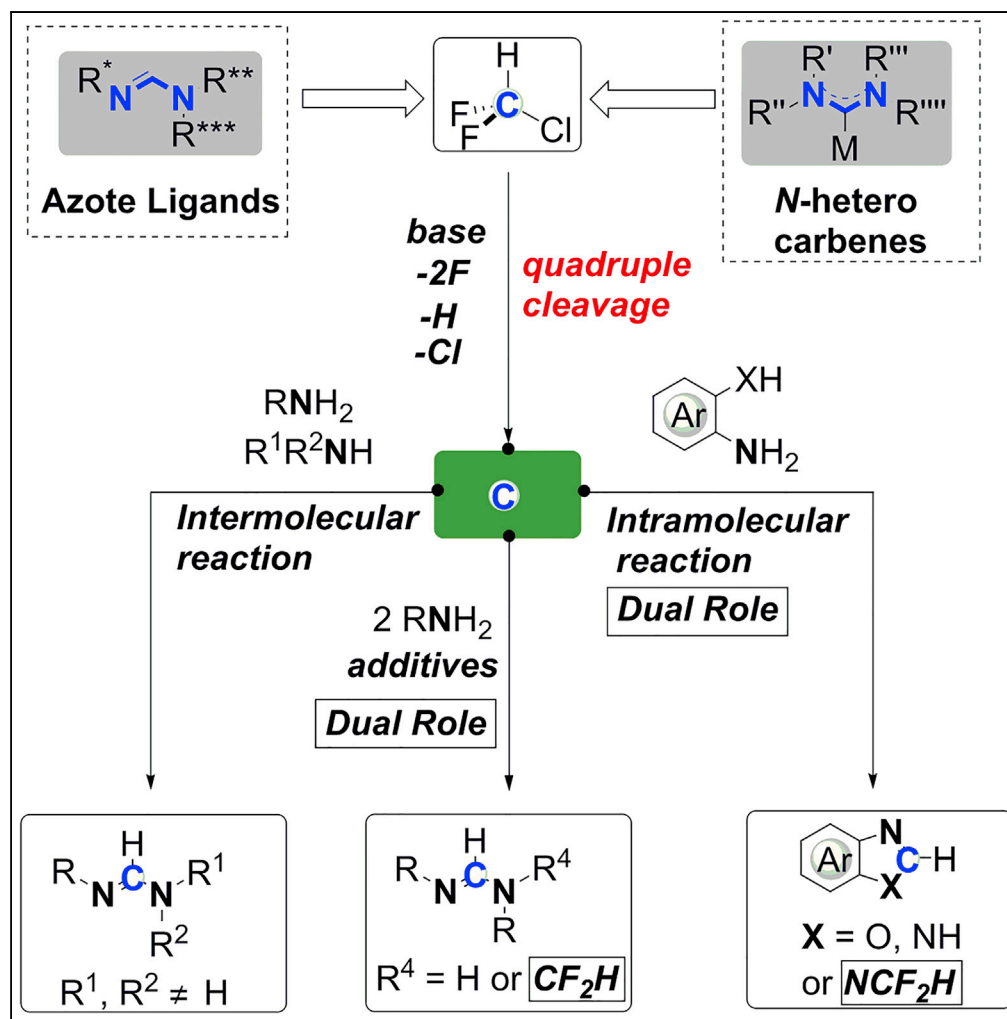


## Article

## Chlorodifluoromethane as a C1 Synthone in the Assembly of N-Containing Compounds



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## HIGHLIGHTS

Quadruple cleavage of  $\text{ClCF}_2\text{H}$  to afford a C1 synthone

The cleavage of two stable  $\text{C}(\text{sp}^3)\text{-F}$  bonds in aliphatic *gem*-difluoroalkanes

Enrich C1 chemistry, green chemistry, and fluorine chemistry

Various N-containing compounds were afforded via different role of  $\text{ClCF}_2\text{H}$

## Article

## Chlorodifluoromethane as a C1 Synthone in the Assembly of N-Containing Compounds

Xingxing Ma,<sup>1</sup> Jianke Su,<sup>1</sup> Xingang Zhang,<sup>2,\*</sup> and Qiuling Song<sup>1,3,4,5,\*</sup>

## SUMMARY

The development of C1 synthons to afford the products that add one extra carbon has become an important research theme in the past decade, and significant progress has been achieved with CO<sub>2</sub>, CO, HCOOH, and others as C1 units. Despite the great advance, the search for new C1 synthons that display unique reactivity, complement to the current C1 sources, and add more value to C1 chemistry is still desirable. Herein, we report a quadruple cleavage of chlorodifluoromethane to yield a C1 source, which was successfully employed in the construction of various N-containing compounds especially with pharmaceutical molecules under mild conditions. This strategy provides a useful method for late-stage modification of pharmaceutical compounds. Four bonds in ClCF<sub>2</sub>H were orderly cleaved under basic conditions in the absence of transition metals. Preliminary mechanistic studies revealed that (E)-N-phenylformimidoyl fluoride intermediate is involved in this process by *in situ* <sup>1</sup>H NMR studies and control experiments.

## INTRODUCTION

The C1 chemistry has emerged as an elegant strategy for efficient preparation of homologous compounds, which added one extra carbon in modern chemical transformations (Aresta et al., 2014; Sakakura et al., 2007; Huang et al., 2011; Yan et al., 2012; Natte et al., 2017; Wakade et al., 2017; Senadi et al., 2019). There are ample significance and a plethora of characteristics for C1 chemistry, for instance, carbon chain increasing (Aresta et al., 2014), construction of importance functional groups (carboxylic or carbonyl groups) (Huang et al., 2011; Cokoja et al., 2011), incorporation of two or more organic small molecules to yield important products (Oh and Hu, 2013), and modification of the pharmaceutical or natural products for value-added bulk (Liu et al., 2015; Ma et al., 2018a). Among all known C1 synthons, CO<sub>2</sub>, CO, and formic acid are the most famous ones, which have been widely used in various reaction processes, and many beautiful transformations have been developed with them, which further attracted more and more chemists devoted to this field (Aresta et al., 2014; Sakakura et al., 2007; Aresta et al., 2014; Huang et al., 2011; Cokoja et al., 2011; Oh and Hu, 2013; Sordakis et al., 2018; Gibson, 1969; Enthaler et al., 2010). Despite the significance and great advance of C1 chemistry, the search for C1 synthons that display unique reactivity, complement to the current C1 sources, and add more value to C1 chemistry is still highly desirable. Thus, direct introduction of one extra carbon from cheap and available materials under mild conditions to provide a cost-efficient, pragmatic, and valuable alternative avenue would be popular in the field of synthetic and pharmaceutical communities, which might have deep impact on industry as well.

Chlorodifluoromethane (ClCF<sub>2</sub>H) is well known as an inexpensive and abundant industrial raw material (Hudlicky and Pavlath, 1995) for the construction of various fluorinated compounds (Wang et al., 2014; Fier and Hartwig, 2012; Gu et al., 2014; Yu et al., 2017; Wu et al., 2019; Miao et al., 2018; Zhang et al., 2019), featuring thermodynamic stability and kinetic inertness as well as atomic economy as fluorine source. Therefore, efficient transformations of this easily accessible raw material to create valuable chemicals have deservedly gained great attention. The most common transformation of ClCF<sub>2</sub>H involves the formation of difluorocarbene (:CF<sub>2</sub>) by the cleavage of both C-Cl and C-H bonds (Figure 1Aa) (Feng et al., 2017), usually under basic conditions with heteroatom nucleophiles, rendering the corresponding difluoromethylated heteroatom compounds (Hine and Porter, 1957; Nawrot and Jonczyk, 2007). Pyrolysis of ClCF<sub>2</sub>H at high temperature or pressure leads to the important raw industrial material tetrafluoroethylene (Hudlicky and Pavlath, 1995; Sung et al., 2004). Very recently a reaction by palladium-catalyzed cross-coupling between arylboronic acids and ClCF<sub>2</sub>H via a metal-difluorocarbene intermediate has been reported (Feng et al., 2017; Yu et al., 2019), representing the catalytic transformation of ClCF<sub>2</sub>H. Other conversion processes that do not involve difluorocarbene species were still difluoromethylation-related ones in which only one

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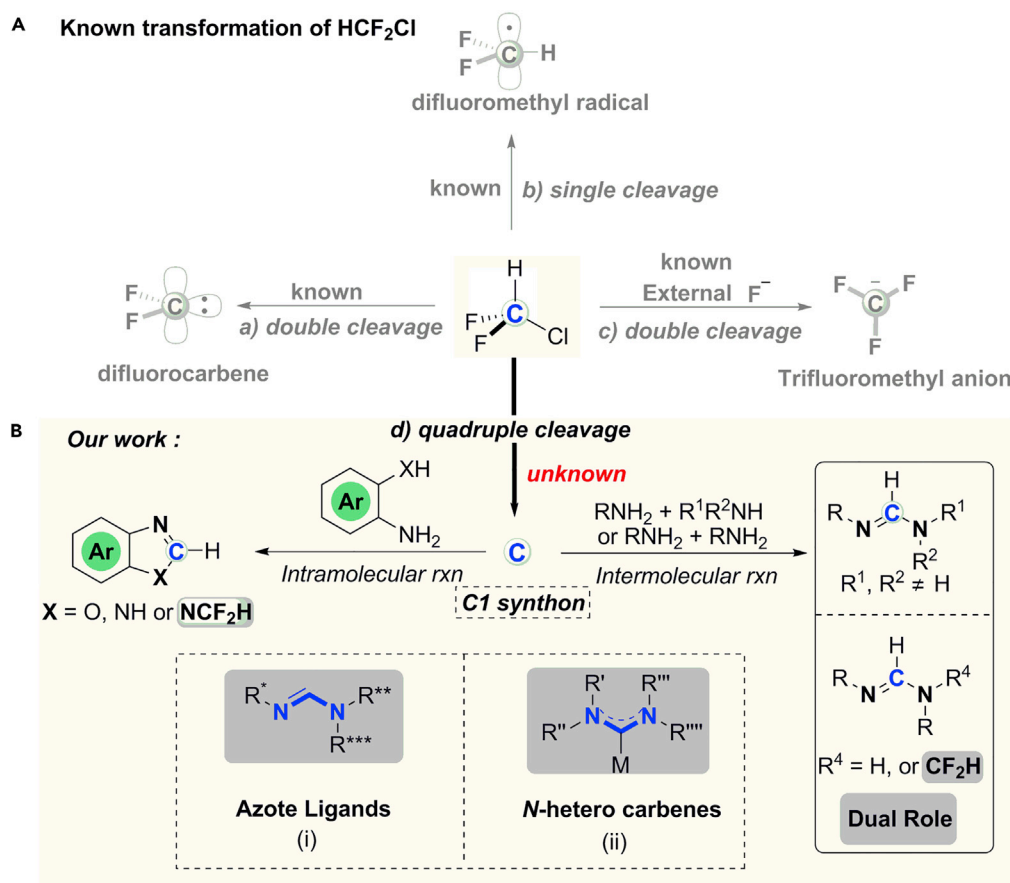
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**Figure 1. Various Transformations of  $\text{ClCF}_2\text{H}$**

(A) Known transformations of  $\text{ClCF}_2\text{H}$ .

(a) Double cleavage of  $\text{ClCF}_2\text{H}$  to lead to difluorocarbene species.

(b) Single cleavage of  $\text{ClCF}_2\text{H}$  to lead to difluoromethyl radical.

(c) Double cleavage of  $\text{ClCF}_2\text{H}$  with external  $\text{F}^-$  to lead to trifluoromethyl anion.

(B) Our work.

(d) Quadruple cleavage of  $\text{ClCF}_2\text{H}$  as a C1 source.

C-Cl bond was broken through a difluoromethyl radical pathway (Figure 1Ab) (Xu et al., 2018). Trifluoromethyl anion ( $\text{CF}_3^-$ ) is readily derived from the difluorocarbene species and external fluorine source via double cleavage of  $\text{ClCF}_2\text{H}$  (Figure 1Ac) (Zheng et al., 2015). Intriguingly and surprisingly, quadruple cleavage of  $\text{ClCF}_2\text{H}$  to provide versatile C1 synthons, by breaking one C-Cl bond, two stable C-F bonds, and one C-H bond orderly in a single-vessel reaction (Figure 1B), has never been reported to date, probably mainly because of the high BDE of  $\text{C}(\text{sp}^3)\text{-F}$  bonds (the bond dissociation energy of a single C-F bond: 485 KJ/mol) (O'Hagan, 2008).

Herein, we report a quadruple cleavage of chlorodifluoromethane as a type of C1 source to access valuable formimidamide derivatives that are widely employed as ligands or forming metal complexes as quasi-N-heterocyclic carbenes (NHCs) (Figure 1 (i) and (ii)) (Schröder et al., 2009, 2010; Bitterlich et al., 2007; Boogaerts and Nolan, 2010; Ohishi et al., 2008; Hopkinson et al., 2014). Despite the importance of these compounds, their elegant syntheses are very rare. Therefore, expanding the toolbox of methods for their synthesis will enrich diversity of this kind of compounds. Amines are very common raw materials as well as crucial building blocks with rich chirality (France et al., 2014); we envision that formimidamides could be readily generated in a single-vessel synthesis from two amines with  $\text{ClCF}_2\text{H}$  as C1 source due to the special reactivity of  $\text{ClCF}_2\text{H}$ . These processes represent a significant reaction modality for  $\text{ClCF}_2\text{H}$ , which might promote and enrich C1 chemistry, organic fluorine chemistry (Gouverneur and Seppelt,

2015), as well as green chemistry (Horváth, 2007). Meanwhile,  $\text{ClCF}_2\text{H}$  provides a unique and alternative approach for the current known C1 sources: the control and comparison experiments with CO,  $\text{CO}_2$ , and formic acid as C1 synthons were performed under our standard conditions as well as the reported procedures; notably, no desired formimidamides were ever formed or obtained under those reaction conditions. These results further underscore the uniqueness and peculiarity of  $\text{ClCF}_2\text{H}$  as a C1 source (for further details, see also Schemes S1 and S2).

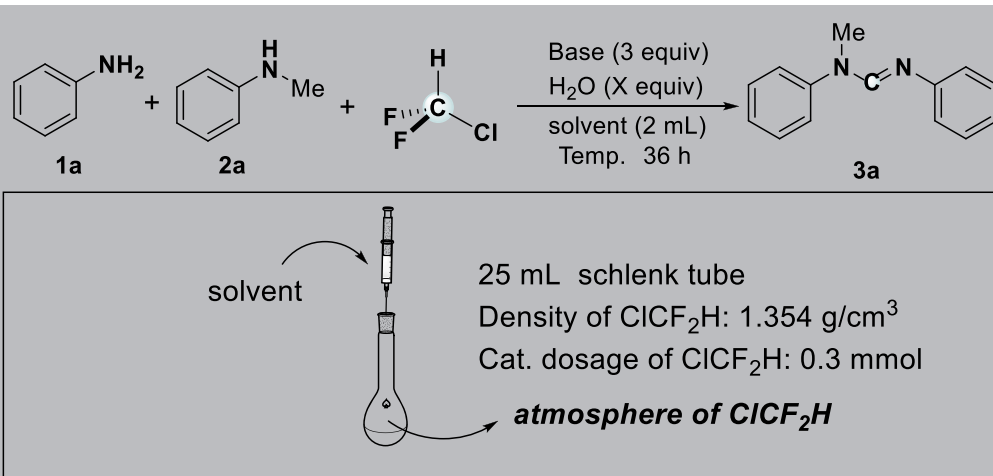
## RESULTS AND DISCUSSION

### Optimization of Reaction Conditions

Our design is based on our recent discovery in which ethyl bromodifluoroacetate ( $\text{BrCF}_2\text{COOEt}$ ) (Ma et al., 2018b; Deng et al., 2019) could act as a C1 source and formylating reagent with amines via quadruple cleavage under basic conditions (Ma et al., 2018a, 2018c, 2018d); we postulated that the quadruple cleavage of  $\text{ClCF}_2\text{H}$  could also be occurred under the similar sets since it is known that difluorocarbene could be readily accessible from  $\text{ClCF}_2\text{H}$  under basic conditions. Moreover, compared with  $\text{BrCF}_2\text{COOEt}$ ,  $\text{ClCF}_2\text{H}$  is obviously much cheaper and more atomic economical. We commenced our hypothesis by using low-cost and widely available aniline (**1a**) and *N*-methyl aniline (**2a**) as model substrates. To our delight, the yield of 76% of the anticipated product **3a** (Zhao et al., 2005) was obtained from the reaction of **1a** with **2a** under the  $\text{ClCF}_2\text{H}$  atmosphere without water (entry 1). More delightfully, the yield was significantly increased to 83%–92% with the increase of dosage of water (entries 2–3); notably, excess water caused deteriorated effect on the reaction, since some unknown by-products were observed when the amount of water was increased to 20–30 equivalents, and the yield of the desired product was dropped to 83% (entry 2 versus entry 3, and for further details, see also Table S2). Replacing KOH with either  $\text{Cs}_2\text{CO}_3$  or  $\text{K}_2\text{CO}_3$  as the base resulted in lower yields (entries 4–5). To our surprise, this transformation was completely suppressed with  $\text{Na}_2\text{CO}_3$  and  $\text{NaHCO}_3$  as the base (entries 6–7). The solvent was so crucial that no reaction occurred in other solvents, such as in THF and dioxane (entries 8–9) (for further details, see also Table S3). In addition, the yield of the desired product was slightly higher at the ambient temperature than at 50°C. In terms of reaction time, the longer time (36 h) led to the best result (entry 11).

### Substrate Scope for Intermolecular Transformation

With the optimal reaction conditions in hand (entry 2 in Table 1), we explored the generality and limitation of this transformation (Figure 2). First, a variety of *para*-substituted anilines with electron-donating groups (alkoxy, phenoxy, alkyl, and *N,N*-dimethyl) (**1b–1j**), as well as electron-withdrawing groups, such as halogen (**1k–1m**) and nitro group (**1n**), delivered the desired formimidamide derivatives (**3a–3n**) in good to excellent yields under the standard conditions. We next examined [1,1'-biphenyl]-4-amine (**1o**) under this reaction condition to provide the desired product **3o** in 77% yield. Besides, a large-scale (10 mmol) reaction of the *N*-methyl aniline (**2a**) has been carried out to afford **3a** in 62% yield (for further details, see also Scheme S3). Similar result could be obtained for *meta*-substituted (*m*-Br) aniline (**1p**). Using the disubstituted 3,4-dimethylaniline (**1q**) and trisubstituted 2,4,6-trimethylaniline (**1r**), the corresponding products (**3q** and **3r**) could be obtained in good yields (83%–85%). 5,6,7,8-Tetrahydronaphthalen-1-amine (**1s**) and 9*H*-fluoren-2-amine (**1t**) were carried out under the standard conditions to provide the target molecules (**3s** and **3t**) in 80% and 76% yields, respectively. The absolute molecular structure of product **3t** was unambiguously confirmed by X-ray crystallography analysis (Figure 2, and for further details, see also Table S1 and Data S1) (CCDC: 1874971). The fused polycyclic amines 9,9-diphenyl-9*H*-fluoren-2-amine (**1u**) and naphthalen-1-amine (**1v**) were subjected under the optimized reaction conditions, rendering the expected products (**3u–3v**) in moderate yields (68%–77%). Heterocyclic compounds, such as benzo[*d*]thiazol-2-amine (**1w**), were also amenable to this transformation, and the corresponding product was obtained in 62% yield. We then further investigated the scope of the *N*-substituted aniline derivatives with aniline (**1a**) under the viable reaction conditions. Delightedly, the corresponding products (**3x–3z**, **3aa–3ac**) were obtained in good to excellent yields with good functional group tolerance. In addition, given the prevailing existence of amines in pharmaceutical molecules and natural products (Ma et al., 2018a; Brunet and Neibecker, 2001), we selected Benzocaine (**1ad**, local anesthetic), Amoxapine (**2ae**, antidepressant), 2-(piperazin-1-yl)-4-(trifluoromethyl)pyrimidine (**2af**, medical/material intermediates), and multi-functional Vildagliptin (**2ag**, inhibit glucagon/chiral reagent/medicinalintermediate) and exposed them under the standard conditions; the corresponding products were obtained in 59%, 76%, 61%, and 71% yields, respectively. Gratifyingly, the chiral molecule (*S*)-*N*-benzyl-1-phenylethan-1-amine (**2ah**) experienced the optimal reaction conditions to deliver (*S,E*)-*N*-benzyl-*N'*-phenyl-*N*-(1-phenylethyl)formimidamide (**3ah**) in 60% yield, which might be a potential chiral ligand to realize enantioselective-control reactions.



Entry	Base (3 Equiv)	$\text{H}_2\text{O}$ (X Equiv)	Solvent (2 mL)	T (°C)	Yield (%) <sup>a</sup>
1	KOH	0	$\text{CH}_3\text{CN}$	r.t.	76
2	KOH	5	$\text{CH}_3\text{CN}$	r.t.	92 (88) <sup>b</sup>
3	KOH	30	$\text{CH}_3\text{CN}$	r.t.	83
4	$\text{Cs}_2\text{CO}_3$	5	$\text{CH}_3\text{CN}$	r.t.	76
5	$\text{K}_2\text{CO}_3$	5	$\text{CH}_3\text{CN}$	r.t.	79
6	$\text{Na}_2\text{CO}_3$	5	$\text{CH}_3\text{CN}$	r.t.	N.D.
7	$\text{NaHCO}_3$	5	$\text{CH}_3\text{CN}$	r.t.	N.D.
8	KOH	5	THF	r.t.	N.D.
9	KOH	5	Dioxane	r.t.	N.D.
10	KOH	5	$\text{CH}_3\text{CN}$	50	70
11 <sup>c,d</sup>	KOH	5	$\text{CH}_3\text{CN}$	r.t.	62 <sup>c</sup> (79) <sup>d</sup>
12 <sup>e</sup>	KOH	5	$\text{CH}_3\text{CN}$	r.t.	N.D.

**Table 1. Representative Results for Optimization of the Formation of (E)-N-methyl-N,N-diphenylformimidamide (3a)**

Reaction condition: aniline (**1a**, 1.2 equiv, 0.12 mmol), *N*-methylaniline (**2a**, 0.1 mmol), the atmosphere of chlorodifluoromethane ( $\text{ClCF}_2\text{H}$ ) (cat. 0.3 mmol), base (3 equiv.), solvent (2 mL), for 36 h.

r.t., room temperature; N.D., not detected.

<sup>a</sup>GC yields.

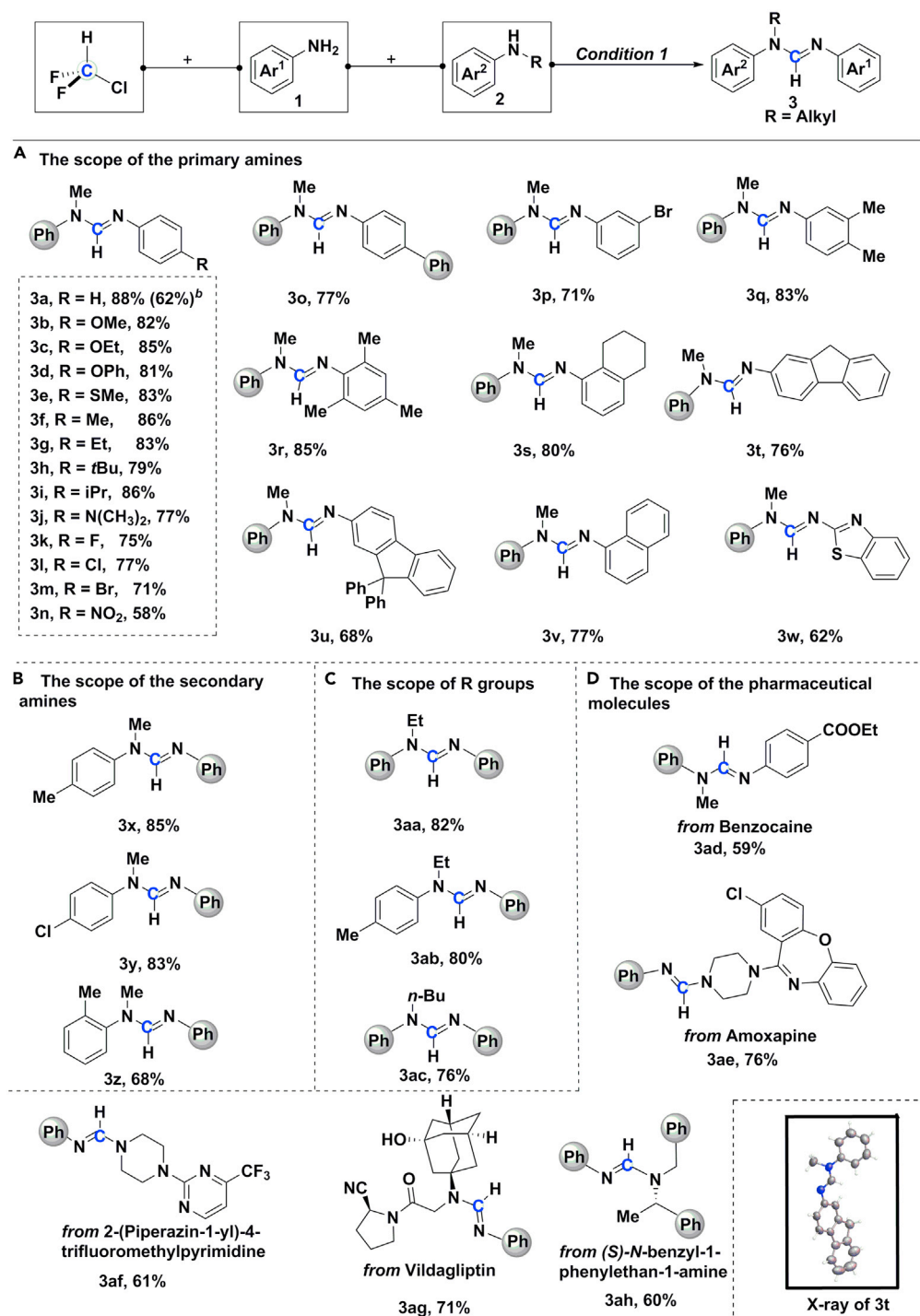
<sup>b</sup>Isolated yields.

<sup>c</sup>For 12 h.

<sup>d</sup>For 24 h.

<sup>e</sup>No  $\text{ClCF}_2\text{H}$ .

In addition, we found that aliphatic secondary amine is compatible under the standard conditions as well; in terms of the substrate dicyclohexylamine (**4**), the corresponding product **5** was acquired in 76% yield (Equation 1 in Figure 3A). It is worth mentioning that our strategy is highly regio-selective, for example, when *N*<sup>1</sup>-isopropyl-*N*<sup>3</sup>-phenylbenzene-1,3-diamine (**6**) was investigated under viable reaction condition, only compound **7** was afforded with diphenylamine part intact (Equation 2). In addition, when the target **3a** was hydrolyzing under 1 M HCl, the two original substrates (**1a** and **2a**) as well as two formylated compounds **1a-1** and **2a-1** were obtained, respectively (Ma et al., 2018a) (for further details, see also Scheme S4), which infers that our strategy might be a potential method for drug delayed or sustainable release when two different pharmaceutical molecules are combined by one extra carbon with our strategy (Equation 3). We carried out, therefore, correlative experiment using Benzocaine (**1ad**) and Vildagliptin



**Reaction Condition 1:** the primary amine (1, 0.12 mmol), the secondary amine (2, 0.1 mmol), KOH (3 equiv), H<sub>2</sub>O (5 equiv), CH<sub>3</sub>CN (2 mL), rt for 36 h under ClCF<sub>2</sub>H atmosphere; isolated yield. <sup>b</sup> 2a 10 mmol.

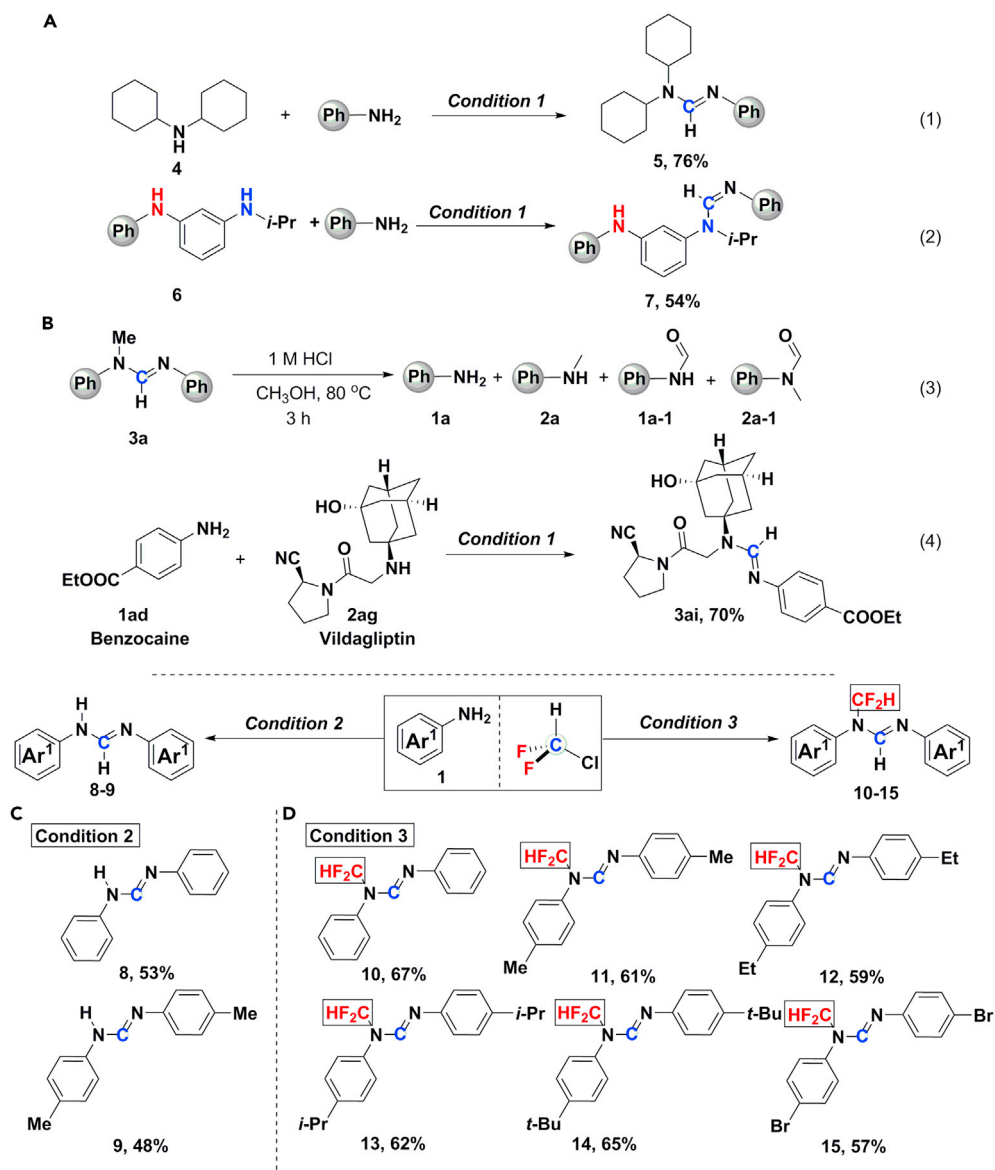
**Figure 2. Synthesis of Formimidamide Derivatives**

(A) Scope of the primary amines.

(B) Scope of the secondary amines.

(C) Scope of R groups.

(D) Scope of the pharmaceutical molecules.



**Reaction condition 1:** the primary amine (**1**, 0.12 mmol), the secondary amine (**2**, 0.1 mmol), KOH (3 equiv), H<sub>2</sub>O (5 equiv), CH<sub>3</sub>CN (2 mL), rt for 36 h under ClCF<sub>2</sub>H atmosphere; isolated yield. **Reaction condition 2:** aniline derivative (**1**, 0.2 mmol), K<sub>2</sub>CO<sub>3</sub> (3 equiv), phenol (10 mol%), H<sub>2</sub>O (5 equiv), CH<sub>3</sub>CN (2 mL), 80 °C for 12 h under ClCF<sub>2</sub>H atmosphere, isolated yield. **Reaction condition 3:** aniline derivative (**1**, 0.2 mmol), Cs<sub>2</sub>CO<sub>3</sub> (3 equiv), S<sub>8</sub> (5 mol%), CH<sub>3</sub>CN (5 mL), 80 °C for 26 h under ClCF<sub>2</sub>H atmosphere, isolated yield.

**Figure 3. High Regio- and Chemoselectivity of Our Strategy and Intriguing Products**

(A) High regio-selectivity.

(B) The dispose of target product and the combination of two pharmaceutical molecules.

(C) Selective synthesis of formimidamides with two primary amines.

(D) Selective synthesis of *N*-difluoromethyl-formimidamides from two primary amines with ClCF<sub>2</sub>H as both C1 source and difluoromethylating reagent.

(**2ag**) as the substrates under standard reaction **condition 1**; to our delight, the corresponding product **3ai** was obtained in 70% yield (Equation 4). More interestingly, a highly chemoselective process was disclosed with two primary amines, in which *N,N'*-diphenylformimidamide and *N*-(difluoromethyl)-*N,N'*-diphenylformimidamide were obtained, respectively, by careful control of reaction conditions. Bases and additives played key roles on these two successful transformations: with K<sub>2</sub>CO<sub>3</sub> as base, phenol and water as

additives (see **condition 2** in Figure 3 and for further details, see also Table S4), *N,N'*-diphenylformimidamides (**8** and **9**) were obtained in moderate yields; with Cs<sub>2</sub>CO<sub>3</sub> as the base and S<sub>8</sub> as additive (see **condition 3** in Figure 3, and for further details, see also Table S5) (Zheng et al., 2017), *N*-(difluoromethyl)-*N,N'*-diphenylformimidamides (**10–15**) were acquired in good yields. In the latter transformation, ClCF<sub>2</sub>H played a dual role as both C1 source and difluorocarbene source (Figure 3C).

### Substrate Scope for Intramolecular Transformation

The success of the above-mentioned intermolecular transformation prompted us to exploit the intramolecular transformations, since the latter one always leads to cyclic compounds that are the essential skeletons in pharmaceutical and natural products (Sasaki et al., 2006; Kubo et al., 1993). Gratifyingly, when *N*<sup>1</sup>-methylbenzene-1,2-diamine (**16**) was subjected to the standard conditions for intermolecular transformation, benzimidazole **17** was obtained in 90% yield, which could be readily converted into 2-bromo-benzimidazole **18** in the presence of NBS. Then, after a series of transformation, Telmisartan, a potent angiotensin II receptor antagonist used in the treatment of essential hypertension, will be afforded (Figure 4A) (Martin et al., 2015). In addition, the transformation could be easily scaled up to 70 times from **16** to **17** without loss of the efficiency (for details, see also Scheme S6). Encouraged by this promising result, we next focused on the exploration of the formation of benzo[d]oxazoles and 1*H*-benzo[d]imidazoles compounds via intramolecular pattern, since it is well known that benzo[d]oxazoles and 1*H*-benzo[d]imidazoles are prevalent molecular scaffolds in various bioactive natural products, agrochemicals, and pharmaceuticals. After many attempts, an optimized condition was obtained (for further details, see also Tables S6 and S7). These transformations demonstrated a good functional group tolerance (Figure 4B). Different substituent groups on the benzene ring, including alkyl (**19a**, **19b**), halo groups (**19c**, **19d**), were all compatible, rendering the corresponding products (**20a–20d**) in moderate to good yield (68%–81%). Surprisingly, no desired products were detected when 2-amino-4-nitrophenol (**19e**) and 2-amino-5-nitrophenol (**19f**) underwent the same conditions, instead, the selective difluoromethylation of hydroxyl group occurred (**20e'** and **20f'**). Good yields were achieved on various benzene-1,2-diamine compounds under the standard Reaction Condition **5** with K<sub>2</sub>CO<sub>3</sub> as base in CH<sub>3</sub>CN (2 mL) and H<sub>2</sub>O (0.5 mL) at 100°C for 16 h (Figure 4C). Remarkably, the products of difluoromethylation of benzimidazoles (**21–29**) were acquired in moderate yields via the slight adjustment of reaction condition (see **reaction condition 6** for details); once again, ClCF<sub>2</sub>H played a dual role as both C1 source and difluorocarbene source in this transformation (Figure 4D).

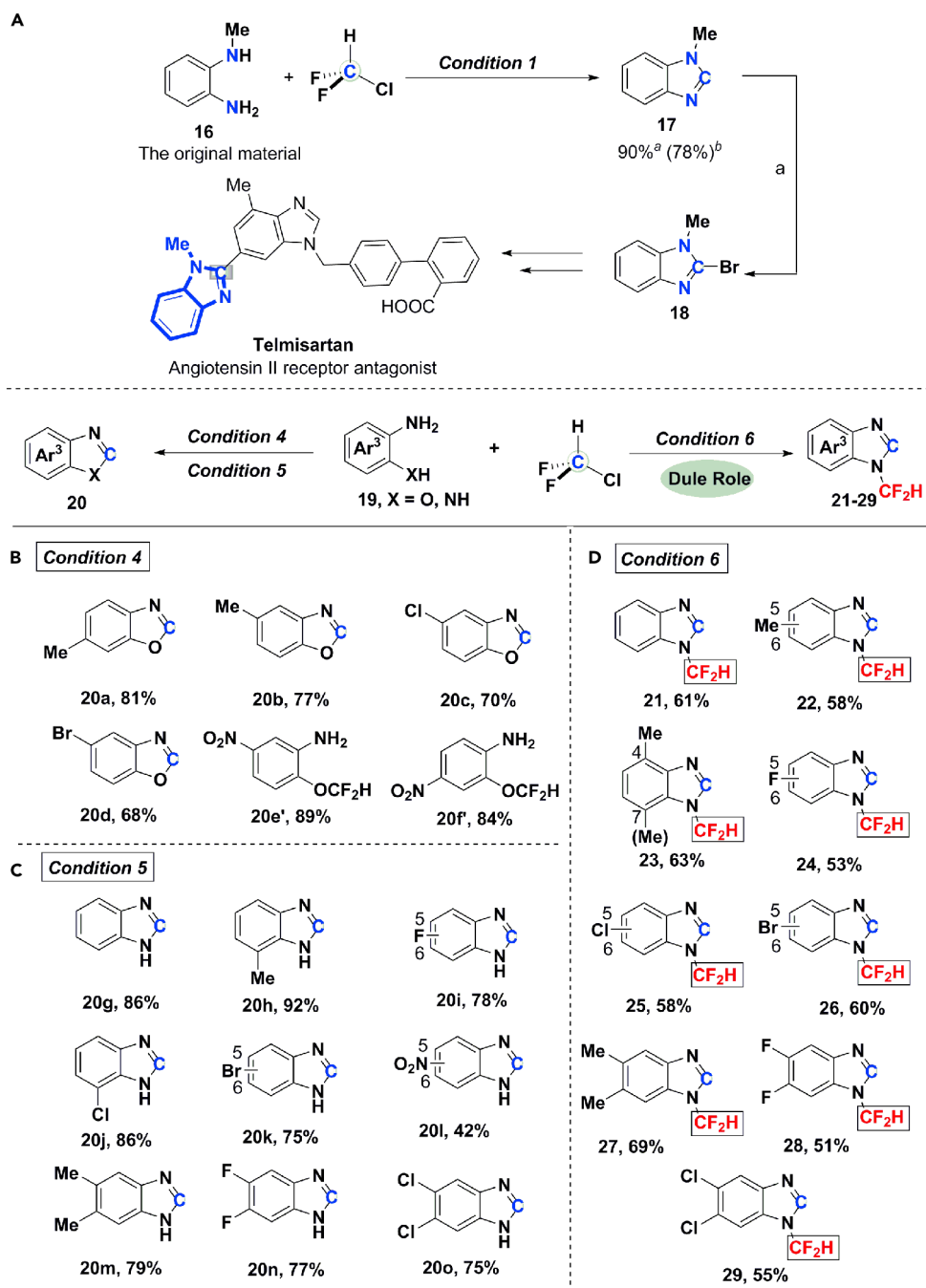
### Mechanism Investigation

To gain more insights into the mechanism of the aforementioned transformations, some control experiments were performed. Initially, isotope labeling experiments were conducted, 84% (**3a'**) and 78% (**20g'**) of D atoms were incorporated into the final products correspondingly for intermolecular and intramolecular versions, and N-H of benzimidazole was replaced by N-D completely (Figures 5A and 5B). These results suggested that the hydrogen atom attached on the extra introduced carbon (from ClCF<sub>2</sub>H) was originated from H<sub>2</sub>O in this process possibly (for further details, see also Scheme S8). The trace amount of the desired product **3a** was observed when benzimidazole was added into the reaction system as a difluorocarbene scavenger; instead, 1-(difluoromethyl)-1*H*-benzo[d]imidazole was detected by GC-MS (Figure 5C). When *N*-methyl-*N*-phenylformamide (**30**) or isocyanobenzene (**31**) was subjected to the earlier standard reaction conditions with amines, the corresponding target products **3a** and **8** were not obtained (Figure 5D), indicating that the compounds **30** and **31** are not intermediates for this transformation, which is in sharp contrast to our previous reports in which isocyanides are the key intermediates for those transformations with BrCF<sub>2</sub>COOEt (Ma et al., 2018c, 2018d). To thoroughly understand the reaction sequence, two more control experiments were carried out, in which the primary amine and the secondary amine were added to the reaction mixture stepwise instead of one-pot to check which one is the first amine species interacting with ClCF<sub>2</sub>H. It turned out that primary amine might react with ClCF<sub>2</sub>H before the secondary one since 47% of the desired product was obtained in the primary-secondary amine sequence, whereas no desired product was detected with the secondary-primary amine sequence (Figures 5E and 5F). Finally, we carried out comparison experiments for CO<sub>2</sub>, CO and HCOOH as C1 source with amines **1a** and **2a** under various reaction conditions; no desired product **3a** was detected (Figure 5G), which further highlighted the uniqueness of ClCF<sub>2</sub>H as the C1 source in these transformations.

### Proposed Mechanism

To thoroughly figure out the possible reactive intermediate, we carried out *in situ* <sup>1</sup>H NMR studies between 4-ethoxyaniline (**1c**) and ClCF<sub>2</sub>H (Figure 6A). Since isocyanides have been ruled out to be the possible





<sup>a</sup> The scale of the original material **16** is 0.1 mmol; <sup>b</sup> The scale of the original material **16** is 7 mmol. (a) 1-Methylbenzimidazole (**17**) (5 mmol) and *N*-bromosuccinimide (3 equiv) in 25 mL of THF were heated under reflux for 1 h. **Condition 4**: The amine (0.2 mmol), K<sub>2</sub>CO<sub>3</sub> (3 equiv), H<sub>2</sub>O (5 equiv.), CH<sub>3</sub>CN (2 mL), 50 °C for 12 h under the atmosphere of ClCF<sub>2</sub>H, isolated yield; **Condition 5**: The amine (0.2 mmol), K<sub>2</sub>CO<sub>3</sub> (3 equiv), H<sub>2</sub>O (0.5 mL), CH<sub>3</sub>CN (2 mL), 100 °C for 16 h under the atmosphere of ClCF<sub>2</sub>H, isolated yield. **Condition 6**: The amine (0.1 mmol), K<sub>2</sub>CO<sub>3</sub> (5 equiv), H<sub>2</sub>O (30 μL), CH<sub>3</sub>CN (2 mL), 110 °C for 48 h under the atmosphere of ClCF<sub>2</sub>H.

**Figure 4. The Synthetic Route of the Telmisartan and the Intramolecular Reaction Scope**

(A) Telmisartan synthesis with our strategy.  
 (B) Scope of benzoxazoles.  
 (C) Scope of benzimidazoles.  
 (D) Scope of *N*-difluoromethyl benzimidazoles.

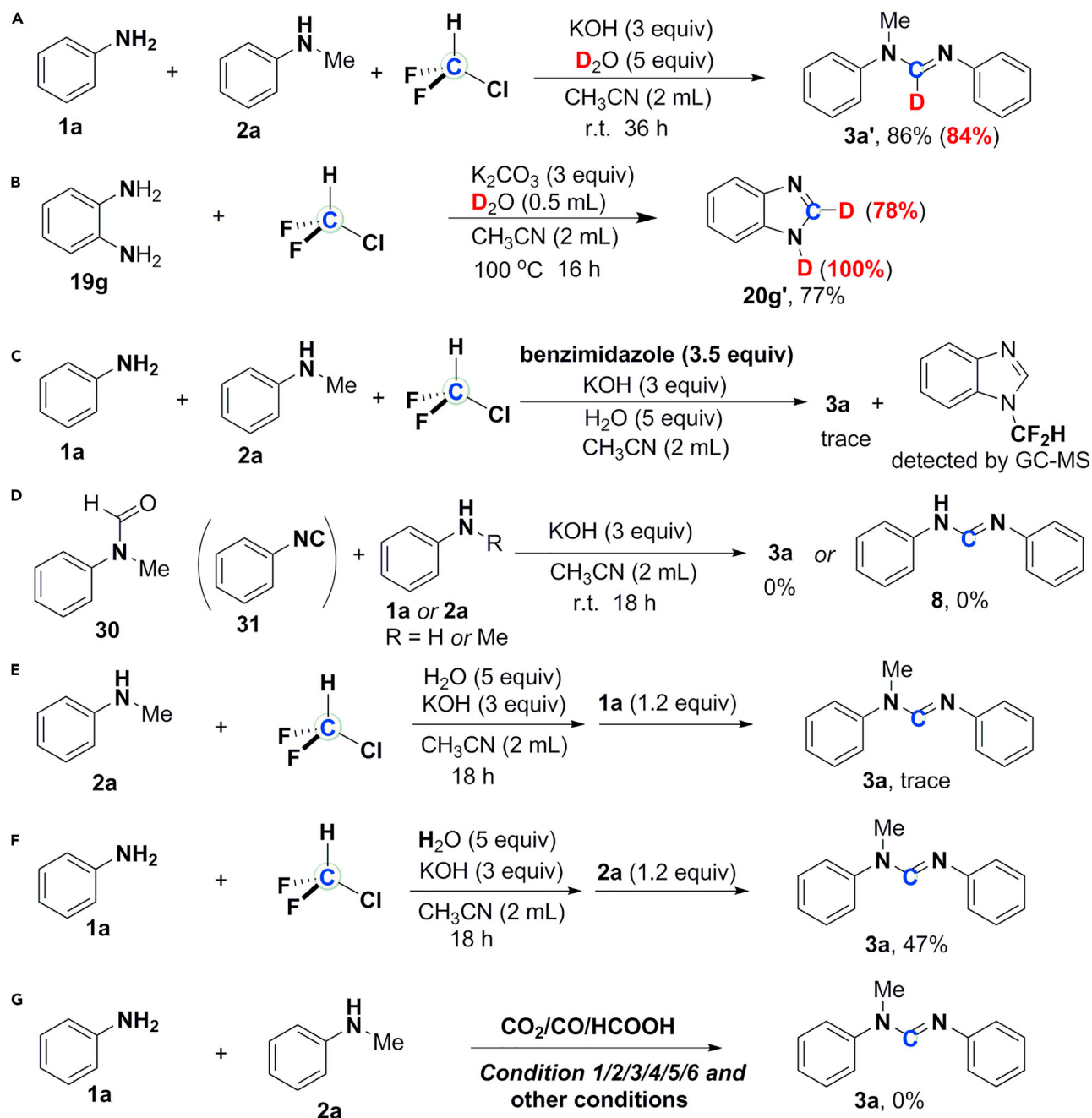
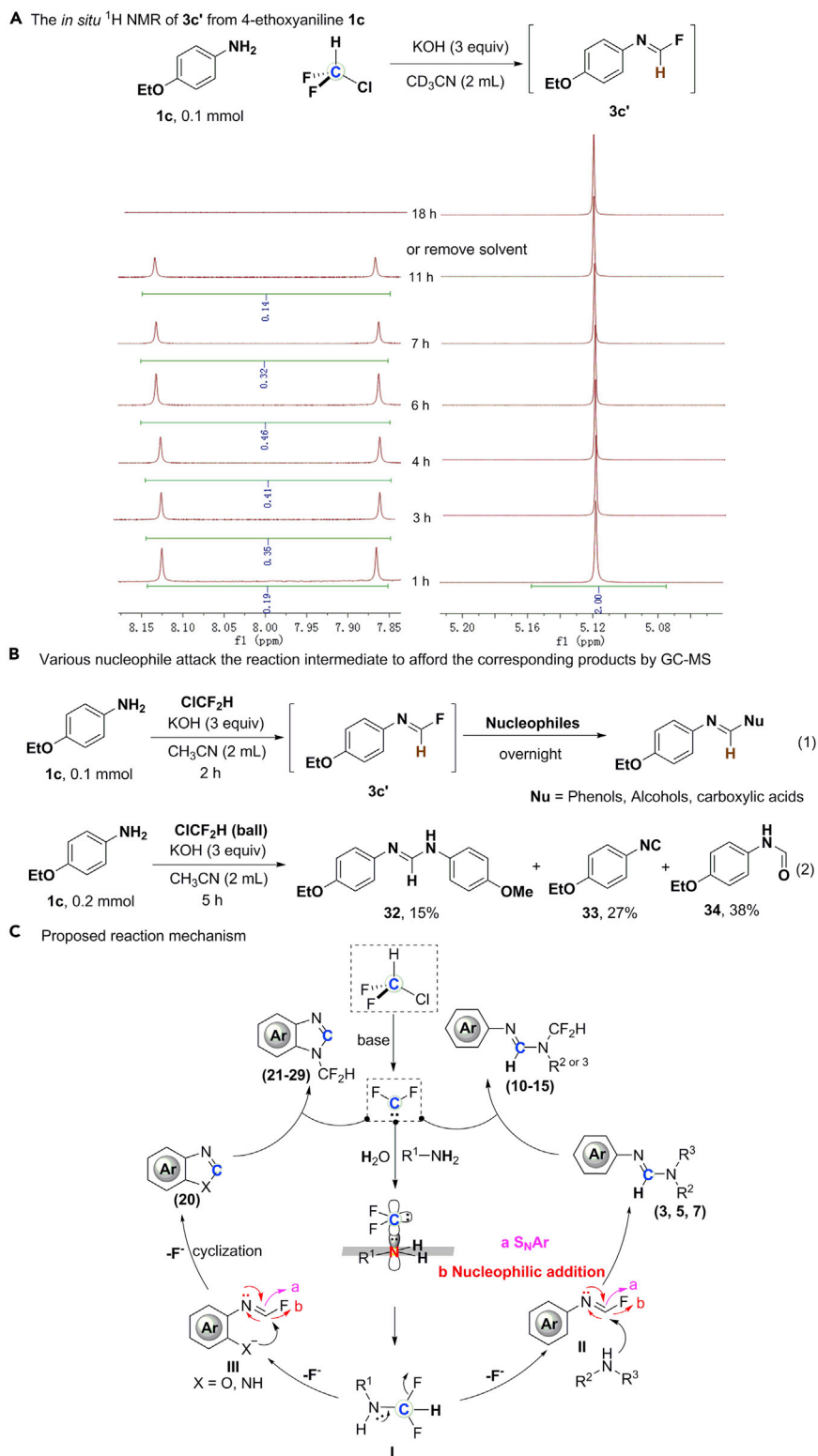


Figure 5. Mechanistic Studies

intermediates for this transformation, we envision that a type of intermediate **3c'** might be formed in this transformation. To our delight, *in situ*  $^1\text{H}$  NMR studies indeed indicated the formation of (*E*)-*N*-(4-ethoxyphenyl)formimidoyl fluoride (**3c'**), which was increased continually at the first 6 h, whereafter it started to decline probably owing to its volatile property and the existence of various nucleophiles in the reaction system, such as  $\text{H}_2\text{O}$  and amines. The intermediate **3c'** was totally consumed after 18 h or during the process of stripping the solvent (for further details, see also Schemes S9–S11). To validate its presence, various nucleophiles (phenols, alcohols, amines, and carboxylic acids) were added into the system after 2 h, and the corresponding desired products were detected in GC-MS (Equation 1 in Figure 6B, and for further details, Scheme S12). In addition, one more control experiment was carried out with a  $\text{ClCF}_2\text{H}$  balloon for 5 h;



**Figure 6.** *In situ*  $^1\text{H}$  NMR, the Capture of Reaction Intermediates and the Proposed Mechanism

(A) *In situ*  $^1\text{H}$  NMR studies.

(B) The capture of reaction intermediates.

(C) The plausible reaction mechanism.

the product **32**, isocyanide **33**, and *N*-(4-ethoxyphenyl)formamide (**34**) were obtained in 15%, 27%, and 38% yields, respectively (Equation 2 in Figure 6B), suggesting that the intermediate is a chemically active compound, which will further decompose into isocyanide by one more C-F bond cleavage easily. We have carried out the control experiments in the presence of radical scavengers; the reactions proceeded smoothly at room temperature to afford desired products in moderate yields. Those results suggest that the single electron transfer (SET) pathway could not be involved in this transformation (for further details, see also Scheme S13). On the basis of the above-mentioned results, a proposed mechanism for the reaction of ClCF<sub>2</sub>H as a C1 source is depicted in Figure 6C. The base coordinates with ClCF<sub>2</sub>H to generate difluorocarbene first. Then the primary amine traps the *in situ* generated difluorocarbene affording intermediate I, which is very sensitive under basic conditions to lead to monofluoroimine species via the cleavage of one C-F bond; subsequent inter- or intramolecular nucleophilic attack on the imine species (II and III) eventually delivers products **3**, **5**, **7**, and **20** by S<sub>N</sub>Ar substitution (path a) or nucleophilic addition (path b) (Ma et al., 2018a). As either R<sup>2</sup> or R<sup>3</sup> is H, the product could embark on capturing one more *in situ* generated difluorocarbene unceasingly to render the products (**10–15**). The products **21–29** were obtained in one-pot synthesis when compound **20** (X = NH) meets with excess ClCF<sub>2</sub>H in basic conditions as a difluorocarbene scavenger.

### Conclusion

In summary, we have disclosed a C1 source generated from chlorodifluoromethane (ClCF<sub>2</sub>H). This method allows the synthesis of a broad range of the formimidamides and benzo[d]oxazoles, benzo[d]imidazole derivatives via intermolecular and intramolecular reactions with good efficiency as well as high regio- and chemoselectivity under mild reaction condition. To our knowledge, this is the first example that ClCF<sub>2</sub>H proceeds quadruple cleavage to act as a C1 synthon and the valuable products were fabricated from readily available starting materials under transition-metal-free conditions. This process might enrich C1 chemistry, green chemistry, and fluorine chemistry as well as might partially solve the problem of the disposition of ODS. Preliminary mechanistic studies revealed that (*E*)-*N*-phenylformimidoyl fluoride intermediate is involved in this process, which is a distinct intermediate from BrCF<sub>2</sub>COOEt case. Further studies toward the detailed mechanism and transformations and applications as well as exploration on more intriguing methodologies with this unusual C1 source are under way in our laboratory.

### Limitation of the Study

Primary aliphatic amines showed poor or no reactivity toward this reaction system. In addition, reactive intermediate (e.g., **3c'**) was not isolated owing to its high reactivity.

### METHODS

All methods can be found in the accompanying Transparent Methods supplemental file.

### DATA AND CODE AVAILABILITY

The structures of **3t** reported in this article have been deposited in the Cambridge Crystallographic Data Centre under accession numbers CCDC: 1874971.

### SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at <https://doi.org/10.1016/j.isci.2019.07.005>.

### ACKNOWLEDGMENTS

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### AUTHOR CONTRIBUTIONS

X.M. and J.S. performed the experiments and developed the reactions. X.Z. checked the manuscript and came up with suggestions for this transformation. Q.S. designed and directed the project and wrote the manuscript with the feedback of X.M.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

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**Supplemental Information**

