Double Duty Synthons in Epoxide Synthesis

and

Palladium-Catalyzed Carbonylative Heterocyclizations

BY

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THESIS

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LIST OF ABBREVIATIONS

Ac	acetyl
Alk	alkyl
aq	aqueous
Ar	aryl
atm	atmosphere, atmospheric
Bn	benzyl
Bz	benzoyl
n-Bu	butyl
t-Bu	tert-butyl
Calcd	calculated
cat.	catalytic amount
CO	carbon monoxide
Cy	cyclohexyl
δ	chemical shifts in parts per million downfield from tetramethylsilane (NMR)
2D	two-dimensional (NMR)
d	doublet
dba	dibenzylidene acetone
DCM	dichloromethane
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEPT	distortionless enhancement by polarization transfer

LIST OF ABBREVIATIONS (continued)

DFT	density functional theory
DMA	dimethylacetamide
DMB	2,4-dimethoxybenzyl
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppm	1,1'-bis(diphenylphosphino)methane
EB	3-ethylbutyryl
EDG	electron-donating group
EE	ethoxyethyl
EI	electron impact ionization (in mass spectrometry)
Equiv.	equivalent
Et	ethyl
eq, equiv.	molar equivalent
EWG	electron-withdrawing group
G	group, Gibbs free energy
g	gram
GC	gas chromatography
h, hrs	hour(s)
n-Hex	hexyl
HR	high resolution (mass spectrometry)
Hz	Hertz

LIST OF ABBREVIATIONS (continued)

J	spin-spin coupling constant (NMR)
L	ligand
LDA	lithium diisopropyl amide
m	multiplet (NMR)
mp	melting point
μ	micro
[M]	metal
M	molar
MS	mass spectrometry
M.S.	molecular sieves
Me	methyl
Mes	mesityl
mg	milligram
min	minute
mL, ml	milliliter
mm	millimeter
mmol	millimole
mol	mole
MOM	methoxymethyl
MHz	megahertz
Ms	methanesulfonyl

LIST OF ABBREVIATIONS (continued)

m/z	mass to charge ratio
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ns	*p*-nitrobenzenesulfonyl
c-Pent	cyclopentyl
pfb	perflurobutyrate, heptafluorobutyrate
PG	protecting group
Ph	phenyl
Phth	phthalyl
Piv	pivaloyl, trimethylacetyl
PMB	*p*-methoxybenzyl
ppm	parts per million
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl
Py	pyridine
q	quartet (NMR)
quint	quintet (NMR)
rt	room temperature
s	singlet (NMR)

LIST OF ABBREVIATIONS (continued)

sept	septet (NMR)
t	triplet (NMR)
TBDMS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol, tol	tolyl
Ts	*p*-toluenesulfonyl
TBHP	*tert*-Butyl hydroperoxide
TTBP	2,4,6-tris-*tert*-butylpyrimidine

Summary

This thesis describes the development of double duty of cyanogen bromide and bromoperfluoroarenes in highly efficient synthesis of densely substituted epoxides from enolizable ketones, as well as the development of palladium-catalyzed carbonylative arylation/cyclization approach toward 2-aroyl indolizines.

The first part of the thesis focuses on the concept of double duty synthons and their applications in epoxide synthesis. The diverse reactivity of bromoalkynes, particularly the its first-time found double duty, is summarized at the beginning of the Chapter 1. The divergent reactivity of cyanogen bromide and bromopentafluorobenzene is summarized at the end of Chapter 1. Chapter 2 and Chapter 3 discuss the double duty of cyanogen bromide and bromoperfluoroarenes separately, in efficient synthesis of epoxides. The corresponding experimental data are detailed in Chapter 4.

The second part of this thesis describes development of methods for the palladium-catalyzed carbonylative arylation/cyclization cascade approach toward sparsely reported 2-aroyl indolizines. In Chapter 5, an overview of palladium-catalyzed carbonylative heterocyclization processes toward efficient assembly of carbonyl-containing heterocycles is discussed. Next, Chapter 6 describes the concept and successful development of the palladium-catalyzed carbonylative cyclization of readily available propargyl pyridines into 2-aroyl indolizines. The experimental details of transformations discussed in Chapter 6 are provided in Chapter 7.

PART ONE

Double Duty of Cyanogen Bromide and Bromopentafluorobenzene in Epoxide Synthesis

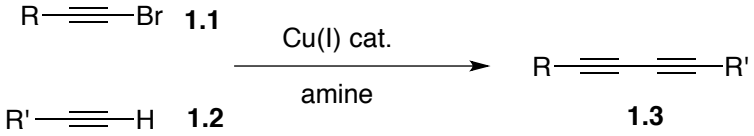
1. Introduction

1.1. Divergent Reactivity of Bromoalkynes

Bromoalkynes are valuable building blocks for introducing alkyne functionality.[1] By tuning substituents and reagents, the C(*sp*)–Br bond of bromoalkynes can selectively be cleaved in different modes, which are summarized below.

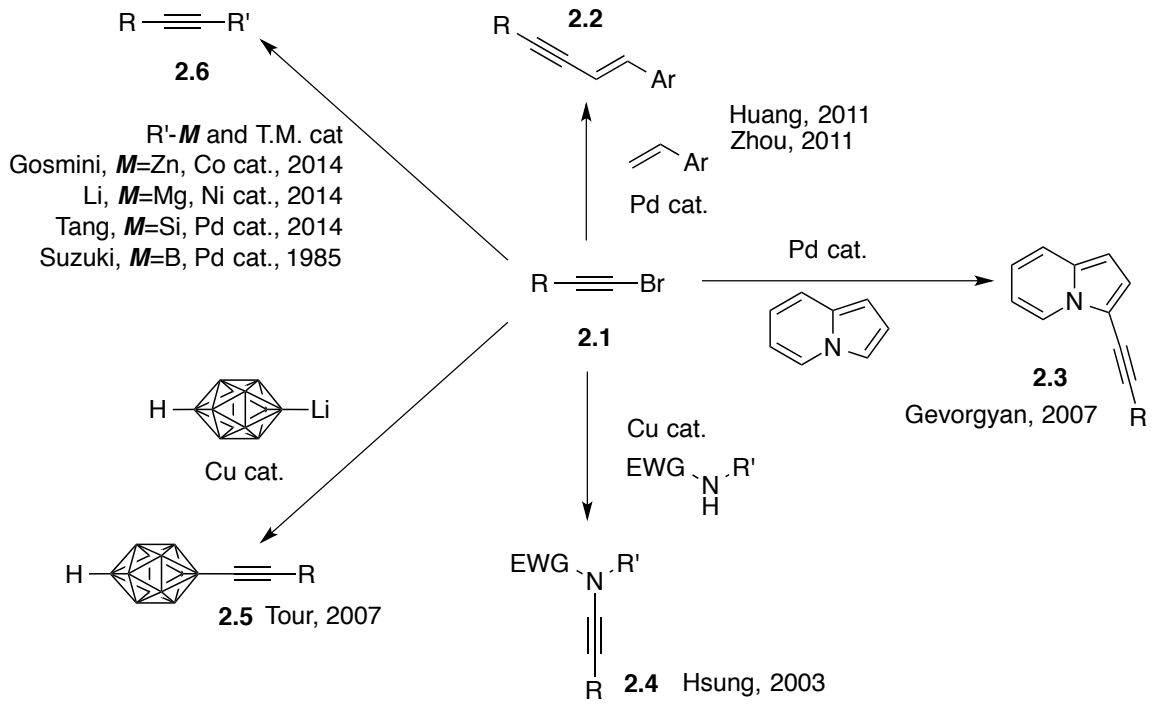
1.1.1. Bromoalkyne as a Source of Electrophilic Alkynes

Cadiot and Chodkiewicz first utilized bromoalkynes as a source of electrophilic alkynes in the copper-catalyzed cross–coupling reactions with terminal alkynes **1.2** to produce unsymmetrical conjugated diynes **1.3** (Scheme 1).[2]



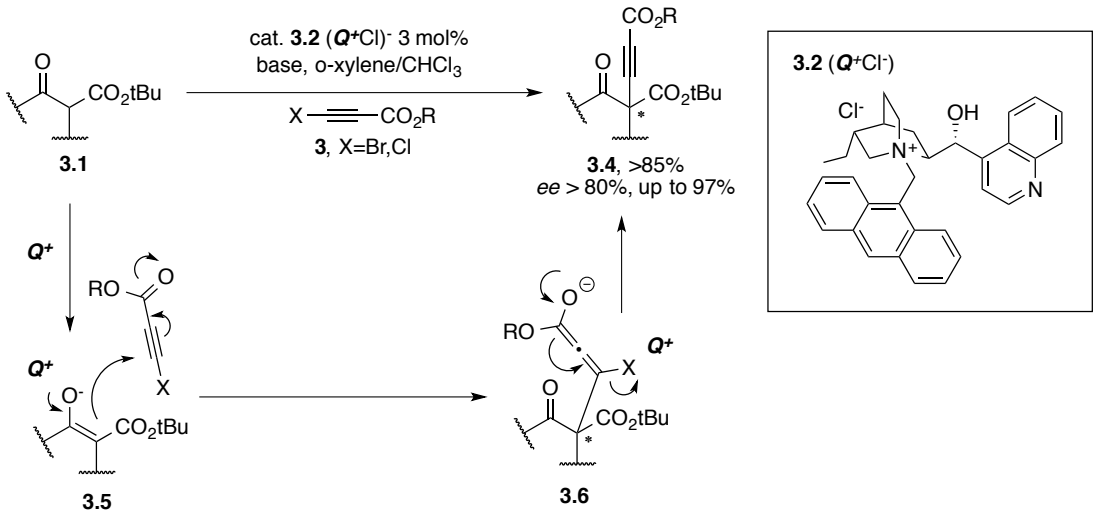
Scheme 1.

Bromoalkynes were also reported to participate in a series of transition metal-catalyzed cross–coupling reactions of alkenes,[3] heteroarenes,[4] amides,[5] lithiated carboranes,[6] organozinc,[7] Gringard reagents,[8] silanes,[9] and organoborones[10] to produce the corresponding conjugate enynes **2.2**, hetero-arylalkynes **2.3**, ynamide **2.4**, alkynyl carborane **2.5** and other cross–coupling products **2.6** (Scheme 2).



Scheme 2.

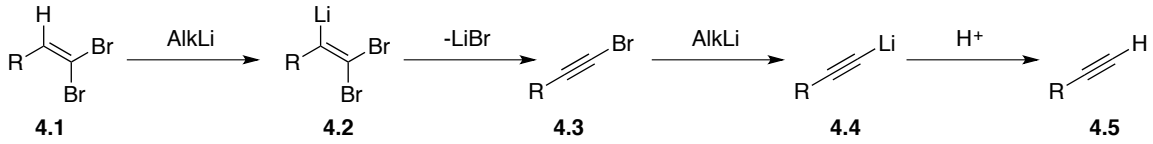
It was also shown that, some electron-deficient bromoalkynes, like β-bromopropiolates, may directly react with a stronger nucleophile to provide β-substituted propiolates via an addition-elimination pathway.[11] Moreover, Jørgensen reported an organocatalytic enantioselective α-alkynylation of β-ketoesters **3.1** using β-halopropiolates **3.3** (Scheme 3). This reaction proceeds via a conjugate addition of ammonium enolate **3.5** to β-halopropiolate **3.3** that provided haloallenonolate **3.6**, which upon an elimination of halide leads to the alkynylation product **3.4**.[12]



Scheme 3.

1.1.2. Bromoalkyne as a Source of Metal Acetylide

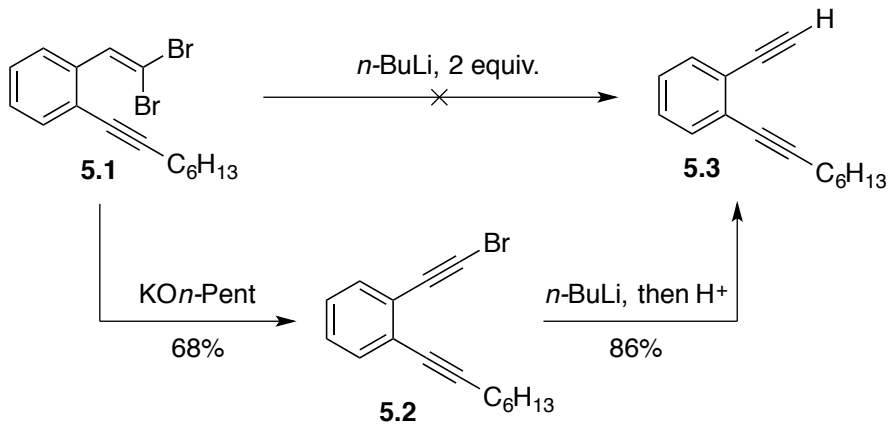
Although simple terminal alkynes are the most frequently used precursors of acetylides, bromoalkynes were also reported to be precursors of metal acetylides. Thus, in the Corey-Fuchs synthesis of alkyne, the *in situ* formed bromoalkyne **4.3** is converted to a lithium acetylide **4.4** in the presence of alkyl lithium reagents via a metal-halogen exchange reaction (Scheme 4).[13]



Scheme 4.

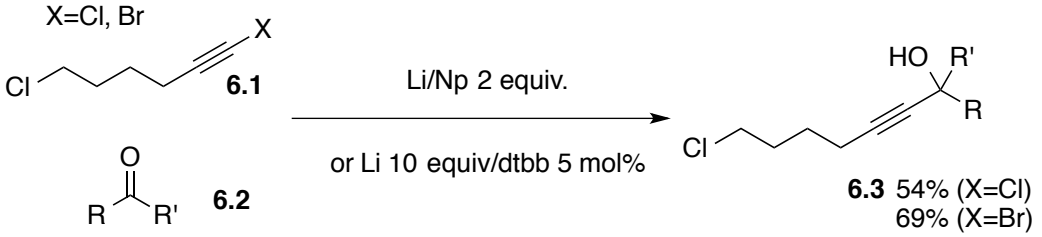
Buckle reported synthesis of diyne **5.3** by debromination of bromoalkyne **5.2** using butyllithium (Scheme 5).[14] Bromoalkyne **5.2** was separately prepared from *o*-alkynyl styrene dibromide **5.1**, which was a substrate for Corey-Fuchs alkyne synthesis. This interrupted Corey-Fuchs synthesis of alkyne was developed due to an unsuccessful one-pot conversion of dibromide **5.1** to **5.3** using general conditions of the Corey-Fuchs

alkyne synthesis. Suzuki, [15] Muramatsu, [16] Yang, [17] and Tan [18] also demonstrated conversions of simple bromoalkynes into acetylides using alkyllithium or Grignard reagents.



Scheme 5.

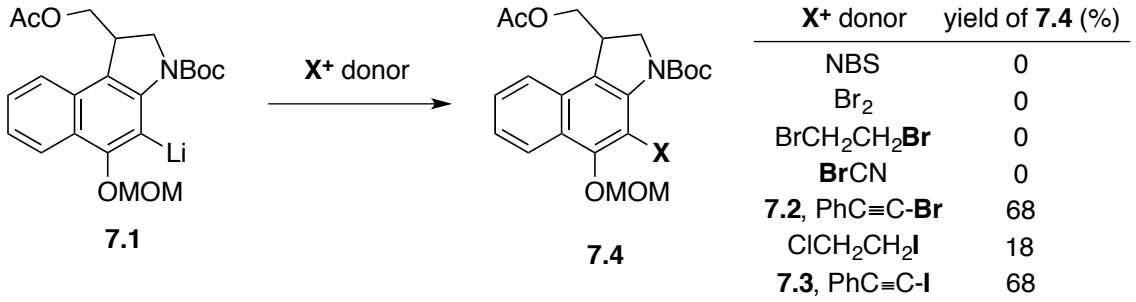
Yus reported a selective metallation of C(*sp*)–X bond of 1,6-dihalohex-1ynes **6.1** using lithium naphthalenide (LiNp) in efficient synthesis of chlorohydrines **6.3**. It is worth mentioning that alkyl chloride **6.1** and carbonyl functionalities of **6.2**, which are susceptible to common metallation reagents like alkyllithium and Grignard reagents, were both introduced into the reaction medium at the same time, and were well tolerated under these conditions (Scheme 6).[19]



Scheme 6.

1.1.3. Bromoalkyne as a Source of Electrophilic Bromine

The metal-halogen exchange reaction of bromoalkyne also takes place in the presence of an aryl lithium reagent, leading to the formation of bromoarene and lithium acetylide. Thus, bromoalkynes can serve as electrophilic brominating reagents. Boger reported synthesis of halogen-substituted indolene **7.4** by bromination of sterically hindered aryl lithium **7.1**. Bromoalkyne **7.2** was found to be the only effective brominating reagent after unsuccessful attempts on employing other common bromination reagents, such as NBS, Br_2, 1,2-dibromoethane, and cyanogen bromide. Similarly, iodoalkyne **7.3** was also proven to be an efficient iodinating reagent (Scheme 7).[20]



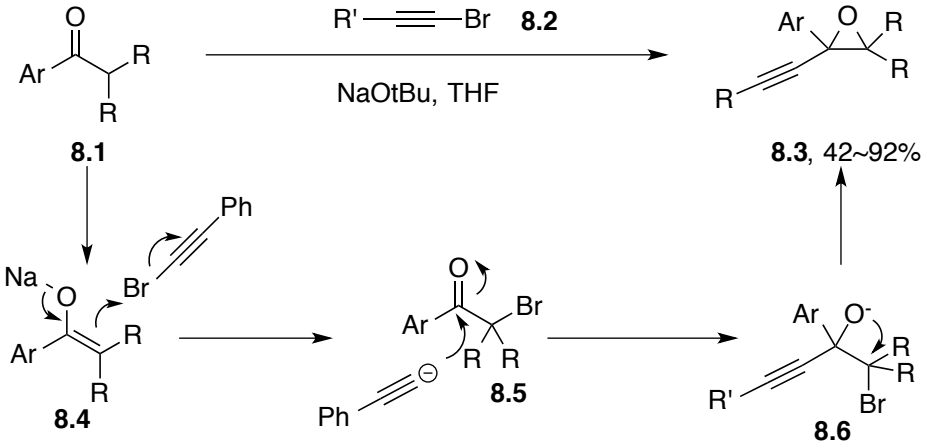
X+ donor	yield of **7.4** (%)
NBS	0
Br_2	0
$BrCH_2CH_2$**Br**	0
BrCN	0
7.2, PhC≡C-**Br**	68
$ClCH_2CH_2$**I**	18
7.3, PhC≡C-**I**	68

Scheme 7.

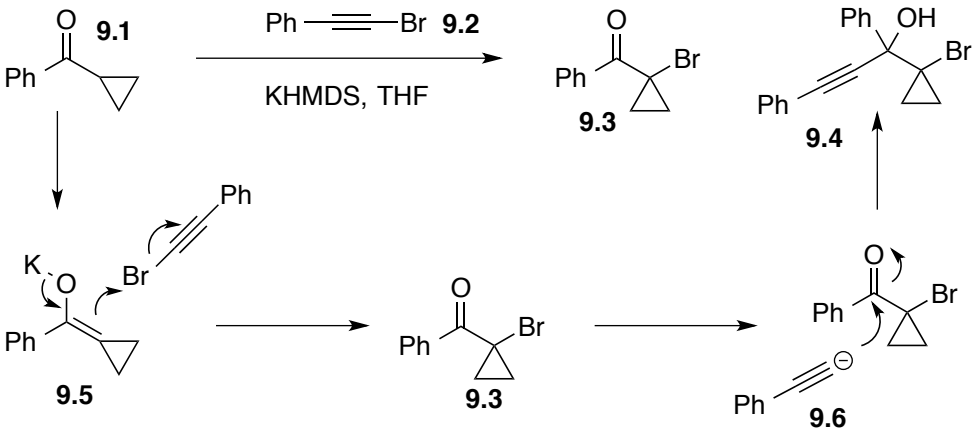
1.1.4. Double Duty of Bromoalkyne

In all aforementioned reaction modes of bromoalkynes, there is one part of bromoalkyne, either alkyne or bromine, which is not utilized through the overall transformation. Therefore, a high atom-economical transformation of bromoalkyne, which incorporates both alkyne and bromine in one reaction, would be highly desired. In 2008, Gevorgyan group reported a new reaction mode that enabled a full utilization of bromoalkyne **8.2** in a cascade transformation of sodium enolates **8.4** into alkynyl

epoxides **8.3**.[21] Various bromoalkynes bearing aryl–, alkyl–, and silyl–substitution were equally reactive under these reaction conditions. This reaction was proposed to proceed via an α-bromination of enolate **8.4** by bromoalkyne **8.2** to produce free acetylide and α-bromoketone **8.5**. The following nucleophilic addition of acetylide at bromoketone **8.5** produced alkoxide **8.6**, which underwent an intramolecular displacement of bromine to yield epoxide **8.3** (Scheme 8). This reaction pathway was supported by the observation of a mixture of α-bromoketone **9.3** and α-bromomethylpropargyl alcohol **9.4** from the reaction of potassium enolate **9.5** and bromoethynylbenzene **9.2** (Scheme 9). In this transformation, bromoalkyne served a combination of Br^+ and acetylide, which were both involved in this transformation (**8.6**; **9**.**4**). Therefore, this mode was named double duty.

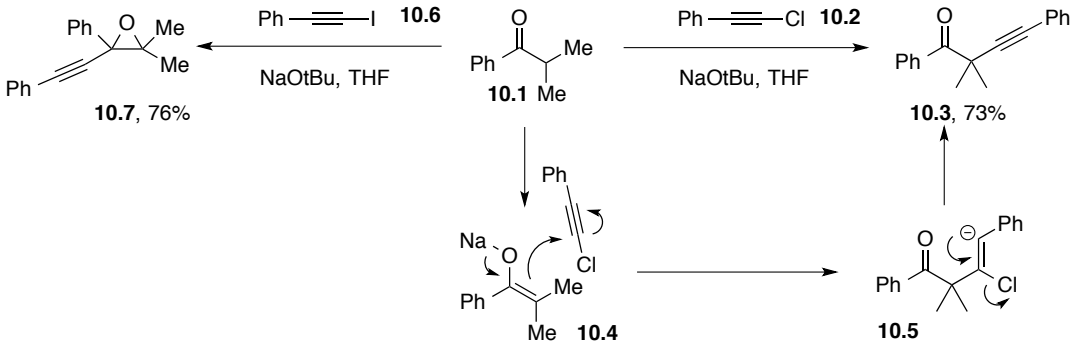


Scheme 8.



Scheme 9.

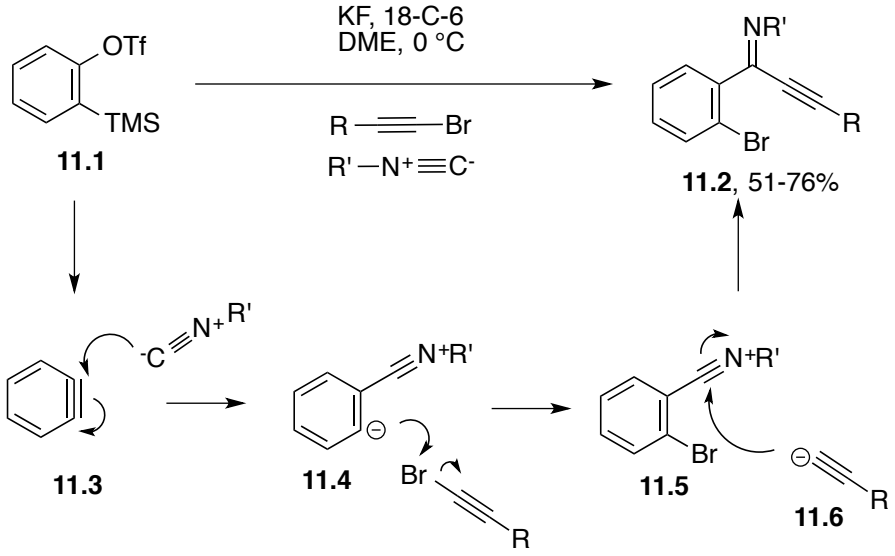
Other haloalkynes were also tested under the same reaction conditions. Iodoalkyne **10.6** showed double duty at comparable efficiency, while chloroalkyne **10.2** produced α-alkynyl ketone **10.3**, thus acting as an electrophilic alkyne donor (Scheme 10).



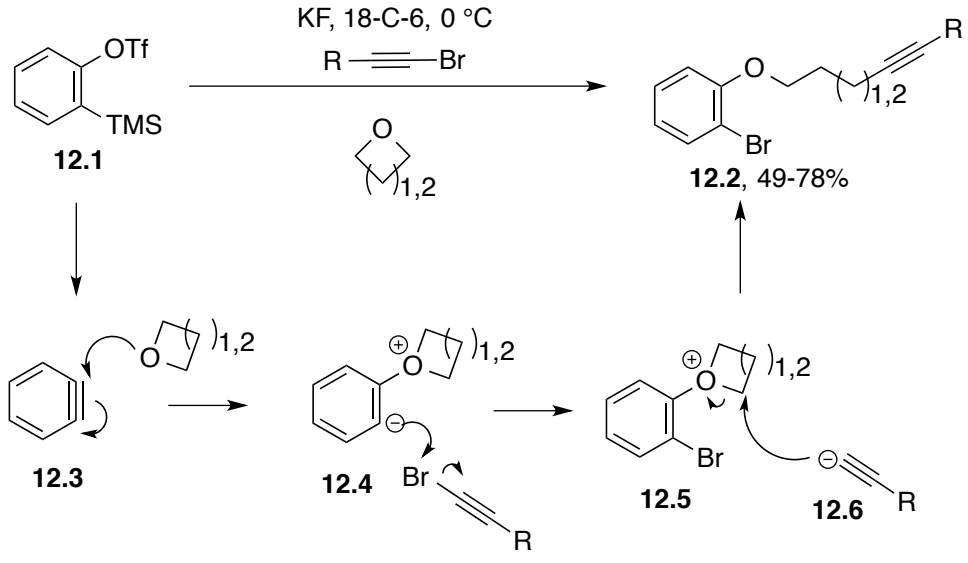
Scheme 10.

After Gevorgyan's first report on the double duty concept of bromoalkynes, several other modes of double duty transformations of bromoalkynes were discovered. Thus, Yoshida and co-workers disclosed synthesis of *ortho*-iminopropynyl bromobenzenes **11.2** via a three-component reaction of benzyne, isocyanide, and bromoalkyne (Scheme 11). This reaction proceeds via an abstraction of bromine from

bromoalkyne by a 1,4-dipolar adduct **11.4** of benzyne **11.3** and isocyanide to produce nitrillium species **11.5** and free acetylide **11.6**. The addition of **11.6** to **11.5** yielded product **11.2.** A similar cascade transformation employing 1,3-dipolar adduct **11.4** of benzyne and cyclic ether to produce alkynyl-substituted ether **12.2** was also demonstrated (Scheme 12). [22]

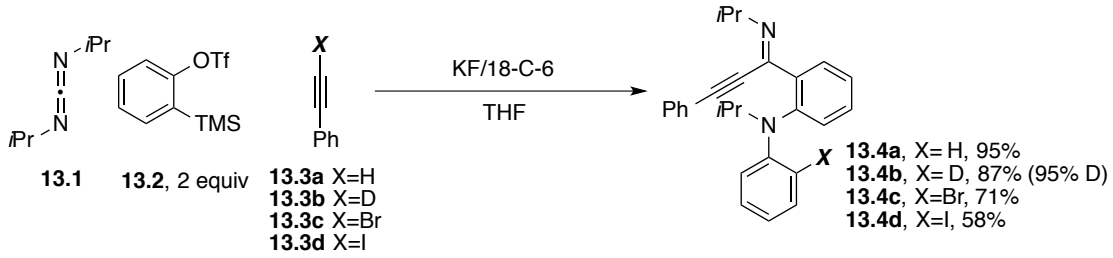


Scheme 11.

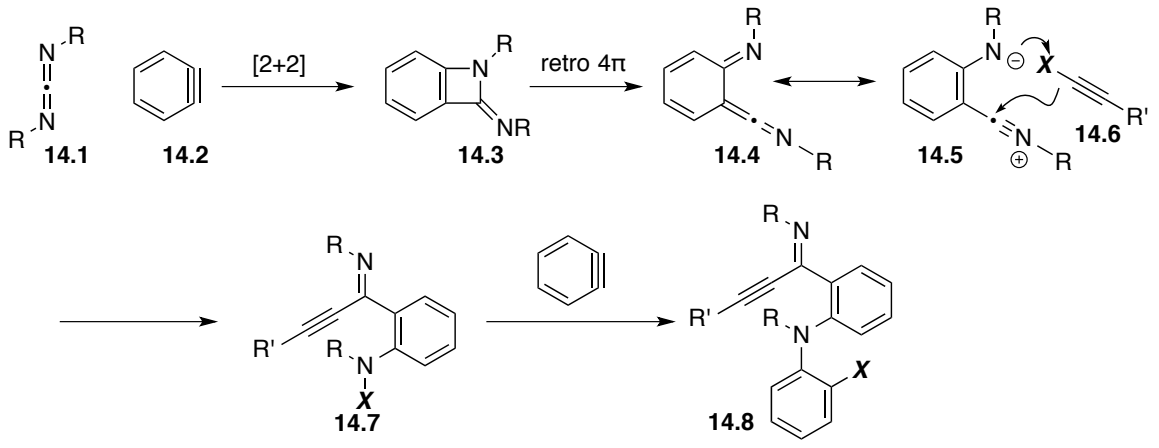


Scheme 12.

Xi and co-workers reported another mode of double duty of haloalkyne in a multi-component synthesis of 2-iminopropynyl aniline **13.4** using carbodiimide **13.1**, benzyne **13.2**, and alkyne **13.3** (Scheme 13).[23] Interestingly, terminal alkynes **13.3a**, **13.3b**, as well as haloalkynes **13.3c**, **13.3d** provided similar products **13.4a-4d**. Particularly, a high retention of deuterium was observed in product **13.4b**. Based on these observations, the following mechanism of this cascade transformation was proposed (Scheme 14). A formal [2+2] cycloaddition of carbodiimide **14.1** and the first equivalent benzyne **14.2** leads to the formation of benzoazitidinimine **14.3**, which is converted into ketenimine **14.4** after a retro-4π electrocyclization. A [4+2] cycloaddition-like step converts **14.4** and alkyne **14.6** into 2-iminopropynyl aniline **14.7**. Finally, the amination of benzyne by **14.6** leads to the product **14.8**.

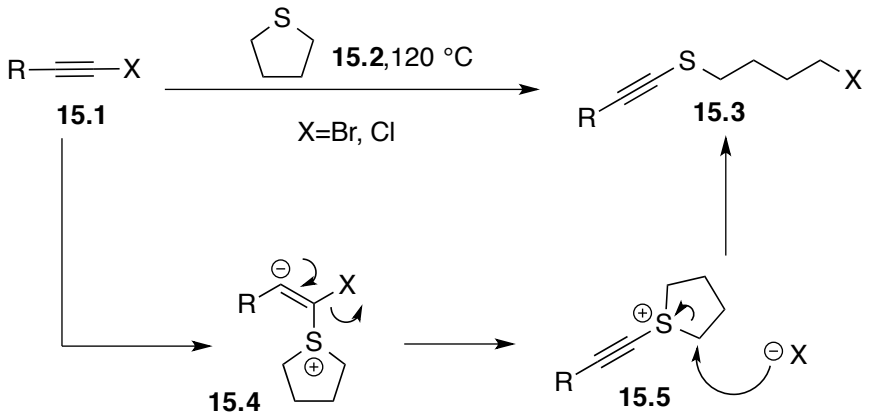


Scheme 13.

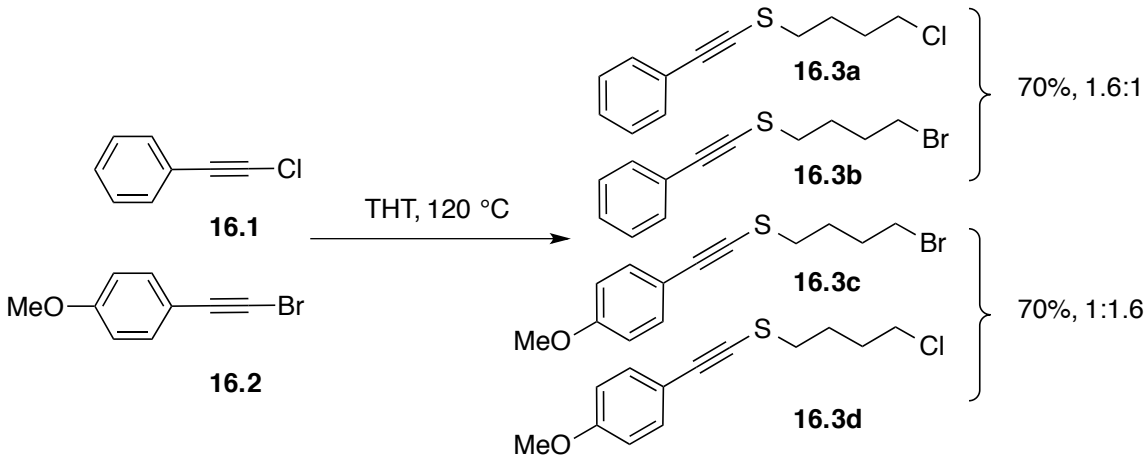


Scheme 14.

Liang and co-workers reported a reversed double duty transformation of haloalkynes **15.1** in reaction with tetrahydrothiophene (THT) **15.2** to provide alkynyl 4-bromobutylsulfide **15.3**. [24] Bromoalkynes and chloroalkynes furnished the same transformation at a comparable efficiency. The authors proposed the formation of intermediate alkynyl sulfonium **15.5** by elimination of halide from the 1,3-dipolar adduct **15.4** of haloalkyne and THT. Diffused free halides then induced the followed ring opening of sulfonium **15.5** to give product **15.3** (Scheme 15). This proposed mechanism was supported by the observation of the crossover products **16.3b** and **16.3d** in a competition experiment between chloroalkynes **16.1** and bromoalkyne **16.2** (Scheme 16). Thus, in this transformation, bromoalkyne serves as a combination of alkyne^{+} and Br^{-}, a reversed double duty previously reported by Gevorgyan,[21] Yoshida,[22] and Xi.[23]



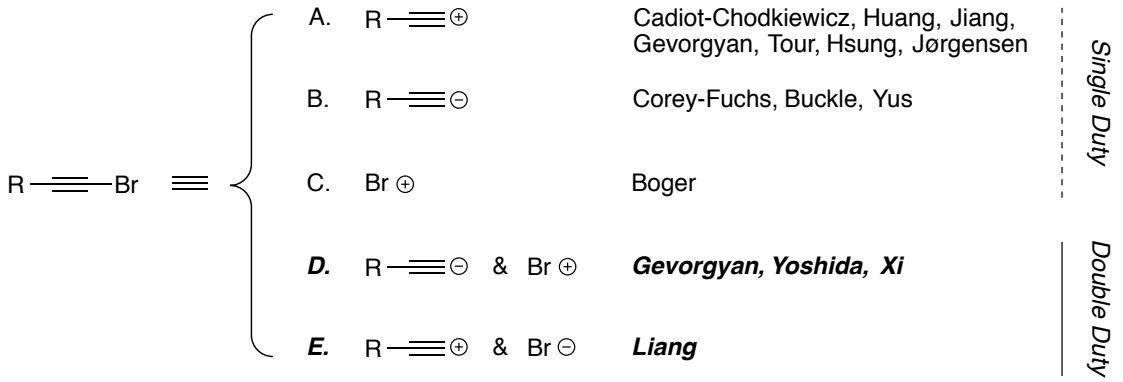
Scheme 15.



Scheme 16.

1.1.5. Summary

In summary, rich reactivity of bromoalkynes has been demonstrated. In transition metal-catalyzed cross–coupling reactions, bromoalkyne serves as a source of electrophilic alkyne (Scheme 17, A). It was also proven to be an alternative precursor of either acetylides (Scheme 17, B) or electrophilic bromine (Scheme 17, C) in reactions with organometallic reagents. Furthermore, it exhibits unprecedented double duty (Scheme 17, ***D***) and reverse double duty (Scheme 17, ***E***) reactivities in a series of atom-economical transformations.



Scheme 17.

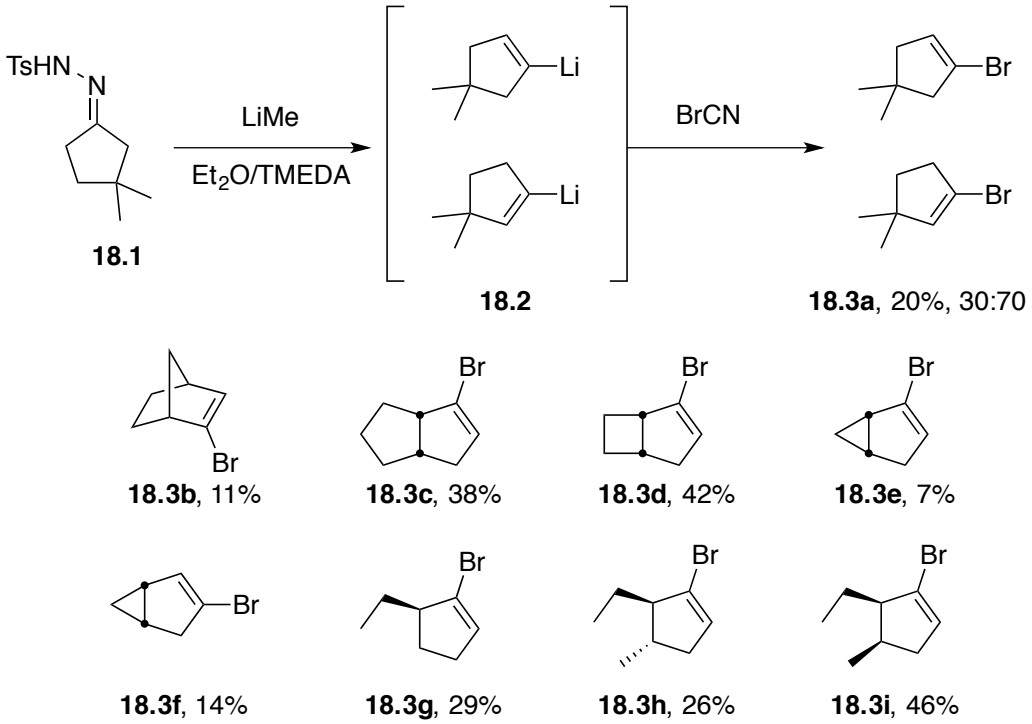
Recently developed different modes of double duty transformations of bromoalkynes have significantly diversified the scope of reaction partners in reactions with haloalkynes. In contrast, the scope of double duty synthons yet remained limited to bromoalkyne. Thus, the development of new double duty synthons is highly justified.

1.2. Divergent Reactivity of Cyanogen Bromide

Since bromoalkynes and cyanogen bromide bear the same *sp* C-Br fragment, they are isoelectronic structures. Hence, it is not unanticipated that they may share some common reactivity.

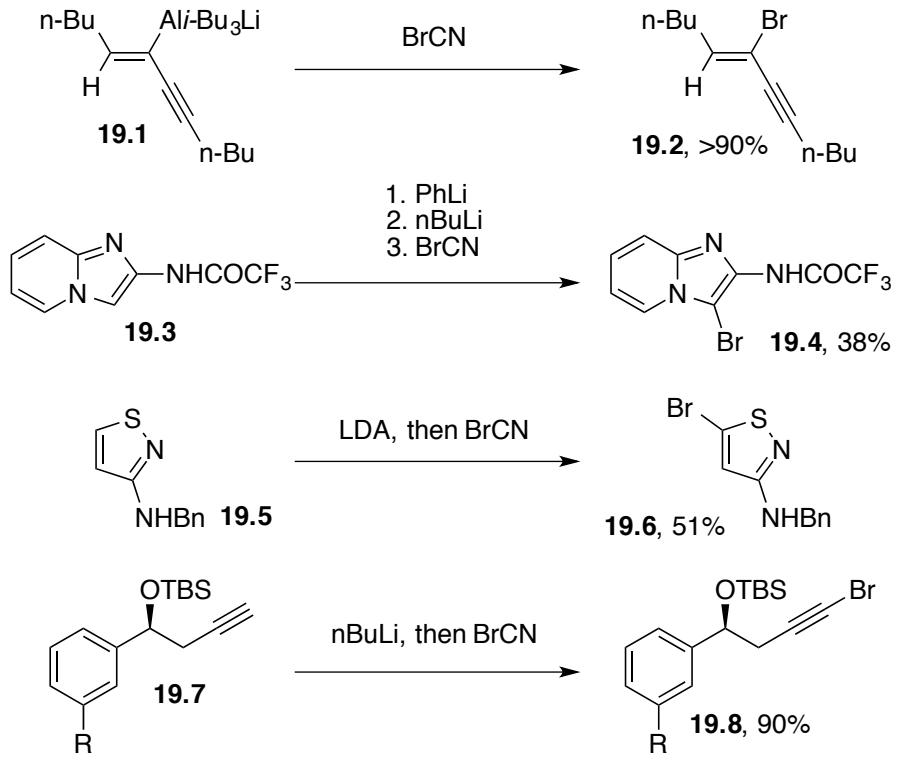
1.2.1. Cyanogen Bromide as a Source of Electrophilic Bromine

Cyanogen bromide was reported to serve a Br^+ donor in reactions with nucleophilic organometallic reagents in the same fashion with bromoalkynes. Paquette first employed cyanogen bromide to convert a series of vinyl lithium intermediates **18.2** into the corresponding vinyl bromides **18.3** in low to moderate yields (Scheme 18).[25]



Scheme 18.

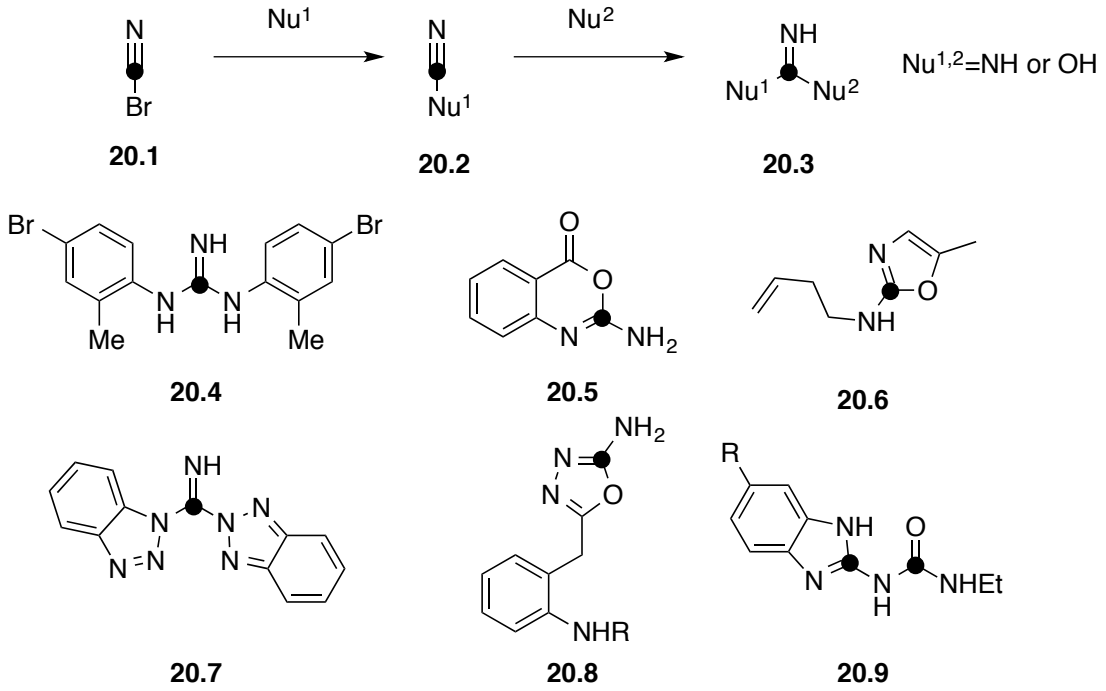
Though cyanogen bromide had been well successfully adopted in electrophilic bromination reactions, the production of a harmful byproduct, a metal cyanide, strongly dimmed the synthetic value of this process. Several more benign and convenient electrophilic bromination reagents, like 1,2-dibromotetrafluoroethane,[25a] 1,2-dibromotetrachloroethane,[26] dibromomalonate[27] and NBS,[28] remain the mainstream choices. After Paquette's intial report, cyanogen bromide has been sparsely mentioned in bromination reactions. For example, Zweifel,[29] Jaramillo,[30] Kobayashi,[31] and Casoni[32] separately reported synthesis of vinyl bromides **19.2**, bromoarenes **19.4** and **19.6**, and bromoalkynes **19.8** by bromination of the corresponding vinyl aluminate **19.1**, and lithiated **19.3**, **19.5**, and **19.7** with cyanogen bromide in moderate to high yields (Scheme 19).



Scheme 19.

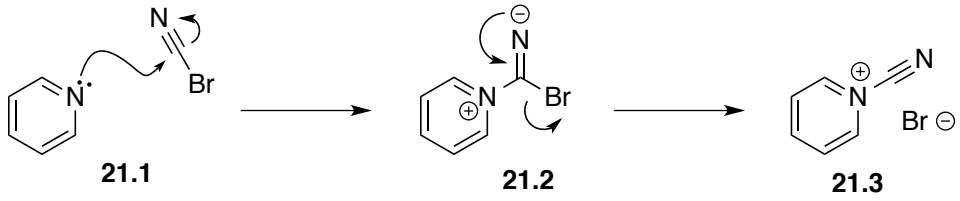
1.2.2. Cyanogen Bromide as an Electrophilic Cyanation Reagent

It was reported that cyanogen bromide could serve as an equivalent of CN^+ in reactions with N-H amines or alcohols under mild conditions to provide cyanamides[33] or cyanates **20.2**.[34] These intermediates react further with a second nucleophile to provide carbamimidate derivatives **20.3**, which are widely engaged motifs in biologically active molecules, including guanidines **20.4**[35] and **20.7**,[36] aminoxazinone **20.5**,[37] aminoxazoles **20.6**,[38] aminoxadiazole **20.8**,[39] and aminoimidazoles **20.9**.[40] (Scheme 20)



Scheme 20.

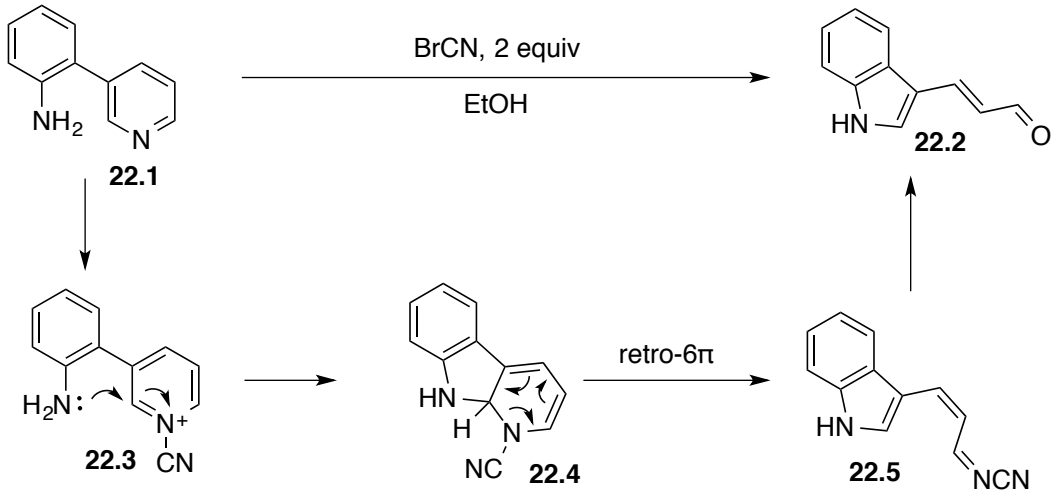
König reported formation of *N*-cyanopyridinium bromide from cyanogen bromide and pyridine via an electrophilic cyanation of pyridine following a Steiglich acylation-like pathway (Scheme 21).[41] This reaction was considered a convenient route toward activated pyridines, which are used in Zincke reaction.[42]



Scheme 21.

Vanderwal group recently revisited König's pyridine activation in synthesis of indole-substituted propenals **22.2** via an intramolecular Zincke reaction.[43] This transformation proceeds via a *5-exo-trig* addition of aniline to cyanogen bromide-

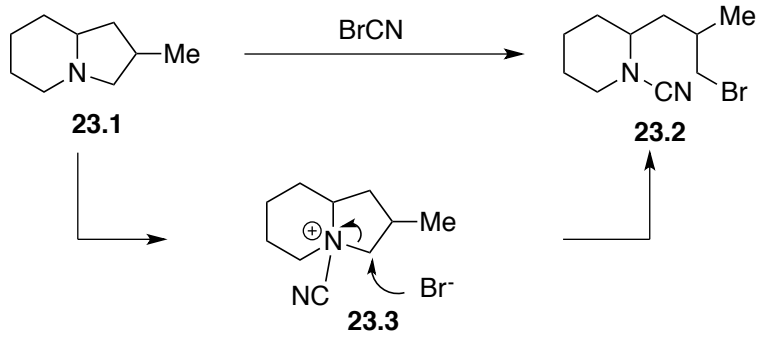
activated pyridine **22.3**, followed by a retro-6π electrocyclization of **22.4** to give *N*-cyanoimine **22.5**, which provided the enal product **22.2** upon hydrolysis (Scheme 22).



Scheme 22.

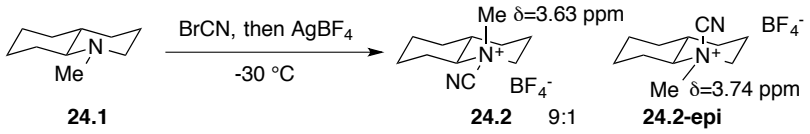
1.2.3. Double Duty of Cyanogen Bromide

Dealkylation/cyanation transformation of tertiary amines with cyanogen bromide is known as von Braun reaction.[44] For instance, Ochiai and co-workers reported synthesis of bromine-substituted cyanamide **23.2** in reaction of indolizidine **23.1** with cyanogen bromide (Scheme 23).[45,46]



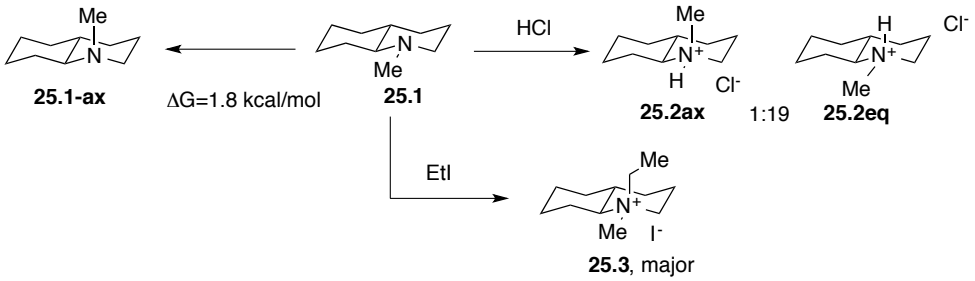
Scheme 23.

A *N*-cyanoammonium **23.3** had been proposed to be the intermediate of the von Braun reaction. However, the intermediacy of *N*-cyannoammonium in von Braun reaction remained uncertain, until Fordor reported isolation of *N*-cyanoammonium tetrafluoroborate **24.2** from a reaction of *trans*-*N*-methyl-decahydroquinoline **24.1** with cyanogen bromide and silver tetrafluoroborate at -30 °C (Scheme 24).[47] Single crystal structure analysis of the product revealed a major epimer **24.2** possessing an unusual axial *N*-methyl group.



Scheme 24.

Importantly, Grishina[48] and McKeena's[49] reported that in both protonation and alkylation reactions, electrophiles primarily approached *trans*-*N*-methyl-decahydroquinoline from the axial direction, thus provided products **25.2eq** and **25.3** (Scheme 25).



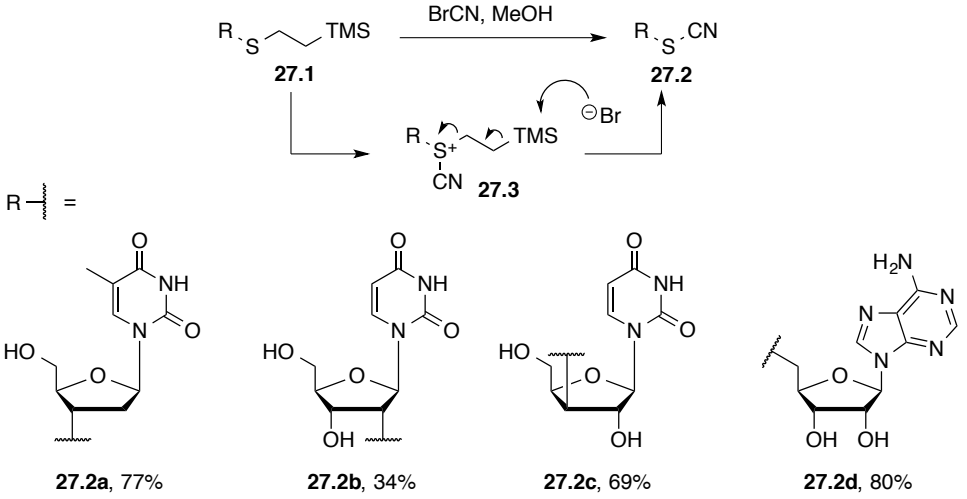
Scheme 25.

Accordingly, one can propose that, the observed "inversion" of nitrogen-stereogenic center in Fordor's study should be an outcome of the following two-stage transformation (Scheme 26): first, *N*-bromination of **26.1** yielded **26.3**, in which *N*-methyl

remains equatorial; second, the released cyanide replaces bromine of **26.3** in an S_N2 fashion to produce **26.2**, hence forming the "inverted" axial *N*-methyl. Thus, cyanogen bromide functions as a combination of Br^+ and CN^- in the von Braun reaction, which represents the first mode of the double duty of cyanogen bromide.

Scheme 26.

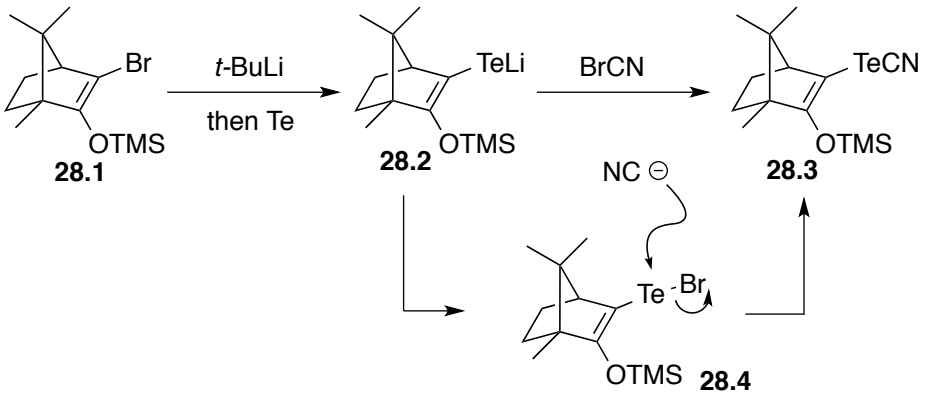
Chambert and co-workers reported synthesis of thiocyanate **27.2** by selective cleavage of trimethylsilylethylthioether **27.1** with cyanogen bromide. This transformation proceeded via an activation of substrate by *S*-cyanation with the release of bromide. The following bromodesilylation/elimination led to the formation of *S*-cynation product **27.2** (Scheme 27).[50]



Scheme 27.

Back reported that, lithium vinyltellurolate **28.2** undergoes reaction with cyanogen bromides to produce vinyltellurium cyanide **28.3** in the presence of cyanogen

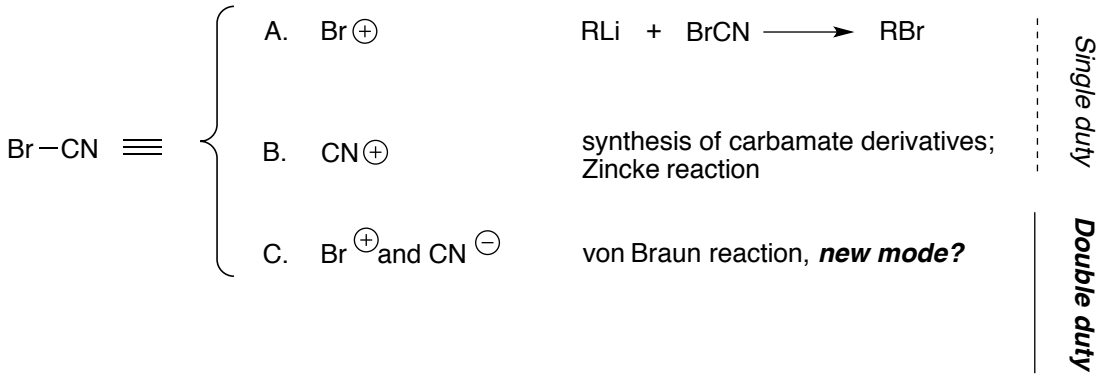
bromide.[51] This reaction may follow the same pathway to that of von Braun reaction, the first formed tellurium bromide **28.4** undergoes an S_N2 substitution by cyanide to form product **28.3** (Scheme 28). This Te-centered transformation constitutes a second double duty mode of cyanogen bromide



Scheme 28.

1.2.4. Summary

In summary, it has been shown that, the Br-C bond of cyanogen bromide can be cleaved in diverse manners under different conditions. Thus, cyanogen bromide was shown to serve a donor of Br^+ in reactions with strongly nucleophilic organometallic reagents to provide the corresponding vinyl- or aryl bromides (Scheme 29, mode A). In synthesis of carbamate derivatives and Zincke reaction, cyanogen bromide reacts with alcohols, amines and pyridines, behaving as an equivalent of CN^+ (Scheme 29, mode B). Furthermore, in von Braun reaction, BrCN shows double duty as a combination of Br^+ and CN^- (Scheme 29, mode C). In contrast to a double duty of haloalkynes, that of cyanogen bromide is under established. Therefore, development of new modes of double duty transformation of cyanogen bromide is warranted.



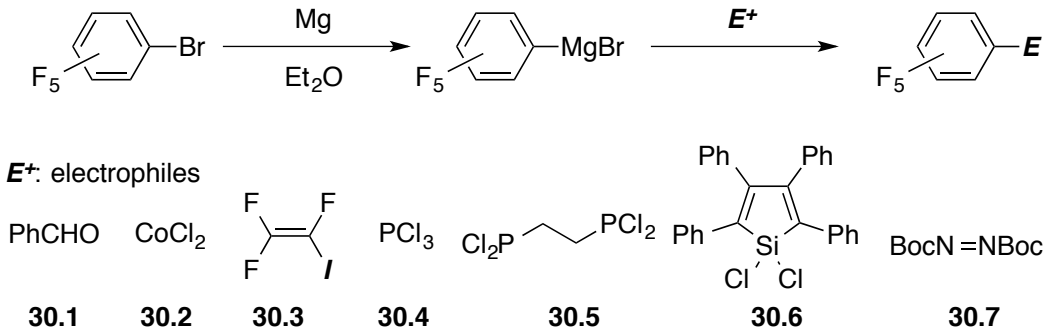
Scheme 29.

1.3. Divergent Reactivity of Bromopentafluorobenzene

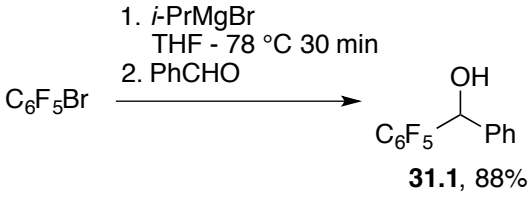
Bromopentafluorobenzene (C_6F_5Br, PFPBr) is an important building block toward molecules containing pentafluorophenyl subunit. Due to the presence of five fluorine atoms, beside common metallation reactions of C-Br bond, PFPBr was also reported to be an electrophilic bromination reagent, as discussed below.

1.3.1. PFPBr as a Precursor of Pentafluorophenyl Anion

The most frequently reported transformation of bromopentafluorobenzene is the metallation of C-Br bond to form pentafluorophenyl metal reagents, which react with various electrophiles. Thus Pummer reported the preparation of PFPMgBr in the presence of magnesium metal and the consequent reactions with electrophiles including aldehyde **30.1**, cobalt chloride **30.2**, trifluoroiodoethylene **30.3**, and phosphorus trichloride **30.4** and **30.5**.[52] Later, the scope of electrophiles was expanded to silicon chloride **30.6**,[53] and azodicarboxylates **30.7** (Scheme 30).[54] The magnesiation can also be achieved via the Knochel's protocol by treating PFPBr with *i*-PrMgBr (Scheme 31).[55]

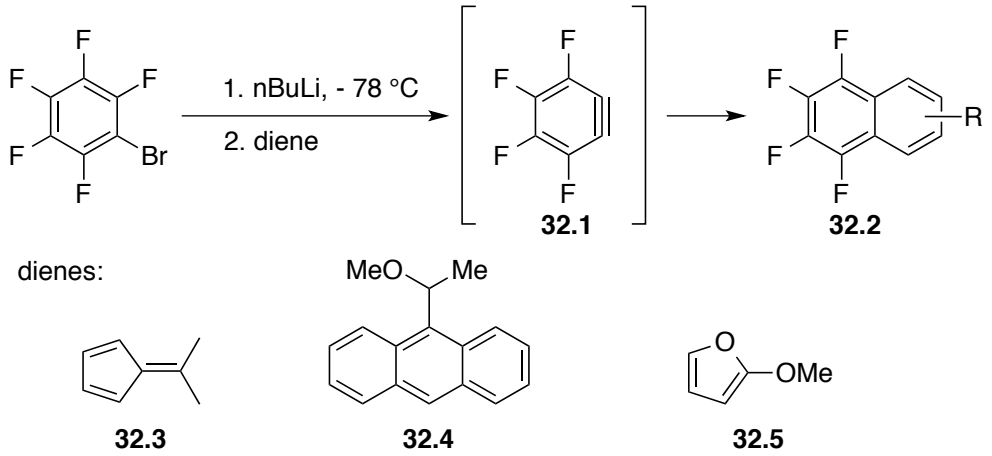


Scheme 30.



Scheme 31.

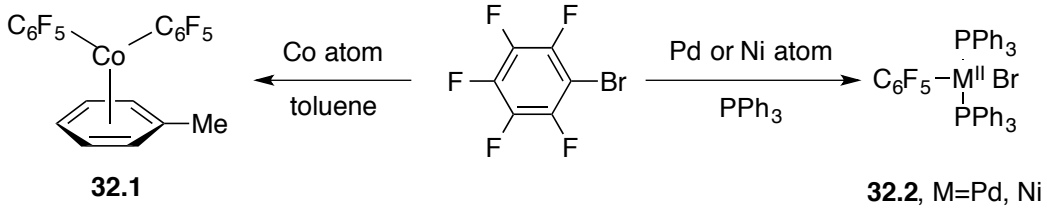
In contrast to the room-temperature stable PFPMgBr, the PFPLi, generated by treatment of PFPBr with butyl lithium, even at a low temperature spontaneously transforms into tetrafluorobenzyne **32.1** via an *ortho*-elimination of lithium fluoride. This benzyne was shown to participate as a dienophile in Diels-Alder reactions with a number of dienes, including cyclopentadienes **32.3**,[56] anthracenes **32.4**,[57] and furans **32.5**,[58] producing tetrafluoro-naphthalene derivatives **32.2** (Scheme 32).



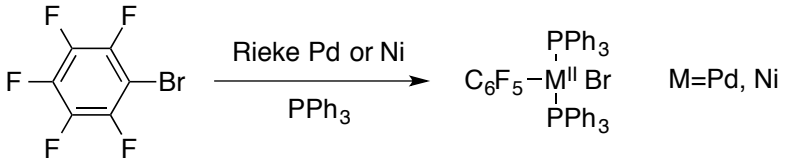
Scheme 32.

1.3.2. PFPBr as a Precursor of Electrophilic Pentafluorophenyl Species

The metallation of PFP-Br bond also occurs through its oxidative addition to a series of transition metals. Hence, Pummer reported the preparation of perfluorobiphenyl from PFPBr via a copper-mediated Ullmann reaction.[52a] Later, some stable C_6F_5-transition metal complexes **33.1** and **33.2** were isolated from the condensed mixture of metal vapor and PFPBr (Scheme 33)[59] and from the reactions of PFPBr and highly reactive Rieke metals (Scheme 34).[60]

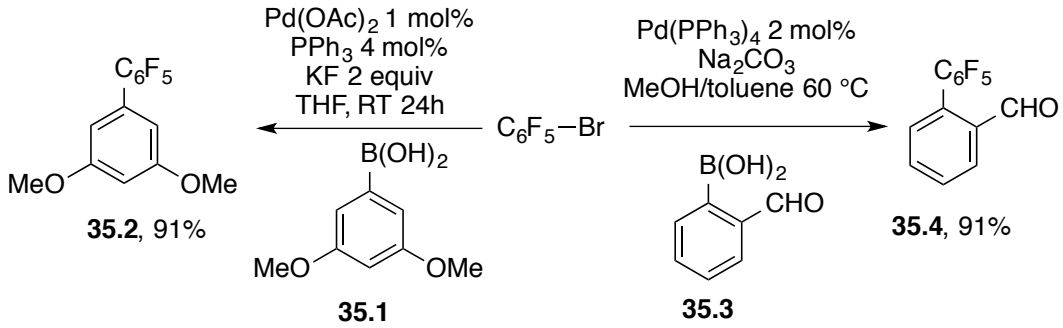


Scheme 33.

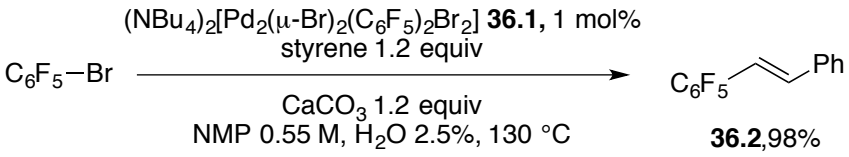


Scheme 34.

Only a limited number of efficient transition metal-catalyzed cross–coupling reactions of C_6F_5Br have been reported. Thus, Escher and Brookhart separately reported efficient Suzuki coupling reactions [61] of C_6F_5Br with arylboronic acids **35.1** and **35.3** (Scheme 35). Milstein reported the Heck coupling reactions of C_6F_5Br and styrene, which required a specific catalyst **36.1**. [62] (Scheme 36)



Scheme 35.

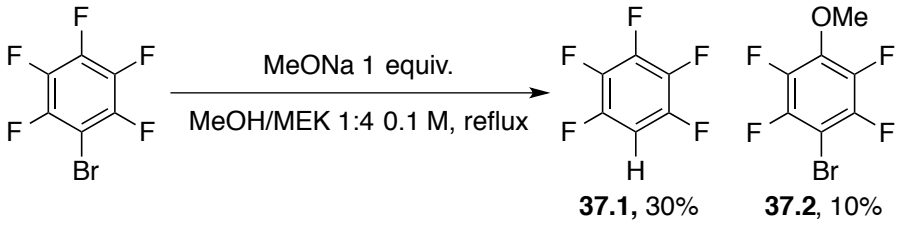


Scheme 36.

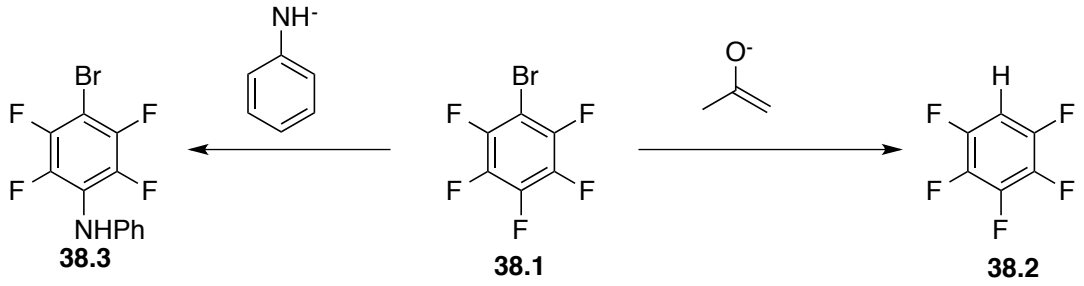
1.3.3. PFPBr as a Source of Electrophilic Bromine

Due to the strong cumulative electron-withdrawing ability of five fluorine atoms, the bromine atom of C_6F_5Br is electrophilic toward a series of nucleophiles. For example, Bolton first studied the debromination of PFPBr under basic conditions, and found formation of a major debrominating product **37.1** and an S_NAr substitution minor product **37.2** (Scheme 37).[63] Gronert recently re-examined this transformation, and found that the selectivity between debromination and S_NAr pathways greatly depended on the nature of nucleophile employed in this reaction. For example, enolate produced primarily

debromination product **38.2**, while anilide favored an S_NAr pathway leading to the formation of substituted product **38.3** (Scheme 38).[64]

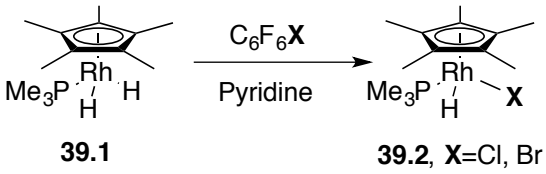


Scheme 37.



Scheme 38.

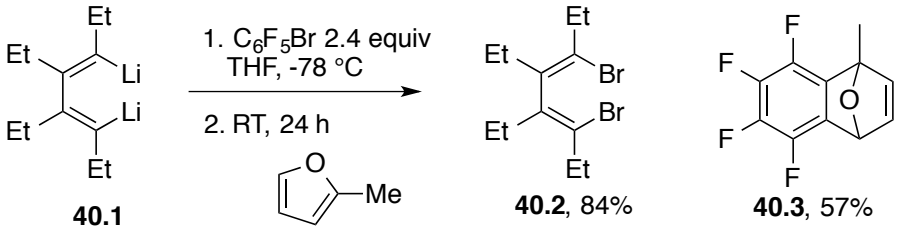
Johns also reported a debromination of PFPBr and PFPCl using a hydridorhodium complex **39.1** (Scheme 39).[65] However, this process was believed to take place via a radical chain process.[66]



Scheme 39.

Xi and co-workers recently reported synthesis of dibromobutadiene **40.2** by quenching dilithiated butadiene **40.1** with PFPBr in good yield. The produced PFPLi

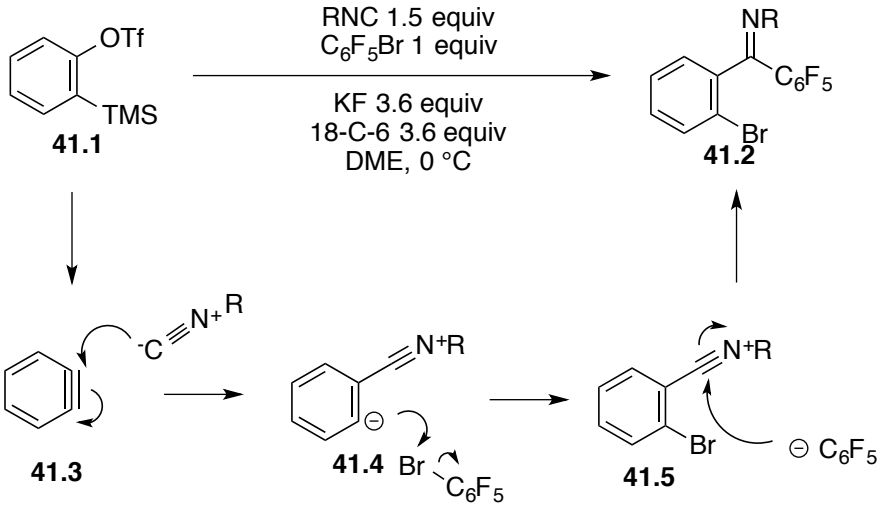
rapidly degraded into tetrafluorobenzyne, which was trapped by a subsequently added of 2-methyl furan to give product **40.3** (Scheme 40).[67]



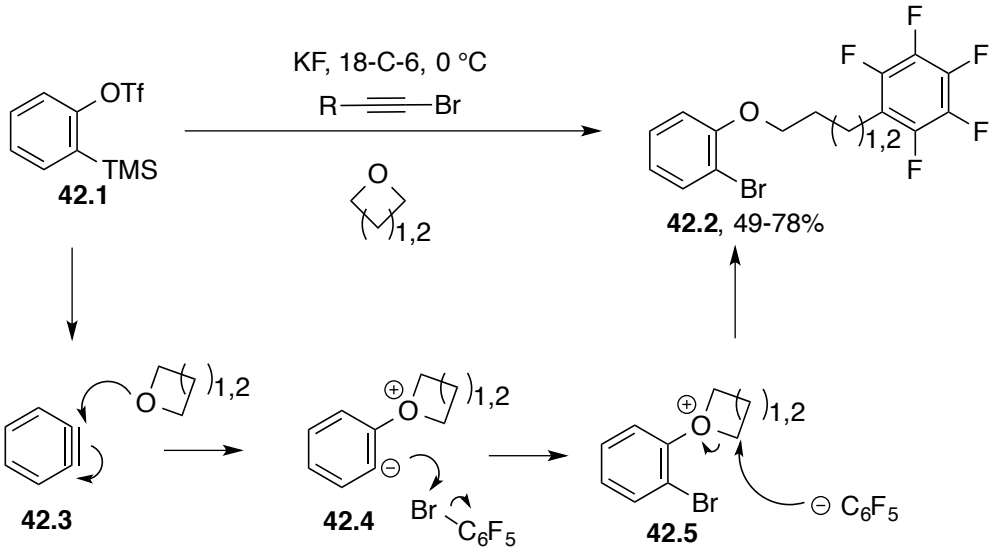
Scheme 40.

1.3.4. Double Duty of PFPBr

Yoshida and co-workers reported double duty transformation of PFPBr in synthesis of diarylmethanimine derivatives **41.2** via a three-component reaction of benzyne, isocyanide and PFPBr (Scheme 41). This reaction proceeds via an abstraction of Br^+ from PFPBr by a 1,4-dipolar adduct **41.4** of benzyne and isocyanide to produce the bromine-substituted nitrillium species **41.5** and the pentafluorophenyl anion. The addition of PFP anion to **41.5** yielded **41.2**. A similar cascade transformation employing 1,3-dipolar adduct **42.4** of benzyne and cyclic ether to produce alkynyl-substituted ether **42.2** was also demonstrated (Scheme 42).[22] Thus, PFPBr serves as a combination of Br^+ and PFP^- in this transformation. This independent work was published simultaneously with our report on another mode of double duty transformation of PFPBr (*vide infra*).[68]



Scheme 41.

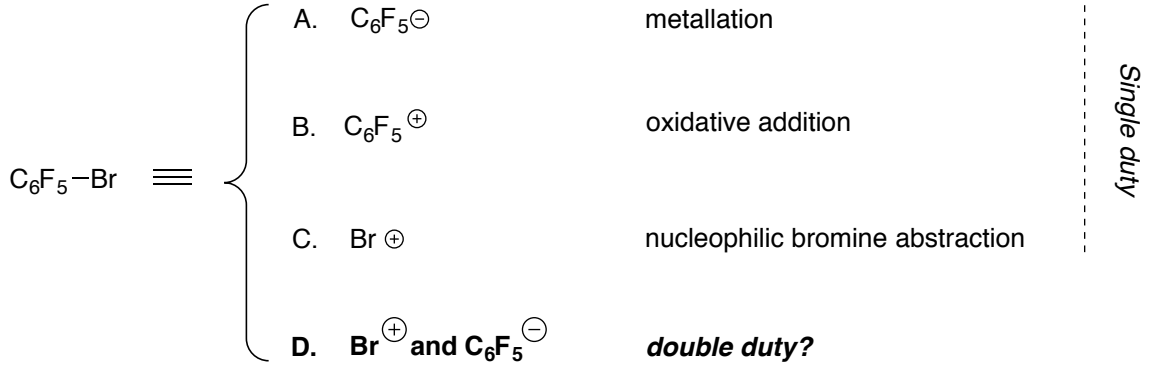


Scheme 42.

1.3.5. Summary

The divergent reactivity of PFPBr has been widely recognized. Through metallation reactions with earth metals or metallation reagents, PFPBr serves an equivalent of the PFP anion, which participates in reactions with a series of electrophiles

(Scheme 43, mode A). It also serves as a source of electrophilic pentafluorophenyl by oxidative addition to transition metals, hence participates in cross-coupling reactions (Scheme 43, mode B). On the other hand, the Br^+ abstraction from PFPBr by nucleophiles has also been reported (Scheme 43, mode C). Although it has not been discovered, it is reasonable to hypothesize and test a double duty of PFPBr as a combination of Br^+ and $C_6F_5^-$ in cascade transformations.

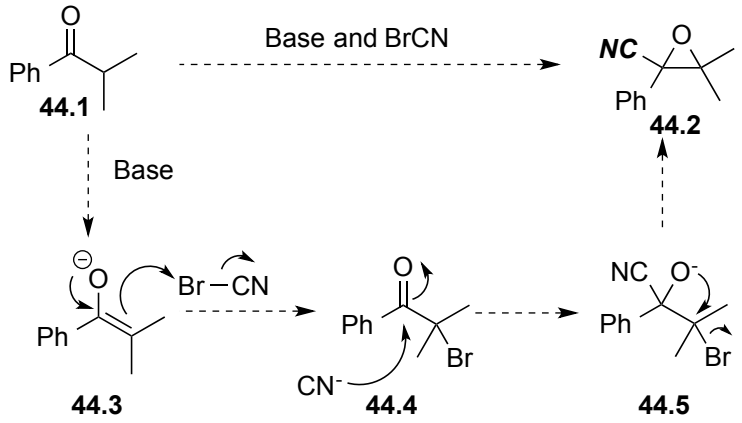


Scheme 43.

2. Double Duty of Cyanogen Bromide in Epoxide Synthesis

2.1. New Mode of Double Duty Transformation of Cyanogen Bromide

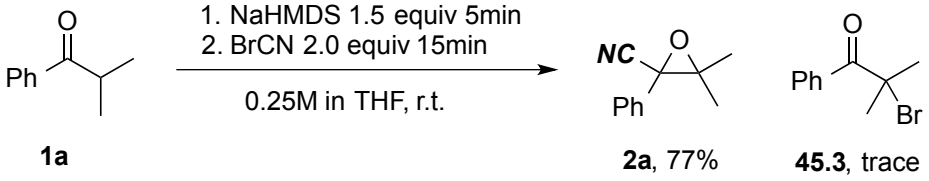
The divergent reactivity of cyanogen bromide has been summarized above (Section 1.2.4, on page 19). It functions as an electrophilic bromination or cyanation reagent in reactions with various nucleophiles. In addition, although not recognized earlier, the nontrivial double duty of cyanogen bromide has emerged from the von Braun reaction as the first, and the only known to date mode of the double duty of cyanogen bromide. Inspired by Gevorgyan group's initial report on the double duty of bromoalkynes,[21] which served as equivalents of both Br^+ and acetylide in a highly efficient transformation of ketones into densely substituted alkynyl oxiranes, we hypothesized a potential utilization of cyanogen bromide in a similar transformation of ketones **44.1** into the corresponding epoxynitriles **44.2** (Scheme 44). It was anticipated that an enolate **44.3** would abstract the bromine atom of cyanogen bromide to generate the α-bromoketone **44.4**. Then, a nucleophilic addition of the formed cyanide at the formed α-bromoketone **44.4** would produce cyanohydrin **44.5**, which upon an intramolecular S_N2 reaction would produce the epoxynitrile **44.2**. Thus, cyanogen bromide would act as equivalents of both Br^+ and cyanide in one cascade transformation.



Scheme 44.

2.2. Optimization of the Reaction Conditions, Scope, and Limitations

To test the above hypothesis, we examined the reaction of isobutyrophenone **1a** and cyanogen bromide in the presence of a strong base. It was found that the enolization of isobutyrophenone **1a** with LiHMDS, followed by addition of cyanogen bromide resulted in formation of epoxynitrile **2a** in good yield, along with observation of trace amounts of α-bromoketone **45.3** by GC-MS, which provided support for the proposed path for this transformation (Scheme 45).[69]

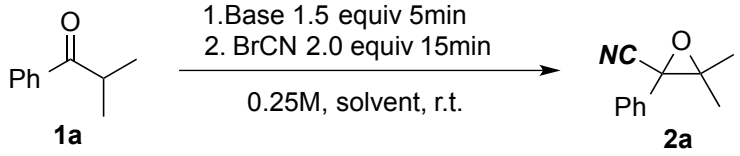


Scheme 45.

A brief optimization of the reaction conditions (Table 1) revealed that employment of other ethereal solvents, such as diethyl ether or 1,4-dioxane, did not improve the yield of **2** (entries 2, 5). Increasing the concentration of reaction mixture by addition of NaHMDS solution to a neat ketone resulted in a l 28 ield, but this result

was not reproducible on other ketones (entry 3). Changing solvent to dichloromethane barely suppressed the reaction (entry 4). Finally, employment of DMF as solvent has substantially improved the yield with a complete conversion of the intermediate α-bromoketone (entry 6). Switching base to LiHMDS slightly further improved the yield (entry 7). Employment of weak bases, such as triethylamine and cesium carbonate, was not efficient in this transformation (entry 8, 9).

Table 1.

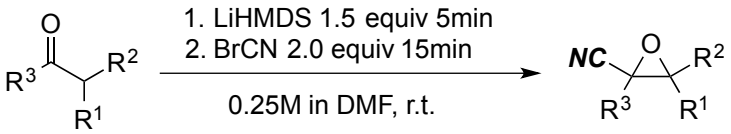


Entry	Solvent	Base	Yield (%)[a]
1	THF	NaHMDS[b]	77
2	Et_2O	NaHMDS	62
3	THF[c]	NaHMDS	88
4	CH_2Cl_2	NaHMDS	N.R.
5	1,4-Dioxane	NaHMDS	44
6	DMF	NaHMDS	90
7	**DMF**	**LiHMDS[b]**	**92**
8	DMF	Triethylamine	N.R.
9	DMF	Cs_2CO_3	N.R.
10	DMF	$B(OMe)_3$	37

[a] Yield was determined by GC-MS using diphenyl ether as an internal standard. [b] 1M in THF. [c] THF solution of NaHMDS was added to a neat ketone.

With the optimized conditions in hand, the generality of this cascade transformation was examined (Table 2). First, aryl ketones were tested. It was found that α,α-disubstituted benzophenons, including isopropyl, cyclophentyl, and cyclohexyl ketones were efficient in this reaction (**1a-c**). Isopropyl ketones usually provide better yield compared to that of the corresponding cyclopentyl and cyclopentyl counterparts that bear the same aryl group. A relatively lower yield for the latter was probably caused by a competing elimination of HBr during the reaction.[70] Certain groups at the aromatic moiety of ketone, such as methoxy (**1d**) and nitrile (**1e-g**), were also tolerated. Cyanoepoxidation of unsymmetrically substituted ketone ^{1}H produced almost 1:1 diasteriomeric mixture of epoxynitrile **2h** in low yield. The low diastereoselectivity of this transformation is due to non-selective addition of the cyanide at the carbonyl group of the intermediate α-bromoketone. Similar results were observed by Platt in reduction of analogous substrates **46.1** (Scheme 46).[71] A slightly better yield of epoxynitrile was obtained in cyclization of α,α-diphenylacetophenone (entry 9). This reaction turned out to be efficient with pyridyl-containing ketones as well. Thus, 3-pyridinyl ketones **1j-l** (entries 10-12) and 2-pyridinyl ketones **1m-o** (entries 13-15) were smoothly converted into the corresponding epoxynitriles **2j-o** in good to excellent yields. Finally, it was found that the alkynyl ketone **1p** is a suitable substrate for this reaction producing the alkynyl cyanooxirane **2p** in high yield (entry 16). However, reactions employing propiophenone, acetophenone, and *tert*-butyl methyl ketone failed to provide analyzable result.

Table 2.



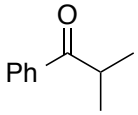
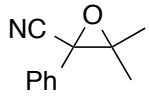
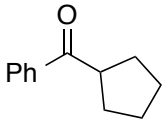
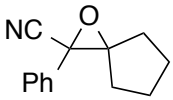
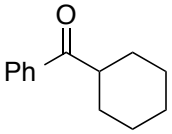
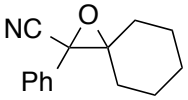
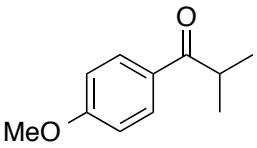
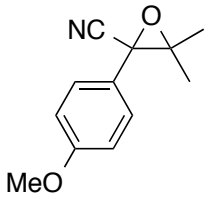
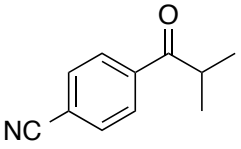
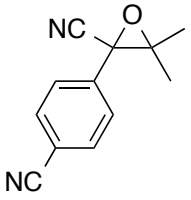
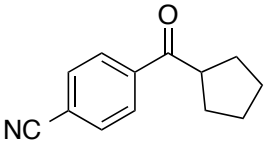
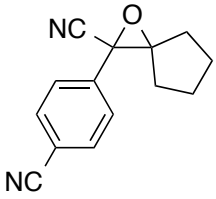
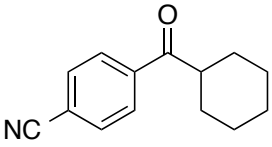
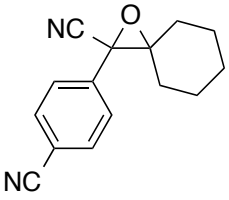
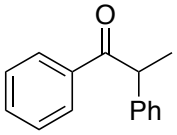
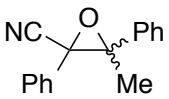
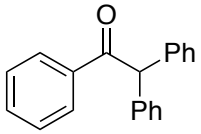
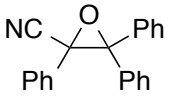
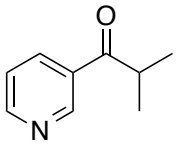
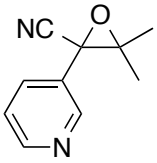
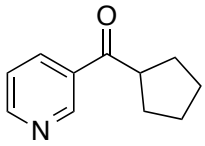
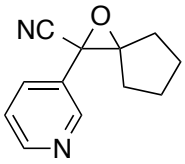
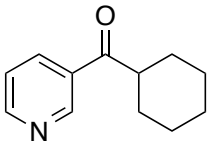
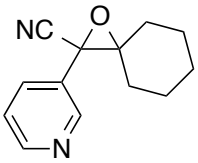
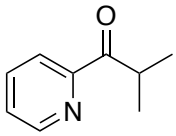
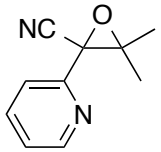
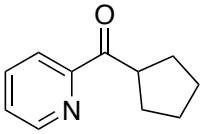
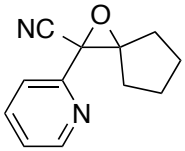
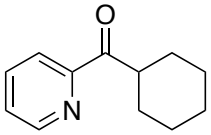
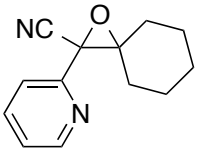
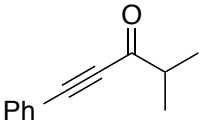
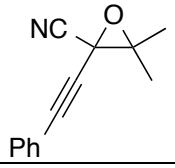
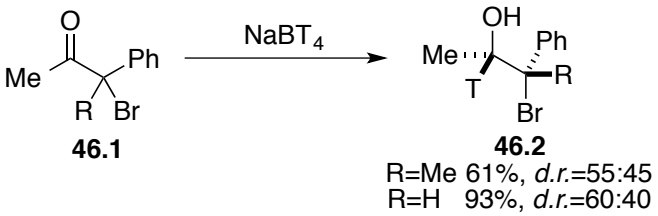
Entry		Substrate **1**		Product **2**	Yield [%][a]
1	**1a**		**2a**		78
2	**1b**		**2b**		75
3	**1c**		**2c**		66
4	**1d**		**2d**		71
5	**1e**		**2e**		70
6	**1f**		**2f**		70
7	**1g**		**2g**		80
8	**1h**		**2h**		40 (1:1)

Table 2. (continued)

Entry	Substrate **1**		Product **2**		Yield [%][a]
9	**1i**		**2i**		52
10	**1j**		**2j**		84
11	**1k**		**2k**		70
12	**1l**		**2l**		80
13	**1m**		**2m**		93
14	**1n**		**2n**		90
15	**1o**		**2o**		78
16	**1p**		**2p**		85

[a] Isolated yield.



46.1 **46.2**

R=Me 61%, *d.r.*=55:45
R=H 93%, *d.r.*=60:40

Scheme 46.

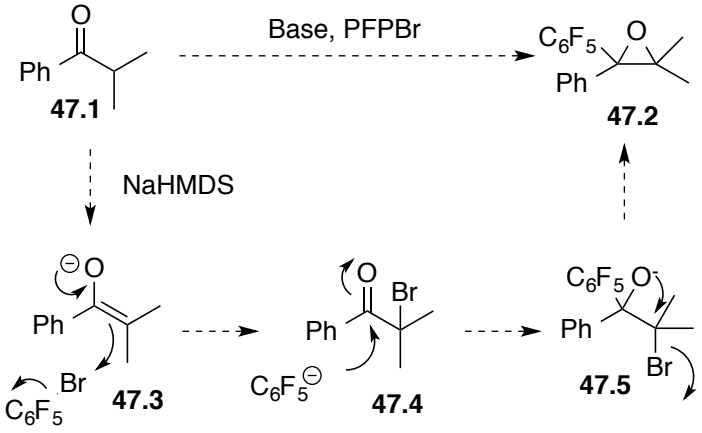
2.3. Summary

In summary, we have demonstrated that cyanogen bromide could serve an equivalent of both Br^+ and CN^- in a cascade conversion of ketones to epoxynitriles. This reaction proceeds via α-bromination of a ketone by cyanogen bromide, followed by a nucleophilic addition of the produced cyanide at the ketone and a subsequent replacement of α-bromide by a cyanohydrine. This provides a convenient and efficient route toward fully substituted diverse epoxynitriles from easily available ketones.[72]

3. Double Duty of Bromopentafluorobenzene in Epoxide Synthesis

3.1. Proposal of the Double Duty of PFPBr

As summarized above (Section 1.3.5, on page 26), under different conditions, the Br-C bond of PFPBr can be functionalized in a diverse manner. It serves as a precursor of pentafluorophenyl anion through a metal-halogen exchange reaction. In the presence of transition metal, it serves as an electrophilic pentafluorophenyl moiety. Moreover, several nucleophiles can abstract bromine from PFPBr, which serves as a donor of Br^+. Building upon Gevorgyan's first report on the double duty of bromoalkynes, and then double duty of cyanogen bromide,[73] we hypothesized that PFPBr could potentially be involved in a similar transformation of ketones into pentafluorophenyl epoxides as equivalents of both Br^+ and $C_6F_5^-$ (Scheme 47). It was expected that an enolate **47.3** would abstract the bromine atom of cyanogen bromide to generate the α-bromoketone **47.4**. Then a nucleophilic addition of the formed $C_6F_5^-$ at the α-bromoketone **47.4** would form alkoxide **47.5**, which upon an intramolecular S_N2 reaction would produce the oxirane **47.2**. Thus, PFPBr would supply equivalents of both Br^+ and $C_6F_5^-$ in one cascade transformation.

