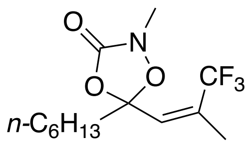


19k

crude product

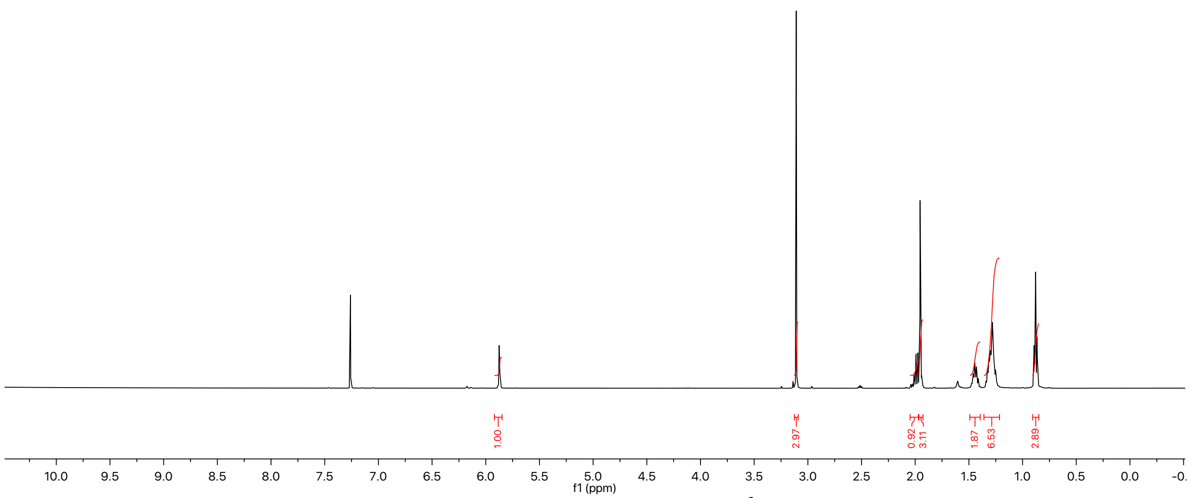
^{19}F NMR (CDCl$_3$)

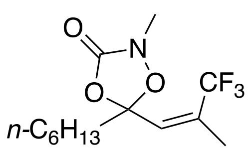




19l

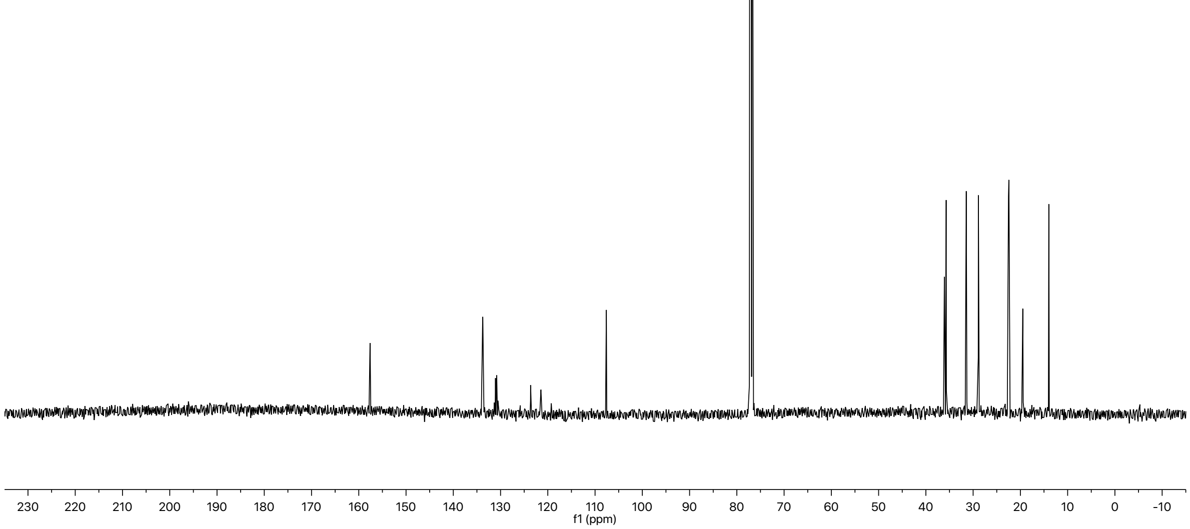
^{1}H NMR ($CDCl_3$)

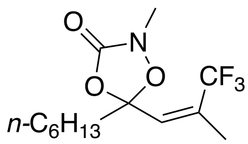




19l

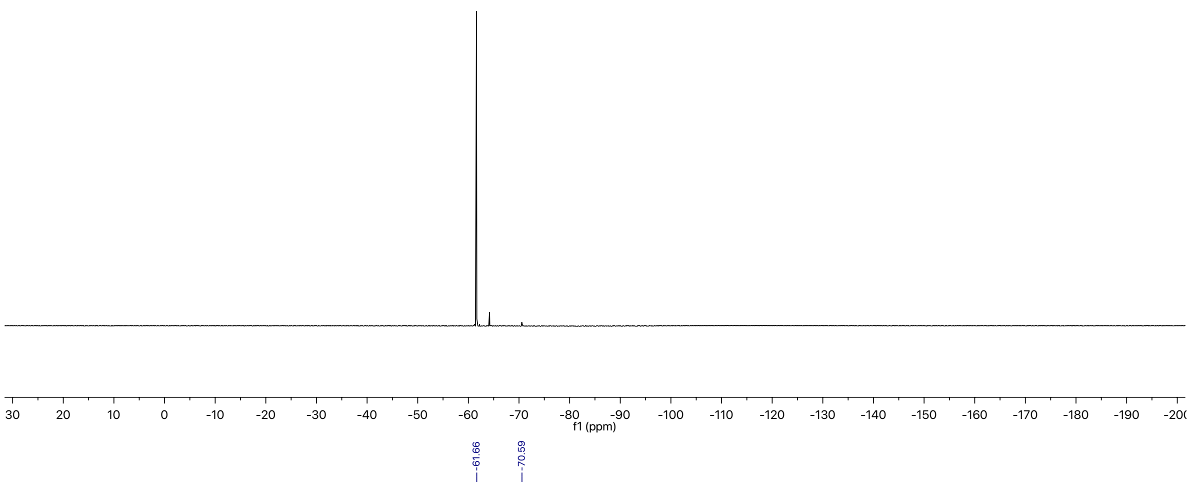
^{13}C NMR ($CDCl_3$)

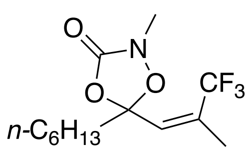




19l

^{19}F NMR ($CDCl_3$)

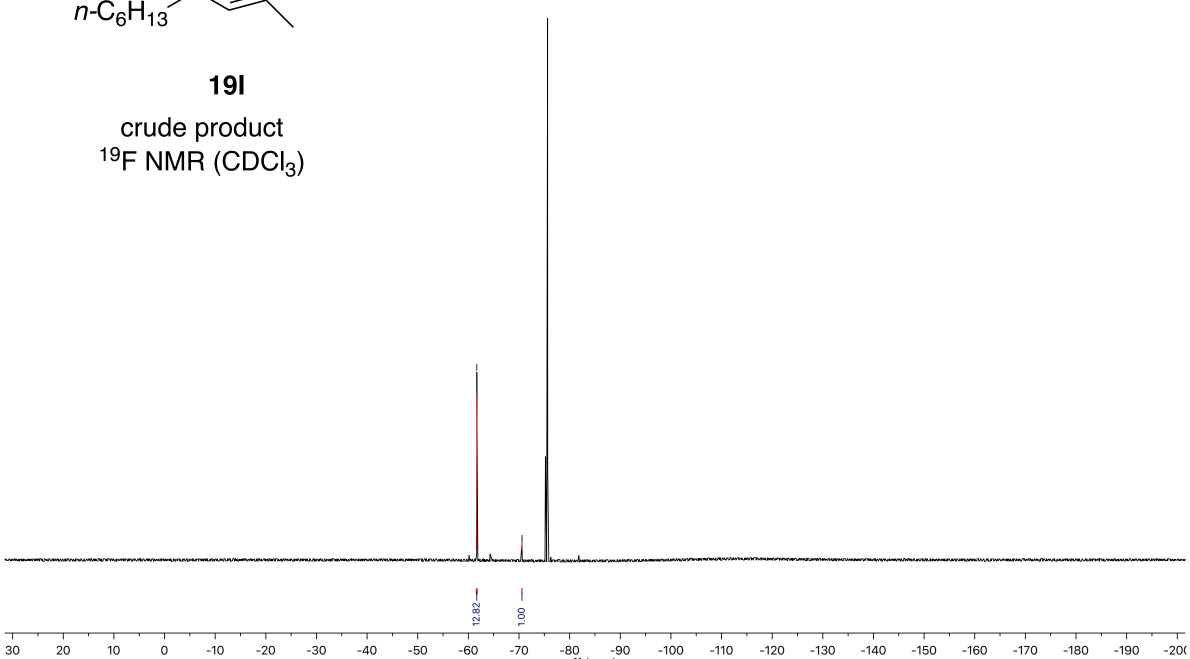


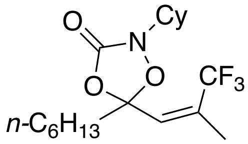


19l

crude product

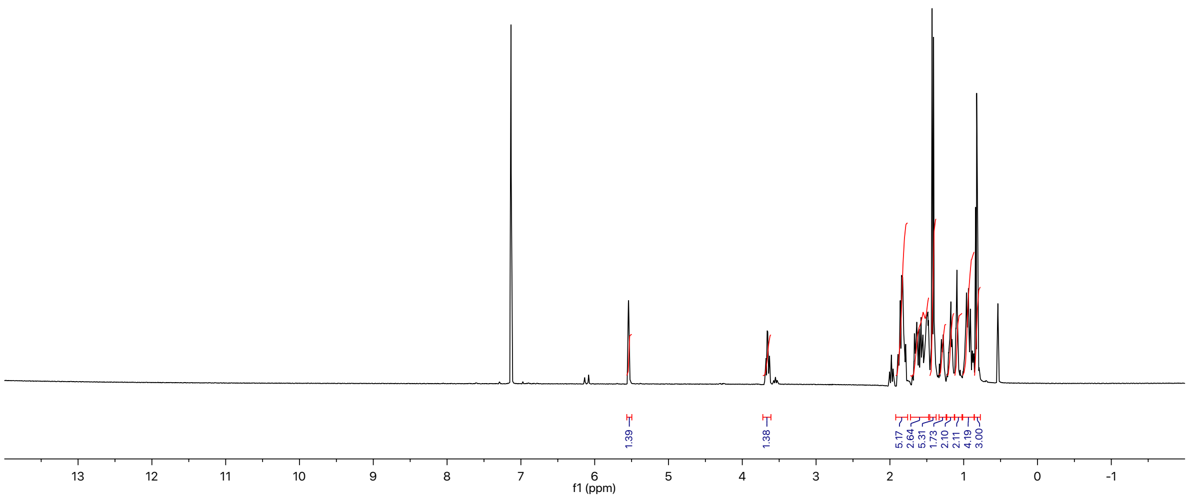
^{19}F NMR ($CDCl_3$)

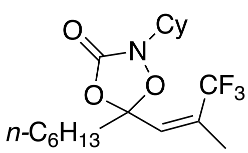




19m

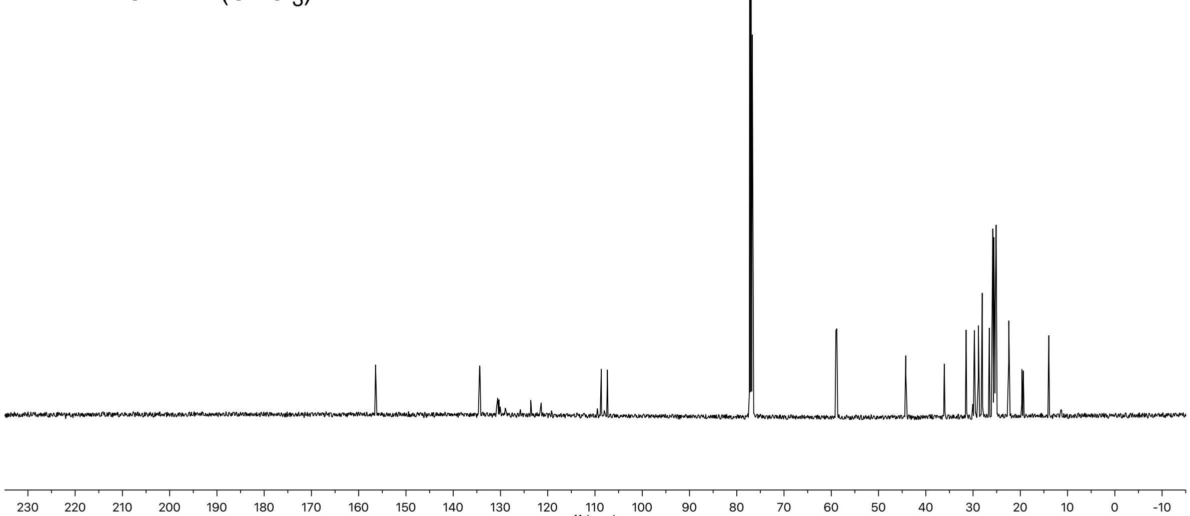
^{1}H NMR (C_6D_6)

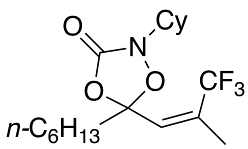




19m

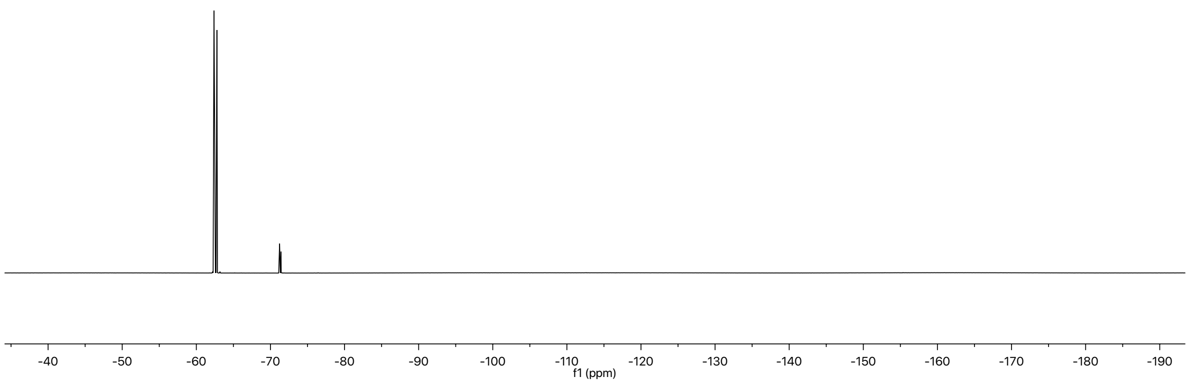
^{13}C NMR ($CDCl_3$)

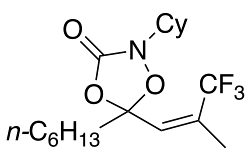




19m

^{19}F NMR ($CDCl_3$)

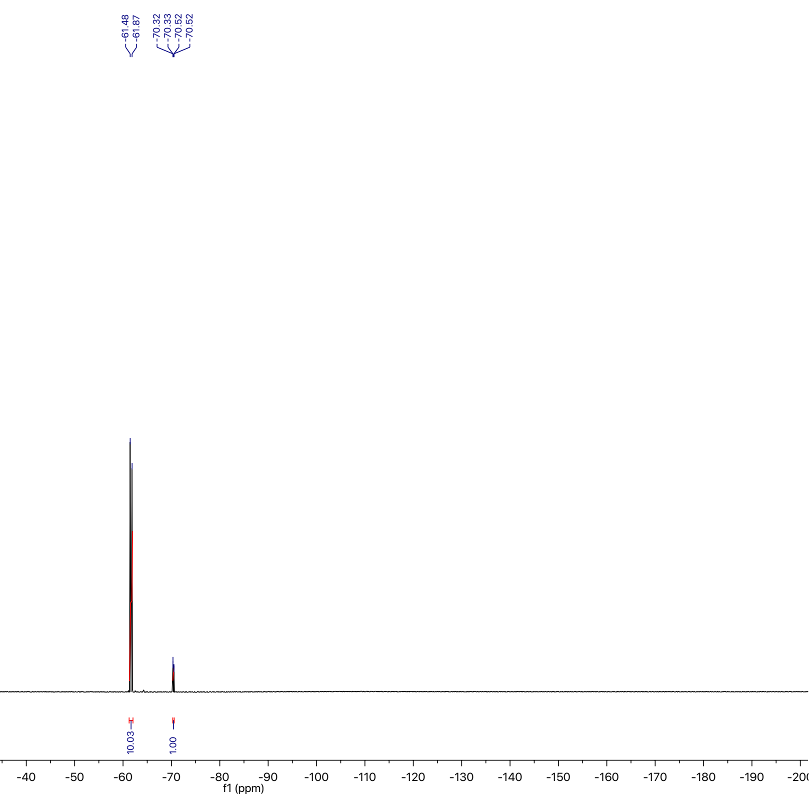




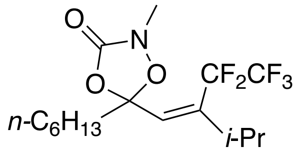
19m

crude product

^{19}F NMR ($CDCl_3$)

