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Studies of Novel Transition-Metal-Catalyzed Oxidative Coupling Reactions

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Studies in Novel Transition-Metal-Catalyzed Oxidative Coupling Reactions

For the degree of Doctor of Philosophy

Is approved by the final examining committee:

Haibo Ge Chair	Chengde Mao
Robert Minto	
Martin O'Donnell	
Mingji Dai	

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Approved by Major Professor(s): Haibo Ge

Approved by: Eric Long 4/19/2016

Head of the Departmental Graduate Program Date

STUDIES IN NOVEL TRANSITION-METAL-CATALYZED OXIDATIVE COUPLING REACTIONS

A Dissertation

Submitted to the Faculty

of

Purdue University

by

Jinmin Miao

In Partial Fulfillment of the

Requirements for the Degree

of

Doctor of Philosophy

May 2016

Purdue University

West Lafayette, Indiana

For my parents. I hope this achievement will contribute to the dream that you had for me.

For my beloved wife, Peggy.

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ABSTRACT

Miao, Jinmin. Ph.D., Purdue University, May 2016. Studies in Novel Transition-Metal-Catalyzed Oxidative Coupling Reactions. Professor: Haibo Ge.

Transition-metal-catalyzed oxidative coupling reactions are important tools for the construction of carbon-carbon (C−C) and carbon-heteroatom (C−X) bonds from simple starting materials. A series of novel and synthetically useful reactions have been developed and are herein described.

Palladium-catalyzed chemoselective decarboxylative cross-coupling of benzoic acids with α-oxocarboxylic acids was realized via an arene sp^2 C−H functionalization process. This work represents the first example of transition-metal-catalyzed cross-coupling reactions with two acids acting in different roles. The synthetic utility of this method was confirmed by the synthesis of pitofenone, an antispasmodic used in the combined drug Spasmalgon.

A highly site-selective and diastereoselective fluorination of aliphatic amides via a palladium−catalyzed bidentate ligand-directed C−H bond functionalization process on unactivated sp^3 carbons was developed. A wide variety of β-fluorinated amino acid derivatives and aliphatic amides, important motifs in medicinal and agricultural chemistry, were prepared with palladium acetate as the catalyst and selectfluor as the fluorine source.

The synthesis for cinnolines from *N*-phenylhydrazones was performed through an oxidation/cyclization sequence, representing the first copper-catalyzed coupling reaction of hydrazones through a C(sp^3)−H bond functionalization process. The method provides an environmentally friendly and atom-efficient approach to biologically active cinnoline derivatives.

A novel rhodium-catalyzed imination of sulfoxides using *O*-(2,4-dinitrophenyl)-hydroxylamine was developed under mild conditions with good functional group tolerance. The reaction provides an efficient access to free *NH*-sulfoximines, an important structural unit in a variety of biologically active compounds.

CHAPTER 1. INTRODUCTION

Construction of new carbon-carbon and carbon-heteroatom bonds is essential in organic chemistry. Traditionally, this process primarily relies on the use of prefunctionalized substrates, such as alkyl halides, triflates, boron or tin reagents. Despite its broad application in organic synthesis, the prefunctionalization of the starting materials usually requires additional synthetic steps, and thus reduces the overall efficiency of the approach. Moreover, in many cases, stoichiometric amounts of often toxic metal waste are generated in the process, which constitutes an environmental issue. As a promising tool for the efficient formation of C-C and C-X bonds, transition-metal-catalyzed direct functionalization of unreactive C−H bonds has emerged as a major topic of research in recent years. During the past decade, transition-metal-catalyzed direct C−H functionalization reactions have emerged as an essential topic in the field of organic synthetic methodology. Efficient and selective reactions of this type will definitely find widespread application in natural product research, material sciences, and pharmaceuticals.

In this dissertation, chapters 2−4 describe three novel transition-metal-catalyzed C−H functionalization reactions that were developed during my graduate research. In chapter 5, a rhodium-catalyzed oxidative coupling reaction of sulfoxides with a nitrene precursor is discussed.

CHAPTER 2. PALLADIUM-CATALYZED DIRECT ORTHO-ACYLATION OF BENZOIC ACIDS

(Reproduced in part with permission from Miao, J.-M.; Ge, H.-B. "Palladium-Catalyzed Chemoselective Decarboxylative Ortho Acylation of Benzoic Acids with α-Oxocarboxylic Acids", *Org. Lett*. **2013**, *15*, 2930-2933. Copyright 2013 American Chemical Society)

2.1 Introduction

2-Benzoylbenzoic acid derivatives are important intermediates for the synthesis of various bioactive compounds,[1] and are often encountered as subunits of many biologically active compounds[2] including natural products, pharmaceuticals, and agrochemical compounds. For example, balanol, a fungal metabolite produced by the fungus *Verticillium*

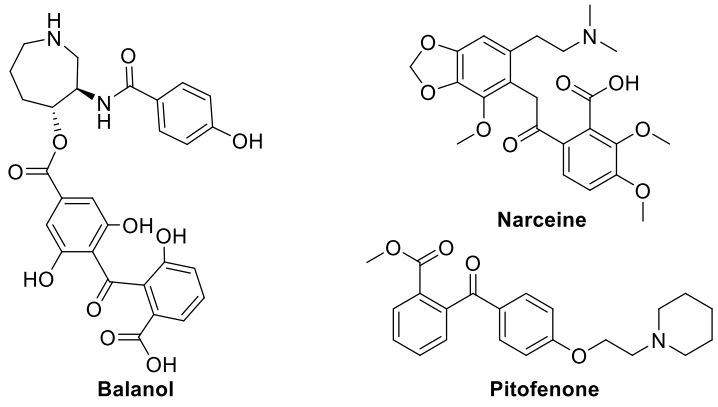
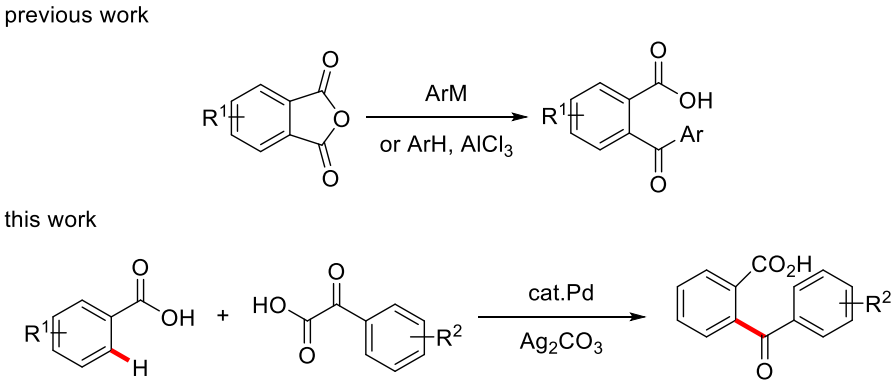


Figure 2.1 Representative Biologically Active Compounds Containing 2-Acylbezoic Acid/Ester Moiety.

balanoides and other fungi, is a potent inhibitor of protein kinase C (PKC);[1j,k] narceine, an opium alkaloid produced by the *Papaver somniferum* plant, is a bitter compound with narcotic effects;[1i] pitofenone, the key ingredient in Spasmalgon (a combined drug), is an antispasmodic (Figure 2.1).[1d] Additionally, 2-benzoylbenzoic acids are often used as functional groups or substrates in photochemistry,[3] chromatography[4] and food chemistry.[5]



Scheme 2.1 Synthesis of 2-Acylbenzoic Acids

Despite the demonstrated biological importance of 2-acylbenzoic acids, synthetic methods for these species are far from maturity. The most common routes start from 1,3-isobenzofurandione derivatives and involve either a nucleophilic addition/elimination process by organometallic reagents[6] or a Friedel-Crafts acylation process (Scheme 1.1).[7] In many cases, these reactions suffer severely from poor regioselectivity on the benzofurandione, and thus substituted 2-acylbenzoic acids are difficult to obtain in a satisfactory yield.[6b,7c] Therefore, the need for complementary, concise, and effective approaches to access these compounds is clear. On the basis of our success on direct ortho acylation of 2-phenylpyridines and acetanilides,[8] we proposed that an efficient approach for the synthesis of 2-acylbenzoic acids could be achieved by decarboxylative cross-

coupling of benzoic acids with α-oxocarboxylic acids by a Pd(II)-catalyzed C−H functionalization process (Scheme 2.1).

Transition-metal-catalyzed cross-coupling reactions remain one of the most powerful methods for carbon-carbon (C−C) bond formation.[9] Among these methods, Pd(0)-catalyzed decarboxylative cross-coupling has recently attracted considerable attention due to the low cost, ready availability, and environmentally benign properties of carboxylic acids.[10] Along with the well-studied benzoic acids, alkyl, alkenyl and alkynyl acids, α-oxocarboxylates, and oxalates have also been demonstrated as effective substrates, which enable the installation of a variety of functional groups on aromatic rings. Furthermore, since Crabtree first reported a direct decarboxylative cross-coupling of arenes with aromatic acids through a Pd(II)-catalyzed C−H functionalization process,[11] the method has attracted considerable attention because the prefunctionalization of reaction substrates is avoided.[12]

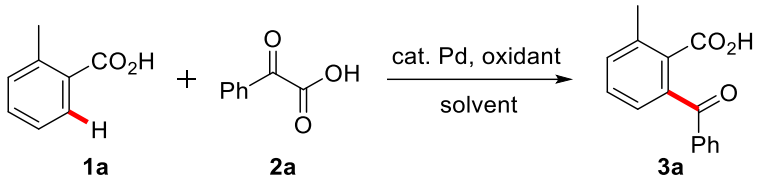
As substrates, benzoic acids have been extensively studied in decarboxylative cross-coupling reactions by both Pd(0) and Pd(II) catalysis. It has been demonstrated that either a silver or copper source could effectively mediate the decarboxylation. On the other hand, from Yu's studies, benzoic acid derivatives were fairly stable at high temperature (130 ˚C) in the presence of a catalytic amount of a Pd(II) source and an excess Ag(I) source.[13] Moreover, α-oxocarboxylic acids, utilized in Goossen's laboratory in Pd(0)-catalyzed decarboxylative cross-couplings,[14] have also been demonstrated as effective coupling partners in Pd(II) catalysis in our laboratory with either a silver or persulfate source as an oxidant and the decarboxylation reagent.[8,15] It was also noted that, along with

actanilides and 2-phenylpyridines, cyclic enamides[16], *O*-methyl oximes[17], phenylacetamides[18], *O*-phenyl carbamates[19], and 1-(pyrimidin-2-yl)-1*H*-indoles[20] were also effective substrates for the direct decarboxylative acylation. These results support the feasibility of chemoselective decarboxylative cross-coupling of benzoic acids with α-oxocarboxylic acids through Pd(II) catalysis under well-defined reaction conditions. It is noteworthy that, although the benzoic acid derivatives have been well studied as the substrates in metal-catalyzed C−H bond activation reactions,[9] direct *ortho*-acylation of benzoic acids remains a challenge. Furthermore, transition-metal-catalyzed cross-coupling of two carboxylic acids with different roles in the reaction has not been reported. As part of our program to develop novel transition-metal-catalyzed cross-coupling reactions with diverse substrates,[8,15,21] we have developed the synthesis of 2-acylbenzoic acid derivatives through chemoselective decarboxylative cross-coupling of benzoic acids with α-oxocarboxylic acids via a palladium-catalyzed C−H bond functionalization process.

2.2 Results and Discussion

Considering that an α-oxocarboxylic acid is a potential source of benzoic acid through decarboxylation and oxidation, 2-methylbenzoic acid was chosen as the substrate for the decarboxylative cross-coupling reaction with α-oxocarboxylic acid in the presence of a catalytic amount of $Pd(TFA)_2$ and an excess amount of Ag_2CO_3 as the oxidant and the decarboxylation reagent on the basis of our previous reports.[8,21] After an extensive solvent screening, DME and dioxane were shown to be optimal solvents for this coupling, providing the desired product in moderate yields (Table 2.1, entries 4 and 5). The following survey of catalysts indicated that although $PdCl_2(MeCN)_2$ and $Pd(OAc)_2$ could also

Table 2.1 Optimization of Reaction Conditions for Acylation[a]



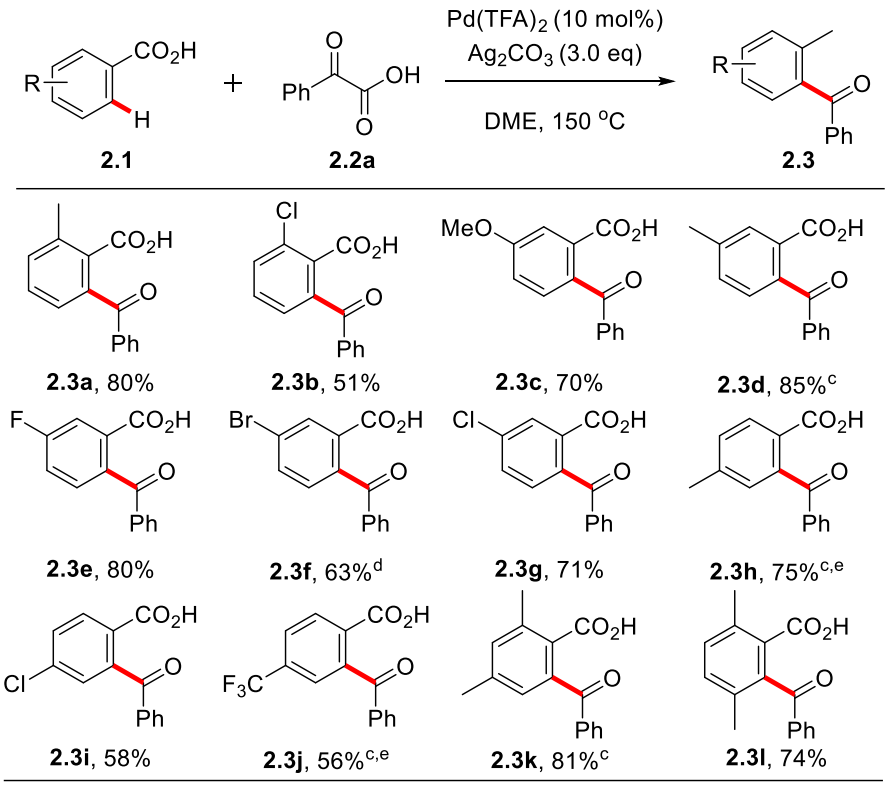
1a 2a 3a

Entry	Pd Source (mol %)	Oxidant (equiv)	Solvents (mL)	Yield (%)[b]
1	$Pd(TFA)_2$	Ag_2CO_3 (2.0)	DMF	trace
2	$Pd(TFA)_2$	Ag_2CO_3 (2.0)	THF	trace
3	$Pd(TFA)_2$	Ag_2CO_3 (2.0)	^{t}BuOH	32
4	$Pd(TFA)_2$	Ag_2CO_3 (2.0)	dioxane	55
5	$Pd(TFA)_2$	Ag_2CO_3 (2.0)	DME	58
6	$PdCl_2(PhCN)_2$	Ag_2CO_3 (2.0)	DME	trace
7	$PdCl_2(MeCN)_2$	Ag_2CO_3 (2.0)	DME	41
8	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DME	48
9	$Pd(TFA)_2$	Ag_2O (2.0)	DME	20
10	$Pd(TFA)_2$	AgOAc (2.0)	DME	38
11	$Pd(TFA)_2$	$(NH_4)_2S_2O_8$ (2.0)	DME	0
12[c]	$Pd(TFA)_2$	Ag_2CO_3 (2.0)	DME	60
13	$Pd(TFA)_2$	Ag_2CO_3 (3.0)	DME	64
14[d]	**$Pd(TFA)_2$**	**Ag_2CO_3 (3.0)**	**DME**	**80**
15	$Pd(TFA)_2$	Ag_2CO_3 (3.0)	DME	56
16[d]	$Pd(TFA)_2$	Ag_2CO_3 (3.0)	dioxane	67

[a] Conditions: **1a** (0.2 mmol), Pd source, oxidants, **2a** (0.6 mmol), 2 mL of solvent, 120 ˚C, 24 h unless otherwise noted. [b] Isolated yields. [c] 48 h. [d] At 150 ˚C.

catalyze this reaction, $Pd(TFA)_2$ is more effective (entries 7 and 8). A further survey of oxidants showed that silver carbonate was the best choice. Due to our success in the decarboxylation of α-oxocarboxylic acids with a persulfate salt[8], replacement of Ag_2CO_3 with $K_2S_2O_8$, $Na_2S_2O_8$, or $(NH_4)_2S_2O_8$ was also examined. However, the addition of these

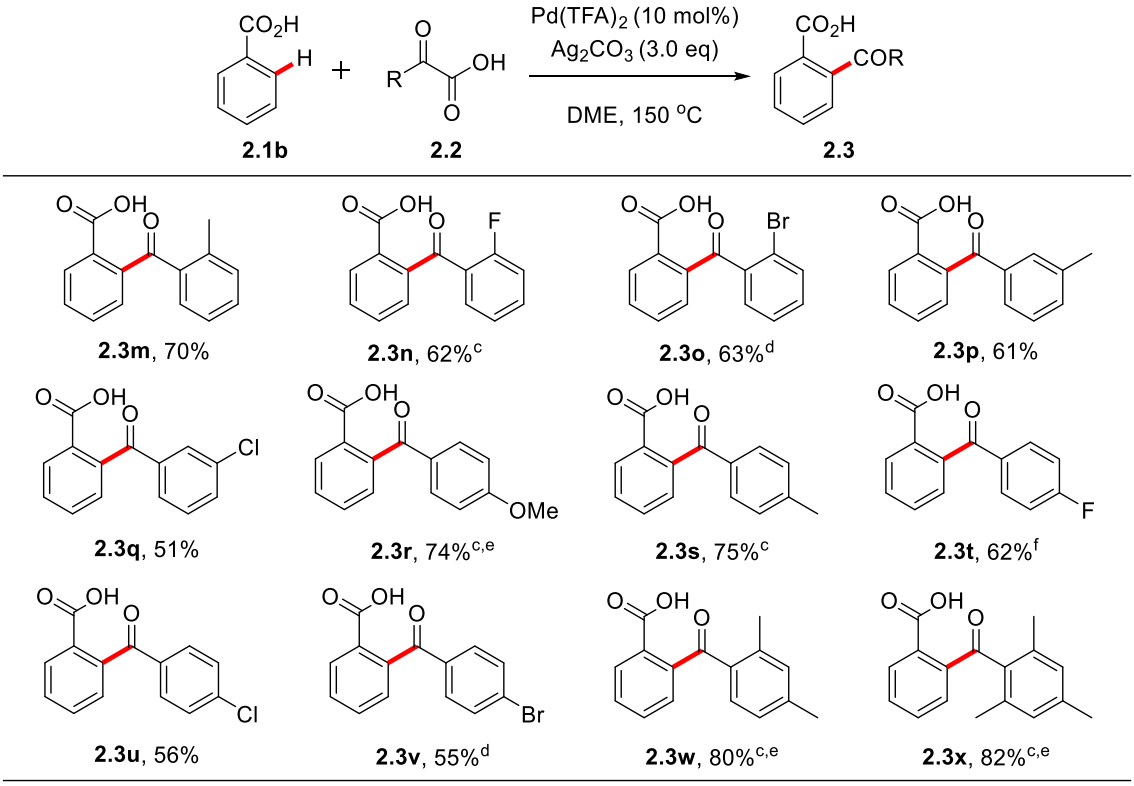
persulfate salts led to the decarboxylation of both acids and no desired product was obtained (entry 11). Further optimization of reaction conditions showed that although increasing the reaction time had no apparent effect on this reaction, the yield was significantly improved by increasing the amount of Ag_2CO_3 and raising the reaction temperature (entries 12-14). It was also noted that the coupling product could be obtained either with less Pd catalyst or when dioxane was used as the solvent, albeit in lower yields (entries 15 and 16).



Scheme 2.2 Substrate Scope of Benzoic Acids[a,b]. [a] Conditions: **2.1** (0.2 mmol), $Pd(TFA)_2$ (0.02 mmol), **2.2a** (0.6 mmol), Ag_2CO_3 (0.6 mmol), 2 mL of DME, 150 ˚C, 24 h unless otherwise noted. [b] Isolated yields. [c] 165 °C. [d] 130 °C. [e] 48 h.

With the optimized reaction conditions in hand, we then carried out the substrate scope study of substituted benzoic acids. As shown in Scheme 2.2, this transformation is

compatible with electron-donating and electron-withdrawing groups substituting the benzoic acids (**2.3a-j**), while substrates containing electron-donating groups provided higher yields than their electron-withdrawing counterparts, with the exception of **2.3e**. As expected, halogens (F, Cl, and Br) were tolerated under the current reaction system, allowing the further manipulation of the initial products. Furthermore, good yields were also observed with disubstituted benzoic acids (**2.3k**,**l**).

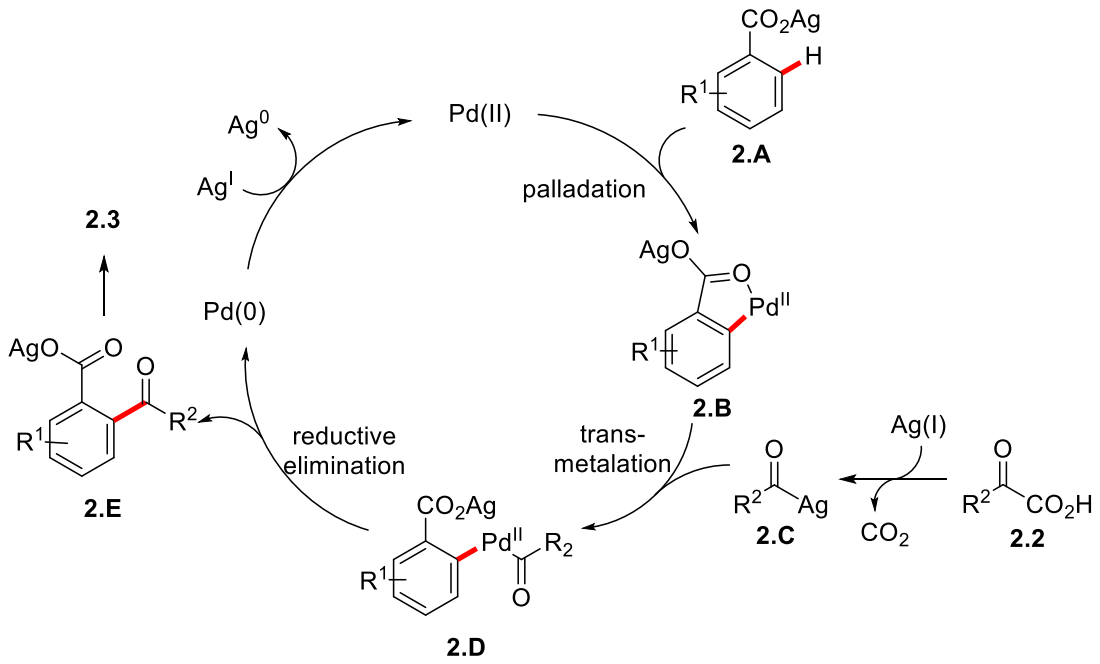


Scheme 2.3 Substrate Scope of α-Oxocarboxylic Acids[a,b]. [a] Conditions: **2.1b** (0.2 mmol), $Pd(TFA)_2$ (0.02 mmol), **2.2** (0.6 mmol), Ag_2CO_3 (0.6 mmol), 2 mL of DME, 150 ˚C, 24 h unless otherwise noted. [b] Isolated yields. [c] 165 °C. [d] 130 °C. [e] 48 h. [f] Ag_2CO_3 (0.5 mmol).

Next, a substrate scope study for the α-oxocarboxylic acids was carried out. As shown in Scheme 2.3, electron-rich groups (MeO and Me), and halogens (F, Cl, and Br) are compatible with the current reaction conditions (**2.3m-v**). Unfortunately, strong

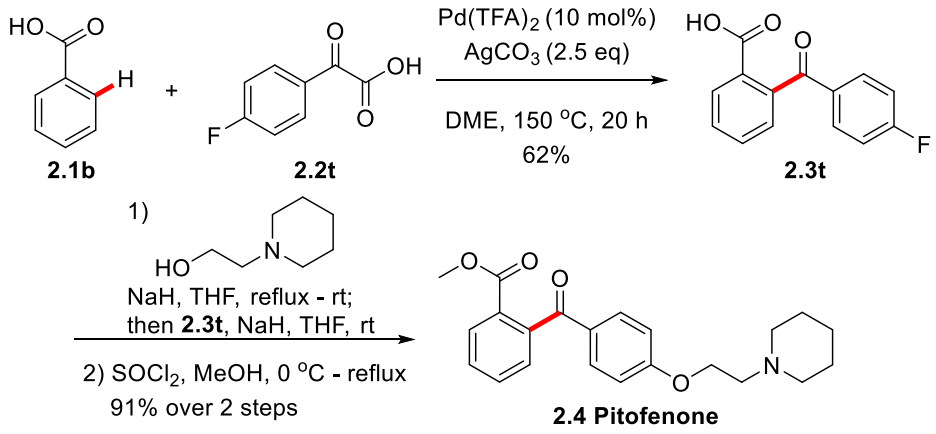
electron-withdrawing groups are not well tolerated in the current reaction system. As observed in our previous studies,[8] there is not significant steric effect with these substrates (**2.3n**,**o**). In contrast, there is a clear electronic effect. Furthermore, the sterically hindered substrate 2,4,6-trimethylbenzoylformic acid also provided the desired product **2.3x** in high yield.

On the basis of the reports from Yu[13,22] and our laboratory[8,21], a decarboxylative cross-coupling reaction mechanism is proposed (Scheme 2.4). It is believed that this transformation starts with the palladation of silver benzoate **2.A** into the Pd(II) intermediate **2.B**, which then undergoes a transmetalation step with the acylsilver species **2.C** formed by the silver-mediated decarboxylation of **2.2**, to generate the Pd(II) intermediate **2.D**. Reductive elimination of **2.D** provides the silver salt **2.E** and Pd(0), which will be reoxidized into Pd(II) by Ag_2CO_3. Protonation of intermediate **2.E** provides the desired product **2.3**.



Scheme 2.4 Proposed Mechanism for Acylation

To demonstrate the synthetic utility of this method, it was applied to the synthesis of pitofenone (Scheme 2.5). Pd(II)-catalyzed direct decarboxylative ortho acylation of benzoic acid with (4-fluorobenzoyl)formic acid provided 2-(4-fluorobenzoyl)benzoic acid (**2.3t**) in 62% yield. Nucleophilic substitution of **2.3t** by 1-(2-hydroxyethyl)piperidine, followed by methylation, produced pitofenone in 91% yield over the two steps. It is noteworthy that this route also allows the installation of extra substituents on the phenyl rings, which facilitates the medicinal chemistry study of this compound.



Scheme 2.5 Synthesis of Pitofenone

2.3 Summary

In summary, an efficient decarboxylative cross-coupling reaction of benzoic acids with α-oxocarboxylic acids has been developed via a palladium-catalyzed C−H bond functionalization process. This transformation is the first example of direct *ortho*-acylation of benzoic acids. The method provides an efficient access to 2-acylbenzoic acid derivatives. Furthermore, the synthesis of pitofenone was also achieved by employing this transformation as a key step. Compared with the two reported syntheses,[17] this route

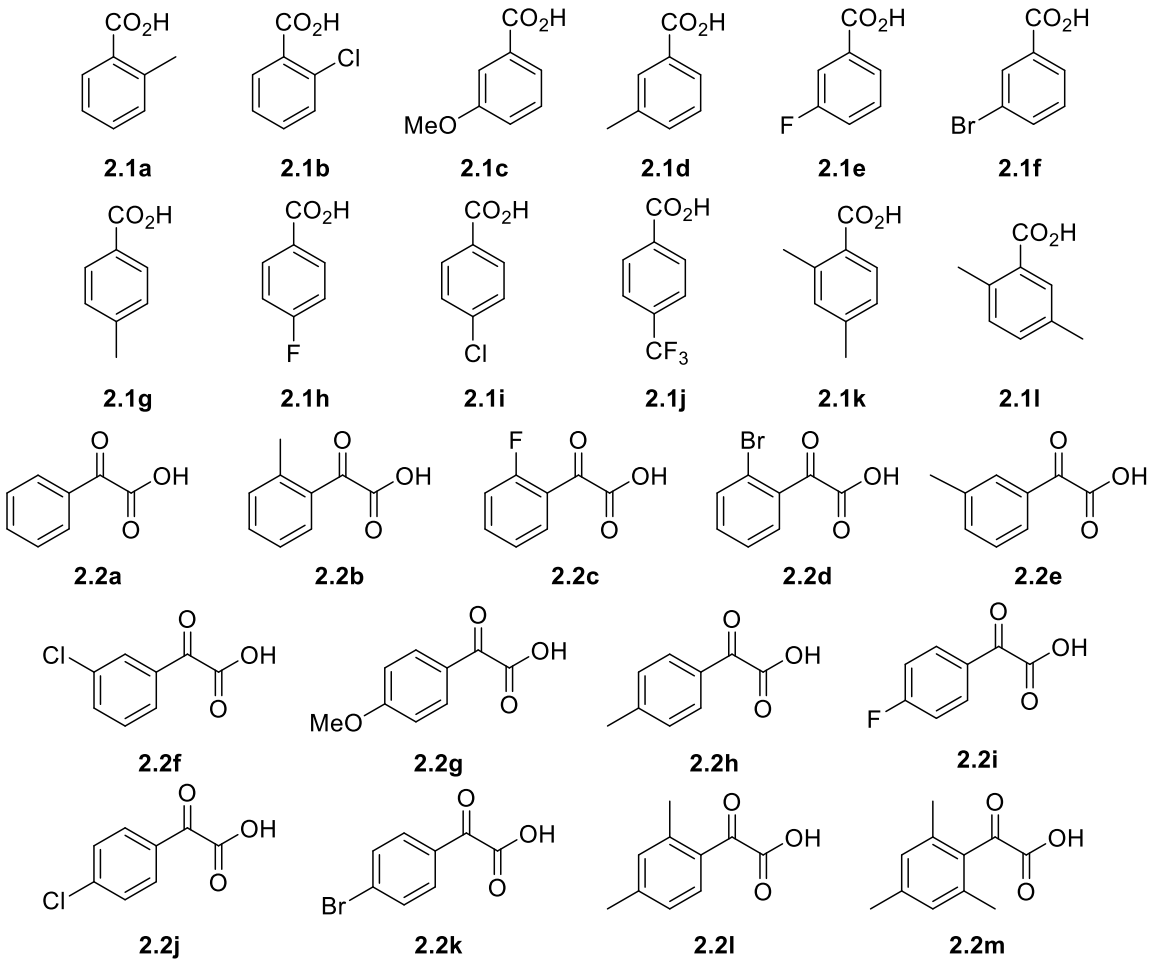
provides a more efficient approach to access this compound. In addition, this route also enables the systematic medicinal chemistry study of this compound, which could not be easily achieved by the current methods.

2.4 Experimental

General Methods. All the solvents and commercially available reagents were purchased from commercial sources and used directly. For TLC analysis, precoated plates (w/h F254, Dynamic Adsorbents Inc, 0.25 mm thick) were used; for air-flashed column chromatography, Flash Silica Gel (Dynamic Adsorbents Inc, 32-63 μm) was used. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker 500 MHz NMR Fourier transform spectrometer. ^{1}H NMR data was reported as: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR data was reported in terms of chemical shift (δ ppm), multiplicity, and coupling constant (Hz). The infrared spectra were obtained using a Thermo Nicolet IR 330 Spectrometer. High Resolution Mass (MS) analysis was obtained using MAT-95 series GC-MS system with Electrospray Ionization (ESI).

Preparation of Starting Materials:

Benzoic acids (**2.1a-m)** and α-oxocarboxylic acids (**2.2a**, **2.2n**, **2.2q** and **2.2r**) were purchased from Sigma-Aldrich, TCI, Alfa Aesar or Acros. Other α-oxocarboxylic acids were prepared from oxidation of corresponding methyl ketones with SeO_2 according to the reported procedure.[1]



Scheme 2.6 Starting Materials for Acylation

General procedure for the decarboxylative acylation recations. A 20 mL oven-dried pressure tube was charged with benzoic acid (**2.1**, 0.2 mmol), α-oxocarboxylic acid (**2.2**, 0.6 mmol), $Pd(TFA)_2$ (6.6 mg, 0.02 mmol), Ag_2CO_3 (0.5-0.6 mmol), and DME (2.0 mL). The tube was then sealed and stirred vigorously at 150-165 ˚C for 24-48 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc, filtered through a pad of Celite, and the filtrate was then concentrated in vacuo. The residue was purified

by flash chromatography on silica gel (gradient elution with 1% AcOH and 8 to 15% EtOAc in hexanes, v/v) to yield the desired product **2.3**.

2-Benzoyl-6-methylbenzoic acid (2.3a). White solid, yield: 80% (150 °C, 24 h, known compound[2]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.62 (s, 3H), 7.28-7.31 (m, 2H), 7.37-7.39 (m, 3H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.60-7.61 (m, 2H); MS (ESI): m/z = 239.1, $[M - H^+]$.

2-Benzoyl-6-chlorobenzoic acid (2.3b). White solid, yield: 51% (150 °C, 12 h, known compound[3]). ^{1}H NMR (500 MHz, DMSO) δ: 7.42-7.45 (m, 2H), 7.52-7.56 (m, 4H), 7.78-7.80 (m, 2H), 13.27 (br s, 1H); MS (ESI): m/z = 259.0, $[M - H^+]$.

2-Benzoyl-5-methoxybenzoic acid (2.3c). White solid, yield: 70% (150 °C, 24 h, known compound[4]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.88 (s, 3H), 7.11 (dd, *J* = 2.6, 8.5 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.48-7.52 (m, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 10.04 (br s, 1H); MS (ESI): m/z = 255.1 $[M - H^+]$.

2-Benzoyl-5-methylbenzoic acid (2.3d). White solid, yield: 85% (165 °C, 24 h, known compound[2]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.45 (s, 3H), 7.26 (d, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.44 (dd, *J* = 0.7, 7.8 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.69 (dd, *J* = 0.7, 7.4 Hz, 2H), 7.85 (s, 1H), 11.02 (br s, 1H); MS (ESI): m/z = 239.1, $[M - H^+]$.

2-Benzoyl-5-fluorobenzoic acid (2.3e). White solid, yield: 80% (150 °C, 24 h, known compound[5]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34-7.45 (m, 4H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.75 (dd, *J* = 2.3, 8.9 Hz, 1H); MS (ESI): m/z = 243.3 $[M - H^+]$.

2-Benzoyl-5-bromobenzoic acid (2.3f). White solid, yield: 63% (130 °C, 24 h, known compound[6]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.26 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.69-7.71 (m, 2H), 7.79 (dd, *J* = 2.0, 8.0 Hz, 1H), 8.21 (d, *J* = 2.0 Hz, 1H); MS (ESI): m/z = 303.0 [$M^- H^+$].

2-Benzoyl-5-chlorobenzoic acid (2.3g). White solid, yield: 71% (150 °C, 24 h, known compound[5]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.63 (dd, *J* = 2.0, 8.2 Hz, 1H), 7.69 (d, *J* =7.3 Hz, 2H), 8.03 (d, *J* = 2.0 Hz, 1H), 10.03 (br s, 1H); MS (ESI): m/z = 259.0 [$M^- H^+$].

2-Benzoyl-4-methylbenzoic acid (2.3h). White solid, yield: 75% (150 °C, 48 h, known compound[1]). ^{1}H NMR (500 MHz, DMSO) δ: 2.41 (s, 3H), 7.22 (s, 1H), 7.45-7.51 (m, 3H), 7.60-7.63 (m, 3H), 7.90 (d, *J* = 8.0 Hz, 1H), 13.00 (br s, 1H); MS (ESI): m/z = 239.3 [$M^- H^+$].

2-Benzoyl-4-chlorobenzoic acid (2.3i). Pale yellow solid, yield: 58% (150 °C, 24 h, known compound[7]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (d, *J* = 2.0 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.51-7.57 (m, 2H), 7.69 (d, *J* = 7.5 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 1H), 10.14 (br s, 1H); MS (ESI): m/z = 259.0 [$M^- H^+$].

2-Benzoyl-4-(trifluoromethyl)benzoic acid (2.3j). White solid, yield: 56% (165 °C, 48 h, known compound[8]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44 (t, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.64 (s, 1H), 7.70 (d, *J* = 7.5 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 8.0 Hz, 1H); MS (ESI): m/z = 293.3 [$M^- H^+$].

2-Benzoyl-4,6-dimethylbenzoic acid (2.3k). White solid, yield: 81% (165 °C, 24 h, known compound[9]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.37 (s, 3H), 2.60 (s, 3H), 7.08 (s,

1H), 7.11 (s, 1H), 7.38-7.40 (m, 3H), 7.60-7.62 (m, 2H); MS (ESI): m/z = 253.2 [M − H^+].

2-Benzoyl-3,6-dimethylbenzoic acid (2.3l). White solid, yield: 74% (150 °C, 24 h, known compound[10]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.12 (s, 3H), 2.40 (s, 3H), 7.29 (s, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 2H), 7.74 (s, 1H), 10.73 (br s, 1H); MS (ESI): m/z = 253.2 [M − H^+].

2-(2-Methylbenzoyl)benzoic acid (2.3m). White solid, yield: 70% (150 °C, 24 h, known compound[11]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.61 (s, 3H), 7.09 (d, *J* = 7.5 Hz, 1H), 7.15 (dd, *J* = 1.0, 7.7 Hz, 1H), 7.23-7.27 (m, 1H), 7.35 (dt, *J* = 1.4, 7.5 Hz, 1H), 7.43 (dd, *J* = 0.9, 7.5 Hz, 1H), 7.55 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.65 (dt, *J* = 1.2, 7.6 Hz, 1H), 8.10 (dd, *J* = 0.9, 7.8 Hz, 1H), 9.64 (br s, 1H); MS (ESI): m/z = 239.1 [M − H^+].

2-(2-Fluorobenzoyl)benzoic acid (2.3n). White solid, yield: 62% (165°C, 24 h, known compound[5]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.02-7.06 (m, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.48-7.52 (m, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.80 (dt, *J* = 1.7, 7.6 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 10.82 (br s, 1H); MS (ESI): m/z = 243.3 [M − H^+].

2-(2-Bromobenzoyl)benzoic acid (2.3o). White solid, yield: 63% (130 °C, 24 h, known compound[5]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.29-7.32 (m, 2H), 7.38-7.41 (m, 1H), 7.46 (dd, *J* = 1.0, 7.4 Hz, 1H), 7.57-7.67 (m, 3H), 7.99 (d, *J* = 7.4 Hz, 1H); MS (ESI): m/z = 303.0 [M − H^+].

2-(3-Methylbenzoyl)benzoic acid (2.3p). White solid, yield: 61% (150 °C, 24 h, known compound[5]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.35 (s, 3H), 7.27 (t, *J* = 7.7 Hz, 1H),

7.33-7.35 (m, 2H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.53-7.56 (m, 2H), 7.64 (dt, *J* = 1.2, 7.5 Hz, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 11.03 (br s, 1H); MS (ESI): m/z = 239.1 [M − H^+].

2-(3-Chlorobenzoyl)benzoic acid (2.3q). Pale yellow solid, yield: 51% (150 °C, 24 h, known compound[7]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33-7.37 (m, 2H), 7.49-7.51 (m, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.59 (dt, *J* = 1.2, 7.8 Hz, 1H), 7.67-7.71 (m, 2H), 8.09 (d, *J* = 7.8 Hz, 1H); MS (ESI): m/z = 259.0 [M − H^+].

2-(4-Methoxybenzoyl)benzoic acid (2.3r). White solid, yield: 74% (165 °C, 48 h, known compound[12]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.85 (s, 3H), 6.89 (d, *J* = 8.9 Hz, 2H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.56 (dt, *J* = 1.1, 7.7 Hz, 1H), 7.65 (dt, *J* = 1.1, 7.5 Hz, 1H), 7.70-7.72 (m, 2H), 8.10 (d, *J* = 7.8 Hz, 1H); MS (ESI): m/z = 255.1 [M − H^+].

2-(4-Methylbenzoyl)benzoic acid (2.3s). White solid, yield: 75% (165 °C, 24 h, known compound[12]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.39 (s, 3H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.34 (dd, *J* = 0.9, 7.5 Hz, 1H), 7.54 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.59-7.65 (m, 3H), 8.06 (dd, *J* = 0.9, 7.8 Hz, 1H), 8.44 (br s, 1H); MS (ESI): m/z = 239.2 [M − H^+].

2-(4-Fluorobenzoyl)benzoic acid (2.3t). White solid, yield: 62% (150 °C, 24 h, known compound[5]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.05 (t, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.55 (dt, *J* = 1.0, 7.6 Hz, 1H), 7.64 (dt, *J* = 1.0, 7.6 Hz, 1H), 7.69-7.72 (m, 2H), 8.04 (d, *J* = 7.7 Hz, 1H), 11.47 (br s, 1H); MS (ESI): m/z = 243.2 [M − H^+].

2-(4-Chlorobenzoyl)benzoic acid (2.3u). Pale yellow solid, yield: 56% (150 °C, 24 h, known compound[12]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35-7.39 (m, 3H), 7.58 (dt, *J* = 0.8, 7.7 Hz, 1H), 7.63-7.67 (m, 3H), 8.08 (d, *J* = 7.8 Hz, 1H), 9.85 (br s, 1H); MS (ESI): m/z = 259.0 [M − H^+].

2-(4-Bromobenzoyl)benzoic acid (2.3v). White solid, yield: 55% (130 °C, 24 h, known compound[13]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (d, *J* = 7.5 Hz, 1H), 7.54-7.60 (m, 5H), 7.68 (t, *J* = 7.4 Hz, 1H), 8.09 (d, *J* = 7.8 Hz, 1H); MS (ESI): m/z = 303.0 [M + H^+].

2-(2,4-Dimethylbenzoyl)benzoic acid (2.3w). White solid, yield: 80% (165 °C, 48 h, known compound[14]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 2.60 (s, 3H), 6.89 (d, *J* = 7.9 Hz, 1H), 7.05- 7.08 (m, 2H), 7.40 (dd, *J* = 0.8, 7.5 Hz, 1H), 7.54 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.63 (dt, *J* = 1.2, 7.5 Hz, 1H), 8.02 (dd, *J* = 0.9, 7.8 Hz, 1H), 8.70 (br s, 1H). MS (ESI): m/z = 253.3 [M − H^+].

2-(2,4,6-Trimethylbenzoyl)benzoic acid (2.3x). White solid, yield: 82% (165 °C, 48 h, known compound[13]). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.16 (s, 6H), 2.32 (s, 3H), 6.89 (s, 2H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 1.2, 7.5 Hz, 1H), 7.59 (dt, *J* = 0.8, 7.5 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 9.76 (br s, 1H); MS (ESI): m/z = 267.3 [M − H^+].

Procedure for the synthesis of pitofenone. To a suspension of NaH (60%, 32 mg, 0.8 mmol) in dry THF was added 1-(2-hydroxyethyl)piperidine (85 μL, 0.6 mmol) at room temperature. Then the mixture was refluxed for 30 min. After cooled to room temperature, the mixture was slowly added a suspension of 3u (73mg, 0.3 mmol) and NaH (60%, 20mg, 0.5 mmol) in dry THF at room temperature. The resulting reaction mixture was stirred overnight, and then quenched with MeOH. Next, 1M HCl was added to adjust the pH to 2, and the solvent was removed under vacuo. The residue was dissolved with anhydrous MeOH (3 mL), and cooled to 0 °C. To this solution was slowly added $SOCl_2$ (280 uL) at 0 °C, and then warmed to room temperature. The reaction mixture was stirred at room temperature for 2 h, and refluxed for another 2 h. After cooled to room temperature, the

solvent was evaporated under vacuo, and the residue was dissolved with 1N NaOH, and extracted with DCM (3 x 10 mL). The organic layer was combined and washed with water, brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified with flash chromatography (gradient eluent of 1% Et_3N and 50% EtOAc in hexanes, v/v) to give 100 mg of the desired compound pitofenone as a pale yellow oil.

Methyl 2-(4-(2-(piperidin-1-yl)ethoxy)benzoyl)benzoate (pitofenone, 2.4). Pale yellow solid, yield: 91% (from 3u). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.42-1.46 (m, 2H), 1.57-1.61 (m, 4H), 2.49 (br s, 4H), 2.77 (t, *J* = 6.0 Hz, 2H), 3.63 (s, 3H), 4.14 (t, *J* = 6.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 7.37 (dd, *J* = 1.1, 7.5 Hz, 1H), 7.54 (dt, *J* = 1.3, 7.5 Hz, 1H), 7.61 (dt, *J* = 1.3, 7.5 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 2H), 8.04 (dd, *J* = 1.0, 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.2, 26.0, 52.2, 55.1, 57.7, 66.3, 114.3, 127.7, 129.1, 129.3, 130.1, 130.2, 131.6, 132.3, 142.1, 162.9, 166.5, 195.8. IR (neat) ν 3067, 2934, 2852, 2786, 1916, 1726, 1666, 1560, 1576, 1508, 1281, 1255 cm^{-1}; Ms (ESI): m/z = 368.3 [M + H^+].

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2.6 References

1. (a) Aeberli, P.; Eden, P.; Gogerty, J. H.; Houlihan, W. J.; Penberthy, C. *J. Med. Chem*. **1975**, *18*, 177. (b) Van der Mey, M.; Hatzelmann, A.; Van der Laan, I. J.; Sterk, G. J.; Thibaut, U.; Timmerman, H. *J. Med. Chem*. **2001**, *44*, 2511. (c) Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Moritani, Y.; Saruta, K.; Higashijima, T.; Kotera, J.; Takagi, M.; Kikkawa, K.; Omori, K. J. *Med. Chem*. **2001**, *44*, 2204–2218; (d) Watson, A. F.; Liu, J.-F.; Bennaceur, K.; Drummond, C. J.; Endicott, J. A.; Golding, B. T.; Griffin, R. J.; Haggerty, K.; Lu, X.-H.; McDonnell, J. M.; Newell, D. R.; Noble, M. E. M.; Revill, C. H.; Riedinger, C.; Xu, Q.; Zhao, Y.; Lunec, J.; Hardcastle, I. R. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 5916. (e) Cueva, J. P.; Gallardo-Godoy, A.; Juncosa, J. I.; Vidi, P. A.; Lill, M. A.; Watts, V. J.; Nichols, D. E. *J. Med. Chem*. **2011**, *54*, 5508. (f) Lim, C. J.; Kim, S. H.; Lee, B. H.; Oh, K.-S.; Yi, K. Y. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 427.
2. (a) Sexton, W. A.; Templeman, W. G. *Nature* **1948**, *141*, 974. (b) Evans, D.; Cracknell, M. E.; Saunders, J. C.; Smith, C. E.; Williamson, W. R. N.; Dawson, W.; Sweatman, W. J. F. *J. Med. Chem*. **1987**, *30*, 1321. (c) Gapinski, D. M.; Mallett, B. E.; Froelich, L. L.; Jackson, W. T. *J. Med. Chem*. **1990**, *33*, 2798. (d) Wyss, D. F.; Arasappan, A.; Senior, M. M.; Wang, Y.-S.; Beyer, B. M.; Njoroge, F. G.; McCoy, M. A. *J. Med. Chem.* **2004**, *47*, 2486. (e) Gobec, S.; Brozic, P.; Rizner, T. L. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 5170.
3. (a) Jones, P. B.; Porter, N. A. *J. Am. Chem. Soc*. **1999**, *121*, 2753; (b) Sui, Y.-L.; Yan, B. *Inorg. Mater*. **2006**, *42*, 144. (c) Yan, B.; Wang, W.-J.; Song, Y.-S. J. *Fluoresc*. **2006**, *16*, 495.

4. (a) Bieganowska, M. L.; Soczewinski, E.; Janowska, M. *Chromatographia* **1984**, *18*, 99. (b) Bieganowska, M. L.; Petruczynik, A. *Chromatographia* **1995**, *40*, 453. (c) Waksmundzka-Hajnos, M.; Bieganowska, M. L.; Petruczynik, A. *J. Chromatogr., A* **1996**, *730*, 195.

5. Arnoldi, A.; Bassoli, A.; Borgonovo, G.; Merlini, L. *J. Agric. Food Chem*. **1997**, *45*, 2047.

6. (a) Fieser, L. F.; Hershberg, E. B. *J. Am. Chem. Soc*. **1937**, *59*, 2331. (b) Newman, M. S.; Muth, C. W. *J. Am. Chem. Soc*. **1950**, *72*, 5191. (c) LaBudde, J. A.; Heidelberger, C. *J. Am. Chem. Soc*. **1958**, *80*, 1225. (d) Seo, S.; Slater, M.; Greaney, M. F. *Org. Lett*. **2012**, *14*, 2650.

7. (a) Newman, M. S.; Scheurer, P. G. *J. Am. Chem. Soc*. **1956**, *78*, 5004. (b) Reinheckel, H. A.; Haage, K. *Angew. Chem., Int. Ed*. **1966**, *5*, 511. (c) Watson, A. F.; Liu, J.-F.; Bennaceur, K.; Drummond, C. J.; Endicott, J. A.; Golding, B. T.; Griffin, R. J.; Haggerty, K.; Lu, X.-H.; McDonnell, J. M.; Newell, D. R.; Noble, M. E. M.; Revill, C. H.; Riedinger, C.; Xu, Q.; Zhao, Y.; Lunec, J.; Hardcastle, I. R. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 5916. (d) Wang, X.; Li, J.-Z.; Zhao, N.; Wan, X.-B. *Org. Lett*. **2011**, *13*, 709. (e) Yu, H.-B.; Xiao, Y.; Guo, H.-Y. *Org. Lett*. **2012**, *14*, 2014.

8. (a) Li, M.-Z.; Ge, H.-B. *Org. Lett.* **2010**, *12*, 3464. (b) Fang, P.; Li, M.-Z.; Ge, H.-B. *J. Am. Chem. Soc*. **2010**, *132*, 11898.

9. For selected recent reviews, see: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed*. **2009**, *48*, 5094. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev*. **2011**, *111*, 1293. (d) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev*. **2011**, *40*, 1885. (e) Boorman, T. C.; Larrosa, I. *Chem. Soc. Rev*. **2011**, *40*, 1910. (f) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed*. **2011**, *50*, 3362. (g) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev*. **2011**, *40*, 4740. (h) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev*. **2011**, *40*, 5068. (i) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res*. **2012**, *45*, 788.

10. For selected recent reviews, see: (a) Baudoin, O. *Angew. Chem. Int. Ed*. **2007**, *46*, 1373. (b) Goossen, L. J.; Goossen, K.; Rodriguez, N.; Blanchot, M.; Linder, C.; Zimmermann, B. *Pure Appl. Chem*. **2008**, *80*, 1725. (c) Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed*. **2008**, *47*, 3100. (d) Goossen, L. J.; Collet, F.; Goossen, K. *Isr. J. Chem*. **2010**, *50*, 617. (e) Rodriguez, N.; Goossen, L. J. Chem. *Soc. Rev*. **2011**, *40*, 5030. (f) Cornella, J.; Larrosa, I. *Synthesis* **2012**, *44*, 653.

11. Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun*. **2008**, 6312.

12. For recent examples of decarboxylative C_H arylation reactions, see: (a) Cornella, J.; Lu, P.-F.; Larrosa, I. *Org. Lett*. **2009**, *11*, 5506. (b) Wang, C.-Y.; Piel, I.; Glorius, F. *J. Am. Chem. Soc*. **2009**, *131*, 4194. (c) Yu, W.-Y.; Sit, W. N.; Zhou, Z.-Y.; Chan, A. S. C. *Org. Lett*. **2009**, *11*, 3174. (d) Zhang, F.-Z.; Greaney, M. F. *Angew. Chem., Int. Ed*. **2010**, *49*, 2768. (e) Xie, K.; Yang, Z.-Y.; Zhou, X.-J.; Li, X.-J.; Wang, S.-Z.; Tan, Z.; An, X.-Y.; Guo, C.-C. *Org. Lett*. **2010**, *12*, 1564. (f) Zhou, J.; Hu, P.; Zhang, M.; Huang, S.; Wang, M.; Su, W. *Chem. Eur. J*. **2010**, *16*, 5876. (g) Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc*. **2010**, *132*, 14006. (h) Zhao, H.; Wei, Y.; Xu, J.; Kan, J.; Su, W.; Hong, M. *J. Org. Chem*. **2011**, *76*, 882. (i) Hu, P.; Zhang, M.; Jie, X.; Su, W. *Angew. Chem. Int. Ed*. **2012**, *51*, 227

13. (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc*. **2007**, *129*, 3510. (b) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc*. **2008**, *130*, 14082.

14. (a) Goossen, L. J.; Rudolphi, F.; Oppel, C.; Rodrı´guez, N. *Angew. Chem. Int. Ed*. **2008**, *47*, 3043. (b) Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem., Int. Ed*. **2008**, *47*, 7103.

15. Li, M.-Z.; Wang, C.; Ge, H.-B. *Org. Lett*. **2011**, *13*, 2062.

16. Wang, H.; Guo, L.-N.; Duan, X.-H. *Org. Lett*. **2012**, *14*, 4358.

17. (a) Kim, M.; Park, J.; Sharma, S.; Kim, A.; Park, E.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Chem. Commun*. **2013**, 925. (b) Yang, Z.-Y.; Chen, X.; Liu, J.-D.; Gui, Q.-W.; Xie, K.; Li, M.-M.; Tan, Z. *Chem. Commun*. **2013**, 1560.

18. Park, J.; Kim, M.; Sharma, S.; Park, E.; Kim, A.; Lee, S. H.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Chem. Commun*. **2013**, 1654.

19. Sharma, S.; Kim, A.; Park, E.; Park, J.; Kim, M.; Kwak, J. H.; Lee, S. H.; Jung, Y. H.; Kim, I. S. *Adv. Synth. Catal*. **2013**, *355*, 667.

20. Pan, C.-D.; Jin, H.-M.; Liu, X.; Cheng, Y.-X.; Zhu, C.-J. *Chem. Commun*. **2013**, 2933.

21. Li, M.-Z.; Wang, C.; Fang, P.; Ge, H.-B. *Chem. Commun*. **2011**, *47*, 6587.

22. (a) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc*. **2008**, *130*, 17676. (b) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc*. **2009**, *131*, 14654. (c) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc*. **2010**, *132*, 460. (d) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc*. **2010**, *132*, 14137. (e) Engle, K. M.; Thuy-Boun, P. S.; Dang, M.; Yu, J.-Q. *J. Am. Chem. Soc*. **2011**, *133*, 18183.

23. (a) Fisnerova, L.; Brunova, B. CS 248548, 1987. (b) Staneva, T. D.; Nacheva, E. B.; Lazarov, V. K.; Bacheva, B. L.; Katsarski, D. E. BG 107390, 2004.

CHAPTER 3. PALLADIUM-CATALYZED SITE-SELECTIVE FLUORINATION OF UNACTIVATED SP^3 C−H BONDS

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3.1 Introduction

Fluorine substitution is of great interest in the fields of medicinal chemistry, agricultural chemistry, and material science.[1] Fluorination affects nearly all physical and chemical properties including stability, solubility, lipophilicity, conformation, and bioavailability compared to the parent molecules.[2] It has been estimated that fluorine-containing molecules account for about 25% of all pharmaceuticals and 30-40% of agrochemicals, including three of the top five best-selling drugs in 2013.[3] Furthermore, the importance of fluorine in medical imaging technologies has also been demonstrated.[4] Therefore, the discovery of selective incorporation methods for fluorine atoms into biologically relevant organic molecules has been an active research area in organic chemistry over the past 40 years.[5]

Transition metal-catalyzed C−H functionalization has been extensively studied in the past decades due to the avoidance of the prefunctionalization step in this process

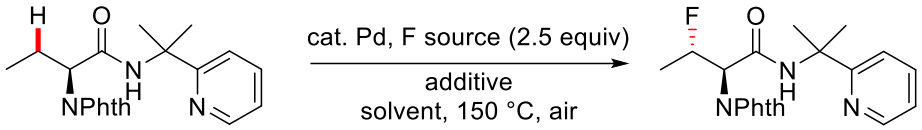
compared to the classical approaches.[6] Within this reaction class, site-selective direct fluorination of aromatic C−H bonds has been documented recently via a palladium or copper catalysis.[7] Despite a challenging process, transition metal-catalyzed direct fluorination of sp^3 carbons has also been established.[8] Copper,[9] iron,[10] manganese,[11] palladium,[12] silver,[13] and vanadium[14] have all been demonstrated as effective catalysts in this process. However, current studies on unactivated sp^3 C−H bonds suffer from low to moderate site-selectivity. In addition, fluorination on C−H bonds of the relatively reactive benzylic or allylic sp^3 carbons is typically favored over that on unactivated sp^3 bonds, which limits the potential applications of this approach. Inspired by the Pd-catalyzed ligand-directed C−H functionalization of unactivated β-sp^3 carbons of amides,[15] we have investigated the direct site-selective fluorination of α-amino acid derivatives and aliphatic amides via palladium catalysis with the assistance of a bidentate directing group.

3.2 Results and Discussion

Fluorinated amino acids have attracted considerable attention in the past decades due to the importance of these compounds in medicinal chemistry research.[16] Current synthetic methods of these molecules primarily rely on the nucleophilic substitution reaction, which requires pre-installation of a functional group to the C−H bonds.[17] In order to provide a direct synthetic approach for fluorinating unactivated sp^3 carbons, we began our investigation on palladium-catalyzed fluorination of amino acid derivatives with the assistance of a bidentate ligand. Although 8-aminoquinoline has been widely used as a directing group for transition metal-catalyzed C−H functionalization, electrophilic aromatic substitution on this moiety could be a potential problem with an electrophilic

fluorine reagent. Therefore, 2-(pyridin-2-yl)isopropyl amine[18] was chosen as the directing group for fluorination of the 2-aminobutyric acid derivative **3.1a** (Scheme 1). Initial studies showed that the desired β-fluorinated product **3.2a** could be obtained with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis(tetrafluoroborate) (Selectfluor) as the fluorinating reagent in dichloroethane (entry 1). To our delight, the reaction yield was significantly improved with the addition of AgOAc or Ag_2CO_3 (entries 3 and 4). Next, an extensive solvent screening was carried out, and the mixture of dichloroethane and isobutyronitrile proved to be optimal, providing **3.2a** in 38% yield (entry 11). Further screening of the palladium catalysts showed that $Pd(OAc)_2$ is optimal although several other catalysts could also provide the desired product (entries 13-15). Interestingly, the addition of $Mn(OAc)_2$ or $Fe(OAc)_2$ significantly improved the reaction yield, with 0.3 equivalents of $Fe(OAc)_2$ giving the best result (entries 16-18). As we expected, this reaction showed a high site-selectivity by favoring β-C−H bonds due to the preference of the formation of a five-membered ring intermediate in the cyclopalladation step. Delightfully, a high diastereoselectivity was also observed by favoring the *anti* diastereoisomer. It is noteworthy that only low to moderate diastereoselectivities have been reported in previous Pd-catalyzed sp^3 C−H functionalization of linear aliphatic α-amino acids with relatively small functional groups, such as Me[15g], OMe[17a], and Oac[19]. It should be mentioned that under the optimized conditions, 2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)butanamide with 8-aminoquinoline as the bidentate directing group failed to provide the corresponding β–fluorinated product.

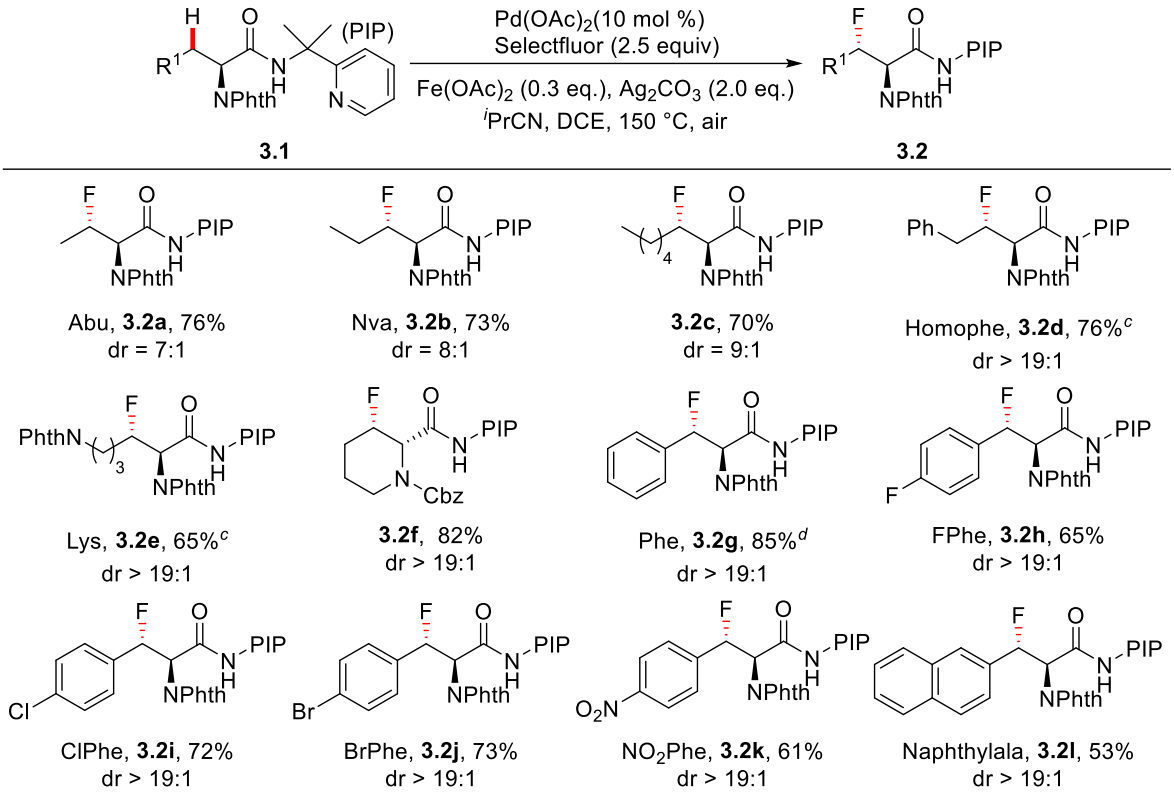
Table 3.1 Optimization of Reaction Conditions for Fluorination[a]



3.1a **3.2a**

Entry	Pd Source (10 mol %)	Additive (equiv)	Solvents (mL)	Yield (%)[b]
1	$Pd(OAc)_2$	-	DCE (3.0)	trace
2	$Pd(OAc)_2$	$AgNO_3$ (2.0)	DCE (3.0)	trace
3	$Pd(OAc)_2$	AgOAc (2.0)	DCE (3.0)	21
4	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)	25
5	$Pd(OAc)_2$	Na_2CO_3 (2.0)	DCE (3.0)	-
6	$Pd(OAc)_2$	K_2CO_3 (2.0)	DCE (3.0)	-
7	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	MeCN (3.0)	-
8	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DME (3.0)	18
9	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	chloroform (3.0)	5
10	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/MeCN (0.3)	31
11	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	38
12	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{t}BuCN (0.3)	33
13	$Pd(TFA)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	29
14	$Pd(acac)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	12
15	$PdCl_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	6
16	$Pd(OAc)_2$	Ag_2CO_3 (2.0)/ $Mn(OAc)_2$ (1.0)	DCE (3.0)/^{i}PrCN (0.3)	44
17	$Pd(OAc)_2$	Ag_2CO_3 (2.0)/ $Fe(OAc)_2$ (1.0)	DCE (3.0)/^{i}PrCN (0.3)	56
18	**$Pd(OAc)_2$**	**Ag_2CO_3 (2.0)/ $Fe(OAc)_2$ (0.3)**	**DCE (3.0)/^{i}PrCN (0.3)**	**80(76[f])**
19	-	Ag_2CO_3 (2.0)/ $Fe(OAc)_2$ (0.3)	DMF	-
20	$Pd(OAc)_2$	$Fe(OAc)_2$ (0.3)	DMF	27

[a] Reaction conditions: **3.1a** (0.30 mmol), Pd source (10 mol %), F source (2.5 equiv), Ag_2CO_3 (2.0 equiv), additive, solvent, 150 °C, air, 14 h. [b] Yields are based on **3.1a**, determined by ^{1}H NMR. [f] Isolated yield, dr = 7:1. Selectfluor=1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis(tetrafluoroborate).



Scheme 3.1 Scope of Amino Acid Derivatives[a,b]. [a] Reaction conditions: **3.1** (0.30 mmol), $Pd(OAc)_2$ (10 mol %), Selectfluor (2.5 equiv), Ag_2CO_3 (2.0 equiv), $Fe(OAc)_2$ (0.3 equiv), ^{i}PrCN (300 µL), 3.0 mL DCE, 150 ˚C, air, 14 h. [b] Isolated yields. [c] 0.25 equiv of $Fe(OAc)_2$. [d] Without $Fe(OAc)_2$. PIP = 2-(pyridin-2-yl)isopropyl.

With optimized conditions in hand, the scope of amino acids was studied (Scheme 3.1). As expected, good yields were obtained with linear aliphatic amino acid derivatives with high diastereoselectivities (**3.2a-e**). In addition, the cyclic amino acid derivative **3.1f** was an effective substrate, affording the desired product **3.2f** in 82% yield. Moreover, a predominant preference of functionalizing β-C−H bonds over the relatively reactive benzylic γ-C−H bonds was also observed (**3.2d**), distinguishing this process from the current direct fluorination methods which favor the benzylic C−H bonds. Furthermore, phenylalanine and naphthylalanine derivatives were also effective substrates, providing the

corresponding β-fluorinated amino acid derivatives in good yields with excellent diastereoselectivities (**3.2g-l**).

Additionally, the structure and absolute configuration of the phenylalanine derivative ***L*-3.2g** (CCDC no. 1052086) were confirmed with X-ray analysis (Figure 3.1).

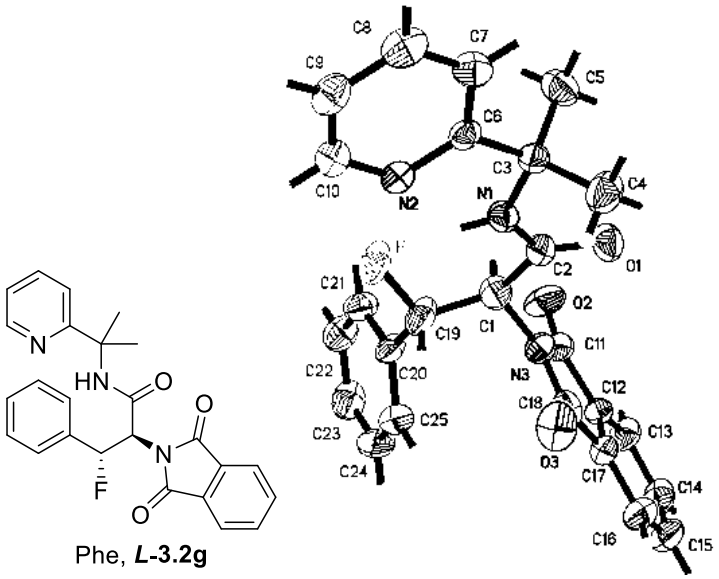
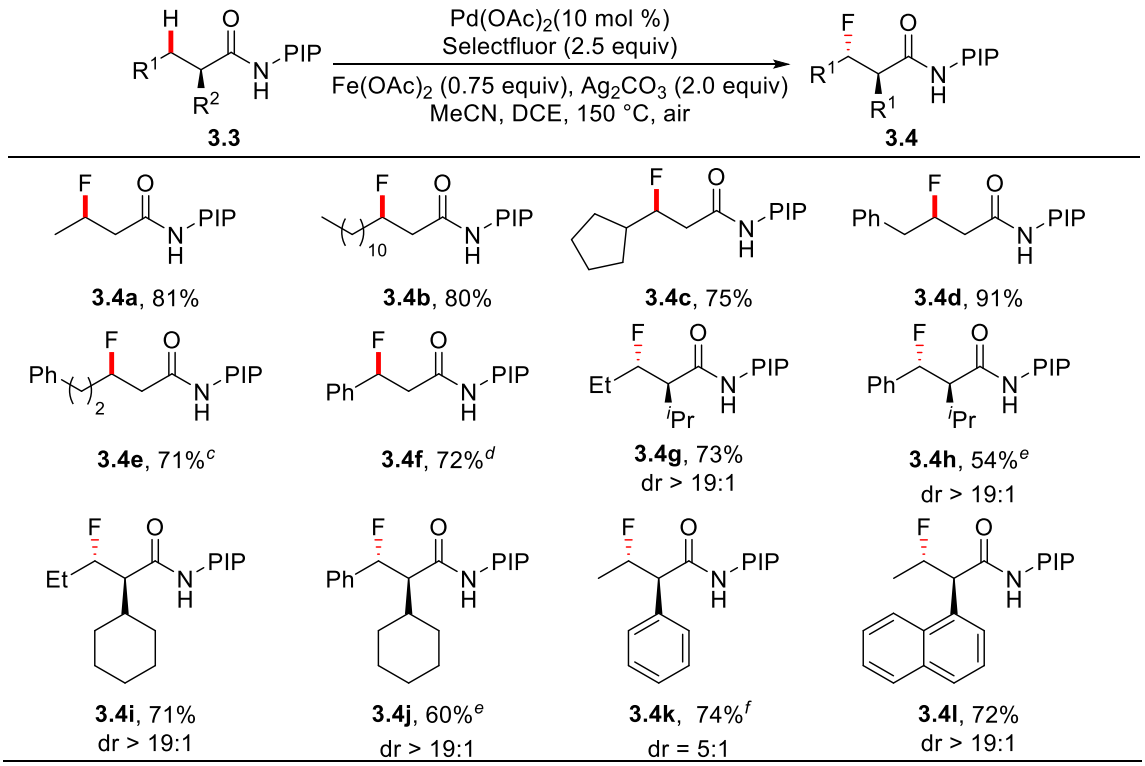


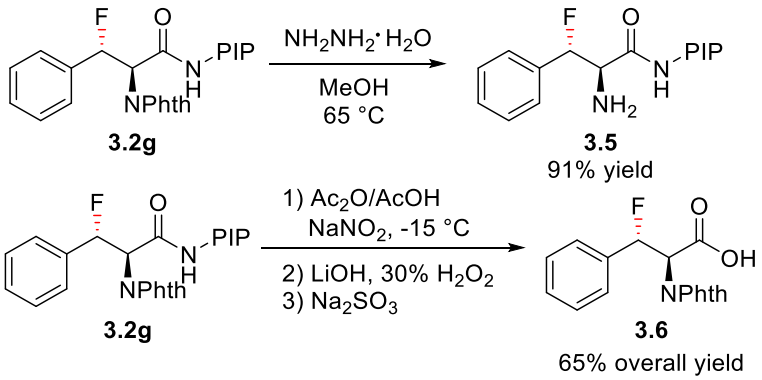
Figure 3.1 X-Ray crystal structure of ***L*-3.2g**

Next, substrate scope study of non-amino acid aliphatic amides was carried out. As shown in Scheme 3.2, both linear and α-branched aliphatic amides afforded the desired products in good yields under modified reaction conditions (**3.4a-l**). Similarly, functionalization of β-C−H bonds was favored over the relatively reactive benzylic γ- or δ-C−H bonds (**3.4d** and **3.4e**). As expected, high diastereoselectivity was also observed with α-branched aliphatic amides (**3.4g-l**). Furthermore, it was found that the current process favored functionalization of β-C−H bonds of the sp^3 carbons over γ-C−H bonds of the sp^2 carbons, indicating that formation of a five-membered ring intermediate is preferred to the six-membered ring intermediate in the cyclopalladation step (**3.4k** and **3.4l**).



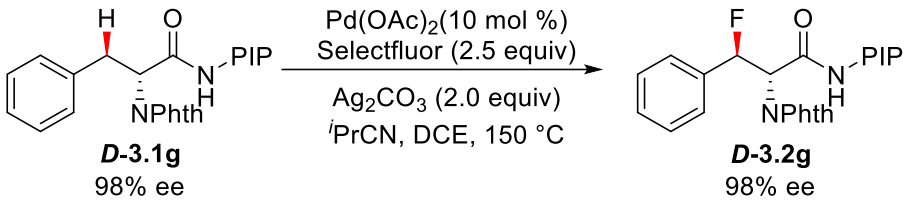
Scheme 3.2 Scope of Aliphatic Amides[a,b]. [a] Reaction conditions: **3.3** (0.30 mmol), $Pd(OAc)_2$ (10 mol %), Selectfluor (2.5 equiv), Ag_2CO_3 (2.0 equiv), $Fe(OAc)_2$ (0.75 equiv), MeCN (400 µL), 3.0 mL DCE, 150 °C, air, 14 h. [b] Isolated yields. [c] 3.0 equiv Selectfluor. [d] 0.2 equiv $Fe(OAc)_2$. [e] No $Fe(OAc)_2$. [f] 0.5 equiv $Fe(OAc)_2$. PIP = 2-(pyridin-2-yl)isopropyl.

To further demonstrate the synthetic utility of this fluorination method, removal of the protecting and the directing group PIP was carried out, and the corresponding products were obtained in good yields (Scheme 3.3).



Scheme 3.3 Removal of Protecting Group and Directing Group

In addition, no apparent epimerization of the α-chiral center was observed during the fluorination of the *D*-2-(1,3-dioxoisoindolin-2-yl)-3-phenyl-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (***D*-1g**) (Scheme 3.4).

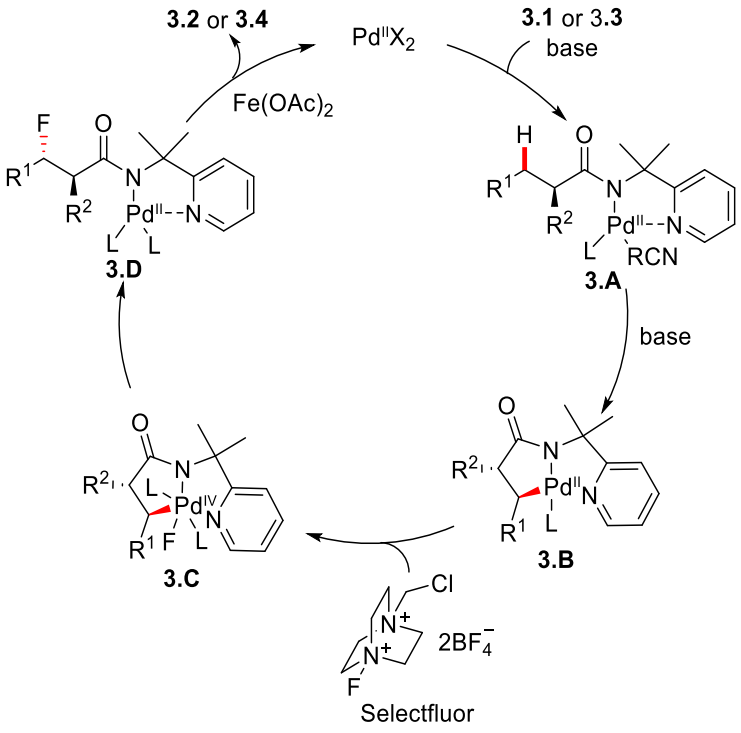


***D*-3.1g**
98% ee

***D*-3.2g**
98% ee

Scheme 3.4 Synthesis of ***D*-3.2g**

On the basis of the above obtained results and the previous reports,[7,12b,20] a plausible reaction mechanism is proposed (Scheme 3.5). Coordination of amide **3.1** or **3.3** to a palladium species followed by a base-promoted ligand exchange process in the presence of MeCN or ^{i}PrCN produces the palladium complex **3.A**. Subsequently, cyclometalation of the palladium complex **3.A** occurs to generate the intermediate **3.B** via a C−H bond activation process. Oxidative addition of the intermediate **3.B** with Selectfluor provides the palladium (IV) species **3.C**, which then gives rise to the final product **3.2** or **3.4** via reductive elimination followed by ligand dissociation.[21] Although the exact role of Ag_2CO_3 in the reaction is not clear, it is believed that this species participates in the ligand exchange and subsequent C−H bond cleavage steps by acting as a base, and also possibly promotes the oxidative addition of Selectfluor to the intermediate **3.B**. On the other hand, the role of $Fe(OAc)_2$ in the reaction could be the promotion of releasing the Pd(II) species from the intermediate **3.D**.



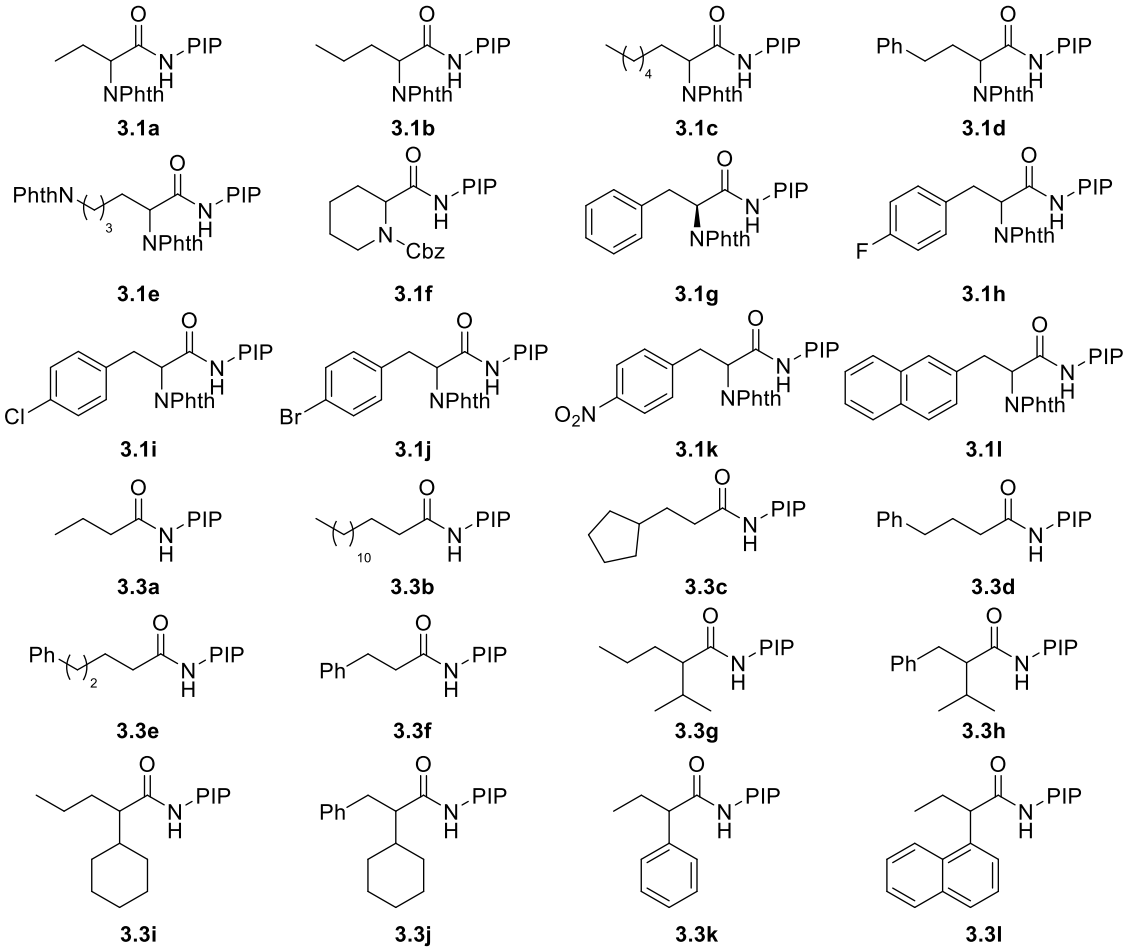
Scheme 3.5 Proposed Catalytic Cycle for β–Fluorination

3.3 Summary

In summary, the palladium-catalyzed, ligand-directed, highly site-selective fluorination of amino acid derivatives and aliphatic amides was developed via an sp^3 C–H bond functionalization process. This reaction featues good diastereoselectivity and functional group compatibility. Additionally, a great preference for functionalizing the C–H bonds of β-sp^3 carbons over those of relatively reactive γ-sp^2 or benzylic sp^3 carbons was observed. As mentioned earlier, current methods for the direct fluorination of unactivated sp^3 carbons suffer from poor site-selectivity, incompatibility with benzylic carbons, and low diastereoselectivity in many cases. Therefore, this reported process provides a complementary and advantageous approach to access fluorine-containing

organic molecules. The detailed mechanistic study of this transformation is currently underway in our laboratory.

3.4 Experimental



Scheme 3.6 Starting Materials for Fluorination

General Methods. All solvents and commercially available reagents were purchased from commercial sources and used directly. Thin layer chromatography (TLC) was performed on EMD precoated plates (silica gel 60 F254, Art 5715) and visualized by fluorescence quenching under UV light. Column chromatography was performed on EMD

Silica Gel 60 (200–300 Mesh) using a forced flow of 0.5–1.0 bar. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker 500 MHz NMR Fourier transform spectrometer (500 MHz and 125 MHz, respectively) or a Bruker AVANCE III–400 spectrometer (400 MHz and 100 MHz, respectively) using tetramethylsilane as an internal reference, and chemical shifts (δ) and coupling constants (*J*) were expressed in ppm and Hz, respectively. Infrared spectra were obtained using a Thermo Nicolet IR 330 spectrometer or a Nicolet 6700 spectrophotometer and reported as wave number (cm^{-1}). Mass (MS) analysis was obtained using Agilent 1100 series LC/MSD system with Electrospray Ionization (ESI). Mass (HRMS) analysis was obtained using Agilent 6200 Accurate-Mass TOF LC/MS system with Electrospray Ionization (ESI).

Preparation of Starting Materials (Scheme 3.6):

Starting materials **3.1g**[22], **3.3a**, **3.3d**, and **3.3f**[23] were prepared according to literature procedures. 2-(Pyridin-2-yl)isopropylamine was prepared according to literature procedures.[24]

General procedure for protection of amino acids (3.1a-3.1e and 3.1h-3.1l):

In a round-bottom flask fitted with Dean-Stark apparatus and a reflux condenser, phthalic acid anhydride (1.48 g, 10 mmol) and appropriate amino acids (10 mmol, or 20 mmol for lysine) were refluxed in toluene in the presence of 0.1 mL triethylamine overnight. The organic solvents were removed under reduced pressure to get a sticky oily mass. Water was added to this oily mass and the mixture was acidified with hydrochloric acid, and stirred for 30 min to get a white solid. This product was filtered off, washed with water, and dried in *vacuo* to give a target *N*-phthaloyl amino acid.[25]

General procedure for synthesis of substrates 3.3g, h, i, j, and l: A solution of LDA (10 mmol) in THF was prepared from diisopropylamine (1.5 mL, 10.7 mmol) and 2.5 M *n*-BuLi in hexane (4.0 mL, 10 mmol) at -78 °C. To this LDA solution, the corresponding carboxylate ethyl ester (10 mmol) was added dropwise at -78 °C, and the mixture was stirred at this temperature for 1 h. Alkyl halide (15 mmol) was then added dropwise to the solution at -78 °C. After the addition, the mixture was warmed to room temperature and stirred overnight. Then the mixture was quenched with water at 0 °C, and extracted with Et_2O (15 mL x 3). The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated in *vacuo* to give the crude esters.[26]

To the ester was added a solution of NaOH (2 M, 8.0 mL) and methanol (10 mL). The mixture was stirred overnight at 60 °C. After removal of methanol in vacuo, the pH of the mixture was adjusted to 2 with 3.0 M HCl. The mixture was then saturated with NaCl and extracted with Et_2O (15 mL x 3). The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated in *vacuo* to give the crude carboxylic acid, which was used directly for the coupling with 2-(pyridin-2-yl)isopropylamine without further purification.[26]

General Procedure for amide synthesis:

Acyl chlorides were prepared by following a reported procedure.[27] Carboxylic acid (12 mmol), thionyl chloride (4.4 mL, 60 mmol) and 3 drops of DMF were reacted in toluene (20 mL) at 80 °C in a 100 ml round-bottom flask equipped with a condenser and a stir bar for 4-5 h. After the reaction, toluene and the excess of thionyl chloride were removed by vacuum distillation. The crude residual acyl chloride was dissolved in anhydrous CH_2Cl_2 for the next reaction.

2-(Pyridin-2-yl)isopropylamine (10 mmol) and 2,6-lutidine were dissolved in anhydrous CH_2Cl_2 (25 mL) in a 100 ml round-bottom flask followed by dropwise addition of acyl chloride solution in CH_2Cl_2 through cannula. The reaction mixture was stirred overnight. The reaction was diluted with CH_2Cl_2 (25 mL), washed by aqueous 1.0 M HCl (20 mL), saturated $NaHCO_3$ aqueous solution (20 mL), brine (30 mL), and dried over Na_2SO_4. The organic solvent was removed by evaporation. Purification by column chromatography afforded pure amides.

2-(1,3-Dioxoisoindolin-2-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)butanamide (3.1a). White solid, overall yield from 2-aminobutyric acid: 2.10 g, 72%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (br s, 1H), 8.25 (d, J = 4.5 Hz, 1H), 7.90-7.86 (m, 2H), 7.77-7.73 (m, 2H), 7.72-7.67 (m, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.16-7.11 (m, 1H), 4.81 (dd, J = 11.0, 5.5 Hz, 1H), 2.48-2.28 (m, 2H), 1.76 (s, 3H), 1.75 (s, 3H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ168.17, 167.37, 164.13, 147.25, 137.22, 134.12, 131.85, 123.37, 121.86, 119.39, 56.60, 56.55, 27.36, 27.24, 22.00, 11.21. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3326, 3058, 2975, 2934, 1774, 1715, 1593, 1514, 1470, 1432, 1384, 1093, 897, 787, 720. HRMS (ESI, *m/z*): calcd. for $C_{20}H_{22}N_3O_3$ $(M+H)^+$: 352.1661, found: 352.1655.

2-(1,3-Dioxoisoindolin-2-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)pentanamide (3.1b). White solid, overall yield from norvaline: 2.16 g, 71%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (br s, 1H), 8.23 (dd, J = 5.0, 1.0 Hz, 1H), 7.90-7.85 (m, 2H), 7.76-7.65 (m, 3H), 7.37 (d, J = 8.0 Hz, 1H), 7.15-7.09 (m, 1H), 4.88 (dd, J = 11.5, 5.0 Hz, 1H), 2.48-2.38 (m, 1H), 2.22-2.14 (m, 1H), 1.74 (s, 3H), 1.74 (s, 3H), 1.43-1.32 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.21, 167.55, 164.21, 147.27, 137.22, 134.05, 131.94, 123.43, 121.85, 119.42, 56.57, 54.76, 30.61, 27.37, 27.25, 19.92, 13.51. IR (neat)

$\bar{\upsilon}$ (cm^{-1}) 3327, 2964, 2933, 3873, 1774, 1714, 1678, 1513, 1469, 1383, 787, 720. HRMS (ESI, *m/z*): calcd. for $C_{21}H_{24}N_3O_3$ $(M+H)^+$: 366.1818, found: 366.1825.

2-(1,3-Dioxoisoindolin-2-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)octanamide (3.1c). White solid, overall yield from 2-aminooctanoic acid: 2.32 g, 68%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 8.24-8.21 (m, 1H), 7.91-7.85 (m, 2H), 7.77-7.73 (m, 2H), 7.71-7.67 (m, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.14-7.10 (m, 1H), 5.72-5.56 (m, 1H), 4.87 (dd, J = 11.0, 5.0 Hz, 1H), 2.47-2.38 (m, 1H), 2.28-2.20 (m, 1H), 1.75 (s, 3H), 1.74 (s, 3H), 1.44-1.20 (m, 7H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.18, 167.55, 164.21, 147.26, 137.21, 134.07, 131.94, 123.42, 121.84, 119.41, 56.57, 55.11, 31.58, 28.69, 28.63, 27.37, 27.25, 26.66, 22.52, 14.01. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3328, 3057, 2956, 2928, 2857, 1775, 1715, 1681, 1514, 1432, 1382, 1085, 997, 787, 720. HRMS (ESI, *m/z*): calcd. for $C_{24}H_{30}N_3O_3$ $(M+H)^+$: 408.2287, found: 408.2273.

2-(1,3-Dioxoisoindolin-2-yl)-4-phenyl-*N*-(2-(pyridin-2-yl)propan-2-yl)butanamide (3.1d). White solid, overall yield from homophenylalanine: 2.50 g, 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (br s, 1H), 8.17-8.14 (m, 1H), 7.85-7.81 (m, 2H), 7.73-7.68 (m, 2H), 7.67-7.62 (m, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.20-7.16 (m, 4H), 7.10-7.04 (m, 2H), 4.91 (dd, J = 11.0, 4.5 Hz, 1H), 2.87-2.57 (m, 4H), 1.72 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.05, 167.19, 164.00, 147.16, 140.44, 137.20, 134.04, 131.80, 128.37, 128.31, 125.93, 123.31, 121.81, 119.33, 56.51, 54.81, 33.07, 29.92, 27.29, 27.20. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3324, 3060, 2979, 2931, 1775, 1715, 1594, 1514, 1470, 1452, 1432, 1381, 1266, 997, 876, 787, 769, 719, 700. HRMS (ESI, *m/z*): calcd. for $C_{26}H_{26}N_3O_3$ $(M+H)^+$: 428.1974, found: 428.1964.

2,6-Bis(1,3-dioxoisoindolin-2-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)hexanamide (3.1e). White solid, overall yield from lysine: 2.84 g, 65%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (br s, 1H), 8.23-8.20 (m, 1H), 7.87-7.83 (m, 2H), 7.80-7.65 (m, 7H), 7.36 (d, J = 8.5 Hz, 1H), 7.14-7.09 (m, 1H), 4.84 (dd, J = 11.0, 5.0 Hz, 1H), 3.67 (t, J = 7.5 Hz, 2H), 2.50-2.40 (m, 1H), 2.35-2.26 (m, 1H), 1.86-1.66 (m, 8H), 1.47-1.35 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.30, 168.12, 167.16, 164.12, 147.27, 137.19, 134.06, 133.84, 132.09, 131.90, 123.46, 123.16, 121.84, 119.38, 56.57, 54.75, 37.61, 28.21, 28.02, 27.35, 27.22, 24.05. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3327, 3058, 2977, 2937, 1773, 1713, 1570, 1468, 1382, 1036, 890, 788, 720. HRMS (ESI, *m/z*): calcd. for $C_{30}H_{29}N_4O_5$ $(M+H)^+$: 525.2138, found: 525.2145.

Benzyl 2-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)piperidine-1-carboxylate (3.1f). Colorless oil, yield from Cbz-2-piperidinecarboxylic acid: 2.42 g, 76%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47-8.28 (m, 2H), 7.71-7.64 (m, 1H), 7.45-7.10 (m, 7H), 5.34-5.05 (m, 2H), 4.94-4.76 (m, 1H), 4.31-4.11 (m, 1H), 3.13-2.96 (m, 1H), 2.40-2.32 (m, 1H), 1.77-1.35 (m, 11H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.43, 164.43, 156.36, 155.66, 147.65, 137.02, 136.73, 128.44, 127.94, 127.70, 121.77, 119.27, 67.35, 56.39, 56.04, 55.49, 42.19, 41.96, 27.51, 27.29, 26.12, 25.85, 25.07, 20.48. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3332, 3061, 2939, 2861, 1699, 1592, 1506, 1472, 1418, 1357, 1257, 1199, 1044, 829, 843, 766, 735, 698. HRMS (ESI, *m/z*): calcd. for $C_{22}H_{28}N_3O_3$ $(M+H)^+$: 382.2123, found: 382.2128.

2-(1,3-Dioxoisoindolin-2-yl)-3-(4-fluorophenyl)-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.1h). White solid, overall yield from 4-fluoro-phenylalanine: 2.37 g, 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.10 (d, J = 4.4 Hz, 1H), 7.83-7.81(m, 2H), 7.73-7.67 (m, 3H), 7.37 (d, J = 8.0 Hz, 1H), 7.20-7.17 (m, 2H), 7.13-7.08 (m, 1H), 6.88 (t, J = 8.4 Hz, 2H), 5.16 (dd, J = 10.4, 6.0 Hz, 1H), 3.69-3.63 (m, 2H), 1.76 (s, 6H).^{13}C

NMR (100 MHz, $CDCl_3$) δ 167.88, 166.65, 163.88, 161.66 (d, J = 243.0 Hz), 146.99, 137.45, 134.12, 133.04 (d, J = 3.0 Hz), 131.59, 130.42 (d, J = 8.0 Hz), 123.44, 121.94, 119.48, 115.40 (d, J = 22.0 Hz), 56.56, 55.99, 33.79, 27.30, 27.22. ^{19}F NMR (376 MHz, $CDCl_3$) -111.02 (d, J = 4.9 Hz), -162.8. IR (KBr) $\bar{\upsilon}$ (cm^{-1}) 3320, 3059, 2980, 2934, 1776, 1716, 1680, 1510, 1471, 1382, 1223, 1108, 788, 721. HRMS (ESI, *m/z*): calcd. for $C_{25}H_{22}FN_3NaO_3$ $(M+Na)^+$: 454.1543, found: 454.1537.

3-(4-Chlorophenyl)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.1i). White solid[23], overall yield from 4-chloro-phenylalanine: 2.50 g, 67%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (br s, 1H), 8.09-8.05 (m, 1H), 7.82-7.78 (m, 2H), 7.73-7.65 (m, 3H), 7.35 (d, J = 10.0 Hz, 1H), 7.18-7.13 (m, 4H), 7.11-7.07 (m, 1H), 5.15 (dd, J = 10.5, 6.5 Hz, 1H), 3.68-3.58 (m, 2H), 1.75 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.88, 166.50, 163.95, 147.11, 137.28, 135.93, 134.13, 132.53, 131.62, 130.29, 128.72, 123.48, 121.89, 119.38, 56.6, 55.81, 33.97, 27.26, 27.24. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3317, 2978, 2930, 1776, 1714, 1679, 1512, 1492, 1469, 1381, 1092, 1015, 961, 875, 786, 720. Ms (ESI): *m*/*z* = 448.1 $[M+H]^+$.

3-(4-Bromophenyl)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.1j). White solid, overall yield from 4-bromo-phenylalanine: 2.80 g, 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.16 (d, J = 3.2 Hz, 1H), 7.84-7.72 (m, 5H), 7.43 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.21-7.18 (m, 1H), 7.12 (d, J = 8.4 Hz, 2H), 5.17 (dd, J = 10.0, 6.8 Hz, 1H), 3.71-3.60 (m, 2H), 1.76 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.87, 166.63, 163.70, 146.70, 137.86, 136.40, 134.14, 131.65, 131.59, 130.68, 123.49, 122.08, 120.64, 119.68, 56.49, 55.66, 34.02, 27.31, 27.19. ^{19}F NMR (376 MHz, $CDCl_3$) 164.6. IR (KBr) $\bar{\upsilon}$ (cm^{-1}) 3321, 3029, 2980, 2933, 1776, 1716, 1681, 1513,

1382, 1112, 1012, 876, 786, 721, 530. HRMS (ESI, *m/z*): calcd. for $C_{25}H_{22}BrN_3NaO_3$ $(M+Na)^+$: 514.0742, found: 514.0717.

2-(1,3-Dioxoisoindolin-2-yl)-3-(4-nitrophenyl)-N-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.1k). Pink solid, overall yield from 4-nitro-phenylalanine: 2.22 g, 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.10-8.07 (m, 3H), 7.84-7.70 (m, 5H), 7.46-7.42 (m, 3H), 7.22-7.19 (m, 1H), 5.25 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.87-3.75 (m, 2H), 1.80 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.73, 166.08, 163.61, 146.83, 146.78, 145.51, 137.71, 134.38, 131.38, 129.86, 123.75, 123.58, 122.08, 119.56, 56.51, 55.23, 34.41, 27.21, 27.19. ^{19}F NMR (376 MHz, $CDCl_3$) 168.7. IR (KBr) $\bar{\upsilon}$ (cm^{-1}) 3317, 3059, 2981, 2934, 1776, 1715, 1597, 1519, 1346, 1111, 1087, 886, 787, 721, 557. HRMS (ESI, *m/z*): calcd. for $C_{25}H_{22}N_4NaO_5$ $(M+Na)^+$: 481.1488, found: 481.1461.

2-(1,3-Dioxoisoindolin-2-yl)-3-(naphthalen-2-yl)-N-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.1l). White solid, overall yield from 2-naphthylalanine: 2.12 g, 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.02 (d, *J* = 2.8 Hz, 1H), 7.82-7.63 (m, 9H), 7.45-7.35 (m, 4H), 7.09-7.04 (m, 1H), 5.38 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.90-3.84 (m, 2H), 1.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.02, 166.89, 163.83, 146.98, 137.45, 134.92, 134.03, 133.48, 132.34, 131.65, 128.36, 127.77, 127.60, 127.57, 126.97, 125.96, 125.54, 123.38, 121.93, 119.46, 56.65, 55.91, 34.92, 27.36, 27.31. ^{19}F NMR (376 MHz, $CDCl_3$) 162.6. IR (KBr) $\bar{\upsilon}$ (cm^{-1}) 3320, 3055, 2979, 2932, 1775, 1715, 1676, 1510, 1382, 1099, 874, 788, 720, 479. HRMS (ESI, *m/z*): calcd. for $C_{29}H_{25}N_3NaO_3$ $(M+Na)^+$: 486.1794, found: 486.1784.

***N*-(2-(Pyridin-2-yl)propan-2-yl)butyramide (3.3a).** Colorless oil[2], yield from butyric acid: 1.75 g, 85%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53-8.49 (m, 1H), 7.73-7.67 (m,

2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.21-7.17 (m, 1H), 2.24 (t, *J* = 7.5 Hz, 2 H), 1.76 (s, 6H), 1.74-1.65 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 172.24, 164.73, 147.60, 137.04, 121.80, 119.50, 56.36, 39.77, 27.56, 19.21, 13.74. IR (neat) ῡ (cm^{-1}) 3312, 3062, 2964, 2932, 2872, 1650, 1591, 1569, 1542, 1475, 1430, 1379, 1291, 1214, 1127, 993, 787, 748, 623. Ms (ESI): *m/z* = 207.2 $[M+H]^+$.

***N*-(2-(Pyridin-2-yl)propan-2-yl)tetradecanamide (3.3b).** White solid, yield from myristic acid: 2.84 g, 82%. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.52-8.49 (m, 1H), 7.73-7.68 (m, 2H), 7.42-7.38 (m, 1H), 7.20-7.16 (m, 1H), 2.25 (t, *J* = 7.5 Hz, 2H), 1.76 (s, 6H), 1.70-1.62 (m, 2H), 1.36-1.20 (m, 19H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 172.40, 164.76, 147.60, 137.01, 121.77, 119.49, 56.35, 37.86, 31.93, 29.69, 29.66, 29.64, 29.53, 29.36, 27.56, 25.81, 22.69. IR (neat) ῡ (cm^{-1}) 3317, 3066, 2954, 2919, 2872, 2850, 1646, 1547, 1473, 1464, 1355, 784, 747, 647, 621. HRMS (ESI, *m/z*): calcd. for $C_{22}H_{39}N_2O$ $(M+H)^+$: 347.3062, found: 347.3065.

3-Cyclopentyl-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.3c). White solid, yield from cyclopentanepropionic acid: 2.23 g, 86%. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.53-8.50 (m, 1H), 7.73-7.65 (m, 2H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.21-7.16 (m, 1H), 2.30-2.24 (m, 2H), 1.84-1.45 (m, 15H), 1.18-1.07 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 172.51, 164.75, 147.62, 137.03, 121.79, 119.50, 56.34, 39.82, 37.15, 32.52, 31.99, 27.55, 25.18. IR (neat) ῡ (cm^{-1}) 3310, 3062, 2948, 2865, 1651, 1591, 1542, 1474, 1430, 1380, 1328, 1292, 1207, 1126, 993, 786, 747, 623. HRMS (ESI, *m/z*): calcd. for $C_{16}H_{25}N_2O$ $(M+H)^+$: 261.1967, found: 261.1956.

5-Phenyl-*N*-(2-(pyridin-2-yl)propan-2-yl)pentanamide (3.3e). White solid, yield from 5-phenylvaleric acid 2.20 g, 74%. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.51-8.48 (m,

1H), 7.73-7.66 (m, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.27-7.23 (m, 2H), 7.18-7.13 (m, 4H), 2.64 (t, J = 7.0 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 1.77-1.63 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.06, 164.64, 147.58, 142.41, 137.03, 128.40, 128.26, 125.66, 121.79, 119.47, 56.36, 37.56, 35.76, 31.07, 27.54, 25.44. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3317, 3004, 2919, 2850, 1647, 1547, 1464, 1428, 1175, 784, 747, 647. HRMS (ESI, *m/z*): calcd. for $C_{19}H_{25}N_2O$ $(M+H)^+$: 297.1967, found: 297.1964.

2-Isopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)pentanamide (3.3g). White solid, overall yield from ethyl isovalerate and *n*-iodopropane: 1.05 g, 48%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53-8.47 (m, 1H), 7.82 (br s, 1H), 7.73-7.68 (m, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.20-7.16 (m, 1H), 1.85-1.72 (m, 8H), 1.65-1.55 (m, 1H), 1.50-1.20 (m, 3H), 1.00-0.87 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.51, 164.84, 147.55, 136.96, 121.74, 119.54, 56.43, 55.72, 32.70, 30.98, 27.50, 27.47, 21.07, 21.02, 20.57, 14.32. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3308, 3052, 2955, 2933, 2870, 1644, 1593, 1541, 1476, 1428, 1380, 1271, 1234, 1125, 788, 750, 738, 666, 624. HRMS (ESI, *m/z*): calcd. for $C_{16}H_{27}N_2O$ $(M+H)^+$: 263.2123, found: 261.2119.

2-Benzyl-3-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)butanamide (3.3h). White solid, overall yield from ethyl isovalerate and benzyl bromide: 1.09 g, 42%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43-8.40 (m, 1H), 7.62-7.56 (m, 1H), 7.29 (br s, 1H), 7.23-7.18 (m, 4H), 7.17-7.14 (m, 1H), 7.13-7.08 (m, 2H), 2.89-2.84 (m, 2H), 2.14-2.08 (m, 1H), 1.98-1.90 (m, 1H), 1.62 (s, 3H), 1.49 (s, 3H), 1.07 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.03, 164.60, 147.45, 140.66, 136.75, 129.19, 128.12, 125.82, 121.52, 119.37, 57.84, 56.43, 36.62, 30.95, 27.42, 27.34, 20.76. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3335, 2967, 2931, 2871, 1651, 1593, 1569, 1509, 1473, 1430, 1379, 1227, 1126, 786, 746, 700, 623. HRMS (ESI, *m/z*): calcd. for $C_{20}H_{27}N_2O$ $(M+H)^+$: 311.2123, found: 311.2121.

2-Cyclohexyl-*N*-(2-(pyridin-2-yl)propan-2-yl)pentanamide (3.3i). White solid, overall yield from ethyl 2-cyclohexylacetate and *n*-iodopropane: 1.39 g, 55%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, J = 4.5 Hz, 1H), 7.79 (br s, 1H), 7.73-7.68 (m, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.20-7.16 (m, 1H), 1.89-1.83 (m, 2H), 1.78-1.30 (m, 14H), 1.27-0.86 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.51, 164.84, 147.54, 136.96, 121.73, 119.55, 56.44, 54.80, 40.36, 32.23, 31.29, 30.95, 27.55, 27.49, 26.60, 26.47, 26.37, 21.02, 14.33. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3303, 3007, 2928, 2851, 1644, 1542, 1477, 1429, 1358, 1252, 1224, 787, 749. HRMS (ESI, *m/z*): calcd. for $C_{19}H_{31}N_2O$ $(M+H)^+$: 303.2436, found: 303.2435.

2-Cyclohexyl-3-phenyl-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.3j). White solid, overall yield from ethyl 2-cyclohexylacetate and benzyl bromide: 1.52 g, 52%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43-8.40 (m, 1H), 7.61-7.56 (m, 1H), 7.28 (br s, 1H), 7.22-7.07 (m, 7H), 2.92-2.81 (m, 2H), 2.17-2.10 (m, 1H), 1.99-1.93 (m, 1H), 1.83-1.57 (m, 8H), 1.47 (s, 3H), 1.32-1.02 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.01, 164.62, 147.47, 140.75, 136.75, 129.23, 128.10, 125.78, 121.52, 119.37, 57.06, 56.43, 40.39, 36.22, 31.13, 31.09, 27.48, 27.24, 26.56, 26.47, 26.35. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3317, 2925, 2851, 1649, 1592, 1535, 1497, 1473, 1449, 1430, 1379, 1248, 1211, 1125, 784, 745, 700, 673. HRMS (ESI, *m/z*): calcd. for $C_{23}H_{31}N_2O$ $(M+H)^+$: 351.2436, found: 351.2433.

2-Phenyl-*N*-(2-(pyridin-2-yl)propan-2-yl)butanamide (3.3k). White solid, yield from 2-phenylbutyric acid: 2.12 g, 75%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46-8.43 (m, 1H), 7.74 (br s, 1H), 7.68-7.63 (m, 1H), 7.38-7.29 (m, 5H), 7.26-7.21 (m, 1H), 7.16-7.12 (m, 1H), 3.32 (t, J = 7.5 Hz, 1H), 2.22-2.13 (m, 1H), 1.85-1.74 (m, 1H), 1.72 (s, 3H), 1.66 (s, 3H), 0.92 (t, J = 7.5Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.53, 164.61, 147.55, 140.71, 136.93, 128.54, 127.96, 126.80, 121.70, 119.37, 56.47, 56.12, 27.54, 27.38, 26.70, 12.42.

IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3327, 2966, 2932, 2874, 1655, 1592, 1570, 1505, 1473, 1452, 1431, 1275, 1222, 1127, 786, 747, 731, 699. HRMS (ESI, *m/z*): calcd. for $C_{18}H_{23}N_2O$ $(M+H)^+$: 283.1810, found: 283.1807.

2-(Naphthalen-1-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)butanamide (3.3l). White solid, overall yield from ethyl 2-naphthylacetate and iodoethane: 2.16 g, 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 4.4 Hz, 1H), 7.87-7.83 (m, 5H), 7.71-7.66 (m, 1H), 7.56 (d, J = 9.2 Hz, 1H), 7.51-7.46 (m, 2H), 7.35 (d, J = 8.4 Hz, 1H), 7.17 (dd, J = 6.8, 5.2 Hz, 1H), 3.54 (t, J = 7.6 Hz, 1H), 2.32-2.25 (m, 1H), 1.98-1.87 (m, 1H), 1.76 (s, 3H), 1.69 (s, 3H), 0.97 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.57, 164.37, 147.15, 138.19, 137.45, 133.57, 132.58, 128.25, 127.83, 127.62, 126.77, 126.19, 125.97, 125.56, 121.88, 119.62, 56.40, 56.06, 27.46, 26.62, 12.46. ^{19}F NMR (376 MHz, $CDCl_3$) 171.0. IR (KBr) $\bar{\upsilon}$ (cm^{-1}) 3326, 3054, 2966, 2932, 2873, 1656, 1506, 1473, 1380, 1127, 815, 748, 478. HRMS (ESI, *m/z*): calcd. for $C_{22}H_{25}N_2O$ $(M+H)^+$: 333.1967, found: 333.1969.

General procedure for Palladium-Catalyzed β-Fluorination of Amides:

An oven-dried 50 mL Schlenk flask was charged with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), Selectfluor (265.7 mg, 0.75 mmol), Ag_2CO_3 (165.4 mg, 0.6 mmol) and $Fe(OAc)_2$, and then a solution of amide (**3.1** or **3.3**, 0.30 mmol) in DCE (3.0 mL) was added, followed by addition of ^{i}PrCN or MeCN. The vial was sealed, and the reaction mixture was stirred vigorously at 150 ˚C for 14 h. The mixture was cooled to room temperature, diluted with EtOAc (10 mL), filtered through a celite pad, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient eluent of 5~20% acetone in hexanes, v/v) to give the desired product.

2-(1,3-Dioxoisoindolin-2-yl)-3-fluoro-*N*-(2-(pyridin-2-yl)propan-2-yl)butanamide (3.2a + 3.2a'), 84.2 mg, 76% yield (d.r. = 7:1), with 0.3 equivalents of $Fe(OAc)_2$ and 300 µL of ^{i}PrCN. Compound **3.2a**: white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, J = 7.5 Hz, 1H), 8.49-8.46 (m, 1H), 7.89-7.84 (m, 2H), 7.75-7.66 (m, 3H), 7.38 (d, J = 8.0 Hz, 1H), 7.18-7.14 (m, 1H), 5.86-5.70 (m, 1H), 4.91 (dd, J = 14.5, 9.0 Hz, 1H), 1.77 (s, 3H), 1.74 (s, 3H), 1.44 (dd, J = 25.0, 6.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.94, 164.88, 164.08, 147.75, 137.06, 134.26, 131.90, 123.72, 121.86, 119.28, 88.68 (d, J = 164.8 Hz), 57.68 (d, J = 30.5 Hz), 57.38, 27.51, 27.42, 19.08 (d, J = 22.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -171.9 (m, 1F). IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3364, 3324, 2984, 2936, 2912, 1773, 1716, 1684, 1520, 1471, 1455, 1389, 1335, 1297, 1116, 1090, 913, 887, 789, 717, 652. HRMS (ESI, *m/z*): calcd. for $C_{20}H_{21}FN_3O_3$ $(M+H)^+$: 370.1567, found: 370.1568. Compound **3.2a'**: white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 8.24-8.21 (m, 1H), 7.94-7.89 (m, 2H), 7.79-7.74 (m, 2H), 7.70-7.65 (m, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.13-7.09 (m, 1H), 5.62-5.55(m, 1H), 4.87 (dd, J = 10.0, 9.0 Hz, 1H), 1.73 (s, 6H), 1.63 (dd, J = 10.0, 6.5, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.78, 164.65, 163.87, 147.47, 137.15, 134.27, 131.83, 123.68, 121.89, 119.32, 86.31 (d, J = 172.9 Hz), 59.33 (d, J = 20.0 Hz), 56.88, 27.26 (d, J =28.9 Hz), 19.67 (d, J = 21.3 Hz). IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3313, 2956, 2924, 2853, 1772, 1718, 1684, 1521, 1472, 1457, 1385, 1297, 1125, 1067, 913, 886, 788, 719, 668. ^{19}F NMR (470 MHz, $CDCl_3$) δ -191.7 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{20}H_{21}FN_3O_3$ $(M+H)^+$: 370.1567, found: 370.1570.

2-(1,3-Dioxoisoindolin-2-yl)-3-fluoro-*N*-(2-(pyridin-2-yl)propan-2-yl)pentanamide (3.2b + 3.2b'). 84.0 mg, 73% yield (d.r. = 8:1), with 0.3 equivalents of $Fe(OAc)_2$ and 300 µL of ^{i}PrCN. Compound **3.2b**: white solid; ^{1}H NMR (500 MHz, $CDCl_3$)

δ 8.59 (d, J = 6.5 Hz, 1H), 8.50 (br s, 1H), 7.90-7.83 (m, 2H), 7.76-7.66 (m, 3H), 7.42-7.36 (m, 1H), 7.20-7.14 (m, 1H), 5.70-5.53 (m, 1H), 5.00-4.92 (m, 1H), 1.87-1.56 (m, 8H), 1.05 (t, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.99, 165.09, 164.11, 147.81, 137.05, 134.24, 131.94, 123.70, 121.85, 119.28, 92.37 (d, J = 165.3 Hz), 57.42, 56.09 (d, J = 30.9 Hz), 27.52, 27.46, 25.79 (d, J = 20.8), 8.26 (d, J = 4.3 Hz). IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3323, 2976, 2928, 1779, 1718, 1681, 1513, 1470, 1384, 1362, 1100, 1077, 671. ^{19}F NMR (470 MHz, $CDCl_3$) δ -183.6 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{21}H_{23}FN_3O_3$ $(M+H)^+$: 384.1723, found: 384.1725. Compound **3.2b'**: white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (br s, 1H), 8.23-8.20 (m, 1H), 7.93-7.88 (m, 2H), 7.79-7.64 (m, 2H), 7.70-7.66 (m, 1H), 7.35 (d, J = 8.5 Hz, 1H) 7.13-7.09 (m, 1H), 5.48-5.33 (m, 1H), 5.00-4.92 (dd, J = 10.5, 8.5 Hz, 1H), 2.13-1.97 (m, 1H), 1.88-1.68 (m, 7H), 1.11 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.82, 164.88, 164.82, 163.86, 147.45, 137.15, 134.26, 131.81, 123.67, 121.88, 119.32, 90.52 (d, J = 175.6 Hz), 57.57 (d, J = 19.6 Hz), 56.87, 27.27 (d, J = 28.3 Hz), 26.67 (d, J = 20.3 Hz), 9.23 (d, J = 4.1 Hz). IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3317, 3060, 2975, 2926, 2852, 1773, 1721, 1685, 1512, 1471, 1380, 1294, 1194, 1075, 788, 719. ^{19}F NMR (470 MHz, $CDCl_3$) δ -190.7 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{21}H_{23}FN_3O_3$ $(M+H)^+$: 384.1723, found: 384.1728.

2-(1,3-Dioxoisoindolin-2-yl)-3-fluoro-*N*-(2-(pyridin-2-yl)propan-2-yl)octanamide 3.2c + 3.2c'). 89.4 mg, 70% yield (d.r. = 9:1), with 0.3 equivalents of $Fe(OAc)_2$ and 300 µL of ^{i}PrCN. Compound **3.2c**: White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J = 7.5 Hz, 1H), 8.49 (d, J = 3.5 Hz, 1H), 7.89-7.84 (m, 2H), 7.75-7.65 (m, 3H), 7.38 (d, J = 8.0 Hz, 1H), 7.17-7.14 (m, 1H), 5.74-5.55 (m, 1H), 4.94 (dd, J = 13.0, 10.0, 1H), 1.78-1.45 (m, 10H), 1.34-1.20 (m, 4H), 0.88-0.82 (m, 3H). ^{13}C NMR (125 MHz,

$CDCl_3$) δ 167.98, 165.08, 164.19, 147.84, 137.02, 134.21, 132.00, 123.72, 121.83, 119.27, 91.61 (d, J = 166.9 Hz), 57.46, 56.51 (d, J = 30.8 Hz), 32.68 (d, J = 20.5 Hz), 31.41, 27.55, 27.48, 23.78 (d, J = 2.9 Hz), 22.45, 13.89. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3328, 3058, 2956, 2928, 1775, 1715, 1682, 1594, 1514, 1379, 1360, 1335, 1267, 1201, 1193, 1125, 1085, 997, 877, 787, 719, 650. ^{19}F NMR (470 MHz, $CDCl_3$) δ -181.6 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{24}H_{29}FN_3O_3$ $(M+H)^+$: 426.2193, found: 426.2190. Compound **3.2c'**: white solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 8.24-8.20 (m, 1H), 7.93-7.87 (m, 2H), 7.79-7.73 (m, 2H), 7.69-7.64 (m, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.13-7.09 (m, 1H), 5.53-5.38 (m, 1H), 4.91 (dd, J = 10.5, 8.5, 1H), 2.07-1.90 (m, 1H), 1.81-1.45 (m, 9H), 1.38-1.24 (m, 4H), 0.91-0.85 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.83, 164.87, 163.89, 147.45, 137.13, 134.25, 131.82, 123.70, 121.88, 119.32, 89.52 (d, J = 175.5 Hz), 57.94 (d, J = 19.9 Hz), 56.88, 33.48 (d, J = 20.0 Hz), 31.51, 27.41, 27.15, 24.63 (d, J = 2.5 Hz), 22.52, 13.99. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3314, 2955, 2926, 2857, 1773, 1718, 1684, 1594, 1520, 1381, 1195, 1125, 1086, 997, 875, 787, 719, 668. ^{19}F NMR (470 MHz, $CDCl_3$) δ -190.6 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{24}H_{29}FN_3O_3$ $(M+H)^+$: 426.2193, found: 426.2198.

2-(1,3-Dioxoisoindolin-2-yl)-3-fluoro-4-phenyl-*N*-(2-(pyridin-2-yl)propan-2-yl)butanamide (3.2d). White solid, 101.6 mg, 76% yield, with 0.25 equivalents of $Fe(OAc)_2$ and 300 µL of ^iPrCN. ^1H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, J = 7.5 Hz, 1H), 8.47-8.43 (m, 1H), 7.88-7.84 (m, 2H), 7.76-7.71 (m, 2H), 7.70-7.65 (m, 1H), 7.36 (d, J = 9.5 Hz, 1H), 7.27-7.13 (m, 6H), 5.96-5.80 (m, 1H), 4.98 (dd, J = 13.5, 9.5 Hz, 1H), 3.16-2.90 (m, 2H), 1.74 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.94, 164.74, 164.00, 147.80, 137.02, 135.61, 135.60, 134.24, 131.91, 129.51, 128.46, 126.87, 123.71, 121.82, 119.22, 91.62 (d, J = 169.9 Hz), 57.45, 56.60 (d, J = 30.5 Hz), 39.38 (d, J = 20.8),

27.46, 27.45. IR (neat) ῡ (cm^{-1}) 3325, 3061, 3030, 2980, 2923, 1779, 1717, 1682, 1513, 1471, 1385, 1336, 1124, 1088, 996, 787, 750, 723, 702, 650. ^{19}F NMR (470 MHz, $CDCl_3$) δ -179.1 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{26}H_{25}FN_3O_3$ $(M+H)^+$: 446.1880, found: 446.1890.

2,6-Bis(1,3-dioxoisoindolin-2-yl)-3-fluoro-*N*-(2-(pyridin-2-yl)propan-2-yl)hexanamide (3.2e). White solid, 105.8 mg,: 65% yield, with 0.25 equivalents of $Fe(OAc)_2$ and 300 µL of ^{i}PrCN. ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J = 7.5 Hz, 1 H), 8.48-8.45 (m, 1H), 7.87-7.82 (m, 2H), 7.79-7.66 (m, 7H), 7.37 (d, J = 8.0 Hz, 1H), 7.18-7.14 (m, 1H), 5.75-5.58 (m, 1H), 4.93 (dd, J = 14.0, 9.0 Hz, 1H), 3.68 (t, J = 8.0 Hz, 2H), 2.02-1.64 (m, 10H), 1.60 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.21, 167.94, 164.74, 164.04, 147.77, 137.05, 134.23, 133.88, 132.05, 131.92, 123.76, 123.21, 121.85, 119.25, 91.01 (d, J = 168.3 Hz), 57.42, 56.38 (d, J = 30.6 Hz), 37.51, 30.08 (d, J = 20.5 Hz), 27.48, 27.42, 23.49 (d, J = 2.9 Hz). IR (neat) ῡ (cm^{-1}) 3321, 3059, 2977, 2933, 1774, 1683, 1613, 1571, 1451, 1433, 1393, 1382, 1268, 1088, 1040, 996, 881, 788, 734, 720. ^{19}F NMR (470 MHz, $CDCl_3$) δ -181.8 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{30}H_{28}FN_4O_5$ $(M+H)^+$: 543.2044, found: 543.2044.

Benzyl 3-fluoro-2-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)piperidine-1-carboxylate (3.2f). Colorless oil, 98.3 mg,: 82% yield, with 0.3 equivalents of $Fe(OAc)_2$ and 300 µL of ^{i}PrCN. ^1H NMR (500 MHz, $CDCl_3$) δ 8.50-8.44 (m, 1H), 8.04 (br s, 1H), 7.70-7.63 (m, 1H), 7.41-7.22 (m, 6H), 7.17-7.12 (m, 1H), 5.23-4.69 (m, 4H), 4.07-3.85 (m, 1H), 3.36-3.23 (m, 1H), 2.08-1.93 (m, 1H), 1.85-1.66 (m, 7H), 1.65-1.50 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.54, 164.27, 156.34, 147.80, 136.92, 136.42, 128.46, 128.02, 127.87, 121.74, 119.28, 89.15 (d, J = 178.9 Hz), 67.61, 57.09 (2C), 40.33, 27.55, 26.15,

22.59. IR (neat) ῡ (cm^{-1}) 3335, 3062, 2953, 2870, 1683, 1592, 1570, 1514, 1430, 1357, 1261, 1158, 1114, 1038, 996, 894, 787, 735, 698. ^{19}F NMR (470 MHz, $CDCl_3$) δ -179.0 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{22}H_{27}FN_3O_3$ $(M+H)^+$: 400.2036, found: 400.2038.

2-(1,3-Dioxoisoindolin-2-yl)-3-fluoro-3-phenyl-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.2g). White solid, 110.0 mg, 85% yield, with no $Fe(OAc)_2$ and 300 µL of ^{i}PrCN. ^1H NMR (500 MHz, $CDCl_3$) δ 8.84 (d, *J* = 7.5 Hz, 1H), 8.51-8.48 (m, 1H), 7.74-7.68 (m, 3H), 7.63-7.58 (m, 2H), 7.45-7.40 (m, 3H), 7.30-7.23 (m, 3H), 7.20-7.16 (m, 1H), 6.55 (dd, *J* = 47.5, 9.5 Hz, 1H), 5.34 (dd, *J* = 14.5, 9.5 Hz, 1H), 1.83 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.40, 164.63 (d, *J* = 1.9 Hz), 164.07, 147.77, 137.11, 135.59 (d, *J* = 18.9 Hz), 134.00, 131.57, 129.66, 128.60, 127.19 (d, *J* = 10.9 Hz), 123.48, 121.91, 119.31, 92.00 (d, *J* = 168.9 Hz), 57.49, 56.78 (d, *J* = 35.5 Hz), 27.53, 27.45. IR (neat) ῡ (cm^{-1}) 3316, 3062, 2977, 2924, 2853, 1778, 1718, 1682, 1594, 1514, 1471, 1389, 1296, 1264, 1194, 1122, 1088, 997, 957, 787, 749, 722, 700. ^{19}F NMR (470 MHz, $CDCl_3$) δ -164.1 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{23}FN_3O_3$ $(M+H)^+$: 432.1723, found: 432.1725.

2-(1,3-Dioxoisoindolin-2-yl)-3-fluoro-3-(4-fluorophenyl)-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.2h). Colorless oil, 87.6 mg, 65% yield, with 0.3 equivalents of $Fe(OAc)_2$ and 300 µL of ^{i}PrCN. ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 5.6 Hz, 1H), 8.53 (d, *J* = 4.0 Hz, 1H), 7.80-7.65 (m, 5H), 7.45- 742 (m, 3H), 7.26- 7.23 (m, 1H), 6.98 (t, *J* = 8.4 Hz, 2H), 6.57 (dd, *J* = 47.6, 9.6 Hz, 1H), 5.33 (dd, *J* = 14.4, 9.6 Hz, 1H), 1.85 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.36, 164.58 (d, *J* = 2.0 Hz), 163.71, 163.26 (dd, *J* = 247.0, 3.0 Hz), 147.29, 137.77, 134.15, 131.54 (dd, *J* =19.0, 4.0 Hz), 131.46, 129.24 (dd, *J* =8.0, 5.0 Hz), 123.58, 122.17, 119.66, 115.72 (d, *J* = 21.0

Hz), 91.27 (d, *J* = 170.0 Hz), 57.32, 56.68 (d, *J* = 36.0 Hz), 27.49, 27.43. IR (KBr) $\bar{\upsilon}$ (cm^{-1}) 3315, 3058, 2980, 2929, 1779, 1717, 1684, 1514, 1386, 1228, 1122, 998, 841, 721, 566, 528. ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.0, 162.8. HRMS (ESI, *m/z*): calcd. for $C_{25}H_{21}F_2N_3NaO_3$ $(M+H)^+$: 472.1449, found: 472.1436.

3-(4-Chlorophenyl)-2-(1,3-dioxoisoindolin-2-yl)-3-fluoro-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.2i). White solid, 100.6 mg, 72% yield, with 0.3 equivalents of $Fe(OAc)_2$ and 300 μL of ^{i}PrCN. ^1H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, *J* = 6.5 Hz, 1H), 8.50-8.47 (m, 1H), 7.75-7.69 (m, 3H), 7.67-7.62 (m, 2H), 7.42-7.35 (m, 3H), 7.28-7.24 (m, 2H), 7.21-7.17 (m, 1H), 6.54 (dd, *J* = 48.0, 9.5 Hz, 1H), 5.29 (dd, *J* = 15.0, 9.5 Hz, 1H), 1.82 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.43, 164.33 (d, *J* = 2.3 Hz), 163.70, 147.71, 137.17, 135.59 (d, *J* = 3.4 Hz), 134.23 (d, *J* = 12.6 Hz), 134.12, 131.50, 128.93, 128.61 (d, *J* = 5.4 Hz), 123.62, 121.97, 119.32, 91.27 (d, *J* = 169.6 Hz), 57.47, 56.71 (d, *J* = 35.9 Hz), 27.48, 27.40. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3332, 3060, 2880, 2936, 1781, 1722, 1679, 1596, 1469, 1392, 1124, 1090, 836, 786, 751, 718. ^{19}F NMR (470 MHz, $CDCl_3$) δ -164.3 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{25}H_{22}ClFN_3O_3$ $(M+H)^+$: 466.1334, found: 466.1336.

3-(4-Bromophenyl)-2-(1,3-dioxoisoindolin-2-yl)-3-fluoro-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.2j). White solid, 111.8 mg, 73% yield, with 0.3 equivalents of $Fe(OAc)_2$ and 300 μL of ^{i}PrCN. ^1H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 6.4 Hz, 1H), 8.51 (d, *J* = 4.4 Hz, 1H), 7.76-7.66 (m, 5H), 7.43 (d, *J* = 8.4 Hz, 3H), 7.33 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.22 (dd, *J* = 7.2, 5.2 Hz, 1H), 6.55 (dd, *J* = 47.6, 9.6 Hz, 1H), 5.31 (dd, *J* = 14.4, 9.6 Hz, 1H), 1.84 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.42, 164.41 (d, *J* = 2.0 Hz), 163.77, 147.43, 137.57, 134.67 (d, *J* = 19.0 Hz), 134.20,

131.88, 131.48, 128.88 (d, *J* = 5.0 Hz), 123.91 (d, *J* = 4.0 Hz), 123.64, 122.11, 119.53, 91.28 (d, *J* = 169.0 Hz), 57.38, 56.63 (d, *J* = 35.0 Hz) 27.48, 27.42. IR (KBr) ῡ (cm^{-1}) 3314, 3059, 2981, 2929, 1779, 1720, 1685, 1514, 1385, 1013, 724. ^{19}F NMR (376 MHz, $CDCl_3$) δ -164.6. HRMS (ESI, *m/z*): calcd. for $C_{25}H_{21}BrFN_3NaO_3$ $(M+Na)^+$: 532.0648, found: 532.0629.

2-(1,3-Dioxoisoindolin-2-yl)-3-fluoro-3-(4-nitrophenyl)-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.2k). White solid, 87.2 mg, 61% yield, with 0.3 equivalents of $Fe(OAc)_2$ and 300 µL of ^{i}PrCN. ^1H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, *J* = 5.6 Hz, 1H), 8.46 (d, *J* = 4.8 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.77-7.73 (m, 3H), 7.70-7.63 (m, 4H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.23-7.20 (m, 1H), 6.69 (dd, *J* = 47.6, 9.6 Hz, 1H), 5.33 (dd, *J* = 15.2, 9.6 Hz, 1H), 1.84 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.39, 163.88 (d, *J* = 1.0 Hz), 163.63, 148.50 (d, *J* = 3.0 Hz), 147.33, 142.55 (d, *J* = 19.0 Hz), 137.65, 134.43, 131.30, 128.11 (d, *J* = 6.0 Hz), 123.82, 123.76, 122.18, 119.55, 90.58 (d, *J* = 172.0 Hz), 57.36, 56.73 (d, *J* = 34.0 Hz), 27.40, 27.35. IR (KBr) ῡ (cm^{-1}) 3318, 3061, 2981, 2922, 1779, 1718, 1683, 1526, 1471, 1383, 1348, 1126, 1017, 1000, 853, 787, 722. ^{19}F NMR (376 MHz, $CDCl_3$) δ -168.7. HRMS (ESI, *m/z*): calcd. for $C_{25}H_{21}FN_4NaO_5$ $(M+Na)^+$: 499.1394, found: 499.1384.

2-(1,3-Dioxoisoindolin-2-yl)-3-fluoro-3-(naphthalen-2-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.2l). White solid, 76.6 mg, 53% yield, with 0.3 equivalents of $Fe(OAc)_2$ and 300 µL of ^{i}PrCN. ^1H NMR (400 MHz, $CDCl_3$) δ ^1H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, *J* = 7.2 Hz, 1H), 8.55 (d, *J* = 4.4 Hz, 1H), 7.92 (s, 1H), 7.84-7.75 (m, 4H), 7.70-7.68 (m, 2H), 7.62-7.57 (m, 3H), 7.49-7.46 (m, 3H), 7.23 (dd, *J* = 7.2, 5.2 Hz, 1H), 6.76 (dd, *J* = 47.6, 9.6 Hz, 1H), 5.52 (dd, *J* = 14.4, 9.6 Hz, 1H), 1.88 (s, 3H),

1.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.45, 164.93 (d, J = 2.0 Hz), 163.56, 147.02, 138.21, 134.00, 133.79 (d, J = 2.0 Hz), 132.80 (d, J = 19.0 Hz), 132.75, 131.50, 128.81, 128.40, 127.92 (d, J = 7.0 Hz), 127.68, 126.85, 126.38, 123.61 (d, J = 4.0 Hz), 123.52, 122.30, 119.89, 92.23 (d, J = 169.0 Hz), 57.29, 56.57 (d, J = 36.0 Hz), 27.53. IR (KBr) $\bar{\upsilon}$ (cm^{-1}) 3315, 3058, 2979, 2930, 1778, 1716, 1682, 1514, 1471, 1385, 1266, 1127, 997, 751,723, 553. ^{19}F NMR (376 MHz, $CDCl_3$) δ -162.6. HRMS (ESI, *m/z*): calcd. for $C_{29}H_{24}FN_3NaO_3$ $(M+Na)^+$: 504.1691, found:504.1699.

3-Fluoro-*N*-(2-(pyridin-2-yl)propan-2-yl)butanamide (3.4a). Colorless oil, 54.5 mg, 81% yield, with 0.75 equivalents of $Fe(OAc)_2$ and 400 µL of MeCN. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53-8.49 (m, 1H), 7.88 (br s, 1H), 7.74-7.69 (m, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.21-7.17 (m, 1H), 5.22-5.05 (m, 1H), 2.70-2.60 (m, 1H), 2.55-2.43 (m, 1H), 1.76 (s, 3H), 1.76 (s, 3H), 1.43 (dd, J = 24.0, 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.39, 164.36, 147.65, 137.09, 121.87, 119.42, 88.16 (d, J = 164.8 Hz), 56.72, 45.33 (d, J = 17.8 Hz), 27.51, 27.48, 20.88 (d, J = 22.0 Hz). IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3318, 3063, 2981, 2934, 2872, 1737, 1651, 1591, 1538, 1383, 1319, 1230, 1128, 1058, 994, 926, 837, 788, 749, 700. ^{19}F NMR (470 MHz, $CDCl_3$) δ -172.1 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{12}H_{18}FN_2O$ $(M+H)^+$: 225.1403, found: 225.1406.

3-Fluoro-*N*-(2-(pyridin-2-yl)propan-2-yl)tetradecanamide (3.4b). White solid, 87.5 mg, 80% yield, with 0.75 equivalents of $Fe(OAc)_2$ and 400 µL of MeCN. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53-8.49 (m, 1H), 7.83 (br s, 1H), 7.73-7.66 (m, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.21-7.15 (m, 1H), 5.05-4.87 (m, 1H), 2.65-2.40 (m, 2H), 1.82-1.55 (m, 8H), 1.53-1.15 (m, 18 H), 0.92-0.85 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.62 (d, J = 4.4 Hz), 164.48, 147.70, 137.04, 121.83, 119.42, 91.55 (d, J = 167.3 Hz), 56.77, 43.88 (d, J =

22.5 Hz), 35.03 (d, *J* = 20.4), 29.65, 29.63, 29.55, 29.50, 29.37, 29.35, 27.55, 27.51, 24.97 (d, *J* = 4.3 Hz), 22.69, 14.10. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3318, 3064, 2923, 2853, 1651, 1591, 1545, 1473, 1431, 1579, 1206, 1127, 1048, 993, 786, 747, 74. ^{19}F NMR (470 MHz, $CDCl_3$) δ -179.1 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{22}H_{38}FN_2O$ $(M+H)^+$: 365.2968, found: 365.2974.

3-Cyclopentyl-3-fluoro-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.4c). White solid, 62.6 mg, 75% yield, with 0.75 equivalents of $Fe(OAc)_2$ and 400 µL of MeCN. ^1H NMR (500 MHz, $CDCl_3$) δ 8.53-8.49 (m, 1H), 7.83 (br s, 1H), 7.73-7.66 (m, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.20-7.15 (m, 1H), 4.87-4.72 (m, 1H), 2.62-2.45 (m, 2H), 2.17-2.04 (m, 1H), 1.85-1.45 (m, 13H), 1.35-1.23 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.85 (d, *J* = 2.0 Hz), 164.42, 147.68, 137.06, 121.83, 119.43, 94.53 (d, *J* = 169.4 Hz), 56.76, 44.07 (d, *J* = 19.1 Hz), 43.06 (d, *J* = 22.9 Hz), 28.52 (d, *J* = 6.4 Hz), 28.07 (d, *J* = 3.3 Hz), 27.55, 27.49, 25.64, 25.61. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3317, 3062, 2956, 2869, 1651, 1591, 1544, 1474, 1431, 1380, 1207, 1127, 1048, 1023, 995, 857, 787, 748, 622. ^{19}F NMR (470 MHz, $CDCl_3$) δ -180.3 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{16}H_{24}FN_2O$ $(M+H)^+$: 225.1873, found: 279.1867.

3-Fluoro-4-phenyl-*N*-(2-(pyridin-2-yl)propan-2-yl)butanamide (3.4d). White solid, 82.0 mg, 91% yield, with 0.75 equivalents of $Fe(OAc)_2$ and 400 µL of MeCN. ^1H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.0 Hz, 1H), 7.82 (br s, 1H), 7.73-7.68 (m, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.33-7.22 (m, 5H), 7.21-7.16 (m, 1H), 5.28-5.12 (m, 1H), 3.03 (dd, *J* = 23.0, 6.0 Hz, 2H), 2.71-2.46 (m, 2H), 1.76 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.28, 164.29, 147.64, 137.10, 136.48, 129.59, 128.49, 126.76, 121.88, 119.42, 91.46 (d, *J* = 170.9 Hz), 56.76, 42.86 (d, *J* = 22.5 Hz), 41.17 (d, *J* = 20.9 Hz),

27.51, 27.47. IR (neat) ῡ (cm^{-1}) 3318, 3062, 3029, 2926, 2855, 1653, 1591, 1543, 1512, 1474, 1430, 1380, 1204, 1127, 1031, 997, 787, 748, 700. ^{19}F NMR (470 MHz, $CDCl_3$) δ -188.9 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{18}H_{22}FN_2O$ $(M+H)^+$: 301.1716, found: 301.1723.

3-Fluoro-5-phenyl-*N*-(2-(pyridin-2-yl)propan-2-yl)pentanamide (3.4e). White solid, 67.0 mg, 71% yield, with 3.0 equivalents. of Selectfluor, 0.75 equivalents of $Fe(OAc)_2$ and 400 µL of MeCN. ^1H NMR (500 MHz, $CDCl_3$) δ 8.52-8.49 (m, 1H), 7.87 (br s, 1H), 7.73-7.67 (m, 1H), 7.41-7.38 (m, 1H), 7.30-7.25 (m, 2H), 7.22-7.16 (m, 4H), 5.08-4.92 (m, 1H), 2.89-2.43 (m, 4H), 2.11-1.86 (m, 2H), 1.76 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.30 (d, J = 4.6 Hz), 164.31, 147.64, 141.17, 137.09, 128.48, 128.44, 126.04, 121.88, 119.42, 90.70 (d, J = 168.0 Hz), 56.73, 43.76 (d, J = 22.5 Hz), 36.78 (d, J = 20.8 Hz), 31.26 (d, J = 4.4 Hz), 27.48. IR (neat) ῡ (cm^{-1}) 3309, 2964, 2926, 2852, 1645, 1592, 1537, 1471, 1429, 1274, 1127, 956, 787, 749, 622. ^{19}F NMR (470 MHz, $CDCl_3$) δ -180.9 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{19}H_{24}FN_2O$ $(M+H)^+$: 315.1873, found: 315.1876.

3-Fluoro-3-phenyl-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.4f). White solid, 61.8 mg, 72% yield, with 0.2 equivalents of $Fe(OAc)_2$ and 400 µL of MeCN. ^1H NMR (500 MHz, $CDCl_3$) δ 8.51-8.48 (m, 1H), 7.89 (br s, 1H), 7.72-7.67 (m, 1H), 7.41-7.30 (m, 6H), 7.20-7.16 (m, 1H), 5.99 (ddd, J = 47.0, 9.0, 4.0 Hz, 1H), 2.99-2.90 (m, 1H), 2.79-2.66 (m, 1H), 1.77 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167. 80 (d, J = 4.1 Hz), 164.24, 147.59, 139.37 (d, J = 19.4 Hz), 137.10, 128.57, 128.53 (d, J = 1.5 Hz), 125.52 (d, J = 6.9 Hz), 121.88, 119.41, 91.51 (d, J = 170.3 Hz), 56.79, 45.91 (d, J = 25.4 Hz), 27.46, 27.44. IR (neat) ῡ (cm^{-1}) 3316, 3064, 2978, 1652, 1590, 1544, 1513, 1474,

1431, 1380, 1216, 1127, 1015, 994, 787, 748, 699. ^{19}F NMR (470 MHz, $CDCl_3$) δ -174.5 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{17}H_{20}FN_2O$ $(M+H)^+$: 287.1560, found: 287.1554.

3-Fluoro-2-isopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)pentanamide (3.4g). White solid, 61.4 mg, 73% yield, with 0.75 equivalents of $Fe(OAc)_2$ and 400 µL of MeCN. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53-8.50 (m, 1H), 7.86 (br s, 1H), 7.72-7.67 (m, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.18-7.14 (m, 1H), 4.78-4.63 (m, 1H), 2.14-1.96 (m, 2H), 1.84 (m, 8H), 1.07-0.99 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.78, 164.67, 147.73, 136.86, 121.70, 119.47, 94.08 (d, J = 170.9 Hz), 59.83 (d, J = 19 Hz), 56.61, 27.72 (d, J = 5.3 Hz), 27.58, 27.27, 26.06 (d, J = 21.4 Hz), 20.84, 20.38, 9.97 (d, J = 5.5 Hz). IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3318, 3062, 3029, 2926, 2855, 1653, 1591, 1543, 1512, 1474, 1430, 1380, 1204, 1127, 1031, 997, 787, 748, 700. ^{19}F NMR (470 MHz, $CDCl_3$) δ -190.8 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{16}H_{26}FN_2O$ $(M+H)^+$: 281.2029, found: 281.2031.

2-(Fluoro(phenyl)methyl)-3-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)butanamide (3.4h). White solid, 53.2 mg, 54% yield, with no $Fe(OAc)_2$ and 400 µL of MeCN. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52-8.49 (m, 1H), 7.85 (br s, 1H), 7.69-7.64 (m, 1H), 7.43-7.28 (m, 6H), 7.19-7.15 (m, 1H), 5.82 (dd, J = 46.0, 7.5 Hz, 1H), 2.57-2.48 (m, 1H), 1.85-1.63 (m, 7H), 1.07-0.93 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.75, 164.56, 147.56, 138.16 (d, J = 19.9 Hz), 136.94, 128.57 (d, J = 1.5 Hz), 128.45, 128.46 (d, J = 6.4 Hz), 121.71, 119.47, 93.86 (d, J = 171.0 Hz), 60.27 (d, J = 21.8 Hz), 56.77, 27.59 (d, J = 6.5 Hz), 27.55, 27.28, 21.61, 19.06. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3339, 3062, 2965, 2932, 2873, 1743, 1668, 1592, 1508, 1473, 1454, 1379, 1218, 1127, 1049, 995, 864, 787, 749, 700. ^{19}F NMR (470 MHz, $CDCl_3$) δ -176.9 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{20}H_{26}FN_2O$ $(M+H)^+$: 329.2029, found: 329.2043.

2-(Fluoro(phenyl)methyl)-3-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)butanamide (3.4i). White solid, 68.3 mg, 71% yield, with 0.75 equivalents of $Fe(OAc)_2$ and 400 µL of MeCN. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54-8.50 (m, 1H), 7.84 (br s, 1H), 7.72-7.66 (m, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.19-7.15 (m, 1H), 4.81-4.66 (m, 1H), 2.14-2.03 (m, 1H), 1.96-1.90 (m, 1H), 1.82-1.60 (m, 13H), 1.36-0.97 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.78, 164.68, 147.73, 136.85, 121.70, 119.48, 93.49 (d, J = 170.9 Hz), 58.89 (d, J = 19.0 Hz), 56.63, 37.03 (d, J = 4.8 Hz), 31.10, 30.57, 27.63, 27.32, 26.40, 26.26 (2C), 26.08, 25.91, 9.98 (d, J = 5.5 Hz). IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3309, 2964, 2926, 2852, 1645, 1592, 1537, 1477, 1429, 1274, 1127, 956, 787, 749, 622. ^{19}F NMR (470 MHz, $CDCl_3$) δ -190.5 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{19}H_{30}FN_2O$ $(M+H)^+$: 321.2342, found: 321.2340.

2-Cyclohexyl-3-fluoro-3-phenyl-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (3.4j). White solid, 66.3 mg, 60% yield, with no $Fe(OAc)_2$ and 400 µL of MeCN. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53-8.50 (m, 1H), 7.82 (br s, 1H), 7.68-7.64 (m, 1H), 7.41-7.28 (m, 6H), 7.18-7.15 (m, 1H), 5.86 (dd, J = 46.0, 7.5 Hz, 1H), 2.54 (dt, J = 20.0, 7.0 Hz, 1H), 1.80-1.43 (m, 12H), 1.30-1.00 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.84, 164.56, 147.56, 138.28 (d, J = 19.9 Hz), 136.92, 128.47 (d, J = 1.5 Hz), 128.41, 126.33 (d, J = 6.8 Hz), 121.69, 119.47, 93.28 (d, J = 171.5 Hz), 60.00 (d, J = 21.9 Hz), 56.75, 37.22 (d, J = 5.8 Hz), 31.85, 29.65, 27.54, 27.32, 26.43, 26.29. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3337, 3062, 2928, 2852, 1740, 1688, 1654, 1592, 1508, 1473, 1450, 1431, 1378, 1216, 1126, 1066, 994, 968, 786, 747, 699. ^{19}F NMR (470 MHz, $CDCl_3$) δ -178.2 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{23}H_{30}FN_2O$ $(M+H)^+$: 369.2342, found: 369.2335.

3-Fluoro-2-phenyl-*N*-(2-(pyridin-2-yl)propan-2-yl)butanamide (3.4k + 3.4k'), 66.7 mg, 74% yield (d.r. = 5:1), with 0.5 equivalents of $Fe(OAc)_2$ and 400 µL of MeCN. Compound **3.4k**: white solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.49-8.46 (m, 1H), 7.92 (br s, 1H), 7.69-7.64 (m, 1H), 7.43-7.39 (m, 2H), 7.35-7.27 (m, 4H), 7.18-7.14 (m, 1H), 5.40-5.24 (m, 1H), 3.56 (dd, *J* = 11.0, 9.0 Hz, 1H), 1.77 (s, 3H), 1.66 (s, 3H), 1.21 (dd, *J* = 24.0, 6.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.72, 164.33, 147.53, 137.01, 136.20 (d, *J* = 10.0 Hz), 128.74, 128.46, 127.65, 121.77, 119.37, 91.34 (d, *J* = 169.3 Hz), 60.57 (d, *J* = 22.5 Hz), 56.77, 27.55, 27.31, 18.87 (d, *J* = 22.0 Hz). IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3326, 3061, 2862, 2933, 1659, 1592, 1539, 1506, 1474, 1381, 1266, 1127, 1078, 994, 868, 786, 748, 700. ^{19}F NMR (470 MHz, $CDCl_3$) δ -171.3 (m, 1F). HRMS (ESI, *m/z*): calcd. for $C_{18}H_{22}FN_2O$ $(M+H)^+$: 301.1716, found: 301.1703.

3-Fluoro-2-(naphthalen-1-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)butanamide (3.4l). White solid, 75.7 mg,: 72% yield, with 0.75 equivalents of $Fe(OAc)_2$ and 400 µL of MeCN. ^1H NMR (400 MHz, $CDCl_3$) δ ^1H NMR (400 MHz, $CDCl_3$) δ 8.50-8.48 (m, 1H), 8.03 (s, 1H), 7.93 (s, 1H), 7.88-7.83 (m, 3H), 7.68 (td, *J* = 7.6, 1.6 Hz, 1H), 7.59 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.53-7.47 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.20-7.17 (m, 1H), 5.56-5.38 (m, 1H), 3.78 (dd, *J* = 10.8, 9.2 Hz, 1H), 1.81 (s, 3H), 1.69 (s, 3H), 1.26 (dd, *J* = 24.4, 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.81 (d, *J* = 2.0 Hz), 164.10, 147.19, 137.45, 133.65 (d, *J* = 2.0 Hz), 133.45, 132.84, 128.46, 127.95, 127.63, 127.49, 126.32, 126.21, 126.02, 121.93, 119.59 , 91.37 (d, *J* = 169.0 Hz), 60.52 (d, *J* = 23.0 Hz), 56.73, 27.45 (d, *J* = 18.0 Hz), 18.99 (d, *J* = 21.0 Hz). IR (KBr) $\bar{\upsilon}$ (cm^{-1}) 3325, 3056, 2981, 2932, 1718, 1661, 1508, 1382, 1132, 1074, 790, 750. ^{19}F NMR (376 MHz, $CDCl_3$) δ -171.0. HRMS (ESI, *m/z*): calcd. for $C_{22}H_{23}FN_2NaO$ $(M+Na)^+$: 373.1692, found: 373.1691.

Deprotection of product 3.2g. To a 35 mL oven-dried pressure tube, **3.2g** (129.3g, 0.3 mmol, 1.0 equiv) and hydrazine hydrate (30.0 mg, 0.6 mmol, 2.0 equiv) were dissolved in 2 mL of MeOH. The tube was then sealed and stirred at 65 ^{o}C for 10 h. After the reaction, the solvent was removed. The crude product was dissolved in 20 mL DCM, and undissolved solid was filtered. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel to yield the desired product **3.5**. Colorless oil, 82.3 mg, 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.50 (d, J = 4.4 Hz, 1H), 7.70 – 7. 66 (m, 1H), 7.41 – 7.30 (m, 6H), 7.17 (dd, J = 7.2, 5.2 Hz, 1H), 6.23 (dd, J = 45.2, 4.0 Hz, 1H), 4.01 (dd, J = 12.4, 4.0 Hz, 1H), 1.70 (s, 3H), 1.74 (s, 3H), 1.60 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.56 (d, J = 11.1 Hz), 164.36, 147.96, 136.84, 135.47 (d, J = 21.0 Hz), 128.50, 128.33, 126.21 (d, J = 8.4 Hz), 121.74, 119.32, 93.89 (d, J = 173.5 Hz), 60.04 (d, J = 25.9 Hz), 56.48, 27.46, 27.25. ^{19}F NMR (376 MHz, $CDCl_3$) -188.33. IR (KBr) $\bar{\upsilon}$ (cm^{-1}) 3312, 3291, 3063, 2980, 2933, 1667, 1511, 1474, 1126, 913, 747, 705, 557 cm^{-1}. HRMS (ESI, *m/z*): calcd. for $C_{17}H_{19}FN_3O$ $(M-H)^-$: 300.1518, found: 300.1531.

