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STEREOSELECTIVE IRON-CATALYZED INTERMOLECULAR OLEFIN
AMINO-OXYGENATION, AMINO-FLUORINATION AND TRIFLUOROMETHYL AZIDATION

by

CHENGLIANG ZHU

Under the Direction of Hao Xu, PhD

ABSTRACT

This dissertation is concerned about four types of iron-catalyzed selective nitrogen atom transfer reactions developed in Xu group during 2012 and 2017, which can facilitate efficient access to valuable functional molecules from readily available petro-chemicals and other abundant starting olefinic materials. These iron-catalyzed stereoselective olefin difunctionalization processes include intermolecular olefin *amino-oxygenation*, *amino-fluorination* and *trifluoromethyl azidation*.

Compared to all other existing methods, our strategies have a broader substrate scope as well as improved or complementary selectivity in terms of regioselectivity, diastereoselectivity and enantioselectivity. To achieve a fine balance between catalyst reactivity, stability, and reaction selectivity, we explored a variety of iron catalysts, ligands and new amination reagents. Our methods allow chemists to conveniently transform a broad range of simple, abundant olefin precursors to a variety of functionalized vicinal *amino alcohols* and vicinal *fluoro primary amines* that are valuable in both organic synthesis and biomedical sciences.

INDEX WORDS: Iron catalysis, Stereoselective reaction, Olefin difunctionalization, Nitrogen atom transfer reaction, Asymmetric catalysis, Iron-nitrenoid, Radical reaction

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CHENGLIANG ZHU

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

in the College of Arts and Sciences

Georgia State University

2017

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Chengliang Zhu
2017

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August 2017

DEDICATION

To my parents,

my wife, and

my son

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I am also very grateful to my committee members, including Prof. Al Baumstark, Prof. Peng George Wang and Prof. Ivaylo Ivanov. They are very helpful and patient during my time at Georgia State University. In particular, I want to thank Prof. Baumstark for the tremendous valuable and inspiring suggestions he gave me for my research.

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LIST OF ABBREVIATIONS

Boc ₂ O–di- <i>tert</i> -butyl dicarbonate	TEAB–tetraethylammonium bromide
Bz–benzoyl	TOAB–tetra- <i>n</i> -octylammonium bromide
CDI–1,1'-carbonyldiimidazole	THF–tetrahydrofuran
CH ₂ Cl ₂ –dichloromethane	TIPS–triisopropylsilyl
DCC– <i>N,N'</i> -dicyclohexylcarbodiimide	Troc–2,2,2-trichloroethoxycarbonyl
DMAP–4-dimethylaminopyridine	
<i>dr</i> –diastereomeric ratio	
<i>ee</i> –enantiomeric excess	
EtOAc–ethyl acetate	
Et ₂ O–diethyl ether	
EtOH–ethanol	
HPLC–high-performance liquid chromatography	
HRMS–high resolution mass spectrometry	
LAH–lithium aluminum hydride	
MeCN–acetonitrile	
MeOH–methanol	
MS–molecular sieves	
Ns–nitrobenzenesulfonyl	
NMR–nuclear magnetic resonance	
RT–room temperature	
TBAC–tetra- <i>n</i> -butylammonium chloride	
TBDPS– <i>tert</i> -butyldiphenylsilyl	
TBS– <i>tert</i> -butyldimethylsilyl	
TEA–triethylamine	

1 IRON(II)-CATALYZED INTERMOLECULAR AMINO-OXYGENATION OF OLEFINS*

Abstract

In this chapter, a highly efficient and selective iron (II)-catalyzed intermolecular olefin amino-oxygenation reaction is described. This process goes through an iron-nitrenoid intermediate, which generated by the *N*-*O* bond cleavage of a functionalized hydroxylamine.[†] In this reaction, an easy-prepared and bench-stable hydroxylamine derivative is used as the source of both nitrogen and oxygen functionalities. A broad range of synthetically valuable unfunctionalized olefins is excellent candidates for this reaction and many of them are incompatible with existing amino-oxygenation methods. With this method, simple and unfunctionalized olefins can be converted to vicinal amino alcohols regioselectively and diastereoselectively.

1.1 Introduction

Vicinal amino alcohols are important structural motifs in many pharmaceuticals, biologically active molecules and synthetically valuable building blocks (Figure 1.1). Therefore, direct olefin difunctionalization that can introduce both amino groups and hydroxyl groups simultaneously are highly desired and well-studied in the last few decades.

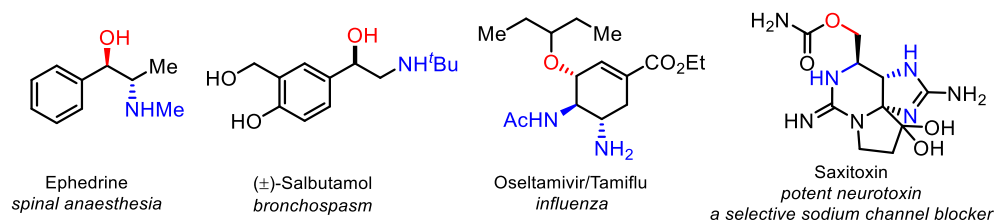


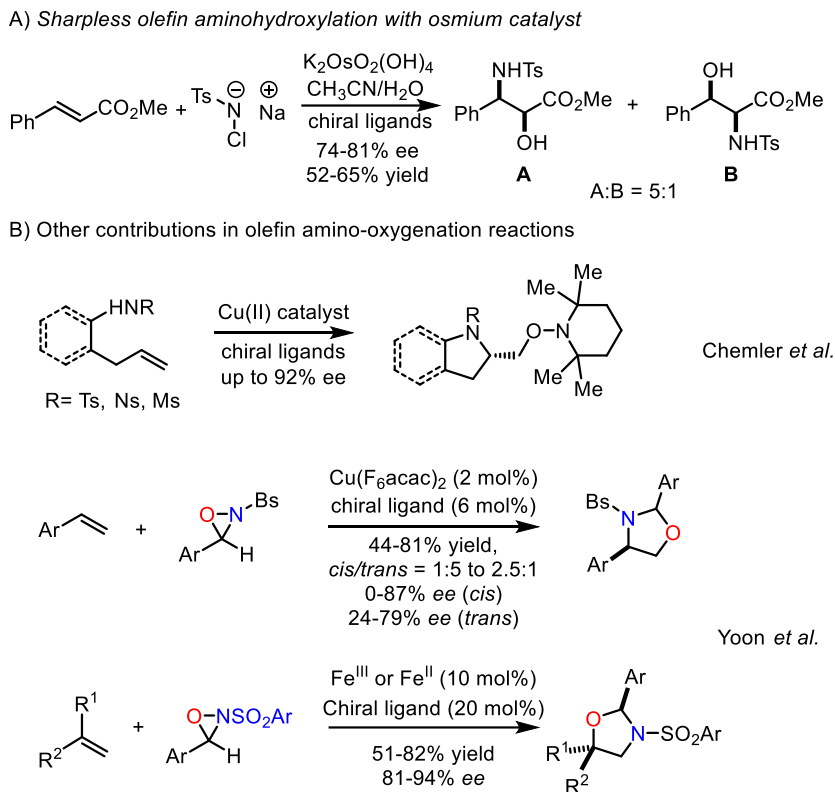
Figure 1.1 Representative nitrogen containing pharmaceuticals

Sharpless and coworkers discovered the first osmium-catalyzed racemic olefin aminohydroxylation reaction in 1970s and they further developed the asymmetric reaction (with *ee* approaching 90% or higher)

* This chemistry was carried out with collaboration with the following co-workers: Lu, D.F. and Jia, Z.X.

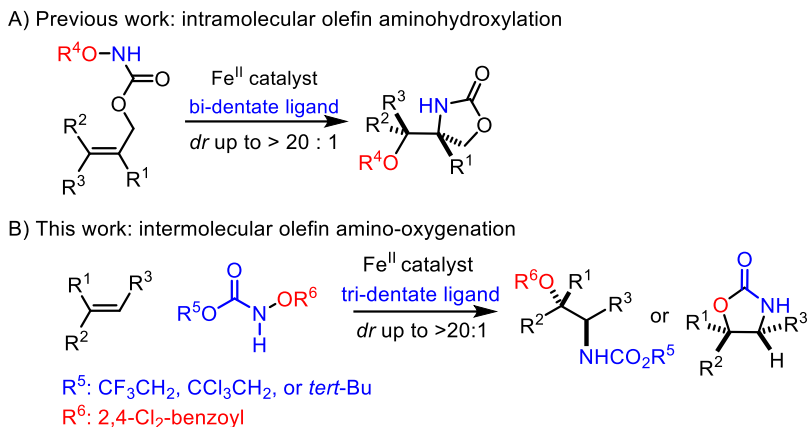
[†] Contents in this chapter were published in: (1) Lu, D. F.; Zhu, C. -L.; Jia, Z. X.; Xu, H. *J. Am. Chem. Soc.* **2014**, *136*, 13186–13189; (2) Zhu, C.-L.; Lu, D.-F.; Sears, J. D.; Jia, Z.-X.; Xu, H. *Synthesis* **2016**, *48*, 3031–3041.

in 1990s.^{1,2} (Scheme 1.1A) The Sharpless' aminohydroxylation is a powerful tool even today. However, this transformation is not perfect and there are quite a few intrinsic limitations associated with this process. The first limitation is regioselectivity. In most cases, the Sharpless aminohydroxylation always gives a pair of regio isomers, and often times the ratio is about 1 to 1. In addition to that, this transformation suffered from its limited substrate scope. A large number of synthetic valuable olefins with labile C-H bonds are not even compatible with the racemic Sharpless aminohydroxylation reactions. In spite of its limitations, the osmium-based Sharpless aminohydroxylation continues to be a prevalent stereospecific method for olefin amino-oxygenation. To overcome these limitations, many other amino hydroxylation strategies and approaches have been developed to achieve broader substrate scope and better regioselectivity.³⁻⁹ In addition to those precious late-transition-metal catalyzed methods, sustainable and less expensive first-row transition metal catalyzed amino-oxygenation reactions emerged with great interest. (Scheme 1.1B) Chemler and coworkers developed copper-catalyzed olefin amino-oxygenation and other difunctionalization methods;^{4,5,10,11} Yoon's groups developed Cu- and Fe-catalyzed amino hydroxylation with sulfonyl oxaziridine reagent.^{3,6-8} Complementary regioselectivity could be achieved under specific reaction conditions. One of the great strength of Yoon's method is its asymmetric version is uniquely effective for terminal olefins, however, the enantioselective variant of this method is ineffective for internal olefins because of lack of reactivity. In addition to that, because of the highly electrophilic nature of this sulfonyl oxaziridine reagent, a number of synthetically valuable olefins with sensitive groups are not compatible with this method, including cyclopentadiene, indene, enol ether, allyl silane and glycol.



Scheme 1.1 Selected previous approaches for olefin aminohydroxylation

Given all these great discoveries, we like to develop new first-row transition metal-catalyzed olefin amino-oxygenation methods, which have a broader substrate scope and improved or complementary regio- and stereoselectivity to other existing methods. In particular, we have a long-standing interest in iron catalyzed olefin difunctionalization, but the intermolecular olefin amino-oxygenation mediated by iron catalyst has not been reported in the literature. Unlike the rhodium nitrenoid catalyzed olefin amination reactions,¹²⁻¹⁵ the iron nitrenoid will more likely to add to olefins through step-wise radical addition pathways, because iron has a greater crystal field splitting energy than rhodium and usually in high-spin state.¹⁶⁻²³ Therefore, the discrepancy between iron nitrenoid and rhodium nitrenoid opens the way for us to explore its new reactivity. Our group have previously discovered iron-catalyzed intramolecular amino-oxygenation and amino-fluorination reactions of olefins with functionalized hydroxylamines (Scheme 1.2A).²⁴⁻²⁶ The mechanistic studies indicate that an iron nitrenoid is a reactive intermediate within both transformations and their stereo selectivity can be controlled by ligands.²⁷⁻²⁹



Scheme 1.2 Iron-catalyzed olefin amino-oxygenation with functionalized hydroxylamines

We started an intermolecular olefin amino-oxygenation with the same catalyst, same solvent and a similar oxidant that are previously used in the intramolecular amino-oxygenation. To our surprise, no desired product was detected from this system, and olefin substrate was recovered. To balance the catalyst reactivity and stability, we studied a range of new oxidants, iron catalyst and ligands. After lots of exploration, we discovered an intermolecular olefin amino-oxygenation method based upon *N*-*O* bond cleavage and redox iron catalysis that can convert a broad range of simple and unfunctionalized olefins to vicinal amino alcohol derivatives efficiently and selectively. In this transformation, a bench-stable hydroxylamine derivative is applied as both the amination reagent and oxidant (Scheme 1.2B).

Compared to the existing iron-catalyzed olefin amino-oxygenation method with sulfonyl oxaziridines, this method has a few advantages.^{7,8} Firstly, we observed significant asymmetric induction with internal olefins in this method, while the sulfonyl oxaziridine-based asymmetric approach is uniquely effective for terminal olefins. Secondly, this method tolerates a variety of synthetically valuable olefins with sensitive functional groups, such as cyclopentadiene, allyl silanes, indene, enol ethers and glycals, which are all incompatible with the existing iron-catalyzed olefin amino-oxygenation method with sulfonyl oxaziridines.^{7,8} Additionally, this method will afford amino alcohol derivatives with improved or complementary regioselectivity to other existing amino-oxygenation methods.

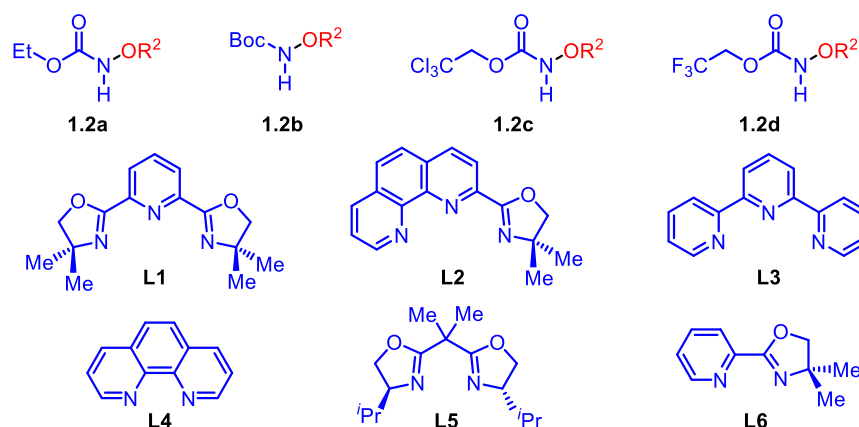
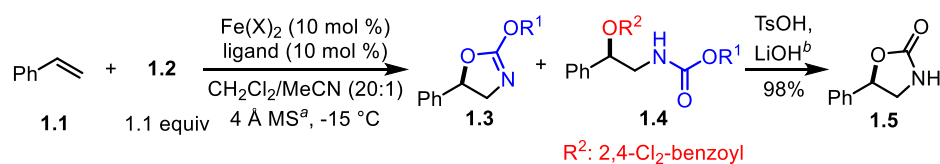
1.2 Results and discussions

1.2.1 Catalyst discovery

To achieve the proposed *intermolecular* amino-oxygenation, we chose styrene **1.1** as a model substrate for catalyst discovery (Table 1.1). Styrene was selected in the initial study for a few reasons: (1) it is commercially available and less expensive; (2) the relatively compact size will favor intermolecular reactions to take place; (3) the benzylic position is known to stabilize both carbocation or carboradical intermediate generated during the reaction process; (4) it is UV active but not very volatile, which makes it convenient to monitor the reaction progress with TLC technique. Iron (II) catalyst with *N,N'*-bi-dentate ligands work very well in our previously reported *intramolecular* aminohydroxylation reactions. However, our initial attempts with Fe(OTf)₂-*N,N'*-bi-dentate ligands failed in the *intermolecular* reaction due to the lack of reactivity (entries 7–9). We subsequently studied a range of ligands and found that the nitrogen-based tri-dentate bisoxazoline tetramethyl PyBOX ligand **L1** is uniquely effective. With a range of functionalized hydroxyl amines (**1.2a–1.2d**, entries 1–4), the Fe(OTf)₂-**L1** complex catalyzes an styrene amino-oxygenation affording an alkoxyl oxazoline **1.3** and a protected amino alcohol **1.4** (a direct aminohydroxylation product) product. Good to excellent combined yields were obtained in these transformation with complementary regioselectivity to the osmium-based methods.¹ Fortunately, both alkoxyl oxazoline and amino alcohol could be readily converted to the same oxazolidinone building block with high yield through simple hydrolysis procedures. Furthermore, we noted that the electronic nature of oxidants affects the reactivity greatly. From ethoxy carbamate, *tert*-butoxy carbamate, to trichloroethoxy and trifluoroethoxy carbamate, the oxidation ability gets stronger and more electrophilic reagents lead to higher reactivity (entries 3–4 vs 1–2). Regarding ligand effect, a significantly smaller Fe(OTf)₂-phenanthroline-oxazoline hybrid ligand (**L2**) complex is less reactive than the tri-dentate bisoxazoline tetramethyl PyBOX ligand **L1**, while an Fe(OTf)₂-terpyridine (**L3**) complex is totally inactive (entries 5–6). The four methyl groups in ligand **L1** are necessary and crucial to this transformation. Without methyl groups, the iron–ligand catalyst will do abstraction reactions, which will subsequently destroy the

catalyst itself (entry 6). In terms of the counter ion effect, we observed that Fe(NTf₂)₂ is equally reactive compared to Fe(OTf)₂, while FeCl₂ is inactive (entries 10–11).

Table 1.1 Catalyst discovery for the iron-catalyzed intermolecular olefin amino-oxygenation



entry ^b	Fe(X) ₂	ligand	1.2	conversion ^c	yield (1.3) ^d	yield (1.4) ^d	yield (1.5) ^d
1	Fe(OTf) ₂	L1	1.2a	76%	51%	8%	57%
2	Fe(OTf) ₂	L1	1.2b	69%	<5% ^e	6%	48% ^e
3	Fe(OTf) ₂	L1	1.2c	>95%	71%	12%	82%
4	Fe(OTf) ₂	L1	1.2d	>95%	63%	10%	72%
5	Fe(OTf) ₂	L2	1.2c	67%	44%	14%	57%
6	Fe(OTf) ₂	L3	1.2c	<5%	<5%	<5%	<5%
7	Fe(OTf) ₂	L4	1.2c	<5%	<5%	<5%	<5%
8	Fe(OTf) ₂	L5	1.2c	<5%	<5%	<5%	<5%
9	Fe(OTf) ₂	L6	1.2c	<5%	<5%	<5%	<5%
10	Fe(NTf ₂) ₂	L1	1.2c	>95%	62%	15%	76%
11	FeCl ₂	L1	1.2c	<5%	<5%	<5%	<5%

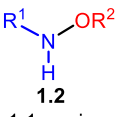

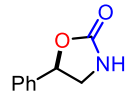

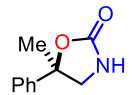
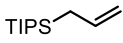
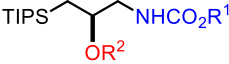

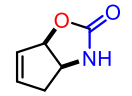

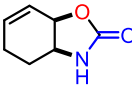

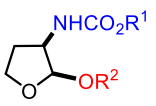

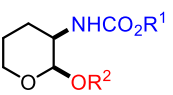
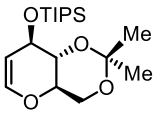
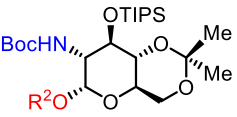
^aMolecular sieves were used to remove deleterious moisture. ^bReactions were carried out under N₂ in 1 h and then quenched with saturated NaHCO₃ solution. The crude mixture was first subjected to an acidic condition with TsOH (1.0 equiv) and then to a basic condition with LiOH (2.0 equiv) to afford 5. ^cConversion was measured by GC. ^dIsolated yield. ^eAn oxazolidinone was isolated directly without the additional step (41% yield). OTf: trifluoromethanesulfonate, NTf₂: trifluoromethanesulfonimide.

1.2.2 Substrate scope

With the optimized condition in hand, we next explored a variety of olefins to explore the scope and limitations of this method (Table 1.2).

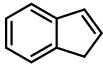
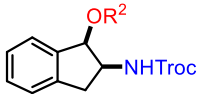

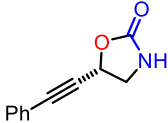
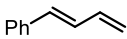
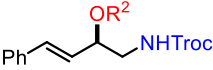
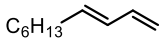
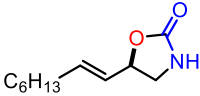
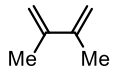
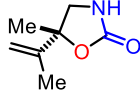
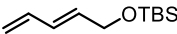
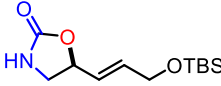
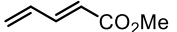
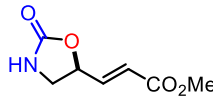
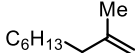
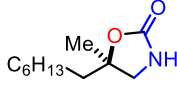
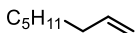
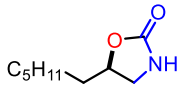
We first studied α -methyl styrene, which is a 1,1-disubstituted olefin with our optimal condition. Oxazolidinone was isolated in excellent yield after hydrolysis (entry 2, 75% yield). Next, we evaluated those olefins that are problematic substrates for the existing amino-oxygenation methods (entries 3–8).

Table 1.2 Substrate scope of the iron-catalyzed olefin amino-oxygenation

olefins + 		$\xrightarrow[\text{4 \AA MS, -15 }^\circ\text{C}]{\text{Fe(X)}_2 \text{ (10 mol \%)} \text{ ligand (10 mol \%)} \text{ CH}_2\text{Cl}_2/\text{MeCN (20:1)}$				
		olefin amino-oxygenation products				
		R^1 : F_3CCH_2 , Cl_3CCH_2 , or <i>tert</i> -Bu R^2 : 2,4- Cl_2 -benzoyl				
entry ^a	olefin	X	ligand	1.2	product	yield ^b
1 ^{c,d}		OTf	L1	1.2c		82%
2 ^{d,e}		OTf	L1	1.2c		75%
3		OTf	L1	1.2d		78%
4 ^{f,g}		OTf	L2	1.2b		61% <i>dr</i> > 20:1
5 ^{f,g}		OTf	L2	1.2b		62% <i>dr</i> > 20:1
6 ^e		OTf	L1	1.2d		72% <i>dr</i> > 20:1
7 ^h		OTf	L1	1.2d		77% <i>dr</i> = 10:1
8 ^{h,i}		NTf ₂	L1	1.2b		63% <i>dr</i> > 20:1

Allyl silane is a substrate that is incompatible with other iron-catalyzed amino hydroxylation methods, but it can be efficiently amino-oxygenated with **1.2d** (entry 3, 78% yield). We further studied amino-oxygenation of cyclopentadiene with a labile C–H bond. With less oxidative oxidant **1.2b** and at low temperature, we observed the double bond in cyclopentadiene was selectively difunctionalized and converted to an oxazolidinone with a decent yield and excellent *dr* (entry 4, 61% yield).

Table 1.2 continued

entry ^a	olefin	X	ligand	1.2	product	yield ^b
9 ^{c,i}		NTf ₂	L1	1.2c		63% <i>dr</i> > 20:1
10 ^{d,j}		OTf	L1	1.2c		62%
11 ^{c,k}		Cl+OTf	L1	1.2c		84%
12 ^{f,g}		OTf	L2	1.2b		61%
13 ^{f,g}		OTf	L2	1.2b		76%
14 ^{f,g}		OTf	L1	1.2b		63%
15 ^{f,g}		OTf	L1	1.2b		54%
16 ^{f,g}		ClO ₄	L1	1.2b		51%
17 ^{d,l}		OTf	L1	1.2c		48%

^aReactions were carried out under argon in 2 h, unless stated otherwise. ^bIsolated yield. ^cReaction time: 1 h.

^dThe crude mixture was treated with TsOH and then LiOH. ^eReaction temperature: -40 °C. ^fCatalyst loading:

20 mol %; reaction temperature: 0 °C. ^gReaction time: 12 h. ^hReaction temperature: -30 °C. ⁱFe(NTf₂)₂ (15 mol

%), L1 (15 mol %). ^jCatalyst loading: 15 mol %. ^kFe(OTf)₂ (2.5 mol %) and FeCl₂ (2.5 mol %) were used.

^lCatalyst loading: 30 mol %; reaction temperature: 0 °C; reaction time: 24 h.

We further observed that cyclohexadiene could be converted to an oxazolidinone with oxygen at the allylic position (entry 5, 62%). Although enol ethers have been challenging substrates for existing amino-oxygenation methods, they are excellent candidates for this iron-catalyzed method which delivers protected amino alcohols with good yields as single *syn*-isomers (entries 6–7, yield up to 77% and *dr* up to >20:1). The regio-selectivity in enol ether amino-oxygenation reaction can be explained by the fact the oxygen's lone pair better stabilize the radical or carbocation intermediates at 2-position through resonance to the p-orbitals, which will favor the amino group first attack 3-position. One of the examples highlights the distinct strength of this method is glycal amino-hydroxylation. A protected glycal can participate in the reaction with **1.2b** and afford a 2-amino- α -sugar with decent yield and excellent *regioselectivity* as well as *diastereoselectivity* (entry 8, 63% yield, *dr*>20:1 at both C1 and C2 positions).

In addition, Fe(NTf₂)₂ and **L1** complex can catalyze efficient indene amino-hydroxylation with exclusive single regioselectivity and diastereoselectivity. This reaction affords a protected *cis*-2-amino indanol, which is a valuable building block that is difficult to obtain directly with existing amino-oxygenation methods (entry 9, 71% yield, *dr*>20:1). For comparison, osmium-catalyzed racemic indene aminohydroxylation will provide mixtures of 1- and 2-amino indanols.^{30,31} We also explored conjugated ene-yne and dienes (entries 10–15). An ene-yne is an excellent substrate for this amino-oxygenation reaction (entry 10, 62% overall yield). Conjugated aliphatic diene and aromatic phenyl diene can also be efficiently transformed into protected 1,2-amino alcohols or oxazolidinones with excellent yields and regioselectivity (entries 11–13). It is worth noting that to achieve amino-oxygenation with phenyl diene, mixed salts of Fe(OTf)₂ and FeCl₂ were applied as the catalyst (entry 11). Fe(OTf)₂ alone led to rapid polymerization and decomposition of the diene substrate; while FeCl₂ was inactive in this transformation as described previously. This method is also compatible with a silyl dienol with an active alpha protons (entry 14, 63% yield). Furthermore, an electron deficient dienoate will afford desired amino-oxygenation product under this condition with acceptable yield (entry 15). Presumably, the relatively low yield due to the electron-deficient nature of this particular substrate.

To our delight, this method is also applicable to many isolated olefins. A 1,1-disubstituted olefin can be converted to oxazolidinone product with $\text{Fe}(\text{ClO}_4)_2\text{-L1}$ complex (entry 16, 51% yield). When other iron salts were applied, rapid addition-elimination occurs, which leads to the undesired allylic amination products. Mono-substituted olefins are challenging substrates because of lack of stabilizing neighboring group. With excess amount of catalyst loading and prolonged reaction time, we observed that the $\text{Fe}(\text{OTf})_2\text{-L1}$ complex catalyzes the reaction of 1-octene with **1.2c** to afford the oxazolidinone with a synthetically useful yield (entry 17, 48% yield).

It is worth pointing out that in the amino-oxygenation of those diene substrates (entries 4, 5, 12 and 13), a significantly smaller ligand **L2** rather than **L1** was applied to favor the *N*-atom radical addition step.

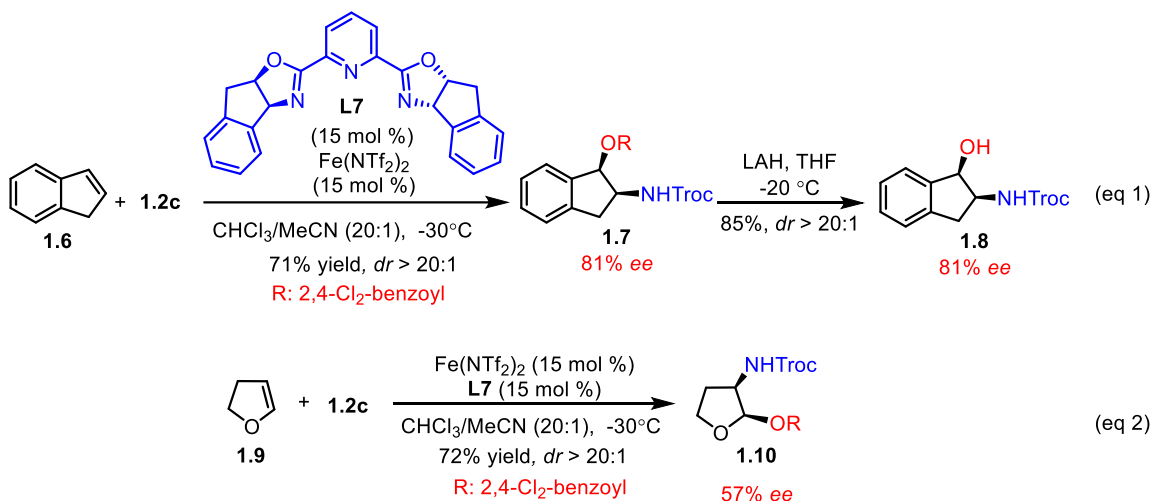
1.2.3 *Asymmetric induction*

One of the goals of this research is to achieve improved or complementary selectivity compared to other existing amino-hydroxylation methods. A good example is indene **1.6** asymmetric amino hydroxylation. Before our research, literature does not have an example of direct enantioselective indene amino-hydroxylation. The osmium-based approaches always provide a pair of racemic 1-, and 2-amino indanol as regio-isomers.^{30,31} To address this limitation, we explored a range of chiral ligands. We discovered that an iron-chiral ligand **L7** complex is uniquely in asymmetric induction for indene amino-oxygenation, which delivers a chiral 2-amino indanol derivative **1.7** with enhanced enantioselectivity (Scheme 1.3, eq 1, 81% *ee*, *dr*>20:1). Interestingly, I isolated a significant amount of unexpected amino-ethoxylation product when the commercially available chloroform solvent was not pre-treated with water before re-distillation.[‡] Presumably, the small amount ethanol residue in solvent participated the reaction as competing nucleophile and generated the undesired amino-ethoxylation product. This observation makes it possible to introduce other external *O*-based nucleophiles to form more diverse amino-oxygenation products. Simple reduction and deprotection will transform **1.7** to a chiral 2-indanol building **1.8** without

[‡] Commercially available anhydrous chloroform contains 0.5-1.0% ethanol as stabilizer.

decreasing its *ee* and *dr*. Notably, compound **1.8** is a valuable chiral building block in many chiral indenyl-derived ligands synthesis.

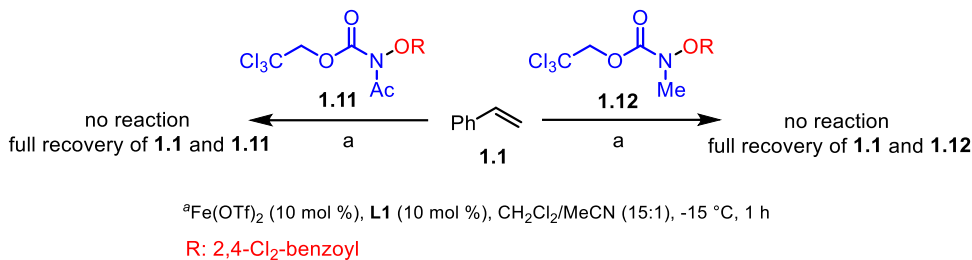
In addition to indene asymmetric amino-hydroxylation, we also observed iron salt-**L7** complex catalyzed asymmetric enol ether amino-oxygenation, which was not reported in the literature. Enantio-enriched 3-amino-tetrahydrofuran-alcohol derivative **1.9** was obtained with moderate enantioselectivity (Scheme 1.3, eq 2, 57% *ee*, *dr*>20:1).



Scheme 1.3 Iron-catalyzed asymmetric olefin amino-oxygenation

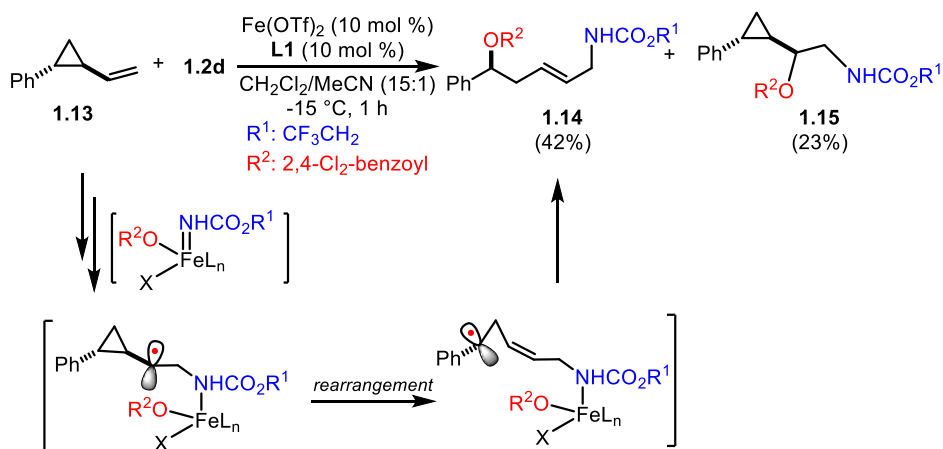
1.2.4 Control experiments that provide mechanistic insights

To better understand this reaction, we have carried out several control experiments to probe the possible mechanisms (Scheme 1.4–Scheme 1.8). First of all, when N-H groups in oxidant **1.2c** were replaced by acetyl (Ac) or methyl (Me) group (**1.11** and **1.12**), neither of them are still reactive under standard reaction conditions (Scheme 1.4). These results suggest that the N–H group in **1.2c** is crucial for its activation.



Scheme 1.4 Amino-oxygenation with N-Ac and N-Me protected acyloxyl carbamates

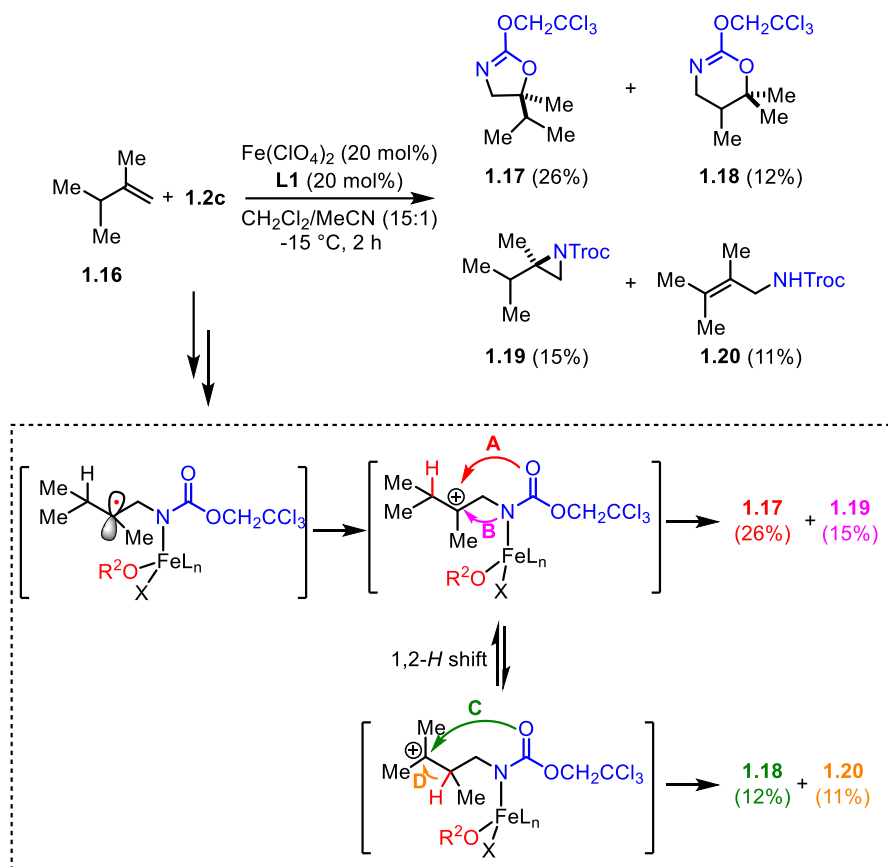
A cyclopropyl-substituted olefin **1.13** is widely used as a radical clock probe in many catalytic reactions to prove the existence of radical species. If the reaction goes through a radical process, once the radical generated, the cyclopropane ring will open due to strain and radical will migrate to the benzylic position. In this case, a ring opened product are expected to form. Under the reaction condition, we observed both ring-opened product **1.14** as well as the direct 1,2-amino-hydroxylation product **1.15** (Scheme 1.5). Isolation of ring opening product **1.14** strongly suggests that the reaction proceeds through a stepwise radical amination pathway.



Scheme 1.5 Iron-catalyzed amino-oxygenation of trans-2-phenyl-1-vinylcyclopropane

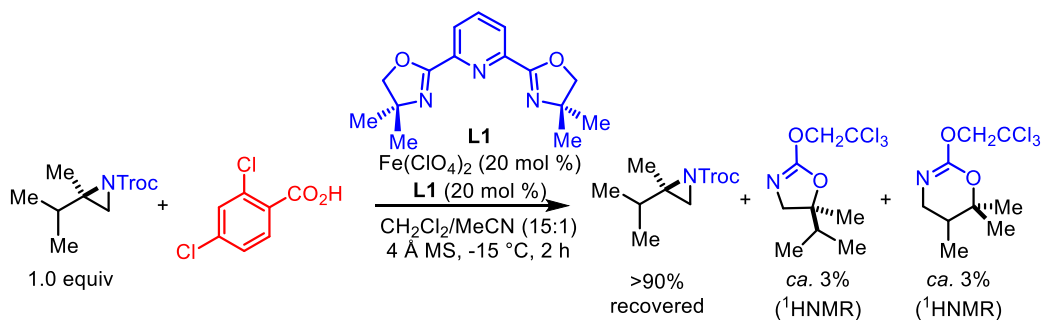
When reaction condition was applied to 2,3-dimethylbutene **1.16**, which is usually used as a carbocation probe, we isolated four products (Scheme 1.6). In addition to the standard cyclic 1,2 amino-oxygenation product **1.17**, we also isolated a 1,3-amino-oxygenation product **1.18**, an aziridine species **1.19**, and *N*-Troc protected allylic amine product **1.20**. In fact, the products **1.18** and **1.20** came from 1,2-hydride shift process after carbocation species was generated at 2-position after the radical amination step. The

presence of 1,2-hydride shift products (**1.18** and **1.20**) indicate that a carbocation intermediate may be involved in the olefin amino-oxygenation process.



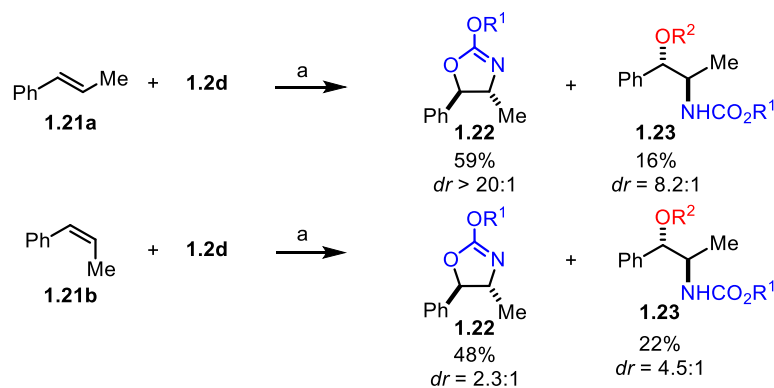
Scheme 1.6 Iron-catalyzed amino-oxygenation of 2,3-dimethyl-1-butene

Importantly, the aziridine **1.19** cannot be converted to any of three other products under the reaction conditions, which indicate that amino-oxygenation products generated from carbocation reactive intermediate rather than an aziridine ring opening pathway. (Scheme 1.7)



Scheme 1.7 Aziridine is not an intermediate in the amino-oxygenation reaction

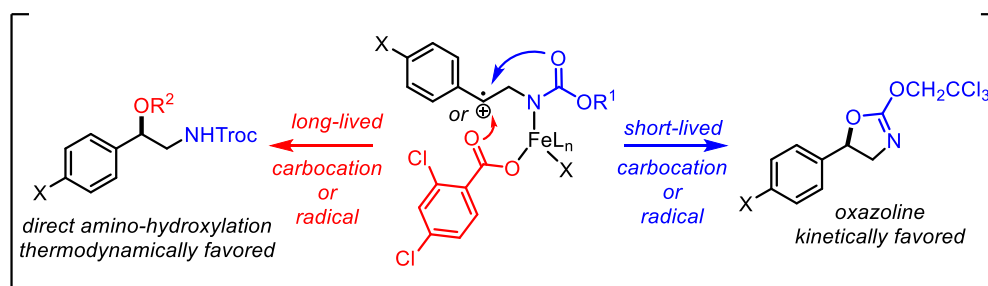
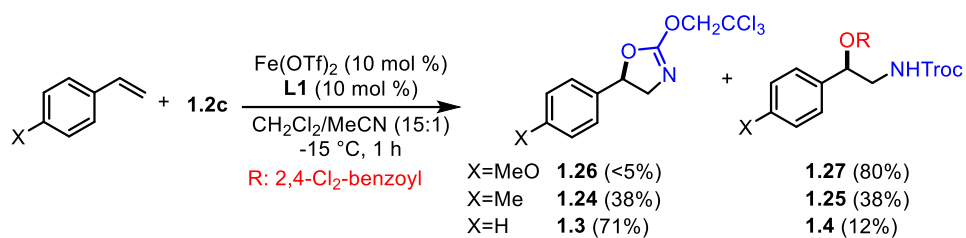
Iron-catalyzed intermolecular amino-oxygenation of *cis/trans* β -methyl styrenes provided some interesting mechanistic insights (Scheme 1.8). The $\text{Fe}(\text{OTf})_2\text{-L2}$ complex has to be used to achieve efficient amino-oxygenation of both *cis/trans* β -methyl styrenes. While the $\text{Fe}(\text{OTf})_2\text{-L1}$ complex will promote undesirable C–H abstraction and decompose the catalyst. There are three observations I want to highlight. First of all, the *trans*-isomer (**1.21a**) is more reactive than its *cis* counterpart (**1.21b**).³² Secondly, better diastereoselectivity was observed in the *trans*- β -methyl styrene (**1.21a**) reaction compared to the *cis* isomer's reaction (**1.21b**). In addition to that, this method offers a significantly improved regioselectivity compared with the osmium-based method.¹ These above-mentioned observations corroborate our initial hypothesis that the amino-oxygenation occurs in a stepwise fashion and the C–N bond formation is more likely the rate-determining step.



^a $\text{Fe}(\text{OTf})_2$ (20 mol%), **L2** (20 mol%), $\text{CH}_2\text{Cl}_2/\text{MeCN}$ (4:1); 0 °C, 2 h. R^1 : CF_3CH_2 ; R^2 : 2,4- Cl_2 -benzoyl.

Scheme 1.8 Iron-catalyzed amino-oxygenation of *cis/trans* β -methyl styrenes

We also observed an interesting product distribution pattern in the styrenyl olefins amino-oxygenation reactions (Scheme 1.9). Electron-rich styrene, such as 4-methoxy styrene, provide an exclusively direct amino-hydroxylation product; while in non-substituted styrene reaction, the cyclized oxazoline became the major product. Presumably, the electron-donating group (such as $\text{X}=\text{OMe}$) will further stabilize the benzylic radical species and allow more time for carboxylate group transfer; while, in the amino-oxygenation reaction of nonsubstituted styrene, the intramolecular cyclization is kinetically favored and affords alkoxy oxazoline as the major product.



Scheme 1.9 Electronic effect on iron-catalyzed amino-oxygenation of styrenes

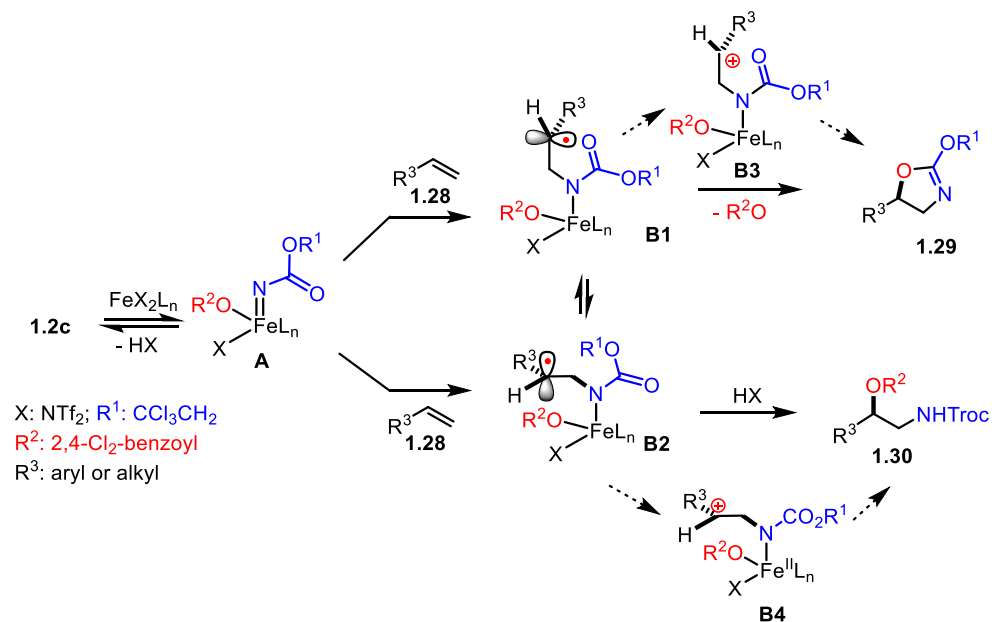
With the experimental evidence obtained, we proposed a mechanistic working hypothesis for this iron-catalyzed intermolecular olefin amino-oxygenation reaction (Scheme 1.10A). First of all, the *N*-*O* bond in oxidant **1.2c** is reductively cleaved by the iron–ligand complex and an iron-nitrenoid **A** was generated. After a stepwise, radical addition process, **A** subsequently added to olefin **1.28** with the formation of a radical species **B1**, which equilibrates with its conformer **B2**. **B1** can be oxidized to a carbocation **B3** by the iron center,^{33,34} presumably through outer-sphere electron transfer. **B3** will go through an intramolecular cyclization and is captured by the neighboring carbamate group to form oxazoline product **1.29**.[§] Similarly, **B2** could also be oxidized by the iron (III) center through one-electron oxidation to generate a carbocation **B4**, which will bond with carboxylate group to generate the direct amino-hydroxylation product **1.30**. It is also possible that **B2** couples with the carboxylate group through inner-sphere carboxylate group transfer to deliver **1.30**.^{**}

[§] For evidence for involvement of a possible carbocation intermediate, see Scheme 1.6.

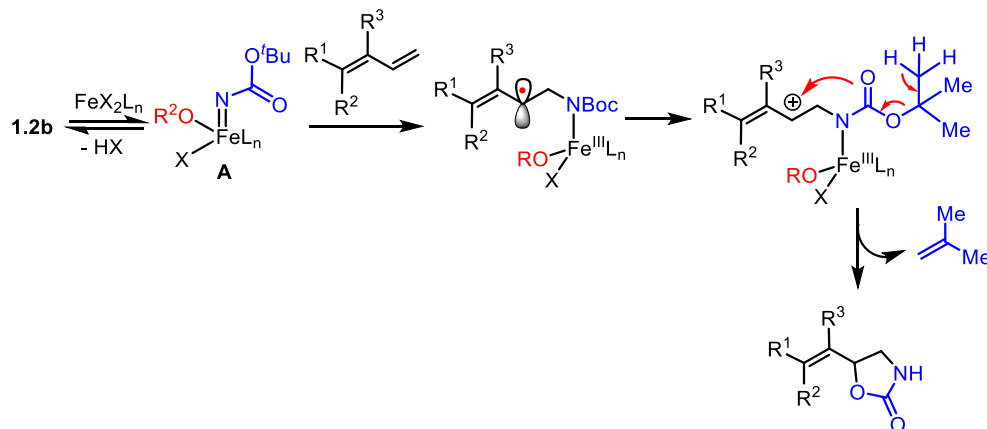
^{**} This hypothesis is supported by the *cis*-configuration of indene amino-oxygenation product.

Mechanism of the iron-catalyzed intermolecular amino-oxygenation of those conjugated diene substrates using *tert*-butoxy carbamate as oxidant (**1.2b**) is a bit different in the last step, which affords oxazolidinone through an intramolecular cyclization and elimination of isobutene (Scheme 1.10B).

A) Plausible mechanism of oxazoline and direct amino-hydroxylation products generation



B) Plausible mechanism for oxazolidinone formation



Scheme 1.10 Mechanistic working hypothesis for the iron-catalyzed olefin amino-oxygenation

1.3 Experimental section^{††}

1.3.1 Materials and general information

Materials: Commercial reagents were purchased from Sigma Aldrich, Fluka, EM Science, and Lancaster and used as received. All solvents were used after being freshly distilled unless otherwise noted.

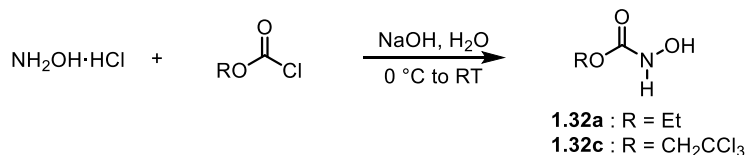
Instrumentation: Proton nuclear magnetic resonance (¹H NMR) spectra, carbon nuclear magnetic resonance (¹³C NMR) spectra and fluorine nuclear magnetic resonance (¹⁹F NMR) were recorded on Bruker UltraShield-400 (400 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak (CHCl₃: δ 7.26). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent (CDCl₃: δ 77.0). Chemical shifts for fluorine are reported in parts per million downfield and are referenced to the fluorine resonances of CFCl₃. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and integration. The mass spectroscopic data were obtained at the Georgia State University mass spectrometry facility using a Micromass Platform II single quadrupole instrument. Infrared (IR) spectra were obtained using a Perkin Elmer Spectrum 100 FT-IR spectrometer. Data are represented as follows: frequency of absorption (cm⁻¹) and absorption strength (s = strong, m = medium, w = weak).

All reactions were performed in oven-dried or flame-dried round-bottom flasks and vials. Stainless steel syringes and cannula were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230-400 mesh) from Sigma–Aldrich.

^{††} (1) compounds characterization spectra are in Appendix A.1; (2) detailed procedures for the complete substrate table can be found in: Lu, D. F.; Zhu, C. -L.; Jia, Z. X.; Xu, H. *J. Am. Chem. Soc.* **2014**, *136*, 13186–13189.

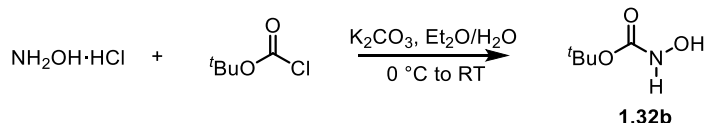
1.3.2 Procedures for amino-oxygenation reagents preparation

A: preparation of *N*-hydroxyl ethyl carbamate **1.32a** and *N*-hydroxyl trichloroethyl carbamate **1.32c**.



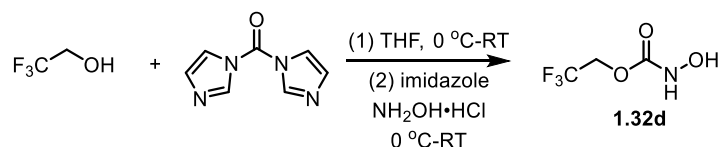
Hydroxylamine hydrochloride (13.9 g, 200 mmol) was added to aqueous solution of NaOH (1.5 M, 160 mL, 240 mmol). The solution was cooled to 0 °C and ethyl or 2,2,2-trichloroethyl chloroformate (38 mmol) was added drop-wise. Upon the completion of addition, the mixture was warmed up to room temperature and stirred for additional 2 h. The reaction was then acidified with aqueous HCl (6 M) till pH is around 4.5. Then the mixture was extracted with Et₂O (200 mL × 3) and the combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After removal of the solvent *in vacuo*, the *N*-hydroxyl carbamate **1.32a** and **1.32c** were used directly for the next step without further purification.

B: preparation of *N*-hydroxyl tert-butyl carbamate **1.32b**.



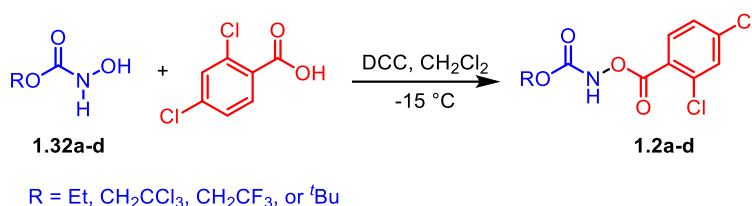
A suspension of NH₂OH·HCl (9.6 g, 0.14 mol, 1.5 equiv) and K₂CO₃ (7.2 g, 0.07 mol, 1.5 equiv) in Et₂O (60 mL) and H₂O (2 mL) was stirred for about 1 h at room temperature with evolution of CO₂ gas. A solution of Boc₂O (20.0 g, 92 mmol) in Et₂O (40 mL) was then added drop-wise at 0 °C and the suspension was stirred at room temperature for 12 h. The organic phase was decanted and the solid was washed with Et₂O (30 mL × 2) and the organic layers were combined and concentrated. Recrystallization with a cyclohexane/toluene mixture afforded the desired product **1.32b**.

C: preparation of *N*-hydroxyl trifluoroethyl carbamate **1.32d**.



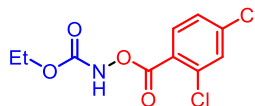
To a flame-dried 100 mL round bottom flask equipped with a stir bar was added CDI (1.78 g, 11 mmol) in anhydrous THF (30 mL). The flask was cooled to 0 °C and trifluoroethanol (0.72 mL, 10 mmol) was added drop-wise. The mixture was stirred for additional 1 h at room temperature and then $\text{NH}_2\text{OH}\cdot\text{HCl}$ (1.04 g, 15 mmol) and imidazole (0.82g, 12 mmol) were added in one portion. The reaction was monitored by TLC, until the starting material disappeared (about 1 h). Then the mixture was filtered and concentrated *in vacuo*. The residue was dissolved in EtOAc (40 mL) and washed with aqueous HCl (1 M, 20 mL \times 3). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford the crude product **S1d** as colorless oil (1.35g, 85% yield), which was used directly for the next step.

D: general procedure for the DCC coupling reaction.



To a 250 mL flame-dried round bottom flask equipped with a stir bar, an *N*-hydroxyl carbamate **1.32 (a-d)**, 20 mmol, 1.0 equiv), 2,4-dichlorobenzoic acid (4.01 g, 21 mmol) and anhydrous CH_2Cl_2 (80 mL) were added. The flask was cooled to -15 °C. DCC (4.53 g, 22 mmol, dissolved in 20 mL of anhydrous CH_2Cl_2) solution was then added drop-wise. The reaction mixture was stirred at the same temperature for additional 30 min until the *N*-hydroxyl carbamate was fully consumed (monitored by TLC). The white precipitate (*N,N'*-dicyclohexylurea) was removed by filtration and the filtrate was concentrated *in vacuo* and dissolved again in Et_2O (30 mL). The solution was cooled to -20 °C for 2 h and filtered again to remove additional precipitate. The organic layer was then concentrated *in vacuo* and the residue was recrystallized from hexanes and EtOAc to afford corresponding acyloxyl carbamate **1.2 (1.2a-d)**, yields 73–76%).

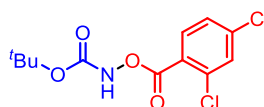
The amino-oxygenation reagent **1.2a** was recrystallized from hexanes/EtOAc as white solid (73% yield, m.p. 71–73 °C).



1.2a

Ethyl (2,4-dichlorobenzoyl)oxycarbamate (1.2a): IR ν_{\max} (neat)/ cm^{-1} : 3230 (m), 2982 (w), 1780 (s), 1709 (s), 1580 (m), 1496 (m), 1472 (m); ^1H NMR (400 MHz, CDCl_3) δ 8.35 (s, 1H), 7.94 (d, $J = 8.4$ Hz, 1H), 7.54 (s, 1H), 7.37 (d, $J = 8.5$ Hz, 1H), 4.31 (q, $J = 7.1$ Hz, 2H), 1.34 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.9, 156.4, 139.9, 135.7, 132.8, 131.3, 127.3, 125.0, 63.1, 14.2; HRMS (ESI, m/z): calcd for $\text{C}_{10}\text{H}_8\text{Cl}_2\text{NO}_4^-$, $[\text{M} - \text{H}^+]$, 275.9836, found 275.9836.

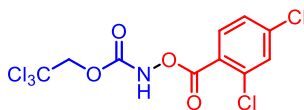
The amino-oxygenation reagent **1.2b** was recrystallized from hexanes/EtOAc as white solid (73% yield, m.p. 48–49 °C).



1.2b

tert-butyl (2,4-dichlorobenzoyl)oxycarbamate (1.2b): IR ν_{\max} (neat)/ cm^{-1} : 3281 (w), 2977 (w), 1772 (m), 1732 (s), 1583 (m), 1469 (m); ^1H NMR (400 MHz, CDCl_3) δ 8.20 (s, 1H), 7.95 (d, $J = 8.4$ Hz, 1H), 7.53 (s, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.1, 155.4, 139.7, 135.6, 132.8, 131.2, 127.3, 125.1, 83.7, 28.0; HRMS (ESI, m/z): calcd for $\text{C}_{12}\text{H}_{12}\text{Cl}_2\text{NO}_4^-$, $[\text{M} - \text{H}^+]$, 304.0149, found 304.0148.

The amino-oxygenation reagent **1.2c** was recrystallized from hexanes/EtOAc as white solid (76% yield, m.p. 85–87°C).

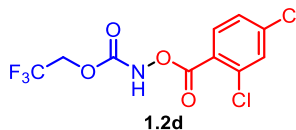


1.2c

2,2,2-Trichloroethyl (2,4-dichlorobenzoyl)oxycarbamate (1.2c): IR ν_{\max} (neat)/ cm^{-1} : 3271 (m), 2957 (w), 1747 (s), 1583 (s), 1556 (w), 1469 (m); ^1H NMR (400 MHz, CDCl_3) δ 8.68 (br, 1H), 7.97 (d, $J = 8.5$ Hz, 1H), 7.55 (s, 1H), 7.38 (d, $J = 8.5$ Hz, 1H), 4.86 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.4, 154.5, 140.3,

136.0, 132.9, 131.4, 127.4, 124.3, 94.3, 75.3; HRMS (ESI, m/z): calcd for $C_{10}H_6Cl_5NNaO_4^+$, $[M + Na^+]$, 401.8632, found 401.8615.

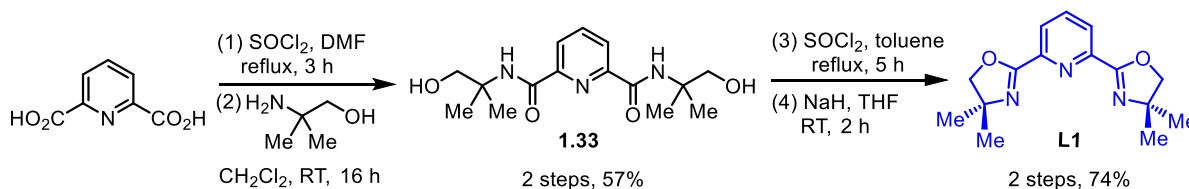
The amino-oxygenation reagent **1.2d** was recrystallized from hexanes/EtOAc as white solid (74% yield, m.p. 80–81°C).



2,2,2-Trifluoroethyl (2,4-dichlorobenzoyl)oxycarbamate (1.2d): IR ν_{max} (neat)/ cm^{-1} : 3230 (m), 2972 (w), 1783 (m), 1735 (s), 1583 (m), 1497 (m); 1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.94 (d, $J = 8.5$ Hz, 1H), 7.56 (d, $J = 1.6$ Hz, 1H), 7.39 (d, $J = 8.5, 1.9$ Hz, 1H), 4.61 (q, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 154.4, 140.3, 136.0, 132.8, 131.5, 127.4, 124.2, 122.4 (q, $J = 277.5$ Hz), 62.1 (q, $J = 37.4$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.10 (t, $J = 8.2$ Hz); HRMS (ESI, m/z): calcd for $C_{10}H_5Cl_2F_3NO_4^-$, $[M - H^+]$, 329.9553, found 329.9552.

1.3.3 Procedures nitrogen-based tri-dentate ligands synthesis

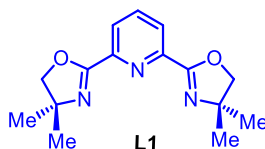
A: the ligand L1 was synthesized according to a modified literature procedure.³⁵



To a 100 mL flame-dried flask charged with a stir bar and a reflux condenser was added 2,6-pyridinedicarboxylic acid (3.34 g, 20 mmol). After the flask was evacuated and backfilled with N_2 twice, $SOCl_2$ (30 mL) and DMF (0.2 mL) were added. The reaction was heated under a reflux condition for 3 h. Then the mixture was cooled to room temperature and concentrated *in vacuo* to afford the 2,6-pyridinedicarbonyl dichloride as a white solid which can be used directly in the next step. Under N_2 atmosphere, to a solution of 2-amino-2-methyl-1-propanol (6.23g, 70 mmol) and Et_3N (10.1g, 100 mmol) in CH_2Cl_2 (70 mL), were added 2,6-pyridinedicarbonyl dichloride in CH_2Cl_2 (30 mL) drop-wise at 0 °C.

After the reaction mixture was stirred at room temperature for 16 h, the mixture was poured into an ice-water mixture (60 mL), which was then extracted with CH₂Cl₂ (60 mL × 3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexanes/acetone: from 10:1 to 1:1) to afford the intermediate **1.33** as a white solid (3.53 g, 57% yield for 2 steps) as a known compound.³⁵

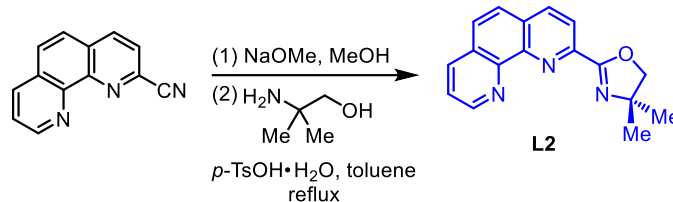
The intermediate **1.33** (3.09 g, 10 mmol) was dissolved in toluene (40 mL) in a 100 mL flame-dried flask charged with a stir bar and a reflux condenser. SOCl₂ (7.14 g, 60 mmol) was added via a syringe and the mixture was heated under a reflux condition. The reaction was monitored with TLC. When the starting material disappeared, the reaction was cooled to 0 °C and quenched with saturated NaHCO₃ solution (30 mL). The organic layer was separated from the aqueous one which was then extracted with EtOAc (30 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was filtered through a short silica gel pad with EtOAc as an eluent and concentrated again. The obtained oil was dissolved in anhydrous THF (50 mL) under N₂ atmosphere and cooled to 0 °C. NaH (2.0 g, 50 mmol, 60% in mineral oil) was added to the solution portion-wise and the whole mixture was then warmed up to room temperature and monitored by TLC until the starting material was fully consumed. The reaction mixture was filtered through a Celite pad, concentrated and purified through a silica gel flash column (hexanes/acetone: from 20:1 to 2:1) to provide the ligand **L1** as a white solid (2.02 g, 74% yield for 2 steps).



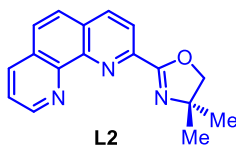
2,6-Bis(4,4-dimethyl-4,5-dihydrooxazol-2-yl)pyridine (L1): ligand **L1** was further purified by recrystallization from a mixture of hexanes/EtOAc (9:1) as a colorless crystalline solid. m.p. 139–141 °C. IR ν_{max} (neat)/cm⁻¹: 3423 (w), 2967 (m), 2927 (w), 2896 (w), 1641 (s), 1573 (s), 1459 (s), 1365 (s), 1302 (s); ¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, *J* = 7.9 Hz, 2H), 7.87 (t, *J* = 7.9 Hz, 1H), 4.24 (s, 4H), 1.42 (s,

12H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.9, 147.0, 137.1, 125.7, 79.8, 68.0, 28.4; HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_{20}\text{N}_3\text{O}_2^+$, $[\text{M} + \text{H}^+]$, 274.1550, found 274.1554.

B: the ligand L2 was synthesized from 2-cyanophenanthroline according to a published procedure.³⁶



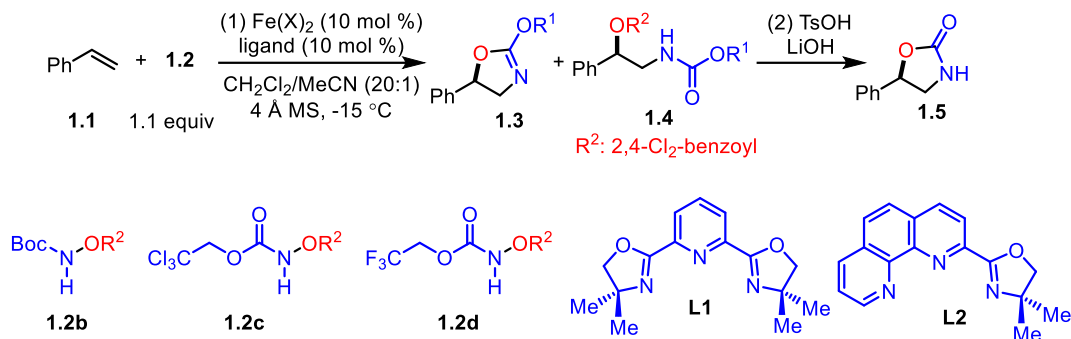
2-Cyanophenanthroline (4.10g, 20 mmol) was dissolved in anhydrous methanol (60 mL) in a flame-dried flask equipped with a stir bar. NaOMe (108 mg, 2 mmol) was added to the reaction. The reaction mixture was stirred at room temperature and monitored with TLC until the starting material was fully consumed. The reaction was then quenched with acetic acid (0.22 mL) and the mixture was filtered and concentrated *in vacuo*. The residue was dissolved in toluene (100 mL) together with 2-amino-2-methyl-1-propanol (1.87 g, 21 mmol) and *p*-TsOH·H₂O (380 mg, 2 mmol). The reaction mixture was then heated under a reflux condition with a Dean–Stark apparatus until the intermediate was consumed. After the reaction was cooled to room temperature, the solvent was removed *in vacuo* and the residue was purified through a silica gel flash column (hexanes/acetone: from 2:1 to 1:2) to afford **L2** as a white solid (3.6g, 65% yield).



4,4-Dimethyl-2-(1,10-phenanthrolin-2-yl)-4,5-dihydrooxazole (L2): ligand **L2** was further purified by recrystallization from a hexanes/EtOAc mixture as a white solid. m.p. 106–108 °C). IR ν_{max} (neat)/ cm^{-1} : 3385 (m), 3223 (m), 2966 (w), 1646 (s), 1493 (m), 1400 (s); ^1H NMR (400 MHz, CDCl_3) δ 9.25 (dd, $J = 4.3, 1.3$ Hz, 1H), 8.43 (d, $J = 8.3$ Hz, 1H), 8.34 (d, $J = 8.3$ Hz, 1H), 8.29 (d, $J = 6.9$ Hz, 1H), 7.86 (q, $J = 8.8$ Hz, 2H), 7.68 (dd, $J = 8.1, 4.4$ Hz, 1H), 4.34 (s, 2H), 1.49 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.7,

150.4, 146.4, 145.9, 145.5, 136.6, 136.2, 129.4, 128.9, 128.0, 126.1, 123.4, 122.7, 79.8, 68.1, 28.5; HRMS (ESI, m/z): calcd for $C_{17}H_{16}N_3O^+$, $[M + H^+]$, 278.1288, found 278.1289.

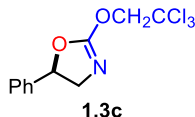
1.3.4 General procedure for the iron-catalyzed intermolecular olefin amino-oxygenation reaction



Step 1: iron-catalyzed olefin amino-oxygenation:

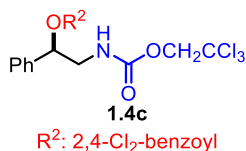
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added an iron salt (0.04 mmol) and a ligand (0.04 mmol). After the vial was evacuated and backfilled with N_2 for three times, anhydrous CH_2Cl_2 (1.0 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stir bar were added freshly activated 4 Å molecular sieves (50 mg) and the corresponding acyloxyl carbamate **1.2** (0.44 mmol). The vial was evacuated and backfilled with N_2 for three times and then anhydrous CH_2Cl_2 (2.8 mL) was added. Both vials were degassed with brief evacuation and backfilling with N_2 twice. Subsequently, freshly distilled styrene **1.1** (46 μL , 0.4 mmol) was added to vial **B** and the catalyst solution in vial **A** was added through a syringe pump over 15 min to vial **B** at $-15\text{ }^\circ\text{C}$. The reaction was kept at this temperature for additional 45 min and quenched with saturated $NaHCO_3$ solution (2 mL). The organic layer was separated from the aqueous one, which was extracted with CH_2Cl_2 (2 mL \times 2) and EtOAc (2 mL \times 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was further purified through a silica gel flash column (hexanes/EtOAc as the eluent) to afford the amino-oxygenation products **1.3** and **1.4**.

Compound **1.3c** was obtained from the reaction of styrene **1.1** with **1.2c** and isolated through a silica gel flash column (hexanes (buffered with 1% TEA)/acetone: from 50:1 to 10:1) as colorless oil (83.7 mg, 71% yield).



5-Phenyl-2-((2,2,2-trichloroethoxy)-4,5-dihydrooxazole (1.3c): IR ν_{max} (neat)/ cm^{-1} : 2952 (w), 2881 (w), 1671 (s), 1396 (s), 1330 (s), 1249 (s); ^1H NMR (400 MHz, CDCl_3) δ 7.49 – 7.33 (m, 5H), 5.74 (t, $J = 8.2$ Hz, 1H), 4.93 (dd, $J = 16.4, 11.6$ Hz, 2H), 4.27 (dd, $J = 12.8, 9.6$ Hz, 1H), 3.82 (dd, $J = 12.9, 7.7$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.6, 139.5, 128.9, 128.7, 125.7, 94.2, 83.2, 79.6, 59.7; HRMS (ESI, m/z): calcd for $\text{C}_{11}\text{H}_{11}\text{Cl}_3\text{NO}_2^+$ [$\text{M} + \text{H}^+$], 293.9850, found 293.9849.

Compound **1.4c** was obtained from the reaction of styrene **1.1** with **1.2c** and isolated through a silica gel flash column (hexanes (buffered with 1% TEA)/acetone: from 50:1 to 10:1) as colorless oil (23.3 mg, 12% yield).



1-Phenyl-2-(((2,2,2-trichloroethoxy)carbonyl)amino)ethyl 2,4-dichlorobenzoate (1.4c): IR ν_{max} (neat)/ cm^{-1} : 3347 (w), 2927 (m), 2851 (w), 1727 (s), 1585 (m), 1522 (m); ^1H NMR (400 MHz, CDCl_3) δ 7.87 (d, $J = 8.4$ Hz, 1H), 7.52 (s, 1H), 7.46 – 7.30 (m, 6H), 6.13 (dd, $J = 7.7, 4.3$ Hz, 1H), 5.29 (brs, 1H), 4.80 – 4.66 (m, 2H), 3.87 – 3.64 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.0, 154.6, 138.8, 136.8, 134.9, 132.9, 131.1, 128.9, 128.8, 127.9, 127.2, 126.6, 95.4, 76.1, 74.6, 46.1; HRMS (ESI, m/z): calcd for $\text{C}_{18}\text{H}_{13}\text{Cl}_5\text{NO}_4^-$ [$\text{M} - \text{H}^+$], 481.9293, found 481.9289.

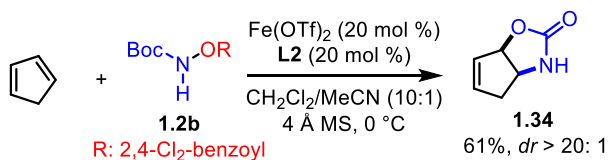
Step 2: hydrolysis:

The mixture of amino-oxygenation products **1.3** and **1.4** were dissolved in THF/H₂O (3:1) mixed solvent (3 mL) and cooled to 4 °C. After the addition of *p*-TsOH·H₂O (38 mg, 0.2 mmol), the reaction was stirred at the same temperature and monitored by TCL until **1.3** was consumed. The reaction mixture was then concentrated *in vacuo*, treated with saturated NaHCO₃ solution (2 mL) and extracted with EtOAc (2 mL× 3). The organic phase was concentrated *in vacuo* and dissolved again in THF/MeOH/H₂O (2:2:1) mixture (3 mL). After addition of LiOH (12 mg, 0.5 mmol), the mixture was stirred at room temperature for 4 h and then quenched by aqueous HCl (1.0 M, 0.6 mL). After concentrated *in vacuo*, the aqueous phase was extracted with EtOAc (2 mL× 3). The combined organic layers were concentrated and purified by column. **1.5** was isolated through a silica gel flash column (hexanes/acetone: from 10:1 to 2:1) as a white solid, which is a known compound.³⁷

1.3.5 Procedures for iron-catalyzed amino-oxygenation of selected olefin substrates

A: procedure for iron-catalyzed amino-oxygenation of cyclopentadiene.

Cyclopentadiene was freshly obtained *via retro*-Diels–Alder reaction by heating commercially available cyclopentadiene dimer above 150 °C.

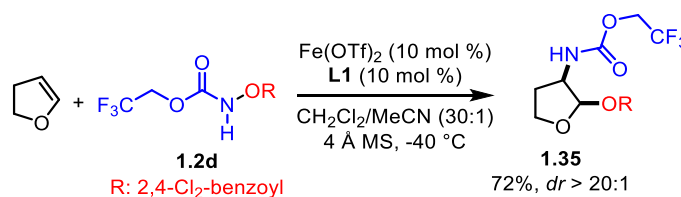


To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added Fe(OTf)₂ (28.3 mg, 0.08 mmol) and **L2** (22.2 mg, 0.08 mmol). After the vial was evacuated and backfilled with N₂ for three times, anhydrous CH₂Cl₂ (0.7 mL) and MeCN (0.5 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To another flame dried 3-dram vial (vial **B**) equipped with a stir bar were added activated 4Å molecular sieves (200 mg) and **1.2b** (122.4 mg, 0.40 mmol). The vial was evacuated and backfilled with N₂ for three times and then anhydrous CH₂Cl₂ (4.8 mL) was added via a syringe. Both solutions were degassed with brief evacuation and backfilling with N₂ twice. Then, freshly distilled 1,3-cyclopentadiene (67.2 μL, 0.8 mmol) was added to vial **B** and the catalyst solution (vial **A**)

was added by a syringe pump over 30 min to vial **B** at 0 °C. The reaction was kept stirring at the same temperature for 12 h until it was completed monitored by TLC. The reaction was quenched with saturated NaHCO₃ aqueous solution (2 mL) and stirred vigorously for additional 10 min. The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (2 mL × 2) and EtOAc (2 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. Product **1.34** was isolated through a silica gel flash column (hexanes/EtOAc: from 4:1 to 1:1) as a white solid (30.5 mg, 61% yield) which is a known compound.³⁸

B: procedure for iron-catalyzed amino-oxygenation of 2,3-dihydrofuran.

2,3-Dihydrofuran is commercially available and it was distilled before usage.



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added Fe(OTf)₂ (14.2 mg, 0.04 mmol) and **L1** (10.9 mg, 0.04 mmol). After the vial was evacuated and backfilled with N₂ for three times, anhydrous CH₂Cl₂ (1.0 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To another flame dried 3-dram vial (vial **B**) equipped with a stir bar were added activated 4Å molecular sieves (200 mg) and **1.2d** (132.8 mg, 0.40 mmol). The vial was evacuated and backfilled with N₂ for three times and then anhydrous CH₂Cl₂ (4.8 mL) was added via a syringe. Both solutions were degassed with brief evacuation and backfilling with N₂ twice. Then, 2,3-dihydrofuran (36.3 μL, 0.48 mmol) was added to vial **B** and the catalyst solution (vial **A**) was added by a syringe pump over 30 min to vial **B** at -40 °C. The reaction was kept stirring at -40 °C for another 1.5 h. The reaction was quenched with saturated NaHCO₃ aqueous solution (2 mL) and stirred vigorously for additional 10 min. The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (2 mL × 2) and EtOAc (2 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. Product **1.35** was isolated through a silica gel flash column (hexanes/EtOAc: from

20:1 to 4:1) as white solid (115.8 mg, 72% yield, m.p. 110–111 °C). Compound **1.35** was recrystallized from EtOAc/hexanes and its stereochemistry was confirmed by X-ray crystallographic analysis (Figure 1.1).

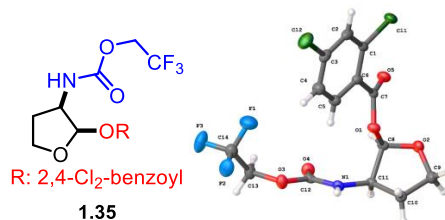
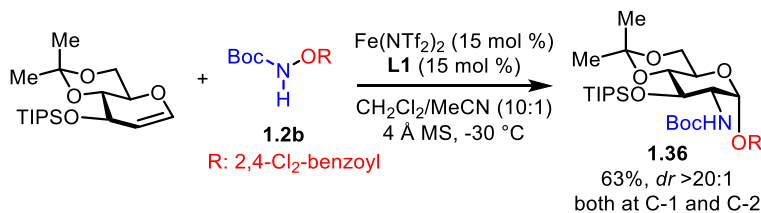


Figure 1.2 X-ray crystal structure of the 2,3-dihydrofuran amino-oxygenation product

3-(((2,2,2-Trifluoroethoxy)carbonyl)amino)tetrahydrofuran-2-yl 2,4-dichlorobenzoate (1.35): IR ν_{max} (neat)/ cm^{-1} : 3347 (w), 2972 (w), 2906 (w), 1724 (s), 1585 (m), 1530 (m); ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, $J = 8.4$ Hz, 1H), 7.51 (s, 1H), 7.40 – 7.31 (m, 1H), 6.44 (d, $J = 4.3$ Hz, 1H), 5.36 (d, $J = 8.9$ Hz, 1H), 4.59 – 4.35 (m, 3H), 4.24 (td, $J = 9.3, 2.5$ Hz, 1H), 4.07 (dd, $J = 16.8, 8.7$ Hz, 1H), 2.52 – 2.40 (m, 1H), 2.08 – 1.92 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.2, 153.8, 139.0, 134.2, 133.2, 131.1, 128.1, 127.4, 122.9 (q, $J = 277.5$ Hz), 96.4, 67.5, 61.2 (q, $J = 36.6$ Hz), 53.5, 28.6; ^{19}F NMR (376 MHz, CDCl_3) δ -74.25 (t, $J = 8.4$ Hz); HRMS (ESI, m/z): calcd for $\text{C}_{14}\text{H}_{12}\text{Cl}_2\text{F}_3\text{NNaO}_5^+$, $[\text{M} + \text{Na}^+]$, 423.9937, found 423.9941.

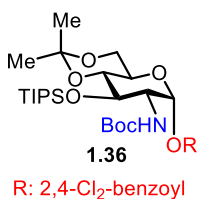
C: procedure for iron-catalyzed amino-oxygenation of D-glucal.

The D-glucal was protected based on a known two-step procedure.³⁹



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{NTf}_2)_2$ (36.9 mg, 0.06 mmol) and **L1** (16.4 mg, 0.06 mmol). After the vial was evacuated and backfilled with N_2 for three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To another flame dried 2-dram vial (vial **B**) equipped with a stir bar

were added activated 4Å molecular sieves (100 mg), protected D-glucal (137.0 mg, 0.4 mmol) and **1.2b** (183.6 mg, 0.60 mmol). The vial was evacuated and backfilled with N₂ for three times and then anhydrous CH₂Cl₂ (1.0 mL) was added via a syringe. Both solutions were degassed with brief evacuation and backfilling with N₂ twice. Then the catalyst solution (vial **A**) was added by a syringe pump over 30 min to vial **B** at -30 °C. The reaction was kept stirring at the same temperature for another 2.5 h. The reaction was quenched with saturated NaHCO₃ aqueous solution (2 mL) and stirred vigorously for additional 10 min. The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (2 mL × 2) and EtOAc (2 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. Product **1.36** was isolated through a silica gel flash column (hexanes/ether: from 10:1 to 4:1) as colorless oil (163.5 mg, 63% yield, [α]_D²⁰ = +88.4 (c 1.0, CH₂Cl₂)).

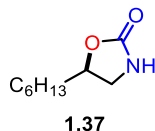


(4aR,6R,7R,8R,8aR)-7-((tert-Butoxycarbonyl)amino)-2,2-dimethyl-8

((triisopropylsilyl)oxy)hexahydroprano[3,2-*d*][1,3]dioxin-6-yl 2,4-dichlorobenzoate (1.36): IR ν_{\max} (neat)/cm⁻¹: 2942 (m), 2866 (m), 1724 (s), 1585, 1499, 1368, 1269, 1130 (s), 982 (s); ¹H NMR (400 MHz, C₆D₆) δ 7.41 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 1.7 Hz, 1H), 6.77 (brd, *J* = 2.5 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 4.87 (d, *J* = 8.7 Hz, 1H), 4.38 (t, *J* = 8.2 Hz, 1H), 4.18 (t, *J* = 9.4 Hz, 1H), 3.88 (td, *J* = 10.1, 5.3 Hz, 1H), 3.70 (dd, *J* = 10.6, 5.1 Hz, 1H), 3.47 (t, *J* = 10.6 Hz, 1H), 3.39 (t, *J* = 9.3 Hz, 1H), 1.42 (s, 9H), 1.36 (s, 3H), 1.21 (d, *J* = 9.1 Hz, 21H), 1.19 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 163.6, 155.0, 139.4, 134.5, 133.8, 131.3, 127.5, 99.7, 94.3, 80.0, 74.6, 71.3, 66.5, 62.0, 55.2, 28.9, 28.3, 18.8, 18.3, 18.2, 12.8; HRMS (ESI, *m/z*): calcd for C₃₀H₄₆Cl₂NO₈Si⁻, [M - H⁺], 646.2375, found 646.2352.

D: procedure for iron-catalyzed amino-oxygenation of 1-octene.

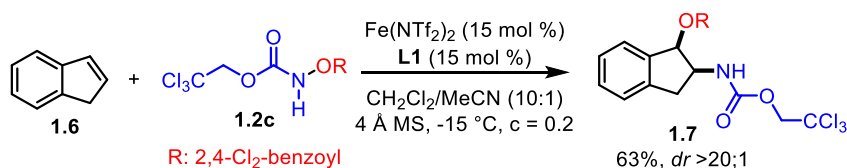
1-Octene is commercially available and it was distilled before usage.



5-Hexyloxazolidin-2-one (1.37): IR ν_{\max} (neat)/ cm^{-1} : 2927 (m), 2856 (w), 1745 (s), 1489 (w), 1264 (w), 1239 (m), 1077 (m); ^1H NMR (400 MHz, CDCl_3) δ 6.04 (brs, 1H), 4.73 – 4.56 (m, 1H), 3.68 (dd, $J = 11.2$, 5.4 Hz, 1H), 3.25 (t, $J = 7.8$ Hz, 1H), 1.86 – 1.75 (m, 1H), 1.72 – 1.59 (m, 1H), 1.53 – 1.43 (m, 1H), 1.42 – 1.24 (m, 7H), 0.90 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.3, 77.2, 46.0, 34.9, 31.6, 28.9, 24.6, 22.5, 14.0; HRMS (ESI, m/z): calcd for $\text{C}_9\text{H}_{18}\text{NO}_2^+$ [$\text{M} + \text{H}^+$], 172.1332, found 172.1324.

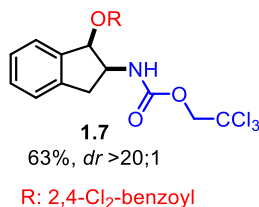
E: procedure for iron-catalyzed amino-oxygenation of indene.

Indene **1.6** is commercially available and it was distilled before usage.



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{NTf}_2)_2$ (36.9 mg, 0.06 mmol) and **L1** (16.4 mg, 0.06 mmol). After the vial was evacuated and backfilled with N_2 for three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To another flame dried 2-dram vial (vial **B**) equipped with a stir bar were added activated 4Å molecular sieves (100 mg) and **1.2c** (182.9 mg, 0.48 mmol). The vial was evacuated and backfilled with N_2 for three times and then anhydrous CH_2Cl_2 (1.0 mL) was added via a syringe. Both solutions were degassed with brief evacuation and backfilling with N_2 twice. Then indene **1.6** (46.6 μL , 0.40 mmol) was added to vial **B** and the catalyst solution (vial **A**) was added by a syringe pump over 30 min to vial **B** at -15 °C. The reaction was kept stirring at the same temperature for another 30 min. The reaction was quenched with saturated NaHCO_3 aqueous solution (2 mL) and stirred vigorously for additional 10 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 mL \times 2) and EtOAc (2 mL \times 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*.

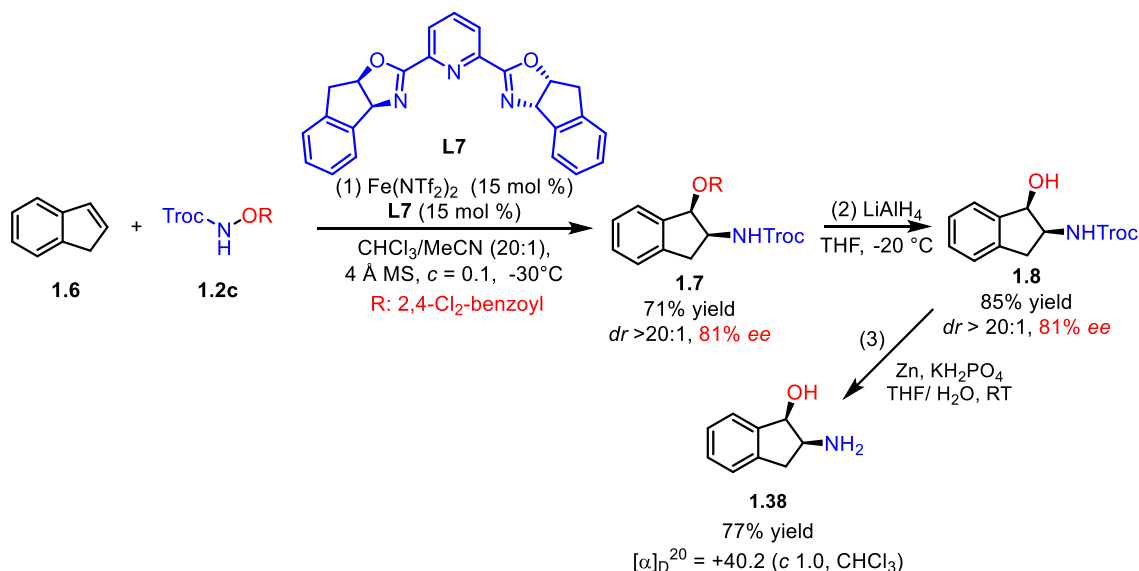
Product **1.7** was isolated through a silica gel flash column (hexanes/Acetone: from = 50:1 to 10:1) as a white solid (125.4 mg, 63% yield, m.p. 130–131 °C).



2-(((2,2,2-Trichloroethoxy)carbonyl)amino)-2,3-dihydro-1H-inden-1-yl 2,4-dichlorobenzoate (1.7):

IR ν_{max} (neat)/cm⁻¹: 3352 (w), 2952 (w), 1717 (w), 1853 (m), 1515 (m); ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.48 (s, 1H), 7.41 – 7.35 (m, 1H), 7.31 (d, *J* = 9.8 Hz, 3H), 6.35 (d, *J* = 5.5 Hz, 1H), 5.66 (d, *J* = 8.6 Hz, 1H), 4.93 – 4.66 (m, 3H), 3.38 (dd, *J* = 15.4, 7.4 Hz, 1H), 3.08 (dd, *J* = 15.5, 8.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 164.5, 154.2, 141.5, 138.7, 138.3, 134.3, 133.0, 131.0, 130.1, 128.4, 127.5, 127.2, 127.1, 125.0, 95.4, 77.9, 74.7, 53.8, 36.9; HRMS (ESI, *m/z*): calcd for C₁₉H₁₄Cl₆NO₄⁻ [M + Cl⁻], 529.9059, found 529.9054.

1.3.6 Procedure for iron-catalyzed asymmetric amino-oxygenation of indene



Step (1): to a flame-dried sealable 2-dram vial (vial A) equipped with a stir bar were added Fe(NTf₂)₂ (36.9 mg, 0.06 mmol) and a chiral ligand **L7** (0.06 mmol). After the vial was evacuated and backfilled with N₂ for three times, anhydrous CHCl₃ (0.8 mL) and MeCN (0.2 mL) were added via a syringe

and the mixture was stirred at room temperature for 20 min. To another flame dried 2-dram vial (vial **B**) equipped with a stir bar were added activated 4Å molecular sieves (100 mg) and **1.2c** (152.4 mg, 0.40 mmol). The vial was evacuated and backfilled with N₂ for three times and then anhydrous CHCl₃ (3.0 mL) was added via a syringe. Both solutions were degassed with brief evacuation and backfilling with N₂ twice. Then indene (55.9 µL, 0.48 mmol) was added to vial **B** and the catalyst solution (vial **A**) was added by a syringe pump over 30 min to vial **B** at -30 °C. The reaction was kept stirring at the same temperature for another 30 min. The reaction was quenched with saturated NaHCO₃ aqueous solution (2 mL) and stirred vigorously for additional 10 min. The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (2 mL × 2) and EtOAc (2 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The product **1.7** was isolated through a silica gel flash column (hexanes/acetone: from 50:1 to 6:1) as a white solid (141.3 mg, 71% yield, *dr* >20:1, 81% *ee*, $[\alpha]_{\text{D}}^{20} = -60.1$ (*c* 1.0, CHCl₃)). The *ee* was measured by Chiral HPLC analysis (Chiral S.S. Whelk, 1.0 mL/min, 254 nm, 5% EtOH in hexanes, *t_r* (minor) = 20.66 min, *t_r* (major) = 24.88 min).

Step (2): compound **1.7** (99.5 mg, 0.20 mmol) was dissolved in anhydrous THF (3 mL) in a 10 mL flask equipped with a stir bar. The flask was cooled to -20 °C and then LiAlH₄ powder (15.2 mg, 0.4 mmol) was added in three portions. The reaction mixture was stirred at the same temperature and monitored by TLC. After about 20 to 30 min, the reaction was quenched with saturated NH₄Cl aqueous solution (1 mL) and aqueous HCl (1M, 2 mL) successively. The whole mixture was filtered through a short Celite pad and concentrated *in vacuo*. The resting aqueous phase was extracted with EtOAc (2 mL × 3) and dried over anhydrous Na₂SO₄. After removal of the solvent, the residue was purified through a silica gel flash column (hexanes/EtOAc: from 6:1 to 2:1) to afford the *N*-Troc-2-aminoindanol **1.8** as a white solid (53.2 mg, 85% yield, *dr* >20:1, m.p. 130–131 °C, 81% *ee*, $[\alpha]_{\text{D}}^{20} = +23.2$ (*c* 1.0, CHCl₃)). The *ee* was determined by Chiral HPLC analysis (Chiral S.S. Whelk, 1.0 mL/min, 265 nm, 15% EtOH in hexanes, *t_r* (major) = 12.24 min, *t_r* (minor) = 16.74 min).^{‡‡}

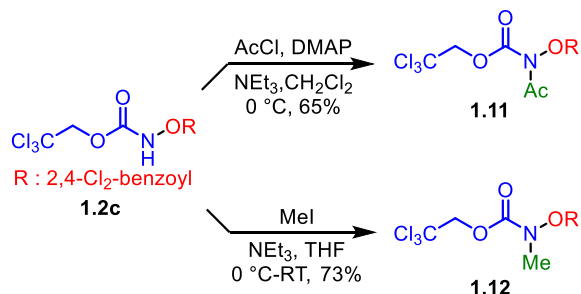
^{‡‡} HPLC trace is in Appendix A.2

2,2,2-Trichloroethyl (1-hydroxy-2,3-dihydro-1*H*-inden-2-yl)carbamate (1.8): IR ν_{max} (neat)/ cm^{-1} : 3412 (m), 2952 (w), 1711 (s), 1507 (s), 1401 (m), 1242 (m), 1110 (m), 1012 (m); ^1H NMR (400 MHz, CDCl_3) δ 7.42 (d, $J = 7.1$ Hz, 1H), 7.37 – 7.19 (m, 3H), 5.79 (d, $J = 7.1$ Hz, 1H), 5.06 (s, 1H), 4.74 (q, $J = 12.0$ Hz, 2H), 4.48 – 4.36 (m, 1H), 3.28 (dd, $J = 15.7, 7.3$ Hz, 1H), 2.94 (dd, $J = 15.8, 7.2$ Hz, 1H), 2.17 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.7, 141.8, 140.8, 129.5, 127.5, 125.3, 125.1, 95.5, 74.6, 74.6, 55.1, 36.7; HRMS (ESI, m/z): calcd for $\text{C}_{12}\text{H}_{11}\text{Cl}_3\text{NO}_3^-$ [$\text{M} - \text{H}^+$], 321.9810, found 321.9807.

Step (3): to a solution of **1.8** (0.15 mmol) and activated Zn powder (245 mg, 3.75 mmol) in THF (2.0 mL) at room temperature was added aqueous KH_2PO_4 (1 M, 0.4 mL). After being stirred for 1 h at room temperature, the mixture was filtrated through a Celite pad, concentrated and purified through a silica gel flash column ($\text{CHCl}_3/\text{MeOH}$: from 20:1 to 10:1), **1.38** was obtained as a white solid (17.2 mg, 77% yield), which is determined to be *syn* by comparing its ^1H NMR data with ones from a known compound.^{40,41}

1.3.7 Procedure for amino-oxygenation of styrene with *N*-Ac and *N*-Me protected acyloxyl carbamates

*A: procedures for preparation of *N*-Ac and *N*-Me protected acyloxyl carbamates.*



*A1: procedure for preparation of *N*-Ac protected acyloxyl carbamate (1.11).*

Acyloxyl carbamate **1.2c** (191 mg, 0.5 mmol) was dissolved in CH_2Cl_2 (3 mL) with DMAP (1.2 mg, 0.01 mmol) and the mixture was cooled to 0 °C. To the above solution, acetyl chloride (43 μL , 0.6 mmol, dissolved in 1 mL CH_2Cl_2) and TEA (83 μL , 0.6 mmol, dissolved in 1 mL CH_2Cl_2) were added dropwise at the same time. The reaction was kept stirring and monitored by TLC. After **2c** was consumed, the white precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was

subsequently purified through a silica gel flash column (hexanes/EtOAc: from 30:1 to 5:1) to afford **1.11** as colorless oil (133 mg, 63% yield).

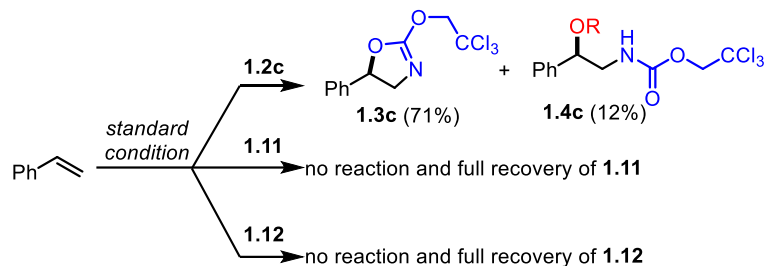
2,2,2-Trichloroethyl acetyl((2,4-dichlorobenzoyl)oxy)carbamate (1.11): IR ν_{\max} (neat)/ cm^{-1} : 3192, 3056, 2973, 1790 (s), 1765 (s), 1740 (s), 1583, 1375, 1295 (s), 1226 (s), 1125 (s), 1074, 1006, 956; ^1H NMR (400 MHz, CDCl_3) δ 8.03 (d, $J = 8.4$ Hz, 1H), 7.56 (s, 1H), 7.39 (d, $J = 8.4$ Hz, 1H), 4.88 (s, 2H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.7, 161.0, 149.8, 140.3, 136.2, 133.1, 131.4, 127.3, 123.9, 93.6, 76.1, 24.8; HRMS (ESI, m/z): calcd for $\text{C}_{12}\text{H}_9\text{Cl}_5\text{NO}_5^+$ [$\text{M} + \text{H}^+$], 421.8918, found 421.8899.

A2: procedure for preparation of N-Me protected acyloxyl carbamate (1.12).

Acyloxyl carbamate **1.2c** (191 mg, 0.5 mmol) was dissolved in THF (3 mL) with iodomethane (51 μL , 1 mmol) and the mixture was cooled to 0 $^\circ\text{C}$. After addition of TEA (70 μL , 0.5 mmol), the reaction was then warmed up to room temperature gradually and kept stirring for another 5 h. The reaction mixture was quenched by 0.5 mL EtOH and concentrated *in vacuo* and the residue was purified through a silica gel flash column (hexanes/EtOAc: from 30:1 to 7:1) to afford **1.12** as colorless oil (144 mg, 73% yield).

2,2,2-Trichloroethyl (2,4-dichlorobenzoyl)oxy(methyl)carbamate (1.12): IR ν_{\max} (neat)/ cm^{-1} : 2982 (w), 1782 (m), 1732 (s), 1583 (m), 1373 (m), 1231 (s), 1160, 1074, 1041, 982; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, $J = 8.4$ Hz, 1H), 7.54 (s, 1H), 7.37 (dd, $J = 8.4, 1.7$ Hz, 1H), 4.81 (s, 2H), 3.50 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.3, 153.7, 139.8, 135.6, 132.7, 131.2, 127.3, 125.1, 94.6, 75.6, 38.0; HRMS (ESI, m/z): calcd for $\text{C}_{11}\text{H}_9\text{Cl}_5\text{NO}_4^+$ [$\text{M} + \text{H}^+$], 393.8969, found 393.8951.

B: procedure for amino-oxygenation of styrene with acyloxyl carbamates 1.11 and 1.12.

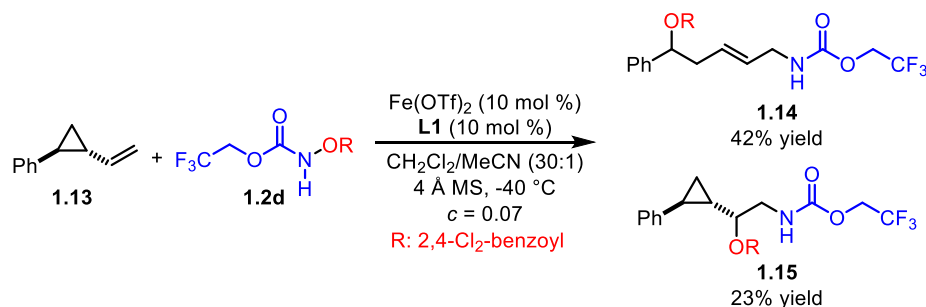


standard condition: Fe(OTf)₂ (10 mol%), L1 (10 mol%), CH₂Cl₂/MeCN (20:1), 4A MS, -15 °C, c = 0.1.
 R: 2,4-Cl₂-benzoyl

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added Fe(OTf)₂ (7.1 mg, 0.02 mmol) and **L1** (5.5 mg, 0.02 mmol). After the vial was evacuated and backfilled with N₂ for three times, anhydrous CH₂Cl₂ (0.5 mL) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 30 min. To another flame dried 2-dram vial (vial **B**) equipped with a stir bar were added activated 4Å molecular sieves (50 mg) and potential amino-oxygenation reagents (0.22 mmol). The vial was evacuated and backfilled with N₂ for three times and then anhydrous CH₂Cl₂ (1.4 mL) was added via a syringe. Both vials were degassed with brief evacuation and backfilling with N₂ twice. Then, freshly distilled styrene (23 uL, 0.2 mmol) was added to vial **B** and the catalyst solution in vial **A** was added with a syringe pump over 30 min to vial **B** at -15 °C. The reaction was kept stirring at the same temperature for another 30 min. Both **1.11** and **1.12** were fully recovered (>95% recovery) under this condition.

1.3.8 Procedure for iron-catalyzed amino-oxygenation of *trans*-2-phenyl-1-vinylcyclopropane

trans-2-Phenyl-1-vinylcyclopropane **1.13** was synthesized according to a literature procedure.⁴²



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added Fe(OTf)₂ (7.1 mg, 0.02 mmol) and **L1** (5.5 mg, 0.02 mmol). After the vial was evacuated and backfilled with N₂ for three

times, anhydrous CH₂Cl₂ (0.5 mL) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To another flame dried 2-dram vial (vial **B**) equipped with a stir bar were added activated 4Å molecular sieves (100 mg) and **1.2d** (66.4 mg, 0.20 mmol). The vial was evacuated and backfilled with N₂ for three times and then anhydrous CH₂Cl₂ (2.4 mL) was added via a syringe. Both solutions were degassed with brief evacuation and backfilling with N₂ twice. Then, *trans*-2-phenyl-1-vinylcyclopropane **1.13** (34.6 mg, 0.24 mmol) was added to vial **B** and the catalyst solution (vial **A**) was added by a syringe pump over 30 min to vial **B** at -40 °C. The reaction was kept stirring at -40 °C for another 30 min. The reaction was quenched with saturated NaHCO₃ aqueous solution (2 mL) and stirred vigorously for additional 10 min. The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (2 mL × 2) and EtOAc (2 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. Ring opening product **1.14** and direct amino-oxygenation product **1.15** were isolated through a flash column (hexanes/EtOAc, from 50:1 to 6:1) in 42% and 23% yield, respectively.

(E)-1-Phenyl-5-(((2,2,2-trifluoroethoxy)carbonyl)amino)pent-3-en-1-yl 2,4-dichlorobenzoate (1.14):

IR ν_{\max} (neat)/cm⁻¹: 3352 (w), 2916 (w), 2846, 1722 (s), 1585, 1517, 1376, 1279 (s), 1241(s), 1163(s), 1100 (m), 1047 (m), 969 (m); ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, *J* = 8.4 Hz, 1H), 7.50 (s, 1H), 7.47 – 7.30 (m, 6H), 6.04 (t, *J* = 6.7 Hz, 1H), 5.71 – 5.47 (m, 2H), 4.84 (s, 1H), 4.45 (q, *J* = 8.5 Hz, 2H), 3.76 (t, *J* = 5.5 Hz, 2H), 2.87 – 2.74 (m, 1H), 2.74 – 2.63 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 164.0, 139.2, 138.5, 134.9, 132.6, 131.1, 129.3, 128.6, 128.3, 128.0, 127.1, 126.6, 123.1 (q, *J* = 277.5 Hz), 60.9 (q, *J* = 36.6 Hz), 42.9, 39.3; ¹⁹F NMR (376 MHz, CDCl₃) δ -74.34 (t, *J* = 8.5 Hz); HRMS (ESI, *m/z*): C₂₁H₁₇Cl₂F₃NO₄ [M - H⁺], 474.0492, found 474.0487.

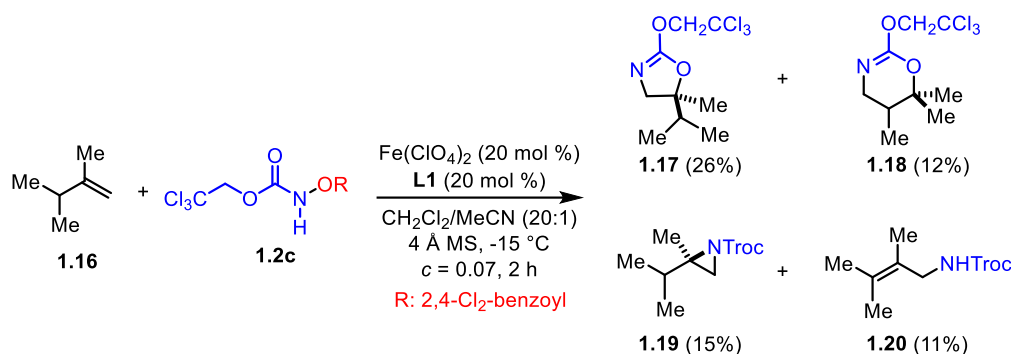
2-Phenylcyclopropyl-2-(((2,2,2-trifluoroethoxy)carbonyl)amino)ethyl 2,4-dichlorobenzoate (1.15): IR

ν_{\max} (neat)/cm⁻¹: 2921 (m), 1727 (s), 1585, 1522, 1375, 1282 (s), 1241, 1168 (s), 1100, 1050; ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, *J* = 8.3 Hz, 1H), 7.53 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 2H), 5.21 (t, *J* = 5.5 Hz, 1H), 4.86 (td, *J* = 8.3, 4.2 Hz, 1H), 4.53 – 4.41 (m, 1H), 4.40 – 4.29 (m, 1H), 3.81 – 3.69 (m, 1H), 3.66 – 3.54 (m, 1H), 2.08 – 1.98 (m, 1H), 1.47 –

1.38 (m, 1H), 1.14 – 1.07 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.7, 154.4, 141.0, 138.6, 134.7, 132.6, 131.1, 128.5, 128.3, 127.2, 126.2, 125.9, 123.0 (q, $J = 277.4$ Hz), 60.9 (q, $J = 36.6$ Hz), 44.7, 29.7, 24.2, 21.4, 14.1; ^{19}F NMR (376 MHz, CDCl_3) δ -74.33 (t, $J = 8.5$ Hz); HRMS (ESI, m/z): $\text{C}_{21}\text{H}_{17}\text{Cl}_2\text{F}_3\text{NO}_4$ [$\text{M} - \text{H}^+$], 474.0492, found 474.0496.

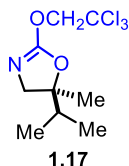
1.3.9 Procedure for the iron-catalyzed amino-oxygenation of 2,3-dimethyl-1-butene

2,3-Dimethyl-1-butene is commercially available and redistilled before usage.



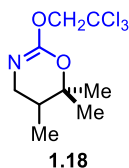
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{ClO}_4)_2$ (20.4 mg, 0.08 mmol), **L1** (21.8 mg, 0.08 mmol) and activated 4Å molecular sieves (40 mg). After the vial was evacuated and backfilled with N_2 for three times, anhydrous CH_2Cl_2 (1.5 mL) and MeCN (0.3 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To another flame dried 3-dram vial (vial **B**) equipped with a stir bar were added activated 4Å molecular sieves (200 mg) and **1.2c** (152.4 mg, 0.40 mmol). The vial was evacuated and backfilled with N_2 for three times and then anhydrous CH_2Cl_2 (4.2 mL) was added via a syringe. Both solutions were degassed with brief evacuation and backfilling with N_2 twice. Then 2,3-dimethyl-1-butene **1.16** (99 μL , 0.8 mmol) was added to vial **B** and the catalyst solution (vial **A**) was added by a syringe pump over 30 min to vial **B** at -15°C . The reaction was kept stirring at the same temperature for 1.5 h until it was completed monitored by TLC. The reaction was quenched with saturated NaHCO_3 aqueous solution (2 mL) and stirred vigorously for additional 10 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 mL \times 2) and EtOAc (2 mL \times 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Four products were isolated through a flash column (hexanes (with 1% TEA)/EtOAc from 50:1 to 10:1).

Compound **1.17** was isolated as colorless oil (28.6 mg, 26% yield).



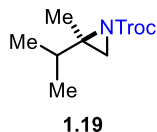
5-iso-Propyl-5-methyl-2-(2,2,2-trichloroethoxy)-4,5-dihydrooxazole (1.17): IR ν_{\max} (neat)/ cm^{-1} : 2967 (w), 2876 (w), 1689 (s), 1449 (w), 1396 (m), 1333 (m); ^1H NMR (400 MHz, CDCl_3) δ 4.90 – 4.77 (m, 2H), 3.68 (d, $J = 12.7$ Hz, 1H), 3.42 (d, $J = 12.7$ Hz, 1H), 2.05 – 1.88 (m, 1H), 1.40 (s, 3H), 0.98 (t, $J = 5.5$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.5, 94.3, 92.2, 79.1, 60.4, 36.2, 22.6, 16.9, 16.8; HRMS (ESI, m/z): calcd for $\text{C}_9\text{H}_{15}\text{Cl}_3\text{NO}_2^+$ [$\text{M} + \text{H}^+$], 274.0163, found 274.0154.

Compound **1.18** was isolated as colorless oil (13.2 mg, 12% yield).