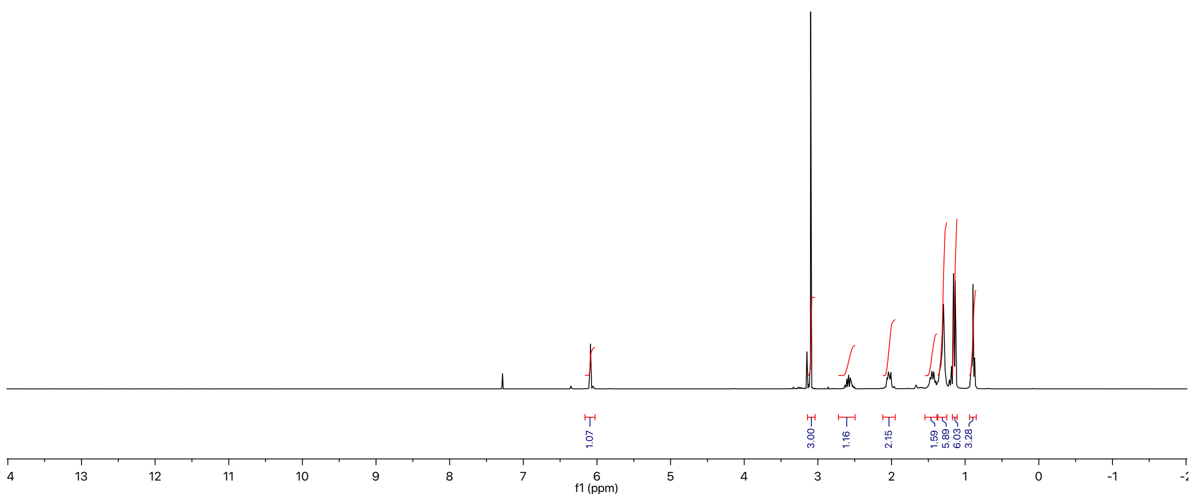


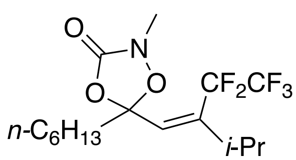
1064



19n

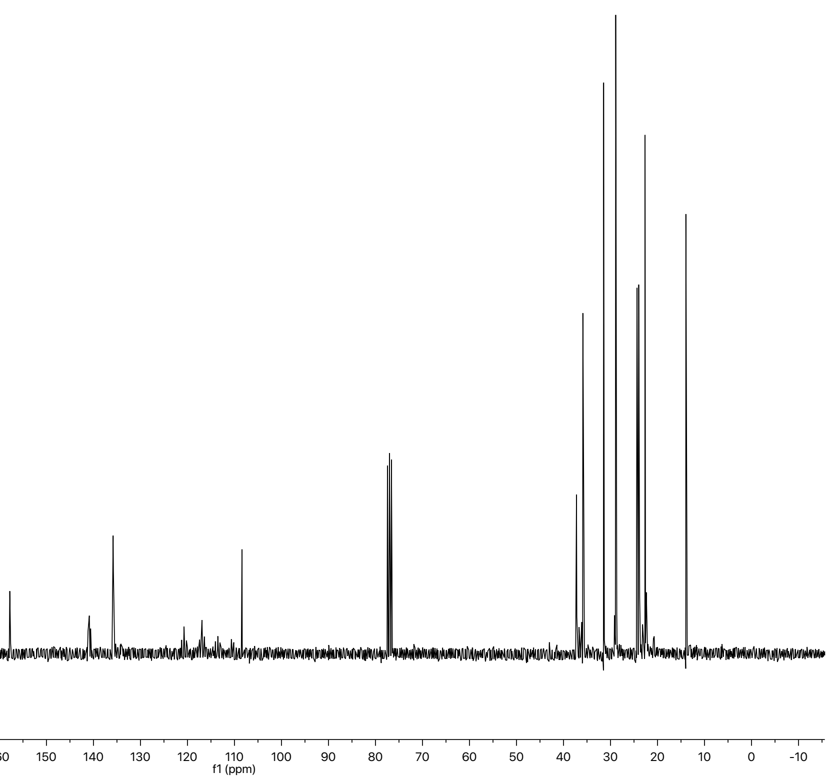
^{1}H NMR ($CDCl_3$)

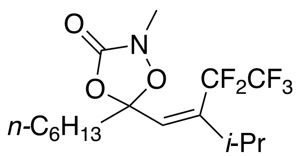




19n

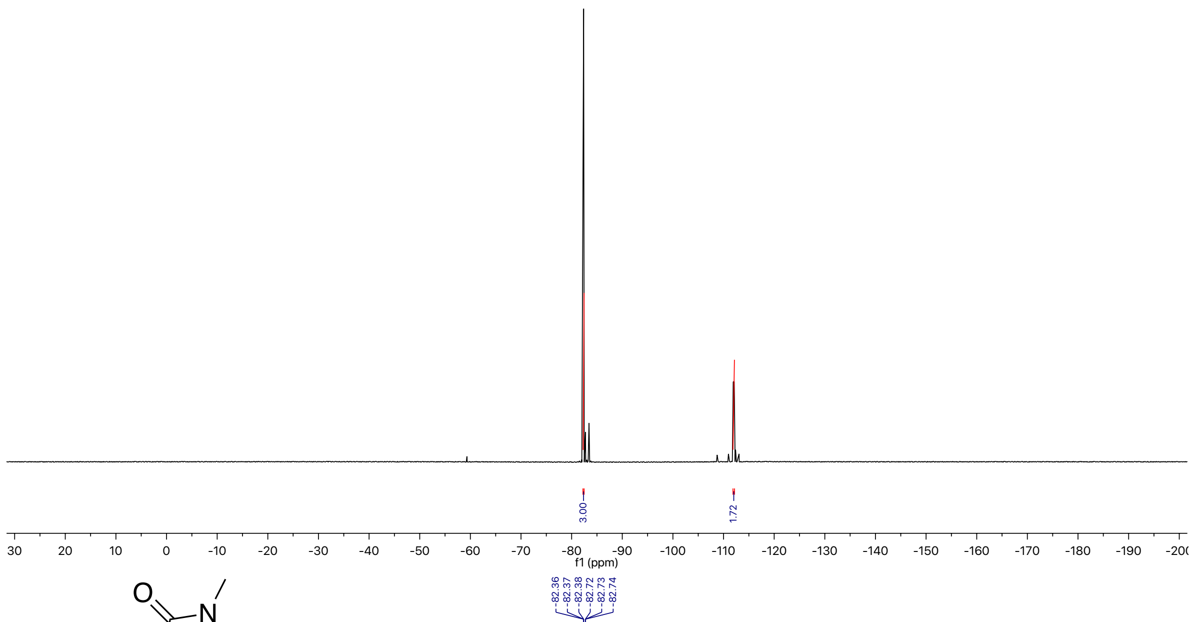
^{13}C NMR ($CDCl_3$)

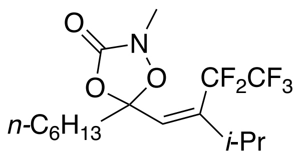




19n

^{19}F NMR ($CDCl_3$)

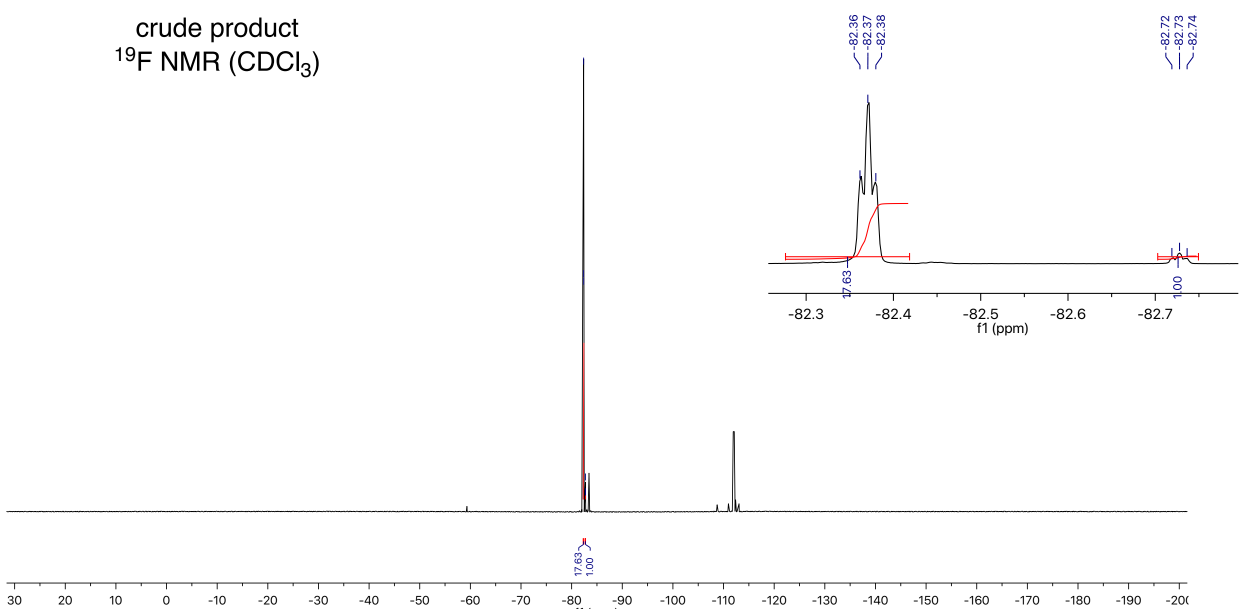




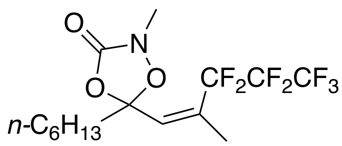
19n

crude product

^{19}F NMR ($CDCl_3$)

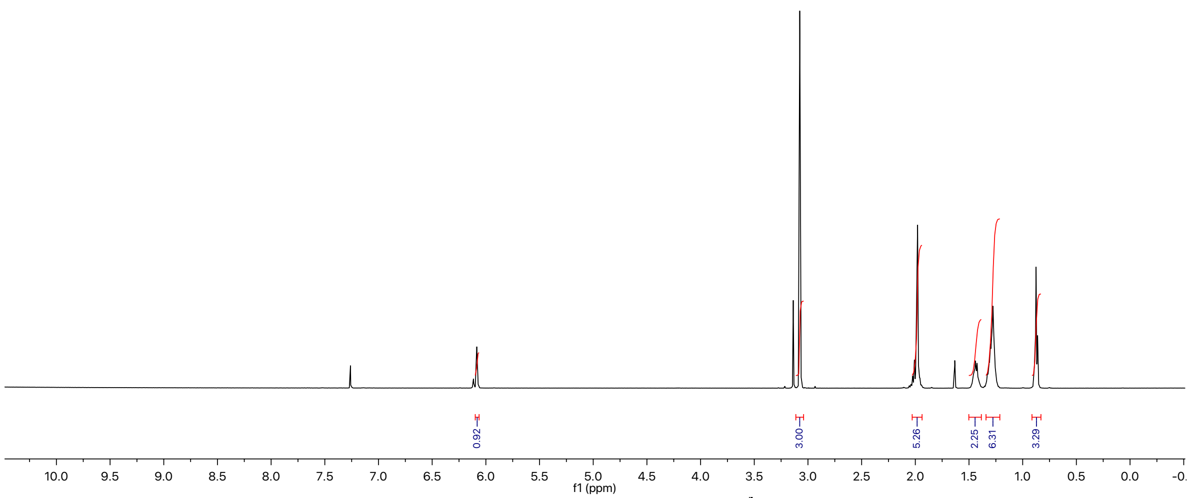


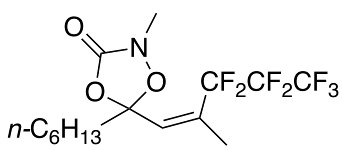
1090



19o

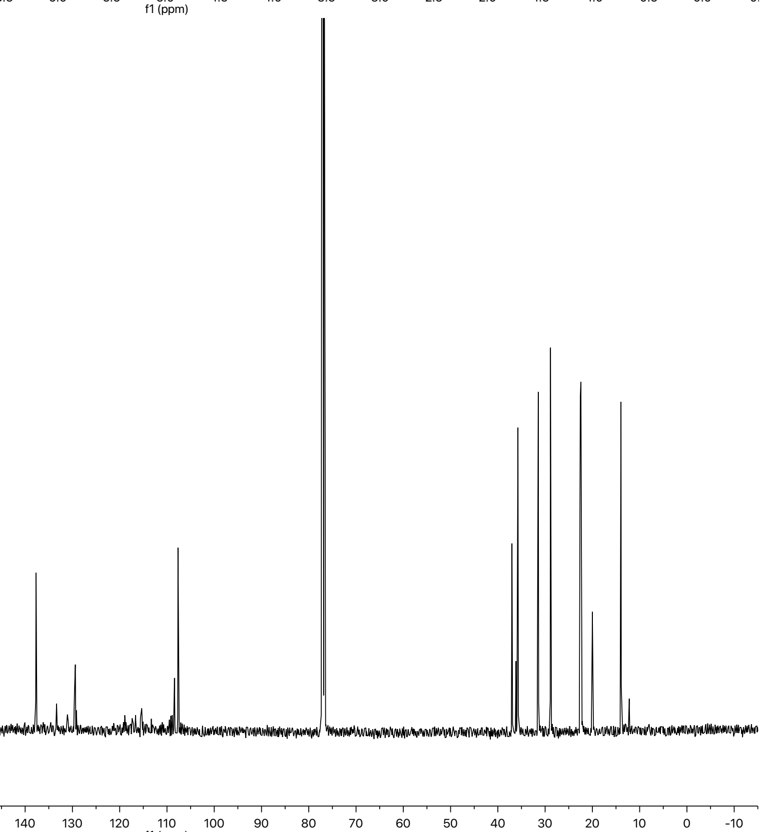
^{1}H NMR ($CDCl_3$)

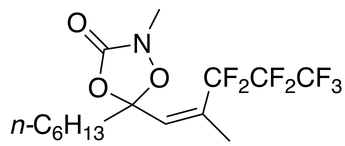




19o

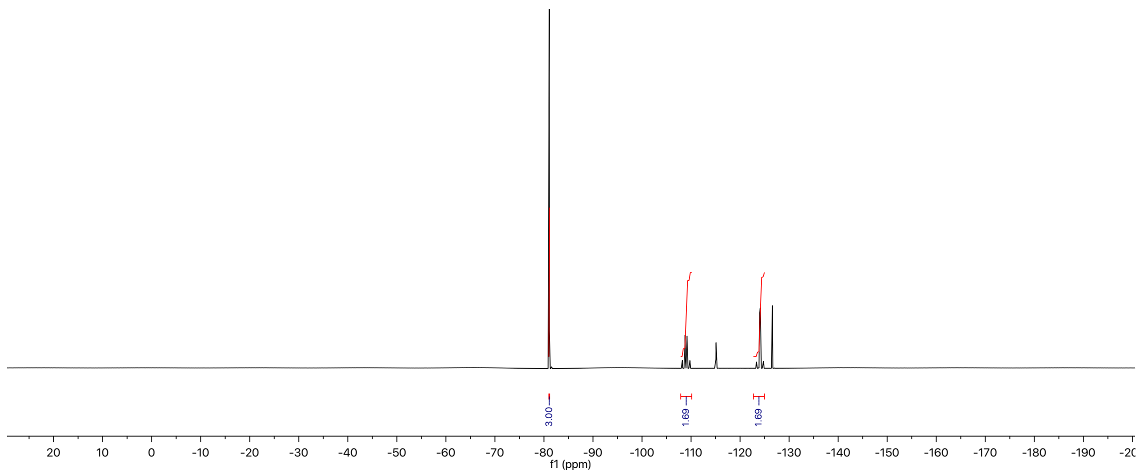
^{13}C NMR ($CDCl_3$)

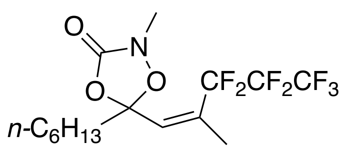




19o

^{19}F NMR ($CDCl_3$)

