DISSERTATION

ESTABLISHING BASE-CATALYZED HALOGEN TRANSFER AS A GENERAL PLATFORM FOR C–H FUNCTIONALIZATION

Submitted by

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ABSTRACT

ESTABLISHING BASE-CATALYZED HALOGEN TRANSFER AS A GENERAL PLATFORM FOR C–H FUNCTIONALIZATION

In contrast to traditional multi-step routes, C–H functionalization offers a resource and time efficient route to desired products. Current methods for oxidative C–H functionalization are developed on three predominate reactivity platforms (1) hydrogen atom transfer, (2) single-electron transfer, and (3) C–H insertion. Despite their synthetic power, methods built on these platforms are restricted to similar bond conversions, substrates, and selectivities. Thus, there remains a strong demand for new mechanistic approaches to oxidative C–H functionalization that offer a departure from traditional reactivity. In efforts to address this need, new methods for oxidative coupling based on a base-catalyzed halogen transfer (X-transfer) reactivity platform are described herein.

Chapter one provides an overview on the development of a X-transfer enabled direct C–H hydroxylation of mildly acidic *N*-heteroarenes and benzenes. Hydroxylated (hetero)arenes are valued in many industries as both key constituents of end products and diversifiable synthetic building blocks. Accordingly, the development of reactions that complement and address the limitations of existing methods for the introduction of aromatic hydroxyl groups is an important goal. To this end, this chapter discusses the development of a protocol that employs an alkoxide base to catalyze X-transfer from sacrificial 2-halothiophene oxidants to aryl substrates, forming S_NAr-active intermediates that undergo nucleophilic hydroxylation. Key to this process is the use of 2-phenylethanol as an inexpensive hydroxide surrogate that, after aromatic substitution and

rapid elimination, provides the hydroxylated arene and styrene byproduct. Use of simple 2-halothiophenes allows for C–H hydroxylation of 6-membered *N*-heteroarenes and 1,3-azole derivatives, while a rationally designed 2-halobenzothiophene oxidant extends the scope to electron-deficient benzene substrates. Mechanistic studies indicate that aromatic X-transfer is reversible, suggesting that the deprotonation, halogenation, and substitution steps operate in synergy, manifesting in unique selectivity trends that are not necessarily dependent on the most acidic aryl position. The utility of this method is further demonstrated through streamlined target molecule syntheses, examples of regioselectivity that contrast alternative C–H hydroxylation methods, and the scalable recycling of the thiophene oxidants.

Chapter two describes the elaboration the X-transfer enabled C–H functionalization platform to encompass benzylic C(sp^3)–H bonds. Thus, a benzylic C–H oxidative coupling reaction with alcohols that proceeds through a synergistic deprotonation, halogenation and substitution sequence is discussed. In contrast to existing radical-based pathways for C–H functionalization, this process is guided by C–H acidity trends. This gives rise to new synthetic capabilities, including the ability to functionalize diverse methyl(hetero)arenes, tolerance of oxidizable and nucleophilic functional groups, precision regioselectivity for polyalkylarenes and use of a double C–H etherification process to controllably oxidize methylarenes to benzaldehydes.

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CHAPTER ONE

INTRODUCTION

C–H functionalization is the process of directly converting a C–H bond into a diversified functional group. This offers a much more streamlined route to desired products as compared to traditional synthesis where you generally need to perform many synthetic steps, working through reactive synthetic intermediates, to achieve similar functionalization (Figure 1-1a). Due to this advantage, there has been a concentrated effort by synthetic chemists over the last several decades to develop new methods for C–H functionalization where the unifying goal of this work is to be able to view any C–H bond as a diversifiable functional handle.

Currently, there are a variety of mechanistic platforms to achieve C–H functionalization and methods developed based on these mechanistic approaches have provided impressive selectivity and reactivity for C–H functionalization. For oxidative C–H functionalization in particular, there are three main activation platforms: 1) hydrogen atom transfer, 2) single electron oxidation, and 3) C–H insertion. Although methods developed based on these have been useful, there remains limitations in the types of amenable C–H bonds as platform has distinct scope and selectivity trends. Thus, the Bandar group has set out to develop a novel mechanistic platform for C–H functionalization where we hope to offer a departure from traditional reactivity with distinct advantages. Our research group develops novel C–H functionalization methodology through creative application of intermolecular base-catalyzed halogen transfer (X-transfer). We sequence this reactivity with tandem substitution reactions to enable regioselective C–H functionalization (Figure 1-1b).

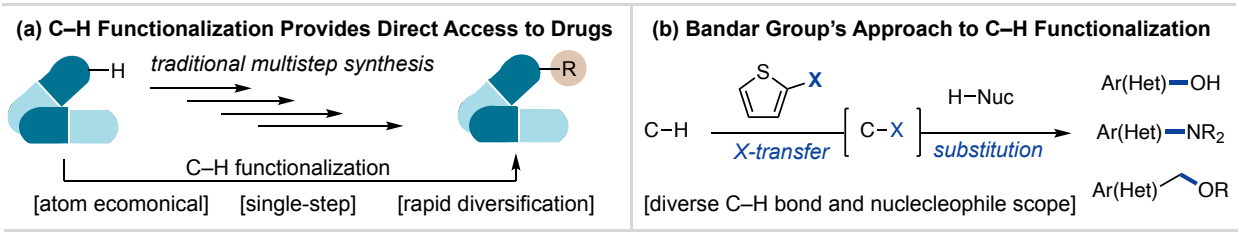


Figure 1-1: C–H functionalization provides rapids and direct derivatization and our groups development in C–H functionalization methodology.