**Chlorodifluoromethane as a C1 Synthon  
in the Assembly of *N*-Containing Compounds**

**Xingxing Ma, Jianke Su, Xingang Zhang, and Qiuling Song**

## Supplementary Figures

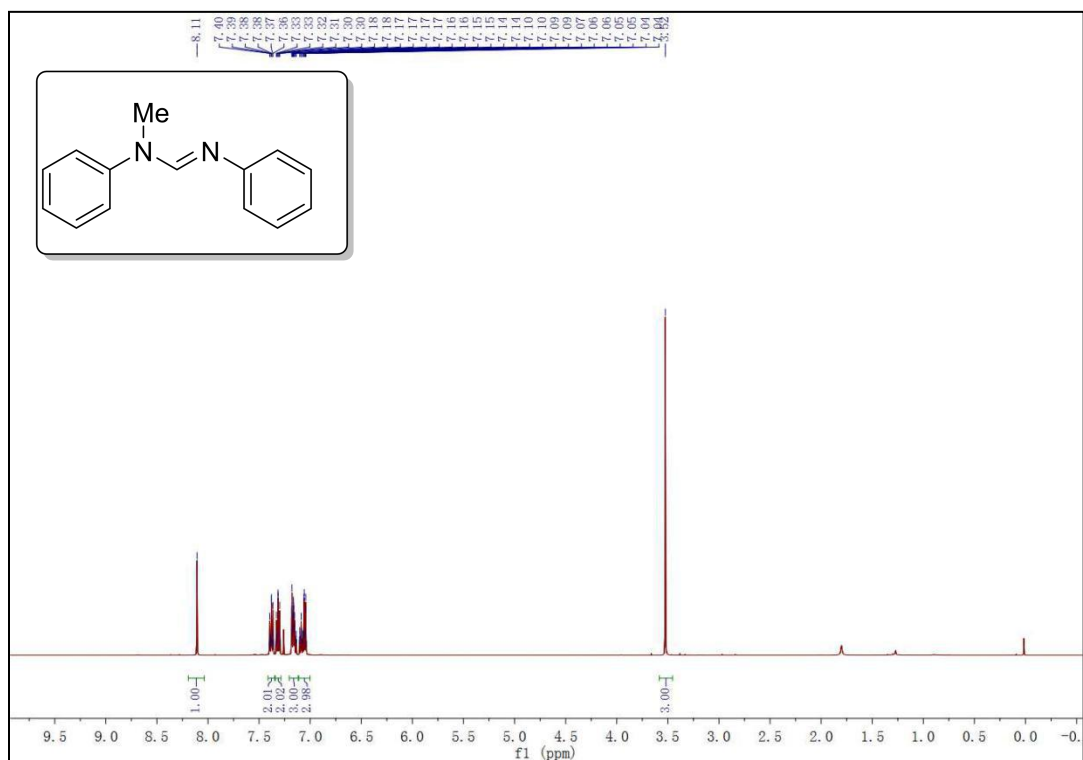


Figure S1. <sup>1</sup>H NMR spectrum of 3a, related to Figure 2

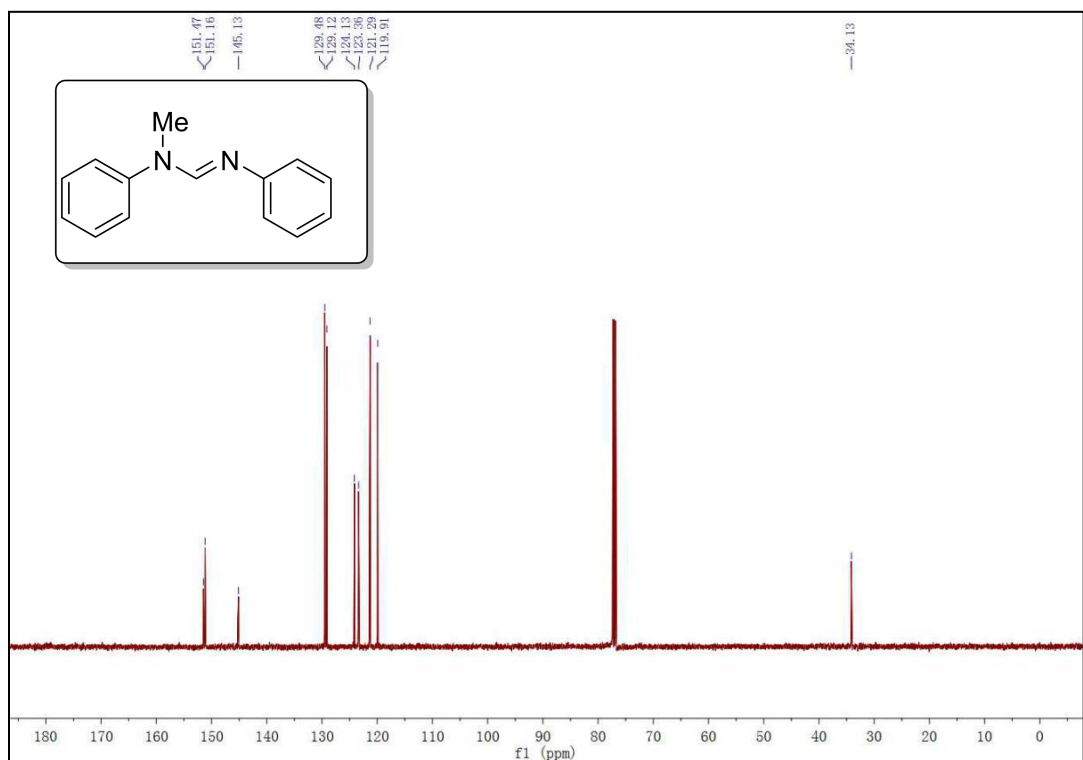


Figure S2. <sup>13</sup>C NMR spectrum of 3a, related to Figure 2



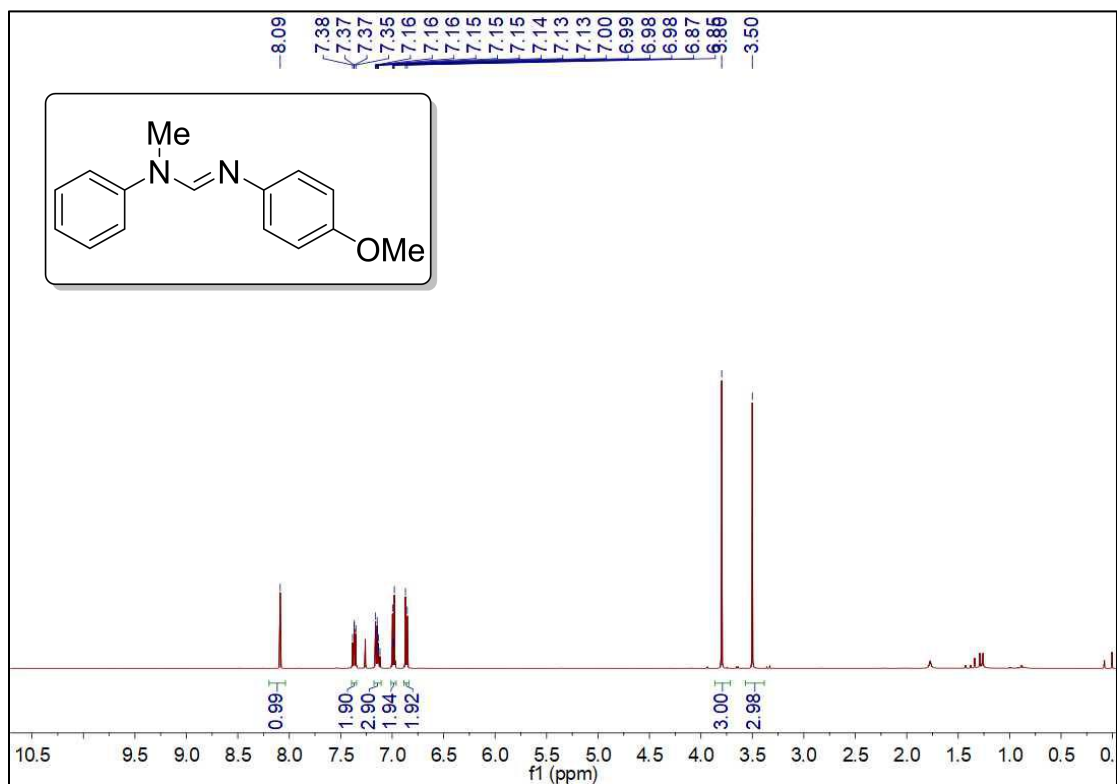


Figure S3. <sup>1</sup>H NMR spectrum of 3b, related to Figure 2

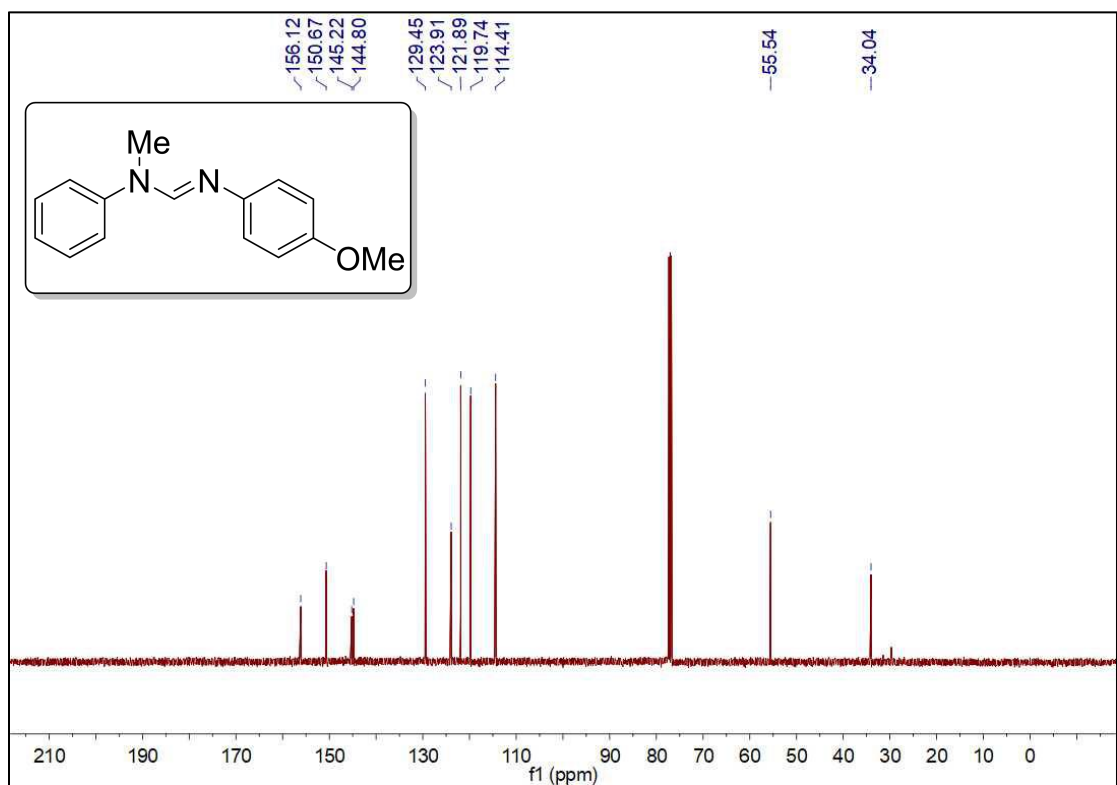


Figure S4. <sup>13</sup>C NMR spectrum of 3b, related to Figure 2

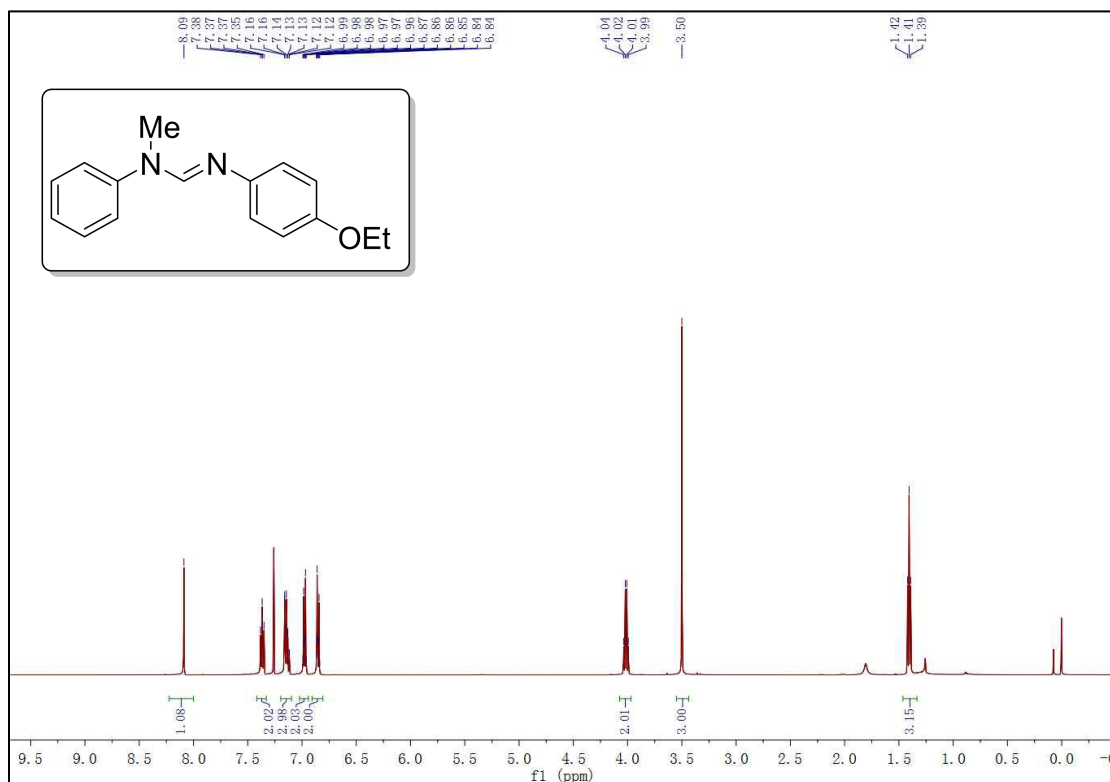


Figure S5. <sup>1</sup>H NMR spectrum of 3c, related to Figure 2

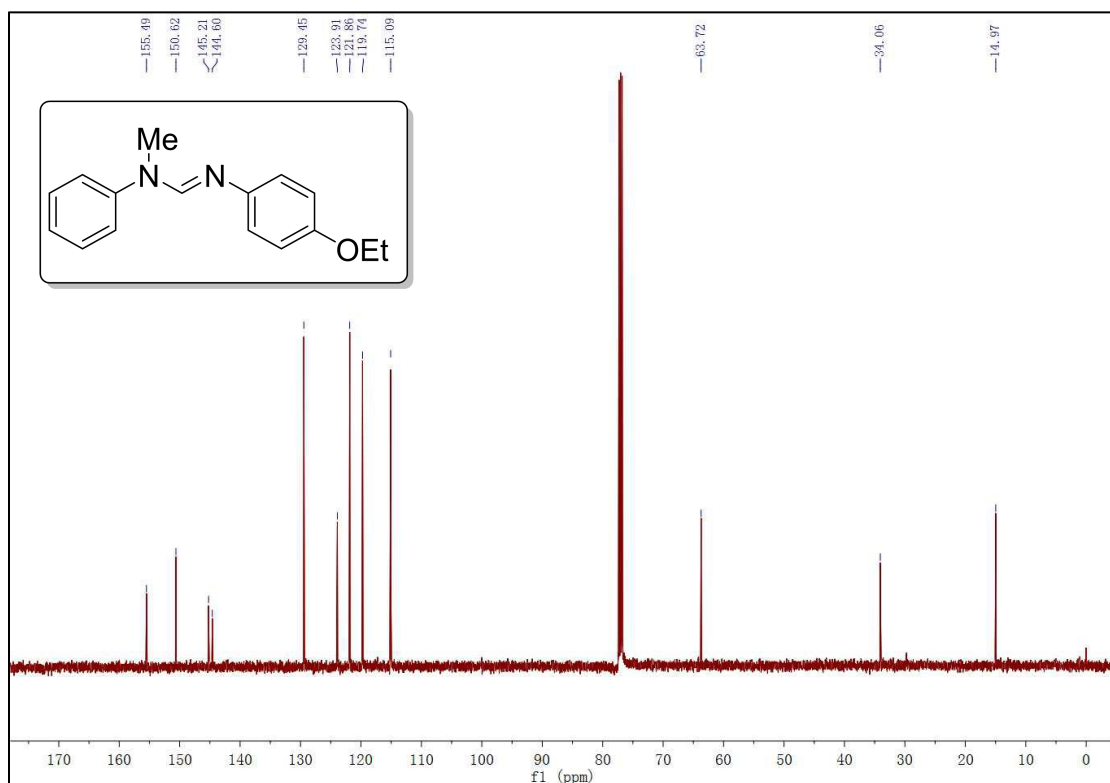


Figure S6. <sup>13</sup>C NMR spectrum of 3c, related to Figure 2

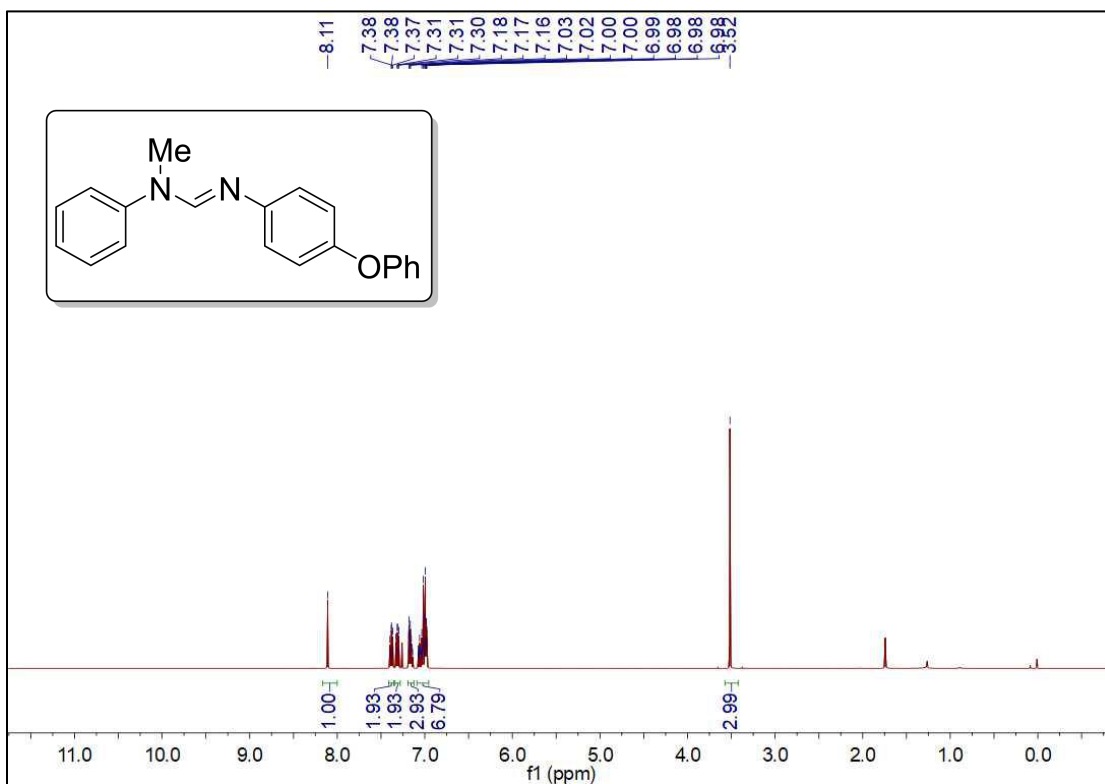


Figure S7. <sup>1</sup>H NMR spectrum of 3d, related to Figure 2

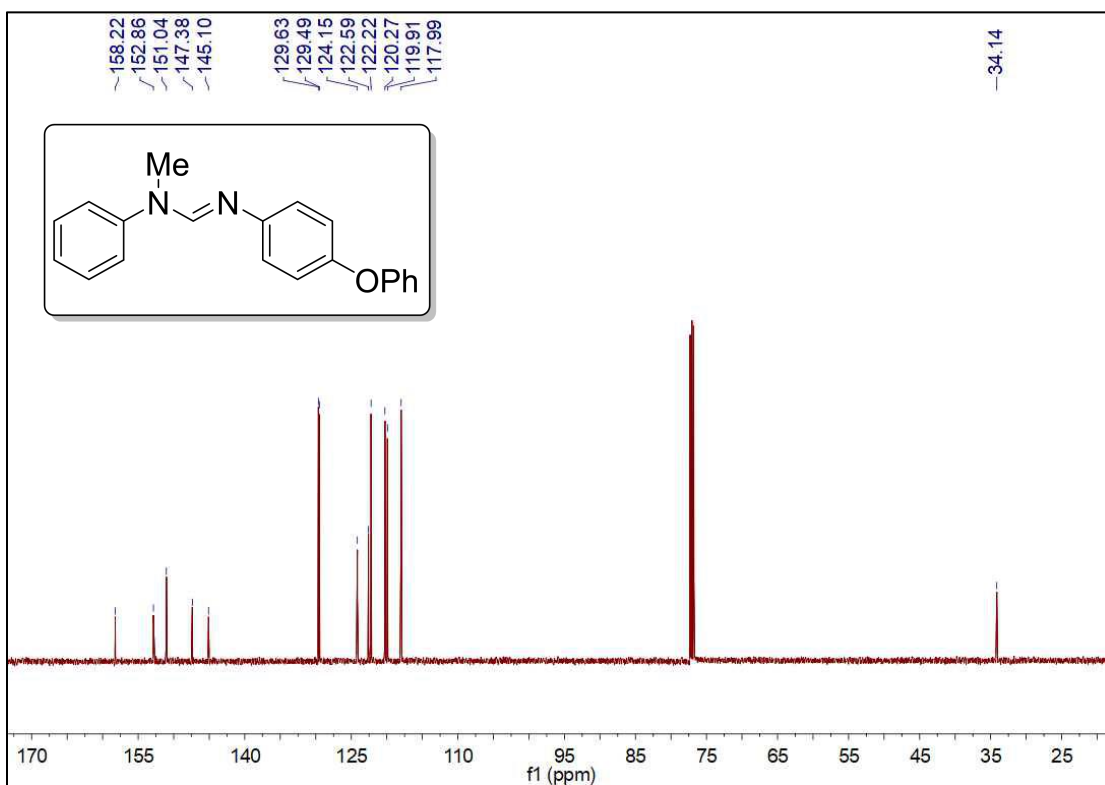


Figure S8. <sup>13</sup>C NMR spectrum of 3d, related to Figure 2

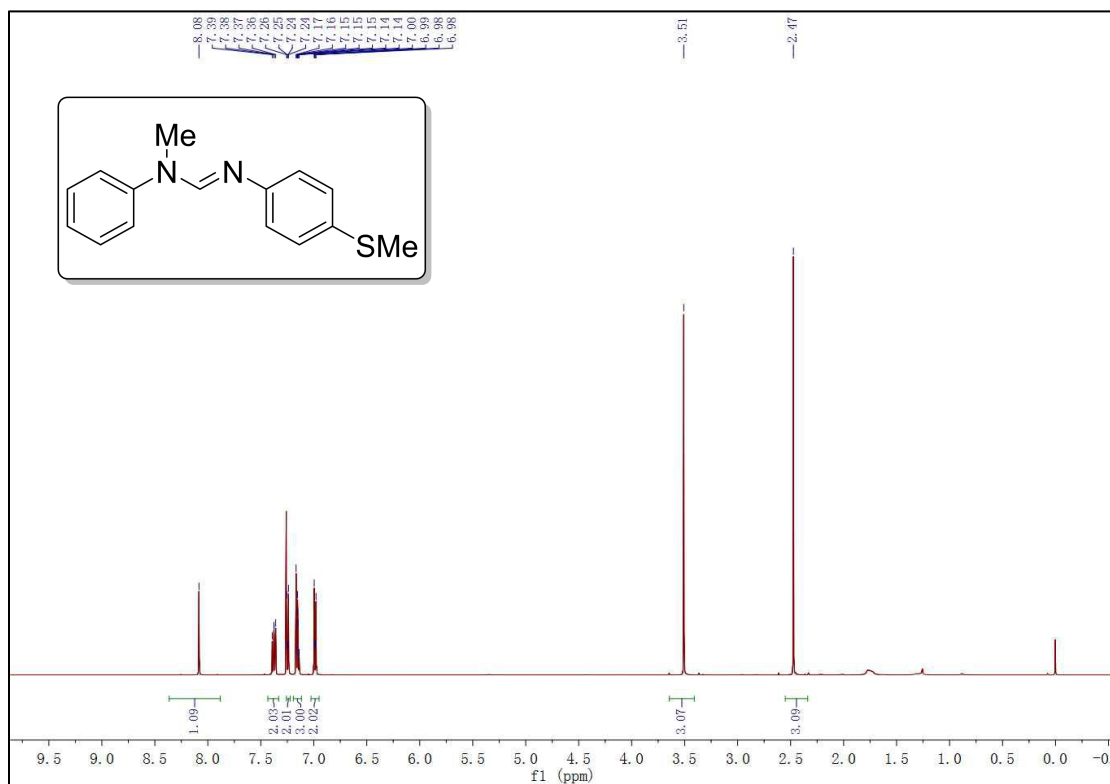


Figure S9. <sup>1</sup>H NMR spectrum of 3e, related to Figure 2

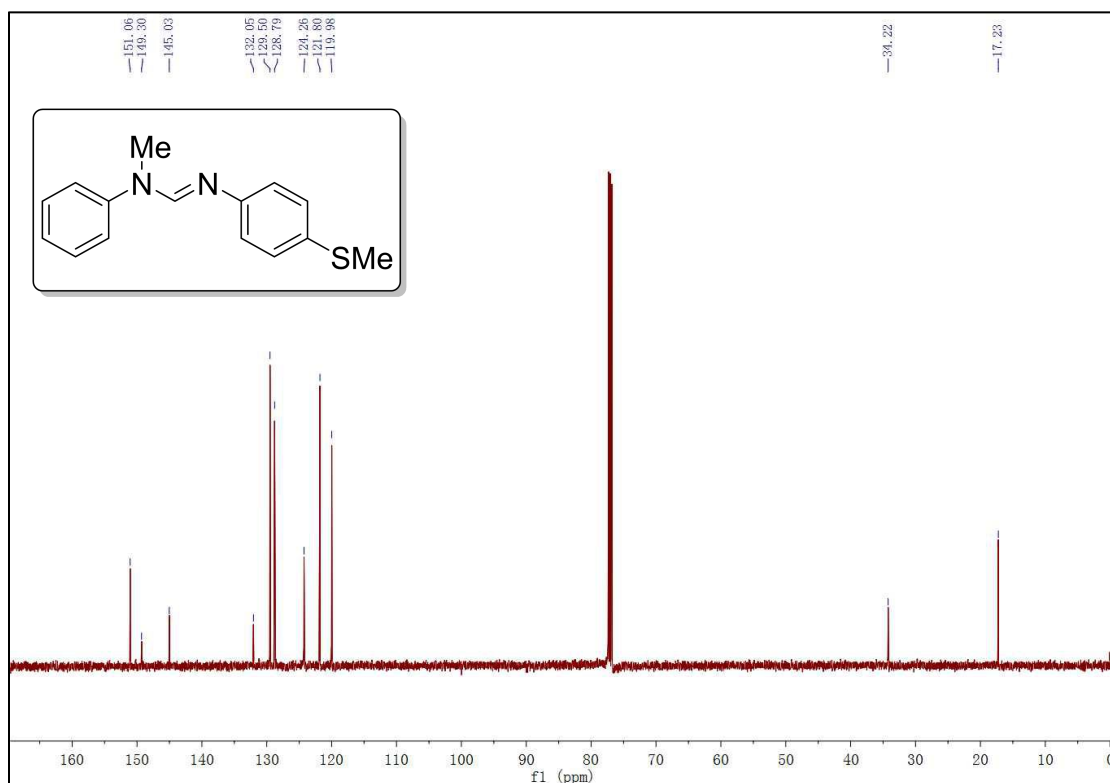


Figure S10. <sup>13</sup>C NMR spectrum of 3e, related to Figure 2

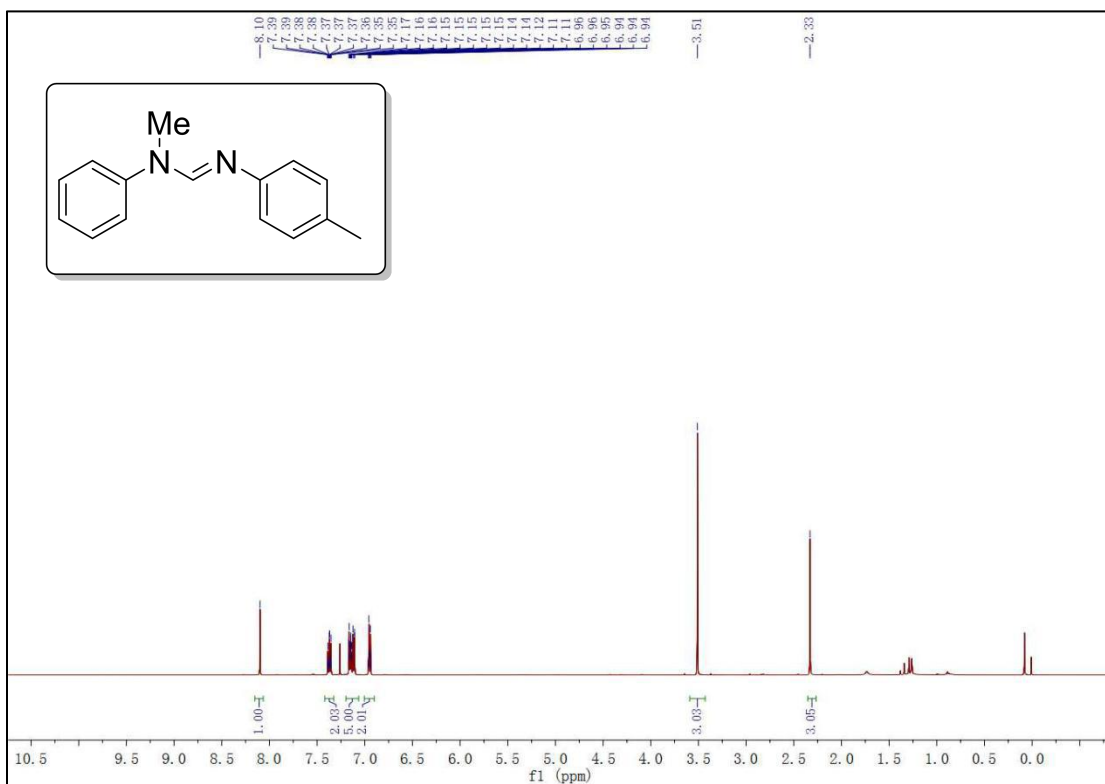


Figure S11. <sup>1</sup>H NMR spectrum of 3f, related to Figure 2

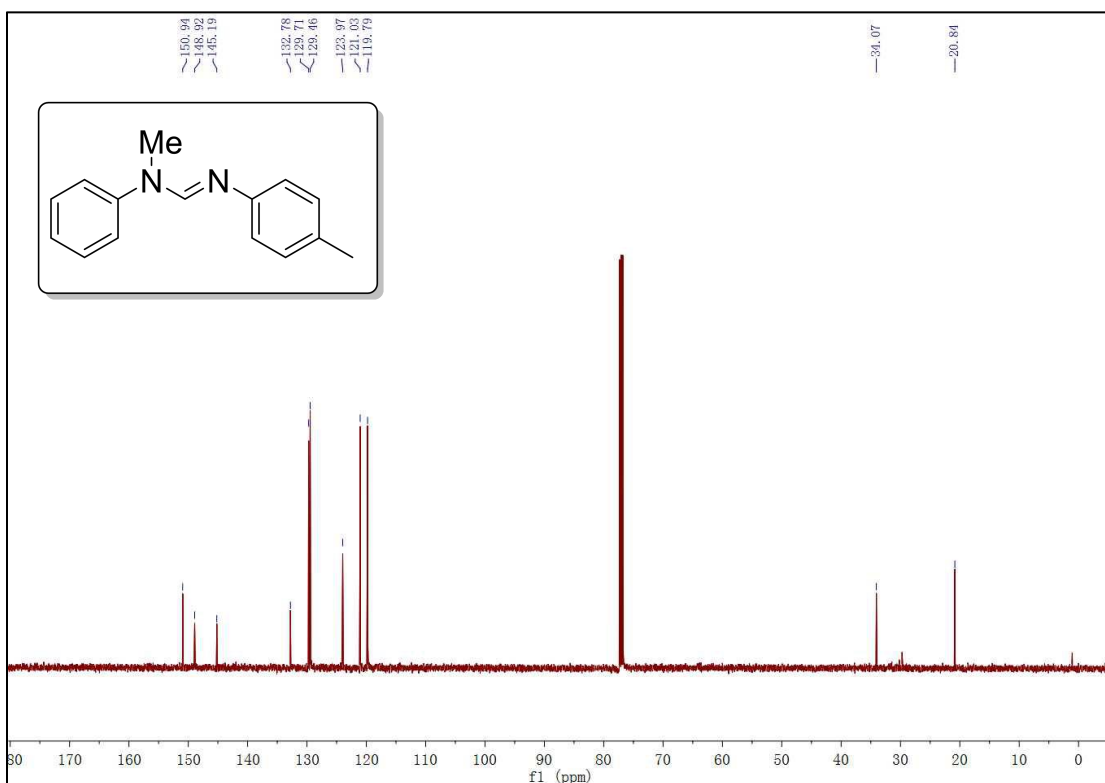


Figure S12. <sup>13</sup>C NMR spectrum of 3f, related to Figure 2

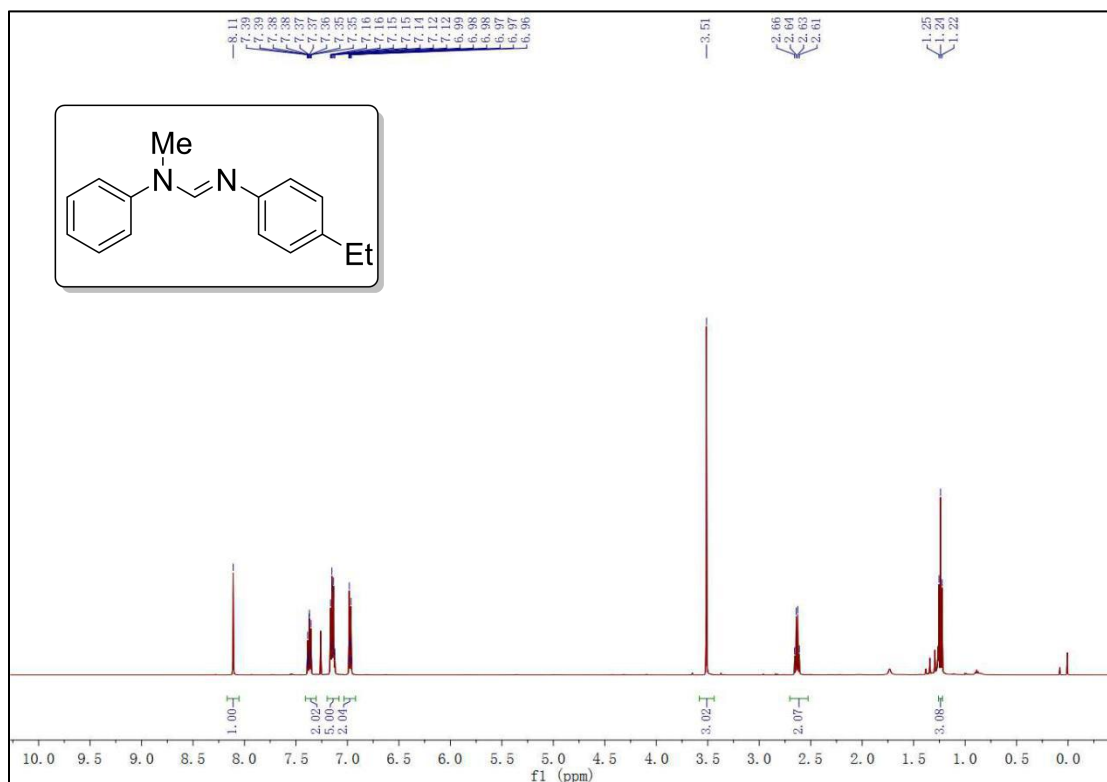


Figure S13. <sup>1</sup>H NMR spectrum of 3g, related to Figure 2

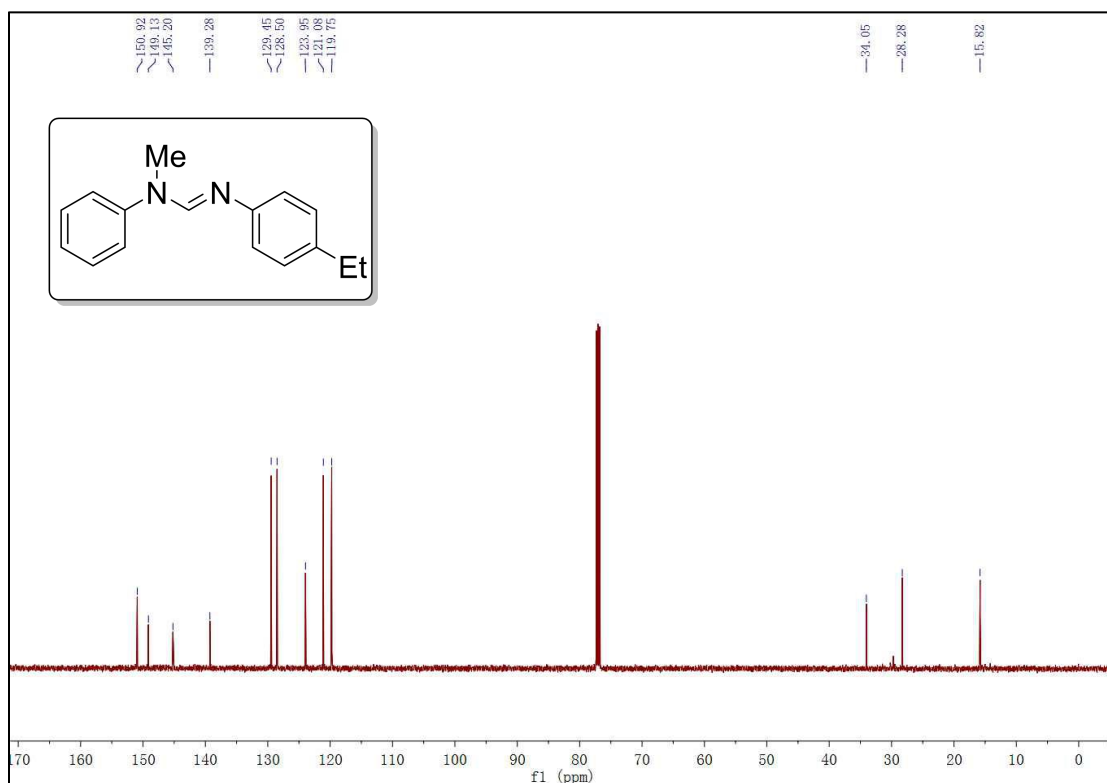


Figure S14. <sup>13</sup>C NMR spectrum of 3g, related to Figure 2

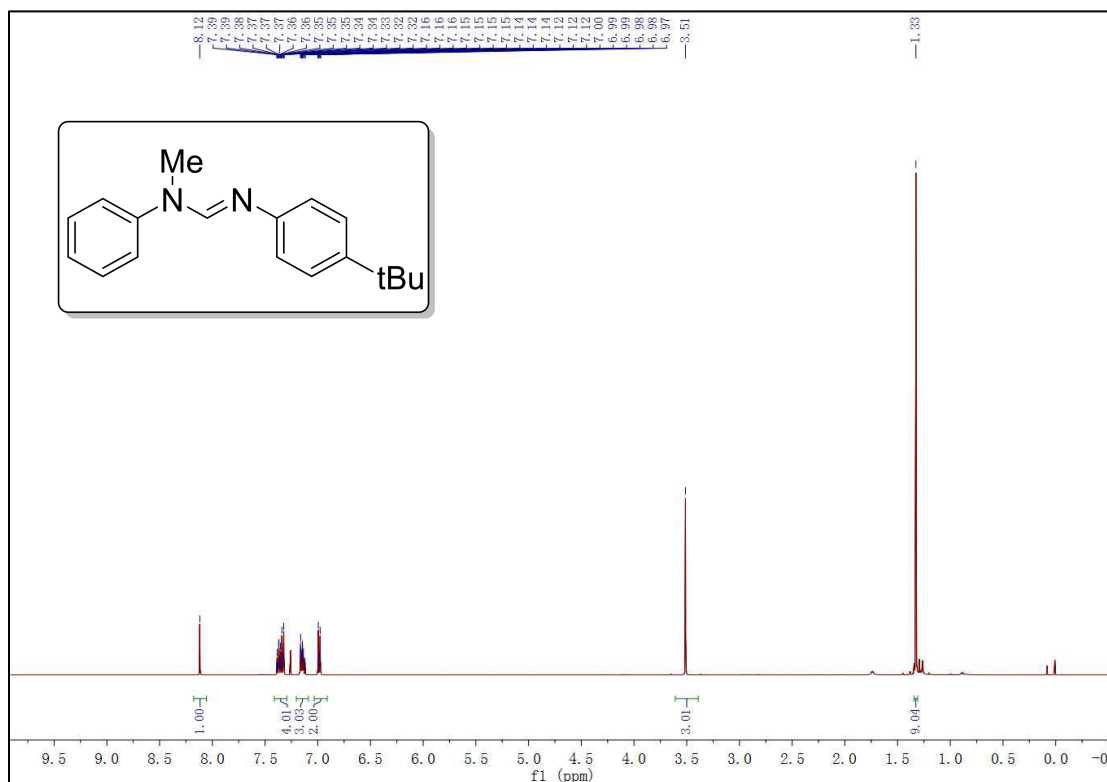


Figure S15. <sup>1</sup>H NMR spectrum of 3h, related to Figure 2

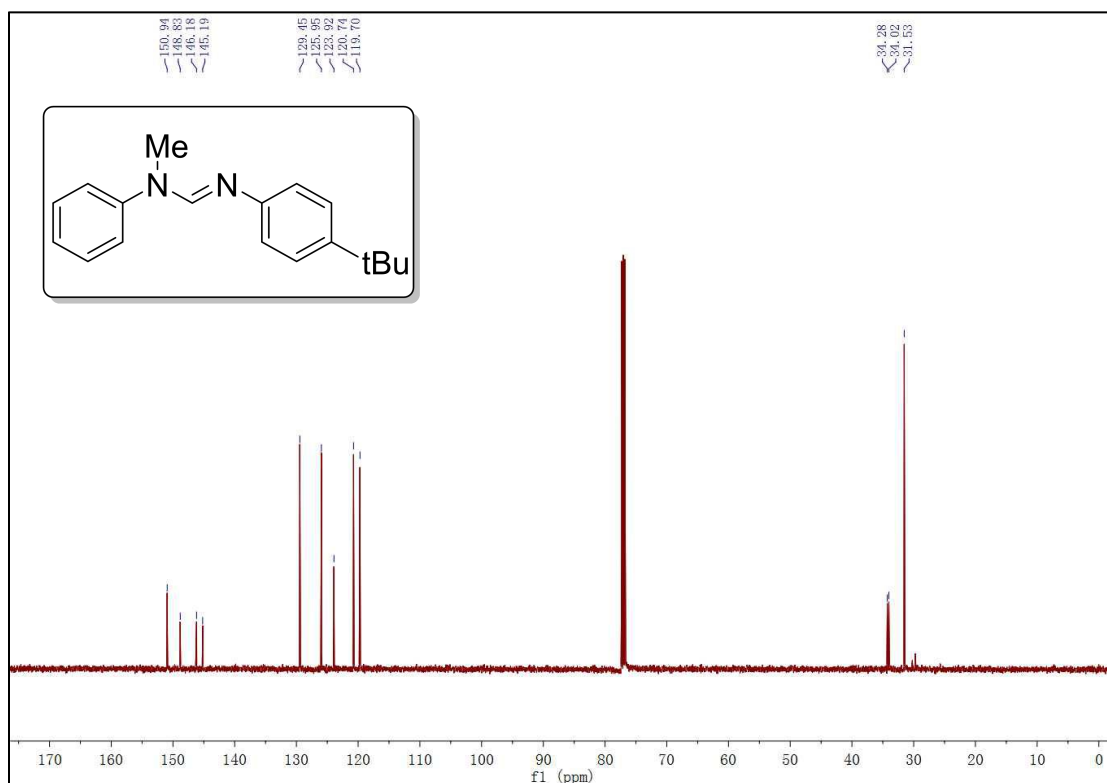


Figure S16. <sup>13</sup>C NMR spectrum of 3h, related to Figure 2

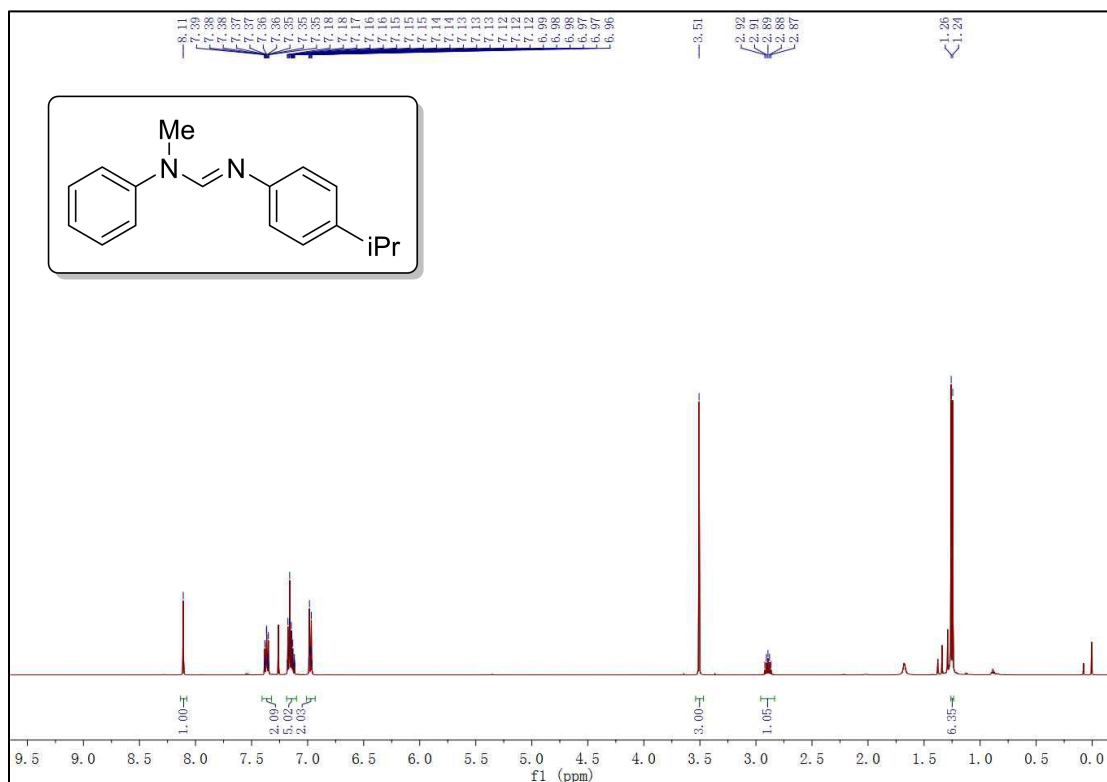


Figure S17. <sup>1</sup>H NMR spectrum of 3i, related to Figure 2

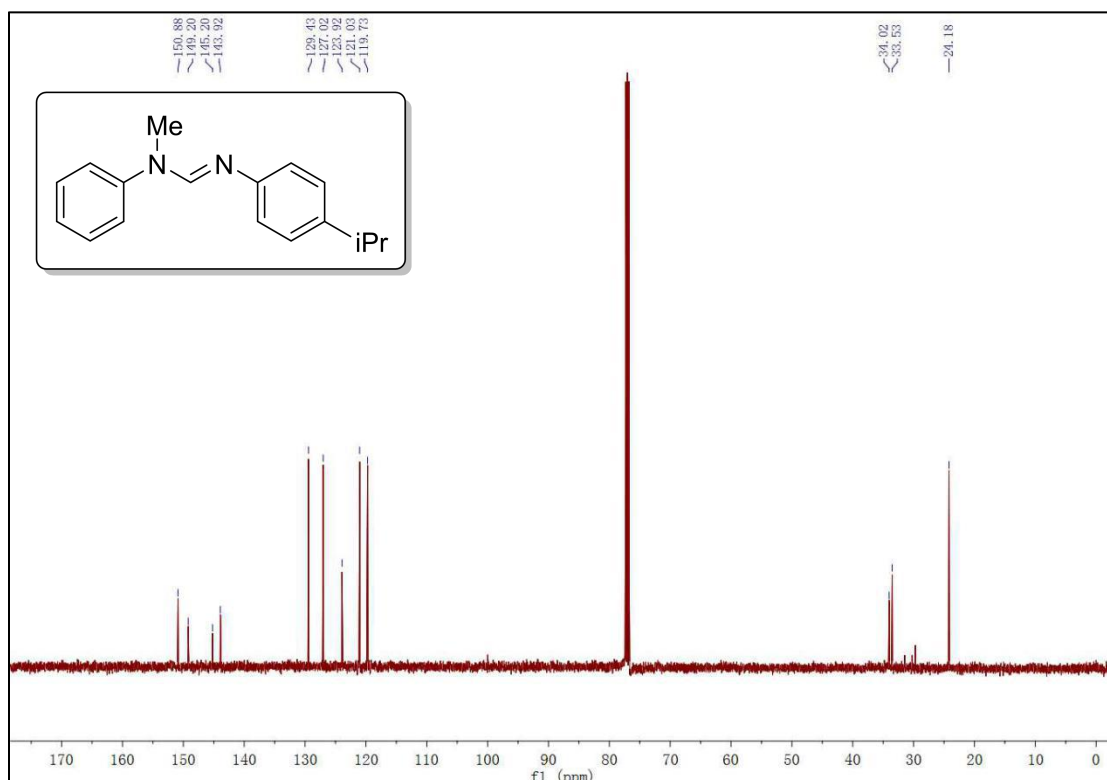


Figure S18. <sup>13</sup>C NMR spectrum of 3i, related to Figure 2



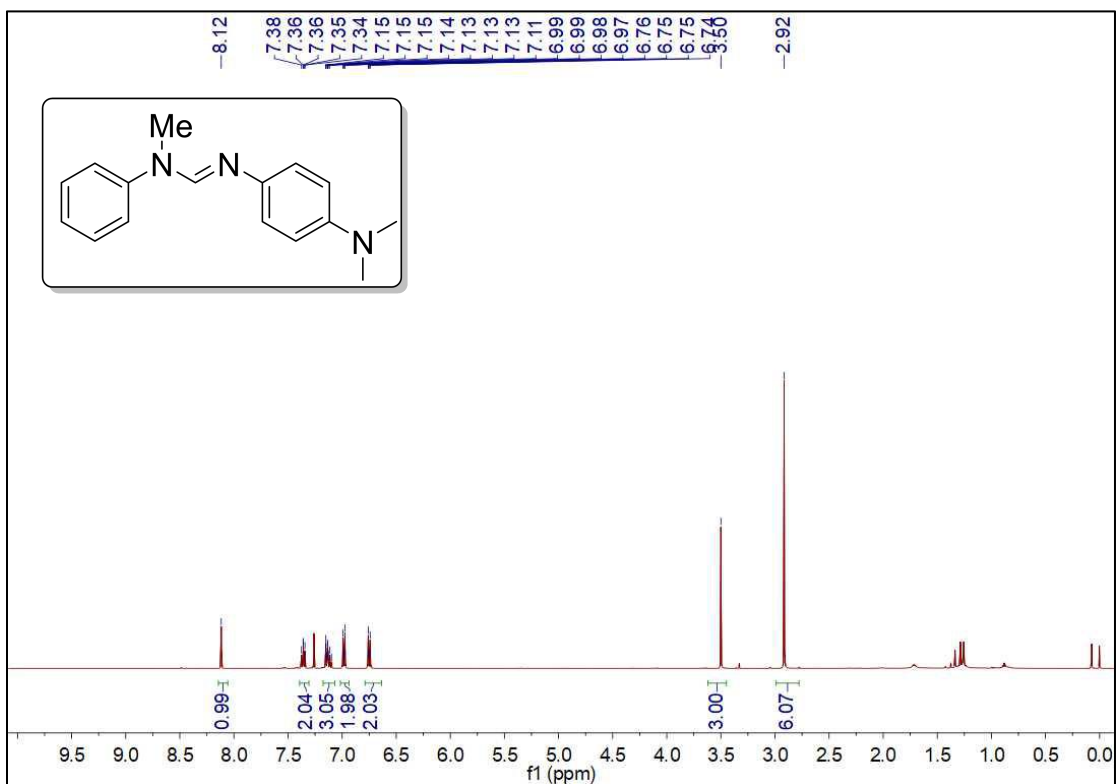


Figure S19. <sup>1</sup>H NMR spectrum of 3j, related to Figure 2

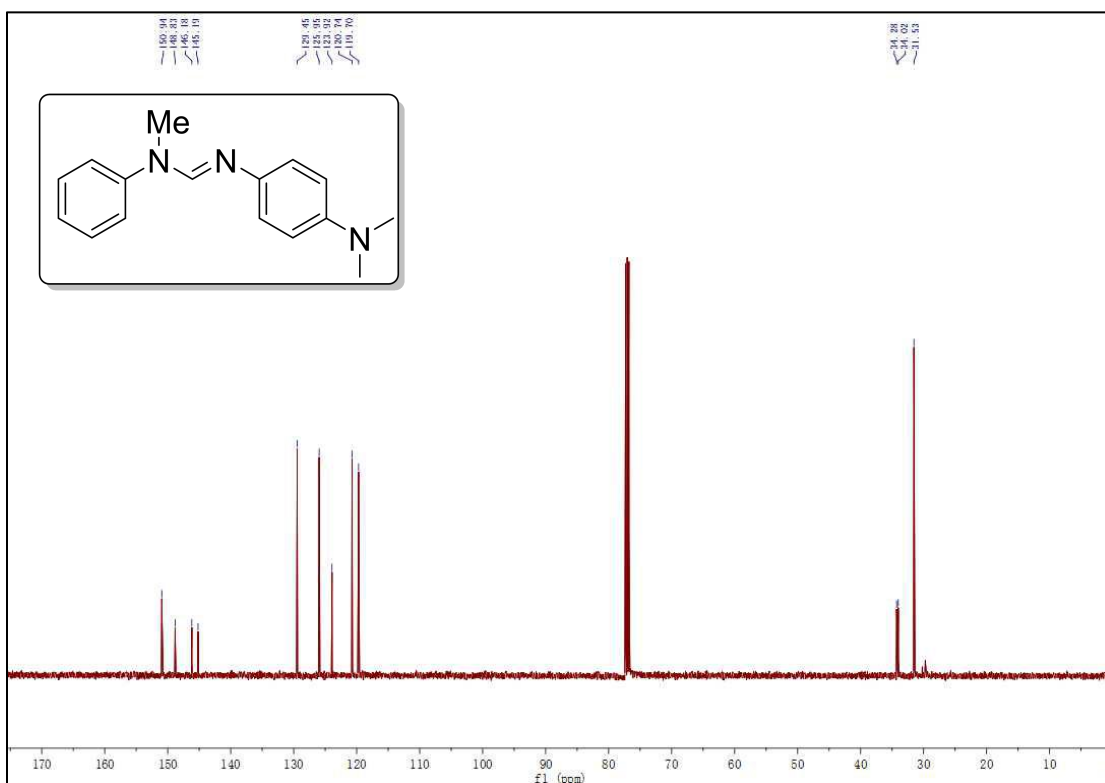


Figure S20. <sup>13</sup>C NMR spectrum of 3j, related to Figure 2

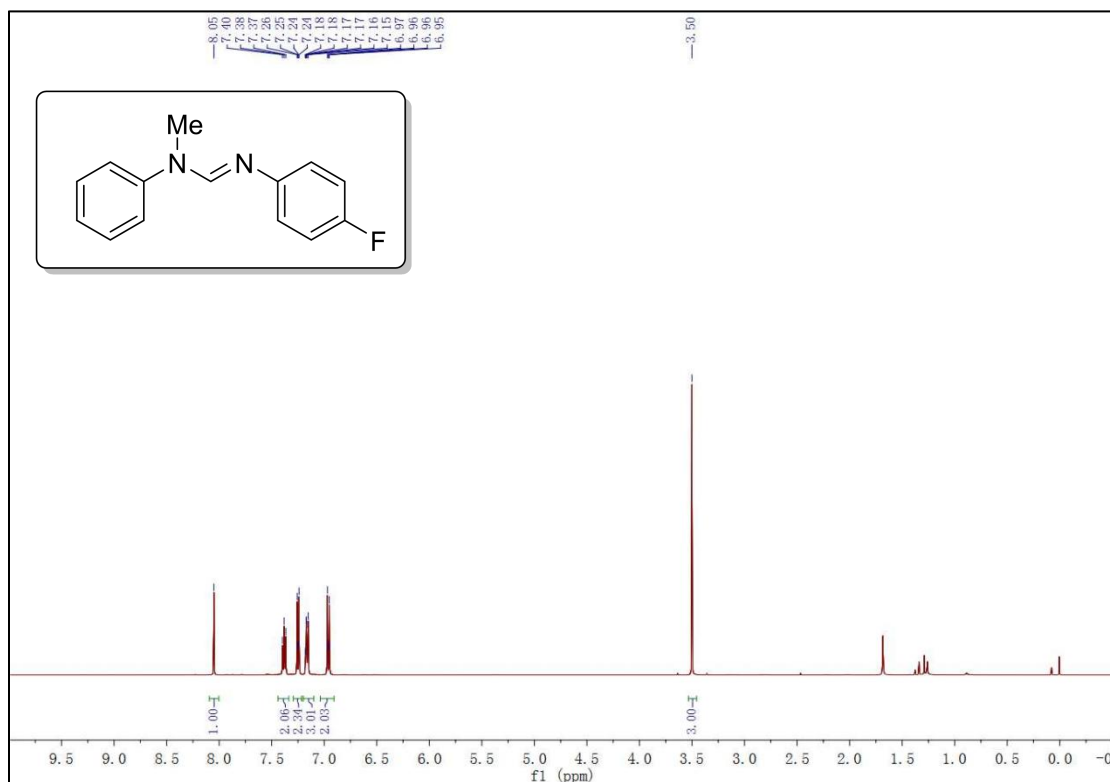


Figure S21. <sup>1</sup>H NMR spectrum of 3k, related to Figure 2

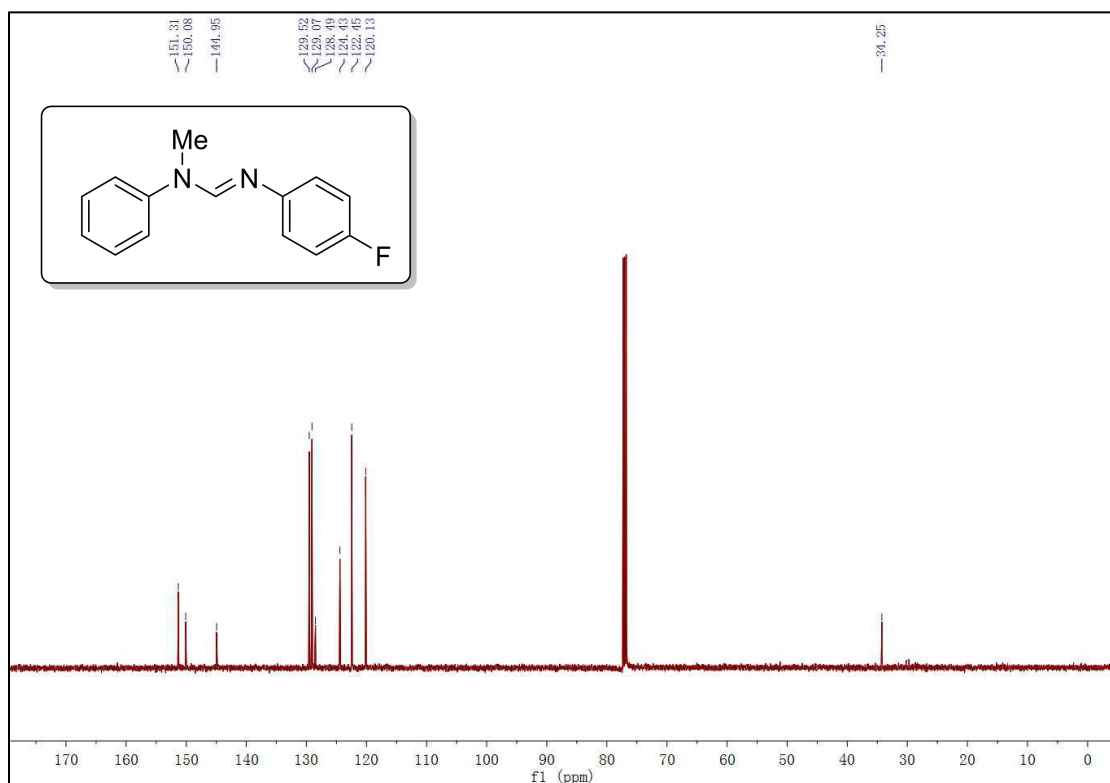


Figure S22. <sup>13</sup>C NMR spectrum of 3k, related to Figure 2

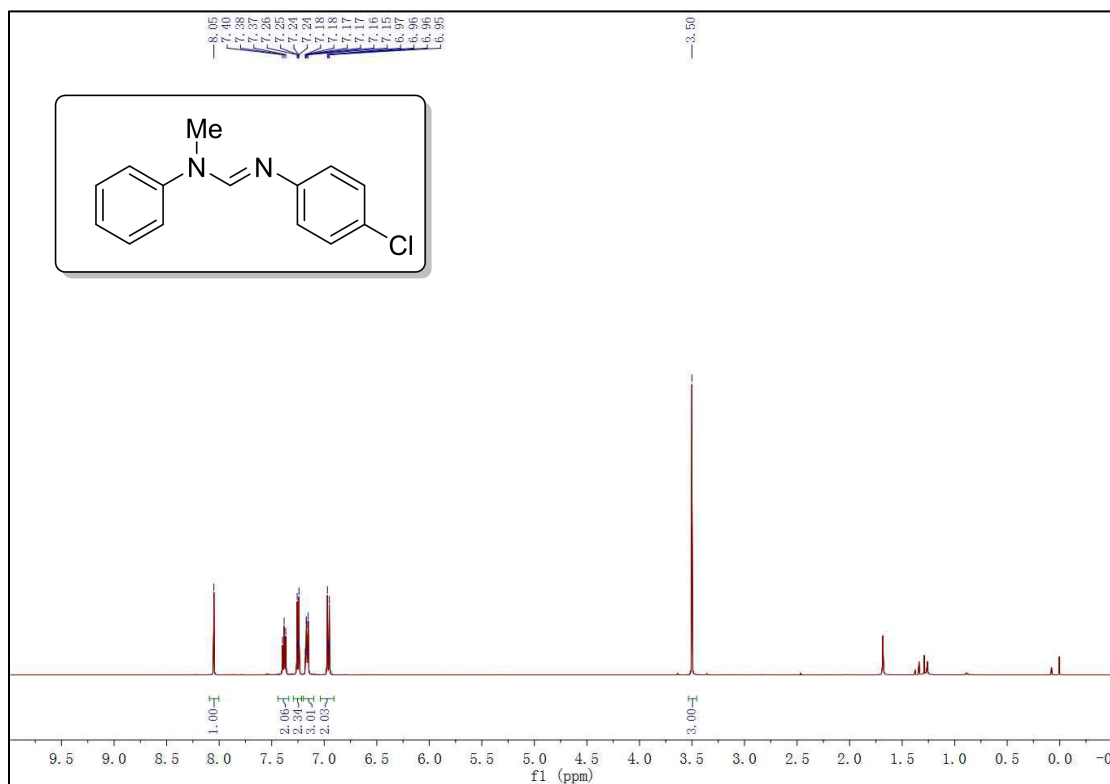


Figure S23. <sup>1</sup>H NMR spectrum of 3l, related to Figure 2

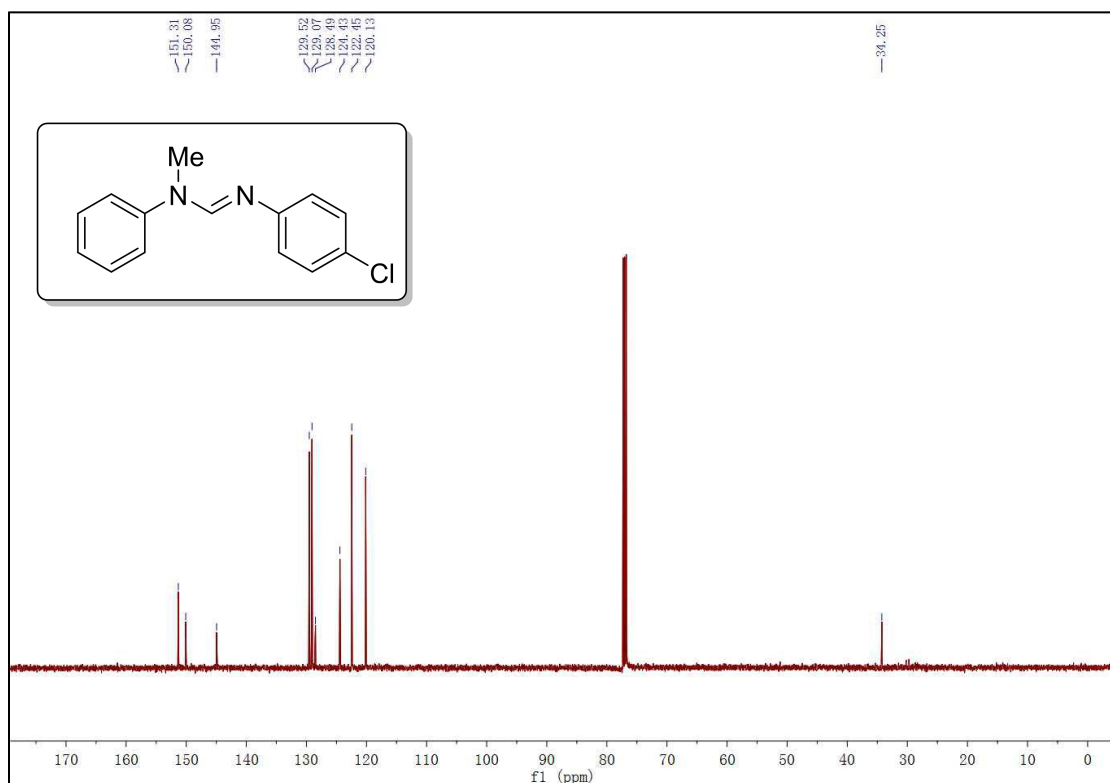


Figure S24. <sup>13</sup>C NMR spectrum of 3l, related to Figure 2

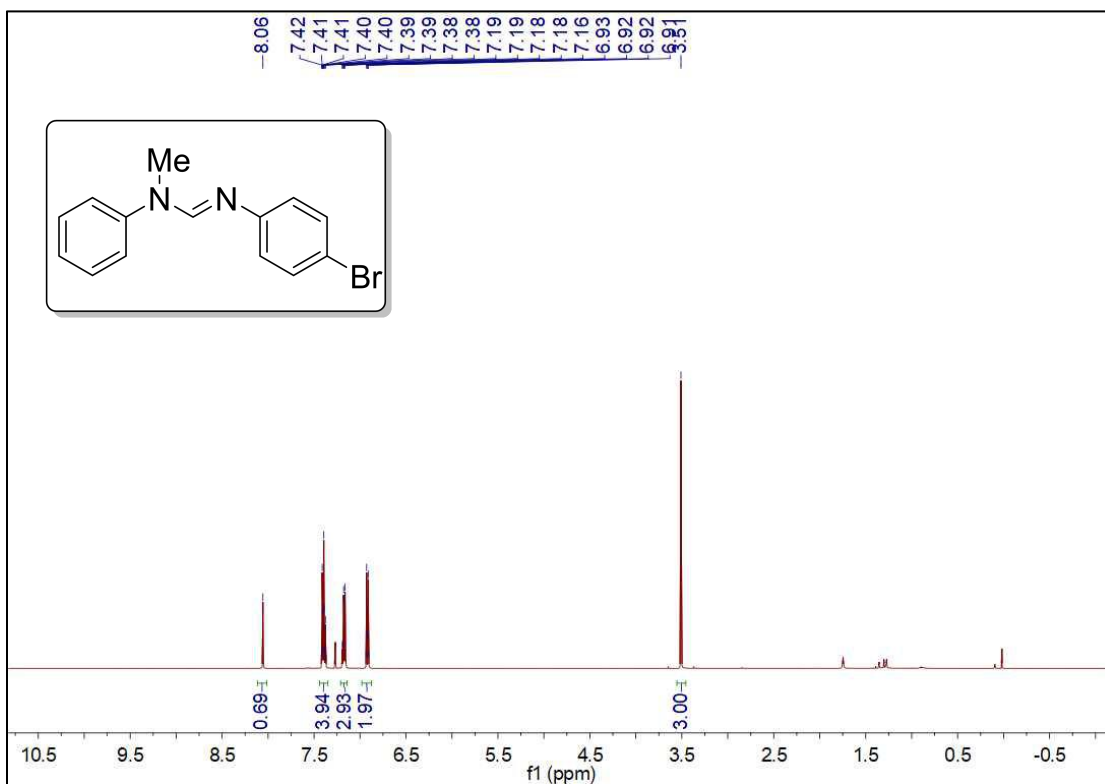


Figure S25.  $^1\text{H}$  NMR spectrum of 3m, related to Figure 2

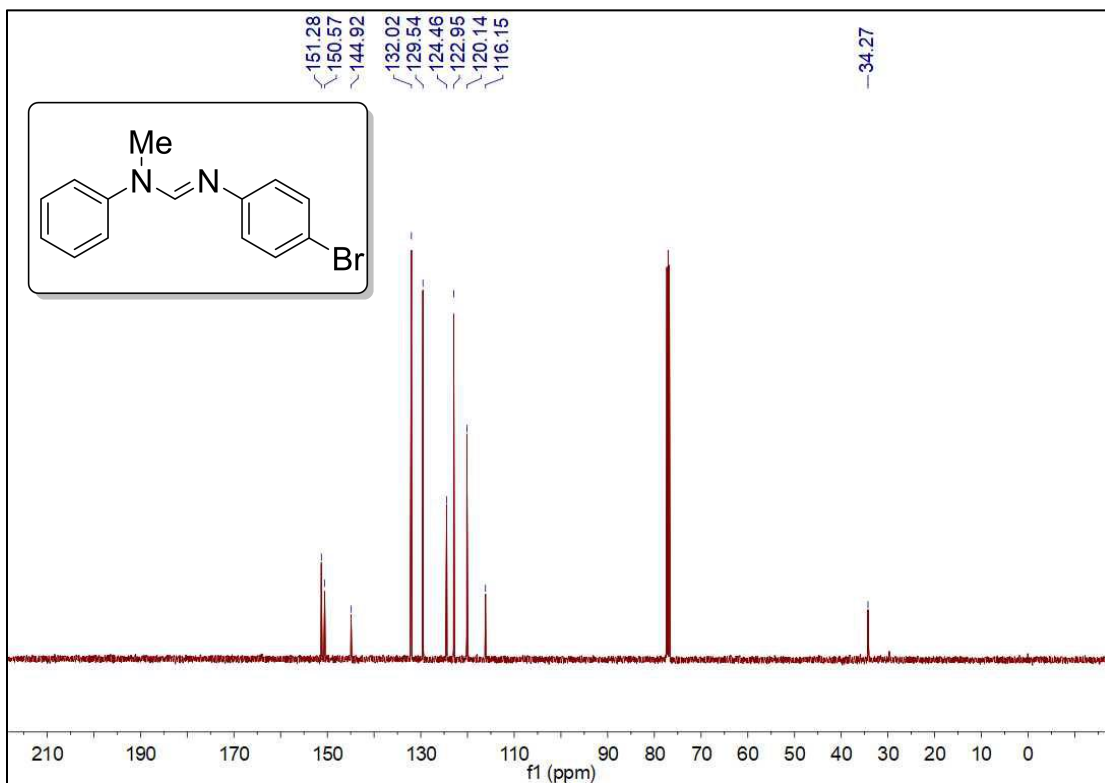