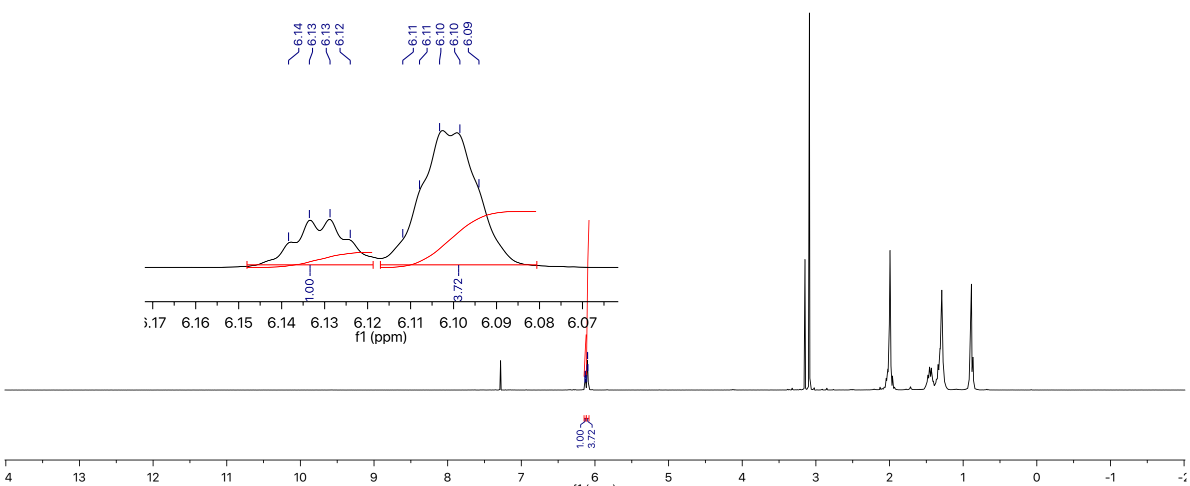


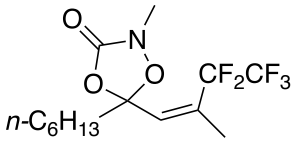


19o

crude product

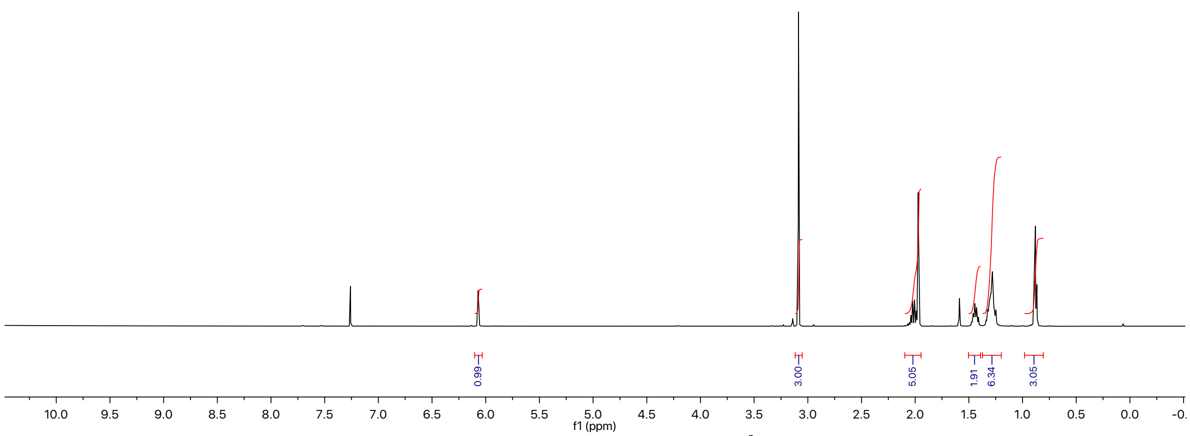
^{1}H NMR ($CDCl_3$)

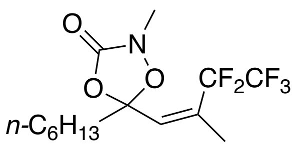




19p

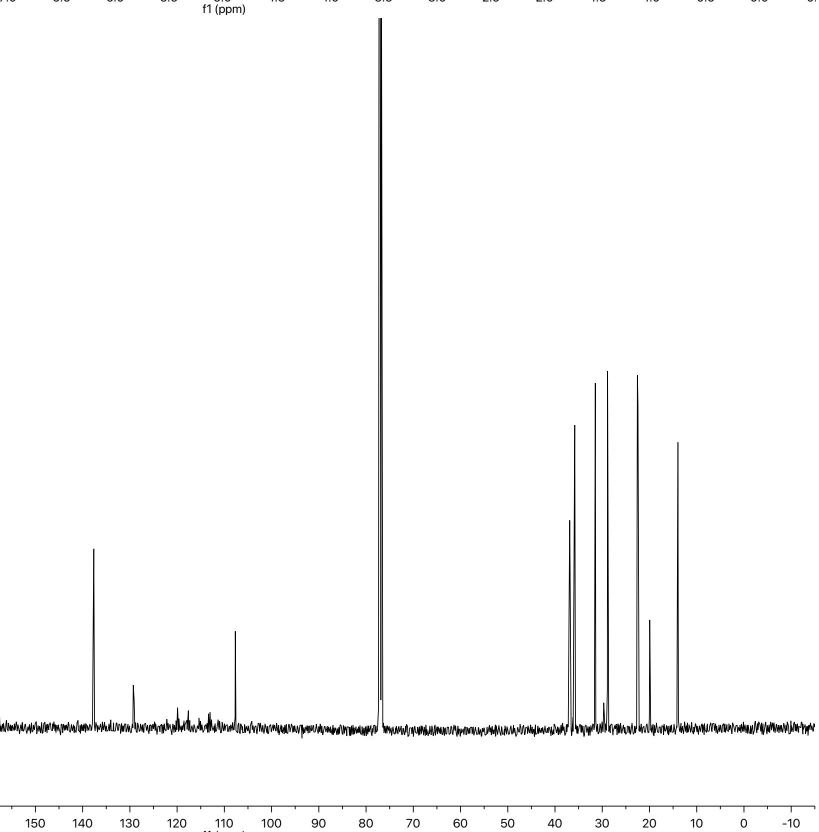
^{1}H NMR ($CDCl_3$)

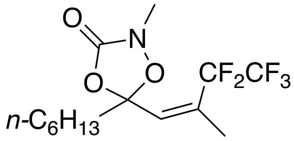




19p

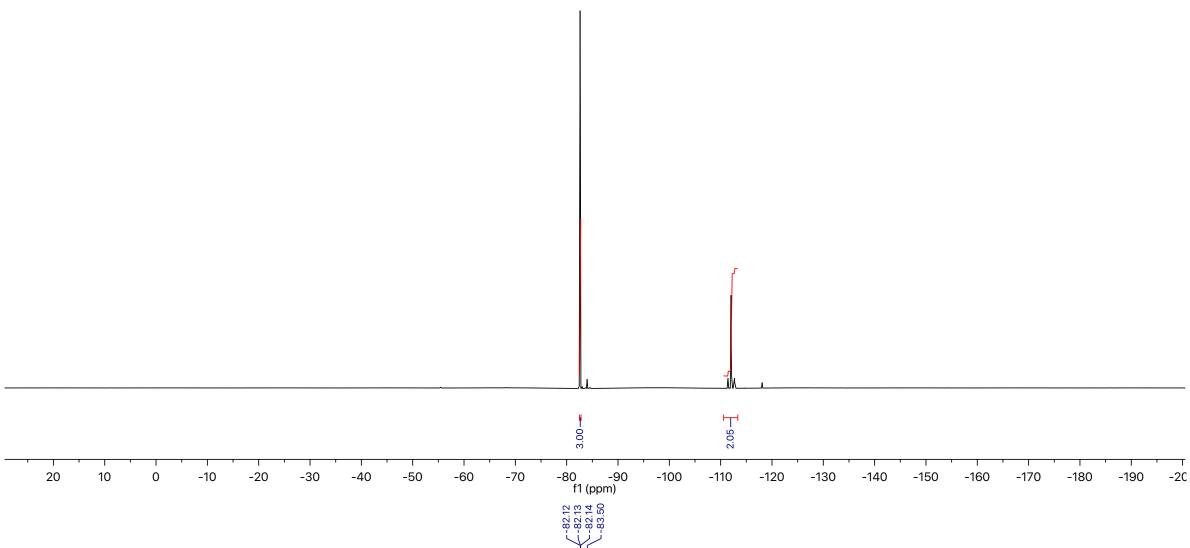
^{13}C NMR ($CDCl_3$)

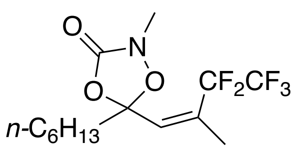




19p

^{19}F NMR (CDCl$_3$)

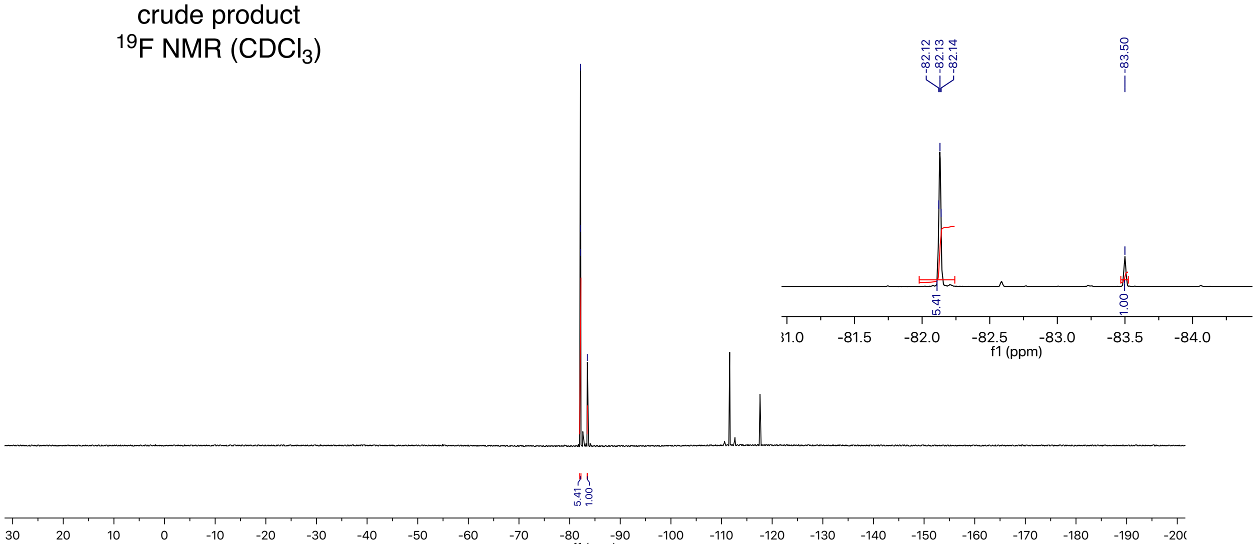




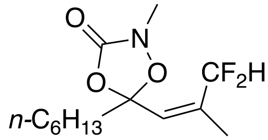
19p

crude product

^{19}F NMR (CDCl$_3$)

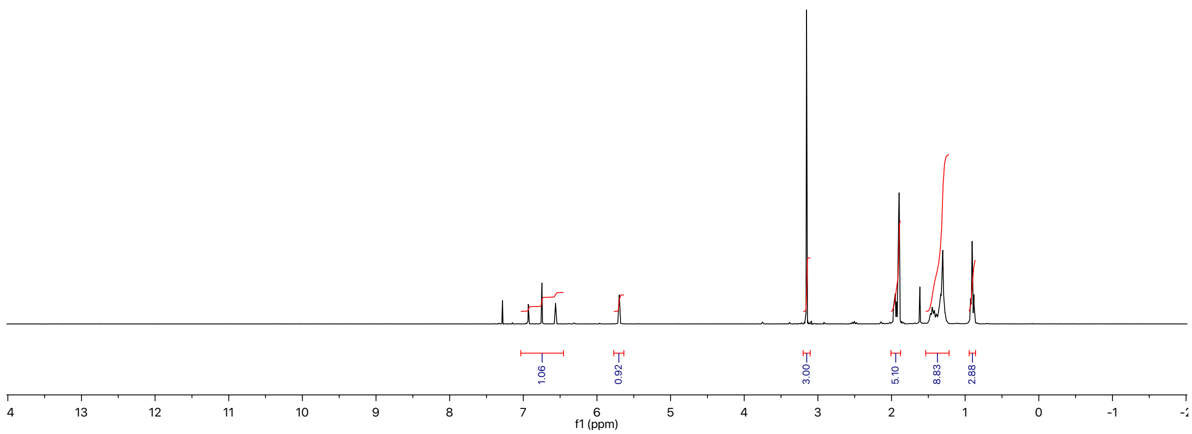


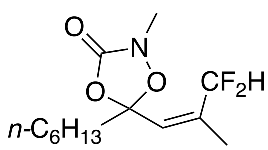
1075



19q

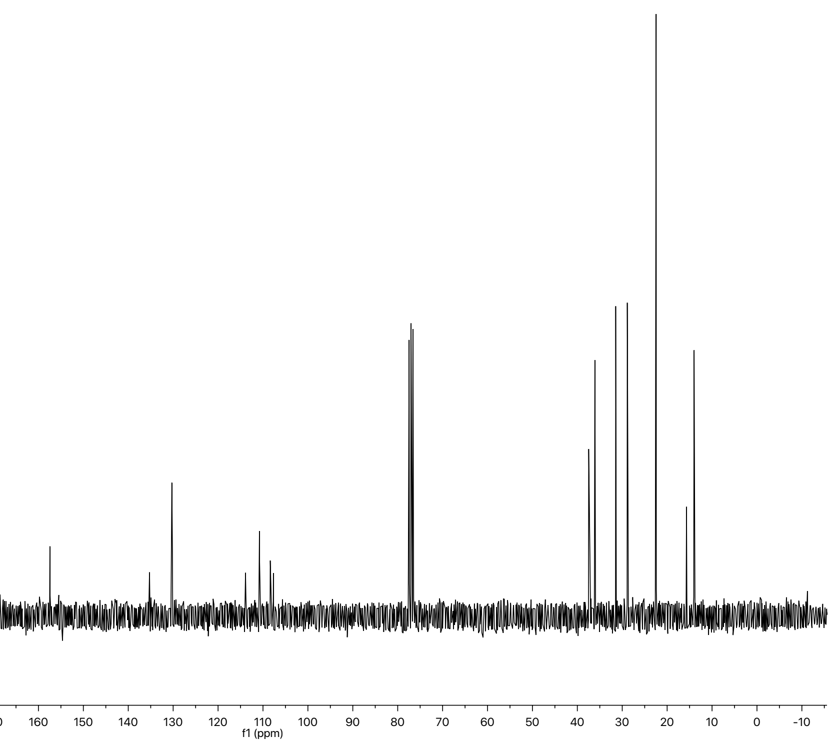
^{1}H NMR ($CDCl_3$)

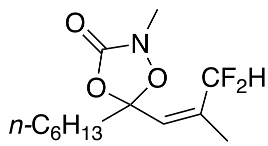




19q

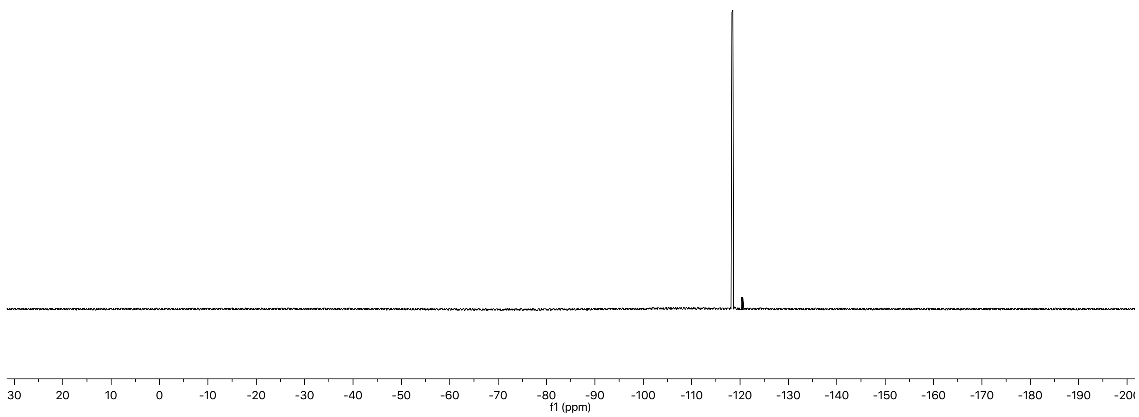
^{13}C NMR ($CDCl_3$)

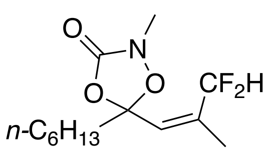




19q

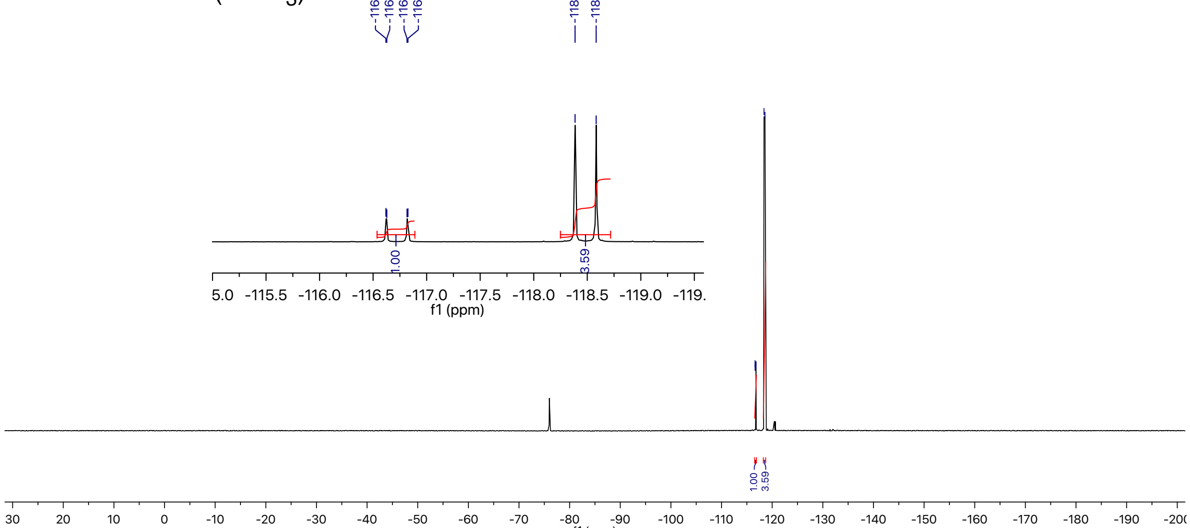
^{19}F NMR ($CDCl_3$)