CHAPTER TWO

DIRECT C–H HYDROXYLATION OF *N*-HETEROARENES AND BENZENES *VIA* BASE-CATALYZED HALOGEN TRANSFER

2.1 Chapter Overview

Direct C–H functionalization allows for the rapid transformation of simple building blocks into value-added compounds. Thus, new and general platforms for C–H activation that access complementary product scopes and achieve unique selectivity under practical conditions are in strong demand. The Bandar Group is developing a mechanistically novel approach that harnesses base-catalyzed halogen transfer (X-transfer), where X-transfer refers to the movement of a halogen from a haloarene to a carbanion. We sequence this reactivity with tandem substitution reactions to enable regioselective C–H functionalization of mildly acidic C–H bonds. Chapter One will discuss my work expanding this mechanistic approach toward a deprotonative C–H hydroxylation protocol of electron deficient (hetero)arenes, that, due to the synthetic versatility of the hydroxyl group, can serve as a general platform for aromatic C–H functionalization (Figure 2-1). This Chapter will also briefly discuss my preliminary results in leveraging the insights gained throughout the development of the C–H hydroxylation protocol toward a X-transfer enabled protocol for direct (hetero)aryl amination.

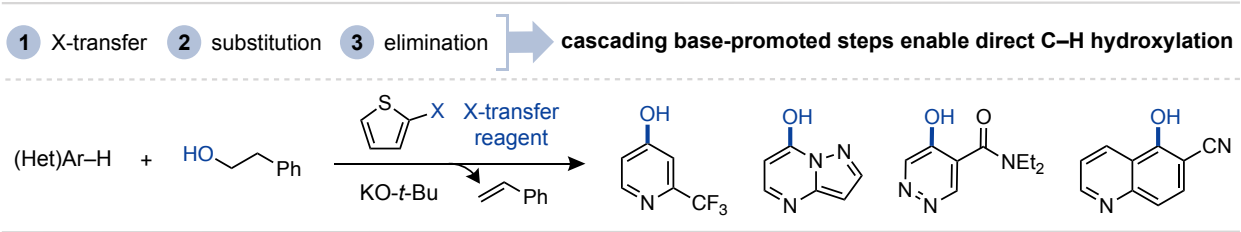


Figure 2-1: Direct C–H hydroxylation reaction that will be covered in Chapter 1

2.2. Background on Base-Catalyzed Halogen Transfer in Bandar Group

Our group's advance in C–H functionalization is a modern extension of the base-catalyzed halogen transfer (X-transfer). In 1951, Nord reported the first known example of X-transfer wherein 2-bromothiophene disproportionates into tetrabromothiophene and other thiophene byproducts *via* iterative metal-halogen transpositions (Figure 2-2, right).[1] The mechanism of this process was unclear until described in a series of publications by Bunnett in the early 1970's.[1] The utility of this mechanistic process has largely been applied in metalated haloarene isomerization/electrophilic functionalization methodology, but we apply X-transfer in a fundamentally distinct manner to achieve C–H functionalization (Figure 2-2, left). In this approach, a (hetero)aryl C–H bond is deprotonated to form a (hetero)aryl carbanion. The carbanion then attacks the halogen of the sacrificial aryl halide forming a diversifiable heteroaryl halide intermediate and turning over the base-catalyst. The (hetero)aryl halide intermediate then undergoes nucleophilic aromatic substitution to yield C–H functionalized products.

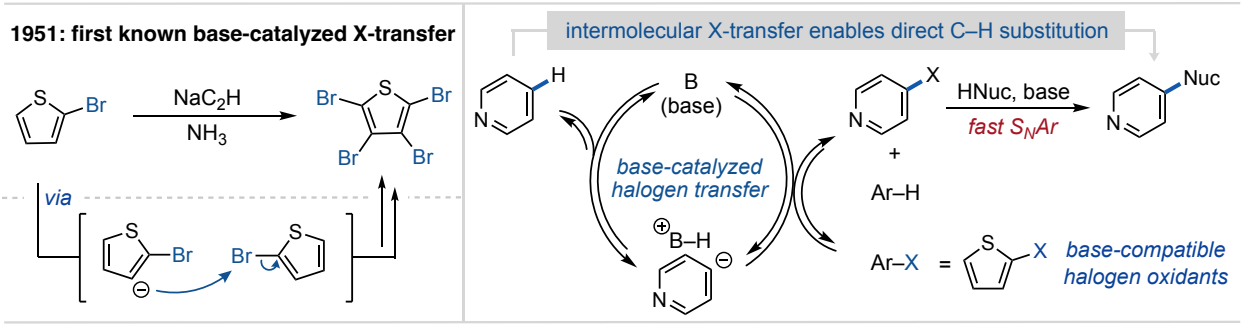


Figure 2-2: Nord's report of 2-bromothiophene disproportionation and mechanism of intermolecular X-transfer functionalization demonstrated on pyridine model substrate.

Sequencing X-transfer with a substitution reaction has several intrinsic requirements that require careful consideration: (1) the sacrificial aryl halide must effectively transfer halogens to transient aryl anions (2) X-transfer is a reversible process necessitating a thermodynamic driving force to avoid X-transfer back to the sacrificial aryl halide or other disproportionation reactions,

and (3) the X-transfer reagent must be compatible with the strong base and not be prone to nucleophilic substitution. We also realized widespread adoption of this methodology would also demand the X-transfer reagents to be air-stable and inexpensive to make or purchase.

With these considerations and inspiration from Nord's seminal report in mind, our group found that 2-halothiophenes act as X-transfer reagents to enable site-selective etherification of 1,3-azoles and (di)azines (Figure 2-3). This novel C–H etherification of heteroarenes was reported by my colleagues Tom Puleo and Danielle Klaus in a *JACS* publication (2021) where inexpensive and practical reagents such as KO-*t*-Bu and commercially available 2-halothiophenes are used.[2] This platform is compatible with a broad range of heterocycles including imidazoles, thiazoles, oxazoles, benzofused azoles, pyridines, pyrimidines, pyridazines, and fused (di)azines. The reaction also tolerates an impressive range of functional groups including sulfonamides, sulphones, 2-haloheteroarenes, benzylic protons, and amides. This major contribution in C–H functionalization methodology provides a novel approach to directly access heteroaryl ethers.