Figure S26.  $^{13}\text{C}$  NMR spectrum of 3m, related to Figure 2

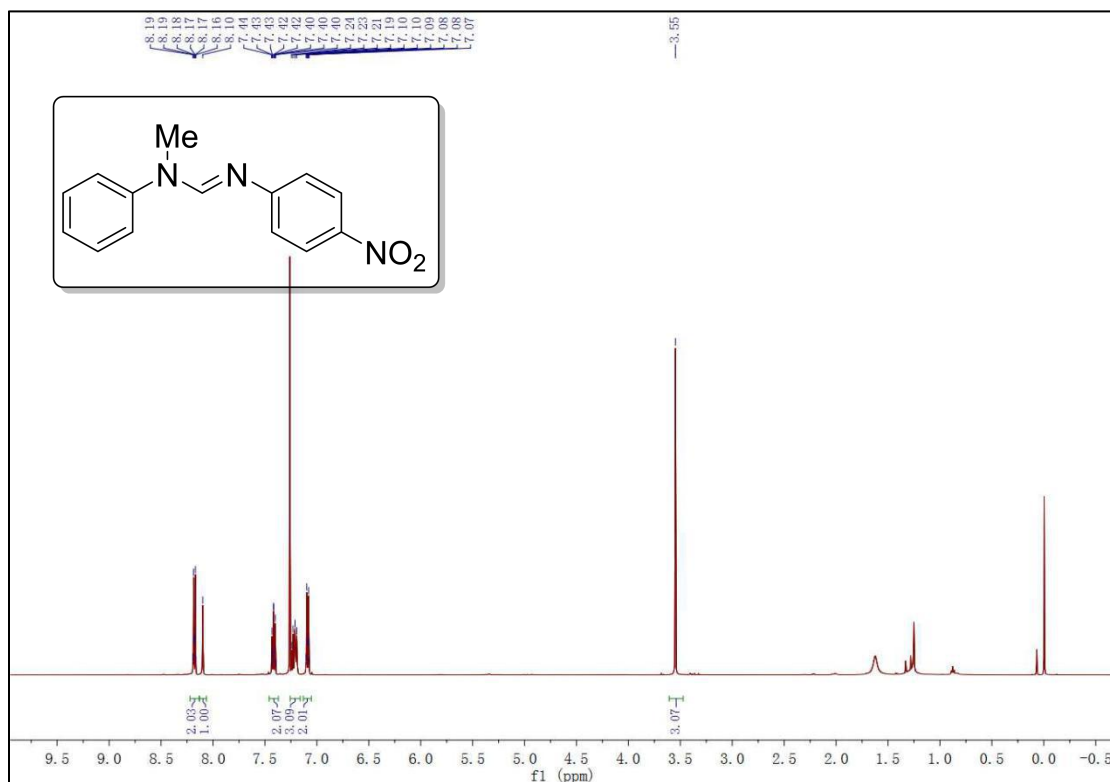


Figure S27. <sup>1</sup>H NMR spectrum of 3n, related to Figure 2

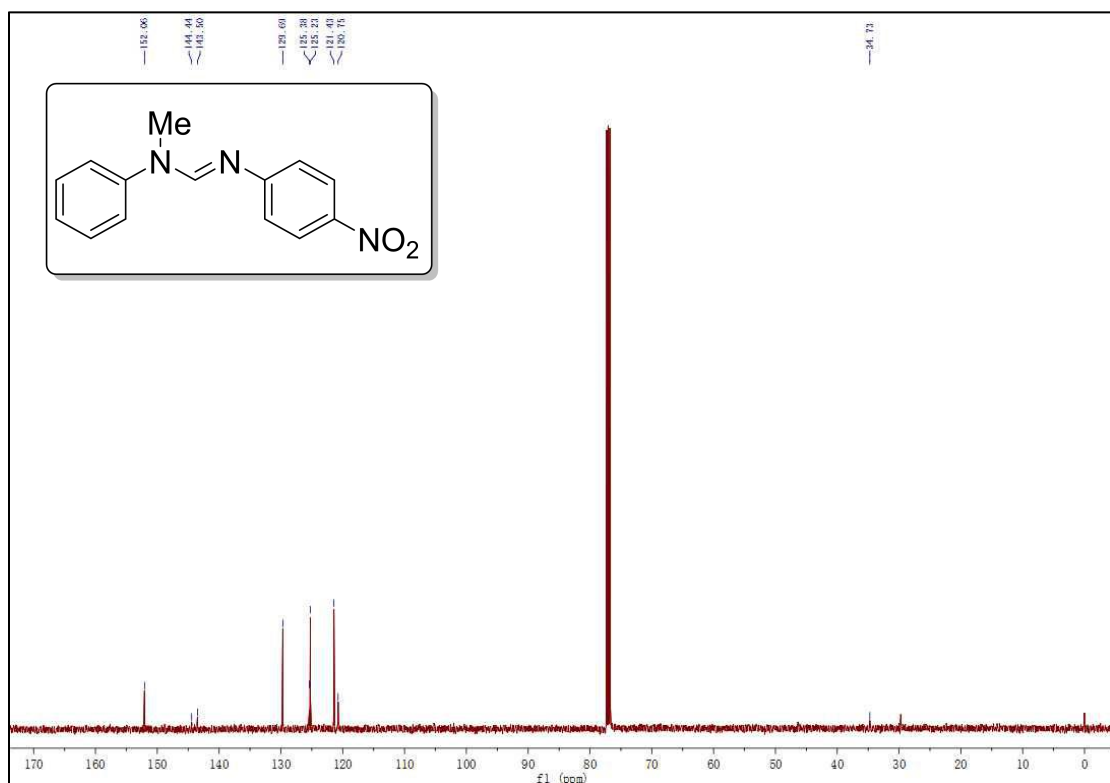


Figure S28. <sup>13</sup>C NMR spectrum of 3n, related to Figure 2

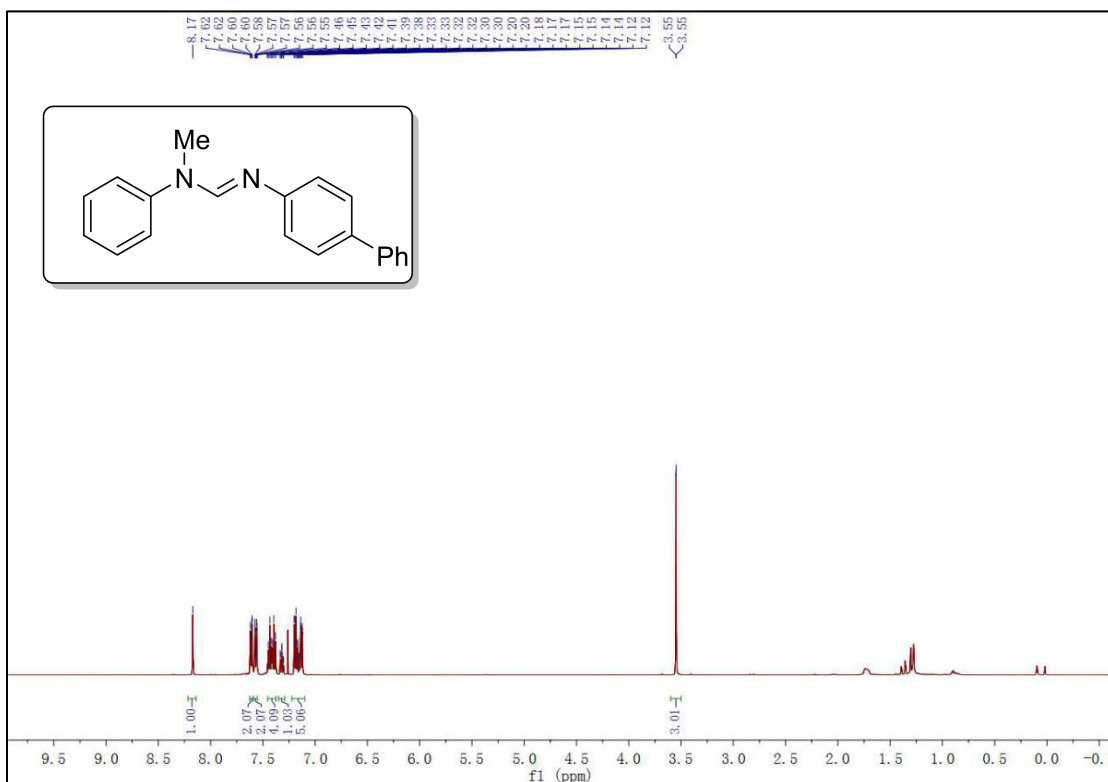


Figure S29. <sup>1</sup>H NMR spectrum of 30, related to Figure 2

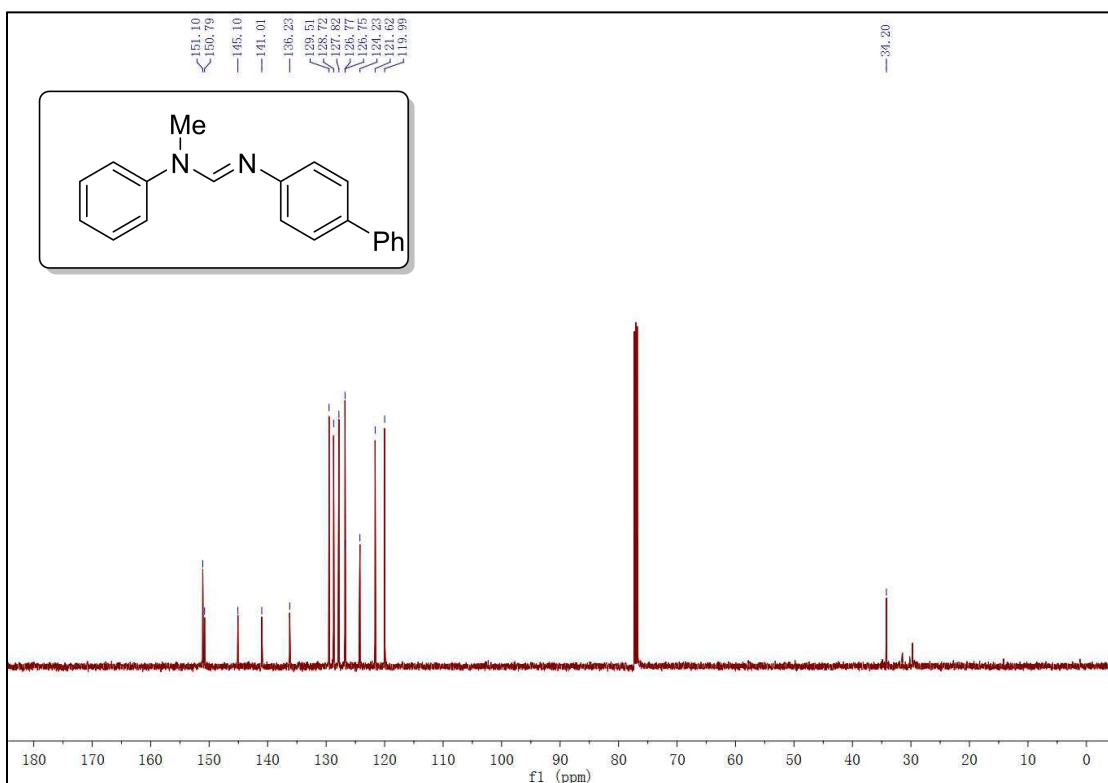


Figure S30. <sup>13</sup>C NMR spectrum of 30, related to Figure 2

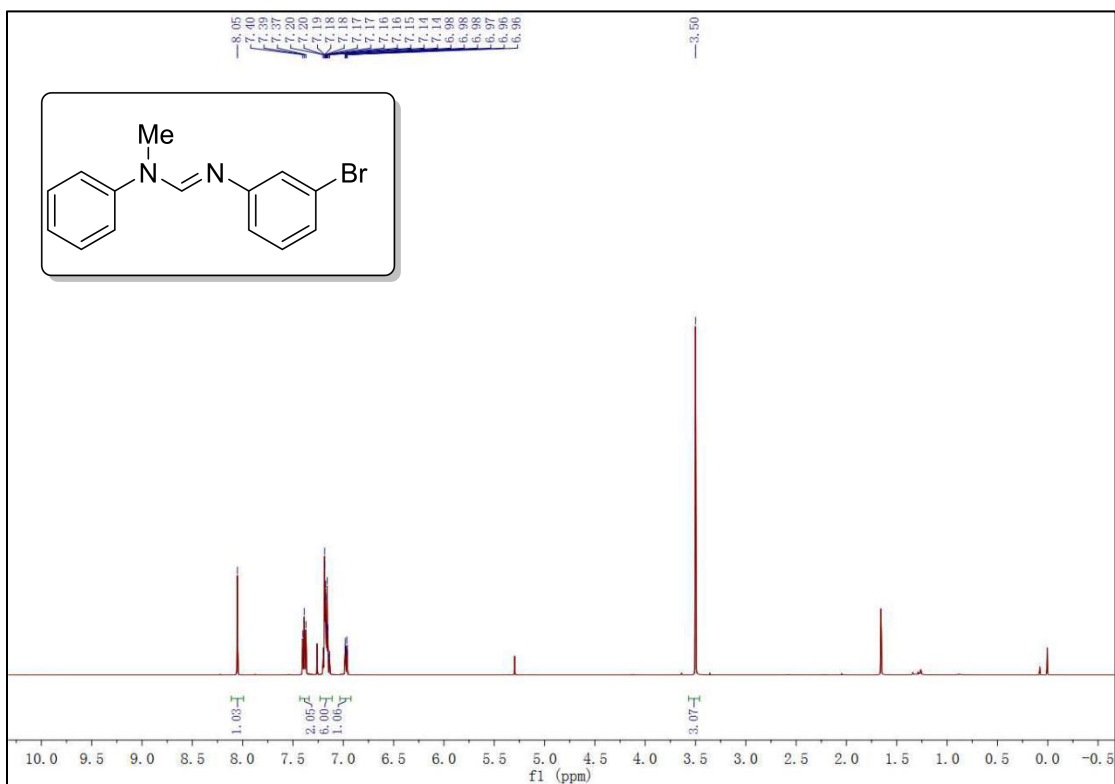


Figure S31. <sup>1</sup>H NMR spectrum of 3p, related to Figure 2

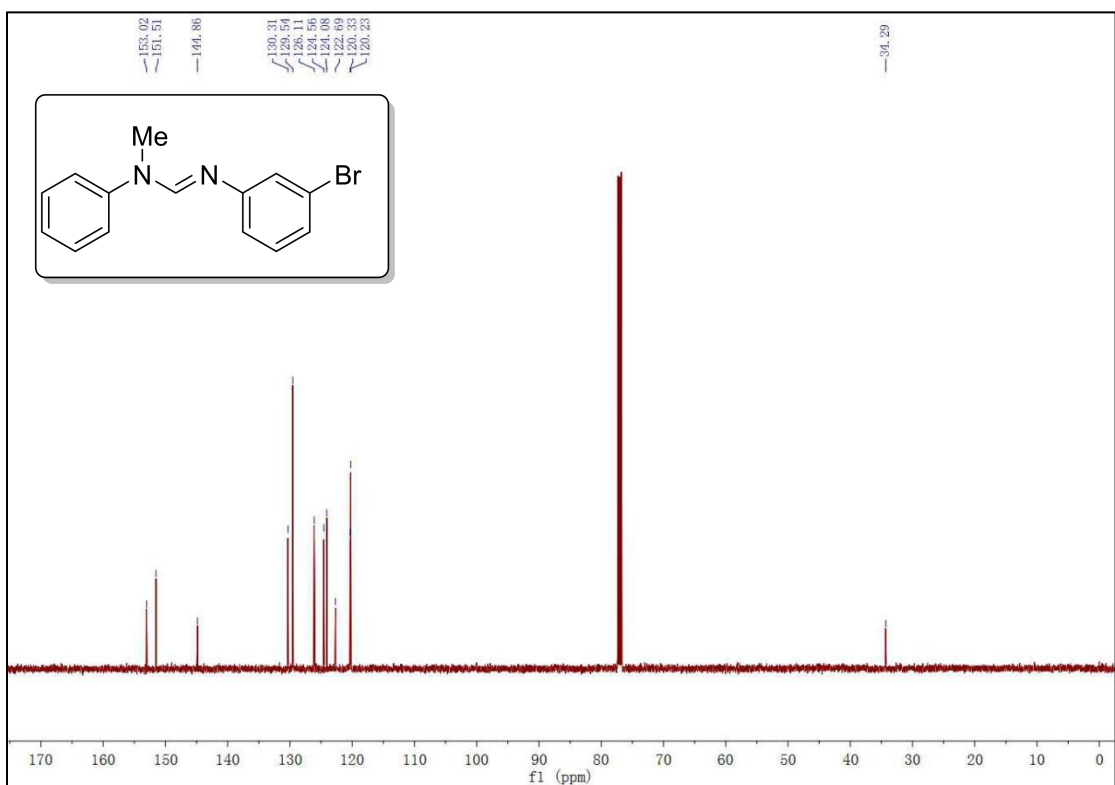


Figure S32. <sup>13</sup>C NMR spectrum of 3p, related to Figure 2

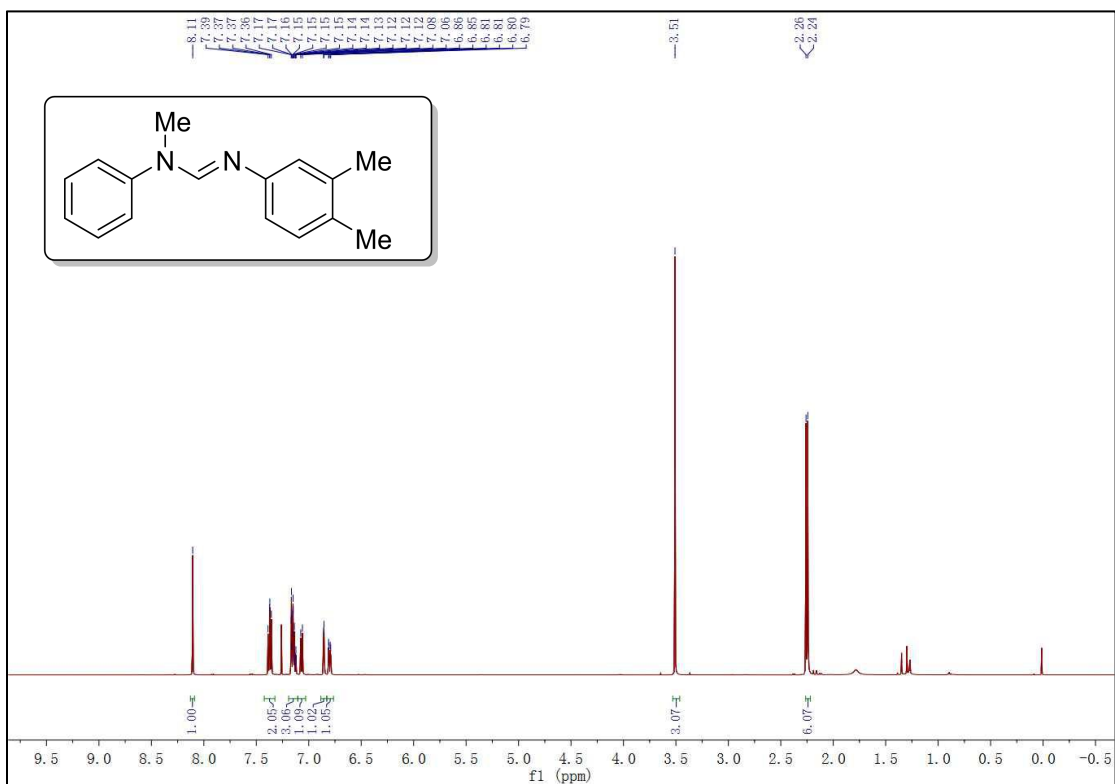


Figure S33. <sup>1</sup>H NMR spectrum of 3q, related to Figure 2

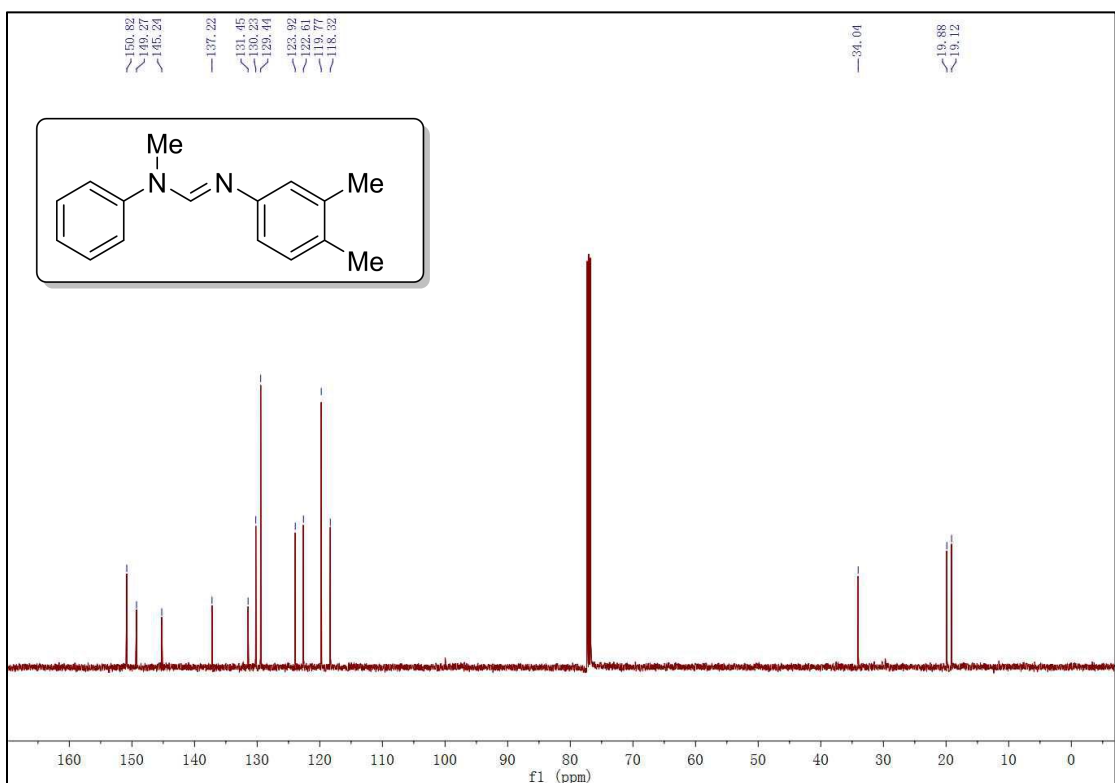


Figure S34. <sup>13</sup>C NMR spectrum of 3q, related to Figure 2



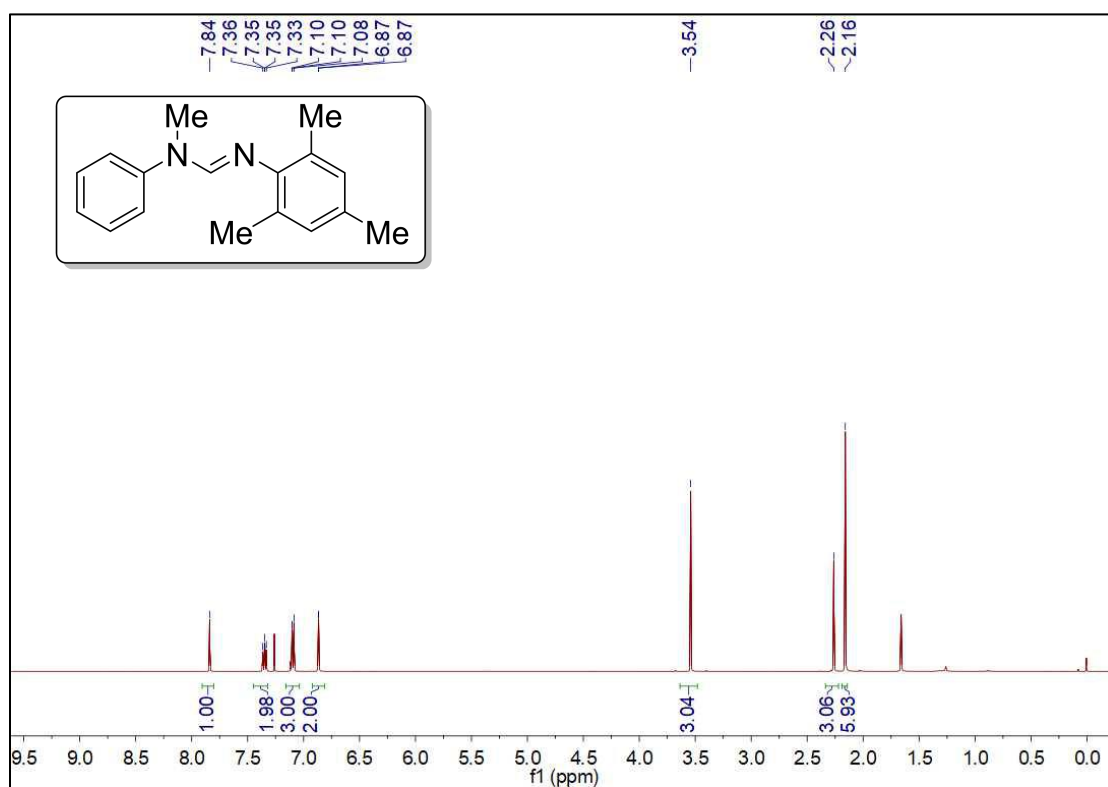


Figure S35.  $^1\text{H}$  NMR spectrum of 3r, related to Figure 2

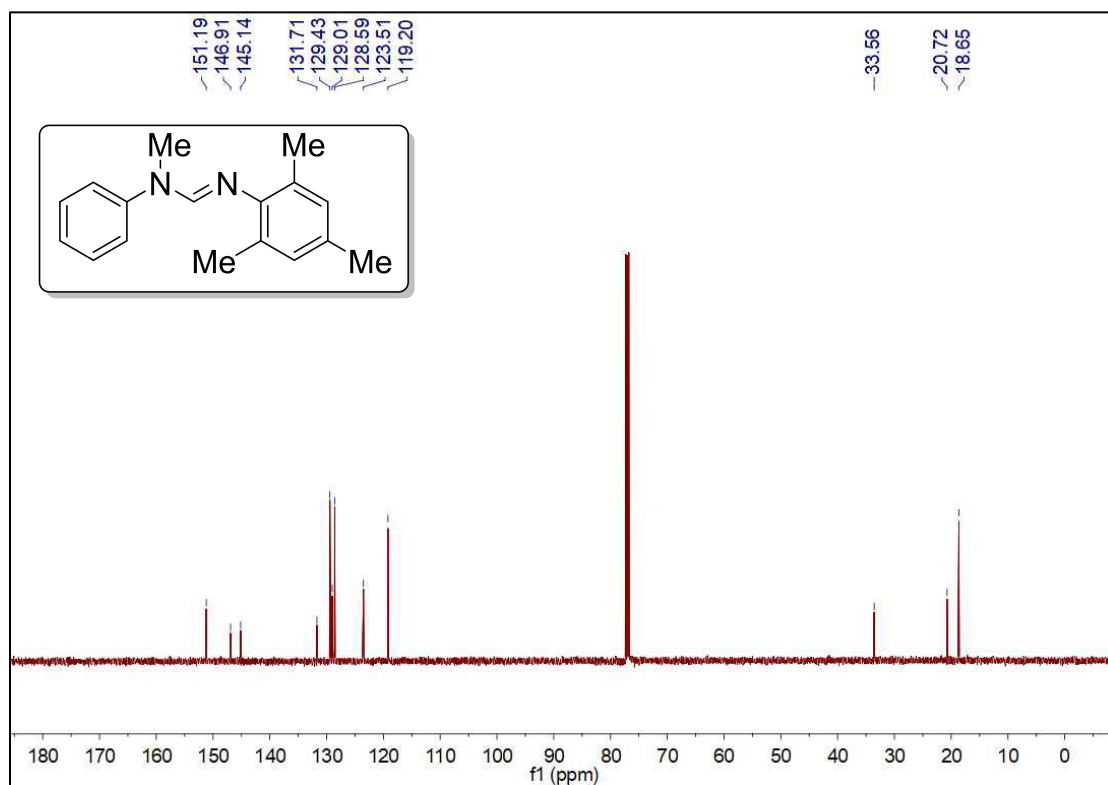


Figure S36.  $^{13}\text{C}$  NMR spectrum of 3r, related to Figure 2

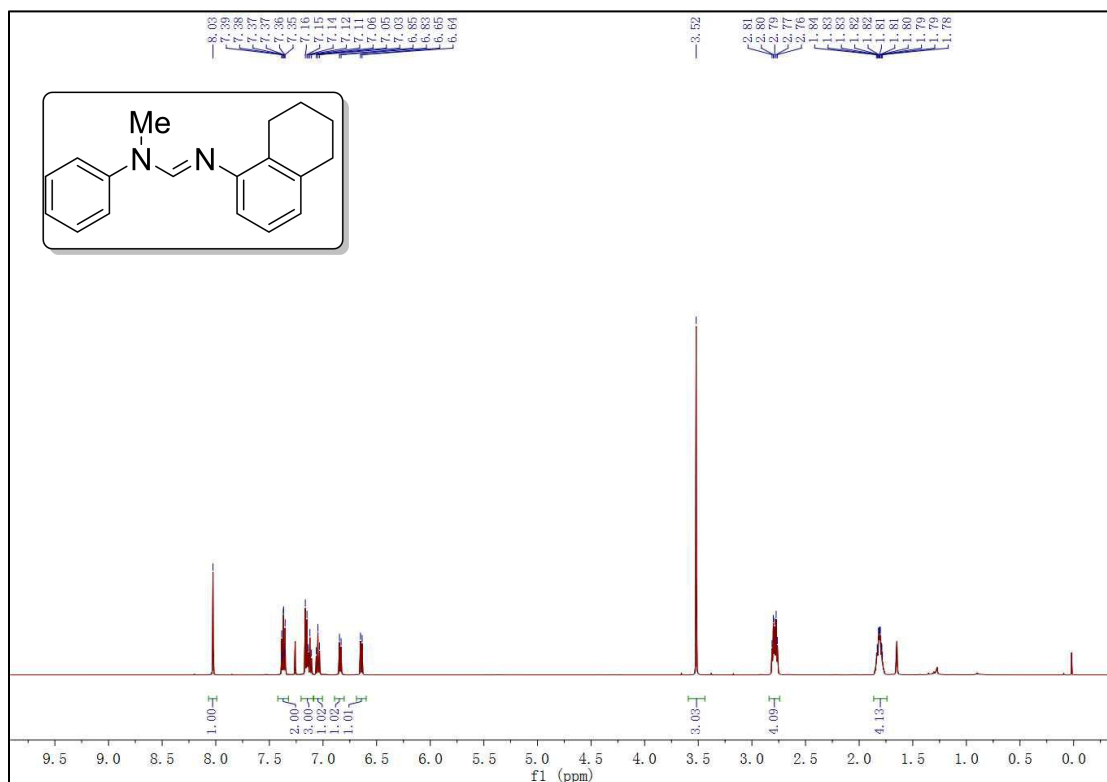


Figure S37. <sup>1</sup>H NMR spectrum of 3s, related to Figure 2

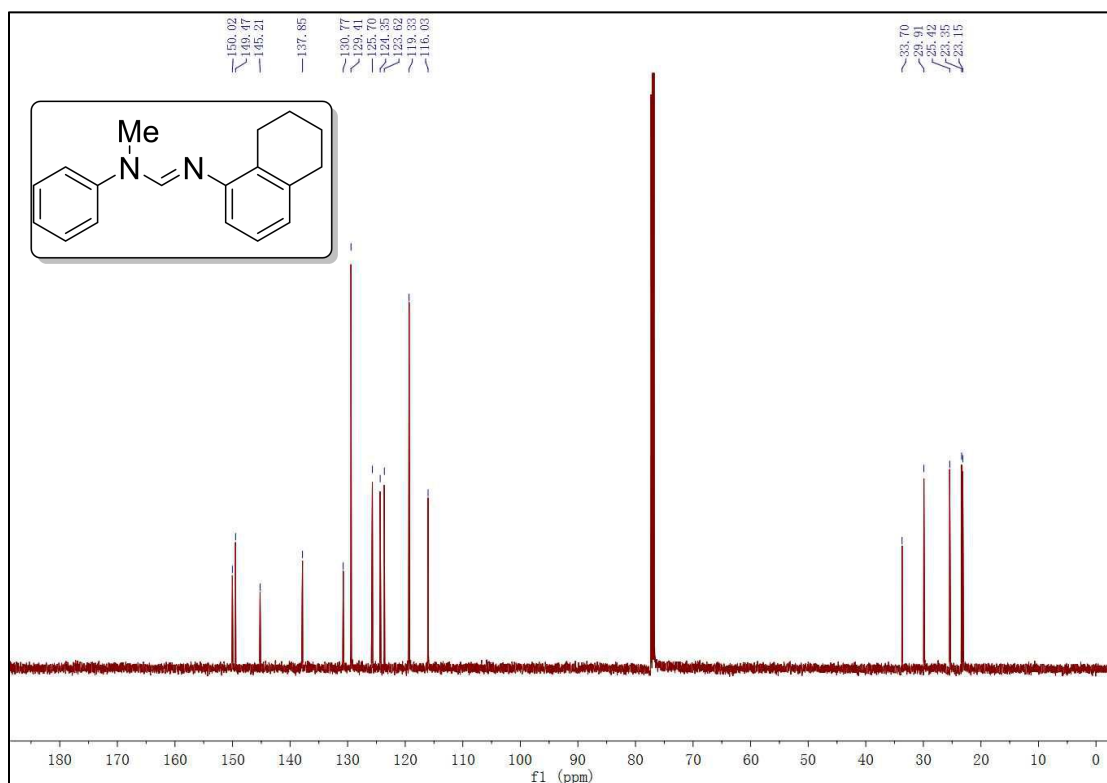


Figure S38. <sup>13</sup>C NMR spectrum of 3s, related to Figure 2

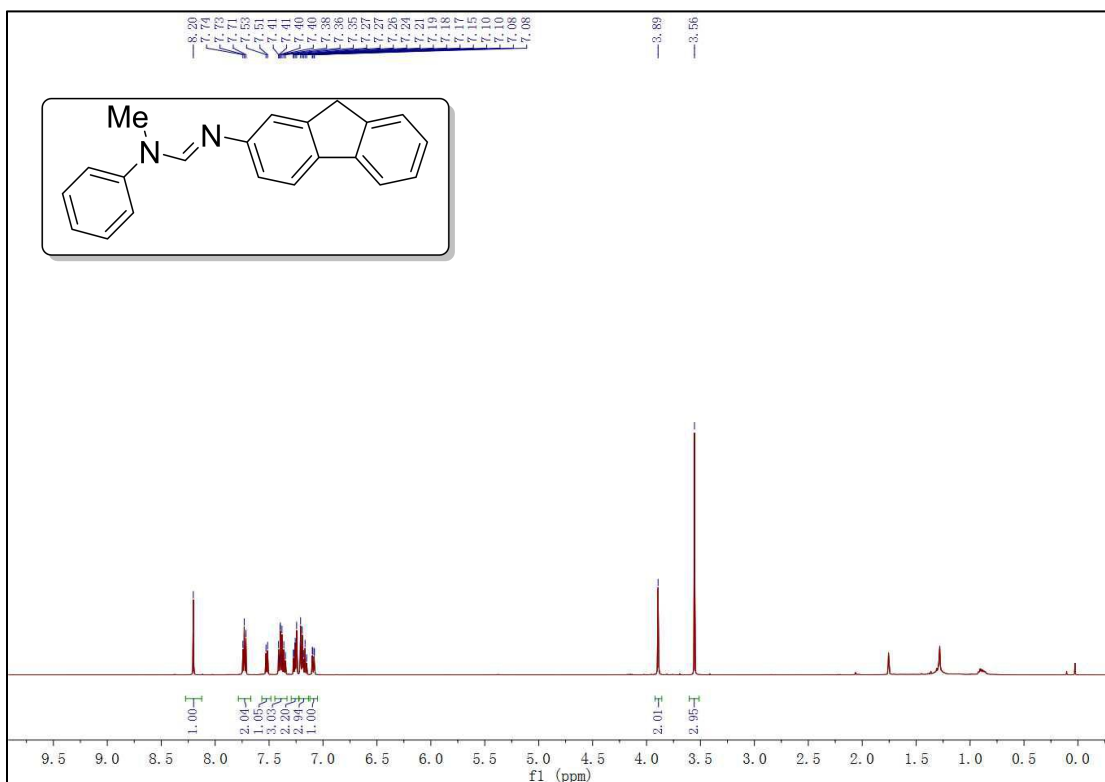


Figure S39. <sup>1</sup>H NMR spectrum of 3t, related to Figure 2

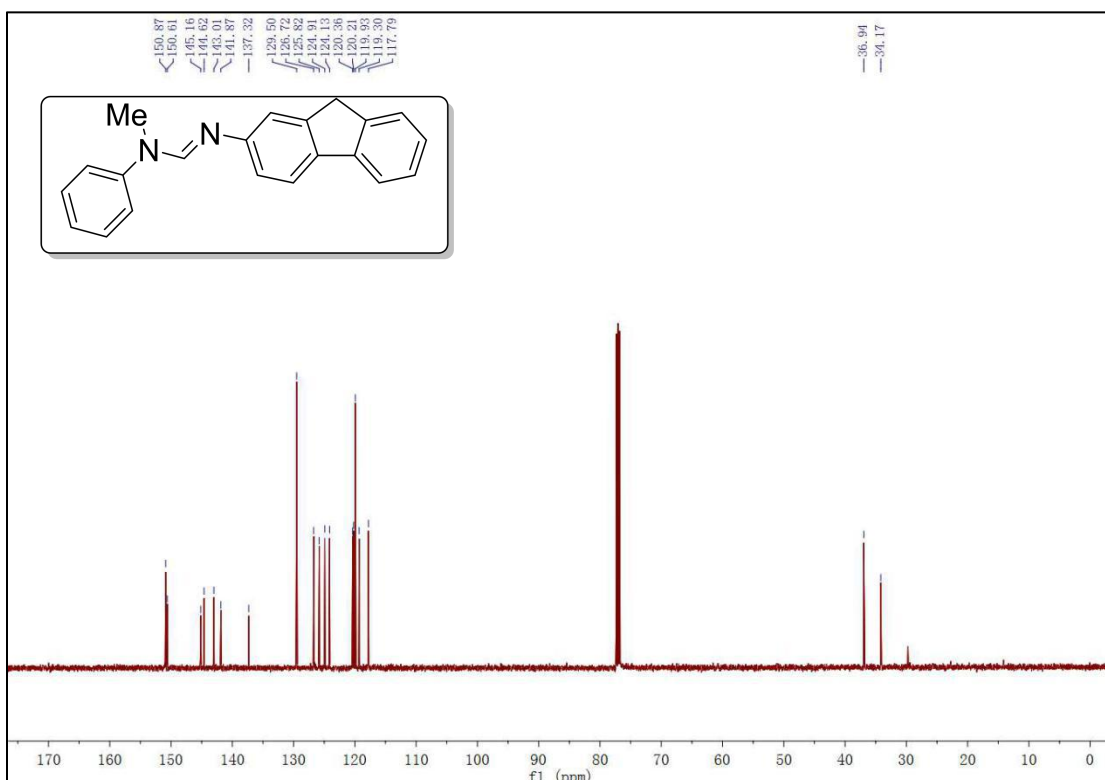


Figure S40. <sup>13</sup>C NMR spectrum of 3t, related to Figure 2

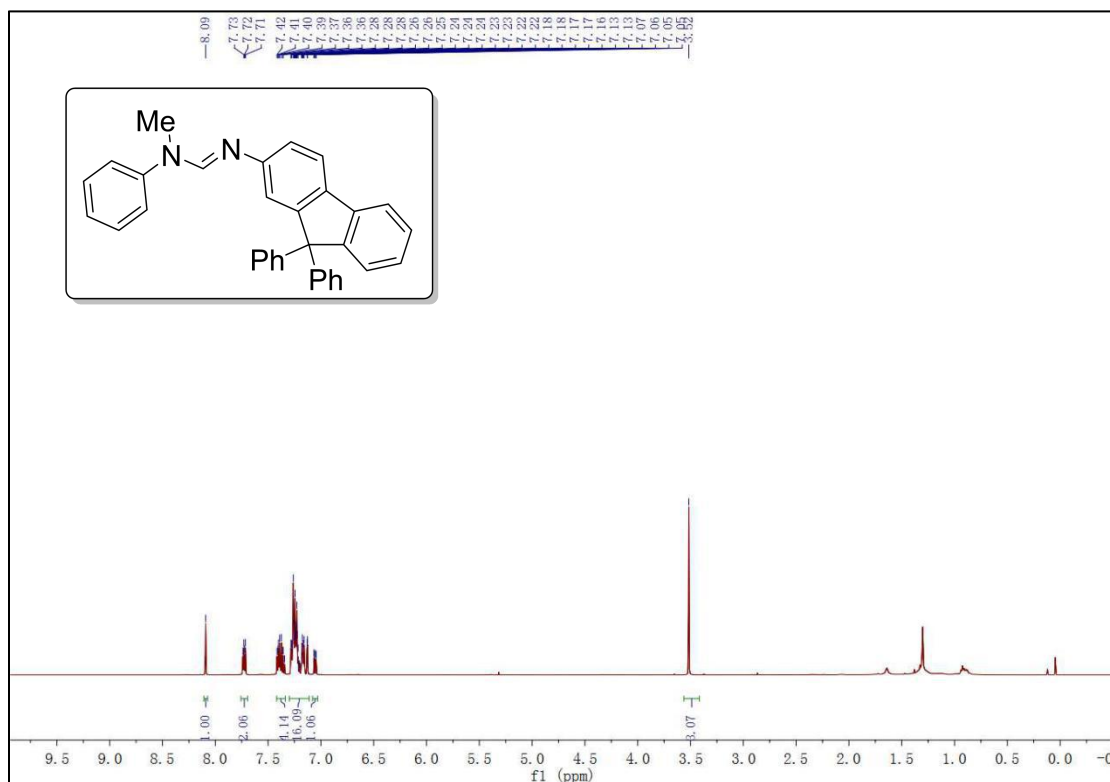


Figure S41. <sup>1</sup>H NMR spectrum of 3u, related to Figure 2

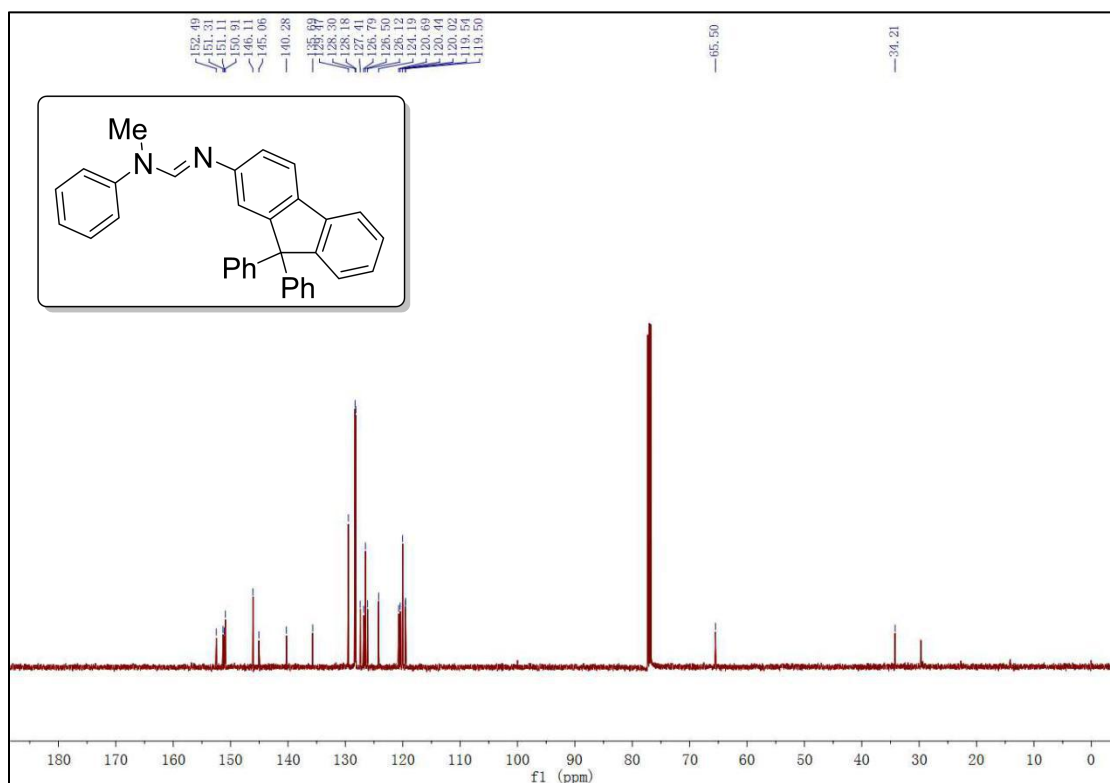


Figure S42. <sup>13</sup>C NMR spectrum of 3u, related to Figure 2

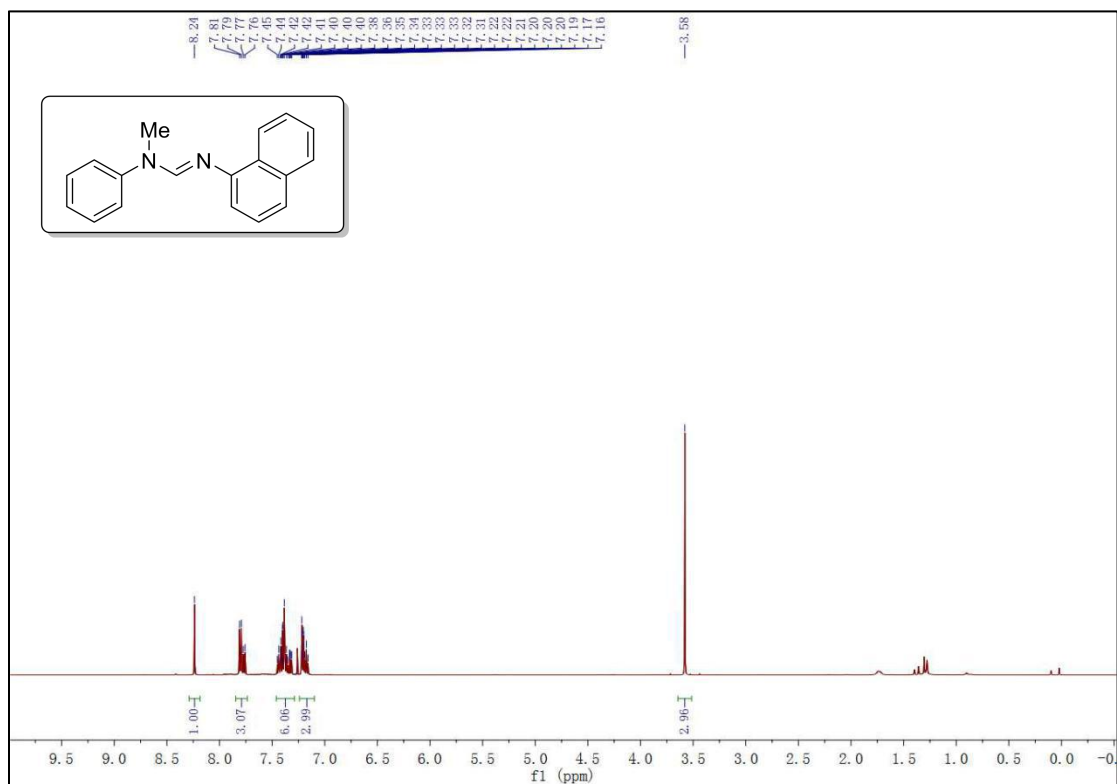


Figure S43. <sup>1</sup>H NMR spectrum of 3v, related to Figure 2

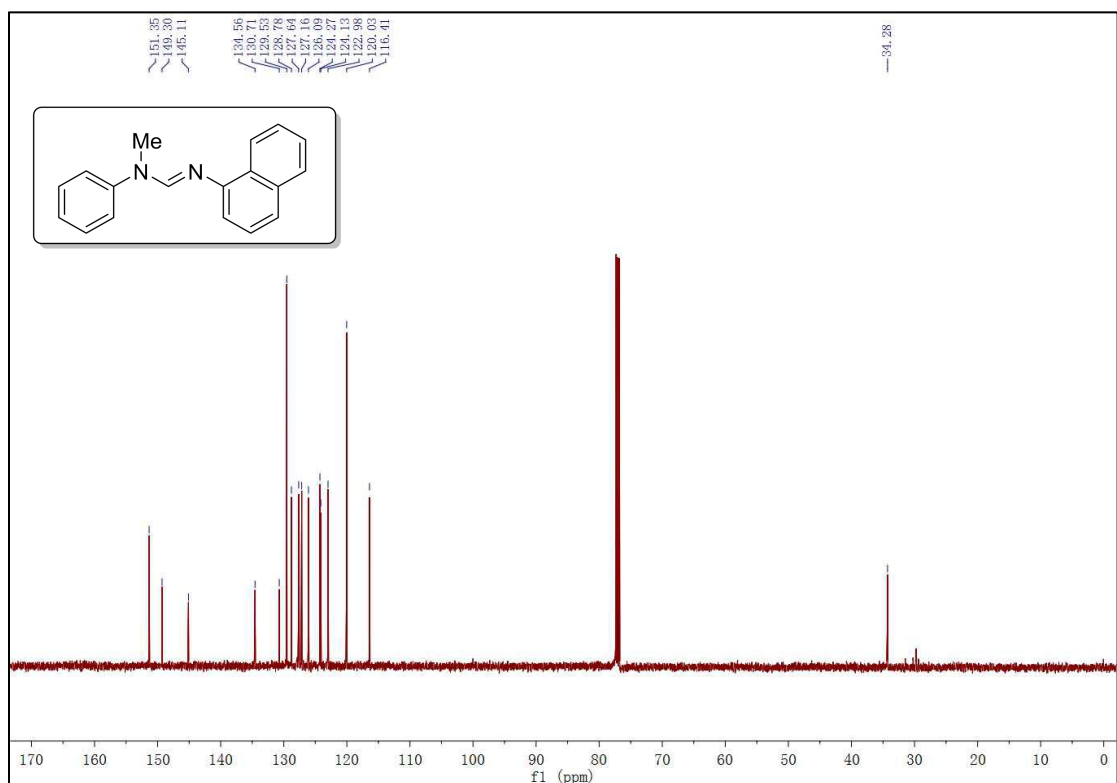


Figure S44. <sup>13</sup>C NMR spectrum of 3v, related to Figure 2

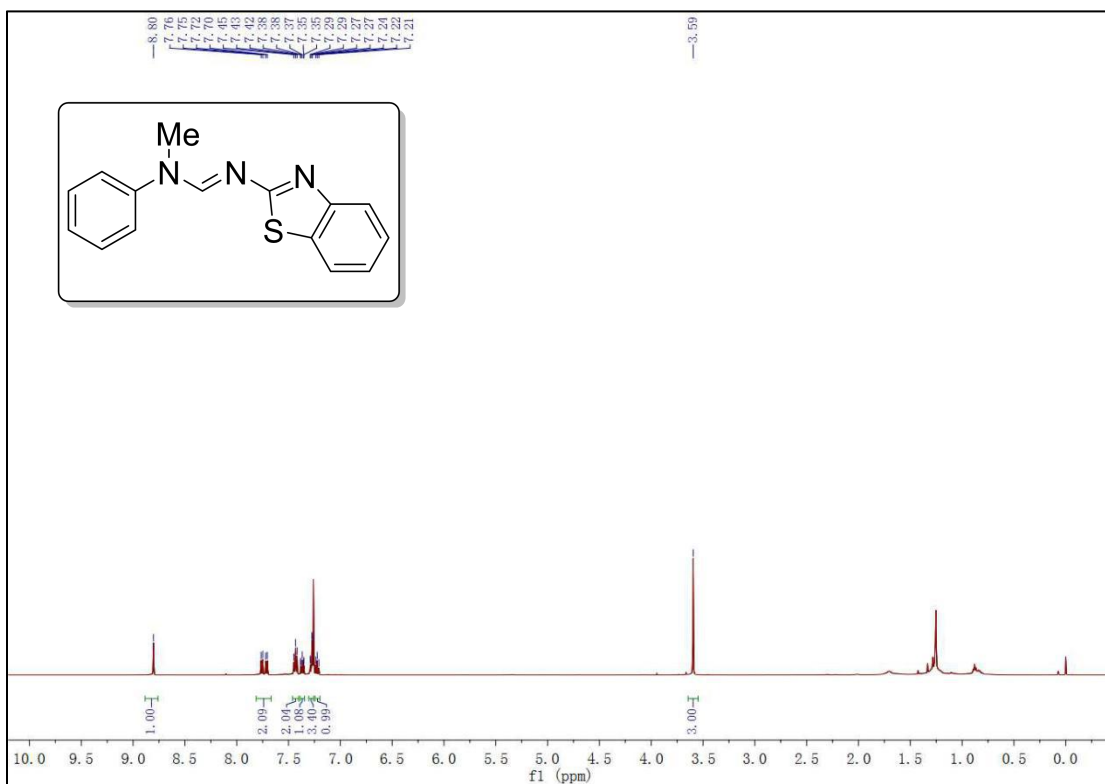


Figure S45. <sup>1</sup>H NMR spectrum of 3w, related to Figure 2

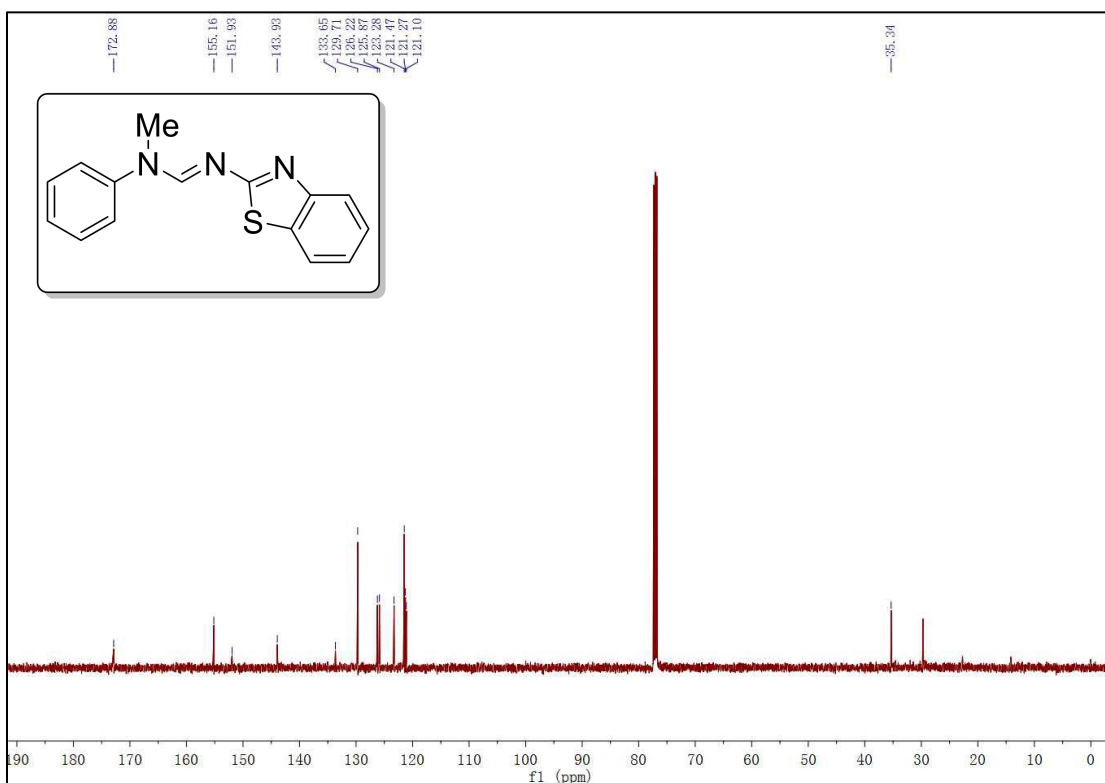


Figure S46. <sup>13</sup>C NMR spectrum of 3w, related to Figure 2

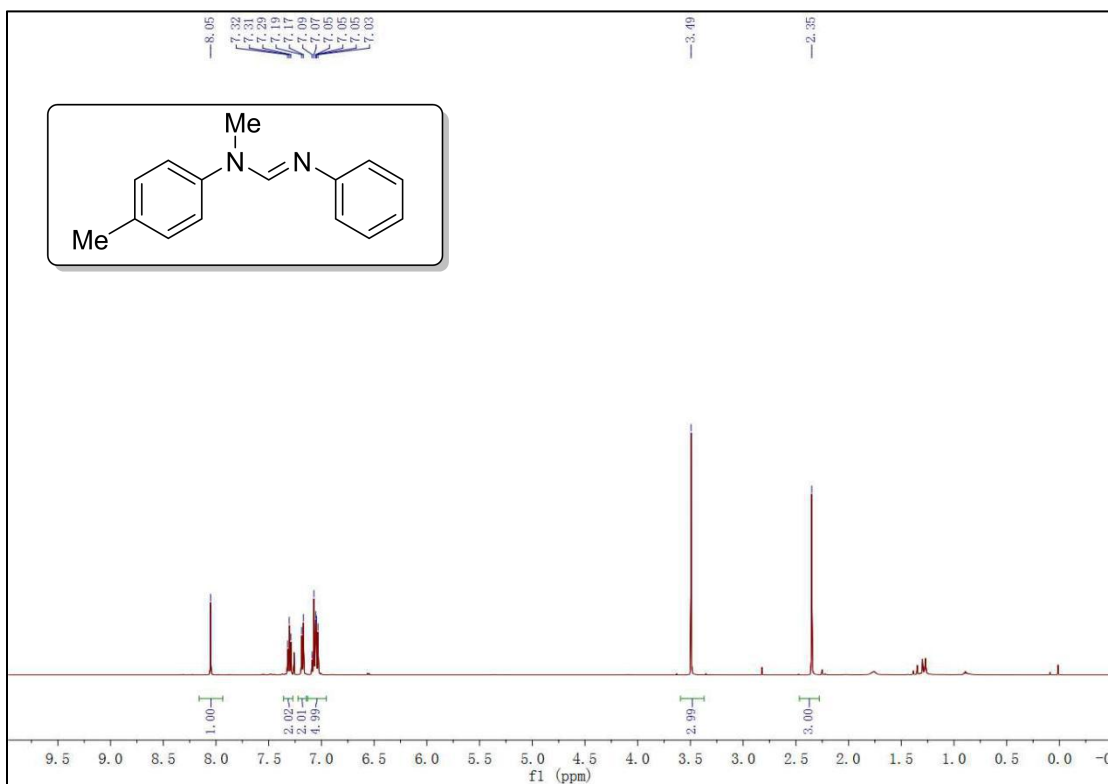


Figure S47. <sup>1</sup>H NMR spectrum of 3x, related to Figure 2

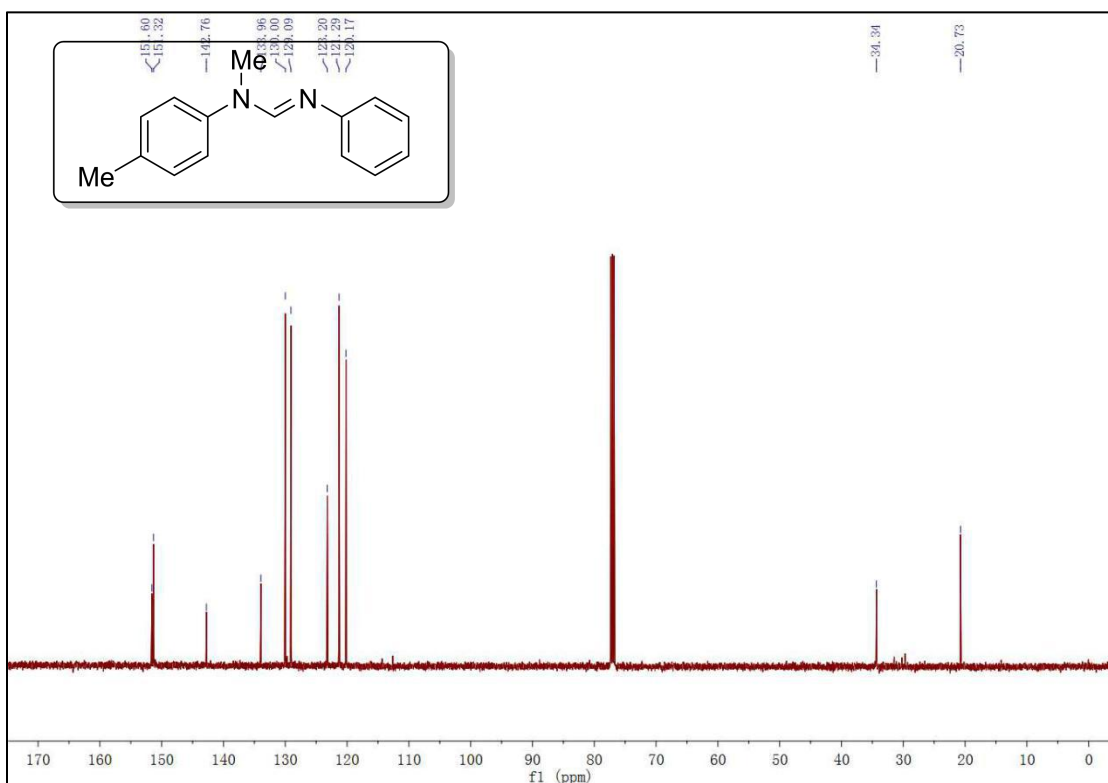


Figure S48. <sup>13</sup>C NMR spectrum of 3x, related to Figure 2

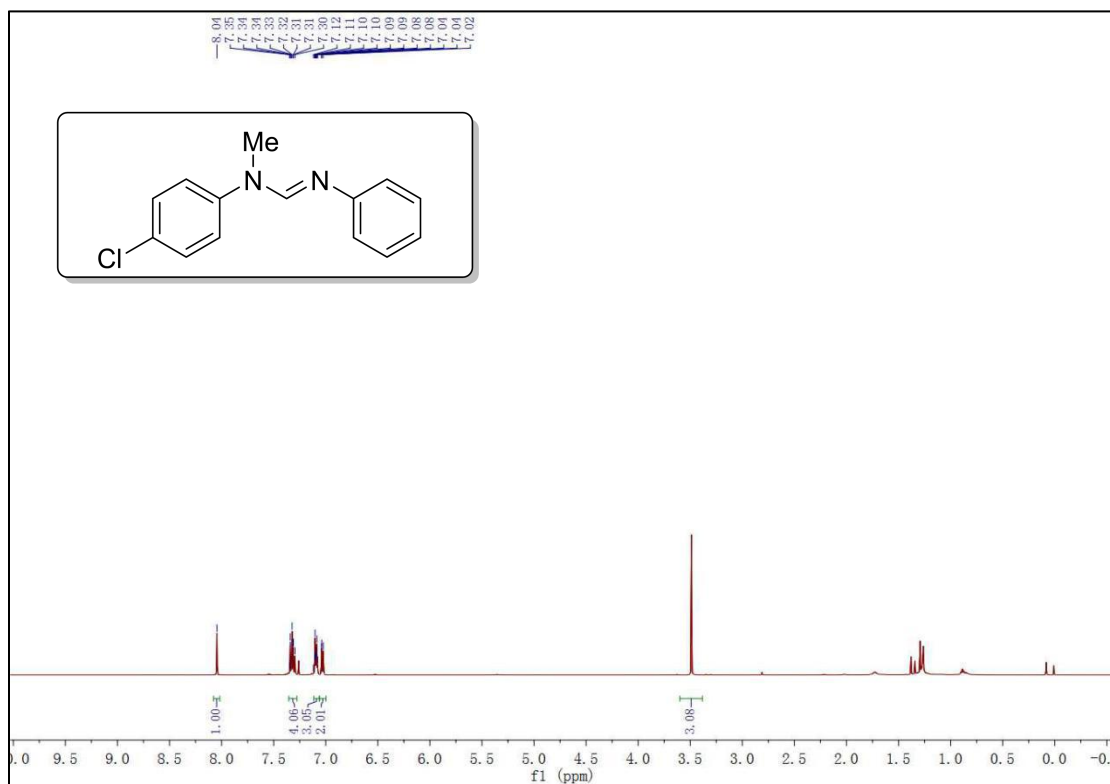


Figure S49. <sup>1</sup>H NMR spectrum of 3y, related to Figure 2

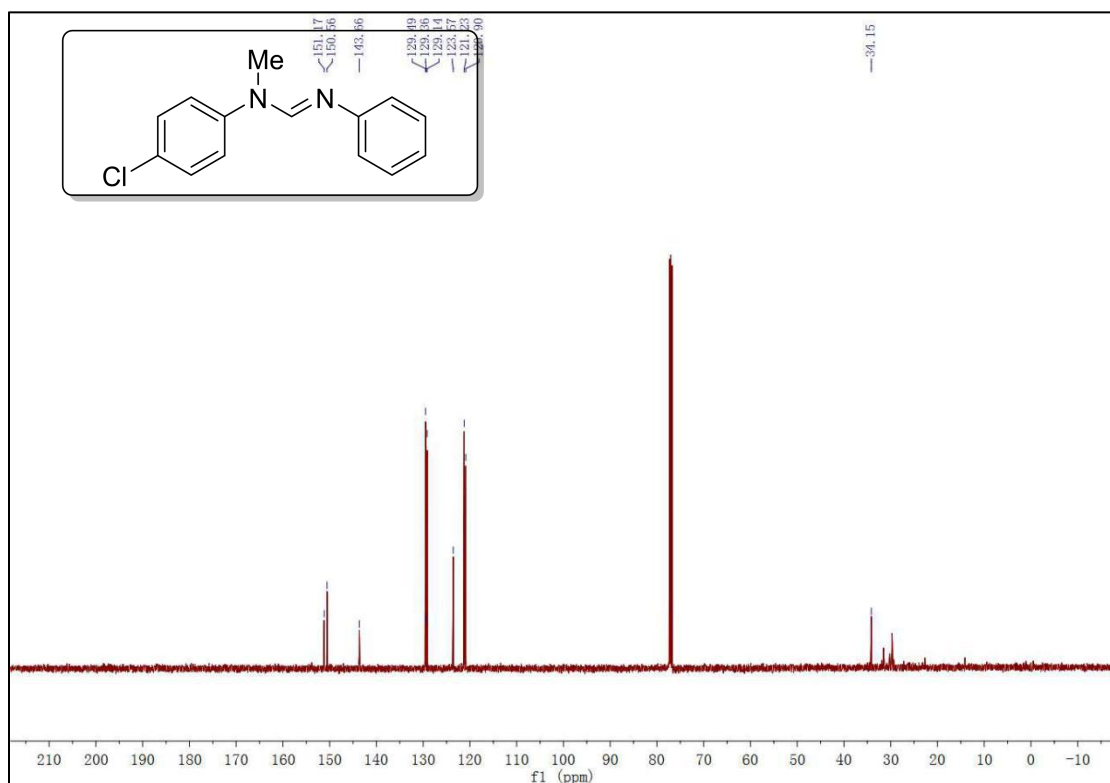


Figure S50. <sup>13</sup>C NMR spectrum of 3y, related to Figure 2



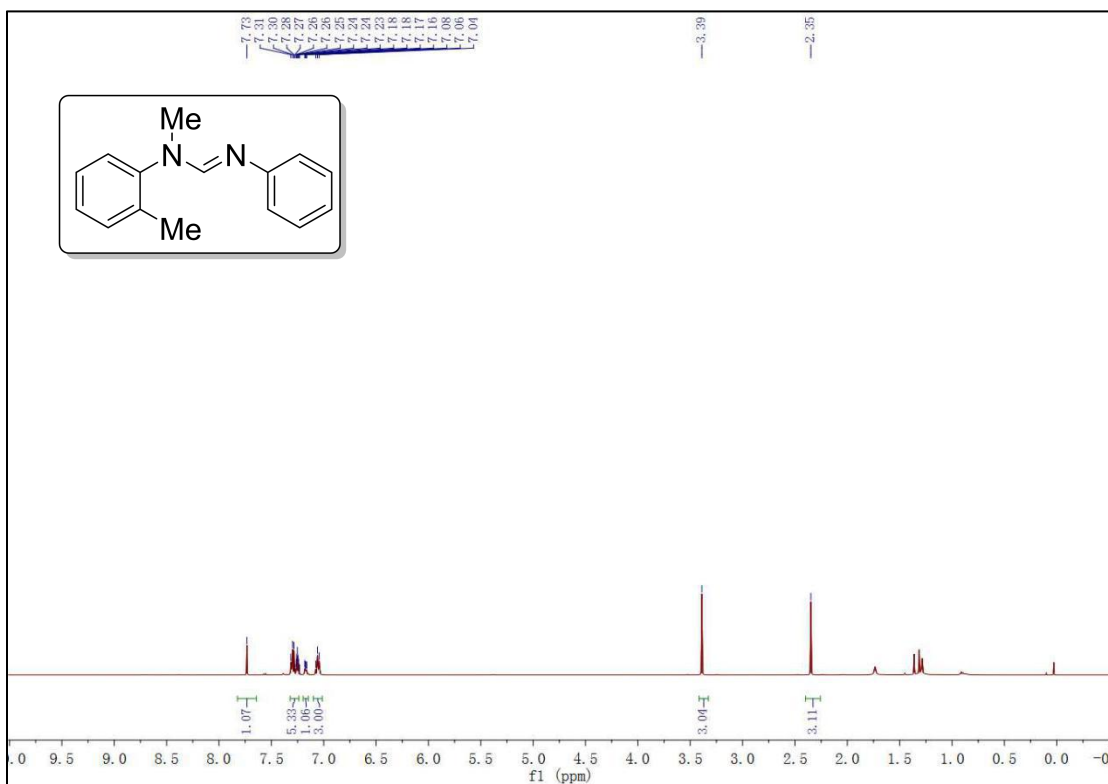


Figure S51. <sup>1</sup>H NMR spectrum of 3z, related to Figure 2

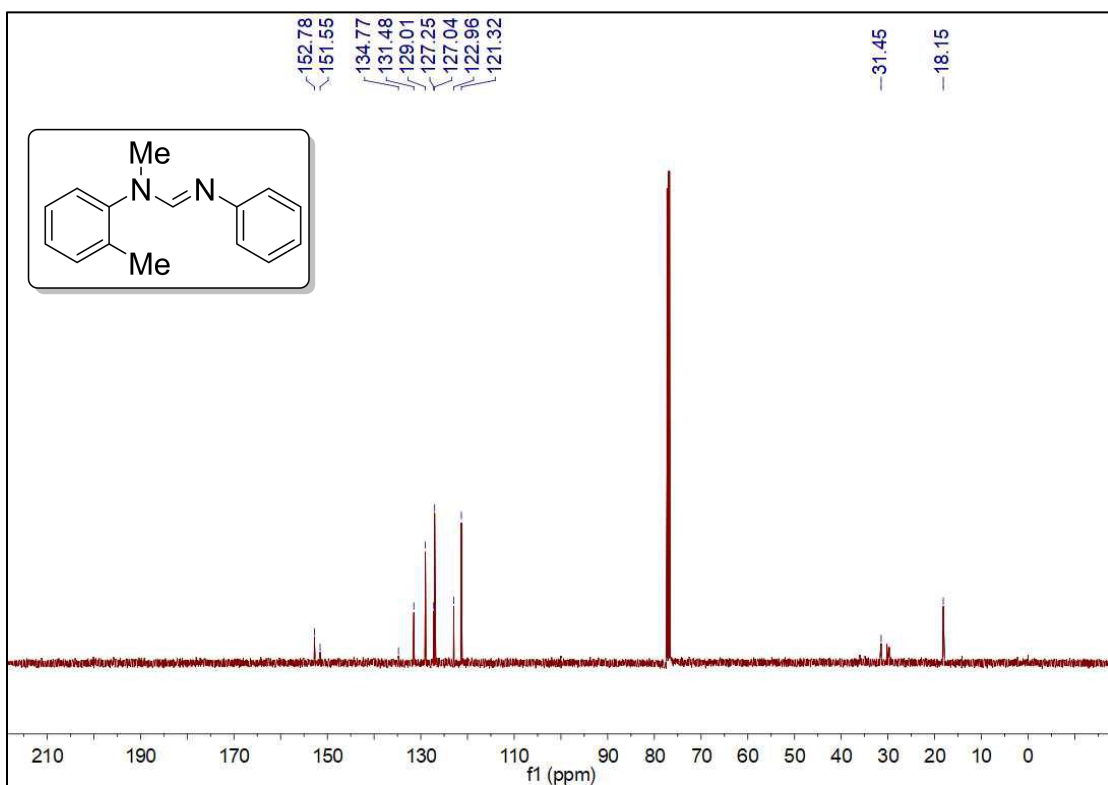
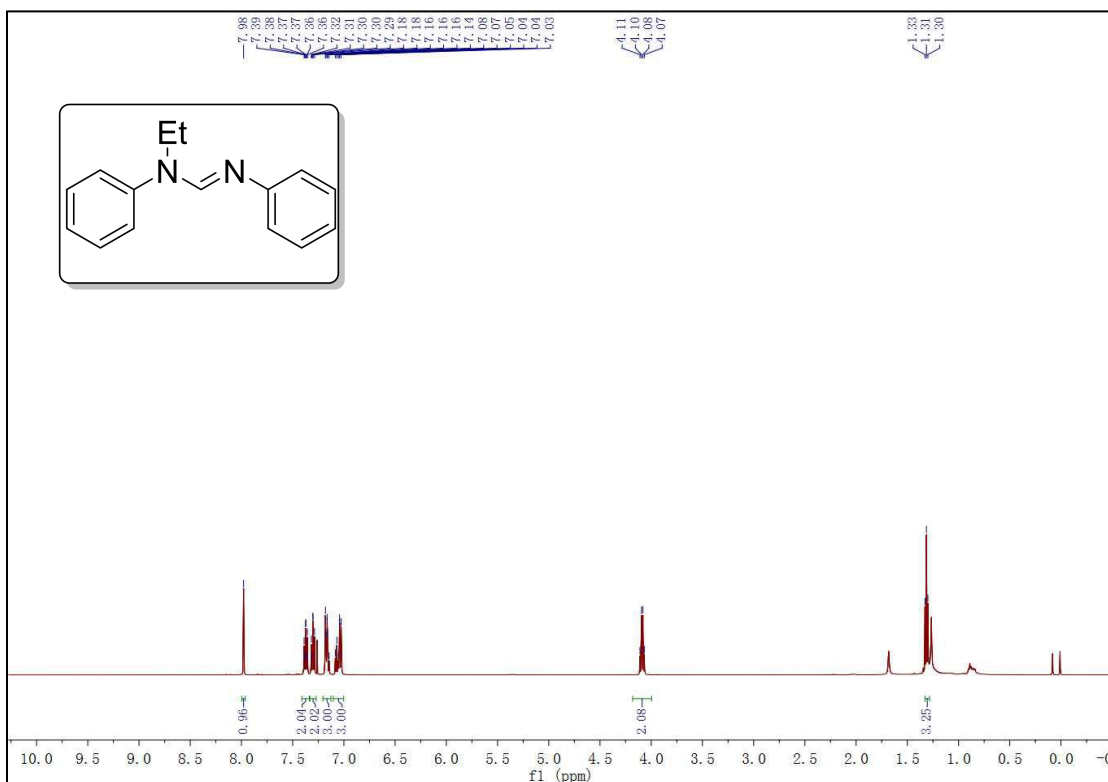
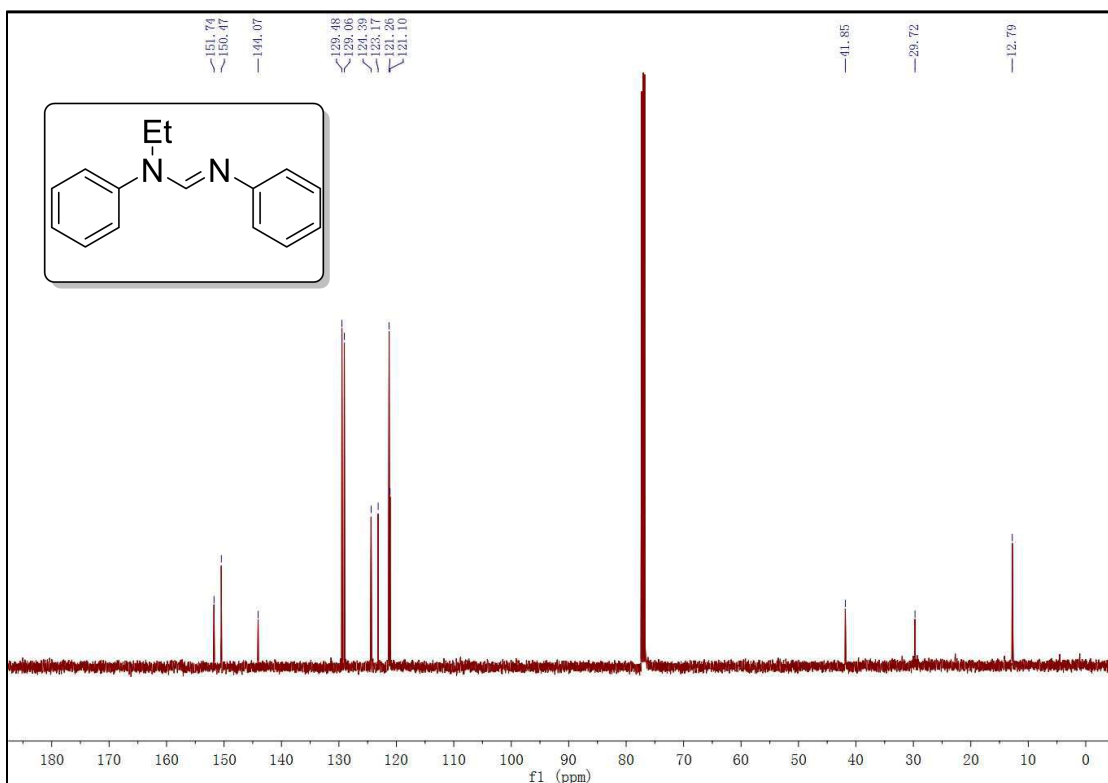