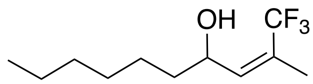




19q

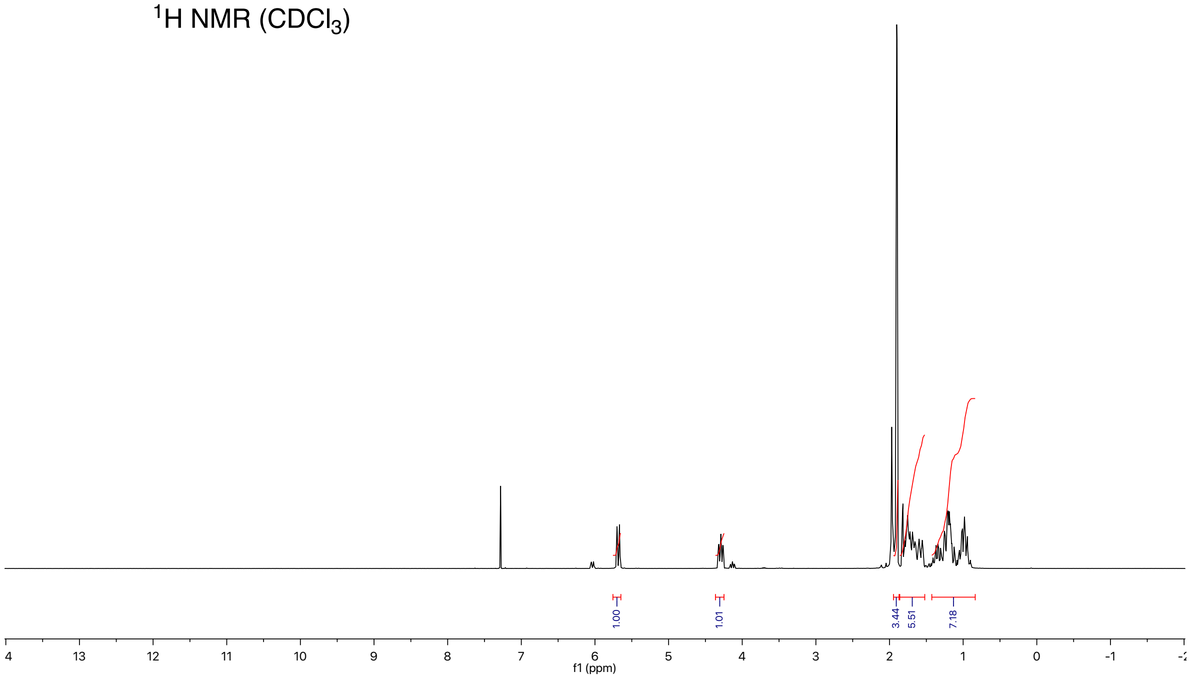
crude product
^{19}F NMR ($CDCl_3$)

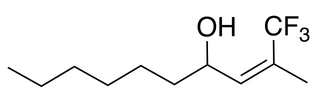




34

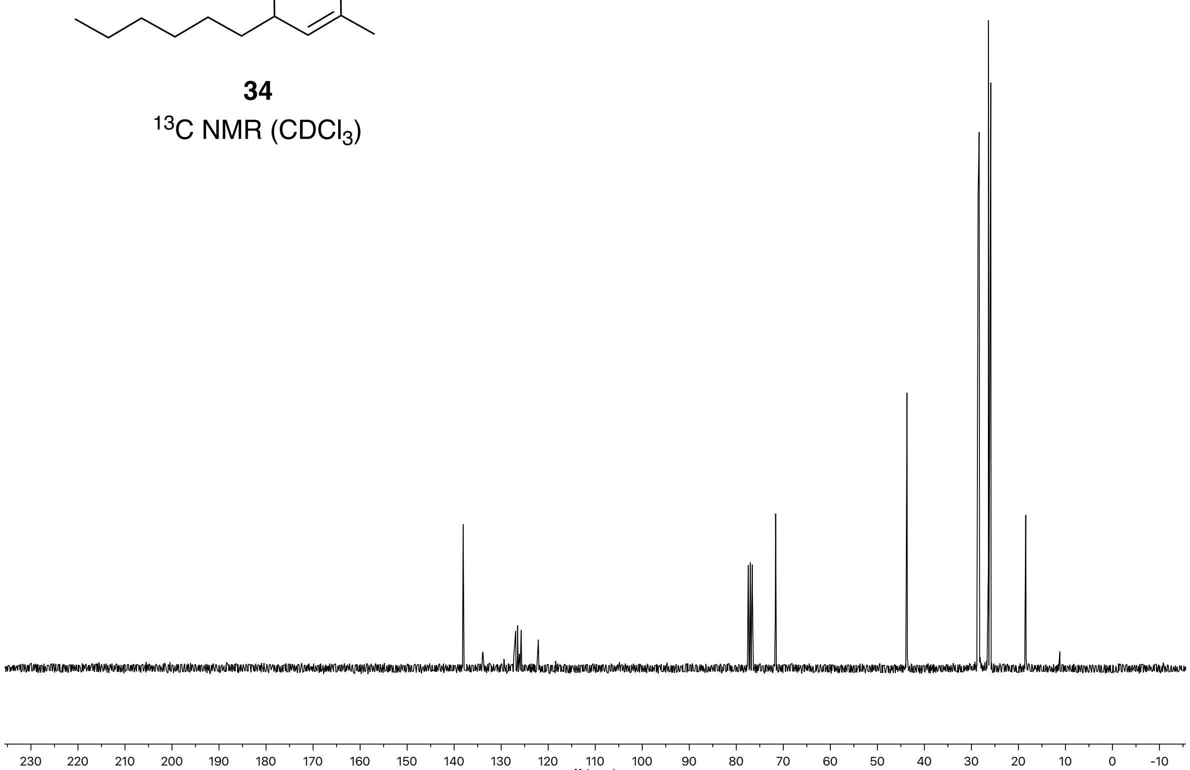
^{1}H NMR ($CDCl_3$)

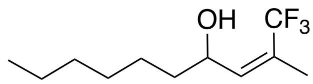




34

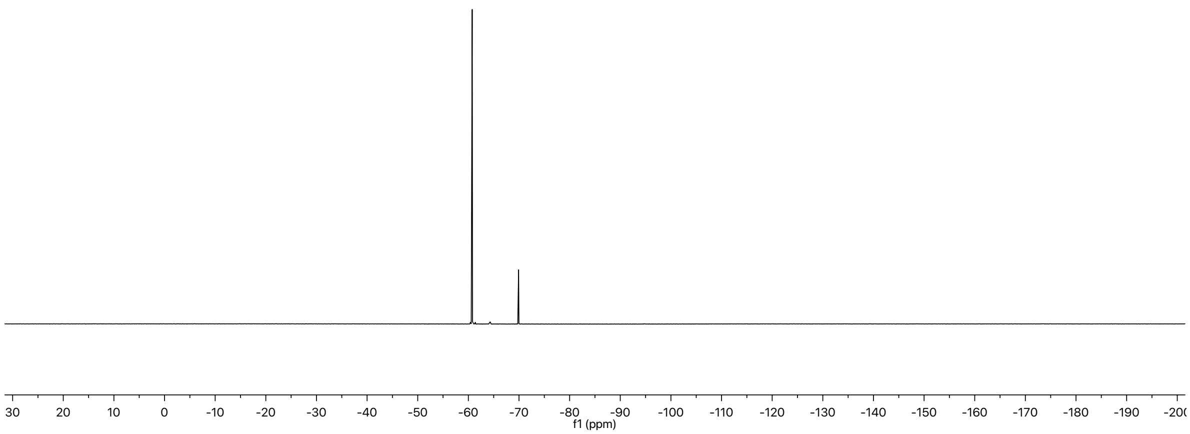
^{13}C NMR ($CDCl_3$)





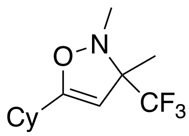
34

^{19}F NMR ($CDCl_3$)



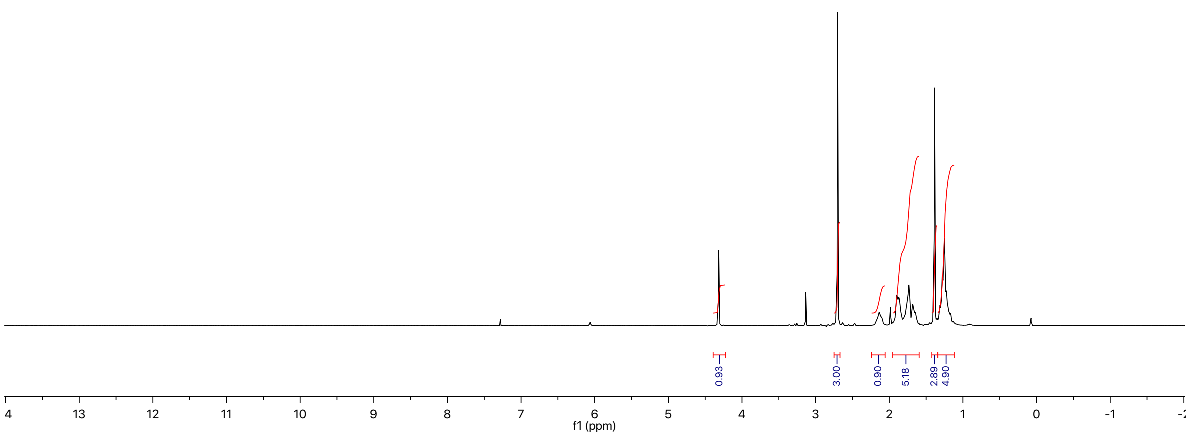
994

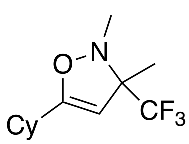
NMR spectrums for 4-isoxazolines (**20a**, **20d**-**20f**, **20j**, **20h**, **20k**, **20l**, **20r**) and diene **35** and **36**.



20a

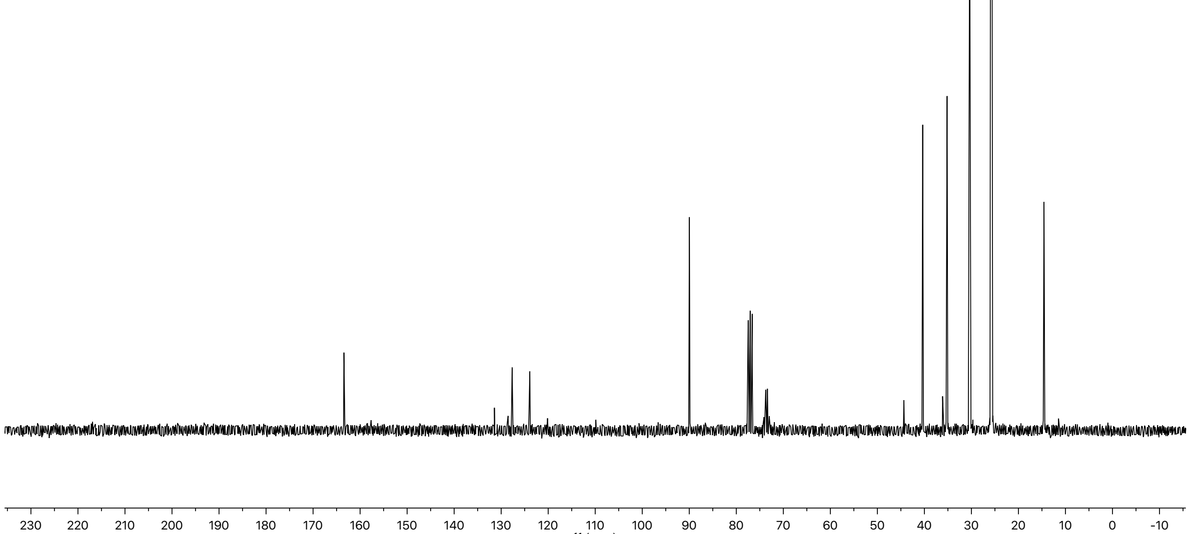
^1H NMR ($CDCl_3$)

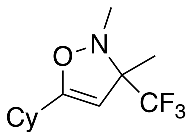




20a

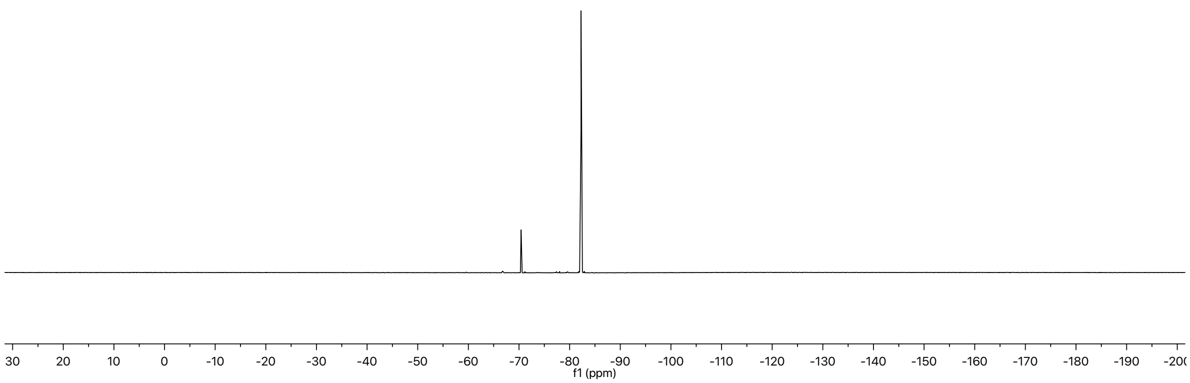
^{13}C NMR ($CDCl_3$)



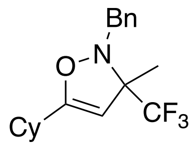


20a

^{19}F NMR ($CDCl_3$)

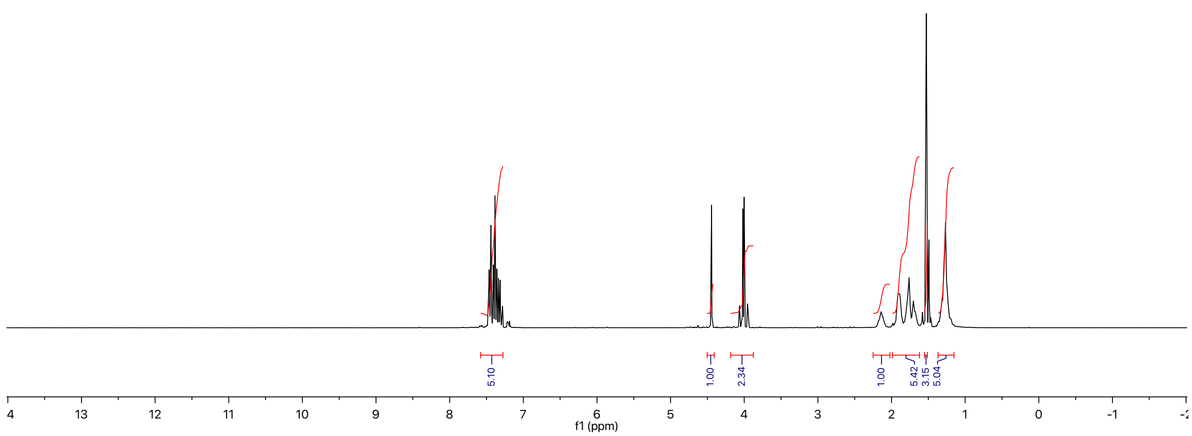


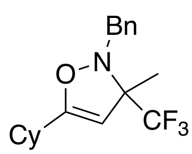
1098



20d

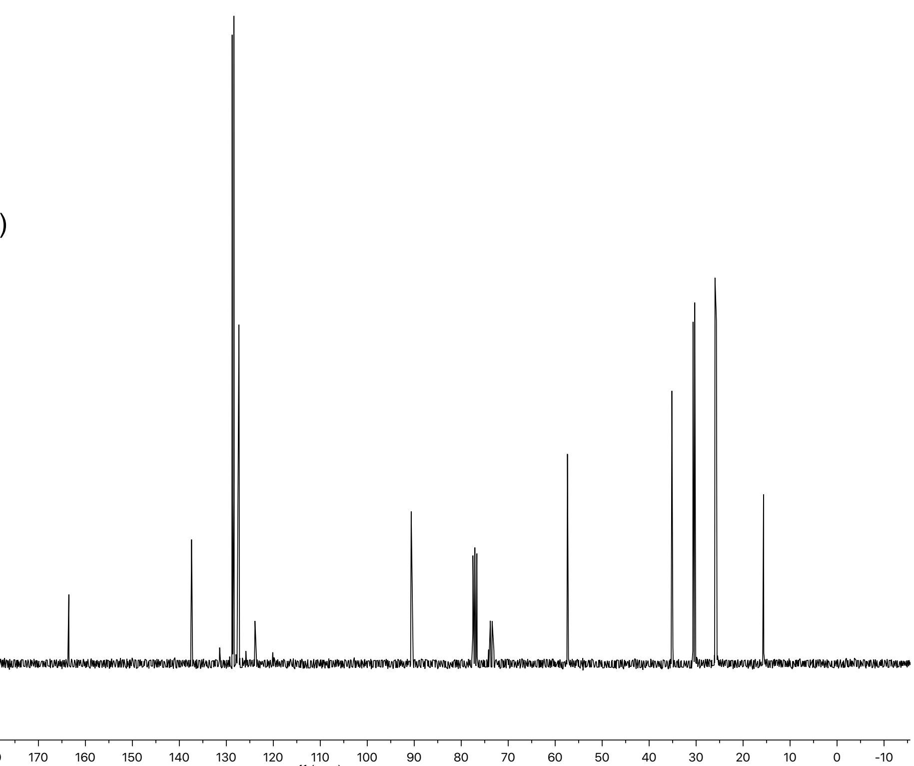
^{1}H NMR ($CDCl_3$)