Cleavage of directing group. To a solution of **3.2g** (129 mg, 0.3 mmol) in acetic acid (0.5 mL) mixed with acetic anhydride (2.5 mL) in -15 ^{o}C was slowly added $NaNO_2$ (420 mg, 6.2 mmol) in portions over 1.5 hour. After stirring for 3 days at -15 ^{o}C, the reaction was poured into a mixture of ice and water. The mixture was extracted with cold ether. The organic phase was then washed with icy water for 4 times and dried with anhydrous Na_2SO_4 in an ice bath. The solvent was removed under reduce pressure at 0 ^{o}C. The residue was dissolved in THF (5 mL) mixed with H_2O (2 mL) and cooled to -15 ^{o}C. Then H_2O_2 (30% in water, 0.6 ml), followed by lithium hydroxide (144 mg, 6.0 mmol) was added to the reaction. The mixture was stirred at -15 ^{o}C for 3 hours and then at 0 ^{o}C for

another 3 hours. Finally, the mixture was treated with aqueous Na_2SO_3 (170 mg in 2 mL H_2O), followed by acidification with HCl (1M) to pH 2-3. The mixture was extracted with ether and the organic layer was then washed with brine, dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel to yield the desired product **3.6**. Yellow solid, 61.1 mg 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 7.76 – 7.67 (m, 4H), 7.34 (d, *J* = 4.8 Hz, 2H), 7.25 – 7.24 (m, 3H), 6.37 (dd, *J* = 46.6, 8.4 Hz, 1H), 5.34 (dd, *J* = 15.4, 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.38, 166.55, 134.99 (d, *J* = 19.6 Hz), 134.36, 131.15, 129.57 (d, *J* = 1.9 Hz), 128.48, 126.92 (d, *J* = 5.6 Hz), 123.70, 90.53 (d, *J* = 177.5 Hz), 54.50 (d, *J* = 35.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) -170.11. IR (KBr) $\bar{\upsilon}$ (cm^{-1}) 3005, 2989, 1778, 1717, 1471, 1391, 1275, 1260, 913, 750, 647 cm^{-1}. HRMS (ESI, *m/z*): calcd. for $C_{17}H_{111}FNO_4$ $(M-H)^-$: 312.0687, found: 312.0682.

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3.6 References

1. (a) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Okazoe, T. *Proc. Jpn. Acad., Ser. B* **2009**, 85, 276.
2. (a) Jeschke, P. *ChemBioChem* **2004**, *5*, 570. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.
3. Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev*. **2014**, *114*, 2432.
4. Phelps, M. E. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 9226.
5. (a) Kirk, K. L. *Org. Process Res. Dev*. **2008**, *12*, 305. (b) Perutz, R. N. *Science* **2008**, *321*, 1168. (c) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160.
6. (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, *16*, 2654. (f) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (g) Davis, H. M. L.; Du Bois, J.; Yu, J.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1855. (h) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. (i) White, M. C. *Science* **2012**, 335, 807.

7. (a) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc*. **2006**, *128*, 7134. (b) Wang, X.-S.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc*. **2009**, *131*, 7520. (c) Engle, K. M.; Mei, T.-S.; Wang, X.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed*. **2011**, 50, 1478. (d) Chan, K. S. L.; Wasa, M.; Wang, X.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed*. **2011**, *50*, 9081. (e) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc*. **2013**, *135*, 9342.

8. (a) Lin, A.-J.; Huehls, B.; Yang, J. *Org. Chem. Front*. **2014**, *1*, 434. (b) Ma, J. A.; Li, S. *Org. Chem. Front*. **2014**, *1*, 712. (c) Lin, X.-X.; Weng, Z.-Q. *Dalton Trans*. **2015**, *44*, 2021. (d) Brooks, A. F.; Topczewski, J. J.; Ichiishi, N.; Sanford, M. S.; Scott, P. J. *Chem. Sci.* **2014**, *5*, 4545.

9. Bloom, S; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 10580.

10. Bloom, S.; Pitts, C. R.; Woltornist, R.; Griswold, A.; Holl, M. G.; Lectka, T. *Org. Lett.* **2013**, *15*, 1722.

11. (a) Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard III, W. A.; Groves, J. T. *Science* **2012**, *337*, 1322. (b) Liu, W.; Groves, J. T. *Angew. Chem., Int. Ed.* **2013**, *52*, 6024. (c) Huang, X.; Liu, W.; Ren, H.; Neelamegam, R.; Hooker, J. M.; Groves, J. T. *J. Am. Chem. Soc*. **2014**, 136, 6842.

12. (a) Braun, M.-G.; Doyle, A. G. *J. Am. Chem. Soc*. **2013**, *135*, 12990. (b) McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4094.

13. Xu, P.; Guo, S.; Wang, L.-Y.; Tang, P.-P. *Angew. Chem., Int. Ed*. **2014**, *53*, 5955.

14. Xia, B.-B.; Ma, Y.; Chen, C. *Org. Chem. Front.* **2014**, *1*, 468.

15. (a) Zaitsev, V.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc*. **2005**, *127*, 13154. (b) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc*. **2010**, *132*, 17378. (c) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc*. **2011**, *133*, 19598. (d) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc*. **2012**, *134*, 18570. (e) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc*. **2013**, *135*, 3387. (f) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc*. **2013**, *135*, 12135. (g) Figg, T. M.; Wasa, M.; Yu, J.-Q.; Musaev, D. G. *J. Am. Chem. Soc*. **2013**, 135, 14206. (h) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed*. **2013**, *52*, 11124. (i) Fan, M.-Y.; Ma, D.-W. *Angew. Chem., Int. Ed.* **2013**, *52*, 12152. (j) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc*. **2014**, *136*, 8138. (k) He, J.; Li, S.-H.; Deng, Y.-Q.; Fu, H.-Y.; Laforteza, B. N.; Spangler, J. E.; Hom, A.; Yu, J.-Q. *Science*, **2014**, *343*, 1216. (l) Zhu, R.-Y.; He, J.; Wang, X.-C.; Yu, J.-Q. *J. Am. Chem. Soc*. **2014**, *136*, 13194. (m) Gong, W.; Zhang, G.-F.; Liu, T.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc*. **2014**, *136*,16940.

16. (a) Tsushima, T.; Kawada, K.; Tsuji, T.; Tawara, K. *J. Med. Chem.* **1985**, *28*, 253. (b) Hart, B. P.; Haile, W. H.; Licato, N. J.; Bolanowska, W. E.; McGuire, J. J.; Coward, J. K. *J. Med. Chem.* **1996**, *39*, 56. (c) de Villiers, J.; Koekemoer, L.; Strauss, E. *Chem. Eur. J*. **2010**, *16*, 10030. (d) Chia, P. W.; Livesey, M. R.; Slawin, A. M. Z.; Mourik, T. V.; Wyllie, D. J. A.; O'Hagan, D. *Chem. Eur. J*. **2012**, *18*, 8813.

17. (a) Kukhar, V. P.; Sorochinsky, A. E.; Soloshonok, V. A. *Future Med. Chem.* **2009**, *1*, 793. (b) Acena, J. L.; Simon-Fuentes, A.; Fustero, S. *Curr. Org. Chem.* **2010**, *14*, 928.
18. (a) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci*. **2013**, *4*, 4187. (b) Zhang, Q.; Chen, K.; Rao, W.-H.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588.
19. Chen, K; Zhang, S.-Q.; Jiang, H.-Z.; Xu, J.-W.; Shi, B.-F. *Chem. Eur. J.* **2015**, *21*, 3264.
20. Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177.
21. Racowski, J. M.; Gary, B. G.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3414.
22. Zhang, Q.; Chen, K.; Rao, W.-H.; Zhang, Y.-J.; Chen, F.-J.; Shi, B.-F. *Angew. Chem., Int. Ed*. **2013**, *52*, 13588.
23. Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci*. **2013**, *4*, 4187.
24. Zhang, Q.; Yin, X.-S.; Zhao, S.; Fang, S.-L.; Shi, B.-F. *Chem. Commun*., **2014**, *50*, 8353.
25. Pande, S. V.; Utale, P. S.; Gholse, S. B.; Tekade, P. V.; Patil, S. G. *Pharm. Chem. J*. **2014**, *48*, 29.
26. Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. J. *Am. Chem. Soc*. **2013**, *135*, 6030.
27. Ma, T.; Gao, Q.; Chen, Z.; Wang, L.; Liu, G. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 1079.

CHAPTER 4. SYNTHESIS OF CINNOLINES VIA COPPER-CATALYZED AEROBIC DEHYDROGENATIVE CYCLIZATION OF *N*-METHYL-*N*-PHENYLHYDRAZONES

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4.1 Introduction

Selective carbon-carbon (C−C) bond formation is one of the most important processes in organic chemistry since it enables key steps in the synthesis of complex organic molecules from simple precursors. Traditionally, the construction of C−C bonds relies primarily on prefunctionalized substrates, which usually requires additional synthetic steps, and thus reduces the overall efficiency of this transformation.[1] For this reason, C−C bond forming reactions through transition-metal-catalyzed direct functionalization of relatively unreactive C−H bonds have emerged as a major topic of research in organic chemistry.[2] Among them, copper-catalyzed aerobic dehydrogenative coupling reactions from two carbon-hydrogen (C−H) bonds have received a renewed interest in recent years with the following inherent advantages: maximizing atom economy by avoiding prefunctionalization of the coupling partners, and avoidance of toxic byproducts

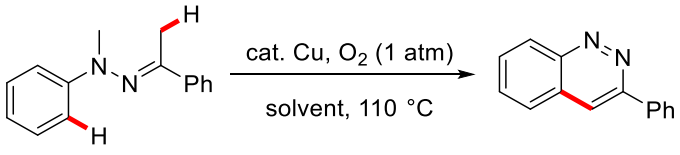
with molecular oxygen as the sole oxidant.[3] Since the discovery of the over 140 years old Glaser reaction, the oxidative dimerization of terminal alkynes,[4] many efforts have been devoted into this field to construct new C−C bonds and a number of copper-catalyzed aerobic dehydrogenative coupling reactions via an sp or sp^2 C−H bond functionalization process have been developed, including oxidative dimerization of phenols,[5] naphthols[6] and electron-deficient arenes,[7] cross-coupling of terminal alkynes with electron-deficient arenes,[8] and intramolecular dehydrogenative cyclization of anilides.[9] In comparison, the development of copper-catalyzed aerobic dehydrogenative coupling on sp^3 carbons is still in its infancy and the current advances suffer severely from the restricted substrate scope, namely only substrates with the sp^3 carbon adjacent to a heteroatom[10] or malonic amide derivatives.[11] During our investigation of transition-metal-catalyzed coupling reactions including the synthesis of pyrazolines from hydrazones,[12] *N*-methyl-*N*-phenylhydrazones were discovered as unprecedented substrates for copper-catalyzed aerobic intramolecular dehydrogenative cyclization for the formation of cinnolines, a privileged structure in medicines, and many medicinal compounds with a broad range of biological activities including antibacterial, anti-cancer, antifungal, antihypertensive, antiinflammatory, and anti-ulcer activities.[13]

4.2 Results and Discussion

Our investigation began with the oxidative cyclization of 1-methyl-1-phenyl-2-(1-phenylethylidene)hydrazine (**4.1a**) with catalytic $CuSO_4$ in the presence of 1 atm O_2. To our delight, the cyclization reaction was successful with DMF, DMA or DCE as the solvent,

albeit in low yields (Table 4.1, entries 1-3). The following extensive catalyst screening showed that although other Cu^{II} and Cu^{I} sources could catalyze the cyclization of **4.1a**, none of these catalysts improved the yield (entries 8-16). Subsequently, a series of nucleophilic bases, such as pyridine, DMAP, and DABCO, were screened. However, none of these bases improved the yield. Interestingly, the yield was increased by the addition of an acid along with excess pyridine, and the optimal results were obtained with 1 equivalent of CF_3SO_3H and 3.5 equivalent of pyridine (entry 22). It is worth mentioning that the methyl group on the nitrogen is required for this reaction since 1-phenyl-2-(1-phenylethylidene)hydrazine gave less than 10% yield of the desired product due to the decomposition of the starting material under the current reaction conditions.

Table 4.1 Optimization of Reaction Conditions for Cinnolines Synthesis[a]



4.1a **4.2a**

Entry	Cu Source	Additive	Solvents	Yield (%)[b]
1	$CuSO_4$ (20)	-	DMF	37
2	$CuSO_4$ (20)	-	DMA	32
3	$CuSO_4$ (20)	-	CH_3CN	30
4	$CuSO_4$ (20)	-	DMSO	<5
5	$CuSO_4$ (20)	-	NMP	trace
6	$CuSO_4$ (20)	-	DMF	trace
7	-	-	DMF	0
8	$Cu(OAc)_2$ (20)	-	DMF	22
9	$CuBr_2$ (20)	-	DMF	20

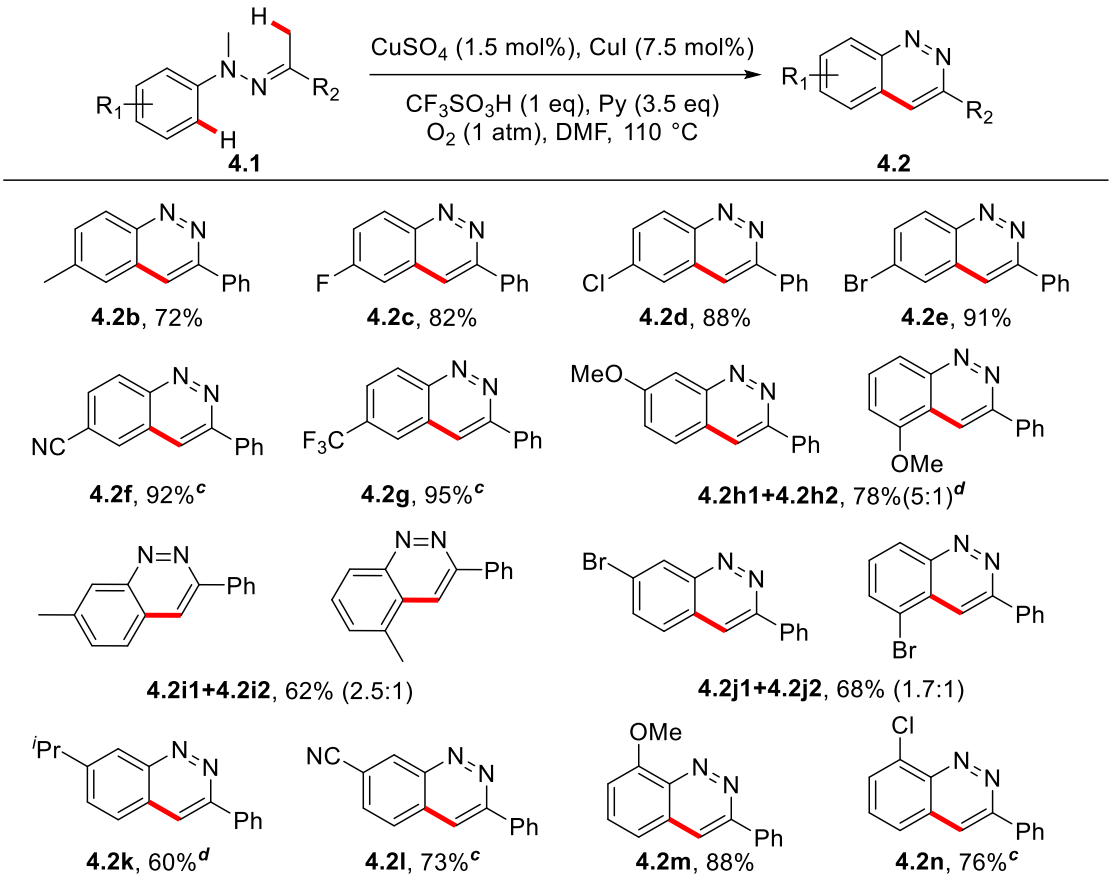
Table 4.1 continued.

10	$CuCl_2$ (20)	-	DMF	19
11	CuF_2 (20)	-	DMF	17
12	$Cu(OH)_2CO_3$ (20)	-	DMF	16
13	CuI (20)	-	DMF	15
14	CuBr·DMS (20)	-	DMF	12
15	$CuSO_4$ (20)	-	DMF	25
16	$CuSO_4$ (20)	-	DMF	22
17	$CuSO_4$ (20)	Py (3.5)/CF_3SO_3H (1)	DMF	73
18	$CuSO_4$ (20)	Py (3.5)/TsOH (1)	DMF	55
19	$CuSO_4$ (10)/ CuI (10)	Py (3.5)/CF_3CO_2H (1)	DMF	47
20	$CuSO_4$ (10)/ CuI (10)	Py (3.5)/AcOH (1)	DMF	43
21	$CuSO_4$ (10)/ CuI (10)	Py (3.5)/$PhCO_2H$ (1)	DMF	42
22	**$CuSO_4$ (1.5)/ CuI (7.5)**	**Py (3.5)/CF_3CO_2H (1)**	**DMF**	**83(80)[b]**
23	$CuSO_4$ (1.5)/ CuI (5)	Py (3.5)/CF_3CO_2H (1)	DMF	70
24	$CuSO_4$ (1.5)/ CuI (7.5)	Py (3.5)/CF_3CO_2H (1)	DMF	20

[a] Conditions: **4.1a** (0.3 mmol), Cu source, additive, O_2 (1 atm), 3 mL of solvent, 110 °C, 14 h unless otherwise noted. [b] Isolated yields. [c] Under air.

As shown in Scheme 4.1, this transformation is compatible with electron-rich and electron-deficient *N*-phenyl ring (Scheme 4.1, **4.2b**-**o**). There is no apparent electronic or steric effect on this ring, and good to high yields of products were obtained with either an electron-donating or electron-withdrawing group substituted substrate on the *p*-, *m*-, or *o*-position. It was noted that the *m*-OMe, Me, or Br substituted substrates gave a mixture of *p*- and *o*-products (**4.2h**-**j**), favoring the *p*-products while the more hindered ^{i}Pr group and the electron-withdrawing CN group substituted substrates provided only the single *p*-

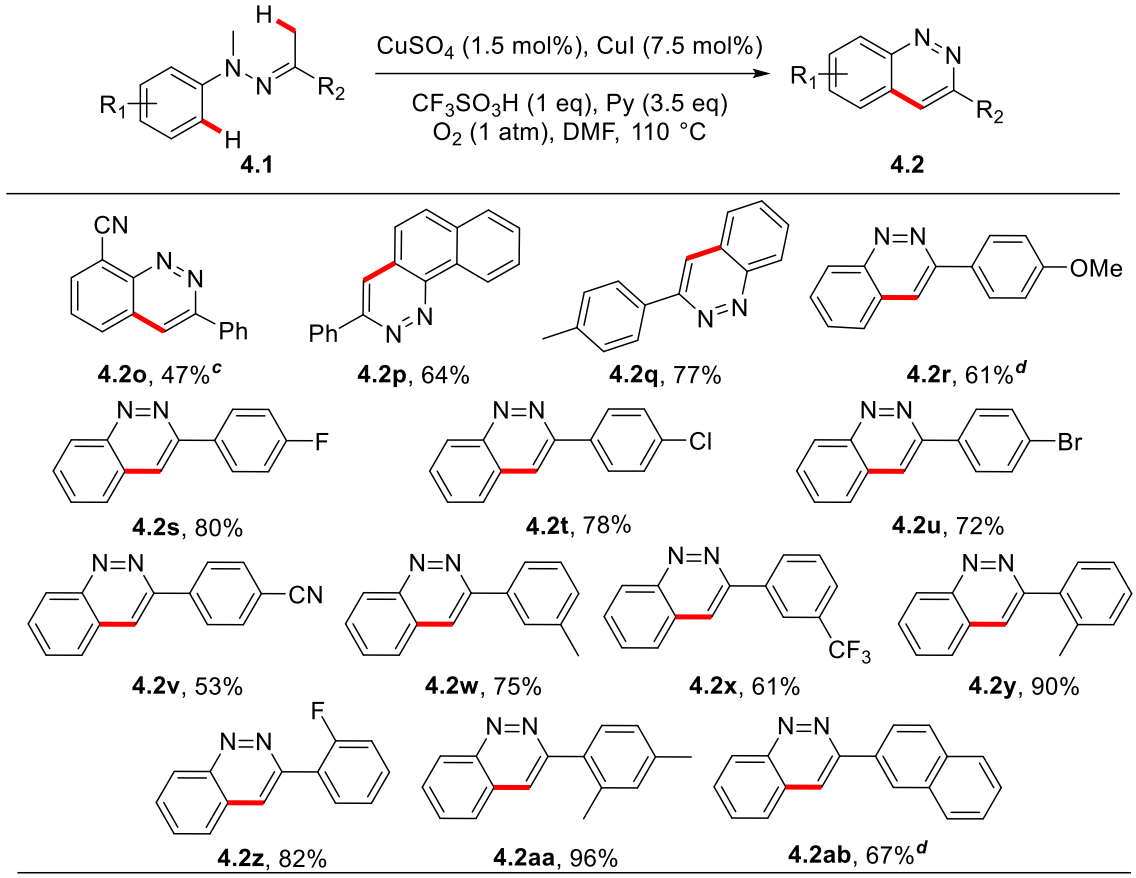
products (**4.2k** and **4.2l**). As expected, halogens (F, Cl, and Br) were tolerated under the current reaction system, allowing for the further manipulation of the initial products.



Scheme 4.1 Scope of *N*-Methyl-*N*-phenylhydrazones (1)[a,b]. [a] Conditions: **4.1** (0.3 mmol), $CuSO_4$ (1.5 mol%), CuI (7.5 mol%), Py (3.5 eq), CF_3SO_3H (1.0 eq), O_2 (1 atm), 3 mL of DMF, 110 °C, 14 h unless otherwise noted. [b] Isolated yields. [c] The reaction was run at 150 °C for 20 h. [d] The reaction was run at 95 °C for 48 h.

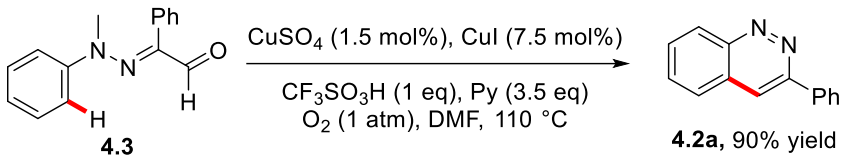
In contrast, there is an electronic effect on the other phenyl ring (Scheme 4.2, **4.2q-z**). Generally, strong electron-donating groups on this ring provide higher yields than strong electron-withdrawing groups. It should be mentioned that replacement of this phenyl group with an alkyl group gave only trace amount of product, due to the decomposition of the starting material under the oxidative conditions. It was also observed that this reaction

was completely prohibited with the introduction of an alkyl group on the α-carbon to the imine moiety (**4.2ac**).



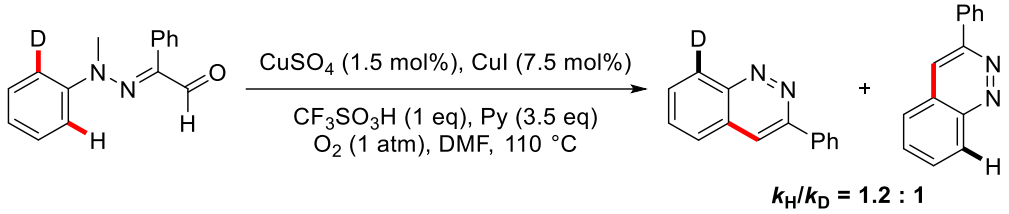
Scheme 4.2 Scope of *N*-Methyl-*N*-phenylhydrazones (2)[a,b]. [a] Conditions: **1** (0.3 mmol), $CuSO_4$ (1.5 mol%), CuI (7.5 mol%), Py (3.5 eq), CF_3SO_3H (1.0 eq), O_2 (1 atm), 3 mL of DMF, 110 °C, 14 h unless otherwise noted. [b] Isolated yields. [c] The reaction was run at 150 °C for 20 h. [d] The reaction was run at 95 °C for 48h.

It is noteworthy that a small amount of 2-(*N*-methyl-*N*-phenylhydrazono)-2-phenylacetaldehyde (**4.3**) was isolated along with the desired product **4.2a** from the reaction of 1-methyl-1-phenyl-2-(1-phenylethylidene)hydrazine (**4.1a**) under the current reaction conditions. Furthermore, treatment of **4.3** under the cyclization reaction conditions provided **4.1a** in 90% yield (Scheme 4.3).



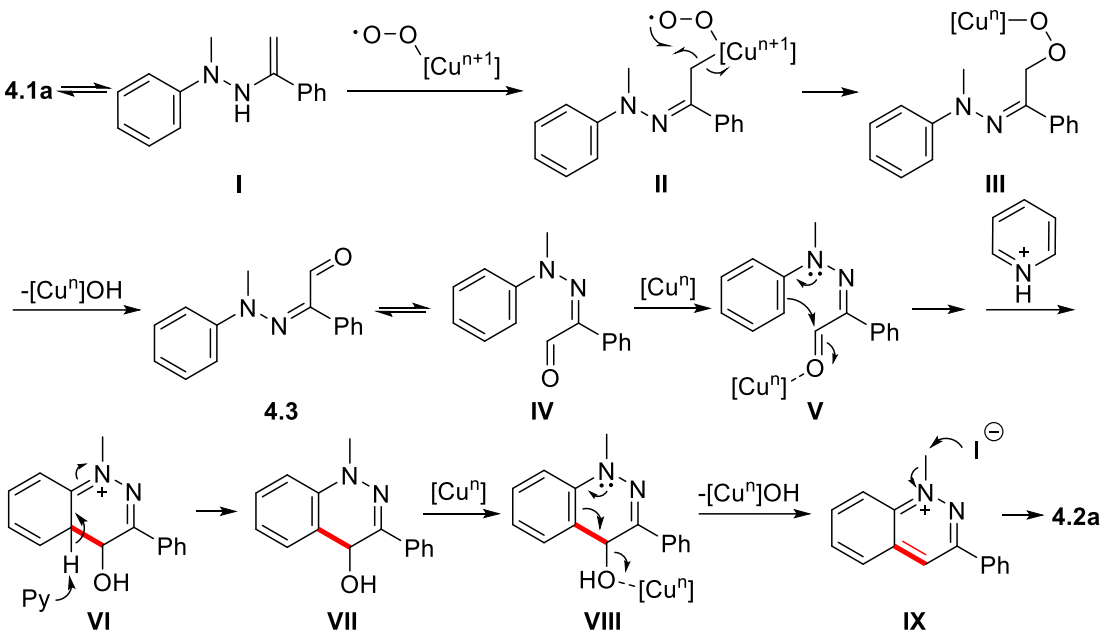
Scheme 4.3. Cyclization of 2-(*N*-Methyl-*N*-phenylhydrazono)-2-phenylacetaldehyde

To further probe the reaction mechanism, deuterium-labeling experiments were conducted (Scheme 4.4). No significant kinetic isotope effect was observed in the reaction of [D1]-1a, thus suggesting that the arene C(sp^2)-H bond cleavage might not be involved in the rate-determining step.[14]



Scheme 4.4. Deuterium-Labeling Experiments

Based on the above observation, the cyclization reaction mechanism of *N*-methyl-*N*-phenyl-2-(1-phenylethylidene)hydrazine (**4.1a**) is proposed (Scheme 4.5). It is believed that this transformation starts with the oxidation of **4.1a** into 2-(*N*-Methyl-*N*-phenylhydrazono)-2-phenylacetaldehyde (**4.3**) through a copper-catalyzed process in the presence of oxygen.[15] Copper-assisted Freidel-Crafts-type cyclization of **4.3** generates the intermediate **VII**. Activation of **VII** by a copper species, followed by the loss of the hydroxyl group and subsequent methyl group by nucleophilic substitution of iodine provides the desired product **4.2a**.



Scheme 4.5 Proposed Mechanism for Cinnoline Synthesis.

4.3 Summary

In summary, an efficient Cu-catalyzed aerobic dehydrogenative intramolecular cyclization reaction of *N*-methyl-*N*-phenylhydrazones has been developed via a sequential sp^3 C−H oxidation, cyclization, and aromatization process. This transformation is the first example of copper-catalyzed coupling reactions of hydrazones via a sp^3 C−H bond functionalization pathway. This novel method provides an efficient access to cinnoline derivatives.

4.4 Experimental

General Methods. All the solvents and commercially available reagents were purchased from commercial sources and used directly. For TLC analysis, precoated plates

(w/h F254, Dynamic Adsorbents Inc, 0.25 mm thick) were used; for air-flashed column chromatography, Flash Silica Gel (Dynamic Adsorbents Inc, 32-63 μm) was used. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker 500 MHz NMR Fourier transform spectrometer. ^{1}H NMR data was reported as: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR data was reported in terms of chemical shift (δ ppm), multiplicity, and coupling constant (Hz). The infrared spectra were obtained using a Thermo Nicolet IR 330 Spectrometer. Mass (MS) analysis was obtained using Agilent 1100 series LC/MSD system with Electrospray Ionization (ESI).

General procedure for the preparation of *N*-methyl-*N*-phenylhydrazones 4.1a-4.1e, 4.1g-4.1k, 4.1m-4.1n, and 4.1p-4.1ab[16,17]:

A 250 mL three-necked flask was charged with 50 mL anhydrous ethanol, ketone (20 mmol), acyl hydrazine (25 mmol) and acetic acid (114.4 μL, 2 mmol). The reaction mixture was then refluxed for 2-4 h (monitored by TLC). After removal of ethanol, the residue was dissolved in ethyl acetate (100 mL), washed with a mixture of acetic acid (100 mL) and water (100 mL), and the organic phase was dried over Na_2SO_4 and concentrated under vacuum. The hydrazone, which was usually obtained in nearly quantitative yield, was used directly for the next step without further purification.

To a solution of hydrazone (5 mmol) in dry THF (20 mL) was added NaH (95%, 1.2 g, 47.5 mmol) at 0 °C. The mixture was stirred for 15 min, and then methyl iodide (7.5 mmol) was added dropwise. After stirring at room temperature for 3 h, the reaction mixture was refluxed for another 2 h. The reaction mixture was cooled to the room temperature, and then the solvent was removed under reduced pressure. The residue was diluted with water (15 mL), extracted with ether (25 mL x 3), and dried over Na_2SO_4. After removal of

the solvent, the residue was purified by flash chromatography column on silica gel (gradient eluent of EtOAc in hexanes: 1 ~ 5%, v/v) to yield the product **1** as a yellow oil.

1-Methyl-2-(1-phenylethylidene)-1-(p-tolyl)hydrazine (4.1b). Yellow oil, yield: 85% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$, a mixture of (Z/E) isomers in ratio ca. 4.3:1, the minor isomer is marked with an *) δ: 2.28 (s, 3H), 2.31 (s, 3H), 3.15 (s, 3H), 6.88 (d, *J* = 5.0 Hz, 2H), 7.08 (d, *J* = 5.0 Hz, 2H), 7.40-7.41 (m, 3H), 7.88-7.91 (m, 2H); 1.75* (s, 3H), 2.41* (s, 3H), 3.40* (s, 3H), 7.23-7.38* (m, 5H), 7.54* (d, *J* = 5.0 Hz, 2H), 7.72* (d, *J* = 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.4, 20.5, 43.5, 116.1, 122.6, 126.6, 128.3, 129.4, 129.6, 138.4, 149.4, 164.6; 21.4*, 24.5*, 51.8*, 116.1*, 126.7*, 127.8*, 128.3*, 129.6*, 141.3*, 141.5*, 149.8*, 164.6*; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3050, 2953, 1510, 1493, 1457, 1376, 1363, 1309, 1095, 1070, 819, 760; MS (ESI): m/z = 239.3 [M + H^+].

1-(4-Fluorophenyl)-1-methyl-2-(1-phenylethylidene)hydrazine (4.1c). Yellow oil, yield: 91% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 3.10 (s, 3H), 6.91-6.99 (m, 4H), 7.40-7.41 (m, 3H), 7.87-7.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.4, 43.4, 115.3 (d, J_{CF} = 21.2 Hz), 117.1 (d, J_{CF} = 7.5 Hz), 126.6 (d, J_{CF} = 10.0 Hz), 128.3, 129.8, 138.2, 148.1, 157.5 (d, J_{CF} = 236.2 Hz), 165.1; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3054, 2963, 2874, 1608, 1505, 1445, 1364, 1223, 1101, 827; MS (ESI): m/z = 243.3 [M + H^+].

1-(4-Chlorophenyl)-1-methyl-2-(1-phenylethylidene)hydrazine (4.1d). Yellow oil, yield: 83% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 3.14 (s, 3H), 6.89 (d, *J* = 10.0 Hz, 2H), 7.22 (d, *J* = 10.0 Hz, 2H), 7.42-7.43 (m, 3H), 7.89-7.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.5, 42.5, 116.5, 124.8, 126.6, 128.4, 128.6, 130.0, 138.0, 149.9, 165.9; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3059, 2963, 2875, 1593, 1490, 1445, 1315, 1098, 1069, 822; MS (ESI): m/z = 260.3 [M + H^+].

1-(4-Bromophenyl)-1-methyl-2-(1-phenylethylidene)hydrazine (4.1e). Yellow oil, yield: 76% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 3.04 (s, 3H), 6.74-6.75 (m, 2H), 7.26-7.28 (m, 2H), 7.32-7.35 (m, 3H), 7.80-7.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.5, 41.3, 111.2, 115.8, 125.6, 127.4, 129.0, 130.5, 136.9, 149.2, 165.0; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3058, 2962, 2874, 1588, 1487, 1315, 1097, 1074, 819; MS (ESI): m/z = 305.3 [$M + H^+$].

1-Methyl-2-(1-phenylethylidene)-1-(4-(trifluoromethyl)phenyl)hydrazine (4.1g). Yellow oil, yield: 95% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.38 (s, 3H), 3.20 (s, 3H), 6.96 (d, J = 10.0 Hz, 2H), 7.42-7.46 (m, 3H), 7.50 (d, J = 10.0 Hz, 2H), 7.92-7.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.6, 41.6, 116.5, 120.9 (q, J_{CF} = 32.5 Hz), 125.0 (q, J_{CF} = 268.7 Hz), 126.1 (q, J_{CF} = 3.7 Hz), 126.8, 128.5, 130.3, 137.7, 153.1, 167.3; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3058, 2965, 2881, 1613, 1577, 1519, 1325, 1160, 1111, 1068, 830, 761; MS (ESI): m/z = 293.3 [$M + H^+$].

1-(3-Methoxyphenyl)-1-methyl-2-(1-phenylethylidene)hydrazine (4.1h). Yellow oil, yield: 79% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 3.16 (s, 3H), 3.79 (s, 3H), 6.46-6.48 (m, 1H), 6.54-6.59 (m, 2H), 7.17-7.20 (m, 1H), 7.41-7.43 (m, 3H), 7.90-7.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.9, 42.6, 55.1, 101.8, 106.0, 108.1, 126.6, 128.3, 129.5, 129.8, 138.2, 152.6, 160.3, 165.6; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3059, 2997, 2958, 2833, 1599, 1490, 1465, 1445, 1363, 1315, 1288, 1220, 1048, 994; MS (ESI): m/z = 255.3 [$M + H^+$].

1-Methyl-2-(1-phenylethylidene)-1-(m-tolyl)hydrazine (4.1i). Yellow oil, yield: 86% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 2.34 (s, 3H), 3.16 (s, 3H), 6.72-6.78 (m, 3H), 7.15-7.18 (m, 1H), 7.42-7.43 (m, 3H), 7.91-7.92 (m, 2H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ: 16.4, 21.8, 42.8, 112.6, 116.3, 120.9, 126.6, 128.3, 128.6, 129.7, 138.3, 138.5, 151.3, 165.3; IR (neat) ῡ (cm^{-1}) 3039, 2961, 2869, 1602, 1583, 1489, 1444, 1315, 1101, 995; MS (ESI): m/z = 239.3 [M + H^+].

1-(3-Bromophenyl)-1-methyl-2-(1-phenylethylidene)hydrazine (4.1j). Yellow oil, yield: 85% (from ketone). ^1H NMR (500 MHz, $CDCl_3$) δ: 2.37 (s, 3H), 3.14 (s, 3H), 6.85-6.87 (m, 1H), 6.99-7.00 (m, 1H), 7.09-7.14 (m, 2H), 7.43-7.46 (m, 3H), 7.90-7.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.5, 42.1, 113.5, 117.9, 122.5, 122.9, 126.7, 128.4, 130.0, 130.1, 137.9, 152.3, 166.7; IR (neat) ῡ (cm^{-1}) 3061, 2965, 2874, 1588, 1558, 1477, 1444, 1321, 1100, 986; MS (ESI): m/z = 305.4 [M + H^+].

1-(3-Isopropylphenyl)-1-methyl-2-(1-phenylethylidene)hydrazine (4.1k). Yellow oil, yield: 72% (from ketone). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.25 (d, *J* = 10.0 Hz, 6 H), 2.34 (s, 3H), 2.83-2.90 (m, 1H), 3.17 (s, 3 H), 6.79-6.84 (m, 3H), 7.19-7.22 (m, 1H), 7.41-7.43 (m, 3H), 7.90-7.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.6, 24.1, 34.5, 42.9, 113.3, 114.0, 118.3, 126.7, 128.4, 128.8, 129.8, 138.4, 149.7, 151.4, 165.1; IR (neat) ῡ (cm^{-1}) 3056, 2959, 2924, 2868, 1601, 1581, 1484, 1458, 1381, 1362, 1310, 1099, 1026, 938, 774; MS (ESI): m/z = 267.3 [M + H^+].

1-(2-Methoxyphenyl)-1-methyl-2-(1-phenylethylidene)hydrazine (4.1m). Yellow oil, yield: 77% (from ketone). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.98 (s, 3H), 3.24 (s, 3H), 3.94 (s, 3 H), 6.83-6.87 (m, 1H), 6.93-6.95 (m, 1H), 7.03-7.10 (m, 2H), 7.36-7.40 (m, 3H), 7.77-7.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.0, 47.0, 55.6, 111.7, 121.1, 121.4, 124.4, 126.3, 128.3, 129.0, 139.2, 142.5, 151.9, 160.0; IR (neat) ῡ (cm^{-1}) 3059, 2960, 2866, 1589, 1493, 1455, 1363, 1281, 1123, 1103, 1026, 917; MS (ESI): m/z = 255.3 [M + H^+].

1-(2-Chlorophenyl)-1-methyl-2-(1-phenylethylidene)hydrazine (4.1n). Yellow oil, yield: 88% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.04 (s, 3H), 3.20 (s, 3H), 7.00-7.03 (m, 1H), 7.15-7.18 (m, 1H), 7.24- 7.29 (m, 1H), 7.36-7.41 (m, 4H), 7.77-7.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.9, 46.8, 123.2, 125.0, 126.5, 127.8, 128.4, 128.5, 129.4, 130.6, 138.8, 150.9, 161.8; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3061, 2964, 2862, 1585, 1473, 1443, 1273, 1050, 915, 757; MS (ESI): m/z = 260.5 [M + H^+].

1-Methyl-1-(naphthalen-1-yl)-2-(1-phenylethylidene)hydrazine (4.1p). Yellow oil, yield: 65% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.97 (s, 3H), 3.34 (s, 3H), 7.28-7.30 (m, 1H), 7.33-7.41 (m, 4H), 7.49- 7.56 (m, 2H), 7.59 (d, *J* = 10.0 Hz, 1H), 7.80-7.86 (m, 3H), 8.36 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.0, 48.8, 117.7, 123.4, 124.4, 125.8, 125.9, 126.0, 126.4, 128.3 (2C), 128.6, 129.1, 134.8, 139.1, 151.0, 160.4; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3055, 2960, 2878, 1592, 1573, 1493, 1461, 1445, 1388, 1332, 1299, 1021, 1013, 913, 791; MS (ESI): m/z = 275.4 [M + H^+].

1-Methyl-1-phenyl-2-(1-(p-tolyl)ethylidene)hydrazine (4.1q). Yellow oil, yield: 86% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 3.14 (s, 3H), 3.86 (s, 3H), 6.87-6.90 (m, 1H), 6.93-6.95 (m, 4H), 7.25-7.28 (m, 2H), 7.89 (d, *J* = 10.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.1, 42.6, 55.4, 113.7, 115.2, 119.7, 128.2, 128.8, 130.8, 151.4, 161.1, 165.7; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3057, 3001, 2960, 2836, 1597, 1511, 1492, 1311, 1253, 1176, 1029, 834; MS (ESI): m/z = 255.4 [M + H^+].

2-(1-(4-Methoxyphenyl)ethylidene)-1-methyl-1-phenylhydrazine (4.1r). Yellow oil, yield: 82% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 2.40 (s, 3H), 3.15 (s, 3H), 6.87-6.96 (m, 3H), 7.22 (d, *J* = 5.0 Hz, 2H), 7.26-7.29 (m, 2H), 7.81 (d, J = 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.4, 21.4, 42.6, 115.4, 119.9, 126.7,

128.9, 129.1, 135.5, 140.0, 151.4, 165.8; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3058, 2921, 1683, 1591, 1492, 1314, 1096, 817; MS (ESI): m/z = 239.4 [M + H^+].

2-(1-(4-Fluorophenyl)ethylidene)-1-methyl-1-phenylhydrazine (4.1s). Yellow oil, yield: 95% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 3.15 (s, 3H), 6.89-6.96 (m, 3H), 7.07-7.11 (m, 2H), 7.24-7.29 (m, 2H), 7.89-7.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.4, 42.7, 115.2 (d, J_{CF} = 21.2 Hz), 115.5, 120.1, 128.5 (d, J_{CF} = 8.7 Hz), 128.8, 134.4 (d, J_{CF} = 3.7 Hz), 151.2, 163.9 (d, J_{CF} = 248.7 Hz), 164.3; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3061, 2962, 2873, 1598, 1540, 1508, 1405, 1313, 1158, 837; MS (ESI): m/z = 243.4 [M + H^+].

2-(1-(4-Chlorophenyl)ethylidene)-1-methyl-1-phenylhydrazine (4.1t). Yellow oil, yield: 92% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 3.16 (s, 3H), 6.89-6.96 (m, 3H), 7.28-7.29 (m, 2H), 7.37 (d, *J* = 10.0 Hz, 2H), 7.84 (d, *J* = 10.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.4, 42.9, 115.6, 120.2, 127.9, 128.5, 128.8, 135.8, 136.7, 151.2, 163.7; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3059, 2918, 2873, 1598, 1579, 1465, 1398, 1278, 1179, 1091, 1028, 995; MS (ESI): m/z = 260.3 [M + H^+].

2-(1-(4-Bromophenyl)ethylidene)-1-methyl-1-phenylhydrazine (4.1u). Yellow oil, yield: 86% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 3.16 (s, 3H), 6.89-6.96 (m, 3H), 7.28-7.29 (m, 2H), 7.52 (d, *J* = 5.0 Hz, 2H), 7.77 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.4, 42.9, 115.6, 120.3, 124.1, 128.1, 128.8, 131.4, 137.1, 151.2, 163.5; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3058, 3024, 2873, 1598, 1492, 1393, 1315, 1278, 1077, 1008; MS (ESI): m/z = 304.1 [M + H^+].

4-(1-(2-Methyl-2-phenylhydrazono)ethyl)benzonitrile (4.1v). Yellow oil, yield: 93% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.23 (s, 3 H), 3.16 (s, 3H), 6.89-6.93

(m, 3H), 7.17-7.24 (m, 2H), 7.61 (d, *J* = 10.0 Hz, 2H), 7.92 (d, *J* = 10.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.8, 42.7, 111.7, 115.1, 117.7, 119.9, 125.9, 127.9, 131.0, 141.5, 150.0, 159.4; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3060, 2963, 2806, 1599, 1578, 1529, 1492, 1275, 1179, 1028, 913; MS (ESI): m/z = 250.4 [$M + H^+$].

1-Methyl-1-phenyl-2-(1-(m-tolyl)ethylidene)hydrazine (4.1w). Yellow oil, yield: 86% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 2.41 (s, 3H), 3.16 (s, 3H), 6.89-6.97 (m, 3H), 7.23-7.32 (m, 4H), 7.67 (d, *J* = 10.0 Hz, 1H), 7.76 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.6, 21.4, 42.6, 115.4, 120.0, 123.9, 127.2, 128.2, 128.8, 130.6, 138.0, 138.2, 151.2, 166.1; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3058, 2958, 2923, 1598, 1491, 1362, 1315, 1096, 1071, 1028, 994, 752; MS (ESI): m/z = 239.4 [$M + H^+$].

1-Methyl-1-phenyl-2-(1-(3-(trifluoromethyl)phenyl)ethylidene)hydrazine (4.1x). Yellow oil, yield: 93% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.35 (s, 3H), 3.21 (s, 3H), 6.92-7.00 (m, 3H), 7.28-7.32 (m, 2H), 7.51-7.57 (m, 1H), 7.67 (d, *J* = 5.0 Hz, 1H), 8.10 (d, *J* = 5.0 Hz, 1H), 8.15 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.6, 43.3, 115.9, 120.6, 122.7, 123.3 (q, J_{CF} = 3.7 Hz), 124.1 (q, J_{CF} = 270.0 Hz), 126.2 (q, J_{CF} = 3.7 Hz), 128.8, 128.9, 129.7, 139.1, 151.2, 162.6; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3064, 2965, 2877, 1599, 1492, 1336, 1308, 1265, 1167, 1071, 803; MS (ESI): m/z = 293.4 [$M + H^+$].

1-Methyl-1-phenyl-2-(1-(o-tolyl)ethylidene)hydrazine (4.1y). Yellow oil, yield: 80% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$, a mixture of (Z/E) isomers in ratio ca. 5:3, the minor one is marked with an *) δ: 2.27 (s, 3H), 2.43 (s, 3H), 3.18 (s, 3H), 6.70-6.84 (m, 3H), 7.11-7.34 (m, 6H); 2.17* (s, 3H), 2.37* (s, 3H), 2.74* (s, 3H), 6.70-6.84* (m, 3H), 7.11-7.34* (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.3, 20.5, 43.0, 115.9, 120.3, 125.9, 127.7, 128.5, 128.9, 130.9, 135.1, 139.8, 151.4, 169.9; 19.8*, 25.8*, 40.8*, 114.6*, 119.5*,

125.7*, 126.6*, 128.1*, 128.7*, 130.3*, 134.3*, 139.4*, 150.9*, 162.3*; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3059, 2960, 2870, 1597, 1493, 1453, 1312, 1094, 752; MS (ESI): m/z = 239.4 [$M + H^+$].

2-(1-(2-Fluorophenyl)ethylidene)-1-methyl-1-phenylhydrazine (4.1z). Yellow oil, yield: 89% (from ketone). ^1H NMR (500 MHz, $CDCl_3$) δ: 2.34 (d, J = 5.0 Hz, 3H), 3.19 (s, 3H), 6.91-6.95 (m, 1H), 6.99-7.00 (m, 2H), 7.09-7.13 (m, 1H), 7.17-7.20 (m, 1H), 7.28-7.31 (m, 2H), 7.34-7.39 (m, 1H), 7.75-7.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.7 (d, J_{CF} = 5.0 Hz), 42.8, 115.8, 116.1 (d, J_{CF} = 22.5 Hz), 120, 124.2 (d, J_{CF} = 3.7 Hz), 127.4 (d, J_{CF} = 12.5 Hz), 128.8, 129.6 (d, J_{CF} = 2.5 Hz), 130.8 (d, J_{CF} = 8.7 Hz), 151.1, 160.7 (d, J_{CF} = 247.5 Hz), 163.9; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3061, 2966, 2873, 1598, 1581, 1490, 1450, 1317, 1287, 1095, 1029, 995, 826; MS (ESI): m/z = 243.3 [$M + H^+$].

2-(1-(2,4-Dimethylphenyl)ethylidene)-1-methyl-1-phenylhydrazine (4.1aa). Yellow oil, yield: 81% (from ketone). ^1H NMR (500 MHz, $CDCl_3$, a mixture of (Z/E) isomers in ratio ca. 2:1, the minor one is marked with an *) δ: 2.25 (s, 3H), 2.32 (s, 3H), 2.42 (s, 3H), 3.15 (s, 3H), 6.87-6.90 (m, 1H), 6.97-7.04 (m, 5H), 7.22-7.28 (m, 2H); 2.12* (s, 3H), 2.30* (s, 3H), 2.34* (s, 3H), 2.73* (s, 3H), 6.70-6.84* (m, 3H), 6.97-7.04* (m, 2H), 7.22-7.28* (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.3, 20.6, 21.2, 42.9, 115.8, 120.2, 126.5, 127.8, 128.9, 131.7, 135.1, 136.9, 138.3, 151.4, 170.0; 19.8*, 20.6*, 25.9*, 40.6*, 114.4*, 119.4*, 126.4*, 126.5*, 128.7*, 131.1*, 134.2*, 136.5*, 137.8*, 150.9*, 162.7*; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3058, 2960, 2869, 1597, 1494, 1451, 1312, 1287, 1094, 1029, 877; MS (ESI): m/z = 253.4 [$M + H^+$].

1-Methyl-2-(1-(naphthalen-2-yl)ethylidene)-1-phenylhydrazine (4.1ab). Yellow solid, yield: 80% (from ketone). ^1H NMR (500 MHz, $CDCl_3$) δ: 2.47 (s, 3H), 3.23 (s, 3H), 6.90-7.03 (m, 3H), 7.28-7.32 (m, 2H), 7.49- 7.53 (m, 2H), 7.85-7.90 (m, 3H), 8.22-

8.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.5, 42.9, 115.6, 120.1, 123.9, 126.3, 126.7, 126.8, 127.7, 127.9, 128.7, 128.9, 133.1, 134.1, 135.7, 151.4, 164.9; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3057, 2962, 2872, 1598, 1491, 1368, 1313, 1234, 1154, 1094, 1066, 859; MS (ESI): m/z = 275.4 [M + H^+].

General procedure for the preparation of *N*-methyl-*N*-phenylhydrazones 4.1f, 4.1l, and 4.1o[18]

A 50-mL Schlenk tube was charged with tris(dibenzylideneacetone)dipalladium(0) (4.6 mg, 0.005 mmol), 1,1′-ferrocenediyl-bis(diphenylphosphine) (5.5 mg, 0.01 mmol), and $Zn(CN)_2$ (42.3 mg, 0.36 mmol). Then *N*-bromophenyl-*N*-methylhydrazone (91.0 mg, 0.3 mmol) in DMF (3 mL) was added, and the vial was evacuated and filled with argon. After stirring at 120-150 ˚C for 20 h, the reaction mixture was cooled to room temperature, diluted with EtOAc (15 mL) and filtered through a pad of Celite. The filtrate was washed with water (20 mL x 3) to remove the DMF. The organic phase was dried over Na_2SO_4, concentrated, and the residue was purified by flash chromatography on silica (gradient eluent of EtOAc in hexanes: 4 ~ 5%, v/v) to yield the desired product as a yellow oil.

4-(1-Methyl-2-(1-phenylethylidene)hydrazinyl)benzonitrile (4.1f). Yellow oil, yield: 72% (from **4.1e**). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.37 (s, 3H), 3.20 (s, 3H), 6.88-6.91 (m, 2H), 7.41-7.90 (m, 5H), 7.91-7.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.7, 41.0, 100.7, 113.7, 120.2, 126.7, 128.5, 130.5, 133.0, 137.2, 152.9, 168.1; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3057, 2920, 2881, 2215, 1603, 1572, 1509, 1464, 1335, 1176, 1098, 828; MS (ESI): m/z = 250.2 [M + H^+].

3-(1-Methyl-2-(1-phenylethylidene)hydrazinyl)benzonitrile (4.1l). Yellow oil, yield: 82% (from **4.1j**). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.39 (s, 3H), 3.15 (s, 3H), 7.12-

7.15 (m, 2H), 7.20 (s, 1H), 7.31-7.34 (m, 1H), 7.43-7.46 (m, 3H), 7.90-7.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.6, 41.7, 112.6, 117.7, 118.8, 119.5, 122.8, 126.7, 128.5, 129.5, 130.4, 137.9, 151.3, 167.3; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3065, 2967, 2878, 2227, 1595, 1576, 1487, 1444, 1364, 1329, 1293, 1100, 1073, 997; MS (ESI): m/z = 250.2 [M + H^+].

2-(1-Methyl-2-(1-phenylethylidene)hydrazinyl)benzonitrile (4.1o). Yellow oil, yield: 73% (from ketone). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.38 (s, 3H), 3.21 (s, 3H), 7.00-7.03 (m, 1H), 7.28 (d, J = 5.0 Hz, 1H), 7.39- 7.42 (m, 3H), 7.44-7.47 (m, 1H), 7.57-7.59 (m, 1H), 7.86-7.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.9, 44.2, 104.2, 118.1, 118.5, 121.9, 126.8, 128.4, 130.1, 133.3, 134.5, 137.7, 155.3, 167.6; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3061, 2965, 2922, 2877, 2219, 1595, 1445, 1364, 1293, 1064, 760; MS (ESI): m/z = 250.4 [M + H^+].

General procedure for the dehydrogenative cyclization recations

A 50-mL Schlenk tube was charged with *N*-methyl-*N*-phenylhydrazones (**4**, 0.3 mmol), $CuSO_4$ (1.0 mg, 0.0045 mmol), CuI (4.2 mg, 0.0225 mmol), Py (84.4 μL, 1.05 mmol), and DMF (2.7 mL). Then the solution of CF_3SO_3H (26.5 μL, 0.3 mmol) in DMF (0.3 mL) was slowly added. The vial was evacuated and filled with 1 atm O_2, and stirred rigorously at 95-150 ˚C for 14-48 h. After removal of the solvent, the residue was purified by flash chromatography on silica gel (gradient eluent of 5% EtOAc and 1% Et_3N in hexanes, v/v) to give the desired product as a colorless or pale yellow solid.

3-Phenylcinnoline (4.2a). Pale yellow solid (known compound[19]), yield: 80%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.46-7.48 (m, 1H), 7.52-7.55 (m, 2H), 7.68-7.83 (m, 3H), 8.11 (s, 1H), 8.23 (d, *J* = 10.0 Hz, 2H), 8.52 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 118.7, 126.4, 127.0, 127.2, 129.0, 129.4, 129.7, 130.2, 131.2, 136.9, 149.8, 153.4.

6-Methyl-3-phenylcinnoline (4.2b). Pale yellow solid, yield: 72%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47-7.63 (m, 5H), 8.06 (s, 1H), 8.23 (d, *J* = 10.0 Hz, 2H), 8.42 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.1, 118.2, 125.3, 126.7, 127.2, 129.0, 129.3, 129.5, 132.8, 137.1, 141.9, 149.0, 153.4; IR (neat) ῡ (cm^{-1}) 3056, 2922, 2852, 1733, 1717, 1695, 1652, 1558, 1521, 1456, 819; MS (ESI): m/z = 221.3 [M + H^+].

6-Fluoro-3-phenylcinnoline (4.2c). Pale yellow solid, yield: 82%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44-7.46 (m, 1H), 7.48-7.52 (m, 1H), 7.54-7.59 (m, 3H), 8.11 (s, 1H), 8.22-8.24 (m, 2H), 8.56-8.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 109.6 (d, J_{CF} = 22.5 Hz), 118.3 (d, J_{CF} = 6.2 Hz), 121.4 (d, J_{CF} = 27.5 Hz), 127.3, 127.9 (d, J_{CF} = 1.2 Hz), 129.1, 129.7, 133.2 (d, J_{CF} = 10.0 Hz), 136.5, 147.9, 153.6, 163.1 (d, J_{CF} = 255.0 Hz); IR (neat) ῡ (cm^{-1}) 3045, 3019, 1626, 1481, 1455, 1175, 913; MS (ESI): m/z = 225.3 [M + H^+].

6-Chloro-3-phenylcinnoline (4.2d). Pale yellow solid, yield: 88%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47-7.56 (m, 3H), 7.69-7.71 (m, 1H), 7.81-7.82 (m, 1H), 8.03 (s, 1H), 8.21 (d, *J* = 10.0 Hz, 2H), 8.46 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 117.5, 125.5, 127.1, 127.3, 129.1, 129.7, 131.4, 131.5, 136.4, 137.5, 148.1, 153.9; IR (neat) ῡ (cm^{-1}) 3035, 2923, 1733, 1700, 1684, 1606, 1490, 1295, 1103, 908; MS (ESI): m/z = 242.3 [M + H^+].

6-Bromo-3-phenylcinnoline (4.2e). Pale yellow solid, yield: 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47-7.55 (m, 3H), 7.83 (d, *J* = 10.0 Hz, 1H), 8.01-8.02 (m, 2H), 8.21 (d, *J* = 10.0 Hz, 2H), 8.38 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 117.3, 126.2, 127.3, 127.4, 128.9, 129.1, 129.7, 131.4, 133.9, 136.3, 148.2, 153.9; IR (neat) ῡ (cm^{-1}) 3035, 2922, 1700, 1684, 1652, 1558, 1540, 1449, 824; MS (ESI): m/z = 258.3 [M + H^+].

3-Phenylcinnoline-6-carbonitrile (4.2f). Pale yellow solid, yield: 92%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.54-7.63 (m, 3H), 7.94-7.96 (m, 1H), 8.21 (s, 1H), 8.27 (d, *J* = 5.0 Hz, 2H), 8.33 (s, 1H), 8.70 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 115.1, 117.9, 118.0, 125.6, 127.4, 129.3, 130.2, 130.3, 131.6, 133.8, 135.9, 148.9, 154.9; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3769, 3669, 1733, 1717, 1652, 1558, 1540, 1506, 1456; MS (ESI): m/z = 232.4[M + H^+].

3-Phenyl-6-(trifluoromethyl)cinnoline (4.2g). Pale yellow solid, yield: 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.49-7.57 (m, 3H), 7.94-7.96 (m, 1H), 8.20-8.24 (m, 4H), 8.67 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 119.0, 123.3 (q, J_{CF} = 271.2 Hz), 125.4 (q, J_{CF} = 5.0 Hz), 125.5, 125.7 (q, J_{CF} = 3.7 Hz), 127.3, 129.2, 129.9, 131.3, 132.6 (q, J_{CF} = 32.5 Hz), 136.1, 149.7, 154.5; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3050, 3035, 1573, 1362, 1265, 1122, 921; MS (ESI): m/z = 275.3 [M + H^+].

7-Methoxy-3-phenylcinnoline (4.2h1) and 5-methoxy-3-phenylcinnoline (4.2h2). Pale yellow solid, yield: 78%. ^{1}H NMR (500 MHz, $CDCl_3$, a mixture of isomers **4.2h1** and **4.2h2** in ratio ca. 5:1, the minor one is marked with an *) δ: 4.02 (s, 3H), 7.36-7.38 (m, 1H), 7.45-7.49 (m, 1H), 7.52-7.57 (m, 2H), 7.72-7.76 (m, 2H), 8.06 (s, 1H), 8.19-8.21 (m, 2H); 4.03* (s, 3H), 6.95* (d, *J* = 10.0 Hz, 1H), 7.45-7.49* (m, 1H), 7.52-7.57* (m, 2H), 7.65-7.69* (m, 1H), 8.10* (d, *J* = 10.0 Hz, 1H), 8.26-8.28* (m, 2H), 8.52* (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.8, 105.7, 118.9, 122.4, 125.7, 126.9, 128.0, 128.9, 129.1, 137.1, 151.3, 152.6, 160.9; 55.9*, 107.3*, 113.9*, 120.0*, 122.4*, 127.2*, 128.8*, 129.2*, 130.1*, 131.4*, 150.2*, 153.3*, 154.3*; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3066, 2936, 2850, 1620, 1577, 1452, 1266, 1112, 1024, 903; MS (ESI): m/z = 237.3 [M + H^+].

7-Methyl-3-phenylcinnoline (4.2i1) and 5-methyl-3-phenylcinnoline (4.2i2). Pale yellow solid, yield: 62%. ^{1}H NMR (500 MHz, $CDCl_3$, a mixture of isomers **4.2i1** and **4.2i2** in ratio ca. 2.2:1, the minor one is marked with an *) δ: 2.74 (s, 3H), 7.48-7.52 (m, 1H), 7.54-7.59 (m, 3H), 7.68-7.71 (m, 1H), 8.23-8.27 (m, 3H), 8.40 (d, *J* = 5.0 Hz, 1H); 2.63* (s, 3H), 7.48-7.52* (m, 1H), 7.54- 7.59* (m, 3H), 7.77* (d, *J* = 10.0 Hz, 1H), 8.23-8.27* (m, 3H), 8.31* (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.8, 115.7, 127.1, 127.9, 129.0, 129.3, 129.8, 131.1, 133.8, 134.1, 137.3, 150.1, 153.3; 22.0*, 118.6*, 124.7*, 126.1*, 126.5*, 128.2*, 128.8,* 129.0*, 129.2*, 131.6*, 140.8*, 150.1*, 153.3*; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3059, 2921, 2857, 1733, 1717, 1695, 1615, 1451, 1317, 1110, 892; MS (ESI): m/z = 221.3 [$M + H^+$].

7-Bromo-3-phenylcinnoline (4.2j1) and 5-bromo-3-phenylcinnoline (4.2j2). Pale yellow solid, yield: 68%. ^{1}H NMR (500 MHz, $CDCl_3$, a mixture of isomers **4.2j1** and **4.2j2** in ratio ca. 1.7:1, the minor one is marked with an *) δ: 7.51-7.61 (m, 3H), 7.67- 7.70 (m, 1H), 8.00 (d, *J* = 5.0 Hz, 1H), 8.29-8.31 (m, 2H), 8.43 (s, 1H), 8.55 (d, *J* = 5.0 Hz, 1H); 7.51-7.61* (m, 3H), 7.74-7.81* (m, 2H), 8.13* (s, 1H), 8.23-8.24* (m, 2H), 8.74* (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 117.7, 127.5, 129.1 (2C), 129.7, 129.8, 130.4, 131.9, 134.4, 136.5, 150.2, 154.6; 118.4*, 121.2*, 124.0*, 125.1*, 126.5*, 128.0*, 128.4,* 128.5*, 131.9*, 136.4*, 150.0*, 153.8*; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3024, 1565, 1438, 1307, 1100, 817; MS (ESI): m/z = 286.2 [$M + H^+$].

7-Isopropyl-3-phenylcinnoline (4.2k). Pale yellow solid, yield: 60%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.41 (d, *J* = 5.0 Hz, 6H), 3.16-3.23 (m, 1H), 7.47-7.50 (m, 1H), 7.55-7.58 (m, 2H), 7.65- 7.67 (m, 1H), 7.81 (d, *J* = 10.0 Hz, 1H), 8.13 (s, 1H), 8.24 (d, *J* = 10.0 Hz, 2H), 8.36 (s, 1H); ^{13}C NMR (125 MHz, CDCl3) δ: 23.4, 34.4, 118.6, 125.1, 125.4,

126.7, 127.1, 129.0, 129.2, 131.7, 137.1, 150.3, 151.5, 153.1; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3057, 2961, 2927, 2870, 1695, 1586, 1577, 1540, 1113, 903; MS (ESI): m/z = 249.3 [$M + H^+$].

3-Phenylcinnoline-7-carbonitrile (4.2l). Pale yellow solid, yield: 73%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.55-7.64 (m, 3H), 7.89-7.92 (m, 1 H), 8.19-8.21 (m, 1H), 8.31-8.33 (m, 2H), 8.45 (s, 1H), 8.84 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 110.1, 115.4, 115.5, 126.5, 127.6, 129.1, 129.3, 130.4, 135.4, 135.7, 137.6, 148.4, 155.0; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3064, 2924, 1733, 1717, 1684, 1616, 1521, 1313, 1105, 893; MS (ESI): m/z = 232.4 [$M + H^+$].

8-Methoxy-3-phenylcinnoline (4.2m). Pale yellow solid, yield: 88%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.16 (s, 3H), 7.05 (d, *J* = 10.0 Hz, 1H), 7.37 (d, *J* = 5.0 Hz, 1H), 7.46-7.64 (m, 4H), 8.06 (s, 1H), 8.25 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 56.2, 107.9, 118.3, 118.4, 127.2, 127.8, 129.0, 129.4, 131.9, 136.9, 142.8, 153.9, 156.2; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3062, 2934, 2848, 1684, 1614, 1551, 1454, 1429, 1390, 1282, 1109; MS (ESI): m/z = 237.4 [$M + H^+$].

8-Chloro-3-phenylcinnoline (4.2n). Pale yellow solid, yield: 76%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.48-7.51 (m, 1H), 7.54-7.57 (m, 2H), 7.61-7.64 (m, 1H), 7.77-7.78 (m, 1H), 7.84-7.86 (m, 1H), 8.13 (s, 1H), 8.26 (d, *J* = 10.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 118.4, 126.2, 127.2, 128.1, 129.1, 129.8, 130.2, 131.2, 134.9, 136.2, 145.9, 154.1; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3063, 2923, 2851, 1698, 1610, 1588, 1111, 989; MS (ESI): m/z = 242.3 [$M + H^+$].

3-Phenylcinnoline-8-carbonitrile (4.2o). Pale yellow solid, yield: 47%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.54-7.62 (m, 3H), 7.82-7.85 (m, 1H), 8.15-8.16 (m, 1H), 8.23-8.25 (m, 1H), 8.25 (s, 1H), 8.28-8.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 114.1, 115.7,

118.4, 126.6, 127.4, 129.3, 130.2, 130.3, 132.1, 135.8, 136.6, 147.8, 155.2; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 2925, 2854, 1733, 1700, 1684, 1646, 1576, 1558, 1512; MS (ESI): m/z = 232.4 [M + H^+].

3-Phenylbenzo[*h*]cinnoline (4.2p). Pale yellow solid, yield: 64%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.49-7.53 (m, 1H), 7.56-7.59 (m, 2H), 7.64 (d, *J* = 10 Hz, 1H), 7.76-7.79 (m, 1H), 7.83- 7.86 (m, 1H), 7.90-7.95 (m, 2H), 8.16 (s, 1H), 8.28-8.30 (m, 2H), 9.62 (d, *J* = 10 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 119.4, 123.7, 124.2, 126.4, 127.1, 128.2, 128.6, 129.1, 129.4, 129.6, 129.9, 133.2, 133.3, 136.8, 147.6, 155.3; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3750, 3675, 3058, 2924, 2852, 1772, 1733, 1675, 1646, 1540, 1465, 1441, 1386, 1261, 903, 805, 771, 753; MS (ESI): m/z = 257.4 [M + H^+].

3-(*p*-Tolyl)cinnoline (4.2q). Pale yellow solid, yield: 61%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.87 (s, 3H), 7.04-7.07 (m, 2H), 7.66-7.76 (m, 2H), 7.80 (d, *J* = 10.0 Hz, 1H), 8.04 (s, 1H), 8.18-8.21 (m, 2H), 8.50 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.3, 114.4, 117.8, 126.5, 126.8, 128.5, 129.4, 129.7, 129.8, 131.1, 149.6, 153.1, 160.8; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3060, 2936, 2836, 1772, 1700, 1606, 1515, 1438, 1292, 1258, 1175, 1035, 1020, 832; MS (ESI): m/z = 237.3 [M + H^+].

3-(4-Methoxyphenyl)cinnoline (4.2r). Pale yellow solid, yield: 77%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.43 (s, 3H), 7.35 (d, *J* = 5.0 Hz, 2H), 7.68-7.83 (m, 3H), 8.09 (s, 1H), 8.13 (d, *J* = 5.0 Hz, 2H), 8.52 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.3, 118.2, 126.5, 126.9, 127.1, 129.7 (2C), 130.0, 131.0, 134.1, 139.5, 149.7, 153.4; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3038, 2916, 2854, 1772, 1739, 1717, 1610, 1540, 1437, 1328, 1183, 1096; MS (ESI): m/z = 221.3 [M + H^+].

3-(4-Fluorophenyl)cinnoline (4.2s). Pale yellow solid, yield: 80%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.21-7.27 (m, 2H), 7.71-7.75 (m, 1H), 7.79-7.85 (m, 2H), 8.10 (s, 1H), 8.21-8.23 (m, 2H), 8.53 (d, J = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 116.1 (d, J_{CF} = 21.2 Hz), 118.4, 126.4, 126.9, 129.1 (d, J_{CF} = 8.7 Hz), 129.8, 130.3, 131.4, 133.1 (d, J_{CF} = 3.7 Hz), 149.8 (d, J_{CF} = 2.5 Hz), 152.5 (d, J_{CF} = 25.0 Hz), 163.8 (d, J_{CF} = 247.5 Hz); IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3057, 2923, 1733, 1717, 1699, 1652, 1588, 1513, 1231, 833; MS (ESI): m/z = 225.3 [M + H^+].

3-(4-Chlorophenyl)cinnoline (4.2t). Pale yellow solid, yield: 78%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.50-7.53 (m, 2H), 7.73-7.76 (m, 1H), 7.80-7.86 (m, 2H), 8.12 (s, 1H), 8.17-8.19 (m, 2H), 8.54 (d, J = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 118.6, 126.3, 126.9, 128.4, 129.2, 129.8, 130.4, 131.5, 135.3, 135.7, 149.9, 152.2; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3033, 2923, 1736, 1652, 1599, 1558, 1496, 1091; MS (ESI): m/z = 242.3 [M + H^+].

3-(4-Bromophenyl)cinnoline (4.2u). Pale yellow solid, yield: 72%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65-7.67 (m, 2H), 7.73-7.76 (m, 1H), 7.80-7.86 (m, 2H), 8.10-8.12 (m, 3H), 8.54 (d, J = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 118.5, 124.0, 126.3, 126.9, 128.7, 129.8, 130.5, 131.4, 132.2, 135.8, 149.9, 152.3; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3035, 2922, 1700, 1684, 1652, 1593, 1558, 1540, 1495, 826; MS (ESI): m/z = 286.1 [M + H^+].

4-(Cinnolin-3-yl)benzonitrile (4.2v). Pale yellow solid, yield: 53%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.80-7.86 (m, 3H), 7.89-7.94 (m, 2H), 8.25 (s, 1H), 8.39 (d, J = 10.0 Hz, 2H), 8.60 (d, J = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 113.0, 118.6, 119.7, 126.1, 127.1, 127.7, 129.9, 131.2, 131.8, 132.8, 141.1, 150.2, 151.3; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3744, 3648, 1733, 1717, 1652, 1558, 1540, 843; MS (ESI): m/z = 232.4 [M + H^+].

3-(*m*-Tolyl)cinnoline (4.2w). Pale yellow solid, yield: 75%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.48 (s, 3H), 7.26-7.30 (m, 1H), 7.42-7.45 (m, 1H), 7.70-7.85 (m, 3H), 8.01 (d, J = 5.0 Hz, 1H), 8.09 (s, 1H), 8.13 (s, 1H), 8.54 (d, J = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.6, 118.7, 124.5, 126.5, 126.9, 128.0, 128.9, 129.8, 130.1, 130.2, 131.2, 136.8, 138.7, 149.8, 153.6; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3055, 2956, 2920, 2853, 1699, 1684, 1617, 1581, 1495, 1439, 1321, 1178, 1100, 798; MS (ESI): m/z = 221.2 [M + H^+].

3-(3-(Trifluoromethyl)phenyl)cinnoline (4.2x). Pale yellow solid, yield: 61%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.67-7.80 (m, 3H), 7.84-7.92 (m, 2H), 8.22 (s, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.53 (s, 1H), 8.58 (d, J = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 119.1, 124.0 (q, J_{CF} = 3.7 Hz), 124.1 (q, J_{CF} = 271.2 Hz), 126.0 (q, J_{CF} = 3.7 Hz), 126.3, 127.1, 129.6, 129.9, 130.4, 130.8, 131.4, 131.6, 137.7, 150.1, 151.9; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3769, 3758, 1733, 1700, 1646, 1558, 1540, 1456, 1341, 1307, 1112, 1070, 754; MS (ESI): m/z = 275.3 [M + H^+].

3-(*o*-Tolyl)cinnoline (4.2y). Pale yellow solid, yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 7.33-7.40 (m, 3H), 7.54 (d, J = 5.0 Hz, 1H), 7.73-7.77 (m, 1H), 7.82-7.86 (m, 2H), 7.90 (s, 1H), 8.58 (d, J = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.5, 122.2, 126.0, 126.1, 126.8, 128.9, 129.8, 130.3, 130.5, 131.0, 131.2, 136.6, 137.6, 149.3, 156.1; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3058, 3022, 2957, 2924, 1717, 1603, 1472, 1321, 1241, 1119, 1092, 967; MS (ESI): m/z = 221.3 [M + H^+].

3-(2-Fluorophenyl)cinnoline (4.2z). Colorless solid, yield: 82%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.22-7.27 (m, 1H), 7.36-7.39 (m, 1H), 7.44-7.48 (m, 1H), 7.74-7.77 (m, 1H), 7.83-7.88 (m, 2H), 8.34 (s, 1H), 8.41-8.44 (m, 1H), 8.56 (d, J = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 116.3 (d, J_{CF} = 22.5 Hz), 122.9 (d, J_{CF} = 10.0 Hz), 124.8 (d,

J_{CF} = 3.7 Hz), 125.0 (d, J_{CF} = 11.2 Hz), 125.9, 127.5 (d, J_{CF} = 15.1 Hz), 127.2, 129.7, 130.6, 131.0 (d, J_{CF} = 8.7 Hz), 131.3, 131.4 (d, J_{CF} = 2.5 Hz), 149.5 (d, J_{CF} = 25.0 Hz), 160.7 (d, J_{CF} = 247.5 Hz); IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3062, 1733, 1717, 1684, 1576, 1569, 1489, 1455, 1204, 909; MS (ESI): m/z = 225.3 [M + H^+].

3-(2,4-Dimethylphenyl)cinnoline (4.2aa). Yellow oil, yield: 96%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.40 (s, 3 H), 2.42 (s, 3H), 7.15-7.18 (m, 2H), 7.45 (d, J = 10.0 Hz, 1H), 7.71-7.75 (m, 1H), 7.80-7.84 (m, 2H), 7.87 (s, 1H), 8.56 (d, J = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.5, 21.2, 122.1, 126.1, 126.8, 126.9, 129.7, 130.2, 130.4, 131.1, 131.2, 134.8, 136.4, 138.7, 149.2, 156.2; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3035, 3013, 2955, 2920, 2856, 2925, 1733, 1669, 1615, 1583, 1558, 1472, 1326, 1125, 968; MS (ESI): m/z = 235.4 [M + H^+].

3-(Naphthalen-2-yl)cinnoline (4.2ab). Pale yellow solid, yield: 67%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.49-7.52 (m, 2H), 7.67-7.70 (m, 1H), 7.75-7.78 (m, 1H), 7.81-7.87 (m, 2H), 7.95-7.98 (m, 2H), 8.20 (s, 1H), 8.31 (d, J = 5.0 Hz, 1H), 8.53 (d, J = 10.0 Hz, 1H), 8.73 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 118.8, 124.4, 126.4, 126.5, 126.8 (2C), 126.9, 127.7, 128.7 (2C), 129.8, 130.2, 131.2, 133.5, 133.7, 134.1, 149.8, 153.2; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3055, 1653, 1617, 1583, 1506, 1470, 1436, 1094, 896; MS (ESI): m/z = 257.3 [M + H^+].

Experimental procedure for the transformation of 4.3 to 4.2a

A 50-mL Schlenk tube was charged with **4.3** (71.4 mg, 0.3 mmol), $CuSO_4$ (1.0 mg, 0.0045 mmol), CuI (4.2 mg, 0.0225 mmol), pyridine (84.4 µL, 1.05 mmol), and DMF (2.7 mL). Then the solution of CF_3SO_3H (26.5 µL, 0.3 mmol) in DMF (0.3 mL) was slowly added. The vial was evacuated and filled with 1 atm O_2, and stirred rigorously at 110 ˚C for 14h.

After removal of the solvent, the residue was purified by flash chromatography on silica gel (gradient eluent of 5% EtOAc and 1% Et_3N in hexanes, v/v) to give **4.2a** in 90% yield.

2-(2-Methyl-2-phenylhydrazono)-2-phenylacetaldehyde (4.3). Brown solid. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.15 (s, 3H), 7.09-7.12 (m, 1H), 7.26-7.28 (m, 2H), 7.36-7.42 (m, 5H), 7.44-7.46 (m, 2H), 9.70 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 42.1, 117.0, 123.6, 127.9, 128.6, 129.1, 129.6, 133.2, 141.8, 148.0, 191.7; IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3058, 2731, 2699, 1693, 1585, 1431, 893; MS (ESI): m/z = 239.4 [$M + H^+$].

4.5 Acknowledgements

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4.6 References

1. Metal Catalyzed Cross-Coupling Reactions, 2nd ed.; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.
2. For selected recent reviews, see: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (c) Yin, L.-X.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (e) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (f) Catellani, M.; Motti, E.; Della Ca′, N. *Acc. Chem. Res.* **2008**, *41*, 1512. (g) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555. (h) Zhang, M. *Adv. Synth. Catal*. **2009**, *351*, 2243. (i) Thansandote, P.; Lautens, M. *Chem. Eur. J*. **2009**, *15*, 5874. (j) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (k) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (l) De Ornellas, S.; Storr, T. E.; Williams, T. J.; Baumann, C. G.; Fairlamb, I. J. S. *Curr. Org. Chem.* **2011**, *8*, 79. (m) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (n) Boorman, T. C.; Larrosa, I. *Chem. Soc. Rev.* **2011**, *40*, 1910. (o) Newhouse, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 3362. (p) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (q) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740.

3. For selected recent reviews, see: (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Yoo, W.-J.; Li, C.-J. *Top. Curr. Chem.* **2010**, *292*, 281. (c) Scheuermann, C. J. *Chem. Asian J.* **2010**, *5*, 436. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Wendlandt, A. W.; Suess, A. M.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 11062. (e) Liu, C.; Zhang, H.; Shi, W.; Lei, A.-W. *Chem. Rev.* **2011**, *111*, 1780. (f) Schnürch, M.; Dastbaravardeh, N.; Ghobrial, M.; Mrozek, B.; Mihovilovic, M. D. *Curr. Org. Chem.* **2011**, *15*, 2694. (g) Zhang, C.; Tang, C.-H.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381.

4. (a) Glaser, C. *Chem. Ber.* **1869**, *2*, 422. (b) Hay, A. S. *J. Org. Chem*. **1962**, *27*, 3320. (c) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem. Int. Ed.* **2000**, *39*, 2632.

5. (a) Hay, A. S.; Blanchard, H. S.; Endres, G. F.; Eustance, J. W. *J. Am. Chem. Soc.* **1959**, *81*, 6335. (b) Armstrong, D. R.; Cameron, C.; Nonhebel, D. C.; Perkins, P. G. *J. Chem. Soc. Perkin Trans. 2* **1983**, 581. (c) Armstrong, D. R.; Cameron, C.; Nonhebel, D. C.; Perkins, P. G. *J. Chem. Soc. Perkin Trans. 2* **1983**, 587.

6. (a) Noji, M.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1994**, *35*, 7983. (b) Nakajima, M.; Kanayama, K.; Miyoshi, I.; Hashimoto, S.-I. *Tetrahedron Lett.* **1995**, *36*, 9519. (c) Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.-I.; Noji, M.; Koga, K. *J. Org. Chem.* **1999**, *64*, 2264. (d) Li, X.-L.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137. (e) Kim, K. H.; Lee, D.-W.; Lee, Y.-S.; Ko, D.-H.; Ha, D.-C. *Tetrahedron* **2004**, *60*, 9037.

7. (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc*. **2009**, *131*, 17052. (b) Li, Y.; Jin, J.; Qian, W.; Bao, W. *Org. Biomol. Chem*. **2010**, *8*, 326. (c) Monguchi, D.; Yamamura, A.; Fujiwara, T.; Somete, T.; Mori, A. *Tetrahedron Lett.* **2010**, *51*, 850.

8. (a) Wei, Y.; Zhao, H.-Q.; Kan, J.; Su, W.-P.; Hong, M.-C. *J. Am. Chem. Soc*. **2010**, *132,* 2522. (b) Matsuyama, N.; Kitahara, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett*. **2010**, *12*, 2358.

9. Tang, B.-X.; Song, R.-J.; Wu, C.-Y.; Liu, Y.; Zhou, M.-B.; Wei, W.-T.; Deng, G.-B.; Yin, D.-L.; Li, J.-H. *J. Am. Chem. Soc.* **2010**, *132*, 8900.

10. (a) Baslé, O.; Li, C.-J. *Green. Chem.* **2007**, *9*, 1047. (b) Yoo, W.-J.; Correia, C. A.; Zhang, Y.-H.; Li, C.-J. *Synlett* **2009**, *138*. (c) Shen, Y.-M.; Li, M.; Wang, S.-Z.; Zhan, T.-G.; Tan, Z.; Guo, C.-C. *Chem. Commun.* **2009**, 953. (d) Huang, L.-H.; Niu, T.-M.; Wu, J.; Zhang, Y.-H. *J. Org. Chem.* **2011**, *76*, 1759. (e) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317.

11. (a) Jia, Y.-X.; Kündig, E. P. *Angew. Chem. Int. Ed*. **2009**, *48*, 1636. (b) Klein, J. E. M. N.; Perry, A.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2010**, *12*, 3446.

12. (a) Zhang, G.-W.; Zhao, Y.; Ge, H.-B. *Angew. Chem. Int. Ed*. **2013**, *52*, 2559.

13. (a) Bekhit, A. A. *Boll. Chim. Farmac*. **2001**, *140*, 243. (b) Lewgowd, W.; Stanczak, A. *Arch. Pharm. Chem. Life Sci.* **2007**, *340*, 65. (c) Gautam, N.; Chourasia, O. P. *Ind. J. Chem., Section B: Org. Chem. Inc. Med. Chem*. **2010**, *49*, 830. (d) Parasuraman, P.; Shanmugarajan, R. S.; Aravazhi, T.; Nehru, K.; Mathiazhagan, T.; Rajakumari, R. *Int. J. Pharm. Life Sci*. **2012**, *3*, 1430.

14. Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed*. **2012**, *51*, 3066.

15. (a) Toh, K. K.; Wang, Y.-F.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 13942. (b) Toh, K. K.; Sanjaya, S.; Sahnoun, S.; Chong, S. Y.; Chiba, S. *Org. Lett.* **2012**, *14*, 2290.

16. Mann, F. G.; Saunders, B. C. *Practical Organic Chemistry*, 4th ed.; Longman Inc.: London, **1974**.

17. Sharma, S. D.; Pandhi, S. B. *J. Org. Chem*. **1990**, *55*, 2196.

18. Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett*. **1999**, *40*, 8193.

19. Baumgarten, H. E.; Furnas, J. L. *J. Org. Chem*. **1961**, *26*, 1536.

CHAPTER 5. RHODIUM-CATALYZED DIRECT SYNTHESIS OF SULFOXIMINES FROM SULFOXIDES

(Reproduced in part with permission from Miao, J.-M.; Richards, N. G. J.; Ge, H.-B. "Rhodium-Catalyzed Direct Synthesis of Unprotected *NH*-Sulfoximines from Sulfoxides", *Chem. Commun*. **2014**, *50*, 9687-9689. Copyright 2014 Royal Society of Chemistry)

5.1 Introduction

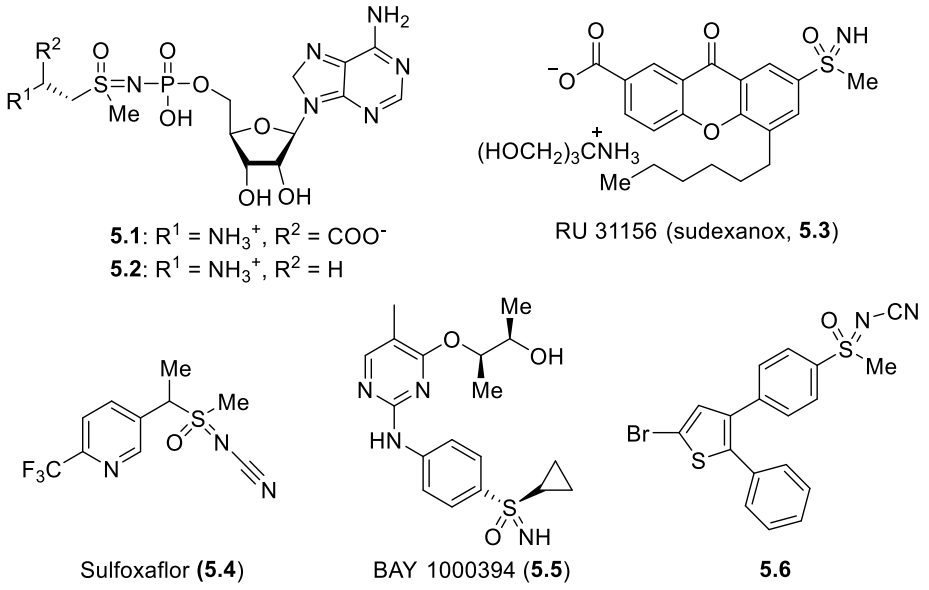
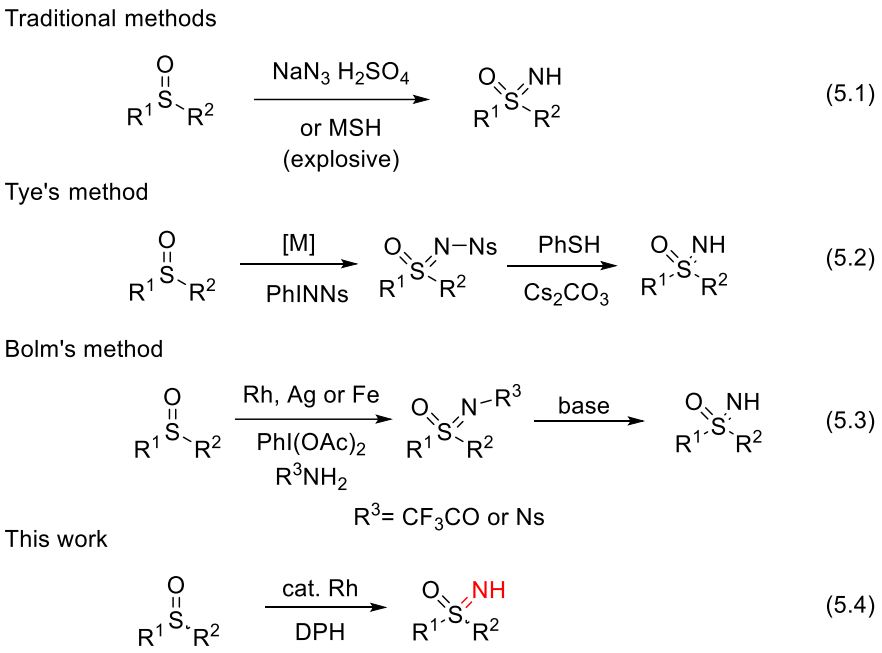


Figure 5.1 Bioactive Sulfoximines

Sulfoximines have recently attracted great attention in biochemistry and medicinal chemistry because of their versatile chemical properties and diverse bioactivities.[1] Since the discovery of the first sulfoximine, methionine sulfoximine, a number of bioactive

compounds containing a sulfoximine moiety in the pharmacophore have been reported (Figure 5.1). For example, compound **5.1** and **5.2** are transition-state-analogue inhibitors of L-asparagine synthetase;[2] sudexanox (RU31156, **5.3**) was selected for clinic studies as a prophylactic antiasthmatic;[3] sulfoxaflor (**5.4**) is the first commercially available sulfoximine insecticide;[4] Bay 1000394 (**5.5**) is an excellent cyclin-dependent kinase inhibitor, which is currently being evaluated in a Phase I clinical trial for activity against advanced solid tumors;[5] finally, one of the enantiomers of **5.6** shows good anti-proliferative activity against various cancer cell lines.[6]



Scheme 5.1 Preparation of Unprotected *NH*-Sulfoximines

Among the small number of synthetic strategies for preparing sulfoximines, the most straightforward approach employs direct imination of sulfoxides (Scheme 5.1). However, traditional methods require the usage of either toxic or potentially explosive reagents, such as the combination of NaN_3 and sulfuric acid,[7] or *O*-mesitylene

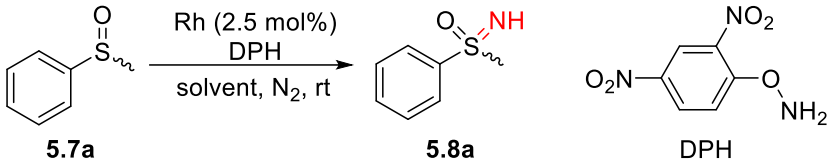
sulfonylhydroxylamine (MSH) (eq. 5.1).[8] To overcome these drawbacks, considerable efforts have been devoted to developing transition metal-catalyzed sulfoxide imination, with significant progress being achieved in recent years.[9] For example, Tye reported the synthesis of sulfoximines by copper-catalyzed imination of sulfoxides with PhI=NNs (Ns = para-nitrobenzenesulfonyl) and PhI=NSes (Ses = trimethylsilylethylsulfonyl) (eq. 5.2);[9f] Bolm discovered that this process could be efficiently performed via rhodium[9h], silver[9i], or iron[9l,m] catalysis using iminoiodinanes generated *in-situ* from the oxidation of amides by $PhI(OAc)_2$ (eq. 5.3). In spite of this powerful approach, the transition metal-catalyzed imination of sulfoxides gives protected sulfoximines, requiring an additional step for removal of the undesired protecting group. Inspired by a recent report from Kürti and co-workers describing the rhodium-catalyzed synthesis of unprotected *NH*-aziridines from olefins using *O*-(2,4-dinitrophenyl)hydroxylamine (DPH),[10] we have developed the first transition metal-catalyzed *direct* synthesis of free *NH*-sulfoximines from sulfoxides under mild conditions (eq. 5.4).

5.2 Results and Discussion

Our investigation began with direct imination of phenyl methyl sulfoxide using 1.5 eq. of *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) in the presence of 2.5 mol % of $Rh_2(esp)_2$ at room temperature. After screening a large number of solvents, trifluoroethanol (TFE) was found to be optimal, giving the desired free *NH*-sulfoximine product **5.8a** in 61% yield (Table 5.1, entry 1). Further screening of Rh(II) catalysts revealed that this process could also be catalyzed by $Rh_2(OAc)_4$, albeit with lower efficiency (entry 11). Additionally,

Rh(I) did not show catalytic activity in the imination reaction (entry 13).[10] Finally, using an increased amount of DPH gave an optimal yield for the imination reaction (entry 19).

Table 5.1 Optimization of Reaction Conditions for Sulfoximination[a]

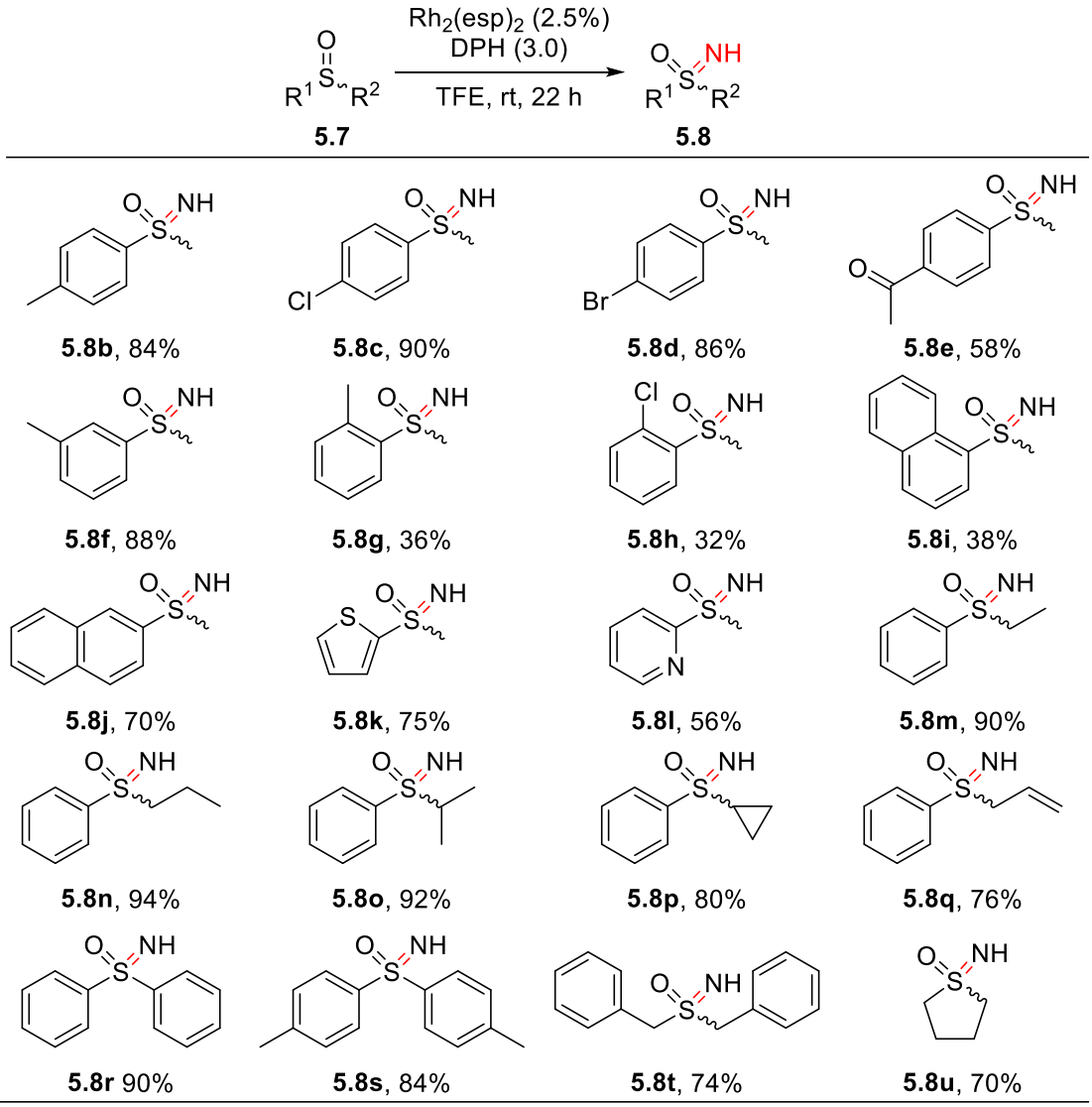


5.7a **5.8a** DPH

Entry	Pd catalyst	Equiv of DPH	Solvent	Yield (%)[b]
1	$Rh_2(esp)_2$	1.5	TFE	61
2	$Rh_2(esp)_2$	1.5	MeOH	32
3	$Rh_2(esp)_2$	1.5	MeCN	48
4	$Rh_2(esp)_2$	1.5	nPrCN	44
5	$Rh_2(esp)_2$	1.5	PhCN	42
6	$Rh_2(esp)_2$	1.5	EtOH	30
7	$Rh_2(esp)_2$	1.5	iPrOH	22
8	$Rh_2(esp)_2$	1.5	tBuOH	trace
9	$Rh_2(esp)_2$	1.5	HFIP	39
10	$Rh_2(esp)_2$	1.5	DCM	12
11	$Rh_2(OAc)_4$	1.5	TFE	23
12	$Rh_2(TFA)_4$	1.5	TFE	trace
13	$Rh(PPh_3)_3Cl$	1.5	TFE	0
14	$Rh_2(oct)_4$	1.5	TFE	0
15[c]	$Rh_2(esp)_2$	1.5	TFE	50
16[d]	$Rh_2(esp)_2$	1.5	TFE	60
17	$Rh_2(esp)_2$	1.0	TFE	48
18	$Rh_2(esp)_2$	2.0	TFE	72
19	**$Rh_2(esp)_2$**	**3.0**	**TFE**	**78**

[a] Reactions were conducted on a 0.3 mmol scale. Conditions: **5.7a** (0.3 mmol), Rh catalyst (2.5 mol %), DPH (1 -3 equiv), 3 ml solvent, room temperature under N_2 atmosphere, 22 h unless otherwise noted. [b] Isolated yields. [c] 40 ˚C. [d] 0 ˚C. DPH = *O*-(2,4-dinitrophenyl)hydroxylamine. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate. TFE

= 2,2,2-tifluoroethanol. HFIP = hexafluoroisopropanol. The substrate and product are racemic mixtures.



Scheme 5.2 Scope of Sulfoxides. Reactions were conducted on a 0.3 mmol scale. Conditions: **5.7** (0.3 mmol), $Rh_2(esp)_2$ (0.0075 mmol, 2.5 mol%), DPH (0.9 mmol, 3.0 eq.), TFE (3 ml, 0.1 M), room temperature, N_2 atmosphere, 22 h. The substrates and products are racemic mixtures.

With optimized conditions in hand, we evaluated the generality of the method using a variety of sulfoxides as substrates (Scheme 5.2). As expected, functional groups such as methyl, halogen (Cl, Br), or an acyl group on the phenyl ring were well tolerated (**5.8a-h**).

Not surprisingly, the *para*-acyl substituted sulfoxide led to a lower yield, perhaps as a result of the electron-withdrawing effect of the acyl group acting to decrease the reactivity of sulfoxide (**5.8e**). Furthermore, an apparent steric effect was observed in the imination reaction because significantly lower yields were observed with sulfoxides bearing a substituent at the *ortho* position of the phenyl ring (**5.8g** and **5.8h**). The nature of the aryl sulfoxide was not limited, however, to the phenyl ring and naphthanyl. Electron-rich 2-thiophenyl, and electron-deficient 2-pyridyl methyl sulfoxides were also found to be effective substrates for the Rh(II)-catalyzed imination reaction (**5.8i-l**). On the other hand, 1-naphthyl and 2-pyridyl methyl sulfoxides provided only modest yields, presumably due to steric and electronic factors, respectively (**5.8i** and **5.8l**). In an important observation for the preparation of sulfoximine-based small molecules, the methyl group on the phenyl methyl sulfoxide could be successfully replaced by other alkyl groups, including the cyclopropyl group, to afford the corresponding sulfoximines in high yields (**5.8m**-**p**). Interestingly, when phenyl allyl sulfoxide was employed in the reaction, selective sulfoximination was favoured over aziridination (**5.8q**).[10]

In addition, diaryl sulfoximines could be effectively prepared with this method from the corresponding sulfoxides (**5.8r** and **5.8s**), and we were pleased to find that both acyclic and cyclic dialkyl sulfoxides were compatible with this reaction (**5.8t** and **5.8u**).

Although the reaction mechanism of this transformation has not been investigated, it is likely that a rhodium-nitrene species is an intermediate based on prior literature reports.[9h,10] Thus, coordination of DPH to $Rh_2(esp)_2$, followed by loss of dinitrophenol, likely generates a reactive nitrene intermediate, which then oxidizes the metal-coordinated sulfoxide to the corresponding sulfoximine.

5.3 Summary

In summary, a novel, efficient, and safe method for the preparation of free *NH*-sulfoximines has been developed via rhodium-catalyzed imination of sulfoxides using *O*-(2,4-dinitrophenyl)hydroxylamine. This new approach features mild conditions and good functional group tolerance, which should permit its application to the synthesis of structurally complex sulfoximines with agrochemical and clinical utility.[1g]

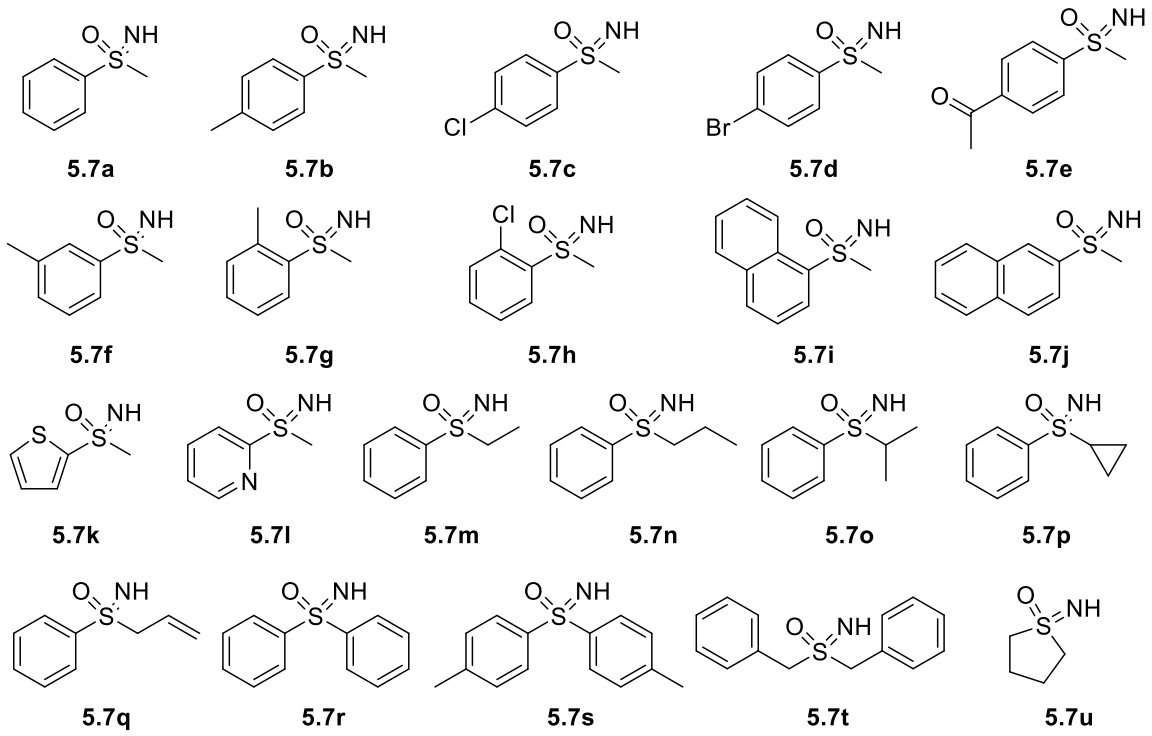
5.4 Experimental

General Methods. All the solvents and commercially available reagents were purchased from commercial sources and used directly. For TLC analysis, precoated plates (w/h F254, Dynamic Adsorbents Inc, 0.25 mm thick) were used; for air-flashed column chromatography, Flash Silica Gel (Dynamic Adsorbents Inc, 32-63 μm) was used. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker 500 MHz NMR Fourier transform spectrometer. ^{1}H NMR data was reported as: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR data was reported in terms of chemical shift (δ ppm), multiplicity, and coupling constant (Hz). The infrared spectra were obtained using a Thermo Nicolet IR 330 Spectrometer. Mass (MS) analysis was obtained using Agilent 1100 series LC/MSD system with Electrospray Ionization (ESI). *O*-(2,4-Dinitrophenyl)hydroxylamine (DPH) was purchased from Matrix Sci. and used directly.

Preparation of Starting Materials (Scheme 5.3):

Sulfoxides **5.7a**, **5.7b**, **5.7p**, **5.7r**, **5.7s**, **5.7t**, and **5.7u** were purchased from Sigma-Aldrich, TCI, Alfa Aesar, or MP Biomedicals. **5.7c**, **5.7d**, **5.7e**, **5.7f**, **5.7g**, **5.7h**, **5.7i**, **5.7j**, **5.7l**, **5.7m**, **5.7n**, **5.7o and 5.7q** were prepared from the corresponding thiophenols by the

addition of alkyl bromides or iodides,[12] followed by the oxidation with *t*-BuOOH according to the reported procedure.[13] **5.7k** was prepared by the oxidation of the corresponding sulfide based on the reported protocol.



Scheme 5.3 Starting Materials for Racemic Sulfoximination

General procedure for the imination of sulfoxides. An oven-dried schlenk flask was charged with $Rh_2(esp)_2$ (11.4 mg, 0.015 mmol) and DPH (0.9 mmol), and then a solution of sulfoxide (**5.7**, 0.3 mmol) in CF_3CH_2OH was added under nitrogen flow. The reaction mixture was stirred at 0 ˚C for 2 h under nitrogen, and then warmed to room temperature and stirred for another 20 h. The reaction mixture was diluted with EtOAc, filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was

purified by flash chromatography on silica gel (hexane/EtOAc 4:1~1:2, v/v) to yield the desired product **5.8**.

***S*-Methyl-*S*-phenylsulfoximine** (**5.8a**, racemic, known compound[14]). Yellow oil, yield: 78%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.69 (br s, 1 H), 3.08 (s, 3H), 7.51-7.56 (m, 2H), 7.57-7.62 (m, 1H), 7.97-8.01 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 46.5, 127.9, 129.5, 133.3, 143.9. MS (ESI): m/z = 156.1, [M + H^+].

***S*-Methyl-*S*-(4-methylphenyl)sulfoximine** (**5.8b**, racemic). Yellow oil, yield: 84%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 2.50 (br s, 1H), 3.06 (s, 3H), 7.32 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.8, 46.6, 128.0, 130.1, 140.9, 144.2. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3271, 3060, 3025, 2926, 1539, 1455, 1409, 1224, 1097, 1004, 1027, 799, 750, 625, 525; MS (ESI): m/z = 170.1, [M + H^+].

***S*-Methyl-*S*-(4-chlorophenyl)sulfoximine** (**5.8c**, racemic). Yellow oil, yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.72 (br s, 1H), 3.09 (s, 3H), 7.51 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 46.6, 129.6, 129.9, 140.1, 142.5. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3269, 3086, 3019, 2926, 1580, 1470, 1409, 1393, 1321, 1225, 1085, 1002, 829, 762, 731, 557, 519; MS (ESI): m/z = 190.0, [M + H^+].

***S*-Methyl-*S*-(4-bromophenyl)sulfoximine** (**5.8d**, racemic). Yellow oil, yield: 86%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.71 (br s, 1H), 3.07 (s, 3H), 7.67 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 46.5, 128.5, 129.6, 132.8, 142.9. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3268, 3084, 3015, 2926, 2853, 1572, 1472, 1387, 1321, 1225, 1093, 1066, 999, 823, 760, 717; MS (ESI): m/z = 234.0, 236.0, [M + H^+].

***S*-Methyl-*S*-(4-acetylphenyl)sulfoximine** (**5.8e**, racemic). Yellow solid, yield: 58%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.63 (s, 3H), 2.74 (s, 3H), 7.72 (d, J = 8.5 Hz, 2H),

8.08 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 27.1, 44.1, 124.0, 129.4, 139.4, 151.3, 197.3. IR (neat) ῡ (cm^{-1}) 3084, 2990, 2912, 2851, 1675, 1425, 1396, 1362, 1295, 1269, 1092, 1047, 959, 828, 596; MS (ESI): m/z = 198.1, [M + H^+].

***S*-Methyl-*S*-(3-methylphenyl)sulfoximine** (**5.8f**, racemic). Yellow oil, yield: 88%. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 2.23-2.67 (br s, 1H), 2.45 (s, 3H), 3.08 (s, 3H), 7.38-7.44 (m, 2H), 7.76-7.82 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 21.6, 46.5, 125.1, 128.3, 129.4, 134.1, 139.8, 143.7. IR (neat) ῡ (cm^{-1}) 3271, 3061, 3021, 2925, 1599, 1477, 1411, 1321, 1226, 1094, 1019, 993, 792, 750, 687; MS (ESI): m/z = 170.1, [M + H^+].

***S*-Methyl-*S*-(2-methylphenyl)sulfoximine** (**5.8g**, racemic). Yellow oil, yield: 36%. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 2.71-2.77 (br s, 1H), 2.76 (s, 3H), 3.13 (s, 3H), 7.28-7.37 (m, 2H), 7.44-7.50 (m, 1H), 8.09 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 21.1, 44.9, 127.0, 129.7, 133.2, 133.3, 137.8, 142.0. IR (neat) ῡ (cm^{-1}) 3272, 3059, 3015, 2928, 2854, 1470, 1456, 1410, 1319, 1274, 1222, 1195, 1069, 1003, 768, 747; MS (ESI): m/z = 170.1, [M + H^+].

***S*-Methyl-*S*-(2-chlorophenyl)sulfoximine** (**5.8h**, racemic). Yellow oil, yield: 32%. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 2.91 (br s, 1H), 3.30 (s, 3H), 7.42-7.47 (m, 1H), 7.49-7.55 (m, 2H), 8.17 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 43.8, 127.7, 131.0, 132.4, 132.7, 134.3, 141.3. IR (neat) ῡ (cm^{-1}) 3273, 3084, 3008, 2928, 2853, 1576, 1450, 1431, 1319, 1231, 1118, 1050, 1003, 959, 755; MS (ESI): m/z = 190.0, [M + H^+].

***S*-Methyl-*S*-(naphth-2-yl)sulfoximine** (**5.8i**, racemic). Yellow solid, yield: 38%. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 2.98 (br s, 1H), 3.28 (s, 3H), 7.56-7.64 (m, 2H), 7.67-7.72 (m, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 8.38 (dd, *J* = 1.0, 8.0 Hz, 1H), 8.99 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 45.3, 124.8, 125.0, 127.2, 128.7,

129.3, 129.6, 130.0, 134.8, 134.9, 139.0. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3272, 3059, 3010, 2927, 2854, 1592, 1506, 1225, 1019, 952, 807, 772, 750; MS (ESI): m/z = 206.1, [M + H^+].

***S*-Methyl-*S*-(naphth-1-yl)sulfoximine** (**5.8j**, racemic). Yellow solid, yield: 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.79 (br s, 1H), 3.16 (s, 3H), 7.58-7.67 (m, 2H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.94-8.00 (m, 3H), 8.56 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 46.5, 123.2, 127.9, 128.2, 129.3 (2C), 129.6, 129.9, 132.6, 135.3, 140.7. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3264, 3050, 3034, 3014, 2931, 1584, 1407, 1343, 1324, 1222, 1123, 1076, 1004, 948, 823, 760, 631; MS (ESI): m/z = 206.1, [M + H^+].

***S*-Methyl-*S*-(thiophen-2-yl)sulfoximine** (**5.8k**, racemic). Yellow oil, yield: 75%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.10 (br s, 1H), 3.23 (s, 3H), 7.08-7.12 (m, 1H), 7.63-7.67 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 47.9, 128.2, 133.5, 133.8, 146.3. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3267, 3091, 3021, 2926, 1506, 1404, 1342, 1321, 1225, 1096, 1024, 994, 854, 731, 568; MS (ESI): m/z = 162.0, [M + H^+].

***S*-Methyl-*S*-(pyridin-2-yl)sulfoximine** (**5.8l**, racemic). Yellow oil, yield: 56%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.84 (br s, 1H), 3.26 (s, 3H), 7.48-7.53 (m, 1H), 7.91-7.97 (m, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.73 (d, *J* = 4.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 42.7, 121.4, 127.0, 138.6, 150.4, 161.0. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3262, 3013, 2925, 2853, 1655, 1578, 1454, 1426, 1317, 1223, 1136, 1068, 1014, 991, 783, 756, 511; MS (ESI): m/z = 157.0, [M + H^+].

***S*-Ethyl-*S*-phenylsulfoximine** (**5.8m**, racemic). Yellow oil, yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.21-1.26 (m, 3H), 2.61 (br s, 1H), 3.15 (q, *J* = 7.5 Hz, 2H), 7.50-7.56 (m, 2H), 7.57-7.63 (m, 1H), 7.95 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 7.1, 51.1, 127.8, 128.4, 132.3, 140.7. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3269, 3063, 2976, 2937, 2877,

1647, 1583, 1477, 1446, 1409, 1380, 1231, 1201, 1098, 973, 761, 721, 691, 674, 568, 510; MS (ESI): m/z = 170.1, [M + H^+].

***S*-Propyl-*S*-phenylsulfoximine** (**5.8n**, racemic). Yellow solid, yield: 94%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.94 (t, J = 7.5 Hz, 3H), 1.59-1.80 (m, 2H), 2.58 (br s, 1H), 3.03-3.15 (m, 2H), 7.49-7.54 (m, 2 H), 7.56-7.61 (m, 1H), 7.94 (d, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.1, 17.2, 59.5, 128.7, 129.4, 133.3, 142.4. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3268, 3063, 2969, 2935, 2877, 1701, 1446, 1406, 1224, 1100, 985, 754, 690, 572, 544, 510; MS (ESI): m/z = 184.1, [M + H^+].

***S*-Isopropyl-*S*-phenylsulfoximine** (**5.8o**, racemic). Yellow solid, yield: 92%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.21-1.34 (m, 6H), 2.41 (br s, 1H), 3.19-3.29 (m, 1H), 7.50-7.56 (m, 2H), 7.58-7.63 (m, 1H), 7.94 (d, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.3, 16.7, 56.8, 129.3, 129.7, 133.3, 140.2. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3270, 3063, 2975, 2929, 2872, 1666, 1467, 1445, 1385, 1366, 1261, 1214, 1105, 978, 759, 716, 692, 650, 565, 548; MS (ESI): m/z = 184.1, [M + H^+].

***S*-Cyclopropyl-*S*-phenylsulfoximine** (**5.8p**, racemic). Yellow oil, yield: 80%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.85-0.94 (m, 1 H), 0.99-1.07 (m, 1H), 1.13-1.21 (m, 1H), 1.33-1.41 (m, 1H), 2.32-2.62 (m, 2H), 7.49-7.55 (m, 2H), 7.56-7.61 (m, 1H), 7.95 (d, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 5.9, 6.3, 34.5, 128.1, 129.4, 133.0, 143.5. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3267, 3060, 3015, 2924, 2853, 1477, 1445, 1418, 1305, 1224, 1188, 1096, 984, 884, 827, 758, 718, 690, 562, 525; MS (ESI): m/z = 182.1, [M + H^+].

***S*-Allyl-*S*-phenylsulfoximine** (**5.8q**, racemic). Yellow oil, yield: 76%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.84 (br s, 1H), 3.78-3.90 (m, 2H), 5.13 (d, J = 17.0 Hz, 1H), 5.33 (d, J = 1.0 Hz, 1H), 5.78-5.88 (m, 1H), 7.51-7.56 (m, 2H), 7.59-7.64 (m, 1H), 7.95 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 62.8, 124.7, 125.7, 129.1, 129.3, 133.5, 141.2. MS (ESI): m/z = 182.1, [M + H^+].

***S,S*-Diphenylsulfoximine** (**5.8r**, racemic). Yellow solid, yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.07 (br s, 1H), 7.42-7.52 (m, 6H), 8.03 (d, J = 7.5 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 128.1, 129.4, 132.8, 143.6. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3269, 3062, 3003, 2923, 1583, 1476, 1447, 1230, 1129, 1094, 1069, 980, 760, 721, 688, 569, 542; MS (ESI): m/z = 218.1, [M + H^+].

***S,S*-Di(4-methyl-phenyl)sulfoximine** (**5.8s**, racemic). Yellow solid, yield: 84%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.37 (s, 6H), 2.97 (br s , 1H), 7.26 (d, J = 8.0 Hz, 4H), 7.91 (d, J = 8.0 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.8, 128.2, 130.1, 141.1, 143.6. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3272, 3060, 3027, 2956, 2923, 2855, 720, 1596, 1491, 1450, 1401, 1380, 1228, 1130, 1095, 1019, 977, 818, 662, 623, 541; MS (ESI): m/z = 246.1, [M + H^+].

***S,S*-Dibenzylsulfoximine** (**5.8t**, racemic). Yellow solid, yield: 74%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.17 (d, J = 8.0 Hz, 2H), 4.28 (d, J = 8.0 Hz, 2H), 7.39-7.42 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 60.8, 128.2, 129.2, 129.3, 131.4. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3250, 3086, 3064, 3030, 2976, 2919, 1493, 1455, 1417, 1259, 1246, 1156, 1150, 1073, 1039, 776, 697, 586; MS (ESI): m/z = 246.1, [M + H^+].

***S,S*-Tetramethylenesulfoximine** (**5.8u**, racemic). Yellow oil, yield: 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.19-2.29 (m, 4H), 2.75 (br s, 1H), 3.06-3.16 (m 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.3, 55.7. IR (neat) $\bar{\upsilon}$ (cm^{-1}) 3386, 3262, 2951, 2926, 2876, 2854, 1654, 1603, 1448, 1416, 1110, 1138, 1078, 1009, 895, 796, 720; MS (ESI): m/z = 120.0, [M + H^+].

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5.6 References

1. For reviews on the synthesis and application of sulfoximines, see: (a) Johnson, C. R. *Aldrichimica Acta* **1985**, *18*, 3; (b) Pyne, S. G. S*ulfur Rep*. **1992**, *12*, 57; (c) Worch, C.; Mayer, A. C.; Bolm, C. *Organosulfur Chemistry in Asymmetric Synthesis* (Ed.: T. Toru, C. Bolm), Wiley-VCH, Weinheim, **2008**, 209; (d) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1; (e) Chemla, F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 275; (f) Okamura, H.; Bolm, C. *Chem. Lett*. **2004**, *33*, 482; (g) Lucking, U. *Angew. Chem. Int. Ed*. **2013**, *52*, 9399; (h) Bizet, V.; Kowalczykb, R.; Bolm, C. *Chem. Soc. Rev*. **2014**, *43*, 2426.
2. (a) Ikeuchi, H.; Ahn, Y.-M.; Otokawa, T.; Watanabe, B.; Hegazy, L.; Hiratake, J.; Richards, N. G. J. *Bioorg. Med. Chem.* **2012**, *20*, 5915; (b) Gutierrez, J. A.; Pan, Y.-X.; Koroniak, L.; Hiratake, J.; Kilberg, M. S.; Richards, N. G. J. *Chem. Biol*. **2006**, *13*, 1339. (c) Ikeuchi, H.; Meyer, M. E.; Ding, Y.; Hiratake, J.; Richards, N. G. J. *Bioorg. Med. Chem.* **2009**, *17*, 6641; (d) Richards, N. G. J.; Kilberg, M. S. *Annu. Rev. Biochem.* **2006**, *75*, 629.
3. Miller, P.; James, G. W. L. *Arch. Int. Pharmacodyn. Ther*. **1978**, *231*, 328.

4. (a) Zhu, Y.; Loso, M. R.; Watscon, G. B.; Sparks, T. C.; Rogers, R. B.; Huang, J. X.; Gerwick, B. C.; Babcock, J. M.; Kelley, D.; Hedge, V. B.; Nugent, B. M.; Renga, J. M.; Denholm, I.; Gorman, K.; DeBoer, G. J.; Hasler, J.; Meade, T.; Thomas, J. D. *J. Agric. Food Chem*. **2011**, *59*, 2950; (b) Babcock, J. M.; Gerwick, C. B.; Huang, J. X.; Loso, M. R.; Nakamura, G.; Nolting, C. P.; Rogers, R. B.; Sparks, T. C.; Thomas, J.; Watson, G. B.; Zhu, Y. *Pest Manage. Sci*. **2011**, *67*, 328; (c) Watson, G. B.; Loso, M. R.; Babcock, J. M.; Hasler, J. M.; Letherer, T. J.; Young, C. D.; Zhu, Y.; Casida, J. E.; Sparks, T. C. *Insect Biochem. Mol. Biol*. **2011**, *41*, 432.

5. (a) Lucking, U.; Siemeister, G.; Lienau, P.; Jautelat, R.; Schulze, J. *EP 2179991*, **2010**; (b) Lucking, U.; Jautelat, R.; Kruger, M.; Brumby, T.; Lienau, P.; Schafer, M.; Briem, H.; Schulze, J.; Hillisch, A.; Reichel, A.; Siemeister, G. *ChemMedChem* **2013**, *8*, 1021.

6. Park, S. J.; Baars, H.; Mersmann, S.; Buschmann, H.; Baron, J. M.; Amann, P. M.; Czaja, K.; Hollert, H.; Bluhm, K.; Redelstein, R.; Bolm, C. *ChemMedChem* **2013**, *8*, 217.

7. (a) Bentley, H. R.; Whitehead, J. K. *J. Chem. Soc*. **1952**, 1572; (b) Johnson, C. R.; Haake, M.; Schroeck, C. W. *J. Am. Chem. Soc*. **1970**, *92*, 6594; (c) Stoss, P.; Satzinger, G. *Angew. Chem., Int. Ed.* **1971**, *10*, 76; (d) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc*. **1973**, *95*, 7418; (e) Rynbrandt, R. H.; Balgoyen, D. P. *J. Org. Chem*. **1978**, *43*, 1824; (f) Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *8*, 909.

8. (a) Tamura, Y.; Sumoto, K.; Minamikawa, J.; Ikeda, M. T*etrahedron Lett.* **1972**, 4137; (b) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem*. **1973**, *38*, 1239; (c) Johnson, C. R.; Kirchhoff, R. A.; Corkins, H. G. *J. Org. Chem*. **1974**, *39*, 2458; (d) Allenmark, S.; Claeson, S.; Lowendahl, C. *Tetrahedron: Asymmetry* **1996**, *7*, 361.

9. Cu-catalyzed: (a) Muller, J. F. K.; Vogt, P. *Tetrahedron Lett*. **1998**, *39*, 4805; (b) Takada, H.; Ohe, K.; Uemura, S. *Angew. Chem. Int. Ed.* **1999**, *38*, 1288; (c) Bolm, C.; MuCiz, K.; Aguilar, N.; Kesselgruber, M.; Raabe, R. *Synthesis* **1999**, 1251; (d) Nakayama, J.; Otani, T.; Sugihara, Y.; Sano, Y.; Ishii, A.; Sakamoto, A. *Heteroat. Chem.* **2001**, *12*, 333; (e) Lacote, E.; Amatore, M.; Fensterbank, L.; Malacria, M. *Synlett* **2002**, 116. (f) Cren, S.; Kinahan, T. C.; Skinner, C. L.; Tye, H. *Tetrahedron Lett.* **2002**, *43*, 2749. (g) Tomooka, C. S.; Carreira, E. M. *HelV. Chim. Acta*. **2003**, *85*, 3773; Rh-catalyzed : (h) Okamura, H.; Bolm, C. *Org. Lett*. **2004**, *6*, 1305; Ag-catalyzed: (i) Cho, G. Y.; Bolm, C. *Org. Lett*. **2005**, *7*, 4983; Fe-catalyzed: (j) Bach, T.; Korber, C. *Tetrahedron Lett*. **1998**, *39*, 5015; (k) Bach, T.; Kcrber, C. *Eur. J. Org. Chem*. **1999**, *64*, 1033; (l) Garcia Mancheno, O.; Bolm, C. *Org. Lett*. **2006**, *8*, 2349; (m) Garcia Mancheno, O.; Dallimore, J.; Plant, A.; Bolm, C. *Org. Lett*. **2009**, *11*, 2429.

10. Jat, J. L.; Paudyal, M. P.; Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Devarajan, D.; Ess, D. H.; Kurti, L.; Falck, J. R. *Science* **2014**, *343*, 61.

11. For selected recent reviews on Rh-nitrene mediated reactions, see: (a) Muller, P.; Fruit, C. *Chem. Rev*. **2003**, *103*, 2905; (b) Espino, C. G.; Du Bois, J. *Modern Rhodium-Catalyzed Organic Reactions* (Ed.: P. A. Evans), Wiley-VCH, Weinheim, **2005**, 379; (c) Davies, H. M. L.; Manning, J. R. *Nature*, **2008**, *451*, 417; (d) Collet, F.; Dodd, R.; Dauban, P. *Chem. Commun*. **2009**, 5061; (e) Du Bois, J. *Org. Process Res. Dev*. **2011**, *15*, 758; (f) Dequirez, G.; Pons, V.; Dauban, P. *Angew. Chem. Int. Ed*. **2012**, *51*, 7384; (g) Diaz-Requejo, M. M.; Caballero, A.; Fructos, M. R.; Perez, P. J. *Catalysis by Metal Complexes* **2012**, *38*, 229; (h) Jennifer, L. R.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res*. **2012**, *45*, 911.
12. Hughes, M.; Boultwood, T.; Zeppetelli, G.; Bull, J. A. *J. Org. Chem*. **2013**, *78*, 844.
13. Das, R.; Chakraborty, D. *Synthesis* **2011**, 277.
14. Mancheno, O. G.; Bistri, O.; Bolm, C. *Org. Lett*. **2007**, *9*, 3809.

APPENDICES

Appendix A Crystallographic Data for *L*-**2.2g**

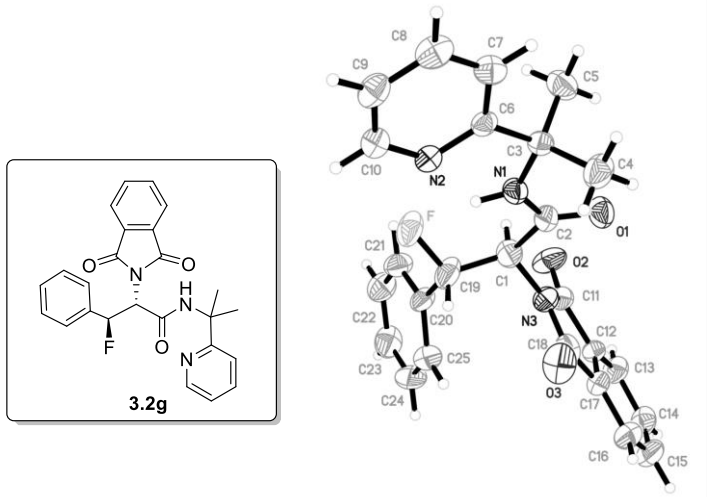
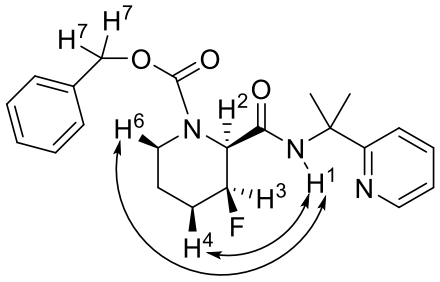


Figure A 1 Crystallographic Structure of ***L*-2.2g**

Table A 1 Crystallographic Data and Structure Refinement for ***L*-2.2g**

Identification code	b
Empirical formula	C_{25} H_{22} F N_3 O_3
Formula weight	431.46
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P21/N
Unit cell dimensions	a = 11.943(2) A alpha = 90 deg. b = 12.618(3) A beta = 90.20(3) deg. c = 14.512(3) A gamma = 90 deg.
Volume	2186.9(8) A^3
Z, Calculated density	4, 1.310 Mg/m^3
Absorption coefficient	0.093 mm^-1
F(000)	904
Crystal size	0.30 x 0.20 x 0.10 mm
Theta range for data collection	2.14 to 25.42 deg.
Limiting indices	0<=h<=14, 0<=k<=15, -17<=l<=17
Reflections collected / unique	
Completeness to theta = 25.42	99.7 %
Absorption correction	Psi-scan
Max. and min. transmission	0.9907 and 0.9726
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4026 / 0 / 289
Goodness-of-fit on F^2	1.006
Final R indices [I>2sigma(I)]	R1 = 0.0676, wR2 = 0.1345
R indices (all data)	R1 = 0.1521, wR2 = 0.1626
Largest diff. peak and hole	0.263 and -0.189 e.A^-3

Appendix B NOESY Spectra of **3.2f**



H^1-H^4 and H^1-H^6 correlations were observed.

H^1-H^3 correlation was not observed.

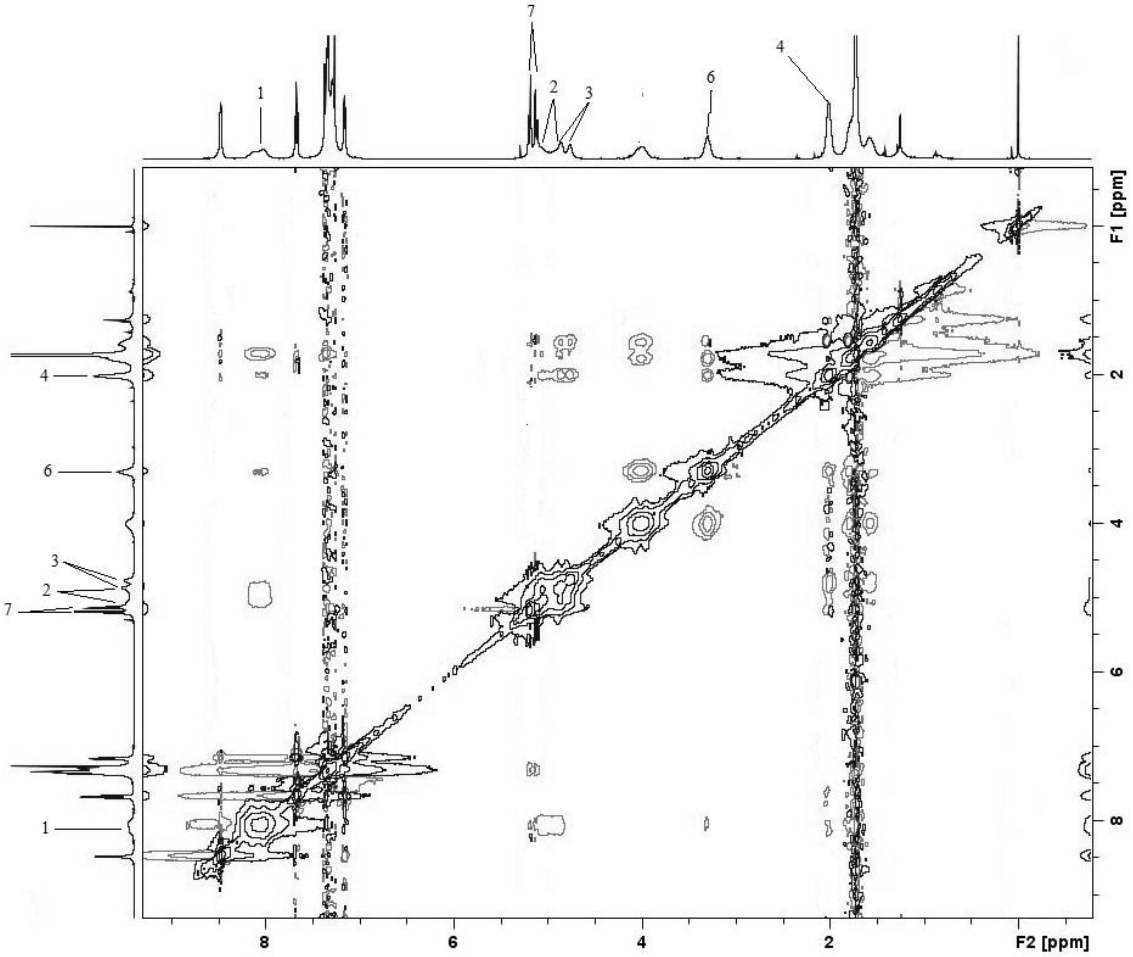
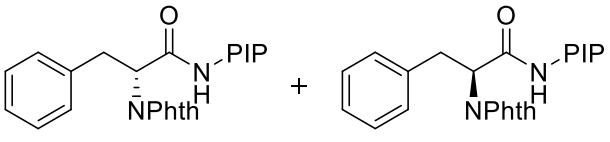


Figure B 1 NOESY Spectra of **3.2f**

Appendix C HPLC Data for **3.1g** and **3.2g**

Chiral Stationary phase: Chiralpak ® AD-H, n-hexane/isopropanol = 92:8, 0.70 mL/min

Signal: VWD1 A, Wavelength=210 nm.