Figure S52. <sup>13</sup>C NMR spectrum of 3z, related to Figure 2



**Figure S53.** <sup>1</sup>H NMR spectrum of 3aa, related to Figure 2



**Figure S54.** <sup>13</sup>C NMR spectrum of 3aa, related to Figure 2

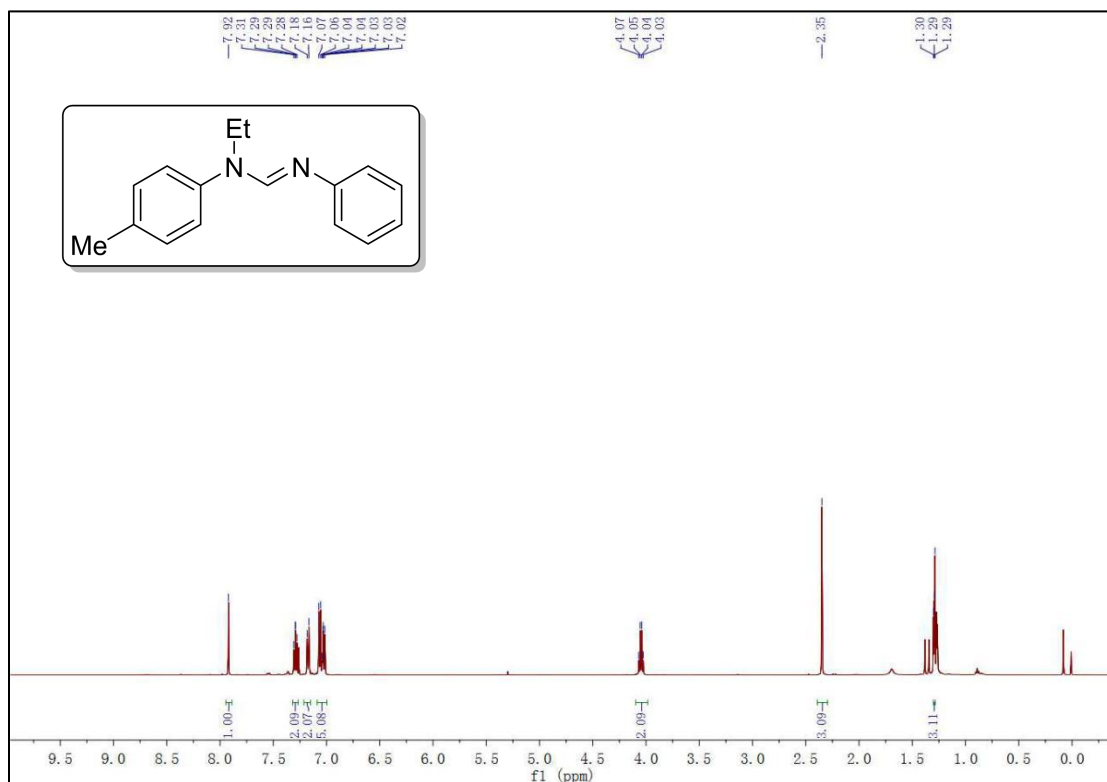


Figure S55. <sup>1</sup>H NMR spectrum of 3ab, related to Figure 2

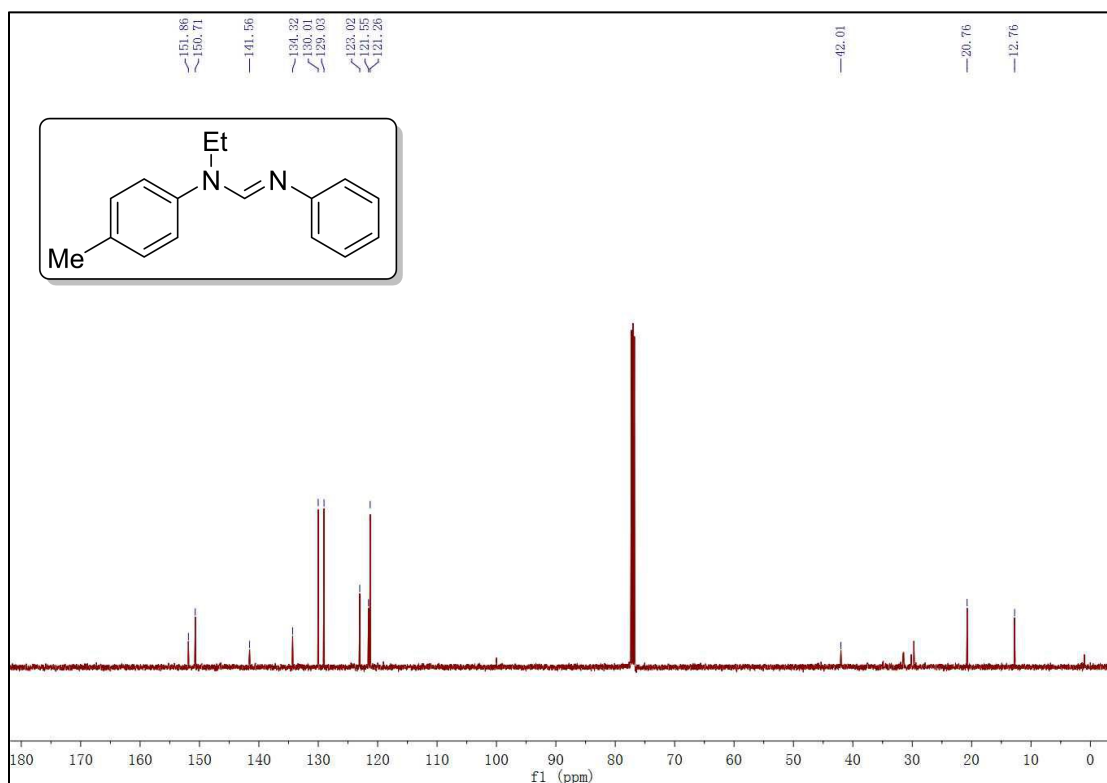


Figure S56. <sup>13</sup>C NMR spectrum of 3ab, related to Figure 2

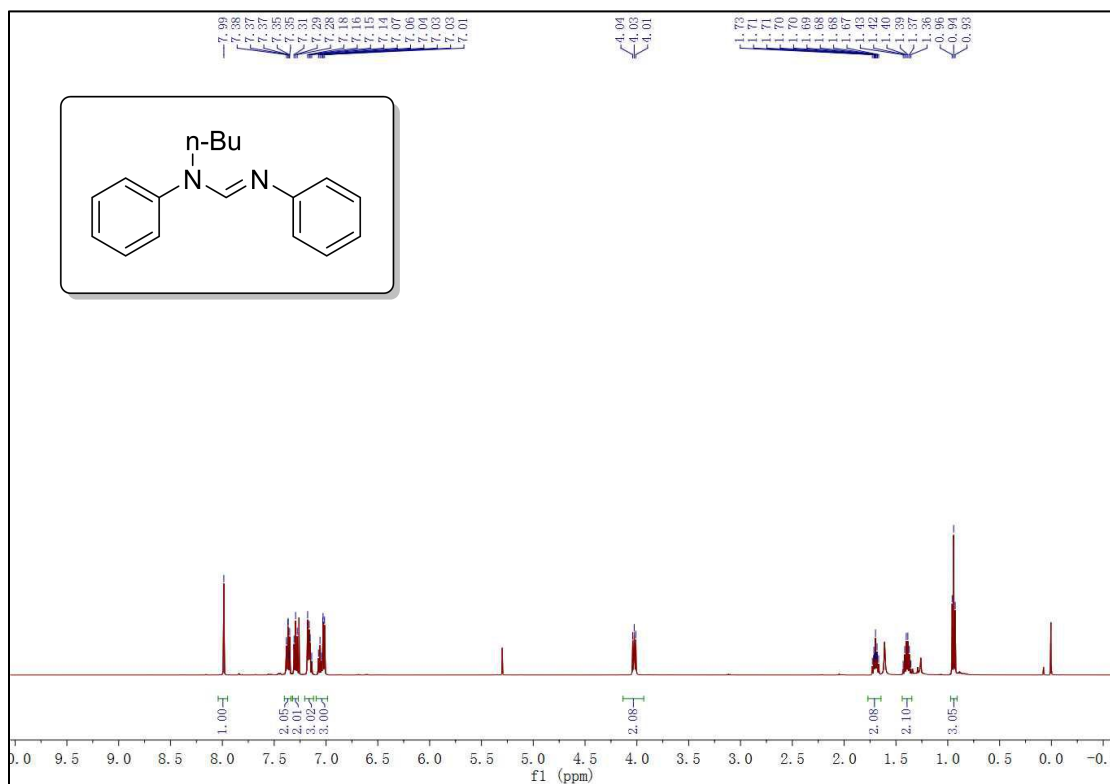


Figure S57. <sup>1</sup>H NMR spectrum of 3ac, related to Figure 2

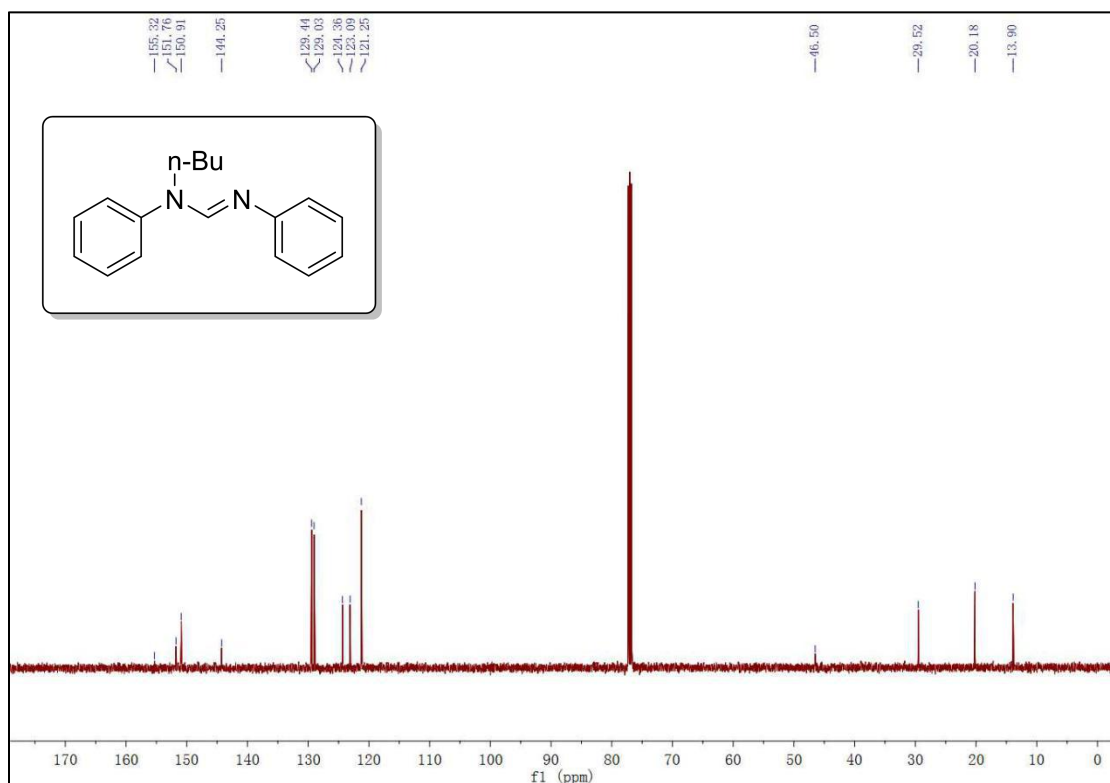


Figure S58. <sup>13</sup>C NMR spectrum of 3ac, related to Figure 2



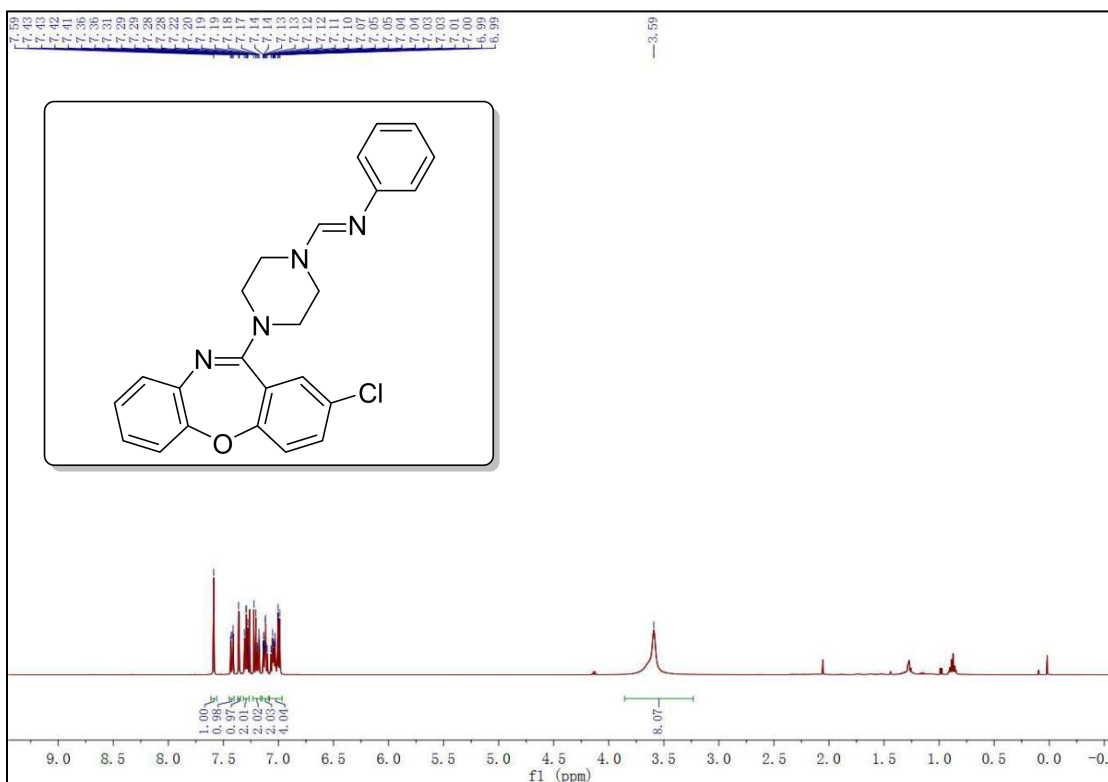


Figure S61. <sup>1</sup>H NMR spectrum of 3ae, related to Figure 2

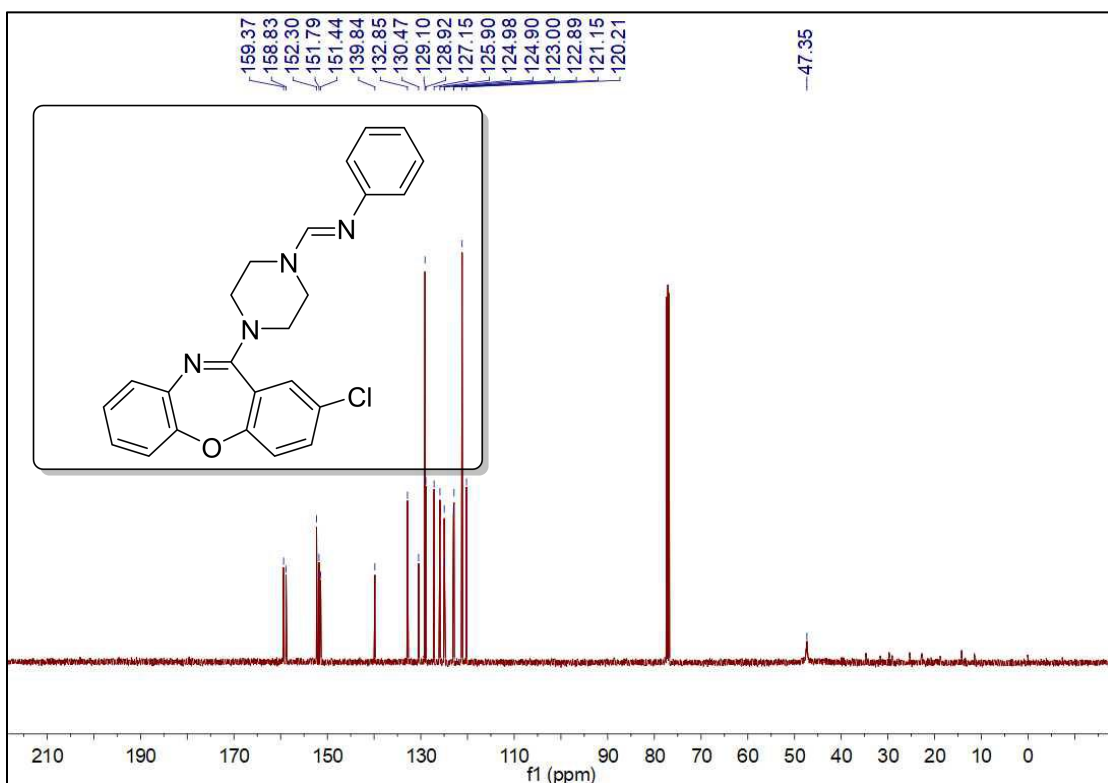


Figure S62. <sup>13</sup>C NMR spectrum of 3ae, related to Figure 2

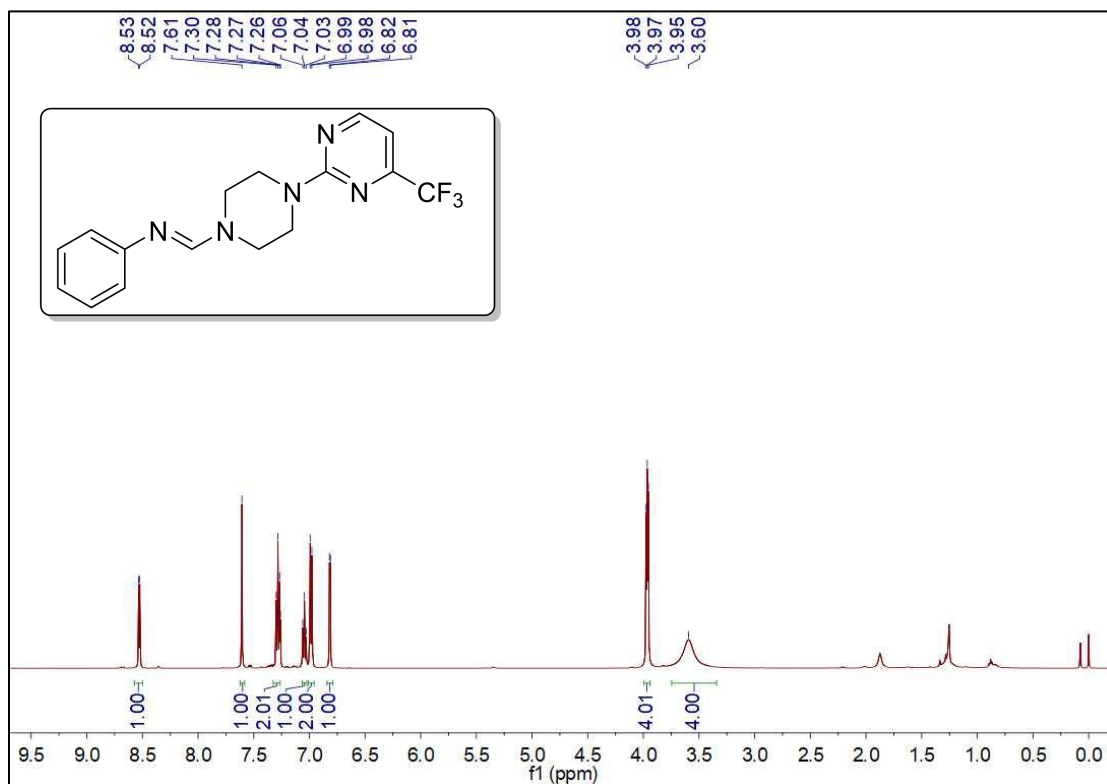


Figure S63. <sup>1</sup>H NMR spectrum of 3af, related to Figure 2

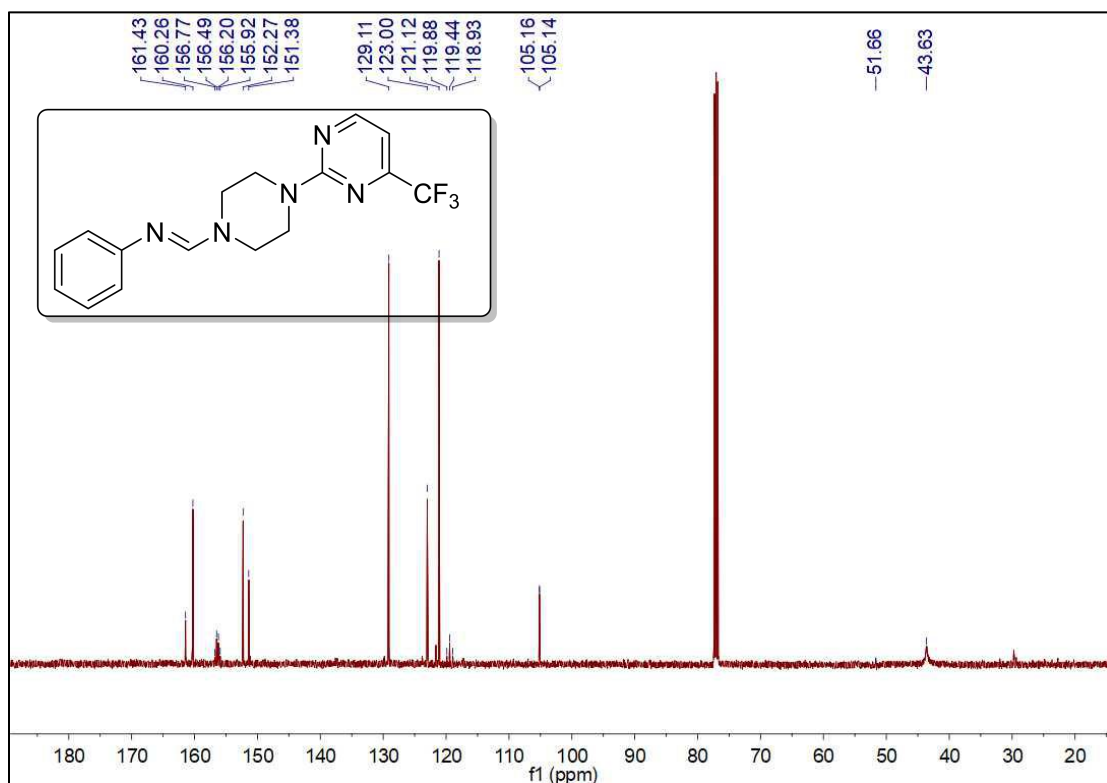
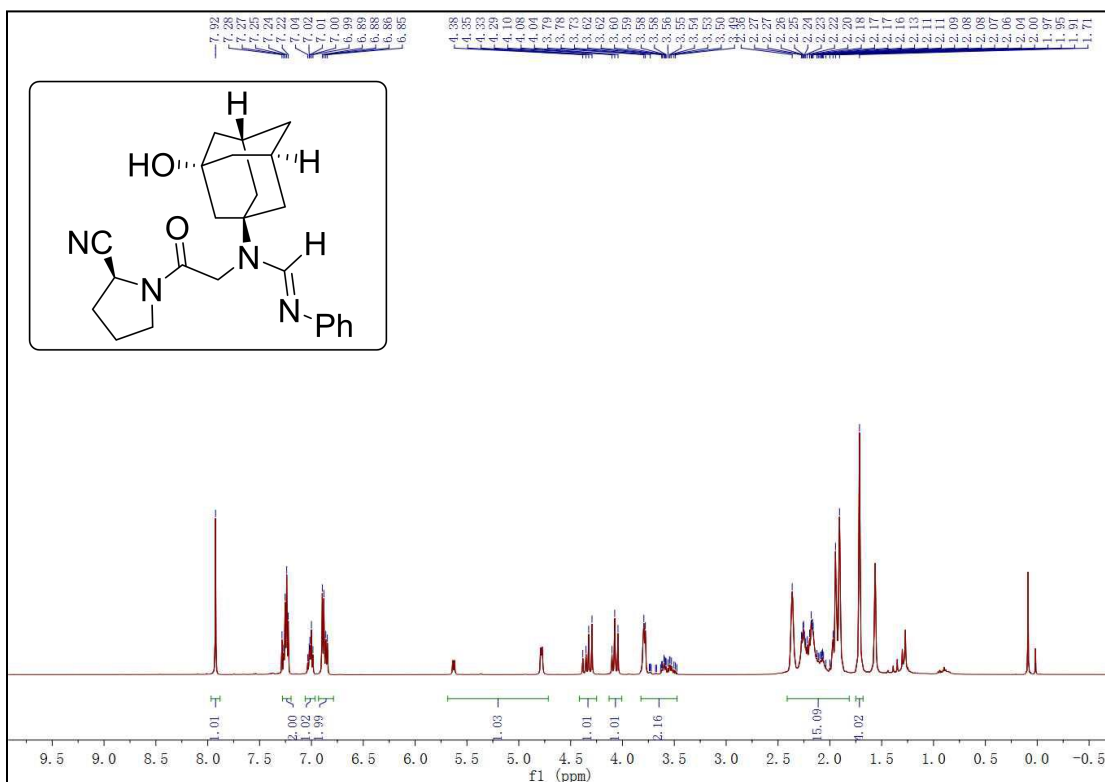
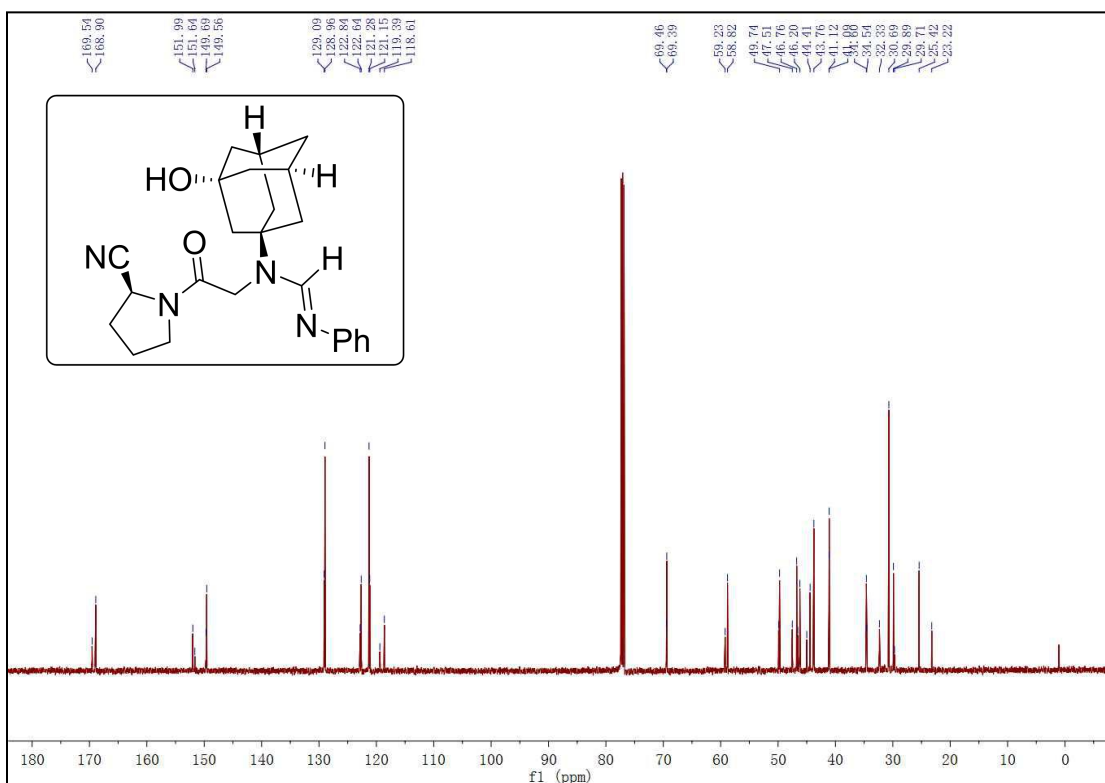