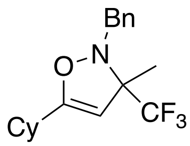




20d

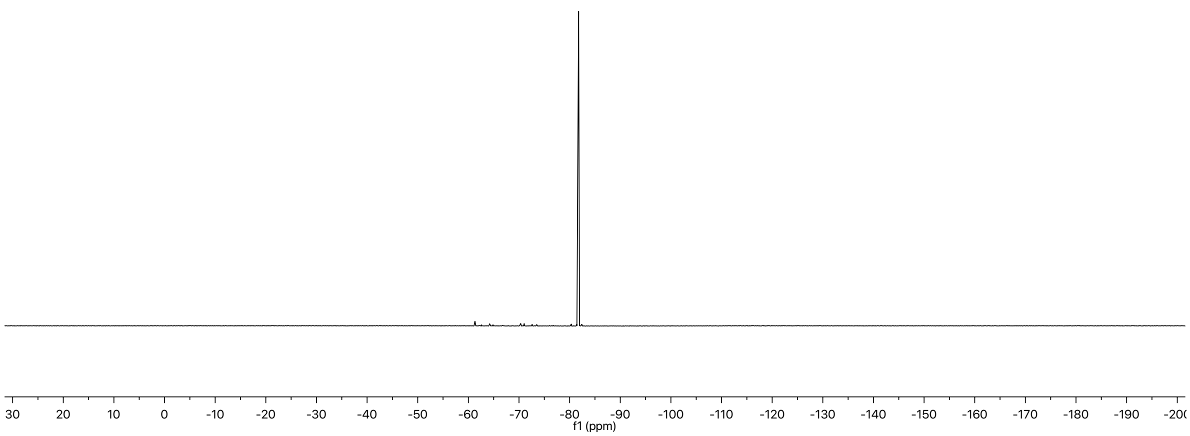
^{13}C NMR ($CDCl_3$)



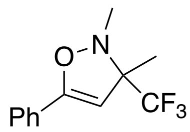


20d

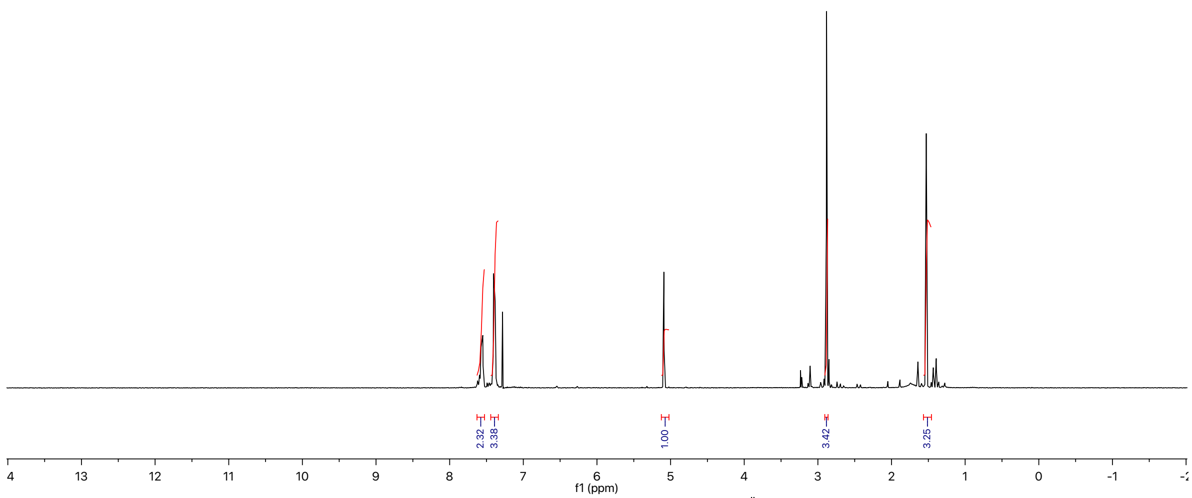
^{19}F NMR ($CDCl_3$)

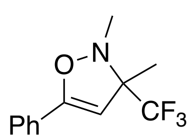


1100

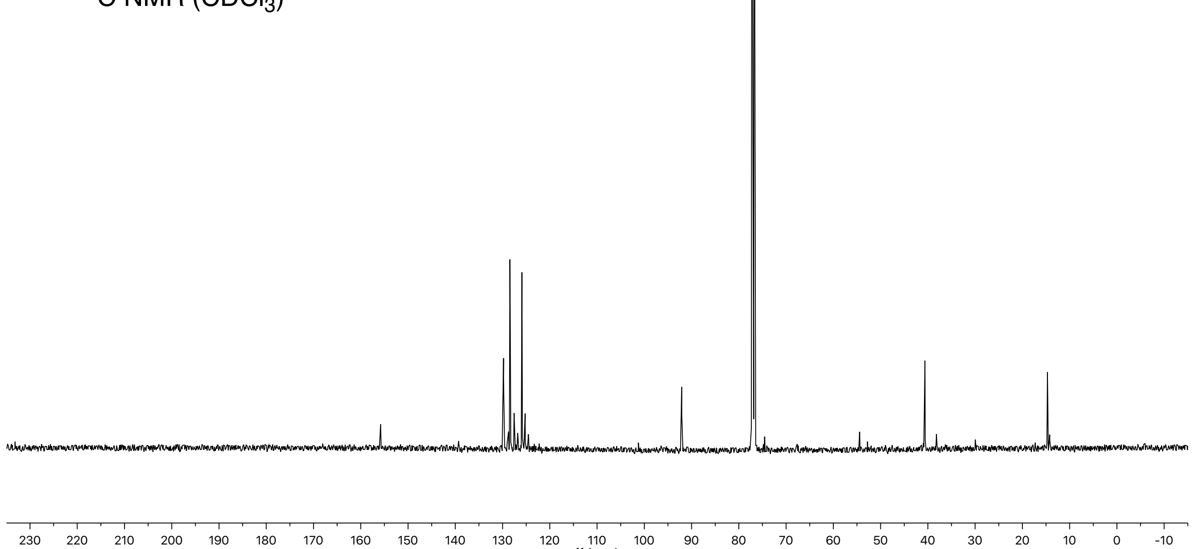


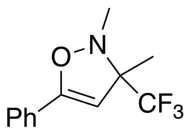
20e
^{1}H NMR ($CDCl_3$)





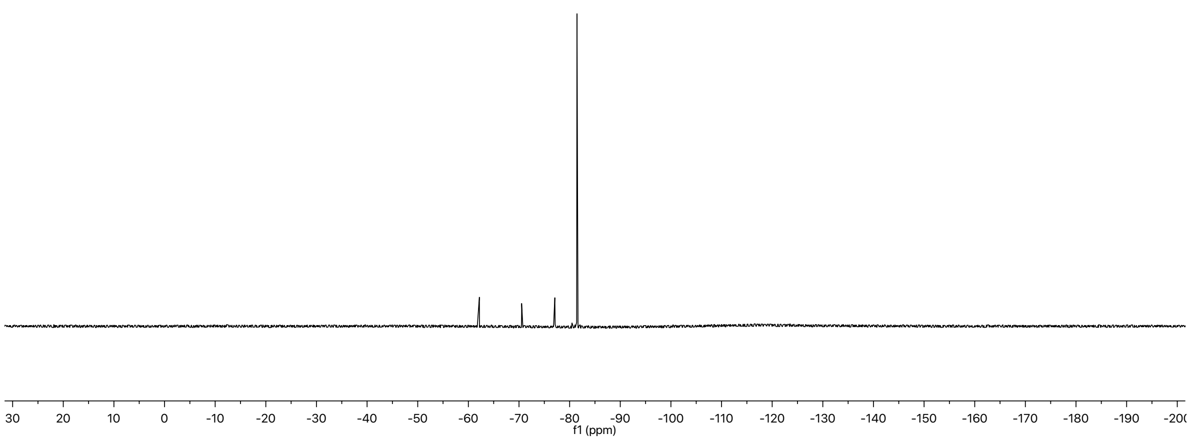
20e
^{13}C NMR ($CDCl_3$)



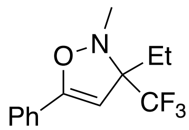


20e

^{19}F NMR ($CDCl_3$)

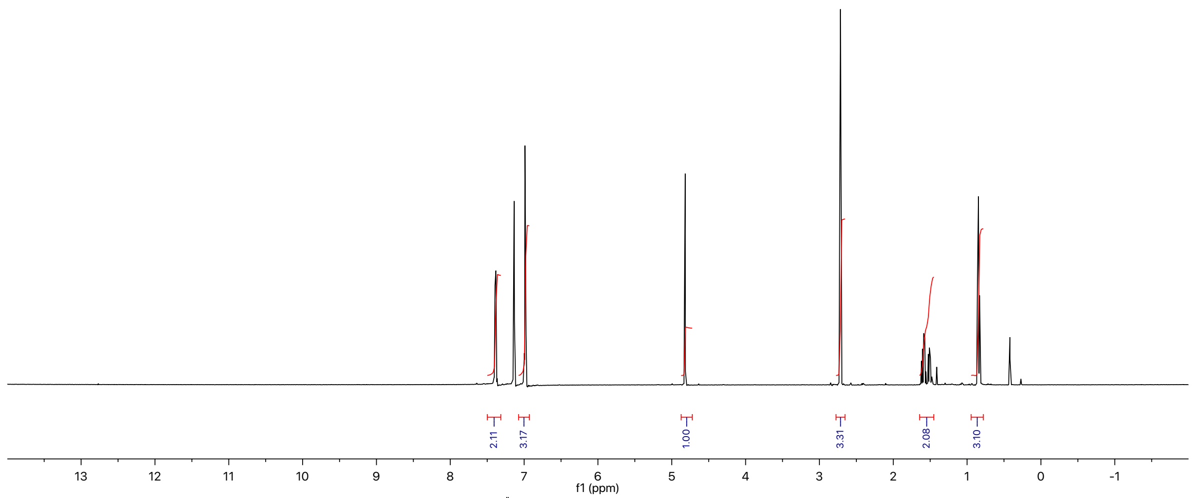


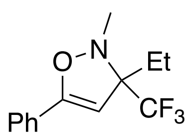
1103



20f

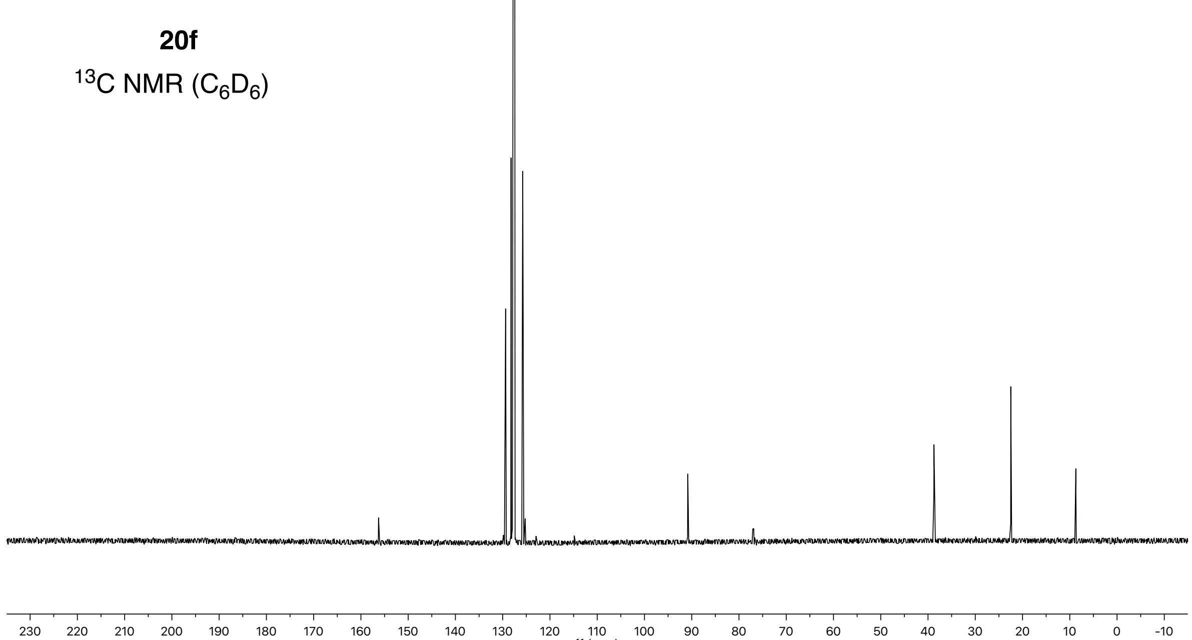
^{1}H NMR (C_6D_6)

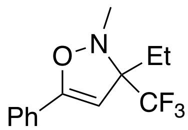




20f

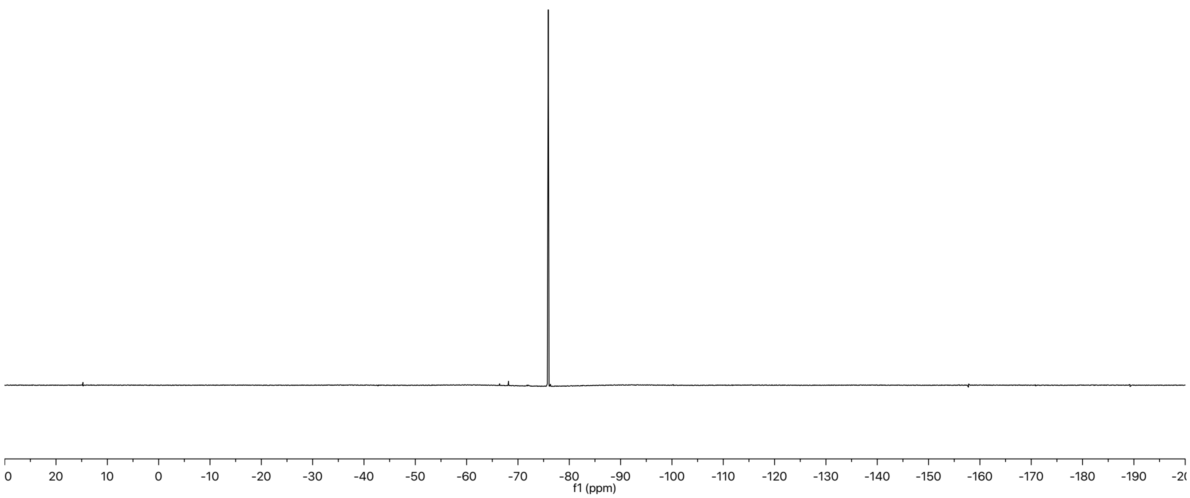
^{13}C NMR (C_6D_6)



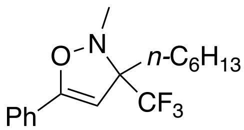


20f

^{19}F NMR (C_6D_6)