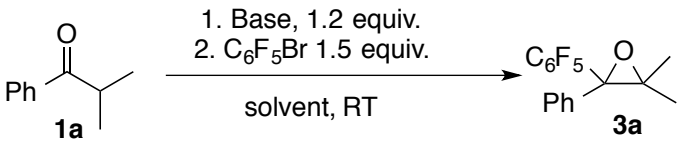


Scheme 47.

3.2. Optimization of the Reaction Conditions, Scope, and Limitations

To test the above hypothesis, the reaction of isobutyrophenone **1** and PFPBr has been examined (Table 3). Gratifyingly, it was found that employment of LiHMDS in THF led to 23% yield of the epoxide **3a** (entry 3). Further brief optimization of the reaction conditions revealed that isobutyrophenone **1a** in the presence of NaHMDS in 1,4-dioxane almost was quantitatively converted into tetrasubstituted epoxide **3a** (entry 9). Notably, reaction in toluene provided similar yield being to that in 1,4-dioxnane, thus toluene was found to be another optimal solvent for this transformation (entry 10).

Table 3.



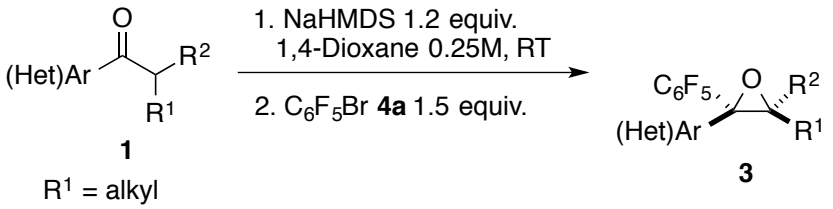
Entry	Base	Solvent	Result[a]
1	LiHMDS	DMF	trace
2	LiHMDS	Et_2O	N.R.
3	LiHMDS	THF	23
4	LiHMDS	1,4-Dioxane	N.R.
5	LiO^iPr	THF	N.R.
6	LiO^iPr	1,4-Dioxane	N.R.
7	NaHMDS	THF	40%
8	NaHMDS	Et_2O	75%
9	**NaHMDS**	**1,4-Dioxane**	**96%**
10	**NaHMDS**	**Toluene**	**92%**
11	KO^tBu	THF	decomposition
12	KO^tBu	1,4-Dioxane	decomposition

[a] GC yields, using pentadecane as an internal standard.

Next, the generality of the cascade transformation was examined. First, reactions of different ketones with PFPBr **4a** were tested (Table 4). It was found that α,α-disubstituted methyl aryl ketones remain suitable substrates for this transformation. Thus, isopropyl- (**1a**), cyclobutyl (**1q**), cyclopentyl (**1b**), and cyclohexyl (**1c**) phenyl ketones

smoothly reacted with PFPBr to produce epoxides **3a-d** in good to excellent yields. Pyran-4-yl ketone **1r** was also successfully converted into the corresponding product **3e**. Diverse substituents at the phenyl ring, such as 4-methoxy (**1d**) and 4-cyano (**1e, g**), were tolerated in this reaction (entries 6-8). Moreover, different heteroaryl ketones, including pyridin-3-yl ketone **1j, l** and *N*-tosyl-indole-3-yl ketone **1s**, were converted into the corresponding epoxides **3i-k** in good yields (entries 9-11). Importantly, in contrast to the epoxidation reaction with alkynyl bromides[21] and cyanogen bromide,[73] PFPBr smoothly reacted with enolates derived from propiophenone **1t** and butyrophenone **1u** producing the corresponding trisubstituted oxiranes **3l**, **3m** in good yield and very high *trans*-diastereoselectivity (entries 12, 13). The "*trans*"-configuration of the major diastereomers was established by NOE analysis. The diastereoselectivity, which occurred during the addition of PFP anion at the α-bromoketone, can be explained by the Felkin-Anh model for carbonyl compounds posessing an electron withdrawing α-substitution (Scheme 48, eq. 1)[74] Similar diastereoselectivity has been observed in reduction of α-bromoketone (Scheme 48, eq. 2), and in addition of acetylides to α-chloroketone (Scheme 48, eq. 3).[71,75] It should be mentioned that this reaction is easily scalable, as 10 mmol reaction of propiophenone **3t** with PFPBr resulted in outcome similar to that for 0.5 mmol reaction (entry 12). Reaction of acetophenone **1v** yielded detectable amount of desired product **3u** according to GC-MS, however, attempts on purifying **3u** was unsuccessful.

Table 4.



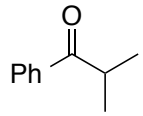
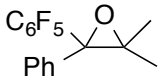
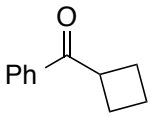
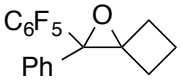
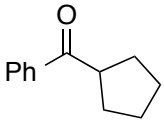
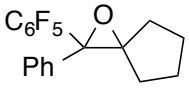
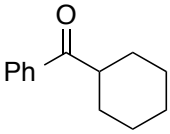
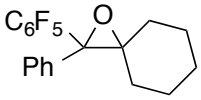
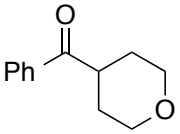
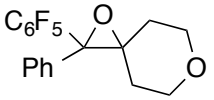
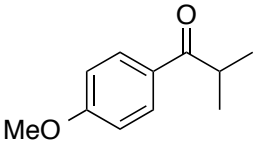
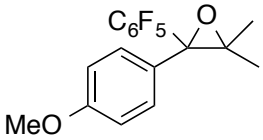
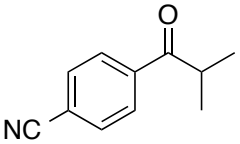
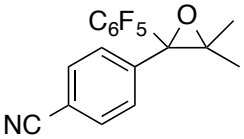
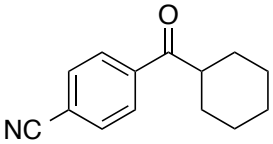
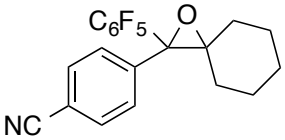
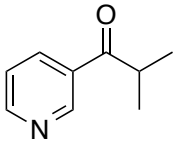
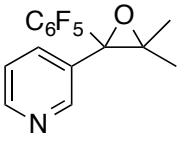
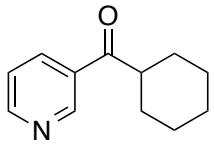
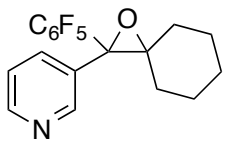
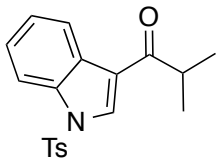
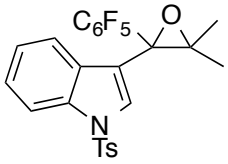
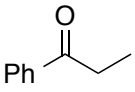
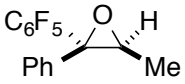
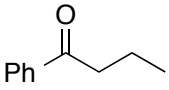
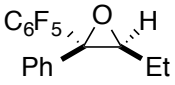
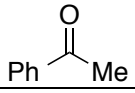
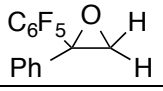
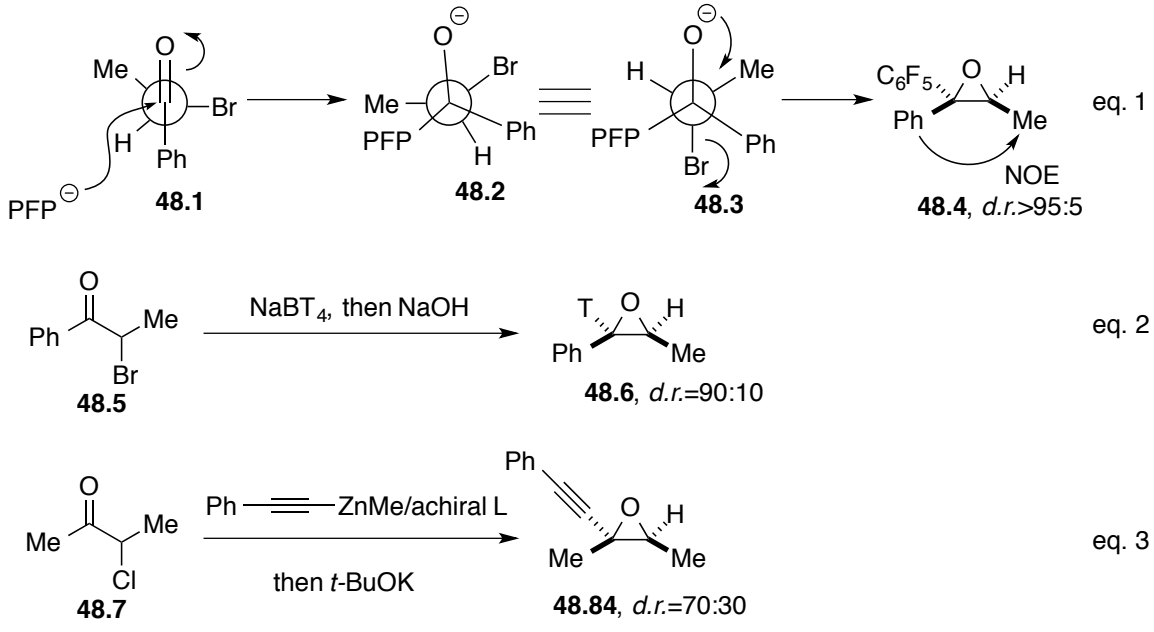
Entry		Ketone		Product	Yield, %[a] *(d.r.)*
1	**1a**		**3a**		92 90[b]
2	**1q**		**3b**		>99
3	**1b**		**3c**		74
4	**1c**		**3d**		70
5	**1r**		**3e**		66
6	**1d**		**3f**		88
7	**1e**		**3g**		65
8	**1g**		**3h**		82
9	**1j**		**3i**		53

Table 4. (continued)

Entry		Ketone		Product	Yield, %[a] *(d.r.)*
10	**1l**		**3j**		62
11	**1s**		**3k**		60
12	**1t**		**3l**		81 (> 95:5) 90 (> 95:5) [c]
13	**1u**		**3m**		85 (93:7)
14	**1v**		**3u**		0[d]

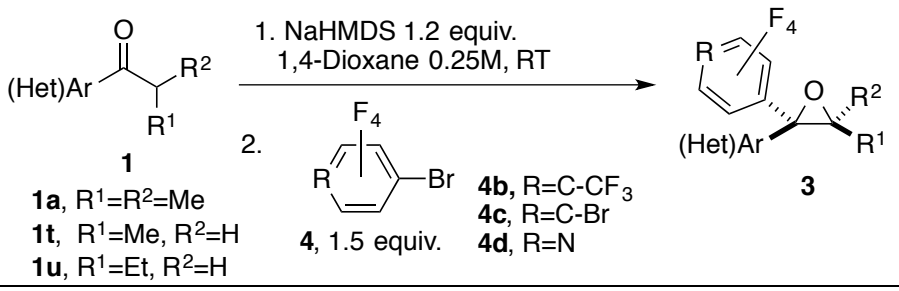
[a] Isolated yields of 0.5 mmol reactions. [b] Reaction was run in toluene medium. [c] Reaction was run at 10 mmol scale in toluene. [d] Product decomposed during column chromatography purification.



Scheme 48.

Next, the scope of bromopolyfluroarenes was tested (Table 5). It was found that 1-bromo-4-trifluoromethytetrafluorolbenzene (**4b**), 1,4-dibromotetrafluorobenzene (**4c**), and 4-bromotetrafluoropyridine (**4d**) were all competent reactants in this cascade transformation, producing the corresponding polyfluoro -aryl or -hetaryl epoxides in good yields (**3n-t**). Although the reactions of **4b-d** with propiophenone and butyrophenone produced the trisubstituted epoxides **3q-t** in good yields, the diastereoselectivities were lower (entries 4-7) being compared to these of the analogous reactions with PFPBr (Table 4, entries 12, 13). The reduced of diastereoselectivity is correlated to the decreased inductivity of *para*-substitution. Less electron-deficient polyfluorobromoarenes, including 1-bromo-2,3,4,6-tetrafluorobenzene and 5-bromo-2,3,4,6-tetrafluorotoluene, cannot afford a good leaving group that can well carry a negative charge, thus failed to be incorporated in this double duty transformation. Furthermore, attempts on transformation of 1-bromoperfluorobutane and 1-iodoperfluorobutane, which are known to participate in a feasible debromination or deiodination reactions with nucleophiles,[76] were unsuccessful in our transformation.

Table 5.

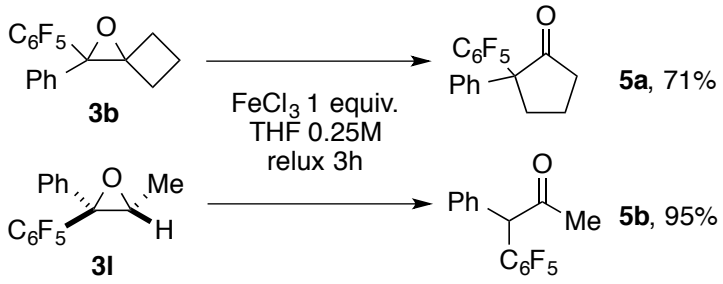


Entry	Ketone	Bromide	Product	Yield (%), (d.r.)[a]
1	**1a**	**4b**	**3n**	80
2	**1a**	**4c**	**3o**	84
3	**1a**	**4d**	**3p**	60
4	**1t**	**4b**	**3q**	86 (85:15)
5	**1u**	**4b**	**3r**	81 (77:23)
6	**1u**	**4c**	**3s**	75 (90:10)
7	**1u**	**4d**	**3t**	77 (90:10)

[a] Isolated yields of 0.5 mmol reactions.

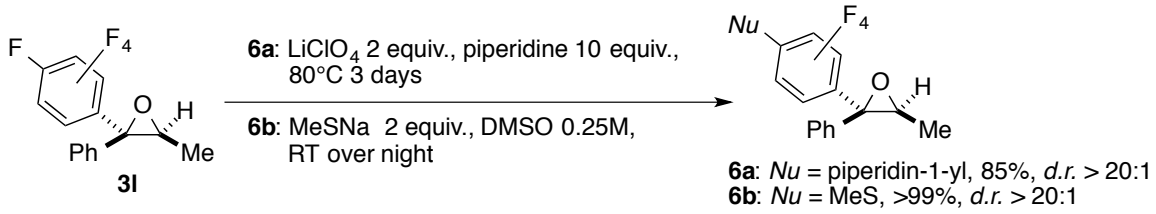
3.3. Functionalization of Perfluoroaryl Epoxides

The synthetic usefulness of the obtained polyfluorophenyl oxiranes was showed by their further transformations. First, it was demonstrated that oxiranes **3b** and **3l** in the presence of stoichiometric amounts of $FeCl_3$ undergo a facile semipinacol rearrangement[77] to produce the ring expansion product **5a** and a *H*-migration product **5b**, respectively, in good to excellent yields (Scheme 49).



Scheme 49.

Secondly, it was shown that the obtained polyfluorophenyl oxiranes are excellent substrates for S_NAr reactions[78] (Scheme 50). Thus, **3l** underwent efficient substitution reaction with piperidine and sodium methylthiolate to produce the expected products **6a** and **6b** in excellent yields without detecting any oxirane ring-opening product.[79]



Scheme 50.

3.4. Conclusion

In conclusion, we have demonstrated that amphoteric bromopolyfluoro-arenes(heteroarenes) could serve equivalents of both Br^+ and perfluoroaryl(hetaryl)

anions in the same cascade transformation. Thus, reaction of enolizable ketones with bromopolyfluoroarenes allowed for synthesis of a variety of valuable tri- and tetra-substituted epoxides[80] in good to excellent yields and diastereoselectivity. A synthetic usefulness of the obtained polyfluorophenyl-containing epoxides was further demonstrated in their transformations, including a semi-pinacol rearrangement and S_NAr reactions.

3.5. Summary of the Double Duty Synthons in Epoxide Synthesis

The double duty of cyanogen bromide[73] and bromopolyfluoroarenes[68] has been demonstrated in their highly productive transformations of enolizable phenones into densely substituted epoxides via an electrophilic α-bromination/nucleophilic addition/nucleophilic substitution cascade reaction. The future development of this chemistry may focus on expanding the scope of reactants. First, since haloperfluoro-alkanes and -alkenes have been proved to be good donors of electrophilic halogen in reaction with strong nucleophiles,[25,76] the feasibility of using haloperfluoro-alkanes and -alkenes as sp^3-hybridized double duty synthons in epoxide synthesis would be tested. Meanwhile, development of effective methods to transform other challenging carbonyl functionalities, particularly aldehydes, with a double duty synthon into epoxides would provide epoxides bearing different substitution patterns. Furthermore, in order to facilitate the prediction of other potential double duty synthons, the qualitative and quantitative correlation between double duty and chemical structure has to be determined.

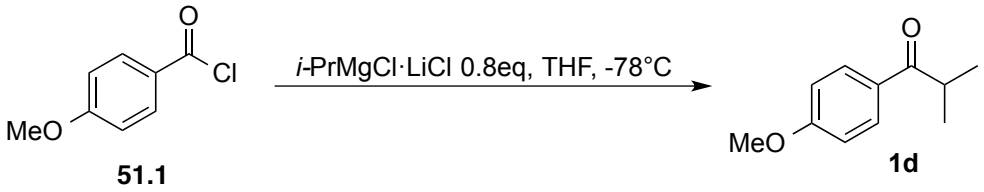
4. Experimental Section

4.1. Instrumentations

NMR spectra were recorded on a Bruker Avance DRX-500 (500 MHz) or DPX-400 instruments. All signals in ^{13}C DEPT 135 spectra are positive by default, except notation with (-)/minus sign. Since ^{13}C -^{19}F decoupling is not practical on our NMR instrument, only sufficiently intensive ^{13}C signals were provided. ^{19}F spectra were provided. 1D selective NOE spectra were provided for relative configuration analysis.[81] $CDCl_3$ was purchased from Cambridge Isotope Laboratories, stored over potassium carbonate and activated 4Å M.S.. GC/MS analysis was performed on a Hewlett Packard 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). Column chromatography was carried out employing Silicycle Silica-P Flash silica gel (40-63μm). Aluminum-backed TLC plates pre-coated with F-254 silica gel were used for thin-layer analytical chromatography. Anhydrous solvents were purchased from Aldrich and distilled over sodium or calcium hydride prior to use, and stored over 4Å M.S. under inert atmosphere. 1,4-dioxane was purchased from Sigma Aldrich, distilled and stored over CaH_2 under argon atmosphere. Cyanogen bromide, ketones **1a-d**, and bromopolyfluorobenzenes were purchased from Aldrich and TCI America, used without any additional purification. **All operations involving cyanogen bromide should be performed in a well-ventilated fume hood, with appropriate personal protective equipment, including double-layered gloves and breathing masks. All reaction vessels contacted cyanogen bromide should be bleached before removing from fume hood.**

4.2. Preparation of Substrates

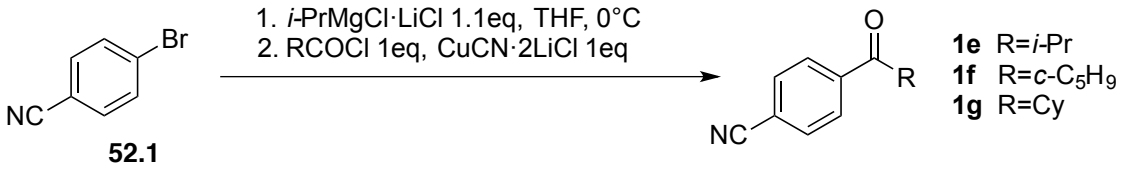
Preparation of 1d



Scheme 51.

To a solution of 1.35 mL of *p*-anisoyl chloride **51.1** (10 mmol) in 5 mL of THF was added 6.2 mL of *i*-PrMgCl·LiCl solution (1.3 M in THF, 0.8 equiv.) at -78 °C. Reaction was monitored by GC-MS and allowed to warm up to room temperature. Reaction was quenched by adding 20 mL saturated ammonium chloride aqueous solution, and filtered through a celite pad. Organic phase was separated and aqueous phase was extracted with 10 mL of ethyl acetate for 3 times. The combined organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography with hexanes/ethyl acetate, yielding colorless oil as final product.

Preparation of ketones 1e, 1f, 1g

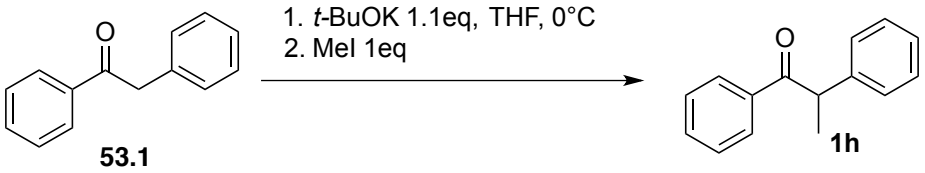


Scheme 52.

A dry, argon-flushed 50 mL flask, equipped with a magnetic stirrer and a septum, was charged with 4.3 mL *i*-PrMgCl·LiCl solution (1.3 M in THF, 1.1 equiv.). A solution of 0.63 mL 4-bromobenzonitrile (5 mmol, 1.0 equiv.) in 5 mL THF was added dropwise

at -20 °C. The progress of halogen-metal exchange was monitored by GC-MS, until bromide was mostly consumed. Then corresponding acyl chloride (1.0 equiv.) and CuCN·2LiCl solution (1 equiv., 1M in THF) was added in one portion. The reaction mixture was stirred at -20 °C for 2 hours, and then allowed to warm up to room temperature overnight. Reaction was quenched by adding 20 mL saturated ammonium chloride aqueous solution, and filtered through a celite pad. Organic phase was separated, and aqueous phase was extracted with ethyl acetate 10 mL for 3 times. The combined organic extract was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography with hexanes/ethyl acetate, yielding final product in the form of a light yellow oil.

Preparation of ketone 1h

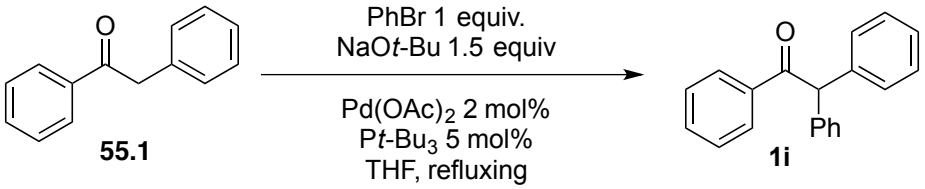


Scheme 53.

To a solution of 1.96 g deoxybenzoin (10 mmol) in 20 mL THF was added a solution of 1.23 g of *t*-BuOK (11 mmol, 1.1 equiv.) in 10 mL THF by dropwise at 0 °C, and there formed a deep yellow solution. The solution was stirred for 20 min, and then 0.62 mL of iodomethane (10 mmol, 1 equiv.) was added. The solution was stirred for 2 hours, and allowed to warm up to room temperature. Then 30 mL of hydrochloric acid (1 M in water) and 20 mL of ethyl acetate was added. The organic phase was separated, and aqueous phase was extracted by 30 mL ethyl acetate for 3 times. The combined organic

phase was washed by 30 mL brine, and dried by sodium sulfate. After filtering, removing solvent under reduced pressure, the crude product was purified by column chromatography with hexane and ethyl acetate, yielding final product in the form of a white solid.

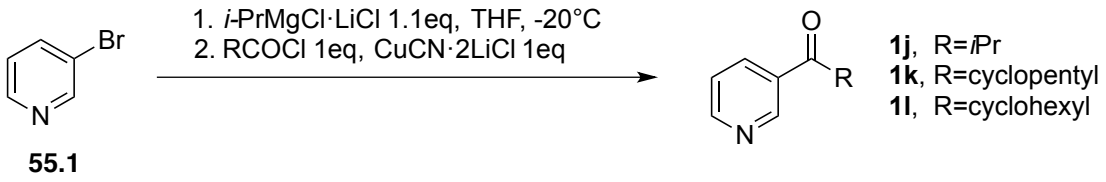
Preparation of ketone 1i



Scheme 54.

The α-arylation of ketone was following a reported procedure.[82] To an oven-dried Schlenk flask was added 1.079 g deoxybenzoin (5.5 mmol, 1.1 equiv), 22.4 mg $Pd(OAc)_2$ (0.1 mmol, 2 mol%), 30.3 mg *t*-Bu_3P (0.15 mmol, 3 mol%) and 0.675 g NaO*t*-Bu (7.5 mmol, 1.5 equiv) in a nitrogen-filled glovebox. Then 5 mL THF and 0.785 g of bromo benzene (0.526 mL, 5 mmol) were added through syringes to flask. The mixture was heated to refluxing and monitored by TLC. After 6 hours, the mixture was cooled down, and 20 mL of water was added to flask. The mixture was extracted by 10 mL of ethyl acetate for 3 times, and the combined organic phase was dried over Na_2SO_4. After removing solvent under reduced pressure, the product was purified by column chromatography, using hexane-EtOAc (10:1, v:v) as eluent and provided 0.574 g final product (42%) in the form of a light yellowish solid.

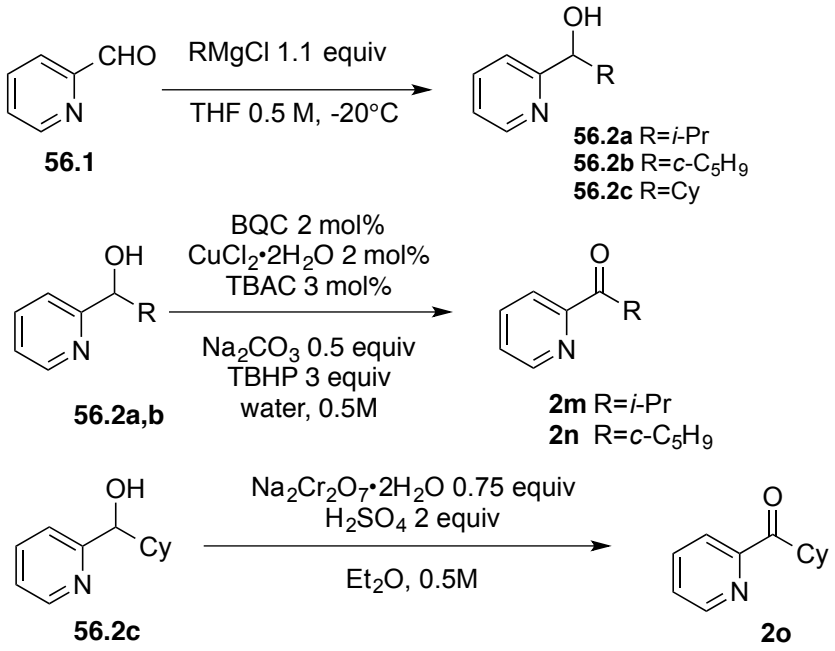
Preparation of 1j, 1k and 1l



Scheme 55.

A dry, argon flushed 50 mL flask, equipped with a magnetic stirrer and a septum, was charged with 4.3 mL of *i*-PrMgCl·LiCl solution (1.3 M in THF, 1.1 equiv.). 0.63 mL of 3-bromopyridine **55.1** (5 mmol in 5 mL THF, 1.0 equiv.) was added dropwise at -20 °C. The progress of halogen-metal exchange was monitored by GC-MS until bromide was mostly consumed, then corresponding acyl chloride (1.0 equiv.) and CuCN·2LiCl (1 equiv., 1M in THF) was added in one portion. The reaction mixture was stirred at -20 °C for 2 hours, and then left to warm up to room temperature overnight. Reaction was quenched by adding 20 mL saturated ammonium chloride aqueous solution, and filtered through a celite pad. Organic phase was separated, and aqueous phase was extracted with 10 mL ethyl acetate for 3 times. The combined organic phase was dried over sodium sulfate, and then filtered. After removing solvent under reduced pressure, the crude mixture was purified by column chromatography with hexanes/ethyl acetate, yielding light yellow oil as final product.

Preparation of ketones 1m, 1n, 1o



Scheme 56.

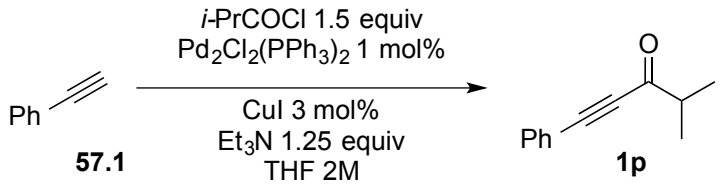
An oven-dried flask was charged with argon, and added 1.1 g of 2-pyridinecarboxaldehyde **56.1** (10 mmol, 1 equiv.) and 20 mL THF. The solution was cooled down to -20 °C, and a solution of corresponding Grignard reagent (1.1 equiv.) was added dropwisely. The mixture was allowed to warm up after 3 hours and quenched after 6 hours by adding saturated ammonium chloride solution. The reaction mixture was extracted with 20 mL ethyl acetate for 3 times. The combined organic extract was dried over sodium sulfate, filtered, and concentrated under reduced pressure, yielding deep red liquid as intermediate 2-pyridinyl alcohols **56.2a-c**. The crude products were directly transferred to next reaction without any purification.

The oxidation of alcohols to corresponding ketones was following a reported procedure.[83] Under air atmosphere, 20 mL distilled water, 8.5 mg $CuCl_2$•$2H_2O$ (0.05 mmol), 210 mg Na_2CO_3 (2.5 mmol), and 24 mg 2,2'-biquinoline-4,4-dicarboxylic acid

dipotassium salt trihydrate (BQC, 0.05 mmol), and 42 mg TBAC (0.15 mmol) were added to a flask. After stirring for 5 minutes, crude alcohol **56.2a** or **56.2b** (approx. 10 mmol) was added. To this purple mixture was added 2 mL TBHP solution (70% in water, 15 mmol). Reaction was stirred under room temperature, monitored by GC-MS, until alcohol was complete consumed. 2 g Sodium sulfite was added to reaction mixture to quench excess TBHP, and the reaction mixture was extracted by 20 mL ethyl acetate for 3 times, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and product was purified by column chromatography (hexane/EtOAc 4:1), yielding corresponding ketone in the form of yellowish oil with 44% (**2m**) and 33% (**2n**) yield.

A solution of crude 1.65 g **56.2c** (approx. 8.6 mmol) in 20 mL diethyl ether was cooled to 0 °C, and a solution of 1.505 g $Na_2Cr_2O_7 \cdot 2H_2O$ (5 mmol) and 1.91 g H_2SO_4 in 20 mL water was added dropwise. After 6 hours, reaction was quenched by saturated ammonium chloride solution, extracted by 30 mL EtOAc for 3 times, dried over sodium sulfate, filtered through a celite pad, and concentrated under reduced pressure. Final product ketone was purified by column chromatography (hexane/EtOAc 4:1), yielding 1.1 g **2o** (65%) in the form of a light yellow oil.

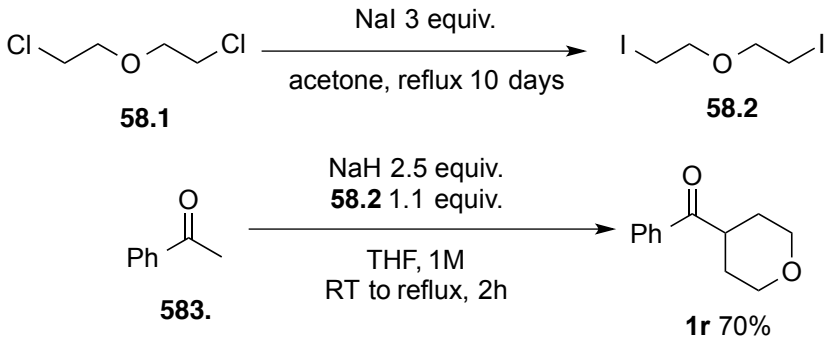
Preparation of ketone 1p



Scheme 57.

To a solution of the *i*-PrCOCl (3 mmol) and phenyl acetylene **57.1** (2 mmol) in anhydrous THF (4 mL), under a N_2 atmosphere, was added $PdCl_2(PPh_3)_2$ (12.6 mg, 0.9 mol%) then CuI (11.4 mg, 3 mol%). After 1 min of stirring, Et_3N (2.5 mmol, distilled over KOH) was added, and the reaction left to stir for 40 min at RT. After 2 hours, reaction was quenched by adding 10 mL water, and then diluted by 20 mL diethyl ether. Aqueous phase was extracted by dichloromethane, and combined organic phase was dried over sodium sulfate. After removing solvent under reduced pressure, final product was purified by column chromatography (hexane:EtOAc 20:1), yielding 0.454 g **1p** (52%) in the form of a clear liquid.

Preparation of 1r

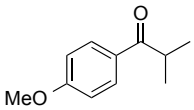


Scheme 58.

To a solution of bis(2-chloroethyl)ether **58.1** (11.7 mL, 100 mmol) in acetone (40 mL, 2.5 M) was added sodium iodide (45 g, 300 mmol). The mixture was heated to reflux and reaction was monitored by GC-MS. After 10 days, **58.1** was completely consumed. The mixture was filtered through a celite pad. The celite pad was further washed by 40 mL pentane. To the combined filtrate, 20 mL water was added and extracted by 20 mL pentane for 3 times. Combined organic extract was washed with water (10 mL), 20 mL saturated sodium sulfite aqueous solution (to eliminate iodine), and 10 mL brine. Extract

was dried by Na_2SO_4, filtered, and concentrated under reduced pressure. **58.2** was stored over copper dust, and used in next step without further purification.

To an argon-flushed Schlenk flask was loaded sodium hydride (0.6 g, 25 mmol). 10 mL of THF was added to the flask followed by addition of a solution of acetophenone **58.3** (1.1 mL, 10 mmol) in 2 mL of THF. The mixture was cooled down to 0 °C, and **58.2** (3.58 g, 11 mmol) was added in one portion. The reaction mixture was gently heated to 65 °C and cooled down to room temperature for 2 hours. The mixture was heated to reflux for another 2 hours. The final mixture was poured into ice water, extracted by pentane (10 mL X 3). The combined organic phase was washed with brine and dried over sodium sulfate. After filtering off desiccant and removing solvent, crude **1r** was purified by column chromatography using 20:1 to 10:1 hexane/ethyl acetate mixture as eluent. Spectra data was identical to report.[84]

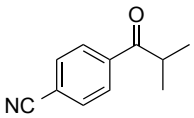


1d

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.94 (m, 2H), 6.95-6.93 (m, 2H), 3.87 (s, 3H), 3.56-3.48 (spt, J = 5.0 Hz, 1H), 1.21-1.20 (d, J = 5.0 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.05, 163.26, 130.55, 129.18, 113.74, 55.44, 34.95, 19.30

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 130.99, 114.16, 55.87, 35.36, 19.74

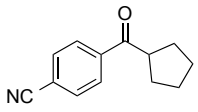


1e

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04-8.02 (m, 2H), 7.78-7.76 (m, 2H), 3.57-3.49 (spt, J = 5.0 Hz, 1H), 1.23-1.21 (d, J = 5.0 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.99, 139.32, 132.81, 132.51, 128.71, 117.97, 116.05, 35.64, 18.84

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 132.95, 129.15, 36.27, 19.28

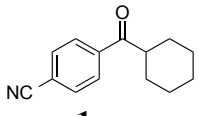


1f

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02-8.01 (m, 2H), 7.74-7.72 (m, 2H), 3.69-3.62 (m, 1H), 1.94-1.81 (m, 4H), 1.71-1.59 (m, 4H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.24, 139.96, 132.40, 128.84, 118.00, 115.93, 46.66, 29.47, 26.23

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 132.84, 129.27, 47.07, 30.16 (-), 26.67 (-)

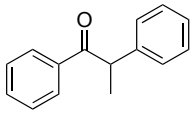


1g

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02-8.00 (m, 2H), 7.77-7.75 (m, 2H), 3.24-3.19 (m, 1H), 1.87-1.84 (m, 4H), 1.76-1.73 (m, 1H), 1.52-1.35 (m, 4H), 1.31-1.23 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.36, 139.48, 132.48, 128.64, 118.00, 116.00, 45.96, 29.17, 25.81, 25.68.

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 132.92, 129.09, 46.38, 29.17 (-), 26.23 (-), 26.11 (-)

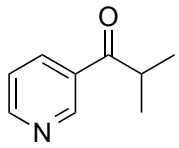


1h

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03-8.01 (m, 2H), 7.49-7.45 (m, 1H), 7.40-7.31 (m, 6H), 7.24-7.22 (m, 1H), 4.75-4.72 (q, J = 5.0Hz, 1H), 1.60-1.59 (d, J = 5.0 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.32, 141.57, 136.53, 132.85, 129.06, 128.84, 128.56, 127.84, 126.98, 47.93, 19.62

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 133.27, 129.48, 129.26, 128.97, 128.26, 127.39, 48.36, 20.04.

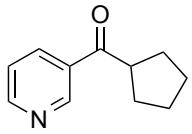


1j

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.77 (s, 1H), 8.24-8.22 (m, 1H), 7.44-7.41 (m, 1H). 3.56-3.48 (spt, *J* = 5.0 Hz, 1H), 1.24-1.23 (d, *J* = 5.0 Hz, 6H)

^{13}C (126 MHz, $CDCl_3$) δ 203.13, 153.17, 149.70, 135.77, 131.42, 123.73, 35.95, 18.82

^{13}C-DEPT (126 MHz, $CDCl_3$) δ 153.60, 150.13, 136.22, 124.17, 36.37, 16.26

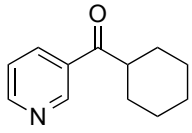


1k

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.72 (s, 1H), 8.21-8.19 (m, 1H), 7.39-7.36 (m, 1H), 3.68-3.61 (m, 1H), 1.92-1.88 (m, 4H), 1.68-1.63 (m, 4H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 210.39,153.90, 149.95, 135.69, 132.05, 123.56, 467.73, 29.65, 26.23

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 153.53, 150.38, 136.14, 124.01, 47.14, 30.07(-), 26.67(-)

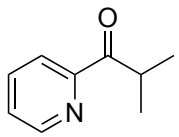


1l

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (br, s, 1H), 8.73-8.72 (m, 1H), 8.19-8.17 (m, 1H), 7.40-7.37 (m, 1H), 3.22-3.19 (m, 1H), 1.89-1.80 (m, 4H), 1.73-1.69(m, 1H), 1.50-1.32 (m, 4H), 1.27-1.20 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.48, 153.12, 149.68, 135.63, 131.49, 123.64, 46.05, 29.12, 25.83, 25.68

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 153.57, 150.11, 136.08, 124.09, 46.46, 29.55 (-), 26.25 (-), 26.11 (-)

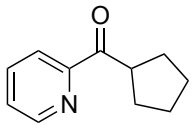


1m

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03-8.01 (d, J = 4.4 Hz, 1 H), 8.05 (m, 1 H), 7.84 (m, 1 H), 7.40 - 7.51 (m, 1 H), 4.12 (spt, J = 6.6 Hz, 1 H), 1.22 (d, J = 6.6 Hz, 6 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 205.65, 152.99, 148.82, 136.83, 126.77, 122.42, 34.20, 18.63.

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 149.26, 137.29, 127.24, 122.86, 34.63, 19.07.

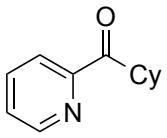


1n

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 - 8.77 (m, 1 H) 7.99 - 8.11 (m, 1 H) 7.83 (m, 1 H) 7.45 (m, 1 H) 4.25 (m, 1 H) 1.92 - 2.03 (m, 2 H) 1.78 - 1.88 (m, 2 H) 1.62 - 1.77 (m, 4 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 204.209, 153.639, 148.863, 136.11, 126.669, 122.307, 45.279, 29.728, 26.290

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 149.303, 137.186, 127.155, 122.768, 14.690, 30.154 (-), 26.730 (-)



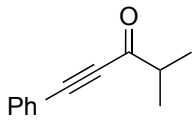
1o

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 - 8.73 (m, 1 H), 7.99 - 8.07 (m, 1 H), 7.84-7.82 (m, 1 H), 7.46-7.43 (m, 1 H), 3.88, (m, 1 H), 1.87 - 1.94 (m, 2 H), 1.77 - 1.86 (m, 2 H), 1.70 - 1.77 (m, 1 H), 1.38 - 1.51 (m, 4 H), 1.19 - 1.33 (m, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 204.954, 153.14, 148.80, 136.83, 126.71, 122.41, 43.95, 28.88, 26.08, 25.75.

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 149.233, 137.287, 127.171, 122.853,

44.363, 29.284 (-), 26.484 (-), 26.168 (-)



1p

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 - 7.60 (m, 2 H), 7.42 - 7.48 (m, 1 H), 7.34 - 7.41 (m, 2 H), 2.76 (spt, J = 6.7 Hz, 1 H), 1.27 (d, J = 6.7 Hz, 6 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 192.064, 132.973, 130.558, 128.582, 120.170, 91.529, 86.847, 43.077, 18.012

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 133.40, 130.99, 129.00, 43.52, 18.45

4.3. Synthesis of Epoxynitriles

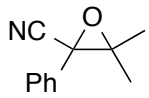
Preparation of Stock Solution of Cyanogen Bromide, 10 M in THF

In a well-ventilated fume hood, to a graduated 20 mL threaded vial placed on a balance was loaded 10.5 g cyanogen bromide. This vial was rapidly vacuumed/backfilled by argon over a high vacuum manifold three times. Dry THF was added to vial under a positive flow of argon, until the level of liquid reached the graduation of 10 mL. This 10 M THF solution of cyanogen bromide can be stored in a -20 °C freezer over 6 months without significant hydrolysis.

Procedure of epoxidation

To an oven dried 2.5 mL Wheaton vial was loaded ketone (0.5 mmol) and the vessel was vacuumed and backfilled by argon 3 times. 1.1 mL of anhydrous DMF was added and stirred until ketone was completely dissolved. Then 0.8 mL LiHMDS solution (1.0 M in THF) was added and stirred 5 minutes followed by adding 0.1 mL of 10 M BrCN solution in THF (see previous section). The final solution was stirred at room

temperature for 15 minutes and quenched by 10 mL of water and 10 mL ethyl acetate was added. Organic phase was separated and aqueous phase was extracted by ethyl acetate 10 mL for 3 times. Combined organic phase was dried over sodium sulfate. After removing solvent under reduced pressure, crude product was purified by column chromatography with hexanes/ethyl acetate. The silica gel should be pre-treated by triethylamine to prevent product decomposing on column.



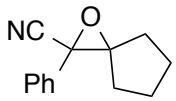
2a

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.40 (m, 5H), 1.75 (s, 3H), 1.09 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.80, 129.34, 128.70, 126.56, 118.31, 67.03, 58.72, 22.71, 18.49

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 129.35, 128.71, 126.56, 22.72, 18.50

HR EI MS: *m/z* 173.8436, calcd for C11H11ON 173.8407



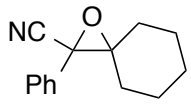
2b

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.40 (m, 5H), 2.38-2.34 (m, 1H), 2.01-1.98 (m, 1H), 1.94-1.88 (m, 1H), 1.86-1.74 (m, 2H), 1.64-1.53 (m, 2H), 1.46-1.140 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.92, 129.24, 128.67, 125.98, 117.95, 78.54, 57.63, 32.62, 28.84, 25.21

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 129.67, 129.10, 126.41, 33.06 (-), 29.27 (-), 25.66 (-)

HR EI MS: *m/z* 199.10001, calcd for C13H13ON 199.09972



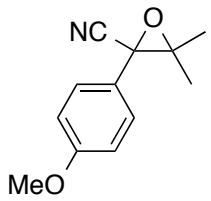
2c

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.40 (m, 5H), 2.02-1.97 (m, 2H), 1.94-1.88 (m, 1H), 1.79-1.71 (m, 1H), 1.60-1.53 (m, 2H), 1.51-1.45 (m, 1H), 1.41-1.36 (m, 1H), 1.35-1.29 (m, 1H), 1.24-1.20 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.60, 129.17, 128.56, 126.56, 118.14, 71.19, 58.81, 33.09, 28.60, 25.08, 24.94, 24.34

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 129.61, 128.99, 126.98, 33.51 (-), 29.02 (-), 25.51 (-), 25.36 (-), 24.78 (-)

HR EI MS: *m/z* 213.11635, calcd for C14H15ON 213.11537



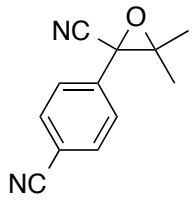
2d

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.34 (m, 2H), 6.94-6.92 (m, 2H), 3.83 (s, 3H), 1.73 (s, 3H), 1.10 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.30, 127.87, 123.70, 118.38, 114.09, 66.88, 58.51, 55.37, 22.61, 18.43

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 128.29, 114.51, 55.80, 23.06, 18.86

HR EI MS: *m/z* 203.9578, calcd for C12H13NO2 203.09463



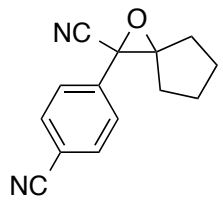
2e

1 H NMR (500 MHz, $CDCl_3$) δ 7.75-7.73 (m, 2H), 7.59-7.58 (m, 2H), 1.78 (s, 3H), 1.10 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.92, 123.50, 127.48, 117.91, 117.21, 113.54, 67.83, 58.15, 22.71, 18.44

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 132.94, 127.90, 23.14,

18.86 HR EI MS: *m/z* 198.08003, calcd for C12H10N2O 198.07932



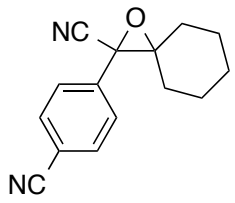
2f

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73-7.71 (m, 2H), 7.56-7.54 (m, 2H), 2.38-2.32 (m, 1H), 2.03-1.98 (m, 1H), 1.95-1.88 (m, 1H), 1.87-1.76 (m, 2H), 1.67-1.52 (m, 2H), 1.39-1.33 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.11, 132.52, 126.91, 117.96, 116.94, 113.38, 79.40, 57.05, 32.69, 28.83, 25.23, 25.14

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 132.95, 127.33, 33.13 (-), 29.25 (-), 25.67 (-), 25.58 (-)

HR EI MS: *m/z* 224.09523, calcd for C14H12N2O 224.09497



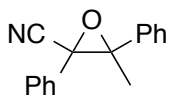
2g

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.71 (m, 2H), 7.59-7.57 (m, 2H), 2.02-1.98 (m, 2H), 1.89-1.88 (m, 1H), 1.74-1.70 (m, 1H), 1.56-1.54 (m, 2H), 1.48-1.46 (m, 1H), 1.36-1.33 (m, 1H), 1.30-1.23 (m, 1H), 1.16-1.14 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.75, 132.41, 127.49, 117.94, 117.14, 113.39, 72.16, 56.27, 30.40, 28.54, 25.01, 24.73, 24.35

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 132.85, 127.92, 33.47 (-), 28.95 (-), 24.44 (-), 25.16 (-), 24.78 (-)

HR EI MS: *m/z* 238.11055, calcd for C15H14N2O 238.11062



2h

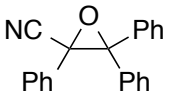
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57-7.55 (m, 3H), 7.49-7.42 (m,4H), 7.25-7.23 (m, 2H), 7.18-7.14 (m, 8H), 2.09 (s, 3H), 1.48

(s, 2.2H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.64, 135.54, 131.61, 130.90, 129.57, 128.98, 128.84, 128.67, 128.14, 1.8.08, 126.63, 126.50, 125.93, 117.92, 117.39, 71.05, 70.07, 60.84, 59.65, 23.59, 18.39

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 130.01, 129.42, 129.27, 129.10, 128.58, 128.51, 127.05, 126.91, 126.36, 24.03, 18.81

HR EI MS: *m/z* 235.09929, calcd for C16H13NO 235.09972



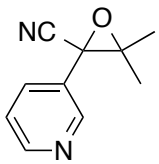
2i

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02-8.00 (m, 1H), 7.59-7.58 (m, 1H), 7.44-7.39 (m, 3H), 7.33-7.17 (m, 10H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.49, 133.42, 129.91, 129.55, 129.51, 129.36, 128.95, 128.77, 128.55, 127.58, 127.30, 126.86, 125.47, 75.00, 65.76

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 129.91, 129.55, 129.51, 128.95, 128.77, 128.55, 127.58, 127.30, 126.86,

HR EI MS: *m/z* 297.11669, calcd for C21H15NO 297.11537



2j

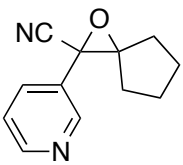
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 -8.67 (m, 2 H), 7.76 (dd, *J* = 8.0, 1.97 Hz, 1 H), 7.37 (dd, *J* = 8.0, 4.89 Hz, 1 H), 1.78 (s, 3 H) 1.13 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.64, 148.09, 134.34, 128.02, 123.28, 117.39, 67.37, 56.96, 22.60, 18.57

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 151.08, 148.50, 134.79,

123.74, 23.06, 19.00

HR EI MS: *m/z* 174.07876, calcd for C10H10N2O 174.07932



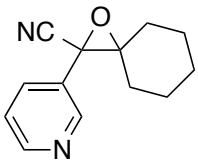
2k

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70-8.65 (m, 2 H), 7.74 - 7.72 (m, 1 H), 7.37-7.35 (mz, 1 H), 2.39-2.33 (m, 1H), 2.60-2.00 (m, 1H), 1.97-1.91 (m, 1H), 1.89-1.78 (m, 2H), 1.68-1.56 (m, 2H), 1.46-1.40 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.57, 147.64, 133.81, 128.09, 123.27, 117.08, 109.25, 79.06, 55.88, 40.72, 32.63, 28.90, 25.25

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 150.99, 148.06, 134.25, 123.17, 33.06 (-), 23.33 (-), 25.67 (-)

HR EI MS: *m/z* 200.09515, calcd for C12H12N2O 200.09497



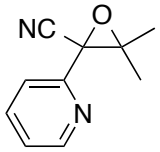
2l

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 - 8.68 (m, 2 H), 7.79-7.77 (dt, *J* = 7.9, 1.8 Hz, 1 H), 7.39-7.26 (dd, *J* = 7.4, 4.9 Hz, 1 H), 2.05-1.99 (m, 1H), 1.95-1.90 (m, 1H), 1.79-1.73 (m, 1H), 1.59-1.56 (m, 2H), 1.54-1.49 (m, 1H), 1.43-1.37 (m, 1H), 1.36-1.30 (m, 1H), 1.25-1.19 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.53, 148.06, 134.35, 123.25, 117.32, 71.70, 57.07, 32.99, 28.66, 25.00, 24.79, 24.33

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 150.97, 148.47, 134.80, 123.70, 33.42 (-), 29.07 (-), 25.44 (-), 25.22 (-), 24.76 (-),

HR EI MS: *m/z* 214.11067, calcd for C13H14N2O 214.11062



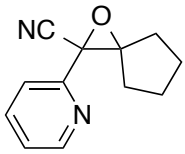
2m

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65-8.64 (m, 1H), 7.75-7.73 (m, 1H), 7.35-7.32 (m, 2H), 1.76 (s, 3H), 1.12 (s, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.69, 149.75, 136.86, 124.05, 121.24, 117.39, 67.17, 59.61, 22.64, 18.38

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 150.173,137.291, 124.484, 121.660, 23.057, 18.776

HR EI MS: *m/z* 174.07899, calcd for C10H10N2O 174.07932



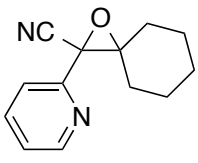
2n

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65-8.64 (m, 1H), 7.75-7.71 (m, 1H), 7.32-7.27 (m, 2H), 2.40-2.37 (m, 1H), 2.02-2.00 (m, 1H), 1 .181-1.78 (m, 3H), 1.60-1.56 (m, 2H), 1.44-1.43 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.928, 149.686, 36.950, 123.971, 120.196, 117.202, 78.537, 58,58.493, 32.612, 28.870, 25.239, 25.082

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 150.110, 127.379, 124.398, 120.620, 33.038 (-), 29.293 (-), 25.667 (-), 25.510 (-)

HR EI MS: *m/z* 200.09466, calcd for C12H12N2O 200.09497



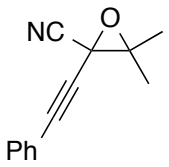
2o

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66-8.65 (m, 1H), 7.66-7.73 (m, 1H), 7.38-7.30 (m, 2H), 2.07-2.05 (m, 2H), 2.01-2.00 (m, 2H), 1.56-1.38 (m, 5H), 1.26-1.25 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.536, 149.679, 136.681, 123.931, 121.410, 117.303, 71.489, 59.725, 33.033, 28.693, 24.887, 24.276

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 150.108,137.120, 124.364, 121.835, 33.458 (-), 29.109 (-), 25.300 (-), 24.704 (-)

HR EI MS: *m/z* 214.10974, calcd for C13H14N2O 214.11062



2p

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H), 7.41-7.40 (m, 1H), 7.37-7.34 (m, 2H), 1.670 (s, 3H), 1.609 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 132.14, 129.85, 128.50, 120.42, 115.42, 87.74, 79.56, 67.65, 47.67, 21.38, 20.49.

^{13}C-DEPT NMR (126 MHz, $CDCl_3$) δ 132.556, 130.266, 128.925, 21.795, 20.903

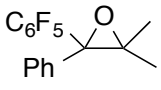
HR EI MS: *m/z* 197.08438, calcd for C13H11NO 197.08407

4.4. Synthesis of Perfluoroaryloxiranes

To an oven dried conical vial equipped with a magnetic stirring bar and a PTFE-topped screw cap, ketone (0.5 mmol) was added, and the vessel was evacuated and backfilled by argon 3 times. Then anhydrous 1,4-dioxane (2.5 mL) was added and the mixture was stirred until the ketone was completely dissolved. NaHMDS (0.6 mL, 1M in THF) was subsequently added to the solution of ketone aforementioned and the mixture was stirred for 5 minutes. Then PFPBr or other other arylbromide was added drop wise to the mixture and the reaction mixture was stirred for another 15 minutes and the

precipitation of sodium bromide was observed. Reaction mixture was filtered through a silica or zeolite pad, washed with 50 mL diethyl ether. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography of silica gel with hexane/ethyl acetate.

Bromide **3b, 3c** was dissolved in THF (1M) then injected into enolate solution.



3a

90%, clear oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 ~ 7.46 (m, 2 H), 7.35 ~ 7.41 (m, 2 H), 7.27 ~ 7.34 (m, 1 H), 1.43 (s, 3 H), 1.20 (s, 3 H)

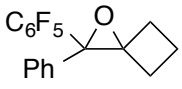
^{13}C NMR (126 MHz, $CDCl_3$) δ 138.07, 128.92, 128.55, 126.61, 64.89, 64.72, 22.42, 20.72

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 128.92, 128.57, 126.60, 22.42, 20.73

^{19}F NMR (471 MHz, $CDCl_3$) δ: -142.27 ~ -141.75 (m, 2 F), -156.33 ~ -155.97 (m, 1 F), -162.32 ~ -161.96 (m, 1 F), -163.74 ~ -163.33 (m, 1 F)

HR EI MS: *m/z* 314.07133 calcd. for $C_{16}H_{11}OF_5$ 314.07302

TLC: hexane/ethyl acetate 20:1 R_f=0.5. Column chromatography: hexane/ethyl acetate 100:1



3b

>99%, clear oil

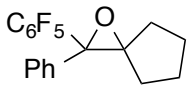
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 ~ 7.44 (m, 3 H), 7.24 ~ 7.31 (m, 2 H), 2.45 ~ 2.59 (m, 2 H), 2.19 ~ 2.29 (m, 1 H), 2.03 ~ 2.12 (m, 1 H), 1.91 ~ 2.00 (m, 1 H), 1.81 ~ 1.91 (m, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.61, 128.83, 128.69, 126.30, 71.05, 62.53, 31.00, 29.31, 12.94

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 128.83, 128.70, 126.30, 31.00 (-), 29.31 (-), 12.94 (-)

^{19}F NMR (471 MHz, $CDCl_3$) δ: -141.91 (br. s., 2 F), -156.23 ~ -154.31 (m, 1 F), -162.59 (br. s., 2 F)

HR EI MS: *m/z* 326.07181 calcd. for $C_{17}H_{11}OF_5$ 326.07302



3c

74%, clear oil

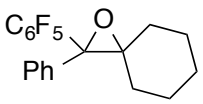
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 ~ 7.43 (m, 2 H), 7.34 ~ 7.41 (m, 2 H), 7.27 ~ 7.34 (m, 1 H), 1.74 ~ 1.95 (m, 4 H), 1.64 ~ 1.73 (m, 2 H), 1.58 ~ 1.63 (m, 1 H), 1.46 ~ 1.55 (m, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.08, 128.88, 128.54, 126.30, 76.29, 63.26, 32.70, 30.69, 25.66, 25.23

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 138.08, 128.88, 128.54, 126.30, 76.29, 63.26, 32.70 (-), 30.69 (-), 25.66 (-), 25.23 (-)

^{19}F NMR (471 MHz, $CDCl_3$) δ: -141.93 ~ -141.58 (m, 1 F), -142.29 ~ -141.96 (m, 1 F), -156.65 ~ -155.24 (m, 1 F), -162.45 ~ -161.00 (m, 1 F), -163.94 ~ -162.98 (m, 1 F)

HR EI MS: *m/z* 340.08948 calcd. for $C_{18}H_{13}OF_5$ 340.09867



3d

70%, clear oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (m, 2 H), 7.34 ~ 7.39 (m, 2

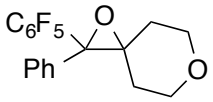
H), 7.26 ~ 7.33 (m, 1 H), 1.86 ~ 1.96 (m, 1 H), 1.75 ~ 1.83 (m, 1 H), 1.51 ~ 1.75 (m, 5 H), 1.29 ~ 1.49 (m, 2 H), 1.12 ~ 1.25 (m, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.88, 128.88, 128.49, 126.66, 126.63, 68.48, 65.79, 32.25, 30.60, 25.76, 24.64, 24.50

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 128.89, 128.51, 126.63, 32.22 (-), 30.60 (-), 25.75 (-), 24.66 (-), 24.50 (-)

^{19}F NMR (471 MHz, $CDCl_3$) δ: -141.29 ~ -141.22 (m, 1 F), -142.07 ~ -141.84 (m, 1 F), -156.42 ~ -156.24 (m, 1 F), -162.31 ~ -161.99 (m, 1 F), -163.76 ~ -163.41 (m, 1 F)

HR EI MS: *m/z* 354.10497 calcd. for $C_{19}H_{15}OF_5$ 354.10432



3e

66%, clear oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2 H), 7.35 ~ 7.42 (m, 2 H), 7.30 ~ 7.35 (m, 1 H), 3.98 ~ 4.05 (m, 1 H), 3.92 (m 1 H), 3.66 ~ 3.82 (m, 2 H), 2.21 ~ 2.37 (m, 1 H), 1.91 (m, 1 H), 1.21 ~ 1.32 (m, 1 H), 1.13 (m, 1 H)

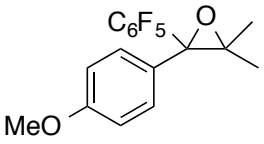
^{13}C NMR (126 MHz, $CDCl_3$) δ 136.85, 129.04, 128.85, 126.63, 66.35, 66.28, 66.17, 65.38, 32.85, 31.29

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 129.05, 128.85, 126.63, 66.36 (-), 66.29 (-), 32.83 (-), 31.28 (-)

^{19}F NMR (471 MHz, $CDCl_3$) δ: -141.71 ~ -141.56 (m, 1 F), -141.85 ~ -141.72 (m, 1 F), -155.63 ~ -155.05 (m, 1 F), -161.99 ~ -

161.21 (m, 1 F), -163.32 ~ -162.31 (m, 1 F)

HR EI MS: *m/z* 356.08457 calcd. for $C_{18}H_{13}O_2F_5$ 356.08357



3f

88%, clear oil

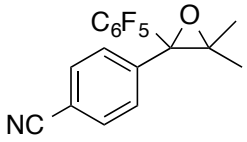
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 2 H), 6.82 ~ 6.95 (m, 2 H), 3.81 (s, 3 H), 1.41 (d, *J* = 2.6 Hz, 3 H), 1.20 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.80, 130.20, 127.86, 114.32, 64.70, 55.64, 22.39, 20.64

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 127.86, 114.30, 55.66, 22.39, 22.36, 20.66

^{19}F NMR (471 MHz, $CDCl_3$) δ: -143.12 ~ -141.69 (m, 2 F), -157.51 ~ -155.50 (m, 1 F), -162.70 ~ -161.38 (m, 1 F), -164.50 ~ -163.10 (m, 1 F)

HR EI MS: *m/z* 344.08460 calcd. for $C_{17}H_{13}O_2F_5$ 344.08358



3g

65%, clear oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 ~ 7.70 (m, 2 H), 7.57 ~ 7.62 (m, 2 H), 1.44 (s, 3 H), 1.18 (s, 3 H)

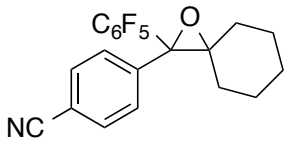
^{13}C NMR (126 MHz, $CDCl_3$) δ 143.14, 132.83, 127.52, 118.64, 112.70, 65.35, 64.28, 22.32, 22.29, 20.64

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 132.85, 127.55, 22.31, 20.66

^{19}F NMR (471 MHz, $CDCl_3$) δ: -142.89 ~ -140.84 (m, 2 F), -155.63 ~ -153.35 (m, 1 F), -161.76 ~ -160.31 (m, 1 F), -163.81 ~ -

162.00 (m, 1 F)

HR EI MS: *m/z* 339.06656 calcd. for $C_{17}H_{10}ONF_5$ 339.06826



3h

82%, clear oil

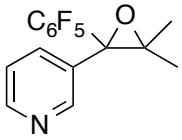
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 ~ 7.70 (m, 2 H), 7.57 ~ 7.62 (m, 2 H), 1.86 ~ 1.98 (m, 1 H), 1.75 ~ 1.82 (m, 1 H), 1.54 ~ 1.75 (m, 5 H), 1.50 ~ 1.53 (m, 1 H), 1.23 ~ 1.46 (m, 3 H), 1.02 ~ 1.14 (m, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.97, 132.79, 127.58, 118.67, 112.60, 69.19, 65.19, 32.10, 30.56, 25.58, 24.58, 24.45

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 132.79, 127.58, 32.11 (-), 30.56 (-), 25.58 (-), 24.58 (-), 24.45 (-).

^{19}F NMR (471 MHz, $CDCl_3$) δ: -141.31 ~ -140.50 (m, 1 F), -142.19 ~ -141.44 (m, 1 F), -155.16 ~ -154.05 (m, 1 F), -161.79 ~ -160.86 (m, 1 F), -163.35 ~ -162.21 (m, 1 F)

HR EI MS: *m/z* 379.09796 calcd. for $C_{20}H_{14}ONF_5$ 379.09956



3i

53%, yellowish oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.58 ~ 8.57 (m, 1H), 7.80-7.79 (d, J = 8.0 Hz), 7.33-7.29 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H)

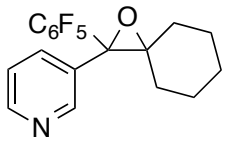
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.95, 148.36, 134.41, 133.97, 123.70, 64.98, 63.07, 22.32, 22.29, 20.75

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 149.97, 148.36,

148.33, 134.41, 123.72, 22.32, 22.29, 20.76

^{19}F NMR (471 MHz, $CDCl_3$) δ: -142.99 ~ -141.06 (m, 2 F), -155.53 ~ -153.80 (m, 1 F), -161.90 ~ -160.79 (m, 1 F), -163.16 ~ -162.21 (m, 1 F)

HR EI MS: *m/z* 315.06799 calcd. For $C_{15}H_{10}ONF_5$ 315.06826



3j

62%, yellowish oil

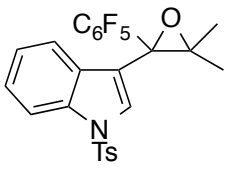
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 ~ 8.77 (m, 1 H), 8.56 (dd, *J* = 5.0, 1.7 Hz, 1 H), 7.80 (d, *J* = 8.1 Hz, 1 H), 7.23 ~ 7.40 (m, 1 H), 1.84 ~ 1.97 (m, 1 H), 1.76 ~ 1.81 (m, 1 H), 1.55 ~ 1.75 (m, 5 H), 1.23 ~ 1.47 (m, 3 H), 1.09 ~ 1.18 (m, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.88, 148.36, 148.33, 134.48, 133.77, 123.67, 68.78, 63.97, 32.10, 30.58, 25.61, 24.58, 24.44

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 149.88, 148.35, 134.49, 123.69, 32.11 (-), 30.58 (-), 25.61 (-), 24.58 (-), 24.45 (-)

^{19}F NMR (471 MHz, $CDCl_3$) δ: -141.51 ~ -141.16 (m, 1 F), -142.18 ~ -141.84 (m, 1 F), -155.31 ~ -154.92 (m, 1 F), -161.77 ~ -161.14 (m, 1 F), -163.22 ~ -162.60 (m, 1 F)

HR EI MS: *m/z* 355.09916 calcd. for $C_{18}H_{14}OF_5N$ 355.09956



3k

60%, yellowish wax

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.4 Hz, 1 H), 7.74 ~ 7.80 (m, 3 H), 7.72 (s, 1 H), 7.32 ~ 7.39 (m, 1 H), 7.26 ~ 7.31 (m, 1 H), 7.23 (d, *J* = 8.1 Hz, 2 H), 2.36 (s, 3 H), 1.45 (s, 3 H), 1.27

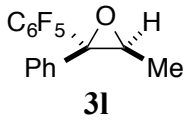
(s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.63, 135.38, 135.29, 130.29, 128.82, 127.23, 125.52, 125.42, 124.16, 120.83, 120.29, 114.20, 77.67, 77.42, 77.17, 64.30, 60.29, 22.07, 22.04, 21.94, 20.95

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 130.29, 127.24, 125.52, 125.44, 124.16, 120.83, 114.22, 110.00, 22.07, 22.04, 21.94, 20.95

^{19}F NMR (471 MHz, $CDCl_3$) δ: -141.64 ~ -141.34 (m, 1 F), -141.97 ~ -141.66 (m, 1 F), -155.79 ~ -155.38 (m, 1 F), -162.09 ~ -161.63 (m, 1 F), -163.45 ~ -162.75 (m, 1 F)

HR EI MS: *m/z* 507.09149 calcd. for $C_{25}H_{18}O_3NF_5S$ 507.09276



3l

81%, clear oil

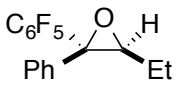
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 ~ 7.45 (m, 2 H), 7.37 ~ 7.41 (m, 2 H), 7.32 ~ 7.37 (m, 1 H), 3.58 (q, *J* = 5.1 Hz, 1 H), 1.21 (d, *J* = 5.1 Hz, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.48, 144.52, 140.64, 138.79, 136.92, 135.98, 128.82, 128.72, 127.08, 125.70, 60.55, 59.26, 14.10

^{13}C NMR-DEPT 135 (126 MHz, $CDCl_3$) δ 128.82, 128.72, 127.08, 60.57, 14.10

^{19}F NMR (471 MHz, $CDCl_3$) δ: -143.30 ~ -141.83 (m, 2 F), -156.05 ~ -155.11 (m, 1 F), -163.62 ~ -162.47 (m, 2 F)

HR EI MS: *m/z* 300.05688 calcd. for $C_{15}H_9OF_5$ 300.05737



3m

85%, clear oil

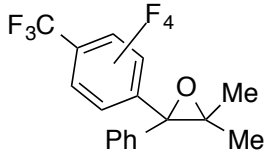
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 ~ 7.47 (m, 2 H), 7.31 ~ 7.42 (m, 3 H), 3.42 (dd, *J* = 6.2 Hz, 1 H), , 1.46 ~ 1.58 (m, 1 H), 1.29 ~ 1.41 (m, 1 H), 1.03 (dd, *J* = 7.7 Hz, 4 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.48, 144.49, 142.67, 140.64, 138.94, 136.92, 136.05, 128.67, 126.99, 125.72, 65.85, 59.33, 23.97, 21.67, 10.86, 9.79

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 129.07, 128.77, 128.76, 128.67, 126.99, 125.72, 65.85, 21.67 (-),9.81

^{19}F NMR (471 MHz, $CDCl_3$) δ: -143.23 ~ -141.96 (m, 2 F), -156.19 ~ -155.29 (m, 1 F), -163.32 ~ -162.84 (m, 2 F)

HR EI MS: *m/z* 314.07324 calcd. for $C_{16}H_{11}OF_5$ 314.07324



3n

80%, clear oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 2 H), 7.28 ~ 7.41 (m, 3 H), 1.43 (s, 3 H), 1.21 (s, 3 H)

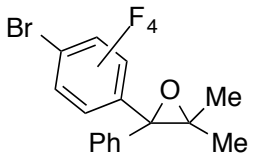
^{13}C NMR (126 MHz, $CDCl_3$) δ 137.23, 129.08, 128.88, 126.69, 65.08, 64.82, 22.42, 20.72

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 129.08, 128.88, 126.70, 22.42, 20.73

^{19}F NMR (471 MHz, $CDCl_3$) δ: -58.32 ~ -57.66 (m, 3 F), -140.36 ~ -139.77 (m, 2 F), -140.89 ~ -140.43 (m, 1 F), -142.18 ~ -141.76

(m, 1 F)

HR EI MS: *m/z* 364.07009 calcd. for $C_{17}H_{11}OF_7$ 364.06980



3o

84%, clear oil

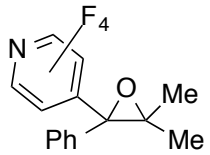
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 2 H), 7.29 ~ 7.41 (m, 3 H), 1.45 (s, 3 H), 1.22 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.85, 128.95, 128.60, 126.69, 65.25, 64.73, 22.45, 20.78

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 128.95, 128.61, 126.69, 22.48, 20.79

^{19}F NMR (471 MHz, $CDCl_3$) δ: -133.83 ~ -133.13 (m, 1 F), -135.13 ~ -134.20 (m, 1 F), -140.87 ~ -140.62 (m, 1 F), -141.07 ~ -140.87 (m, 1 F)

HR EI MS: *m/z* 373.99197 calcd. for $C_{16}H_{11}OBrF_4$ 373.99294



3p

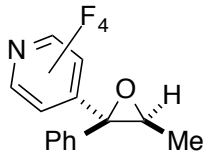
60%, clear oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (m, 2 H), 7.32 ~ 7.44 (m, 3 H), 1.45 (s, 3 H), 1.23 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.51, 129.19, 126.74, 65.14, 64.80, 22.47, 20.75

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 129.20, 129.11, 126.74, 22.45, 20.76

^{19}F NMR (471 MHz, $CDCl_3$) δ: -91.31 ~ -90.59 (m, 1 F), -92.11 ~ -91.39 (m, 1 F), -143.62 ~ -142.94 (m, 2 F)



3q

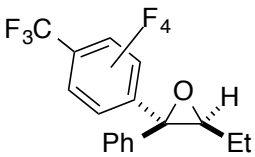
86%, clear oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 ~ 7.51 (m, 5 H), 3.62 (q, *J* = 5.4, Hz, 1 H), 1.24 (d, *J* = 5.4 Hz, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.67, 142.80, 141.52, 139.44, 134.39, 129.23, 129.10, 127.16, 125.86, 62.23, 60.33, 59.50, 16.07, 14.17

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 129.10, 127.16, 125.86, 60.33, 14.19

^{19}F NMR (471 MHz, $CDCl_3$) δ: -92.63 ~ -90.19 (m, 2 F), -145.14 ~ -142.39 (m, 2 F)



3r

81%, clear oil

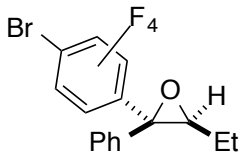
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 ~ 7.52 (m, 2 H), 7.33 ~ 7.43 (m, 3 H), 3.44 (dd, *J* = 6.2 Hz, 1 H), 1.47 ~ 1.60 (m, 1 H), 1.32 ~ 1.43 (m, 1 H), 1.05 (dd, *J* = 7.50 Hz, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.32, 145.47, 144.42, 143.39, 137.86, 135.17, 129.20, 128.97, 128.94, 127.02, 125.82, 125.22, 67.80, 65.75, 60.76, 59.51, 24.04, 21.72, 10.85, 9.75

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 129.20, 129.14, 128.98, 128.94, 127.02, 125.82, 65.76, 21.73 (-), 9.76

^{19}F NMR (471 MHz, $CDCl_3$) δ: -58.29 ~ -57.66 (m, 3 F), -140.90 ~ -140.48 (m, 2 F), -141.70 ~ -141.25 (m,2 F)

HR EI MS: *m/z* 364.06935 calcd. for $C_{17}H_{11}OF_7$ 364.06980



3s

75%, clear oil

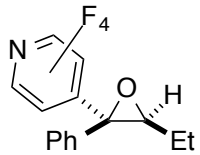
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 ~ 7.47 (m, 2 H), 7.31 ~ 7.41 (m, 3 H), 3.43 (dd, *J* = 6.4 Hz, 1 H), 1.47 ~ 1.58 (m, 1 H), 1.30 ~ 1.42 (m, 1 H), 1.03 (dd, *J* = 7.5 Hz, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.29, 144.29, 135.82, 129.10, 128.91, 128.80, 128.72, 127.05, 125.79, 120.61, 100.51, 68.03, 65.80, 59.67, 24.03, 21.73, 10.92, 9.84

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 128.80, 128.72, 127.05, 65.80, 21.73 (-), 9.85

^{19}F NMR (471 MHz, $CDCl_3$) δ: -134.57 ~ -133.50 (m, 2 F), -142.08 ~ -140.94 (m, 2 F)

HR EI MS: *m/z* 373.99180 calcd. for $C_{16}H_{11}OBrF_4$ 373.99294



3t

77%, clear oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 ~ 7.49 (m, 2 H), 7.33 ~ 7.44 (m, 3 H), 3.45 (dd, *J* = 6.40 Hz, 1 H), 1.47 ~ 1.58 (m, 1 H), 1.33 ~ 1.44 (m, 1 H), 1.17 (dd, *J* = 1.00 Hz, 1 H), 1.04 (dd, *J* = 7.3 Hz, 3 H)

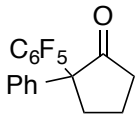
^{13}C NMR (126 MHz, $CDCl_3$) δ 144.67, 142.79, 141.70, 139.63, 137.17, 134.47, 129.05, 127.05, 125.89, 67.54, 65.58, 59.57, 24.03, 21.72, 10.85, 9.76

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 129.05, 127.05, 125.89, 67.57, 65.60, 21.73, 9.78(-)

^{19}F NMR (471 MHz, $CDCl_3$) δ: -91.60 ~ -91.01 (m, 2 F), -144.19 ~ -143.38 (m, 2 F)

4.5. Semipinacol Rearrangement of Perfluorophenyl Oxiranes

To a conical vial in a nitrogen-filled glove box, 80 mg $FeCl_3$ (0.5 mmol) was added, followed by addition of a solution of epoxide **2b** or **2l** (0.5 mmol) in 4 mL THF. The mixture was heated to 80 °C overnight, then cooled down, filtered through a celite pad, and washed with 10 mL Et_2O. The filtrate was concentrated under reduced pressure, and the crude product were purified by column chromatography over silica gel.



4a

71%, clear oil

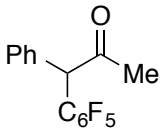
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 ~ 7.54 (m, 2 H), 7.30 ~ 7.43 (m, 3H), 3.01 ~ 3.15 (m, 1 H), 2.53 ~ 2.69 (m, 1 H), 2.37 ~ 2.52 (m, 2 H), 2.02 ~2.17 (m, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 212.83, 146.88, 144.92, 144.89, 141.69, 139.27, 137.27, 136.36, 129.07, 128.14, 128.10, 127.92, 119.22, 57.82, 36.47, 35.86, 19.59

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 129.07, 128.16, 128.10, 36.47 (-), 35.83 (-), 19.60 (-)

19F NMR (471 MHz, $CDCl_3$) d: -136.14 (d, J = 17.27 Hz, 2 F), -157.52 ~ -156.60 (m, 1 F), -163.99 ~ -162.89 (m, 2 F)

HR EI MS: *m/z* 326.07351 calcd. for $C_{17}H_{11}OF_5$ 300.0574



4b

95%, clear oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 ~ 7.45 (m, 2 H), 7.32 ~ 7.39 (m, 3H), 5.24 (s, 1 H), 2.27 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.70, 146.35, 144.38, 141.97, 139.13, 136.24, 129.63, 129.54, 128.63, 55.41, 29.03

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 129.63, 129.54, 128.63, 55.42, 29.04

19F NMR (471 MHz, $CDCl_3$) d: -143.13 ~ -138.54 (m, 2 F), -158.33 ~-154.09 (m, 1 F), -165.75 ~ -160.10 (m, 2 F)

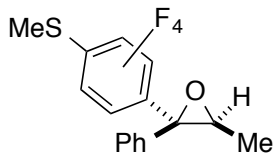
HR EI MS: *m/z* 300.05781 calcd. for $C_{15}H_9F_5O$ 300.05781

4.6. Nucleophilic Substitution on Pentafluorophenyl

5a. To a conical vial, NaSMe (55 mg, 0.75 mmol) was added to a solution of epoxide **2l** (0.15 g, 0.5 mmol) in DMSO (2M). The mixture was stirred under room temperature for two hours and monitored by GC untile complete conversion of substrate. The mixture was poured into water (10 mL), extracted with EtOAc (10 mL X3). Solvent was removed under reduced pressure and crude product was purified by column chromatography over silica gel to provide final product (0.162 g, >99%)

5b. To a conical vial in glove box, LiClO4 (0.106 g, 1 mmol) was loaded, followed by addition of piperidine (0.246 mL, 2.5 mmol) and epoxide **2l** (0.15 g, 0.5 mmol) The mixture was heated to 80 °C for 2 days and it is turned to solid. The mixture was filtered through a silica gel pad and washed by Et2O. Filtrate was concentrated under

reduced pressure and crude product was purified by column chromatography to provide the final product (0.150 g, 85%).



5a

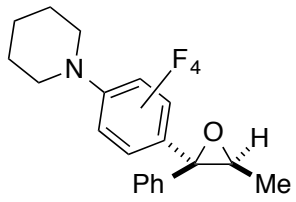
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 ~ 7.48 (m, 2 H), 7.31 ~ 7.41 (m, 3 H), 3.59 (q, *J* = 5.14 Hz, 1 H), 2.52 (s, 3 H), 1.21 (d, *J* = 5.10 Hz, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.85, 145.89, 144.24, 136.08, 128.79, 128.64, 127.17, 125.82, 120.30, 116.86, 60.53, 59.58, 17.94, 14.19

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 128.79, 128.64, 127.17, 60.53, 17.98, 17.95, 17.92, 14.20

19F NMR (471 MHz, $CDCl_3$) d: -137.11 ~ -135.22 (m, 2 F), -143.76 ~ -142.22 (m, 2 F)

HR EI MS: *m/z* 328.05500 calcd. for $C_{16}H_{12}OF_4S$ 328.05450



5b

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 ~ 7.53 (m, 2 H), 7.26 ~ 7.40 (m, 3 H), 3.58 (q, *J* = 5.50 Hz, 1 H), 3.14 ~ 3.25 (m, 4 H), 1.65~ 1.77 (m, 4 H), 1.54 ~ 1.65 (m, 2 H), 1.20 (d, *J* = 5.50 Hz, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 128.61, 128.30, 127.19, 60.54, 52.64, 26.89, 24.47, 14.19

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) d: 128.61, 128.30, 127.19, 60.54, 52.64, 26.89, 24.47, 14.19

19F NMR (471 MHz, $CDCl_3$) d: -146.06 ~ -145.07 (m, 2F), -153.16 ~ -152.19 (m, 2 F)

HR EI MS: *m/z* 365.14044 calcd. for $C_{20}H_{19}ONF_4$ 365.14028

PART TWO

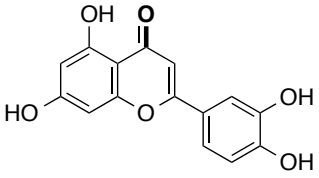
Synthesis of 2-Aroylindolizines via Palladium-Catalyzed Carbonylative Arylation/Cyclization Cascade of Propargyl Pyridines

5. Introduction

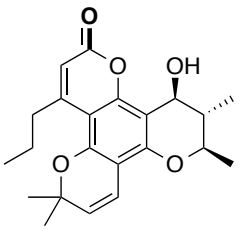
5.1. Transition Metal-Catalyzed Carbonylative Approaches toward Carbonyl-Contaning Heterocycles

Carbonyl-containing heteroaromatics, including indenones, indolenones, acyl pyrroles/furans/thiophenes, quinolinones, chromones, and coumarins, exist in prevalent range of nature products, marketed drugs, and biologically active molecules (Figure 1).[85] From synthetic standpoint, these carbonyl-containing heterocycles can be either synthesized via Friedel-Crafts acylation of pre-existing electron-rich heteroaromatics cores, or through construction of heterocycles employing various condensation reactions (Scheme 59). However, these methods have several limitations, including a multistep preparation of substrates containing a carbonyl group, narrow scope of reactive substrates, low functional group compatibility, and, moreover, lack of generality. Thus development of methodology toward efficient synthesis of carbonyl-containing heterocycles is of high demand.

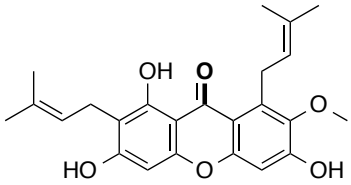
Natural Products



Luteolin

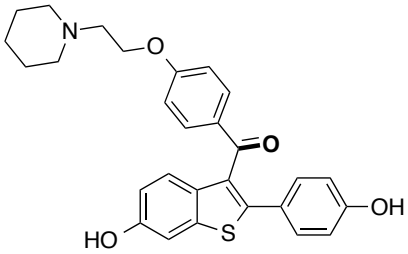


(+)-Calanolide A

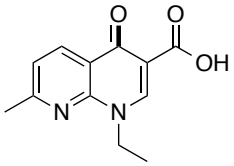


Mangostin

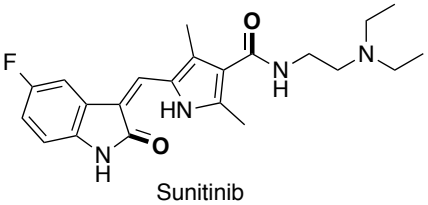
Marketed Drugs



Raloxifene

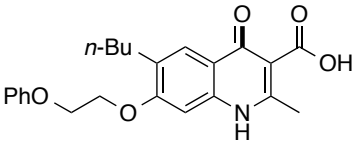


Nalidixic acid

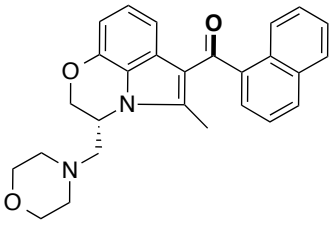


Sunitinib

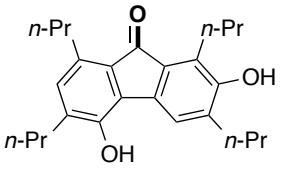
Biologically Active Molecules



ICI-58,780

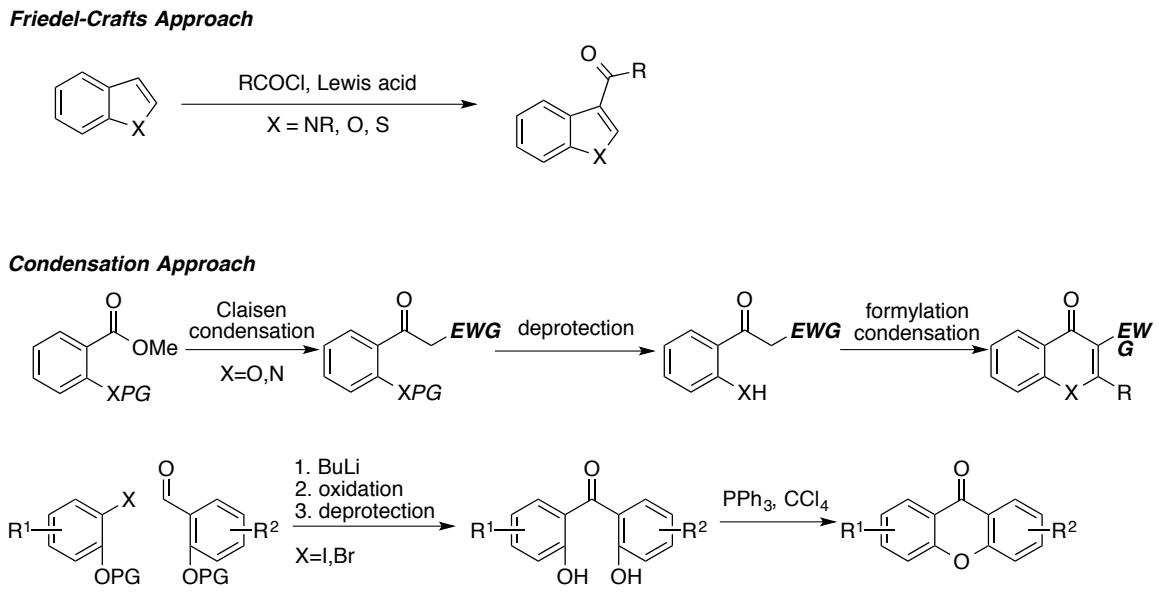


WIN 55,212-2



OPC-34165

Figure 1.

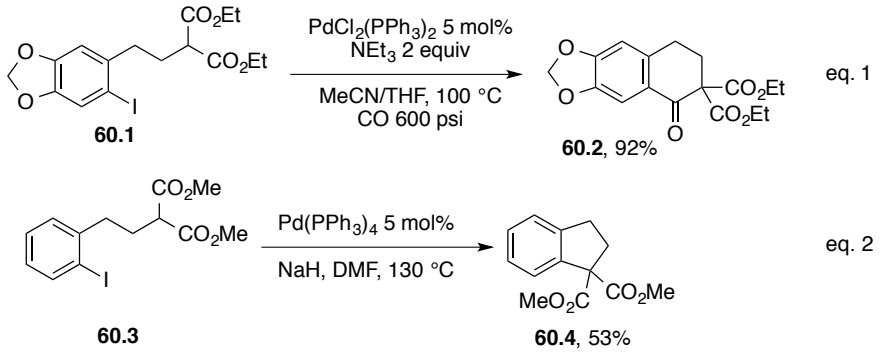


Scheme 59.

In contrast to previously described approaches, transition metal-catalyzed/mediated carbonylation processes employ carbon monoxide as the source of carbonyl group, thus eliminated the dependence on carbonyl-containing substrates. The easy migratory insertion of carbon monoxide into a carbon-metal bond allowed for a rapid extension of the existing transition metal-catalyzed coupling reactions into the corresponding carbonylative versions without significant modification of reaction conditions. In addition, the homologation of reaction intermediate by carbon monoxide alternates the steric environment around the metal and ligand, thus sometimes allows for an extended scope of reaction. Furthermore, the general availability, easiness of handling, relative stability, and cost-effectiveness make carbon monoxide one of the optimal sources of a carbonyl group.

Palladium and other transition metal-catalyzed annulation reactions have been recognized to be valuable tools toward heterocycles in laboratory and industrial environment. Thus rendering known cyclization processes into the corresponding

carbonylative cyclizations serve as reasonable and practical approaches toward carbonyl-containing heterocycles.[86] Thus, Negishi[87] reported the first highly efficient palladium-catalyzed cyclocarbonylation for the synthesis tetralone **60.2** from malonate derivative **60.1** (Scheme 60, eq. 1). It represents a carbonylative version of the palladium-catalyzed cyclization of **60.1**, reported by Ciufolini for synthesis of indane **60.4** (Scheme 60, eq. 2).[88]



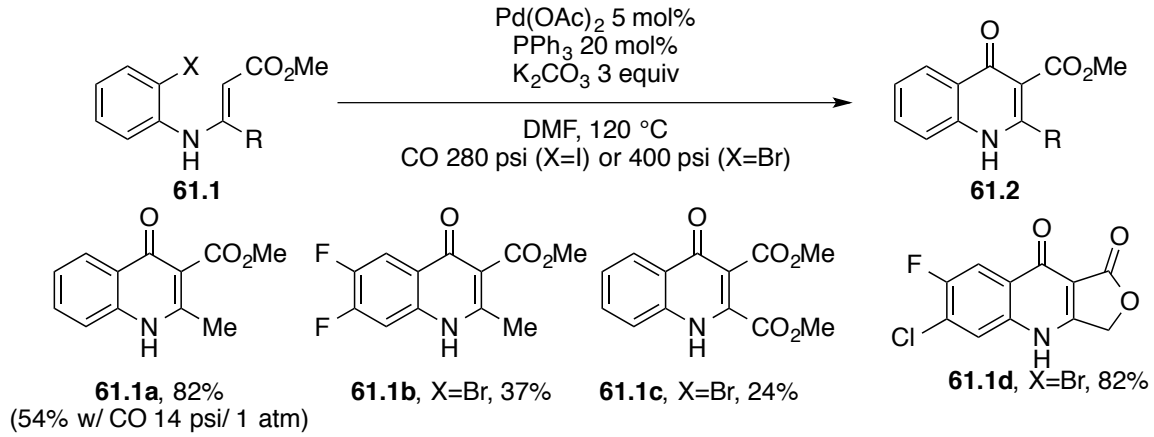
Scheme 60.

Negishi's report regards for the first Pd-catalyzed carbonylative cyclization reaction via a construction of two C-C bonds. Thus, not surprisingly, it inspired chemistry community to explore the full potential of this transformation in synthesis of heterocycles.