Figure S64. <sup>13</sup>C NMR spectrum of 3af, related to Figure 2



**Figure S65.**  $^1\text{H}$  NMR spectrum of **3ag**, related to Figure 2



**Figure S66.**  $^{13}\text{C}$  NMR spectrum of **3ag**, related to Figure 2



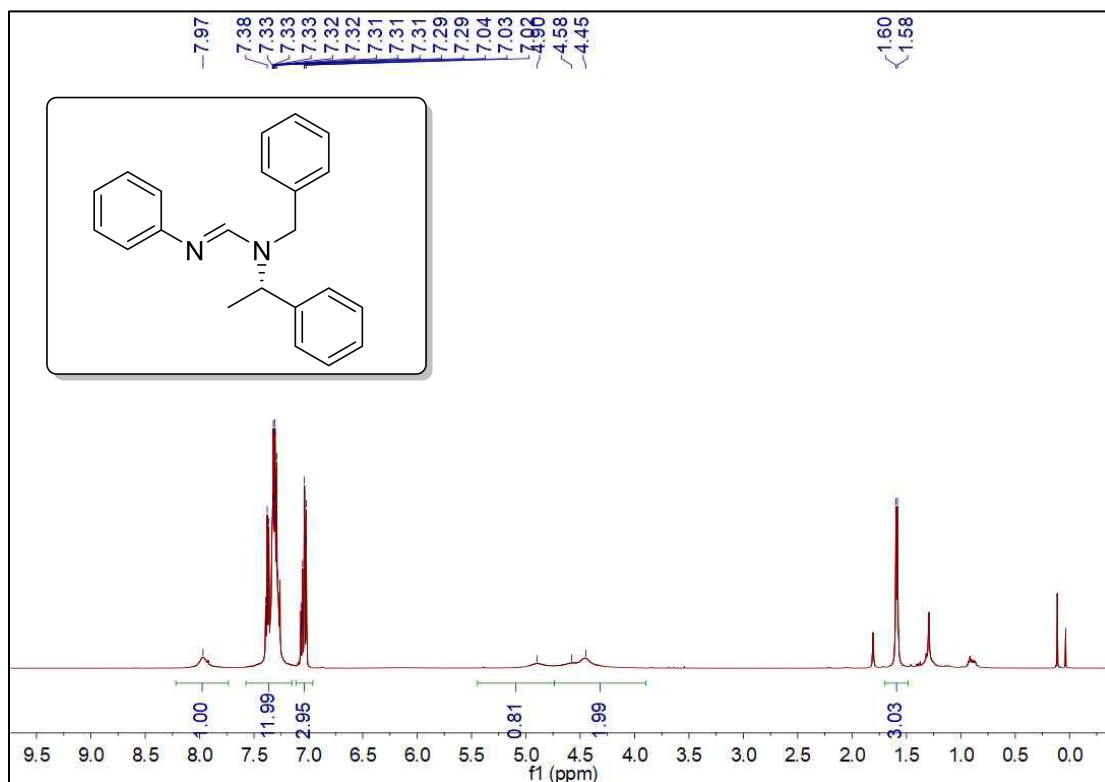


Figure S67.  $^1\text{H}$  NMR spectrum of 3ah, related to Figure 2

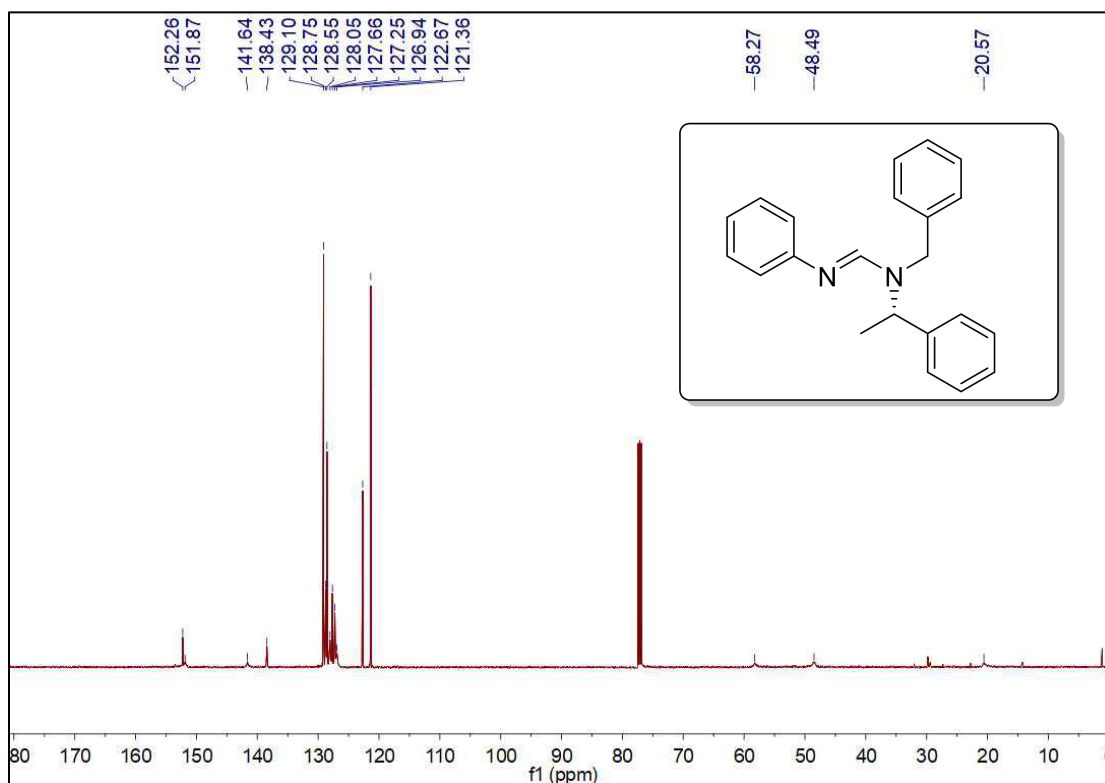


Figure S68.  $^{13}\text{C}$  NMR spectrum of 3ah, related to Figure 2

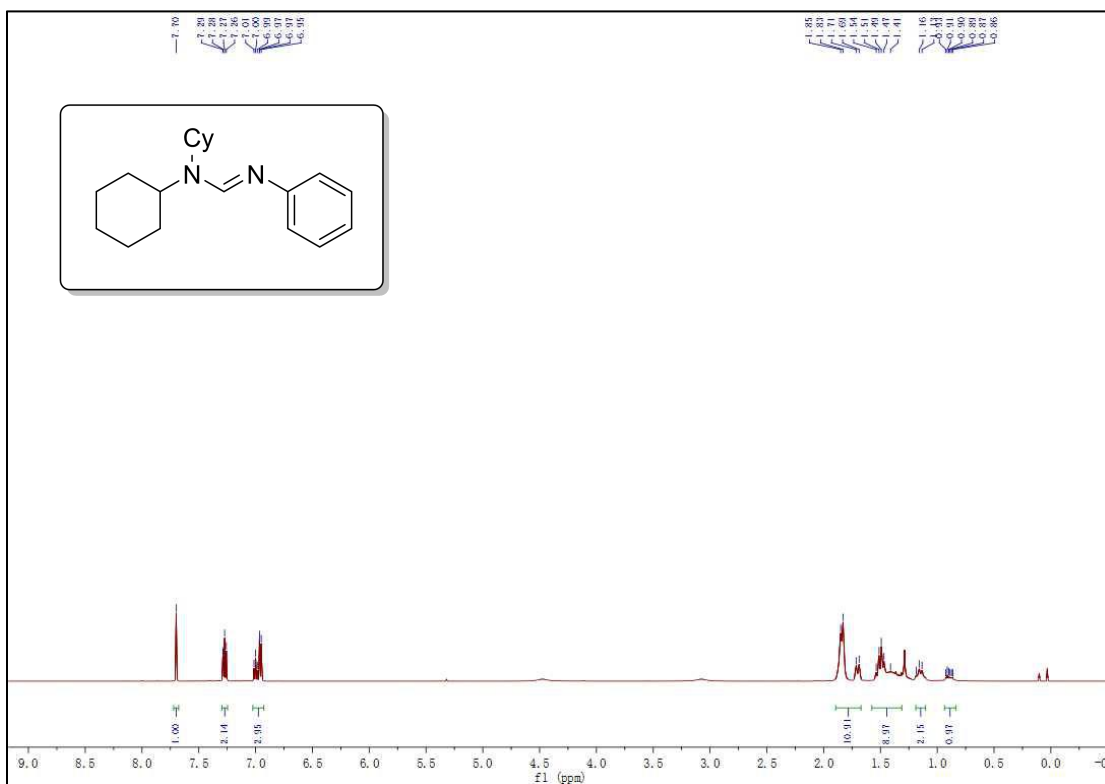


Figure S69. <sup>1</sup>H NMR spectrum of 5, related to Figure 3

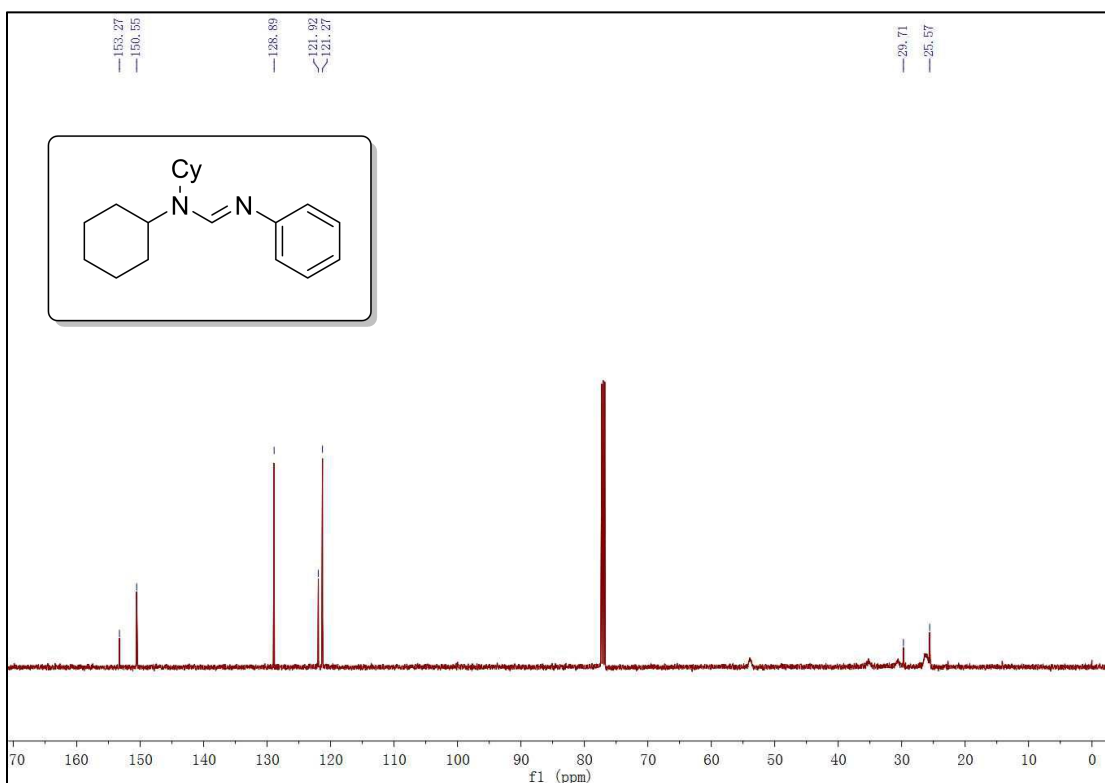


Figure S70. <sup>13</sup>C NMR spectrum of 5, related to Figure 3

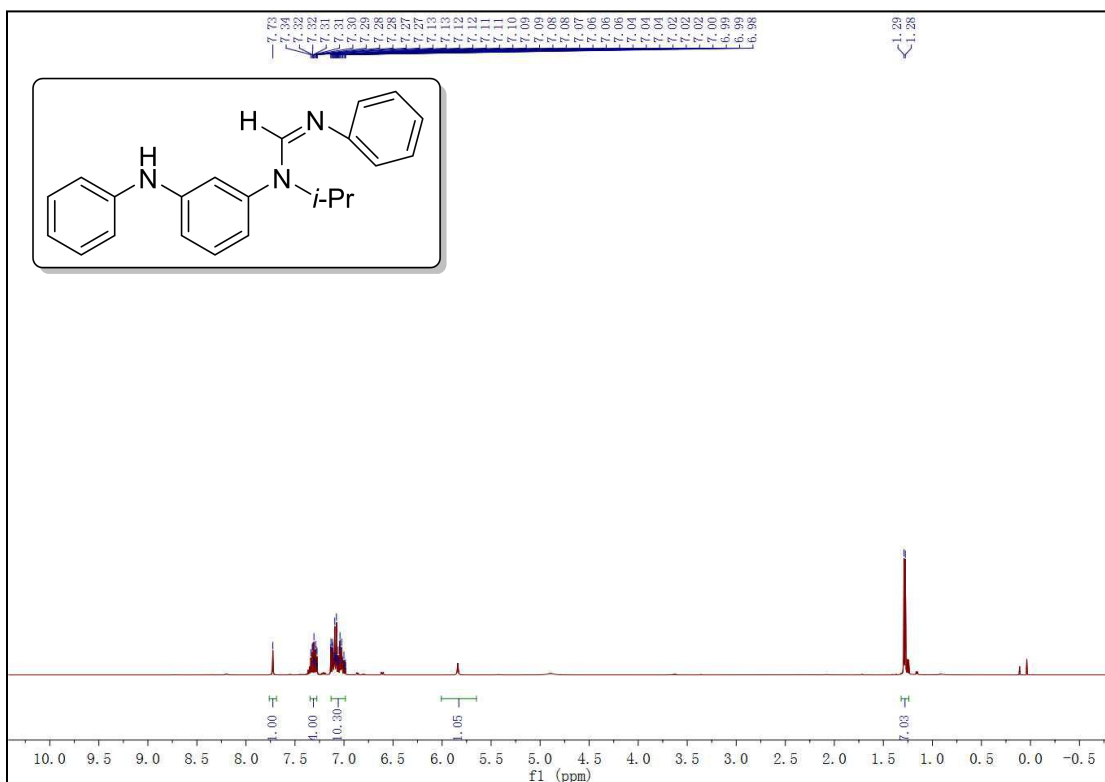


Figure S71. <sup>1</sup>H NMR spectrum of 7, related to Figure 3

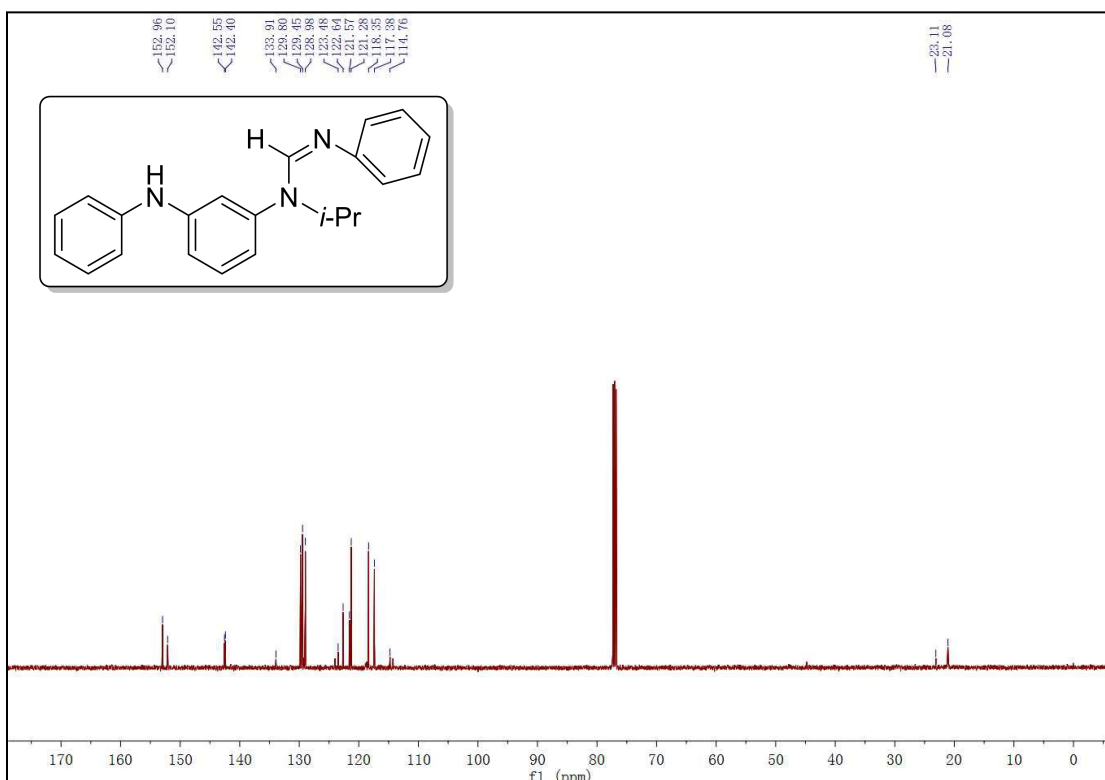


Figure S72. <sup>13</sup>C NMR spectrum of 7, related to Figure 3

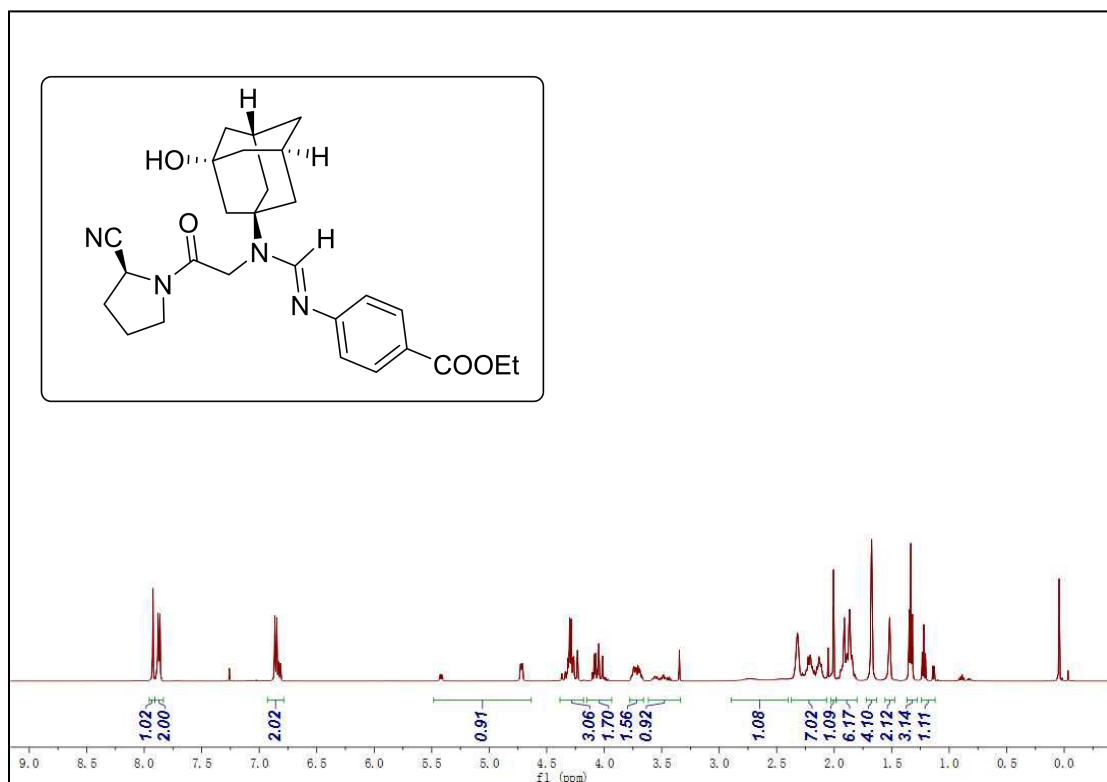


Figure S73. <sup>1</sup>H NMR spectrum of 3ai, related to Figure 3

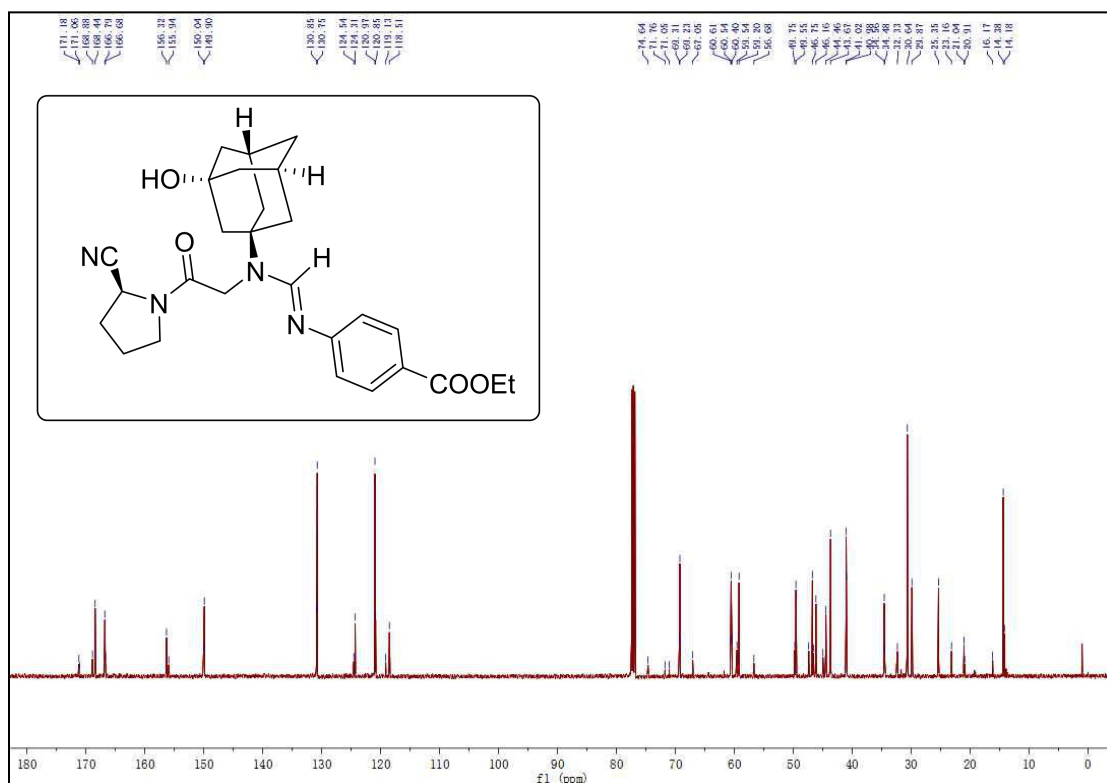


Figure S74. <sup>13</sup>C NMR spectrum of 3ai, related to Figure 3

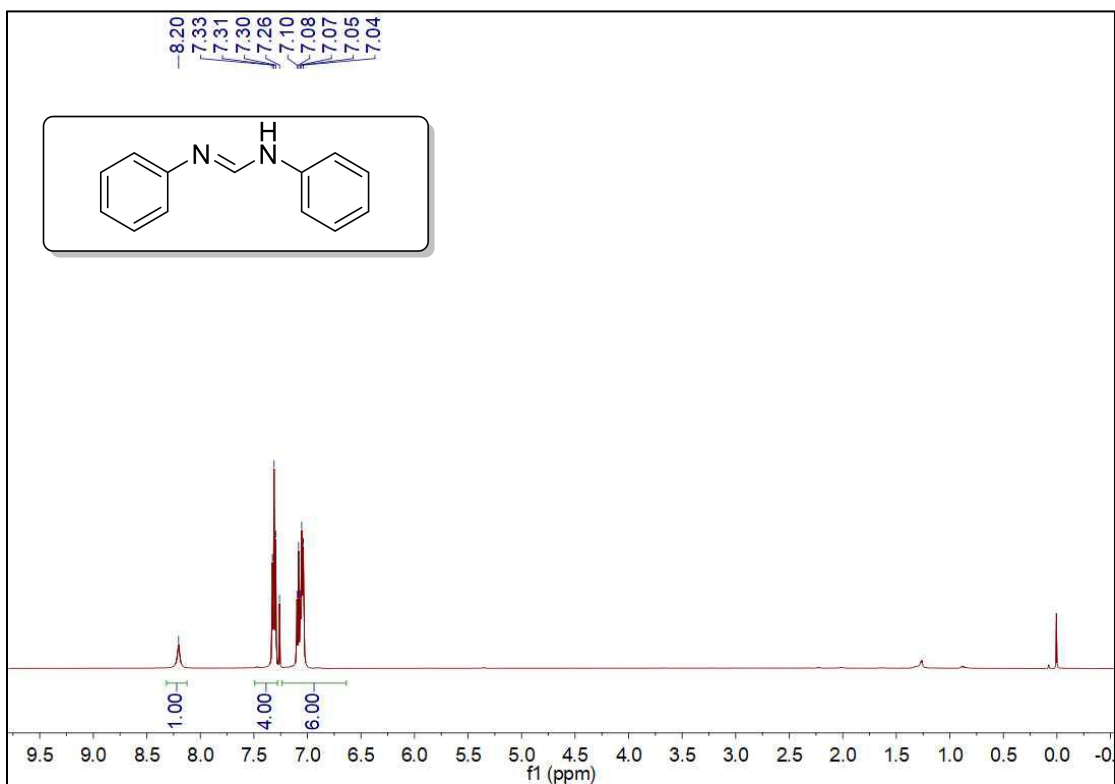


Figure S75. <sup>1</sup>H NMR spectrum of 8, related to Figure 3

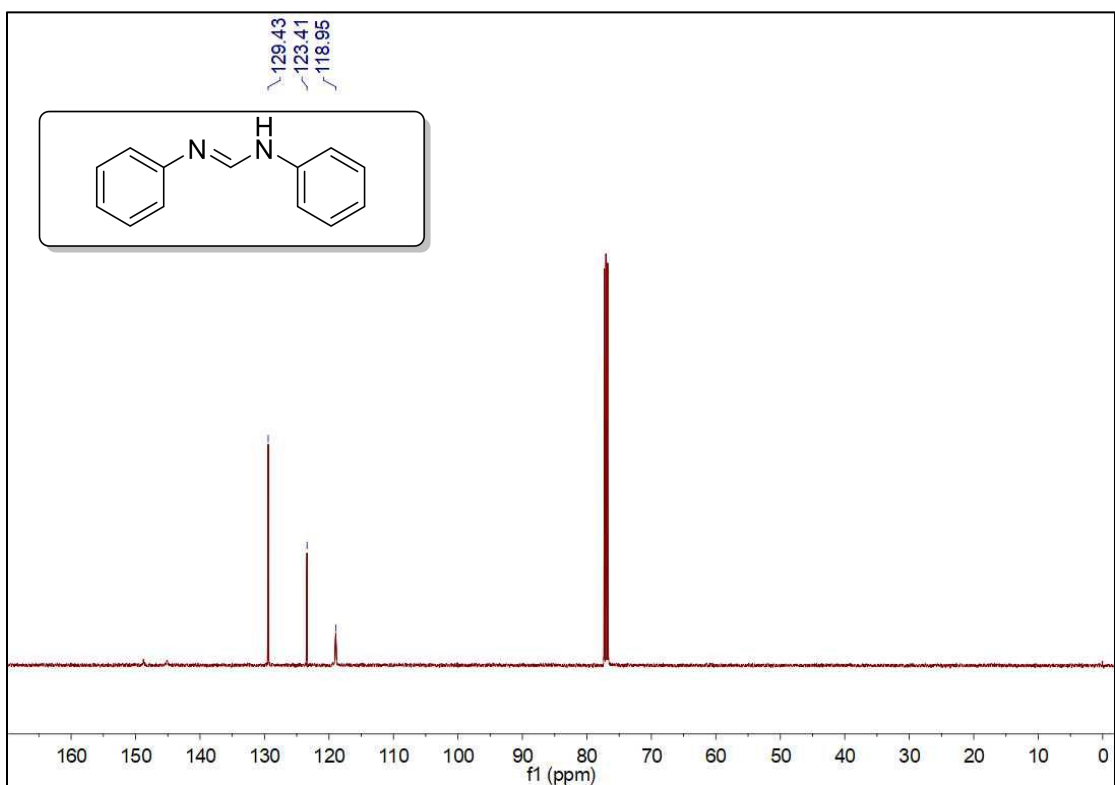


Figure S76. <sup>13</sup>C NMR spectrum of 8, related to Figure 3

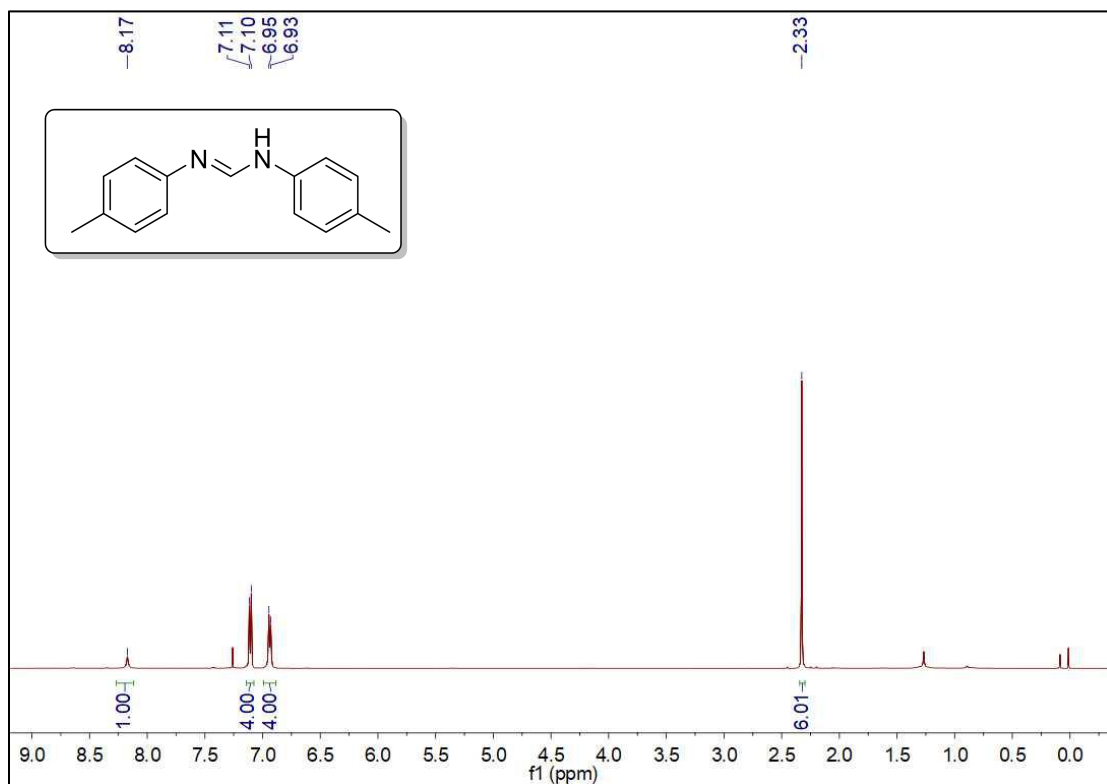


Figure S77. <sup>1</sup>H NMR spectrum of 9, related to Figure 3

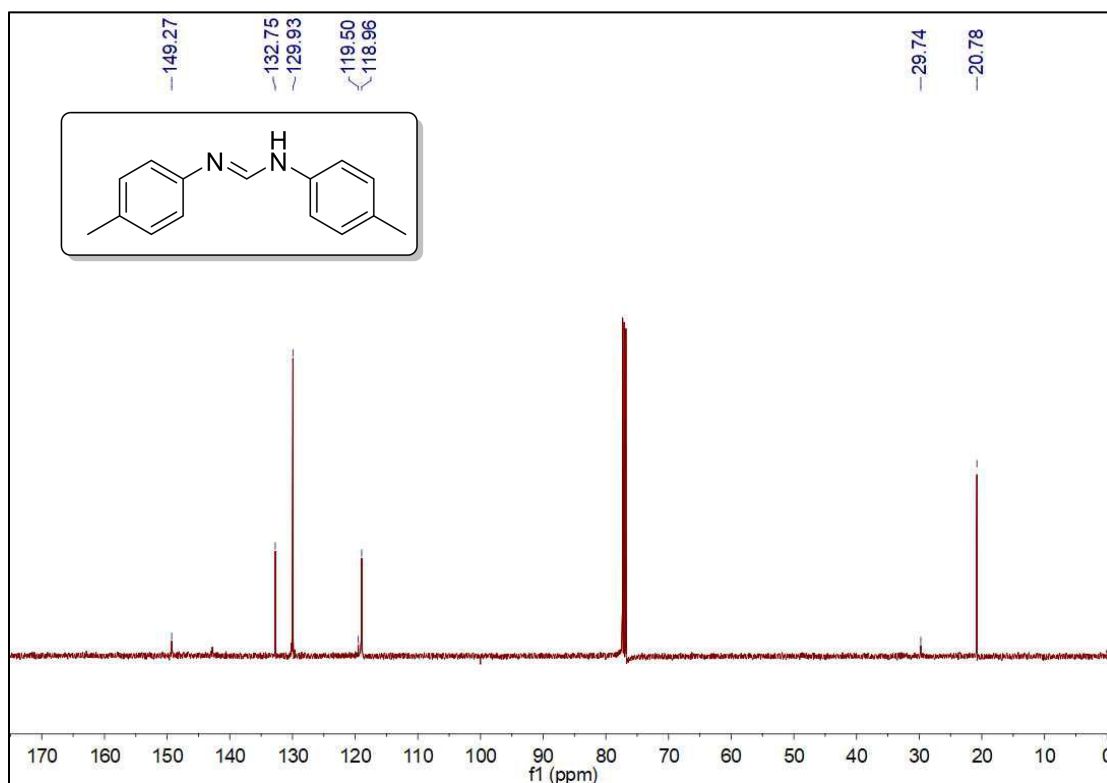


Figure S78. <sup>13</sup>C NMR spectrum of 9, related to Figure 3

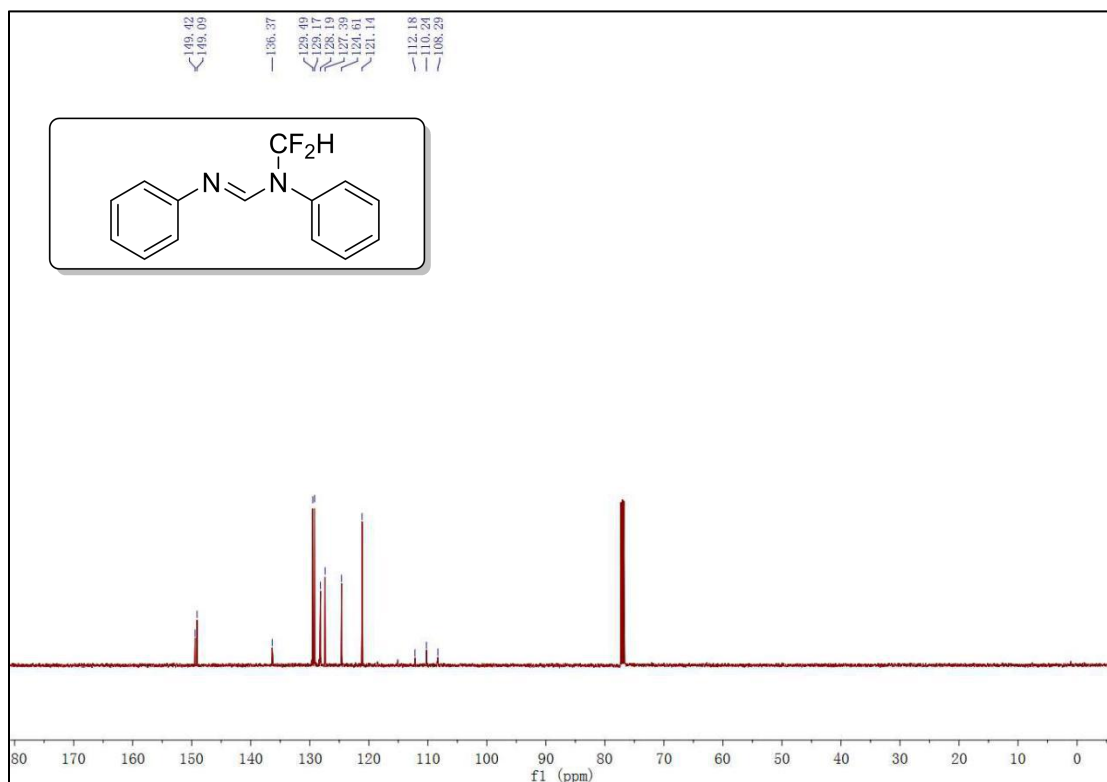


Figure S79. <sup>13</sup>C NMR spectrum of 10, related to Figure 3

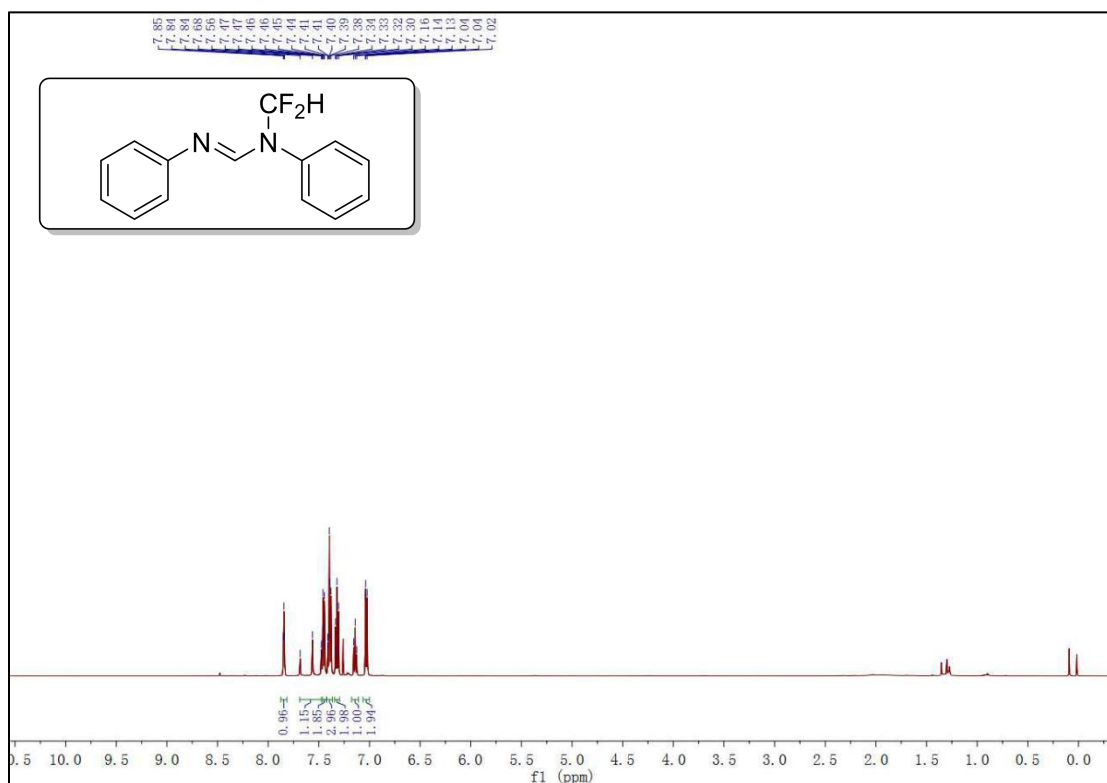


Figure S80. <sup>1</sup>H NMR spectrum of 10, related to Figure 3

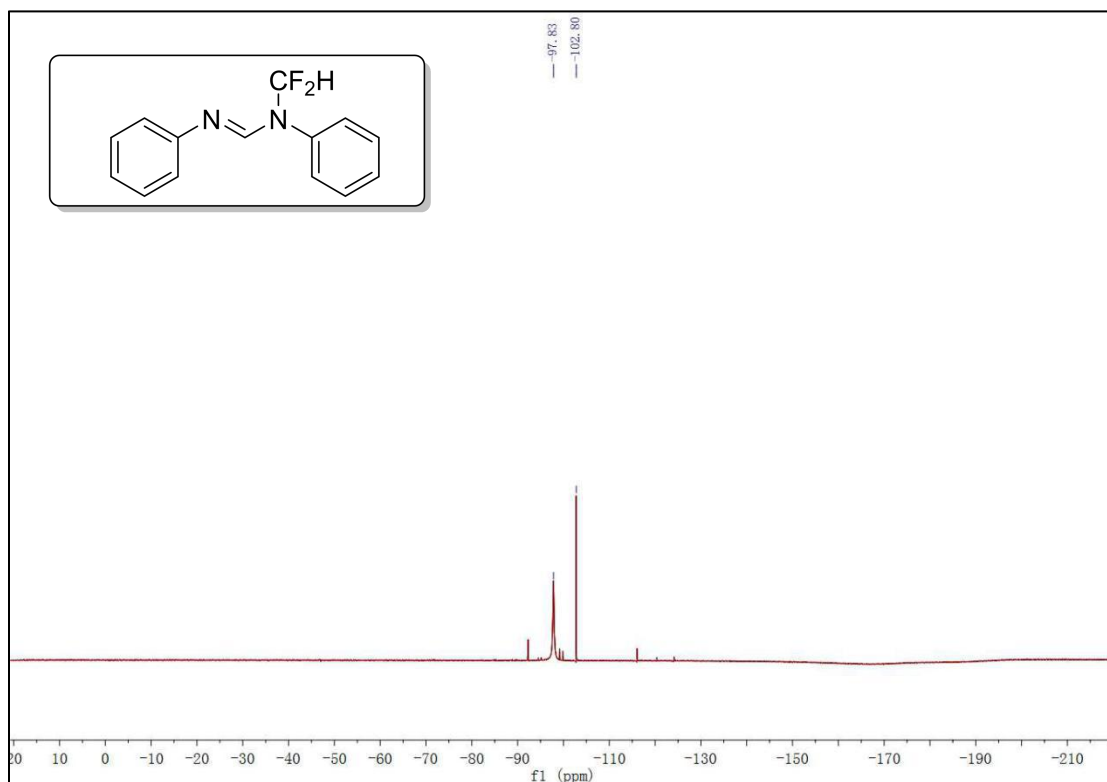


Figure S81.  $^{19}\text{F}$  NMR spectrum of 10, related to Figure 3

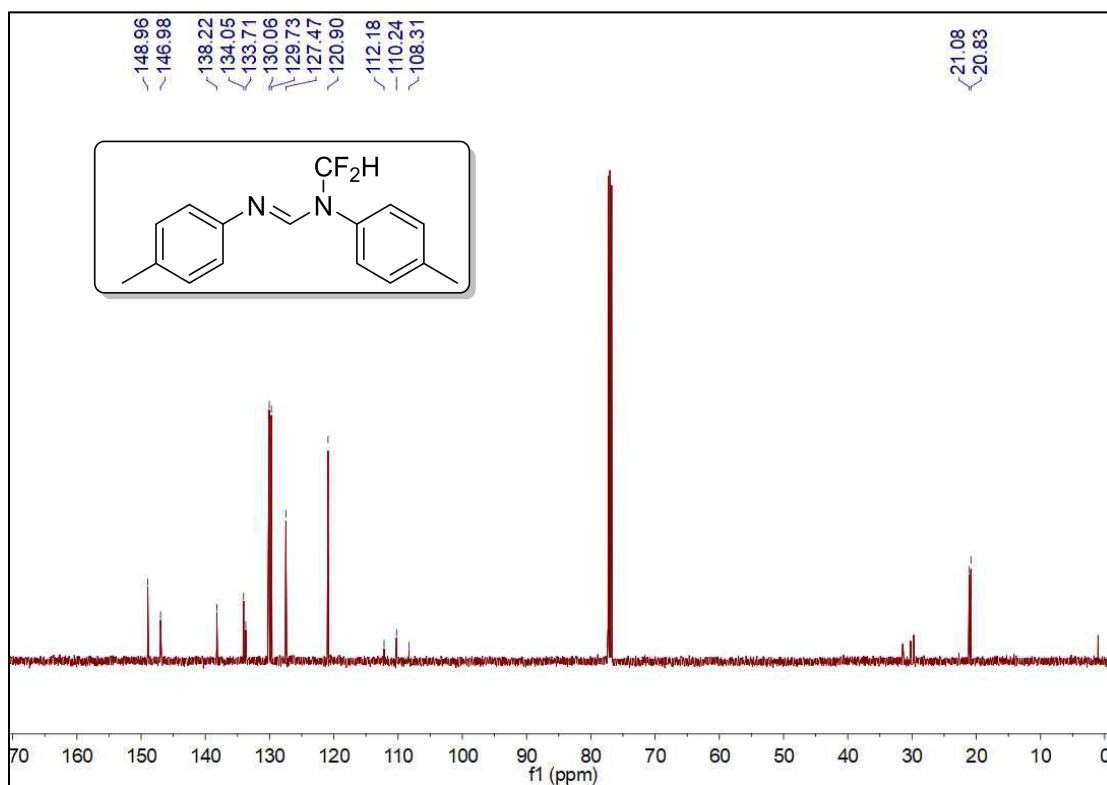


Figure S82.  $^{13}\text{C}$  NMR spectrum of 11, related to Figure 3



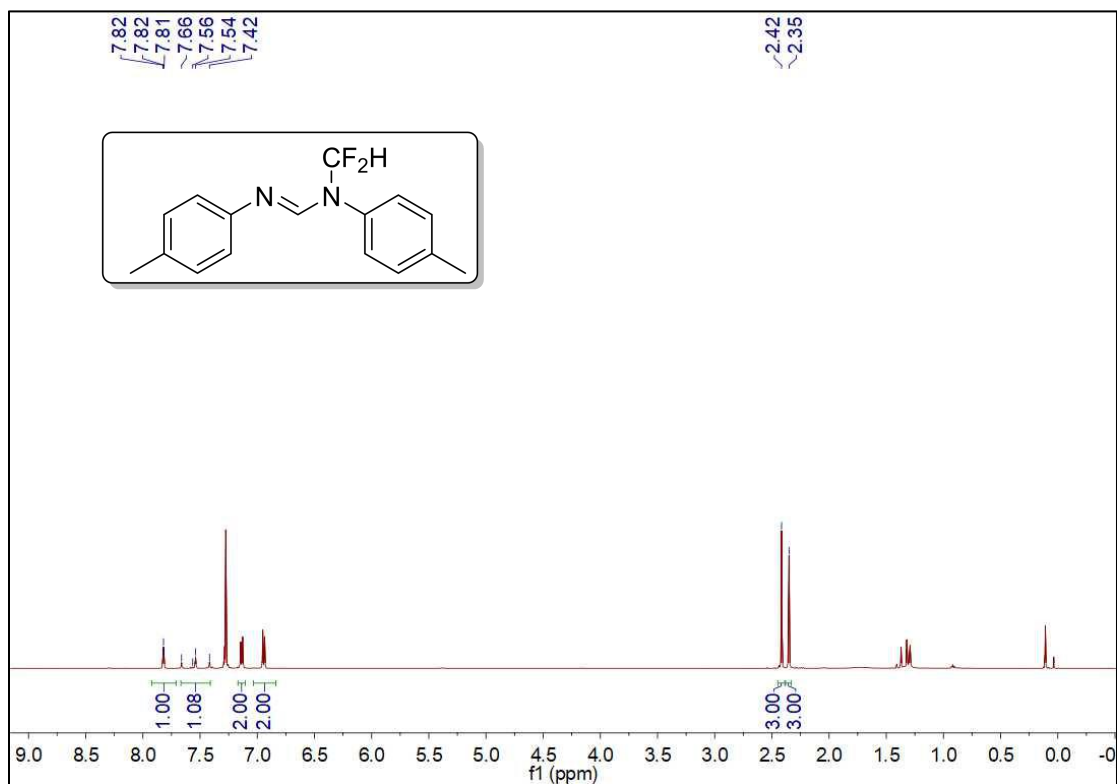


Figure S83. <sup>1</sup>H NMR spectrum of 11, related to Figure 3

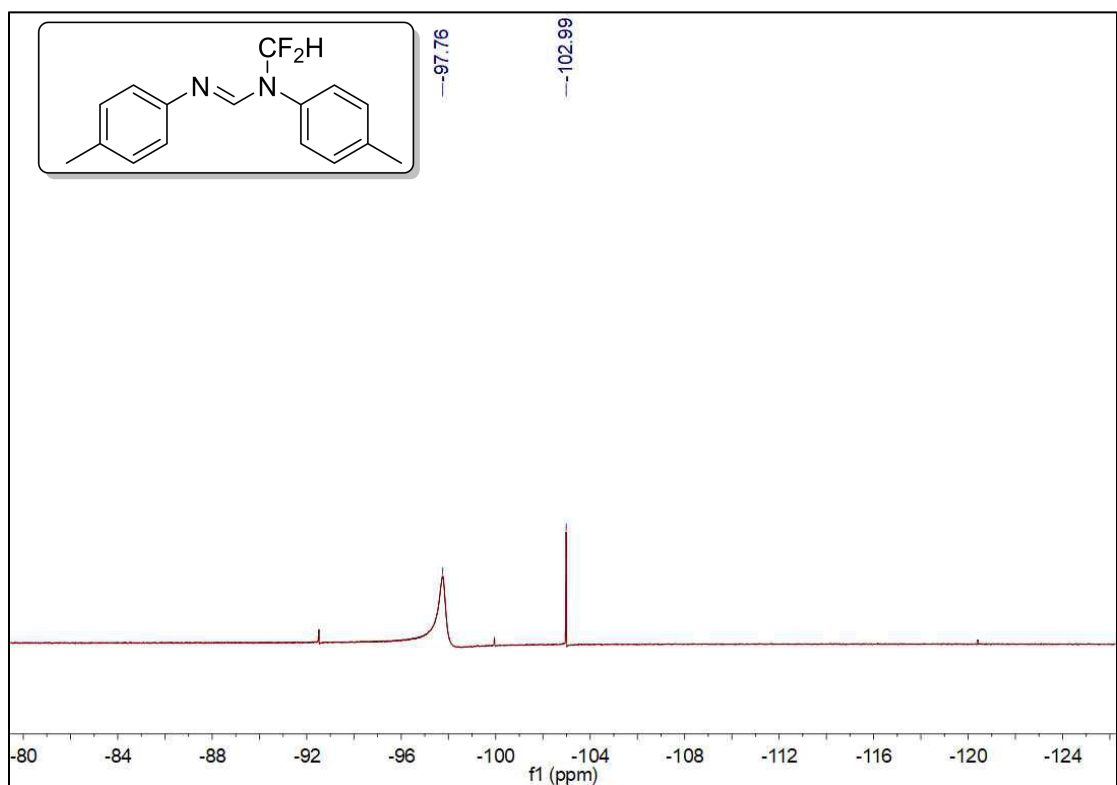


Figure S84. <sup>19</sup>F NMR spectrum of 11, related to Figure 3

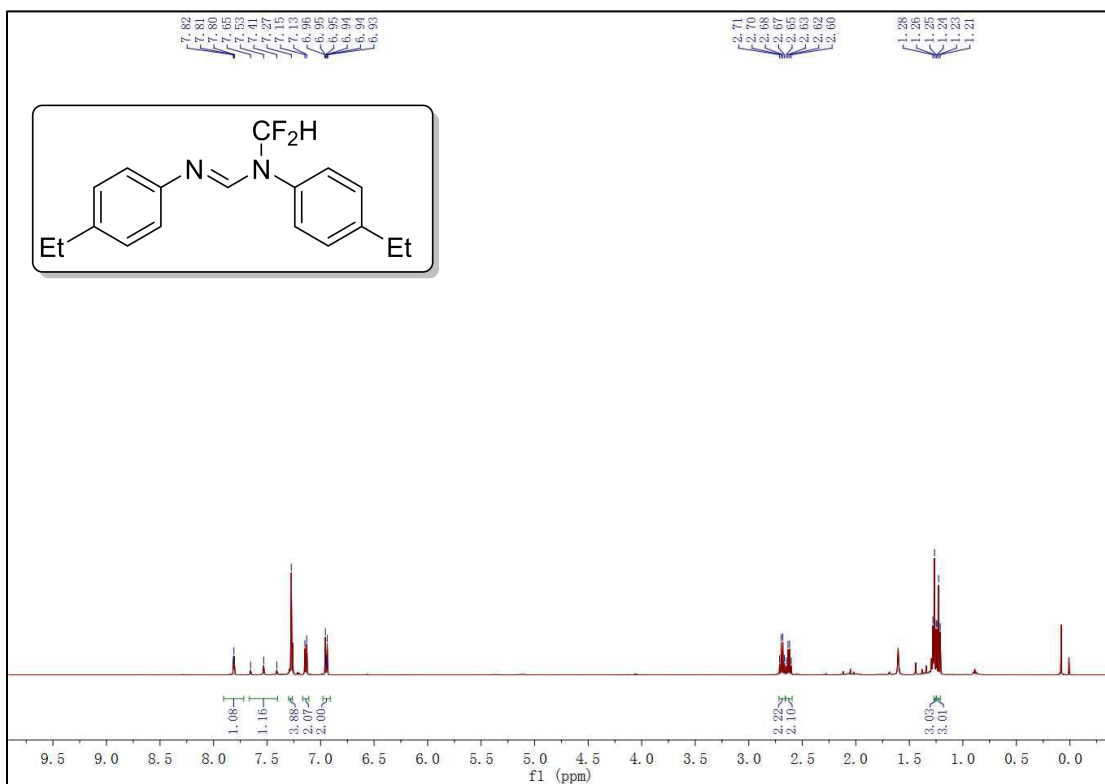


Figure S85. <sup>1</sup>H NMR spectrum of 12, related to Figure 3

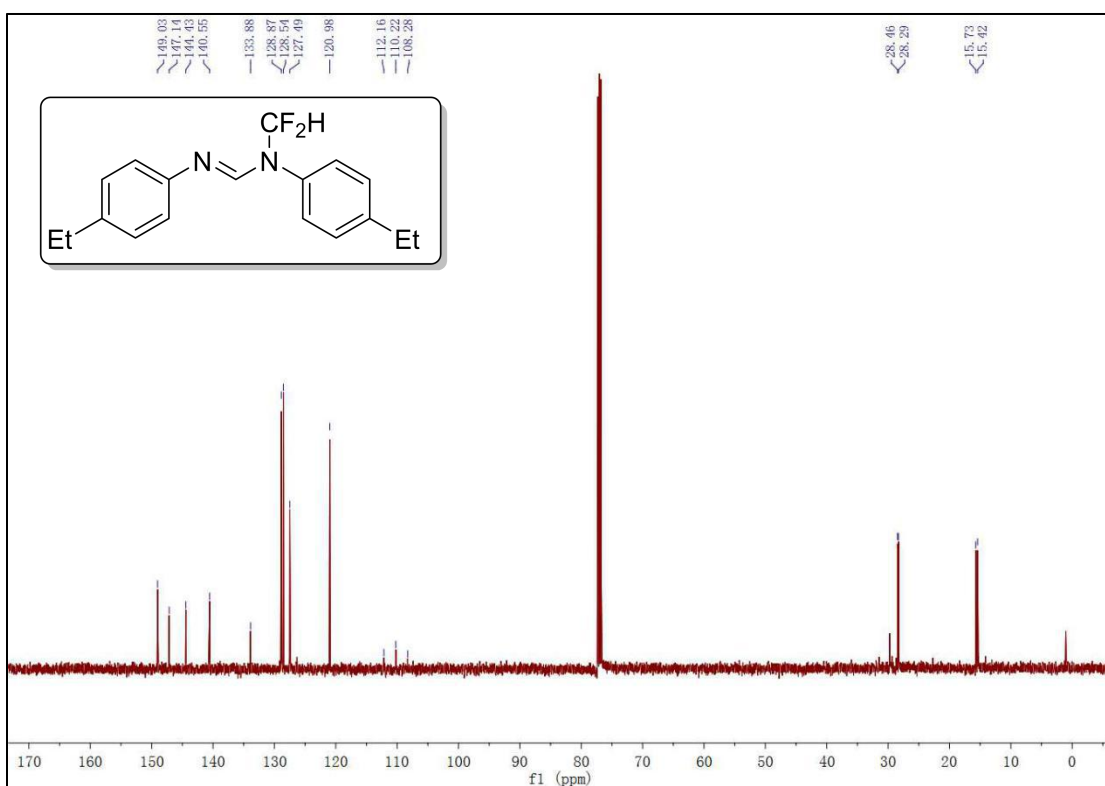


Figure S86. <sup>13</sup>C NMR spectrum of 12, related to Figure 3

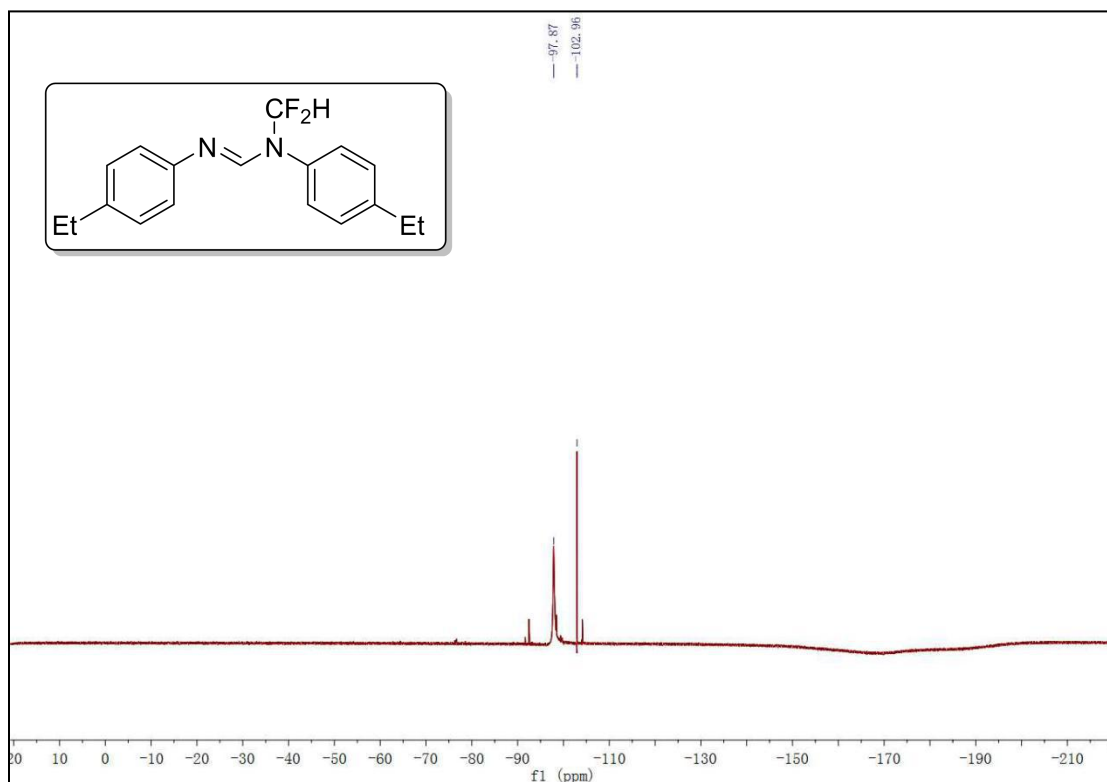


Figure S87.  $^{19}\text{F}$  NMR spectrum of 12, related to Figure 3

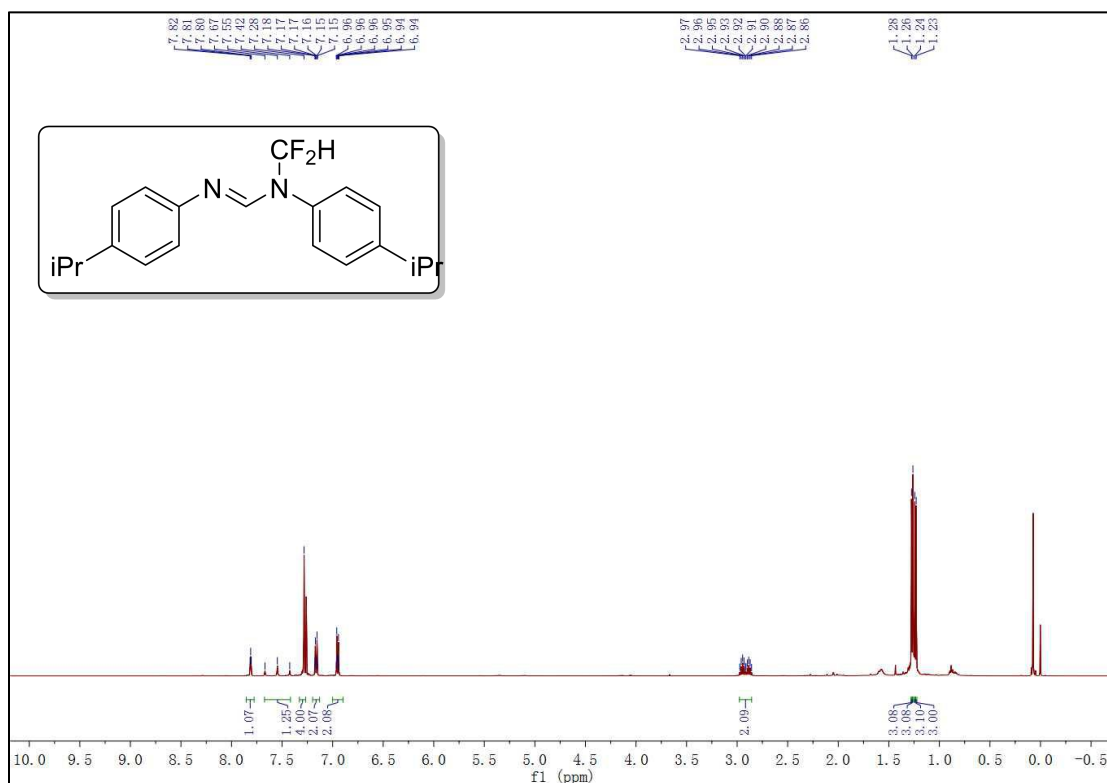


Figure S88.  $^1\text{H}$  NMR spectrum of 13, related to Figure 3

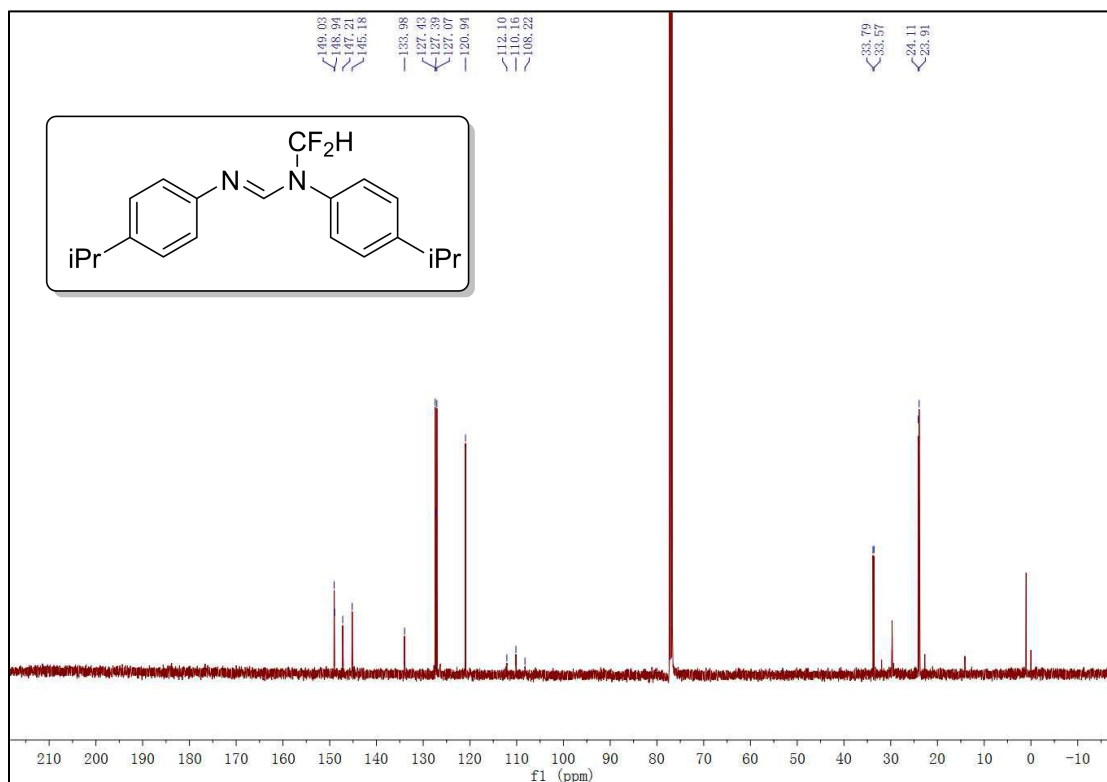


Figure S89. <sup>13</sup>C NMR spectrum of 13, related to Figure 3

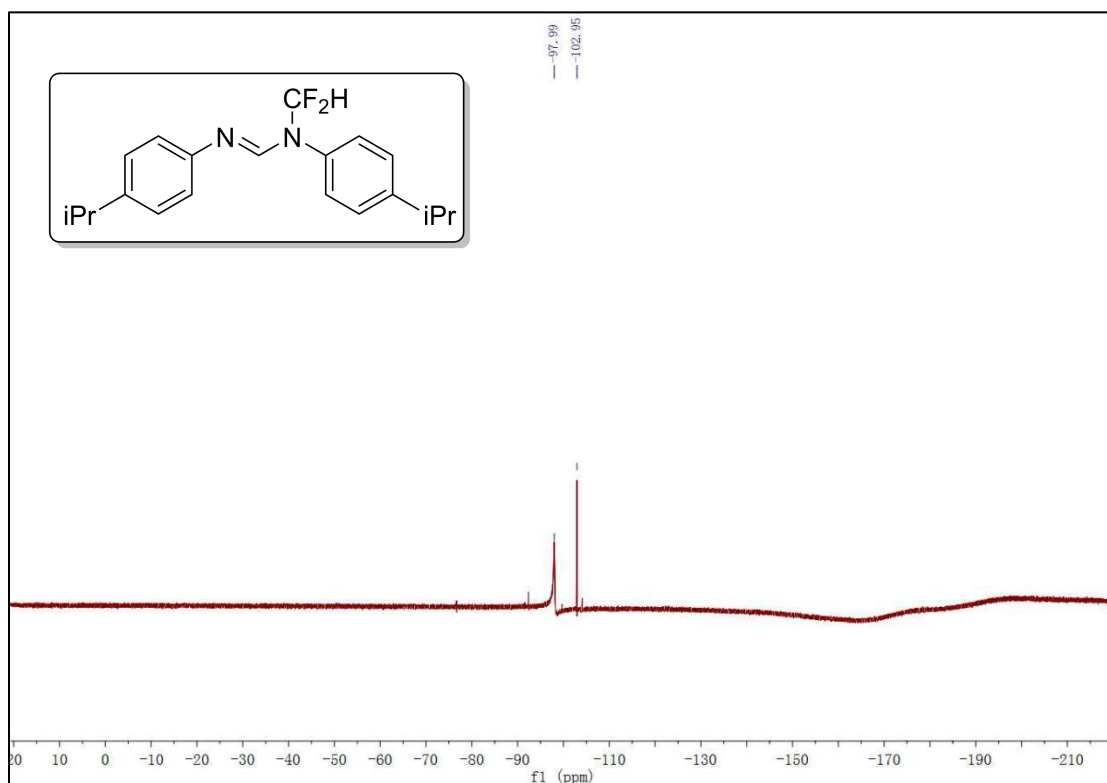


Figure S90. <sup>1</sup>H NMR spectrum of 13, related to Figure 3

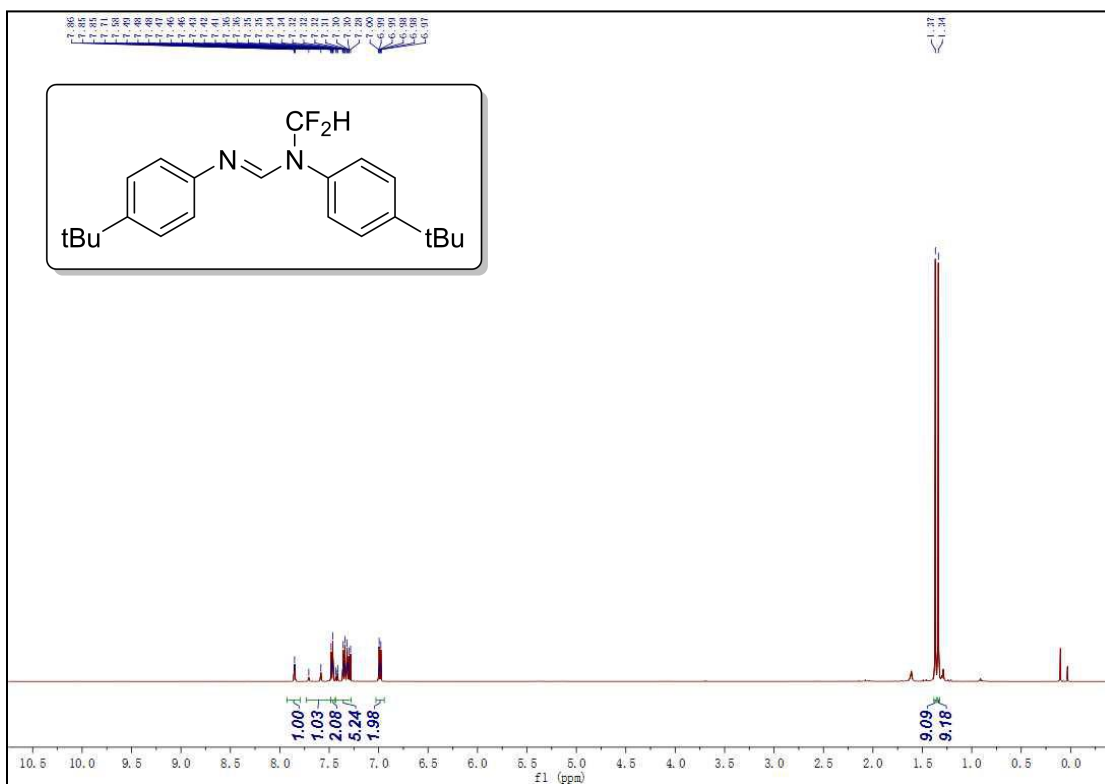


Figure S91. <sup>1</sup>H NMR spectrum of 14, related to Figure 3

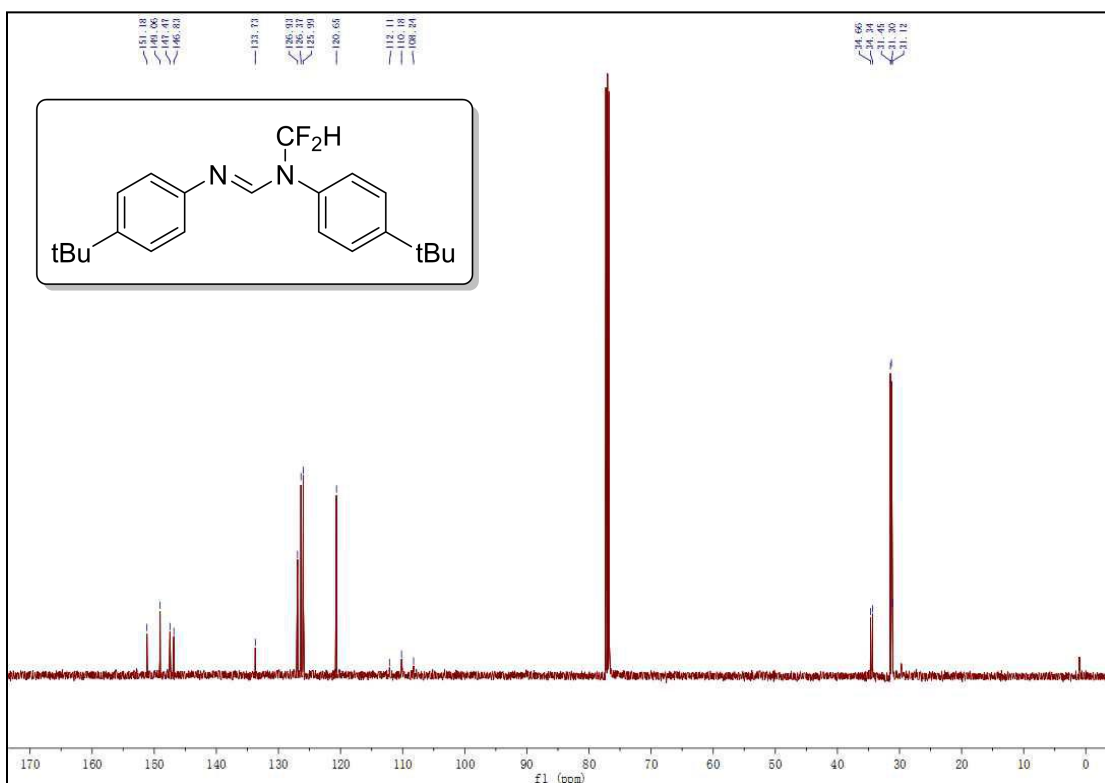


Figure S92. <sup>13</sup>C NMR spectrum of 14, related to Figure 3

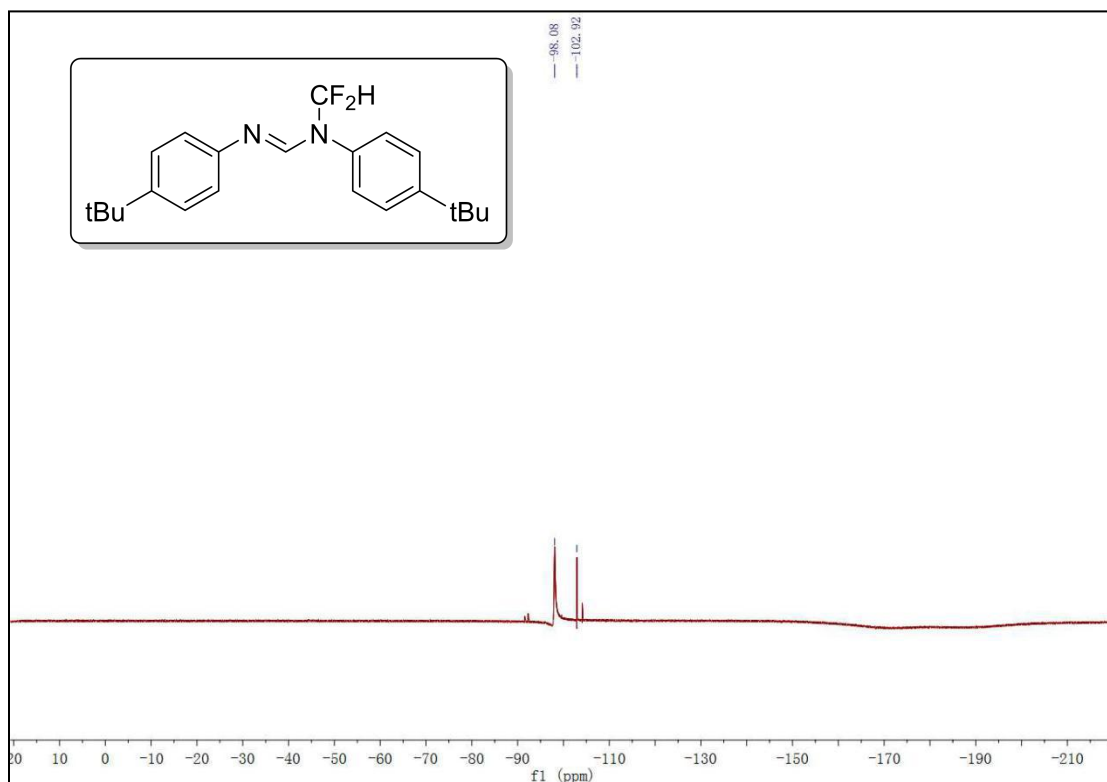


Figure S93.  $^{19}\text{F}$  NMR spectrum of 14, related to Figure 3

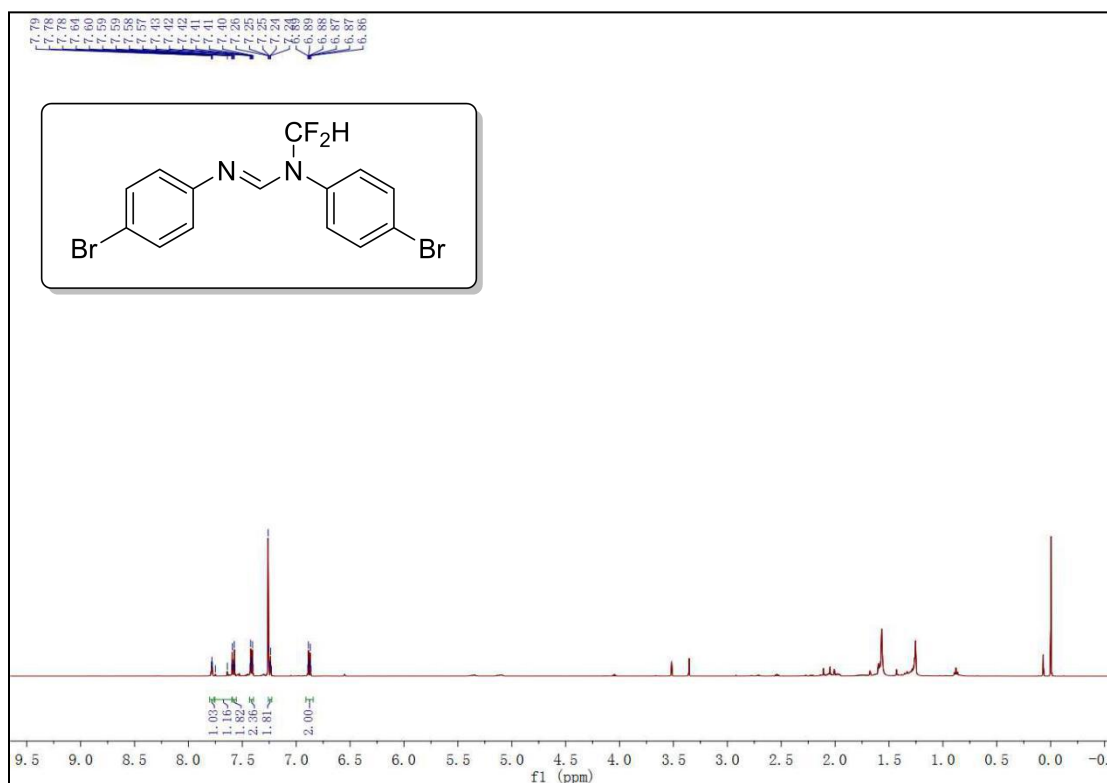


Figure S94.  $^1\text{H}$  NMR spectrum of 15, related to Figure 2

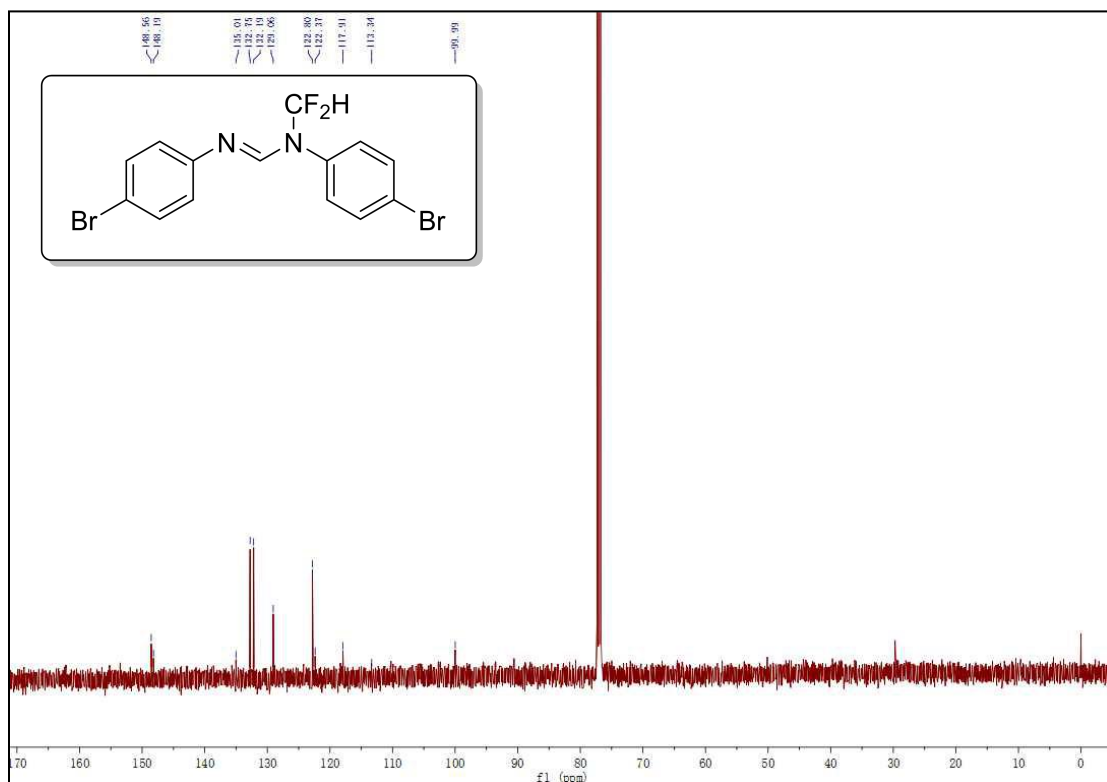


Figure S95. <sup>13</sup>C NMR spectrum of 15, related to Figure 3

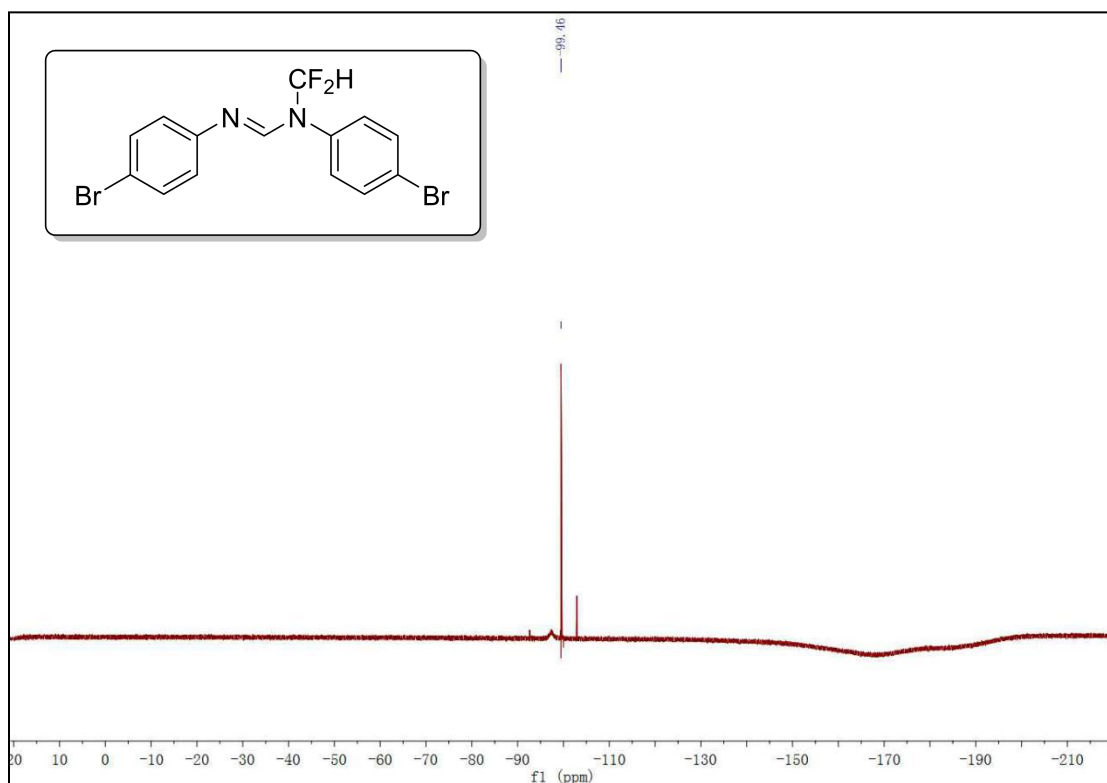


Figure S96. <sup>19</sup>F NMR spectrum of 15, related to Figure 3

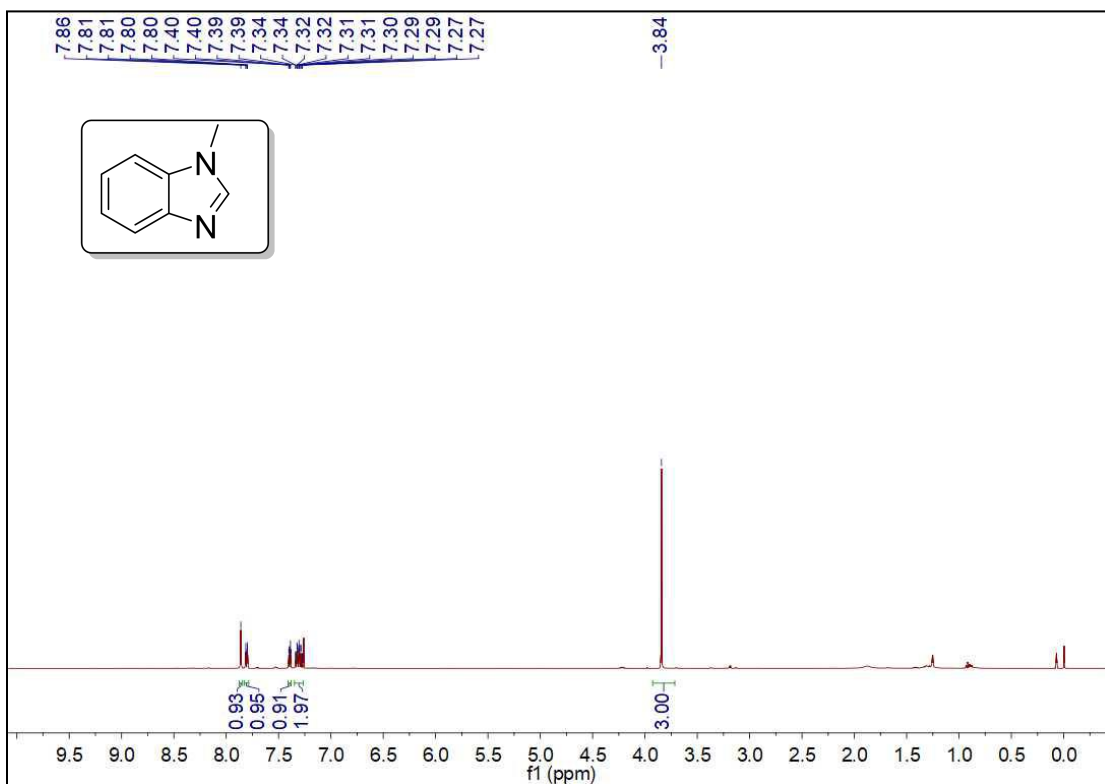


Figure S97.  $^1\text{H}$  NMR spectrum of 17, related to Figure 4

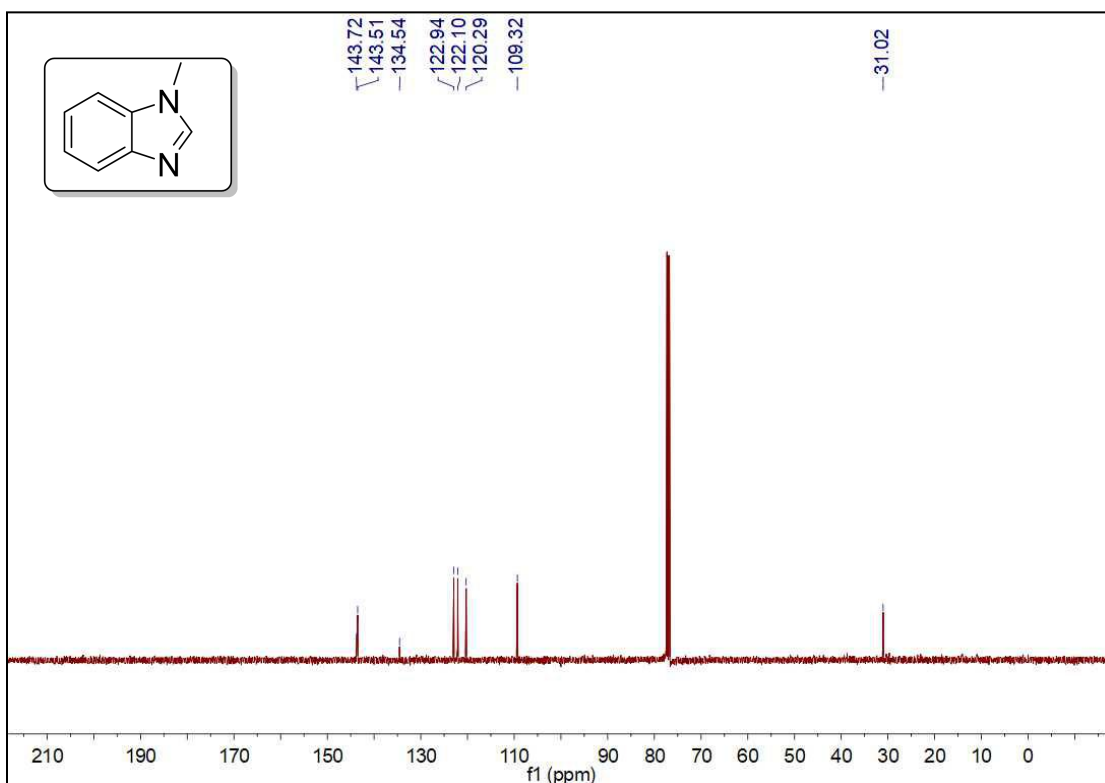
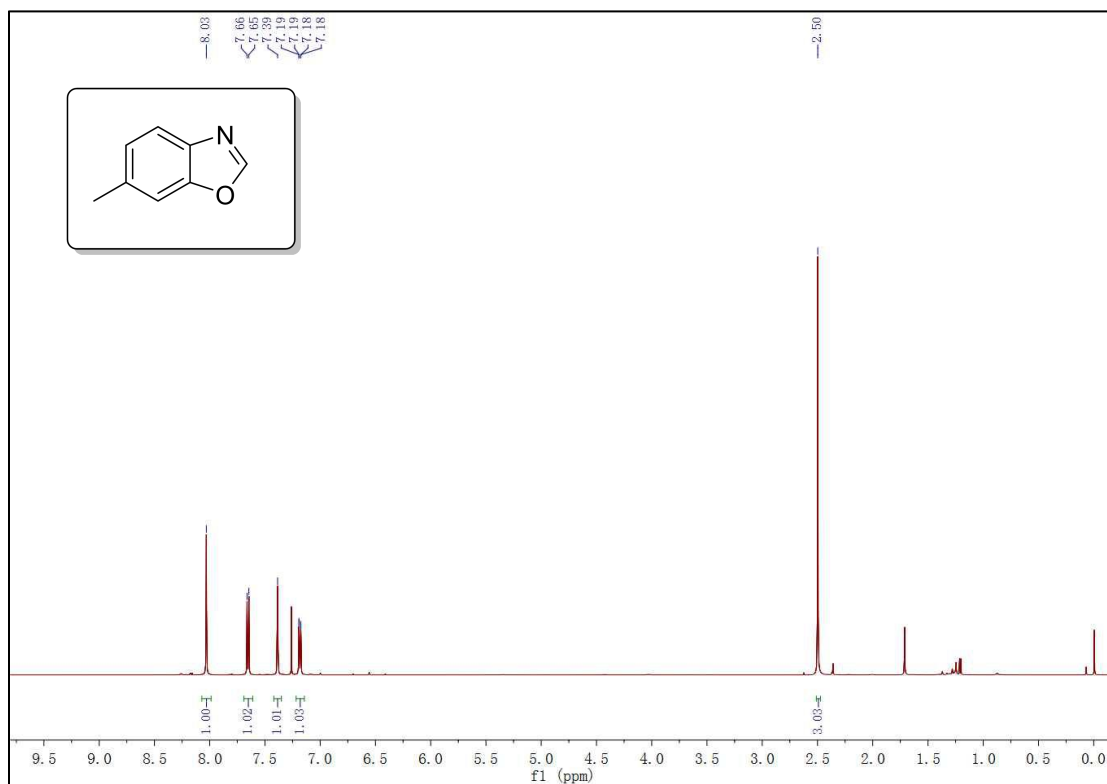
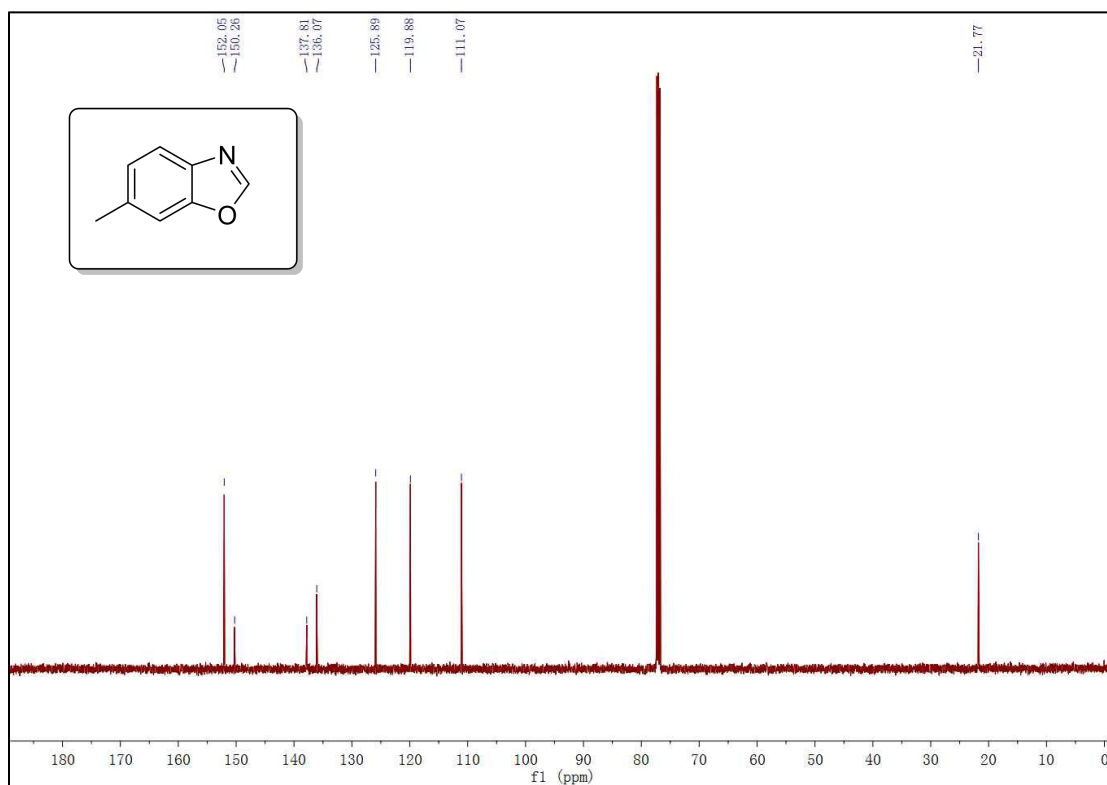


Figure S98.  $^{13}\text{C}$  NMR spectrum of 17, related to Figure 4





**Figure S99.**  $^1\text{H}$  NMR spectrum of 20a, related to Figure 4



**Figure S100.**  $^{13}\text{C}$  NMR spectrum of 20a, related to Figure 4

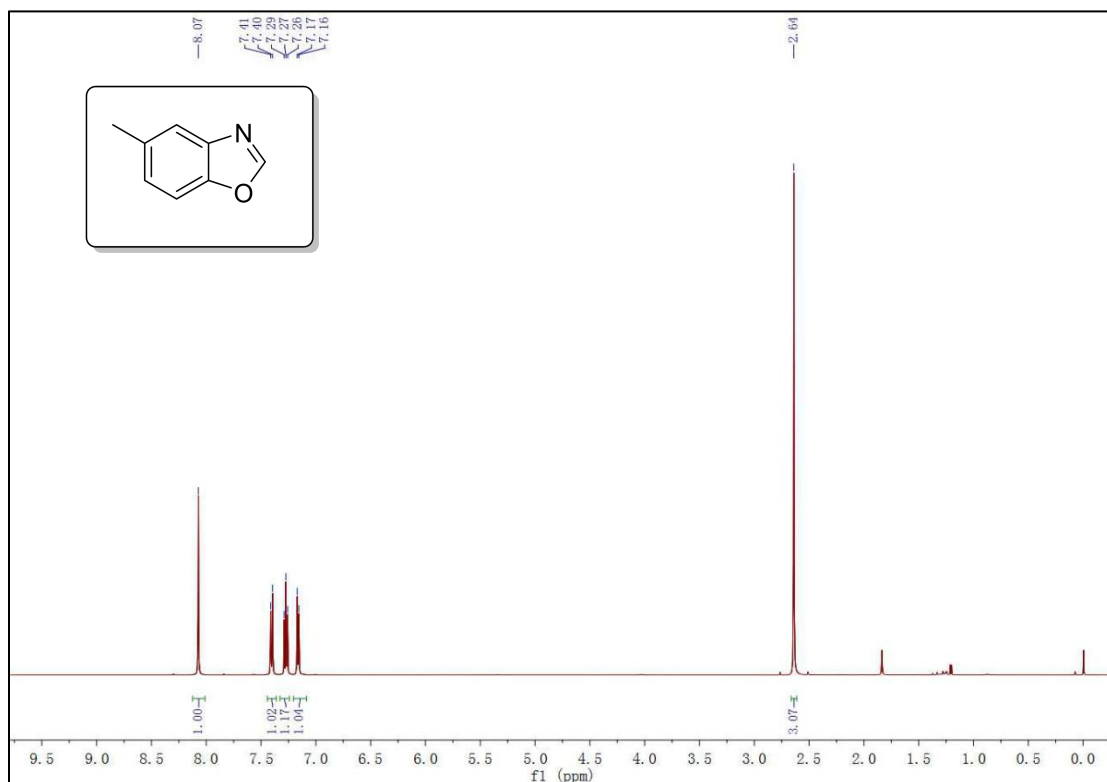


Figure S101. <sup>1</sup>H NMR spectrum of 20b, related to Figure 4

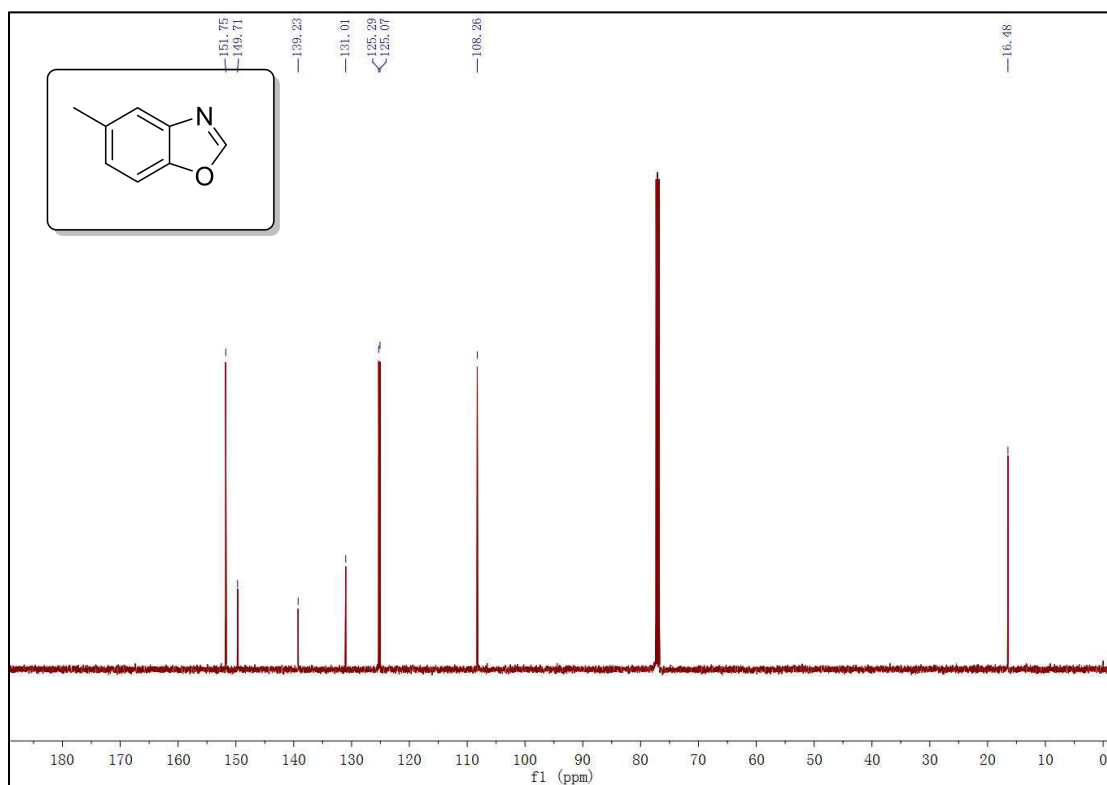


Figure S102. <sup>13</sup>C NMR spectrum of 20b, related to Figure 4

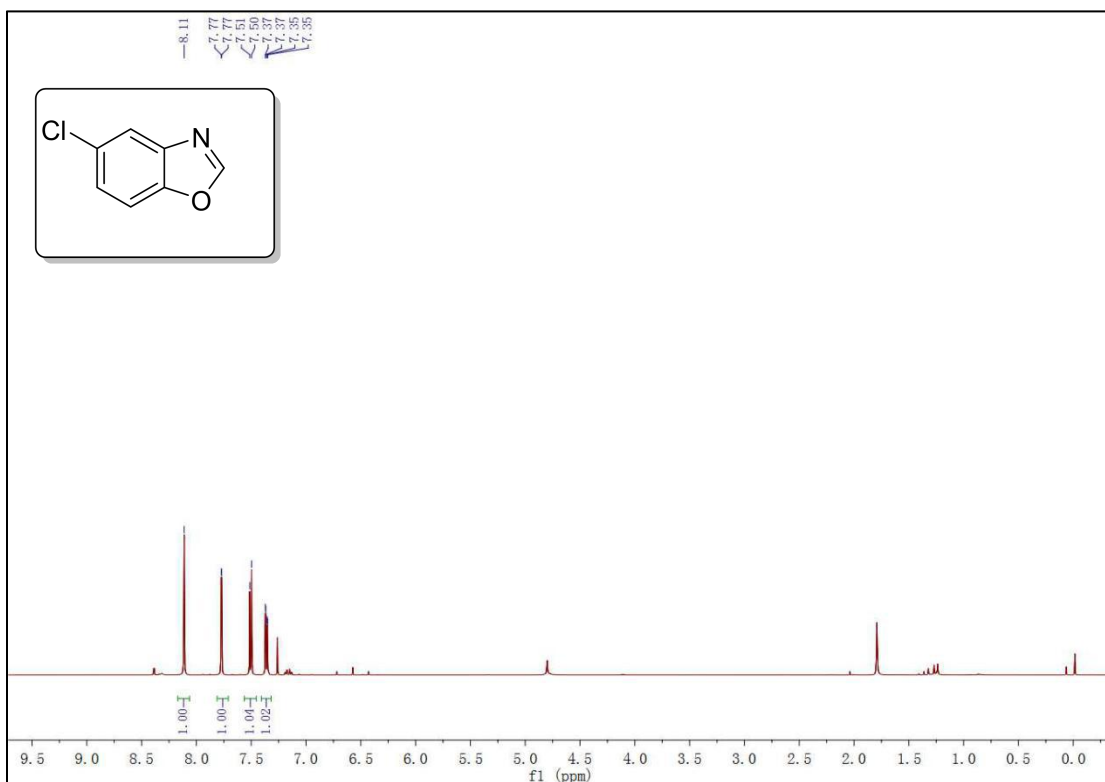


Figure S103. <sup>1</sup>H NMR spectrum of 20c, related to Figure 4

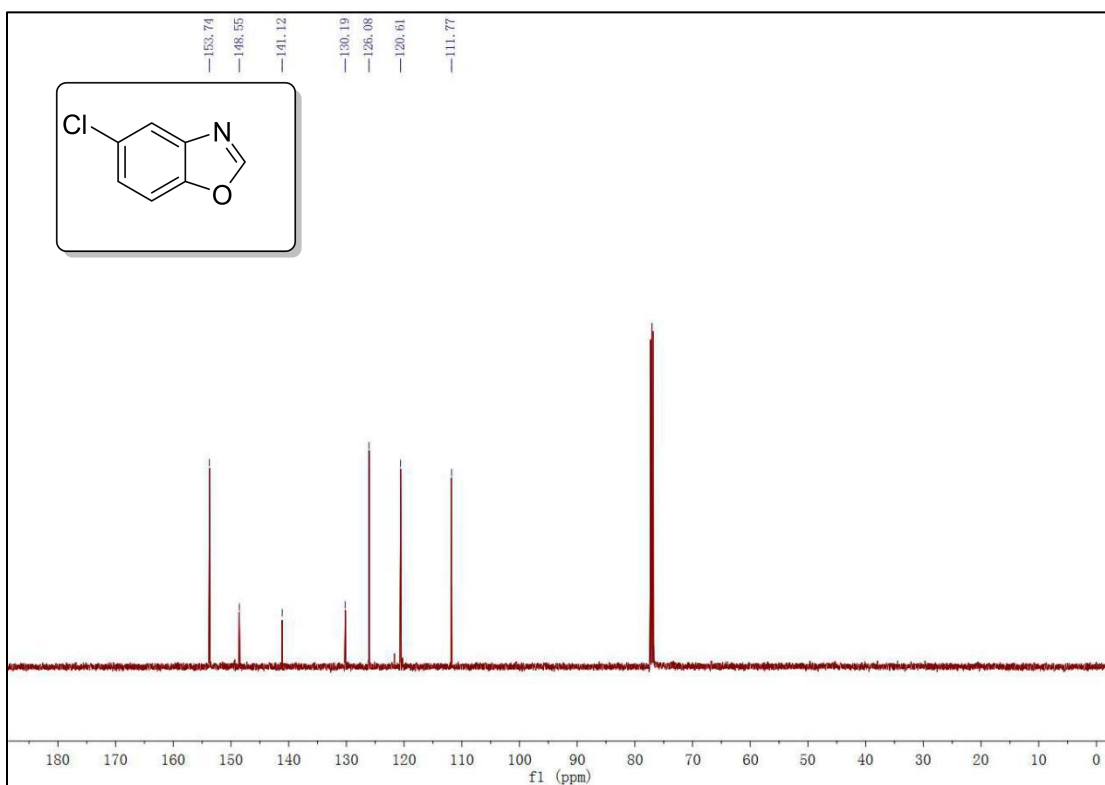


Figure S104. <sup>13</sup>C NMR spectrum of 20c, related to Figure 4

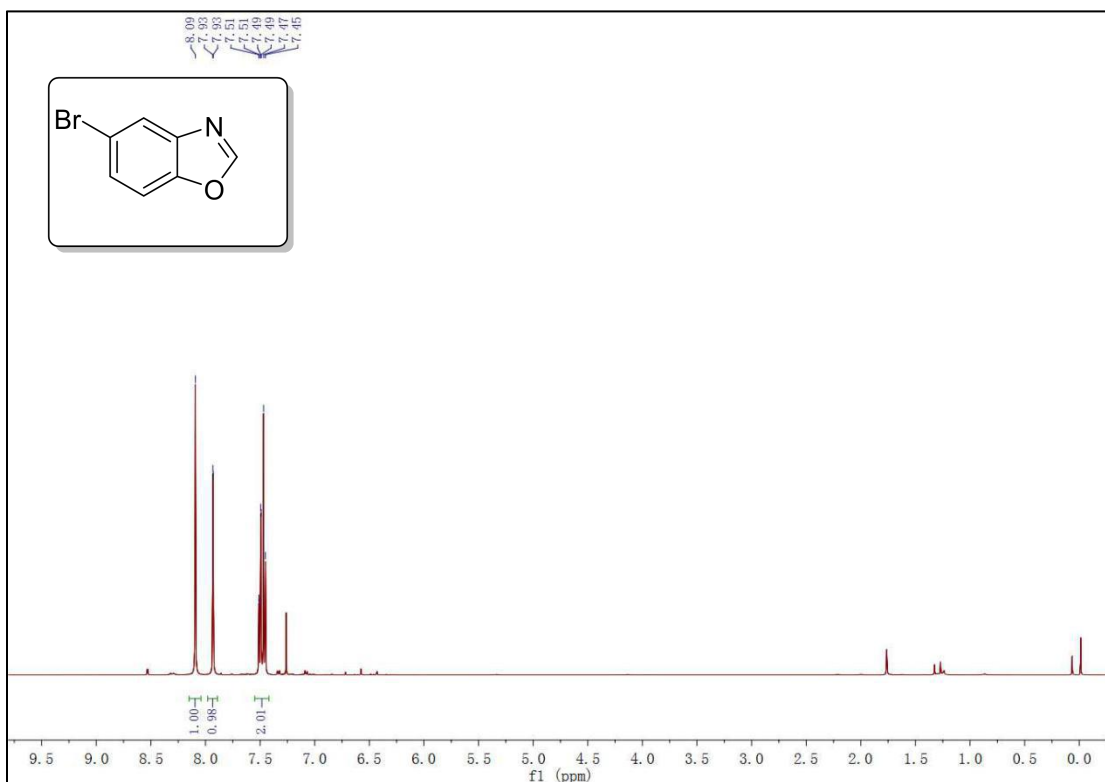


Figure S105. <sup>1</sup>H NMR spectrum of 20d, related to Figure 4

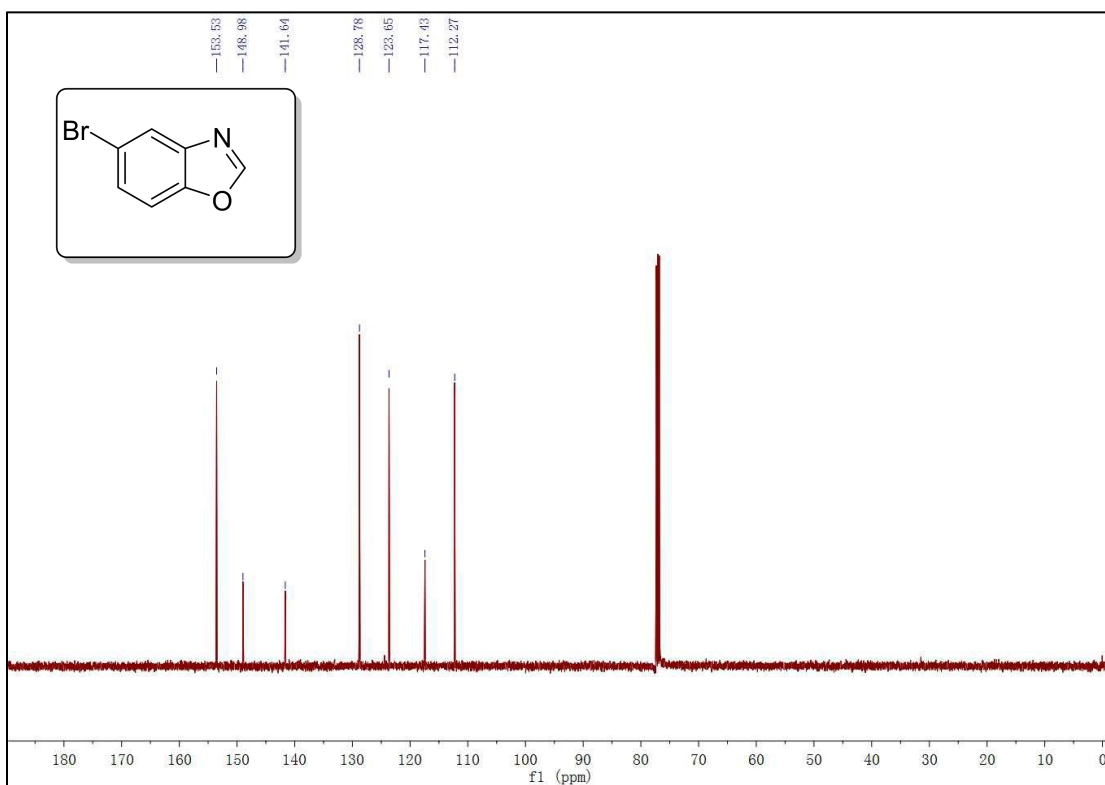
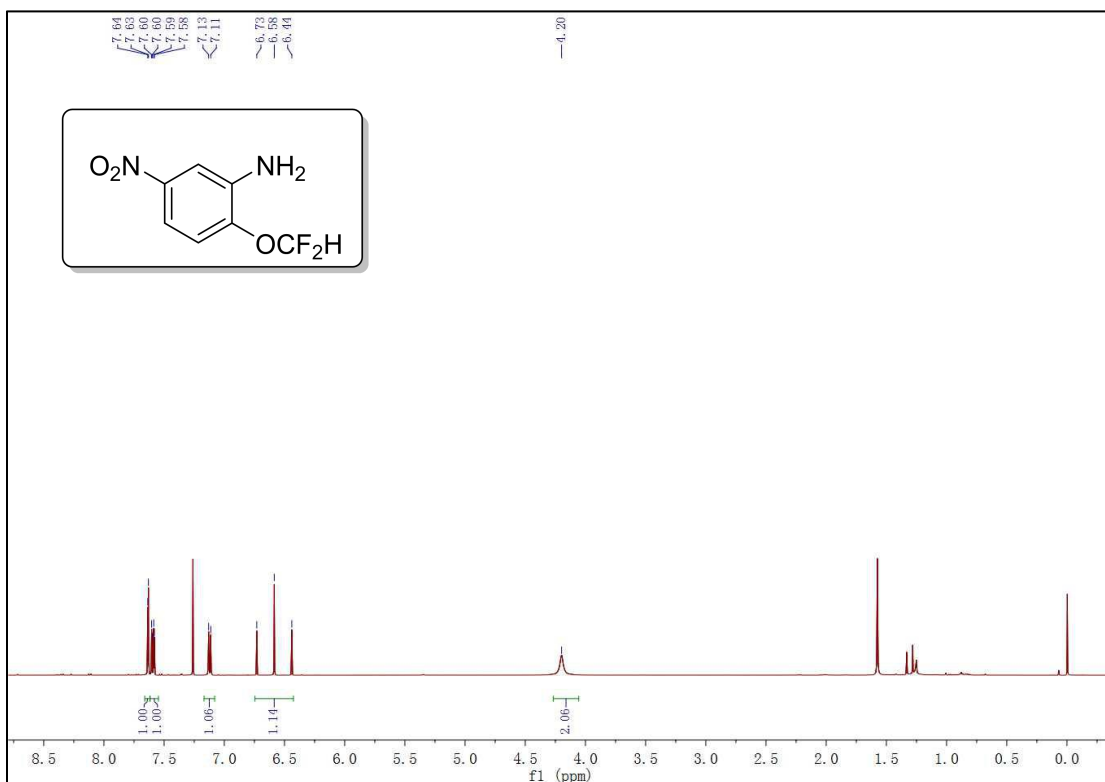
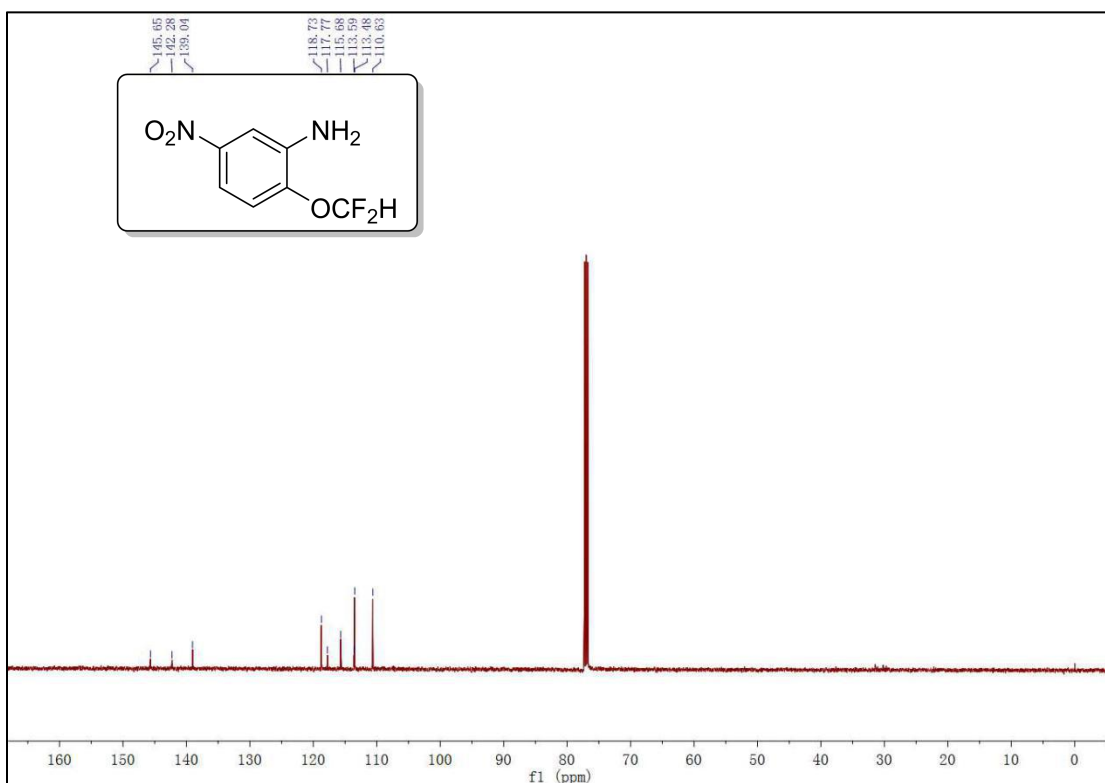