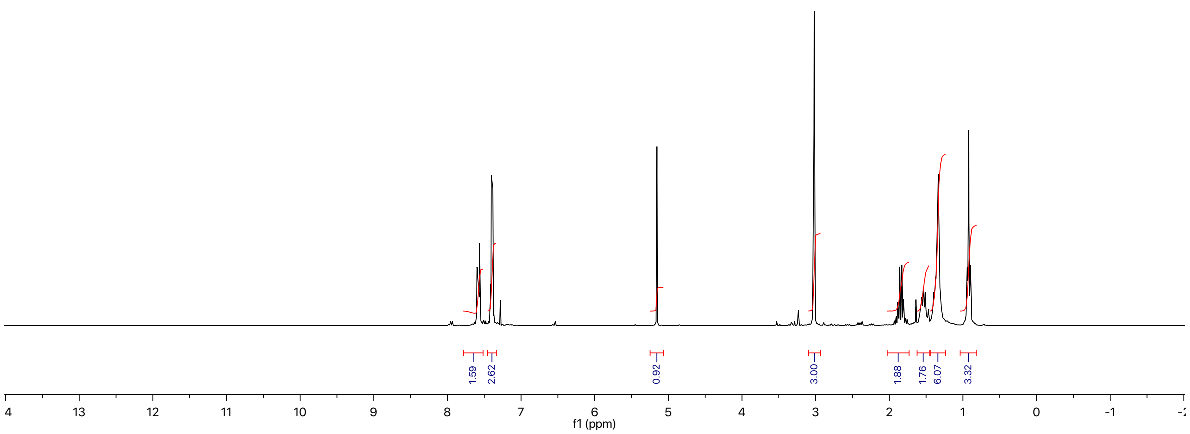


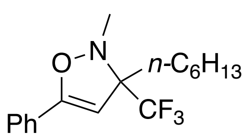
686



20h

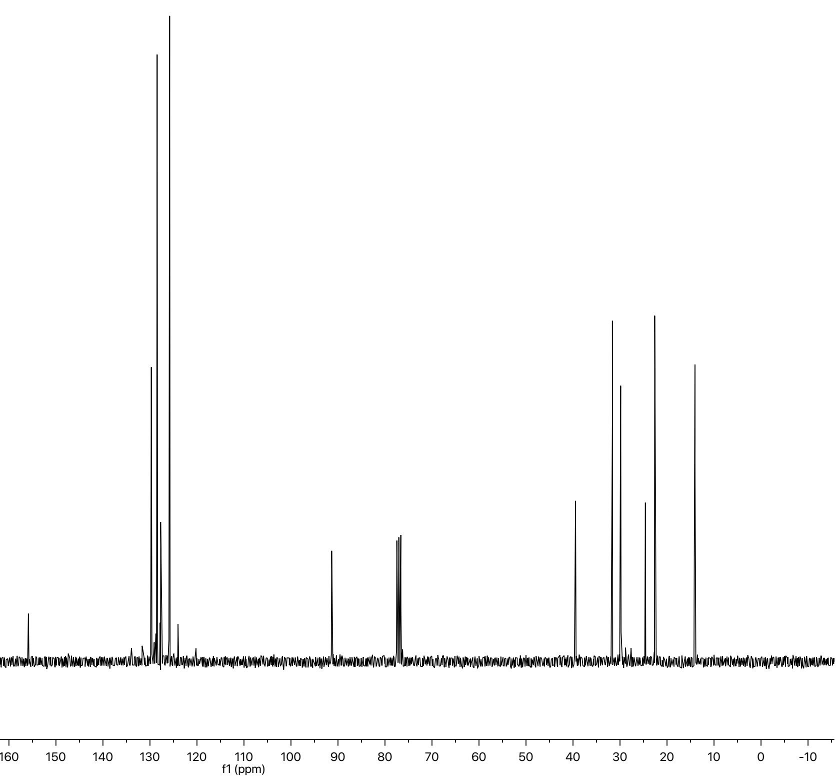
^1H NMR ($CDCl_3$)

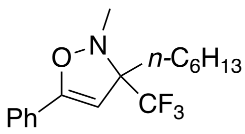




20h

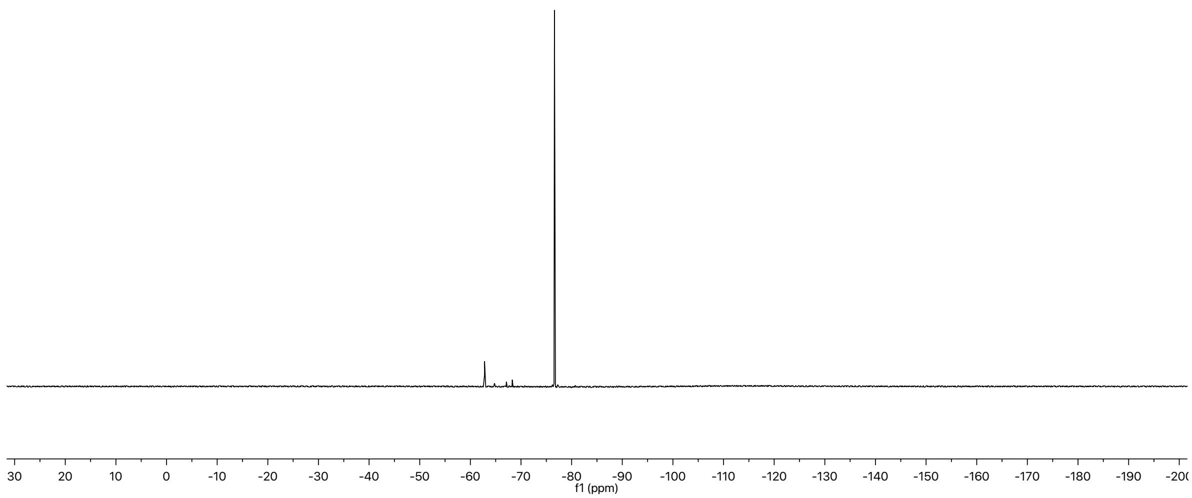
^{13}C NMR ($CDCl_3$)



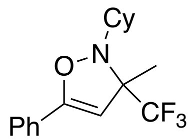


20h

^{19}F NMR ($CDCl_3$)

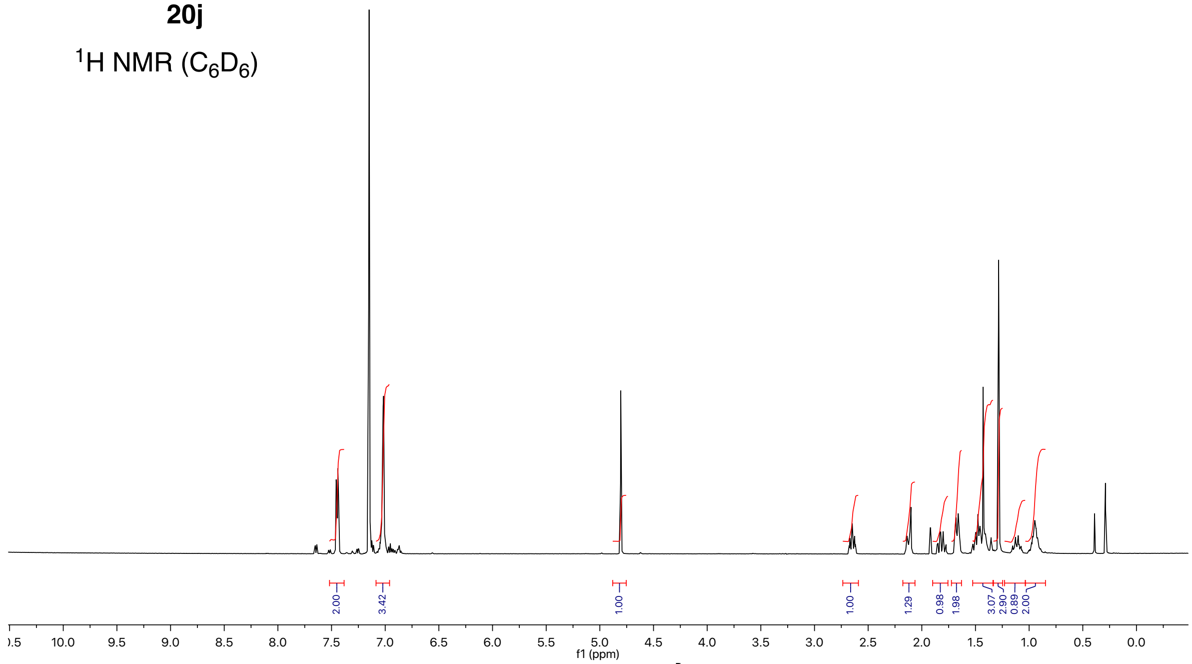


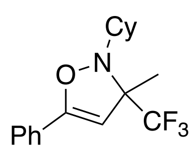
1097



20j

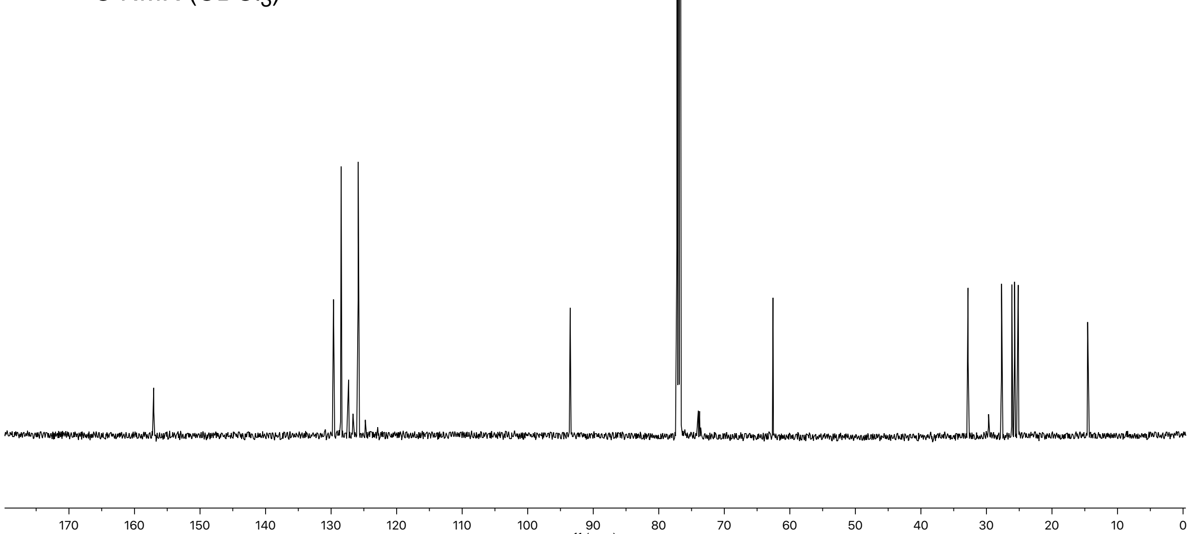
^{1}H NMR (C_6D_6)

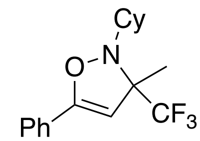




20j

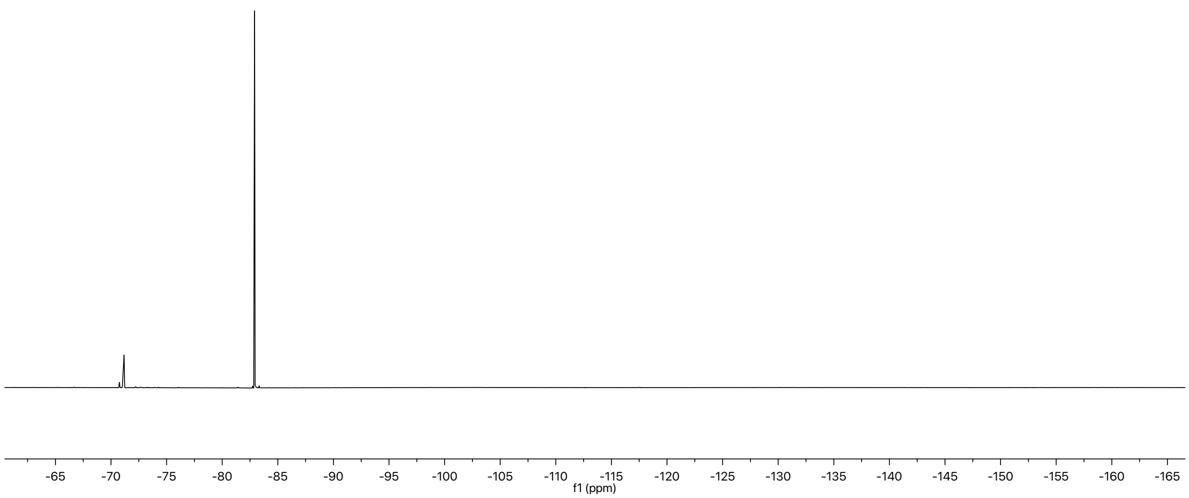
^{13}C NMR ($CDCl_3$)



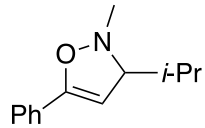


20j

^{19}F NMR (C_6D_6)

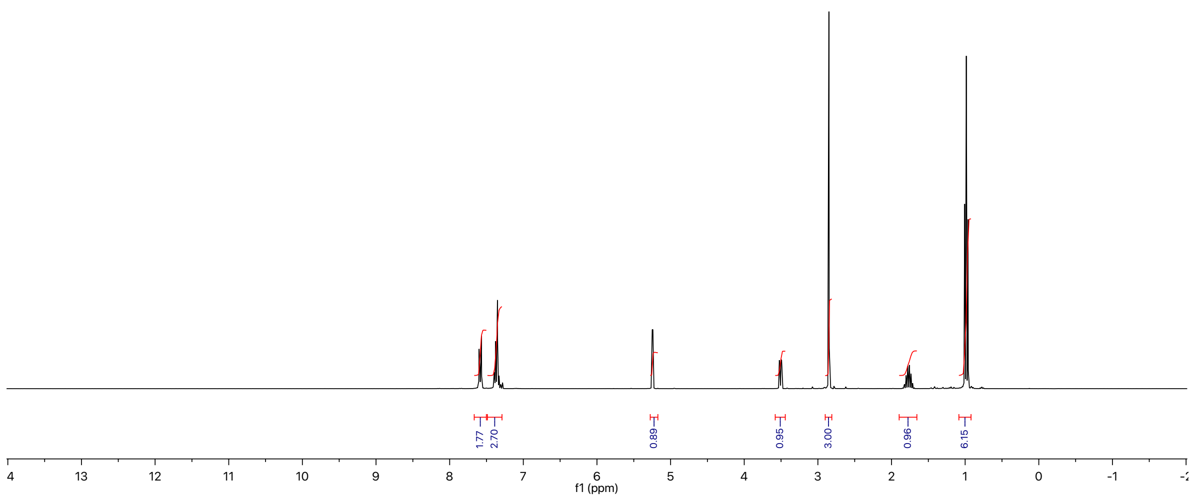


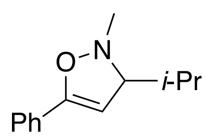
678



20r

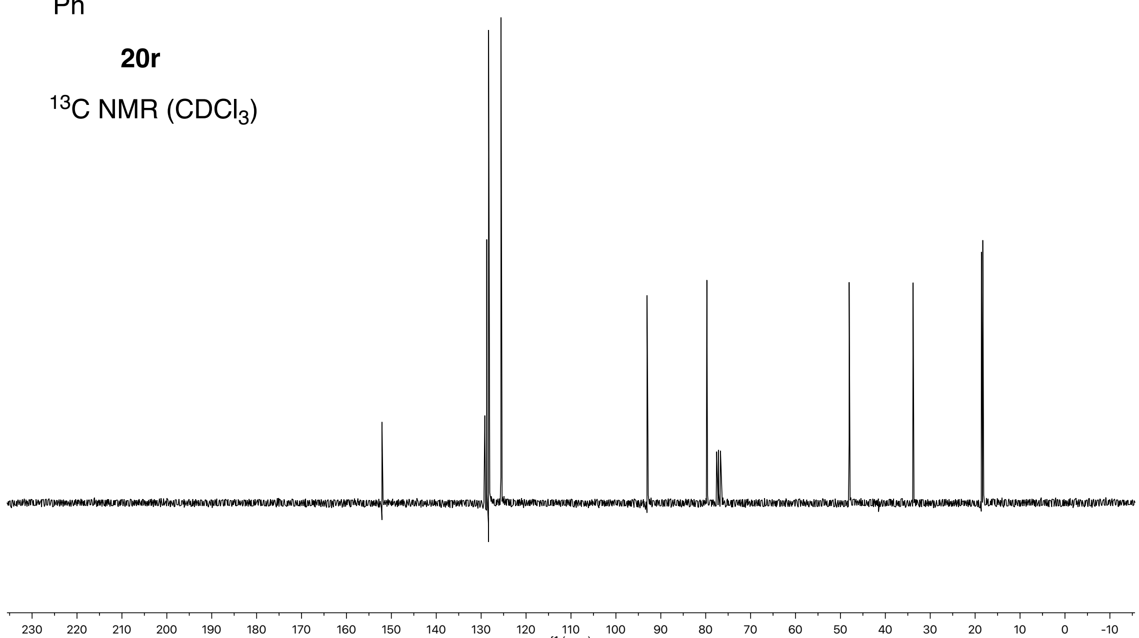
^{1}H NMR ($CDCl_3$)