5,6,6-Trimethyl-2-(2,2,2-trichloroethoxy)-5,6-dihydro-4H-1,3-oxazine (1.18): IR ν_{\max} (neat)/ cm^{-1} : 2977 (w), 1686 (s), 1456 (w), 1370 (m), 1279 (s), 1199 (m); ^1H NMR (400 MHz, CDCl_3) δ 4.83 – 4.65 (m, 2H), 3.38 (dd, $J = 15.7, 5.3$ Hz, 1H), 3.06 (dd, $J = 15.7, 10.2$ Hz, 1H), 1.90 – 1.77 (m, 1H), 1.42 (s, 3H), 1.25 (s, 3H), 0.95 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.7, 95.2, 82.1, 76.5, 47.8, 35.6, 27.1, 20.5, 13.4; HRMS (ESI, m/z): calcd for $\text{C}_9\text{H}_{15}\text{Cl}_3\text{NO}_2^+$ [$\text{M} + \text{H}^+$], 274.0163, found 274.0154.

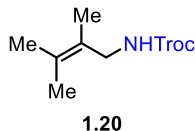
Compound **1.19** was isolated as colorless oil (16.5 mg, 15% yield).



2,2,2-Trichloroethyl 2-isopropyl-2-methylaziridine-1-carboxylate (1.19): IR ν_{\max} (neat)/ cm^{-1} : 2922 (w), 1727 (s), 1378 (m), 1305 (m), 1226 (s), 1135 (m); ^1H NMR (400 MHz, CDCl_3) δ 4.78 (q, $J = 11.9$ Hz, 2H), 2.23 (d, $J = 3.7$ Hz, 2H), 1.56 – 1.45 (m, 1H), 1.07 (d, $J = 6.8$ Hz, 3H), 1.00 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR

(100 MHz, CDCl₃) δ 160.3, 95.1, 75.5, 48.9, 38.1, 34.7, 18.5, 18.2, 15.8; HRMS (ESI, m/z): calcd for C₉H₁₅Cl₃NO₂⁺ [M + H⁺], 274.0163, found 274.0155.

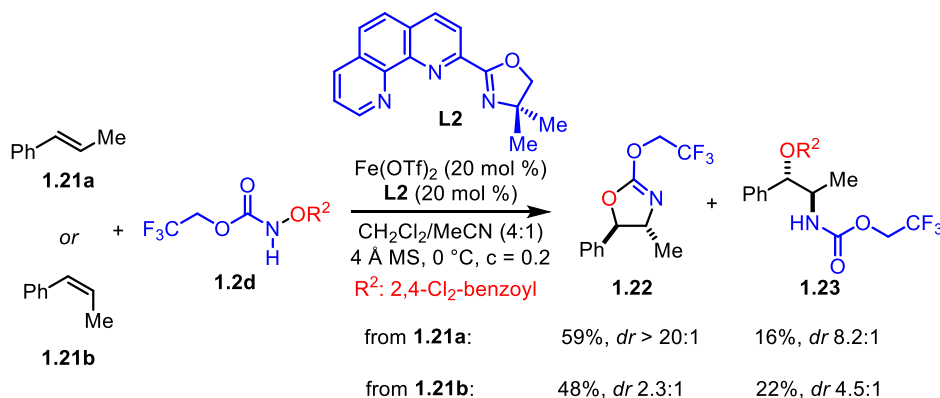
Compound **1.20** isolated as colorless oil (12.1 mg, 11% yield).



2,2,2-Trichloroethyl (2,3-dimethylbut-2-en-1-yl)carbamate (1.20): IR ν_{\max} (neat)/cm⁻¹: 3332 (w), 2916 (w), 1714 (s), 1520 (m), 1489 (w), 1234 (s), 1135 (s); ¹H NMR (400 MHz, CDCl₃) δ 4.86 (brs, 1H), 4.78 (s, 2H), 3.87 (d, *J* = 5.4 Hz, 2H), 1.76 (s, 3H), 1.71 (s, 3H), 1.70 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 154.7, 129.8, 123.7, 95.7, 74.5, 44.0, 20.8, 20.2, 16.9; HRMS (ESI, m/z): calcd for C₉H₁₅Cl₃NO₂⁺ [M + H⁺], 274.0163, found 274.0154.

1.3.10 Procedure for amino-oxygenation of *cis/trans* β -methyl styrenes

Both *trans* (**1.21a**) and *cis* β -methylstyrene (**1.21b**) are commercially available and they were distilled before usage.



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added Fe(OTf)₂ (28.3 mg, 0.08 mmol) and **L2** (22.2 mg, 0.08 mmol). After the vial was evacuated and backfilled with N₂ for three times, anhydrous CH₂Cl₂ (0.7 mL) and MeCN (0.5 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To another flame dried 2-dram vial (vial **B**) equipped with a stir bar were added activated 4 Å molecular sieves (100 mg) and **1.2d** (132.8 mg, 0.40 mmol). The vial was

evacuated and backfilled with N₂ for three times and then anhydrous CH₂Cl₂ (0.8 mL) was added via a syringe. Both solutions were degassed with brief evacuation and backfilling with N₂ twice. Then, **1.21a** or **1.21b** (94.6 mg, 0.8 mmol) was added to vial **B** and the catalyst solution (vial **A**) was added by a syringe pump over 30 min to vial **B** at 0 °C. The reaction was kept stirring at the same temperature until it was completed (another 1.5 h for *trans* and 2.5 h for *cis*). The reaction was quenched with saturated NaHCO₃ aqueous solution (2 mL) and stirred vigorously for additional 10 min. The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (2 mL × 2) and EtOAc (2 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated *in vacuo* and purified through a silica gel flash column (hexanes (with 1% TEA)/acetone: from 50:1 to 10:1)

Compound **1.22-anti** was isolated from the reaction of **1.21a** as colorless oil (61.2 mg, 59% yield).

anti-4-Methyl-5-phenyl-2-(2,2,2-trifluoroethoxy)-4,5-dihydrooxazole (1.22-anti): IR ν_{\max} (neat)/cm⁻¹: 2967 (w), 1761 (s), 1421 (m), 1345 (m), 1264 (s), 1166 (s); ¹H NMR (400 MHz, CDCl₃) δ 7.48 – 7.30 (m, 5H), 5.16 (d, *J* = 7.5 Hz, 1H), 4.67 (q, *J* = 8.0 Hz, 2H), 4.04 (p, *J* = 6.7 Hz, 1H), 1.41 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.5, 138.8, 128.9, 126.7, 125.6, 122.5 (q, *J* = 277.6 Hz), 90.5, 67.7, 66.2 (q, *J* = 37.1 Hz), 21.6; ¹⁹F NMR (377 MHz, CDCl₃) δ -74.26 (t, *J* = 8.2 Hz); HRMS (ESI, *m/z*): calcd for C₁₂H₁₃F₃NO₂⁺ [*M* + H⁺], 260.0893, found 260.0882.

Compound **1.22-syn** was isolated from the reaction of **1.21b** as colorless oil (15.1 mg, 14% yield).

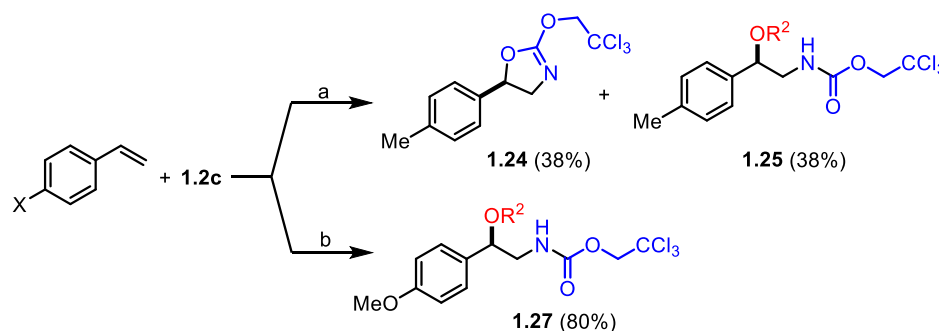
syn-4-Methyl-5-phenyl-2-(2,2,2-trifluoroethoxy)-4,5-dihydrooxazole (1.22-syn): IR ν_{\max} (neat)/cm⁻¹: 2968 (w), 1761 (s), 1421 (m), 1343 (m), 1264 (s), 1167 (s); ¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.31 (m, 3H), 7.31 – 7.19 (m, 2H), 5.84 (d, *J* = 9.1 Hz, 1H), 4.76 – 4.59 (m, 2H), 4.45 (dq, *J* = 13.9, 6.9 Hz, 1H), 0.79 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 161.2, 135.7, 128.4, 128.2, 125.8, 122.5 (d, *J* = 277.3 Hz), 86.3, 66.2 (q, *J* = 37.1 Hz), 62.7, 18.2; ¹⁹F NMR (377 MHz, CDCl₃) δ -74.25 (t, *J* = 8.2 Hz); HRMS (ESI, *m/z*): calcd for C₁₂H₁₃F₃NO₂⁺ [*M* + Na⁺], 260.0893, found 260.0887.

The relative stereochemistry of **1.22-anti** and **1.22-syn** was determined through *NOE* analysis for both diastereomers.

Compound **1.23-anti** was isolated from the reaction of **1.21a** as colorless oil (major diastereomer, 32.0 mg, 16% yield).

anti-1-Phenyl-2-(((2,2,2-trifluoroethoxy)carbonyl)amino)propyl 2,4-dichlorobenzoate (1.23-anti): IR ν_{max} (neat)/ cm^{-1} : 3352 (w), 2977 (w), 1719 (s), 1585 (m), 1520 (m), 1279 (m), 1163 (s); ^1H NMR (400 MHz, CDCl_3) δ 7.93 (d, $J = 8.4$ Hz, 1H), 7.52 (d, $J = 1.6$ Hz, 1H), 7.44 – 7.29 (m, 6H), 6.13 (d, $J = 3.3$ Hz, 1H), 5.12 (d, $J = 9.0$ Hz, 1H), 4.57 – 4.39 (m, 2H), 4.39 – 4.24 (m, 1H), 1.21 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.9, 153.8, 138.8, 136.0, 134.9, 133.1, 131.2, 128.6, 128.5, 127.8, 127.2, 126.6, 79.0, 50.9, 15.7; ^{19}F NMR (377 MHz, CDCl_3) δ -74.25 (t, $J = 8.5$ Hz); HRMS (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{F}_3\text{NNaO}_4^+ [\text{M} + \text{H}^+]$, 472.0301, found 472.0281.

1.3.11 Procedure for iron-catalyzed amino-oxygenation of 4-Me and 4-OMe styrenes



^a $\text{Fe}(\text{OTf})_2$ (10 mol %), **L1** (10 mol %), $\text{CH}_2\text{Cl}_2/\text{MeCN}$ (20:1), 4 Å MS, -15 °C, $c = 0.1$;

^b $\text{Fe}(\text{OTf})_2$ (2.5 mol %), FeCl_2 (2.5 mol %), **L1** (5 mol %), $\text{CH}_2\text{Cl}_2/\text{MeCN}$ (20:1), 4 Å MS, -15 °C, $c = 0.1$;

R^2 : 2,4- Cl_2 -benzoyl

A: procedure for the iron-catalyzed amino-oxygenation of 4-methyl styrene.

4-Methyl styrene was commercially available and it was distilled before usage.

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{OTf})_2$ (14.2 mg, 0.04 mmol) and **L1** (10.9 mg, 0.04 mmol). After the vial was evacuated and backfilled with N_2 for three times, anhydrous CH_2Cl_2 (1.0 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To another flame dried 3-dram vial (vial **B**) equipped with a stir bar were added activated 4Å molecular sieves (100 mg) and **1.2c** (167.6 mg, 0.44 mmol). The vial was evacuated and backfilled with N_2 for three times and then anhydrous CH_2Cl_2 (2.8 mL) was added via a

syringe. Both solutions were degassed with brief evacuation and backfilling with N₂ twice. Then, 4-methyl styrene (52.7 μ L, 0.40 mmol) was added to vial **B** and the catalyst solution (vial **A**) was added by a syringe pump over 30 min to vial **B** at -15 °C. The reaction was kept stirring at the same temperature for another 30 min. The reaction was quenched with saturated NaHCO₃ aqueous solution (2 mL) and stirred vigorously for additional 10 min. The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (2 mL \times 2) and EtOAc (2 mL \times 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*.

Product **1.24** was isolated through a silica gel flash column (hexanes (with 1% TEA)/acetone from 50:1 to 10:1) as colorless oil (46.9 mg, 38% yield).

5-(*p*-Tolyl)-2-(2,2,2-trichloroethoxy)-4,5-dihydrooxazole (1.24): IR ν_{\max} (neat)/cm⁻¹: 2951 (w), 2921 (m), 1667 (s), 1396 (s), 1328 (s); ¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.16 (m, 4H), 5.71 (t, *J* = 8.6 Hz, 1H), 5.01 – 4.83 (m, 2H), 4.24 (dd, *J* = 12.4, 10.0 Hz, 1H), 3.81 (dd, *J* = 12.9, 7.8 Hz, 1H), 2.38 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 161.7, 138.7, 136.4, 129.5, 125.8, 94.2, 83.3, 79.5, 59.6, 21.2; HRMS (ESI, *m/z*): calcd for C₁₂H₁₃Cl₃NO₂⁺ [*M* + H⁺], 308.0006, found 307.9999.

Product **1.25** was isolated through a silica gel flash column (hexanes (with 1% TEA)/acetone from 50:1 to 10:1) as colorless oil (75.9 mg, 38% yield).

1-(*p*-Tolyl)-2-(((2,2,2-trifluoroethoxy)carbonyl)amino)ethyl 2,4-dichlorobenzoate (1.25): IR ν_{\max} (neat)/cm⁻¹: 3352 (w), 2947 (w), 2921 (w), 1719 (s), 1953 (m), 1515 (m); ¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.39 – 7.30 (m, 3H), 7.22 (d, *J* = 7.9 Hz, 2H), 6.09 (dd, *J* = 7.4, 4.7 Hz, 1H), 5.31 (t, *J* = 4.7 Hz, 1H), 4.78 – 4.69 (m, 2H), 3.86 – 3.66 (m, 2H), 2.37 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 164.0, 154.6, 138.7, 138.7, 134.9, 133.8, 132.9, 131.1, 129.6, 128.0, 127.2, 126.6, 95.5, 76.0, 74.6, 46.0, 21.2; HRMS (ESI, *m/z*): calcd for C₁₉H₁₆Cl₂NNaO₄⁺ [*M* + Na⁺], 519.9414, found 519.9405.

B: procedure for the iron-catalyzed amino-oxygenation of 4-methoxyl styrene.

4-Methoxyl styrene is commercially available and it was distilled before usage.

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added Fe(OTf)₂ (3.5 mg, 0.01 mmol), FeCl₂ (1.3 mg, 0.01 mmol) and **L1** (5.5 mg, 0.02 mmol). After the vial was evacuated and backfilled with N₂ for three times, anhydrous CH₂Cl₂ (1.0 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min and then 4-methoxyl styrene (53.9 μL, 0.40 mmol) was added to it. To another flame dried 2-dram vial (vial **B**) equipped with a stir bar were added activated 4Å molecular sieves (100 mg) and **1.2c** (167.6 mg, 0.44 mmol). The vial was evacuated and backfilled with N₂ for three times and then anhydrous CH₂Cl₂ (2.8 mL) was added via a syringe. Both solutions were degassed with brief evacuation and backfilling with N₂ twice. Then the solution in vial **A** was added by a syringe pump over 30 min to vial **B** at -15 °C. The reaction was kept stirring at the same temperature for another 30 min. The reaction was quenched with saturated NaHCO₃ aqueous solution (2 mL) and stirred vigorously for additional 10 min. The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (2 mL × 2) and EtOAc (2 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated *in vacuo*.

Product **1.27** was isolated through silica gel flash column (hexanes: EtOAc = 30:1 to 5:1) as colorless oil (165.0 mg, 80% yield).

1-(4-Methoxyphenyl)-2-(((2,2,2-trifluoroethoxy)carbonyl)amino)ethyl 2,4-dichlorobenzoate (1.27):
 IR ν_{\max} (neat)/cm⁻¹: 3362 (w), 2952 (w), 1724 (s), 1583 (m), 1512 (s); ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 0.8 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.08 (t, *J* = 6.1 Hz, 1H), 5.35 (t, *J* = 5.6 Hz, 1H), 4.78 – 4.68 (m, 2H), 3.82 (s, 3H), 3.75 (t, *J* = 6.1 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 164.0, 159.9, 154.6, 138.7, 134.9, 132.9, 131.1, 128.8, 128.2, 127.2, 114.2, 95.5, 75.8, 74.6, 55.3, 45.9; HRMS (ESI, *m/z*): calcd for C₁₉H₁₆Cl₅NNaO₅⁺ [*M* + Na⁺], 535.9363,

1.4 Conclusion

We developed an iron-catalyzed intermolecular olefin amino-oxygenation method, which does not occur under our previously reported intramolecular conditions. With the exploration of a range of iron salts, ligands as well as oxidants (the amination reagents), we achieved a fine balance between the catalyst stability and reactivity. We also observed that non-coordinating counter ions and bulky nitrogen-based tridentate ligands are indispensable for the reaction and the protecting groups of hydroxylamine is crucial to its reactivity. This method is compatible with a broad range of synthetically valuable olefins including those that are incompatible with the existing amino-hydroxylation methods, such as cyclopentadienes, enol ethers, glycols, indene, and allyl silanes. It can effectively afford amino alcohol derivatives with regio- and stereochemical selectivity complementary to existing methods. The potential practical application of this new catalytic method was demonstrated by the gram-scale reactions of indene and glycol, which afford the valuable vicinal amino alcohol derivatives with very good yield and excellent stereoselectivity. Our preliminary mechanistic studies suggest that an iron-nitrenoid is a possible reactive intermediate, and this transformation goes through a stepwise, radical amination pathway.

2 IRON(II)-CATALYZED INTERMOLECULAR AMINOFLUORINATION OF OLEFINS^{§§}

Abstract

In this chapter, an iron-catalyzed intermolecular olefin aminofluorination method using nucleophilic fluoride ion will be discussed.^{***} Alike the intermolecular olefin amino-oxygenation method in Chapter 1, this method tolerates a broad range of unfunctionalized olefins, including styrenyl olefins and non-styrenyl olefins. With comparison to other existing olefin aminofluorination methods, this new approach has its advantage in broader substrate scope, complementary regio-selectivity and less expensive catalyst. With this method, vicinal fluoro carbamates with fluorine at the internal position can be achieved from simplest olefin precursors in a straightforward way. Our preliminary mechanistic studies suggest that it goes through a stepwise radical amination pathway with both an iron-nitrenoid and carbocation species as reactive intermediates.

2.1 Introduction

Introducing fluorine atoms to drug molecules will change their biological activities dramatically. Intermolecular olefin aminofluorination reactions are particularly useful because it can directly convert simple olefin starting materials to vicinal fluoro primary amines that are important structural motifs in many pharmaceuticals and biological probes (Figure 2.1).⁴³ In particular, intermolecular olefin difunctionalization via fluorine atom transfer represents a convenient approach to synthesize these high-value building blocks with fluorine-containing stereogenic centers.⁴⁴⁻⁵¹ Among a variety of olefin fluorination reactions, the intermolecular aminofluorination of unfunctionalized olefins is of great importance since it can readily deliver vicinal fluoro primary amines that are valuable building blocks in medicinal chemistry.⁵²

^{§§} This chemistry was carried out with collaboration with the following co-workers: Lu, D.F. and Sears, J. D.

^{***} Contents in this chapter were published in: Lu, D.-F.; Zhu, C.-L.; Sears, J. D.; Xu, H. *J. Am. Chem. Soc.* **2016**, *138*, 11360–11367.

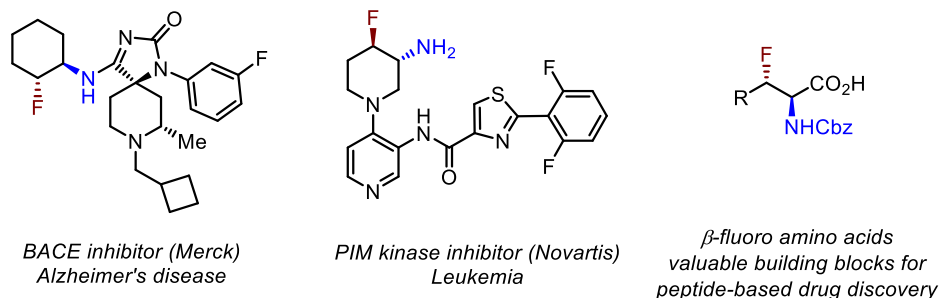
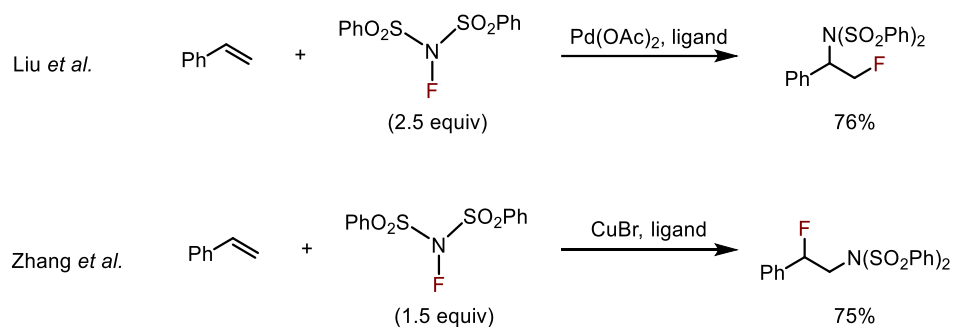


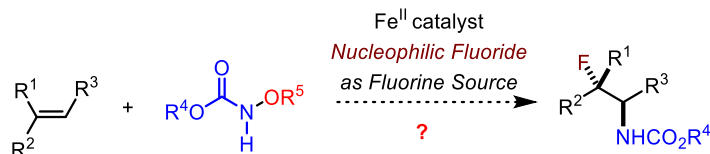
Figure 2.1 Fluoro amines and fluoro amino acids as biological probes

Due to their significant advantages, olefin aminofluorination reactions attracted great attention and a few methods were reported in the literature. However most of them use electrophilic fluorine source and were exclusively compatible with styrenyl olefins.⁵³⁻⁵⁸ Among these strategies, Liu reported a palladium-catalyzed styrene aminofluorination using electrophilic NFSI, which affords terminal sulfonamido fluorides;⁵⁴ the same group later documented a related styrene aminofluorination using AgF that provides sulfonamido fluorides with fluorine at the internal position.⁵⁶ Zhang reported a copper-catalyzed styrene aminofluorination with NFSI, which affords the same internal sulfonamide fluorides as Liu's method with AF (Scheme 2.1).



Scheme 2.1 Existing intermolecular olefin aminofluorination methods with electrophilic fluorine species

In spite of these exiting strategies with electrophilic fluorine source, a catalytic amino-fluorination method for unfunctionalized olefins with nucleophilic fluorine donors is highly desirable (Scheme 2.2).



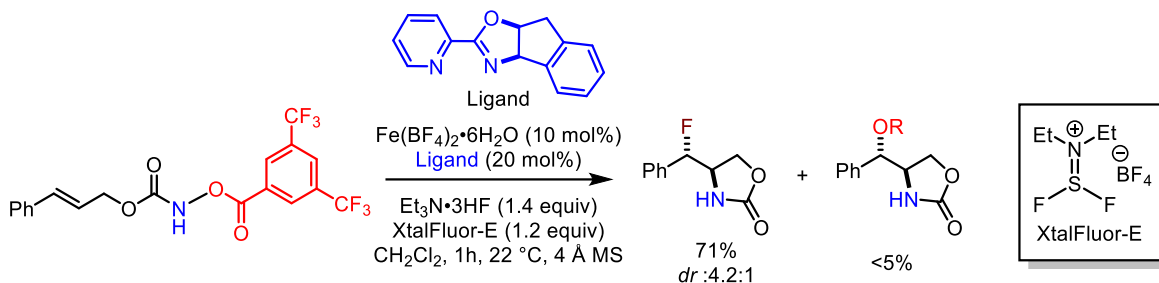
Scheme 2.2 Proposed iron-catalyzed intermolecular olefin aminofluorination using fluoride ion

This new aminofluorination approach are expected to have two obvious advantages compared to other existing methods: first, it affords vicinal fluoro primary amines directly from simplest unfunctionalized olefin precursors; additionally, this method is potentially applicable in ^{18}F PET imaging, considering the only readily available radioactive fluorine source is K^{18}F with weakly nucleophilic fluoride.

Built upon our success in both *intra* and *intermolecular* olefin amino-oxygenation reactions, we wanted to extend this iron-catalyzed olefin difunctionalization methodology to aminofluorination reaction.

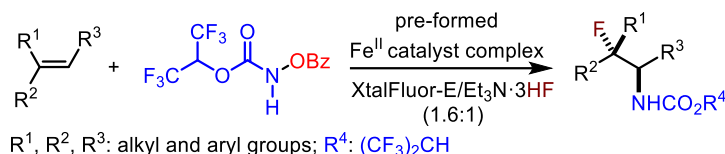
However, the development of an iron-catalyzed intermolecular olefin aminofluorination reaction with nucleophilic fluoride donor is challenging. First of all, due to the strong Fe–F bond, it is unlikely that fluoride can be transferred from the highly stable Fe–F bond.^{59†††} Secondly, those nucleophilic fluoride sources that are compatible with iron catalysis are usually weak nucleophiles.⁶⁰ Regardless those difficulties, our group have discovered an efficient iron-catalyzed intramolecular aminofluorination of olefins with functionalized hydroxylamines (Scheme 2.3). In this reaction, $\text{Et}_3\text{N}\cdot 3\text{HF}$ was used as nucleophilic fluoride source and XtalFluor-E was applied to trap the carboxylate group (3,5-*bis*(trifluoromethyl)-benzoyl) generated after N–O bond cleavage to suppress the competing aminohydroxylation side-reactions.²⁶ Although XtalFluor-E was reported to be fluorine sources in some other deoxy-fluorination reactions, itself alone cannot deliver fluorine to olefins in this iron-catalyzed aminofluorination reaction.

††† BDE for Fe–F is 107 kcal/mol, while BDEs for Fe–Cl and Fe–Br are 80 and 58 kcal/mol, respectively.



Scheme 2.3 Iron-catalyzed intramolecular olefin aminofluorination

In this chapter, a more challenging *intermolecular* olefin aminofluorination based on redox iron catalysis and N–O bond cleavage with nucleophilic fluoride ion is described (Scheme 2.4).

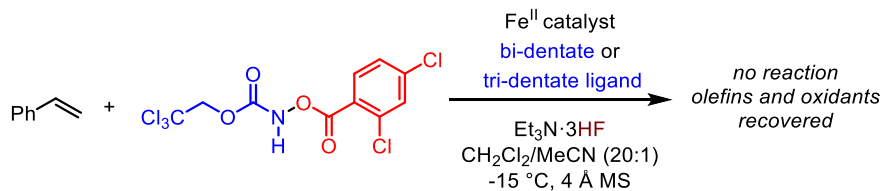


Scheme 2.4 Iron-catalyzed intermolecular olefin aminofluorination using fluoride ion

2.2 Results and discussions

2.2.1 Unsuccessful attempts for intermolecular olefin aminofluorination

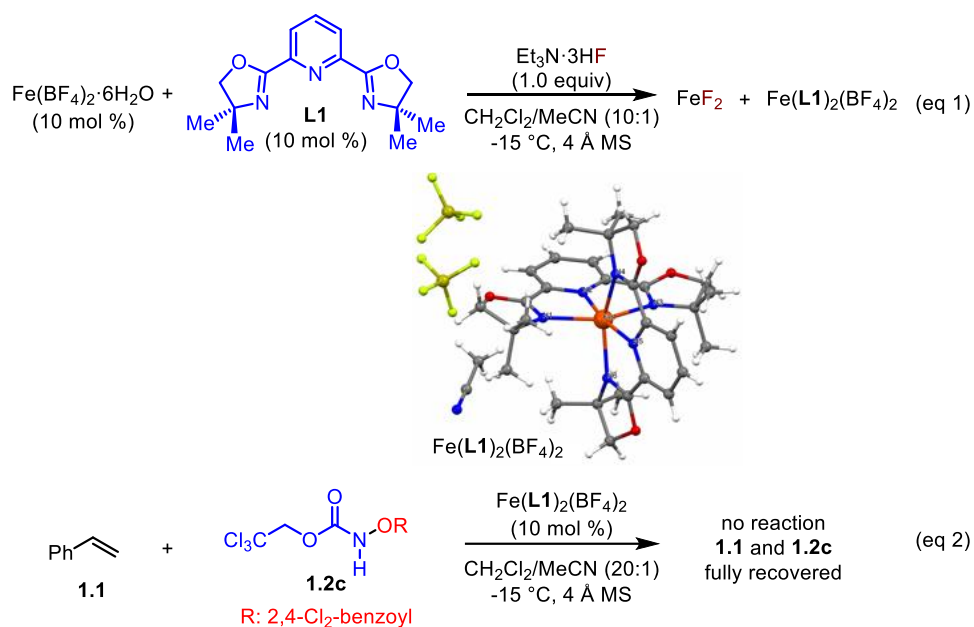
Inspired by our previous discovery in iron-catalyzed *intramolecular* aminofluorination and *intermolecular* amino-oxygenation, we simply combined both reaction conditions to do the *intermolecular* aminofluorination. When the oxidant, catalyst and ligand that are used in the *intermolecular* amino-oxygenation and the fluorine source in the *intramolecular* aminofluorination were applied to styrene, no reaction was observed and both olefin and oxidants were recovered. This nonproductive outcome indicates that the catalysts are unable to promote the desired *intermolecular* olefin aminofluorination under the reaction condition described above (Scheme 2.5).



Scheme 2.5 Early unsuccessful attempts for intermolecular olefin aminofluorination

2.2.2 Fluoride-induced catalyst deactivation

To find out the possible reason of catalyst deactivation under the initial reaction conditions, a few control experiments were carried out (Scheme 2.6). When we mixed $\text{Fe}(\text{BF}_4)_2$ catalyst and **L1** ligand in the presence of nucleophilic fluorine source $\text{Et}_3\text{N}\cdot 3\text{HF}$, two compounds were isolated from this system (Scheme 2.6, eq 1). One is insoluble FeF_2 species and it is unlikely that FeF_2 can transfer fluoride by breaking the strong Fe–F bond. The other iron complex was recrystallized from EtOAc/hexanes mixed solvents and was analyzed by X-ray crystallography. Its crystal structure was determined to be $\text{Fe}(\text{L1})_2(\text{BF}_4)_2$, in which the iron center hexa-coordinated with two ligands. Further experiments showed that this $\text{Fe}(\text{L1})_2(\text{BF}_4)_2$ complex was unable to catalyze known styrene aminohydroxylation reaction. This result suggests that the iron catalyst was deactivated by the nucleophilic $\text{Et}_3\text{N}\cdot 3\text{HF}$.



Scheme 2.6 Fluoride-induced catalyst deactivation

2.2.3 Discovery of the intermolecular olefin aminofluorination reaction

Styrene was selected as a model substrate and the same catalyst as well as oxidant in the *intermolecular* amino-oxygenation were used to explore the *intermolecular* olefin aminofluorination reaction (Table 2.1). Since we observed significant XtalFluor-E effect in *intramolecular* olefin aminofluorination reaction, it was added to this *intermolecular* reaction system as the same amount as the

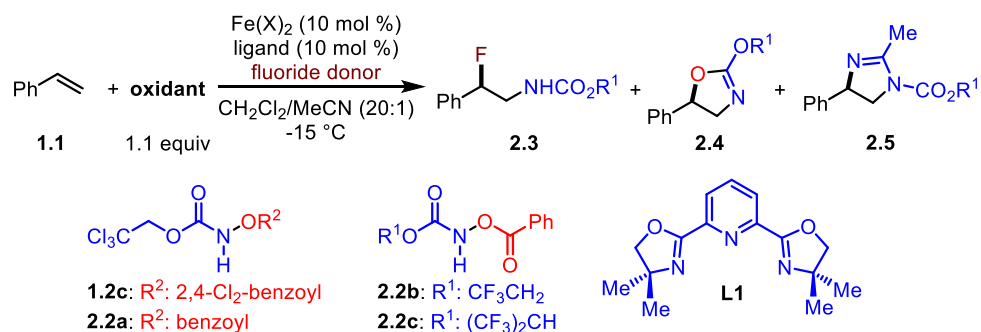
fluorine source ($\text{Et}_3\text{N}\cdot 3\text{HF}$). The desired aminofluorination product, vicinal amino fluoride **2.3**, was isolated for the first time although in a low yield (16%), together with the competing amino-oxygenation oxazoline product **2.4** (entry 1). In addition, it is not a surprise that the iron catalyst is necessary to facilitate this transformation (entry 2).

With one more equivalent of XtalFluor-E, we observed a higher yield of desired fluorination product **2.3**, but at the same time, an undesired side product imidazoline **2.5** was also detected (entry 3). The overall mass balance under the condition of entry 3 is approximately 70% with the excessive oxidant consumed. We suspected that the oxidant **1.2c** was too reactive and decomposed rapidly under reaction condition.

When **1.2c** was replaced with less oxidative **2.2a**, the reaction afforded the desired aminofluorination product in a comparable yield, but with a better mass balance (entry 4). Further increasing the XtalFluor-E loading resulted in a decreased yield of desired fluorination product (entry 5). Notably, no desired product was observed in the absence of $\text{Et}_3\text{N}\cdot 3\text{HF}$ (entry 6).

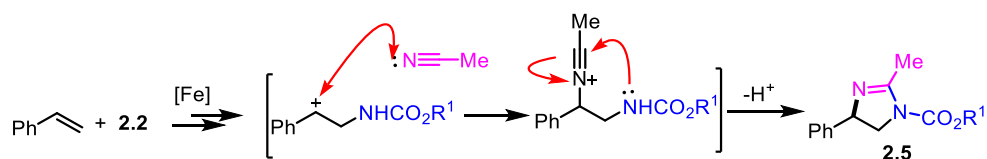
This reaction affords both **2.3** and **2.4** efficiently when trichloroethoxy carbamate **2.2a** was replaced by the more electrophilic trifluoroethoxy carbamate **2.2b** (entry 7). To disfavor the formation of undesired oxazoline **2.4**, the trifluoroethyl group was replaced with hexafluoroisopropyl group and we observed a significantly improved yield of desired aminofluorination product (entry 8). Higher loading of XtalFluor-E and $\text{Et}_3\text{N}\cdot 3\text{HF}$ is beneficial to the yield of desired fluorination product (entry 9, 81% yield).

Table 2.1 Reaction discovery for the iron-catalyzed intermolecular olefin amino-fluorination



entry	Fe(X) ₂	ligand	oxidant	Et ₃ N·3HF (equiv)	XtalFluor-E (equiv)	yield (3)	yield (4)	yield (5)
1	Fe(NTf ₂) ₂	L1	1.2c	1.5	1.5	16%	30%	<5%
2	none	-	1.2c	1.5	1.5	-	-	-
3	Fe(NTf ₂) ₂	L1	1.2c	1.5	2.5	42%	17%	8%
4	Fe(NTf ₂) ₂	L1	2.2a	1.5	2.5	45%	23%	7%
5	Fe(NTf ₂) ₂	L1	2.2a	1.5	3.0	23%	52%	10%
6	Fe(NTf ₂) ₂	L1	2.2a	none	1.5	-	-	50%
7	Fe(NTf ₂) ₂	L1	2.2b	1.5	2.5	46%	44%	9%
8	Fe(NTf ₂) ₂	L1	2.2c	1.5	2.5	73%	<5%	8%
9	Fe(NTf ₂) ₂	L1	2.2c	2.4	4.0	81%	<5%	11%
10	Fe(L1)(BF ₄) ₂ (MeCN)(H ₂ O) ₂	-	2.2c	1.5	2.5	88%	<5%	<5%

Presumably, the side product **2.5** was generated from MeCN (co-solvent) participated Ritter-type reaction, which is believed to go through a carbocation intermediate (Scheme 2.8).

Scheme 2.7 Mechanism of the CH₃CN involved Ritter-type reaction

To suppress the MeCN incorporated side-reaction, a preformed orange-red crystalline *iron-ligand solid complex* (**cat. 1**) was prepared (see experimental section for preparation). To our surprise, **cat. 1** can catalyze styrene aminofluorination effectively in the absence of the MeCN. Aminofluorination product **2.3** was isolated in excellent yield with minimal amount of side products **2.4** and **2.5** (Table 2.1, entry 10, 88%). X-ray analysis reveals that the crystal structure of **cat. 1** is Fe(L1)(MeCN)(H₂O)₂(BF₄)₂, in which the iron

center coordinated with one ligand, two H₂O molecules and one MeCN molecule (Figure 2.2). Presumably, in the reaction process, H₂O and MeCN disassociate from the iron center and leave it open for the iron-nitrene generation. For comparison, in the aforementioned catalytically inactive iron complex Fe(L1)₂(BF₄)₂ (Scheme 2.6), the iron center is fully occupied by two ligands, in which case the iron-nitrene generation is prohibited.

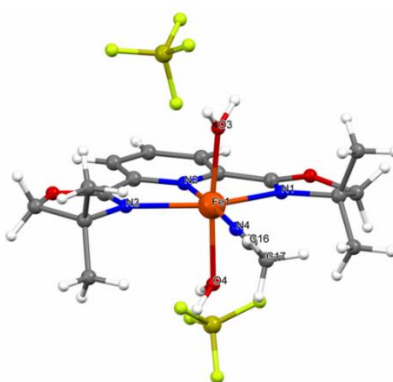
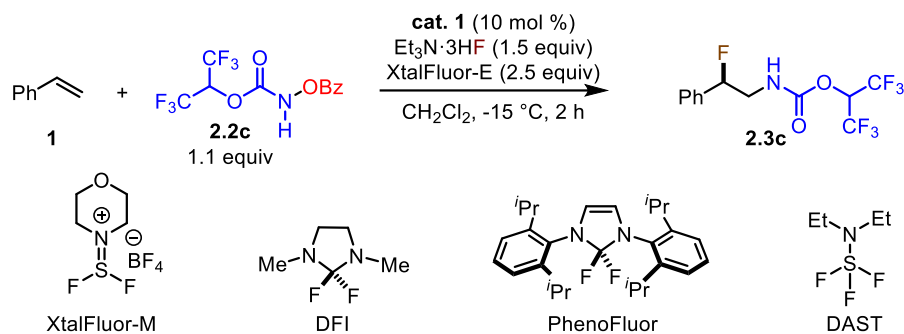


Figure 2.2 X-ray crystal structure of Fe(L1)(MeCN)(H₂O)₂(BF₄)₂ (*cat. 1*)

2.2.4 Screening of other nucleophilic fluorination reagents

To test the applicability of this novel iron-catalyzed aminofluorination method, we explored variant other nucleophilic fluorination reagents as fluoride donors under the optimized conditions (Table 2.2). First, replacements of Et₃N·3HF with Et₃N·HF, Et₃N·2HF, TBAF·(*t*-BuOH)₄, KF, or AgF all lead to decomposition of the oxidant **2.2c** (entry 1). Presumably, the reaction medium may be slightly basic due to solvation of above fluorine source with trace amount of moisture in the reaction system and we suspect that the acyloxy carbamate decomposes under weakly basic conditions.

Table 2.2 Screen other nucleophilic fluorination reagents



entry ^a	other fluorine donor	observations
1	XtalFluor-E/Fluorine donor (F^-) (2.5 equiv/1.5 equiv) $\text{F}^- = \text{Et}_3\text{N}\cdot\text{HF}, \text{Et}_3\text{N}\cdot 2\text{HF}, \text{TBAF}\cdot(\text{tBuOH})_4, \text{KF}$ or AgF	decomposition of 2.2c no desired product
2	XtalFluor-M/ $\text{Et}_3\text{N}\cdot 3\text{HF}$ (2.5 equiv/1.5 equiv)	65% yield of 2.3c > 95% conversion
3	benzoyl fluoride (2.5 equiv)	51% yield of 2.3c 66% conversion ^b
4	DFI or PhenoFluor (2.5 equiv)	decomposition of 2.2c no desired product
5	DAST (2.5 equiv)	decomposition of 2.2c no desired product
6	DAST/XtalFluor-E (1.5 equiv/1.0 equiv)	51% yield of 2.3c > 95% conversion

^aReactions were carried out under N_2 at $-15\text{ }^\circ\text{C}$ in 2 h and 4 Å molecular sieves were used to remove deleterious moisture. ^bAmino-oxygenation product **2.4c** (42%) and benzoylated **2.2c** (24%) were isolated.

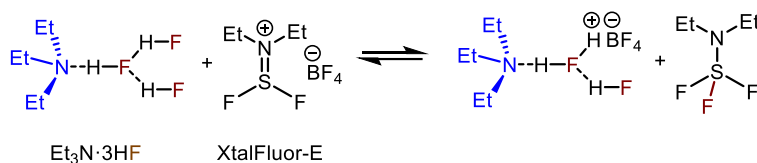
Next, XtalFluor-M also affords the desired product although in a lower yield (entry 2, 65% yield). Furthermore, using benzoyl fluoride instead of $\text{Et}_3\text{N}\cdot 3\text{HF}$ /XtalFluor-E leads to benzoylation of **2.2c** rather than aminofluorination product (entry 3). Furthermore, using DFI,⁶¹ PhenoFluor,⁶² or DAST,⁶³ reagents that can presumably sequester benzoates, leads to unproductive decomposition of **2.2c** (entries 4–5). Surprisingly, the DAST/XtalFluor-E (1.5:1) combination can provide the desired amino fluoride **2.3c** with good yield (entry 6).

These results showed that XtalFluor-E and $\text{Et}_3\text{N}\cdot 3\text{HF}$ combination is uniquely effective in this transformation. And their relative ratio (1.6:1) will be discussed in the next section.

2.2.5 The XtalFluor-E effects: a twofold purpose

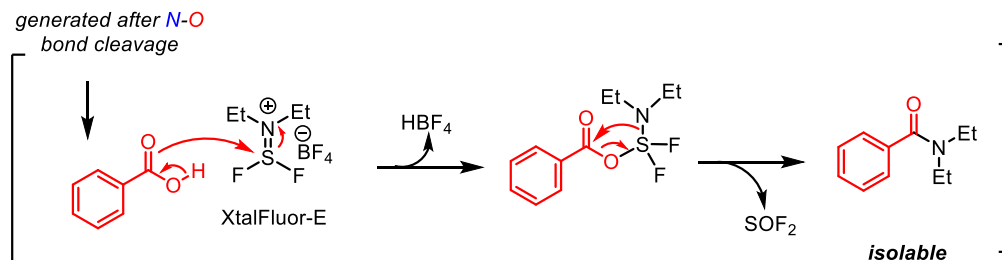
According to the accumulated observations, the reagent XtalFluor-E was used for two purposes in this intermolecular olefin aminofluorination reaction.

First, XtalFluor-E will react $\text{Et}_3\text{N}\cdot 3\text{HF}$ to generate a catalyst-friendly XtalFluor-E/ $\text{Et}_3\text{N}\cdot 3\text{HF}$ dynamic complexes, which could attenuate the concentration of hydrofluoric acid and therefore significantly slow down the fluoride-induced catalyst deactivation (Scheme 2.9).



Scheme 2.8 Proposed XtalFluor-E/ $\text{Et}_3\text{N}\cdot 3\text{HF}$ complex formation

In addition, XtalFluor-E also served as carboxylate group sequester that suppresses competing aminohydroxylation. A possible mechanism that XtalFluor-E takes carboxylate group is described in Scheme 2.10 and the carboxylate ends up as an *N,N*-diethyl amide byproduct.



Scheme 2.9 Proposed mechanism of carboxylate group trapped by XtalFluor-E

2.2.6 Substrate scope

With the optimized reaction condition, we next explored a broad range of olefins with this new aminofluorination approach (Table 2.3). First, this iron-catalyzed intermolecular aminofluorination works very well for the styrenyl olefins, including both electron-rich styrenes and electron deficient styrenes (entries 1a–1d). Additionally, conjugated ene-yne and 1,1-disubstituted α -methyl styrene are both compatible with this method (entries 2–3).

An allyl silane with active α -protons was converted to an internal amino fluoride with excellent yield and regioselectivity (entry 4, 82% yield). The TBDP (*tert*-Butyldiphenyl) protecting group is necessary to prevent the α -protons from elimination. The silyl dienol substrate has one of its double bonds selectively difunctionalized. Notably, the silyl protecting group survived in the presence of fluoride ion, indicating our fluorination method is considerably mild (entry 5). The ethyl dienoate substrate, an electro-deficient conjugate diene, was also tolerated by this method to produce amino allylic fluorides in reasonable yield (entry 6). Isoprene is also an excellent substrate, which provided a pair of vicinal amino allylic fluorides with an excellent yield and good regioselectivity (entry 7). Furthermore, a linear aliphatic diene would generate both 1,2- and 1,4-amino fluorides with excellent combined yield, which are separable from each other (entry 8).

Not surprisingly, 1,1-disubstituted olefin was an excellent candidate for this reaction (entry 9). Moreover, even with the least reactive, unfunctionalized, monosubstituted olefin, our method still gave a synthetically useful yield, even though with increased catalyst loading and amount of fluorination reagents (entry 10).

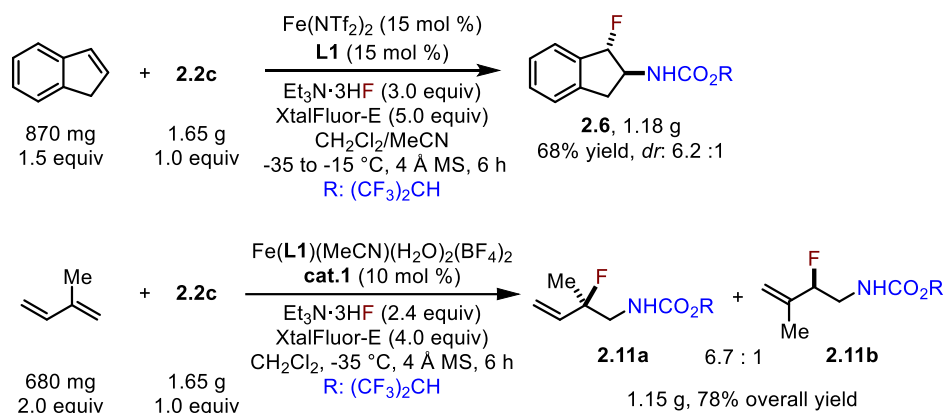
Table 2.3 Substrate scope of the iron-catalyzed olefin aminofluorination reaction

$\text{R}^1, \text{R}^2, \text{R}^3$: alkyl and aryl groups; R^4 : $(\text{CF}_3)_2\text{CH}$

entry ^a	olefins	vincinal fluoro carbamates	yield
1			a: R=H 88% b: R=Me 82% c: R=Br 87% d: R=CO ₂ Me 81%
2			75%
3 ^b			83%
4			82%
5 ^{c,d}			65%
6 ^{e,f}			65%
7 ^d			84%
8 ^b			91%
9 ^{b,c}			71%
10 ^{f,h}			62%

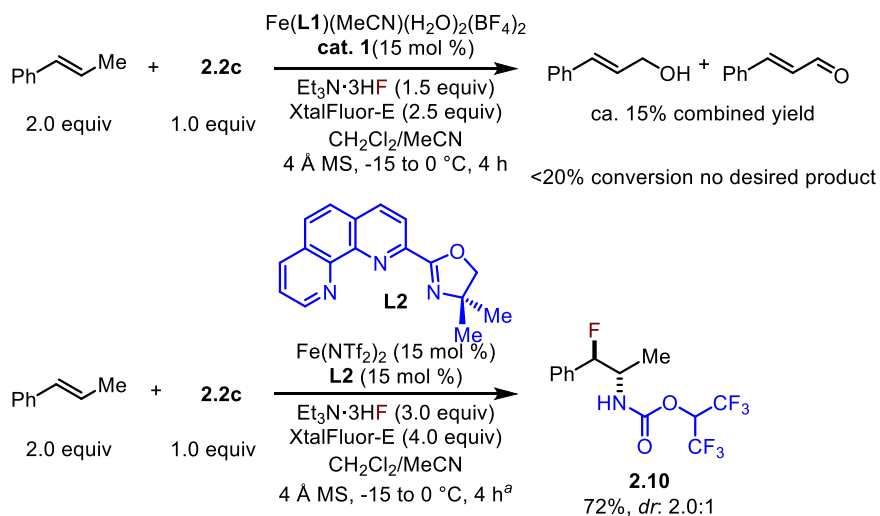
^aReactions were carried out under N₂ with pre-formed catalysts **cat.1** (10 mol %), unless stated otherwise. ^bXtalFluor-E (3.0 equiv)/Et₃N·3HF (1.8 equiv). ^cCatalyst loading: 15 mol %. ^dXtalFluor-E (4.0 equiv)/Et₃N·3HF (2.4 equiv). ^eCatalyst loading: 20 mol %. ^fAdditional XtalFluor-E (2.5 equiv)/Et₃N·3HF (2.5 equiv) were added after 1 h. ^gXtalFluor-E (5.0 equiv)/Et₃N·3HF (3.0 equiv). ^hCatalyst loading: 30 mol %, XtalFluor-E (1.5 equiv)/Et₃N·3HF (0.9 equiv).

We subsequently explored indene aminofluorination with the $\text{Fe}(\text{NTf}_2)_2$ -**L1** complex: an *anti*-2-amino fluoride was isolated as the major product with excellent regioselectivity and significant diastereoselectivity (Scheme 2.11). The gram-scale aminofluorination of both indene and isoprene demonstrated its great potential practicality of this methodology.



Scheme 2.10 Iron-catalyzed gram-scale aminofluorination of indene and isoprene

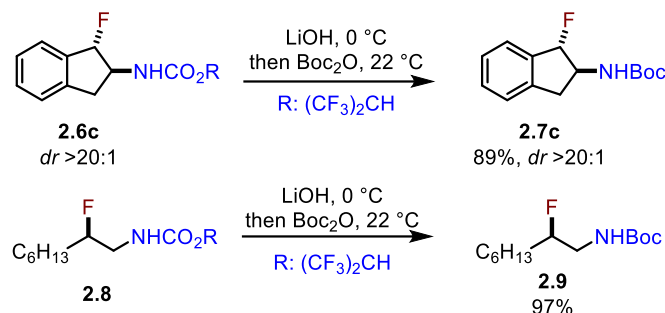
Fluorinated amphetamines are of great interest to biological studies of the central nervous system; therefore, we evaluated the aminofluorination of *trans*- β -methyl styrene (Scheme 2.12).⁶⁴ Interestingly, although the $\text{Fe}(\text{BF}_4)_2$ -**L1** complex **cat.1** promotes undesirable C–H abstraction, a less sterically hindered $\text{Fe}(\text{NTf}_2)_2$ -**L2** complex catalyzes efficient aminofluorination to afford **2.10** (72% yield, dr: 2.0:1).



^aReaction condition: $\text{Fe}(\text{NTf}_2)_2$ (15 mol %), **L2** (15 mol %), XtalFluor-E (2.5 equiv)/ $\text{Et}_3\text{N}\cdot 3\text{HF}$ (1.5 equiv), 4 Å MS, $\text{CH}_2\text{Cl}_2/\text{MeCN}$, $-35 \text{ }^\circ\text{C}$, 1 h; then another portion of XtalFluor-E (1.5 equiv)/ $\text{Et}_3\text{N}\cdot 3\text{HF}$ (1.5 equiv), $-15 \text{ }^\circ\text{C}$, 3 h.

Scheme 2.12 Ligand-controlled iron-catalyzed aminofluorination of *trans*- β -methyl styrene

Vicinal fluoro carbamates that are obtained after aminofluorination reaction, can be easily derivatized to *N*-Boc protected vicinal fluoro primary amines in excellent yields through simple base-catalyzed hydrolysis and protection procedures (Scheme 2.13).



Scheme 2.11 Derivatization of olefin aminofluorination products to vicinal fluoro amines

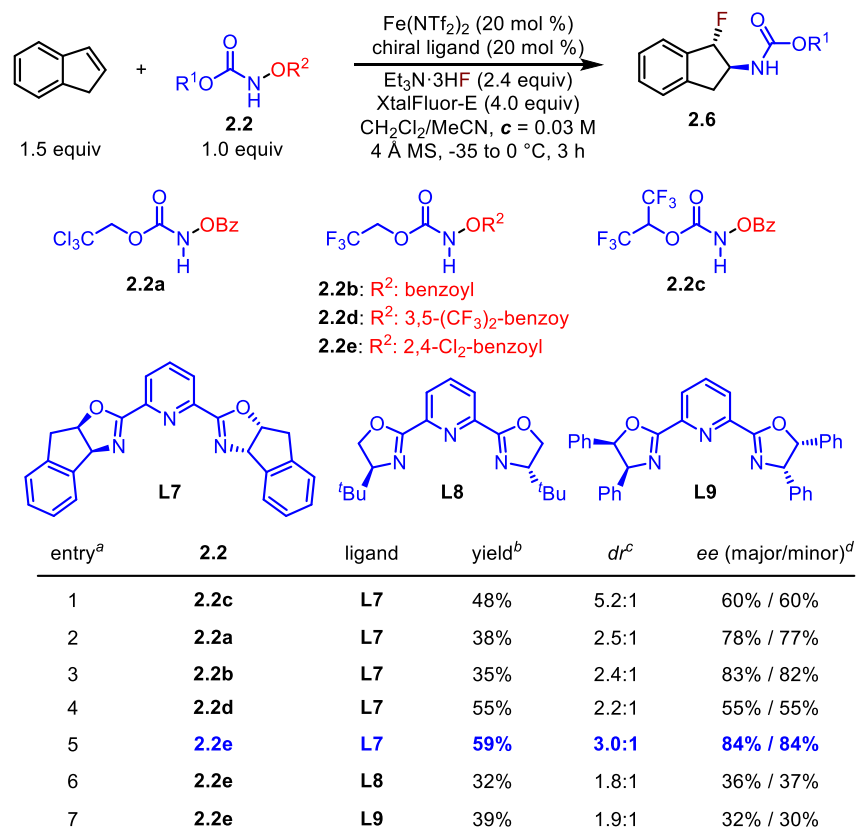
2.2.7 Asymmetric indene aminofluorination

Direct enantioselective aminofluorination of unfunctionalized olefins has been a challenging problem in organic synthesis.⁶⁵⁻⁶⁸ With indene as a model substrate, we explored a range of chiral ligand and oxidants to achieve the asymmetric induction (Table 2.4).

With $\text{Fe}(\text{NTf}_2)_2$ -chiral indanol PyBOX ligand **L7** complex as catalyst and **2.2c** as the oxidant, we observed significant enantioselectivity induction in indene aminofluorination that affords *anti*-2-amino fluoride **2.6c** (entry 1, 60% *ee*). Further investigation showed that less sterically hindered acyloxyl carbamates, **2.2a** and **2.2b**, lead to increased *ee*, but both reactions evidently suffer from lower reactivity (entries 2–3, 78–83% *ee*). In order to achieve better reactivity, the benzoyl activating group in **2.2b** was switched to 3,5-bis(trifluoromethyl)-benzoyl group (**2.2d**), while a dramatically decreased *ee* was observed (entry 4, 55% *ee*). By replacing the oxidant **2.2c** with **2.2e**, we observed a significantly improved enantioselectivity in indene aminofluorination in synthetically useful yield (entry 5, 59% yield, 84% *ee*). Other chiral ligands, including tridentate **L8** and **L9**, were less effective. The results of oxidant screening (entries 1–5) indicated that the acyloxyl moiety are crucial for stereochemistry induction in this iron-catalyzed indene aminofluorination and the benzoate group generated during N–O bond cleavage may be

involved in the *ee*-determining step. Additionally, since the same *ee* was observed for both diastereomers of **2.6**, it is likely that the C–N bond formation step is *ee*-determining.

Table 2.4 Catalyst discovery for iron-catalyzed enantioselective indene aminofluorination



^aUnless stated otherwise, the reactions were carried out under a nitrogen atmosphere with 4 Å molecular sieves. ^bIsolated yield. ^c*Dr* was determined by ¹H NMR. ^dEnantiomeric excess (*ee*) was measured by HPLC with chiral columns; the absolute stereochemistry was determined by X-ray crystallographic analysis of **2.6c** (R: (CF₃)₂CH).

The absolute stereochemistry of **2.6a, b, c, d, e** was determined by X-ray crystallographic analysis of enantio-enriched aminofluorination product **2.6c** (Figure 2.2). The major product has fluorine atom and amino group *trans* to each other with the fluoride at the internal position.

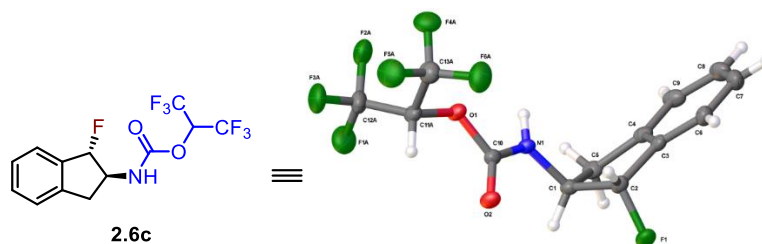
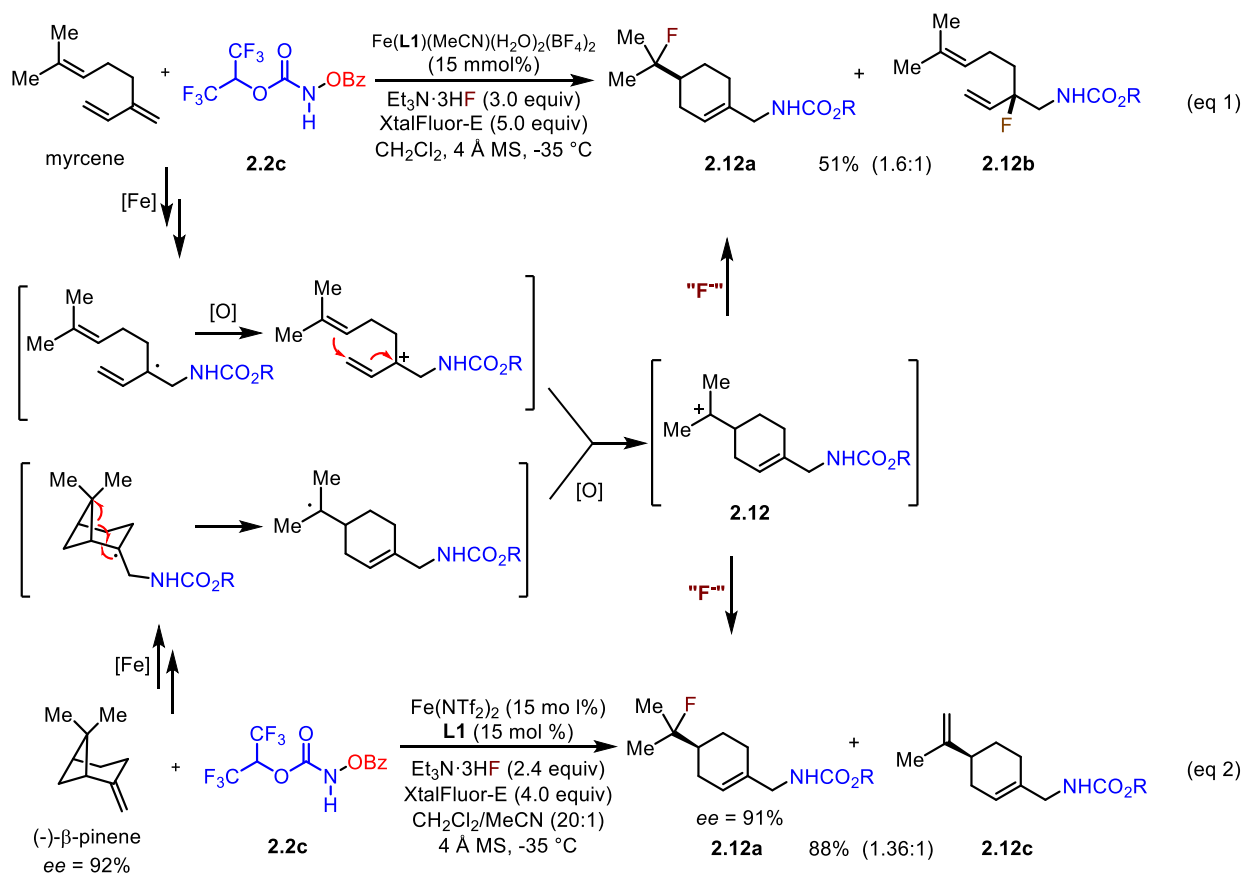


Figure 2.1 X-ray crystal structure of enantio-pure indene aminofluorination product

2.2.8 Aminofluorination of myrcene and (-)- β -pinene

We also evaluated two complex natural product substrates, myrcene and (-)- β -pinene. The aminofluorination of both substrates provides interesting mechanistic insight. Myrcene is a highly reactive system that contains both a 1,1,2-trisubstituted olefin and a conjugated diene. The aminofluorination of myrcene readily affords both a direct 1,2-aminofluorination product **2.12b** and a cyclized 1,6-aminofluorination product **2.12a** (Scheme 2.14, eq 1). Presumably, once the carbo radical was generated and it was quickly oxidized the carbocation species. A following cascade cyclization will provide the stable tertiary cation intermediate **2.12**, which will subsequently afford the cyclized 1,6-aminofluorination product **2.12a** after fluoride transfer.



Scheme 2.12 Iron-catalyzed aminofluorination of myrcene and (-)- β -pinene

Interestingly, in the aminofluorination of (-)- β -pinene, we didn't observe any 1,2-addition product, but rather the cyclized 1,6-aminofluorination product **2.12a** and an elimination product (Scheme 2.14, eq

2). Unlike the myrcene's pathway, in (-)- β -pinene aminofluorination, once the carbo radical was generated, the ring will open and radical migrated to the tertiary carbon, which will be oxidized to the same carbo cation species **2.12**. The cyclized 1,6-aminofluorination product **2.12a** will be formed after fluoride transfer. At the same time, elimination of one proton from the methyl groups will afford **2.12c**. Notably, the enantio pure starting material ($ee=92\%$) was converted to the enantio pure aminofluorination product ($ee=91\%$) with the stereochemistry remained after aminofluorination–rearrangement cascade. The structure of cyclized 1,6-aminofluorination product **2.12a** was confirmed by X-ray analysis (Figure 2.3).

The observation of aminofluorination product **2.12a** in myrcene reaction and elimination product **2.12c** in (-)- β -pinene reaction strongly indicate that carbocation species got involved in both pathways.

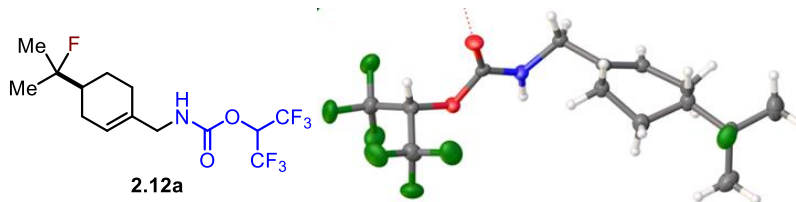
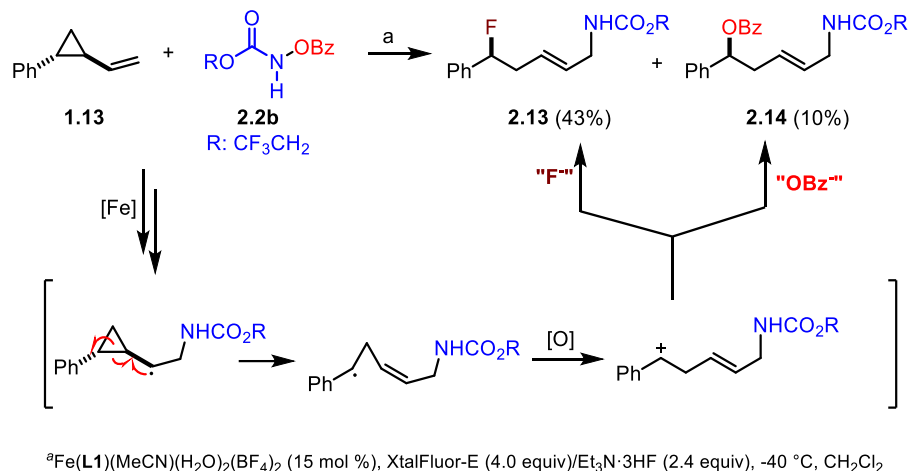


Figure 2.2 X-ray crystal structure of myrcene 1,6-aminofluorination product

2.2.9 Control experiments for mechanistic studies

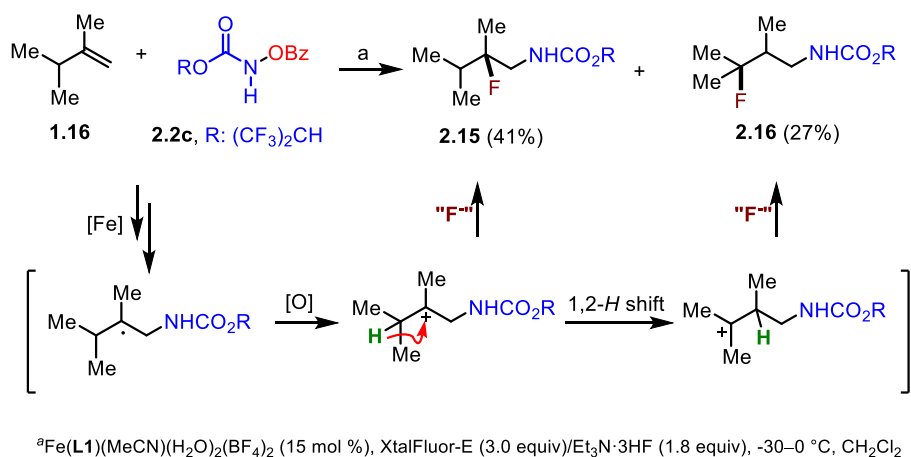
We next carried out several control experiments to collect more evidence for its mechanism.

A cyclopropyl-substituted olefin **1.13** was chosen as a radical clock probe, and the aminofluorination of **1.13** afforded only the ring-opening aminofluorination product **2.13** together with a small amount of competing amino-oxygenation product **2.14** (Scheme 2.15). This result suggests that the reaction proceeds through a stepwise radical amination pathway. Moreover, unlike the amino-oxygenation of the same radical clock probe (Scheme 1.5), no direct 1,2-addition products were detected under the aminofluorination condition. This discrepancy suggests that the cyclopropyl ring opening step is fast, while the fluoride or carboxylate transfer is rate-determining.



Scheme 2.13 Iron-catalyzed aminofluorination of trans-2-phenyl-1-vinylcyclopropane

When the reaction condition was applied to a carbo cation probe **1.16**, we observed both 1,2- amino fluoride **2.15** and 1,3-aminofluoride **2.16**. Presumably, the product **2.16** is obtained through 1,2-hydride shift from a carbocation intermediate, which is a strong evidence that carbocation species are also involved in the reaction pathway (Scheme 2.16).

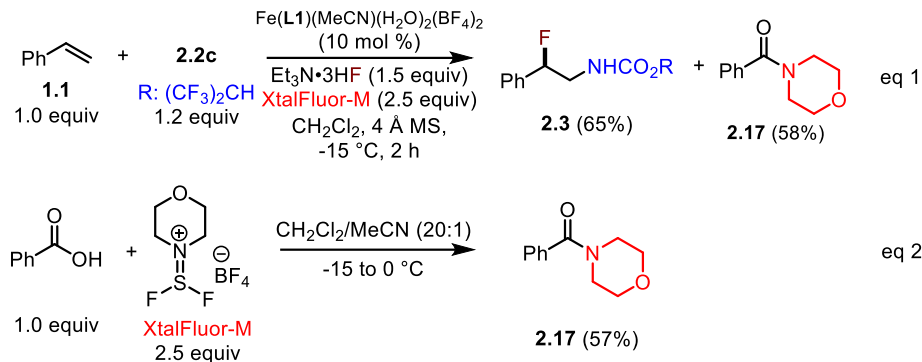


Scheme 2.14 Iron-catalyzed aminofluorination of 2,3-dimethyl-1-butene

To prove the role of XtalFluor-E as benzoate trapping agent, its analog XtalFluor-M was used to replace XtalFluor-E in standard styrene aminofluorination. ^{†††} Benzoylated morpholine **2.17** was isolated

^{†††} XtalFluor-M was used rather than XtalFluor-E because the benzoylated morpholine **2.17** has been fully characterized in the literature and is easier to isolate.

as a byproduct (Scheme 2.17, eq 1). In a control reaction between benzoic acid and XtalFluor-M, the same benzoylated morpholine product was isolated (Scheme 2.17, eq 2). These results suggest that XtalFluor-E or XtalFluor-M can sequester benzoic acids to suppress the competing aminohydroxylation process.

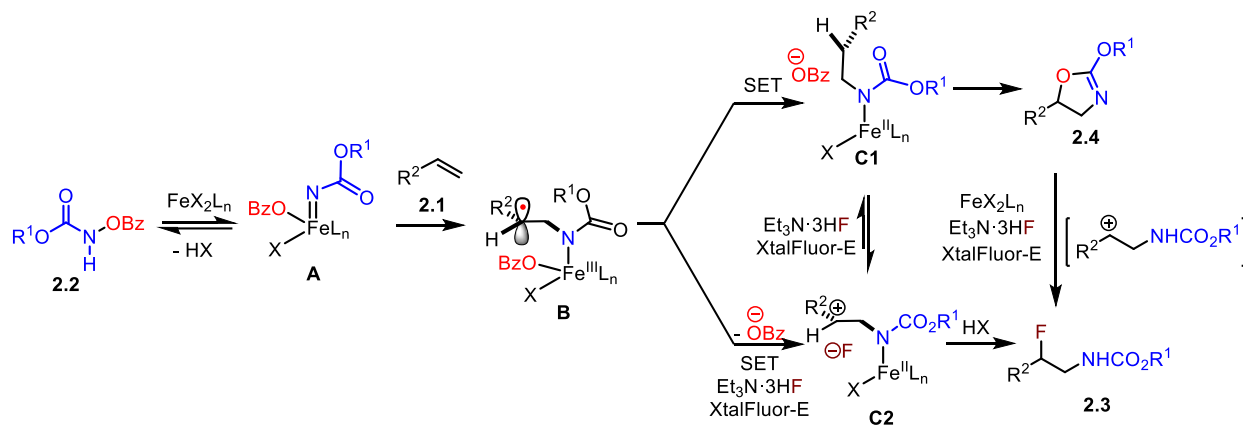


Scheme 2.15 XtalFluor-M as benzoate sequester in the intermolecular aminofluorination

2.2.10 Plausible working hypothesis for the iron-catalyzed intermolecular olefin aminofluorination

The iron-catalyzed olefin aminofluorination proceeds in a similar way as the amino-oxygenation reaction that is described in Chapter 1 (Scheme 2.18).

First, the iron catalyst reductively cleaves the *N*–*O* bond in oxidant **2.2** and generates a reactive iron-nitrenoid species **A**. Next, **A** readily initiates radical addition to olefin **2.1** with formation of carbo-radical species **B**. Subsequently, the high-valent iron intermediate may oxidize the radical to a carbocation **C1** and its conformer **C2**, presumably through outer sphere single electron transfer pathway (SET). In the absence of nucleophilic fluoride, **C1** may be efficiently captured by the neighboring carbamate group to afford amino-oxygenation product **2.4**. While in the presence of a suitable nucleophilic fluoride and benzoate sequestering reagent (e.g., Et₃N·3HF/XtalFluorE), **C2** can be converted to amino fluoride **2.3** after fluorine transfer. Notably, the oxazoline **2.4** can be converted to amino fluoride **2.3** under reaction conditions, presumably through ring opening process and with carbocation **C1** as an intermediate.



Scheme 2.18 Mechanistic working hypothesis for the iron-catalyzed intermolecular olefin aminofluorination

2.3 Experimental section^{§§§}

2.3.1 Materials and general information

Materials: Commercial reagents were purchased from Sigma Aldrich, Fluka, EM Science, and Lancaster and used as received. All solvents were used after being freshly distilled unless otherwise noted.

Instrumentation: Proton nuclear magnetic resonance (^1H NMR) spectra, carbon nuclear magnetic resonance (^{13}C NMR) spectra and fluorine nuclear magnetic resonance (^{19}F NMR) were recorded on Bruker UltraShield-400 (400 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak (CHCl_3 : δ 7.26). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent (CDCl_3 : δ 77.0). Chemical shifts for fluorine are reported in parts per million downfield and are referenced to the fluorine resonances of CFCl_3 . Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and integration. When ^{19}F NMR is used for quantitative purpose (*dr* determination), 30 degrees pulse and a longer delay time ($d1 = 5$ s) were employed and the receiver gain

^{§§§} (1) the characterization spectra can be found in Appendix A.2; (2) detailed procedures for complete substrate stable can be found in: Lu, D.-F.; Zhu, C.-L.; Sears, J. D.; Xu, H. J. *Am. Chem. Soc.* 2016, 138, 11360–11367.

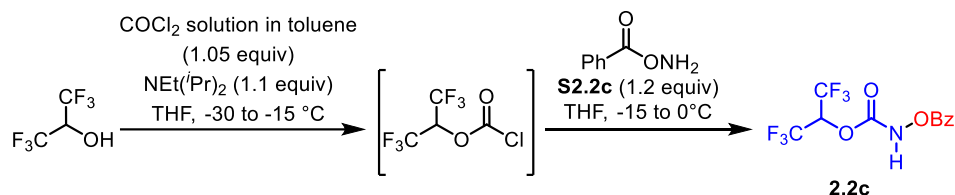
CDCl₃) δ 165.5, 154.6, 134.5, 130.1, 128.8, 126.3, 94.4, 75.2; HRMS (ESI, m/z): calcd for C₁₀H₈Cl₃NNaO₄⁺, [M + Na⁺], 333.9411, found 333.9418.

Compound **2.2b** was prepared according to the above procedure and isolated as white solid (4.48 g, 81% yield, m.p. 68–70°C).

2,2,2-Trifluoroethyl (benzoyloxy)carbamate (2.2b): IR ν_{\max} (neat)/cm⁻¹: 3249 (m), 2994 (w), 2967 (w), 1773 (s), 1731 (s), 1492 (m), 1230 (m), 1172 (s), 1129 (m), 704 (m); ¹H NMR (400 MHz, CDCl₃) δ 8.63 (s, 1H), 8.15–8.02 (m, 2H), 7.71–7.59 (m, 1H), 7.53–7.45 (m, 2H), 4.59 (q, *J* = 8.2 Hz, 1H); ¹⁹F NMR (376 MHz, CDCl₃) δ -74.15 (t, *J* = 8.2 Hz, 3F); ¹³C NMR (100 MHz, CDCl₃) δ 165.4, 154.5, 134.5, 130.0, 128.8, 126.2, 122.5 (q, *J* = 277.4 Hz), 61.9 (q, *J* = 37.4 Hz); HRMS (ESI, m/z): calcd for C₁₀H₈F₃NNaO₄⁺, [M + Na⁺], 286.0298, found 286.0301.

B: procedures for the synthesis of acyloxyl carbamate 2.2c.

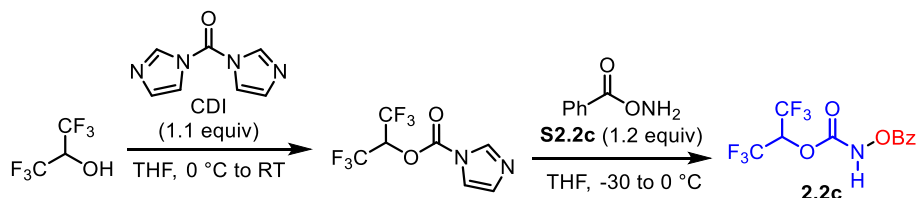
Method A:



To an oven-dried 200 mL round bottom flask equipped with a stir bar was added hexafluoro-2-propanol (1.8 mL, 17.1 mmol) in anhydrous THF (30 mL). The mixture was cooled to -30 °C and then phosgene solution (12.8 mL, 18.0 mmol, 15 wt % in toluene) was added dropwise (*note: phosgene solution should be handled carefully in a fume hood*). NEt(iPr)₂ (3.27 mL, 18.8 mmol in 10 ml THF) was added to the reaction mixture in 40 min via a syringe-pump. Then the reaction mixture was warmed up to -15 °C and stirred for another 10 min to generate the putative carbonochloridate intermediate. *O*-benzoylhydroxylamine **S2.2c** (prepared according to literature procedures,^{69,70} 2.81 g, 20.5 mmol in 20 mL THF) was then added dropwise to the reaction mixture, which was warm up to 0 °C in 1 h. After **S2.2c** was fully consumed monitored by TLC, the reaction was quenched with H₂O (30 mL). After removal of THF *in vacuo*, the aqueous phase was extracted with Et₂O (30 mL × 3). The combine organic layers were

dried over Na_2SO_4 and were concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexanes/EtOAc: from 50:1 to 9:1) to afford **2.2c** as a white solid (4.13 g, 73% yield, m.p. 48–49°C).

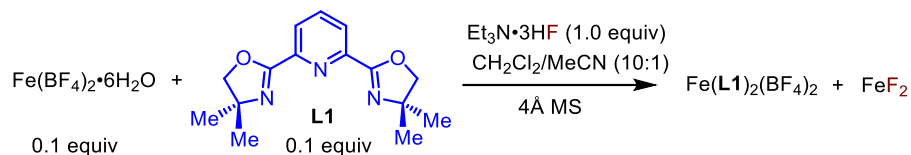
Method B:



To an oven-dried 250 mL round bottom flask equipped with a stir bar were added CDI (7.14 g, 44 mmol) and THF (100 mL) under N_2 . After the flask was cooled to 0 °C, hexafluoro-2-propanol (4.2 mL, 40 mmol) was added dropwise via a syringe and the solution was then warmed up to room temperature. The reaction was monitored by ^{19}F NMR until hexafluoro-2-propanol was fully consumed. The mixture was then cooled to -30 °C and **S2.2c** (5.5 g, 40 mmol in 30 mL THF) was added dropwise. The reaction mixture was warmed up to 0 °C in 1 h. After the intermediate was consumed (monitored by TLC), the reaction mixture was concentrated *in vacuo* and re-dissolved in EtOAc (100 mL), which was washed with 0.5 M HCl (50 mL \times 2) and concentrated again. The residue was purified through a silica gel flash column (hexanes/EtOAc: from 50:1 to 9:1) to afford **2.2c** as a white solid (7.42 g, 56% yield, m.p. 48–49°C).

1,1,1,3,3,3-Hexafluoropropan-2-yl (benzyloxy)carbamate (2.2c): IR ν_{max} (neat)/ cm^{-1} : 3269 (m), 2990 (w), 1778 (m), 1754 (s), 1486 (m), 1382 (s), 1360 (m), 1198 (s), 1131 (s), 1128 (s), 990 (s), 906 (s), 881 (m), 689 (m); ^1H NMR (400 MHz, CDCl_3) δ 8.14–8.05 (m, 2H), 7.67 (dd, $J = 10.7, 4.3$ Hz, 1H), 7.51 (t, $J = 7.8$ Hz, 2H), 5.80–5.65 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.1, 152.6, 134.7, 130.1, 128.9, 125.8, 120.2 (q, $J = 283.4$ Hz), 69.17–67.59 (m); ^{19}F NMR (376 MHz, CDCl_3) δ -73.46 (d, $J = 6.2$ Hz); HRMS (ESI, m/z): calcd for $\text{C}_{11}\text{H}_8\text{F}_6\text{NO}_4^+$, $[\text{M} + \text{H}^+]$, 332.0352, found 332.0350.

2.3.3 Studies of the fluoride-induced catalyst deactivation



To a flame-dried 2-dram vial equipped with a stir bar were added $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ (34 mg, 0.1 mmol), ligand **L1** (27.3 mg, 0.1 mmol) and freshly activated 4Å powdered molecular sieves. After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (4.0 mL) and MeCN (0.4 mL) were added via a syringe and the mixture was stirred at room temperature for 1 h. The solution was filtered through a cotton wool under N_2 into another 2-dram vial equipped with a stir bar followed by addition of $\text{Et}_3\text{N} \cdot 3\text{HF}$ (163 μL , 1.0 mmol). The mixture was stirred at room temperature for 2 h and it was filtered through a cotton wool under N_2 to remove white FeF_2 precipitate. The filtrate was then concentrated and dried in vacuo to afford dark-red residue. The residue was suspended and sonicated in anhydrous Et_2O . After Et_2O was removed via a syringe, the solid was dried in vacuo to afford dark-red powder.

For the purpose of X-ray crystallographic analysis, the solid (30 mg) was recrystallized from $\text{CH}_2\text{Cl}_2/\text{MeCN}$ (0.5/0.1 mL) and Et_2O (4 mL) through vapor diffusion. The structure of $\text{Fe}(\text{L1})_2(\text{BF}_4)_2$, has been deposited to The Cambridge Crystallographic Data Centre as CCDC 1404792 (Figure 2.3).

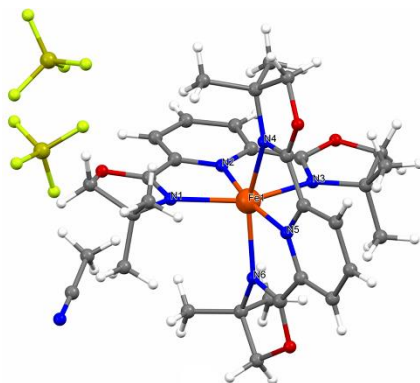
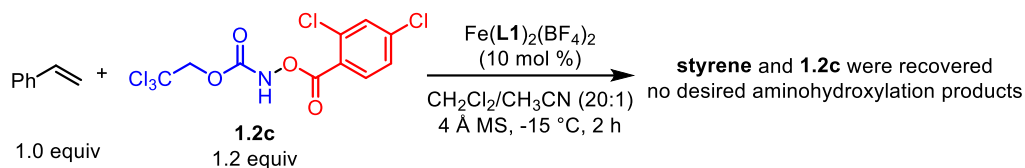


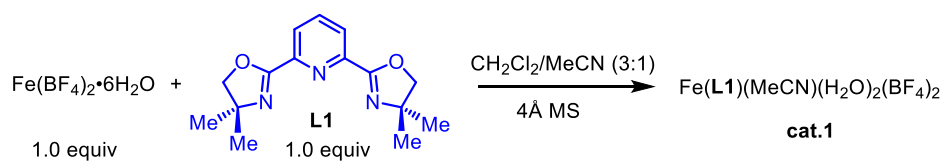
Figure 2.3 X-ray crystal structure of catalytically inactive $\text{Fe}(\text{L1})_2(\text{BF}_4)_2$ complex

Test of reactivity of catalyst $\text{Fe}(\text{L1})_2(\text{BF}_4)_2$ in styrene aminohydroxylation:



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added catalyst $\text{Fe(L1)}_2(\text{BF}_4)_2$ (17.1 mg, 0.02 mmol), and freshly activated 4 Å powdered molecular sieves (20 mg). Vial **A** was degassed and backfilled with N_2 three times and then anhydrous CH_2Cl_2 (0.5 mL) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stir bar were added freshly activated 4 Å powdered molecular sieves (50 mg) and the corresponding acyloxyl carbamate **1.2c** (91 mg, 0.24 mmol). The vial was evacuated and backfilled with N_2 for three times and then anhydrous CH_2Cl_2 (1.5 mL) was added. Both vials were degassed with N_2 twice and vial **B** was then cooled to -15°C . Freshly distilled styrene (23 μL , 0.2 mmol) was added to vial **B** and the catalyst solution in vial **A** was added through a syringe pump over 15 min to vial **B** at -15°C . The reaction was kept at this temperature for additional 2 h and quenched with saturated NaHCO_3 solution (2 mL). Styrene and **1.2c** were recovered and there is no desired olefin aminohydroxylation product formation.

2.3.4 Catalytically active $\text{Fe(L1)(MeCN)(H}_2\text{O)}_2(\text{BF}_4)_2$ complex preparation

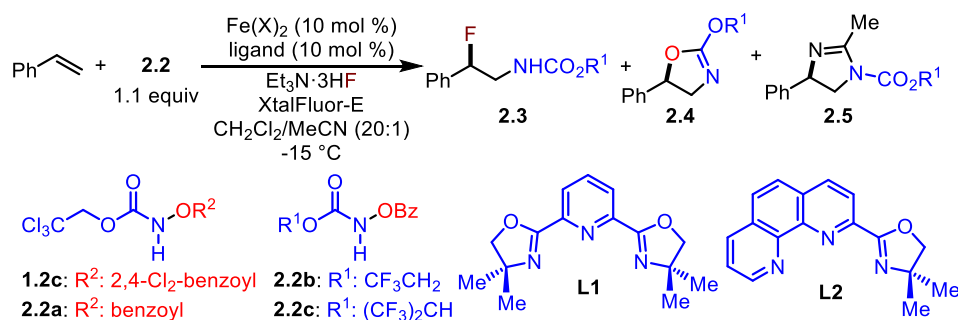


To a flame-dried 25 mL round bottom flask equipped with a stir bar were added $\text{Fe(BF}_4)_2 \cdot 6\text{H}_2\text{O}$ (168.8 mg, 0.5 mmol), ligand **L1** (136.5 mg, 0.5 mmol) and freshly activated 4 Å powdered molecular sieves. After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (6 mL) and MeCN (2 mL) were added via a syringe and the mixture was stirred at room temperature for 1 h. The solution was filtered through a cotton wool under N_2 and the filtrate was concentrated and dried in vacuo to afford orange color residue, which was suspended and sonicated in anhydrous Et_2O under N_2 . After Et_2O

was removed via a syringe, the catalyst complex was further dried *in vacuo*, which can be directly used in catalytic reactions. For the purpose of X-ray crystallographic analysis, the aforementioned solid (30 mg) was recrystallized from CH₂Cl₂/MeCN (0.5/0.1 mL) and Et₂O (4 ml) through vapor diffusion. The structure of **cat.1** has been deposited to The Cambridge Crystallographic Data Centre as CCDC 1404791 (Figure 2.1).

2.3.5 General procedure for the iron-catalyzed intermolecular olefin aminofluorination reaction

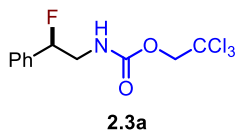
Procedure A: with pre-mixed Fe(NTf₂)₂/ligand catalyst.



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added Fe(NTf₂)₂ (12.3 mg, 0.02 mmol) and **L1** (5.5 mg, 0.02 mmol). After vial **A** was evacuated and backfilled with N₂ three times, anhydrous CH₂Cl₂ (0.5 mL) and MeCN (0.08 mL) were added and the mixture was stirred at room temperature for 20 min. To a second flame-dried sealable 2-dram vial (vial **B**) equipped with a stir bar were added XtalFluor-E (various equivalents for different experiments) and freshly activated powdered 4 Å molecular sieves (50 mg). After vial **B** was evacuated and backfilled with N₂ three times, anhydrous CH₂Cl₂ (2.0 mL) and Et₃N·3HF (various equivalents for different experiments) were added. The mixture was stirred at room temperature for 10 min. To a third flame-dried sealable 3-dram vial (vial **C**) equipped with a stir bar were added acyloxyl carbamate **2.2** (0.22 mmol) and freshly activated powdered 4 Å molecular sieves (100 mg). It was evacuated and backfilled with N₂ three times and then anhydrous CH₂Cl₂ (0.5 mL) was added. After vial **C** was cooled to -15 °C, freshly distilled styrene (23 μL, 0.2 mmol) was added, followed by the addition of fluorinating reagents in vial **B** via a syringe. The catalyst solution in vial **A** was then added to vial **C** via a syringe pump at -15 °C over 15 min and the reaction was kept at this temperature for

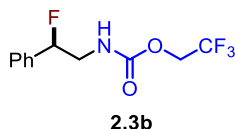
additional 2 h and quenched with saturated NaHCO₃ solution (3 mL). The organic layer was separated from the aqueous one, which was extracted with CH₂Cl₂ (2 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexanes/acetone: from 100:1 to 4:1) to afford the desired styrene aminofluorination product.

Compound **2.3a** was isolated from the experimental condition in entry 4 of Table 2.1 as a white solid (28.3 mg, 45% yield, m.p. 57–58 °C).



2,2,2-Trichloroethyl-(2-fluoro-2-phenylethyl)carbamate (2.3a): IR ν_{\max} (neat)/cm⁻¹: 3344 (m), 2946 (w), 1703 (s), 1540 (s), 1453 (m), 1250 (s), 1161 (m), 1040 (m), 959 (m), 832 (m), 650 (m); ¹H NMR (400 MHz, CDCl₃) δ 7.48–7.29 (m, 5H), 5.58 (ddd, $J = 48.2, 8.3, 3.1$ Hz, 1H), 5.46 (brs, 1H), 4.79–4.69 (m, 2H), 3.77 (dddd, $J = 30.2, 14.8, 7.5, 3.2$ Hz, 1H), 3.54 (dddd, $J = 17.8, 14.7, 8.3, 4.9$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 154.7, 136.7 (d, $J = 19.5$ Hz), 129.0 (d, $J = 1.7$ Hz), 128.7, 125.5 (d, $J = 7.1$ Hz), 95.4, 92.8 (d, $J = 173.4$ Hz), 74.7, 46.9 (d, $J = 24.1$ Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -183.75 (ddd, $J = 48.0, 30.2, 17.7$ Hz, 1F), -184.88 (ddd, $J = 48.0, 30.2, 17.7$ Hz, rotamer); HRMS (ESI, m/z): calcd for C₁₁H₁₂Cl₃FNO₂⁺, [M + H⁺], 313.9912, found 313.9919.

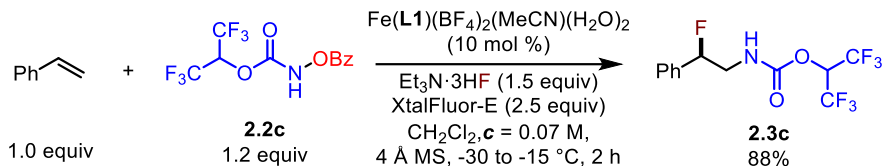
Compound **2.3b** was isolated from the experimental condition in entry 7 of Table 2.1 as a white solid (24.4 mg, 46% yield, m.p. 56–57 °C).



2,2,2-Trifluoroethyl-(2-fluoro-2-phenylethyl)carbamate (2.3b): IR ν_{\max} (neat)/cm⁻¹: 3335 (m), 2970 (w), 1709 (s), 1551 (s), 1247 (m), 1155 (s), 968 (m), 795 (m), 697 (m); ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.32 (m, 5H), 5.58 (ddd, $J = 48.3, 8.3, 3.1$ Hz, 1H), 5.33 (brs, 1H), 4.50 (q, $J = 8.5$ Hz, 2H), 3.78 (dddd, $J = 30.3, 14.8, 7.7, 3.2$ Hz, 1H), 3.53 (dddd, $J = 17.5, 14.7, 8.4, 4.7$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ

154.5, 136.7 (d, $J = 19.5$ Hz), 129.0 (d, $J = 1.7$ Hz), 128.7, 125.5 (d, $J = 7.1$ Hz), 123.0 (q, $J = 277.4$ Hz), 92.7 (d, $J = 173.5$ Hz), 61.1 (q, $J = 36.7$ Hz), 46.9 (d, $J = 24.2$ Hz); ^{19}F NMR (376 MHz, CDCl_3) δ -74.32 (t, $J = 8.5$ Hz, 3F), -184.00 (ddd, $J = 48.0, 30.4, 17.5$ Hz, 1F), -184.83 (ddd, $J = 48.0, 30.4, 17.5$ Hz, rotamer); HRMS (ESI, m/z): calcd for $\text{C}_{11}\text{H}_{11}\text{F}_4\text{NO}_2\text{Na}^+$, $[\text{M} + \text{Na}^+]$, 288.0618, found 288.0623.

Procedure B: optimized with pre-formed solid $\text{Fe}(\text{L1})(\text{MeCN})(\text{H}_2\text{O})_2(\text{BF}_4)_2$ complex (*cat.1*).



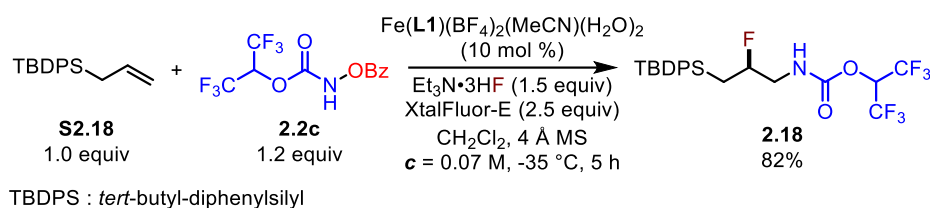
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added XtalFluor-E (115 mg, 0.5 mmol) and freshly activated 4 Å powdered molecular sieves (50 mg). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (1.5 mL) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (49 μL , 0.3 mmol) were added successively via syringes. The mixture was stirred at room temperature for 20 min. To another flame-dried sealable 3-dram vial (vial **B**) equipped with a stir bar were added **cat.1** ($\text{Fe}(\text{L1})(\text{MeCN})(\text{H}_2\text{O})_2(\text{BF}_4)_2$, 11.6 mg, 0.02 mmol), and freshly activated 4 Å powdered molecular sieves (100 mg). Vial **B** was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (0.75 mL) was added. Both vials were degassed and backfilled with N_2 twice and vial **B** was cooled to -30 °C. Freshly distilled styrene (23 μL , 0.2 mmol) was then added into vial **B** followed by addition of the fluorinating reagents in vial **A** via a syringe. Acyloxyl carbamate **2.2c** (79.4 mg, 0.24 mmol) in 0.75 mL CH_2Cl_2 was added dropwise at last to vial **B**. The reaction was kept at -30 °C for 30 min and allowed to warm up gradually to -15 °C. The reaction was kept at this temperature for additional 1 h and quenched with saturated NaHCO_3 solution (3 mL). The organic layer was separated from the aqueous one, which was extracted with CH_2Cl_2 (2 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexanes/acetone: from 100:1 to 4:1) to afford **2.3c** as a white solid (58.6 mg, 88% yield, m.p. 95–97 °C).

1,1,1,3,3,3-Hexafluoropropan-2-yl (2-fluoro-2-phenylethyl)carbamate (2.3c): IR ν_{\max} (neat)/ cm^{-1} : 3327 (m), 2967 (w), 1740 (s), 1555 (s), 1383 (m), 1253 (s), 1190 (s), 1162 (m), 1107 (s), 960 (m), 903 (m), 763 (m), 699 (m); ^1H NMR (400 MHz, C_6D_6) δ 7.08–6.99 (m, 3H), 6.98–6.92 (m, 2H), 5.77–5.66 (m, 1H), 5.01 (ddd, $J = 48.0, 8.0, 3.2$ Hz, 1H), 4.41 (brs, 1H), 3.13 (dddd, $J = 28.4, 14.7, 7.0, 3.3$ Hz, 1H), 2.91 (dddd, $J = 17.8, 14.5, 8.0, 5.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.7, 136.3 (d, $J = 19.5$ Hz), 129.1 (d, $J = 1.6$ Hz), 128.8, 125.4 (d, $J = 7.1$ Hz), 120.6 (q, $J = 282.5$ Hz), 92.4 (d, $J = 173.9$ Hz), 68.9–66.6 (m), 47.1 (d, $J = 24.3$ Hz); ^{19}F NMR (376 MHz, C_6D_6) δ -73.72 (d, $J = 6.2$ Hz, 6F), -183.86 (ddd, $J = 48.0, 29.0, 18.2$ Hz, 1F), -184.72 (ddd, $J = 48.0, 29.0, 18.2$ Hz, rotamer); HRMS (ESI, m/z): calcd for $\text{C}_{12}\text{H}_{10}\text{F}_7\text{NO}_2\text{Na}^+$, [$\text{M} + \text{Na}^+$], 356.0492, found 356.0481.

2.3.6 Procedures for iron-catalyzed aminofluorination of selected olefin substrates

A: procedure for iron-catalyzed aminofluorination of allyl(*tert*-butyl)diphenylsilane.

Allyl(*tert*-butyl)diphenylsilane **S2.18** was synthesized according to a literature procedure.⁷¹



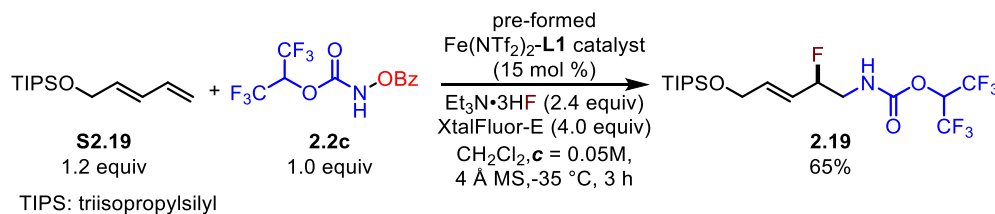
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added XtalFluor-E (115 mg, 0.5 mmol) and freshly activated 4 Å powdered molecular sieves (50 mg). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (1.5 mL) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (49 μL , 0.3 mmol) were added successively via syringes. The mixture was stirred at room temperature for 20 min. To another flame-dried sealable 3-dram vial (vial **B**) equipped with a stir bar were added the preformed catalyst $\text{Fe}(\mathbf{L1})(\text{BF}_4)_2(\text{MeCN})(\text{H}_2\text{O})_2$ (11.6 mg, 0.02 mmol) and freshly activated 4 Å powdered molecular sieves (100 mg). Vial **B** was evacuated and backfilled with N_2 three times and then anhydrous CH_2Cl_2 (0.75 mL) was added. Both vials were degassed and backfilled with N_2 twice and vial **B** was cooled to -35 °C. Allyl silane **S2.18** (56.1 mg, 0.2 mmol) was added into vial **B** followed by addition of fluorinating reagent solution in vial **A** via a syringe. Acyloxyl carbamate **2.2c** (79.4 mg, 0.24 mmol) in 0.75 mL CH_2Cl_2 was

added dropwise at last to vial **B**. The reaction was kept at $-35\text{ }^{\circ}\text{C}$ for 4 h and quenched with saturated NaHCO_3 solution (3 mL). The organic layer was separated from the aqueous one, which was extracted with CH_2Cl_2 (2 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified through a silica gel flash column (hexanes/acetone: from 100:1 to 10:1) to afford the desired product **2.18** as white foam (88.7 mg, 87% yield).

1,1,1,3,3,3-Hexafluoropropan-2-yl (3-(*tert*-butyldiphenylsilyl)-2-fluoropropyl)carbamate (2.18): IR ν_{max} (neat)/ cm^{-1} : 3348 (m), 2934 (w), 2861 (w), 1754 (s), 1527 (s), 1387 (m), 1236 (s), 1198 (s), 1109 (m), 701 (m); ^1H NMR (400 MHz, CDCl_3) δ 7.72–7.53 (m, 4H), 7.53–7.30 (m, 6H), 5.72–5.55 (m, 1H), 5.22 (brs, 1H), 4.65 (dddd, $J = 49.1, 14.3, 7.6, 2.6$ Hz, 1H), 3.34 (dddd, $J = 28.9, 14.5, 7.0, 2.6$ Hz, 1H), 3.16 (dddd, $J = 19.4, 14.4, 7.5, 5.1$ Hz, 1H), 1.78 (td, $J = 15.3, 7.7$ Hz, 1H), 1.48 (ddd, $J = 21.4, 15.5, 7.1$ Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.5, 135.95, 135.86, 133.5, 133.2, 129.62, 129.55, 127.9, 127.8, 120.6 (q, $J = 282.2$ Hz), 91.1 (d, $J = 170.9$ Hz), 68.8–66.6 (m), 47.5 (d, $J = 21.4$ Hz), 27.6, 18.0, 15.5 (d, $J = 21.4$ Hz); ^{19}F NMR (376 MHz, CDCl_3) δ -73.45–73.82 (m, 6F), -169.3–169.8 (m, 1F); HRMS (ESI, m/z): calcd for $\text{C}_{23}\text{H}_{26}\text{F}_7\text{NO}_2\text{SiNa}^+$, $[\text{M} + \text{Na}^+]$, 532.1513, found 532.1493.

B: procedure for iron-catalyzed aminofluorination of (*E*)-triisopropyl(penta-2,4-dien-1-yloxy)silane.

(*E*)-triisopropyl(penta-2,4-dien-1-yloxy)silane **S2.19** was prepared according to a literature procedure.⁷²



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added XtalFluor-E (184 mg, 0.8 mmol) and freshly activated 4 Å powdered molecular sieves (50 mg). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (2.5 mL) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (79 μL , 0.48 mmol) were added successively via syringes. The mixture was stirred at room temperature for 20 min. To another flame-dried sealable 3-dram vial (vial **B**) equipped with a stir bar were added the preformed $\text{Fe}(\text{NTf}_2)_2\text{-L1}$ complex (27.9 mg, 0.03 mmol) and freshly activated 4 Å powdered molecular sieves (100

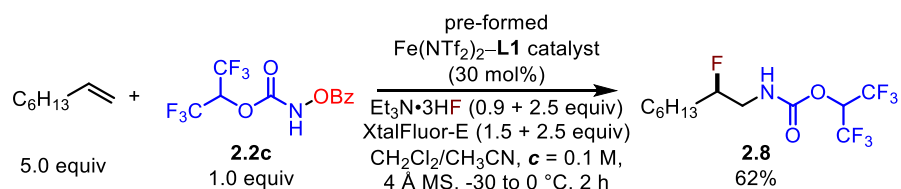
mg). Vial **B** was evacuated and backfilled with N₂ three times and then anhydrous CH₂Cl₂ (0.75 mL) was added. Both vials were degassed and backfilled with N₂ twice and vial **B** was cooled to -35 °C. (*E*)-Triisopropyl(penta-2,4-dien-1-yloxy)silane **S2.19** (68 μL, 0.24 mmol) was then added into vial **B** followed by the addition of fluorinating reagent solution in vial **A** via a syringe. Acyloxyl carbamate **2.2c** (66.2 mg, 0.20 mmol) in 0.75 mL CH₂Cl₂ was added dropwise at last to vial **B** and the reaction was kept at -35 °C for 3 h and quenched with saturated NaHCO₃ solution (3 mL). The organic layer was separated from the aqueous one, which was extracted with CH₂Cl₂ (2 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexanes/acetone: from 100:1 to 10:1) to afford the desired product **2.19** as colorless oil (61.1 mg, 65% yield).

1,1,1,3,3,3-Hexafluoropropan-2-yl (*E*)-(2-fluoro-5-((tri-*iso*-propylsilyl)oxy)pent-3-en-1-yl)carbamate

(2.19): IR ν_{\max} (neat)/cm⁻¹: 2942 (m), 2866 (m), 1747 (s), 1527 (m), 1385 (m), 1290 (m), 1232 (s), 1193 (s), 1108 (s); ¹H NMR (400 MHz, CDCl₃) δ 6.05–5.93 (m, 1H), 5.87–5.76 (m, 1H), 5.73–5.61 (m, 1H), 5.46 (brs, 1H), 5.16–4.91 (m, 1H), 4.34–4.27 (m, 2H), 3.62 (dddd, *J* = 27.6, 14.6, 7.2, 3.2 Hz, 1H), 3.38 (dddd, *J* = 19.4, 14.6, 7.7, 5.0 Hz, 1H), 1.18–0.98 (m, 21H); ¹³C NMR (100 MHz, CDCl₃) δ 152.7, 135.5 (d, *J* = 10.5 Hz), 122.9 (d, *J* = 18.8 Hz), 120.6 (q, *J* = 282.7 Hz), 91.2 (d, *J* = 169.8 Hz), 68.8–66.7 (m), 62.5 (d, *J* = 0.9 Hz), 45.6 (d, *J* = 22.8 Hz), 17.9, 12.0; ¹⁹F NMR (376 MHz, CDCl₃) δ -73.60–73.85 (m, 6F), -181.45–-181.96 (m, 1F); HRMS (ESI, *m/z*): calcd for C₁₈H₃₁F₇NO₃SiNa⁺, [*M* + Na⁺], 470.1956, found 470.1961.

C: procedure for iron-catalyzed aminofluorination of 1-octene.

1-Octene is commercially available and it was distilled before usage.



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added Fe(NTf₂)₂ (36.9 mg, 0.06 mmol) and **L1** (16.4 mg, 0.06 mmol). After vial **A** was evacuated and backfilled with N₂ three

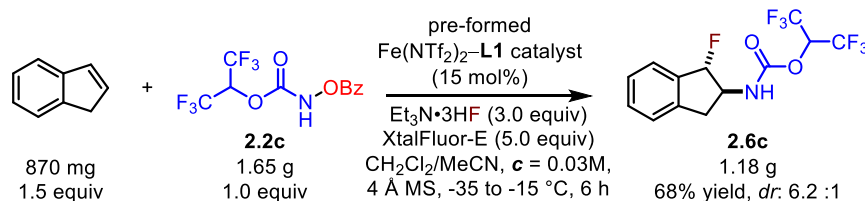
times, anhydrous CH_2Cl_2 (0.65 mL) and MeCN (0.15 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To a second flame-dried sealable 2-dram vial (vial **B**) equipped with a stir bar were added XtalFluor-E (69 mg, 0.3 mmol) and freshly activated 4 Å powdered molecular sieves (50 mg). After vial **B** was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (1.0 mL) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (29 μL , 0.18 mmol) were added successively via syringes. The mixture was stirred at room temperature for 20 min. To another flame-dried sealable 3-dram vial (vial **C**) equipped with a stir bar were added acyloxyl carbamate **2.2c** (66.2 mg, 0.20 mmol) and freshly activated 4 Å powdered molecular sieves (100 mg). Vial **C** was evacuated and backfilled with N_2 three times and then anhydrous CH_2Cl_2 (0.3 mL) was added. All three vials were degassed and backfilled with N_2 twice and vial **C** was cooled to $-30\text{ }^\circ\text{C}$. Freshly distilled 1-octene (157 μL , 1.0 mmol) was then added into vial **C** followed by the addition of fluorinating reagent solution in vial **B** via a syringe. The catalyst solution in vial **A** was added with a syringe pump over 20 min to vial **C** at $-30\text{ }^\circ\text{C}$ and the reaction was warmed up to $0\text{ }^\circ\text{C}$ and kept stirring for additional 5 minutes. Meanwhile, to another flame-dried sealable 2-dram vial (vial **D**) equipped with a stir bar was added XtalFluor-E (115 mg, 0.5 mmol). Vial **D** was evacuated and backfilled with N_2 three times, then anhydrous CH_2Cl_2 (1.0 mL) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (82 μL , 0.5 mmol) were added successively via syringes. After being stirred at room temperature for 10 min, the solution in vial **D** was added to vial **C** via a syringe at $0\text{ }^\circ\text{C}$. The reaction in vial **C** was stirred at $0\text{ }^\circ\text{C}$ for additional 2 h and quenched with saturated NaHCO_3 solution (3 mL). The organic layer was separated from the aqueous one, which was extracted with CH_2Cl_2 (2 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexanes/acetone: from 100:1 to 10:1) to afford the desired product **2.8** as a white solid (42.3 mg, 62% yield, m.p. $55\text{--}56\text{ }^\circ\text{C}$).

1,1,1,3,3,3-Hexafluoropropan-2-yl (2-fluorooctyl)carbamate (2.8): IR ν_{max} (neat)/ cm^{-1} : 3669 (m), 3331 (m), 2969 (m), 1741 (s), 1558 (m), 1385 (m), 1251 (s), 1197 (s), 1153 (m), 1107 (s), 1066 (m), 951 (m), 903(m), 690 (m); ^1H NMR (400 MHz, CDCl_3) δ 5.75–5.62 (m, 1H), 5.41 (brs, 1H), 4.68–4.45 (m, 1H), 3.57 (dddd, $J = 29.5, 14.6, 7.1, 2.6\text{ Hz}$, 1H), 3.32 (dddd, $J = 19.7, 14.5, 7.6, 5.1\text{ Hz}$, 1H), 1.81–1.22 (m, 10H), 0.89 (t, $J = 6.7\text{ Hz}$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.8, 120.6 (q, $J = 283.2\text{ Hz}$), 92.7 (d, $J =$

169.8 Hz), 69.1–66.6 (m), 45.5 (d, $J = 20.6$ Hz), 32.1 (d, $J = 19.9$ Hz), 31.6, 28.9, 24.7 (d, $J = 4.7$ Hz), 22.5, 14.0; ^{19}F NMR (376 MHz, CDCl_3) δ -73.51–73.82 (m, 6F), -186.23–186.79 (m, 1F); HRMS (ESI, m/z): calcd for $\text{C}_{12}\text{H}_9\text{F}_7\text{NO}_2^+$, $[\text{M} + \text{H}^+]$, 342.1299, found 342.1285.

D: procedure for iron-catalyzed aminofluorination of indene at gram scale.

Indene is commercially available and it was distilled before usage.