Figure S106. <sup>13</sup>C NMR spectrum of 20d, related to Figure 4



**Figure S107. <sup>1</sup>H NMR spectrum of 20e', related to Figure 4**



**Figure S108. <sup>13</sup>C NMR spectrum of 20e', related to Figure 4**

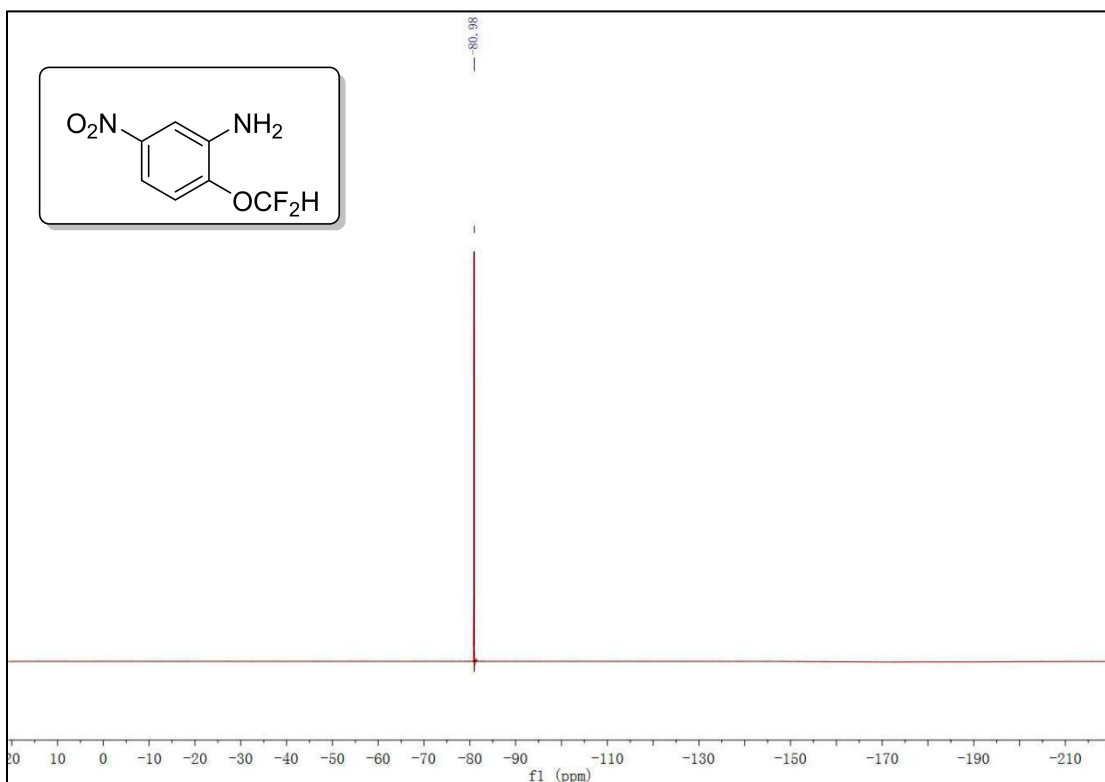


Figure S109.  $^{19}\text{F}$  NMR spectrum of 20e', related to Figure 4

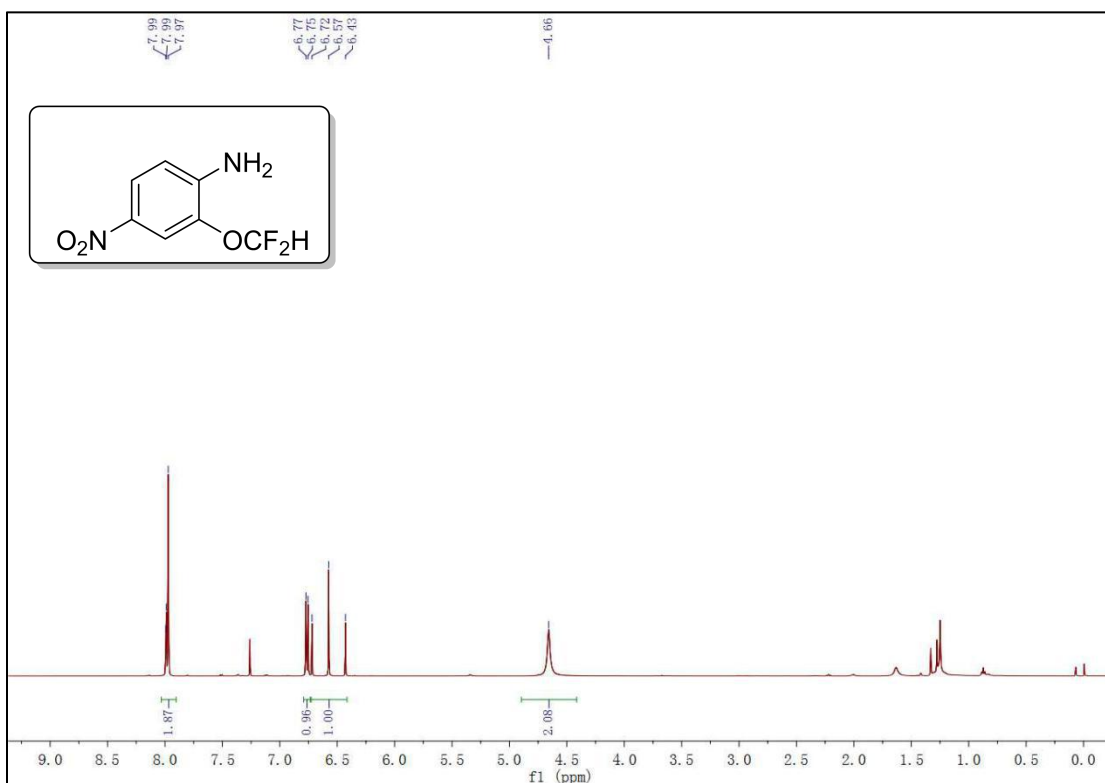


Figure S110.  $^1\text{H}$  NMR spectrum of 20f', related to Figure 4

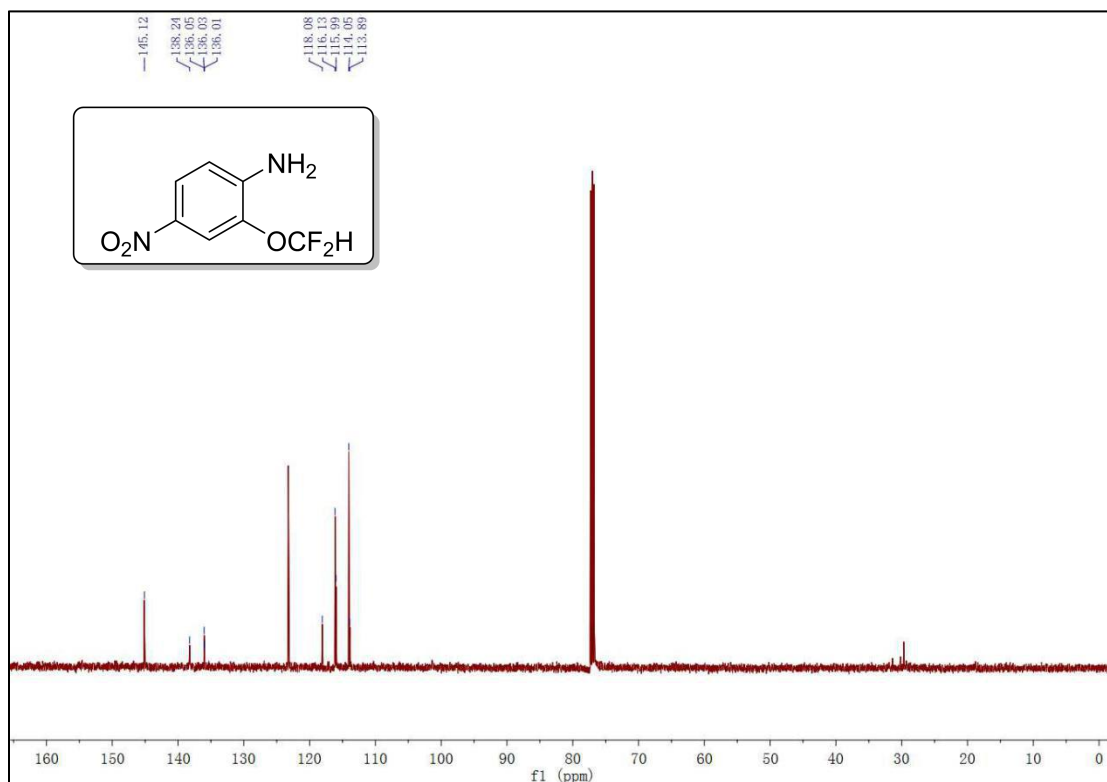


Figure S11. <sup>13</sup>C NMR spectrum of 20f', related to Figure 4

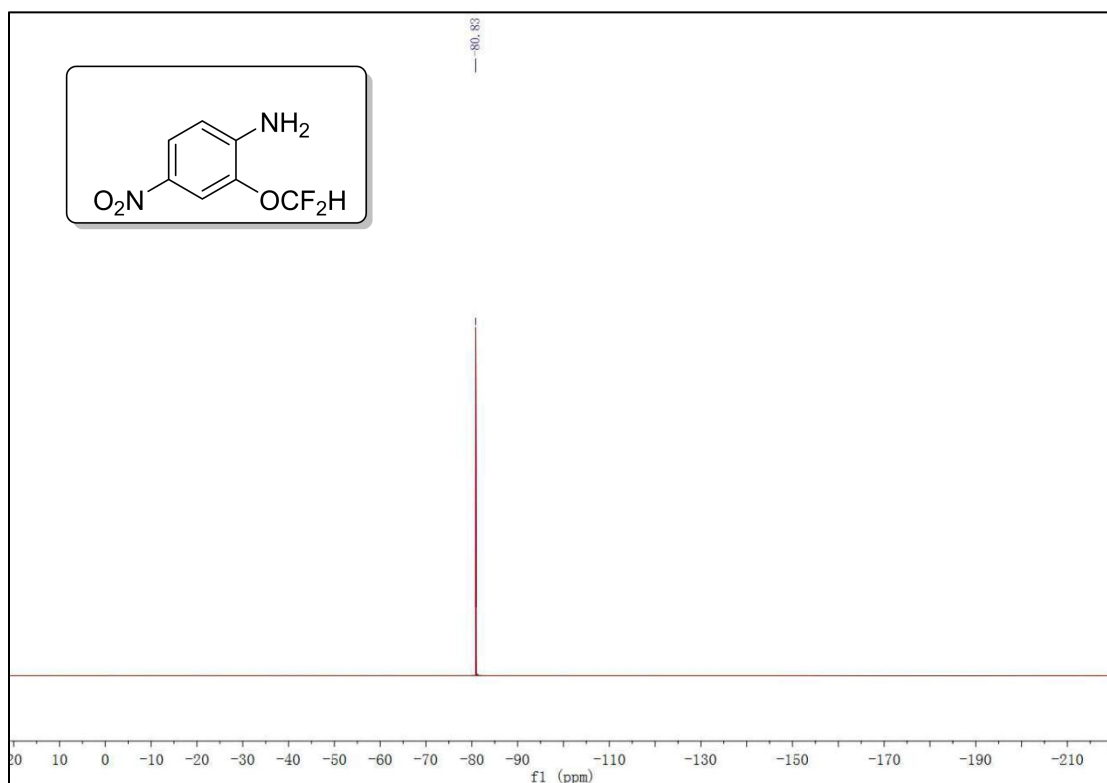


Figure S12. <sup>19</sup>F NMR spectrum of 20f', related to Figure 4

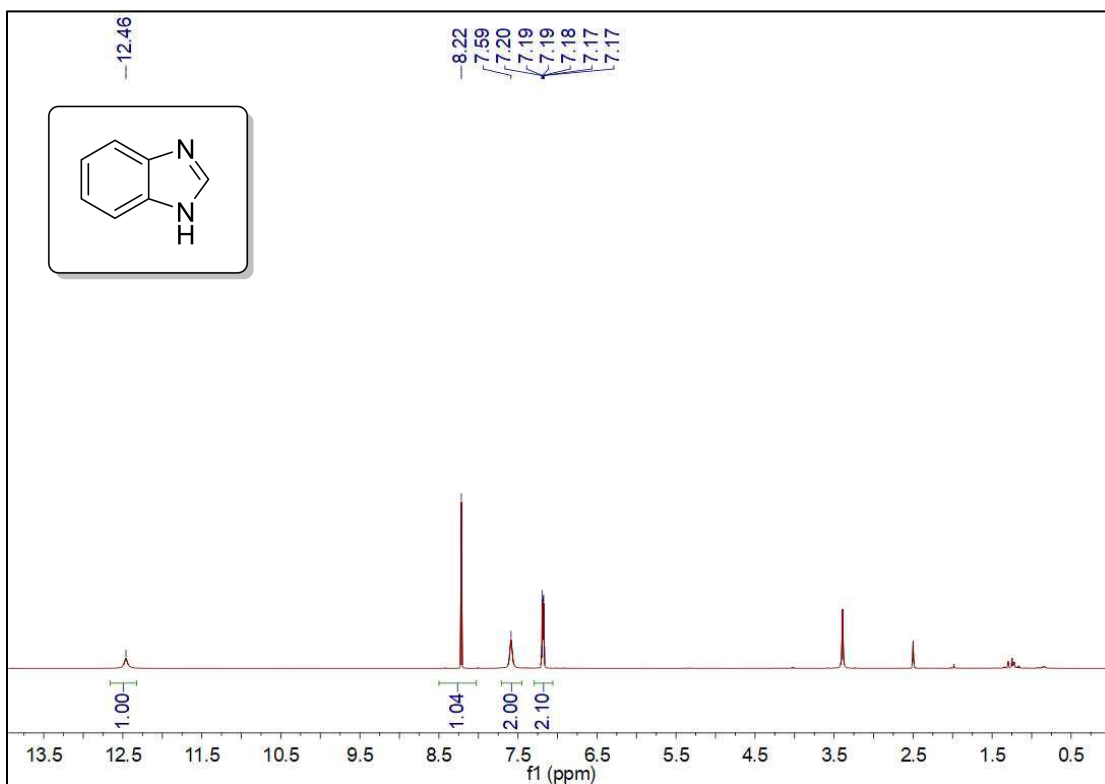


Figure S113. <sup>1</sup>H NMR spectrum of 20g, related to Figure 4

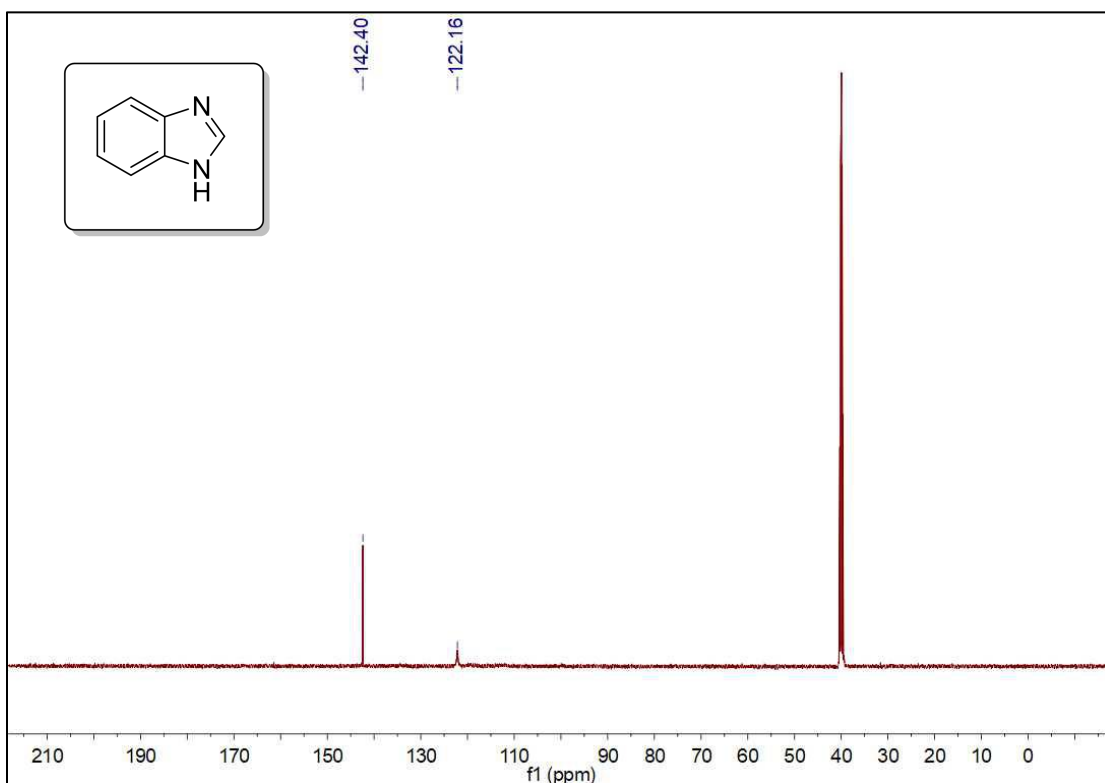


Figure S114. <sup>13</sup>C NMR spectrum of 20g, related to Figure 4



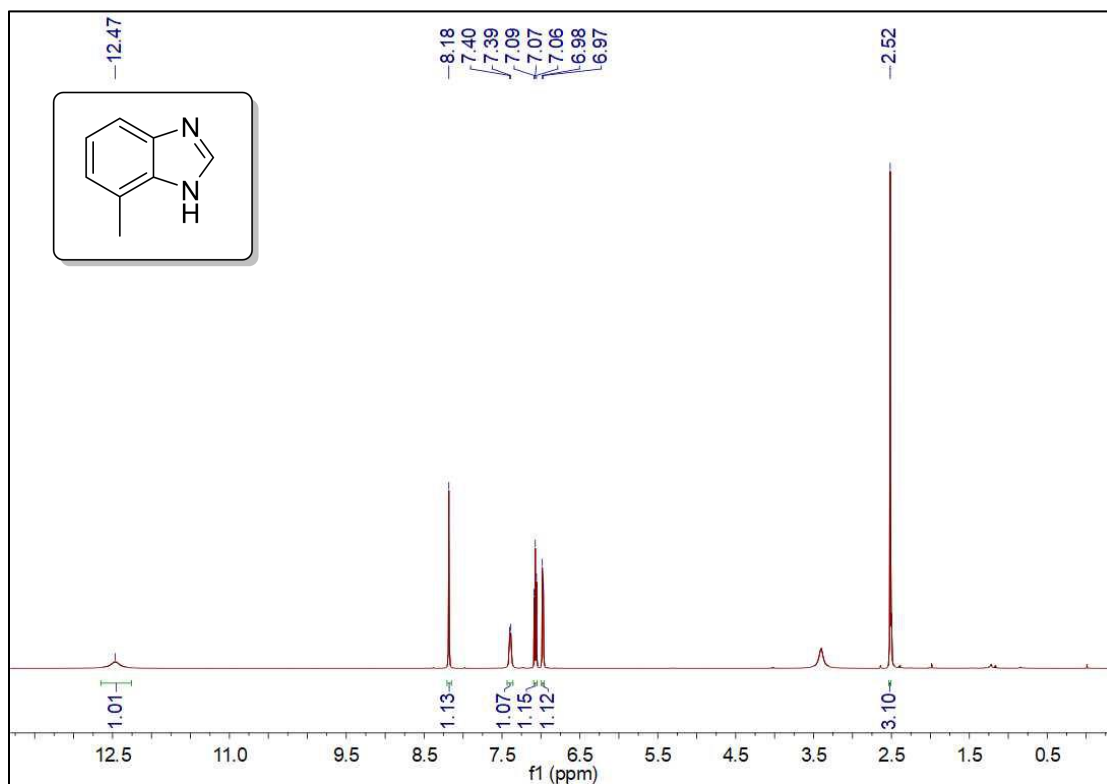


Figure S115. <sup>1</sup>H NMR spectrum of 20h, related to Figure 4

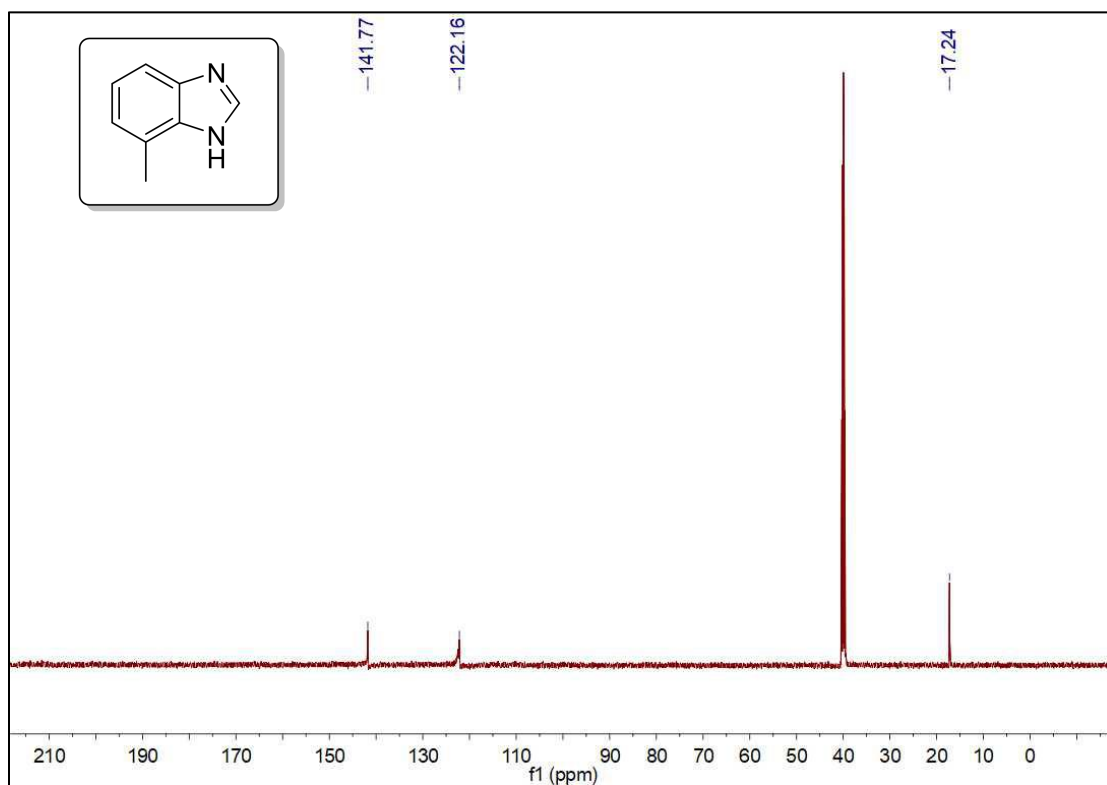


Figure S116. <sup>13</sup>C NMR spectrum of 20h, related to Figure 4

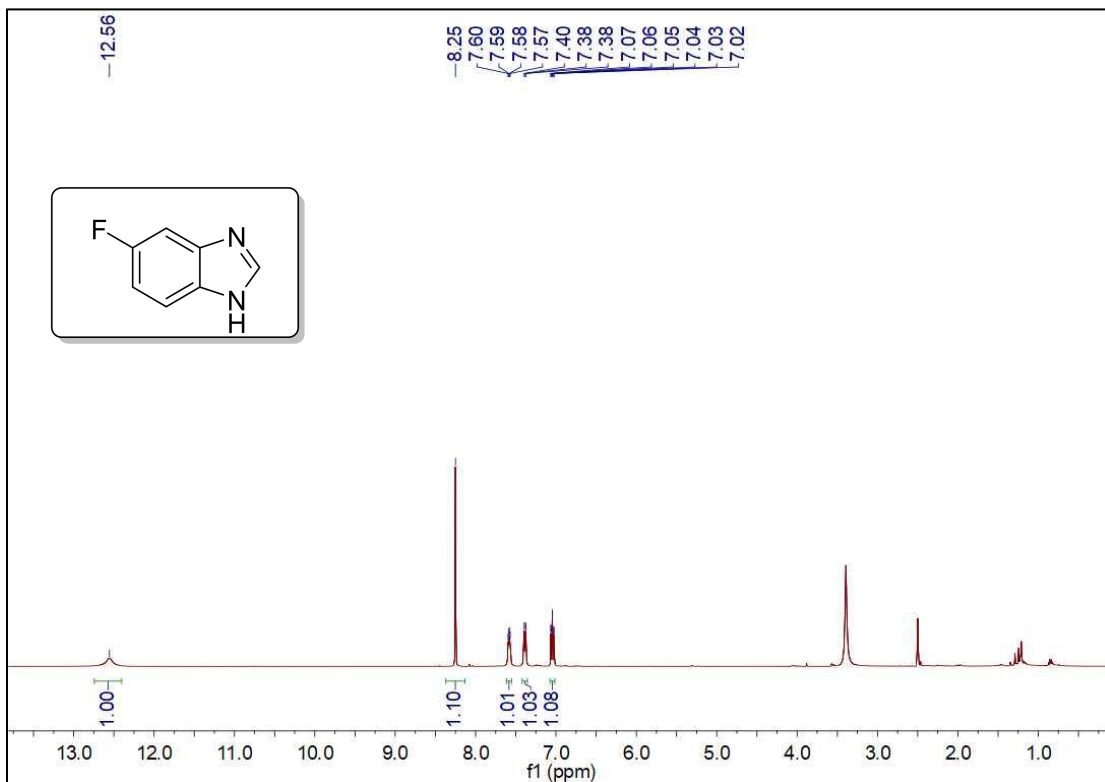


Figure S117. <sup>1</sup>H NMR spectrum of 20i, related to Figure 4

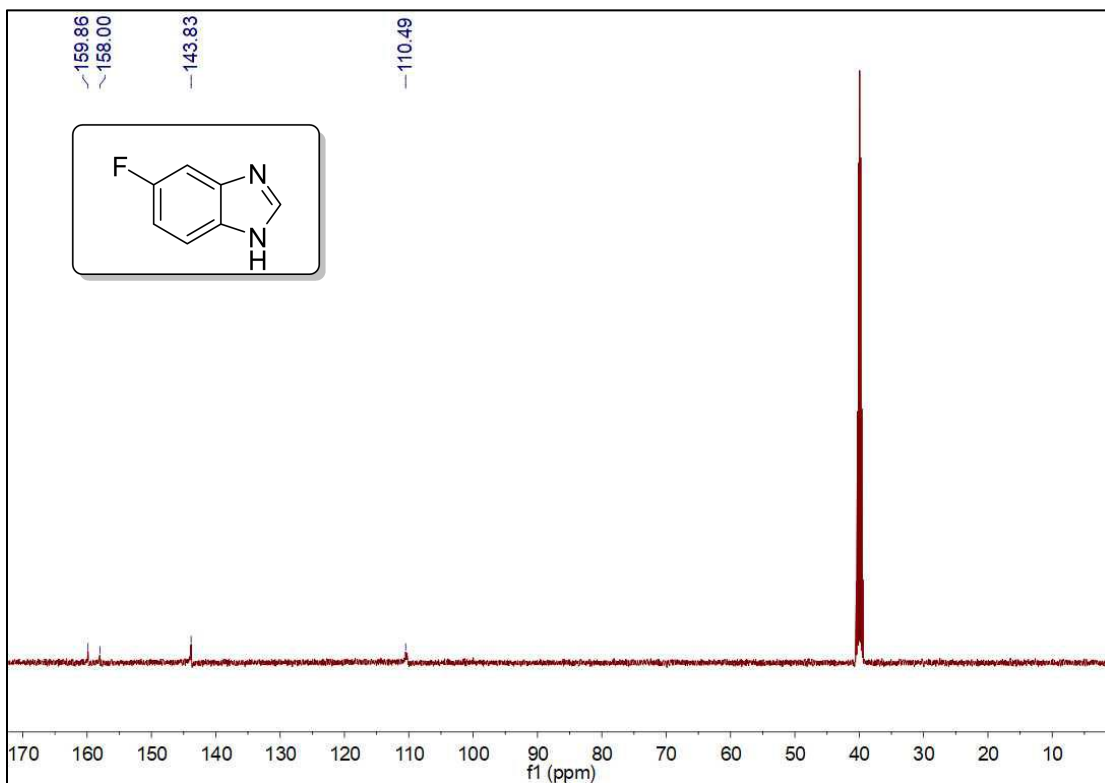


Figure S118. <sup>13</sup>C NMR spectrum of 20i, related to Figure 4

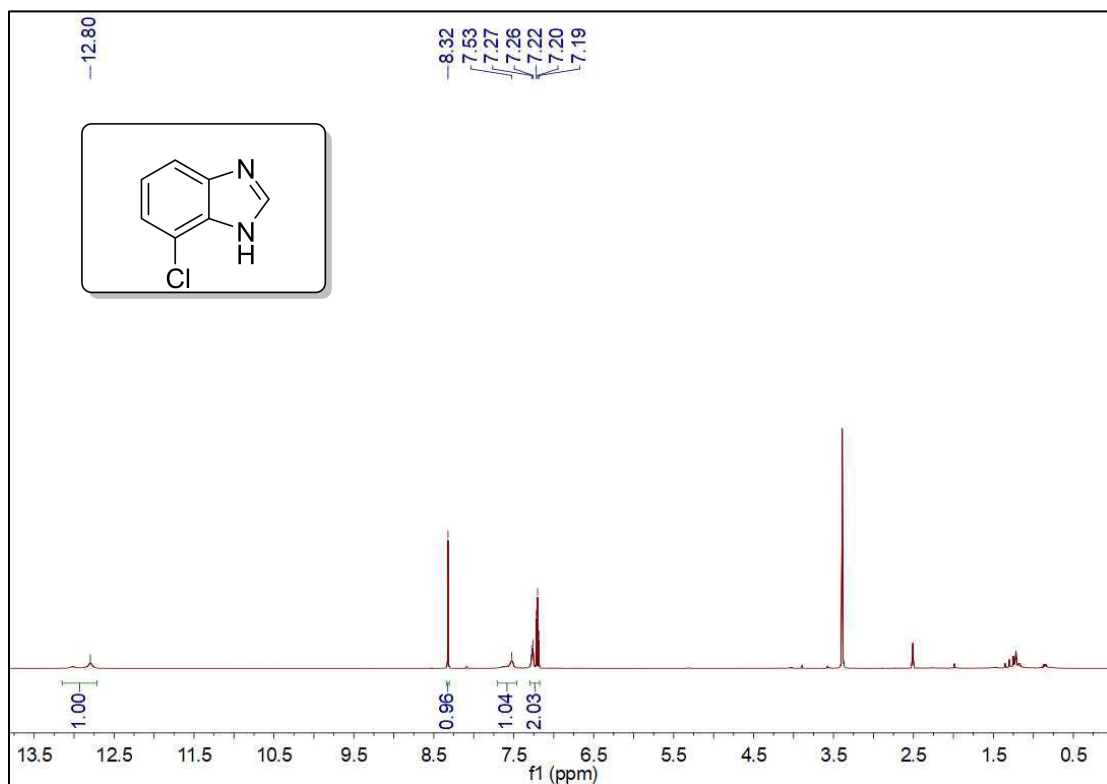


Figure S119.  $^1\text{H}$  NMR spectrum of 20j, related to Figure 4

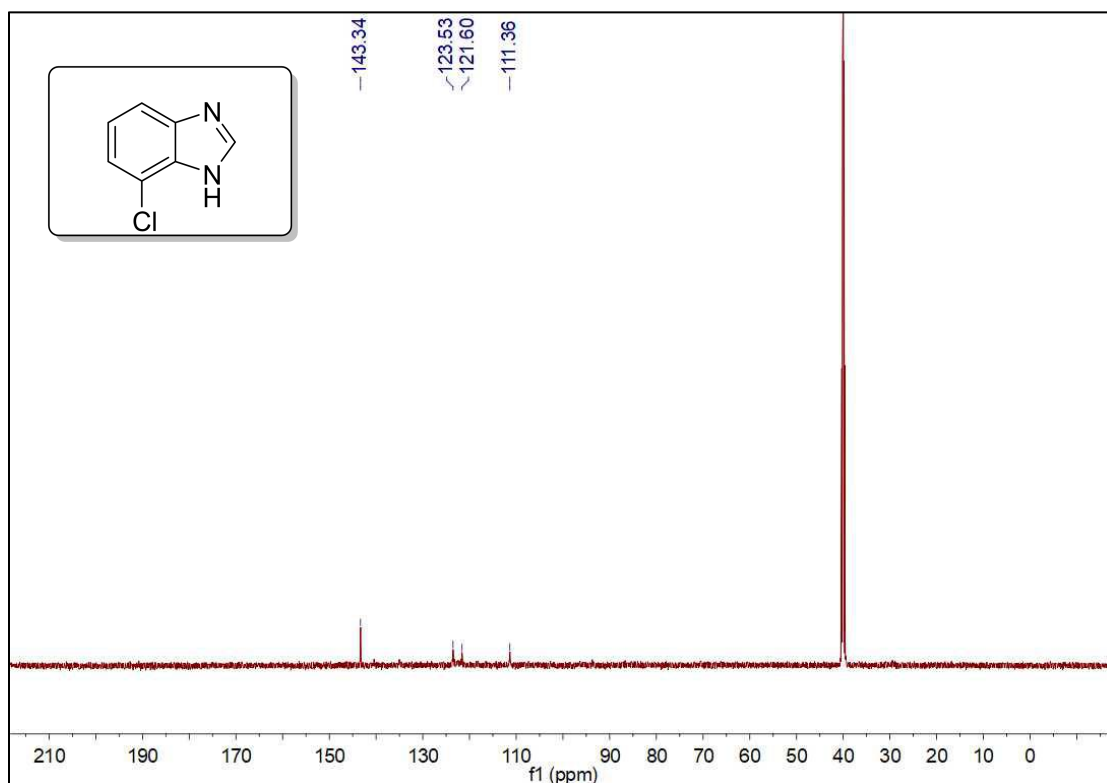


Figure S120.  $^{13}\text{C}$  NMR spectrum of 20j, related to Figure 4

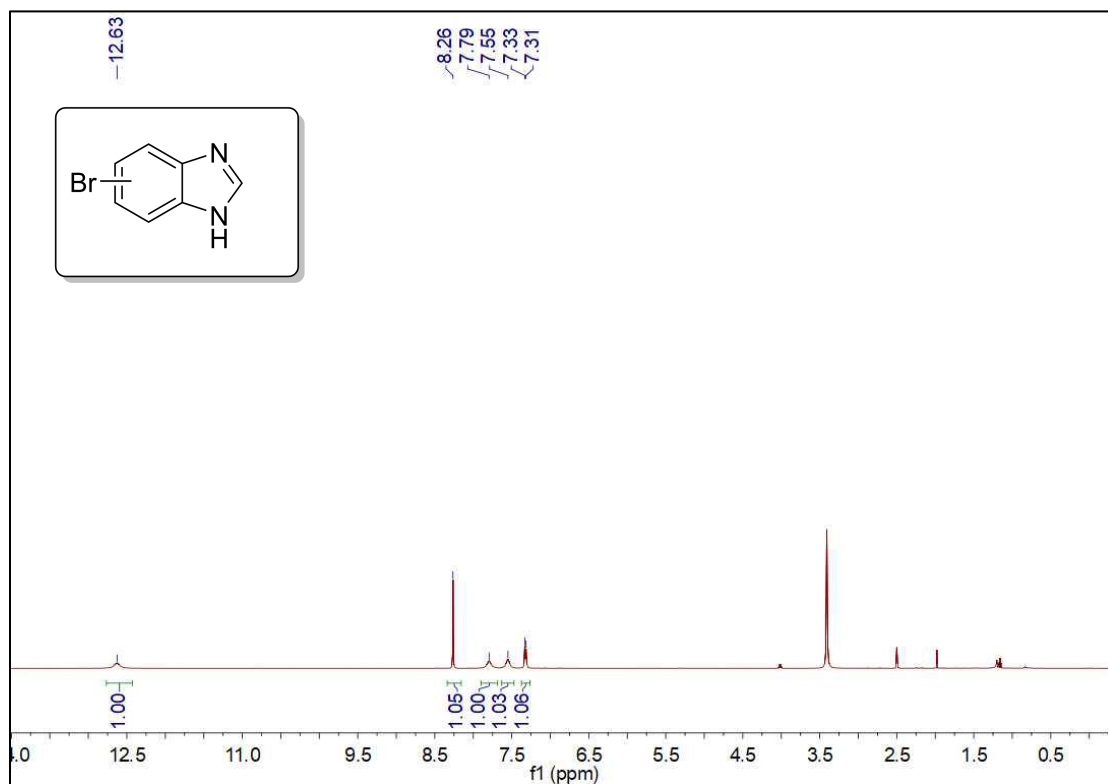


Figure S121. <sup>1</sup>H NMR spectrum of 20k, related to Figure 4

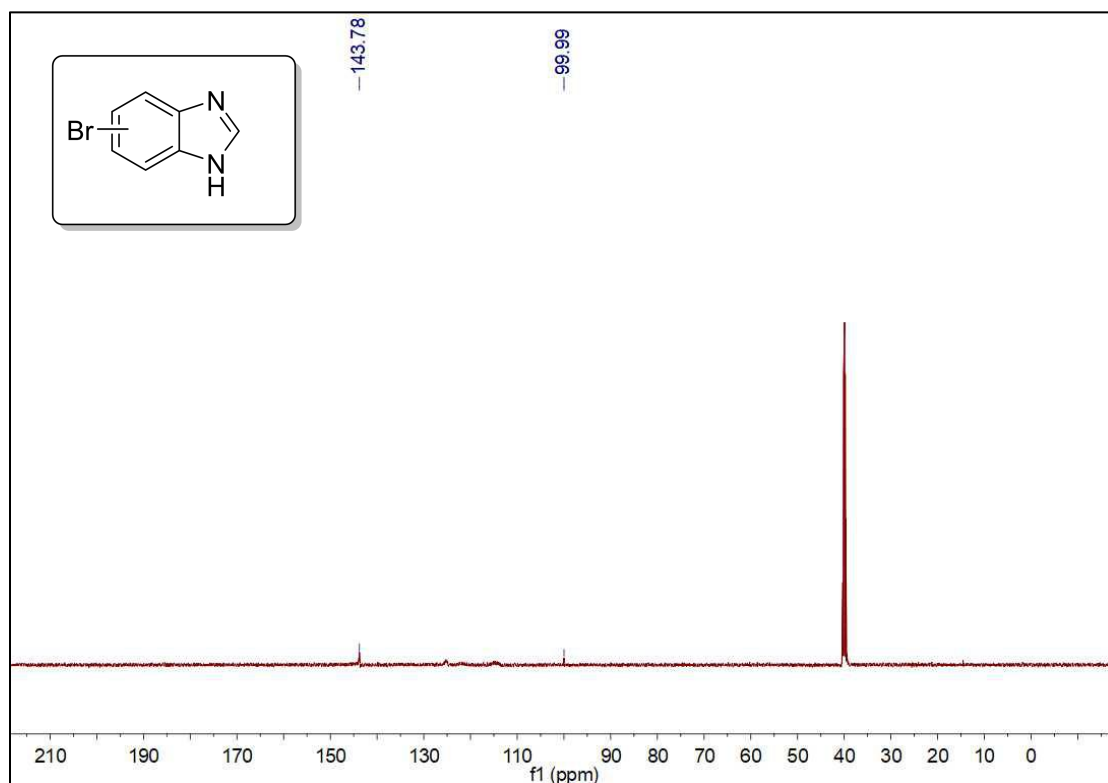


Figure S122. <sup>13</sup>C NMR spectrum of 20k, related to Figure 4

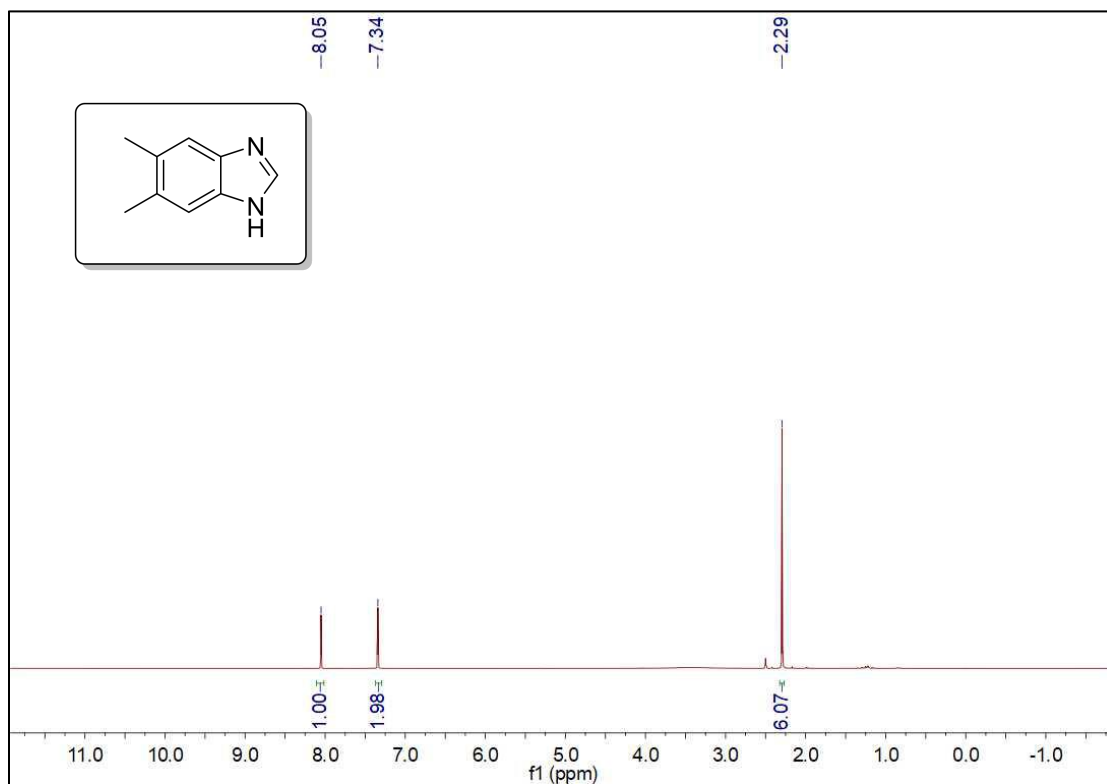


Figure S123. <sup>1</sup>H NMR spectrum of 20m, related to Figure 4

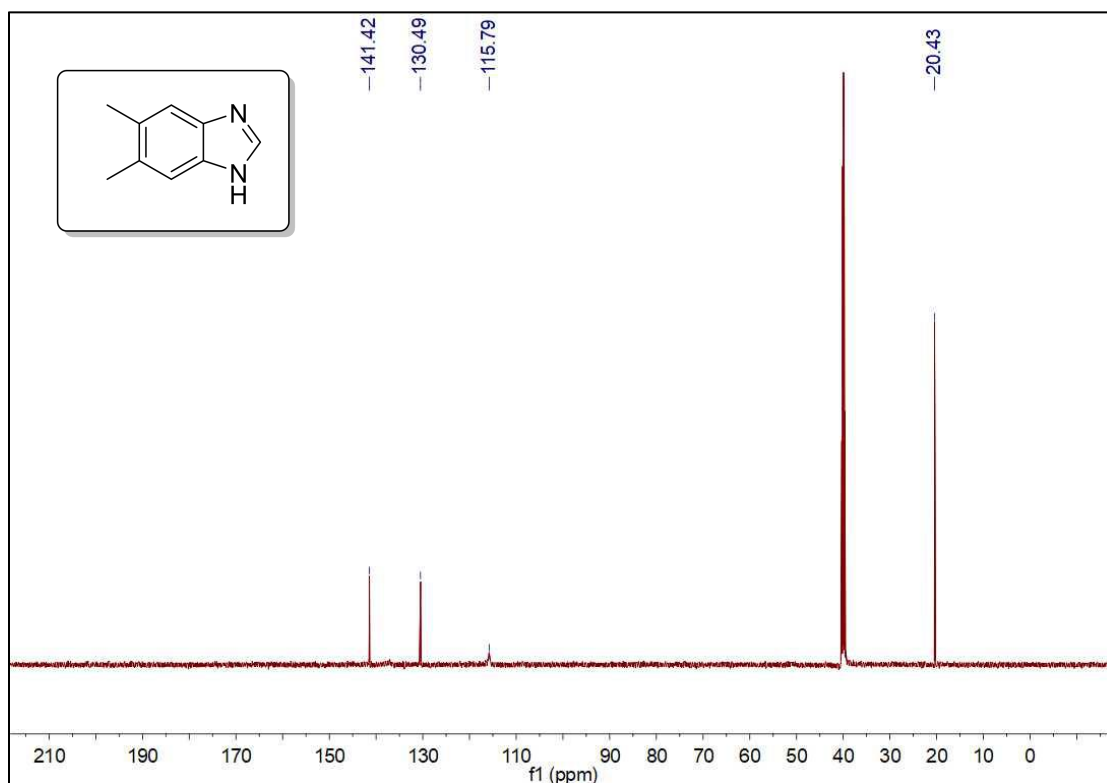
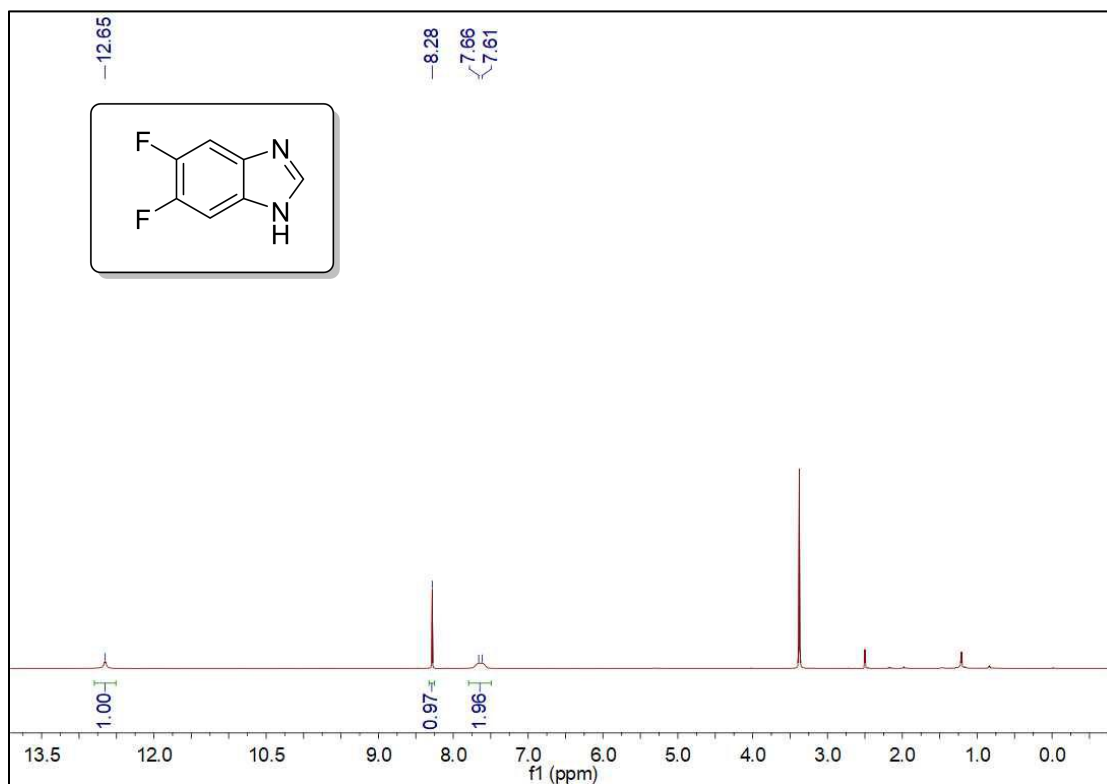
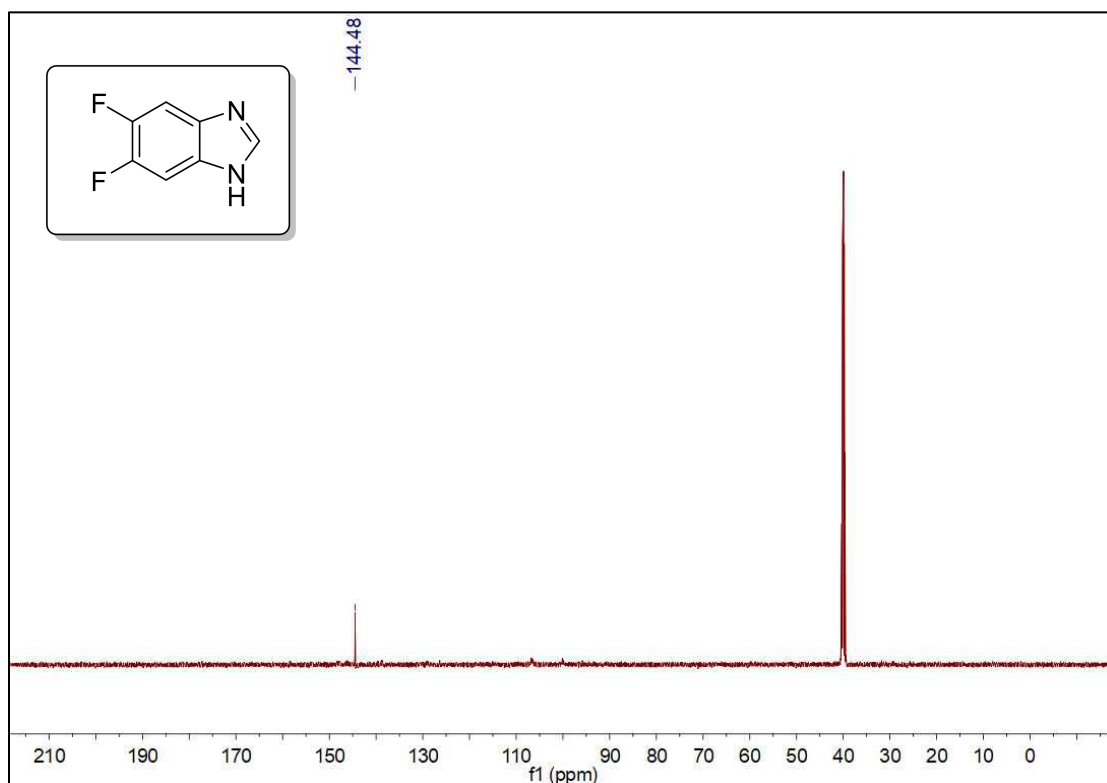


Figure S124. <sup>13</sup>C NMR spectrum of 20m, related to Figure 4



**Figure S125.** <sup>1</sup>H NMR spectrum of 20n, related to Figure 4



**Figure S126.** <sup>13</sup>C NMR spectrum of 20n, related to Figure 4

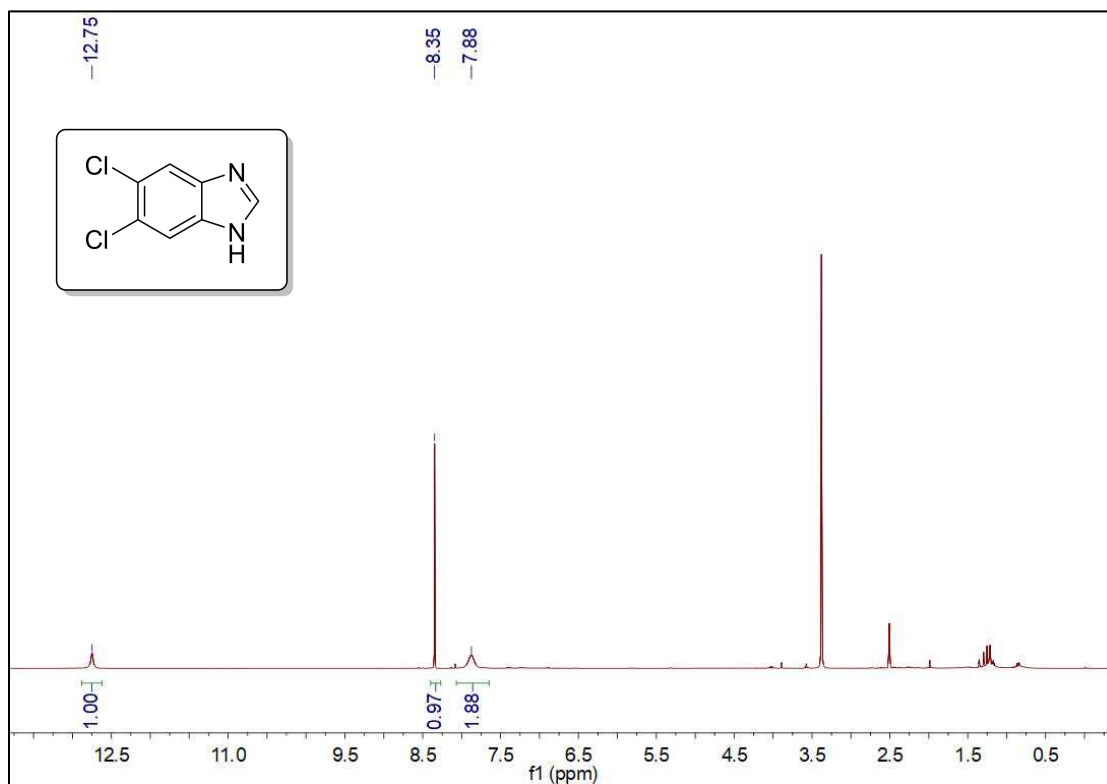


Figure S127.  $^1\text{H}$  NMR spectrum of 20o, related to Figure 4

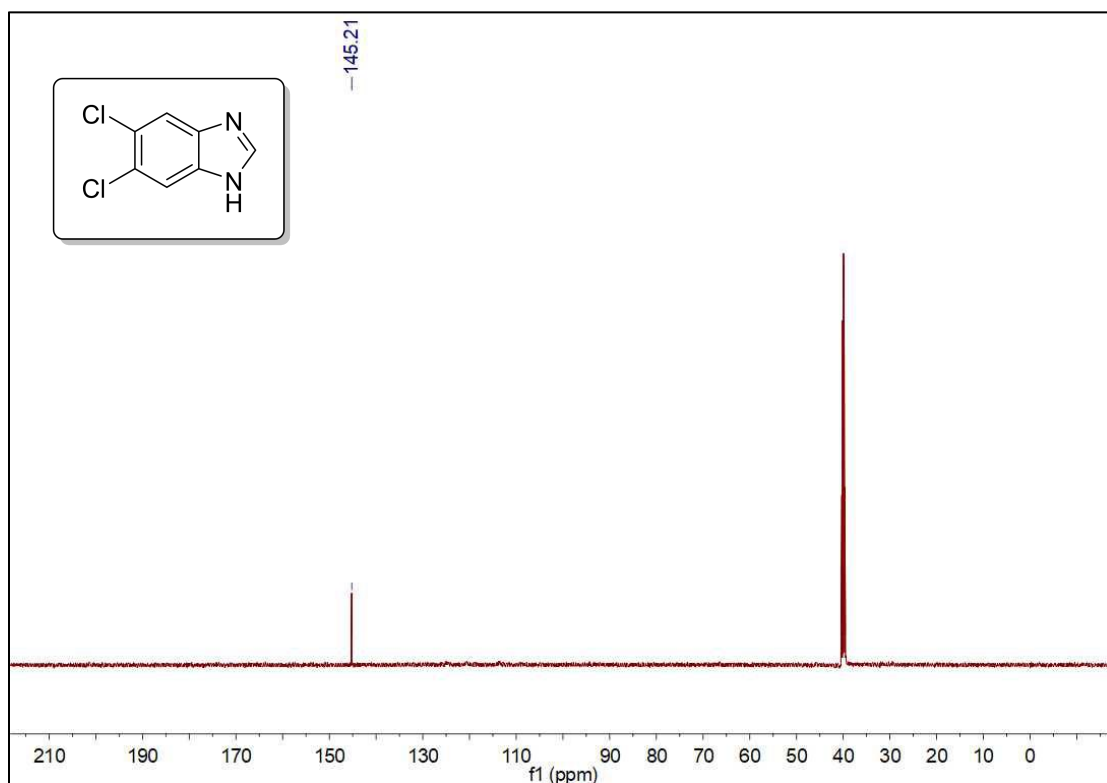


Figure S128.  $^{13}\text{C}$  NMR spectrum of 20o, related to Figure 4

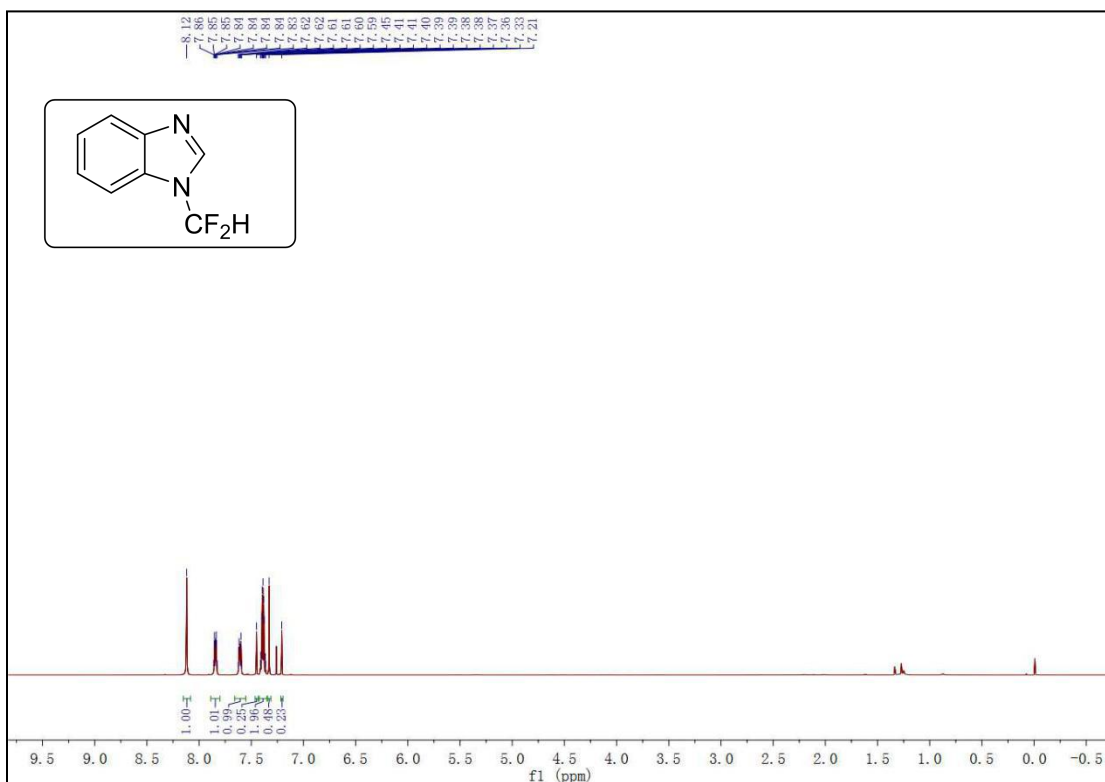


Figure S129.  $^1\text{H}$  NMR spectrum of 21, related to Figure 4

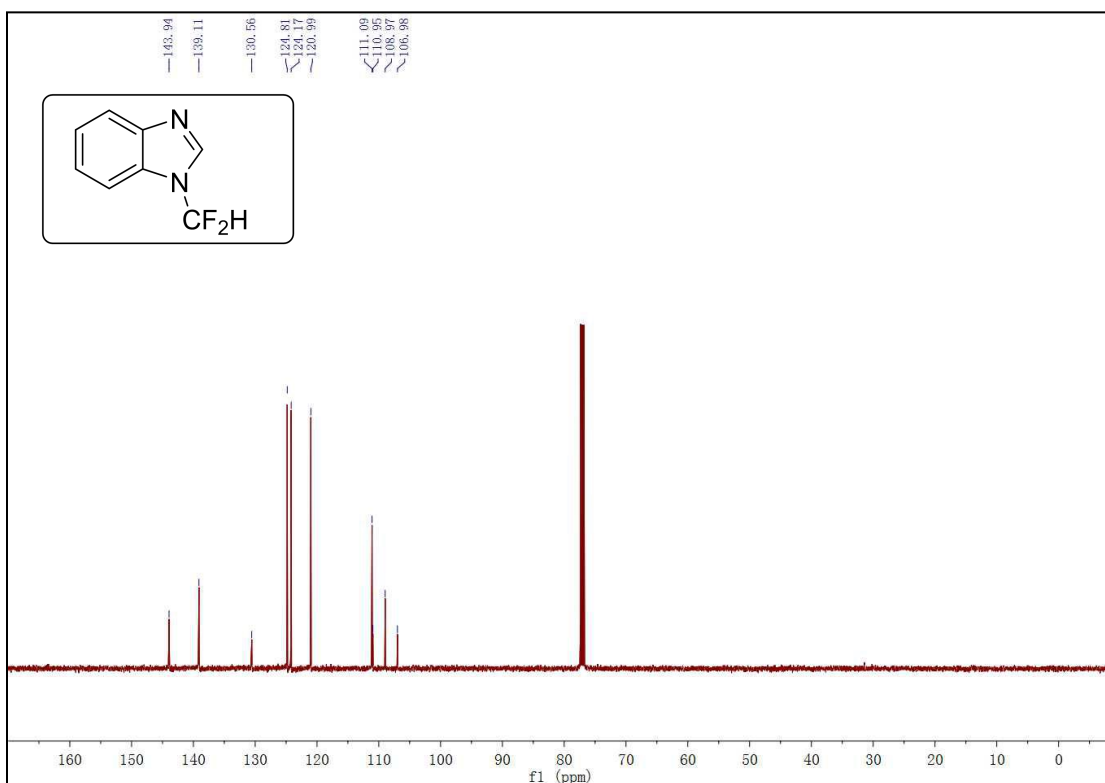


Figure S130.  $^{13}\text{C}$  NMR spectrum of 21, related to Figure 4



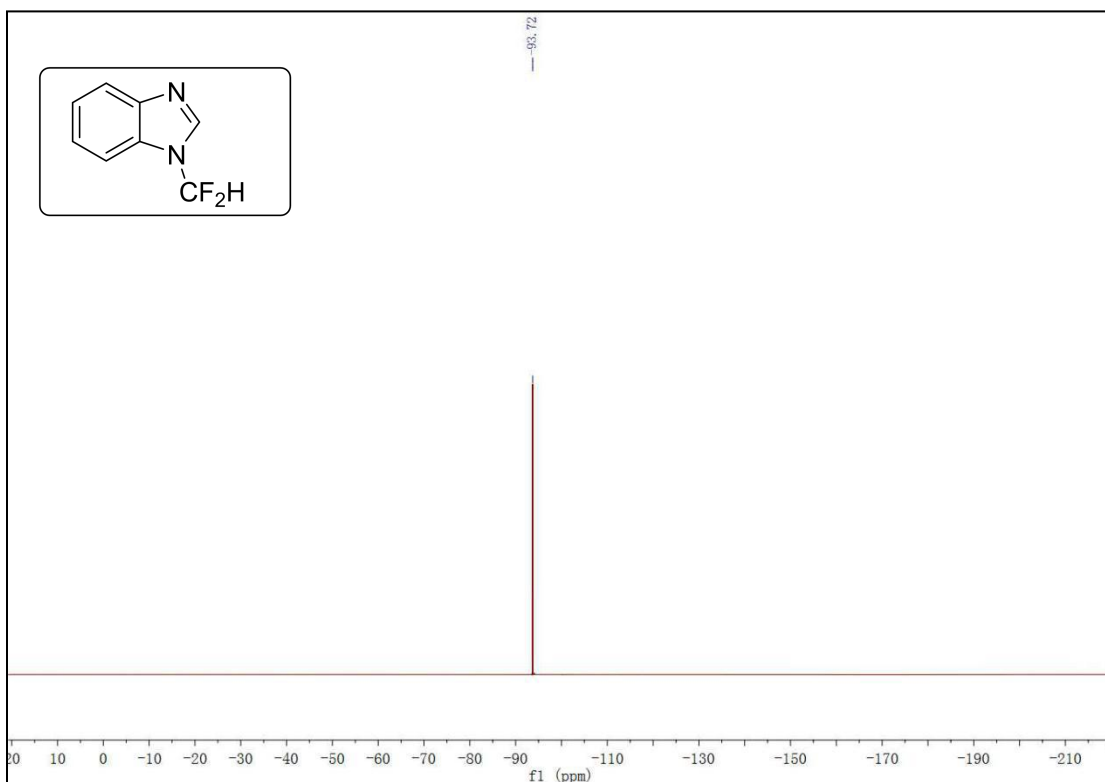


Figure S131.  $^{19}\text{F}$  NMR spectrum of 21, related to Figure 4

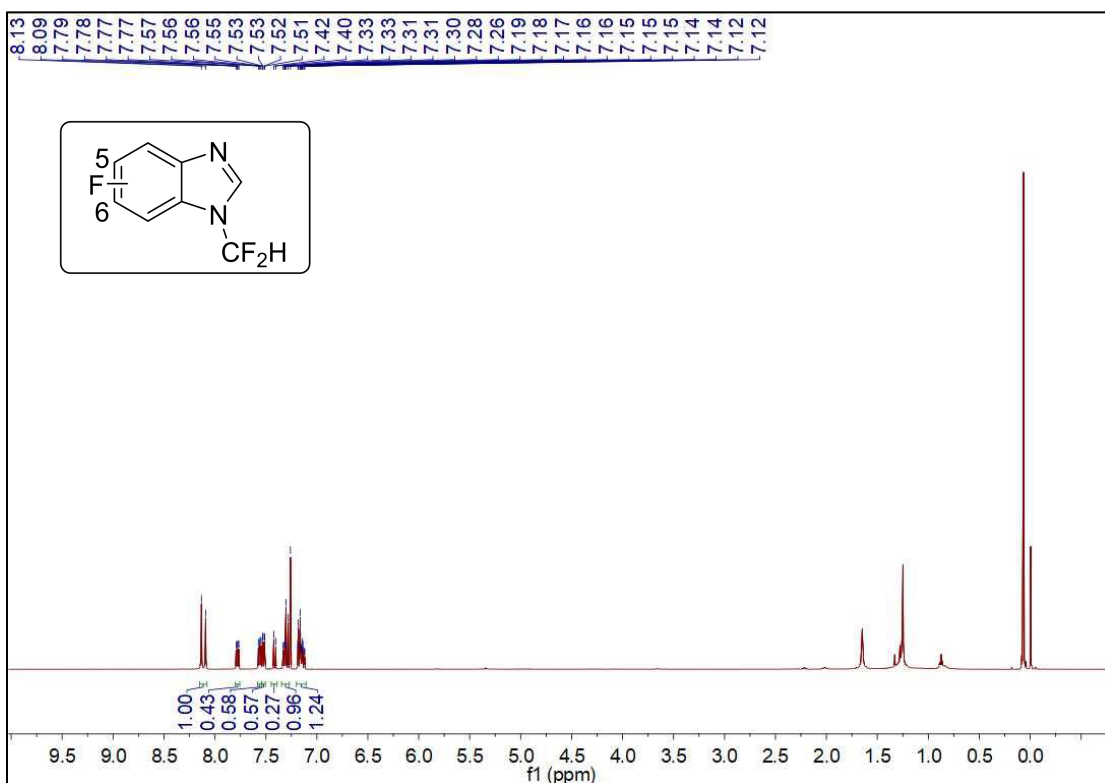


Figure S132.  $^1\text{H}$  NMR spectrum of 22, related to Figure 4

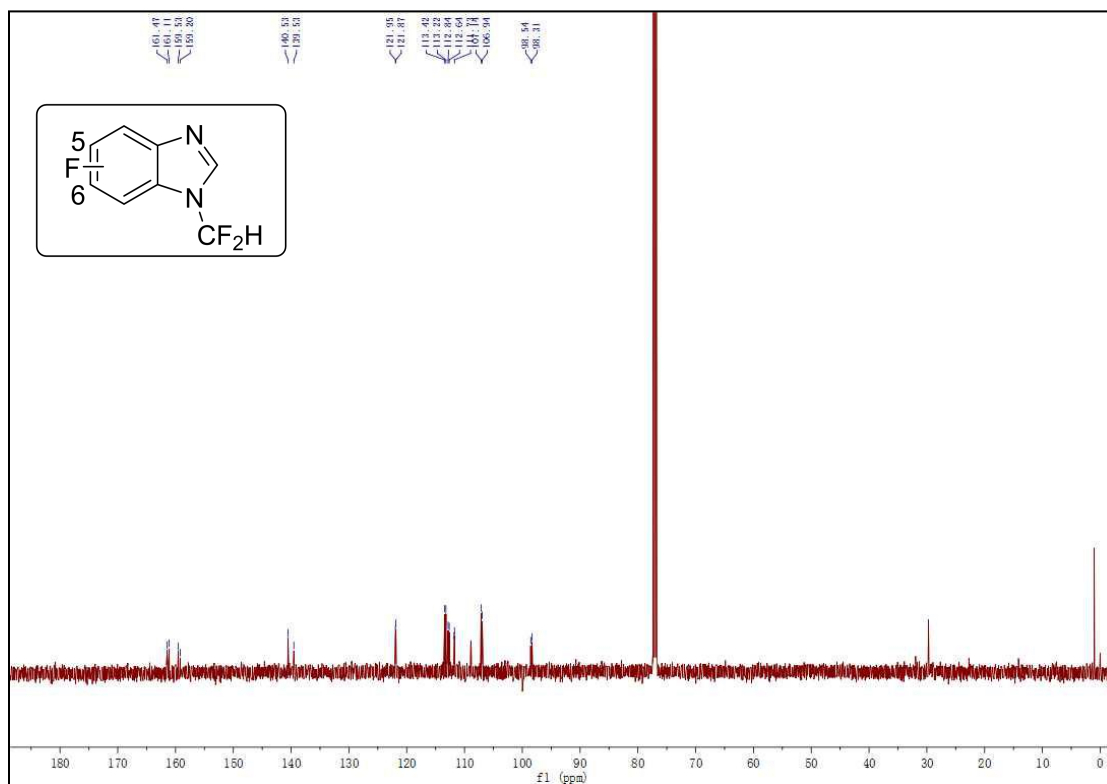


Figure S133. <sup>13</sup>C NMR spectrum of 22, related to Figure 4

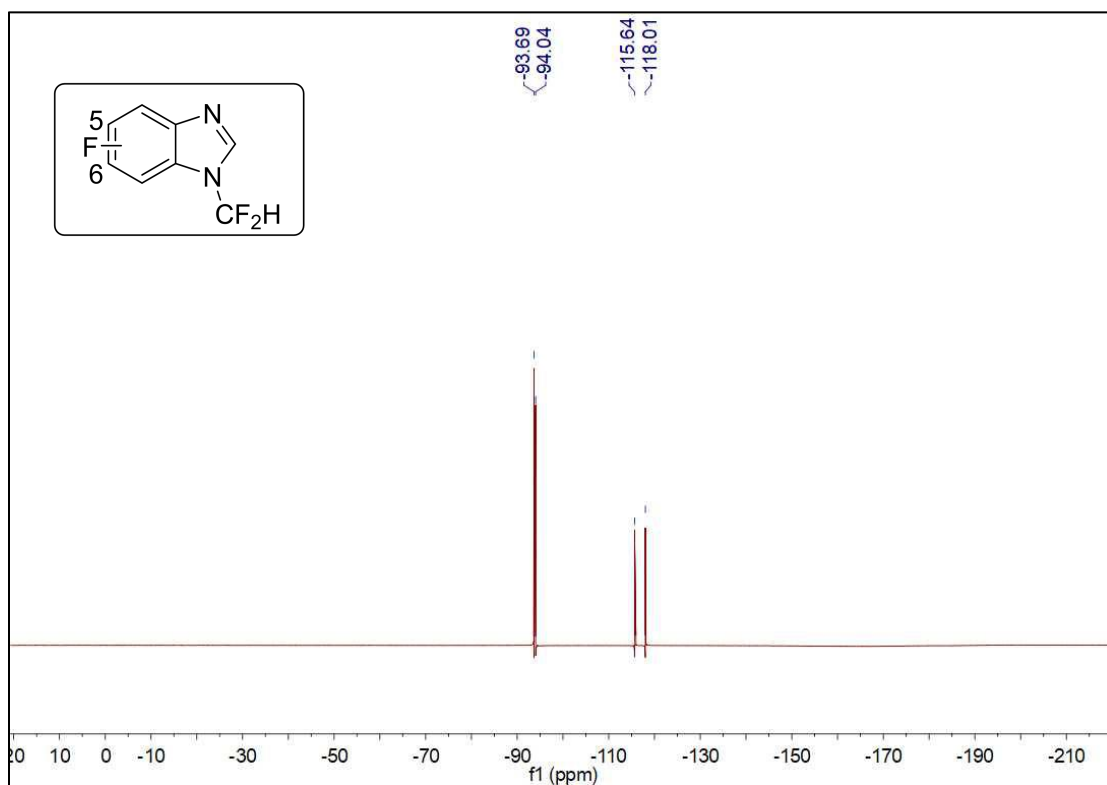
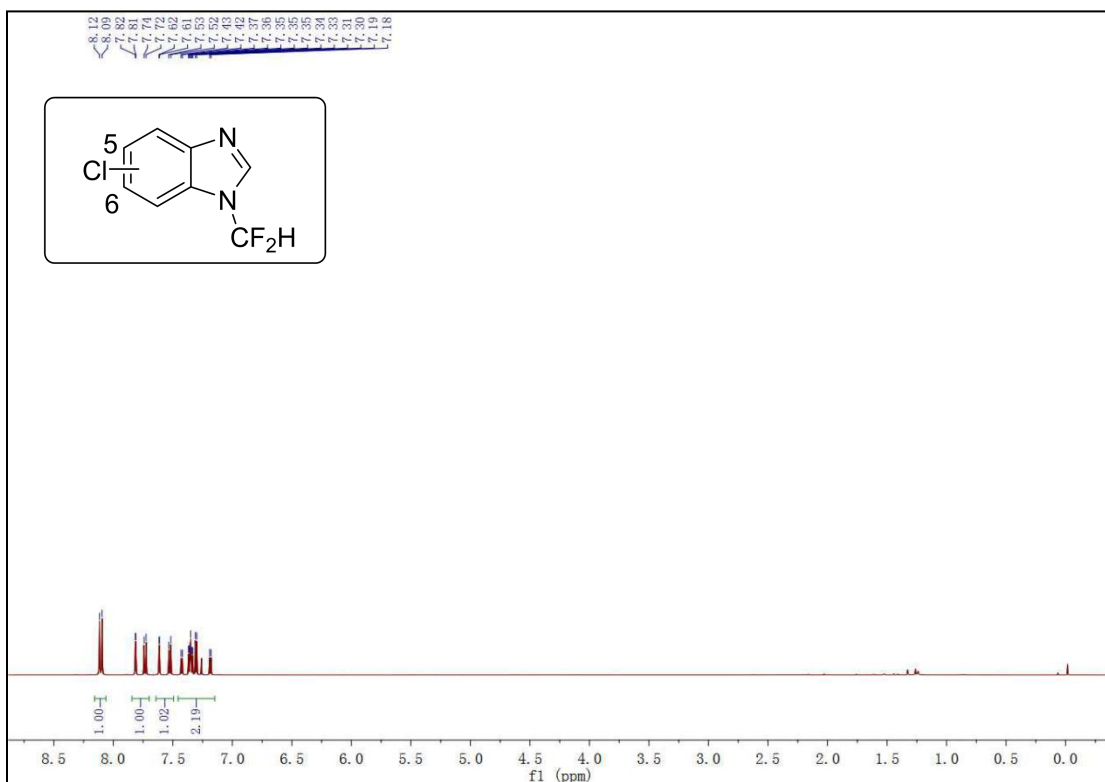
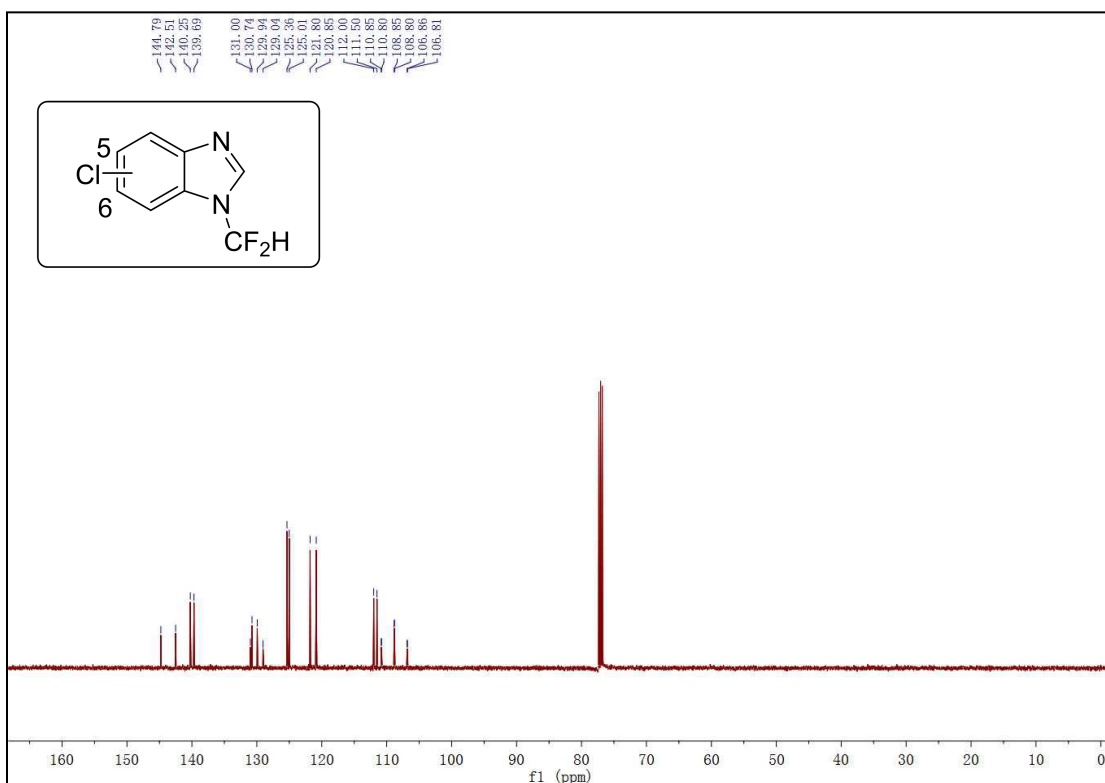


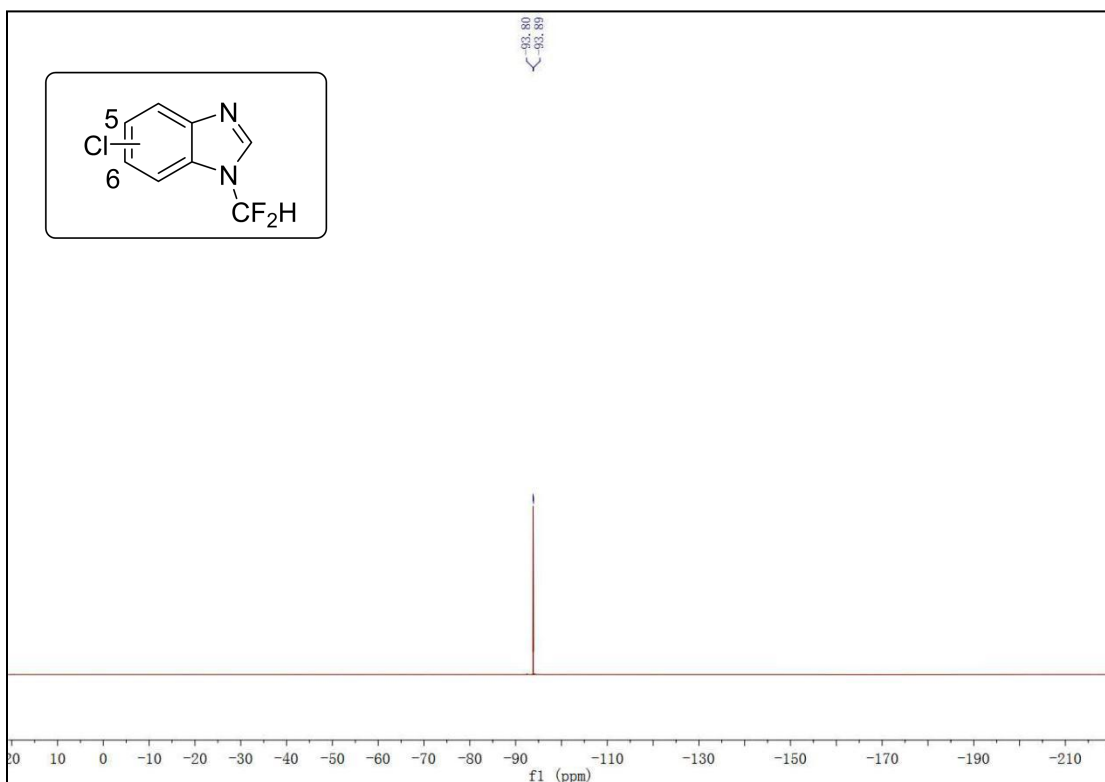
Figure S134. <sup>19</sup>F NMR spectrum of 22, related to Figure 4