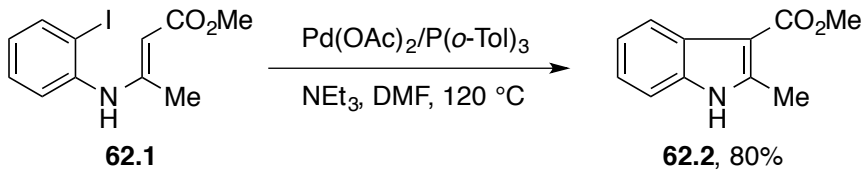
5.2. Pd-Catalyzed Cyclocarbonylation in Synthesis of Heteroaromatics

Inspired by Negishi's report,[87] Torii and co-workers disclosed synthesis of quinolin-4-ones **61.2** using the Pd-catalyzed cyclocarbonylation of enamines **61.1** under high pressure of CO (> 280 psi) (Scheme 61).[89] A variety of quinolin-4-ones **61.2** bearing different substituents were synthesized, and in low-to-high yields. The high pressure of CO was necessary to maintain a high material balance, but also to suppress

the formation of undesired non-carbonylative product **62.2** that had been reported by Yamanaka and co-workers (Scheme 62).[90]

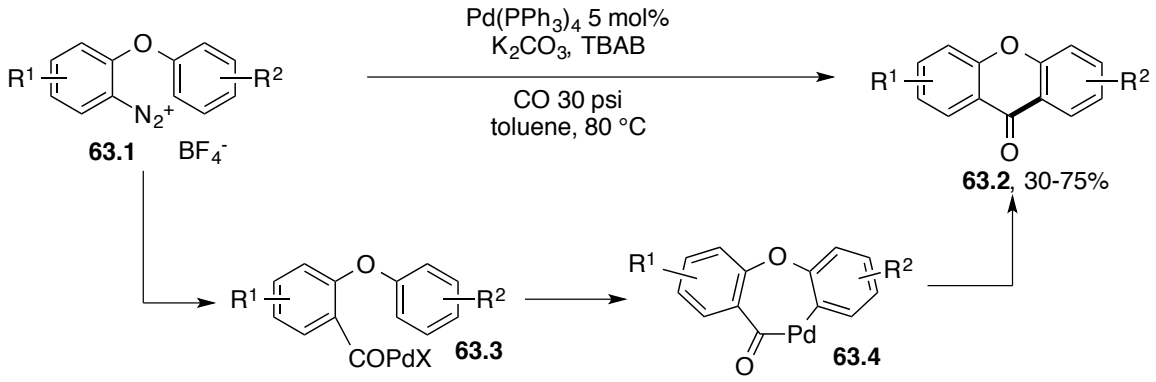


Scheme 61.



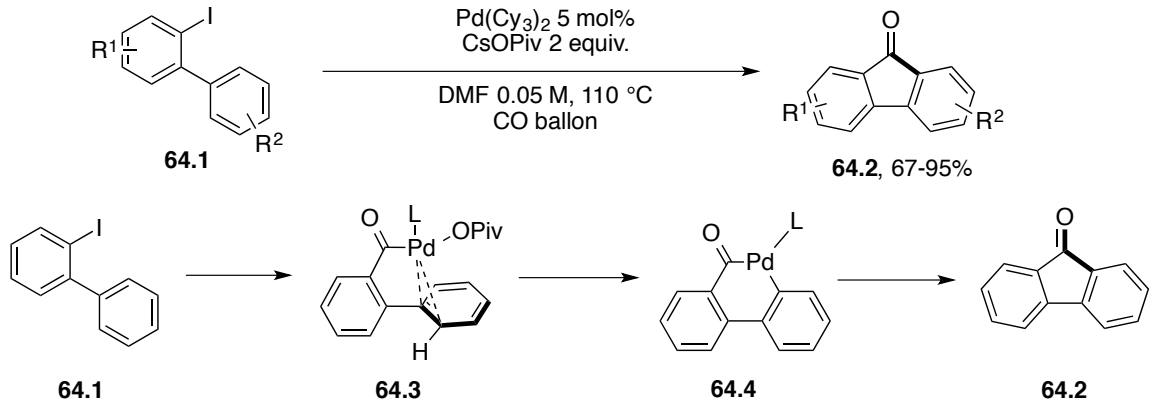
Scheme 62.

A Pd-catalyzed cyclocarbonylation of *o*-aryloxy aryldiazonium salts **63.1** into xanthones **63.2** was recently reported by Du group (Scheme 63).[91] A highly selective formation of cyclocarbonylation product can be achieved under relatively low pressure of CO (30 psi).[92] Reaction proceeds via extrusion of nitrogen and migratory insertion of carbonyl to form an acylpalladium (II) species **63.3**, which undergoes a direct C-H palladation to form palladacycle **63.4**. A reductive elimination of the latter affords product **63.2**, and regenerates the palladium catalyst.



Scheme 63.

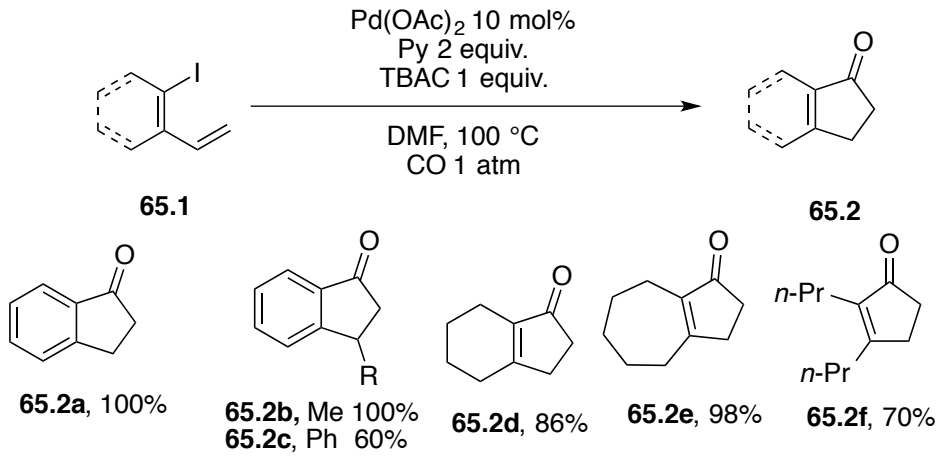
Larock's group reported synthesis of fluorenones **64.2** using the Pd-catalyzed cyclocarbonylation of 2-iodobiaryl **64.1** under ambient pressure of CO (Scheme 64).[93] The high pressure of CO atmosphere was not necessary, as no non-carbonylative cyclization product was observed.[94] The formation of a biarylcarbonyl Pd(II) pivalate **64.3** after oxidative addition of Pd, and migratory insertion of CO was proposed. With the assistance of a pivalate ligand, a direct C-H palladation step led to a 6-membered palladacycle **64.4**, which yielded product **64.2** upon a reductive elimination.



Scheme 64.

Later, the same group extended the scope of substrates of this Pd-catalyzed cyclocarbonylation to *ortho*-halogenated styrenes and iodobutadienes **65.1** (Scheme

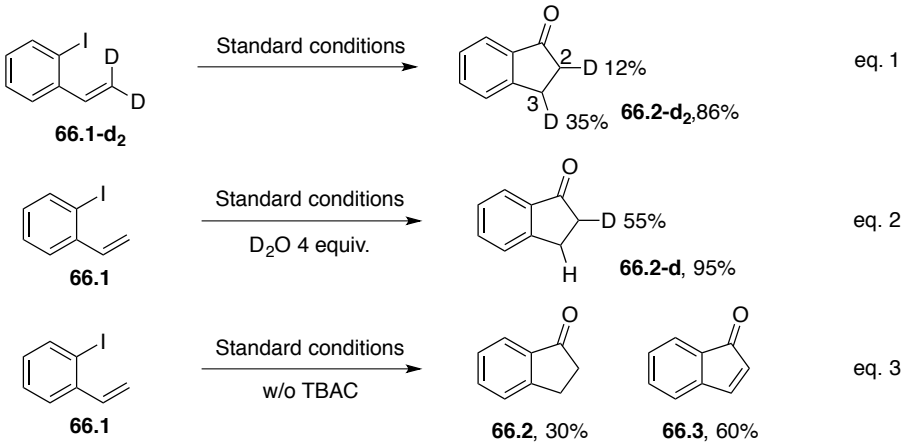
65).[95] To their surprise, in contrast to the expected indenones and cyclopentadienones, efficient formation of the corresponding reduction products, indanones and cyclopentanones **65.2**, was observed.



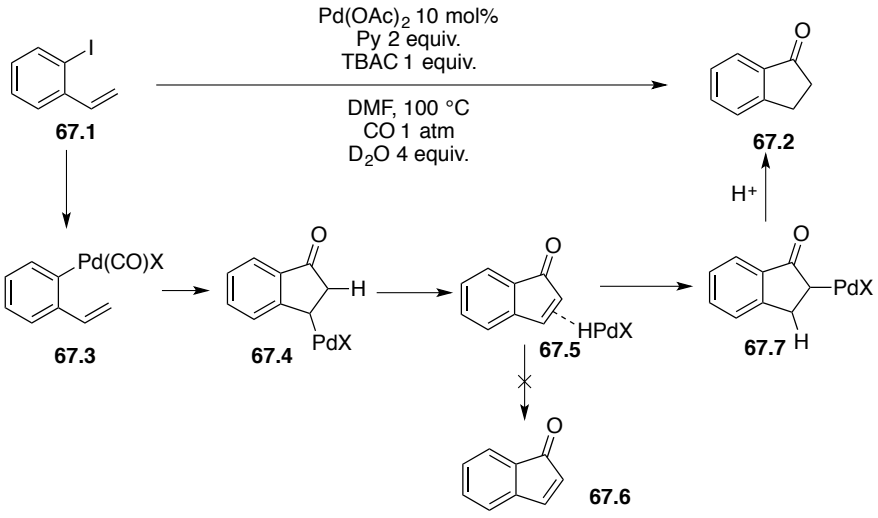
Scheme 65.

In order to figure out the origin of this unusual reduction, a series of deuterium labeling experiments were performed. First, reaction of β,β-dideuterated styrene **66.1-d$_2$** under standard reaction conditions yielded **66.2-d$_2$** with a distribution of deuterium among C3 and C2 (Scheme 66, eq. 1). Next, the addition of D_2O to reaction of **66.1** yielded **66.2-d** with exclusive deuterium-incorporation at C2 (Scheme 66, eq. 2). In addition, eliminating tetrabutylammonium chloride (TBAC) from the reaction conditions yielded a mixture of 30% indanone **66.2** and 60% indenone **66.3** (Scheme 66, eq. 3). Hence, the authors proposed the following reaction pathway (Scheme 67). First, upon the oxidative addition of aryl iodide to Pd(0) and migratory insertion of CO produced an acyl palladium intermediate **67.3**. A subsequent intramolecular acyl palladation of styrene yielded palladium homoenolate **67.4**, which upon a subsequent β-hydride elimination led to the hydridopalladium(II)-indenone complex **67.6**. Contrary to a normal Heck reaction,

in which an instantaneous reductive elimination of HX released Pd(0) to initiate the next catalytic cycle, a reduction of indenone by hydridopalladium(II) gave rise to the formation of the Pd(II) *C*-enolate **67.7**, which produced **67.2** after a protiodemetallation. TBAC played an important role in this transformation, since its Hofmann elimination in the presence of pyridine produces hydrogen chloride and tributyl amine. The hydrogen chloride was necessary to release product and catalyst from **67.7**, whereas the regeneration of the Pd(0) catalyst from the released palladium (II) species was greatly depended on the presence of tributyl amine.[96]

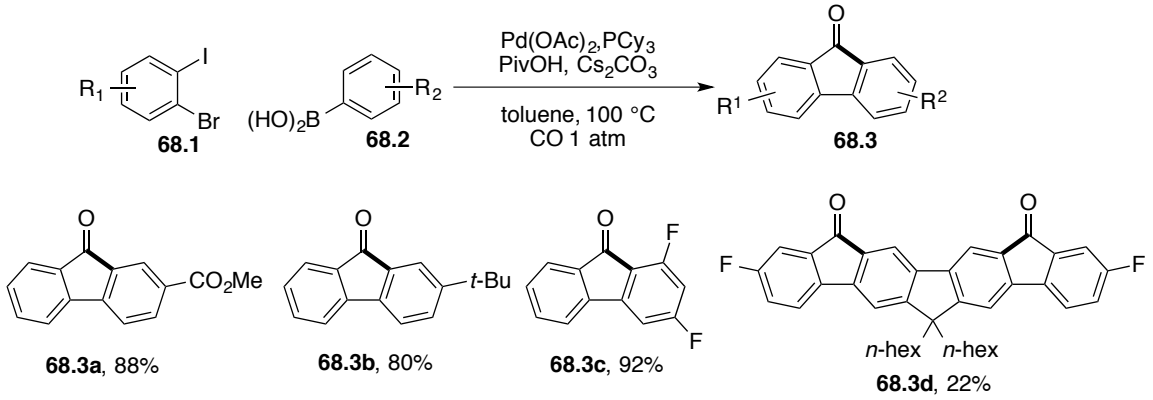


Scheme 66.



Scheme 67.

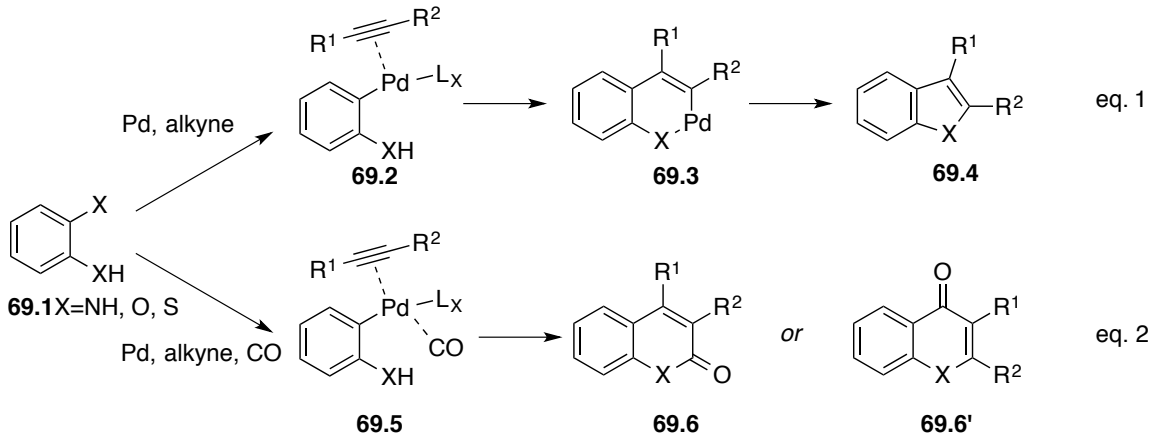
Based on Larock's synthesis of fluorenone discussed above (Scheme 64),[93] Liu and co-workers developed a one-pot Pd-catalyzed Suzuki coupling/cyclocarbonylation cascade approach toward fluorenones from 1,2-dihalobenzene **68.1** and aryl boronic acid **68.2** under ambient pressure of CO. A series of fluorenones posessing different substituents can be prepared using this strategy. Difluorenone **68.3** can be also accessed via a two-fold carbonylative cyclization (Scheme 68).[97]



Scheme 68.

5.3. Pd-Catalyzed Carbonylative Two-Component Coupling Reactions in Synthesis of Heterocycles

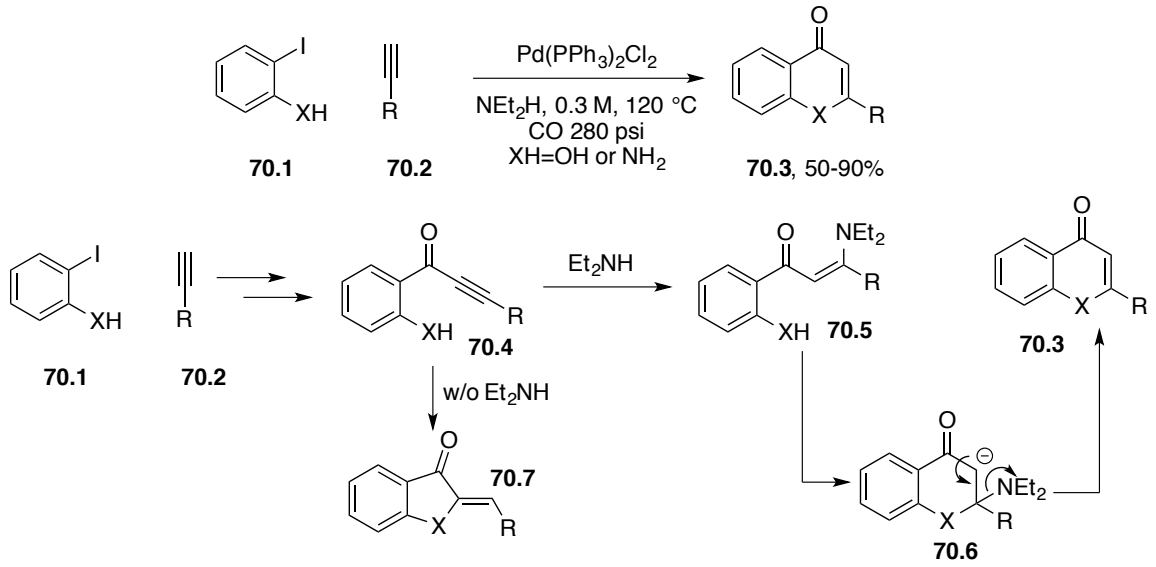
The Pd-catalyzed annulation reactions of 2-halophenol or -aniline **69.1** with alkyne provides effective access toward benzofuran and indole moieties **69.4**.[86] The migratory insertion of alkyne into an aryl-Pd bond of **69.2** produces key 6-membered palladacycle intermediate **69.3**, which upon a further reductive elimination produces product **69.4** (Scheme 69, eq. 1). In the presence of carbon monoxide, two competing successive migratory insertions of alkyne and carbon monoxide may produce regioisomers **69.6** and **69.6'** (Scheme 69, eq. 2).



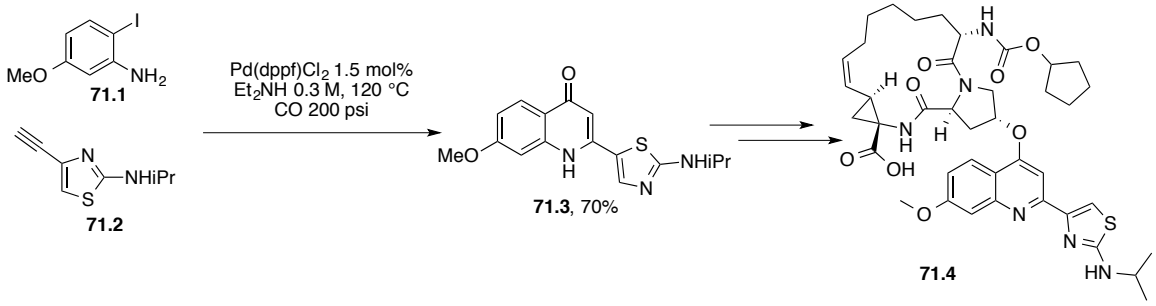
Scheme 69.

Torri and Kalinin first reported the Pd-catalyzed two-component synthesis of chromones and quinolin-4-ones **70.3** from terminal alkyne **70.1** and 2-iodophenol or 2-iodoaniline **70.2** in diethylamine under 280 psi of CO. The high pressure of CO was important to accelerate the reaction and improve the yields. Reaction proceeded with the formation of detectable ynone **70.4** intermediate via a Cu-free carbonylative Sonogashira coupling reaction. Upon a Michael addition of a secondary amine, like diethylamine, to the ynone **70.4**, β-ketoenamine **70.5** is produced, which upon an intramolecular Michael

addition of phenol or aniline formed adduct **70.6**, which is then converted into the product **70.3** upon elimination of diethylamine. In absence of a secondary amine, an undesired *5-exo-dig* cyclization product **70.7** was observed (Scheme 70).[98,99] Later, this method was employed in synthesis of quinolinone fragment **71.3** of protease inhibitor BILN-2061 **71.4** (Scheme 71).[100]



Scheme 70.

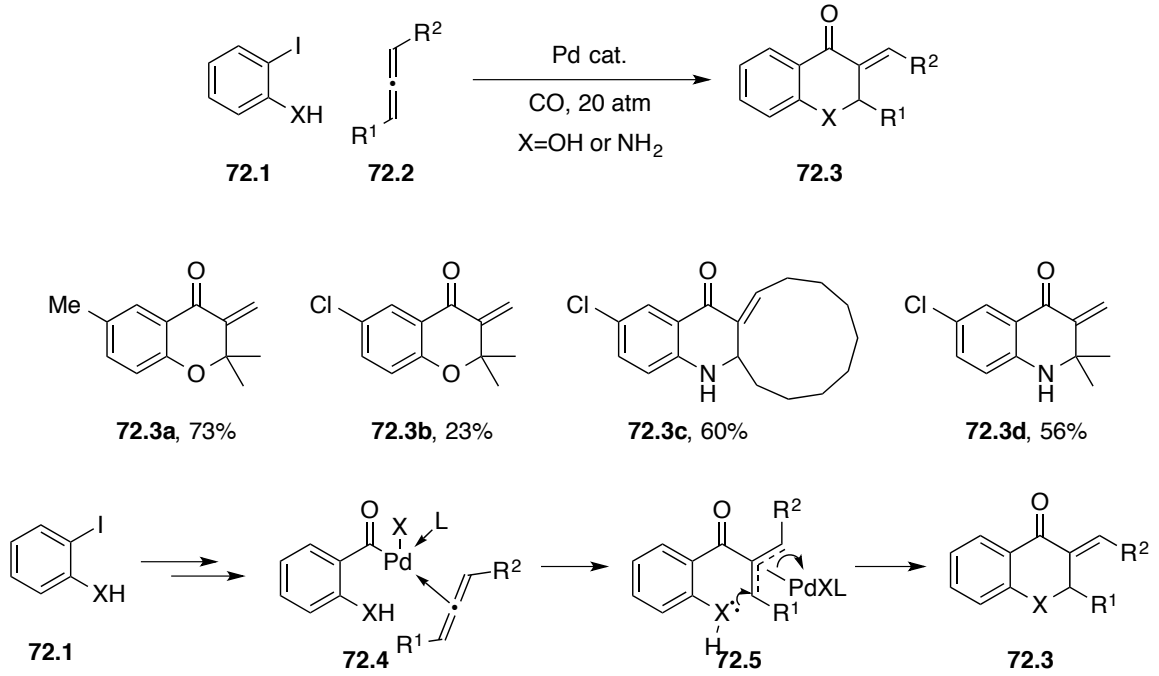


Scheme 71.

Later, Yang group successfully reduced pressure of CO in this reaction to ambient pressure without loosing the efficiency of reaction by employing an effective $Pd(PPh_3)_2Cl_2$/thiourea catalyst system.[101] Similarly, Capretta group demonstrated that

using a bulky phosphine ligand and a microwave heating allows for achievingcarbonylation reaction under low pressure of CO.[102]

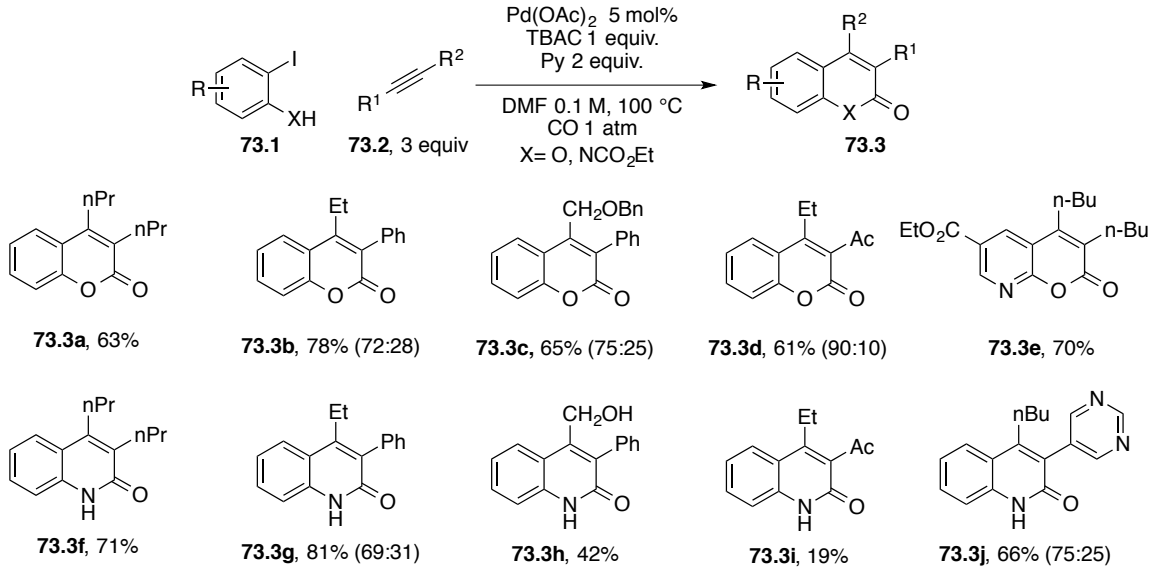
Alper's group reported the Pd-catalyzed a moderately efficient two-component regioselective synthesis of chromones and quinoline-4-ones **72.3** from allenes **72.2** and 2-iodophenols or 2-haloanilines **72.1** under high pressure of CO (Scheme 72).[103] This method is compatible with 2-haloanilines and -phenols posessing different substituents and diversely substituted allenes. According to the observed regioselectivity, it can be anticipated that migratory insertion of CO into aryl-Pd bond took place prior to arylpalladation of allene. The subsequent acylpalladation of allene with **72.4** yielded the allyl palladium intermediate **72.5**, which produced **72.3** upon a reductive elimination.



Scheme 72.

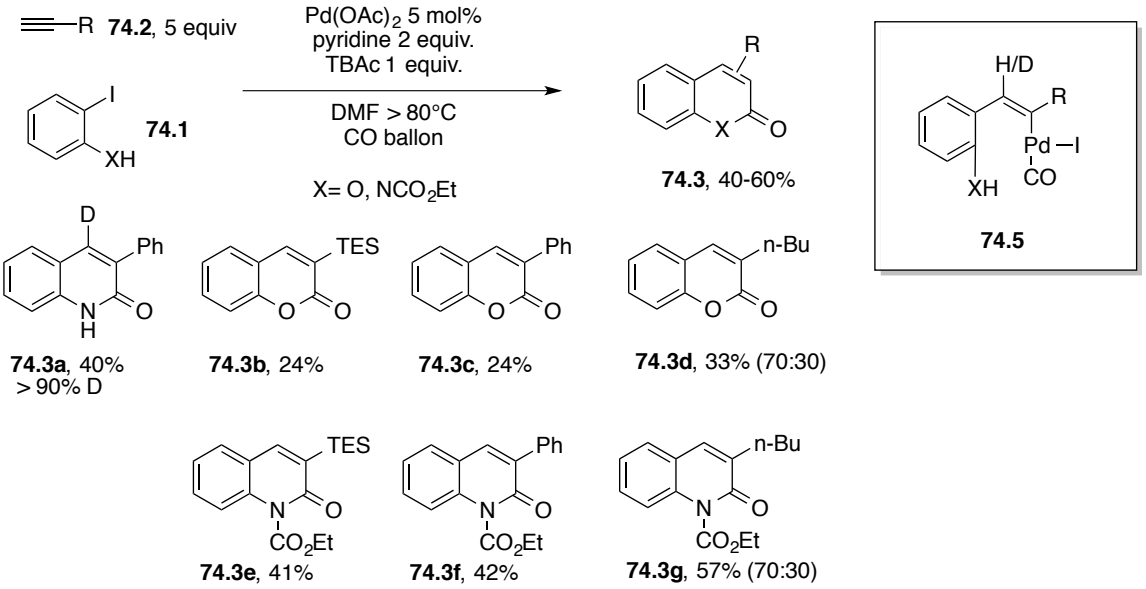
Larock's group found that under ambient pressure of CO and in the presence of excess amount of alkyne (more than 3 equivalents), the carbopalladation of alkyne took

place prior to the migratory insertion of carbon monoxide, which allowed for the development of the Pd-catalyzed carbonylative two-component synthesis of coumarins and quinoline-2-ones **73.3** from 2-iodoanilines or 2-iodophenols **73.1** and internal alkynes (Scheme 73).[104] A series of coumarins and quinoline-2-ones can be obtained using this methodology in low-to-moderate yields. Unsymmetrical alkynes yielded mixture of regioisomers with low-to-moderate selectivity.

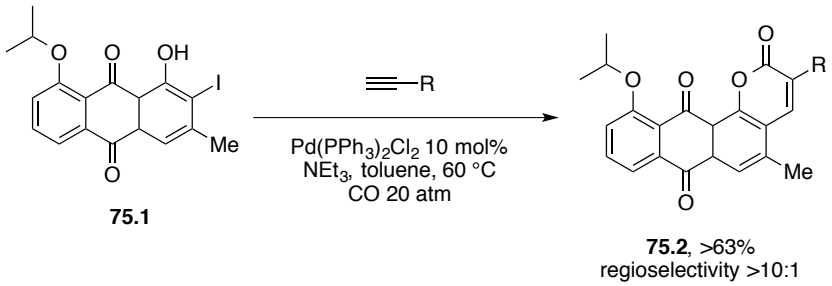


Scheme 73.

Later, the same group reported a successful utilization of terminal alkynes **74.2** in this transformation. However, the yields were reduced significantly (Scheme 74).[105] The high retention of deuterium in product **74.3a** of an experiment using deuterated phenyl acetylene underlined a carbopalladation pathway involving intermediate **74.5**.[98] Rixson recently improved both the yield and the regioselectivity of this transformation by increasing pressure of CO, and using sterically hindered substrates. These refined conditions were used in synthesis of **75.2**, the surrogate of a nature product BE-26554A.[106]

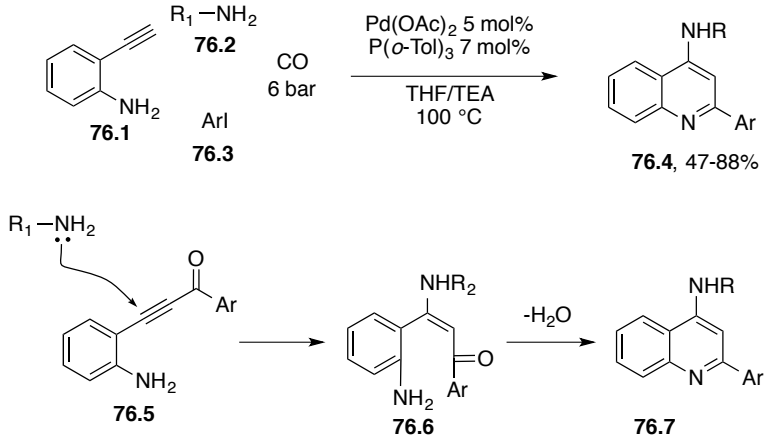


Scheme 74.



Scheme 75.

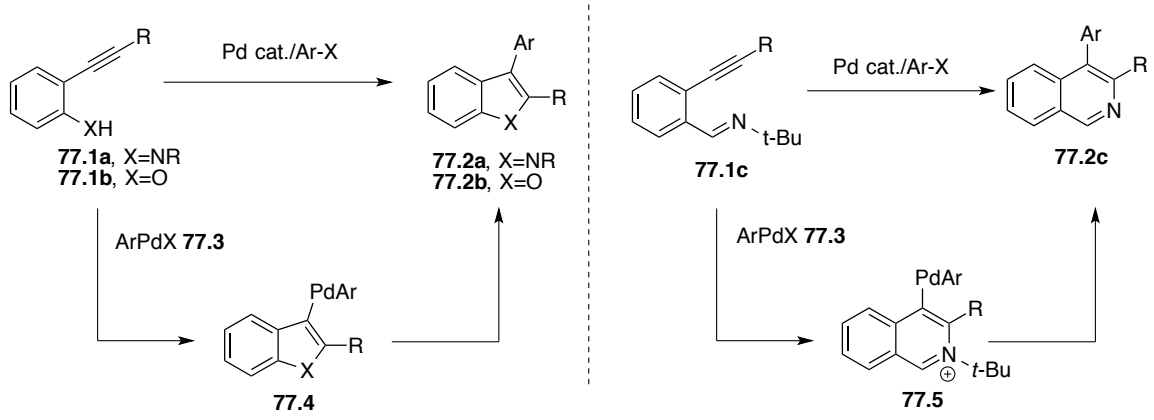
Abbiati reported synthesis of 4-aminoquioline **76.4** via the Pd-catalyzed three-component carbonylative coupling of 2-aminophenylacetylene **76.1**, amine **76.2**, and aryl iodide **76.3**. Reaction proceeds via an initial Cu-free carbonylative Sonogashira coupling to yield an ynone **76.5**. The Michael addition of an amine at ynone **76.5** yielded β-ketoenamine **76.6**, which upon condensation with aniline forms **76.4**.[107]



Scheme 76.

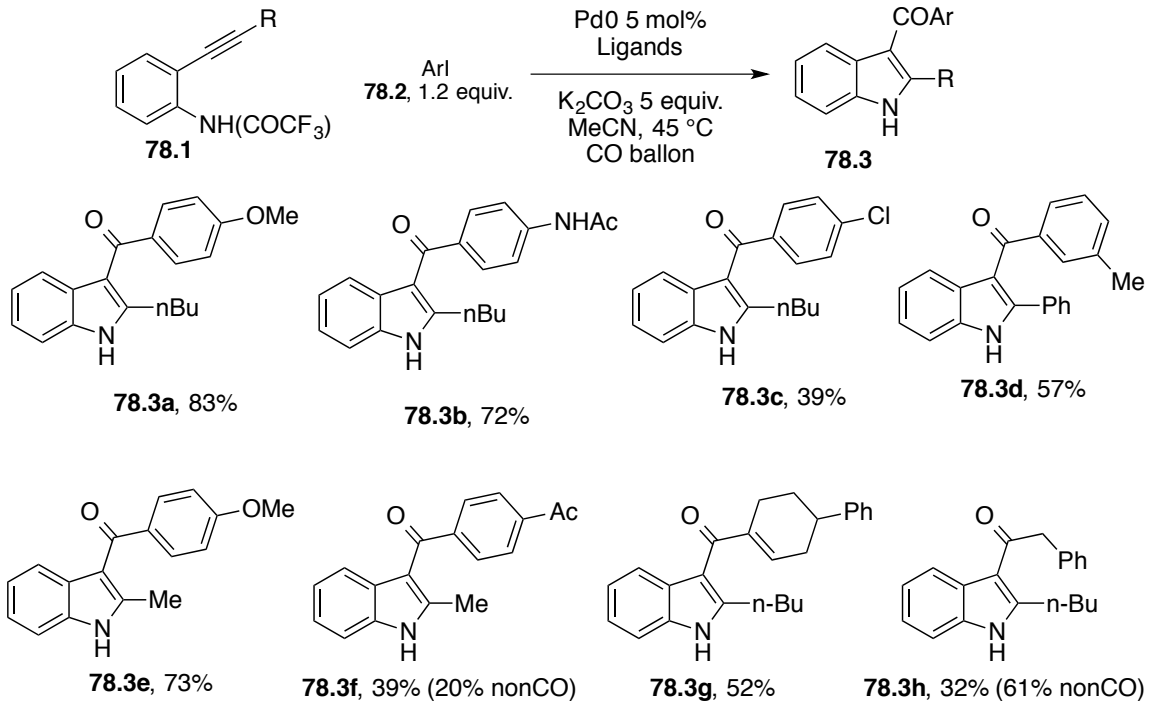
5.4. Pd-Catalyzed Cyclization/Carbonylative Coupling Cascade Transformations

2-Alkynyl aniline **77.1a**, 2-alkynyl phenol **77.1b**, and 2-alkynylbenzaldemine **77.1c** are reported to cyclize with an aryl electrophile into an arylated indoles **77.2a**,[108] benzofurans **77.2b**,[109] and isoquinolines **77.2c**[110] in the presence of a Pd(0)-catalyst (Scheme 77).[111,86] Reaction proceeds via an initial formation of aryl palladium(II) species **77.3**, which triggered the amino- or oxy- palladation of alkyne **1a-1c** to produce a biarylpalladium(II) intermediate **77.4** and **77.5**, which upon reductive elimination furnished expected product **77.2**.



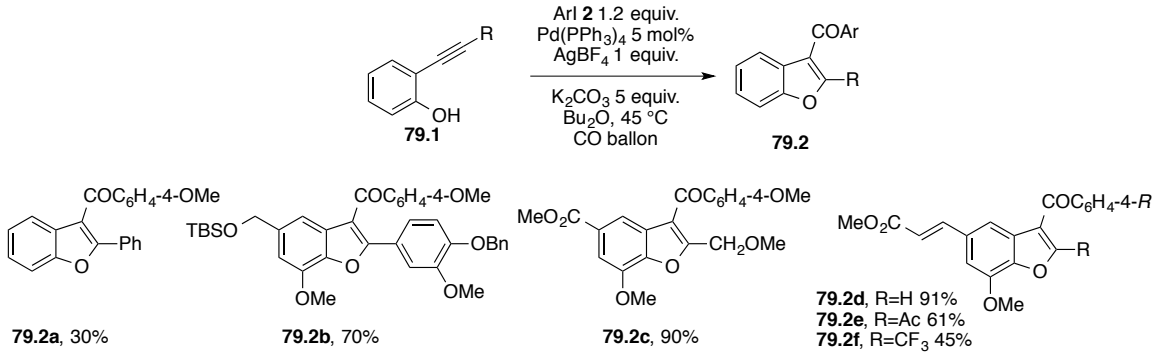
Scheme 77.

Cacchi's group first extended the aforementioned arylative cyclization mode to the Pd-catalyzed carbonylative cyclization for synthesis of a series of 3-benzoyl indoles from *ortho*-alkynyl aniline **78.1** with carbon electrophiles under low pressure of CO.[112] Electron-rich aryl electrophiles (**78.2a**, **78.2b**) provided better material balance and higher yields of carbonylation products compared to their electron-deficient analogues (**78.3c**, **78.3f**). Compare with aryl electrophiles, benzyl bromide provided the best material balance, however, the carbonylation product **78.3h** was the minor component in mixture with benzylation product (Scheme 78). The same group attempted synthesizing 3-acylbenzofurans from *ortho*-alkynyl phenol using the same strategy. However, most reactions provided desired carbonylative cyclization products in low yields, and competitive esterification reaction of phenol cannot be prevented.[113]



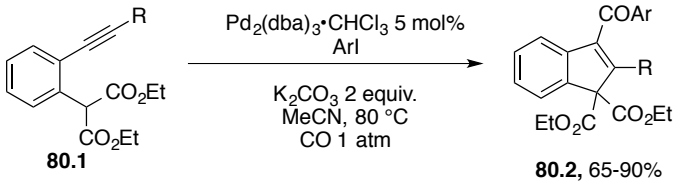
Scheme 78.

Yang's group solved the chemoselectivity issue in Cacchi's synthesis of 3-acylbenzofurans[113] via two modifications: 1) by enhancing the carbophilicity of the Pd(II) intermediate by adding $AgBF_4$, thus suppressing the side esterification reaction; or 2) by installing another *ortho*-substituent next to phenol to increase steric hindrance around the OH group, thus inhibiting the undesired esterification reaction. These modified conditions allowed a highly selective and effective synthesis of benzofurans **79.2** (Scheme 79).[114]



Scheme 79.

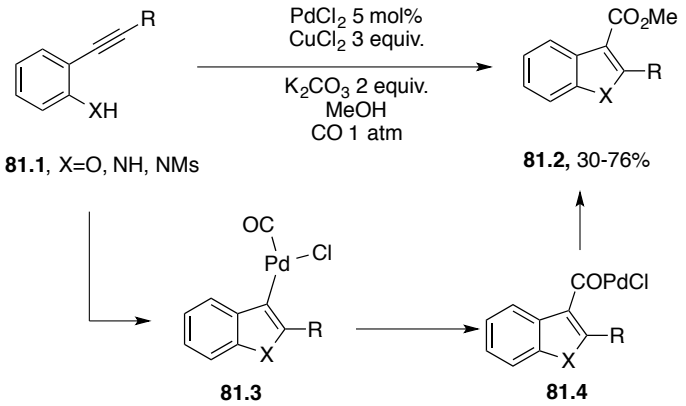
Later, this methodology was used by Duan's group for synthesis of 3-benzoylindenes **80.2** via a cyclization/carbonylative coupling of malonate derivatives **80.1** with aryl electrophiles under ambient pressure of CO (Scheme 80).[115]



Scheme 80.

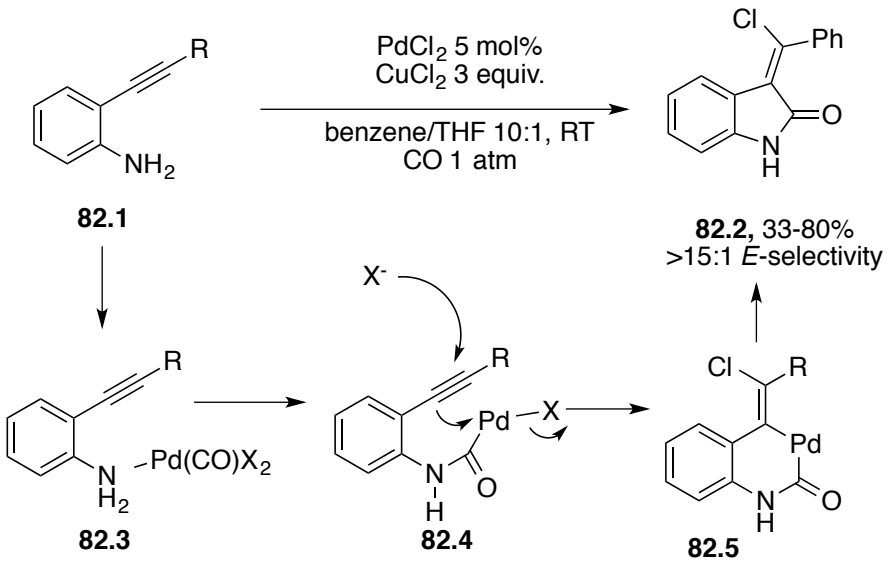
Kondo [116] and Yang [117] reported synthesis of indole-3-carboxylates and benzofuran-3-carboxylates **81.2** via the Pd(II)-catalyzed cyclization of *ortho*-alkynyl

aniline or phenol **81.1** in methanol (Scheme 81). This transformation proceeds via formation of a heteroaryl carbonyl Pd(II) chloride species **81.3** from a Pd(II)-assisted *5-endo-dig* cyclization of **81.1**. The migratory insertion of CO produces **81.4**, which upon esterification produces **81.2** and releases the Pd(0) catalyst. Copper(II) chloride oxidizes Pd(0) to Pd(II) to initiate another catalytic cycle.



Scheme 81.

Interestingly, Tang reported that, after replacing the solvent of the aforementioned reaction from methanol to a mixture of benzene/THF, the reaction of unprotected *ortho*-alkynyl anilines **82.1** yielded chlorine-substituted isatin derivatives **82.2** with *E*-selectivity. The authors proposed the mechanism, which starts with the formation of an amine-Pd(II) complex **82.3**. A subsequent nucleophilic addition of an amine at the carbon monoxide produced intermediate **82.4**. A *trans*-chloropalladation of alkyne produced palladacycle **82.5**. A subsequent reductive elimination of **82.5** released the reaction product **82.2** (Scheme 82).[118]

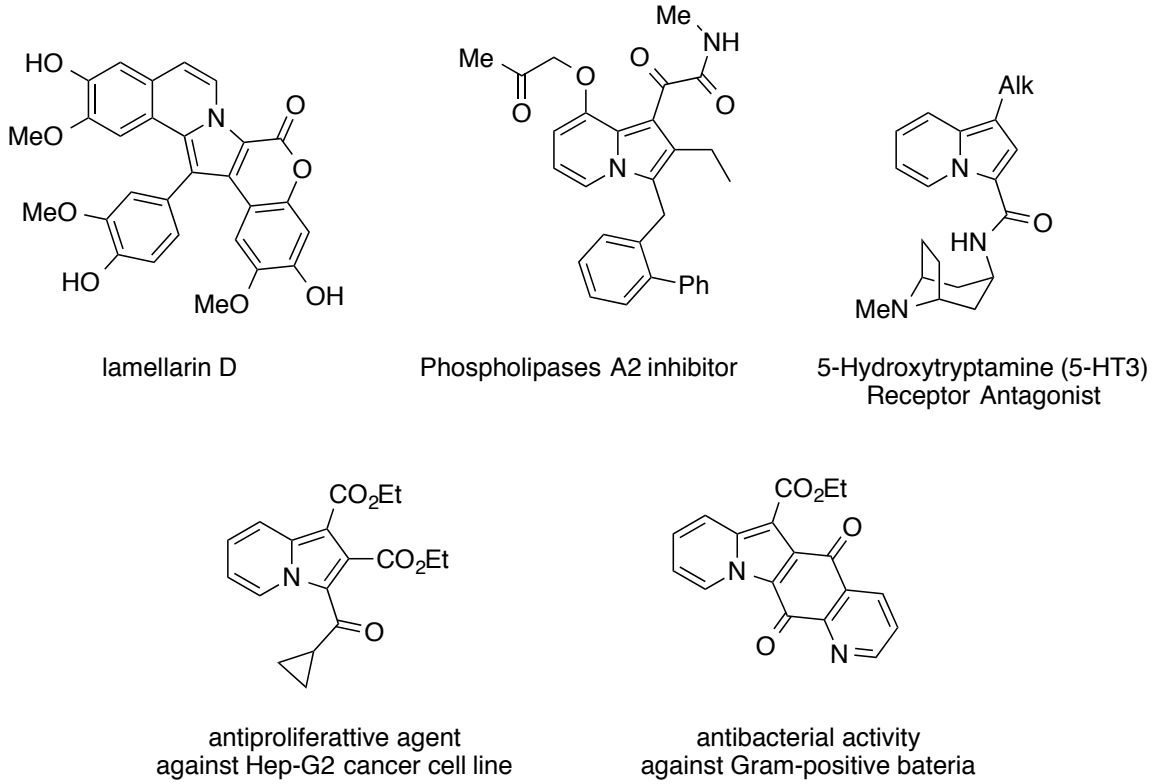

R
NH2
PdCl2 5 mol%
CuCl2 3 equiv.
benzene/THF 10:1, RT
CO 1 atm
Cl
Ph
O
N
H
82.1
82.2, 33-80%
>15:1 E-selectivity
X-
R
N
H2
Pd(CO)X2
Pd
X
O
82.3
82.4
Cl
R
Pd
82.5

Scheme 82.

6. Palladium-Catalyzed Carbonylative Arylation/Cyclization Cascade of Propargyl Pyridines

6.1. Proposed Carbonylative Approach toward 2-Aroyl Substituted Indolizines

Indolizines have attracted noteworthy attention in recent years due to their profound biological profolios.[119] Both naturally occurring and synthetic indolizines, particularly those possessing a C-2 substituent, [120] have shown great potential in pharmaceutical research as cytotoxins[121], anti-inflammatory agents,[122] and 5-HT3 receptor antagonists (Figure 2).[123,124] In this regard, transformations that utilize readily available substrates to provide access to diversely substituted indolizines, especially those bearing an electron-withdrawing group at the C-2, are in high demand.



lamellarin D

Phospholipases A2 inhibitor

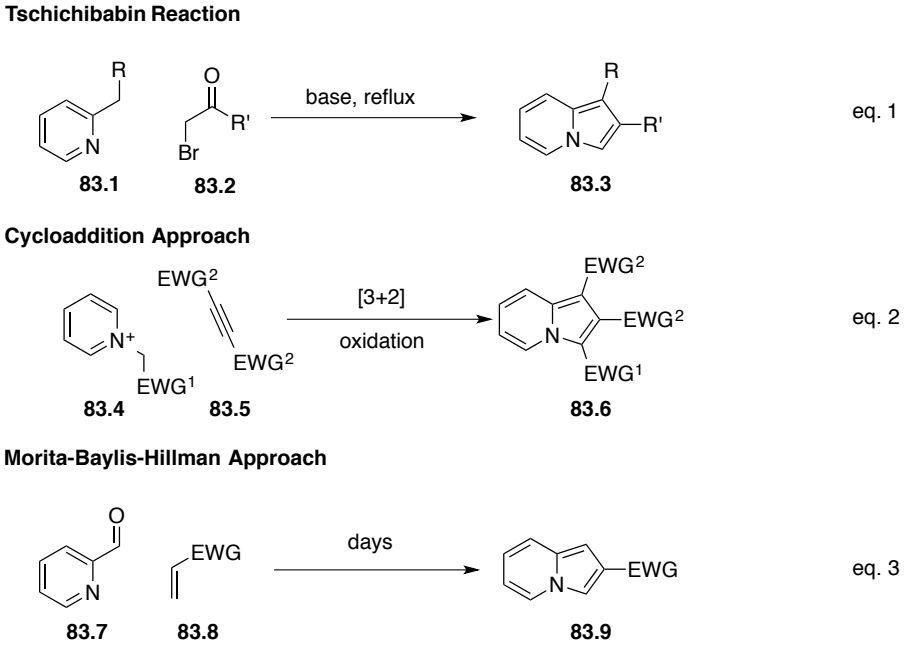
5-Hydroxytryptamine (5-HT3) Receptor Antagonist

antiproliferattive agent against Hep-G2 cancer cell line

antibacterial activity against Gram-positive bateria

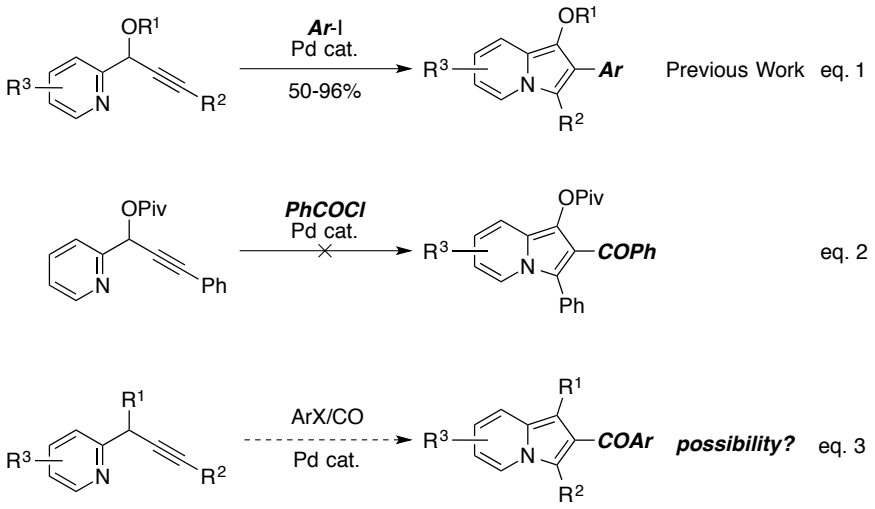
Figure 2.

The classic Tschichibabin reaction provides a straightforward access to C-2 substituted indolizines **83.3** via the condensation of picolines **83.1** and α-bromo-acetophenone derivatives **83.1** (Scheme 83, eq. 1).[125] However, the limited availability of starting materials restricts the substitution pattern of the product. The [3+2] cycloaddition of pyridinium ylides **83.4** with electron-deficient alkynes **83.5** provides another viable route to the indolizine core. However, the regioselectivity issue, limited scope of substrate, as well as the moderate yields caused by necessary oxidation of the formed intermediate, limits its synthetic application (Scheme 83, eq. 2).[126] The Morita-Baylis-Hillman reaction can also be utilized for the preparation of indolizin-2-yl ketone **83.9** from a pyridinecarboxaldehyde **83.7** and an appropriate Michael acceptor **83.8**. However, it suffers from the narrow range of starting materials that can be used, and the usually low reactivity of the substrates (Scheme 83, eq. 3).[127]



Scheme 83.

In addition to the traditional condensation methods, transition metal catalysis has been widely used for the construction of diversely functionalized, especially heteroatom-substituted indolizines, under mild conditions.[128] Nonetheless, the selective introduction of functionality at the C-2 position is still a challenging task. Along this line, Gevorgyan group has recently reported a synthesis of 2-aryl indolizines via the palladium catalyzed arylative *5-endo-dig* cyclization of 2-propargylpyridine (Scheme 84, eq. 1).[129] Continuing with our efforts on the synthesis of diversely functionalized indolizines, we thought that the employment of an acyl palladium species instead of an aryl palladium species as electrophile in this cascade cyclization would provide 2-benzoyl indolizine. However, our experiment shown that benzoyl chloride, which was widely used as benzoylation reagent in palladium catalysis, caused significant decomposition of substrates during the reaction producing no trace amounts of the desired product (Scheme 84, eq. 2). Since (1) an acyl palladium species can be easily formed via a migratory insertion of carbon monoxide into an aryl-palladium bond; and (2) there have been reported examples on synthesis of diaryl ketones via the palladium catalyzed carbonylative cyclization/arylation cascades (Section 5, page 81), we attempted a Pd-catalyzed cascade carbonylative cyclization/arylation approach towards 2-aroyl indolizines (Scheme 84, eq. 3).



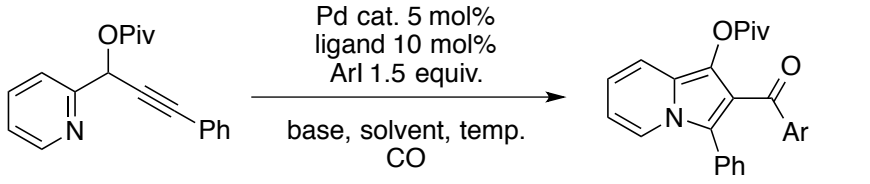
Scheme 84.

6.2. Optimization of Reaction Conditions, Scope, and Limitations

To test this idea, we examined the carbonylative cyclization of pivalate **7a** and different aryl halides in a Schlenk flask connected to a 10 psi CO outlet. Initially we found that the carbonylative cyclization of **7a** and iodobenzene in the presence of $Pd(PPh_3)Cl_2$ catalyst produced **8a** in high yield (Table 1, entry 1). However, aryl halides bearing electron-withdrawing groups, such as methyl *p*-iodobenzoate, were not competent reactants under these conditions (entry 2). On the contrary, the combination of $Pd(OAc)_2$ catalyst, PCy_3 ligand and triethylamine base afforded benzoate **8f** in 90% yield (entry 3). Under the same conditions, the yield of **8a** was only 19% along with a substantial amount of palladium black produced, which implied decomposition of an excessively reactive catalyst (entry 4). The yield of **8a** was improved to 51% by switching ligand to PPh_3 (entry 5). The reaction then was performed in a sealed 25 mL Schlenk tube, which simplified the reaction setup, and allowed a higher pressure (20 psi and above), provided **8a** in 86% yield at 20 psi CO (entry 6). Finally the screening of

different solvents revealed that acetonitrile was the optimal choice at a lower temperature (entries 7-9).

Table 6.



7a

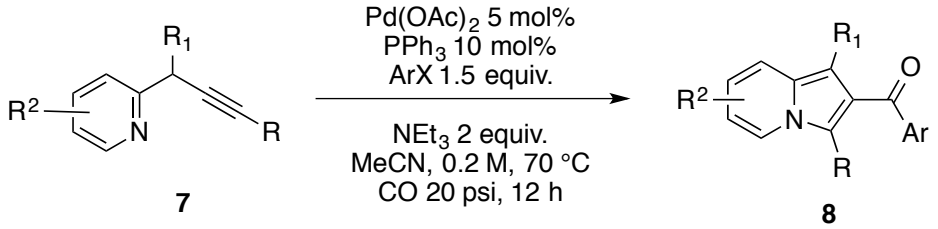
8a Ar=Ph
8f Ar=C_6H_4-*p*-CO_2Me

entry	ligand	base	solvent	temp.	CO[a]	yield (%)[b]
1	$Pd(PPh_3)_2Cl_2/PPh_3$	K_2CO_3	DMF	100	A	**8a**, > 95[c]
2	$Pd(PPh_3)_2Cl_2/PPh_3$	K_2CO_3	DMF	100	A	**8f**, decomp[c]
3	$Pd(OAc)_2/PCy_3$	NEt_3	DMF	80	A	**8f**, 90
4	$Pd(OAc)_2/PCy_3$	NEt_3	DMF	80	A	**8a**, 19
5	$Pd(OAc)_2/PPh_3$	NEt_3	DMF	80	A	**8a**, 51
6	$Pd(OAc)_2/PPh_3$	NEt_3	DMF	80	B	**8a**, 86
7	$Pd(OAc)_2/PPh_3$	NEt_3	DMF	70	B	**8a**, 65
8	$Pd(OAc)_2/PPh_3$	NEt_3	toluene	70	B	**8a**, 45
9	$Pd(OAc)_2/PPh_3$	NEt_3	MeCN	70	B	**8a,** 95

[a] A: Reactions were conducted in flask with continuous 10 psi CO supply. B: Reacitons were conducted in sealed Schlenk tube with 20 psi CO. [b] Isolated yields of 0.5 mmol reactions. [c] 1 equivalent of TBAI was added.

With the optimized conditions in hand, the scope of reaction was examined. It was found that a series of iodoarenes bearing different substituents at various positions smoothly underwent this carbonylative cyclization with **7a**, yielding indolizines **8a** to **8i** in moderate to excellent yields (Table 2, entries 1-9). The cyclization of *n*-hexyl, *n*-butyl and cyclohexenyl substituted propargyl pivalates also provided the expected products **8j-o** in good yields (entry 10 to 15). Substrates possessing a functionalized pyridine ring at C-5 produced indolizines **8p**, **8q** and pyrrolo[1,2-*a*]quinoline **8r** in moderate to good yields (entries 16-18). On the contrary, cyclization of 3-methyl substituted pyridine-derived **8s** gave a relative low yield, probably due to the steric hindrance between bulky pivaloyl group and 8-methyl group (entry 19). In addition to various pivalates, a TBDMS ether was equally effective in this reaction, yielding **8t** in 80% yield (entry 20). More interestingly, the cyclization of 1-(1-pyridin-2-yl-propargyl)morpholine resulted in the 1-morpholin-1-yl indolizine **8u** in 71% yield, which provided the first convenient access to the C-2 substituted 1-amino-indolizines.[130] Propargyl phosphate (R^1=OPO(OEt)$_2$ in **7**) decomposed rapidly under reaction conditions. Also, attempts on employing 2-halogen substituted pyridine, halogen substituted benzamides, and halogen substituted nitrobenzenes as electrophile in this transformation resulted in complete decomposition of starting materials.

Table 7.



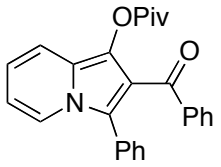
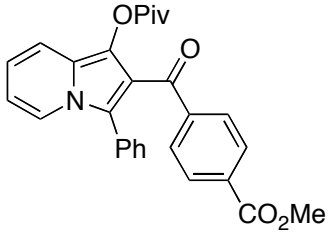
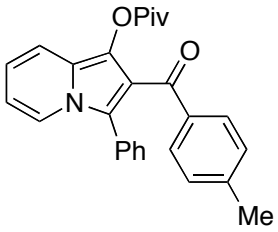
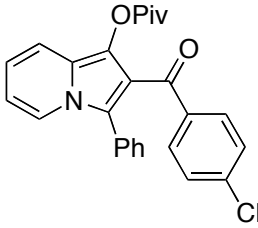
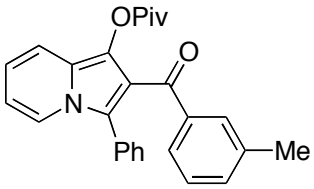
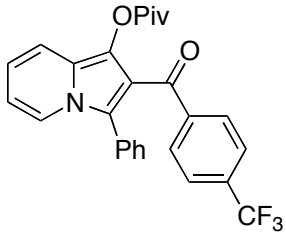
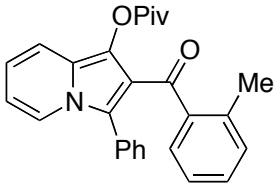
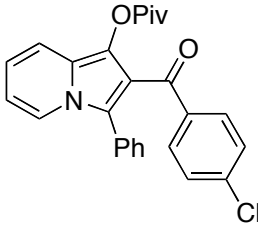
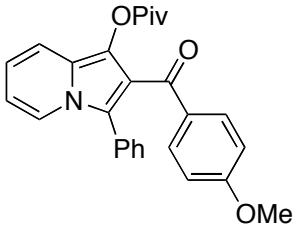
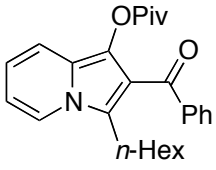
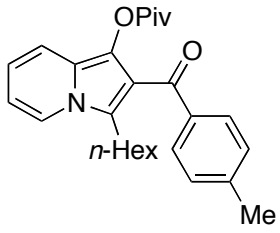
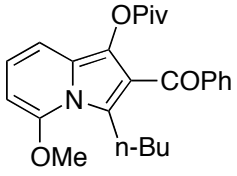
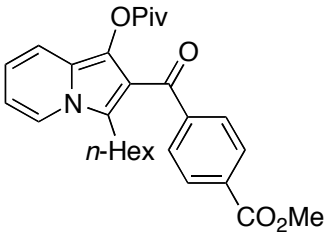
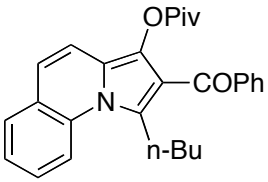
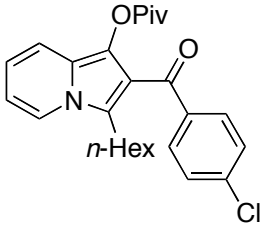
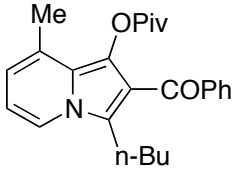
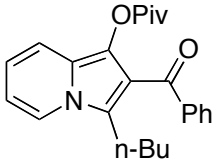
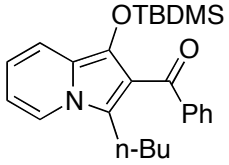
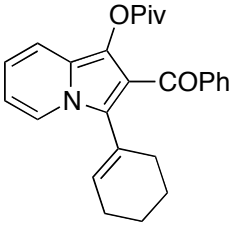
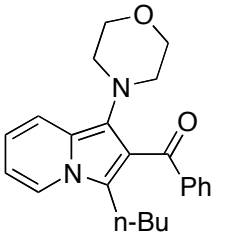
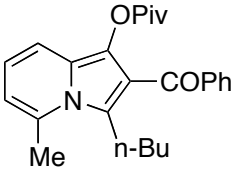
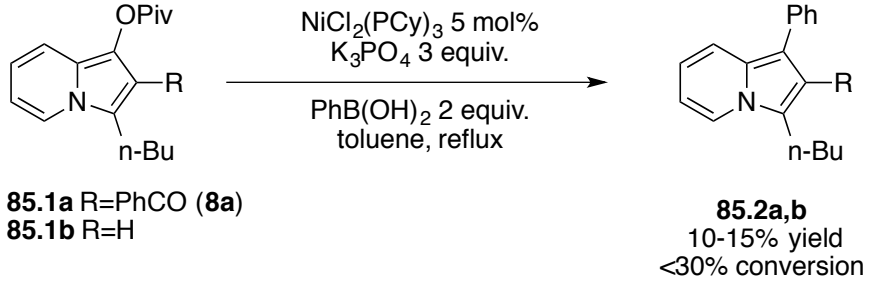
entry	**2**		Yield (%)[b]	entry	**2**		Yield (%)[b]
1		**8a**	95	6		**8f**	61
2		**8b**	77	7		**8g**	69
3		**8c**	78	8		**8h**	64
4		**8d**	99	9		**8i**	64
5		**8e**	59	10		**8j**	80

Table 7. (continued)

entry	**2**		Yield (%)[b]	entry	**2**		Yield (%)[b]
11		**8k**	80	17		**8q**	85
12		**8l**	64	18		**8r**	53
13		**8m**	81	19		**8s**	35
14		**8n**	67	20		**8t**	80
15		**8o**	72	21		**8u**	71
16		**8p**	90				

[a] Conditions: $Pd(OAc)_2$ 5 mol%, PPh_3 10 mol%, Ar-I 1.5 equiv., triethylamine 2 equiv., MeCN 0.2 M, 70 °C, CO 20 psi in sealed Schlenk tube, 12 h. [b] Isolated yields of 0.5 mmol reactions.

Next, the reactivity of obtained 2-aroyl indolizine **8a** in the Ni-catalyzed Suzuki reaction was tested (Scheme 85).[131] However, **8a** or its C-2 unsubstituted analogue **85.1b** shown poor conversion in this transformation with low material balance.



85.1a R=PhCO (**8a**)
85.1b R=H

85.2a,b
10-15% yield
<30% conversion

Scheme 85.

6.3. Conclusion

In summary, the Pd-catalyzed carbonylative cyclization/arylation approach to 2-aroyl indolizines has been developed. This new method allows for efficient and selective synthesis of a broad scope of 2-aroyl indolizines from readily available propargyl pyridines and iodoarenes under a carbon monoxide atmosphere with an easy setup and mild reaction conditions.

7. Experimental Section

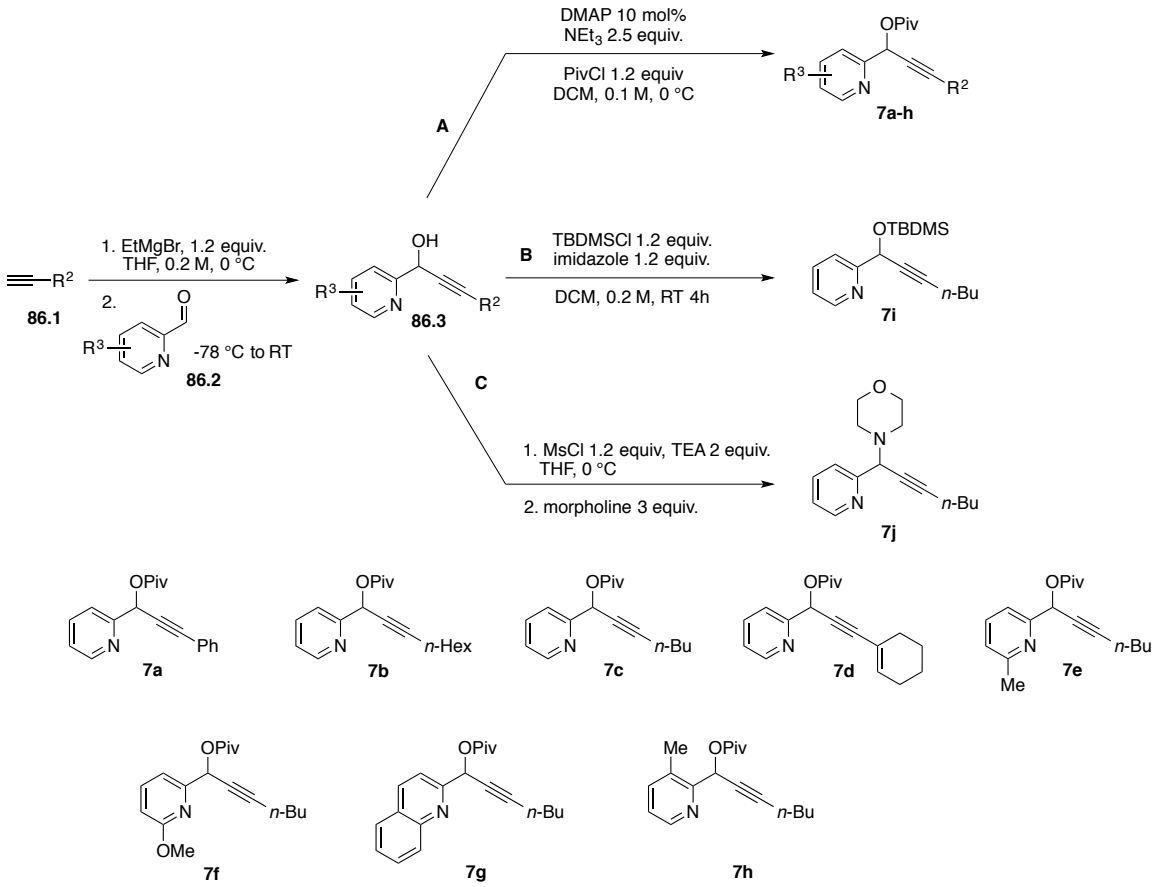
7.1. Instrumentations

NMR spectra were recorded on a Bruker Avance DRX-500 (500 MHz) or DPX-400 instrument. Spectra processing was performed in the ACD/Labs NMR Processor Academic Edition. Without notification, all signals in ^{13}C DEPT 135 spectra are positive except those followed with minus/(-) sign. $CDCl_3$ was purchased from Cambridge Isotope Laboratories, stored over potassium carbonate and activated 4Å M.S.. GC/MS analysis was performed on a Hewlett Packard Model 6890 GC (15 m x 0.25 mm capillary column, HP-5MS) interfaced to a Hewlett Packard Model 5973 mass selective detector. Column chromatography was carried out employing Silicycle Silica-P Flash silica gel (40-63μm). The silica gel was pre-treated by 1% (v/v) triethylamine in hexane before packing column. Pre-coated F-254 silica gel plates were used for thin-layer analytical chromatography. Anhydrous solvents and triethylamine were purchased from Aldrich and distilled over sodium or calcium hydride prior to use, and stored over 4Å M.S. under argon atmosphere. Carbon monoxide cylinder was purchased from Airgas and used without further purification. All commercially available compounds were used without further purification. Schlenk tubes were purchased from Chemglass (catalogue # AF-0096).

7.2. Preparation of Substrates

Substrates **7a**, **7b**, **7c**, **7d**, **7f**, **7g**, **7l** and **7i** were prepared according to procedures described in our previous report.[132] The synthetic routes are outlined below (Scheme 86).

The reactions described below were performed with 10 mmol of aldehyde.



Scheme 86.

Preparation of Propargyl Alcohol (General Procedure)

To a stirring solution of the terminal alkyne **86.1** (1.1 equiv.) in anhydrous THF (0.2 M) was added ethylmagnesium bromide (3 M in THF, 1.2 equiv.) at 0 °C (ice bath) under argon atmosphere. The resulting solution was stirred for 30 min to 1 h, then cooled to –78 °C (dry ice/acetone bath) for 5 min. A solution of aldehyde **86.2** (10 mmol, 1 equiv.) in anhydrous THF (1 M) was added via syringe, and the reaction mixture was stirred for 1 hour under -78 °C, then allowed warming to room temperature. For aldehydes, which exhibited low solubility in THF, the alkynyl magnesium bromide solution was added to the THF solution of aldehyde at 0 °C via cannula. The reaction was quenched by adding 20 mL of saturated aqueous ammonium chloride solution reaction at

0 °C, then extracted with 20 mL of ethyl acetate for 3 times. The combined organic phase was washed brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield the crudepropargyl alcohol **86.3**, which was submitted to further transformation directly without additional purification.

Preparation of Pivalates 7a—7h

To a solution of crude alcohol **86.3** in anhydrous dichloromethane (0.1 M) was added DMAP (10 mol%) and triethylamine (2.5 equiv.) at 0 °C (ice bath). After 5 minutes, neat PivCl (1.2 equiv.) was added to the aforementioned solution in one portion via syringe. The progress of reaction was monitored by TLC. Upon completion (40 min. approx.), 50 mL of water was added to the reaction mixture, extracted with 50 of mL dichloromethane for 3 times. The combined organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified through triethylamine-neutralized silica gel column using gradient elution (hexane/ethyl acetate 100:1 to 20:1 v/v).

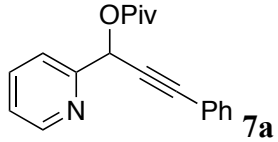
Preparation of Silyl Ether 7i

To a solution of crude alcohol **86.3** in anhydrous THF (0.2 M) was added imidazole (1.2 equiv.) at 0 °C (ice bath). Upon the complete dissolving of imidazole, crystalline TBDMSCl (1.1 equiv.) was added in one portion. The progress of reaction was monitored by TLC. Upon the completion, water (50 mL) was added to reaction mixture, extracted with 50 mL of ethyl acetate for 3 times. The combined organic phase was dried over sodium sulfate and concentrated by rotary evaporation and the residue was purified through silica gel column using gradient elution (hexane/ethyl acetate 100:1 to 20:1 v/v). Substrate **7i** was prepared according to this procedure.

Preparation of Propargyl Amine 7j

To a solution of crude propargyl alcohol **86.3** in anhydrous THF (0.2 M) was added triethylamine (2 equiv.) at 0 °C (ice bath). The resulting solution was stirred for 5 min, then methanesulfonyl chloride (1.5 equiv.) was added in one portion. The progress of esterification reaction was monitored by TLC. Upon the completion of esterification (30 min. approx.), morpholine (3 equiv.) was added in one portion under 0 °C. The reaction mixture was stirred over night, followed by filtration through a celite pad and the filter cake was rinsed with 50 mL of diethyl ether in order to remove ammonium salt. To the filtrate was added 50 mL of water, extracted with 20 mL of ethyl acetate for 3 times. Combined organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified through silica gel column using gradient elution (hexane/ethyl acetate 50:1 to 5:1 v/v).

Detailed Procedure for Preparation of Individual Substrates

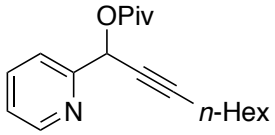


7a

The overall yield is 2.25 g, 77 %, with respect to 10 mmol of aldehyde.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (ddd, J = 4.81, 1.70, 0.83 Hz, 1 H), 7.73 - 7.77 (m, 1 H), 7.58 - 7.63 (m, 1 H), 7.45 - 7.48 (m, 2 H), 7.23 - 7.33 (m, 4 H), 6.72(s, 1 H), 1.27 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 156.5, 149.5, 137.0, 131.9, 128.7, 128.2, 123.3, 122.2, 121.3, 87.0, 85.1, 67.0, 38.8, 27.0.

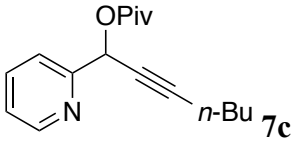


7b

The overall yield is 1.92 g, 64 %, with respect to 10 mmol of aldehyde.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (ddd, J = 4.8, 1.7, 0.8 Hz, 1 H), 7.70 (td, J = 7.7, 1.8 Hz, 1 H), 7.49 -7.52 (m, 1 H), 7.22 (ddd, J = 7.6, 4.8, 1.01 Hz, 1 H), 6.45 (t, J = 2.1 Hz, 1 H), 2.22 (td, J = 7.2, 2.1 Hz, 2 H), 1.44 - 1.53 (m, 2H), 1.30 - 1.38 (m, 2 H), 1.21 - 1.29 (m, 13 H), 0.85 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 157.0, 149.4, 136.8, 123.1, 121.1, 88.3, 76.2, 66.9, 38.7, 31.2, 28.4, 28.3, 27.0, 22.5, 18.8, 14.0.

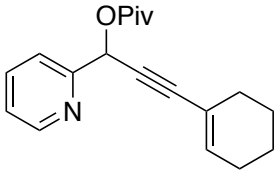


7c

The overall yield is 1.69 g, 62%, with respect to 10 mmol of aldehyde.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (ddd, J = 4.8, 1.7, 0.9 Hz, 1 H), 7.70 (td, J = 7.7, 1.8 Hz, 1H), 7.50 - 7.53 (m, 1 H), 7.22 (ddd, J = 7.5, 4.8, 1.1 Hz, 1 H), 6.45 (t, J = 2.1 Hz, 1 H), 2.20 - 2.28 (m, 2 H), 1.44 - 1.55 (m, 2 H), 1.32 - 1.42 (m, 2 H), 1.23 (s, 9 H), 0.87 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 157.0, 149.4, 136.8, 123.1, 121.1, 88.3, 76.2, 66.9, 38.7, 30.4, 27.0, 21.8, 18.5, 13.5.

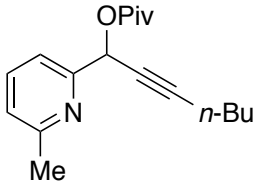


7d

The overall yield is 1.66 g, 56%, with respect to 10 mmol of aldehyde.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 4.8, 1.7, 0.8 Hz, 1 H), 7.70 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.51 - 7.55 (m, 1 H), 7.22 (ddd, *J* = 7.5, 4.78, 1.1 Hz, 1 H), 6.58 (br. s., 1 H), 6.12 - 6.17 (m, 1 H), 2.02 - 2.13 (m, 4 H), 1.49 - 1.63 (m, 4 H), 1.22 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 156.8, 149.4, 136.9, 136.3, 123.1, 121.2, 119.8, 88.9, 82.3, 67.0, 38.7, 28.8, 27.0, 25.6, 22.1, 21.3.



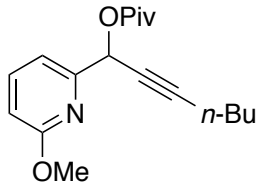
7e

The overall yield is 2.18 g, 76%, with respect to 10 mmol of aldehyde.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61 (dd, *J* = 7.3 Hz, 1 H), 7.34 (d, *J* = 7.3 Hz, 1 H), 7.10 (d, *J* = 7.3 Hz, 1 H), 6.42 (br. s., 1 H), 2.57 (s, 3 H), 2.21 - 2.31 (m, 2 H), 1.46 - 1.60 (m, 2 H), 1.35 - 1.45 (m, 2 H), 1.26 (s, 9 H), 0.88 (t, *J* = 6.6 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 177.30, 158.54, 156.91, 137.39, 123.11, 118.30, 88.53, 67.51, 39.14, 30.82, 27.45, 24.79, 22.26, 19.01, 13.94.

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 137.41, 123.13, 118.30, 67.51, 30.82 (-), 27.45, 24.79, 22.26 (-), 19.01 (-), 13.95.

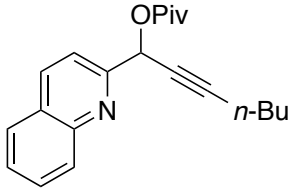


7f

The overall yield is 1.87 g, 62%, with respect to 10 mmol of aldehyde.

^{1}H NMR (400 MHz, $CDCl_3$) d: 7.54 (1 H, dd, *J* = 7.0, 8.2 Hz), 7.11 (1 H, d, *J* = 7.0 Hz), 6.64 (1 H, dd, *J* = 8.2 Hz), 6.37 (1 H, s), 3.88 (3 H, s), 2.23 (2 H, td, *J* = 7.0 Hz), 1.49 (2 H, m), 1.39 (2 H, m), 1.23 (9 H, s), 0.88 (3 H, t, *J* = 7.3 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.96, 163.55, 154.41, 138.98, 138.71, 113.51, 110.38, 109.56, 87.72, 76.34, 66.27, 53.26, 38.74, 30.43, 27.21, 27.18, 27.04, 21.81, 18.50, 13.51 .

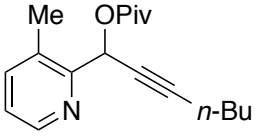


7g

The overall yield is 1.45 g, 45%, with respect to 10 mmol of aldehyde.

^{1}H NMR (400 MHz, C6D6) δ 8.26 (d, *J* = 8.3 Hz, 1 H), 7.68 - 7.82 (m, 2 H), 7.36 - 7.49 (m, 2 H), 7.18 - 7.30 (m, 2 H), 2.02 - 2.07 (m, 2 H), 1.26 - 1.36 (m, 13 H), 0.75 - 0.80 (m, 3 H).

^{13}C NMR (101 MHz, C6D6) δ 176.8, 158.0, 148.5, 137.4, 130.5, 130.1, 128.0, 127.2, 119.4, 89.2, 77.9, 68.5, 39.3, 31.0, 27.6, 22.4, 19.1, 14.0.



7h

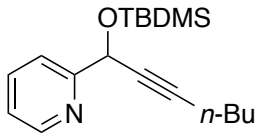
The overall yield is 1.82 g, 63%, with respect to 10 mmol of aldehyde.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.40 - 8.51 (m, 1 H), 7.50 (m, 1

H), 7.17 (dd, *J* = 7.3, 4.8 Hz, 1 H), 6.58 (t, *J* = 2.2 Hz, 1 H), 2.51 (s, 3 H), 2.25 (td, *J* = 7.2, 2.2 Hz, 2 H), 1.45 - 1.56 (m, 2 H), 1.38 (dq, *J* = 4.9, 7.3 Hz, 2 H), 1.24 (s, 9 H), 0.89 (t, *J* = 7.3 Hz, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$) δ: 177.52, 154.88, 147.16, 139.26, 132.07, 123.70, 89.00, 75.92, 66.57, 39.22, 31.98, 30.81, 27.56, 27.45, 22.29, 19.06, 18.53, 13.94

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 177.52, 154.88, 147.16, 139.26, 132.07, 123.70, 89.00, 75.92, 66.57, 39.22, 31.98, 30.81 (-), 27.56, 27.45, 22.29 (-), 19.06 (-), 18.53, 13.94.

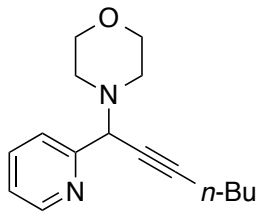


7i

The overall yield is 2.25 g, 77 %, with respect to 10 mmol of aldehyde.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1 H), 7.70 (m, 1 H), 7.59 - 7.63 (m, 1 H), 7.17 (ddd, *J* = 7.4, 4.8, 1.1 Hz, 1 H), 5.53 (t, *J* = 2.0 Hz, 1 H), 2.17 - 2.23 (m, 2 H), 1.42 - 1.51 (m, 2 H), 1.32 - 1.42 (m, 2 H), 0.93 (s, 9H), 0.87 (t, *J* = 7.3 Hz, 3 H), 0.18 (s, 3 H), 0.14 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.4, 148.6, 136.9, 122.4, 119.8, 86.3, 80.4, 66.6, 30.5, 25.8, 21.9, 18.6, 13.5, -4.6, -5.0.



7j

The overall yield is 1.19g, 46%, with respect to 10 mmol alcohol.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.58 - 8.66 (1 H, m), 7.66 - 7.73 (1 H, m), 7.61 - 7.66 (1 H, m), 7.20 (1 H, ddd, *J* = 7.34, 4.95, 1.28 Hz), 4.64 (1 H, t, *J* = 2.2 Hz), 3.63 - 3.85 (4 H, m), 2.89 (1 H, s), 2.59 (4 H, t, *J* = 4.8 Hz), 2.32 (2 H, td, *J* = 7.1, 2.0 Hz), 1.51 - 1.63 (2 H, m), 1.39 - 1.50 (2 H, m), 0.94 (3 H, t, *J* = 7.3 Hz)

^{13}C NMR (126 MHz, $CDCl_3$) δ: 158.27, 149.82, 136.69, 123.42, 122.88, 85.92, 75.39, 67.36, 64.2460, 50.47, 31.42, 22.45, 18.97, 14.00

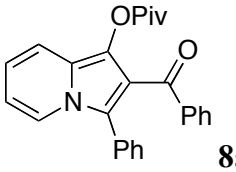
^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 149.82, 136.70, 123.42, 122.88, 67.36 (-), 64.2460, 50.45 (-), 31.42 (-), 22.45 (-), 18.97 (-), 14.00.

7.3. Carbonylative Cyclization of Propargyl Pyridines

All reactions were performed in 0.5 mmol scale. To a dry screw-thread vial was added propargyl pyridine **7** (1 equiv.) and iodoarene (1.5 equiv.). Iodoarenes that exhibits low solubility in acetonitrile were added to an oven-dried Schlenk tube, which will be vacuumed/recharged with argon 3 times before being transferred into a nitrogen-filled glove box. The vial was connected via an adapter (Chemglass CG-1318) to a vacuum/argon manifold and rapidly vacuumed/recharged with argon 3 times, then

anhydrous triethylamine (2 equiv.) and acetonitrile 2.5 mL were added to vial under a positive pressure of argon. This vial was brought into glove box together with an oven dried pressure tube (Chemglass AF-0096), and a stirring bar. Inside glove box, $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%, or other ligands) were added to the Schlenk tube with a stirring bar. The stock solution of substrates was transferred into the pressure tube by a pipette. The closed pressure tube was removed from the glove box, and connected to a vacuum/carbon monoxide manifold. After being vacuumed/recharged with 20 psi carbon monoxide 3 times under stirring, the Schlenk tube was sealed, disconnected from carbon monoxide source, and heated to 70 °C in an oil bath. Reactions were left overnight, usually finished within 12 hours as judged by GC-MS analysis.

Upon completion, the reaction mixture was transferred to a test tube containing 5 mL dichloromethane and 0.5 g of silica gel. The Schlenk tube was rinsed by 5 mL of dichloromethane for three times, and combined with silica gel slurry. The silica gel slurry was dried over rotary evaporation, and loaded onto a silica gel column which was flushed by hexane containing triethylamine (1%, v/v). The indolizines **8** were purified by silica gel chromatography using gradient elution (hexane/ethyl acetate). These indolizines usually show characteristic bright yellow spot on TLC (hexane/ethyl acetate 10:1 v/v, Rf = 0.4~0.5).



8a

The overall yield is 188.2 mg, 95%, with respect to pivalate. Yellowish solid, melting point 152~153 °C.

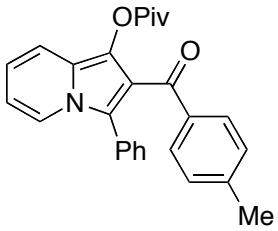
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.91 - 8.02 (1 H, m), 7.74 - 7.86 (2 H, m), 7.40 - 7.49 (3 H, m), 7.34 - 7.40 (2 H, m),

7.27 - 7.34 (3 H, m), 7.22 (1 H, dd, *J* = 9.17, 1.10 Hz), 6.66 - 6.78 (1 H, m), 6.45 - 6.55 (1 H, m), 1.17 (9 H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 192.04, 176.95, 139.24, 132.69, 131.02, 130.19, 130.10, 129.10, 128.72, 128.39, 126.16, 123.94, 122.92, 122.47, 118.80, 118.42, 117.42, 112.77, 39.38, 27.33

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 132.70, 131.02, 130.20, 129.10, 128.72, 128.41, 122.47, 118.42, 117.42, 112.79, 27.33

HRMS (EI): found *m/z* 397.16693, calculated for $C_{26}H_{23}O_3N$ 397.16780.



8b

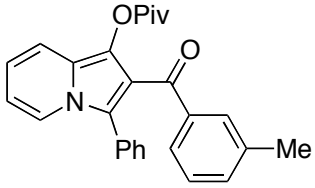
The overall yield is 160.8 mg, 77%, with respect to pivalate. Yellowish wax.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (1 H, dd, *J* = 7.3, 1.1 Hz), 7.66 - 7.76 (2 H, m), 7.41 - 7.50 (2 H, m), 7.37 (2 H, m), 7.27 - 7.34 (1 H, m), 7.17 - 7.27 (1 H, m), 7.10 - 7.17 (2 H, m), 6.67 - 6.77 (1 H, m), 6.49 (1 H, td, *J* = 6.9, 1.28 Hz), 2.36 (3 H, s), 1.17 (9 H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 191.69, 176.91, 143.45, 136.66, 130.94, 130.41, 130.17, 129.10 (overlap), 128.63, 126.04, 123.61, 122.88, 122.44, 119.10, 118.32, 117.41, 112.66, 39.35, 27.32, 21.97

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 130.94, 130.41, 129.10, 128.63, 122.44, 118.32, 117.41, 112.66, 27.31, 21.97

HRMS (EI): found *m/z* 411.18432, calculated for $C_{27}H_{25}O_3N$ 411.18345.



8c

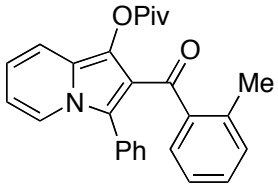
The overall yield is 162.9 mg, 78%, with respect to pivalate. Yellowish oil

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.97 (1 H, d, *J* = 7.0 Hz), 7.53 - 7.66 (2 H, m), 7.39 - 7.48 (2 H, m), 7.33 - 7.39 (2 H, m), 7.26 - 7.33 (1 H, m), 7.14 - 7.26 (3 H, m), 6.65 - 6.77 (1 H, m), 6.42 - 6.61 (1 H, m), 2.30 (3 H, s), 1.18 (9 H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 192.16, 176.92, 139.14, 137.99, 133.44, 131.01, 130.98, 130.19, 129.04, 128.67, 128.38, 127.23, 126.20, 123.92, 122.91, 122.47, 118.92, 118.36, 117.44, 112.73, 39.38, 27.32, 21.47

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 133.45, 131.02, 130.98, 129.04, 128.69, 128.38, 127.23, 122.47, 118.38, 117.44, 112.75, 27.32, 21.48

HRMS (EI): found *m/z* 411.18280, calculated for $C_{27}H_{25}O_3N$ 411.18345.



8d

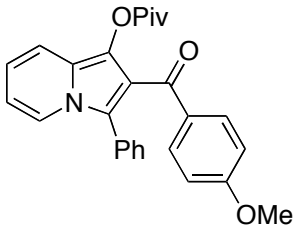
The overall yield is 204.2 mg, > 98%, with respect to pivalate. Yellowish wax.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.82 (1 H, d, J = 7.3 Hz), 7.42 (1 H, dd, J = 7.7, 1.1 Hz), 7.33 - 7.40 (4 H, m), 7.27 - 7.33 (1 H, m), 7.17 - 7.26 (2 H, m), 7.02 - 7.11 (2 H, m), 6.66 - 6.74 (1 H, m), 6.44 - 6.51 (1 H, m), 2.43 (3 H, s), 1.20 (9 H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 193.91, 177.08, 140.02, 138.08, 131.26, 131.02, 130.91, 130.61, 130.07, 128.95, 128.76, 126.33, 125.44, 124.72, 122.89, 122.45, 119.82, 118.32, 117.36, 112.88, 39.41, 27.38, 20.48

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 131.26, 131.02, 130.91, 130.63, 128.97, 128.76, 125.44, 122.45, 118.32, 117.36, 112.88, 27.38, 20.48

HRMS (EI): found *m/z* 411.18266, calculated for $C_{27}H_{25}O_3N$ 411.18345



8e

The overall yield is 126.2 mg, 59%, with respect to pivalate.Yellowish oil.