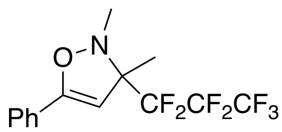




20r

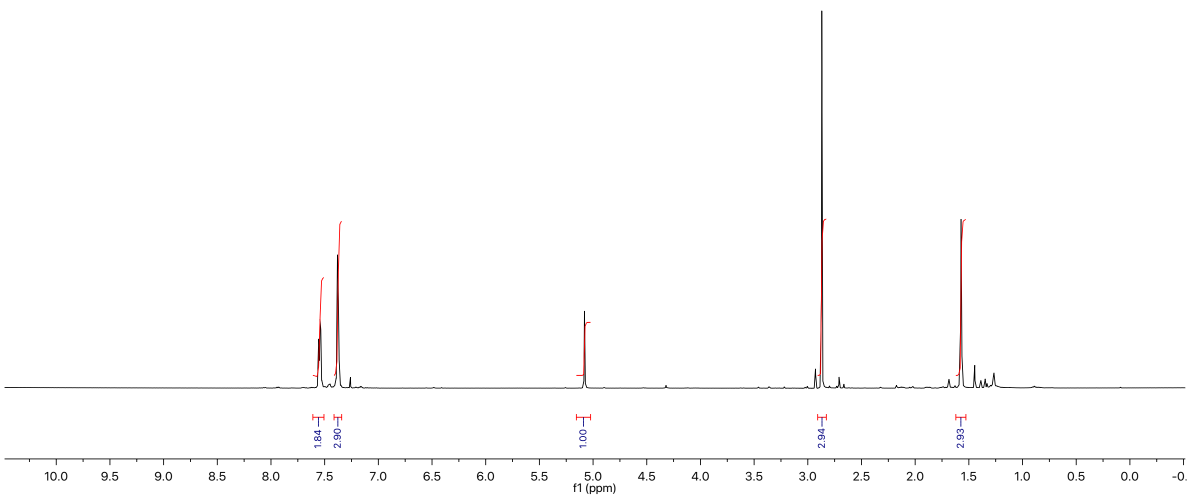
^{13}C NMR ($CDCl_3$)

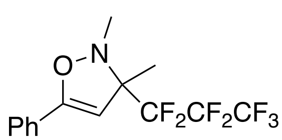




20k

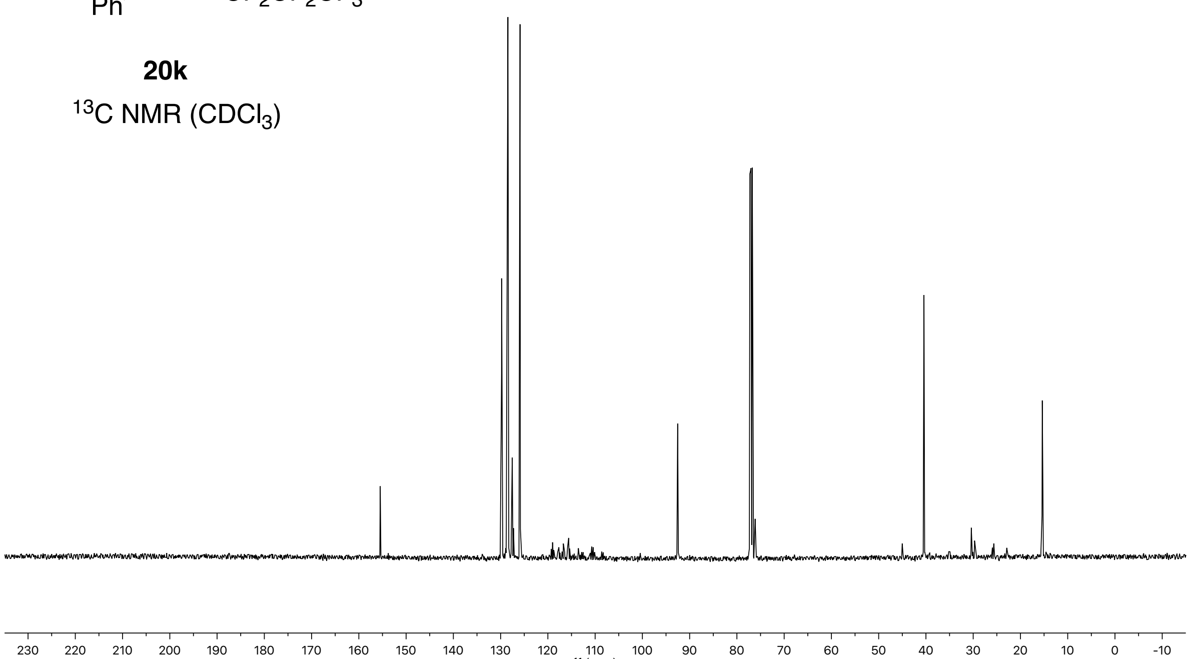
^{1}H NMR ($CDCl_3$)

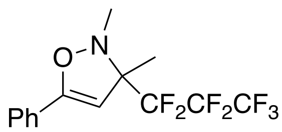




20k

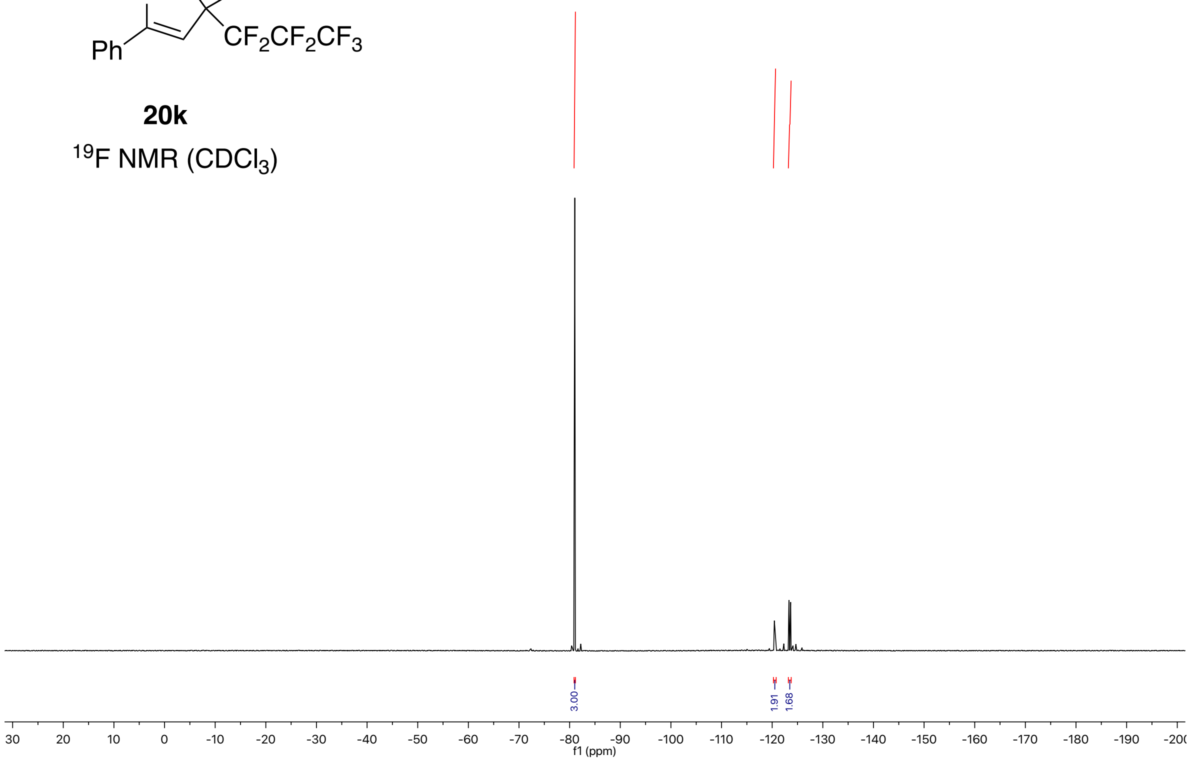
^{13}C NMR ($CDCl_3$)



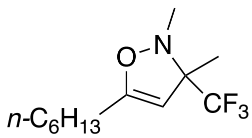


20k

^{19}F NMR ($CDCl_3$)

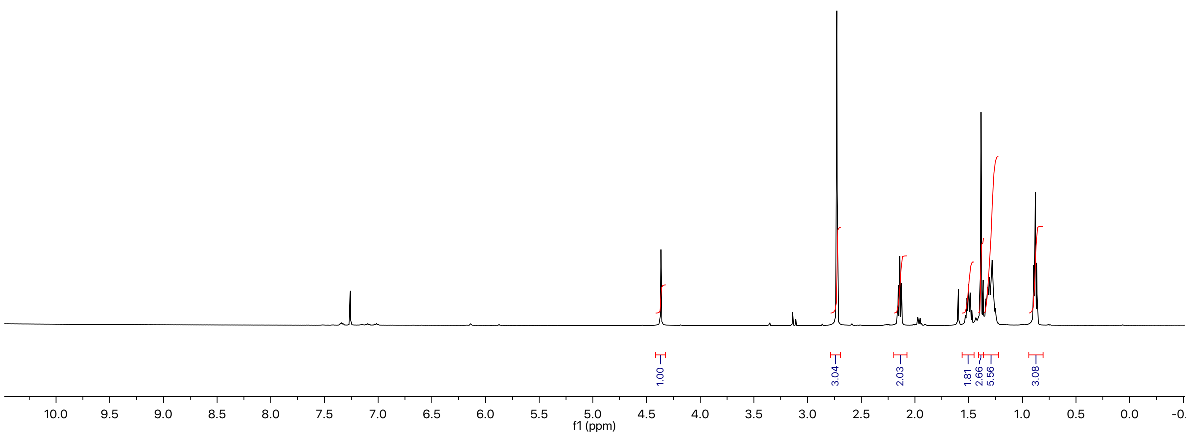


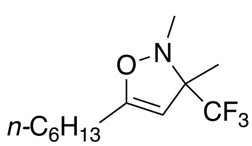
1106



20l

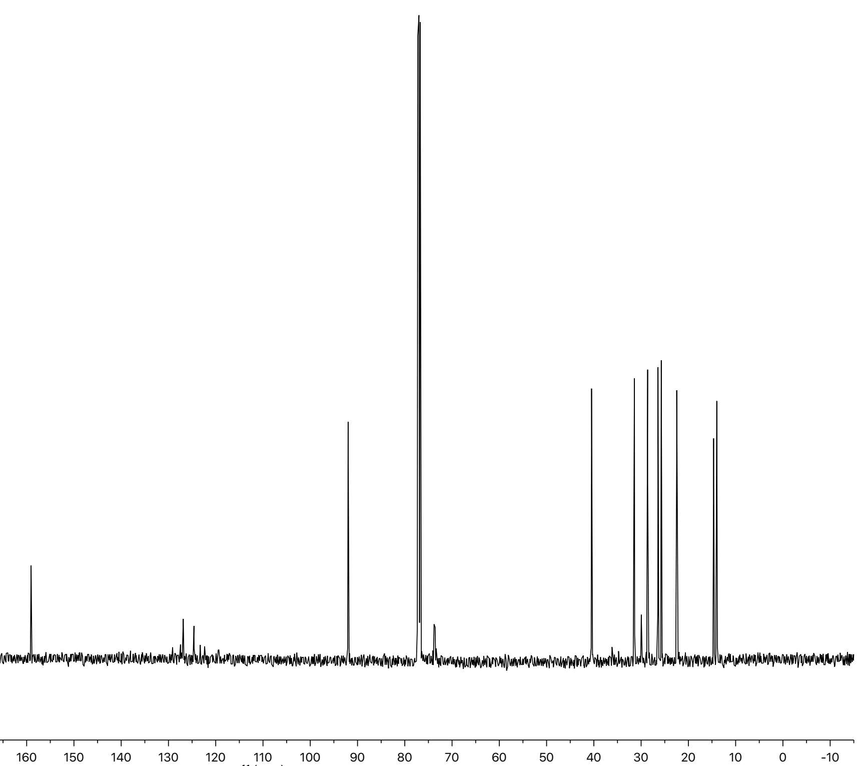
^{1}H NMR ($CDCl_3$)

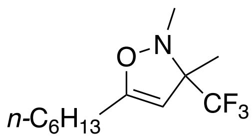




20l

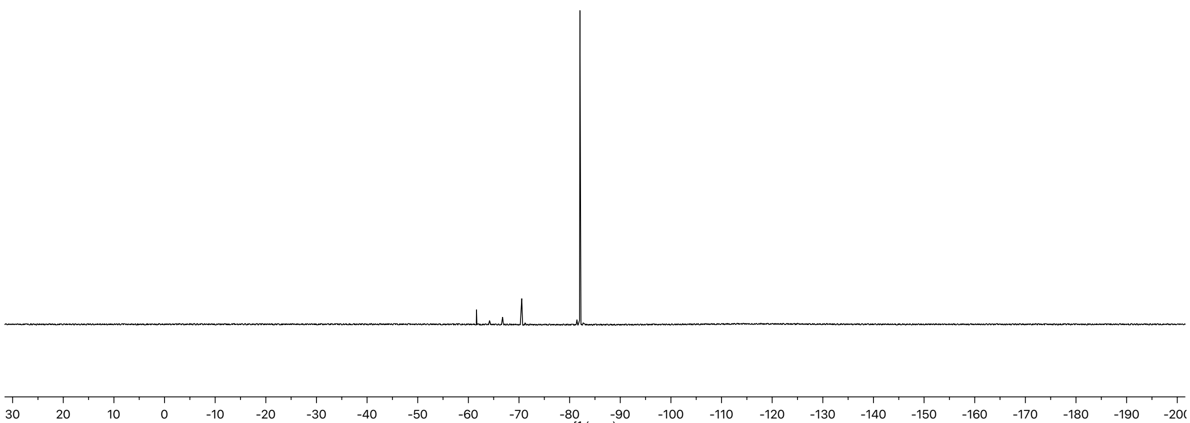
^{13}C NMR ($CDCl_3$)

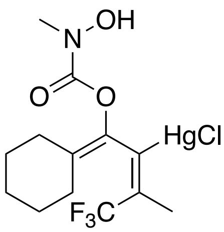




20l

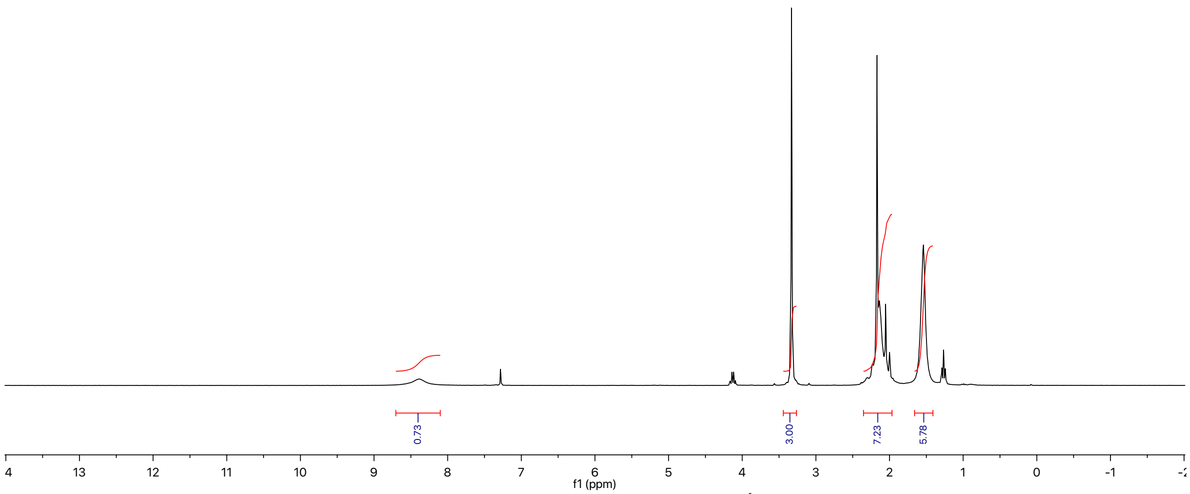
^{19}F NMR ($CDCl_3$)

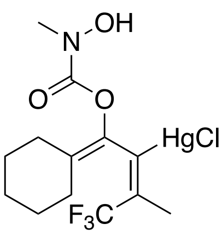




35

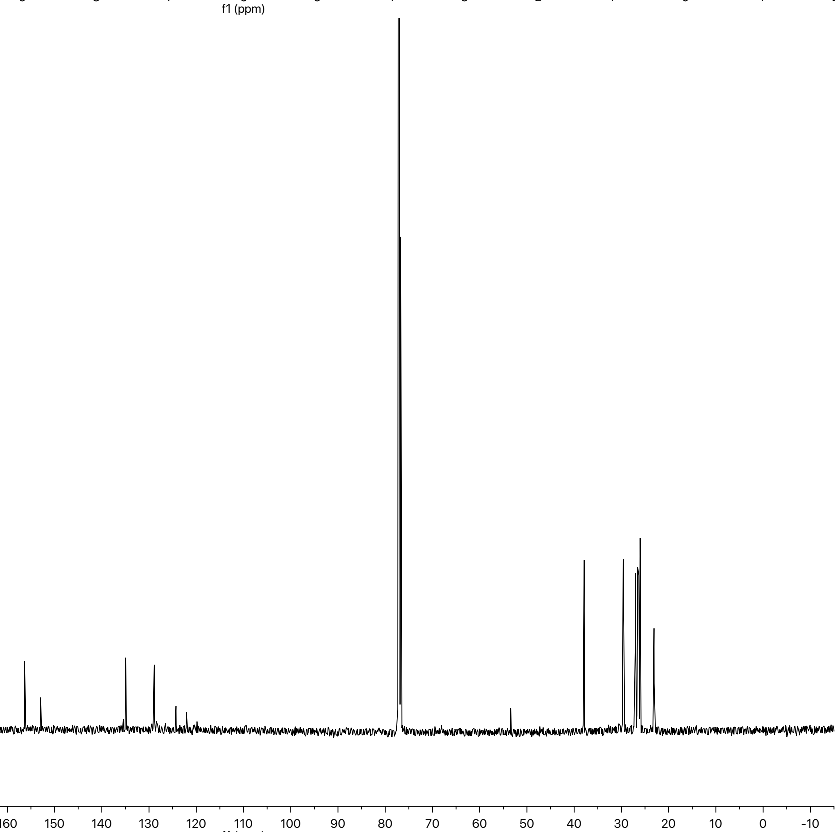
^1H NMR ($CDCl_3$)