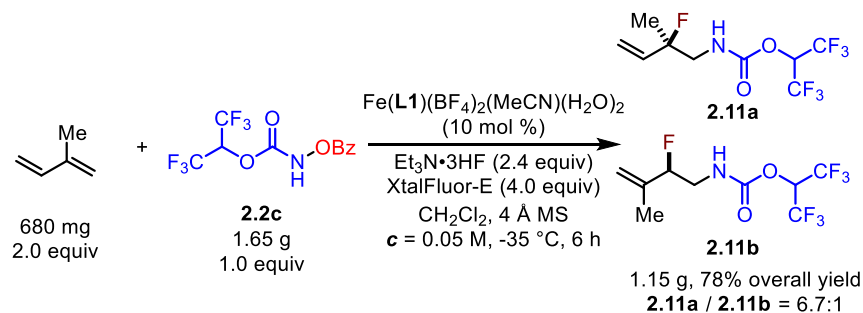
To a flame-dried 25 mL round bottom flask (flask **A**) equipped with a stir bar were added $\text{Fe}(\text{NTf}_2)_2$ (461 mg, 0.75 mmol) and **L1** (205 mg, 0.75 mmol). After flask **A** was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (8.0 mL) and MeCN (1.6 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To a second flame-dried 100 mL round bottom flask (flask **B**) equipped with a stir bar were added XtalFluor-E (5.73 g, 25 mmol) and freshly activated 4 Å powdered molecular sieves (1.5 g). After flask **B** was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (60 mL) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (2.44 mL, 15 mmol) were added successively via syringes. The mixture was stirred at room temperature for 20 min. To another flame-dried sealable 250 mL round bottom flask (flask **C**) equipped with a stir bar were added **2.2c** (1.655g, 5.0 mmol) and freshly activated 4 Å powdered molecular sieves (2.5 g). Flask **C** was evacuated and backfilled with N_2 three times and then anhydrous CH_2Cl_2 (100 mL) was added. All three flasks were degassed and backfilled with N_2 twice and flask **C** was cooled to -78 °C. Freshly distilled indene (0.9 mL, 7.5 mmol) was added into flask **C**. Pre-cooled fluorinating reagent solution in flask **B** (in -35 °C cold bath) was quickly transferred to flask **C** (in -78 °C cold bath) via a stainless steel cannula. Flask **C** was moved to -35 °C cold bath and the catalyst solution in flask **A** was added with a syringe pump over 20 min to flask **C**. The reaction was kept at -35 °C for additional 3 h and allowed to warm up gradually to -15 °C. After being stirred at -15 °C for 3 h, the reaction mixture was quenched with saturated NaHCO_3 solution (50 mL) and stirred vigorously for 10 min. The organic layer

was separated from the aqueous one, which was extracted with CH₂Cl₂ (20 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexanes/EtOAc: from 100:1 to 9:1) to afford the desired products as white solid (1.18 g, 68% overall yield of two diastereomers, *dr*: 6.2:1).

(±)1,1,1,3,3,3-Hexafluoropropan-2-yl (*trans*-1-fluoro-2,3-dihydro-1*H*-inden-2-yl)carbamate (2.6c-*trans*): m.p. 98–100 °C; IR ν_{\max} (neat)/cm⁻¹: 3334 (m), 2970 (m), 1733 (s), 1546 (m), 1380 (m), 1262 (m), 1186 (s), 1165 (m), 1107 (s), 980 (m), 904 (m), 889 (m), 744 (m), 690 (m); ¹H NMR (400 MHz, CDCl₃) δ 7.48 (d, *J* = 7.3 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.36–7.24 (m, 2H), 5.87 (dd, *J* = 55.8, 3.5 Hz, 1H), 5.76–5.65 (m, 1H), 5.37 (brd, *J* = 5.6 Hz, 1H), 4.62–4.44 (m, 1H), 3.55 (dd, *J* = 16.3, 7.6 Hz, 1H), 2.93–2.82 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 152.1, 140.4 (d, *J* = 4.7 Hz), 137.4 (d, *J* = 18.4 Hz), 130.4 (d, *J* = 3.4 Hz), 127.8 (d, *J* = 2.7 Hz), 125.7 (d, *J* = 1.5 Hz), 125.2 (d, *J* = 1.9 Hz), 120.5 (q, *J* = 282.3 Hz), 98.8 (d, *J* = 183.3 Hz), 68.9–66.6 (m), 58.6 (d, *J* = 26.2 Hz), 36.2 (d, *J* = 2.0 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -73.58 (d, *J* = 5.6 Hz, 6F), -170.55 (dd, *J* = 55.9, 18.4 Hz, 1F); HRMS (ESI, *m/z*): calcd for C₁₃H₁₀F₇NO₂Na⁺, [M + Na⁺], 368.0492, found 368.0482.

(±)1,1,1,3,3,3-Hexafluoropropan-2-yl (*cis*-1-fluoro-2,3-dihydro-1*H*-inden-2-yl)carbamate (2.6c-*cis*): m.p. 91–92 °C; IR ν_{\max} (neat)/cm⁻¹: 3335 (m), 2976 (m), 1732 (s), 1540 (m), 1380 (m), 1261 (m), 1182 (s), 1168 (m), 1109 (s), 980 (m), 901 (m), 896 (m), 742 (m), 685 (m); ¹H NMR (400 MHz, CDCl₃) δ 7.53 (dd, *J* = 12.7, 6.0 Hz, 1H), 7.50–7.39 (m, 1H), 7.33 (t, *J* = 7.1 Hz, 2H), 5.74 (dd, *J* = 58.0, 4.8 Hz, 1H), 5.73 (m, 2H), 4.54 (dddd, *J* = 16.6, 13.4, 8.5, 4.9 Hz, 1H), 3.37 (dt, *J* = 20.9, 10.5 Hz, 1H), 3.02 (ddd, *J* = 15.5, 8.5, 3.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 152.4, 142.2 (d, *J* = 5.3 Hz), 136.9 (d, *J* = 15.4 Hz), 131.2 (d, *J* = 4.5 Hz), 129.7 (q, *J* = 171.2 Hz), 127.7 (d, *J* = 3.7 Hz), 126.5 (d, *J* = 2.6 Hz), 125.3 (d, *J* = 3.1 Hz), 93.9 (d, *J* = 178.6 Hz), 69.15–66.27 (m), 54.3 (d, *J* = 19.2 Hz), 36.4; ¹⁹F NMR (376 MHz, CDCl₃) δ -70.72–75.24 (m, 6F), -178.96 (dd, *J* = 57.7, 24.3 Hz, 1F); HRMS (ESI, *m/z*): calcd for C₁₃H₁₀F₇NO₂Na⁺, [M + Na⁺] 368.0492, found 368.0478.

***E*: procedure for iron-catalyzed aminofluorination of isoprene at gram scale.**



Isoprene is commercially available and it was distilled before usage.

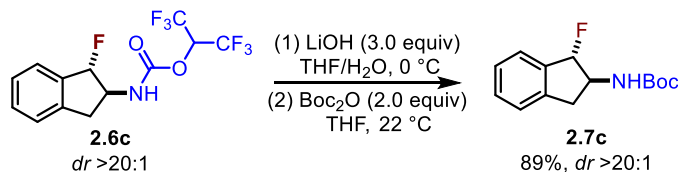
To a flame-dried sealable 100 mL round bottom flask (flask **A**) equipped with a stir bar were added XtalFluor-E (5.04 g, 20 mmol) and freshly activated 4 Å powdered molecular sieves (1.5 g). After the vial was evacuated and backfilled with N₂ three times, anhydrous CH₂Cl₂ (50 mL) and Et₃N·3HF (2.15 mL, 12 mmol) were added successively via syringes. The mixture was stirred at room temperature for 20 min. To another flame-dried sealable 200 mL flask (flask **B**) equipped with a stir bar were added the preformed catalyst **cat.1**, Fe(L1)(BF₄)₂(MeCN)(H₂O)₂ (300 mg, 0.5 mmol) and freshly activated 4 Å powdered molecular sieves (2.0 g). Flask **B** was evacuated and backfilled with N₂ three times and then anhydrous CH₂Cl₂ (30 mL) was added. Both flasks were degassed and backfilled with N₂ twice and flask **B** was cooled to -78 °C and freshly distilled isoprene (1 mL, 10 mmol) was added into flask **B**. Pre-cooled fluorinating reagent solution in flask **A** (in -35 °C cold bath) was quickly transferred to flask **B** (in -78 °C cold bath) via a stainless steel cannula, and then flask **B** was moved to -35 °C cold bath. Acyloxyl carbamate **2.2c** (1.65 g, 5.0 mmol) in 4.0 mL CH₂Cl₂ was added dropwise at last to flask **B** and the reaction was kept at -35 °C for 3 h and quenched with saturated NaHCO₃ solution (30 mL). The organic layer was separated from the aqueous one, which was extracted with CH₂Cl₂ (20 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexanes/acetone: from 100:1 to 8:1) to afford the aminofluorination products as white solid (1.15 g, 78% yield).

1,1,1,3,3,3-Hexafluoropropan-2-yl (2-fluoro-2-methylbut-3-en-1-yl)carbamate (2.11a): m.p.53–55 °C; IR ν_{max} (neat)/cm⁻¹: 3338 (m), 2971 (m), 1740 (s), 1553 (m), 1385 (m), 1241 (s), 1192 (s), 1152 (m), 1105

(s), 1073 (s), 933 (m), 903 (m), 687 (m); ^1H NMR (400 MHz, CDCl_3) δ 5.83 (ddd, $J = 18.7, 17.4, 11.0$ Hz, 1H), 5.72–5.62 (m, 1H), 5.38 (d, $J = 17.4$ Hz, 1H), 5.33 (brs, 1H), 5.25 (d, $J = 11.0$ Hz, 1H), 3.46 (dd, $J = 21.2, 6.3$ Hz, 2H), 1.44 (d, $J = 21.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.0, 137.0 (d, $J = 22.0$ Hz), 120.6 (q, $J = 281.6$ Hz), 116.0 (d, $J = 11.0$ Hz), 95.2 (d, $J = 172.7$ Hz), 68.9–66.6 (m), 49.0 (d, $J = 22.8$ Hz), 22.8 (d, $J = 23.7$ Hz); ^{19}F NMR (376 MHz, CDCl_3) δ -73.67 (d, $J = 6.2$ Hz, 6F), -154.86–156.17 (m, 1F); HRMS (ESI, m/z): calcd for $\text{C}_9\text{H}_{11}\text{F}_7\text{NO}_2^+$, $[\text{M} + \text{H}^+]$, 298.0673, found 298.0671.

2.3.7 Procedures for aminofluorination products derivatization

A: procedure for derivatization of indene aminofluorination product.

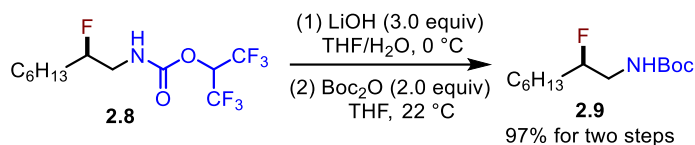


In a 2-dram vial equipped with a stir bar, vicinal fluorocarbamate **7** (69.0 mg, 0.2 mmol) was dissolved in THF (2 mL) and cooled to 0 °C. LiOH (14.4 mg, 0.6 mmol) in 0.4 mL water was added and the reaction was vigorously stirred for 1.5 h until the starting material was consumed (monitored by TLC). To the above reaction mixture, di-*tert*-butyl dicarbonate (87 mg, 0.4 mmol) in 1.0 mL THF was added at 0 °C. The resulting mixture was warmed up to room temperature and kept stirring for additional 3 h. The reaction was then neutralized with dilute aqueous HCl solution (1M). After evaporation of THF *in vacuo*, the residue was extracted with EtOAc (4 × 2 mL). The combined organic layer was dried over anhydrous Na_2SO_4 , concentrated *in vacuo* and the residue was purified through a silica gel column to afford **2.7c** as white foam (44.8 mg, 89% yield, $dr >20:1$).

tert-Butyl-1-fluoro-2,3-dihydro-1H-inden-2-yl carbamate (2.7c): IR ν_{max} (neat)/ cm^{-1} : 3334 (m), 2977 (m), 2931 (w), 1681 (s), 1518 (s), 1366 (m), 1277 (m), 1163 (s), 752 (s); ^1H NMR (400 MHz, CDCl_3) δ 7.46 (d, $J = 7.4$ Hz, 1H), 7.35 (t, $J = 7.1$ Hz, 1H), 7.32 – 7.22 (m, 2H), 5.81 (d, $J = 56.1$ Hz, 1H), 4.78 (s, 1H), 4.43 (d, $J = 14.0$ Hz, 1H), 3.48 (dd, $J = 16.3, 7.5$ Hz, 1H), 2.77 (d, $J = 16.1$ Hz, 1H), 1.46 (s, 9H); ^{19}F NMR (376 MHz, CDCl_3) δ -170.15 (dd, $J = 55.7, 17.7$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 155.3, 141.4,

138.1 (d, $J = 18.3$ Hz), 130.1 (d, $J = 3.4$ Hz), 127.4 (d, $J = 2.7$ Hz), 125.7 (d, $J = 1.5$ Hz), 125.2 (d, $J = 2.0$ Hz), 99.5 (d, $J = 178$ Hz), 79.9, 57.9, 36.8, 28.4; HRMS (ESI, m/z): calcd for $C_{14}H_{18}FNO_2Na^+$, $[M + Na^+]$, 274.1214, found 274.1215.

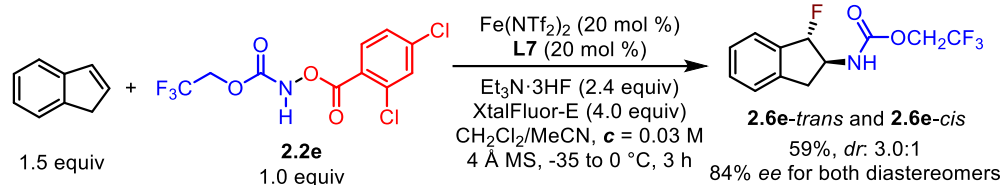
B: procedure for derivatization of 1-octene aminofluorination product.



In a 2-dram vial equipped with a stir bar, vicinal fluorocarbamate **2.8** (68.3 mg, 0.2 mmol) was dissolved in THF (2 mL) and cooled to 0 °C. LiOH (14.4 mg, 0.6 mmol) in 0.4 mL water was added and the reaction was vigorously stirred for 1.5 h until the starting material was consumed (monitored by TLC). To the above reaction mixture, di-*tert*-butyl dicarbonate (87 mg, 0.4 mmol) in 1.0 mL THF was added at 0 °C. The resulting mixture was warmed up to room temperature and kept stirring for additional 3 h. The reaction was then neutralized with dilute aqueous HCl solution (1M). After evaporation of THF *in vacuo*, the residue was extracted with EtOAc (4 × 2 mL). The combined organic layer was dried over anhydrous Na_2SO_4 , concentrated *in vacuo* and the residue was purified through a silica gel column to afford **2.9** as colorless oil (48 mg, 97% yield).

tert-Butyl-(2-fluorooctyl)carbamate (2.9): IR ν_{max} (neat)/ cm^{-1} : 3337 (m), 2926 (s), 2855 (m), 1694 (s), 1512 (m), 1365 (m), 1249 (m), 1165 (s); ^1H NMR (400 MHz, CDCl_3) δ 4.86 (brs, 1H), 4.65 – 4.41 (m, 1H), 3.46 (ddd, $J = 30.8, 13.7, 6.6$ Hz, 1H), 3.25 – 3.05 (m, 1H), 1.74 – 1.52 (m, 2H), 1.52 – 1.40 (m, 10H), 1.39 – 1.22 (m, 7H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{19}F NMR (376 MHz, CDCl_3) δ -184.14 – -187.49 (m); ^{13}C NMR (100 MHz, CDCl_3) δ 155.9, 93.6 (d, $J = 167.0$ Hz), 79.5, 44.6 (d, $J = 20.2$ Hz), 32.3 (d, $J = 20.1$ Hz), 31.6, 29.0, 28.4, 24.8 (d, $J = 4.8$ Hz), 22.5, 14.0; HRMS (ESI, m/z): calcd for $C_{13}H_{26}FNO_2Na^+$, $[M + Na^+]$, 270.1840, found 270.1833.

2.3.8 Procedures for the iron-catalyzed asymmetric aminofluorination of indene



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{NTf}_2)_2$ (24.6 mg, 0.04 mmol) and a chiral ligand **L7** (15.7 mg, 0.04 mmol). After vial **A** was degassed and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.5 mL) and MeCN (0.08 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To a second flame-dried sealable 2-dram vial (vial **B**) equipped with a stir bar were added XtalFluor-E (183 mg, 0.8 mmol) and freshly activated 4 Å powdered molecular sieves (50 mg). After vial **B** was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (4.0 mL) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (78 μL , 0.48 mmol) were added successively via syringes. The mixture was stirred at room temperature for 20 min. To another flame-dried sealable 3-dram vial (vial **C**) equipped with a stir bar were added acyloxyl carbamate **2.2e** (0.20 mmol) and freshly activated 4 Å powdered molecular sieves (100 mg). Vial **C** was evacuated and backfilled with N_2 three times and then anhydrous CH_2Cl_2 (2.0 mL) was added. All three vials were cooled to $-35 \text{ }^\circ\text{C}$. Freshly distilled indene (35 μL , 0.3 mmol) was then added into vial **C** followed by the addition of fluorinating reagent solution in vial **B** via a syringe. The catalyst solution in vial **A** was added to vial **C** via a syringe pump over 20 min and the reaction was kept at the same temperature for 2 h. Meanwhile, to another flame-dried sealable 2-dram vial (vial **D**) equipped with a stir bar was added XtalFluor-E (46 mg, 0.2 mmol). Vial **D** was evacuated and backfilled with N_2 three times, then anhydrous CH_2Cl_2 (1.0 mL) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (33 μL , 0.2 mmol) were added successively via syringes. After stirring at room temperature for 10 min, the solution in vial **D** was added to vial **C** the reaction mixture was warmed up to $0 \text{ }^\circ\text{C}$ and stirred for additional 1 h. The reaction was then quenched with saturated NaHCO_3 solution (3 mL). The organic layer was separated from the aqueous one, which was extracted with CH_2Cl_2 (2 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*.

Compound **2.6e-trans** was isolated through a silica gel flash column (hexanes/EtOAc: from 30:1 to 10:1) as white solid (24.3 mg, 44% yield, m.p. 60–62 °C, $[\alpha]_D^{20} = +4.5^\circ$ (*c* 2.0, CHCl₃)).

2,2,2-Trifluoroethyl ((1*S*,2*S*)-1-fluoro-2,3-dihydro-1*H*-inden-2-yl)carbamate (2.6e-trans): IR ν_{\max} (neat)/cm⁻¹: 3330 (m), 2970 (w), 1731 (s), 1545 (m), 1388 (m), 1260 (m), 1181 (s), 1100 (s), 970 (m), 914 (m), 890 (m), 740 (m), 696 (m); ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, *J* = 7.5 Hz, 1H), 7.42–7.34 (m, 1H), 7.34–7.27 (m, 2H), 5.85 (dd, *J* = 56.0, 4.1 Hz, 1H), 5.21 (brd, *J* = 7.3 Hz, 1H), 4.81–4.23 (m, 3H), 3.51 (dd, *J* = 16.2, 7.7 Hz, 1H), 2.84 (dt, *J* = 16.5, 4.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 154.0, 140.6 (d, *J* = 4.7 Hz), 137.7 (d, *J* = 18.4 Hz), 130.3 (d, *J* = 3.4 Hz), 127.7 (d, *J* = 2.8 Hz), 125.6 (d, *J* = 1.6 Hz), 125.2 (d, *J* = 1.8 Hz), 123.0 (q, *J* = 277.4 Hz), 99.0 (d, *J* = 182.9 Hz), 61.1 (q, *J* = 36.7 Hz), 58.3 (d, *J* = 25.8 Hz), 36.4; ¹⁹F NMR (376 MHz, CDCl₃) δ -74.26 (t, *J* = 8.5 Hz, 3F), -170.98 (dd, *J* = 56.1, 18.6 Hz, 1F); HRMS (ESI, *m/z*): calcd for C₁₂H₁₁F₄NO₂Na⁺, [M + Na⁺], 300.0618, found 300.0625.

The *ee* was determined by Chiral HPLC analysis (Chiralcel OD-H column, 5% isopropanol in hexanes, flow rate = 1.0 mL/min, UV detection at 210 nm). *t_r* (minor) = 23.5 min, *t_r* (major) = 16.7 min, 84% *ee*.

Compound **2.6e-cis** was isolated through a silica gel flash column (hexanes/EtOAc: from 30:1 to 10:1) as white solid (8.3 mg, 15% yield, m.p. 47–48 °C, $[\alpha]_D^{20} = +7.6^\circ$ (*c* 1.2, CHCl₃)).

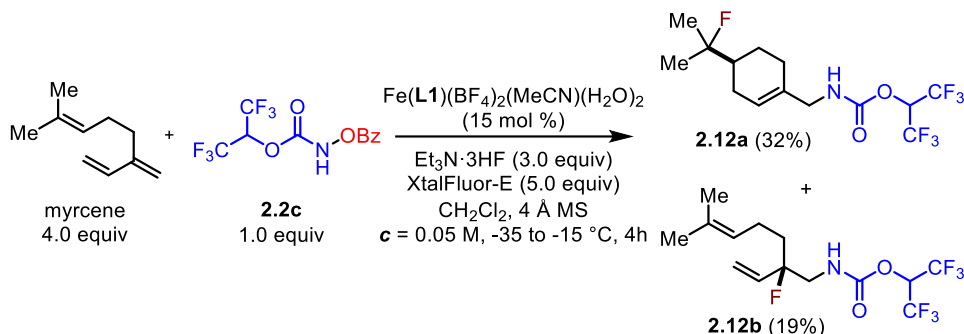
2,2,2-Trifluoroethyl ((1*R*,2*S*)-1-fluoro-2,3-dihydro-1*H*-inden-2-yl)carbamate (2.6e-cis): IR ν_{\max} (neat)/cm⁻¹: 3330 (m), 2970 (w), 1732 (s), 1530 (m), 1279 (m), 1182 (s), 1170 (m), 1100 (s), 980 (m), 900 (m), 894 (m), 741 (m), 680 (m); ¹H NMR (400 MHz, CDCl₃) δ 7.55–7.47 (m, 1H), 7.46–7.37 (m, 1H), 7.31 (t, *J* = 6.3 Hz, 2H), 5.71 (dd, *J* = 58.1, 4.7 Hz, 1H), 5.54 (brd, *J* = 7.7 Hz, 1H), 4.69–4.39 (m, 3H), 3.34 (dd, *J* = 15.8, 7.4 Hz, 1H), 2.98 (ddd, *J* = 15.6, 8.5, 3.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 154.2, 142.5 (d, *J* = 5.4 Hz), 137.1 (d, *J* = 15.4 Hz), 131.0 (d, *J* = 4.5 Hz), 127.6 (d, *J* = 3.7 Hz), 126.5 (d, *J* = 2.6 Hz), 125.2 (d, *J* = 3.0 Hz), 123.0 (q, *J* = 277.6 Hz), 94.1 (d, *J* = 178.1 Hz), 61.1 (q, *J* = 36.5 Hz), 54.1 (d, *J* = 19.2 Hz), 36.5; ¹⁹F NMR (376 MHz, CDCl₃) δ -74.24 (t, *J* = 8.2 Hz, 3F), -179.07 (dd, *J* = 58.1, 25.0 Hz, 1F); HRMS (ESI, *m/z*): calcd for C₁₂H₁₁F₄NO₂Na⁺, [M + Na⁺], 300.0618, found 300.0625.

The *ee* was determined by Chiral HPLC analysis (Chiralpak AD-H column, 15% EtOH in hexanes, flow rate = 1.0 mL/min, UV detection at 210 nm). t_r (minor) = 12.2 min, t_r (major) = 8.02 min, 84% *ee*.

2.3.9 Procedures for the iron-catalyzed aminofluorination of myrcene and (-)- β -pinene

A: procedure for iron-catalyzed aminofluorination of myrcene.

Myrcene is commercially available and it was distilled before usage.



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added XtalFluor-E (229 mg, 1.0 mmol) and freshly activated 4 Å powdered molecular sieves (50 mg). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (3.0 mL) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (98 μL , 0.6 mmol) were added successively via syringes. The mixture was stirred at room temperature for 20 min. To another flame-dried sealable 3-dram vial (vial **B**) equipped with a stir bar were added the preformed catalyst **cat.1**, $\text{Fe(L1)(BF}_4)_2(\text{MeCN})(\text{H}_2\text{O})_2$ (17.4 mg, 0.03 mmol) and freshly activated 4 Å powdered molecular sieves (100 mg). Vial **B** was evacuated and backfilled with N_2 three times and then anhydrous CH_2Cl_2 (0.5 mL) was added. Both vials were degassed and backfilled with N_2 twice and vial **B** was cooled to -35 °C. Myrcene (134 μL , 0.8 mmol) was then added into vial **B** followed by addition of fluorinating reagent solution in vial **A** via a syringe. Acyloxyl carbamate **2.2c** (66.2 mg, 0.20 mmol) in 0.5 mL CH_2Cl_2 was added dropwise at last to vial **B** and the reaction was kept at -35 °C for 2 h and gradually warmed up to -15 °C. After the reaction was kept at -15 °C for another 2 h, it was then quenched with saturated NaHCO_3 solution (3 mL). The organic layer was separated from the aqueous one, which was extracted with CH_2Cl_2 (2 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*.

Compound **2.12a** was isolated through a silica gel flash column (hexanes/Et₂O: from 100:1 to 8:1) as a white solid (23.4 mg, 32% yield, m.p. 48–49 °C). Its structure was confirmed through X-ray crystallographic analysis (Figure 2.3), which has been deposited to The Cambridge Crystallographic Data Centre as CCDC 1429400.

1,1,1,3,3,3-Hexafluoropropan-2-yl ((4-(2-fluoropropan-2-yl)cyclohex-1-en-1-yl)methyl) carbamate

(2.12a): IR ν_{\max} (neat)/cm⁻¹: 3340 (w), 2967 (w), 1740 (s), 1531 (m), 1385 (m), 1234 (w), 1194 (s), 1109 (m), 904 (m), 689 (m); ¹H NMR (400 MHz, CDCl₃) δ 5.75–5.64 (m, 1H), 5.64–5.58 (m, 1H), 5.09 (brs, 1H), 3.76 (d, J = 6.2 Hz, 2H), 2.19–2.09 (m, 1H), 2.08–2.01 (m, 2H), 1.98–1.67 (m, 3H), 1.35 (s, 3H), 1.38–1.24 (m, 1H), 1.29 (s, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ -73.65 (d, J = 6.4 Hz, 6F), -140.01–-142.40 (m, 1F); ¹³C NMR (100 MHz, CDCl₃) δ 152.6, 133.4, 123.3, 120.6 (q, J = 282.4 Hz), 97.3 (d, J = 166.5 Hz), 68.5–66.8 (m), 47.3, 43.3 (d, J = 22.4 Hz), 26.8, 26.3 (d, J = 7.3 Hz), 24.7 (d, J = 24.9 Hz), 23.9 (d, J = 25.3 Hz), 23.3 (d, J = 5.1 Hz); HRMS (ESI, m/z): calcd for C₁₄H₁₈F₇NO₂Na⁺, [M + Na⁺], 388.1118, found 388.1108.

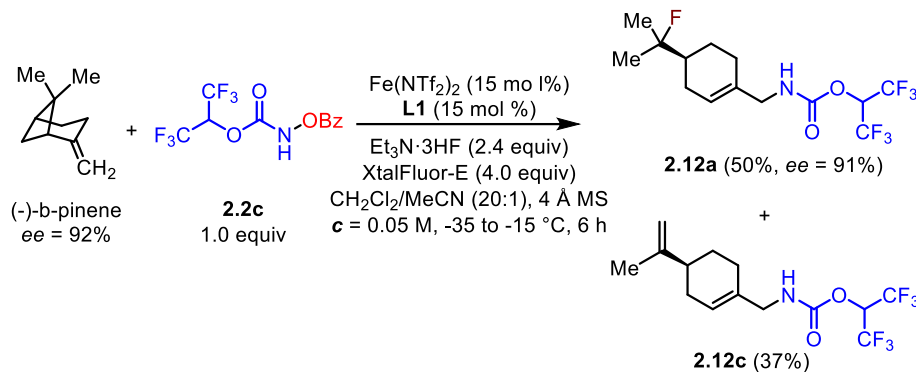
Compound **2.12b** was isolated through a silica gel flash column (hexanes/Et₂O: from 100:1 to 8:1) as a white solid (13.9 mg, 19% yield, m.p. 64–65 °C).

1,1,1,3,3,3-Hexafluoropropan-2-yl (2-fluoro-6-methyl-2-vinylhept-5-en-1-yl)carbamate (2.12b): IR

ν_{\max} (neat)/cm⁻¹: 3343 (m), 2978 (m), 2928 (m), 1731 (s), 1552 (m), 1383 (m), 1242 (s), 1196 (s), 1148 (m), 1105 (s), 949 (m), 905 (m), 882 (m), 693 (m); ¹H NMR (400 MHz, CDCl₃) δ 5.84–5.59 (m, 2H), 5.38 (dd, J = 17.4, 1.2 Hz, 1H), 5.30 (dt, J = 11.1, 1.6 Hz, 1H), 5.06 (t, J = 7.3 Hz, 1H), 3.52–3.41 (m, 2H), 2.14–1.97 (m, 2H), 1.82–1.57 (m, 2H), 1.68 (s, 3H), 1.59 (s, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ -73.61–-73.73 (m, 6F), -165.51–-166.65 (m, 1F); ¹³C NMR (100 MHz, CDCl₃) δ 152.9, 135.5 (d, J = 21.6 Hz), 132.6, 123.0, 120.6 (q, J = 282.2 Hz), 116.7 (d, J = 11.4 Hz), 97.4 (d, J = 177.3 Hz), 68.8–66.5 (m), 48.1 (d, J = 22.2 Hz), 36.3 (d, J = 21.7 Hz), 25.6, 21.6 (d, J = 5.1 Hz), 17.6; HRMS (ESI, m/z): calcd for C₁₄H₁₉F₇NO₂⁺, [M + H⁺], 366.1299, found 366.1294.

B: procedure for iron-catalyzed aminofluorination of (-)- β -pinene.

(-)- β -Pinene was purchased from Sigma-Aldrich (with ee = 92%) and it was distilled before usage.

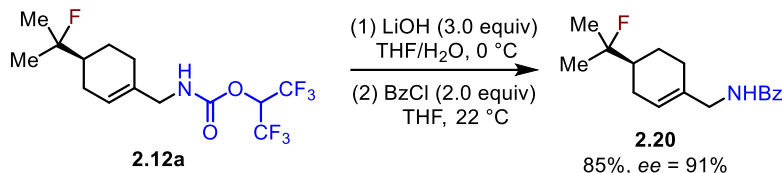


To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{NTf}_2)_2$ (18.5 mg, 0.03 mmol) and **L1** (8.2 mg, 0.03 mmol). After vial **A** was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.5 mL) and MeCN (0.08 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To a second flame-dried sealable 2-dram vial (vial **B**) equipped with a stir bar were added XtalFluor-E (184 mg, 0.8 mmol) and freshly activated 4 Å powdered molecular sieves (30 mg). After vial **B** was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (2.0 mL) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (79 μL , 0.48 mmol) were added successively via syringes. The mixture was stirred at room temperature for 20 min. To another flame-dried sealable 3-dram vial (vial **C**) equipped with a stir bar were added acyloxyl carbamate **2.2c** (66.2 mg, 0.20 mmol) and freshly activated 4 Å powdered molecular sieves (60 mg). Vial **C** was evacuated and backfilled with N_2 three times and then anhydrous CH_2Cl_2 (1.5 mL) was added. All three vials were degassed and backfilled with N_2 twice and vial **C** was cooled to -35 °C. Freshly distilled (-)- β -pinene (63 μL , 0.4 mmol) was then added into vial **C** followed by the addition of fluorinating reagent solution in vial **B** via a syringe. The catalyst solution in vial **A** was added with a syringe pump over 20 min to vial **C** at -35 °C and the reaction was kept at the same temperature for 2.5 h and allowed to warm up gradually to -15 °C. The reaction was kept at this temperature for additional 3.5 h and quenched with saturated NaHCO_3 solution (3 mL). The organic layer was separated from the aqueous one, which was extracted with CH_2Cl_2 (2 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified through a silica gel flash column

(hexanes/EtOAc: from 100:1 to 9:1) to afford both the aminofluorination product (**2.12a**) and a side-product through elimination (**2.12c**).

Compound **2.12a** was isolated as a white solid (36 mg, 50% yield). The *ee* of **2.12a** as determined by HPLC analysis after hydrolysis and *N*-benzoylation (procedure is below).

C: procedure for product derivatization.



In a 2-dram vial equipped with a stir bar, **2.12a** (47 mg, 0.128 mmol) was dissolved in THF (2 mL) and cooled to 0 °C. LiOH (10 mg, 0.39 mmol) in 0.2 mL water was added and the reaction was vigorously stirred for 1.5 h until the starting material was consumed (monitored by TLC). To the above reaction mixture, benzoyl chloride (30 μ L, 0.256 mmol) in 1.0 mL THF was added at 0 °C. The resulting mixture was warmed up to room temperature and kept stirring for additional 3 h. The reaction was then neutralized with dilute aqueous HCl solution (1M). After evaporation of THF *in vacuo*, the residue was extracted with EtOAc (4 \times 2 mL). The combined organic layer was dried over anhydrous Na₂SO₄, concentrated *in vacuo* and the residue was purified through a silica gel column (hexanes/EtOAc: from 20:1 to 5:1) to afford **2.20** as clear oil (30.0 mg, 85% yield).

(R)-N-((4-(2-fluoropropan-2-yl) cyclohex-1-en-1-yl) methyl) benzamide (2.20): IR ν_{max} (neat)/cm⁻¹: 3321 (br), 2924 (m), 2846 (w), 1640 (s), 1539 (s), 1490 (m), 1289 (m), 708 (m); ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, *J* = 7.8 Hz, 2H), 7.54 – 7.47 (m, 1H), 7.43 (t, *J* = 7.3 Hz, 2H), 6.16 (s, 1H), 5.71–5.57 (m, 1H), 4.07 – 3.90 (m, 2H), 2.20 – 2.05 (m, 3H), 1.99 – 1.68 (m, 3H), 1.34 (s, 3H), 1.32 – 1.18 (m, 4H); ¹⁹F NMR (376 MHz, CDCl₃) δ -140.87 (m, 1F); ¹³C NMR (100 MHz, CDCl₃) δ 167.4, 134.6, 134.5, 131.4, 128.6, 126.9, 122.5, 97.4 (d, *J* = 166.1 Hz), 45.4, 43.5 (d, *J* = 22.3 Hz), 27.2, 26.4 (d, *J* = 7.1 Hz), 24.7 (d, *J* = 24.9 Hz), 23.9 (d, *J* = 25.2 Hz), 23.5 (d, *J* = 5.2 Hz); HRMS (ESI, *m/z*): calcd for C₁₇H₂₂FNONa⁺, [M + Na⁺], 298.1578, found 298.1580.

The *ee* of **2.20** was determined by Chiral HPLC analysis (Chiralcel OD-H column, 10% isopropanol in hexanes, flow rate = 0.6 mL/min, UV detection at 254 nm). t_r (major) = 32.5 min, t_r (minor) = 34.4 min, 91% *ee*.

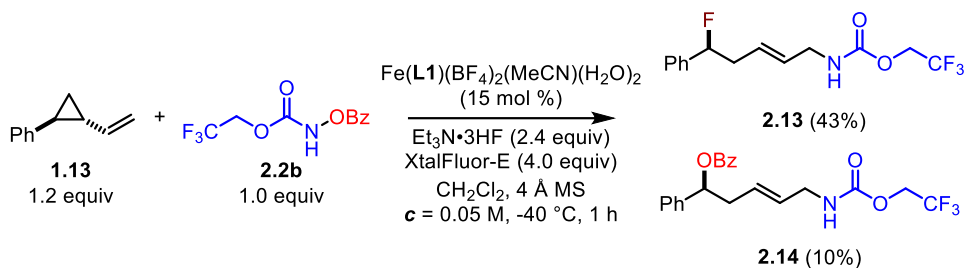
Compound **2.12c** was isolated through a silica gel column (hexanes/EtOAc: from 20:1 to 5:1) as colorless oil (25.6 mg, 37% yield).

1,1,1,3,3,3-Hexafluoropropan-2-yl (R)-((4-(prop-1-en-2-yl) cyclohex-1-en-1-yl) methyl) carbamate (2.12c):

IR ν_{\max} (neat)/ cm^{-1} : 3330 (m), 3079 (w), 2969 (w), 2919 (w), 2843 (w), 1735 (s), 1551 (m), 1384 (m), 1249 (m), 1189 (s), 1105 (s), 902 (m), 689 (m); ^1H NMR (400 MHz, CDCl_3) δ 5.77–5.65 (m, 1H), 5.63 (s, 1H), 5.07 (s, 1H), 4.72 (d, J = 10.8 Hz, 2H), 3.76 (d, J = 5.8 Hz, 2H), 2.27 – 1.79 (m, 7H), 1.73 (s, 3H); ^{19}F NMR (376 MHz, CDCl_3) δ -73.65 (d, J = 6.2 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 152.6, 149.4, 133.1, 123.8, 120.6 (q, J = 282.2 Hz), 108.9, 68.7–66.8 (m), 47.4, 40.8, 30.4, 27.3, 26.7, 20.8; HRMS (ESI, m/z): calcd for $\text{C}_{14}\text{H}_{17}\text{F}_6\text{NO}_2\text{Na}^+$, $[\text{M} + \text{Na}^+]$, 368.1056, found 368.1054.

2.3.10 Procedure for the iron-catalyzed aminofluorination of trans-2-phenyl-1-vinylcyclopropane

trans-2-Phenyl-1-vinylcyclopropane **1.13** was synthesized according to a literature procedure.⁴²



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added XtalFluor-E (184 mg, 0.8 mmol) and freshly activated 4 Å powdered molecular sieves (50 mg). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (2.5 mL) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (79 μL , 0.48 mmol) were added successively via syringes. The mixture was stirred at room temperature for 20 min. To another flame-dried sealable 3-dram vial (vial **B**) equipped with a stir bar were added **cat.1** (17.4 mg, 0.03 mmol) and freshly activated 4 Å powdered molecular sieves (100 mg). Vial **B** was evacuated and backfilled with N_2 three times and then anhydrous CH_2Cl_2 (0.75 mL) was added. Both vials were degassed and

backfilled with N₂ twice and vial **B** was cooled to -40 °C. **1.13** (38 μL, 0.24 mmol) was then added into vial **B** followed by the addition of fluorinating reagent solution in vial **A** via a syringe. Acyloxyl carbamate **2.2b** (53 mg, 0.20 mmol) in 0.75 mL CH₂Cl₂ was added dropwise at last to vial **B** and the reaction was kept at -40 °C for 1 h and then quenched with saturated NaHCO₃ solution (3 mL). The organic layer was separated from the aqueous one, which was extracted with CH₂Cl₂ (2 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*.

Compound **2.13** was isolated through a silica gel flash column (hexanes/acetone: from 100:1 to 10:1) as colorless oil (26.3 mg, 43% yield).

2,2,2-Trifluoroethyl (E)-(5-fluoro-5-phenylpent-2-en-1-yl)carbamate (2.13): IR ν_{\max} (neat)/cm⁻¹: 3419 (w), 3340 (w), 3032 (w), 2975 (w), 1719 (s), 1518 (m), 1284 (m), 1237 (m), 1163 (s), 967 (m), 760 (m), 699 (m); ¹H NMR (400 MHz, CDCl₃) δ 7.42–7.28 (m, 5H), 5.71–5.54 (m, 2H), 5.45 (ddd, *J* = 47.5, 7.9, 4.8 Hz, 1H), 4.88 (brs, 1H), 4.46 (q, *J* = 8.5 Hz, 2H), 3.79 (t, *J* = 5.8 Hz, 2H), 2.87–2.45 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 154.2, 139.6 (d, *J* = 19.7 Hz), 129.2, 128.5, 128.4 (d, *J* = 2.1 Hz), 127.6 (d, *J* = 4.9 Hz), 125.5 (d, *J* = 6.9 Hz), 123.1 (q, *J* = 277.4 Hz), 93.6 (d, *J* = 173.1 Hz), 60.9 (q, *J* = 36.3 Hz), 43.0, 40.0 (d, *J* = 24.6 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -74.33 (t, *J* = 8.5 Hz, 3F), -175.01 (ddd, *J* = 46.8, 27.8, 18.1 Hz, 1F); HRMS (ESI, *m/z*): calcd for C₁₄H₁₅F₄NO₂Na⁺, [*M* + Na⁺], 328.0931, found 328.0930.

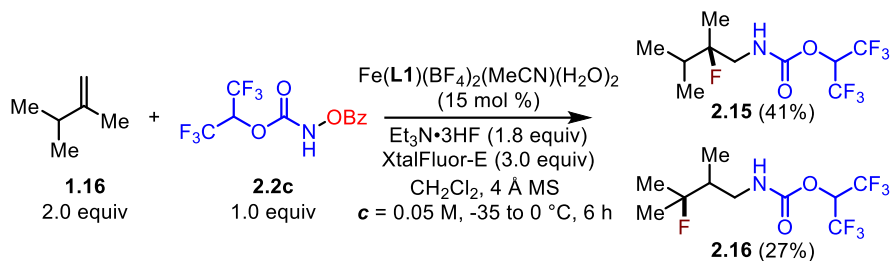
Compound **2.14** was isolated through a silica gel flash column (hexanes/acetone: from 100:1 to 10:1) as colorless oil (8.0 mg, 10% yield).

(E)-1-Phenyl-5-(((2,2,2-trifluoroethoxy)carbonyl)amino)pent-3-en-1-yl benzoate (2.14): IR ν_{\max} (neat)/cm⁻¹: 3353 (w), 2914 (w), 2846 (w), 1717 (s), 1585 (m), 1376 (m), 1279 (s), 1241(s), 1163(s), 1047 (m), 969 (m); ¹H NMR (400 MHz, CDCl₃) δ 8.10–8.04 (m, 2H), 7.61–7.54 (m, 1H), 7.48–7.43 (m, 2H), 7.42–7.29 (m, 5H), 6.03 (dd, *J* = 7.7, 5.6 Hz, 1H), 5.63 (dt, *J* = 14.9, 6.8 Hz, 1H), 5.53 (dt, *J* = 15.5, 5.8 Hz, 1H), 4.74 (brs, 1H), 4.41 (q, *J* = 8.5 Hz, 2H), 3.72 (t, *J* = 5.8 Hz, 2H), 2.82–2.72 (m, 1H), 2.71–2.62 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 165.7, 154.1, 139.9, 133.1, 130.3, 129.6, 129.1, 128.5, 128.43, 128.40, 128.1, 126.4, 123.1 (q, *J* = 277.5 Hz), 75.6, 60.9 (q, *J* = 36.6 Hz), 43.0, 39.5; ¹⁹F NMR (376 MHz, CDCl₃)

δ -74.32 (t, J = 8.5 Hz); HRMS (ESI, m/z): calcd for $C_{21}H_{21}F_3NO_4Na^+$, $[M + Na^+]$, 408.1417, found 408.1408.

2.3.11 Procedures for the iron-catalyzed aminofluorination of 2,3-dimethyl-1-butene

2,3-Dimethyl-1-butene is commercially available and it was distilled before usage.



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added XtalFluor-E (138 mg, 0.6 mmol) and freshly activated 4 Å powdered molecular sieves (50 mg). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (2.5 mL) and $Et_3N \cdot 3HF$ (59 μ L, 0.36 mmol) were added successively via syringes. The mixture was stirred at room temperature for 20 min. To another flame-dried sealable 3-dram vial (vial **B**) equipped with a stir bar were added catalyst **cat.1**, $Fe(L1)(BF_4)_2(MeCN)(H_2O)_2$ (17.4 mg, 0.03 mmol) and freshly activated 4 Å powdered molecular sieves (100 mg). Vial **B** was evacuated and backfilled with N_2 three times and then anhydrous CH_2Cl_2 (0.75 mL) was added. Both vials were degassed and backfilled with N_2 twice and vial **B** was cooled to -35 °C. 2, 3-Dimethyl-1-butene (50 μ L, 0.4 mmol) was then added into vial **B** followed by the addition of fluorinating reagent solution in vial **A** via a syringe. Acyloxyl carbamate **2.2c** (66.2 mg, 0.20 mmol) in 0.75 mL CH_2Cl_2 was added dropwise at last to vial **B** and the reaction was kept at -35 °C for 1 h and then gradually warmed up to 0 °C. After the reaction was kept at 0 °C for 5 h, it was quenched with saturated $NaHCO_3$ solution (3 mL). The organic layer was separated from the aqueous one, which was extracted with CH_2Cl_2 (2 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*.

Compound **2.15** was purified through a silica gel flash column (hexanes/ Et_2O : from 100:1 to 10:1) as colorless oil (25.7 mg, 41% yield).

1,1,1,3,3,3-Hexafluoropropan-2-yl (2-fluoro-2,3-dimethylbutyl)carbamate (2.15): IR ν_{\max} (neat)/ cm^{-1} : 3351 (m), 2973 (m), 1744 (s), 1532 (m), 1386 (m), 1231 (s), 1198 (s), 1140 (m), 1108 (s), 904 (m), 689 (m); ^1H NMR (400 MHz, CDCl_3) δ 5.74–5.64 (m, 1H), 5.34 (brs, 1H), 3.58–3.36 (m, 2H), 2.04–1.91 (m, 1H), 1.23 (d, $J = 22.2$ Hz, 3H), 1.00 (d, $J = 6.9$ Hz, 3H), 0.93 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.0, 120.6 (q, $J = 280.8$ Hz), 99.1 (d, $J = 170.8$ Hz), 69.9–65.1 (m), 47.6 (d, $J = 21.2$ Hz), 33.9 (d, $J = 21.5$ Hz), 17.5 (d, $J = 12.2$ Hz), 17.3 (d, $J = 4.4$ Hz), 16.5 (d, $J = 5.4$ Hz); ^{19}F NMR (376 MHz, CDCl_3) δ -72.90–74.54 (m, 6F), -152.70–153.79 (m, 1F); HRMS (ESI, m/z): calcd for $\text{C}_{10}\text{H}_{15}\text{F}_7\text{NO}_2^+$, [$\text{M} + \text{H}^+$], 314.0986, found 314.0974.

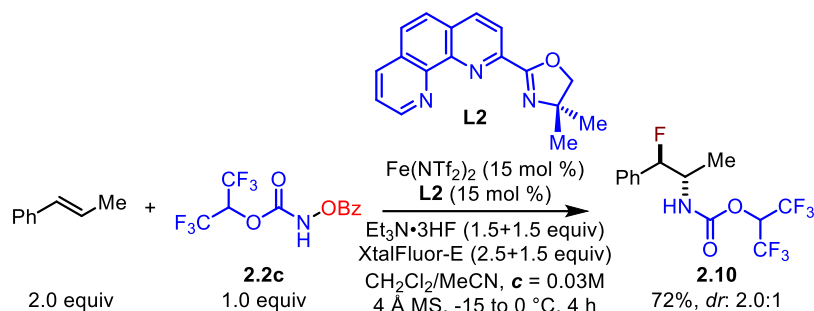
Compound **2.16** was purified through a silica gel flash column (hexanes/ Et_2O : from 100:1 to 10:1) as white foam (16.9 mg, 27% yield).

1,1,1,3,3,3-Hexafluoropropan-2-yl (3-fluoro-2,3-dimethylbutyl)carbamate (2.16): IR ν_{\max} (neat)/ cm^{-1} : 3364 (m), 2987 (m), 1745 (s), 1520 (m), 1385 (m), 1232 (s), 1198 (s), 1140 (m), 1108 (s), 904 (m), 689 (m); ^1H NMR (400 MHz, CDCl_3) 5.73–5.62 (m, 1H), 5.38 (brs, 1H), 3.40 (ddd, $J = 13.8, 6.4, 4.7$ Hz, 1H), 3.27 (dt, $J = 13.8, 6.7$ Hz, 1H), 2.04–1.88 (m, 1H), 1.40 (d, $J = 22.6$ Hz, 3H), 1.32 (d, $J = 22.2$ Hz, 3H), 0.97 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.7, 120.7 (q, $J = 280.6$ Hz), 98.6 (d, $J = 165.3$ Hz), 69.2–65.8 (m), 43.7 (d, $J = 3.8$ Hz), 42.4 (d, $J = 20.3$ Hz), 26.3 (d, $J = 24.8$ Hz), 22.4 (d, $J = 24.9$ Hz), 13.6 (d, $J = 7.4$ Hz); ^{19}F NMR (376 MHz, CDCl_3) δ -73.61–74.08 (m, 6F), -138.35–138.84 (m, 1F); HRMS (ESI, m/z): calcd for $\text{C}_{10}\text{H}_{15}\text{F}_7\text{NO}_2^+$, [$\text{M} + \text{H}^+$], 314.0986, found 314.0974.

2.3.12 Procedure for the iron-catalyzed aminofluorination of *trans*- β -methyl styrene

A: procedure for iron-catalyzed aminofluorination of *trans*- β -methyl styrene.

trans- β -Methylstyrene is commercially available and it was distilled before usage.



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{NTf}_2)_2$ (18.5 mg, 0.03 mmol) and **L3** (8.3 mg, 0.03 mmol). After vial **A** was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.5 mL) and MeCN (0.05 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To a second flame-dried sealable 2-dram vial (vial **B**) equipped with a stir bar were added XtalFluor-E (115 mg, 0.5 mmol) and freshly activated 4 Å powdered molecular sieves (50 mg). After vial **B** was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (3.0 mL) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (49 μL , 0.3 mmol) were added successively via syringes. The mixture was stirred at room temperature for 20 min. To another flame-dried sealable 3-dram vial (vial **C**) equipped with a stir bar were added acyloxyl carbamate **2.2c** (66.2 mg, 0.2 mmol) and freshly activated 4 Å powdered molecular sieves (100 mg). Vial **C** was evacuated and backfilled with N_2 three times and then anhydrous CH_2Cl_2 (3.0 mL) was added. All three vials were degassed and backfilled with N_2 twice and vial **C** was cooled to -15 °C. Freshly distilled *trans*- β -methyl styrene (52 μL , 0.40 mmol) was then added into vial **C** followed by the addition of fluorinating reagent solution in vial **B** via a syringe. The catalyst solution in vial **A** was added with a syringe pump over 20 min to vial **C** at -15 °C and the reaction was stirred at this temperature. After 1.0 h, to another flame-dried sealable 2-dram vial (vial **D**) equipped with a stir bar was added XtalFluor-E (69 mg, 0.3 mmol). Vial **D** was evacuated and backfilled with N_2 three times, then anhydrous CH_2Cl_2 (1.0 mL) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (49 μL , 0.3 mmol) were added successively via syringes. After being stirred at room temperature for 10 min, the solution in vial **D** was added to vial **C** via a syringe in order to convert the corresponding oxazoline that was generated simultaneously to the desired amino fluoride. The reaction in vial **C** was stirred at 0 °C for additional 3 h and quenched with saturated NaHCO_3 solution (3 mL). The

organic layer was separated from the aqueous one, which was extracted with CH₂Cl₂ (2 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*.

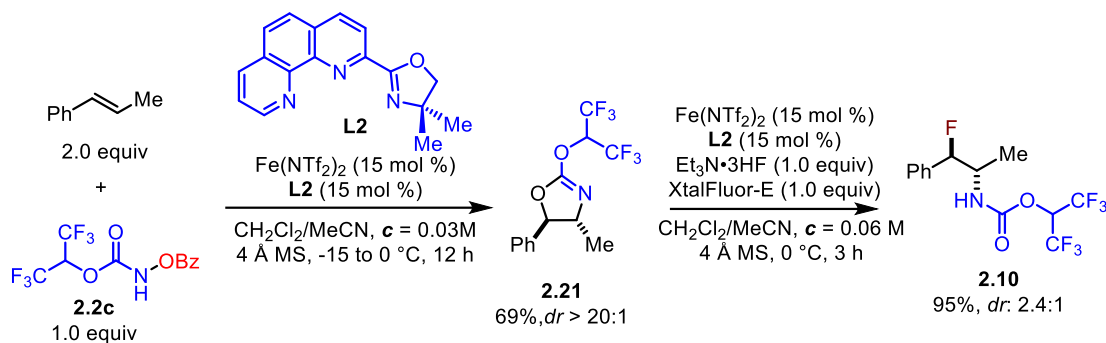
The *anti* aminofluorination product **2.10a** was isolated through a silica gel flash column (hexanes/acetone: from 100:1 to 10:1) as a white solid (33.3 mg, 48% yield, m.p. 71–73 °C).

(±)1,1,1,3,3,3-Hexafluoropropan-2-yl ((anti)-1-fluoro-1-phenylpropan-2-yl)carbamate (2.10a): IR ν_{\max} (neat)/cm⁻¹: 3326 (m), 2969 (m), 1734 (s), 1540 (m), 1454 (m), 1383 (m), 1250 (s), 1194 (s), 1105 (s), 1093 (s), 977 (m), 885 (m), 700 (m); ¹H NMR (400 MHz, C₆D₆) δ 7.12–6.95 (m, 5H), 5.83–5.68 (m, 1H), 5.16 (dd, *J* = 47.7, 3.4 Hz, 1H), 4.48 (brd, *J* = 8.5 Hz, 1H), 3.90–3.71 (m, 1H), 0.58 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 151.9, 136.3 (d, *J* = 20.2 Hz), 128.6 (d, *J* = 1.4 Hz), 128.5 (d, *J* = 1.0 Hz), 125.0 (d, *J* = 8.7 Hz), 120.6 (q, *J* = 285.9 Hz), 94.7 (d, *J* = 178.7 Hz, 1H), 70.0–65.9 (m), 52.3 (d, *J* = 22.8 Hz), 13.4 (d, *J* = 5.9 Hz); ¹⁹F NMR (376 MHz, C₆D₆) δ -72.78–74.87 (m, 6F), -198.29 (dd, *J* = 47.7, 23.9 Hz, 1F); HRMS (ESI, m/z): calcd for C₁₃H₁₂F₇NO₂Na⁺, [M + Na⁺], 370.0648, found 370.0634.

The *syn* aminofluorination product **2.10b** was isolated through a silica gel flash column (hexanes/acetone: from 100:1 to 10:1) as a white solid (16.7 mg, 24% yield, m.p. 67–68 °C).

(±)1,1,1,3,3,3-Hexafluoropropan-2-yl ((syn)-1-fluoro-1-phenylpropan-2-yl)carbamate (2.10b): IR ν_{\max} (neat)/cm⁻¹: 3347 (m), 2966 (m), 1733 (s), 1540 (m), 1385 (m), 1237 (s), 1190 (s), 1130 (m), 1105 (s), 972 (m), 904 (m), 689 (m); ¹H NMR (400 MHz, C₆D₆) δ 7.10–6.92 (m, 5H), 5.70–5.56 (m, 1H), 4.83 (dd, *J* = 46.2, 4.6 Hz, 1H), 4.35–4.23 (m, 1H), 3.95–3.76 (m, 1H), 0.62 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 151.9, 136.2 (d, *J* = 20.5 Hz), 128.8 (d, *J* = 1.5 Hz), 128.5, 125.6 (d, *J* = 7.5 Hz), 120.5 (q, *J* = 286.1 Hz), 94.9 (d, *J* = 178.1 Hz), 68.4–66.8 (m), 51.9 (d, *J* = 19.5 Hz), 17.0 (d, *J* = 3.7 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -73.67 (m, 6F), -192.11 (dd, *J* = 45.9, 20.2 Hz, 1F); HRMS (ESI, m/z): calcd for C₁₃H₁₂F₇NO₂Na⁺, [M + Na⁺], 370.0648, found 370.0634.

B: procedure for iron-catalyzed amino-oxygenation of trans- β -methyl styrene and following ring-opening with fluoride.



Iron-catalyzed amino-oxygenation (step 1): to a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{NTf}_2)_2$ (18.5 mg, 0.03 mmol) and **L2** (8.3 mg, 0.03 mmol). After vial **A** was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.5 mL) and MeCN (0.05 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To a second flame-dried sealable 3-dram vial (vial **B**) equipped with a stir bar were added acyloxyl carbamate **2.2c** (66.2 mg, 0.2 mmol) and freshly activated 4 Å powdered molecular sieves (100 mg). Vial **B** was evacuated and backfilled with N_2 three times and then anhydrous CH_2Cl_2 (6.0 mL) was added. Both vials were degassed with N_2 twice and vial **B** was cooled to -15 °C. Freshly distilled *trans*- β -methyl styrene (52 μL , 0.40 mmol) was then added into vial **B**. Then the catalyst solution in vial **A** was added with a syringe pump over 20 min to vial **B** at -15 °C and the reaction was kept at this temperature for 1.5 h. The reaction in vial **B** was moved to 0 °C and stirred for additional 12 h and quenched with saturated NaHCO_3 solution (3 mL). The organic layer was separated from the aqueous one, which was extracted with CH_2Cl_2 (2 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was further purified through a silica gel flash column (hexanes/acetone: from 100:1 to 10:1) to afford the desired product **2.21** isolated as white foam (45.2 mg, 69% yield, $dr > 20:1$).

2-((1,1,1,3,3,3-Hexafluoropropan-2-yl)oxy)-4-methyl-5-phenyl-4,5-dihydrooxazole (2.21): IR ν_{max} (neat)/ cm^{-1} : 2968 (m), 1681(s), 1384 (m), 1346 (m), 1271 (m), 1200 (s), 1107 (s), 1006 (m), 905 (m), 688 (m); ^1H NMR (400 MHz, CDCl_3) δ 7.46–7.34 (m, 3H), 7.34–7.29 (m, 2H), 5.86 (hept, $J = 6.1$ Hz, 1H), 5.23 (d, $J = 7.3$ Hz, 1H), 4.06 (p, $J = 6.7$ Hz, 1H), 1.40 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.1, 138.3, 129.0, 125.5, 120.3 (q, $J = 283.2$ Hz), 91.6, 74.3–71.4 (m), 67.5, 21.4; ^{19}F NMR (376 MHz,

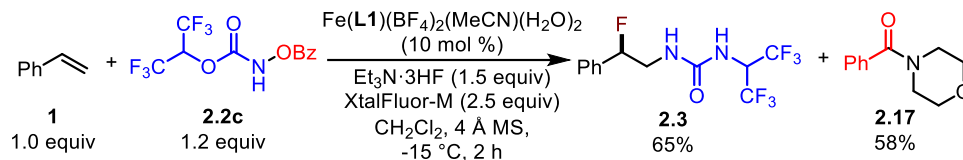
CDCl_3) δ -65.65--84.56 (m); HRMS (ESI, m/z): calcd for $\text{C}_{13}\text{H}_{12}\text{F}_6\text{NO}_2^+$, $[\text{M} + \text{H}^+]$, 328.0767, found 328.0772.

Iron-catalyzed ring-opening with fluoride (step 2): To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{NTf}_2)_2$ (18.5 mg, 0.03 mmol) and **L2** (8.3 mg, 0.03 mmol). After vial **A** was degassed and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.5 mL) and MeCN (0.05 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To a second flame-dried sealable 2-dram vial (vial **B**) equipped with a stir bar were added XtalFluor-E (46 mg, 0.2 mmol). After vial **B** was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (1.0 mL) and $\text{Et}_3\text{N}\cdot 3\text{HF}$ (33 μL , 0.2 mmol) were added successively via syringes. The mixture was stirred at room temperature for 10 min. To another flame-dried sealable 3-dram vial (vial **C**) equipped with a stir bar were added **2.21** (65.4 mg, 0.20 mmol), and freshly activated 4 Å powdered molecular sieves (50 mg). Vial **C** was evacuated and backfilled with N_2 three times and then anhydrous CH_2Cl_2 (1.5 mL) was added. All three vials were degassed with N_2 twice. Vial **C** were cooled to 0 °C followed by addition of fluorinating reagent solution in vial **B** via a syringe. The catalyst solution in vial **A** was added to vial **C** via a syringe pump over 20 min and the reaction was kept at the same temperature for 3 h. **** The reaction was then quenched with saturated NaHCO_3 solution (3 mL). The organic layer was separated from the aqueous one, which was extracted with CH_2Cl_2 (2 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexanes/acetone: from 100:1 to 10:1) to afford the desired product **2.10** as white solid (66 mg, 95%, *dr*: 2.4:1).

2.3.13 Procedures for the XtalFluor-M trapping experiment

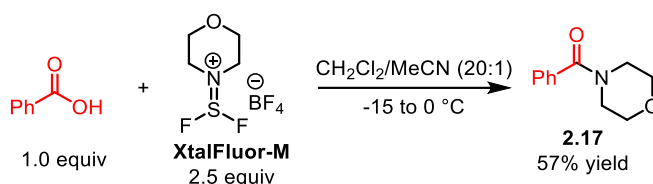
A: procedure for iron-catalyzed aminofluorination of styrene with XtalFluor-M/ $\text{Et}_3\text{N}\cdot 3\text{HF}$.

**** Note: there is no reaction at -15 °C and the starting material is recovered.



The reaction was carried out by following the general procedure, where XtalFluor-E was replaced by XtalFluor-M as a benzoate sequestering reagent. Morpholino(phenyl)methanone **2.17** was isolated, which is a known compound.^{73,74}

B: procedure for the benzoate group trapping experiment with XtalFluor-M.



To an oven-dried sealable 2-dram vial equipped with a stir bar were added XtalFluor-M (121.5 mg, 0.5 mmol) and anhydrous CH_2Cl_2 (2.0 mL). After the vial was evacuated and backfilled with N_2 three times, benzoic acid (24.4 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (1.0 mL) was added at $-15\text{ }^\circ\text{C}$ via syringe. The mixture was moved to $0\text{ }^\circ\text{C}$ and stirred under this temperature for 6 h. Then, saturated NaHCO_3 solution (2 mL) was added to quench the reaction. The organic layer was separated from the aqueous one, which was extracted with CH_2Cl_2 (2 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexanes/acetone: from 15:1 to 4:1) to afford **2.17** as colorless oil (22 mg, 57% yield).

2.4 Conclusion

In this chapter, an iron-catalyzed *intermolecular* olefin aminofluorination method was described. This new approach tolerates a broad range of simple unfunctionalized olefin precursors and uses nucleophilic fluoride ion (commercially available Et₃N·3HF/XtalFluor-E complex) as fluorine source. It also readily affords a variety of vicinal fluoro carbamates at gram-scale that can be converted to synthetically valuable vicinal fluoro primary amines through simple derivatization.

We systematically described the reaction discovery, screening of various fluoride donors, substrate scope, enantioselectivity induction as well as the derivatization of vicinal fluoro carbamates products.

A series of control experiments and preliminary mechanistic studies demonstrate that both an iron nitrenoid and a carbocation species (generated after radical amination step) may be possible reactive intermediates. The observations in asymmetric indene aminofluorination suggest that the C–N bond formation is *ee*-determining step.

The limitations of this method include that: (1) it is less efficient with those electro deficient olefins with deactivating groups, such as alkyl cinnamates; (2) it barely affords desired aminofluorination products with indoles and glycals, which are both important olefinic substrates in pharmaceuticals and carbohydrate chemistry; (3) carbocation-mediated substrates polymerization is a severe side reaction in styrenyl dienes and other electro-rich olefins.

3 IRON(II)-CATALYZED OLEFIN TRIFLUOROMETHYL-AZIDATION FOR VICINAL TRIFLUOROMETHYLATED PRIMARY AMINE SYNTHESIS

Abstract

This chapter is about a recently developed iron-catalyzed olefin azido-trifluoromethylation method, which affords an efficient synthetic route to a wide variety of vicinal trifluoromethylated primary amines. A readily available Togni's Reagent II and the commercially available TMSN_3 were used as source of CF_3 and N_3 functional groups. Compared to other trifluoromethyl azidation approaches, this method tolerates a broad range of simple and complex olefins, including styrenyl olefins, terminal and internal olefins, *N*-heterocycles and monoterpenes. Many of them have been challenging substrates for existing methods. Additionally, our preliminary mechanistic studies and crystal structure of the catalytically active *iron-ligand-azide complex* suggest that both the oxidant activation and rapid azido-group transfer steps may proceed through *iron-ligand-azide species* that are assembled *in situ* and activated thereafter.

3.1 Introduction

Vicinal trifluoromethylated primary amines are important structural motifs in a number of pharmaceuticals and biologically active molecules. Therefore, direct amino trifluoromethylation is of great interest in both organic synthesis and medicinal chemistry (Figure 3.1).⁷⁵

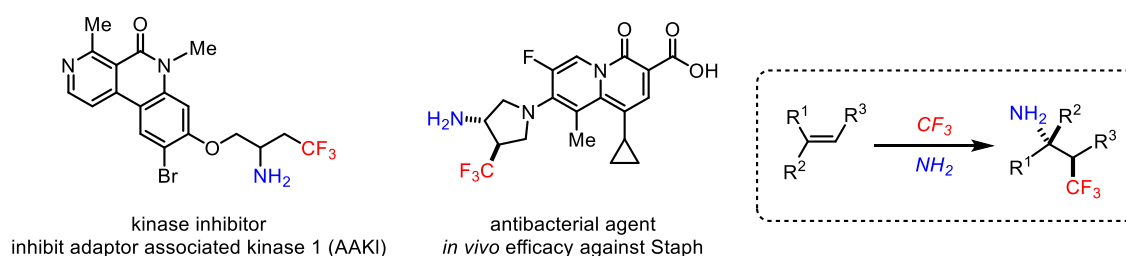
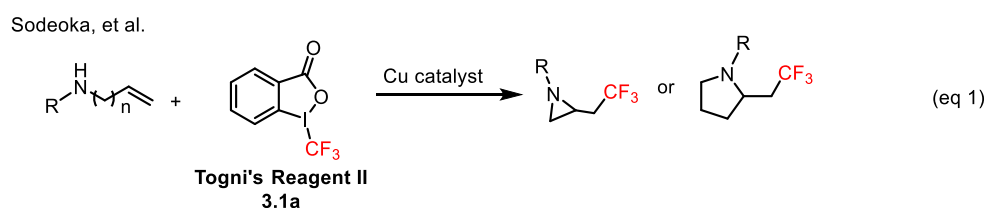


Figure 3.3.1 Vicinal trifluoromethylated primary amines with potential bioactivities

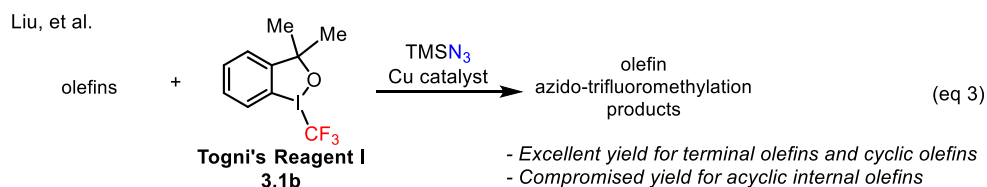
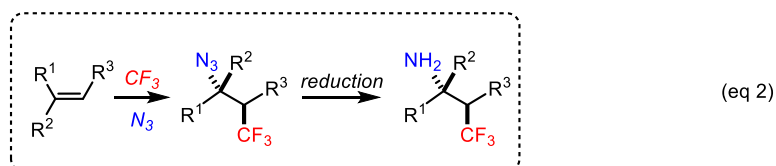
Prior to our research, a few olefin amino trifluoromethylation methods have been developed: Sodeoka reported an intramolecular method to generate trifluoromethylated *N*-aryl aziridines and pyrrolidines using Togni's Reagent II (**3.1a**), which was applied to convert *N*-aryl allylic amines to β -trifluoromethyl amino alcohols via a rearrangement (Scheme 3.1, eq 1).^{76,77} Existing intermolecular amino

trifluoromethylation methods are exclusively limited to styrenyl olefins, which afford trifluoromethylated amides and anilines via the Ritter-type processes through β -trifluoromethyl carbenium ions.⁷⁸

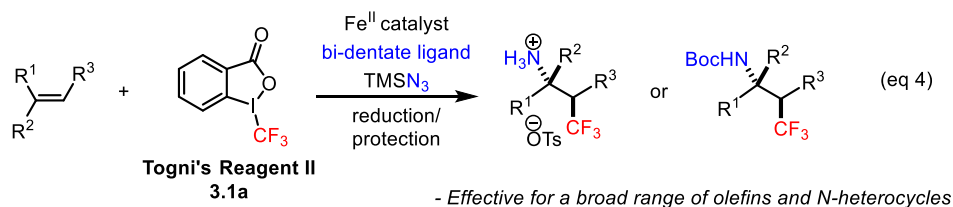
An alternative efficient synthesis of these vicinal trifluoromethylated amines is simple reduction from its trifluoromethylated orangoazides precursor (Scheme 3.1, eq 2). Therefore, direct trifluoromethyl azidation with following reduction becomes one of the most straightforward ways to incorporate these valuable building blocks in organic molecules with double bonds. Liu developed a method that effectively transfers the CF_3 group of Togni's Reagent I (**3.1b**) to a range of terminal and cyclic olefins (Scheme 3.1, eq 3).⁷⁹ Most recently, Hartwig also reported an iron-catalyzed azido-trifluoromethylation method for complex natural products with **3.1b**.⁸⁰ Although other methods through photo-redox catalysis for styrenyl olefins, enamides and enol ethers have been reported, only moderate yields are observed for isolated olefins.⁷⁸



Alternative way to prepare vicinal trifluoromethyl amines



This chemistry:



Scheme 3.1 Copper and iron-catalyzed methods for vicinal trifluoromethyl amine synthesis

These existing olefin amino- and azido-trifluoromethylation methods are synthetically useful; however, there still have a few limitations associated with these transformations. First, there are a number of synthetically useful olefins are not compatible with the existing methods, especially those olefins contain labile allylic C–H or C–C bonds and therefore are prone to undergo β -H elimination *or* rearrangement, including allyl benzene, allyl acetate, and β -pinene. Next, β -trifluoromethylated amino-*N*-heterocycles are of great interest in medicinal chemistry; however, an efficient intermolecular azido-trifluoromethylation method for *N*-heterocycles has not been reported yet.

In this chapter, an iron-catalyzed olefin azido-trifluoromethylation method for efficient synthesis of a wide variety of vicinal trifluoromethylated primary amines is described (Scheme 3.1, eq 4). This method tolerates a broad range of unfunctionalized olefins, *N*-heterocycles and monoterpene natural products. Preliminary mechanistic and crystallographic studies suggest that an unprecedented iron–azide species that are assembled *in situ* would activate the oxidant and transfer azido-group to olefins rapidly.

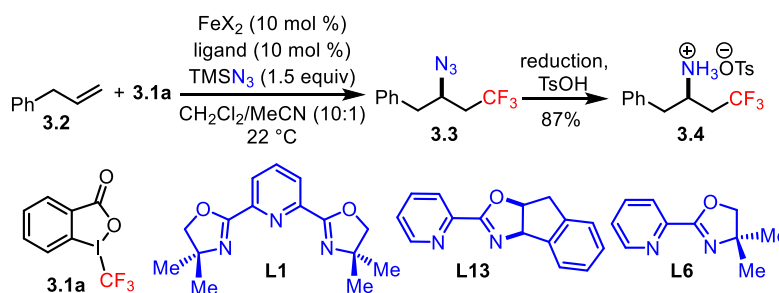
3.2 Results and discussions

3.2.1 Reaction discovery

We selected allyl benzene (**3.2**) as a model substrate for catalyst discovery because it is known to undergo facile olefin trifluoromethylation followed by elimination to afford an allylic trifluoromethylation product.⁸¹ Our group previously discovered Fe(NTf₂)₂–tridentate ligand **L1** complex can catalyzed efficient olefin diazidation reactions.⁸² When the same catalyst was used together with oxidant **3.1a** and TMSN₃, we observed an effective regio-selective olefin azido-trifluoromethylation affording the vicinal trifluoromethylated azide **3.3** with moderate yield (Table 3.1, entry 1). It was noted that oxidant decomposed in the presence of Fe(NTf₂)₂–tridentate ligand **L1** complex and lead to inefficient conversion of olefin starting material. We also observed that both **3.2** and **3.1a** are fully recovered in the absence of the iron catalyst, which indicate the iron-catalyst is necessary in this transformation (entry 2). Next, because we observed quick decomposition of oxidant in entry 1, the Fe(NTf₂)₂ was replaced by a less oxidative iron catalyst Fe(OAc)₂ and we are glad to find that Fe(OAc)₂–**L1** complex evidently improved both the

conversion and yield (entry 3, 6 h, 81% yield). To our surprise, the $\text{Fe}(\text{OAc})_2$ –bidentate ligand **L13** / **L6** complex catalyzed the reaction as efficient as $\text{Fe}(\text{OAc})_2$ –tridentate ligand **L1** complex but in shorter reaction time (entry 4–5, 3 h, 83–86% yield). Interestingly, the FeCl_2 –**L6** complex also proves catalytically active; however, the corresponding β -trifluoromethyl chloride was identified as the side product (entry 6). We also evaluated the copper catalyst that was known to catalyze efficient olefin trifluoromethyl azidation.⁷⁹ Unfortunately, this catalyst affords a range of different trifluoromethyl azide products. In addition to the desired **3.3** (44% yield), allylic trifluoromethylation product (14%) and 1,3 addition product (10%). Moreover, **3.3** can be readily converted to β -trifluoromethyl ammonium salt **3.4** through a straightforward reduction–protonation sequence (87% yield).

Table 3.1 Catalyst discovery for iron-catalyzed olefin trifluoromethyl-azidation



Entry ^a	Catalyst	Ligand	Time (h)	Conversion ^b (%)	Yield ^c (%)
1	$\text{Fe}(\text{NTf}_2)_2$	L1	6.0	71	64
2	–	–	12.0	<5	–
3	$\text{Fe}(\text{OAc})_2$	L1	6.0	90	81
4	$\text{Fe}(\text{OAc})_2$	L13	3.0	>95	83
5	$\text{Fe}(\text{OAc})_2$	L6	3.0	>95	86
6 ^d	FeCl_2	L6	3.0	92	68
7 ^e	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	–	12.0	80	44

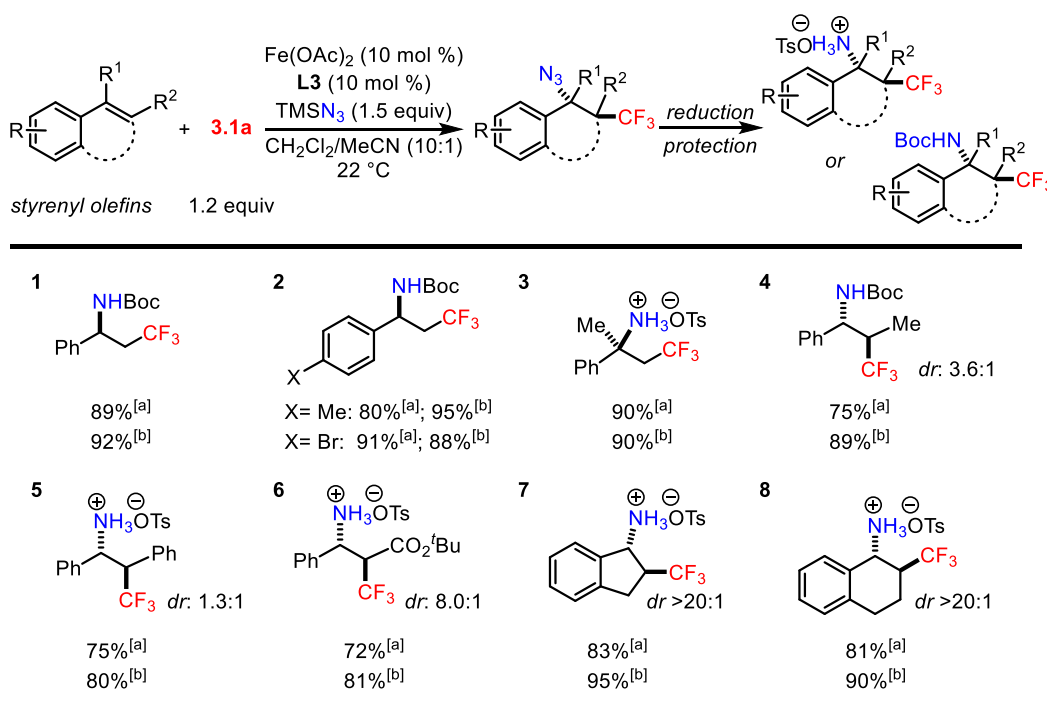
^aReactions were carried out under N_2 with **3.1a** (1.2 equiv) and then quenched with saturated NaHCO_3 solution. Reduction condition: PPh_3 , H_2O , THF, 50°C , 2 h, then TsOH. ^bConversion was measured by ^1H NMR analysis. ^cIsolated yield. ^dAllyl benzene chlorotrifluoromethylation product (12% yield) as isolated as the side product. ^esolvent is DMA.

3.2.2 Substrate scope

With discovery of this transformation, we explored a range of different types of olefins to determine the scope and limitation of this new methodology.

First, we evaluated a variety of styrenyl olefins, including electron-rich, electron-deficient or electron-neutral styrenes, as well as α or β -branch substituted styrenes (Table 3.2, entries 1–6). Not surprisingly, this chemistry is successfully applied to a broad range of substituted and unsubstituted styrenes. Moreover, cyclic styrenyl olefins, including indene and dihydronaphthalene, can also be diastereoselectively converted to vicinal trifluoromethylated ammonium salts with excellent yield and *dr* (Table 3.2, entries 7–8, *dr* >20:1).

Table 3.2 The iron-catalyzed vicinal trifluoromethyl primary amine synthesis from styrenyl olefins

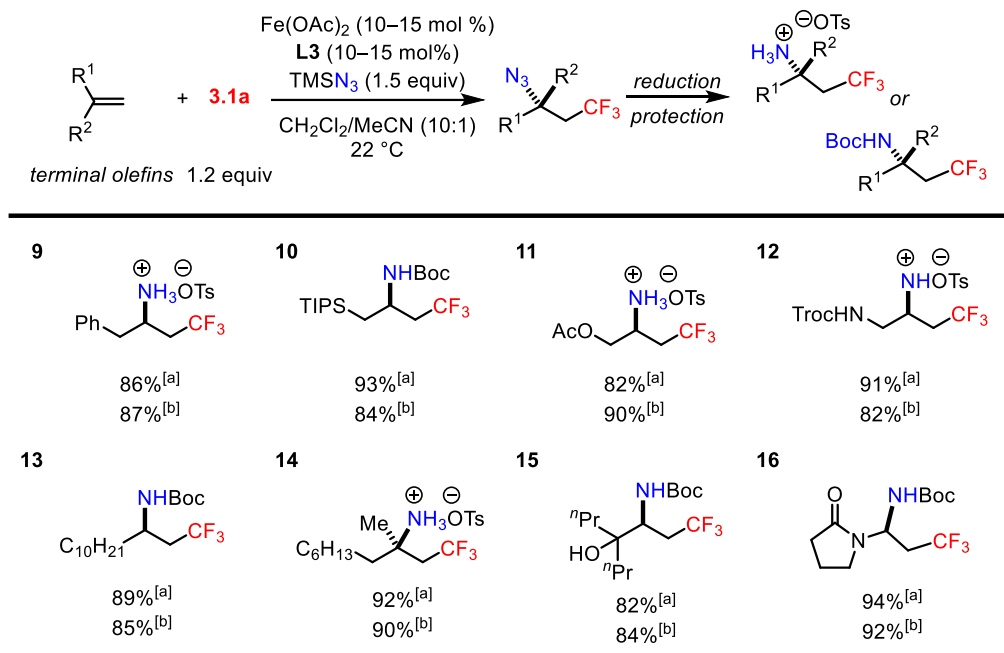


^[a] Isolated yield for the trifluoromethyl-azidation reaction; ^[b] isolated yield for the reduction and protection.

We next studied a variety of isolated terminal olefins (Table 3.3). Trifluoromethyl azidation of those terminal olefins with labile allylic C–H bonds, such as allyl benzene and allyl silane, was not reported in the literature. But they both prove to be an excellent candidate with this condition and no elimination products were detected (entries 9–10). In addition, allyl acetate and an allyl carbamate are compatible with this method, affording vicinal trifluoromethylated amino alcohol and diamine derivatives with excellent yield (entries 11–12). Both mono- and 1,1-disubstituted olefins are excellent substrates (entries 13–14). Moreover, an unprotected tertiary allylic alcohol can be directly applied to afford a trifluoromethylated

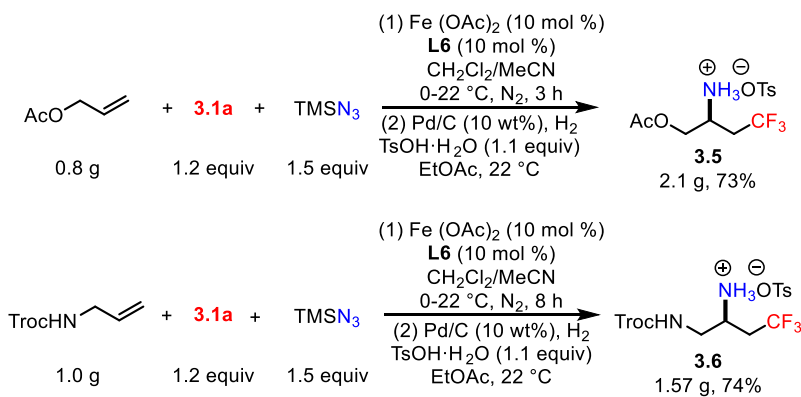
amino alcohol without comprise from a possible competing semi-pinacol rearrangement (entry 15). We are glad to see that an electron-rich enamide are also tolerated by the catalyst (entry 16).

Table 3.3 The iron-catalyzed vicinal trifluoromethyl primary amine synthesis from terminal olefins



^[a] Isolated yield for the trifluoromethyl-azidation reaction; ^[b] isolated yield for the reduction and protection.

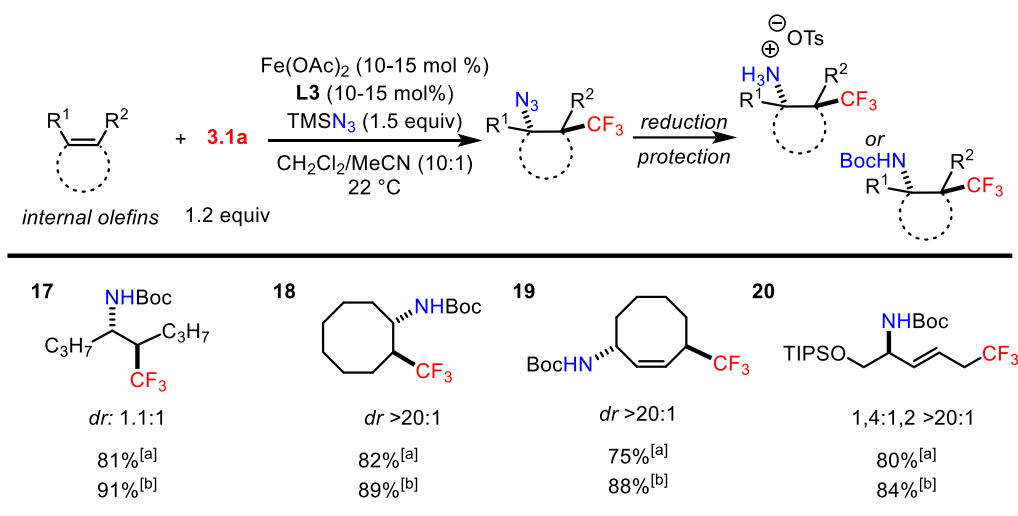
Trifluoromethylated amino alcohols (**3.5**) and diamines (**3.6**) are valuable building blocks in medicinal chemistry; therefore, we explored this reaction of allyl acetate and allyl *N*-Troc-amine on a large scale. We are pleasant to observe that both reactions can be scaled up to gram scale with consistent yield and excellent regio-selectivity (Scheme 3.2).



Scheme 3.2 Iron-catalyzed trifluoromethyl-azidation of allyl acetate and allyl *N*-Troc amine at gram-scale

We noted that acyclic or cyclic internal olefin is a type of substrates that have presented low reactivity toward existing methods. By using this procedure, a aliphatic *trans*-di-substituted olefins and a cyclic cyclooctene can be effectively converted to corresponding trifluoromethylated amines using this procedure (Table 3.4, entries 17–18). Interestingly, we also observed that iron catalyst effectively controls both the regio- and diastereoselectivity of the addition reaction with 1,3-cyclooctadiene (entry 19, *dr* >20:1, 1,4-addition only) and a silyl dienol substrate (entry 20, 1,4-addition only).

Table 3.4 The iron-catalyzed vicinal trifluoromethyl primary amine synthesis from internal olefins

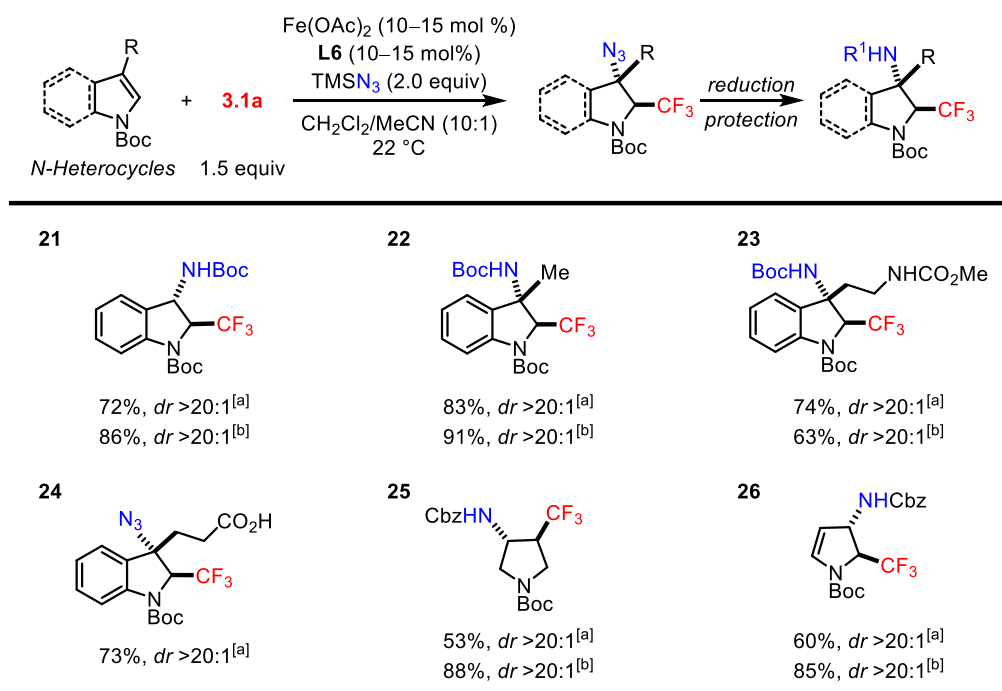


^[a] Isolated yield for the trifluoromethyl-azidation reaction; ^[b] isolated yield for the reduction and protection.

Trifluoromethylated amino-*N*-heterocycles are of great interest in medicinal chemistry; however, *N*-heterocycle amino- or azido-trifluoromethylation has been under-developed. Therefore, we explored this method with indole and pyrrole derivatives (Table 3.5). We discovered that the Fe(OAc)₂–L6 complex selectively transfers the CF₃ group to the indole 2-position while installs the azido group at the 3-position with excellent *dr* (entry 21, *dr* >20:1). Subsequent reduction and *N*-Boc protection readily provided a 2-trifluoromethyl-3-amino-*N*-Boc-indolane. The 3-methyl substitution enhances its reactivity without diminishing diastereoselectivity (entry 22). The iron catalyst proves sufficiently functional group-tolerant such that both tryptamine carbamate and indole propionic acid are compatible with this method (entries 23–24). 3-Trifluoromethyl-4-amino-pyrrolidine motif has been incorporated in biologically probes; however, they used to be prepared through a multistep synthesis.^{83,84} We subsequently evaluated the

reactivity of *N*-Boc protected 3-pyrroline, which eventually afforded 3-trifluoromethyl-4-amino-*N*-Boc-pyrrolidine with excellent *dr* yet in moderate yield (entry 25). Notably, the 3-pyrroline could be oxidized to pyrrole under reaction conditions and afford the corresponding trifluoromethyl azidation products as major side products. Moreover, *N*-Boc-pyrrole is an acceptable substrate and it can be converted to amino trifluoromethylated 2,3-dihydro-*N*-Boc-pyrrole as a single diastereomer (entry 26, *dr* >20:1).

Table 3.5 Iron-catalyzed trifluoromethyl-azidation of *N*-heterocycles

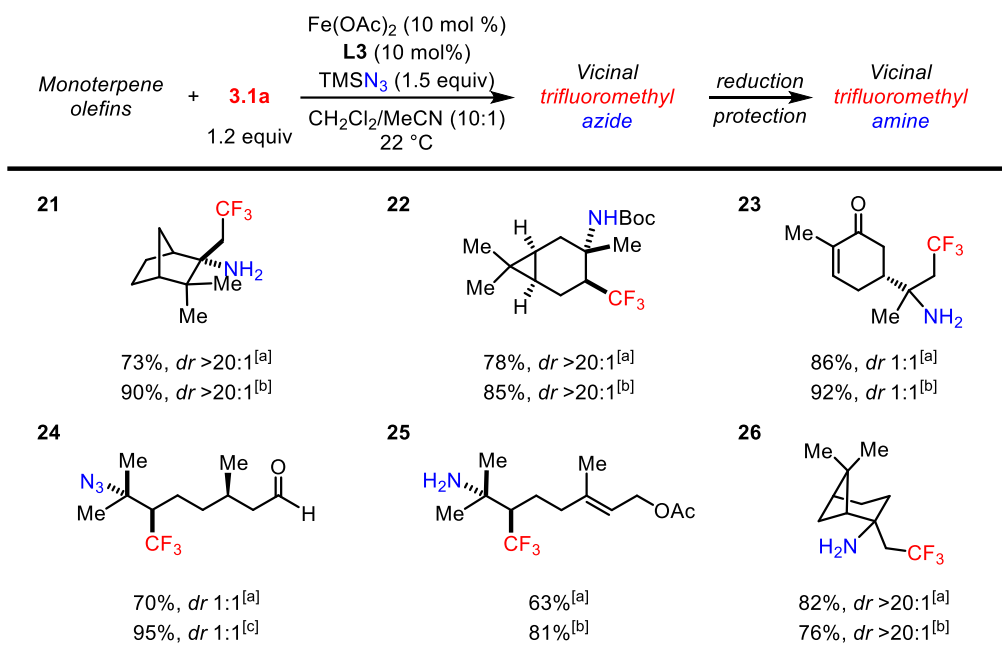


^[a] Isolated yield for the trifluoromethyl-azidation reaction; ^[b] isolated yield for the reduction and protection.

Complex terpenes provide diverse structural motifs with rich stereochemical information; however, complex primary-amine synthesis based upon these readily available natural products has been under-explored. In order to develop a strategy for efficient synthesis of complex primary amines in short steps, we further evaluated this new method with a variety of terpenes (Table 3.6). We observed that both (+)-camphene and (+)-3-carene can be selectively functionalized to the corresponding vicinal trifluoromethylated carbamates as a single diastereomer (entries 21–22). Interestingly, the iron catalyst can electronically differentiate two olefinic moieties within (+)-carvone and selectively transfer the azido-group to the less electron-deficient olefin (entry 23). We also discovered that the labile aldehyde group within in

(±)-citronellal is compatible with the iron catalyst without detrimental aldehyde oxidation (entry 24). Furthermore, the more electron-rich double bond in geranyl acetate preferentially gets functionalized in the presence of an allylic acetate moiety (entry 5).

Table 3.6 Iron-catalyzed trifluoromethyl-azidation of monoterpenes



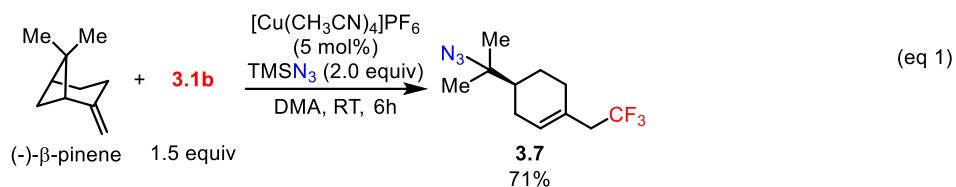
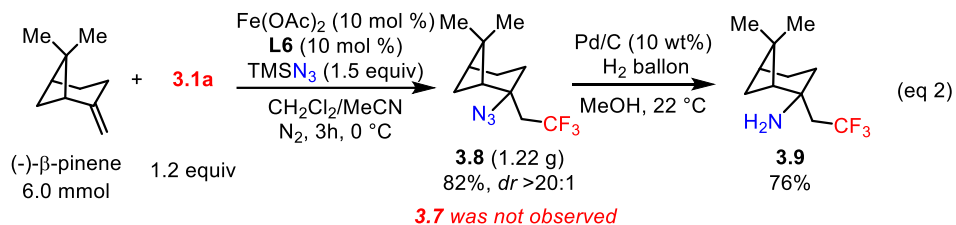
^[a] Isolated yield for the trifluoromethyl-azidation reaction; ^[b] isolated yield for the reduction and protection.

To our great surprise, the iron catalyst can selectively 1,2-difunctionalize the exocyclic olefin of (-)-β-pinene exclusively without ring-opening rearrangement product. A vicinal trifluoromethylated amine was obtained in excellent yield after reduction (entry 6, *dr* >20:1).

3.2.3 Controls experiments to probe working hypothesis

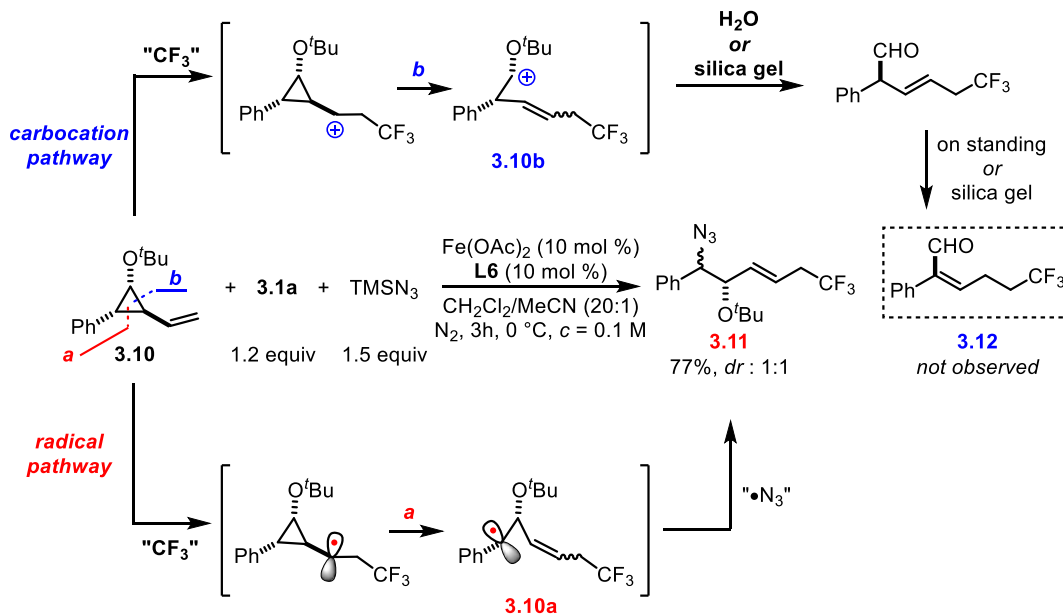
3.2.3.1 Different products observed in Cu and Fe-catalyzed trifluoromethyl azidation of (-)-β-pinene

We noted that the known copper-catalyzed (-)-β-pinene trifluoromethyl azidation method affords the rearrangement product **3.7** only (Scheme 3.3, eq 1). Therefore, the absence of **3.7** in this iron-catalyzed method is mechanistically insightful (Scheme 3.3, eq 2). The product difference in copper and iron-catalyzed azido-trifluoromethylation approaches suggests that iron catalyzed a faster azido-group transfer compared to copper, such that it does not allow time for ring-opening and intermediate rearrangement.

Copper catalyzed intermolecular trifluoromethyl azidation of (-)- β -pineneIron catalyzed intermolecular trifluoromethyl azidation of (-)- β -pineneScheme 3.3 Copper and iron-catalyzed trifluoromethyl-azidation of (-)- β -pinene

3.2.3.2 Proof of radical nature of iron-catalyzed olefin trifluoromethyl azidation reaction

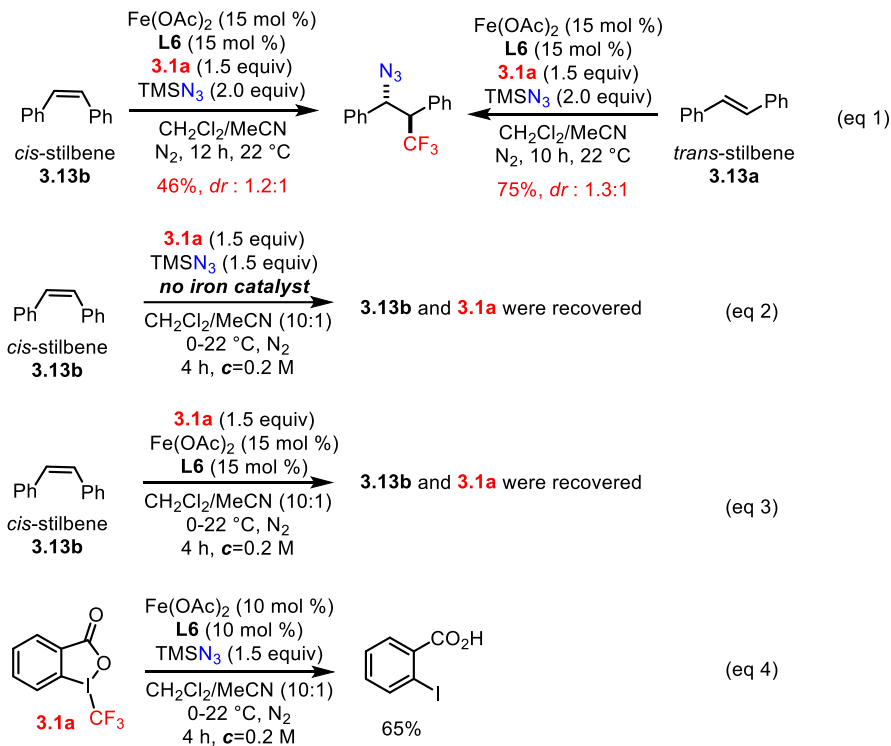
To differentiate between radical and carbocation nature of the reactive intermediate involved in the azido-group transfer process, we evaluated a hypersensitive mechanistic probe **3.10** that was developed by Newcomb (Scheme 3.4).^{84,85} The probe design was based on the simple notion that, in ring openings of cyclopropylcarbinyl systems, a phenyl group will stabilize an incipient radical center more strongly than does an alkoxy group, or *vice versa*. According to this rationale, if a cyclopropyl carbinyl radical was generated through radical addition to **3.10**, the cyclopropyl ring will open by breaking the bond **a** and form a benzylic radical species (**3.10a**), which will eventually afford product **3.11**. It is also reported that a cyclopropyl carbinyl cation intermediate rapidly fragments through bond **b** and leads to an oxo-carbenium ion (**3.10b**). Interestingly, the benzylic azide (**3.11**) was observed exclusively in this iron-catalyzed trifluoromethyl-azidation of **3.10**, presumably through the intermediacy of a benzylic radical species (77% yield, *dr*: 1:1). This result suggests that the iron-catalyzed azido-group transfer proceeds through a carbo-radical rather than a carbocation species.



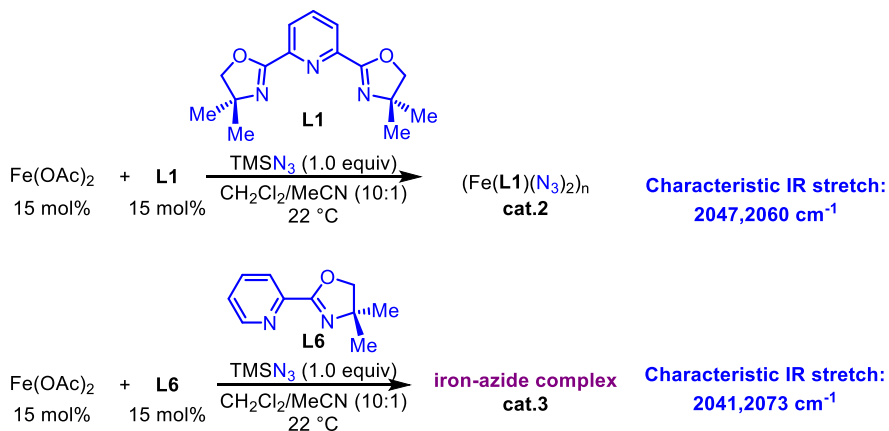
Scheme 3.4 A hypersensitive mechanistic probe for distinguishing between radical and carbocation intermediates

3.2.3.3 Iron-catalyzed trifluoromethyl azidation of *cis*- and *trans*-stilbenes

Next, we compared the reactivity of both *cis*- and *trans*-stilbenes and observed that *trans*-stilbene **3.13a** is much more reactive than *cis*-stilbene **3.13b**. Unlike the iron-catalyzed olefin diazidation, no *cis*–*trans* isomerization was observed during the reaction (Scheme 3.5, eq 1).⁸² This experiment suggests that the C– CF_3 bond forming step is irreversible and rate-limiting. Moreover, the *cis*-stilbene trifluoromethylation was evaluated in the absence of an iron catalyst (eq 2) and in the absence of TMSN_3 (eq 3): both *cis*-stilbene **3.13b** and oxidant **3.1a** were fully recovered under either conditions. However, in the presence of both iron catalyst and TMSN_3 , Togni's reagent II **3.1a** decomposed quickly to 2-iodobenzoic acid even in the absence of an olefin substrate (eq 4). These experiments indicate that both an iron catalyst and TMSN_3 are necessary to activate **3.1a** to initiate the radical reaction.

Scheme 3.5 Iron-catalyzed trifluoromethyl-azidation of *cis/trans*-stilbene

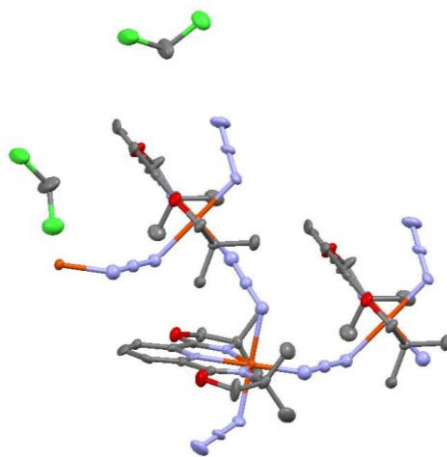
3.2.3.4 Preformed catalytically active iron-azide complex



Scheme 3.6 Preparation of catalytically active iron-azide complex

Based upon these mechanistic insights, we suspect that a catalytically active iron-TMSN₃ complex may be formed *in situ* and activate the oxidant (Togni's reagent) thereafter. Therefore, we premixed Fe(OAc)₂-based catalysts in the presence of stoichiometric amount of TMSN₃ and we observed dark purple solution from both Fe(OAc)₂-L1 and Fe(OAc)₂-L6 complexes. Subsequent ether precipitation readily

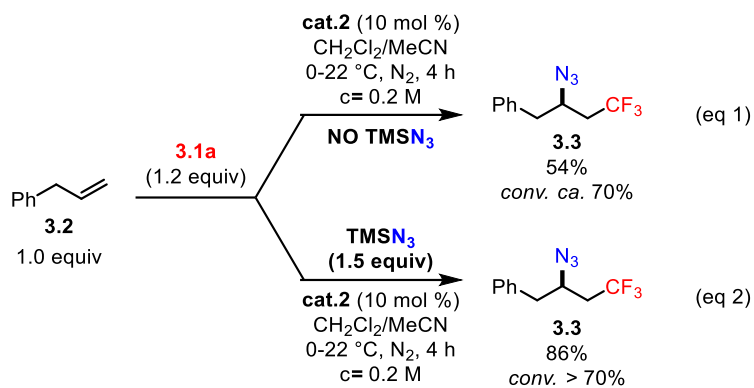
afforded crystalline solids **cat.2** and **cat.3** respectively (Scheme 3.6). IR analysis revealed the presence of the azido group in both solid complexes. X-ray crystallographic analysis of the iron–bi-dentate ligand complex **cat.3** proves challenging; however, we managed to obtain the crystal structure of the iron–tri-dentate ligand complex **cat.2**. To our surprise, **cat.2** exists as an oligomeric iron–azide complex with the formula of $(\text{Fe}(\mathbf{L1})(\text{N}_3)_2)_n$ (Figure 4.2).^{††††} Two type of azide species were observed in the crystal structure: a terminal iron–azide as well as a bridging iron–azide.



*Figure 3.3.2 X-ray crystal structure of $(\text{Fe}(\mathbf{L1})(\text{N}_3)_2)_n$ (**cat.2**)*

We further evaluated the reactivity of $(\text{Fe}(\mathbf{L1})(\text{N}_3)_2)_n$ (**cat.2**) in allyl benzene azido-trifluoromethylation (Scheme 3.7). Surprisingly, it can activate **3.1a** in the absence of TMSN_3 and afford desired trifluoromethyl azidation product **3.3** with excellent mass balance (eq 1). As a control experiment, it also catalyzed allyl benzene azido-trifluoromethylation in the presence of TMSN_3 and afforded **3.3** in good yield (eq 2).

^{††††} Crystal structures of the iron-azide complexes were obtained and analyzed with X-ray crystallography by Prof. Caleb Martin's group at Baylor University.



Scheme 3.7 ($\text{Fe}(\mathbf{LI})(\text{N}_3)_2$)_n complex-catalyzed trifluoromethyl-azidation of allyl benzene

Interestingly, by monitoring the reaction progress with IR technique, we observed that the azido group transferred from preformed iron-azide complex **cat.3** to the desired product along the trifluoromethyl azidation reaction of allyl benzene (Figure 3.3).

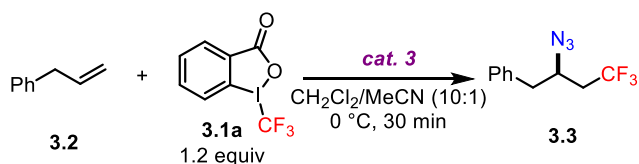
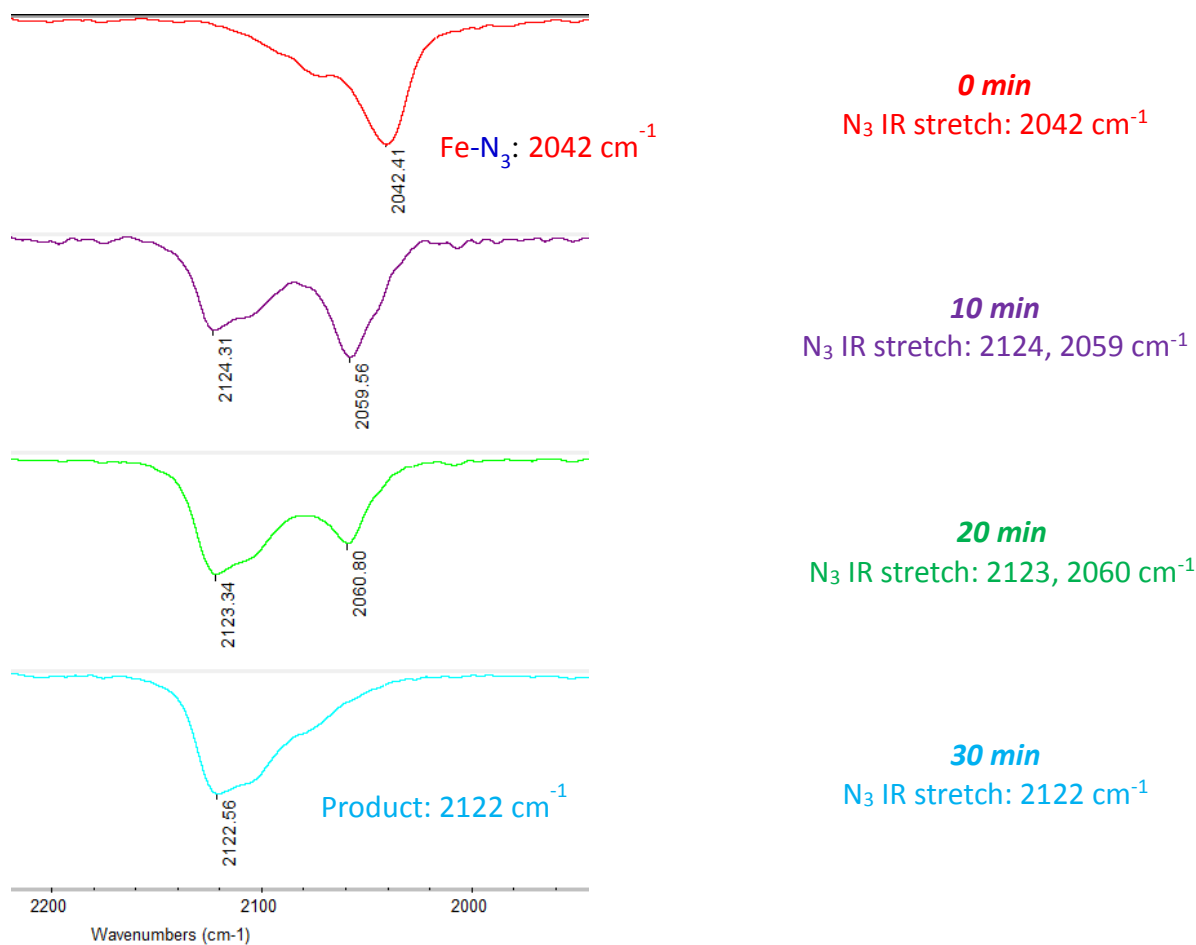
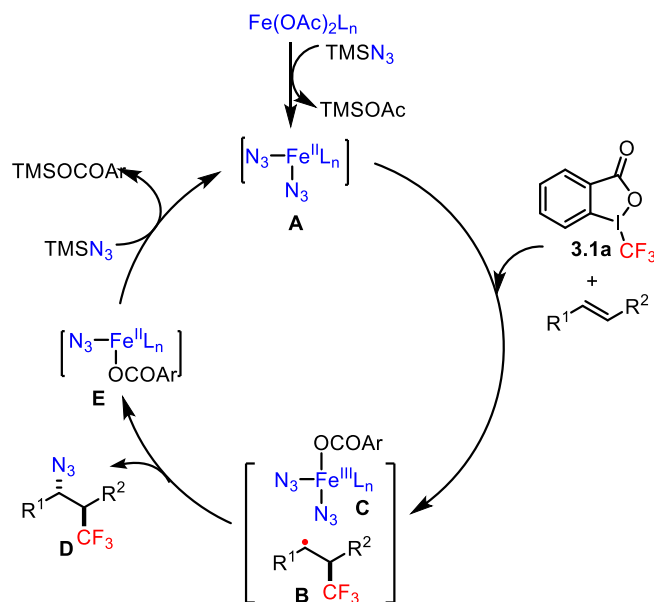


Figure 3.3 IR-absorptions in the iron-azide complex-catalyzed allyl benzene trifluoromethyl-azidation

Based on the collective evidence from the aforementioned control experiments, we proposed the mechanistic working hypothesis that is supported by the experimental data (Scheme 3.8). First, TMSN₃ activates Fe(OAc)₂/ligand complex *in situ*: the azido group is transferred to iron center and a catalytically active iron–ligand–azide complex (intermediate **A**) is generated. During this process, the acetate counter ion is switched off from iron center and presumably forms TMSOAc. Next, Togni's reagent II **3.1a** is activated by intermediate **A**. The I-CF₃ bond is reductively cleaved affording trifluoromethyl radical, which subsequently react with olefin substrate to form C-CF₃ bond and carbo-radical species **B**. At the same time,

iron (II) complex **A** is oxidized to **C** and this high-valent iron species most likely may further oxidize carbo radical **B** through inner-sphere azido ligand-transfer to afford the desired trifluoromethyl-azidation product **D**. Throughout this process, the intermediate **C** is reduced to be a low-valent iron complex **E**. TMSN₃ will abstract carboxylate group from iron center but transfer another equivalent of azido group to regenerate the catalyst **A** and complete the catalytic cycle.