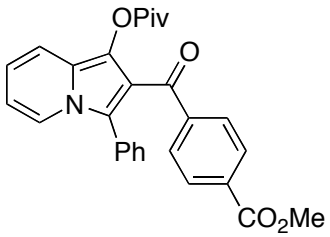
^{1}H NMR (500 MHz, $CDCl_3$) d: 7.99 (1 H, d, J = 7.3 Hz), 7.79 (2 H, m), 7.44 (2 H, m), 7.37 (2 H, m), 7.26 - 7.33 (1 H, m), 7.21 (1 H, d, J = 9.2 Hz), 6.81 (2 H, m), 6.72 (1 H, dd, J = 8.8, 6.6 Hz), 6.49 (1 H, t, J = 6.8 Hz), 3.82 (3 H, s),

1.18 (9 H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 190.63, 176.95, 163.54, 132.57, 132.10, 130.88, 130.22, 129.11, 128.61, 125.91, 123.32, 122.88, 122.42, 119.20, 118.29, 117.36, 113.69, 112.57, 55.85, 39.36, 27.36

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 132.57, 130.88, 129.11, 128.63, 122.42, 118.29, 117.36, 113.69, 112.57, 55.85, 27.36

HRMS (EI): found *m/z* 427.17767, calculated for $C_{27}H_{25}O4N$, 427.17836



8f

The overall yield is 131.2 mg, 61%, with respect to pivalate. Deep yellow wax.

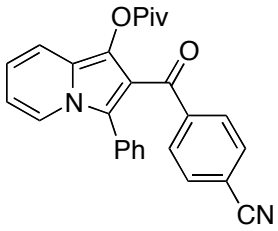
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.87 - 8.04 (3 H, m), 7.72 - 7.84 (2 H, m), 7.36 - 7.43 (2 H, m), 7.31 - 7.36 (2 H, m), 7.26 - 7.31 (1 H, m), 7.24 (1 H, dt, J = 9.2, 1.3 Hz), 6.65 - 6.81 (1 H, m), 6.43 - 6.60 (1 H, m), 3.93 (3 H, s), 1.20 (9 H, s)

^{13}C NMR (126 MHz, $CDCl_3$) δ: 191.49, 177.05, 166.76, 142.72, 133.23, 131.05, 129.95, 129.83, 129.54, 129.14, 128.92, 126.30, 124.19, 123.11, 122.45, 118.63, 118.32, 117.41, 113.04, 52.72, 39.39, 27.36

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 131.05, 129.95,

129.54, 129.14, 128.92, 122.45, 118.64, 117.41, 113.04, 52.73, 27.36

HRMS (EI): found *m/z* 455.17278, calculated for $C_{28}H_{25}O_5N$ 455.17327.



8g

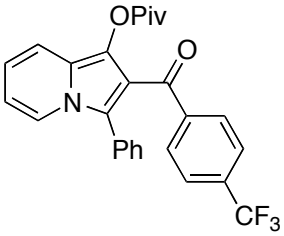
The overall yield is 146.5 mg, 69%, with respect to pivalate. Deep yellow wax.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.93 (1 H, d, J = 7.3 Hz), 7.77 (2 H, m), 7.44 - 7.59 (2 H, m), 7.19 - 7.40 (6 H, m), 6.69 - 6.81 (1 H, m), 6.44 - 6.64 (1 H, m), 1.26 (9 H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 190.69, 177.11, 142.58, 132.05, 131.07, 130.35, 129.67, 129.19, 129.11, 126.48, 124.27, 123.32, 122.42, 118.86, 118.52, 117.82, 117.38, 115.45, 113.29, 39.44, 27.39

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 132.05, 131.07, 130.35, 129.19, 129.11, 122.42, 118.88, 117.38, 113.30, 27.39

HRMS (EI): found *m/z* 422.16374, calculated for $C_{27}H_{22}O_3N_2$ 422.16305.



8h

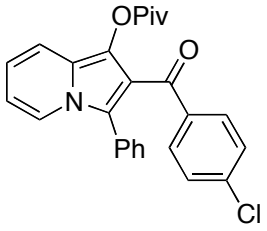
The overall yield is 147.9 mg, 64%, withrespect to pivalate. Yellow wax.

^{1}H NMR (500 MHz, $CDCl_3$) d: 7.89 - 8.01 (1 H, m), 7.82 (2H, m), 7.54 (2 H, m), 7.27 - 7.44 (5 H, m),7.24 (1 H, dt, *J* = 9.12, 1.1 Hz), 6.66 - 6.82 (1 H, m), 6.46 - 6.58(1 H, m), 1.21 (9 H, s)

^{13}C NMR (126 MHz, $CDCl_3$) d: 191.05, 177.07, 142.17,133.86, 133.60, 131.07, 130.27, 129.76, 129.16, 128.98, 126.35, 125.30, 125.27, 125.16, 124.33, 123.14, 122.48, 118.75, 118.10, 117.41, 113.16, 39.41, 27.31 .

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 131.07, 130.29, 129.16, 128.98, 125.33, 125.30, 125.27, 122.48, 118.75, 117.41, 113.16, 27.29 . 19F NMR (471 MHz, $CDCl_3$) δ: -63.56 (3 F, s) .

HRMS (EI): found *m/z* 465.15474, calculated for $C_{27}H_{22}O_3NF_3$ 465.15518.



8i

The overall yield is 138.2 mg, 64%, with respect to pivalate. Bright yellow wax.

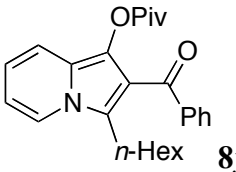
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.93 - 7.99 (1 H, m), 7.66 - 7.73 (2 H, m), 7.20 - 7.44 (8 H, m), 6.69 - 6.78 (1 H, m), 6.47 - 6.56 (1 H, m), 1.22 (9 H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 190.82, 177.04, 138.97,

137.51, 131.55, 130.98, 129.91, 129.17, 128.86, 128.61, 126.14, 123.86, 123.05, 122.44, 118.58, 118.41, 117.36, 112.94, 39.41, 27.36 .

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 131.55, 130.98, 129.17, 128.86, 128.61, 122.44, 118.58, 117.36, 112.94, 27.36.

HRMS (EI): found *m/z* 431.12797, calculated for $C_{26}H_{22}O_3NCl$ 431.12882.



8j

The overall yield is 162.7 mg, 80%, with respect to pivalate. Light yellow wax.

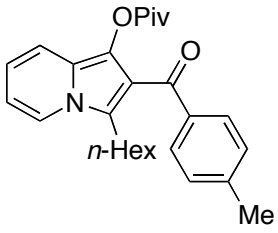
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.83 (2 H, m), 7.75 (1 H, d, *J* = 7.34 Hz), 7.51 - 7.58 (1 H, m), 7.40 - 7.49 (2 H, m), 7.03 - 7.15 (1 H, m), 6.61 - 6.69 (1 H, m), 6.49 - 6.61 (1 H, m), 2.98 - 3.14 (2 H, t, *J*=10.0 Hz), 1.67 (2 H, m), 1.32 - 1.44 (2 H, m), 1.24 - 1.32 (4 H, m), 0.99 (9 H, s), 0.82 - 0.91 (3 H, t, *J*=10.0 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 192.67, 176.70, 140.24, 132.60, 130.04, 128.58, 125.70, 124.79, 121.91, 121.73, 117.67, 117.54, 116.94, 112.42, 39.22, 31.91, 29.53, 28.31, 27.13, 24.66, 22.97, 14.39

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 132.60, 130.02, 128.58, 121.91, 117.67, 116.94, 112.42, 31.91 (-), 29.53 (-

), 28.31 (-), 27.13, 24.66 (-), 22.97 (-), 14.39 .

HRMS (EI): found *m/z* 405.23075, calculated for $C_{26}H_{31}O3N$ 405.23040.



8k

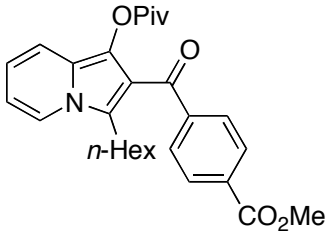
The overall yield is 167.5 mg, 80%, with respect to pivalate. Light yellow wax.

^{1}H NMR (500 MHz, $CDCl_3$) d: 7.74 (3 H, m), 7.24(2 H, m), 7.11 (1 H, d, *J* = 9.12 Hz), 6.61 - 6.69 (1 H,m), 6.49 - 6.60 (1 H, m), 2.95 - 3.14 (2 H, t, *J*=10.0 Hz), 2.42 (3 H, s), 1.65(2 H, quin, *J* = 7.61 Hz), 1.31 - 1.41 (2 H, m), 1.20 - 1.31 (4 H, m),1.01 (9 H, s), 0.79 - 0.93 (3 H, t, *J*=7.8 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 192.39, 176.70,143.29, 137.63, 130.22, 129.24, 125.38, 124.76, 121.91,121.70, 117.80, 117.64, 116.83, 112.30, 39.20, 31.91, 29.51,28.29, 27.13, 24.64, 22.95, 21.95, 14.39 .

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ 130.22, 129.24, 121.91, 117.64, 116.85, 112.32, 31.91 (-), 29.51 (-), 28.29 (-), 27.13, 24.64 (-), 22.95 (-), 21.95, 14.39

HRMS (EI): found *m/z* 419.24563, calculated for $C_{27}H_{33}O_3N$ 419.24605.



8l

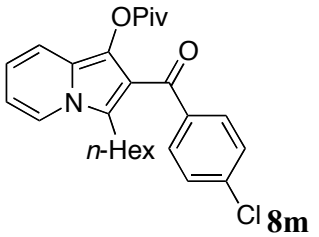
The overall yield is 149.1 mg, 64%, with respect to pivalate. Light yellow wax.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.11 (2 H, m), 7.87 (2 H, m), 7.74 (1 H, d, *J* = 7.3 Hz), 7.11 (1 H, d, *J* = 9.2 Hz), 6.66 (1 H, dd, *J* = 8.8, 6.2 Hz), 6.54 - 6.60 (1 H, m), 3.97 (3 H, s), 2.98 - 3.14 (2 H, t, *J*=7.9 Hz), 1.66 (2 H, quin, *J* = 7.61 Hz), 1.31 - 1.40 (2 H, m), 1.22 - 1.31 (4 H, m), 0.97 (9 H, s), 0.80 - 0.89 (3 H, t, *J*=10.0 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 191.88, 176.73, 166.79, 143.80, 133.41, 129.85 (overlaid), 126.07, 124.76, 121.91, 121.85, 117.67, 117.23, 117.10, 112.72, 52.76, 39.22, 31.88, 29.51, 28.26, 27.11, 24.67, 22.95, 14.38 .

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 129.85, 121.92, 117.67, 117.23, 112.72, 52.76, 31.88 (-), 29.51 (-), 28.26 (-), 27.11, 24.67 (-), 22.95 (-), 14.39 .

HRMS (EI): found *m/z* 463.23675, calculated for $C_{28}H_{33}O_5N$ 463.23587.



8m

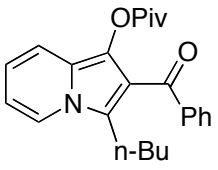
The overall yield is 178.6 mg, 81%, with respect to pivalate. Yellow wax.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71 - 7.84 (3 H, m), 7.39 - 7.47 (2 H, m), 7.11 (1 H, d, *J* = 9.2 Hz), 6.67 (1 H, dd, *J* = 9.0, 6.4 Hz), 6.55 - 6.62 (1 H, m), 3.05 (2 H, t, *J* = 10.0

Hz), 1.66 (2 H, m), 1.32 - 1.41 (2 H, m), 1.24 - 1.32 (4 H, m), 1.03 (9 H, s), 0.86 (3 H, t, *J* = 10.0 Hz).

^{13}C -DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 131.47, 128.86, 121.91, 117.64, 117.16, 112.60, 31.89 (-), 29.51 (-), 28.28 (-), 27.14, 24.64 (-), 22.97 (-), 14.39 .

HRMS (EI): found *m/z* 439.19060, calculated for $C_{26}H_{30}O_3NCl$ 439.19142



8n

The overall yield is 127.1 mg, 67%, with respect to pivalate. Light yellow wax.

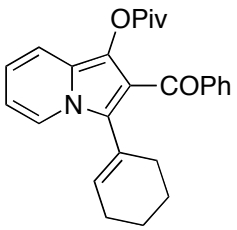
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.78 - 7.86 (2 H, m), 7.75 (1 H, d, *J* = 7.0 Hz), 7.50 - 7.60 (1 H, m), 7.40 - 7.49 (2 H, m), 7.09 - 7.16 (1 H, m), 6.62 - 6.70 (1 H, m), 6.53 - 6.61 (1 H, m), 3.04 - 3.10 (2 H, t, *J* = 10.0 Hz), 1.66 (2 H, m), 1.33 - 1.45 (2 H, m), 0.98 (9 H, s), 0.92 (3 H, t, *J* = 7.3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 192.69, 176.73, 140.24, 132.60, 130.02, 128.61, 125.70, 124.79, 121.92, 121.72, 117.69, 117.51, 116.94, 112.44, 30.44, 27.13, 27.01, 24.42, 22.97, 14.20 .

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 132.61, 130.04, 128.61, 121.92, 117.69, 116.95, 112.44, 30.44 (-), 27.11, 24.42 (-), 22.97 (-), 14.22 .

HRMS (EI): found *m/z* 377.19851, calculated for

$C_{24}H_{27}O_3N$ 377.19910



8o

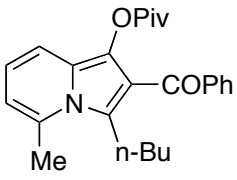
The overall yield is 144.5 mg, 72%, with respect to pivalate. Deep yellow wax.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.81 (1 H, d, J = 7.3 Hz), 7.77 (2 H, m), 7.44 - 7.54 (1 H, m), 7.34 - 7.44 (2 H, m), 7.12 (1 H, dd, J = 9.2, 1.1 Hz), 6.54 - 6.70 (1 H, m), 6.39 - 6.52 (1 H, m), 5.80 - 5.91 (1 H, m), 2.09 - 2.19 (2 H, m), 1.99 - 2.09 (2 H, m), 1.45 - 1.57 (4 H, m), 1.16 (9 H, s)

^{13}C NMR (126 MHz, $CDCl_3$) δ: 192.52, 176.65, 139.81, 133.79, 131.98, 129.44, 128.00, 127.72, 126.50, 125.26, 122.67, 121.85, 117.17, 116.94, 111.80, 38.93, 29.08, 26.93, 25.58, 22.52, 21.61.

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 134.22, 132.41, 129.85, 128.41, 123.08, 117.58, 117.35, 112.23, 29.50 (-), 27.35, 26.00 (-), 22.94 (-), 22.03 (-).

HRMS (EI): found *m/z* 401.19910, calculated for $C_{26}H_{27}O_3N$ 401.19909



8p

The overall yield is 175.2 mg, 90%, with respect to pivalate. Yellow wax.

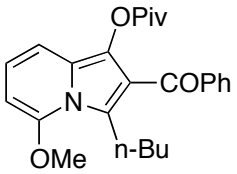
^{1}H NMR (500 MHz, $CDCl_3$) d: 7.79 - 7.89 (2 H, m), 7.53 (1 H, d, J = 7.7 Hz), 7.38 - 7.49 (2 H, m), 6.97 (1 H, d, J =

9.2 Hz), 6.53 (1 H, dd, J = 9.2, 6.6 Hz), 6.27 (1 H, d, J = 6.2 Hz), 3.23 -3.40 (2 H, t, J = 10.0 Hz), 2.81 (3 H, s), 1.59 - 1.73 (2 H, m), 1.34 - 1.46 (3 H, m), 0.95 (9 H, s), 0.90 (3 H, t, J = 7.34 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 193.01, 176.64, 140.20, 134.57, 132.73, 130.16, 128.61, 127.99, 125.16, 124.01, 118.86, 117.23, 115.55, 114.63, 39.19, 35.86, 27.08, 26.86, 22.61, 22.17, 14.23

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 132.73, 130.16, 128.61, 117.23, 115.55, 114.63, 35.88 (-), 27.08, 26.85 (-), 22.61 (-), 22.17, 14.54, 14.25

HRMS (EI): found *m/z* 391.21395, calculated for $C_{25}H_{29}O_3N$ 391.21475.



8q

The overall yield is 171.9 mg, 85%, with respect to pivalate. Light yellow wax.

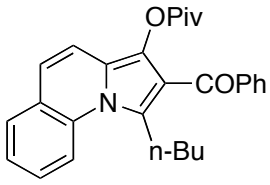
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.80 (2 H, m), 7.50 (1 H, t, J = 7.3 Hz), 7.41 (2 H, m), 6.66 (1 H, d, J = 9.1 Hz), 6.55 (1 H, dd, J = 9.0, 7.1 Hz), 5.67 (1 H, d, J = 7.0 Hz), 3.95 (3 H, s), 3.18 - 3.30 (2 H, t, J = 10.0 Hz), 1.65 (2 H, m), 1.29 - 1.38 (2 H, m), 0.94 (9 H, s), 0.87 (3 H, t, J = 7.3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 192.47, 176.18, 151.73, 139.78, 132.28, 129.72, 128.17, 126.76, 124.36, 123.95,

118.51, 117.89, 109.16, 87.08, 55.95, 38.74, 34.44, 27.12, 26.68, 22.49, 13.91.

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 132.70, 130.14, 128.60, 118.32, 109.57, 87.51, 56.38, 34.87 (-), 27.54 (-), 27.10, 22.91 (-), 14.34

HRMS (EI): found *m/z* 407.20969, calculated for $C_{25}H_{29}NO_4$ 407.20966.



8r

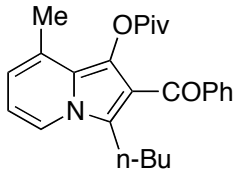
The overall yield is 113.9 mg, 53%, with respect to pivalate. Dark yellow wax.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.19 (1 H, d, *J* = 8.4 Hz), 7.84 (2 H, m), 7.61 (1 H, dd, *J* = 7.7, 1.5 Hz), 7.51 - 7.57 (1 H, m), 7.47 - 7.51 (1 H, m), 7.41 - 7.47 (2 H, m), 7.36 (1 H, t, *J* = 7.5 Hz), 6.98 (1 H, d, *J* = 9.1 Hz), 6.92 (1 H, d, *J* = 9.17 Hz), 3.40 - 3.54 (2 H, t, *J* = 10.0 Hz), 1.83 (2 H, m), 1.47 (2 H, m), 0.91 - 1.01 (12 H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 192.58, 176.60, 140.27, 135.14, 132.79, 132.33, 130.14, 129.45, 128.67, 127.99, 127.52, 126.76, 124.86, 121.55, 119.82, 118.75, 117.52, 116.11, 39.26, 31.41, 27.95, 27.10, 22.83, 14.23.

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 132.82, 130.16, 129.47, 128.69, 128.02, 124.89, 119.85, 117.54, 116.13, 31.41 (-), 27.96 (-), 27.10, 22.84 (-), 14.25.

HRMS (EI): found *m/z* 427.21475., calculated for $C_{28}H_{29}O_3N$ 427.21474.



8s

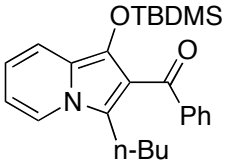
The overall yield is 68.7 mg, 35%, with respect to pivalate. Yellow wax.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 - 7.89 (2 H, m), 7.60 (1 H, d, *J* = 7.3 Hz), 7.52 - 7.58 (1 H, m), 7.42 - 7.50 (2 H, m), 6.46(1 H, t, *J* = 6.79 Hz), 6.38 (1 H, d, *J* = 6.24 Hz), 2.91 - 3.03 (2 H, t, *J* = 10.0 Hz), 2.43 (3 H, s), 1.55 - 1.70 (3 H, m), 1.32 - 1.37 (2 H, m), 0.98 (9 H, s), 0.85 - 0.90 (3 H, t, *J* = 10.0 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 192.64, 177.54, 139.94, 132.74, 130.24, 129.02, 128.64, 125.82, 125.47, 122.08, 119.91, 117.89, 117.30, 112.17, 39.08, 30.29, 27.20, 24.54, 22.92, 19.45, 14.19.

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 132.74, 130.24, 128.64, 119.91, 117.30, 112.17, 30.29 (-), 27.20, 24.54 (-), 22.92 (-), 19.47, 14.19.

HRMS (EI): found *m/z* 391.21439, calculated for $C_{25}H_{29}O_3N$ 391.21475



8t

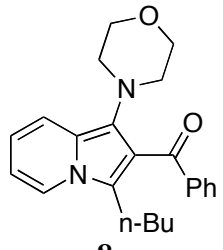
The overall yield is 163.2 mg, 80%, with respect to pyridine. Light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94 (2 H, m), 7.60 - 7.71 (1 H, m), 7.52 (1 H, d, J = 7.3 Hz), 7.42 - 7.50 (2 H, m), 7.27 (1 H, dd, J = 6.1, 3.5 Hz), 6.37 - 6.52 (2 H, m), 3.04 (2 H, t, J = 7.7 Hz), 1.62 (2 H, t, J = 7.70 Hz), 1.30 - 1.44 (2 H, m), 0.90 (3 H, t, J = 7.3 Hz), 0.73 (9 H, s), -0.15 (6 H, s)

^{13}C NMR (126 MHz, $CDCl_3$) δ: 193.95, 139.48, 132.76, 131.07, 130.29, 128.45, 124.14, 121.39, 120.77, 118.67, 117.41, 114.04, 112.13, 30.44, 25.81, 24.36, 22.94, 18.17, 14.25, -4.47 .

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 132.76, 131.07, 128.47, 121.39, 118.67, 114.04, 112.14, 30.44 (-), 25.81, 24.36 (-), 22.94 (-), 14.26, -4.47 .

HRMS (EI): found *m/z* 407.22869, calculated for $C_{25}H_{33}O_2NSi$ 407.22086.



8u

The overall yield is 128.1 mg, 71%, with respect to pyridine. Reddish oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.78 - 7.88 (2 H, m), 7.71 (1 H, d, J = 7.34 Hz), 7.54 - 7.61 (1 H, m), 7.51 (1 H, d, J = 8.80 Hz), 7.42 - 7.48 (2 H, m), 6.54 - 6.60 (1 H, m), 6.46 - 6.54 (1 H, m), 3.30 - 3.43 (4 H, m), 2.98 - 3.09 (4 H, m),

2.86 - 2.96 (2 H, m), 1.59 (2 H, m), 1.30 - 1.40 (2 H, m), 0.81 - 0.94 (3 H, t, J = 7.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 196.27, 140.48, 132.69, 130.14, 128.29, 126.63, 125.36, 124.95, 122.27, 121.58, 119.64, 115.63, 111.80, 67.82, 53.92, 30.26, 24.50, 22.97, 14.14 .

^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$) δ: 132.69, 130.14, 128.29, 122.29, 119.66, 115.63, 111.80, 67.82 (-), 53.91 (-), 30.26 (-), 24.50 (-), 22.97 (-), 14.16 .

HRMS (EI): found *m/z* 362.20025, calculated for $C_{23}H_{26}O_2N_2$ 362.19943

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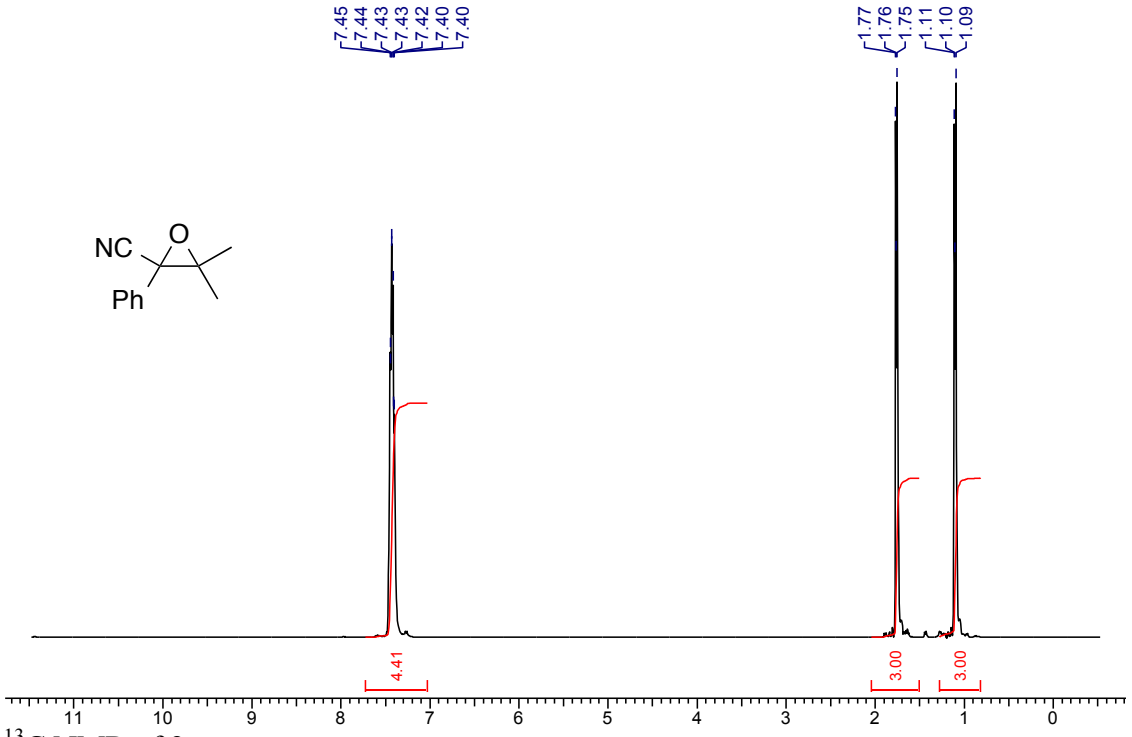
APPENDICES

^{1}H NMR of **2a**



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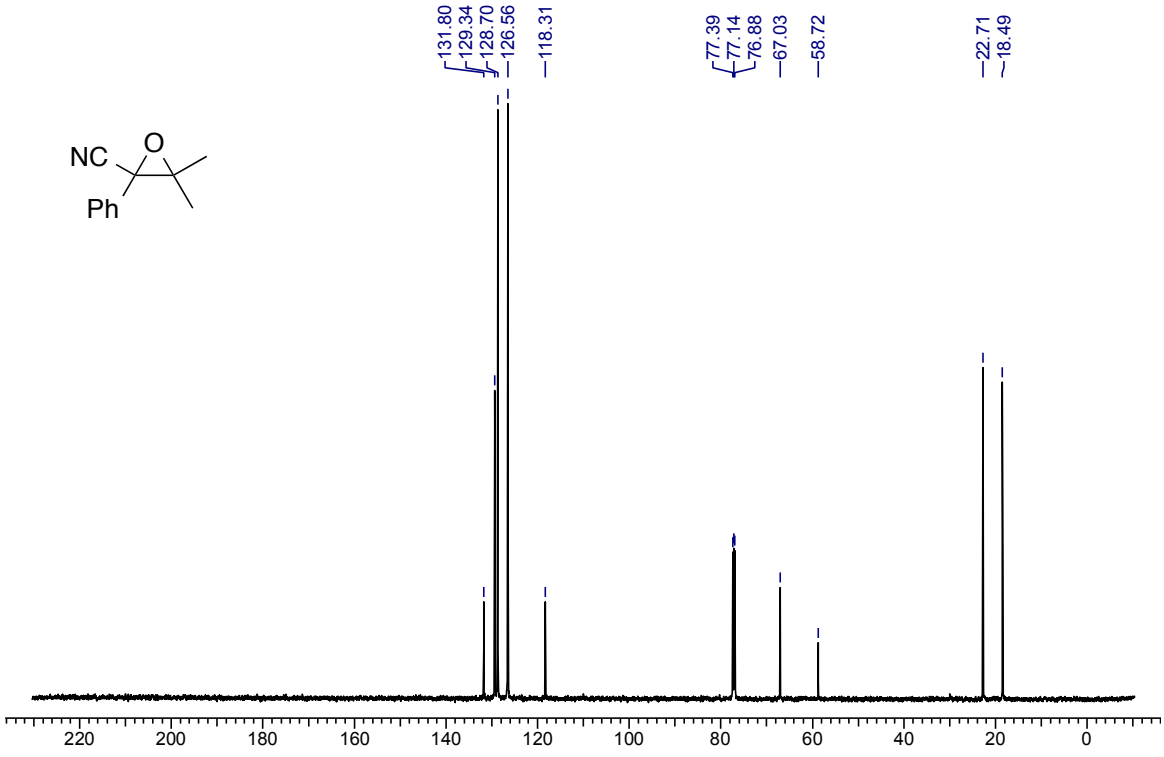

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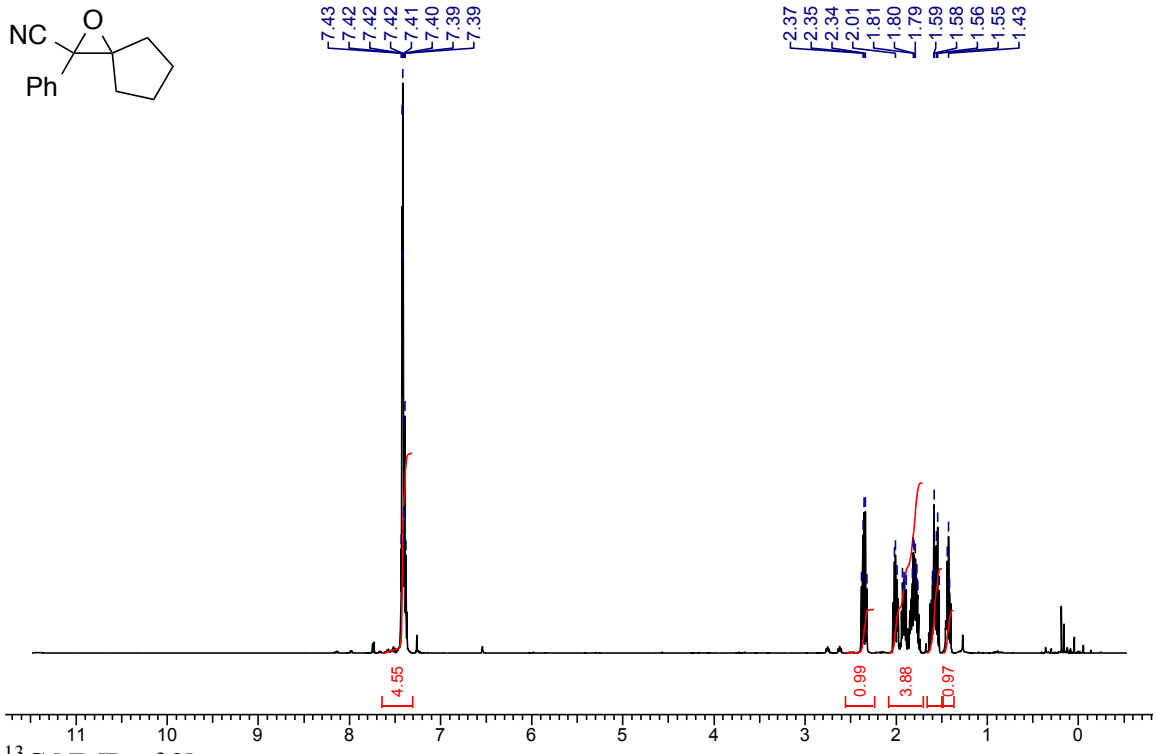

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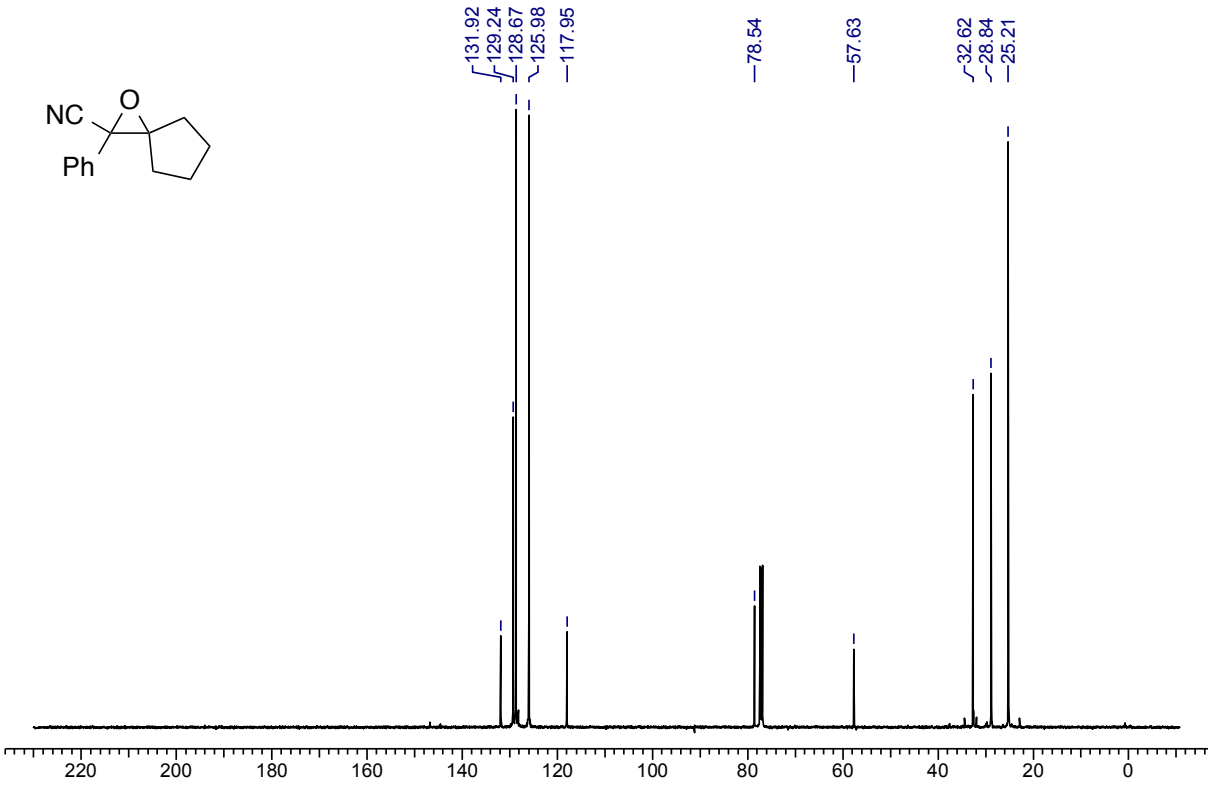

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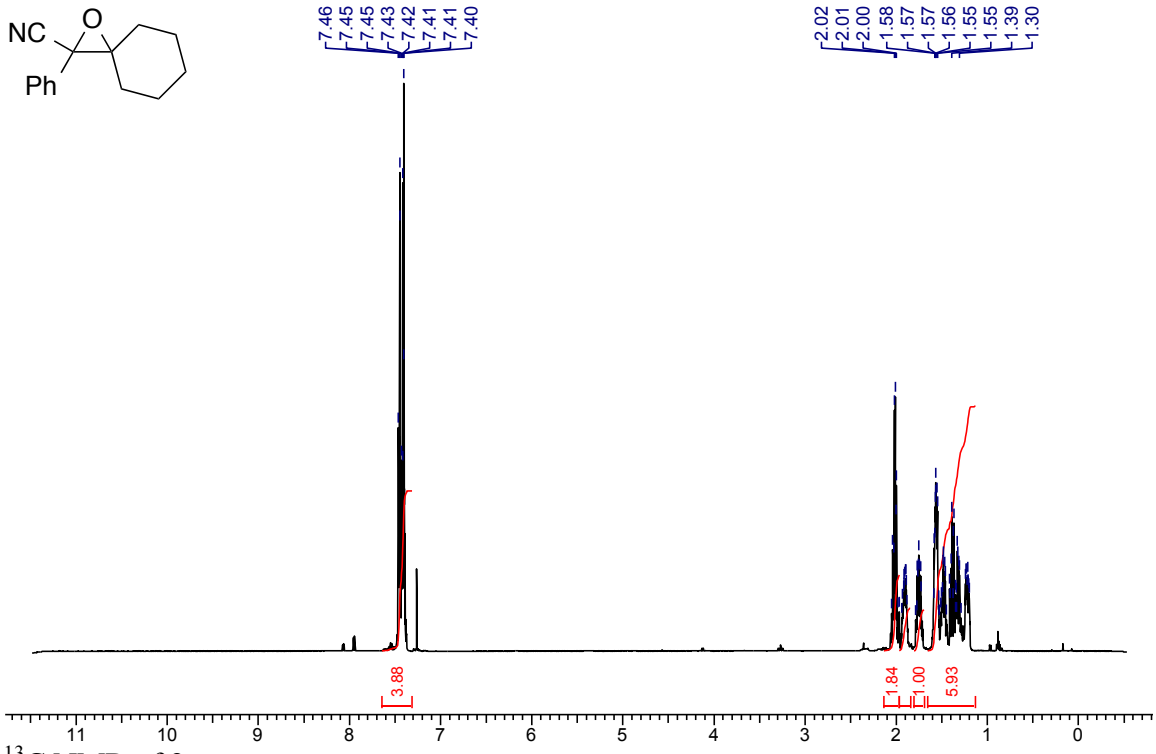

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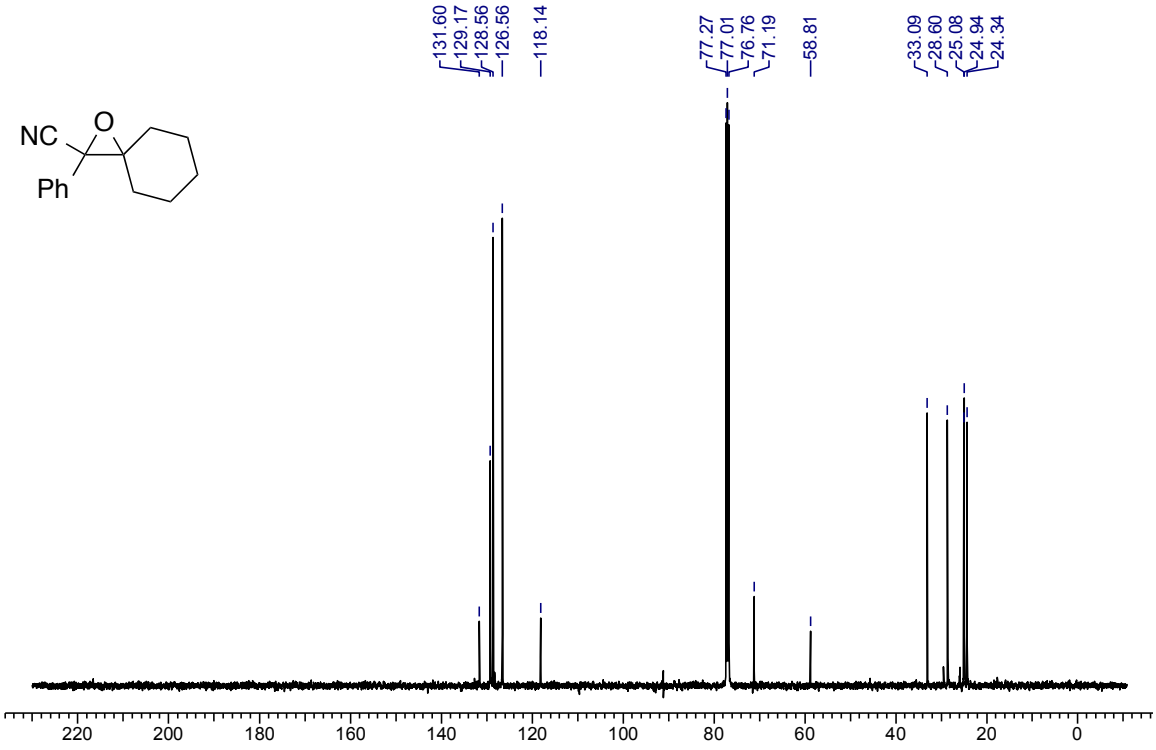

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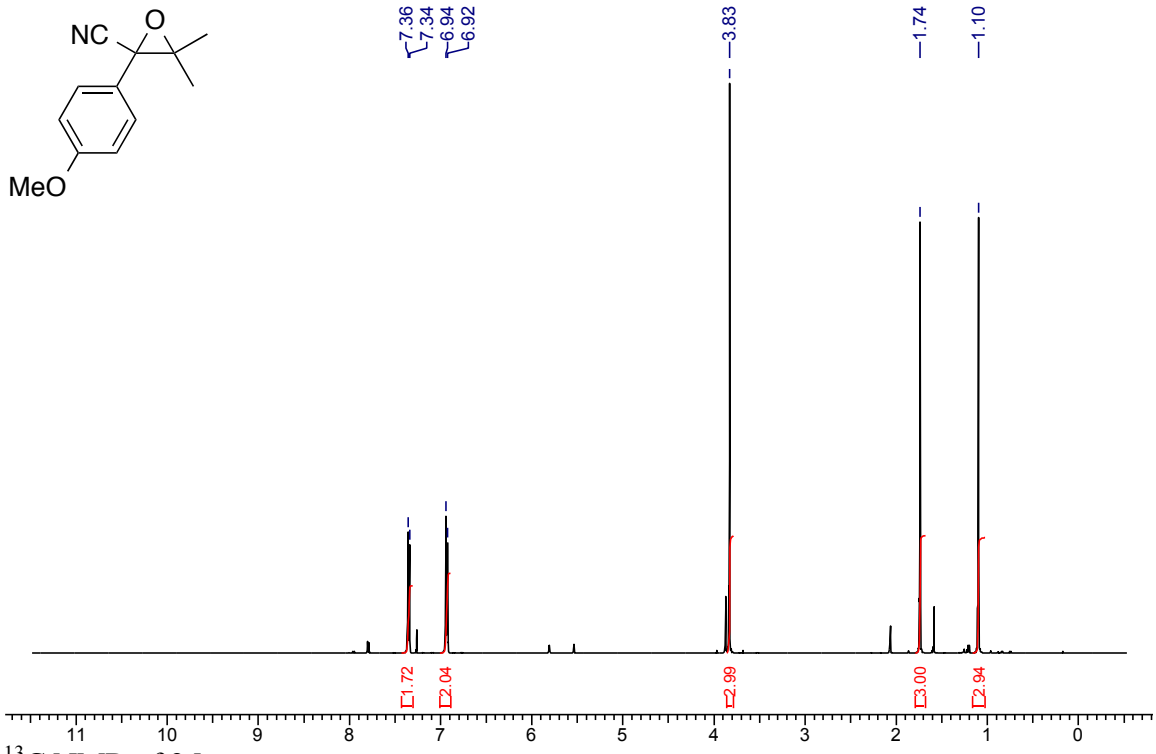

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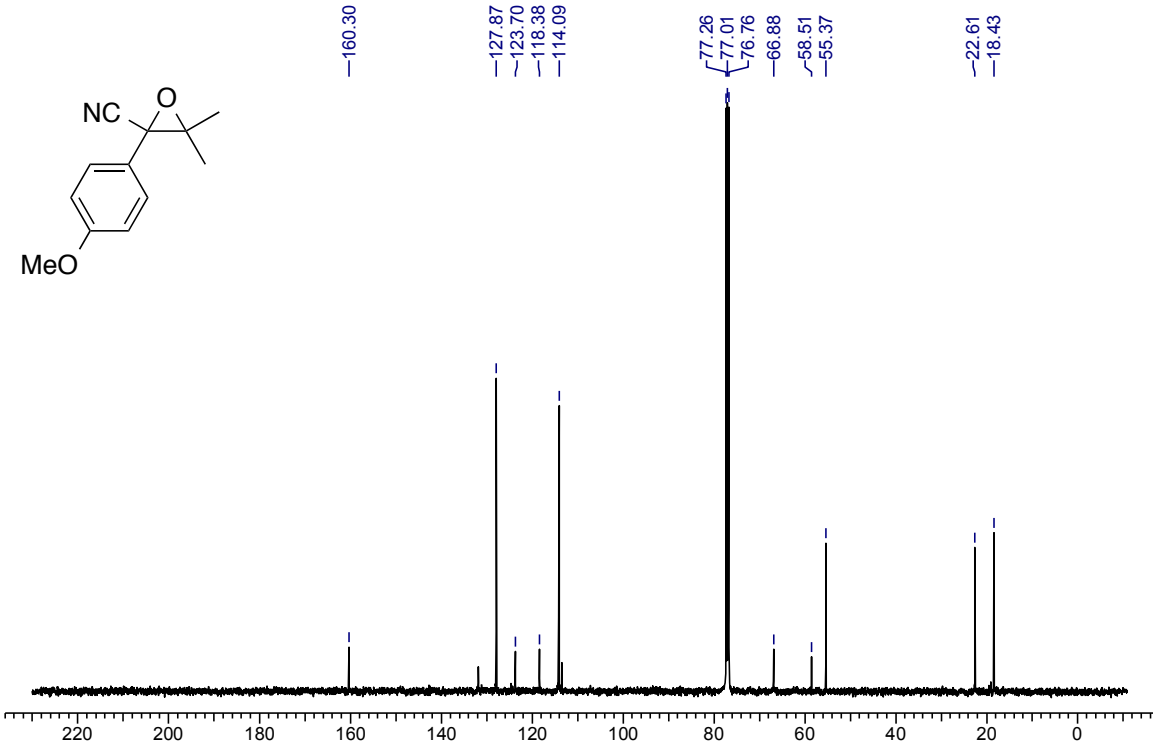

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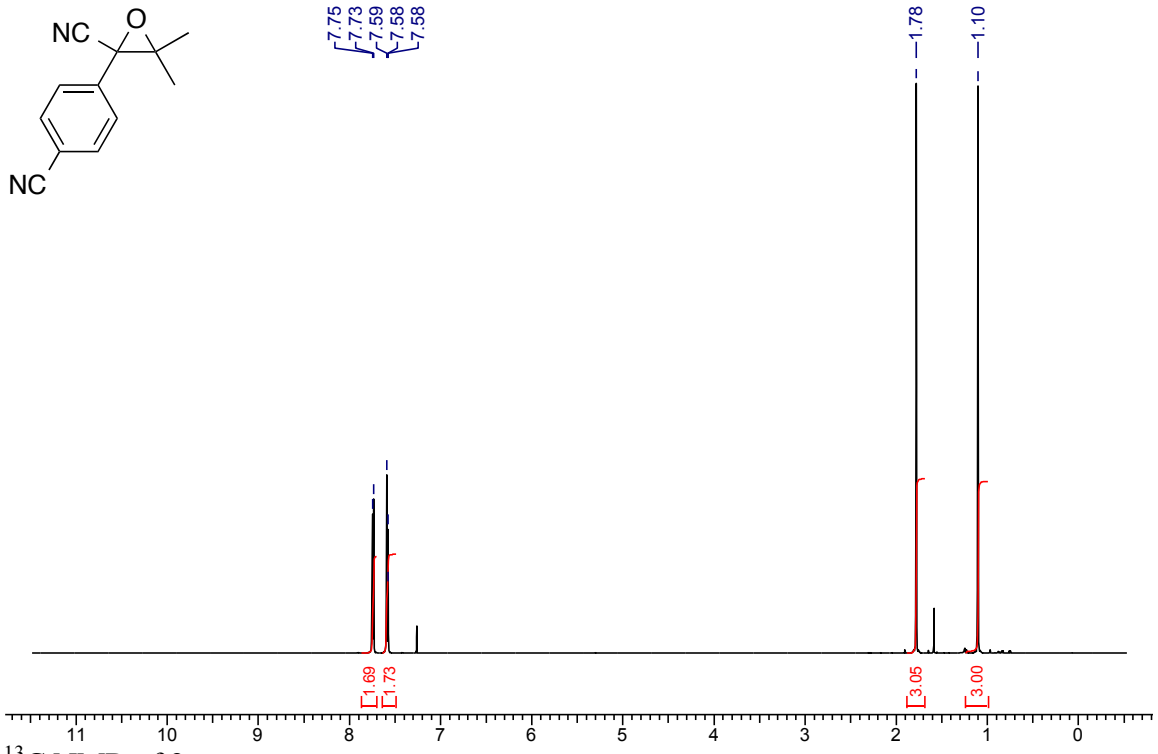

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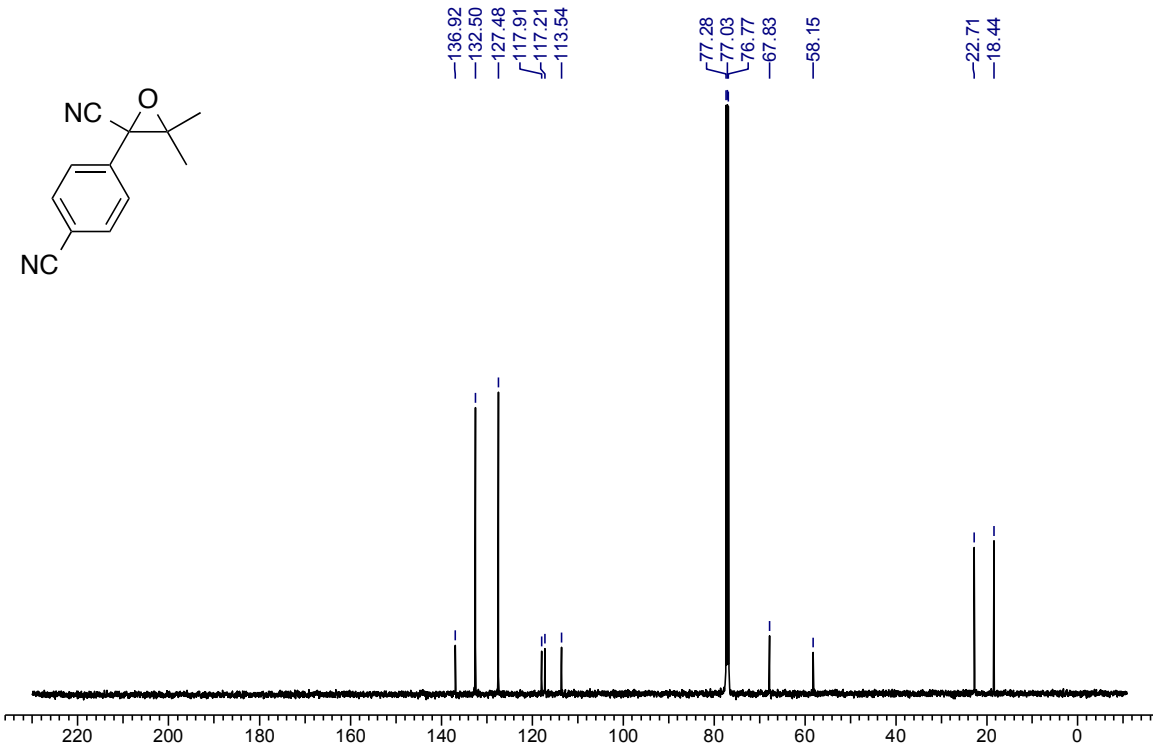

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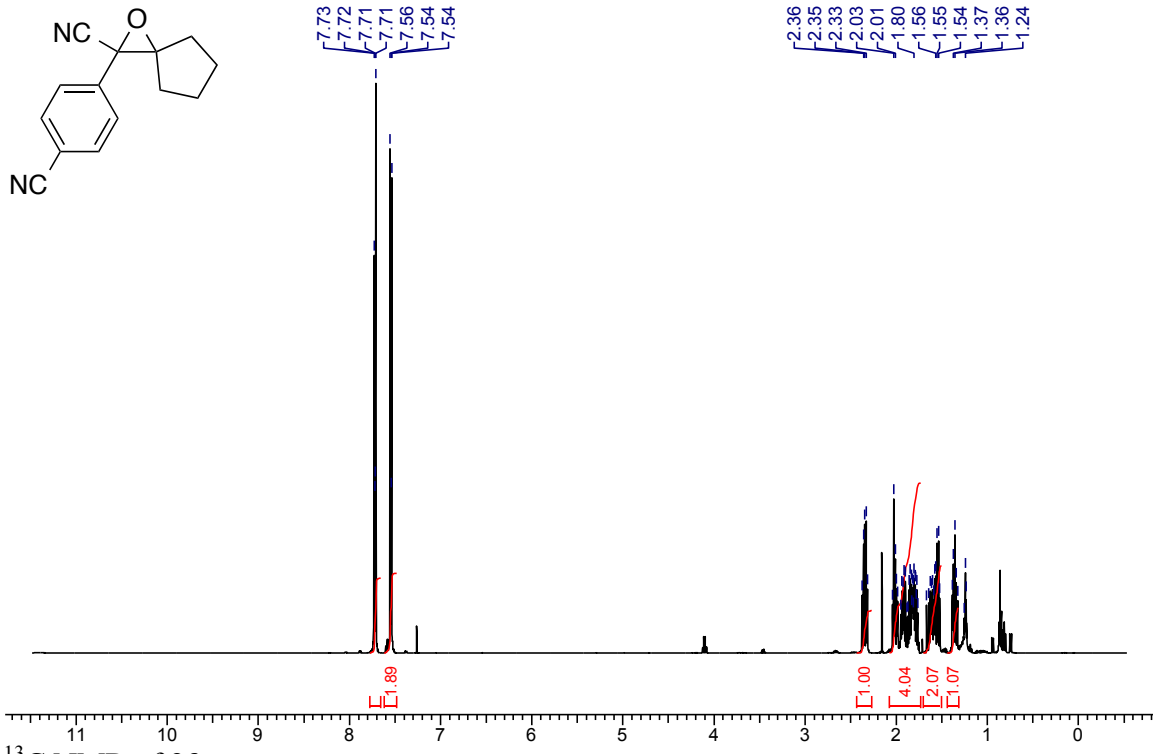

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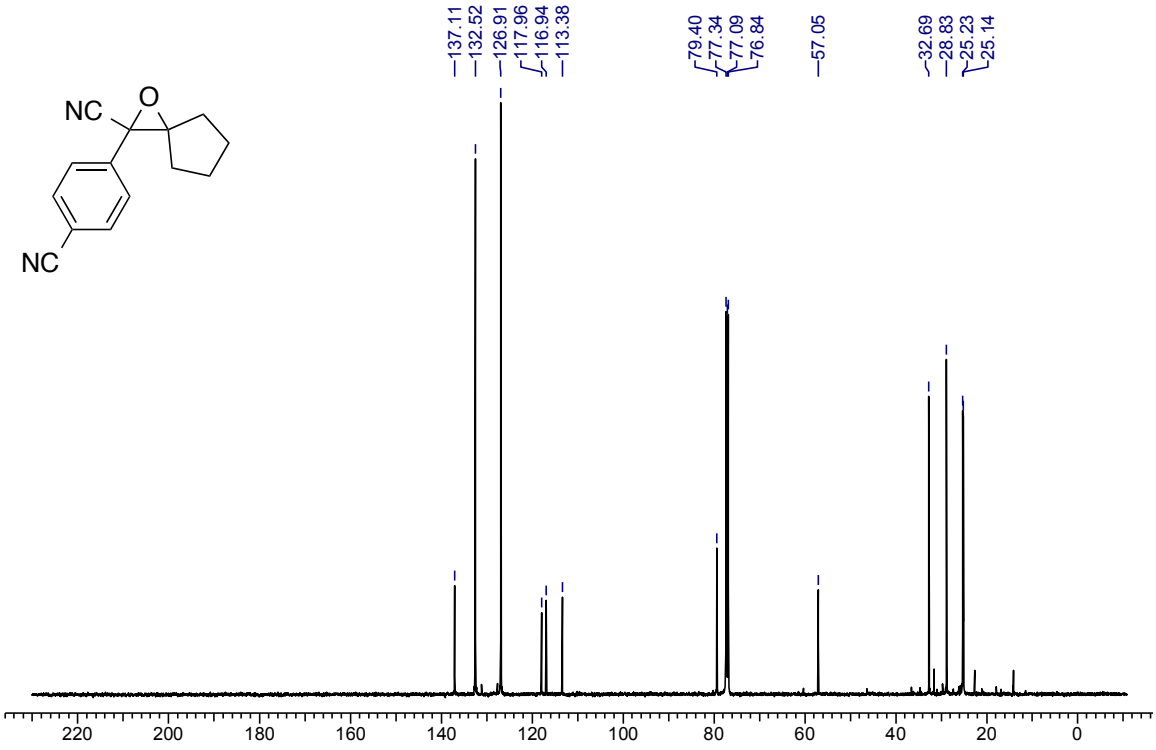

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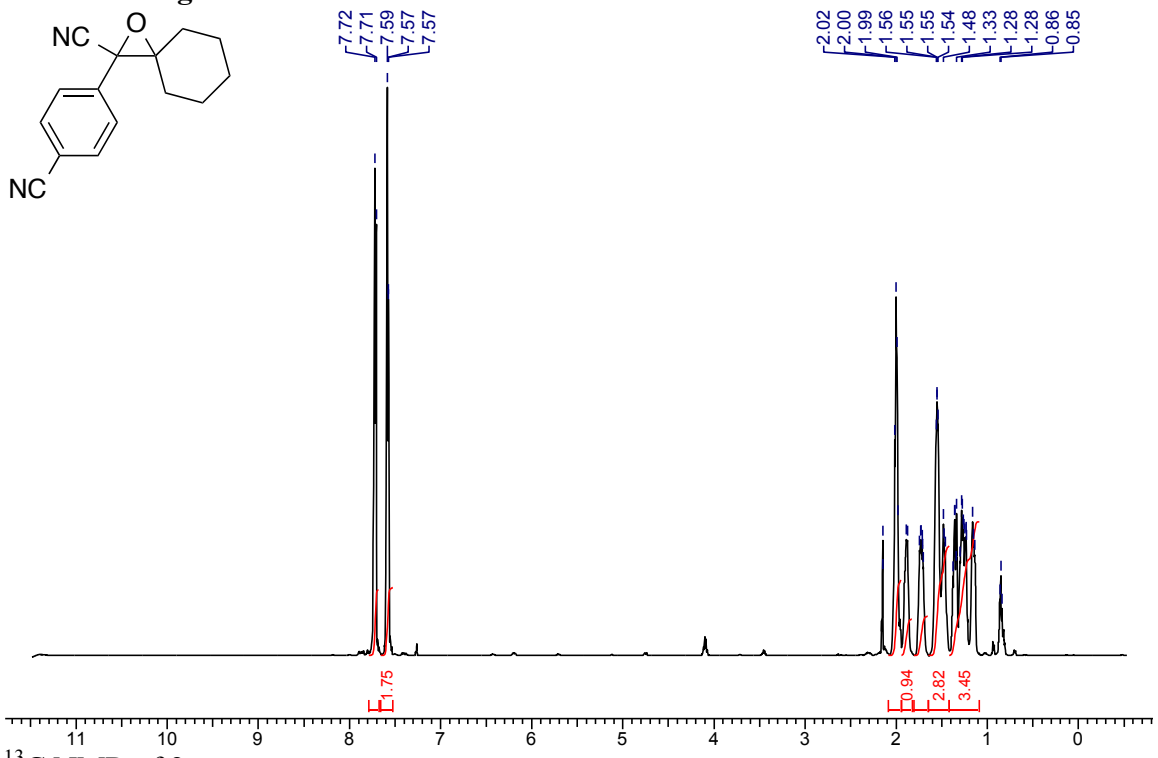

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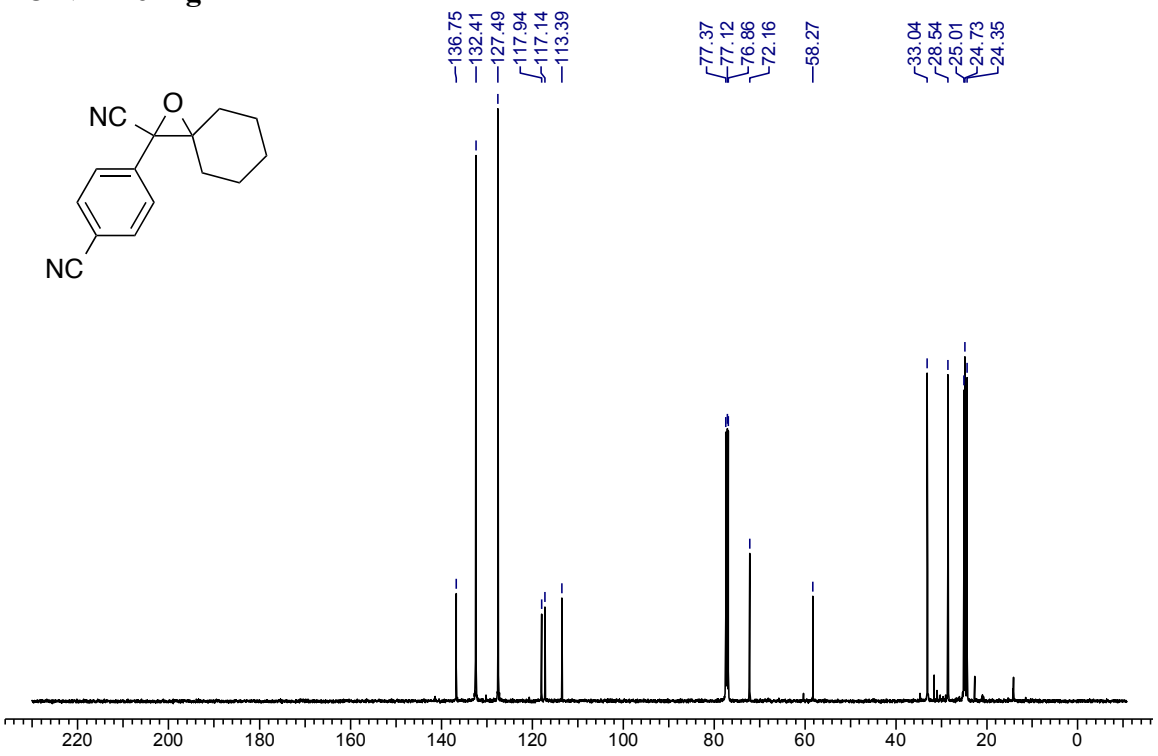

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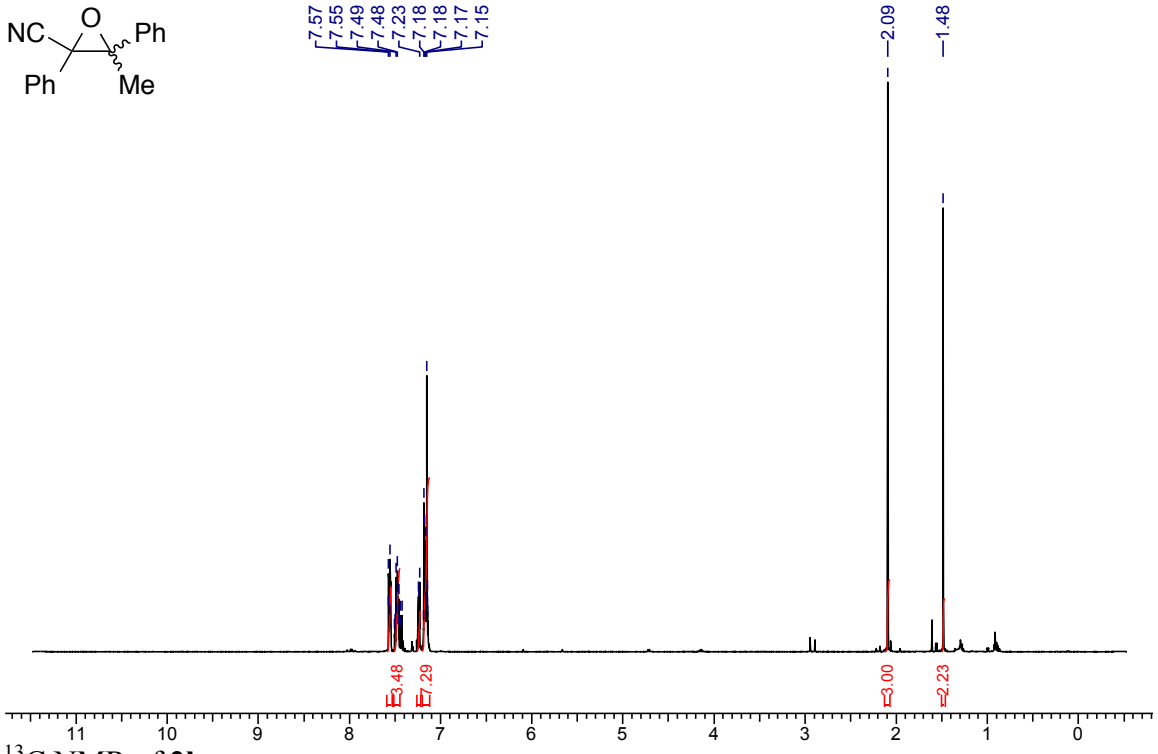

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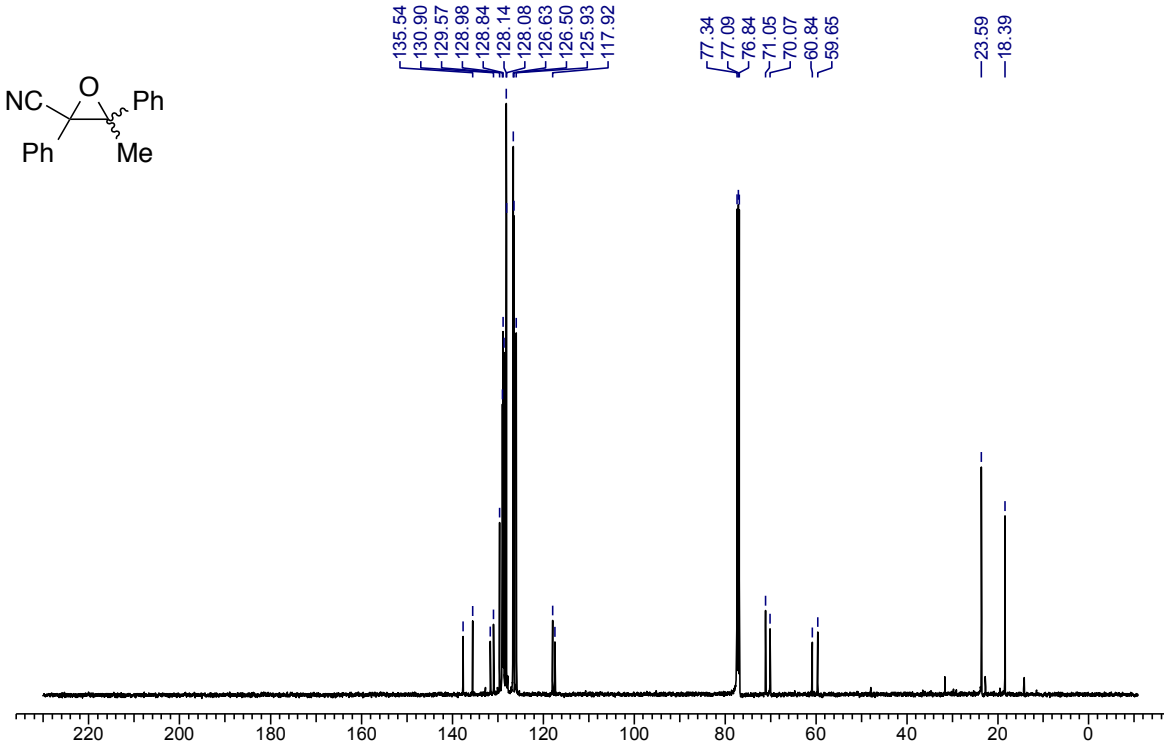

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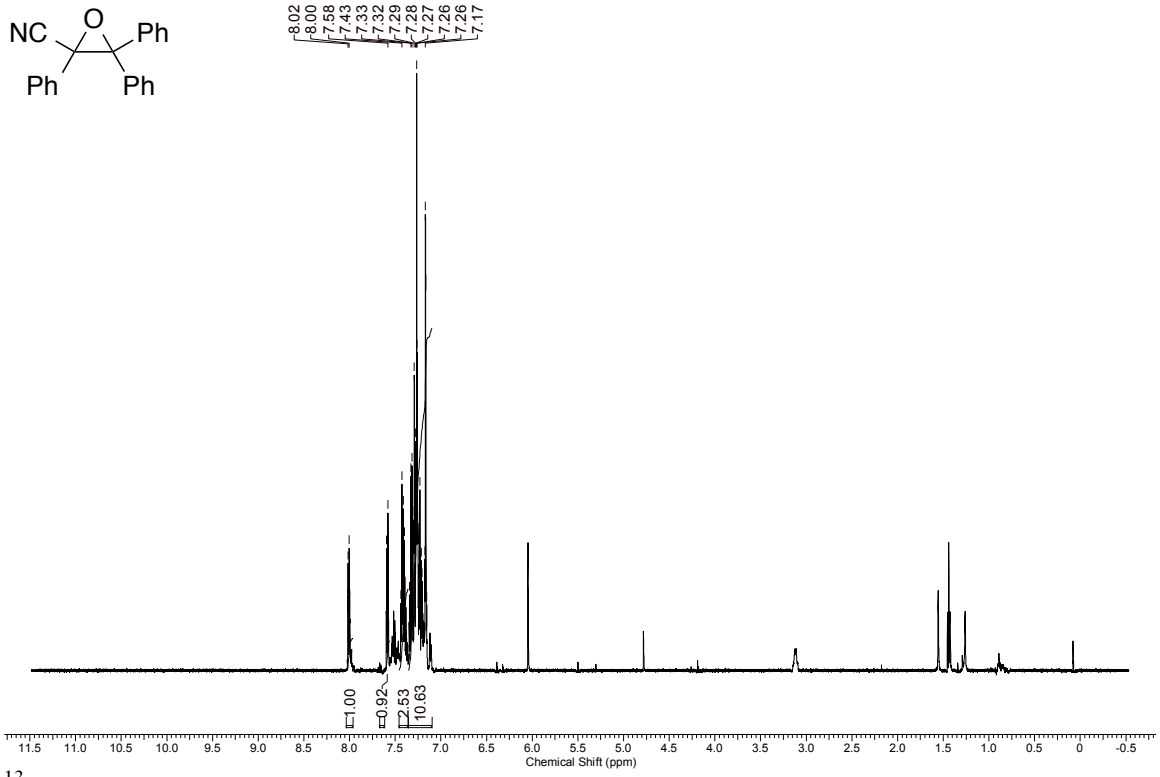

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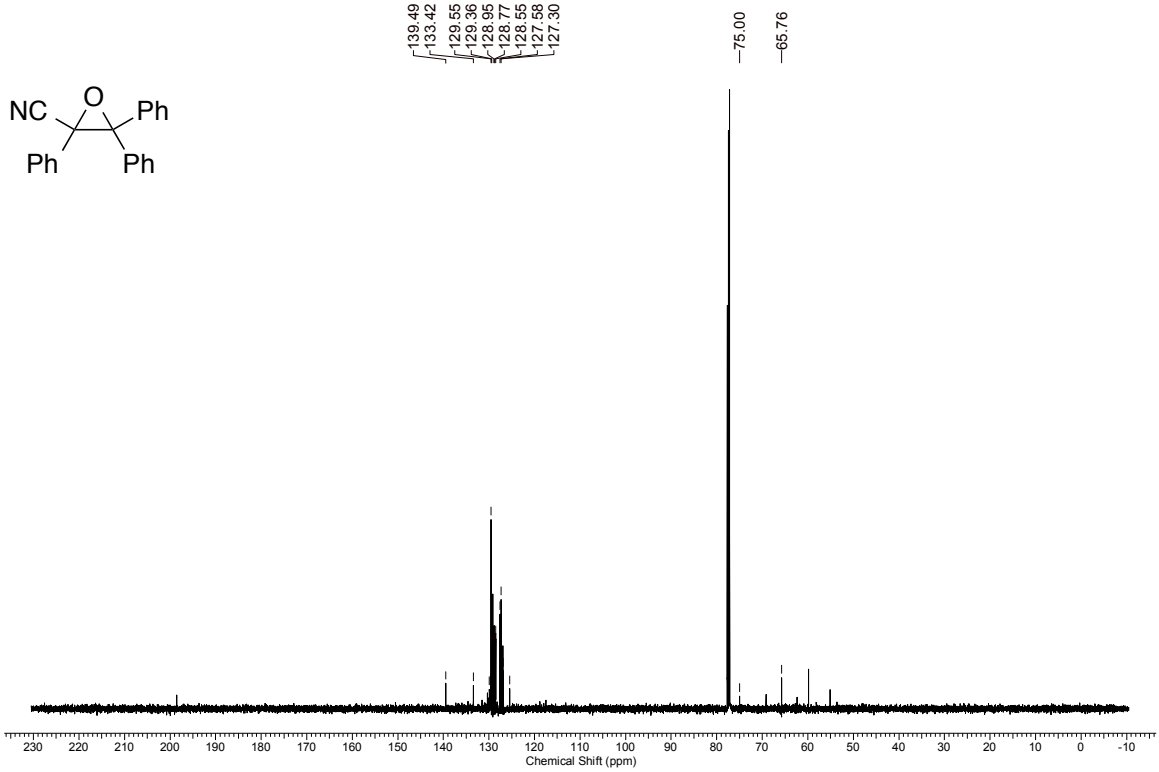

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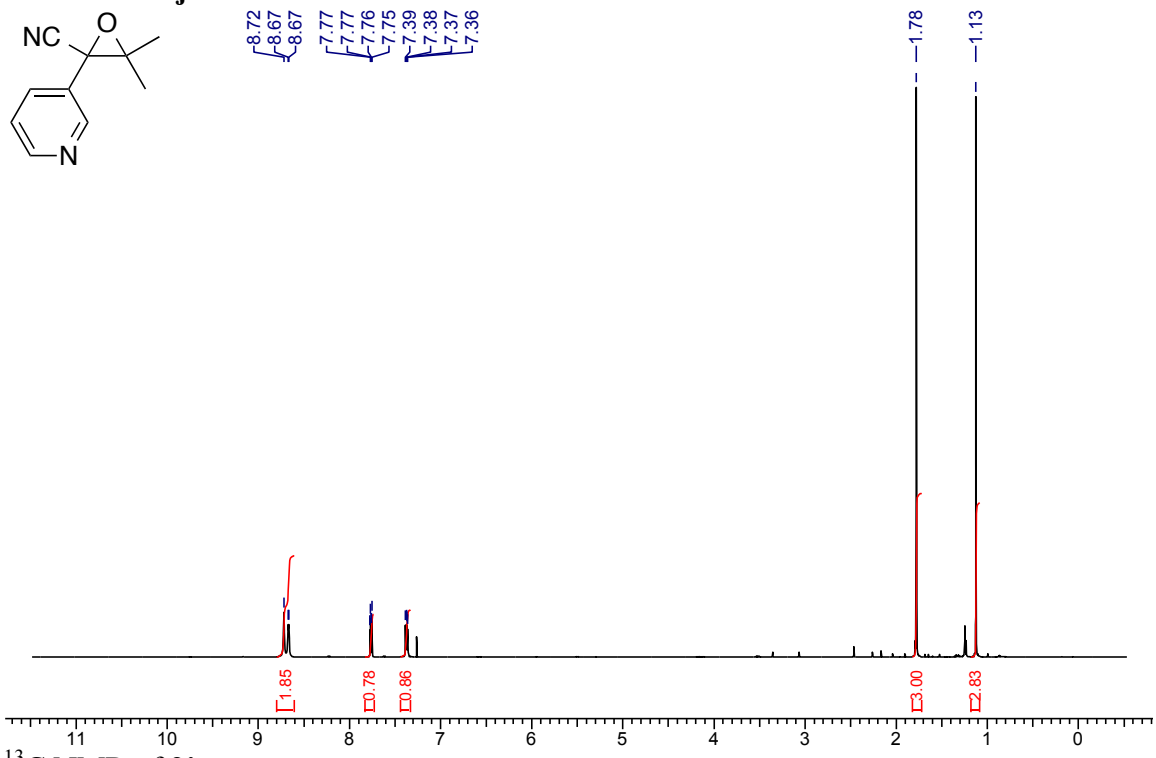

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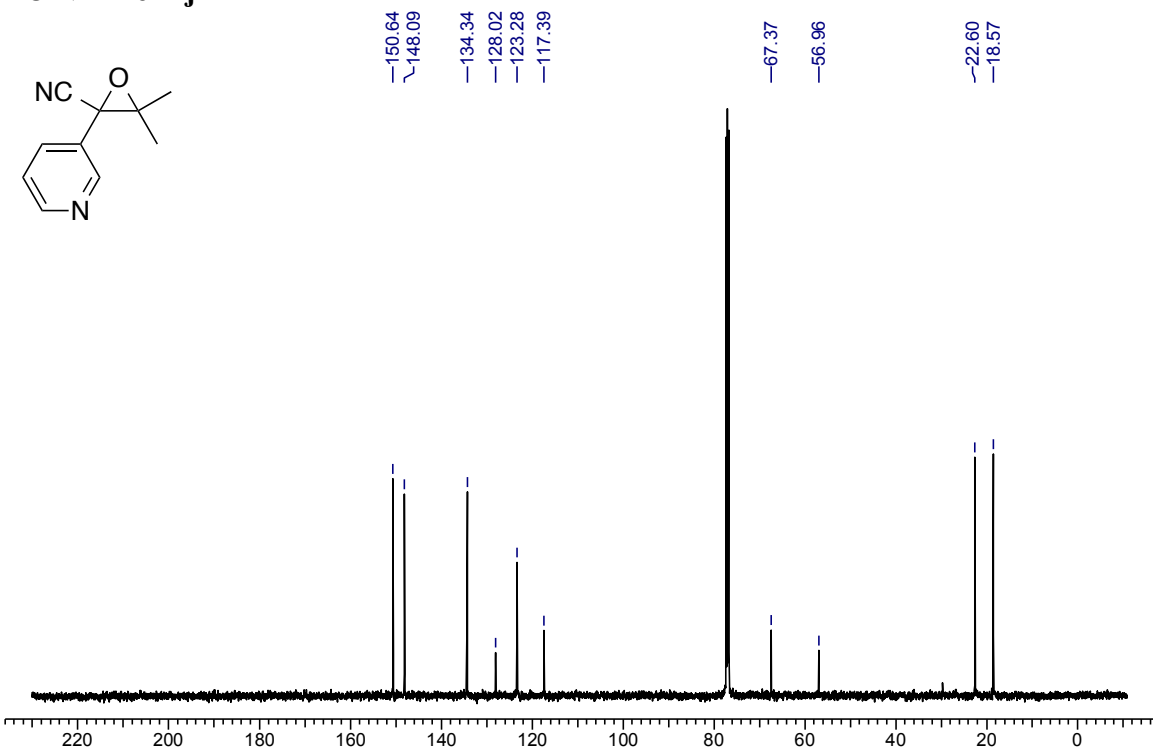

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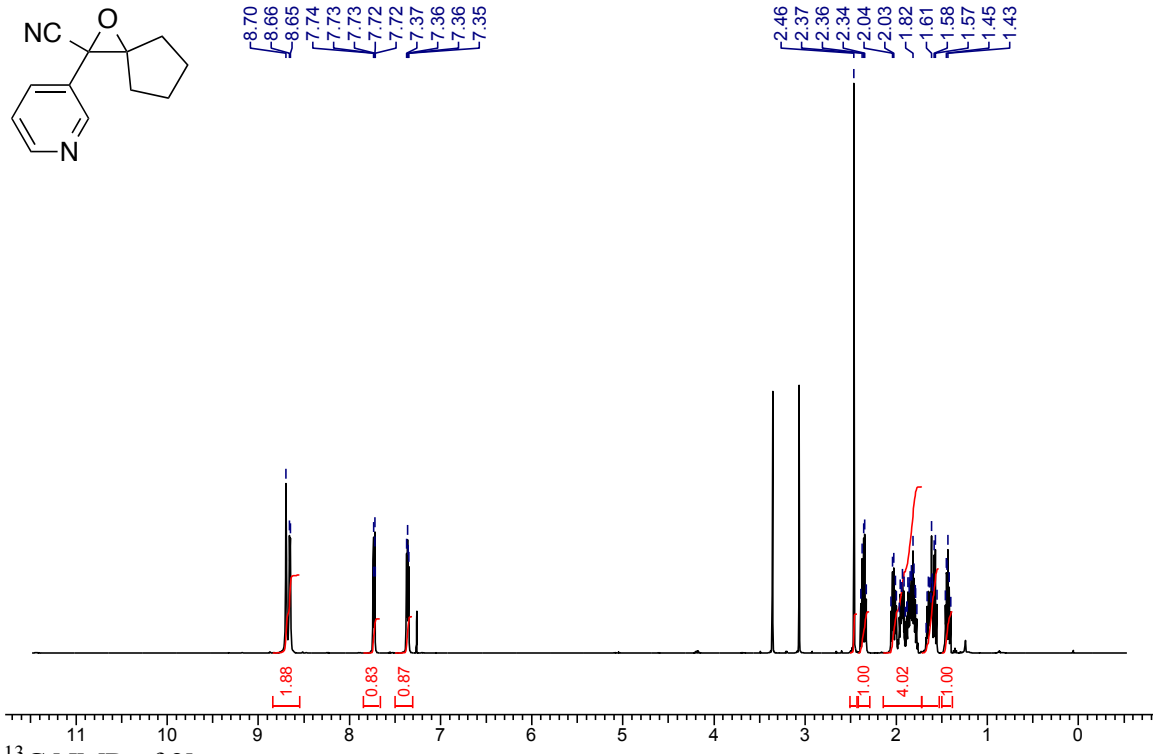

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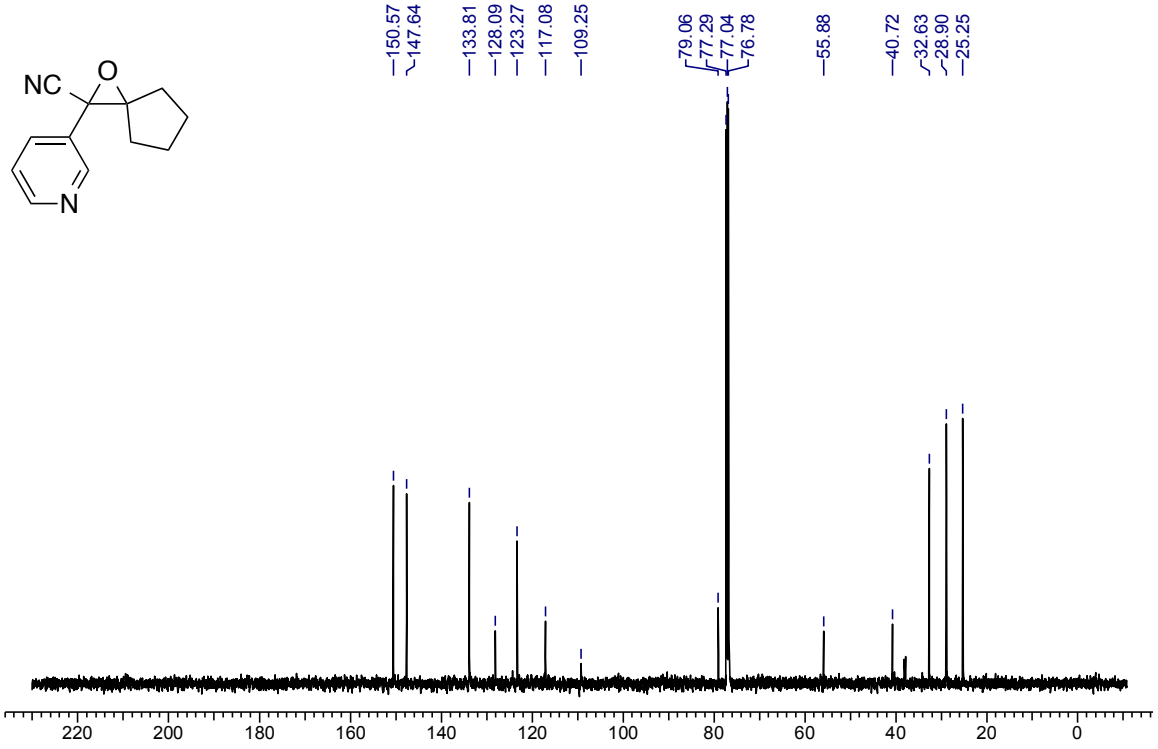

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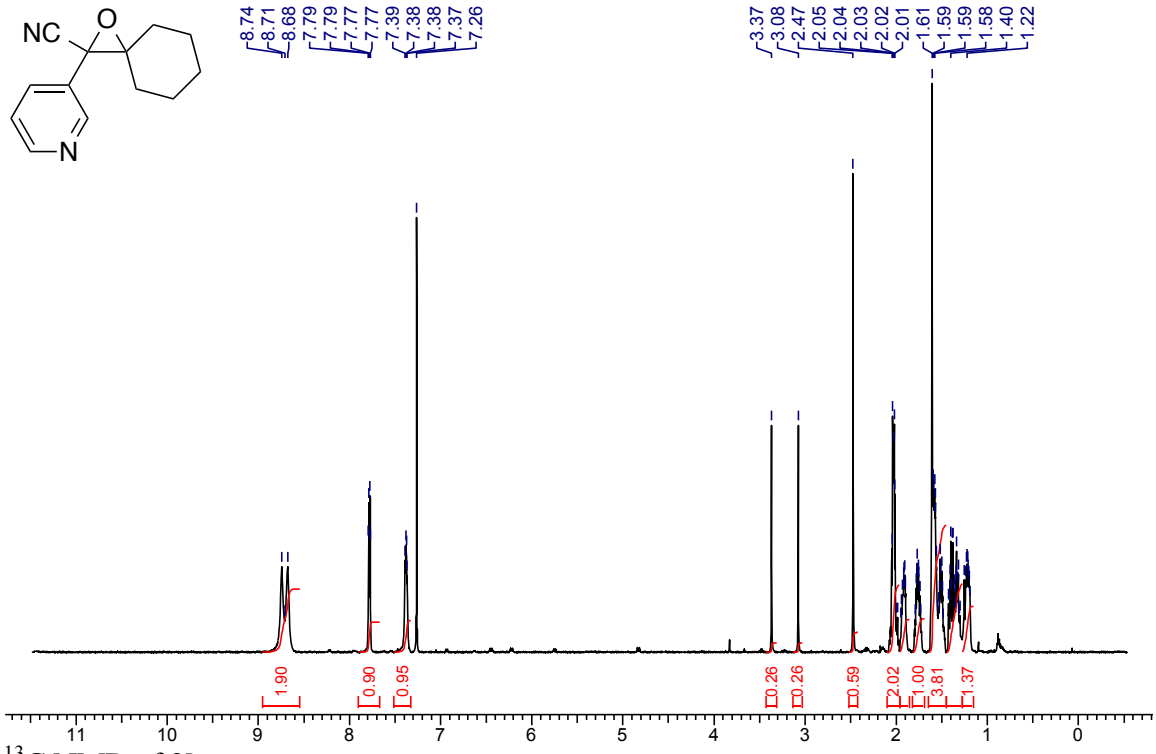

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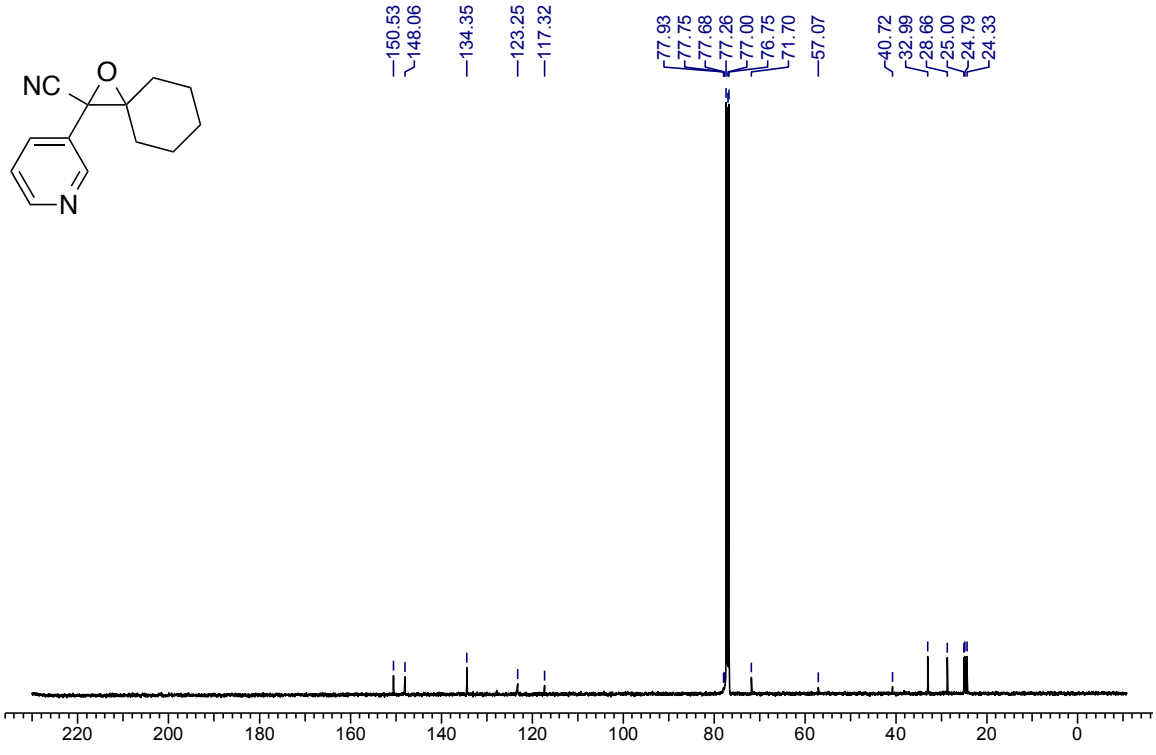

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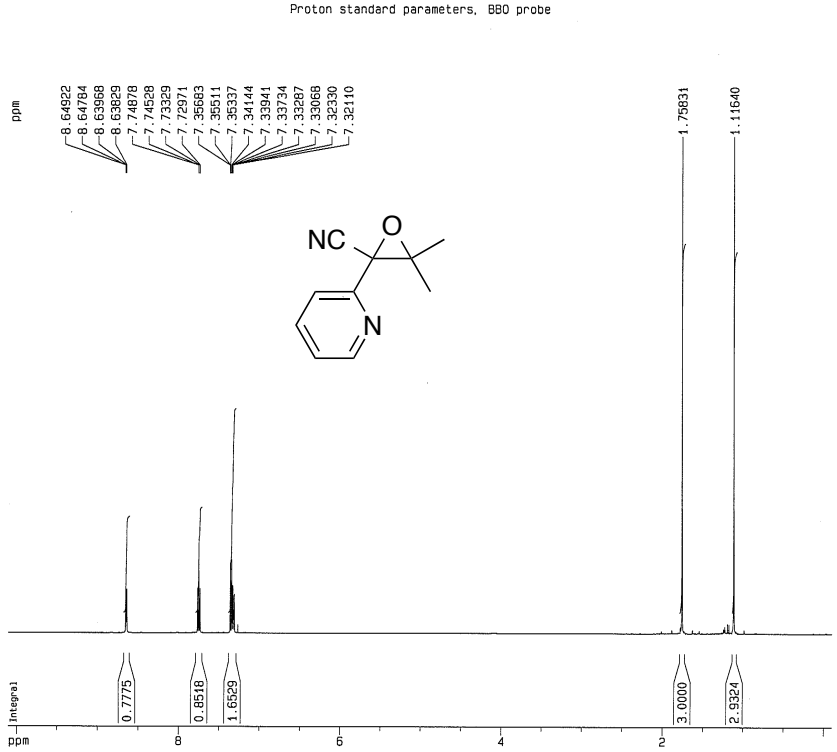