***D,L*-3.1g**

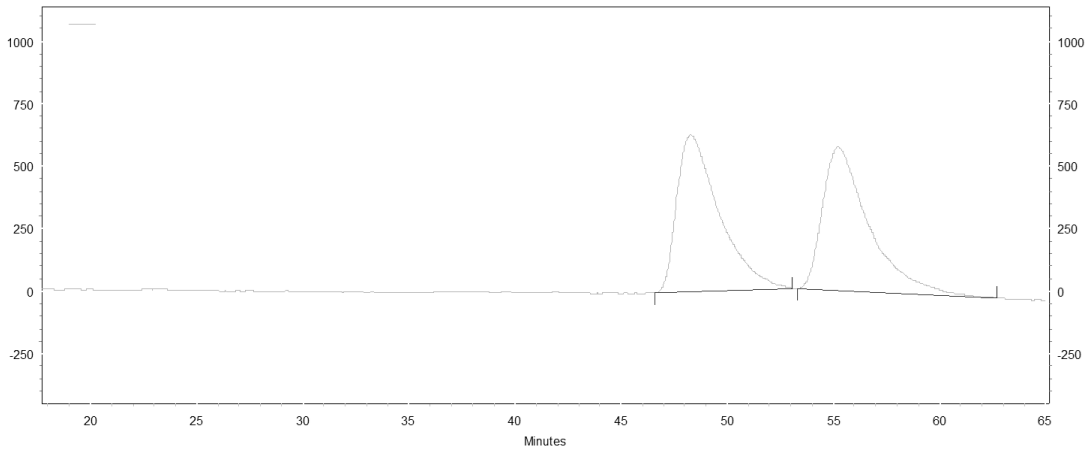
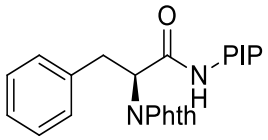


Figure C 1 HPLC Spectra of ***D,L*-3.1g**

Table C 1 HPLC Data for ***D,L*-3.1g**

Retention Time	Area	Area%
48.277	87030121	49.70
55.221	88064648	50.30



***D*-1g**

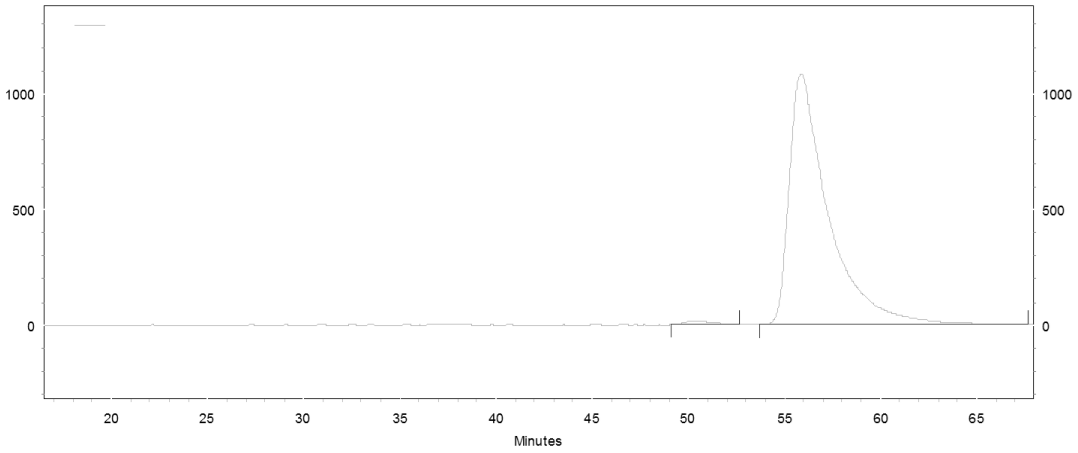


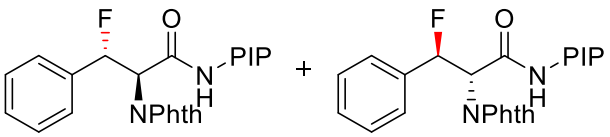
Figure C 2 HPLC Spectra of ***D*-3.1g**

Table C 2 HPLC Data for ***D*-3.1g**

Retention Time	Area	Area%
50.277	1569630	1.01
55.883	153665691	98.99

Chiral Stationary phase: Chiralpak ® AD-H, n-hexane/isopropanol = 75:25, 1.00 mL/min

Signal: VWD1 A, Wavelength=210 nm



***D,L*-3.2g**

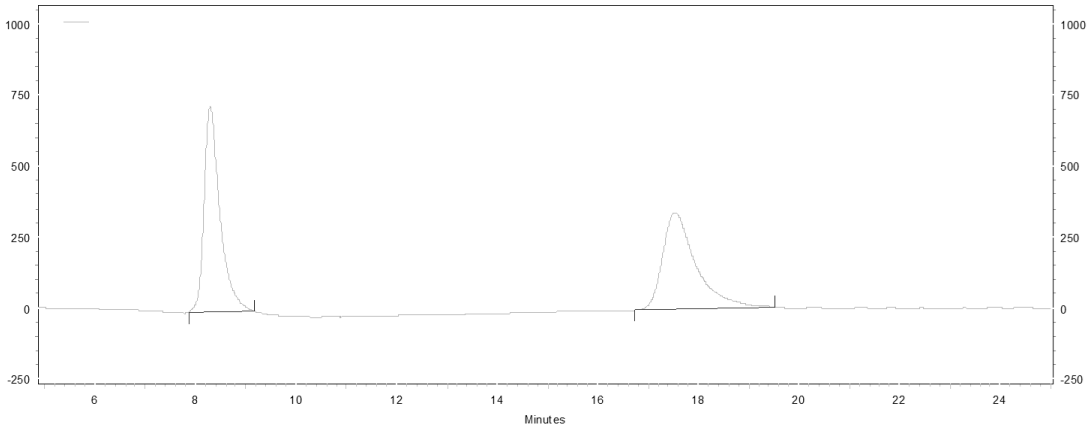
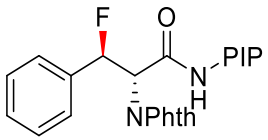


Figure C 3 HPLC Spectra of ***D,L*-3.2g**

Table C 3 HPLC Data for ***D,L*-3.2g**

Retention Time	Area	Area%
8.288	15865404	50.12
17.536	15791706	49.88



***D*-3.2g**

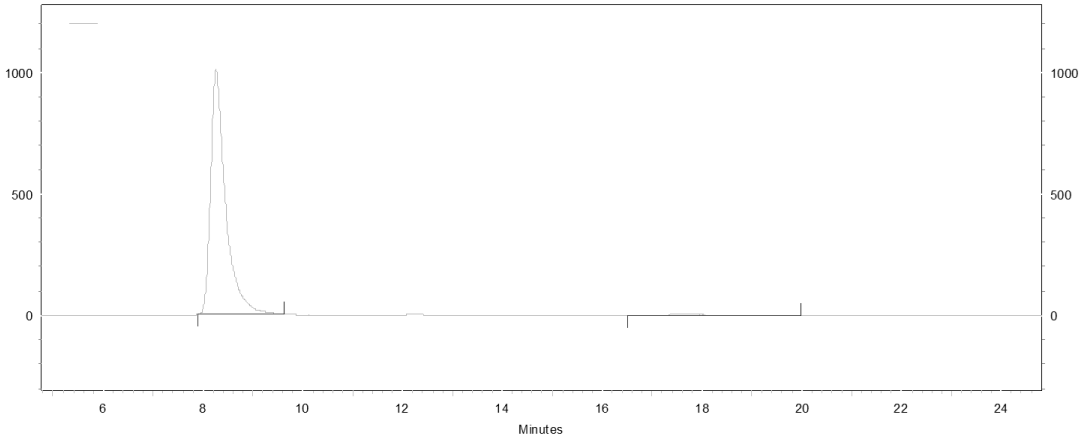
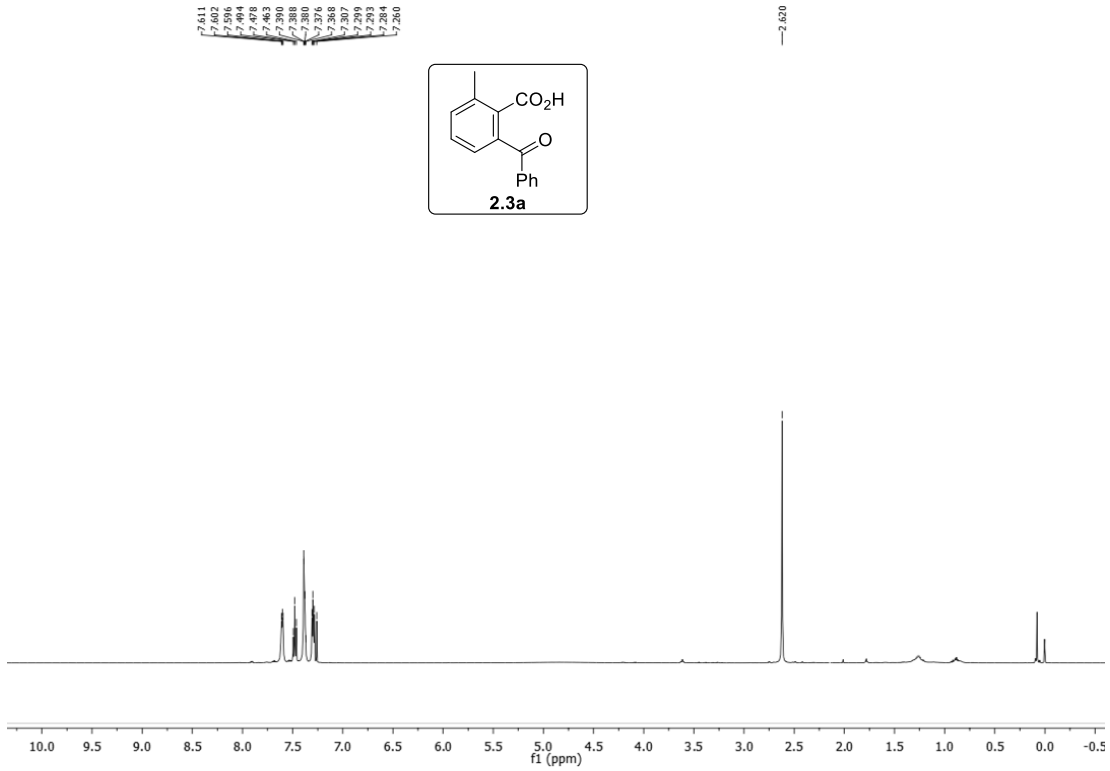


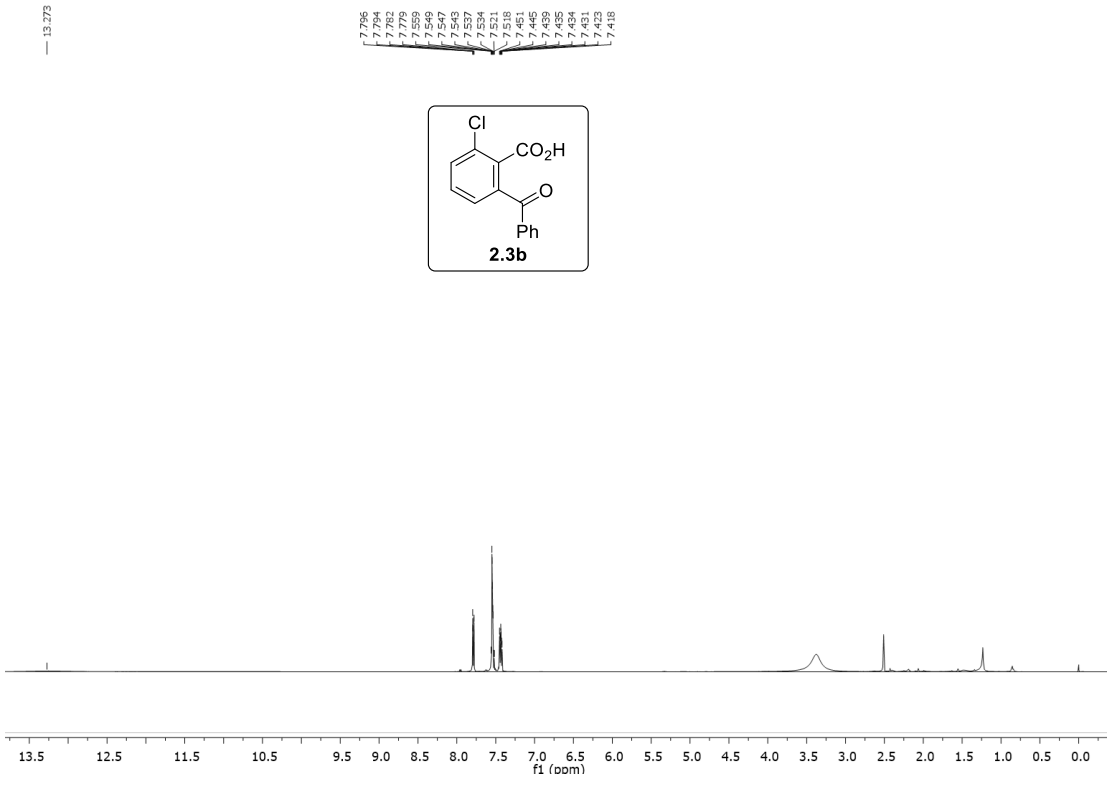
Figure C 4 HPLC Spectra of ***D*-3.2g**

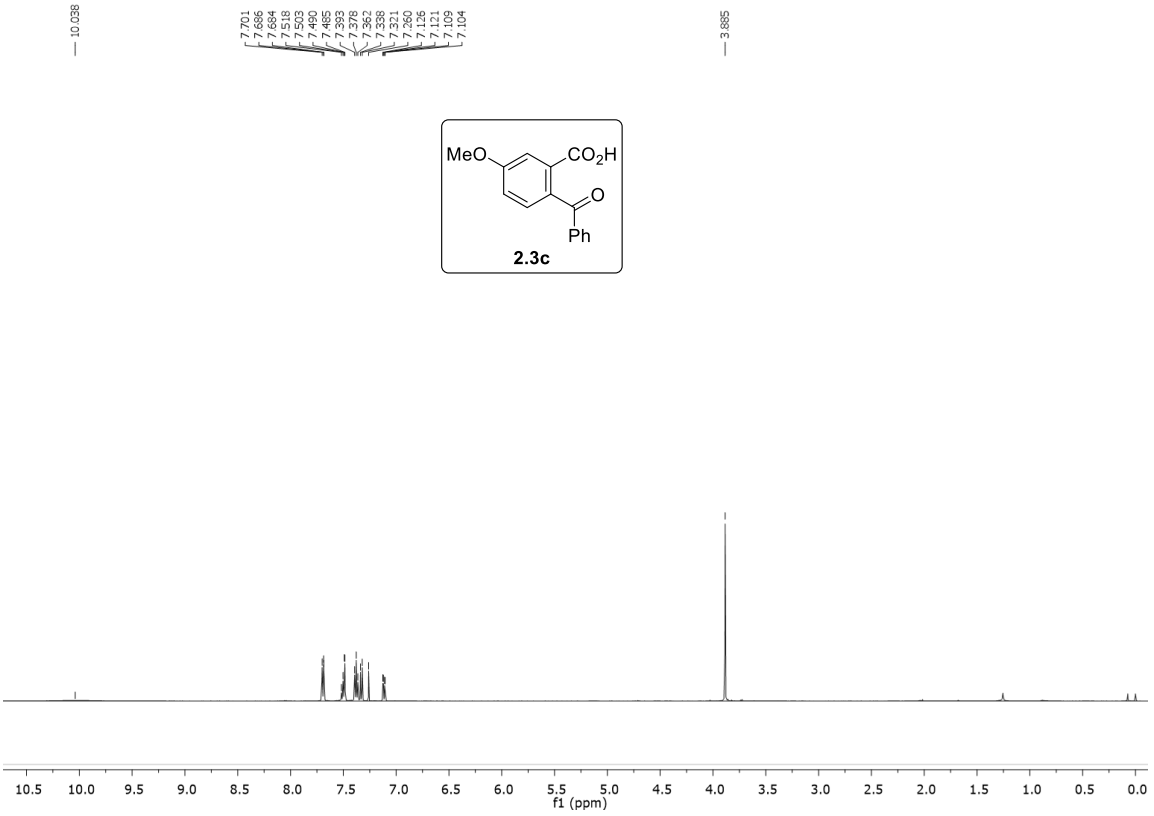
Table C 4 HPLC Data for ***D*-3.2g**

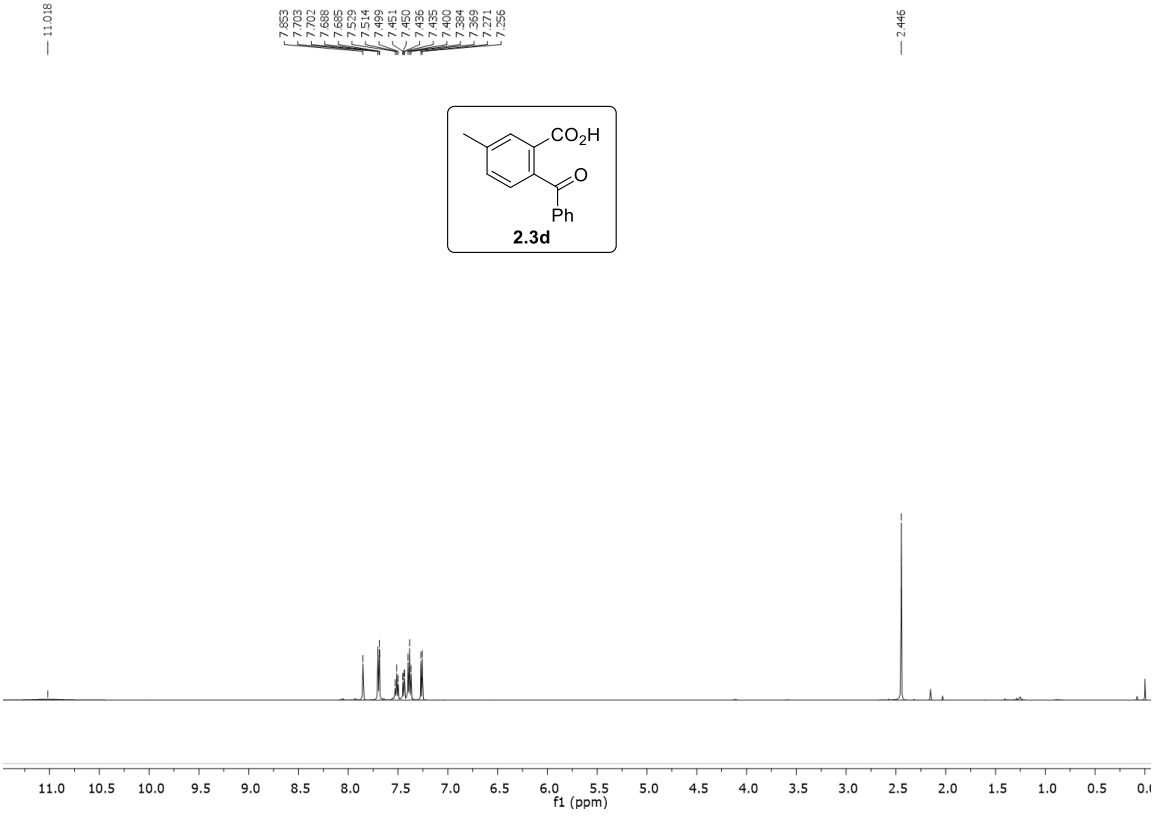
Retention Time	Area	Area%
8.261	20995719	98.76
17.664	264478	1.24

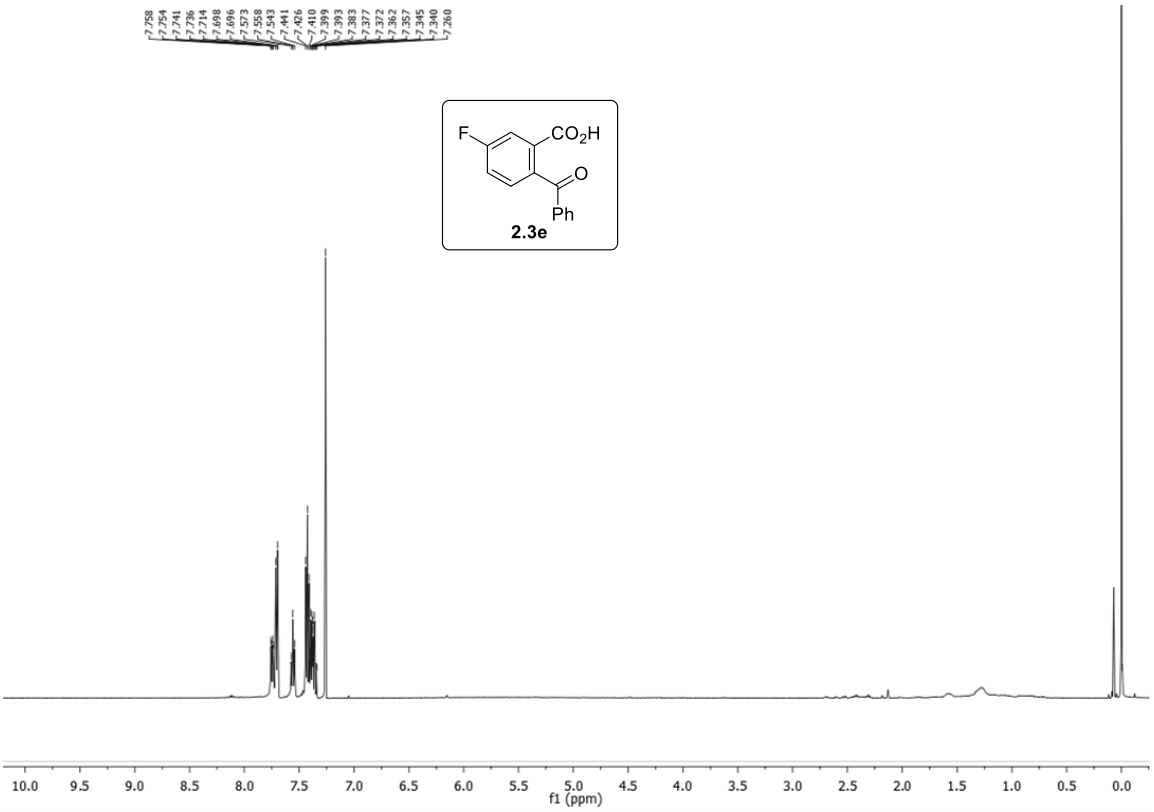
Appendix D ^{1}H NMR and ^{13}C NMR Spectra

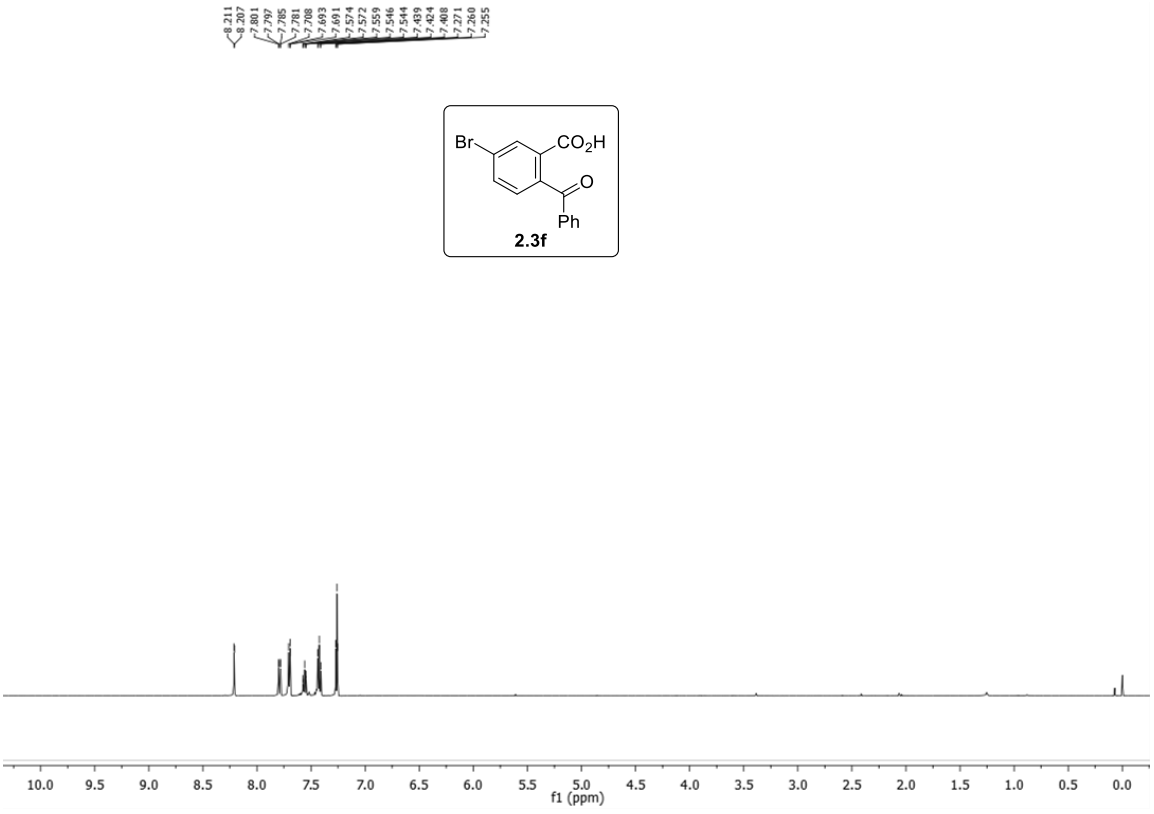


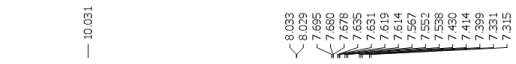



10.038
7.701
7.686
7.684
7.518
7.503
7.490
7.485
7.393
7.378
7.362
7.338
7.321
7.260
7.126
7.121
7.109
7.104
3.885
MeO
CO2H
O
Ph
2.3c
f1 (ppm)


11.018
7.853
7.703
7.702
7.688
7.685
7.529
7.514
7.499
7.451
7.450
7.436
7.435
7.400
7.384
7.369
7.271
7.256
2.446
CO2H
O
Ph
2.3d
f1 (ppm)


7.758
7.754
7.741
7.736
7.714
7.698
7.696
7.573
7.558
7.543
7.441
7.426
7.410
7.399
7.393
7.383
7.377
7.372
7.362
7.357
7.345
7.340
7.260
F
CO2H
O
Ph
2.3e
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


8.211
8.207
7.801
7.797
7.785
7.781
7.708
7.693
7.691
7.574
7.572
7.559
7.546
7.544
7.459
7.424
7.408
7.271
7.260
7.255
Br
CO2H
O
Ph
2.3f
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


10.031
8.033
8.029
7.685
7.680
7.678
7.635
7.631
7.619
7.614
7.567
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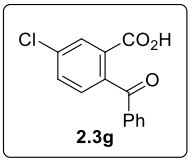
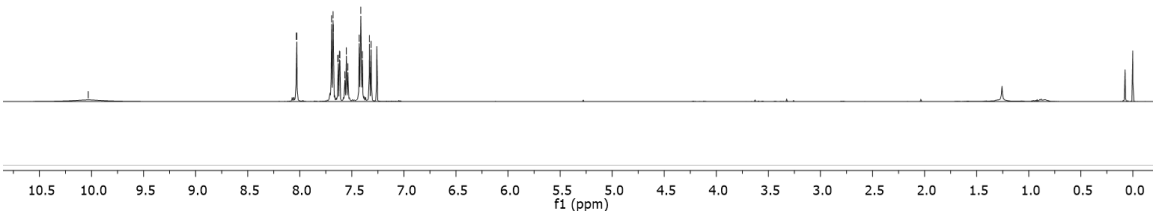
7.538
7.430
7.414
7.399
7.331
7.315


Cl
CO2H
O
Ph

2.3g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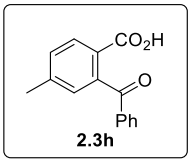
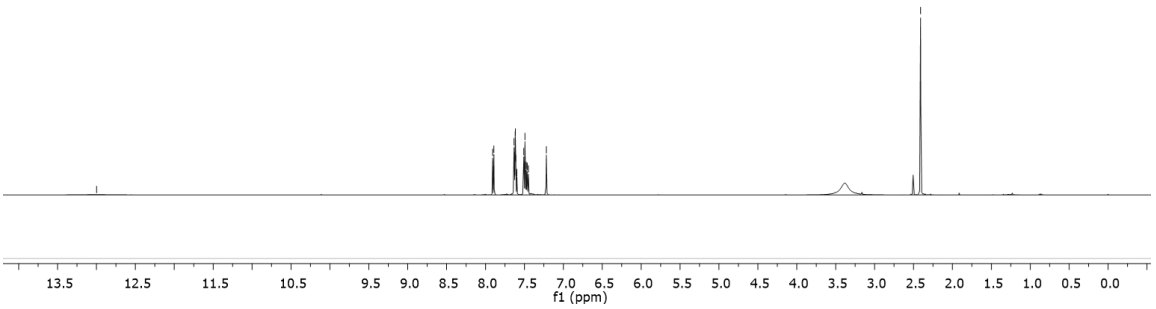
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

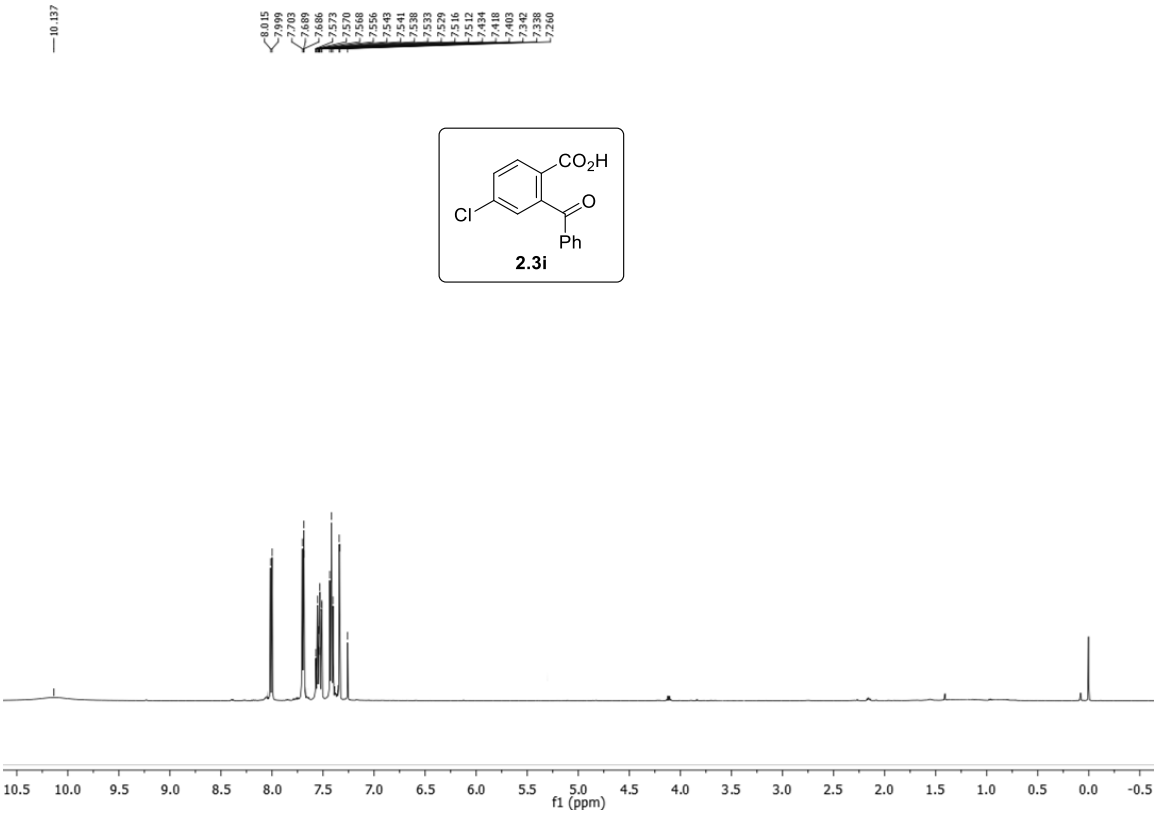

12.998
7.908
7.892
7.634
7.627
7.624
7.619
7.617
7.612
7.600
7.597
7.508
7.493
7.478
7.467
7.465
7.449
7.218

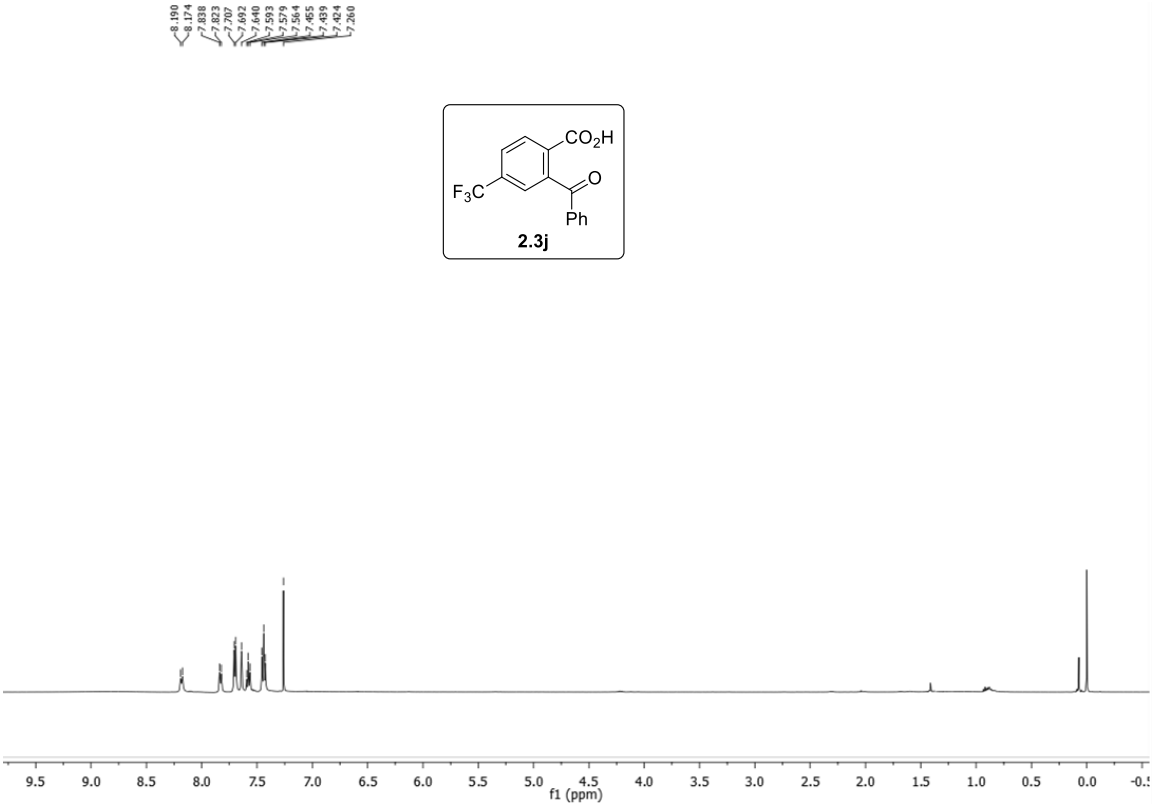
2.410


CO2H
O
Ph

2.3h


13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


10.137
8.015
7.999
7.703
7.689
7.686
7.573
7.570
7.568
7.556
7.543
7.541
7.538
7.533
7.529
7.516
7.512
7.434
7.418
7.403
7.342
7.338
7.260
CO2H
Cl
O
Ph
2.3i
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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8.174
7.838
7.823
7.707
7.692
7.640
7.593
7.579
7.564
7.465
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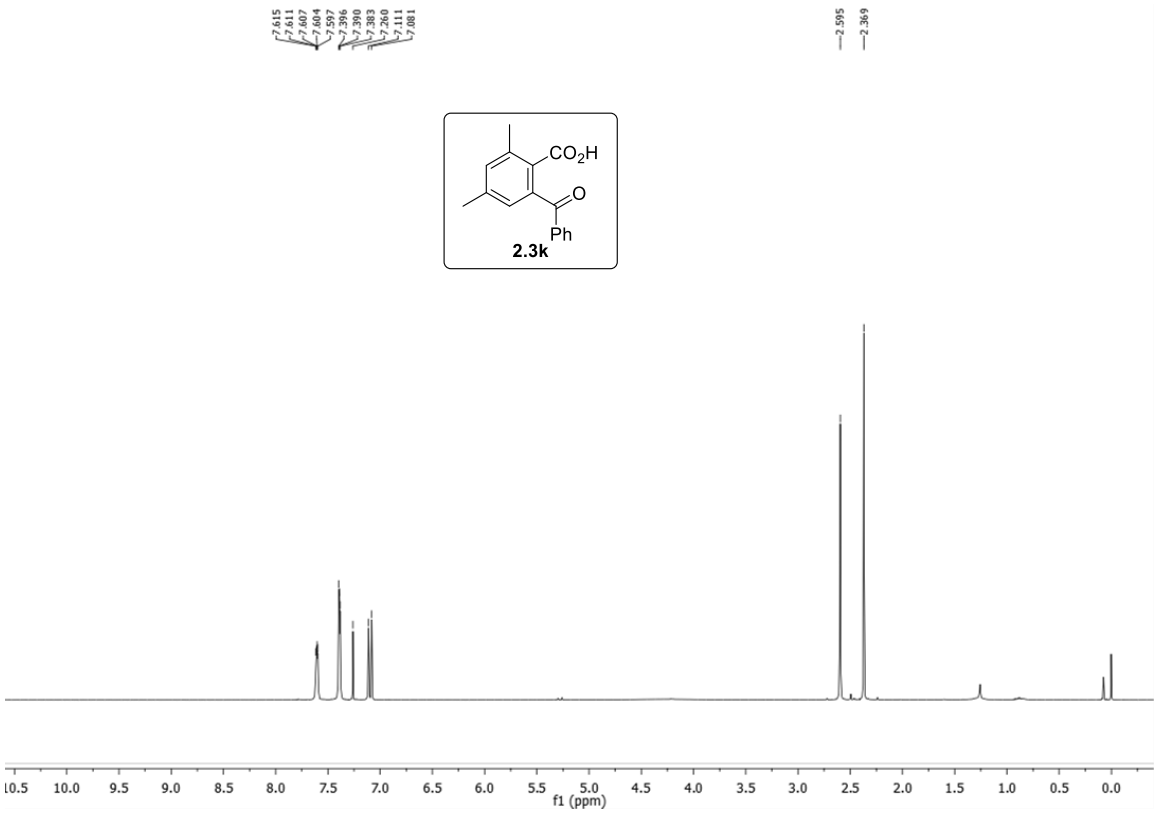
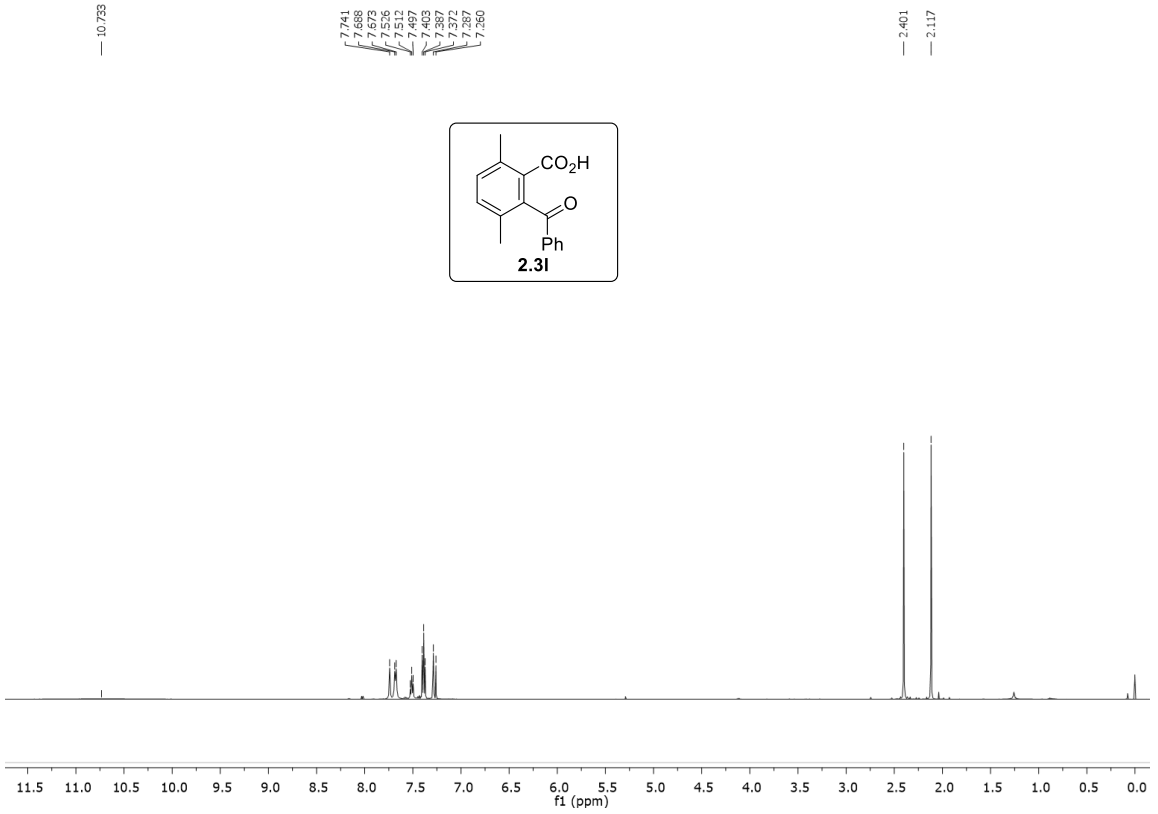
7.424
7.260
CO2H
F3C
O
Ph
2.3j
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


7.615
7.611
7.607
7.604
7.597
7.396
7.390
7.383
7.260
7.111
7.081
2.595
2.369
CO2H
O
Ph
2.3k
f1 (ppm)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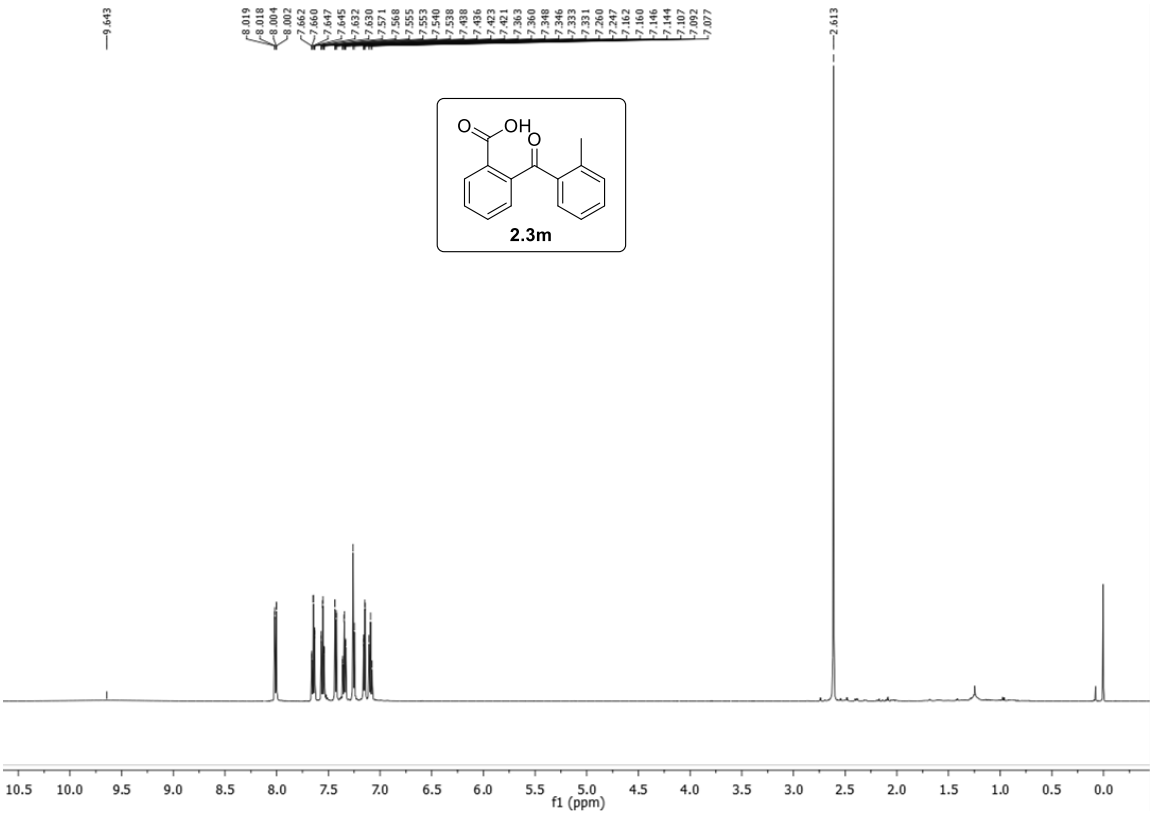
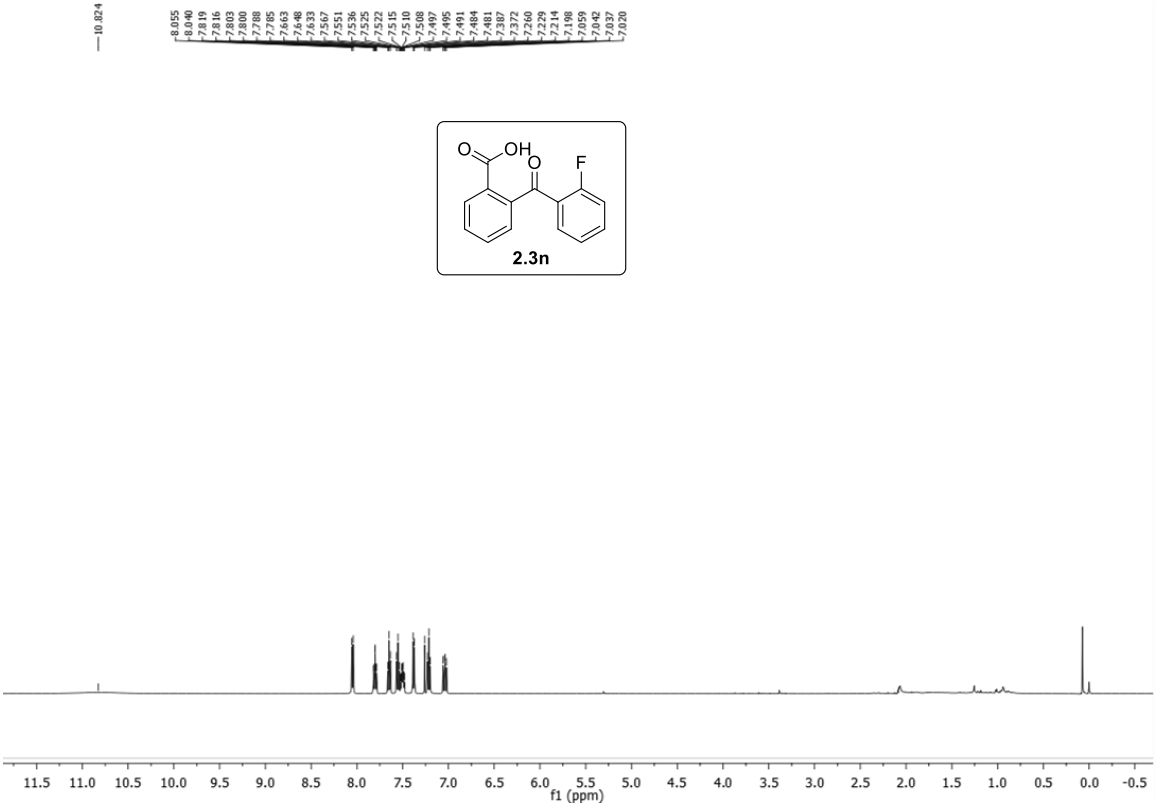
7.688
7.673
7.526
7.512
7.497
7.403
7.387
7.372
7.287
7.260
2.401
2.117
CO2H
O
Ph
2.3l
f1 (ppm)


9.643
8.019
8.018
8.004
8.002
7.662
7.660
7.647
7.645
7.632
7.630
7.571
7.568
7.555
7.553
7.540
7.538
7.438
7.436
7.423
7.421
7.363
7.360
7.348
7.346
7.333
7.331
7.260
7.247
7.162
7.160
7.146
7.144
7.107
7.092
7.077
2.613
O
OH
O
2.3m
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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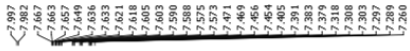
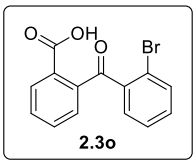
8.055
8.040
7.819
7.816
7.803
7.800
7.788
7.785
7.663
7.648
7.633
7.567
7.551
7.536
7.525
7.522
7.515
7.510
7.508
7.497
7.495
7.491
7.484
7.481
7.387
7.372
7.260
7.229
7.214
7.198
7.059
7.042
7.037
7.020
O
OH
O
F
2.3n
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

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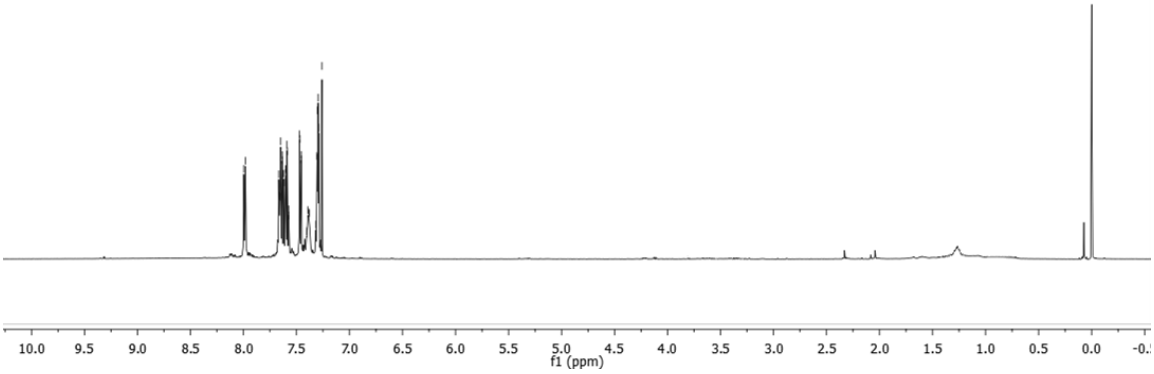
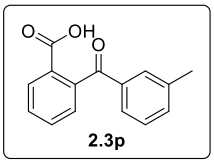
OH
O
Br

2.3o


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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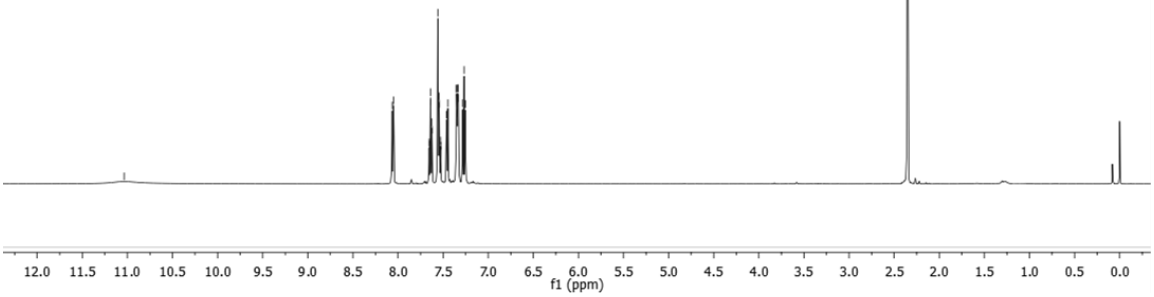
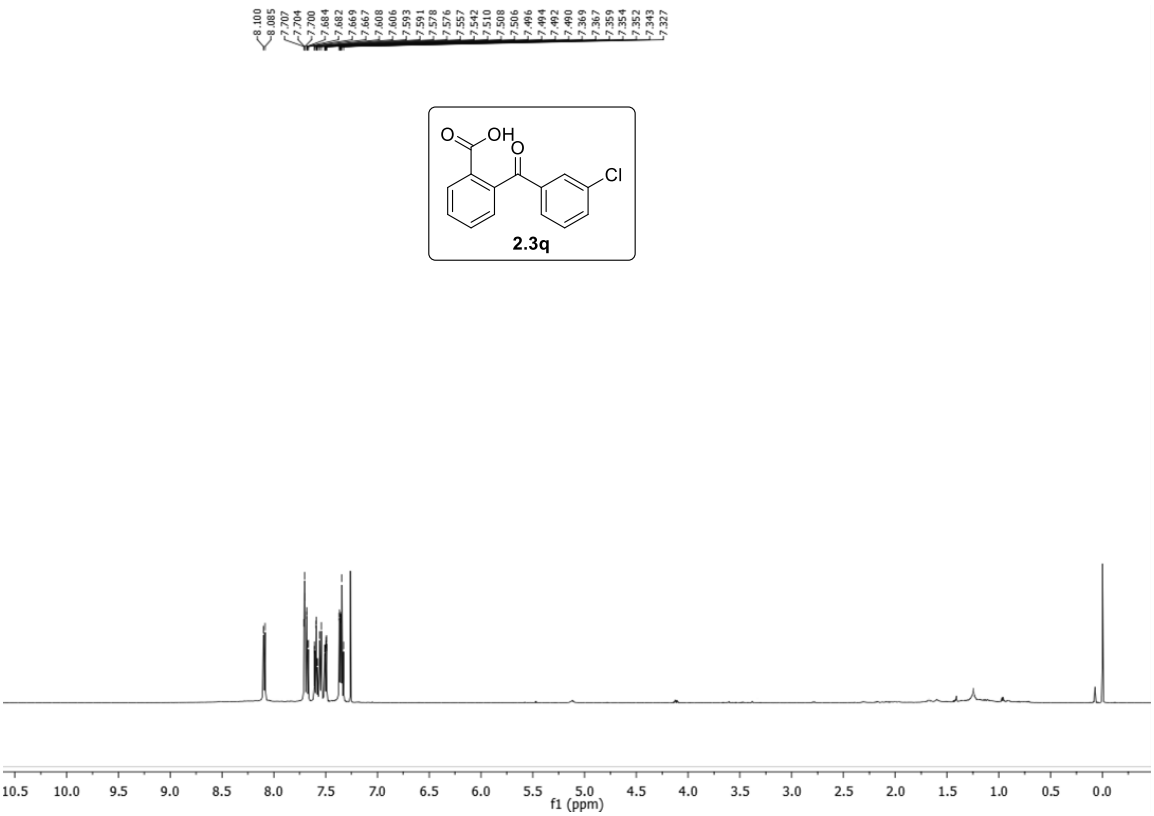
OH
O

2.3p


12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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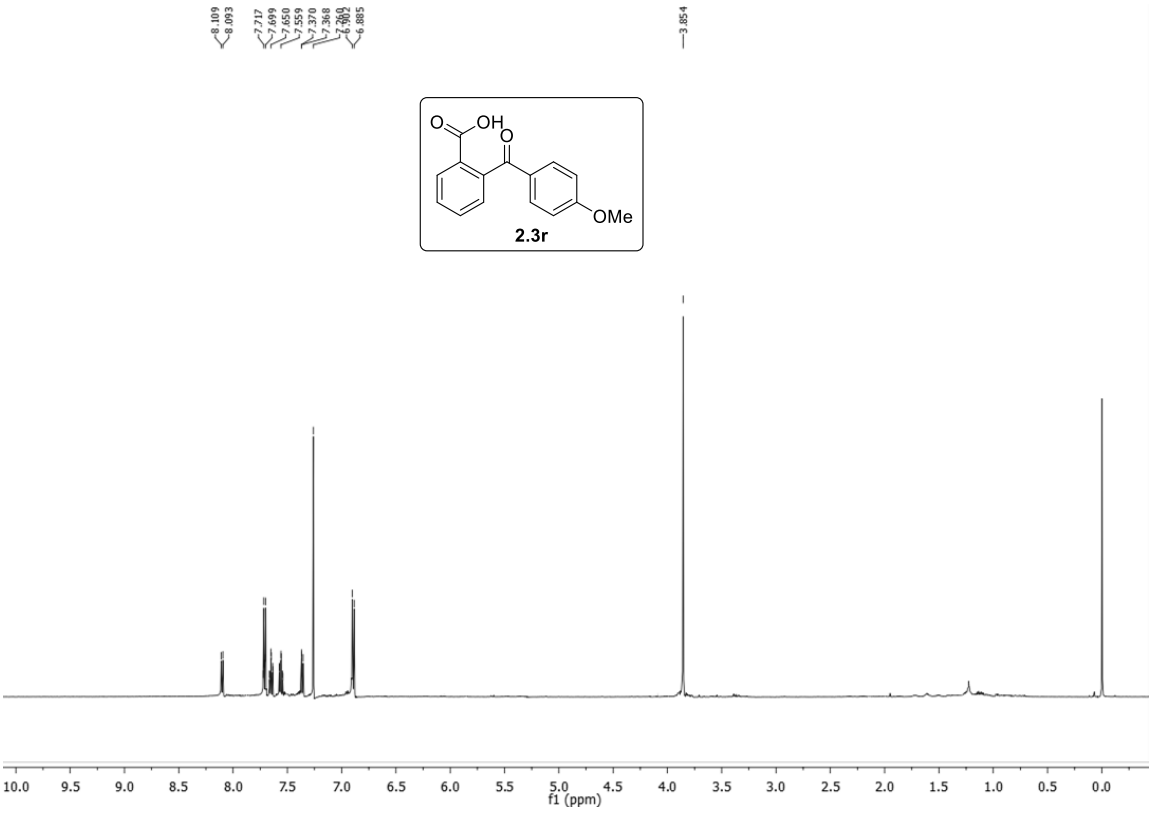
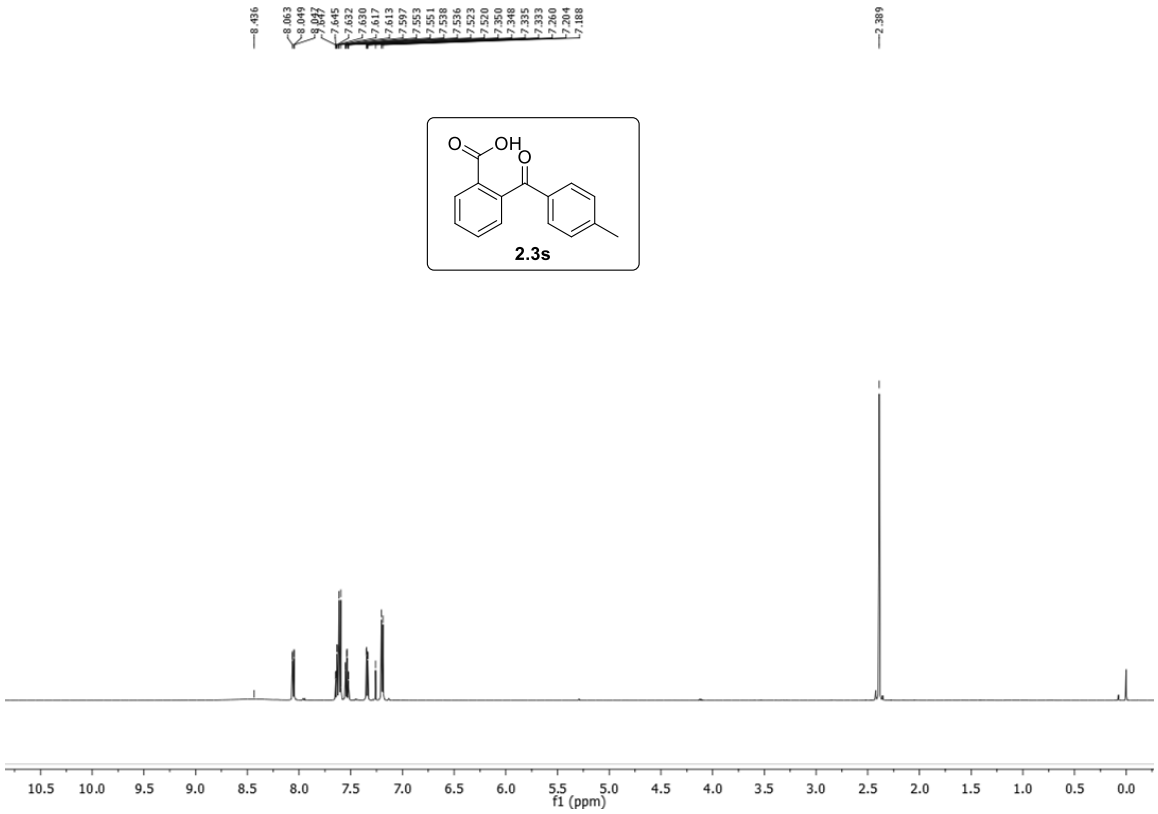
8.085
7.707
7.704
7.700
7.684
7.682
7.669
7.667
7.608
7.606
7.593
7.591
7.578
7.576
7.557
7.542
7.510
7.508
7.506
7.496
7.494
7.492
7.490
7.369
7.367
7.359
7.354
7.352
7.343
7.327
O
OH
O
Cl
2.3q
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


8.109
8.093
7.717
7.699
7.650
7.559
7.370
7.368
6.885
3.854
O
OH
O
OMe
2.3r
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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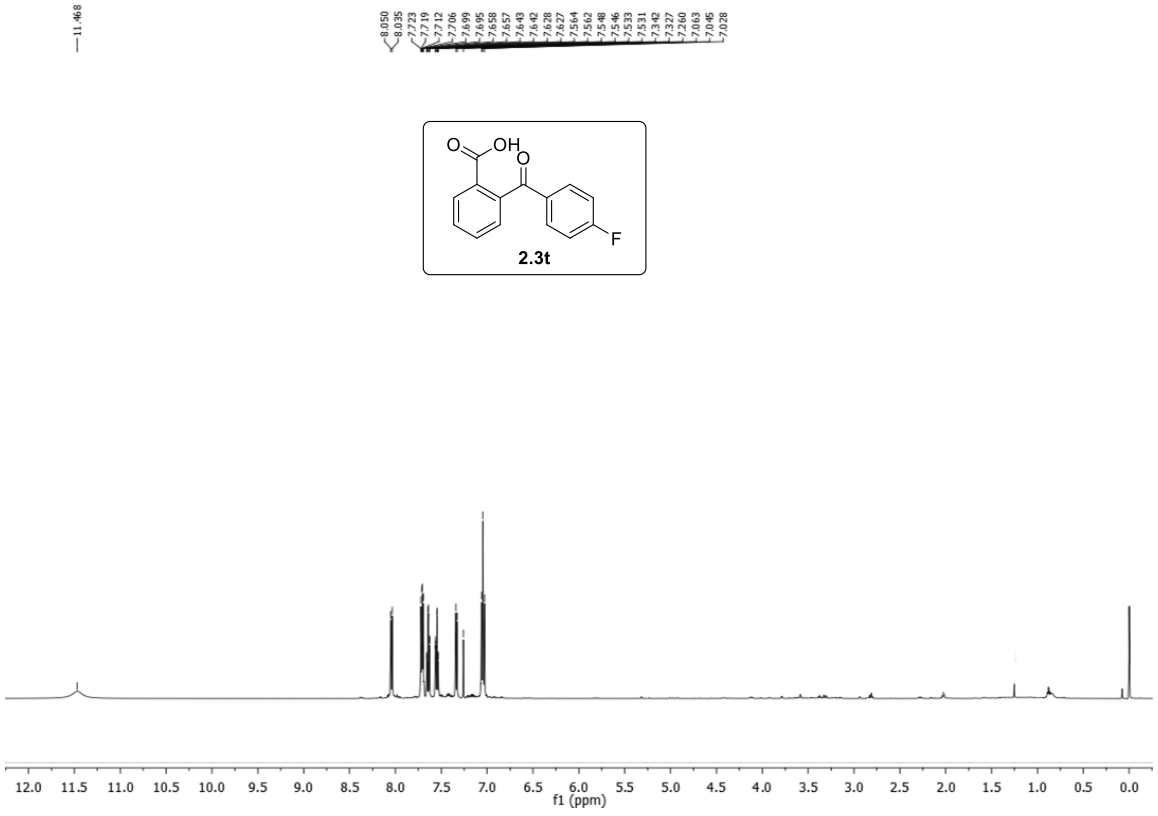
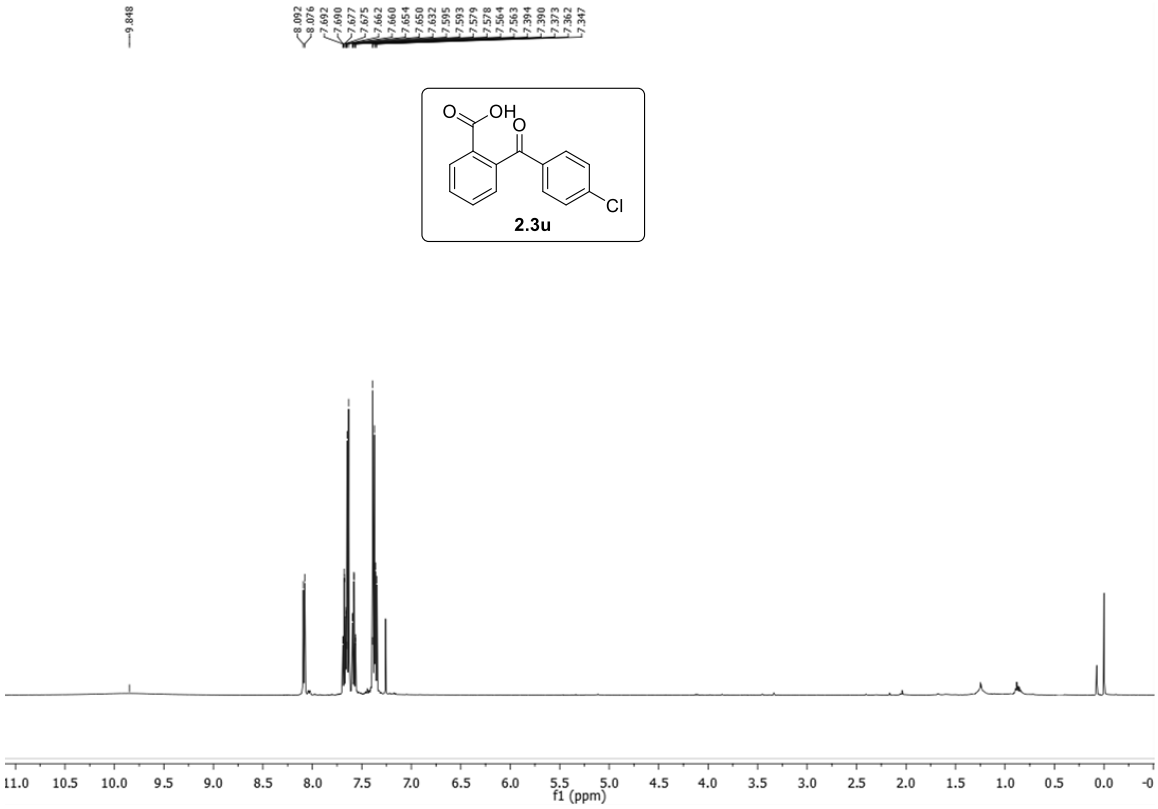
8.063
8.049
8.047
7.645
7.632
7.630
7.617
7.613
7.597
7.555
7.551
7.538
7.536
7.523
7.520
7.350
7.348
7.335
7.333
7.260
7.204
7.188
2.389
O
OH
O
2.3s
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


11.468
8.050
8.035
7.723
7.719
7.712
7.706
7.699
7.695
7.658
7.657
7.643
7.642
7.628
7.627
7.564
7.562
7.548
7.546
7.533
7.531
7.342
7.327
7.326
7.063
7.045
7.028
O
OH
O
F
2.3t
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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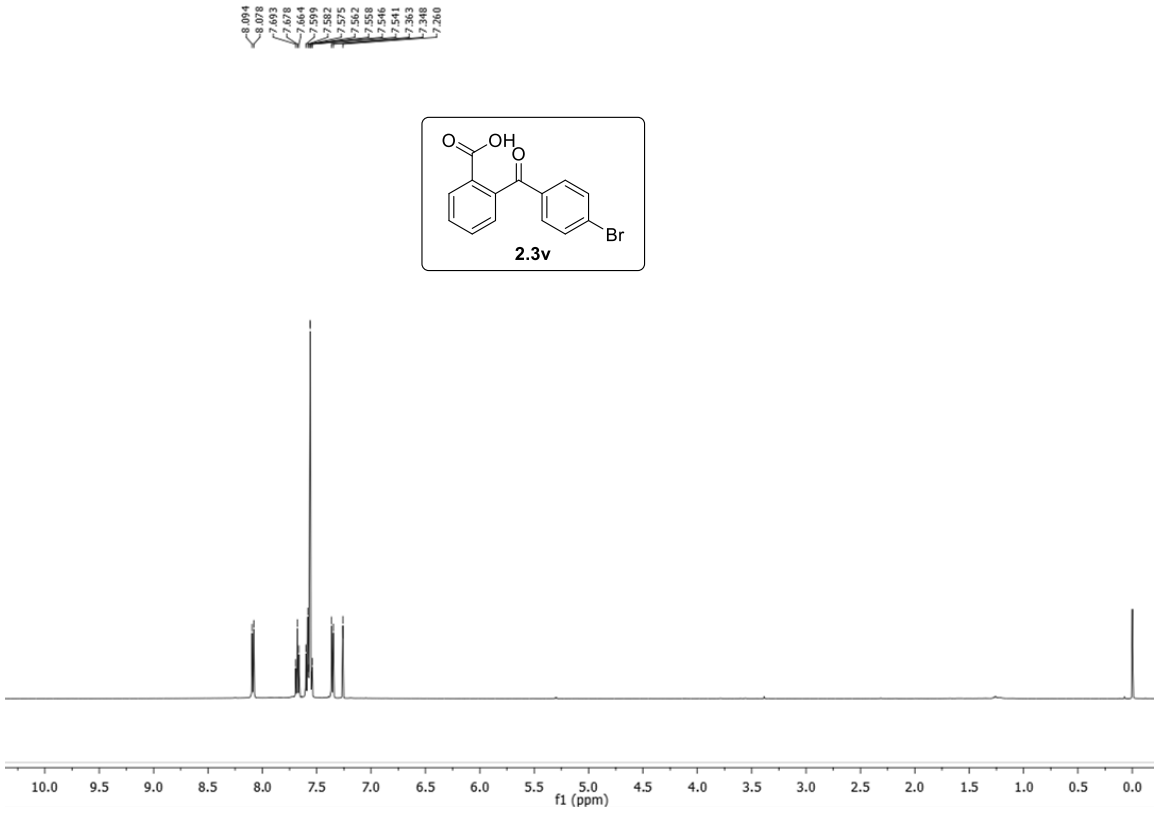
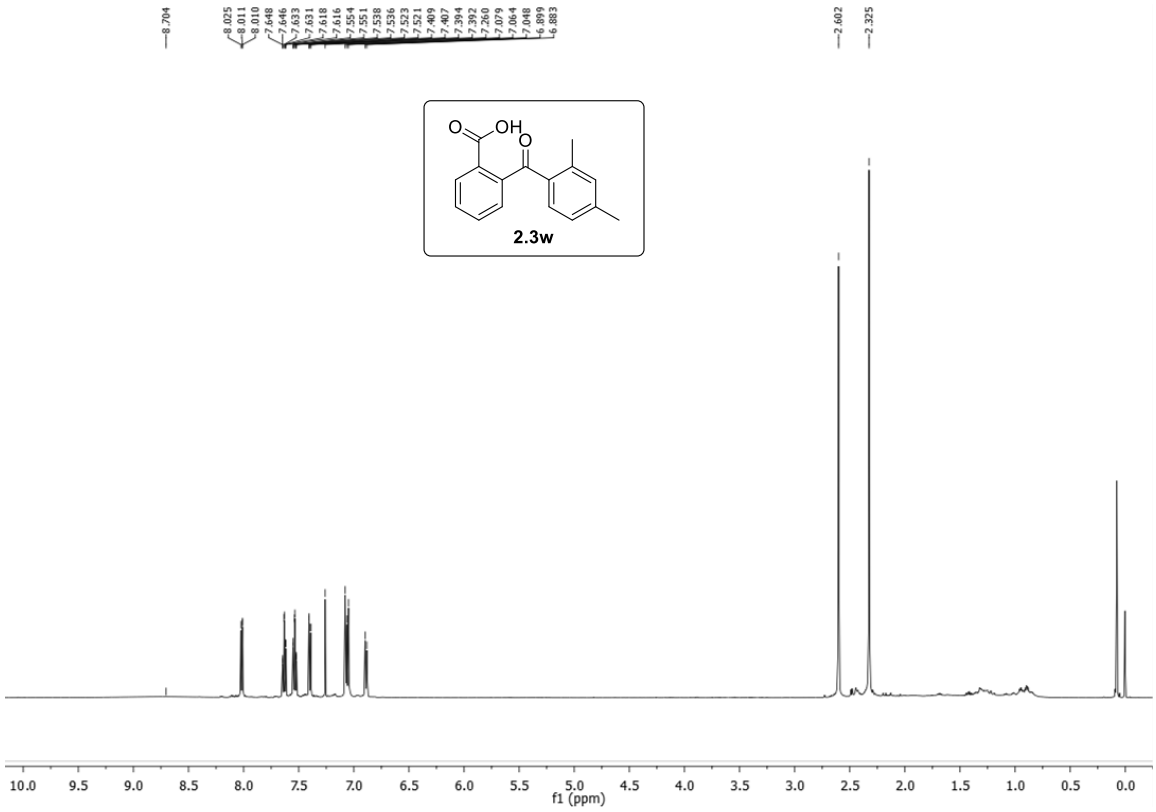
8.092
8.076
7.692
7.690
7.677
7.675
7.662
7.660
7.654
7.650
7.632
7.595
7.593
7.579
7.578
7.564
7.563
7.394
7.390
7.373
7.362
7.347
O
OH
O
Cl
2.3u
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


8.094
8.078
7.693
7.678
7.664
7.599
7.582
7.575
7.562
7.558
7.546
7.541
7.363
7.348
7.260
O
OH
O
Br
2.3v
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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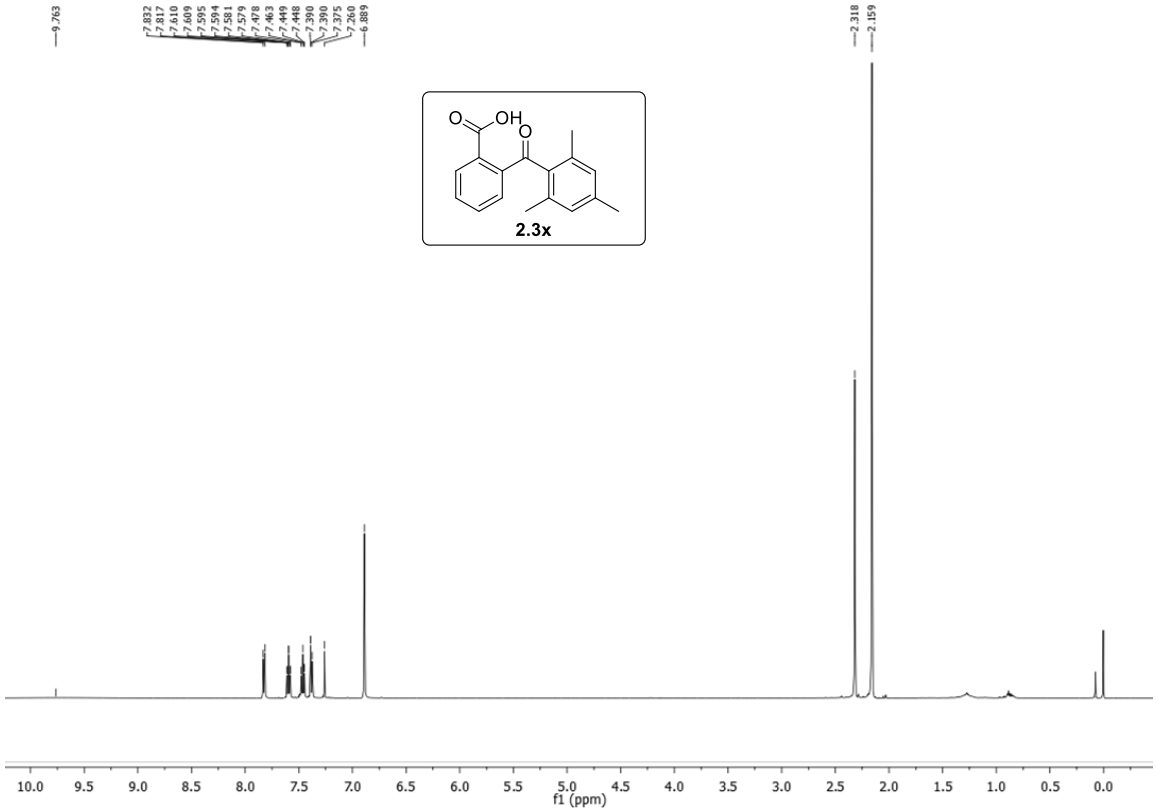
8.025
8.011
8.010
7.648
7.646
7.633
7.631
7.618
7.616
7.554
7.551
7.538
7.536
7.523
7.521
7.469
7.467
7.394
7.392
7.260
7.079
7.064
7.048
6.899
6.883
2.602
2.325
O
OH
O
2.3w
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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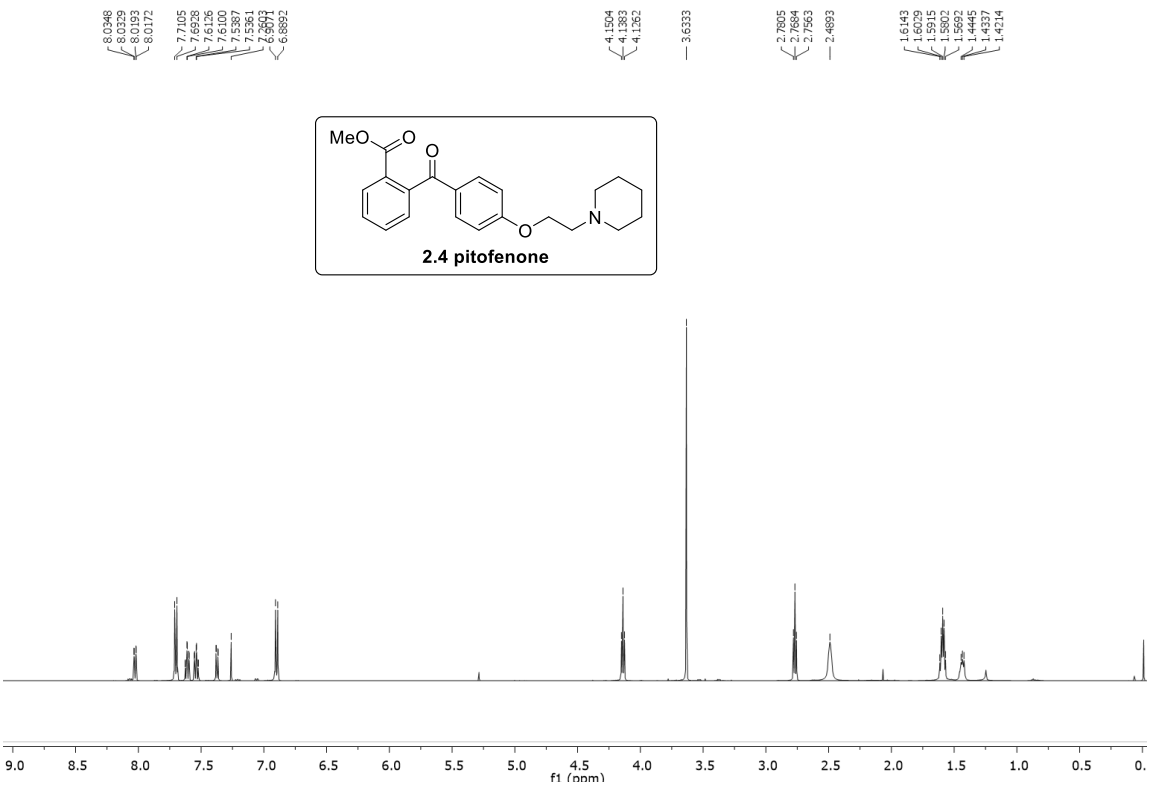
7.817
7.610
7.609
7.595
7.594
7.581
7.579
7.478
7.463
7.449
7.448
7.390
7.375
7.260
6.889
2.318
2.159
O
OH
O
2.3x
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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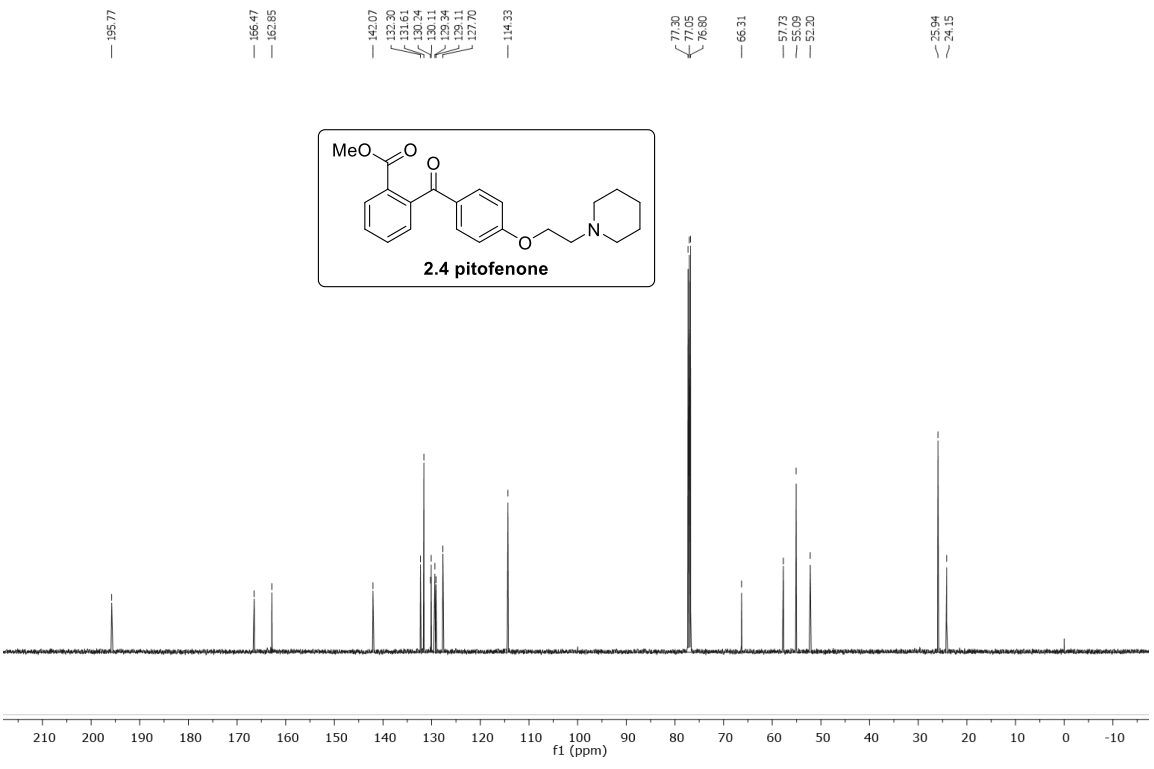
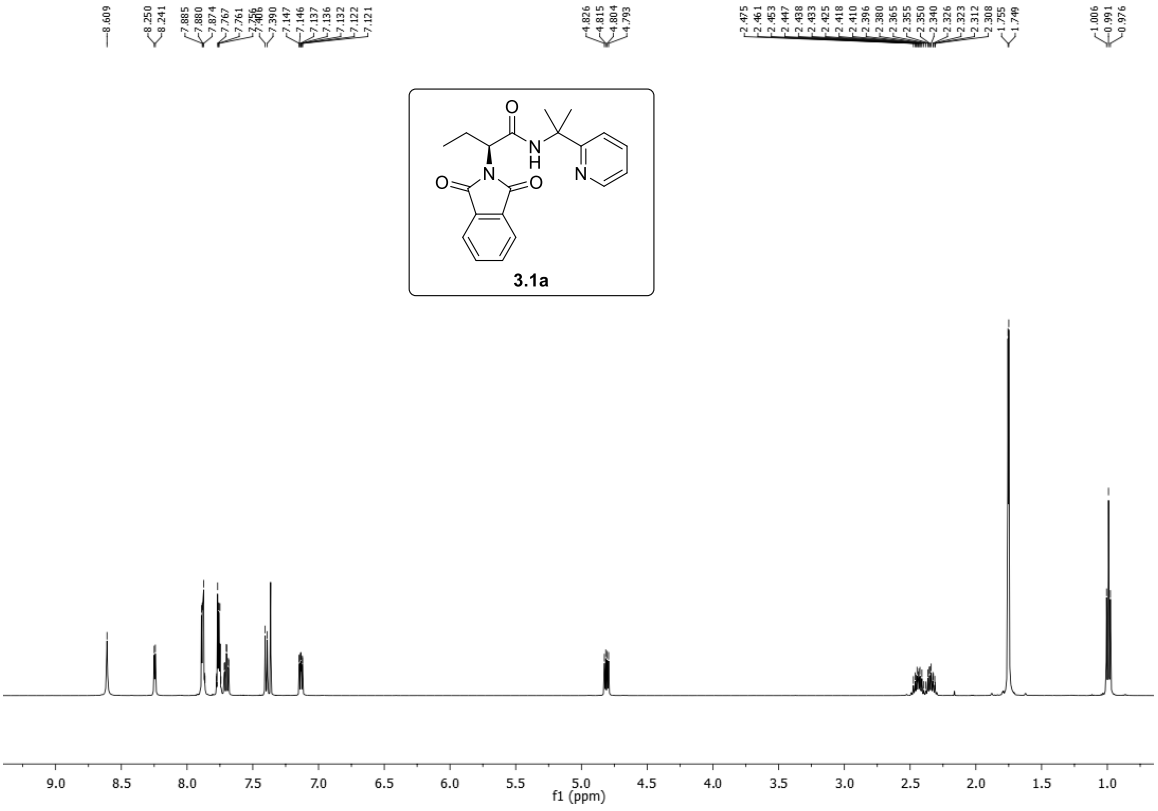
8.0193
8.0172
7.7105
7.6938
7.6126
7.6100
7.5387
7.5361
7.5263
6.9573
6.8892
4.1504
4.1383
4.1262
3.6333
2.7805
2.7684
2.7563
2.4893
1.6143
1.6029
1.5915
1.5802
1.5692
1.4445
1.4337
1.4214
MeO
O
O
O
N
2.4 pitofenone
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


195.77
166.47
162.85
142.07
132.30
131.61
130.24
130.11
129.34
129.11
127.70
114.33
77.30
77.05
76.80
66.31
57.73
55.09
52.20
25.94
24.15
MeO
O
O
O
N
2.4 pitofenone
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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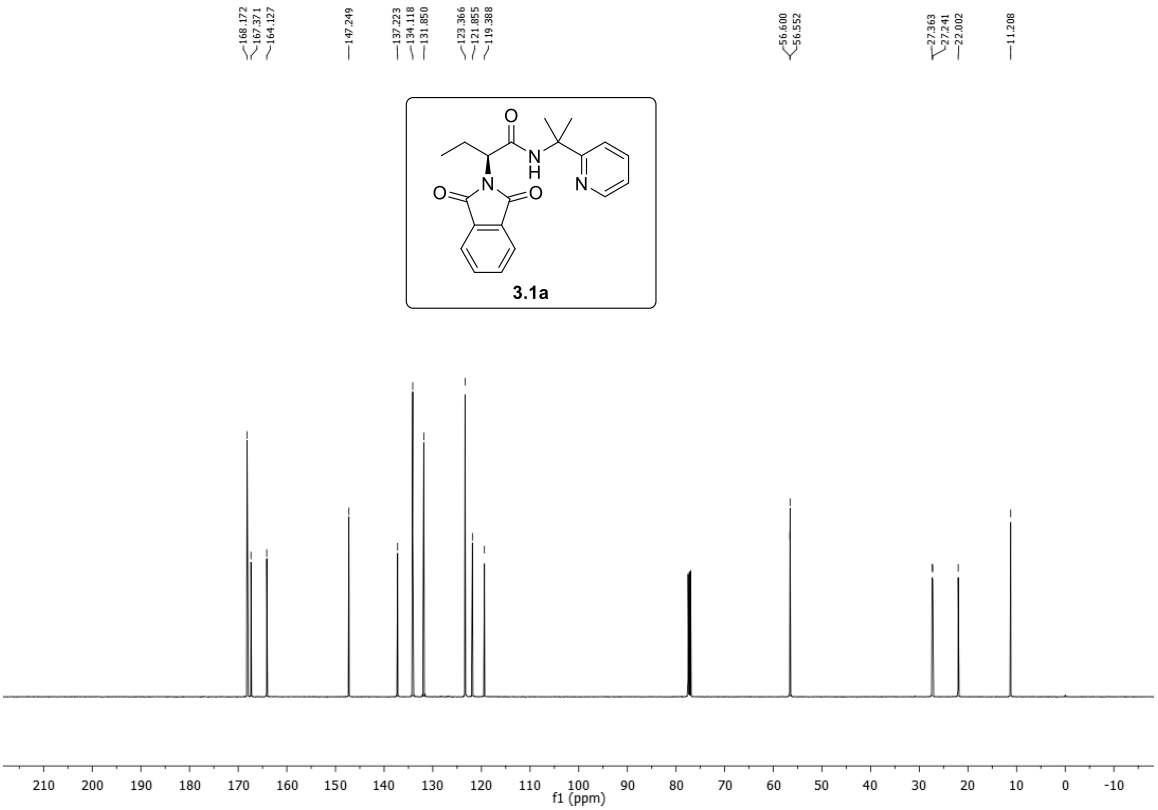
8.250
8.241
7.885
7.880
7.874
7.767
7.761
7.390
7.147
7.146
7.137
7.136
7.132
7.122
7.121
4.826
4.815
4.804
4.793
2.475
2.461
2.453
2.447
2.438
2.425
2.418
2.410
2.396
2.380
2.365
2.355
2.350
2.340
2.326
2.323
2.312
2.308
1.755
1.749
1.006
0.991
0.976
O
N
H
N
O
N
O
3.1a
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)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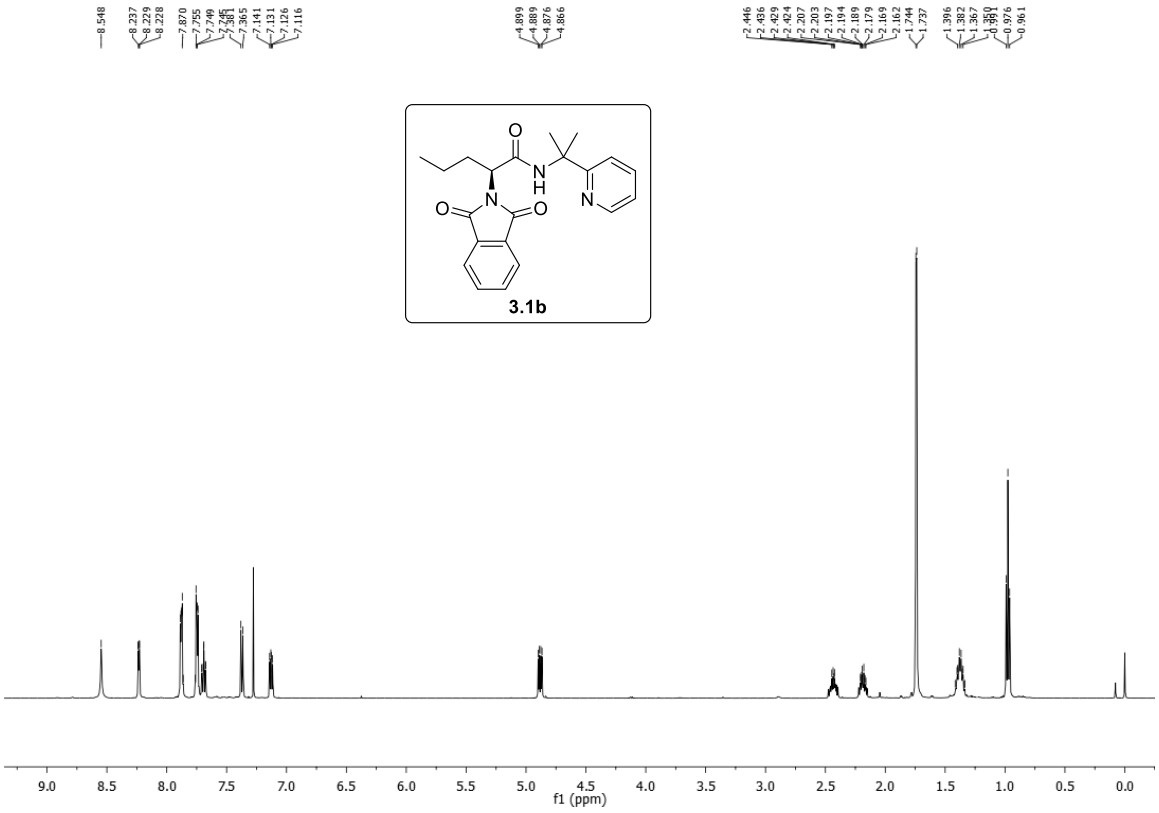
167.371
164.127
147.249
137.223
134.118
131.850
129.366
121.855
119.388
56.600
56.552
27.363
27.241
22.002
11.208
O
N
H
N
O
N
O
3.1a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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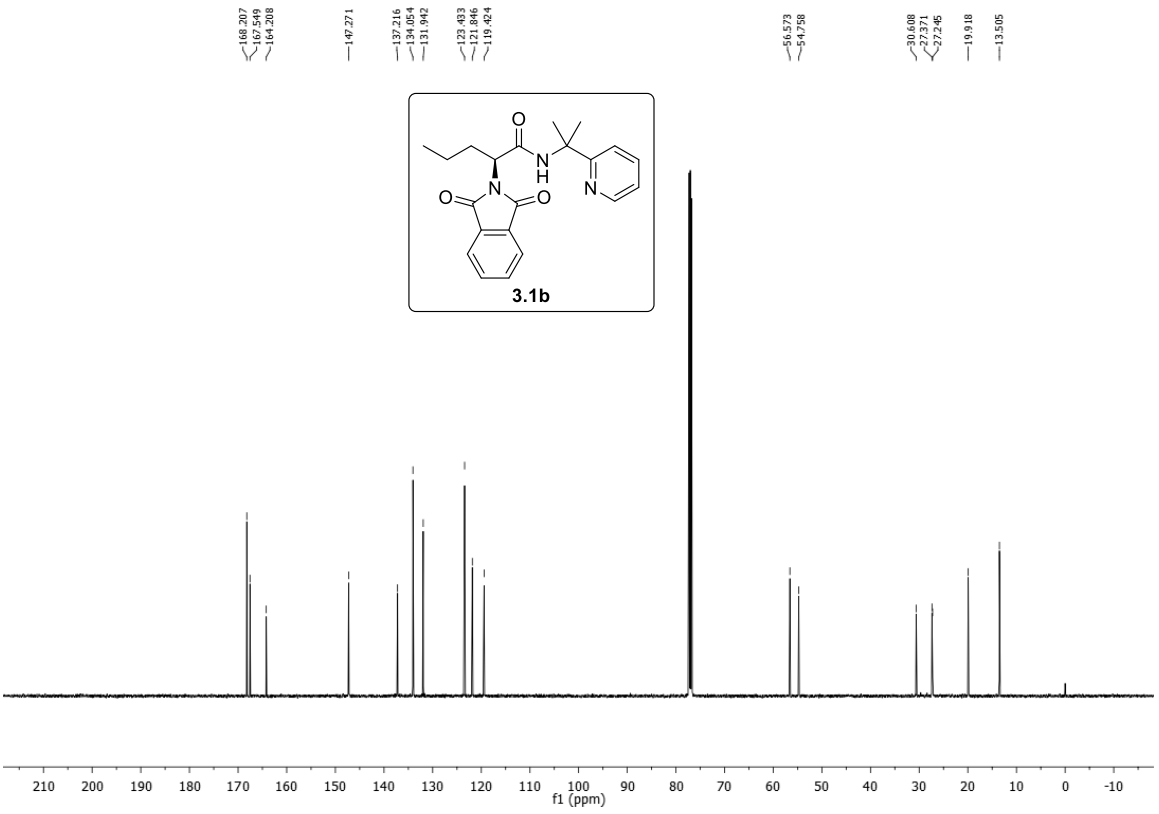
8.229
8.228
7.870
7.755
7.749
7.365
7.141
7.131
7.126
7.116
4.899
4.889
4.876
4.866
2.446
2.436
2.429
2.424
2.207
2.203
2.197
2.194
2.189
2.179
2.169
2.162
1.744
1.737
1.396
1.382
1.367
1.350
0.991
0.976
0.961
O
N
H
N
O
N
O
3.1b
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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164.208
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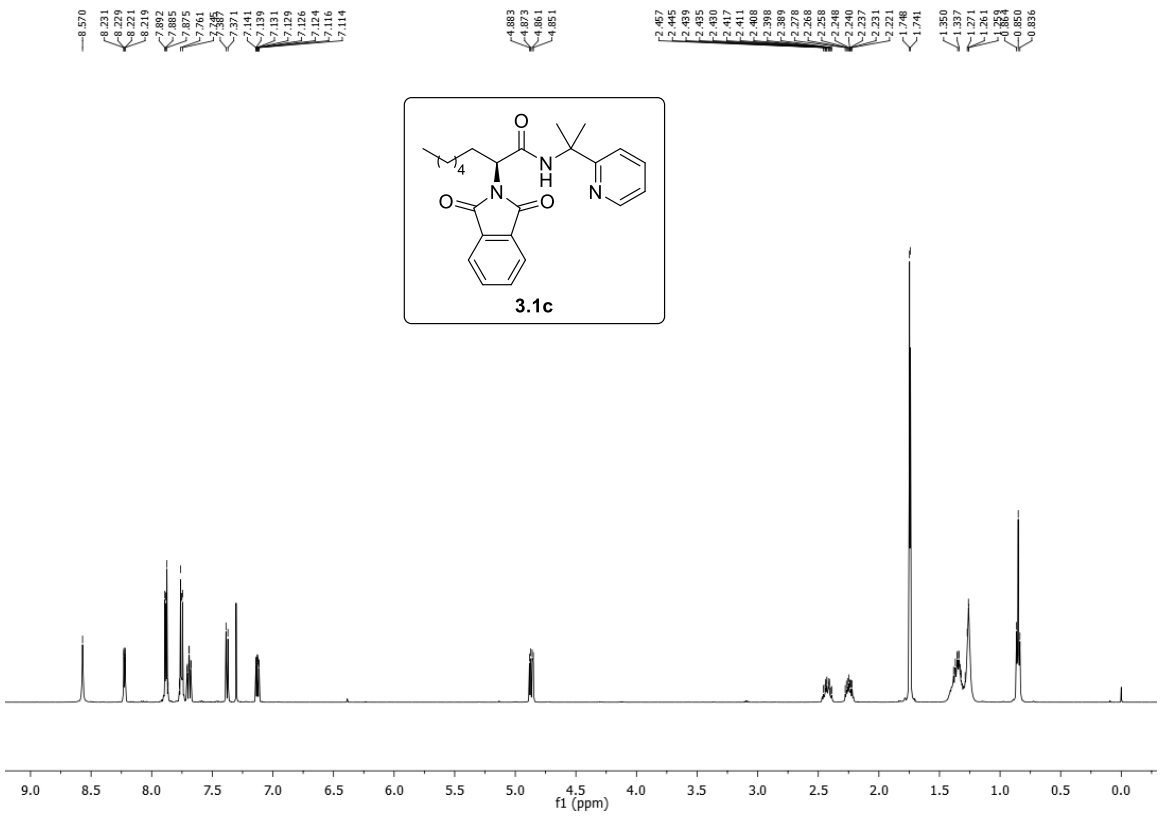
137.216
134.054
131.942
123.433
121.846
119.424
56.573
54.758
30.608
27.371
27.245
19.918
13.505
O
N
H
N
O
N
O
3.1b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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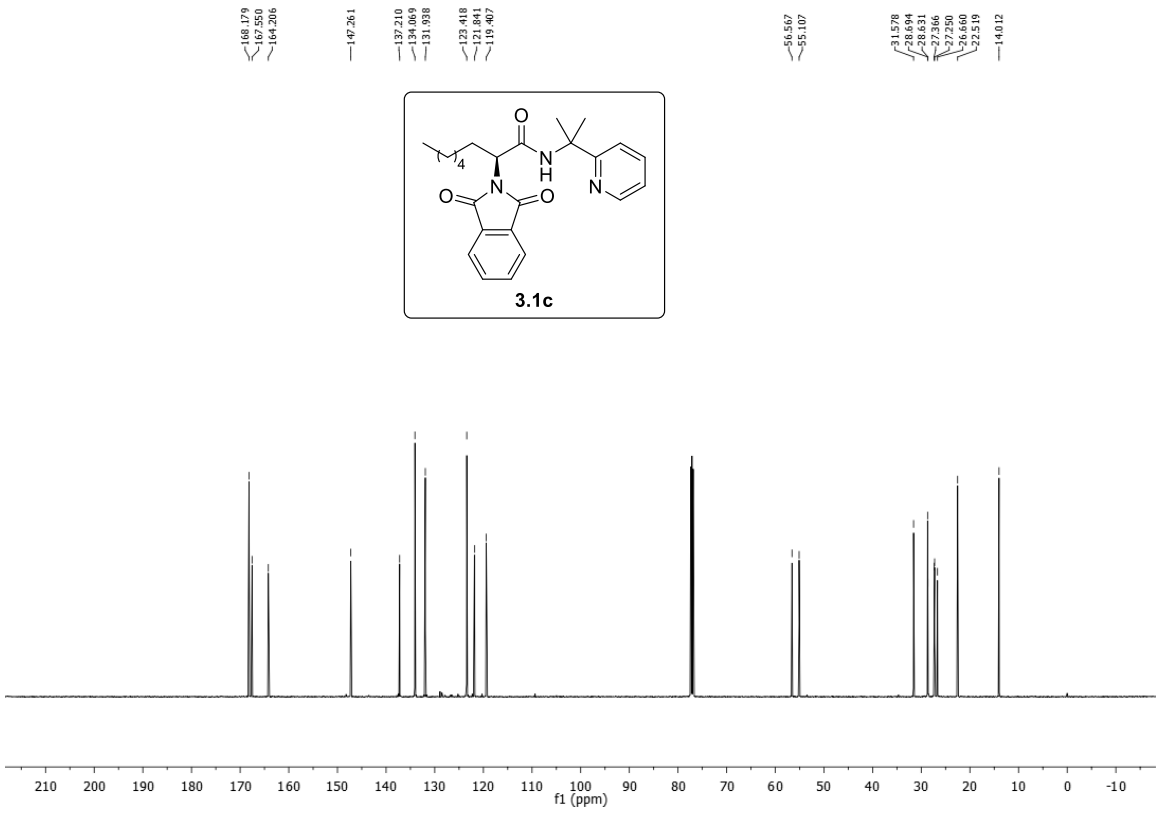
8.221
8.219
7.892
7.885
7.875
7.761
7.371
7.141
7.139
7.131
7.129
7.126
7.124
7.116
7.114
4.883
4.873
4.861
4.851
2.467
2.445
2.439
2.435
2.430
2.417
2.411
2.408
2.398
2.388
2.278
2.268
2.258
2.248
2.240
2.237
2.231
2.221
1.748
1.741
1.350
1.337
1.271
1.261
0.850
0.836
3.1c
f1 (ppm)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164.206
147.261
137.210
134.069
131.938
123.418
121.841
119.407
56.567
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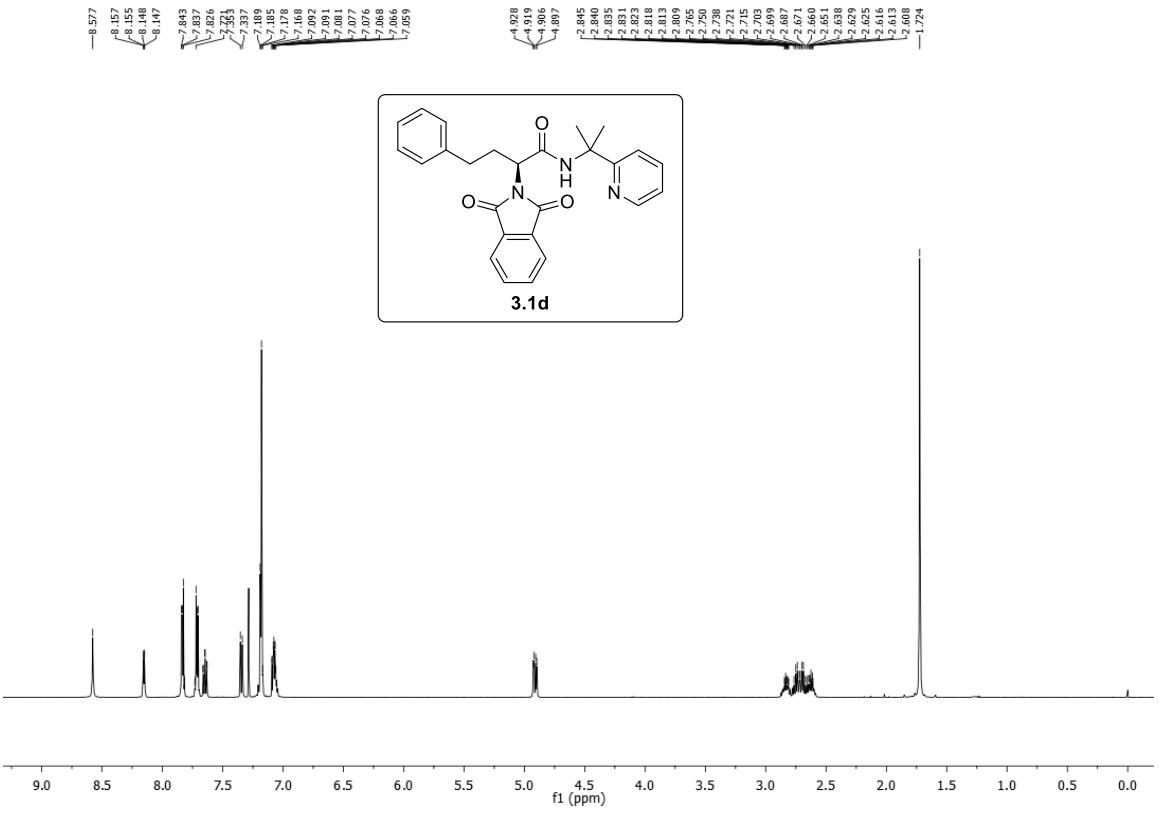
31.578
28.694
28.631
27.366
27.250
26.660
22.519
14.012
3.1c
f1 (ppm)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8.155
8.148
8.147
7.843
7.837
7.826
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7.189
7.185
7.178
7.168
7.092
7.091
7.081
7.077
7.076
7.068
7.066
7.059
4.928
4.919
4.906
4.897
2.845
2.840
2.835
2.831
2.823
2.818
2.813
2.809
2.765
2.750
2.738
2.721
2.715
2.703
2.699
2.687
2.671
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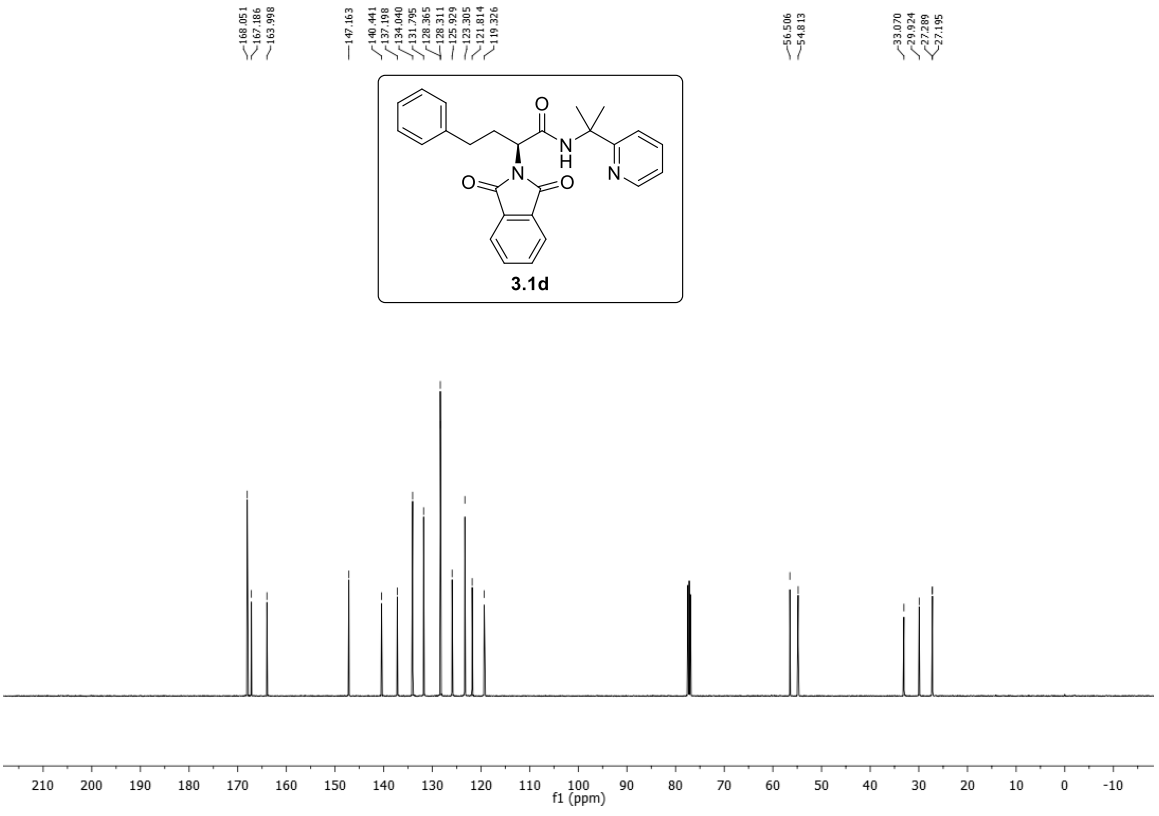
2.638
2.629
2.625
2.616
2.613
2.608
1.724
3.1d
f1 (ppm)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167.186
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147.163
140.441
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134.040
131.795
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128.311
125.929
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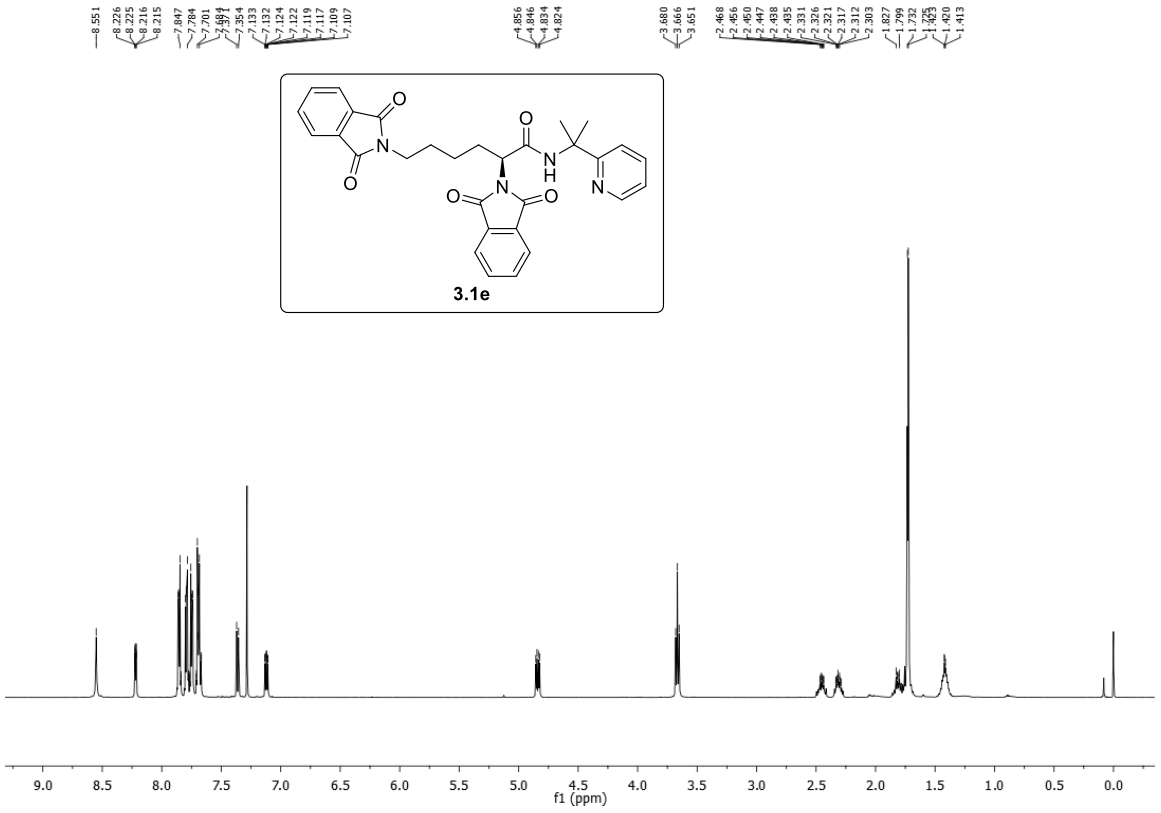
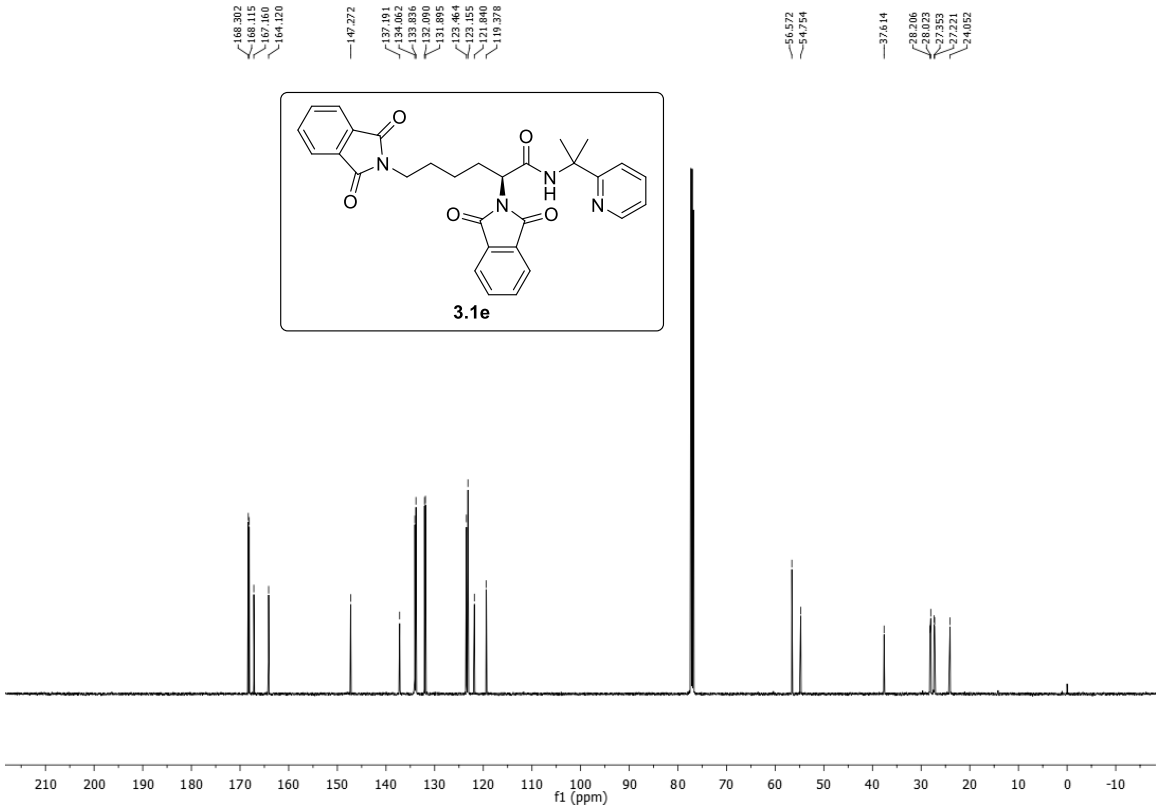
121.814
119.326
56.506
54.813
33.070
29.924
27.289
27.195
3.1d
f1 (ppm)


8.551
8.226
8.225
8.216
8.215
7.847
7.784
7.701
7.691
7.354
7.133
7.132
7.124
7.122
7.119
7.117
7.109
7.107
4.856
4.846
4.834
4.824
3.680
3.666
3.651
2.468
2.456
2.450
2.447
2.438
2.435
2.331
2.326
2.321
2.317
2.312
2.303
1.827
1.799
1.732
1.425
1.420
1.413
3.1e
f1 (ppm)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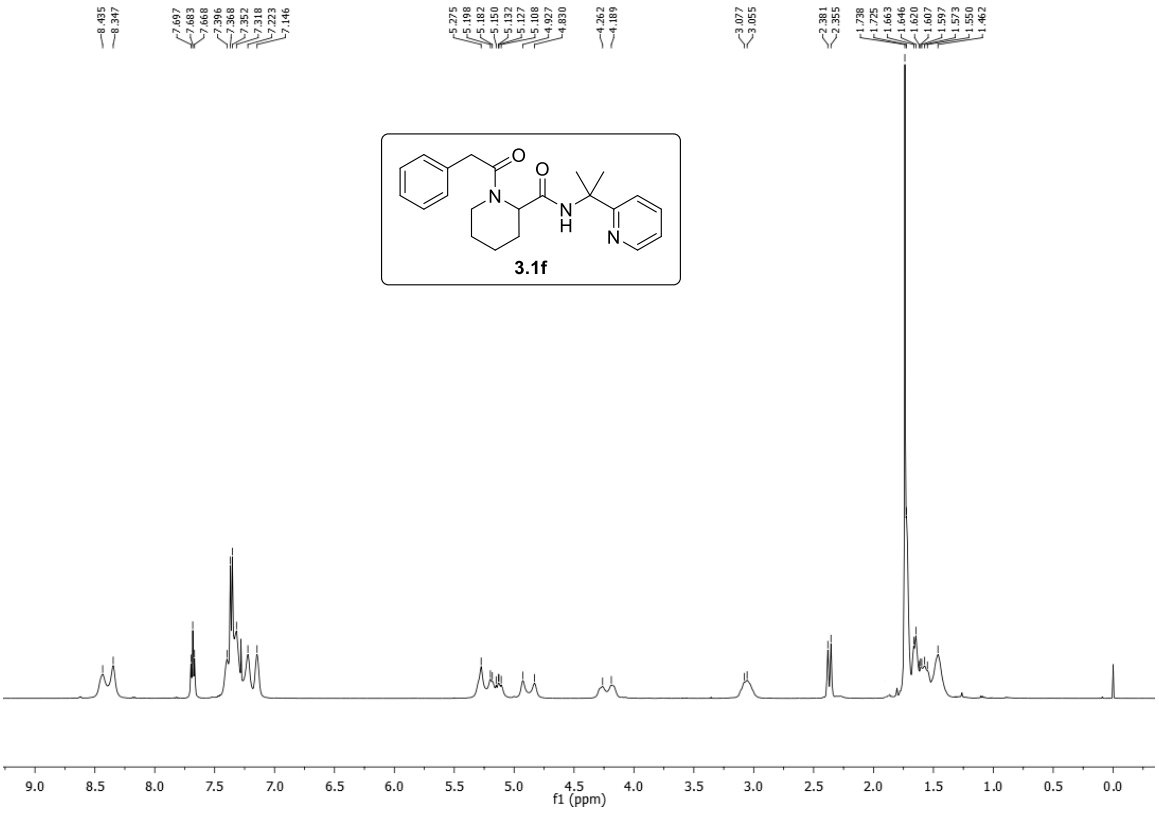
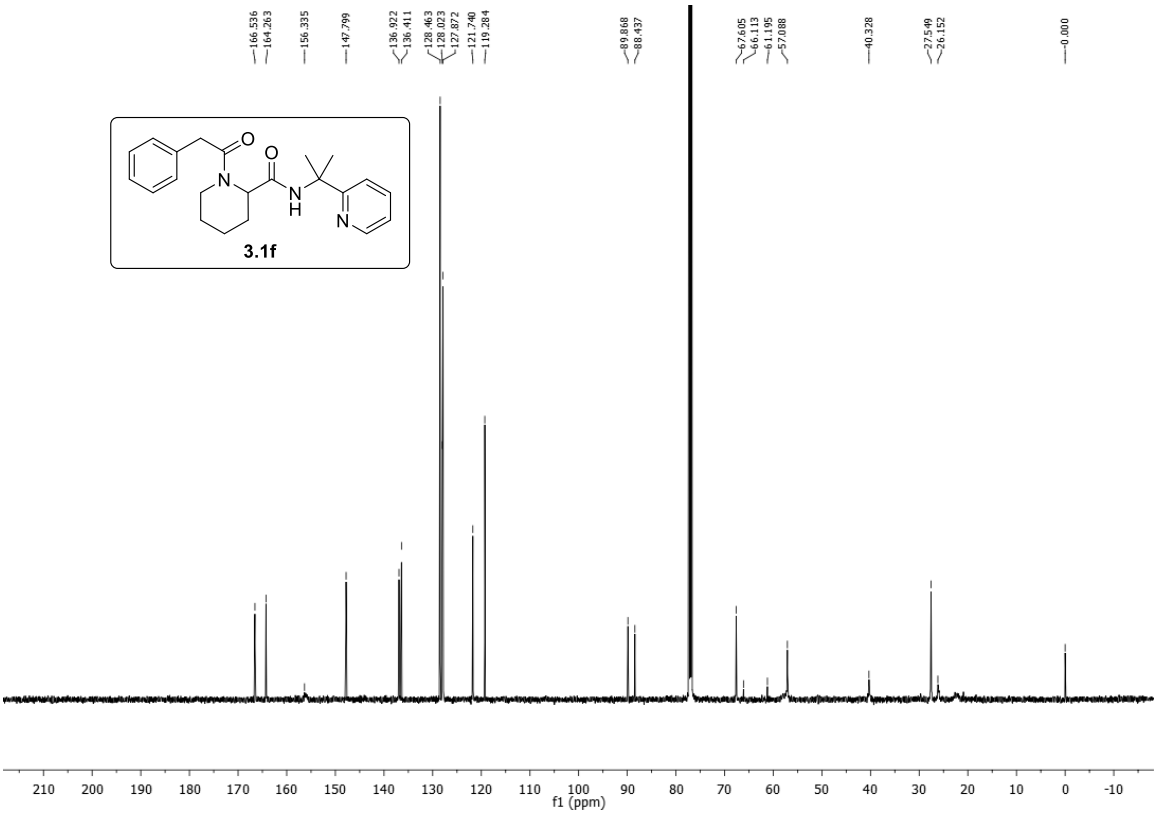
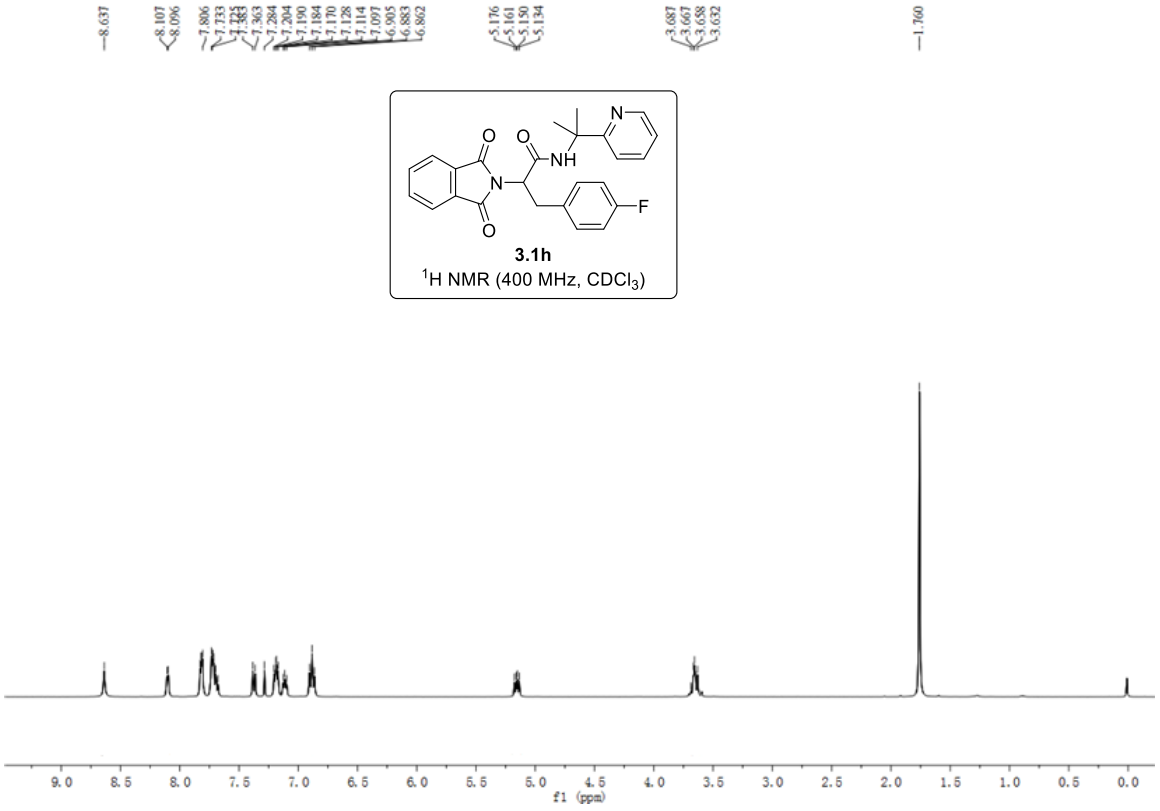
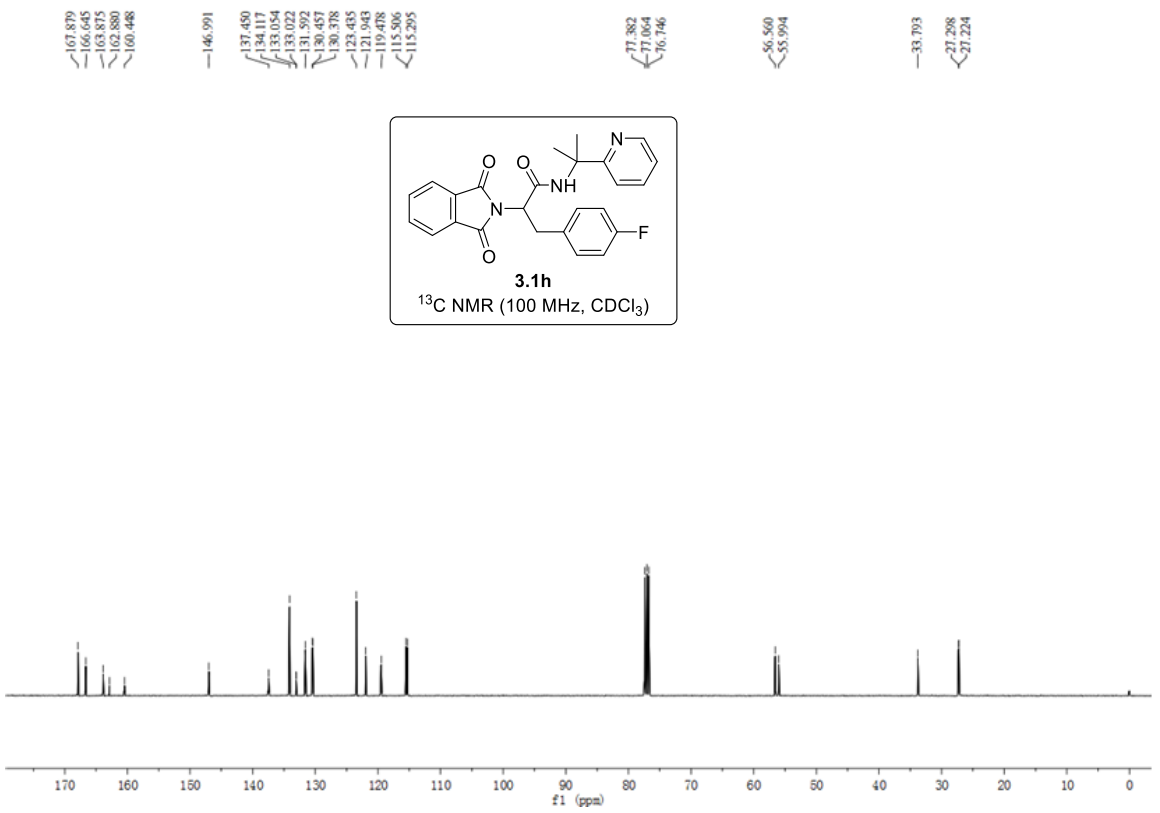
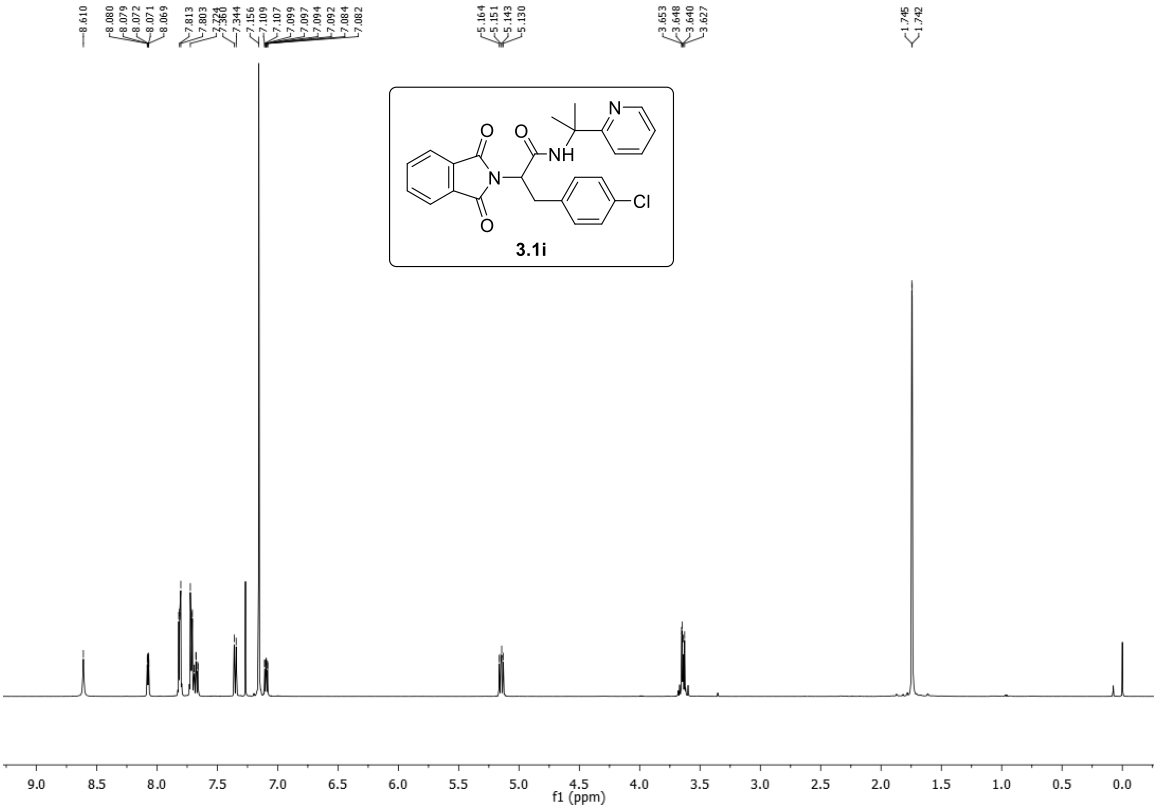
168.115
167.160
164.120
147.272
137.191
134.062
133.836
132.090
131.895
123.464
123.155
121.840
119.378
56.572
54.754
37.614
28.206
28.023
27.353
27.221
24.052
3.1e
f1 (ppm)

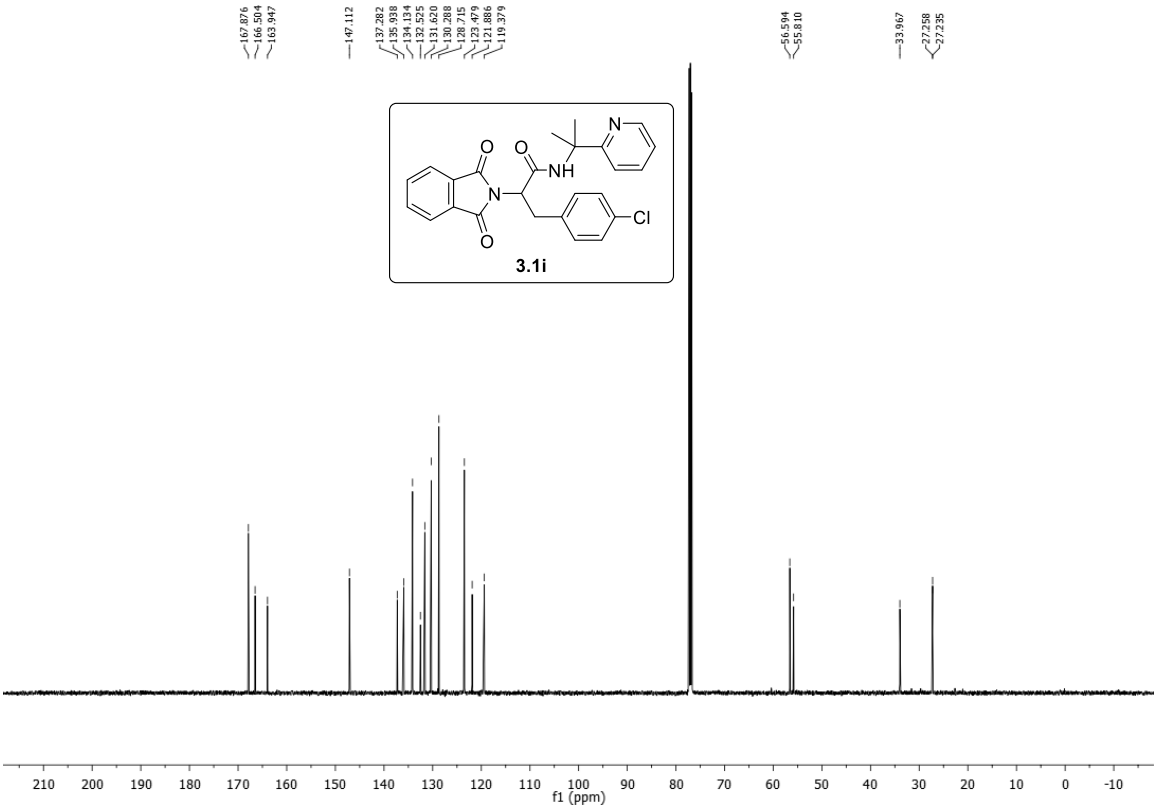

8.435
8.347
7.697
7.683
7.668
7.396
7.368
7.352
7.318
7.223
7.146
5.275
5.198
5.182
5.150
5.132
5.127
5.108
4.927
4.830
4.262
4.189
3.077
3.055
2.381
2.355
1.738
1.725
1.663
1.646
1.620
1.607
1.597
1.573
1.550
1.462
3.1f
f1 (ppm)

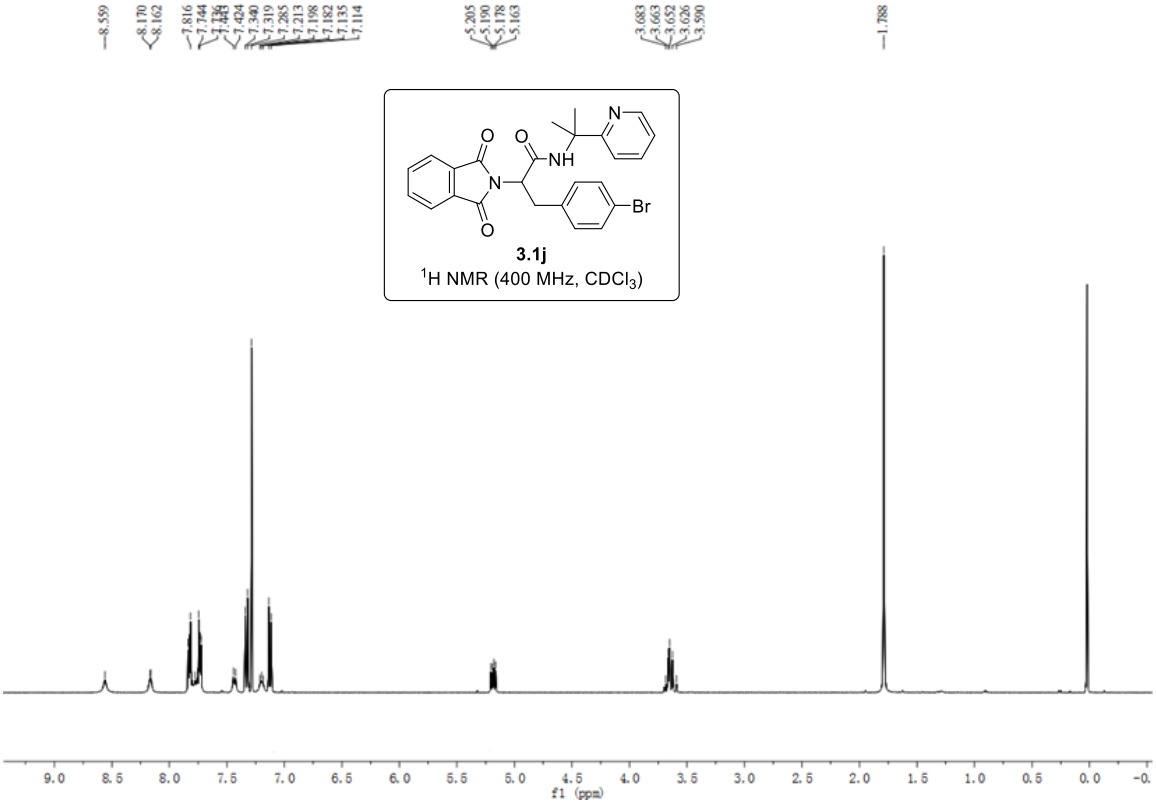

166.536
164.263
156.335
147.799
136.922
136.411
128.463
128.023
127.872
121.740
119.284
89.868
88.437
67.605
66.113
61.195
57.088
40.328
27.549
26.152
0.000
3.1f
f1 (ppm)

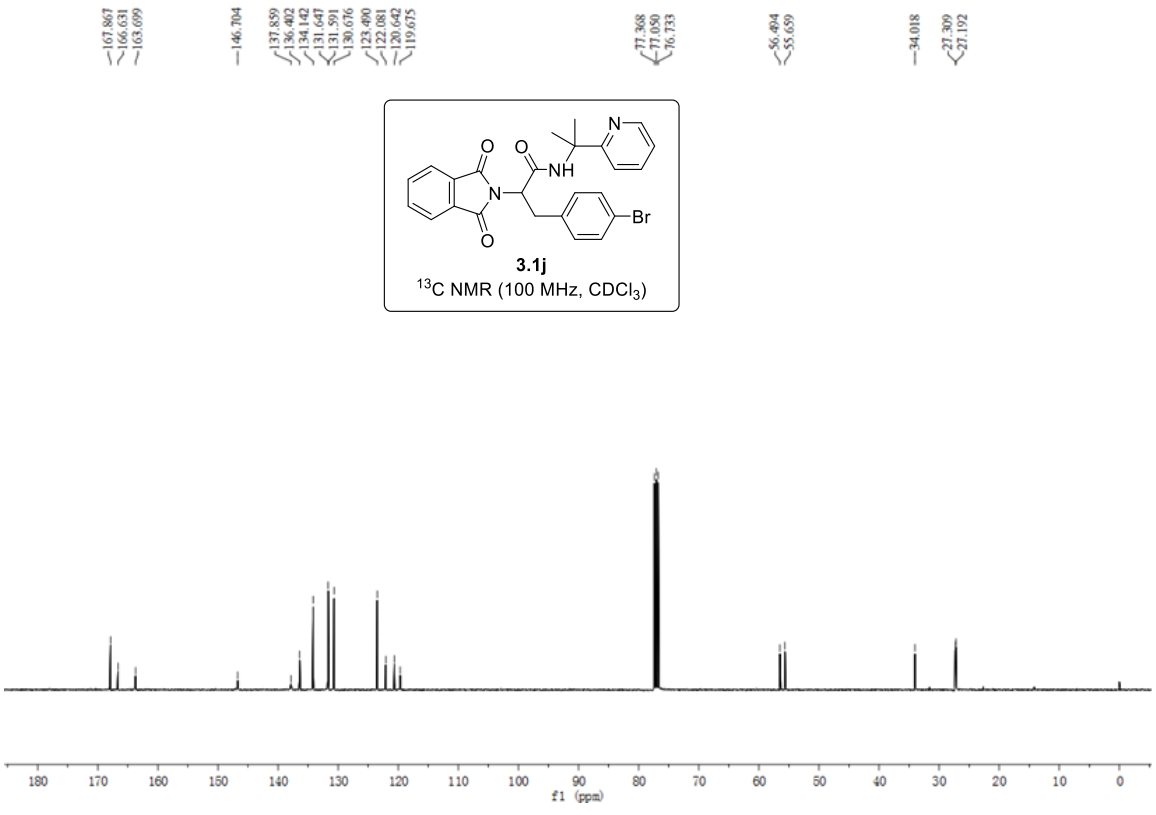

8.637
8.107
8.096
7.806
7.733
7.363
7.284
7.204
7.190
7.184
7.170
7.128
7.114
7.097
6.905
6.883
6.862
5.176
5.161
5.150
5.134
3.687
3.667
3.658
3.632
1.760
O
O
NH
N
N
O
O
F
3.1h
1H NMR (400 MHz, CDCl3)
f1 (ppm)

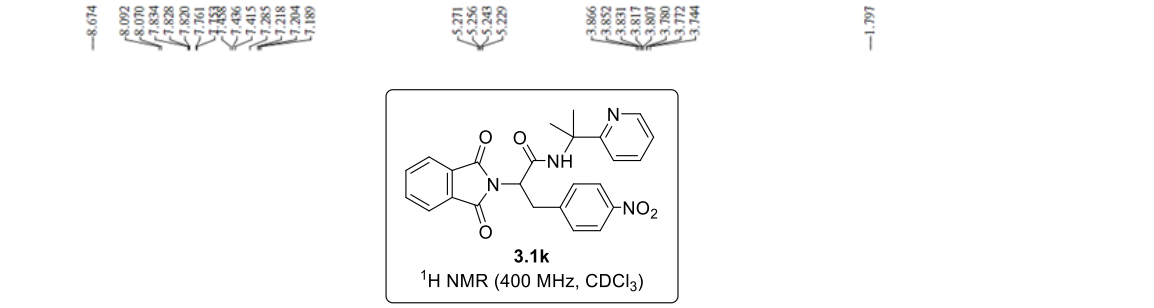

167.879
166.645
163.875
162.880
160.448
146.991
137.450
134.117
133.054
133.022
131.592
130.457
130.378
123.435
121.943
119.478
115.506
115.295
77.382
77.064
76.746
56.560
55.994
33.793
27.298
27.224
O
O
NH
N
N
O
O
F
3.1h
13C NMR (100 MHz, CDCl3)
f1 (ppm)


8.610
8.080
8.079
8.072
8.071
8.069
7.813
7.803
7.724
7.360
7.344
7.156
7.109
7.107
7.099
7.097
7.094
7.092
7.084
7.082
5.164
5.151
5.143
5.130
3.653
3.648
3.640
3.627
1.745
1.742
O
O
NH
N
N
O
O
Cl
3.1i
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


167.876
166.504
163.947
147.112
137.282
135.938
134.134
132.525
131.620
130.288
128.715
123.479
121.886
119.379
56.594
55.810
33.967
27.358
27.235
O
O
NH
N
N
O
O
Cl
3.1i
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

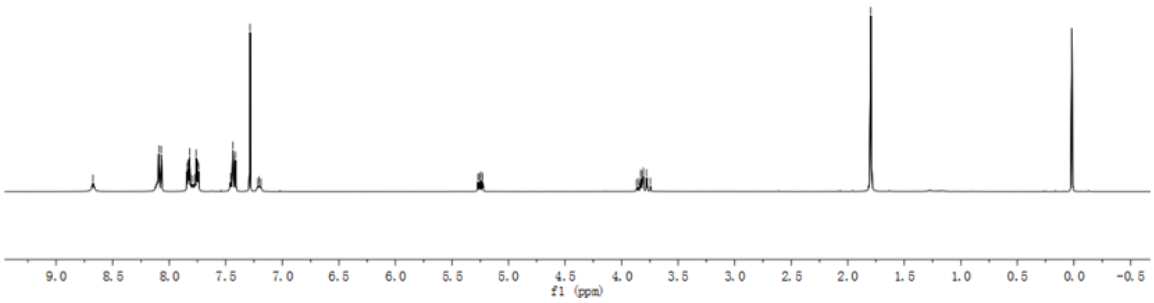

8.559
8.170
8.162
7.816
7.744
7.424
7.340
7.319
7.285
7.213
7.198
7.182
7.135
7.114
5.205
5.190
5.178
5.163
3.683
3.663
3.652
3.626
3.590
1.788
O
O
NH
N
N
O
Br
3.1j
1H NMR (400 MHz, CDCl3)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

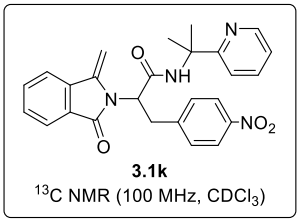

167.867
166.631
163.699
146.704
137.859
136.402
134.142
131.647
131.591
130.676
123.490
122.081
120.642
119.675
77.368
77.050
76.733
56.404
55.659
34.018
27.309
27.192
O
O
NH
N
N
O
Br
3.1j
13C NMR (100 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



3.1k

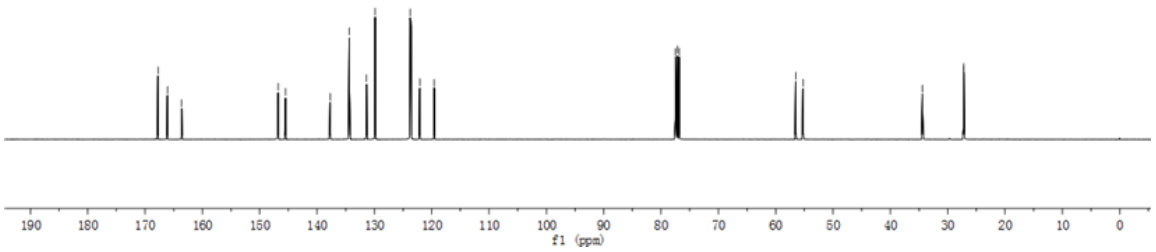
^{1}H NMR (400 MHz, $CDCl_3$)

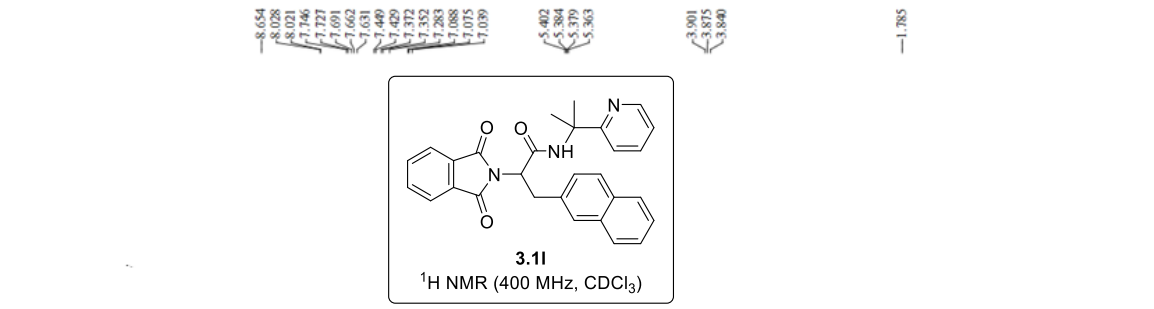




3.1k

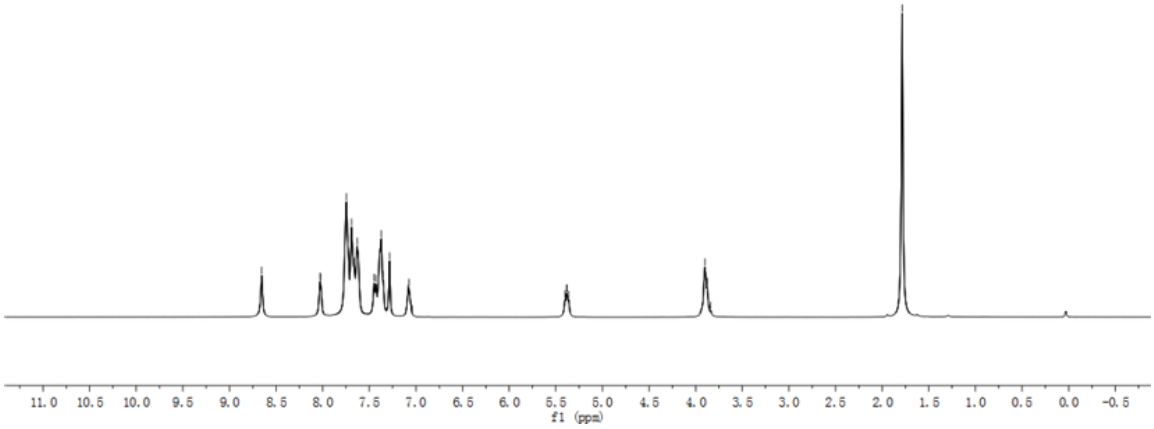
^{13}C NMR (100 MHz, $CDCl_3$)

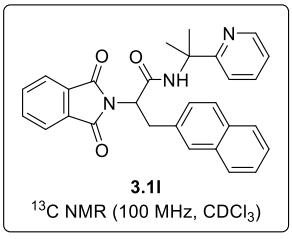




3.1l

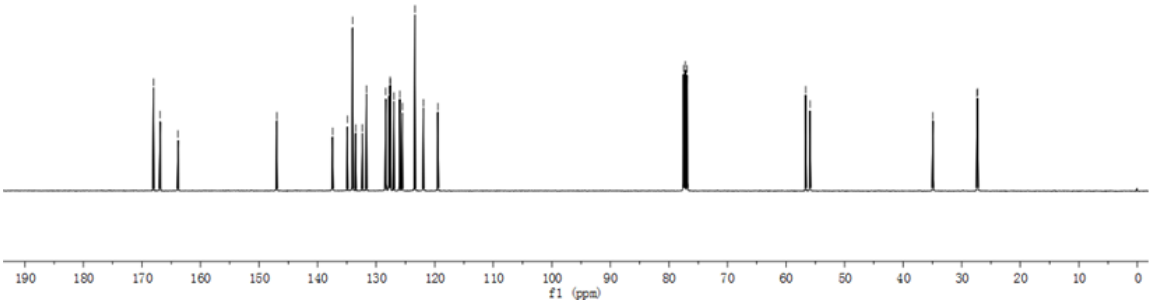
^{1}H NMR (400 MHz, $CDCl_3$)

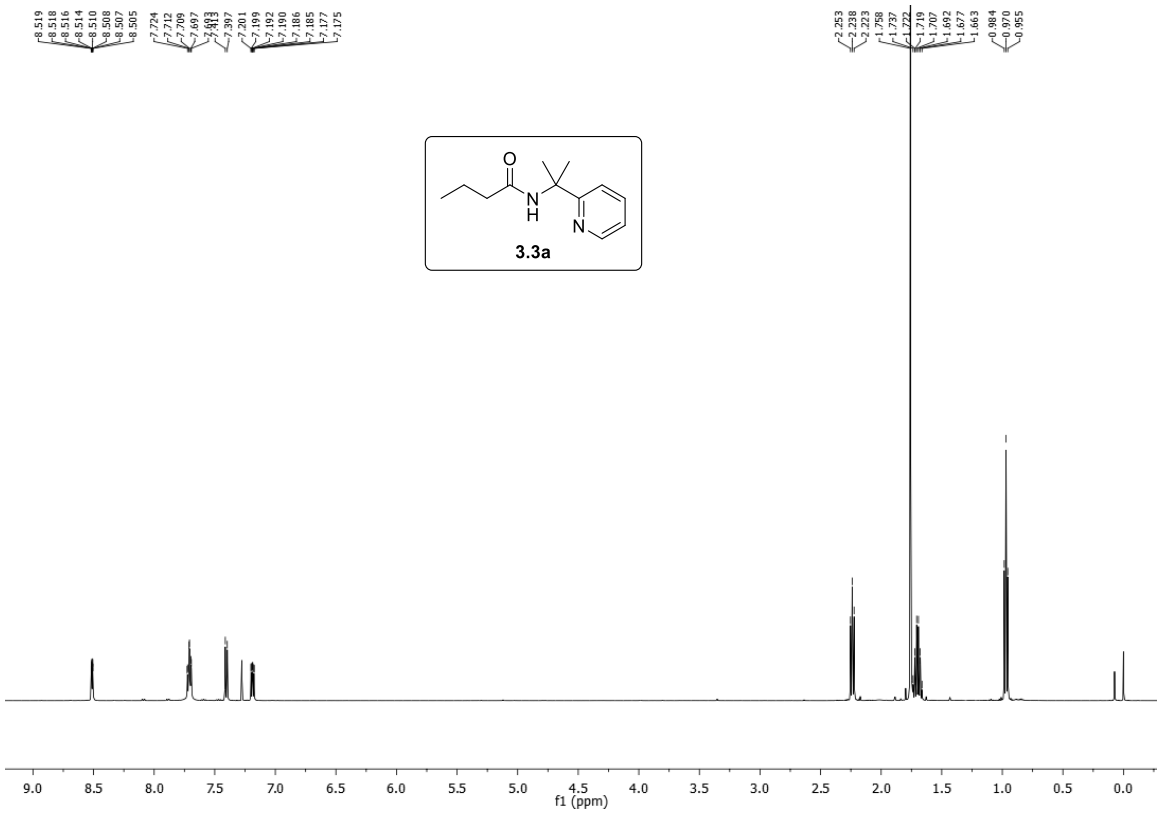


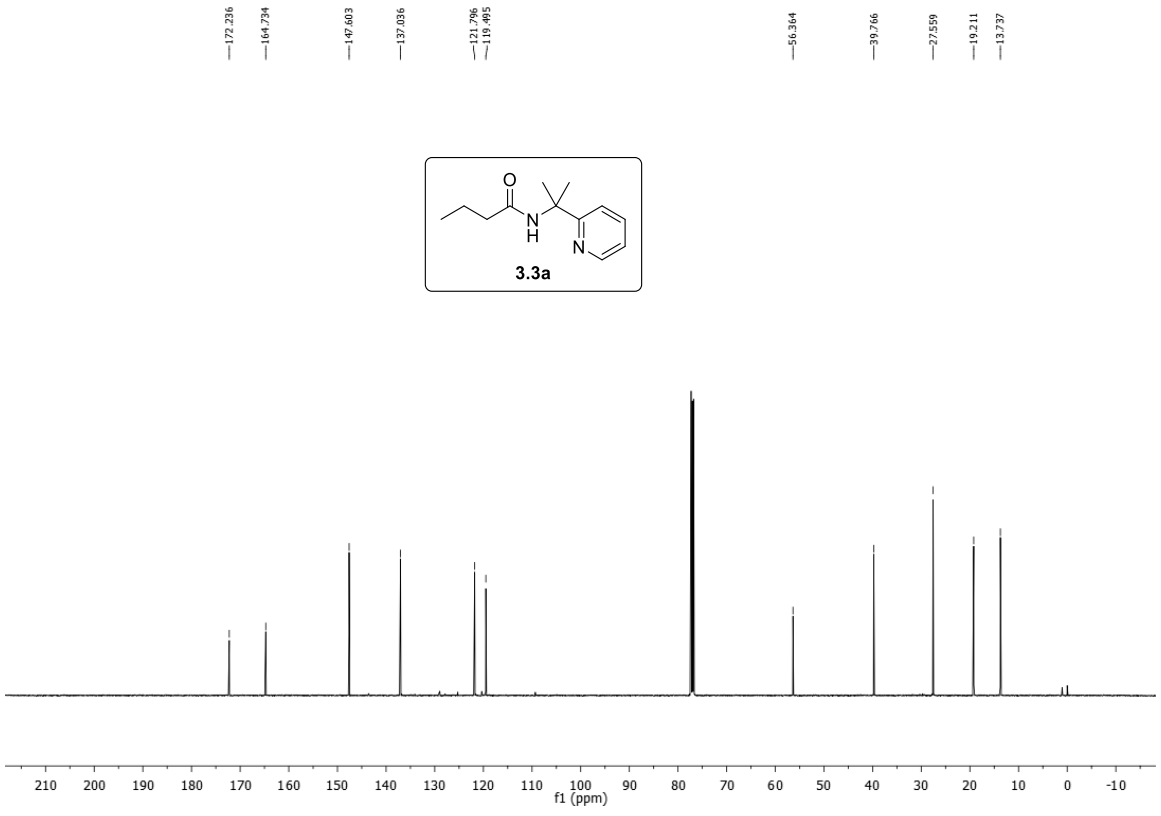


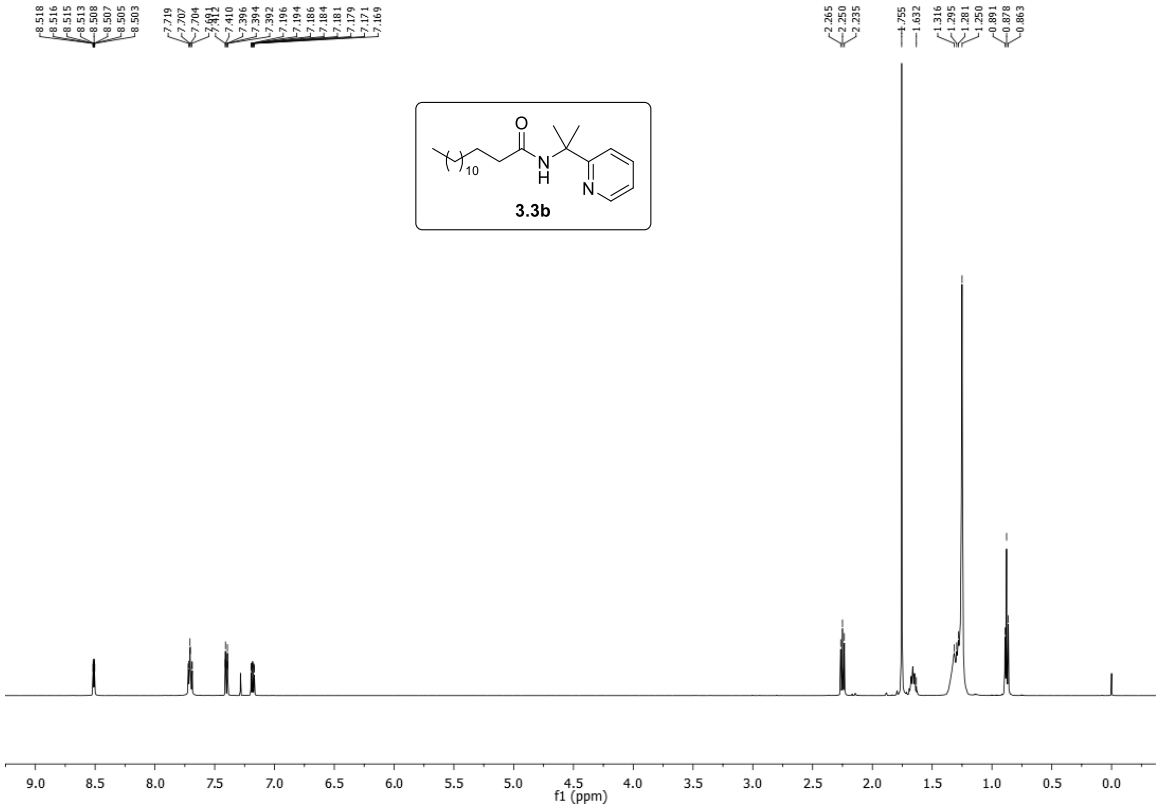
3.1l

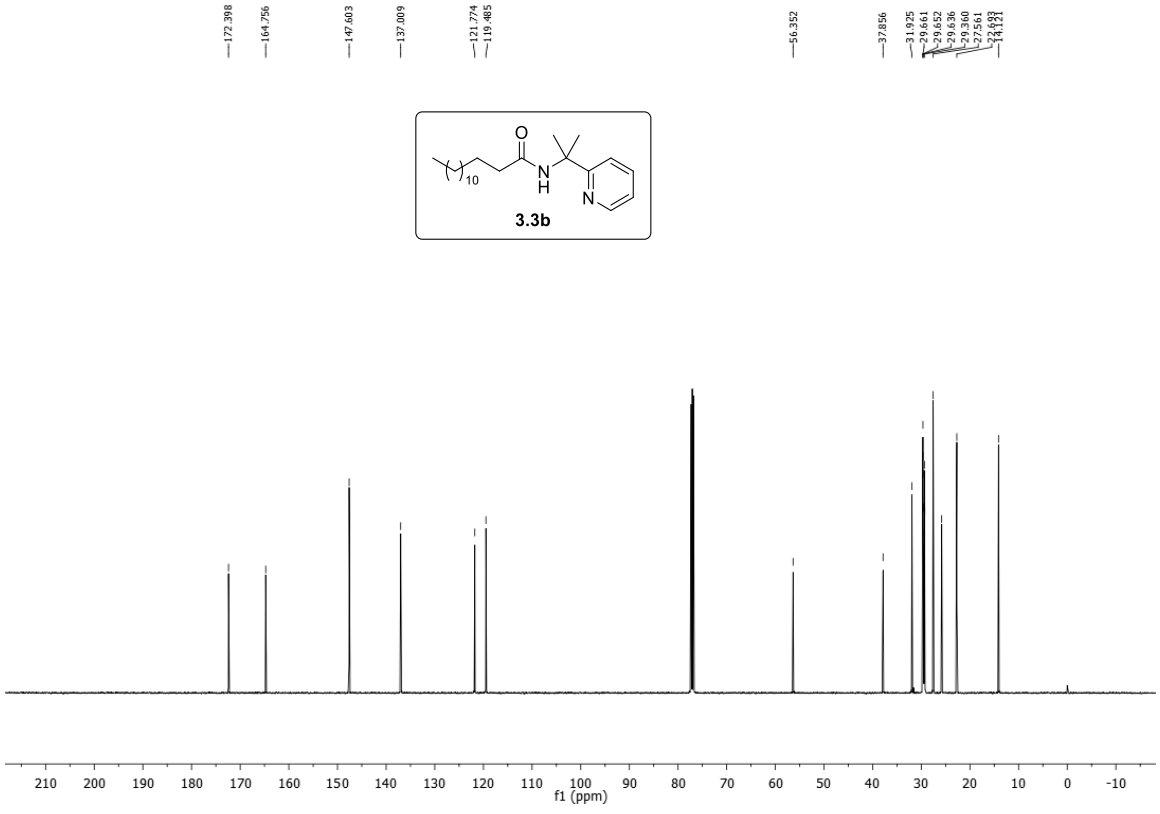
^{13}C NMR (100 MHz, $CDCl_3$)




8.519
8.518
8.516
8.514
8.510
8.508
8.507
8.505
7.724
7.712
7.709
7.697
7.413
7.397
7.201
7.199
7.192
7.190
7.186
7.185
7.177
7.175
2.253
2.238
2.223
1.758
1.737
1.722
1.719
1.707
1.692
1.677
1.663
0.984
0.970
0.955
O
N
H
N
3.3a
f1 (ppm)


172.236
164.734
147.603
137.036
121.706
119.495
56.364
39.766
27.559
19.211
13.737
O
N
H
N
3.3a
f1 (ppm)


8.518
8.516
8.515
8.513
8.508
8.507
8.505
8.503
7.719
7.707
7.704
7.412
7.410
7.396
7.394
7.392
7.196
7.194
7.186
7.184
7.181
7.179
7.171
7.169
2.265
2.250
2.235
1.755
1.632
1.316
1.295
1.281
1.250
0.891
0.878
0.863
O
N
H
N
10
3.3b
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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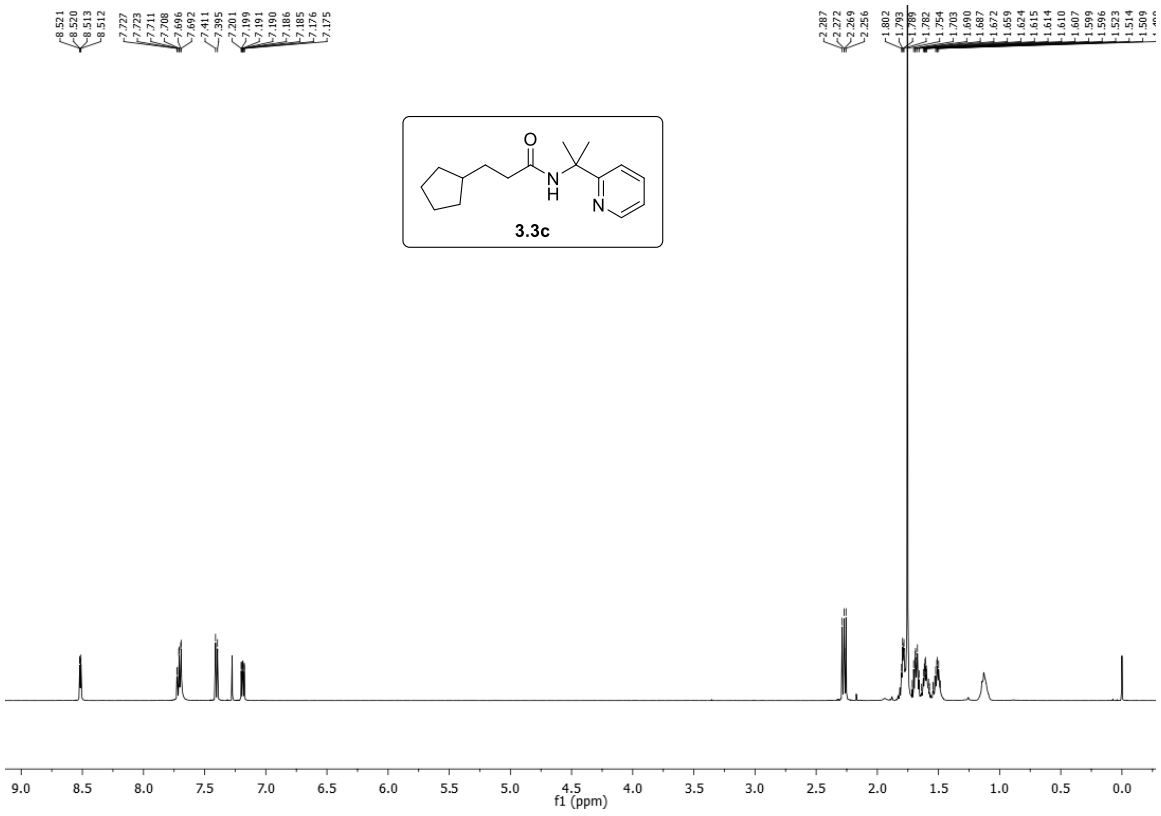
137.009
121.774
119.485
56.352
37.856
31.925
29.661
29.652
29.636
29.360
27.561
14.123
O
N
H
N
10
3.3b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