Scheme 3.8 Mechanistic working hypothesis for the iron-catalyzed olefin trifluoromethyl-azidation

3.3 Experimental section

3.3.1 Materials and general information

Materials: Commercial reagents were purchased from Sigma Aldrich, Fluka, EM Science, and Lancaster and used as received. TMSN₃ and all commercially available olefins were redistilled before use. All solvents were used after being freshly distilled unless otherwise noted.

Instrumentation: Proton nuclear magnetic resonance (¹H NMR) spectra, carbon nuclear magnetic resonance (¹³C NMR) spectra and fluorine nuclear magnetic resonance (¹⁹F NMR) were recorded on Bruker UltraShield-400 (400 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak (CHCl₃: δ 7.26). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon

resonances of the NMR solvent (CDCl_3 : δ 77.0). Chemical shifts for fluorine are reported in parts per million downfield and are referenced to the fluorine resonances of CFCl_3 . Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and integration. When ^{19}F NMR is used for quantitative purpose (dr determination), 30 degrees pulse and a longer delay time ($d1 = 5$ s) were employed and the receiver gain was manually set as 32. The mass spectroscopic data were obtained at the Georgia State University mass spectrometry facility using a Micromass Platform II single quadruple instrument. Infrared (IR) spectra were obtained using a Perkin Elmer Spectrum 100 FT-IR spectrometer. Data are represented as follows: frequency of absorption (cm^{-1}) and absorption strength (s = strong, m = medium, w = weak).

All reactions were performed in oven-dried or flame-dried round-bottom flasks and vials. Stainless steel syringes and cannula were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230-400 mesh) from Sigma–Aldrich.

3.3.2 *General procedure for iron-catalyzed trifluoromethyl-azidation reaction*

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{OAc})_2$ (7.0 mg, 0.04 mmol). After this vial was evacuated and backfilled with N_2 twice, a stock solution of ligand **L6** in anhydrous CH_2Cl_2 (0.8 mL, $c=0.05$ M) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. TMSN_3 (80 μL , 0.6 mmol) was added to vial **A** and the mixture was stirred for additional 10 min. To a second flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **3.1a** (152 mg, 0.48 mmol). Vial **B** was evacuated and backfilled with N_2 twice and then anhydrous CH_2Cl_2 (1.1 mL) was added. Both solutions in vial **A** and vial **B** were degassed with brief evacuation and then backfilling with N_2 . Subsequently, freshly distilled olefin (0.4 mmol) was added to vial **B** followed by drop-wise addition of the catalyst solution in vial **A** at 0°C . The reaction mixture was warmed up to 22°C and kept stirring for 4 h until the olefin was consumed (monitored by TLC). Saturated Na_2CO_3 aqueous solution (0.4 mL) was added to quench the reaction and to remove any residue hydrazoic acid. The reaction mixture was further diluted with hexanes (5 mL) and stirred vigorously for 5 min to precipitate 2-

iodobenzoic acid. The mixture was filtered through a short silica gel pad (*ca.* 1.5 cm long silica gel with cotton stopper in a regular Pasteur pipette) and washed with 20% Et₂O in hexanes (10 mL). After concentration *in vacuo*, the residue was subsequently purified through a silica gel column to afford the desired trifluoromethyl-azidation product.

3.3.3 General procedure for reduction and protection

A: Pd/C, H₂ reduction followed by Tosylation.

To a 2-dram vial equipped with a stir bar was added Pd/C (10 wt%). After the vial was evacuated and backfilled twice with N₂, a solution of vicinal trifluoromethyl azide product from last step (1.0 equiv) in 2 mL MeOH was added. The mixture was degassed with brief evacuation and backfilled three times with H₂, and then vigorously stirred under H₂ balloon at 22 °C until the reduction was complete (the reaction was monitored by TLC until the starting material was consumed). The solution was filtered through Celite and washed with MeOH (3 mL). To the filtrate was added a solution of TsOH·H₂O (1.1 equiv) in MeOH (3 mL). The mixture was stirred for 5 min and concentrated *in vacuo* (to about 0.3 mL solvent left). The residue was diluted with Et₂O (6 mL) and vigorously stirred for 20 min to get most of the product precipitate out. The white precipitates were collected by filtration, washed with Et₂O (2 mL × 3) and dried *in vacuo* to afford the desired β-trifluoromethyl ammonium salt.

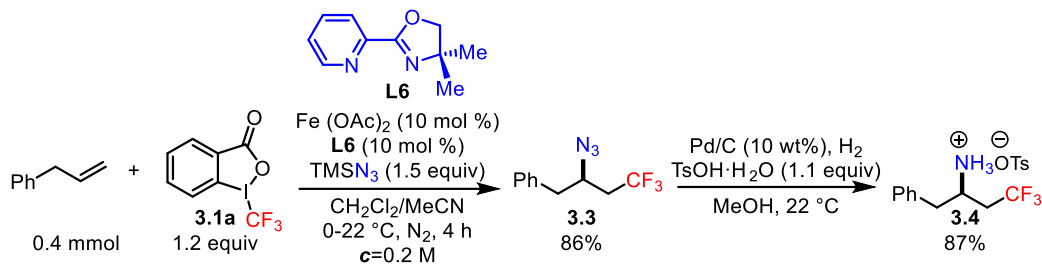
B: Staudinger reduction followed by Boc-protection.

To a 3-dram vial equipped with a stir bar were added the vicinal trifluoromethyl azide product obtained from last step (1.0 equiv), THF (2 mL) and H₂O (10 equiv). After the vial was evacuated and backfilled with N₂ three times, a solution of PMe₃ in THF (2.5 equiv) was added drop-wise at 0 °C. The mixture was warmed up to room temperature and stirred for 2 h (the reaction was monitored by TLC until the starting material was consumed). The mixture was then concentrated *in vacuo* and the residue was further dissolved in CH₂Cl₂ (2 mL). At 0 °C, to the above solution, Boc₂O (2.0 equiv) in 1 mL CH₂Cl₂ was added drop-wise. The resulting mixture was warmed up to room temperature and kept stirring for additional 2 h until the free amine was consumed. After the organic solvent was removed under reduced pressure, the

residue was purified through a silica gel flash column to afford the desired *N*-Boc-protected vicinal trifluoromethyl primary amine.

3.3.4 Procedures for selected vicinal trifluoromethyl amines syntheses

A: Procedure for trifluoromethyl-azidation/reduction of allyl benzene.



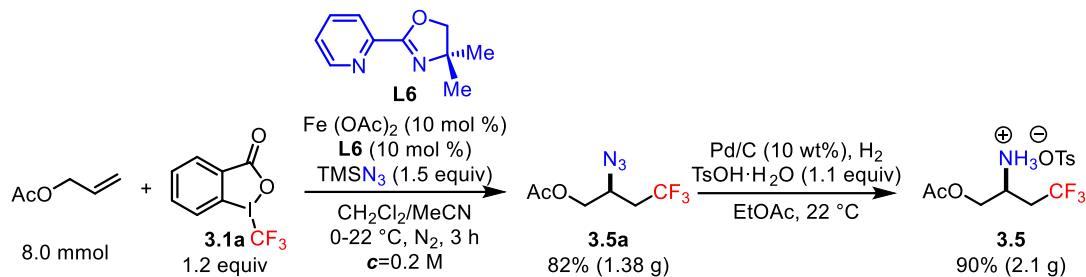
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added Fe(OAc)₂ (7.0 mg, 0.04 mmol). After this vial was evacuated and backfilled with N₂ twice, a stock solution of ligand **L6** in anhydrous CH₂Cl₂ (0.8 mL, c=0.05 M) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. TMSN₃ (80 mL, 0.6 mmol) was added to vial **A** and the mixture was stirred for additional 10 min. To a second flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **3.1a** (152 mg, 0.48 mmol). Vial **B** was evacuated and backfilled with N₂ twice and then anhydrous CH₂Cl₂ (1.1 mL) was added. Both solutions in vial **A** and vial **B** were degassed with brief evacuation and then backfilling with N₂. Subsequently, freshly distilled allyl benzene (53 μL, 0.4 mmol) was added to vial **B** followed by drop-wise addition of the catalyst solution in vial **A** at 0 °C. The reaction mixture was warmed up to 22 °C and kept stirring for 4 h until the olefin was consumed (monitored by TLC). Saturated Na₂CO₃ aqueous solution (0.4 mL) was added to quench the reaction and to remove any residue hydrazoic acid. The reaction mixture was further diluted with hexanes (5 mL) and stirred vigorously for 10 min to precipitate 2-iodobenzoic acid. The mixture was filtered through a short silica gel pad (*ca.* 1.5 cm long silica gel with cotton stopper in a regular Pasteur pipette) and washed with 20% Et₂O in hexanes (10 mL). After concentration *in vacuo*, the residue was subsequently purified through a silica gel column (100% hexanes) to afford the desired trifluoromethyl-azidation product **3.3** as colorless oil (79 mg, 86% yield).

2-Azido-4,4,4-trifluorobutyl benzene (3.3): IR ν_{\max} (neat)/ cm^{-1} : 3032 (w), 2119 (s), 1248 (s), 1142 (s), 1114 (s), 748 (m), 699 (s); ^1H NMR (400 MHz, CDCl_3): δ 7.46–7.08 (m, 5H), 4.03–3.81 (m, 1H), 2.98–2.86 (m, 2H), 2.46–2.19 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 136.0, 129.3, 128.9, 127.4, 125.7 (q, $J = 277.2$ Hz), 57.8 (q, $J = 2.7$ Hz), 41.0, 37.9 (q, $J = 28.4$ Hz); ^{19}F NMR (376 MHz, CDCl_3): δ -63.89 (t, $J = 10.4$ Hz).

To a 2-dram vial equipped with a stir bar was added Pd/C (8.0 mg, 10 wt%). After the vial was evacuated and backfilled twice with N_2 , a solution of **3.3** from last step (79 mg, 0.34 mmol) in 2 mL MeOH was added. The mixture was degassed with brief evacuation and backfilled three times with H_2 , and then vigorously stirred under H_2 balloon at 22 °C until the reduction was complete (the reaction was monitored by TLC until **3.3** was consumed). The solution was filtered through Celite and washed with MeOH (3 mL). To the filtrate was added a solution of TsOH· H_2O (72 mg, 0.38 mmol) in MeOH (3 mL). The mixture was stirred for 5 min and concentrated *in vacuo* (to about 0.3 mL solvent left). The residue was diluted with Et_2O (6 mL) and vigorously stirred for 20 min to get most of the product precipitate out. The white precipitates were collected by filtration, washed with Et_2O (2 mL \times 3) and dried *in vacuo* to afford the desired β -trifluoromethyl ammonium salt **3.4** was obtained as a white solid (111 mg, 87% yield).

4,4,4-Trifluoro-1-phenylbutan-2-aminium 4-methylbenzenesulfonate (3.4): IR ν_{\max} (neat)/ cm^{-1} : 3158 (br), 2952 (w), 1535 (m), 1230 (m), 1117 (s), 1008 (s), 813 (s), 677 (s); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.11 (s, 3H), 7.48 (d, $J = 7.2$ Hz, 2H), 7.42–7.27 (m, 5H), 7.12 (d, $J = 7.5$ Hz, 2H), 3.86–3.72 (m, 1H), 3.02 (dd, $J = 13.8, 6.1$ Hz, 1H), 2.88 (dd, $J = 13.9, 7.5$ Hz, 1H), 2.69–2.52 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 145.4, 138.6, 135.7, 129.9, 129.2, 128.7, 127.7, 126.4 (q, $J = 277.1$ Hz), 126.0, 47.0 (q, $J = 2.5$ Hz), 38.5, 35.4 (q, $J = 28.3$ Hz); 21.3; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$): δ -61.89 (t, $J = 11.3$ Hz); HRMS (ESI, m/z): calcd for $\text{C}_{10}\text{H}_{13}\text{F}_3\text{N}^+$, $[\text{M} + \text{H}^+]$, 204.0995, found 204.1004.

B: procedure for trifluoromethyl-azidation/reduction of allyl acetate.



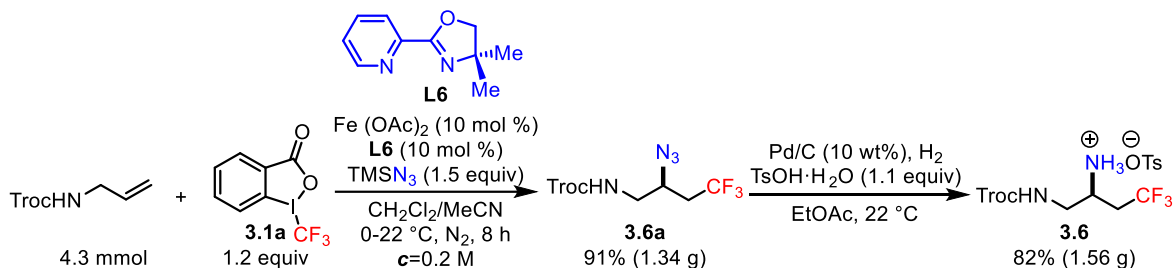
To a flame-dried sealable 3-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{OAc})_2$ (140 mg, 0.8 mmol) and **L6** (140.8 mg, 0.8 mmol). After the vial was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (6.0 mL) and MeCN (1.0 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To another flame dried 50 mL round bottom flask (flask **A**) equipped with a stir bar was added **3.1a** (3.03 g, 9.6 mmol). Flask **A** was evacuated and backfilled with N_2 for twice and then anhydrous CH_2Cl_2 (9.0 mL) was added. Both solutions in vial **A** and Flask **A** were degassed with brief evacuation and then backfilling with N_2 . Subsequently, freshly distilled **allyl acetate** (817 μL , 8.0 mmol) and TMSN_3 (1.58 mL, 12.0 mmol) were added successively to flask **A** followed by drop-wise addition of the catalyst solution in vial **A** at 0 °C. The reaction was kept at this temperature for 30 min, then warmed up to 22 °C, and stirred for additional 3 h. Saturated Na_2CO_3 aqueous solution (10 mL) was added to quench the reaction. The organic layer was separated from the aqueous one, which was extracted with CH_2Cl_2 (10 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* (Note: the reaction mixture was concentrated in ice-water bath with care to minimize the loss of the volatile azidotrifluoromethylation product). The residue was purified through a silica gel column (hexanes/ Et_2O : from 50:1 to 10:1) to afford the desired trifluoromethyl-azidation product **3.5a** as colorless oil (1.38 g, 82% yield).

2-Azido-4,4,4-trifluorobutyl acetate (3.5a): IR ν_{max} (neat)/ cm^{-1} : 2960 (w), 2121 (s), 1746 (s), 1220 (s), 1137 (s), 1043 (s), 603 (m); ^1H NMR (400 MHz, CDCl_3): δ 4.24 (dd, $J = 11.6, 4.3$ Hz, 1H), 4.13 (dd, $J = 11.6, 6.8$ Hz, 1H), 4.00–3.87 (m, 1H), 2.34 (qd, $J = 10.4, 6.4$ Hz, 2H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 170.3, 125.3 (q, $J = 276.9$ Hz), 65.3, 65.3, 54.7, 54.6, 35.5 (q, $J = 29.3$ Hz), 20.6; ^{19}F NMR (376 MHz, CDCl_3): δ -64.12 (t, $J = 10.4$ Hz).

To a 100 mL Schlenk flask equipped with a stir bar was added Pd/C (140 mg, 10 wt%) and TsOH·H₂O (1.42 g, 7.47 mmol). After the flask was evacuated and backfilled twice with N₂, a solution of the **3.5a** from last step (1.37 g, 6.49 mmol) in 50 mL EtOAc was added. The mixture was degassed with brief evacuation and backfilled three times with H₂, and then vigorously stirred under H₂ balloon at 22 °C until the reduction completed (the reaction was monitored by TLC until **3.5a** was consumed, *ca.* 2 h). The solution was then filtered through Celite and washed with MeOH (25 mL). The resulting solution was concentrated *in vacuo* (to about 4 mL solvent left) and diluted with Et₂O (70 mL). The cloudy solution was vigorously stirred for 2 h to get most of the β-trifluoromethyl ammonium salt precipitate out. The white precipitates were collected by filtration, washed with Et₂O (10 mL × 3) and dried *in vacuo* to afford the desired β-trifluoromethyl ammonium salt **3.5** as a white solid (2.1 g, 90% yield).

1-Acetoxy-4,4,4-trifluorobutan-2-aminium 4-methylbenzenesulfonate (3.5): ¹H NMR (400 MHz, DMSO) δ 8.28 (s, 3H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 4.27 (dd, *J* = 12.2, 3.4 Hz, 1H), 4.13 (dd, *J* = 12.2, 5.9 Hz, 1H), 3.86 – 3.74 (m, 1H), 2.89 – 2.74 (m, 1H), 2.74 – 2.60 (m, 1H), 2.30 (s, 3H), 2.08 (s, 3H); ¹³C NMR (100 MHz, DMSO) δ 170.5, 145.5, 138.6, 128.7, 126.1 (q, *J* = 276.7 Hz), 125.9, 63.0, 44.8, 33.3 (q, *J* = 29.0 Hz), 21.2, 21.0; ¹⁹F NMR (376 MHz, DMSO) δ -62.38 (t, *J* = 11.4 Hz).

C: procedure for trifluoromethyl-azidation/reduction of allyl N-Troc-amine.



To a flame-dried sealable 3-dram vial (vial **A**) equipped with a stir bar were added Fe(OAc)₂ (123 mg, 0.65 mmol) and **L6** (125 mg, 0.65 mmol). After the vial was evacuated and backfilled with N₂ twice, anhydrous CH₂Cl₂ (6.0 mL) and MeCN (1.0 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To another flame dried 50 mL round bottom flask (flask **A**) equipped with a stir bar was added **2,2,2-trichloroethyl allylcarbamate** (1.0 g, 4.3 mmol) and **3.1a** (1.6 g, 5.2 mmol). Flask

A was evacuated and backfilled with N₂ twice and then anhydrous CH₂Cl₂ (14.0 mL) was added. Both solutions in vial **A** and flask **A** were degassed with brief evacuation and then backfilling with N₂. Subsequently, freshly distilled TMSN₃ (1.58 mL, 12.0 mmol) were added to flask **A** followed by drop-wise addition of the catalyst solution in vial **A** at 0 °C. The reaction was warmed up to 22 °C and stirred for 8h. Saturated Na₂CO₃ aqueous solution (10 mL) was added to quench the reaction. The organic layer was separated from the aqueous one, which was extracted with CH₂Cl₂ (10 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified through a silica gel column (hexanes/EtOAc: from 50:1 to 4:1) to afford the desired trifluoromethyl-azidation product **3.6a** as colorless oil (1.34 g, 91% yield).

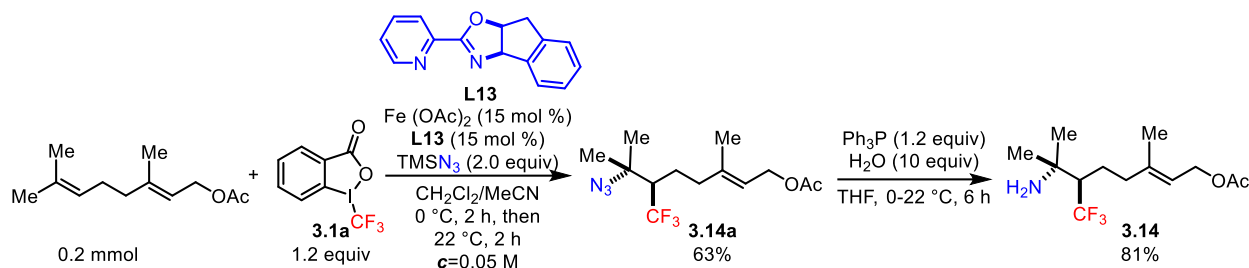
2,2,2-Trichloroethyl (2-azido-4,4,4-trifluorobutyl)carbamate (3.6a): IR ν_{\max} (neat)/cm⁻¹: 3339 (m), 2957 (w), 2125 (s), 1717 (s), 1524 (m), 1242 (s), 1131 (s), 723 (s); ¹H NMR (400 MHz, CDCl₃): δ 5.39 (s, 1H), 4.75 (s, 2H), 4.03–3.86 (m, 1H), 3.60–3.45 (m, 1H), 3.35–3.20 (m, 1H), 2.44–2.25 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 154.7, 125.4 (q, *J* = 276.9 Hz), 95.2, 74.7, 56.43, 44.9, 36.4 (q, *J* = 29.1 Hz); ¹⁹F NMR (376 MHz, CDCl₃): δ -63.88 (t, *J* = 10.4 Hz).

To a 100 mL Schlenk flask equipped with a stir bar was added Pd/C (140 mg, 10 wt%) and TsOH·H₂O (0.82 g, 4.3 mmol). After the flask was evacuated and backfilled twice with N₂, a solution of **3.6a** from last step (1.34 g, 3.9 mmol) in 50 mL EtOAc was added. The mixture was degassed with brief evacuation and backfilled three times with H₂, and then vigorously stirred under H₂ balloon at 22 °C until the reduction completed (the reaction was monitored by TLC until **3.6a** was consumed, *ca.* 4 h). The solution was filtered through Celite and washed with MeOH (25 mL). The resulting solution was concentrated *in vacuo* (to about 4 mL solvent left) and diluted with Et₂O (70 mL). The cloudy solution was vigorously stirred for 2 h to get most of the product precipitate out. The white precipitates were collected by filtration, washed with Et₂O (10 mL × 3) and dried *in vacuo* to afford the desired β -trifluoromethyl ammonium salt **3.6** as a white solid (1.56 g, 82% yield).

4,4,4-Trifluoro-1-(((2,2,2-trichloroethoxy)carbonyl)amino)butan-2-aminium 4-methylbenzenesulfonate (3.6): IR ν_{\max} (neat)/cm⁻¹: 3390 (br), 2990 (w), 1722 (m), 1708 (m), 1514 (m),

1167 (s), 1123 (s), 1035 (s), 1010 (s), 812 (s), 677 (s); ^1H NMR (400 MHz, Acetone) δ 8.42 (s, 2H), 7.74 (d, $J = 8.1$ Hz, 2H), 7.49 (t, $J = 5.7$ Hz, 1H), 7.20 (d, $J = 7.9$ Hz, 2H), 4.74 (dd, $J = 47.5, 12.3$ Hz, 2H), 3.98 (s, 1H), 3.88 – 3.62 (m, 2H), 3.09 – 2.93 (m, 1H), 2.93 – 2.81 (m, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 155.5, 145.6, 138.4, 128.6, 126.2 (q, $J = 276.8$ Hz), 125.9, 96.4, 74.2, 45.7, 42.7, 34.1 (q, $J = 28.7$ Hz), 21.3; ^{19}F NMR (376 MHz, DMSO) δ -62.42 (t, $J = 11.3$ Hz).

D: procedure for trifluoromethyl-azidation/reduction of geranyl acetate.



To a flame-dried 3-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{OAc})_2$ (5.3 mg, 0.03 mmol) and ligand **L2** (7.1 mg, 0.03 mmol). After this vial was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To a second flame-dried 2-dram vial (vial **B**) was added **3.1a** (76 mg, 0.24 mmol). Vial **B** was evacuated and backfilled with N_2 and then anhydrous CH_2Cl_2 (3.0 mL) was added to dissolve **3.1a**. The solution in vial **A** was degassed with brief evacuation and then backfilling with N_2 twice. At $0\text{ }^\circ\text{C}$, freshly distilled geranyl acetate (45 μL , 0.2 mmol) and TMSN_3 (53 μL , 0.4 mmol) were added successively to vial **A**. Subsequently, the solution in vial **B** was added to vial **A** using a syringe pump within 2 h. The reaction mixture was then warmed up to $22\text{ }^\circ\text{C}$ and kept stirring for additional 1 h until the olefin was mostly consumed (monitored by TLC). Saturated Na_2CO_3 aqueous solution (0.4 mL) was added to quench the reaction and to remove any residue hydrazoic acid. The reaction mixture was further diluted with hexanes (5 mL) and stirred vigorously for 10 min to precipitate 2-iodobenzoic acid. The mixture was filtered through a short silica gel pad (*ca.* 1.5 cm long silica gel with cotton stopper in a regular Pasteur pipette) and washed with 30% Et_2O in hexanes (10 mL). After concentration *in vacuo*, the residue was

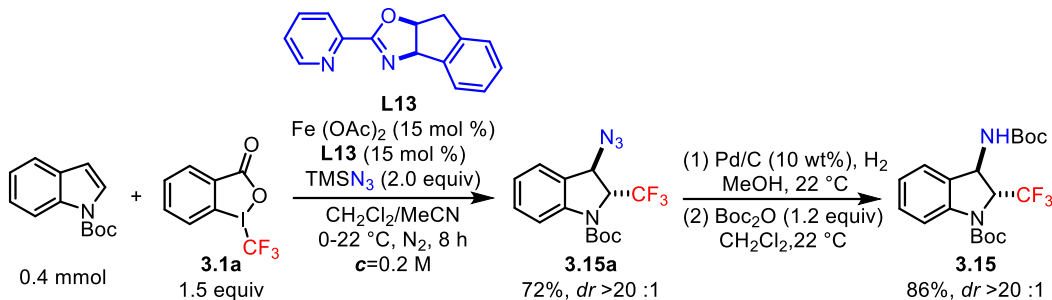
subsequently purified through a silica gel column (hexanes/Et₂O: from 100:1 to 20:1) to afford the desired trifluoromethyl-azidation product **3.14a** as colorless oil (39 mg, 63% yield).

7-Azido-3,7-dimethyl-6-(trifluoromethyl)oct-2-en-1-yl acetate (3.14a): IR ν_{\max} (neat)/cm⁻¹: 2980 (w), 2103 (s), 1737 (s), 1368 (m), 1228 (s), 1138 (s), 1092 (s); ¹H NMR (400 MHz, CDCl₃): δ 5.38 (t, *J* = 6.9 Hz, 1H), 4.59 (d, *J* = 7.0 Hz, 2H), 2.31–2.20 (m, 1H), 2.17–2.09 (m, 1H), 2.09–1.99 (m, 4H), 1.84–1.63 (m, 2H), 1.72 (s, 3H), 1.44 (s, 3H), 1.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 171.0, 140.6, 127.4 (q, *J* = 281.8 Hz), 119.9, 62.0 (q, *J* = 1.3 Hz), 61.1, 50.6 (q, *J* = 23.6 Hz), 39.1 (q, *J* = 1.4 Hz), 25.9 (q, *J* = 2.4 Hz), 23.9 (q, *J* = 2.3 Hz), 23.0 (q, *J* = 2.0 Hz), 21.0, 16.2; ¹⁹F NMR (376 MHz, CDCl₃): δ -63.8 (d, *J* = 9.8 Hz).

To a 3-dram vial equipped with a stir bar were added **3.14a** from last step (38 mg, 0.126 mmol), THF (3 mL) and H₂O (24 μ L, 1.3 mmol). After the vial was evacuated and backfilled with N₂ three times, a solution of PPh₃ (40 mg, 0.15 mmol) in THF (1.5 mL) was added drop-wise at 0 °C. The mixture was warmed up to 22 °C and stirred for 6 h (the reaction was monitored by TLC until **3.14a** was consumed). The mixture was then concentrated *in vacuo* and the residue was purified through a silica gel column (hexanes/EtOAc: from 100:1 to 6:1) to afford the desired β -trifluoromethyl amine **3.14** as clear oil (29 mg, 81% yield).

7-Amino-3,7-dimethyl-6-(trifluoromethyl)oct-2-en-1-yl acetate (3.14): IR ν_{\max} (neat)/cm⁻¹: 3225 (m), 2946 (m), 2854 (w), 1721 (s), 1472 (m), 1245 (s), 1167 (s), 1156 (s), 740(m); ¹H NMR (400 MHz, CDCl₃): δ 5.36 (t, *J* = 6.8 Hz, 1H), 4.56 (t, *J* = 9.5 Hz, 2H), 2.30–2.21 (m, 1H), 2.10 (m, 1H), 2.04 (s, 3H), 1.99–1.85 (m, 1H), 1.71 (s, 3H), 1.73–1.64 (m, 2H), 1.59 (s, 2H), 1.22 (d, *J* = 18.5 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 171.0, 141.0, 128.6 (q, *J* = 282.6 Hz), 119.6, 61.2, 52.6 (q, *J* = 21.9 Hz), 51.2 (q, *J* = 1.1 Hz), 39.7 (q, *J* = 1.2 Hz), 29.4 (dq, *J* = 27.6, 2.1 Hz), 24.2 (q, *J* = 2.4 Hz), 22.6 (d, *J* = 55.6 Hz), 20.9, 16.3; ¹⁹F NMR (376 MHz, CDCl₃): δ -63.4 (d, *J* = 10.3 Hz); HRMS (ESI, m/z): calcd for C₁₃H₂₃F₃NO₂⁺, [M + H⁺], 282.1681, found 282.1688.

E: procedure for trifluoromethyl-azidation/reduction of indole.



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{OAc})_2$ (10.5 mg, 0.06 mmol) and the ligand **L13** (14.2 mg, 0.06 mmol). After this vial was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. TMSN_3 (106 μL , 0.8 mmol) was added to vial **A** and the mixture was stirred for additional 10 min. To a second flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **3.1a** (190 mg, 0.6 mmol). Vial **B** was evacuated and backfilled with N_2 twice and then anhydrous CH_2Cl_2 (1.1 mL) was added. Both solutions in vial **A** and vial **B** were degassed with brief evacuation and then backfilling with N_2 . Subsequently, *N*-Boc protected indole (78 μL , 0.4 mmol) was added to vial **B** followed by drop-wise addition of the catalyst solution in vial **A** at 0 °C. The reaction mixture was warmed up to 22 °C and kept stirring for 8 h until the olefin was consumed (monitored by TLC). Saturated Na_2CO_3 aqueous solution (0.4 mL) was added to quench the reaction and to remove any residue hydrazoic acid. The reaction mixture was further diluted with hexanes (5 mL) and stirred vigorously for 10 min to precipitate 2-iodobenzoic acid. The mixture was filtered through a short silica gel pad (*ca.* 1.5 cm long silica gel with cotton stopper in a regular Pasteur pipette) and washed with 30% Et_2O in hexanes (10 mL). After concentration *in vacuo*, the residue was subsequently purified through a silica gel column (hexanes/ Et_2O : from 100:1 to 20:1) to afford the desired trifluoromethyl-azidation product **3.15a** as colorless oil (95 mg, 72% yield, *dr* >20 :1).

tert-Butyl-3-azido-2-(trifluoromethyl)indoline-1-carboxylate (3.15a): IR ν_{max} (neat)/ cm^{-1} : 2982 (w), 2103 (s), 1718 (s), 1605 (w), 1481 (s), 1369 (s), 1150 (s), 753(m); ^1H NMR (400 MHz, CD_3CN): δ 7.77 (d, $J = 7.4$ Hz, 1H), 7.49 (dd, $J = 18.8, 7.7$ Hz, 2H), 7.21 (t, $J = 7.5$ Hz, 1H), 5.12 (s, 1H), 5.00 (q, $J = 7.3$

Hz, 1H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, CD_3CN): δ 151.5, 142.4, 131.0, 126.6, 125.4, 124.3 (q, $J = 282.5$ Hz), 124.0, 117.3, 116.5, 83.0, 65.6 (q, $J = 30.9$ Hz), 59.6, 27.3; ^{19}F NMR (376 MHz, CD_3CN): δ -76.73 (d, $J = 6.7$ Hz).

To a 2-dram vial equipped with a stir bar was added Pd/C (10 mg, 10 wt%). After the vial was evacuated and backfilled twice with N_2 , a solution of **3.15a** (95 mg, 0.29 mmol) in 2 mL MeOH was added. The mixture was degassed with brief evacuation and backfilled twice with N_2 and then three times with H_2 . The reaction was vigorously stirred under H_2 at room temperature until the reduction completed (the reaction was monitored by TLC until **3.15a** was consumed). The solution was filtered through Celite and washed with MeOH (2 mL). The solution was concentrated and the residue was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. To the above solution, Boc_2O (76 mg, 0.35 mmol) in 1 mL CH_2Cl_2 was added dropwise. The resulting mixture was warmed up to room temperature and kept stirring for additional 2 h until the free amine was consumed. After the organic solvent was removed under reduced pressure, the residue was purified through a silica gel flash column (hexanes/EtOAc: from 20:1 to 6:1) to afford the desired *N*-Boc protected β -trifluoromethyl amine **3.15** as a white solid (101 mg, 86% yield, *dr* > 20:1).

3.15 was recrystallized from EtOAc/hexanes, and its stereochemistry was confirmed by X-ray crystallographic analysis. (Figure 4.3)

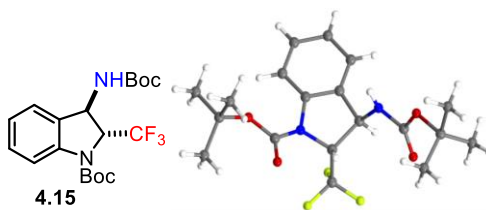
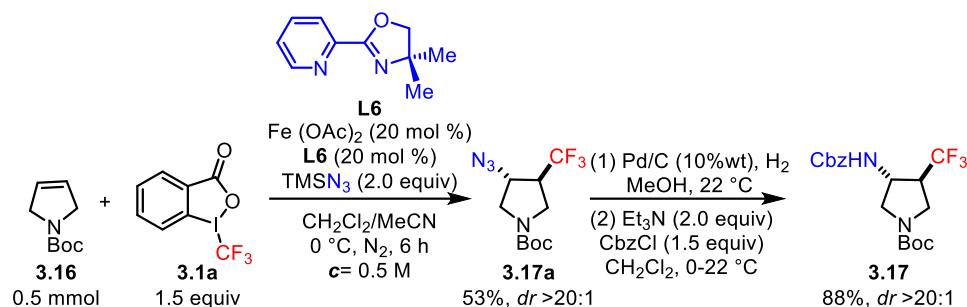


Figure 3.4 X-ray crystal structure of the β -trifluoromethyl-amine from indole

tert-Butyl-3-((tert-butoxycarbonyl)amino)-2-(trifluoromethyl)indoline-1-carboxylate (3.15): IR ν_{max} (neat)/ cm^{-1} : 3337 (m), 2980 (w), 1714 (s), 1483 (m), 1369 (s), 1247 (m), 1154 (s), 752 (s); ^1H NMR (400 MHz, Acetone- d_6): δ 7.7 (d, $J = 4.1$ Hz, 1H), 7.4 (ddt, $J = 7.5, 1.4, 0.7$ Hz, 1H), 7.4–7.3 (m, 1H), 7.1 (td, $J = 7.5, 1.1$ Hz, 1H), 6.9 (s, 1H), 5.2 (d, $J = 8.0$ Hz, 1H), 4.9 (qd, $J = 7.5, 1.8$ Hz, 1H), 1.6 (s, 9H), 1.4 (s, 9H); ^{13}C NMR (100 MHz, Acetone) δ 154.8, 151.7, 142.7, 130.1, 129.4, 127.8 (q, $J = 282.5$ Hz), 125.0,

123.6, 116.1, 81.9, 79.0, 66.4 (q, $J = 33.2$ Hz), 51.7, 27.6, 27.4; ^{19}F NMR (376 MHz, Acetone- d_6): δ -77.0 (d, $J = 7.1$ Hz); HRMS (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{25}\text{F}_3\text{N}_2\text{NaO}_4^+$, $[\text{M} + \text{Na}^+]$, 425.1659, found 425.1662.

F: procedure for trifluoromethyl-azidation/reduction of 2,5-dihydropyrrole.



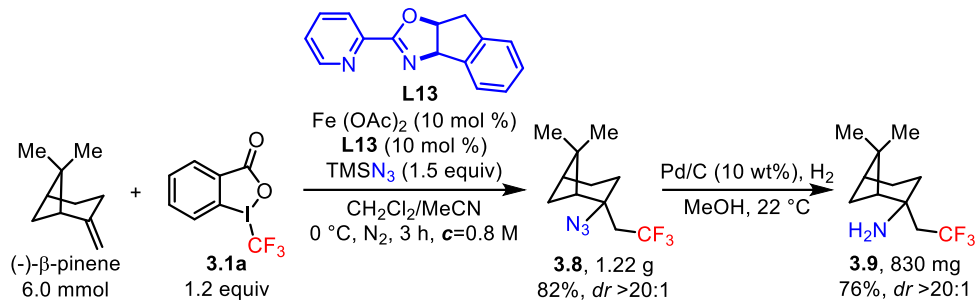
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{OAc})_2$ (17.4 mg, 0.1 mmol). After this vial was evacuated and backfilled with N_2 twice, a stock solution of ligand **L6** in anhydrous CH_2Cl_2 (0.5 mL, $c = 0.2$ M) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. TMSN_3 (198 μL , 1.5 mmol) was added to vial **A** and the mixture was stirred for additional 10 min. To a second flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **3.1a** (316 mg, 1.0 mmol). Vial **B** was evacuated and backfilled with N_2 twice and then anhydrous CH_2Cl_2 (0.5 mL) was added. Both solutions in vial **A** and vial **B** were degassed with brief evacuation and then backfilling with N_2 . Subsequently freshly purified **3.16** (88 μL , 0.5 mmol) was added to vial **B** followed by drop-wise addition of the catalyst solution in vial **A** at 0°C . The reaction mixture was kept stirring at 0°C for 4 h until the olefin was consumed (monitored by TLC). Saturated Na_2CO_3 aqueous solution (0.4 mL) was added to quench the reaction and to remove any residue hydrazoic acid. The reaction mixture was further diluted with hexanes (5 mL) and stirred vigorously for 10 min to precipitate 2-iodobenzoic acid. The mixture was filtered through a short silica gel pad (*ca.* 1.5 cm long silica gel with cotton stopper in a regular Pasteur pipette) and washed with 20% EtOAc in hexanes (10 mL). After concentration *in vacuo*, the residue was subsequently purified through a silica gel column (hexanes/EtOAc: from 100:1 to 10:1) to afford the desired trifluoromethyl-azidation product **3.17a** as colorless oil (74 mg, 53% yield, $dr > 20:1$).

***tert*-Butyl (3*R*,4*S*)-3-azido-4-(trifluoromethyl)pyrrolidine-1-carboxylate (3.17a):** ¹H NMR (400 MHz, CDCl₃) δ 4.21 (dd, *J* = 11.7, 5.6 Hz, 1H), 3.89 – 3.61 (m, 2H), 3.61 – 3.44 (m, 1H), 3.44 – 3.29 (m, 1H), 2.97 – 2.78 (m, 1H), 1.45 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 153.6, 125.6 (q, *J* = 278.1 Hz), 80.6, 59.6, 50.4, 48.4, 43.9, 28.3; ¹⁹F NMR (376 MHz, CDCl₃) δ -70.42.

To a 2-dram vial equipped with a stir bar was added Pd/C (8 mg, 10 wt%). After the vial was evacuated and backfilled twice with N₂, a solution of **3.17a** (74 mg, 0.265 mmol) in 2 mL MeOH was added. The mixture was degassed with brief evacuation and backfilled twice with N₂ and then three times with H₂. The reaction was vigorously stirred under H₂ at room temperature until the reduction completed (the reaction was monitored by TLC until **3.17a** was consumed). The solution was filtered through Celite and washed with MeOH (2 mL). After concentration *in vacuo*, the residue was dissolved in CH₂Cl₂ (4 mL) and cooled to 0 °C. To the above solution, was added Et₃N (74 μL, 0.53 mmol) and CbzCl (57 μL, 0.4 mmol) in 1 mL CH₂Cl₂. The resulting mixture was warmed up to room temperature and kept stirring for additional 2 h until the free amine was consumed. After the organic solvent was removed under reduced pressure, the residue was purified through a silica gel flash column (hexanes/EtOAc: from 20:1 to 6:1) to afford the desired *N*-Cbz protected β-trifluoromethyl amine **3.17** as a white solid (91 mg, 88% yield, *dr* > 20:1). The structure was confirmed by comparing published data.⁸⁶

***tert*-Butyl (3*R*,4*S*)-3-(((benzyloxy)carbonyl)amino)-4-(trifluoromethyl)pyrrolidine-1-carboxylate (3.17):** ¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.27 (m, 5H), 5.39 (s, 1H), 5.09 (s, 2H), 4.37 (s, 1H), 3.78 (dd, *J* = 11.5, 7.3 Hz, 1H), 3.66 (brs, 1H), 3.47 (brs, 1H), 3.26 (brs, 1H), 2.94 (brs, 1H), 1.44 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 155.5, 136.0, 128.6, 128.4, 128.2, 125.9 (q, *J* = 277.0 Hz), 80.4, 67.1, 50.5 (q, *J* = 59.8 Hz), 28.4; ¹⁹F NMR (376 MHz, CDCl₃) δ -70.30 (brs).

G: procedure for trifluoromethyl-azidation/reduction of (-)-β-pinene.



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{OAc})_2$ (104 mg, 0.6 mmol) and ligand **L13** (142 mg, 0.6 mmol). After this vial was evacuated and backfilled with N_2 twice, anhydrous CH_2Cl_2 (5.0 mL) and MeCN (0.5 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To a flame dried 50 mL round bottom flask (flask **B**) equipped with a stir bar was added **3.1a** (2.28 g, 7.2 mmol). Flask **B** was evacuated and backfilled with N_2 twice and then anhydrous CH_2Cl_2 (2.0 mL) was added. Both solutions in vial **A** and flask **B** were degassed with brief evacuation and then backfilling with N_2 . Subsequently, freshly distilled (-)- β -pinene (0.95 mL, 6.0 mmol) and TMSN_3 (1.2 mL, 9.0 mmol) were added successively to flask **B** followed by slow addition of the catalyst solution in vial **A** using syringe pump within 1 h at $0\text{ }^\circ\text{C}$. The reaction was kept stirring at $0\text{ }^\circ\text{C}$ for 2 h and then quenched with saturated Na_2CO_3 solution (10 mL). The organic layer was separated from the aqueous one, which was extracted with CH_2Cl_2 (10 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified through a silica gel flash column (100% hexanes) to afford the desired trifluoromethyl-azidation product **3.8** as colorless oil (1.22 g, 82% yield, $dr >20:1$).

2-Azido-6,6-dimethyl-2-(2,2,2-trifluoroethyl)bicyclo[3.1.1]heptane (3.8): ^1H NMR (400 MHz, CDCl_3): δ 2.65–2.39 (m, 2H), 2.38–2.29 (m, 1H), 2.18 (t, $J = 5.4$ Hz, 1H), 2.05–1.86 (m, 5H), 1.44 (d, $J = 10.5$ Hz, 1H), 1.30 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 125.6 (q, $J = 278.6$ Hz), 49.9, 43.6 (q, $J = 26.7$ Hz), 39.9, 38.4, 28.3, 27.6, 27.2, 25.3, 23.1; ^{19}F NMR (376 MHz, CDCl_3): δ -60.03 (t, $J = 10.8$ Hz).

To a 50 mL round bottle flask equipped with a stir bar and a three-way adapter was added Pd/C (10 wt%, 0.12 g). After the flask was evacuated and backfilled twice with N_2 , a solution of **4.8** from last step (1.22 g, 4.93 mmol) in 15 mL MeOH was added. The mixture was degassed with brief evacuation and

backfilled three times with H₂, and then vigorously stirred under H₂ balloon at 22 °C until the reduction was complete (the reaction was monitored by TLC until **4.8** was consumed). The solution was filtered through Celite and washed with CH₂Cl₂ (20 mL). The mixture was then concentrated *in vacuo* and the residue was purified through a silica gel column (hexanes/EtOAc: from 100:1 to 4:1) to afford the desired β-trifluoromethyl amine **4.9** as white solid (830 mg, 76% yield).

6,6-Dimethyl-2-(2,2,2-trifluoroethyl)bicyclo[3.1.1]heptan-2-amine (3.9): ¹HNMR (400 MHz, CDCl₃): δ 2.54–2.30 (m, 2H), 2.28–2.18 (m, 1H), 2.00–1.81 (m, 5H), 1.72–1.60 (m, 1H), 1.57 (s, 2H), 1.37 (d, *J* = 10.5 Hz, 1H), 1.25 (s, 3H), 1.00 (s, 3H); ¹³CNMR (100 MHz, CDCl₃): δ 126.9 (q, *J* = 279.1 Hz), 54.2 (q, *J* = 1.7 Hz), 53.2 (q, *J* = 1.1 Hz), 46.2 (q, *J* = 24.2 Hz), 40.5, 38.5, 31.2 (q, *J* = 1.4 Hz); 27.7, 27.4, 25.2, 23.5; ¹⁹FNMR (376 MHz, CDCl₃): δ -58.64 (t, *J* = 11.5 Hz).

For X-ray analysis purpose, *N*-Boc-protected β-trifluoromethyl amine **3.9a** was prepared from **3.9** by following the *general procedure B* in **3.3.3** as a white solid (82% yield, *dr* > 20:1). After crystallization from EtOAc/hexanes, its stereochemistry was confirmed by X-ray crystallographic analysis (Figure 3.5).

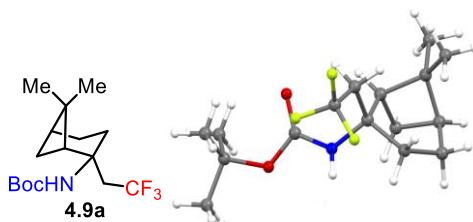
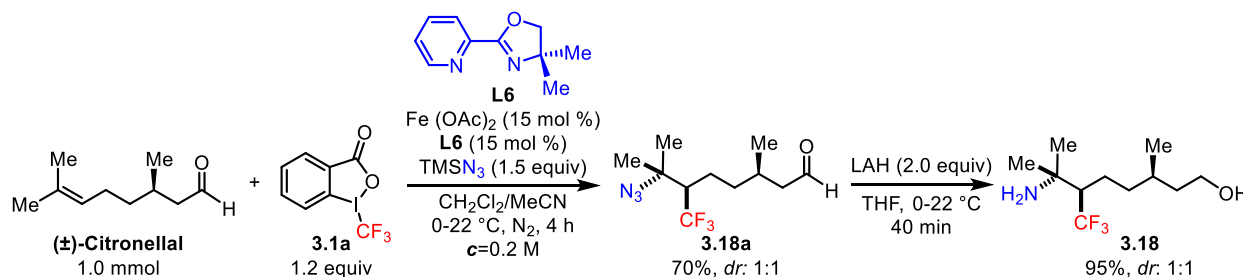


Figure 3.5 X-ray crystal structure of the β-trifluoromethyl-amine from (-)-β-pinene

H: procedure for trifluoromethyl-azidation/reduction of (±)-citronellal.



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added Fe(OAc)₂ (26.1 mg, 0.15 mmol). After this vial was evacuated and backfilled with N₂ twice, a stock solution of ligand **L6**

in anhydrous CH_2Cl_2 (1.0 mL, $c=0.15$ M) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. TMSN_3 (198 mL, 1.5 mmol) was added to vial **A** and the mixture was stirred for additional 10 min. To a second flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **3.1a** (380 mg, 1.2 mmol). Vial **B** was evacuated and backfilled with N_2 twice and then anhydrous CH_2Cl_2 (3.9 mL) was added. Both solutions in vial **A** and vial **B** were degassed with brief evacuation and then backfilling with N_2 . Subsequently the freshly distilled (\pm)-**citronellal** (180 μL , 1.0 mmol) was added to vial **B** followed by drop-wise addition of the catalyst solution in vial **A** at 0 °C. The reaction mixture was warmed up to 22 °C and kept stirring for 4 h until the olefin was consumed (monitored by TLC). Saturated NaHCO_3 aqueous solution (0.4 mL) was added to quench the reaction and to remove any residue hydrazoic acid. The reaction mixture was further diluted with hexanes (5 mL) and stirred vigorously for 10 min to precipitate 2-iodobenzoic acid. The mixture was filtered through a short silica gel pad (*ca.* 1.5 cm \times 1.5 cm silica gel in a filter funnel) and washed with 20% Et_2O in hexanes (15 mL). After concentration *in vacuo*, the residue was subsequently purified through a silica gel column (hexanes/ Et_2O : from 50:1 to 10:1) to afford the desired trifluoromethyl-azidation product **3.18a** as colorless oil (186 mg, 70% yield, *dr*: 1:1).

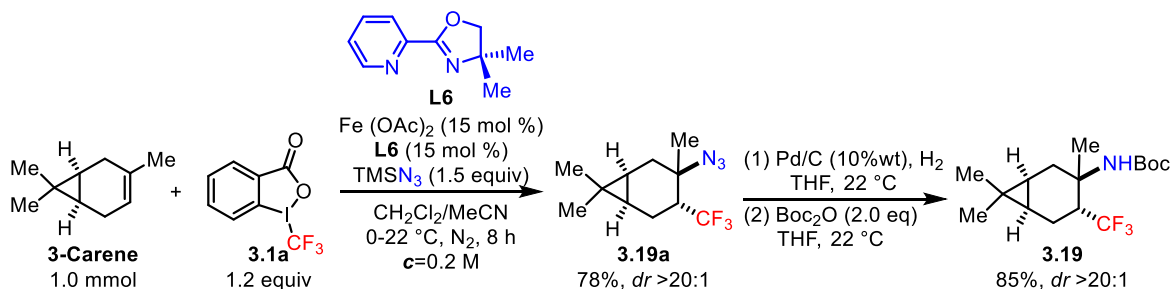
7-Azido-3,7-dimethyl-6-(trifluoromethyl)octanal (3.18a): IR ν_{max} (neat)/ cm^{-1} : 2966 (w), 2926 (w), 2878 (w), 2856 (w), 2136 (s), 2106 (s), 1722 (s), 1247 (m), 1151 (s), 1059 (m); ^1H NMR (400 MHz, CDCl_3) δ 9.75 (t, $J = 2.1$ Hz, 1H), 2.47 – 2.37 (m, 1H), 2.33 – 2.21 (m, 1H), 2.13 – 1.95 (m, 2H), 1.76 – 1.47 (m, 3H), 1.43 (s, 4H), 1.34 (s, 3H), 0.98 (dd, $J = 6.7, 3.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) diastereomer 1: δ 202.2, 127.4 (d, $J = 281.8$ Hz), 62.1 (q, $J = 2.3$ Hz), 51.9 (q, $J = 23.7$ Hz), 50.9, 36.9 (q, $J = 1.2$ Hz), 28.1, 26.0, 23.5 (q, $J = 4.7, 2.3$ Hz), 23.0 (q, $J = 2.1$ Hz), 19.8; diastereomer 2: ^{13}C NMR (100 MHz, CDCl_3) δ 202.2, 127.4 (q, $J = 281.7$ Hz), 62.1 (q, $J = 2.3$ Hz), 51.9 (q, $J = 23.6$ Hz), 50.5, 36.9 (q, $J = 1.3$ Hz), 28.1, 26.0, 23.4 (q, $J = 2.4$ Hz), 23.0 (q, $J = 2.1$ Hz), 19.5; ^{19}F NMR (376 MHz, CDCl_3) diastereomer 1: δ -64.03 (d, $J = 9.9$ Hz); diastereomer 2: δ -64.13 (d, $J = 9.9$ Hz).

3.18a (100 mg, 0.37 mmol) was dissolved in anhydrous THF (3 mL) in a 10 mL flask equipped with a stir bar. The flask was cooled to 0 °C and then LiAlH_4 powder (29 mg, 0.76 mmol) was added in three portions.

The reaction mixture was warmed up to 22 °C and monitored by TLC. After about 40 min, the reaction was quenched with saturated NH₄Cl aqueous solution (2 mL). The mixture was filtered through a short Celite pad and concentrated *in vacuo*. The resting aqueous phase was extracted with EtOAc (3 mL × 3) and dried over anhydrous Na₂SO₄. After removal of the solvent, **3.18** was obtained as colorless oil without further purification (86 mg, 95% yield, *dr*:1:1)

7-Amino-3,7-dimethyl-6-(trifluoromethyl)octan-1-ol (3.18): IR ν_{\max} (neat)/cm⁻¹: 3291 (br), 2959 (m), 2928 (m), 2875 (w), 1247 (s), 1147 (s), 1088 (s); ¹H NMR (400 MHz, CDCl₃) δ 3.81 – 3.48 (m, 3H), 1.94 – 1.81 (m, 1H), 1.69 (brs, 3H), 1.64 – 1.46 (m, 5H), 1.46 – 1.31 (m, 2H), 1.18 (s, 6H), 0.97 – 0.85 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) *diastereomer 1*: δ 128.70 (q, *J* = 282.4 Hz), 60.6, 53.8 (q, *J* = 21.7 Hz), 51.3 (d, *J* = 3.0 Hz), 39.6, 37.8 (q, *J* = 1.1 Hz), 29.8, 29.3 (q, *J* = 2.1 Hz), 23.7 (q, *J* = 2.5 Hz), 19.6; *diastereomer 2*: δ 128.7 (q, *J* = 282.4 Hz), 60.5, 53.8 (q, *J* = 21.7 Hz), 51.3 (d, *J* = 3.0 Hz), 39.4 (s), 37.7 (q, *J* = 1.1 Hz), 29.7, 29.3 (q, *J* = 2.1 Hz), 23.6 (q, *J* = 2.6 Hz), 19.3; ¹⁹F NMR (376 MHz, CDCl₃) *diastereomer 1*: δ -63.37 (d, *J* = 10.4 Hz); *diastereomer 2*: δ -63.48 (d, *J* = 10.4 Hz).

I: procedure for trifluoromethyl-azidation/reduction of 3-carene.



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added Fe(OAc)₂ (26.1 mg, 0.15 mmol). After this vial was evacuated and backfilled with N₂ twice, a stock solution of ligand **L6** in anhydrous CH₂Cl₂ (1.0 mL, c=0.15 M) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. TMSN₃ (198 mL, 1.5 mmol) was added to vial **A** and the mixture was stirred for additional 10 min. To a second flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **3.1a** (380 mg, 1.2 mmol). Vial **B** was evacuated and backfilled with N₂ twice and then anhydrous CH₂Cl₂ (3.9 mL) was added. Both solutions in vial **A** and vial **B** were degassed with brief

evacuation and then backfilling with N₂. Subsequently the freshly distilled **3-carene** (168 μ L, 1.0 mmol) was added to vial **B** followed by drop-wise addition of the catalyst solution in vial **A** at 0 °C. The reaction mixture was warmed up to 22 °C and kept stirring for 8 h until the olefin was consumed (monitored by TLC). Saturated Na₂CO₃ aqueous solution (0.4 mL) was added to quench the reaction and to remove any residue hydrazoic acid. The reaction mixture was further diluted with hexanes (5 mL) and stirred vigorously for 10 min to precipitate 2-iodobenzoic acid. The mixture was filtered through a short silica gel pad (*ca.* 1.5 cm \times 1.5 cm silica gel in a filter funnel) and washed with 20% Et₂O in hexanes (15 mL). After concentration *in vacuo*, the residue was subsequently purified through a silica gel column (100% hexanes) to afford the desired trifluoromethyl-azidation product **3.19a** as colorless oil (193 mg, 78% yield, *dr* > 20:1). **(1S,3R,4R,6R)-3-Azido-3,7,7-trimethyl-4-(trifluoromethyl)bicyclo[4.1.0]heptane (3.19a)**: ¹H NMR (400 MHz, CDCl₃) δ 2.04 (dd, *J* = 14.2, 9.7 Hz, 1H), 2.00 – 1.92 (m, 3H), 1.42 – 1.37 (m, 3H), 1.32 (ddd, *J* = 14.5, 5.5, 1.0 Hz, 1H), 1.03 (d, *J* = 2.6 Hz, 3H), 0.95 (s, 3H), 0.87 – 0.79 (m, 1H), 0.72 – 0.64 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 127.4 (q, *J* = 281.7 Hz), 60.3, 45.4 (q, *J* = 23.9 Hz), 34.2 (q, *J* = 1.1 Hz), 28.4, 18.9, 18.6 (q, *J* = 2.1 Hz), 18.4, 18.3 (q, *J* = 3.2 Hz), 17.1, 14.9; ¹⁹F NMR (376 MHz, CDCl₃) δ -66.57 (d, *J* = 7.5 Hz).

To a 2-dram vial equipped with a stir bar was added Pd/C (10 mg, 10 wt%). After the vial was evacuated and backfilled twice with N₂, a solution of **3.19a** from last step (192 mg, 0.78 mmol) in 3 mL MeOH was added. The mixture was degassed with brief evacuation and backfilled twice with N₂ and then three times with H₂. The reaction was vigorously stirred under H₂ at room temperature until the reduction completed (the reaction was monitored by TLC until **3.19a** was consumed). The solution was filtered through Celite and washed with MeOH (3 mL). The solution was concentrated and the residue was dissolved in CH₂Cl₂ (4 mL) and cooled to 0 °C. To the above solution, Boc₂O (255 mg, 1.17 mmol) in 2 mL CH₂Cl₂ was added drop-wise. The resulting mixture was warmed up to room temperature and kept stirring for additional 2 h until the free amine was consumed. After the organic solvent was removed under reduced pressure, the residue was purified through a silica gel flash column (hexanes/EtOAc: from 20:1 to

6:1) to afford the desired *N*-Boc protected β -trifluoromethyl amine **3.19** as a white solid (213mg, 85% yield, *dr* > 20:1).

tert-Butyl ((1*S*,3*R*,4*R*,6*R*)-3,7,7-trimethyl-4-(trifluoromethyl)bicyclo[4.1.0]heptan-3-yl)carbamate (3.19): ^1H NMR (400 MHz, CDCl_3) δ 4.49 (s, 1H), 3.07 (d, *J* = 8.4 Hz, 1H), 2.32 (d, *J* = 11.0 Hz, 1H), 2.04 – 1.91 (m, 2H), 1.67 (dd, *J* = 15.0, 9.6 Hz, 1H), 1.40 (s, 9H), 1.26 (s, 3H), 1.04 (s, 3H), 0.99 (s, 3H), 0.78 (td, *J* = 9.7, 5.4 Hz, 1H), 0.65 – 0.52 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.2, 128.3 (q, *J* = 282.0 Hz), 79.1, 52.6, 40.4, 31.9, 28.6, 28.4, 21.7, 19.6, 18.5, 18.2, 17.3, 15.3; ^{19}F NMR (376 MHz, CDCl_3) δ -66.32 (d, *J* = 9.5 Hz).

For X-ray analysis purpose, *N*-Ns-protected β -trifluoromethyl amine **3.19b** was prepared from **3.19a** by following the *general procedure B* in **3.3.3** as a white solid (70% yield, *dr* > 20:1). After crystallization from EtOAc/Hexanes, its stereochemistry was confirmed by X-ray crystallographic analysis (Figure 3.6).

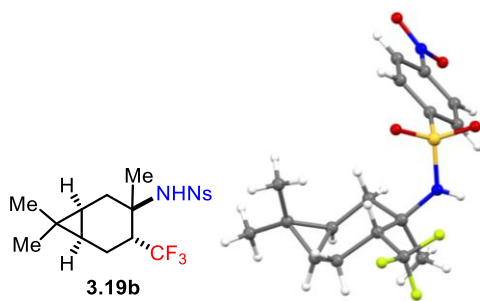
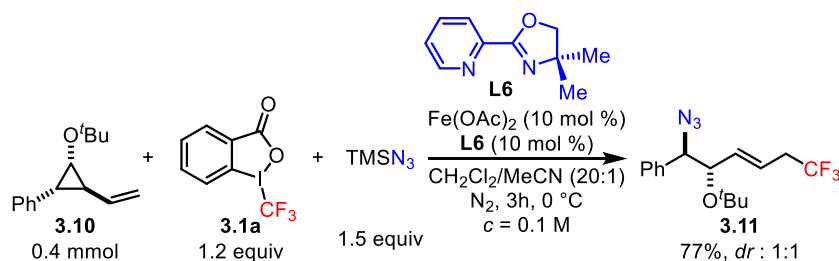


Figure 3.6 X-ray crystal structure of the β -trifluoromethyl-amine from 3-carene

J: procedure for trifluoromethyl-azidation of substituted vinylcyclopropane radical clock probe



The radical clock substrate **3.10** was prepared according to a known procedure.⁸⁴

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $\text{Fe}(\text{OAc})_2$ (7.0 mg, 0.04 mmol). After this vial was evacuated and backfilled with N_2 twice, a stock solution of ligand **L6**

in anhydrous CH_2Cl_2 (0.8 mL, $c=0.05$ M) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. TMSN_3 (80 μL , 0.6 mmol) was added to vial **A** and the mixture was stirred for additional 10 min. To a second flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **3.1a** (152 mg, 0.48 mmol). Vial **B** was evacuated and backfilled with N_2 twice and then anhydrous CH_2Cl_2 (1.1 mL) was added. Both solutions in vial **A** and vial **B** were degassed with brief evacuation and then backfilling with N_2 . Subsequently the radical clock substrate **3.10** (94 μL , 0.4 mmol) was added to vial **B** followed by drop-wise addition of the catalyst solution in vial **A** at 0 °C. The reaction mixture was kept stirring at 0°C for 3 h until the olefin was consumed (monitored by TLC). Saturated Na_2CO_3 aqueous solution (0.4 mL) was added to quench the reaction and to remove any residue hydrazoic acid. The reaction mixture was further diluted with hexanes (5 mL) and stirred vigorously for 10 min to precipitate 2-iodobenzoic acid. The mixture was filtered through a short silica gel pad (*ca.* 1.5 cm long silica gel with cotton stopper in a regular Pasteur pipette) and washed with 20% EtOAc in hexanes (10 mL). After concentration *in vacuo*, the residue was subsequently purified through a silica gel column (hexanes/ Et_2O : from 100:1 to 20:1) to afford the desired trifluoromethyl-azidation product **3.11** as colorless oil (100 mg, 77% yield, a mixture of two diastereomers, *dr*: 1:1).

((1R,2S,E)-1-Azido-2-(tert-butoxy)-6,6,6-trifluorohex-3-en-1-yl)benzene (3.11): *diastereomer 1 (less polar):* ^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.27 (m, 5H), 5.72 (dd, $J = 15.6, 6.2$ Hz, 1H), 5.59 – 5.48 (m, 1H), 4.48 (d, $J = 5.3$ Hz, 1H), 4.14 (t, $J = 5.7$ Hz, 1H), 2.89 – 2.72 (m, 2H), 1.09 (s, 9H); ^{19}F NMR (376 MHz, CDCl_3) δ -66.28 (t, $J = 10.7$ Hz);
diastereomer 2 (more polar): ^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.28 (m, 3H), 7.24 – 7.18 (m, 2H), 5.53 – 5.37 (m, 2H), 4.33 (d, $J = 7.7$ Hz, 1H), 4.14 (dd, $J = 7.6, 5.3$ Hz, 1H), 2.73 – 2.59 (m, 2H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 137.7, 136.8, 128.4, 128.2, 127.8, 125.7 (q, $J = 276.7$ Hz), 120.4 (q, $J = 3.6$ Hz), 76.1, 75.6, 70.5, 36.9 (q, $J = 29.8$ Hz), 28.4; ^{19}F NMR (376 MHz, CDCl_3) δ -66.29 (t, $J = 10.7$ Hz).

3.4 Conclusion

In conclusion, we have discovered a new iron-catalyzed olefin trifluoromethyl-azidation method for efficient synthesis of a wide variety of vicinal trifluoromethylated primary amines. This method tolerates a broad range of unfunctionalized olefins, monoterpenes and *N*-heterocycles, many of which have been challenging substrates for existing approaches. A readily available Togni's Reagent II and the commercially available TMSN_3 were used as source of CF_3 and N_3 functionalities.

Additionally, a range of control experiments and crystallographic studies of the catalytically active iron-azide complex suggest that both oxidant activation and rapid azido-group transfer steps may proceed through an *in situ* formed iron-azide complex.

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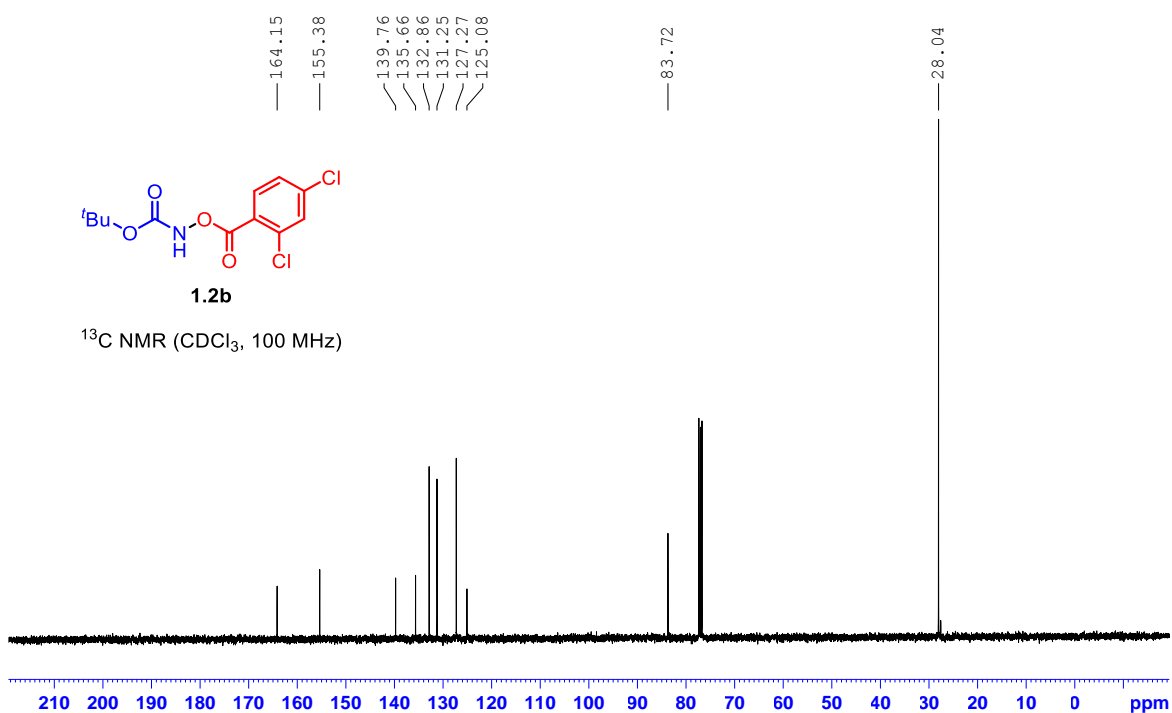
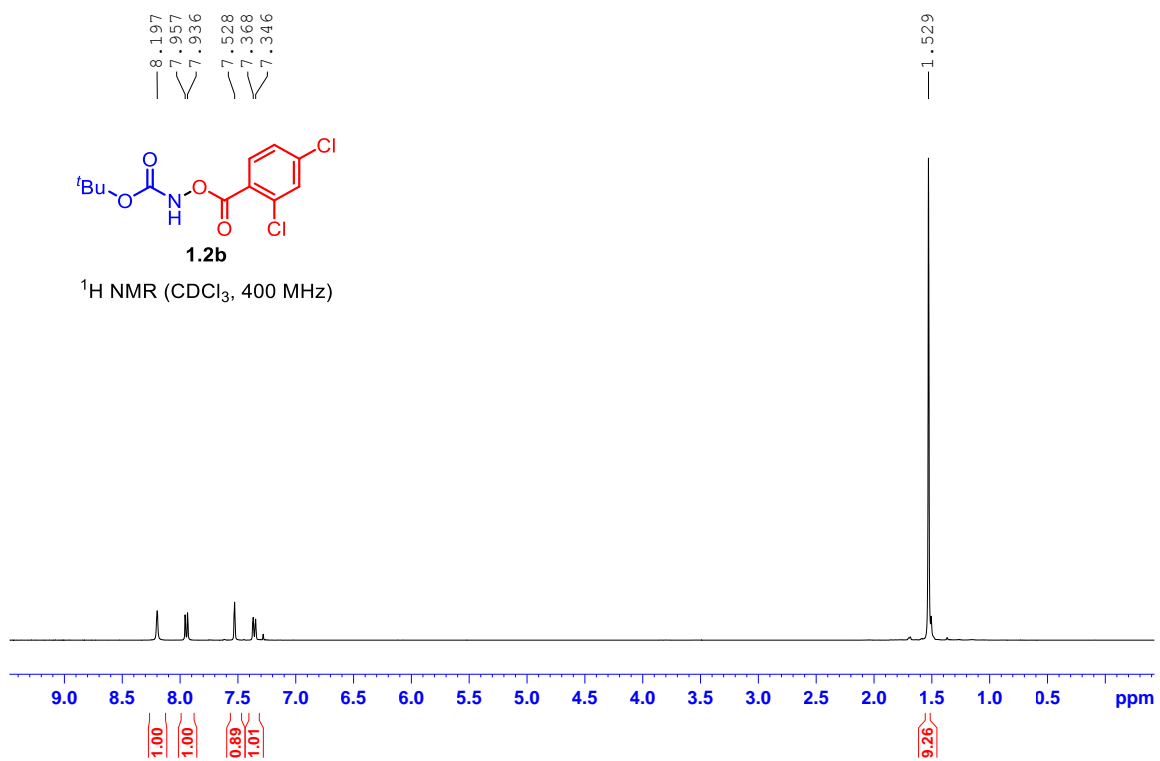
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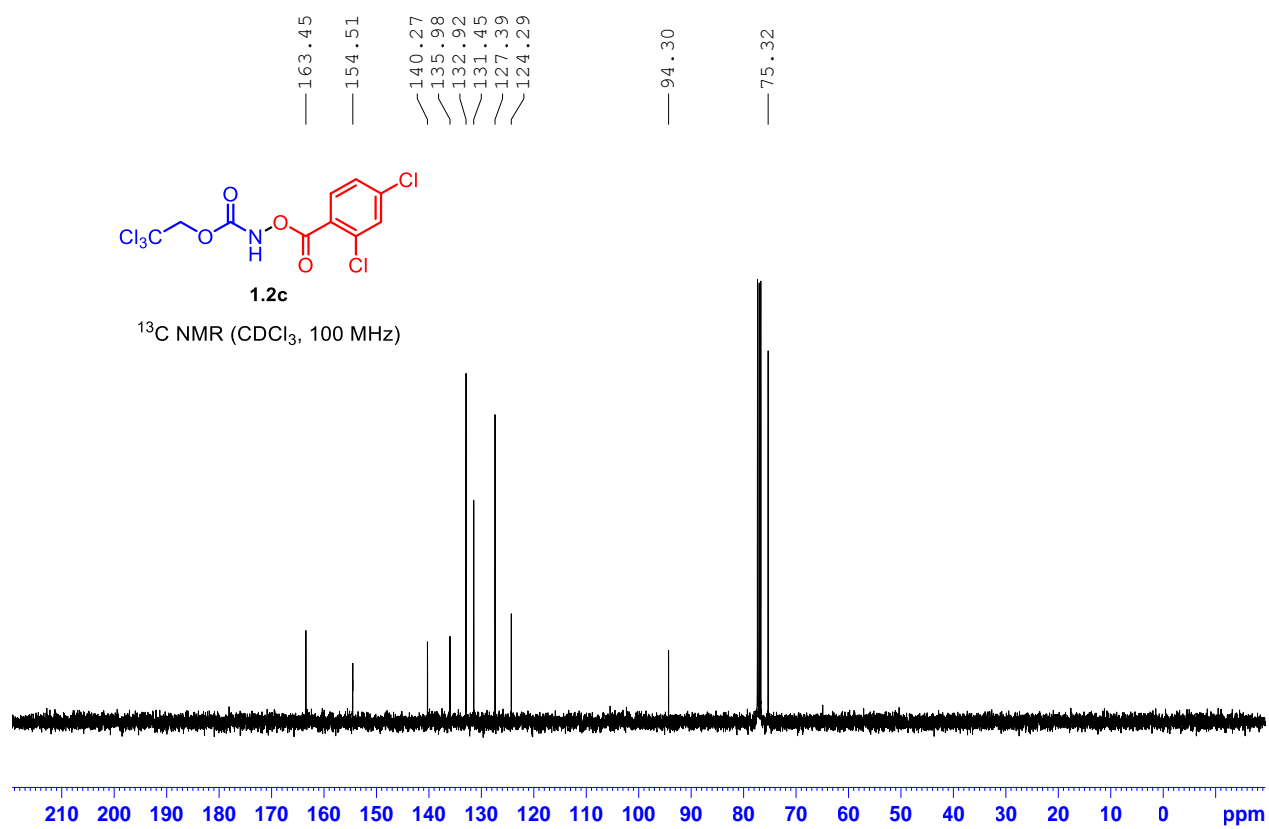
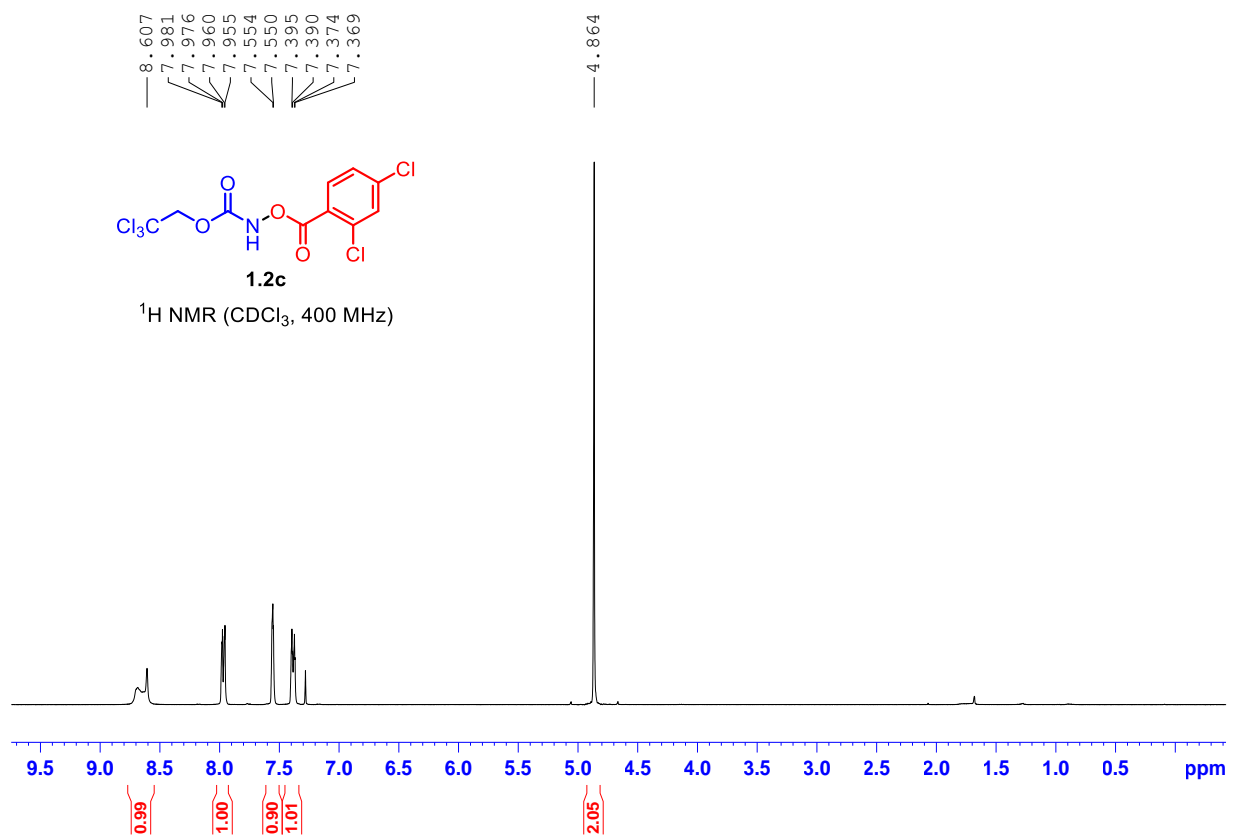
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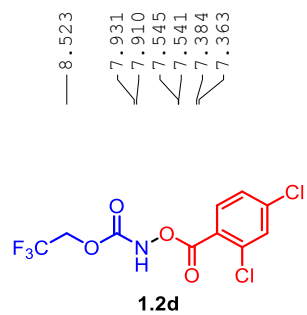
APPENDICES

Appendix A. Representative NMR spectra and HPLC traces in CHAPTER 1

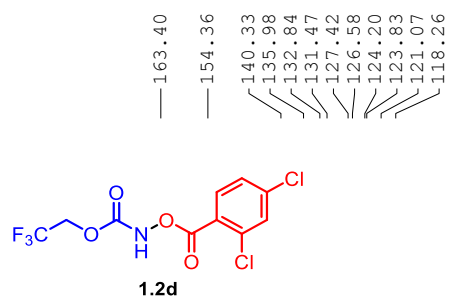
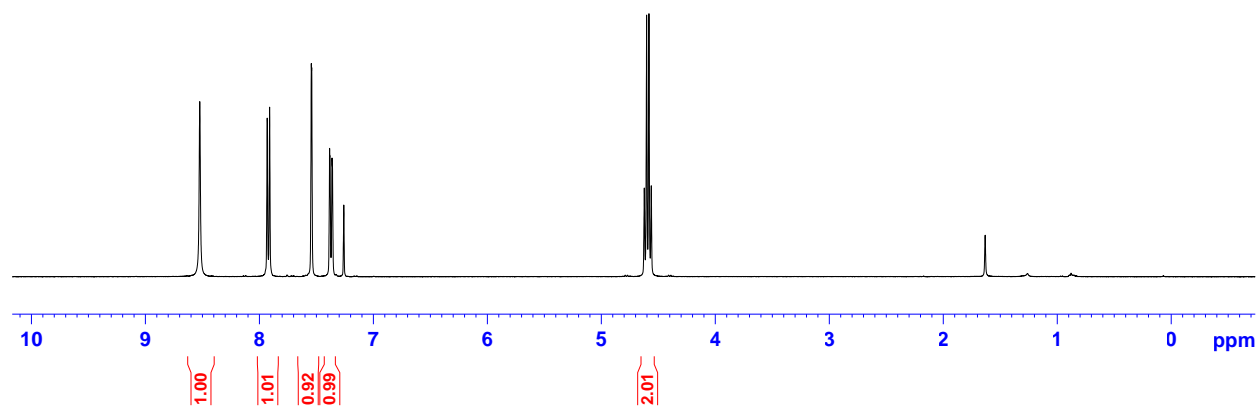
Appendix A.1 NMR Spectra



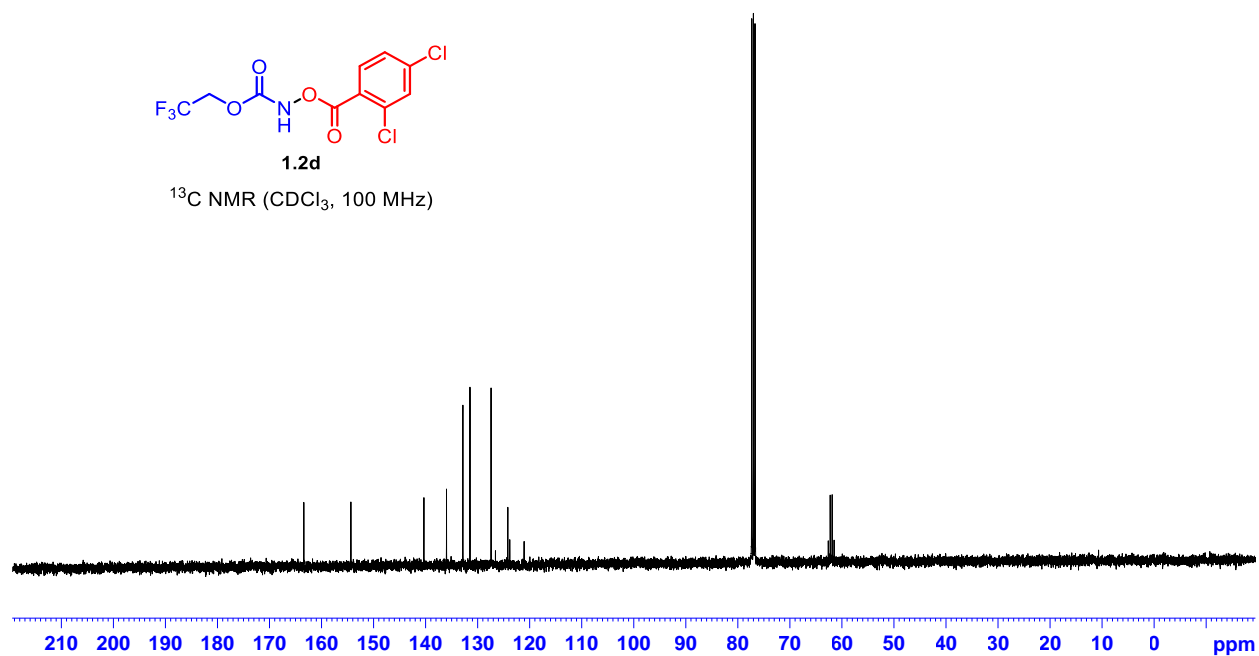


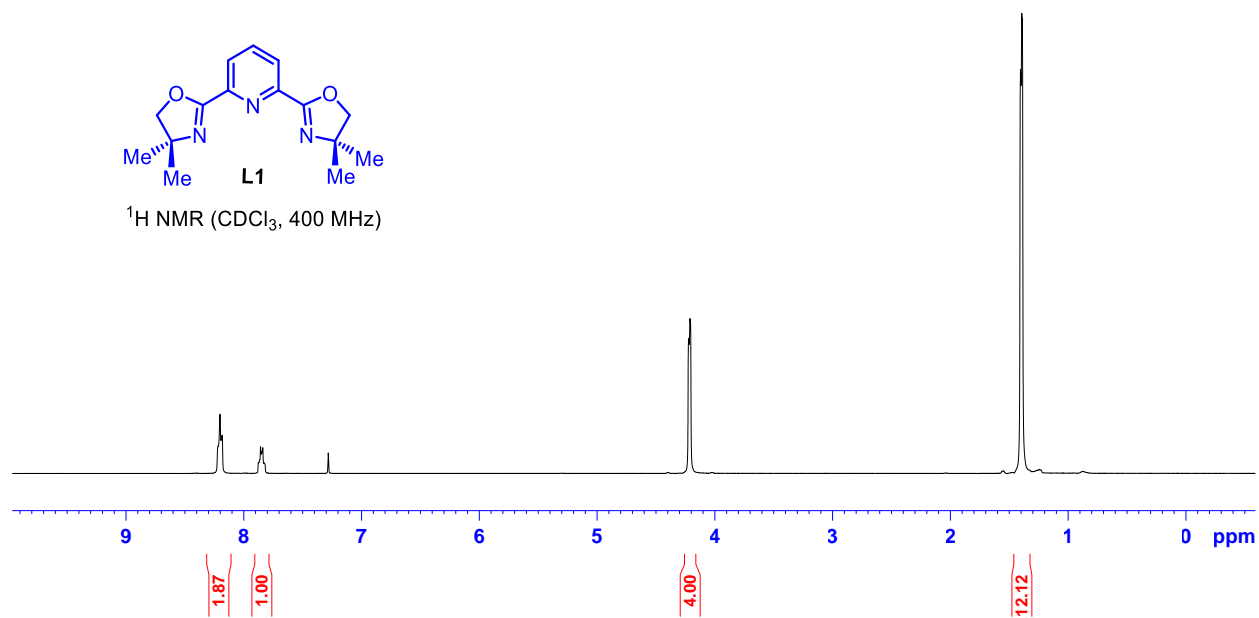
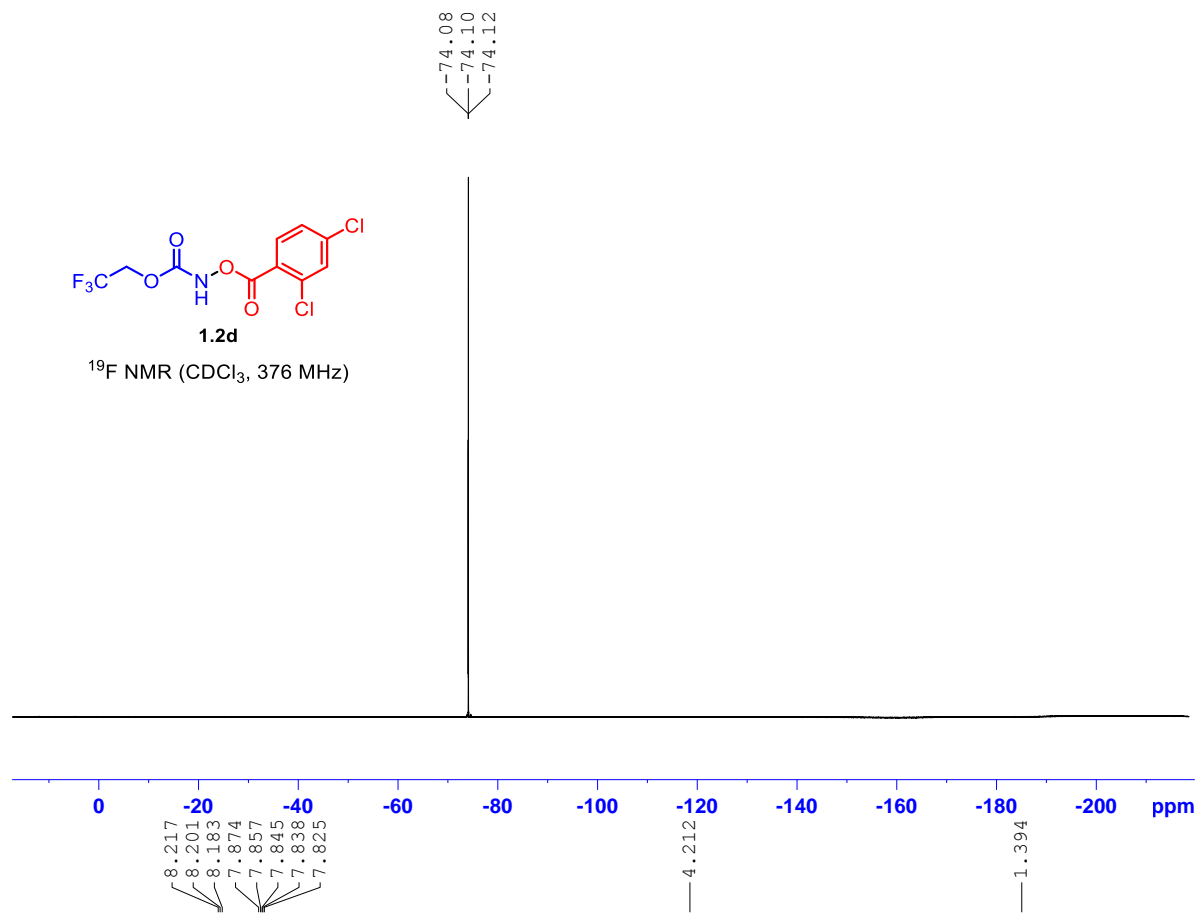


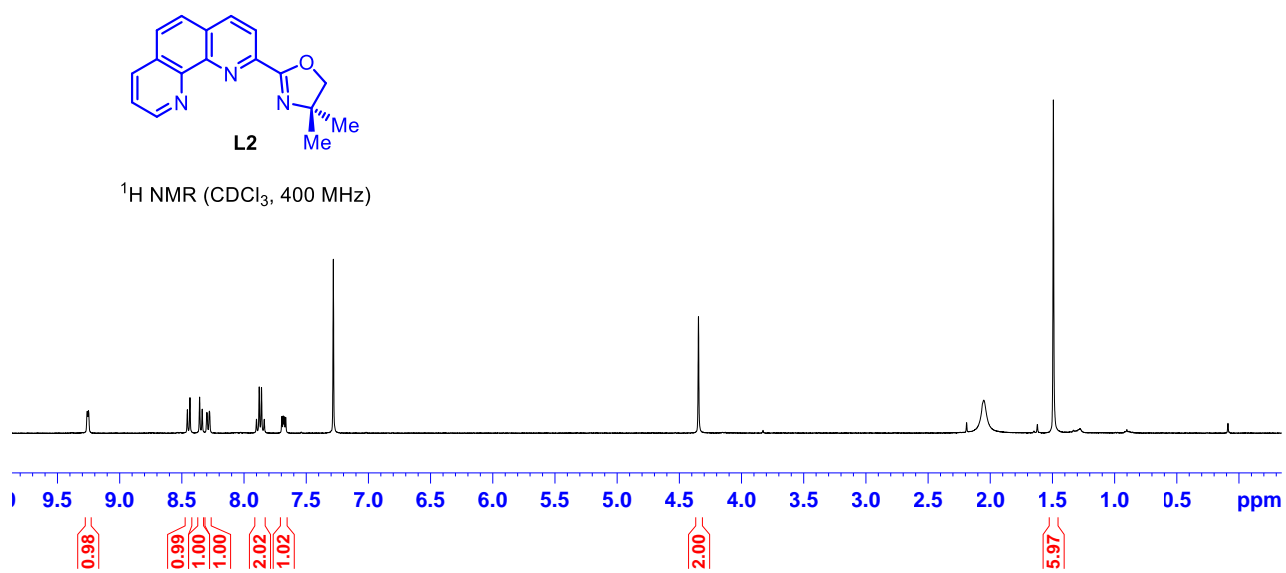
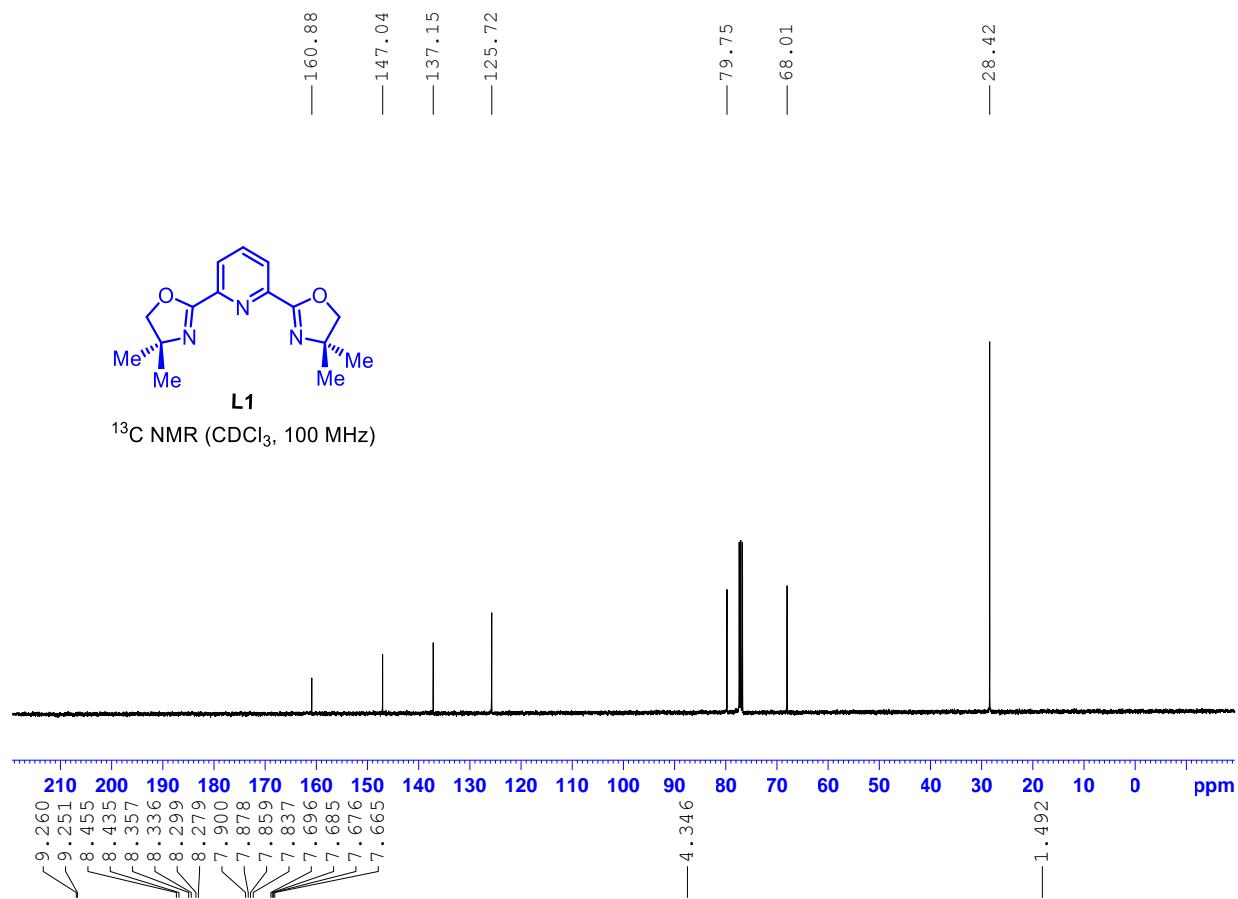
$^1\text{H NMR}$ (CDCl_3 , 400 MHz)

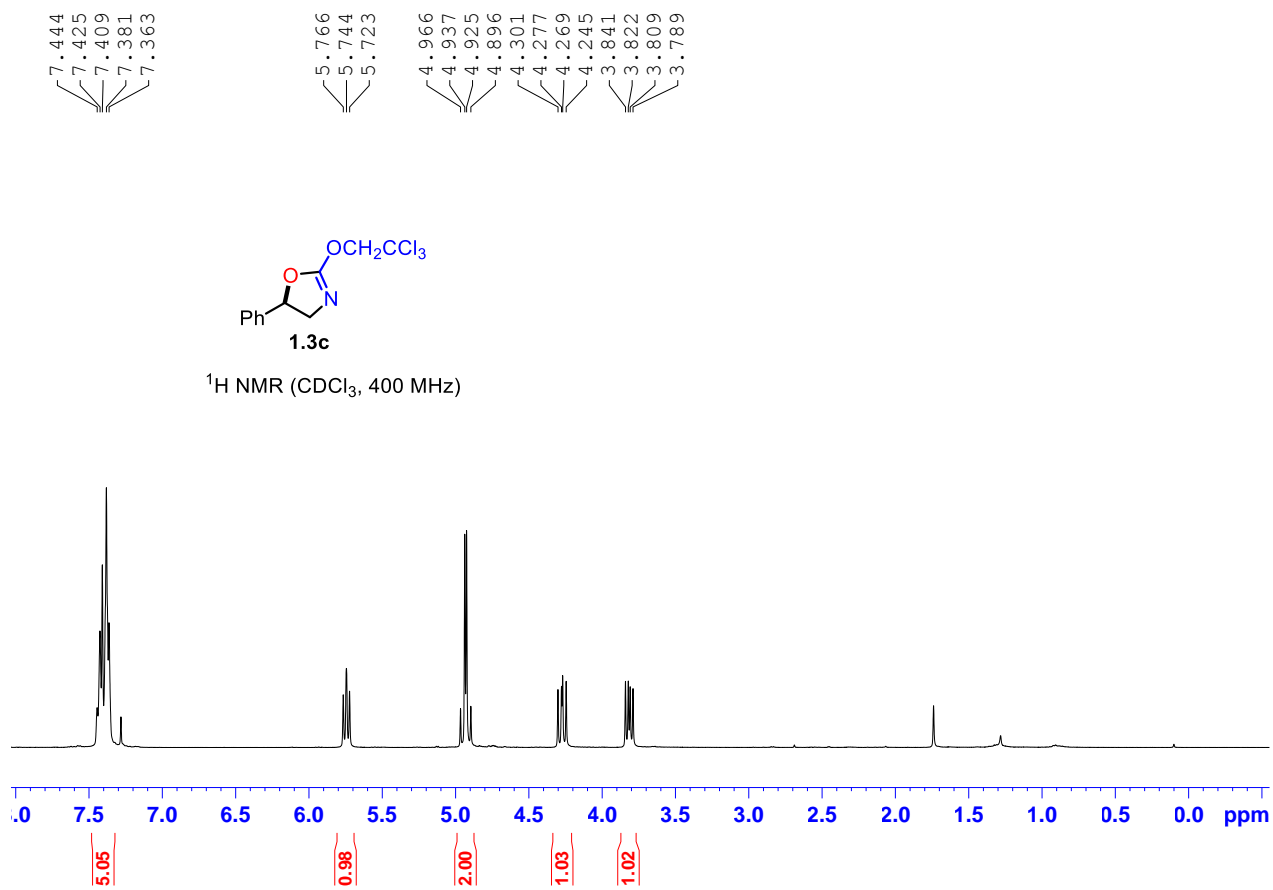
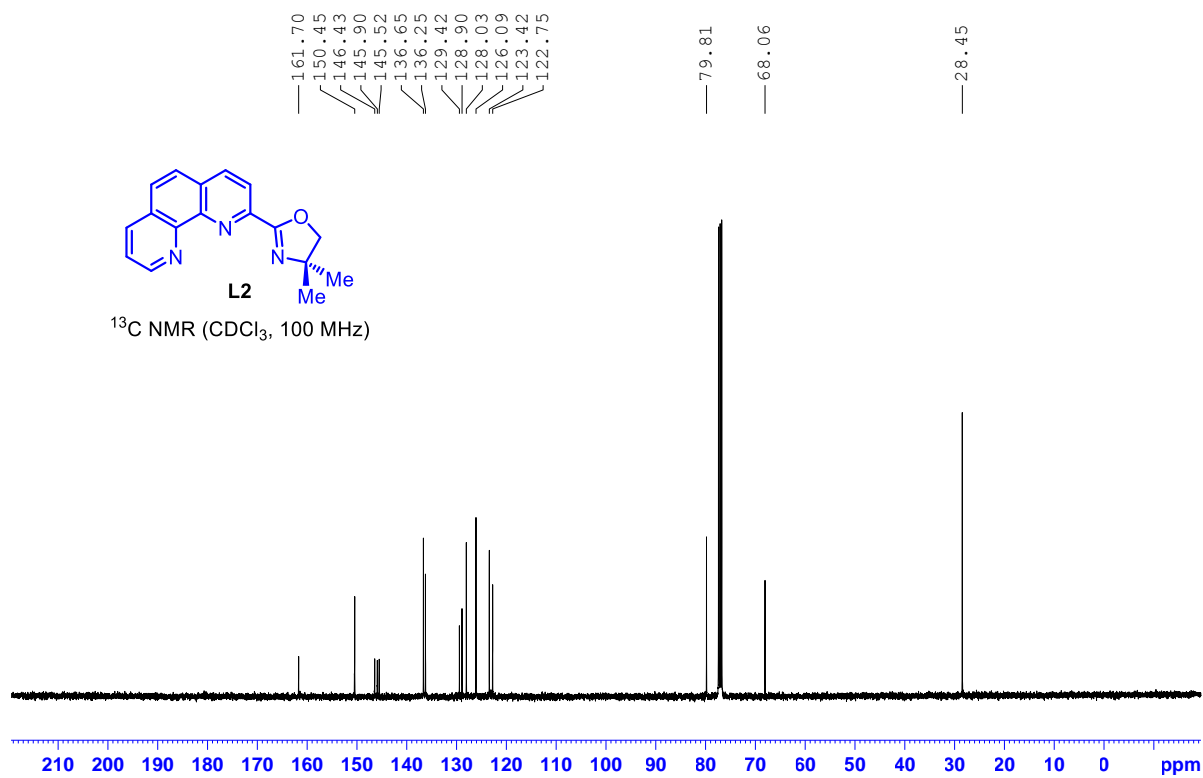


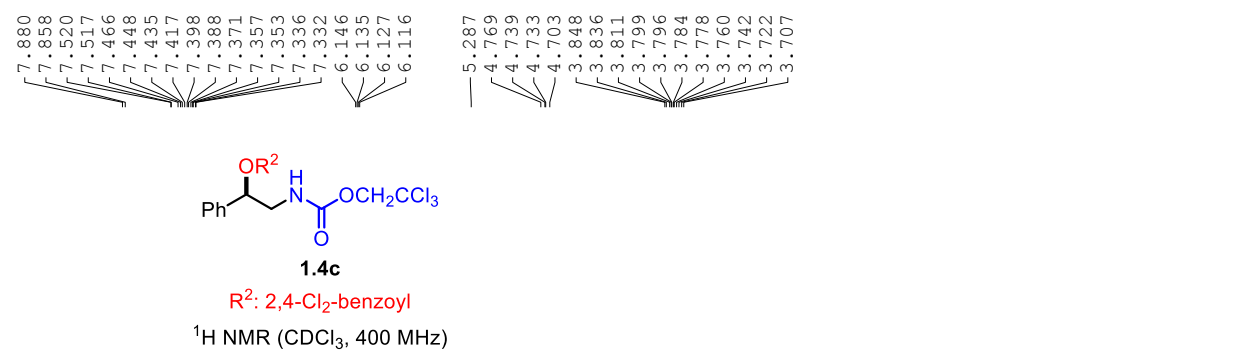
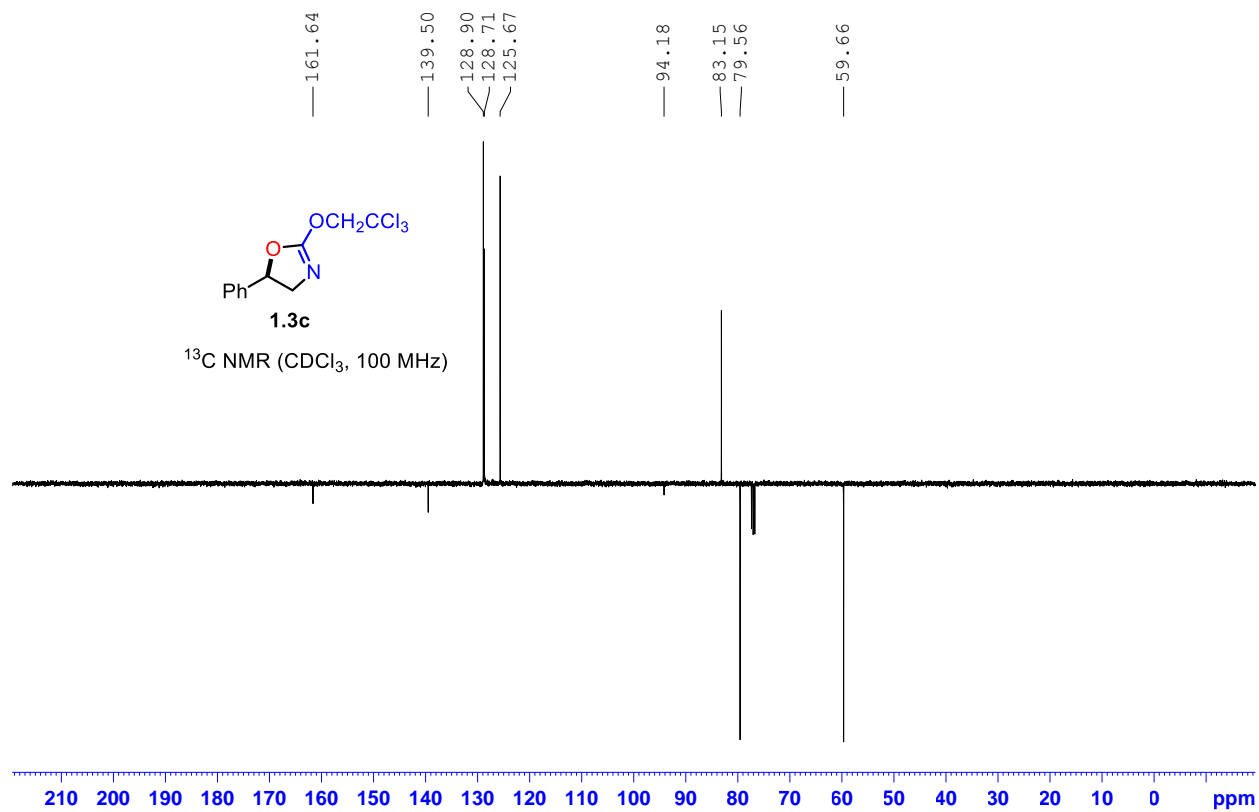
$^{13}\text{C NMR}$ (CDCl_3 , 100 MHz)