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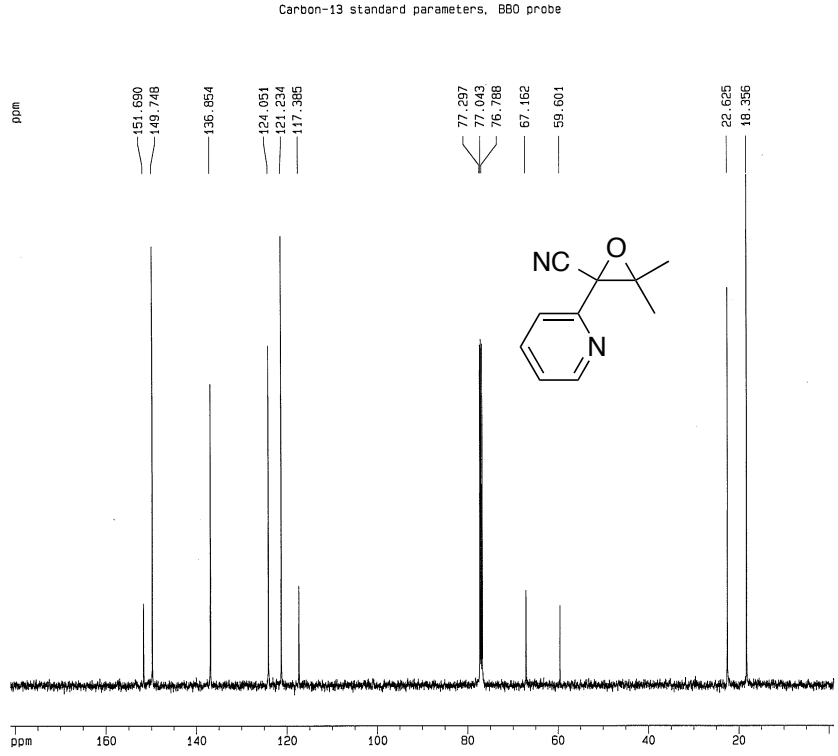


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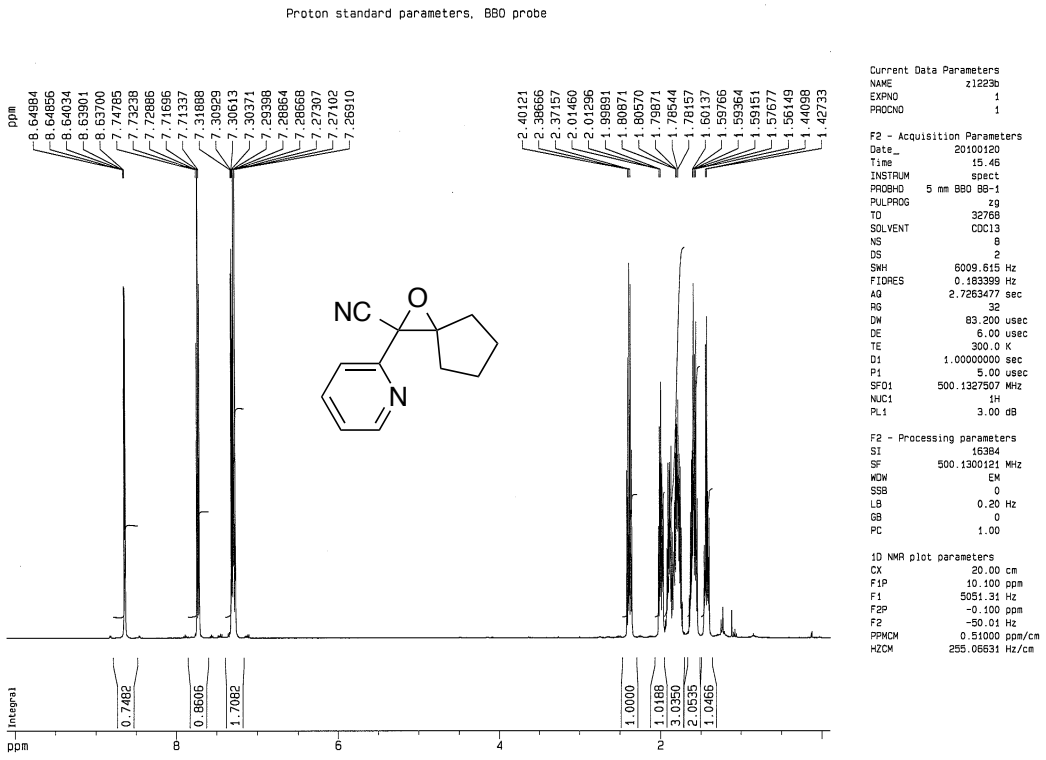

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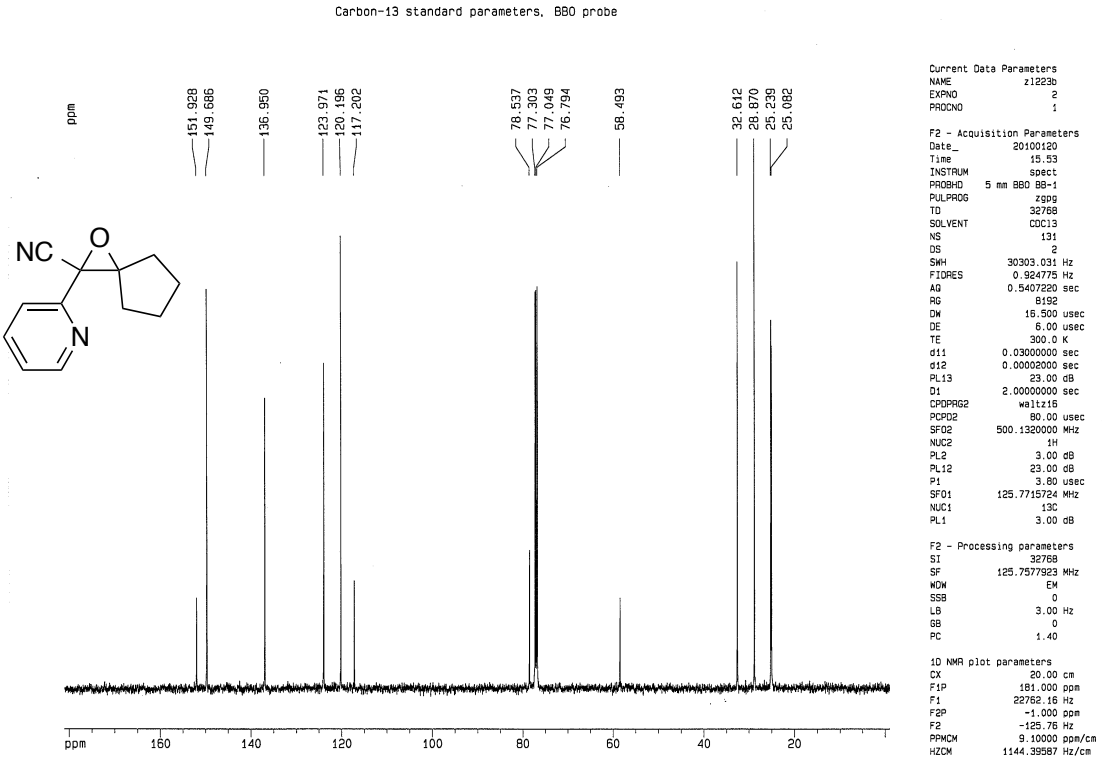

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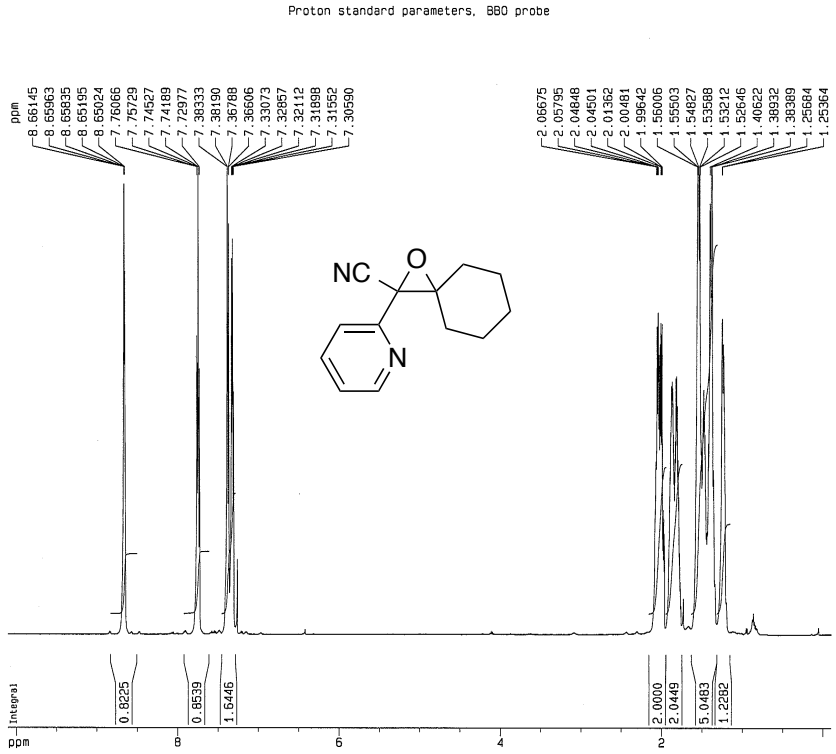


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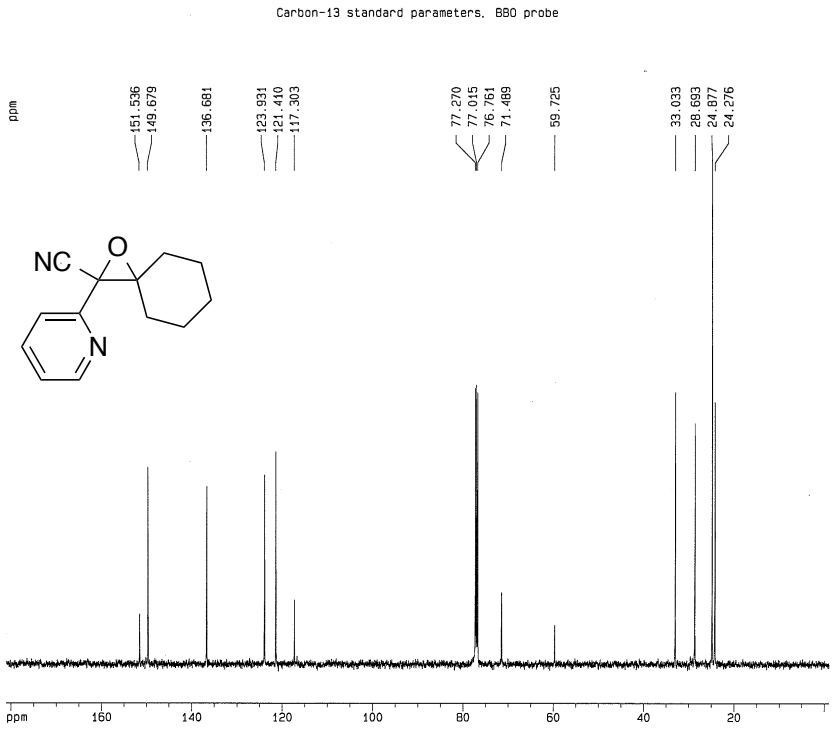


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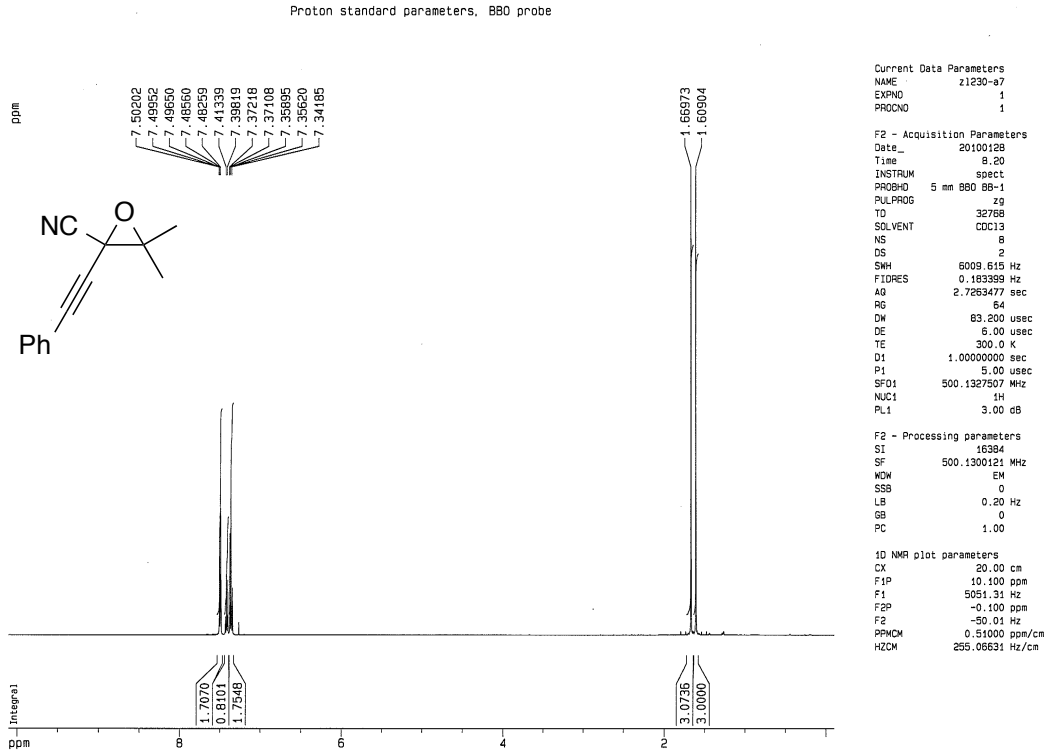

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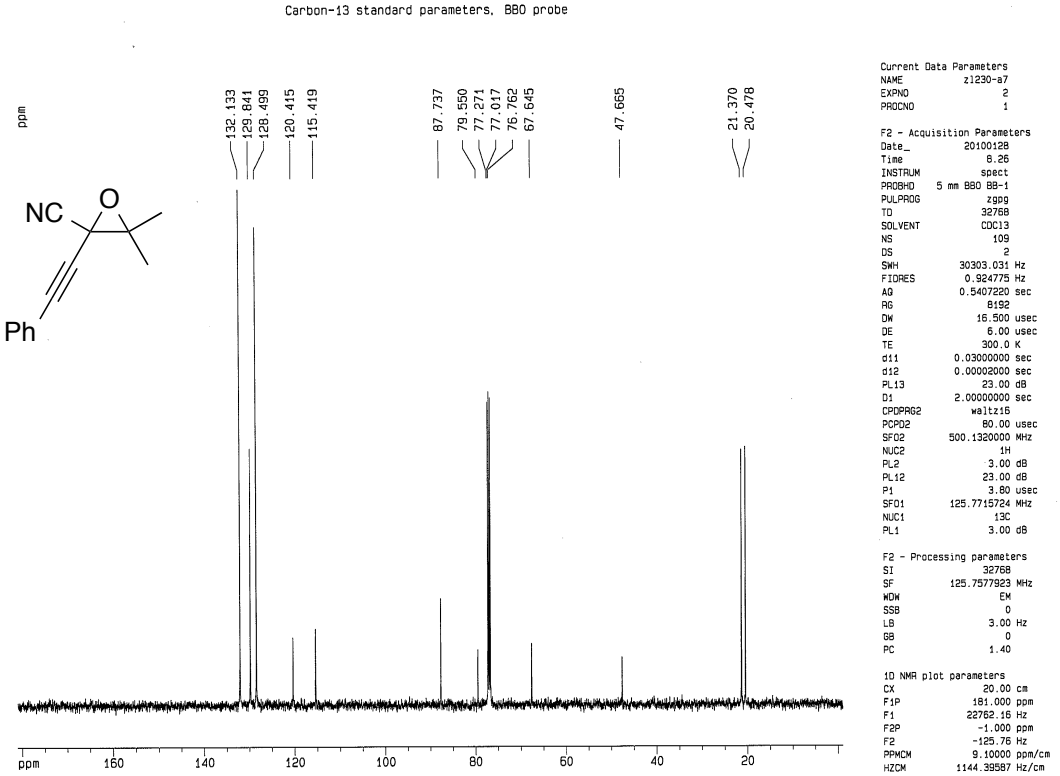

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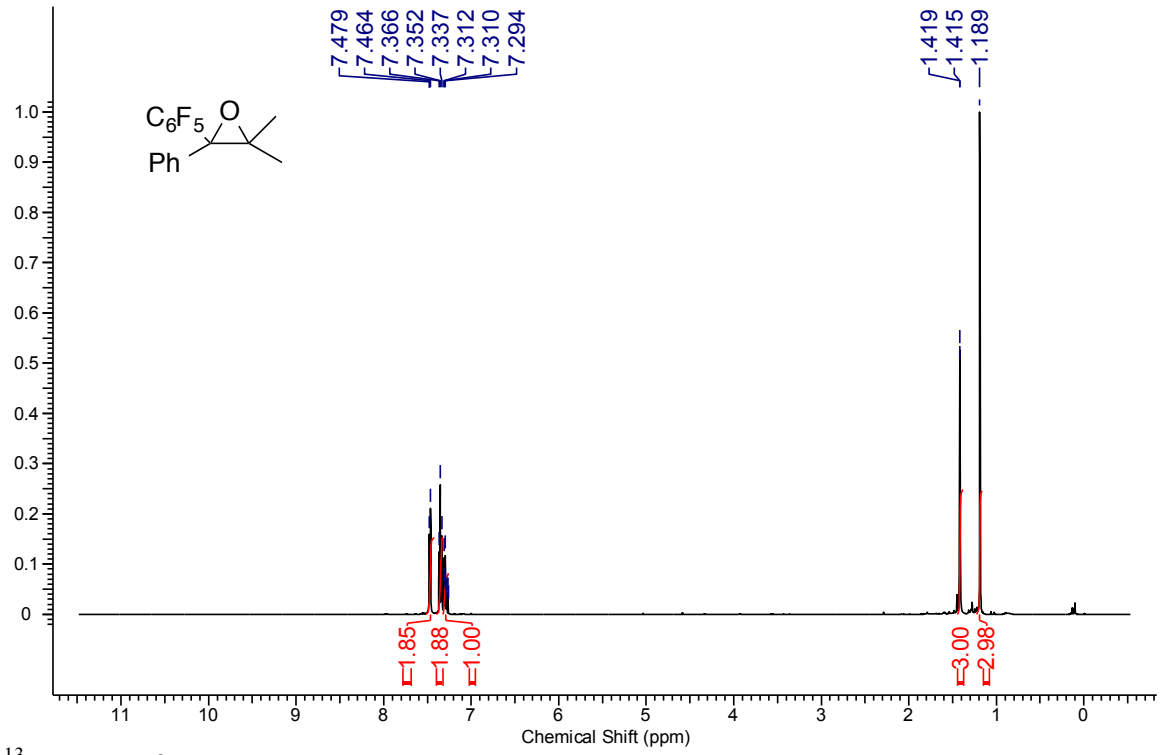

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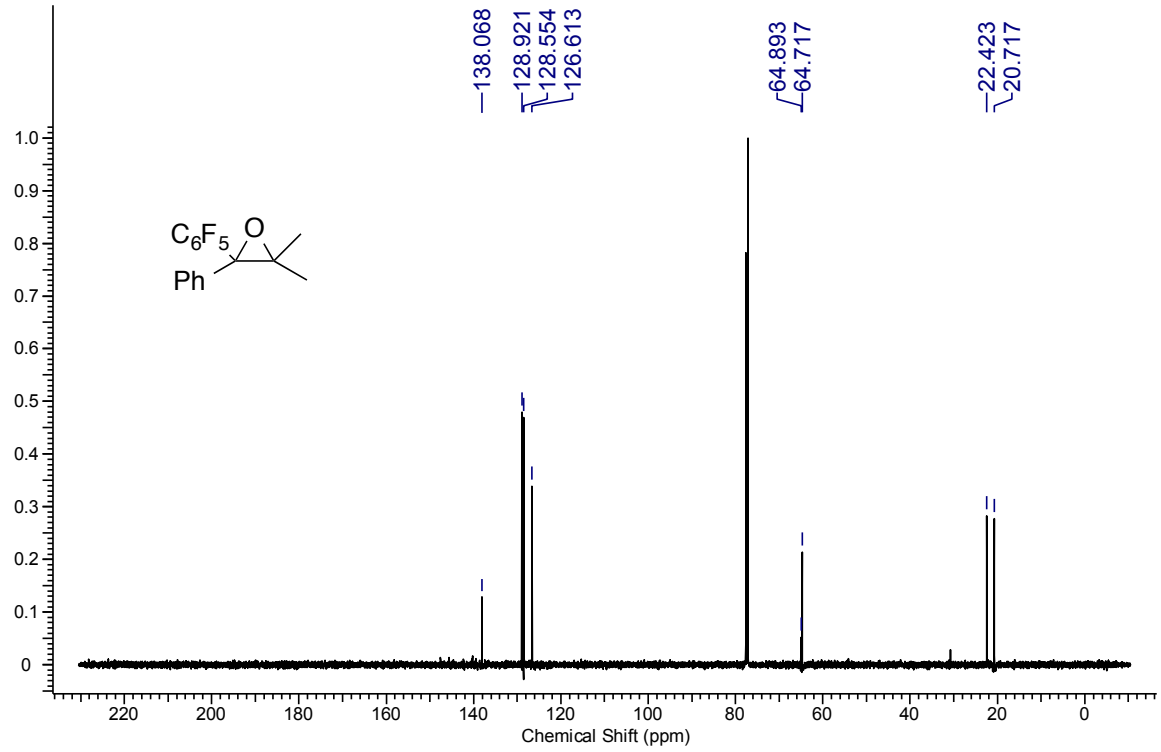

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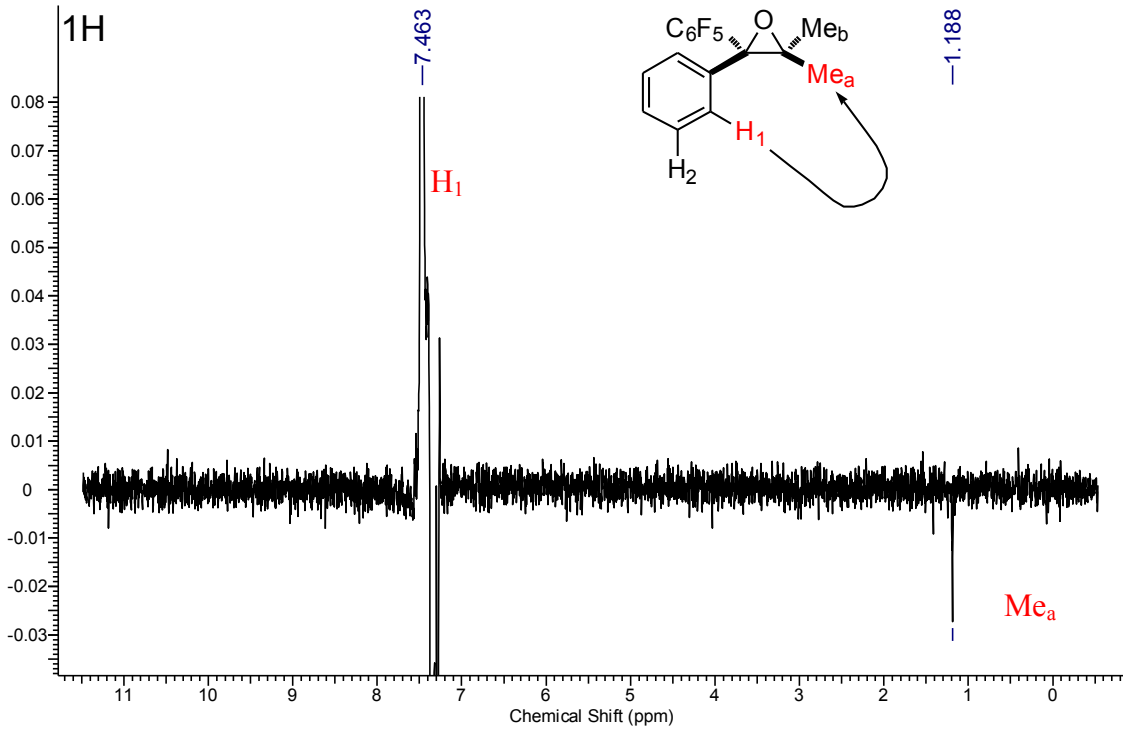
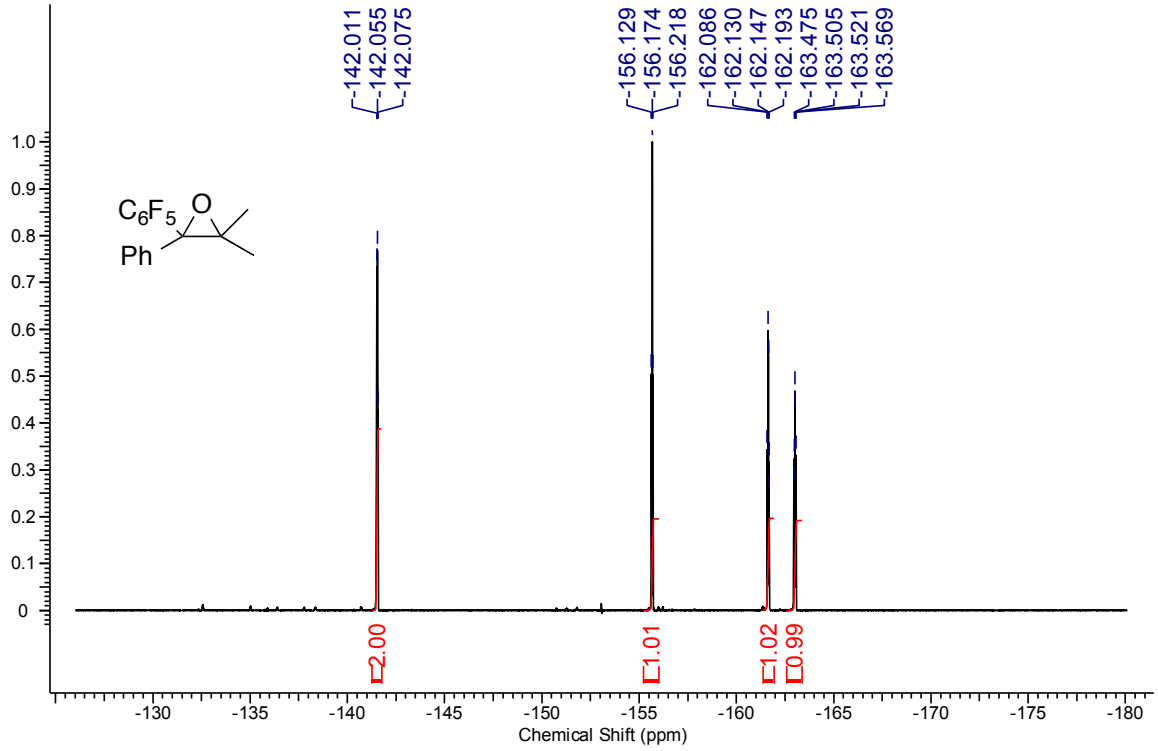


19F NMR of **3a**



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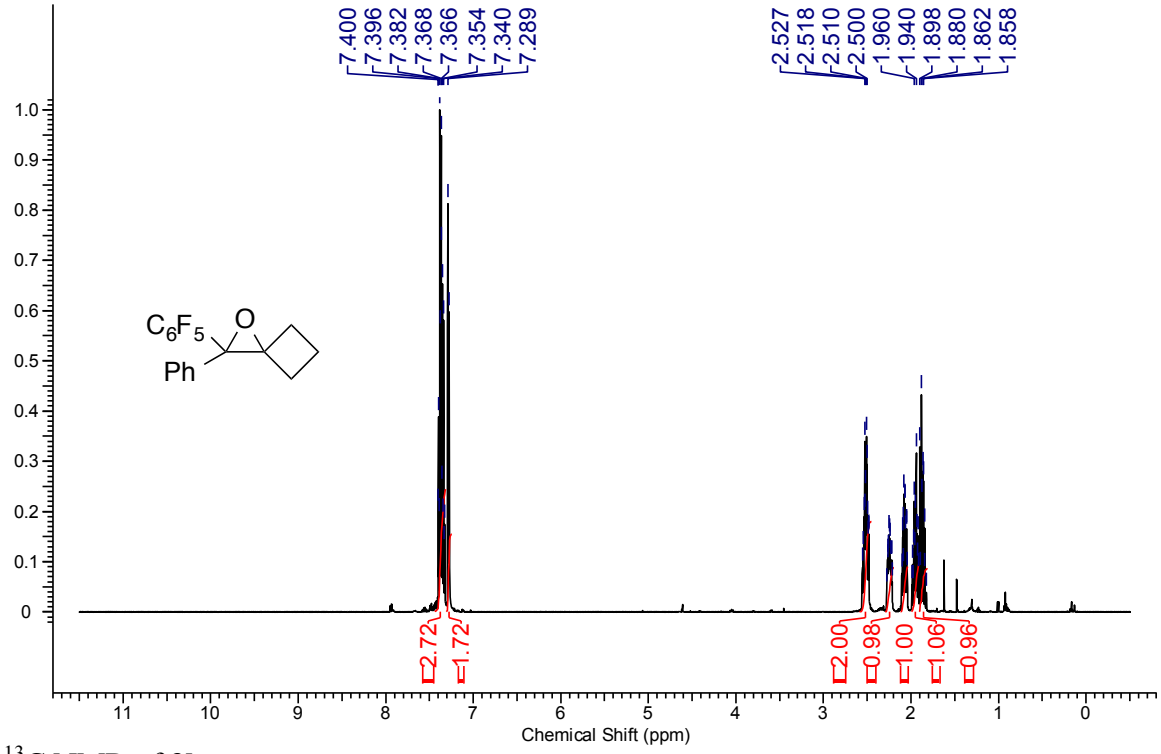
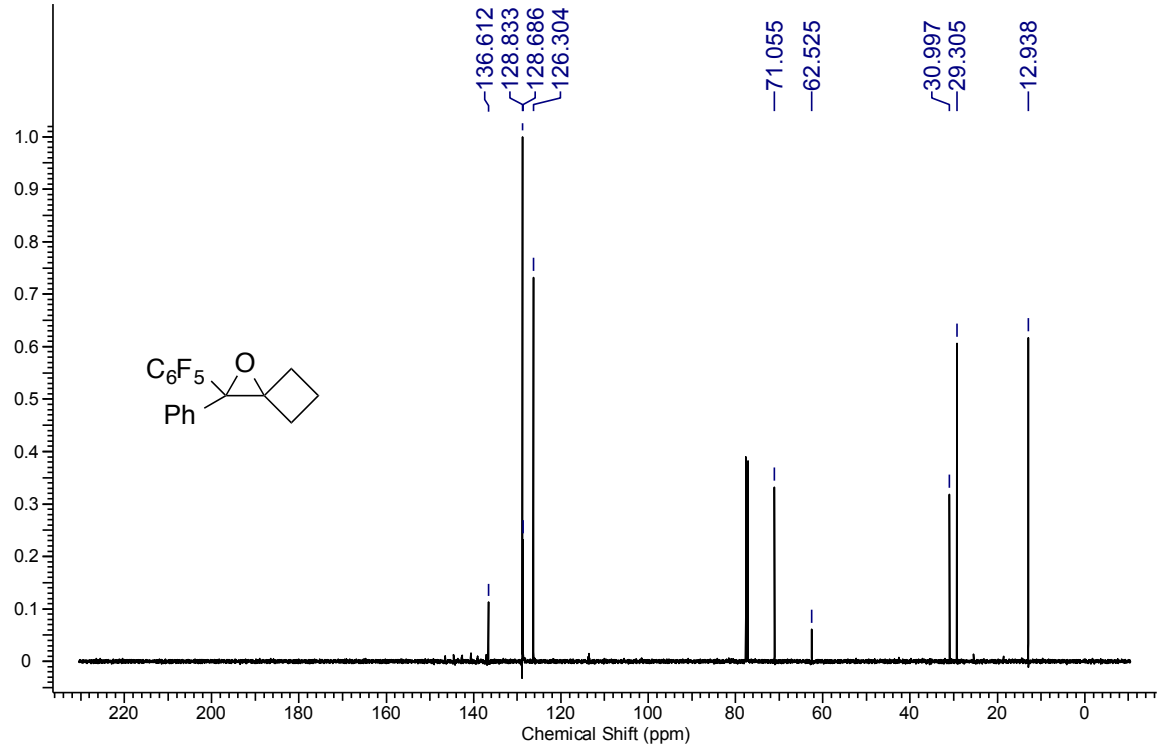
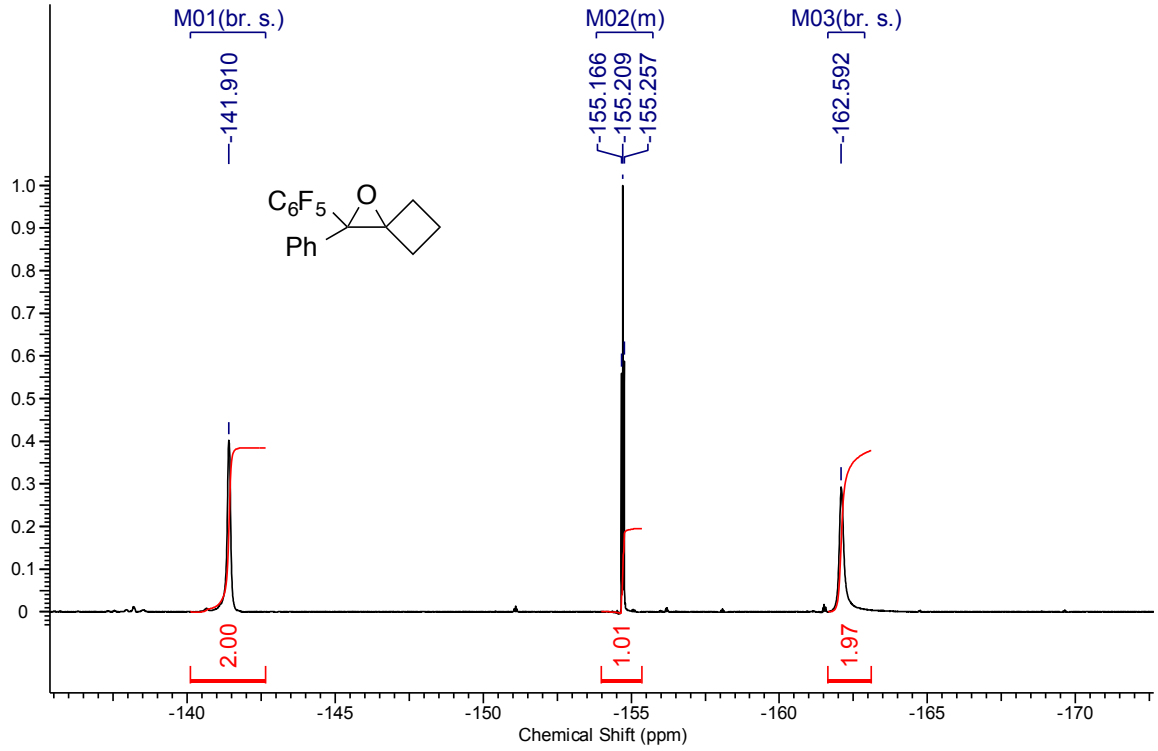


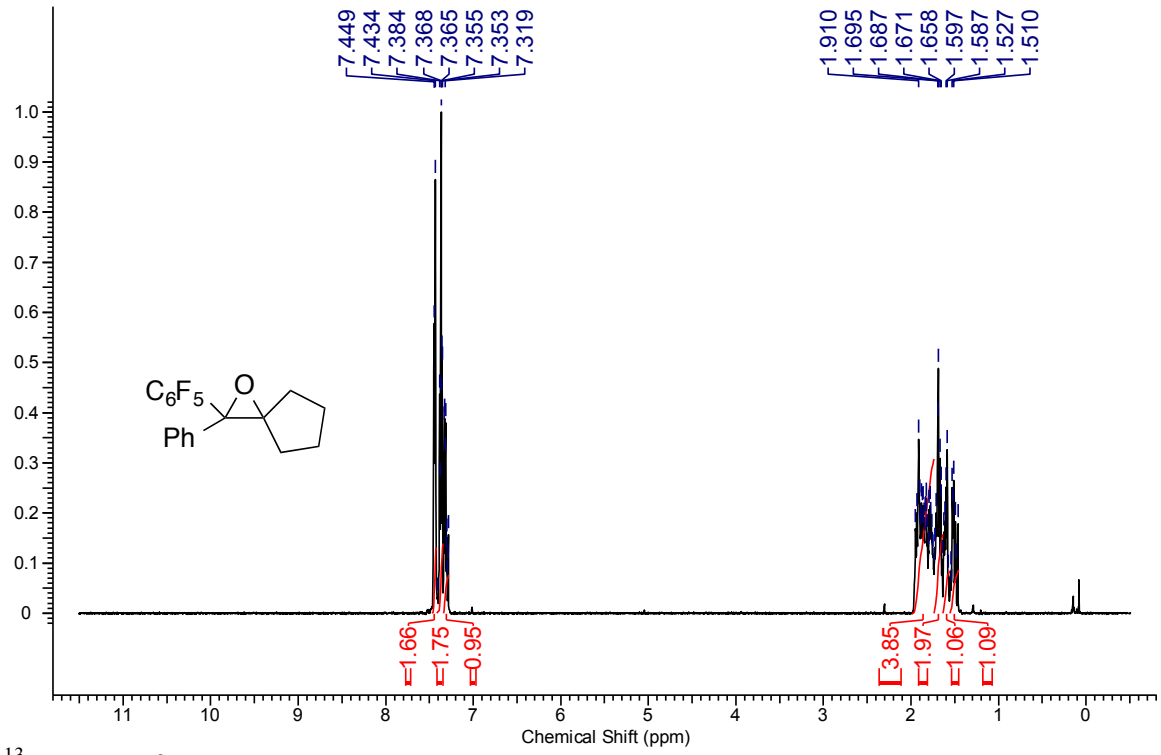
^{13}C NMR of **3b**



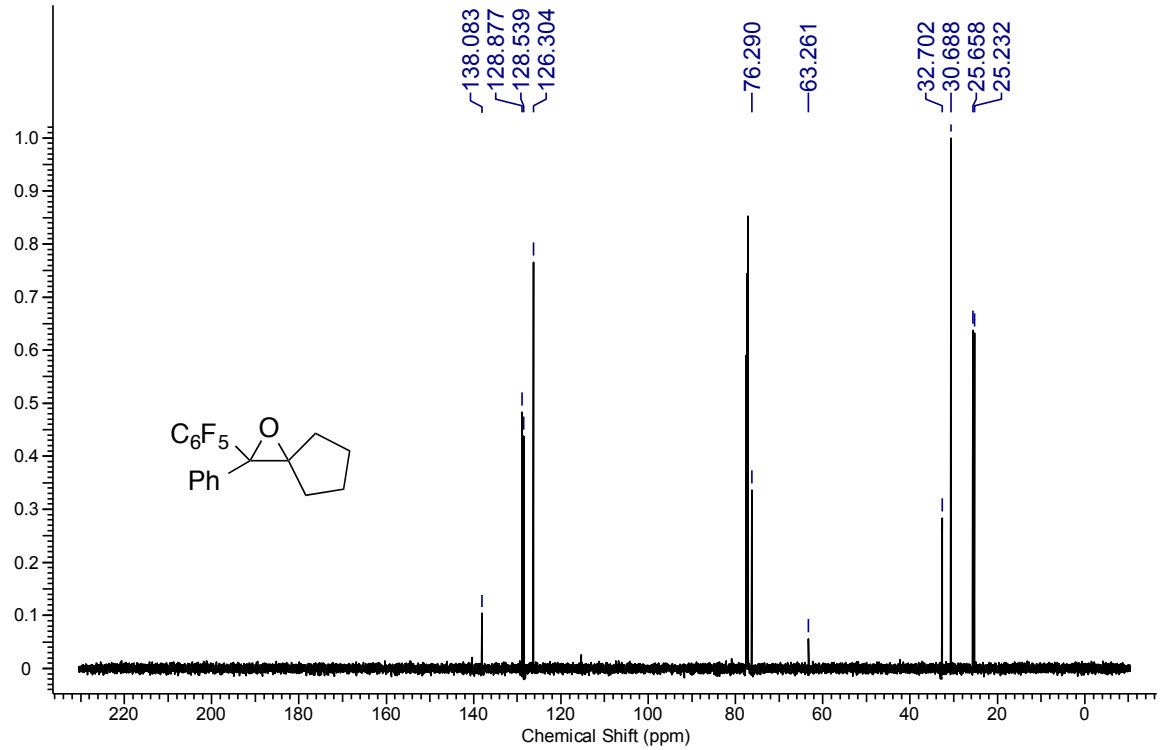
^{19}F NMR of **3b**


M01(br. s.)
M02(m)
M03(br. s.)
-141.910
-155.166
-155.209
-155.257
-162.592
C6F5
O
Ph
2.00
1.01
1.97
Chemical Shift (ppm)

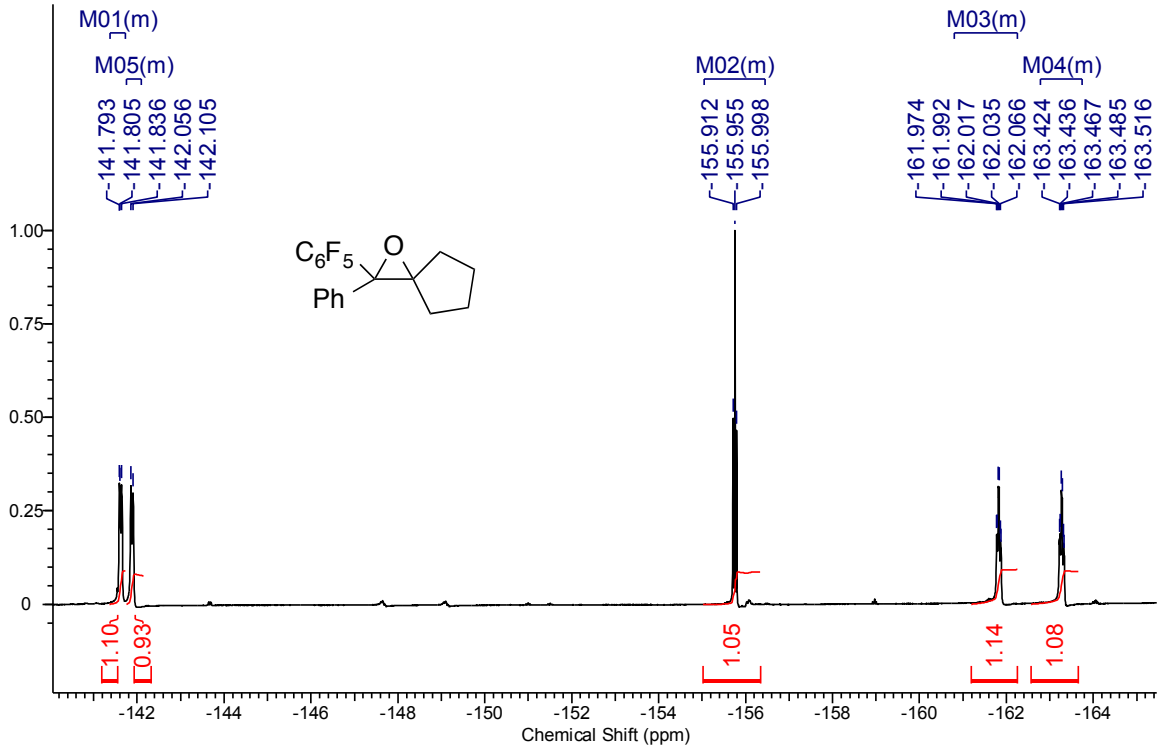
^{1}H NMR of **3c**



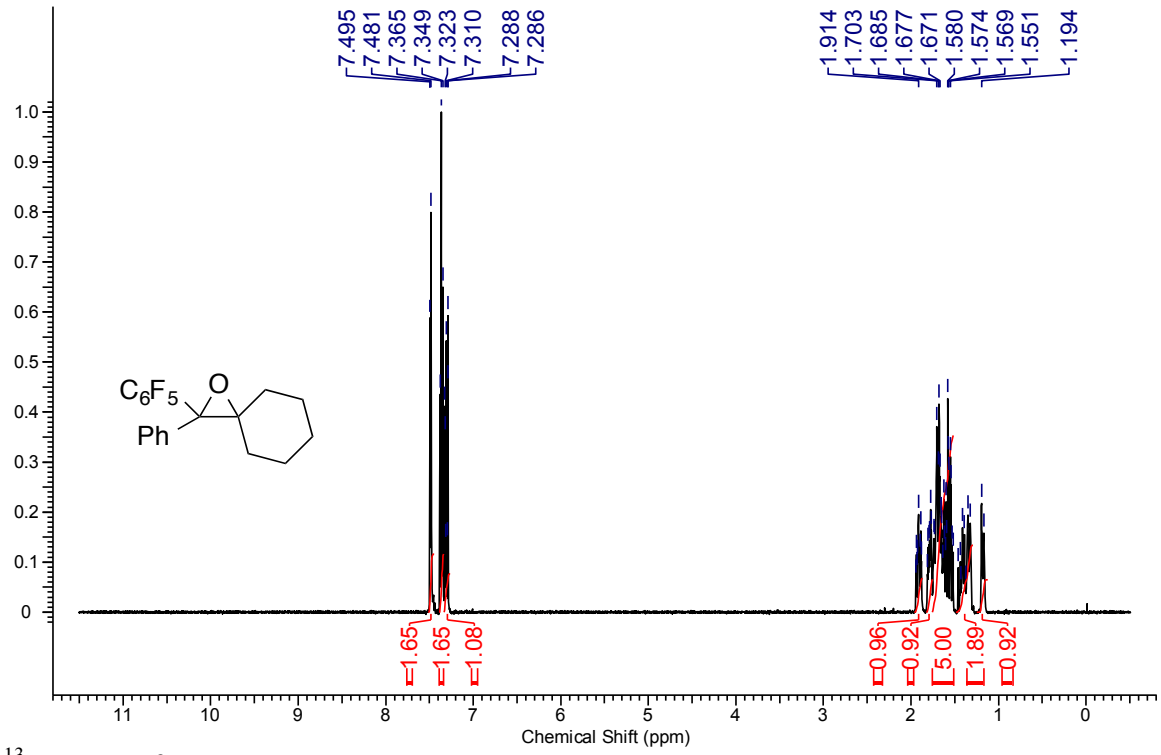
^{13}C NMR of **3c**



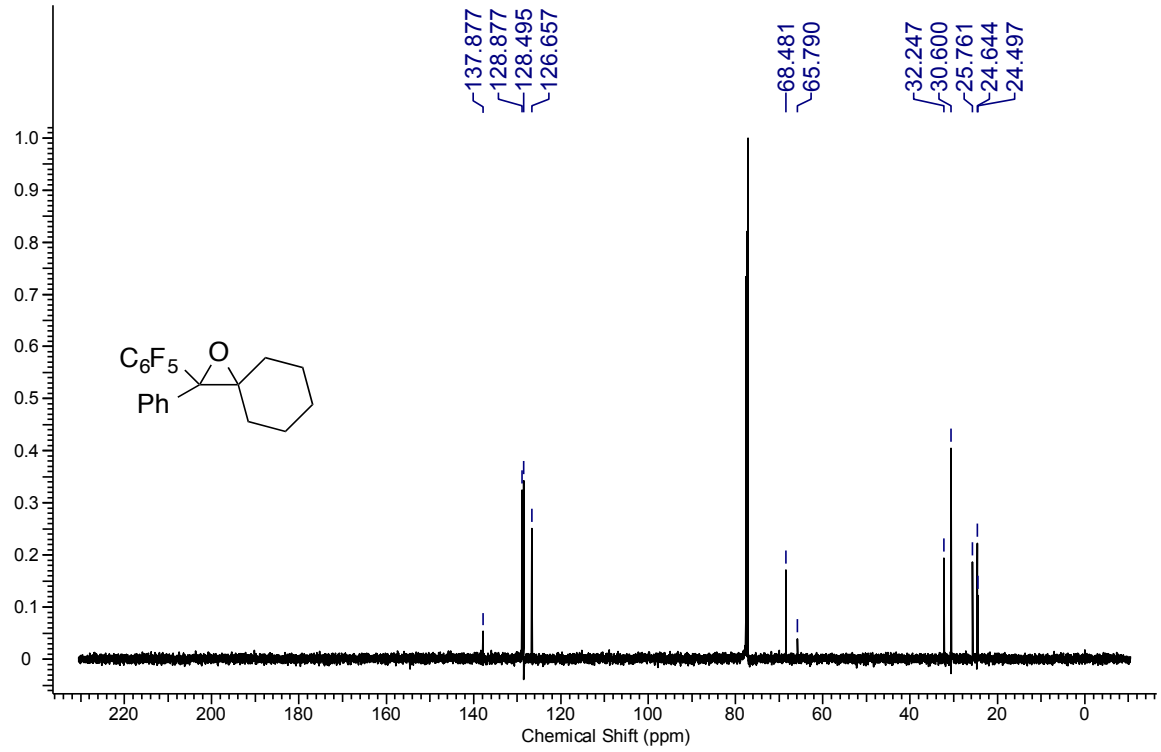
^{19}F NMR of **3c**


M01(m)
M05(m)
M02(m)
M03(m)
M04(m)
141.793
141.805
141.836
142.056
142.105
155.912
155.955
155.998
161.974
161.992
162.017
162.035
162.066
163.424
163.436
163.467
163.485
163.516
C6F5
O
Ph
1.00
0.75
0.50
0.25
0
1.10
0.93
1.05
1.14
1.08
-142
-144
-146
-148
-150
-152
-154
-156
-158
-160
-162
-164
Chemical Shift (ppm)

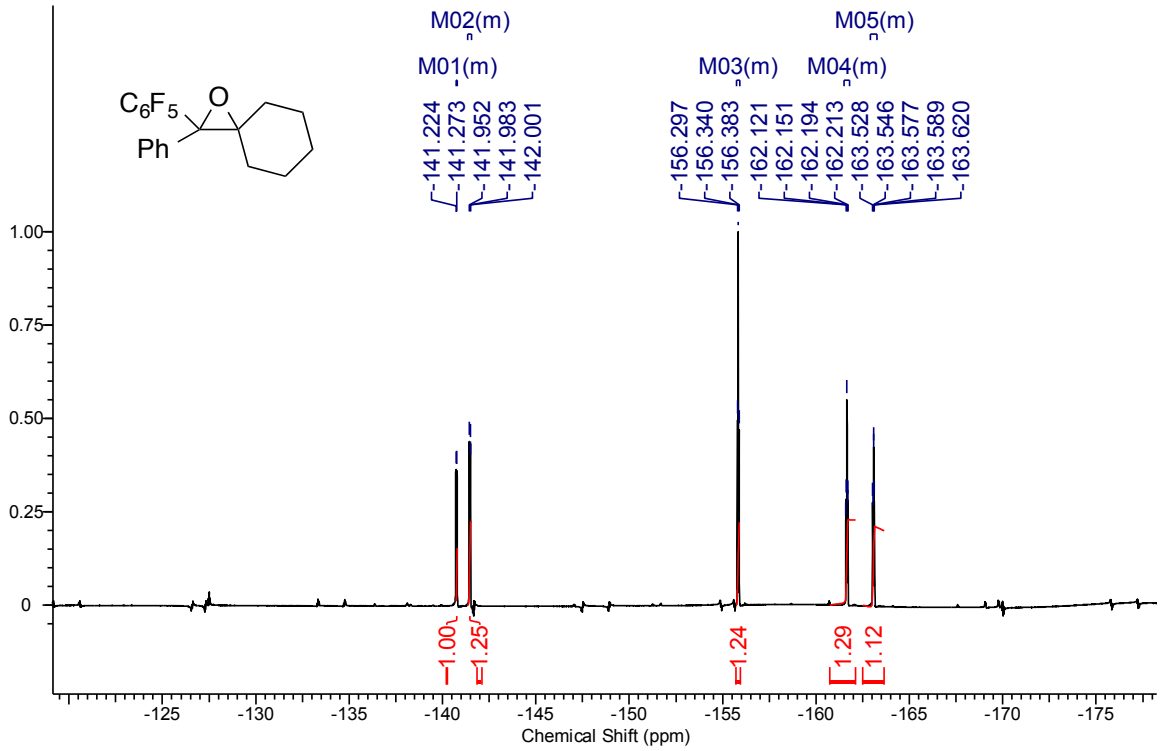
^{1}H NMR of **3d**



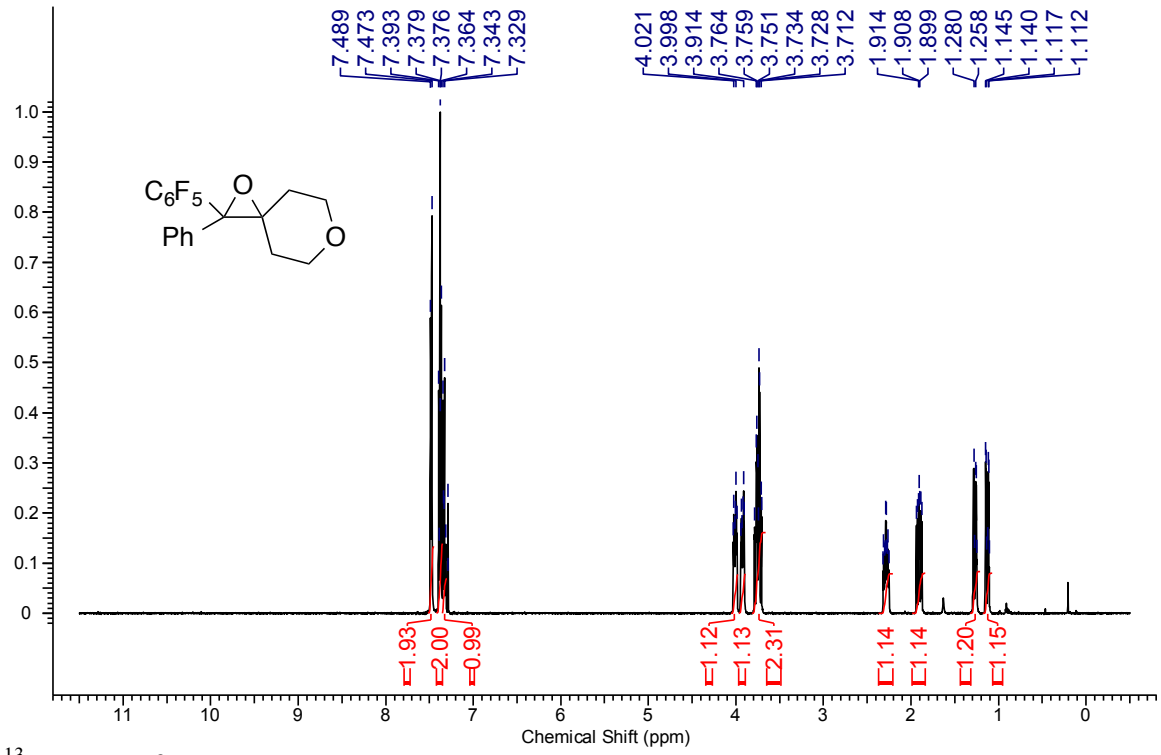
^{13}C NMR of **3d**



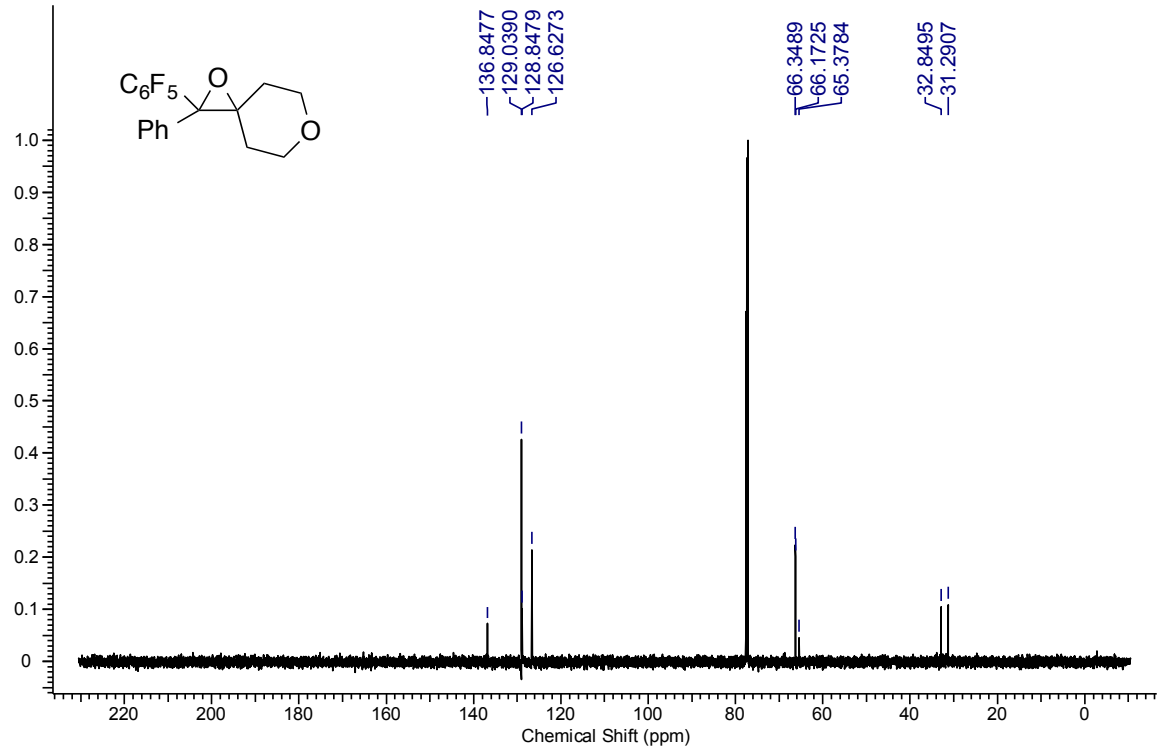
^{19}F NMR of **3d**


M02(m)
M01(m)
M05(m)
M03(m)
M04(m)
C6F5
O
Ph
-141.224
-141.273
-141.952
-141.983
-142.001
-156.297
-156.340
-156.383
-162.121
-162.151
-162.194
-162.213
-163.528
-163.546
-163.577
-163.589
-163.620
1.00
0.75
0.50
0.25
0
1.00
1.25
1.24
1.29
1.12
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
Chemical Shift (ppm)

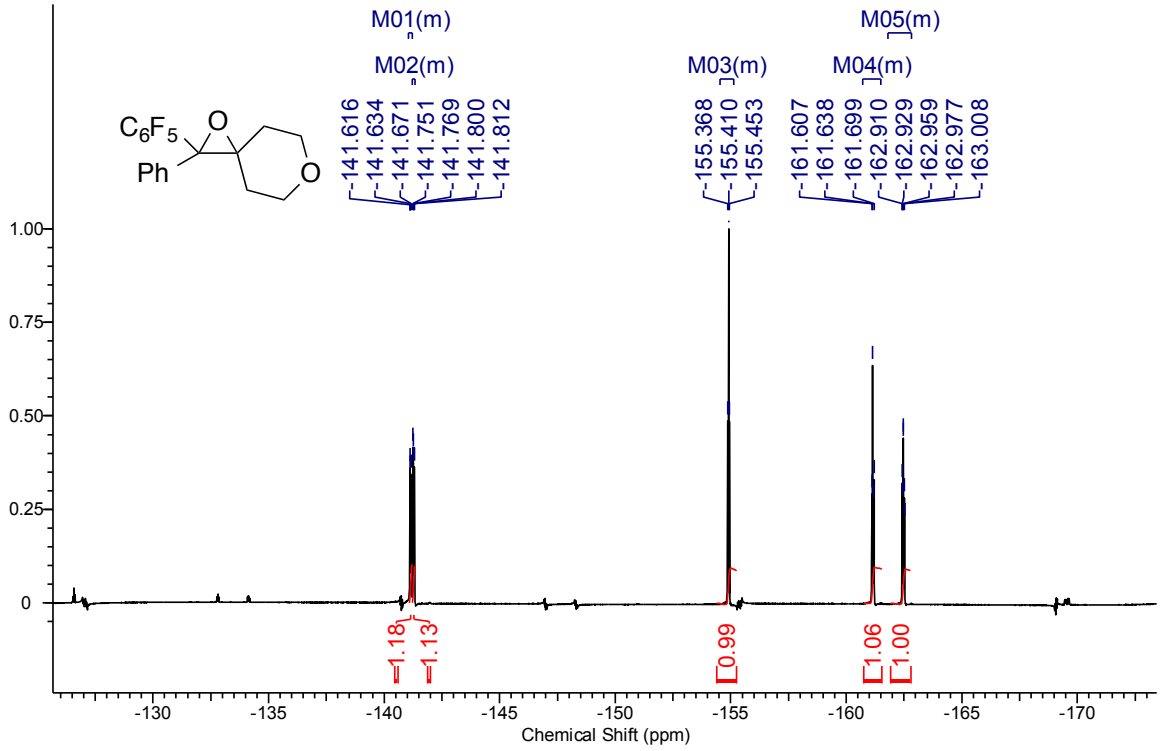
^{1}H NMR of **3e**



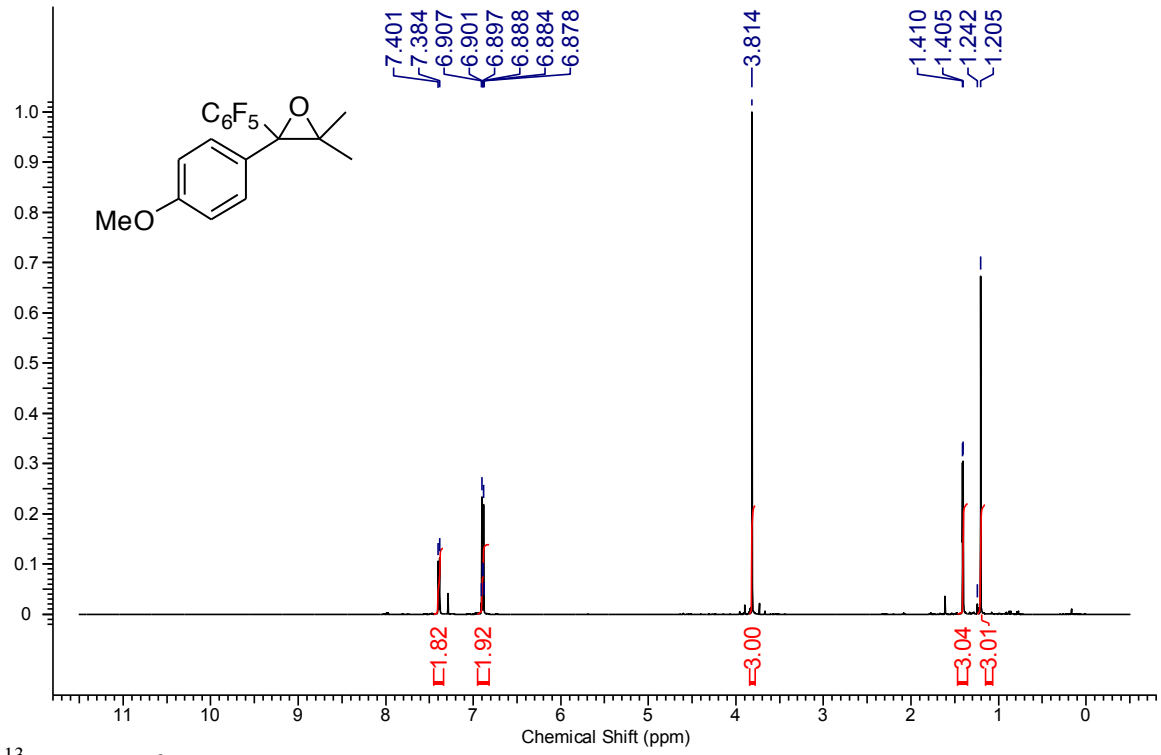
^{13}C NMR of **3e**



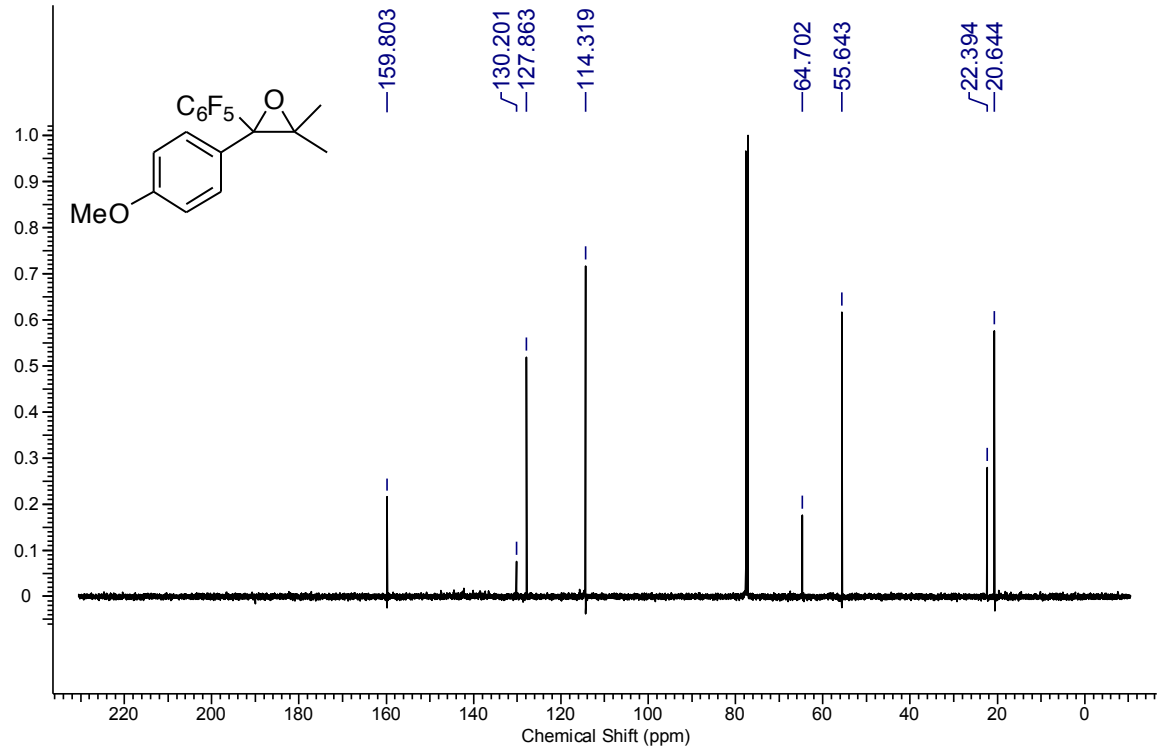
^{19}F NMR of **3e**


M01(m)
M02(m)
M03(m)
M04(m)
M05(m)
C6F5
Ph
O
O
141.616
141.634
141.671
141.751
141.769
141.800
141.812
155.368
155.410
155.453
161.607
161.638
161.699
162.910
162.929
162.959
162.977
163.008
1.00
0.75
0.50
0.25
0
1.18
1.13
0.99
1.06
1.00
-130
-135
-140
-145
-150
-155
-160
-165
-170
Chemical Shift (ppm)

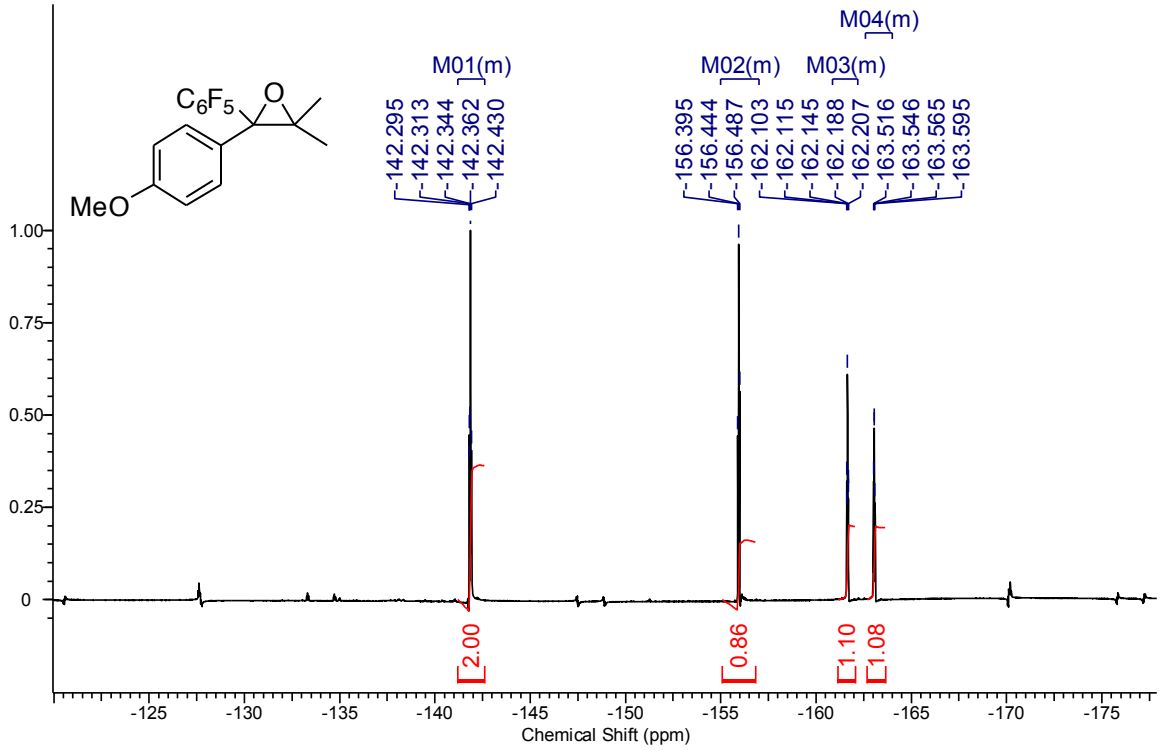
^{1}H NMR of **3f**



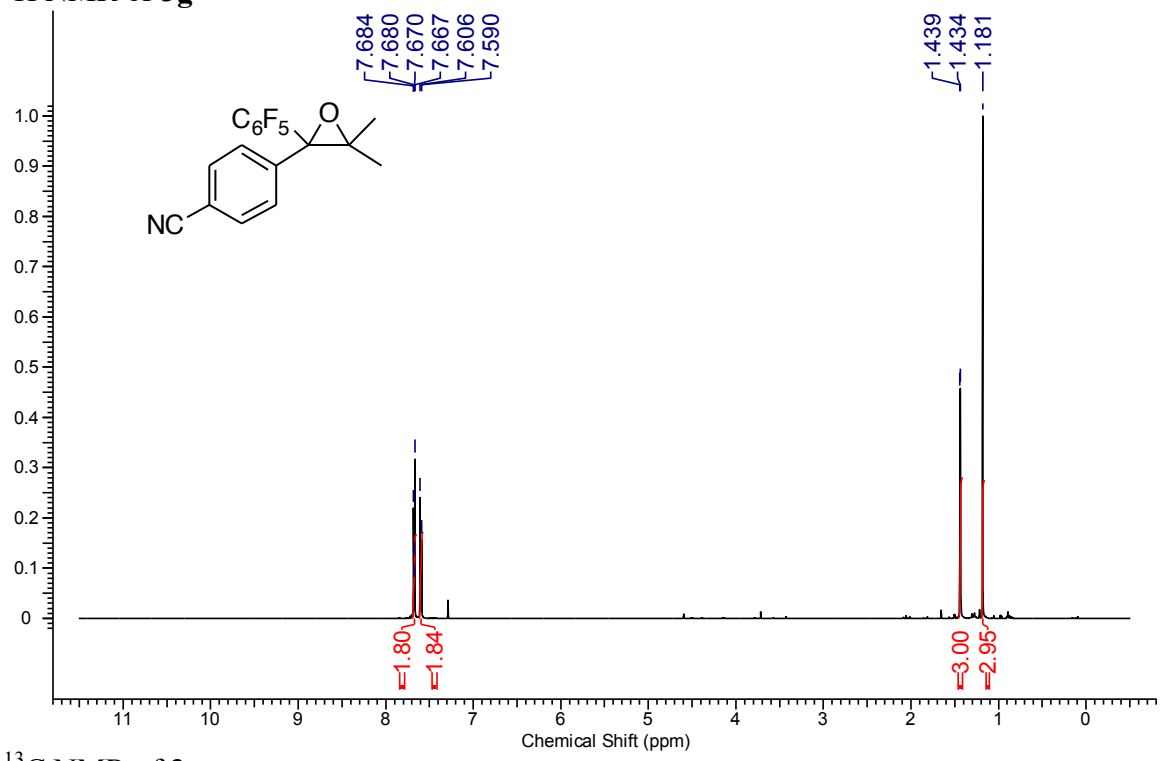
^{13}C NMR of **3f**



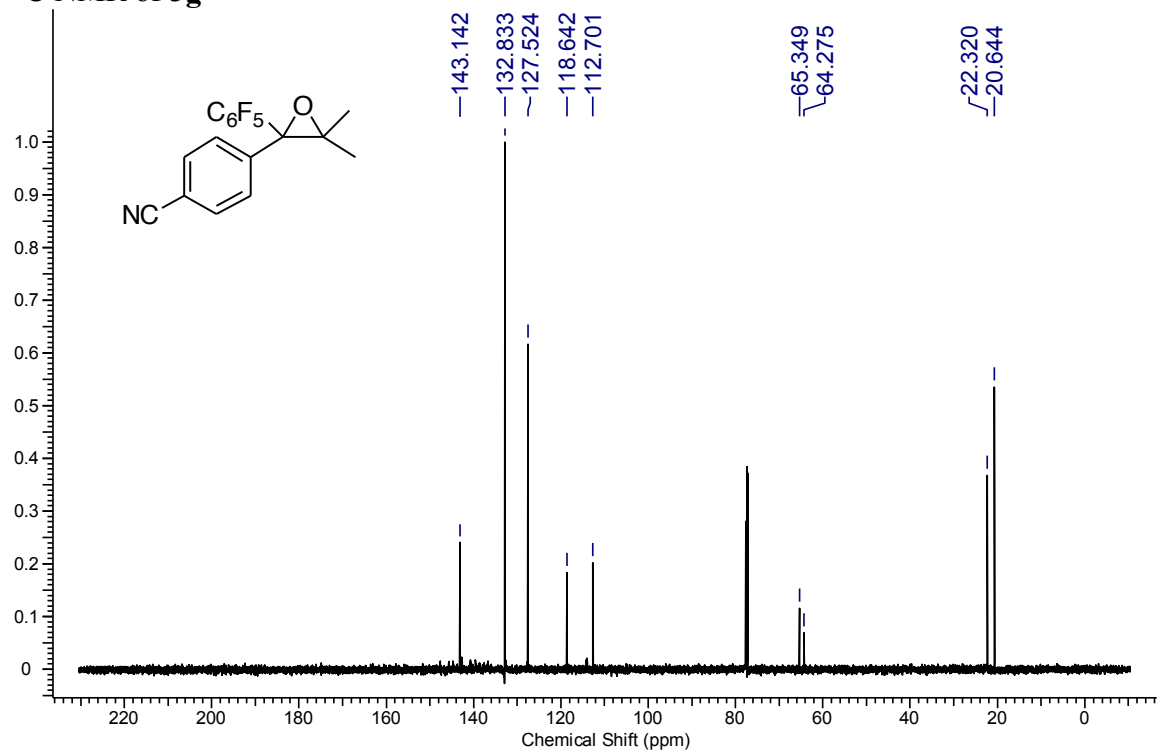
^{19}F NMR of **3f**


M04(m)
M01(m)
M02(m)
M03(m)
142.295
142.313
142.344
142.362
142.430
156.395
156.444
156.487
162.103
162.115
162.145
162.188
162.207
163.516
163.546
163.565
163.595
C6F5
O
MeO
1.00
0.75
0.50
0.25
0
2.00
0.86
1.10
1.08
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
Chemical Shift (ppm)

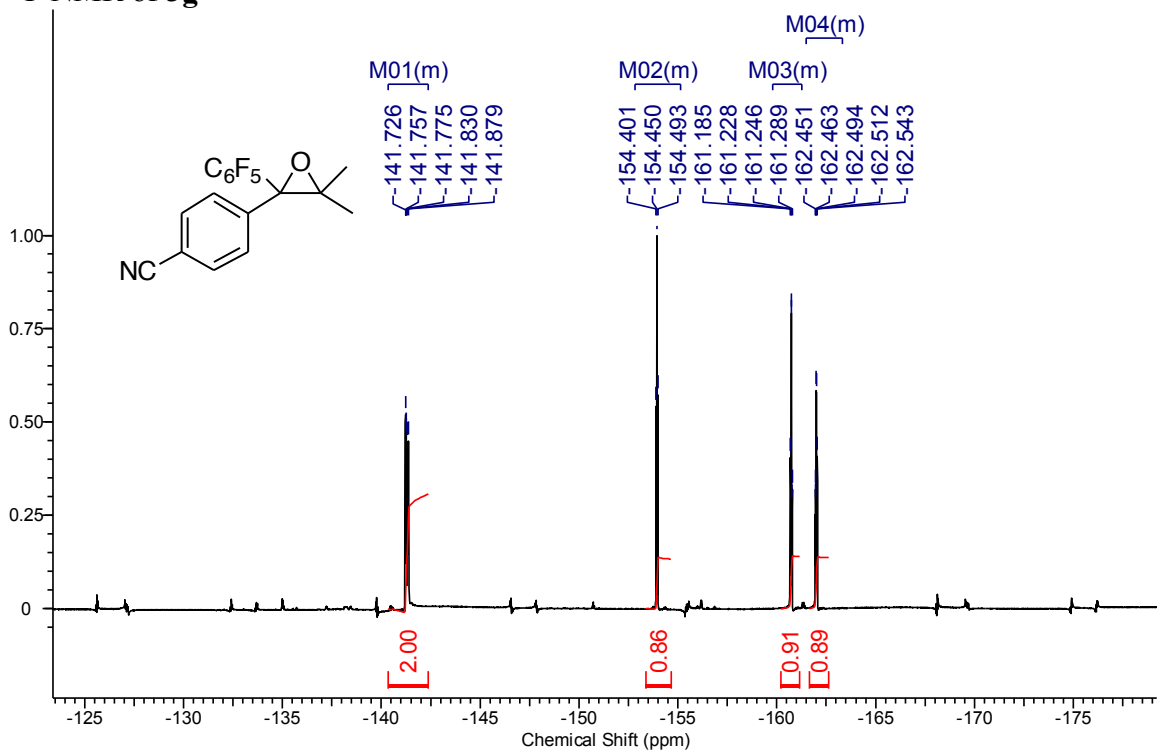
^{1}H NMR of **3g**



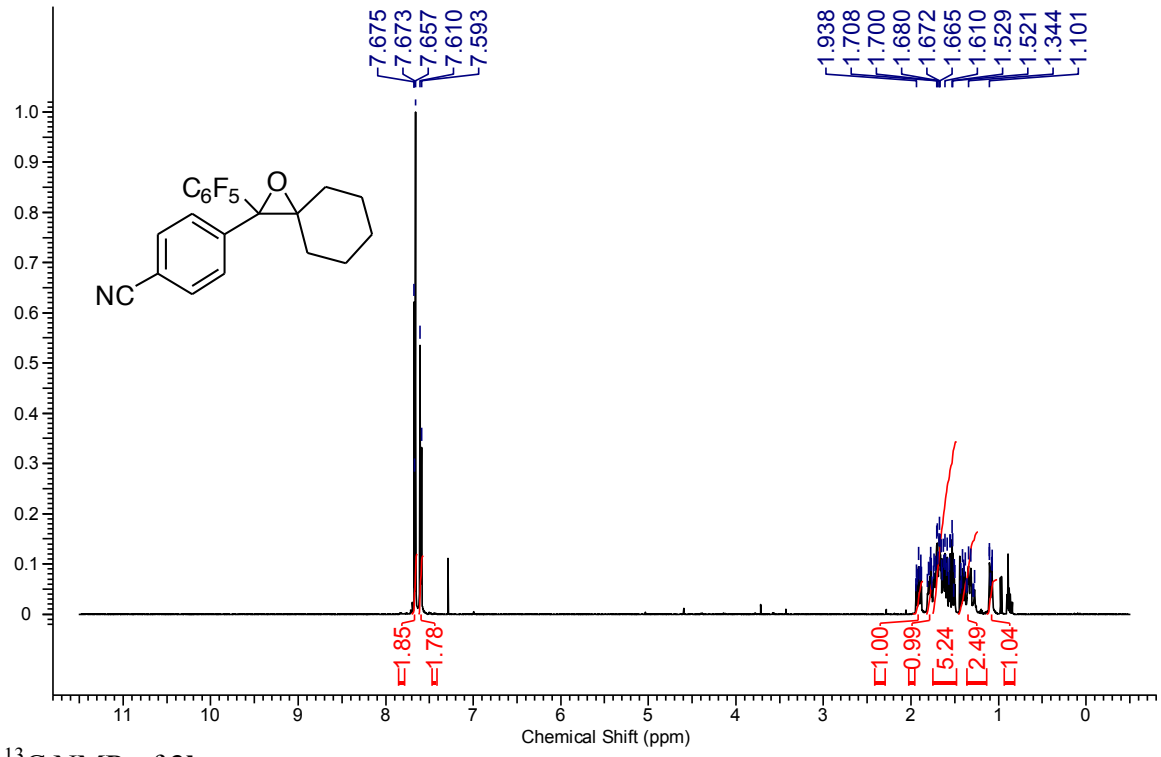
^{13}C NMR of **3g**



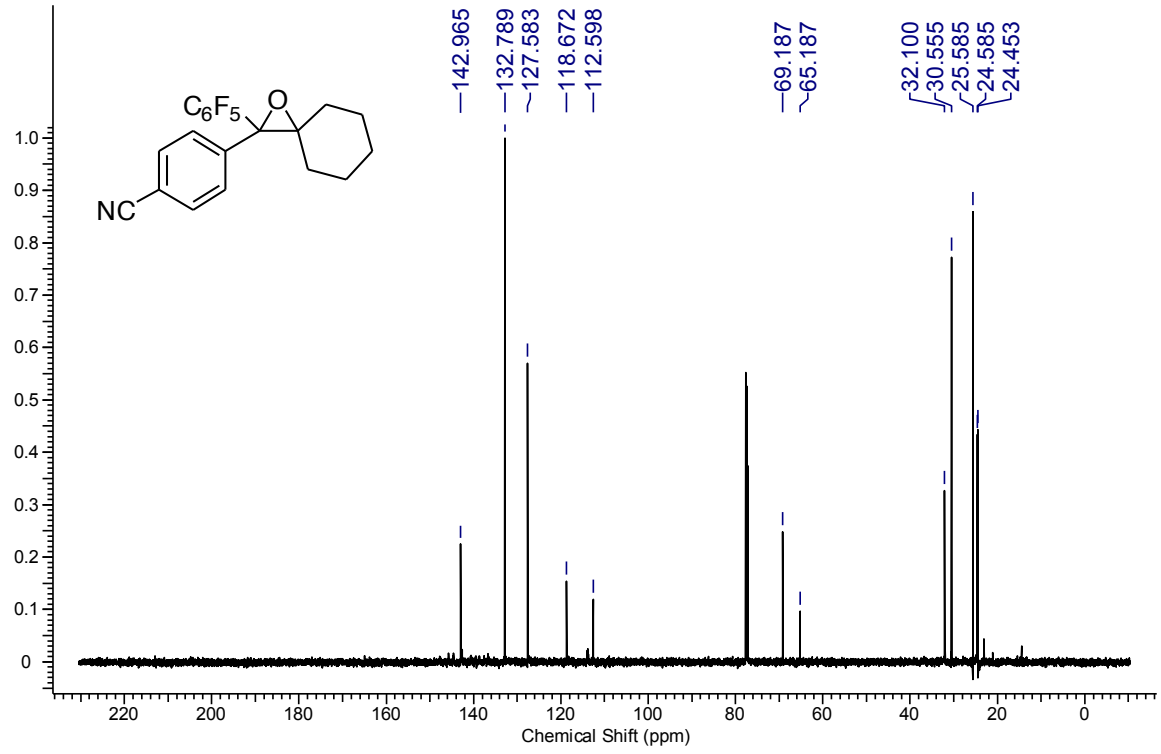
^{19}F NMR of **3g**


M01(m)
M02(m)
M03(m)
M04(m)
141.726
141.757
141.775
141.830
141.879
154.401
154.450
154.493
161.185
161.228
161.246
161.289
162.451
162.463
162.494
162.512
162.543
C6F5
O
NC
1.00
0.75
0.50
0.25
0
2.00
0.86
0.91
0.89
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
Chemical Shift (ppm)

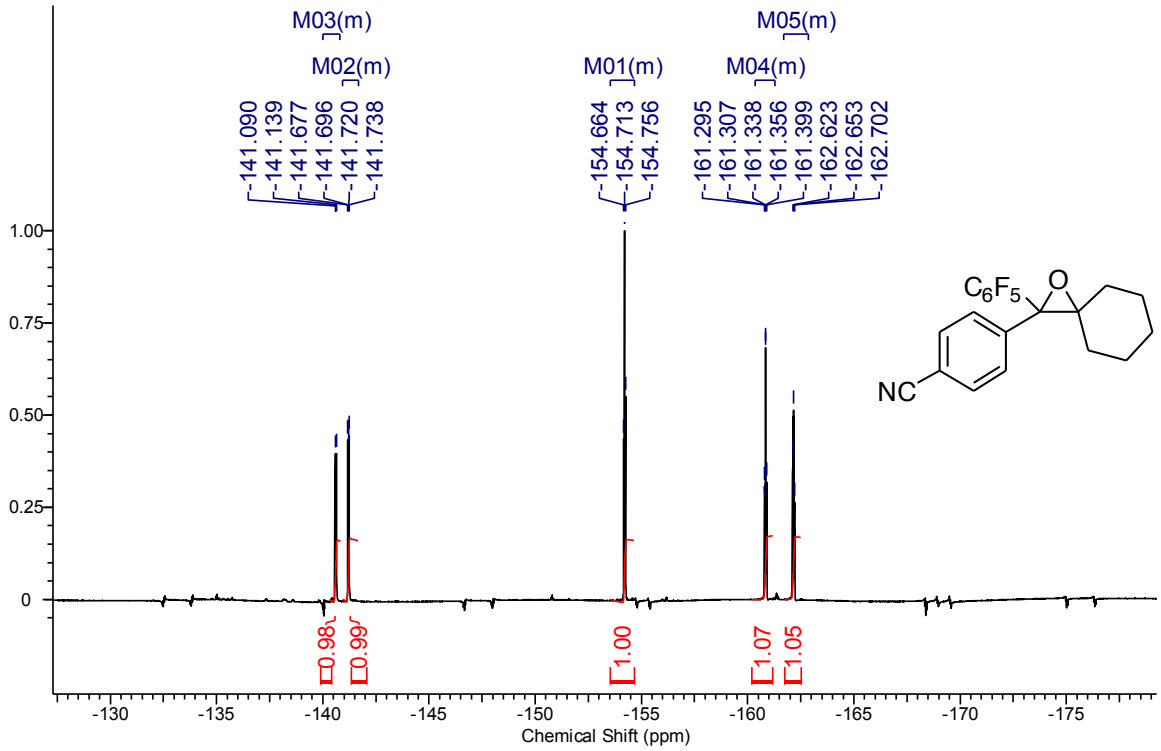
^{1}H NMR of **3h**



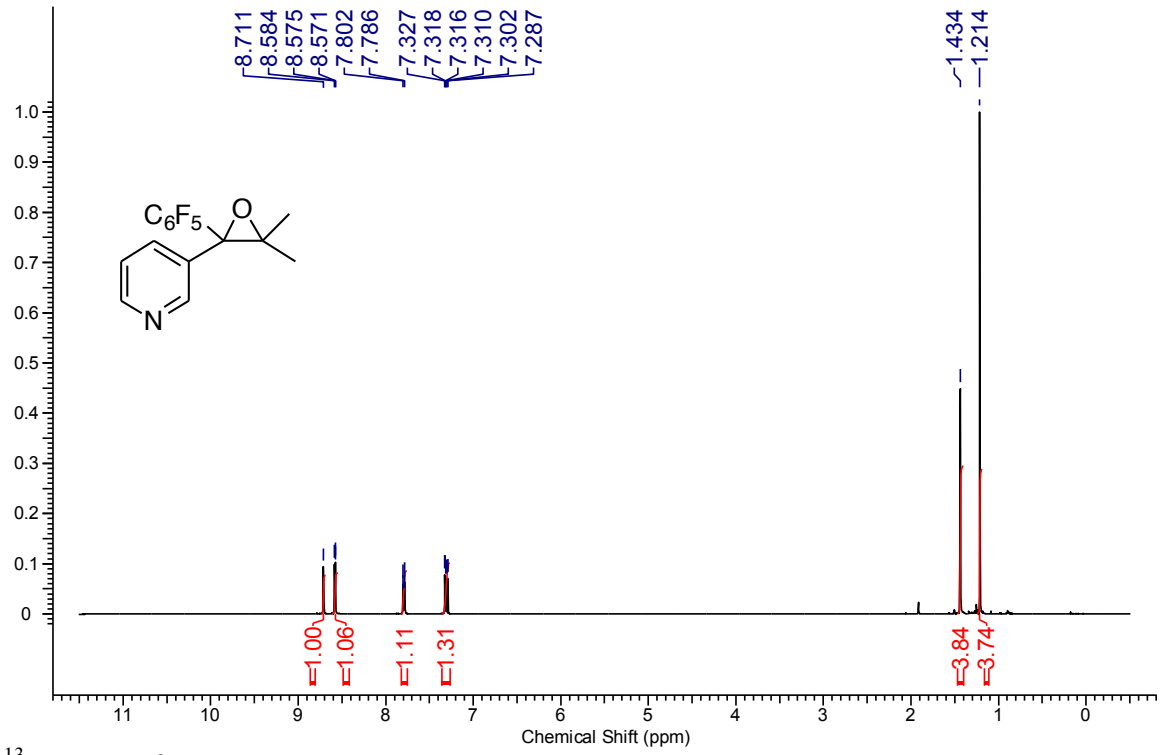
^{13}C NMR of **3h**



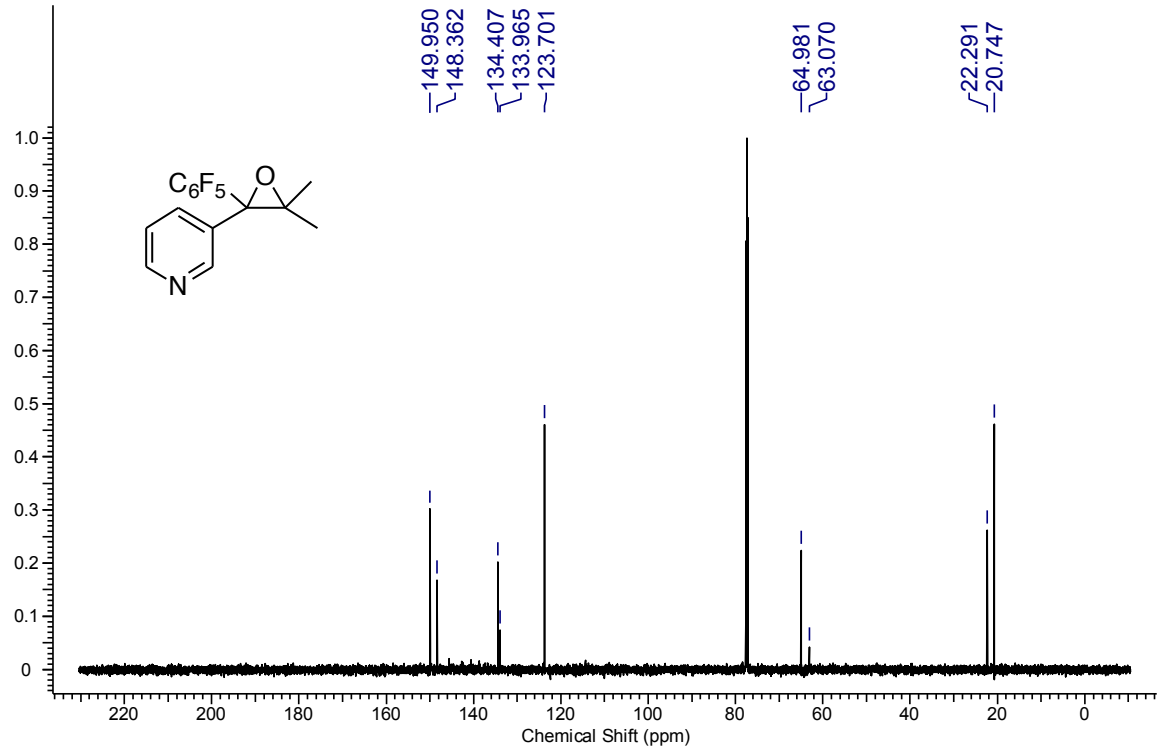
^{19}F NMR of **3h**


M03(m)
M02(m)
M01(m)
M05(m)
M04(m)
-141.090
-141.139
-141.677
-141.696
-141.720
-141.738
-154.664
-154.713
-154.756
-161.295
-161.307
-161.338
-161.356
-161.399
-162.623
-162.653
-162.702
1.00
0.75
0.50
0.25
0
0.98
0.99
1.00
1.07
1.05
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
Chemical Shift (ppm)
C6F5
O
NC