8.521
8.520
8.513
8.512
7.727
7.723
7.711
7.708
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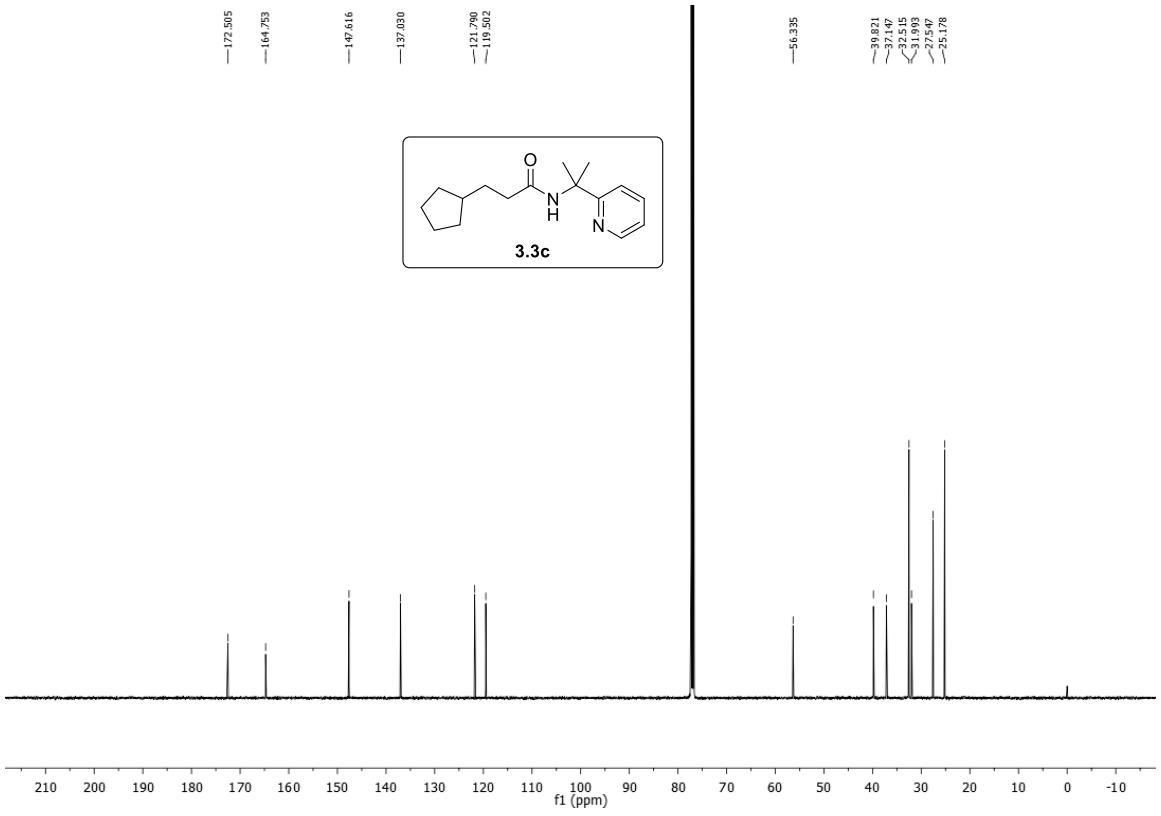
7.692
7.411
7.395
7.201
7.199
7.191
7.190
7.186
7.185
7.176
7.175
2.287
2.272
2.269
2.256
1.802
1.793
1.789
1.782
1.754
1.703
1.690
1.687
1.672
1.659
1.624
1.615
1.614
1.610
1.607
1.599
1.596
1.523
1.514
1.509
O
N
H
N
3.3c
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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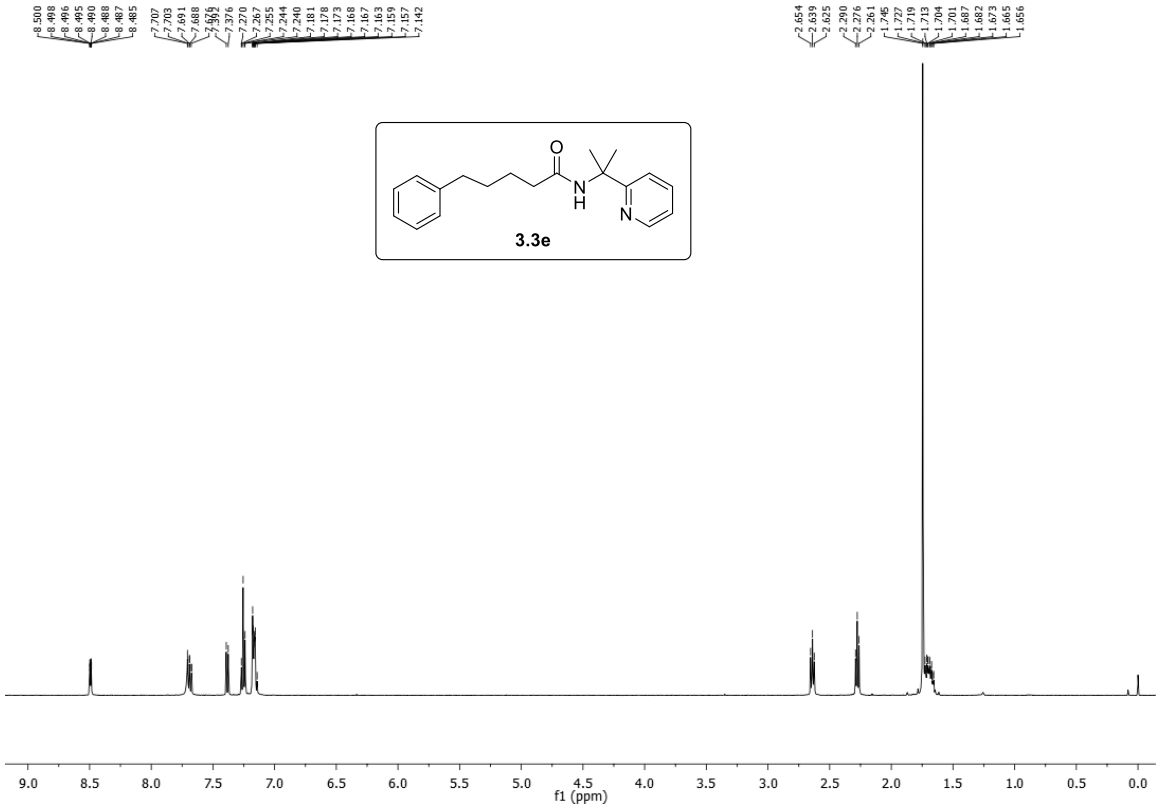
164.753
147.616
137.030
121.790
119.502
56.335
39.821
37.147
32.515
31.993
27.547
25.178
O
N
H
N
3.3c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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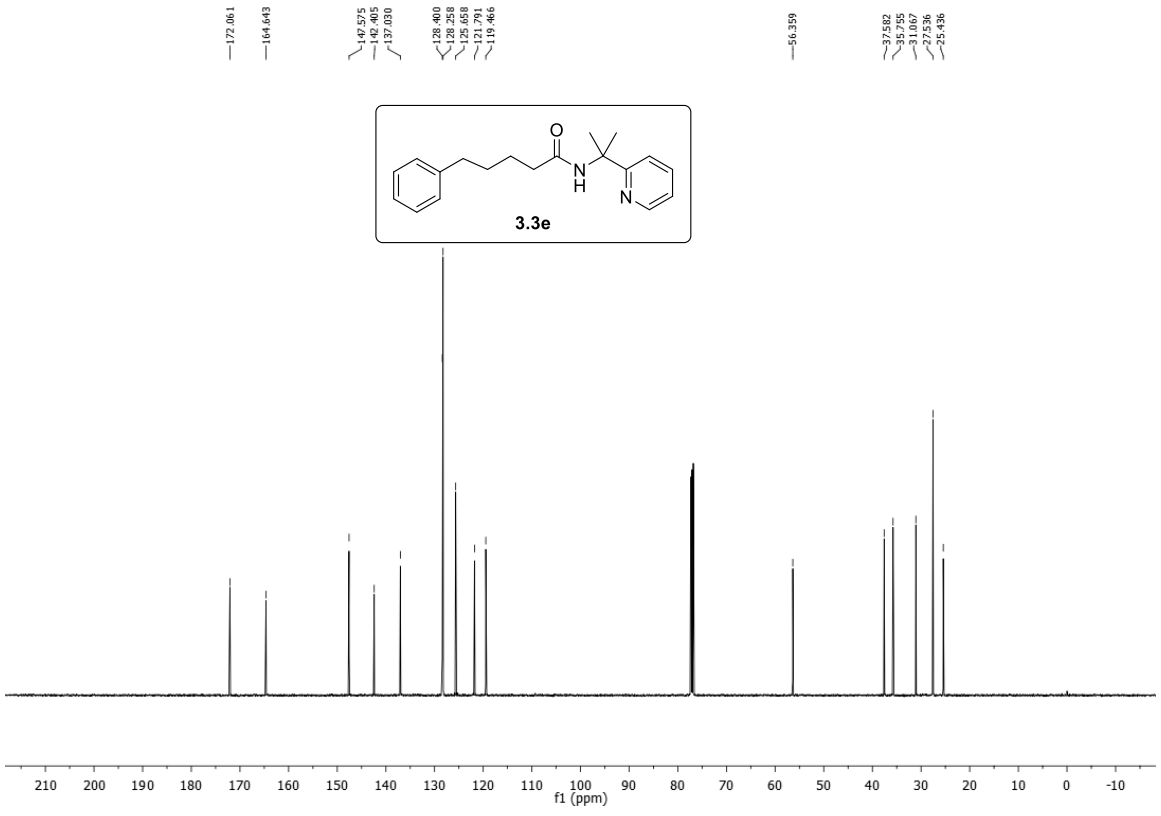
8.498
8.496
8.495
8.490
8.488
8.487
8.485
7.707
7.703
7.691
7.688
7.376
7.270
7.267
7.255
7.244
7.240
7.181
7.178
7.173
7.168
7.167
7.163
7.159
7.157
7.142
2.654
2.639
2.625
2.290
2.276
2.261
1.746
1.727
1.719
1.713
1.704
1.701
1.687
1.682
1.673
1.665
1.656
O
N
H
N
3.3e
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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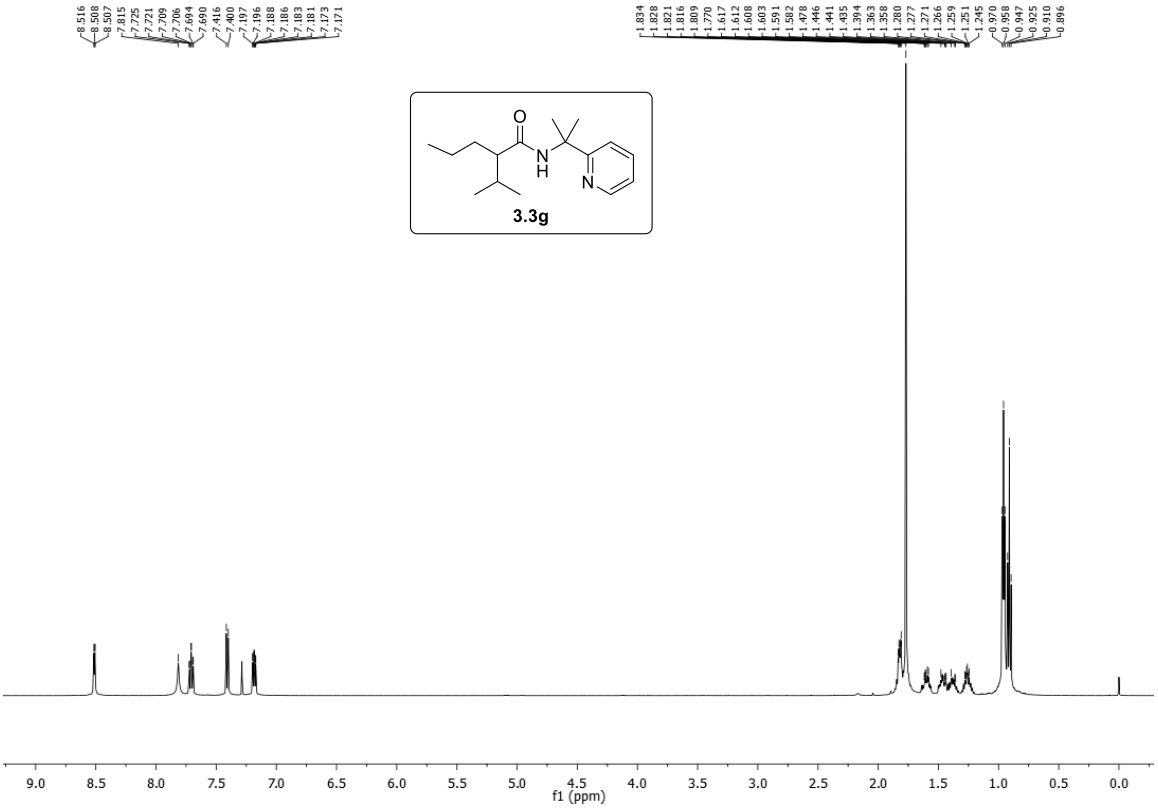
164.643
147.575
147.405
137.030
128.400
128.258
125.658
121.791
119.466
56.359
37.582
35.755
31.067
27.536
25.436
O
N
H
N
3.3e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


8.516
8.508
8.507
7.815
7.725
7.721
7.709
7.706
7.694
7.690
7.416
7.400
7.197
7.196
7.188
7.186
7.183
7.181
7.173
7.171
1.834
1.828
1.821
1.816
1.809
1.770
1.617
1.612
1.608
1.603
1.591
1.582
1.478
1.446
1.441
1.435
1.394
1.363
1.358
1.280
1.277
1.271
1.266
1.259
1.251
1.245
0.970
0.958
0.947
0.925
0.910
0.896
O
N
H
N
3.3g
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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1.0
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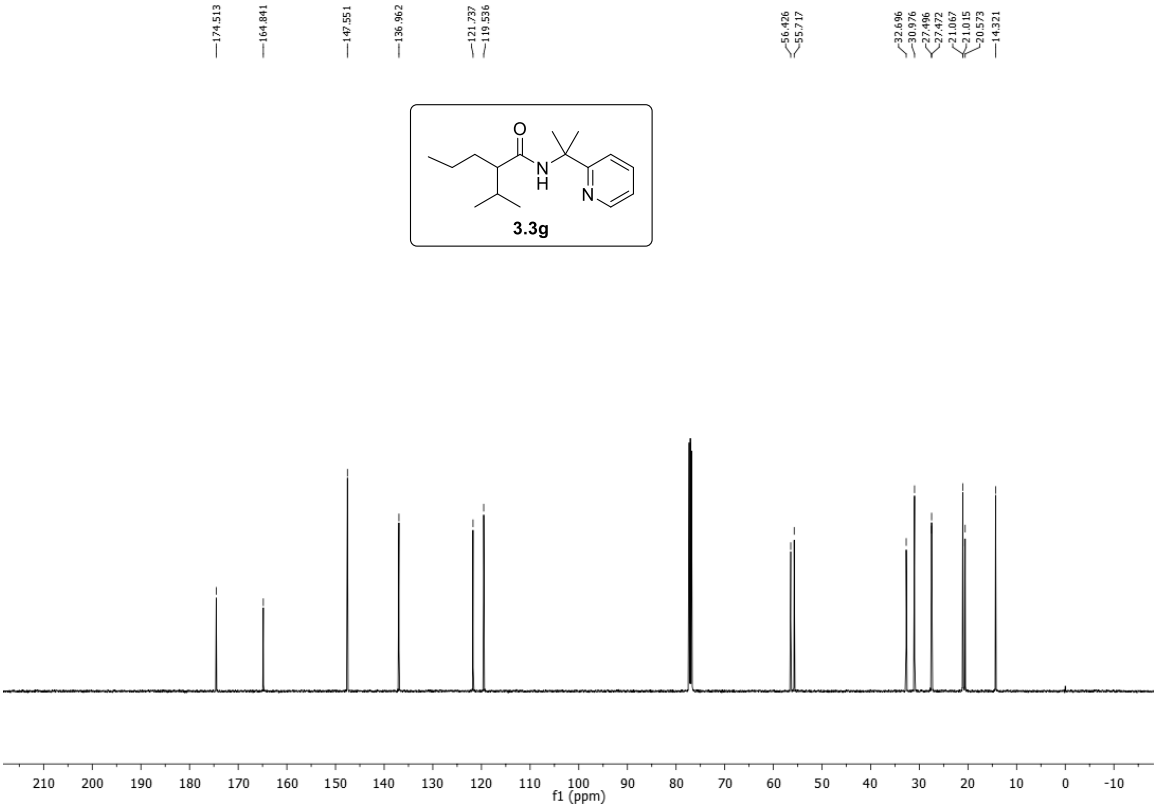
0.0
f1 (ppm)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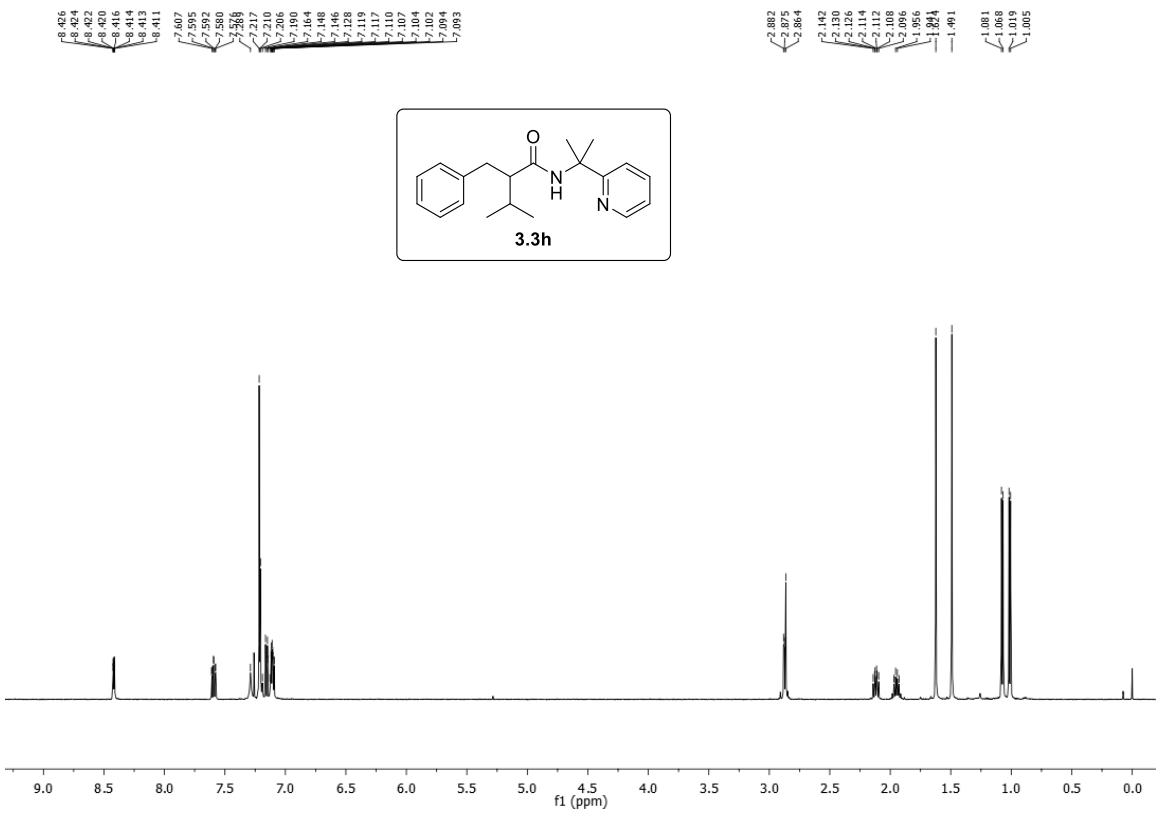
147.551
136.962
121.737
119.536
56.426
55.717
32.696
30.976
27.496
27.472
21.067
21.015
20.573
14.321
O
N
H
N
3.3g
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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8.422
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8.413
8.411
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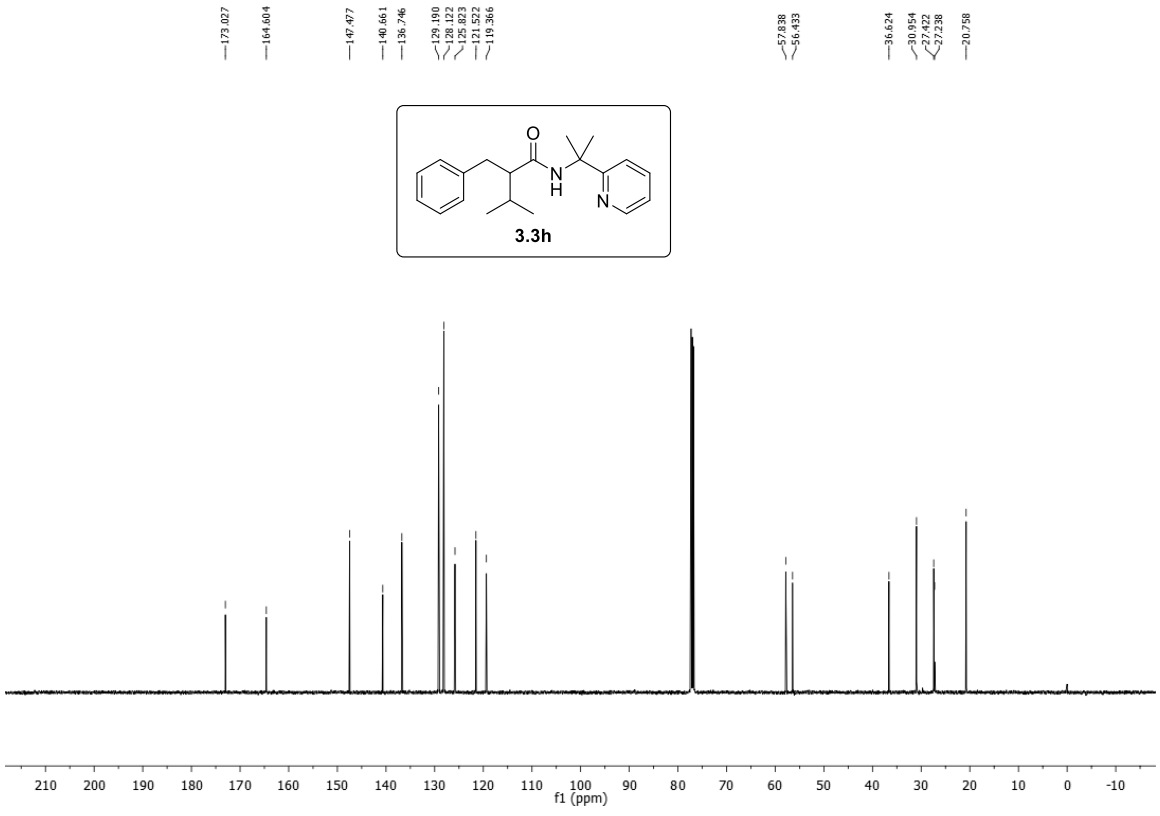
7.595
7.592
7.580
7.576
7.289
7.217
7.210
7.206
7.190
7.164
7.148
7.146
7.128
7.119
7.117
7.110
7.107
7.104
7.102
7.094
7.093
2.882
2.875
2.864
2.142
2.130
2.126
2.114
2.112
2.108
2.096
1.956
1.841
1.824
1.491
1.081
1.068
1.019
1.005
O
N
H
N
3.3h
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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128.122
126.823
121.522
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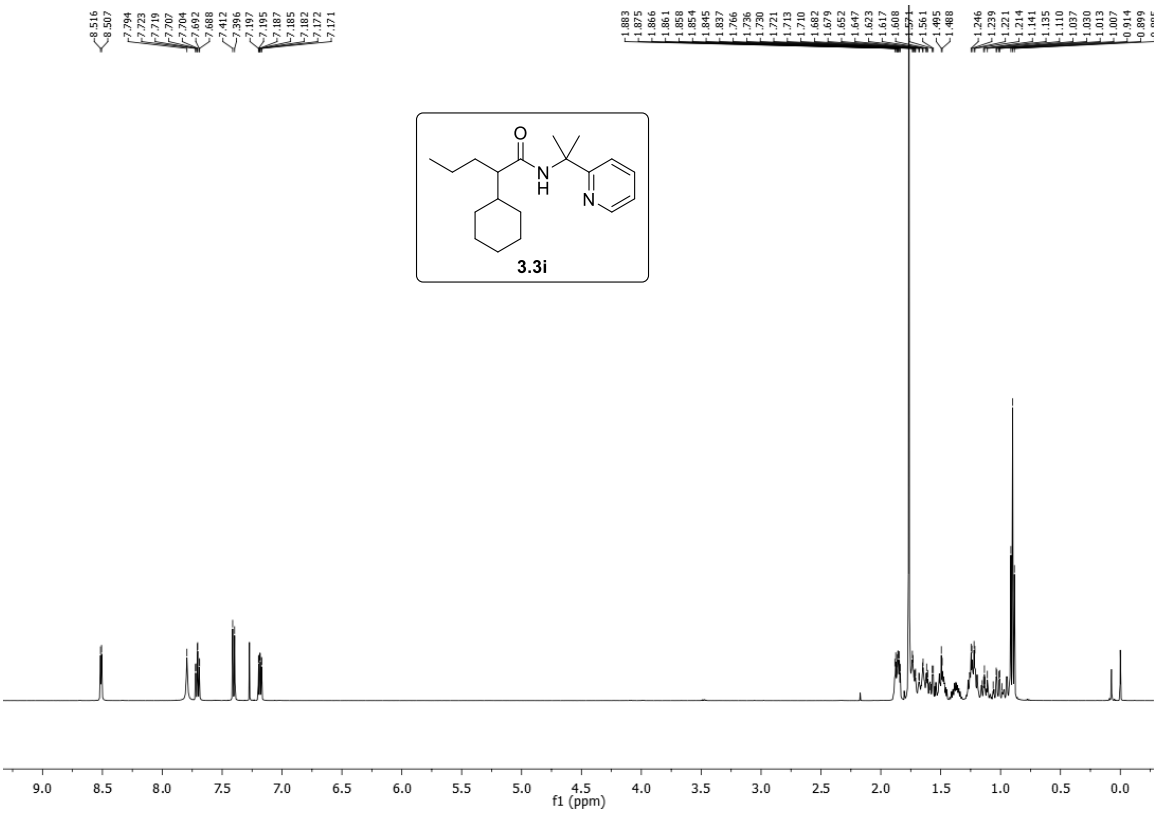
56.433
36.624
30.954
27.422
27.238
20.758
O
N
H
N
3.3h
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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8.507
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7.723
7.719
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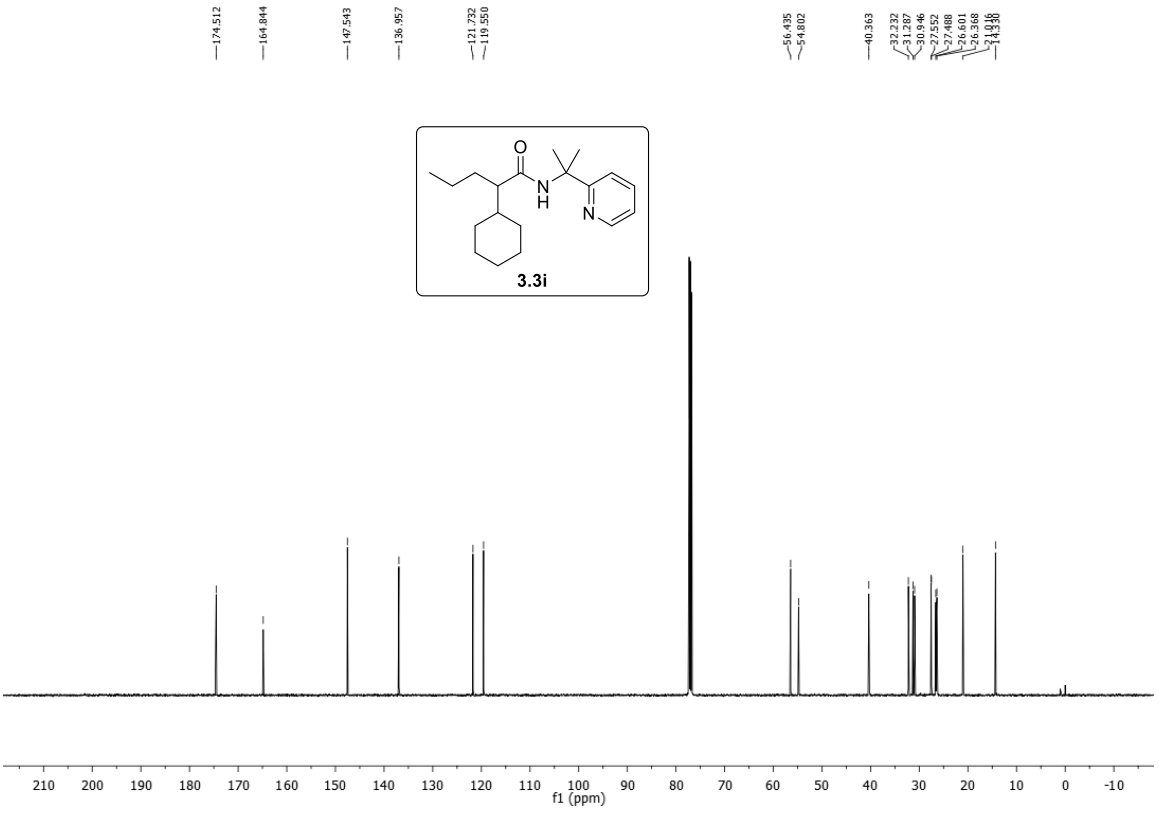
7.195
7.187
7.185
7.182
7.172
7.171
1.883
1.875
1.866
1.861
1.858
1.854
1.845
1.837
1.766
1.736
1.730
1.721
1.713
1.710
1.682
1.679
1.652
1.647
1.623
1.617
1.608
1.571
1.561
1.495
1.488
1.246
1.239
1.221
1.214
1.141
1.135
1.110
1.037
1.030
1.013
1.007
0.914
0.899
O
N
H
N
3.3i
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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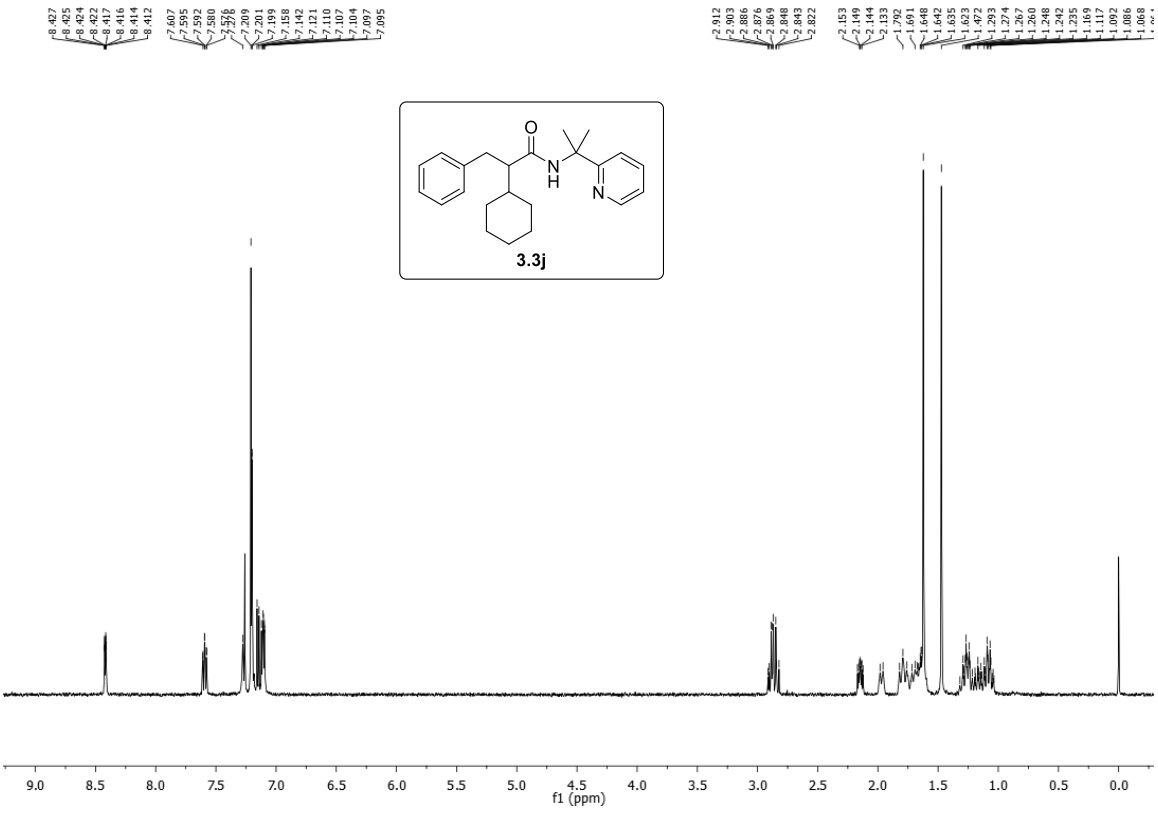
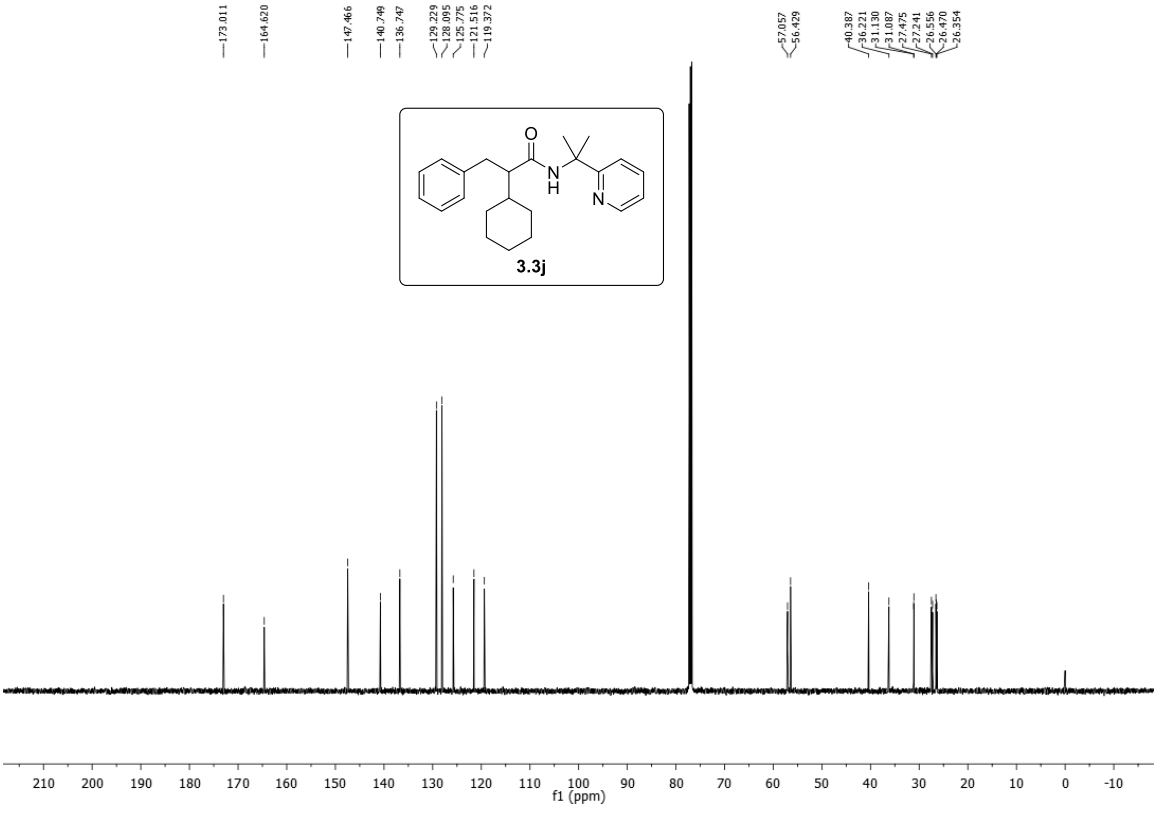
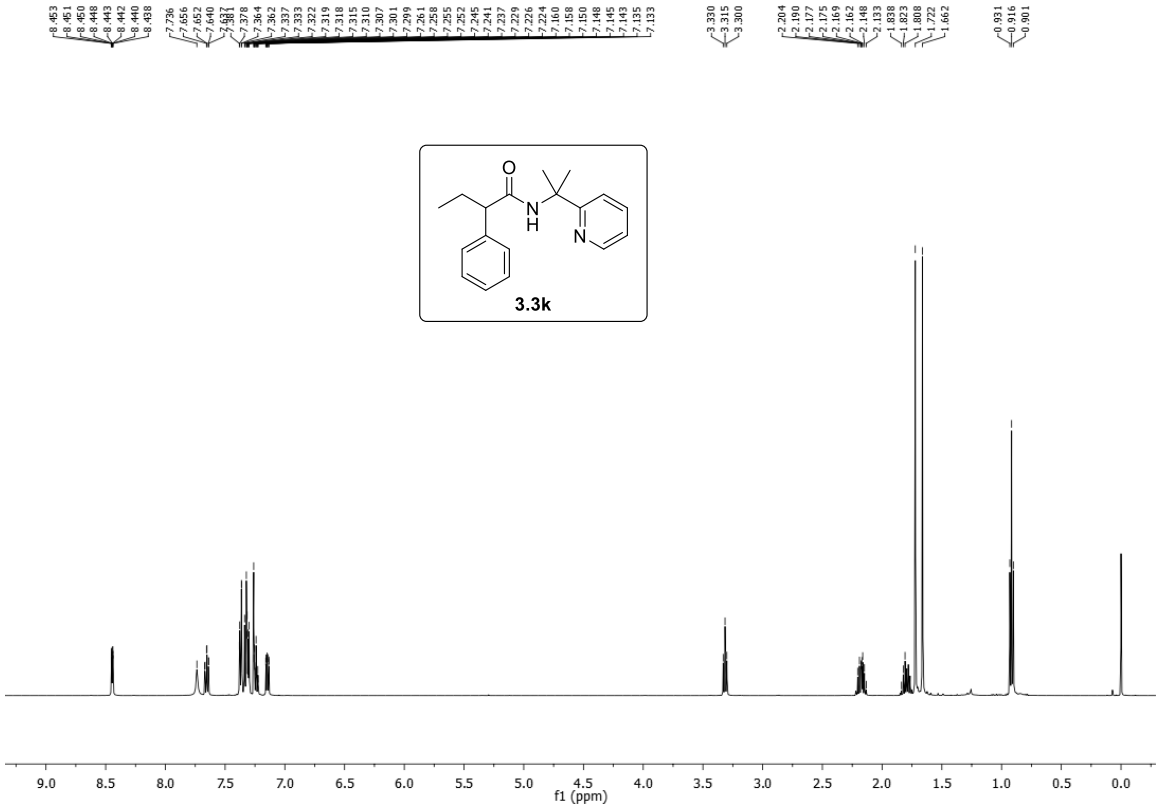
56.435
54.802
40.363
32.232
31.287
30.946
27.552
27.488
26.601
26.368
14.316
14.138
O
N
H
N
3.3i
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


3.3j
f1 (ppm)


3.3j
f1 (ppm)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8.456
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8.443
8.442
8.440
8.438
7.736
7.656
7.652
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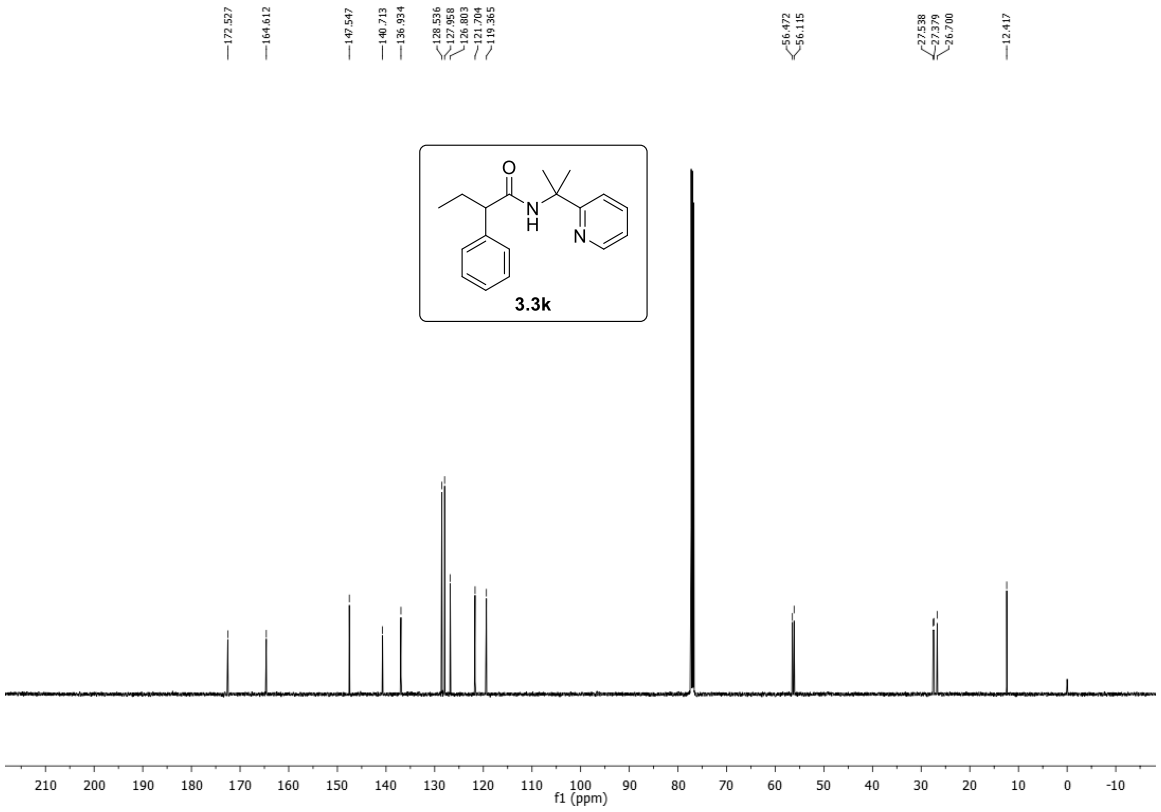
7.381
7.378
7.364
7.362
7.337
7.333
7.322
7.319
7.318
7.315
7.310
7.307
7.301
7.299
7.261
7.258
7.255
7.252
7.245
7.241
7.237
7.229
7.226
7.224
7.160
7.158
7.150
7.148
7.145
7.143
7.135
7.133
3.330
3.315
3.300
2.204
2.190
2.177
2.175
2.169
2.162
2.148
2.133
1.838
1.823
1.808
1.722
1.662
0.931
0.916
0.901
O
N
H
N
3.3k
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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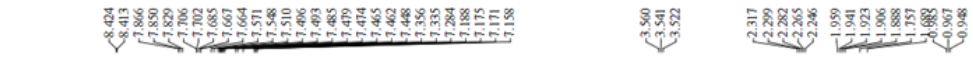
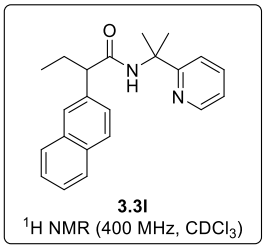
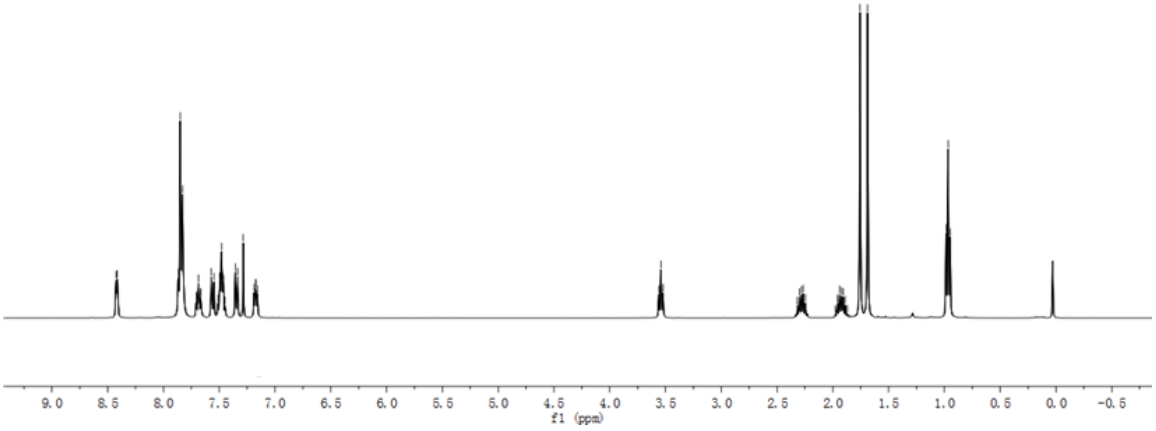
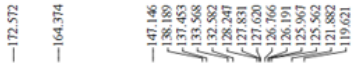
147.547
140.713
136.934
128.536
127.958
126.803
121.704
119.365
56.472
56.115
27.538
27.379
26.700
12.417
O
N
H
N
3.3k
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

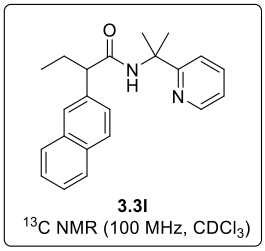




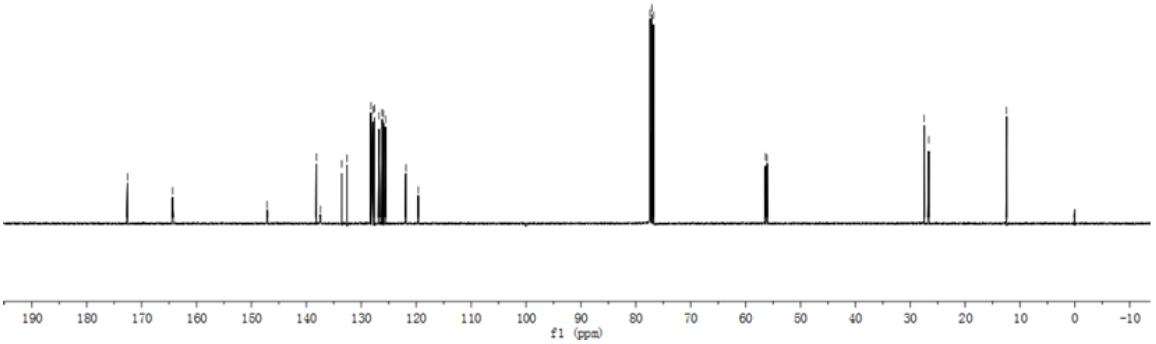
3.3l
^{1}H NMR (400 MHz, $CDCl_3$)

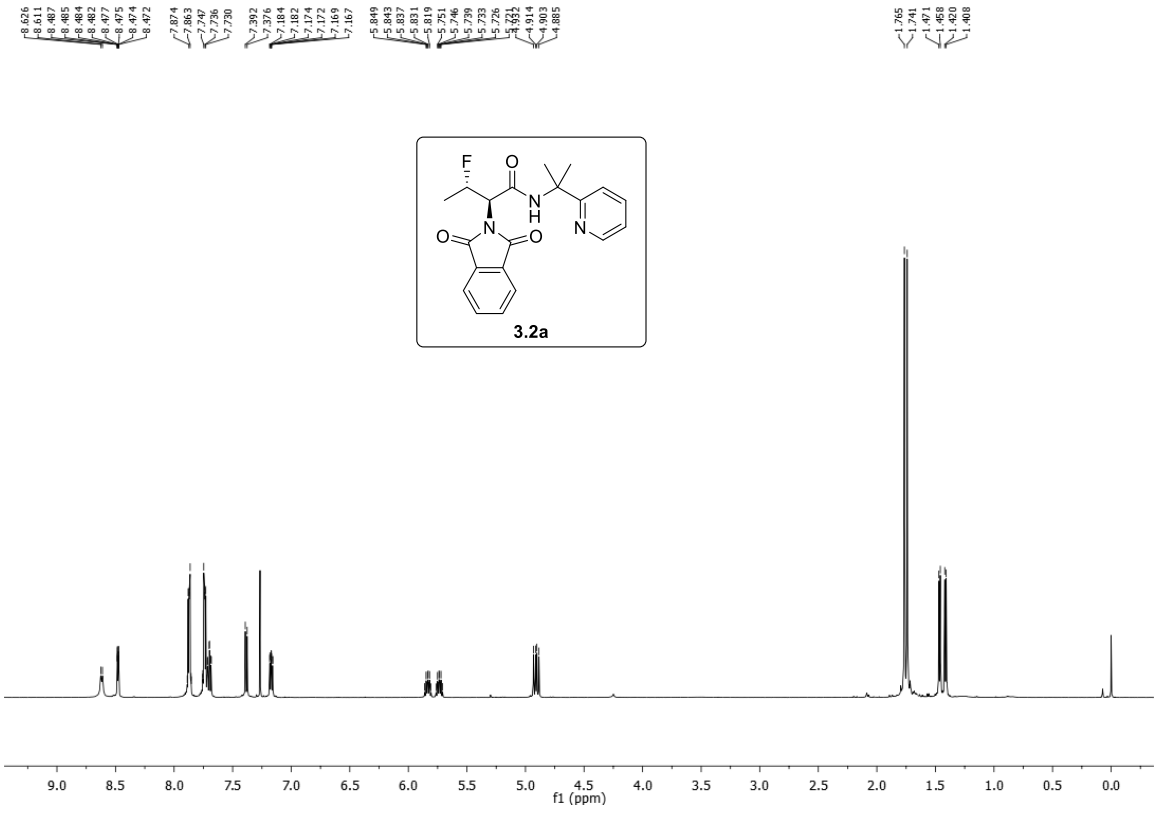






3.3l
^{13}C NMR (100 MHz, $CDCl_3$)

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8.475
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8.472
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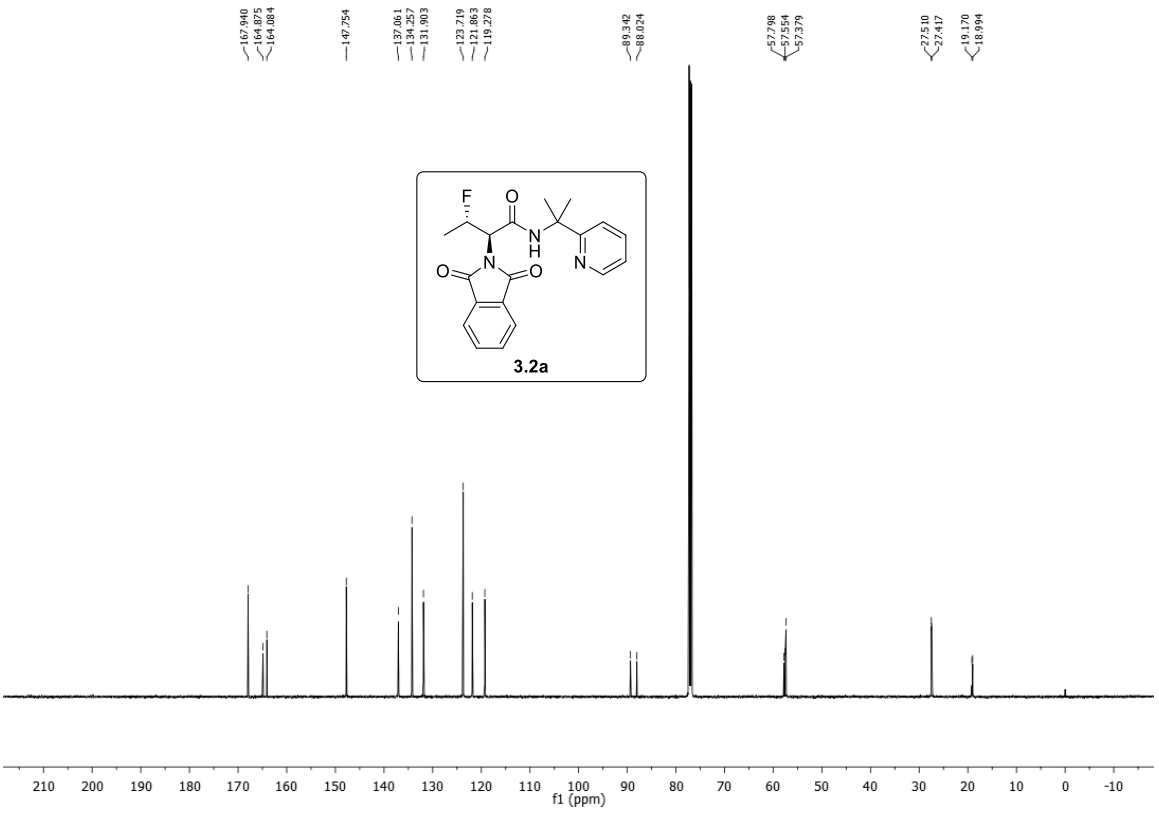
7.747
7.736
7.730
7.392
7.376
7.184
7.182
7.174
7.172
7.169
7.167
5.849
5.843
5.837
5.831
5.819
5.751
5.746
5.739
5.733
5.726
5.721
4.932
4.914
4.903
4.885
1.765
1.741
1.471
1.458
1.420
1.408
F
O
N
H
N
O
N
O
3.2a
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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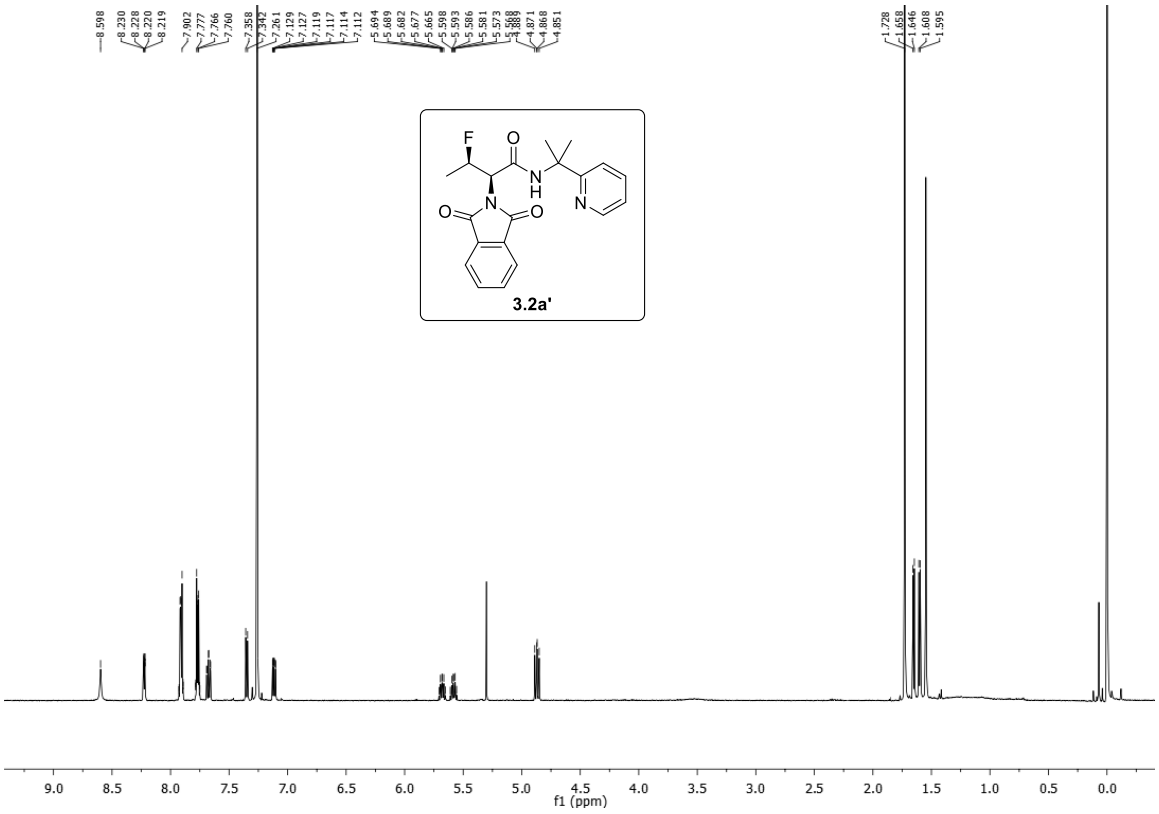
134.257
131.903
123.719
121.863
119.278
89.342
88.024
57.798
57.554
57.379
27.510
27.417
19.170
18.994
F
O
N
H
N
O
N
O
3.2a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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8.220
8.219
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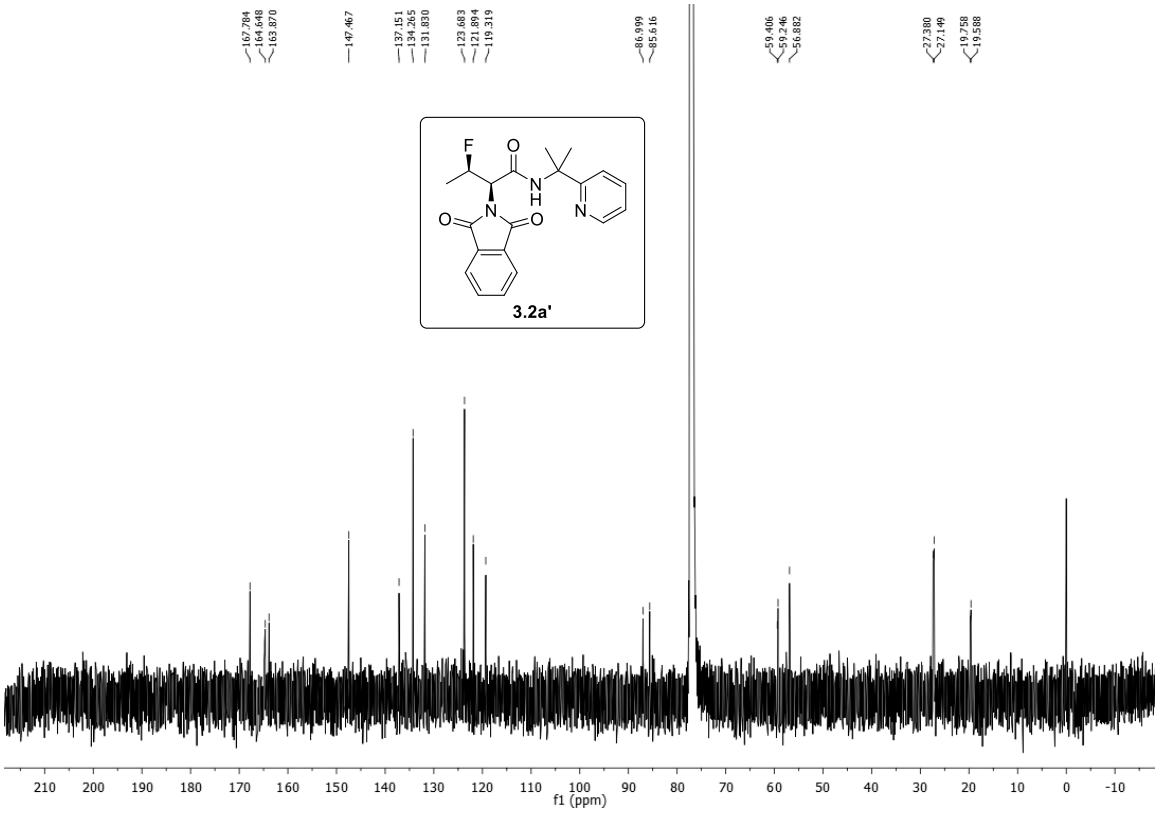
7.777
7.766
7.760
7.358
7.342
7.261
7.129
7.127
7.119
7.117
7.114
7.112
5.694
5.689
5.682
5.677
5.675
5.598
5.593
5.586
5.581
5.573
5.568
4.889
4.871
4.868
4.851
1.728
1.658
1.646
1.608
1.595
F
O
N
H
N
O
N
O
3.2a'
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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131.830
123.683
121.894
119.319
86.999
85.616
59.406
59.246
56.882
27.380
27.149
19.758
19.588
F
O
N
H
N
O
N
O
3.2a'
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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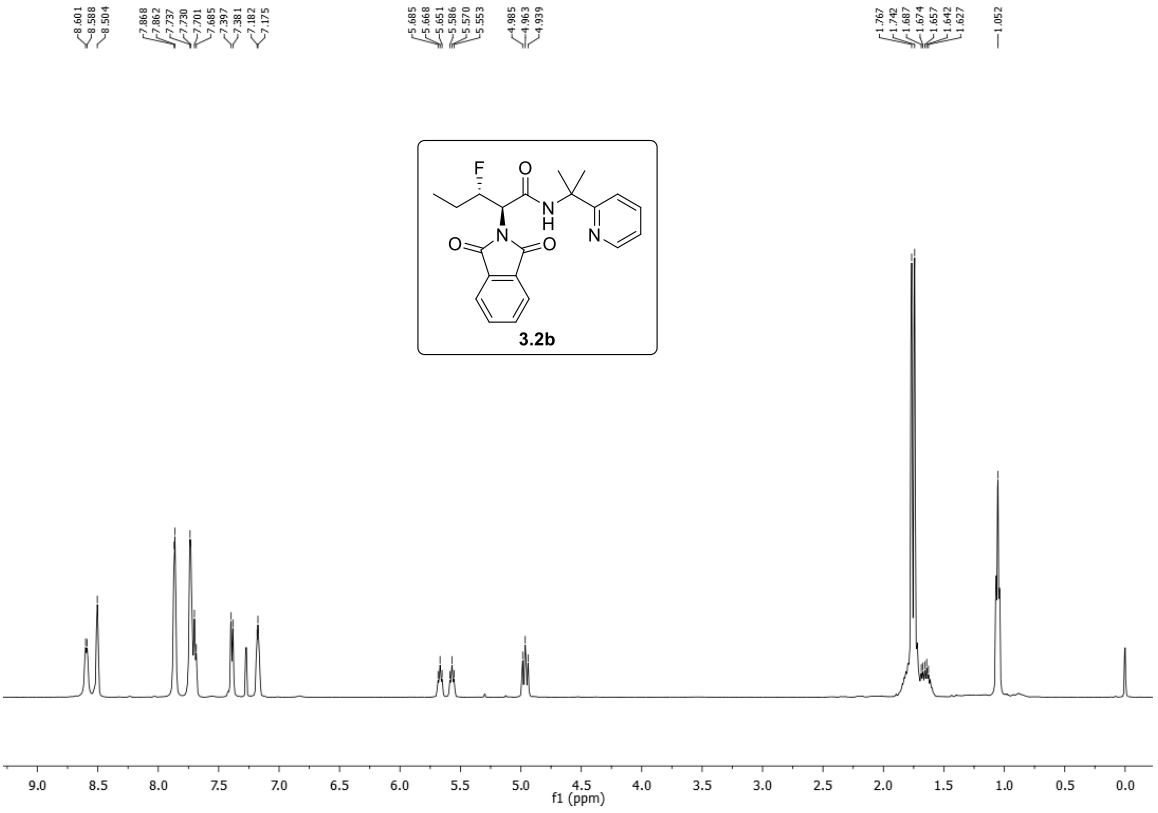
-10
f1 (ppm)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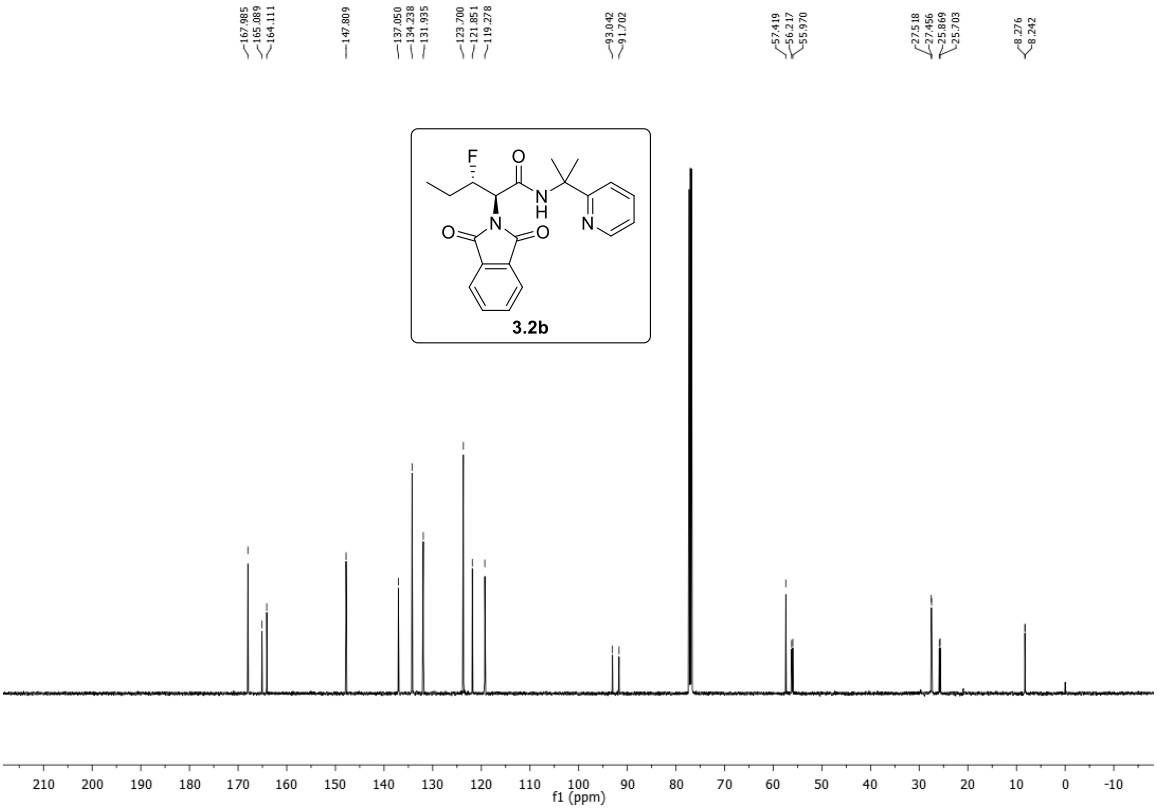
8.588
8.504
7.868
7.862
7.737
7.730
7.701
7.685
7.397
7.381
7.182
7.175
5.685
5.668
5.651
5.586
5.570
5.553
4.985
4.963
4.939
1.767
1.742
1.687
1.674
1.657
1.642
1.627
1.052
F
O
N
H
N
O
O
3.2b
f1 (ppm)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57.419
56.217
55.970
27.518
27.456
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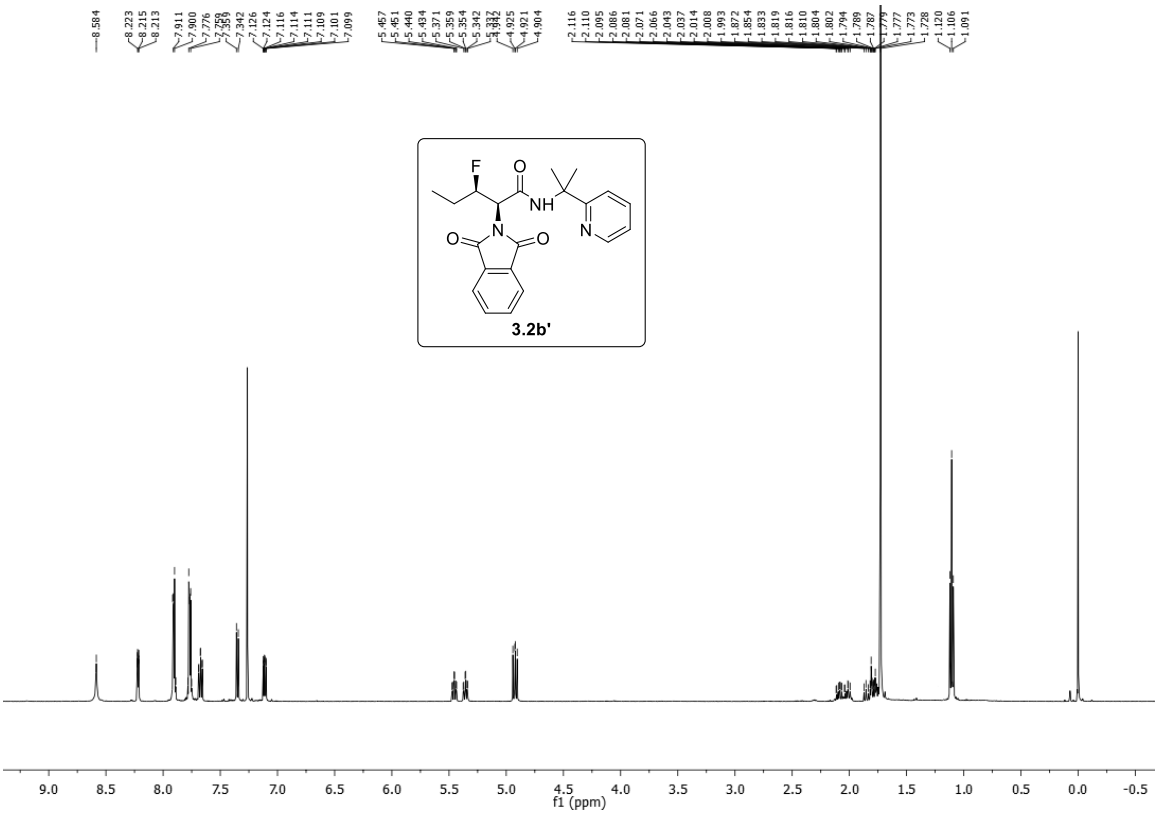
25.703
8.276
8.242
F
O
N
H
N
O
O
3.2b
f1 (ppm)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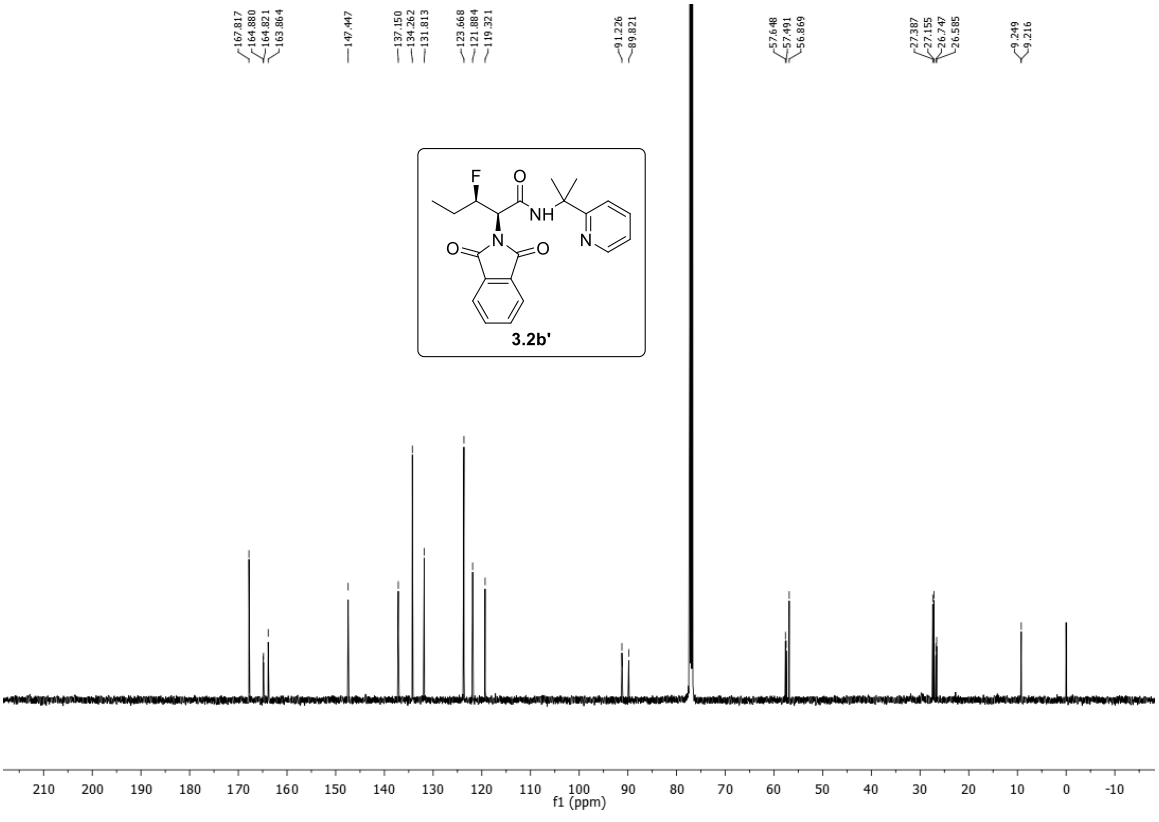
7.124
7.116
7.114
7.111
7.109
7.101
7.099
5.457
5.451
5.440
5.434
5.371
5.359
5.354
5.342
4.925
4.921
4.904
2.116
2.110
2.095
2.086
2.081
2.071
2.066
2.043
2.037
2.014
2.008
1.993
1.872
1.854
1.833
1.819
1.816
1.810
1.804
1.802
1.794
1.789
1.787
1.779
1.777
1.773
1.728
1.120
1.106
1.091
F
O
NH
N
O
O
N
3.2b'
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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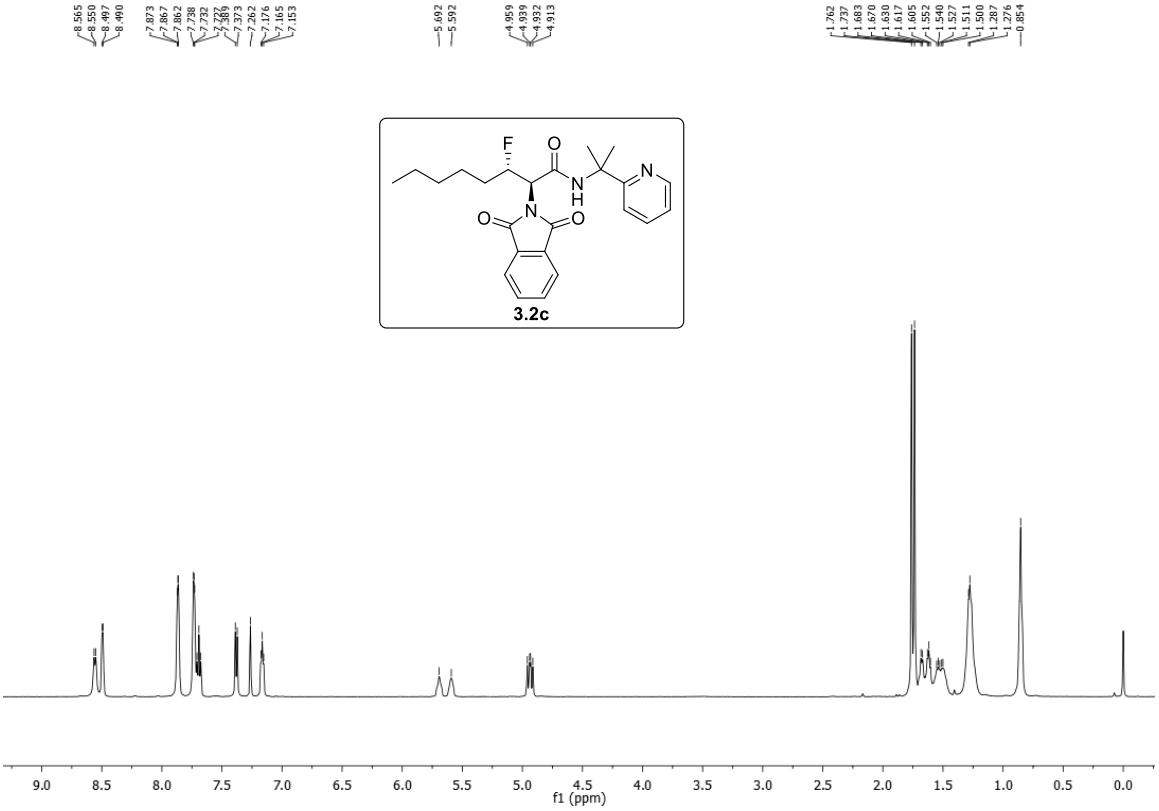
163.864
147.447
137.150
134.262
131.813
123.668
121.884
119.321
91.226
89.821
57.648
57.491
56.869
27.387
27.155
26.747
26.585
9.249
9.216
F
O
NH
N
O
O
N
3.2b'
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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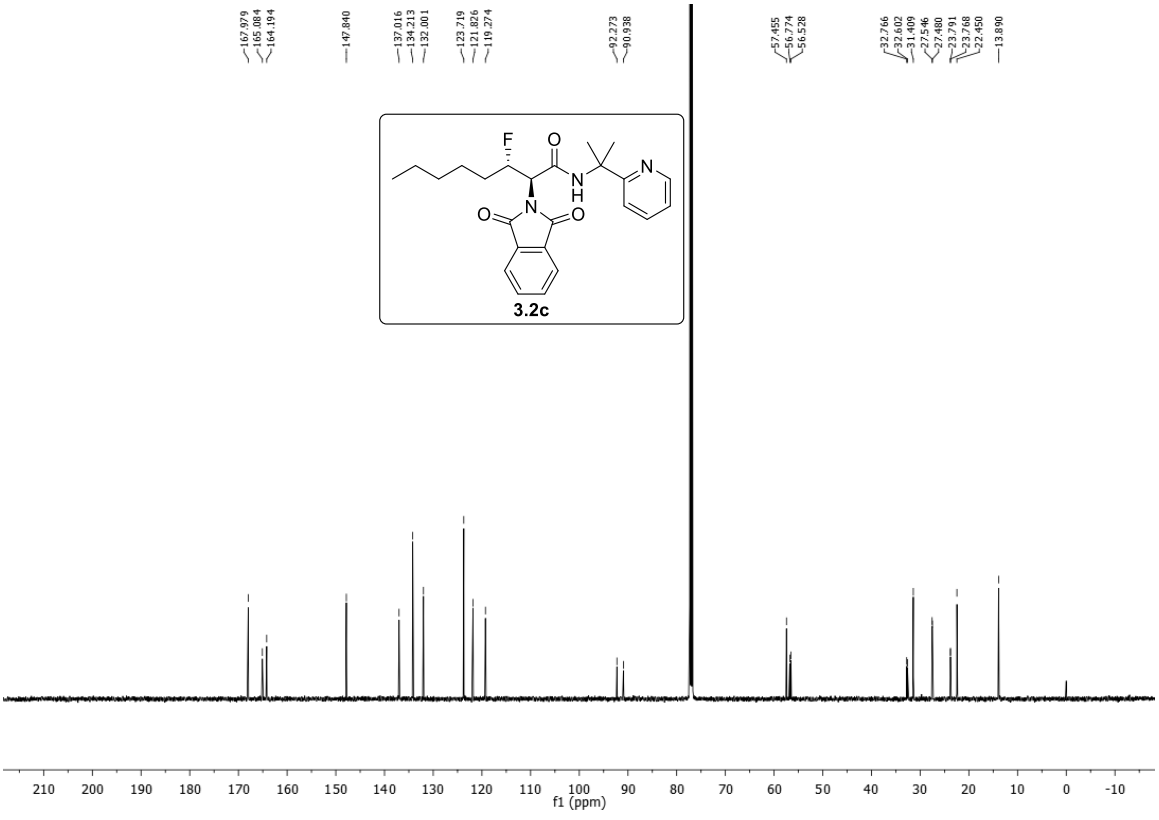
7.867
7.862
7.738
7.722
7.389
7.373
7.262
7.176
7.165
7.153
5.692
5.592
4.959
4.939
4.932
4.913
1.762
1.737
1.683
1.670
1.630
1.617
1.605
1.552
1.540
1.527
1.511
1.500
1.287
1.276
0.854
F
O
N
H
N
O
O
3.2c
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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164.194
147.840
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134.213
132.001
123.719
121.826
119.274
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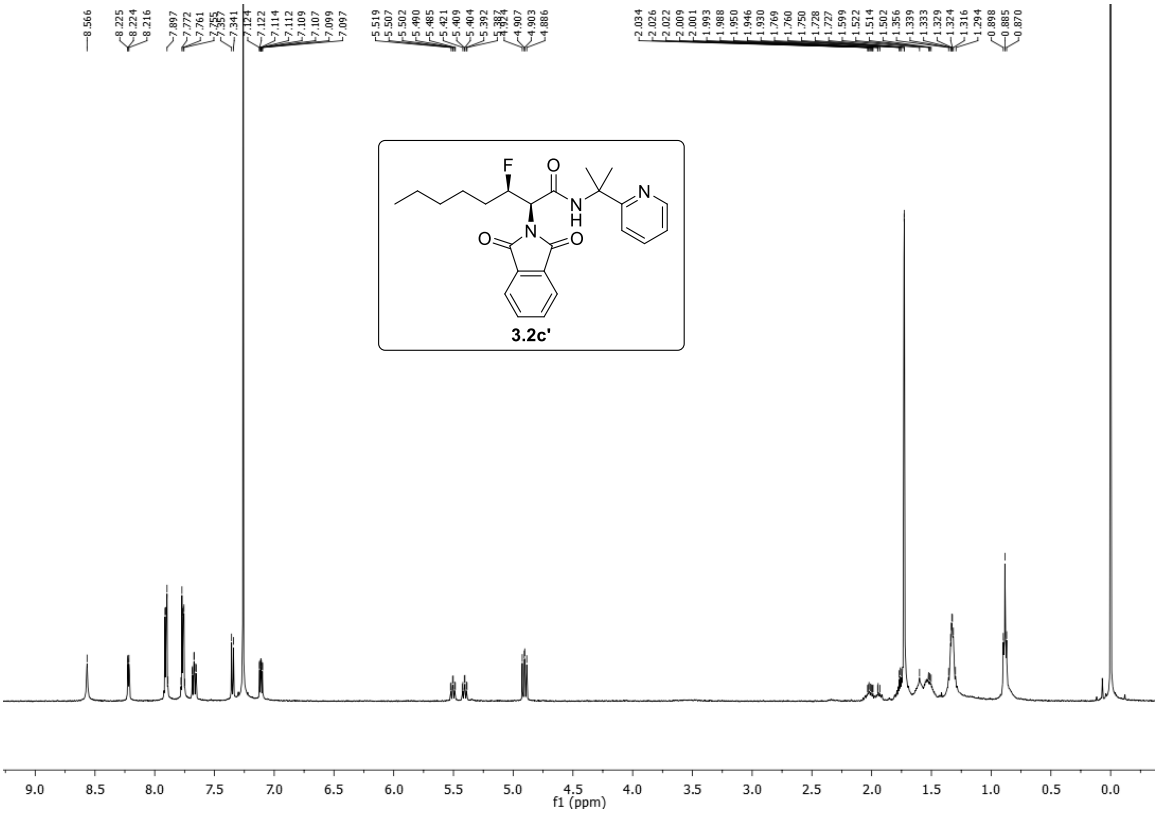
90.938
57.455
56.774
56.528
32.766
32.602
31.409
27.546
27.480
23.791
23.768
22.450
13.890
F
O
N
H
N
O
O
3.2c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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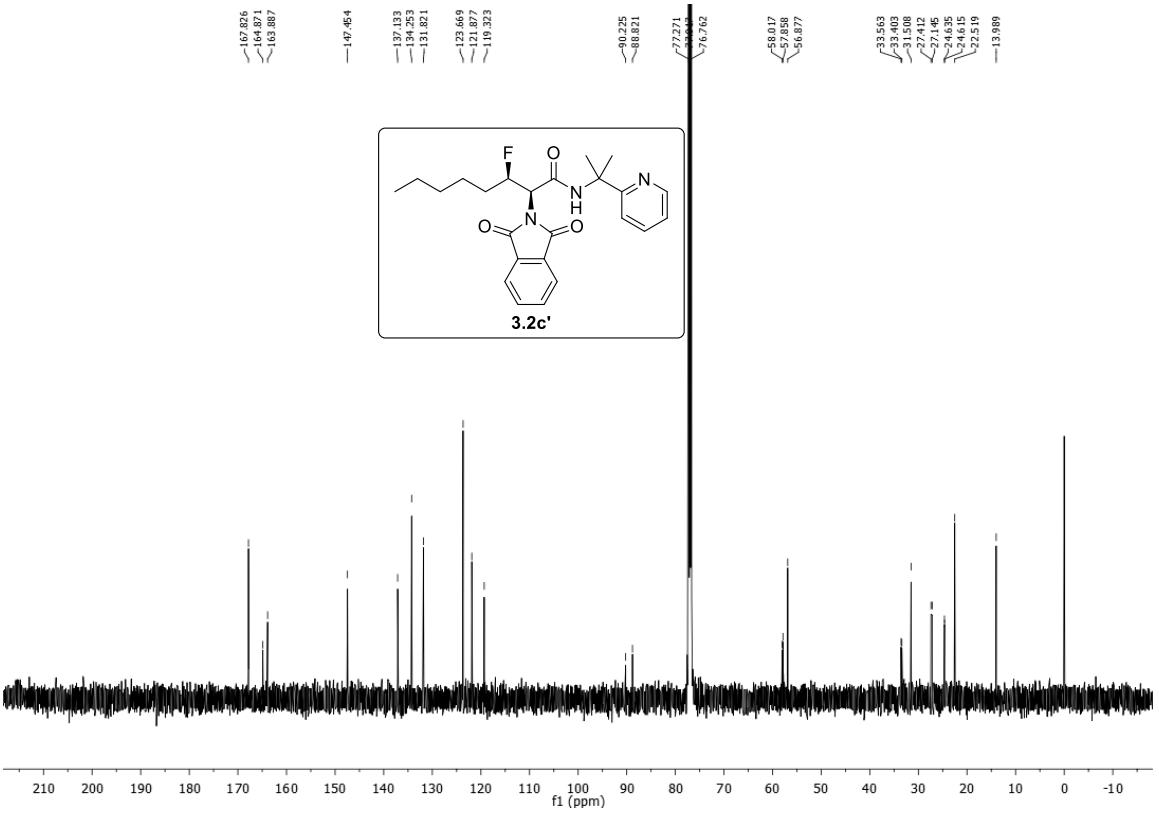
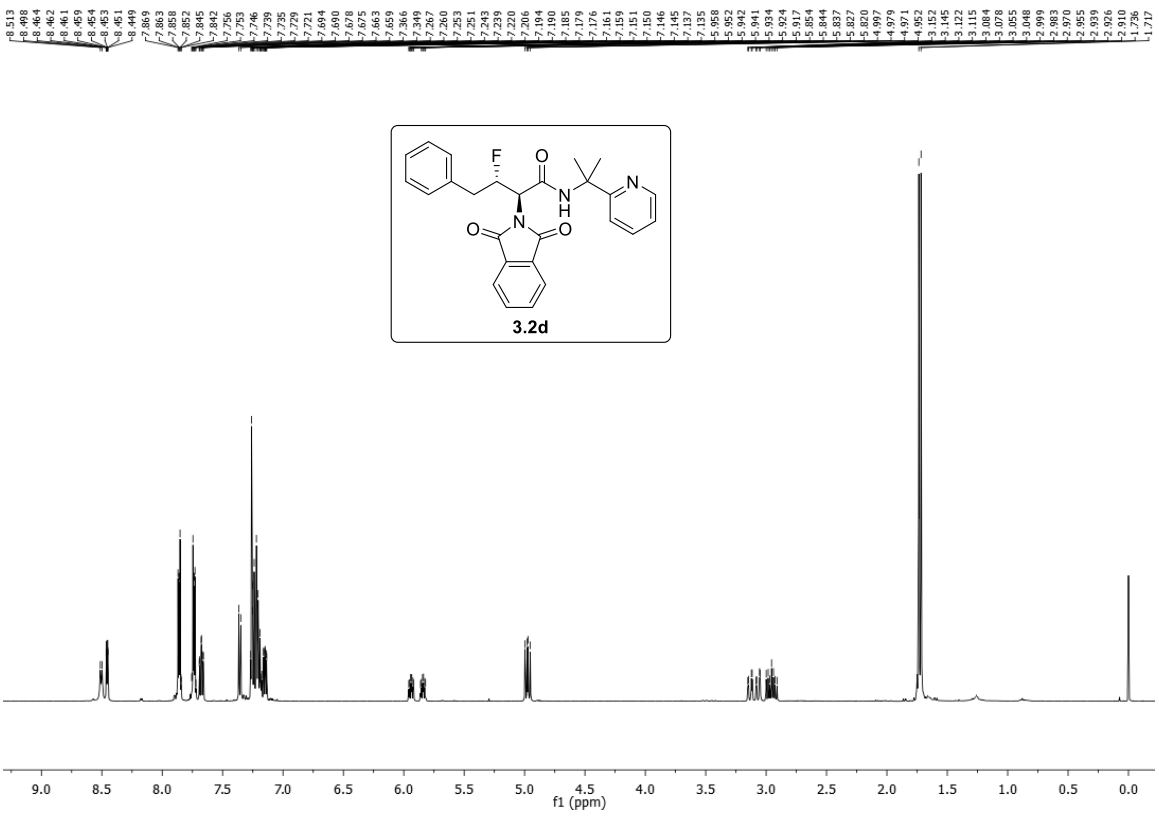
f1 (ppm)


3.2c'
f1 (ppm)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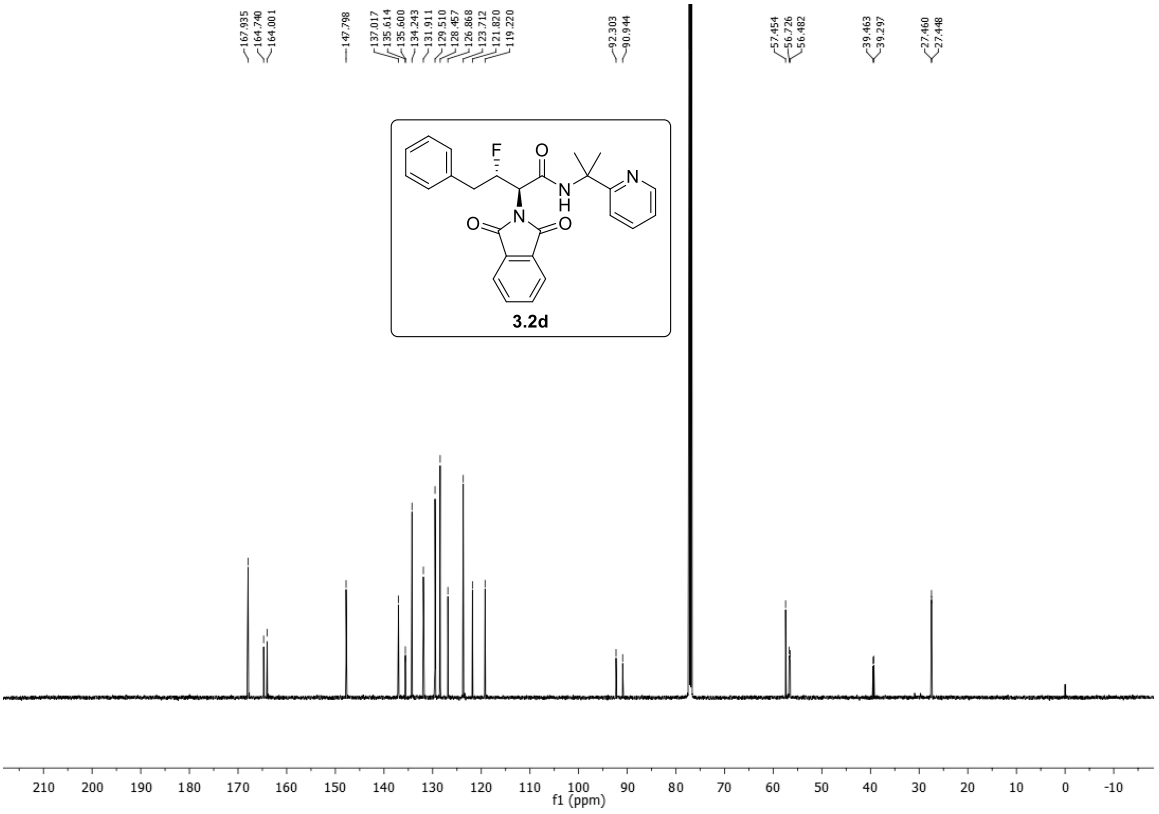
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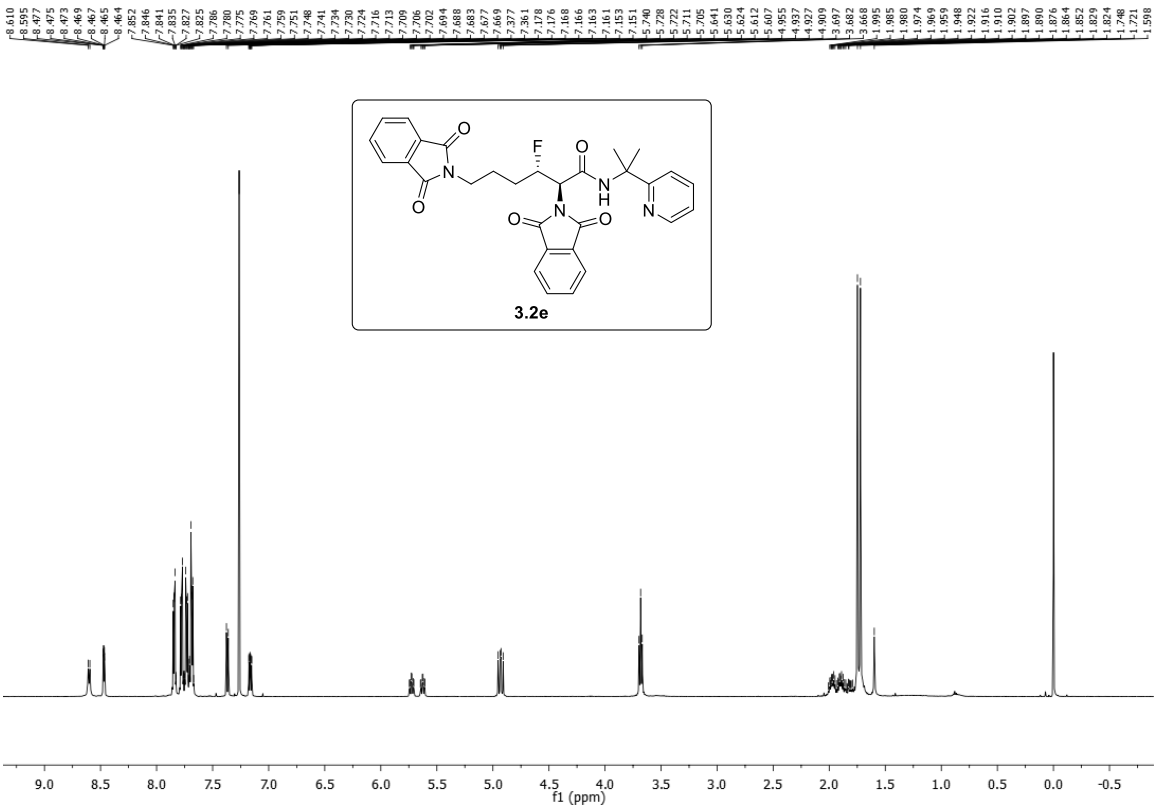
f1 (ppm)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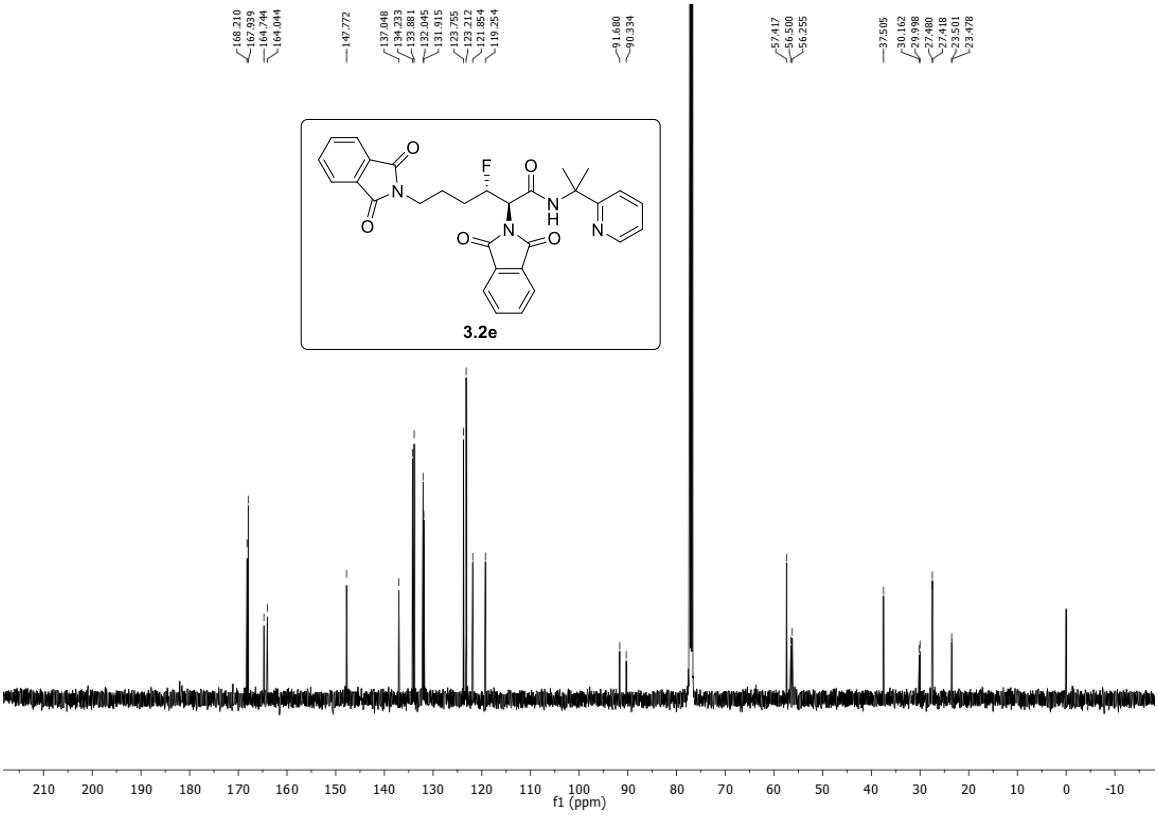
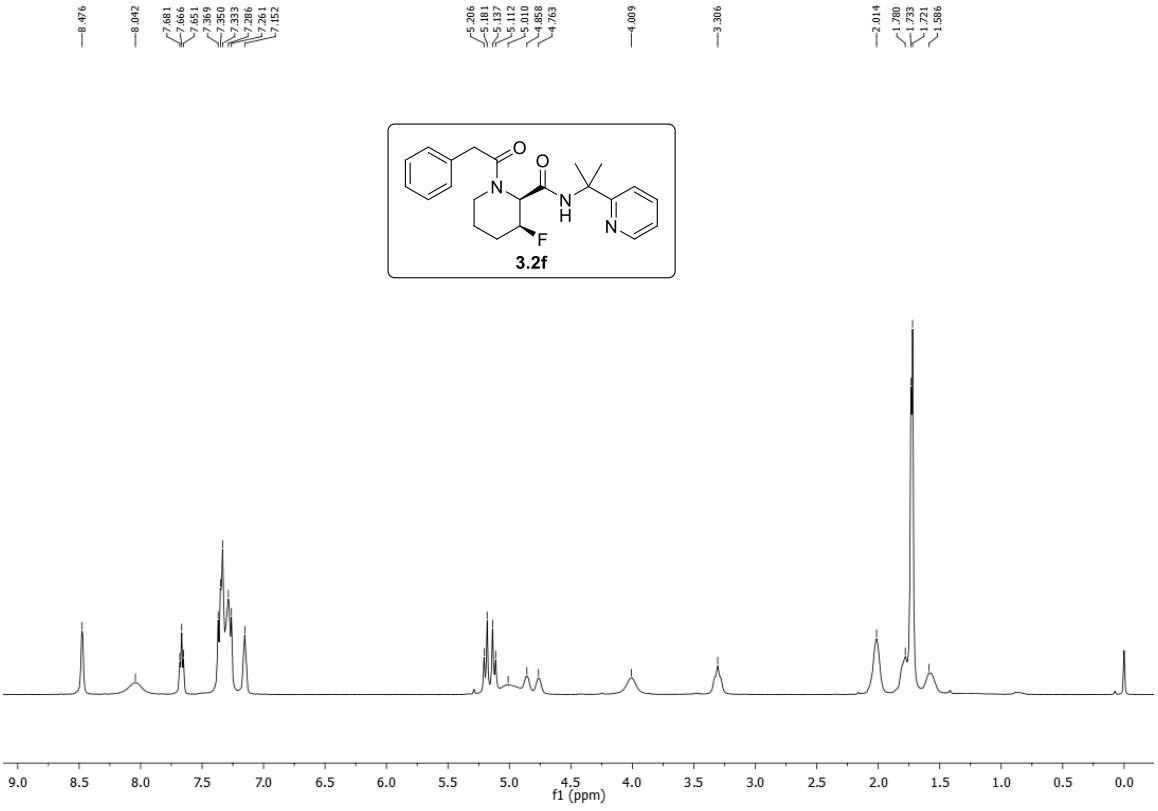
f1 (ppm)


3.2e
f1 (ppm)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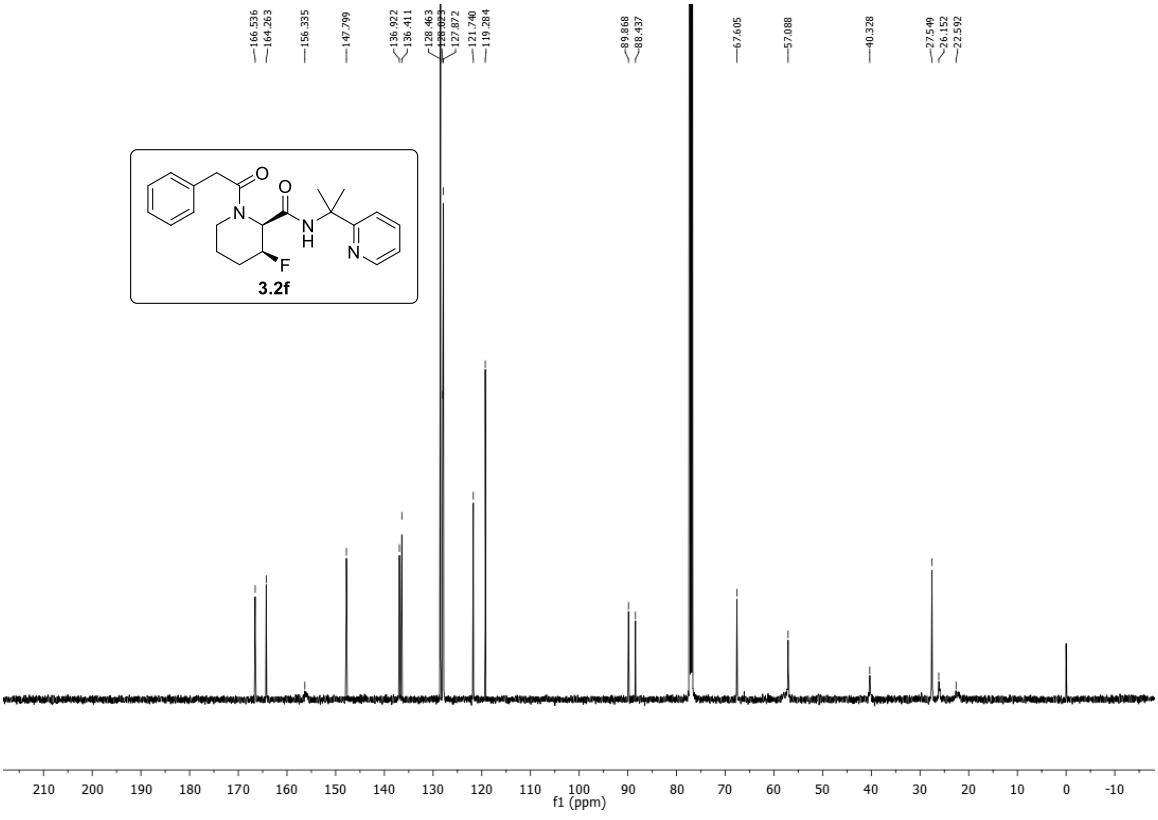
8.042
7.681
7.666
7.661
7.369
7.350
7.333
7.286
7.261
7.152
5.206
5.181
5.137
5.112
5.010
4.858
4.763
4.009
3.306
2.014
1.780
1.733
1.721
1.586
3.2f
f1 (ppm)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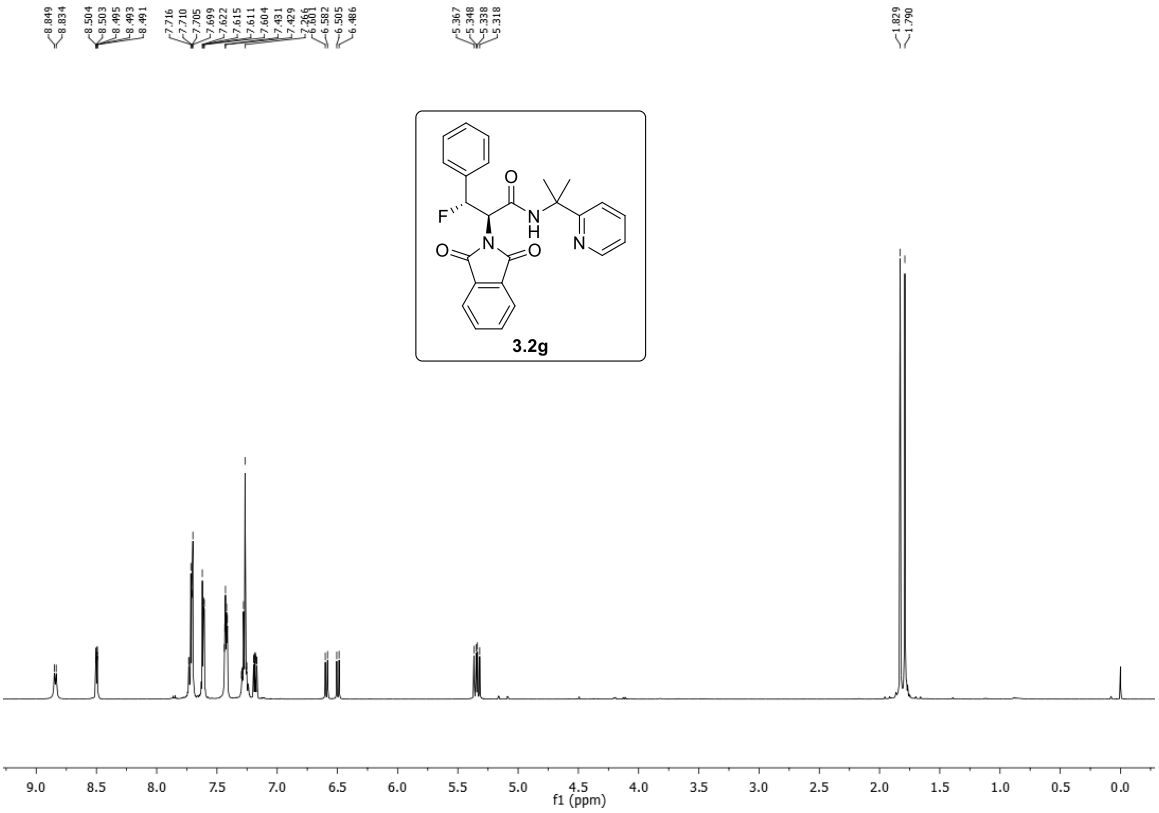
164.263
156.335
147.799
136.922
136.411
128.463
127.872
121.740
119.284
89.868
88.437
67.605
57.088
40.328
27.549
26.152
22.592
3.2f
f1 (ppm)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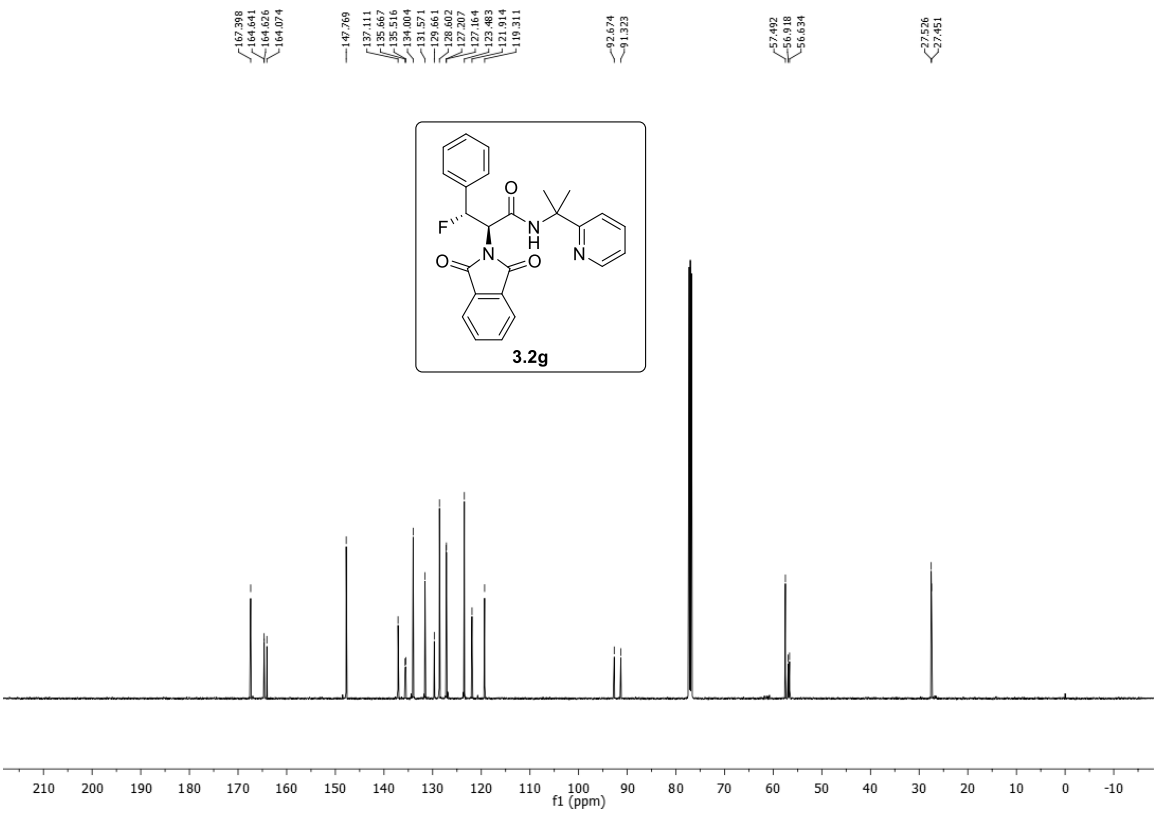
8.834
8.504
8.503
8.495
8.493
8.491
7.716
7.710
7.705
7.699
7.622
7.615
7.611
7.604
7.481
7.429
7.364
7.361
6.582
6.505
6.486
5.367
5.348
5.338
5.318
1.829
1.790
F
O
N
H
O
O
N
N
3.2g
f1 (ppm)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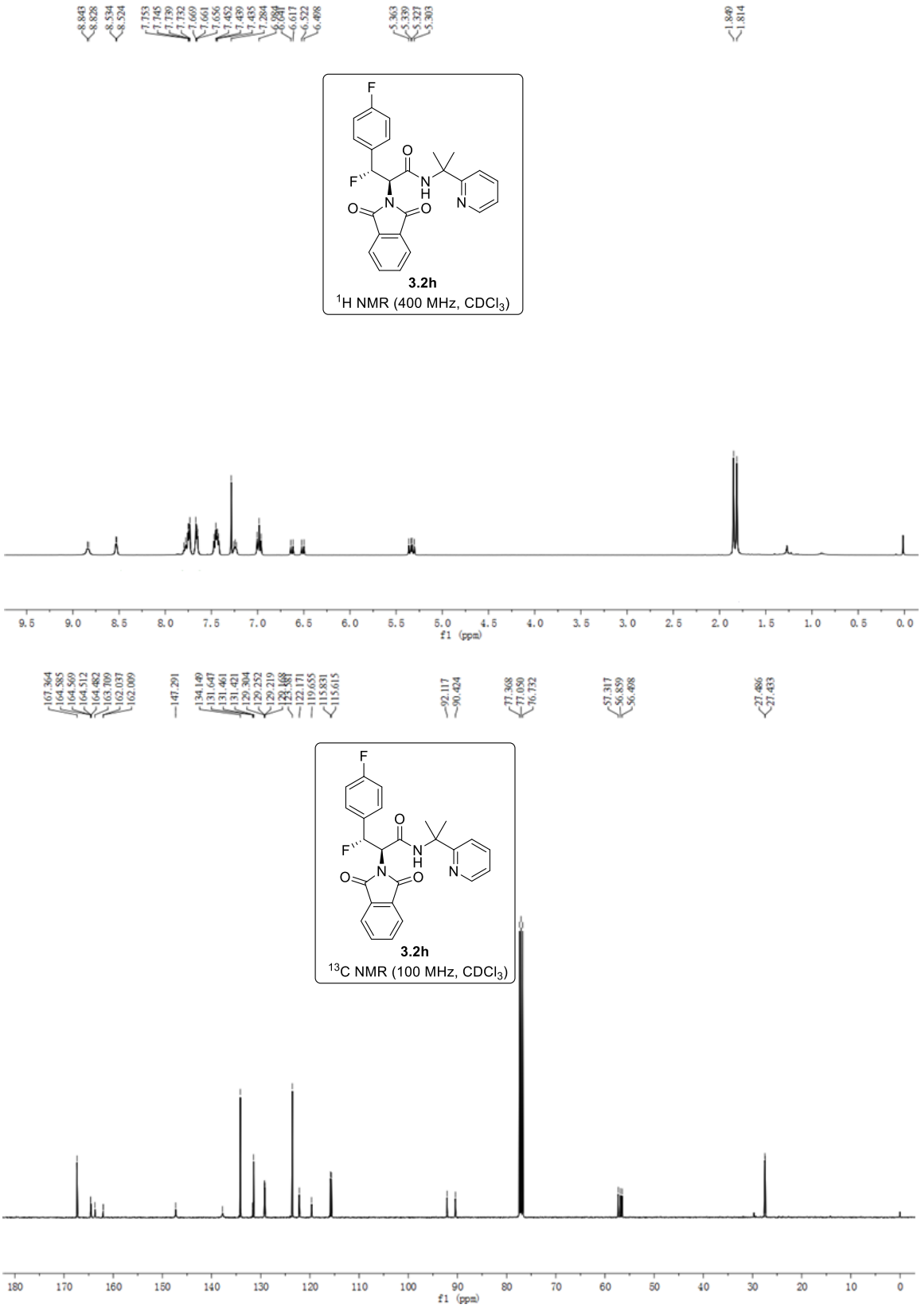
164.641
164.626
164.074
147.769
137.111
135.667
135.516
134.004
131.571
129.661
128.602
127.207
127.164
123.483
121.914
119.311
92.674
91.323
57.492
56.918
56.634
27.526
27.451
F
O
N
H
O
O
N
N
3.2g
f1 (ppm)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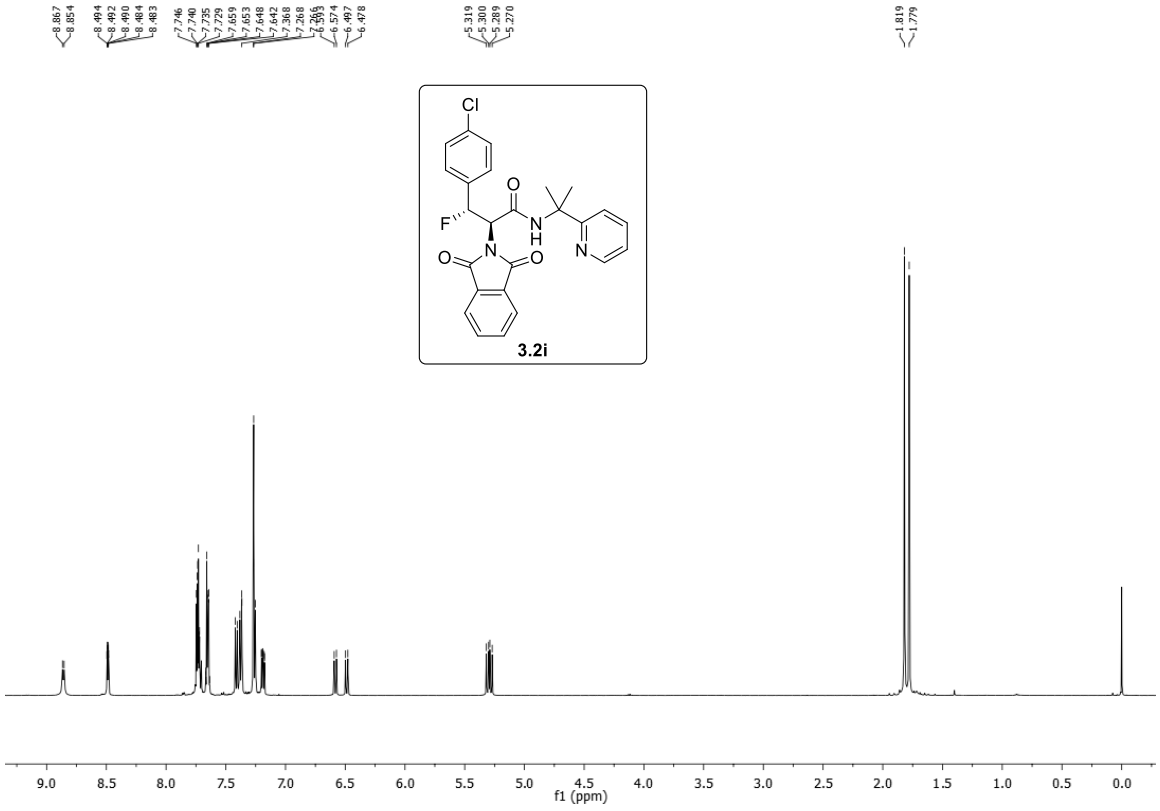
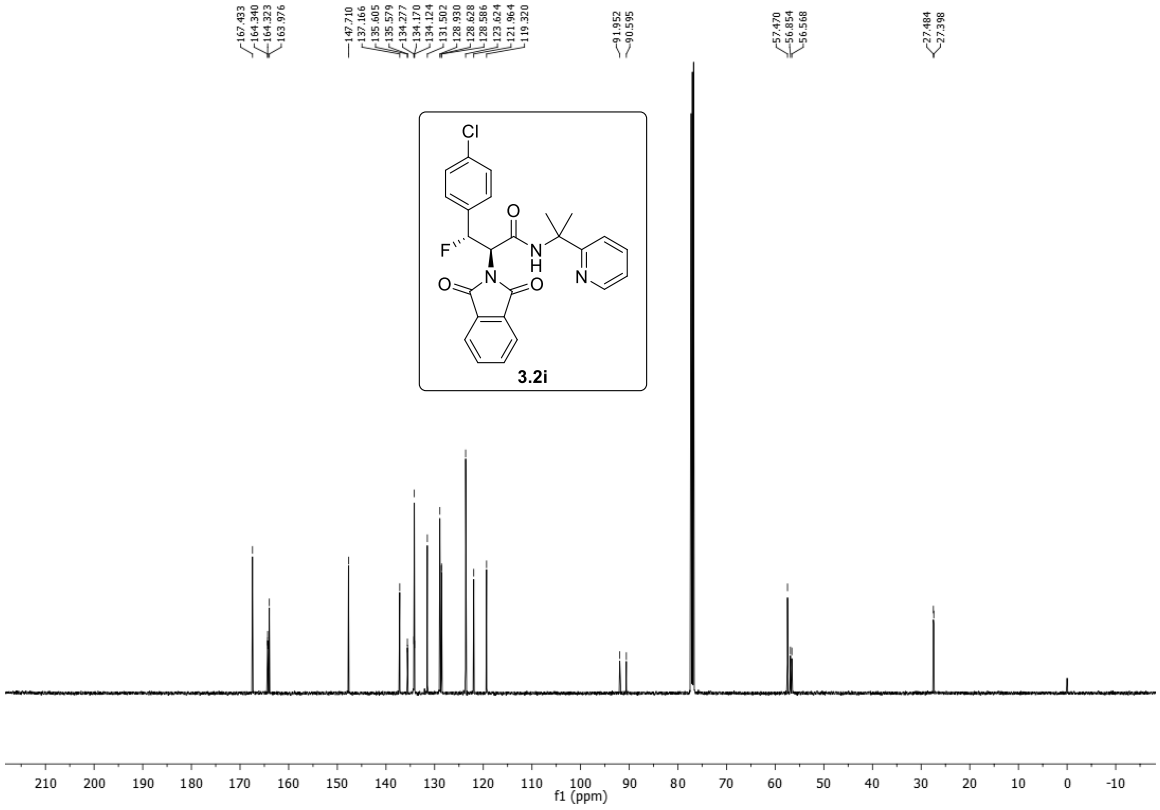
8.828
8.534
8.524
7.753
7.745
7.739
7.732
7.660
7.661
7.656
7.452
7.439
7.435
7.284
6.884
6.617
6.522
6.498
5.363
5.339
5.327
5.303
1.849
1.814
F
O
F
N
H
N
O
N
O
3.2h
1H NMR (400 MHz, CDCl3)
f1 (ppm)
167.364
164.585
164.569
164.512
164.482
163.709
162.037
162.069
147.291
134.149
131.647
131.461
131.421
129.304
129.252
129.219
123.581
122.171
119.655
115.831
115.615
92.117
90.424
77.368
77.050
76.732
57.317
56.859
56.498
27.486
27.433
F
O
F
N
H
N
O
N
O
3.2h
13C NMR (100 MHz, CDCl3)
f1 (ppm)


8.867
8.854
8.494
8.492
8.490
8.484
8.483
7.746
7.740
7.735
7.729
7.659
7.653
7.648
7.642
7.368
7.268
6.574
6.497
6.478
5.319
5.300
5.289
5.270
1.819
1.779
Cl
F
O
N
H
N
O
N
O
3.2i
f1 (ppm)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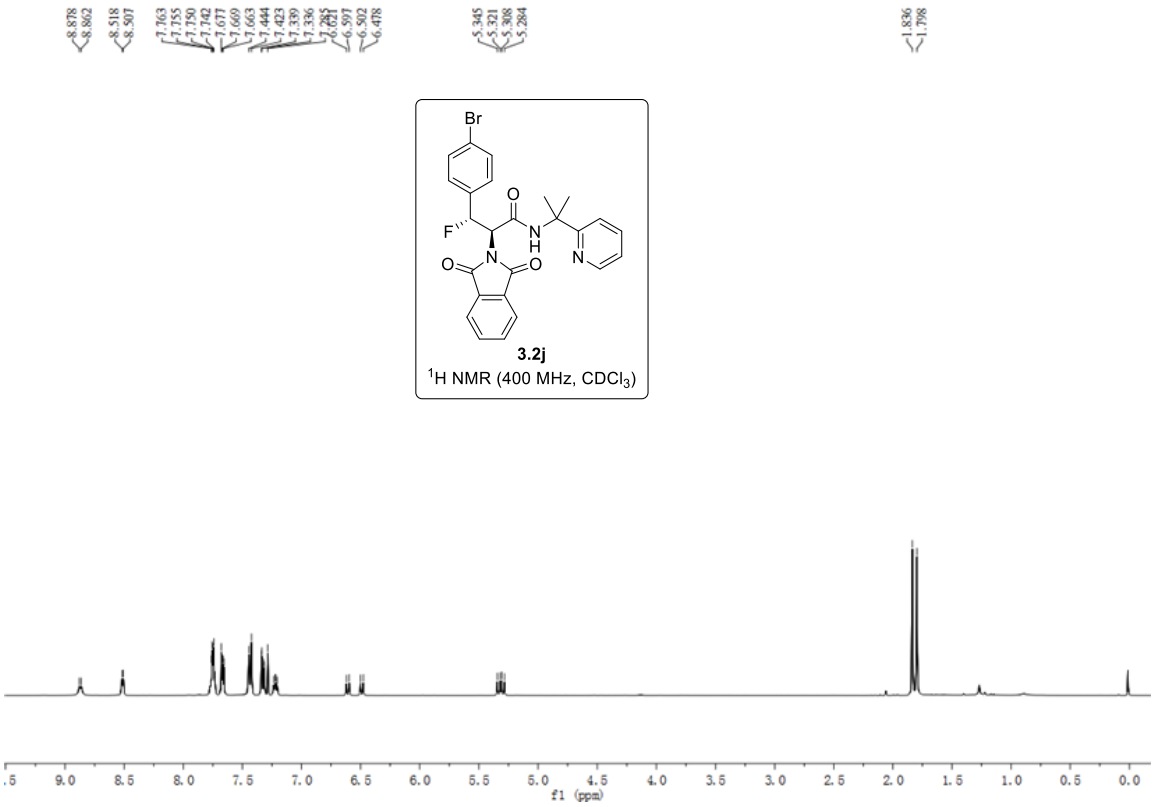
164.340
164.323
163.976
147.710
137.166
135.605
135.579
135.277
134.170
134.124
131.502
128.930
128.628
128.586
123.624
121.964
119.320
91.952
90.595
57.470
56.854
56.568
27.484
27.398
Cl
F
O
N
H
N
O
N
O
3.2i
f1 (ppm)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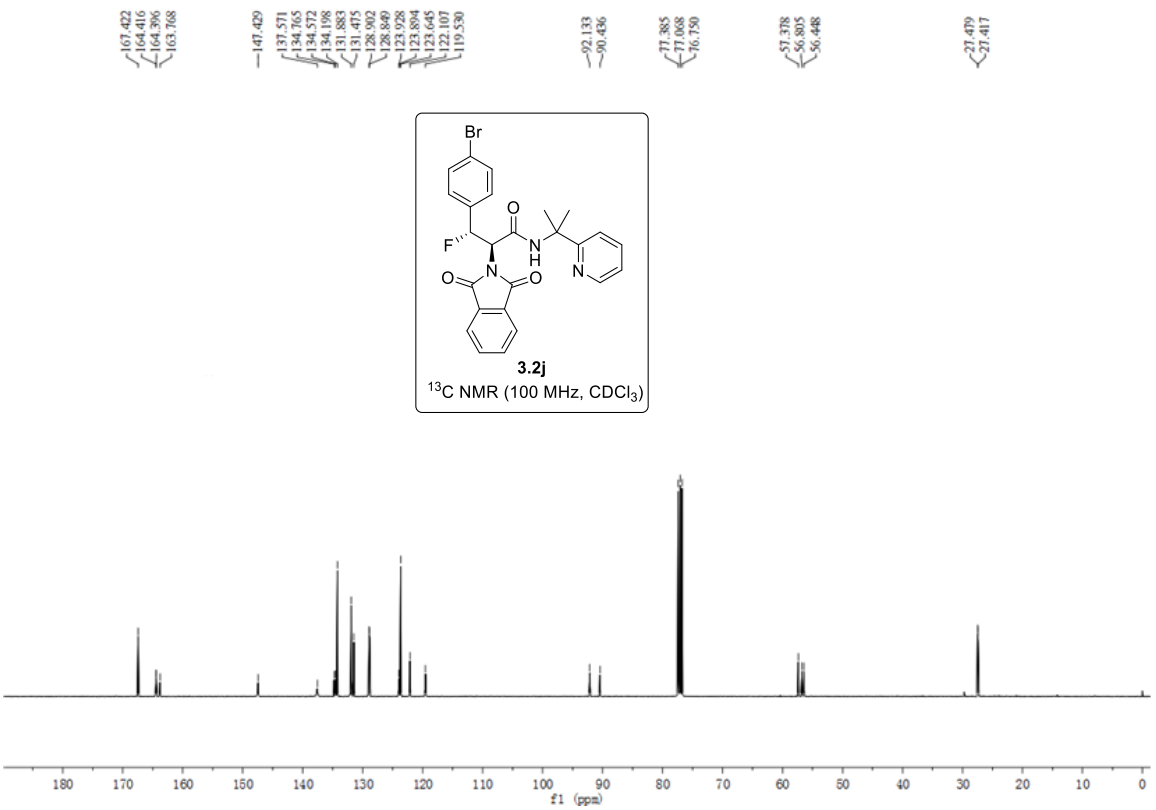
8.862
8.518
8.507
7.763
7.755
7.750
7.742
7.677
7.669
7.663
7.444
7.423
7.339
7.336
6.621
6.597
6.502
6.478
5.345
5.321
5.308
5.284
1.836
1.798
Br
F
O
N
H
N
O
N
O
3.2j
1H NMR (400 MHz, CDCl3)
f1 (ppm)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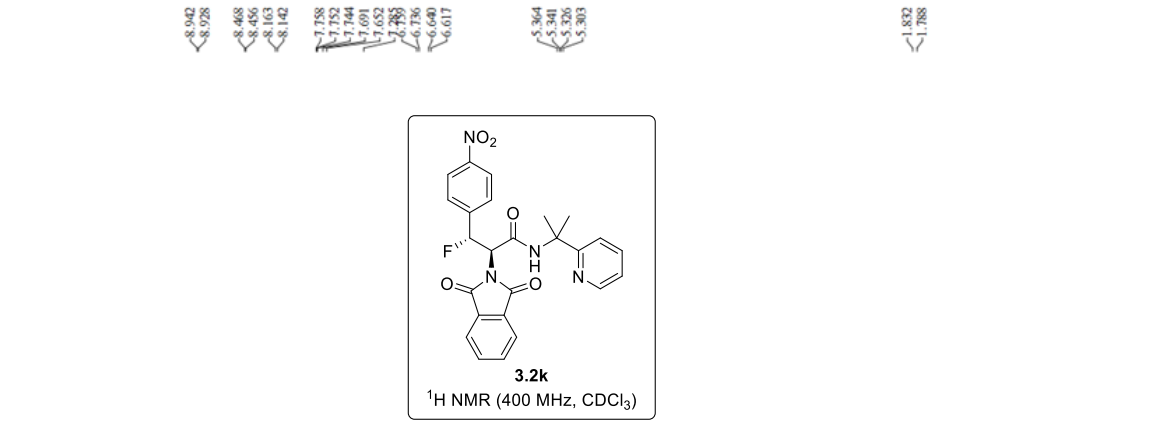
164.416
164.396
163.768
147.429
137.571
134.765
134.572
134.198
131.883
131.475
128.902
128.849
123.928
123.894
123.645
122.107
119.530
92.133
90.436
77.385
77.068
76.750
57.378
56.805
56.448
27.479
27.417
Br
F
O
N
H
N
O
N
O
3.2j
13C NMR (100 MHz, CDCl3)
f1 (ppm)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8.468
8.456
8.163
8.142
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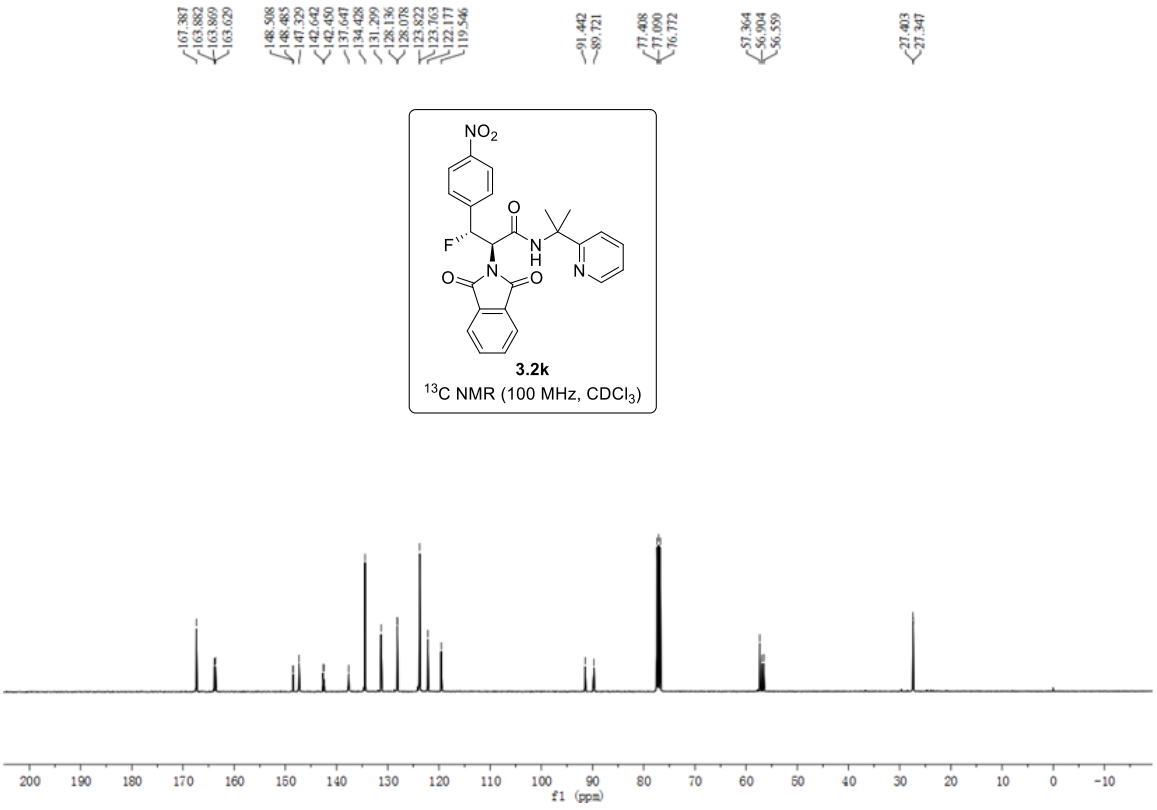
7.752
7.744
7.691
7.652
6.736
6.640
6.617
5.364
5.341
5.326
5.303
1.832
1.788
NO2
O
F
N
H
N
O
O
N
3.2k
1H NMR (400 MHz, CDCl3)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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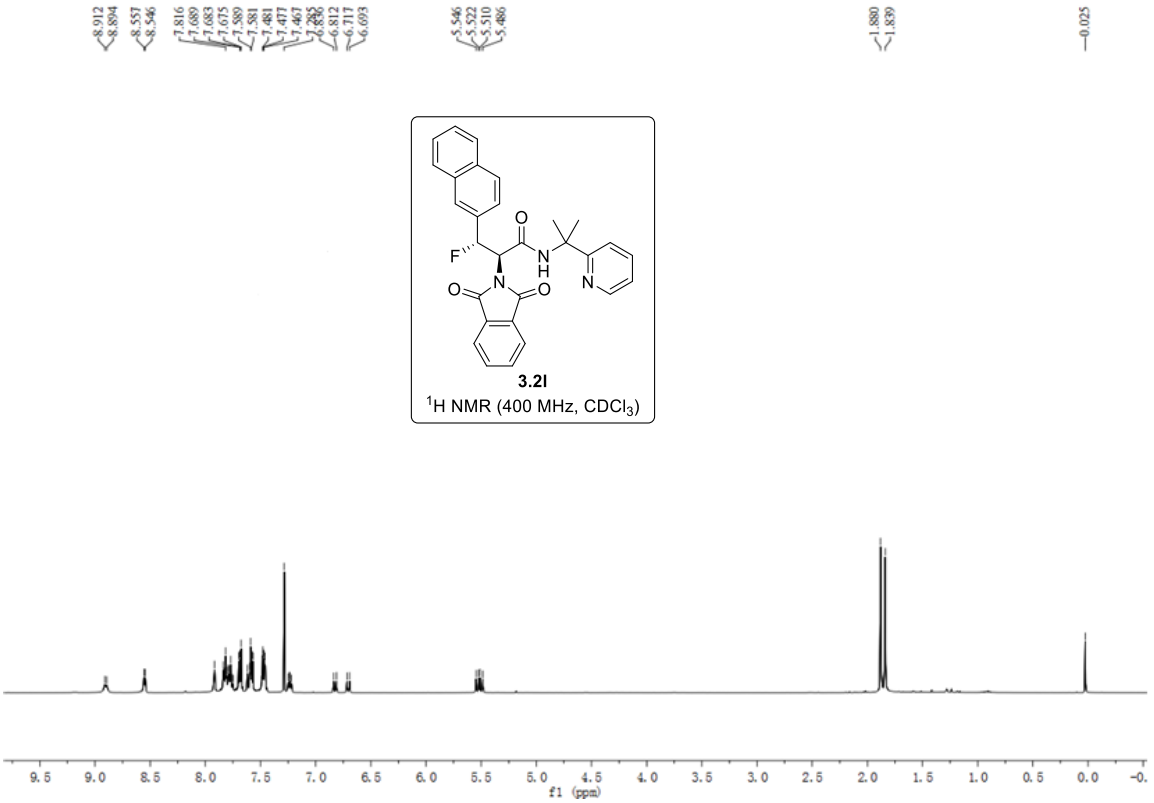
163.629
148.508
148.485
147.329
142.642
142.450
137.641
134.428
131.299
128.136
128.078
123.822
123.763
122.177
119.546
91.442
89.721
77.408
77.090
76.772
57.364
56.904
56.559
27.403
27.347
NO2
O
F
N
H
N
O
O
N
3.2k
13C NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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8.546
7.816
7.689
7.683
7.675
7.589
7.581
7.481
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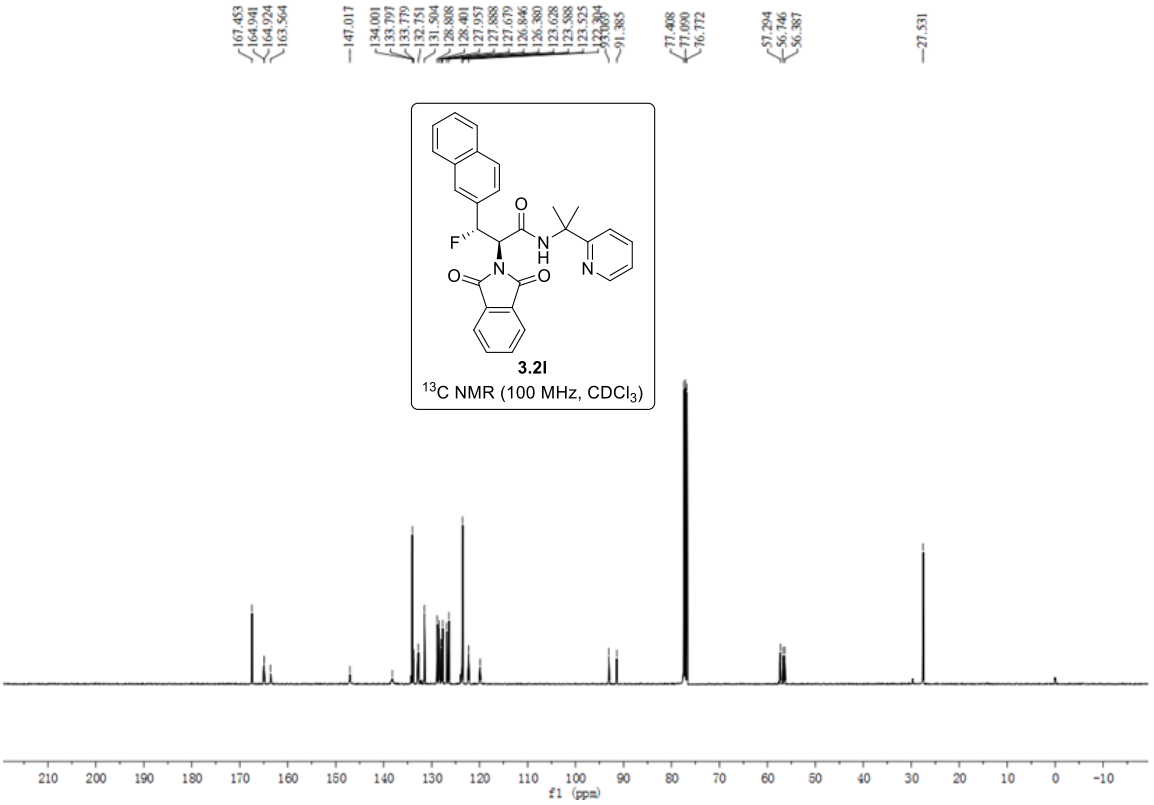
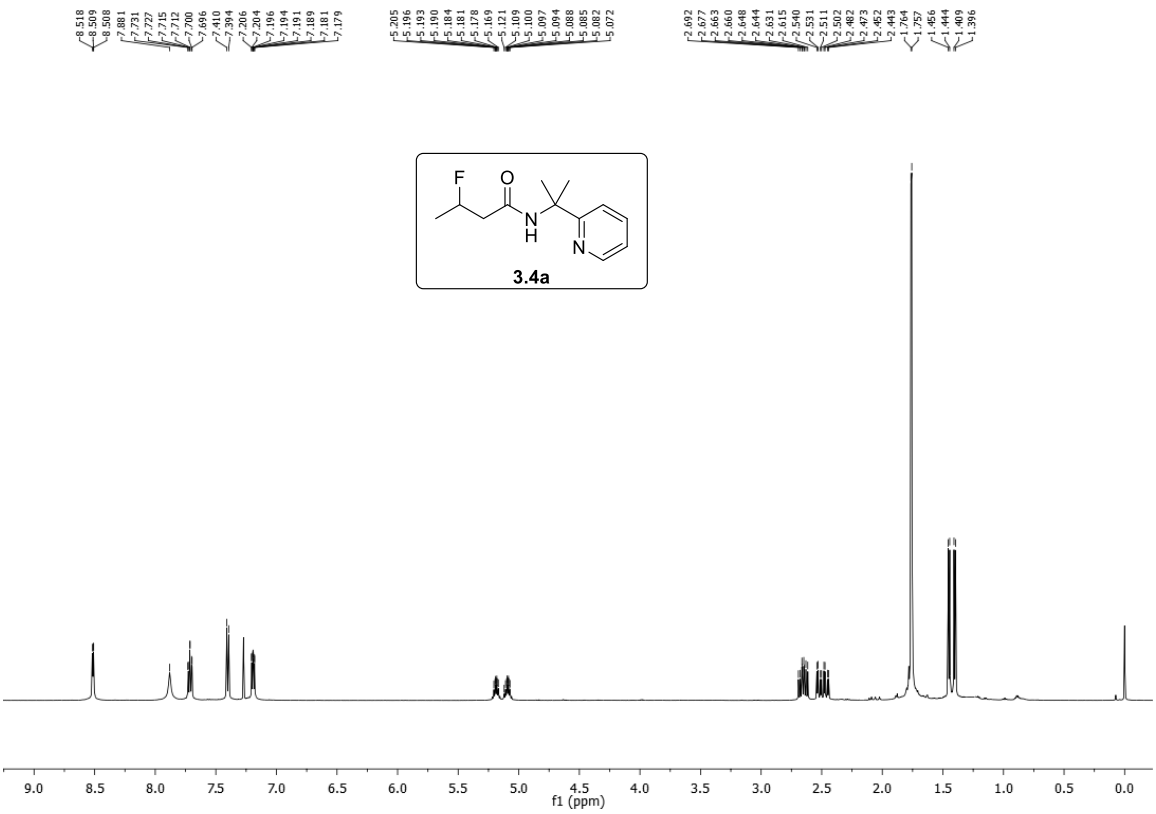
7.467
7.285
6.838
6.812
6.717
6.693
5.546
5.522
5.510
5.486
1.880
1.839
0.025
F
O
N
H
O
O
N
3.2l
1H NMR (400 MHz, CDCl3)
f1 (ppm)