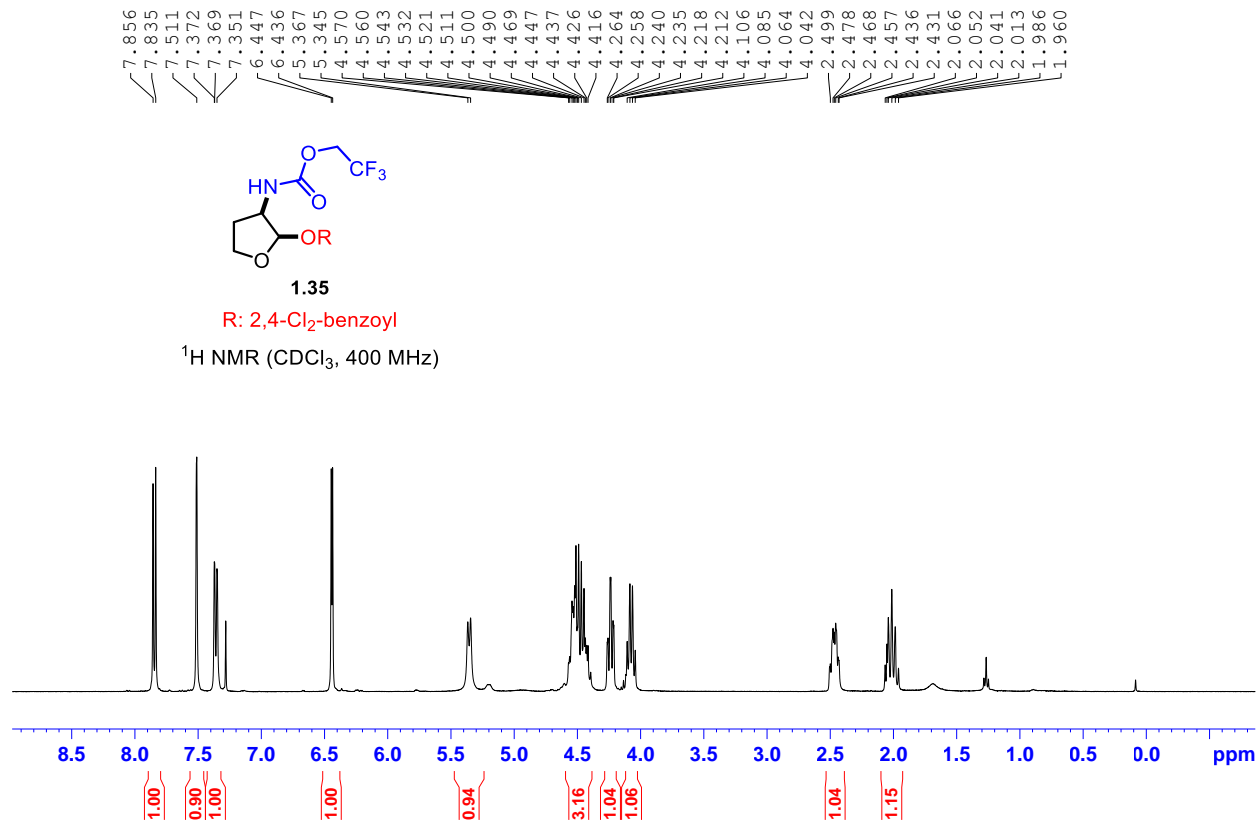
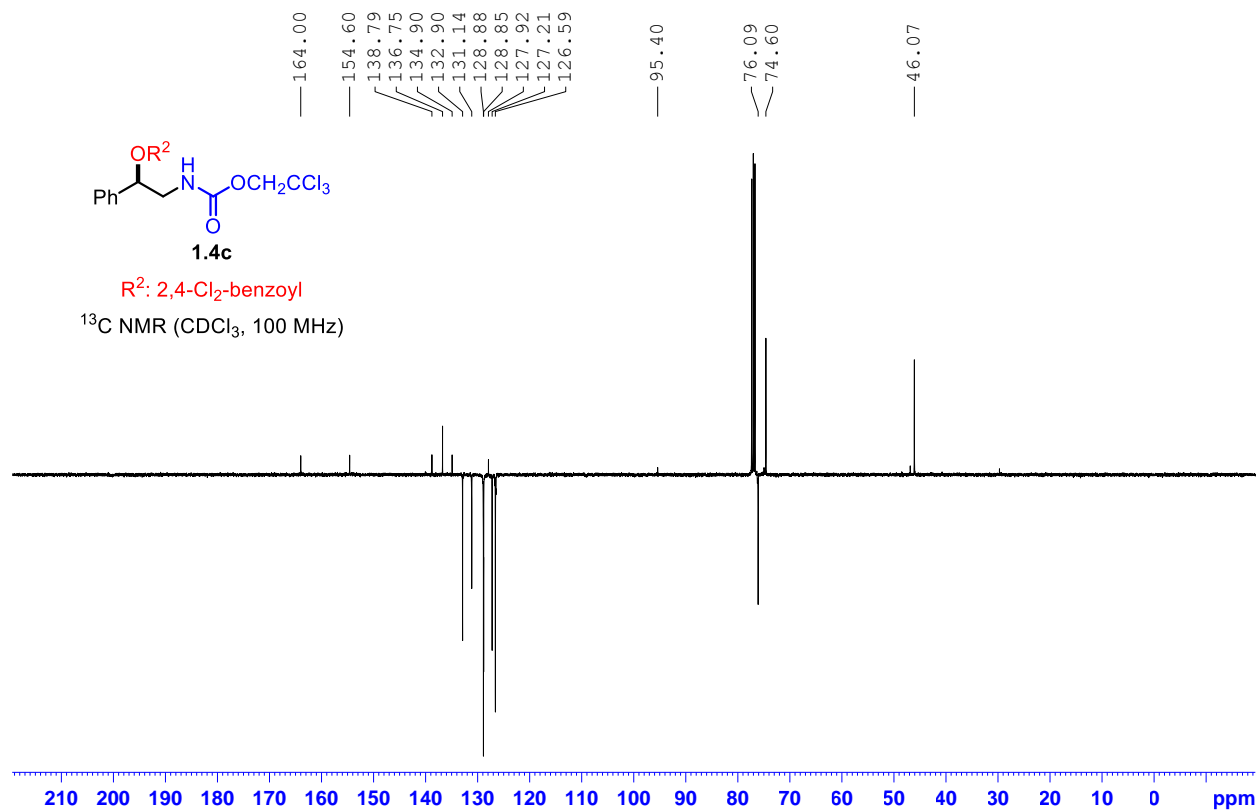


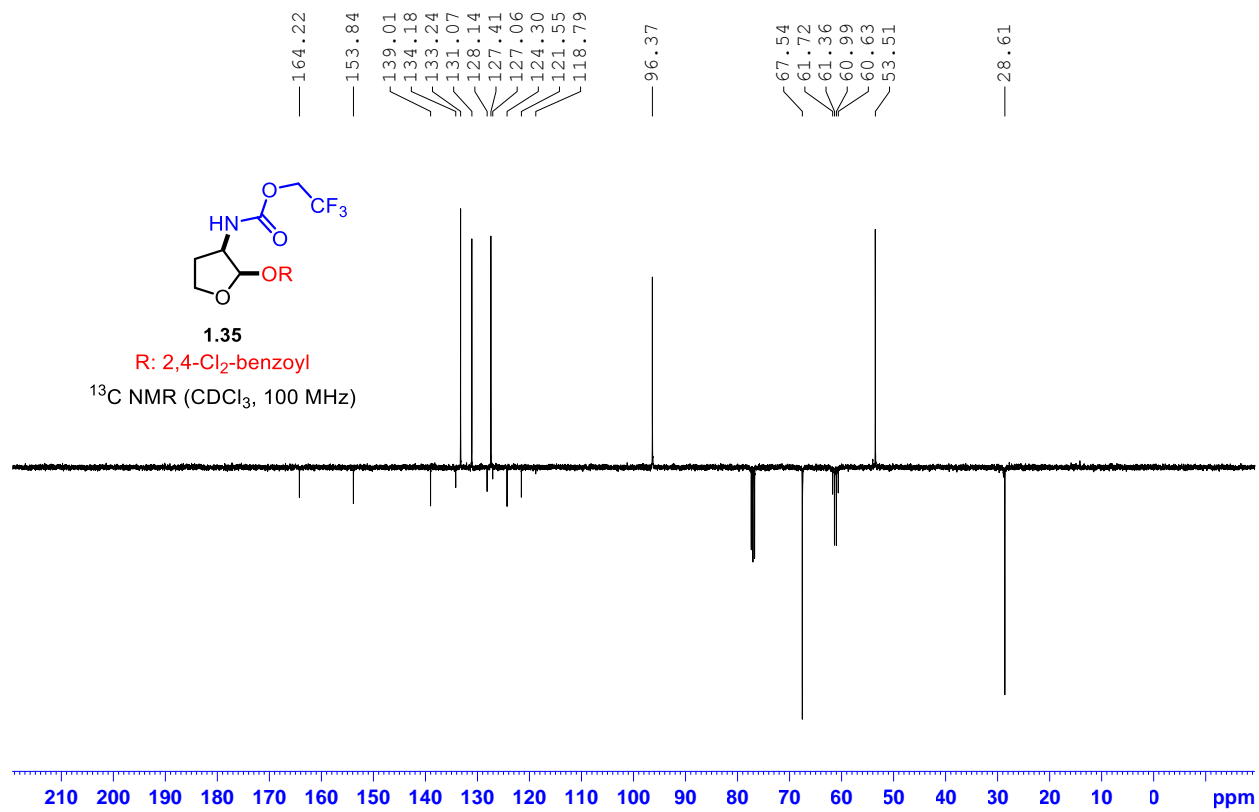


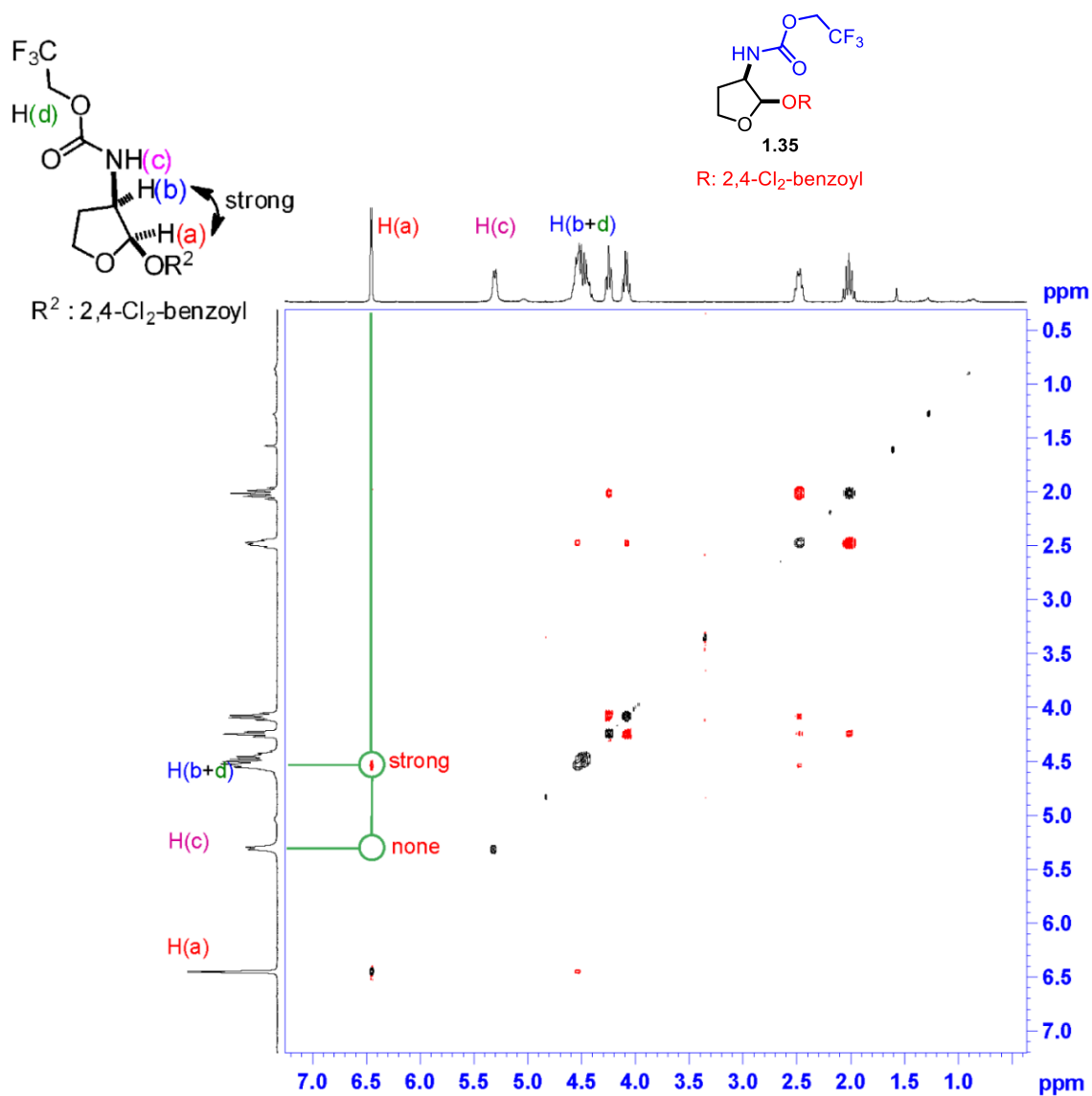




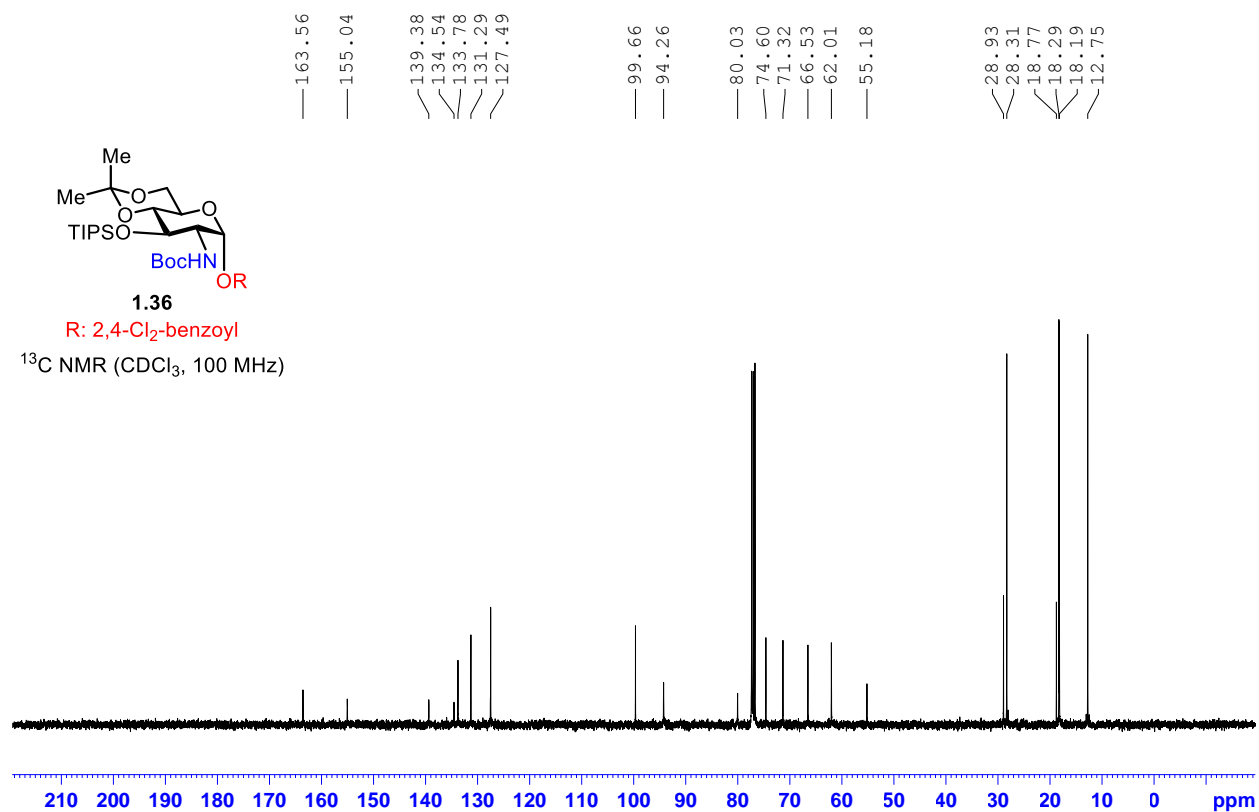
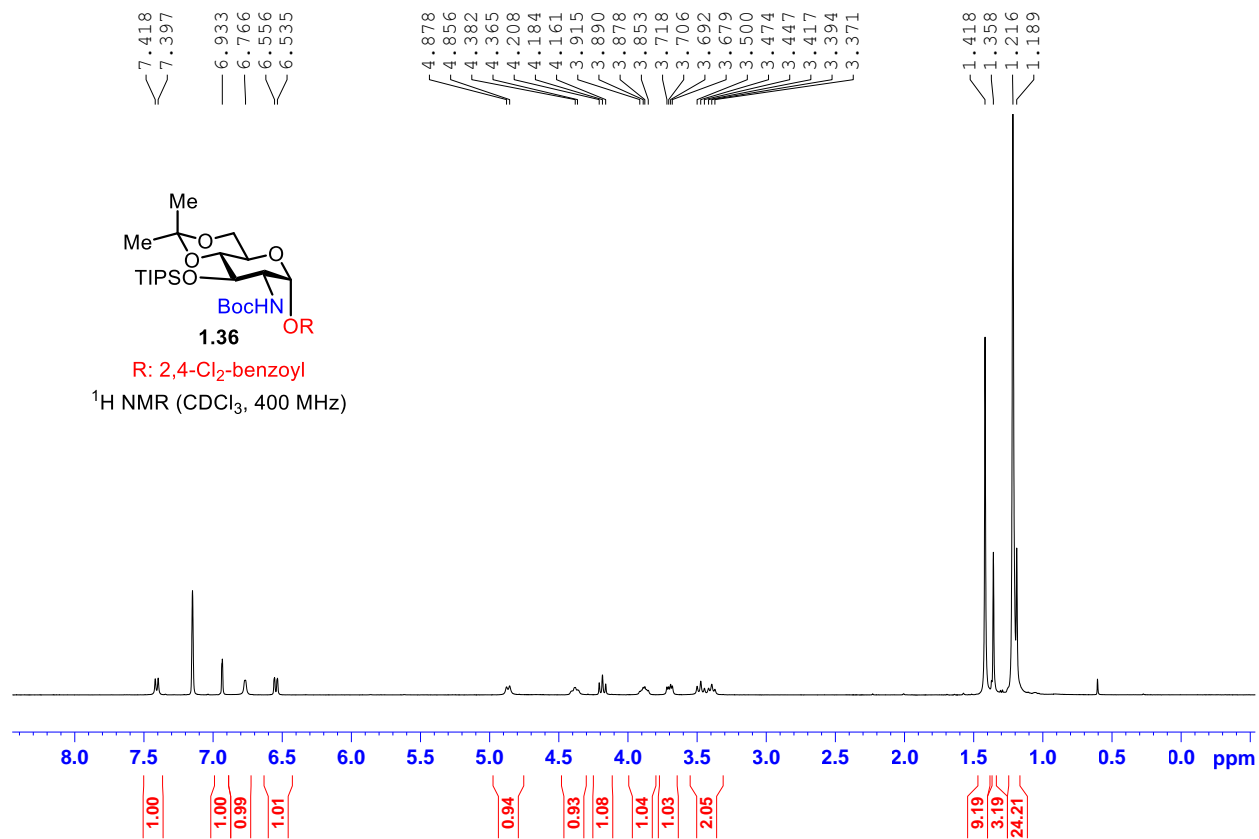


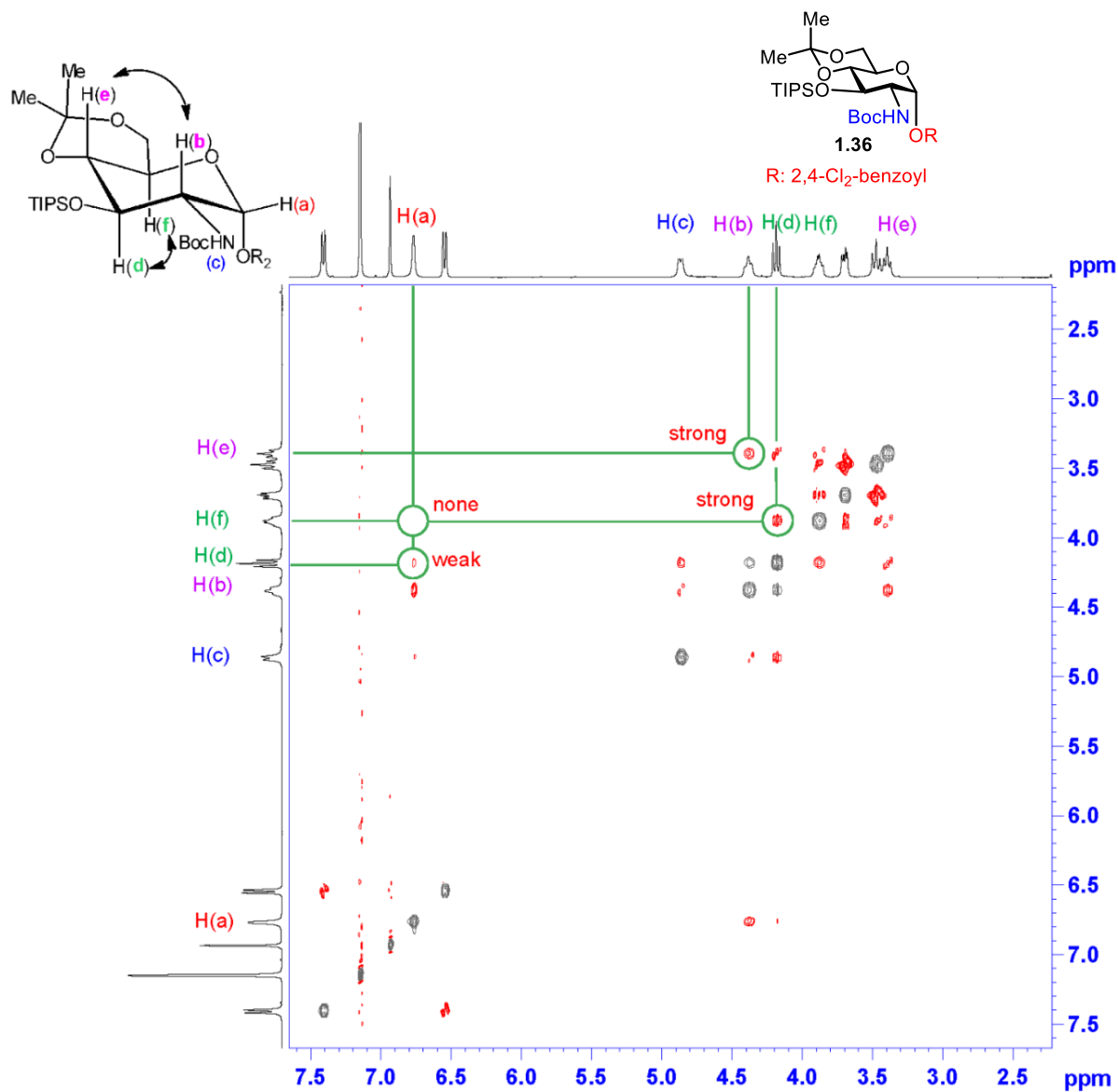




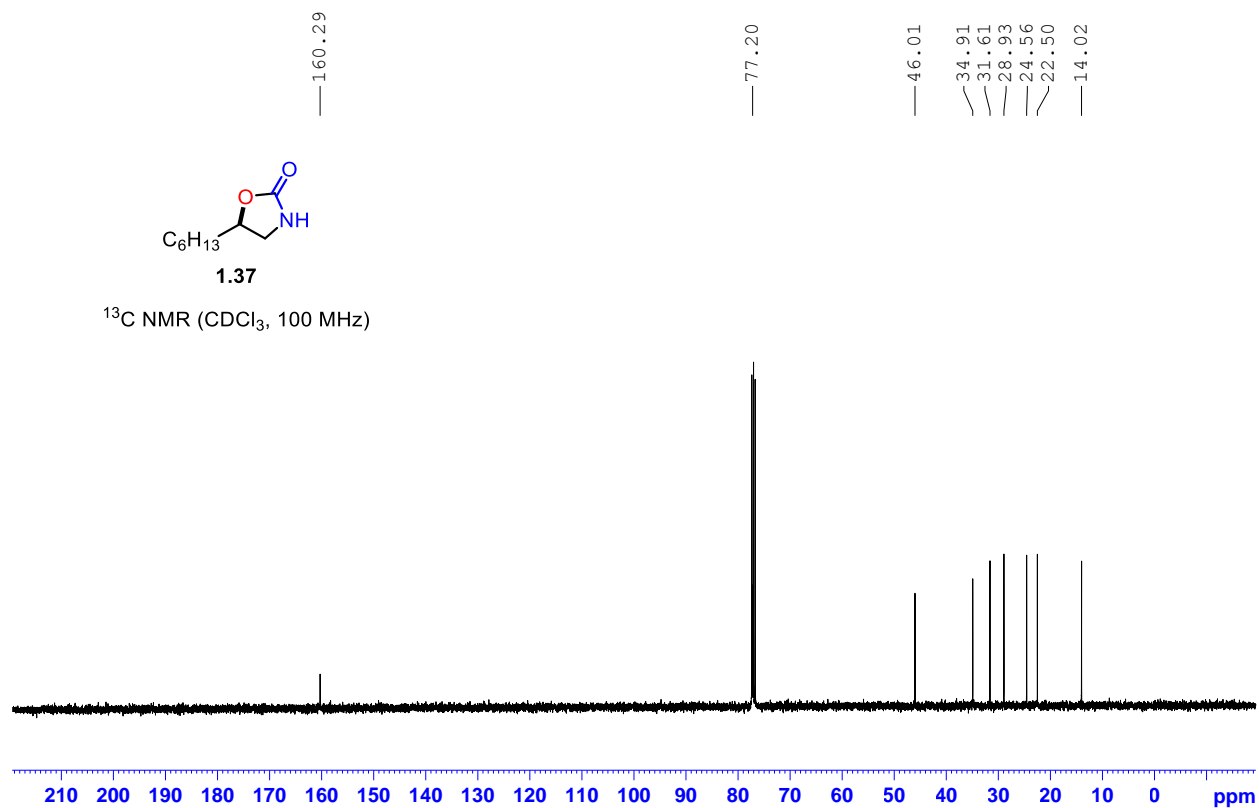
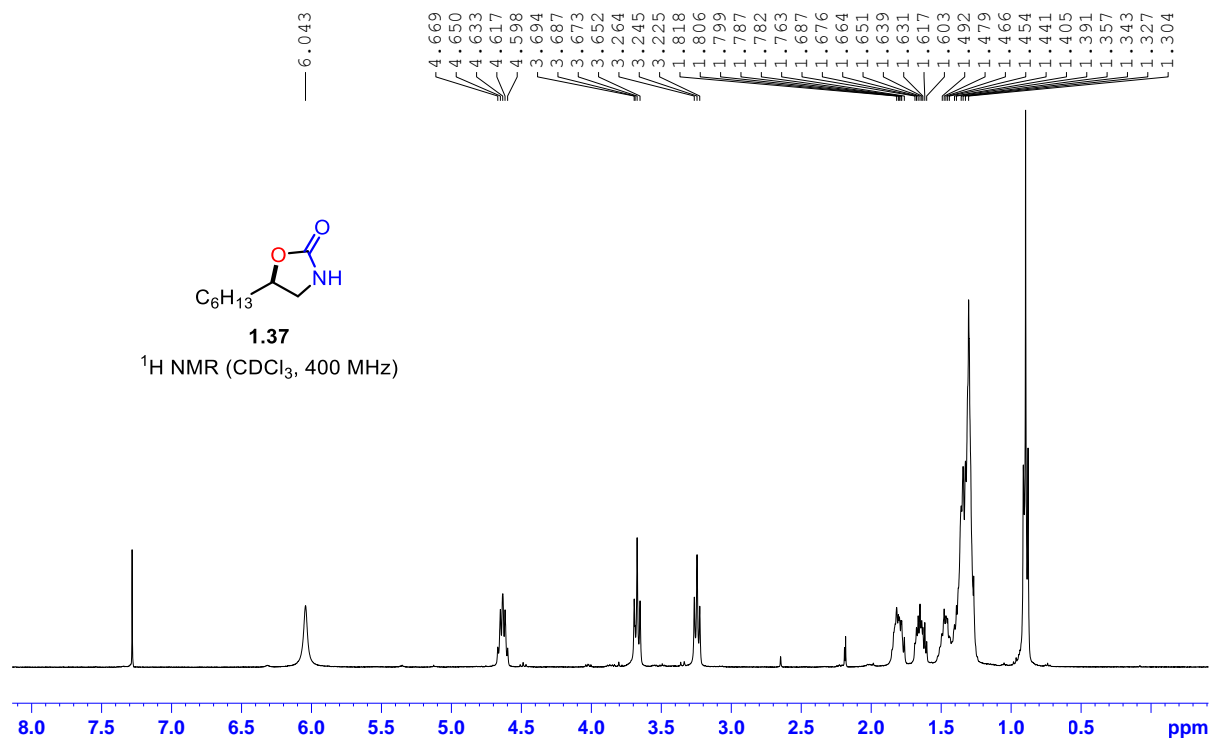


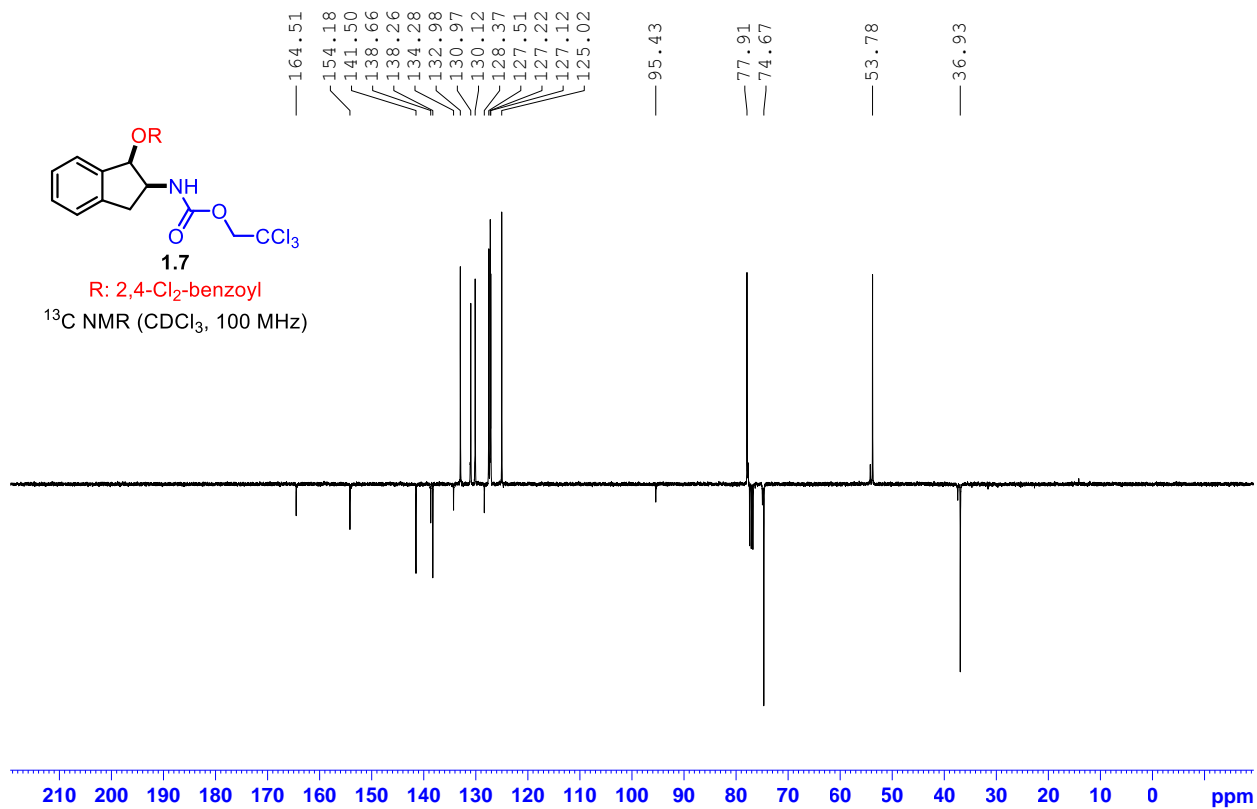
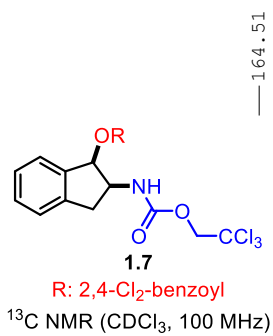
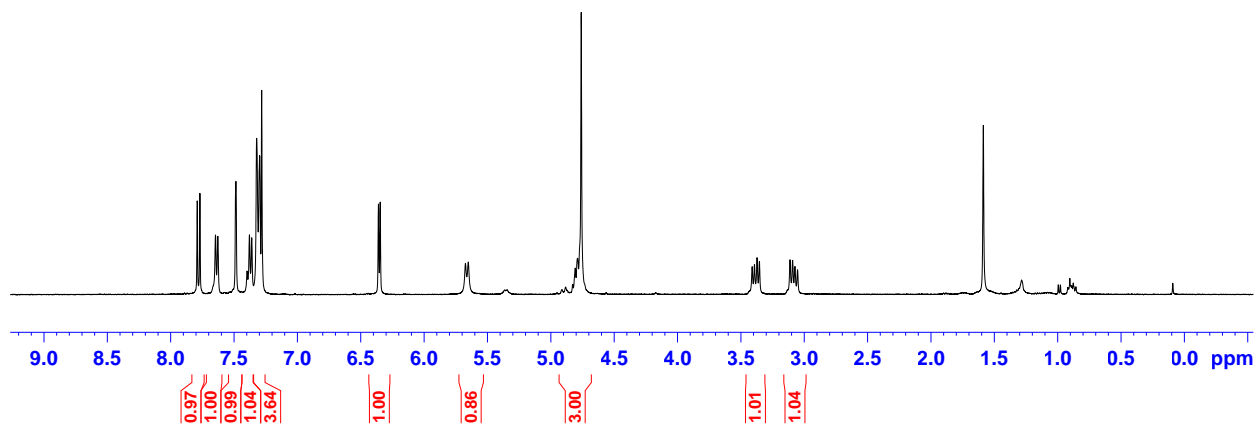
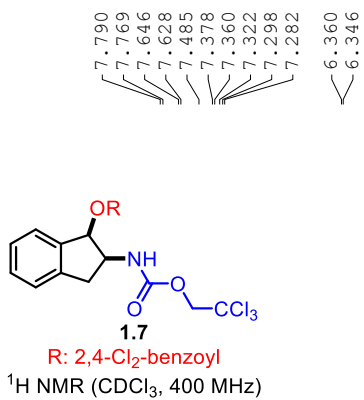
The stereochemistry of **1.35** was determined through *NOE* analysis. There is a strong *NOE* between $\text{H}(\text{a})$ and $\text{H}(\text{b})$, while there is no *NOE* observed between $\text{H}(\text{a})$ and $\text{NH}(\text{c})$. (Note: on ^1H NMR, $\text{H}(\text{b})$ and $\text{H}(\text{d})$ are partially overlapped and $\text{H}(\text{d})$ is in a distance away from $\text{H}(\text{a})$).

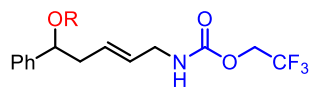
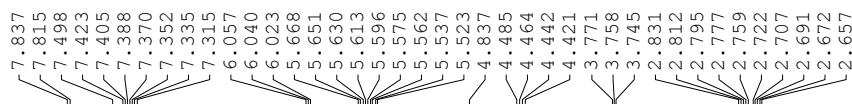




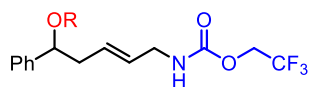
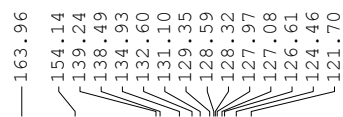
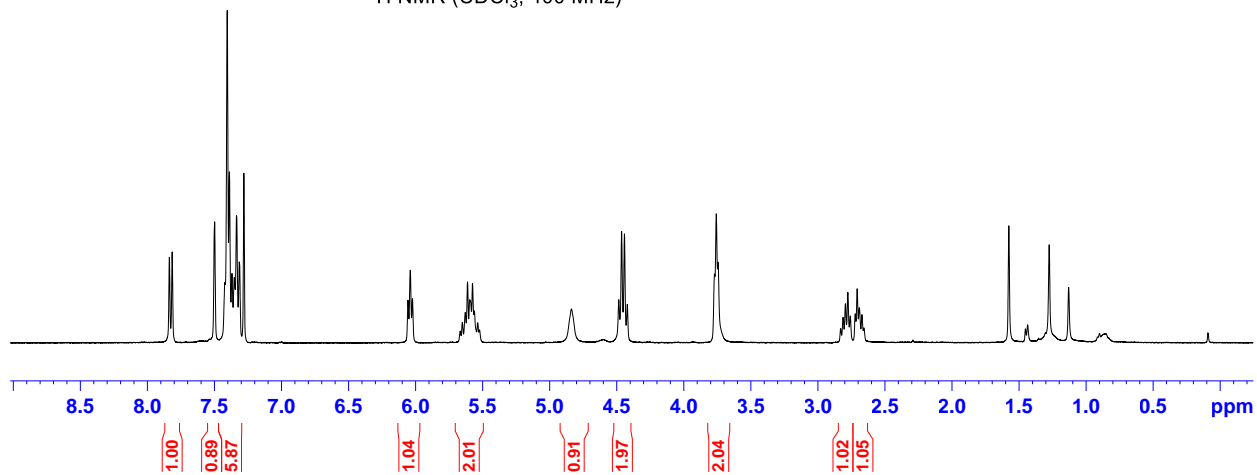
The stereochemistry of **1.36** was determined through *NOE* analysis. We observed strong *NOEs* between H(**b**) and H(**e**), as well as between H(**d**) and H(**f**). The results, together with the stereochemistry of the starting material, suggest that H(**b**) is at the axial position. Additionally, we observed either no *NOE* or a very weak *NOE* between H(**a**) and H(**f**) or H(**d**), which indicates that H(**a**) is at the equatorial position; therefore, the stereochemical relationship between the groups OR, NHBoc, and OTIPS are *syn, anti*.



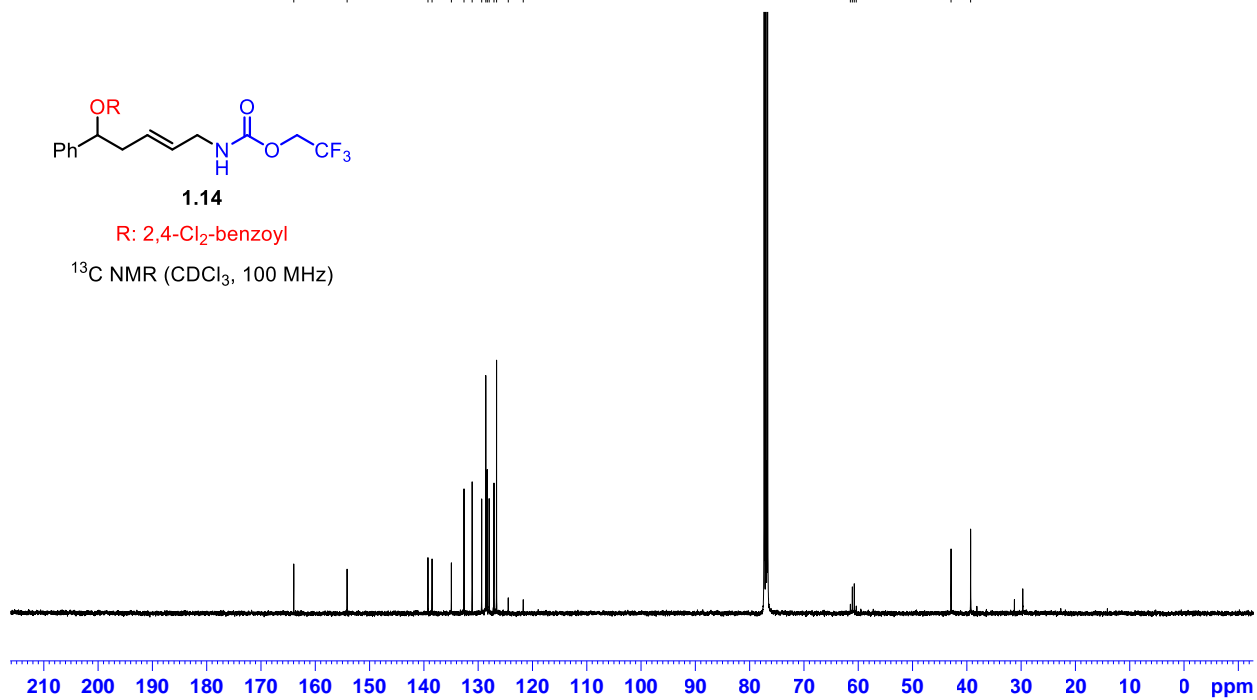


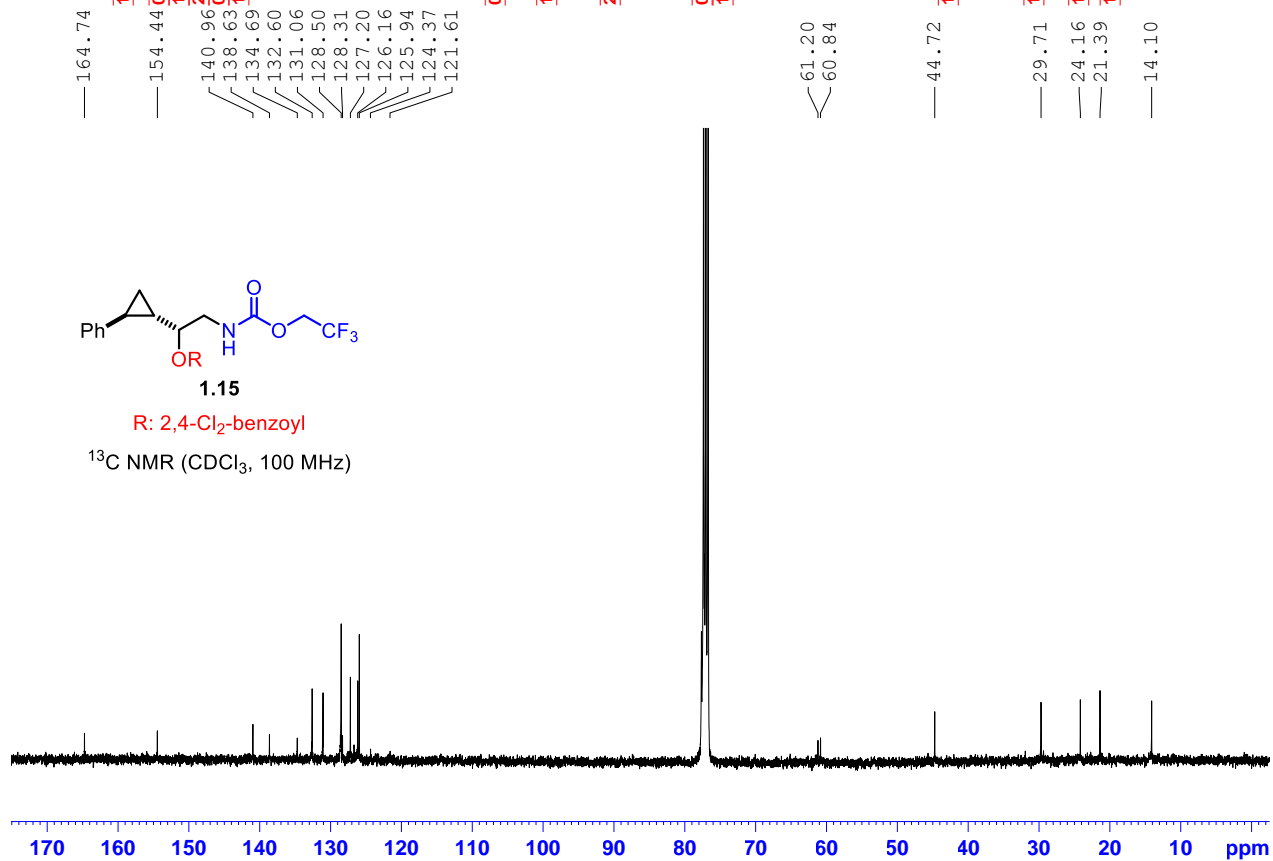
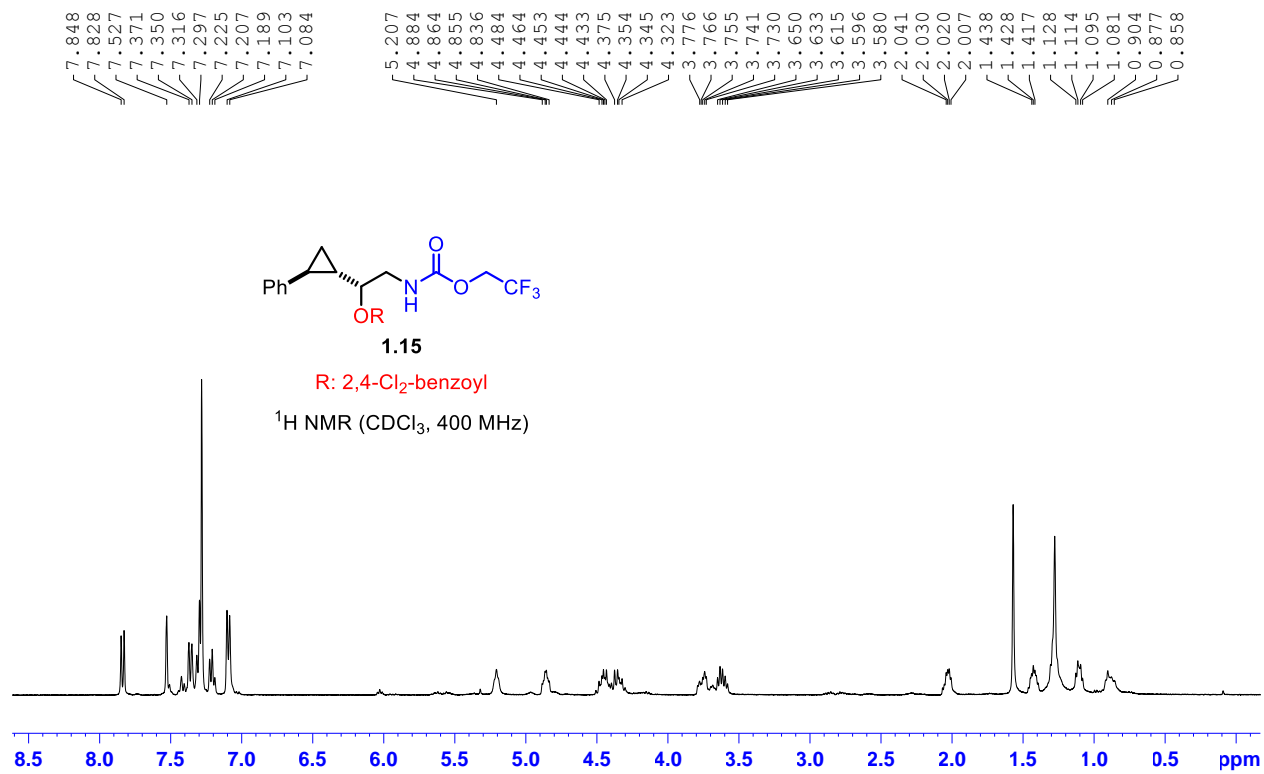


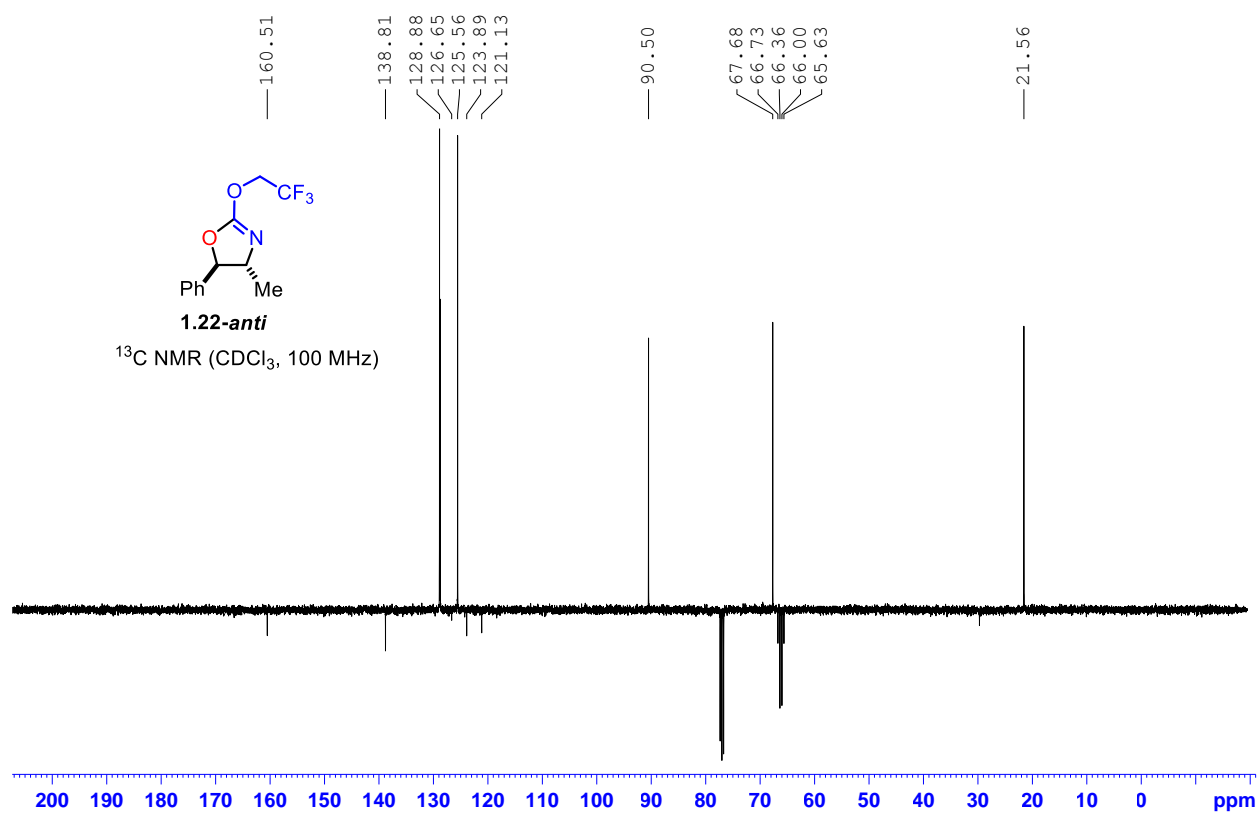
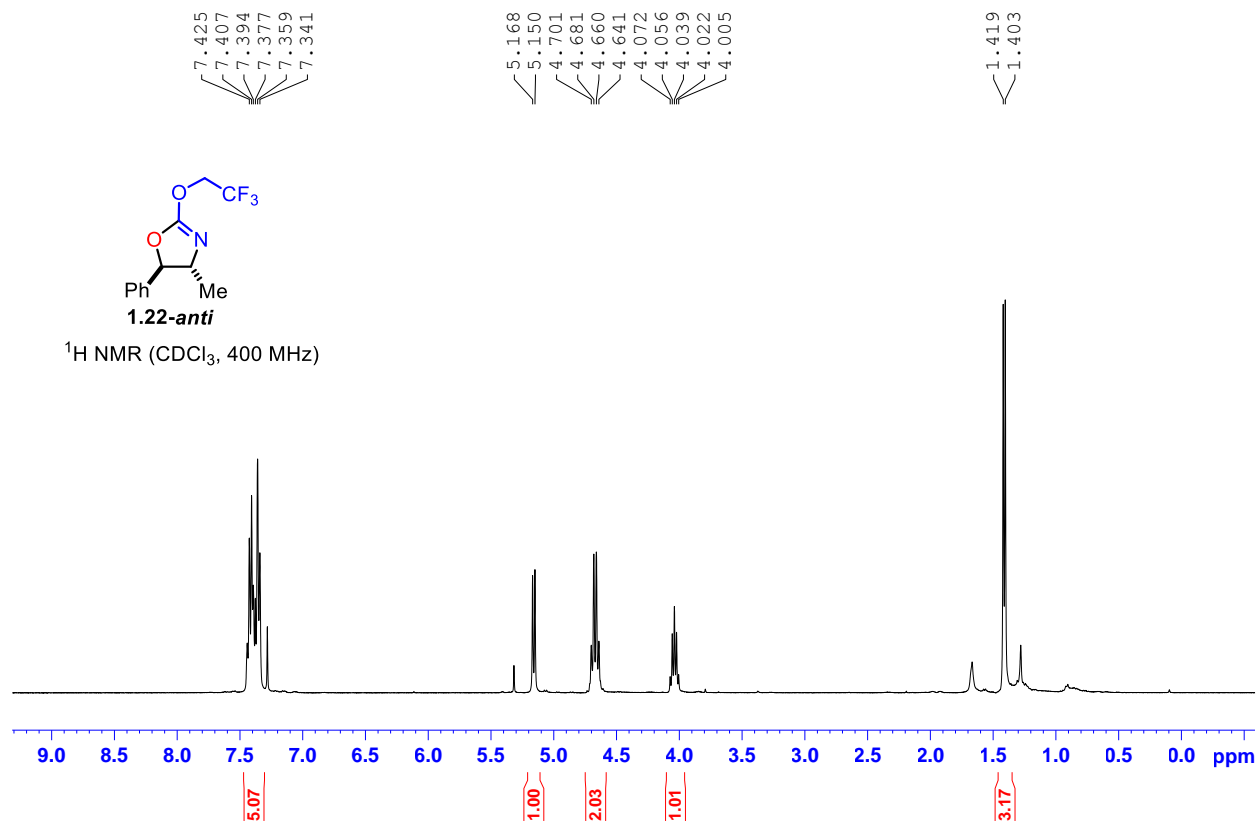
1.14

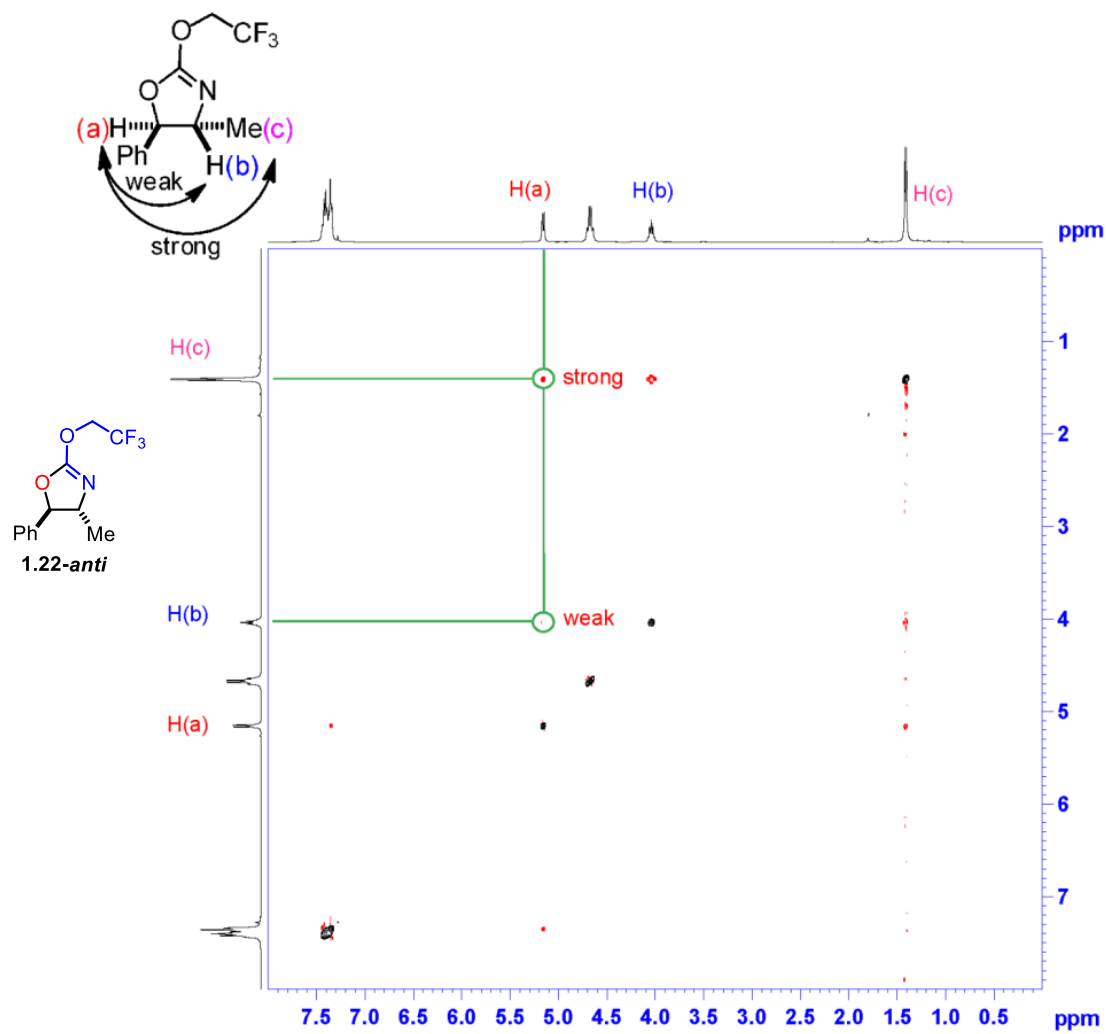
R: 2,4-Cl₂-benzoyl¹H NMR (CDCl₃, 400 MHz)

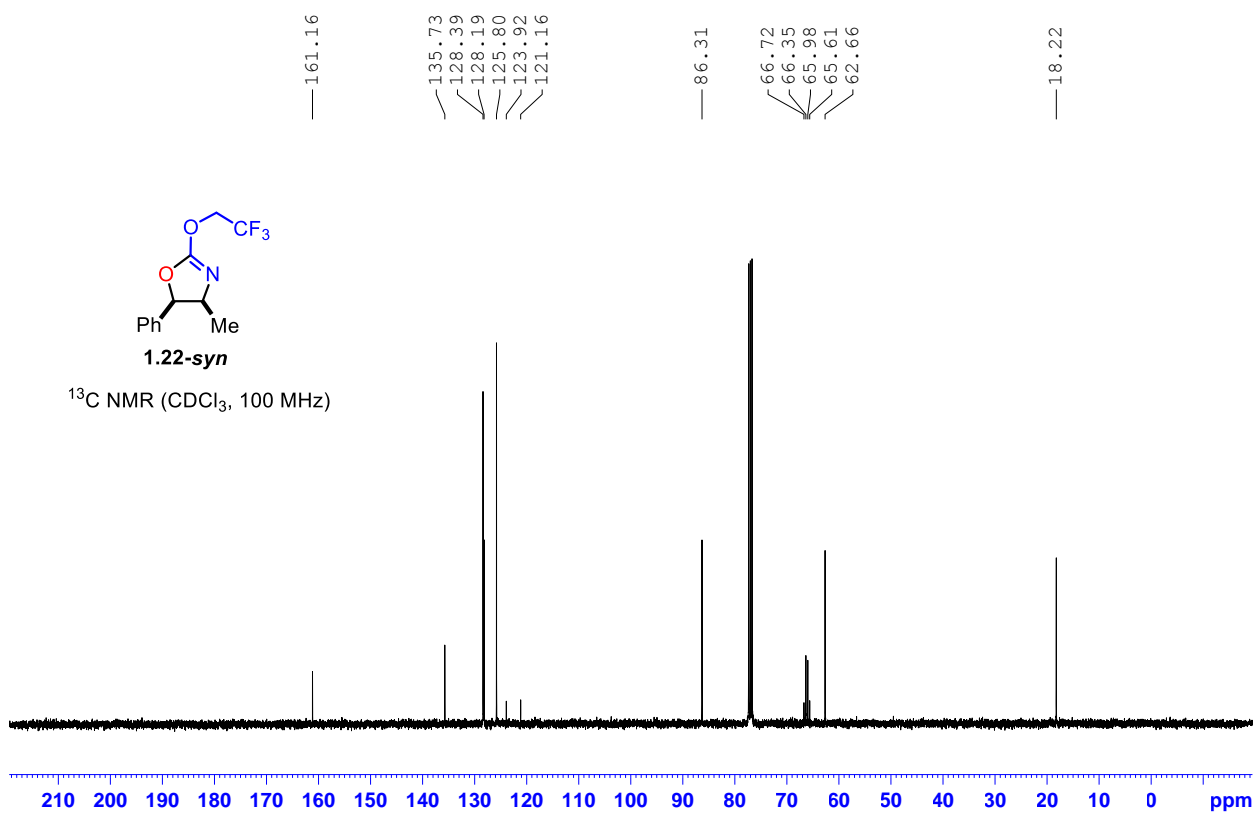
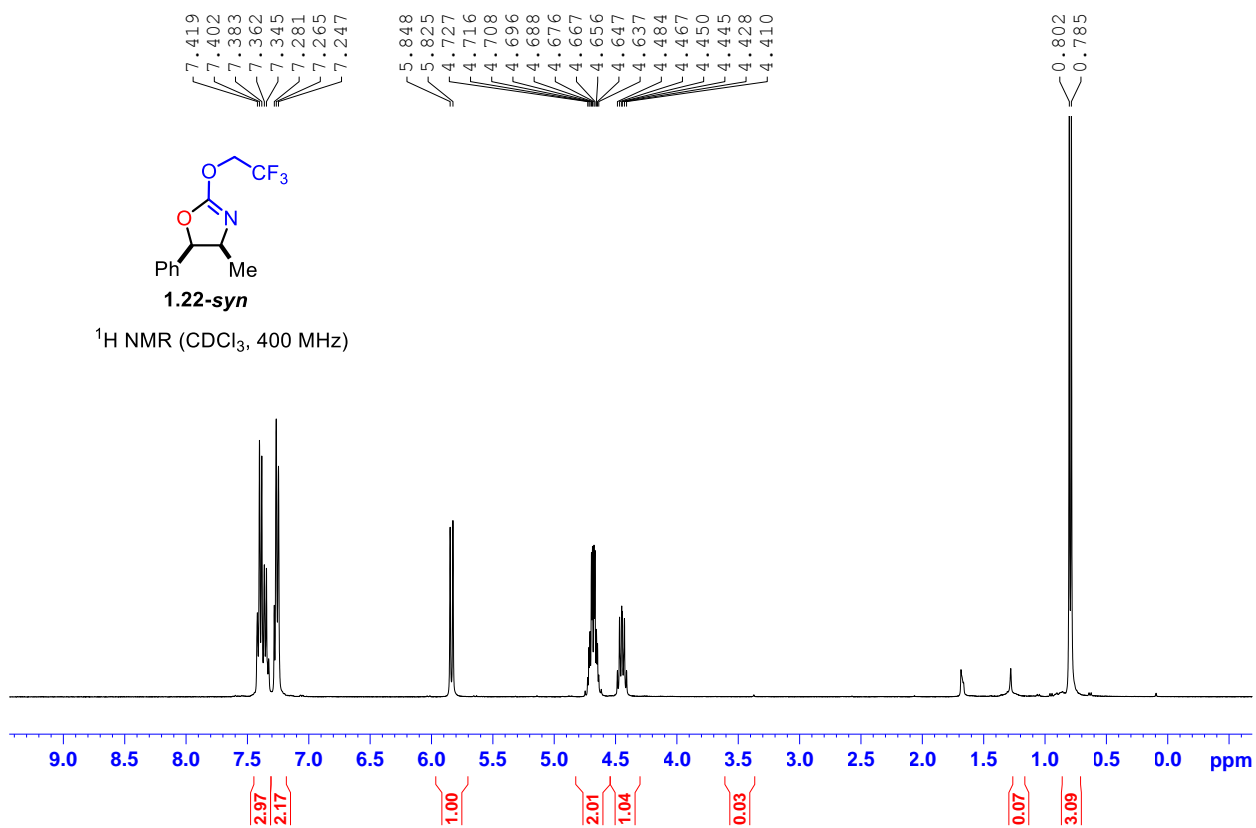
1.14

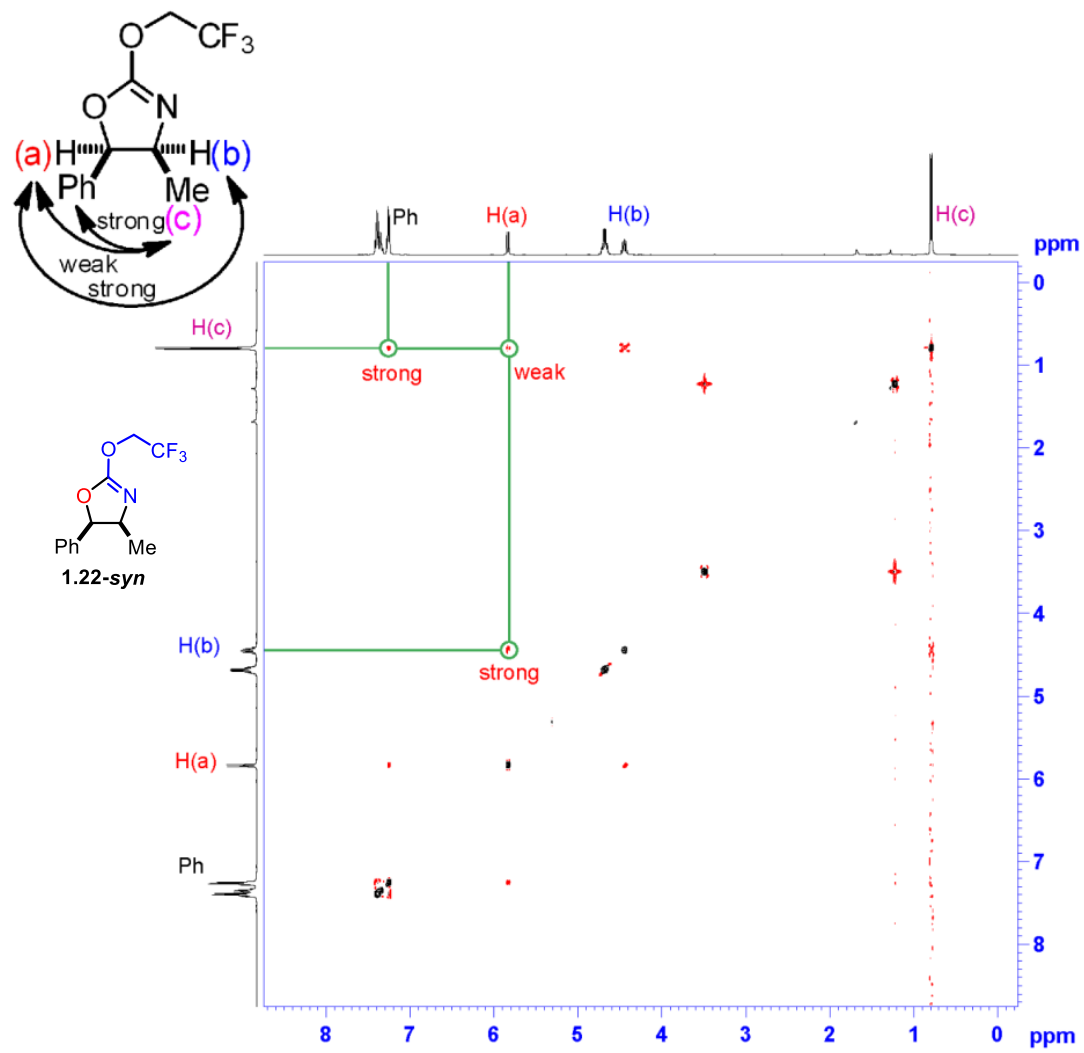
R: 2,4-Cl₂-benzoyl¹³C NMR (CDCl₃, 100 MHz)







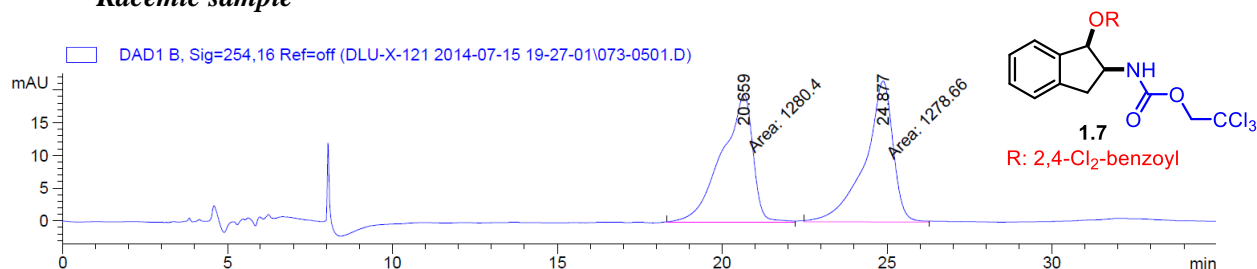




Appendix A.2 HPLC traces of compound 1.7

The *ee* of compound **1.7** was measured by Chiral HPLC analysis (Chiral S.S. Whelk, 1.0 mL/min, 254 nm, 5% EtOH in hexanes, t_r (minor) = 20.66 min, t_r (major) = 24.88 min).

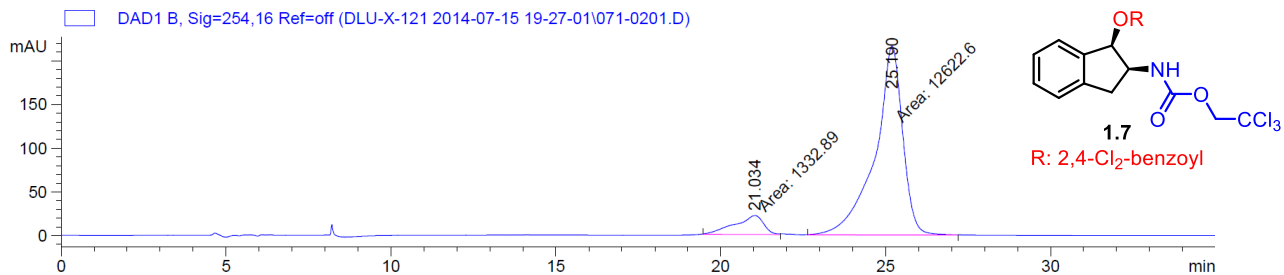
Racemic sample



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.659	MM	1.0946	1280.40137	19.49595	50.0340
2	24.877	MM	0.9894	1278.66064	21.53968	49.9660

Totals : 2559.06201 41.03563

Enantio-enriched sample (81% ee)



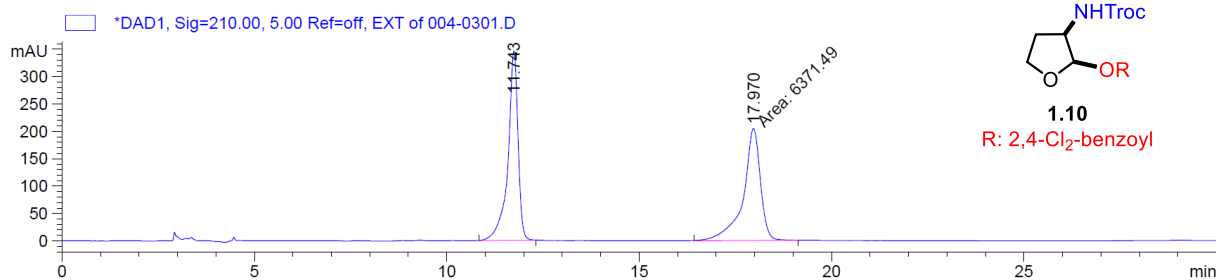
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.034	MM	1.0183	1332.88940	21.81666	9.5510
2	25.190	MM	0.9740	1.26226e4	216.00296	90.4490

Totals : 1.39555e4 237.81962

Appendix A.3 HPLC traces of compound **1.10**

The *ee* of compound **1.10** was measured by Chiral HPLC analysis (Chiral S.S. Whelk, 1.0 mL/min, 210 nm, 15% EtOH in hexanes, t_r (minor) = 11.74 min, t_r (major) = 17.97 min, 57% *ee*).

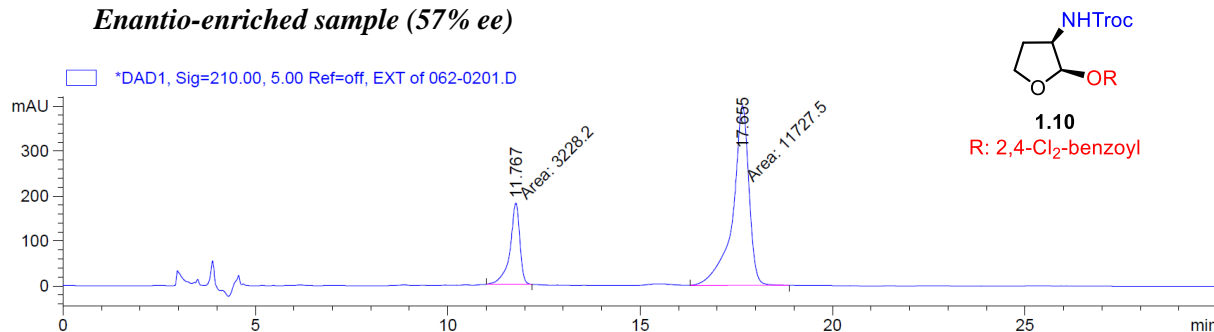
Racemic sample



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.743	BB	0.2681	6352.02979	346.15771	49.9235
2	17.970	MM	0.5188	6371.49463	204.66739	50.0765

Totals : 1.27235e4 550.82510

Enantio-enriched sample (57% ee)

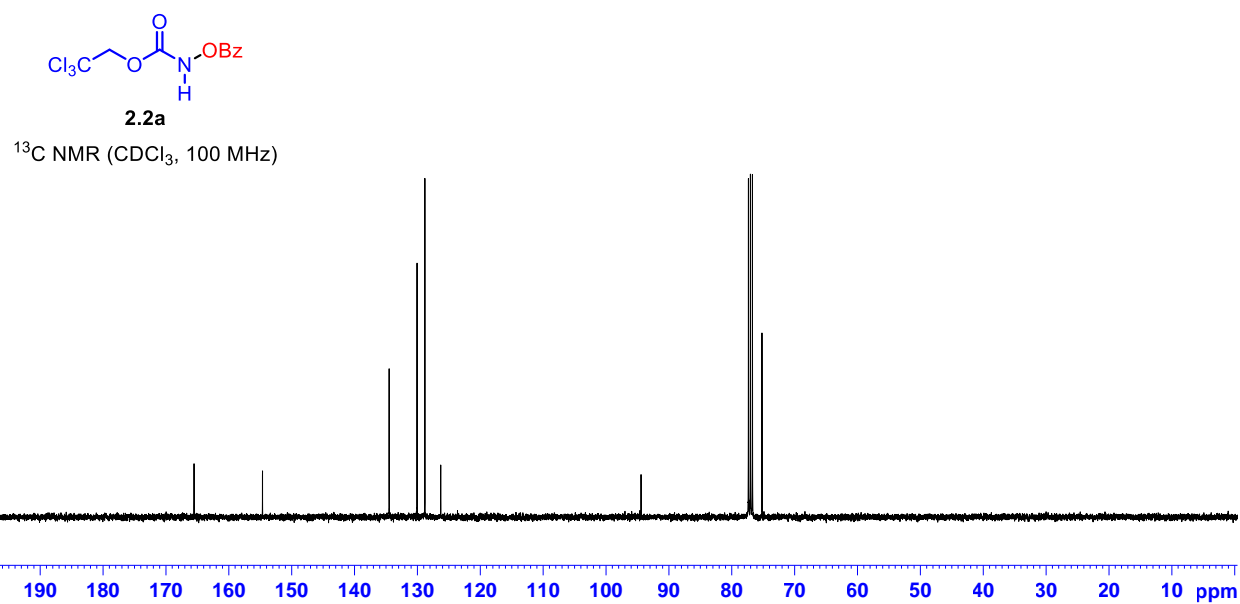
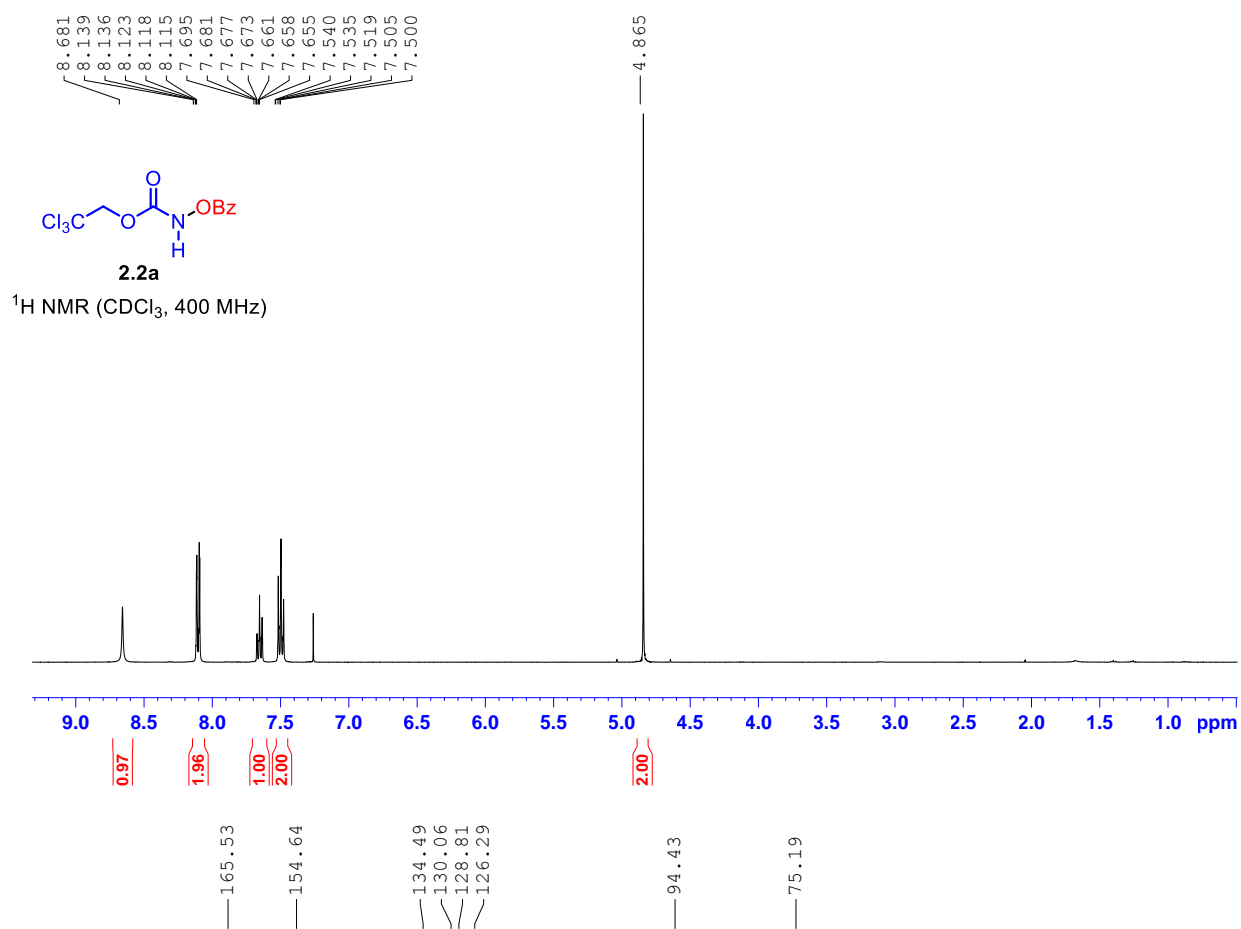


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.767	MM	0.2962	3228.19604	181.66481	21.5851
2	17.655	MM	0.4889	1.17275e4	399.77057	78.4149

Totals : 1.49557e4 581.43538

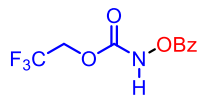
Appendix B. Representative NMR spectra and HPLC traces in CHAPTER 2

Appendix B.1 NMR Spectra

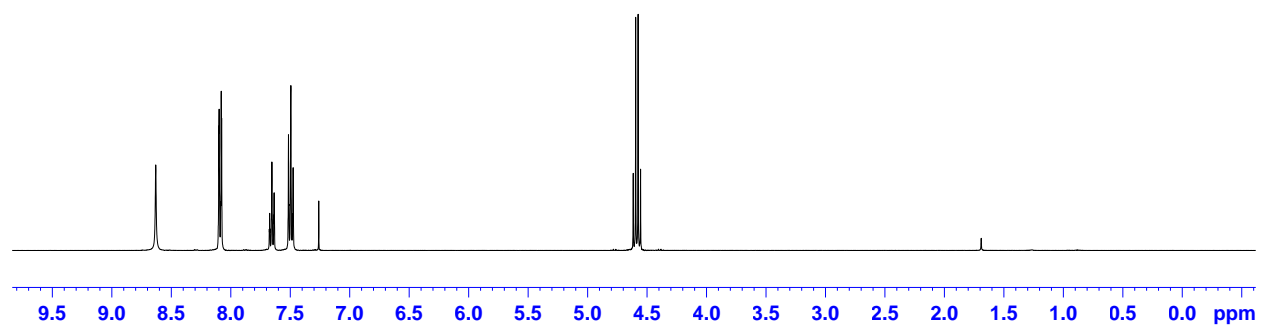


8.631
8.101
8.098
8.085
8.080
8.077
7.673
7.654
7.639
7.636
7.632
7.515
7.511
7.495
7.480
7.476

4.616
4.596
4.575
4.555



2.2a

¹H NMR (CDCl₃, 400 MHz)

— 165.46

— 154.54

134.53

130.03

128.82

126.66

126.18

123.90

121.14

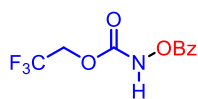
118.39

62.46

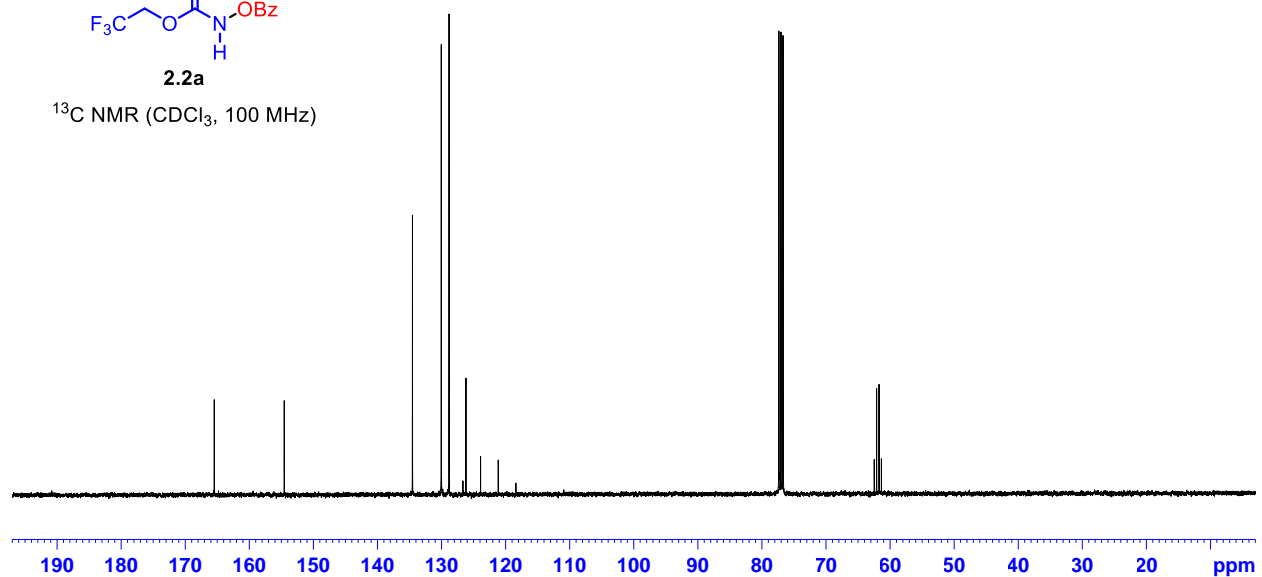
62.09

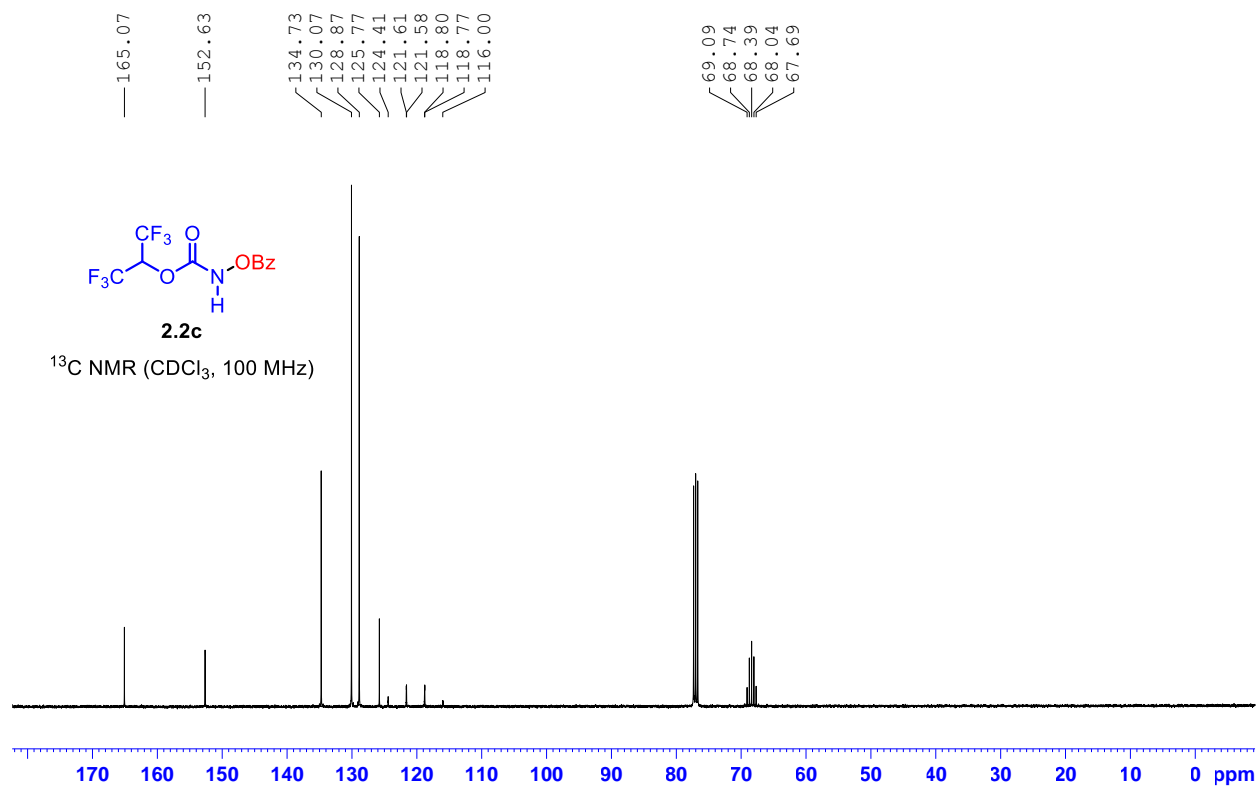
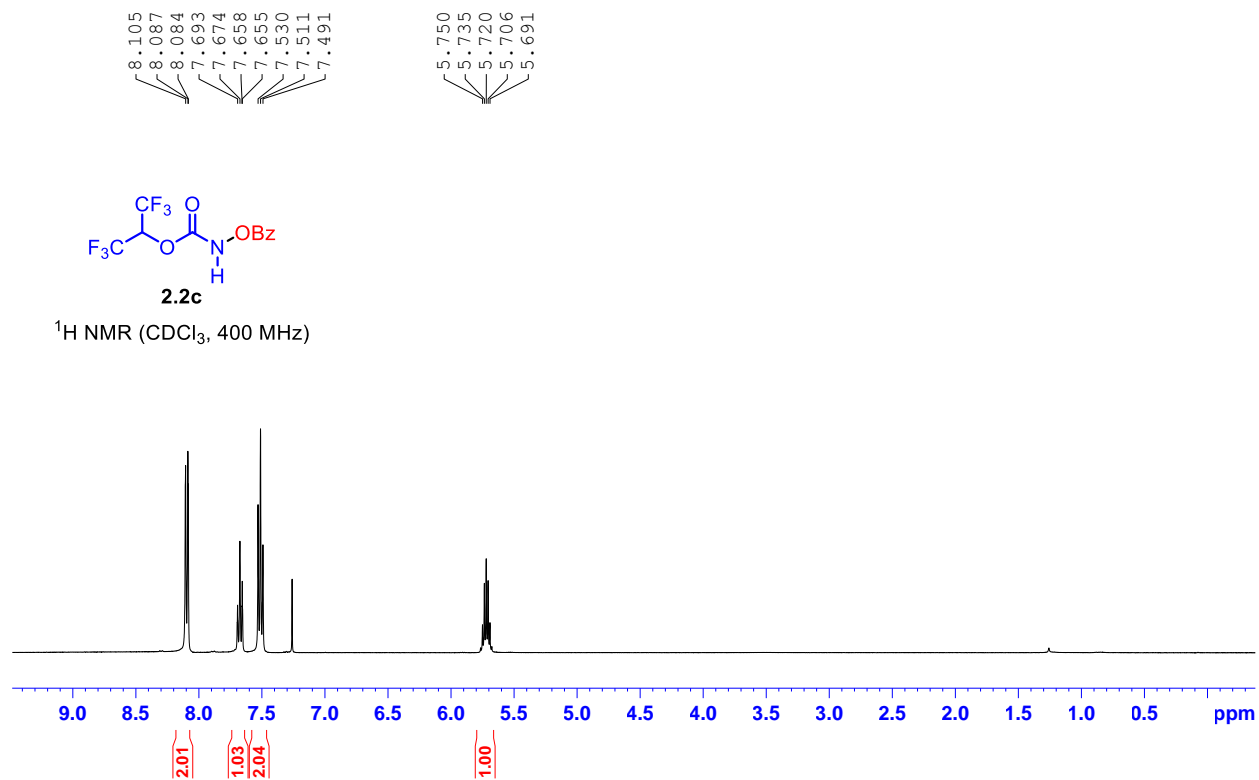
61.72

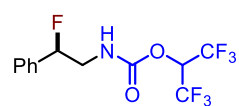
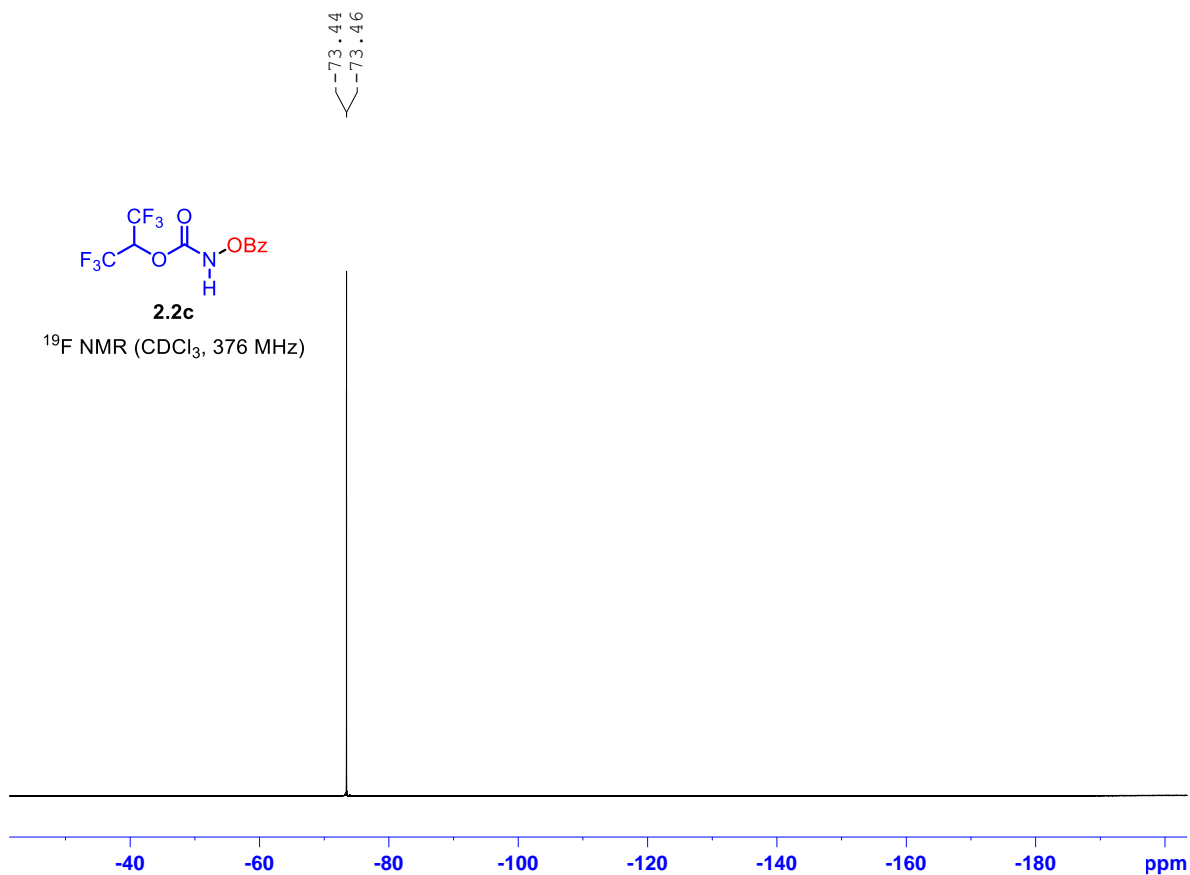
61.35



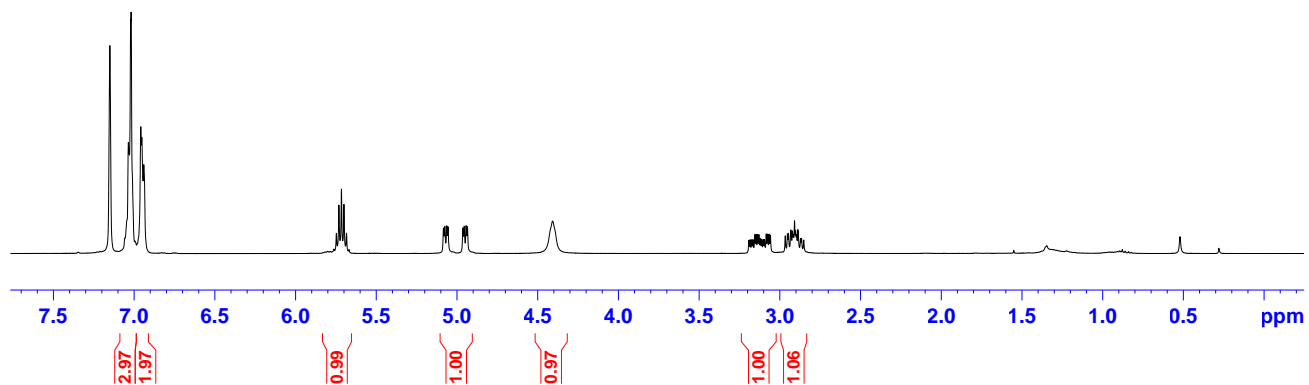
2.2a

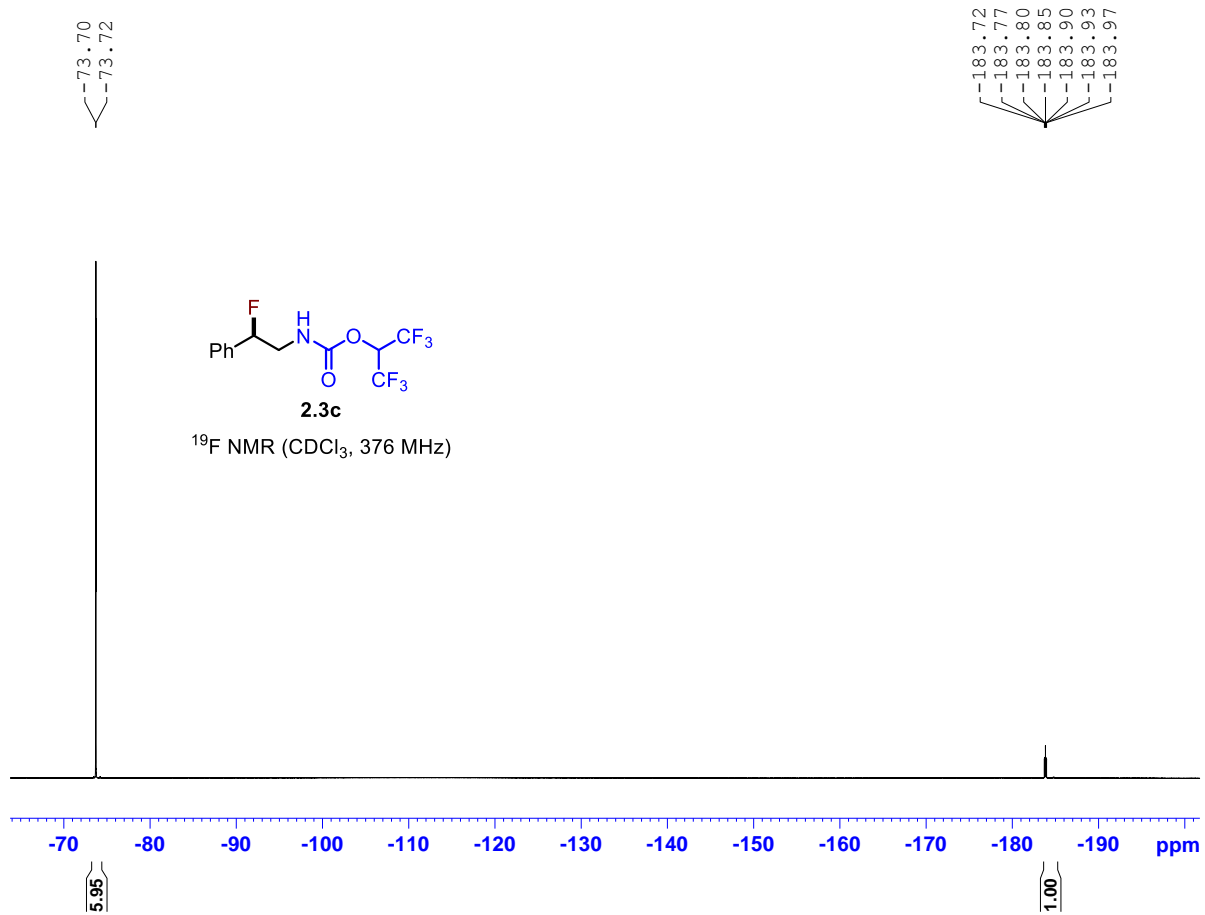
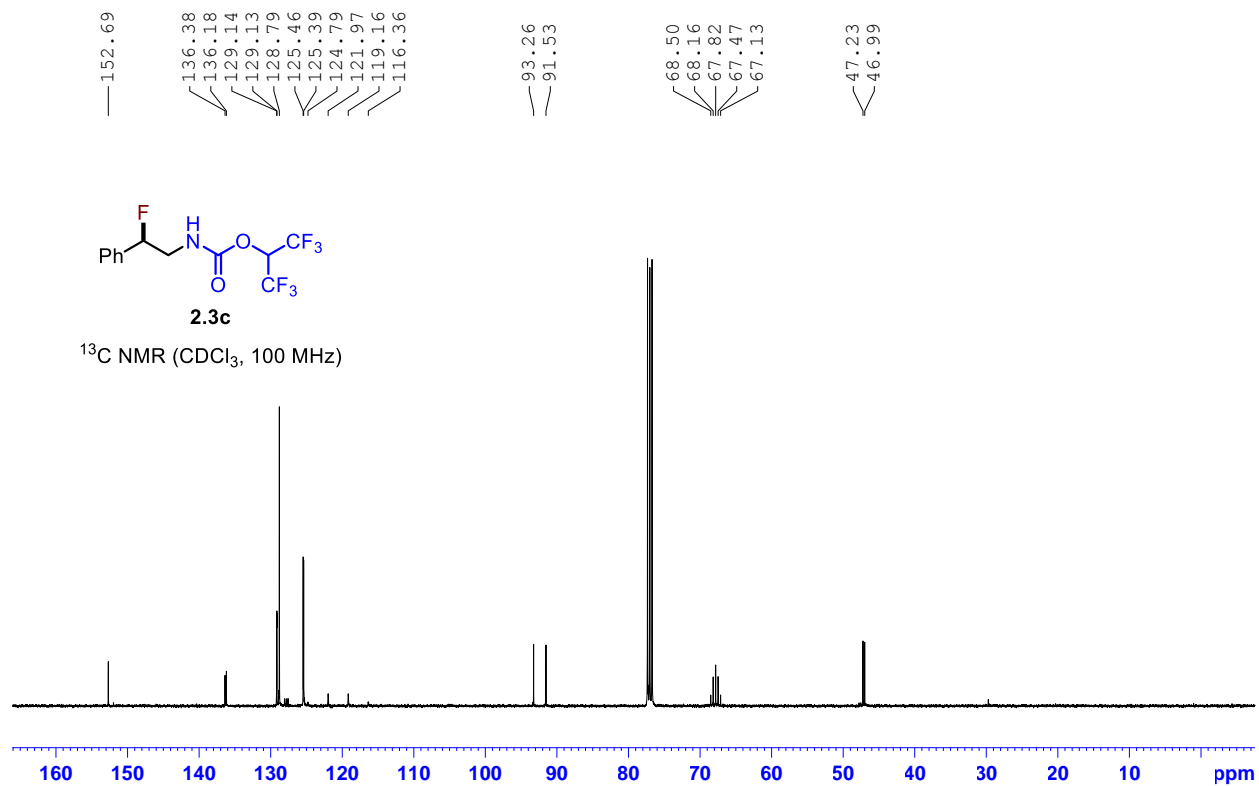
¹³C NMR (CDCl₃, 100 MHz)

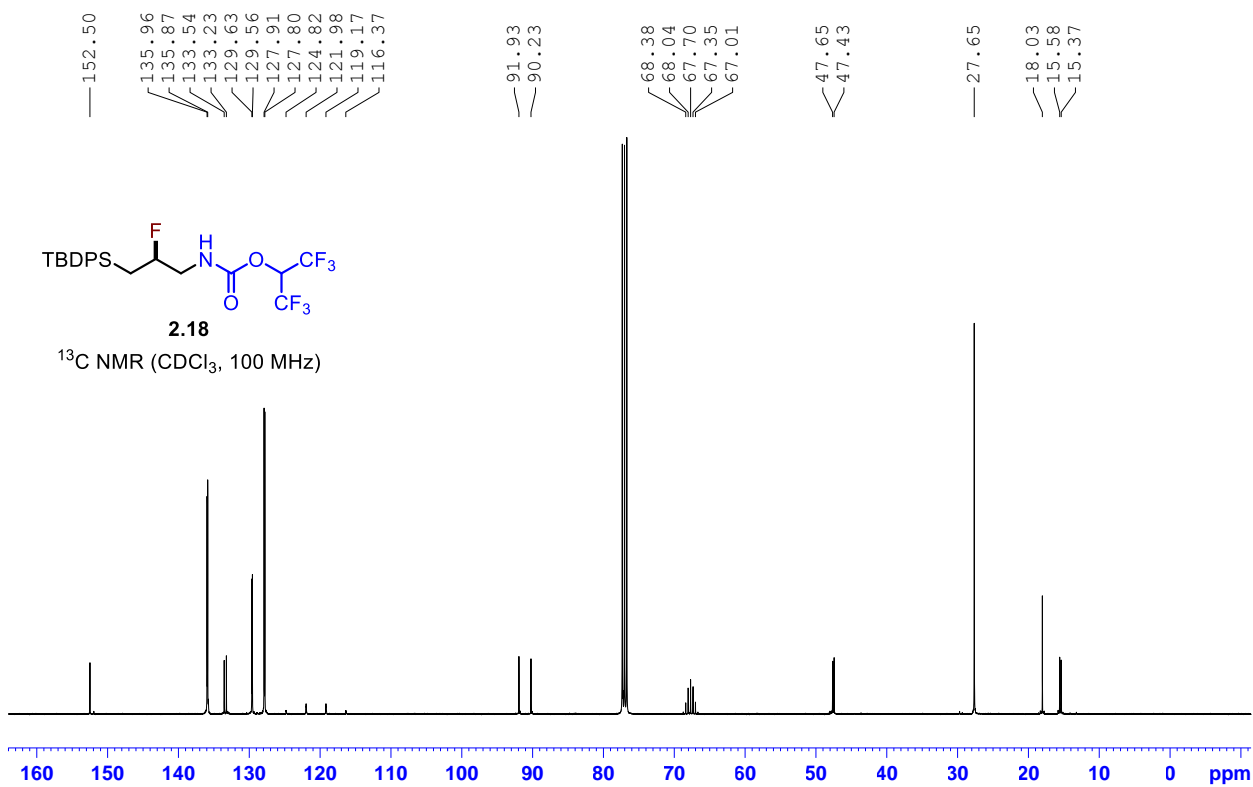
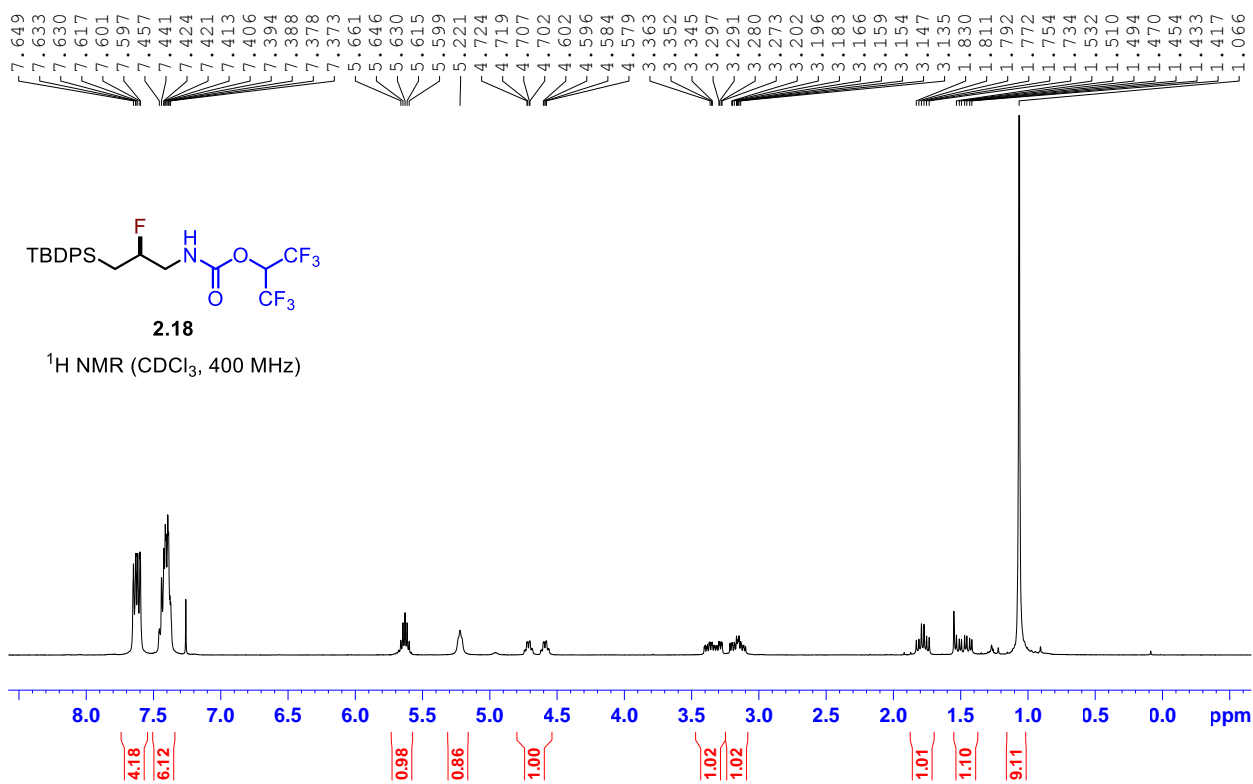