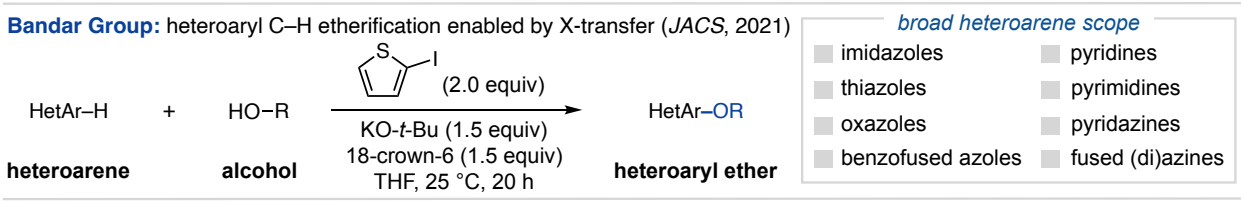


Figure 2-3: Bandar 2021 report of heteroaryl C–H etherification enabled by base-catalyzed X-transfer.

Although the ether functional group accessed in this X-transfer enabled protocol is widely present in high-value products such as bioactive molecules, it is inert to further elaboration. Thus, I sought to expand the utility of the method by installing a readily diversifiable functional group. To do this, I aimed develop a C–H hydroxylation protocol where the resulting hydroxylated products are useful synthetic intermediates (Figure 2-4).

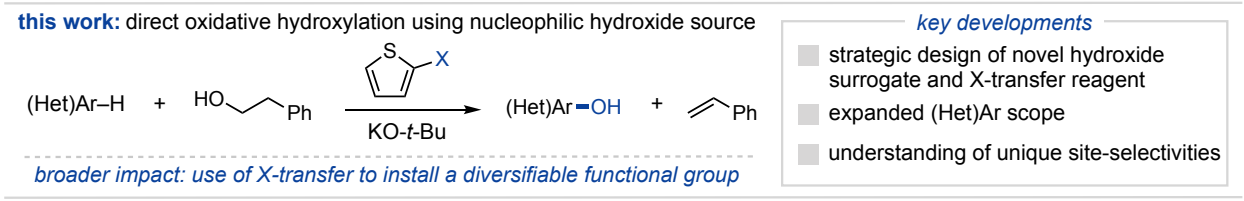


Figure 2-4: Application of base-catalyzed halogen transfer (X-transfer) toward a general C–H hydroxylation platform.

2.3. Importance Hydroxylated Heteroarenes and Electron-Deficient Benzenes

2.3.1. Importance of Hydroxylated Heteroarenes

Heteroarenes are common in a variety of natural products, ligand frameworks, polymers, electronic materials, and a recent survey found that they are present in 59% of pharmaceuticals (Figure 2-5, bottom).[3] The high occurrence of heteroarenes is a result of the unique properties they possess such as their electron deficiency, ability to hydrogen bond, their basic nitrogen center, and high polarity. Hydroxylated heteroarenes are an important subclass of heteroarenes common in bioactive molecules, as the hydroxyl group can act as both a hydrogen bond acceptor and donor and impact a compound's lipophilicity, aqueous solubility, and metabolic stability. In addition to the direct value hydroxylated heteroarenes have in bioactive compounds, they can be easily derivatized to access other motifs.[4] Several common derivatizations include deoxyhalogenation with $POCl_3$, electrophilic aromatic substitution of the arene, and functionalization of either the hydroxyl group or the nitrogen atom (Figure 2-5, top). It is important to note that the major tautomeric form of most 4-hydroxylated pyridines exist as the pyridone tautomer over the pyridinol tautomer, and all structures are depicted accordingly in this report.[5]

2.3.2. Importance of Phenols

The global phenol market is anticipated to reach USD $18.4 billion by 2029 and to continue rising.[6] Responsible for the high demand is the ubiquity of phenols as diversifiable intermediates in the manufacturing of drugs and antioxidants, their use in a large variety of commercial materials

such as dyes, wood preservatives, detergents, thermosetting plastics, laminates, and paper composites among other applications.[7] The utility of phenols in drug synthesis stems from their rich reactivity allowing for *O*-functionalization and electrophilic aromatic substitution (EAS) (Figure 2-5, top).[4] Despite the value of these transformations, they fail on complex phenols; therefore, it is of value to develop generalizable and simple protocols that grant access a wider variety of polyfunctionalized phenols. In addition to their value as versatile synthons, phenols also appear in bioactive molecules and other functional molecules (Figure 2-5, bottom).[8]

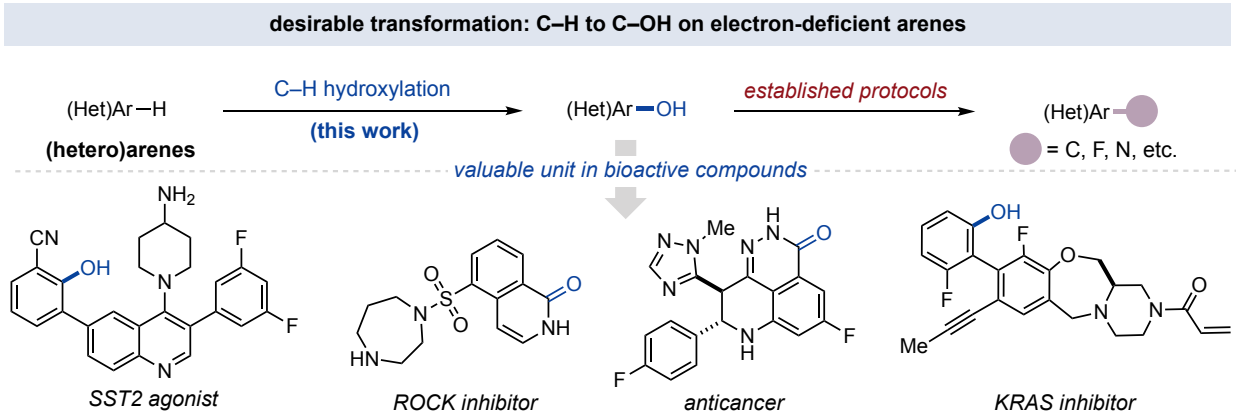


Figure 2-5: Importance of hydroxylated electron-deficient (hetero)arenes in bioactive molecules and as diversifiable intermediates in synthesis.