167.453
164.941
164.924
163.564
147.017
134.001
133.797
133.779
132.751
131.504
128.808
128.401
127.957
127.888
127.679
126.846
126.380
123.628
123.588
123.525
91.385
77.408
77.090
76.772
57.294
56.746
56.387
27.531
F
O
N
H
O
O
N
3.2l
13C NMR (100 MHz, CDCl3)
f1 (ppm)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8.508
7.801
7.731
7.727
7.715
7.712
7.700
7.696
7.410
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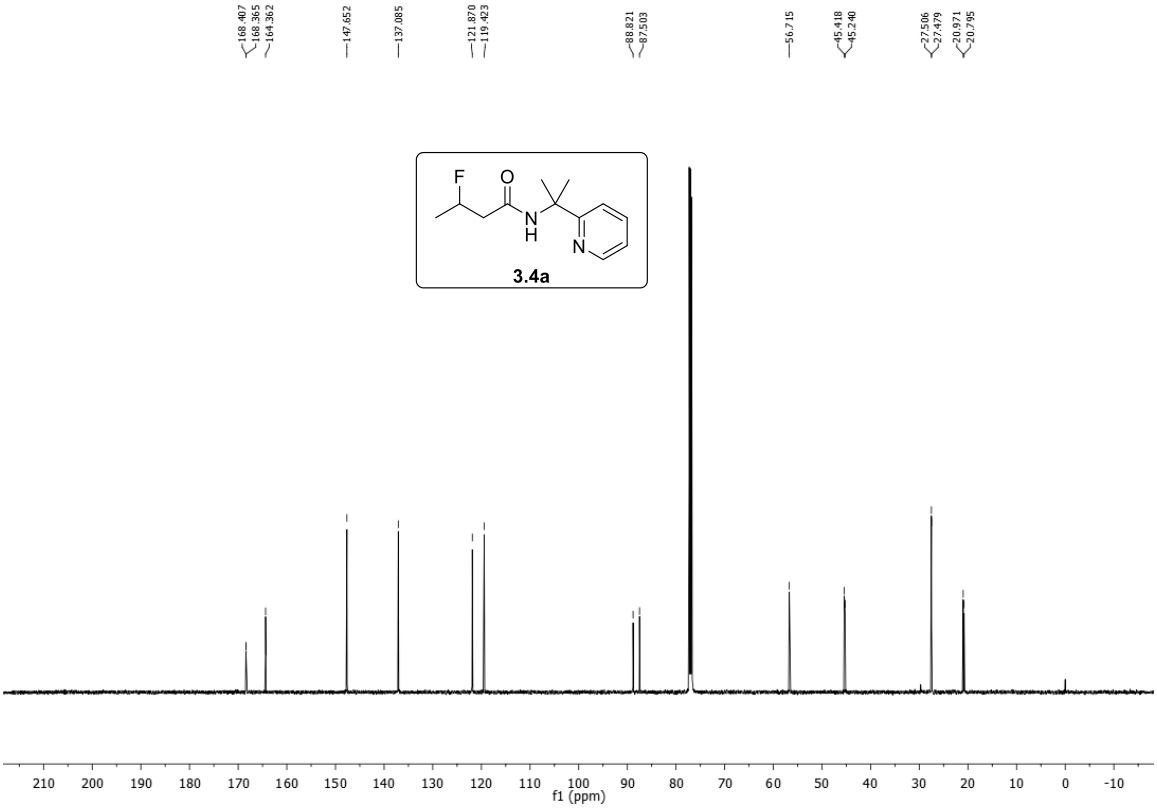
7.206
7.204
7.196
7.194
7.191
7.189
7.181
7.179
5.205
5.196
5.193
5.190
5.184
5.181
5.178
5.169
5.121
5.109
5.100
5.097
5.094
5.088
5.085
5.082
5.072
2.692
2.677
2.663
2.660
2.648
2.644
2.631
2.615
2.540
2.531
2.511
2.502
2.482
2.473
2.462
1.748
1.744
1.757
1.456
1.444
1.409
1.396
F
O
N
H
N
3.4a
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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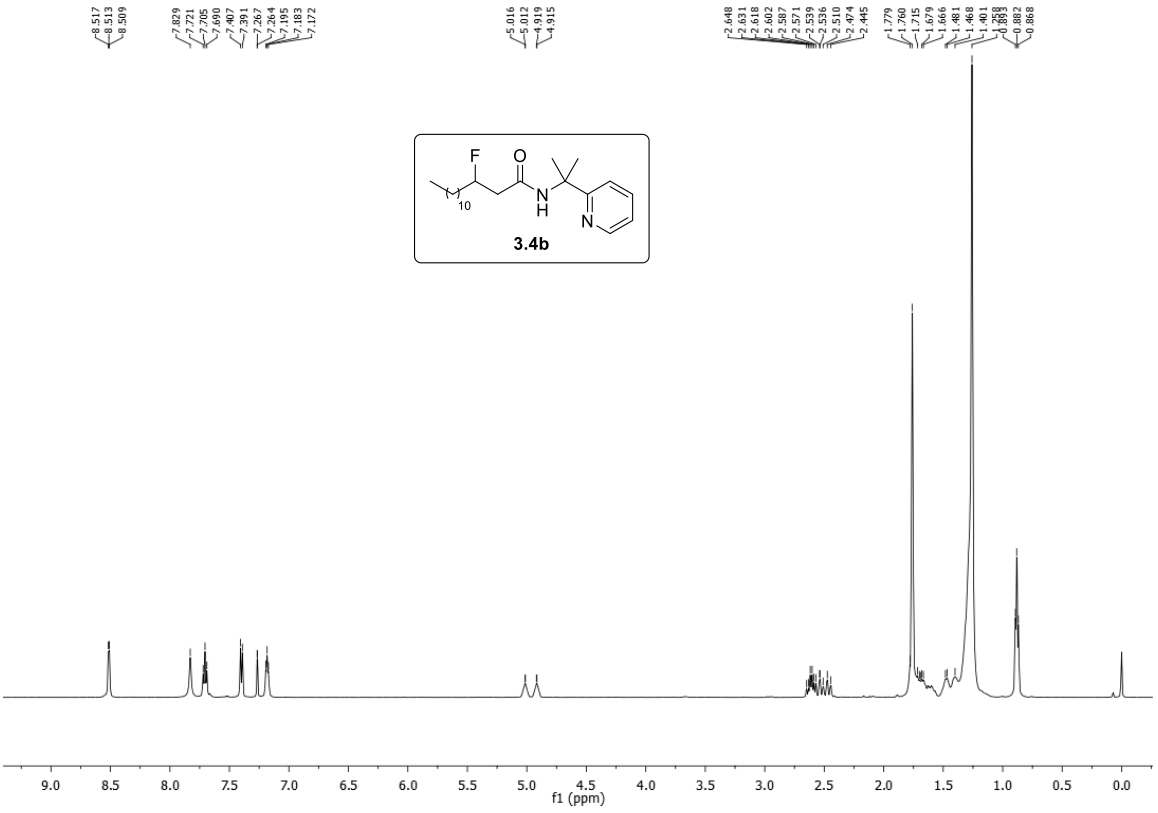
137.085
121.870
119.423
88.821
87.503
56.715
45.418
45.240
27.506
27.479
20.971
20.795
F
O
N
H
N
3.4a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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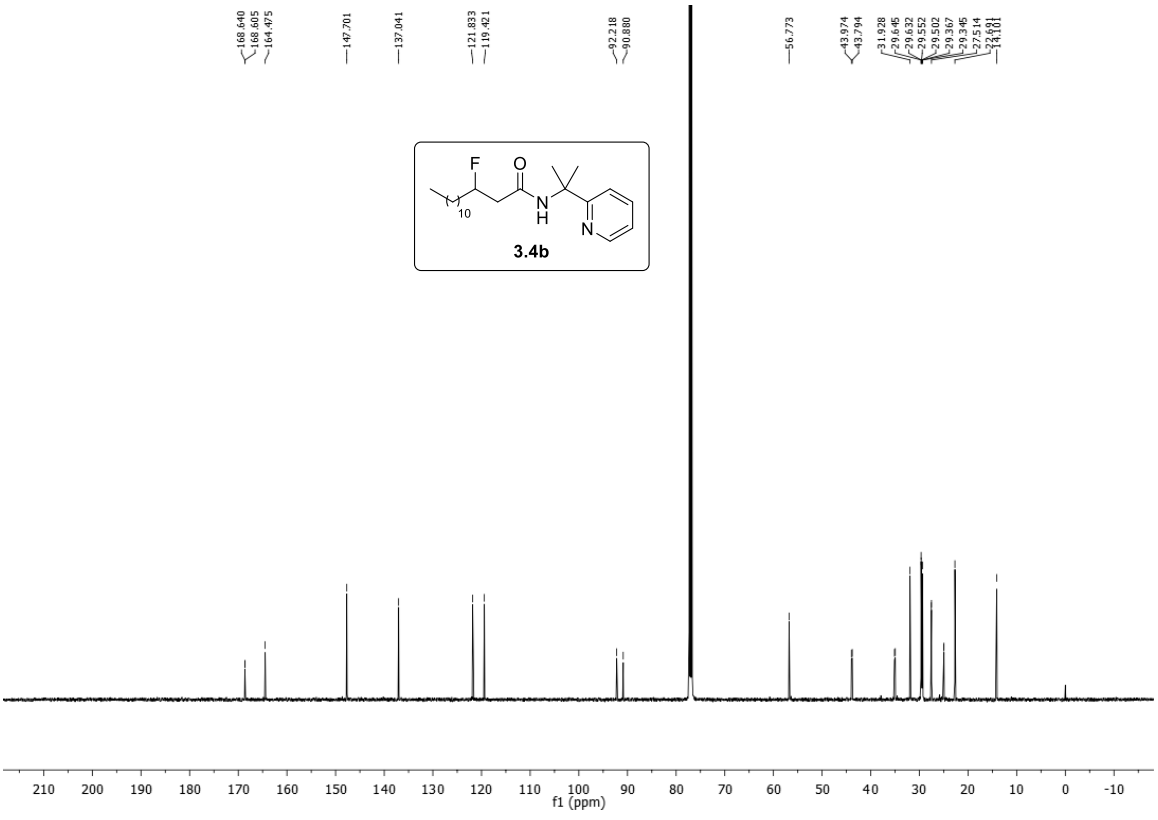
8.513
8.509
7.829
7.721
7.705
7.600
7.407
7.391
7.267
7.264
7.195
7.183
7.172
5.016
5.012
4.919
4.915
2.648
2.631
2.618
2.602
2.587
2.571
2.539
2.536
2.510
2.474
2.445
1.779
1.760
1.715
1.679
1.666
1.481
1.468
1.401
0.893
0.882
0.868
F
O
N
H
10
N
3.4b
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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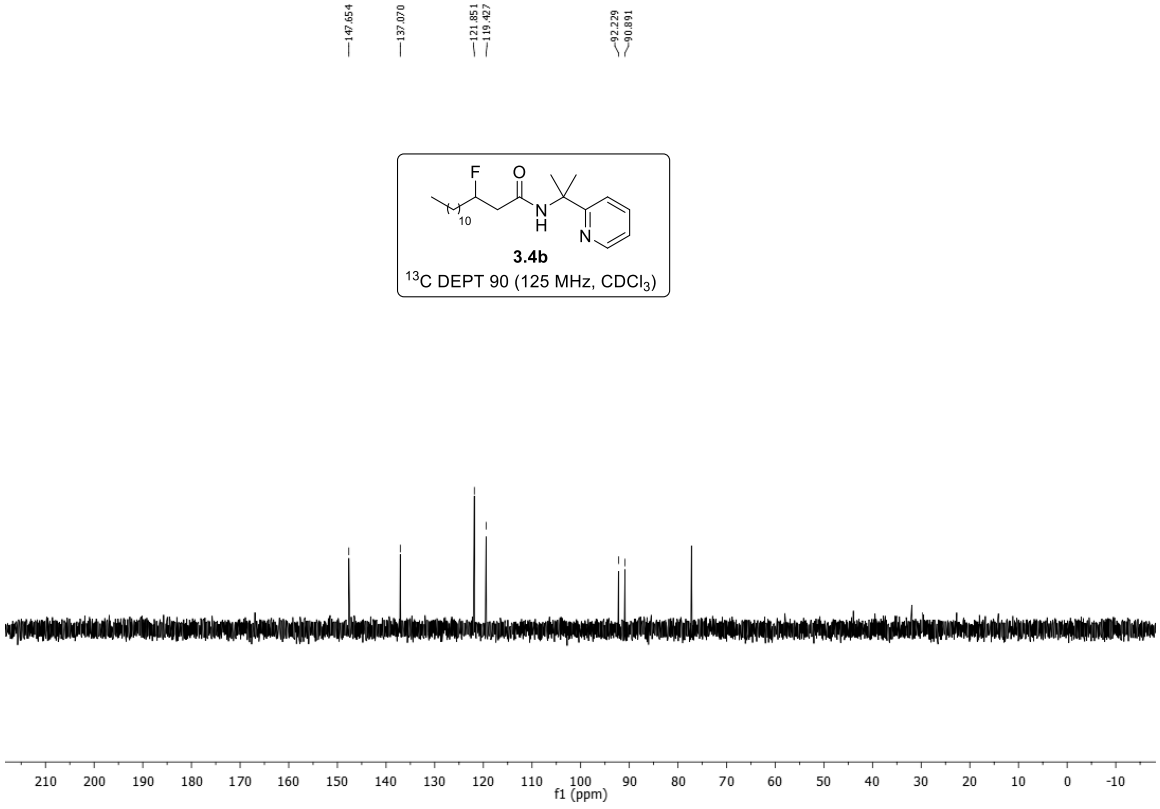
168.605
164.475
147.701
137.041
121.833
119.421
92.218
90.880
56.773
43.974
43.794
31.928
29.645
29.632
29.552
29.502
29.367
29.345
27.514
14.101
F
O
N
H
10
N
3.4b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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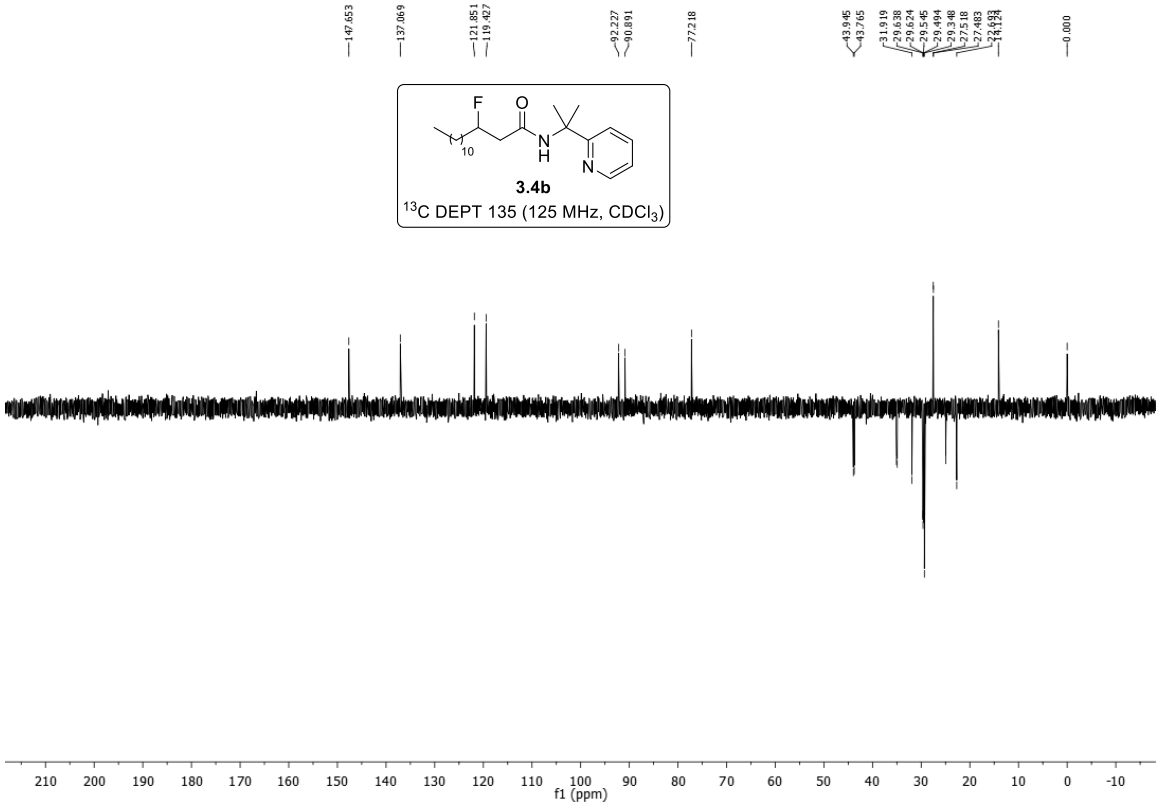
137.070
121.851
119.427
92.229
90.891
F
O
N
H
10
N
3.4b
13C DEPT 90 (125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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43.765
31.919
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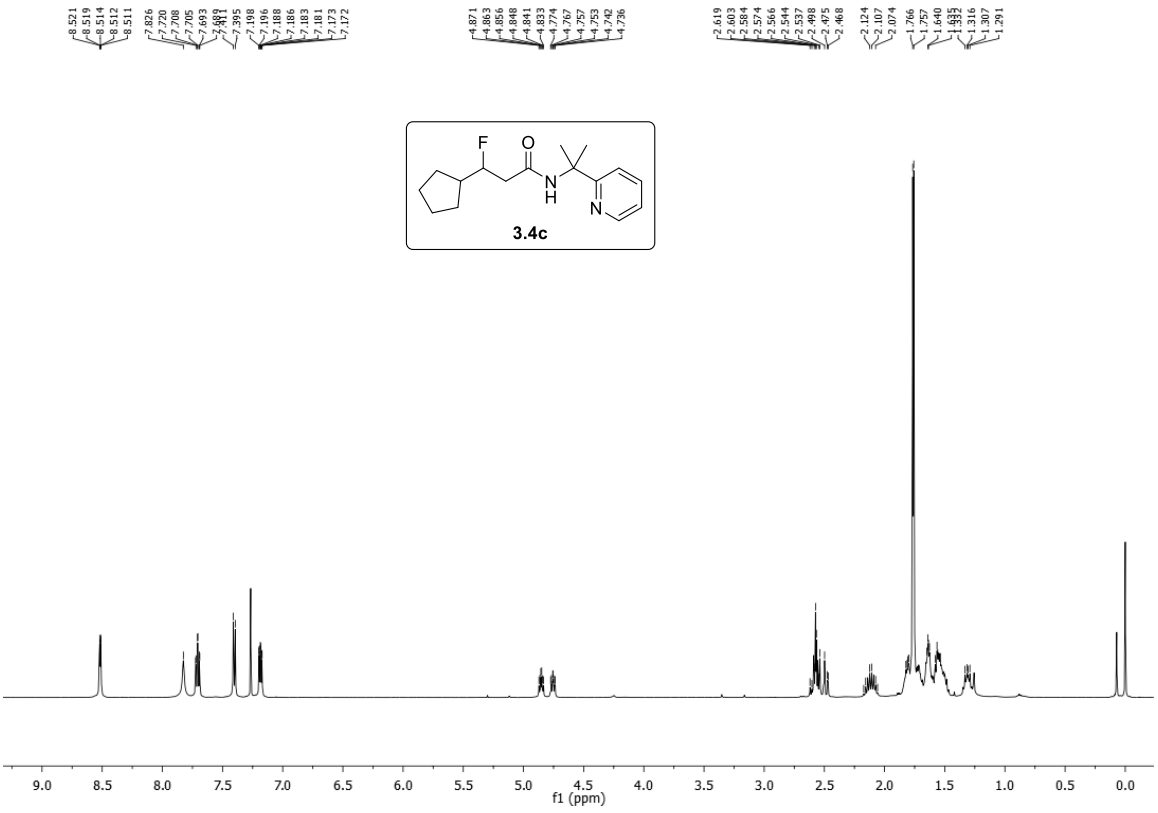
29.624
29.545
29.494
29.348
27.518
27.483
14.134
0.000
F
O
N
H
10
N
3.4b
13C DEPT 135 (125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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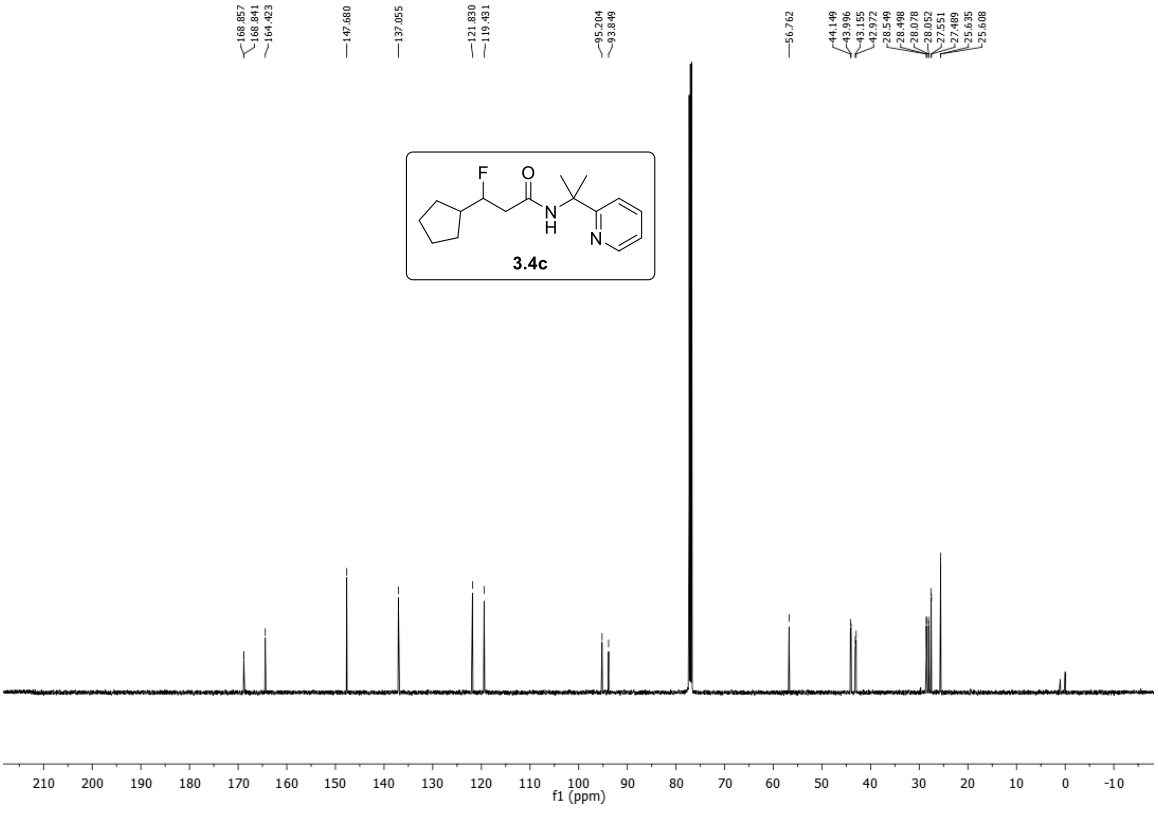
7.395
7.198
7.196
7.188
7.186
7.183
7.181
7.173
7.172
4.871
4.863
4.856
4.848
4.841
4.833
4.774
4.767
4.757
4.753
4.742
4.736
2.619
2.603
2.584
2.574
2.566
2.544
2.537
2.498
2.475
2.468
2.124
2.107
2.074
1.766
1.757
1.640
1.432
1.316
1.307
1.291
F
O
N
H
N
3.4c
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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119.491
95.204
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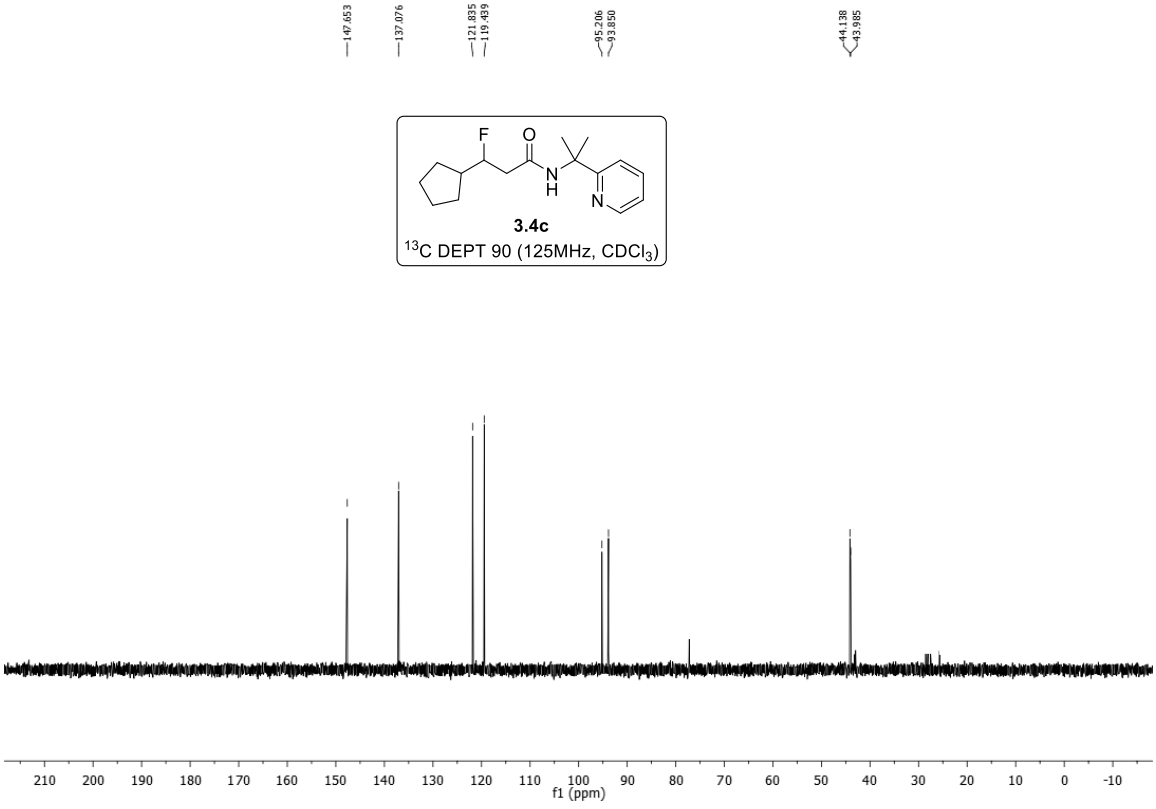
43.996
43.155
42.972
28.549
28.498
28.078
28.052
27.551
27.489
25.635
25.608
F
O
N
H
N
3.4c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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43.985
F
O
N
H
N
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13C DEPT 90 (125MHz, CDCl3)
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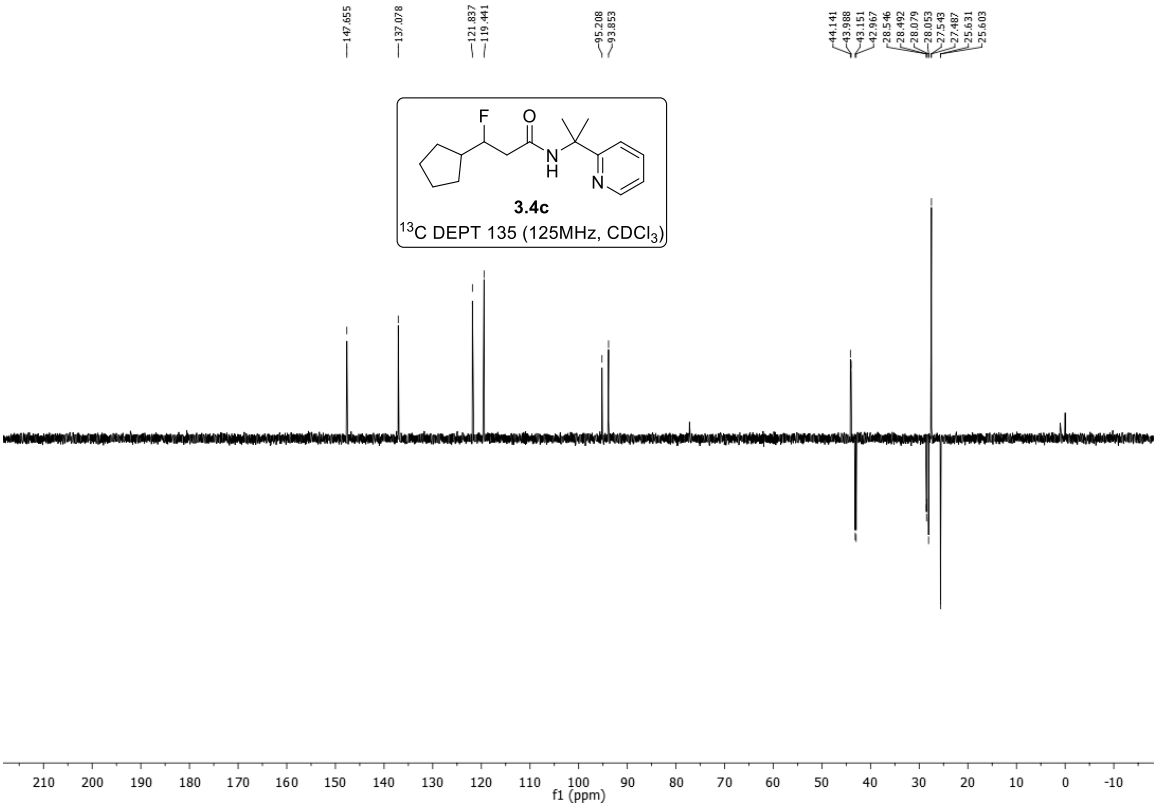
f1 (ppm)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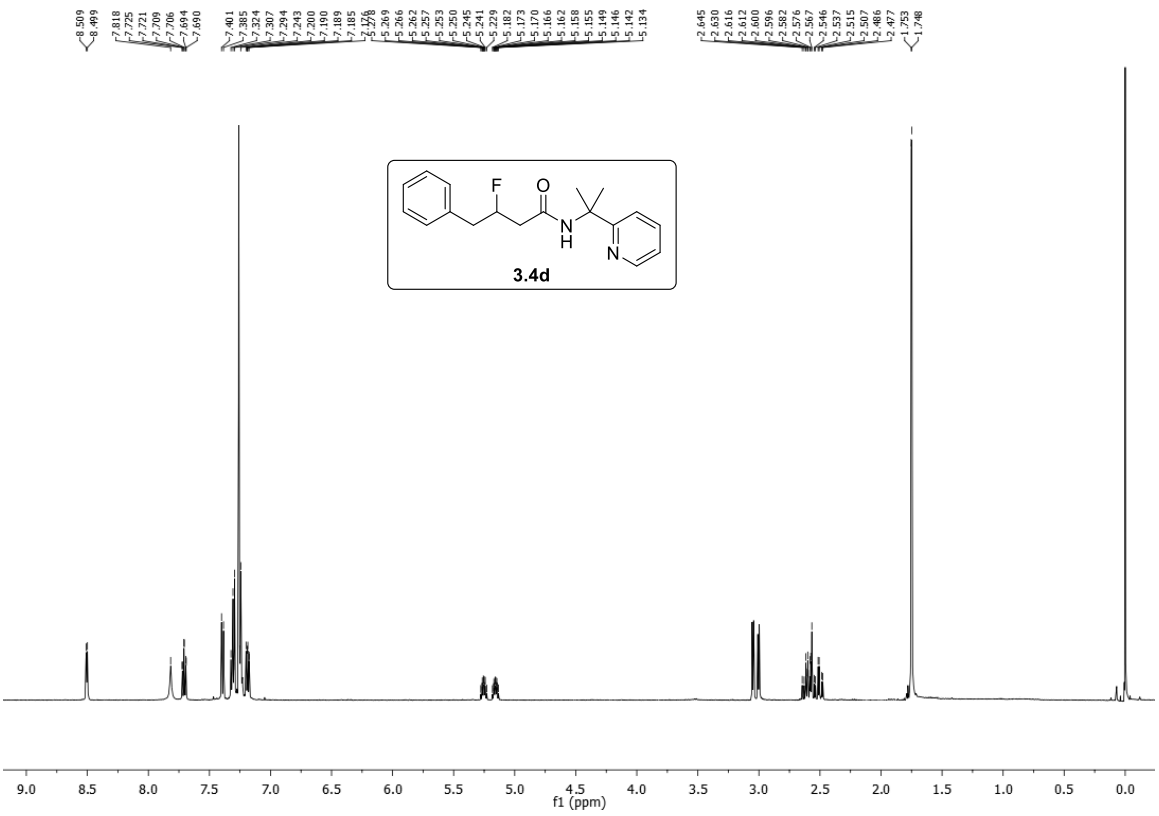
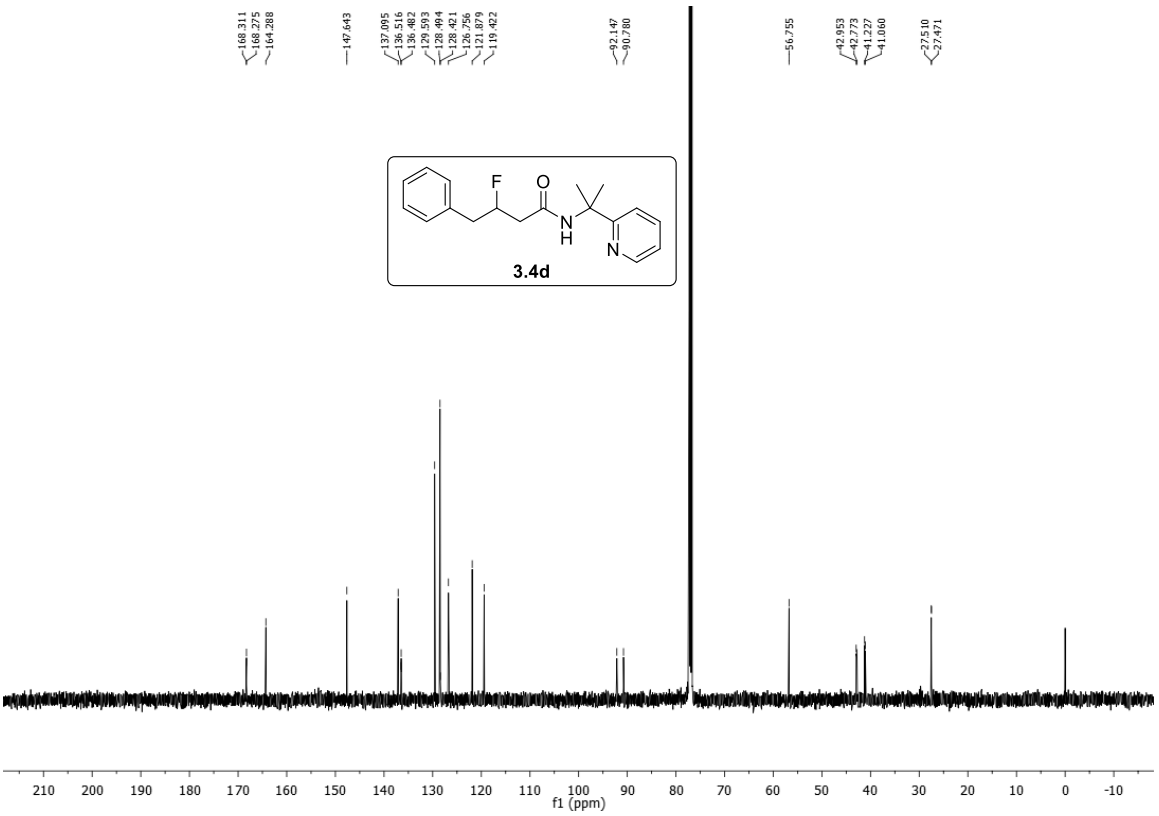
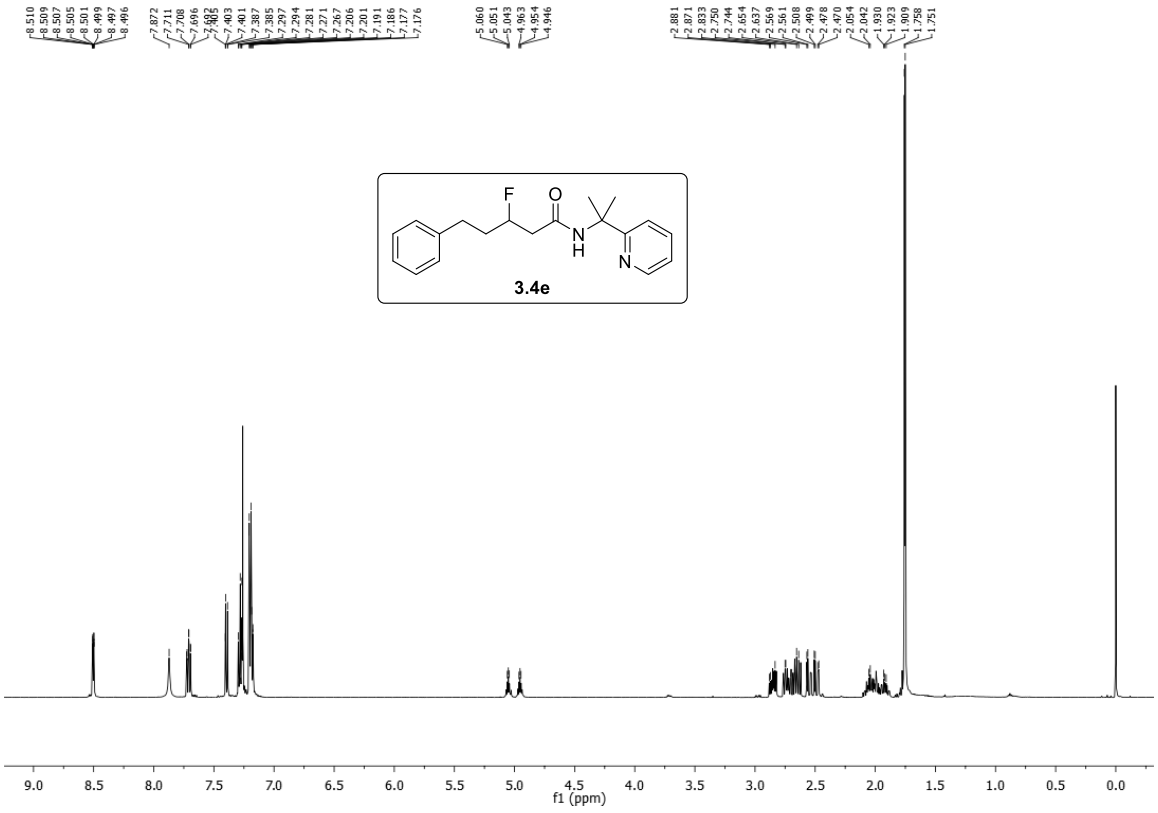
93.853
44.141
43.988
43.151
42.967
28.546
28.492
28.079
28.053
27.543
27.487
25.631
25.603
F
O
N
H
N
3.4c
13C DEPT 135 (125MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


F
O
N
H
N
3.4d
f1 (ppm)


F
O
N
H
N
3.4d
f1 (ppm)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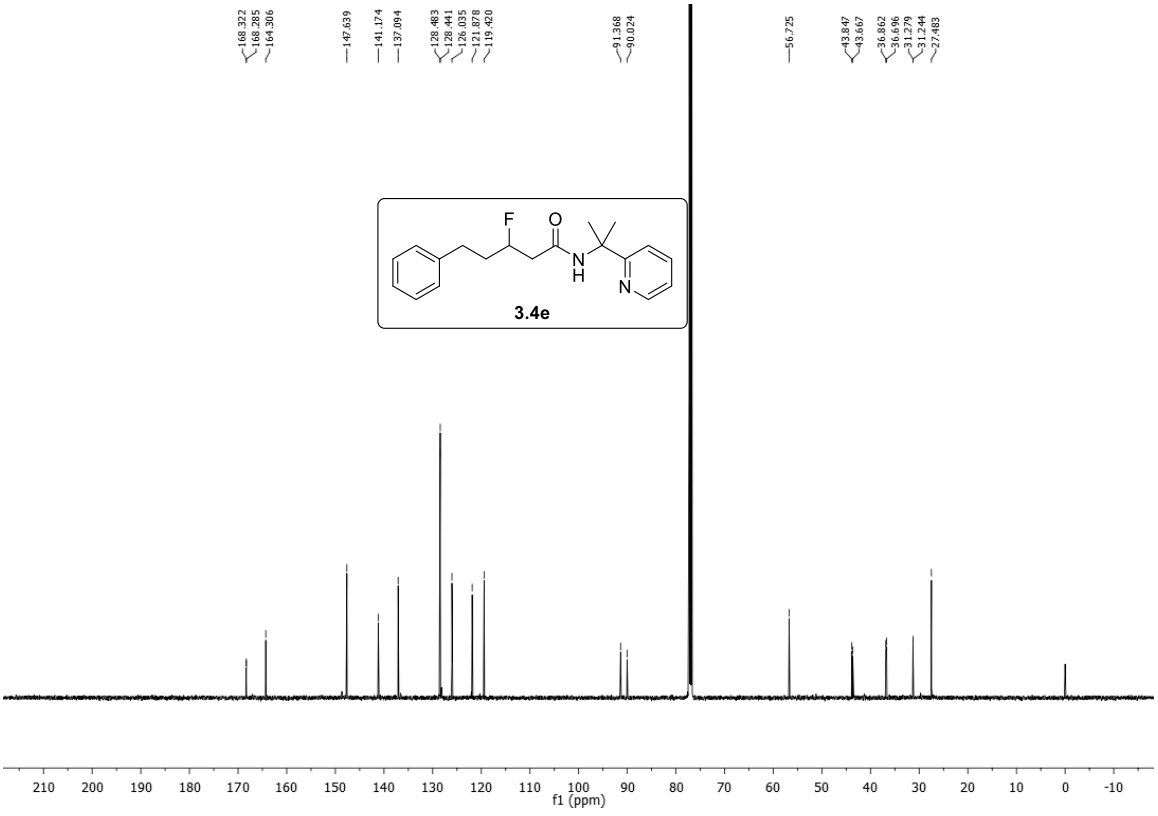
8.509
8.507
8.505
8.501
8.499
8.497
8.496
7.872
7.711
7.708
7.696
7.403
7.401
7.387
7.385
7.297
7.294
7.281
7.271
7.267
7.206
7.201
7.191
7.186
7.177
7.176
5.060
5.051
5.043
4.963
4.954
4.946
2.881
2.871
2.833
2.750
2.744
2.654
2.637
2.569
2.561
2.508
2.499
2.478
2.470
2.054
2.042
1.930
1.923
1.909
1.758
1.751
F
O
N
H
N
3.4e
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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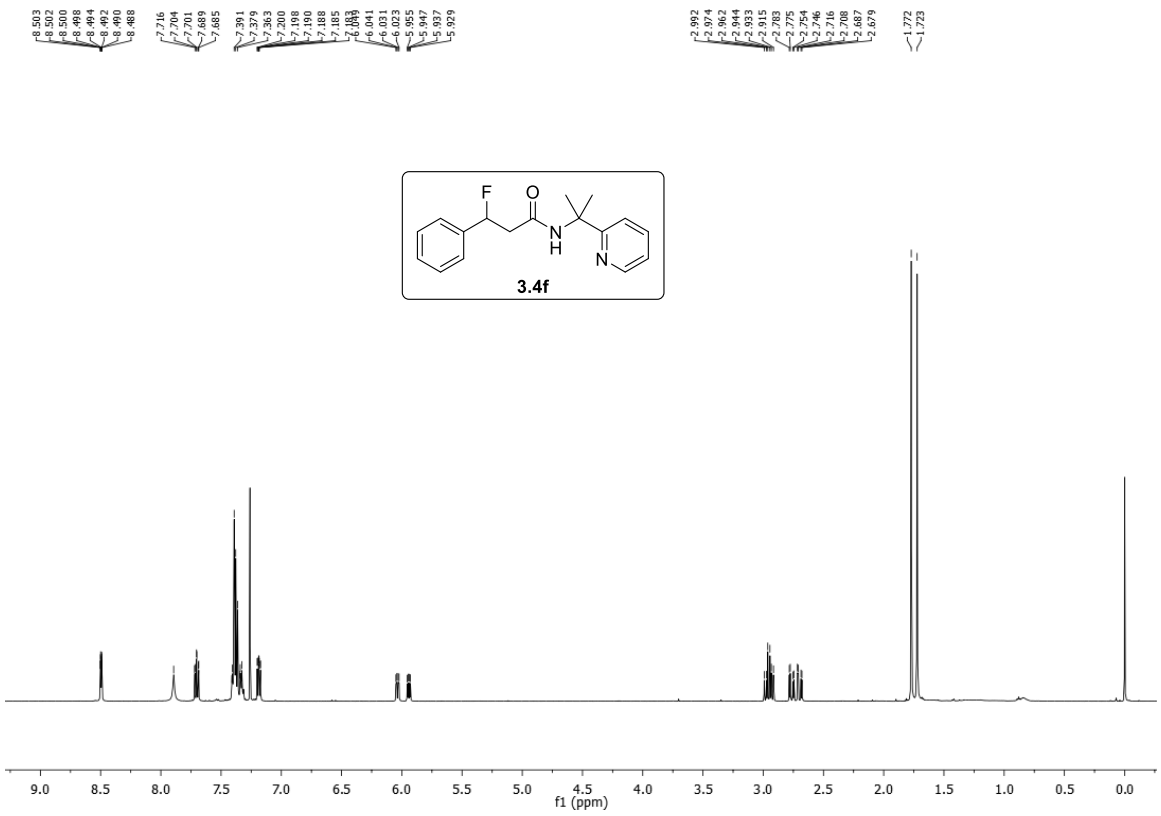
168.285
164.306
147.639
141.174
137.094
128.483
128.441
126.035
121.878
119.420
91.368
90.024
56.725
43.847
43.667
36.862
36.696
31.279
31.244
27.483
F
O
N
H
N
3.4e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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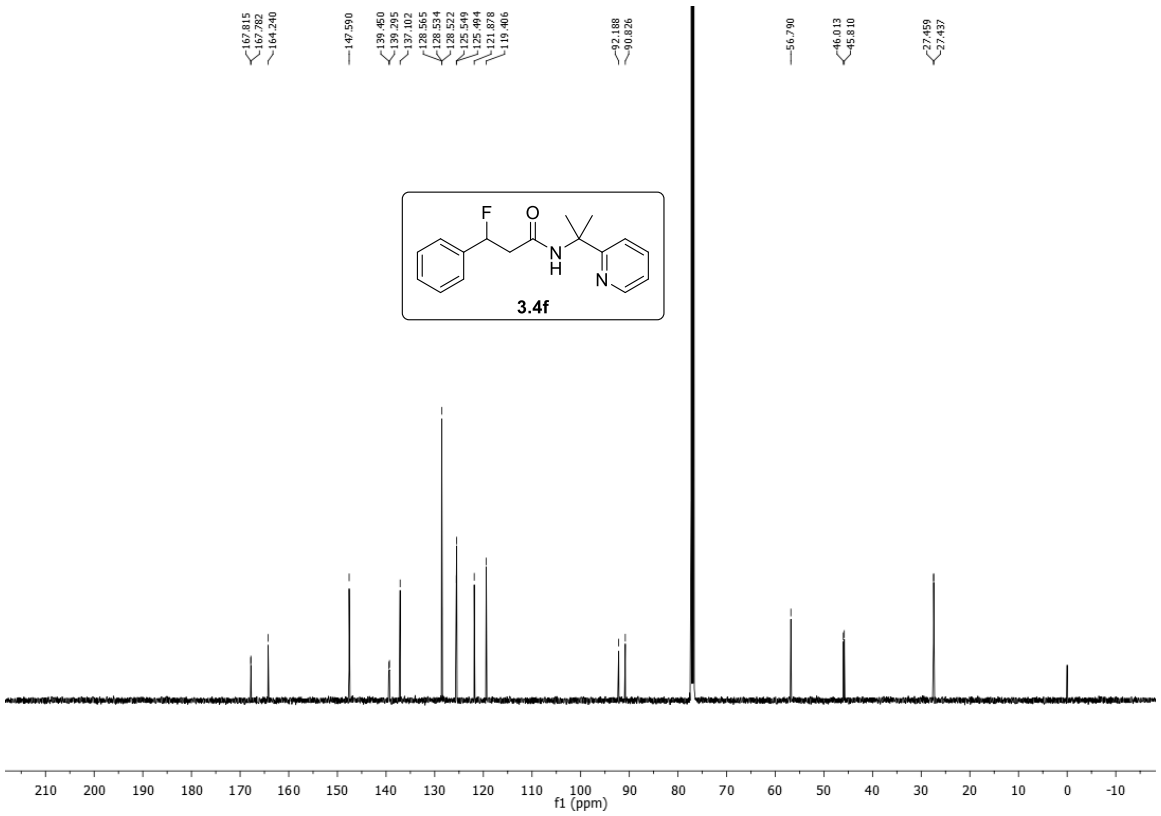
8.500
8.498
8.494
8.492
8.490
8.488
7.716
7.704
7.701
7.689
7.685
7.391
7.379
7.363
7.200
7.198
7.190
7.188
7.185
6.041
6.031
6.023
5.955
5.947
5.937
5.929
2.992
2.974
2.962
2.944
2.933
2.915
2.783
2.775
2.754
2.746
2.716
2.708
2.687
2.679
1.772
1.723
F
O
N
H
N
3.4f
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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147.590
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139.295
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128.565
128.534
128.522
125.549
125.494
121.878
119.406
92.188
90.826
56.790
46.013
45.810
27.459
27.437
F
O
N
H
N
3.4f
210
200
190
180
170
160
150
140
130
120
110
100
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80
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60
50
40
30
20
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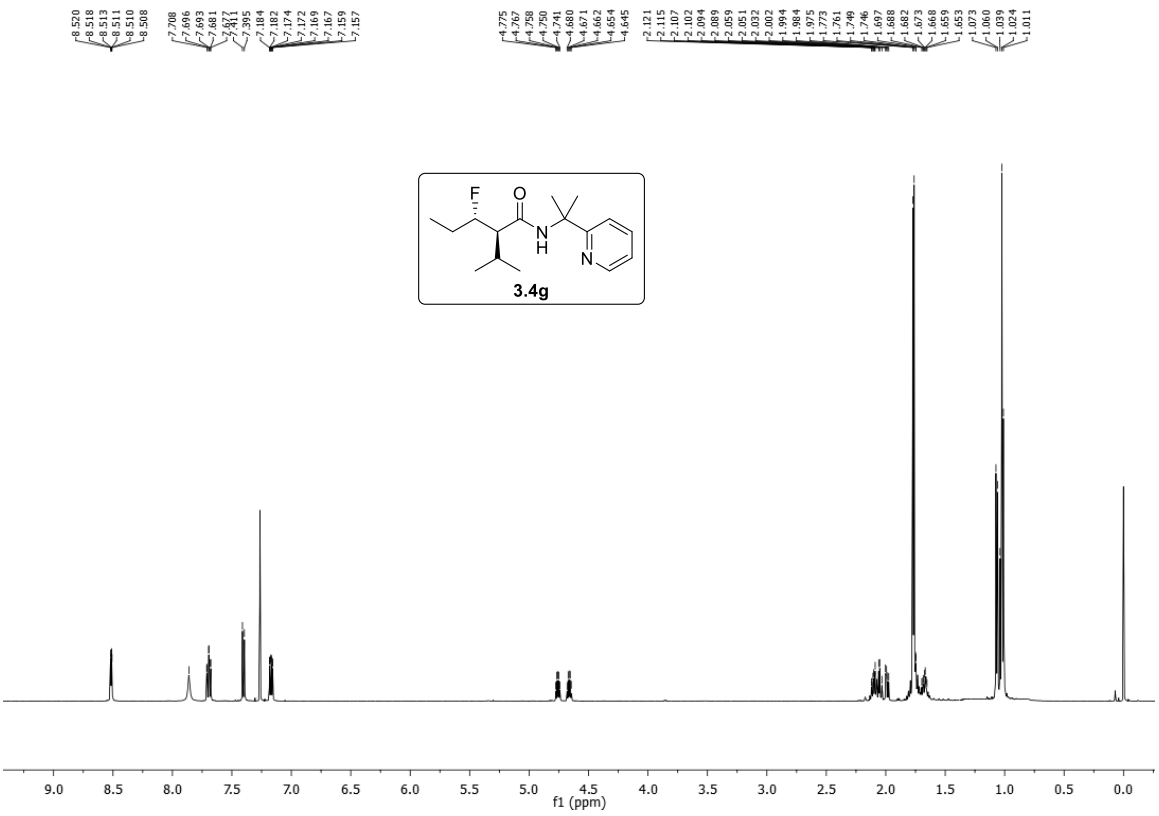
0
-10
f1 (ppm)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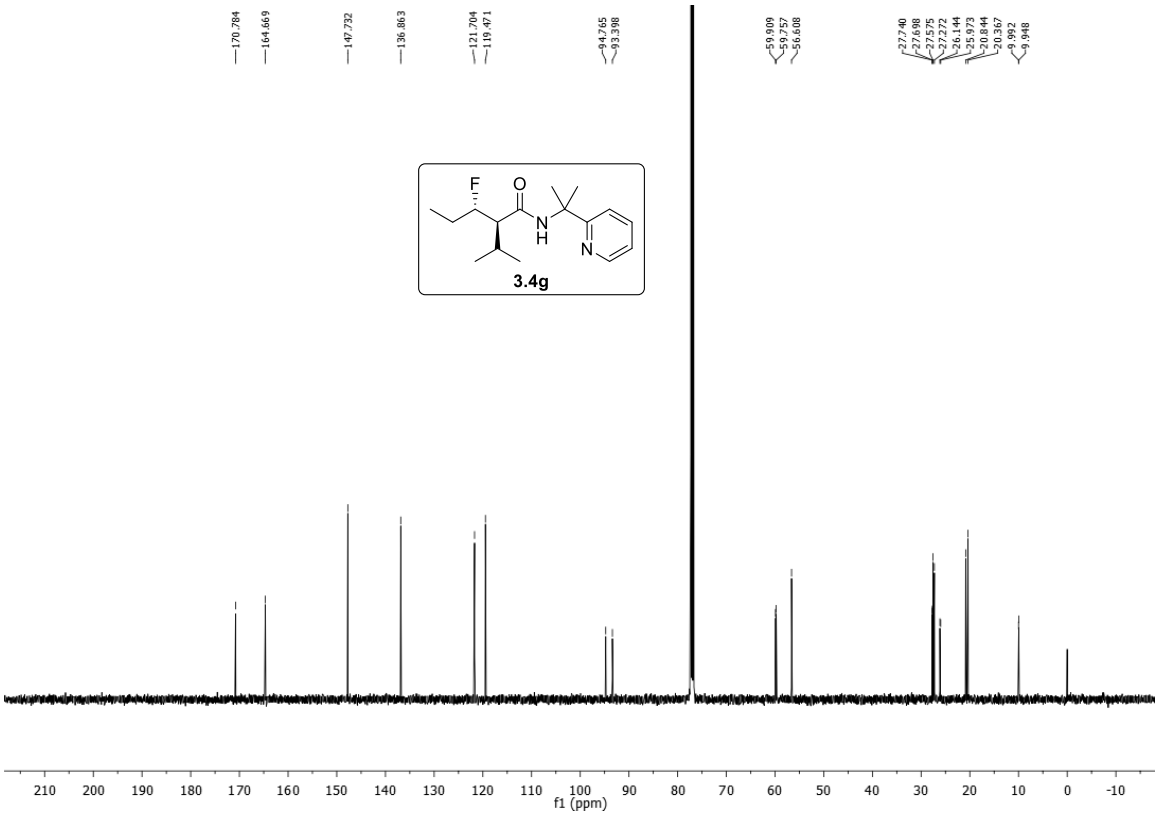
8.518
8.513
8.511
8.510
8.508
7.708
7.696
7.693
7.681
7.477
7.471
7.305
7.184
7.182
7.174
7.172
7.169
7.167
7.159
7.157
4.775
4.767
4.758
4.750
4.741
4.680
4.671
4.662
4.654
4.645
2.121
2.115
2.107
2.102
2.094
2.089
2.059
2.051
2.032
2.002
1.994
1.984
1.975
1.773
1.761
1.749
1.746
1.697
1.688
1.682
1.673
1.668
1.659
1.653
1.073
1.060
1.039
1.024
1.011
F
O
N
H
N
3.4g
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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93.398
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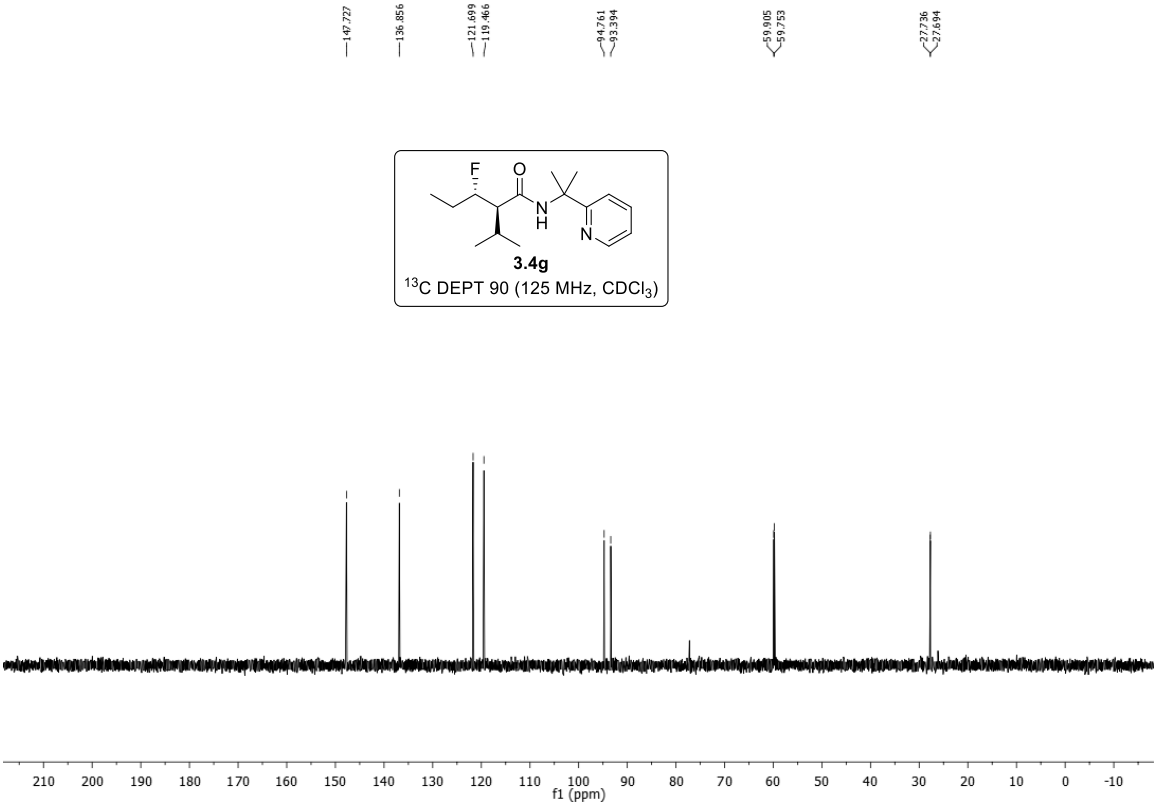
27.698
27.575
27.272
26.144
25.973
20.844
20.367
9.992
9.948
F
O
N
H
N
3.4g
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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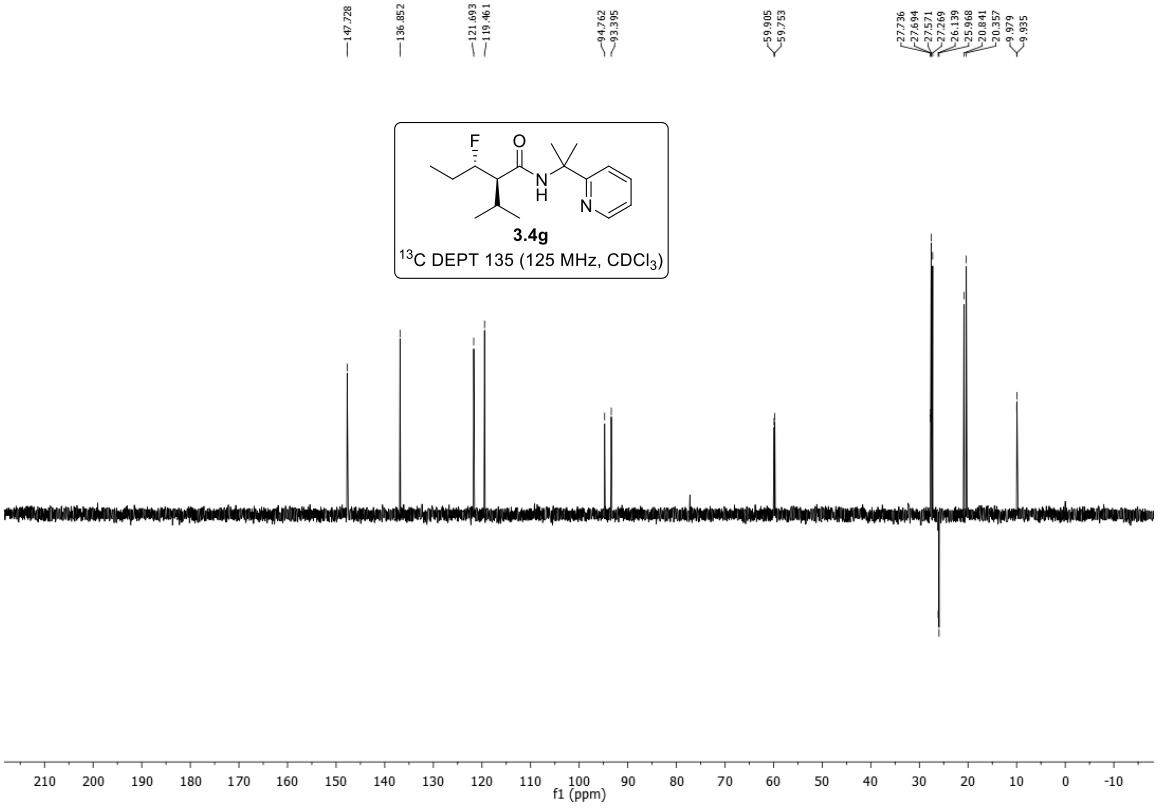
119.466
94.761
93.394
59.905
59.753
27.736
27.694
F
O
N
H
N
3.4g
13C DEPT 90 (125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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93.395
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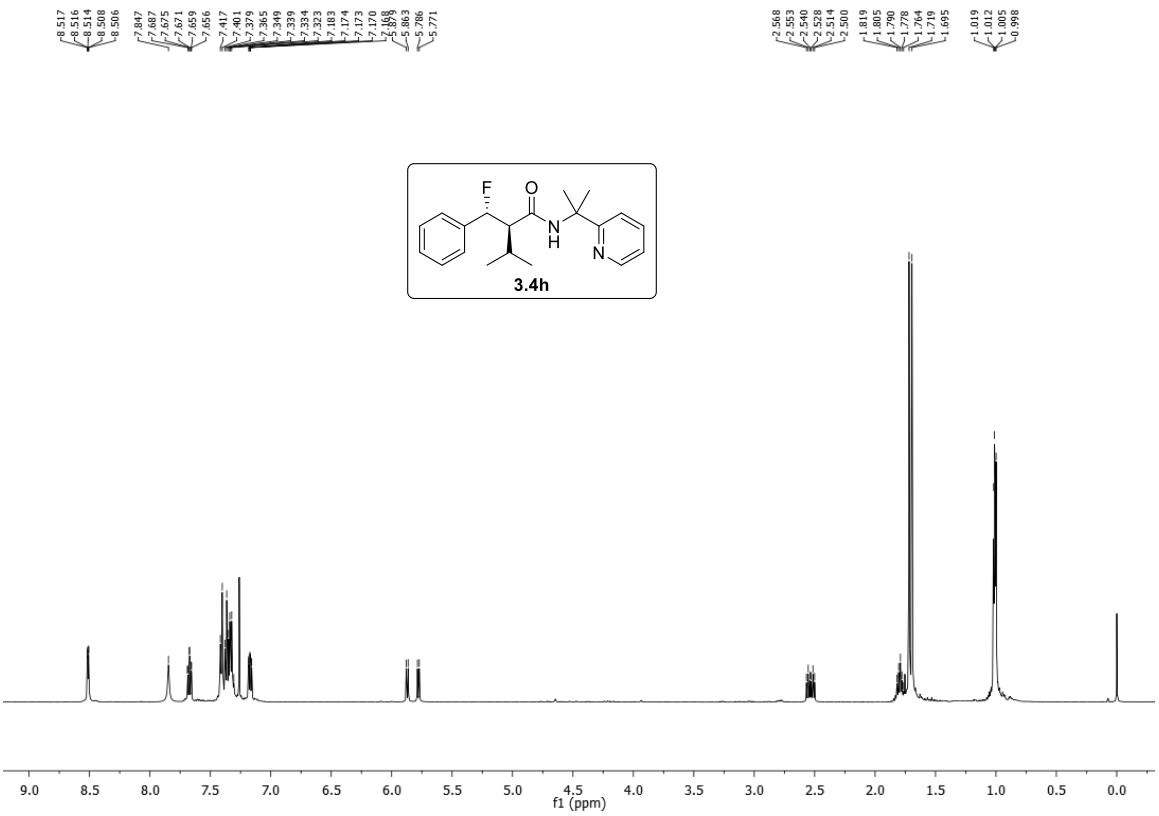
27.269
26.139
25.968
20.841
20.357
9.979
9.935
F
O
N
H
N
3.4g
13C DEPT 135 (125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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8.506
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7.671
7.659
7.656
7.417
7.401
7.379
7.365
7.349
7.339
7.334
7.323
7.183
7.174
7.173
7.170
5.863
5.786
5.771
2.568
2.553
2.540
2.528
2.514
2.500
1.819
1.805
1.790
1.778
1.764
1.719
1.695
1.019
1.012
1.005
0.998
F
O
N
H
N
3.4h
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.0
2.5
2.0
1.5
1.0
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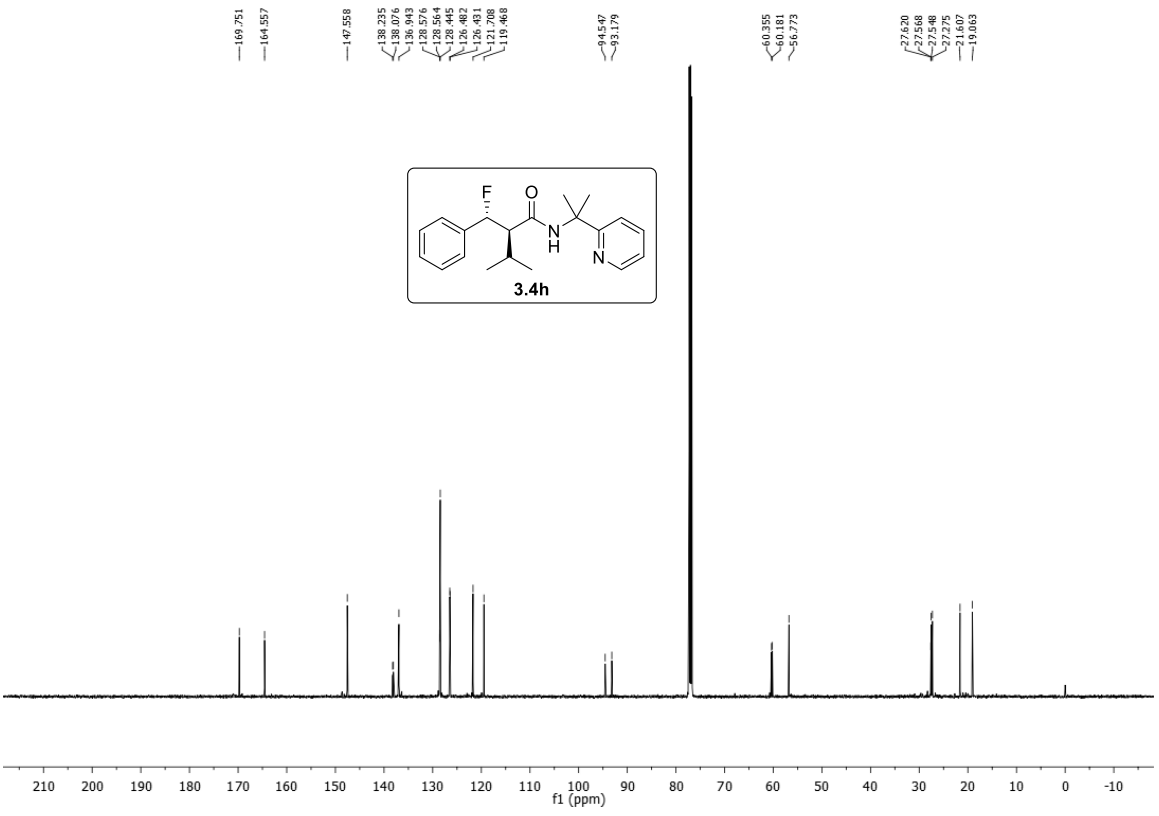
0.0
f1 (ppm)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128.564
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94.547
93.179
60.355
60.181
56.773
27.620
27.568
27.540
27.275
21.607
19.063
F
O
N
H
N
3.4h
210
200
190
180
170
160
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140
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120
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100
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80
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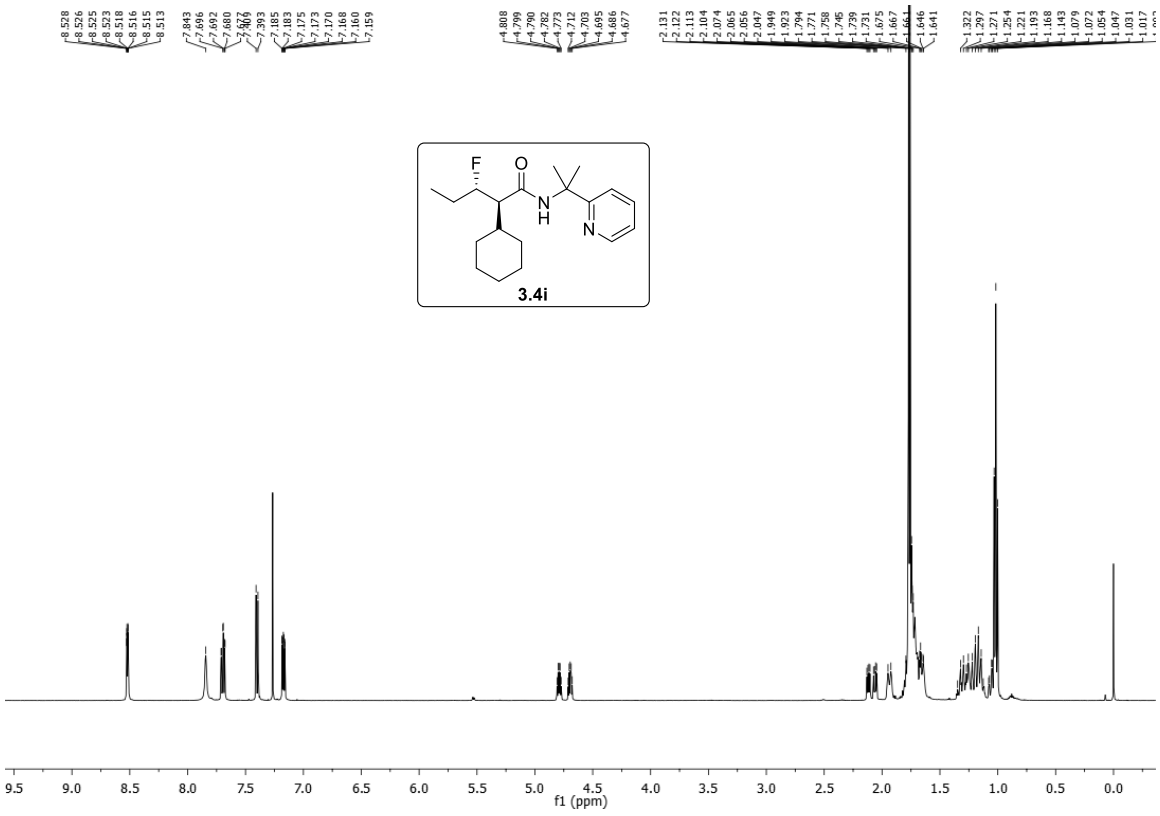
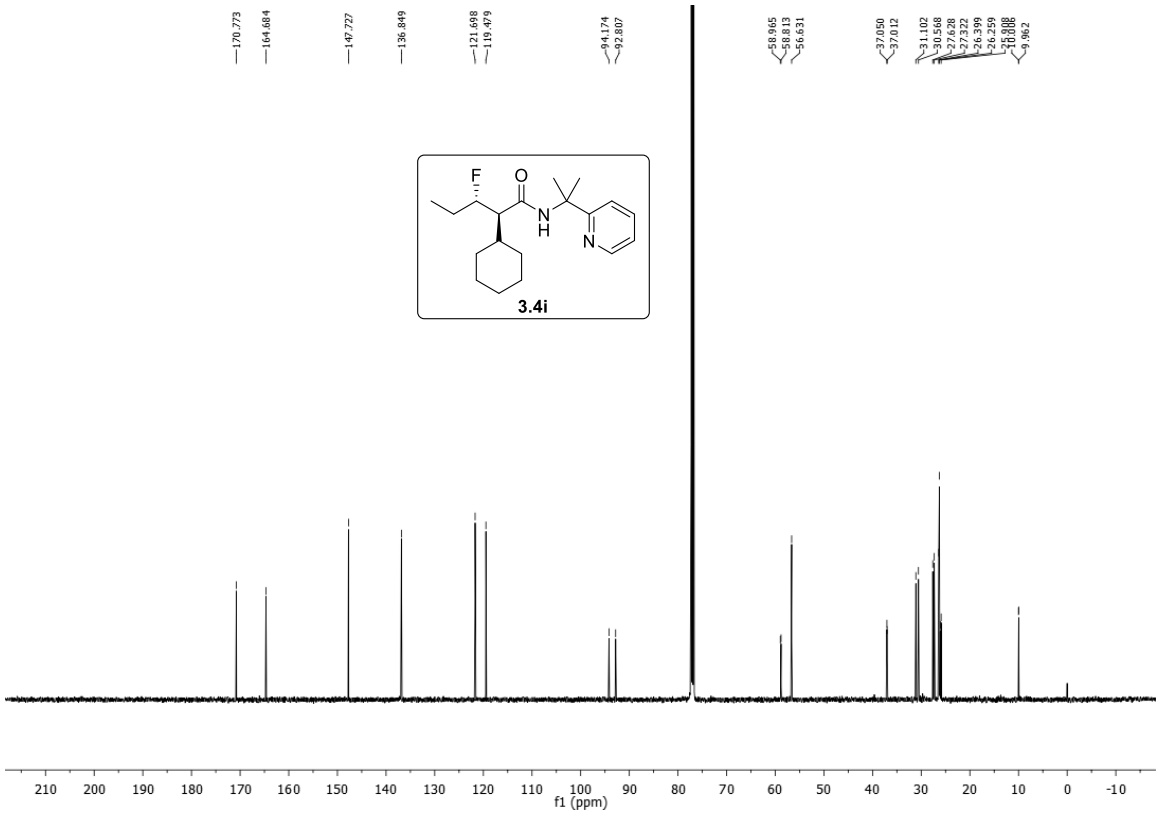
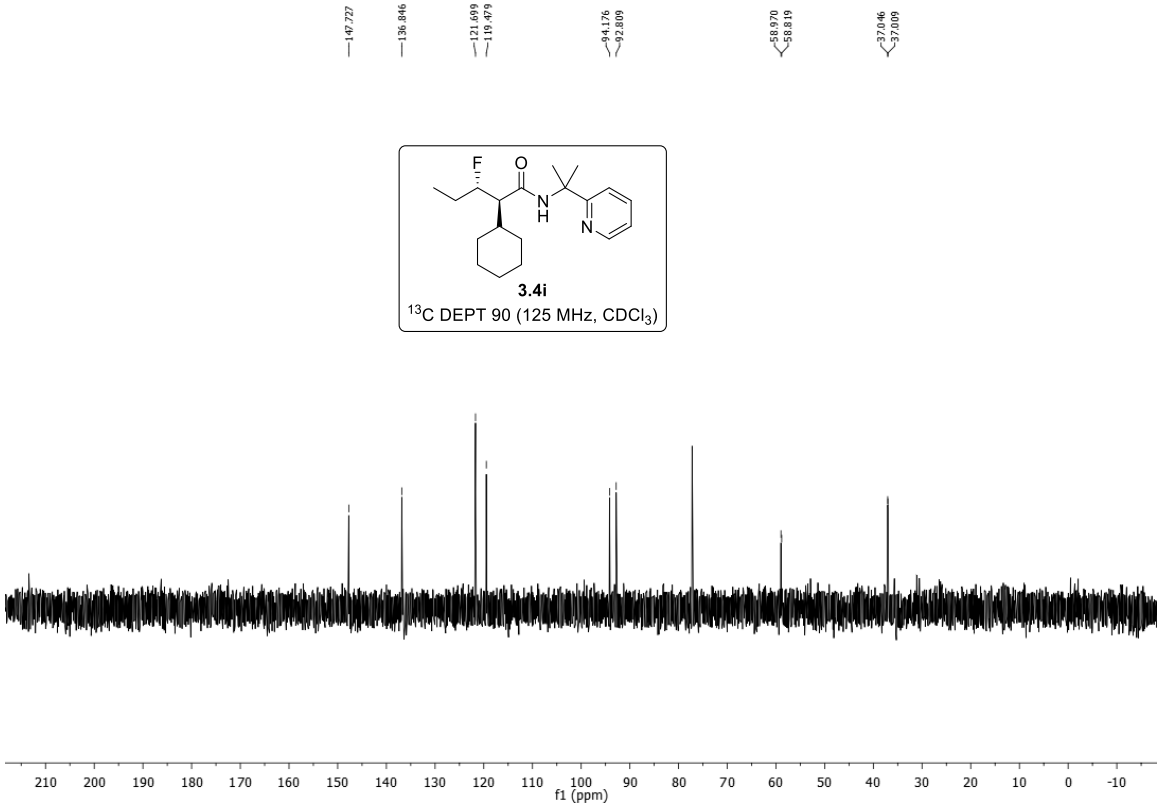
50
40
30
20
10
0
-10
f1 (ppm)


F
O
N
H
N
3.4i
f1 (ppm)


F
O
N
H
N
3.4i
f1 (ppm)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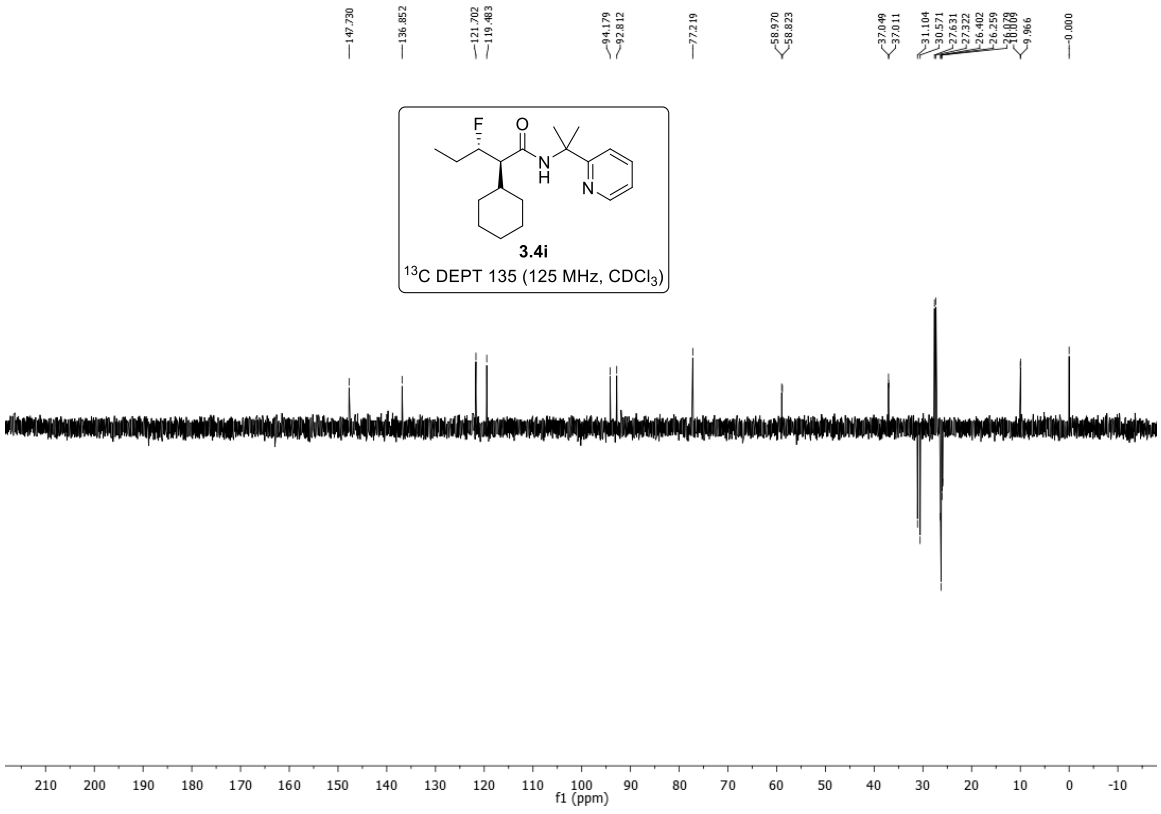
136.846
121.699
119.479
94.176
92.809
58.970
58.819
37.046
37.009
F
O
N
H
N
3.4i
13C DEPT 90 (125 MHz, CDCl3)
f1 (ppm)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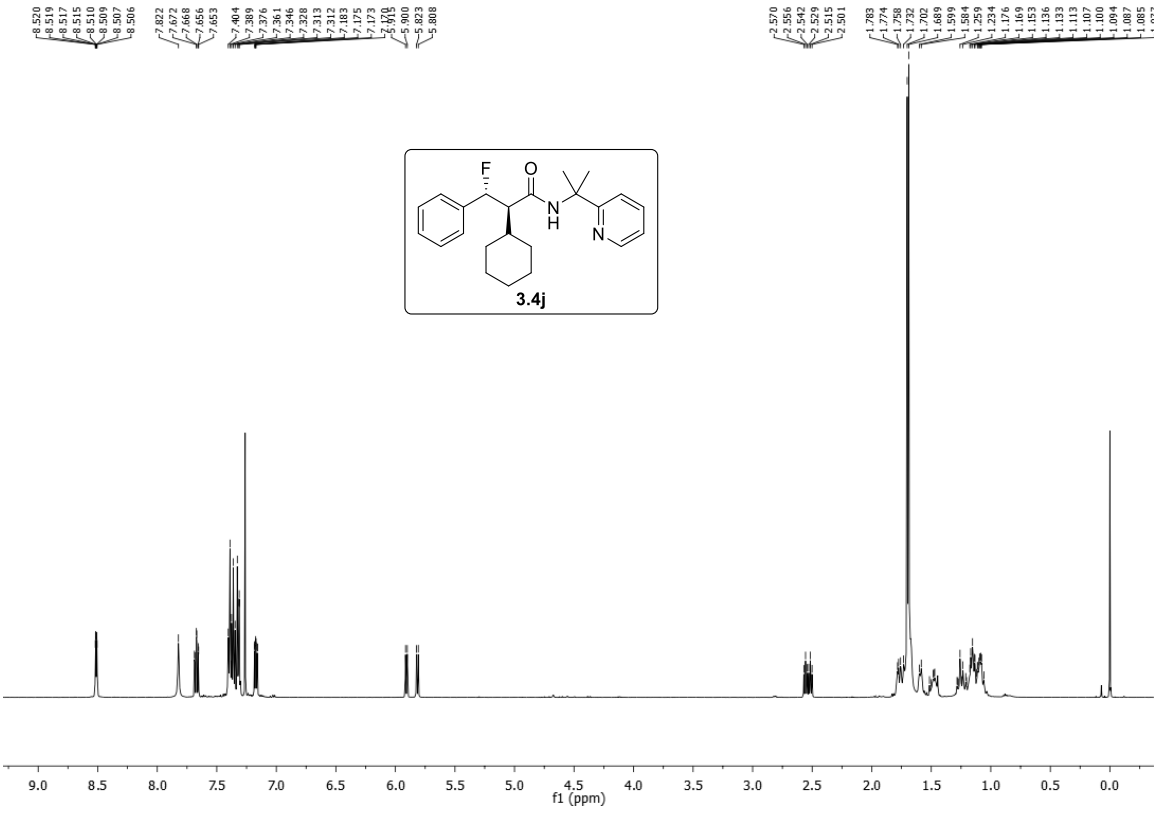
58.823
37.049
37.011
31.104
30.571
27.631
27.322
26.402
26.259
9.966
0.000
F
O
N
H
N
3.4i
13C DEPT 135 (125 MHz, CDCl3)
f1 (ppm)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8.506
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7.668
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7.404
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7.361
7.346
7.328
7.313
7.212
7.183
7.175
7.173
7.170
5.915
5.900
5.823
5.808
2.570
2.556
2.542
2.529
2.515
2.501
1.783
1.774
1.758
1.732
1.702
1.689
1.599
1.584
1.259
1.234
1.176
1.169
1.153
1.136
1.133
1.113
1.107
1.100
1.094
1.087
1.085
F
O
N
H
N
3.4j
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
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2.5
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1.5
1.0
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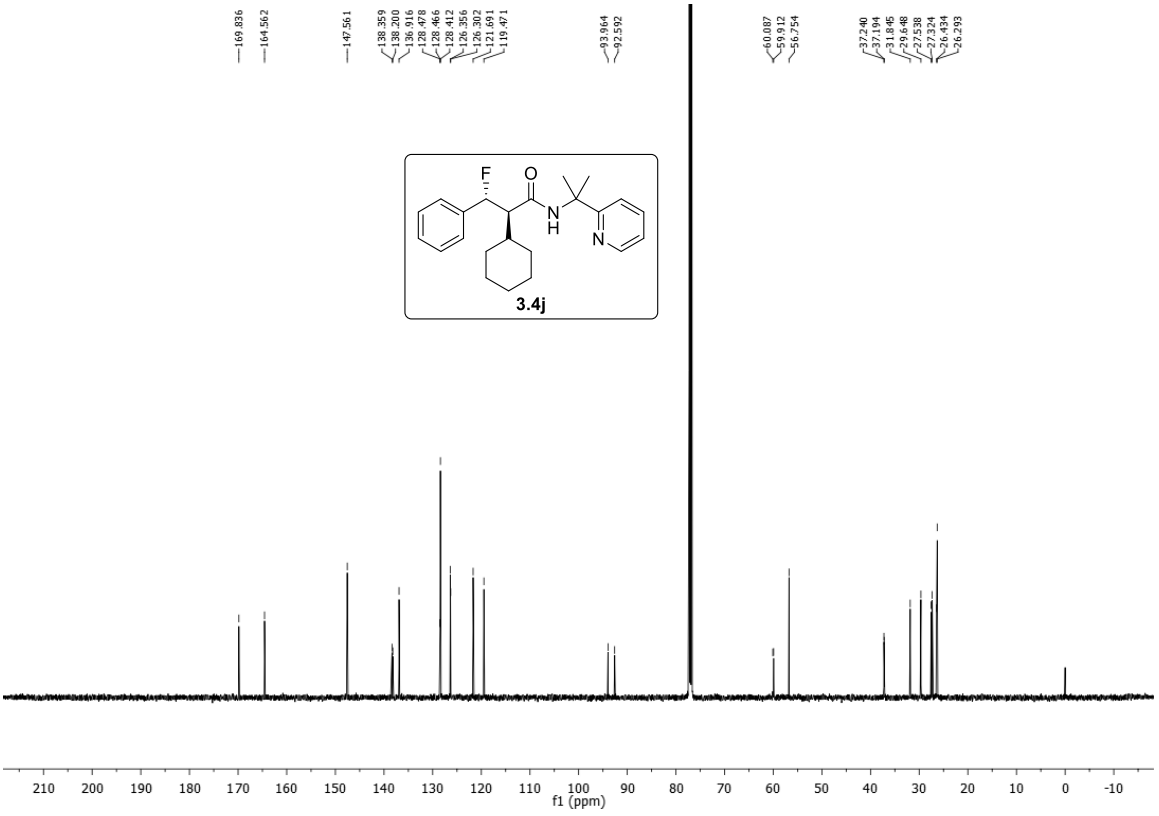
0.0
f1 (ppm)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147.561
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128.466
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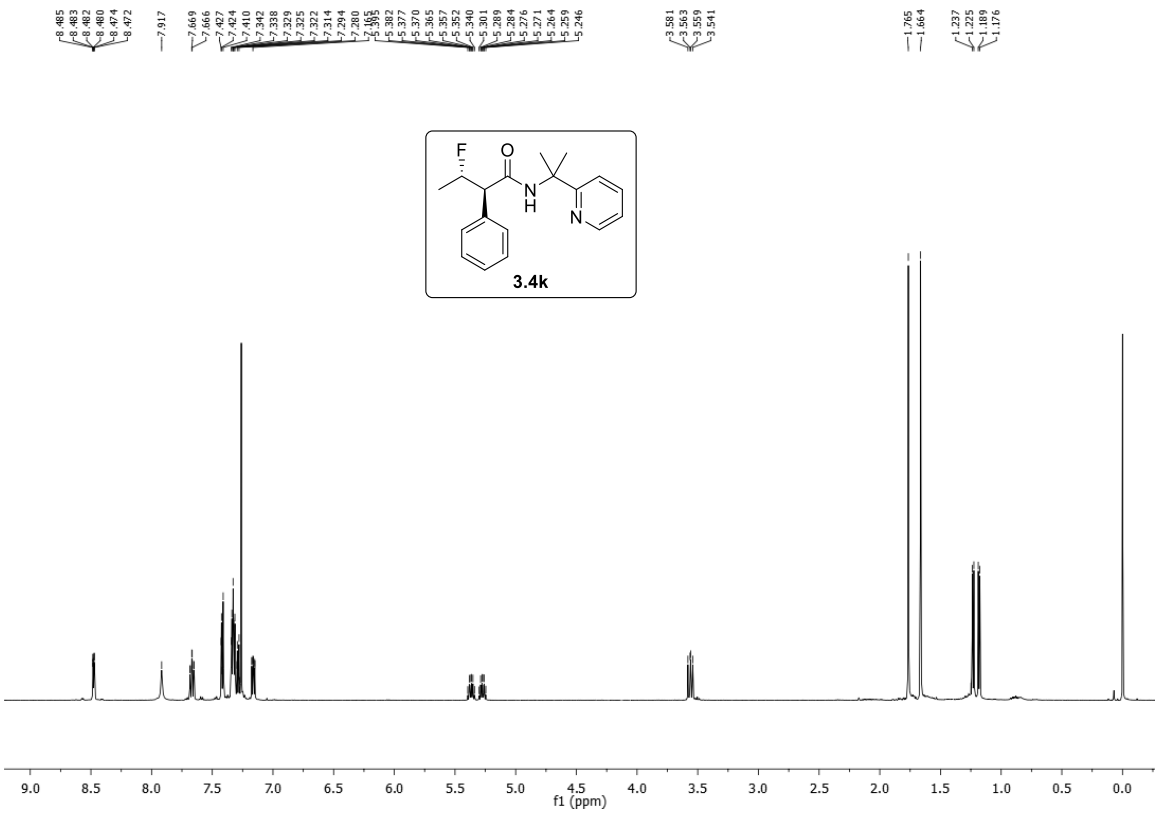
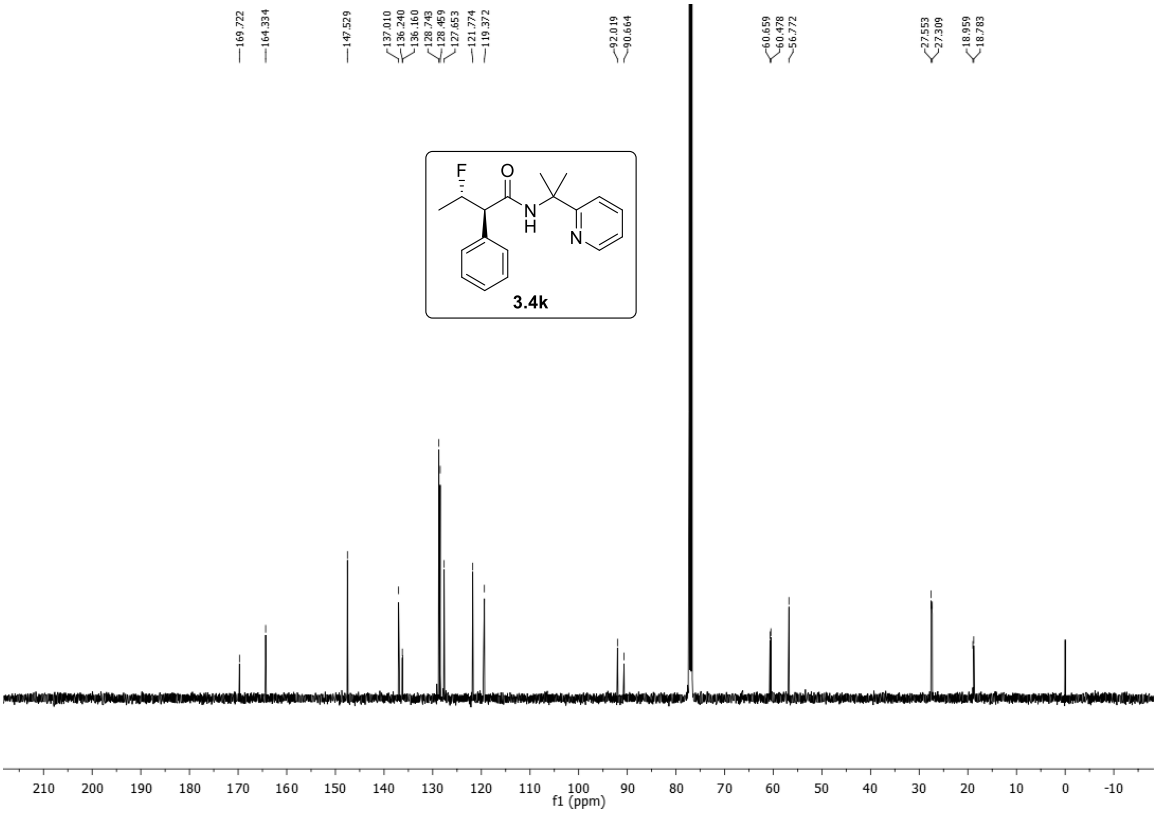
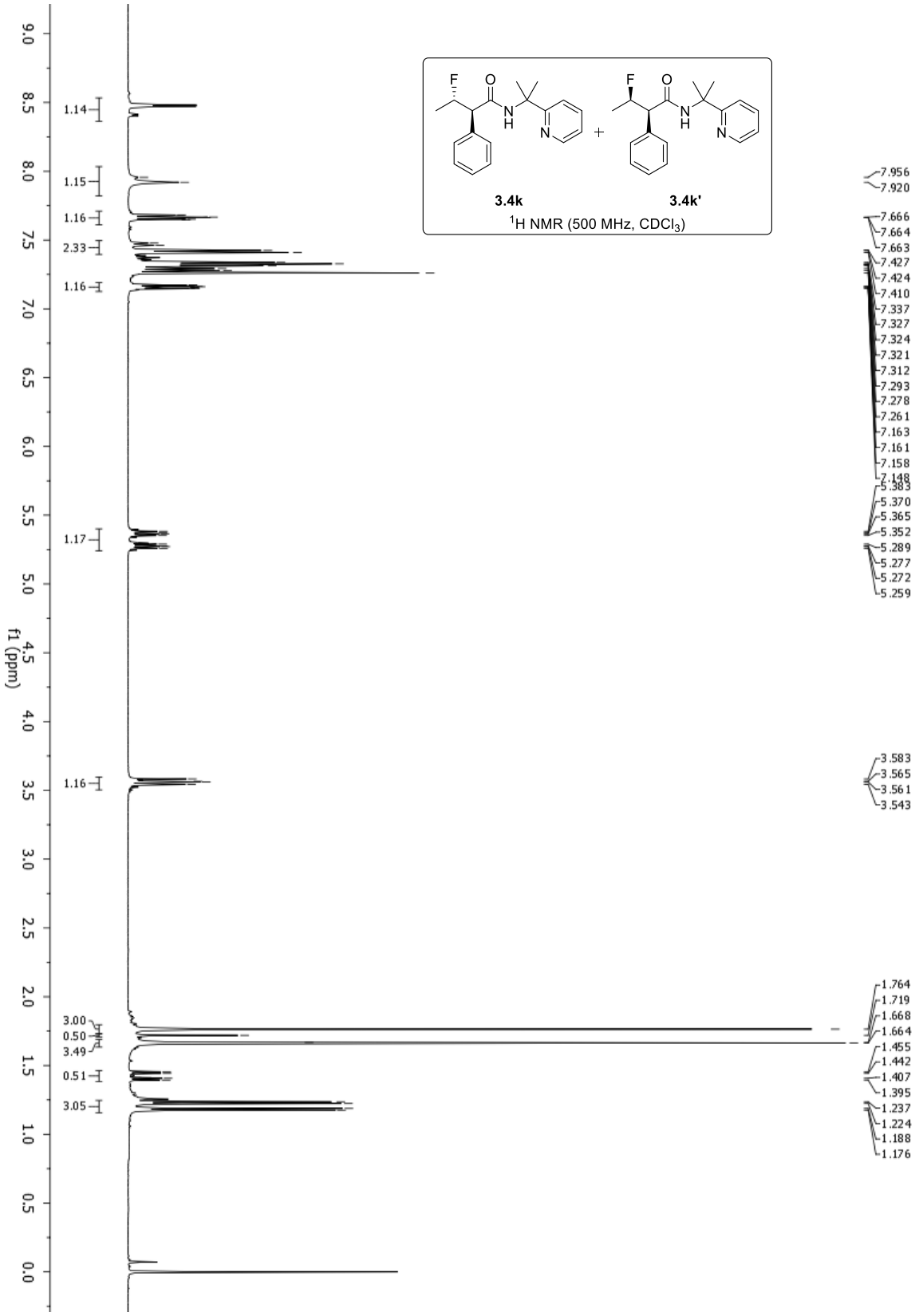
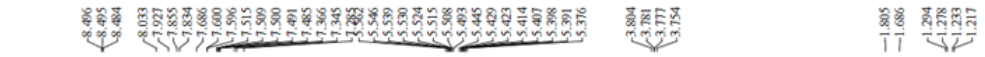
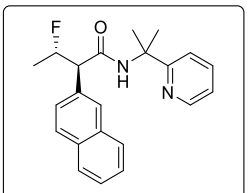
126.302
121.691
119.471
93.964
92.592
60.087
59.912
56.754
37.240
37.194
31.845
29.648
27.538
27.324
26.434
26.293
F
O
N
H
N
3.4j
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


8.485
8.483
8.482
8.480
8.474
8.472
7.917
7.669
7.666
7.427
7.424
7.410
7.342
7.338
7.329
7.325
7.322
7.314
7.294
7.280
5.395
5.382
5.377
5.370
5.365
5.357
5.352
5.340
5.301
5.289
5.284
5.276
5.271
5.264
5.259
5.246
3.581
3.563
3.559
3.541
1.765
1.664
1.237
1.225
1.189
1.176
F
O
N
H
N
3.4k
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


169.722
164.334
147.529
137.010
136.240
136.140
128.749
128.459
127.653
121.774
119.372
92.019
90.664
60.659
60.478
56.772
27.553
27.309
18.959
18.783
F
O
N
H
N
3.4k
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

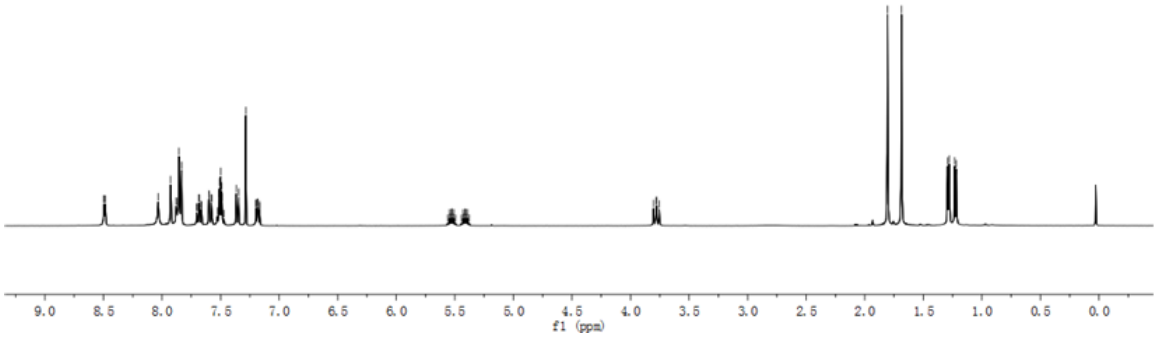

3.4k
3.4k'
^{1}H NMR (500 MHz, $CDCl_3$)
f1 (ppm)
1.14
1.15
1.16
2.33
1.16
1.17
1.16
3.00
0.50
3.49
0.51
3.05
7.956
7.920
7.666
7.664
7.663
7.427
7.424
7.410
7.337
7.327
7.324
7.321
7.312
7.293
7.278
7.261
7.163
7.161
7.158
7.148
5.383
5.370
5.365
5.352
5.289
5.277
5.272
5.259
3.583
3.565
3.561
3.543
1.764
1.719
1.668
1.664
1.455
1.442
1.407
1.395
1.237
1.224
1.188
1.176

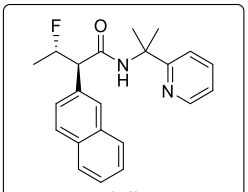




3.4l

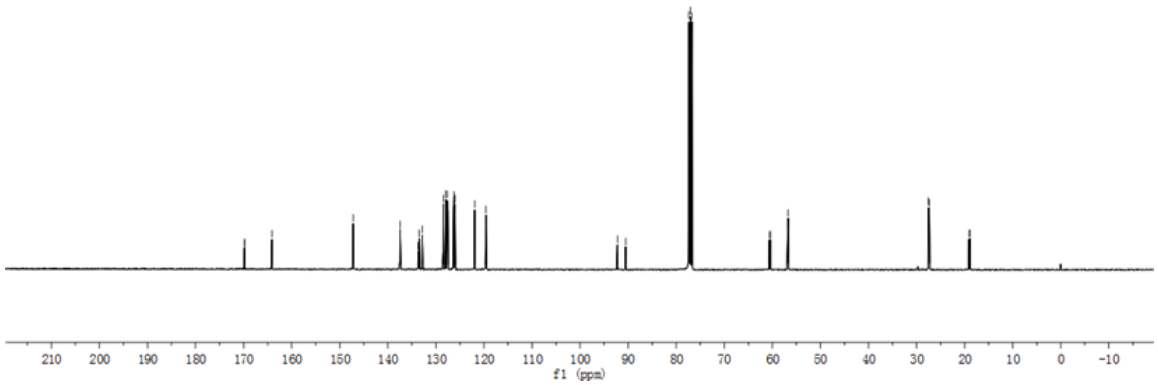
^{1}H NMR (400 MHz, $CDCl_3$)

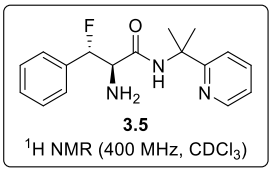




3.4l

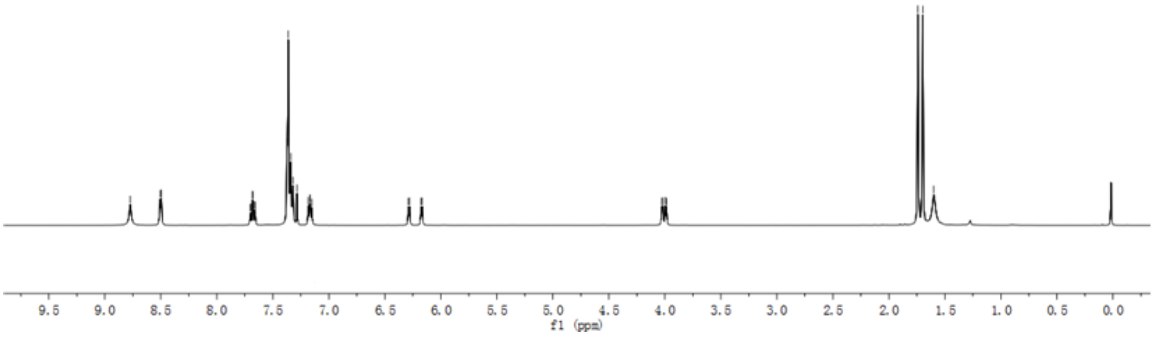
^{1}H NMR (400 MHz, $CDCl_3$)

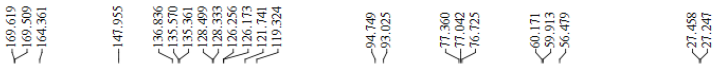


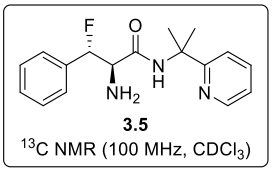


3.5

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

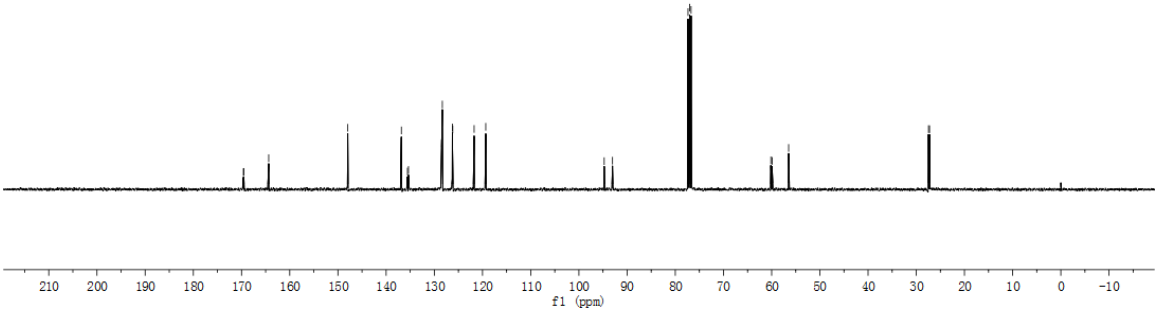


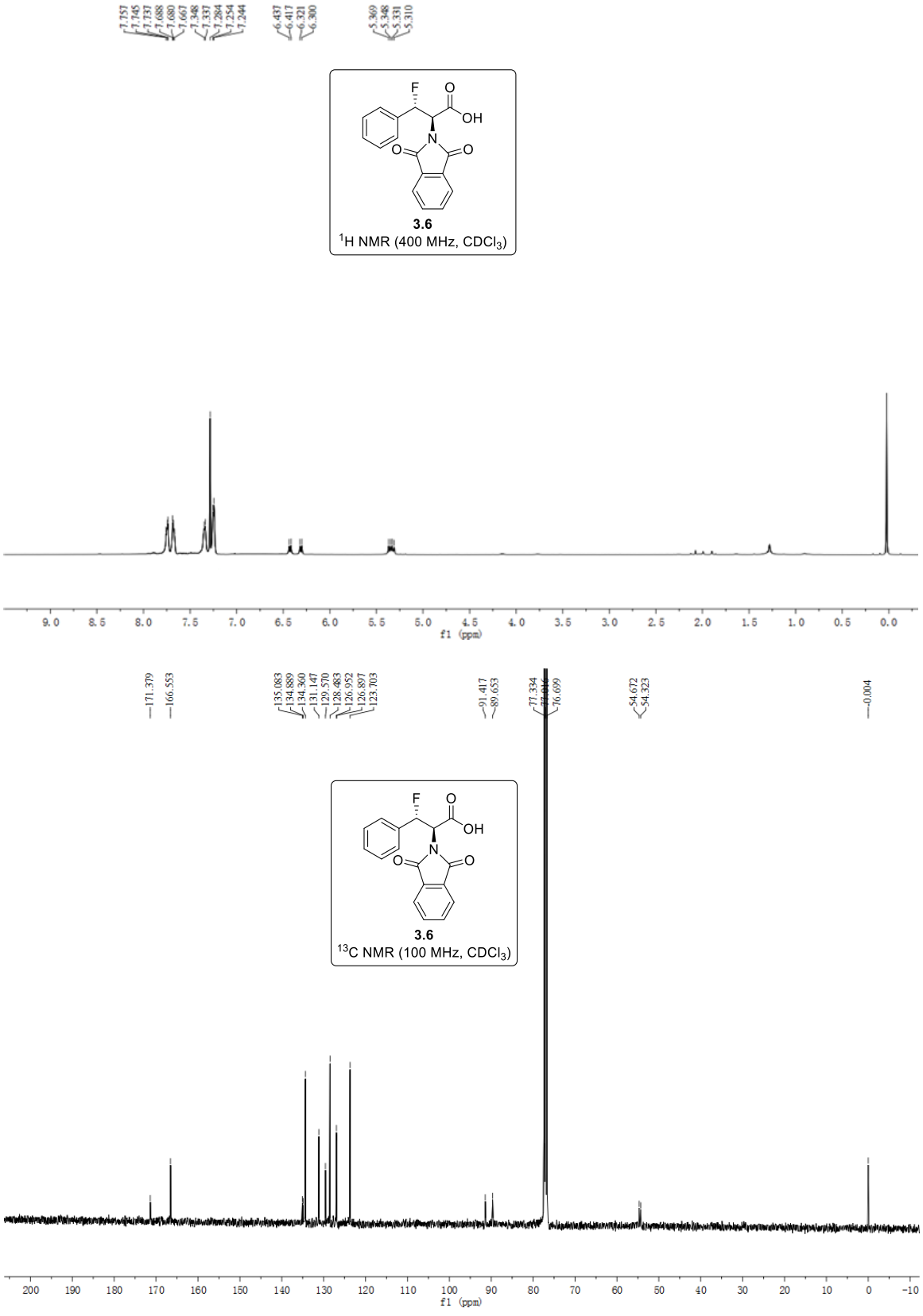




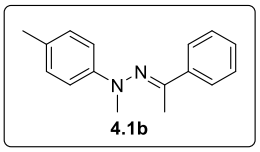
3.5

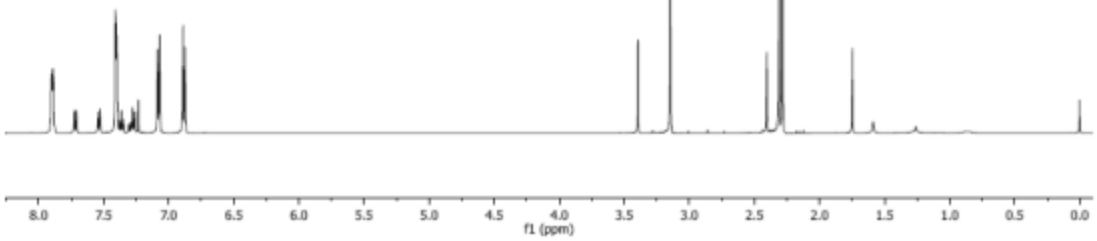
^{13}C NMR (100 MHz, $CDCl_3$)



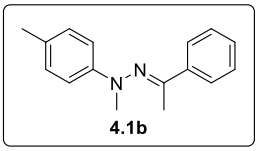

7.757
7.745
7.737
7.688
7.680
7.667
7.348
7.337
7.284
7.254
7.244
6.437
6.417
6.321
6.300
5.369
5.348
5.331
5.310
F
O
OH
N
O
O
3.6
1H NMR (400 MHz, CDCl3)
f1 (ppm)
171.379
166.553
135.083
134.889
134.360
131.147
129.570
128.483
126.952
126.897
123.703
91.417
89.653
77.334
76.699
54.672
54.323
-0.004
3.6
13C NMR (100 MHz, CDCl3)
f1 (ppm)

May28-2012
sm-nh2-4-me

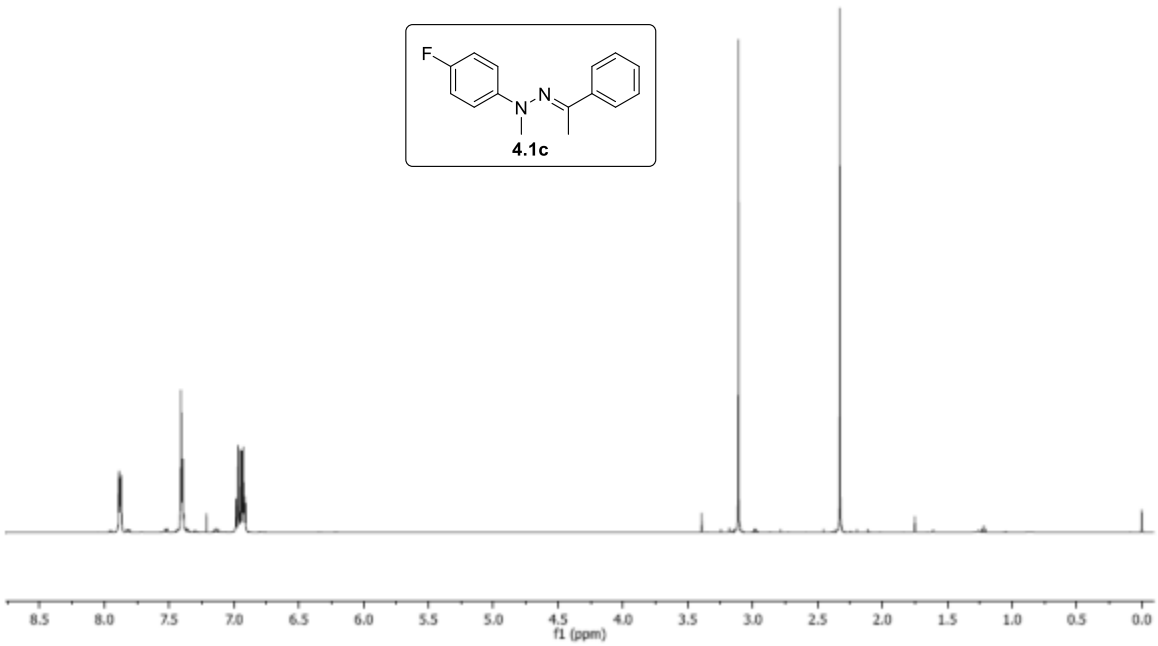




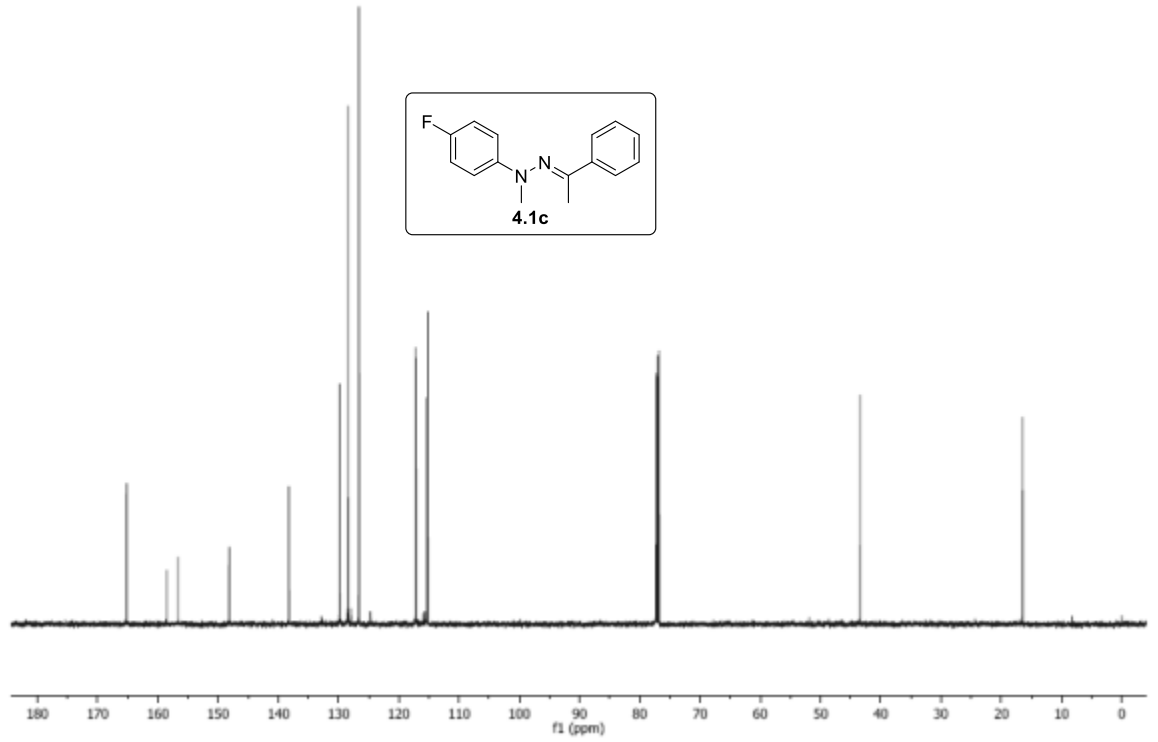
May28-2012
sm-nh2-4-me



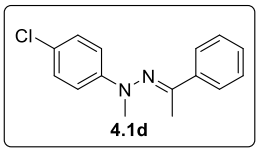
May28-2012
sm-nh2-4-f

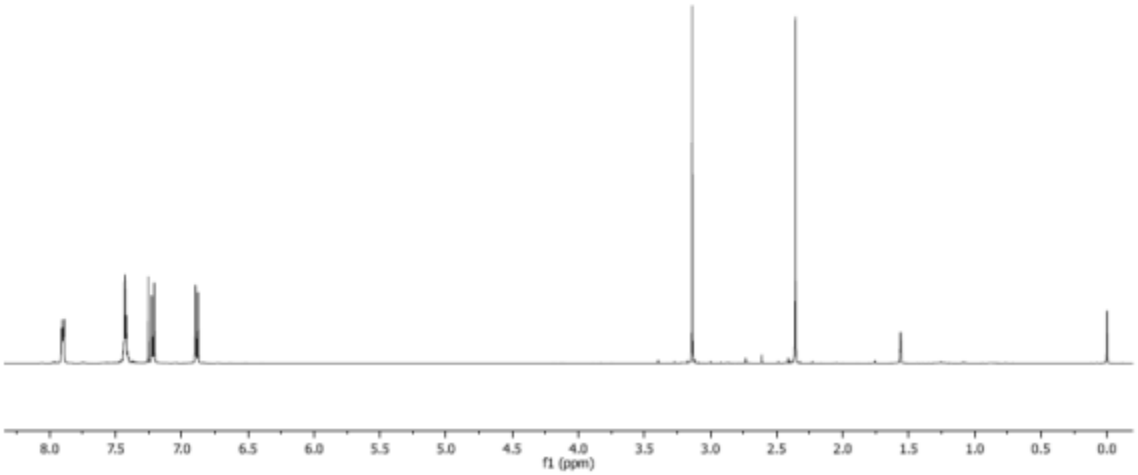


May28-2012
sm-nh2-4-f

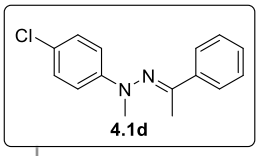


May27-2012
sm-nh2-4-d

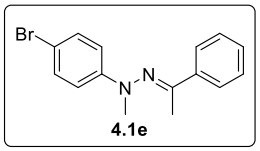


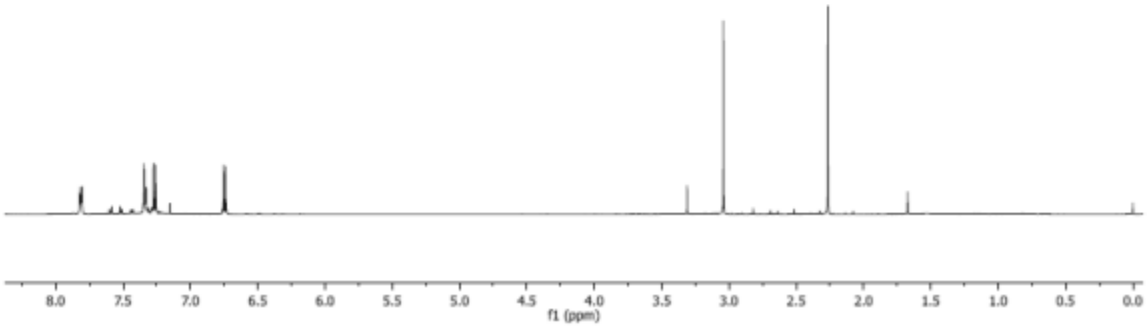


May26-2012
sm-nh2-4-d

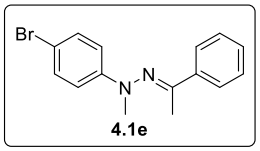


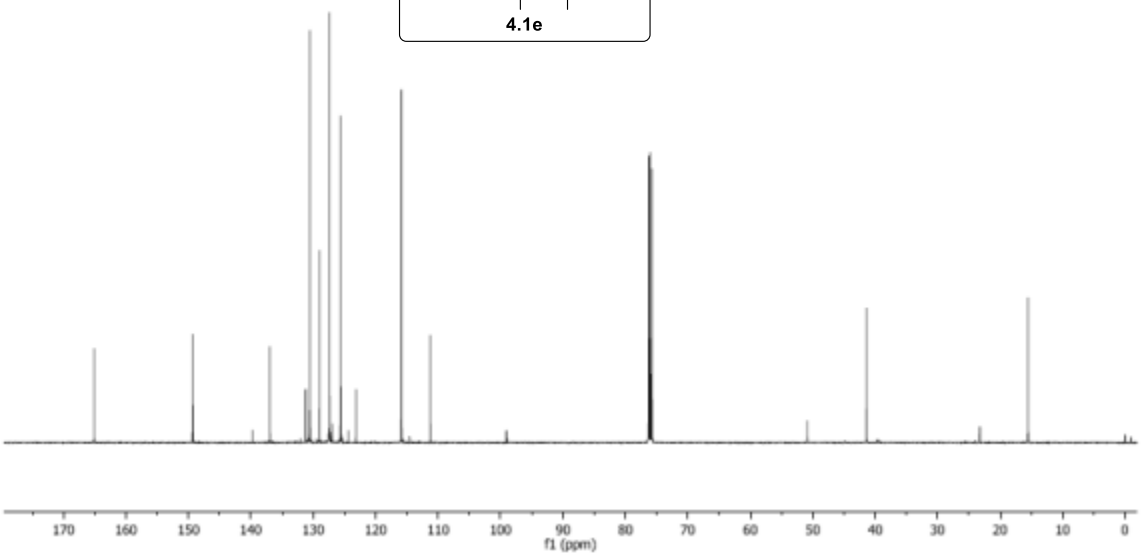
May05-2012
SM-4-BR



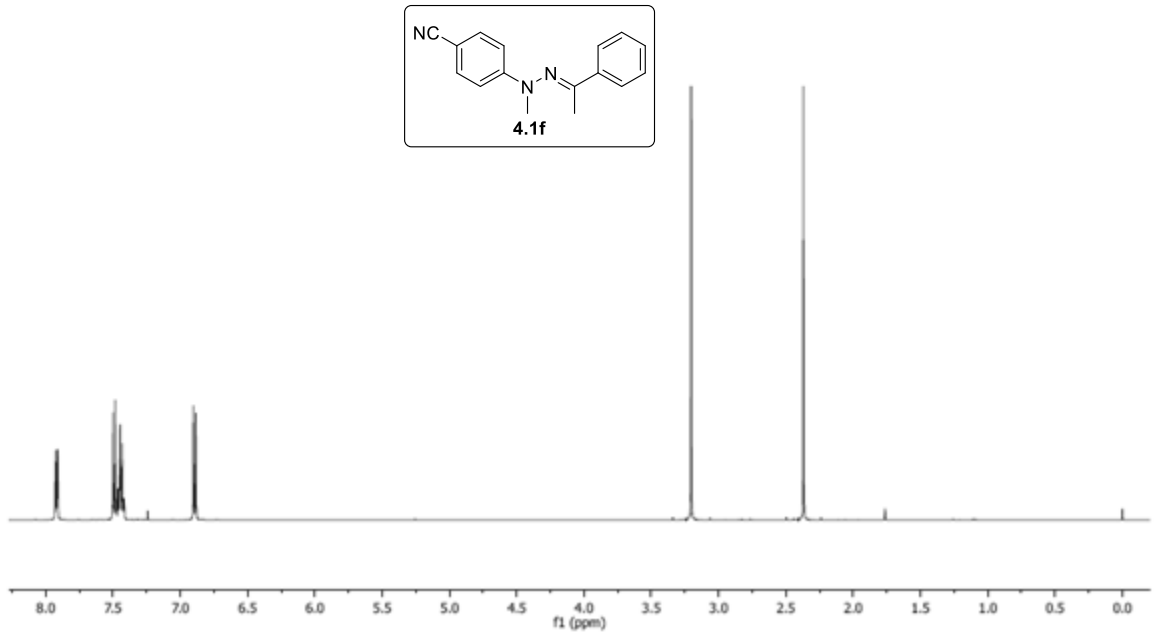


May05-2012
SM-4-BR

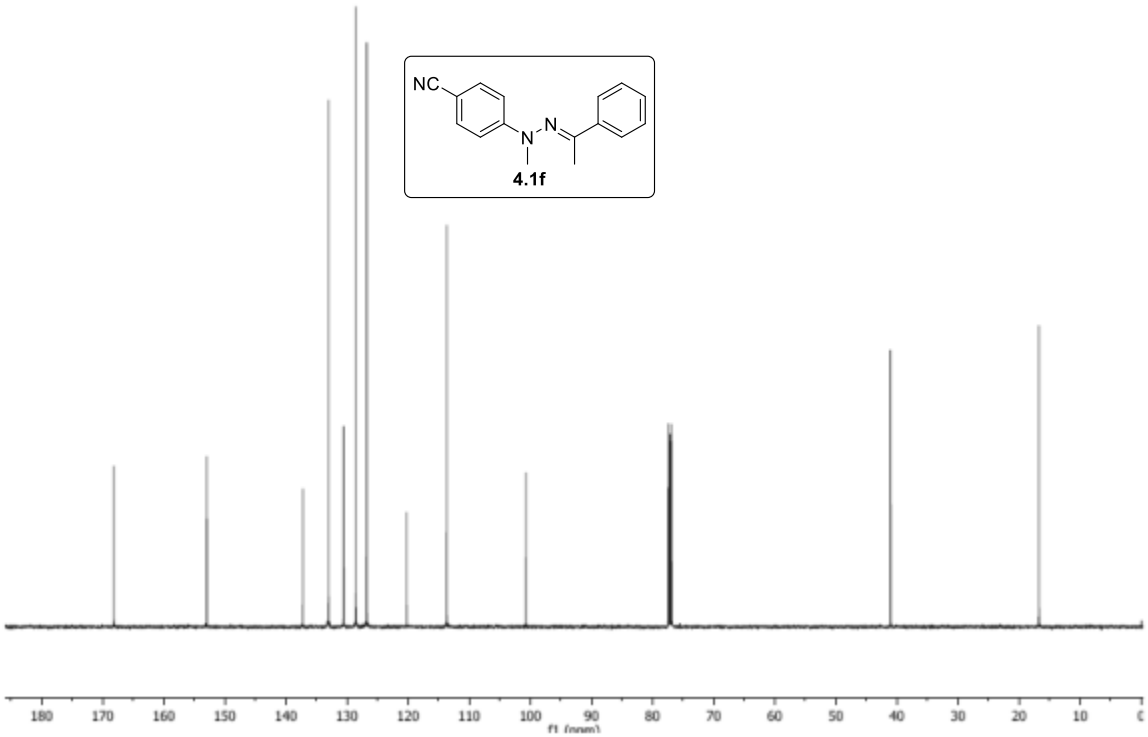




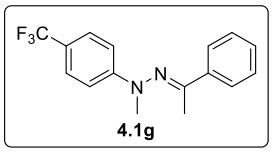
May27-2012
sm-nh2-4-cn



May27-2012
sm-nh2-4-cn

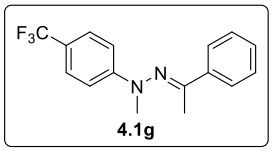


May27-2012
sm-nh2-4-cf3



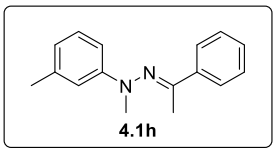
4.1g

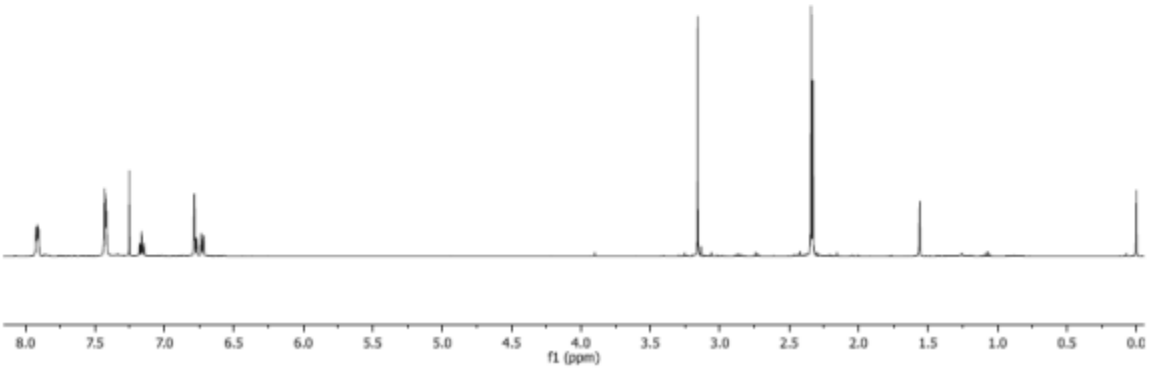
May26-2012
sm-nh2-4-cf3



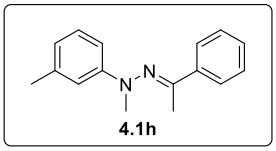
4.1g

May27-2012
sm-nh2-3-me

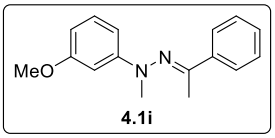




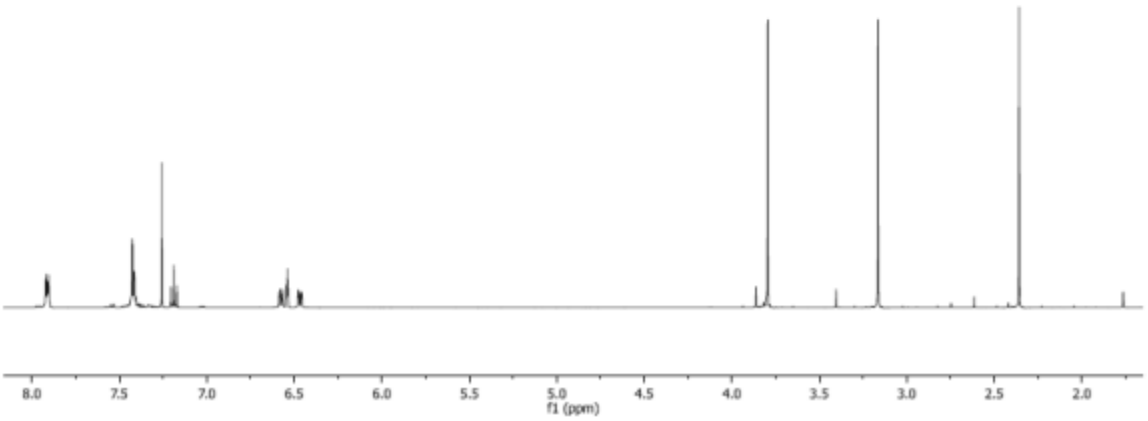
May26-2012
sm-nh2-3-me



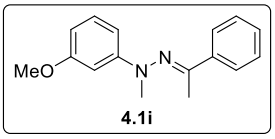
May27-2012
sm-nh2-3-ome



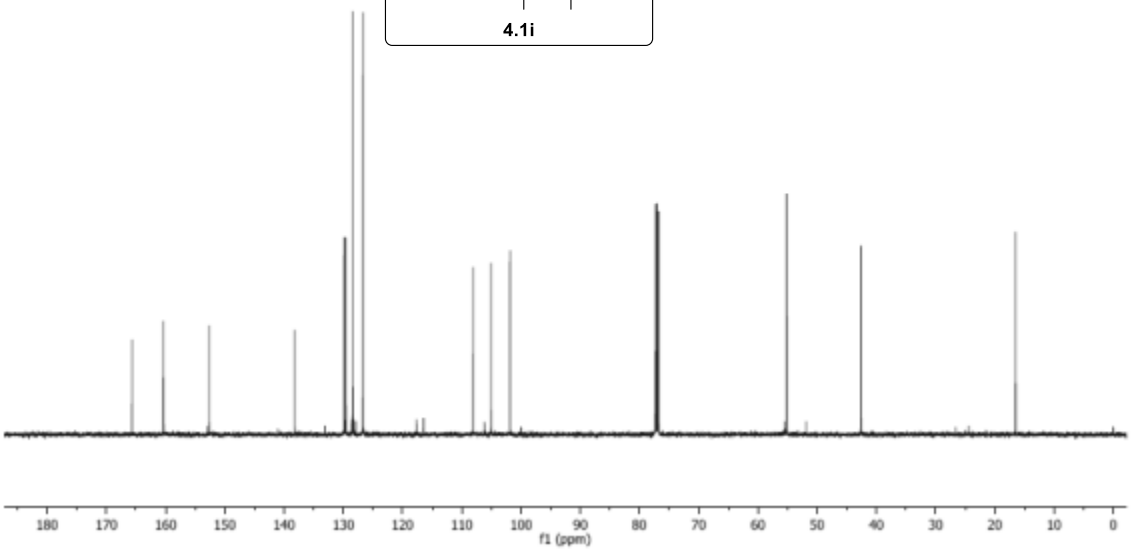
4.1i



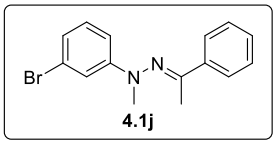
May26-2012
sm-nh2-3-ome



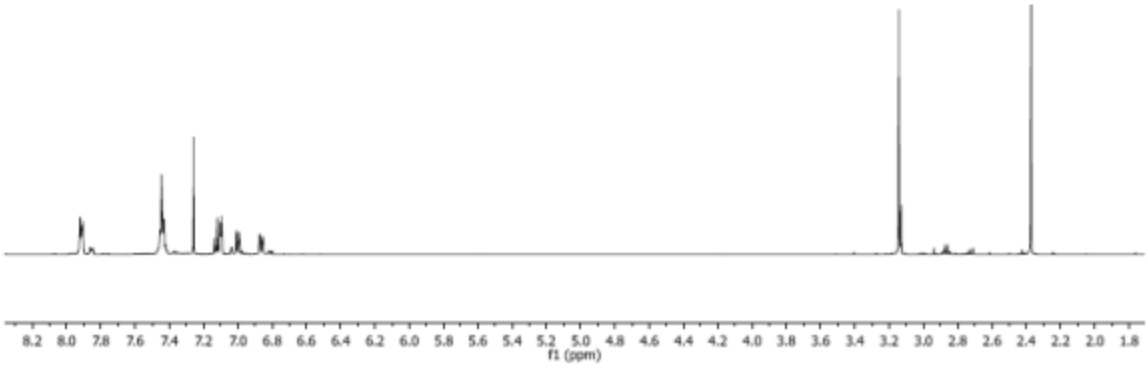
4.1i



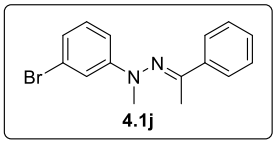
May27-2012
sm-nh2-3-br



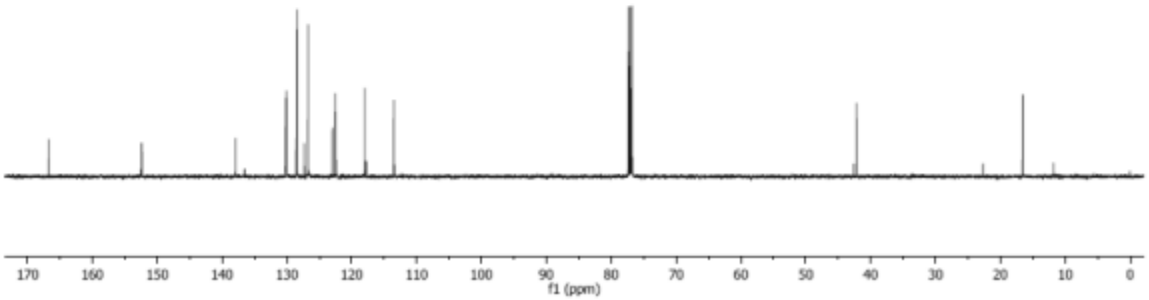
4.1j



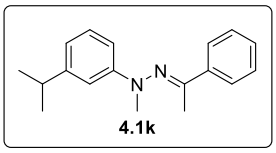
May26-2012
sm-nh2-3-br



4.1j



May27-2012
sm-nh2-3i-pr



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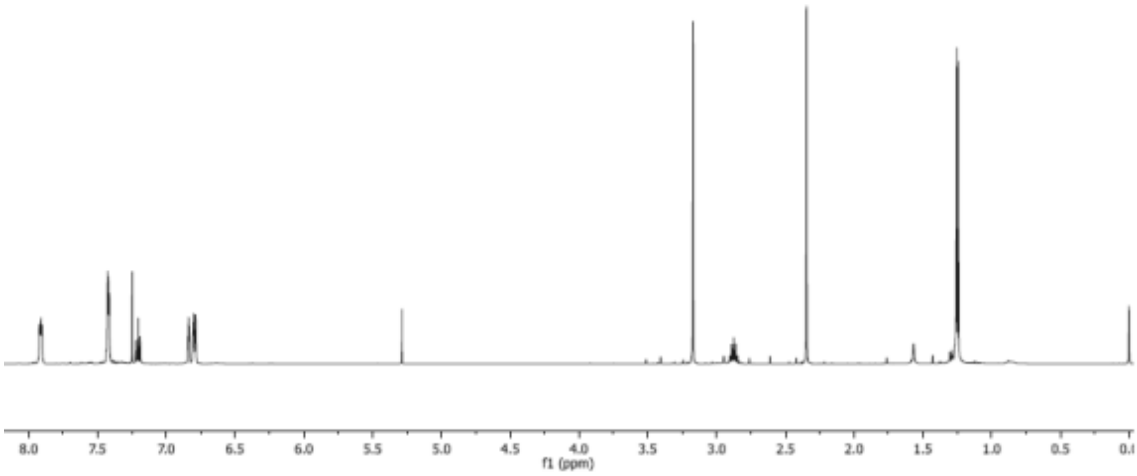

May26-2012
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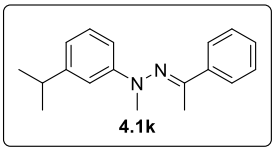

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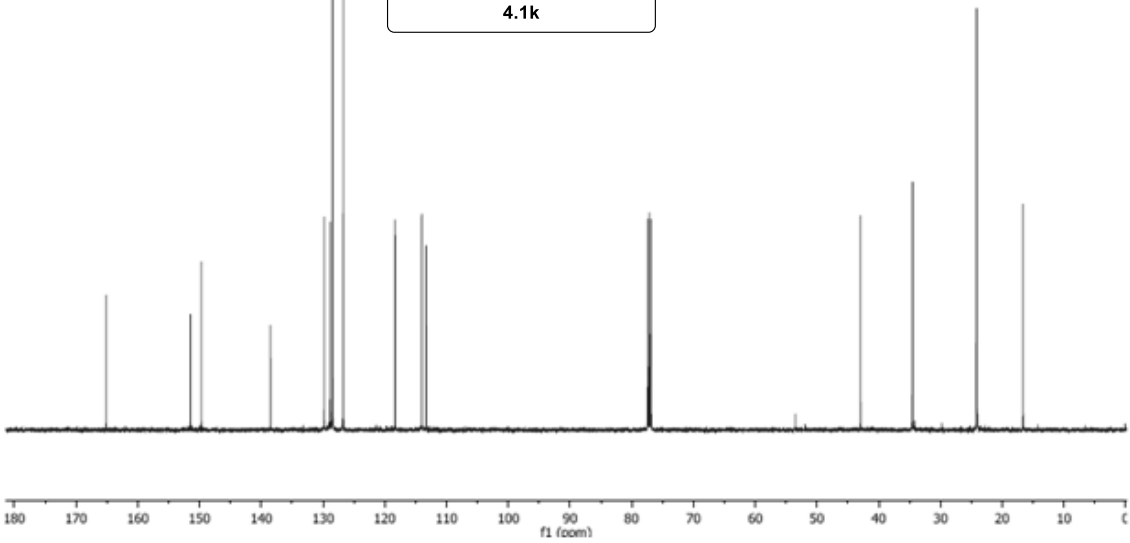

May27-2012
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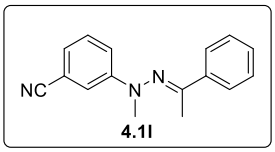

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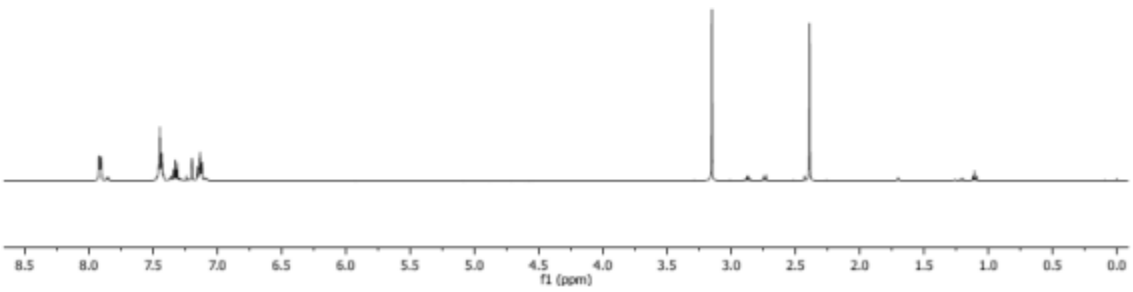

May27-2012
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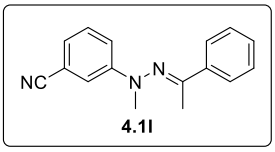

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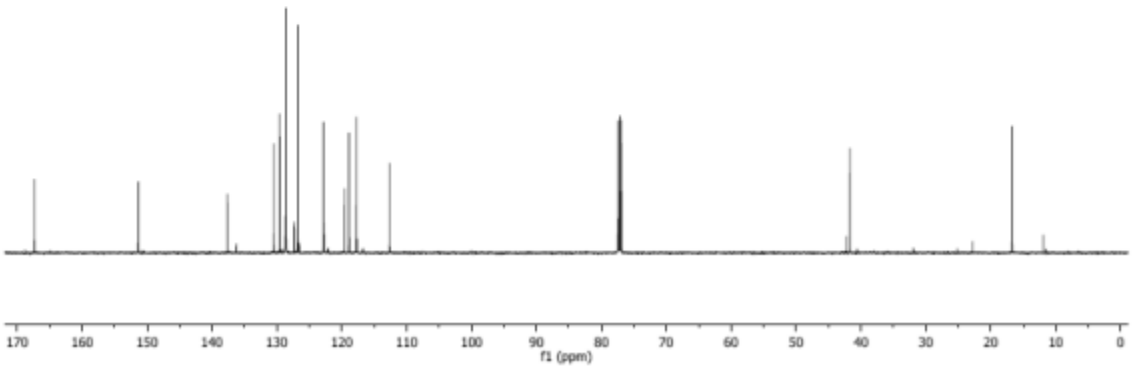

May27-2012
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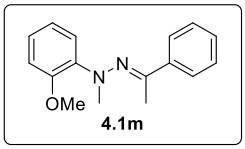
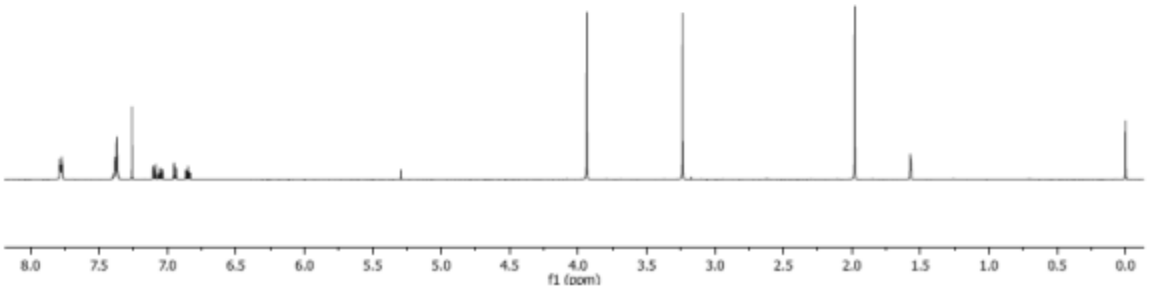
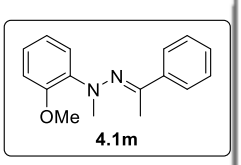




May26-2012
sm-nh2-2-ome



May27-2012
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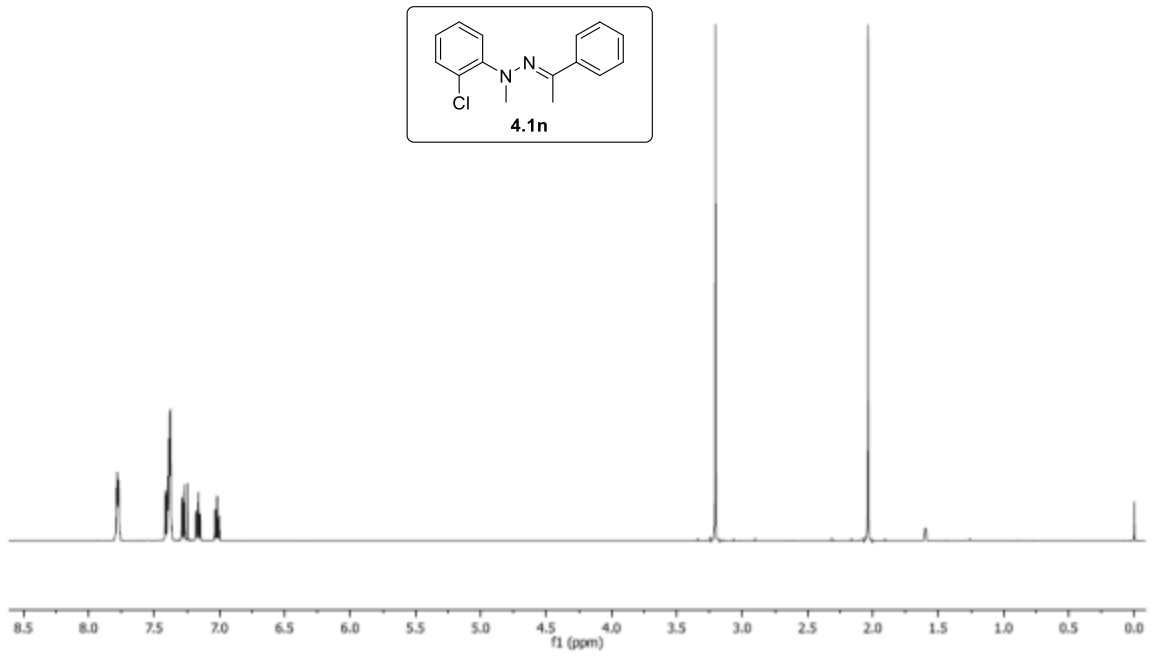

May26-2012
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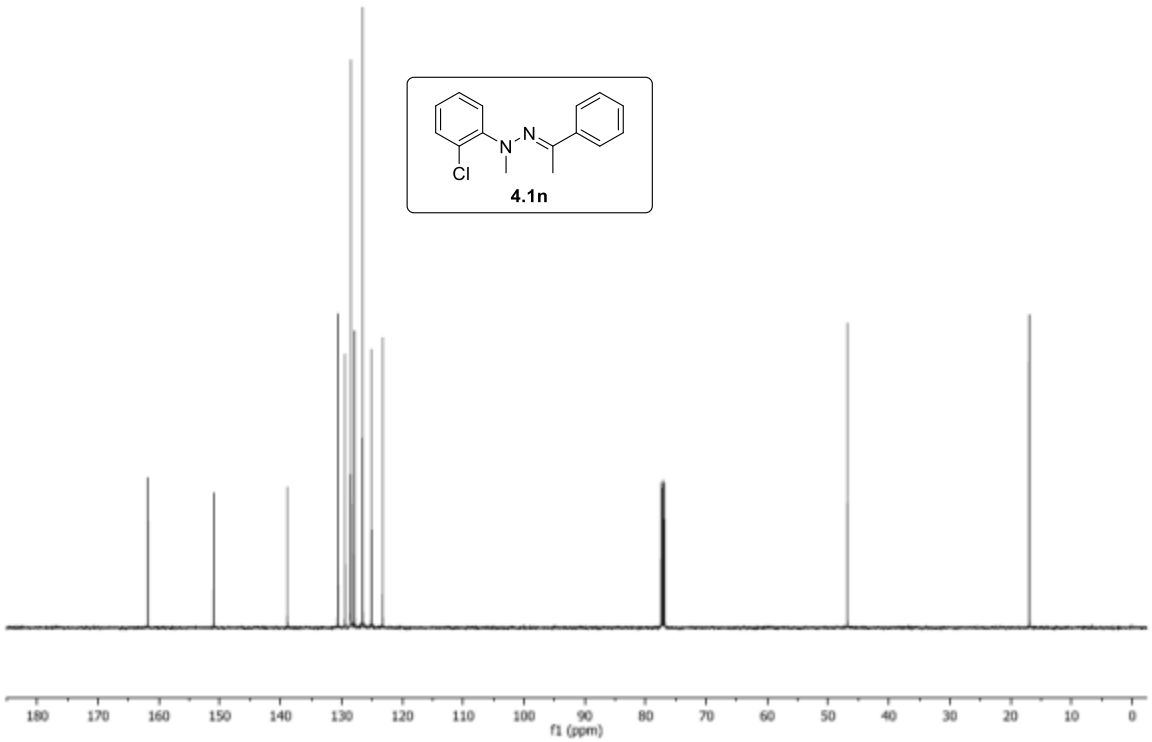