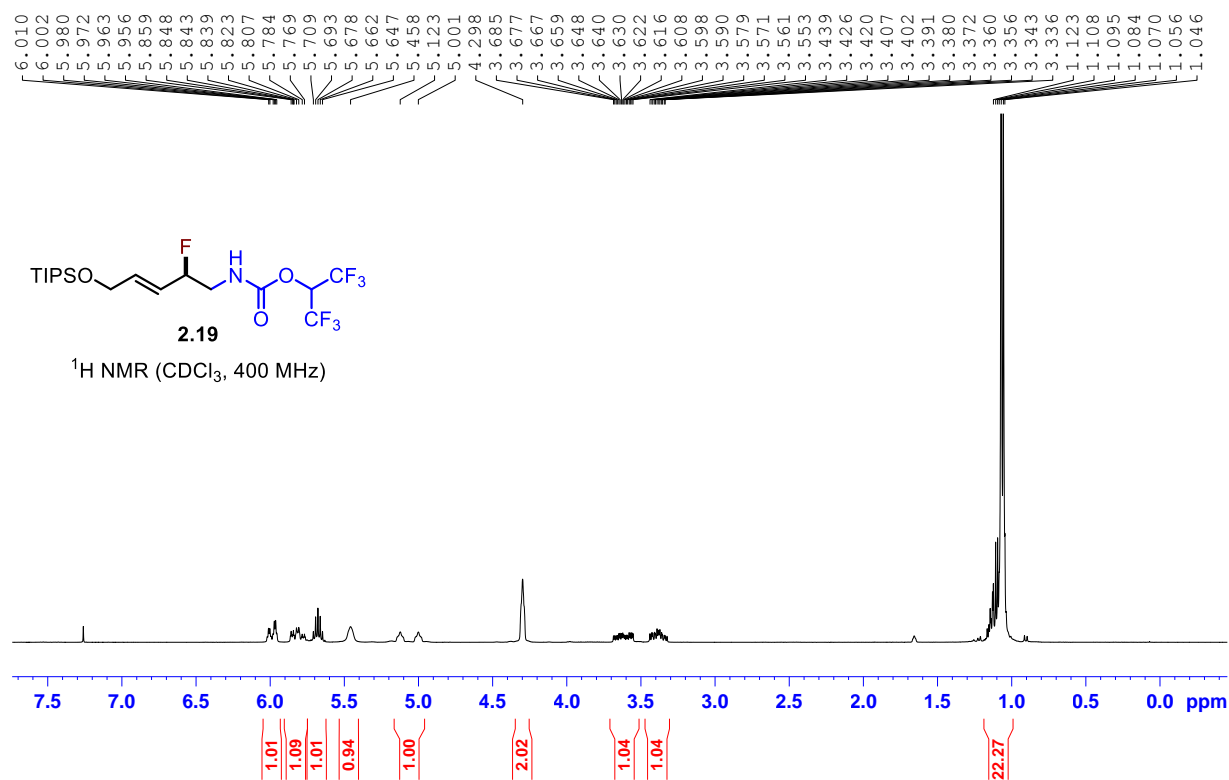
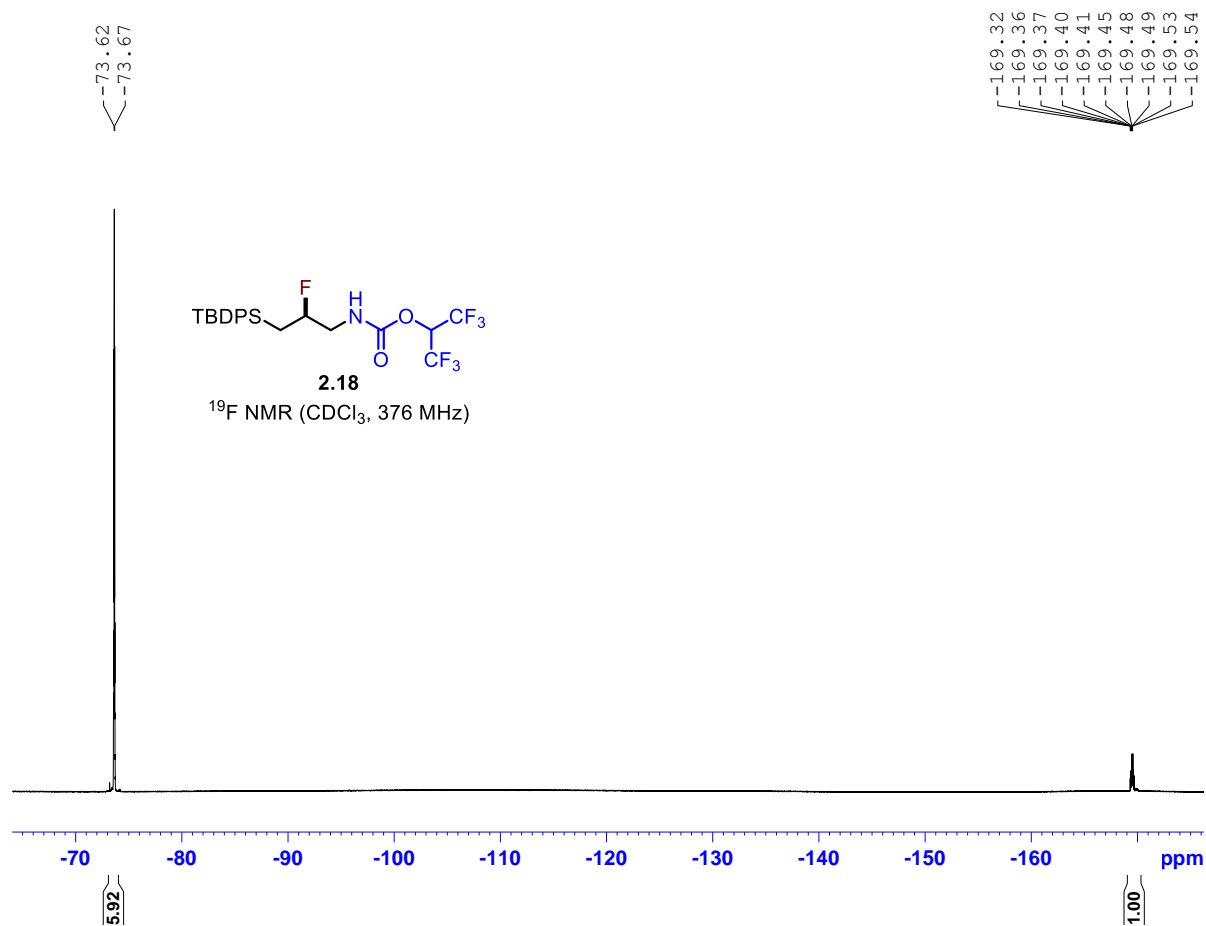


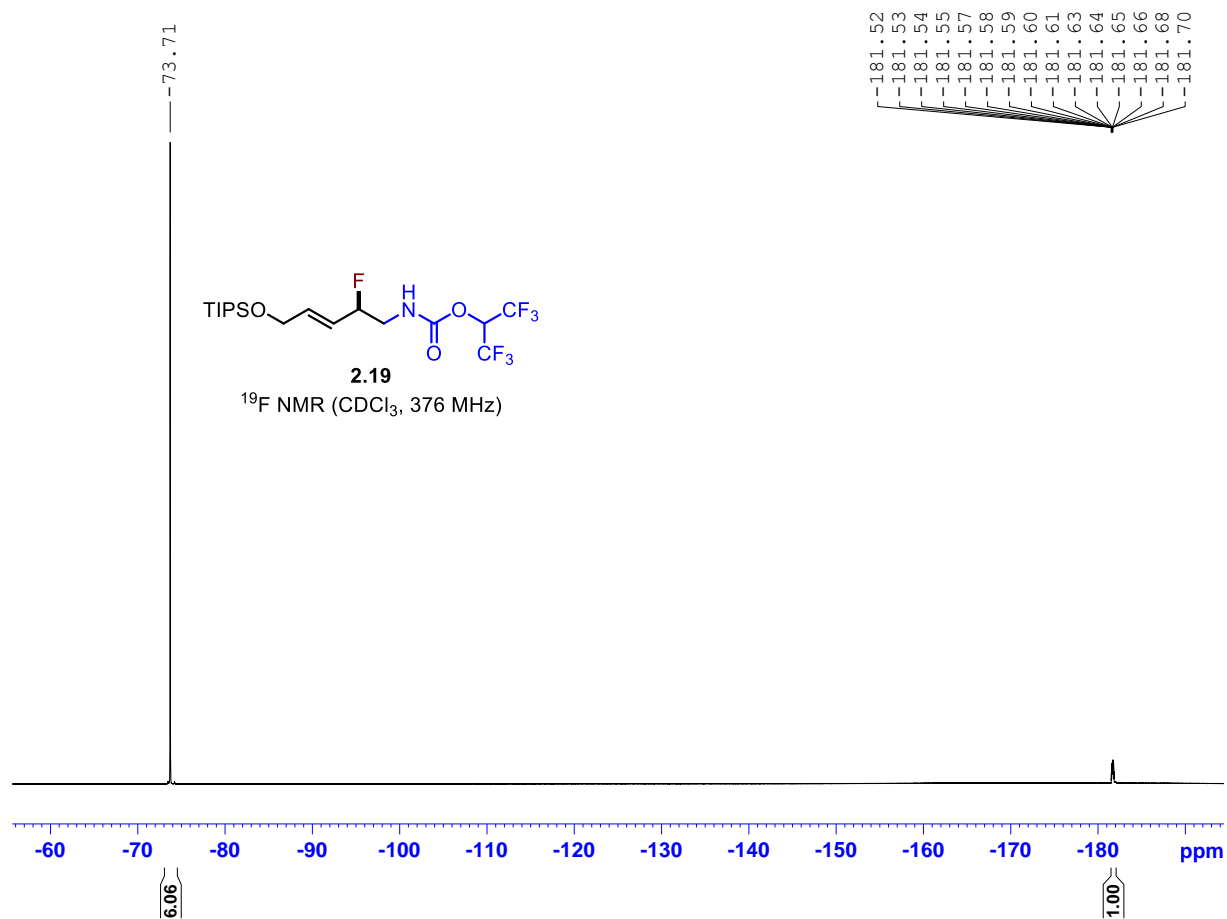
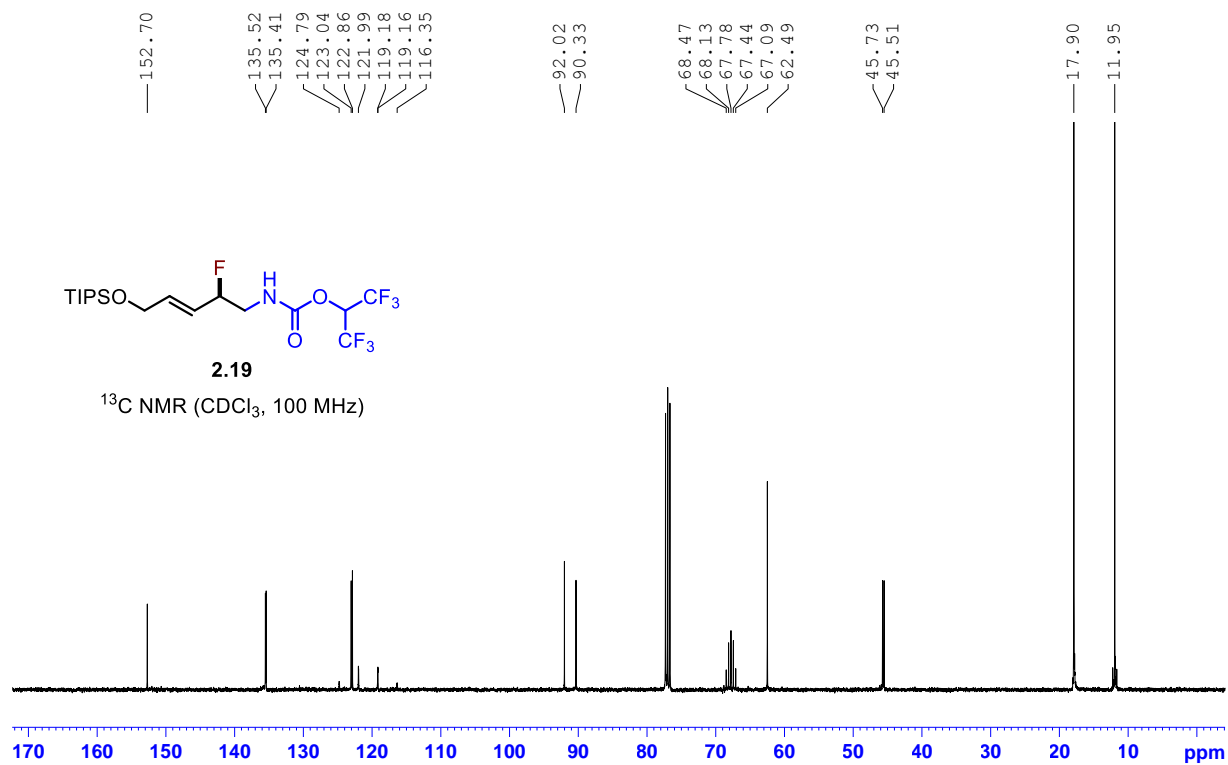
¹H NMR (CDCl₃, 400 MHz)

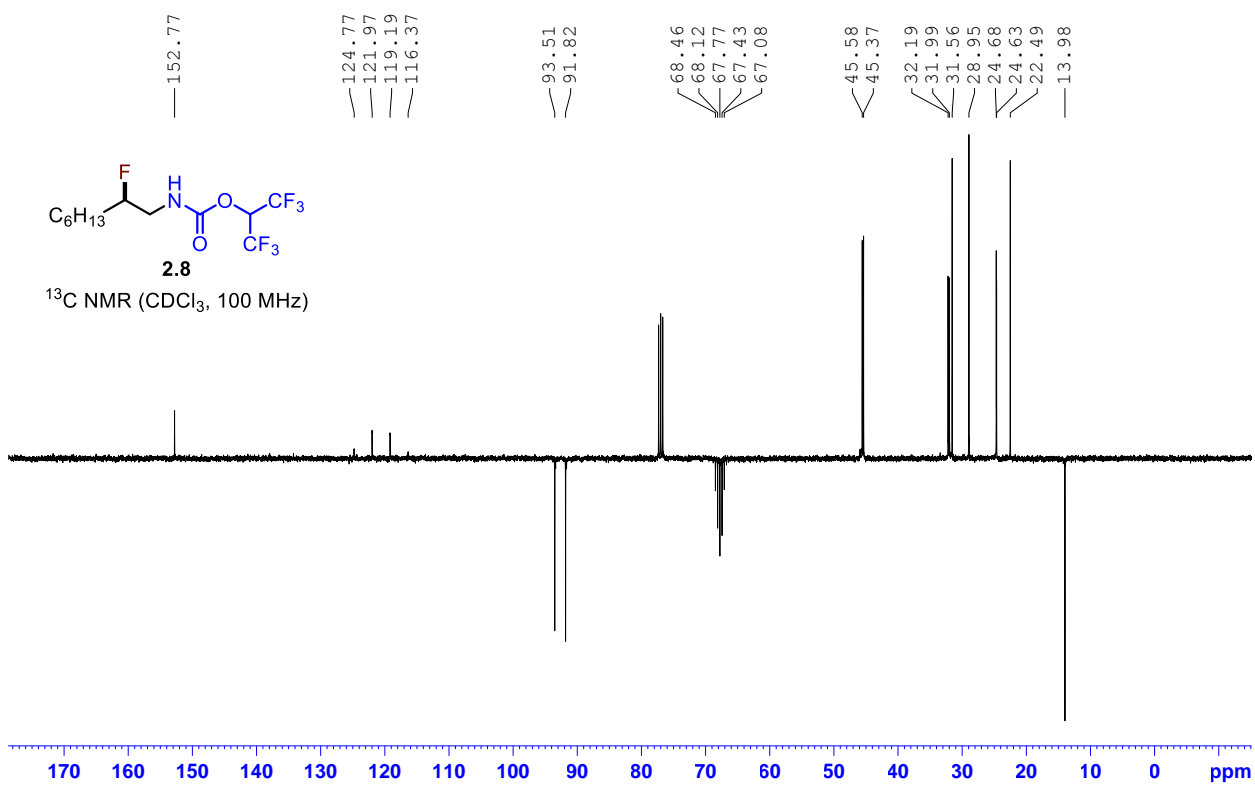
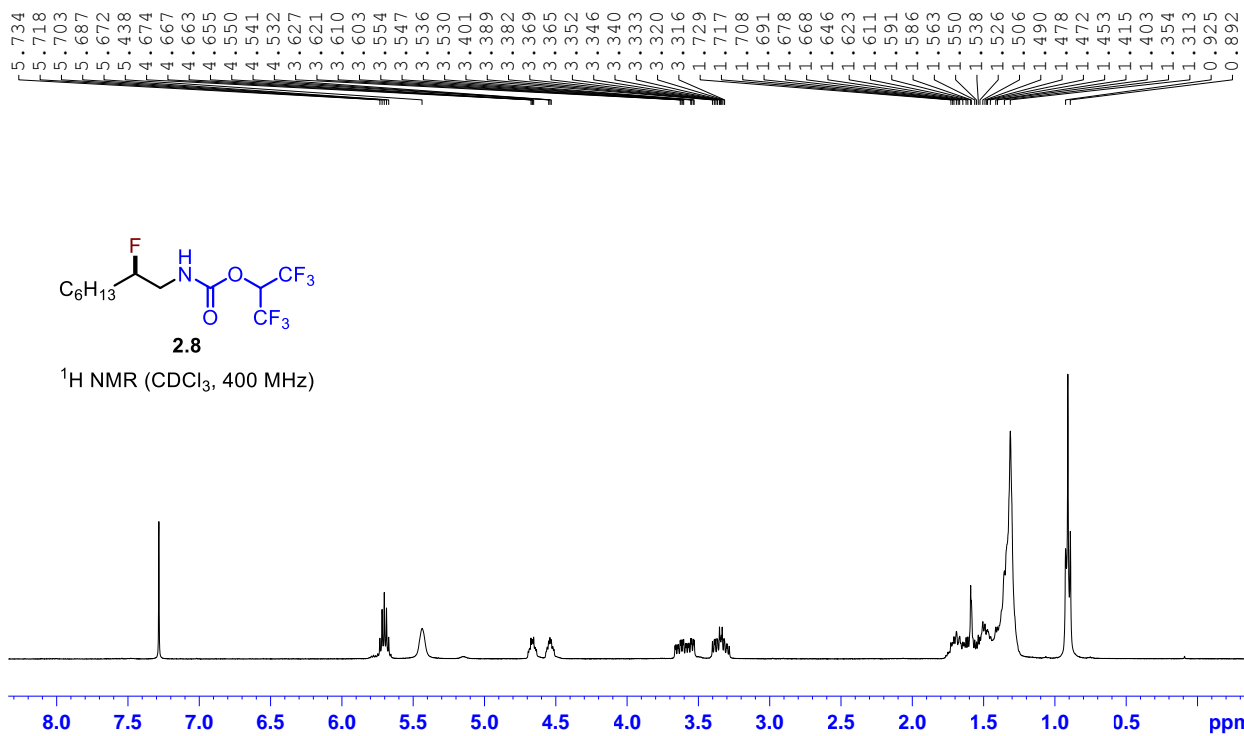


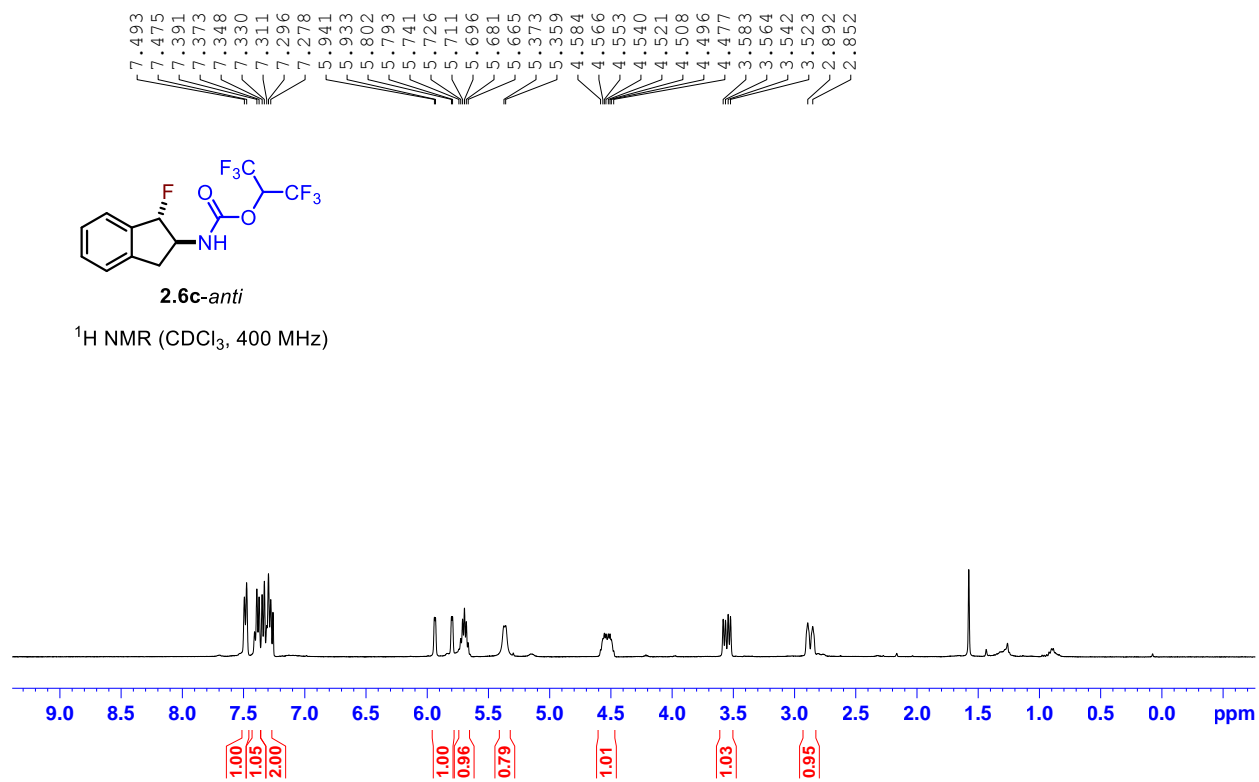
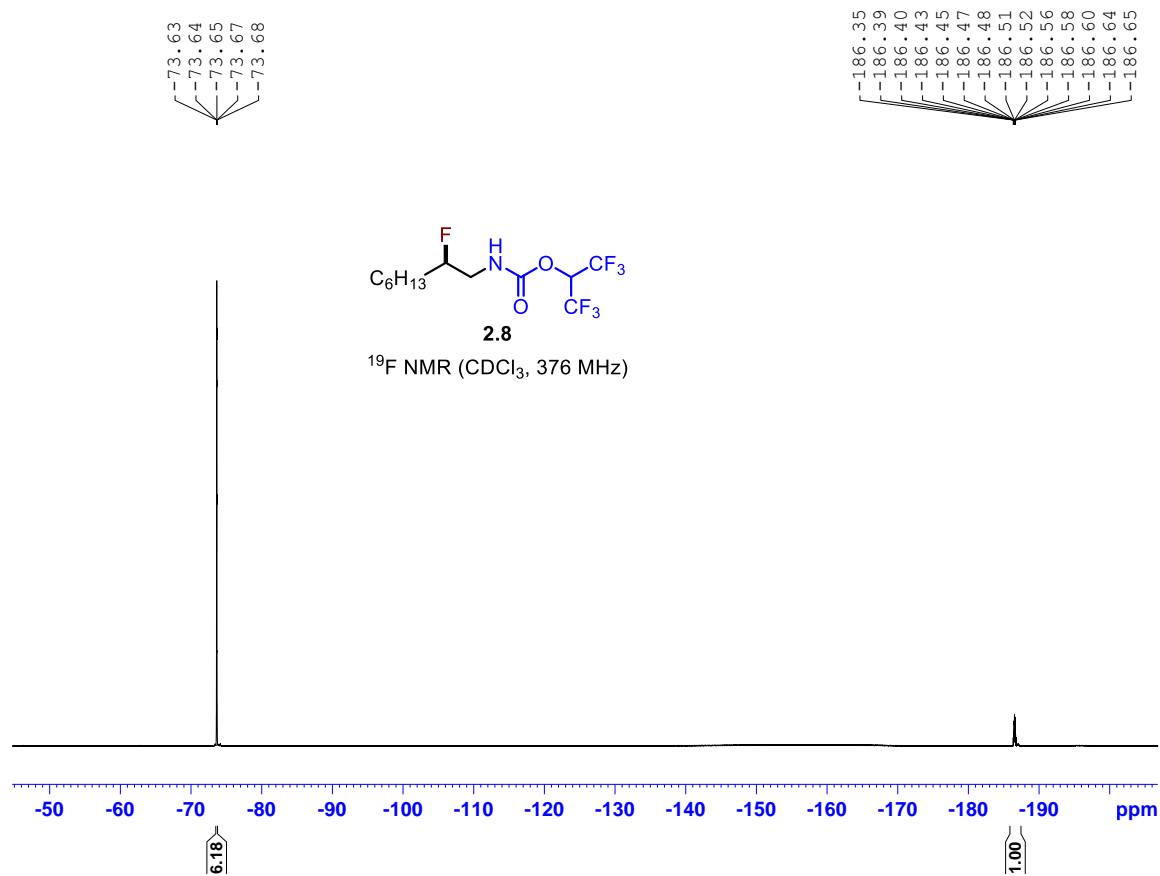


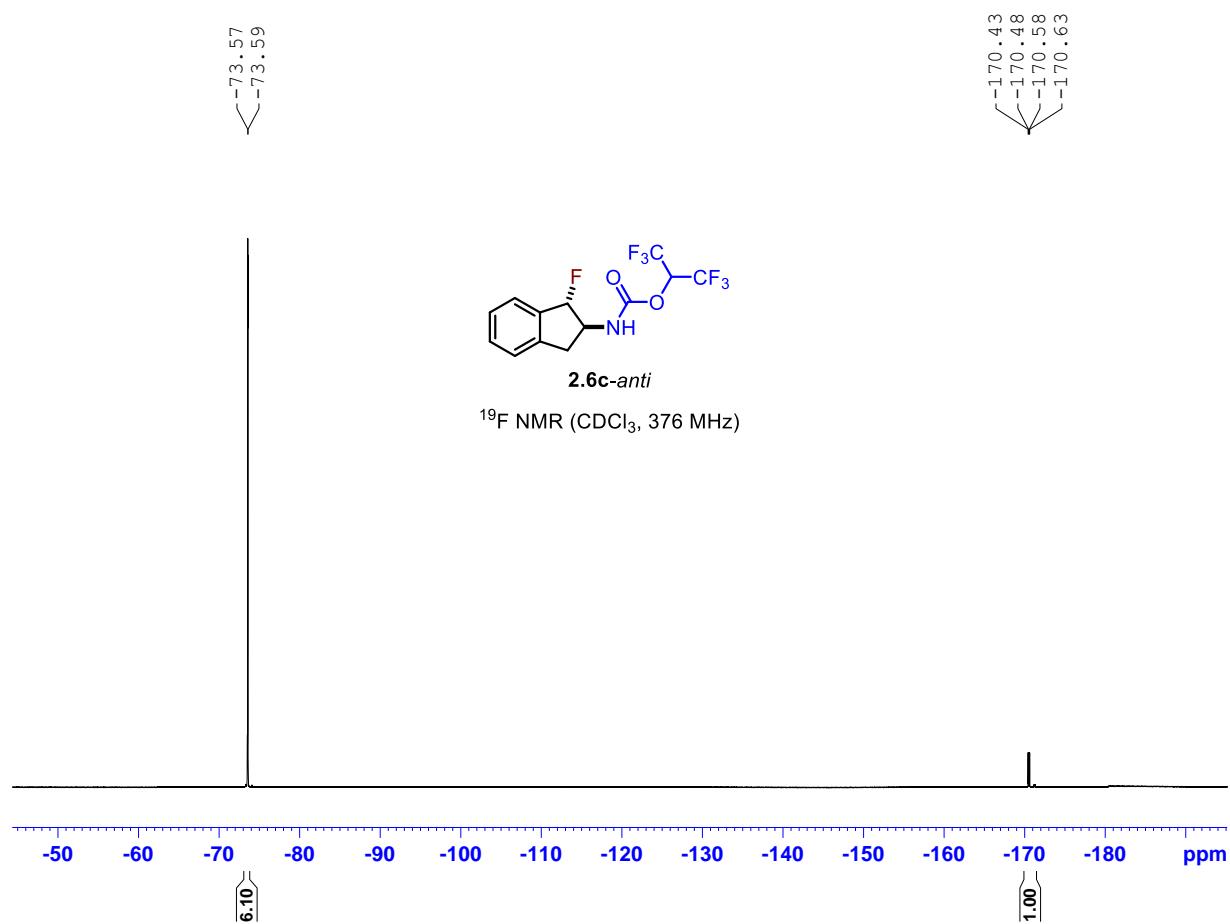
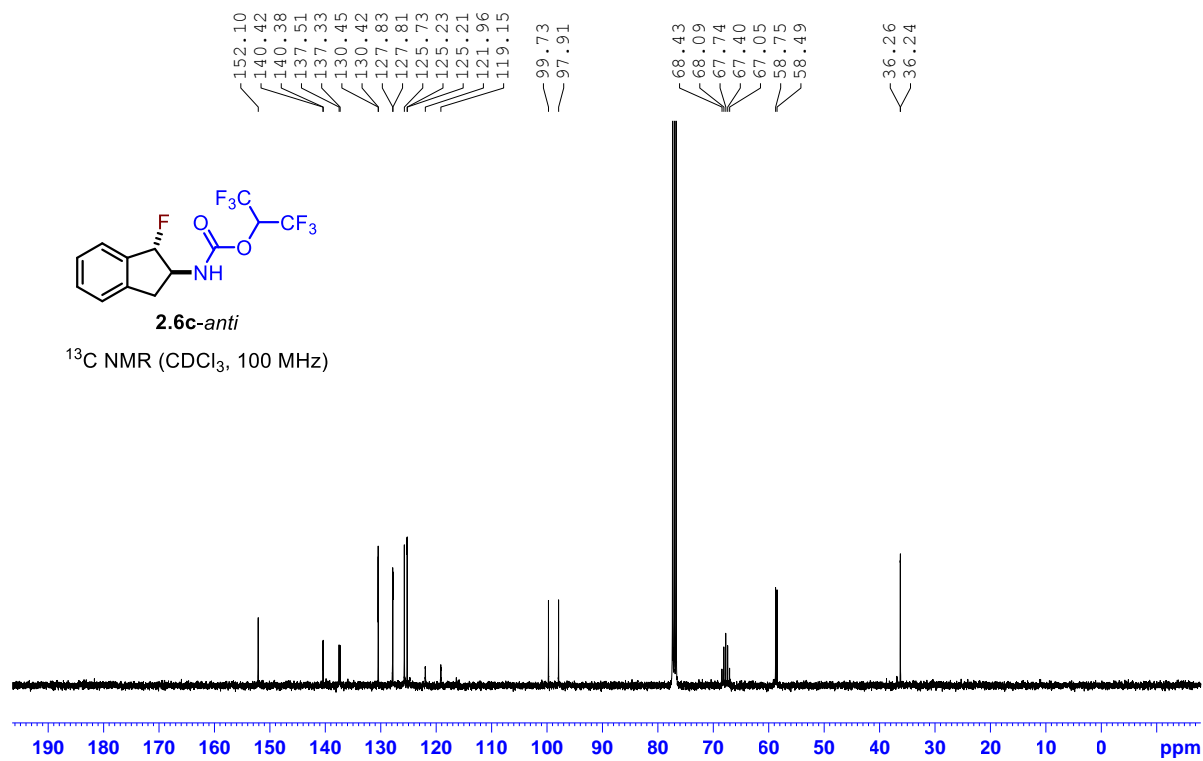


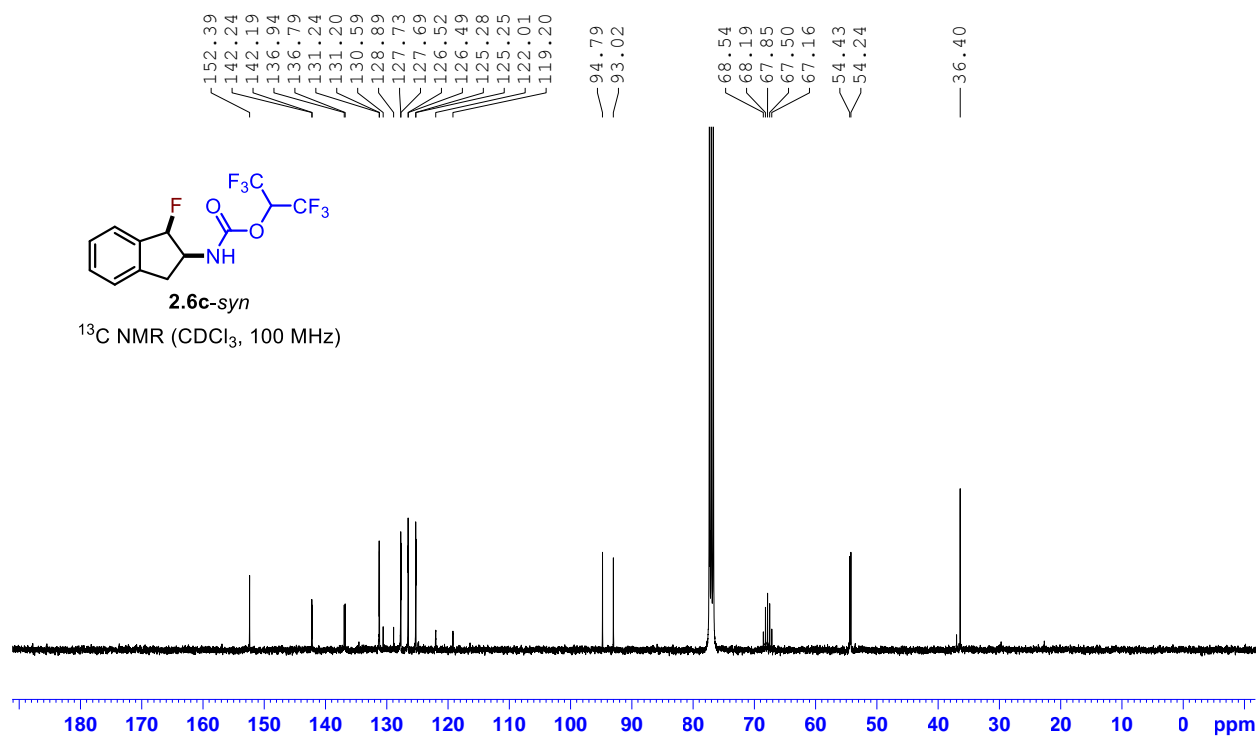
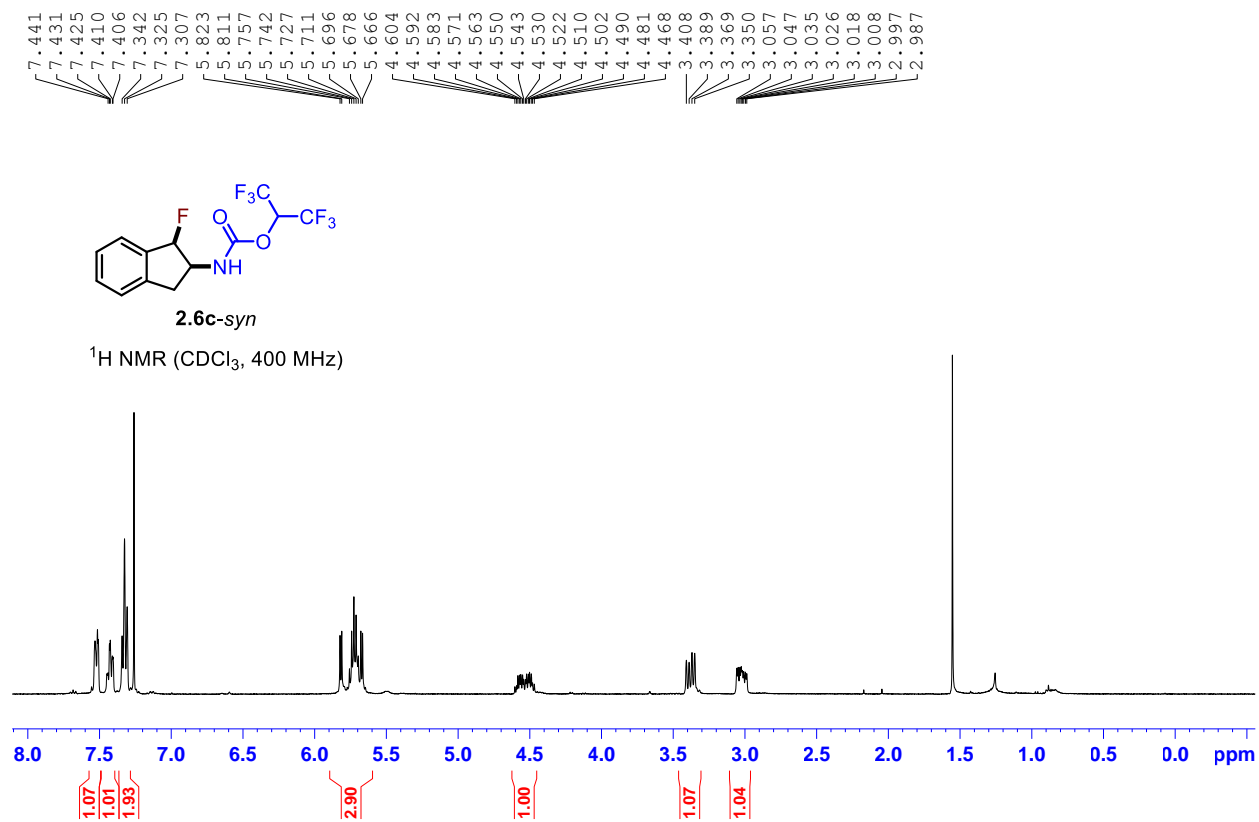


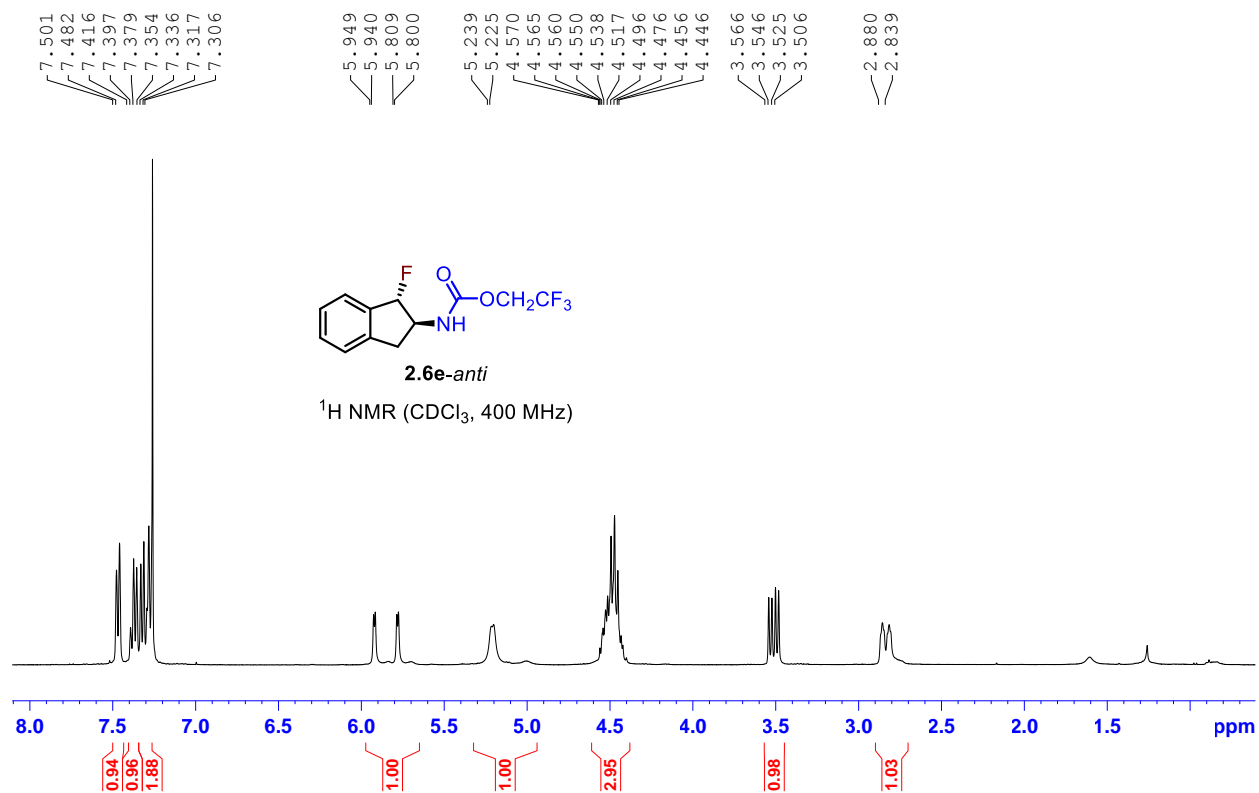
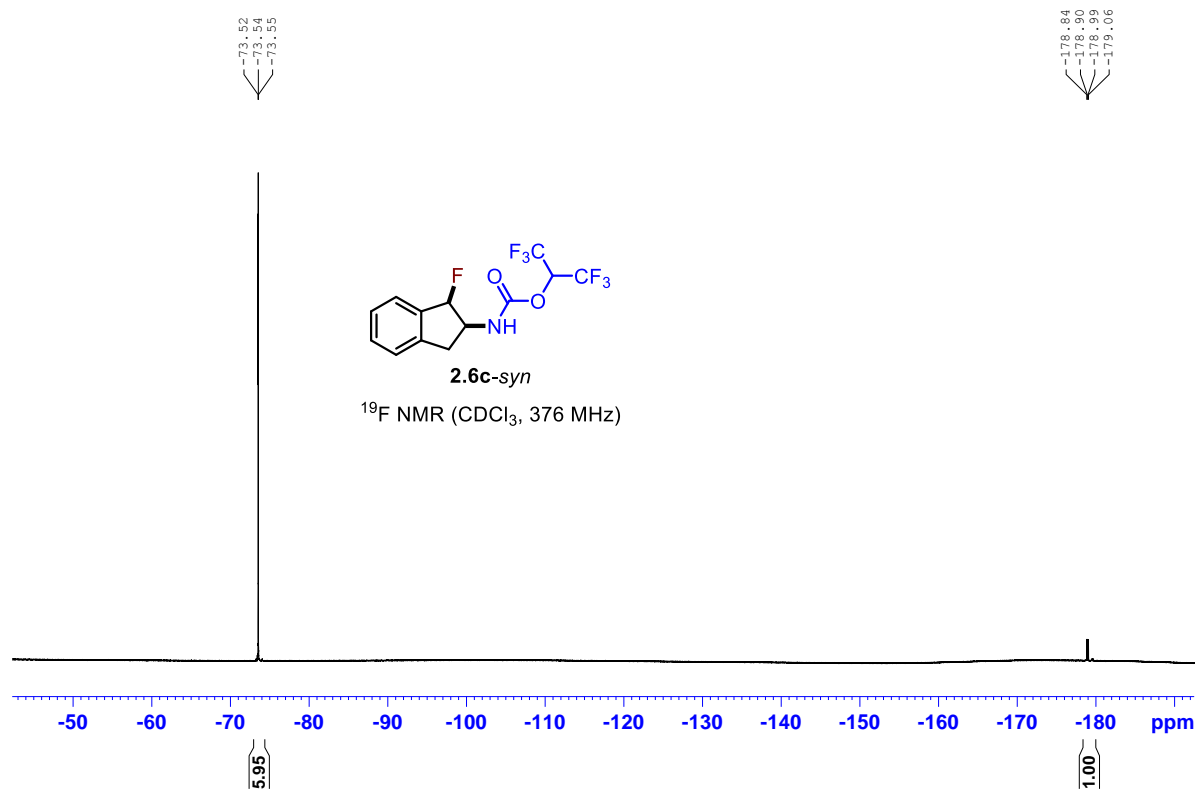


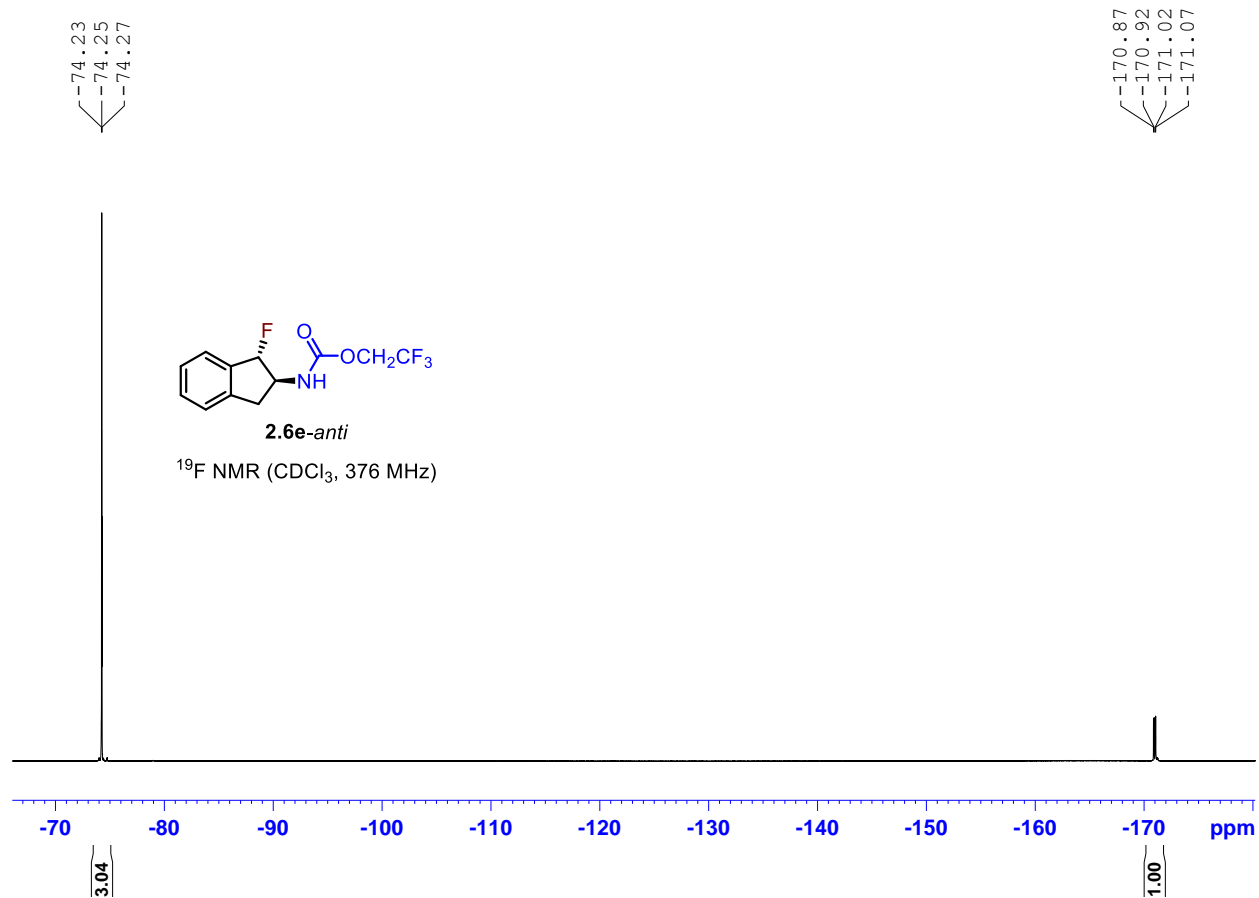
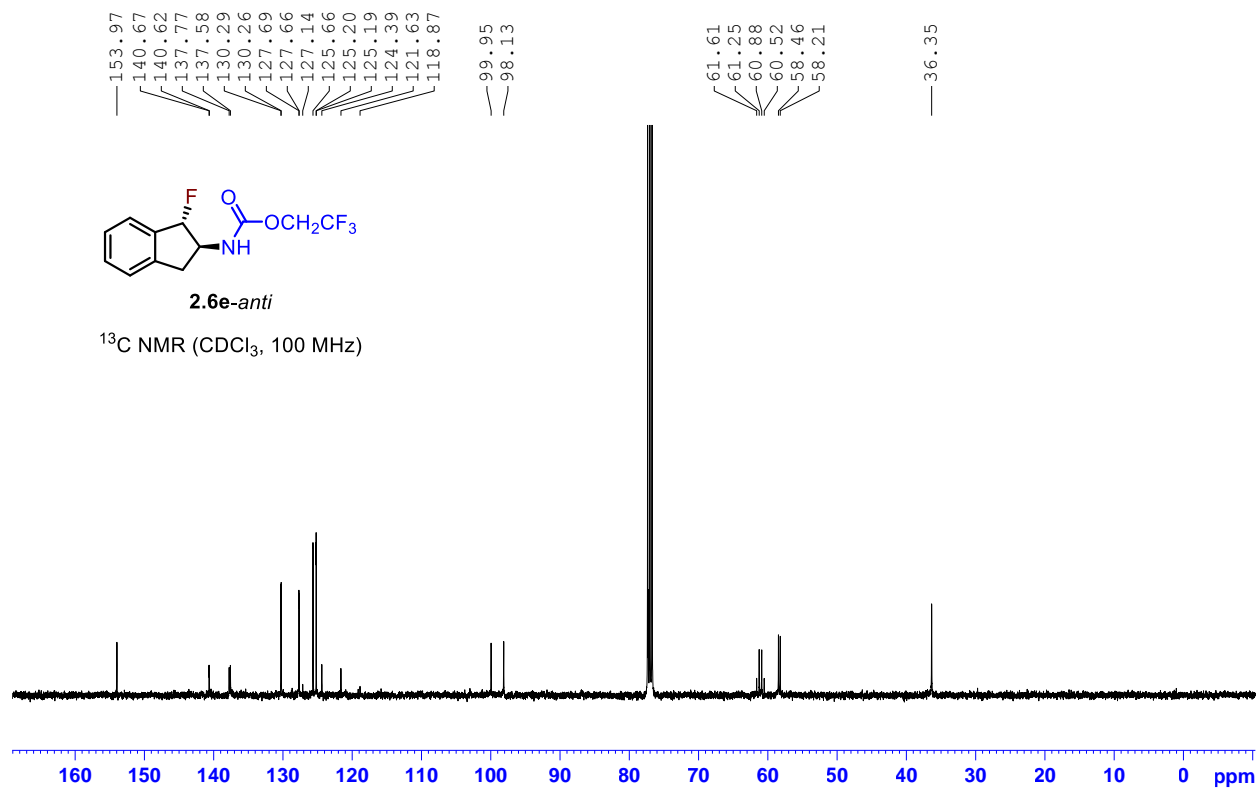


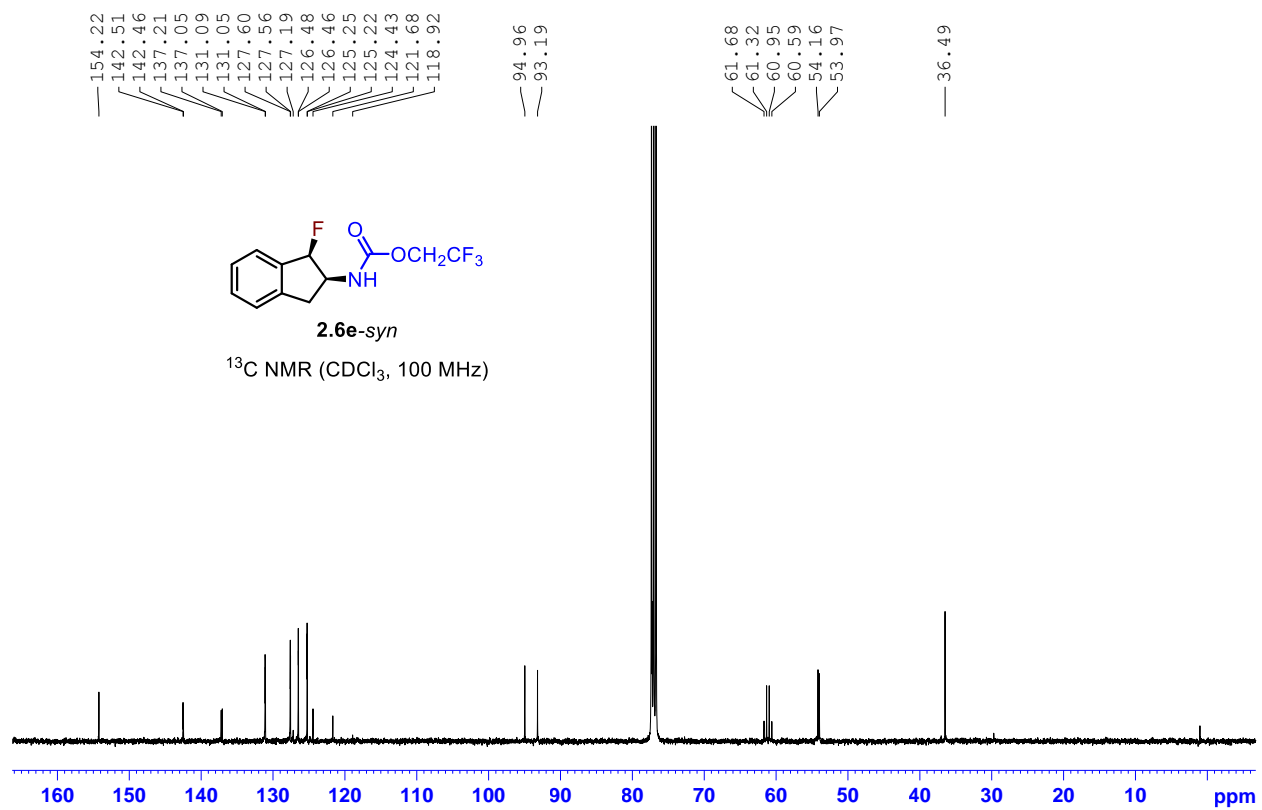
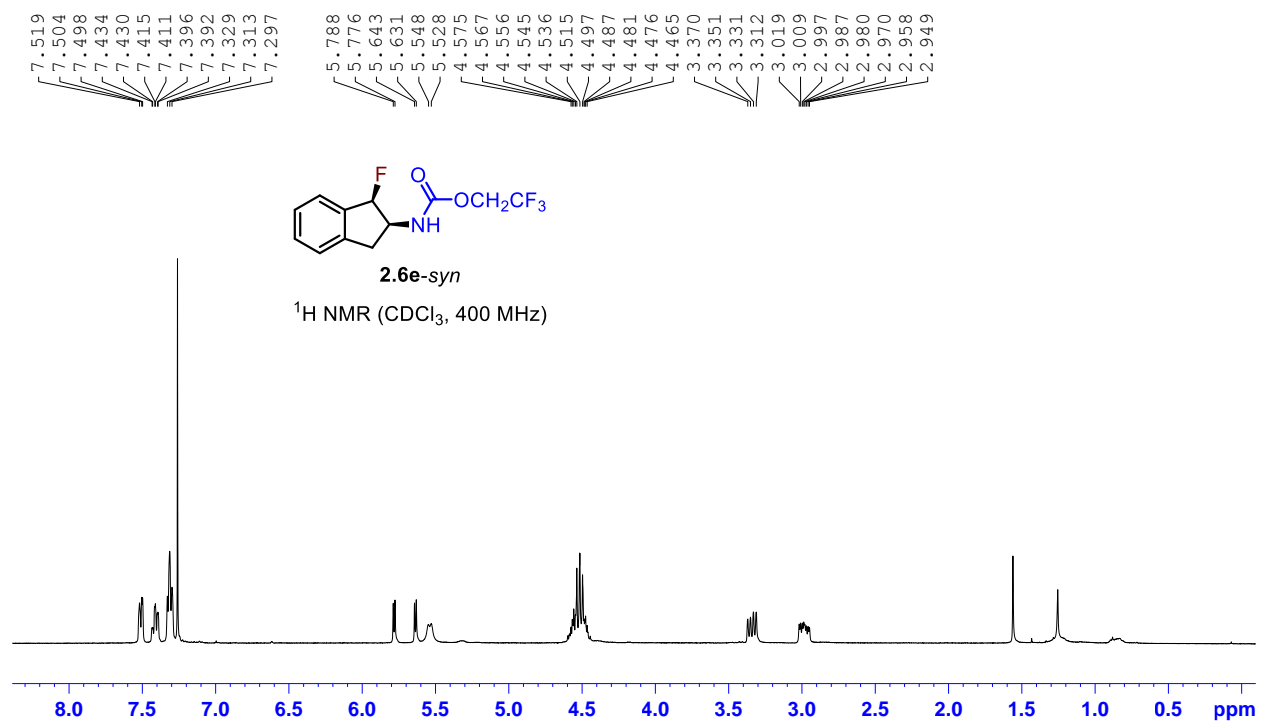


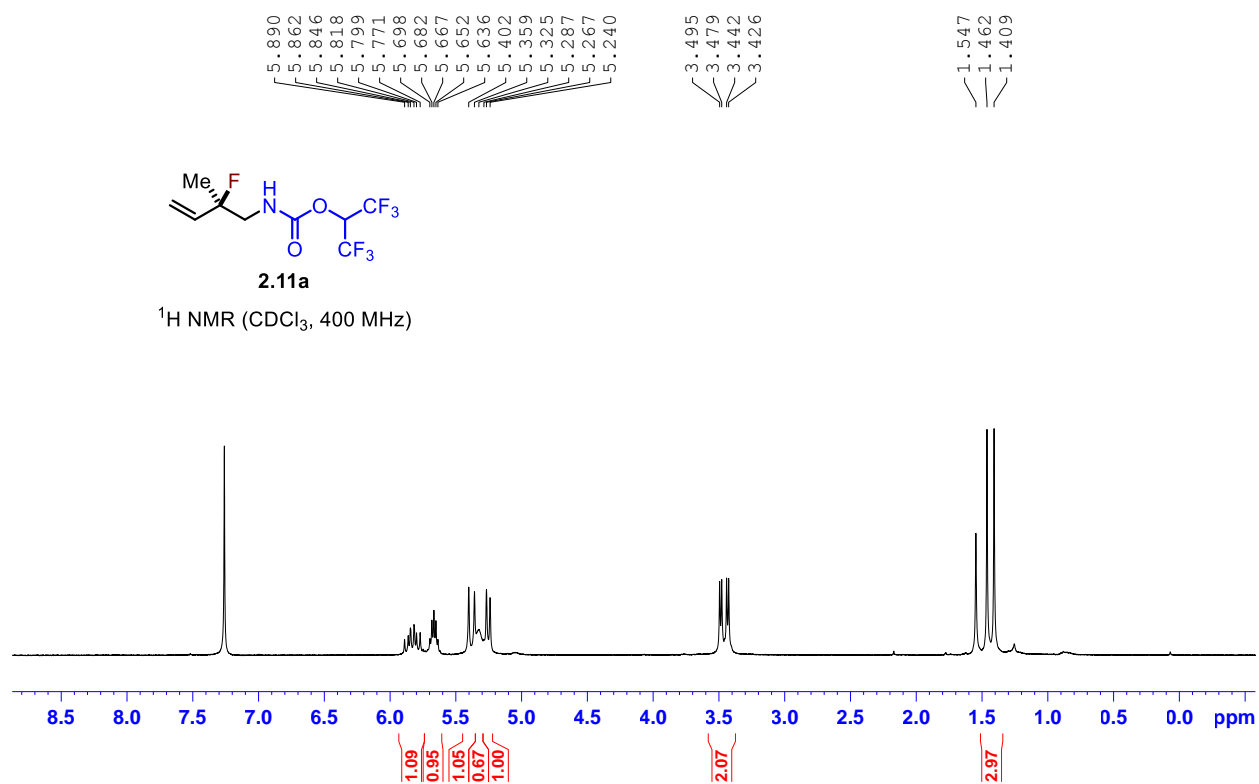
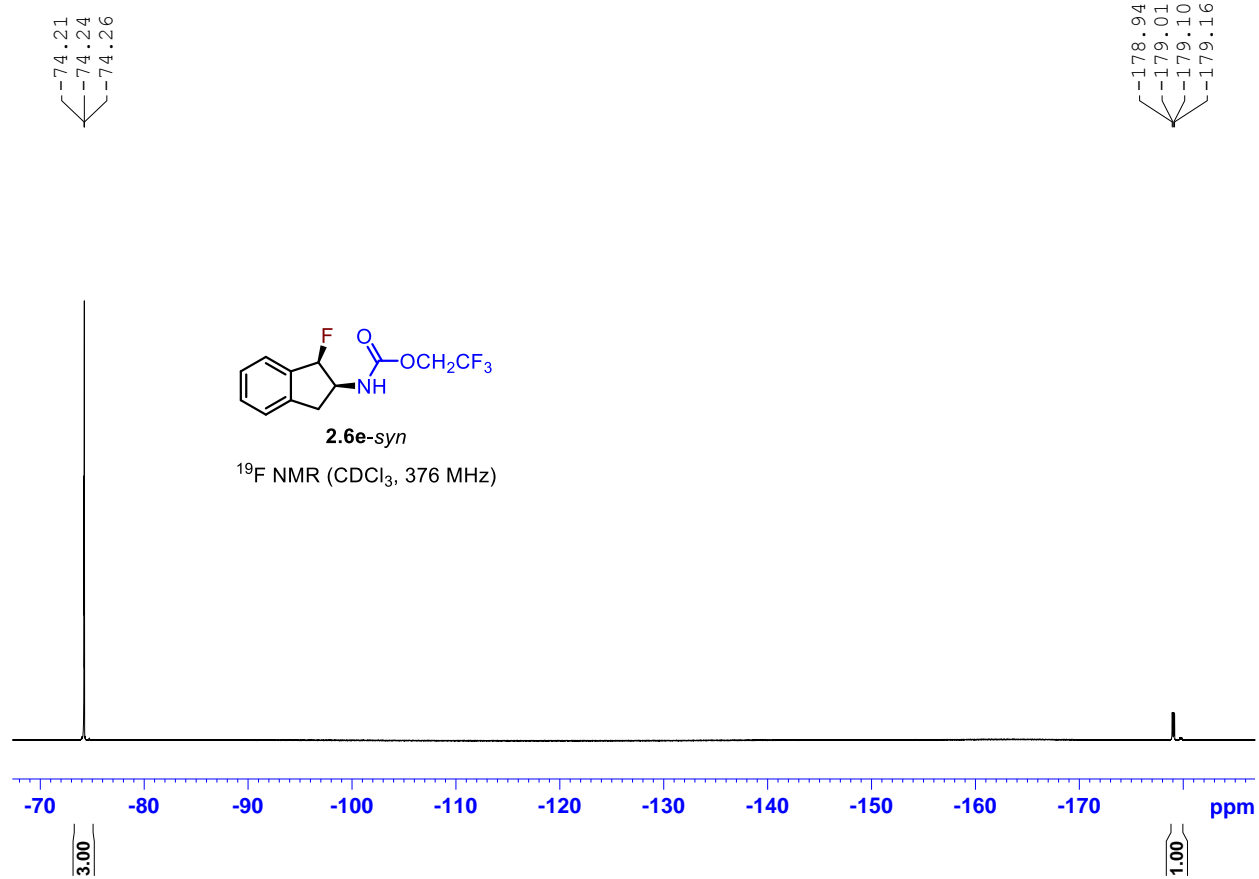


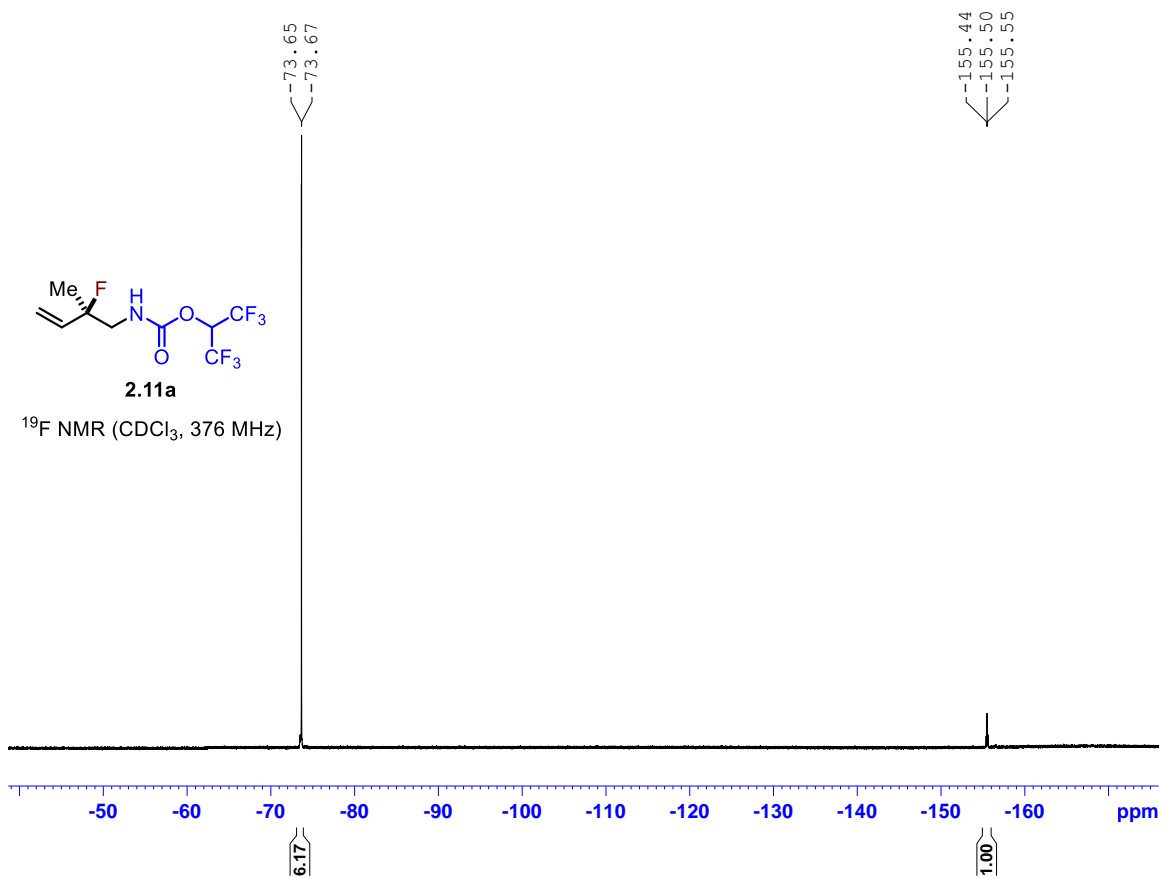
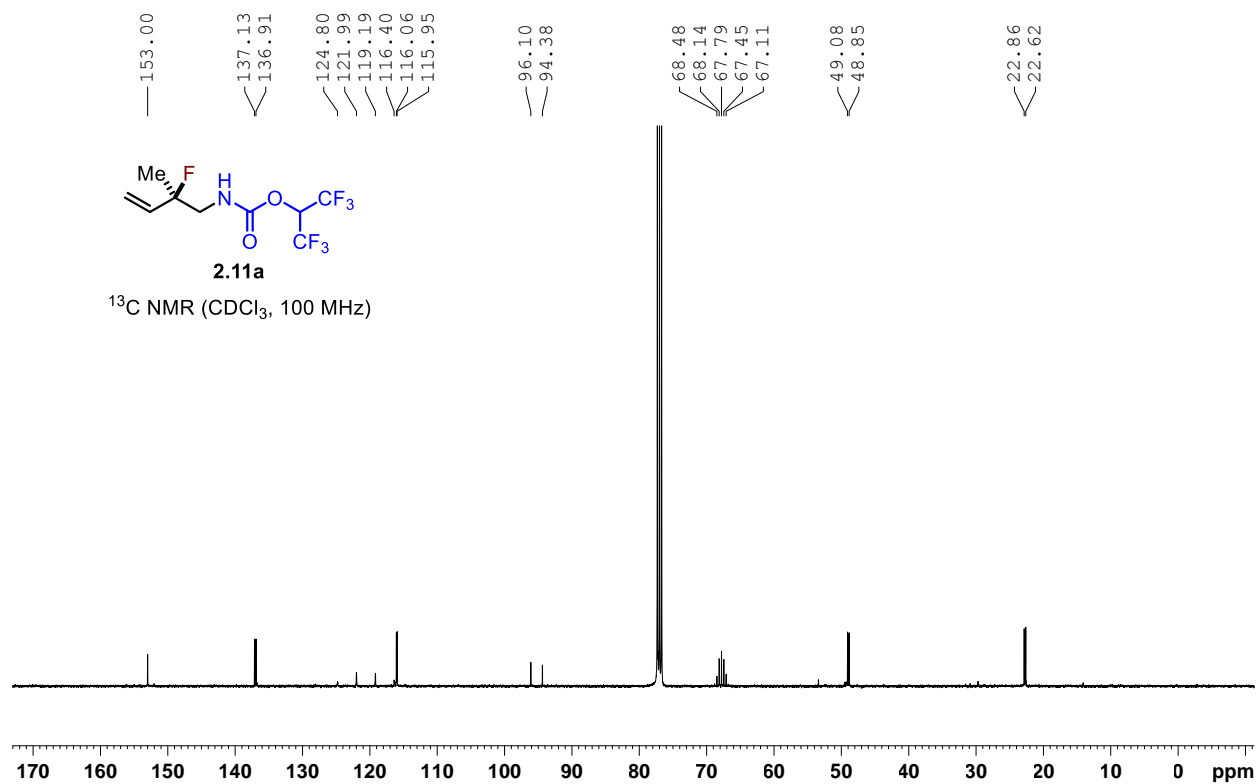


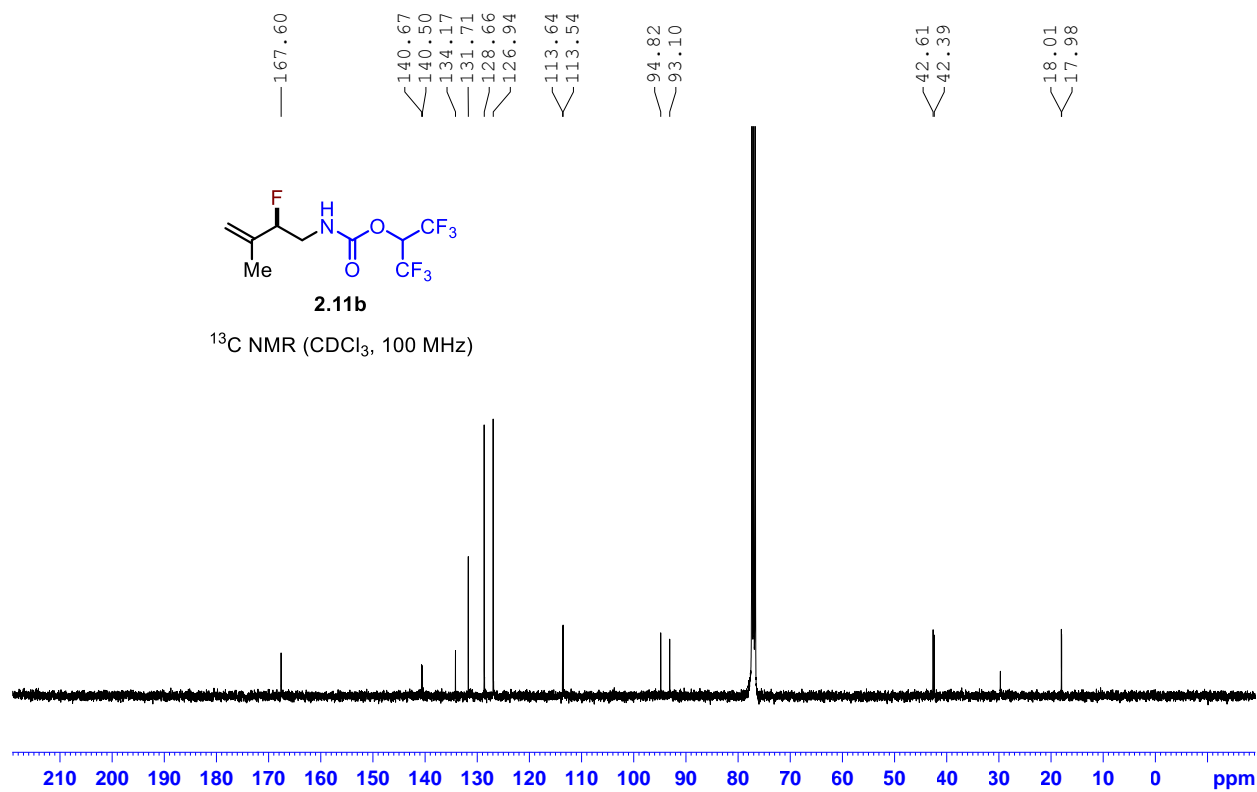
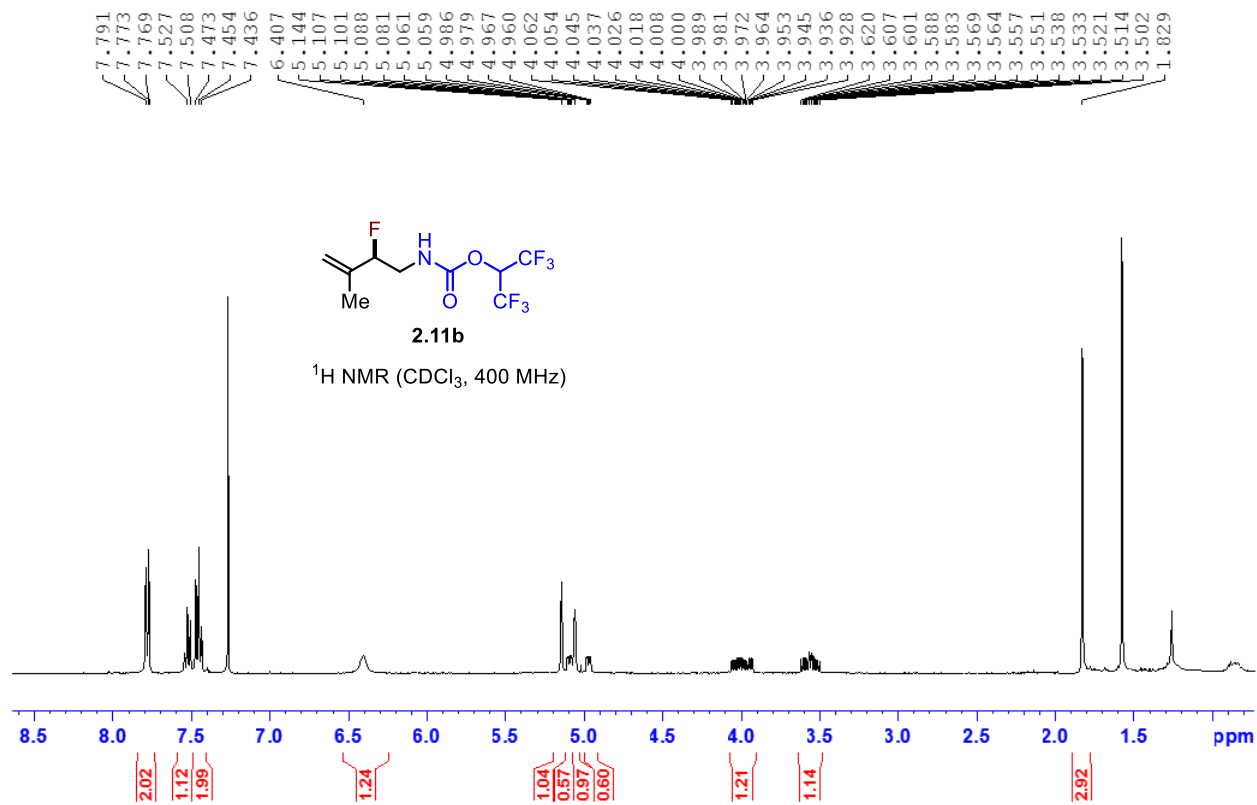


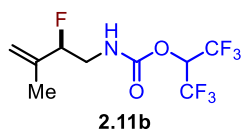




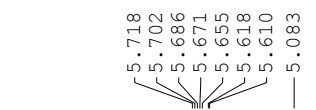
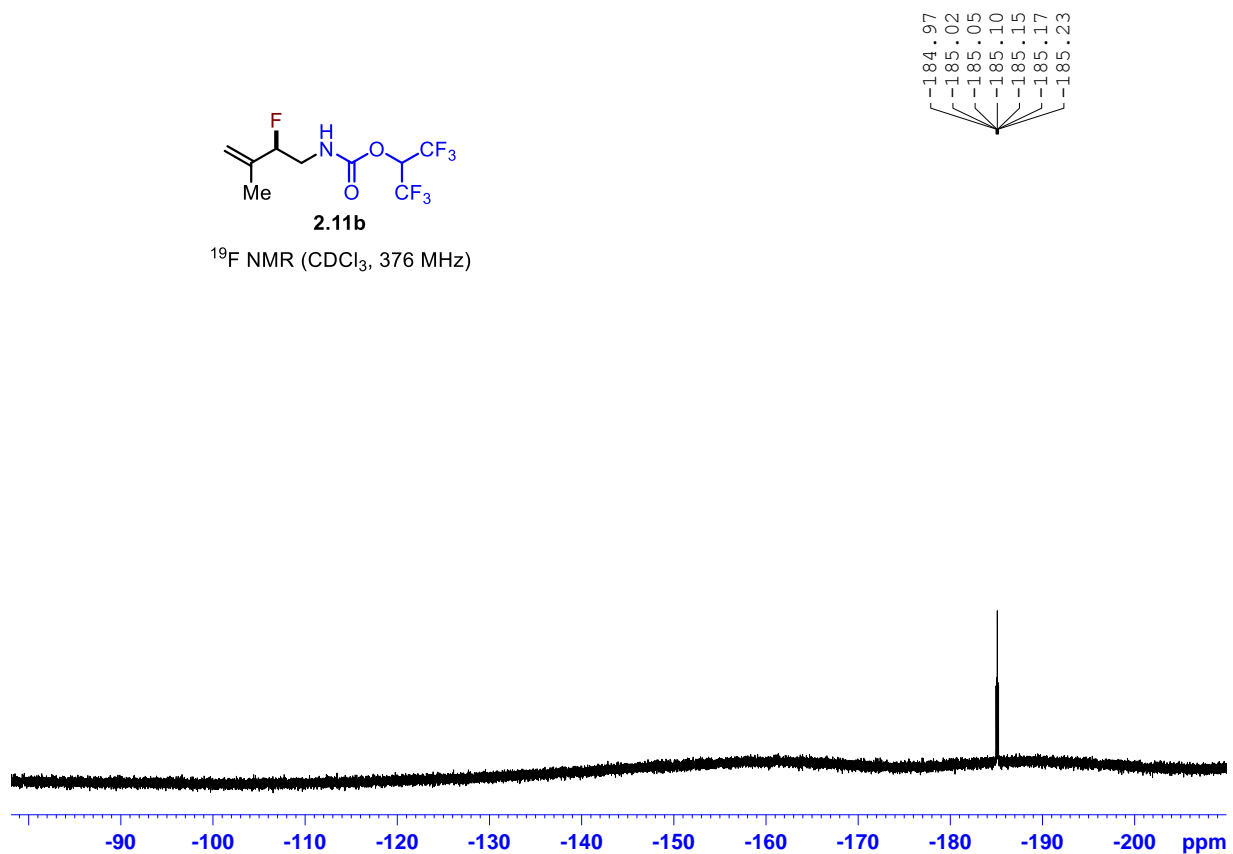




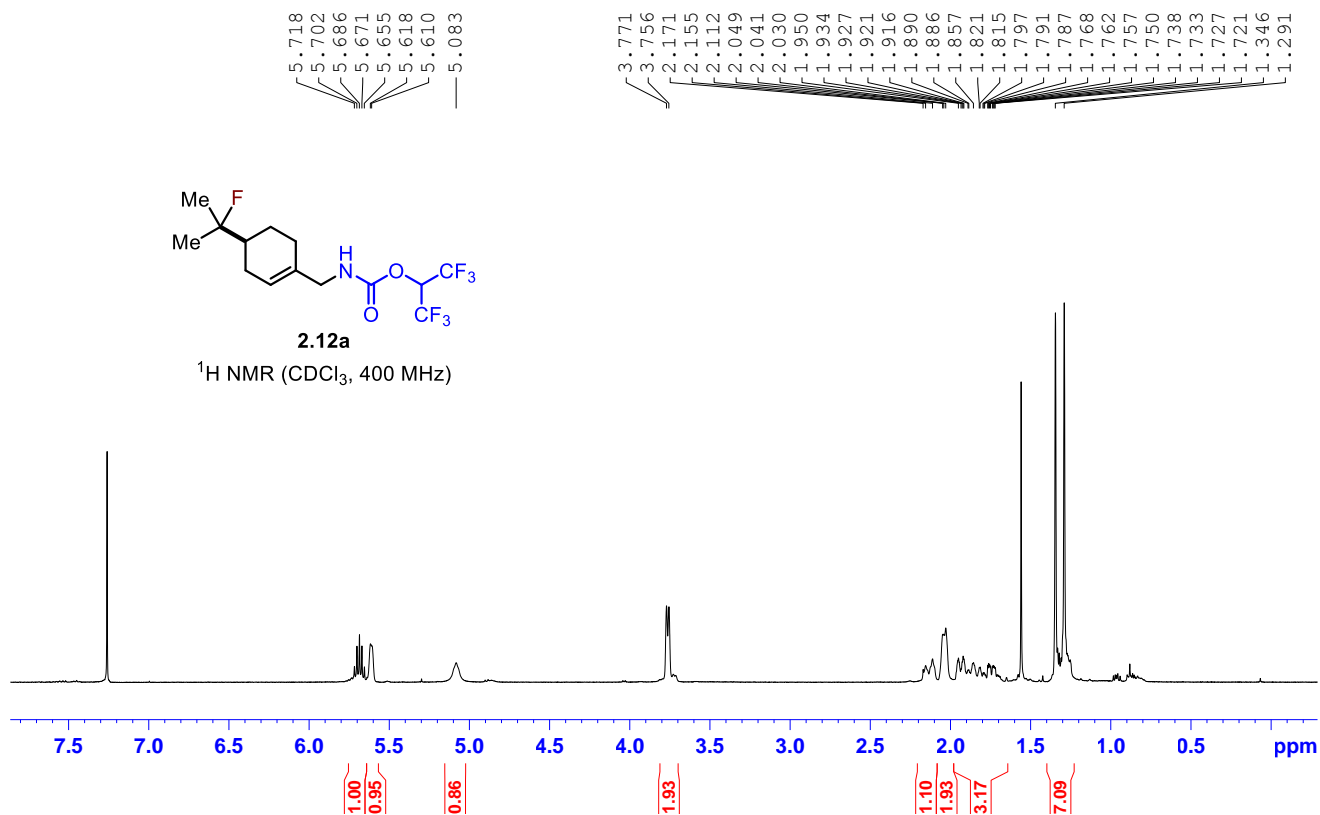


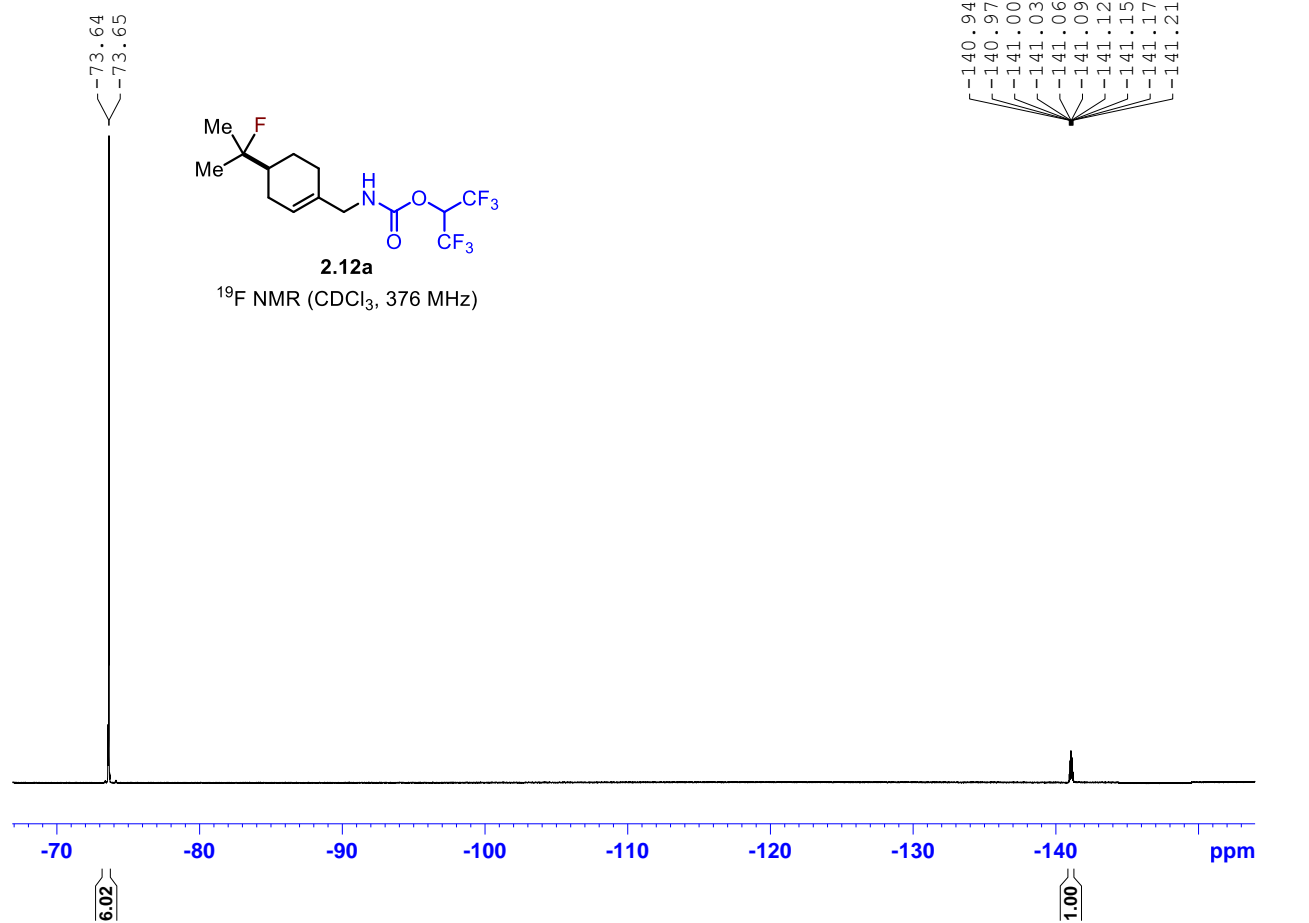
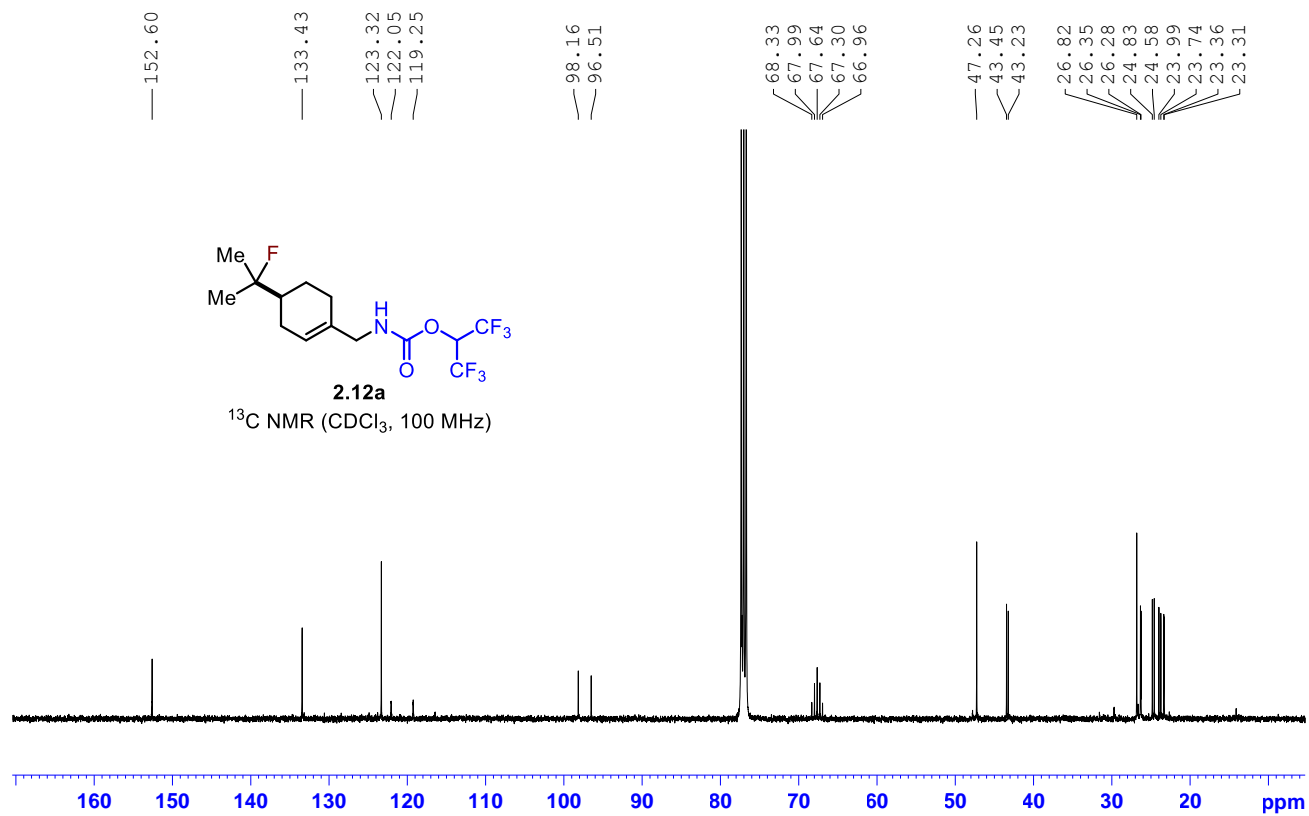


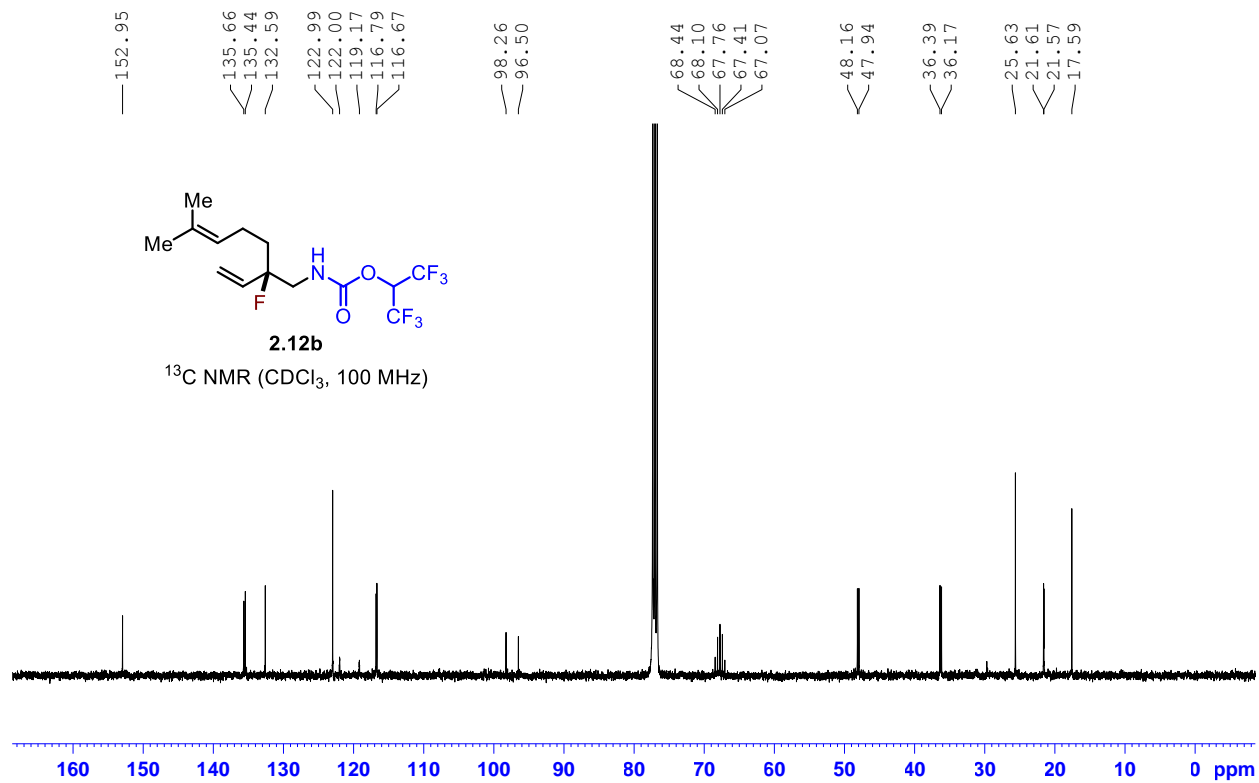
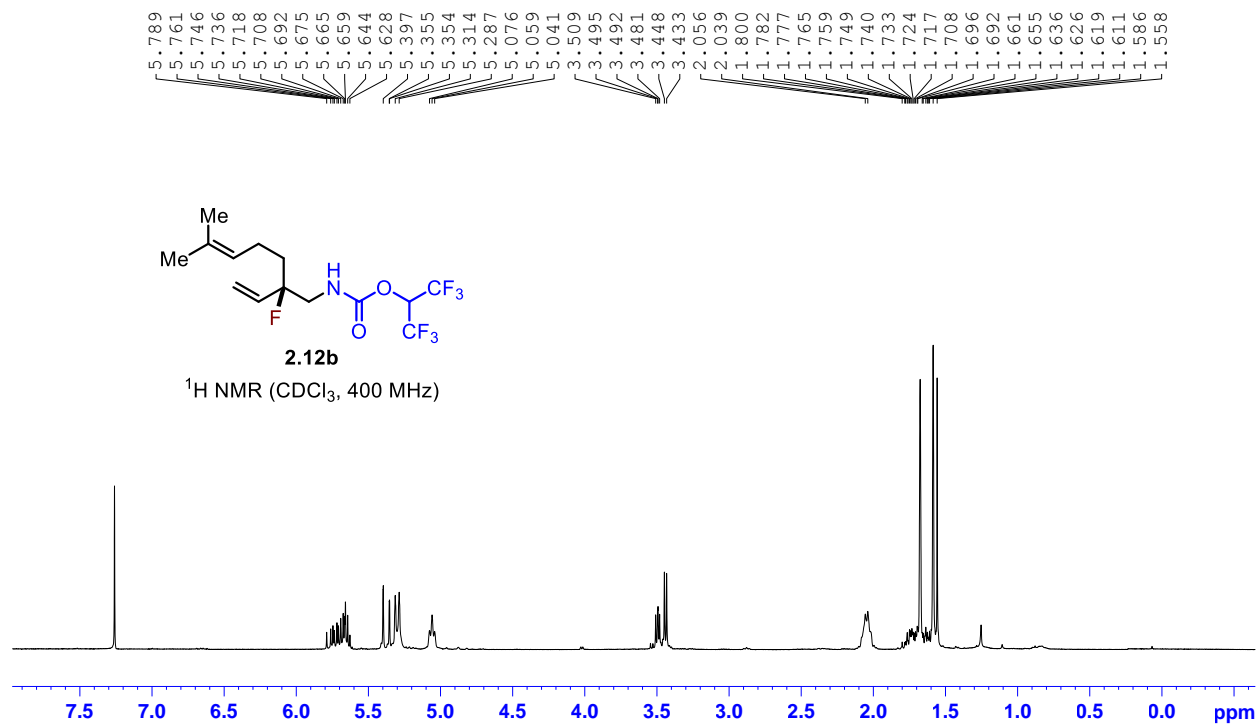
^{19}F NMR (CDCl_3 , 376 MHz)

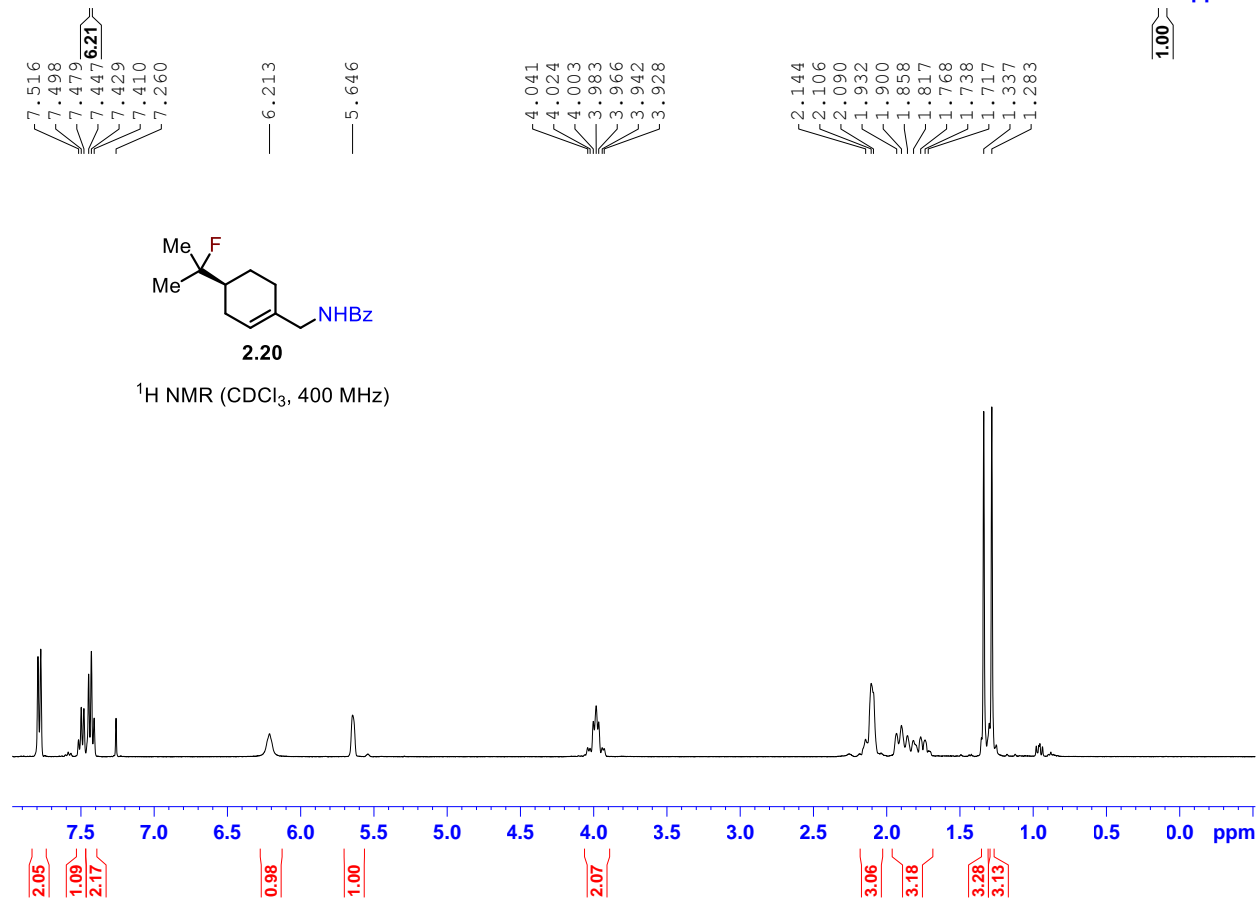
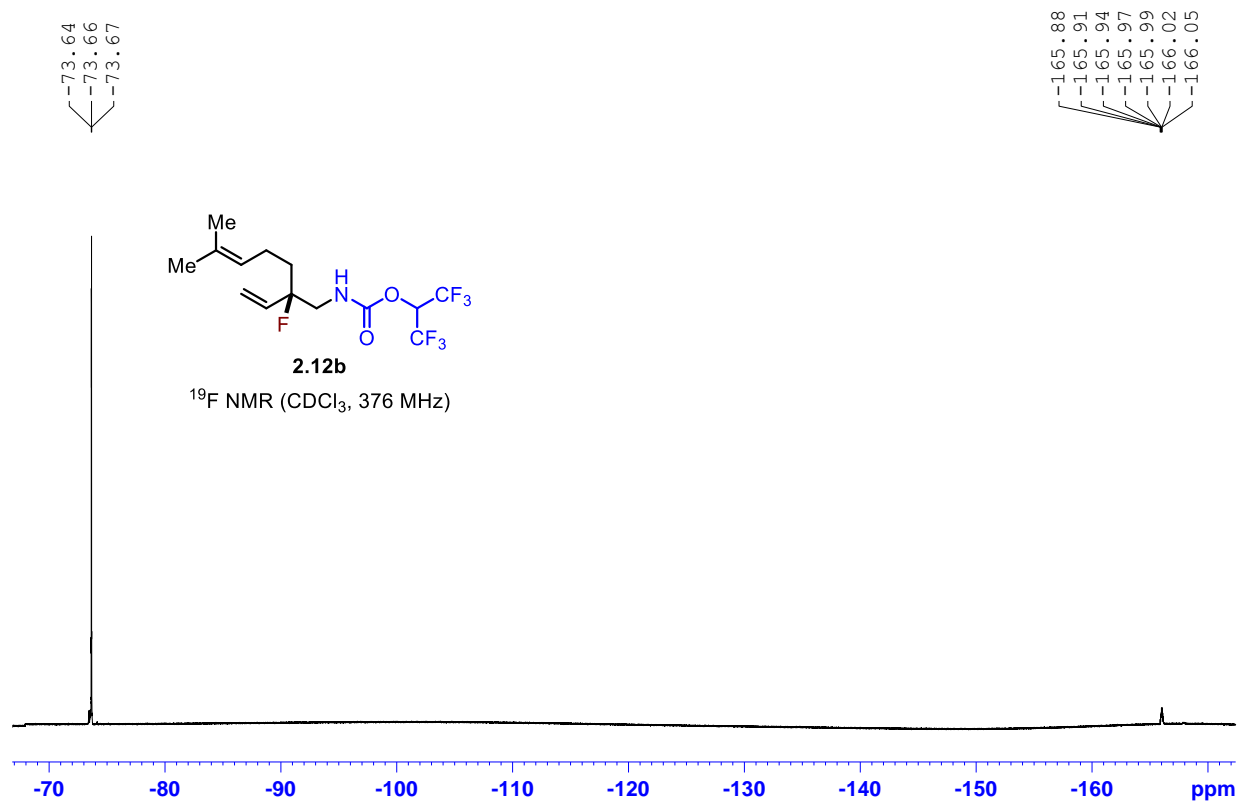


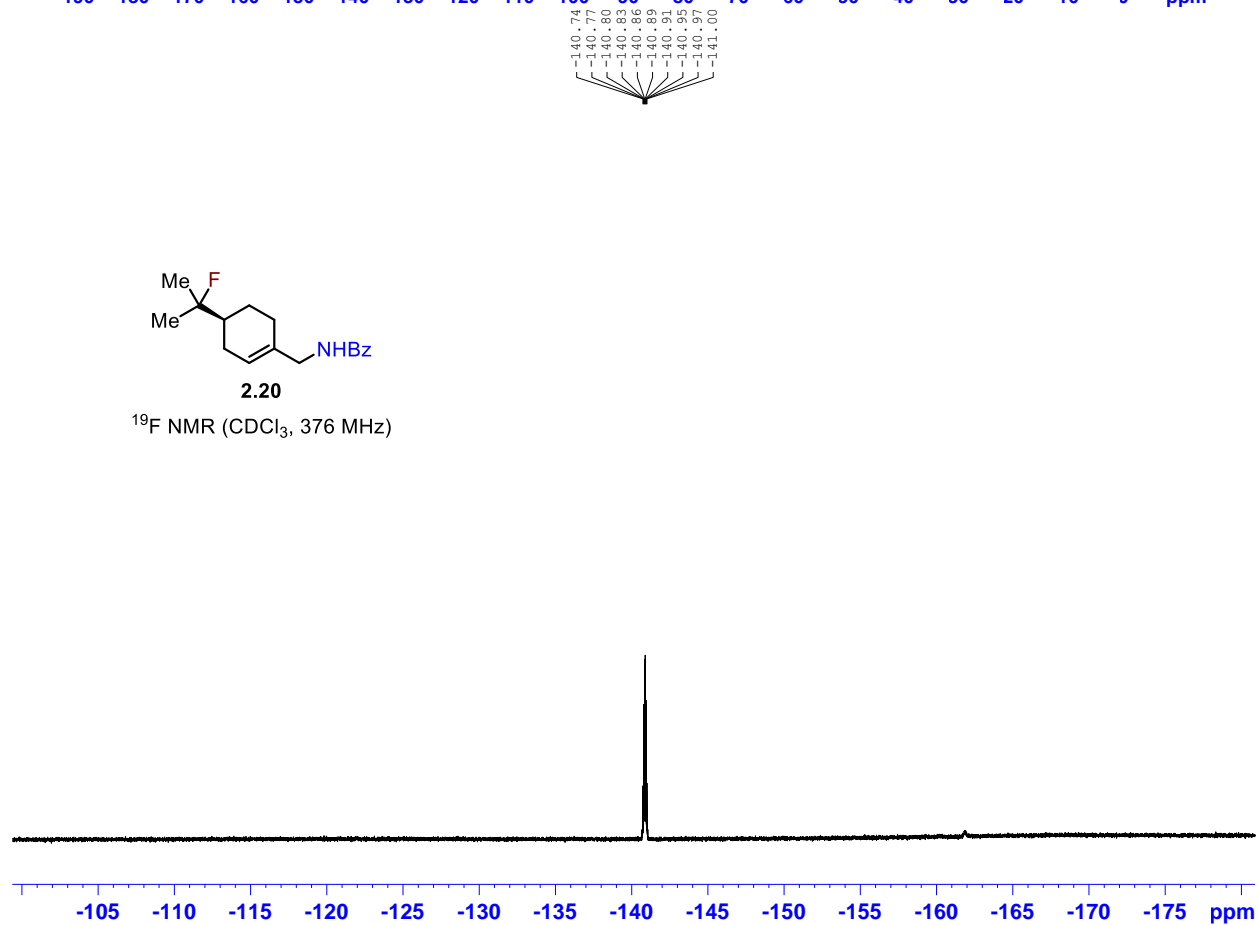
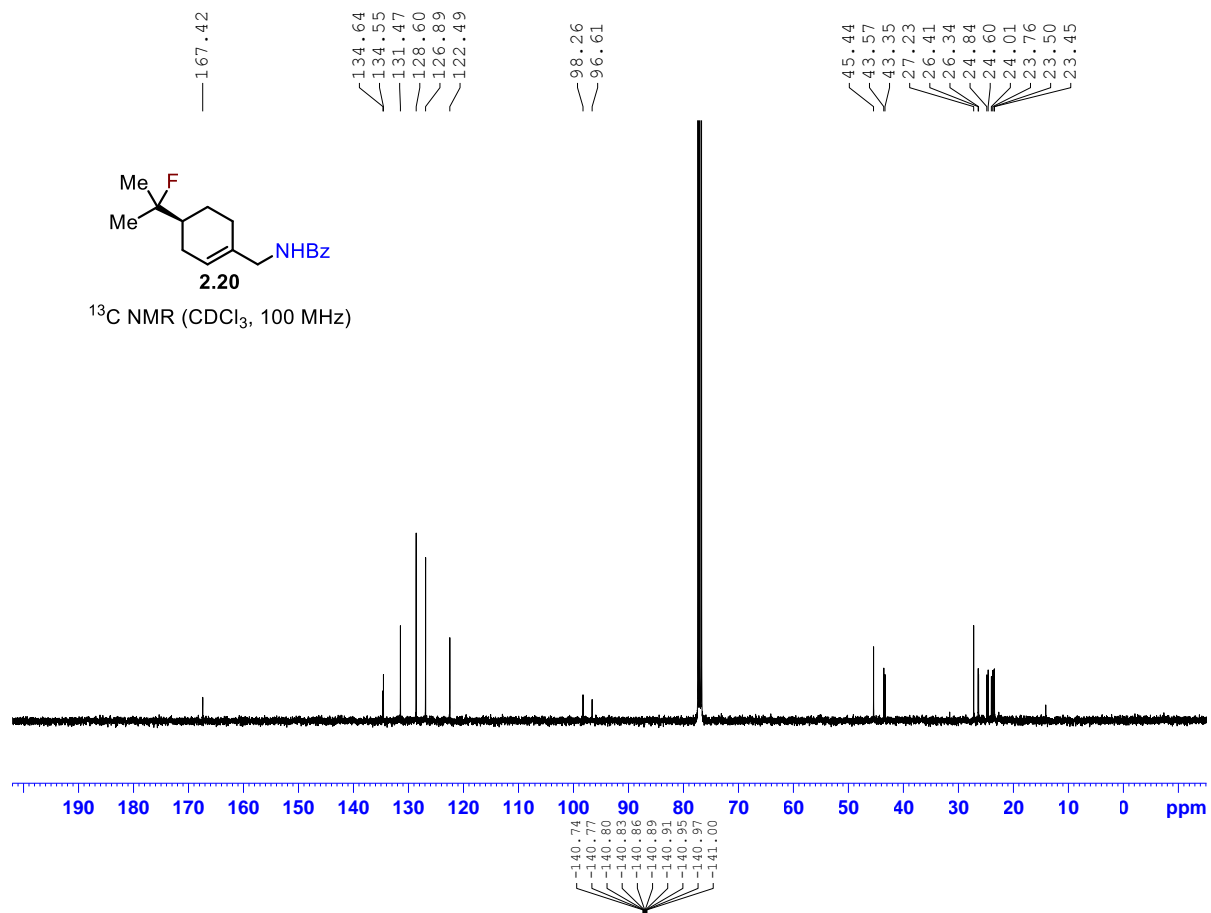
^1H NMR (CDCl_3 , 400 MHz)