2.4. Methods to Access Hydroxylated Heteroarenes and Electron-Deficient Benzenes

The most practiced routes to install hydroxyl groups onto (hetero)arenes require prefunctionalized starting materials, most commonly through S_NAr or metal-catalyzed hydroxylation of heteroaryl halides or oxidation of heteroaryl boronates and silanes (Figure 2-6, right).[9-11] Significant advances in C−H borylation and silylation thus provide a multistep means of net C−H hydroxylation for a broad range of (hetero)arenes, with reviews on the selectivity and scope available.[12,13] Methods for installing alternative functional handles, such as halogen or phosphonium groups, as well as Ritter's C−H oxymesylation protocol, can also be leveraged to access to these classes of hydroxy(hetero)arenes.[14] Alternatively, simple hydroxylated

(hetero)arenes can undergo electrophilic aromatic substitutions, but this often leads to selectivity issues and requires access functionalized hydroxylated (hetero)arenes which are often prohibitively expensive (Figure 2-6, middle).[15] Regarding hydroxylated heteroarenes in particular, condensation reactions of acyclic precursors can be done, but these protocols require a disparate synthesis for each derivative where the acyclic precursors can be time consuming and resource intensive to synthesize (Figure 2-6, left).[15]

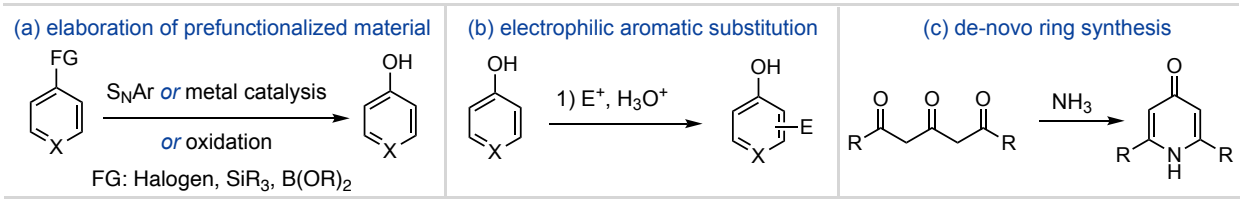


Figure 2-6: Traditional, non-direct methods to access hydroxylated (hetero)arenes.

As a more streamlined route, direct C−H hydroxylation of (hetero)arenes represents an attractive yet underdeveloped reaction.[16] This reactivity is a longstanding challenge as the nonnucleophilic nature and high oxidation potentials of (hetero)arenes generally preclude electrophilic and oxidative activation mechanisms. For example, several well-established approaches for benzene hydroxylation rely on electrophilic oxygen intermediates or single electron arene oxidation pathways that are best suited for electron-neutral to -rich arenes (Figure 2-7, right).[17] This includes a variety of impressive protocols, such as enzymatic, Fe-catalyzed, electro-(photo)catalytic, and phthaloyl peroxide-promoted benzene C−H hydroxylation, among others (Figure 2-7, middle).[18-22] Metal-catalyzed C−H activation methods are not as sensitive to arene electronic properties and provide phenols and *O*-acylated derivatives in the presence of *O*-oxidants.[23-24] However, these methods typically require directing groups for high selectivity and are often inhibited on *N*-heteroarenes due to catalyst coordination, although Yu recently addressed these issues in the context of a Pd-catalyzed method for ortho-hydroxylation of carboxylic groups on pyridines and benzenes (Figure 2-7, left).[25] Several alternative oxidation approaches such as

vicarious S_NAr, peracid- promoted, and microbial metabolic methods can overcome these reactivity challenges but are generally limited to specific substrates or by synthetic practicality.[26-27] Therefore, despite much effort dedicated to advancing aromatic C−H hydroxylation, there remains a lack of mechanistic strategies suited for *N*-heteroarenes and electron-deficient benzenes, especially those devoid of directing groups or that provide alternative selectivity to existing (multistep) protocols.

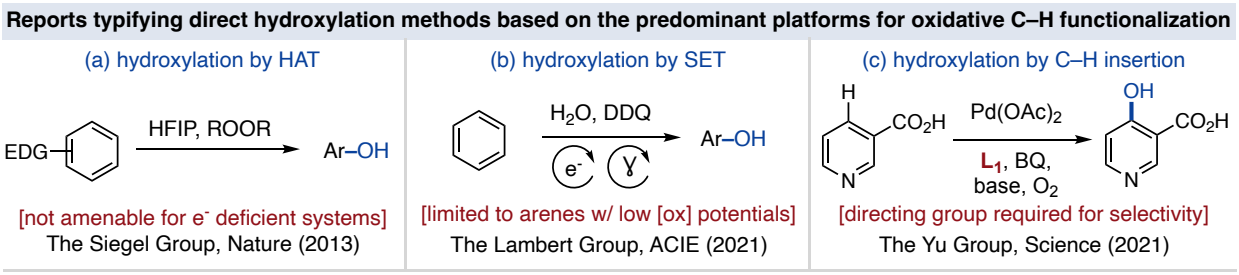


Figure 2-7: State-of-the-art methods to directly access hydroxylated (hetero)arenes.