May27-2012
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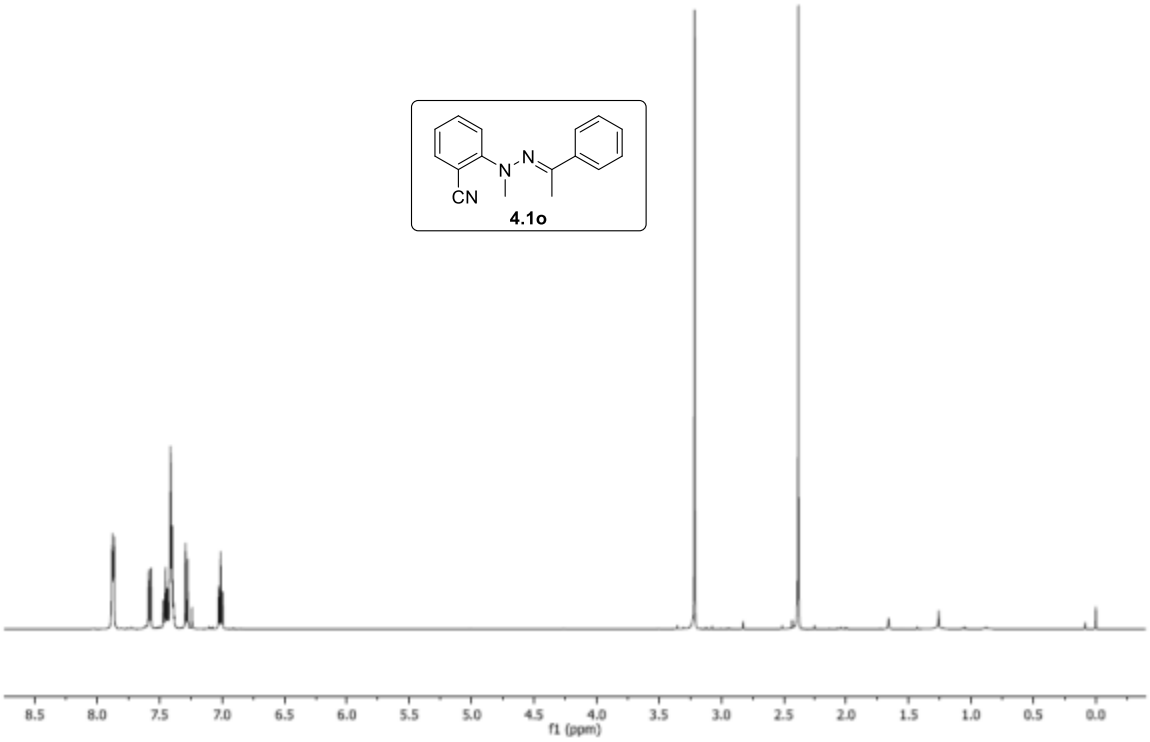

May27-2012
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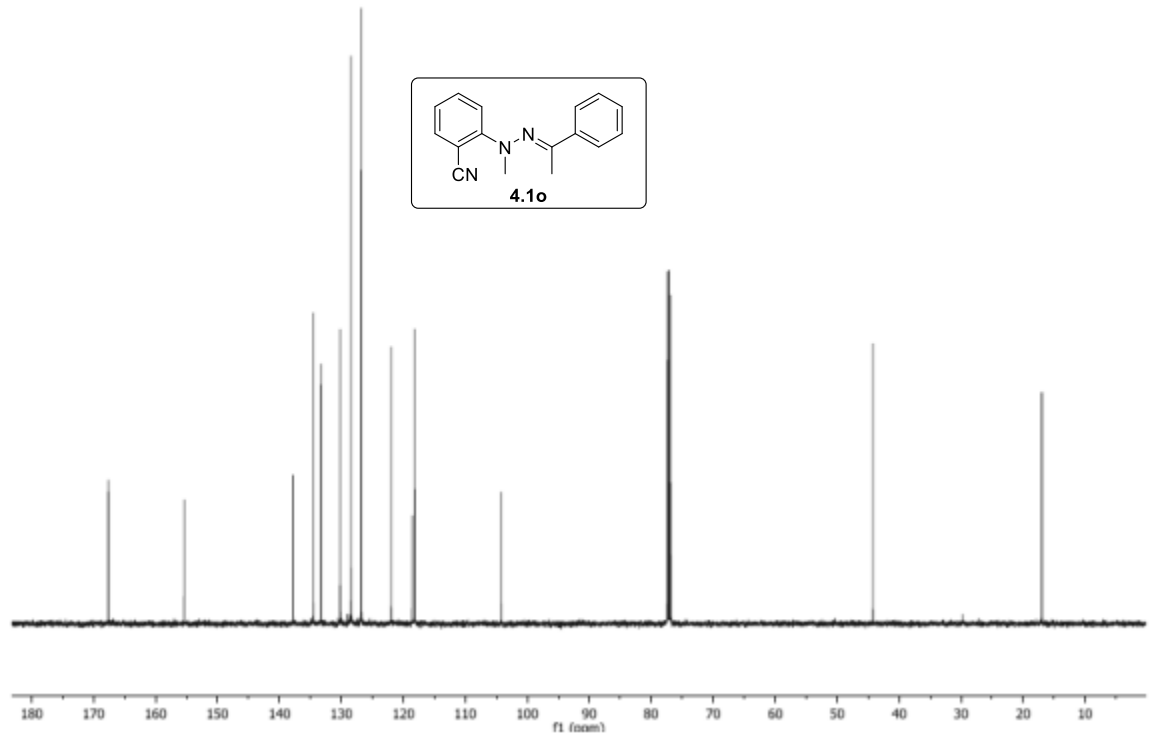
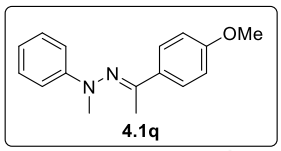


May27-2012
sm-ph-4-ome



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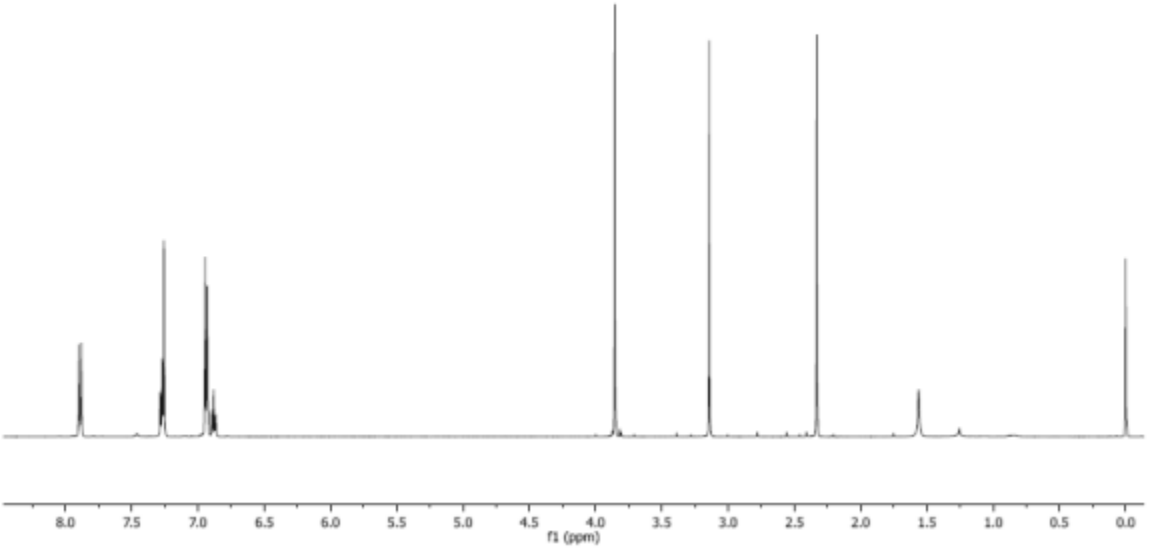

May26-2012
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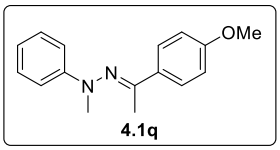
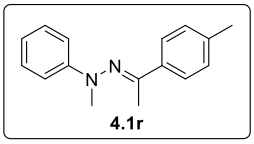
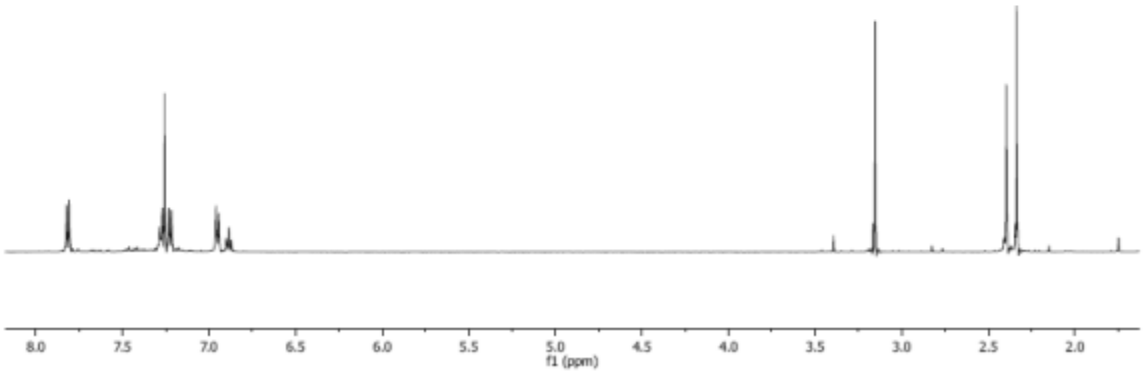


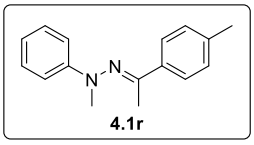
4.1q

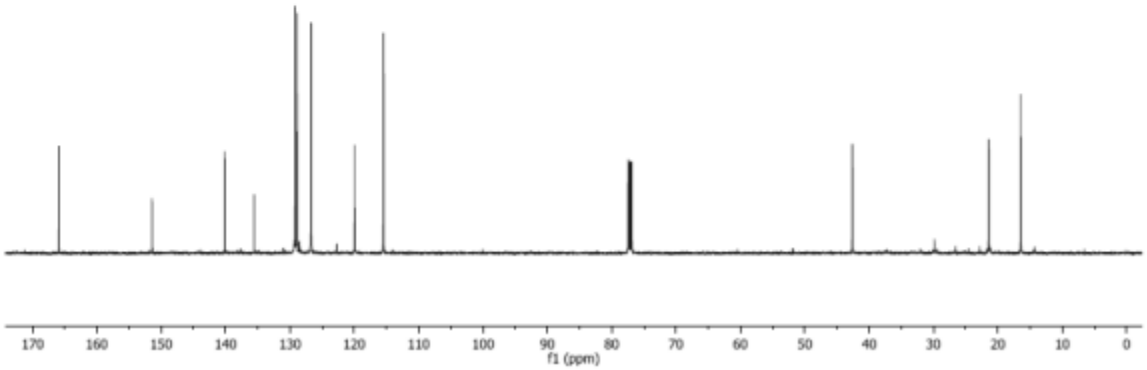
May26-2012
sm-ph-4-me-again



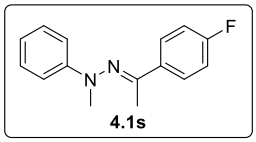


Apr10-2012
4-me





Apr12-2012
4-f



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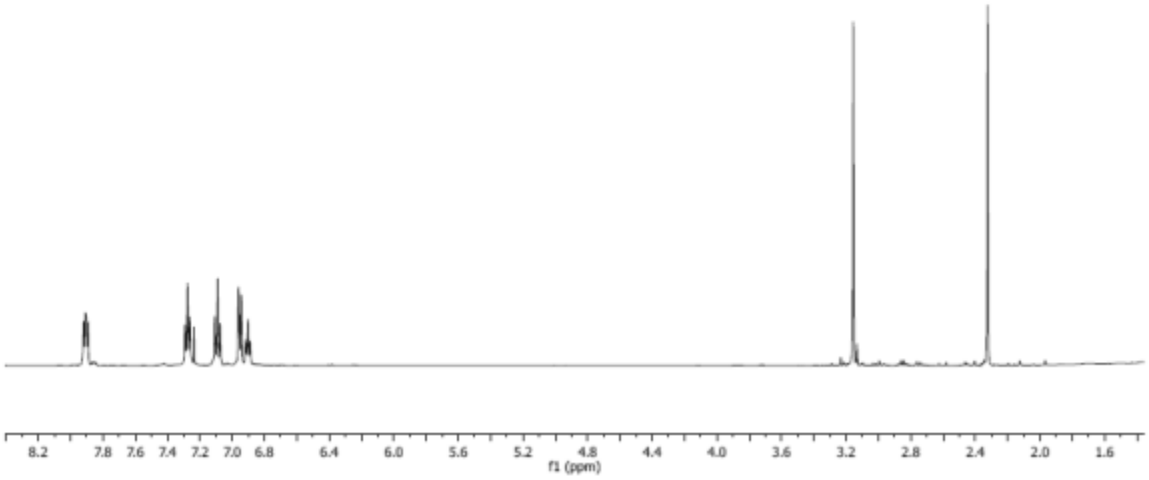
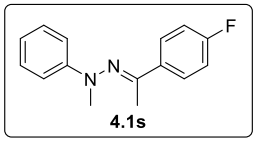


Apr12-2012
4-f



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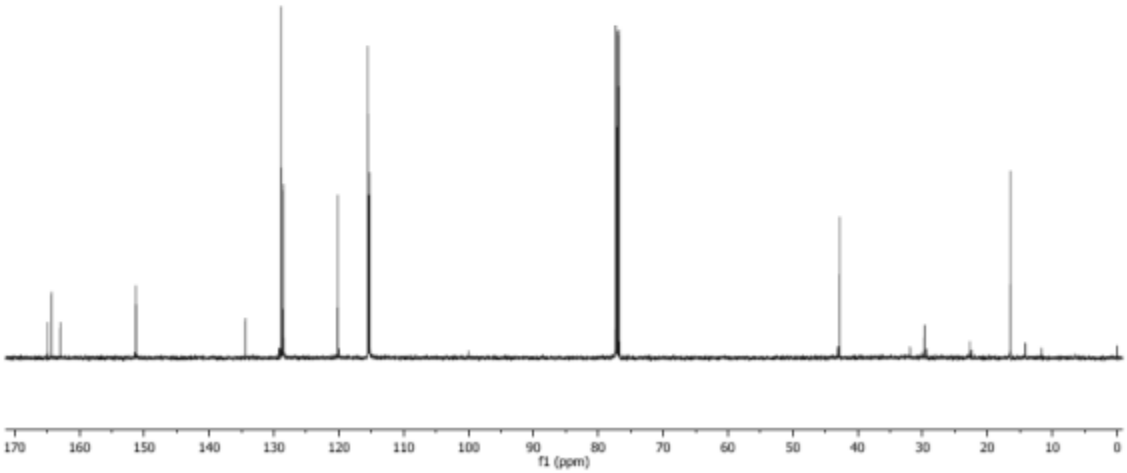
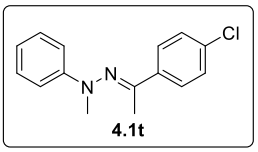


May27-2012
sm-ph-4-cl



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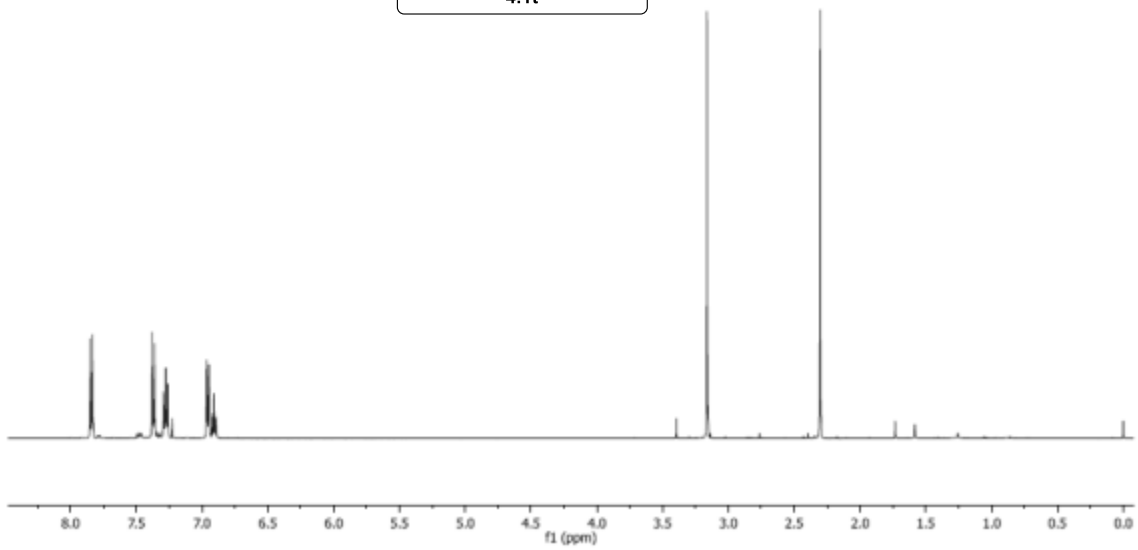
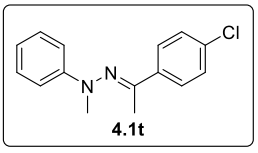


May27-2012
sm-ph-4-cl



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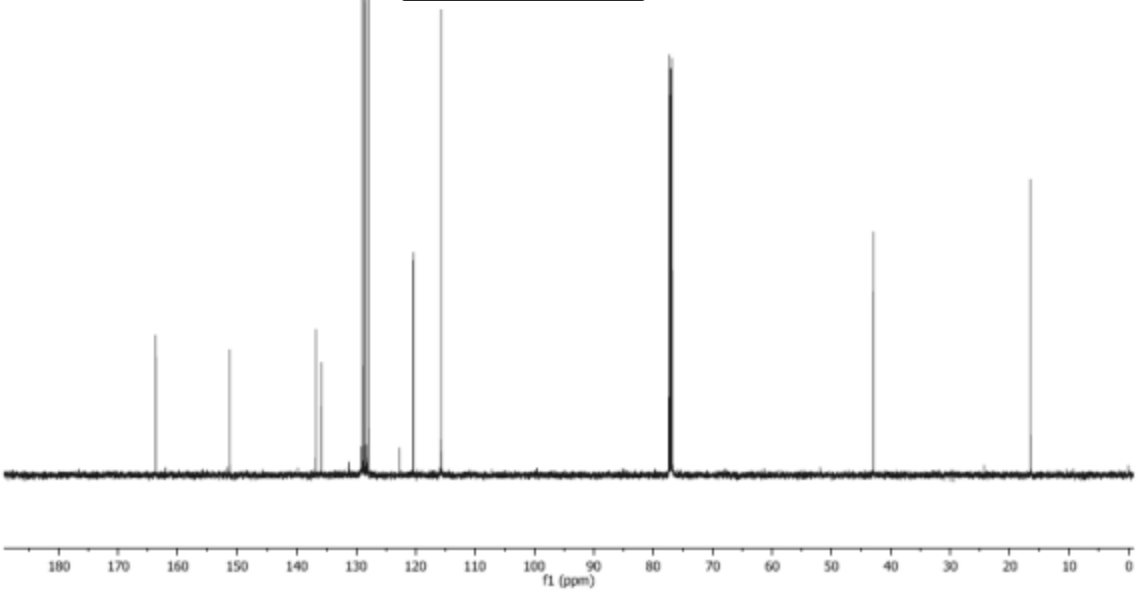
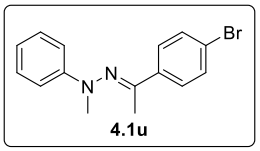


Apr10-2012
4-br



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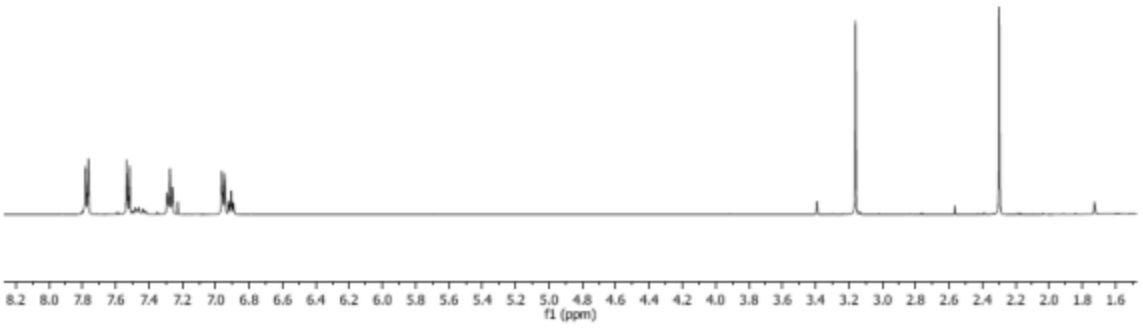
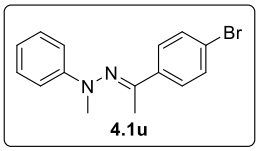


Apr10-2012
4-br



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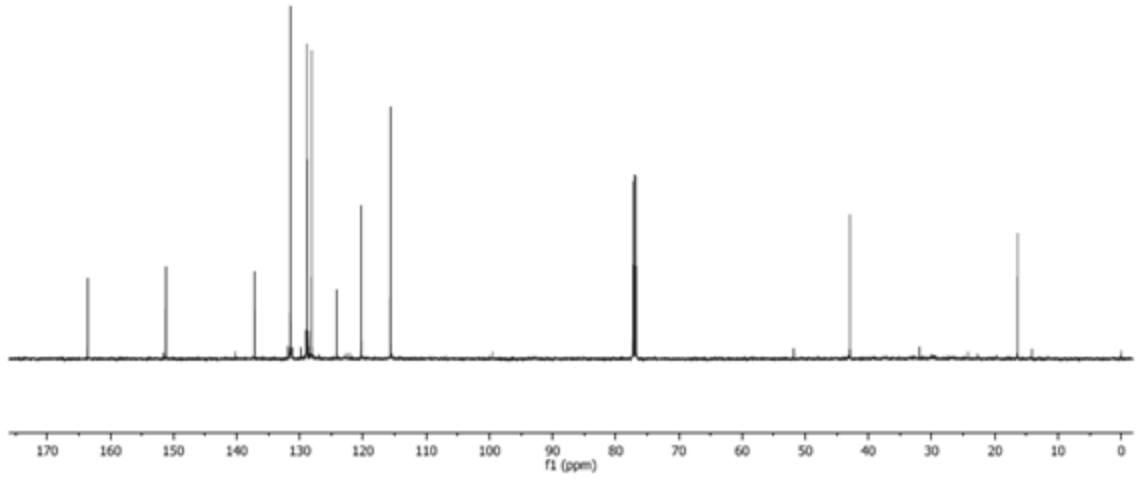
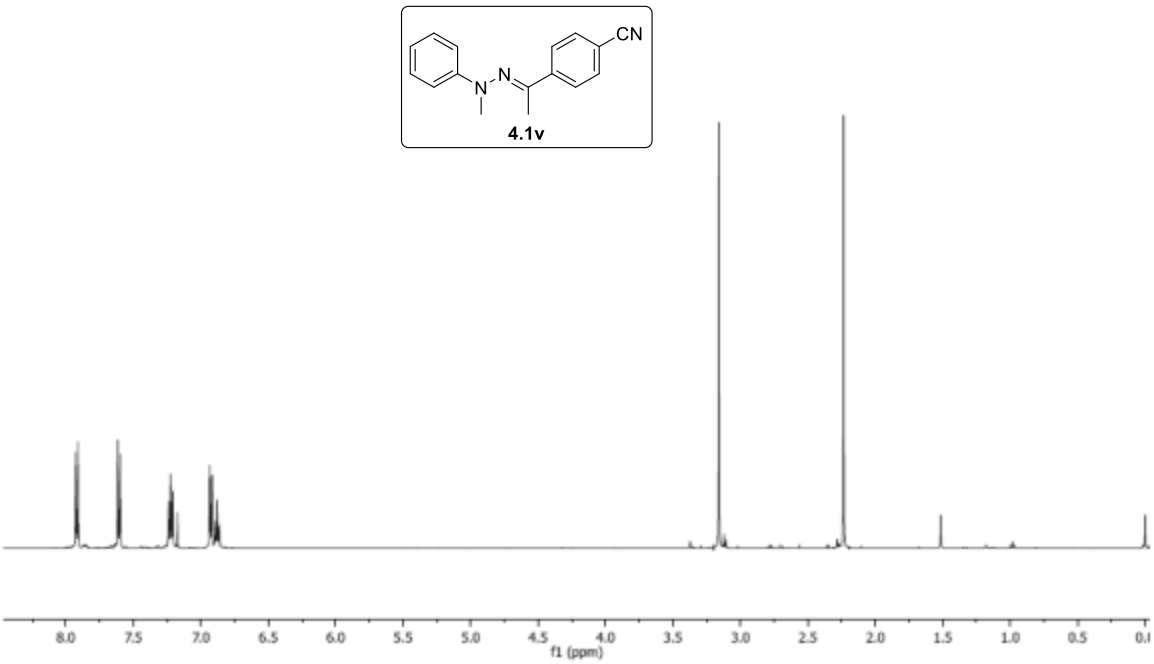
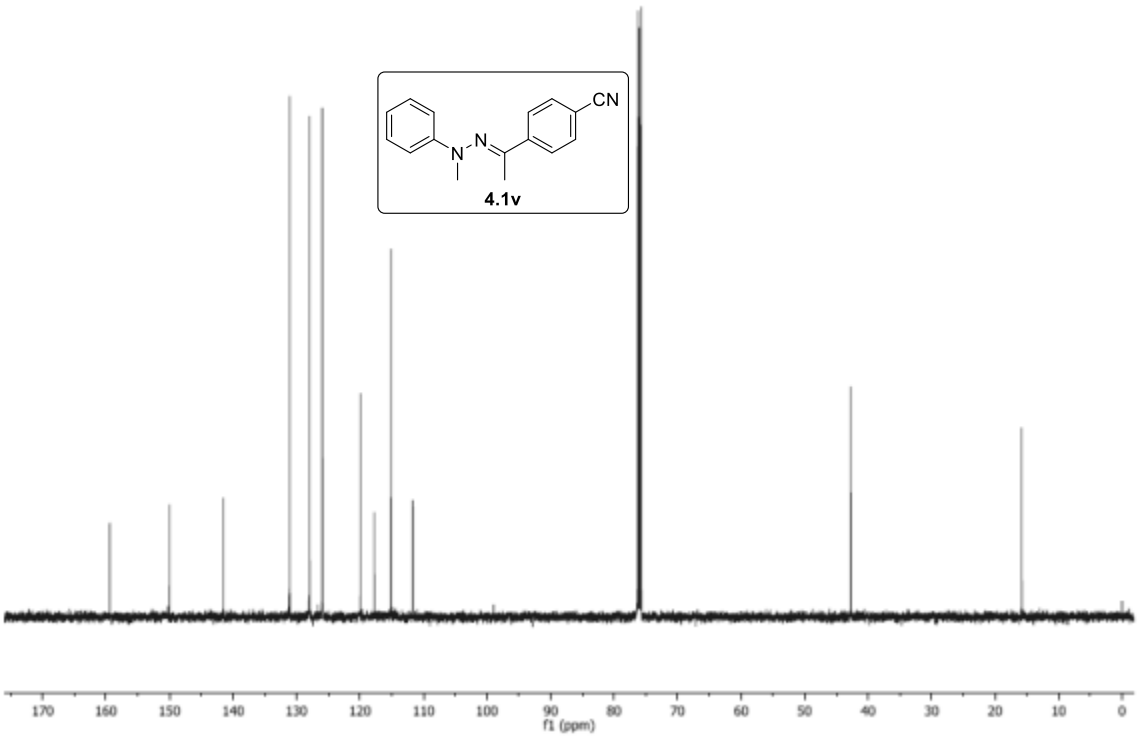


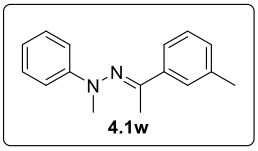
May27-2012
sm-ph-4-cn

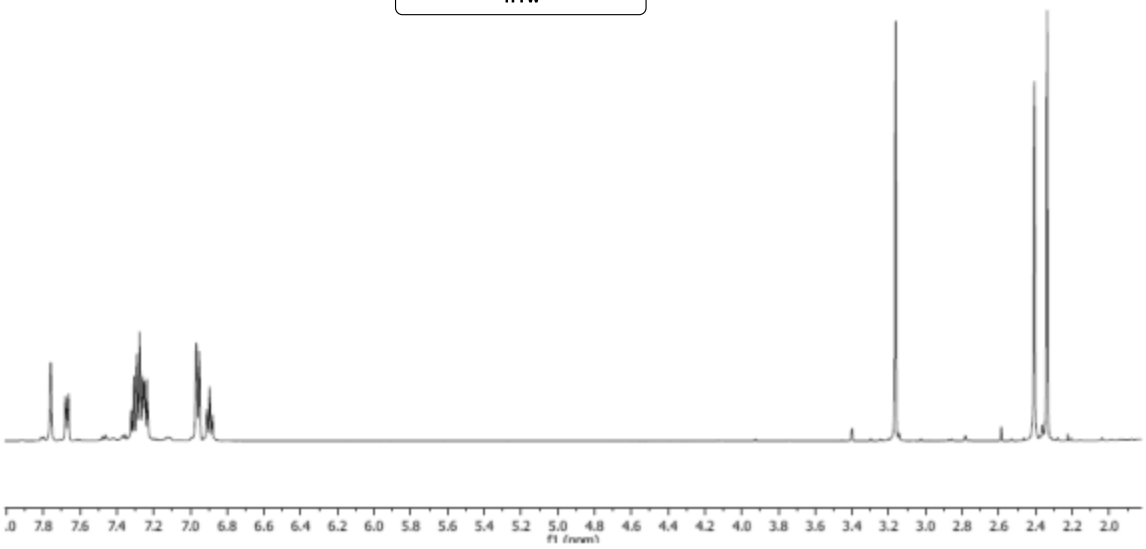


May27-2012
sm-ph-4-cn

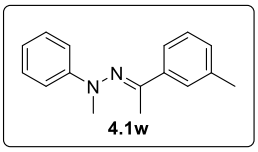


Apr14-2012
3-me

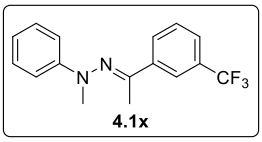




Apr14-2012
3-me



May27-2012
sm-ph-3-cf3



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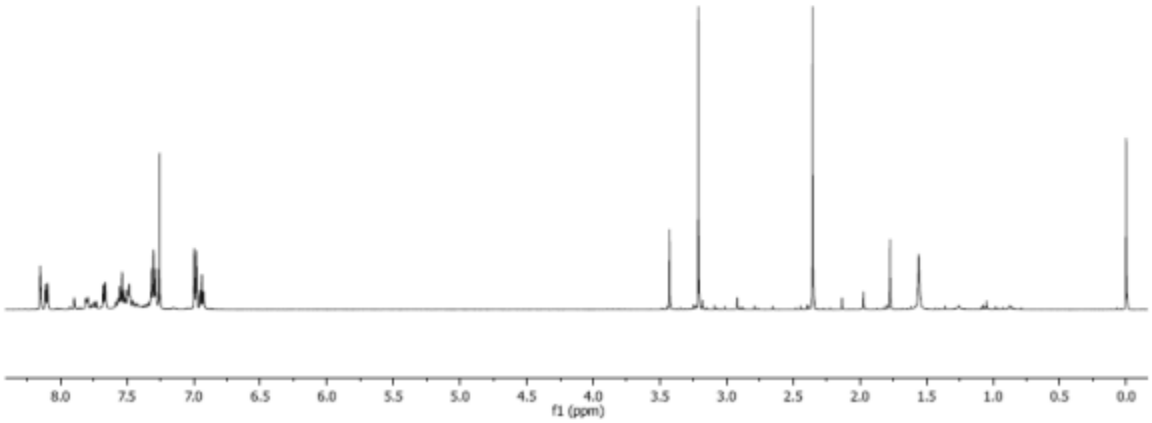
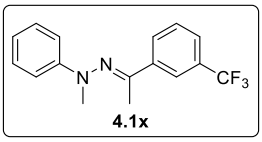


May26-2012
sm-ph-3-cf3



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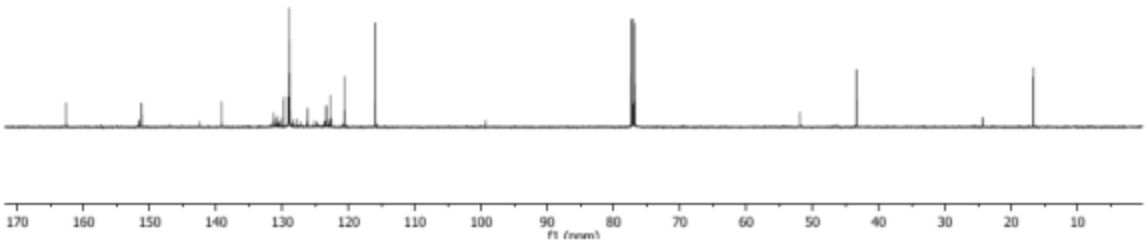
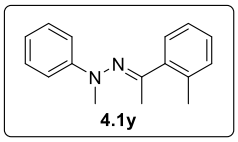
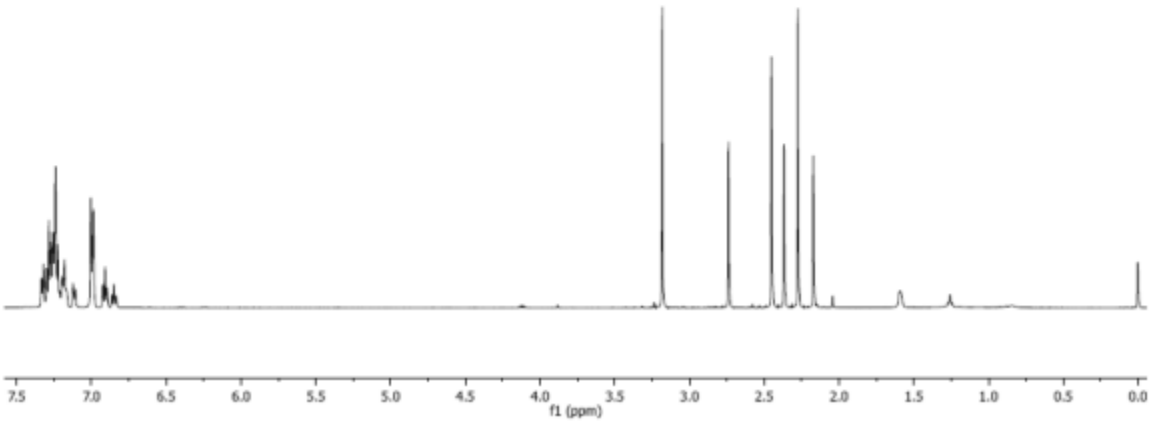
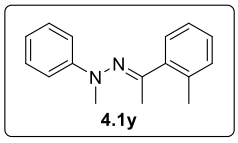


May27-2012
sm-ph-2-me

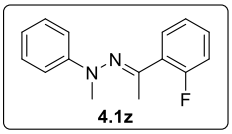




May26-2012
sm-ph-2me

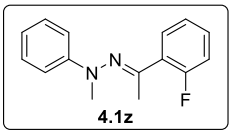


May26-2012
sm-ph-2-f-again



4.1z

Apr10-2012
2-f



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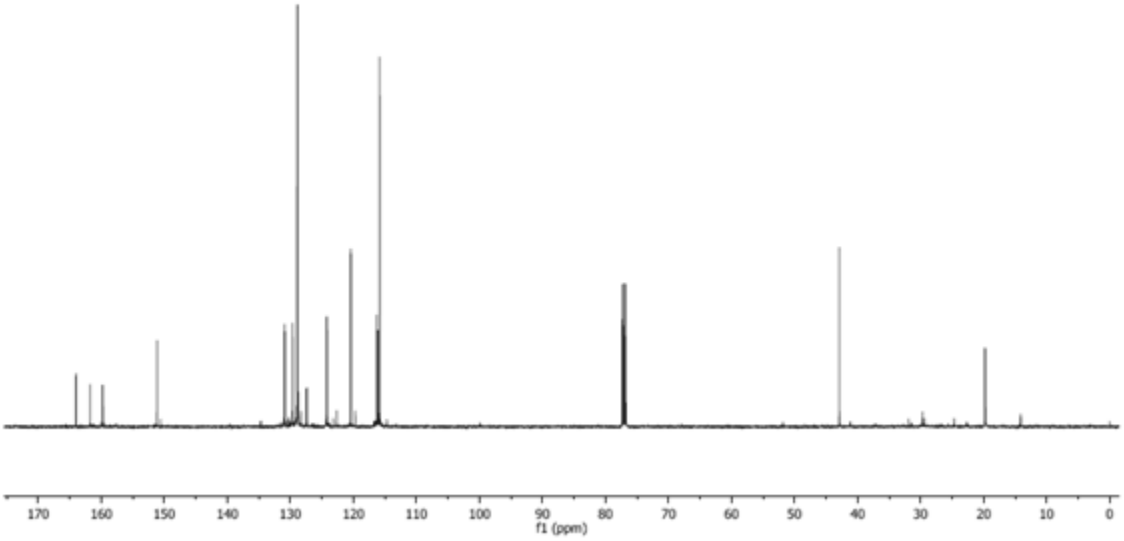
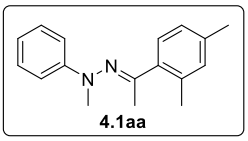
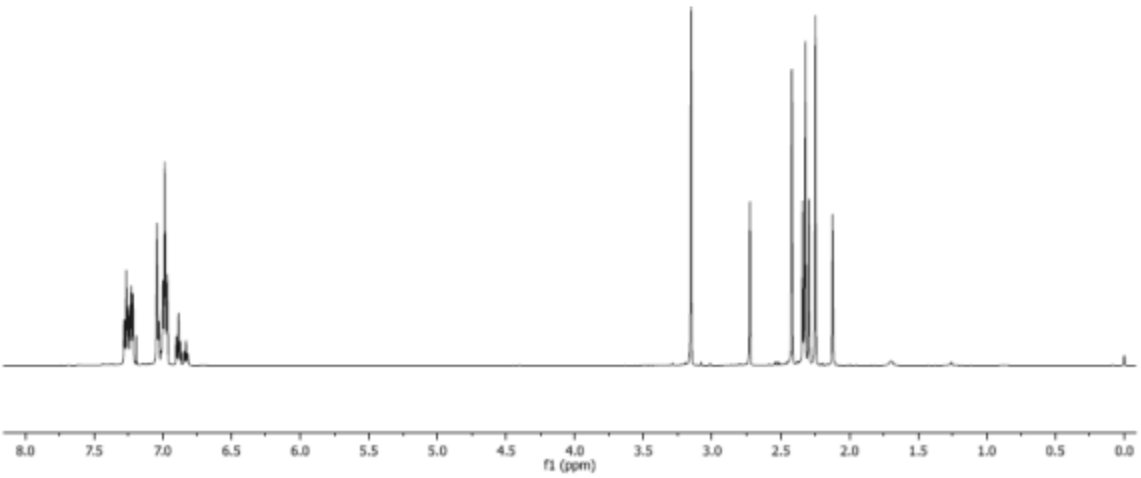
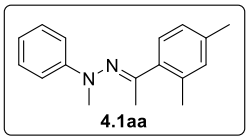


May27-2012
sm-ph-2,4-me

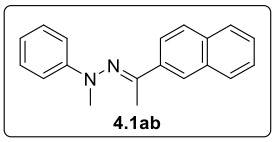


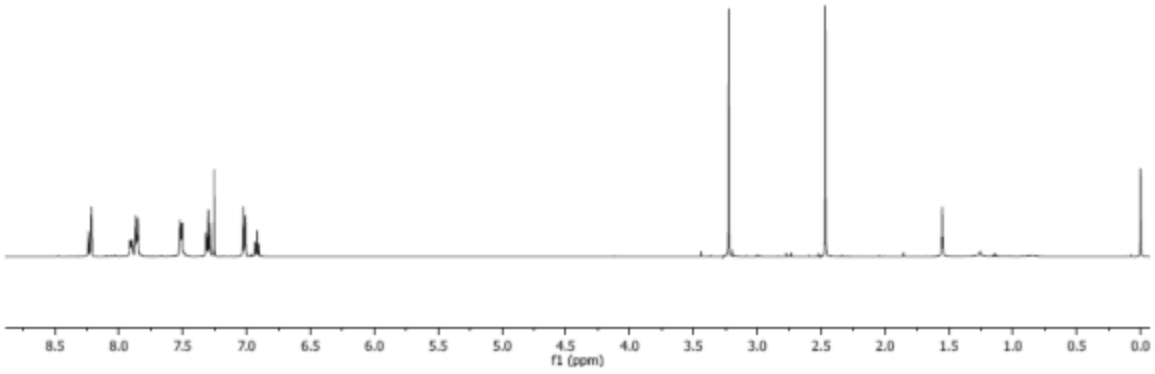


May27-2012
sm-ph-2, 4-me

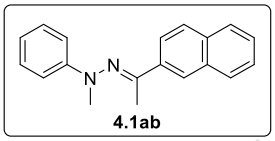


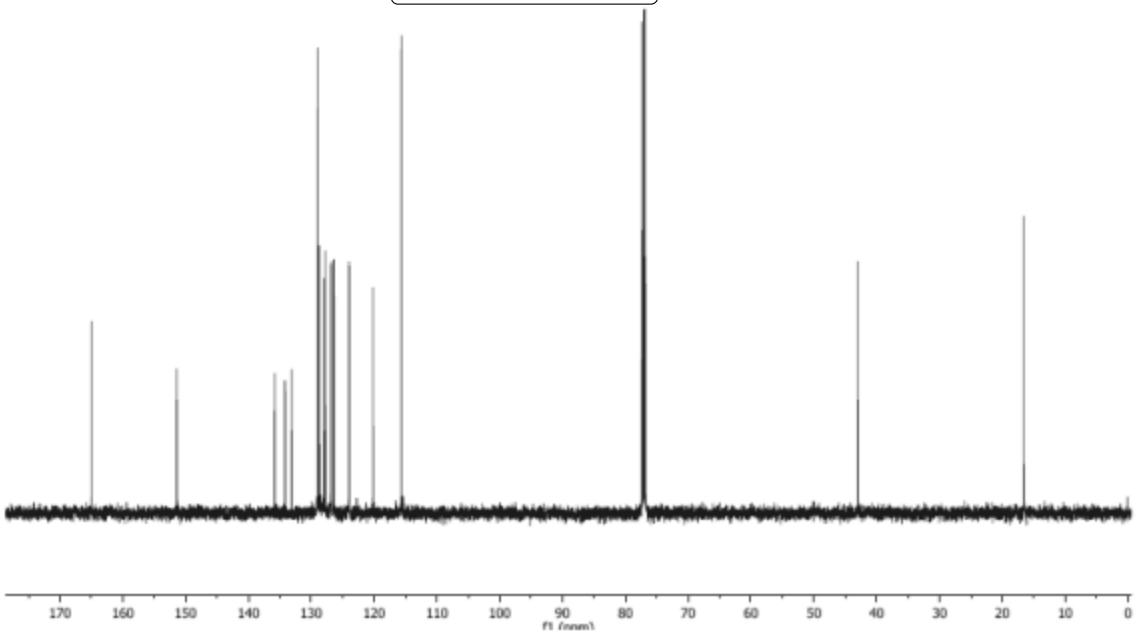
May27-2012
sm-ph-2-np



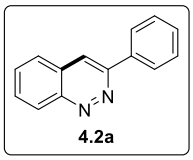


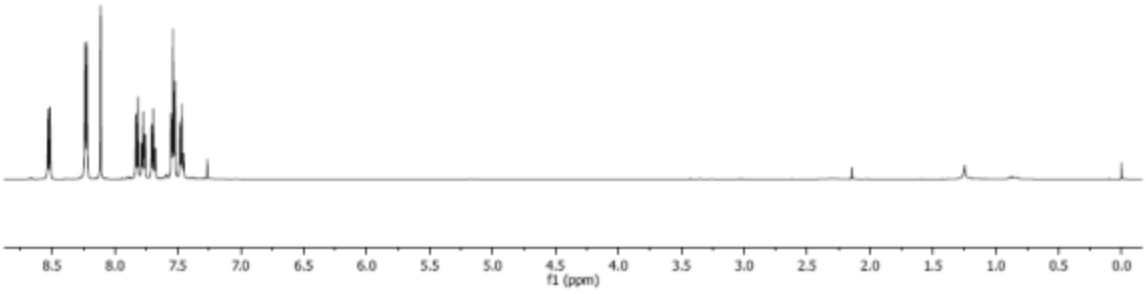
May26-2012
sm-ph-2-np



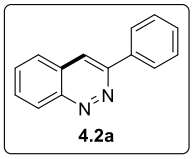


May28-2012
sm-ph-h

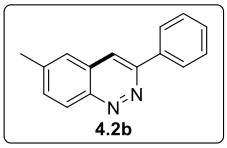


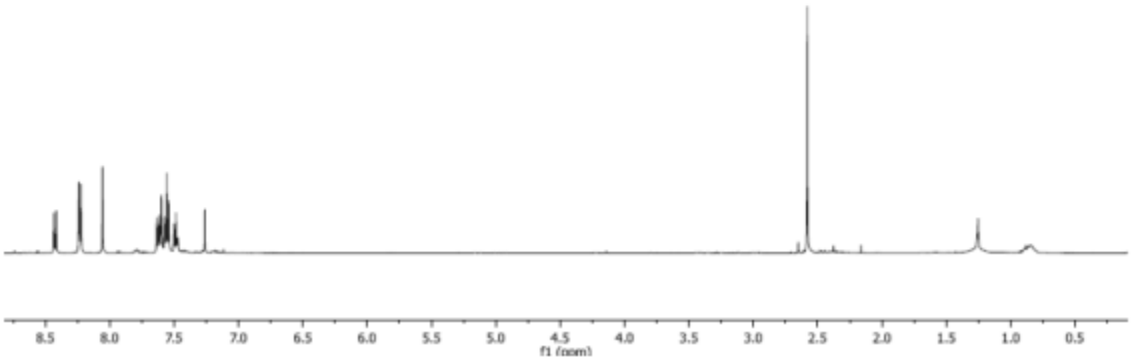


May28-2012
sm-ph-h

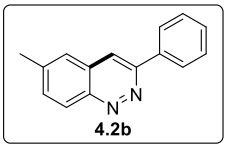


May09-2012
pro-nh2-4-me

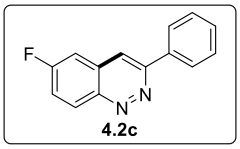




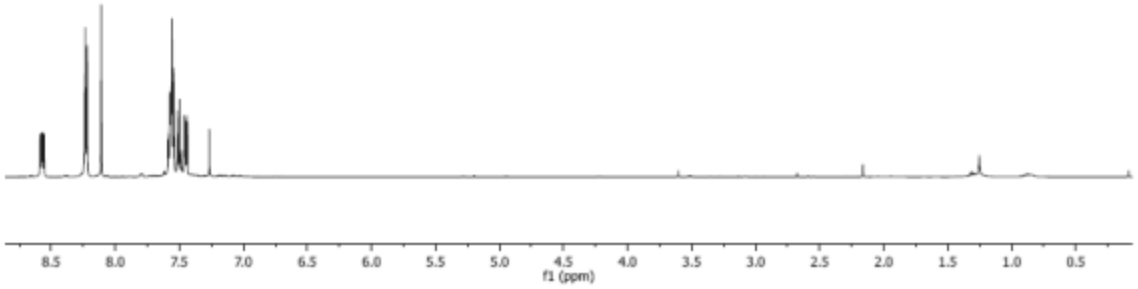
May09-2012
pro-nh2-4-me



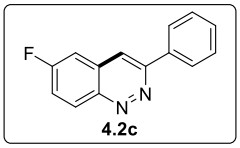
May11-2012
nh2nh-4-f



4.2c

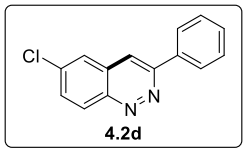


May11-2012
nh2nh-pro-4-f

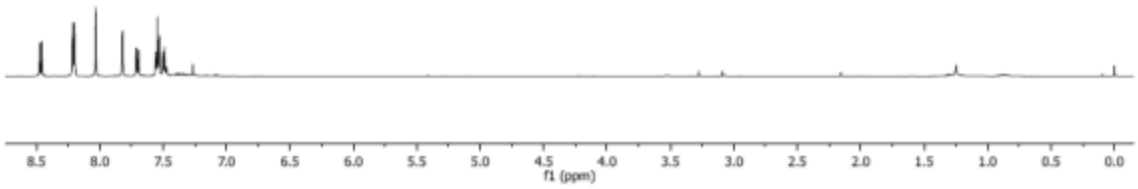


4.2c

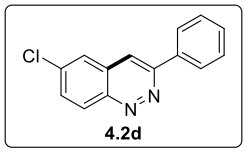
May10-2012
nh2nh-4-cl



4.2d

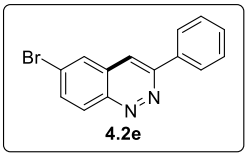


May10-2012
nh2nh-4-cl

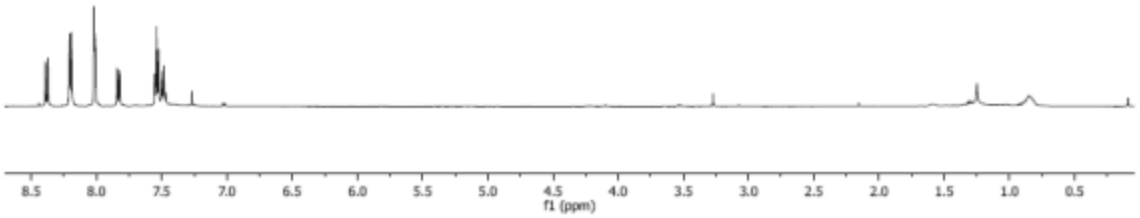


4.2d

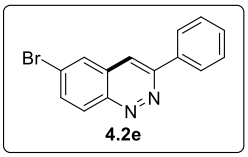
May09-2012
pro-nh2-4-br



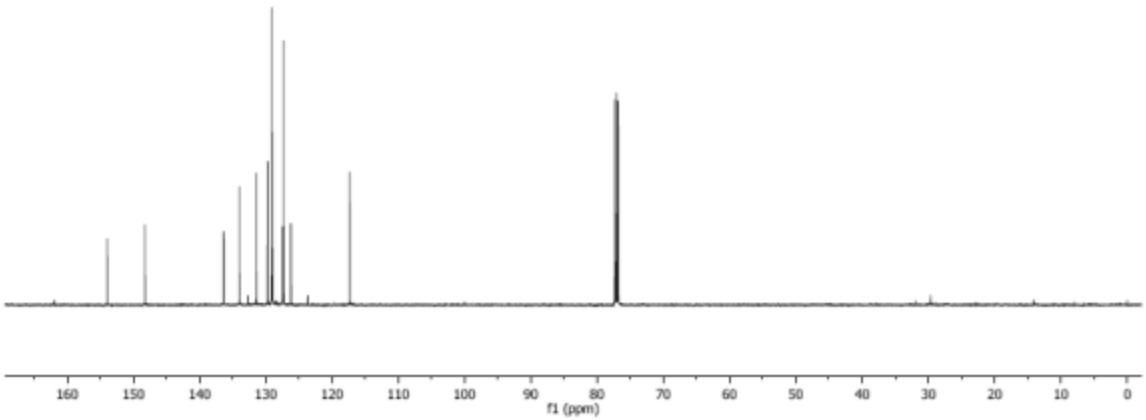
4.2e



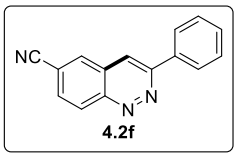
May09-2012
pro-nh2-4-br



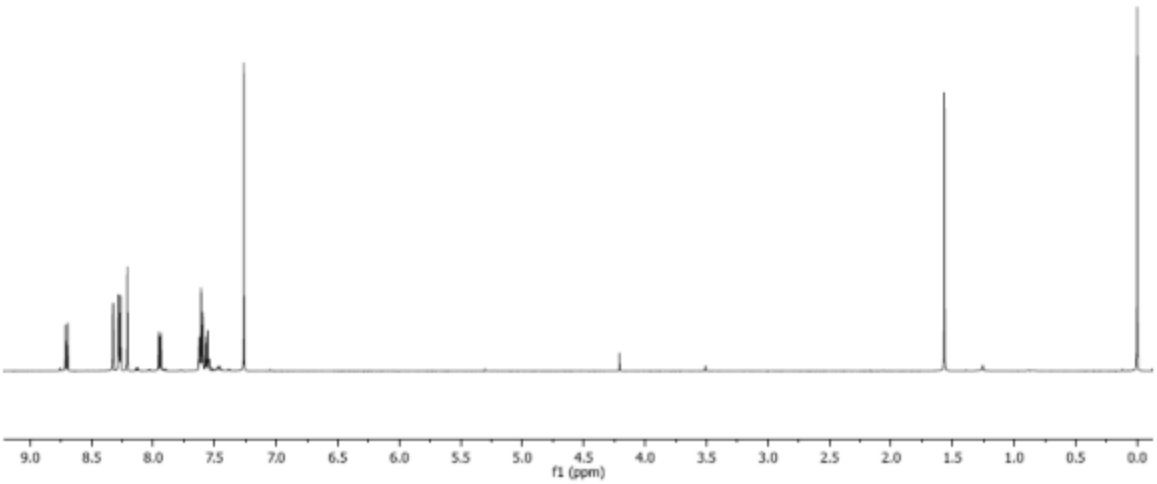
4.2e



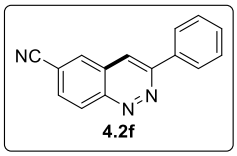
May23-2012
pro-nh2nh-4cn



4.2f

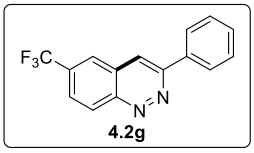


May25-2012
pro-nh2nh-4-cnagain

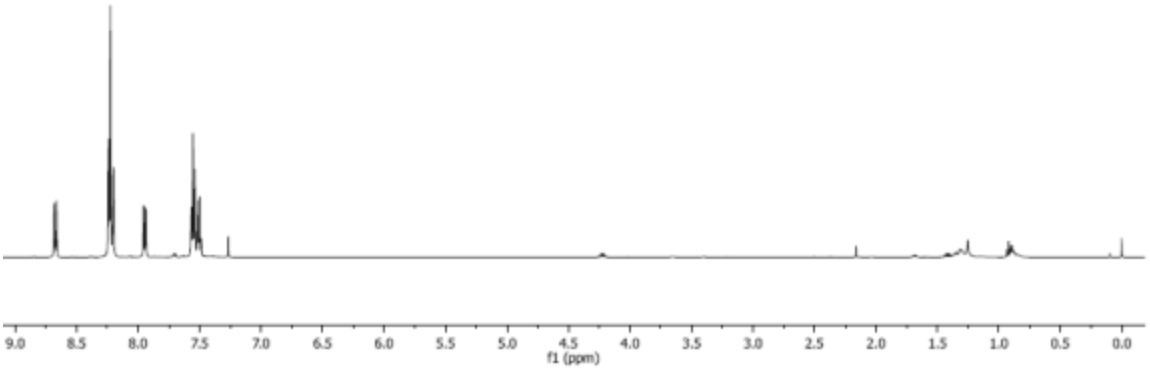


4.2f

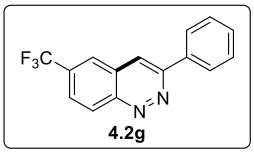
May15-2012
nh2nh-3-cf3-160



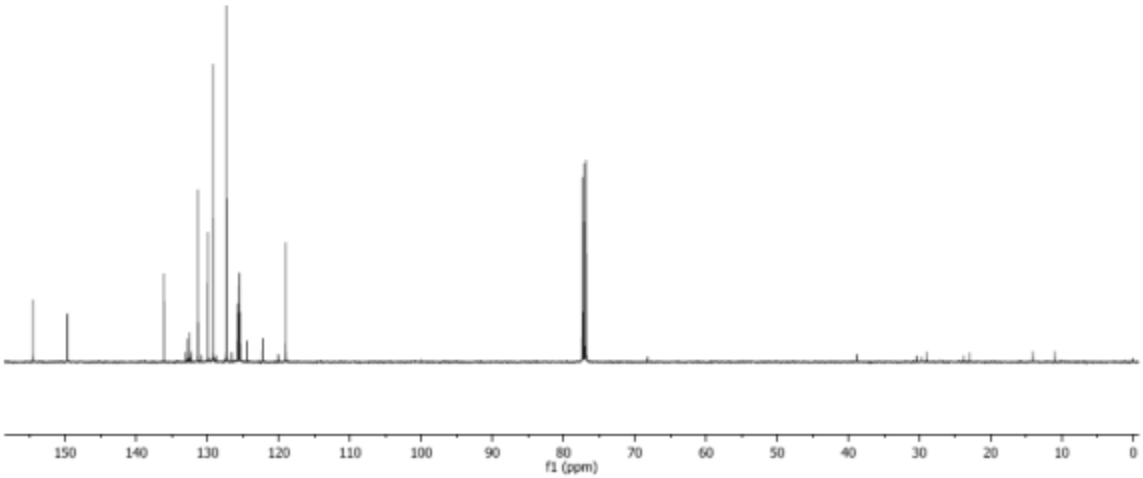
4.2g



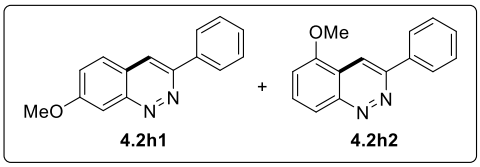
May15-2012
pro-nh2nh-4cf3



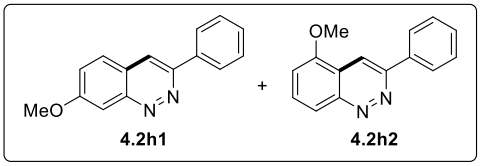
4.2g



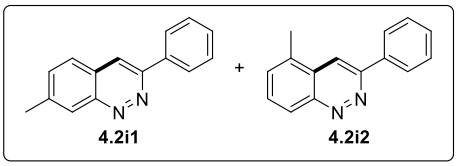
May10-2012
nh2nh-3-ome

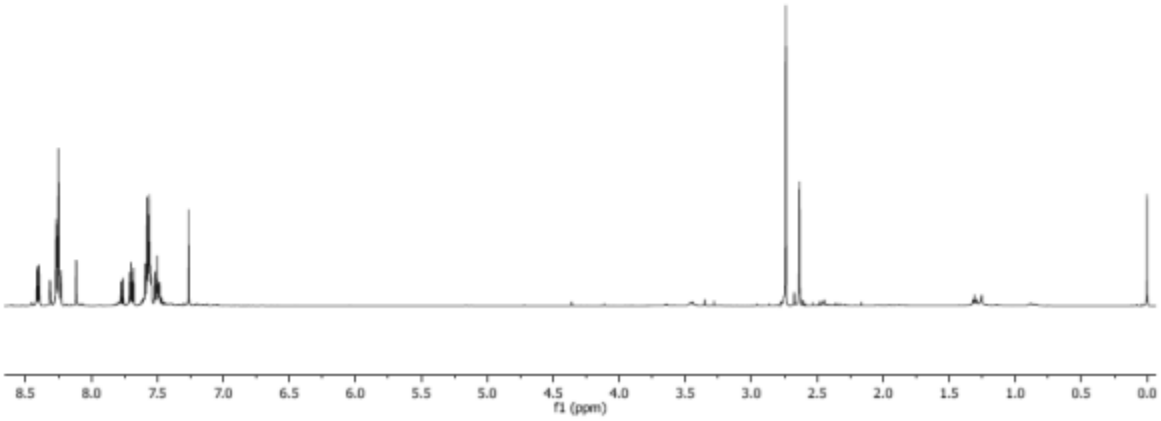


May11-2012
nh2nh-pro-3-ome

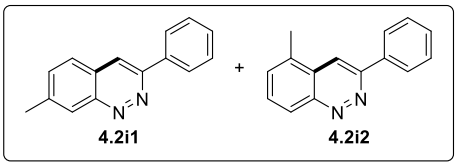


May17-2012
pro-nh2nh-3-me

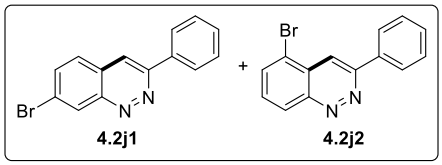


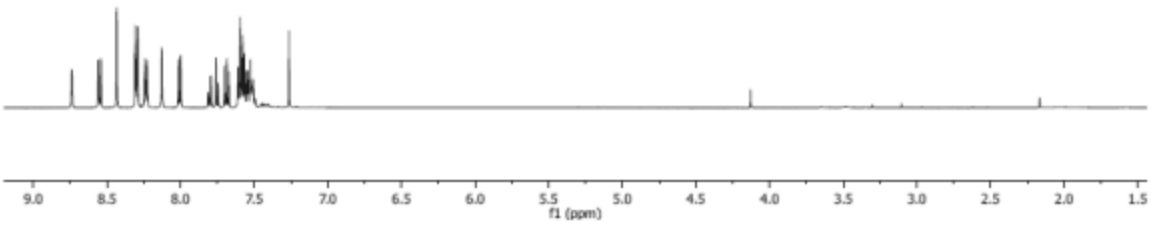


May19-2012
pro-nh2nh-3-me

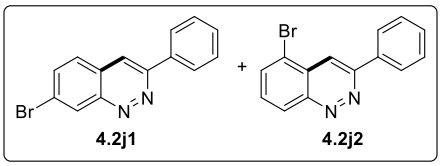


May18-2012
pro-nh2nh-3-br

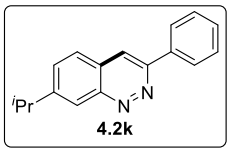




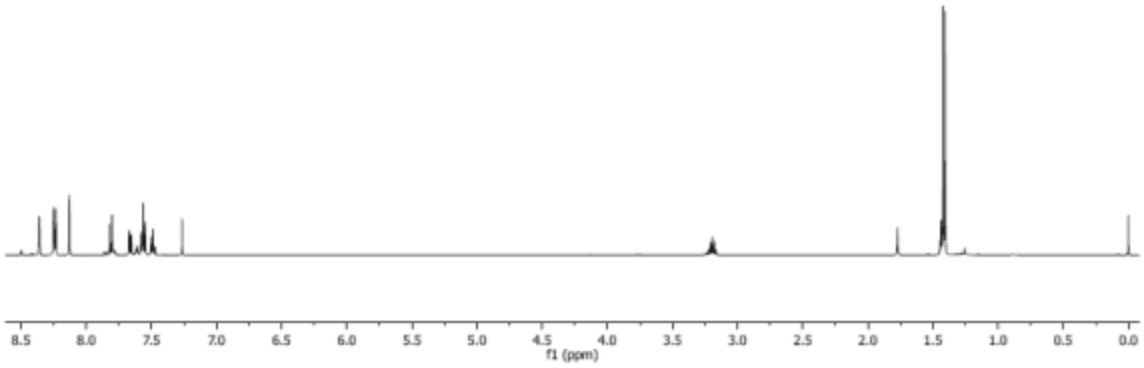
May19-2012
pro-nh2nh-3-br-again



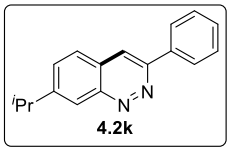
May25-2012
pro-nh2nh-3-ipr-again



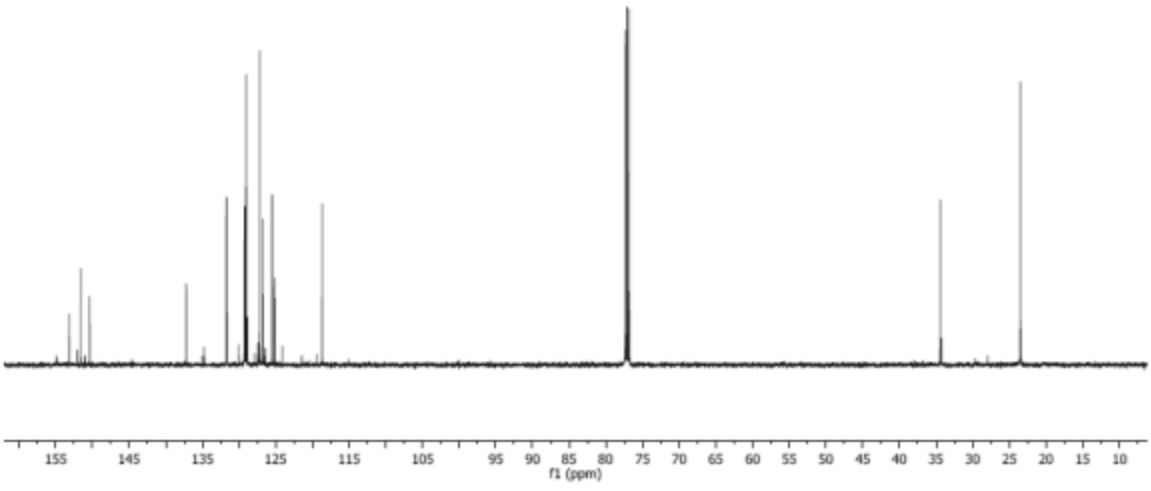
4.2k



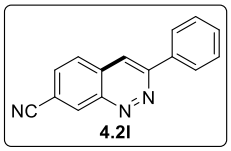
May25-2012
pro-nhnh2-3-ipr-againagain

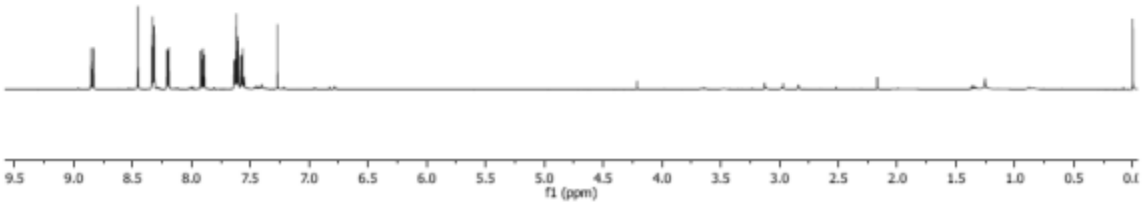


4.2k

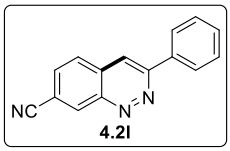


May16-2012
pro-nh2nh-3-cn

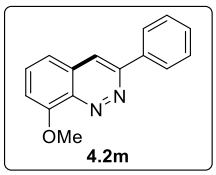




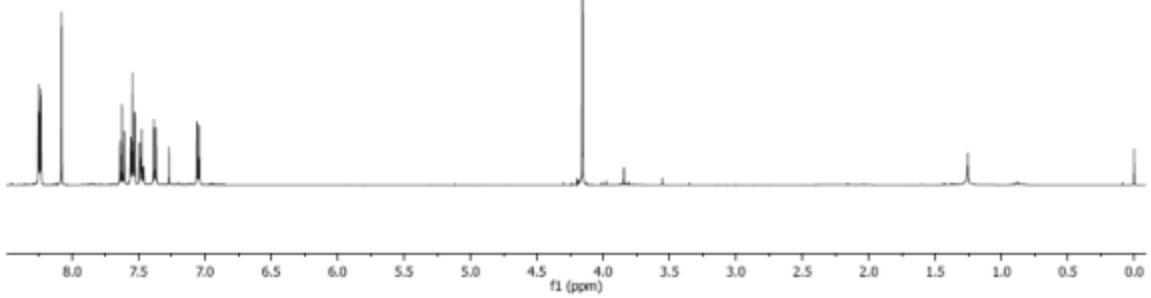
May16-2012
pro-nh2nh-3-cn



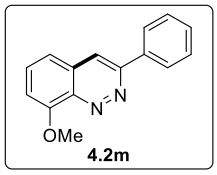
May10-2012
nh2nh-2-ome



4.2m

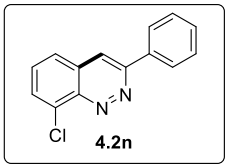


May11-2012
nh2nh-pro-2-ome



4.2m

May15-2012
pro-nh2nh-2cl



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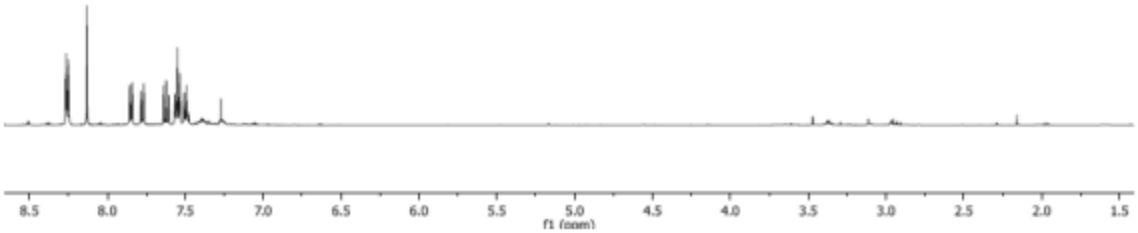

May15-2012
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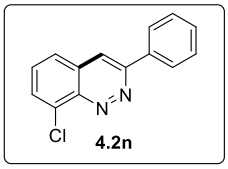

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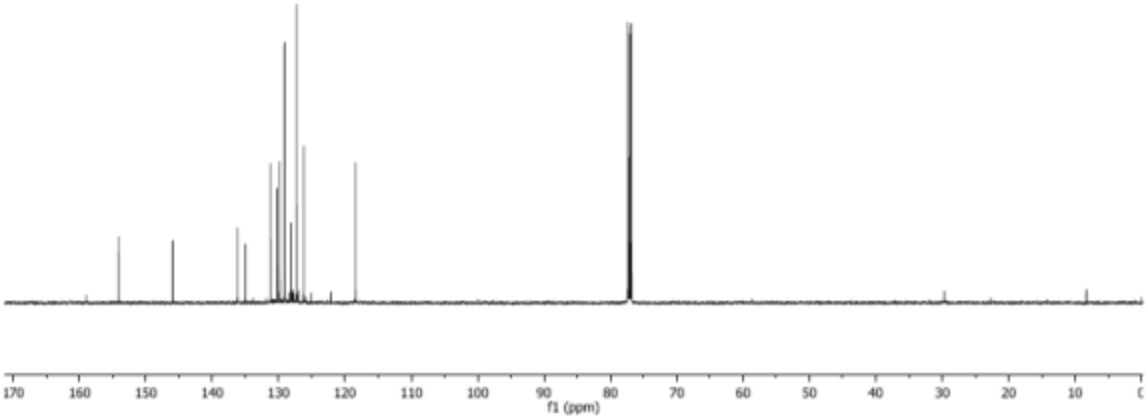

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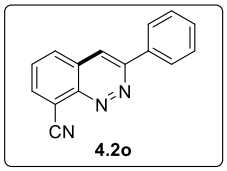

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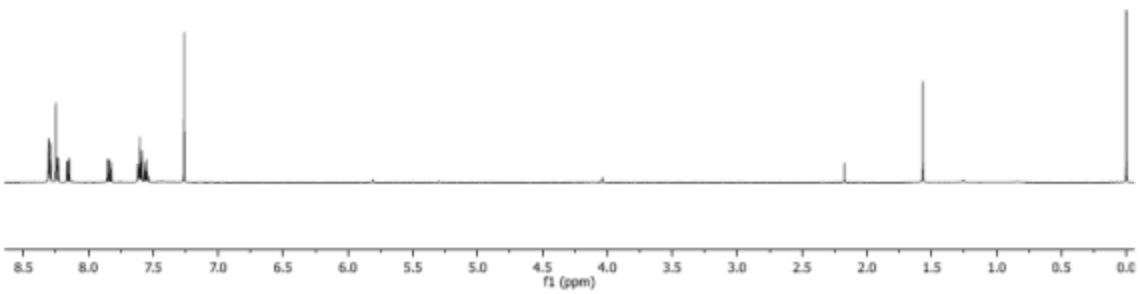

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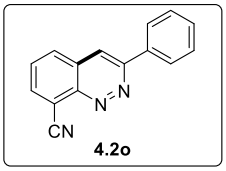

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May25-2012
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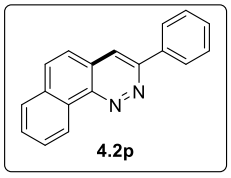

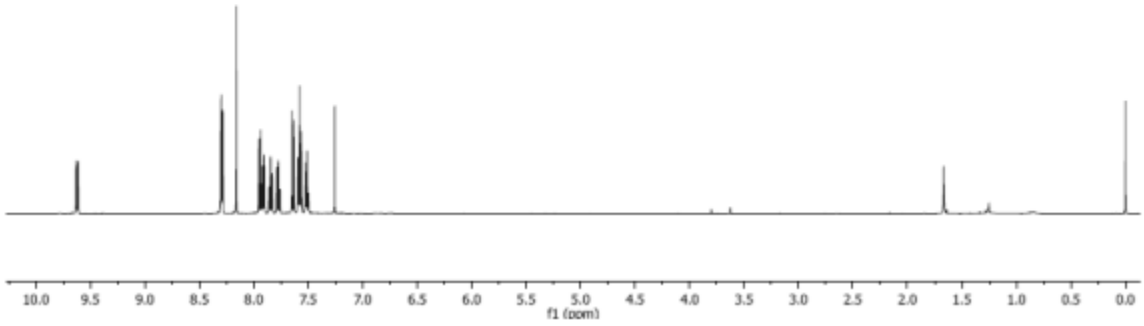

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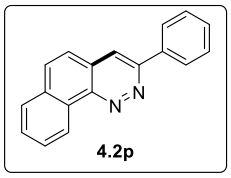
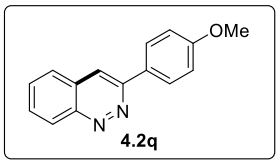


Apr24-2012
4-ome



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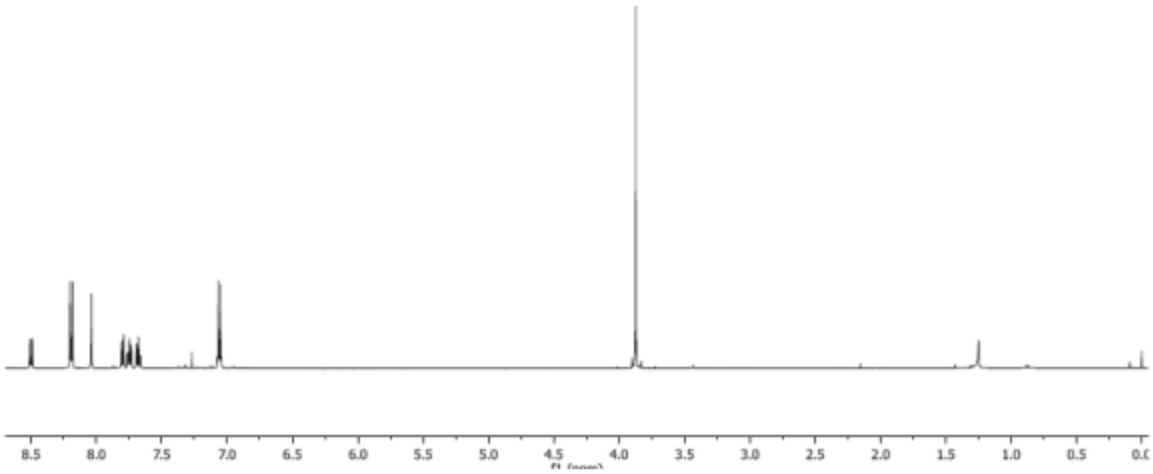

Apr24-2012
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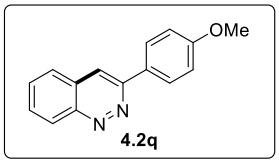

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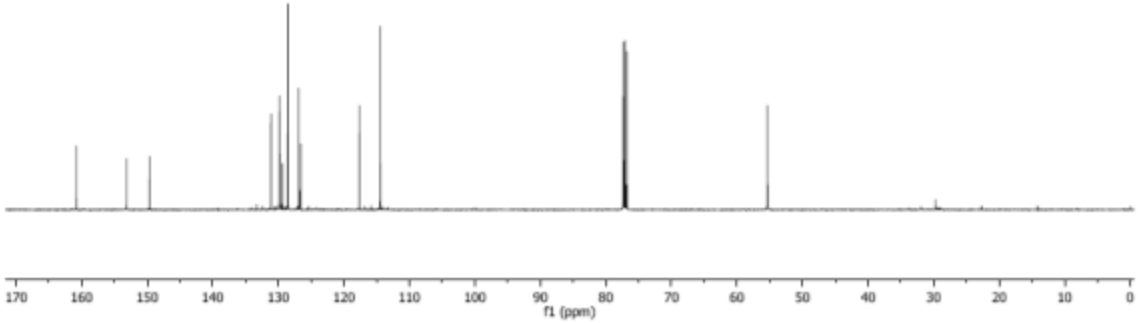
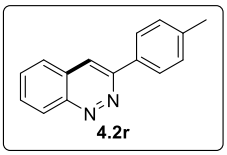
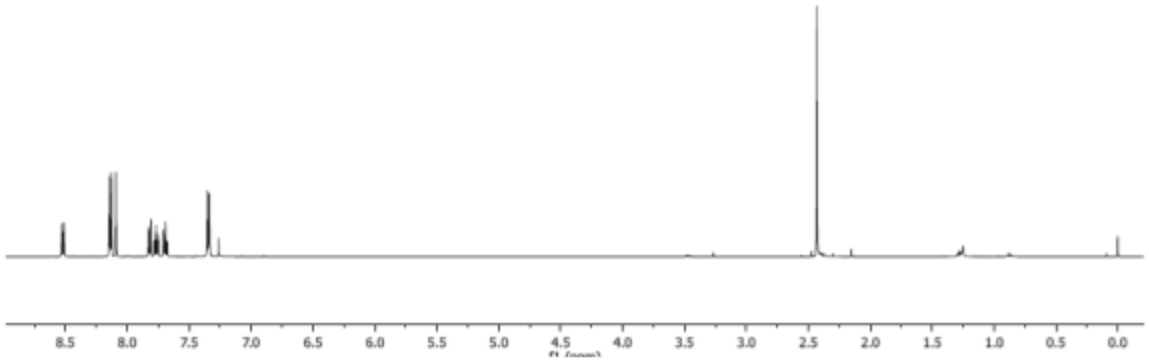


Apr19-2012
4-me-pro





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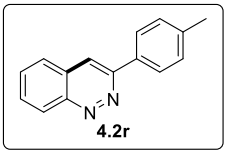

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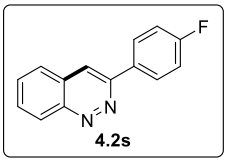

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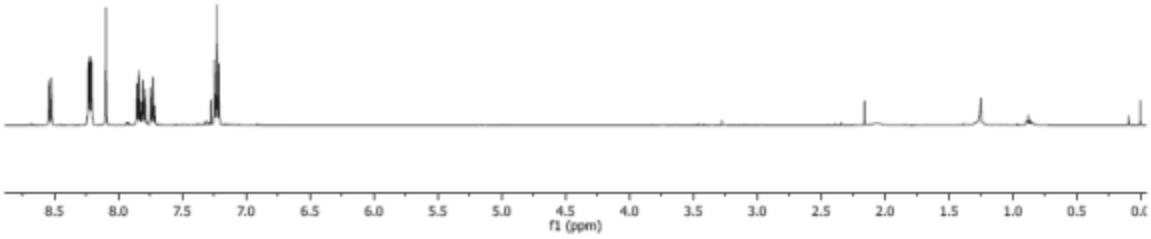

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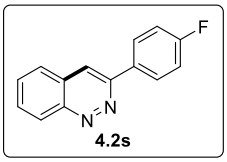
4-f-pro



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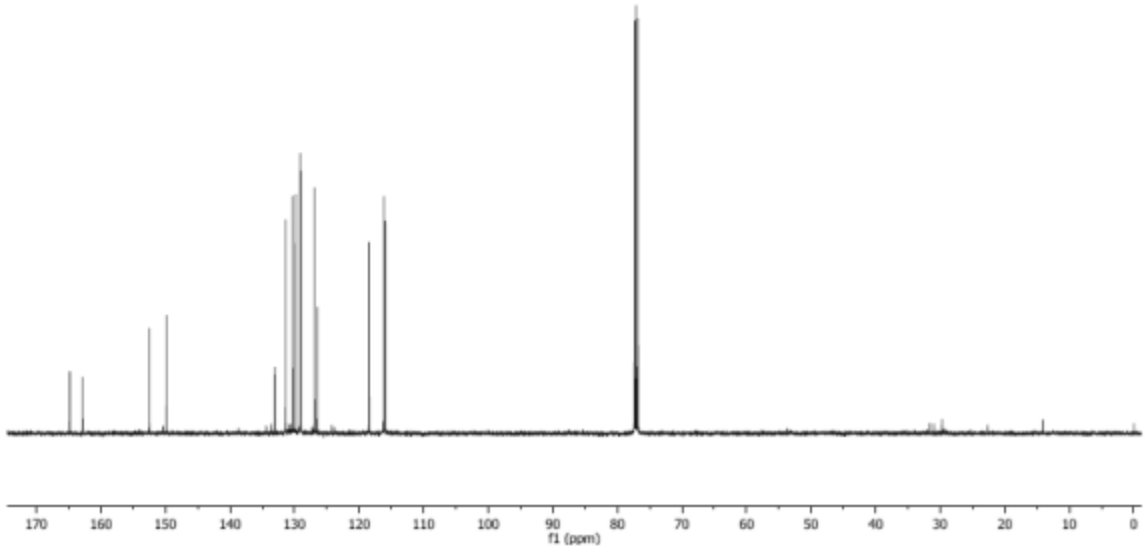

Apr19-2012
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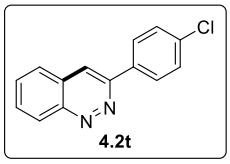

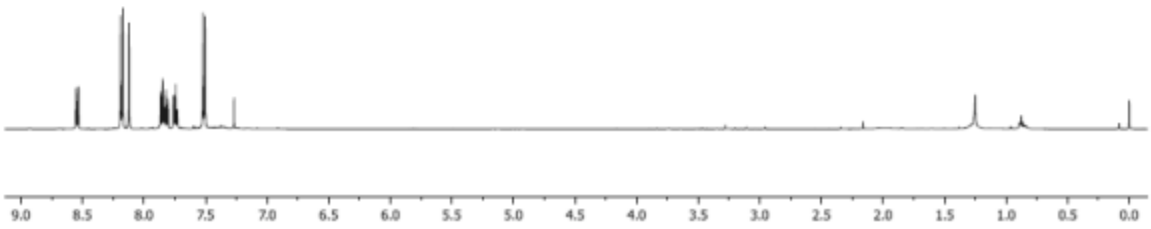

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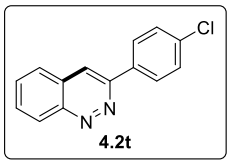
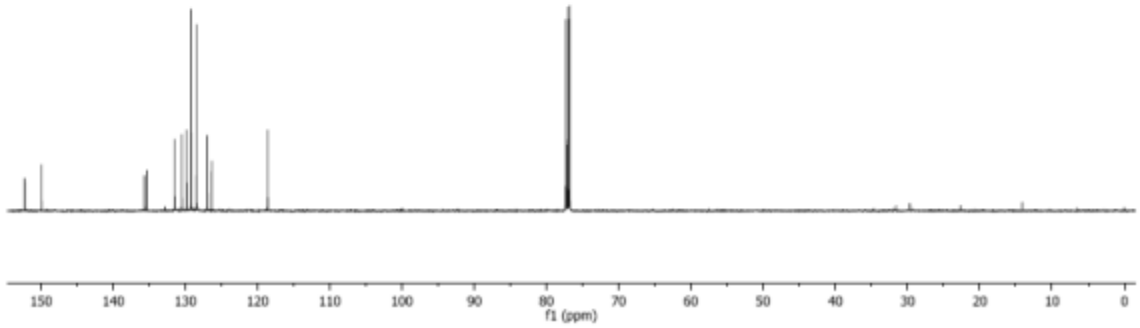
4-cl-pro





Apr21-2012
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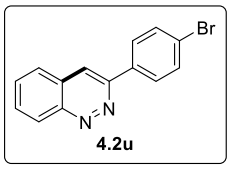

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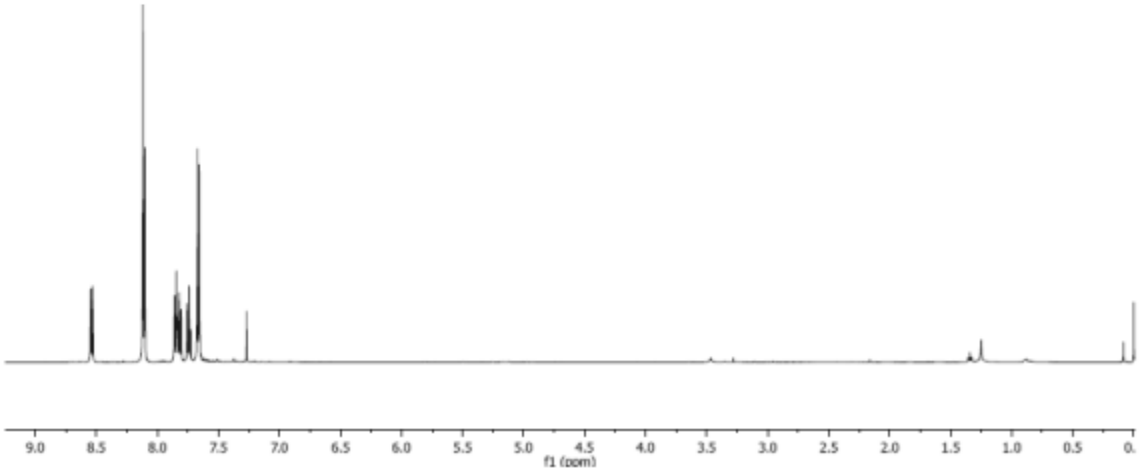

Apr21-2012
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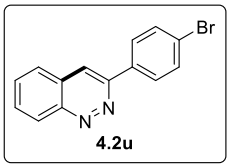

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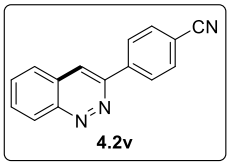
Apr19-2012
4-cn-pro



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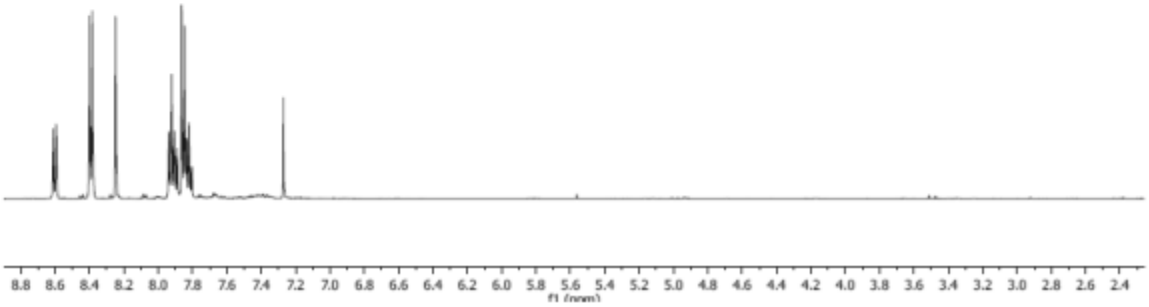

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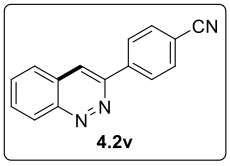

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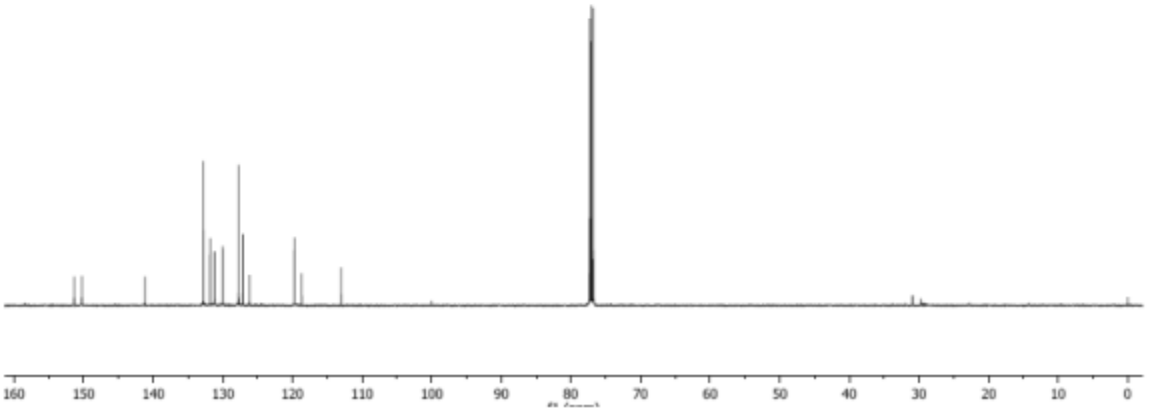
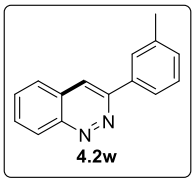
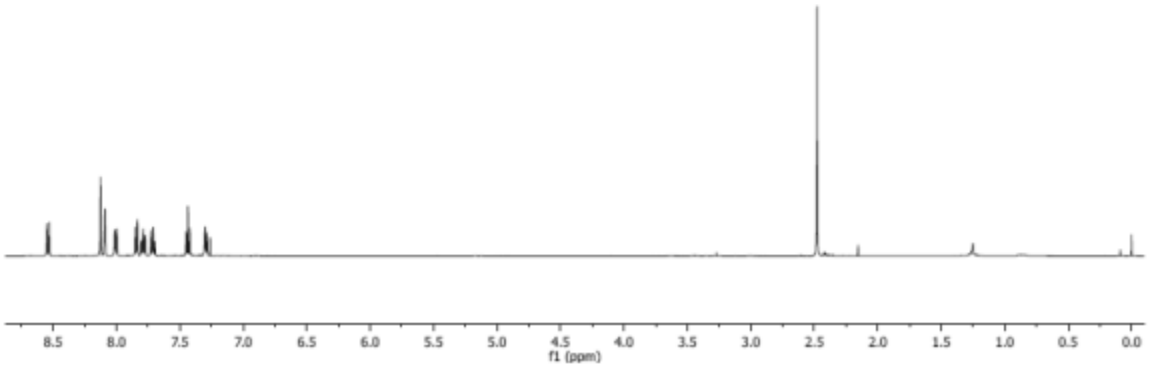
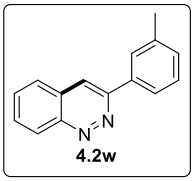


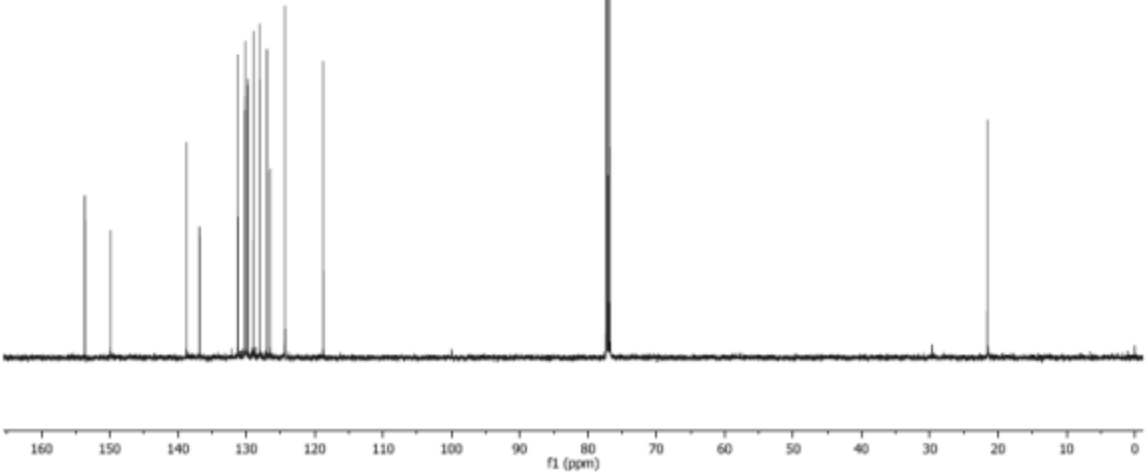
Apr19-2012
3-me-pro





Apr19-2012
3-me-pro





Apr26-2012
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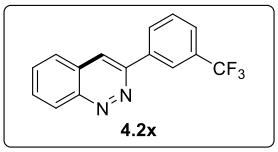

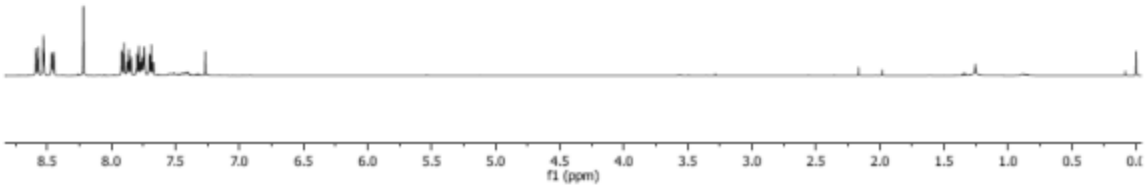

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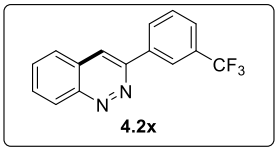
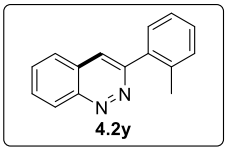
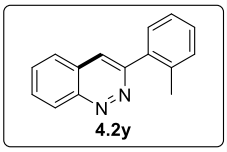


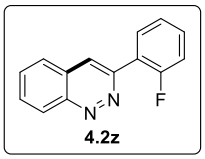
Apr21-2012
2-me-pro



Apr21-2012
2-me-pro



Apr14-2012
2-f-pro



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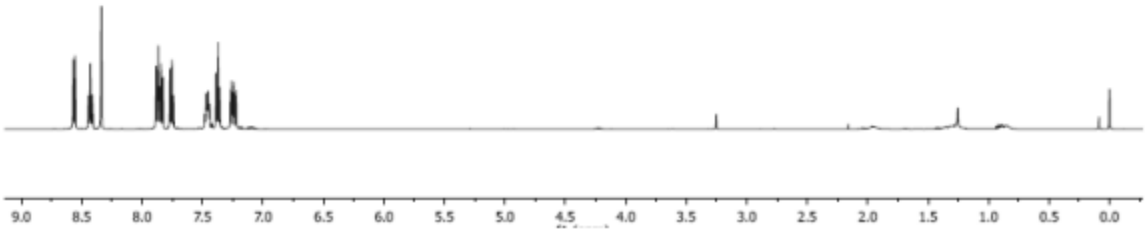
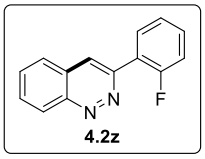
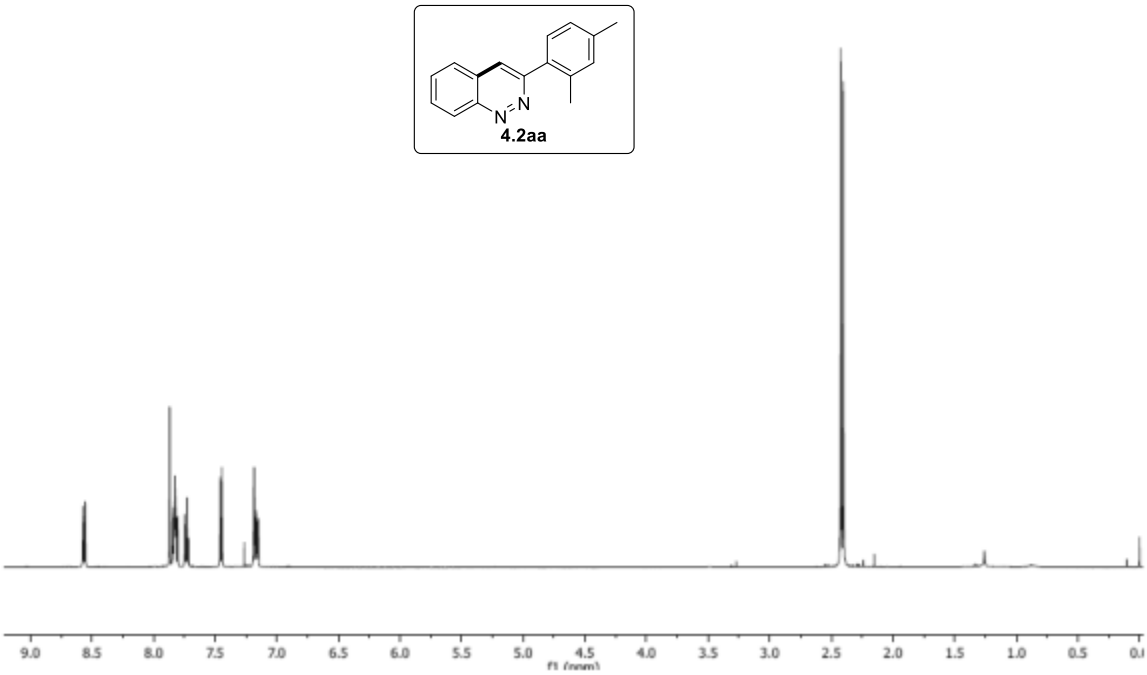


Apr14-2012
2-f-pro

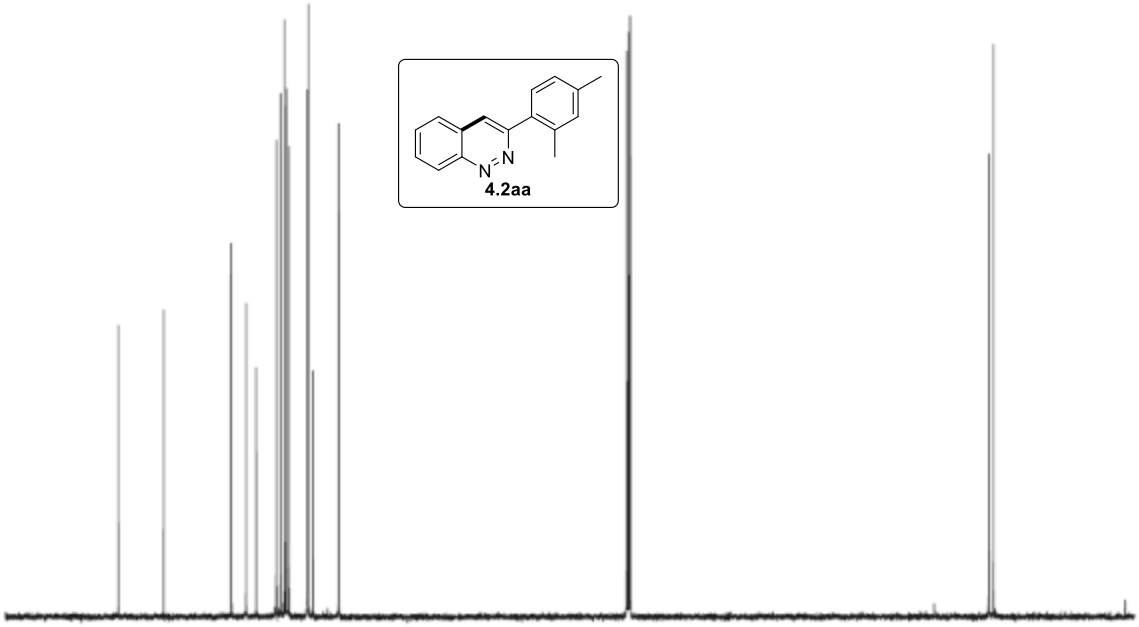


4.2z

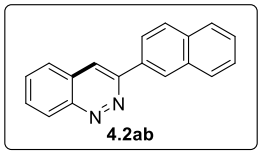
Apr24-2012
2,4-me

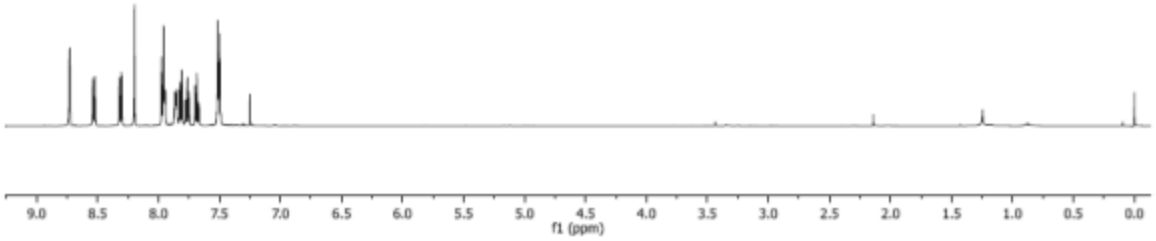


Apr24-2012
2,4-me

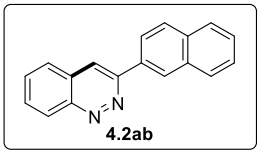


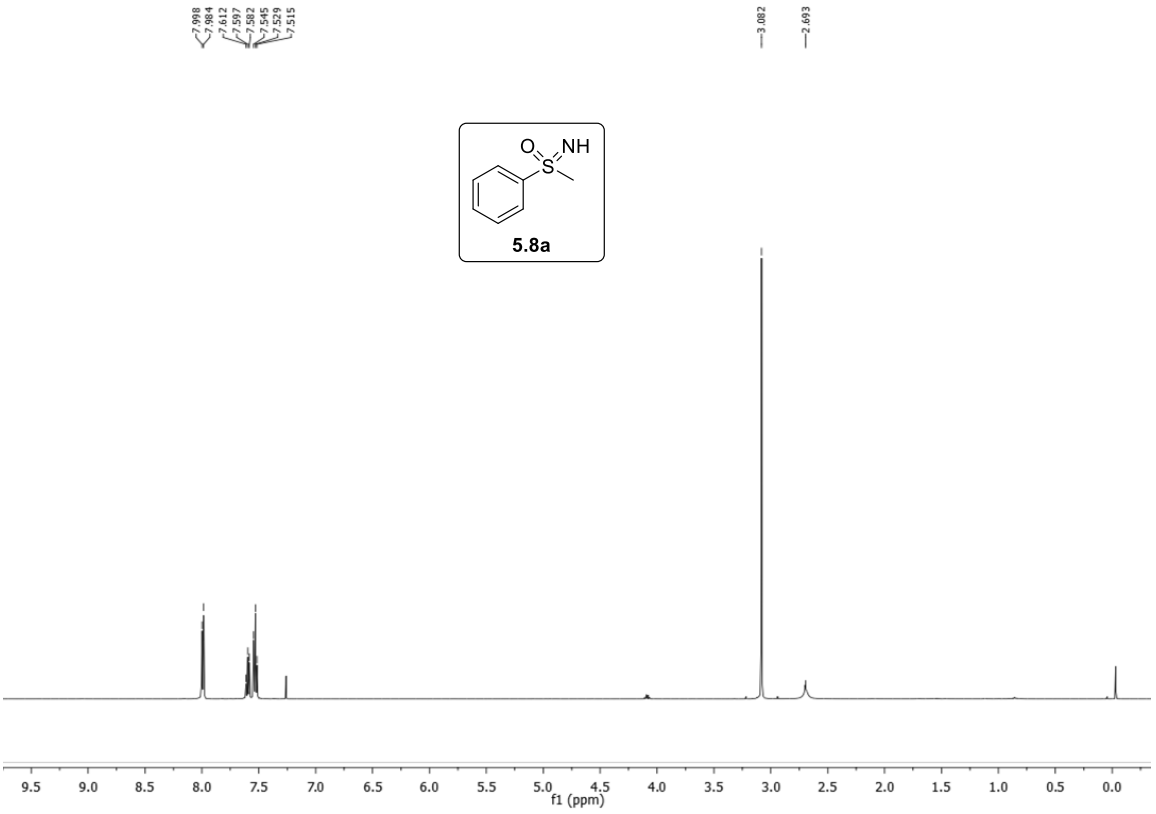
Apr21-2012
2-np-pro





Apr21-2012
2-np-pro

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7.984
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7.597
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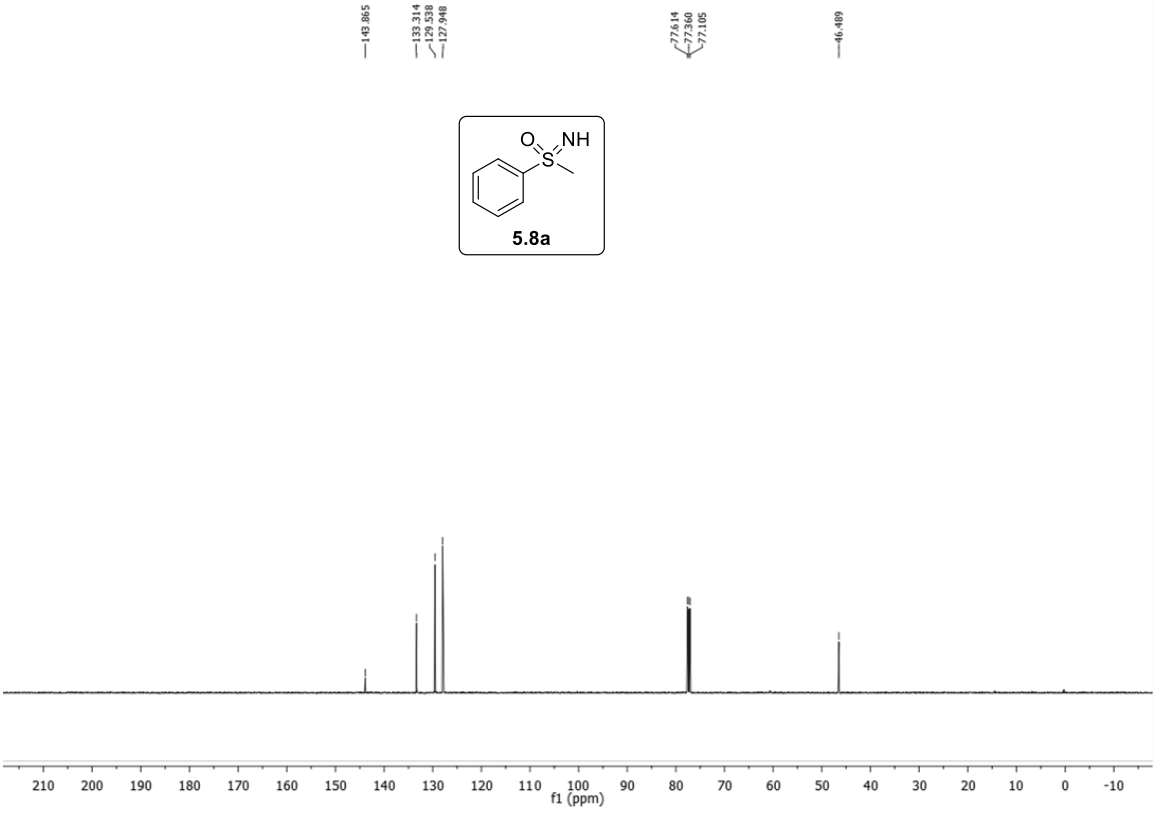
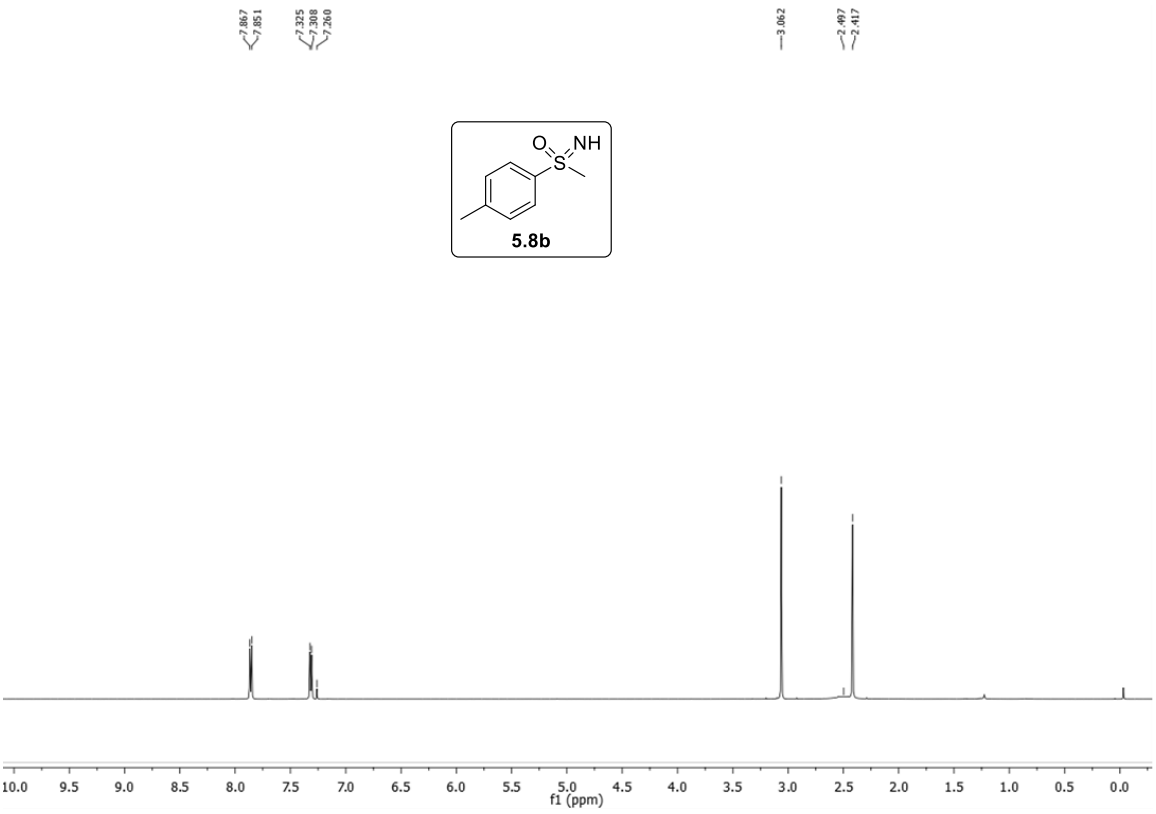
7.545
7.529
7.515
3.082
2.693
O
NH
S
5.8a
f1 (ppm)


143.865
133.314
129.538
127.948
77.614
77.360
77.105
46.489
O
NH
S
5.8a
f1 (ppm)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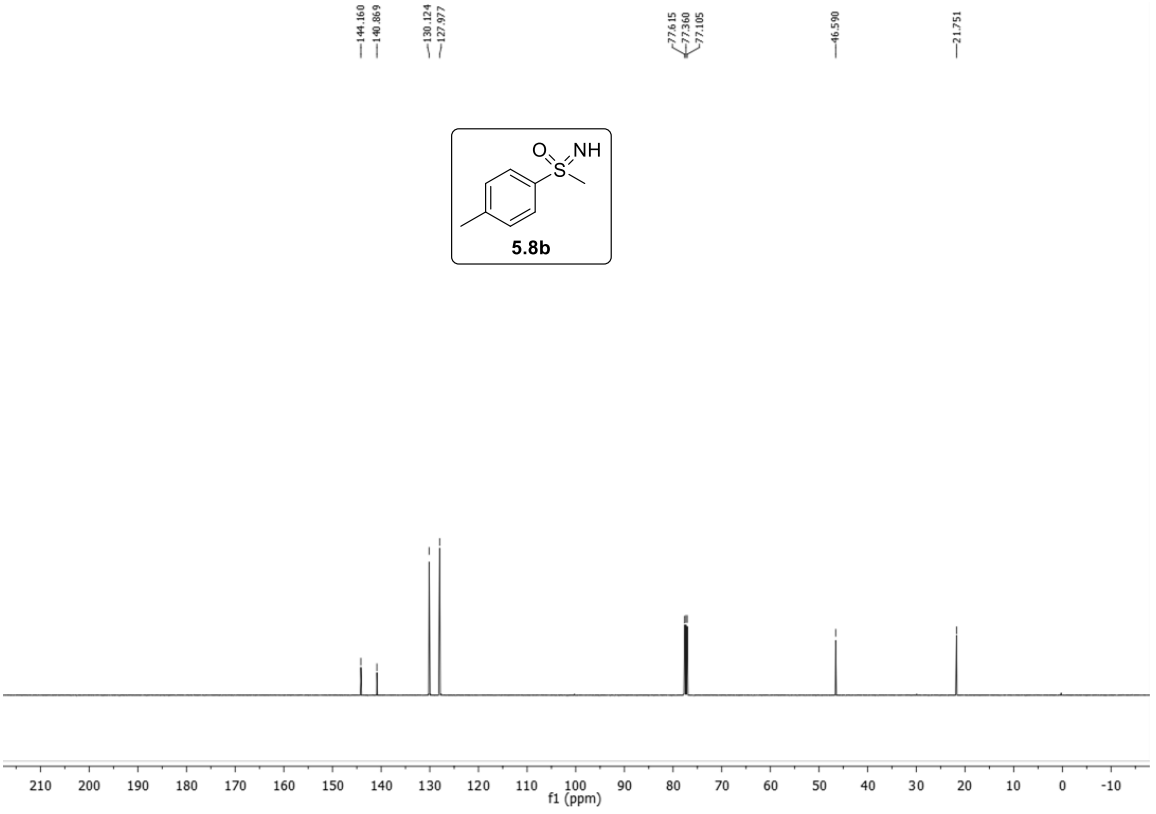
7.851
7.325
7.308
7.260
3.062
2.497
2.417
O
NH
S
5.8b
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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140.869
130.124
127.977
77.615
77.360
77.105
46.590
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O
NH
S
5.8b
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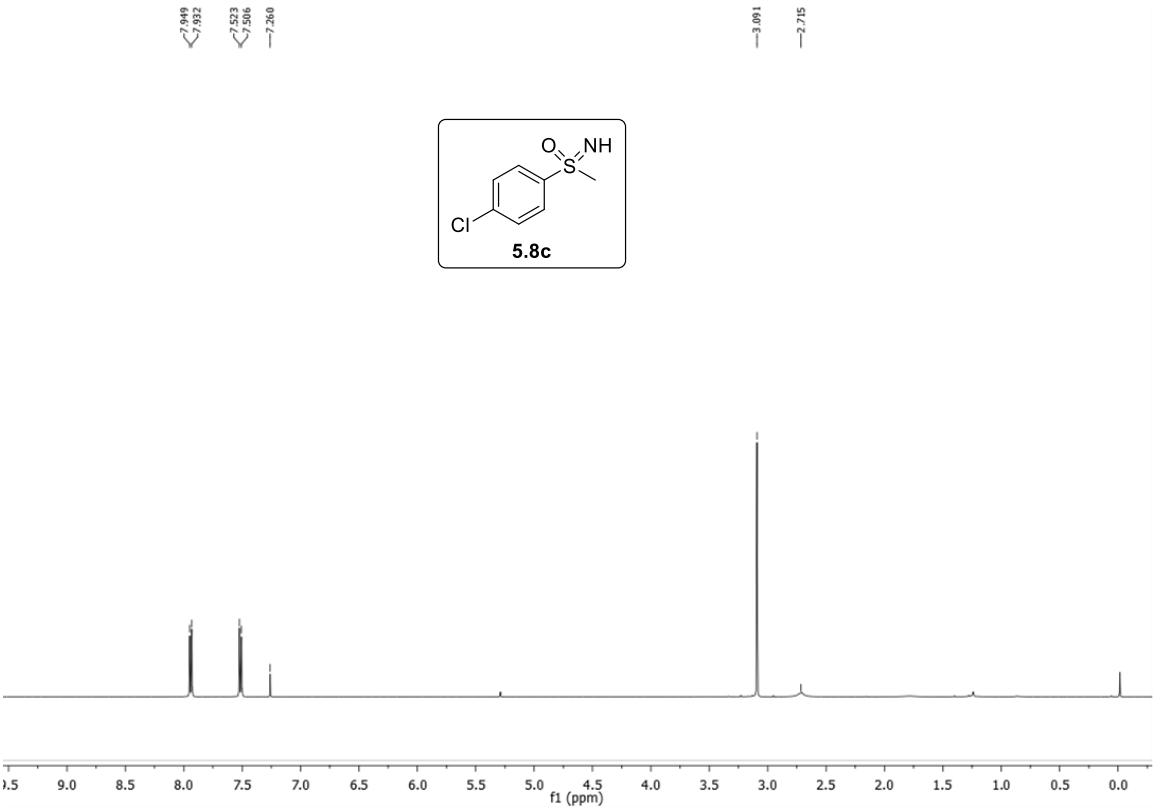
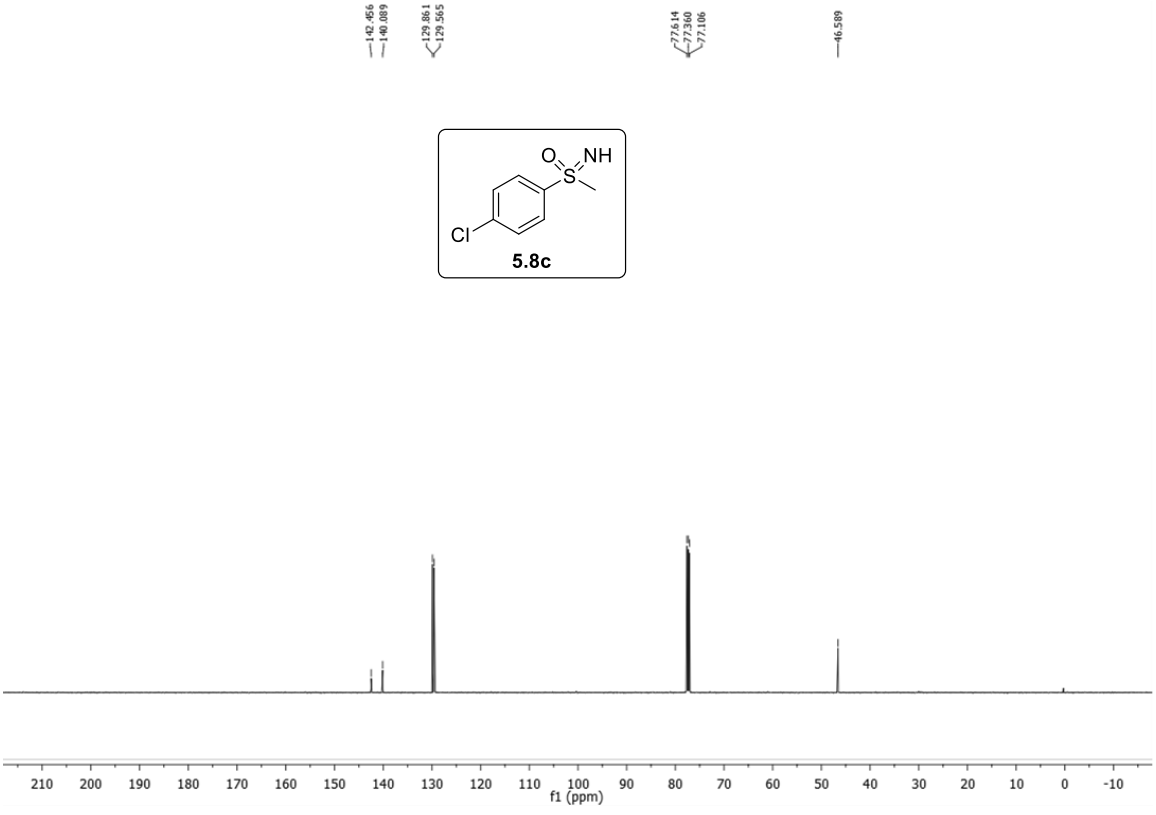
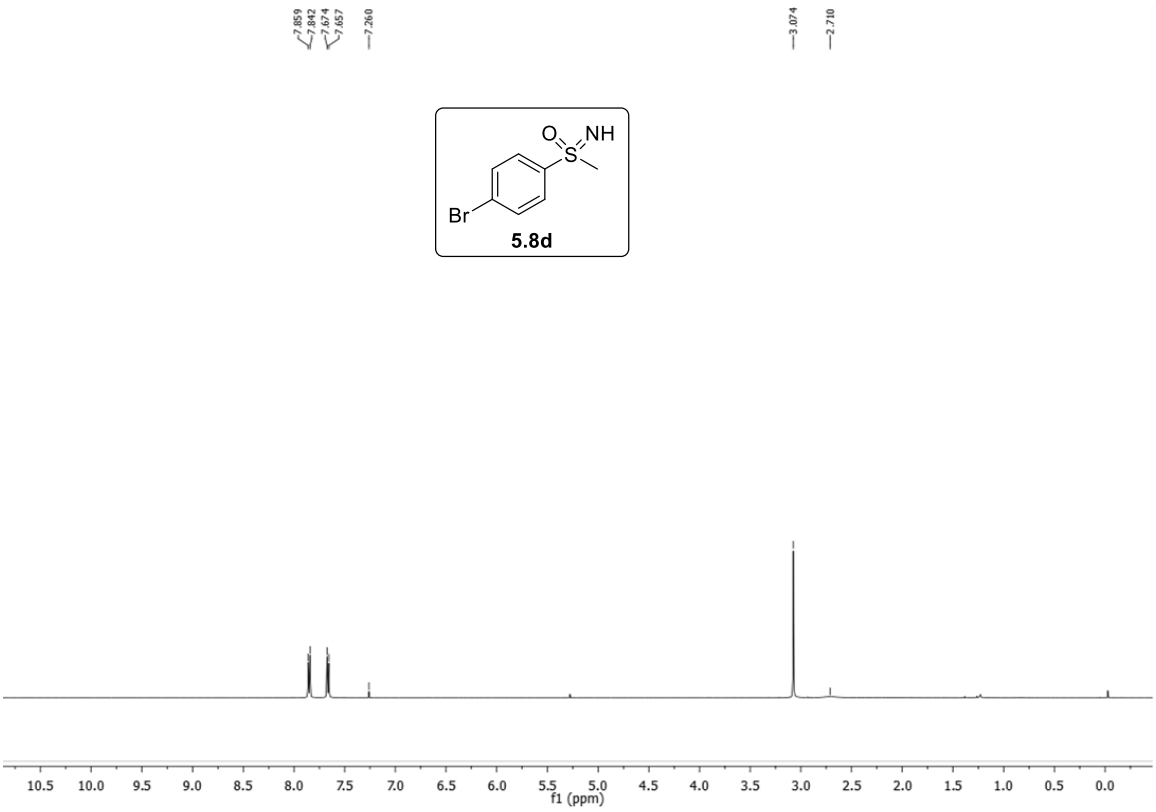
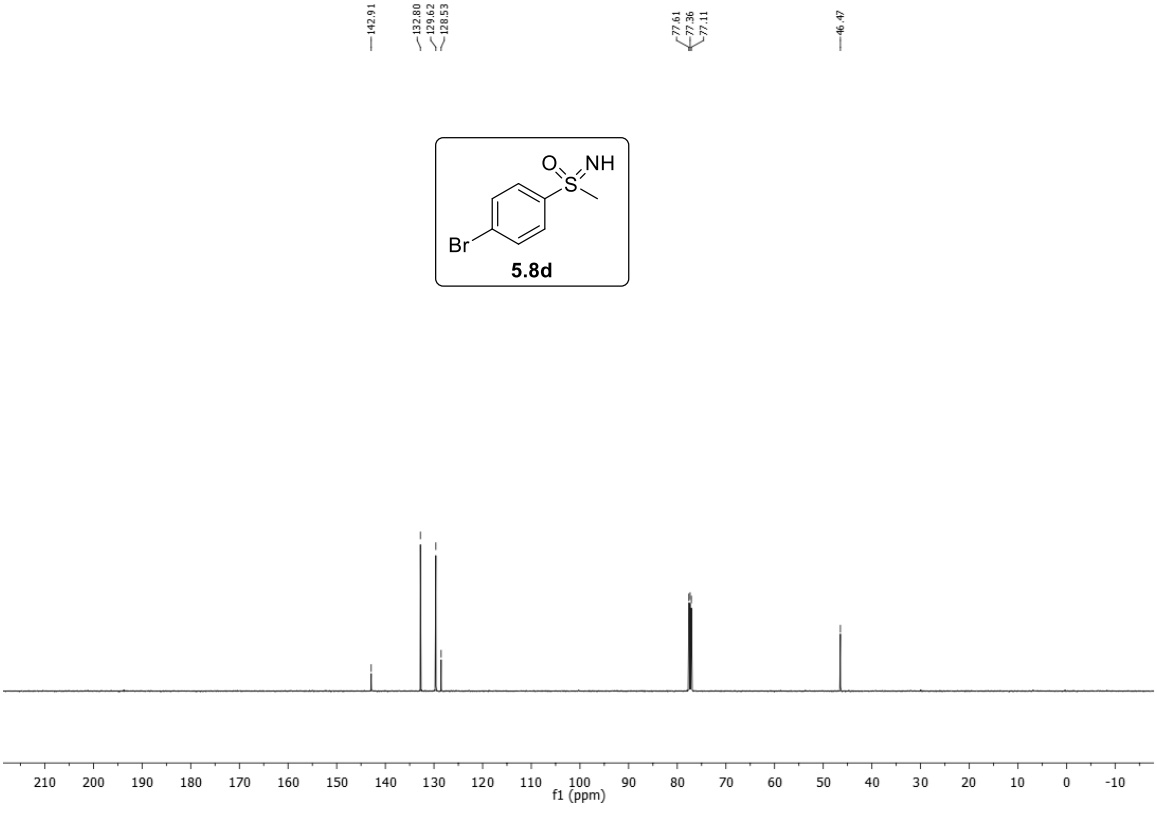
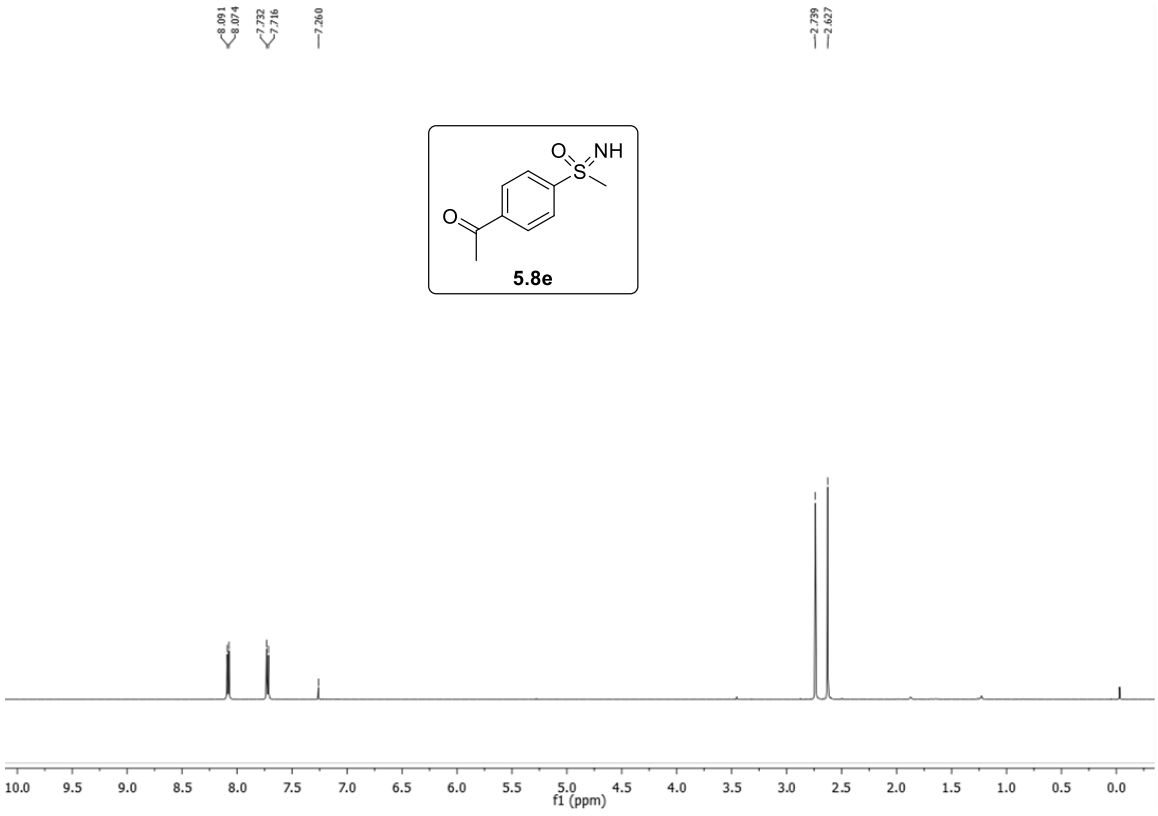
f1 (ppm)

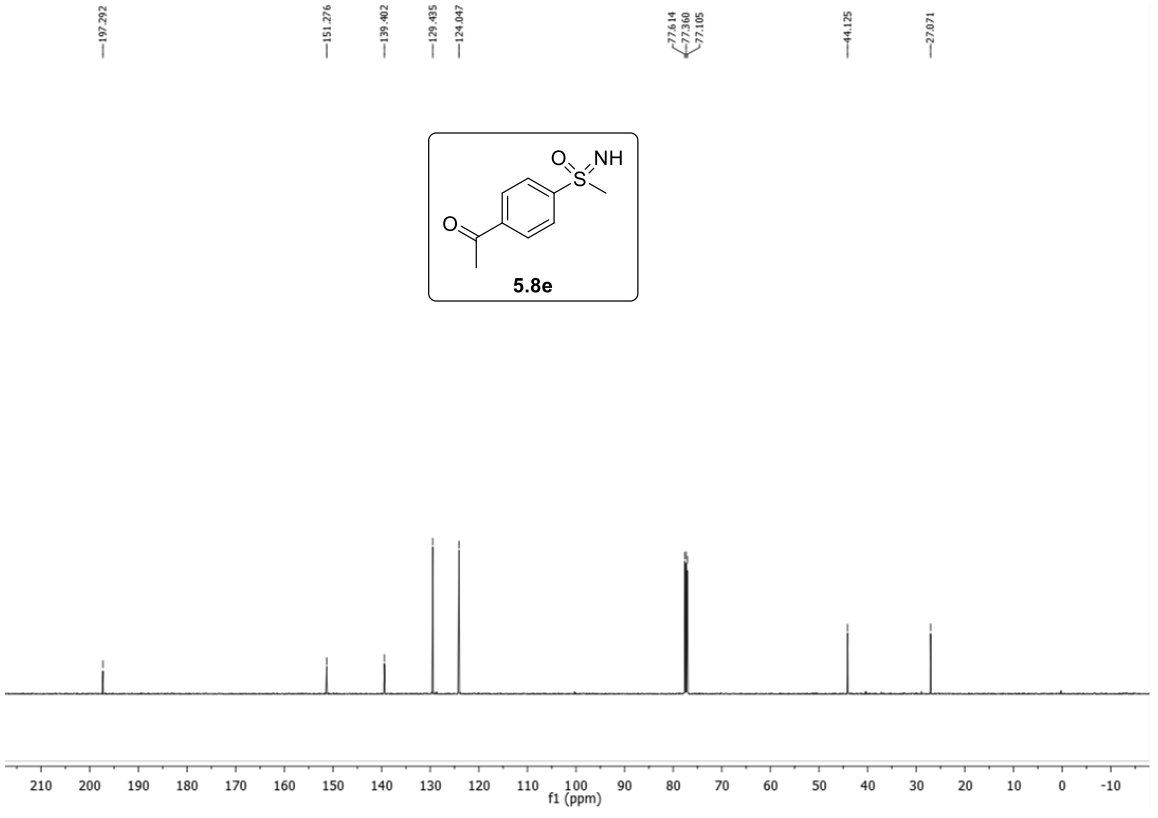

7.949
7.932
7.523
7.506
7.260
3.091
2.715
O
NH
S
Cl
5.8c
f1 (ppm)

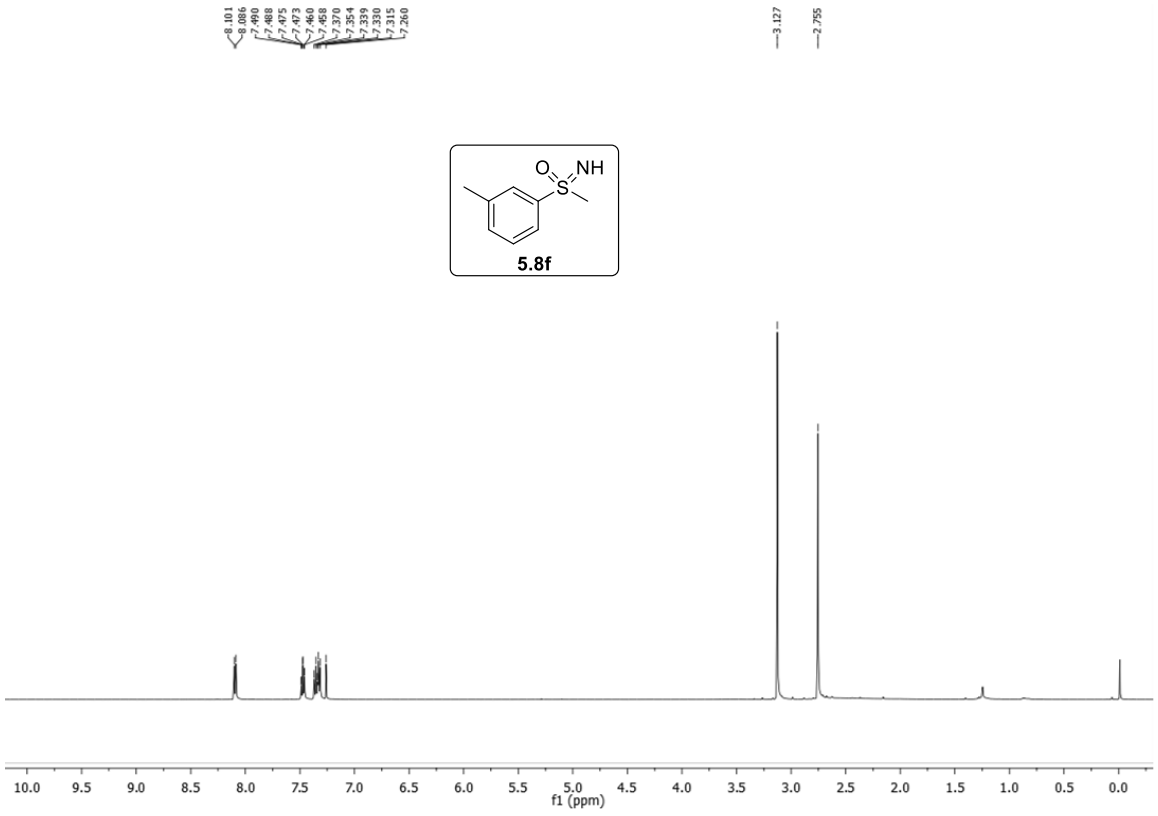

142.456
140.089
129.861
129.565
77.614
77.360
77.106
46.589
O
NH
S
Cl
5.8c
f1 (ppm)

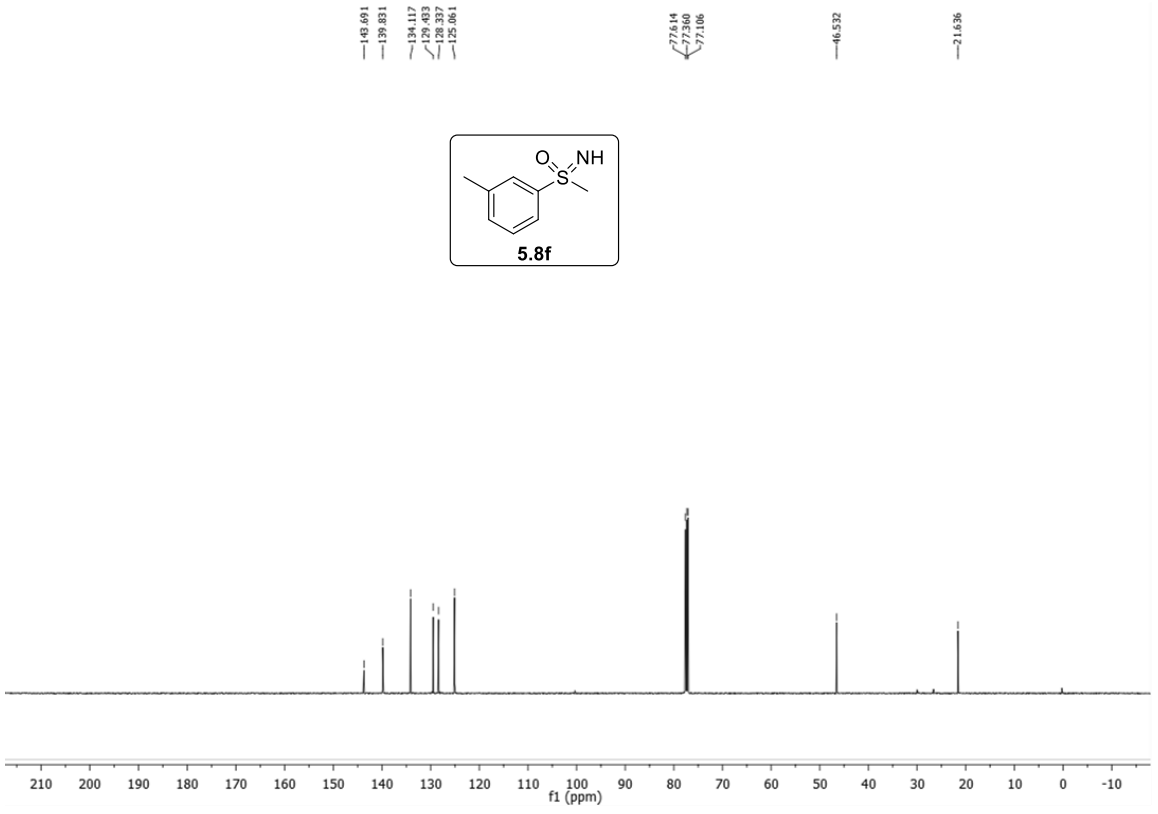

7.859
7.842
7.674
7.657
7.260
3.074
2.710
O
NH
S
Br
5.8d
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

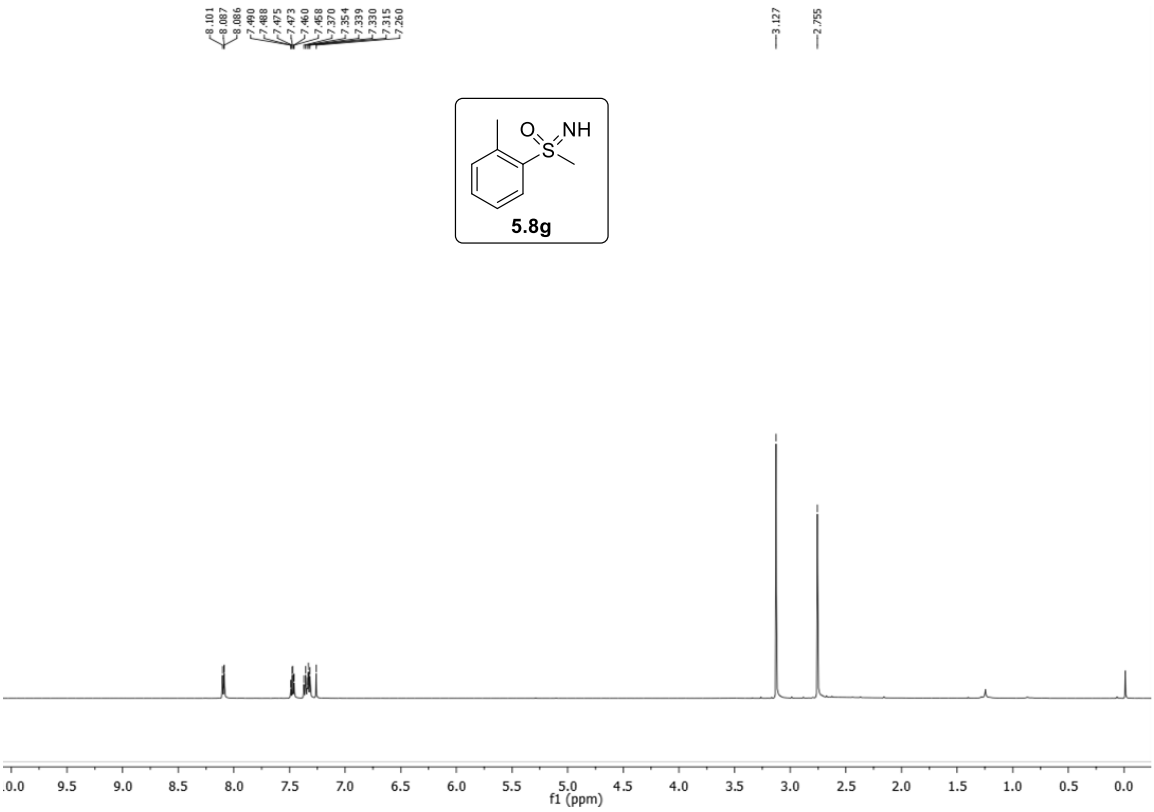

142.91
132.80
129.62
128.53
77.61
77.36
77.11
46.47
O
NH
S
Br
5.8d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

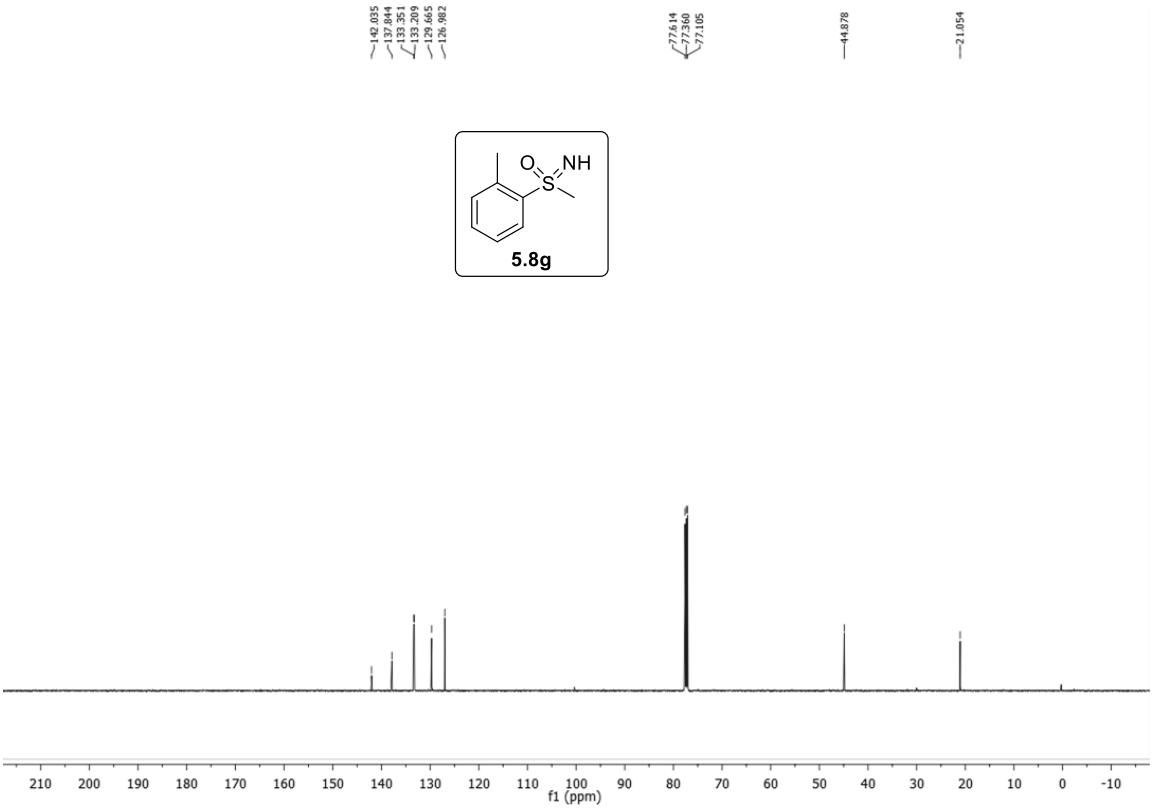

8.091
8.074
7.732
7.716
7.260
2.739
2.627
O
NH
S
O
5.8e
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


197.292
151.276
139.402
129.435
124.047
77.614
77.360
77.105
44.125
27.071
O
NH
S
O
5.8e
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.101
8.086
7.490
7.488
7.475
7.473
7.460
7.458
7.370
7.354
7.339
7.330
7.315
7.260
3.127
2.755
NH
O
S
5.8f
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