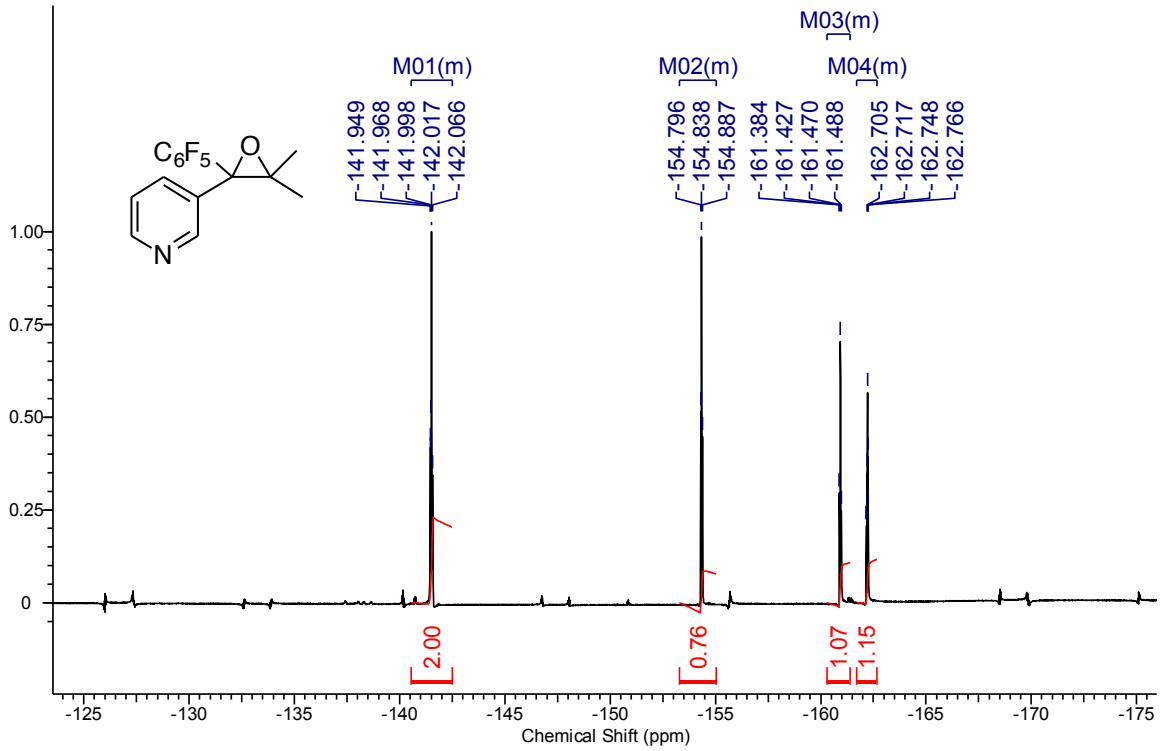
^{1}H NMR of **3i**



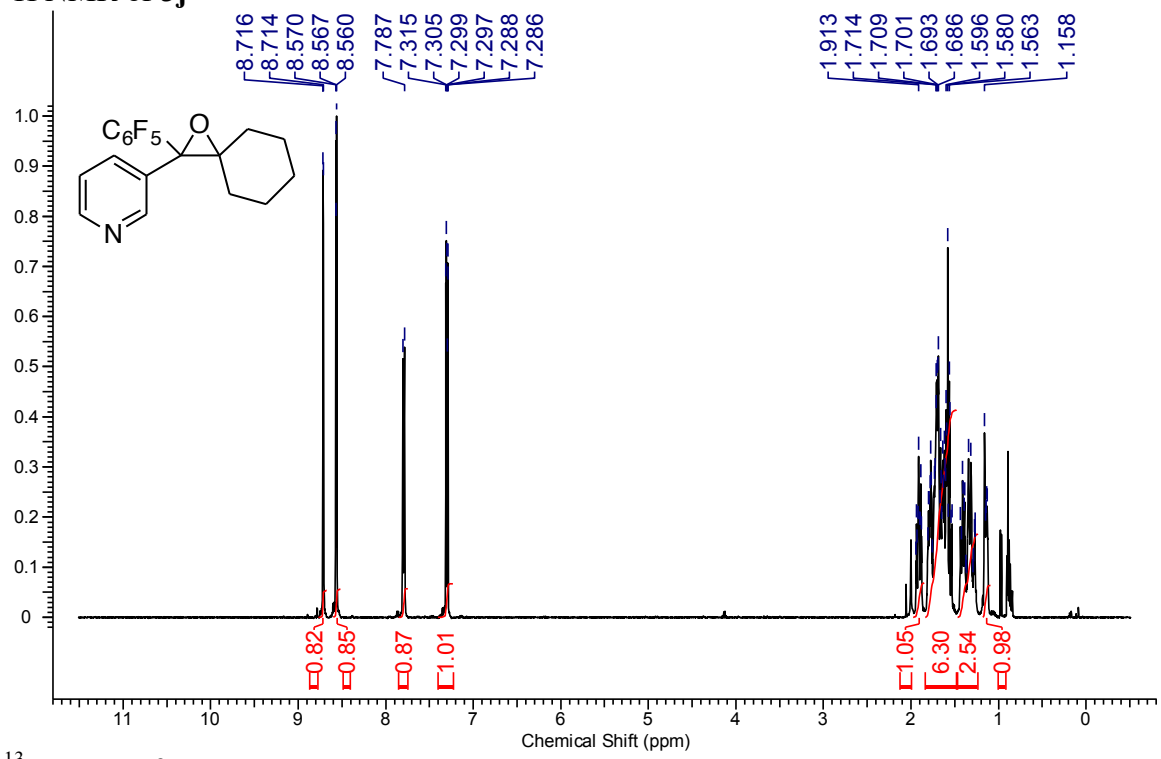
^{13}C NMR of **3i**



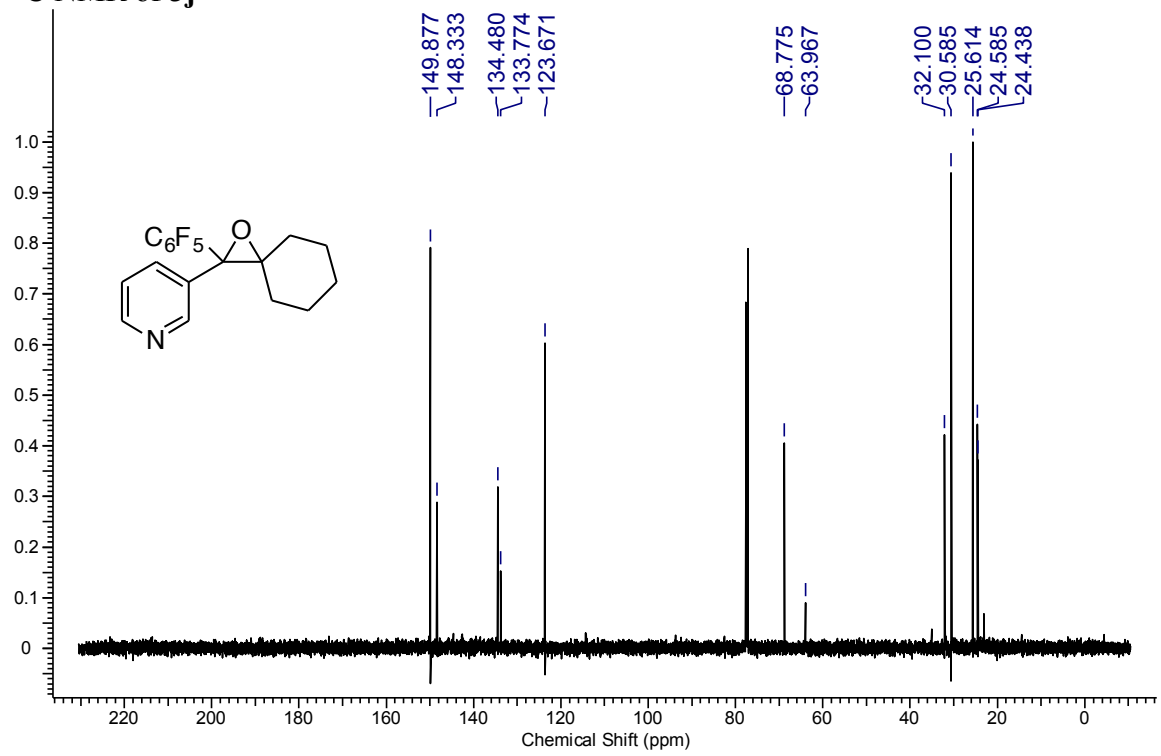
^{19}F NMR of **3i**


M01(m)
M02(m)
M03(m)
M04(m)
-141.949
-141.968
-141.998
-142.017
-142.066
-154.796
-154.838
-154.887
-161.384
-161.427
-161.470
-161.488
-162.705
-162.717
-162.748
-162.766
C6F5
O
N
1.00
0.75
0.50
0.25
0
2.00
0.76
1.07
1.15
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
Chemical Shift (ppm)

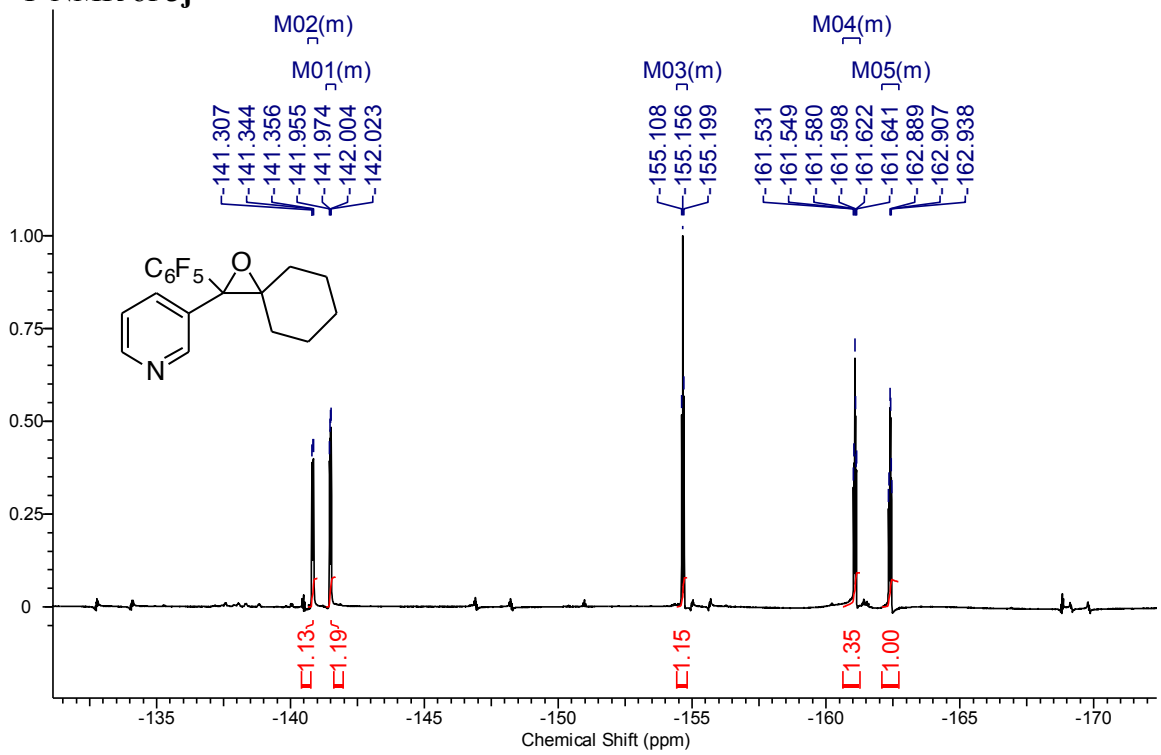
^{1}H NMR of **3j**



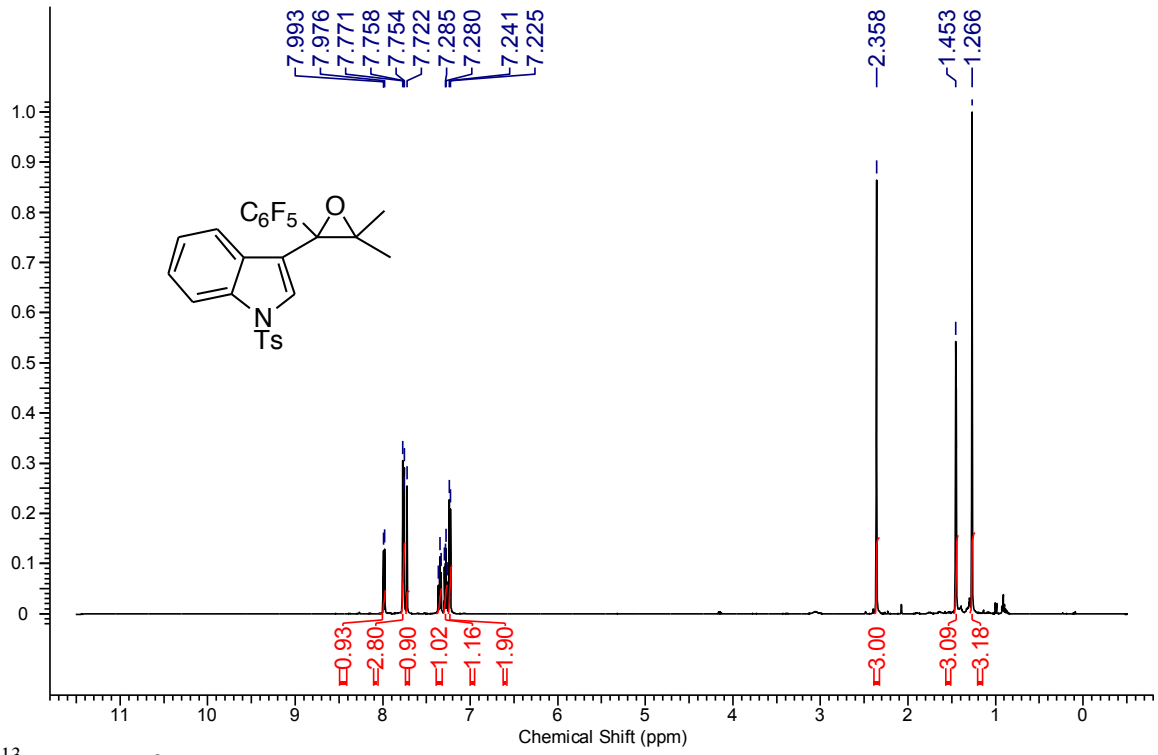
^{13}C NMR of **3j**



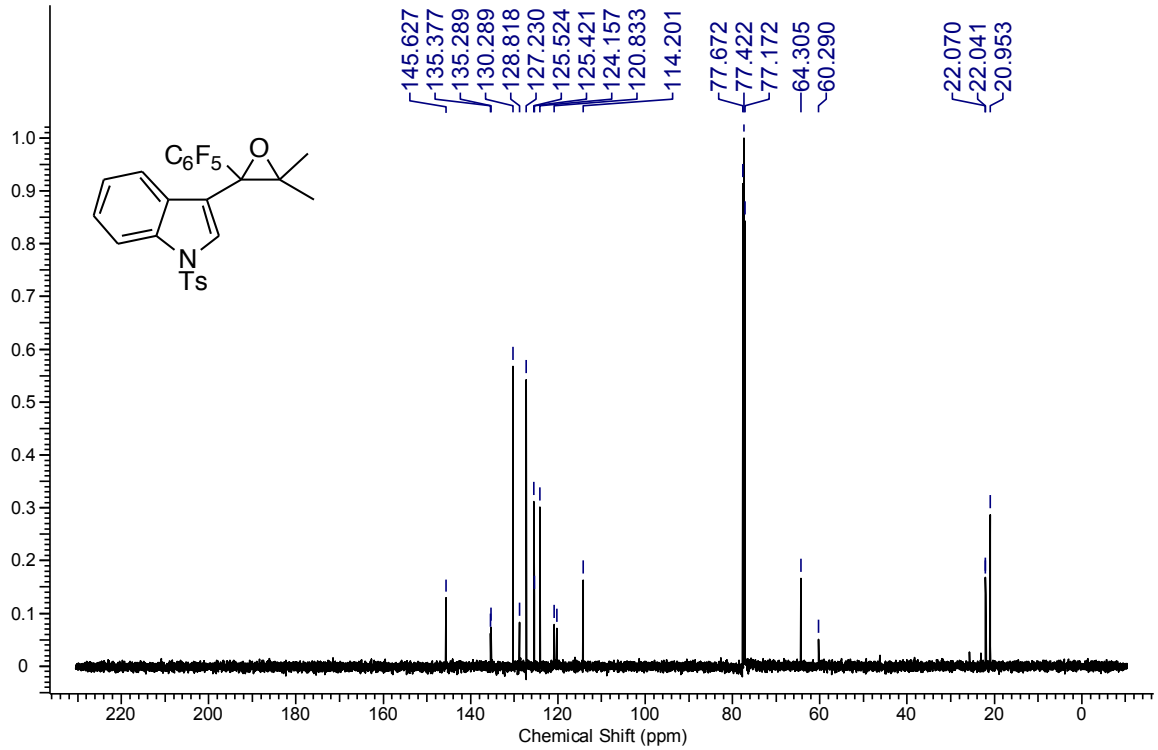
^{19}F NMR of **3j**


M02(m)
M01(m)
M03(m)
M04(m)
M05(m)
-141.307
-141.344
-141.356
-141.955
-141.974
-142.004
-142.023
-155.108
-155.156
-155.199
-161.531
-161.549
-161.580
-161.598
-161.622
-161.641
-162.889
-162.907
-162.938
C6F5
O
N
1.00
0.75
0.50
0.25
0
1.15
1.35
1.00
-135
-140
-145
-150
-155
-160
-165
-170
Chemical Shift (ppm)

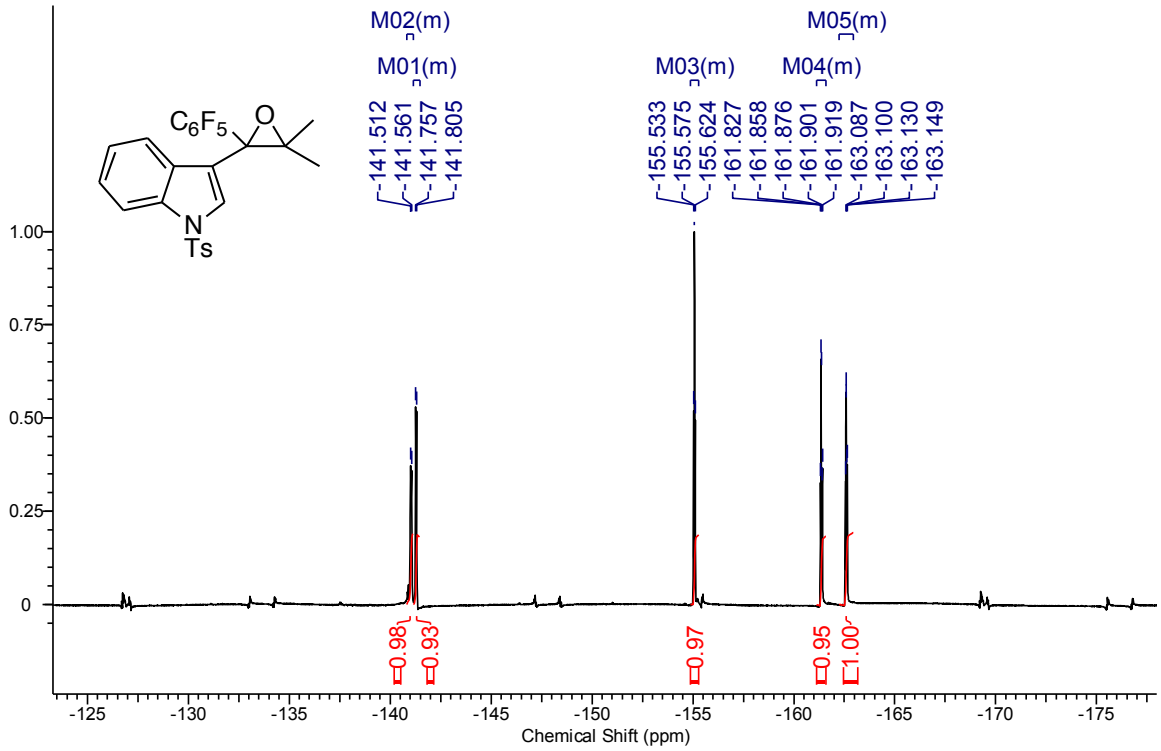
^{1}H NMR of **3k**



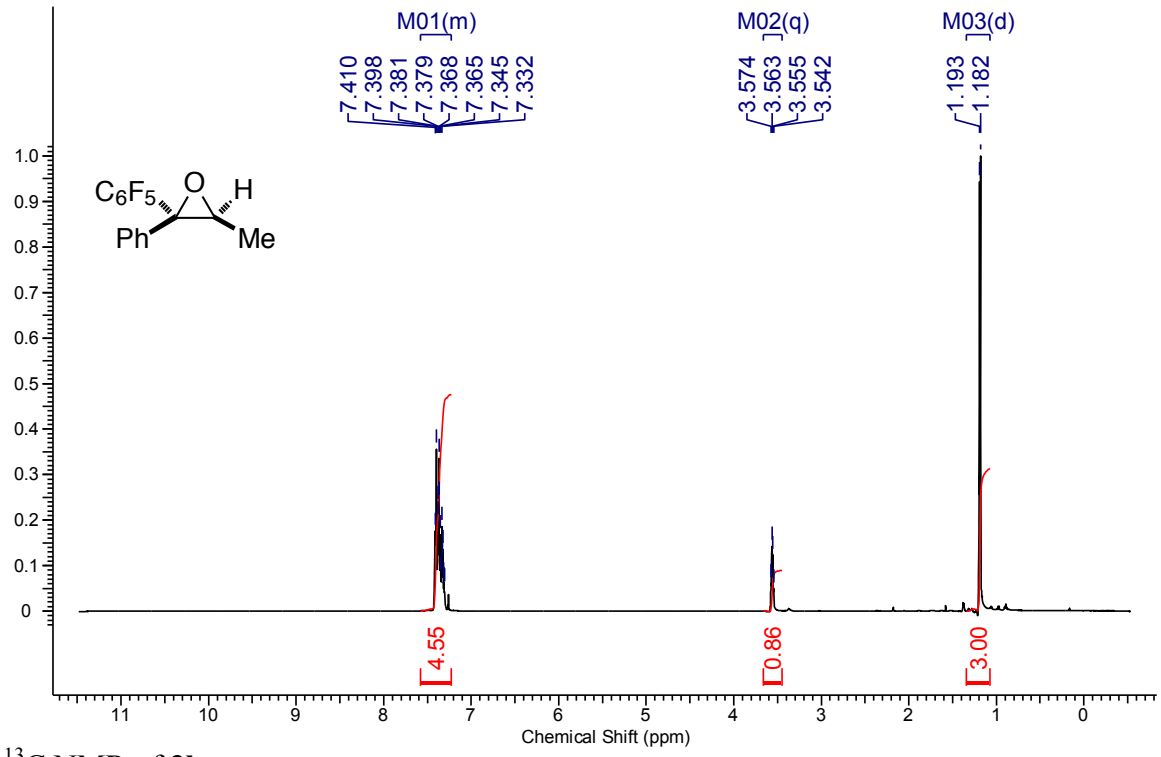
^{13}C NMR of **3k**



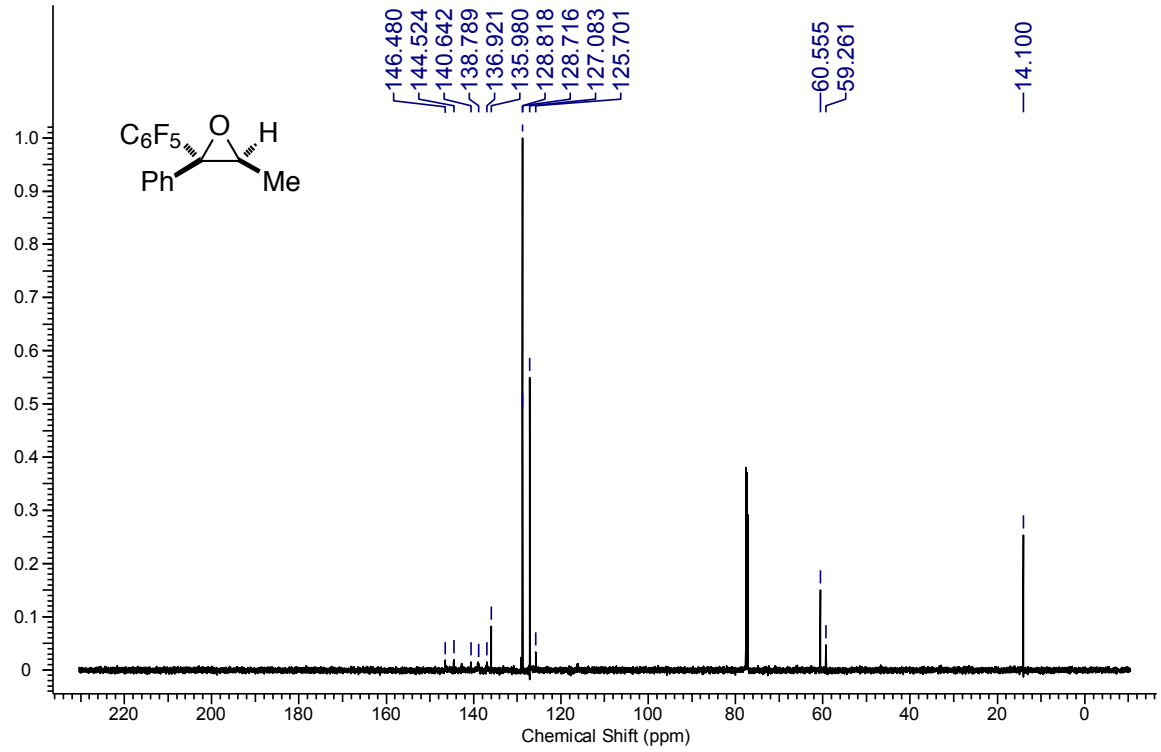
^{19}F NMR of **3k**


M02(m)
M01(m)
M03(m)
M04(m)
M05(m)
-141.512
-141.561
-141.757
-141.805
-155.533
-155.575
-155.624
-161.827
-161.858
-161.876
-161.901
-161.919
-163.087
-163.100
-163.130
-163.149
C6F5
O
N
Ts
1.00
0.75
0.50
0.25
0
0.98
0.93
0.97
0.95
1.00
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
Chemical Shift (ppm)

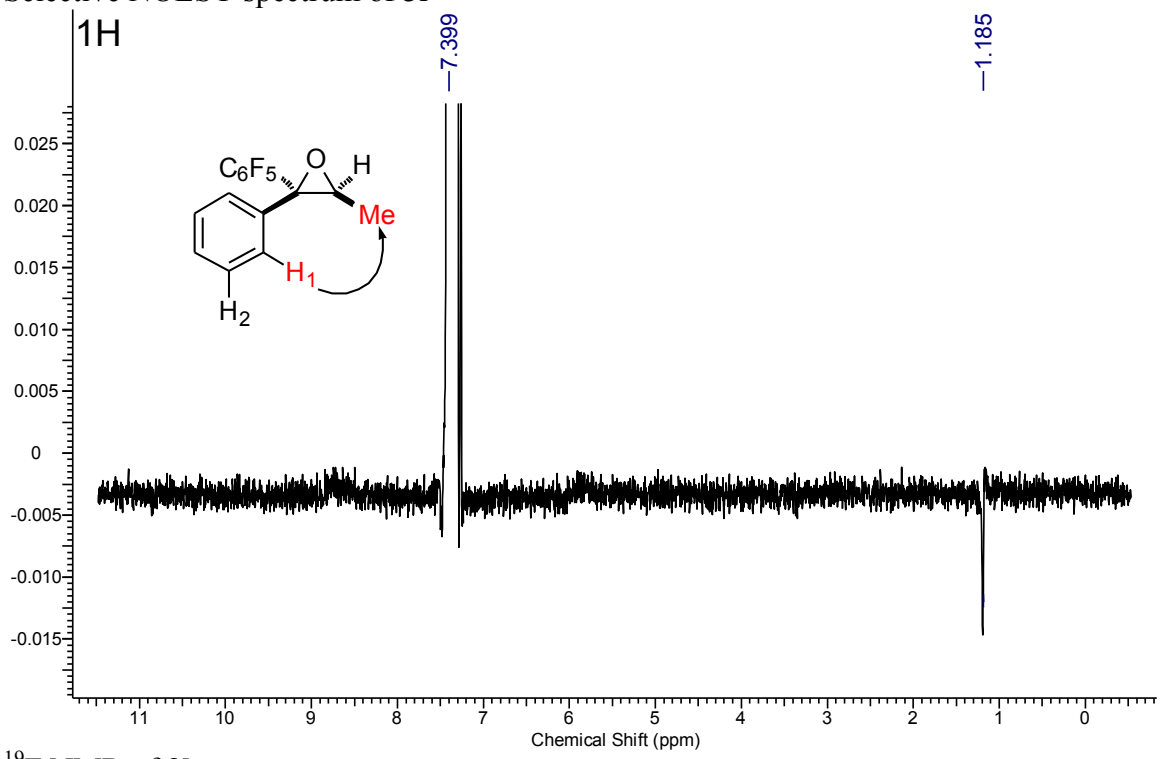
^{1}H NMR of **3l**



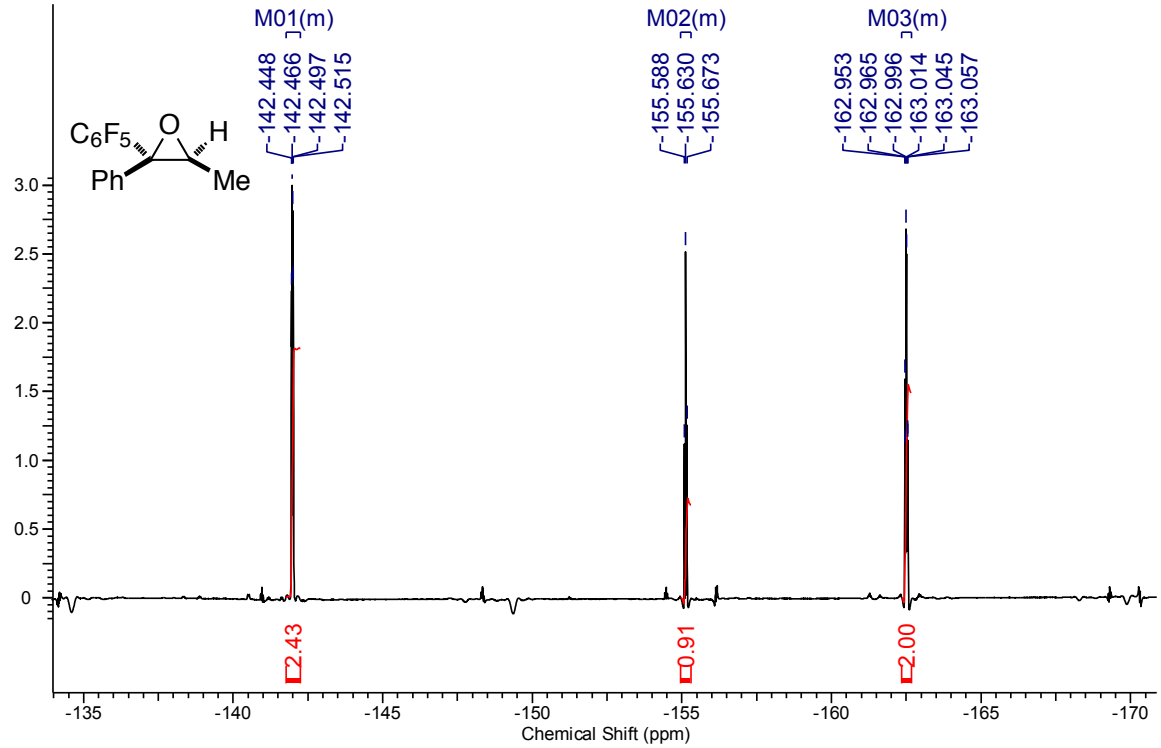
^{13}C NMR of **3l**



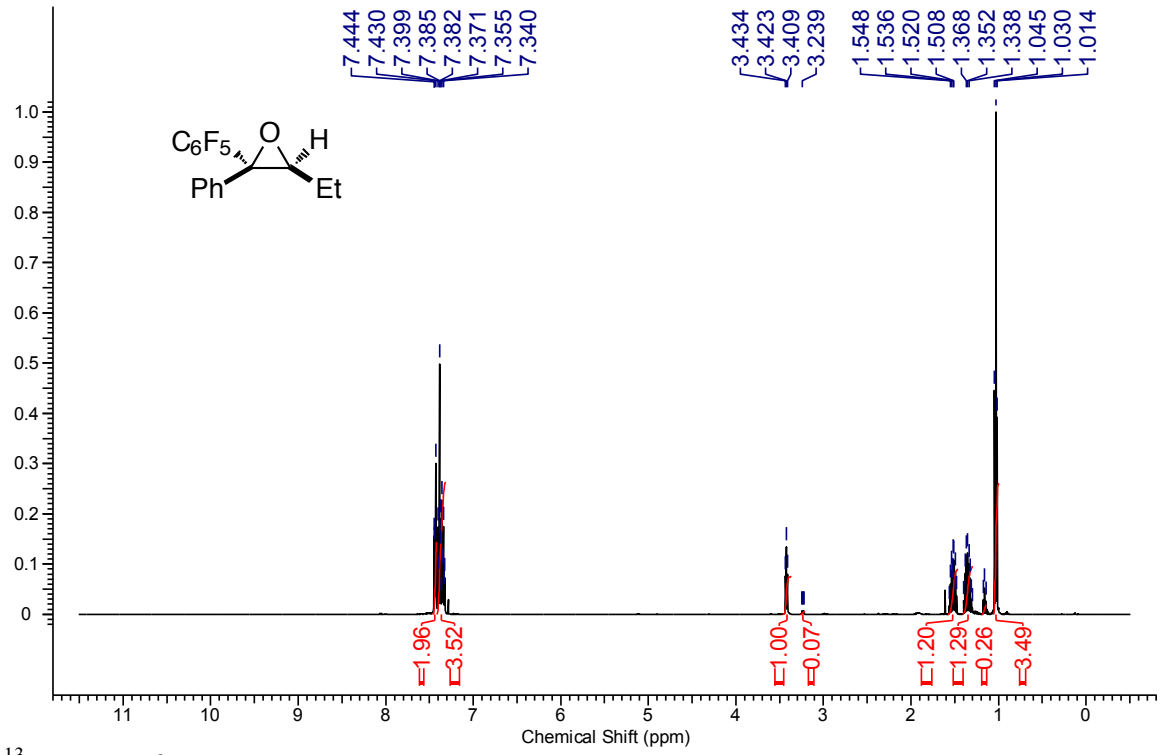
Selective NOESY spectrum of **3i**



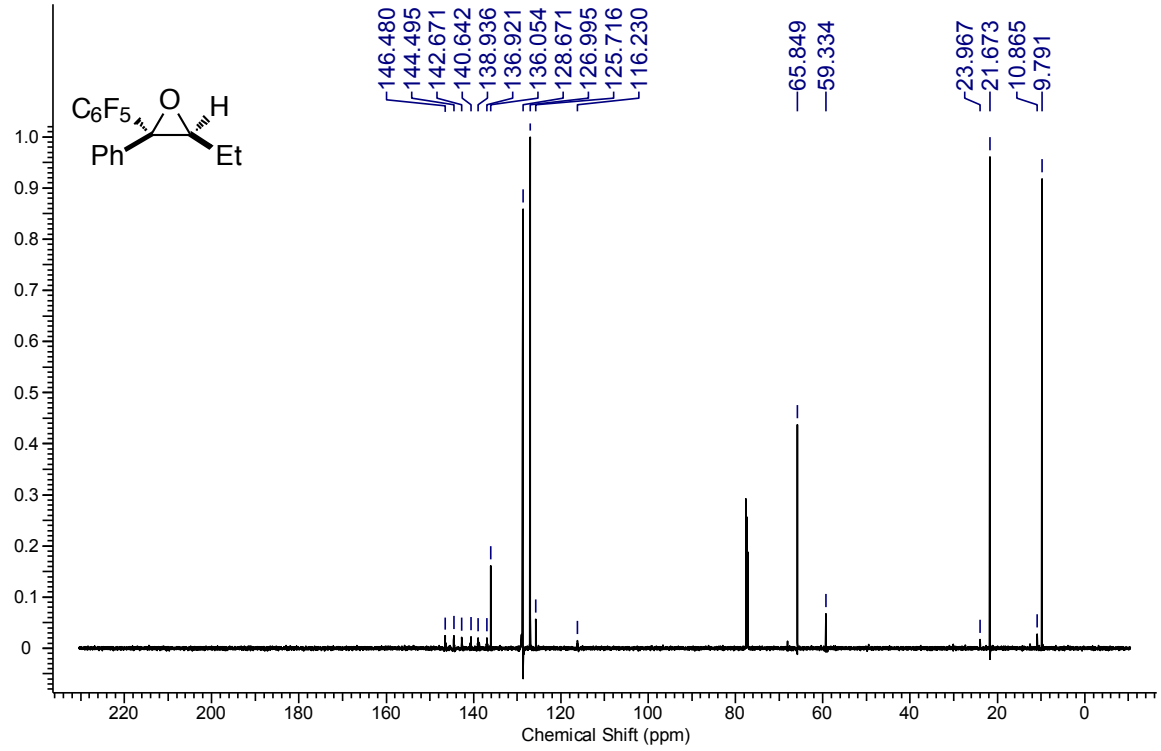
^{19}F NMR of **3l**



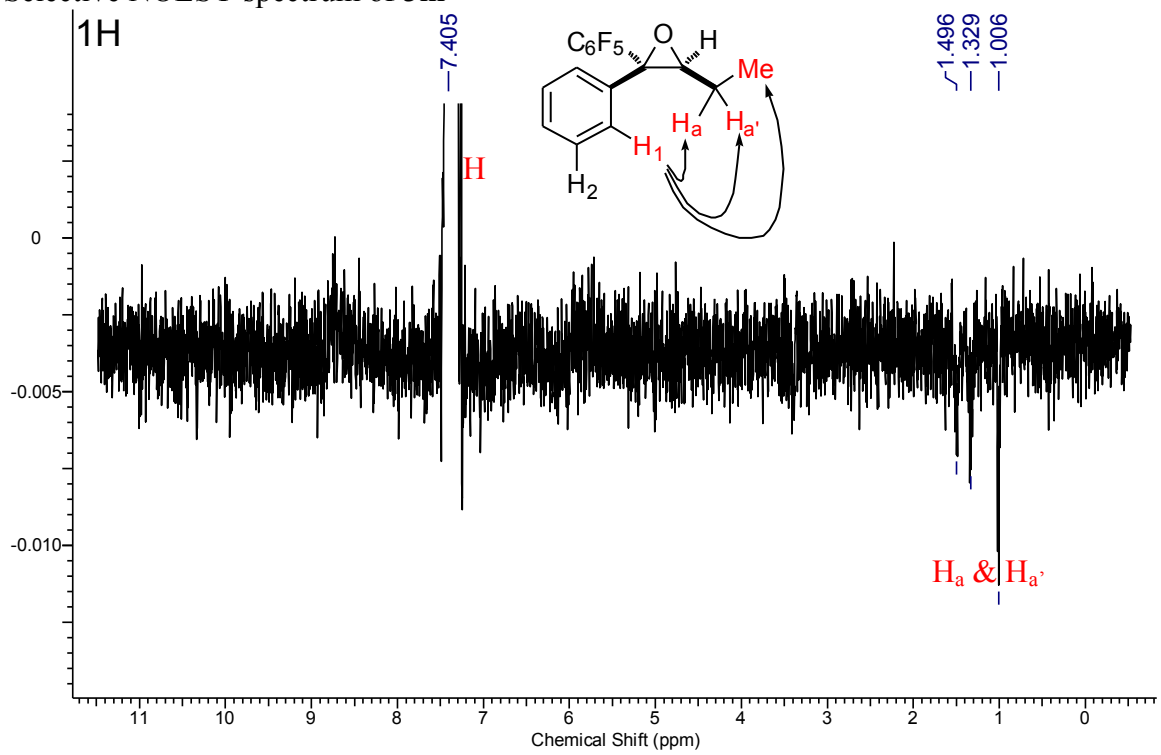
^{1}H NMR of **3m**



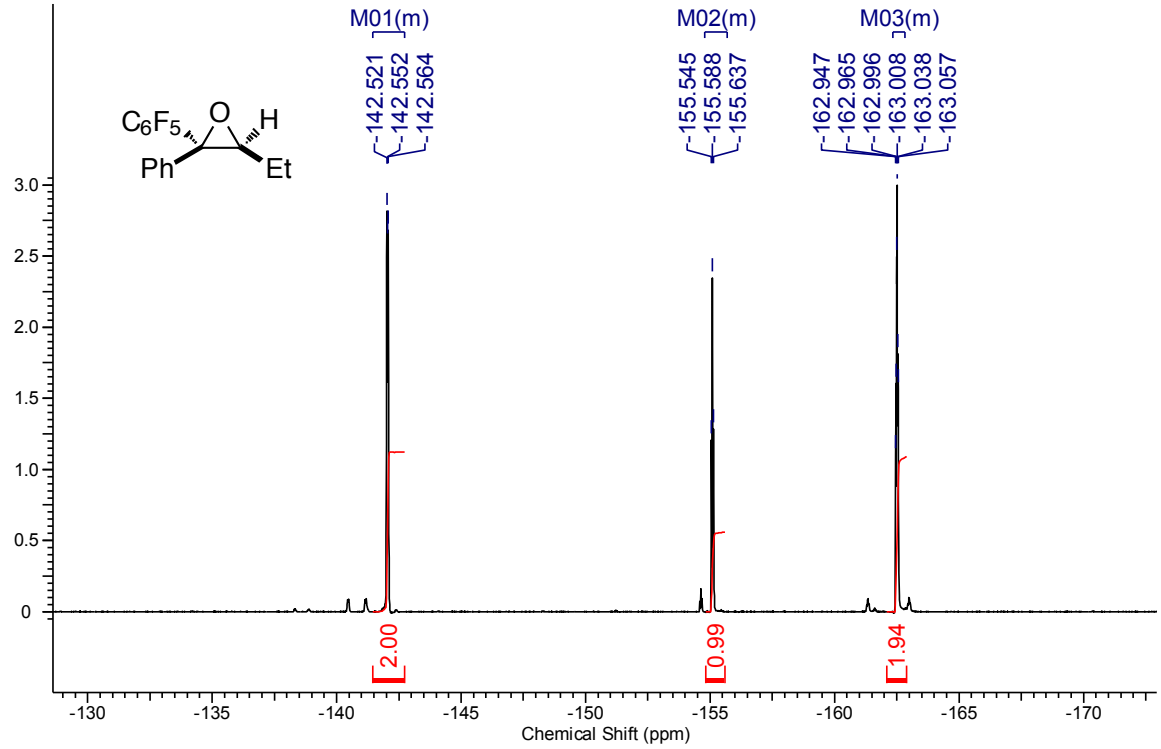
^{13}C NMR of **3m**



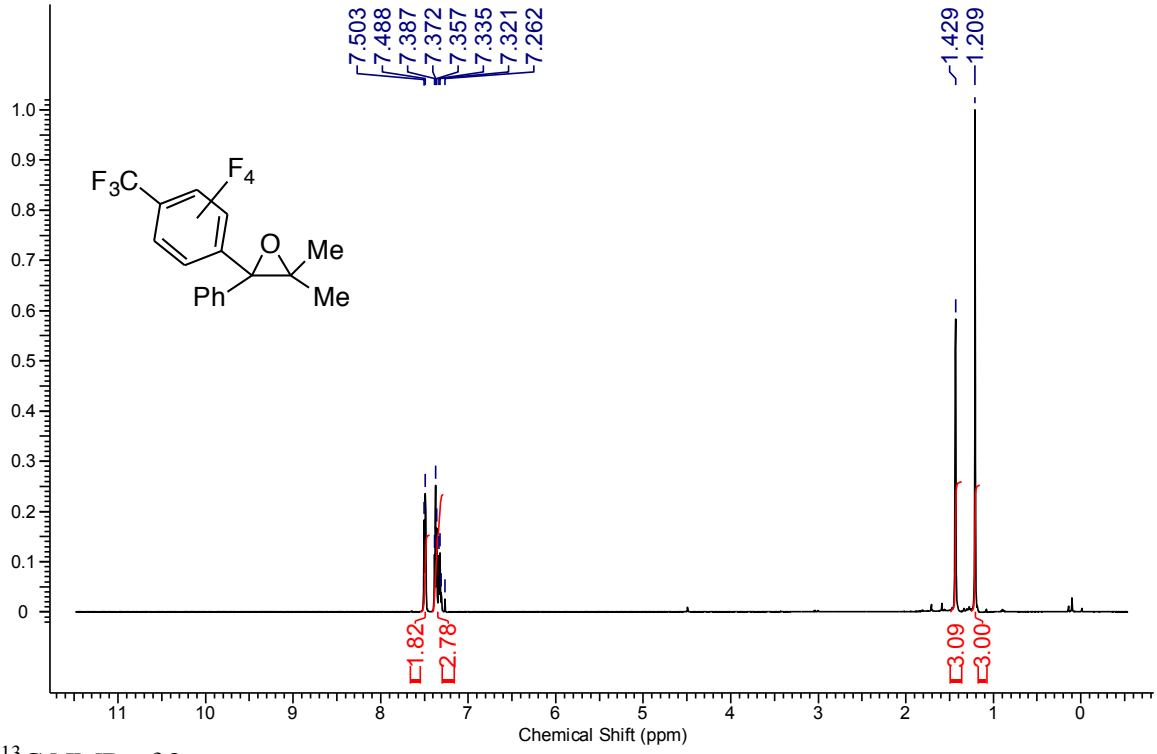
Selective NOESY spectrum of **3m**



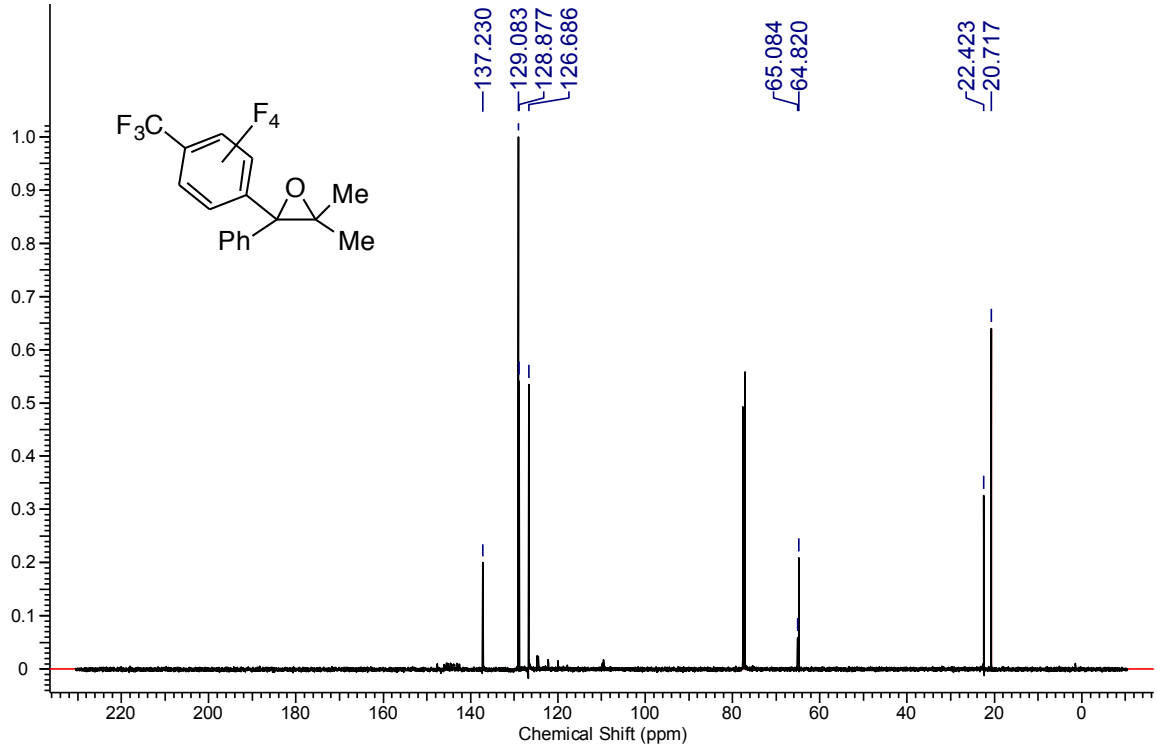
^{19}F NMR of **3m**



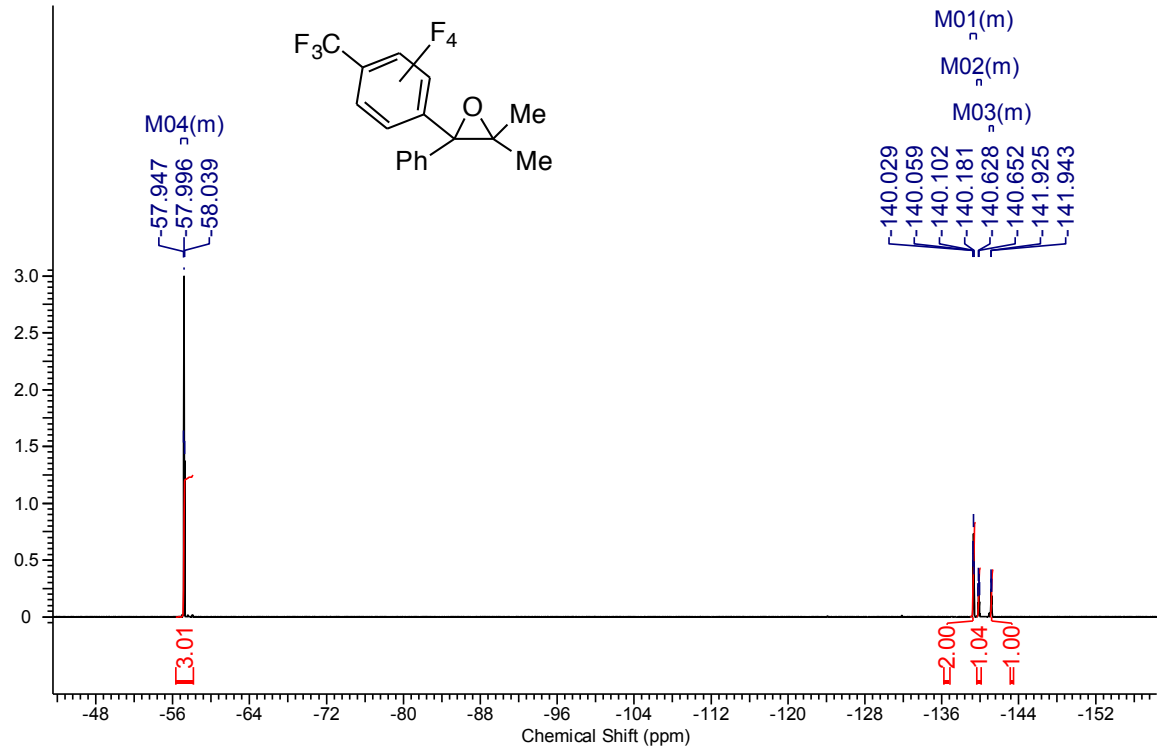
^{1}H NMR of **3n**



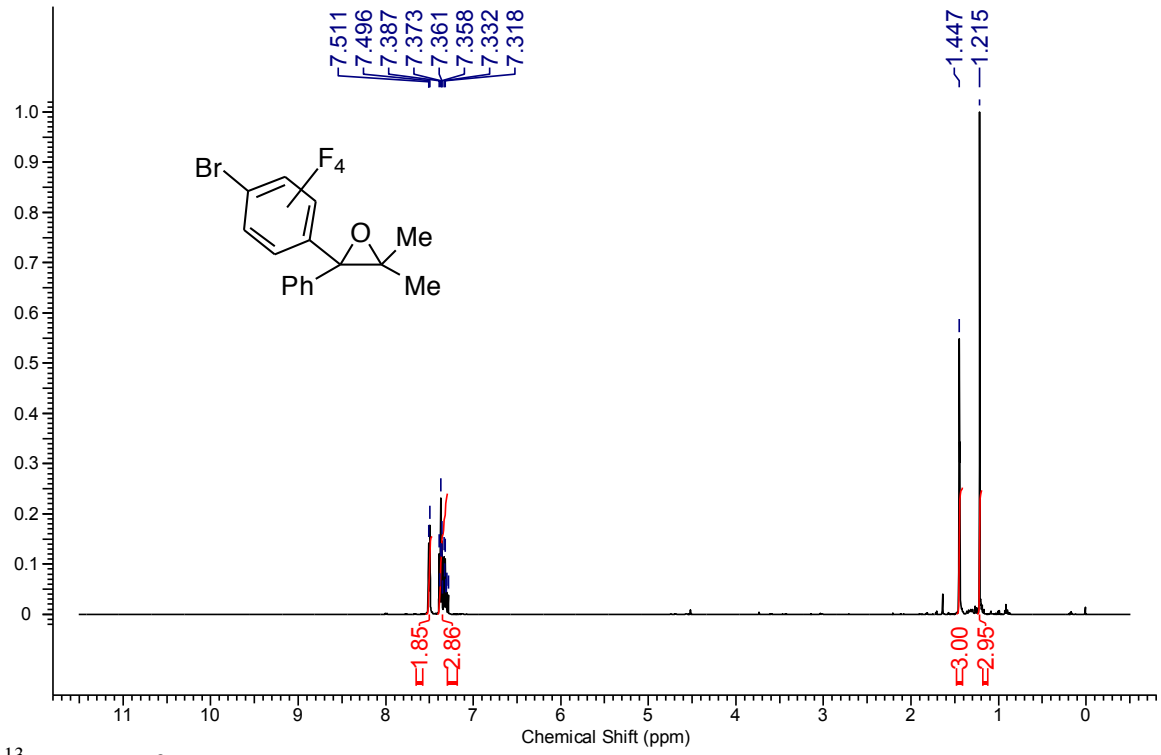
^{13}C NMR of **3n**



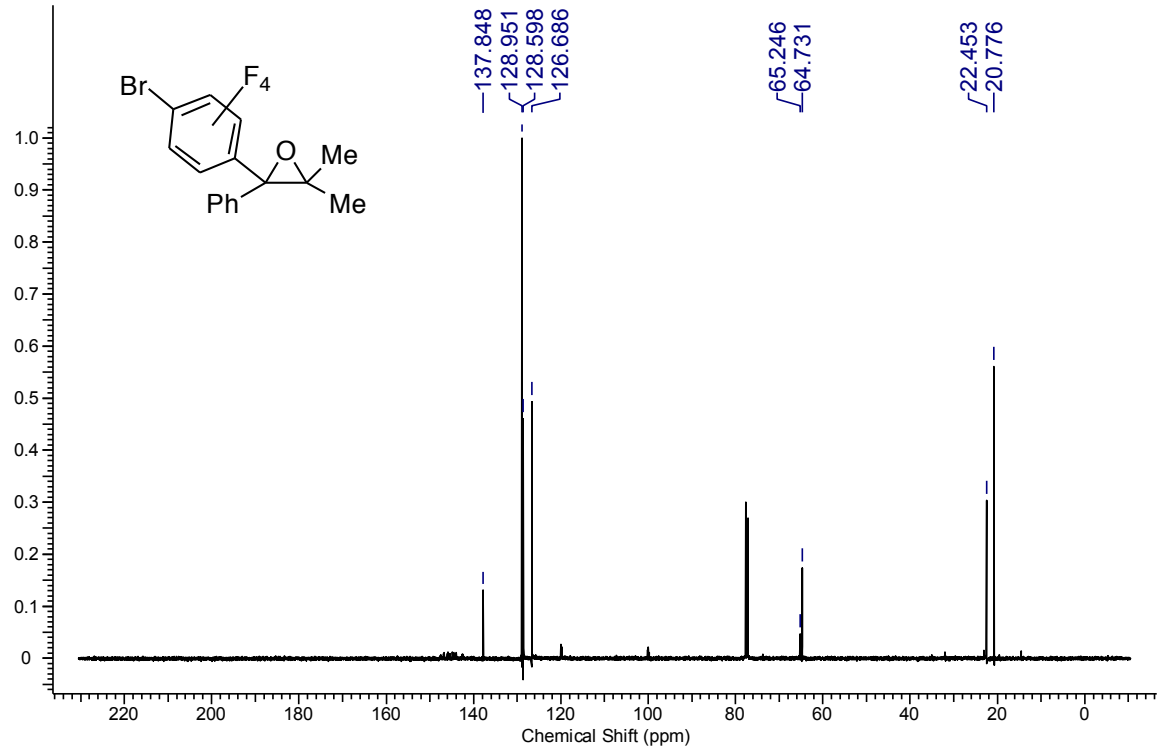
^{19}F NMR of **3n**


F3C
F4
O
Me
Ph
Me
M04(m)
M01(m)
M02(m)
M03(m)
-57.947
-57.996
-58.039
-140.029
-140.059
-140.102
-140.181
-140.628
-140.652
-141.925
-141.943
3.01
2.00
1.04
1.00
Chemical Shift (ppm)

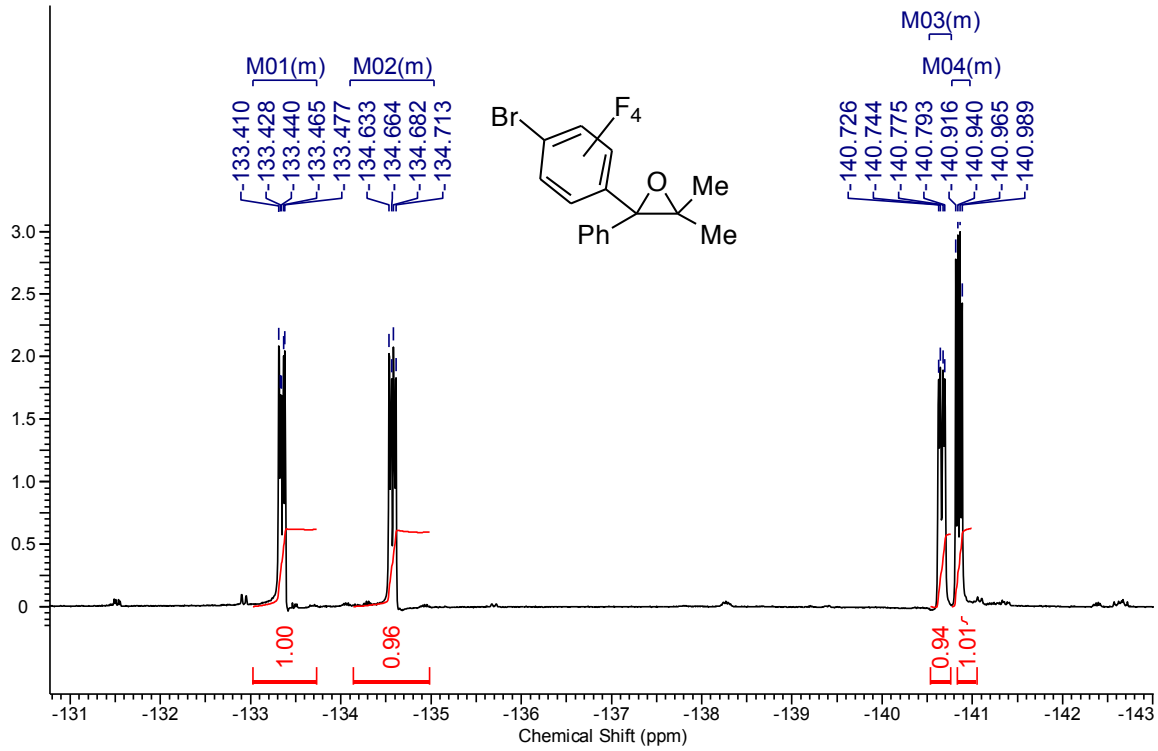
^{1}H NMR of **3o**



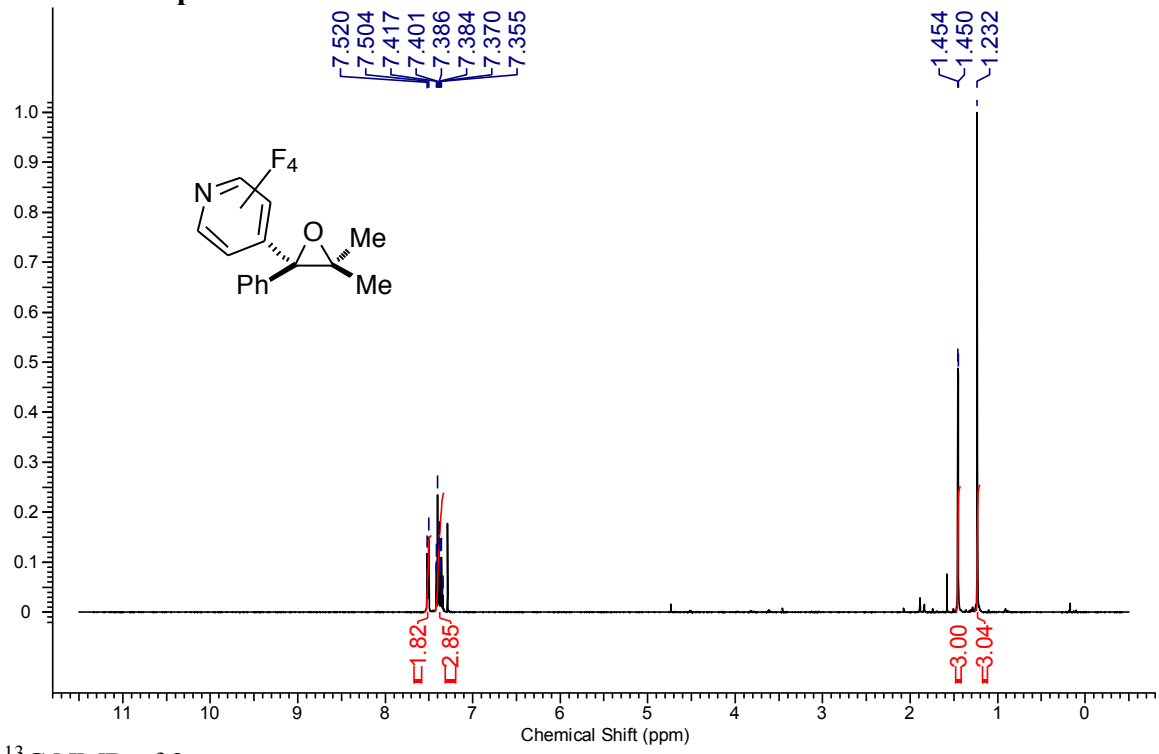
^{13}C NMR of **3o**



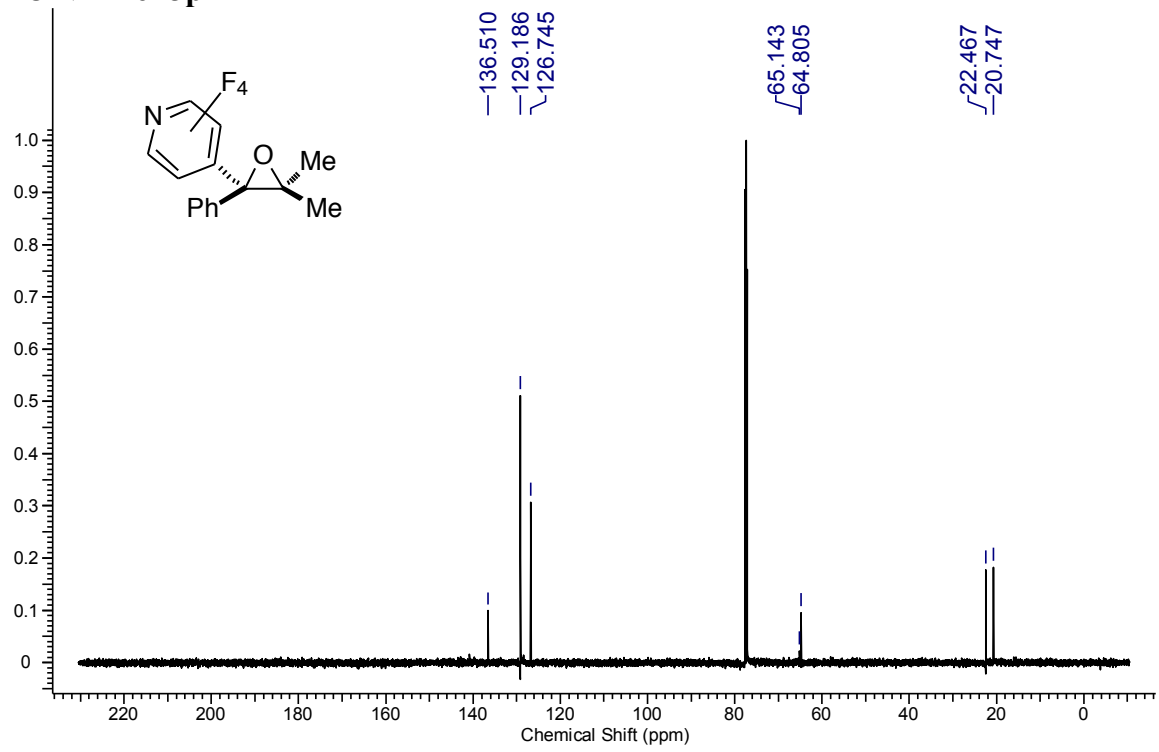
^{19}F NMR of **3o**


M01(m)
M02(m)
M03(m)
M04(m)
133.410
133.428
133.440
133.465
133.477
134.633
134.664
134.682
134.713
140.726
140.744
140.775
140.793
140.916
140.940
140.965
140.989
Br
F4
O
Me
Me
Ph
1.00
0.96
0.94
1.01
Chemical Shift (ppm)

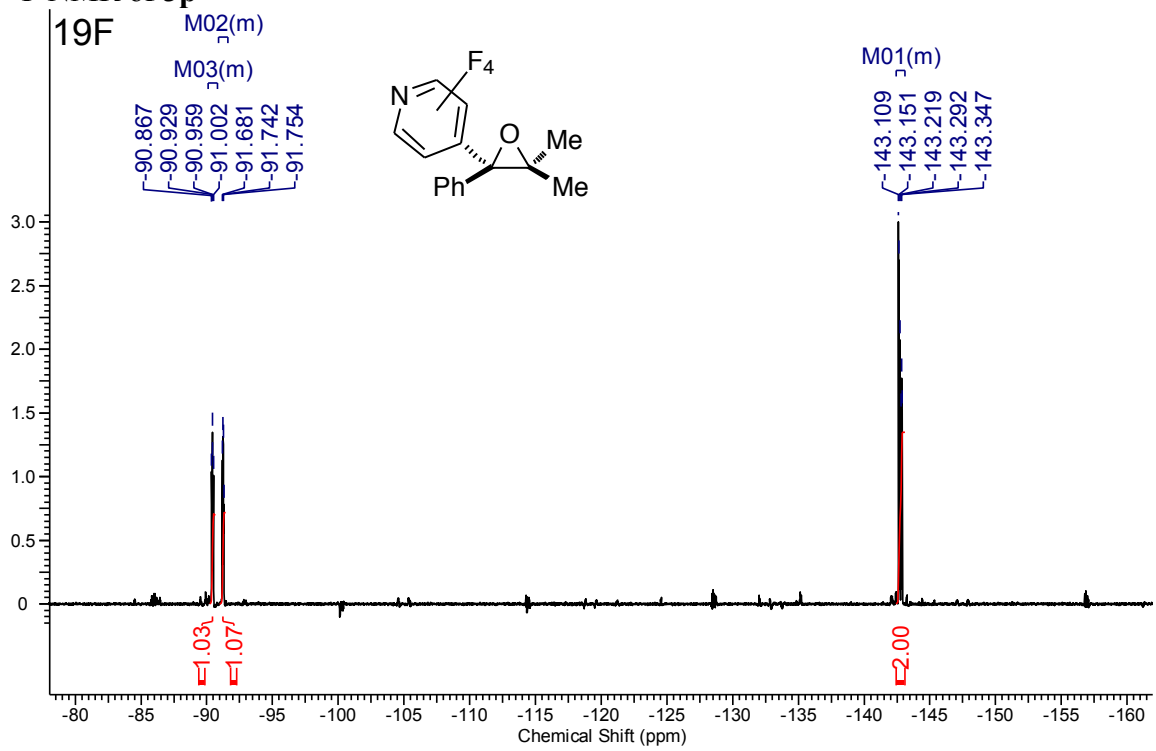
^{1}H NMR of **3p**



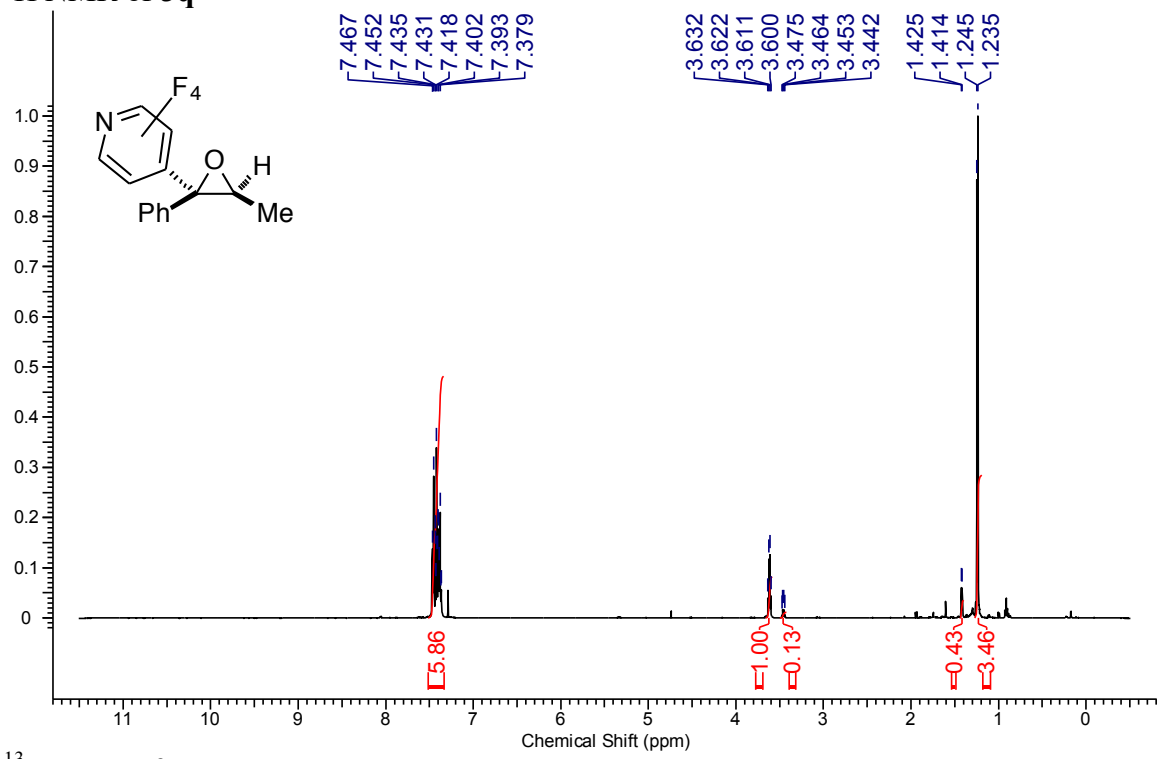
^{13}C NMR of **3p**



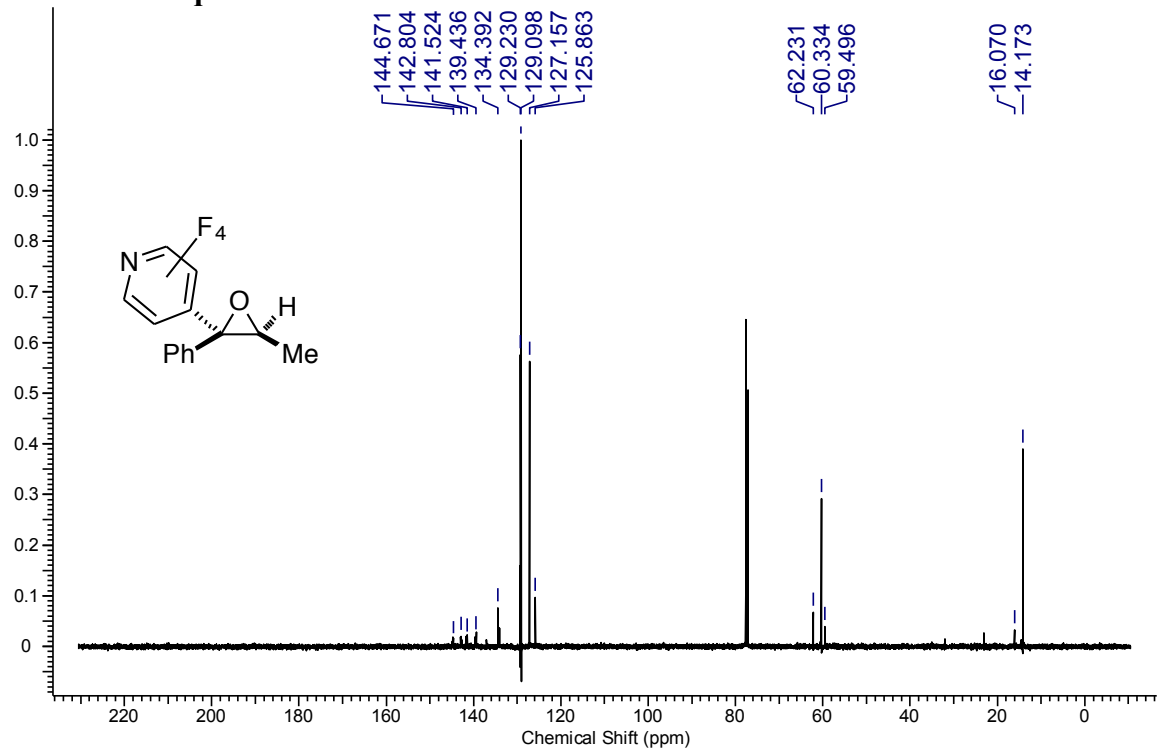
^{19}F NMR of **3p**


19F
M02(m)
M03(m)
M01(m)
-90.867
-90.929
-90.959
-91.002
-91.681
-91.742
-91.754
-143.109
-143.151
-143.219
-143.292
-143.347
F4
N
O
Me
Ph
Me
1.03
1.07
2.00
Chemical Shift (ppm)