A reliable and well-developed approach for electron-deficient arene C−H functionalization is through multistep deprotonative procedures.[29] These protocols employ strongly basic reagents for arene metalation prior to treatment with an electrophile, where site-selectivity is governed by C−H acidity and/or coordinating effects.[30,31] While organoalkali and alkaline intermediates readily undergo electrophilic halogenation, direct access to hydroxylated products is challenging due to a lack of effective electrophilic oxygen sources.[31] For example, treatment of aryl lithium species with dioxygen or peroxides typically gives low hydroxylation yields due to competing aryl dimerization and/or nonproductive protonation events.[32] To address this challenge, Uchiyama reported the use of copper to facilitate redox-mediated hydroxylation of aryl cuprate intermediates with tert-butyl hydroperoxide as an oxidant.[33] This process can also be rendered catalytic for highly acidic arenes, such as benzoxazoles and polyfluorinated benzenes. In practice, however, the

most reliable deprotonative approach to hydroxylate arenes is via a three-step procedure of metalation, coupling to a trialkyl borate, and subsequent oxidation (Figure 2-8).[34]

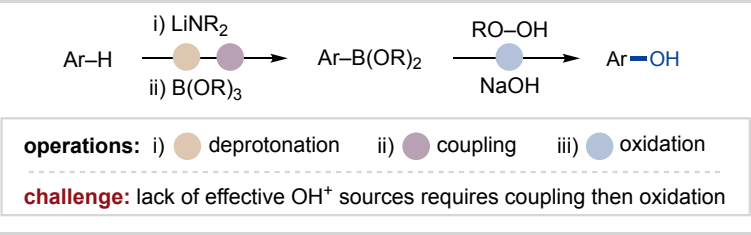


Figure 2-8: Traditional three-step protocol for C–H hydroxylation *via* deprotonation

2.5. Reaction Design Strategy and Identification of an Effective Hydroxide Surrogate

We sought to address the limitations in substrate scope, selectivity, and practicality of current C–H hydroxylation methods through the development of a direct deprotonative hydroxylation method enabled by our recently disclosed X-transfer reactivity platform.[2] To this end, we considered the fundamental processes at the core of the X-transfer reactivity which are that a C–H bond is being oxidized and substitution then occurs. In viewing it at this elementary level, we realized that there was an opportunity to leverage this mechanistic approach toward the development of a C–H hydroxylation protocol that could oxidatively couple a nucleophilic hydroxide surrogate with (hetero)arene C–H bonds. A method built on this mechanistic concept would address longstanding challenges in C–H hydroxylation, as it would select for mildly acidic C–H bonds and would be best-suited for electron-deficient (hetero)arenes. In the broader context, this method would directly install a synthetically versatile functional handle which, in turn, would effectively establish X-transfer chemistry as a general platform for aromatic C–H functionalization.

We set out to develop a C−H hydroxylation method that does not require multiple operations or a discrete deprotection step. To begin, we selected the 4-hydroxylation of 3-bromopyridine (**2-1**) as a model reaction using our previously reported conditions for C−H

etherification (Figure 2-9). Initial reaction attempts using water or metal hydroxides did not yield the desired hydroxylated product. Since S_NAr with these nucleophiles is a known challenge, this lack of reactivity was not unexpected.[35] We therefore sought a pronucleophile that could serve as a hydroxide surrogate through C−O coupling with concomitant base-promoted deprotection. Fier and Maloney have addressed this using benzaldehyde oxime (**2-4**) and acetohydroxamic acid (**2-5**) as hydroxide surrogates in metal-catalyzed coupling and S_NAr reactions of aryl halides, respectively.[9a,10c] However, these reagents did not participate in the X-transfer C−H substitution process, thus necessitating a new hydroxide surrogate.

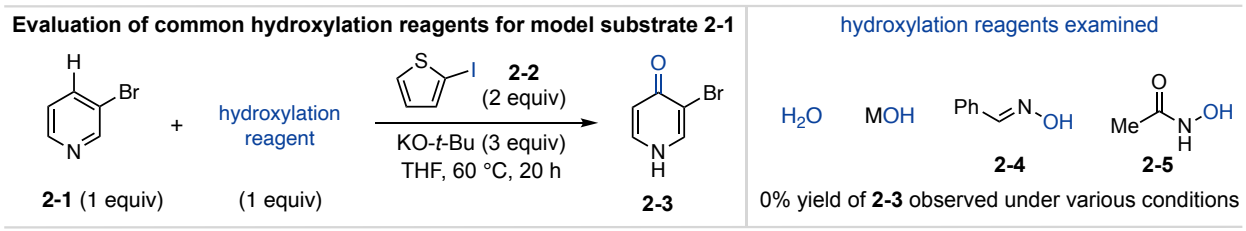


Figure 2-9: Initial investigation into hydroxylation reagents for the 4-hydroxylation of 2-1.

We reasoned that an *in situ* base-promoted deprotection approach could still be viable if a sufficiently nucleophilic alcohol is prone to elimination only after successful etherification of the *N*-heteroarene. To this end, we were inspired by a separate area of work in our laboratory focused on improving base-catalyzed alcohol addition reactions to alkenes.[36] As part of those efforts, we recently reported thermodynamic and kinetic studies on the reversible addition of oxygen pronucleophiles to styrene derivatives.[37] The K_{eq} values for these reactions indicate that phenol pronucleophiles, compared to water, drastically favor the elimination products (Figure 2-10). Additionally, the rate of the elimination reaction is significantly faster for phenol than water. These observations indicate that β-aryl alcohols can be base-stable and, upon *O*- arylation, undergo rapid elimination with a K_{eq} that favors phenoxide formation. We therefore hypothesized that a β-aryl

alcohol could be identified that balances these thermodynamic and kinetic considerations to enable direct aromatic C−H hydroxylation.