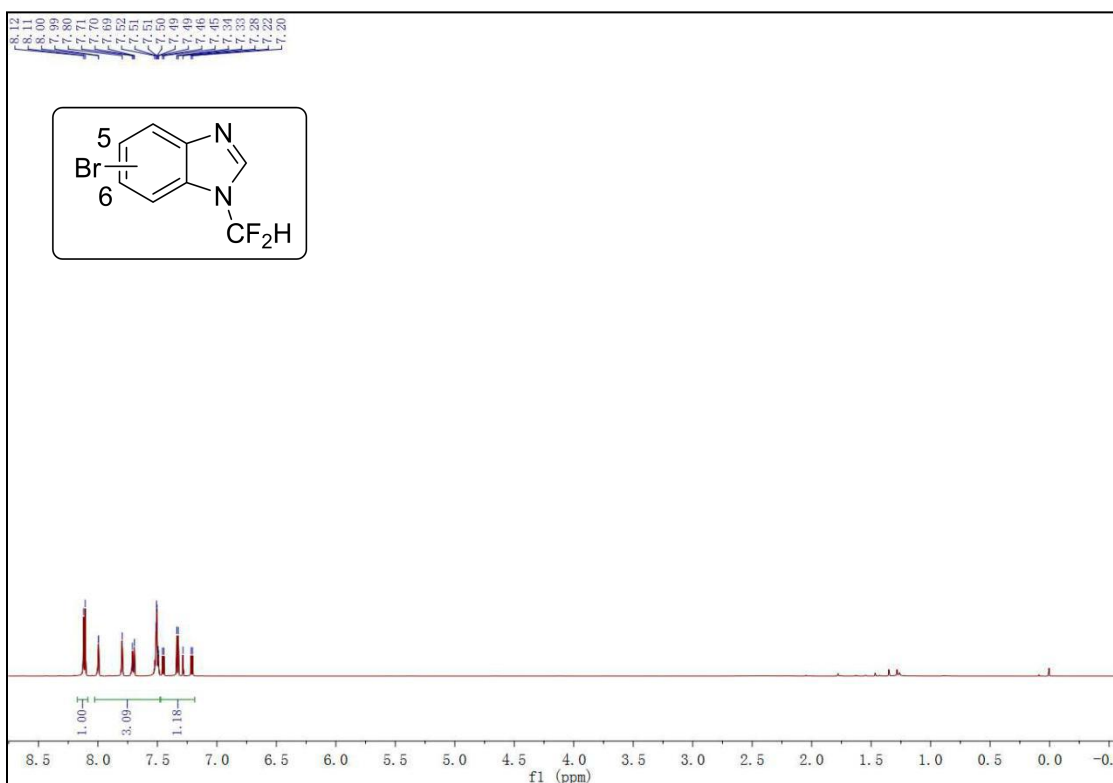
**Figure S135.** <sup>1</sup>H NMR spectrum of 25, related to Figure 4



**Figure S136.** <sup>13</sup>C NMR spectrum of 25, related to Figure 4



**Figure S137.  $^{19}\text{F}$  NMR spectrum of 25, related to Figure 4**



**Figure S138.  $^1\text{H}$  NMR spectrum of 26, related to Figure 4**

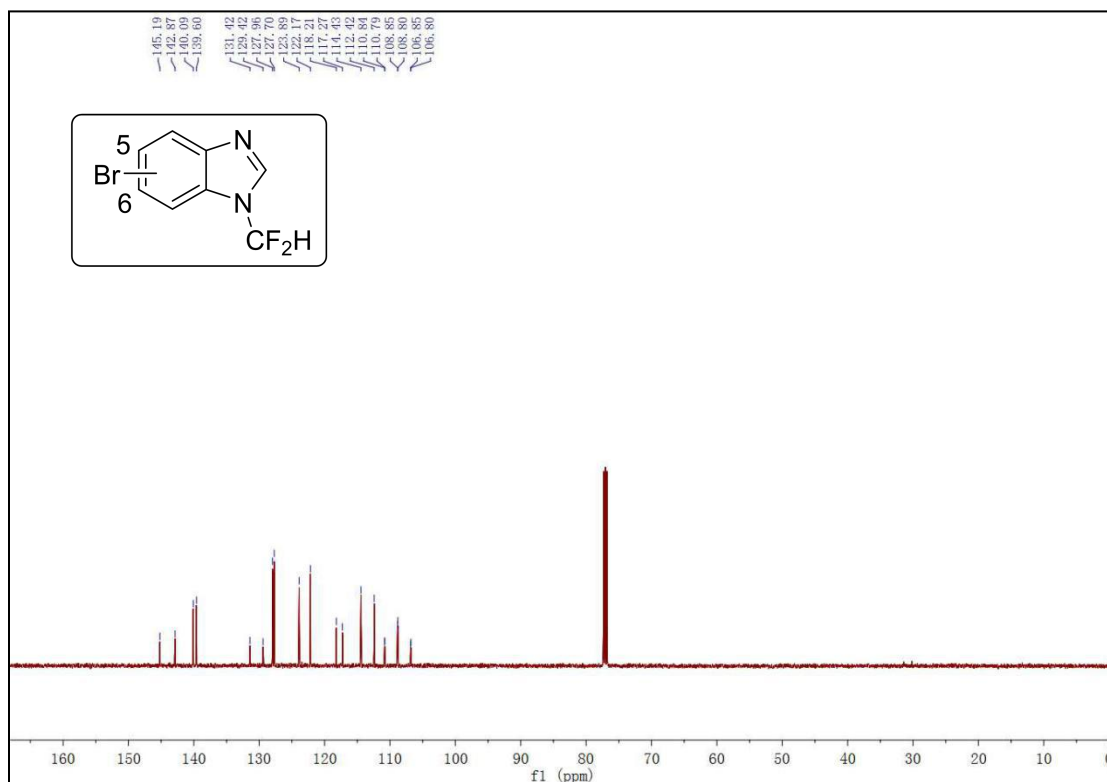


Figure S139.  $^{13}\text{C}$  NMR spectrum of 26, related to Figure 4

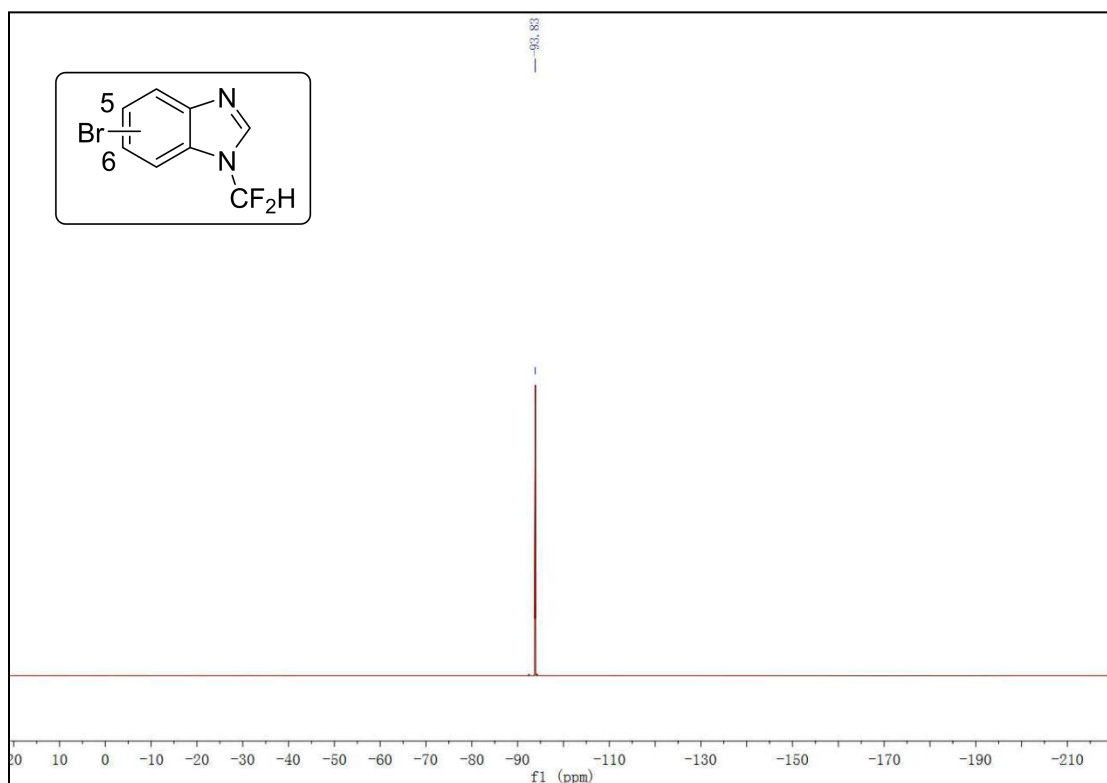


Figure S140.  $^{19}\text{F}$  NMR spectrum of 26, related to Figure 4

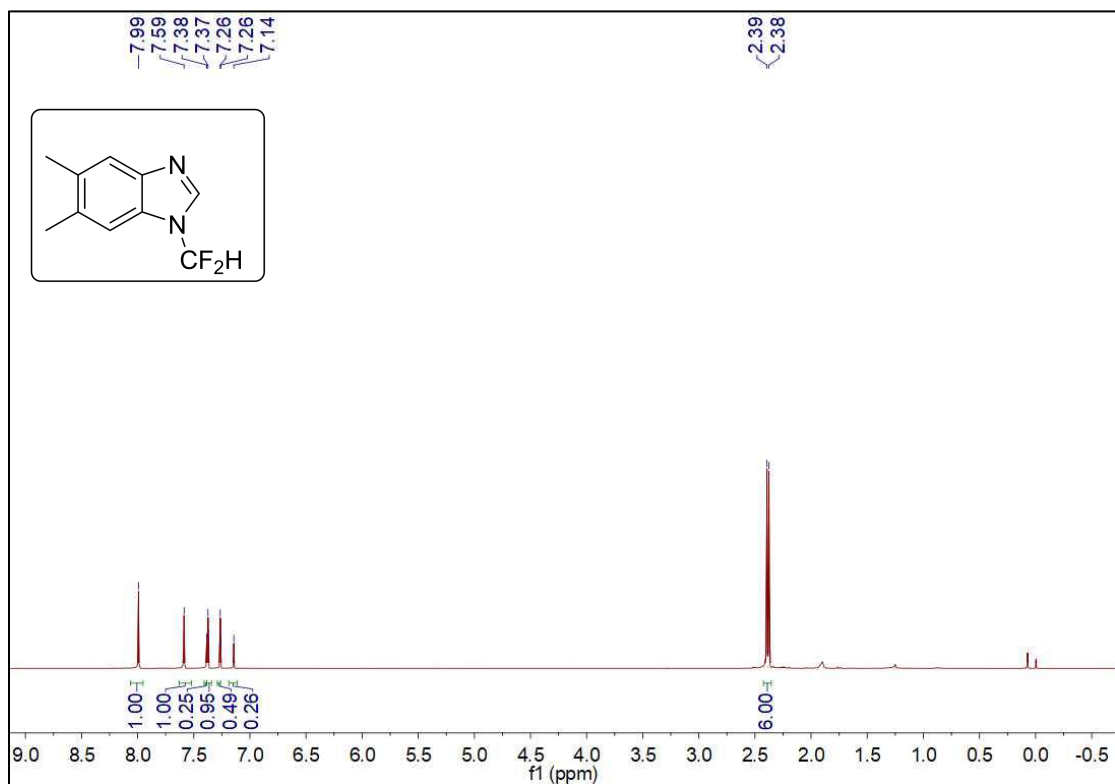


Figure S141.  $^1\text{H}$  NMR spectrum of 27, related to Figure 4

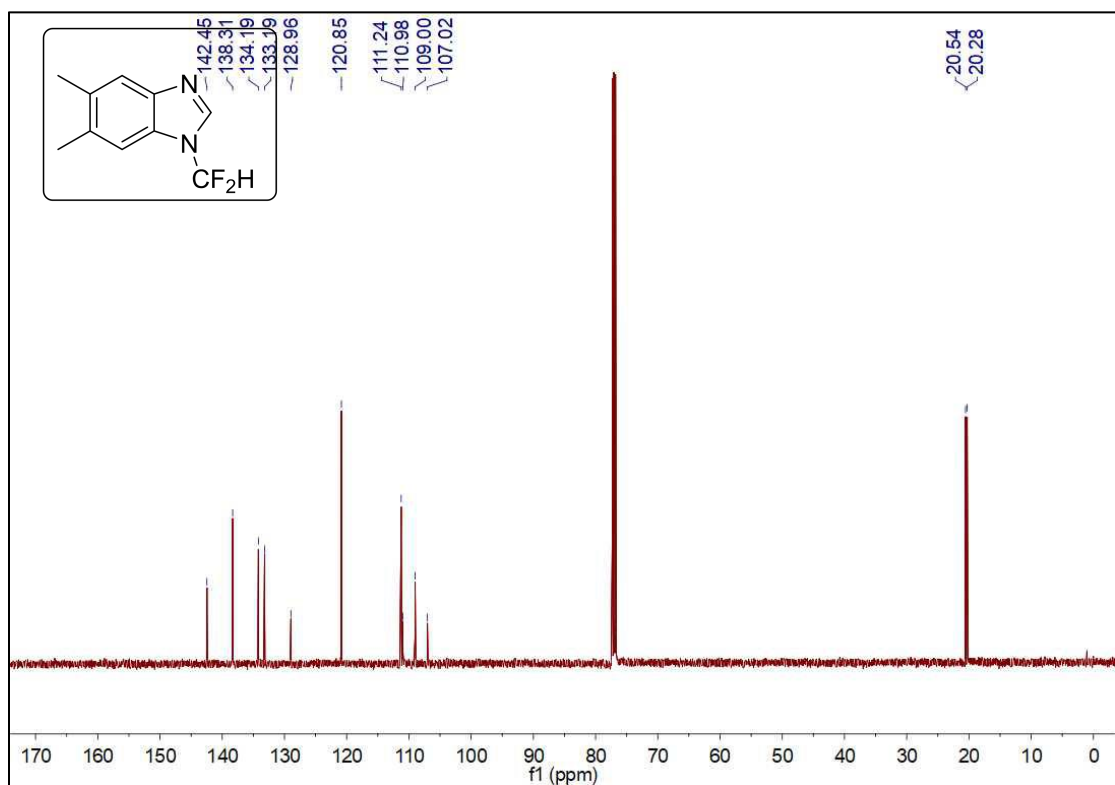


Figure S142.  $^{13}\text{C}$  NMR spectrum of 27, related to Figure 4

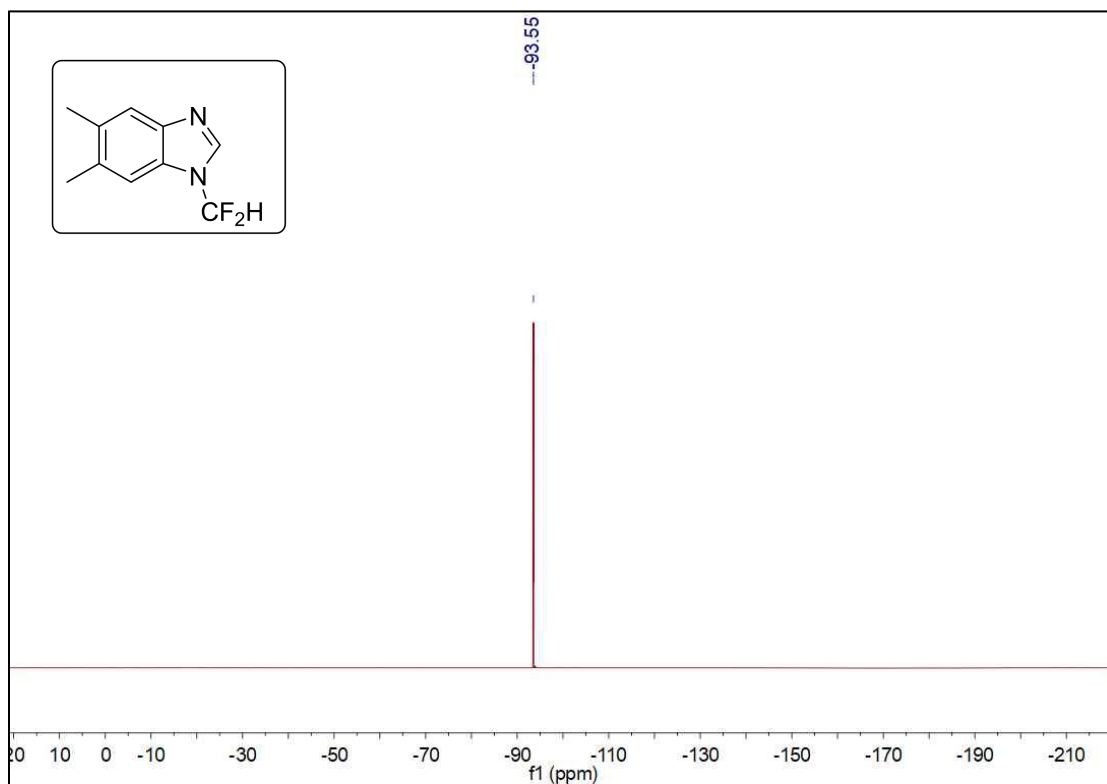


Figure S143.  $^{19}\text{F}$  NMR spectrum of 27, related to Figure 4

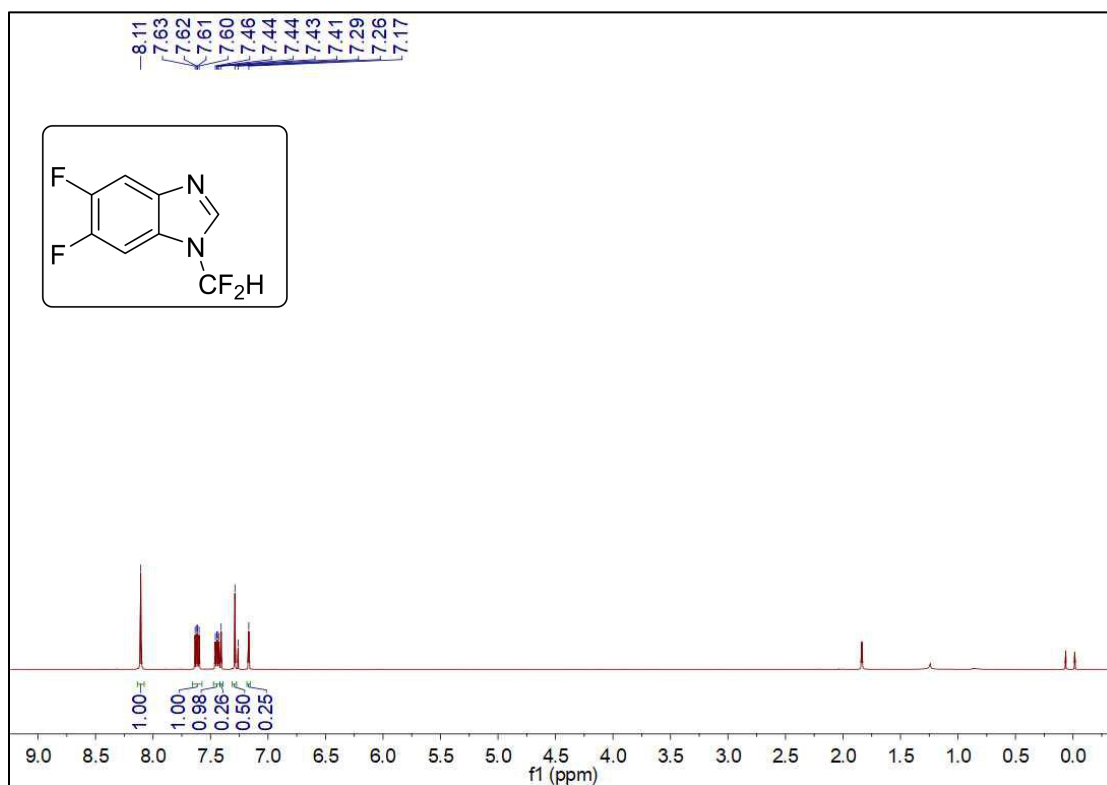
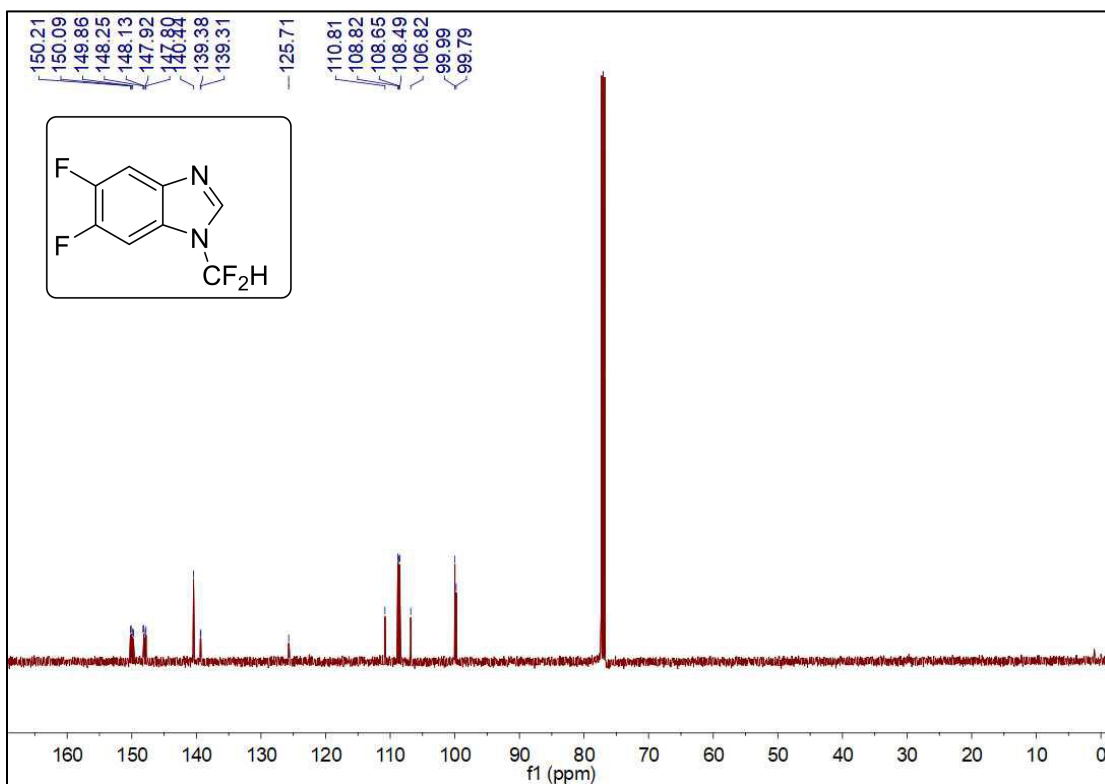
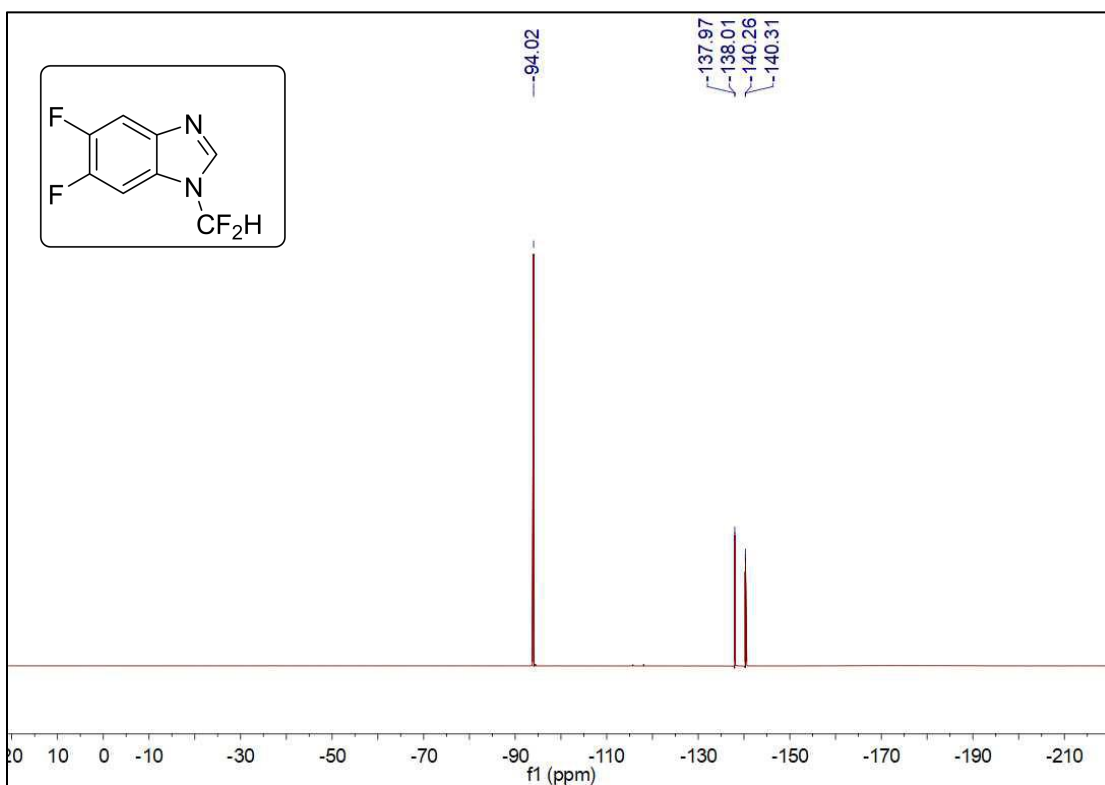


Figure S144.  $^1\text{H}$  NMR spectrum of 28, related to Figure 4



**Figure S145.** <sup>13</sup>C NMR spectrum of 28, related to Figure 4



**Figure S146.** <sup>19</sup>F NMR spectrum of 28, related to Figure 4



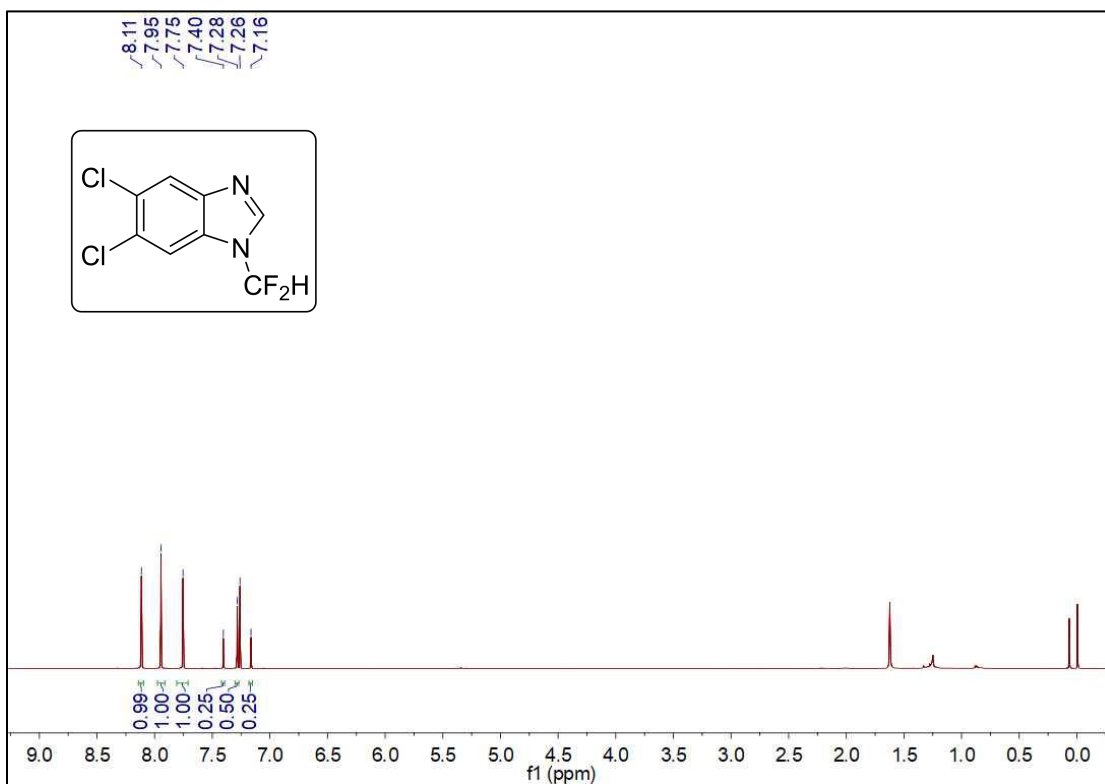


Figure S147. <sup>1</sup>H NMR spectrum of 29, related to Figure 4

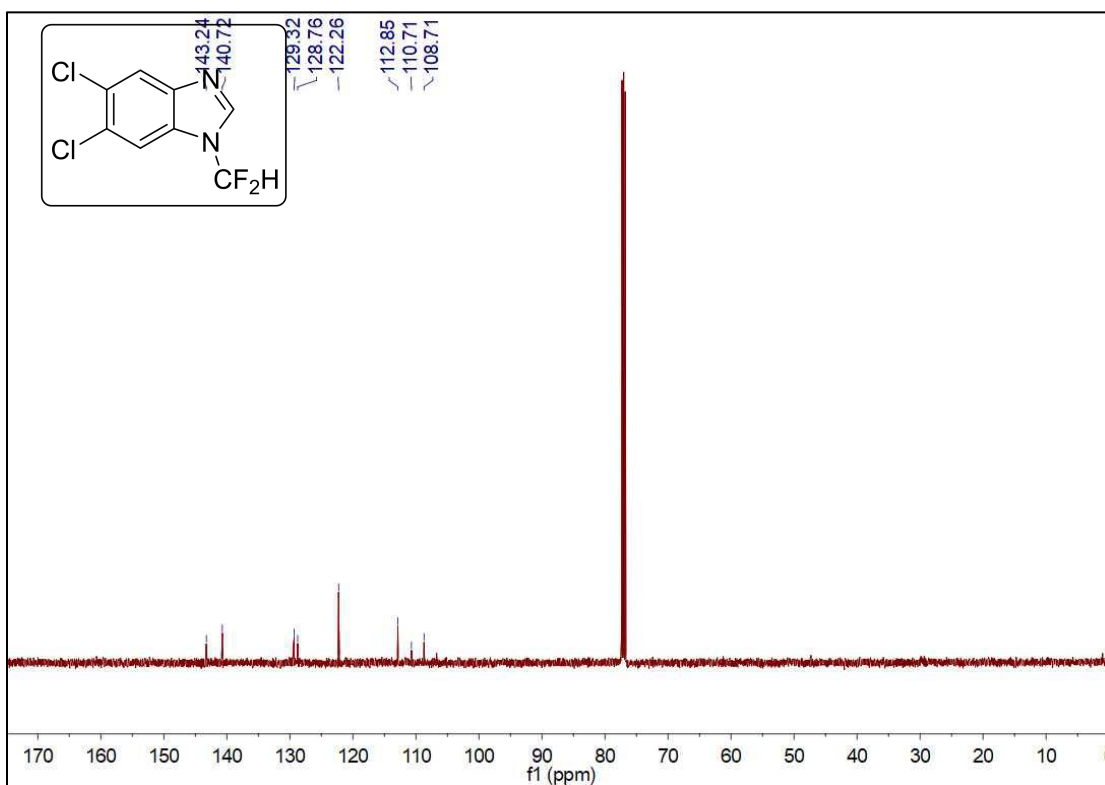


Figure S148. <sup>13</sup>C NMR spectrum of 29, related to Figure 4

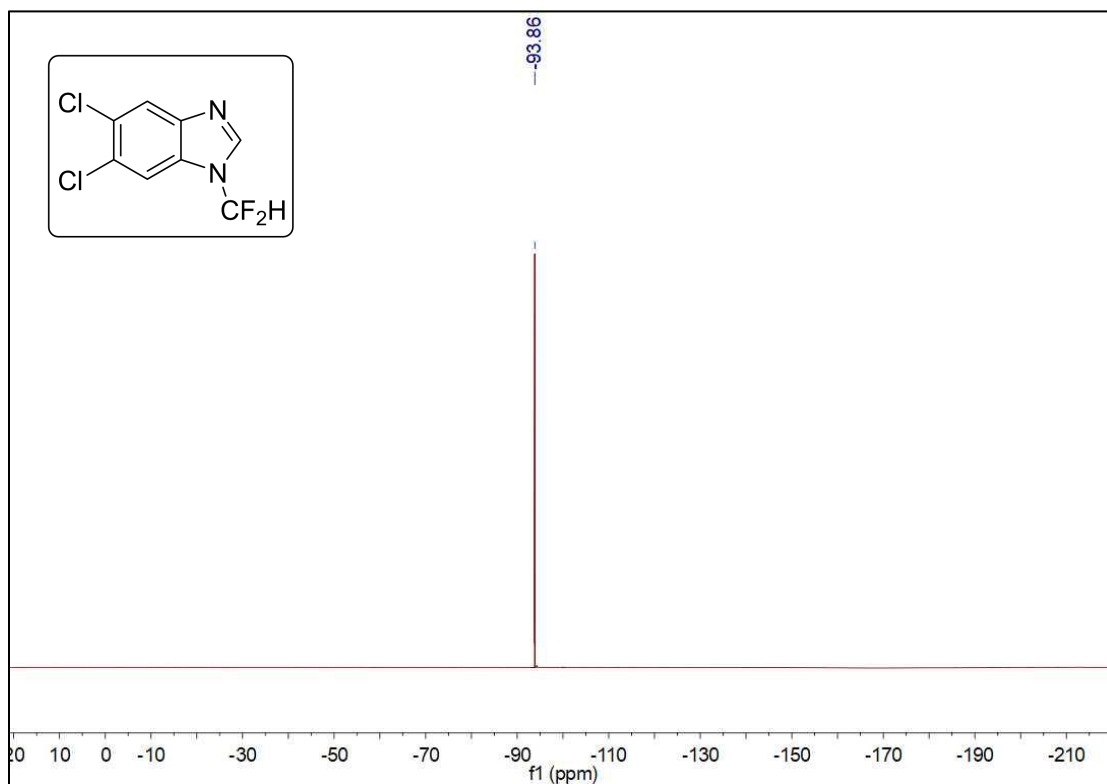


Figure S149.  $^{19}\text{F}$  NMR spectrum of 29, related to Figure 4

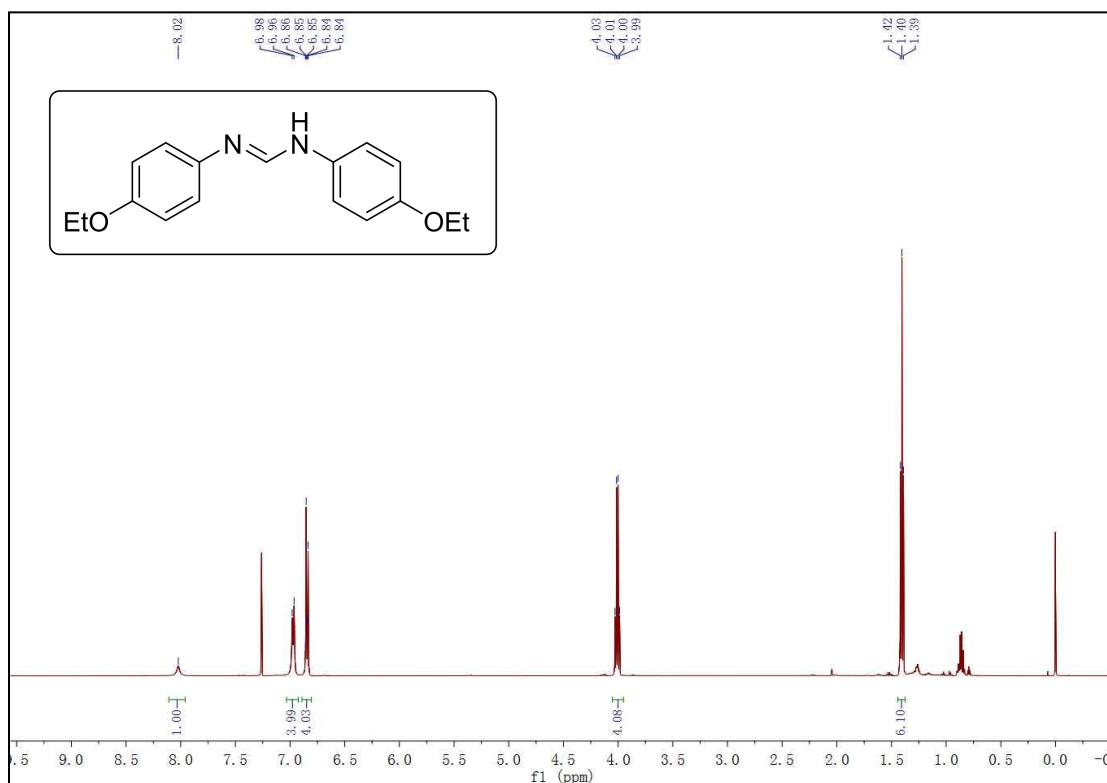


Figure S150.  $^1\text{H}$  NMR spectrum of 32, related to Figure 6

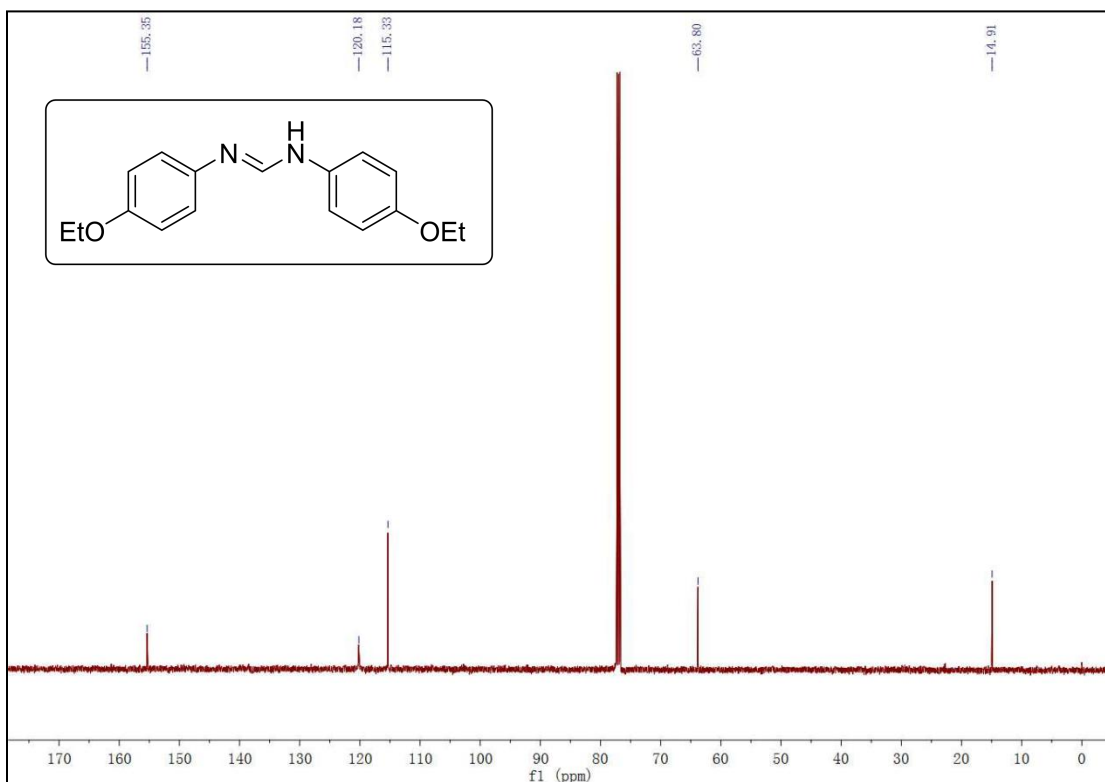


Figure S151. <sup>13</sup>C NMR spectrum of 32, related to Figure 6

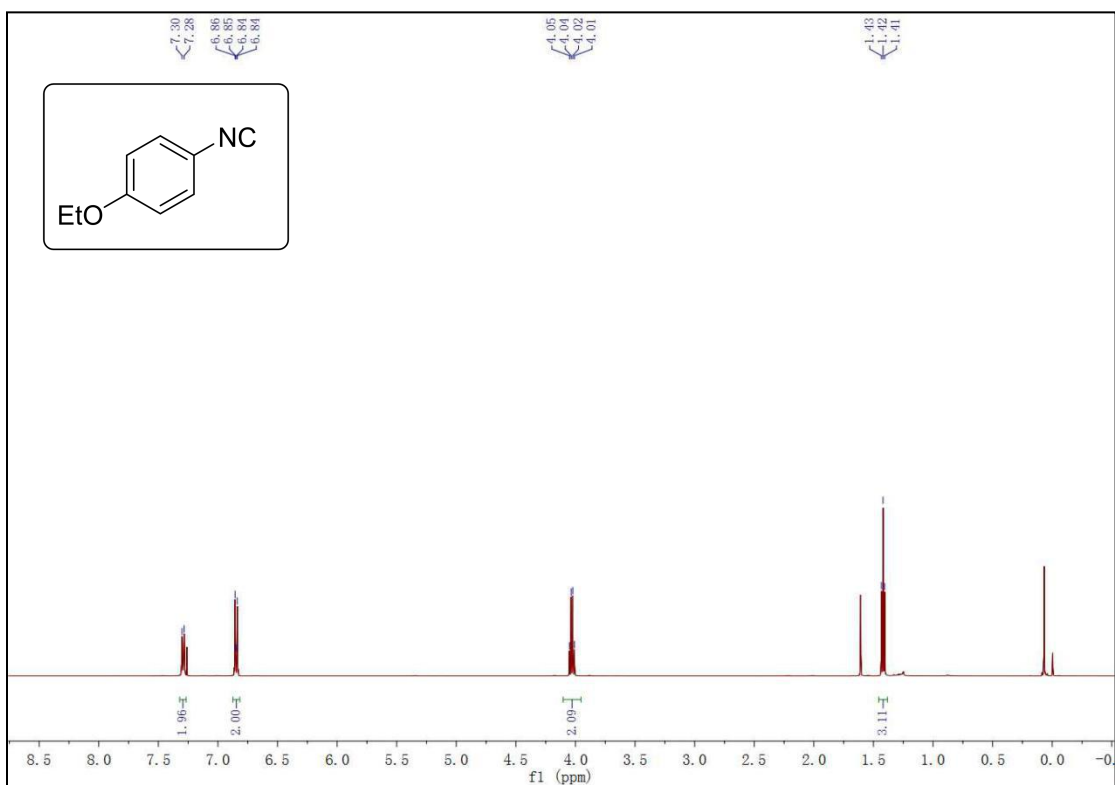


Figure S152. <sup>1</sup>H NMR spectrum of 33, related to Figure 6

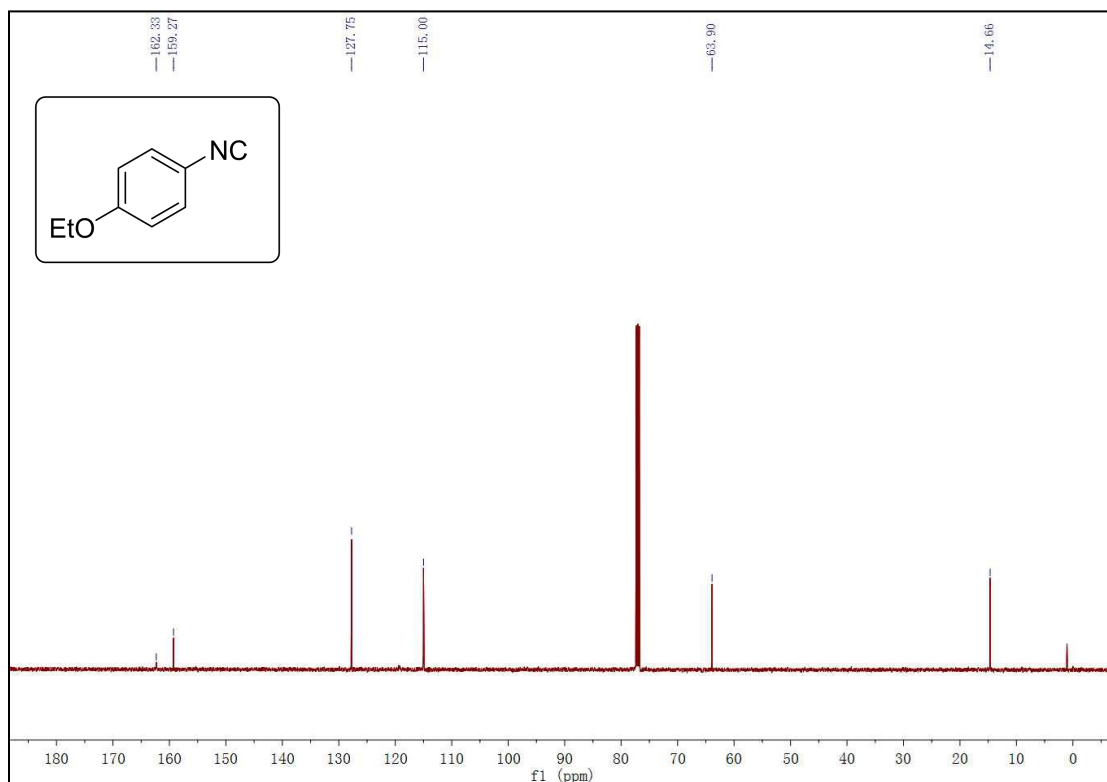


Figure S153. <sup>13</sup>C NMR spectrum of 33, related to Figure 6

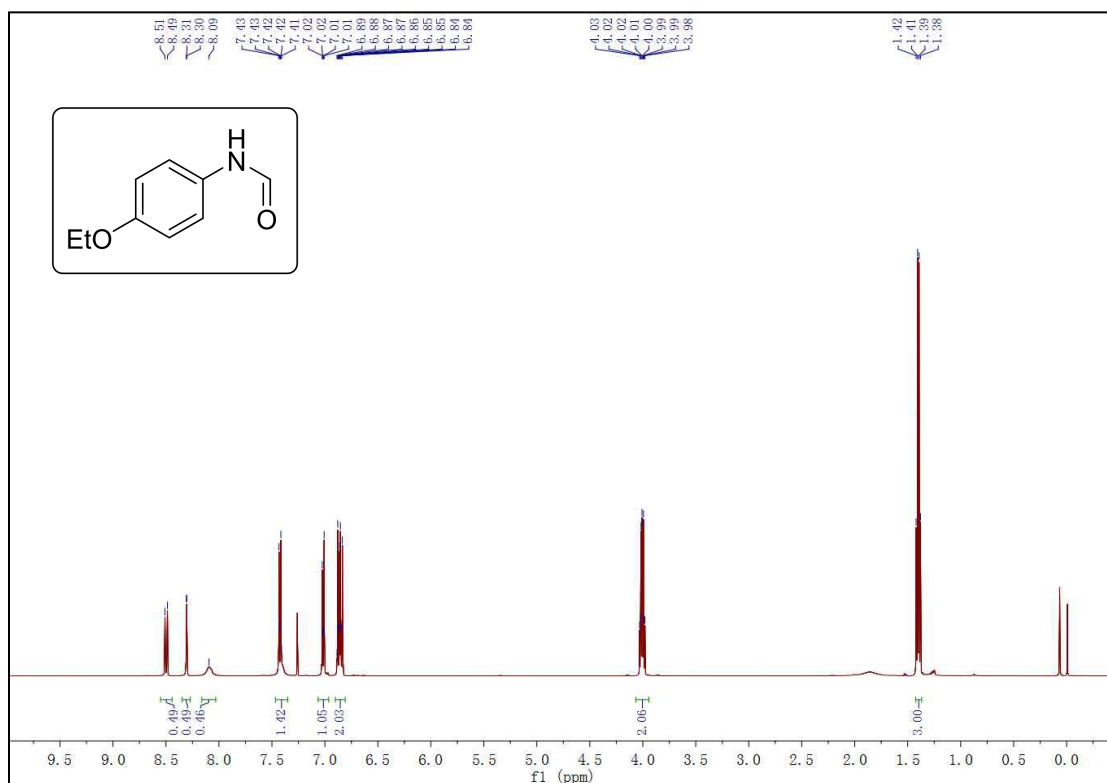
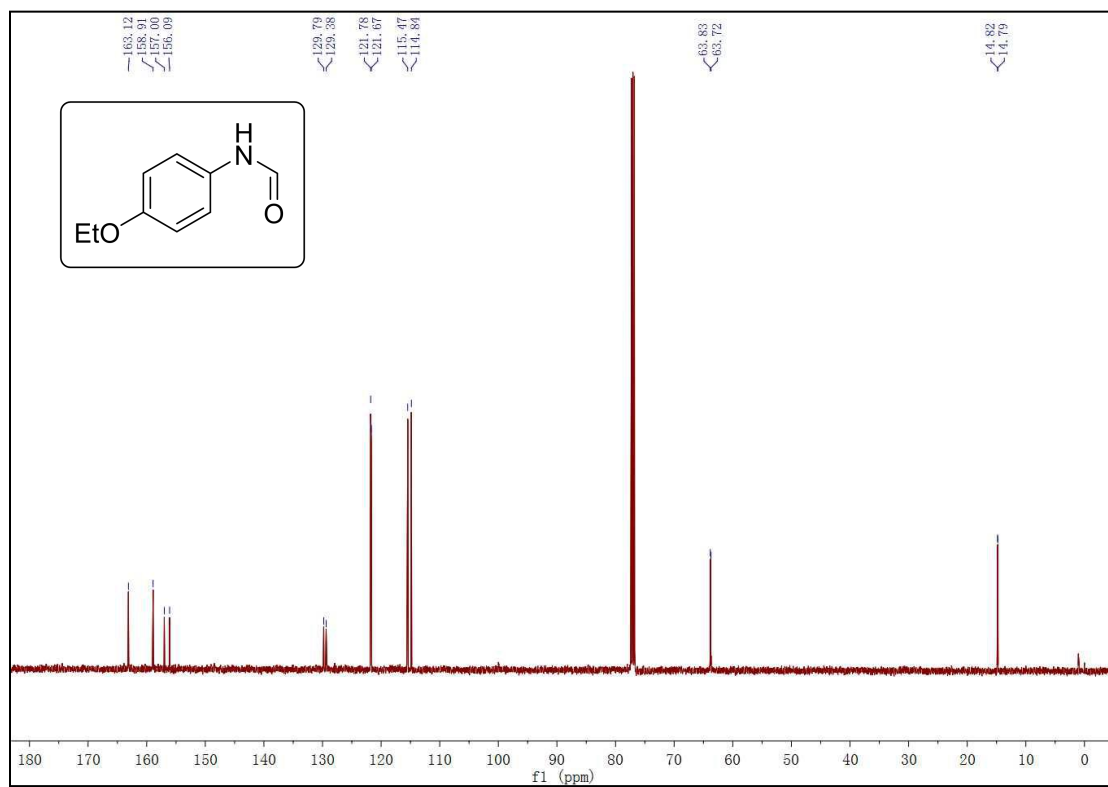


Figure S154. <sup>1</sup>H NMR spectrum of 34, related to Figure 6



**Figure S155.**  $^{13}\text{C}$  NMR spectrum of 34, related to Figure 6

## **Supplemental Item Legends**

**Table S1: Crystal data and structure refinement, related to Figure 2**

**Table S2. The effect of H<sub>2</sub>O for this process, related to Table 1**

**Table S3. The effect of base and solvent for this reaction, related to Table 1**

**Table S4. The optimization experiment conditions of 8, related to Figure 3C.**

**Table S5. The optimization experiment conditions of 10, related to Figure 3D.**

**Table S6. The optimization experiment conditions of 20a, related to Figure 4B.**

**Table S7. The optimization experiment conditions of 20g, related to Figure 4C.**

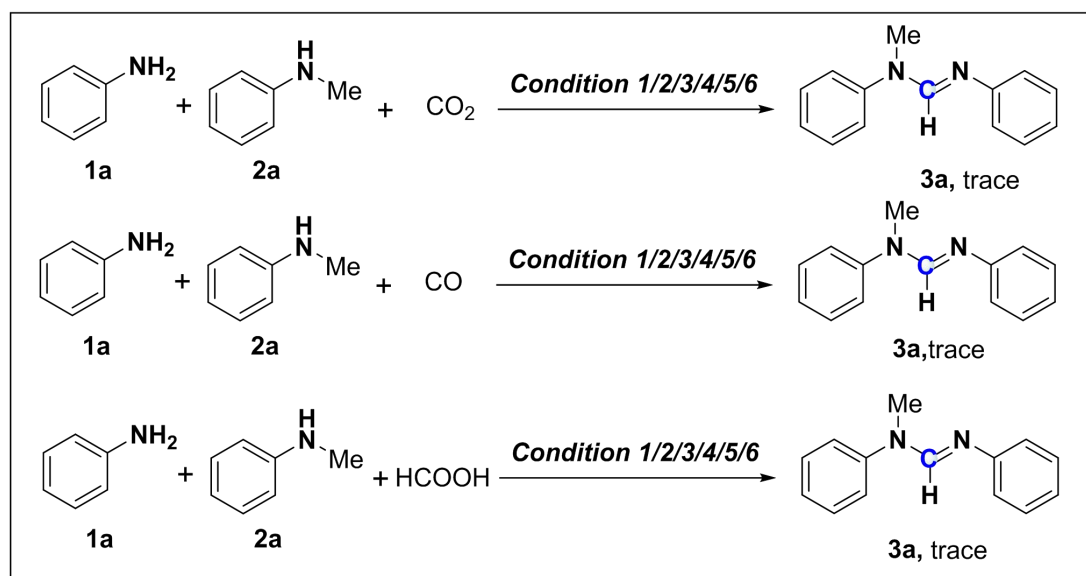
## Transparent Methods

### General Methods for Experiments

All chemicals were purchased from Adamas Reagent, Energy chemical company, Bide Pharmatech Ltd and Shang Fluoro company (ClCF<sub>2</sub>H). Unless otherwise stated, all experiments were conducted in a sealed tube under ClCF<sub>2</sub>H atmosphere. Reactions were monitored by TLC or GC-MS analysis. Flash column chromatography was performed over silica gel (200-300 mesh).

<sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were recorded in CDCl<sub>3</sub> and DMSO-d<sub>6</sub> on a Bruker Avance III 500 MHz NMR spectrometer (500 MHz <sup>1</sup>H, 125 MHz <sup>13</sup>C (CPD), 470 MHz <sup>9</sup>F (CPD)) at room temperature. Chemical shifts were reported in ppm on the scale relative to CDCl<sub>3</sub> (δ = 7.26 for <sup>1</sup>H-NMR, δ = 77.00 for <sup>13</sup>C-NMR) as an internal reference. Coupling constants (*J*) were reported in Hertz (Hz).

### General Procedure for the Transformations of CO<sub>2</sub>, CO and HCOOH as C1 sources.



**Reaction Condition 1:** the amine (**1a**, 0.12 mmol), *N*-metnyl amine (**2a**, 0.1 mmol), KOH (3 equiv), H<sub>2</sub>O (5 equiv), CH<sub>3</sub>CN (2 mL), (HCOOH 3 equiv) rt for 36 h under CO<sub>2</sub>/CO atmosphere.

**Reaction condition 2:** the amine (**1a**, 0.12 mmol), *N*-metnyl amine (**2a**, 0.1 mmol), K<sub>2</sub>CO<sub>3</sub> (3 equiv), phenol (10 mol%), H<sub>2</sub>O (5 equiv), CH<sub>3</sub>CN (2 mL), (HCOOH 3 equiv) 80 °C for 12 h under CO<sub>2</sub>/CO atmosphere.

**Reaction condition 3:** the amine (**1a**, 0.12 mmol), *N*-metnyl amine (**2a**, 0.1 mmol), Cs<sub>2</sub>CO<sub>3</sub> (3 equiv), S<sub>8</sub> (5 mol%), CH<sub>3</sub>CN (5 mL), (HCOOH 3 equiv) 80 °C for 26 h under CO<sub>2</sub>/CO atmosphere.

**Reaction Condition 4:** the amine (**1a**, 0.12 mmol), *N*-metnyl amine (**2a**, 0.1 mmol), K<sub>2</sub>CO<sub>3</sub> (3 equiv), H<sub>2</sub>O (5 equiv.), CH<sub>3</sub>CN (2 mL), (HCOOH 3 equiv) 50 °C for 12 h under CO<sub>2</sub>/CO atmosphere.

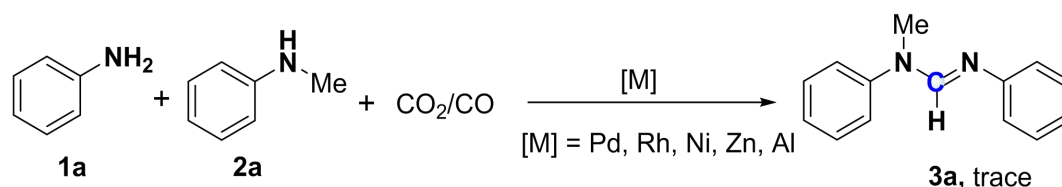
**Reaction Condition 5:** the amine (**1a**, 0.12 mmol), *N*-metnyl amine (**2a**, 0.1 mmol), K<sub>2</sub>CO<sub>3</sub> (3 equiv), H<sub>2</sub>O (0.5

mL), CH<sub>3</sub>CN (2 mL), (HCOOH 3 equiv) 100 °C for 16 h under the atmosphere of ClCF<sub>2</sub>H, isolated yield.

**Reaction Condition 6:** the amine (**1a**, 0.12 mmol), *N*-methyl amine (**2a**, 0.1 mmol), K<sub>2</sub>CO<sub>3</sub> (5 equiv), H<sub>2</sub>O (30 mL), CH<sub>3</sub>CN (2 mL), (HCOOH 3 equiv) 110 °C for 48 h under CO<sub>2</sub>/CO atmosphere.

**Scheme S1. The transformations of CO<sub>2</sub>, CO and HCOOH as C1 sources, related to Figure 1**

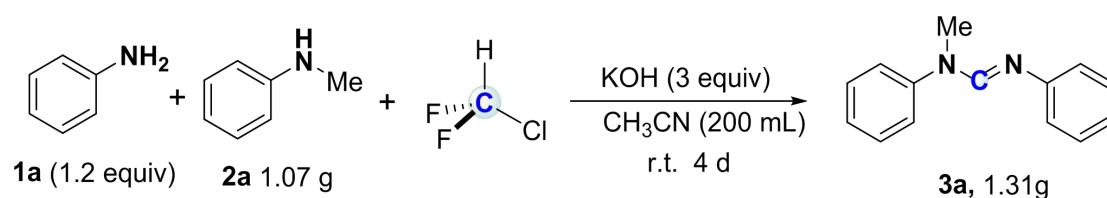
No desired product **3a** was obtained when we carried out many experiments by using CO<sub>2</sub>, CO and HCOOH as C1 sythons under *reaction conditions 1/2/3/4/5/6*.



**Scheme S2. the transformation for CO<sub>2</sub> and CO as C1 sources under transition metals, related to Figure 1**

In addition, various transformations for using CO<sub>2</sub> and CO as C1 sources in presence of transition metals (TM = Pd, Rh, Ni, Zn, Al) were also carried out according to the reported literature procedures (Tlili et al., 2015; Huang et al., 2011), unfortunately, no desired product **3a** was detected.

**General Procedure for Large-scale Reaction of the *N*-methyl Aniline (**2a**).**



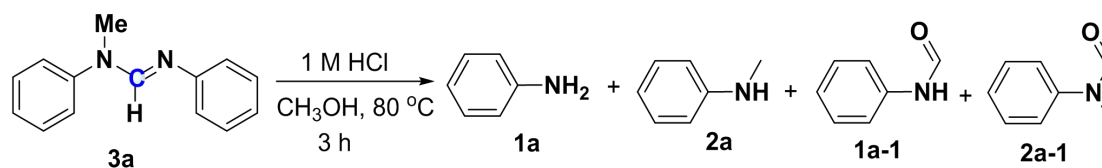
**Scheme S3. Large-scale reaction of the *N*-methyl aniline (**2a**), related to Figure 2**

**Large-scale reaction of the *N*-methyl aniline**

In a dried Schlenk round flask (1500 mL) were placed amine **1a** (12 mmol, 1.2 equiv, 1.1 g), *N*-methyl amine **2a** (10 mmol, 1 equiv, 1.07 g) and KOH (30 mmol, 3 equiv, 1.7 g). Then the flask was filled with ClCF<sub>2</sub>H. Whereafter the solvent was added into Schlenk tube by injector. The resulting mixture was stirred at room temperature for 4 days. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatograph (silica gel, Petroleum ether : Ethyl acetate = 50:1, v/v) to give the desired product **3a** (62%, 1.31 g).



### General Procedure for the Experiment for the Decomposition of Target Product.

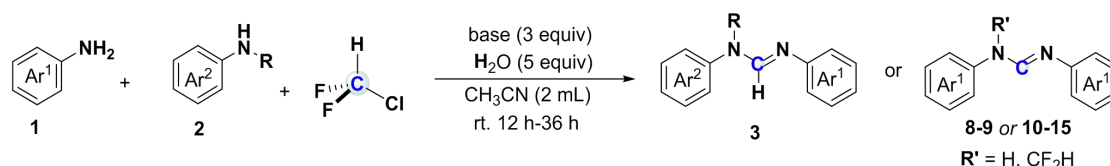


Scheme S4. The experiment for the decomposition of target product, related to Figure 3B

### The Decomposition of Target Product 3a

To a mixture of (*E*)-*N*-methyl-*N,N'*-diphenylformimidamide **3a** (0.2 mmol) in MeOH (2 mL), 1 M HCl was added to the seal tube. The resulting mixture was stirred at 80 °C for 3 h. Upon completion of the reaction, the compounds **1a**, **2a**, **1a-1** and **2a-1** were detected via TLC and GC-MS.

### General Procedure for the synthesis of 3, 8-9 and 10-15.



Scheme S5. General process for the synthesis of 3, 8-9 and 10-15, related to Figure 2, Figure 3C and Figure 3D.

### Preparations of target product 3

In a dried Schlenk tube were placed the primary amines **1** (0.12 mmol, 1.2 equiv), the secondary aniline **2** (0.1 mmol), KOH (0.3 mmol, 3 equiv) and H<sub>2</sub>O (0.5 mmol, 5 equiv). Then the tube was vacuumized for removing the air. Subsequently, chlorodifluoromethane and CH<sub>3</sub>CN (2 mL) were added into the mixtures via an injector. The resulting mixture was stirred at room temperature for 36 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, Petroleum ether : Ethyl acetate = 80:1, v/v) to give the desired product (**3**).

### Preparations of target product 8 and 9

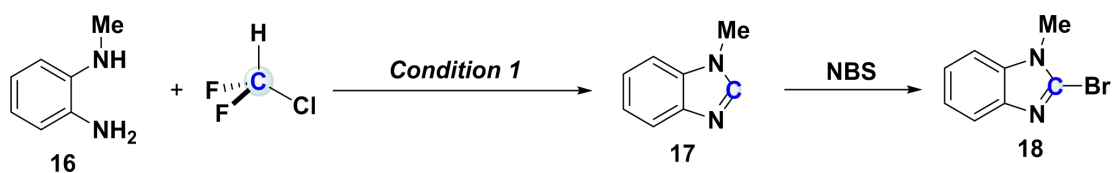
In a dried Schlenk tube were placed the anilines **1** (0.2 mmol, 1.2 equiv), K<sub>2</sub>CO<sub>3</sub> (0.6 mmol, 3 equiv), phenol (0.02 mmol, 10 mol%) and H<sub>2</sub>O (1 mmol, 5 equiv), Then the tube was vacuumized for removing the air. Subsequently, chlorodifluoromethane and CH<sub>3</sub>CN (2 mL) were added into the mixtures via an injector. The resulting mixtures

was stirred at 80 °C for 12 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, Petroleum ether : Ethyl acetate = 50:1, v/v) to give the desired product (**8-9**).

### Preparations of target product 10-15

In a dried Schlenk tube were placed the aniline **1** (0.2 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.6 mmol, 3 equiv), S<sub>8</sub> (0.02 mmol, 10 mol%) and H<sub>2</sub>O (1 mmol, 5 equiv), Then the tube was vacuumized for removing the air. Subsequently, chlorodifluoromethane and CH<sub>3</sub>CN (5 mL) is added into the mixtures via an injector. The resulting mixture was stirred at 80 °C for 26 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, Petroleum ether : Ethyl acetate = 100:1, v/v) to give the desired product (**10-15**).

### General Procedure for the Large-scale Synthesis of 18



Scheme S6. General process for the large-scale synthesis of **18**, related to Figure 4A.

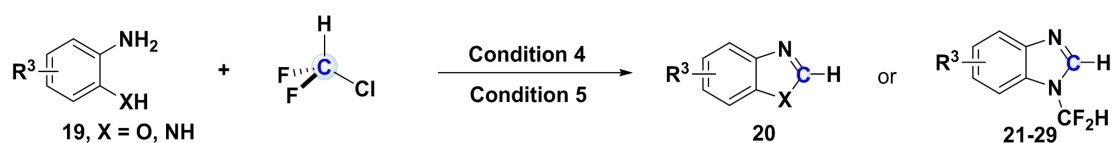
### Preparations of target product 17

In a dried Schlenk tube were placed *N*<sup>1</sup>-methylbenzene-1,2-diamine **16** (7 mmol), KOH (21 mmol, 3 equiv) and H<sub>2</sub>O (35 mmol, 5 equiv), Then the tube was vacuumized for removing the air. Subsequently, chlorodifluoromethane and solvent is added into the mixtures via an injector. The resulting mixture was stirred at room temperature for 48 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, Petroleum ether : Ethyl acetate = 10:1, v/v) to give the desired product **17** in 78% yield.

### Preparations of target product 18

Methylbenzimidazole (**17**) (5 mmol) and *N*-bromosuccinimide (15 mmol) in 30 mL of THF were heated under reflux for 1 h. The solvent was removed by a rotary evaporator, and the residue was recrystallized from EtOAc to afford **18** in 90% yield as a white solid.

### General process for the synthesis of 20 and 21-29.



Scheme S7. General process for the synthesis of 20 and 21-29, related to Figure 4B-4D.

### Preparations of target products 20a-20d, 20e' and 20f'

In a dried Schlenk tube were placed 2-aminophenol compounds (**19a-19f**) (0.2 mmol), K<sub>2</sub>CO<sub>3</sub> (0.6 mmol, 3 equiv) and H<sub>2</sub>O (1 mmol, 5equiv). Then the tube was vacuumized for removing the air. Subsequently, chlorodifluoromethane and CH<sub>3</sub>CN (2 mL) is added into the mixtures via an injector. The resulting mixture was stirred at 50 °C for 12 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, Petroleum ether : Ethyl acetate = 100:1, v/v) to give the desired product.

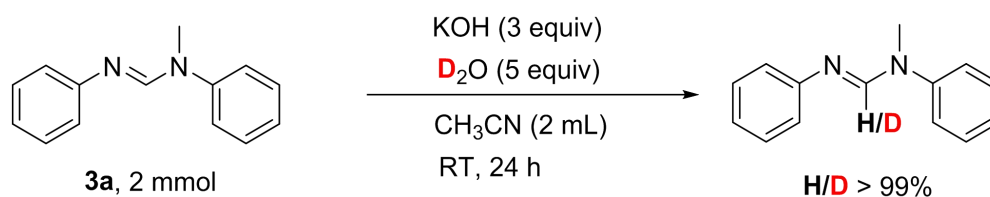
### Preparations of target products 20g-20o

In a dried Schlenk tube were placed benzene-1,2-diamine compounds (0.2 mmol), K<sub>2</sub>CO<sub>3</sub> (0.6 mmol, 3 equiv) and H<sub>2</sub>O (0.5 mL). Then the tube was vacuumized for removing the air. Subsequently, chlorodifluoromethane and CH<sub>3</sub>CN (2 mL) is added into the mixtures via an injector. The resulting mixture was stirred at 100 °C for 16 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, Petroleum ether : Ethyl acetate = 10:1, v/v) to give the desired product.

### Preparations of target products 21-29

In a dried Schlenk tube were placed benzene-1,2-diamine compounds (0.1 mmol), K<sub>2</sub>CO<sub>3</sub> (0.5 mmol, 5 equiv) and H<sub>2</sub>O (0.5 mL). Then the tube was vacuumized for removing the air. Subsequently, chlorodifluoromethane and CH<sub>3</sub>CN (2 mL) is added into the mixtures via an injector. The resulting mixture was stirred at 100 °C for 48 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, Petroleum ether : Ethyl acetate = 50:1, v/v) to give the desired product **21-29**.

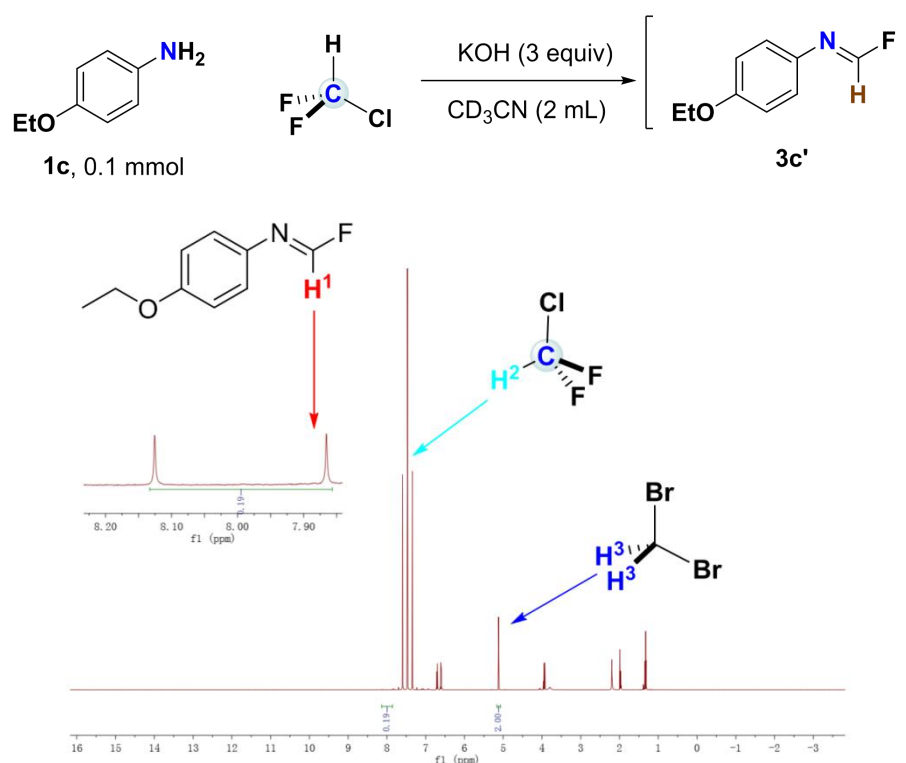
### The experiment for H-scrambling of the target product 3a



**Scheme S8.** The experiment for H-scrambling of the target product **3a**, related to Figure 5a-5b

We carried out a H-scrambling experiment by exposing the product **3a** to the standard condition in the presence of  $D_2O$ . No corresponding deuterium-labeling product **3a-D** was detected (Scheme S8).

### In-situ $^1H$ NMR of **3c'**

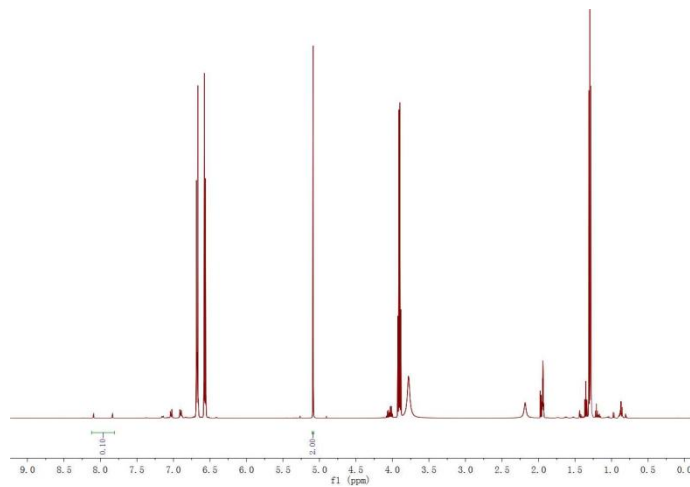


**Scheme S9.** In-situ  $^1H$  NMR of **3c'**, related to Figure 6A.

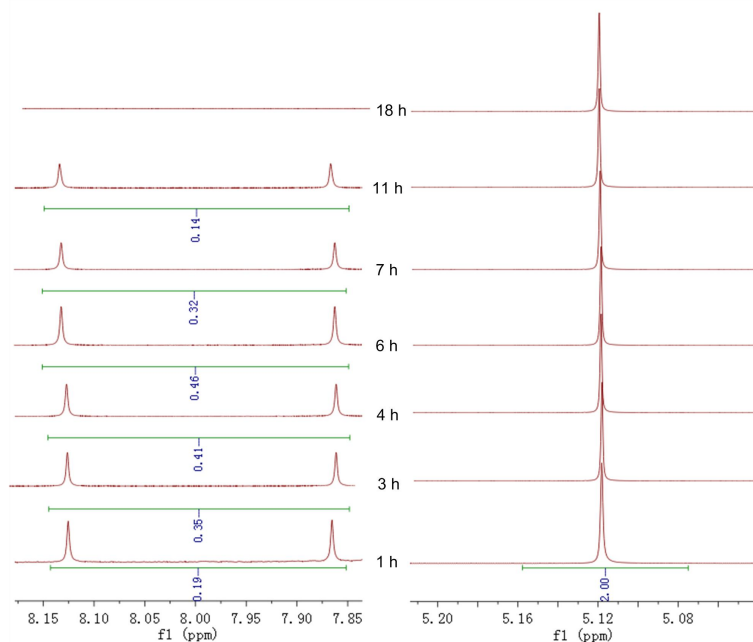
### General Procedure for In-situ $^1H$ NMR of **3c'**

There still is plentiful  $ClCF_2H$  dissolved in solvent ( $CD_3CN$ ) in the first couple of hours, which caused a problem to detect compound **3c'** by NMR analysis (Scheme S9-S11). In order to see  $^1H$  peak of compound **3c'** more clearly, we carried out an experiment for about 1 hour and stripped the excess  $ClCF_2H$  at low temperature, the

resulting mixture was analyzed by in situ NMR. The below figure has shown the change of possible reactive intermediate at different time.