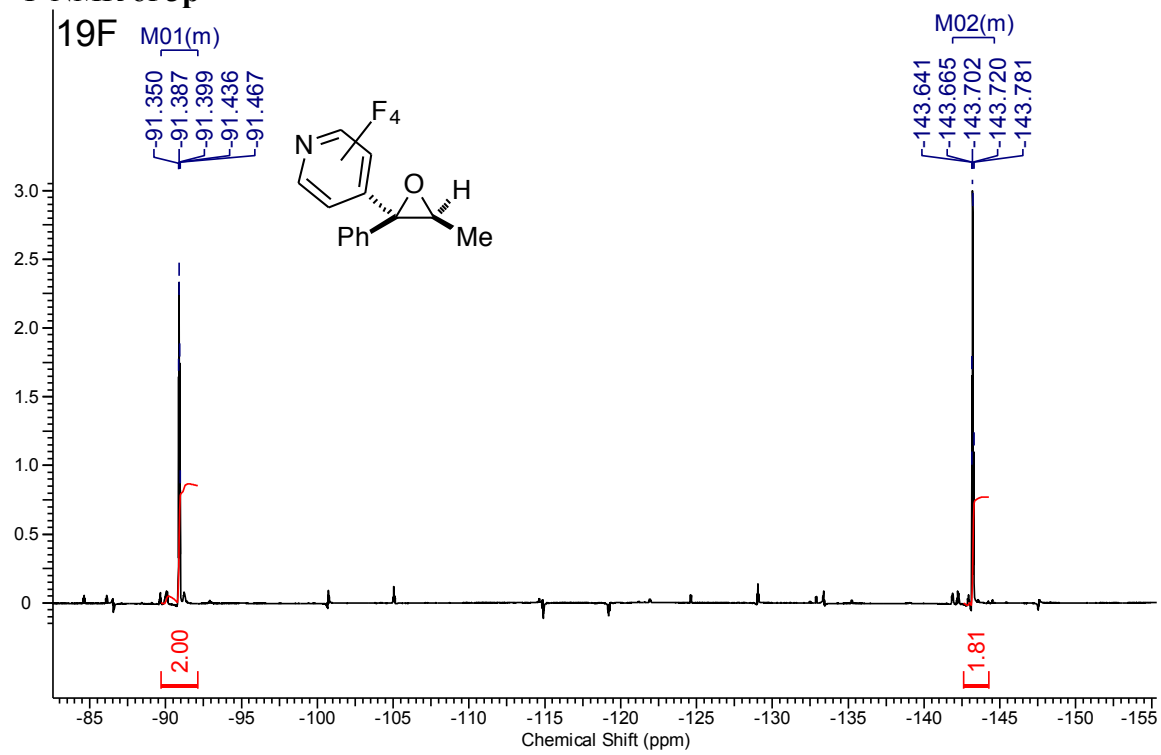
^{1}H NMR of **3q**



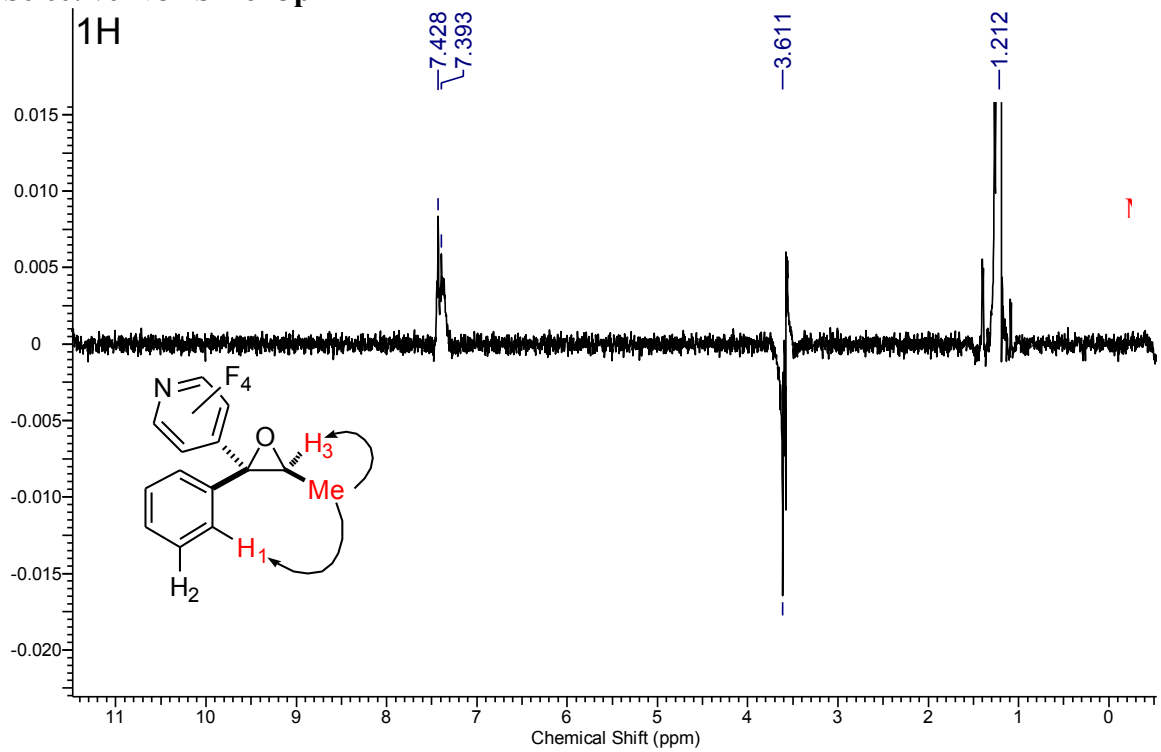
^{13}C NMR of **3q**



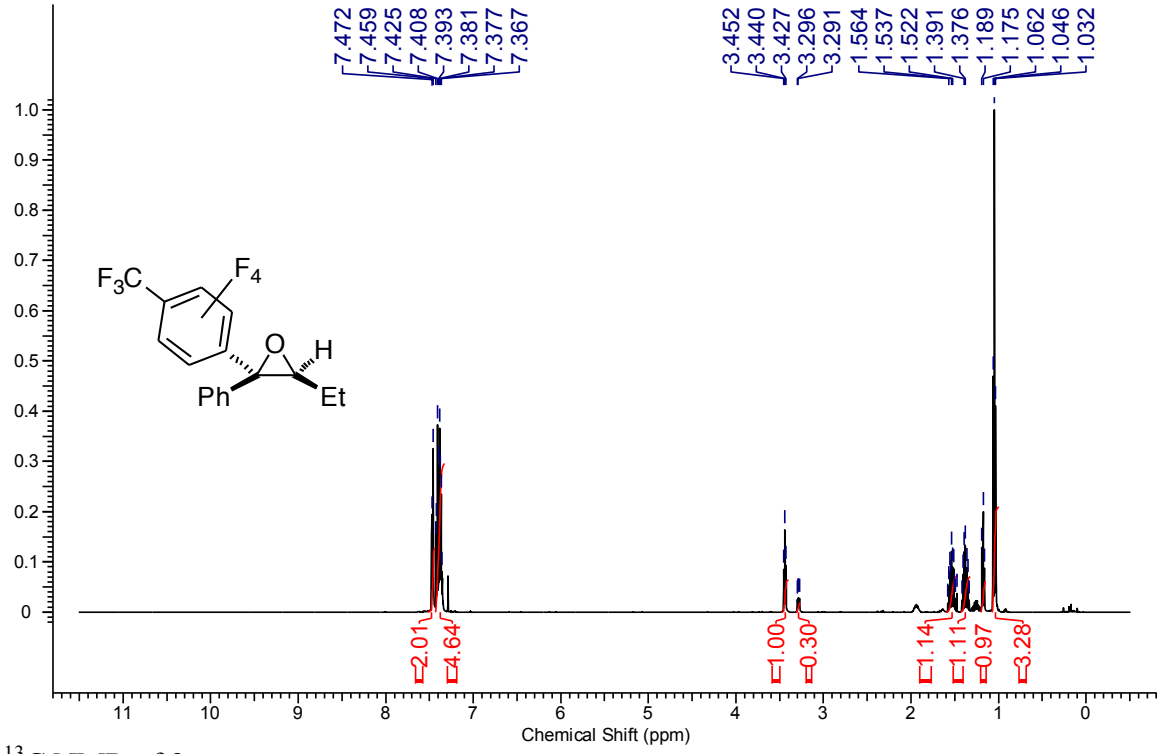
^{19}F NMR of **3p**



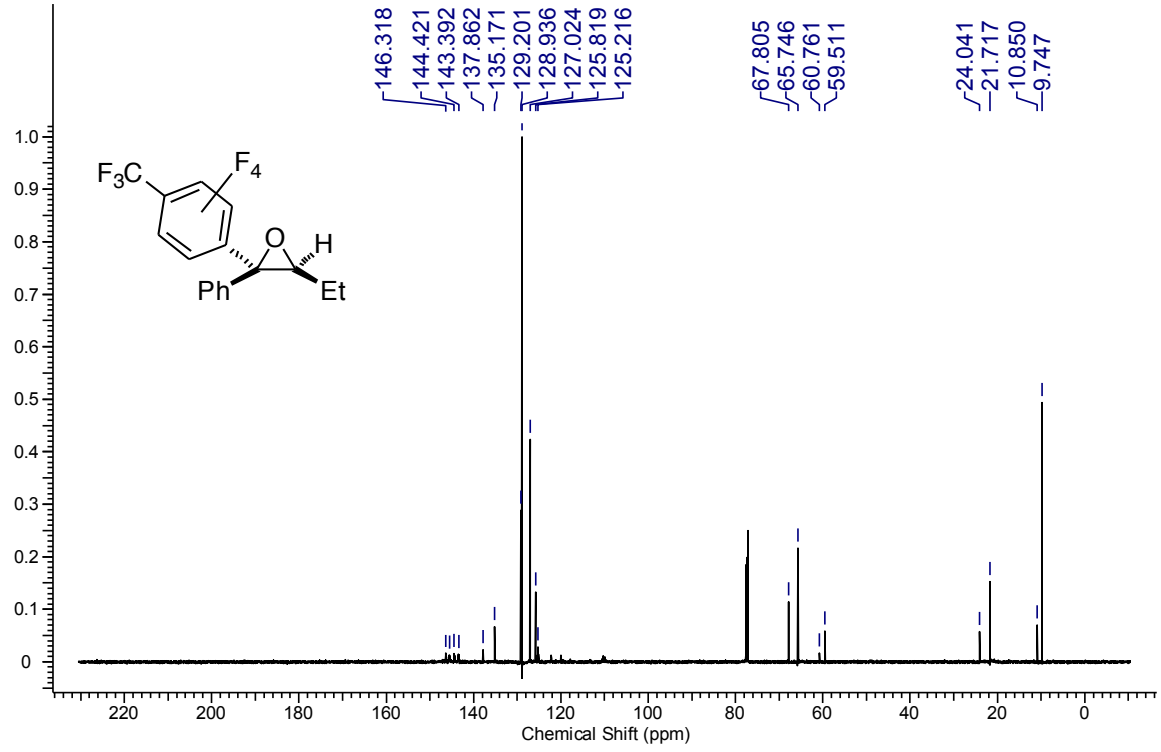
Selective NOESY of **3p**



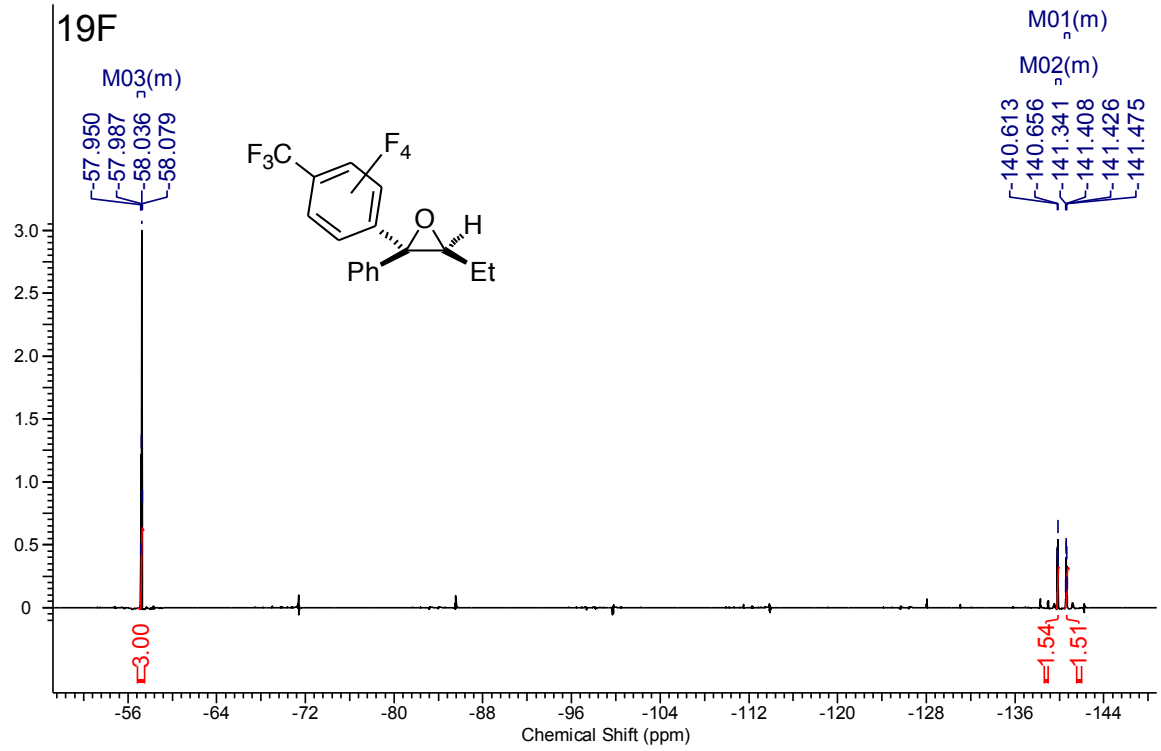
^{1}H NMR of **3r**



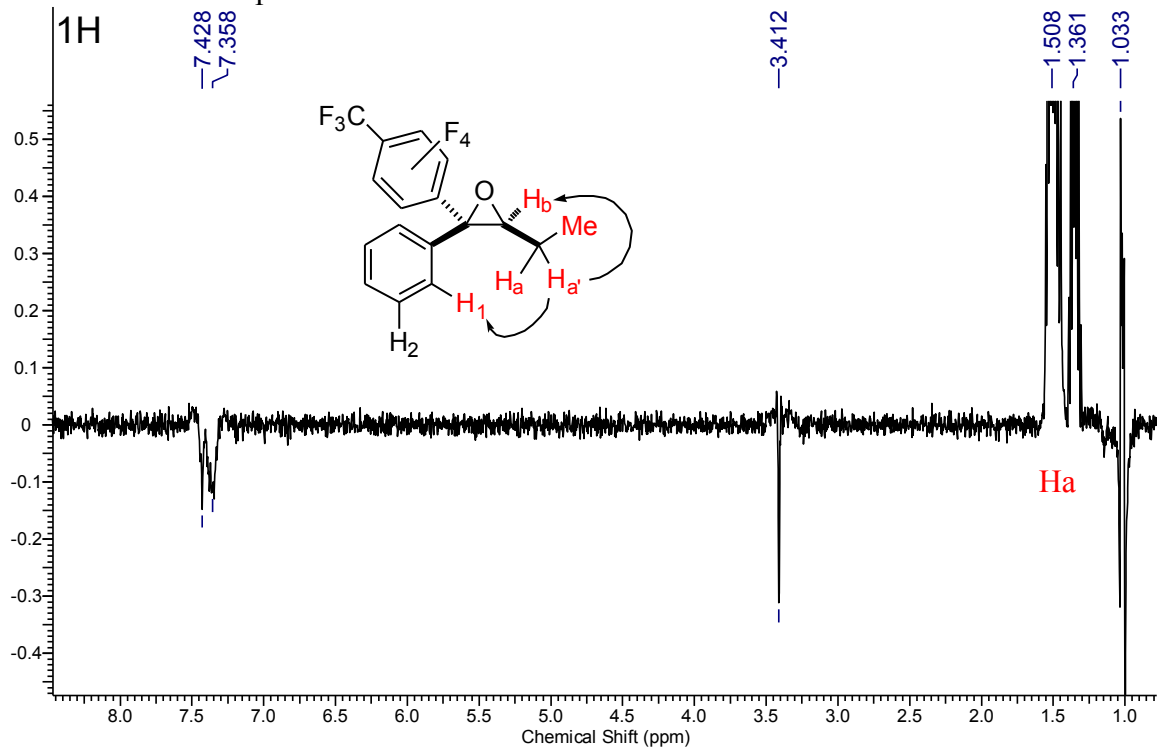
^{13}C NMR of **3r**



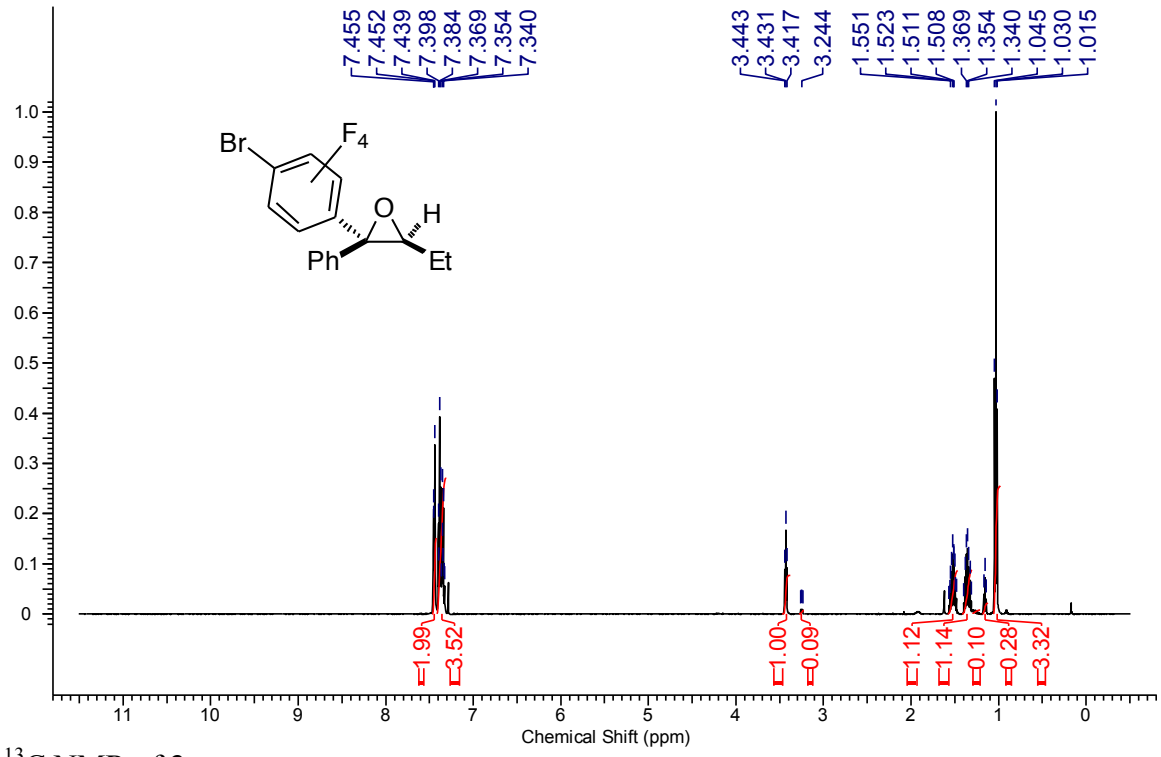
^{19}F NMR of **3r**



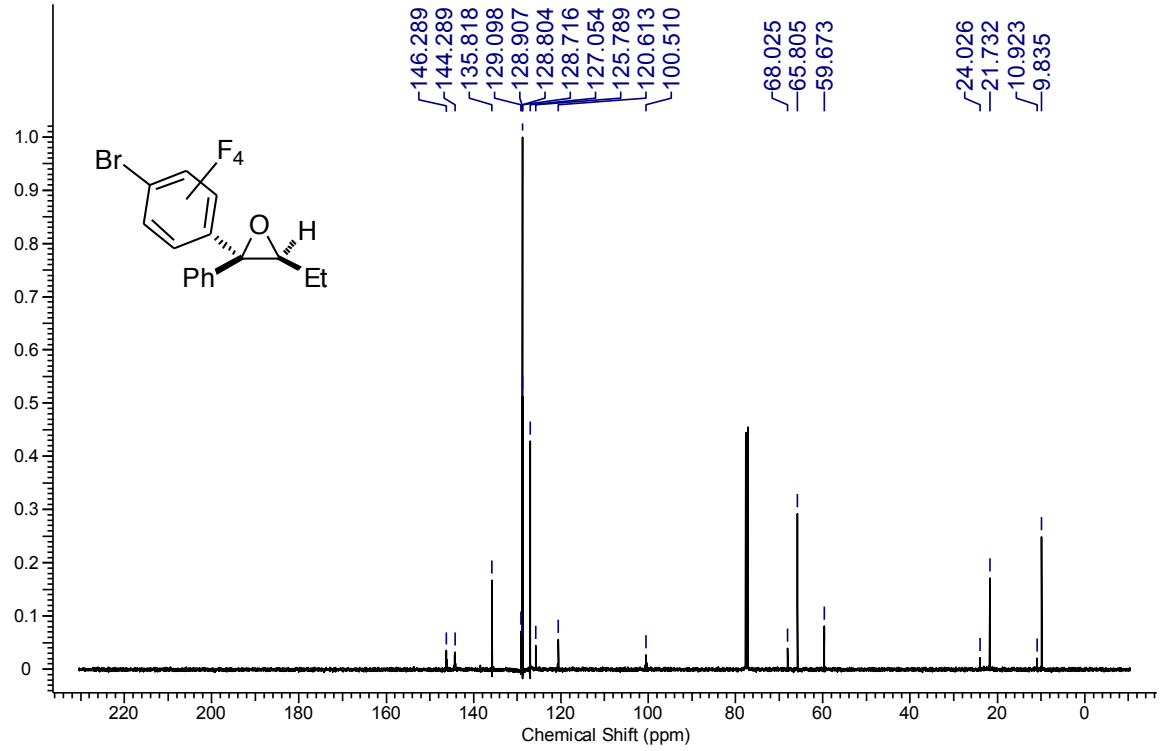
Selective NOESY spectrum of **3r**



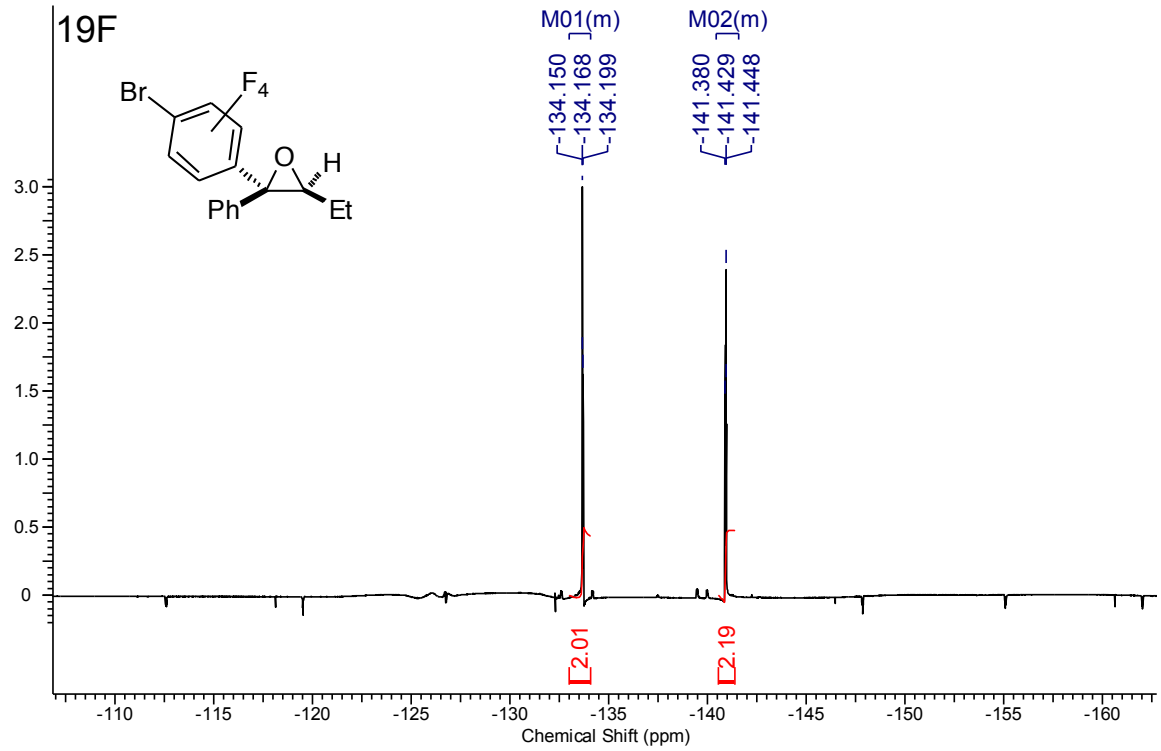
^{1}H NMR of **3s**



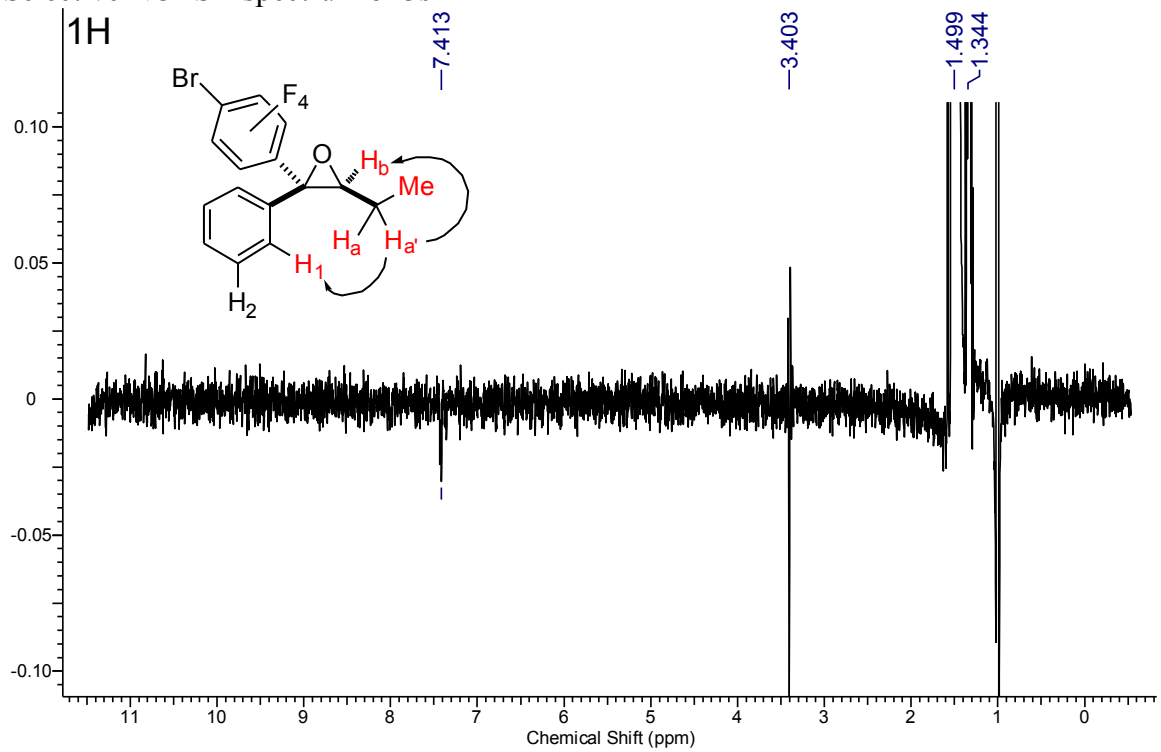
^{13}C NMR of **3s**



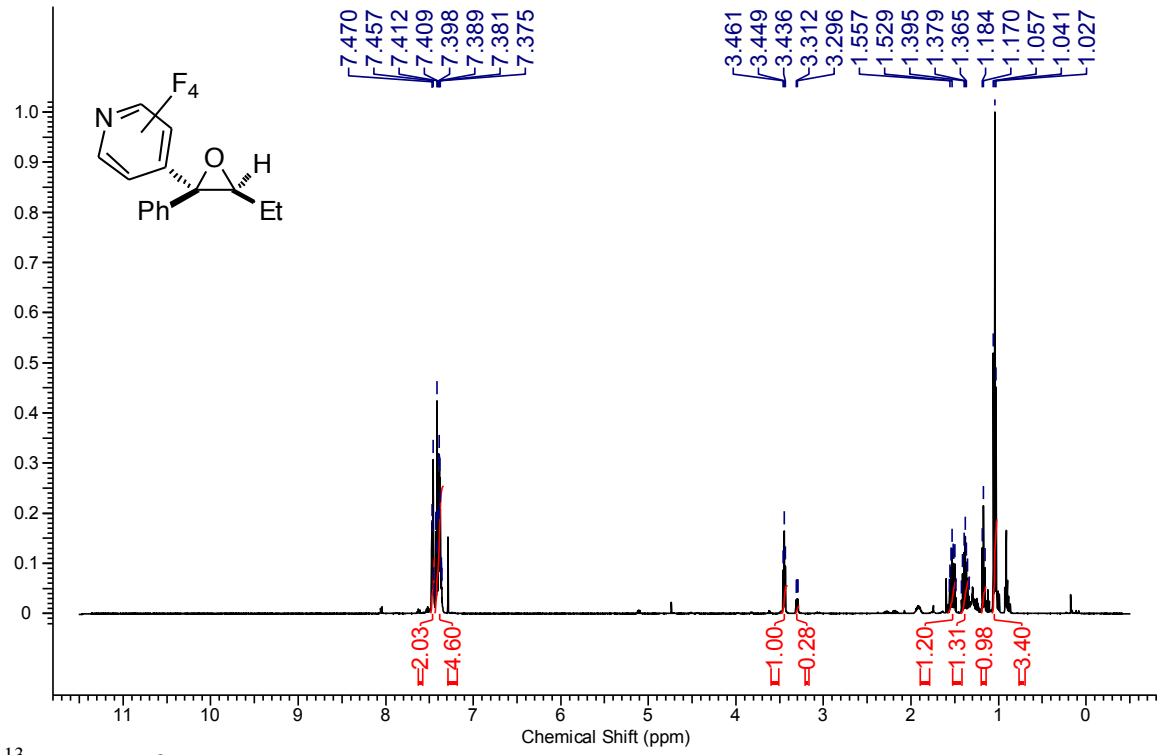
^{19}F NMR of **3s**



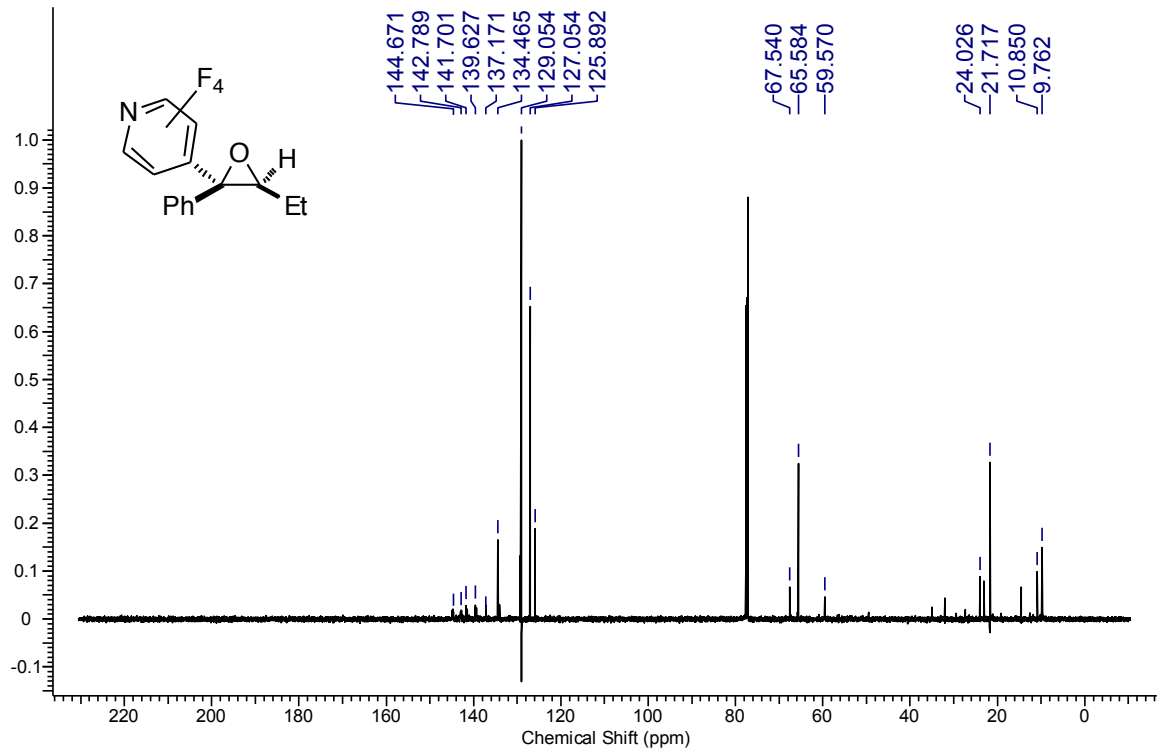
Selective NOESY spectrum of **3s**



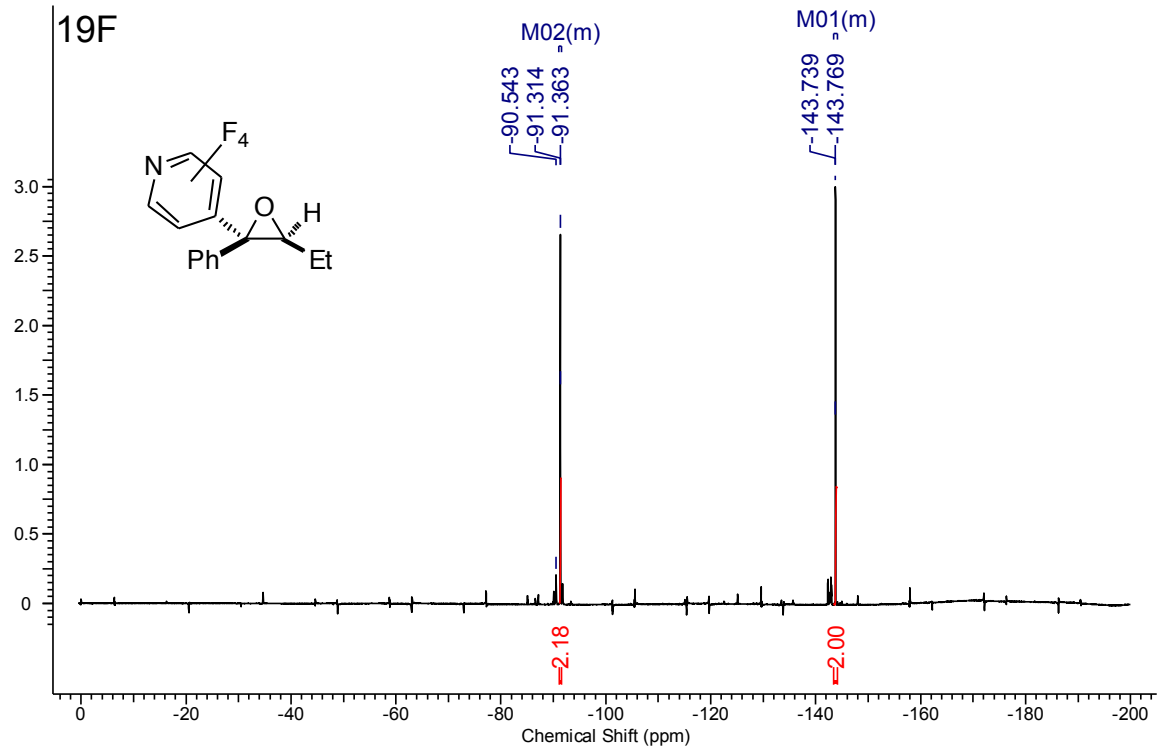
^{1}H NMR of **3t**



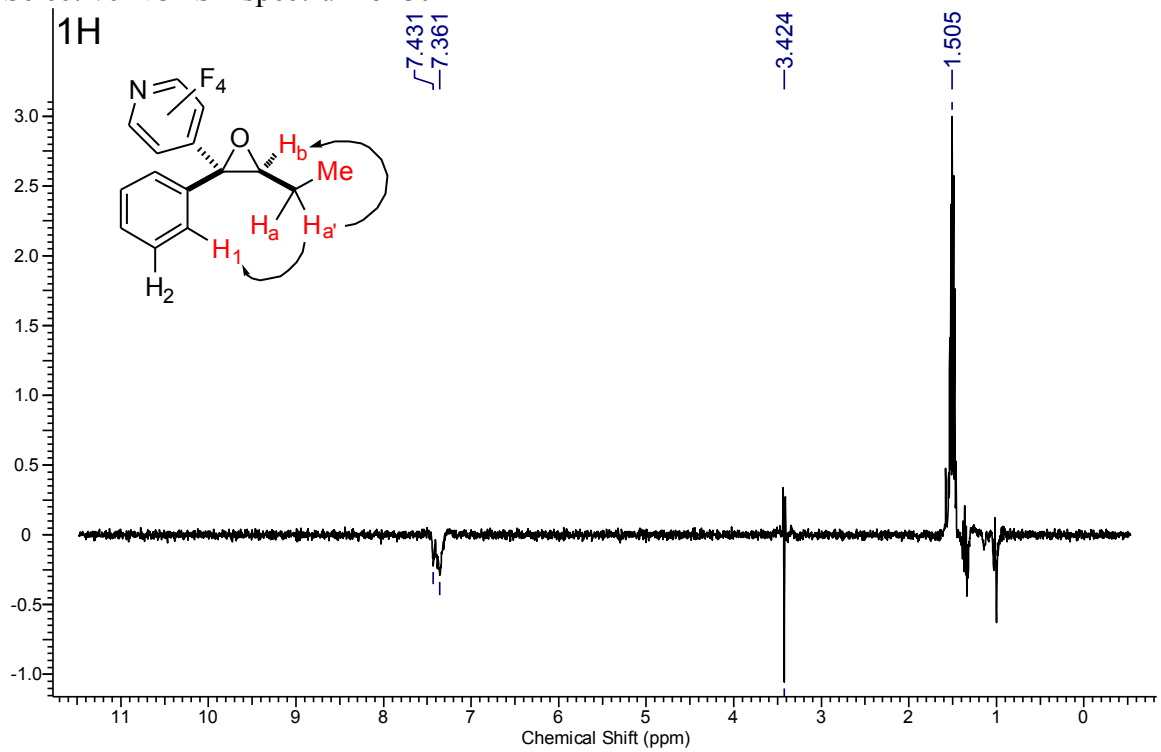
^{13}C NMR of **3t**



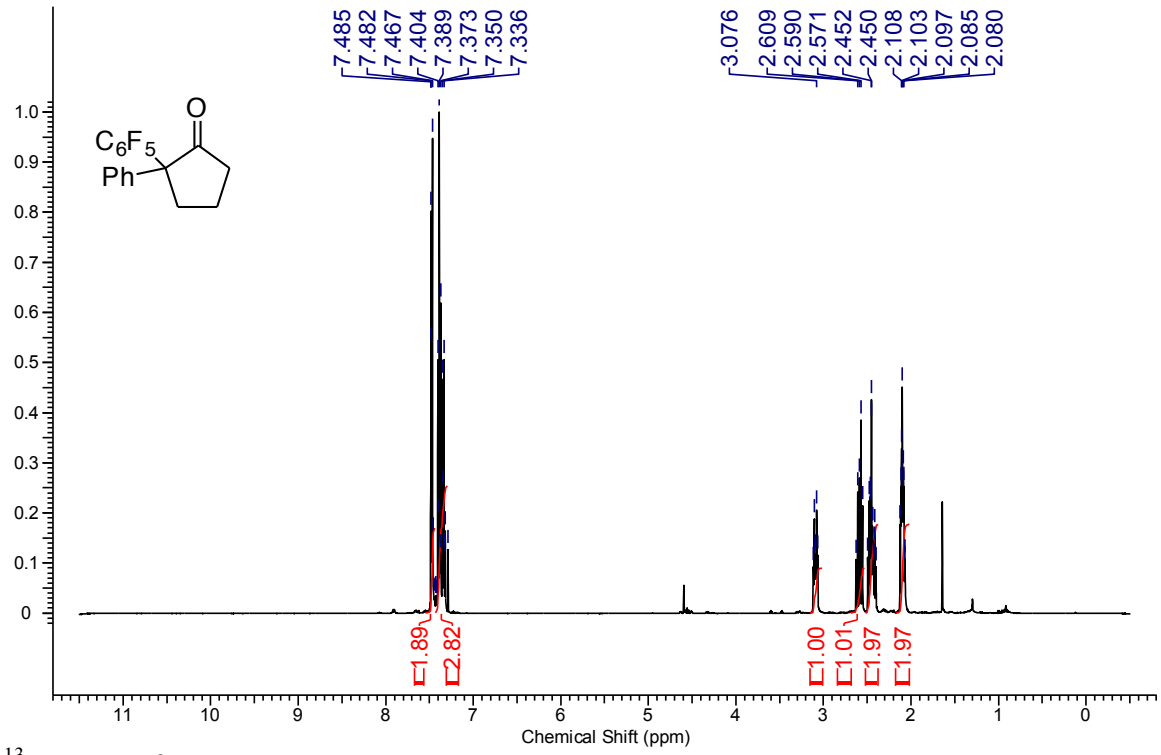
^{19}F NMR of **3t**



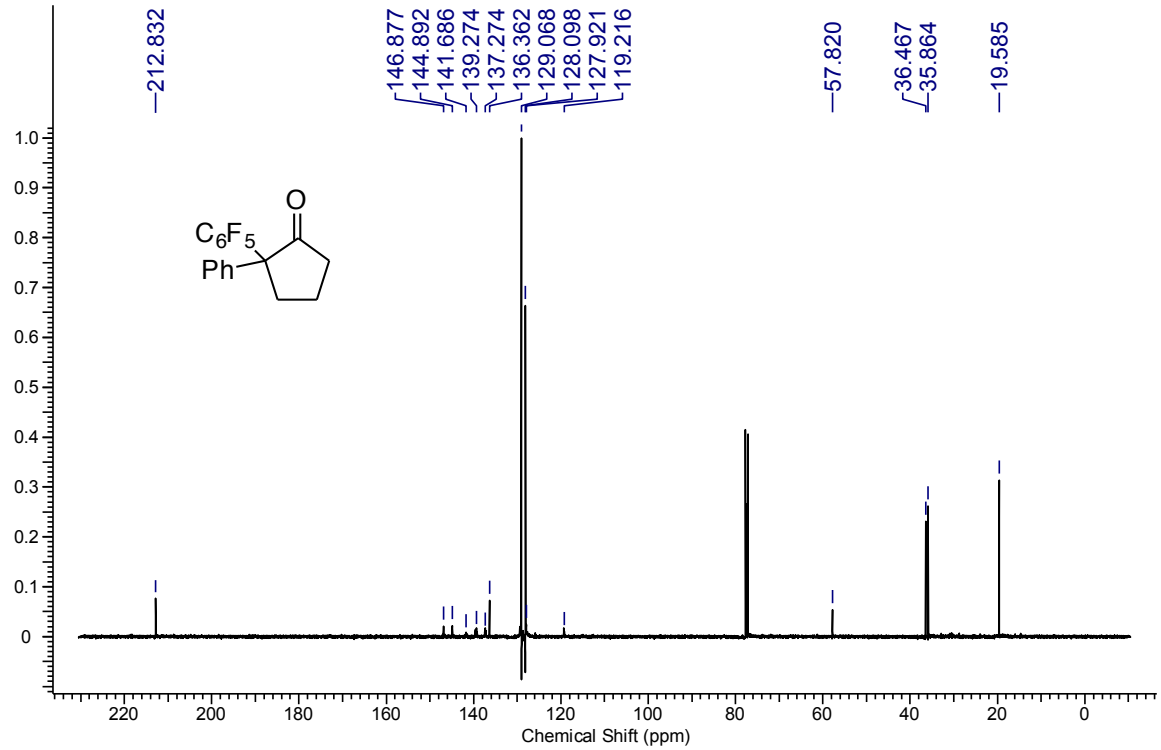
Selective NOESY spectrum of **3t**



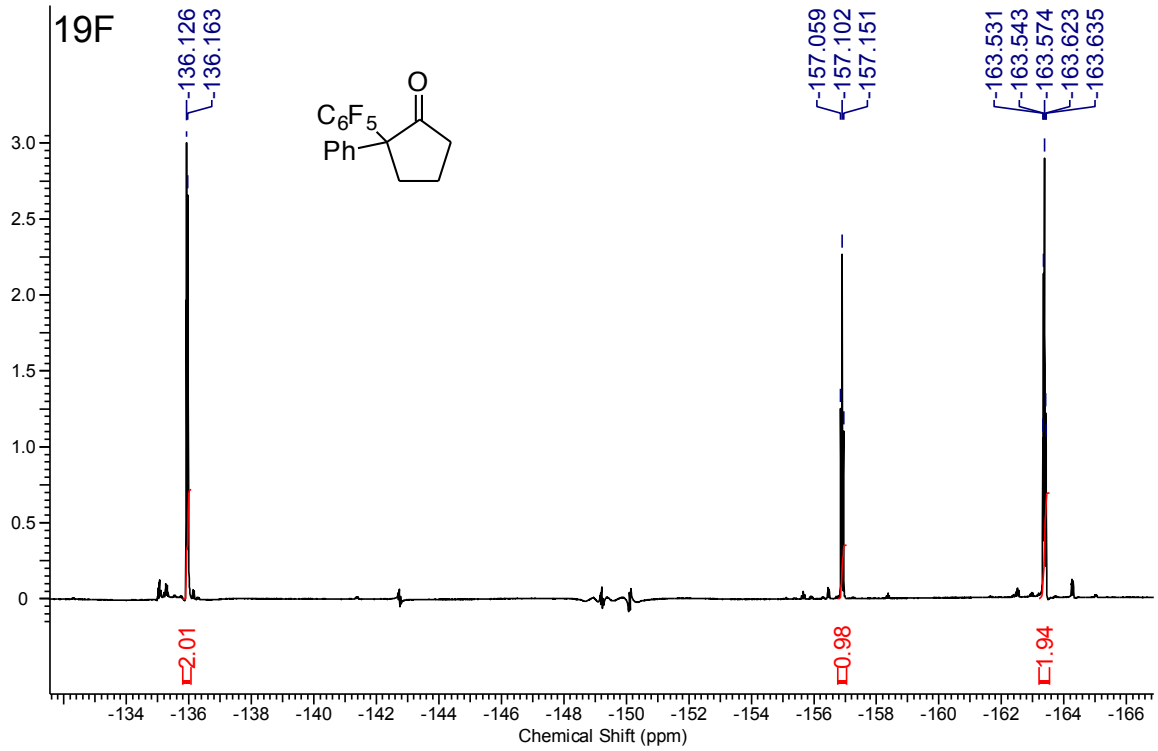
^{1}H NMR of **5a**



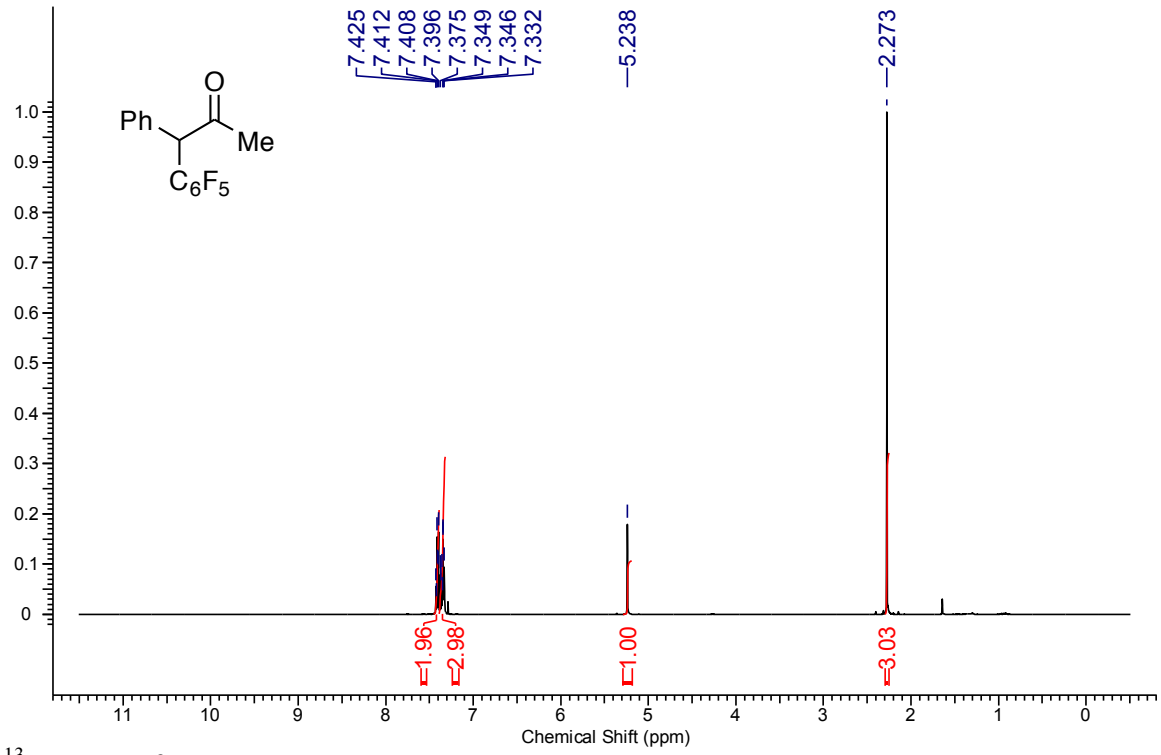
^{13}C NMR of **5a**



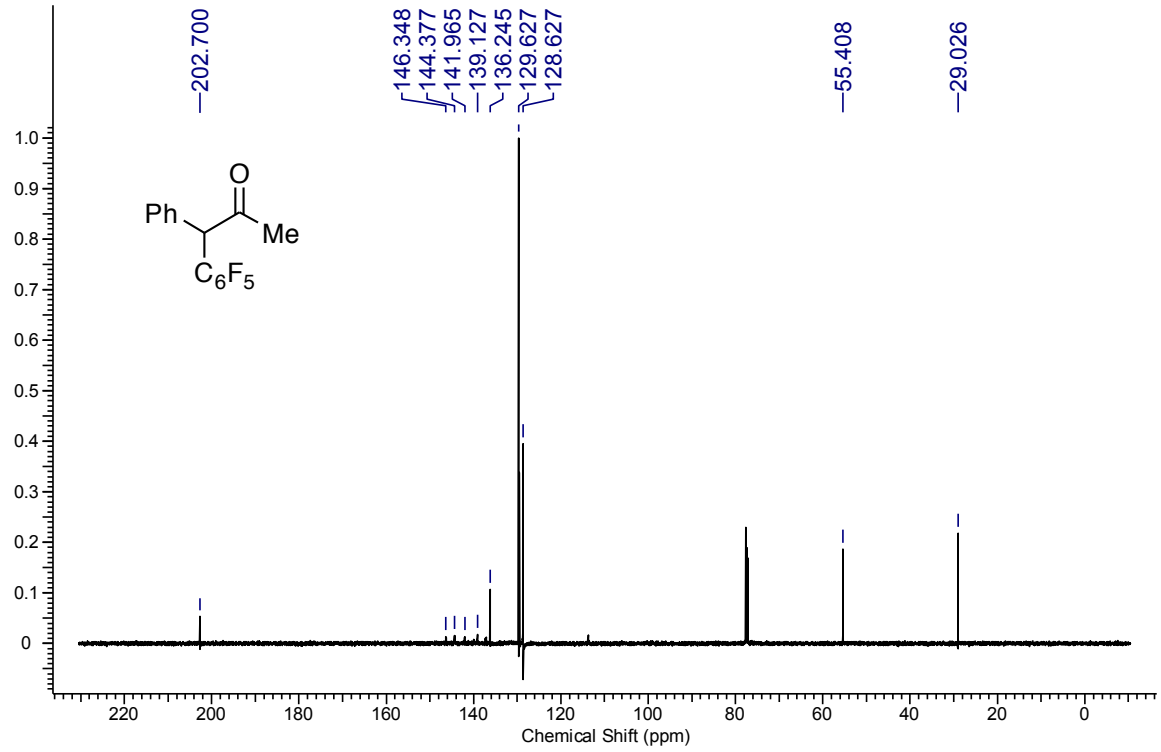
^{19}F NMR of **5a**


19F
-136.126
-136.163
-157.059
-157.102
-157.151
-163.531
-163.543
-163.574
-163.623
-163.635
O
C6F5
Ph
2.01
0.98
1.94
Chemical Shift (ppm)

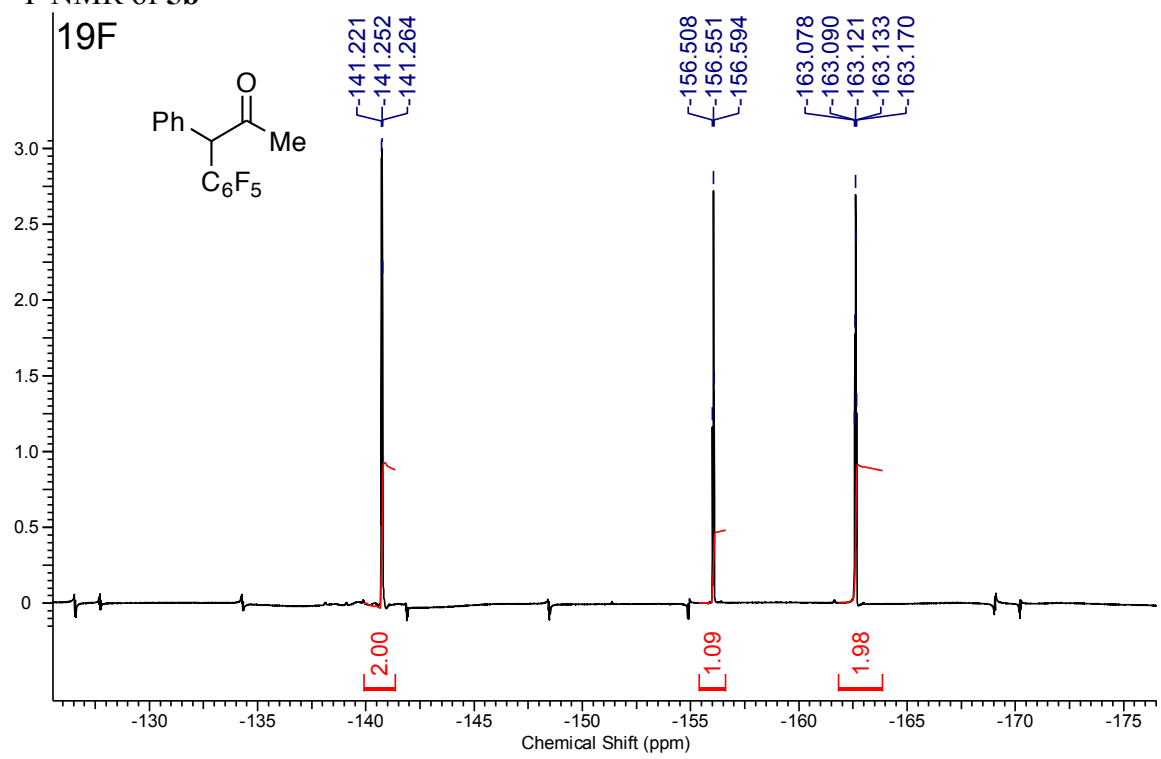
^{1}H NMR of **5b**



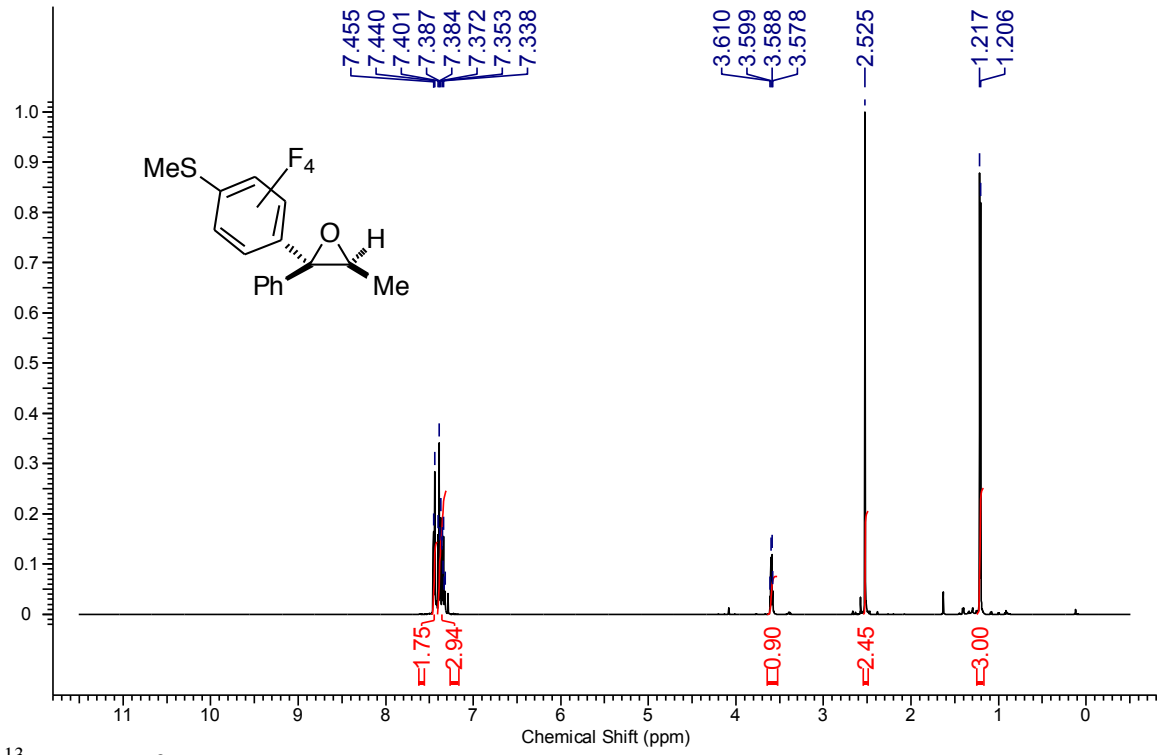
^{13}C NMR of **5b**



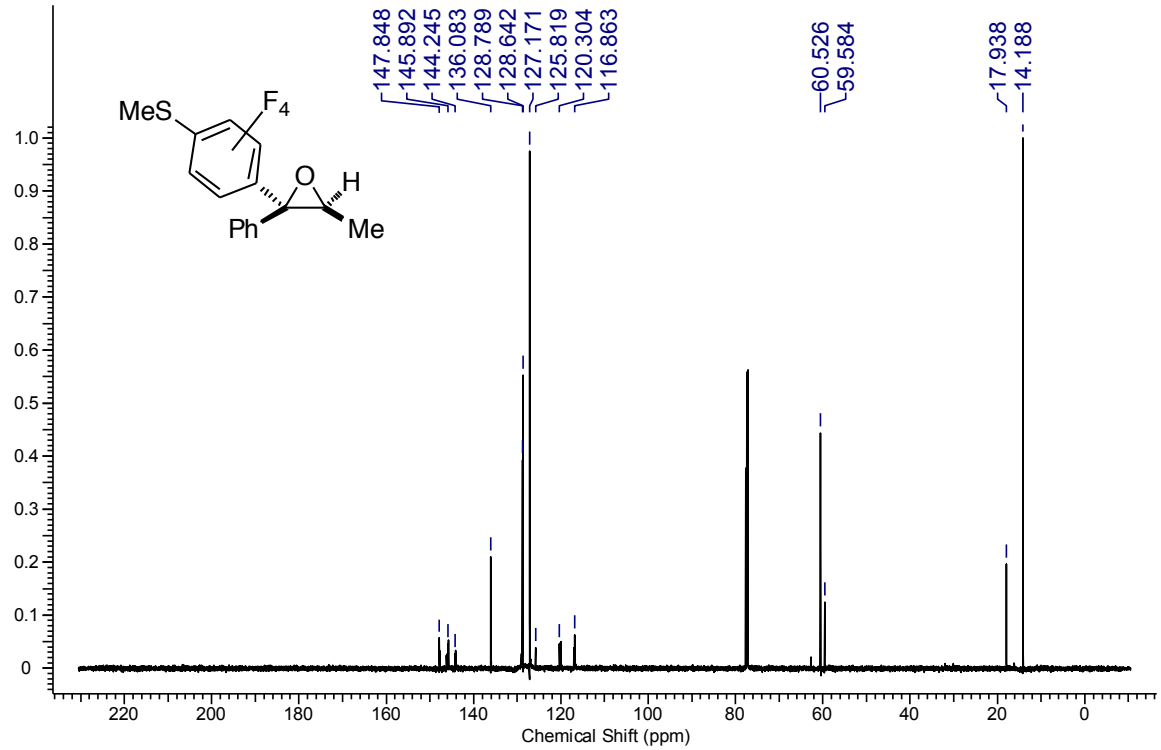
^{19}F NMR of **5b**


19F
O
Ph
Me
C6F5
-141.221
-141.252
-141.264
-156.508
-156.551
-156.594
-163.078
-163.090
-163.121
-163.133
-163.170
2.00
1.09
1.98
Chemical Shift (ppm)

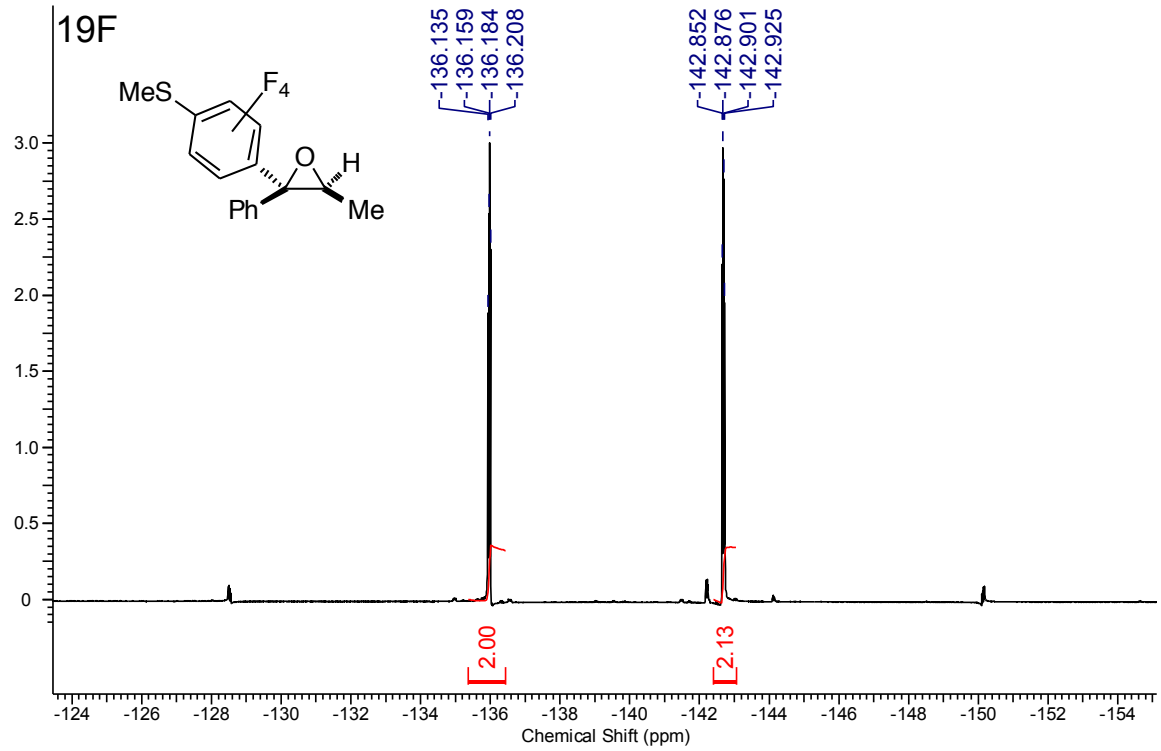
^{1}H NMR of **6a**



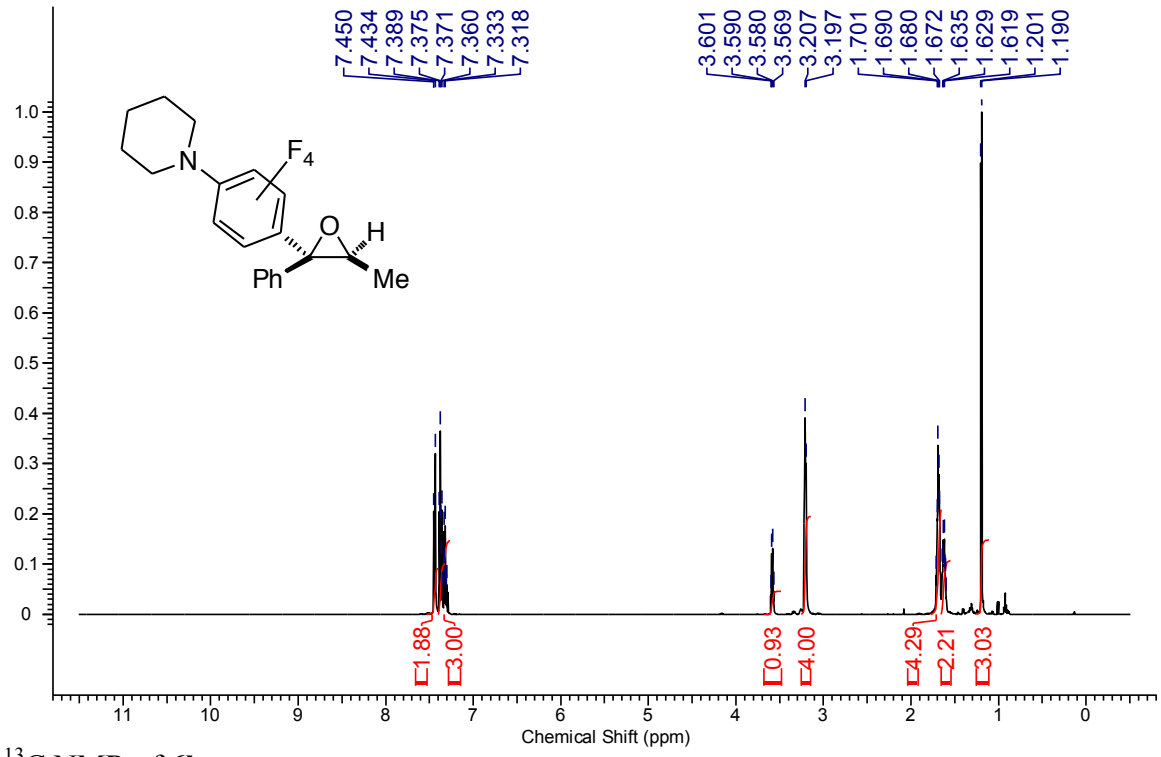
^{13}C NMR of **6a**



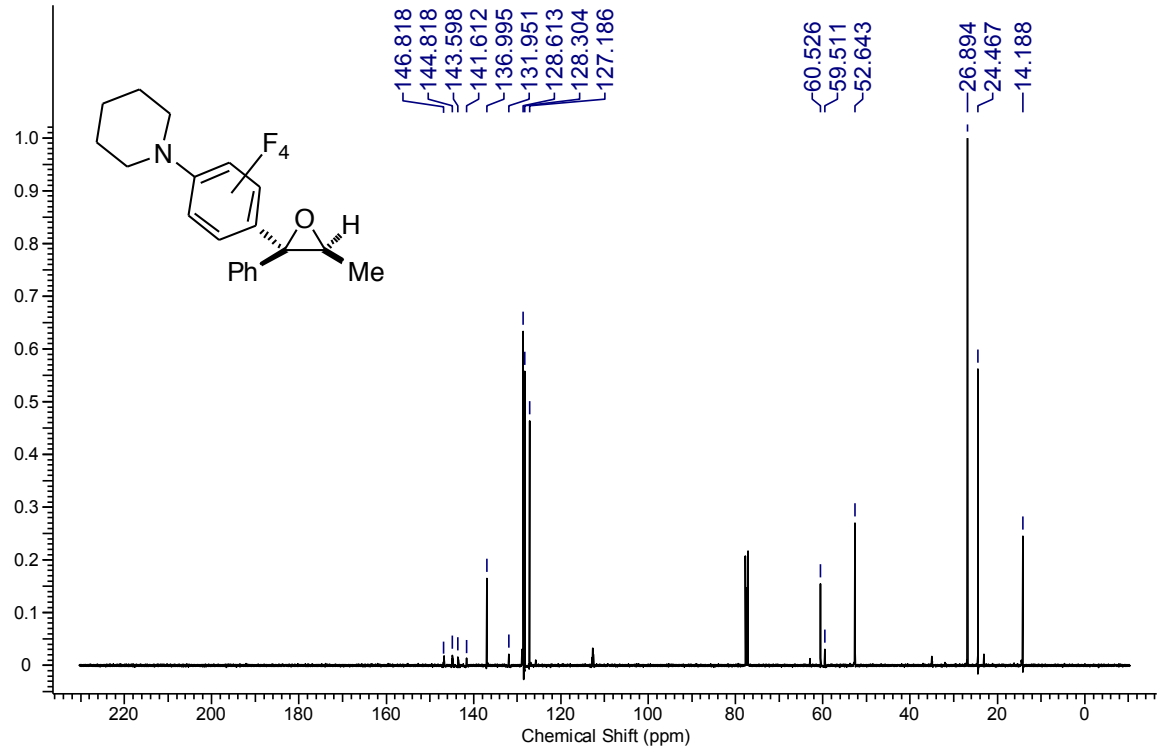
^{19}F NMR of **6a**


19F
MeS
F4
O
H
Ph
Me
-136.135
-136.159
-136.184
-136.208
-142.852
-142.876
-142.901
-142.925
2.00
2.13
Chemical Shift (ppm)

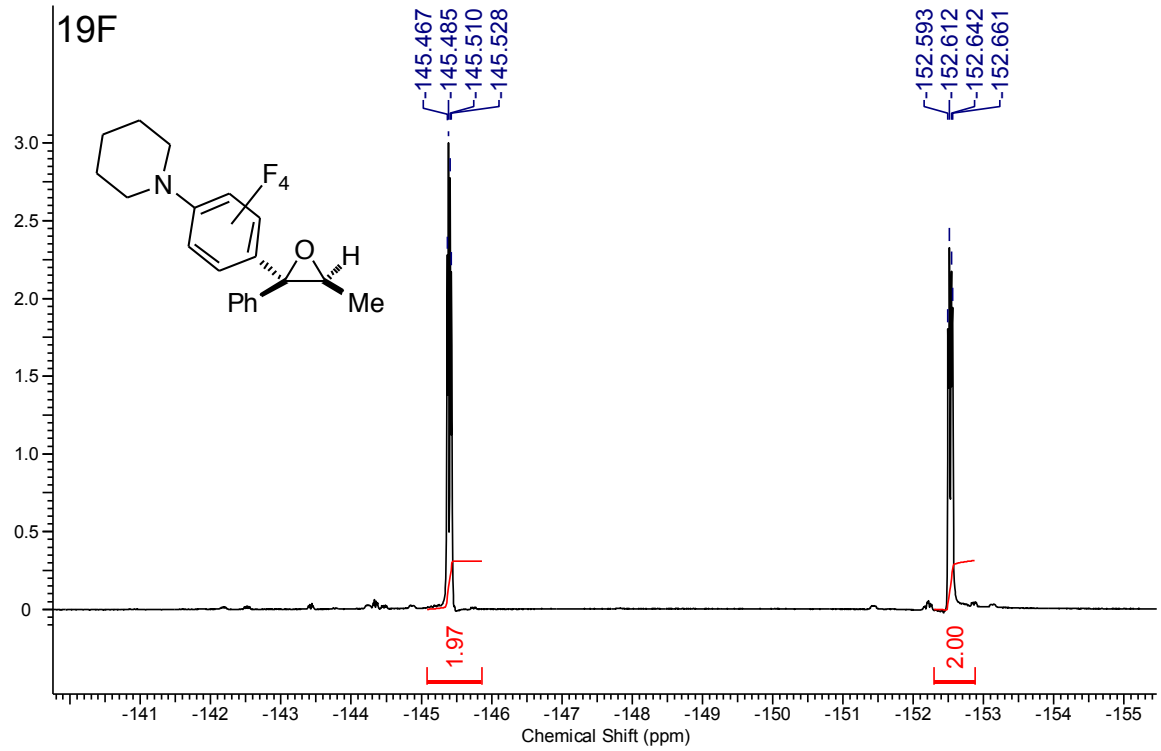
^{1}H NMR of **6b**



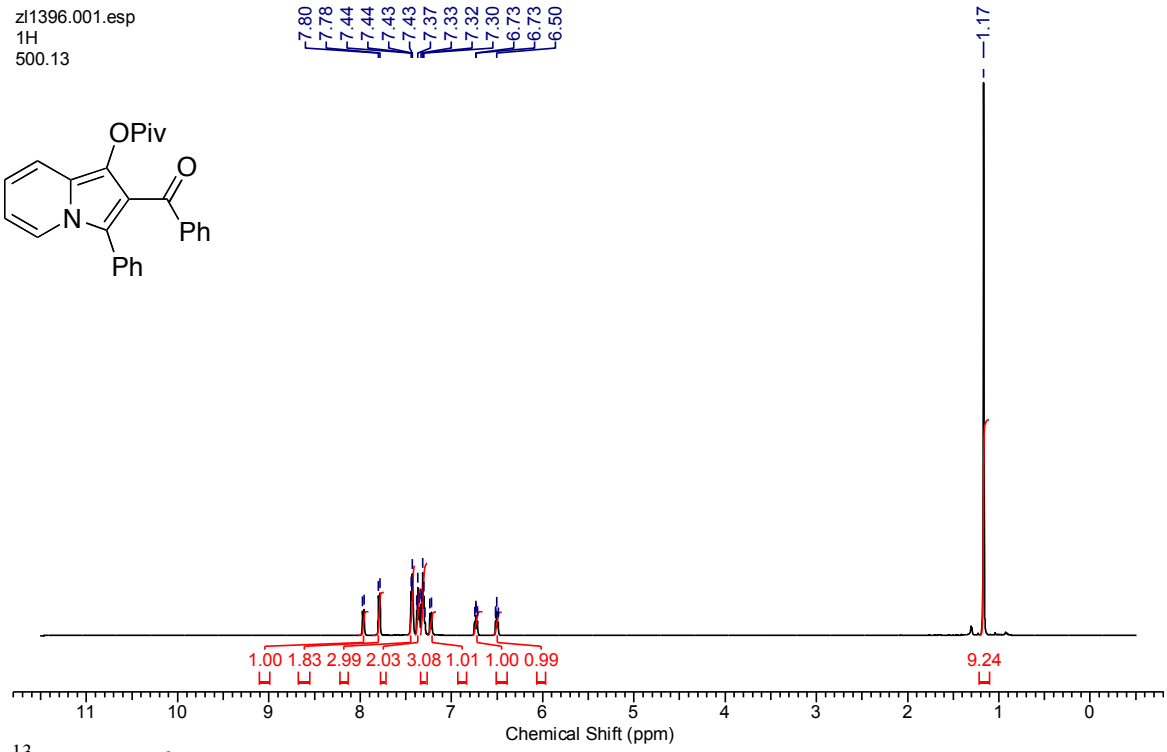
^{13}C NMR of **6b**



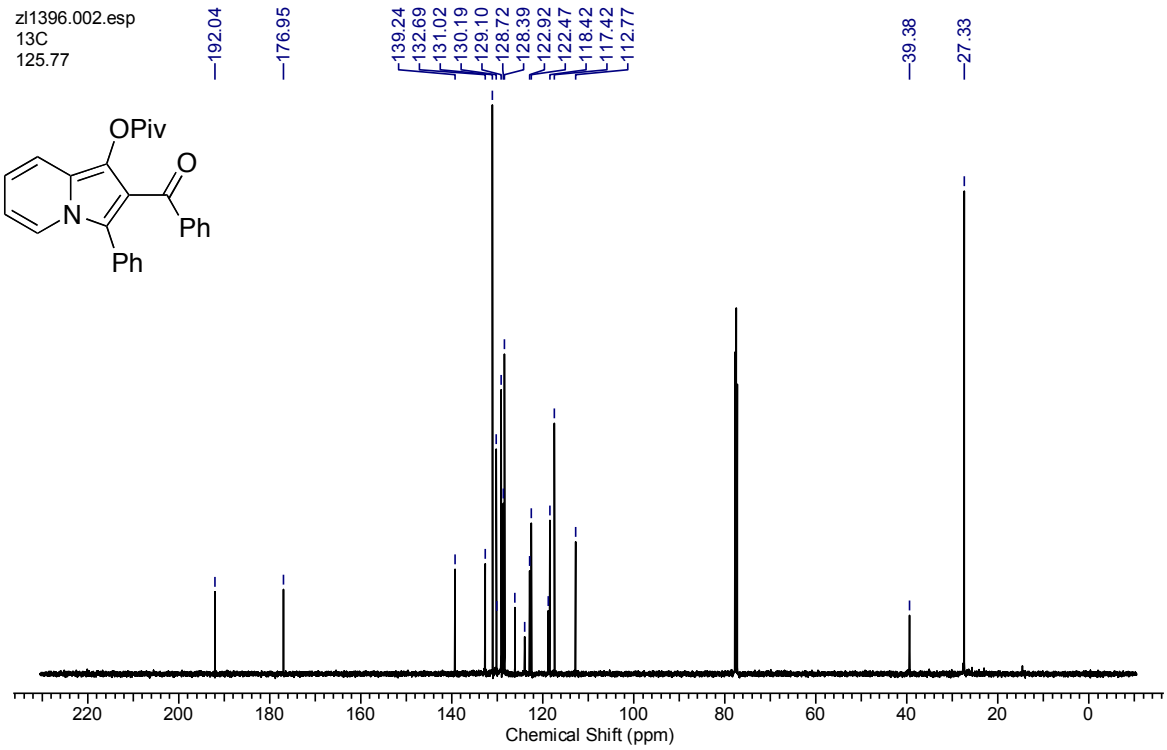
^{19}F NMR of **6b**


19F
-145.467
-145.485
-145.510
-145.528
-152.593
-152.612
-152.642
-152.661
F4
N
O
H
Ph
Me
3.0
2.5
2.0
1.5
1.0
0.5
0
1.97
2.00
-141
-142
-143
-144
-145
-146
-147
-148
-149
-150
-151
-152
-153
-154
-155
Chemical Shift (ppm)