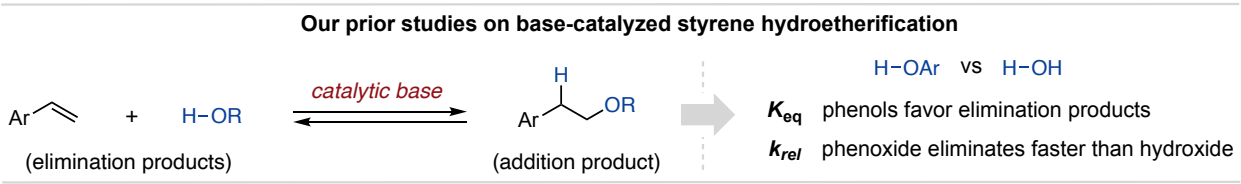


Figure 2-10: Bandar Group studies on alcohol addition into aryl alkenes (*JACS* 2018 & 2022).

To test this hypothesis, we evaluated *β*-aryl alcohols with the model 3-bromopyridine substrate (**2-1**), tracking the formation of the 4-hydroxylated product and alkene byproduct (Figure 2-11). We found that the parent 2-phenylethanol provides 65% yield of 2-3 with 84% styrene formation. Electronic variation of the *β*-aryl group does not improve the yield nor do alcohols with alternative *β*-activating groups. These alcohol derivatives were either not nucleophilic enough to promote facile S_NAr or were not as stable under basic conditions. Thus, 2-phenylethanol has optimal reactivity and is practically advantageous as it is inexpensive (approximately $4/mol) due to its use in the fragrance and food industries.[38] We note that the optimized conditions use 1.0 equiv of 2-phenylethanol and do not require 18-crown-6 additive, an improvement over our reported C−H etherification protocol that typically performs best with 1.5 equiv of both alcohol and 18-crown-6 (see full condition optimization in APPENNDIX ONE). In general, 3 equiv of KO-*t*-Bu provides the highest yields for this C−H hydroxylation protocol given that the S_NAr and elimination steps both consume an equivalent of base.

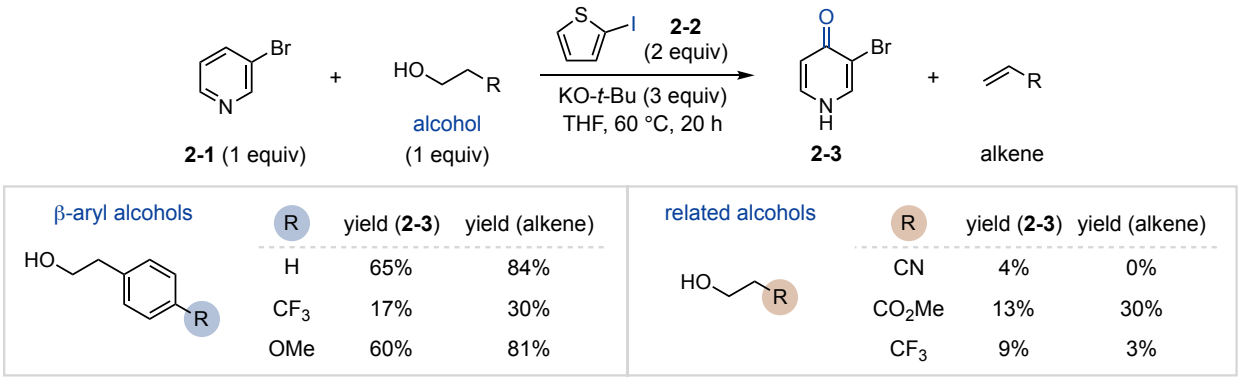


Figure 2-11: Effect of water surrogate identity on yield of the C–H hydroxylation of 3-bromopyridine.

Subjection of the *β*-phenethyl ether intermediate xx to KO-*t*-Bu results in 84% elimination in 5 min, whereas 2-phenylethanol (**2-8**) undergoes only 6% elimination after 24 h. This indicates a >100-fold rate increase for elimination following *O*-arylation, consistent with the proposed hydroxide surrogate design strategy (Figure 3-12). This also indicates that, in the C–H hydroxylation reaction, intermediate **2-6** rapidly eliminates to generate the conjugate base of **2-3**, which does not undergo X- transfer, and thus, no overoxidation products are observed for this protocol.

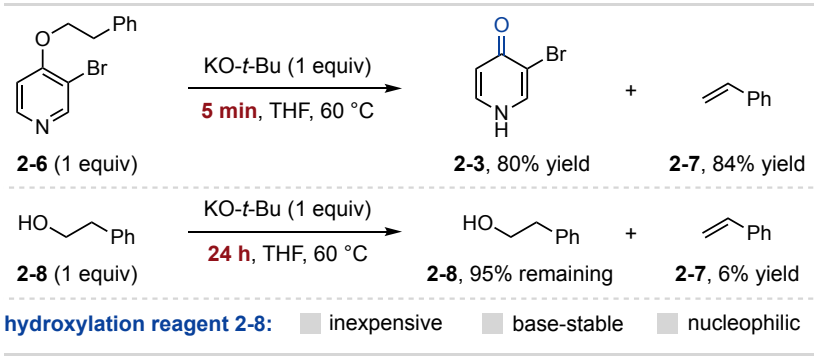


Figure 2-12: Comparison of rate of styrene formation from 2-phenethanol and 3-bromo-4-phenethoxypyridine.