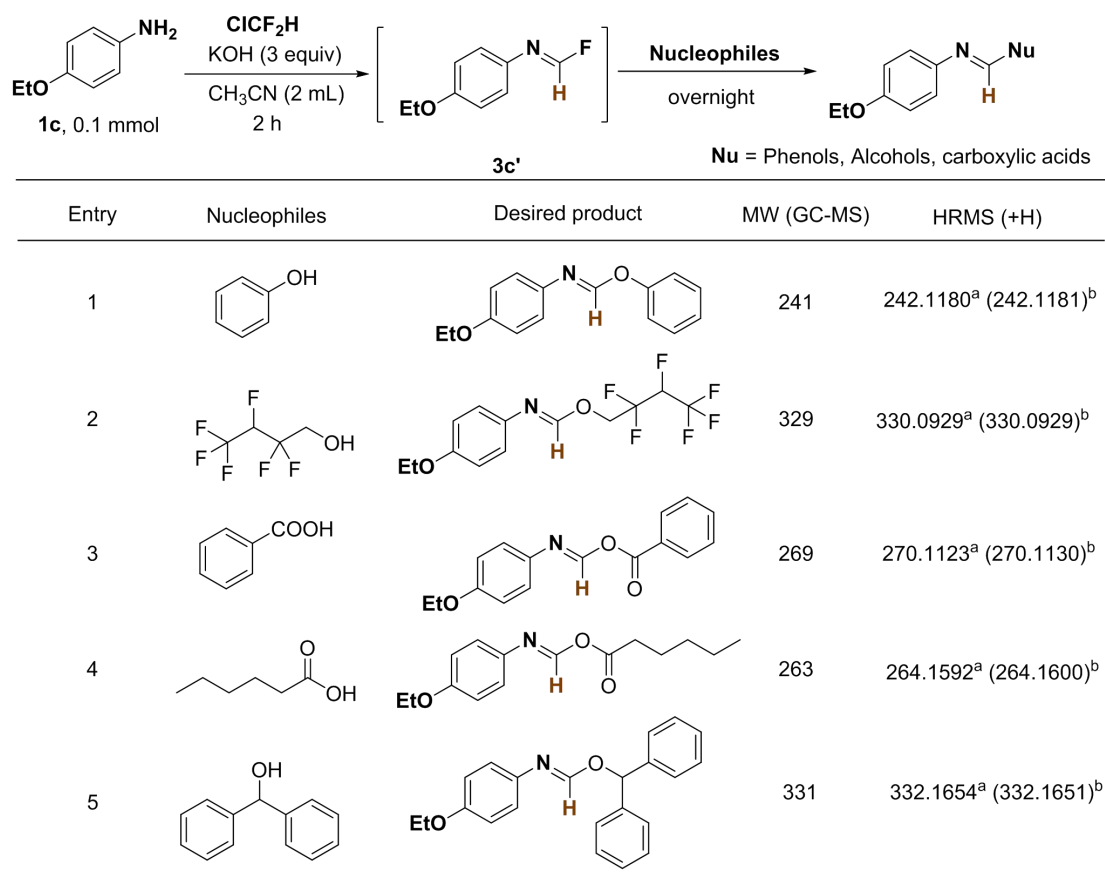


**Scheme S10. In-situ <sup>1</sup>H NMR of 3c', related to Figure 6A.**



**Scheme S11. the change of possible reactive intermediate at different time, related to Figure 6A.**

## The experiments for capturing of reaction intermediate 3c'



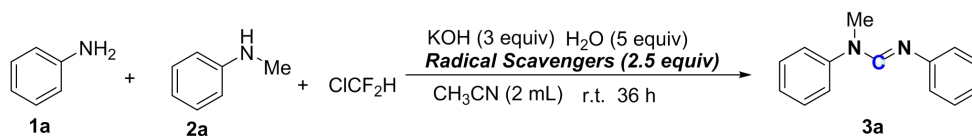
<sup>a</sup> HRMS (ESI, m/z) found; <sup>b</sup> HRMS (ESI, m/z) calcd

### Scheme S12. Various nucleophiles for capturing 3c', related to Figure 6B.

#### General Procedure for various nucleophiles for capturing 3c'

In order to validate the presence of the compound 3c', various nucleophiles, such as phenols, 1,1,2,3,3,3-hexafluoropropan-1-ol, benzoic acid, hexanoic acid and diphenylmethanol were added into the system after 2 h (entries 1-5), the corresponding desired products were detected by GC-MS (MW : 241, 329, 269, 263 and 331). In addition, we conducted the tests of HRMS (ESI, m/z). Delightedly, we detected corresponding m/z of various anticipated products (Scheme S12).

## The experiments for capturing of radical



Entry	Radical Scavengers	Yield of 3a (iso.)
1	TEMPO	79%
2	BHT	57%
3	ethene-1,1-diyldibenzene	85%
4	(1-cyclopropylvinyl)benzene	82%

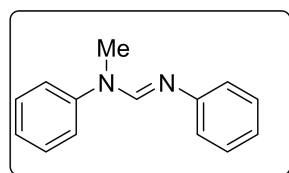
TEMPO: CN1C(C)CC1[O]  
 BHT: Cc1cc(C(C)(C)O)c(C(C)(C)C)cc1C(C)(C)C  
 ethene-1,1-diyldibenzene: C=Cc1ccccc1c2ccccc2  
 (1-cyclopropylvinyl)benzene: C=C1CC1c2ccccc2

**Scheme S13.** The experiments for capturing of radical, related to Figure 6C.

We have carried out the control experiments in presence of radical scavengers (TEMPO, BHT, ethene-1,1-diyldibenzene and (1-cyclopropylvinyl)benzene), the reactions proceeded smoothly at room temperature to afford desired products in moderate yields. Those results suggest the SET pathway could not be involved in this transformation.

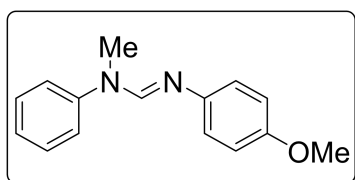
## Characterization data for products

**(E)-N-methyl-N,N'-diphenylformimidamide (3a) (CAS number: 32189-59-6)**



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg, 88%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.11 (s, 1H), 7.41 – 7.35 (m, 2H), 7.34 – 7.29 (m, 2H), 7.20 – 7.12 (m, 3H), 7.11 – 7.00 (m, 3H), 3.52 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 151.5, 151.2, 145.1, 129.5, 129.1, 124.1, 123.4, 121.3, 119.9, 34.1.

**(E)-N'-(4-methoxyphenyl)-N-methyl-N-phenylformimidamide (3b)**

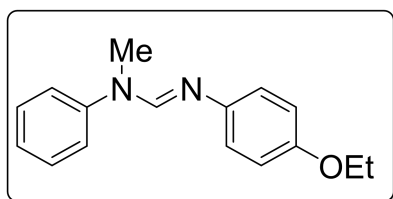


The reaction was performed following the general

procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (20 mg, 82%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.09 (s, 1H), 7.37 (dd, *J* = 8.6, 7.4 Hz, 2H), 7.18 – 7.11 (m, 3H), 7.01 – 6.96 (m, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 3.50 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 156.1, 150.7, 145.2, 144.8, 129.5, 123.9, 121.9, 119.7, 114.4, 55.5, 34.0.

HRMS (ESI, *m/z*) calcd for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O[M+H]<sup>+</sup>: 241.1335; found: 241.1337

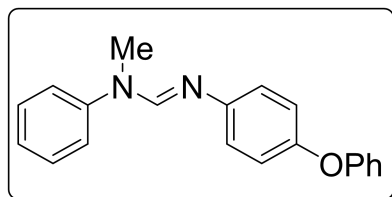
### **(*E*)-*N'*-(4-ethoxyphenyl)-*N*-methyl-*N*-phenylformimidamide (3c)**



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (22 mg, 85%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.09 (s, 1H), 7.37 (dd, *J* = 8.4, 7.5 Hz, 2H), 7.20 – 7.10 (m, 3H), 7.02 – 6.94 (m, 2H), 6.91 – 6.81 (m, 2H), 4.01 (q, *J* = 7.0 Hz, 2H), 3.50 (s, 3H), 1.41 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 155.5, 150.6, 145.2, 144.6, 129.5, 123.99, 121.9, 119.7, 115.1, 63.7, 34.1, 15.0.

HRMS (ESI, *m/z*) calcd for C<sub>16</sub>H<sub>19</sub>N<sub>2</sub>O[M+H]<sup>+</sup>: 255.1492; found: 255.1491.

### **(*E*)-*N*-methyl-*N'*-(4-phenoxyphenyl)-*N*-phenylformimidamide (3d)**

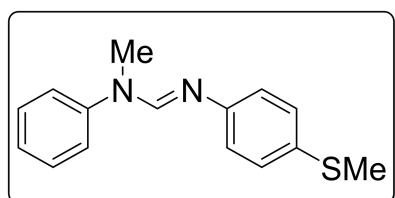


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (24 mg, 81%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.11 (s, 1H), 7.41 – 7.35 (m, 2H), 7.34 – 7.28 (m, 2H), 7.19 – 7.13 (m, 3H), 7.09 – 6.96 (m, 7H), 3.52 (s, 3H). <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>) δ 158.22 (s), 152.9, 151.0, 147.4, 145.1, 129.6, 124.2, 122.6, 122.2, 120.3, 119.9, 118.0, 34.1.

HRMS (ESI, *m/z*) calcd for C<sub>20</sub>H<sub>19</sub>N<sub>2</sub>O[M+H]<sup>+</sup>: 303.1492; found: 303.1491

### **(*E*)-*N*-methyl-*N'*-(4-(methylthio)phenyl)-*N*-phenylformimidamide**

#### **(3e)**

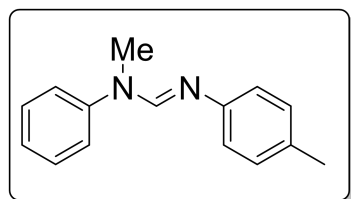


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (21 mg, 83%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.08 (s, 1H), 7.38 (dd, *J* = 8.6, 7.4 Hz, 2H), 7.26 – 7.22 (m, 2H), 7.19 – 7.12 (m, 3H), 7.03 – 6.95 (m, 2H), 3.51 (s, 3H), 2.47 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 151.0, 149.3, 145.0, 132.1, 129.5, 128.8, 124.3, 121.8, 120.0, 34.2, 17.2.



HRMS (ESI, m/z) calcd for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>S[M+H]<sup>+</sup>: 257.1107; found: 257.1109.

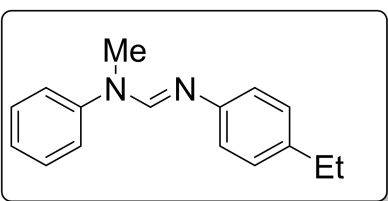
### (*E*)-*N*-methyl-*N*-phenyl-*N'*-(*p*-tolyl)formimidamide (**3f**)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg, 86%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.10 (s, 1H), 7.42 – 7.33 (m, 2H), 7.20 – 7.06 (m, 5H), 7.00 – 6.90 (m, 2H), 3.51 (s, 3H), 2.33 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 150.9, 149.0, 145.2, 132.8, 129.7, 129.5, 124.0, 121.0, 119.8, 34.1, 20.9.

HRMS (ESI, m/z) calcd for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>[M+H]<sup>+</sup>: 225.1386; found: 225.1388.

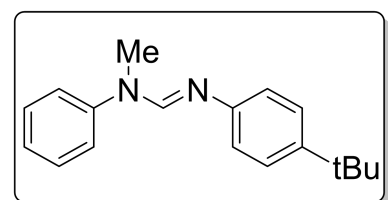
### (*E*)-*N'*-(4-ethylphenyl)-*N*-methyl-*N*-phenylformimidamide (**3g**)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (20 mg, 83%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.11 (s, 1H), 7.41 – 7.30 (m, 2H), 7.20 – 7.08 (m, 5H), 7.03 – 6.92 (m, 2H), 3.51 (s, 3H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 150.9, 149.1, 145.2, 139.3, 129.5, 128.5, 124.0, 121.1, 119.8, 34.1, 28.3, 15.8.

HRMS (ESI, m/z) calcd for C<sub>16</sub>H<sub>19</sub>N<sub>2</sub>[M+H]<sup>+</sup>: 239.1543; found: 239.1543.

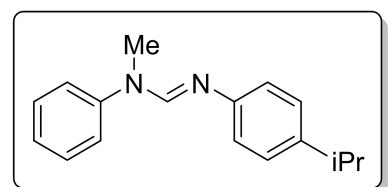
### (*E*)-*N'*-(4-(*tert*-butyl)phenyl)-*N*-methyl-*N*-phenylformimidamide (**3h**)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (21 mg, 79%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.12 (s, 1H), 7.41 – 7.29 (m, 4H), 7.20 – 7.09 (m, 3H), 7.03 – 6.91 (m, 2H), 3.51 (s, 3H), 1.33 (s, 9H). <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>) δ 150.9, 148.8, 146.2, 145.2, 129.5, 126.0, 123.9, 120.7, 119.7, 34.3, 34.0, 31.5.

HRMS (ESI, m/z) calcd for C<sub>18</sub>H<sub>23</sub>N<sub>2</sub>[M+H]<sup>+</sup>: 267.1856; found: 267.1853.

### (*E*)-*N'*-(4-isopropylphenyl)-*N*-methyl-*N*-phenylformimidamide (**3i**)

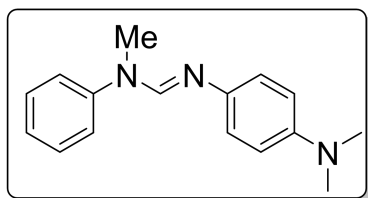


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (22 mg, 86%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.11 (s, 1H), 7.41 – 7.32 (m, 2H), 7.19 – 7.10 (m, 5H), 7.01 – 6.93 (m, 2H), 3.51 (s, 3H), 2.89 (dt, *J*

= 13.8, 6.9 Hz, 1H), 1.25 (d,  $J$  = 6.9 Hz, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  150.9, 149.2, 145.2, 143.9, 129.4, 127.0, 123.9, 121.0, 119.7, 34.0, 33.5, 24.2.  
HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{17}\text{H}_{21}\text{N}_2[\text{M}+\text{H}]^+$ : 253.1699; found: 253.1701.

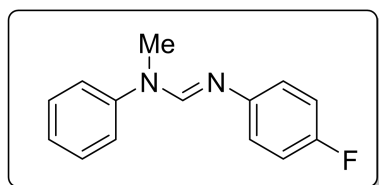
### **(E)-N'-(4-(dimethylamino)phenyl)-N-methyl-N-phenylformimidamide**

**(3j)**



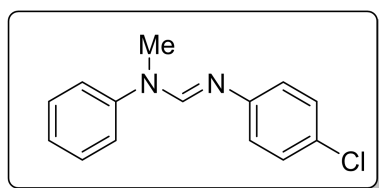
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg, 77%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.12 (s, 1H), 7.39 – 7.31 (m, 2H), 7.18 – 7.07 (m, 3H), 7.02 – 6.94 (m, 2H), 6.79 – 6.64 (m, 2H), 3.50 (s, 3H), 2.92 (s, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  150.9, 148.8, 146.2, 145.2, 129.5, 126.0, 123.9, 120.7, 119.7, 34.3, 34.0, 31.5.  
HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{20}\text{N}_3[\text{M}+\text{H}]^+$ : 254.1652; found: 254.1655.

### **(E)-N'-(4-fluorophenyl)-N-methyl-N-phenylformimidamide (3k)**



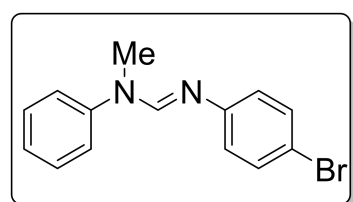
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (17 mg, 75%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.05 (s, 1H), 7.46 – 7.31 (m, 2H), 7.15 (dd,  $J$  = 10.9, 4.2 Hz, 3H), 7.06 – 6.87 (m, 4H), 3.50 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  160.6, 158.6, 151.2, 147.6, 145.1, 129.5, 124.2, 122.2, 120.0, 115.7, 115.5, 34.2.  
HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{14}\text{H}_{13}\text{F}_5\text{N}_2[\text{M}+\text{H}]^+$ : 229.1136; found: 229.1137.

### **(E)-N'-(4-chlorophenyl)-N-methyl-N-phenylformimidamide (3l)**



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg, 77%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.05 (s, 1H), 7.44 – 7.34 (m, 2H), 7.29 – 7.22 (m, 2H), 7.20 – 7.10 (m, 3H), 7.04 – 6.91 (m, 2H), 3.50 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  151.3, 150.1, 145.0, 129.5, 129.1, 128.5, 124.4, 122.5, 120.1, 34.3.  
HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{14}\text{H}_{14}\text{ClN}_2[\text{M}+\text{H}]^+$ : 245.0840; found: 245.0838.

### **(E)-N'-(4-bromophenyl)-N-methyl-N-phenylformimidamide (3m)**

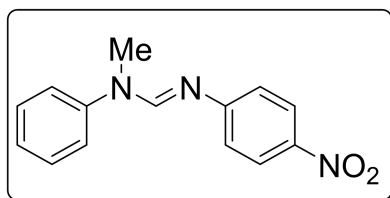


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (21 mg,

71%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.06 (s, 1H), 7.44 – 7.35 (m, 4H), 7.21 – 7.14 (m, 3H), 6.98 – 6.88 (m, 2H), 3.51 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 151.3, 150.6, 144.9, 132.0, 129.5, 124.5, 123.0, 120.1, 116.2, 34.3.

HRMS (ESI, m/z) calcd for C<sub>14</sub>H<sub>14</sub>BrN<sub>2</sub>[M+H]<sup>+</sup>: 289.0335; found: 289.0336.

### **(E)-N-methyl-N'-(4-nitrophenyl)-N-phenylformimidamide (3n)**

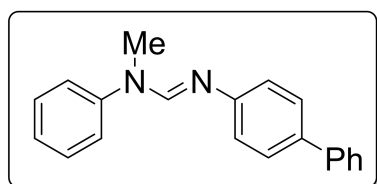


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (15 mg, 58%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.22 – 8.13 (m, 2H), 8.10 (s, 1H), 7.46 – 7.37 (m, 2H), 7.22 (dd,

$J = 17.7, 7.7$  Hz, 3H), 7.13 – 7.05 (m, 2H), 3.55 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 152.1, 144.4, 143.5, 129.7, 125.3, 121.4, 120.7, 34.7.

HRMS (ESI, m/z) calcd for C<sub>14</sub>H<sub>14</sub>N<sub>3</sub>O<sub>2</sub>[M+H]<sup>+</sup>: 256.1081; found: 256.1079.

### **(E)-N'-([1,1'-biphenyl]-4-yl)-N-methyl-N-phenylformimidamide (3o)**

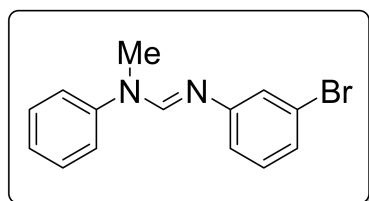


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (22 mg, 77%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.17 (s, 1H),

7.61 (dd,  $J = 7.3, 1.0$  Hz, 2H), 7.57 (dt,  $J = 9.0, 1.8$  Hz, 2H), 7.41 (dt,  $J = 19.8, 7.7$  Hz, 4H), 7.32 (td,  $J = 7.5, 1.1$  Hz, 1H), 7.22 – 7.10 (m, 5H), 3.55 (d,  $J = 0.7$  Hz, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 151.1, 150.8, 145.1, 141.0, 136.2, 129.5, 128.7, 127.8, 126.7, 124.2, 121.6, 120.0, 34.2.

HRMS (ESI, m/z) calcd for C<sub>20</sub>H<sub>19</sub>N<sub>2</sub>[M+H]<sup>+</sup>: 289.1543; found: 289.1544.

### **(E)-N'-(3-bromophenyl)-N-methyl-N-phenylformimidamide (3p)**

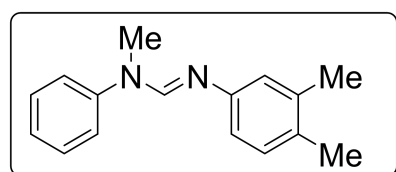


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (21 mg, 71%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.05 (s, 1H), 7.43 – 7.34 (m, 2H), 7.23 – 7.11 (m, 6H), 7.03 – 6.92

(m, 1H), 3.50 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 153.0, 151.5, 144.8, 130.3, 129.5, 126.1, 124.6, 124.1, 1227, 120.3, 34.3.

HRMS (ESI, m/z) calcd for C<sub>14</sub>H<sub>13</sub>BrN<sub>2</sub>[M+H]<sup>+</sup>: 289.0335; found: 289.0333.

### **(E)-N'-(3,4-dimethylphenyl)-N-methyl-N-phenylformimidamide (3q)**

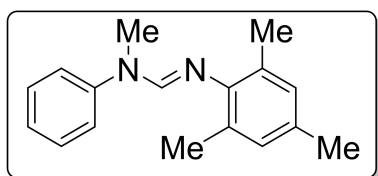


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (20

mg, 83%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.11 (s, 1H), 7.37 (dd, *J* = 8.6, 7.4 Hz, 2H), 7.19 – 7.10 (m, 3H), 7.07 (d, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.80 (dd, *J* = 7.9, 2.3 Hz, 1H), 3.51 (s, 3H), 2.25 (d, *J* = 8.3 Hz, 6H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 150.8, 149.3, 145.2, 137.2, 131.5, 130.3, 129.4, 123.9, 122.6, 119.8, 118.3, 34.0, 19.9, 19.1.

HRMS (ESI, *m/z*) calcd for C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>[M+H]<sup>+</sup>: 239.1543; found: 239.1546.

### (*E*)-*N'*-mesityl-*N*-methyl-*N*-phenylformimidamide (**3r**)

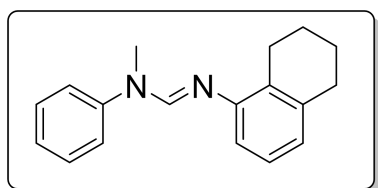


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (22 mg, 85%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.84 (s, 1H), 7.35 (dd, *J* = 8.6, 7.5 Hz, 2H), 7.16 – 7.04 (m, 3H), 6.92 – 6.81 (m, 2H), 3.54 (s, 3H), 2.26 (s, 3H), 2.16 (s, 6H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 151.2, 146.9, 145.1, 131.7, 129.4, 129.0, 128.6, 123.5, 119.2, 33.6, 20.7, 18.7.

HRMS (ESI, *m/z*) calcd for C<sub>17</sub>H<sub>21</sub>N<sub>2</sub>[M+H]<sup>+</sup>: 253.1699; found: 253.1704.

### (*E*)-*N*-methyl-*N*-phenyl-*N'*-(5,6,7,8-tetrahydronaphthalen-1-yl)formimidamide (**3s**)

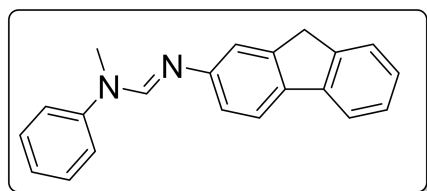


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (21 mg, 80%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.03 (s, 1H), 7.42 – 7.32 (m, 2H), 7.20 – 7.09 (m, 3H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 3.52 (s, 3H), 2.79 (dt, *J* = 12.7, 6.2 Hz, 4H), 1.86 – 1.74 (m, 4H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 150.0, 149.5, 145.2, 137.9, 130.7, 129.4, 125.7, 124.4, 123.6, 119.3, 116.0, 33.7, 29.9, 25.4, 23.4, 23.2.

HRMS (ESI, *m/z*) calcd for C<sub>18</sub>H<sub>21</sub>N<sub>2</sub>[M+H]<sup>+</sup>: 265.1699; found: 265.1702.

### *N*-methyl-*N*-phenylformimidamide (**3t**)

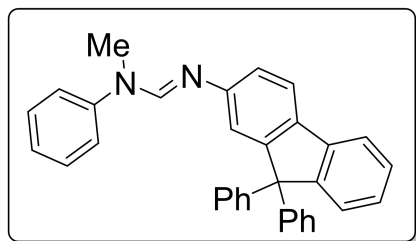


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (23 mg, 76%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.20 (s, 1H), 7.73 (t, *J* = 7.1 Hz, 2H), 7.52 (d, *J* = 7.4 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.26 (dd, *J* = 11.1, 3.7 Hz, 2H), 7.22 – 7.13 (m, 3H), 7.09 (dd, *J* = 8.0, 1.9 Hz, 1H), 3.89 (s, 2H), 3.56 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 151, 150.6, 145.2, 144.6, 143.0, 141.9, 137.3, 129.5, 126.7, 125.8, 124.9, 124.1, 120.3, 120.0, 119.3, 117.8, 37.0, 34.2.

HRMS (ESI, *m/z*) calcd for C<sub>21</sub>H<sub>19</sub>N<sub>2</sub>[M+H]<sup>+</sup>: 299.1543; found: 299.1547.

**(E)-N'-(9H-fluoren-2-yl)-(E)-N'-(9,9-diphenyl-9H-fluoren-2-yl)-N-methyl-N-phenylformimidamide (3u)**

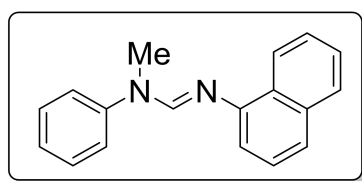


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (31 mg, 68%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.09 (s, 1H), 7.73 (dd, *J* = 7.8, 4.5 Hz, 2H), 7.38 (ddd, *J* = 14.9, 7.4, 6.1 Hz, 4H), 7.30 –

7.11 (m, 16H), 7.06 (dd, *J* = 8.0, 1.9 Hz, 1H), 3.52 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 152.5, 151.3, 151.1, 150.9, 146.1, 145.1, 140.3, 135.7, 129.8, 128.2, 127.4, 126.8, 126.5, 126.1, 124.2, 120.7, 120.4, 120.0, 119.5, 65.5, 34.5.

HRMS (ESI, *m/z*) calcd for C<sub>21</sub>H<sub>19</sub>N<sub>2</sub>[M+H]<sup>+</sup>: 299.1543; found: 299.1541.

**(E)-N-methyl-N'-(E)-N-methyl-N'-(naphthalen-1-yl)-N-phenylformimidamide (3v)**

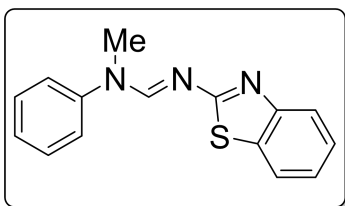


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (20 mg, 77%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.24 (s, 1H), 7.78

(dd, *J* = 18.2, 8.3 Hz, 3H), 7.46 – 7.29 (m, 6H), 7.24 – 7.10 (m, 3H), 3.58 (s, 3H). <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>) δ 151.4, 149.3, 145.1, 134.6, 130.7, 129.5, 128.78, 127.6, 127.11, 126.1, 124.2, 123.0, 120.0, 116.4, 34.3.

HRMS (ESI, *m/z*) calcd for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>[M+H]<sup>+</sup>: 261.1386; found: 261.1383.

**(E)-N'-(benzo[d]thiazol-2-yl)-N-methyl-N-phenylformimidamide (3w)**

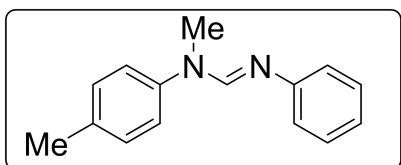


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (17 mg, 62%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.80 (s, 1H), 7.73

(dd, *J* = 22.2, 8.0 Hz, 2H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.39 – 7.35 (m, 1H), 7.28 (dd, *J* = 8.6, 0.8 Hz, 3H), 7.22 (t, *J* = 7.6 Hz, 1H), 3.59 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 172.9, 155.2, 151.9, 143.9, 133.7, 129.7, 126.2, 125.9, 123.3, 121.5, 121.4, 121.2, 35.3.

HRMS (ESI, *m/z*) calcd for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>S[M+H]<sup>+</sup>: 268.0903; found: 268.0902.

**(E)-N-methyl-N'-phenyl-N-(p-tolyl)formimidamide (3x)**

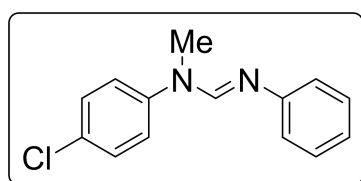


The reaction was performed following the general procedure. The residue was purified by flash

column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg, 85%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.05 (s, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.13 – 6.95 (m, 5H), 3.49 (s, 3H), 2.35 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 151.6, 151.3, 142.7, 134.0, 130.0, 129.1, 123.2, 121.3, 120.2, 34.3, 20.7.

HRMS (ESI, *m/z*) calcd for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>[M+H]<sup>+</sup>: 225.1386; found: 225.1390.

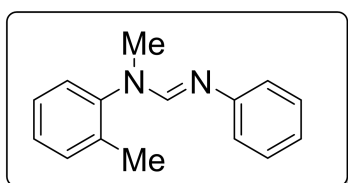
### (*E*)-*N*-(4-chlorophenyl)-*N*-methyl-*N'*-phenylformimidamide (3y)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (20 mg, 83%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.04 (s, 1H), 7.35 – 7.28 (m, 4H), 7.11 – 7.06 (m, 3H), 7.06 – 7.00 (m, 2H), 3.49 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 151.2, 150.6, 143.7, 129.4, 129.1, 123.6, 121.2, 120.9, 34.2.

HRMS (ESI, *m/z*) calcd for C<sub>14</sub>H<sub>13</sub>ClN<sub>2</sub>[M+H]<sup>+</sup>: 245.0840; found: 245.0836.

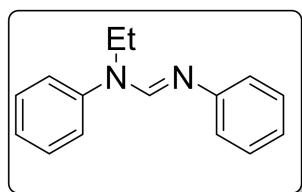
### (*E*)-*N*-methyl-*N'*-phenyl-*N*-(*o*-tolyl)formimidamide (3z)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (15 mg, 68%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.73 (s, 1H), 7.32 – 7.24 (m, 5H), 7.17 (dd, *J* = 6.8, 2.1 Hz, 1H), 7.06 (t, *J* = 8.0 Hz, 3H), 3.39 (s, 3H), 2.35 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 152.8, 151.6, 134.8, 131.5, 129.0, 127.3, 127.0, 123.0, 121.3, 31.5, 18.2.

HRMS (ESI, *m/z*) calcd for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>[M+H]<sup>+</sup>: 225.1386; found: 25.1389.

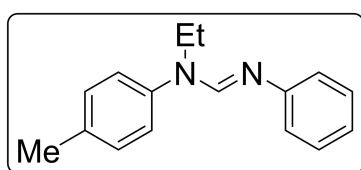
### (*E*)-*N*-ethyl-*N,N'*-diphenylformimidamide (3aa)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (18 mg, 82%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.98 (s, 1H), 7.41 – 7.34 (m, 2H), 7.33 – 7.27 (m, 2H), 7.20 – 7.13 (m, 3H), 7.10 – 7.00 (m, 3H), 4.09 (q, *J* = 7.1 Hz, 2H), 1.31 (d, *J* = 7.1 Hz, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 151.7, 150.5, 144.0, 129.5, 129.1, 124.4, 123.2, 121.3, 121.1, 41.9, 12.8.

HRMS (ESI, *m/z*) calcd for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>[M+H]<sup>+</sup>: 225.1386; found: 225.1390.

### (*E*)-*N*-ethyl-*N'*-phenyl-*N*-(*p*-tolyl)formimidamide (3ab)

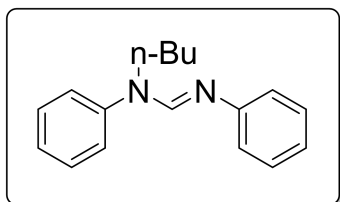


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg,

80%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.92 (s, 1H), 7.29 (dd,  $J = 8.1, 7.5$  Hz, 2H), 7.17 (d,  $J = 8.1$  Hz, 2H), 7.09 – 7.00 (m, 5H), 4.05 (q,  $J = 7.1$  Hz, 2H), 2.35 (s, 3H), 1.30 – 1.28 (m, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  151.9, 150.7, 141.6, 134.3, 130.0, 129.0, 123.0, 121.6, 121.3, 42.0, 20.8, 12.8.

HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{18}\text{N}_2[\text{M}+\text{H}]^+$ : 239.1543; found: 239.1542.

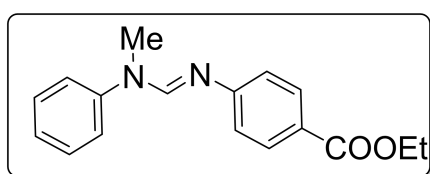
### (*E*)-*N*-butyl-*N,N'*-diphenylformimidamide (3ac)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg, 76%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99 (s, 1H), 7.40 – 7.34 (m, 2H), 7.29 (t,  $J = 7.8$  Hz, 2H), 7.16 (dd,  $J = 12.0, 7.6$  Hz, 3H), 7.10 – 6.99 (m, 3H), 4.13 – 3.93 (m, 2H), 1.70 (tt,  $J = 7.7, 6.7$  Hz, 2H), 1.44 – 1.35 (m, 2H), 0.94 (t,  $J = 7.4$  Hz, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  155.3, 151.8, 150.9, 144.3, 129.4, 129.0, 124.4, 123.1, 121.3, 46.5, 29.5, 20.2, 13.9.

HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{18}\text{N}_2[\text{M}+\text{H}]^+$ : 239.1543; found: 239.1544.

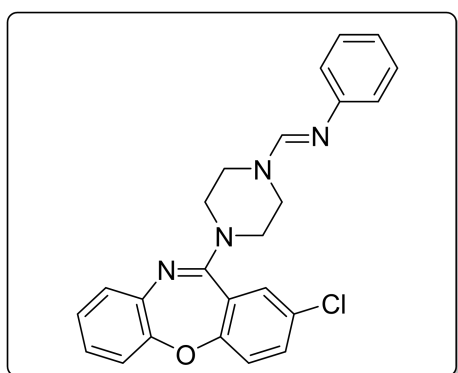
### Ethyl (*E*)-4-(((methyl(phenyl)amino)methylene)amino)benzoate (3ad)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (17 mg, 59%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.13 (s, 1H), 8.07 – 7.98 (m, 2H), 7.47 – 7.36 (m, 2H), 7.21 (dd,  $J = 7.7, 4.8$  Hz, 3H), 7.12 – 7.00 (m, 2H), 4.38 (q,  $J = 7.1$  Hz, 2H), 3.55 (s, 3H), 1.41 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  166.7, 155.7, 151.6, 144.8, 130.9, 129.6, 125.2, 124.7, 121.1, 120.4, 60.7, 34.4, 14.4.

HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2[\text{M}+\text{H}]^+$ : 283.1441; found: 283.1442.

### (*E*)-1-(4-(2-chlorodibenzo[*b,f*][1,4]oxazepin-11-yl)piperazin-1-yl)-*N*-phenylmethanimine (3ae)



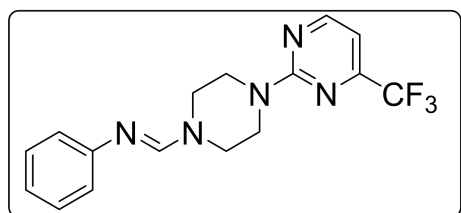
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil 32 mg, 76%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.59 (s, 1H), 7.42 (dd,  $J = 8.7, 2.6$  Hz, 1H), 7.36 (d,  $J = 2.6$  Hz, 1H), 7.32 – 7.27 (m, 2H), 7.23 – 7.16 (m, 2H), 7.12 (ddd,  $J = 13.6, 5.3, 3.7$  Hz, 2H), 7.08 – 6.97 (m, 4H), 3.59 (s, 8H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$

159.4, 158.8, 152.3, 151.8, 151.4, 139.8, 132.8, 130.5, 129.1, 128.9, 127.2, 125.9, 124.9, 122.9, 121.2, 120.2, 47.4.

HRMS (ESI, m/z) calcd for C<sub>24</sub>H<sub>21</sub>ClN<sub>4</sub>O[M+H]<sup>+</sup>: 417.1477; found: 417.1479.

### **(E)-N-phenyl-1-(4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)piperazin-1-yl**

#### **methanimine (3af)**



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (20.5 mg, 61%).<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.53 (d, *J* = 4.8 Hz,

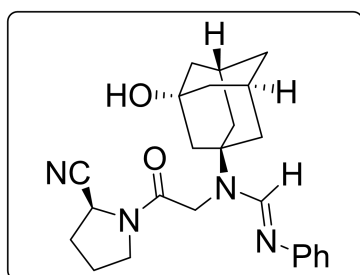
1H), 7.61 (s, 1H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 2H), 6.82 (d, *J* = 4.8 Hz, 1H), 3.99 – 3.94 (m, 4H), 3.60 (s, 4H).<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 161.4, 160.3, 156.8, 156.5, 156.2, 155.9, 152.3, 151.4, 129.1, 123.0, 121.1, 119.9, 119.4, 118.9, 105.2, 43.6.

HRMS (ESI, m/z) calcd for C<sub>16</sub>H<sub>16</sub>F<sub>3</sub>N<sub>5</sub>[M+H]<sup>+</sup>: 336.1431; found: 336.1430.

### **(E)-N-(2-((S)-2-cyanopyrrolidin-1-yl)-2-oxoethyl)-N-((1*r*,3*R*,5*R*,7*S*)-3-**

### **hydroxyadamantan-1-yl)-N'-phenylformimidamide compound with**

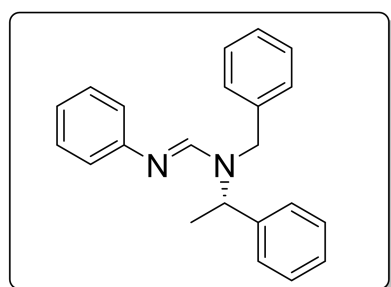
#### **11-methane and methane (1:1:2) (3ag)**



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a yellow oil (29 mg, 71%).<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.92 (s, 1H), 7.25 (dd, *J* = 14.9, 7.3 Hz, 2H), 7.01 (dt, *J* = 14.7, 7.4 Hz, 1H), 6.87 (dd, *J* = 16.8, 7.5 Hz, 2H), 5.69 – 4.72 (m,

1H), 4.34 (dd, *J* = 28.7, 15.6 Hz, 1H), 4.07 (t, *J* = 14.5 Hz, 1H), 3.82 – 3.47 (m, 2H), 2.41 – 1.81 (m, 15H), 1.71 (s, 4H).<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 169.5, 168.9, 152.0, 151.6, 149.7, 149.6, 129.1, 129.0, 122.8, 122.6, 121.3, 121.2, 119.4, 118.6, 69.5, 69.4, 59.2, 58.8, 49.9, 49.7, 47.5, 46.8, 46.6, 46.2, 45.0, 44.4, 43.8, 41.1, 41.1, 34.6, 32.3, 30.7, 29.9, 29.7, 25.4, 23.2.

### **(S,E)-N-benzyl-N'-phenyl-N-(1-phenylethyl)formimidamide (3ah)**



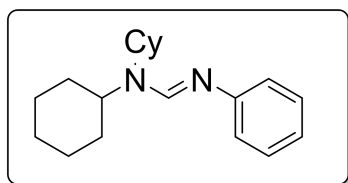
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg, 60%).<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.97 (s, 1H), 7.57 – 7.15 (m, 12H), 7.05 (ddd, *J* = 9.5, 5.2, 1.0 Hz,



3H), 4.90 (s, 1H), 4.51 (d,  $J = 65.1$  Hz, 2H), 1.59 (d,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  152.3, 151.9, 141.6, 138.4, 129.1, 128.7, 128.6, 128.3, 127.7, 127.1, 126.90 – 125.52 (m), 122.7, 121.4, 58.3, 48.5, 20.6.

HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{22}\text{H}_{22}\text{N}_2[\text{M}+\text{H}]^+$ : 315.1856; found: 315.1858.

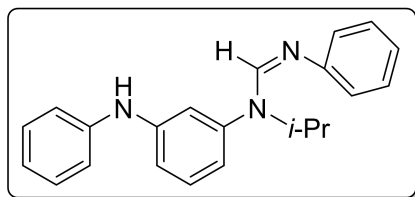
### (*E*)-*N,N*-dicyclohexyl-*N'*-phenylformimidamide (5)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (22 mg, 76%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (s, 1H), 7.28 (dd,  $J = 10.8, 4.8$  Hz, 2H), 7.02 – 6.93 (m, 3H), 1.77 (dd,  $J = 69.6, 11.6$  Hz, 11H), 1.58 – 1.31 (m, 9H), 1.19 – 1.10 (m, 2H), 0.89 (dt,  $J = 12.6, 6.5$  Hz, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  153.3, 150.6, 128.9, 122.0, 121.3, 29.7, 25.6.

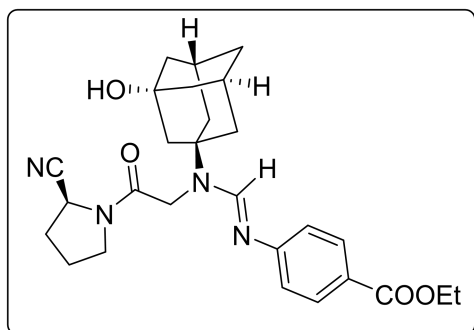
HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{19}\text{H}_{19}\text{N}_2[\text{M}+\text{H}]^+$ : 285.2325; found: 285.2321.

### (*Z*)-*N*-isopropyl-*N'*-phenyl-*N*-(3-(phenylamino)phenyl)formimidamide (7)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (18 mg, 54%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (s, 1H), 7.35 – 7.28 (m, 4H), 7.13 – 6.99 (m, 10H), 5.84 (s, 1H), 1.28 (d,  $J = 6.8$  Hz, 7H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  153.0, 152.1, 142.6, 142.4, 133.9, 129.8, 129.5, 129.0, 123.5, 122.6, 121.6, 121.3, 118.4, 117.4, 114.8, 23.1, 21.1.

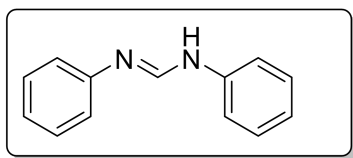
### 4-(((*E*)-((2-((*S*)-2-cyanopyrrolidin-1-yl)-2-oxoethyl)((1*r*,3*R*,5*R*,7*S*)-3-hydroxyadamantan-1-yl)amino)methylene)amino)benzoate (3ai)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 20:1, v/v) to give the product as a yellow oil (33.5 mg, 70%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.92 (s, 1H), 7.88 (dd,  $J = 8.4, 4.6$  Hz, 2H), 6.84 (dd,  $J = 16.5, 8.5$  Hz, 2H), 5.48 – 4.63 (m, 1H), 4.38 – 4.18 (m, 3H), 4.15 – 3.93 (m, 2H), 3.78 – 3.66 (m, 2H), 3.62 – 3.34 (m, 1H), 2.59 (d,  $J = 138.4$  Hz, 1H), 2.37 – 2.07 (m, 7H), 2.03 – 1.98 (m, 1H), 1.98 – 1.80 (m, 6H), 1.67 (s, 4H), 1.56 – 1.47 (m, 2H), 1.33 (t,  $J = 7.1$  Hz, 3H), 1.24 – 1.12 (m, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.2, 171.1, 168.9, 168.4,

166.8, 166.7, 156.3, 155.9, 150.1, 150.0, 130.9, 130.8, 124.3, 121.0, 120.9, 119.1, 118.5, 74.6, 69.3, 69.2, 67.1, 60.6, 60.5, 60.4, 59.6, 59.2, 56.7, 49.7, 49.5, 47.4, 46.8, 46.6, 46.2, 45.0, 44.5, 43.6, 41.0, 41.0, 34.6, 34.5, 32.3, 30.6, 29.9, 25.4, 23.2, 21.1, 21.0, 16.2, 14.4, 14.2.

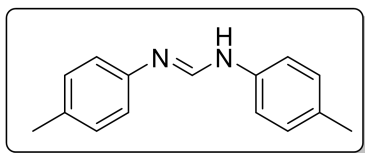
### **(E)-N,N'-diphenylformimidamide (8)**



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 50:1, v/v) to give the product as a yellow oil (11 mg, 53%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.20 (s, 1H), 7.31 (t, *J* = 7.8 Hz, 4H), 7.24 – 6.64 (m, 6H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 129.4, 123.4, 118.9.

HRMS (ESI, *m/z*) calcd for C<sub>13</sub>H<sub>13</sub>N<sub>2</sub>[M+H]<sup>+</sup>:197.1073; found: 197.1076.

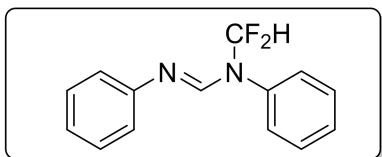
### **(E)-N,N'-di-p-tolylformimidamide (9)**



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 50:1, v/v) to give the product as a yellow oil (11 mg, 48%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.17 (s, 1H), 7.11 (d, *J* = 8.1 Hz, 4H), 6.94 (d, *J* = 8.0 Hz, 4H), 2.33 (s, 6H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 149.3, 132.8, 129.9, 119.5, 118.9, 29.7, 20.7.

HRMS (ESI, *m/z*) calcd for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>[M+H]<sup>+</sup>:225.1386; found: 225.1389.

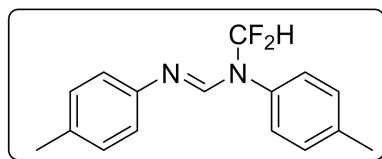
### **(E)-N-(difluoromethyl)-N,N'-diphenylformimidamide (10)**



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a yellow oil (17 mg, 67%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.84 (t, *J* = 2.8 Hz, 1H), 7.57 (t, *J* = 52.5 Hz, 1H), 7.45 (dd, *J* = 6.9, 1.6 Hz, 2H), 7.42 – 7.37 (m, 3H), 7.32 (dd, *J* = 10.7, 5.0 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.06 – 7.00 (m, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 149.4, 149.1, 136.4, 129.5, 129.2, 128.2, 127.4, 124.6, 121.1 110.2 (s, *J*=243.75Hz). <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>) δ -97.8, -102.8.

HRMS (ESI, *m/z*) calcd for C<sub>14</sub>H<sub>13</sub>F<sub>2</sub>N<sub>2</sub>[M+H]<sup>+</sup>:247.1041; found: 247.1042.

### **(E)-N-(difluoromethyl)-N,N'-di-p-tolylformimidamide (11)**

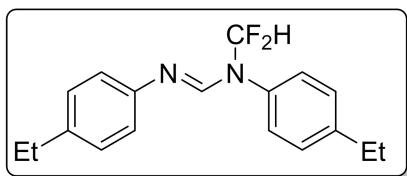


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a yellow oil (17 mg, 61%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.82 (t, *J* =

2.8 Hz, 1H), 7.55 (dd,  $J = 67.5, 54.9$  Hz, 1H), 7.17 – 7.11 (m, 2H), 6.94 (d,  $J = 8.2$  Hz, 2H), 2.42 (s, 3H), 2.35 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  149.0, 147.0, 138.2, 134.1, 133.7, 130.1, 129.7, 127.5, 120.9, 110.2(s,  $J=237.5\text{Hz}$ ), 21.1, 20.8.  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -97.8, -103.0.

HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{16}\text{H}_{17}\text{F}_2\text{N}_2[\text{M}+\text{H}]^+$ :275.1354; found: 275.1356.

### (*E*)-*N*-(difluoromethyl)-*N*,*N'*-bis(4-ethylphenyl)formimidamide (12)



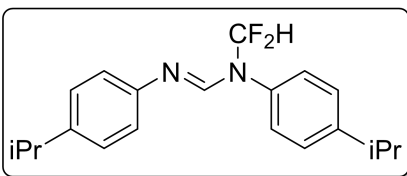
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a yellow oil (18 mg, 59%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.81 (t,  $J = 2.8$  Hz, 1H), 7.53 (t,  $J = 61.2$

Hz, 1H), 7.27 (s, 4H), 7.14 (d,  $J = 8.4$  Hz, 2H), 6.98 – 6.91 (m, 2H), 2.69 (q,  $J = 7.6$  Hz, 2H), 2.63 (q,  $J = 7.6$  Hz, 2H), 1.26 (s, 3H), 1.23 (t,  $J = 7.6$  Hz, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  149.0, 147.1, 144.4, 140.6, 133.9, 128.9, 128.5, 127.5, 121.0, 110.2 (s,  $J=242.5\text{Hz}$ ), 28.5, 28.3, 15.7, 15.4.

$^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -98.5, -103.0.

HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{18}\text{H}_{21}\text{F}_2\text{N}_2[\text{M}+\text{H}]^+$ :303.1667; found: 303.1668.

### (*E*)-*N*-(difluoromethyl)-*N*,*N'*-bis(4-isopropylphenyl)formimidamide (13)

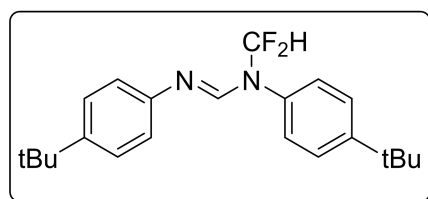


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a yellow oil (21 mg, 62%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.81 (t,  $J = 2.8$  Hz, 1H), 7.55 (t,  $J = 61.2$  Hz, 1H), 7.28 (s, 4H), 7.20 – 7.13

(m, 2H), 7.00 – 6.90 (m, 2H), 2.92 (ddt,  $J = 30.5, 13.8, 6.9$  Hz, 2H), 1.28 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  149.0, 147.2, 145.2, 134.0, 127.4, 127.1, 120.9, 110.2(s,  $J=247.5\text{Hz}$ ), 33.8, 33.6, 24.1, 23.9.  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -98.0, -103.0.

HRMS (ESI,  $m/z$ ) calcd for  $\text{C}_{20}\text{H}_{25}\text{F}_2\text{N}_2[\text{M}+\text{H}]^+$ :331.1980; found: 331.1986.

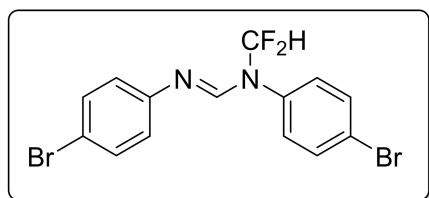
### (*E*)-*N*,*N'*-bis(4-(*tert*-butyl)phenyl)-*N*-(difluoromethyl)formimidamide (14)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a yellow oil (23 mg, 65%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.85 (t,  $J = 2.8$  Hz, 1H), 7.59 (t,  $J = 55.2$

Hz, 1H), 7.48 – 7.44 (m, 2H), 7.44 – 7.28 (m, 5H), 7.03 – 6.94 (m, 2H), 1.37 (s, 9H), 1.34 (s, 9H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 151.2, 149.1, 147.5, 146.8, 133.7, 126.9, 126.4, 126.0, 120.7, 110.2 (t, *J* = 242.5 Hz), 34.7, 34.4, 31.38, 31.1. <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>) δ -98.1, -102.9.

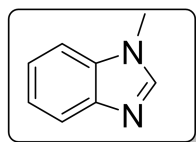
### **(*E*)-*N,N'*-bis(4-bromophenyl)-*N*-(difluoromethyl)formimidamide (15)**



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a yellow oil (23 mg, 57%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.78 (t, *J* = 2.4 Hz, 1H), 7.66 (t, *J* = 38.0

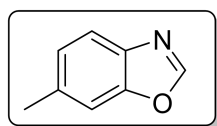
Hz, 1H), 7.59 – 7.56 (m, 2H), 7.43 – 7.40 (m, 2H), 7.26 – 7.23 (m, 2H), 6.91 – 6.84 (m, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 148.6, 135.0, 132.8, 132.2, 129.1, 122.8, 117.9 (t, *J* = 571.3 Hz), 100.0. <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>) δ -99.5, -102.9.

### **1-methyl-1*H*-benzo[*d*]imidazole (17) (CAS number:1632-83-3)**



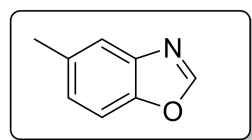
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a yellow oil (12mg, 90%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.86 (s, 1H), 7.81 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.39 (dd, *J* = 7.0, 1.1 Hz, 1H), 7.35 – 7.26 (m, 2H), 3.84 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 143.7, 143.5, 134.5, 122.94 (s), 122.1, 120.3, 109.3, 31.0.

### **6-methylbenzo[*d*]oxazole (20a) (CAS number:10531-80-3)**



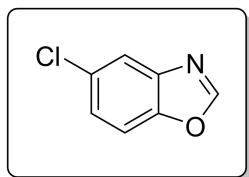
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a colourless oil (21 mg, 81%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.03 (s, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.39 (s, 1H), 7.18 (dd, *J* = 8.1, 0.7 Hz, 1H), 2.50 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 152.1, 150.3, 137.8, 136.1, 125.9, 119.9, 111.1, 21.8.

### **5-methylbenzo[*d*]oxazole (20b) (CAS number:10531-78-9)**



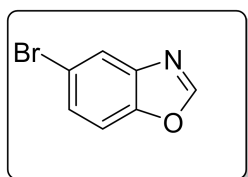
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a colourless oil (21 mg, 77%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.07 (s, 1H), 8.07 (s, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 2.64 (s, 3H), 2.64 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 151.8, 149.7, 139.2, 131.0, 125.3, 125.1, 108.2, 16.5.

### 5-chlorobenzo[d]oxazole (20c) (CAS number:17200-29-2)



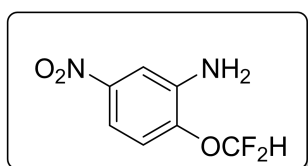
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a colourless oil (22 mg, 70%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.11 (s, 1H), 7.77 (d, *J* = 2.0 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.36 (dd, *J* = 8.7, 2.0 Hz, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 153.7, 148.5, 141.1, 130.2, 126.1, 120.6, 111.8.

### 5-bromobenzo[d]oxazole (20d) (CAS number:132244-31-6)



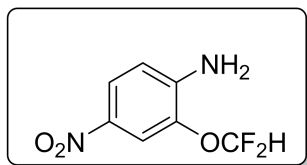
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a colourless oil (25 mg, 68%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.09 (s, 1H), 7.93 (d, *J* = 1.7 Hz, 1H), 7.49 (dt, *J* = 20.0, 5.2 Hz, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 153.5, 149.0, 141.6, 128.8, 123.7, 117.44, 112.3.

### 2-(difluoromethoxy)-5-nitroaniline (20e')



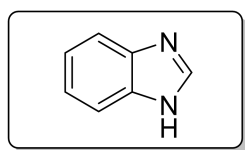
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a colourless oil (36 mg, 89%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.63 (d, *J* = 2.7 Hz, 1H), 7.59 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 6.58 (t, *J* = 72.8 Hz, 1H), 4.20 (s, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 145.7, 142.3, 139.0, 117.8 (s, *J* = 261.25 Hz), 113.5, 110.6. <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>) δ -81.0.

### 2-(difluoromethoxy)-4-nitroaniline (20f')



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a colourless oil (34 mg, 84%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.03 – 7.90 (m, 2H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.57 (t, *J* = 72.9 Hz, 1H), 4.66 (s, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 145.1, 138.2, 136.0, 118.1, 116.1, 116.0 (s, *J* = 262.5 Hz), 114.0. <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>) δ -80.8.

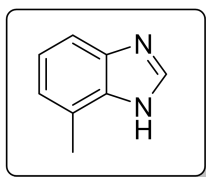
### benzo[d]oxazole (20g) (CAS number:51-17-2)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (20 mg, 86%). <sup>1</sup>H NMR (500 MHz,

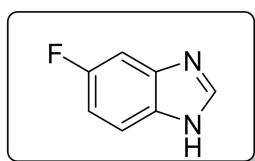
DMSO)  $\delta$  12.46 (s, 1H), 8.22 (s, 1H), 7.59 (s, 2H), 7.29 – 7.06 (m, 2H).<sup>13</sup>C NMR (126 MHz, DMSO)  $\delta$  142.40 (s), 122.16 (s).

### 6-methylbenzo[d]oxazole (20h) (CAS number:4887-83-6)



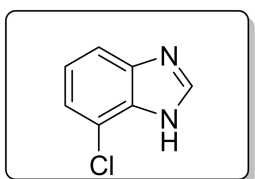
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (24 mg, 92%).<sup>1</sup>H NMR (500 MHz, DMSO)  $\delta$  12.47 (s, 1H), 8.18 (s, 1H), 7.39 (d,  $J$  = 7.6 Hz, 1H), 7.07 (t,  $J$  = 7.6 Hz, 1H), 6.98 (d,  $J$  = 7.2 Hz, 1H), 2.52 (s, 3H).<sup>13</sup>C NMR (125 MHz, DMSO)  $\delta$  141.77 (s), 122.16 (s), 17.24 (s).

### 5-fluoro-1H-benzo[d]imidazole (20i) (CAS number:1977-72-6)



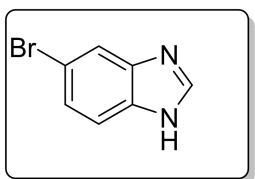
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (21 mg, 78%).<sup>1</sup>H NMR (500 MHz, DMSO)  $\delta$  12.56 (s, 1H), 8.25 (s, 1H), 7.58 (dd,  $J$  = 8.4, 4.9 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.07 – 7.01 (m, 1H).<sup>13</sup>C NMR (125 MHz, DMSO)  $\delta$  159.9, 158.0, 143.8, 110.5.

### 7-chloro-1H-benzo[d]imidazole (20j) (CAS number:16931-35-4)



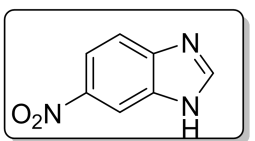
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (26 mg, 86%).<sup>1</sup>H NMR (500 MHz, DMSO)  $\delta$  12.80 (s, 1H), 8.32 (s, 1H), 7.53 (s, 1H), 7.30 – 7.17 (m, 2H).<sup>13</sup>C NMR (125 MHz, DMSO)  $\delta$  143.3, 123.5, 121.6, 111.4.

### 5-bromo-1H-benzo[d]imidazole (20k) (CAS number:4887-88-1)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (29 mg, 75%).<sup>1</sup>H NMR (500 MHz, DMSO)  $\delta$  12.63 (s, 1H), 8.26 (s, 1H), 7.79 (s, 1H), 7.55 (s, 1H), 7.32 (d,  $J$  = 8.2 Hz, 1H).<sup>13</sup>C NMR (125 MHz, DMSO)  $\delta$  143.8, 100.0.

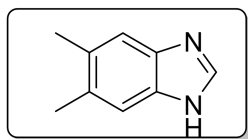
### 6-nitro-1H-benzo[d]imidazole (20l) (CAS number:94-52-0)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a yellow solid (14 mg, 42%).<sup>1</sup>H NMR (500 MHz, DMSO)  $\delta$  8.63 – 8.41 (m, 2H), 8.17 – 7.97 (m, 1H), 7.75 (ddd,  $J$  = 8.4, 7.5, 1.8 Hz,

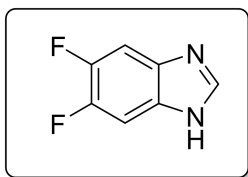
1H). <sup>13</sup>C NMR (126 MHz, DMSO) δ 147.17 (d, *J* = 9.3 Hz), 143.09 (s), 118.00 (d, *J* = 9.4 Hz), 115.29 (s), 113.18 (s).

### 5-5,6-dimethyl-1*H*-benzo[*d*]imidazole (20m) (CAS number:582-60-5)



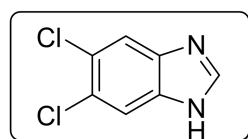
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (23mg, 79%). <sup>1</sup>H NMR (500 MHz, DMSO) δ 8.05 (s, 1H), 7.34 (s, 2H), 2.29 (s, 6H). <sup>13</sup>C NMR (125 MHz, DMSO) δ 141.4, 130.5, 115.8, 20.4.

### 5,6-difluoro-1*H*-benzo[*d*]imidazole (20n) (CAS number: 78581-99-4)



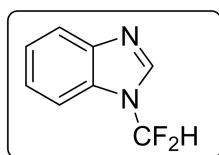
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (24mg, 77%). <sup>1</sup>H NMR (500 MHz, DMSO) δ 12.65 (s, 1H), 8.28 (s, 1H), 7.64 (d, *J* = 22.7 Hz, 2H). <sup>13</sup>C NMR (125 MHz, DMSO) δ 144.5.

### 5,6-dichloro-1*H*-benzo[*d*]imidazole (20o) (CAS number:6478-73-5)



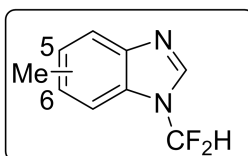
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (28mg, 75%). <sup>1</sup>H NMR (500 MHz, DMSO) δ 12.75 (s, 1H), 8.35 (s, 1H), 7.88 (s, 2H). <sup>13</sup>C NMR (125 MHz, DMSO) δ 145.2

### 1-(difluoromethyl)-1*H*-benzo[*d*]imidazole (21)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (11.4 mg, 61%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.12 (s, 1H), 7.93 – 7.76 (m, 1H), 7.61 (dd, *J* = 5.4, 3.6 Hz, 1H), 7.37 (ddd, *J* = 85.8, 55.8, 43.2 Hz, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 143.9, 139.1, 130.6, 124.8, 124.2, 121.0, 111.1, 109.0 (t, *J* = 248.8 Hz) <sup>19</sup>F NMR (470 MHz, CPD, CDCl<sub>3</sub>) δ -93.7.

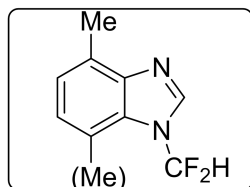
### 1-(difluoromethyl)-5(6)-methyl-1*H*-benzo[*d*]imidazole (22)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (11 mg, 58%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.05 (d, *J* = 11.4 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.62 (s, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.41 (d, *J* = 4.1 Hz, 1H), 7.29 (s, 1H), 7.20 (d, *J* = 11.8, 4.5 Hz, 1H), 7.17 (s, 1H), 2.50 (d, *J* = 8.8 Hz, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 144.2, 142.0,

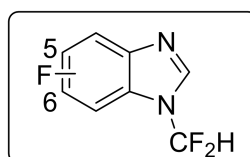
139.1, 138.6, 135.6, 134.1, 130.7, 128.5, 126.2, 125.7, 120.7, 120.4, 110.98 (d,  $J = 5.5$  Hz), 110.56 (s), 108.97 (s), 106.99 (s), 21.79 (s), 21.51 (s).  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -93.6, -93.7.

### 1-(difluoromethyl)-4,7-dimethyl-1*H*-benzo[d]imidazole (23)



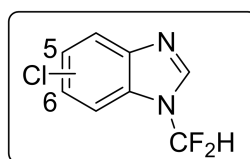
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (11 mg, 63%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.13 (d,  $J = 27.9$  Hz, 1H), 7.69 (d,  $J = 8.1$  Hz, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 7.45 – 7.38 (m, 1H), 7.37 (s, 1H), 7.33 – 7.26 (m, 1H), 7.18 (t,  $J = 6.0$  Hz, 1H), 2.66 (d,  $J = 18.6$  Hz, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  143.2), 139.7, 138.1, 131.1, 130.3, 127.2, 124.7, 124.5, 124.1, 121.6, 118.7, 110.9, 109.0, 108.4, 19.2, 16.6.  $^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -87.3, -93.8.

### 1-(difluoromethyl)-5(6)-fluoro-1*H*-benzo[d]imidazole (24)



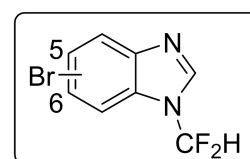
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (10 mg, 53%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.11 (d,  $J = 20.5$  Hz, 1H), 7.78 (dd,  $J = 8.9, 4.7$  Hz, 1H), 7.56 (dd,  $J = 8.9, 4.5$  Hz, 1H), 7.52 (dd,  $J = 8.9, 2.4$  Hz, 1H), 7.41 (d,  $J = 9.8$  Hz, 1H), 7.35 – 7.27 (m, 1H), 7.15 (m,  $J = 13.5, 9.1, 2.2$  Hz, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) 161.5 (d,  $J = 46.3$  Hz), 159.5 (d,  $J = 37.5$  Hz), 140.5, 139.5, 122.8 (d,  $J = 10.0$  Hz), 112.9 (d,  $J = 47.5$  Hz), 112.6 (t,  $J = 113.8$  Hz), 98.4 (d,  $J = 28.8$  Hz).  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -93.7, -94.0, -115.6, -118.0.

### 5(6)-chloro-1-(difluoromethyl)-1*H*-benzo[d]imidazole (25)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (12 mg, 58%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.14 (s, 1H), 7.85 (d,  $J = 1.8$  Hz, 1H), 7.56 (d,  $J = 8.7$  Hz, 1H), 7.45 (s, 1H), 7.40 (dd,  $J = 8.6, 1.9$  Hz, 1H), 7.33 (s, 1H), 7.21 (s, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  144.8, 140.2, 129.9, 129.1, 125.4, 120.9, 112.0, 108.8 ( $J = 248.75$  Hz, ).  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -93.8.

### 5(6)-bromo-1-(difluoromethyl)-1*H*-benzo[d]imidazole (26)

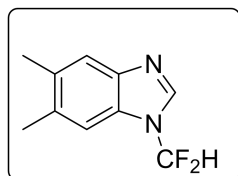


The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (15 mg, 60%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.09 (d,  $J = 7.1$  Hz, 1H), 7.97 (d,  $J = 0.6$  Hz, 1H), 7.77 (s, 1H), 7.68 (d,  $J = 8.6$  Hz, 1H), 7.52 – 7.45 (m, 2H), 7.43 (d,  $J = 6.2$  Hz, 1H),



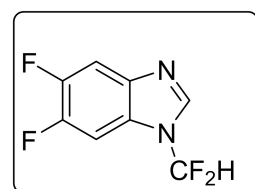
7.31 (d,  $J = 6.1$  Hz, 1H), 7.19 (d,  $J = 6.1$  Hz, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  145.2, 142.9, 140.1, 139.6, 131.4, 129.4, 128.0, 127.7, 123.9, 122.2, 118.2, 117.3, 114.4, 112.4, 108.9 (t,  $J = 250.0$  Hz), 108.8 (t,  $J = 250.0$  Hz).  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -93.8.

### 1-(difluoromethyl)-5,6-dimethyl-1H-benzo[d]imidazole (27)



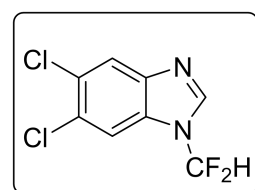
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (13 mg, 69%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99 (s, 4H), 7.99 (s, 4H), 7.59 (s, 4H), 7.59 (s, 4H), 7.38 (s, 1H), 7.38 (d,  $J = 5.7$  Hz, 5H), 7.37 (s, 4H), 7.26 (s, 2H), 7.26 (d,  $J = 2.0$  Hz, 3H), 7.14 (s, 1H), 7.14 (s, 1H), 2.38 (d,  $J = 8.9$  Hz, 25H), 2.38 (d,  $J = 8.9$  Hz, 25H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  142.5, 138.3, 134.2, 133.2, 129.0, 120.9, 111.24, 109.00 (t,  $J = 247.5$ Hz), 20.5, 20.3.  $^{19}\text{F}$  NMR (470MHz,  $\text{CDCl}_3$ )  $\delta$  -93.6.

### 1-(difluoromethyl)-5,6-difluoro-1H-benzo[d]imidazole (28)



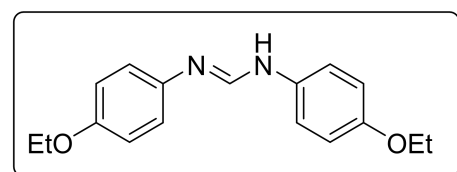
The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (10 mg, 51%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.11 (s, 1H), 7.62 (dd,  $J = 10.0, 7.2$  Hz, 1H), 7.44 (dd,  $J = 9.3, 6.8$  Hz, 1H), 7.41 (s, 1H), 7.29 (s, 1H), 7.17 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  150.15 (d,  $J = 15.5$  Hz), 149.80 (d,  $J = 14.8$  Hz), 148.19 (d,  $J = 15.5$  Hz), 147.86 (d,  $J = 15.0$  Hz), 140.44 (s), 139.35 (d,  $J = 9.0$  Hz), 125.7, , 108.8, 108.7 (t,  $J = 228.8$ Hz), 108.5, 106.8, 100.0, 99.8.  $^{19}\text{F}$  NMR (470MHz,  $\text{CDCl}_3$ )  $\delta$  -94.0, -137.9, -138.0, -140.3, -140.3.

### 5,6-dichloro-1-(difluoromethyl)-1H-benzo[d]imidazole (29)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (13 mg, 55%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.11 (s, 1H), 7.95 (s, 1H), 7.75 (s, 1H), 7.40 (s, 1H), 7.28 (s, 1H), 7.16 (s, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  143.2, 140.7, 129.3, 128.8, 122.3, 112.9, 110.7 (t,  $J = 228.8$ Hz).  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -93.9.

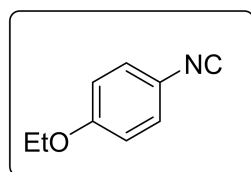
### (E)-N,N'-bis(4-ethoxyphenyl)formimidamide (32)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (8.5 mg, 15%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.02 (s, 1H), 6.97 (d,  $J = 8.6$  Hz, 4H), 6.89 – 6.81 (m, 4H), 4.01

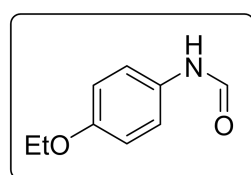
(q,  $J = 7.0$  Hz, 4H), 1.40 (t,  $J = 7.0$  Hz, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  155.4, 120.2, 115.3, 63.8, 14.9.

### 1-ethoxy-4-isocyanobenzene (33)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a colourless oil (8 mg, 27%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 (d,  $J = 8.9$  Hz, 2H), 6.87 – 6.82 (m, 2H), 4.03 (q,  $J = 7.0$  Hz, 2H), 1.42 (t,  $J = 7.0$  Hz, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  162.3, 159.3, 127.8, 115.0, 63.9, 14.7.

### *N*-(4-ethoxyphenyl)formamide (34)



The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a colourless oil (8 mg, 27%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.50 (d,  $J = 11.5$  Hz, 0.49 H), 8.31 (d,  $J = 1.8$  Hz, 0.49 H), 8.09 (s, 0.46 H), 7.47 – 7.35 (m, 1.42 H), 7.06 – 6.96 (m, 1H), 6.90 – 6.81 (m, 2H), 4.00 (qd,  $J = 7.0, 4.3$  Hz, 2H), 1.40 (q,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  163.1, 158.9, 157.0, 156.1, 129.8, 129.4, 121.8, 121.7, 115.5, 114.8, 63.8, 63.7, 14.8, 148.

## References

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2. Huang, K., Sun, C-L., and Shi, Z-J. (2011). Transition-metal-catalyzed C–C bond formation through the fixation of carbon dioxide. *Chem. Soc. Rev.* *40*, 2435–2452.