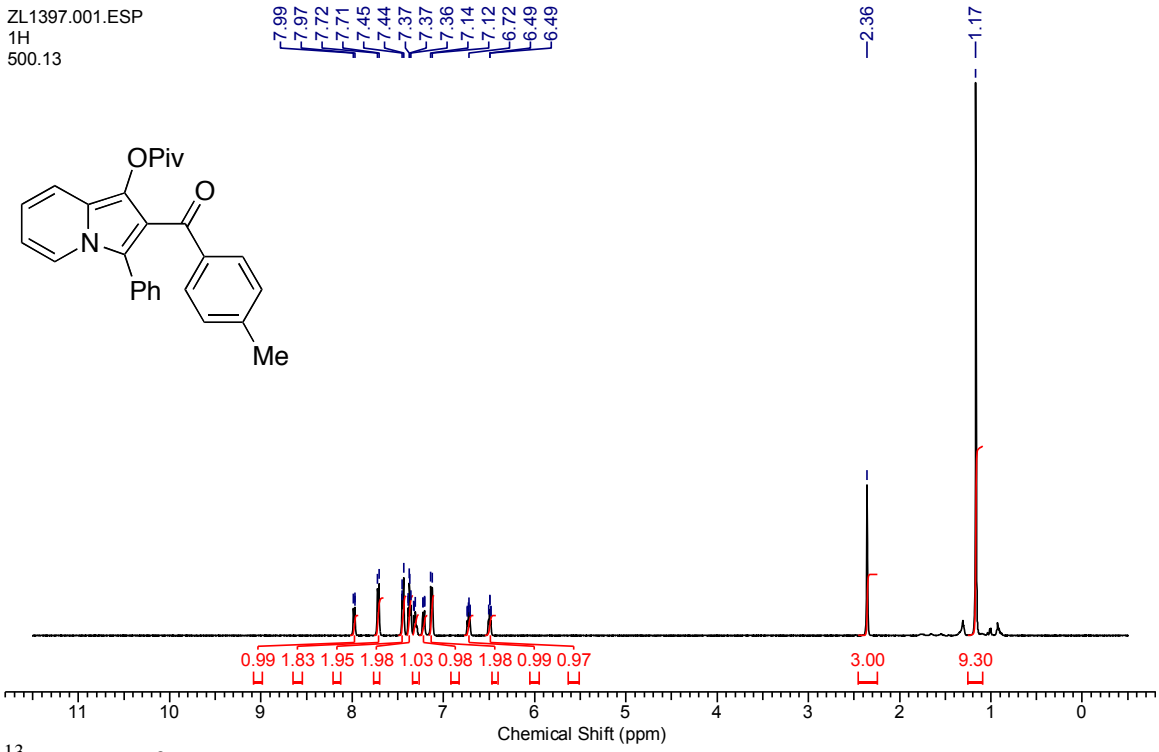
^{1}H NMR of **8a**



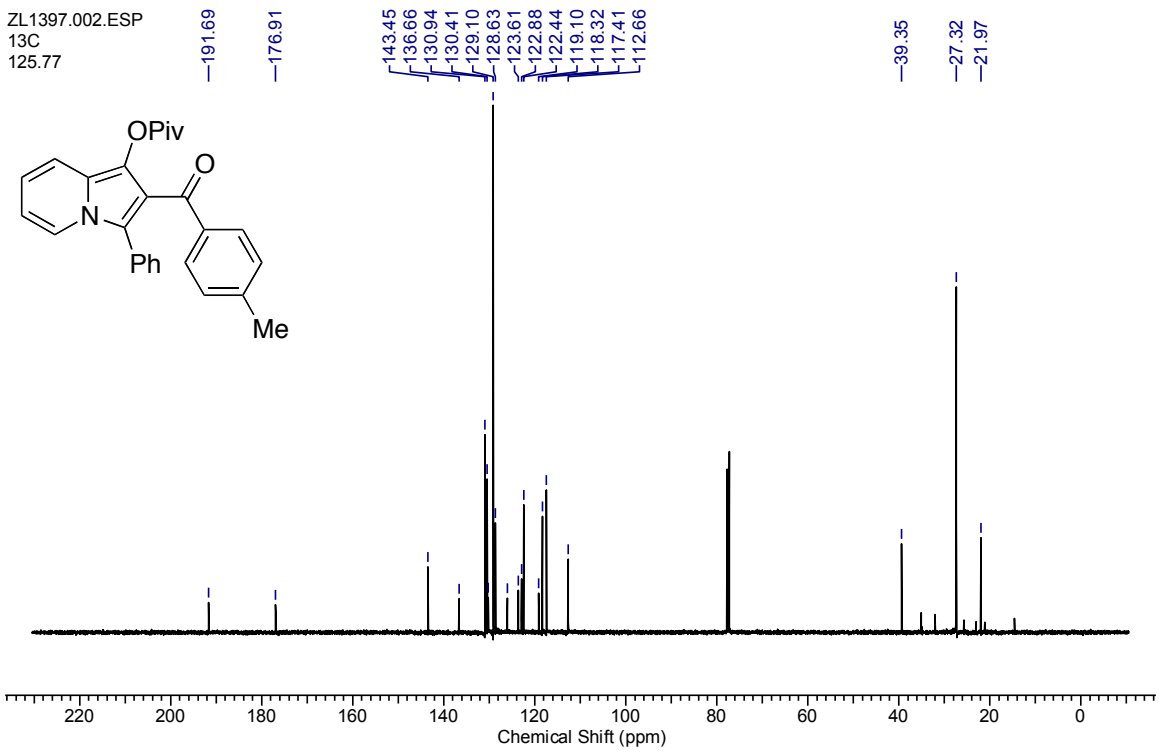
^{13}C NMR of **8a**



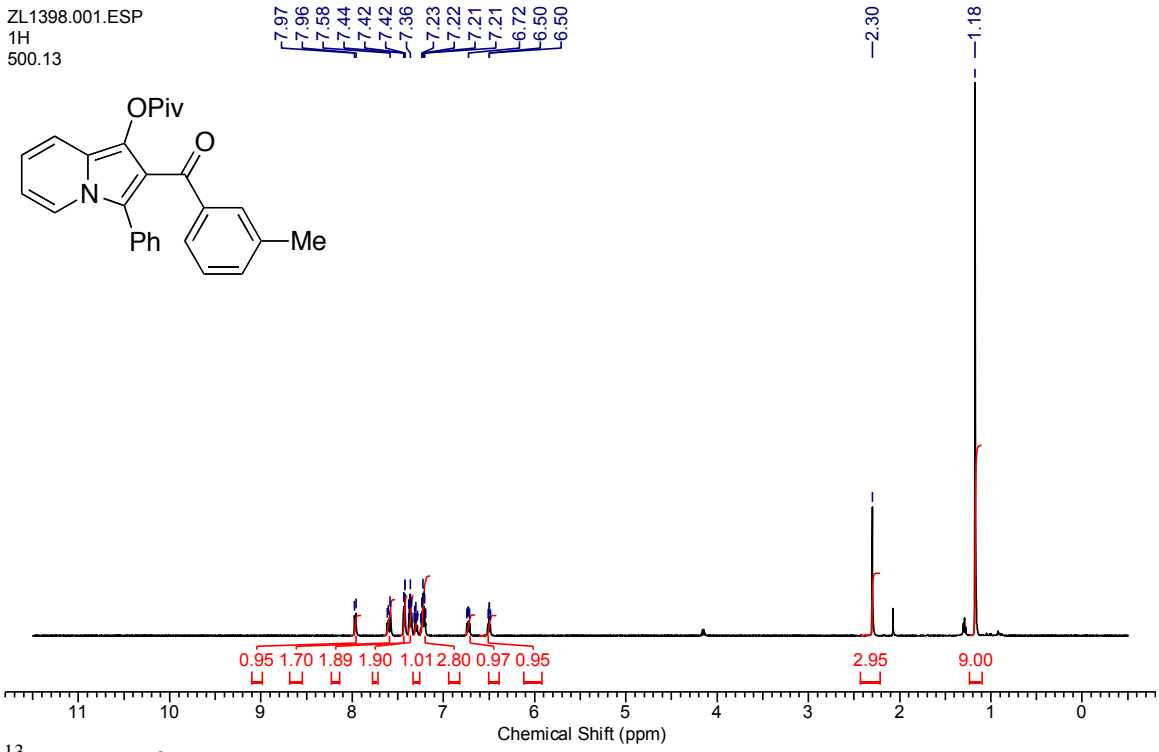
^{1}H NMR of **8b**



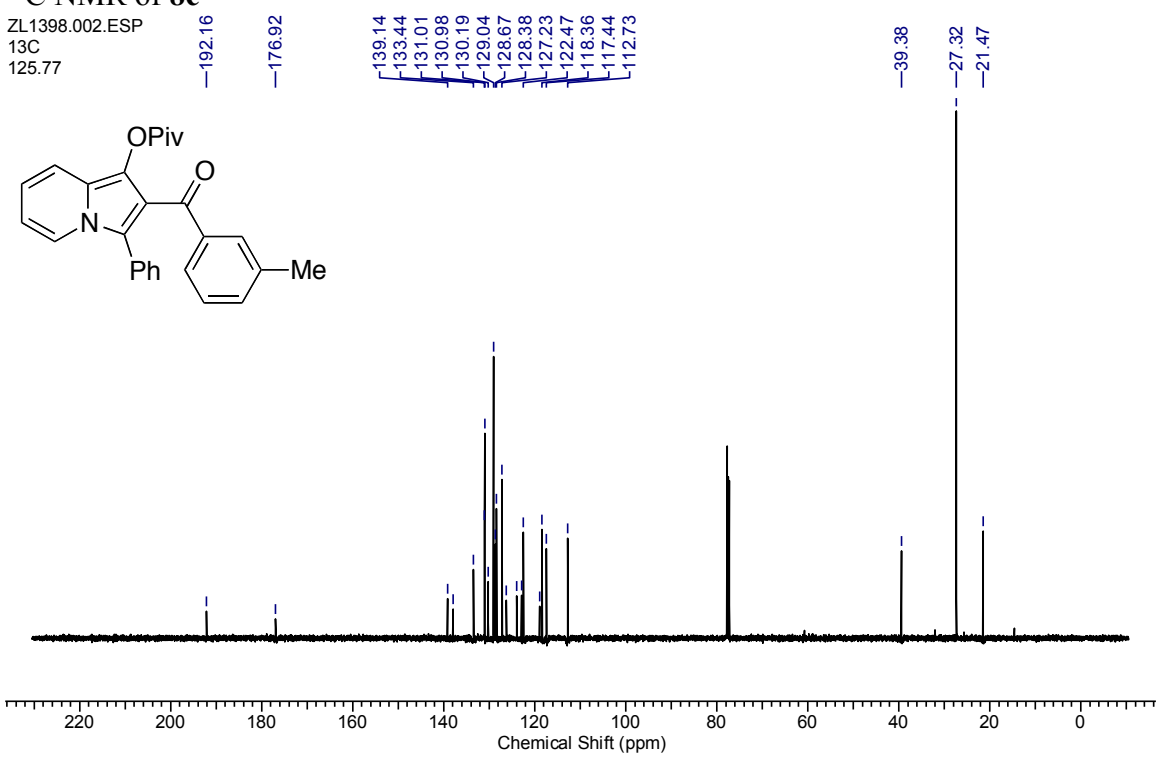
^{13}C NMR of **8b**



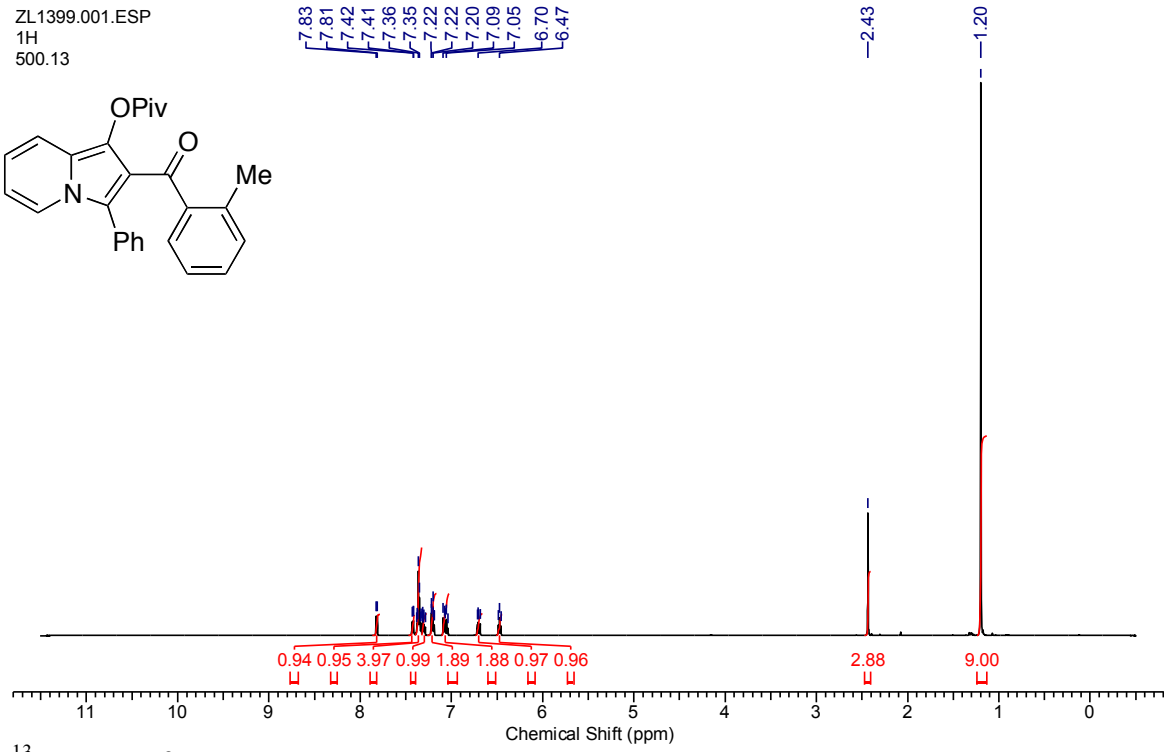
^{1}H NMR of **8c**



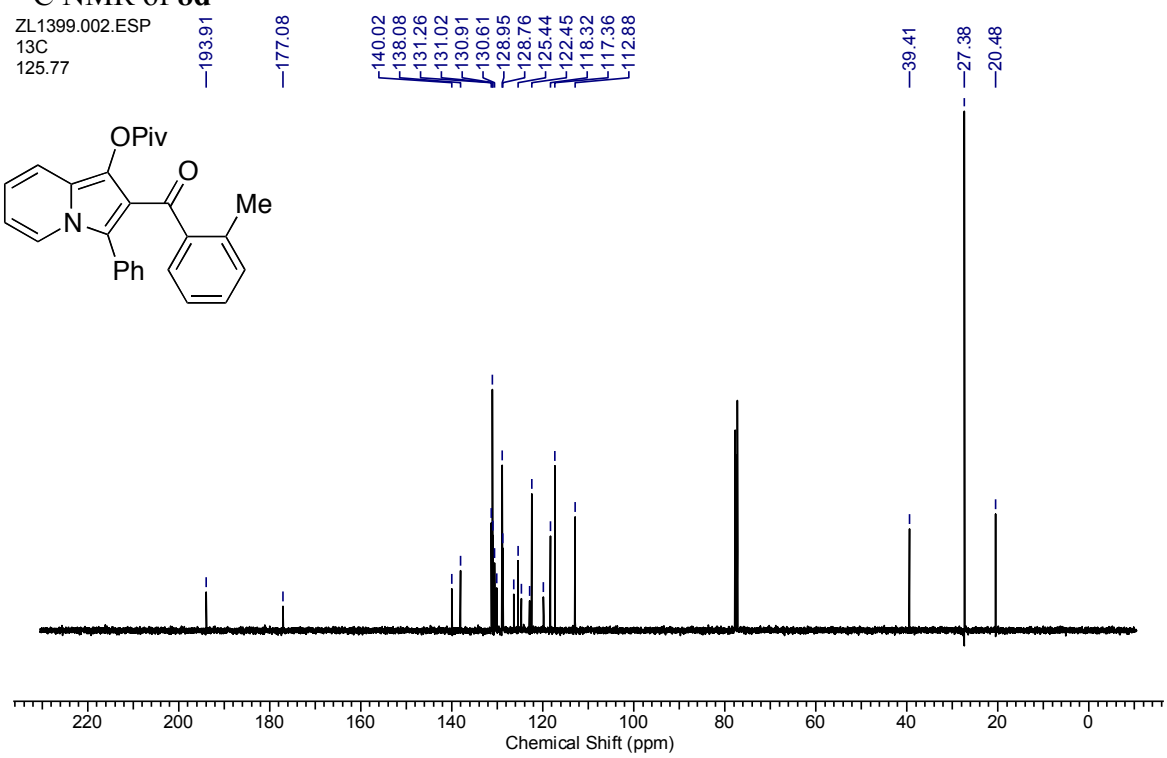
^{13}C NMR of **8c**



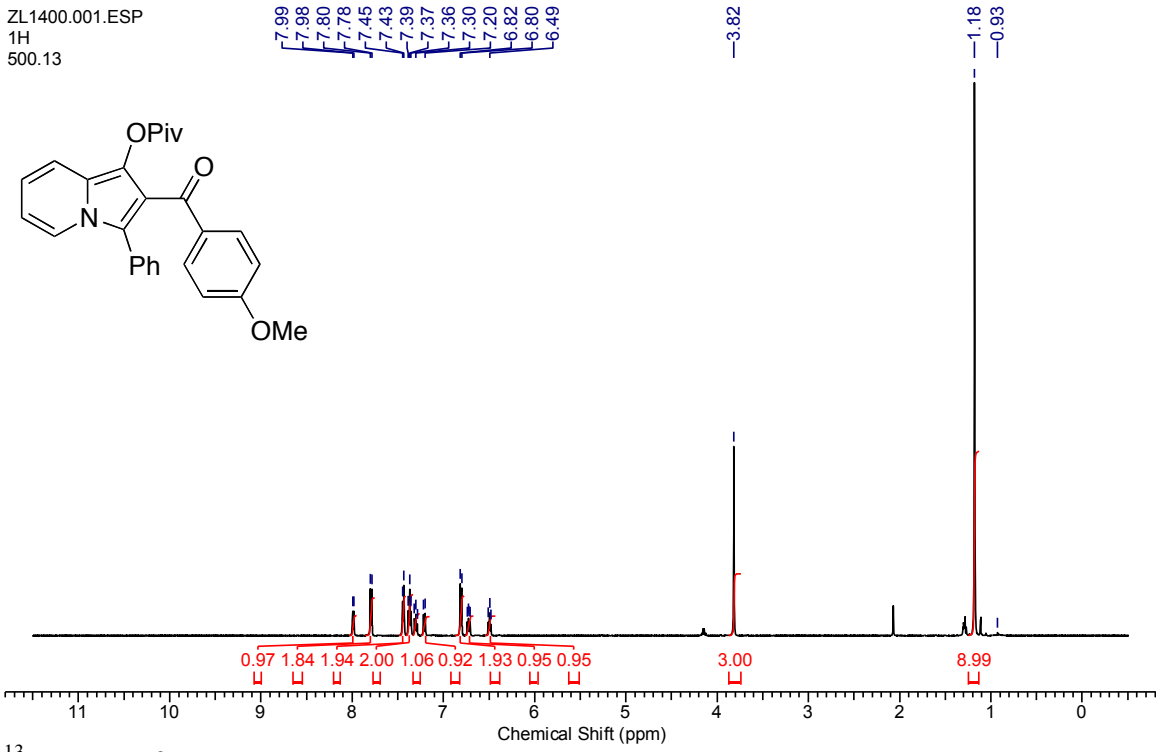
^{1}H NMR of **8d**



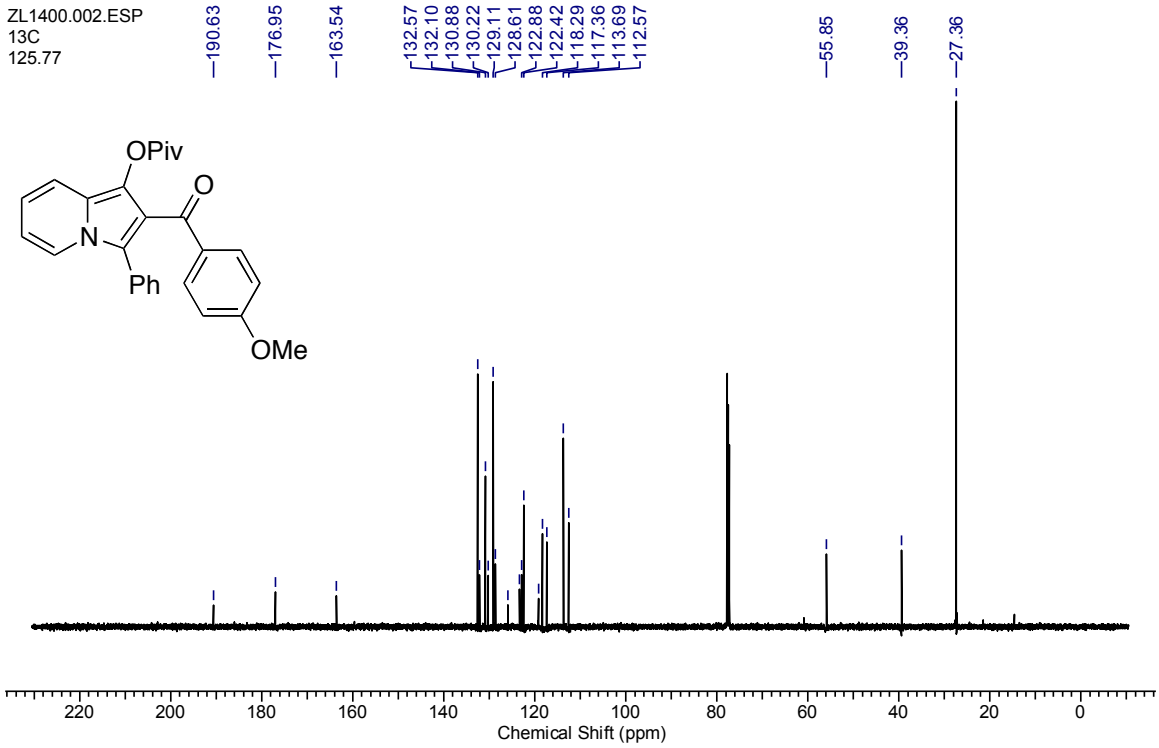
^{13}C NMR of **8d**



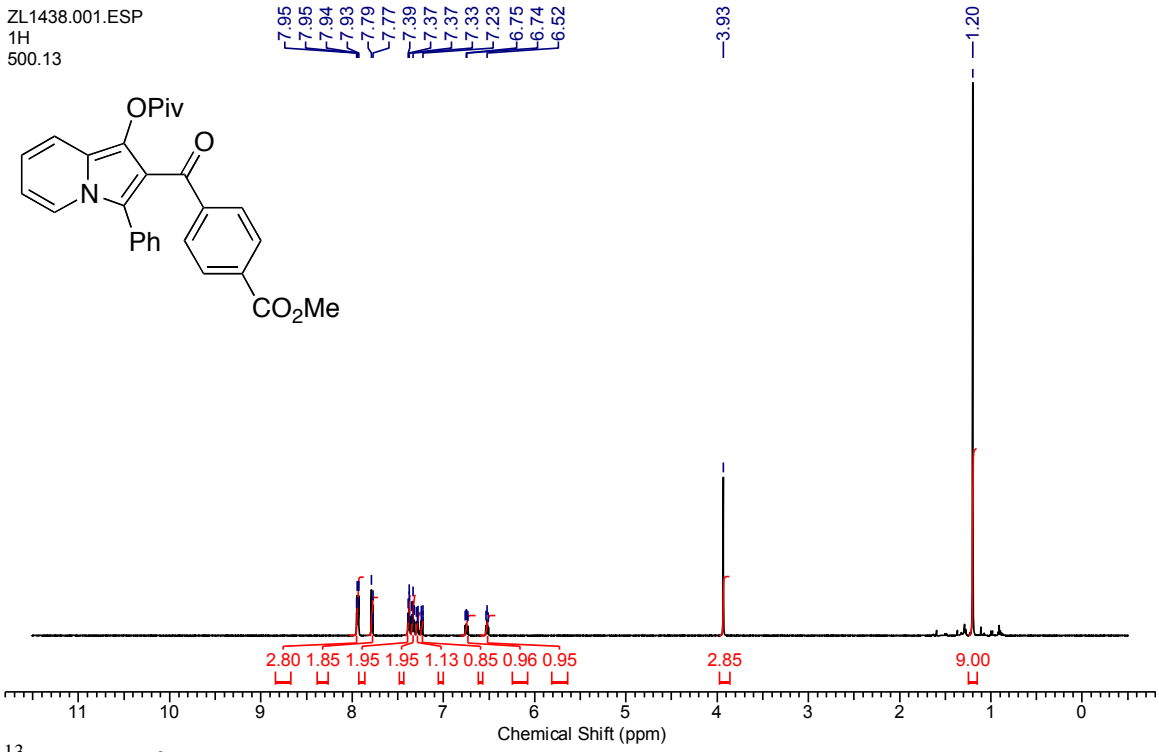
^{1}H NMR of **8e**



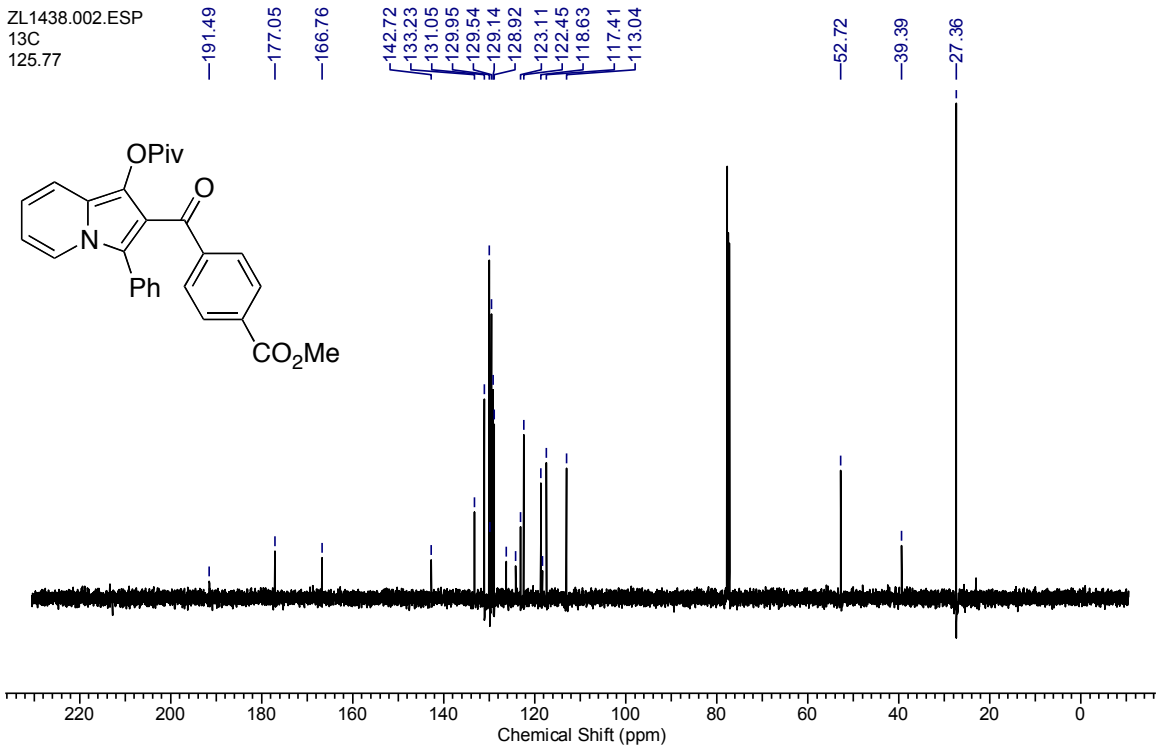
^{13}C NMR of **8e**



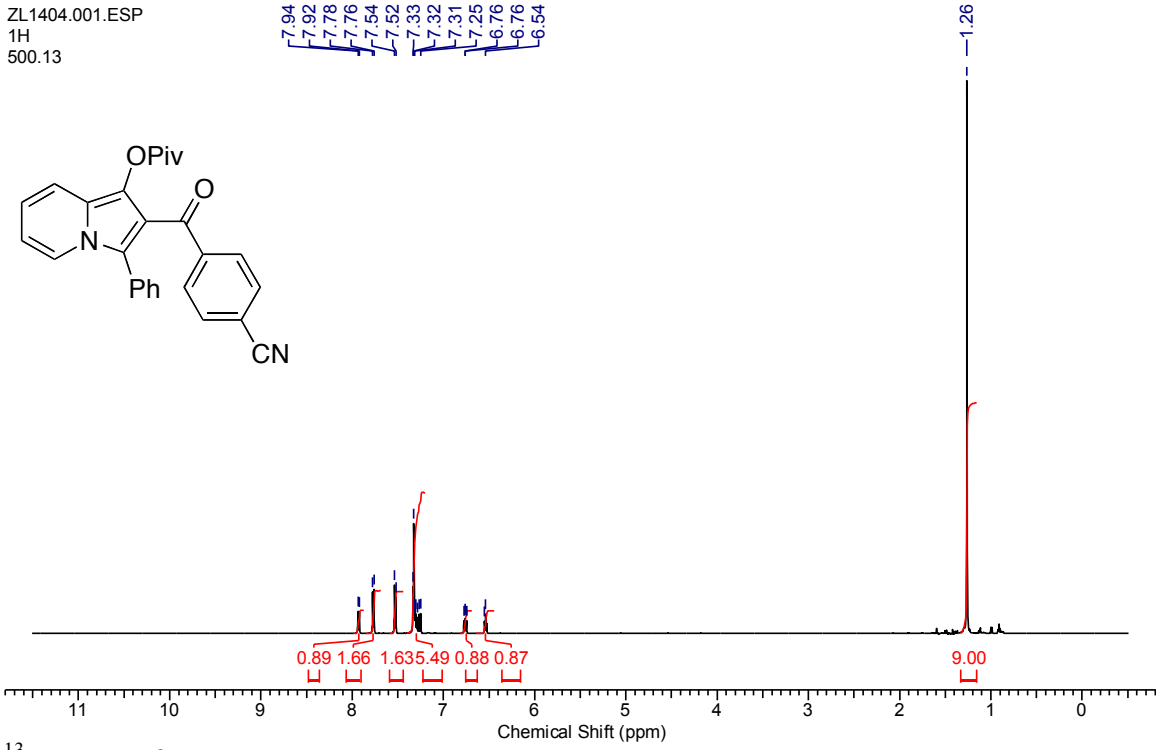
^{1}H NMR of **8f**



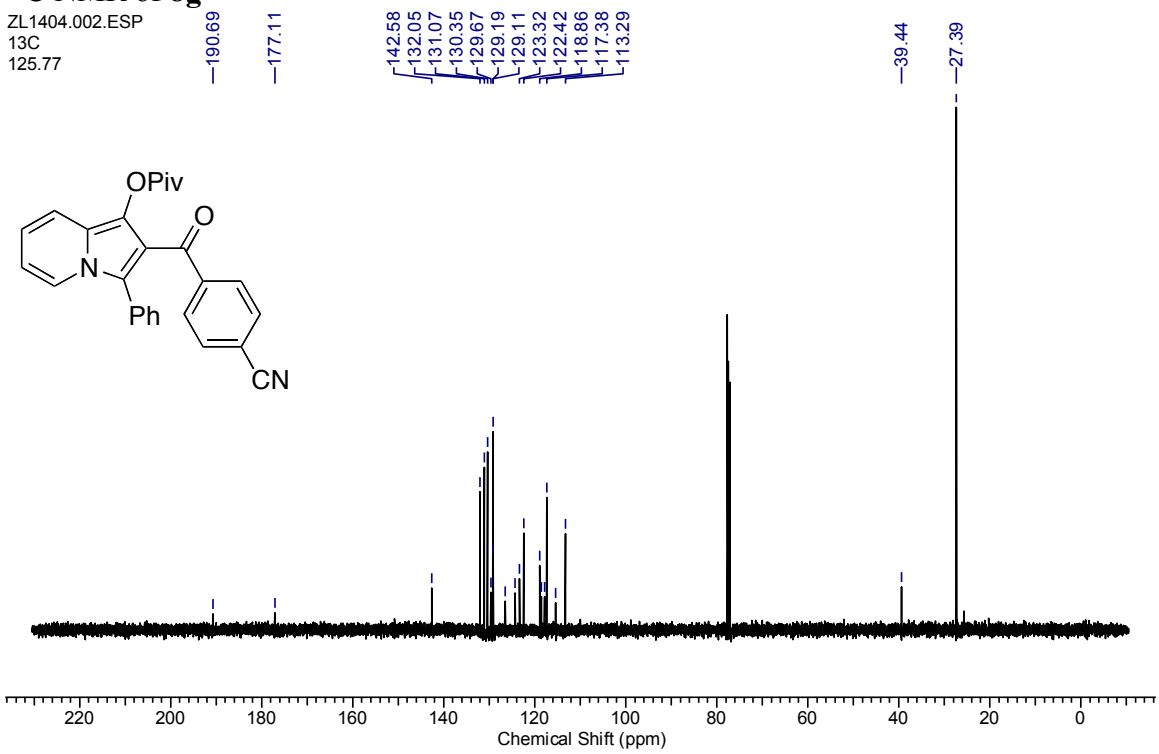
^{13}C NMR of **8f**



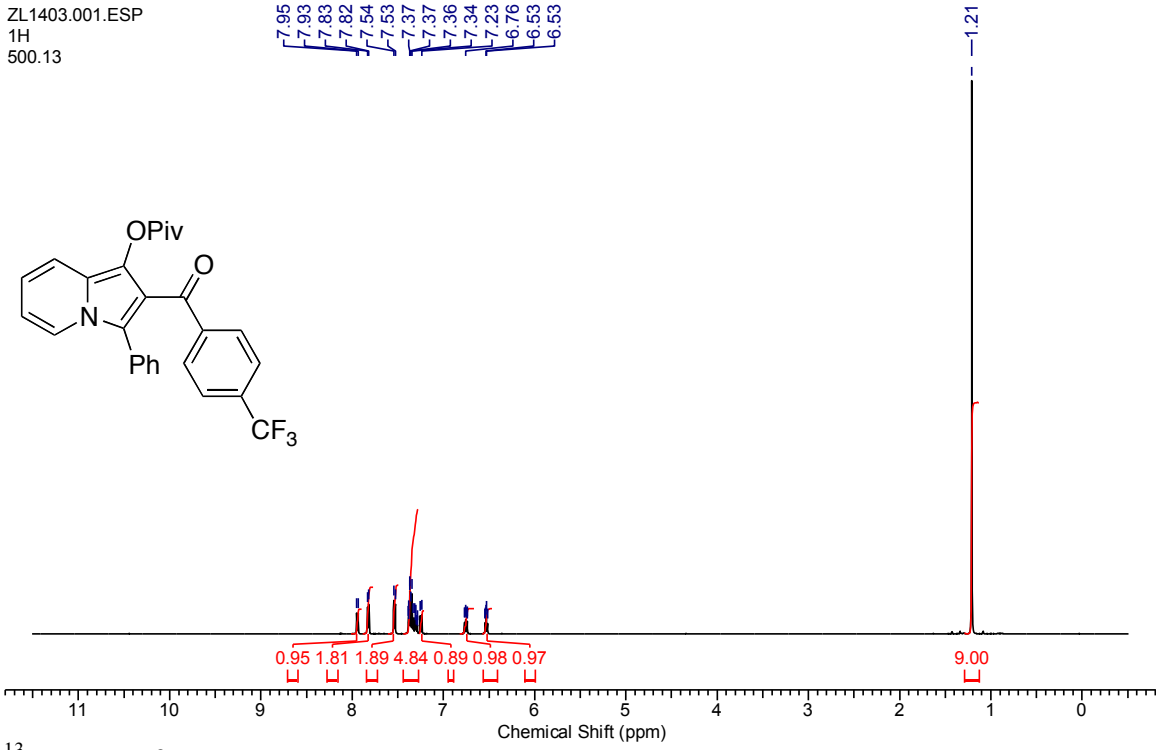
^{1}H NMR of **8g**



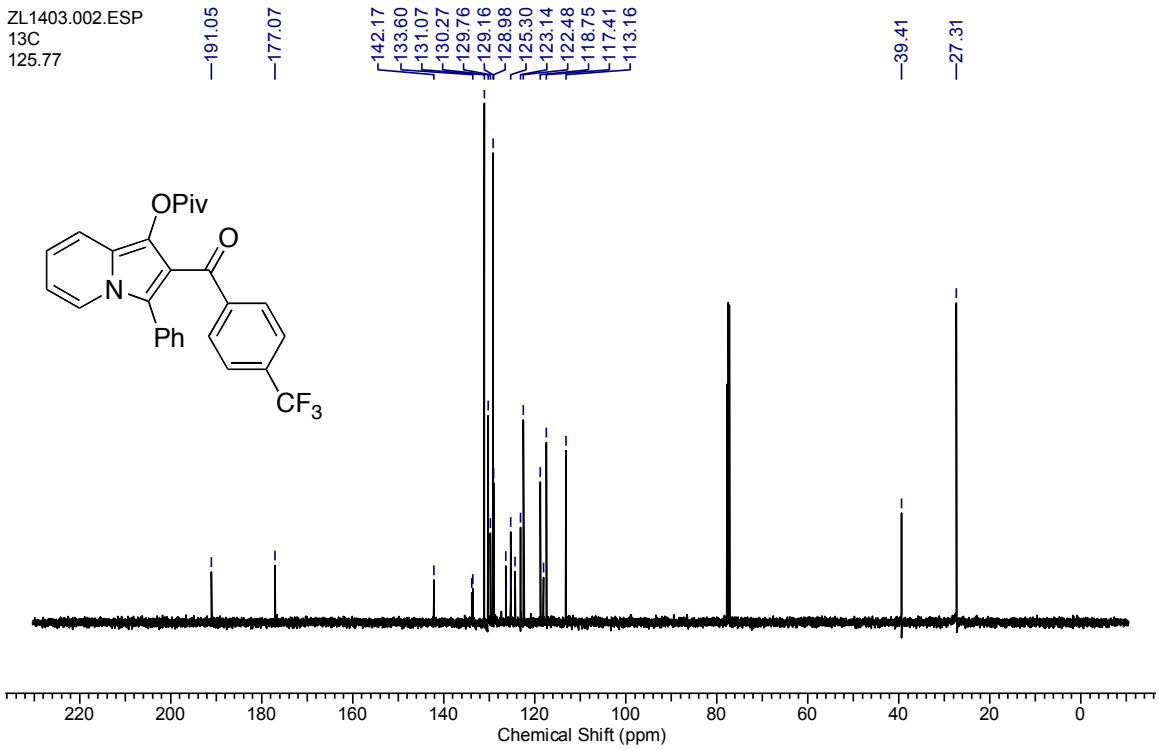
^{13}C NMR of **8g**



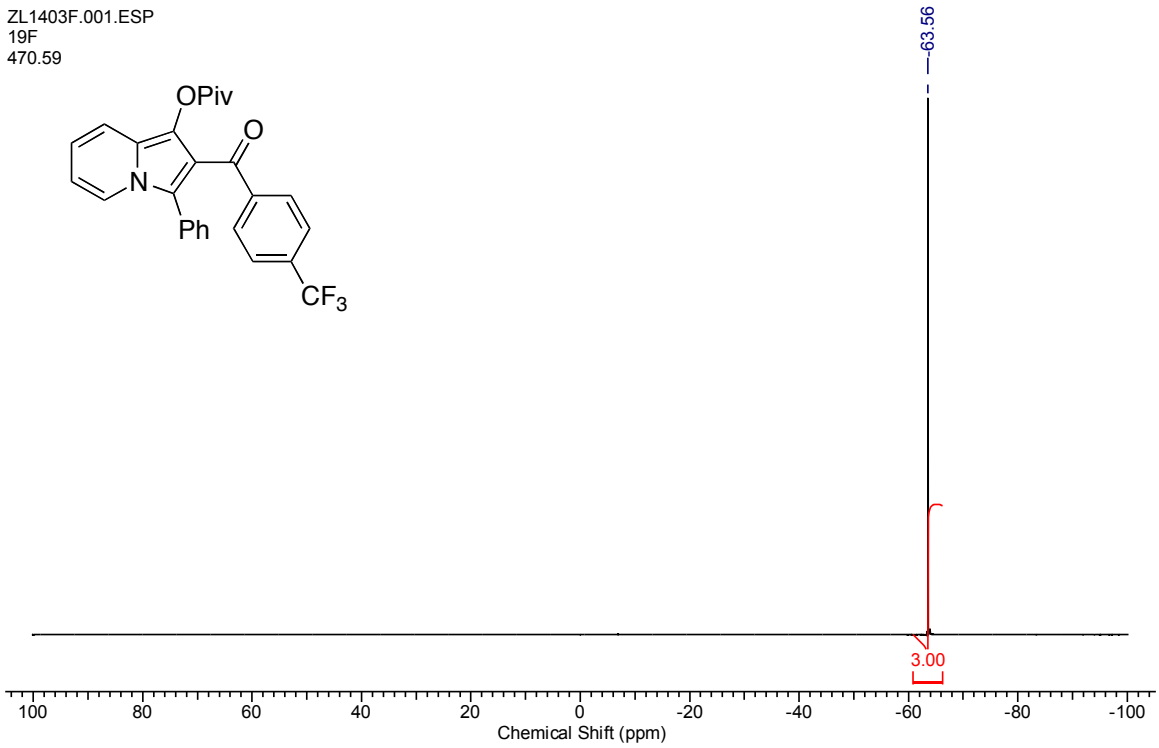
^{1}H NMR of **8h**



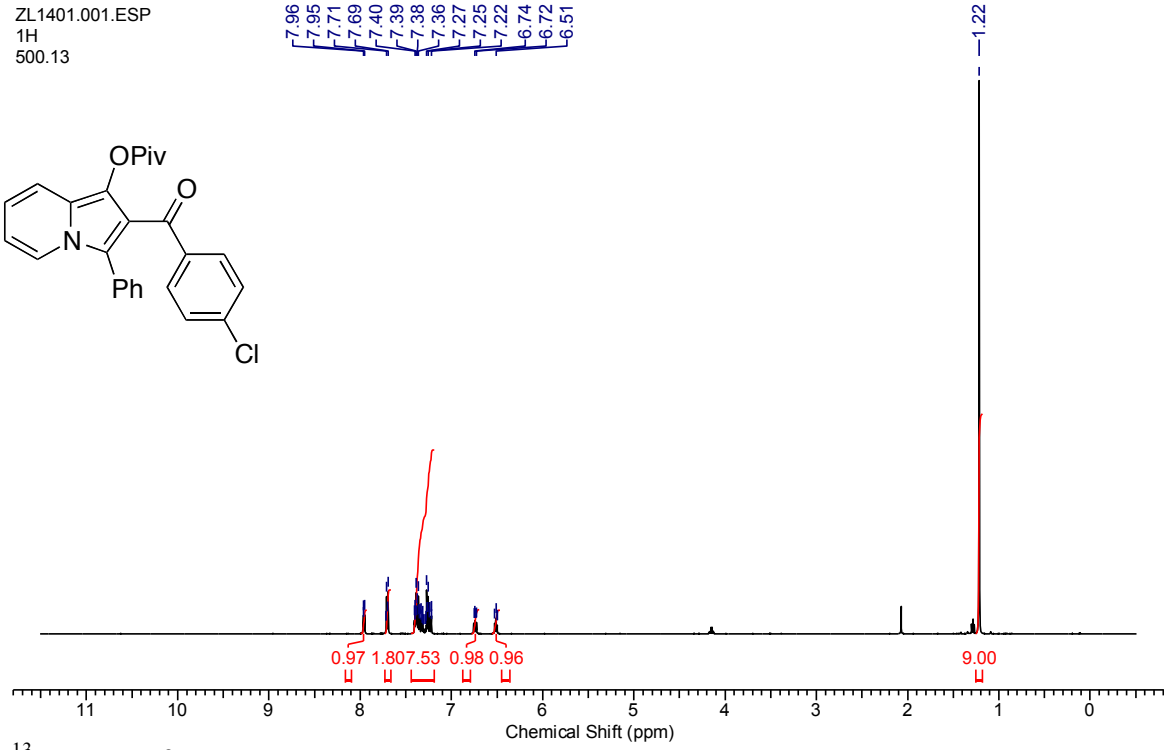
^{13}C NMR of **8h**



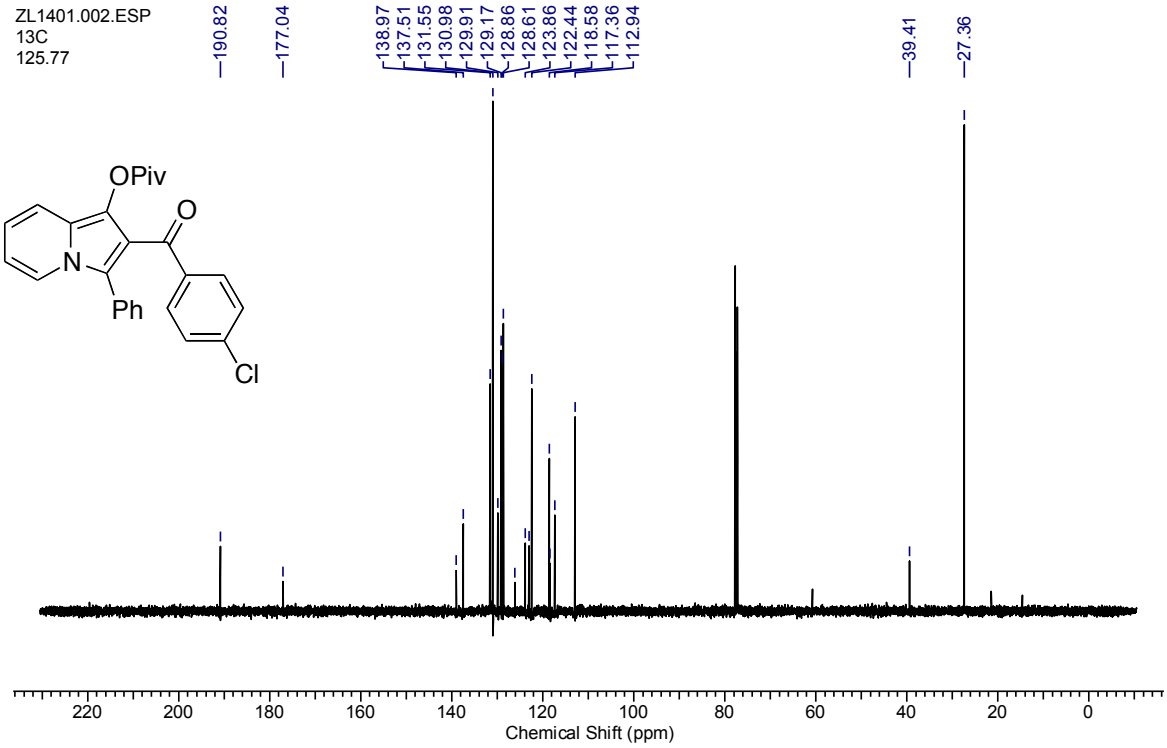
19F NMR of **8h**


ZL1403F.001.ESP
19F
470.59
OPiv
O
N
Ph
CF3
63.56
3.00
100
80
60
40
20
0
-20
-40
-60
-80
-100
Chemical Shift (ppm)

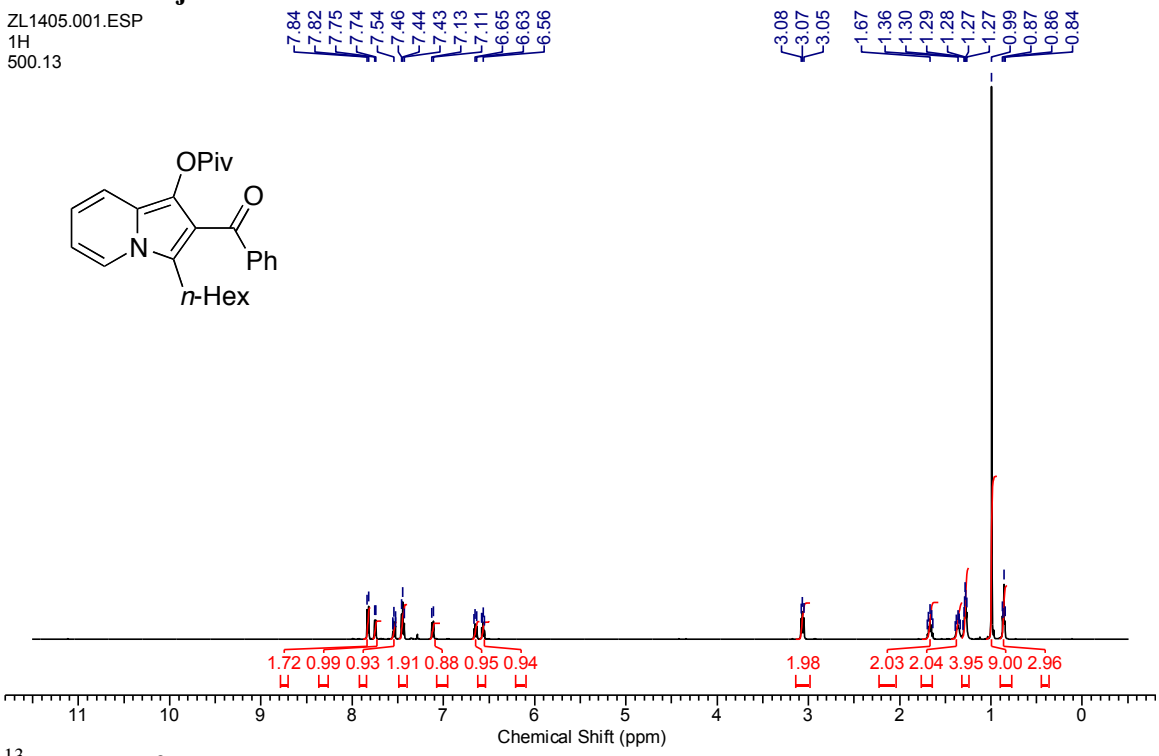
^{1}H NMR of **8i**



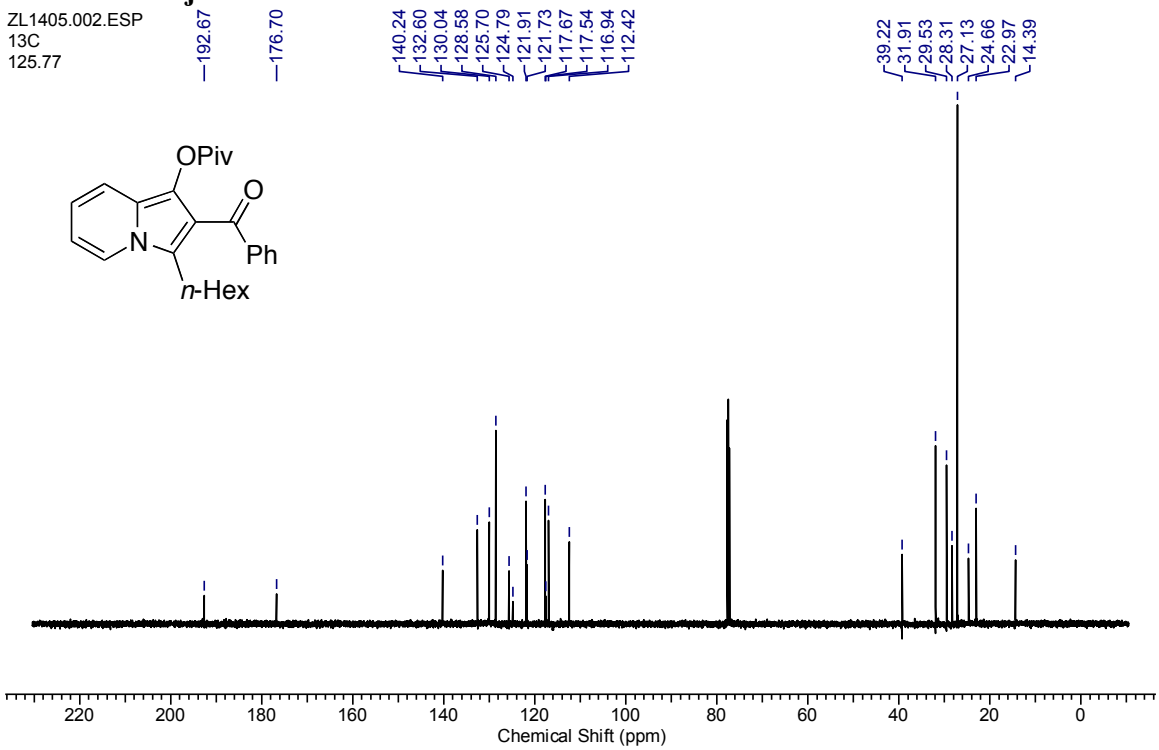
^{13}C NMR of **8i**



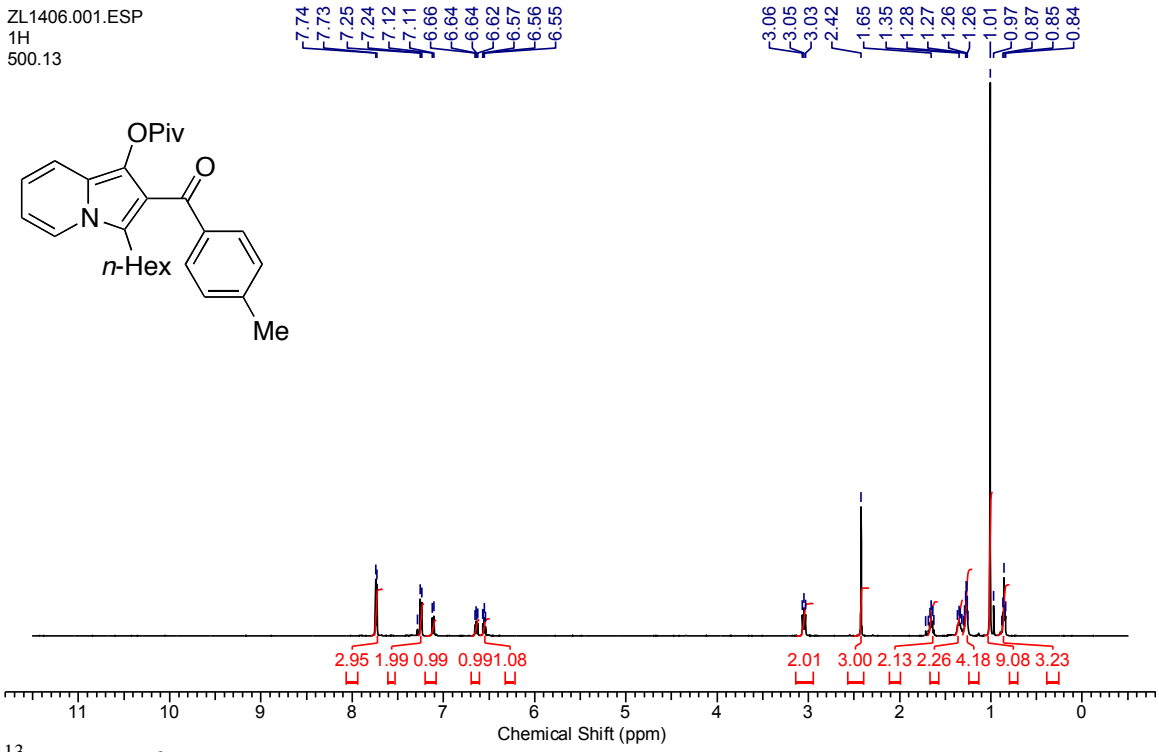
^{1}H NMR of **8j**



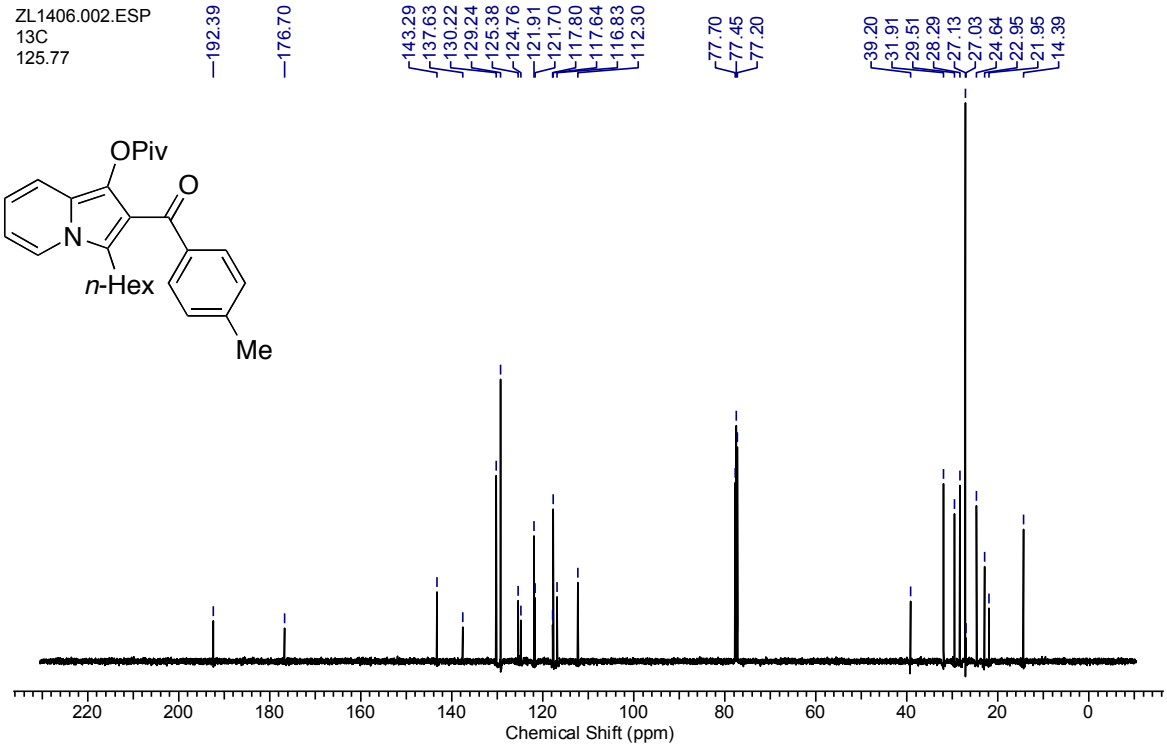
^{13}C NMR of **8j**



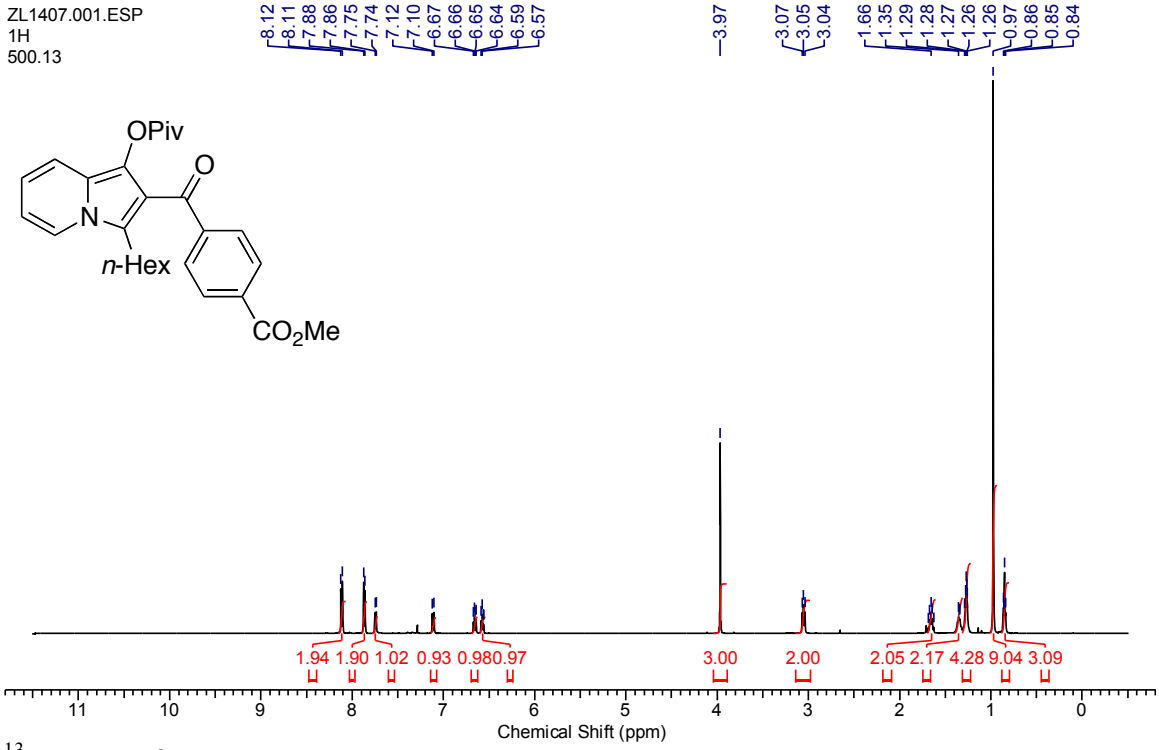
^{1}H NMR of **8k**



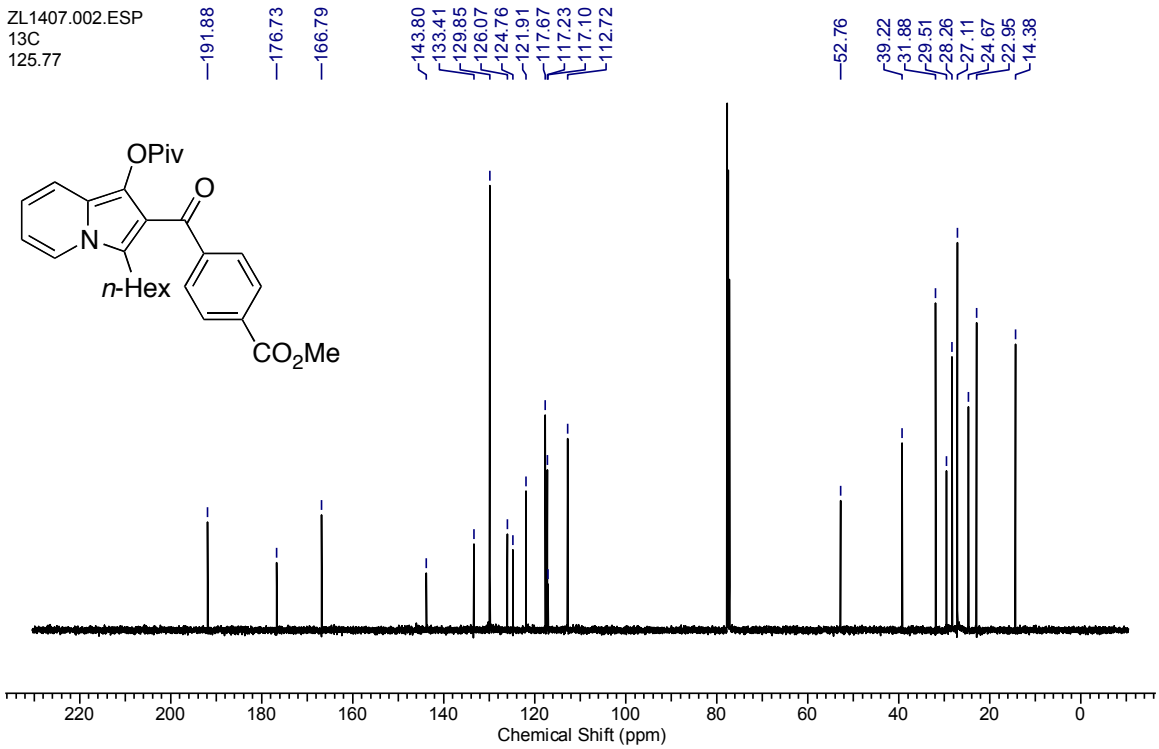
^{13}C NMR of **8k**



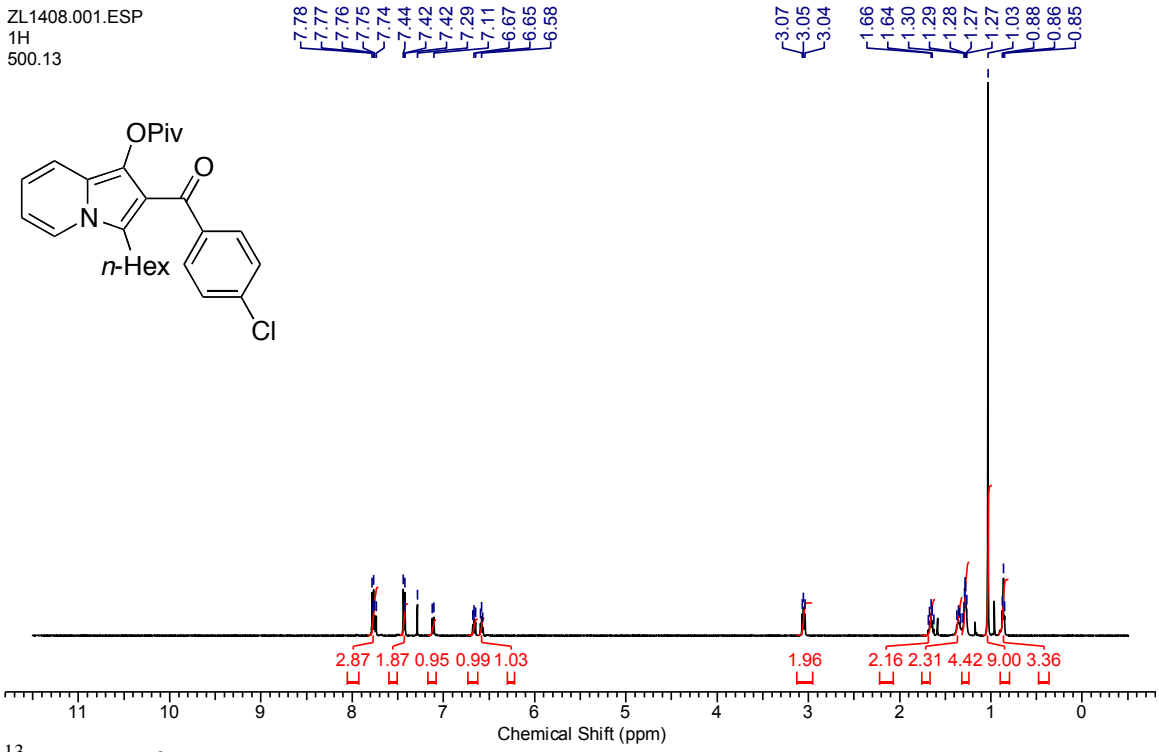
^{1}H NMR of **8l**



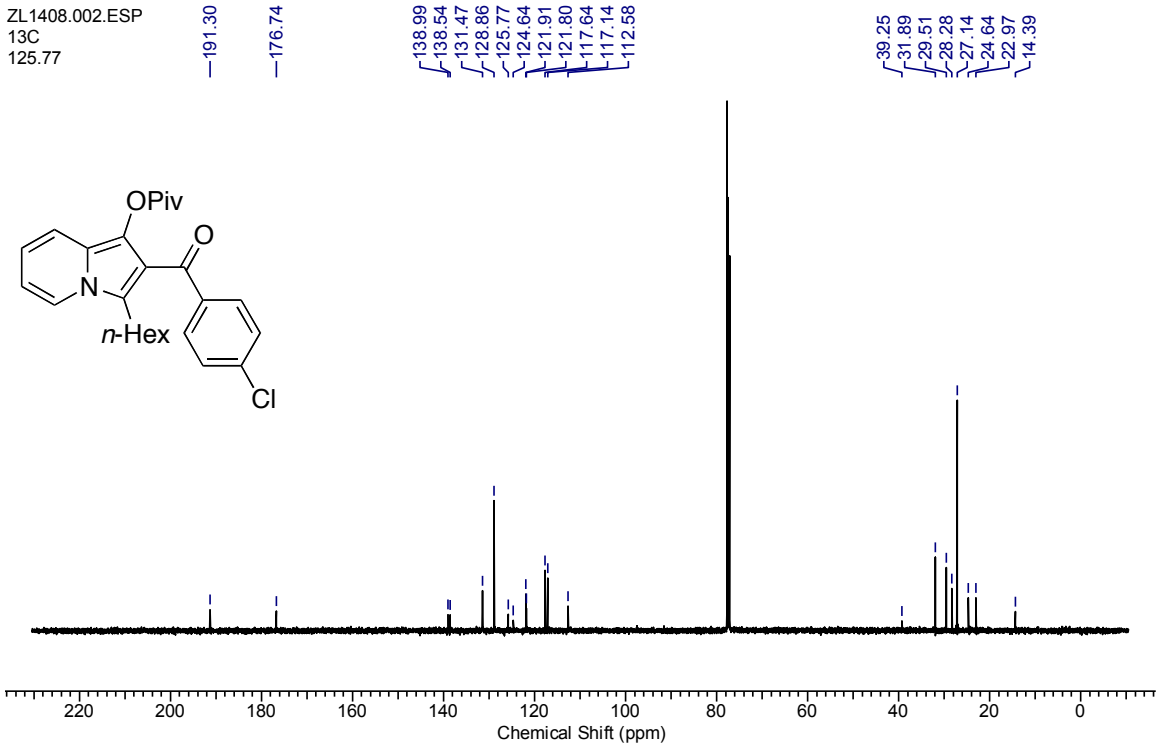
^{13}C NMR of **8l**



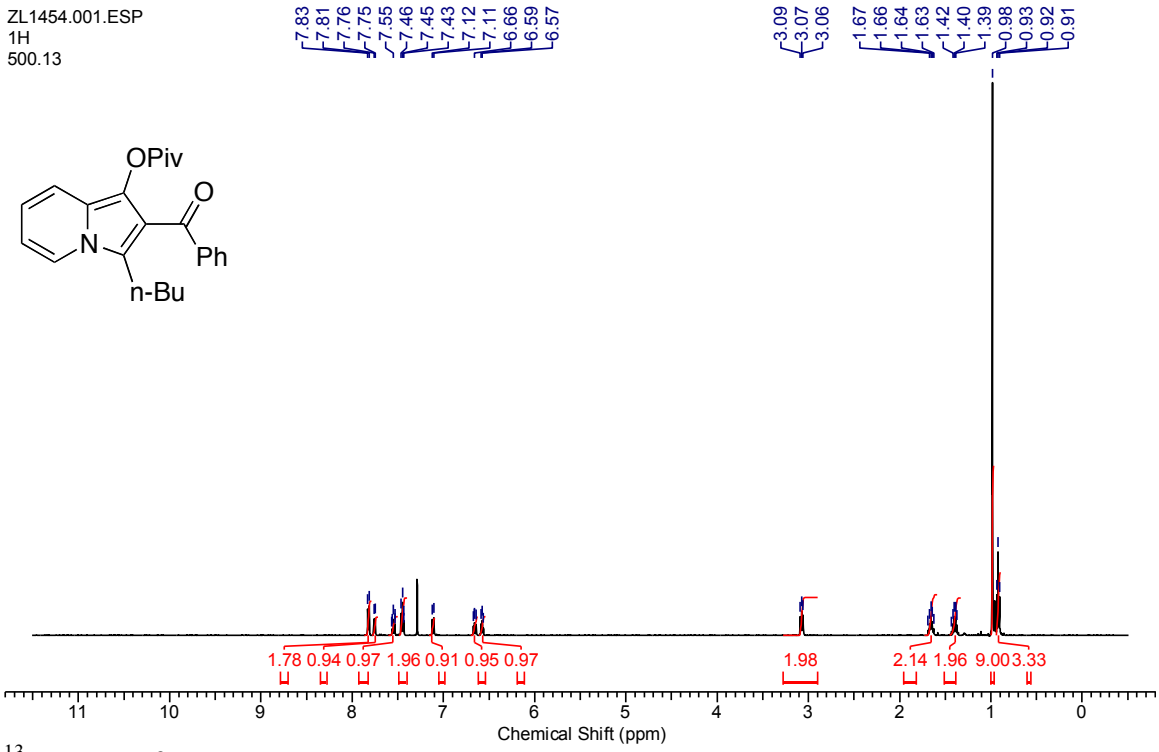
^{1}H NMR of **8m**



^{13}C NMR of **8m**



^{1}H NMR of **8n**



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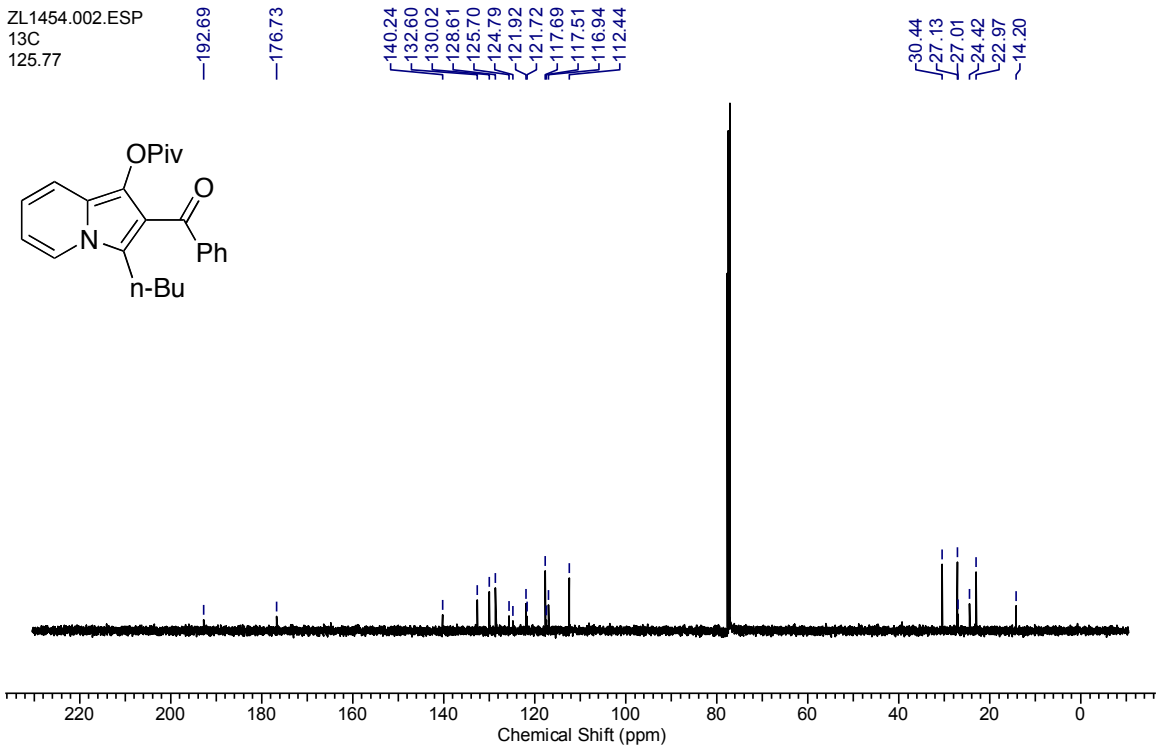
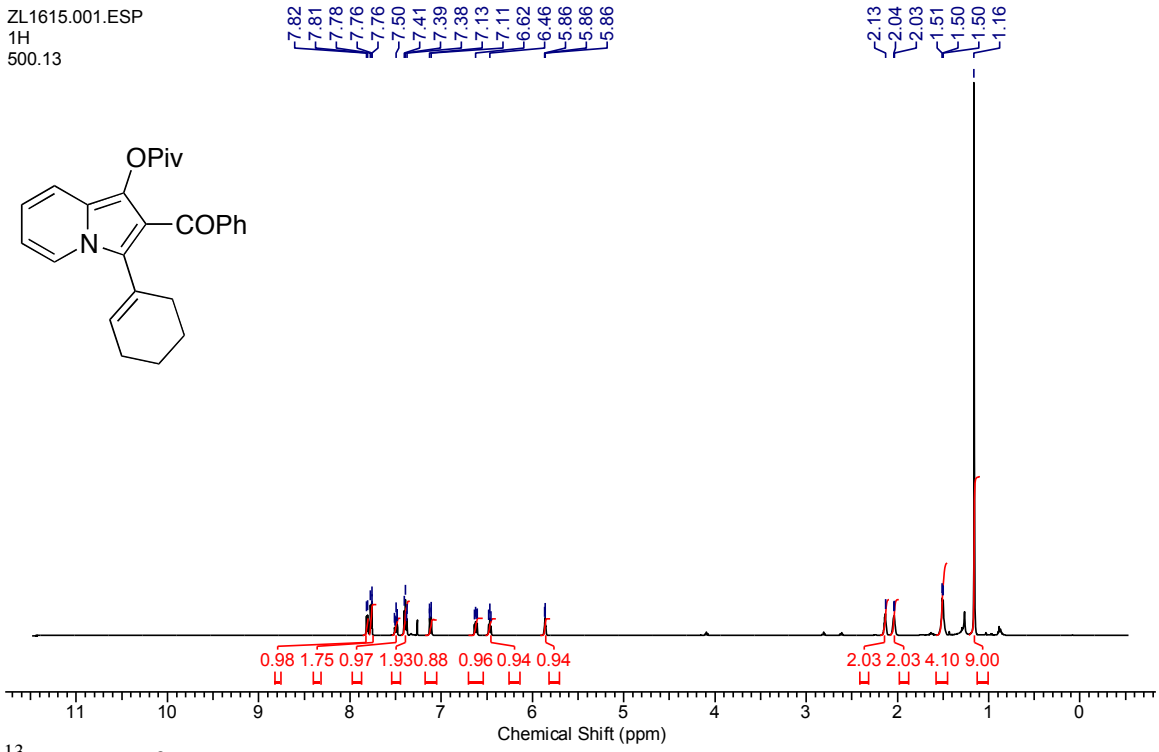
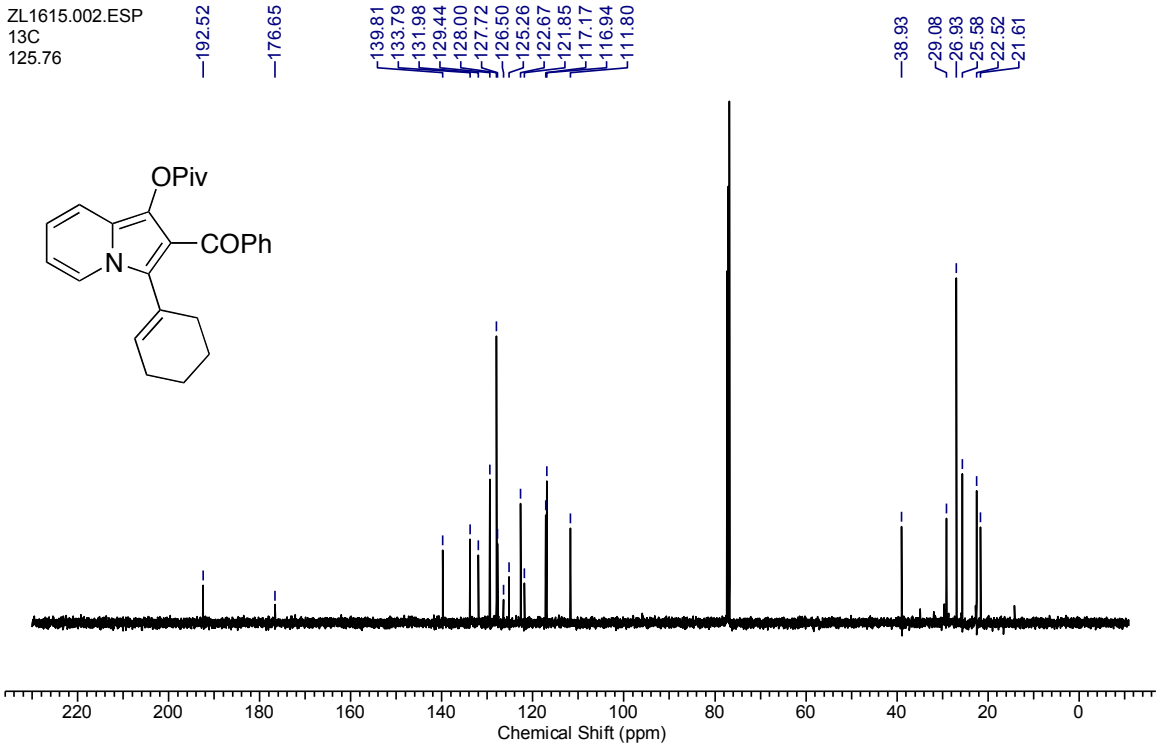


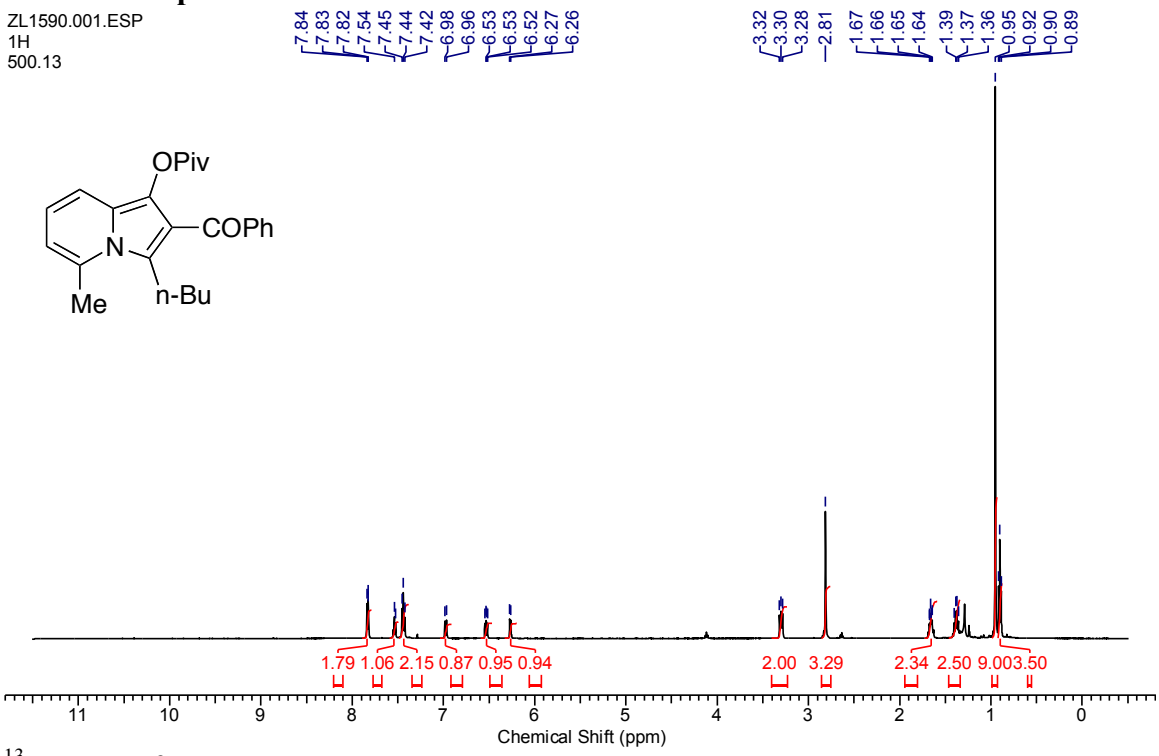
^{1}H NMR of **8o**



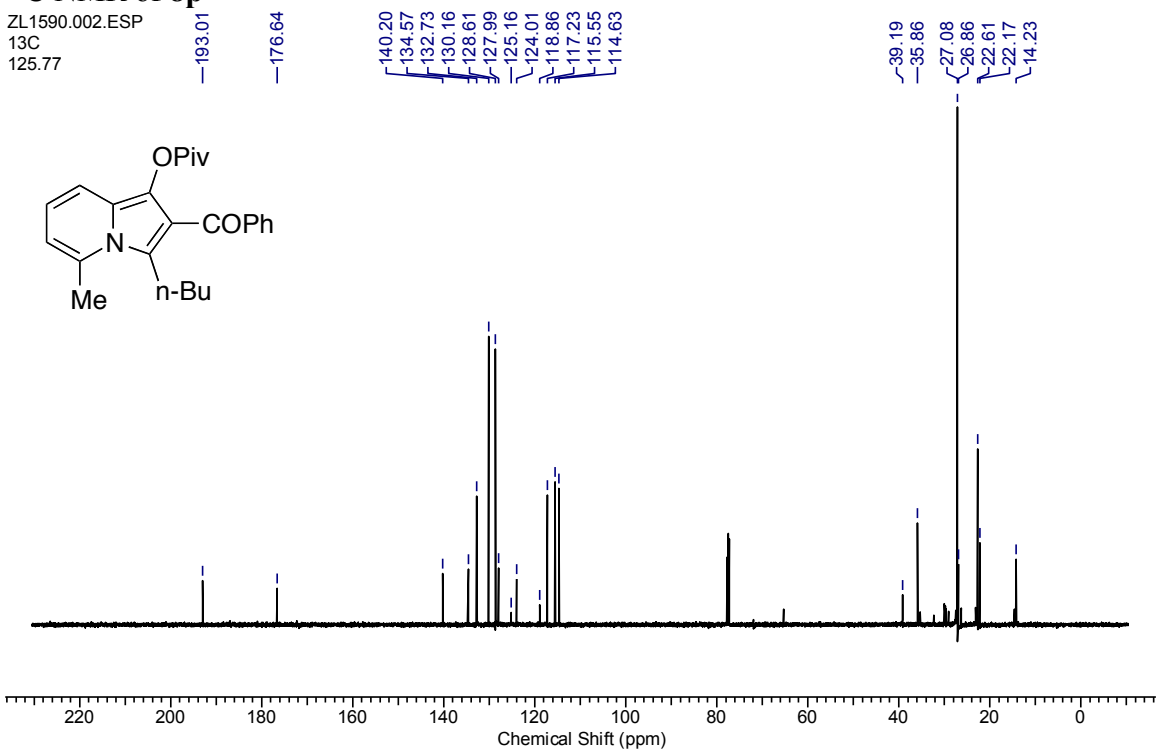
^{13}C NMR of **8o**



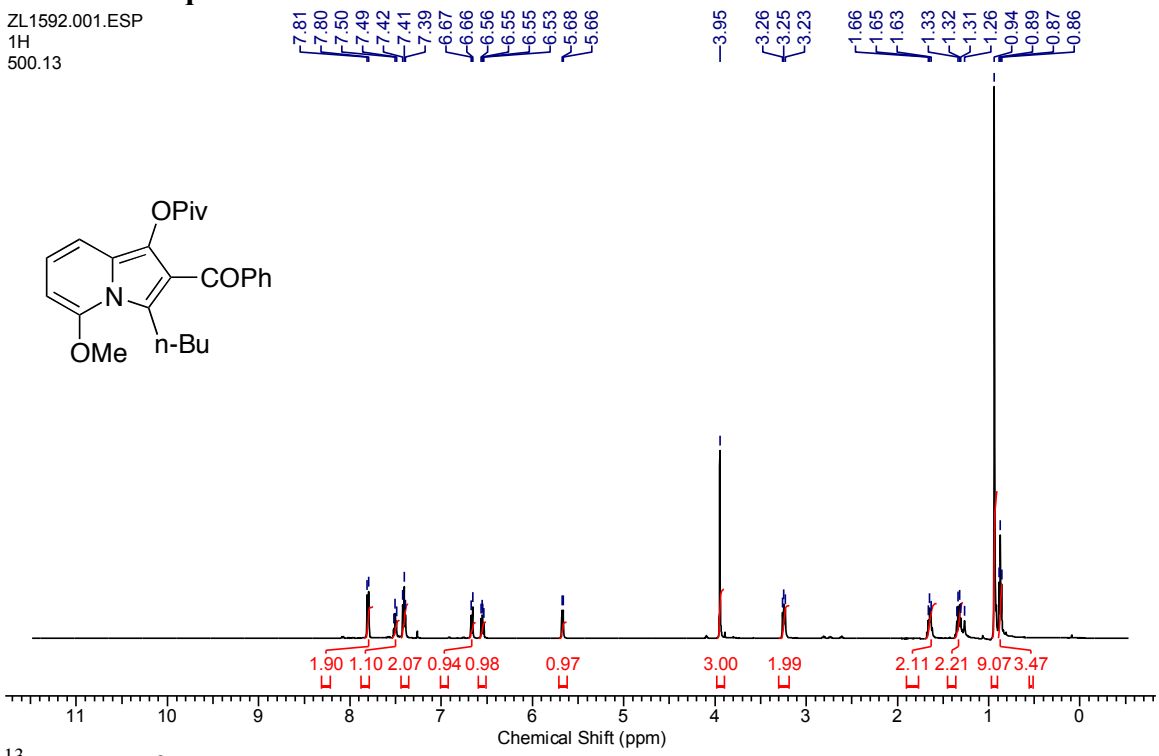
^{1}H NMR of **8p**



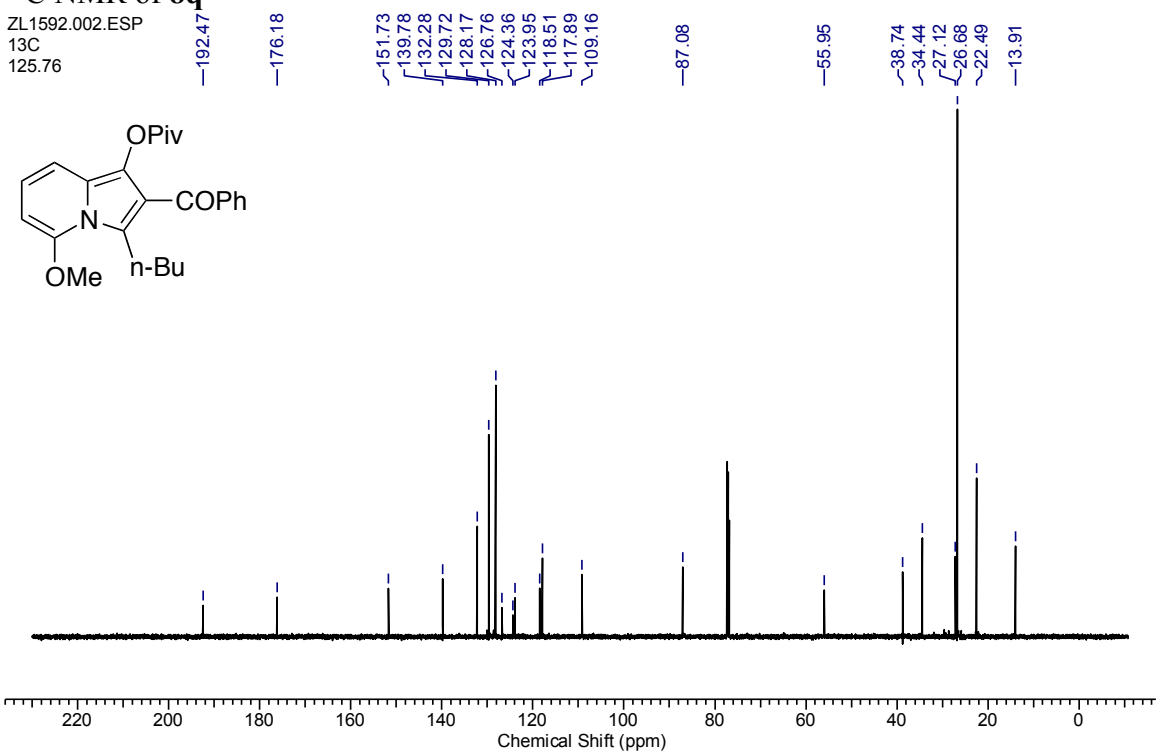
^{13}C NMR of **8p**



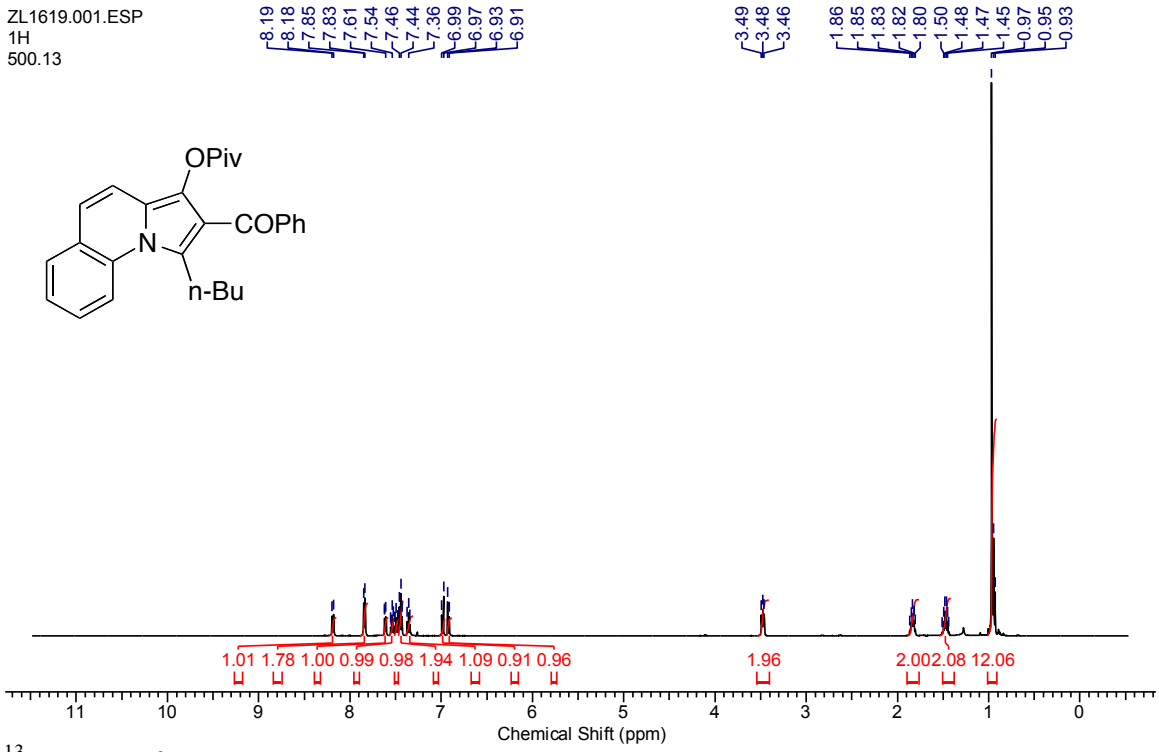
^{1}H NMR of **8q**



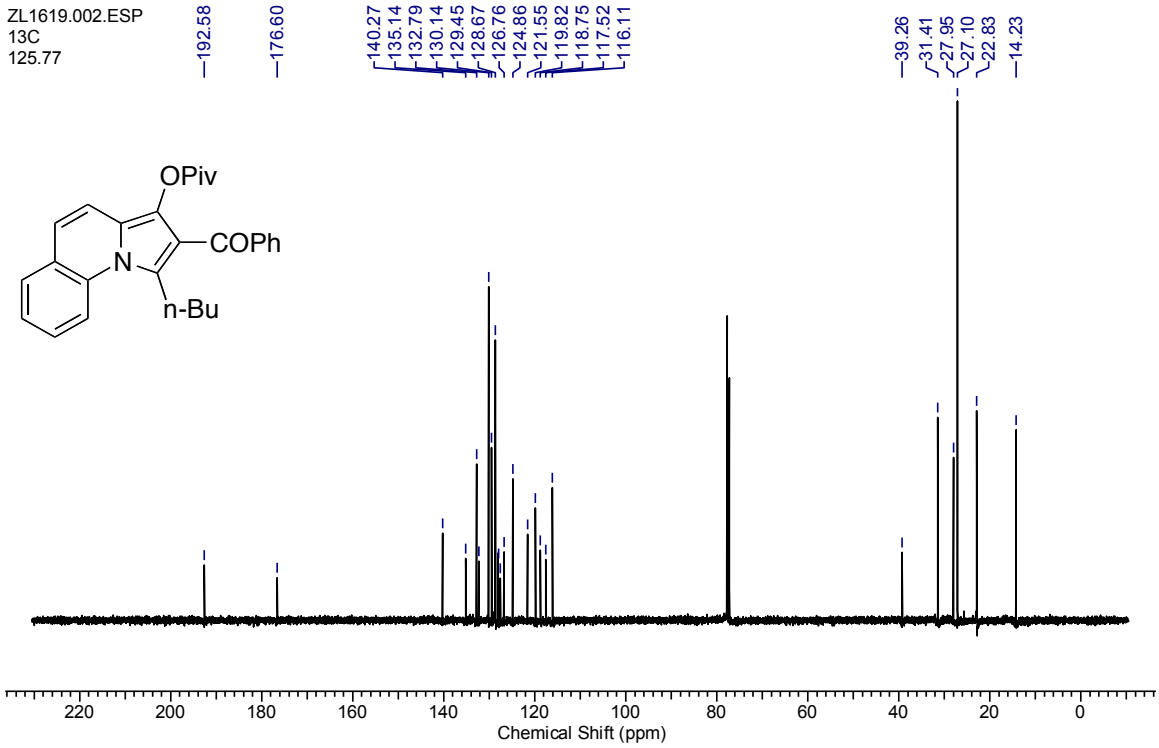
^{13}C NMR of **8q**



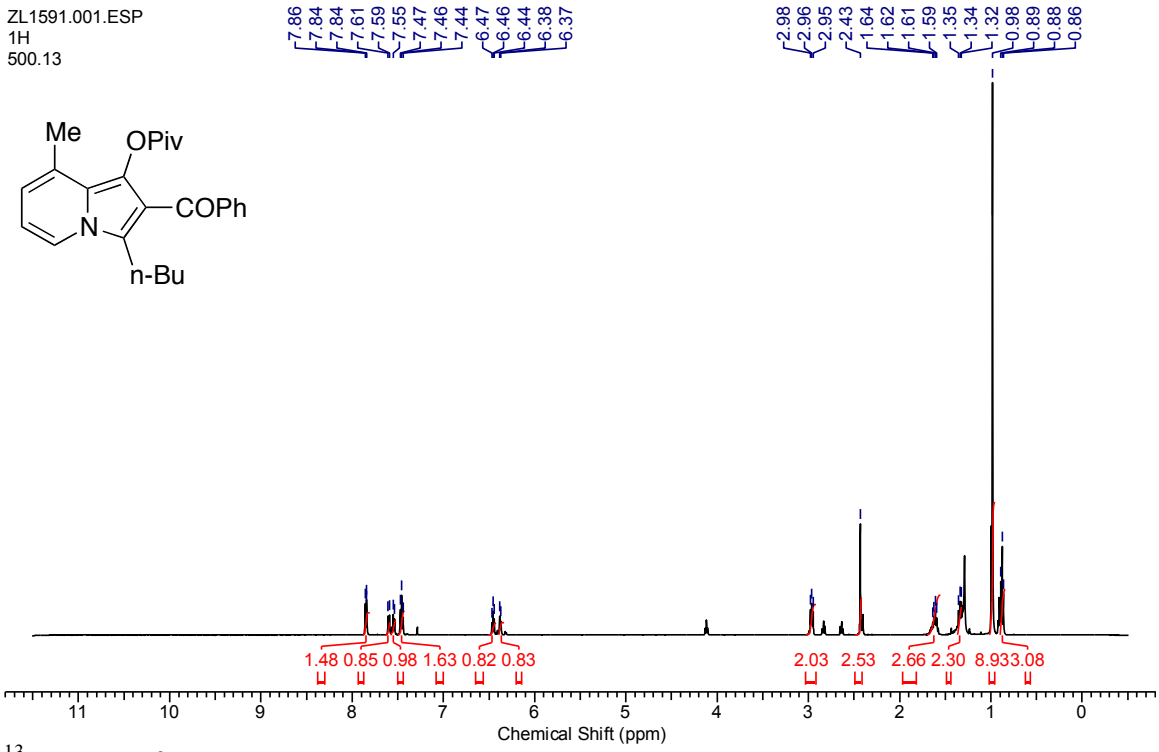
^{1}H NMR of **8r**



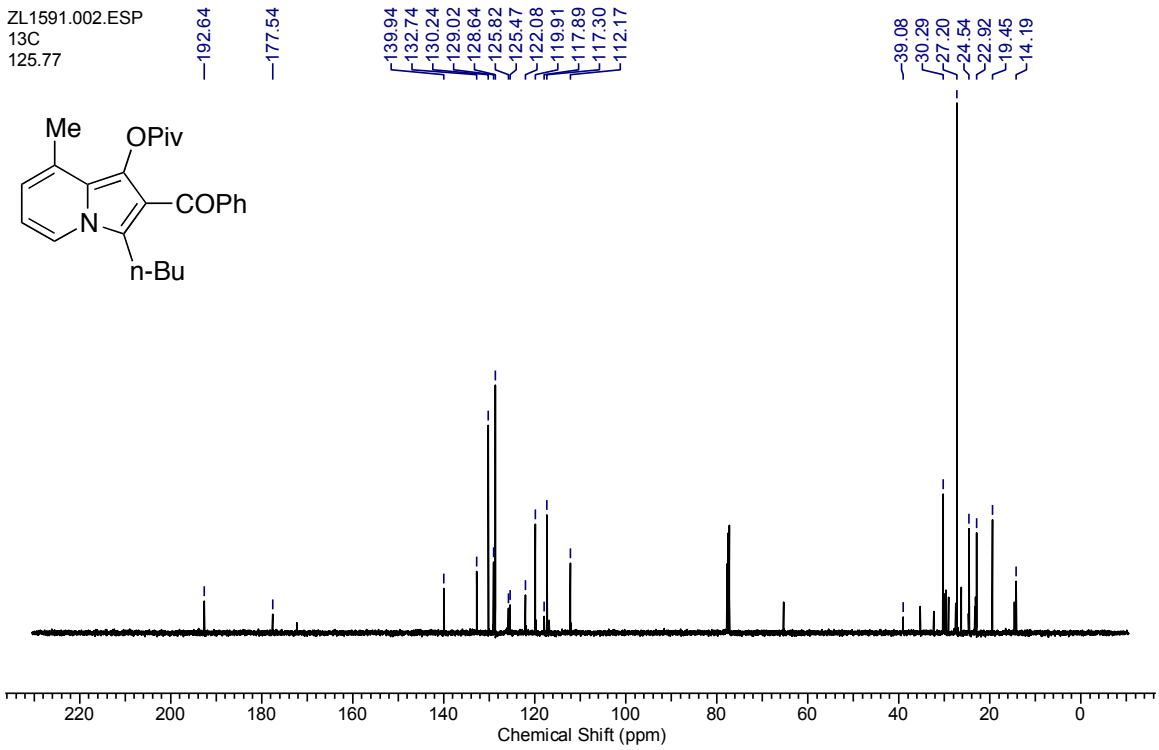
^{13}C NMR of **8r**



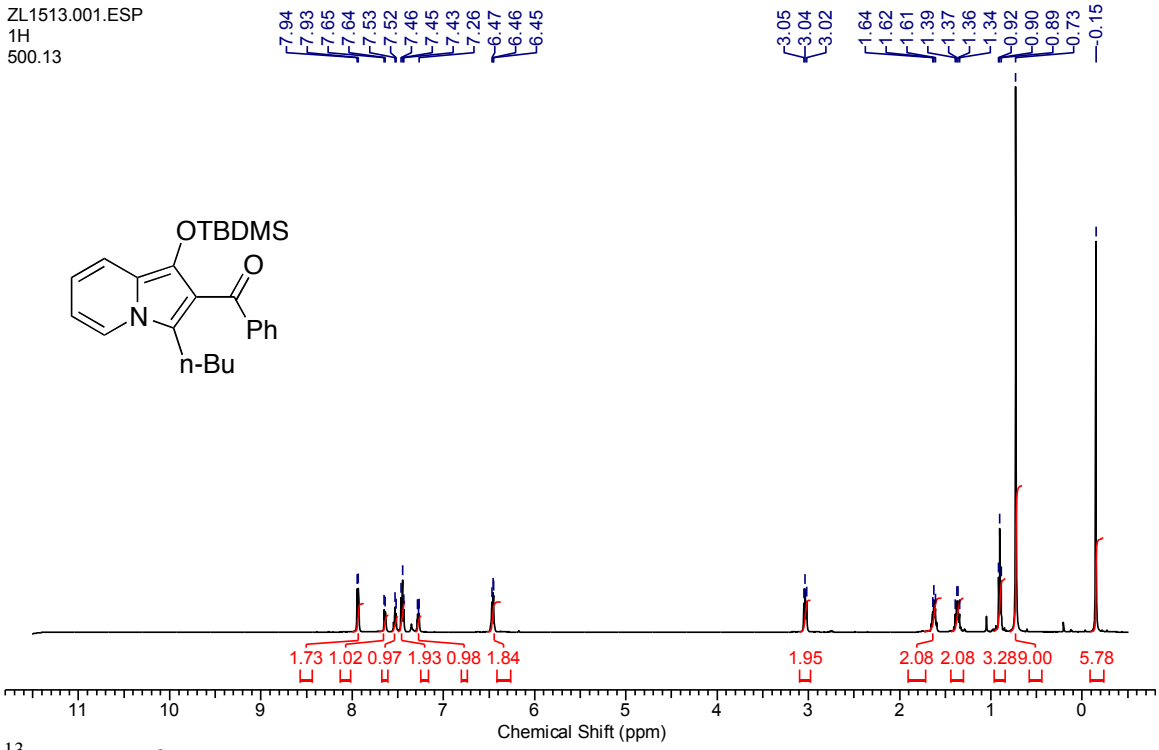
^{1}H NMR of **8s**



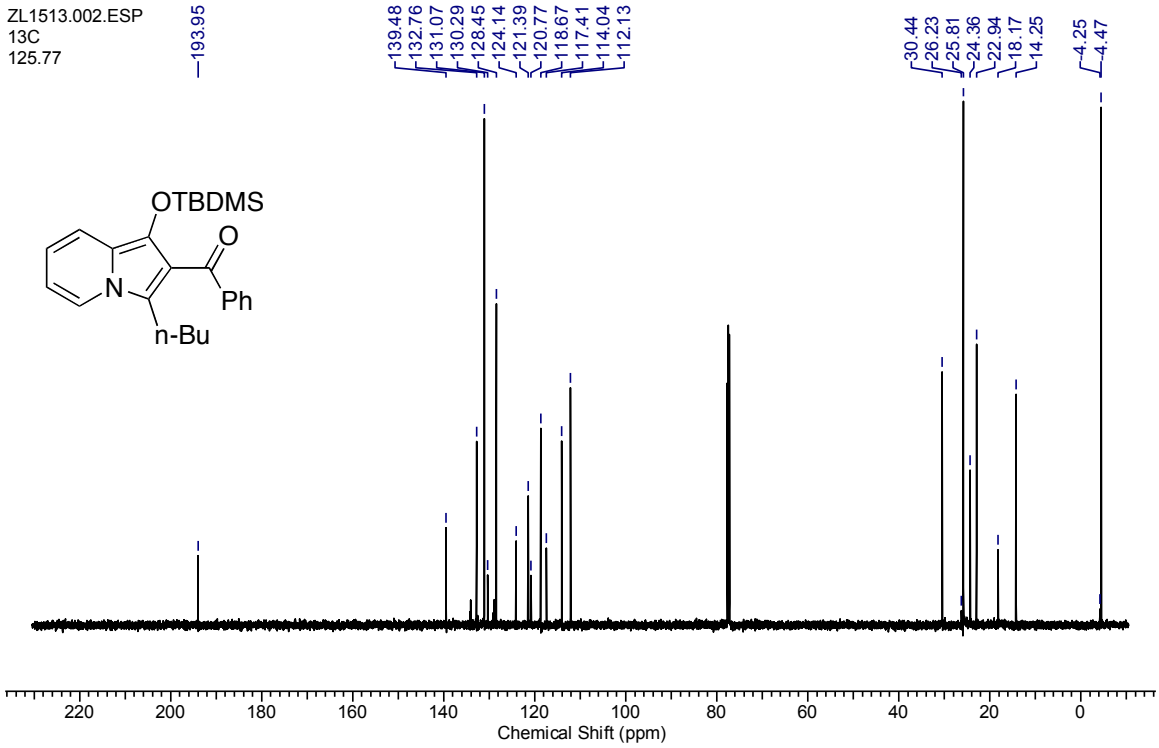
^{13}C NMR of **8s**



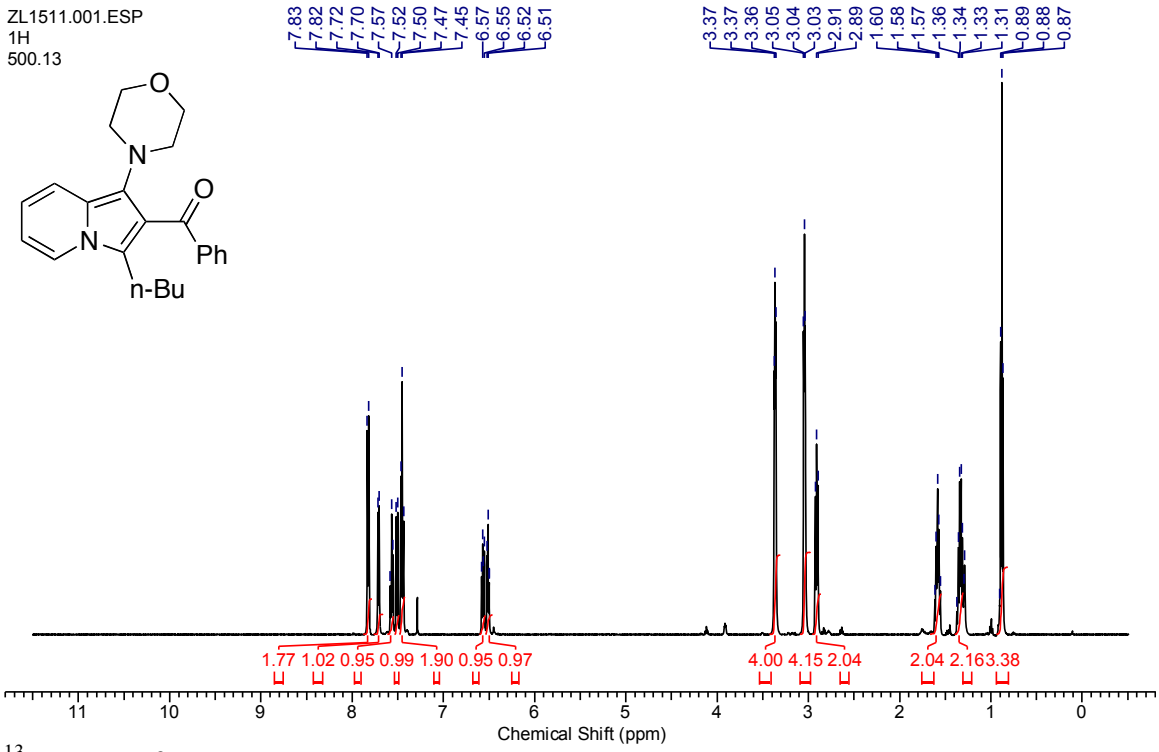
^{1}H NMR of **8t**



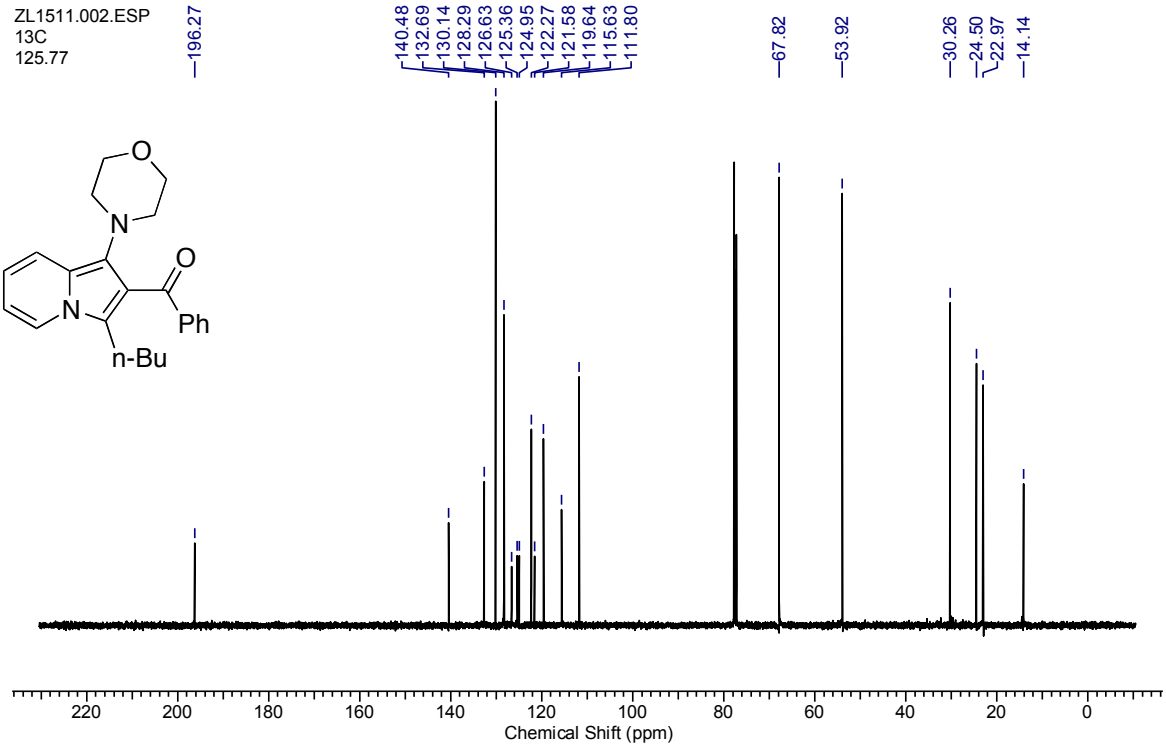
^{13}C NMR of **8t**



^{1}H NMR of **8u**



^{13}C NMR of **8u**



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PUBLICATIONS: "Bromopentafluorobenzene" Li, Z.; Gevorgyan, V. *Encyclopedia of Reagents for Organic Synthesis* **2014**.

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PRESENTATIONS: "Palladium-Catalyzed Carbonylative Cyclization/ Arylation Cascade for 2-Aroylindolizine Synthesis" Li, Z.; Chernyak, D.; Gevorgyan, V. the 30th Brown Lectures, Apr 27th 2013, Purdue University (poster)

"One-Pot Arylative Epoxidation of Ketones by Employing

Amphoteric Bromoperfluoroarenes" Li, Z.; Gevorgyan, V. the 29th Brown Lectures, Jun 9th 2012, Purdue University (poster)

"Cascade Carbopalladation-Annulation Towards Polycyclic Derivatives of Indole and Indolizine" Li, Z.; Chernyak, N.; Tilly, D.; Gevorgyan, V. the 5th Negishi-Brown and CAOSS Lectures, Oct 11th 2010, Purdue University (poster)

"Dual Role of Cyanogen Bromide in One-Pot Synthesis of Cyanoepoxides" Li, Z.; Chernyak, N.; Gevorgyan, V. the 27th Herbert C. Brown Lectures in Organic Chemistry (April 24, Saturday, 2010, Purdue University (poster)