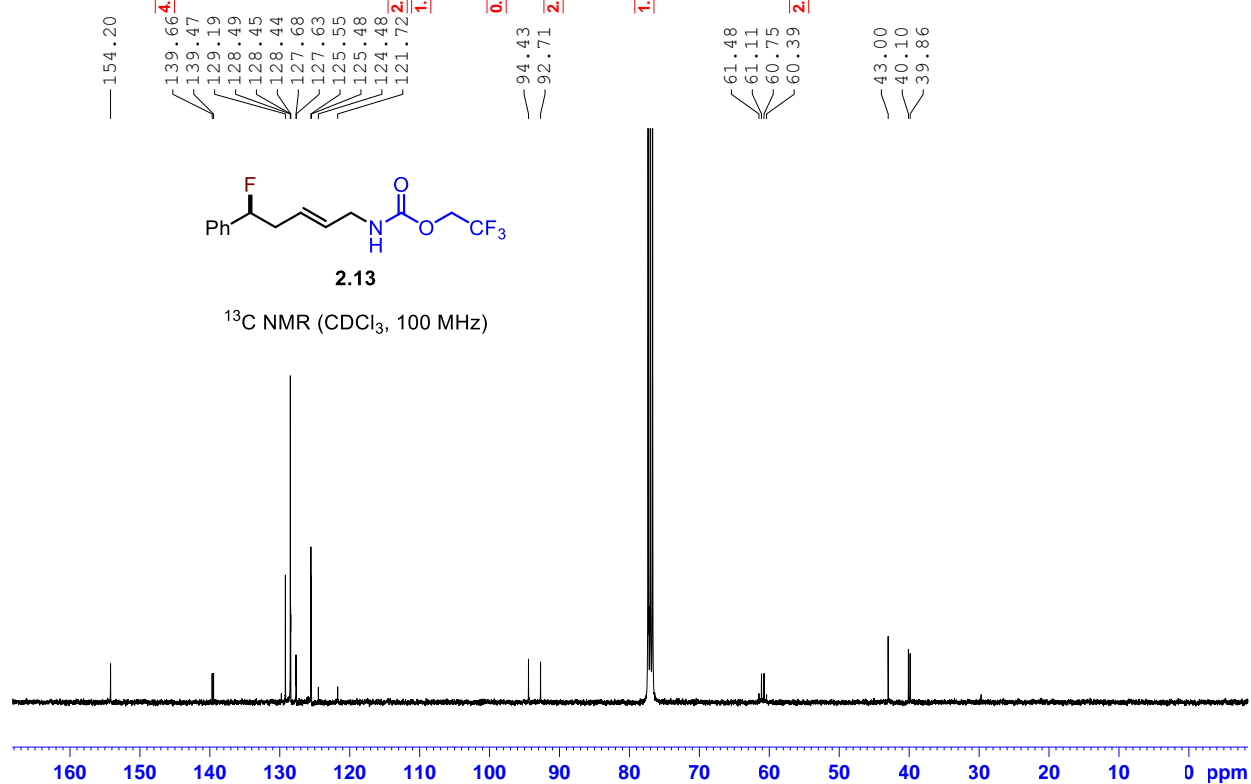
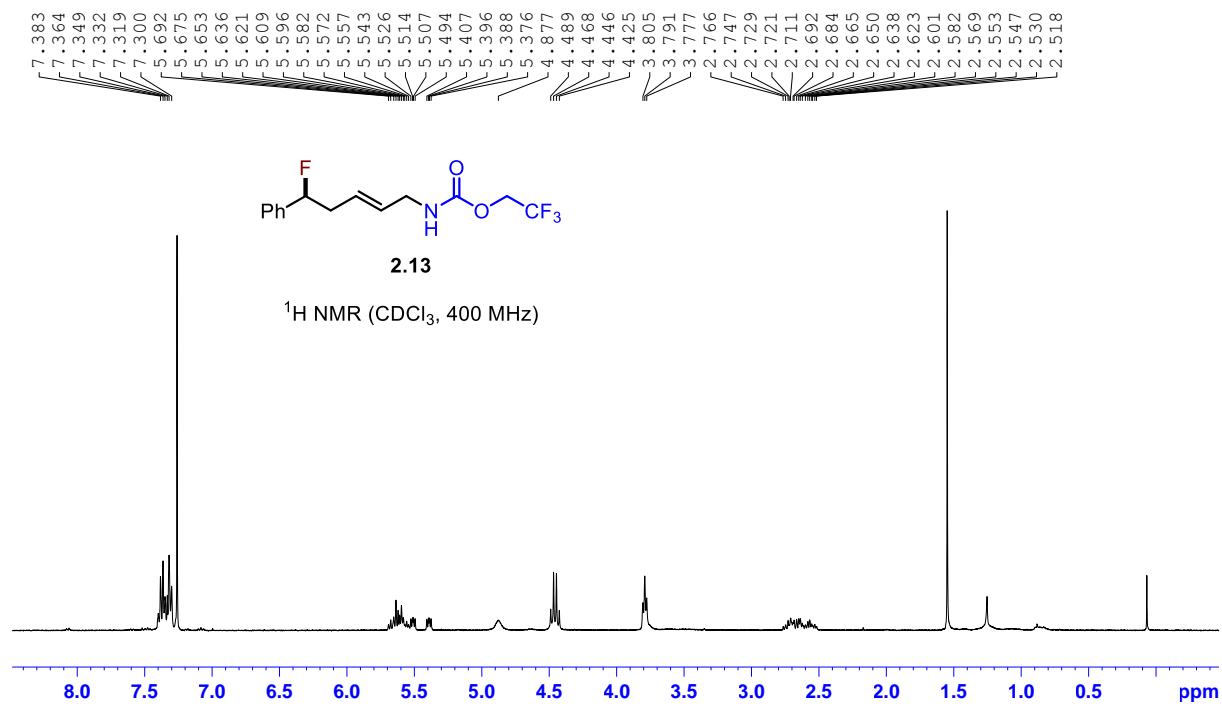


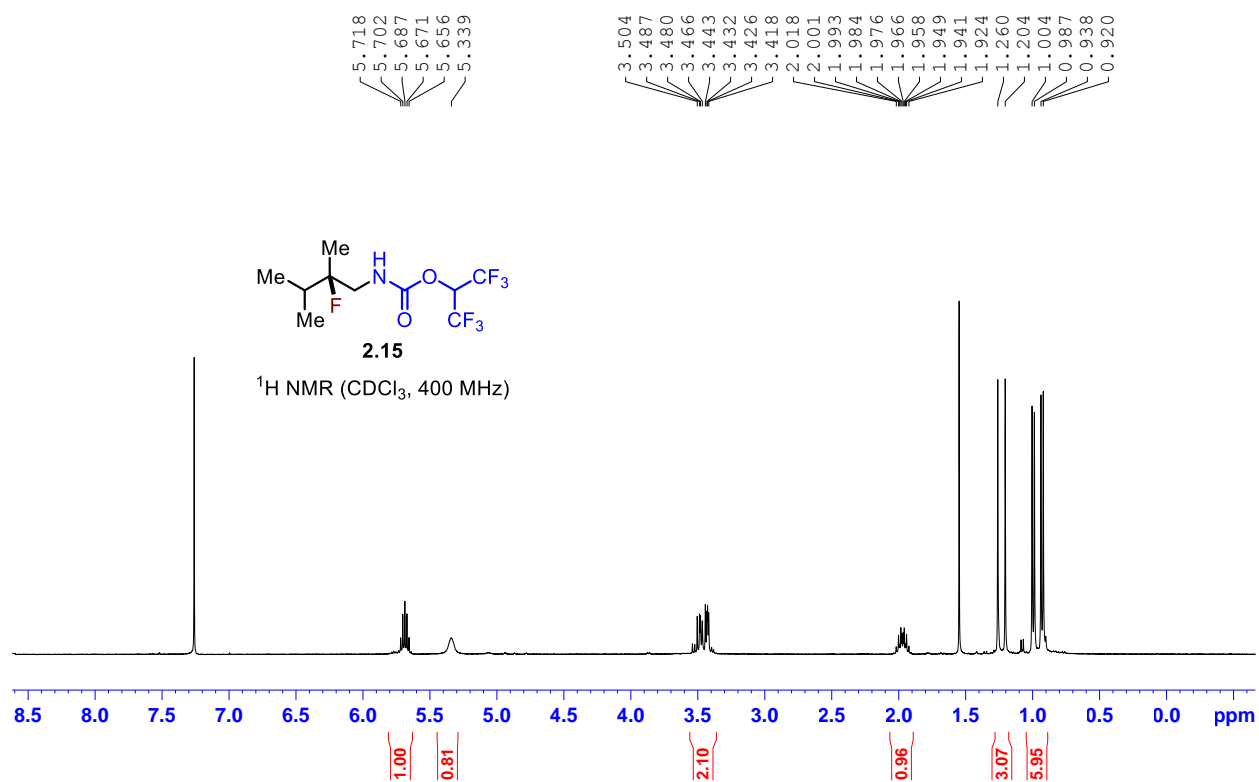
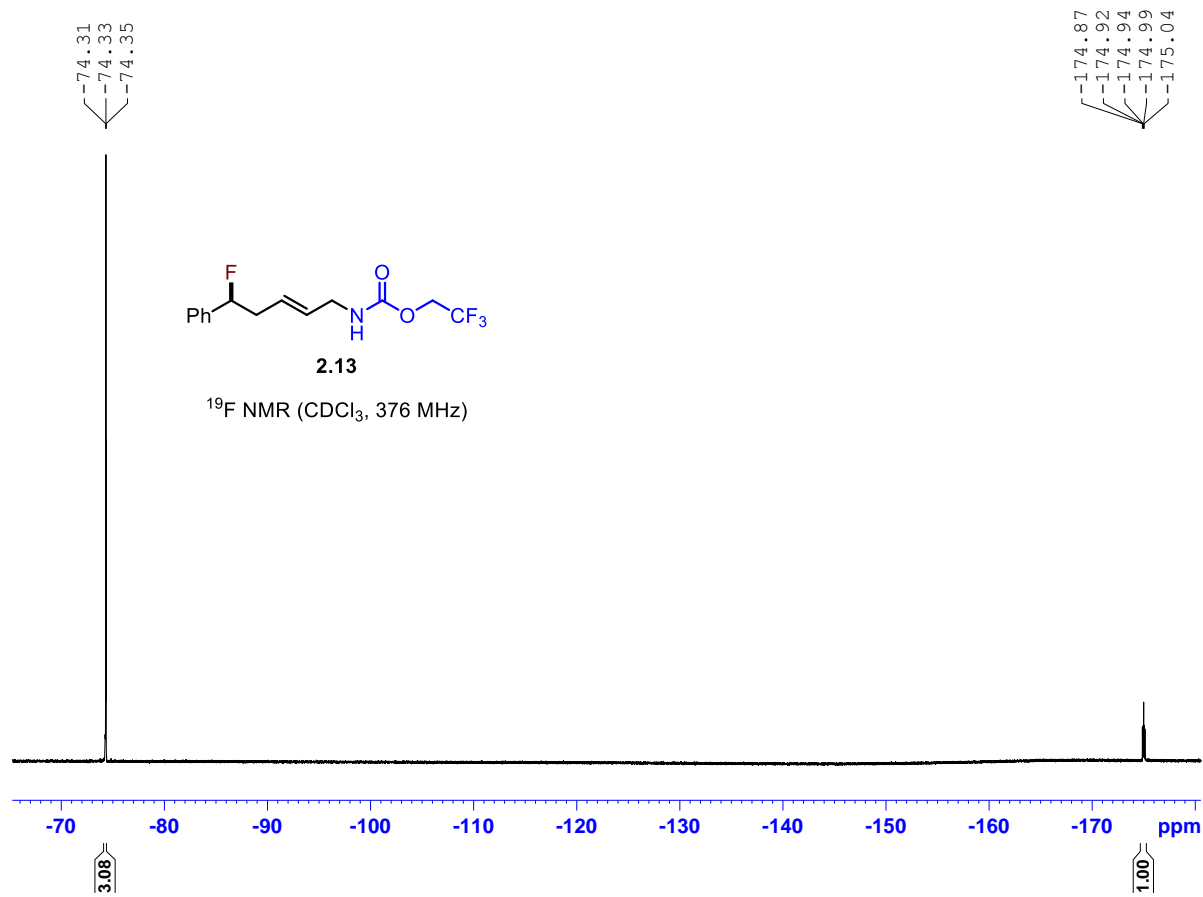


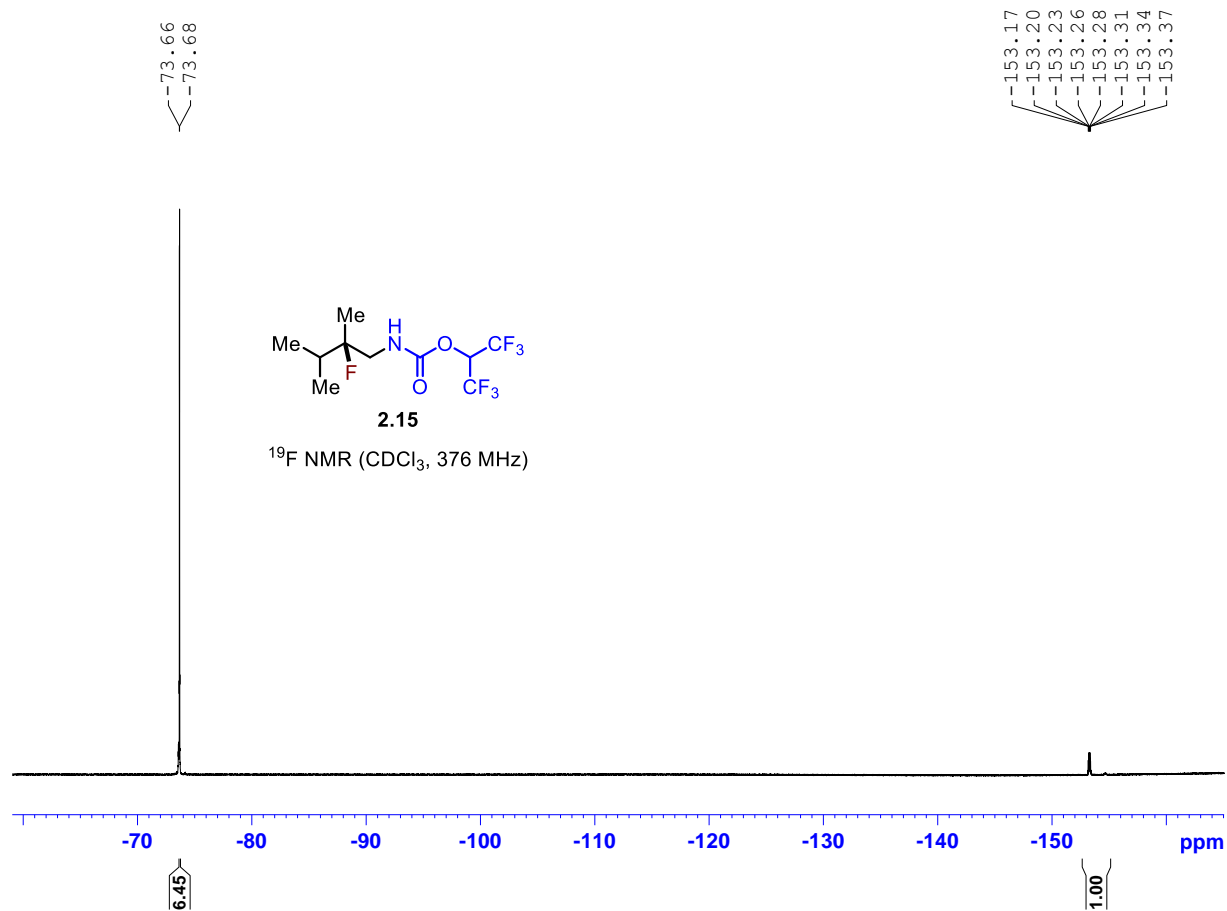
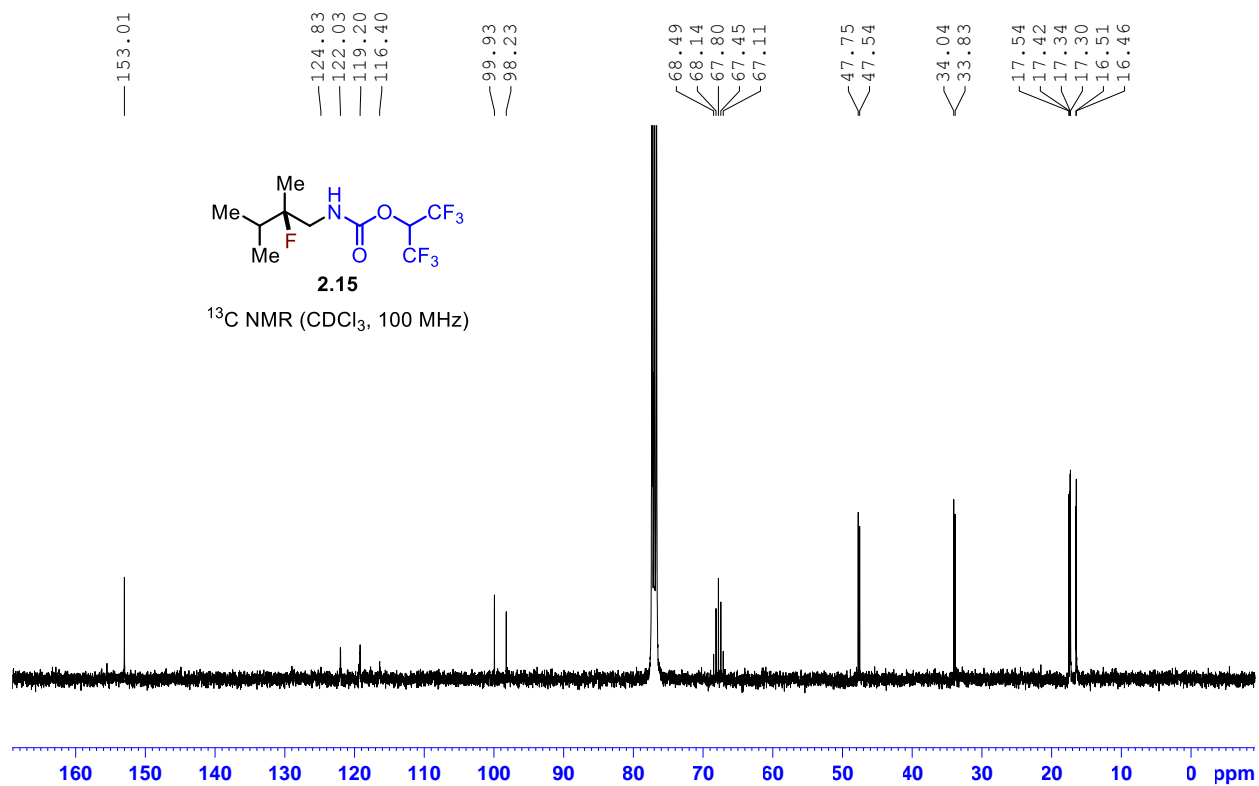


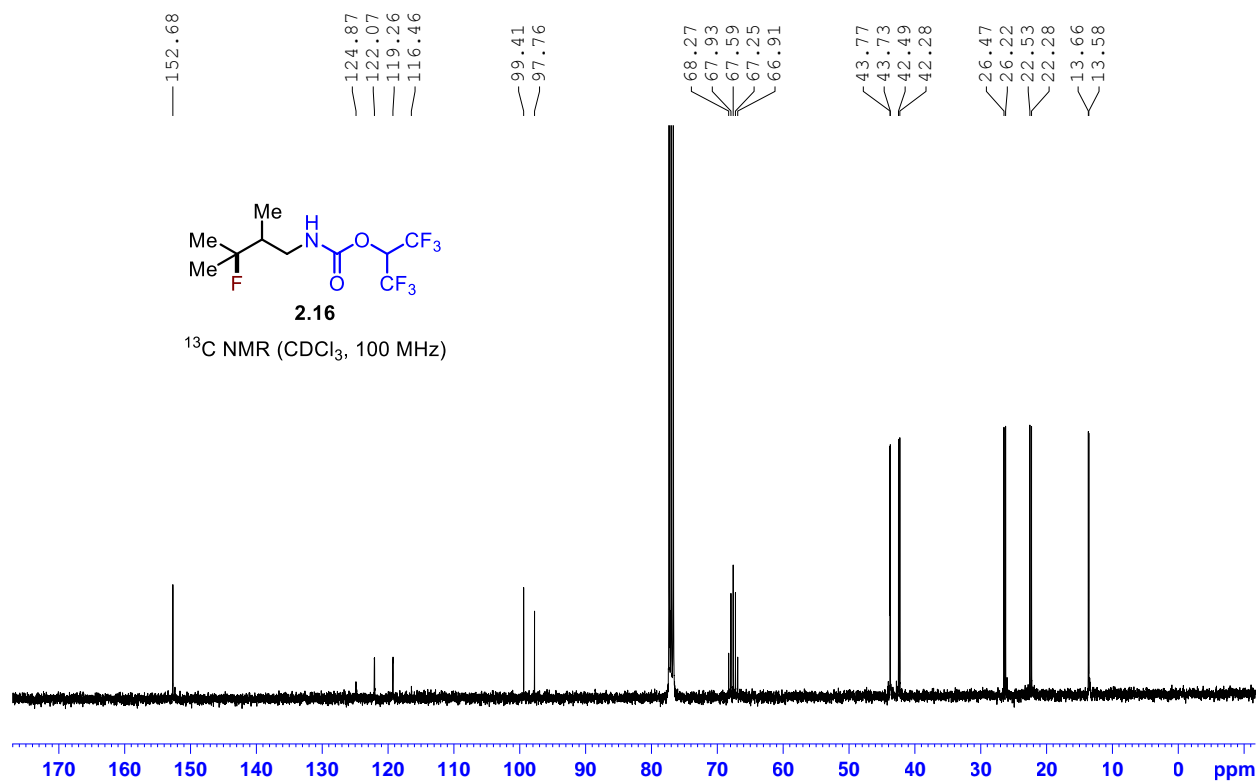
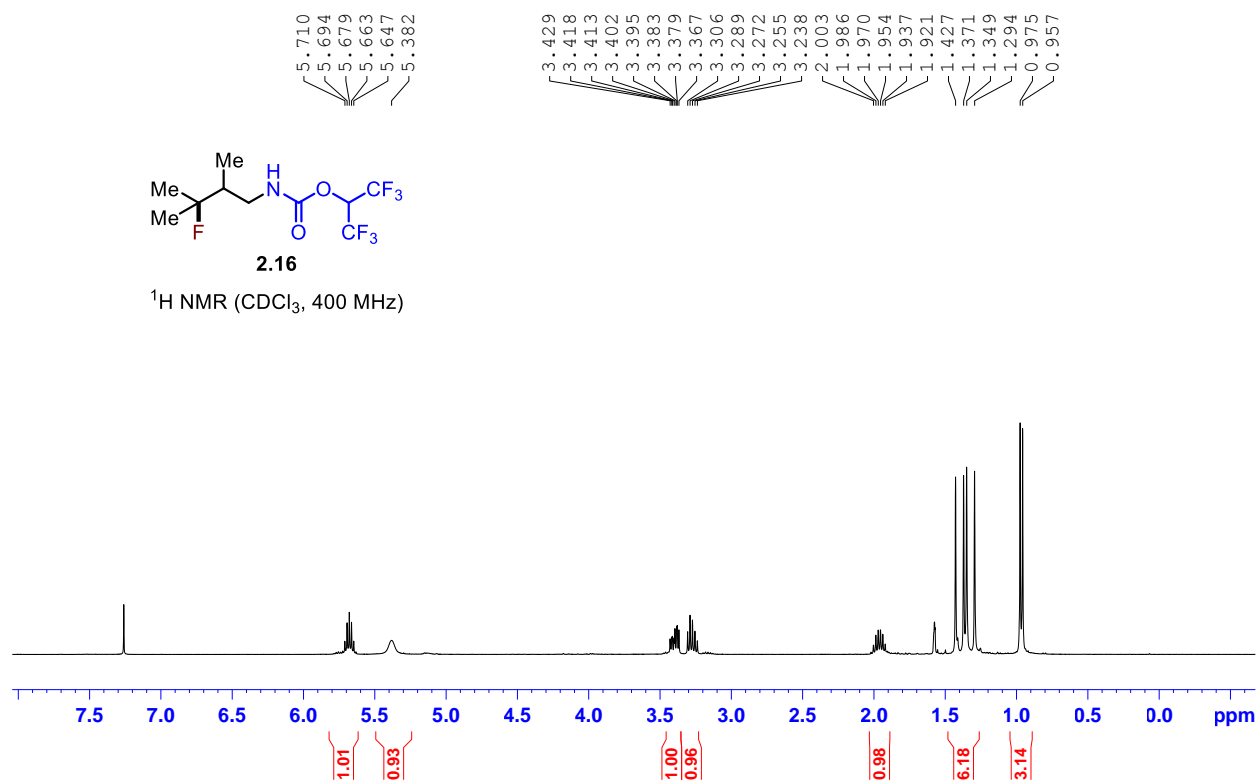


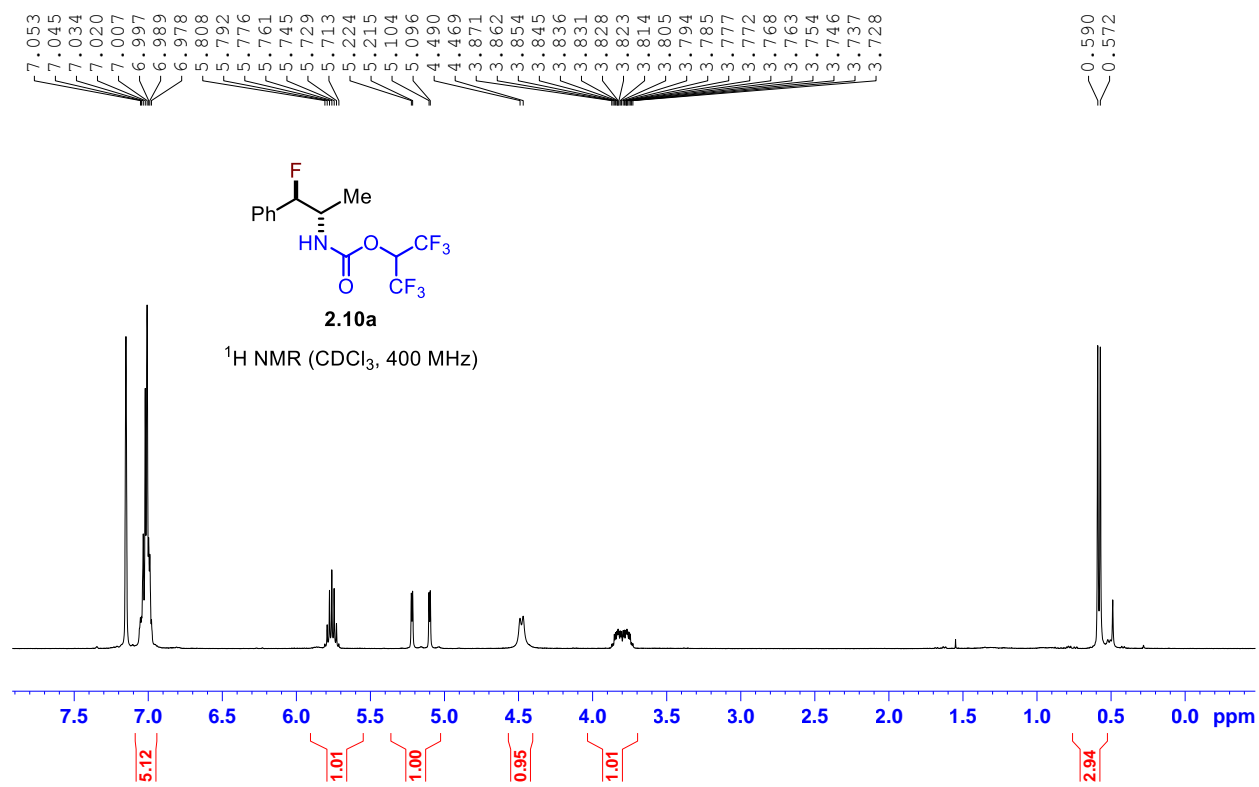
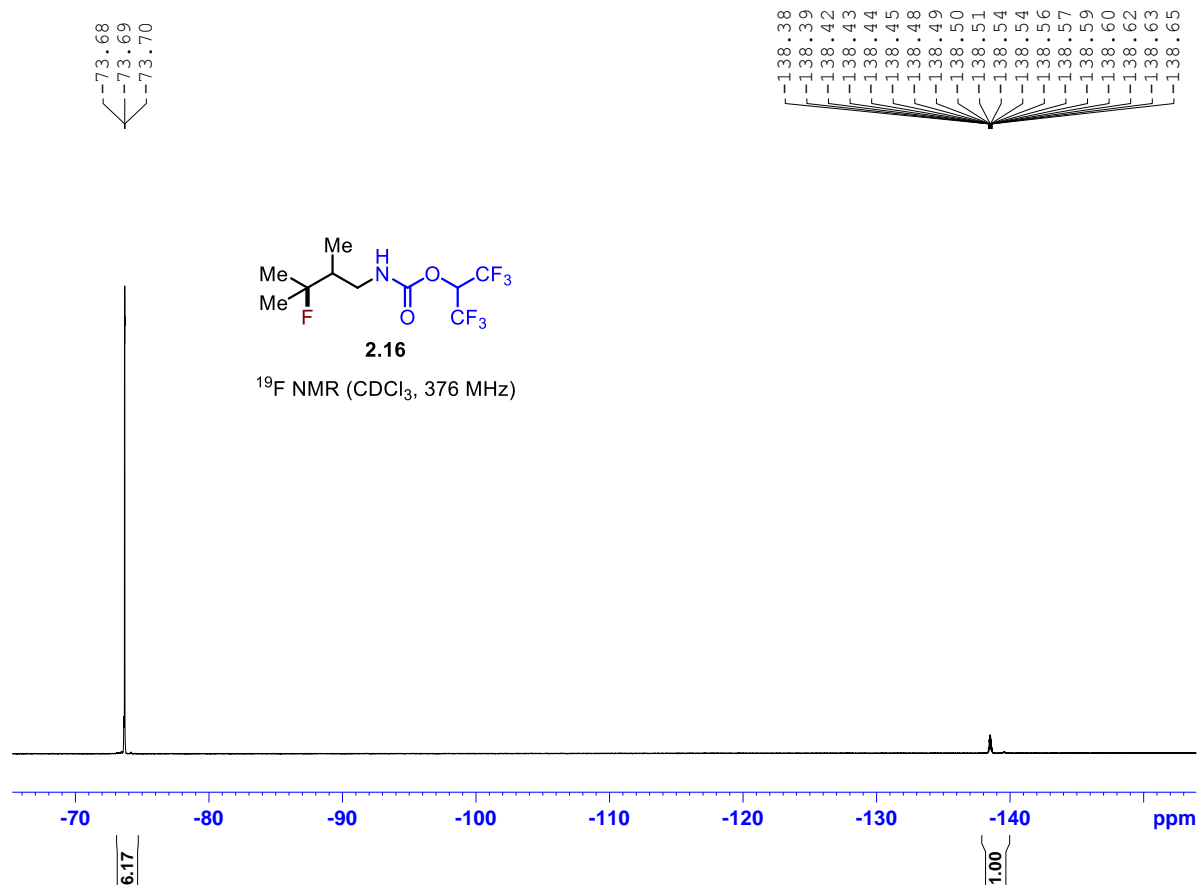


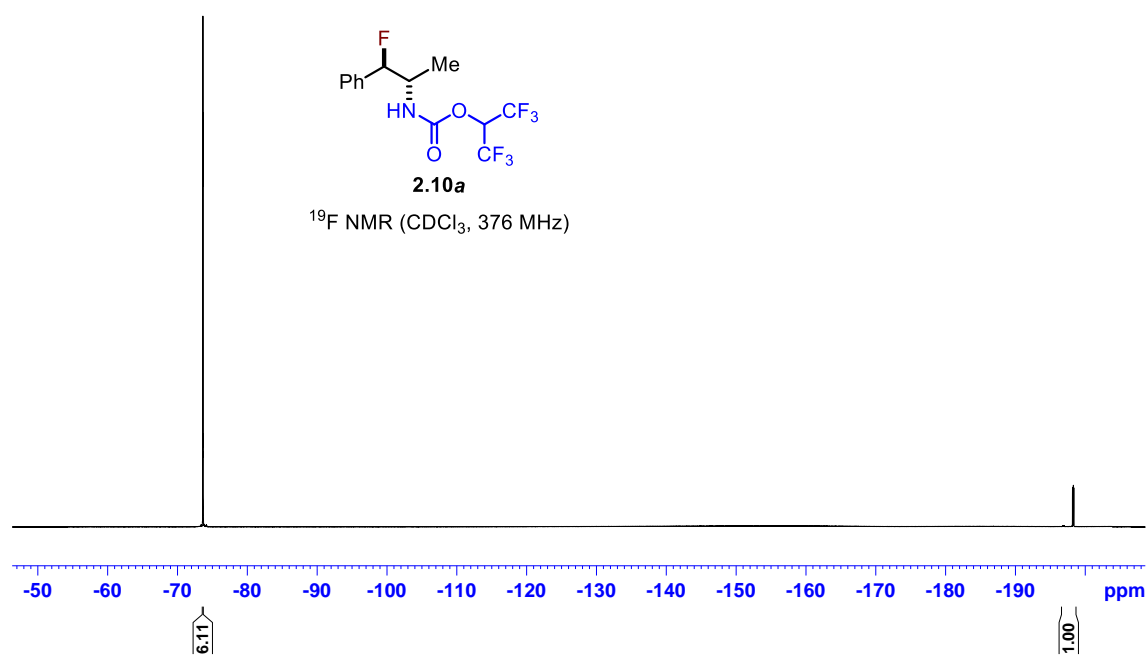
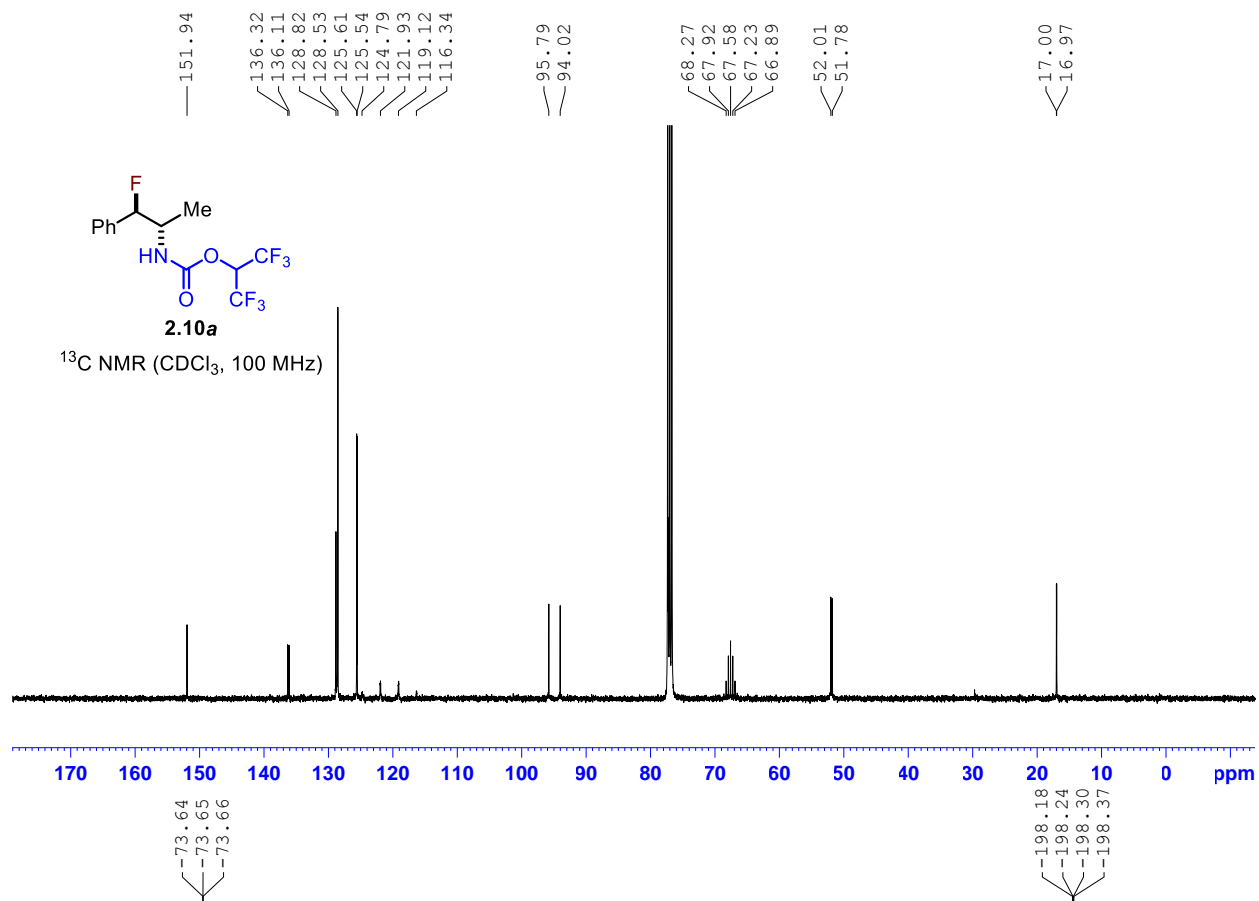


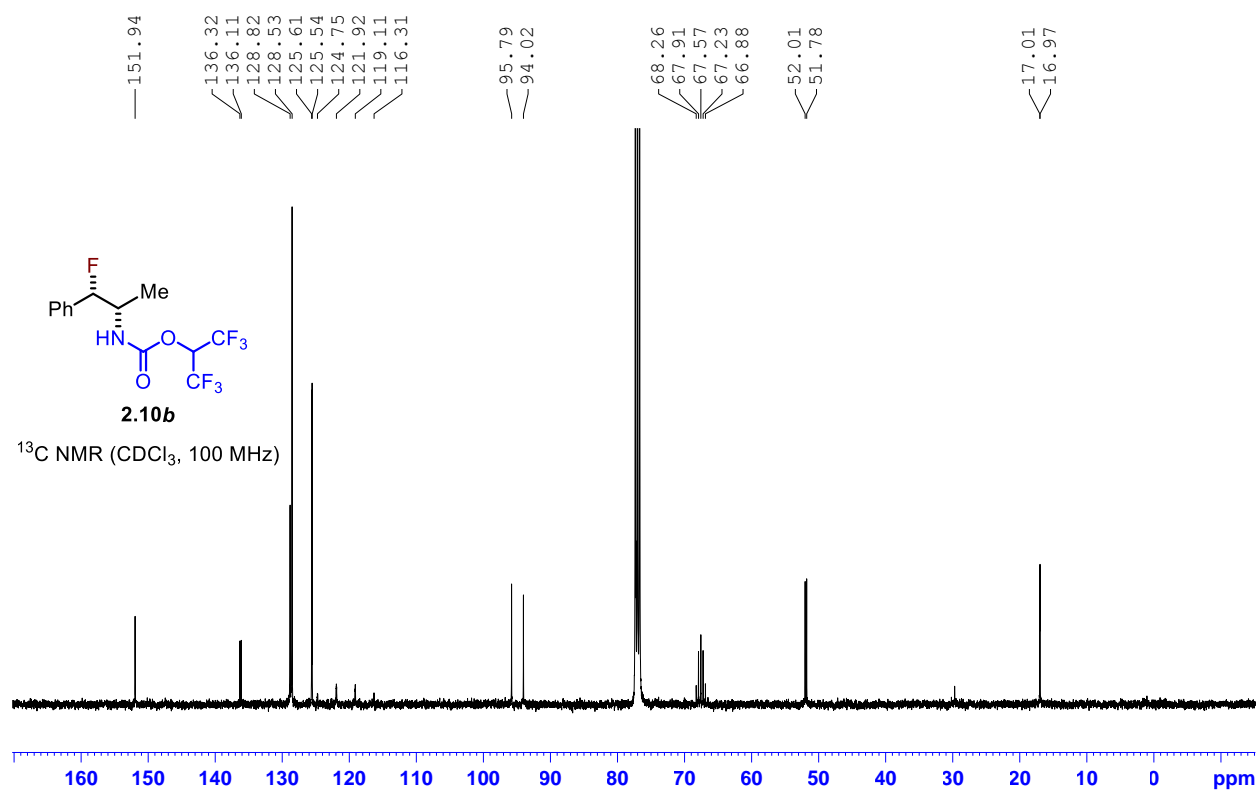
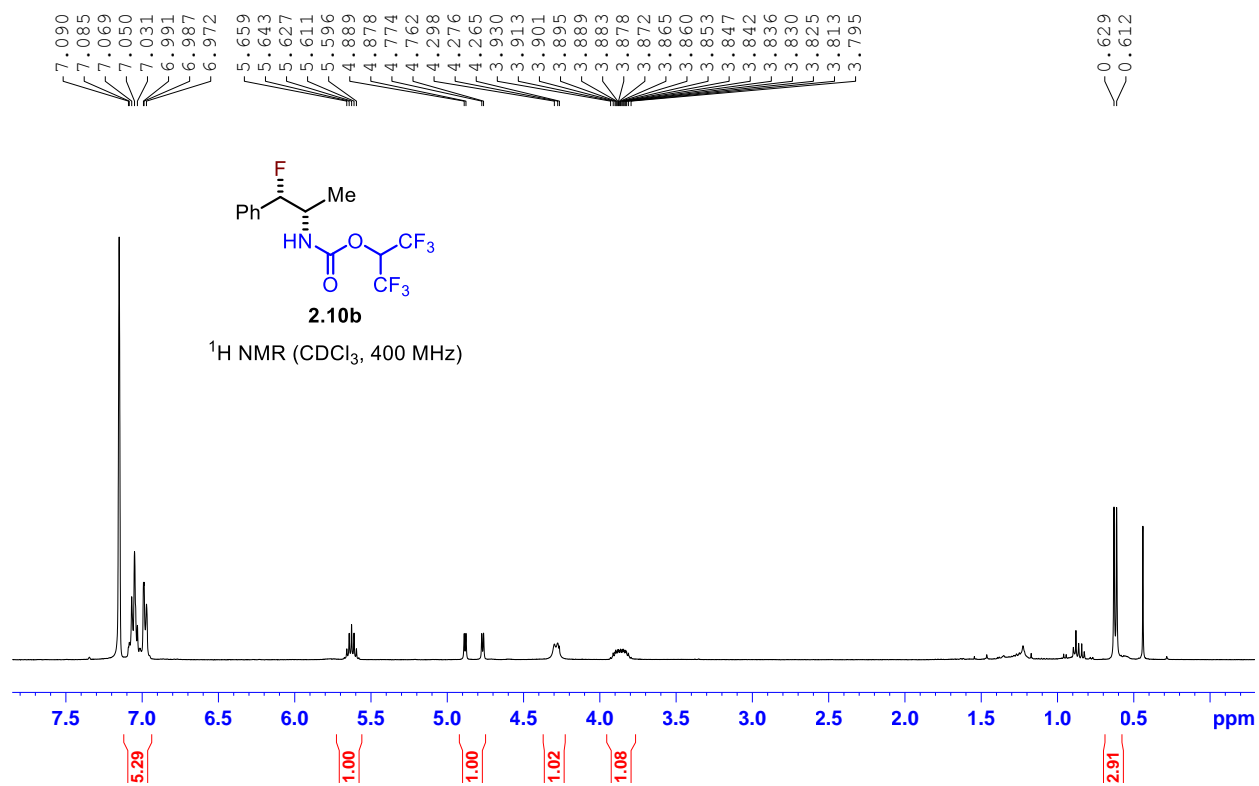


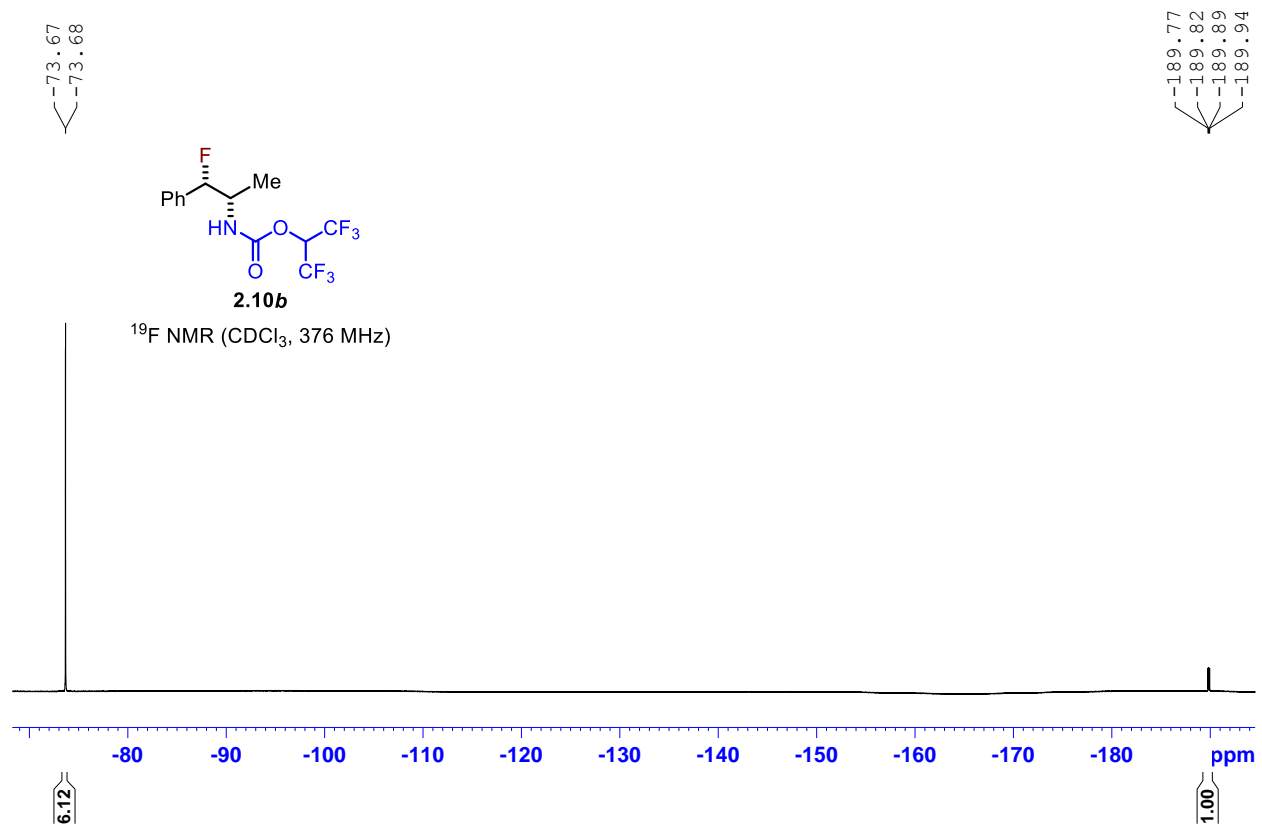








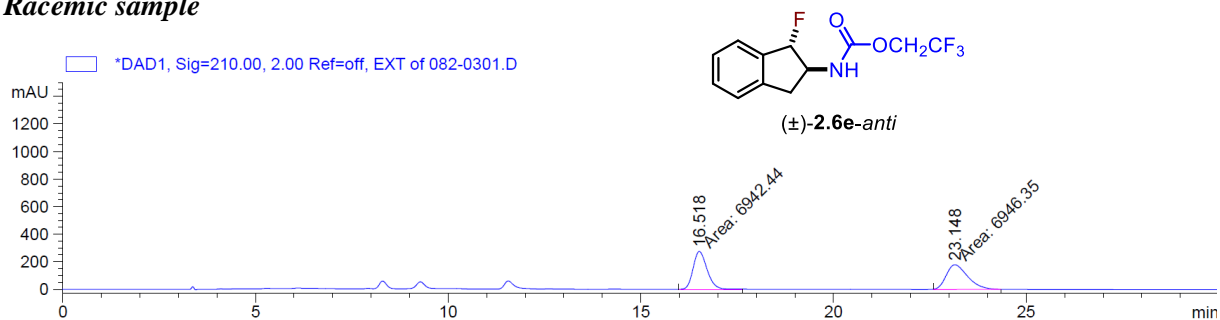




Appendix B.2 HPLC traces of compound **2.6e**

The *ee* of compound **2.6e-anti** was determined by Chiral HPLC analysis (Chiralcel OD-H column, 5% isopropanol in hexanes, flow rate = 1.0 mL/min, UV detection at 210 nm). t_r (minor) = 23.5 min, t_r (major) = 16.7 min, 84% *ee*.

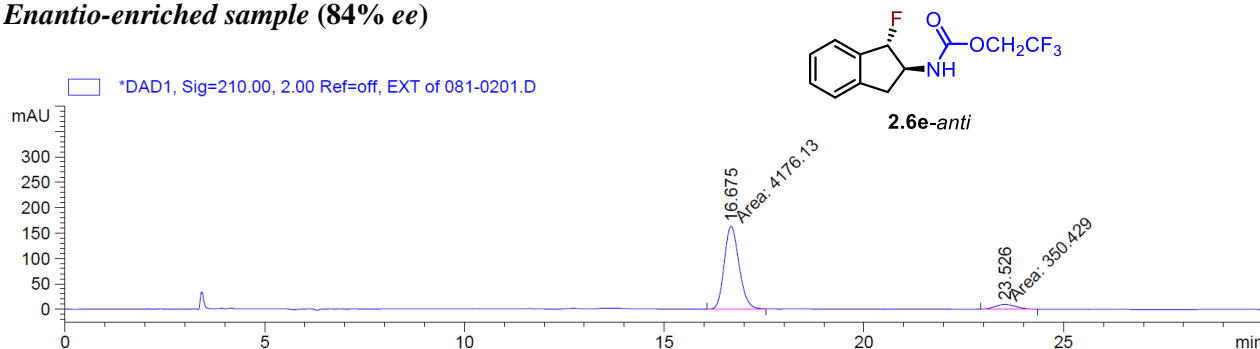
Racemic sample



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.518	MF	0.4212	6942.43750	274.70596	49.9859
2	23.148	FM	0.6478	6946.34619	178.72192	50.0141

Totals : 1.38888e4 453.42789

Enantio-enriched sample (84% *ee*)

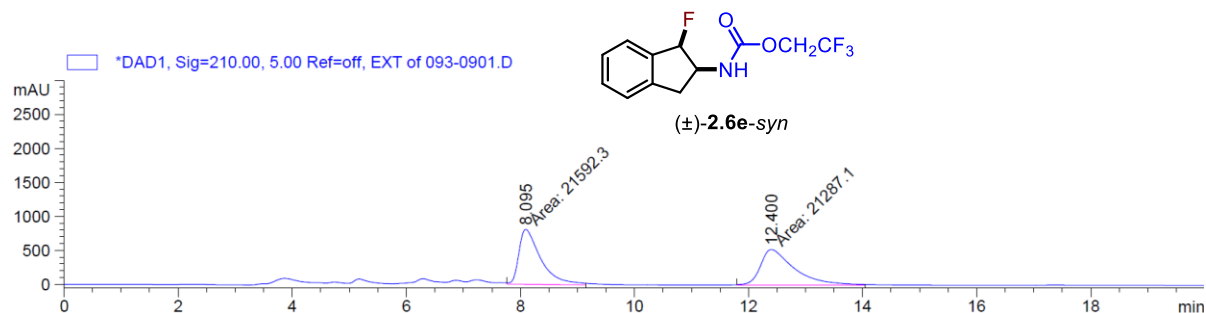


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.675	MF	0.4274	4176.13330	162.86446	92.2584
2	23.526	FM	0.6185	350.42856	9.44314	7.7416

Totals : 4526.56186 172.30759

The *ee* of compound **2.6e-syn** was determined by Chiral HPLC analysis (Chiralpak AD-H column, 15% EtOH in hexanes, flow rate = 1.0 mL/min, UV detection at 210 nm). t_r (minor) = 12.2 min, t_r (major) = 8.02 min, 84% *ee*.

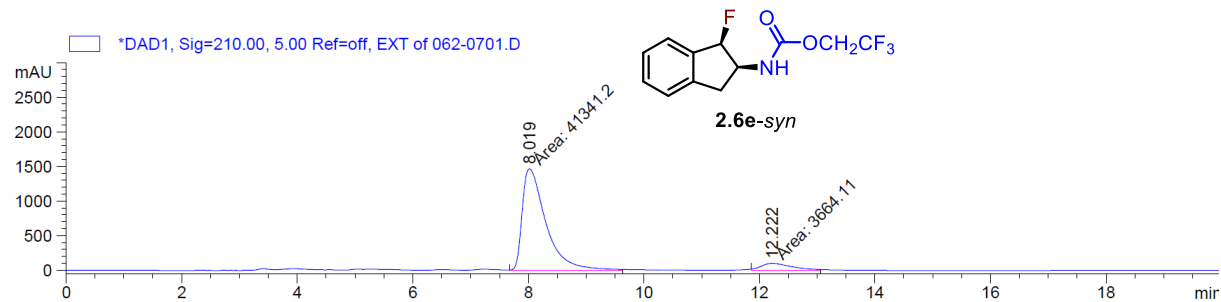
Racemic sample



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.095	MM	0.4452	2.15923e4	808.25409	50.3559
2	12.400	MF	0.6800	2.12871e4	521.73981	49.6441

Totals : 4.28794e4 1329.99390

Enantio-enriched sample (84% ee)



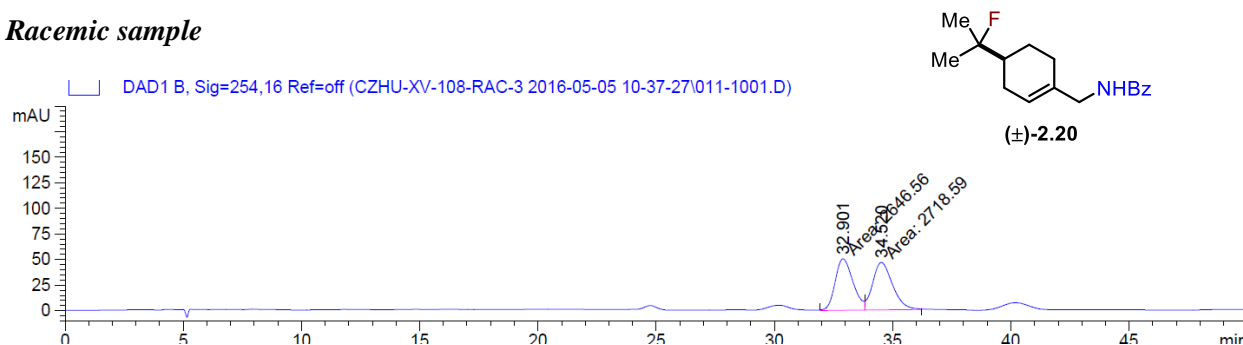
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.019	MF	0.4716	4.13412e4	1460.98621	91.8585
2	12.222	FM	0.6119	3664.10669	99.79760	8.1415

Totals : 4.50053e4 1560.78381

Appendix B.3 HPLC traces of compound 2.20

The *ee* of compound **2.20** was determined by Chiral HPLC analysis (Chiralcel OD-H column, 10% isopropanol in hexanes, flow rate = 0.6 mL/min, UV detection at 254 nm). t_r (major) = 32.5 min, t_r (minor) = 34.4 min, 91% *ee*.

Racemic sample

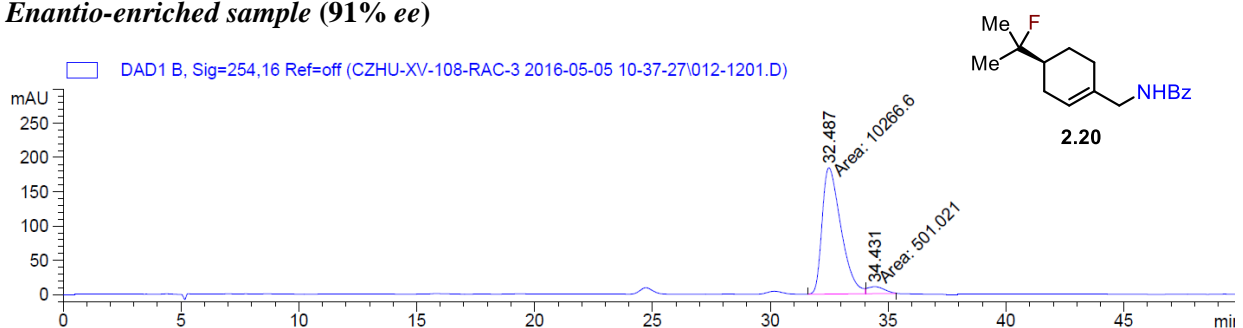


Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.901	MF	0.8769	2646.55859	50.30003	49.3287
2	34.520	FM	0.9745	2718.59497	46.49668	50.6713

Totals : 5365.15356 96.79671

Enantio-enriched sample (91% ee)

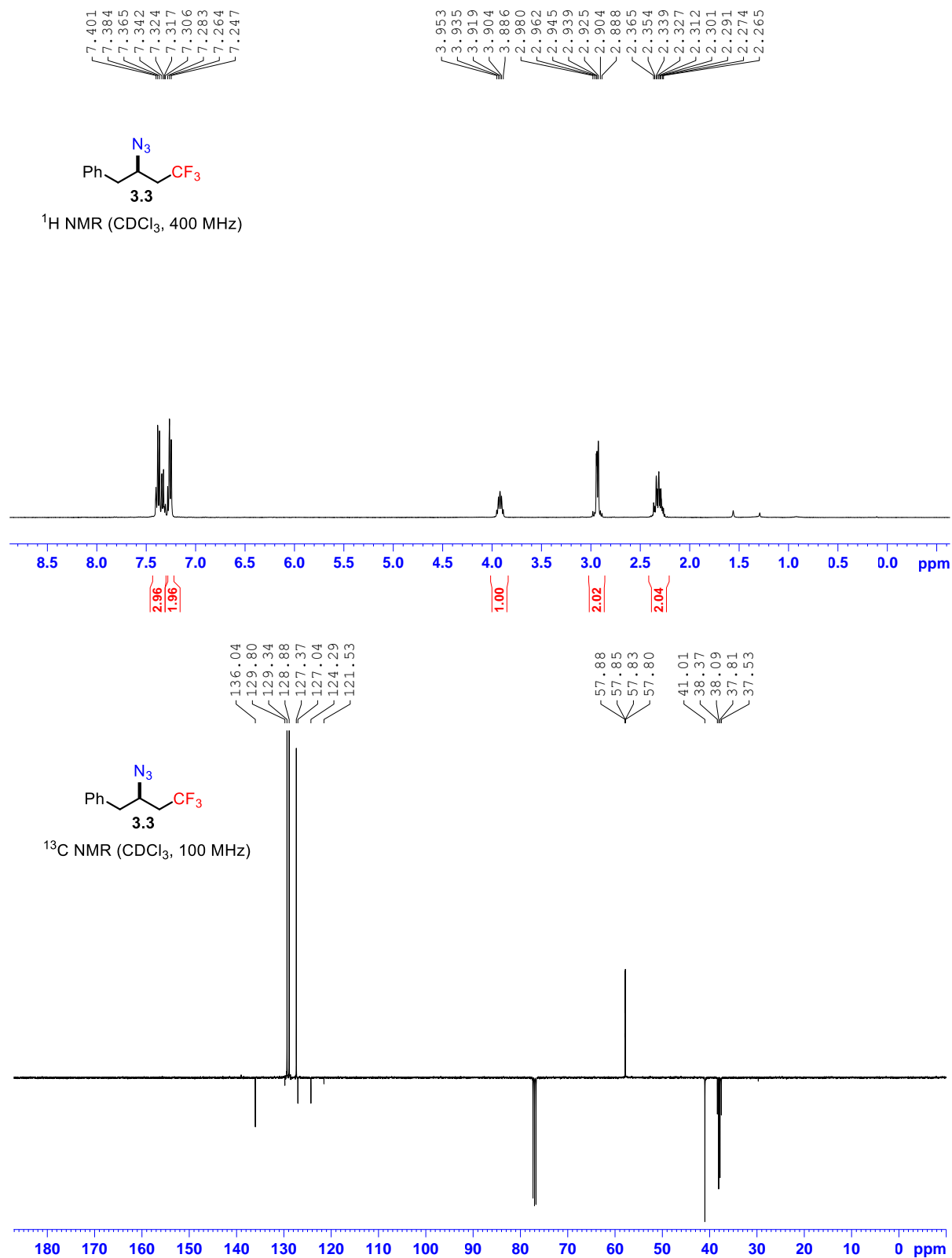


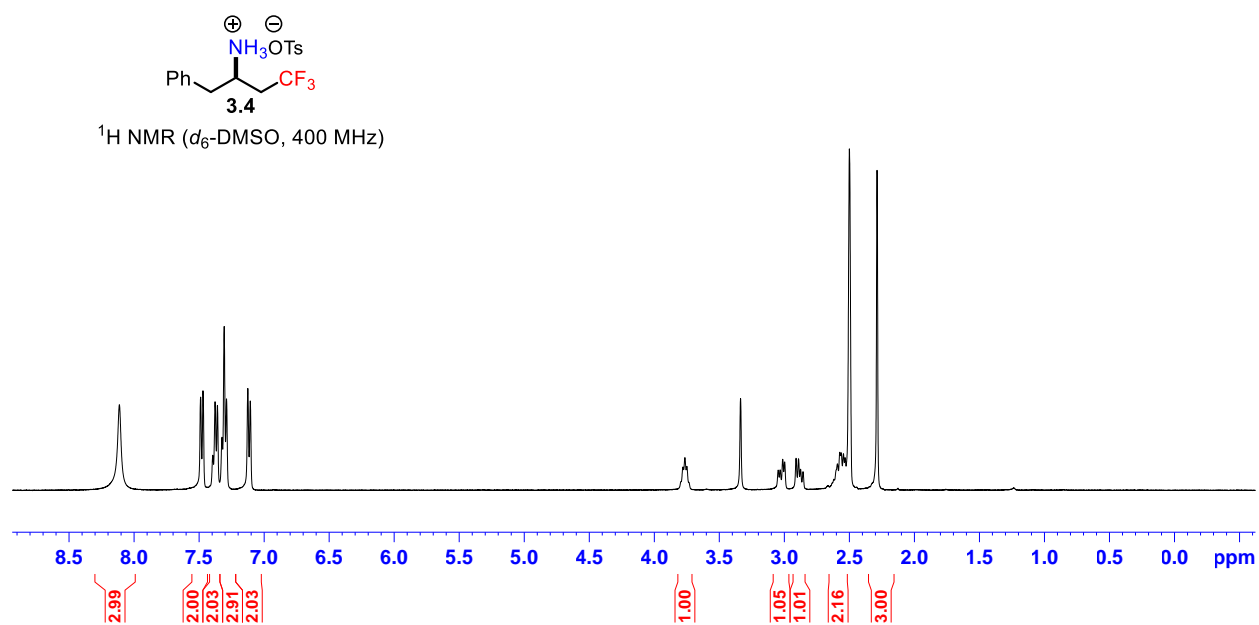
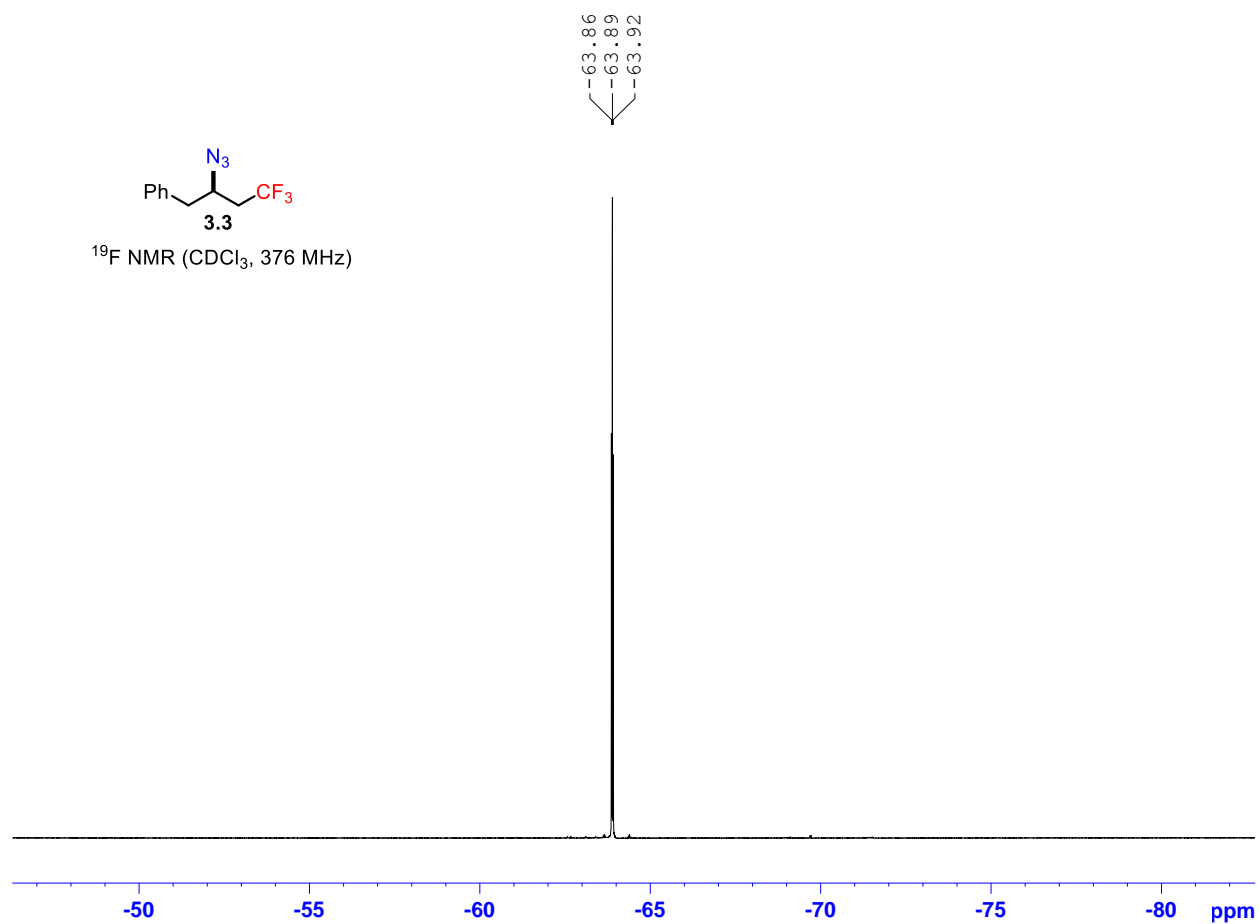
Signal 2: DAD1 B, Sig=254,16 Ref=off

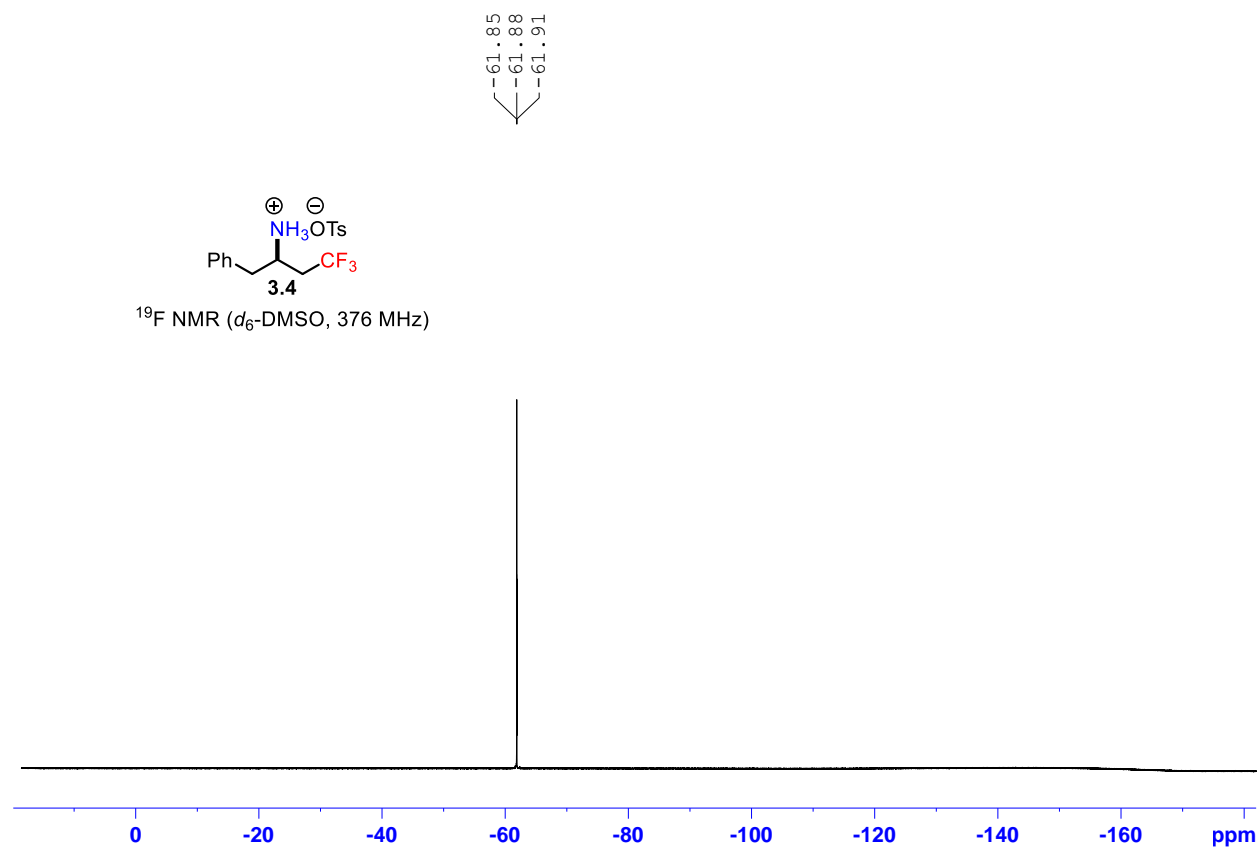
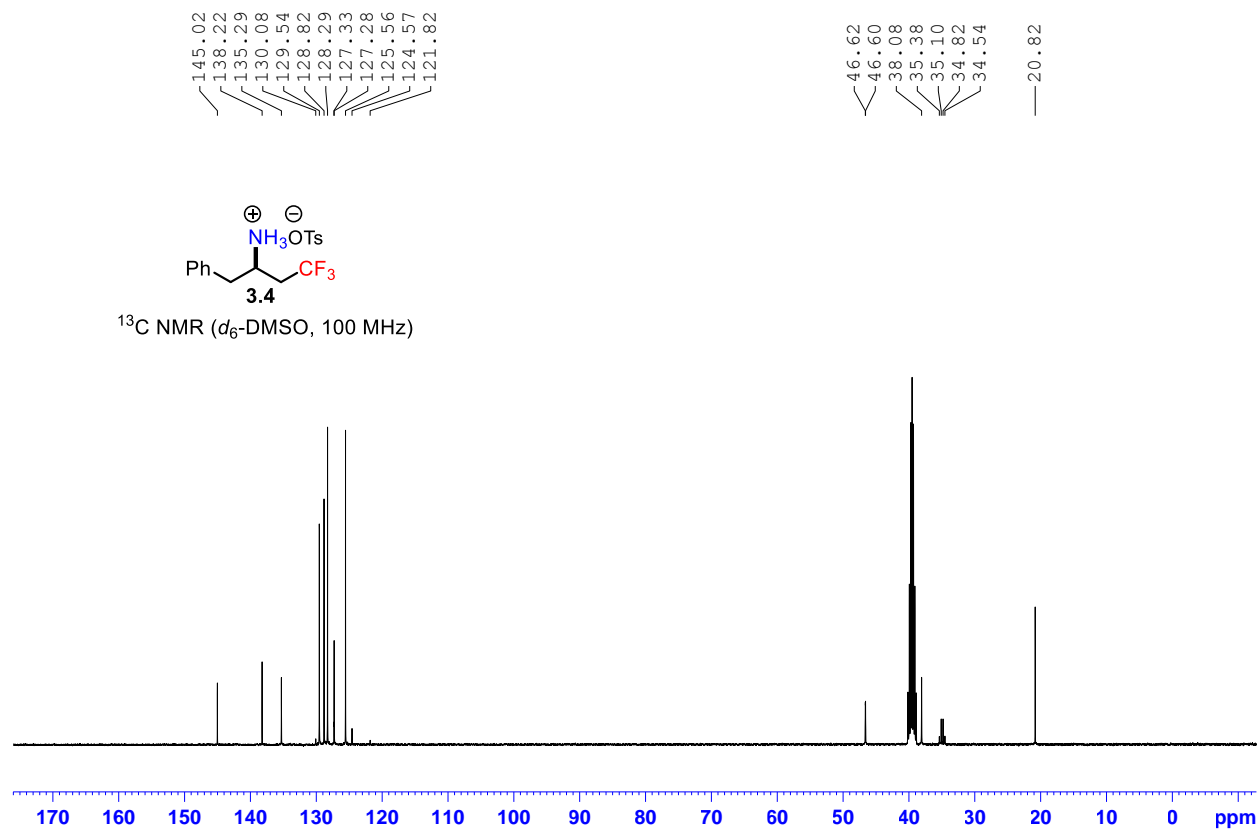
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.487	MF	0.9277	1.02666e4	184.44078	95.3470
2	34.431	FM	0.8228	501.02090	10.14889	4.6530

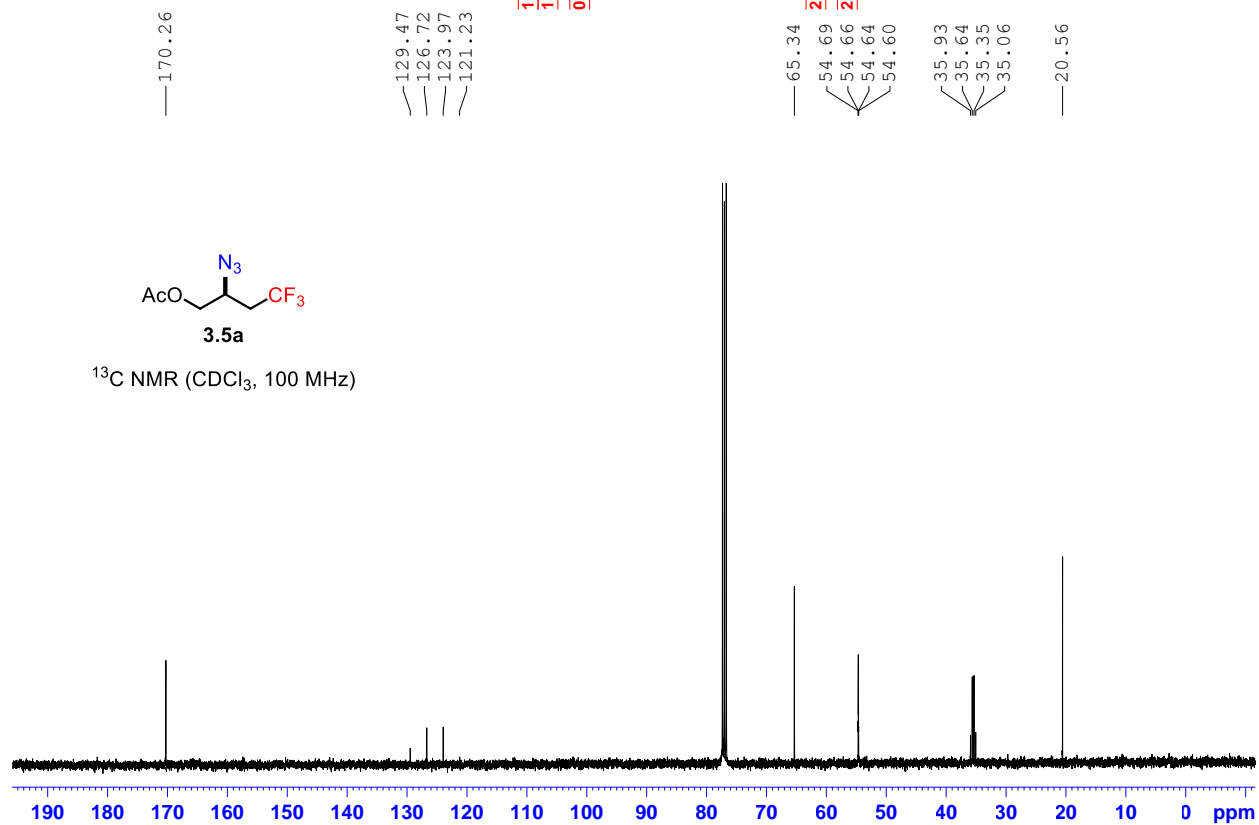
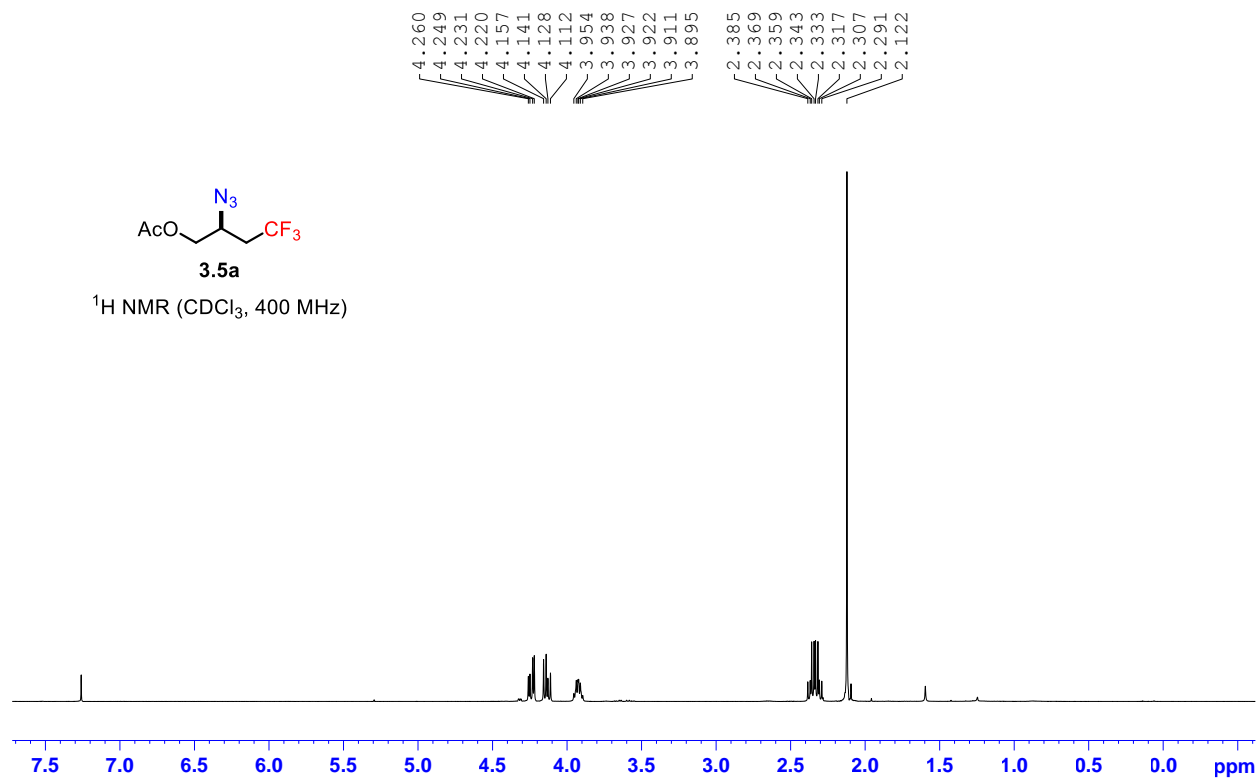
Totals : 1.07676e4 194.58967

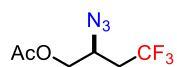
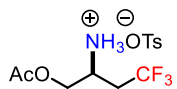
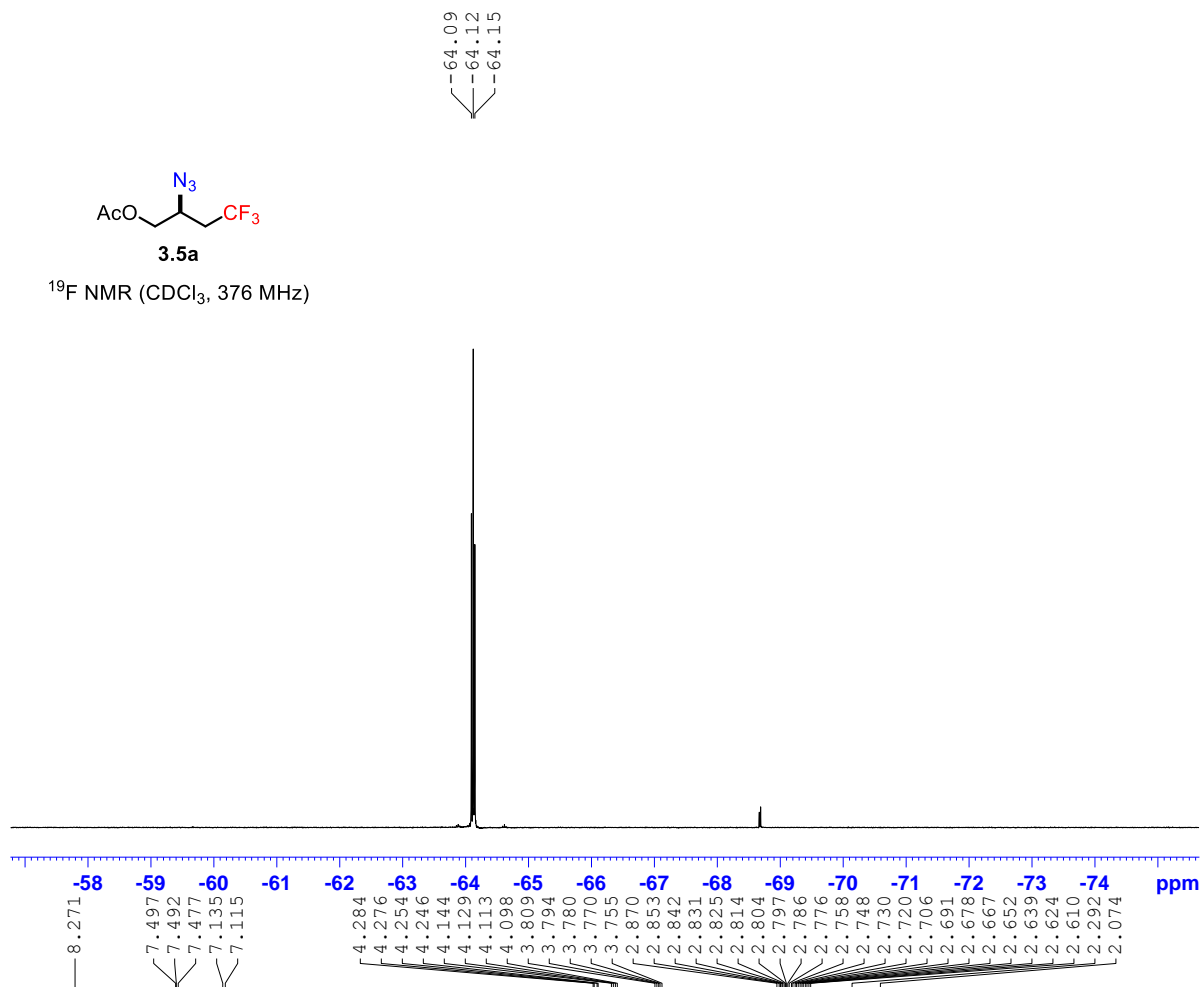
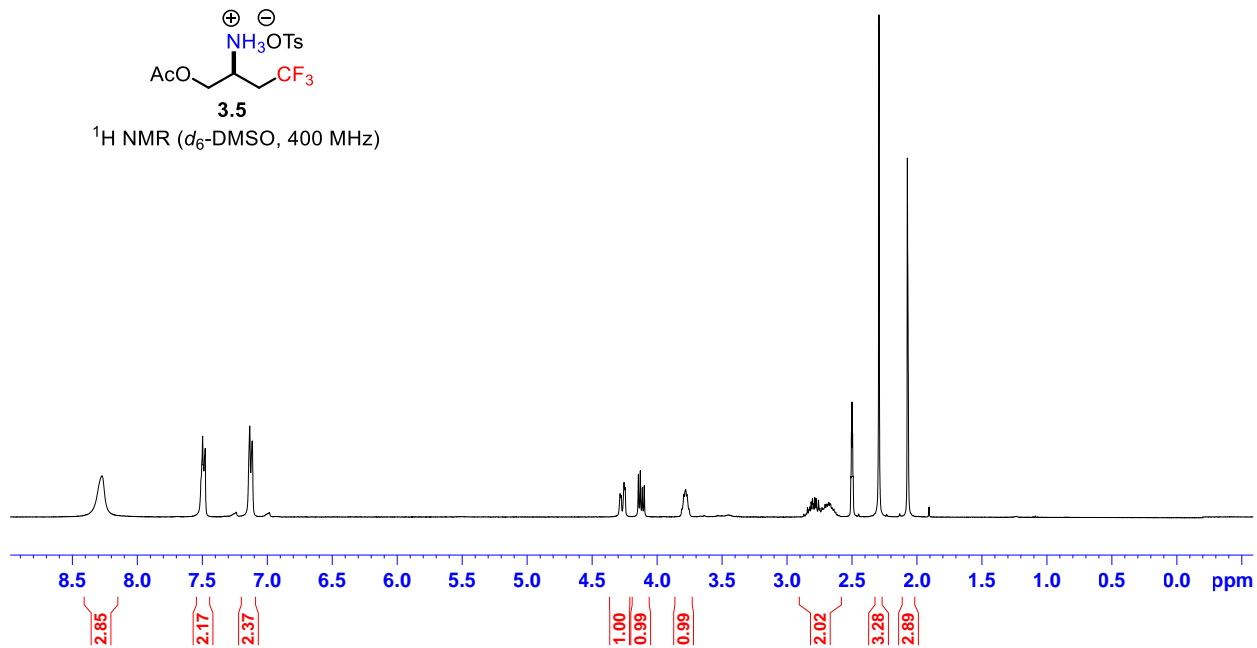
Appendix C. Representative NMR spectra in CHAPTER 3

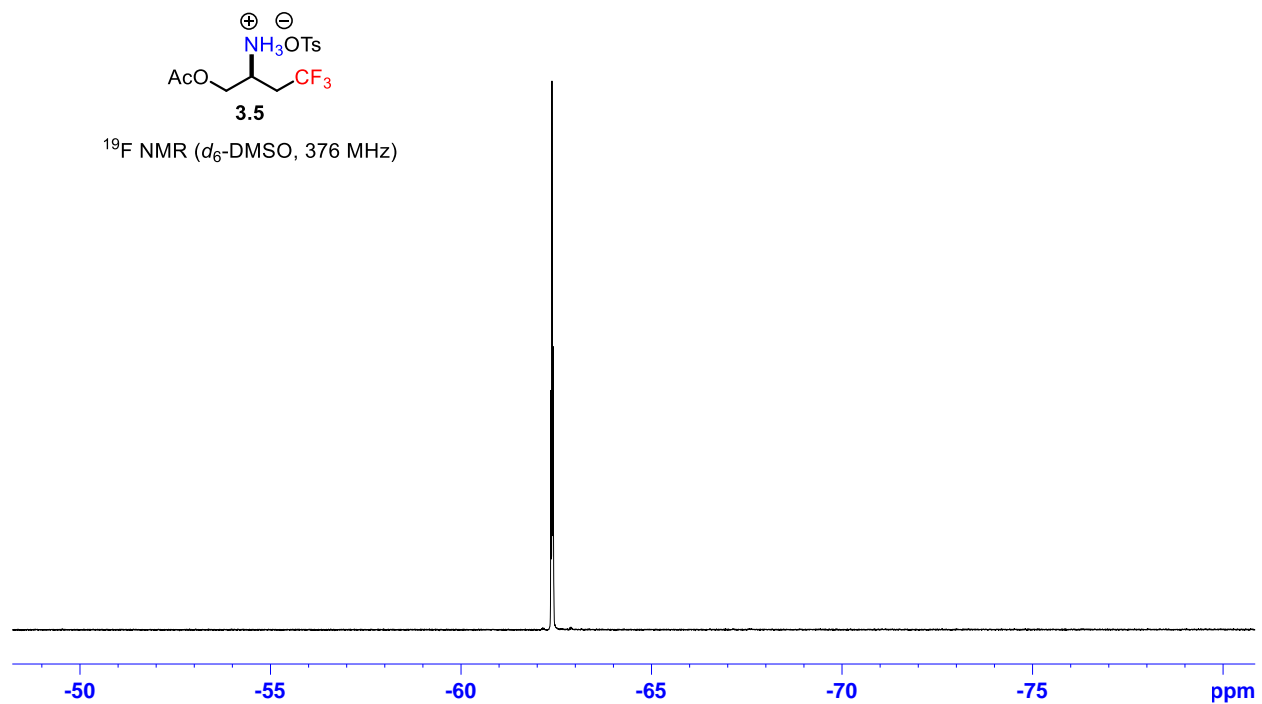
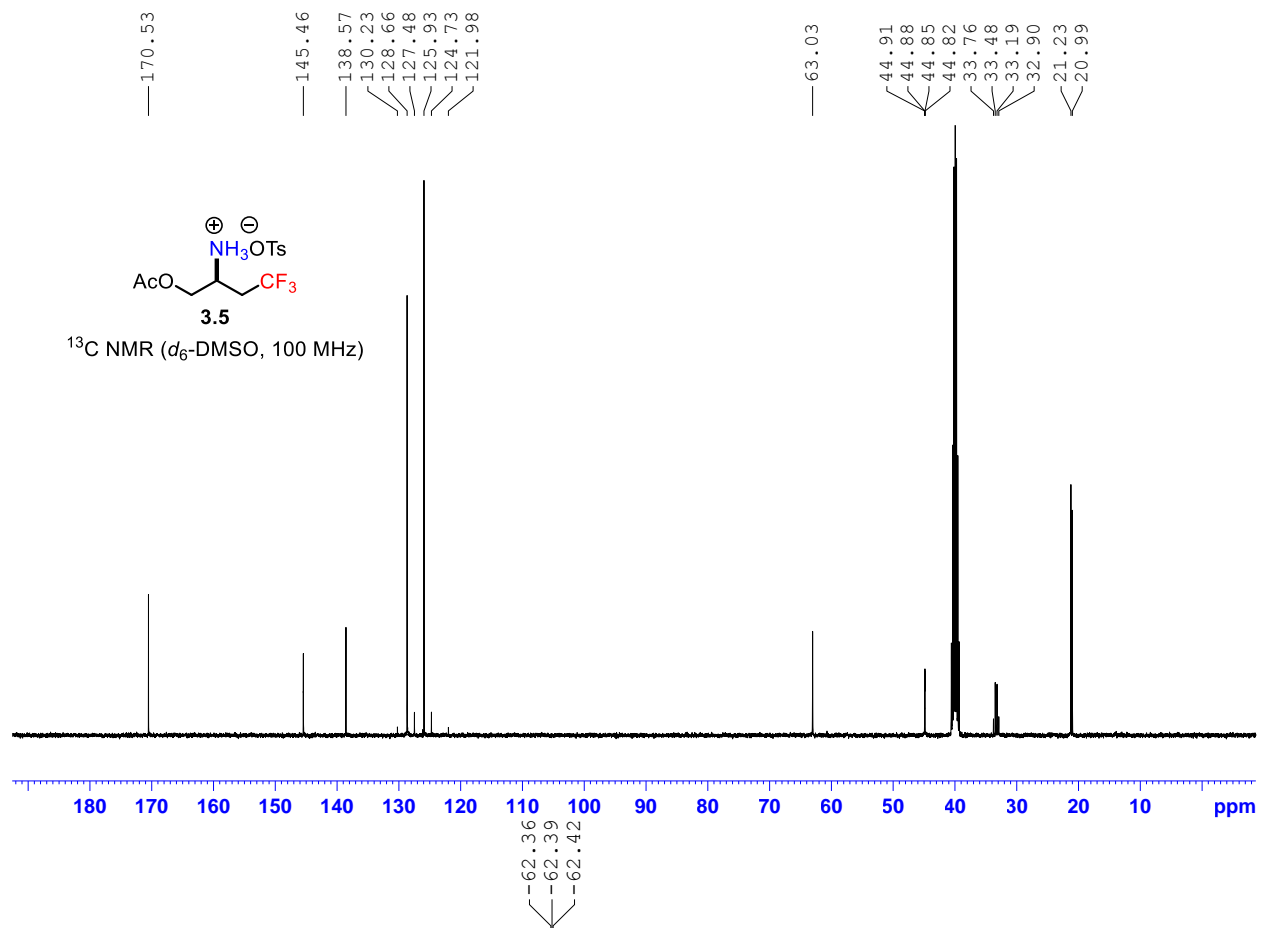


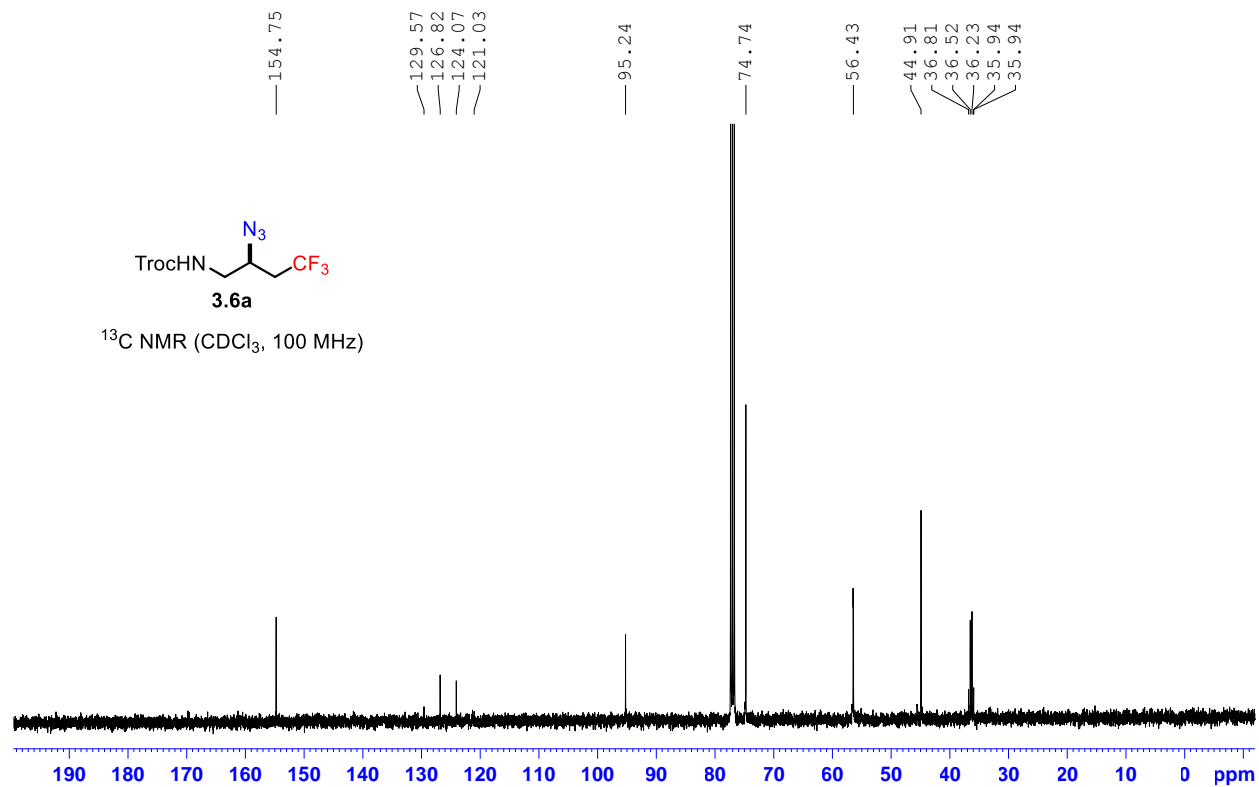
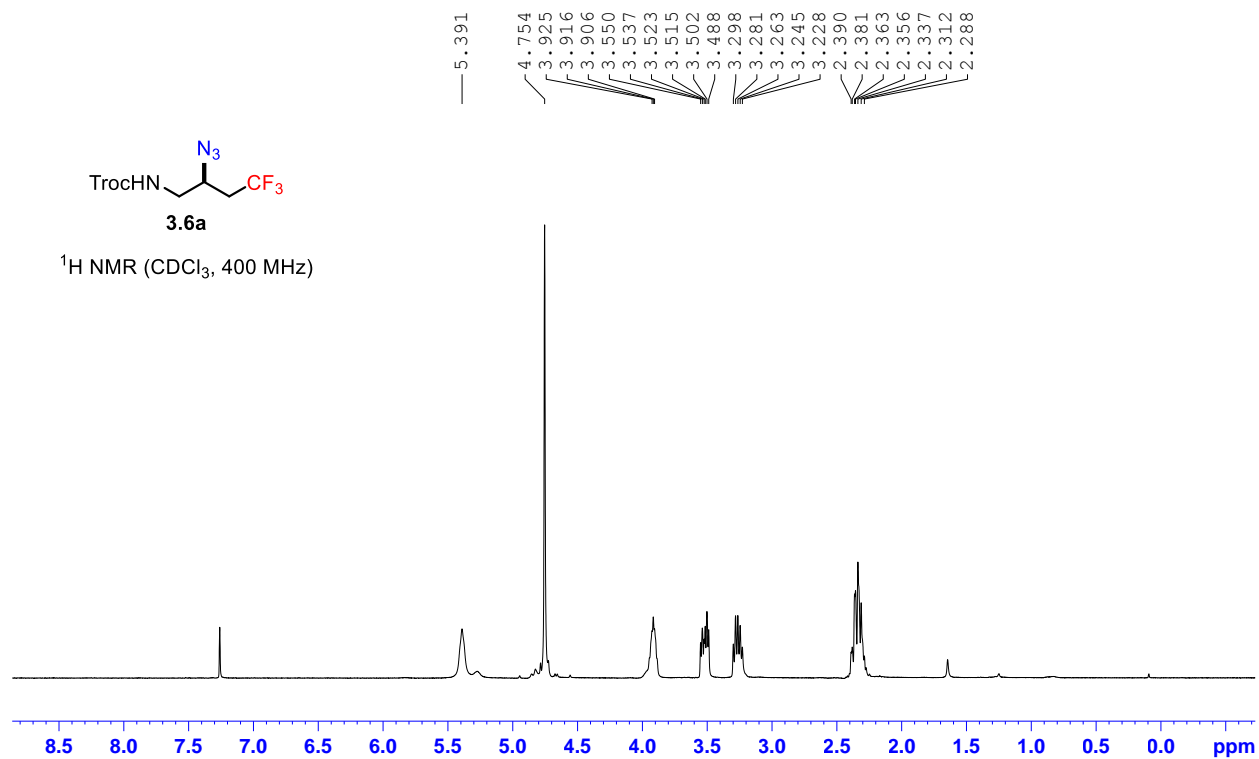


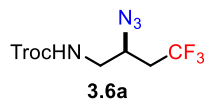




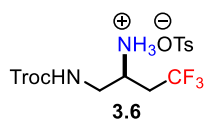
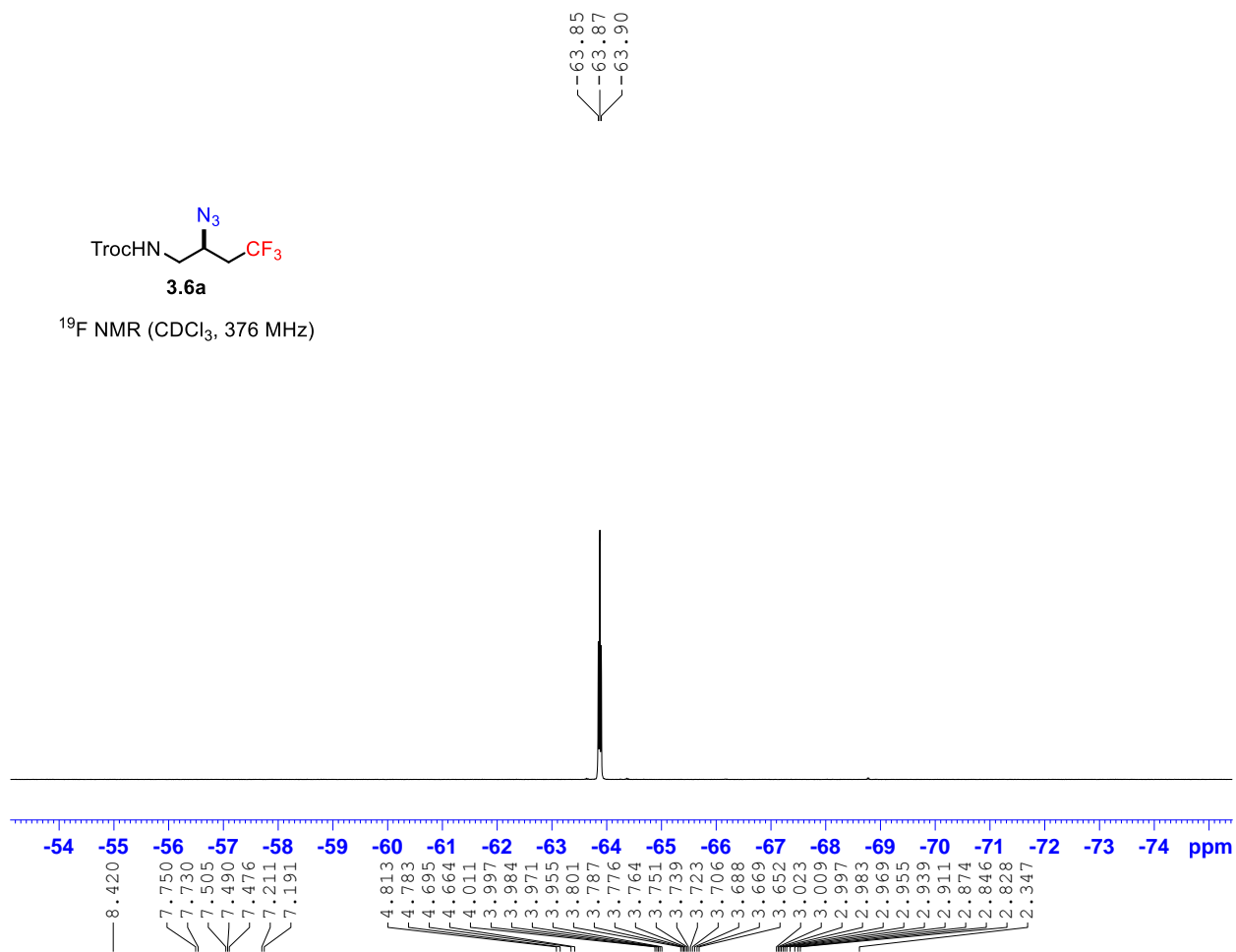
**3.5a**¹⁹F NMR (CDCl₃, 376 MHz)**3.5**¹H NMR (d₆-DMSO, 400 MHz)



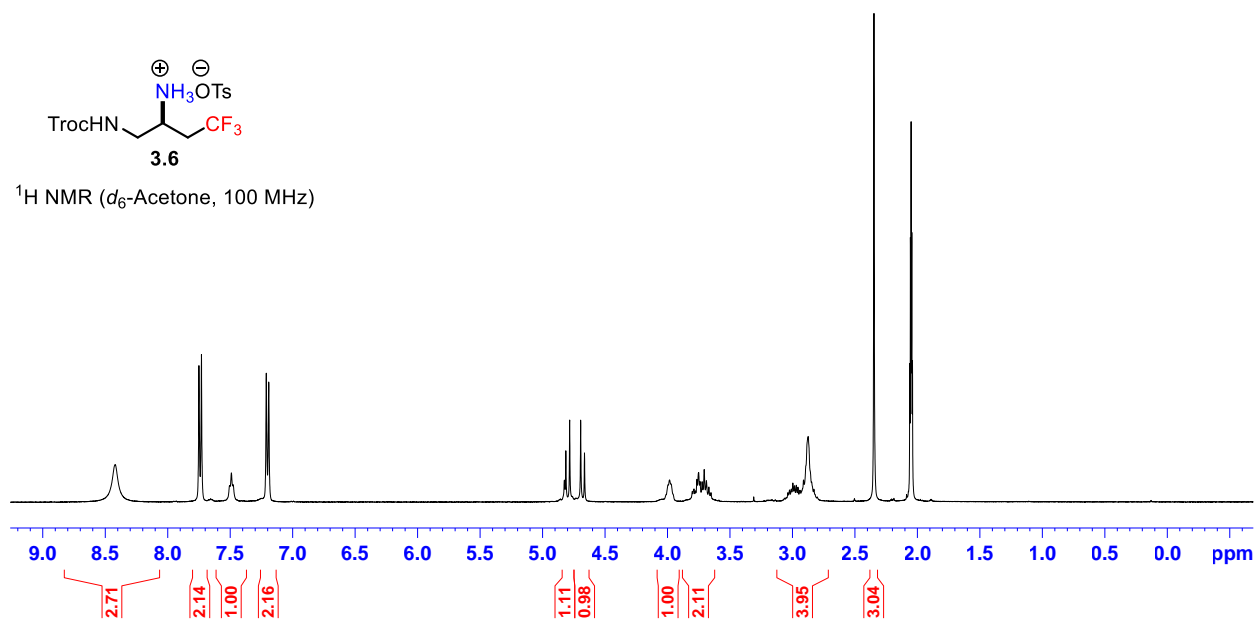


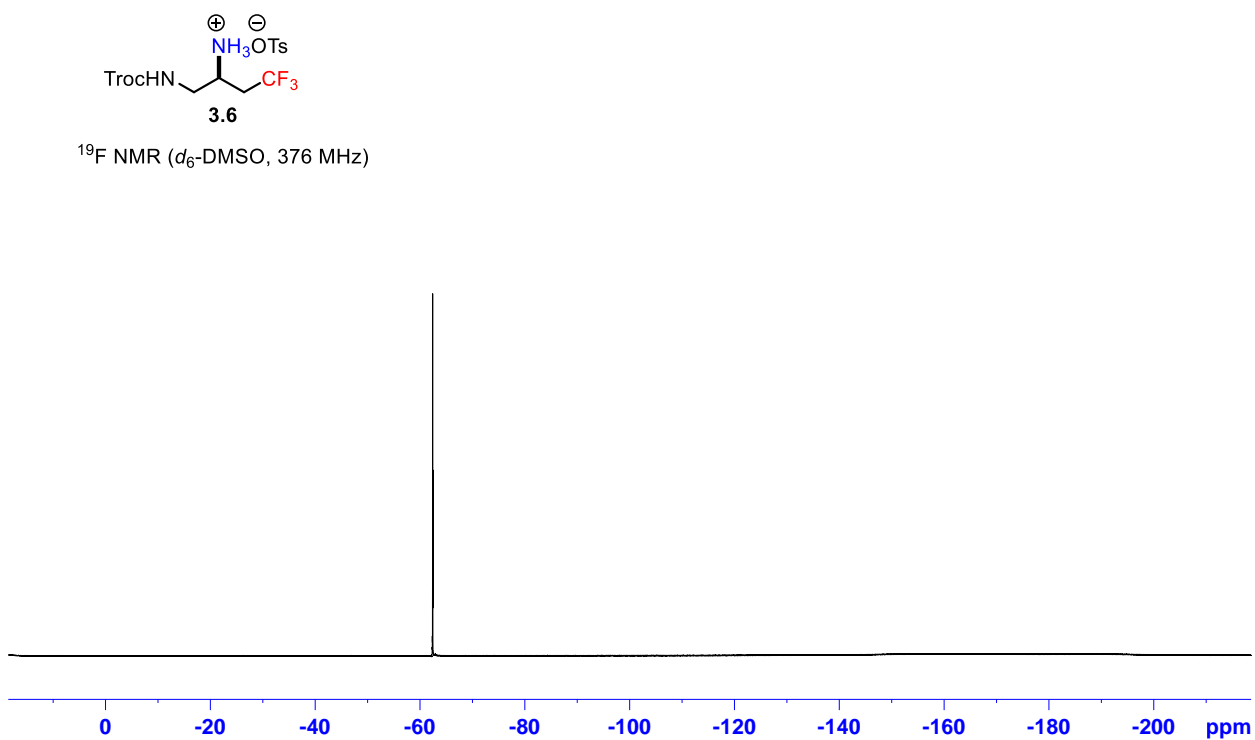
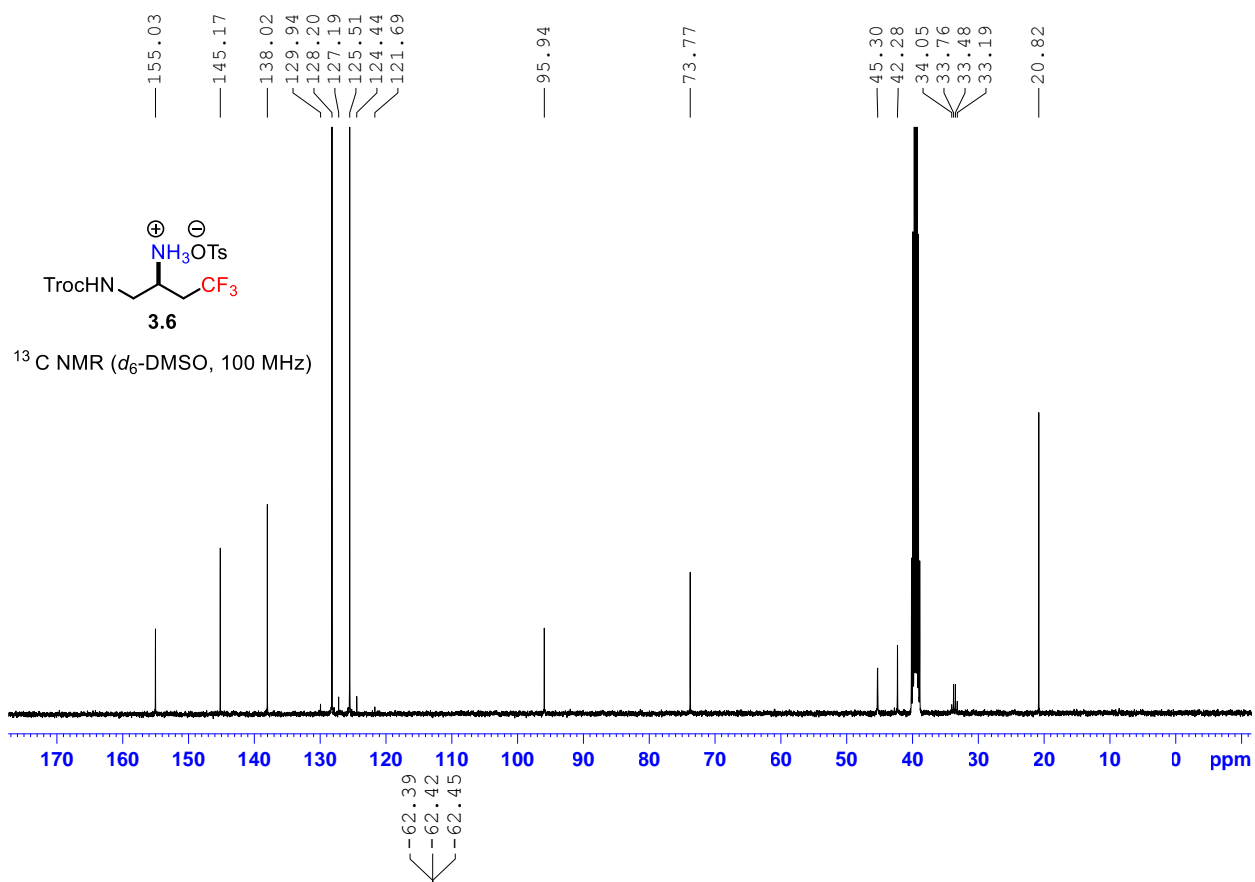