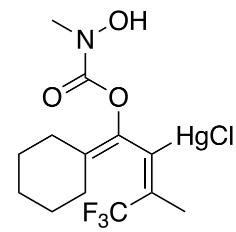




35

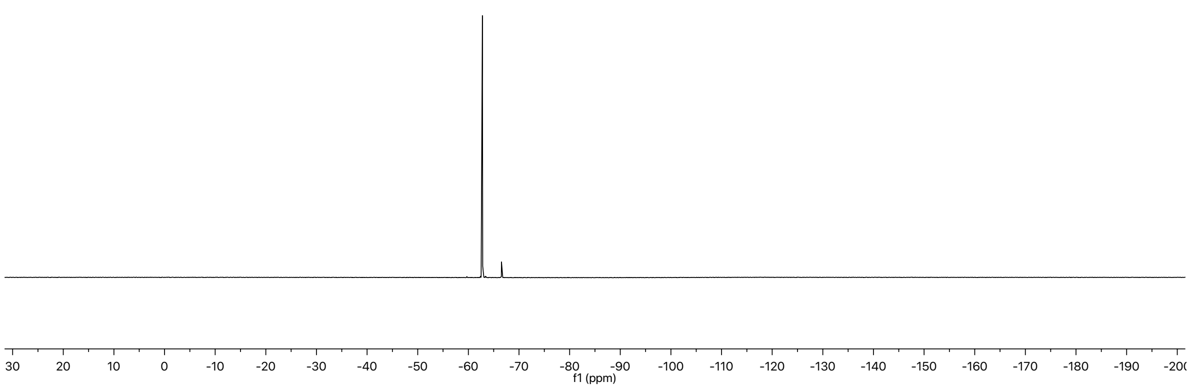
^{13}C NMR ($CDCl_3$)



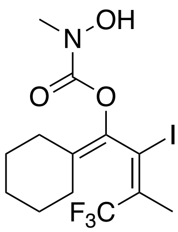


35

^{19}F NMR ($CHCl_3$)

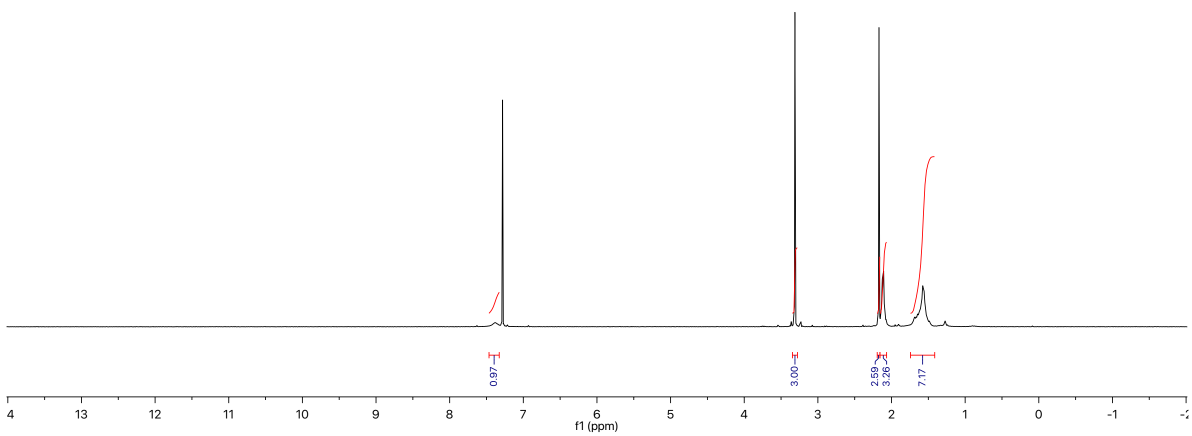


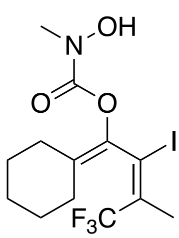
910



36

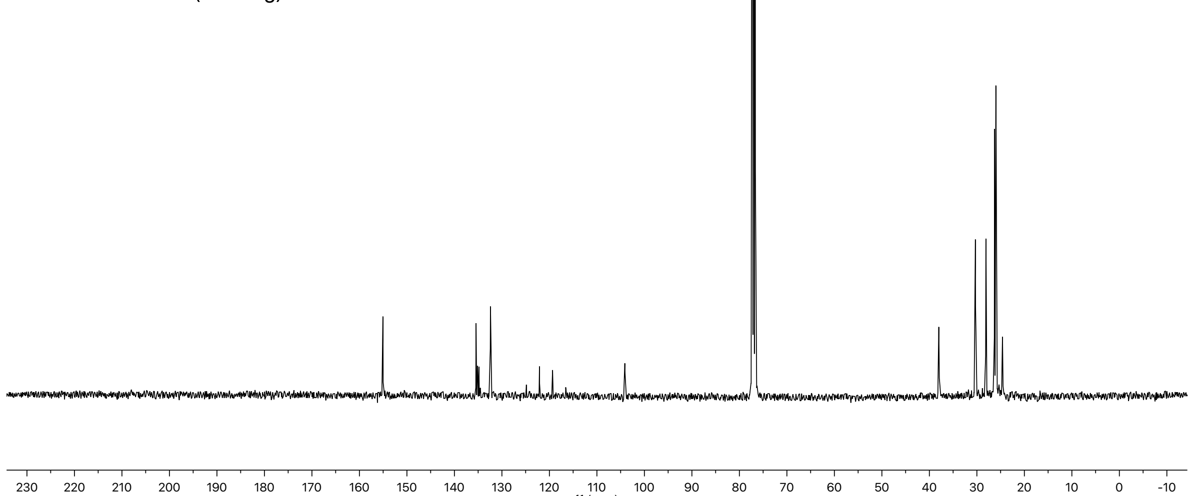
^{1}H NMR ($CDCl_3$)

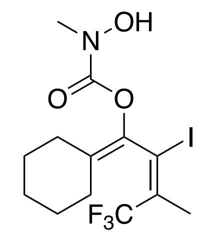




36

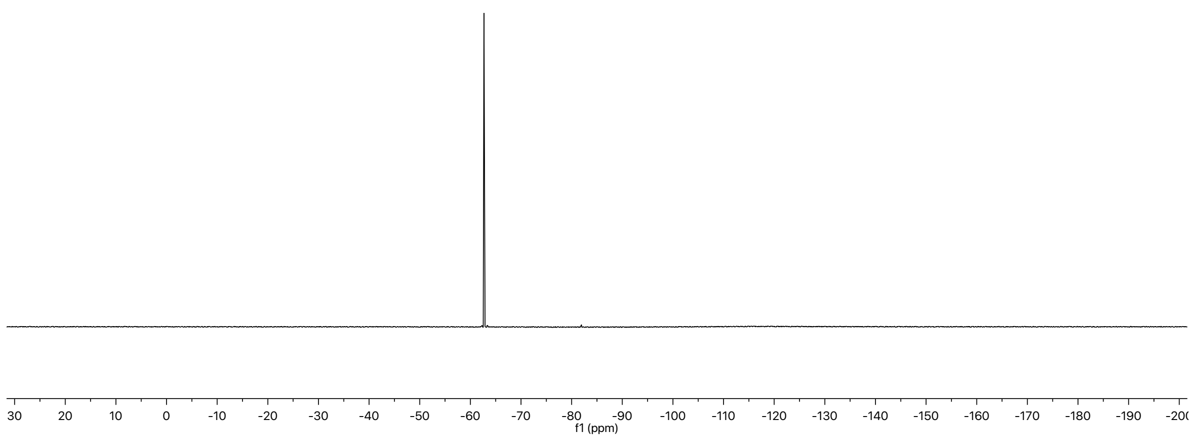
^{13}C NMR ($CDCl_3$)





36

^{19}F NMR ($CDCl_3$)



989

References

[1] H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637-643.

[2] V. Gouverneur, K. Seppelt, *Chem. Rev.* **2015**, *115*, 563-565.

[3] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320-330; b) M. Schlosser, *Angew. Chem. Int. Ed.* **2006**, *45*, 5432-5446.

[4] a) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422-518; b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432-2506.

[5] A. J. Barker, K. H. Gibson, W. Grundy, A. A. Godfrey, J. J. Barlow, M. P. Healy, J. R. Woodburn, S. E. Ashton, B. J. Curry, L. Scarlett, L. Henthorn, L. Richards, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1911-1914.

[6] T. Nakajima, T. Matsugi, W. Goto, M. Kageyama, N. Mori, Y. Matsumura, H. Hara, *Biol. Pharm. Bull.* **2003**, *26*, 1691-1695.

[7] Z.-C. Shi, A. Devasagayaraj, K. Gu, H. Jin, B. Marinelli, L. Samala, S. Scott, T. Stouch, A. Tunoori, Y. Wang, Y. Zang, C. Zhang, S. D. Kimball, A. J. Main, W. Sun, Q. Yang, A. Nouraldeen, X.-Q. Yu, E. Buxton, S. Patel, N. Nguyen, J. Swaffield, D. R. Powell, A. Wilson, Q. Liu, *J. Med. Chem.* **2008**, *51*, 3684-3687.

[8] a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180-3211; b) A. Corma, A. Leyva-Pérez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657-1712; c) S. M. Abu Sohel, R.-S. Liu, *Chem. Soc. Rev.* **2009**, *38*, 2269-2281; d) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351-3378; e) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395-3442; f) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326-3350; g) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266-3325; h) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271-2296; i) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395; j) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449; k) W. A. Nugent, *Angew. Chem. Int. Ed.* **2012**, *51*, 8936-8949.

[9] R. Shen, J. Yang, S. Zhu, C. Chen, L. Wu, *Adv. Synth. Catal.* **2015**, *357*, 1259-1269.

[10] J. Congmon, M. A. Tius, *Eur. J. Org. Chem.* **2018**, *2018*, 2926-2930.

[11] S. Ma, *Chem. Rev.* **2005**, *105*, 2829-2872.

[12] H. A. Wegner, M. Auzias, *Angew. Chem. Int. Ed.* **2011**, *50*, 8236-8247.

[13] D. Wang, X. Ye, X. Shi, *Org. Lett.* **2010**, *12*, 2088-2091.

[14] L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804-16805.

[15] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881-1886; b) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529-2591; c) X. Tang, L. Huang, Y. Xu, J. Yang, W. Wu, H. Jiang, *Angew. Chem. Int. Ed.* **2014**, *53*, 4205-4208; d) H. Egami, M. Sodeoka, *Angew. Chem. Int. Ed.* **2014**, *53*, 8294-8308; e) T. Koike, M. Akita, *Acc. Chem. Res.* **2016**, *49*, 1937-1945; f) H.-Y. Zhang, C. Ge, J. Zhao, Y. Zhang, *Org. Lett.* **2017**, *19*, 5260-5263; g) X. Yang, G. C. Tsui, *Org. Lett.* **2018**, *20*, 1179-1182.

[16] a) A. Hafner, S. Bräse, *Adv. Synth. Catal.* **2011**, *353*, 3044-3048; b) J.-j. Ma, W.-b. Yi, G.-p. Lu, C. Cai, *Adv. Synth. Catal.* **2015**, *357*, 3447-3452; c) N. J. W. Straathof, S. E. Cramer, V. Hessel, T. Noël, *Angew. Chem. Int. Ed.* **2016**, *55*, 15549-15553; d) L.-H. Wu, K. Zhao, Z.-L. Shen, T.-P. Loh, *Org. Chem. Front.* **2017**, *4*, 1872-1875.

[17] a) M. Kelly, J. Kincaid, M. Duncton, K. Sahasrabudhe, S. Janagani, R. Ravindra, G. Wu, Y. Fang, Z. Wei, *WO 2006093832,* **2006**; b) T., S. N. Kuragano, T. Okauchi, Japanese Patent, 19961112, **1996**; c) H. Lu, R. B. Silverman, *J. Med. Chem.* **2006**, *49*, 7404-7412; d) R. Hemelaere, J. Desroches, J.-F. Paquin, *Org. Lett.* **2015**, *17*, 1770-1773; e) K. Monostory, K. Jemnitz, L. Vereczkey, G. Czira, *Drug. Metab. Dispos.* **1997**, *25*, 1370-1378.

[18] a) A. Hafner, T. S. Fischer, S. Bräse, *Eur. J. Org. Chem.* **2013**, *2013*, 7996-8003; b) L. Debien, B. Quiclet-Sire, S. S. Zard, *Org. Lett.* **2012**, *14*, 5118-5121; c) P. G. Janson, I. Ghoneim, N. O. Ilchenko, K. J. Szabó, *Org. Lett.* **2012**, *14*, 2882-2885; d) G. K. S. Prakash, H. S. Krishnan, P. V. Jog, A. P. Iyer, G. A. Olah, *Org. Lett.* **2012**, *14*, 1146-1149; e) H. Lin, X. Dong, Y. Li, Q. Shen, L. Lu, *Eur. J. Org. Chem.* **2012**, *2012*, 4675-4679.

[19] X. Yang, G. C. Tsui, *Org. Lett.* **2019**, *21*, 1521-1525.

[20] C. Feng, T.-P. Loh, *Angew. Chem. Int. Ed.* **2013**, *52*, 12414-12417.

[21] T. Besset, D. Cahard, X. Pannecoucke, *J. Org. Chem.* **2014**, *79*, 413-418.

[22] C. J. M. Frédéric, J. Cornil, M. Vandamme, L. Dumitrescu, A. Tikad, R. Robiette, S. P. Vincent, *Org. Lett.* **2018**, *20*, 6769-6773.

[23] a) K. B. G. Torssell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, **1998**; b) K. V. Gothelf, K. A. Jørgensen, *Chem. Commun.* **2000**, 1449-1458; c) M. S. Wilson, A. Padwa, *J. Org. Chem.* **2008**, *73*, 9601-9609; d) S. Akai, K. Tanimoto, Y. Kanao, S. Omura, Y. Kita, *Chem. Commun.* **2005**, 2369-2371; e) J. K. Gallos, C. I. Stathakis, S. S. Kotoulas, A. E. Koumbis, *J. Org. Chem.* **2005**, *70*, 6884-6890; f) O. Tamura, N. Iyama, H. Ishibashi, *J. Org. Chem.* **2004**, *69*, 1475-1480.

[24] T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.* **2010**, *2010*, 3363-3376.

[25] K. Tanaka, Y. Sugimoto, Y. Okafuji, M. Tachikawa, K. Mitsuhashi, *J. Heterocycl. Chem.* **1989**, *26*, 381-385.

[26] G. A. Molander, L. N. Cavalcanti, *Org. Lett.* **2013**, *15*, 3166-3169.

[27] X. Lv, Z. Kang, D. Xing, W. Hu, *Org. Lett.* **2018**, *20*, 4843-4847.

[28] a) H. Lebel, L. Mamani Laparra, M. Khalifa, C. Trudel, C. Audubert, M. Szponarski, C. Dicaire Leduc, E. Azek, M. Ernzerhof, *Organic & Biomolecular Chemistry* **2017**, *15*, 4144-4158; b) J. Davies, T. D. Svejstrup, D. Fernandez Reina, N. S. Sheikh, D. Leonori, *J. Am. Chem. Soc.* **2016**, *138*, 8092-8095.

[29] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769-3772.

[30] A. Boreux, G. H. Lonca, O. Riant, F. Gagosz, *Org. Lett.* **2016**, *18*, 5162-5165.

[31] D. Riether, C. Harcken, H. Razavi, D. Kuzmich, T. Gilmore, J. Bentzien, E. J. Pack, D. Souza, R. M. Nelson, A. Kukulka, T. N. Fadra, L. Zuvela-Jelaska, J. Pelletier, R. Dinallo, M. Panzenbeck, C. Torcellini, G. H. Nabozny, D. S. Thomson, *J. Med. Chem.* **2010**, *53*, 6681-6698.

[32] a) M. Tredwell, J. A. R. Luft, M. Schuler, K. Tenza, K. N. Houk, V. Gouverneur, *Angew. Chem. Int. Ed.* **2008**, *47*, 357-360; b) C. Sparr, W. B. Schweizer, H. M. Senn, R. Gilmour, *Angew. Chem. Int. Ed.* **2009**, *48*, 3065-3068; c) L. E. Zimmer, C. Sparr, R. Gilmour, *Angew. Chem. Int. Ed.* **2011**, *50*, 11860-11871; d) K. Lee, D. L. Silverio, S. Torker, D. W. Robbins, F. Haeffner, F. W. van der Mei, A. H. Hoveyda, *Nat. Chem.* **2016**, *8*, 768-777; e) F. W. van

der Mei, C. Qin, R. J. Morrison, A. H. Hoveyda, *J. Am. Chem. Soc.* **2017**, *139*, 9053-9065; f) D. C. Fager, K. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2019**, *141*, 16125-16138.

[33] K. M. Miller, T. Luanphaisarnnont, C. Molinaro, T. F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 4130-4131.

[34] A. V. G. Prasanthi, S. Begum, H. K. Srivastava, S. K. Tiwari, R. Singh, *ACS Catal.* **2018**, *8*, 8369-8375.