To independently probe the X-transfer step of this process, we conducted an additional control study where catalytic KO-*t*-Bu (10 mol %) was mixed with 3-bromopyridine (**2-1**) and 2-iodothiophene in the absence of 2-phenethylalcohol. A mixture of 4- and 5-iodinated pyridines (**2-**

9 and **2-10**) are generated in 23% overall yield, demonstrating the catalytic nature of X-transfer and the necessity of the S_NAr step to drive a selective and high-yielding C−H functionalization reaction (Figure 2-13). The yields in Figure 2-13 do not substantially increase with extended time. The 5-iodinated isomer (**2-10**) is likely formed from the 4-iodinated isomer (**2-9**) via a "halogen dance" process.[39] We describe this process to be enabled by base-catalyzed halogen transfer, as demonstrated in Figure 2-2. However, it is not always possible to readily track the formation of halogenated intermediates using this simple control experiment given the instability of the (hetero)aryl halides under the basic conditions, so we note that it is possible for certain substrates the X-transfer step is base-promoted rather than -catalyzed.

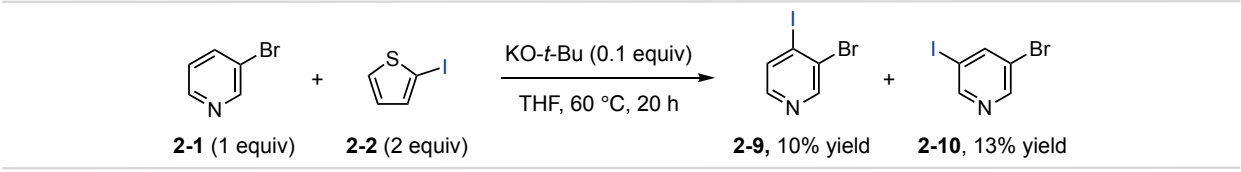


Figure 2-13: Evidence of KO-*t*-Bu-catalyzed iodine transfer to 3-bromopyridine.

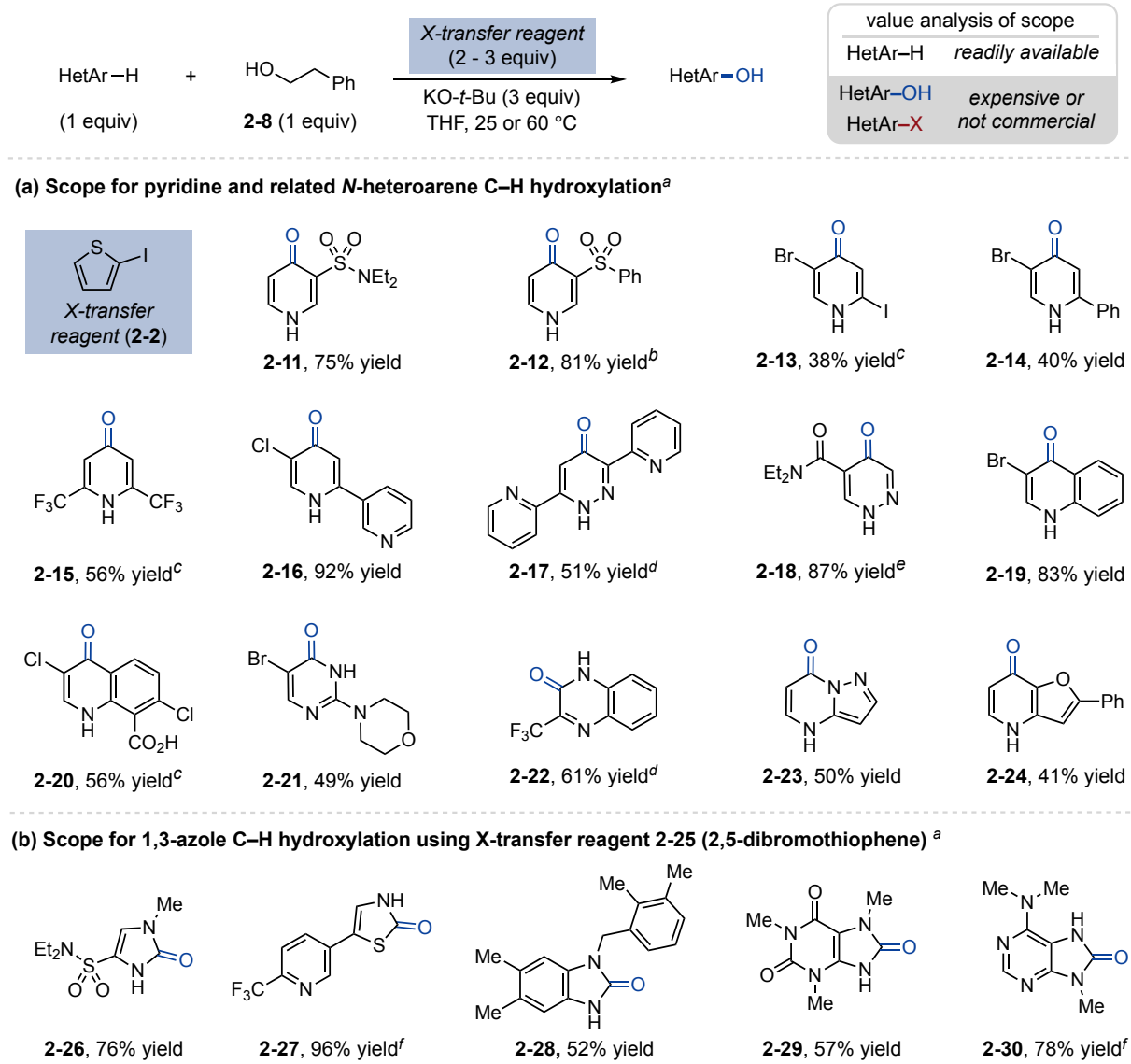
2.6. Substrate Scope for *N*-Heteroarene C−H Hydroxylation.

To demonstrate the scope of this method, we targeted examples wherein the starting materials are inexpensive or readily available relative to the corresponding halogenated congeners that are either not commercial or require multistep preparation. This feature is represented with a diverse scope of *N*-heteroarene products in Figure 2-14, while further discussion of this protocol's utility, comparison to alternative hydroxylation methods, and limitations is provided in Section 2-9 below. For the products shown, >10:1 site-selectivity is observed by ^{1}H NMR spectroscopic analyses of the crude reaction mixtures.