143.691
139.831
134.117
129.433
128.337
125.061
77.614
77.360
77.106
46.532
21.636
NH
O
S
5.8f
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.101
8.087
8.086
7.490
7.488
7.475
7.473
7.460
7.458
7.370
7.354
7.339
7.330
7.315
7.260
3.127
2.755
O
NH
S
5.8g
f1 (ppm)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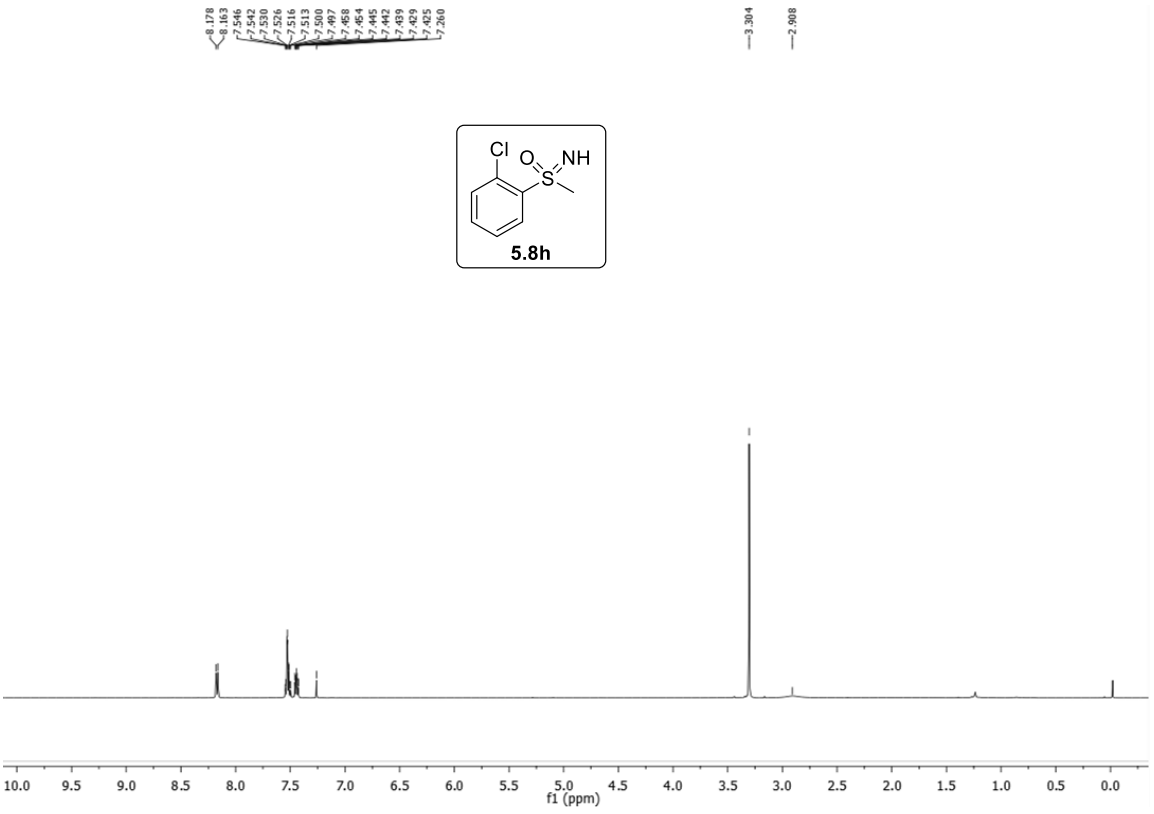
137.844
133.351
133.208
129.665
126.982
77.614
77.360
77.105
44.878
21.054
O
NH
S
5.8g
f1 (ppm)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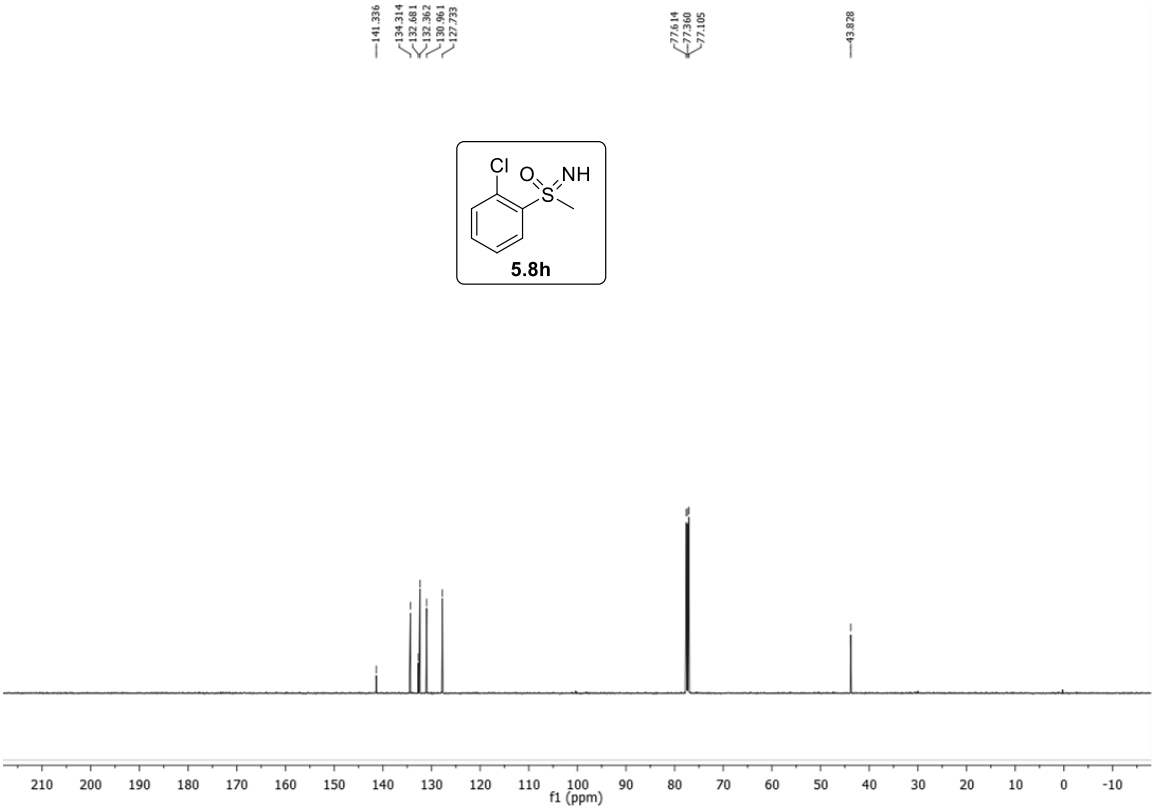
8.163
7.546
7.542
7.530
7.526
7.516
7.513
7.500
7.497
7.468
7.464
7.445
7.442
7.439
7.429
7.425
7.260
3.304
2.908
Cl
O
S
NH
5.8h
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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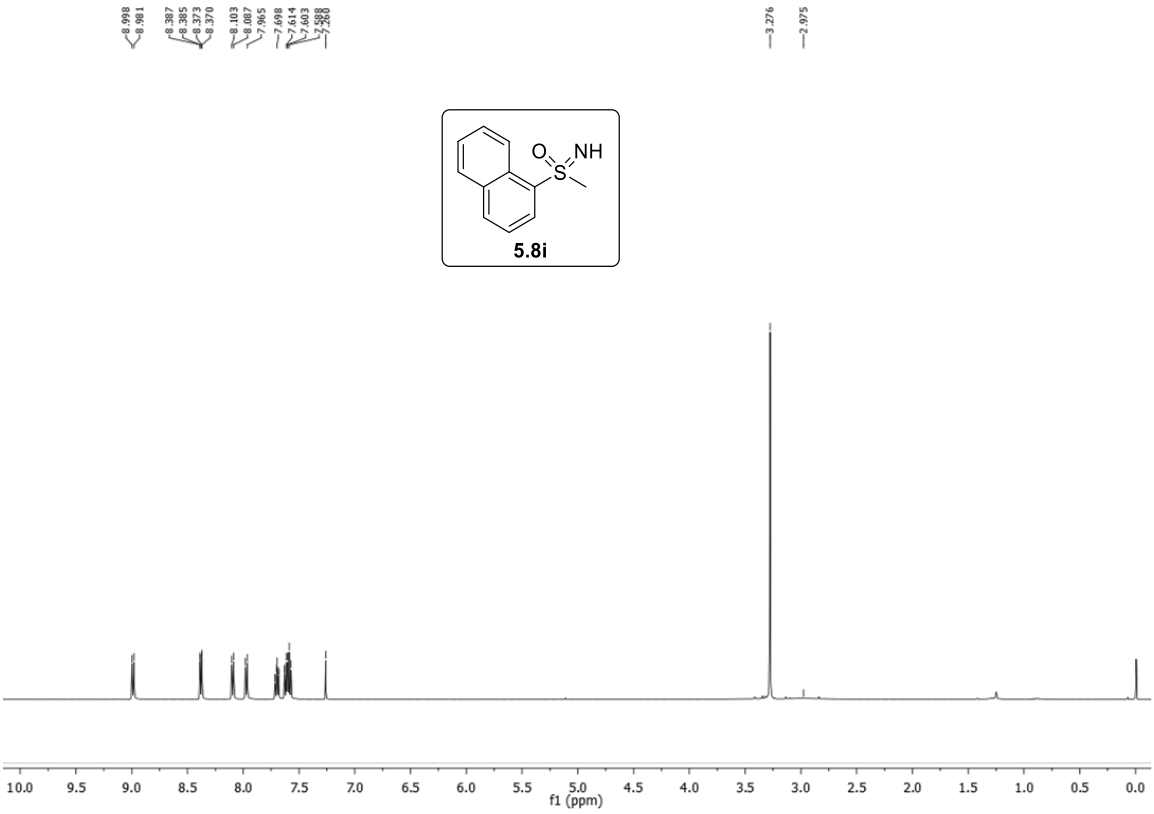
134.314
132.681
132.362
130.961
127.733
77.614
77.360
77.105
43.828
Cl
O
S
NH
5.8h
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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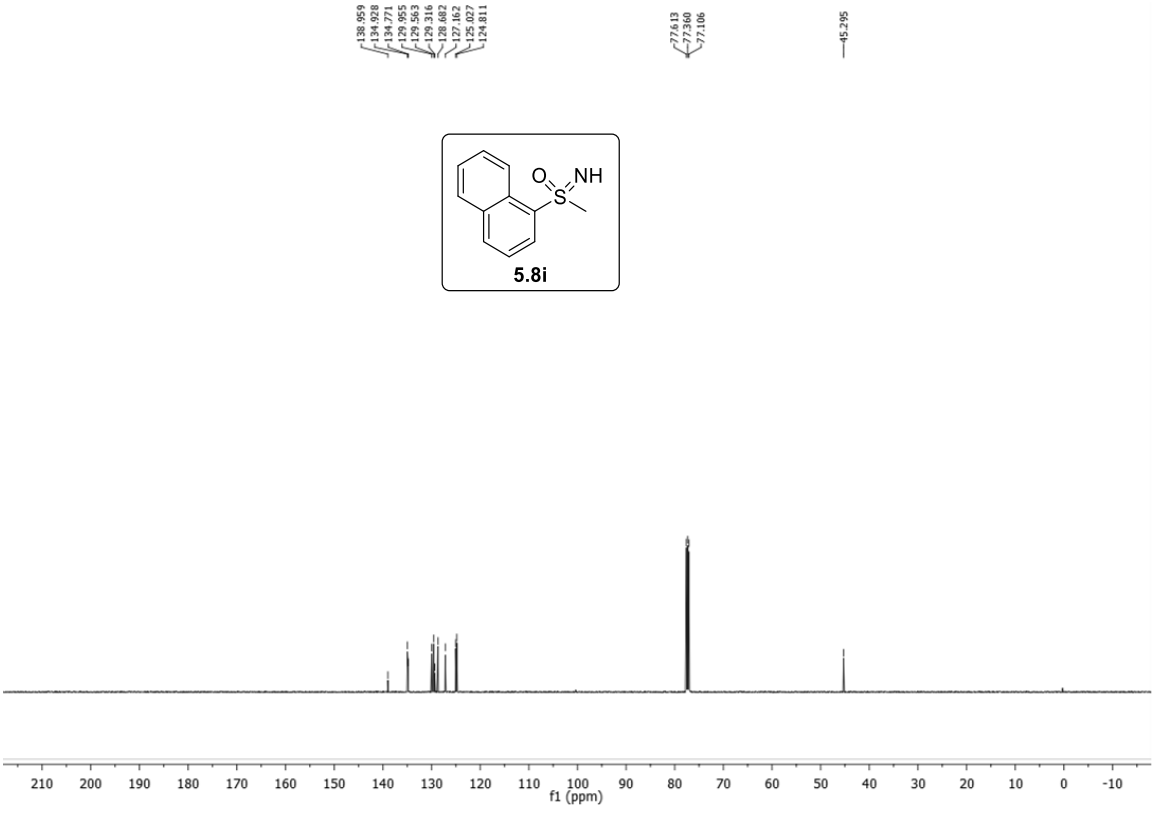
8.981
8.387
8.385
8.373
8.370
8.103
8.087
7.965
7.698
7.614
7.603
7.388
7.368
3.276
2.975
O
NH
S
5.8i
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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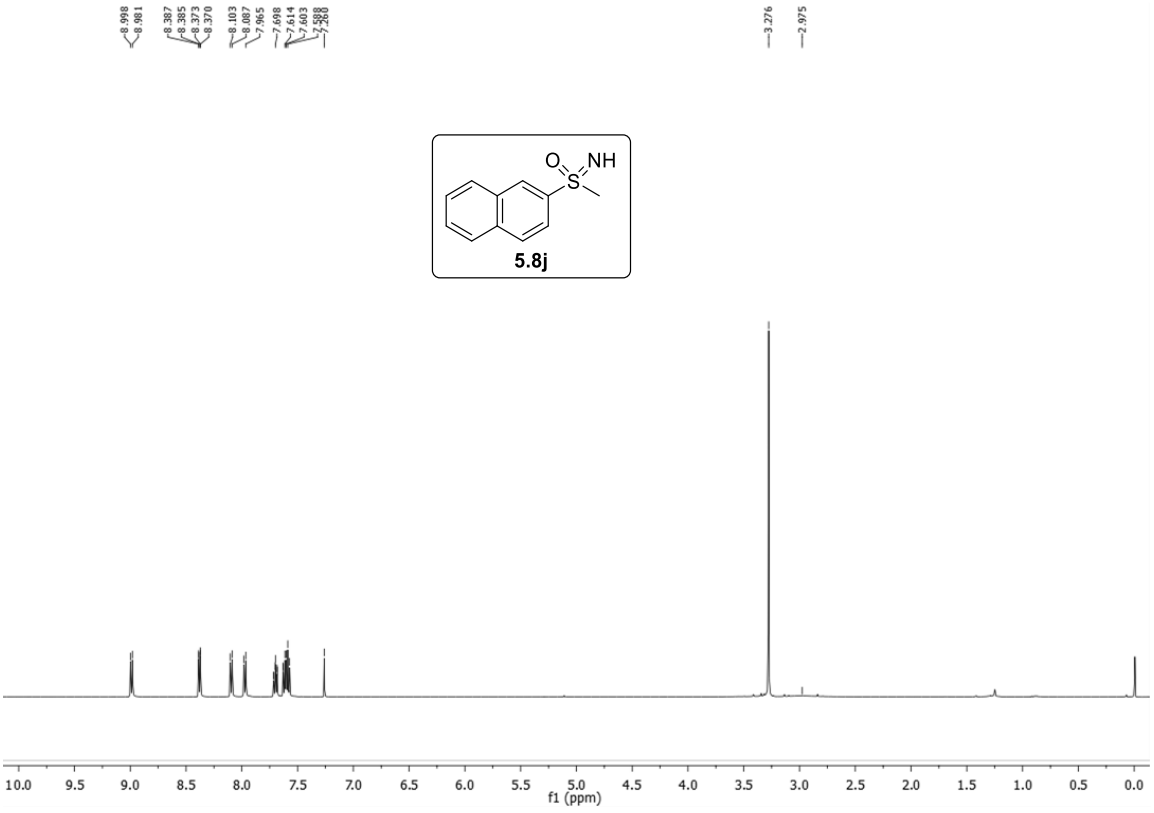
134.928
134.771
129.955
129.563
129.316
128.682
127.162
125.027
124.811
77.613
77.360
77.106
45.295
O
NH
S
5.8i
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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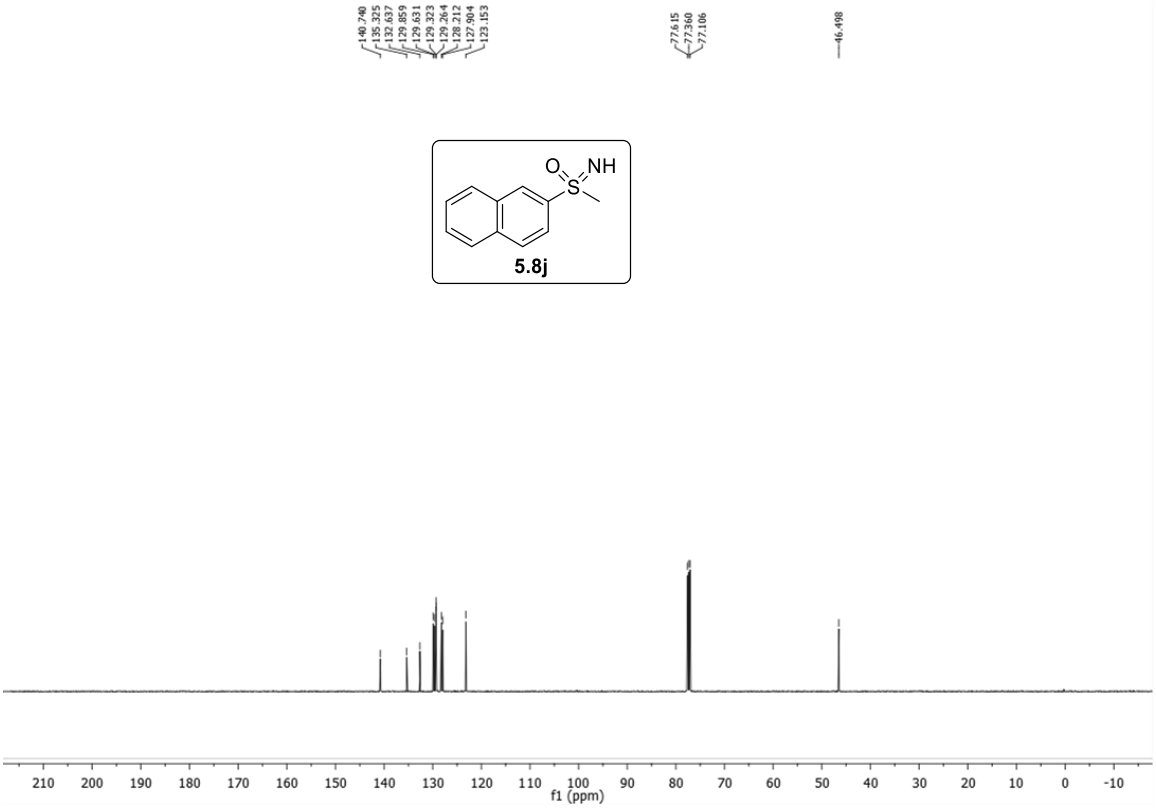
8.981
8.387
8.385
8.373
8.370
8.103
8.087
7.965
7.698
7.614
7.603
7.588
7.268
3.276
2.975
O
NH
S
5.8j
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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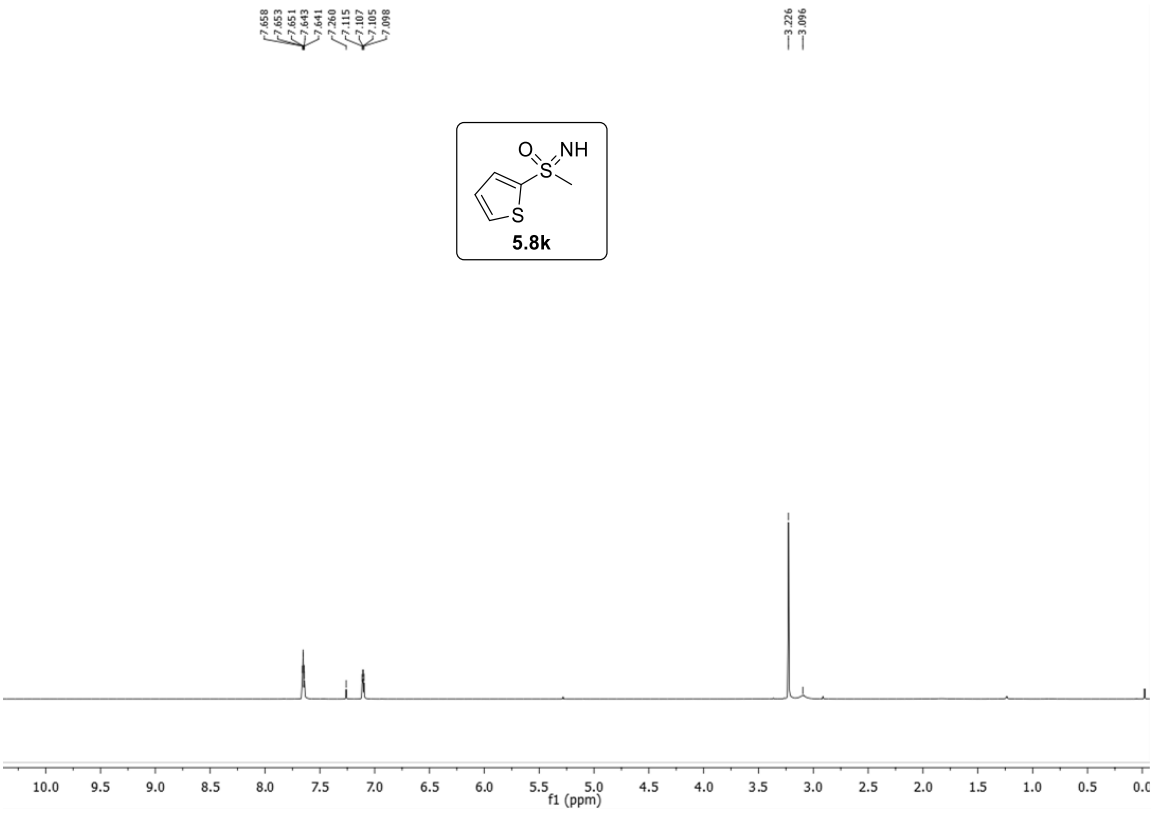
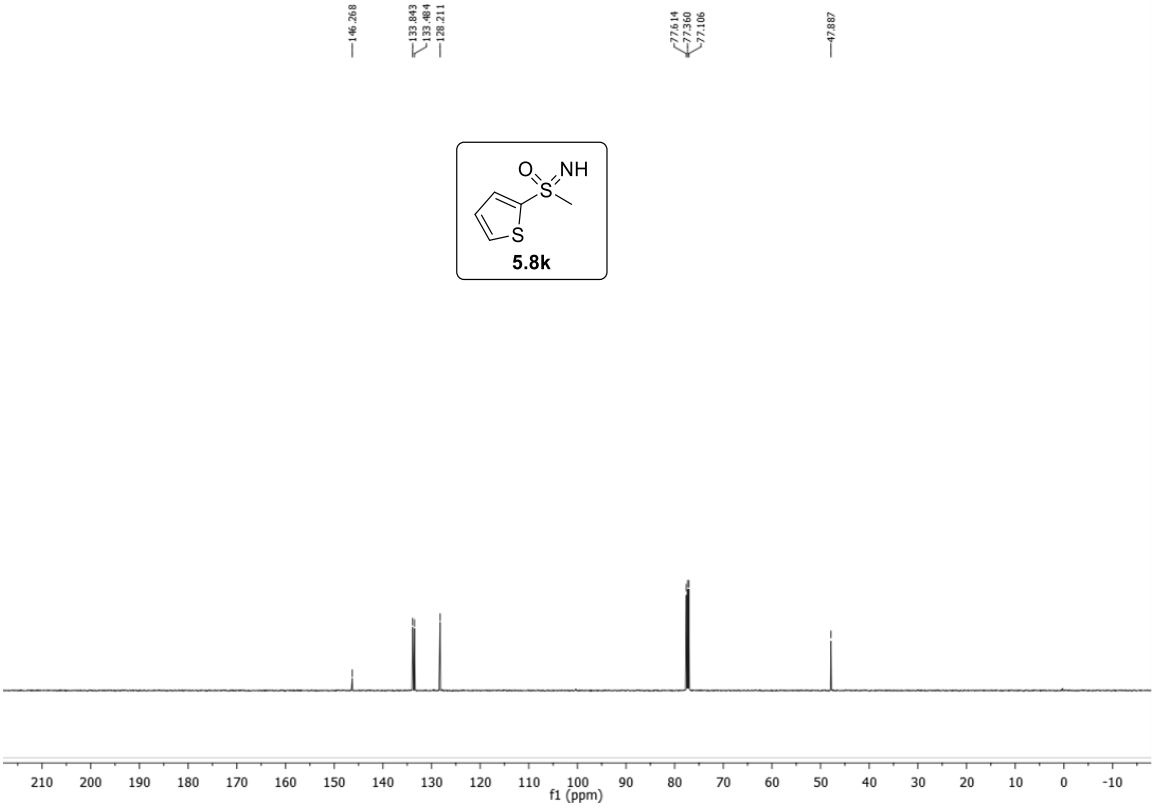
135.525
132.637
129.859
129.631
129.323
129.264
129.212
127.904
123.153
77.615
77.360
77.106
46.498
O
NH
S
5.8j
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.658
7.653
7.651
7.643
7.641
7.260
7.115
7.107
7.105
7.098
3.226
3.096
O
NH
S
S
5.8k
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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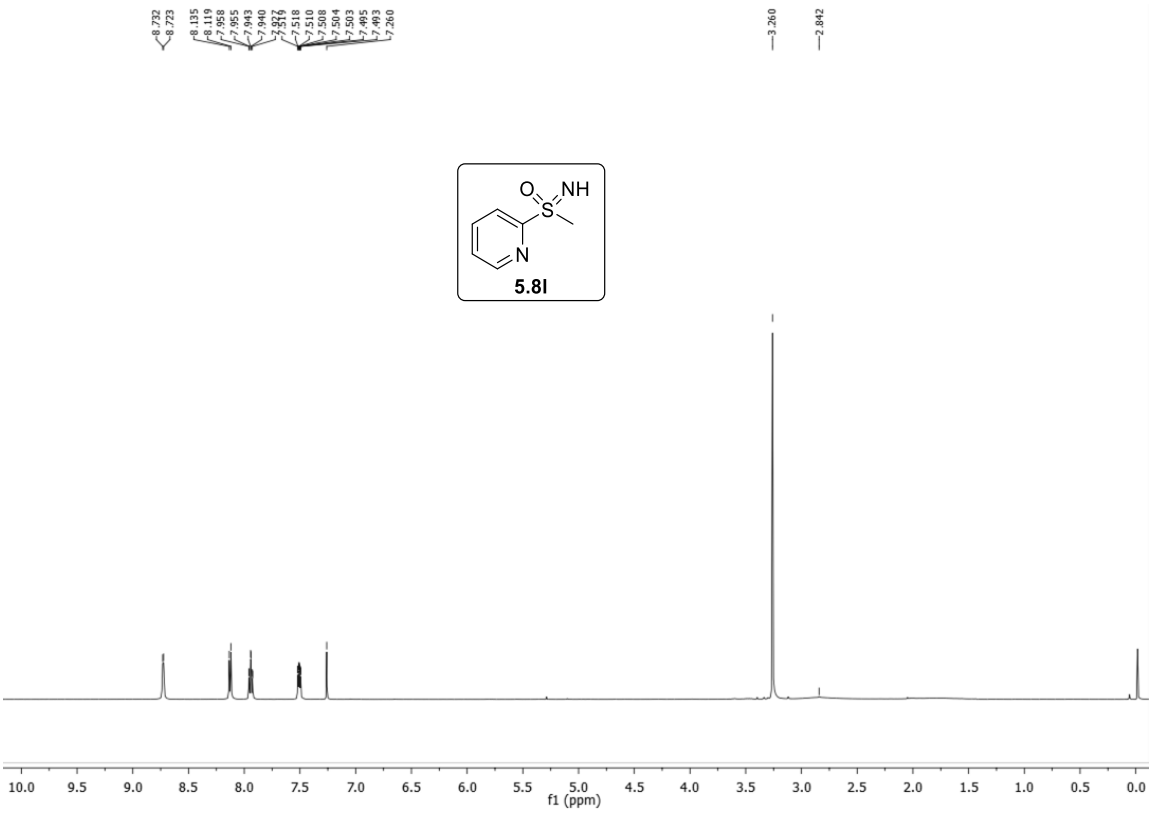
133.843
133.484
128.211
77.614
77.360
77.106
47.887
O
NH
S
S
5.8k
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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8.723
8.135
8.119
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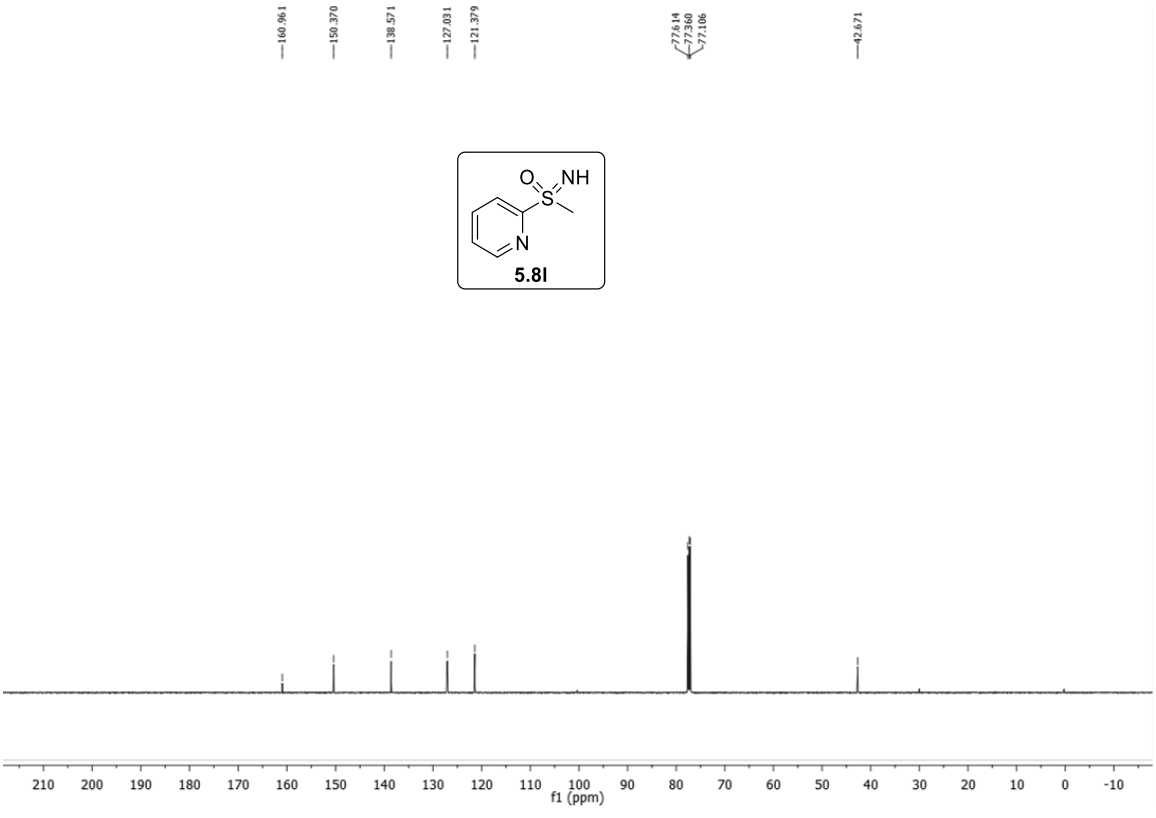
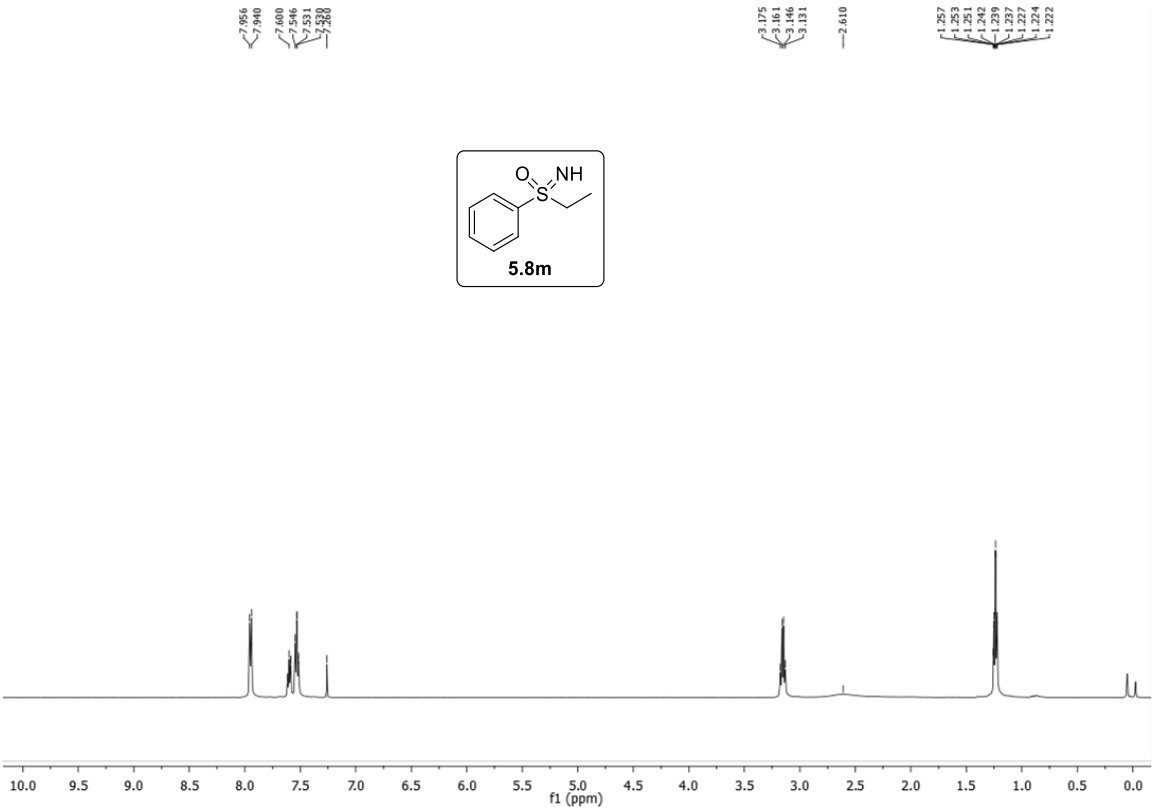
7.955
7.943
7.940
7.518
7.510
7.508
7.504
7.503
7.495
7.493
7.260
3.260
2.842
O
NH
S
N
5.8l
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


160.961
150.370
138.571
127.031
121.379
77.614
77.360
77.106
42.671
O
NH
S
N
5.8l
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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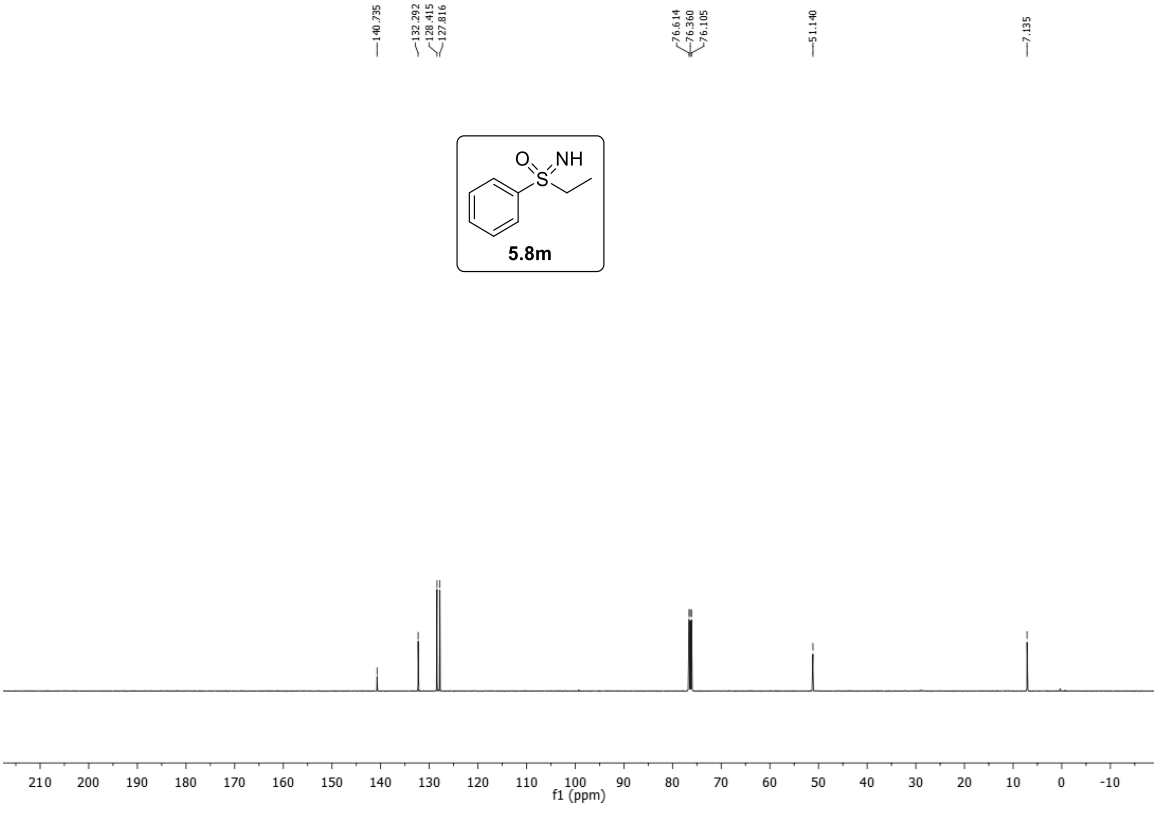
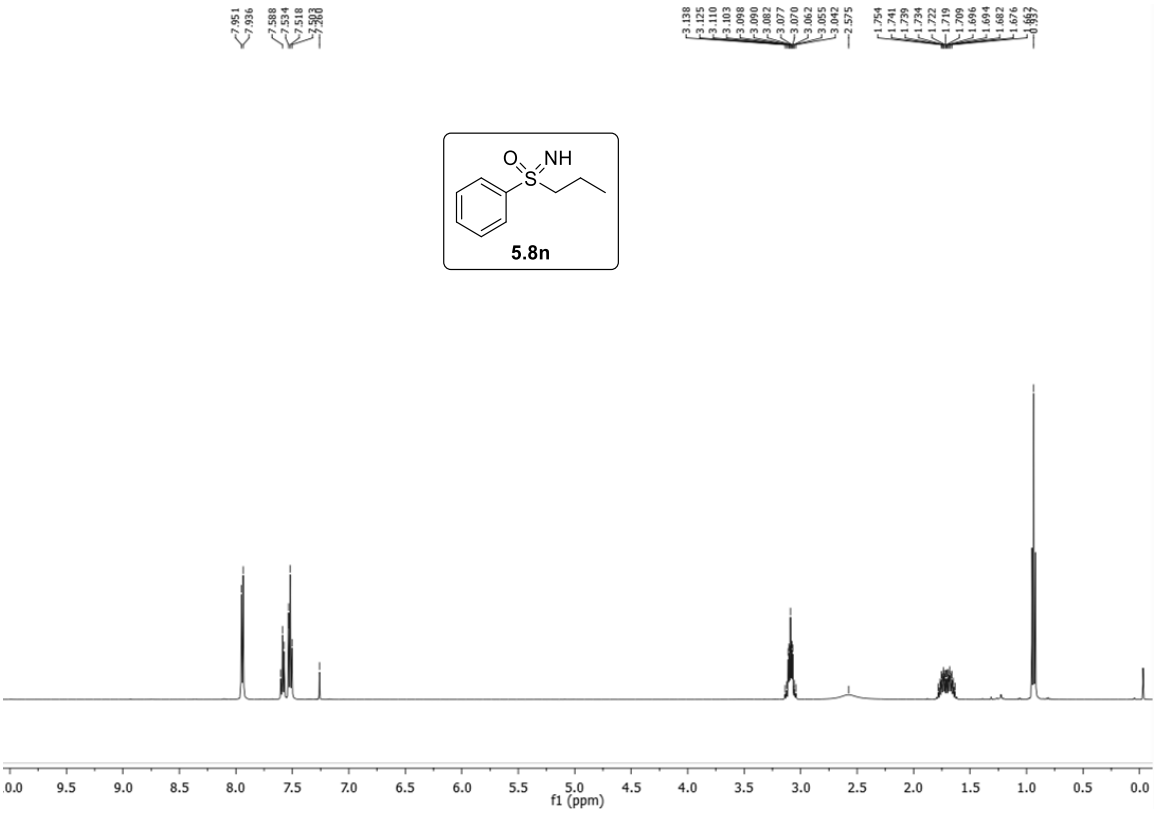
7.531
3.175
3.161
3.146
3.131
2.610
1.257
1.253
1.251
1.242
1.239
1.237
1.227
1.224
1.222
O
NH
S
5.8m
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


140.735
132.292
129.415
128.645
127.816
76.614
76.360
76.105
51.140
7.135
O
NH
S
5.8m
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.951
7.936
7.588
7.534
7.518
3.138
3.125
3.110
3.103
3.098
3.090
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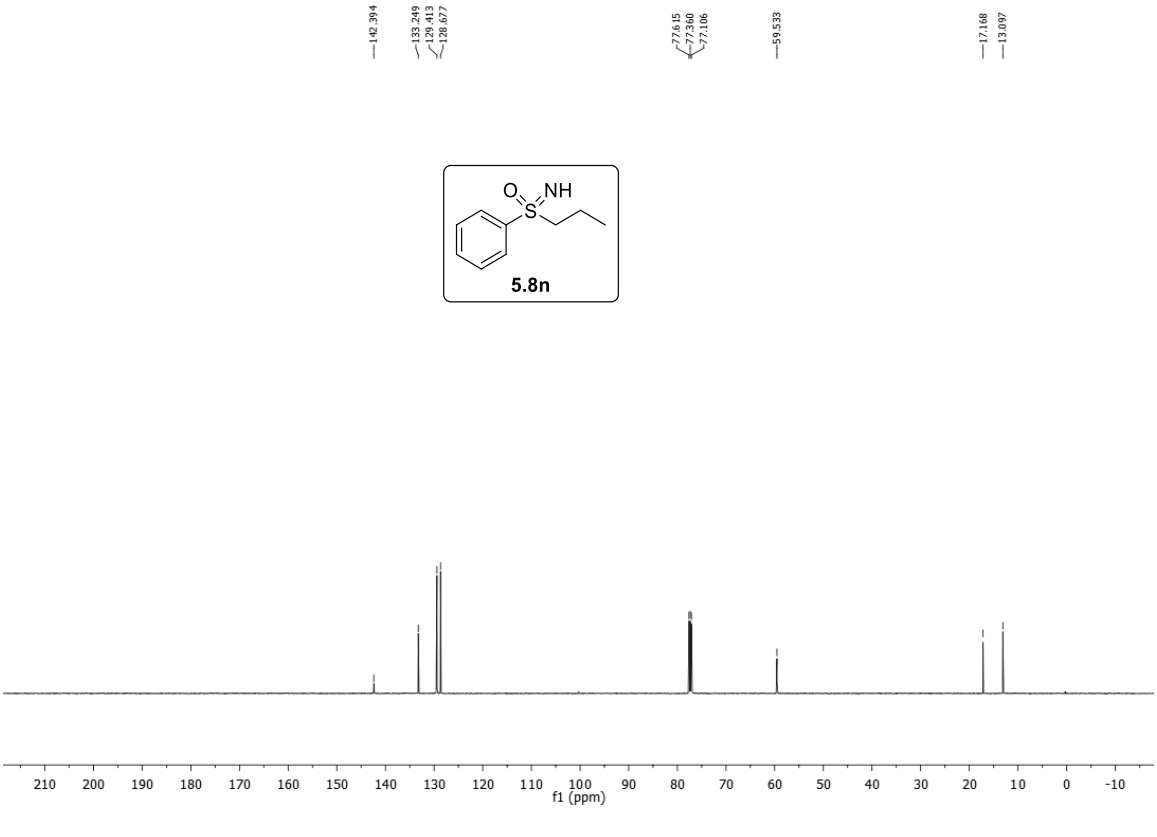
3.077
3.070
3.062
3.055
3.042
2.575
1.754
1.741
1.730
1.719
1.709
1.696
1.694
1.682
1.676
0.957
O
NH
S
5.8n
f1 (ppm)


142.394
133.249
129.413
128.677
77.615
77.360
77.106
59.533
17.168
13.097
O
NH
S
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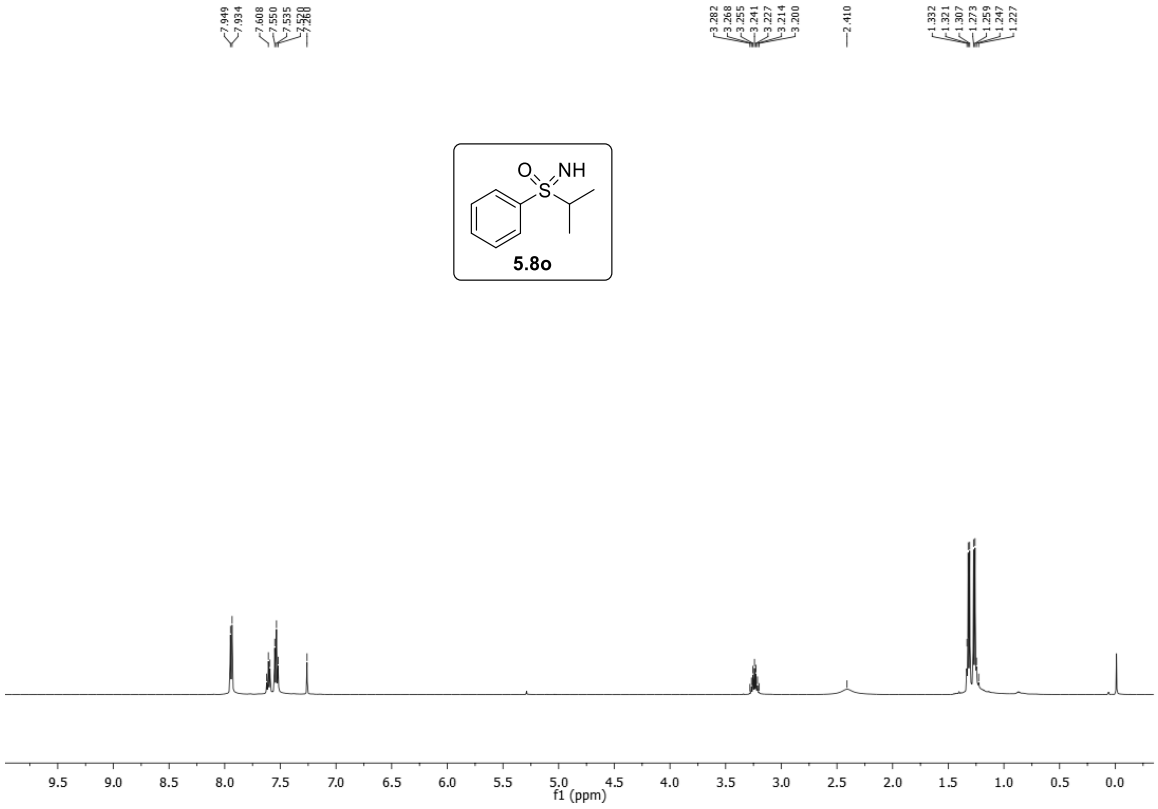
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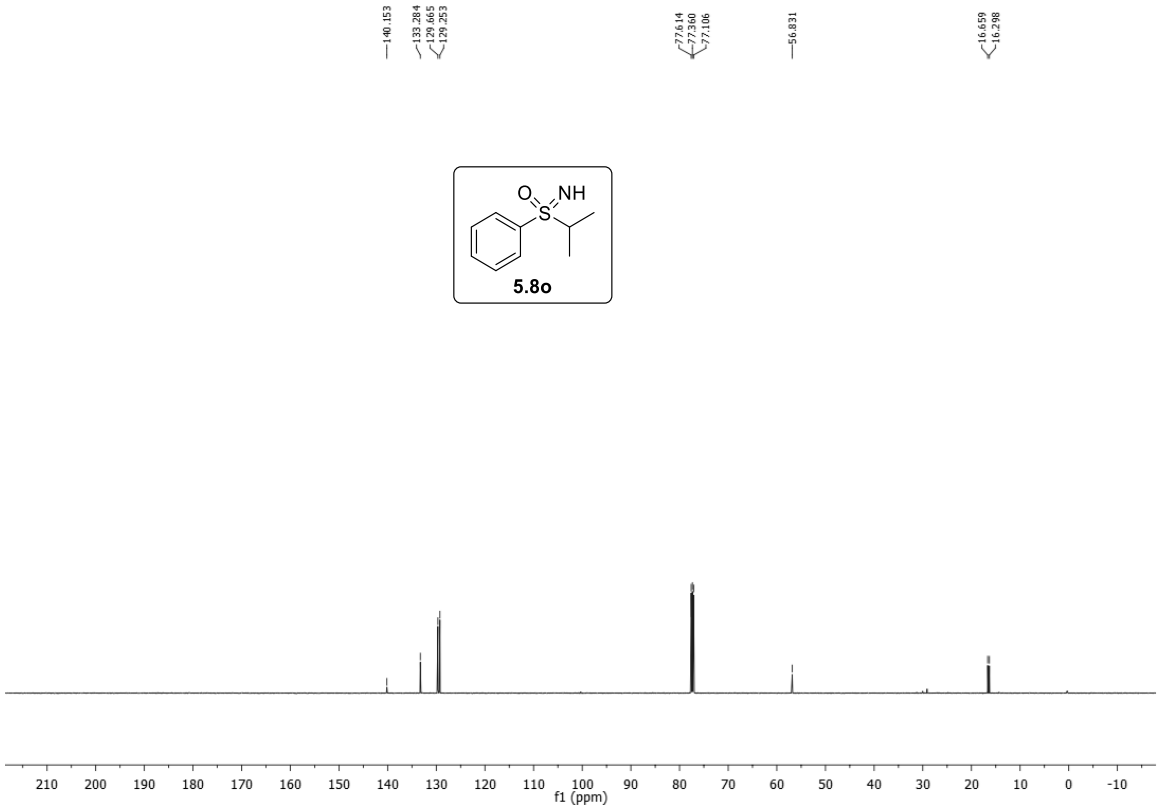
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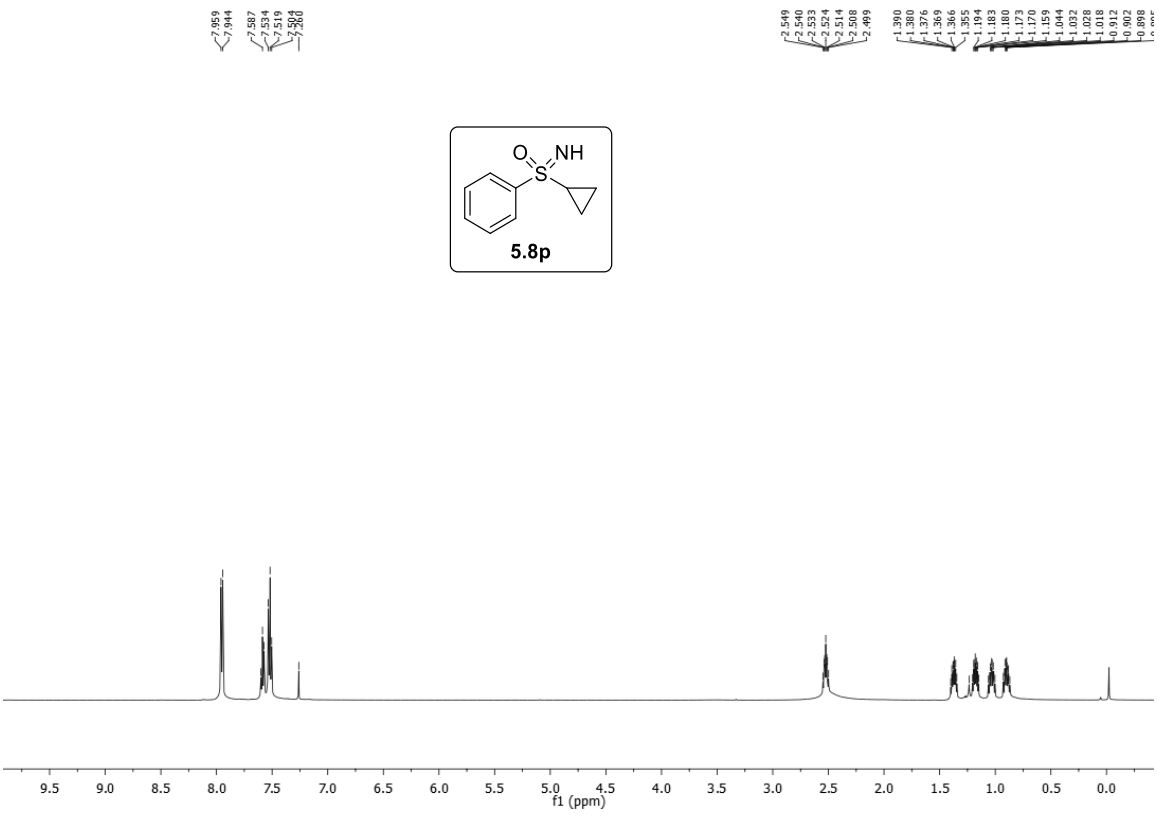
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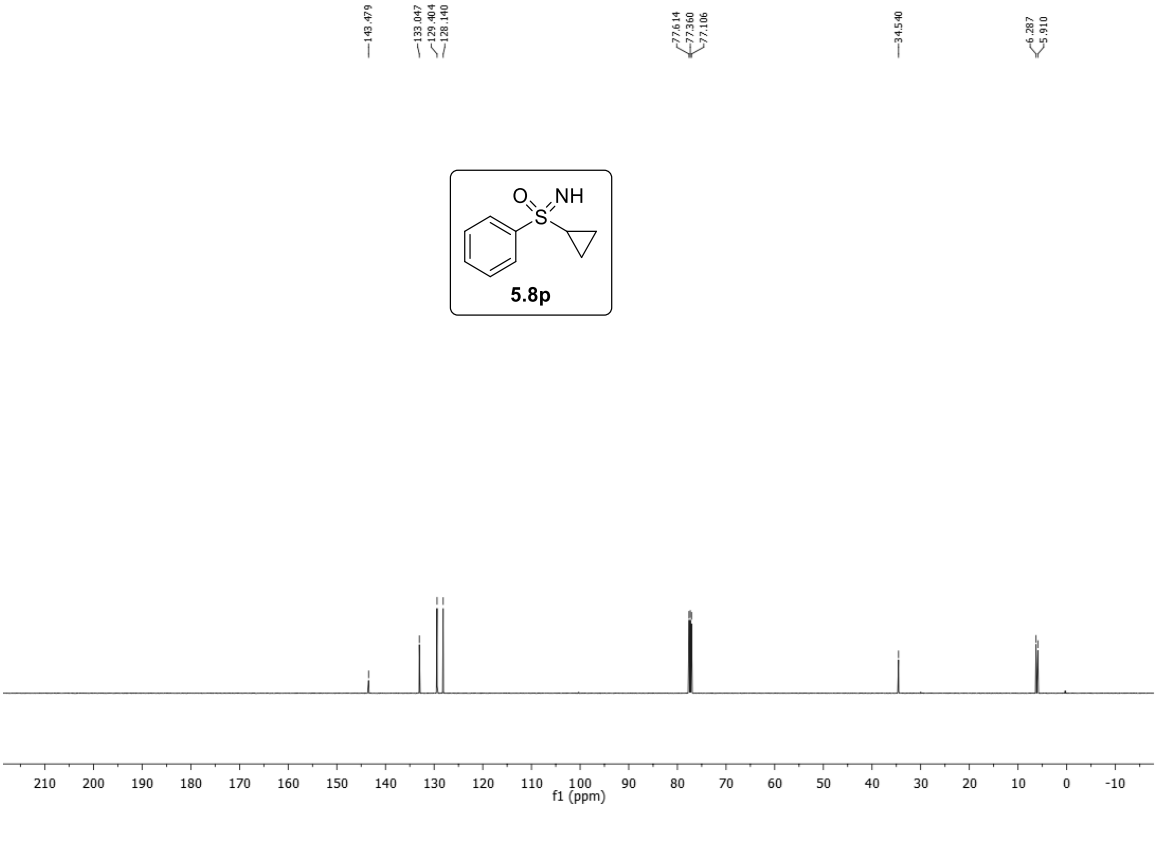
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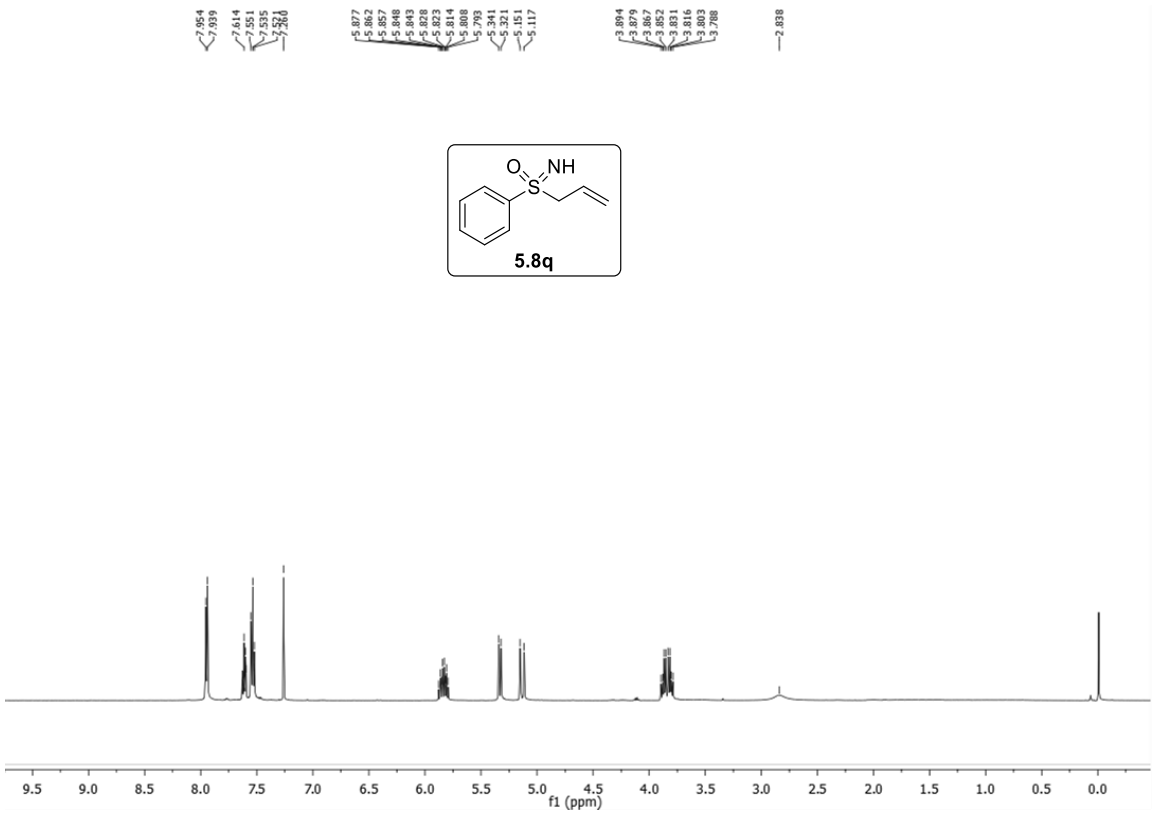
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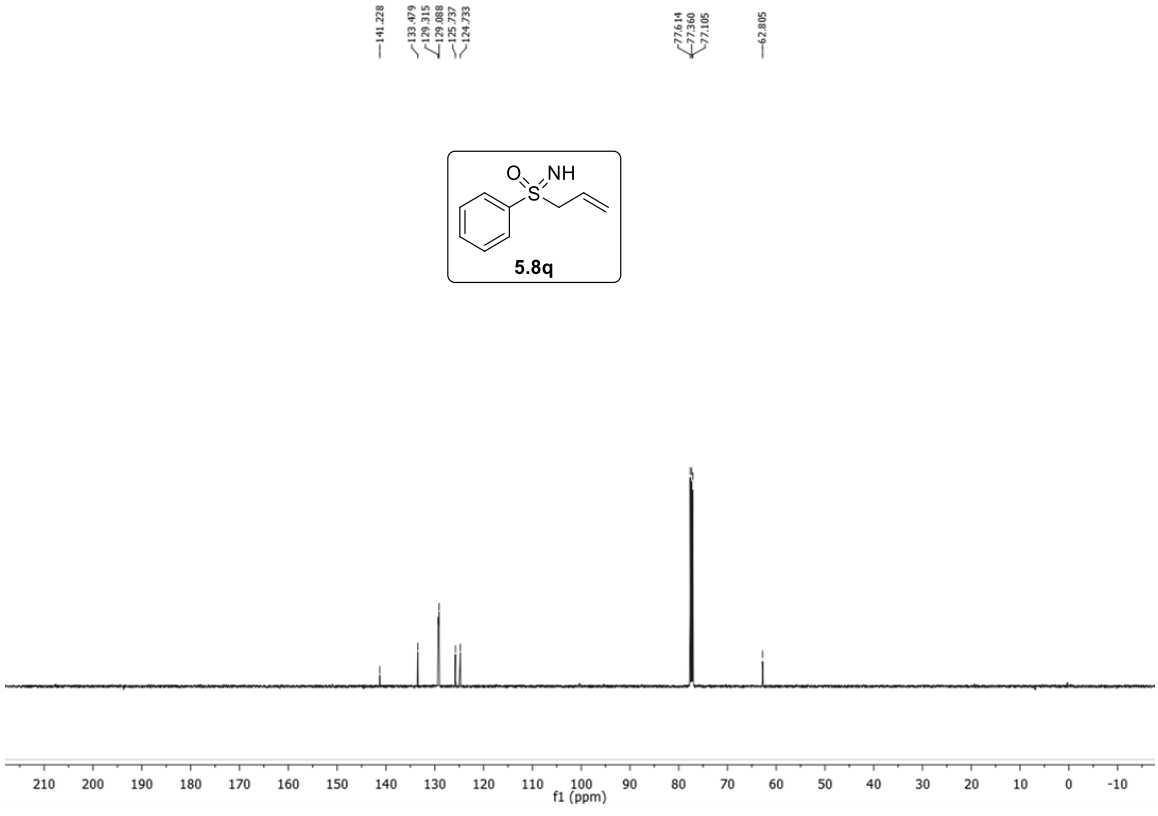
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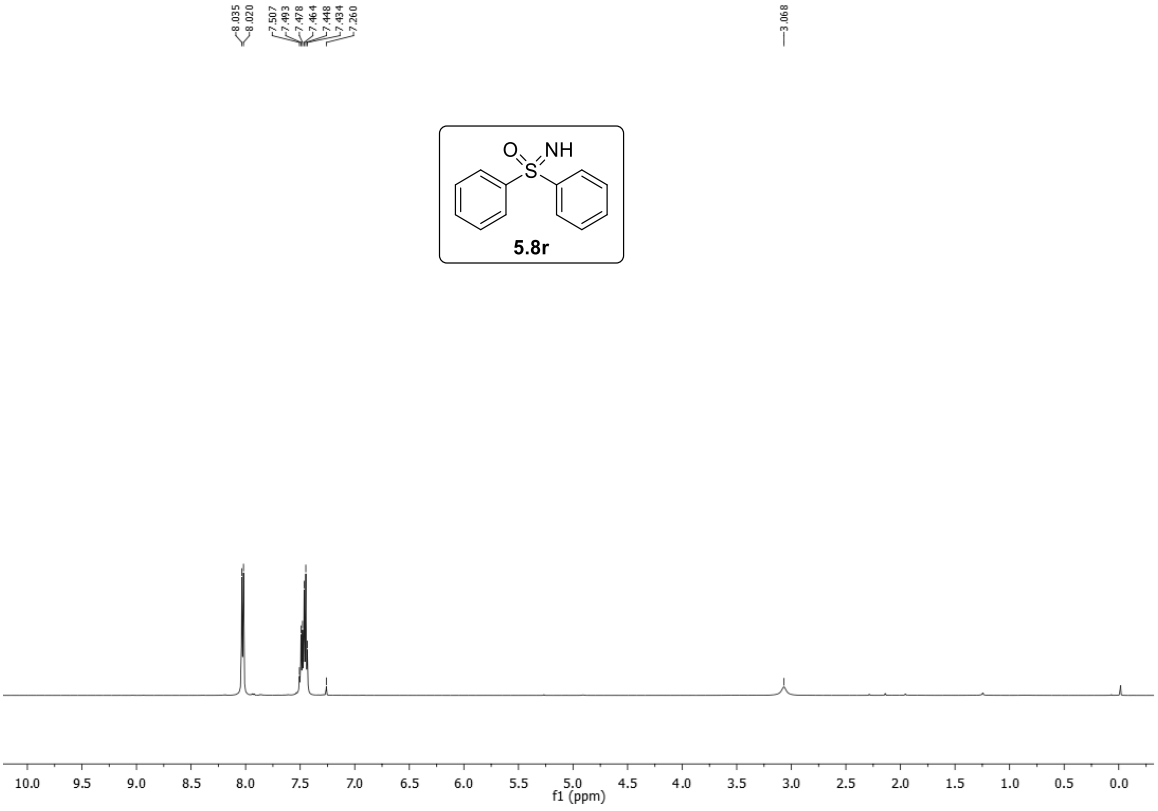
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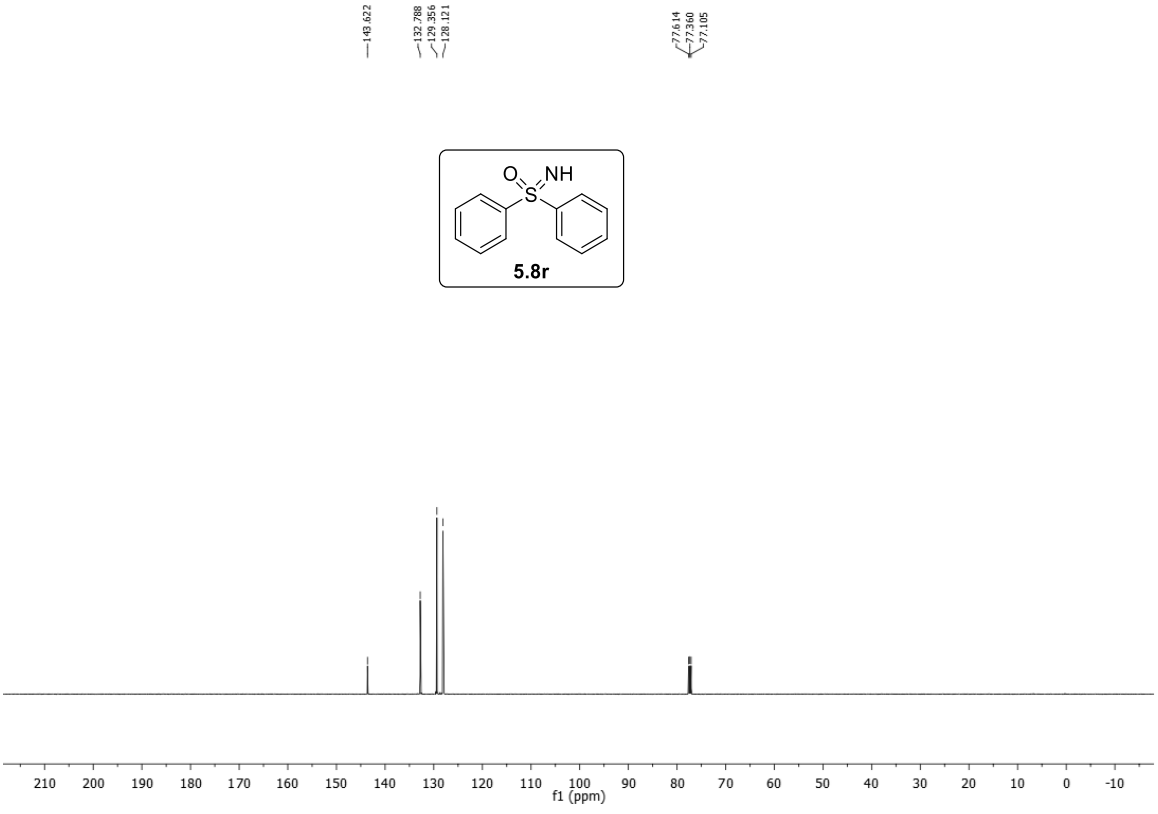
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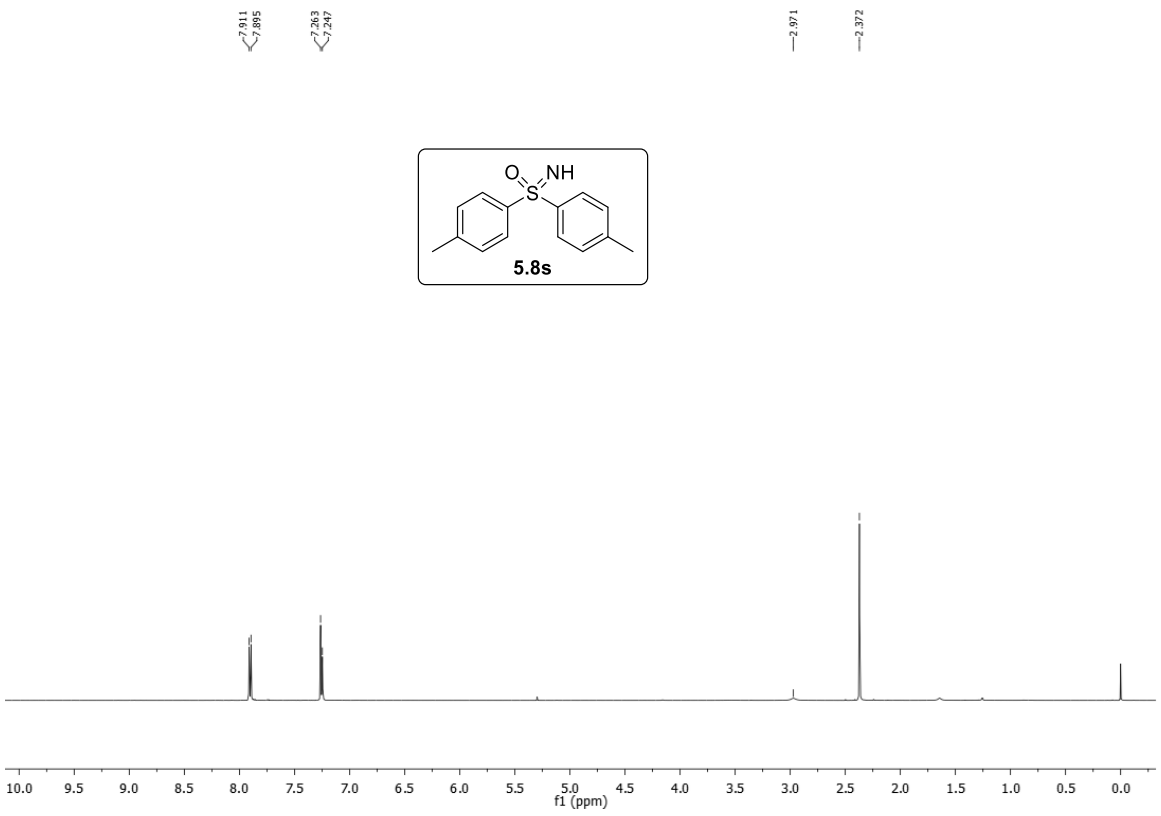
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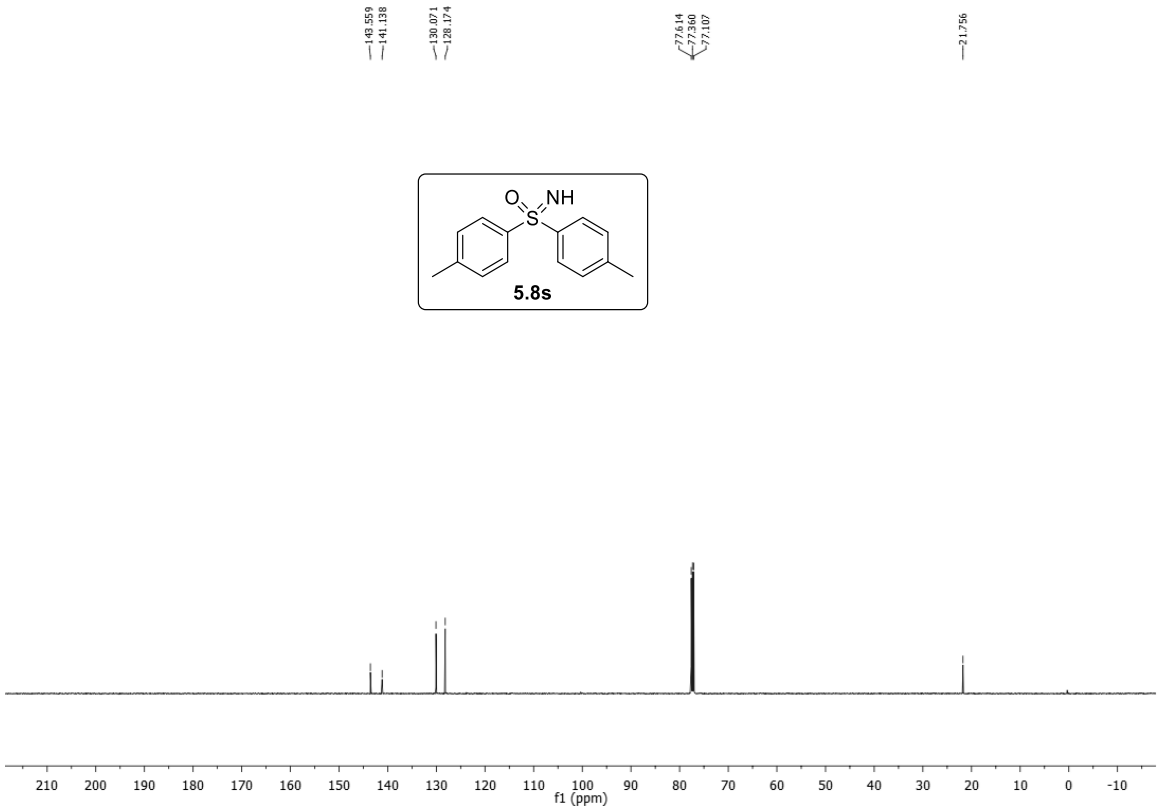
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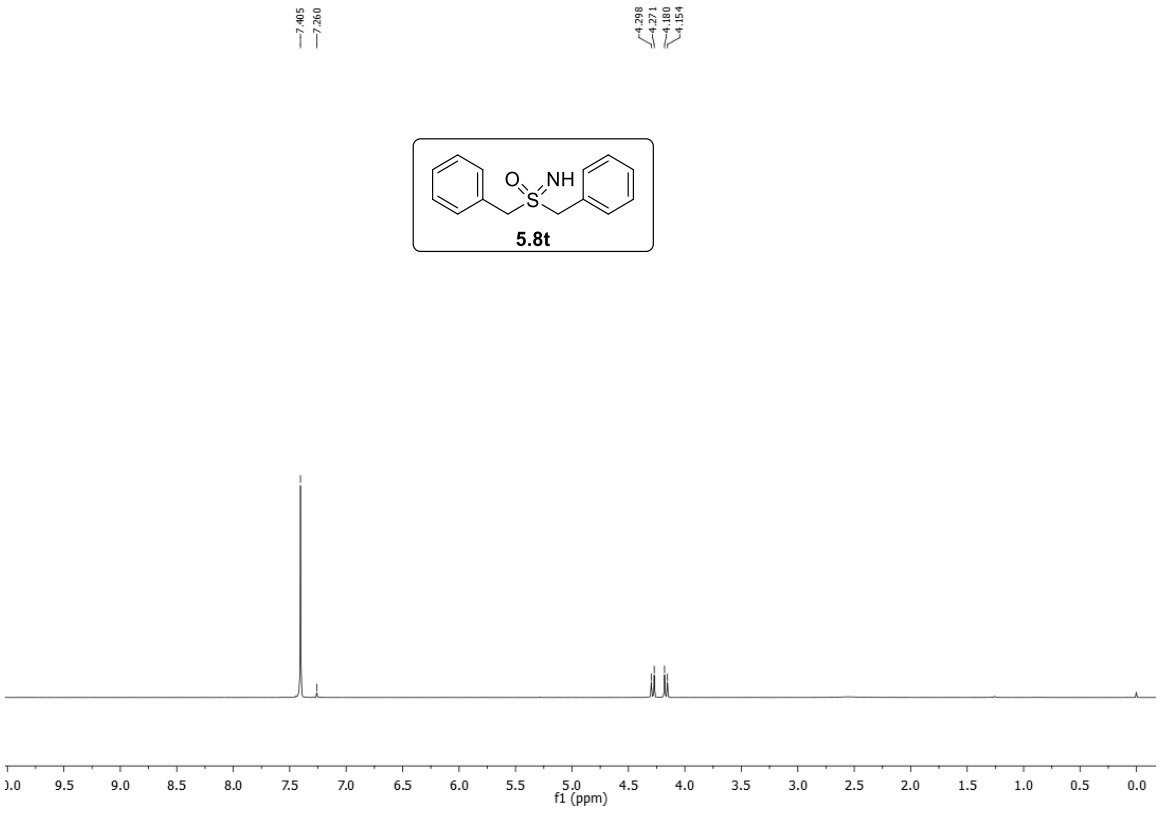
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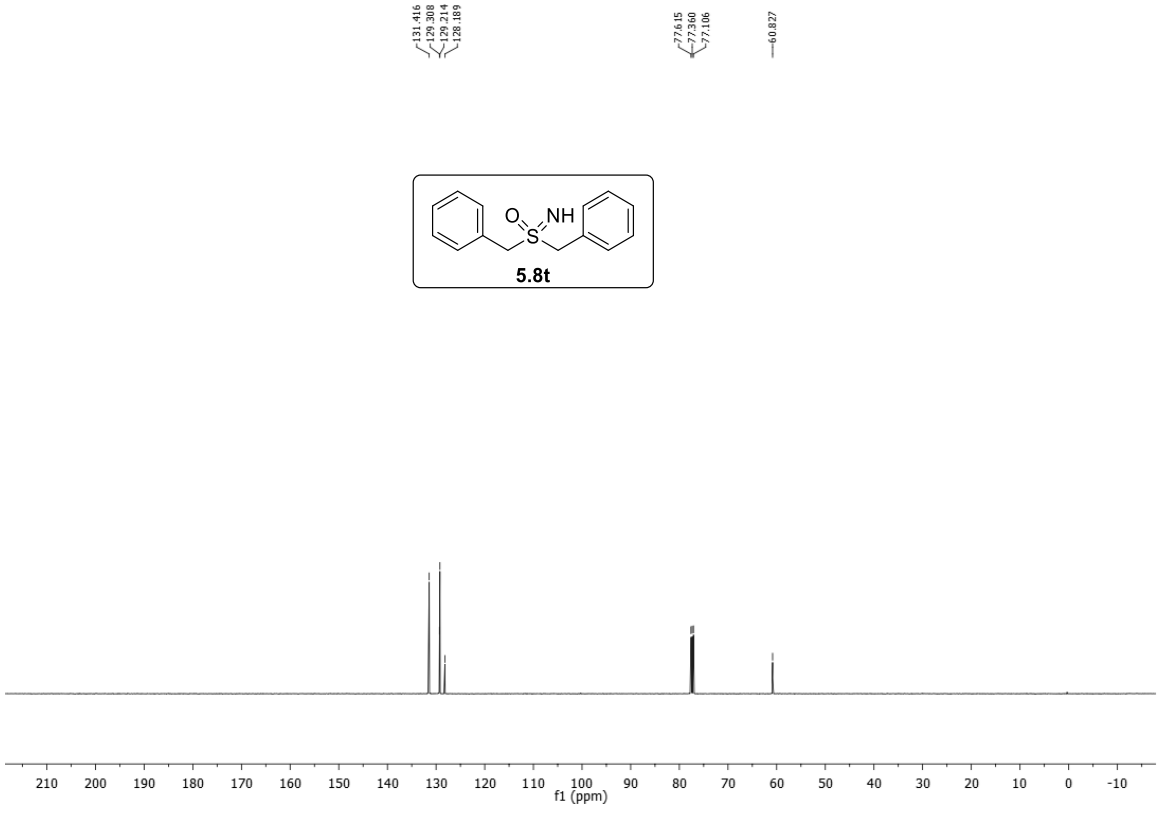
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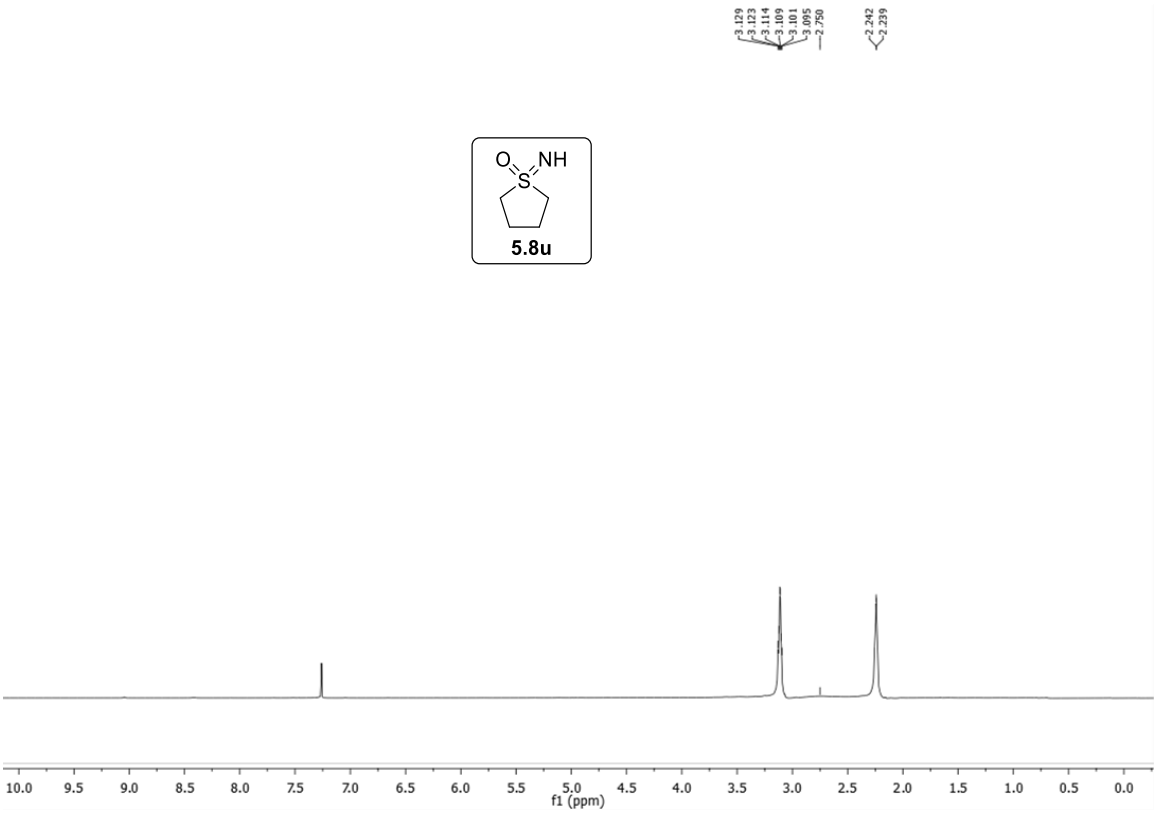
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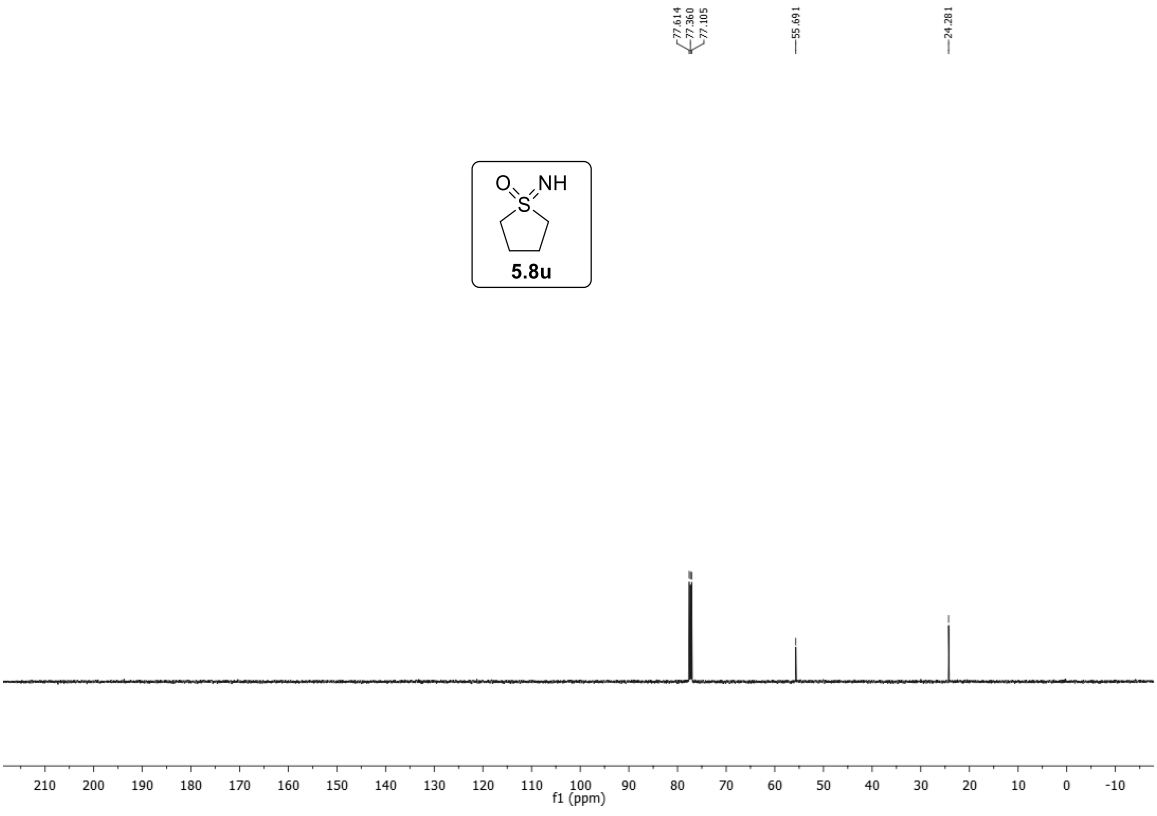
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VITA

VITA

EDUCATION AND RESEARCH

2010 – 2016 **Indiana University Purdue University Indianapolis, IN**

PhD, Major: Organic Chemistry Advisor: Prof. Haibo Ge

- Synthesis of (-)-Ascochlorin via Stille Coupling
- Pd-catalyzed direct *ortho*-acylation of benzoic acids
- Pd-catalyzed decarboxylative alkoxycarbonylation of $ArBF_3K$
- Cu-catalyzed dehydrogenative cyclization of *N*-methyl-*N*-phenylhydrazones
- Rh-catalyzed direct synthesis of unprotected *NH*-sulfoximines from sulfoxides
- Pd-catalyzed β-fluorination of amides via sp^3 C−H activation

2005 - 2009 **Nankai University,** Tianjin, China

Bachelor of Science, Major: Chemistry

Thesis: Design, synthesis and fungicidal activities of succinate dehydrogenase inhibitors

PUBLICATIONS AND POSTERS

Miao, J.-M., Fang, P., Jagdeep, S., Ge, H.-B. Palladium-Catalyzed Decarboxylative Alkoxycarbonylation of Potassium Aryltrifluoroborates with Potassium Oxalate Monoesters *Organic Chemistry Frontiers*, **2016**, *3*, 243-250.

Miao, J.-M., Ge, H.-B. Recent Advances in First-Row Transition Metal-Catalyzed Dehydrogenative Coupling of C(sp^3)–H Bonds *European Journal of Organic Chemistry*, **2015**, 7859-7868.

Miao, J.-M., Yang, K., Kurek, M., Ge, H.-B. Palladium-Catalyzed Site-Selective Fluorination of Unactivated C(sp^3)-H Bonds *Organic Letters*, **2015**, *7*, 3738-3741.

Miao, J.-M., Ge, H.-B. Rhodium-Catalyzed Direct Synthesis of Unprotected NH-Sulfoximines from Sulfoxides. *Chemical Communications*, **2014**, *50*, 9687-9689.

Miao, J.-M., Ge, H.-B. Palladium-Catalyzed Decarboxylative Cross-Coupling of α-Oxocarboxylic Acids and Their Derivatives. *SYNLETT*, **2014**, *25*, 911-919.

Miao, J.-M., Ge, H.-B. Palladium-Catalyzed Chemoselective Decarboxylative *ortho*-Acylation of Benzoic Acids with α-Oxocarboxylic Acids. *Organic Letters*, **2013**, *15*, 2930-2933.

Zhang, G.-W., Miao, J.-M., Ge, H.-B. Copper-Catalyzed Aerobic Dehydrogenative Cyclization of *N*-Methyl-*N*-phenylhydrazones: Synthesis of Cinnolines. *Angewandte Chemie International Edition*, 2012, *51*, 8318-8321.

POSTERS

Miao, J.-M., Haibo, Ge. (2013) Palladium(II)-Catalyzed Decarboxylative Cross-Coupling via C−H Activation. *246th ACS National Meeting*, Indianapolis, IN.

Miao, J.-M., Haibo, Ge. (2011) Chemoselective Decarboxylative *ortho*-Acylation of Aryl Carboxylic Acids with α-Oxocarboxylic Acids via Palladium-Catalyzed sp^2 C−H Bond Activation. *42nd ACS Central Regional Meeting*, Indianapolis, IN.

TEACHING EXPERIENCES

TEACHING ASSISTANTSHIPS

Fall 2011–Spring 2014:

Experimental Chemistry I (C125), Indiana University Purdue University Indianapolis

Laboratory Instructor

Spring 2015–Spring 2016:

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Laboratory Instructor

PUBLICATIONS

Angewandte Communications

Synthetic Methods

DOI: 10.1002/anie.201204339

Copper-Catalyzed Aerobic Dehydrogenative Cyclization of N-Methyl-N-phenylhydrazones: Synthesis of Cinnolines**

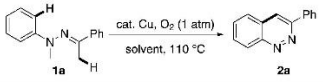
*Guangwu Zhang, Jinmin Miao, Yan Zhao, and Haibo Ge**

Selective carbon–carbon (C–C) bond formation is one of the most important processes in organic chemistry since it enables key steps in the synthesis of complex organic molecules from simple precursors. Traditionally, the construction of C–C bonds relies primarily on prefunctionalized substrates, which usually requires additional synthetic steps, and thus reduces the overall efficiency of this transformation.[1] For this reason, C–C bond formation reactions through transition-metal-catalyzed direct functionalization of relatively unreactive C–H bonds have emerged as a major topic of research in organic chemistry.[2] Among them, copper-catalyzed aerobic dehydrogenative coupling reactions from two carbon–hydrogen (C–H) bonds have received renewed interest in recent years with the following inherent advantages: maximizing atom economy by avoiding prefunctionalization of the coupling partners, and avoidance of toxic by-products with molecular oxygen as the sole oxidant.[3]

Since the discovery of the Glaser reaction or the oxidative dimerization of terminal alkynes[4] over 140 years ago, many efforts have been devoted to this field to construct new C–C bonds. A number of copper-catalyzed aerobic dehydrogenative coupling reactions through a C_{sp}–H or C_{sp^2}–H bond functionalization process have been developed, including oxidative dimerization of phenols,[5] naphthols,[6] and electron-deficient arenes,[7] cross-coupling of terminal alkynes with electron-deficient arenes,[8] and intramolecular dehydrogenative cylization of anilides.[9] In comparison, the development of copper-catalyzed aerobic dehydrogenative coupling at sp^3-carbon atoms is still in its infancy and the current advances suffer severely from restricted substrate scope, namely substrates with the sp^3-carbon atom adjacent to a heteroatom[10] or malonic amide derivative.[11] In our continued efforts toward the development of transition-metal-catalyzed coupling reactions on novel substrates,[12] herein we report N-methyl-N-phenylhydrazones as unprecedented substrates for copper-catalyzed aerobic intramolecular dehydrogenative cyclization for the formation of cinnolines,[13] a privileged structure in many medicinal compounds with a broad range of biological activities including antibacterial, anticancer, antifungal, antihypertensive, antiinflammatory, and antiulcer activities.[14]

Our investigation began with the oxidative cyclization of 1-methyl-1-phenyl-2-(1-phenylethylidene)hydrazine (**1a**) with catalytic $CuSO_4$ in the presence of O_2 (1 atm). To our delight, the cyclization reaction was successful with DMF, DMA, or DCE as the solvent, albeit in low yields (Table 1, entries 1–3). An extensive catalyst screening showed that although other Cu^{II} and Cu^{I} sources could catalyze the

Table 1: Optimization of reaction conditions.[a]



1a **2a**

Entry	Cu source (mol%)	Additives (equiv)	Solvent	Yield [%][b]
1	$CuSO_4$ (20)	–	DMF	37
2	$CuSO_4$ (20)	–	DMA	32
3	$CuSO_4$ (20)	–	DCE	30
4	$CuSO_4$ (20)	–	CH_3CN	<5
5	$CuSO_4$ (20)	–	DMSO	trace
6	$CuSO_4$ (20)	–	NMP	trace
7	–	–	DMF	0
8	$Cu(OAc)_2$ (20)	–	DMF	22
9	$CuBr_2$ (20)	–	DMF	20
10	$CuCl_2$ (20)	–	DMF	19
11	CuF_2 (20)	–	DMF	17
12	$Cu(OH)_2CO_3$ (20)	–	DMF	16
13	$Cu(TFA)_2$ (20)	–	DMF	15
14	$Cu(OTf)_2$ (20)	–	DMF	12
15	CuI (20)	–	DMF	25
16	CuBr-DMS (20)	–	DMF	22
17	$CuSO_4$ (20)	Py (3.5)/CF_3SO_3H (1)	DMF	73
18	$CuSO_4$ (20)	Py (3.5)/TsOH (1)	DMF	55
19	$CuSO_4$ (20)	Py (3.5)/CF_3CO_2H (1)	DMF	47
20	$CuSO_4$ (20)	Py (3.5)/AcOH (1)	DMF	43
21	$CuSO_4$ (10)/CuI (10)	Py (3.5)/$PhCO_2H$ (1)	DMF	42
22	$CuSO_4$ (1.5)/CuI (7.5)	Py (3.5)/CF_3SO_3H (1)	DMF	83 (80)[c]
23	$CuSO_4$ (1.5)/CuI (5)	Py (3.5)/CF_3SO_3H (1)	DMF	70
24[d]	$CuSO_4$ (1.5)/CuI (7.5)	Py (3.5)/CF_3SO_3H (1)	DMF	20

[a] Reaction conditions: **1a** (0.3 mmol), Cu source, additive, O_2 (1 atm), 3 mL of solvent, 110 °C, 14 h unless otherwise noted. [b] Yields and conversions are based on **1a**, and determined by ^1H NMR analysis of the crude reaction mixture using dibromomethane as the internal standard. [c] Yield of isolated product. [d] Under air. DCE = 1,2-dichloroethane, DMF = *N*,*N*′-dimethylformamide, DMA = dimethylacetamide, DMS = dimethylsulfide, DMSO = dimethylsulfoxide, Py = pyridine, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.

[*] Dr. G.-W. Zhang, J.-M. Miao, Y. Zhao, Prof. Dr. H.-B. Ge
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E-mail: geh@iupui.edu

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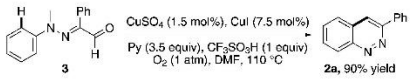
cyclization of **1a**, none of these catalysts improved the yield (entries 8–16). Upon realizing that the addition of a nucleophilic base could facilitate the demethylation, screening of different bases (pyridine, DMAP, DABCO, etc.) was carried out. Unfortunately, none of these bases improved the yield. However, the yield was increased by the addition of an acid along with excess pyridine, and the optimal results were obtained with 1 equivalent of CF_3SO_3H and 3.5 equivalent of pyridine (entry 22).

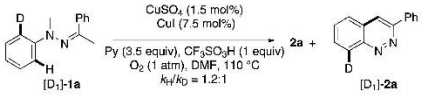
As shown in Table 2, this transformation is compatible with electron-rich and electron-deficient N-phenyl rings (**2b–o**). There is no apparent electronic or steric effect resulting from this ring, and good to high yields of product were obtained with both electron-donating or electron-withdrawing substituents (R^1) on either the *para*, *meta*, and *ortho* positions, with the exception of **2o**. The *meta*-OMe-, Me-, or Br-substituted substrates gave a mixture of *para* and *ortho*-substituted products (**2h–j**) with a preference for the *p*-substituted products, whereas substrates bearing the more hindered *i*Pr group and the electron-withdrawing CN group provided only the *p*-substituted products (**2k** and **2l**, respectively). As expected, halogens (F, Cl, and Br) were tolerated under the current reaction system, thus allowing further manipulation of the initial products. In contrast, there is an electronic effect resulting from substituents (R^2) on the other phenyl ring (**2q–z**). Generally, electron-donating groups on this ring provide higher yields than those with electron-withdrawing groups. It is noted that replacement of this phenyl group with an alkyl group gave only a trace amount of product as a result of the decomposition of the starting material under the oxidative conditions. It was also observed that this reaction failed with the introduction of an alkyl group on the carbon atom α to the imine moiety.

It is noteworthy that under the current reaction conditions, a small amount of 2-(*N*-methyl-*N*-phenylhydrazono)-2-phenylacetaldehyde (**3**) was isolated along with the desired product **2a** from the reaction of **1a**. Furthermore, treatment of **3** under the cyclization reaction conditions provided **1a** in 90% yield (Scheme 1).



Scheme 1. Cyclization of 2-(*N*-methyl-*N*-phenylhydrazono)-2-phenylacetaldehyde (**3**).

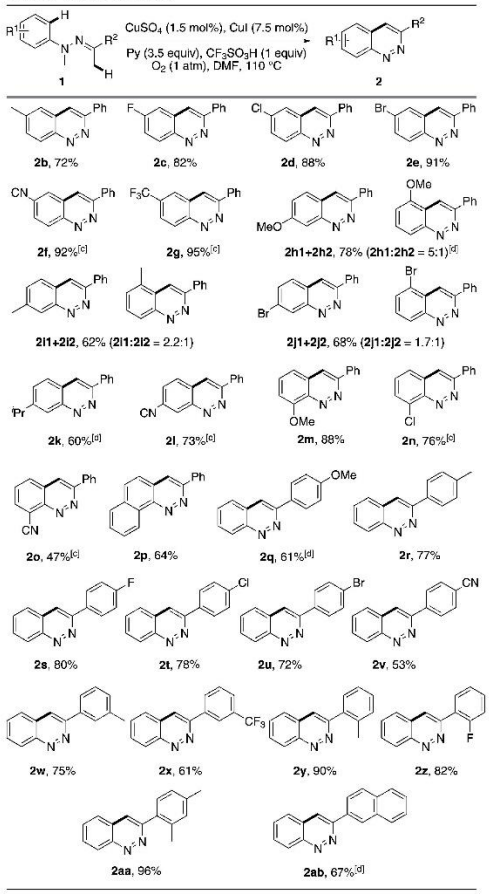
To further probe the reaction mechanism, deuterium-labeling experiments were conducted (Scheme 2). No significant kinetic isotope effect was observed in the reaction of [D_1]-**1a**, thus suggesting that the arene C_{sp^2}–H bond cleavage might not be involved in the rate-determining step.[15]



Scheme 2. Deuterium-labeling experiments.

Based on the above observations, a reaction mechanism for the cyclization of **1a** is proposed (Scheme 3). It is believed that this transformation starts with the oxidation of **1a** into **3** through a copper-catalyzed process in the presence of oxygen.[16] Copper-assisted Friedel–Crafts-type cyclization of **3** generates the intermediate **G**.[17] Activation of **G** by a copper species, followed by loss of the hydroxy group, and a methyl group by nucleophilic substitution by pyridine, provides the desired product **2a**.

Table 2: Substrate scope.[a,b]



[a] Reaction conditions: **1** (0.3 mmol), $CuSO_4$ (1.5 mol%), CuI (7.5 mol%), Py (3.5 eq), CF_3SO_3H (1.0 eq), O_2 (1 atm), 3 mL of DMF, 110 °C, 14 h unless otherwise noted. [b] Yield of isolated product. [c] The reaction was run at 150 °C for 20 h. [d] The reaction was run at 95 °C for 48 h.

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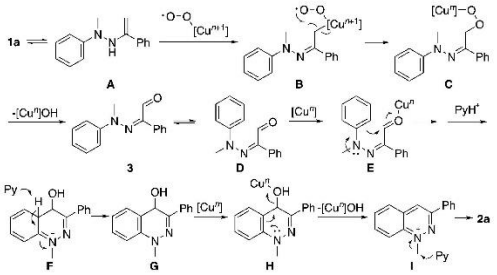

Scheme 3. Proposed reaction mechanism.

In summary, an efficient copper-catalyzed aerobic intramolecular dehydrogenative cyclization reaction of N-methyl-N-phenylhydrazones has been developed through sequential C_{sp^3}–H oxidation, cyclization, and aromatization processes. This transformation is the first example of copper-catalyzed coupling reactions of hydrazones through a C_{sp^3}–H bond functionalization pathway. This novel method provides an efficient access to cinnoline derivatives.

Experimental Section

A 50 mL Schlenk tube was charged with N-methyl-N-phenylhydrazones (**1**, 0.3 mmol), $CuSO_4$ (1.0 mg, 0.0045 mmol), CuI (4.2 mg, 0.0225 mmol), Py (84.4 μL, 1.05 mmol), and DMF (2.7 mL). Then a solution of CF_3SO_3H (26.5 μL, 0.3 mmol) in DMF (0.3 mL) was slowly added. The tube was evacuated and filled with 1 atm O_2, and stirred rigorously at 110°C (unless otherwise noted) for 14–48 h. After removal of the solvent, the residue was purified by flash chromatography on silica gel (gradient eluent of 5% EtOAc and 1% Et_3N in hexanes, *v/v*) to yield the desired product as a colorless or pale-yellow solid.

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Keywords: C–C coupling · copper · heterocycles · oxygen · synthetic methods

[1] *Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.* (Eds.: A. De Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**.

[2] For selected recent reviews, see: a) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873–2920; b) K. Godula, D. Sames, *Science* **2006**, *312*, 67–72; c) L.-X. Yin, J. Liebscher, *Chem. Rev.* **2007**, *107*, 133–173; d) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; e) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318–5365; f) M. Catellani, E. Motti, N. Della Ca', *Acc. Chem. Res.* **2008**, *41*, 1512–1522; g) G. C. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555–1564; h) M. Zhang, *Adv. Synth. Catal.* **2009**, *351*, 2243–2270; i) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; j) P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874–5883; k) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; l) S. De Ornellas, T. E. Storr, T. J. Williams, C. G. Baumann, I. J. S. Fairlamb, *Curr. Org. Chem.* **2011**, *8*, 79–101; m) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293–1314; n) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885–1898; o) T. C. Boorman, I. Larrosa, *Chem. Soc. Rev.* **2011**, *40*, 1910–1925; p) T. Newhouse, P. S. Baran, *Angew. Chem.* **2011**, *123*, 3422–3435; *Angew. Chem. Int. Ed.* **2011**, *50*, 3362–3374; q) J. Wencel-Delord, T. Droge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740–4761; r) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068–5083; s) M. N. Hopkinson, A. D. Gee, V. Gouverneur, *Chem. Eur. J.* **2011**, *17*, 8248–8262.

[3] For selected recent reviews of C–C bond formation, see: a) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344; b) W.-J. Yoo, C.-J. Li, *Top. Curr. Chem.* **2010**, *292*, 281–302; c) C. J. Scheuermann, *Chem. Asian J.* **2010**, *5*, 436–451; d) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; e) C. Liu, H. Zhang, W. Shi, A.-W. Lei, *Chem. Rev.* **2011**, *111*, 1780–1824; f) M. Schnurch, N. Dastbaravardeh, M. Ghobrial, B. Mrozek, M. D. Mihovilovic, *Curr. Org. Chem.* **2011**, *15*, 2694–2730; g) C. Zhang, C.-H. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3381–3430; h) A. W. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem.* **2011**, *123*, 11256–11283; *Angew. Chem. Int. Ed.* **2011**, *50*, 11062–11087; For selected recent examples of C–X bond formation, see: i) P. S. Baran, M. P. DeMartino, *Angew. Chem.* **2006**, *118*, 7241–7244; *Angew. Chem. Int. Ed.* **2006**, *45*, 7083–7086; j) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791; k) T. Hamada, X. Ye, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 833–835; l) G. Brasche, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 1958–1960; *Angew. Chem. Int. Ed.* **2008**, *47*, 1932–1934; m) S. Ueda, H. Nagasawa, *Angew. Chem.* **2008**, *120*, 6511–6513; *Angew. Chem. Int. Ed.* **2008**, *47*, 6411–6413; n) Y.-X. Jia, E. P. Kündig, *Angew. Chem.* **2009**, *121*, 1664–1667; *Angew. Chem. Int. Ed.* **2009**, *48*, 1636–1639; o) O. Baslé, C.-J. Li, *Chem. Commun.* **2009**, 4124–4126; p) S. Ueda, H. Nagasawa, *J. Am. Chem. Soc.* **2009**, *131*, 15080–15081; q) S. Ueda, H. Nagasawa, *J. Org. Chem.* **2009**, *74*, 4272–4277; r) C. Zhang, N. Jiao, *J. Am. Chem. Soc.* **2010**, *132*, 28–29; s) C. Zhang, N. Jiao, *Angew. Chem.* **2010**, *122*, 6310–6313; *Angew. Chem. Int. Ed.* **2010**, *49*, 6174–6177; t) H. Wang, Y. Wang, C. Peng, J. Zhang, Q. Zhu, *J. Am. Chem. Soc.* **2010**, *132*, 13217–13219; u) H. Wang, Y. Wang, D. Liang, L. Liu, J. Zhang, Q. Zhu, *Angew. Chem.* **2011**, *123*, 5796–5799; *Angew. Chem. Int. Ed.* **2011**, *50*, 5678–5681; v) L. M. Huffman, A. Casitas, M. Font, M. Canta, M. Costas, X. Ribas, S. S. Stahl, *Chem. Eur. J.* **2011**, *17*, 10643–10650; w) L. Zhang, Z.-H. Liu, H.-Q. Li, G.-C. Fang, B.-D. Barry, T. A. Belay, X.-H. Bi, Q. Liu, *Org. Lett.* **2011**, *13*, 6536–6539.

[4] a) C. Glaser, *Chem. Ber.* **1869**, *2*, 422–424; b) A. S. Hay, *J. Org. Chem.* **1962**, *27*, 3320–3321; c) P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740–2767; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632–2657.

[5] a) A. S. Hay, H. S. Blanchard, G. F. Endres, J. W. Eustance, *J. Am. Chem. Soc.* **1959**, *81*, 6335–6336; b) D. R. Armstrong, C. Cameron, D. C. Nonhebel, P. G. Perkins, *J. Chem. Soc. Perkin Trans. 2* **1983**, 581–585; c) D. R. Armstrong, C. Cameron, D. C. Nonhebel, P. G. Perkins, *J. Chem. Soc. Perkin Trans. 2* **1983**, 587–589.

[6] a) M. Noji, M. Nakajima, K. Koga, *Tetrahedron Lett.* **1994**, *35*, 7983–7984; b) M. Nakajima, K. Kanayama, I. Miyoshi, S.-I. Hashimoto, *Tetrahedron Lett.* **1995**, *36*, 9519–9520; c) M. Nakajima, I. Miyoshi, K. Kanayama, S.-I. Hashimoto, M. Noji, K. Koga, *J. Org. Chem.* **1999**, *64*, 2264–2271; d) X.-L. Li, J. Yang, M. C. Kozlowski, *Org. Lett.* **2001**, *3*, 1137–1140; e) K. H. Kim, D.-W. Lee, Y.-S. Lee, D.-H. Ko, D.-C. Ha, *Tetrahedron* **2004**, *60*, 9037–9042.

[7] a) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2009**, *131*, 17052–17053; b) Y. Li, J. Jin, W. Qian, W. Bao, *Org. Biomol. Chem.* **2010**, *8*, 326–330; c) D. Monguchi, A. Yamamura, T. Fujiwara, T. Somete, A. Mori, *Tetrahedron Lett.* **2010**, *51*, 850–852.

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[8] a) N. Matsuyama, M. Kitahara, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2358–2361; b) Y. Wei, H.-Q. Zhao, J. Kan, W.-P. Su, M.-C. Hong, *J. Am. Chem. Soc.* **2010**, *132*, 2522–2523.

[9] B.-X. Tang, R.-J. Song, C.-Y. Wu, Y. Liu, M.-B. Zhou, W.-T. Wei, G.-B. Deng, D.-L. Yin, J.-H. Li, *J. Am. Chem. Soc.* **2010**, *132*, 8900–8902.

[10] a) O. Baslé, C.-J. Li, *Green Chem.* **2007**, *9*, 1047–1050; b) W.-J. Yoo, C. A. Correia, Y.-H. Zhang, C.-J. Li, *Synlett* **2009**, 138–142; c) Y.-M. Shen, M. Li, S.-Z. Wang, T.-G. Zhan, Z. Tan, C.-C. Guo, *Chem. Commun.* **2009**, 953–955; d) L.-H. Huang, T.-M. Niu, J. Wu, Y.-H. Zhang, *J. Org. Chem.* **2011**, *76*, 1759–1766; e) E. Boess, C. Schmitz, M. Klussmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317–5325.

[11] a) Y.-X. Jia, E. P. Kündig, *Angew. Chem.* **2009**, *121*, 1664–1667; *Angew. Chem. Int. Ed.* **2009**, *48*, 1636–1639; b) J. E. M. N. Klein, A. Perry, D. S. Pugh, R. J. K. Taylor, *Org. Lett.* **2010**, *12*, 3446–3449.

[12] a) M.-Z. Li, L.-X. Li, H.-B. Ge, *Adv. Synth. Catal.* **2010**, *352*, 2445–2449; b) M.-Z. Li, H.-B. Ge, *Org. Lett.* **2010**, *12*, 3464–3467; c) P. Fang, M.-Z. Li, H.-B. Ge, *J. Am. Chem. Soc.* **2010**, *132*, 11898–11899; d) C. Wang, H.-B. Ge, *Synthesis* **2011**, 2590–2594; e) C. Wang, H.-B. Ge, *Chem. Eur. J.* **2011**, *17*, 14371–14374.

[13] Originally, 1-phenyl-2-(1-phenylethylidene)hydrazine was used as the substrate. However, this reaction gave only less than 10% yield of the desired product because of the decomposition of the starting material.

[14] a) A. A. Bekhit, *Boll. Chim. Farm.* **2001**, *140*, 243–253; b) W. Lewgowd, A. Stanczak, *Arch. Pharm. Chem. Life Sci.* **2007**, *340*, 65–80; c) N. Gautam, O. P. Chourasia, *Indian J. Chem. Sect. B* **2010**, *49*, 830–835; d) P. Parasuraman, R. S. Shanmugarajan, T. Aravazhi, K. Nehru, T. Mathiazhagan, R. Rajakumari, *Int. J. of Pharm. & Life Sci.* **2012**, *3*, 1430–1436; e) H. Tsuji, Y. Yokoi, Y. Sato, H. Tanaka, E. Nakamura, *Chem. Asian J.* **2011**, *6*, 2005–2008.

[15] E. M. Simmons, J. F. Hartwig, *Angew. Chem.* **2012**, *124*, 3120–3126; *Angew. Chem. Int. Ed.* **2012**, *51*, 3066–3072.

[16] a) K. K. Toh, Y.-F. Wang, E. P. J. Ng, S. Chiba, *J. Am. Chem. Soc.* **2011**, *133*, 13942–13945; b) K. K. Toh, S. Sanjaya, S. Sahnoun, S. Y. Chong, S. Chiba, *Org. Lett.* **2012**, *14*, 2290–2292.

[17] In this process, a pyridinium salt is formed by the acid-base reaction of pyridine and trifluoromethanesulfonic acid, and presumably this salt acts as a proton donor to protonate a copper species formed from the Friedel–Crafts-type cyclization of **E**.

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Palladium-Catalyzed Chemoselective Decarboxylative Ortho Acylation of Benzoic Acids with α-Oxocarboxylic Acids

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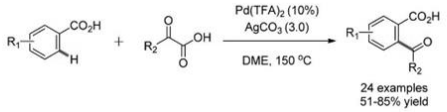
ABSTRACT



Palladium-catalyzed chemoselective decarboxylative cross coupling of benzoic acids with α-oxocarboxylic acids was realized via an arene sp^2 C−H functionalization process. This work represents the first example of transition-metal-catalyzed cross-coupling reactions with two acids acting in different roles. The synthetic utility of this method was confirmed by the synthesis of pitofenone, an antispasmodic used in the combined drug Spasmalgon.

2-Benzoylbenzoic acid derivatives are important intermediates for the synthesis of various bioactive compounds[1] and are often encountered as subunits of many biologically active compounds,[2] including natural products, pharmaceuticals, and agrochemical compounds. For example, balanol, a fungal metabolite produced by the fungus *Verticillium balanoides* and other fungi, is a potent inhibitor of protein kinase C (PKC),[1e,f] narceine, an opium alkaloid produced by the *Papaver sommiferum* plant, is a bitter compound with narcotic effects,[1d] and pitofenone, the key ingredient in Spasmalgon (a combined drug), is an antispasmodic (Figure 1).[1e] Additionally, 2-benzoylbenzoic acids are often used as functional groups or substrates in photochemistry,[3] chromatography,[4] and food chemistry.[5]

Despite the demonstrated biological importance of 2-acylbenzoic acids, synthetic methods for these species are far from maturity. The most common routes start from 1,3-isobenzofurandione derivatives and involve either a nucleophilic addition/elimination process by organometallic reagents[6] or a Friedel–Crafts acylation process (Scheme 1).[7] In many cases, these reactions suffer severely from poor regioselectivity on the benzofurandione, and

(1) (a) Acberli, P.; Eden, P.; Gogerty, J. H.; Houlihan, W. J.; Penberthy, C. *J. Med. Chem.* **1975**, *18*, 177. (b) Van der Mey, M.; Hatzelmann, A.; Van der Laan, I. J.; Sterk, G. J.; Thibaut, U.; Timmerman, H. *J. Med. Chem.* **2001**, *44*, 2511. (c) Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Moritani, Y.; Saruta, K.; Higashijima, T.; Kotera, J.; Takagi, M.; Kikkawa, K.; Omori, K. *J. Med. Chem.* **2001**, *44*, 2204–2218. (d) Watson, A. F.; Liu, J.-F.; Bennaceur, K.; Drummond, C. J.; Endicott, J. A.; Golding, B. T.; Griffin, R. J.; Haggerty, K.; Lu, X.-H.; McDonnell, J. M.; Newell, D. R.; Noble, M. E. M.; Revill, C. H.; Riedinger, C.; Xu, Q.; Zhao, Y.; Lunec, J.; Hardcastle, I. R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5916. (e) Cueva, J. P.; Gallardo-Godoy, A.; Juncosa, J. I.; Vidi, P. A.; Lill, M. A.; Watts, V. J.; Nichols, D. E. *J. Med. Chem.* **2011**, *54*, 5508. (f) Lim, C. J.; Kim, S. H.; Lee, B. H.; Oh, K.-S.; Yi, K. Y. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 427.

(2) (a) Sexton, W. A.; Templeman, W. G. *Nature* **1948**, *141*, 974. (b) Evans, D.; Cracknell, M. E.; Saunders, J. C.; Smith, C. E.; Williamson, W. R. N.; Dawson, W.; Sweatman, W. J. F. *J. Med. Chem.* **1987**, *30*, 1321. (c) Gapinski, D. M.; Mallett, B. E.; Froelich, L. L.; Jackson, W. T. *J. Med. Chem.* **1990**, *33*, 2798. (d) Wyss, D. F.; Arasappan, A.; Senior, M. M.; Wang, Y.-S.; Beyer, B. M.; Njoroge, F. G.; McCoy, M. A. *J. Med. Chem.* **2004**, *47*, 2486. (e) Gobec, S.; Brožič, P.; Rižner, T. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5170.

(3) (a) Jones, P. B.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 2753. (b) Sui, Y.-L.; Yan, B. *Inorg. Mater.* **2006**, *42*, 144. (c) Yan, B.; Wang, W.-J.; Song, Y.-S. *J. Fluoresc.* **2006**, *16*, 495.

(4) (a) Bieganowska, M. L.; Soczewinski, E.; Janowska, M. *Chromatographia* **1984**, *18*, 99. (b) Bieganowska, M. L.; Petruczynik, A. *Chromatographia* **1995**, *40*, 453. (c) Waksmundzka-Hajnos, M.; Bieganowska, M. L.; Petruczynik, A. *J. Chromatogr., A* **1996**, *730*, 195.

(5) Arnoldi, A.; Bassoli, A.; Borgonovo, G.; Merlini, L. *J. Agric. Food Chem.* **1997**, *45*, 2047.

(6) (a) Fieser, L. F.; Hershberg, E. B. *J. Am. Chem. Soc.* **1937**, *59*, 2331. (b) Newman, M. S.; Muth, C. W. *J. Am. Chem. Soc.* **1950**, *72*, 5191. (c) LaBudde, J. A.; Heidelberger, C. *J. Am. Chem. Soc.* **1958**, *80*, 1225. (d) Seo, S.; Slater, M.; Greaney, M. F. *Org. Lett.* **2012**, *14*, 2650.

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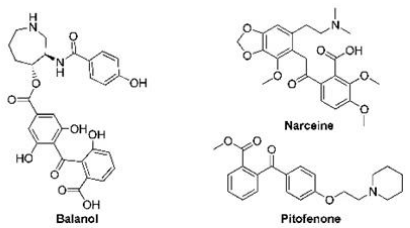
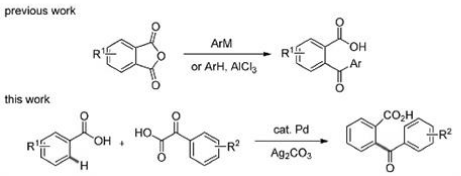


Figure 1. Representative biologically active compounds containing a 2-acylbenzoic acid/ester moiety.

thus substituted 2-acylbenzoic acids are difficult to obtain in a satisfactory yield.[6b,7c] Therefore, the need for complementary, concise, and effective approaches to access these compounds is clear. On the basis of our success on direct ortho acylation of 2-phenylpyridines and acetanilides,[8] we proposed that an efficient approach for the synthesis of 2-acylbenzoic acids could be achieved by decarboxylative cross coupling of benzoic acids with α-oxocarboxylic acids by a Pd(II)-catalyzed C−H functionalization process (Scheme 1).

Scheme 1. Synthesis of 2-Acylbenzoic Acids



Transition-metal-catalyzed cross coupling reactions remain one of the most powerful methods for carbon−carbon (C−C) bond formation.[9] Among these methods, Pd(0)-catalyzed decarboxylative cross coupling has recently attracted considerable attention due to the low cost, ready availability, and environmentally benign properties of carboxylic acids.[10] Along with the well-studied benzoic acids, alkyl, alkenyl and alkynyl acids, α-oxocarboxylates, and oxalates have also been demonstrated as effective substrates, which enable the installation of a variety of functional groups on aromatic rings. Furthermore, since Crabtree first reported a direct decarboxylative cross coupling of arenes with aromatic acids through a Pd(II)-catalyzed C−H functionalization process,[11] the method has attracted considerable attention because the prefunctionalization of reaction substrates is avoided.[12]

As substrates, benzoic acids have been extensively studied in decarboxylative cross-coupling reactions by both Pd(0) and Pd(II) catalysis. It has been demonstrated that either a silver or copper source could effectively mediate the decarboxylation. On the other hand, from Yu's studies, benzoic acid derivatives were fairly stable at high temperature (130 °C) in the presence of a catalytic amount of a Pd(II) source and an excess Ag(I) source.[13] Moreover, α-oxocarboxylic acids, utilized in Goossen's laboratory in Pd(0)-catalyzed decarboxylative cross couplings,[14] have also been demonstrated as effective coupling partners in Pd(II) catalysis in our laboratory with either a silver or persulfate source as an oxidant and the decarboxylation reagent.[8,15] It was also noted that, along with acteanilides and 2-phenylpyridines, cyclic enamides,[16] *O*-methyl oximes,[17] phenylacetamides,[18] *O*-phenyl carbamates,[19] and 1-(pyrimidin-2-yl)-1*H*-indoles[20] were also effective

(7) (a) Newman, M. S.; Scheurer, P. G. *J. Am. Chem. Soc.* **1956**, *78*, 5004. (b) Reinheckel, H. A.; Haage, K. *Angew. Chem., Int. Ed.* **1966**, *5*, 511. (c) Watson, A. F.; Liu, J.-F.; Bennaceur, K.; Drummond, C. J.; Endicott, J. A.; Golding, B. T.; Griffin, R. J.; Haggerty, K.; Lu, X.-H.; McDonnell, J. M.; Newell, D. R.; Noble, M. E. M.; Revill, C. H.; Riedinger, C.; Xu, Q.; Zhao, Y.; Lunec, J.; Hardcastle, I. R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5916. (d) Wang, X.; Li, J.-Z.; Zhao, N.; Wan, X.-B. *Org. Lett.* **2011**, *13*, 709. (e) Yu, H.-B.; Xiao, Y.; Guo, H.-Y. *Org. Lett.* **2012**, *14*, 2014.

(8) (a) Li, M.-Z.; Ge, H.-B. *Org. Lett.* **2010**, *12*, 3464. (b) Fang, P.; Li, M.-Z.; Ge, H.-B. *J. Am. Chem. Soc.* **2010**, *132*, 11898.

(9) For selected recent reviews, see: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (d) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (e) Boorman, T. C.; Larrosa, I. *Chem. Soc. Rev.* **2011**, *40*, 1910. (f) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362. (g) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (h) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (i) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788.

(10) For selected recent reviews, see: (a) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 1373. (b) Goossen, L. J.; Goossen, K.; Rodriguez, N.; Blanchot, M.; Linder, C.; Zimmermann, B. *Pure Appl. Chem.* **2008**, *80*, 1725. (c) Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (d) Goossen, L. J.; Collet, F.; Goossen, K. *Isr. J. Chem.* **2010**, *50*, 617. (e) Rodriguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030. (f) Cornella, J.; Larrosa, I. *Synthesis* **2012**, *44*, 653.

(11) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312.

(12) For recent examples of decarboxylative C−H arylation reactions, see: (a) Cornella, J.; Lu, P.-F.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506. (b) Wang, C.-Y.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (c) Yu, W.-Y.; Sit, W. N.; Zhou, Z.-Y.; Chan, A. S. C. *Org. Lett.* **2009**, *11*, 3174. (d) Zhang, F.-Z.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 2768. (e) Xie, K.; Yang, Z.-Y.; Zhou, X.-J.; Li, X.-J.; Wang, S.-Z.; Tan, Z.; An, X.-Y.; Guo, C.-C. *Org. Lett.* **2010**, *12*, 1564. (f) Zhou, J.; Hu, P.; Zhang, M.; Huang, S.; Wang, M.; Su, W. *Chem. Eur. J.* **2010**, *16*, 5876. (g) Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006. (h) Zhao, H.; Wei, Y.; Xu, J.; Kan, J.; Su, W.; Hong, M. *J. Org. Chem.* **2011**, *76*, 882. (i) Hu, P.; Zhang, M.; Jie, X.; Su, W. *Angew. Chem., Int. Ed.* **2012**, *51*, 227.

(13) (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082.

(14) (a) Goossen, L. J.; Rudolphi, F.; Oppel, C.; Rodriguez, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 3043. (b) Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7103.

(15) Li, M.-Z.; Wang, C.; Ge, H.-B. *Org. Lett.* **2011**, *13*, 2062.

(16) Wang, H.; Guo, L.-N.; Duan, X.-H. *Org. Lett.* **2012**, *14*, 4358.

(17) (a) Kim, M.; Park, J.; Sharma, S.; Kim, A.; Park, E.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Chem. Commun.* **2013**, 925. (b) Yang, Z.-Y.; Chen, X.; Liu, J.-D.; Gui, Q.-W.; Xie, K.; Li, M.-M.; Tan, Z. *Chem. Commun.* **2013**, 1560.

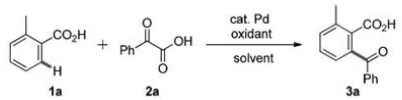
(18) Park, J.; Kim, M.; Sharma, S.; Park, E.; Kim, A.; Lee, S. H.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Chem. Commun.* **2013**, 1654.

(19) Sharma, S.; Kim, A.; Park, E.; Park, J.; Kim, M.; Kwak, J. H.; Lee, S. H.; Jung, Y. H.; Kim, I. S. *Adv. Synth. Catal.* **2013**, *355*, 667.

(20) Pan, C.-D.; Jin, H.-M.; Liu, X.; Cheng, Y.-X.; Zhu, C.-J. *Chem. Commun.* **2013**, 2933.

substrates for the direct decarboxylative acylation. These results support the feasibility of chemoselective decarboxylative cross coupling of benzoic acids with α-oxocarboxylic acids through Pd(II) catalysis under well-defined reaction conditions. It is noteworthy that, although the benzoic acid derivatives have been well studied as the substrates in metal-catalyzed C–H bond activation reactions,[9] direct ortho acylation of the benzoic acids remains a challenge. Furthermore, transition-metal-catalyzed cross coupling of two acids with different roles in the reaction has never been reported. As part of our program to develop novel transition-metal-catalyzed cross coupling reactions with diverse substrates,[8,15,21] we have developed and report herein the synthesis of 2-acylbenzoic acid derivatives through chemoselective decarboxylative cross coupling of benzoic acids with α-oxocarboxylic acids via a palladium-catalyzed C–H bond functionalization process.

Table 1. Optimization of Reaction Conditions[a]

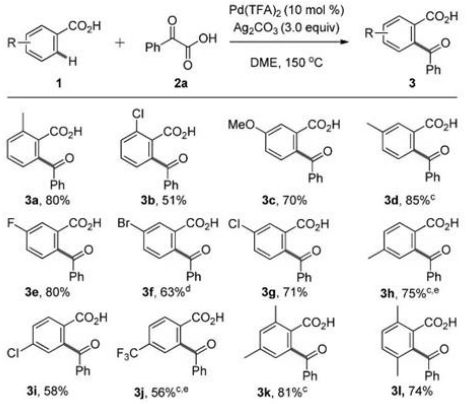


entry	Pd source (amt (mol %))	oxidant (amt (equiv))	solvent	yield (%)[b]
1	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2.0)	DMF	trace
2	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2.0)	THF	trace
3	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2.0)	^{t}BuOH	32
4	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2.0)	dioxane	55
5	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2.0)	DME	58
6	$PdCl_2(PhCN)_2$ (10)	Ag_2CO_3 (2.0)	DME	trace
7	$PdCl_2(MeCN)_2$ (10)	Ag_2CO_3 (2.0)	DME	41
8	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0)	DME	48
9	$Pd(TFA)_2$ (10)	Ag_2O (2.0)	DME	20
10	$Pd(TFA)_2$ (10)	AgOAc (2.0)	DME	38
11	$Pd(TFA)_2$ (10)	$(NH_4)_2S_2O_8$ (2.0)	DME	0
12[c]	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2.0)	DME	60
13	$Pd(TFA)_2$ (10)	Ag_2CO_3 (3.0)	DME	64
14[d]	**$Pd(TFA)_2$ (10)**	**Ag_2CO_3 (3.0)**	**DME**	**80**
15	$Pd(TFA)_2$ (5)	Ag_2CO_3 (3.0)	DME	56
16[d]	$Pd(TFA)_2$ (10)	Ag_2CO_3 (3.0)	dioxane	67

[a] Conditions: **1a** (0.2 mmol), Pd source, oxidants, **2a** (0.6 mmol), 2 mL of solvent, 120 °C, 24 h unless otherwise noted. [b] Isolated yields. [c] 48 h. [d] 150 °C.

Considering that α-oxocarboxylic acid is a potential source of benzoic acid through decarboxylation and oxidation, *o*-methylbenzoic acid was chosen as the substrate for the decarboxylative cross-coupling reaction with α-oxocarboxylic acid in the presence of a catalytic amount of $Pd(TFA)_2$ and an excess of Ag_2CO_3 as the oxidant and the decarboxylation reagent on the basis of our previous reports.[8,21] After an extensive solvent screening, DME and dioxane were shown to be optimal solvents for this coupling, providing the desired product in moderate yields (Table 1, entries 4 and 5). The following survey of catalysts indicated that although $PdCl_2(MeCN)_2$ and $Pd(OAc)_2$ could also catalyze this reaction, $Pd(TFA)_2$ is more effective (entries 7 and 8). Further screening of oxidants showed that silver carbonate was the best choice. Due to our success in the decarboxylation of α-oxocarboxylic acids with a persulfate salt, replacement of Ag_2CO_3 with $K_2S_2O_8$, $Na_2S_2O_8$, and $(NH_4)_2S_2O_8$ was also examined. However, the addition of these persulfate salts led to the decarboxylation of both acids while no desired product was obtained (entry 11). Further optimization of reaction conditions showed that although increasing the reaction time had no apparent effect on this reaction, the yield was significantly improved by increasing the amount of Ag_2CO_3 and raising the reaction temperature (entries 12–14). It was also noted that the coupling product was obtained either with less Pd catalyst or when dioxane was used as the solvent, albeit in lower yields (entries 15 and 16).

Scheme 2. Substrate Scope of Benzoic Acids[a,b]



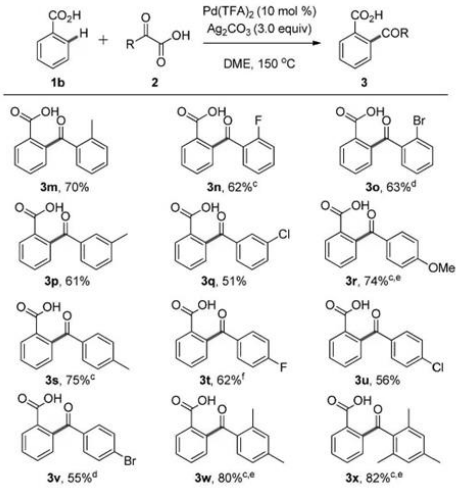
[a] Conditions: **1** (0.2 mmol), $Pd(TFA)_2$ (0.02 mmol), **2a** (0.6 mmol), Ag_2CO_3 (0.6 mmol), 2 mL of DME, 150 °C, 24 h unless otherwise noted. [b] Isolated yields. [c] 165 °C. [d] 130 °C. [e] 48 h.

With the optimized reaction conditions in hand, we then carried out the substrate scope study of substituted benzoic acids. As shown in Scheme 2, this transformation is compatible with electron donating and electron withdrawing group substituted benzoic acids (**3a–j**), while substrates containing electron-donating groups provided higher yields than their electron-withdrawing counterparts, with the exception of **3e**. As expected, halogens (F, Cl, and Br) were tolerated under the current reaction system, allowing the further manipulation of the initial products. Furthermore, good yields were also observed with disubstituted benzoic acids (**3k,l**).

Next, a substrate scope study for the α-oxocarboxylic acids was carried out. As shown in Scheme 3, electron-rich groups (MeO and Me), and halogens (F, Cl, and Br) are compatible with the current reaction conditions (**3m–v**).

(21) Li, M.-Z.; Wang, C.; Fang, P.; Ge, H.-B. *Chem. Commun.* **2011**, *47*, 6587.

Scheme 3. Substrate Scope of α-Oxocarboxylic Acids[a,b]



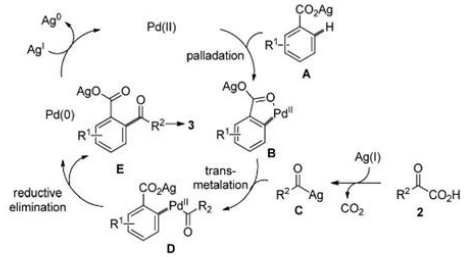
[a] Conditions: **1a** (0.2 mmol), $Pd(TFA)_2$ (0.02 mmol), **2** (0.6 mmol), Ag_2CO_3 (0.6 mmol), 2 mL of DME, 150 °C, 24 h unless otherwise noted. [b] Isolated yields. [c] 165 °C. [d] 130 °C. [e] 48 h. [f] Ag_2CO_3 (0.5 mmol).

Unfortunately, strong electron-withdrawing groups are not well tolerated in the current reaction system. As observed in our previous studies,[8] there is not an apparent steric effect on these substrates (**3n,o**). In contrast, there is a clear electronic effect. Furthermore, the sterically hindered substrate 2,4,6-trimethylbenzoylformic acid also provided the desired product **3x** in high yield.

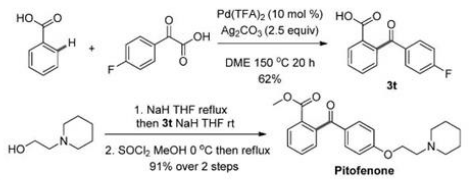
On the basis of the reports from Yu and our laboratory,[8,13,22] a decarboxylative cross-coupling reaction mechanism is proposed (Scheme 4). It is believed that this transformation starts with the palladation of silver benzoate **A** into the Pd(II) intermediate **B**, which then undergoes a transmetalation step with the acylsilver species **C** formed by the silver-mediated decarboxylation of **2**, to generate the Pd(II) intermediate **D**. Reductive elimination of **D** provides the silver salt **E** and Pd(0), which will be reoxidized into Pd(II) by Ag_2CO_3. Protonation of intermediate **E** provides the desired product **3**.

To demonstrate the synthetic utility of this method, it was applied to the synthesis of pitofenone (Scheme 5). Pd(II)-catalyzed direct decarboxylative ortho acylation of benzoic acid with (4-fluorobenzoyl)formic acid provided 2-(4-fluorobenzoyl)benzoic acid (**3t**) in 62% yield. Nucleophilic

Scheme 4. Proposed Reaction Mechanism



Scheme 5. Synthesis of Pitofenone



substitution of **3t** by 1-(2-hydroxyethyl)piperidine, followed by methylation, produced pitofenone in 91% yield over two steps. It is noteworthy that this route also allows the installation of extra substituents on the phenyl rings, which facilitates the medicinal chemistry study of this compound.

In summary, an efficient decarboxylative cross-coupling reaction of benzoic acids with α-oxocarboxylic acids has been developed via a palladium-catalyzed C–H bond functionalization process. This transformation is the first example of direct ortho acylation of benzoic acids. The method provides an efficient access to 2-acylbenzoic acid derivatives. Furthermore, the synthesis of pitofenone was also achieved by employing this transformation as a key step. In comparison with the two reported syntheses,[23] this route provides a more efficient approach to access this compound.

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Supporting Information Available. Text and figures giving experimental details and characterization data for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(22) (a) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676. (b) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654. (c) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460. (d) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137. (e) Engle, K. M.; Thuy-Boun, P. S.; Dang, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 18183.

(23) (a) Fisnerova, L.; Brunova, B. CS 248548, 1987. (b) Staneva, T. D.; Nacheva, E. B.; Lazarov, V. K.; Bacheva, B. L.; Katsarski, D. E. BG 107390, 2004.

Palladium-Catalyzed Decarboxylative Cross-Coupling of α-Oxocarboxylic Acids and Their Derivatives

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Abstract: The development of palladium(II)-catalyzed decarboxylative cross-coupling of α-oxocarboxylic acids and their derivatives is summarized in this account. Acetanilides, 2-phenylpyridines, and benzoic acids were found to be suitable substrates for direct acylation through decarboxylative cross-coupling with α-oxocarboxylic acids. Potassium aryl trifluoroborates were also transformed into ketones, amides, and esters with α-oxocarboxylic acids, oxamic acids, and oxalate monoesters, respectively, in modified catalytic systems.

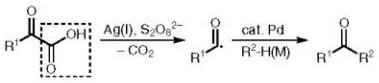
Key words: palladium, catalysis, carboxylic acids, decarboxylation, carbonylation, cross-coupling

1 Introduction

During the last decade, transition-metal-catalyzed decarboxylative cross-coupling has received significant attention because of its environmentally benign properties and its wide applicability in synthetic chemistry.[1] The need to use stoichiometric amounts of organometallic coupling reagents, a major limitation of conventional cross-coupling reactions, is avoided in this case, and toxic metal waste is replaced by harmless carbon dioxide gas. Moreover, carboxylic acids are ideal coupling partners because they are fairly stable, easy to store, and readily available at low cost. Soon after Myers reported the first examples of successful palladium-catalyzed decarboxylative cross-coupling reactions of benzoic acid derivatives with alkenes,[2] various carboxylic acids were found to be efficacious decarboxylation substrates in many different systems. The landmark work in this field was that of Gooßen's group, who developed a palladium/copper-catalyzed decarboxylative cross-coupling reaction of aryl carboxylic acids and aryl halides[3] – an alternative tool for the synthesis of biaryl compounds. Later, the palladium-catalyzed direct arylation of nonactivated arenes with benzoic acids through sp^2 C–H bond functionalization was also demonstrated.[4]

Generally, the decarboxylation of carboxylic acids requires a high reaction temperature, and functional-group tolerance becomes an issue. As a result, it became necessary to develop a more compatible synthetic protocol for practical applications of decarboxylative cross-coupling.

Minisci and co-workers showed that decarboxylation of α-oxocarboxylic acid derivatives to give the corresponding carbonyl radicals could be realized at room temperature in the presence of catalytic amounts of silver species and stoichiometric amounts of persulfate salts.[5] Inspired by this result, we hypothesized that carbonyl radicals formed from α-oxocarboxylic acids might be used as acylating reagents in a palladium(II)-catalyzed cross-coupling that would permit decarboxylative acylation reactions to be performed under mild and convenient conditions (Scheme 1). This account summarizes our recent progress on this subject.



Scheme 1 Proposed decarboxylative cross-coupling reactions

Our studies can be classified into two categories: ligand-directed acylation through C–H bond functionalization and transformation of potassium aryltrifluoroborates into ketones, amides, and esters. In all these processes, α-oxocarboxylic acids and their derivatives are used as coupling partners. First, we performed a direct *ortho*-acylation of acetanilides at ambient temperature. This was followed by the discovery of a direct method for acylation of 2-phenylpyridine and benzoic acids. Finally, potassium aryl trifluoroborates, a class of boronic acid derivatives, were converted into aryl carbonyl compounds by means of the palladium-catalyzed decarboxylative cross-coupling method.

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2 Palladium-Catalyzed Decarboxylative Cross-Coupling Through C–H Bond Functionalization

Aryl ketones are often encountered as important subunits in natural products and bioactive compounds. The first example of the synthesis of aryl ketones through palladium-catalyzed decarboxylative cross-coupling was reported by Gooßen and co-workers, who used aryl halides and α-oxocarboxylic acids as reactants.[6] However, prior functionalization and high reaction temperature are required in this transformation. To overcome these drawbacks, we set out to investigate an unprecedented process for the direct C–H acylation of arenes with α-oxocarboxylic acids.

2.1 Direct *ortho*-Acylation of Acetanilides

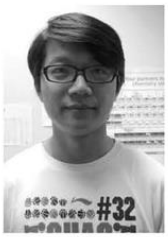
Acetanilides are among the most common substrates for ligand-directed C–H activation cross-coupling, a reaction that has a wide range of applications in synthetic and medicinal chemistry.[7] As a result, considerable efforts have been made to develop methods for the direct *ortho*-functionalization of these compounds, and some significant results have been reported. Importantly, room-temperature palladium-catalyzed direct *ortho*-arylation and olefination have also been demonstrated on acetanilides and their derivatives.[8] We therefore chose acetanilides as the substrates for our initial investigations on direct decarboxylative coupling.[9]

Our early experiments on decarboxylative coupling of acetanilide with oxophenylacetic acid showed that silver was not required for the decarboxylation, and that palladium(II)trifluoroacetate [$Pd(TFA)_2$] was the most efficient catalyst (Table 1). Interestingly, in the absence of persulfate salts, the ketone products were also obtained, albeit with lower yields (Table 1, entries 5 and 6); a palladium species was required for this reaction. This finding implied that palladium might also be involved in the decarboxylation process after palladation. Further studies showed that diglyme was the most efficient solvent (entries 4–9), and that the reaction proceeded well at room temperature, providing the desired product in 93% yield (entry 4).

We then examined the reactivities of various acetanilide derivatives and a series of α-oxocarboxylic acids. As shown in Scheme 2, diverse substituents were tolerated under the optimized conditions. In particular, sterically hindered mesityl(oxo)acetic acid underwent this reaction, whereas this substrate failed in the palladium/copper-catalyzed decarboxylative acylation process.[6] Aliphatic α-oxocarboxylic acids were also found to be compatible with the reaction conditions.

As described above, this decarboxylative cross-coupling can be performed in the absence of persulfate under air, which indicates that it has a different reaction pathway from that of our designed radical-mediated process (Scheme 1). On the basis of a previous report,[10] we proposed the ligand-exchange catalytic cycle shown in Scheme 3. This transformation is believed to be initiated by *ortho*-palladation of the acetanilide, followed by anion exchange with the α-oxocarboxylic acid. Decarboxylation of the intermediate **6** followed by reductive elimination produces the desired aryl ketone product.

Biographical Sketches



Jinmin Miao was born in 1986 in Tianjin, P. R. of China. He received his B.Sc. degree in chemistry from Nankai University in 2009. He is currently a Ph.D. student under the supervision of Professor Haibo Ge at the Department of Chemistry and Chemical Biology, Indiana University – Purdue University Indianapolis (IUPUI). His research is focused on the development of new decarboxylative cross-coupling reactions.

Haibo Ge was born in Yanchen, P. R. of China. He received his Ph.D. degree in medicinal chemistry from The University of Kansas in 2006 with Professor Gunda Georg. He then moved to The Scripps Research Institute for postdoctoral study with Professor Dale Boger. In 2009, he began his independent academic career at the Department of Chemistry and Chemical Biology at Indiana University – Purdue University Indianapolis. Research in his group is mainly focused on the development of novel methods for carbon–carbon and carbon–heteroatom bond formation through transition-metal-catalyzed C–H functionalization. Additionally, his group is working on the synthesis and structure–activity relationship studies of anticancer and antibacterial natural products.

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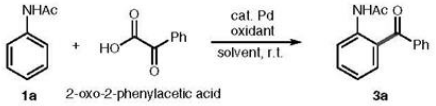
Table 1 Optimization of Conditions for the Acylation of Acetanilide



1a 2-oxo-2-phenylacetic acid **3a**

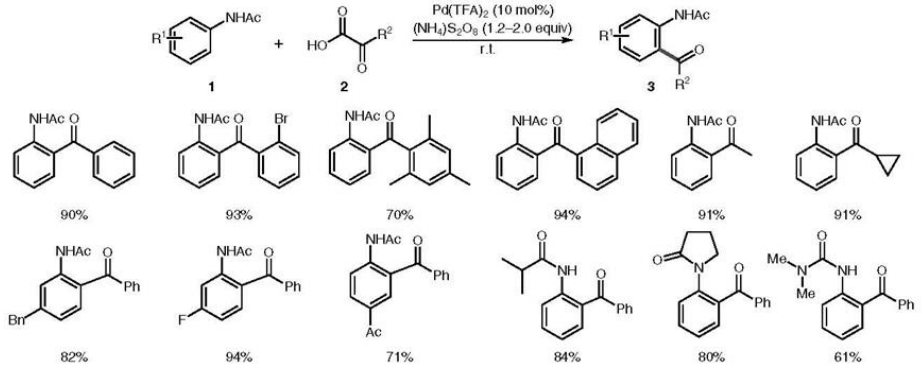
Entry[a]	Catalyst (mol%)	Oxidant (equiv)	Solvent	Yield[b] (%)
1	$Pd(TFA)_2$ (10), $AgNO_3$ (20)	$(NH_4)_2S_2O_8$ (2.0)	CH_2Cl_2	36
2[c]	$Pd(TFA)_2$ (10)	air	CH_2Cl_2	20
3	$Pd(TFA)_2$ (10)	$(NH_4)_2S_2O_8$ (2.0)	DME	82
4	$Pd(TFA)_2$ (10)	$(NH_4)_2S_2O_8$ (2.0)	diglyme	93
5	$Pd(TFA)_2$ (10)	O_2 (1 atm)	diglyme	55
6	$Pd(TFA)_2$ (10)	air	diglyme	52
7	$Pd(TFA)_2$ (10)	$(BzO)_2$	diglyme	61
8	$[Pd(MeCN)_4](BF)_2$ (10)	$(NH_4)_2S_2O_8$ (2.0)	diglyme	87
9[d]	$Pd(TFA)_2$ (5)	$(NH_4)_2S_2O_8$ (2.0)	diglyme	82

[a] *Reaction conditions*: **1a** (0.3 mmol), **2a** (0.6 mmol), catalyst (0.03 mmol), oxidant (0.6 mmol), solvent (3 mL), r.t., 12 h, unless otherwise noted.
[b] Yields and conversions are based on **1a** and were determined by ^1H NMR of the crude product with CH_2Br_2 as the internal standard.
[c] 36 h.
[d] 24 h.

2.2 Direct Acylation of 2-Phenylpyridines

To investigate the generality of this method, we turned our attention to the direct acylation of 2-phenylpyridines. 2-Phenylpyridines are excellent substrates for transition-metal-catalyzed ligand-directed C–H functionalization because of their high stability and because their nitrogen atoms can coordinate strongly with transition metals.[11] Pleasingly, extension of our method to 2-phenylpyridine was successful, and we obtained the desired ketone product under modified reaction conditions (Table 2).[12] In this case, a stoichiometric amount of the silver source was necessary to facilitate decarboxylation of the α-oxocarboxylic acids, and the reactions occurred only at raised temperatures.

Nevertheless, we investigated a diverse range of substrates and we observed similar substituent effects to those found in the acylation of acetanilides (Scheme 4). The yields of the ketones obtained from 2-phenylpyridines were generally lower than the yields of their counterparts obtained from acetanilides. Additionally, aliphatic α-oxocarboxylic acids failed to react, presumably because of



Scheme 2 *ortho*-Acylation of acetanilides and derivatives

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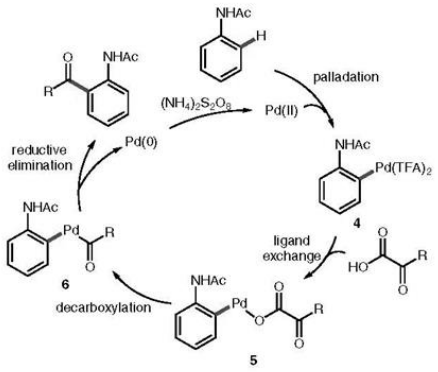
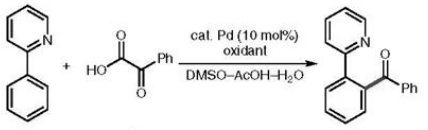


Scheme 3 Proposed catalytic cycle of direct *ortho*-acylation of acetanilide

their poor stability at high reaction temperatures under oxidative conditions.

Because the reactions could be performed with silver oxide or silver carbonate as the sole oxidant, we proposed a different mechanism for the acylation of 2-phenylpyridines (Scheme 5). Silver-mediated decarboxylation of oxo(phenyl)acetic acid provides the acyl silver species **10**, which then undergoes transmetalation with the palladium(II) intermediate **9** to generate intermediate **11**. A reductive elimination reaction of intermediate **11** provides the desired ketone product.

Table 2 Optimization of the Acylation of 2-Phenylpyridine



Entry[a]	Catalyst (mol%)	Oxidant (equiv)	Co-oxidant (equiv)	Yield (%)[b]
1	$Pd(TFA)_2$	Ag_2CO_3 (3.0)	–	61
2	–	Ag_2CO_3 (3.0)	–	0
3	$Pd(TFA)_2$	–	–	0
4	$Pd(OAc)_2$	Ag_2CO_3 (3.0)	–	66
5	$Pd(PhCN)_2Cl_2$	Ag_2CO_3 (3.0)	–	73
6	$Pd(PhCN)_2Cl_2$	Ag_2O (3.0)	–	79
7	$Pd(PhCN)_2Cl_2$	Ag_2O (1.0)	$K_2S_2O_8$ (2.0)	57
8[c]	$Pd(PhCN)_2Cl_2$	Ag_2O (2.0)	$K_2S_2O_8$ (1.0)	84

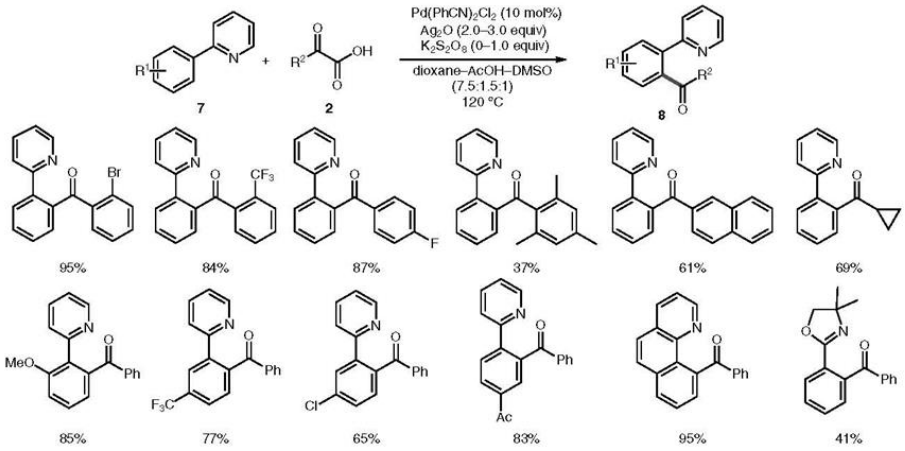
[a] *Reaction conditions*: **7a** (0.3 mmol) **2a** (0.6 mmol), catalyst (10 mol%), Ag(I) salt, co-oxidant, 1,4-dioxane–AcOH–DMSO (7.5:1.5:1, 0.1 M), 120 °C, 16 h unless otherwise noted.

[b] Yields and conversions are based on **1a** and were determined by ^1H NMR of the crude product with CH_2Br_2 as the internal standard.

[c] 12 h.

2.3 Direct *ortho*-Acylation of Benzoic Acids

After performing the investigations described above, we devoted our efforts to a more challenging process: the chemoselective decarboxylative cross-coupling of benzo-



Scheme 4 Acylation of 2-phenylpyridines and derivatives

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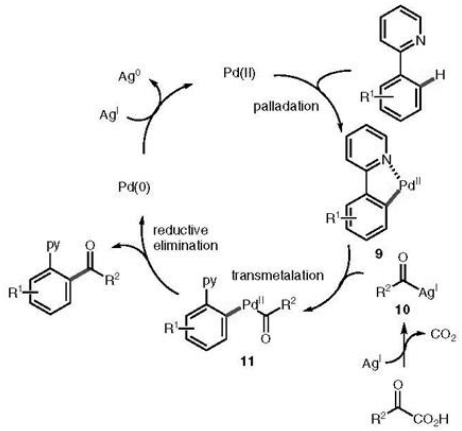
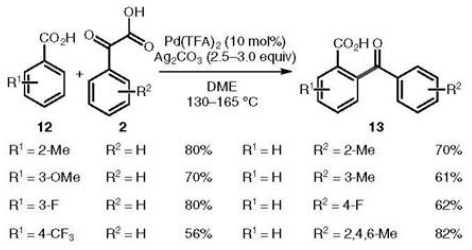
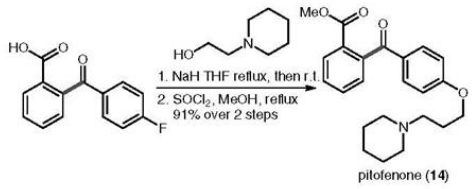


Scheme 5 Proposed catalytic cycle for direct acylation of 2-phenylpyridines



Scheme 6 *ortho*-Acylation of benzoic acids



Scheme 7 Synthesis of pitofenone

ic acids with α–oxocarboxylic acids. 2-Benzoylbenzoic acid derivatives are frequently encountered as subunits of natural products, pharmaceuticals, and agrochemical compounds.[13] However, conventional routes for synthesizing these compounds are far from efficient. The most common methods are nucleophilic addition–elimination of 2-benzofuran-1,3-dione derivatives with organometallic reagents,[14] and Friedel–Crafts acylation reactions of these compounds.[15] However, all these transformations suffer from poor regioselectivity on the benzofurandione.