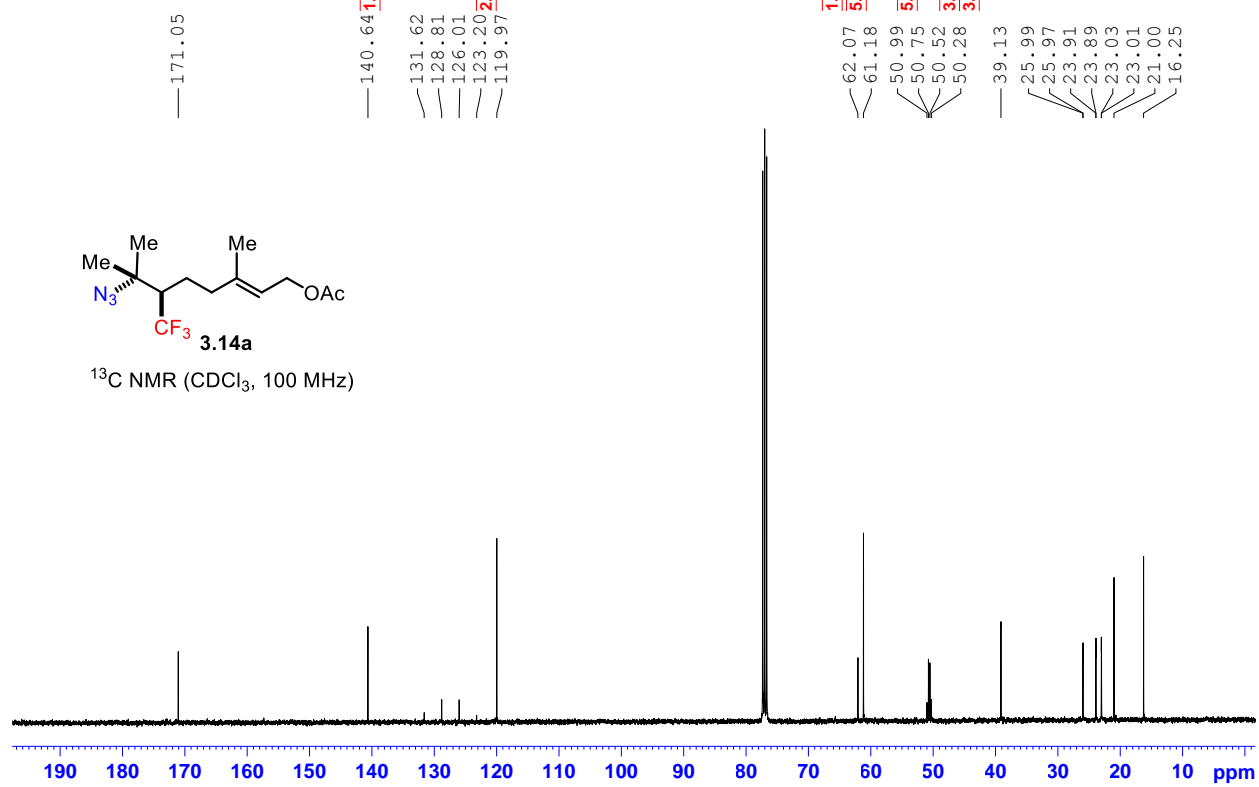
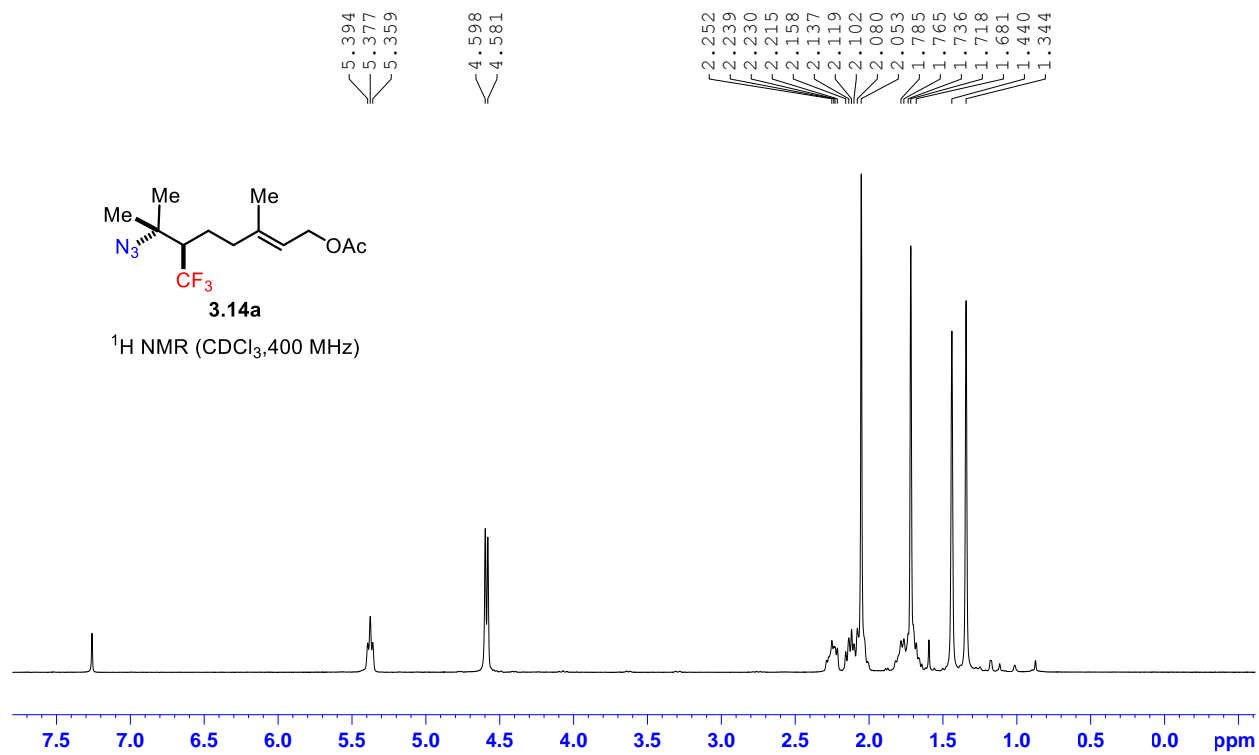
^{19}F NMR (CDCl_3 , 376 MHz)

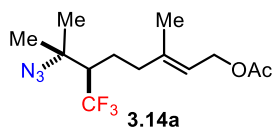


^1H NMR (d_6 -Acetone, 100 MHz)

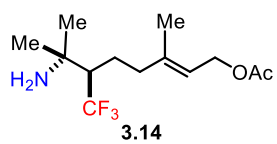
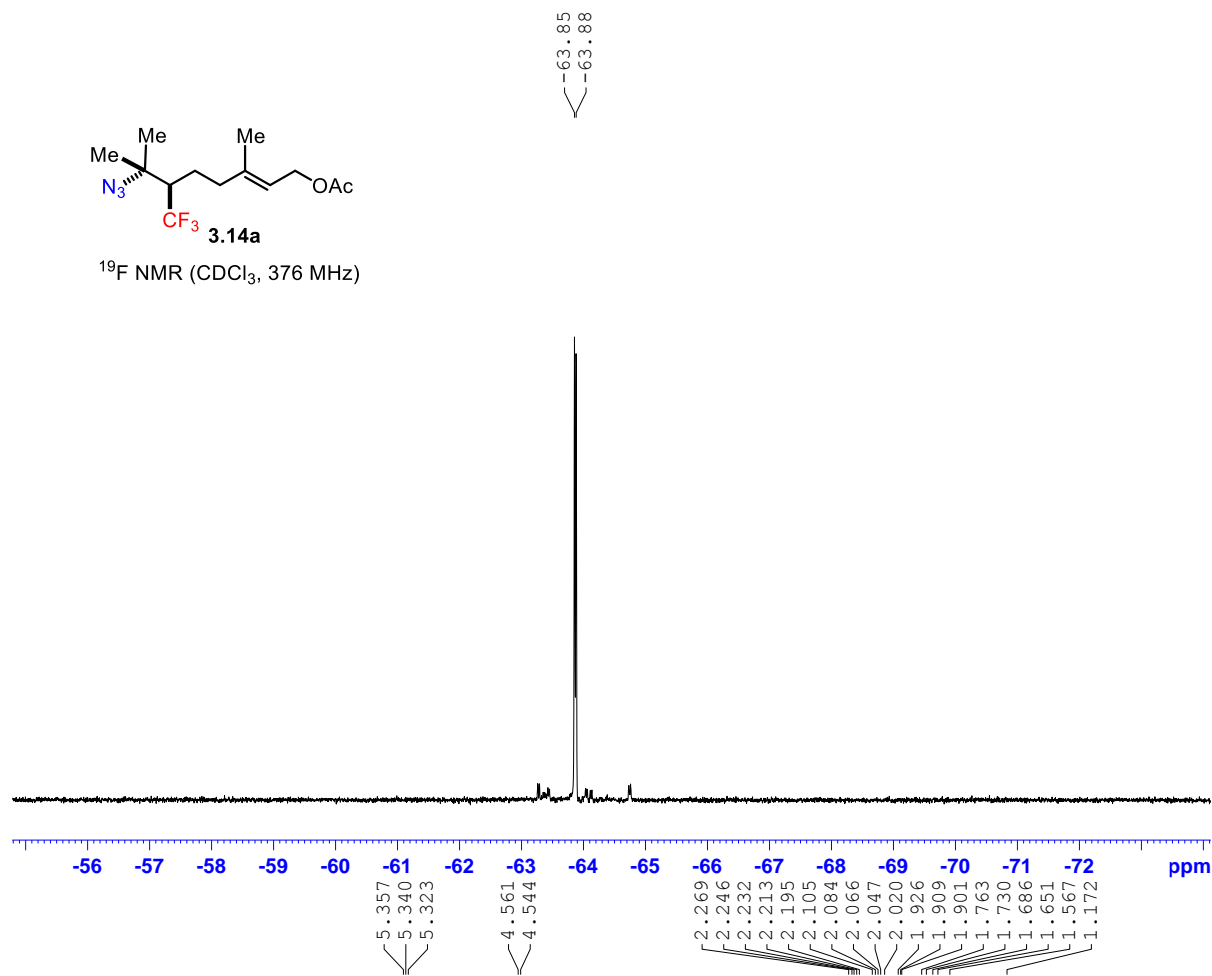




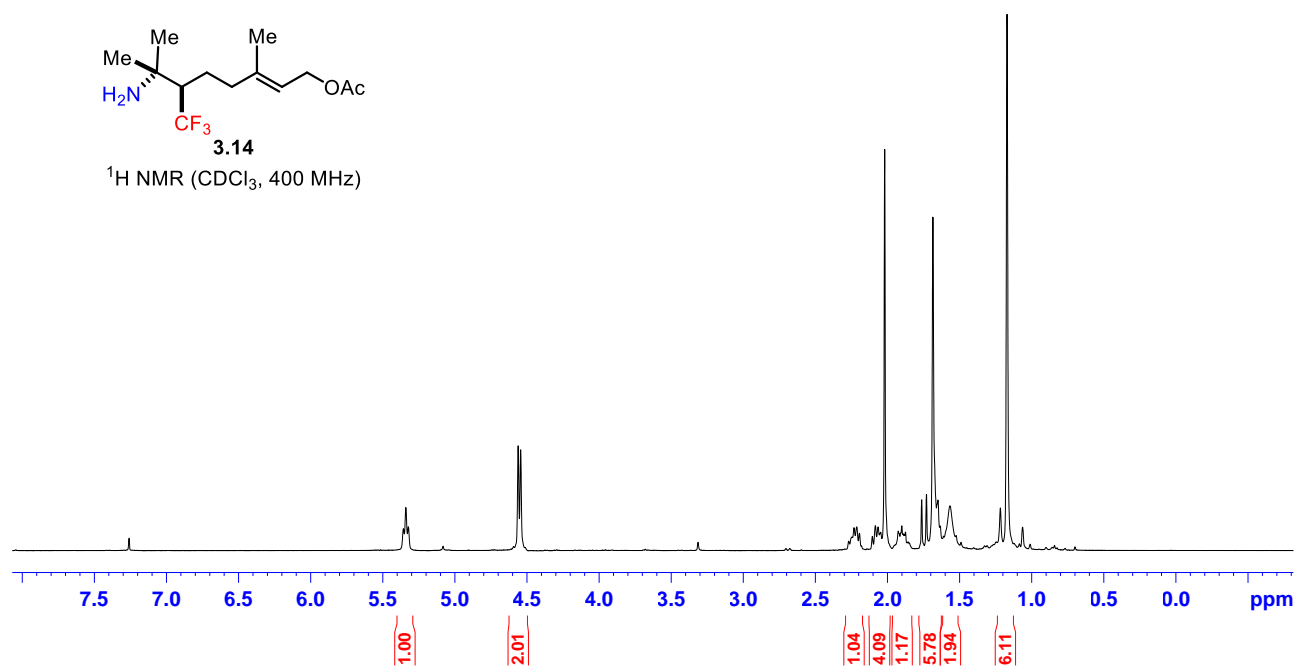


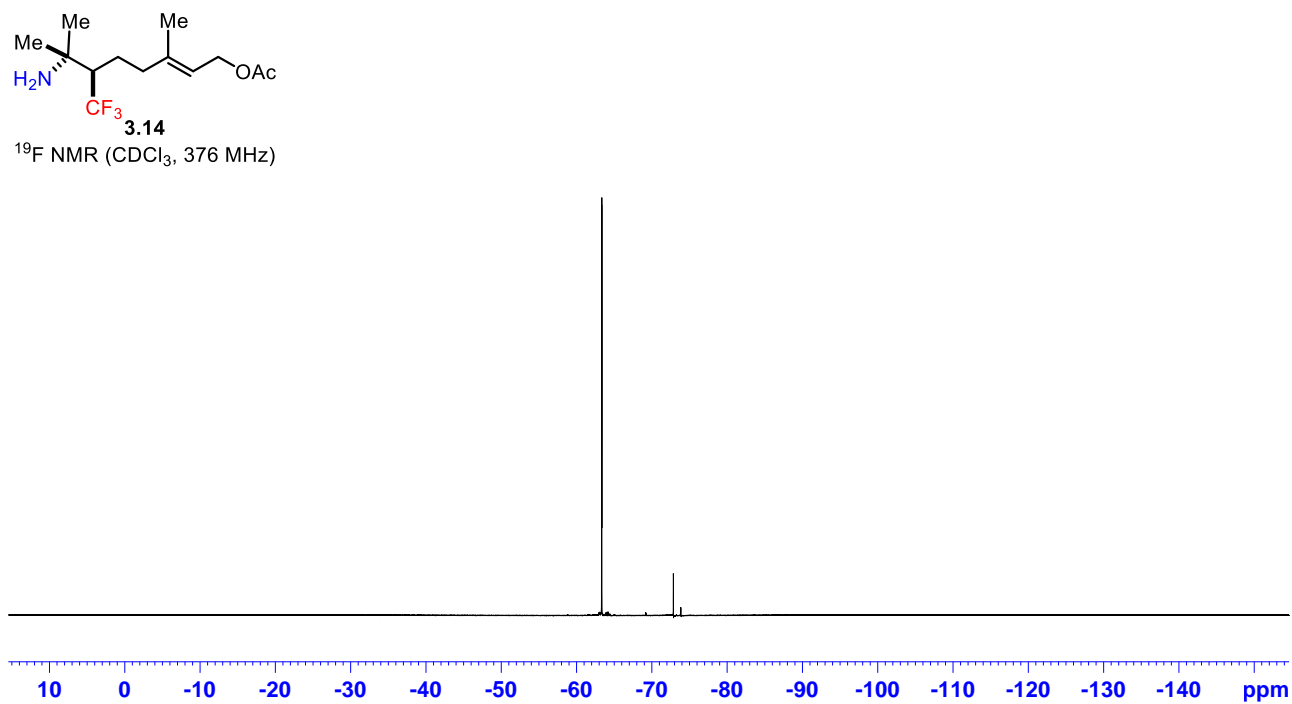
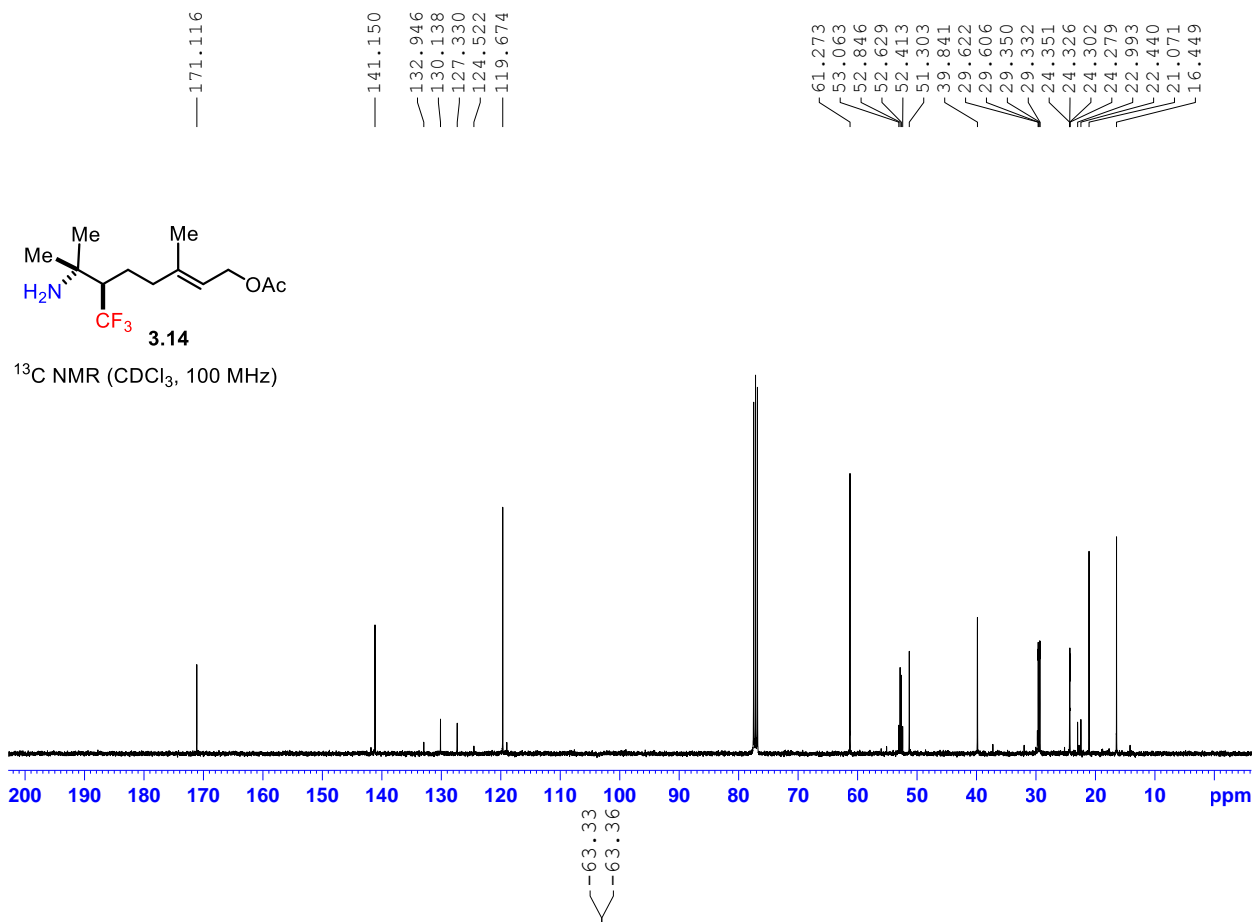


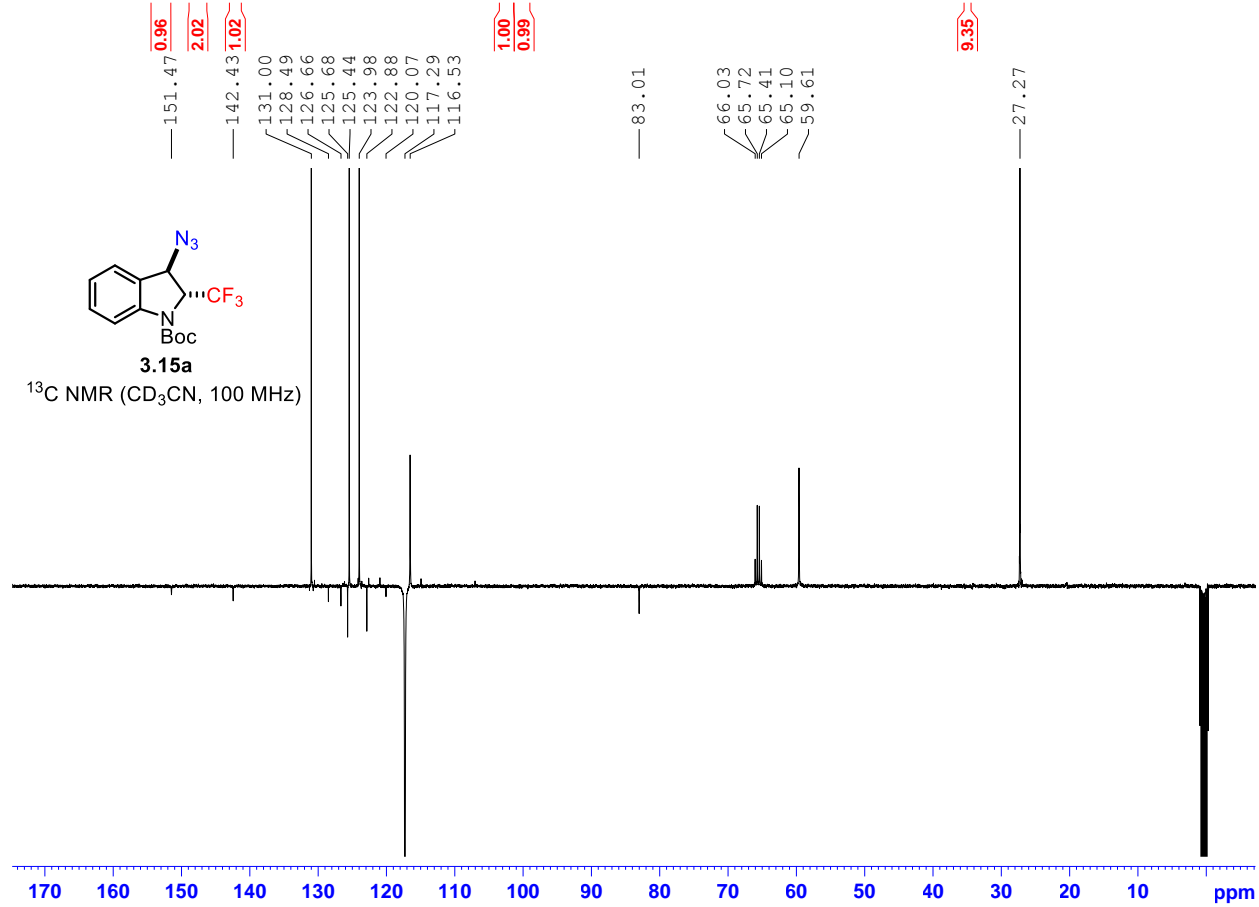
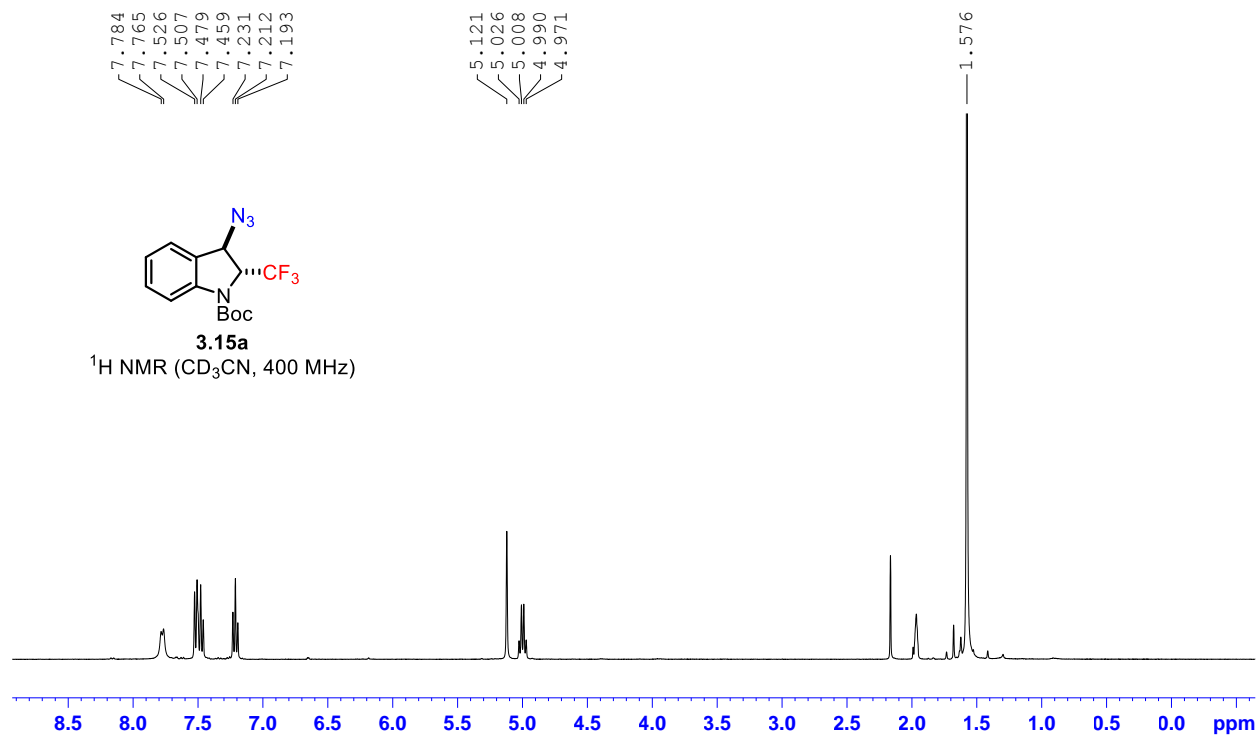
^{19}F NMR (CDCl_3 , 376 MHz)

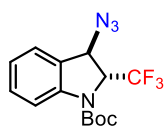
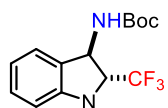
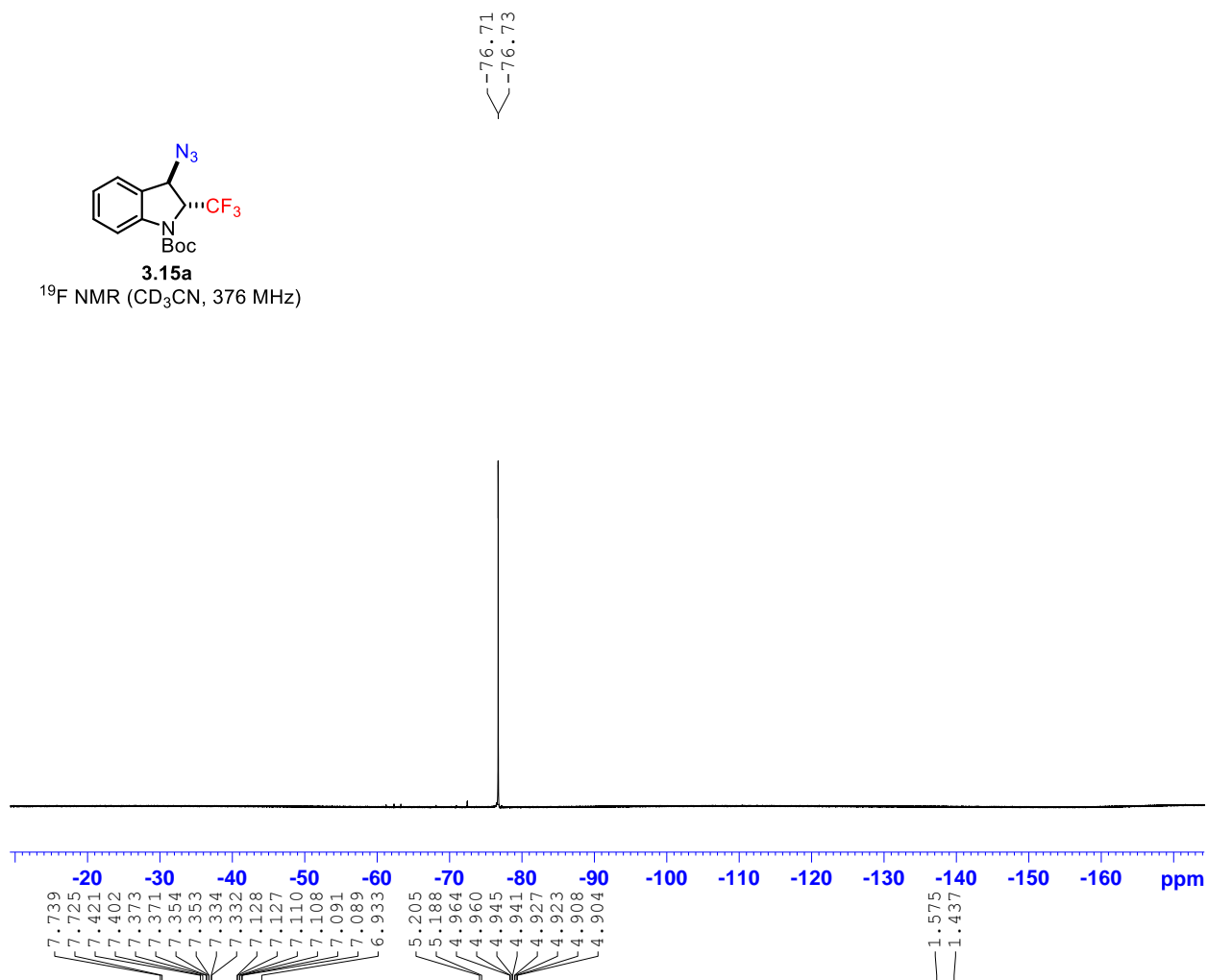
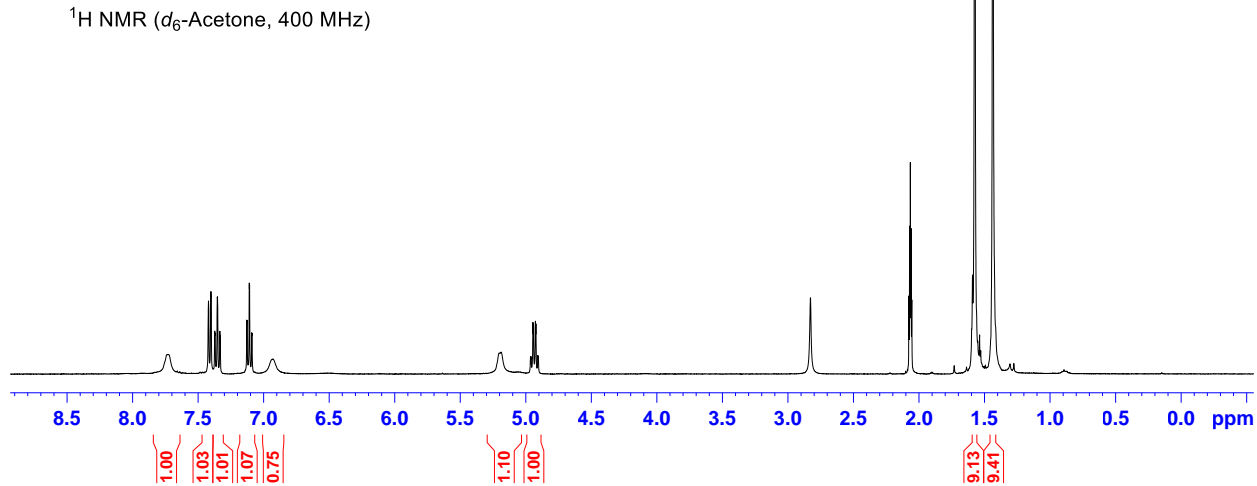


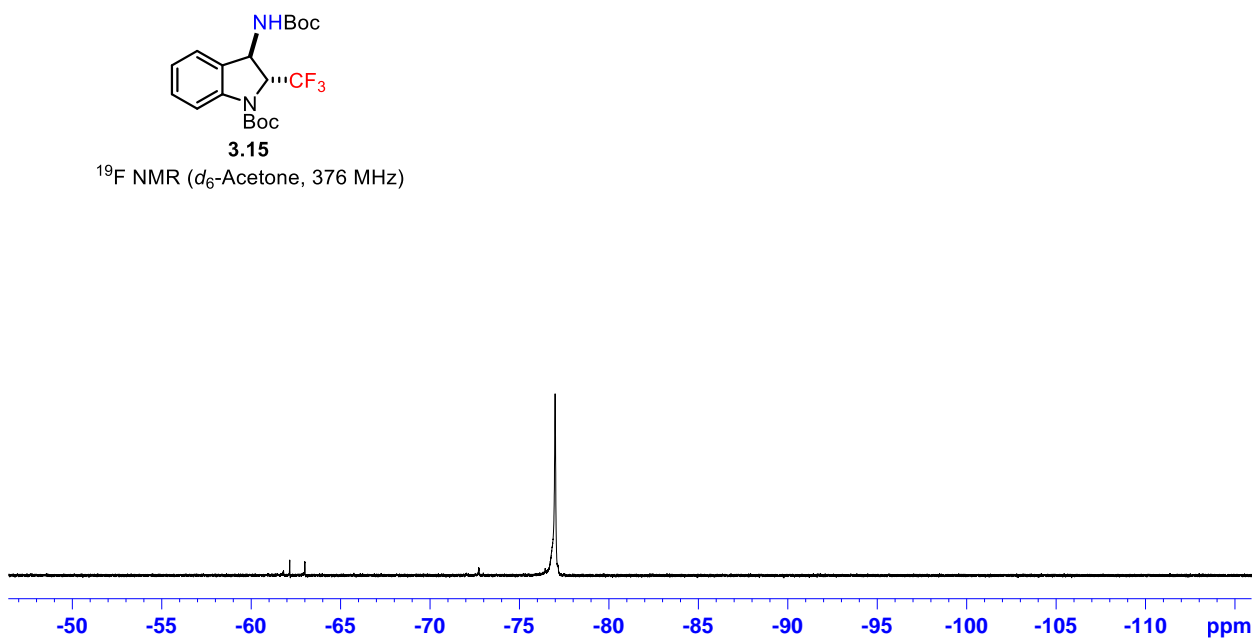
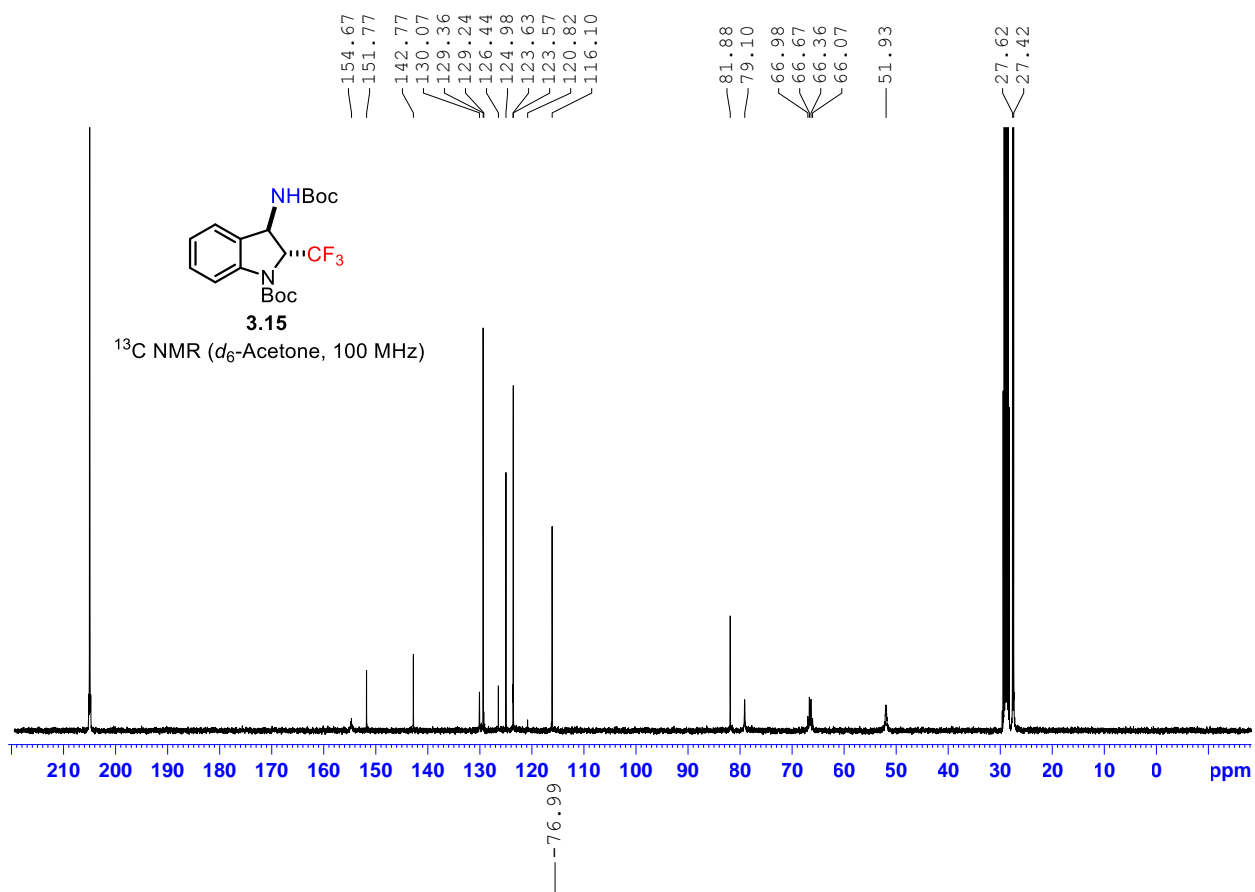
^1H NMR (CDCl_3 , 400 MHz)

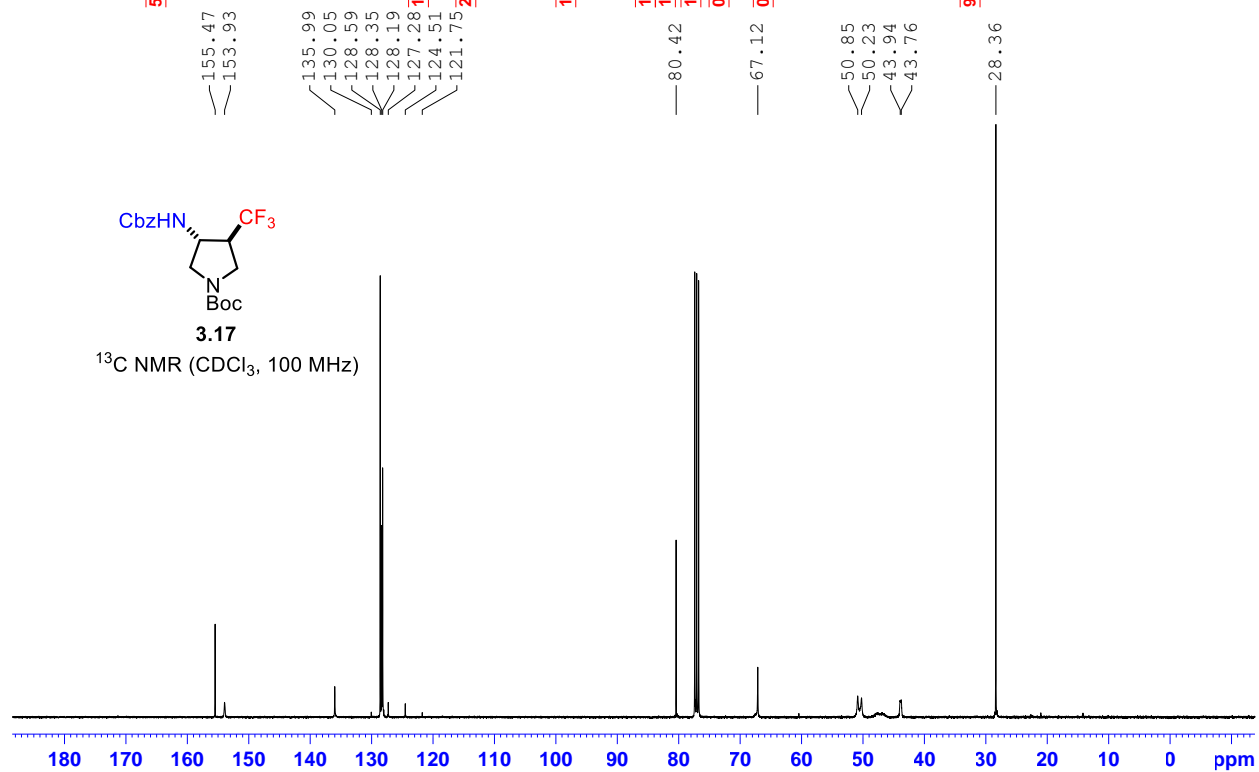
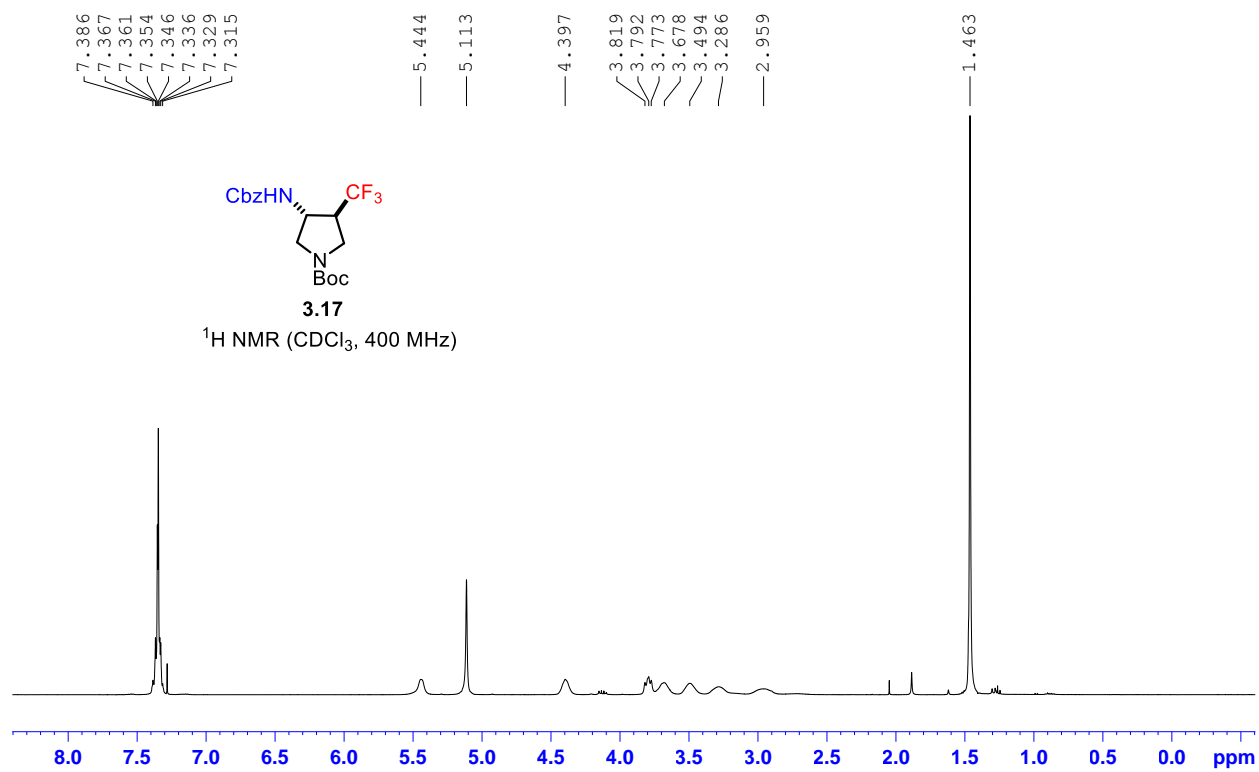


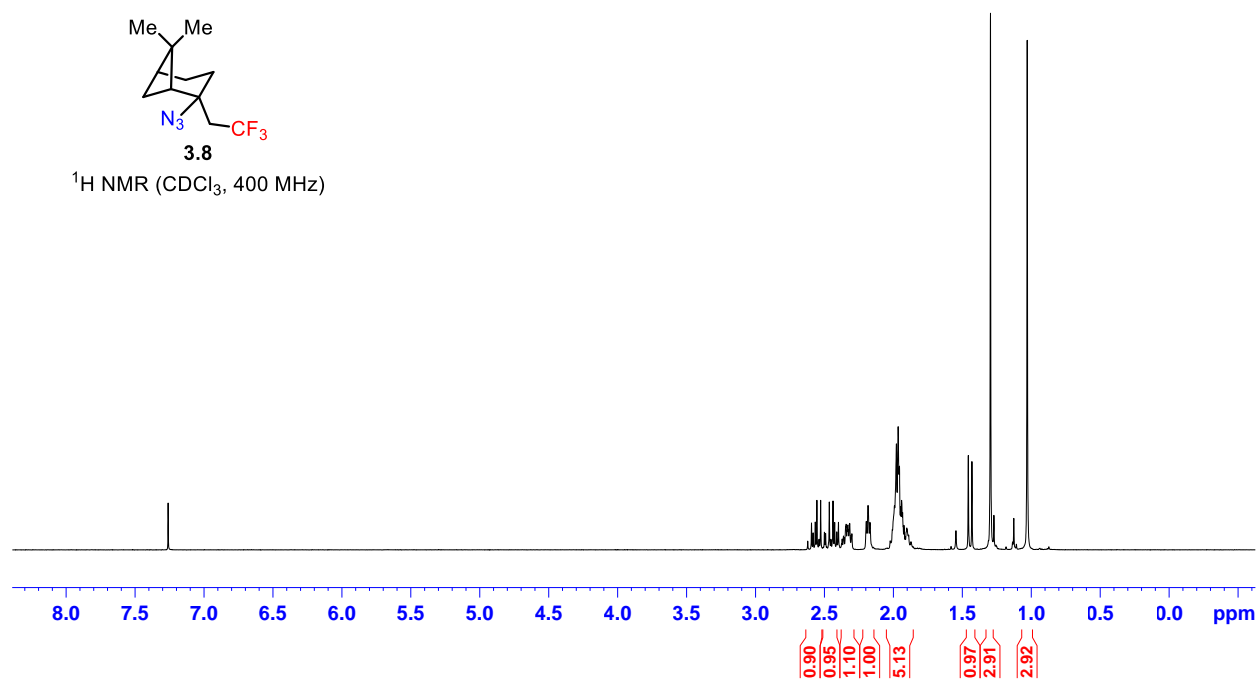
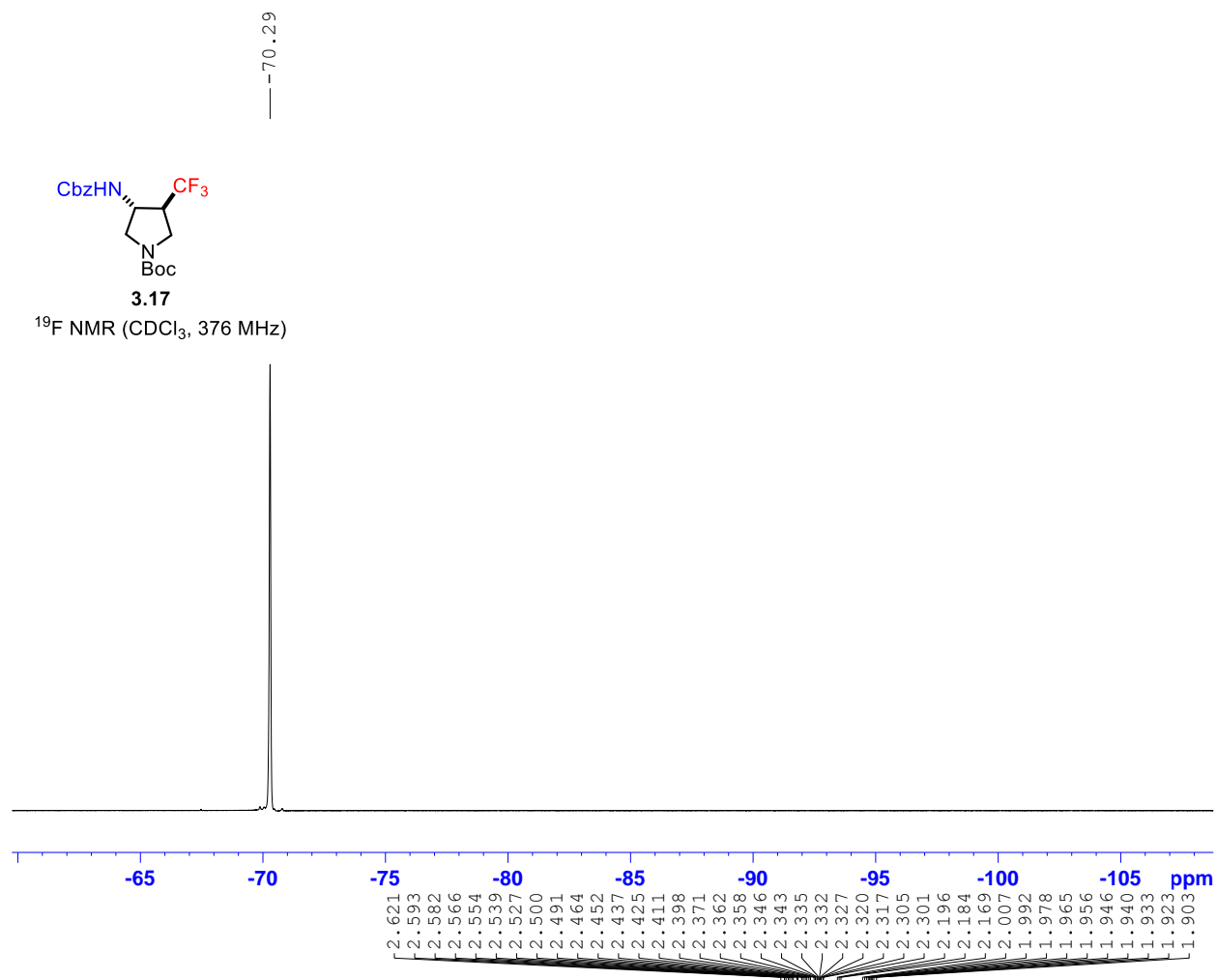


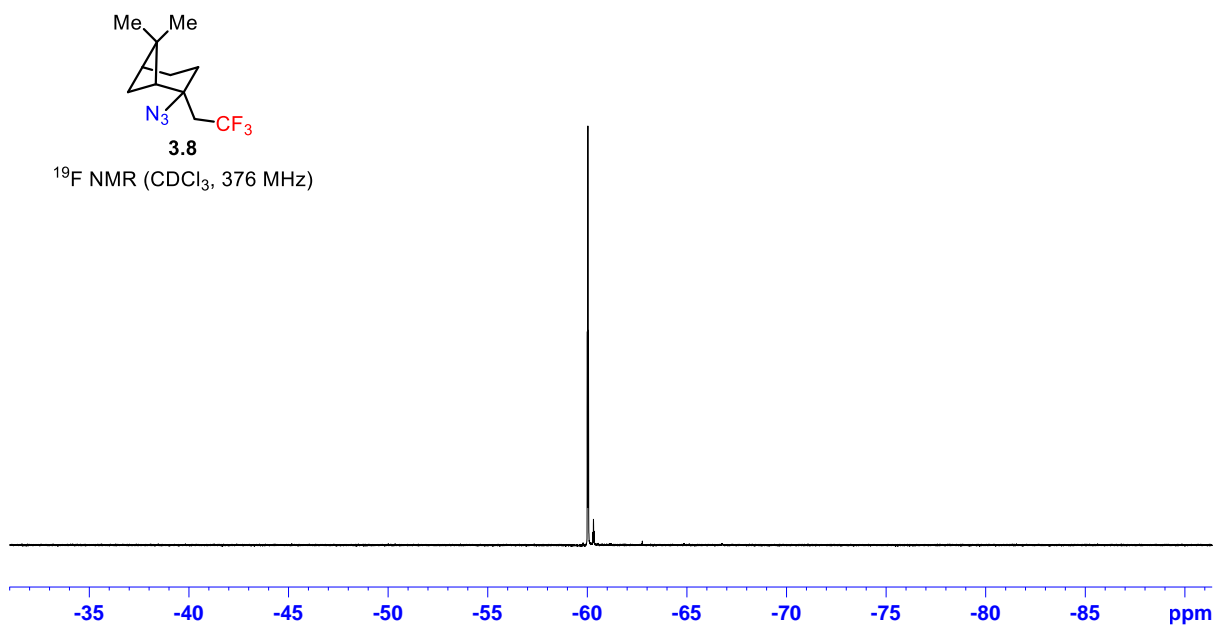
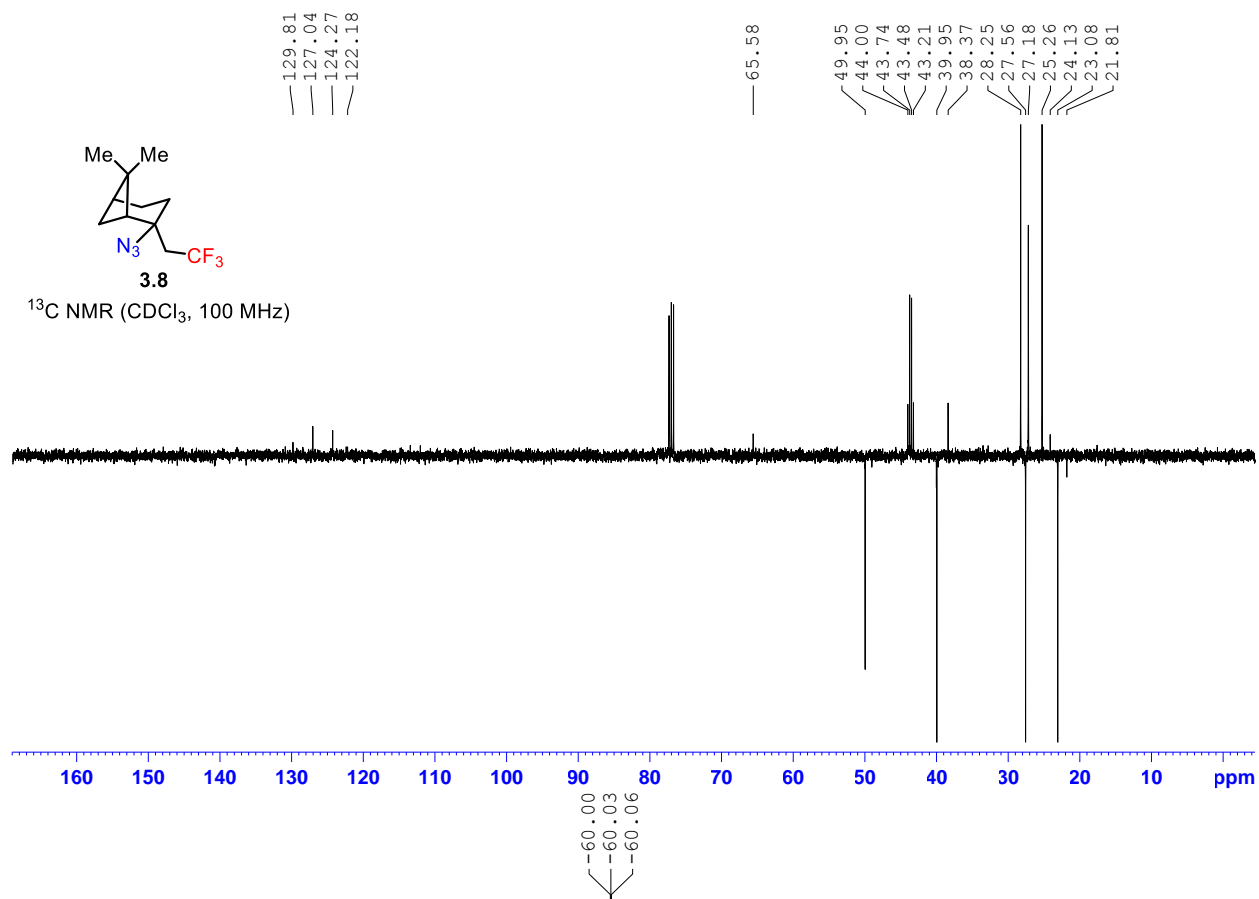


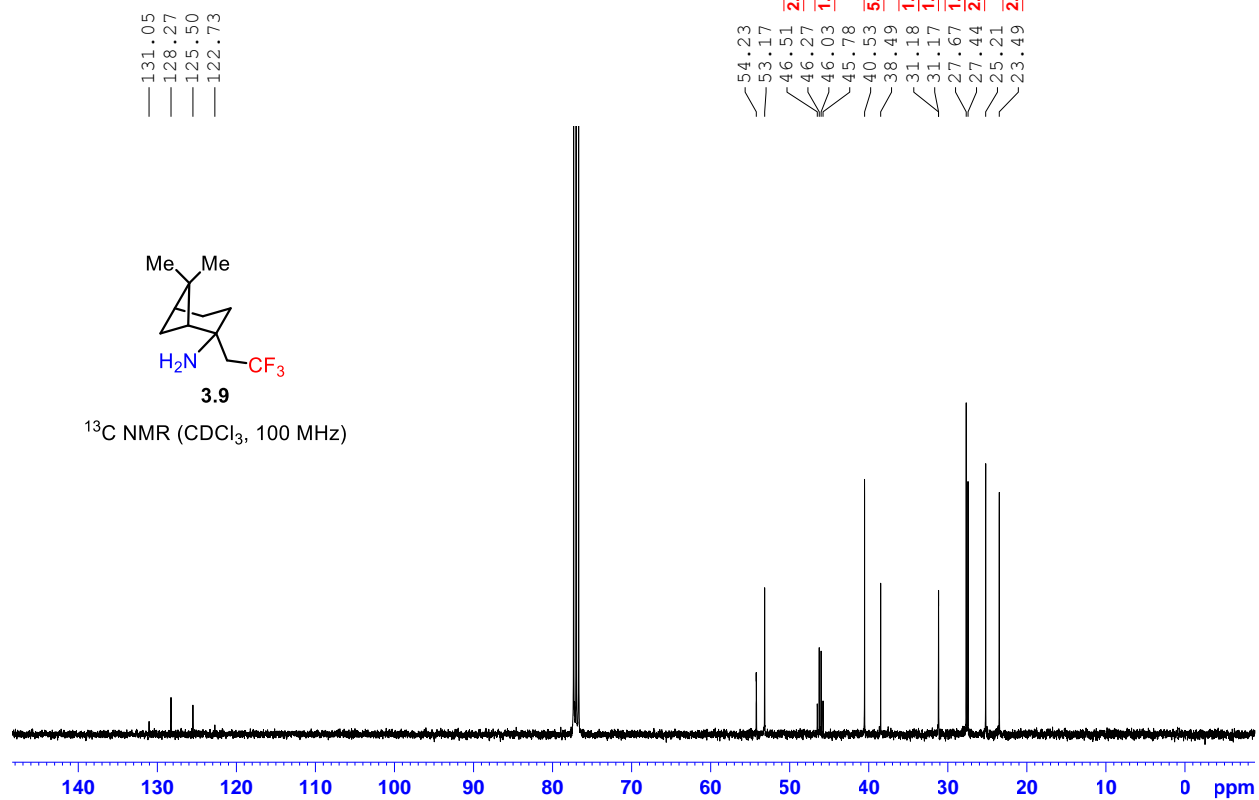
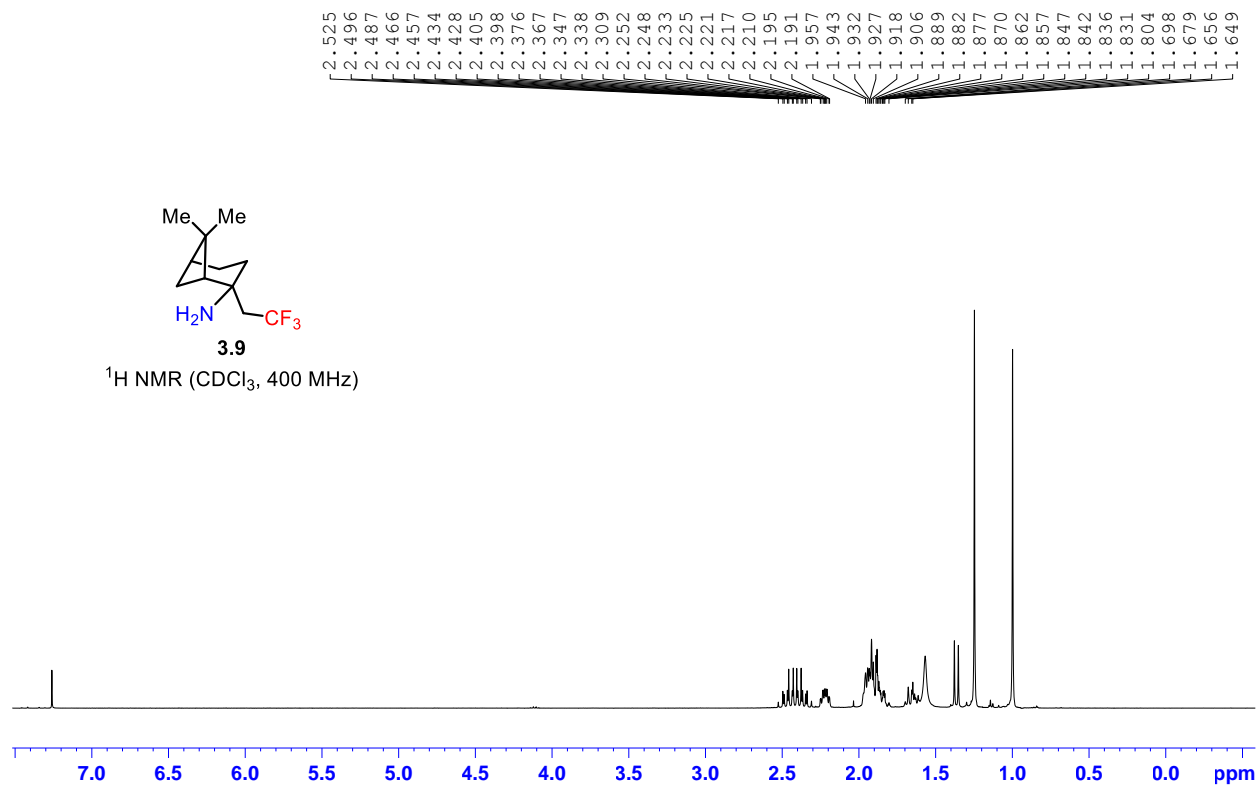
**3.15a** ^{19}F NMR (CD_3CN , 376 MHz)**3.15** ^1H NMR (d_6 -Acetone, 400 MHz)

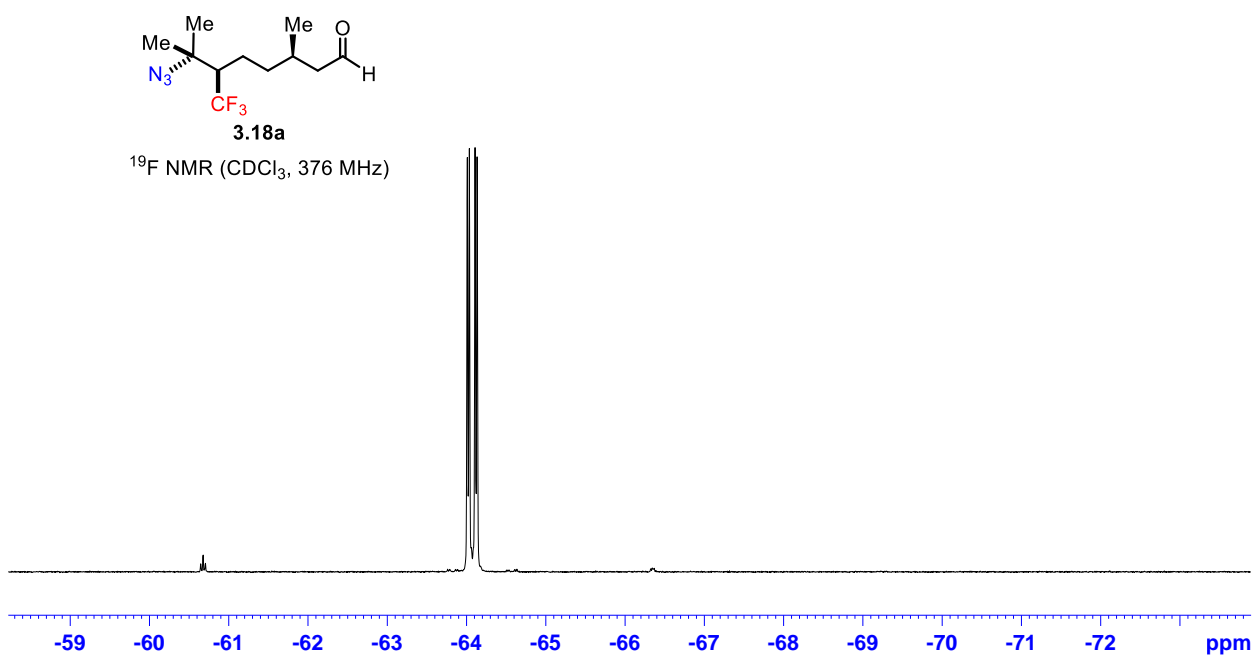
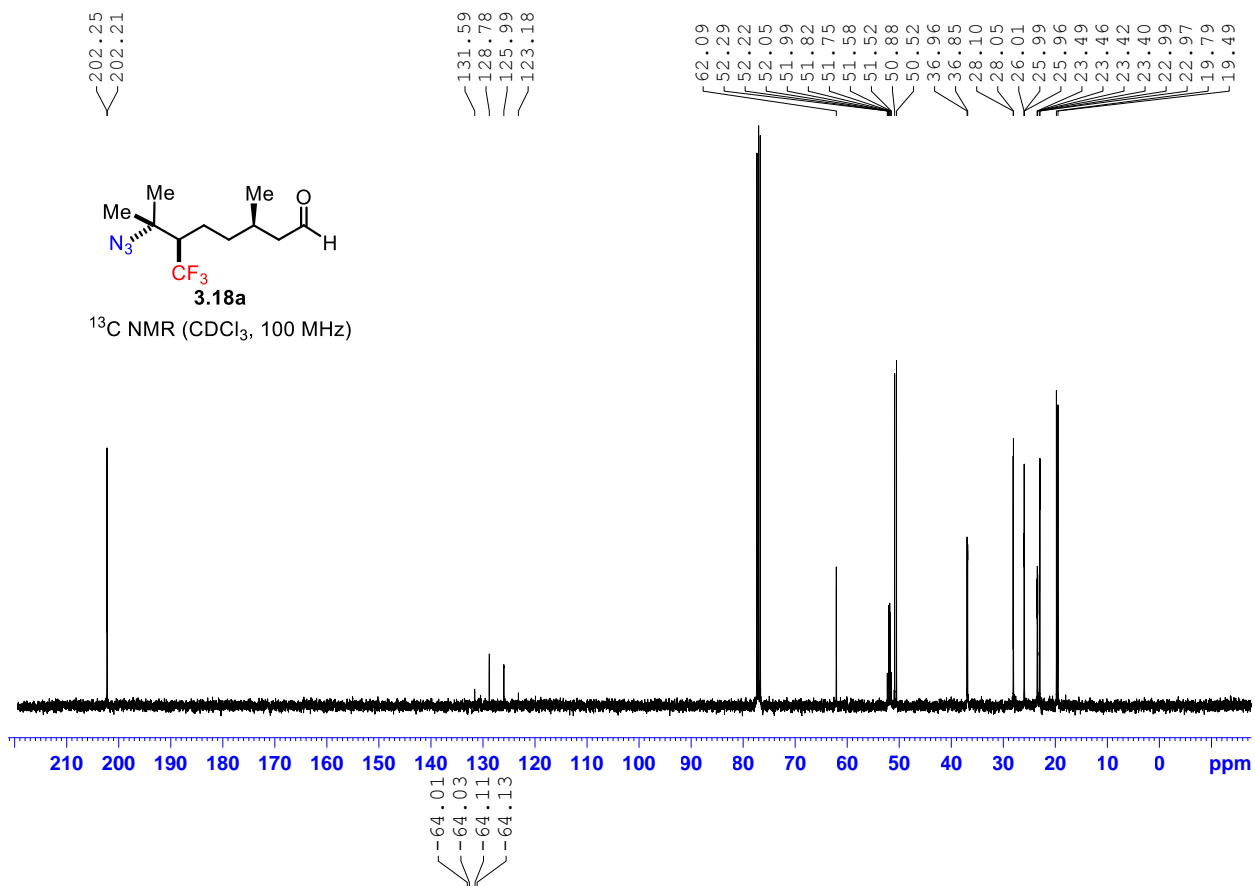


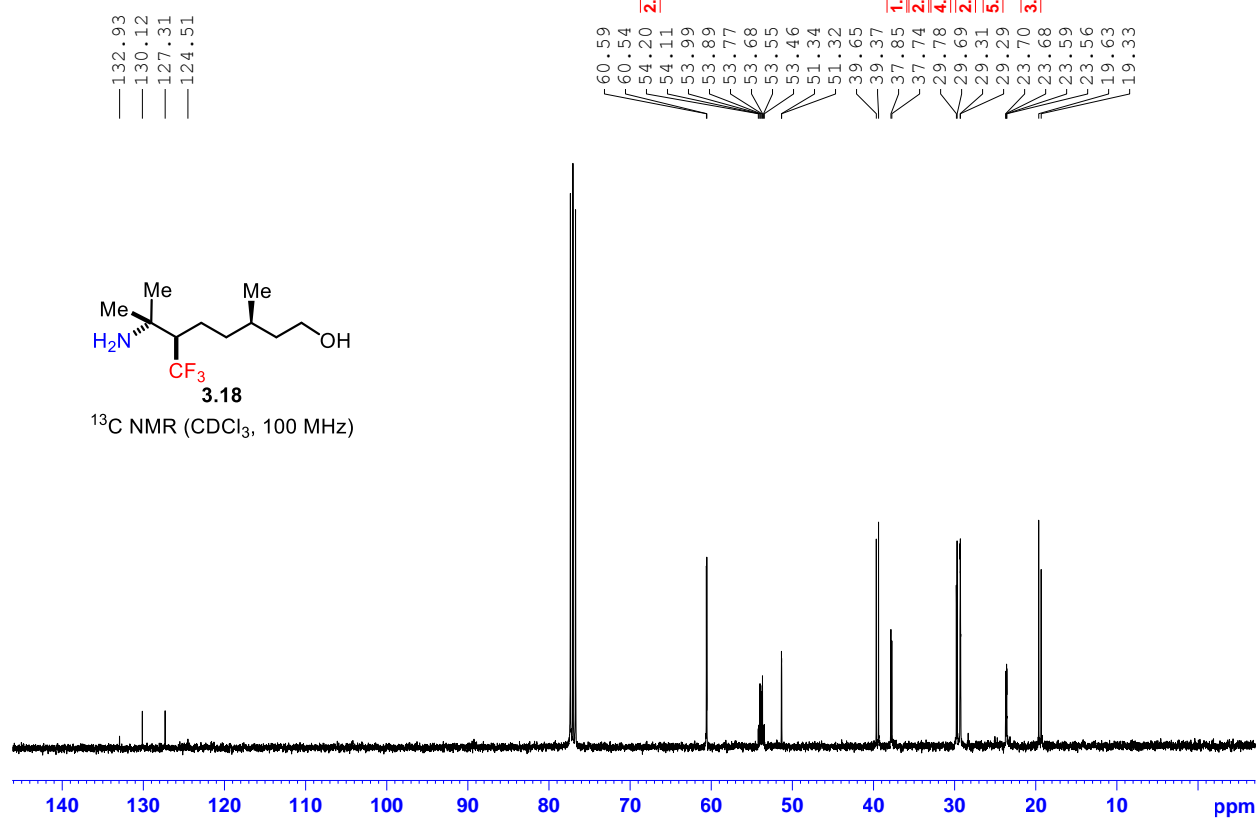
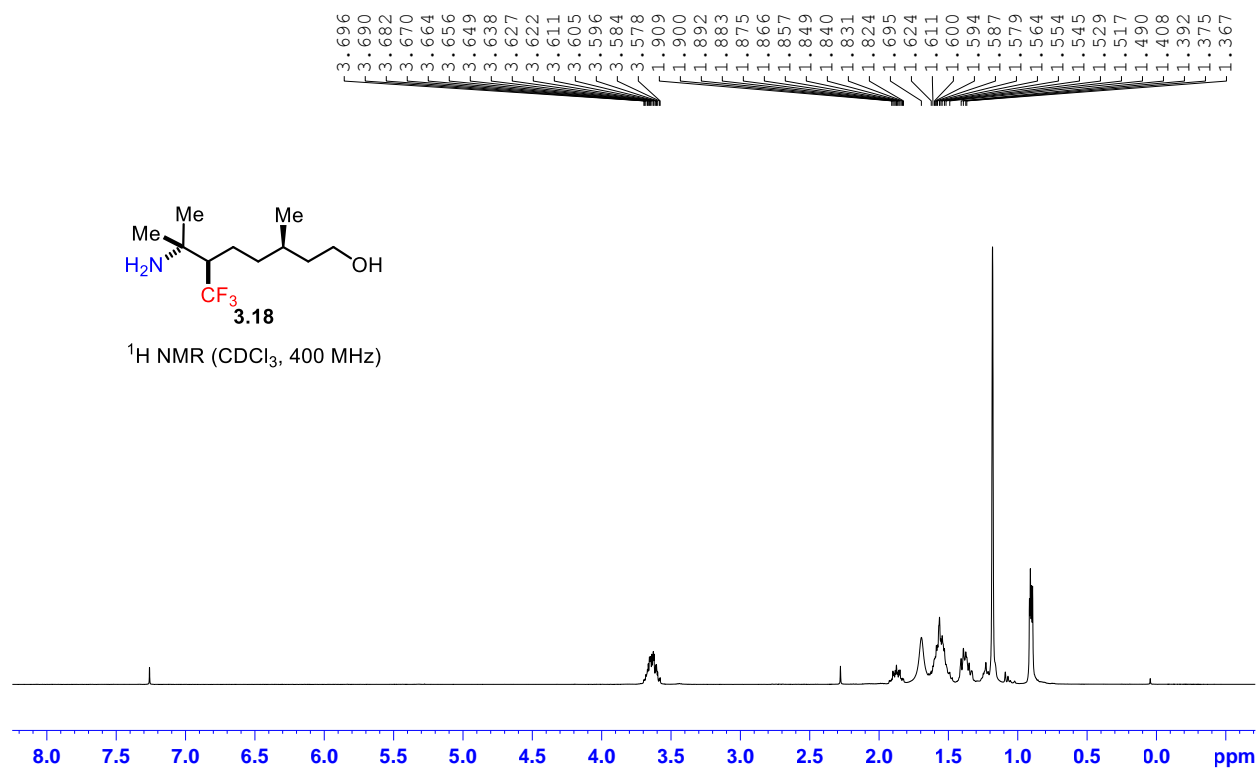


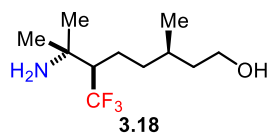




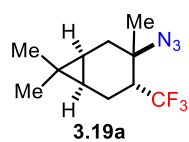
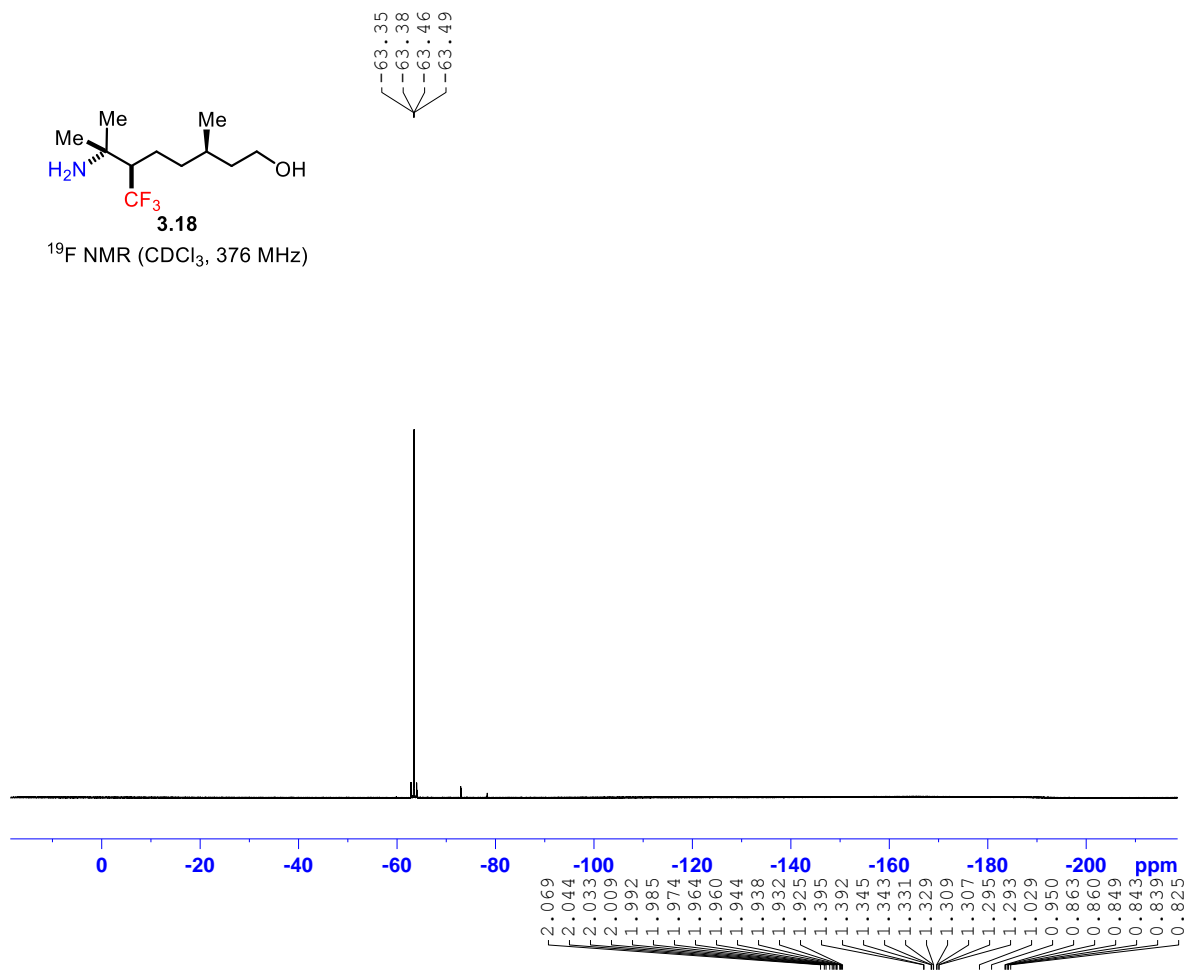




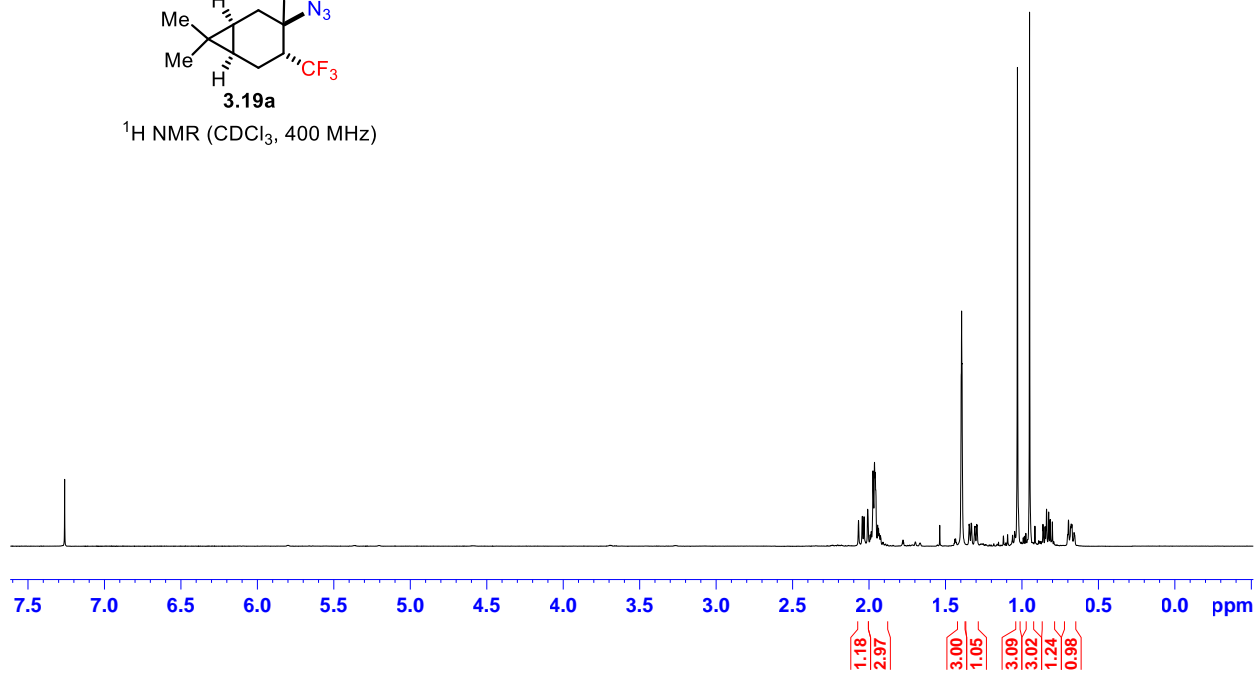


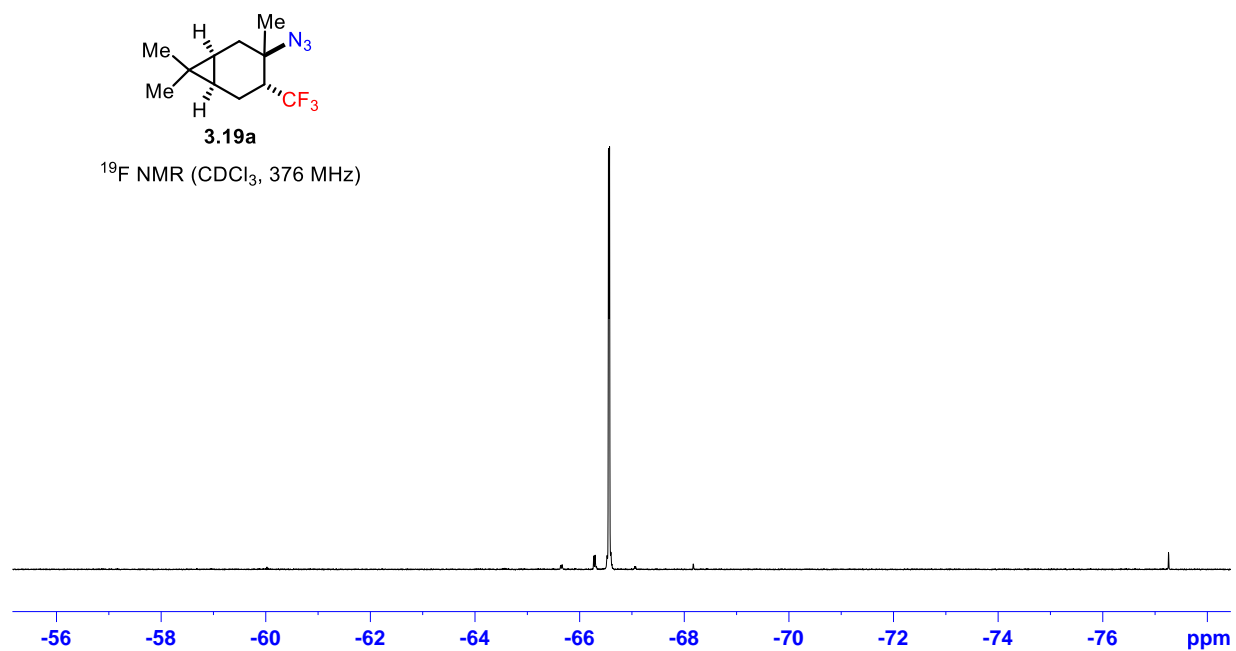
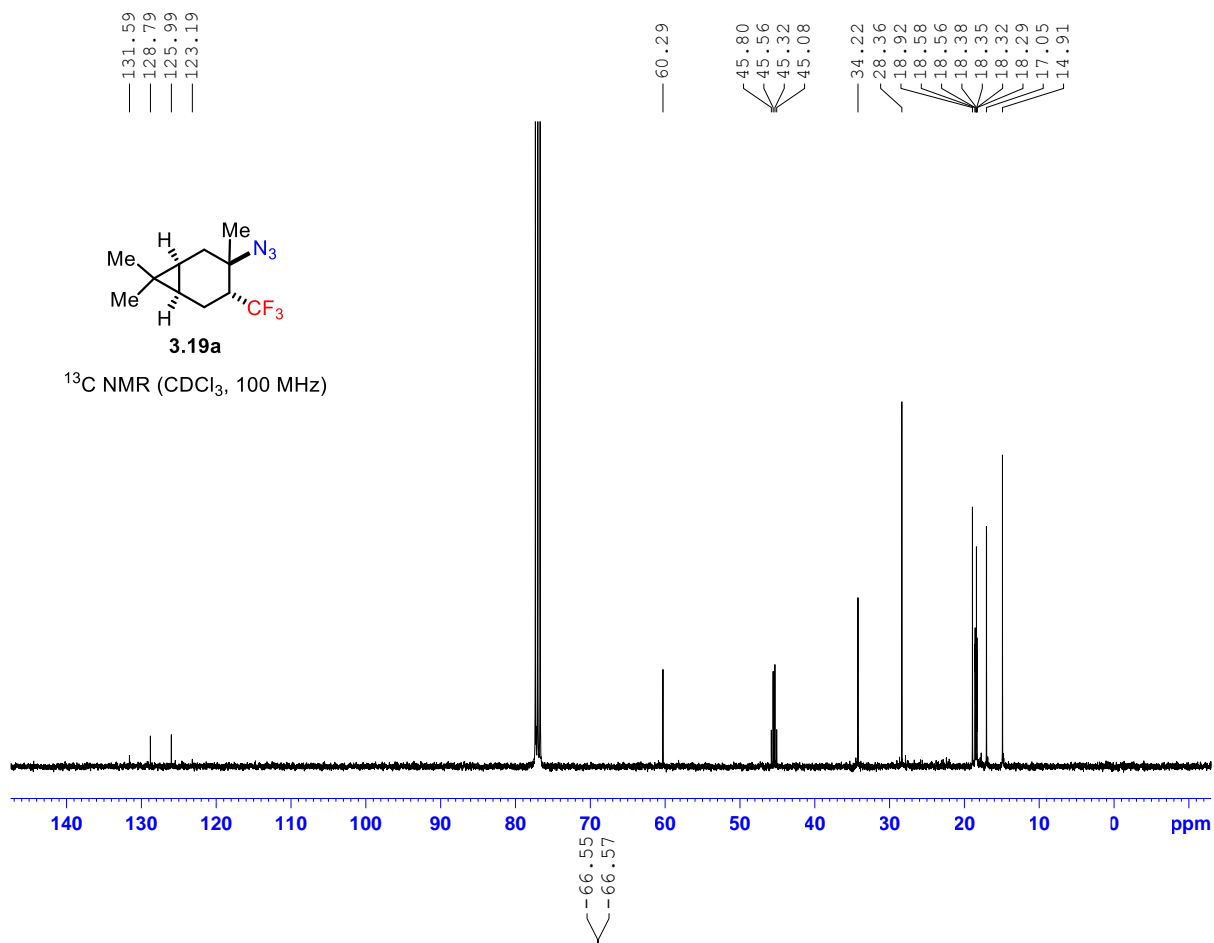


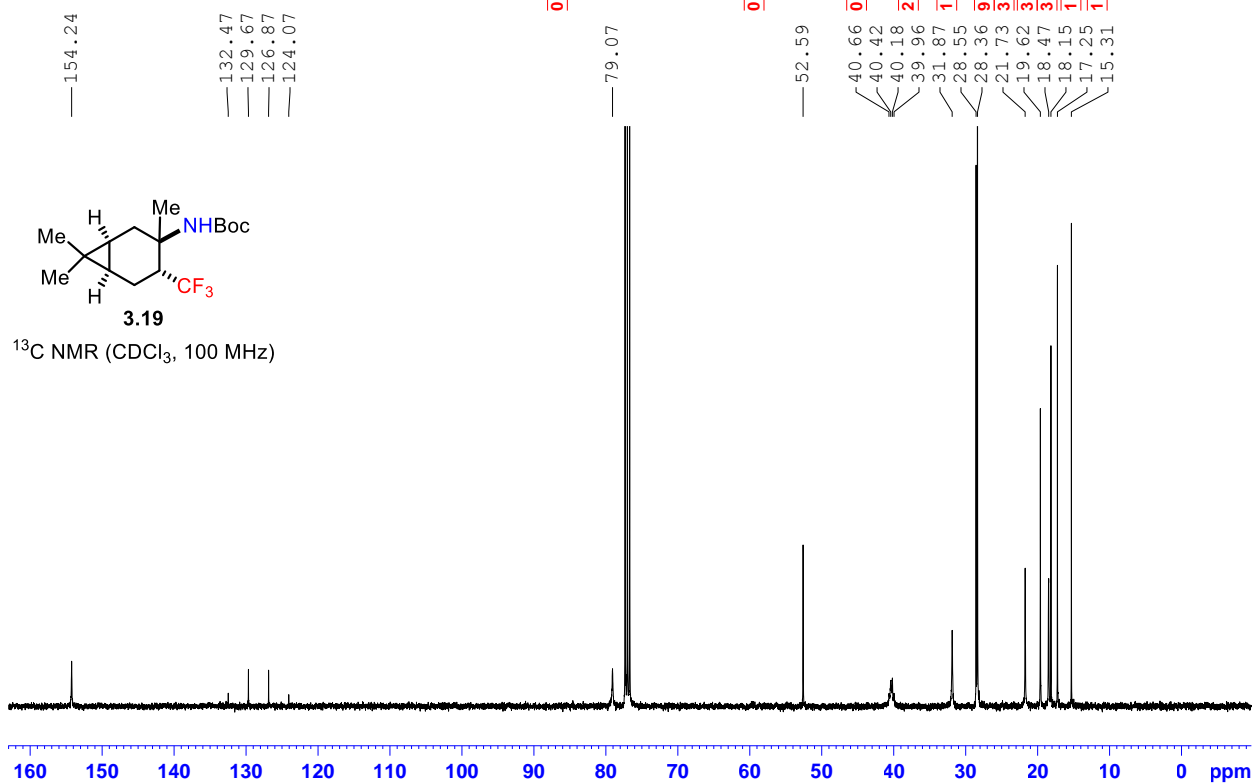
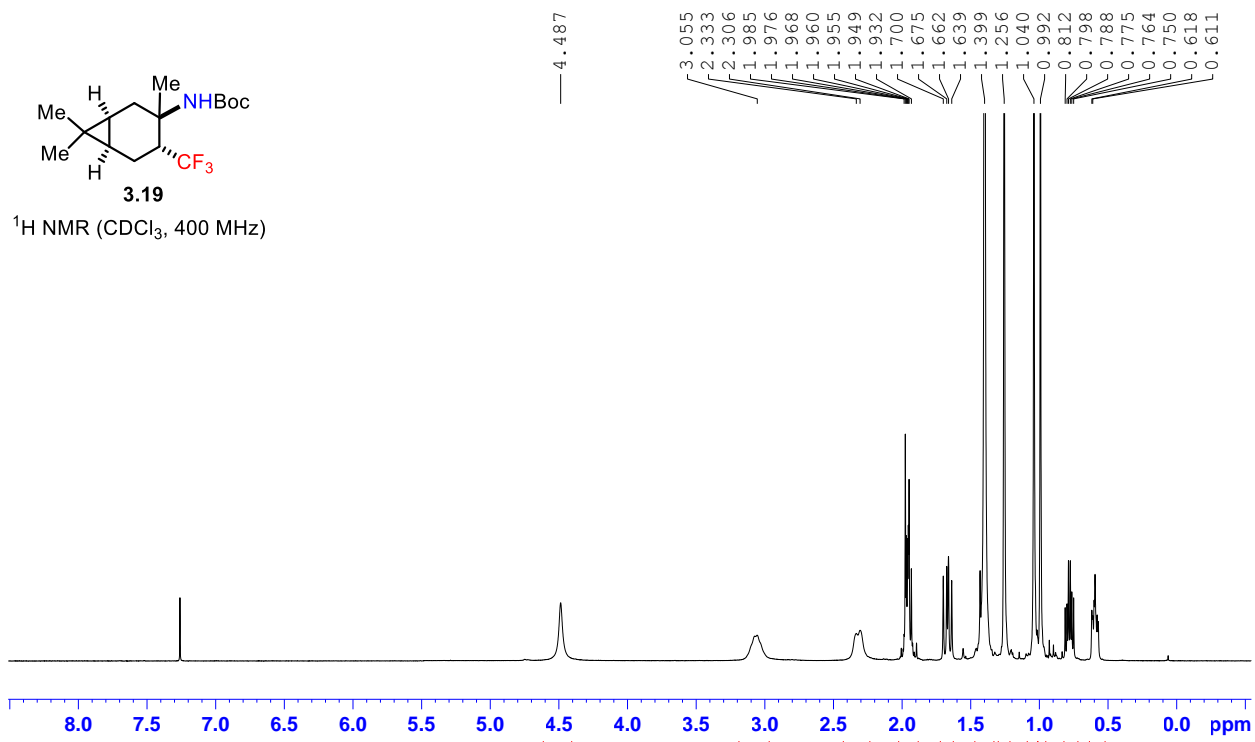
^{19}F NMR (CDCl_3 , 376 MHz)

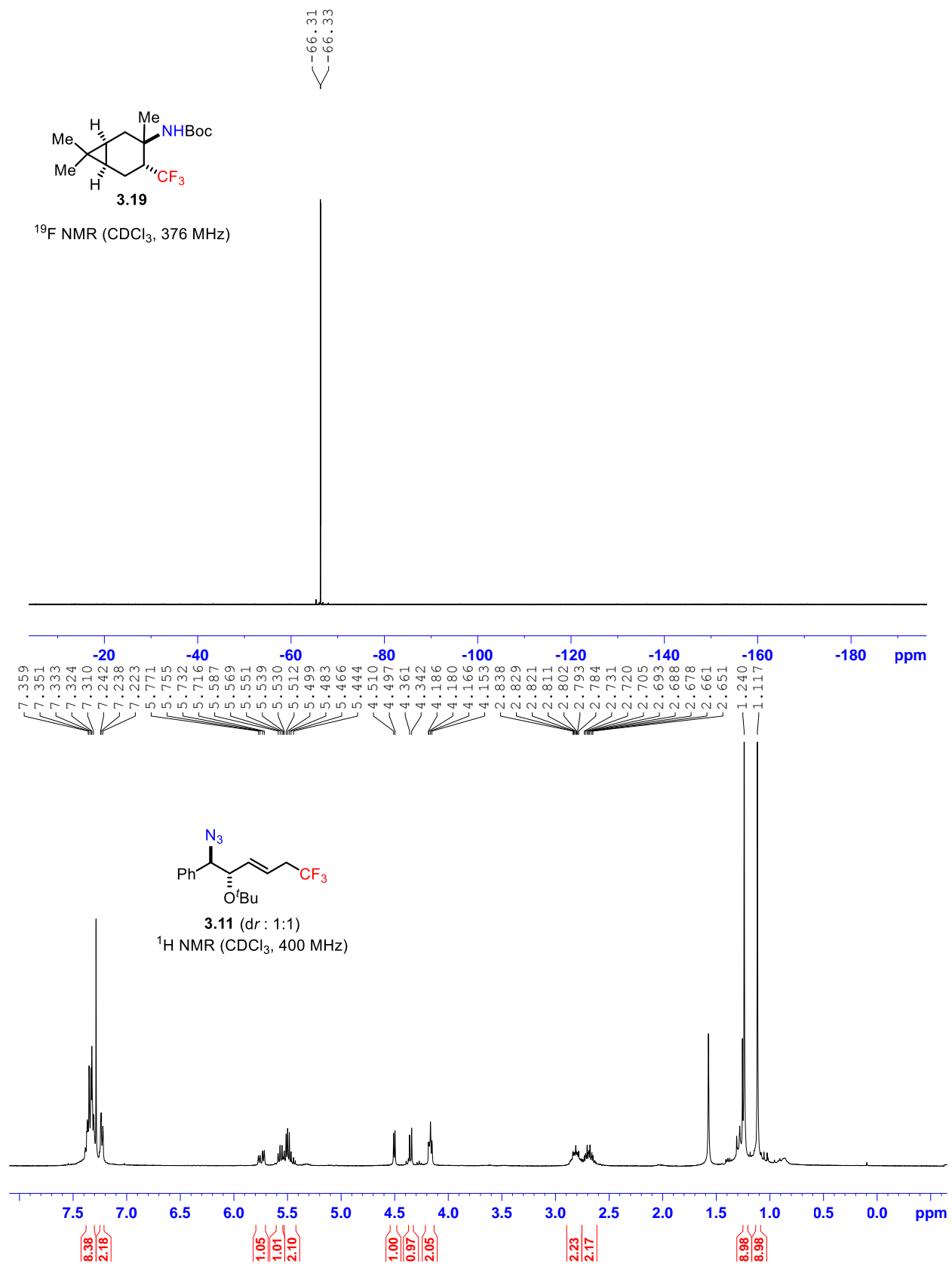


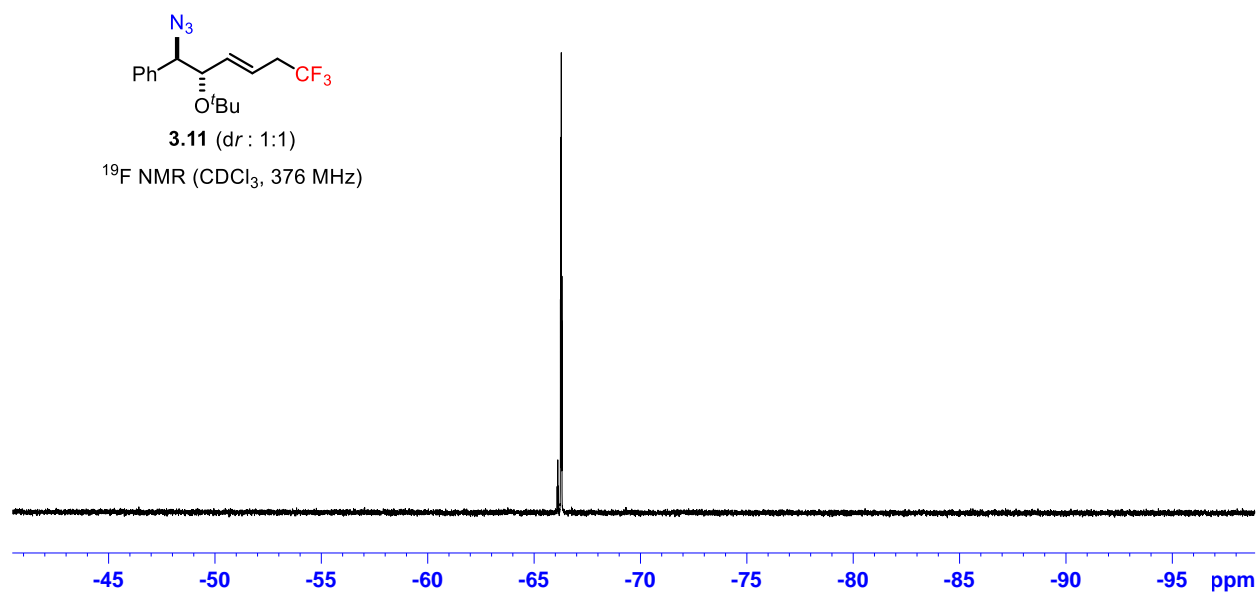
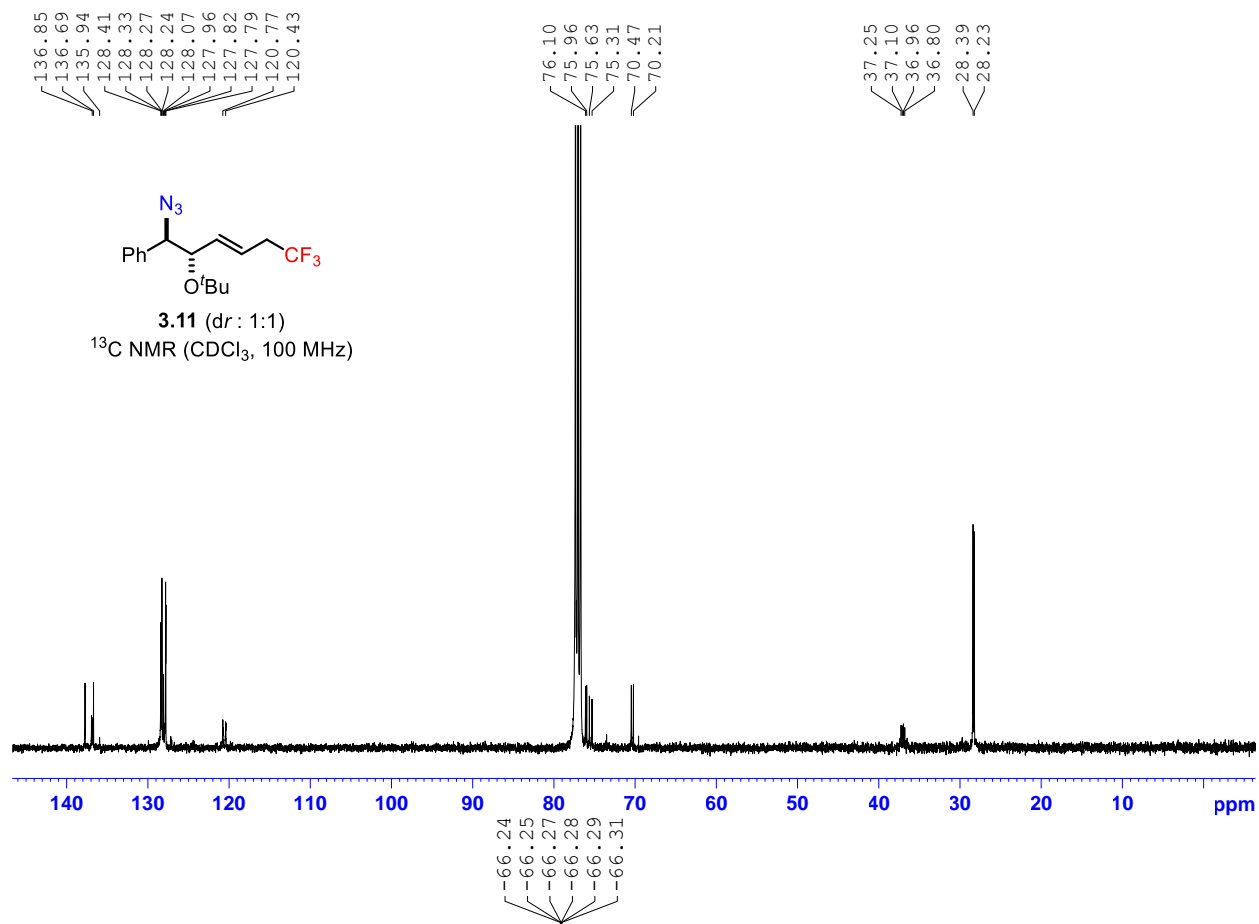
^1H NMR (CDCl_3 , 400 MHz)











Appendix D. Author's Curriculum Vitae

Name: Zhu, Chengliang

Education:

- August 2012–August 2017

Georgia State University, Department of Chemistry, Atlanta, GA

Ph.D. with Professor Hao Xu

Dissertation: “Stereoselective Iron-Catalyzed Intermolecular Olefin Amino-oxygenation, Amino-Fluorination and Trifluoromethyl Azidation”

- August 2009–May 2012

The University of Nevada, Reno, Department of Chemistry, Reno, NV

M.Sc. with Professor Robert S. Sheridan

Thesis: “*ortho*-Tolyl(trifluoromethyl)carbenes: Generation, Calculations, and Reactions Through Quantum Mechanical Tunneling”

- September 2004–July 2008

Hunan University, Department of Chemistry, Changsha, People's Republic of China

B.Sc. in Applied Chemistry (Advisor: Professor Ze Tan)

Selected Honors and Awards (2012–2017):

- | | |
|--|------|
| ❖ Doctoral Gold Award in Chemistry (Chemistry Department, Georgia State University) | 2017 |
| ❖ The Chair's Award (Chemistry Department, Georgia State University) | 2016 |
| ❖ The <i>Sigma–Aldrich</i> Alfred R. Bader Award for Student Innovation (The <i>Sigma–Aldrich</i> Corporation) | 2015 |
| ❖ The Chair's Award (Chemistry Department, Georgia State University) | 2014 |

List of Publications at Georgia State University (2012–2017):

- Zhu, C.-L.; Lu, D.-F.; Xu, H.* “Iron(II) Bis(trifluoromethanesulfonyl)-imide” *e-Encyclopedia of Reagents for Organic Synthesis*. John Wiley & Sons: New York.
- Lu, D.-F.; Zhu, C.-L. (contributed equally with Lu, D.-F); Sears, J. D.; Xu, H.* “Iron(II)-Catalyzed Intermolecular Aminofluorination of Unfunctionalized Olefins Using Fluoride Ion” *J. Am. Chem. Soc.* **2016**, *138*, 11360–11367.

7. **Zhu, C.-L.**; Lu, D.-F.; Sears, J. D.; Jia, Z.-X.; Xu, H.* “Practical Synthetic Procedures of the Iron–Catalyzed Intermolecular Olefin Aminohydroxylation Using Functionalized Hydroxylamines” *Synthesis* **2016**, 48, 3031–3041. (*Invited Contribution for Practical Synthetic Procedure Series*)
6. **Zhu, C.-L.**; Tian, J.-S.; Gu, Z.-Y.; Xing, G.-W.; Xu, H.* “Iron(II)–Catalyzed Asymmetric Intramolecular Olefin Aminochlorination with Chloride Ion” *Chem. Sci.* **2015**, 6, 3044–3050.
5. Tian, J.-S.; **Zhu, C.-L.**; Chen, Y.-R.; Xu, H.* “Iron–Catalyzed Diastereoselective Olefin Aminobromination with Bromide Ion” *Synthesis* **2015**, 47, 1709–1715. (*Invited Contribution for Special Issue–Iron in Organic Synthesis*)
4. **Zhu, C. -L.**; Zhang, Y. Q.; Yuan, Y. A.; Xu, H.* “Copper–Catalyzed Aerobic C–H Trifluoromethylation of Phenanthrolines.” *Synlett.* **2015**, 26, 345–349. (*Invited Cluster Report–Catalysis with Sustainable Metals*)
3. Lu, D. F.; **Zhu, C. -L.**; Jia, Z. X.; Xu, H.* “Iron(II)–Catalyzed Intermolecular Amino–Oxygenation of Olefins through the N–O Bond Cleavage of Functionalized Hydroxylamines” *J. Am. Chem. Soc.* **2014**, 136, 13186–13189.
2. Lu, D. F.; Liu, G. S.; **Zhu, C. -L.**; Yuan, B.; Xu, H.* “Iron(II)–Catalyzed Intramolecular Olefin Aminofluorination.” *Org. Lett.* **2014**, 16, 2912–2915.
1. Lu, D. F.; **Zhu, C. -L.**; Xu, H.* “Copper(I)–Catalyzed Diastereoselective Hydroxytrifluoromethylation of Dienes Accelerated by Phosphine Ligands” *Chem. Sci.* **2013**, 4, 2478–2482.

Oral Presentations and Posters (2012–2017):

3. Poster in the 45th National Organic Chemistry Symposium, University of California, Davis, California, June 2017
Title: “Iron-Catalyzed Stereoselective Aminofluorination for Unfunctionalized Olefins”
2. Oral presentation in the Sigma-Aldrich Graduate Student Innovation Award Symposium. The Sigma–Aldrich Corporation, Milwaukee, WI, August 2015.
Title: “Iron–Catalyzed Stereoselective Aminohydroxylation and Aminofluorination of Alkenes”
1. Oral presentation in the 250th ACS National Meeting, Boston, MA, August 2015 (paper ORGN 410).
Title: “Iron (II)–Catalyzed Stereoselective Intramolecular Olefin Aminofluorination and Aminochlorination”