As mentioned previously, Gooßen and others used benzoic acid derivatives for syntheses of biaryls through the palladium/copper-catalyzed decarboxylative cross-coupling with phenyl halides. Benzoic acids have also been demonstrated by Yu and others[16] to be effective substrates for palladium-catalyzed ligand-directed *ortho* C–H functionalization with various coupling partners. Specifically, it was noted that *ortho*-acylated benzoic acids are fairly stable and tolerate high temperatures in the presence of silver.[16a,b,d] We therefore believed that chemoselective decarboxylative cross-coupling of benzoic acids with α-oxocarboxylic acids might be viable, and we conducted the appropriate research.[17] To our delight, after systematic screening of the reaction conditions, we found that this reaction proceeded well with palladium(II) trifluoroacetate as the catalyst and silver carbonate as the oxidant. Interestingly, replacement of silver carbonate with a persulfate salt also provided the desired products, albeit in lower yields. A study of the substrate scope showed that electron-donating groups and halogens on the phenyl rings were compatible with the oxidative reaction conditions (Scheme 6), but, unsurprisingly, aliphatic α-oxocarboxylic acids were incompatible with the reaction system.

To demonstrate the application of the coupling reactions, we synthesized pitofenone (**14**), a key ingredient of Spasmalgon,[18] from the ketone produced from (4-fluorophenyl)(oxo)acetic acid (Scheme 7).

In addition to the studies described above, other groups have reported decarboxylative cross-coupling reactions of α-oxocarboxylic acids with other aromatic or nonaromatic substrates (Figure 1). Cyclic enamides **15**,[19] *O*-methyl oximes **16**,[20] phenylacetamides **17**,[21] *O*-phenyl carbamates **18**,[22] and 1-(pyrimidin-2-yl)-1*H*-indoles **19**[23] were found to be feasible starting materials, further broadening the substrate scope and the product diversity.

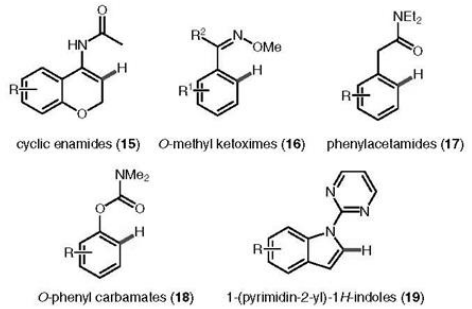


Figure 1 Other substrates for the decarboxylative acylation

3 Transformation of Potassium Aryl Trifluoroborates into Ketones, Esters, and Amides

Direct decarboxylative cross-coupling of arenes through palladium(II)-catalyzed C–H activation provides an effi-

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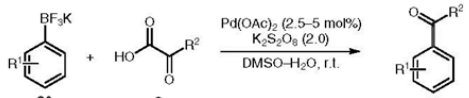
cient approach for the construction of C–C bonds; however, the need to use directing groups restricts the substrate scope. Whereas this limitation does not apply to palladium(0)-catalyzed decarboxylative cross-coupling of aryl halides, harsh reaction conditions are typically required in these reactions, and therefore functional-group tolerance becomes a problem. As a result of our success in decarboxylative acylation of arenes at room temperature, we decided to explore decarboxylative cross-couplings of potassium aryl trifluoroborates with commercially available or readily accessible α-oxocarboxylic, oxamic, and oxalic acids under mild conditions. Boronic acids and derivatives have become a highly useful and effective groups of substrates for transition-metal-catalyzed cross-coupling reactions.[24] Their low toxicity and high activity distinguish them from other common metal-based reactants for coupling reactions. Because of their greater stability, potassium aryl trifluoroborates are considered to be highly valuable alternatives to boronic acids.[25] In the presence of water, boronic acids can be generated in situ from aryl trifluoroborates, and therefore the potential homocoupling of boronic acids can be prevented.

3.1 Formation of Aryl Ketones from Potassium Aryl Trifluoroborates

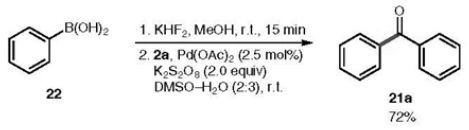
First, we investigated the decarboxylative cross-coupling of potassium aryl Trifluoroborates with α-oxocarboxylic acids.[26] As shown in Scheme 8, the reactions were realized in the presence of 2.5–5 mol% of palladium(II) acetate and 2.0 equivalents of potassium persulfate in a mixture of dimethyl sulfoxide and water at room temperature. It should be mentioned that the presence of water is essential for the generation of active organoboron species from potassium aryl trifluoroborates. A wide range of diversely substituted potassium aryl trifluoroborates **20** and various α-oxocarboxylic acids **2** were studied. With respect to the potassium aryl trifluoroborates **20**, both electron-donating substituents, such as methyl or methoxy, and electron-withdrawing substituents, such as halogens, acetyl, or trifluoromethyl, were well tolerated. With respect to the oxo(aryl)acetic acid **2**, electron-donating groups and halo groups were well tolerated. Furthermore, aliphatic α-oxocarboxylic acids were also compatible with this reaction system.



R^1 = 2-Me	R^2 = Ph	69%	R^1 = H	R^2 = Et	73%
R^1 = 3-Ac	R^2 = Ph	83%	R^1 = H	R^2 = *i*-Pr	83%
R^1 = 4-Cl	R^2 = Ph	90%	R^1 = H	R^2 = cyclopentyl	90%
R^1 = H	R^2 = 2,4,6-$Me_3C_6H_2$	70%	R^1 = H	R^2 = 2-Naph	78%

Scheme 8 Acylation of potassium aryl trifluoroborates

It is noteworthy that a one-pot synthesis of benzophenone (**21a**) from phenylboronic acid (**22**) could also be carried out (Scheme 9). Potassium trifluorophenylborate prepared from phenylboronic acid (**22**) reacted directly with oxo(phenyl)acetic acid (**2a**) to give benzophenone (**21a**) in 72% yield

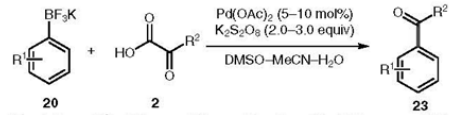


Scheme 9 One-pot synthesis of benzophenone from phenylboronic acid

3.2 Preparation of Aryl Amides and Esters from Potassium Aryl Trifluoroborates

In 2009, Liu and co-workers reported a decarboxylative cross-coupling of aryl halides with oxalate monoesters to give the corresponding esters.[27] Encouraged by these results, we developed a novel pathway for the synthesis of aryl amides and esters from potassium aryl trifluoroborates and oxamic acids or oxalate monoesters, respectively.[28]

During our investigation, we realized that higher temperatures significantly accelerate the decarboxylation of oxamic acids and oxalate monoesters. The reactions of a wide range of oxamic acids **2** with potassium aryl trifluoroborates **20** were investigated under the optimized conditions (Scheme 10). As expected, the reaction had very good generality with respect to the substrates. Both *N*-mono and *N*,*N*-disubstituted aryl amides **23** could be synthesized in moderate to good yields. However, *ortho*-substituted potassium aryl trifluoroborates **20** did not undergo this reaction, possibly as a result of high steric hindrance. Notably, benzoate esters could be synthesized from potassium trifluoro(phenyl)borate and potassium methoxy(oxo)acetate or potassium ethoxy(oxo)acetate under the adjusted conditions. Generally, oxamic acids and oxalate monoesters were less effective in this decarboxylative coupling than were their counterparts in the formation of ketones.



R^1 = 2-Me	R^2 = NEt_2	0%	R^1 = H	R^2 = N*i*-Pr_2	76%
R^1 = 3-Me	R^2 = NEt_2	86%	R^1 = H	R^2 = 1-piperidinyl	82%
R^1 = 4-Br	R^2 = NEt_2	83%	R^1 = H	R^2 = NHCy	75%
R^1 = 4-Ac	R^2 = NEt_2	46%	R^1 = H	R^2 = NHBn	71%
R^1 = H	R^2 = OEt	82%[1]	R^1 = H	R^2 = OMe	76%[1]

Scheme 10 Synthesis of aryl amides and esters from potassium aryl trifluoroborates

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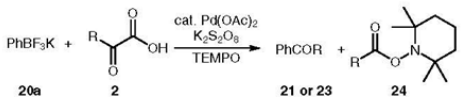
3.3 Mechanistic Studies

In the above studies, it was noticed that a persulfate salt was required for the reactions to proceed. We therefore concluded that these reactions proceed either through the ligand exchange–decarboxylation process shown in Scheme 3 or through a radical-mediated process. To gain some insight into the mechanism, we introduced (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO) into the reaction system as a radical-trapping reagent (Scheme 11), and we found that the coupling reactions were markedly suppressed by the addition of TEMPO. Furthermore, carbonyl–TEMPO adducts **24** were also isolated.



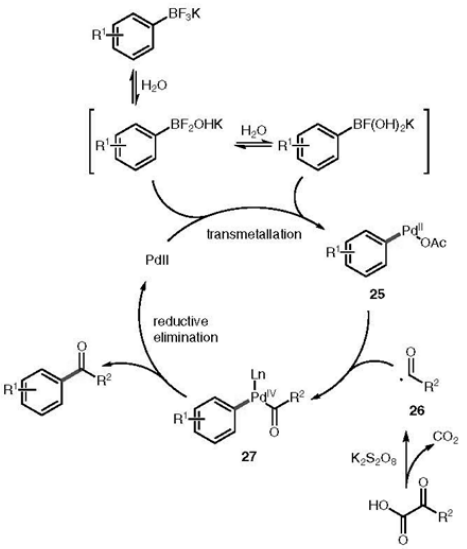
TEMPO	R = Ph	R = NEt$_2$
1.0 equiv	56%	51%
2.0 equiv	35%	26%
3.0 equiv	29%	22%

Scheme 11 Decarboxylative cross-coupling of potassium aryl(trifluoro)borates in the presence of TEMPO

On the basis of these results and previous reports in the literature,[7a,11a,g,29] we proposed the palladium(II)–palladium(IV) catalytic cycle shown in Scheme 12. Carbonyl radical **26**, formed by decarboxylation of the α-oxocarboxylic acid derivative in the presence of potassium persulfate, reacts with the palladium(II) intermediate **25** to give the palladium(IV) intermediate **27**. The subsequent reductive elimination reaction of **27** gives the desired product. It should be mentioned that the formation of a bimetallic palladium(III) species from the palladium(II) species **25** and the radical species **26** cannot be ruled out.

4 Conclusions and Outlook

In conclusion, we have developed a novel approach for the direct acylation of aromatic sp^2 C–H bonds through palladium(II)-catalyzed decarboxylative cross-coupling with α-oxocarboxylic acids. Two reaction pathways involving a palladium(II)–palladium(0) cycle were proposed. With this method, a number of aryl ketones were efficiently synthesized. In addition, potassium aryl trifluoroborates were used in palladium(II)-catalyzed decarboxylative cross-coupling reactions as precursors to aryl ketones, amides, and esters under mild conditions. In this case, a catalytic palladium(II)–palladium(IV) cycle was proposed. Our current studies aim to realize direct acylation of sp^3 C–H bonds, which will expand the scope of cross-coupling reactions.



Scheme 12 Proposed mechanism for the cross-coupling of potassium aryl trifluoroborates with α-oxocarboxylic acids

Acknowledgment

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References

(1) For recent reviews, see: (a) Baudoin, O. *Angew. Chem. Int. Ed.* **2007**, *46*, 1373. (b) Gooßen, L. J.; Gooßen, K.; Rodríguez, N.; Blanchot, M.; Linder, C.; Zimmermann, B. *Pure Appl. Chem.* **2008**, *80*, 1725. (c) Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3100. (d) Gooßen, L. J.; Collet, F.; Gooßen, K. *Isr. J. Chem.* **2010**, *50*, 617. (e) Bonesi, S. M.; Fagnoni, M. *Chem. Eur. J.* **2010**, *16*, 13572. (f) Rodríguez, N.; Gooßen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030. (g) Shang, R.; Liu, L. *Sci. China: Chem.* **2011**, *54*, 1670. (h) Cornella, J.; Larrosa, I. *Synthesis* **2012**, *44*, 653.

(2) Myers, A. G.; Tanaka, D.; Mannion, R. *J. Am. Chem. Soc.* **2002**, *124*, 11250.

(3) (a) Gooßen, L. J.; Deng, G. J.; Levy, L. M. *Science* **2006**, *313*, 662. (b) Gooßen, L. J.; Rodríguez, N.; Melzer, B.; Linder, C.; Deng, G. J.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824.

(4) (a) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312. (b) Hu, P.; Kan, J.; Su, W.-P.; Hong, M.-C. *Org. Lett.* **2009**, *11*, 2341. (c) Yu, W.-Y.; Sit, W. N.; Zhou, Z.; Chan, A. S.-C. *Org. Lett.* **2009**, *11*, 3174. (d) Wei, Y.; Kan, J.; Wang, M.; Su, W.-P.; Hong, M.-C. *Org. Lett.* **2009**, *11*, 3346. (e) Cornella, J.; Lu, P. F.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506. (f) Wang, C. Y.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (g) Zhang, F. Z.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2010**, *49*, 2768. (h) Zhou, J.; Hu, P.; Zhang, M.; Huang, S.; Wang, M.; Su,

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W. *Chem. Eur. J.* **2010**, *16*, 5876. (i) Xie, K.; Yang, Z.; Zhou, X.; Li, X.; Wang, S.; Tan, Z.; An, X.; Guo, C.-C. *Org. Lett.* **2010**, *12*, 1564. (j) Zhao, H.-Q.; Wei, Y.; Xu, J.; Kan, J.; Su, W.-P.; Hong, M.-C. *J. Org. Chem.* **2011**, *76*, 882. (k) Hu, P.; Zhang, M.; Jie, X.-M.; Su, W.-P. *Angew. Chem. Int. Ed.* **2012**, *51*, 227. (l) Hu, P.; Shang, Y.-P.; Su, W.-P. *Angew. Chem. Int. Ed.* **2012**, *51*, 5945.

(5) (a) Minisci, F.; Citterio, A.; Giordano, C. *Acc. Chem. Res.* **1983**, *16*, 27. (b) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489. (c) Fontana, F.; Minisci, F.; Barbosa, M. C. N.; Vismara, E. *J. Org. Chem.* **1991**, *56*, 2866. (d) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991. (e) Punta, C.; Minisci, F. *Trends Heterocycl. Chem.* **2008**, *13*, 1.

(6) (a) Gooßen, L. J.; Rudolphi, F.; Oppel, C.; Rodriguez, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 3043. (b) Gooßen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 7103. (c) Gooßen, L. J.; Zimmermann, B.; Linder, C.; Rodriguez, N.; Lange, P. P.; Hartung, J. *Adv. Synth. Catal.* **2009**, *351*, 2667.

(7) (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (b) Daugulis, O.; Zaitsev, V. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4046. (c) Wan, X.-B.; Ma, Z.-X.; Li, B.-J.; Zhang, K.; Cao, S.-K.; Zhang, S.-W.; Shi, Z.-J. *J. Am. Chem. Soc.* **2006**, *128*, 7416. (d) Yang, S.-D.; Li, B.-J.; Wan, X.-B.; Shi, Z.-J. *J. Am. Chem. Soc.* **2007**, *129*, 6066. (e) Shi, Z.-J.; Li, B.-J.; Wan, X.-B.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.-M.; Wang, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 5554. (f) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066. (g) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 1115. (h) Wang, G.-W.; Yuan, T.-T.; Wu, X.-L. *J. Org. Chem.* **2008**, *73*, 4717. (i) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250. (j) Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 686. (k) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 5524.

(8) (a) Nishikata, T.; Abela, A. R.; Huang, S.-L.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 4978. (b) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 1972.

(9) Fang, P.; Li, M.-Z.; Ge, H.-B. *J. Am. Chem. Soc.* **2010**, *132*, 11898.

(10) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 68.

(11) (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657. (c) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (d) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (e) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (f) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (g) Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z.-Y.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304. (h) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234. (i) Xiao, F.-H.; Shuai, Q.; Zhao, F.; Basle, O.; Deng, G.-J.; Li, C.-J. *Org. Lett.* **2011**, *13*, 1614. (j) Zhou, W.; Li, H.-J.; Wang, L. *Org. Lett.* **2012**, *14*, 4594. (k) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050; see also ref. 4a.

(12) Li, M.-Z.; Ge, H.-B. *Org. Lett.* **2010**, *12*, 3464.

(13) (a) Sexton, W. A.; Templeman, W. G. *Nature* **1948**, *141*, 974. (b) Evans, D.; Cracknell, M. E.; Saunders, J. C.; Smith, C. E.; Williamson, W. R. N.; Dawson, W.; Sweatman, W. J. F. *J. Med. Chem.* **1987**, *30*, 1321. (c) Gapinski, D. M.; Mallett, B. E.; Froelich, L. L.; Jackson, W. T. *J. Med. Chem.* **1990**, *33*, 2798. (d) Wyss, D. F.; Arasappan, A.; Senior, M. M.; Wang, Y.-S.; Beyer, B. M.; Njoroge, F. G.; McCoy, M. A. *J. Med. Chem.* **2004**, *47*, 2486. (e) Gobec, S.; Brožič, P.; Rižner, T. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5170.

(14) (a) Fieser, L. F.; Hershberg, E. B. *J. Am. Chem. Soc.* **1937**, *59*, 2331. (b) Newman, M. S.; Muth, C. W. *J. Am. Chem. Soc.* **1950**, *72*, 5191. (c) LaBudde, J. A.; Heidelberger, C. *J. Am. Chem. Soc.* **1958**, *80*, 1225. (d) Seo, S.; Slater, M.; Greaney, M. F. *Org. Lett.* **2012**, *14*, 2650.

(15) (a) Newman, M. S.; Scheurer, P. G. *J. Am. Chem. Soc.* **1956**, *78*, 5004. (b) Reinheckel, H. A.; Haage, K. *Angew. Chem. Int. Ed.* **1966**, *5*, 511. (c) Watson, A. F.; Liu, J.-F.; Bennaceur, K.; Drummond, C. J.; Endicott, J. A.; Golding, B. T.; Griffin, R. J.; Haggerty, K.; Lu, X.-H.; McDonnell, J. M.; Newell, D. R.; Noble, M. E. M.; Revill, C. H.; Riedinger, C.; Xu, Q.; Zhao, Y.; Lunec, J.; Hardcastle, I. R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5916. (d) Wang, X.; Li, J.-Z.; Zhao, N.; Wan, X.-B. *Org. Lett.* **2011**, *13*, 709. (e) Yu, H.-B.; Xiao, Y.; Guo, H.-Y. *Org. Lett.* **2012**, *14*, 2014.

(16) (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (c) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 5215. (d) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082. (e) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676.

(17) Miao, J.-M.; Ge, H.-B. *Org. Lett.* **2013**, *15*, 2930.

(18) Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Moritani, Y.; Saruta, K.; Higashijima, T.; Kotera, J.; Takagi, M.; Kikkawa, K.; Omori, K. *J. Med. Chem.* **2001**, *44*, 2204.

(19) Wang, H.; Guo, L.-N.; Duan, X.-H. *Org. Lett.* **2012**, *14*, 4358.

(20) (a) Kim, M.; Park, J.; Sharma, S.; Kim, A.; Park, E.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Chem. Commun.* **2013**, *49*, 925. (b) Yang, Z.-Y.; Chen, X.; Liu, J.-D.; Gui, Q.-W.; Xie, K.; Li, M.-M.; Tan, Z. *Chem. Commun.* **2013**, *49*, 1560.

(21) Park, J.; Kim, M.; Sharma, S.; Park, E.; Kim, A.; Lee, S. H.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Chem. Commun.* **2013**, *49*, 1654.

(22) Sharma, S.; Kim, A.; Park, E.; Park, J.; Kim, M.; Kwak, J. H.; Lee, S. H.; Jung, Y. H.; Kim, I. S. *Adv. Synth. Catal.* **2013**, *355*, 667.

(23) Pan, C.-D.; Jin, H.-M.; Liu, X.; Cheng, Y.-X.; Zhu, C.-J. *Chem. Commun.* **2013**, *49*, 2933.

(24) For recent reviews, see: (a) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419. (b) Baudoin, O. *Eur. J. Org. Chem.* **2005**, 4223. (c) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609. (d) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535. (e) Tobisu, M.; Chatani, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 3565. (f) Molander, G. A.; Canturk, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 9240. (g) Miyaura, N. *Synlett* **2009**, 2039. (h) Knappke, C. E. I.; von Wangelin, A. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 3568. (i) Suzuki, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6722. (j) Heravi, M. M.; Hashemi, E. *Tetrahedron* **2012**, *68*, 9145. (k) Blangetti, M.; Rosso, H.; Prandi, C.; Deagostino, A.; Venturello, P. *Molecules* **2013**, *18*, 1188.

(25) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.

(26) Li, M.-Z.; Wang, C.; Ge, H.-B. *Org. Lett.* **2011**, *13*, 2062.

(27) Shang, R.; Fu, Y.; Li, J. B.; Zhang, S. L.; Guo, Q. X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 5738.

(28) Li, M.-Z.; Wang, C.; Fang, P.; Ge, H.-B. *Chem. Commun.* **2011**, *47*, 6587.

(29) (a) Dick, A. R.; Kampf, J.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790. (b) Tong, X.; Beller, M.; Tse, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 4906. (c) Welbes, L. L.;

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Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836. (d) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945. (e) Wang, G.-W.; Yuan, T.-T. *J. Org. Chem.* **2010**, *75*, 476. (f) Lysons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (g) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936.

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Rhodium-catalyzed direct synthesis of unprotected NH-sulfoximines from sulfoxides†

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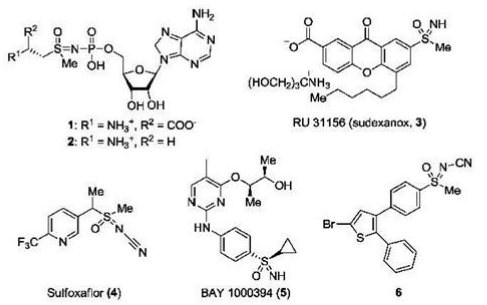
A novel rhodium-catalyzed imination of sulfoxides using *O*-(2,4-dinitrophenyl)hydroxylamine is developed under mild conditions with good functional group tolerance. This method provides an efficient access to free NH-sulfoximines, an important structural unit in a variety of biologically active compounds.

Sulfoximines have recently attracted great attention in biochemistry and medicinal chemistry because of their versatile chemical properties and diverse bioactivities.[1] Since the discovery of the first sulfoximine, methionine sulfoximine, a number of bioactive compounds containing a sulfoximine moiety in the pharmacophore have been reported (Scheme 1). For example, compounds **1** and **2** are transition-state-analogue inhibitors of L-asparagine synthetase;[2] sudexanox (RU31156, **3**) was selected for clinical studies as a prophylactic antiasthmatic;[3] sulfoxaflor (**4**) is the first commercially available sulfoximine insecticide;[4] Bay 1000394 (**5**) is an excellent cyclin-dependent kinase inhibitor, which is currently being evaluated in a Phase I clinical trial for activity against advanced solid tumors;[5] and finally, one of the enantiomers of **6** shows good anti-proliferative activity against various cancer cell lines.[6]



Scheme 1 Bioactive sulfoximines.

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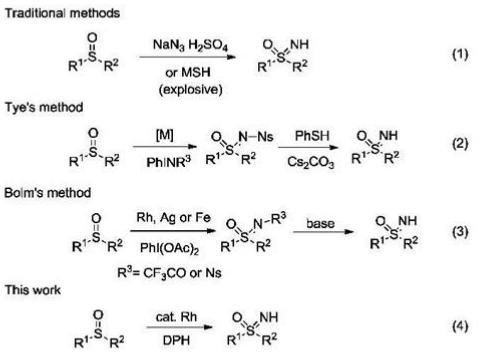
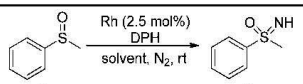
† Electronic supplementary information (ESI) available: Experimental details and spectral data. See DOI: 10.1039/c4cc04349a

Among the small number of synthetic strategies for preparing sulfoximines, the most straightforward approach employs direct imination of sulfoxides (Scheme 2). However, traditional methods require the use of either toxic or potentially explosive reagents, such as a combination of NaN_3 and sulfuric acid,[7] or *O*-mesitylene sulfonylhydroxylamine (MSH) (eqn (1)).[8] To overcome these drawbacks, considerable efforts have been devoted to developing transition metal-catalyzed sulfoxide imination, with significant progress being achieved in recent years.[9] For example, Tye reported the synthesis of sulfoximines by copper-catalyzed imination of sulfoxides with PhI=NNs (Ns = *para*-nitrobenzenesulfonyl) and PhI=NSes (Ses = trimethylsilylethylsulfonyl) (eqn (2));[9f] Bolm discovered that this process could be efficiently performed *via* rhodium,[9h] silver,[9i] or iron[9l,m] catalysis using iminoiodinanes generated *in situ* from the oxidation of amides by $PhI(OAc)_2$ (eqn (3)). In spite of this powerful approach, the transition



Scheme 2 Preparation of unprotected NH-sulfoximines.

Table 1 Optimization of reaction conditions[a]



Entry	Rh catalyst	Eq. of DPH	Solvent	Yield[b] (%)
1	$Rh_2(esp)_2$	1.5	TFE	61
2	$Rh_2(esp)_2$	1.5	MeOH	32
3	$Rh_2(esp)_2$	1.5	MeCN	48
4	$Rh_2(esp)_2$	1.5	^{n}PrCN	44
5	$Rh_2(esp)_2$	1.5	PhCN	42
6	$Rh_2(esp)_2$	1.5	EtOH	30
7	$Rh_2(esp)_2$	1.5	^{i}PrOH	22
8	$Rh_2(esp)_2$	1.5	^{t}BuOH	trace
9	$Rh_2(esp)_2$	1.5	HFIP	39
10	$Rh_2(esp)_2$	1.5	DCM	12
11	$Rh_2(OAc)_4$	1.5	TFE	23
12	$Rh_2(TFA)_4$	1.5	TFE	trace
13	$Rh(PPh_3)_3Cl$	1.5	TFE	0
14	$Rh_2(oct)_4$	1.5	TFE	0
15[c]	$Rh_2(esp)_2$	1.5	TFE	50
16[d]	$Rh_2(esp)_2$	1.5	TFE	60
17	$Rh_2(esp)_2$	1.0	TFE	48
18	$Rh_2(esp)_2$	2.0	TFE	72
19	$Rh_2(esp)_2$	3.0	TFE	78

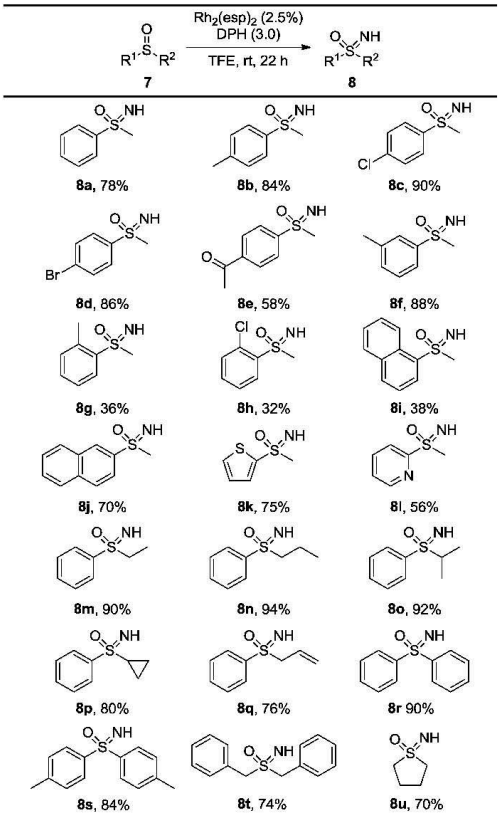
[a] Reactions were conducted on a 0.3 mmol scale. Conditions: **7a** (0.3 mmol), Rh catalyst (2.5 mol%), DPH (1–3 eq.), 3 ml of solvent, room temperature, N_2 atmosphere, 22 h unless otherwise noted. [b] Isolated yields. [c] 40 °C. [d] 0 °C. DPH = *O*-(2,4-dinitrophenyl)hydroxylamine. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate. TFE = 2,2,2-tifluoroethanol. HFIP = hexafluoroisopropanol.

metal-catalyzed imination of sulfoxides gives protected sulfoximines, requiring an additional step for the removal of the undesired protecting group. Inspired by a recent report by Kürti and co-workers describing the rhodium-catalyzed synthesis of unprotected NH-aziridines from olefins using *O*-(2,4-dinitrophenyl)-hydroxylamine (DPH),[10] we have developed the first transition metal-catalyzed *direct* synthesis of free NH-sulfoximines from sulfoxides under mild conditions (eqn (4)).

Our investigation began with direct imination of phenyl methyl sulfoxide using 1.5 equiv. of *O*-(2,4-dinitrophenyl)-hydroxylamine (DPH) in the presence of 2.5 mol% of $Rh_2(esp)_2$ at room temperature. After screening a large number of solvents, trifluoroethanol (TFE) was found to be optimal, giving the desired free NH-sulfoximine product **2a** in 61% yield (Table 1, entry 1). Further screening of Rh(II) catalysts revealed that this process could also be catalyzed by $Rh_2(OAc)_4$, albeit with lower efficiency (entry 11). Additionally, Rh(I) did not show catalytic activity in the imination reaction (entry 13).[10] Finally, using an increased amount of DPH gave an optimal yield for the imination reaction (entry 19).

With optimized conditions in hand, we evaluated the generality of the method using a variety of sulfoxides as substrates (Table 2). As expected, functional groups such as methyl, halogens (Cl and Br), or an acyl group on the phenyl ring were well tolerated (**8a–8h**). Not surprisingly, the *para*-acyl substituted sulfoxide led to a lower yield, perhaps as a result of the electron-withdrawing effect of the acyl group acting to decrease the reactivity of sulfoxide (**8e**). Furthermore, an apparent steric effect was observed in the imination reaction because significantly lower

Table 2 Substrate scope



Reactions were conducted on a 0.3 mmol scale. Conditions: **7** (0.3 mmol), $Rh_2(esp)_2$ (0.0075 mmol, 2.5 mol%), DPH (0.9 mmol, 3.0 eq.), TFE (3 ml, 0.1 M), room temperature, N_2 atmosphere, 22 h.

yields were observed with sulfoxides bearing a substituent at the *ortho* position of the phenyl ring (**8g** and **8h**). However, the nature of the aryl sulfoxides was not limited to the phenyl ring, and naphthyl, electron-rich 2-thiophenyl, and electron-deficient 2-pyridyl methyl sulfoxides were also found to be effective substrates for the Rh(II)-catalyzed imination reaction (**8i–8l**). On the other hand, 1-naphthanyl and 2-pyridyl methyl sulfoxides provided only modest yields, presumably due to steric and electronic factors, respectively (**8i** and **8l**). In an important observation for the preparation of sulfoximine-based small molecules, the methyl group on the phenyl methyl sulfoxide could be successfully replaced by other alkyl groups, including the cyclopropyl group, to afford the corresponding sulfoximines in high yields (**8m–8p**). Interestingly, when phenyl allyl sulfoxide was employed in the reaction, selective sulfoximination was favoured over aziridination (**8q**).[10]

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In addition, diaryl sulfoximines could be effectively prepared by this method from the corresponding sulfoxides (**8r** and **8s**), and we were pleased to find that both acyclic and cyclic dialkyl sulfoxides were compatible with this reaction (**8t** and **8u**).

Although the reaction mechanism of this transformation has not been investigated, it is likely that a rhodium–nitrene species is an intermediate based on prior literature reports.[9h,10,11] Thus, coordination of DPH to $Rh_2(esp)_2$, followed by loss of dinitrophenol, likely generates a reactive nitrene intermediate, which then oxidizes the metal-coordinated sulfoxide to the corresponding sulfoximine.

In summary, a novel, efficient, and safe method for the preparation of free NH-sulfoximines has been developed *via* rhodium-catalyzed imination of sulfoxides using *O*-(2,4-dinitrophenyl)hydroxylamine. This new approach features mild conditions and good functional group tolerance, which should permit its application to the synthesis of structurally complex sulfoximines with agrochemical and clinical utility.[1g]

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Notes and references

1 For reviews on the synthesis and application of sulfoximines, see: (*a*) C. R. Johnson, *Aldrichimica Acta*, 1985, **18**, 3; (*b*) S. G. Pyne, *Sulfur Rep.*, 1992, **12**, 57; (*c*) C. Worch, A. C. Mayer and C. Bolm, in *Organosulfur Chemistry in Asymmetric Synthesis*, ed. T. Toru and C. Bolm, Wiley-VCH, Weinheim, 2008, 209; (*d*) M. Reggelin and C. Zur, *Synthesis*, 2000, 1; (*e*) F. Chemla, *J. Chem. Soc., Perkin Trans. 1*, 2002, 275; (*f*) H. Okamura and C. Bolm, *Chem. Lett.*, 2004, **33**, 482; (*g*) U. Lucking, *Angew. Chem., Int. Ed.*, 2013, **52**, 9399; (*h*) V. Bizet, R. Kowalczykb and C. Bolm, *Chem. Soc. Rev.*, 2014, **43**, 2426.

2 (*a*) H. Ikeuchi, Y.-M. Ahn, T. Otokawa, B. Watanabe, L. Hegazy, J. Hiratake and N. G. J. Richards, *Bioorg. Med. Chem.*, 2012, **20**, 5915; (*b*) J. A. Gutierrez, Y.-X. Pan, L. Koroniak, J. Hiratake, M. S. Kilberg and N. G. J. Richards, *Chem. Biol.*, 2006, **13**, 1339; (*c*) H. Ikeuchi, M. E. Meyer, Y. Ding, J. Hiratake and N. G. J. Richards, *Bioorg. Med. Chem.*, 2009, **17**, 6641; (*d*) N. G. J. Richards and M. S. Kilberg, *Annu. Rev. Biochem.*, 2006, **75**, 629.

3 P. Miller and G. W. L. James, *Arch. Int. Pharmacodyn. Ther.*, 1978, **231**, 328.

4 (*a*) Y. Zhu, M. R. Loso, G. B. Watscon, T. C. Sparks, R. B. Rogers, J. X. Huang, B. C. Gerwick, J. M. Babcock, D. Kelley, V. B. Hedge, B. M. Nugent, J. M. Renga, I. Denholm, K. Gorman, G. J. DeBoer, J. Hasler, T. Meade and J. D. Thomas, *J. Agric. Food Chem.*, 2011, **59**, 2950; (*b*) J. M. Babcock, C. B. Gerwick, J. X. Huang, M. R. Loso, G. Nakamura, C. P. Nolting, R. B. Rogers, T. C. Sparks, J. Thomas, G. B. Watson and Y. Zhu, *Pest Manage. Sci.*, 2011, **67**, 328; (*c*) G. B. Watson, M. R. Loso, J. M. Babcock, J. M. Hasler, T. J. Letherer, C. D. Young, Y. Zhu, J. E. Casida and T. C. Sparks, *Insect Biochem. Mol. Biol.*, 2011, **41**, 432.

5 (*a*) U. Lucking, G. Siemeister, P. Lienau, R. Jautelat and J. Schulze, EP 2179991, 2010; (*b*) U. Lucking, R. Jautelat, M. Kruger, T. Brumby, P. Lienau, M. Schafer, H. Briem, J. Schulze, A. Hillisch, A. Reichel and G. Siemeister, *ChemMedChem*, 2013, **8**, 1021.

6 S. J. Park, H. Baars, S. Mersmann, H. Buschmann, J. M. Baron, P. M. Amann, K. Czaja, H. Hollert, K. Bluhm, R. Redelstein and C. Bolm, *ChemMedChem*, 2013, **8**, 217.

7 (*a*) H. R. Bentley and J. K. Whitehead, *J. Chem. Soc.*, 1952, 1572; (*b*) C. R. Johnson, M. Haake and C. W. Schroeck, *J. Am. Chem. Soc.*, 1970, **92**, 6594; (*c*) P. Stoss and G. Satzinger, *Angew. Chem., Int. Ed.*, 1971, **10**, 76; (*d*) C. R. Johnson and C. W. Schroeck, *J. Am. Chem. Soc.*, 1973, **95**, 7418; (*e*) R. H. Rynbrandt and D. P. Balgoyen, *J. Org. Chem.*, 1978, **43**, 1824; (*f*) J. Brandt and H.-J. Gais, *Tetrahedron: Asymmetry*, 1997, **8**, 909.

8 (*a*) Y. Tamura, K. Sumoto, J. Minamikawa and M. Ikeda, *Tetrahedron Lett.*, 1972, 4137; (*b*) Y. Tamura, J. Minamikawa, K. Sumoto, S. Fujii and M. Ikeda, *J. Org. Chem.*, 1973, **38**, 1239; (*c*) C. R. Johnson, R. A. Kirchhoff and H. G. Corkins, *J. Org. Chem.*, 1974, **39**, 2458; (*d*) S. Allenmark, S. Claeson and C. Lowendahl, *Tetrahedron: Asymmetry*, 1996, **7**, 361.

9 Cu-catalyzed: (*a*) J. F. K. Muller and P. Vogt, *Tetrahedron Lett.*, 1998, **39**, 4805; (*b*) H. Takada, K. Ohe and S. Uemura, *Angew. Chem., Int. Ed.*, 1999, **38**, 1288; (*c*) C. Bolm, K. MuÇiz, N. Aguilar, M. Kesselgruber and R. Raabe, *Synthesis*, 1999, 1251; (*d*) J. Nakayama, T. Otani, Y. Sugihara, Y. Sano, A. Ishii and A. Sakamoto, *Heteroat. Chem.*, 2001, **12**, 333; (*e*) E. Lacote, M. Amatore, L. Fensterbank and M. Malacria, *Synlett*, 2002, 116; (*f*) S. Cren, T. C. Kinahan, C. L. Skinner and H. Tye, *Tetrahedron Lett.*, 2002, **43**, 2749; (*g*) C. S. Tomooka and E. M. Carreira, *HelV. Chim. Acta*, 2003, **85**, 3773; Rh-catalyzed: (*h*) H. Okamura and C. Bolm, *Org. Lett.*, 2004, **6**, 1305; Ag-catalyzed: (*i*) G. Y. Cho and C. Bolm, *Org. Lett.*, 2005, 7, 4983; Fe-catalyzed: (*j*) T. Bach and C. Korber, *Tetrahedron Lett.*, 1998, **39**, 5015; (*k*) T. Bach and C. Kœrber, *Eur. J. Org. Chem.*, 1999, 1033; (*l*) O. Garcia Mancheno and C. Bolm, *Org. Lett.*, 2006, **8**, 2349; (*m*) O. Garcia Mancheno, J. Dallimore, A. Plant and C. Bolm, *Org. Lett.*, 2009, **11**, 2429.

10 J. L. Jat, M. P. Paudyal, H. Gao, Q.-L. Xu, M. Yousufuddin, D. Devarajan, D. H. Ess, L. Kürtis and J. R. Falck, *Science*, 2014, **343**, 61.

11 For selected recent reviews on Rh-nitrene mediated reactions, see: (*a*) P. Muller and C. Fruit, *Chem. Rev.*, 2003, **103**, 2905; (*b*) C. G. Espino and J. Du Bois, in *Modern Rhodium-Catalyzed Organic Reactions*, ed. P. A. Evans, Wiley-VCH, Weinheim, 2005, 379; (*c*) H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417; (*d*) F. Collet, R. Dodd and P. Dauban, *Chem. Commun.*, 2009, 5061; (*e*) J. Du Bois, *Org. Process Res. Dev.*, 2011, **15**, 758; (*f*) G. Dequirez, V. Pons and P. Dauban, *Angew. Chem., Int. Ed.*, 2012, **51**, 7384; (*g*) M. M. Diaz-Requejo, A. Caballero, M. R. Fructos and P. J. Perez, *Catal. Met. Complexes*, 2012, **38**, 229; (*h*) L. R. Jennifer, M. E. Harvey and J. Du Bois, *Acc. Chem. Res.*, 2012, **45**, 911.

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Organic LETTERS

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Palladium-Catalyzed Site-Selective Fluorination of Unactivated C(sp^3)–H Bonds

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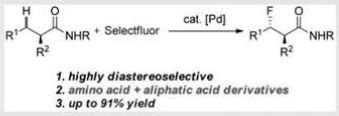
Supporting Information

ABSTRACT: The transition-metal-catalyzed direct C–H bond fluorination is an attractive synthetic tool toward the preparation of organofluorines. While many methods exist for the direct sp^3 C–H functionalization, site-selective fluorination of unactivated sp^3 carbons remains a challenge. Direct, highly site-selective and diastereoselective fluorination of aliphatic amides via a palladium-catalyzed bidentate ligand-directed C–H bond functionalization process on unactivated sp^3 carbons is reported. With this approach, a wide variety of β-fluorinated amino acid derivatives and aliphatic amides, important motifs in medicinal and agricultural chemistry, were prepared with palladium acetate as the catalyst and Selectfluor as the fluorine source.



Fluorine substitution is of great interest in the fields of medicinal chemistry, agricultural chemistry, and material science.[1] Fluorinated compounds affect nearly all physical and chemical properties including stability, solubility, lipophilicity, conformation, and bioavailability compared to the parent molecules.[2] It has been estimated that fluorine-containing molecules account for about 25% of all pharmaceuticals and 30–40% of agrochemicals, including three of the top five best-selling drugs in 2013.[3] Furthermore, the importance of fluorine in medical imaging technologies has also been demonstrated.[4] Therefore, the selective incorporation of a fluorine atom into biologically relevant organic molecules has continuously been an active research area in organic chemistry over the past 40 years.[5]

Transition-metal-catalyzed C–H functionalization has been extensively studied in past decades due to the avoidance of the prefunctionalization step in this process compared to the classical approaches.[6] Within this reaction class, site-selective direct fluorination of aromatic C–H bonds has been documented recently via a palladium or copper catalysis.[7] Despite a challenging process, transition-metal-catalyzed direct fluorination of sp^3 carbons has also been established.[8] Copper,[9] iron,[10] manganese,[11] palladium,[12] silver,[13] and vanadium[14] have all been demonstrated as effective catalysts in this process. However, current studies on unactivated sp^3 C–H bonds suffer from low to moderate site selectivity. In addition, fluorination on C–H bonds of the relatively reactive benzylic or allylic sp^3 carbons is typically favored over that on unactivated sp^3 bonds, which limits the potential applications of this approach. Inspired by the Pd-catalyzed ligand-directed C–H functionalization of unactivated β-sp^3 carbons of amides,[15] we have investigated and report here the direct site-selective fluorination of α-amino acid derivatives and aliphatic amides via palladium catalysis with the assistance of a bidentate directing group. Interestingly, closely related reports were published after original submission of this work.[16]

Fluorine-containing amino acids have attracted considerable attention in past decades due to the importance of these compounds in medicinal chemistry research.[17] Current synthetic methods of these molecules primarily relied on the nucleophilic substitution reaction, which requires preinstallation of a functional group to the C–H bonds.[18] In order to provide a direct synthetic approach for fluorinating unactivated sp^3 carbons, we began our investigation on palladium-catalyzed fluorination of amino acid derivatives with the assistance of a bidentate ligand. Although 8-aminoquinoline has been widely used as a directing group for transition-metal-catalyzed C–H functionalization, electrophilic aromatic substitution on this moiety could be a potential problem with an electrophilic fluorine reagent. Therefore, 2-(pyridin-2-yl)isopropyl amine[19] was chosen as the directing group for fluorination of the 2-aminobutyric acid derivative **1a** (Scheme 1). Initial studies showed that a trace amount of desired β-fluorinated product **2a** could be observed with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) as the fluorinating reagent in dichloroethane (entry 1). To our delight, the reaction yield was significantly improved with the addition of stoichiometric amounts of AgOAc or Ag_2CO_3 (entries 3 and 4). Next, an extensive solvent screening was carried out, and the mixture of dichloroethane and isobutyronitrile proved to be optimal, providing **2a** in 38% yield (entry 11). It was then found that replacement of Selectfluor with another fluorinating reagent gave no or only a trace amount of product (entries 13–15). Further screening of the palladium catalysts showed that $Pd(OAc)_2$ is optimal although several other catalysts could also

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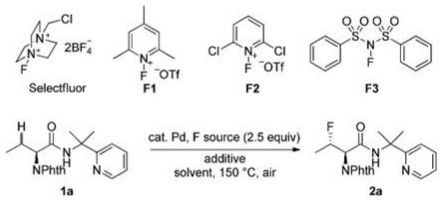
Scheme 1. Optimization of Reaction Conditions[a]



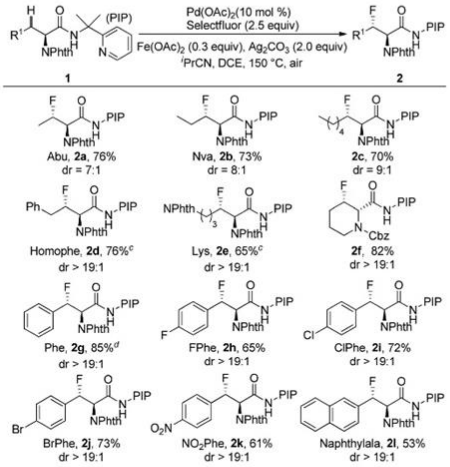
entry	Pd source (10 mol %)	additive (equiv)	solvent (mL)	yield (%)[b]
1	$Pd(OAc)_2$	-	DCE (3.0)	trace
2	$Pd(OAc)_2$	$AgNO_3$ (2.0)	DCE (3.0)	trace
3	$Pd(OAc)_2$	AgOAc (2.0)	DCE (3.0)	21
4	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)	25
5	$Pd(OAc)_2$	Na_2CO_3 (2.0)	DCE (3.0)	-
6	$Pd(OAc)_2$	K_2CO_3 (2.0)	DCE (3.0)	-
7	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	MeCN (3.0)	-
8	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DME (3.0)	18
9	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	chloroform (3.0)	5
10	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/MeCN (0.3)	31
11	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	38
12	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{t}BuCN (0.3)	33
13[c]	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	-
14[d]	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	-
15[e]	$Pd(OAc)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	trace
16	$Pd(TFA)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	29
17	$Pd(acac)_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	12
18	$PdCl_2$	Ag_2CO_3 (2.0)	DCE (3.0)/^{i}PrCN (0.3)	6
19	$Pd(OAc)_2$	Ag_2CO_3 (2.0)/$Mn(OAc)_2$ (1.0)	DCE (3.0)/^{i}PrCN (0.3)	44
20	$Pd(OAc)_2$	Ag_2CO_3 (2.0)/$Fe(OAc)_2$ (1.0)	DCE (3.0)/^{i}PrCN (0.3)	56
21	$Pd(OAc)_2$	Ag_2CO_3 (2.0)/$Fe(OAc)_2$ (0.3)	DCE (3.0)/^{i}PrCN (0.3)	80(76[f])
22	-	Ag_2CO_3 (2.0)/$Fe(OAc)_2$ (0.3)	DCE (3.0)/^{i}PrCN (0.3)	-
23	$Pd(OAc)_2$	$Fe(OAc)_2$ (0.3)	DCE (3.0)/^{i}PrCN (0.3)	27

[a]Reaction conditions: **1a** (0.30 mmol), Pd source (10 mol %), F source (2.5 equiv), Ag_2CO_3 (2.0 equiv), additive, solvent, 150 °C, air, 14 h. [b]Yields are based on **1a**, determined by ^{1}H NMR using dibromomethane as internal standard. [c]2.5 equiv of **F1** were used instead of Selectfluor. [d]2.5 equiv of **F2** were used instead of Selectfluor. [e]2.5 equiv of **F3** were used instead of Selectfluor. [f]Isolated yield, dr = 7:1. Selectfluor = 1-chloromethyl-4fluoro-1,4-diasoniabicyclo[2.2.2]octanebis(tetrafluoroborate). **F1** = 1-Fluoro-2,4,6-trimethylpyridinium triflate. **F2** = 2,6-Dichloro-1-fluoropyridinium triflate. **F3** = *N*-Fluorobenzenesulfonimide.

provide the desired product (entries 16−18). Interestingly, the addition of $Mn(OAc)_2$ or $Fe(OAc)_2$ significantly improved the reaction yield, with 0.3 equiv of $Fe(OAc)_2$ giving the best result (entries 19−21). As we expected, this reaction showed high site selectivity by favoring β-C−H bonds due to the preference of the formation of a five-membered ring intermediate in the cyclopalladation step. Delightfully, high diastereoselectivity was also observed by favoring the *anti* diastereoisomer. It is noteworthy that only low to moderate diastereoselectivities have been reported in previous Pd-catalyzed sp^3 C−H functionalizations of linear aliphatic α-amino acids with relatively small functional groups, such as Me,[15g] OMe,[18a] and OAc.[20] It should be mentioned that, under the optimized conditions, 2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-butanamide with 8-aminoquinoline as the bidentate directing group failed to provide the corresponding β-fluorinated product.

With optimized conditions in hand, the scope of amino acids was studied (Scheme 2). As expected, good yields were obtained with linear aliphatic amino acid derivatives with high

Scheme 2. Scope of Amino Acid Derivatives[a,b]



[a]Reaction conditions: **1** (0.30 mmol), $Pd(OAc)_2$ (10 mol %), Selectfluor (2.5 equiv), Ag_2CO_3 (2.0 equiv), $Fe(OAc)_2$ (0.3 equiv), ^{i}PrCN (300 μL), 3.0 mL of DCE, 150 °C, air, 14 h. [b]Isolated yields. [c]0.25 equiv of $Fe(OAc)_2$. [d]Without $Fe(OAc)_2$. PIP = 2-(pyridin-2-yl)isopropyl.

diastereoselectivities (**2a**−**e**). In addition, the cyclic amino acid derivative, benzyl-2-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)-piperidine-1-carboxylate (**1f**), was an effective substrate, affording the desired product **2f** in 82% yield. Moreover, a predominant preference of functionalizing β-C−H bonds over the relatively reactive benzylic γ-C−H bonds was also observed (**2d**), distinguishing this process from the current direct fluorination methods which favor the benzylic C−H bonds. Furthermore, phenylalanine and naphthylalanine derivatives were also effective substrates, providing the corresponding β-fluorinated amino acid derivatives in good yields with excellent diastereoselectivities (**2g**−**l**). Additionally, the structure and absolute configuration of the phenylalanine derivative *L*-**2g** (CCDC no. 1052086) were confirmed with X-ray analysis (Figure 1).

Next, a substrate scope study of nonamino acid aliphatic amides was carried out. As shown in Scheme 3, both linear and α-branched aliphatic amides afforded the desired products in

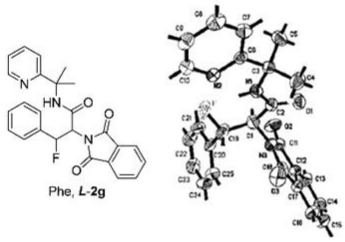


Figure 1. X-ray crystal structure of *L*-**2g**.

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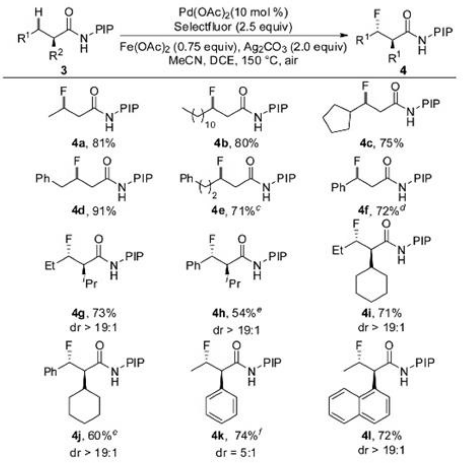
Scheme 3. Scope of Aliphatic Amides[a,b]

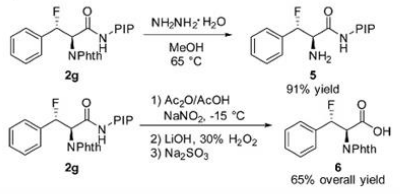


[a]Reaction conditions: **3** (0.30 mmol), $Pd(OAc)_2$ (10 mol %), Selectfluor (2.5 equiv), Ag_2CO_3 (2.0 equiv), $Fe(OAc)_2$ (0.75 equiv), MeCN (400 μL), 3.0 mL of DCE, 150 °C, air, 14 h. [b]Isolated yields. [c]3.0 equiv of Selectfluor. [d]0.2 equiv of $Fe(OAc)_2$. [e]Without $Fe(OAc)_2$. [f]0.5 equiv of $Fe(OAc)_2$. PIP = 2-(pyridin-2-yl)isopropyl.

good yields under modified reaction conditions (**4a**–**l**). Similarly, functionalization of β-C–H bonds was favored over the relatively reactive benzylic γ- or δ-C–H bonds (**4d** and **4e**). As expected, high diastereoselectivity was also observed with α-branched aliphatic amides (**4g**–**l**). Furthermore, it was found that the current process favored functionalization of β-C–H bonds of the sp^3 carbons over γ-C–H bonds of the sp^2 carbons, indicating that formation of a five-membered ring intermediate is preferred to the six-membered ring intermediate in the cyclopalladation step (**4k** and **4l**).

To further demonstrate the synthetic utility of this fluorination method, removal of the protecting and the directing group PIP was carried out, and the corresponding products were obtained in good yields (Scheme 4).

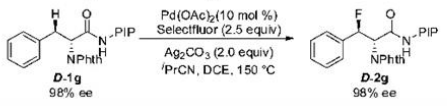
Scheme 4. Removal of Protecting Group and Directing Group



In addition, no apparent racemization of the α-chiral center was observed during the fluorination of the *D*-2-(1,3-dioxoisoindolin-2-yl)-3-phenyl-*N*-(2-(pyridin-2-yl)propan-2-yl)propanamide (***D*-1g**) (Scheme 5).

On the basis of the above obtained results and the previous reports,[7,12b,21] a plausible reaction mechanism is proposed

Scheme 5. Synthesis of *D*-2g



(Figure 2). Coordination of amide **1** or **3** to a palladium species followed by a base-promoted ligand exchange process produces

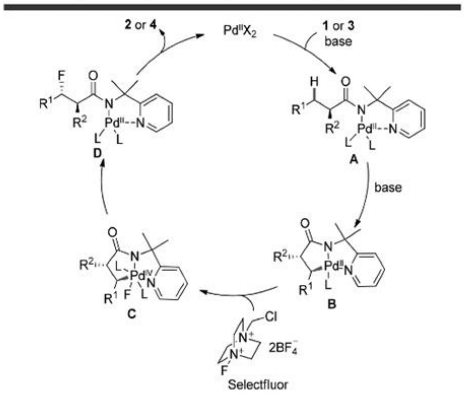


Figure 2. Proposed catalytic cycle of β-fluorination.

the palladium complex **A**. Subsequently, cyclometalation of the palladium complex **A** occurs to generate the intermediate **B** via a C–H bond activation process. Oxidative addition of the intermediate **B** with Selectfluor provides the palladium(IV) species **C**, which then gives rise to the final product **2** or **4** via reductive elimination followed by ligand dissociation.[22] Although the exact role of Ag_2CO_3 in the reaction is not clear, it is believed that this species participates in the ligand exchange and subsequent C–H bond cleavage steps by acting as a base, and also possibly promotes the oxidative addition of Selectfluor to the intermediate **B**. On the other hand, the role of $Fe(OAc)_2$ in the reaction could be the promotion of releasing Pd(II) species from the intermediate **D**.

In summary, the palladium-catalyzed ligand-directed highly site-selective fluorination of amino acid derivatives and aliphatic amides was developed via an sp^3 C–H bond functionalization process. This reaction showed high diastereoselectivity and good functional group compatibility. Additionally, a great preference for functionalizing the C–H bonds of β-sp^3 carbons over those of relatively reactive γ-sp^2 or benzylic sp^3 carbons was observed. As mentioned earlier, current methods for the direct fluorination of unactivated sp^3 carbons suffer from poor site selectivity, incompatibility with benzylic carbons, and low diastereoselectivity in many cases. Therefore, this reported process provides a complementary and advantageous approach to access fluorine-containing organic molecules. The detailed mechanistic study of this transformation is currently underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data for products, NMR spectra of products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01710.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Okazoe, T. *Proc. Jpn. Acad., Ser. B* **2009**, *85*, 276.

(2) (a) Jeschke, P. *ChemBioChem* **2004**, *5*, 570. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

(3) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.

(4) Phelps, M. E. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 9226.

(5) (a) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (b) Perutz, R. N. *Science* **2008**, *321*, 1168. (c) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160.

(6) (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. - Eur. J.* **2010**, *16*, 2654. (f) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (g) Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1855. (h) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. (i) White, M. C. *Science* **2012**, *335*, 807.

(7) (a) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (b) Wang, X.-S.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. (c) Engle, K. M.; Mei, T.-S.; Wang, X.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 1478. (d) Chan, K. S. L.; Wasa, M.; Wang, X.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 9081. (e) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342.

(8) (a) Lin, A.-J.; Huehls, B.; Yang, J. *Org. Chem. Front.* **2014**, *1*, 434. (b) Ma, J. A.; Li, S. *Org. Chem. Front.* **2014**, *1*, 712. (c) Lin, X.-X.; Weng, Z.-Q. *Dalton Trans.* **2015**, *44*, 2021. (d) Brooks, A. F.; Topczewski, J. J.; Ichiishi, N.; Sanford, M. S.; Scott, P. J. *Chem. Sci.* **2014**, *5*, 4545.

(9) Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 10580.

(10) Bloom, S.; Pitts, C. R.; Woltornist, R.; Griswold, A.; Holl, M. G.; Lectka, T. *Org. Lett.* **2013**, *15*, 1722.

(11) (a) Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A., III; Groves, J. T. *Science* **2012**, *337*, 1322. (b) Liu, W.; Groves, J. T. *Angew. Chem., Int. Ed.* **2013**, *52*, 6024. (c) Huang, X.; Liu, W.; Ren, H.; Neelamegam, R.; Hooker, J. M.; Groves, J. T. *J. Am. Chem. Soc.* **2014**, *136*, 6842.

(12) (a) Braun, M.-G.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 12990. (b) McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4094.

(13) Xu, P.; Guo, S.; Wang, L.-Y.; Tang, P.-P. *Angew. Chem., Int. Ed.* **2014**, *53*, 5955.

(14) Xia, B.-B.; Ma, Y.; Chen, C. *Org. Chem. Front.* **2014**, *1*, 468.

(15) (a) Zaitsev, V.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378. (c) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598. (d) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570. (e) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387. (f) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. (g) Figg, T. M.; Wasa, M.; Yu, J.-Q.; Musaev, D. G. *J. Am. Chem. Soc.* **2013**, *135*, 14206. (h) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 11124. (i) Fan, M.-Y.; Ma, D.-W. *Angew. Chem., Int. Ed.* **2013**, *52*, 12152. (j) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138. (k) He, J.; Li, S.-H.; Deng, Y.-Q.; Fu, H.-Y.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216. (l) Zhu, R.-Y.; He, J.; Wang, X.-C.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 13194. (m) Gong, W.; Zhang, G.-F.; Liu, T.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 16940. (n) Chen, G.; Shigenari, T.; Jain, P.; Zhang, Z.-P.; Jin, Z.; He, J.; Li, S.-H.; Mapelli, C.; Miller, M. M.; Poss, M. A.; Scola, P. M.; Yeung, K.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 3338. (o) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (p) Zhang, B.; Guan, H.-X.; Liu, B.; Shi, B.-F. *Youji Huaxue* **2014**, *34*, 1487.

(16) (a) Zhu, R.-Y.; Tanaka, K.; Li, G.-C.; He, J.; Fu, H.-Y.; Li, S.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 7067. (b) Zhang, Q.; Yin, X.-S.; Chen, K.; Zhang, S.-Q.; Shi, B.-F. *J. Am. Chem. Soc.* **2015**, *137*, 8219.

(17) (a) Tsushima, T.; Kawada, K.; Tsuji, T.; Tawara, K. *J. Med. Chem.* **1985**, *28*, 253. (b) Hart, B. P.; Haile, W. H.; Licato, N. J.; Bolanowska, W. E.; McGuire, J. J.; Coward, J. K. *J. Med. Chem.* **1996**, *39*, 56. (c) de Villiers, J.; Koekemoer, L.; Strauss, E. *Chem. - Eur. J.* **2010**, *16*, 10030. (d) Chia, P. W.; Livesey, M. R.; Slawin, A. M. Z.; van Mourik, T.; Wyllie, D. J. A.; O'Hagan, D. *Chem. - Eur. J.* **2012**, *18*, 8813.

(18) (a) Kukhar, V. P.; Sorochinsky, A. E.; Soloshonok, V. A. *Future Med. Chem.* **2009**, *1*, 793. (b) Acena, J. L.; Simon-Fuentes, A.; Fustero, S. *Curr. Org. Chem.* **2010**, *14*, 928.

(19) (a) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187. (b) Zhang, Q.; Chen, K.; Rao, W.-H.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588.

(20) Chen, K.; Zhang, S.-Q.; Jiang, H.-Z.; Xu, J.-W.; Shi, B.-F. *Chem. - Eur. J.* **2015**, *21*, 3264.

(21) Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177.

(22) Racowski, J. M.; Gary, B. G.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3414.

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Recent Advances in First-Row-Transition-Metal-Catalyzed Dehydrogenative Coupling of C(sp^3)–H Bonds

Jinmin Miao[a] and Haibo Ge*[a]

Keywords: Synthetic methods / Homogeneous catalysis / C–H activation / C–C coupling / Dehydrogenative coupling / Nitrogen heterocycles

Transition-metal-catalyzed cross dehydrogenative coupling is a highly efficient tool for functionalization of C(sp^3)–H bonds. In particular, the inexpensive first-row transition metals have been demonstrated as effective catalysts in this process. This microreview summarizes recent progress in two classes of first-row-transition-metal-catalyzed dehydrogenative reactions: intramolecular cyclization for C–C bond formation, and directed site-selective C–H functionalization. These transformations provide concise and practical approaches for preparation of various organic compounds, but so far they are underdeveloped.

1. Introduction

Transition-metal-catalyzed direct functionalization of unactivated C(sp^3)–H bonds has received a great attention in the past two decades.[1] In particular, cross-dehydrogenative coupling (CDC) reactions have emerged as a powerful tool for the selective construction of C–C, C–N, C–O, and C–P bonds.[2] In these transformations, atom economy is maximized by avoiding the prefunctionalization of the substrate and coupling partners. Moreover, molecular oxygen is often employed as the sole oxidant in dehydrogenative reactions, generating water as the by-product. Therefore, in comparison with traditional methods, dehydrogenative C–H bond functionalizations are more efficient and environmentally friendly, and thus it would have broad application in industrial catalysis.

In the past few years, there has been considerable research interest in non-noble-transition-metal-catalyzed direct functionalization of unactivated C–H bonds.[3] The earth abundant first-row transition metals such as iron, cobalt, nickel, and copper, are attractive alternatives to the traditional precious metals in catalysis for their low cost and environmentally friendly properties. However, although copper-catalyzed cross dehydrogenative coupling reactions have been extensively studied, some new trends in this research area involving the employment of other first-row transition metals for sp^3-hybridized carbon atoms are less inspected. The aim of this microreview is to highlight the most important progress that has recently been made in our

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Haibo Ge received his Ph.D. degree in Medicinal Chemistry from the University of Kansas in 2006 with Professor Gunda Georg. He then moved to The Scripps Research Institute for his postdoctoral study with Professor Dale Boger. In 2009, he began his independent academic career at the Department of Chemistry and Chemical Biology at Indiana University Purdue University Indianapolis (IUPUI). Research in his group is mainly focused on the development of novel methods towards carbon–carbon and carbon–heteroatom bond formation through transition-metal-catalyzed C–H functionalization.

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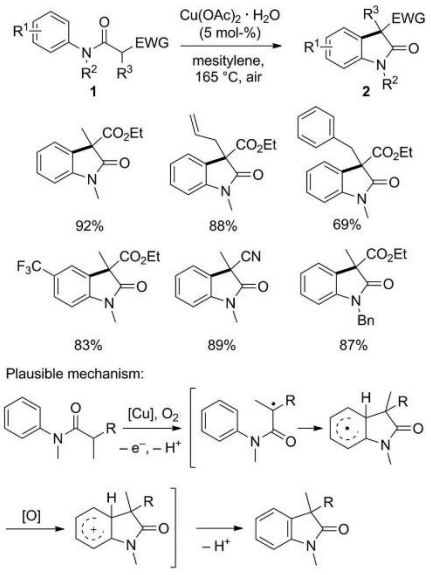
laboratory and by others in the field of first-row-transition-metal-catalyzed dehydrogenative coupling of C(sp^3)–H bonds. Two categories of these reactions are discussed here: 1) intramolecular C–C bond formation, and 2) directed site-selective C–H functionalization.

2. Intramolecular Aerobic Dehydrogenative Construction of C–C Bonds Through C(sp^3)–H Bond Functionalization

Selective C–C bond formation reactions are essential strategies in organic synthesis to set up framework of complex organic molecules.[4] As one of the most efficient tools for C–C bond construction, cross dehydrogenative coupling has become a highly active research area and extensive progress has been achieved in recent years.[5] However, the field of transition-metal-catalyzed intramolecular dehydrogenative C–C bond formation from sp^3 carbons, especially with non-noble metals, is underdeveloped. This transformation should have broad application in synthetic chemistry, because it provides efficient and atom economical pathways toward the preparation of many physiologically and biologically important heterocycles. Pioneering work in this field is discussed in this section.

Cu-Catalyzed Synthesis of Oxindoles

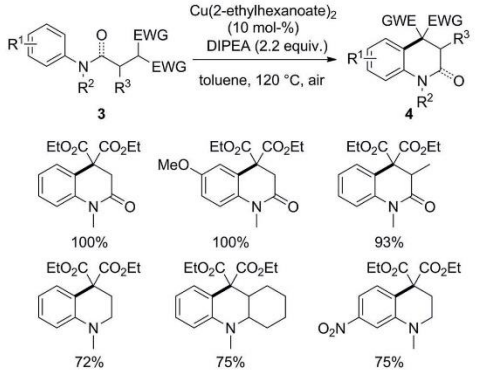
The first example of Cu-catalyzed intramolecular C–C bond formation through C(sp^3)–H bond functionalization was reported by Taylor and co-workers in 2010 for the synthesis of oxindoles, a class of important substructures in natural products and biologically active molecules, from anilindes (Scheme 1).[6] This transformation had previously been achieved with stoichiometric copper salts in Taylor's[7] and Kundig's group.[8] In this innovating catalytic process, the authors devised an efficient procedure using catalytic $Cu(OAc)_2 \cdot H_2O$ in mesitylene under air for the synthesis of oxindoles, and a series of 3,3-disubstituted oxindole products were readily obtained within 3 hours in good yields, albeit at a higher temperature than that with stoichiometric copper. In accordance with the previous proposed mechanism for the stoichiometric process, it is believed that the reaction is initiated by the enolization of the amide, followed by radical generation. The subsequent homolytic aromatic substitution affords the oxindole products. Oxygen in air oxidizes Cu^I to Cu^{II} to complete the catalytic cycle, producing water as by-product.



Scheme 1. Cu-catalyzed synthesis of oxindoles.

Cu-Catalyzed Synthesis of 3,4-Dihydro-1*H*-quinolin-2-ones, and 1,2,3,4-Tetrahydroquinolines

The Taylor's group further extended this intramolecular dehydrogenative cyclization to the synthesis of other biologically and pharmaceutically valuable heterocycles, including thio-oxindoles, 3,4-dihydro-1*H*-quinolin-2-ones, and 1,2,3,4-tetrahydroquinolines (Scheme 2).[9] Cu(2-ethylhexanoate)$_2$ was found to be the most efficient catalyst, and the reactions were performed in toluene at 120 °C. Control experiments and observations in substrate scope studies suggest that radicals and homolytic aromatic substitution are involved in this transformation.



Scheme 2. Cu-catalyzed synthesis of 3,4-dihydro-1*H*-quinolin-2-ones, and 1,2,3,4-tetrahydroquinolines.

Cu-Catalyzed Synthesis of Cinnolines

In 2012, we reported *N*-methyl-*N*-phenylhydrazones as unprecedented substrates for copper-catalyzed intramolecular dehydrogenative cyclization for the formation of cinnolines, which have demonstrated a broad range of biological

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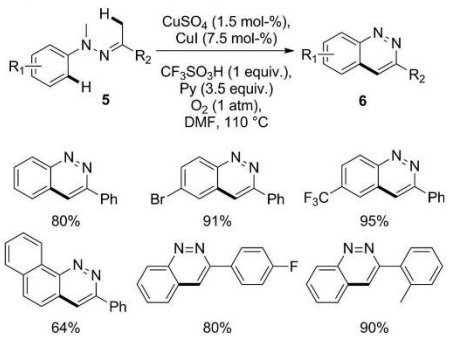
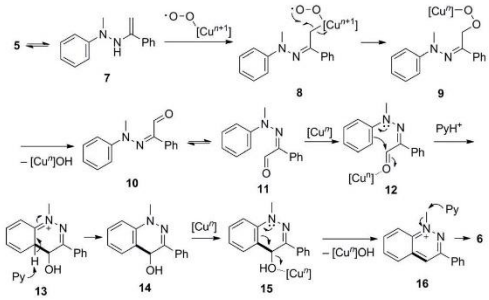
activities (Scheme 3).[10] Interestingly, the combination of CuI and $CuSO_4$ was found to be the optimal catalyst system, and addition of CF_3SO_3H along with excess pyridine significantly improved the yields. Diverse cinnoline derivatives with diverse substituents were prepared by this method through the direct functionalization of C(sp²)–H and C(sp³)–H bonds.



Scheme 3. Cu-catalyzed synthesis of cinnolines.

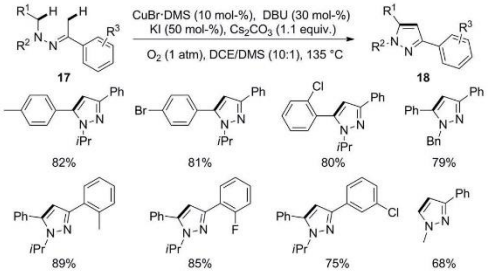
In the deuterium-labeling experiments, the kinetic isotope effect value k_H/k_D was found to be 1.2:1, suggesting that the rate-determine step might not include the cleavage of the aryl C(sp²)–H bond. We believe that the rate-determine step may take place during the oxidation of the methyl group adjacent to the imine moiety. This reaction was proposed to start with the oxidation of **5** into the aldehyde **10** by oxygen and catalytic copper (Scheme 4).[11] Copper-assisted cyclization followed by loss of the hydroxyl group and subsequent nucleophilic substitution of pyridine providing the final product cinnolines **6**.



Scheme 4. Proposed mechanism for Cu-catalyzed synthesis of cinnolines.

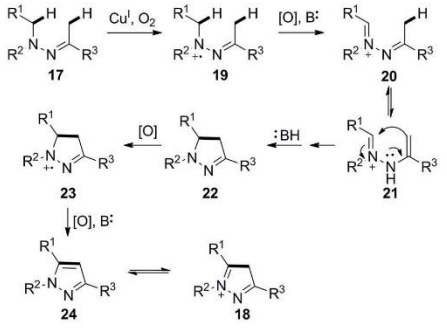
Copper-Catalyzed Synthesis of Pyrazoles and Pyrazolines

The first report of copper-catalyzed intramolecular aerobic dehydrogenative construction of C–C bonds via functionalization of two C(sp³)–H bonds was developed in our group in 2013 (Scheme 5).[12] The five-membered heterocycle, pyrazoles, were prepared from *N*,*N*-disubstituted hydrazones by employment of CuBr·DMS as the catalyst under atmospheric oxygen. It was noted that the addition of dimethylsulfide (DMS) as the co-solvent greatly improved the reaction yields.



Scheme 5. Cu-catalyzed synthesis of pyrazoles.

A time-dependent study showed that a pyrazoline intermediate **22** was rapidly formed during the reaction, and then consumed. Furthermore, this intermediate can be converted into the pyrazole product under the standard reaction conditions in nearly quantitative yield. Based on the above results and previous reports,[13] a plausible catalytic cycle was proposed (Scheme 6). The reaction is believed to be initiated by oxidation of the amine on **17** to generate the iminium ion intermediate **20**. Tautomerization of **20** to the enamine-type structure **21** followed by intramolecular cyclization provides the dihydropyrazole intermediate **22**, which is then oxidized to afford the pyrazole product.



Scheme 6. Proposed mechanism for Cu-catalyzed synthesis of pyrazoles.

Recently, we further investigated the copper-catalyzed aerobic dehydrogenative cyclization of *N*,*N*-disubstituted hydrazones and expanded it to the diastereoselective synthesis of pyrazoline derivatives (Scheme 7).[14] Through modification of reaction conditions, we managed to avoid the oxidation to pyrazoles following the cyclization, and pyrazoline derivatives with two chiral centers were obtained by the direct C(sp³)–H functionalization. Under the opti-

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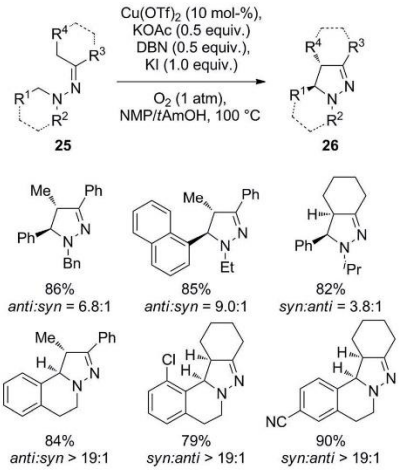
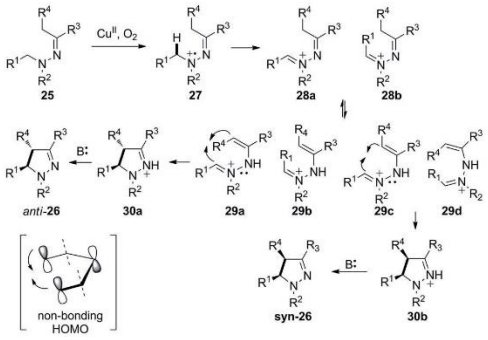
mized conditions, a variety of hydrazone substrates underwent this transformation, affording the pyrazoline products exclusively. To our delight, this reaction also features high diastereoselectivities.



Scheme 7. Cu-catalyzed diastereoselective synthesis of pyrazolines.

A plausible reaction mechanism based on the previous reports was proposed (Scheme 8).[15] The high diastereoselectivity was rationalized by a 5-center/6-electron system according to the reports of Hoffmann and List.[16] In such homoconjugated systems, a U-shaped planar conformation is favored when the electrons are placed in the symmetric 1,5-bonding HOMO orbital. Consequently, a disrotatory mechanism is required for the symmetric HOMO in the case of thermally induced electrocyclic ring closures, and thus corresponding pyrazoline products (*anti* **26** and *syn*-**26**) are produced. A series of computational density functional theory (DFT) studies on representative 5-center/6-electron systems were also carried out, and the results were found to be consistent with experimental observations.



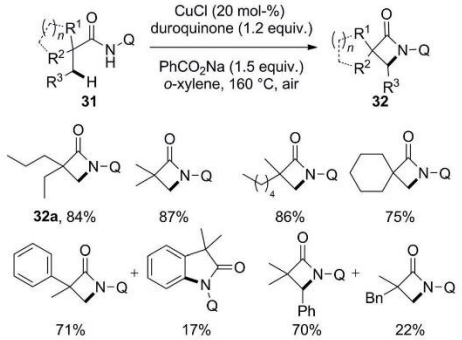
Scheme 8. Proposed mechanism for Cu-catalyzed synthesis of pyrazolines.

3. Directed Dehydrogenative Coupling of Unactivated C(sp³)–H Bonds

A major challenge in transition-metal-catalyzed direct C–H bond functionalization reaction is the requirement of site-selectivity in molecules that contain diverse C–H bonds. This can be solved by the use of substrates that contain coordinating ligands as directing groups.[17] The metal center binds to the ligands and is delivered to a proximal C–H bond through the formation of a metalacyclic intermediate. In 2005, Daugulis reported the use of 8-aminoquinoline and picolinamide as bidentate directing groups for the Pd-catalyzed arylation of unactivated C(sp³)–H bonds.[18] Encouraged by these results, a number of site-selective C(sp³)–H bond functionalization reactions have been developed with bidentate directing groups.[19] Recently, some non-noble metals have been demonstrated to be effective catalysts in these transformations. In this section, directed dehydrogenative coupling of unactivated C(sp³)–H bonds catalyzed by copper, nickel, and cobalt salts is discussed.

Copper-Catalyzed Intramolecular β-Amination of C(sp³)–H Bonds

In 2014, we reported a novel copper-catalyzed intramolecular dehydrogenative amination of aliphatic amides via C(sp³)–H bond functionalization directed by the 8-aminoquinoline ligand (Scheme 9).[20] Previously, only the expensive palladium catalysis was utilized for such reactions.[21] We demonstrated that CuCl is able to efficiently catalyze this reaction with duroquinone as the oxidant and $PhCO_2Na$ as the base. A variety of β-lactams were successfully synthesized under these conditions. A preference of amination of the β-methyl sp³ carbons over γ-aromatic sp² carbons was observed. Furthermore, a reactivity order of β-benzylic carbons > β-methyl carbons > β-ring carbons



Scheme 9. Cu-catalyzed intramolecular amination 1.

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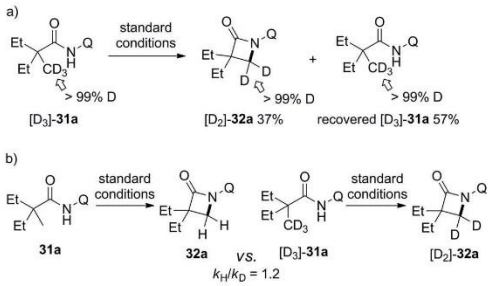
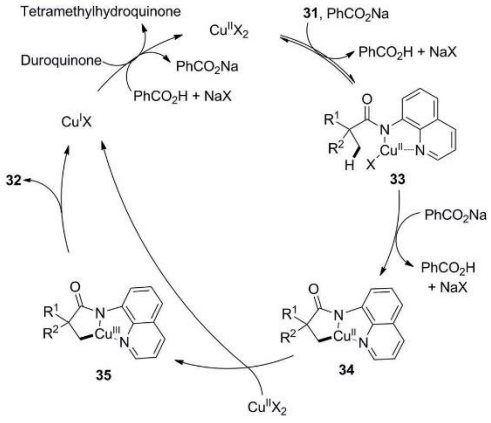
> β-linear carbons was summarized for the C–H functionalization of β-sp³ carbons.

In the deuterium labeling experiments of 2-ethyl-2-methyl-*N*-(quinolin-8-yl)butanamide (**31a**), no apparent H/D exchange was observed during the reaction (Scheme 10). A secondary kinetic isotope effect was observed, suggesting that the cleavage of the sp³ C–H bond should not be involved in the rate-limiting step in the catalytic cycle.



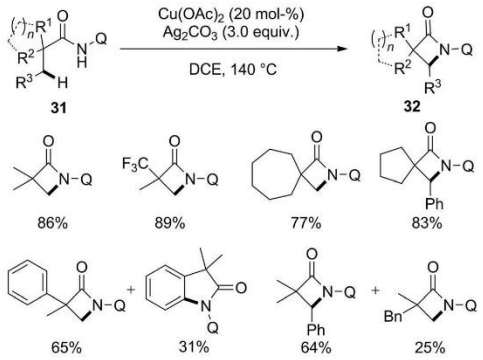
Scheme 10. Deuterium labeling experiments for Cu-catalyzed β-amination.

Subsequently, a postulated mechanism was illustrated (Scheme 11). The reaction begins with coordination of amide **31** to a Cu^{II} species followed by ligand exchange under basic conditions and subsequent cyclometalation to form the alkyl-Cu^{II} species **34**. This intermediate is then oxidized by another Cu^{II} species to generate the alkyl-Cu^{III} complex **35** and a Cu^{I} species. Finally, the β-lactam derivative is obtained via reductive elimination of the Cu^{III} complex **35**.



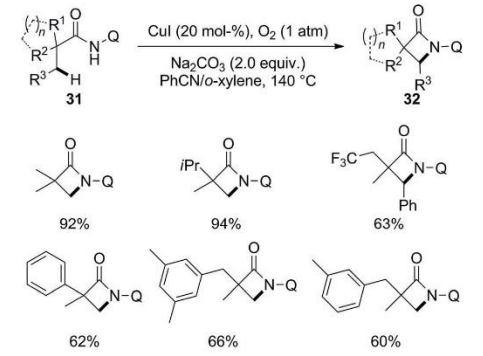
Scheme 11. Proposed mechanism for Cu-catalyzed intramolecular amination.

At the same time, Kanai and co-workers independently developed this intramolecular amination reaction with $Cu(OAc)_2$ in the presence of an excess amount of Ag_2CO_3 (Scheme 12).[22] Similar substrate scope and conversion yields to our work were described. Since Ag_2CO_3 was employed as the oxidant, it is believed that the $Cu(OAc)_2$ is oxidized to a Cu^{III} species before the C–H activation, and thus a Cu^{III}/Cu^{I} catalytic cycle was proposed for the amination process.



Scheme 12. Cu-catalyzed intramolecular amination 2.

You and co-workers recently reported that the above reaction could be performed by catalytic copper with oxygen gas as the sole oxidant (Scheme 13).[23] This aerobic process provides a more economical and practical protocol to the β-lactam compounds. Interestingly, it was observed that the amination of β-methyl carbons is favored over that of β-benzylic carbons under the aerobic conditions.



Scheme 13. Cu-catalyzed intramolecular amination 3.

Nickel-Catalyzed Intramolecular β-Amination of C(sp³)–H Bonds

Inspired by the development of directed Ni^{II}-catalyzed site-selective direct arylation and alkylation reactions of aliphatic amide derivatives by Chatani[24] and our group,[25] respectively, the Ni-catalyzed site-selective intramolecular dehydrogenative cyclization of 2,2-disubstituted propion-

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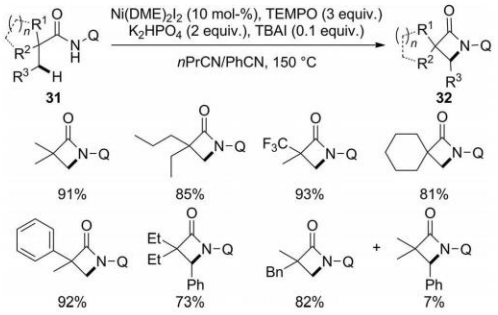
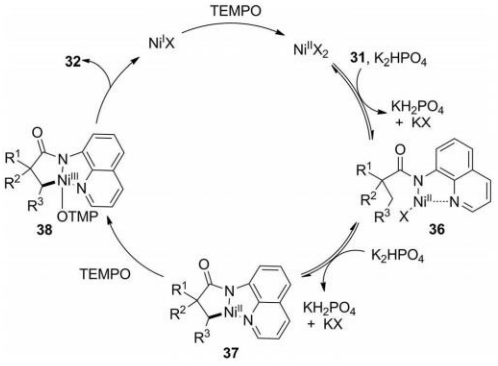
amides was realized in our laboratory (Scheme 14).[26] It was found that $Ni(DME)_2I_2$ could efficiently catalyze the reaction in the presence of TEMPO and bases, affording β-lactams in good to excellent yields. We also discovered that in comparison with the above copper-catalyzed cyclization process, this nickel catalysis system features different regioselectivities toward C–H functionalization of the β-sp^3 carbons: 1) the amination of the sp^3 β-methyl carbons is favored over that of the sp^2 γ-phenyl carbons, indicating that the formation of the five-membered metalacyclic intermediates takes priority; 2) a preference for the reaction on the primary β-methyl carbons was observed over that of the relatively reactive benzylic secondary β-benzylic carbons.



Scheme 14. Ni-catalyzed intramolecular amination.

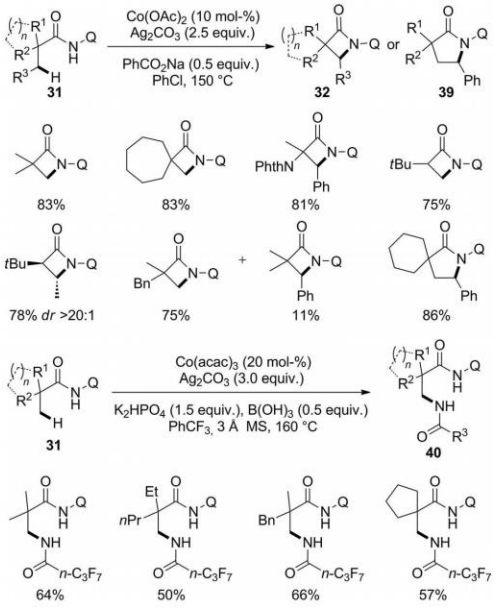
A plausible catalytic $Ni^{II}/Ni^{III}/Ni^{I}$ cycle is proposed for this intramolecular amination reaction (Scheme 15). The Ni^{III} intermediate **36** is believed to be produced from oxidation of the cyclic Ni^{II} species by the single electron oxidant TEMPO. Additionally, H/D exchange was observed for the deuterium-labeled substrate under the amination conditions with and without the TEMPO, suggesting that the conversion from **37** to **38** is reversible. It should be mentioned that a catalytic Ni^{II}/Ni^{IV} cycle cannot be excluded.[27]



Scheme 15. Proposed mechanism for Ni-catalyzed intramolecular amination.

Cobalt-Catalyzed β-Amination of C(sp^3)–H Bonds

Although cobalt-catalyzed C(sp^2)–H bond functionalization has been well established, only a few examples of the direct functionalization on sp^3 C–H bonds with a cobalt salt have been reported.[28] In 2015, we developed the cobalt-catalyzed site-selective direct C–H amination of unactivated sp^3 carbons with the aid of a bidentate directing group (Scheme 16).[29] β- and γ-lactams were prepared with catalytic $Co(OAc)_2$ in the presence of Ag_2CO_3 and $PhCO_2Na$ in PhCl through intramolecular cyclization of amides. It is noteworthy that different from copper- and nickel-catalyzed amination reactions, α-quaternary carbons are not required in the amide substrates, and α-monosubstituted propanamides are viable in the cobalt-catalyzed amination. It was also noticed that functionalization of the γ-benzylic carbons was greatly preferred to that of β-methylene carbons. Furthermore, under modified reaction conditions, intermolecular amination of propanamides with trifluoroacetamide or heptafluorobutanamide was also achieved.



Scheme 16. Co-catalyzed β- and γ-amination of amides.

To further probe the reaction mechanism, deuterium-labeling experiments and control experiments were conducted. In the intramolecular β-amination reaction, a primary kinetic isotope effect was observed for the deuterated amide substrate, suggesting that the cleavage of the C(sp^3)–H bond should be the rate-limiting step. In the intramolecular and intermolecular amination of β-carbons, it was found that the Co^{II} catalyst could be replaced by Co^{III} catalysts, but no amination product could be obtained in the

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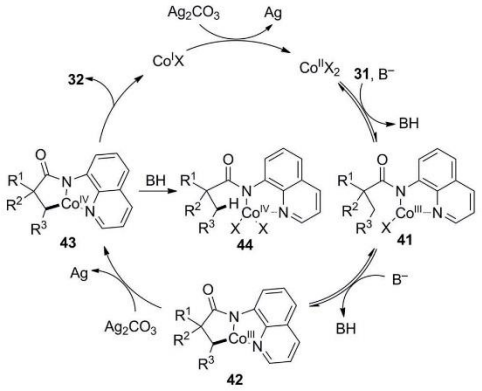
absence of Ag_2CO_3. These results suggest that a Co^{III} species could be involved in the C–H bond activation, but the product is unlikely generated directly by reductive elimination of a Co^{III} intermediate. The addition of TEMPO, a radical inhibitor, showed no significant effect on the reaction yield, implying that radicals might not be involved in the catalytic process. On the basis of above results, a plausible catalytic cycle was proposed for this cobalt-catalyzed intramolecular β-amination (Scheme 17). The coordination of the amide **31** to a cobalt species followed by ligand exchange and subsequent cyclometalation gives rise to the Co^{III} intermediate **42**, which is then oxidized by Ag_2CO_3 to generate the Co^{IV} intermediate **43**. Reductive elimination of intermediate **43** affords the desired β-lactam compound **32**.

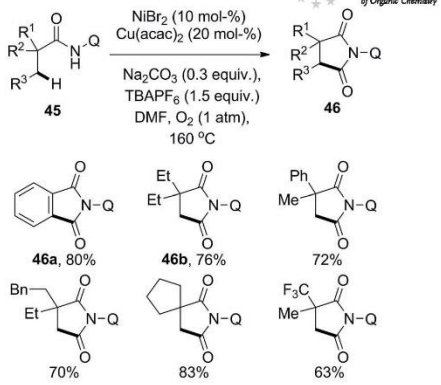


Scheme 17. Proposed mechanism for Co-catalyzed intramolecular amination.

Copper/Nickel-Catalyzed Carbonylation of C(sp³)–H Bonds

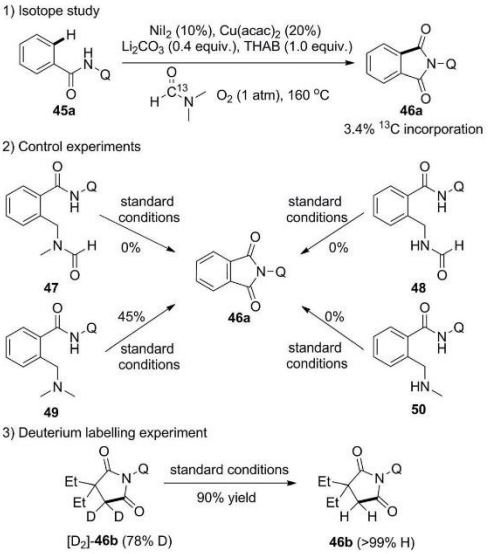
Recently, we developed a novel Ni/Cu synergistic catalysis system with DMF as the CO source for the direct carbonylation of C(sp²)–H and C(sp³)–H bonds (Scheme 18).[30] Succinimide derivatives were prepared from corresponding aromatic or aliphatic amides with 10 mol-% of a Ni^I salt and 20 mol-% $Cu(acac)_2$ in the presence of DMF under oxygen gas. For reactions of aliphatic amides, a predominant preference of functionalizing the methyl group over the methylene groups including the relatively reactive benzyl group was observed.

To gain some insights on the reaction mechanism, isotope studies and control experiments were carried out (Scheme 19). First, to investigate the exact carbonyl source, the isotope labelled DMF(^{13}C=O) was used as the solvent for the carbonylation of **45a**. Only 3.4% of the product **46a** was ^{13}C incorporated, suggesting that the carbonyl carbon might predominantly be from the methyl group of the DMF. Then some potential intermediates were synthesized and exposed to the stardard conditions. It was found the desired phthalimide derivative **46a** was produced exclusively



Scheme 18. Cu/Ni-catalyzed carbonylation of C(sp³)–H bonds.

from 2-[(dimethylamino)methyl]-*N*-(quinolin-8-yl)benzamide (**49**). Additionally, in the deuterium-labeling experiments, an apparent H/D exchange was observed with the deuterated amination product **46b**, implying that an enolate ion might be involved as an intermediate during the formation of the product.



Scheme 19. Cu/Ni-catalyzed carbonylation of C(sp³)–H bonds.

According to the above observations and previous reports,[31] a possible catalytic cycle was proposed (Scheme 20). The initial coordination of amide **45** to a Ni^{II} species, followed by the ligand exchange under basic conditions provides the intermediate **51**. The subsequent cyclometalation of **51** gives rise to the intermediate **52**. Simultaneously, the DMF undergoes decarbonylation, nucleophilic

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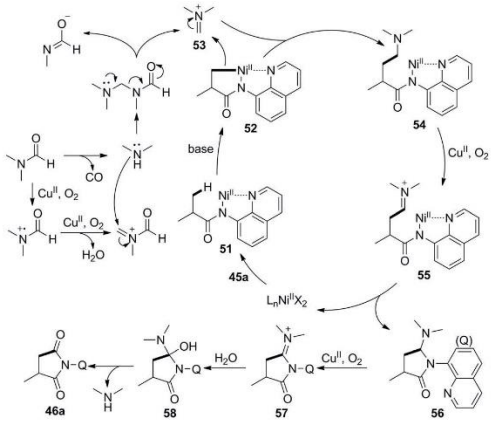
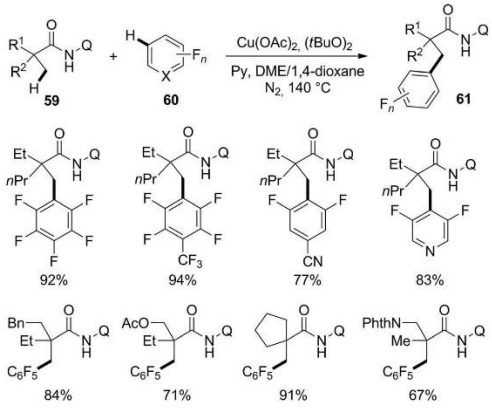
addition, and elimination under copper catalysis with oxygen as the terminal oxidant to generate an iminium ion **53**. Then nucleophilic addition of **52** to **53** produces the intermediate **54**, which undergoes oxidation and intramolecular nucleophilic addition to provide the intermediate **56**. The target product **46** is afforded by oxidation and hydrolysis of the intermediate **56**.



Scheme 20. Proposed mechanism for Cu/Ni-catalyzed carbonylation.

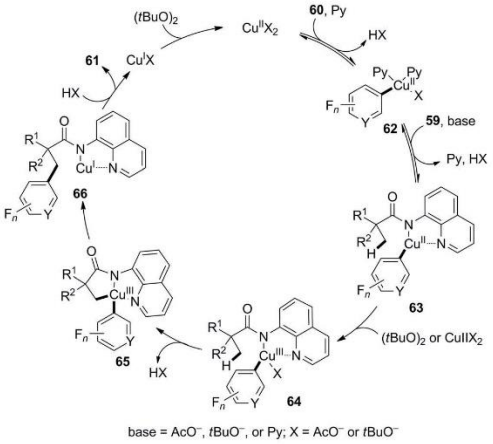
Copper-Promoted β-Arylation of Amides via C(sp^3)–H Bond Activation

In a very recent report by our group, polyfluoroarenes were demonstrated as effective coupling partners in the copper-promoted cross dehydrogenative coupling of unactivated C(sp^3)–H bonds of amides (Scheme 21).[32] It was found that di-*tert*-butyl peroxide is the best oxidant choice, and the addition of pyridine is essential for acquiring high reaction yields. Although satisfactory yields could be obtained only with stoichiometric $Cu(OAc)_2$, utilizing ployfluoroarenes as substrate in the CDC reaction is still a signifcant advance. A variety of fluoroarenes bearing electron-withdrawing and electron-donating groups proved to be feasible in this reaction.



Scheme 21. Cu-promoted β-arylation of amides.

Based on the deuterium-labeling experiments and previous reports,[33] a plausible mechanism was proposed (Scheme 22). The catalytic process begins with the reversible C–H cupration of the polyfluoroarene in the presence of pyridine. Coordination of this Cu^{II} species to the substrate amide **60**, followed by the ligand exchange forms a Cu^{II} intermediate **63**. Subsequent oxidation, cyclometalation, and reductive elimination followed by a ligand dissociation process gives rise to the arylated product **61**.



Scheme 22. Cu-catalyzed β-arylation of amides.

4. Summary and Remarks

In the past few years, significant advances in transition-metal-catalyzed dehydrogenative coupling of C(sp^3)–H bonds have been made. In the field of intramolecular dehydrogenative construction of C–C bonds, some pioneering work was reported. A variety of heterocycles have been synthesized in the atom-economic and cost-effective manners. These results promise dramatic pathways toward the construction of complex organic frameworks from simple starting materials.

On the other hand, directed first-row-transition-metal-catalyzed C(sp^3)–H functionalization is still in its infancy. There are many challenges remaining to be addressed. For example, α-quaternary carbons are generally required for the C–H activation process, and thus the substrate scope is limited. High reaction temperature is another limitation for the application of these transformations. Furthermore, regioselective functionalization of unactivated γ-C(sp^3)–H

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bonds has not been achieved. To overcome these drawbacks, efforts in the exploitation of structurally new directing groups, as well as new catalysts and reagents can be expected.

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[1] For recent reviews, see: a) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654–2672; b) S.-Y. Zhang, F.-M. Zhang, Y.-Q. Tu, *Chem. Soc. Rev.* **2011**, *40*, 1937–1949; c) B.-J. Li, Z.-J. Shi, *Chem. Soc. Rev.* **2012**, *41*, 5588–5598; d) M. Zhang, A.-Q. Zhang, Y. Peng, *J. Organomet. Chem.* **2013**, *723*, 224–232; e) A. F. M. Noisier, M. A. Brimble, *Chem. Rev.* **2014**, *114*, 8775–8806; f) G. Qiu, J. Wu, *Org. Chem. Front.* **2015**, *2*, 169–178; g) X.-X. Guo, D.-W. Gu, Z. Wu, W. Zhang, *Chem. Rev.* **2015**, *115*, 1622–1651.

[2] For recent reviews, see: a) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344; b) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344; c) C. J. Scheuermann, *Chem. Asian J.* **2010**, *5*, 436–451; d) W.-J. Yoo, C.-J. Li, *Top. Curr. Chem.* **2010**, *292*, 281–302; e) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int. Ed.* **2011**, *50*, 11062–11087–11283; *Angew. Chem.* **2011**, *123*, 11256; f) M.-L. Louillat, F. W. Patureau, *Chem. Soc. Rev.* **2014**, *43*, 901–910; g) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74–100; *Angew. Chem.* **2014**, *126*, 76–103; *Angew. Chem.* **2014**, *126*, 76; h) Y. Wu, J. Wang, F. Mao, F. Y. Kwong, *Chem. Asian J.* **2014**, *9*, 26–47; i) I. B. Krylo, V. A. Vil', A. O. Terent'ev, *Beilstein J. Org. Chem.* **2015**, *11*, 92–146.

[3] a) A. A. Kulkarni, O. Daugulis, *Synthesis* **2009**, 4087–4109; b) P. Kumar, J. Louie, *Angew. Chem. Int. Ed.* **2011**, *50*, 10768–10769; *Angew. Chem.* **2011**, *123*, 10956–10958; *Angew. Chem.* **2011**, *123*, 10956; c) N. Yoshikai, *Synlett* **2011**, 1047–1051; d) J. J. Mousseau, A. B. Charette, *Acc. Chem. Res.* **2013**, *46*, 412–424; e) C. Wang, *Synlett* **2013**, *24*, 1606–1613; f) A. Gogoi, S. Guin, S. K. Rout, B. K. Patel, *Org. Lett.* **2013**, *15*, 1802–1805; g) A. Modak, U. Dutta, R. Kancherla, S. Maity, M. Bhadra, S. M. Mobin, D. Maiti, *Org. Lett.* **2014**, *16*, 2602–2605; h) D. Tilly, G. Dayaker, P. Bachu, *Catal. Sci. Technol.* **2014**, *4*, 2756–2777; i) L. Ackermann, *J. Org. Chem.* **2014**, *79*, 8948–8954; j) K. Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208–1219; k) F. Jia, Z. Li, *Org. Chem. Front.* **2014**, *1*, 194–214; l) W. Liu, J. T. Groves, *Acc. Chem. Res.* **2015**, *48*, 1727–1735; m) J.-L. Hu, J. Li, Y.-F. Zhou, *Curr. Green Chem.* **2015**, *2*, 170–191; n) T. K. Hyster, *Catal. Lett.* **2015**, *145*, 458–467.

[4] J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369–375.

[5] C.-J. Li, in: *From C-H to C-C Bonds: Cross-Dehydrogenative-Coupling*, Royal Society of Chemistry (RSC), Cambridge, UK, **2015**.

[6] J. E. M. N. Klein, A. Perry, D. S. Pugh, R. J. K. Taylor, *Org. Lett.* **2010**, *12*, 3446–3449.

[7] a) A. Perry, R. J. K. Taylor, *Chem. Commun.* **2009**, 3249–3251; b) D. S. Pugh, J. E. M. N. Klein, A. Perry, R. J. K. Taylor, *Synlett* **2010**, 934–938.

[8] Y.-X. Jia, E. P. Kundig, *Angew. Chem. Int. Ed.* **2009**, *48*, 1636–1639; *Angew. Chem.* **2009**, *121*, 1664–1667; *Angew. Chem.* **2009**, *121*, 1664.

[9] T. E. Hurst, R. M. Gorman, P. Drouhin, A. Perry, R. J. K. Taylor, *Chem. Eur. J.* **2014**, *20*, 14063–14073.

[10] G.-W. Zhang, J.-M. Miao, Y. Zhao, H.-B. Ge, *Angew. Chem. Int. Ed.* **2012**, *51*, 8318–8321; *Angew. Chem.* **2012**, *124*, 8443–8446; *Angew. Chem.* **2012**, *124*, 8443.

[11] a) K. K. Toh, Y.-F. Wang, E. P. J. Ng, S. Chiba, *J. Am. Chem. Soc.* **2011**, *133*, 13942–13945; b) K. K. Toh, S. Sanjaya, S. Sahnoun, S. Y. Chong, S. Chiba, *Org. Lett.* **2012**, *14*, 2290–2992.

[12] G.-W. Zhang, Y. Zhao, H.-B. Ge, *Angew. Chem. Int. Ed.* **2013**, *52*, 2559–2563; *Angew. Chem.* **2013**, *125*, 2619–2623; *Angew. Chem.* **2013**, *125*, 2619.

[13] a) E. Boess, D. Sureshkumar, A. Sud, C. Wirtz, C. Fares, M. Klussmann, *J. Am. Chem. Soc.* **2011**, *133*, 8106–8109; b) E. Boess, C. Schmitz, M. Klussmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317–5325.

[14] X.-S. Wu, M. Wang, G.-W. Zhang, Y. Zhao, J.-Y. Wang, H.-B. Ge *Chem. Sci.* **2015**, in: press, DOI: c5sc01736j.

[15] Z.-Z. Shi, C. Zhang, C.-H. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3381–3430.

[16] a) R. Hoffman, R. A. Oloson, *J. Am. Chem. Soc.* **1966**, *88*, 943–946; b) S. Muller, B. List, *Angew. Chem. Int. Ed.* **2009**, *48*, 9975–9978; *Angew. Chem.* **2009**, *121*, 10160–10163; *Angew. Chem.* **2009**, *121*, 10160.

[17] a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; b) K. M. Engle, T.-S. Mei, X. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2011**, *50*, 1478–1491; *Angew. Chem.* **2011**, *123*, 1514–1528; *Angew. Chem.* **2011**, *123*, 1514; c) F. Zhang, D. R. Spring, *Chem. Soc. Rev.* **2014**, *43*, 6906–6919; d) G.-F. Shi, Y.-H. Zhang, *Adv. Synth. Catal.* **2014**, *356*, 1419–1442.

[18] V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155.

[19] a) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726–11743; *Angew. Chem.* **2013**, *125*, 11942–11959; *Angew. Chem.* **2013**, *125*, 11942; b) Z.-X. Huang, G.-B. Dong, *Tetrahedron Lett.* **2014**, *55*, 5869–5889; c) E. M. Ferreira, *Nat. Chem.* **2014**, *6*, 94–96; d) Q.-Z. Zheng, N. Jiao, *Tetrahedron Lett.* **2014**, *55*, 1121–1126; e) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053–1064.

[20] X.-S. Wu, Y. Zhao, G.-W. Zhang, H.-B. Ge, *Angew. Chem. Int. Ed.* **2014**, *53*, 3706–3710; *Angew. Chem.* **2014**, *126*, 3780–3784; *Angew. Chem.* **2014**, *126*, 3780.

[21] a) G. He, Y.-S. Zhao, S.-Y. Zhang, C.-X. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3–6; b) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7–10; c) G. He, S.-Y. Zhang, W. A. Nack, Q. Li, G. Chen, *Angew. Chem. Int. Ed.* **2013**, *52*, 11124–11128; *Angew. Chem.* **2013**, *125*, 11330–11334; *Angew. Chem.* **2013**, *125*, 11330.

[22] Z. Wang, J. Ni, Y. Kuninobu, M. Kanai, *Angew. Chem. Int. Ed.* **2014**, *53*, 3496–3499; *Angew. Chem.* **2014**, *126*, 3564–3567; *Angew. Chem.* **2014**, *126*, 3564.

[23] C. Wang, Y. Yang, D. Qin, Z. He, J.-S. You, *J. Org. Chem.* **2015**, *80*, 8424–8429.

[24] Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2014**, *136*, 898–901.

[25] X.-S. Wu, Y. Zhao, H.-B. Ge, *J. Am. Chem. Soc.* **2014**, *136*, 1789–1792.

[26] X.-S. Wu, Y. Zhao, H.-B. Ge, *Chem. Eur. J.* **2014**, *20*, 9530–9533.

[27] N. M. Camasso, M. S. Sanford, *Science* **2015**, *347*, 1218–1220.

[28] a) H.-J. Lu, C.-Q. Li, H.-L. Jiang, C. L. Lizardi, X. P. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 7028–7032; *Angew. Chem.* **2014**, *126*, 7148–7152; *Angew. Chem.* **2014**, *126*, 7148; b) A. D. Bolig, M. Brookhart, *J. Am. Chem. Soc.* **2007**, *129*, 14544–14545; c) F. Hung-Low, J. P. Krogman, J. W. Tye, C. A. Bradley, *Chem. Commun.* **2012**, *48*, 368–370; d) T. W. Lyons, M. Brookhart, *Chem. Eur. J.* **2013**, *19*, 10124–10127.

[29] X.-S. Wu, K. Yang, Y. Zhao, H. Sun, G.-G. Li, H.-B. Ge, *Nat. Commun.* **2015**, *6*, 6462.

[30] X.-S. Wu, Y. Zhao, H. Ge, *J. Am. Chem. Soc.* **2015**, *137*, 4924–4927.

[31] a) M. Iyanaga, Y. Aihara, N. Chatani, *J. Org. Chem.* **2014**, *79*, 11933–11939; b) M.-L. Li, J.-X. Dong, X.-L. Huang, K.-Z. Li,

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Q. Wu, F.-J. Song, J.-S. You, *Chem. Commun.* **2014**, *50*, 3944–3946.
[32] X.-S. Wu, Y. Zhao H.-B. Ge, *Chem. Sci.* **2015**, DOI: 10.1039/c5sc02143j.
[33] a) A. E. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas, S. S. Stahl, *J. Am. Chem. Soc.* **2010**, *132*, 12068–12073; b) A. M. Suess, M. Z. Ertem, C. J. Cramer, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 9797–9804; c) X. Wu, Y. Zhao, H. Ge, *Chem. Asian J.* **2014**, *9*, 2736–2739; Z. Wang, Y. Kuninobu, M. Kanai, *Org. Lett.* **2014**, *16*, 4790–4793; d) J. Zhang, H. Chen, B. Wang, Z. Liu, Y. Zhang, *Org. Lett.* **2015**, *17*, 2768–2771.

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Palladium-catalyzed decarboxylative alkoxycarbonylation of potassium aryltrifluoroborates with potassium oxalate monoesters†

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Palladium-catalyzed decarboxylative alkoxycarbonylation of potassium aryltrifluoroborates with potassium oxalate monoesters in the presence of potassium persulfate was performed under mild conditions. A number of benzoyl esters with a wide variety of substituents at different positions were efficiently synthesized with this method. Mechanism of the palladium-catalyzed decarboxylative carbonylation of aryltrifluoroborates was studied, and a radical-mediated Pd(II)/Pd(IV) catalytic cycle was proposed.

Introduction

During the past decade, transition metal-catalyzed cross coupling has been extensively studied as a powerful synthetic tool for selective carbon–carbon (C–C) bond formation.[1] In particular, transition metal-catalyzed decarboxylative coupling has recently attracted more and more attention.[2] Compared with the traditional coupling reactions, this transformation is more environmentally friendly since stoichiometric organometallic waste is replaced by the innocuous CO_2 gas. In addition, as the coupling partners, carboxylic acids are readily available at low cost, fairly stable and easy to handle and store in laboratory. However, although the first decarboxylative cross-coupling reaction was realized with unsatisfactory yield in 1960s,[3] it remained unelaborated until recent years. In 2002, Myers reported the silver-mediated decarboxylation of benzoic acid derivatives, followed by a palladium-catalyzed Heck reaction with alkenes.[4] This discovery opened the door to a new area of synthetic methodology. Later on, the milestone discoveries were reported by Goossen and co-workers,[5] who developed the synthesis of biaryls *via* palladium/copper-catalyzed decarboxylative coupling of aryl carboxylic acids and aryl halides. Furthermore, alkyl, alkenyl, and alkynyl carboxylic acids were also demonstrated as effective substrates in decarboxylative cross-coupling reactions, turning the methods into highly valuable alternatives to classical reactions for the C–C bond formation.

In 2008, α-oxocarboxylic acids were first utilized as coupling partners by Goossen's group in a Cu/Pd-catalyzed acylation reaction of aryl halides.[6] Alkoxycarbonylation of aryl halides *via* decarboxylation of oxalate monoesters was later realized by Liu and co-workers (Scheme 1, eqn (1)).[7] However, high temperature was required for the decarboxylation process in these reports, which limits the substrate scope of these reactions.

Inspired by Minisci's work on peroxydisulfate,[8] we discovered that decarboxylative *ortho*-carbonylation of acetanilides with α-oxocarboxylic acids can be realized at room temperature in the presence of a persulfate.[9] Recently, Wang's group developed the Pd-catalyzed *ortho*-ethoxycarbonylation of *O*-methylketoximes with potassium oxalate monoester using Ag_2CO_3 and $K_2S_2O_8$ as oxidants (eqn (2)).[10] However, these reactions

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† Electronic supplementary information (ESI) available: Data table of the time-yield curve and copies of ^1H and ^{13}C NMR spectra of new compounds. See DOI: 10.1039/c5qo00349k

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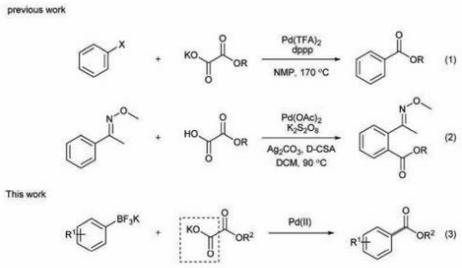


Scheme 1 Synthesis of aryl esters with Pd-catalyzed decarboxylative coupling.

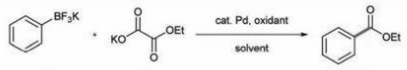
can be performed only on substrates with a directing group, which limits the potential application of this approach. We envisioned that boronic acids or their derivatives may be utilized in the coupling reactions to broaden the product range of the method. Arylboronic acids and their derivatives are staple substrates in Suzuki–Miyaura coupling reactions.[11] However, the most common pathway of direct transformation from arylboronic acids to carbonyl compounds, the insertion of carbon monoxide,[12] suffers from the use of high pressure of the toxic and flammable CO gas, which diminishes its practical utility. To provide an alternative access to aryl ketones, Goossen and Yamamoto developed the Pd-catalyzed decarboxylative cross-coupling reactions of arylboronic acids with anhydrides, carboxylic acids, and α-oxocarboxylic acids, in which the requirement for high temperature or stoichiometrical expensive metal reagents or strong bases is avoided.[13] Inspired by these results, our group realized the decarboxylative acylation and aminocarbonylation of potassium aryltrifluoroborates with α-oxocarboxylic acids and oxamic acids.[14] Herein, as a supplement to the previous methods, we report the Pd-catalyzed decarboxylative alkoxycarbonylation of potassium aryltrifluoroborates with potassium oxalate monoesters under mild conditions.

Results and discussion

On the basis of our success on decarboxylative cross coupling of aryltrifluoroborates with α-oxocarboxylic acids and oxamic acids,[14] we investigated the decarboxylative coupling reaction between potassium phenyltrifluoroborate and potassium 2-ethoxy-2-oxoacetate (Table 1). The ethyl benzoate was obtained with 10 mol% $Pd(OAc)_2$ and 2 equiv. $K_2S_2O_8$ in a mixture of DMSO and water at room temperature (entry 1). Further screening of solvent showed that the mixture of MeCN/DMSO/H_2O was the best (entries 2–5). Although $(NH_4)_2S_2O_8$ was also effective, $K_2S_2O_8$ was found to be the optimal oxidant (entries 6 and 7). Gratifyingly, the product yield was improved when the reaction was heated at 70 °C for 5 min and then cooled to room temperature (entry 8). Finally, a high yield was acquired by increasing the amount of the $K_2S_2O_8$ to 3 equiv. (entry 9). It was noted that $Pd(OAc)_2$ was the most efficient catalyst in this reaction (entries 9–12). Furthermore, the desired coupling product was not observed in the absence of a palladium catalyst (entry 13).

With the optimized conditions in hand, we then investigated the substrate scope of the alkoxycaronylation reaction. As shown in Table 2, a variety of aryl esters were synthesized

Table 1 Optimization of reaction conditions[a]



1a 2a 3a

Entry	Pd catalyst	Oxidant	Solvent (v : v)	Yield[b] (%)
1	$Pd(OAc)_2$	$K_2S_2O_8$	DMSO/H_2O (4 : 1)	21
2	$Pd(OAc)_2$	$K_2S_2O_8$	MeCN/H_2O (4 : 1)	<5
3	$Pd(OAc)_2$	$K_2S_2O_8$	DME/H_2O (4 : 1)	0
4	$Pd(OAc)_2$	$K_2S_2O_8$	diglyme/H_2O (4 : 1)	0
5	$Pd(OAc)_2$	$K_2S_2O_8$	MeCN/DMSO/H_2O (2 : 2 : 1)	30
6	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	MeCN/DMSO/H_2O (2 : 2 : 1)	18
7	$Pd(OAc)_2$	H_2O_2	MeCN/DMSO/H_2O (2 : 2 : 1)	0
8[c]	$Pd(OAc)_2$	$K_2S_2O_8$	MeCN/DMSO/H_2O (2 : 2 : 1)	72
9[c,d]	$Pd(OAc)_2$	$K_2S_2O_8$	MeCN/DMSO/H_2O (2 : 2 : 1)	84(82)
10[c,d]	$Pd(TFA)_2$	$K_2S_2O_8$	MeCN/DMSO/H_2O (2 : 2 : 1)	60
11[c,d]	Pd(acac)$_2$	$K_2S_2O_8$	MeCN/DMSO/H_2O (2 : 2 : 1)	39
12[c,d]	$Pd(MeCN)_2(BF_4)_2$	$K_2S_2O_8$	MeCN/DMSO/H_2O (2 : 2 : 1)	68
13[c,d]	—	$K_2S_2O_8$	MeCN/DMSO/H_2O (2 : 2 : 1)	0

[a] Conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), PdX_2, oxidant (0.6 mmol), 6 mL solvent, rt, overnight. [b] Yields and conversions are based on **1a**, determined by ^{1}H-NMR using dibromomethane as the internal standard. Isolated yield is in parenthesis. [c] Preheated at 70 °C for 5 min, and then rt for 1 h. [d] With 3.0 eq. (0.9 mmol) $K_2S_2O_8$.

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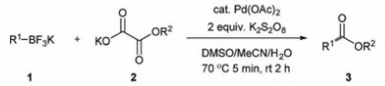
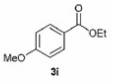
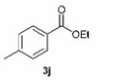
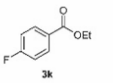
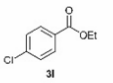
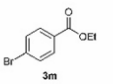
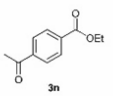
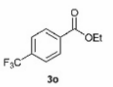
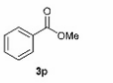
Table 2 Alkoxycarbonylation of potassium aryltrifluoroborates[a]



1 2 3

Product	Yield[b] (%)	Product	Yield[b] (%)
 3a	82	 3i	44
 3b	52	 3j	76
 3c	60	 3k	79
 3d	43	 3l	67
 3e	81	 3m	63
 3f	58	 3n	35
 3g	63	 3o	35
 3h	57	 3p	76

[a] Conditions: **1** (0.3 mmol), **2a** or **2b** (0.6 mmol, 2.0 equiv.), $Pd(OAc)_2$ (0.030 mmol, 10 mol%), $K_2S_2O_8$ (0.9 mmol, 3.0 equiv.), DMSO/MeCN/H_2O (4 : 4 : 2, v/v/v, 6 mL), preheated at 70 °C for 5 min, then at rt for 1 h. [b] Isolated yields based on **1**.

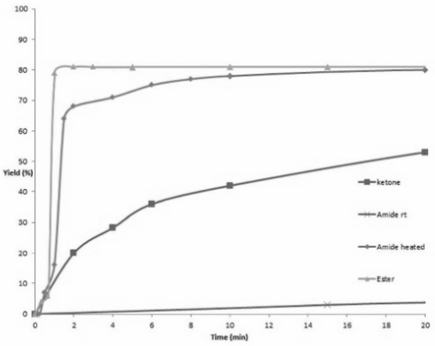


Fig. 1 Time courses of the cross-coupling reactions. 0–20 min.

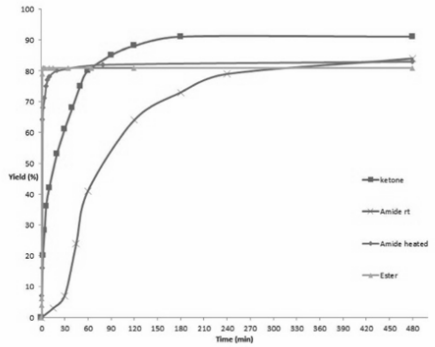
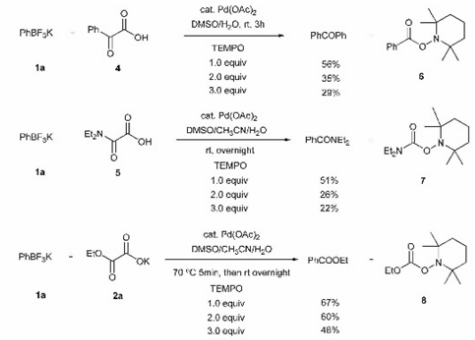


Fig. 2 Time courses of the cross-coupling reactions. 0–480 min.

under the standard conditions. Potassium phenyltrifluoroborates with a methyl group at the *meta*- or *para*-position of the phenyl ring (Table 2, **3e** and **3j**) gave comparable yields to that of **3a**. The *ortho*-methyl phenyltrifluoroborate gave a lower yield than those of the counterparts with a *meta*- or *para*-methyl group (**3b** *vs.* **3e**, **3j**), presumably due to the steric effect. Ester **3k**, which has a fluoro group at the *para*-postion of the phenyl ring, could be produced in a good yield from the corresponding substrate (**3k**). Methoxy-, chloro-, and bromo-substituted phenyltrifluoroborates gave moderate yields (**3c**, **3d**, **3f**, **3g**, **3i**, **3l** and **3m**), while lower yields were observed with the electron-withdrawing groups on the phenyl ring (**3h**, **3n**, **3o**). In addition, potassium 2-methoxy-2-oxoacetate (**7b**) was demonstrated as a feasible substrate, affording a satisfying yield (**3p**).

Mechanistic study

As mentioned above and in our previous reports,[14] the alkoxycarbonylation and aminocarbonylation reactions require heating at the beginning of the reaction. To illustrate the function of increased temperature and thereby to provide some insights of the catalytic process, time courses for acylation, aminocarbonylation, and alkoxycarbonylation of potassium phenyltrifluoroborate were examined (Fig. 1 and 2). Not surprisingly, the reaction rates for production of the ketone and the amide at room temperature were comparatively high at the



Scheme 2 Control experiments with TEMPO.

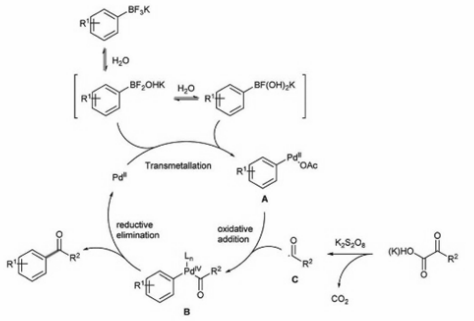


Fig. 3 Plausible reaction mechanism. L = Ligand.

beginning, as most of the product was accumulated in the first 2 hours (Fig. 2, red and purple). In the case of heated reactions, the early reaction rates were extraordinarily fast (Fig. 2, blue and green). Remarkably, the alkoxycarbonylation process was almost completed within 2 min at 70 °C (Fig. 1, pink).

To further study the mechanistic aspects of the catalytic decarboxylative cross-coupling, TEMPO was introduced to the reactions under standard conditions as a radical trapping reagent (Scheme 2). It was found that the formation of the decarboxylative coupling products was suppressed, while TEMPO-aldehyde, amide, and ester adducts were detected by LC-MS respectively. The decarboxylative coupling reactions were not completely inhibited, which is consistent with the reaction rate study since the coupling reactions were so fast at the beginning that they could overwhelm the competing reactions. In addition, the yields of the coupling products were reduced by increasing the amount of TEMPO in the reaction systems. Furthermore, the TEMPO adducts were isolated from the control experiments under the similar conditions in the absence of $PhBF_3K$ and $Pd(OAc)_2$ (see Experimental section). Thus, all the results suggest that radical intermediates are likely formed and involved in these coupling reactions, which indicates a different reaction pathway from the previously proposed ligand exchange process of direct decarboxylative acylation of acetanlides.[9]

Based on the above observations and previous literature reports,[15] a tentative mechanism for the cross coupling is proposed (Fig. 3). The reaction is initiated by the transmetallation between the Pd(II) catalyst and the boronic intermediates derived from hydrolysis of the aryltrifluoroborate to afford the Pd(II) intermediate **A**. Oxidation of **A** in the presence of the carbonyl radical **C**, which is formed by the decarboxylation of an α-oxocarboxylic or oxamic acid, generates the Pd(IV) intermediate **B**. The desired carbonyl product is then produced *via* reductive elimination of **B**, while the Pd(II) species is reproduced. It's noteworthy that a dimeric Pd(III) mechanism cannot be excluded.[16]

Conclusions

In summary, we have demonstrated that a handy and efficient palladium-catalyzed alkoxycarbonylation of potassium aryltrifluoroborates with the decarboxylation of potassium oxalate monoester could be performed under mild and compatible conditions. This unprecedented reaction provides a promising pathway towards a variety of aryl esters. Additionally, the mechanistic study suggests that radicals should be involved in this process, constituting the possible Pd(II)/Pd(IV) catalytic cycle.

Experimental

General methods

All reactions were carried out in oven-dried glassware. Pd(II) catalysts, Ag_2CO_3, $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ were purchased and used directly. All other solvents and commercially available reagents (boronic acids, KHF_2, amines and potassium oxalate monoester) were purchased and used directly. For TLC analysis, precoated plates (0.25 mm thick) were used; for air-flashed column chromatography, flash silica gel (32–63 μm) was used. ^1H NMR and ^{13}C NMR spectra were measured on a 500 MHz spectrometer (^1H at 500 MHz, ^{13}C at 125 MHz), using $CDCl_3$ as solvent with tetramethylsilane (TMS) as an internal standard at room temperature. ^1H NMR data was reported as: chemical shift (δ ppm), multiplicity, coupling constant (Hz), integration. ^{13}C NMR data was reported in terms of chemical shift (δ ppm).

Starting materials

Potassium aryltrifluoroborates (**1a**, **1i**, **1j** and **1l**) and potassium oxalate monoesters (**2a**, **2b**) were purchased and used directly. Other potassium aryltrifluoroborates were prepared from boronic acids with KHF_2 according to the reported procedure.[17] *N*,*N*-Diethyloxamic acid (**5**) was prepared from diethyl oxalate with *N*,*N*-diethylamine according to the reported procedure.[18]

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General procedure for the synthesis of aryl esters (3)

An 8 mL vial was charged with magnetic bar, $ArBF_3K$ (**1**, 0.3 mmol), potassium oxalic acid monoesters (**2**, 0.6 mmol, 2.0 equiv.), $K_2S_2O_8$ (0.9 mmol, 3.0 equiv.), followed by $Pd(OAc)_2$ (DMSO solution, 0.03 mmol/2.4 mL, 10 mol%, 2.4 mL), CH_3CN (2.4 mL) and DI water (1.2 mL). The vial was capped and the reaction mixture was stirred at 70 °C for 5 min, and then cooled down to room temperature and stirred for 1 h. The reaction was quenched by the addition of 3 mL of water and the resulting mixture was extracted with EtOAc (5 mL × 3). The combined organic phase was dried over Na_2SO_4, and then concentrated under vacuum. The desired product was obtained after purification by flash chromatography column on silica gel (gradient eluent of EtOAc in hexanes: 0–30%, v/v).

Ethyl benzoate (3a) (CAS no. 93-89-0). Colorless oil, 36.9 mg, 82% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.36 (t, J = 7.0 Hz, 3 H), 4.35 (q, J = 7.0 Hz, 2 H), 7.36–7.42 (m, 2 H), 7.51 (t, J = 7.5 Hz, 1 H), 8.03 (d, J = 7.5 Hz, 2 H).

Ethyl 2-methylbenzoate (3b) (CAS no. 87-24-1). Colorless oil, 26.1 mg, 53% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (t, J = 7.0 Hz, 3 H), 2.60 (s, 3 H), 4.36 (q, J = 7.0 Hz, 2 H), 7.22–7.26 (m, 2 H), 7.39 (dt, J = 1.5, 7.5 Hz, 1 H), 7.89–7.92 (m, 1 H).

Ethyl 2-chlorobenzoate (3c) (CAS no. 7335-25-3). Colorless oil, 33.2 mg, 60% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.40 (t, J = 7.0 Hz, 3 H), 4.40 (q, J = 7.0 Hz, 2 H), 7.30 (dt, J = 1.5, 7.5 Hz, 1 H), 7.37–7.46 (m, 2 H), 7.80 (dd, J = 1.5, 8.0 Hz, 1 H).

Ethyl 3-methoxybenzoate (3d) (CAS no. 10259-22-0). Colorless oil, 23.2 mg, 43% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (t, J = 7.0 Hz, 3 H), 3.85 (s, 3 H), 4.37 (q, J = 7.0 Hz, 2 H), 7.09 (ddd, J = 1.0, 2.5, 8.0 Hz, 1 H), 7.33 (t, J = 8.0 Hz, 1 H), 7.56 (dd, J = 1.5, 3.0 Hz, 1 H), 7.64 (td, 1.5, 7.5 Hz, 1 H).

Ethyl 3-methylbenzoate (3e) (CAS no. 120-33-2). Colorless oil, 39.9 mg, 81% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (t, J = 7.0 Hz, 3 H), 2.40 (s, 3 H), 4.37 (q, J = 7.0 Hz, 2 H), 7.30–7.37 (m, 2 H), 7.83–7.87 (m, 2 H).

Ethyl 3-chlorobenzoate (3f) (CAS no. 1128-76-3). Colorless oil, 32.1 mg, 58% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.38 (t, J = 7.0 Hz, 3 H), 4.36 (q, J = 7.0 Hz, 2 H), 7.35 (t, J = 7.5 Hz, 1 H), 7.46–7.51 (m, 1 H), 7.90 (d, J = 7.5 Hz, 1 H), 7.99 (t, J = 1.5 Hz, 1 H).

Ethyl 3-bromobenzoate (3g) (CAS no. 24398-88-7). Colorless oil, 43.3 mg, 63% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (t, J = 7.0 Hz, 3 H), 4.37 (q, J = 7.0 Hz, 2 H), 7.30 (t, J = 8.0 Hz, 1 H), 7.65–7.68 (m, 1 H), 7.96 (d, J = 8.0, 1 H), 8.16–8.18 (m, 1 H).

Ethyl 3-acetylbenzoate (3h) (CAS no. 37847-24-8). Colorless oil, 32.9 mg, 57% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.42 (t, J = 7.0 Hz, 3 H), 2.65 (s, 3 H), 4.42 (q, J = 7.0 Hz, 2 H), 7.55 (t, J = 8.0 Hz, 1 H), 8.15 (td, J = 1.5, 7.5 Hz, 1 H), 8.24 (td, J = 1.5, 7.5 Hz, 1 H), 8.59 (t, J = 1.5 Hz, 1 H).

Ethyl 4-methoxybenzoate (3i) (CAS no. 94-30-4). Colorless oil, 23.8 mg, 44% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.38 (t, J = 7.0 Hz, 3 H), 3.86 (s, 3 H), 4.34 (q, J = 7.0 Hz, 2 H), 6.89–6.93 (m, 2 H), 7.98–8.02 (m, 2 H).

Ethyl 4-methylbenzoate (3j) (CAS no. 94-08-6). Colorless oil, 36.9 mg, 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (t, J = 7.0 Hz, 3 H), 2.40 (s, 3 H), 4.36 (q, J = 7.0 Hz, 2 H), 7.23 (d, J = 8.0 Hz, 2 H), 8.11–8.14 (m, 2 H).

Ethyl 4-fluorobenzoate (3k) (CAS no. 451-46-7). Colorless oil, 39.9 mg, 79% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.38 (t, J = 7.0 Hz, 3 H), 4.36 (q, J = 7.0 Hz, 2 H), 7.07–7.11 (m, 2 H), 8.03–8.07 (m, 2 H).

Ethyl 4-chlorobenzoate (3l) (CAS no. 7335-27-5). Colorless oil, 37.1 mg, 67% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (t, J = 7.0 Hz, 3 H), 4.37 (q, J = 7.0 Hz, 2 H), 7.39–7.42 (m, 2 H), 7.96–7.99 (m, 2 H).

Ethyl 4-bromobenzoate (3m) (CAS no. 5798-75-4). Colorless oil, 43.4 mg, 63% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (t, J = 7.0 Hz, 3 H), 4.37 (q, J = 7.0 Hz, 2 H), 7.56–7.58 (m, 2 H), 7.89–7.91 (m, 2 H).

Ethyl 4-acetylbenzoate (3n) (CAS no. 38430-55-6). Colorless oil, 20.2 mg, 35% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.41 (t, J = 7.0 Hz, 3 H), 2.64 (s, 3 H), 4.40 (q, J = 7.0 Hz, 2 H), 7.23 (d, J = 8.0 Hz, 2 H), 7.92–7.95 (m, 2 H).

Ethyl 4-(trilfuoromethyl)benzoate (3o) (CAS no. 93-58-3). Colorless oil, 22.9 mg, 35% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.42 (t, J = 7.0 Hz, 3 H), 4.42 (q, J = 7.0 Hz, 2 H), 7.70 (d, J = 8.0 Hz, 2 H), 8.16 (d, J = 8.0 Hz, 2 H).

Methyl benzoate (3p) (CAS no. 1696-17-9). Colorless oil, 31.0 mg, 76% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.92 (s, 3 H), 7.43 (t, J = 8.0 Hz, 2 H), 7.53–7.58 (m, 1 H), 8.04 (dd, J = 1.5, 8.0 Hz, 2 H).

Time-yield curve in formation of benzophenone (Fig. 1, red markers)

Parallel experiments were carried out with the procedure described below. An 8 mL vial was charged with magnetic stir bar, $ArBF_3K$ (**1a**, 0.3 mmol), 2-oxo-2-phenylacetic acid (4, 0.6 mmol, 2.0 equiv.), $K_2S_2O_8$ (0.6 mmol, 2.0 equiv.), followed by $Pd(OAc)_2$ (DMSO solution, 0.0075 mmol/1.2 mL, 2.5 mol%, 1.2 mL) and DI water (1.8 mL, DMSO : DI water = 1/1.5, v/v, 3 ml in total). The vial was capped and then the reaction mixture was stirred at room temperature. At each interval, NaOH (1 N, 3 mL) was added and the reaction mixture was extracted with EtOAc (5 mL × 3). The combined organic phase was concentrated under vacuum. The yields of benzophenone were determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

Time-yield curve in formation of *N,N*-diethylbenzamide at room temperature (Fig. 1, purple markers)

Parallel experiments were carried out with the procedure described below. An 8 mL vial was charged with magnetic stir bar, $PhBF_3K$ (**1a**, 0.3 mmol), 2-(diethylamino)-2-oxoacetic acid (5, 0.6 mmol, 2.0 equiv.), $K_2S_2O_8$ (0.9 mmol, 3.0 equiv.), followed by $Pd(OAc)_2$ (DMSO solution, 0.015 mmol/2.4 mL, 5 mol%, 2.4 mL), CH_3CN and DI water (DMSO : CH_3CN : DI water = 4/4/2, v/v/v, 6 ml in total). The vial was capped and then the reaction mixture was stirred at room temperature. At each interval, NaOH (1 N, 3 mL) was added and the reaction mixture was

extracted with EtOAc (5 mL × 3). The combined organic phase was concentrated under vacuum. The yields of *N*,*N*-diethylbenzamide were determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

Time-yield curve in formation of *N*,*N*-diethylbenzamide, heated (Fig. 1, orange and blue markers)

Parallel experiments were carried out with the procedure described below. An 8 mL vial was charged with magnetic stir bar, $PhBF_3K$ (**1a**, 0.3 mmol), 2-(diethylamino)-2-oxoacetic acid (**5**, 0.6 mmol, 2.0 equiv.), $K_2S_2O_8$ (0.9 mmol, 3.0 equiv.), followed by $Pd(OAc)_2$ (DMSO solution, 0.015 mmol/2.4 mL, 5 mol%, 2.4 mL), CH_3CN and DI water (DMSO : CH_3CN : DI water = 4/4/2, v/v/v, 6 ml in total). The vial was capped and the reaction mixture was stirred at 70 °C for 10 min, and then stirred at room temperature. At each interval, the vial is cooled with water bath immediately, and then 3 mL water was added and the reaction mixture was extracted with EtOAc (5 mL × 3). The combined organic phase was concentrated under vacuum. The yields of *N*,*N*-diethylbenzamide were determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

Time-yield curve in formation of ethyl benzoate (Fig. 1, pink and green markers)

Parallel experiments were carried out with the procedure described below. An 8 mL vial was charged with magnetic stir bar, $PhBF_3K$ (**1a**, 0.3 mmol potassium 2-ethoxy-2-oxoacetate (**2a**, 0.6 mmol, 2.0 equiv.), $K_2S_2O_8$ (0.9 mmol, 3.0 equiv.), followed by $Pd(OAc)_2$ (DMSO solution, 0.03 mmol/2.4 mL, 10 mol%, 2.4 mL), CH_3CN and DI water (DMSO : CH_3CN : DI water = 4/4/2, v/v/v, 6 ml in total). The vial was capped and the reaction mixture was stirred at 70 °C for 5 min, and then stirred at room temperature. At each interval, the vial is cooled with water bath immediately, and then 3 mL of water was added and the reaction mixture was extracted with EtOAc (5 mL × 3). The combined organic phase was concentrated under vacuum. The yields of ethyl benzoate were determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

Control experiments with TEMPO in the coupling reactions

The reactions were performed with standard procedures described above or in our previous reports[14] except that TEMPO was added into the vial before $Pd(OAc)_2$ and the solvents. Product yields were determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

Synthesis of 2,2,6,6-tetramethylpiperidin-1-yl benzoate (6) (CAS no. 7031-95-0). An 8 mL vial was charge with 2-oxo-2-phenylacetic acid (**4**, 0.6 mmol), $K_2S_2O_8$ (0.6 mmol, 1.0 equiv.) and TEMPO (0.6 mmol, 1.0 equiv.), followed by DMSO (1.2 mL) and DI water (1.8 mL). The vial was capped and the reaction was stirred at room temperature overnight. The reaction mixture was extracted with EtOAc (5 mL × 3), and the combined organic phase was dried over Na_2SO_4, concentrated. Flash chromatography afforded the desired product as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.28 (s, 6 H), 1.44 (s, 6 H), 1.58–1.65 (m, 1 H), 1.70–1.78 (m, 2 H), 1.81–1.98 (m, 3 H), 7.58–7.65 (m, 2 H), 7.69–7.75 (m, 1 H), 8.24 (d, J = 7.4 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.6, 18.4, 29.5, 36.6, 57.9, 126.1, 127.1, 127.3, 130.5, 163.9. IR (neat), ν: 3062, 2974, 2934, 2871, 1749, 1600, 1451, 1254 cm^{-1}. Ms (ESI): m/z = 262.4 [M + H$^+$].

Synthesis of 2,2,6,6-tetramethylpiperidin-1-yl diethylcarbamate (7). An 8 mL vial was charge with 2-(diethylamino)-2-oxoacetic acid (**5**, 0.6 mmol), $K_2S_2O_8$ (0.9 mmol, 1.5 equiv.) and TEMPO (0.6 mmol, 1.0 equiv.), followed by DMSO (2.4 mL), CH_3CN (2.4 mL) and DI water (1.2 mL). The vial was capped and the reaction was stirred at 70 °C for 30 min, and then stirred at room temperature overnight. The reaction mixture was extracted with EtOAc (5 mL × 3), and the combined organic phase was dried over Na_2SO_4, concentrated. Flash chromatography afforded the desired product as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.07–1.21 (m, 18 H), 1.36–1.43 (m, 1 H), 1.47–1.53 (m, 2 H), 1.56–1.66 (m, 1 H), 1.67–1.74 (m, 2 H), 3.30 (q, J = 7.1 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 14.8, 17.4, 21.4, 32.1, 39.4, 41.5, 42.5, 60.3, 157.1. IR (neat), ν: 2973, 2933, 2873, 1729, 1472, 1456, 1412, 1265 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{29}N_2O_2$ 257.2224, found 257.2226.

Synthesis of ethyl (2,2,6,6-tetramethylpiperidin-1-yl) carbonate (8). An 8 mL vial was charge with potassium 2-ethoxy-2-oxoacetate (**2a**, 0.6 mmol), $K_2S_2O_8$ (0.6 mmol, 1.0 equiv.) and TEMPO (0.6 mmol, 1.0 equiv.), followed by DMSO (2.4 mL), CH_3CN (2.4 mL) and DI water (1.2 mL). The vial was capped and the reaction was stirred at 70 °C for 30 min, and then stirred at room temperature overnight. The reaction mixture was extracted with EtOAc (5 mL × 3), and the combined organic phase was dried over Na_2SO_4, concentrated. Flash chromatography afforded the desired product as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.12 (s, 6 H), 1.17 (s, 6 H), 1.31 (t, J = 7.1 Hz, 3 H), 1.37–1.42 (m, 1 H), 1.49–1.55 (m, 2 H), 1.60–1.72 (m, 3 H), 4.22 (q, J = 7.1 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.7, 17.3, 20.8, 31.9, 39.6, 60.8, 64.4, 157.1. IR (neat), ν: 2979, 2935, 2873, 2860, 1775, 1747, 1465, 1365, 1220 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{12}H_{24}NO_3$ 230.1751, found 230.1751.

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Notes and references

1 For recent reviews, see: (*a*) K. Godula and D. Sames, *Science*, 2006, **312**, 67; (*b*) J.-P. Corbet and G. Mignani, *Chem. Rev.*, 2006, **106**, 2651; (*c*) L.-X. Yin and J. Liebscher,

This journal is © the Partner Organisations 2015

Chem. Rev., 2007, **107**, 133; (*d*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (*e*) E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev.*, 2007, **107**, 5318; (*f*) R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461; (*g*) N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395; (*h*) M. Catellani, E. Motti and N. Della Ca', *Acc. Chem. Res.*, 2008, **41**, 1512; (*i*) G. C. Fu, *Acc. Chem. Res.*, 2008, **41**, 1555; (*j*) R. Giri, B.-F. Shi, K. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242; (*k*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (*l*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*m*) S. De Ornellas, T. E. Storr, T. J. Williams, C. G. Baumann and I. J. S. Fairlamb, *Curr. Org. Chem.*, 2011, **8**, 79; (*n*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, **111**, 1293; (*o*) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885; (*p*) W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976; (*q*) T. C. Boorman and I. Larrosa, *Chem. Soc. Rev.*, 2011, **40**, 1910; (*r*) T. Newhouse and P. S. Baran, *Angew. Chem., Int. Ed.*, 2011, **50**, 3362; (*s*) J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (*t*) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068; (*u*) M. N. Hopkinson, A. D. Gee and V. Gouverneur, *Chem. – Eur. J.*, 2011, **17**, 8248; (*v*) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (*w*) S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936.

2 For recent reviews, see: (*a*) O. Baudoin, *Angew. Chem., Int. Ed.*, 2007, **46**, 1373; (*b*) L. J. Goossen, K. Goossen, N. Rodriguez, M. Blanchot, C. Linder and B. Zimmermann, *Pure Appl. Chem.*, 2008, **80**, 1725; (*c*) L. J. Goossen, N. Rodriguez and K. Goossen, *Angew. Chem., Int. Ed.*, 2008, **47**, 3100; (*d*) L. J. Goossen, F. Collet and K. Goossen, *Isr. J. Chem.*, 2010, **50**, 617; (*e*) S. M. Bonesi and M. Fagnoni, *Chem. – Eur. J.*, 2010, **16**, 13572; (*f*) N. Rodriguez and L. J. Goossen, *Chem. Soc. Rev.*, 2011, **40**, 5030; (*g*) R. Shang and L. Liu, *Sci. China, Ser. B*, 2011, **54**, 1670; (*h*) J. Cornella and I. Larrosa, *Synthesis*, 2012, 653.

3 M. Nilsson, *Acta Chem. Scand.*, 1966, **20**, 423.

4 A. G. Myers, D. Tanaka and R. J. Mannion, *Am. Chem. Soc.*, 2002, **124**, 11250.

5 (*a*) L. J. Goossen, G. J. Deng and L. M. Levy, *Science*, 2006, **313**, 662; (*b*) L. J. Goossen, N. Rodriguez, B. Melzer, C. Linder, G. J. Deng and L. M. Levy, *J. Am. Chem. Soc.*, 2007, **129**, 4824.

6 (*a*) L. J. Goossen, F. Rudolphi, C. Oppel and N. Rodriguez, *Angew. Chem., Int. Ed.*, 2008, **47**, 3043; (*b*) L. J. Goossen, B. Zimmermann and T. Knauber, *Angew. Chem., Int. Ed.*, 2008, **47**, 7103; (*c*) Y. Zheng, G. Yu, J. Wu and W.-M. Dai, *Synlett*, 2010, 1075–1080.

7 R. Shang, Y. Fu, J.-B. Li, S.-L. Zhang, Q.-X. Guo and L. Liu, *J. Am. Chem. Soc.*, 2009, **131**, 5738.

8 (*a*) F. Minisci, A. Citterio and C. Giordano, *Acc. Chem. Res.*, 1983, **16**, 27; (*b*) F. Minisci, E. Vismara and F. Fontana, *Heterocycles*, 1989, **28**, 489; (*c*) F. Fontana, F. Minisci, M. C. N. Barbosa and E. Vismara, *J. Org. Chem.*, 1991, **56**, 2866; (*d*) C. Chatgilialoglu, D. Crich, M. Komatsu and I. Ryu, *Chem. Rev.*, 1999, **99**, 1991; (*e*) C. Punta and F. Minisci, *Trends Heterocycl. Chem.*, 2008, **13**, 1.

9 P. Fang, M.-Z. Li and H.-B. Ge, *J. Am. Chem. Soc.*, 2010, **132**, 11898.

10 Z.-Y. Li and G.-W. Wang, *Org. Lett.*, 2015, **17**, 4866.

11 For recent reviews, see: (*a*) F. Bellina, A. Carpita and R. Rossi, *Synthesis*, 2004, 2419; (*b*) O. Baudoin, *Eur. J. Org. Chem.*, 2005, 4223; (*c*) N. T. S. Phan, M. Van Der Sluys and C. W. Jones, *Adv. Synth. Catal.*, 2006, **348**, 609; (*d*) N. Miyaura, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 1535; (*e*) M. Tobisu and N. Chatani, *Angew. Chem., Int. Ed.*, 2009, **48**, 3565; (*f*) G. A. Molander and B. Canturk, *Angew. Chem., Int. Ed.*, 2009, **48**, 9240; (*g*) N. Miyaura, *Synlett*, 2009, 2039; (*h*) C. E. I. Knappke and A. J. V. Wangelin, *Angew. Chem., Int. Ed.*, 2010, **49**, 3568; (*i*) A. Suzuki, *Angew. Chem., Int. Ed.*, 2011, **50**, 6722; (*j*) M. M. Heravi and E. Hashemi, *Tetrahedron*, 2012, **68**, 9145; (*k*) M. Blangetti, H. Rosso, C. Prandi, A. Deagostino and P. Venturello, *Molecules*, 2013, **18**, 1188.

12 Selected recent examples of CO insertion: (*a*) M.-J. Dai, B. Liang, C.-H. Wang, Z.-J. You, J. Xiang, G.-B. Dong, J.-H. Chen and Z. Yang, *Adv. Synth. Catal.*, 2004, **346**, 1669; (*b*) P. J. Tambade, Y. P. Patil, A. G. Panda and B. M. Bhanage, *Eur. J. Org. Chem.*, 2009, 3022; (*c*) M. V. Khedkar, P. J. Tambade, Z. S. Qureshi and B. M. Bhanage, *Eur. J. Org. Chem.*, 2010, 6981; (*d*) F. Jafarpour, P. Rashidi-Ranjbar and A. O. Kashani, *Eur. J. Org. Chem.*, 2011, 2128; (*e*) H.-L. Li, M. Yang, Y.-X. Qi and J.-J. Xue, *Eur. J. Org. Chem.*, 2011, 2662.

13 (*a*) L. J. Goossen and K. Ghosh, *Angew. Chem., Int. Ed.*, 2001, **40**, 3458; (*b*) L. J. Goossen, *Chem. Commun.*, 2001, 2084; (*c*) L. J. Goossen, L. Winkel, A. Dohring, K. Ghosh and J. Paetzold, *Synlett*, 2002, 1237; (*d*) R. Kakino, S. Yasumi, I. Shimizu and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 137; (*e*) R. Kakino, H. Narahashi, I. Shimizu and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 1333.

14 (*a*) M.-Z. Li, C. Wang and H.-B. Ge, *Org. Lett.*, 2011, **13**, 2062; (*b*) M.-Z. Li, C. Wang, P. Fang and H.-B. Ge, *Chem. Commun.*, 2011, 6587.

15 (*a*) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300; (*b*) D. Kalyani, N. R. Deprez, L. V. Desai and M. S. Sanford, *J. Am. Chem. Soc.*, 2005, **127**, 7330; (*c*) A. R. Dick, J. Kampf and M. S. Sanford, *J. Am. Chem. Soc.*, 2005, **127**, 12790; (*d*) G. A. Molander and N. Ellis, *Acc. Chem. Res.*, 2007, **40**, 275; (*e*) X. Tong, M. Beller and M. K. Tse, *J. Am. Chem. Soc.*, 2007, **129**, 4906; (*f*) L. L. Welbes, T. W. Lyons, K. A. Cychosz and M. S. Sanford, *J. Am. Chem. Soc.*, 2007, **129**, 5836; (*g*) W.-Y. Yu, W. N. Sit, K.-M. Lai, Z.-Y. Zhou and A. S. C. Chan, *J. Am. Chem. Soc.*, 2008, **130**, 3304; (*h*) P. A. Sibbald, C. F. Rosewall, R. D. Swartz and F. E. Michael, *J. Am. Chem. Soc.*, 2009, **131**, 15945;

(*i*) G.-W. Wang and T.-T. Yuan, *J. Org. Chem.*, 2010, **75**, 476; (*j*) T. W. Lysons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*k*) S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936.

16 (*a*) D. C. Powers and T. Ritter, *Nat. Chem.*, 2009, **1**, 302; (*b*) D. C. Powers, M. A. L. Geibel, J. E. M. N. Klein and T. Ritter, *J. Am. Chem. Soc.*, 2009, **131**, 17050.

17 G. A. Molander, W. Febo-Ayala and L. Jean-Gerard, *Org. Lett.*, 2009, **11**, 3830.

18 R. Peters, M. Althaus and A.-L. Nagy, *Org. Biomol. Chem.*, 2006, **4**, 498.

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