Figure 2-14a shows the use of 2-iodothiophene (**2-2**) for the hydroxylation of pyridines and related *N*-heteroarenes. Pyridines containing electron-withdrawing substituents such as

sulfonamides (**2-11**), sulfones (**2-12**), and trifluoromethyl groups (**2-15**) in the 2- or 3-positions lead to 4-hydroxylation in good yield. Halogenated substrates (**2-13**, **2-15**) also undergo C−H hydroxylation to provide products with multiple diversifiable functional groups. Regioselectivity is achieved on polyazines, where hydroxylation occurs on the more acidic (di)azine, as highlighted by chloropyridine **2-16** and pyridazine **2-17**. Substituted pyridazines (**2-18**), quinolines (**2-19**), and pyrimidines (**2-21**) are effective, including the herbicide quinclorac (**2-20**) that contains a free carboxylic acid. Structurally diverse fused (di)azines (**2-22**−**2-24**) also undergo C−H hydroxylation. In general, when the yield is less than 75%, the remaining mass balance is primarily the *N*-heteroarene substrate. For example, substrates **2-17**, **2-22**, **2-24**, **2-28**, **2-32**, and **2-40** have > 25% remaining starting material; this is consistent with these substrates having lower acidity that causes less-efficient deprotonative X-transfer.

For 5-membered *N*-heteroarenes (Figure 2-14b), 2,5-dibromothiophene (**2-25**) is used in place of 2-iodothiophene due to the fact that 2-bromoazole intermediates undergo S_NAr with alkoxide nucleophiles under these conditions, in contrast to 2-iodoazoles.[42] 2-Selective C−H hydroxylation is effective for diverse 1,3-azoles (**2-26**−**2-30**), including heterobiaryl systems (**2-27**), benzo-fused azoles (**2-28**), and nucleobases (**2-29**, **2-30**). Notably, for substrates with multiple aryl groups, including polyalkylated arenes (**2-28**), hydroxylation occurs at the more acidic azole ring. This protocol complements Lei's report of Cu-catalyzed, NaO-*t*-Bu-promoted aerobic oxidation of benzoxazoles and benzothiazoles by expanding the scope to nonfused azoles.[29]



[a]Isolated yields of 1 mmol scale reactions, >10:1 site-selectivity as determined by ^{1}H NMR spectroscopy of crude reaction mixtures; conducted at 60 °C for 20 h for Figure 2-14, a and 25 °C for 3 h for Figure 1-14, b. [b]40 °C. [c]18-crown-6 (3 equiv) additive used. [d]3-bromo-2-iodobenzothiophene used in place of **2-2**. [e]DMF solvent. [f]2,3-dibromobenzothiophene used in place of **2-25**.

Figure 2-14: Substrate Scope for *N*-Heteroaryl C–H Hydroxylation.

2.7. Optimization and Substrate Scope for Benzene C–H Hydroxylation

We next reasoned that the X-transfer mechanism should be transferable to benzenes so long as they contain a mildly acidic C–H bond and the postulated halogenated intermediate is S_NAr-active. This would expand the substrate scope of our initial C–H etherification protocol in

which only *N*-heteroarenes were demonstrated.[2] Diphenyl sulfone (**2-31**) was selected as a representative benzene substrate as it is available in bulk quantities, yet the corresponding *ortho*-halo and -hydroxy derivatives are not commercial and are challenging to prepare.[43] To test for the feasibility of the S_NAr step on this substrate, separately prepared iodination diphenyl sulfone was subjected to S_NAr conditions. Hydroxylation occurred in 68% yield which supported that the X-transfer approach could be feasible (see appendix 1).

We were encouraged to find that a slight modification of the *N*-heteroarene hydroxylation conditions with 2-iodothiophene provides phenol **2-32**, albeit in 35% yield (Figure 2-15). Attempts to increase the yield through condition optimization were unsuccessful, motivating us to examine and improve the X-transfer reagent itself.

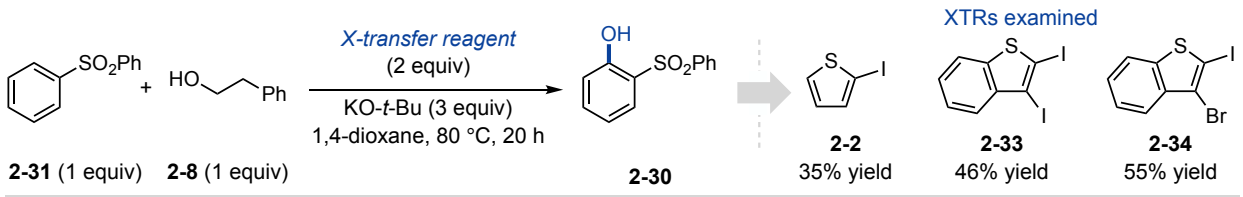


Figure 2-15: Identification of X-transfer reagent for model benzene substrate **2-31**.

In our prior work and for the reactions shown in Figure 2-14, we observed 3-iodothiophene (**2-36**) as a major byproduct when 2-iodothiophene (**2-2**) is used as an oxidant. We speculate that, under basic conditions, 2-iodothiophene disproportionates into 3-iodothiophene *via* 2,3-diiodothiophene (**2-35**, Figure 2-16).[1c, 44] This led us to propose that 2,3-diiodothiophene may be an active X-transfer species, as the 3-iodo substituent polarizes the 2−C−I bond for faster X-transfer and stabilizes the incipient 2-thienyl anion. However, 2,3-diiodothiophene can further disproportionate into inactive 3-iodinated thiophenes (*e.g.*, **2-36** and **2-38**). This nonproductive process is likely to predominate when the arene substrate is not acidic enough to generate a sufficient concentration of carbanion, such as with benzenes.

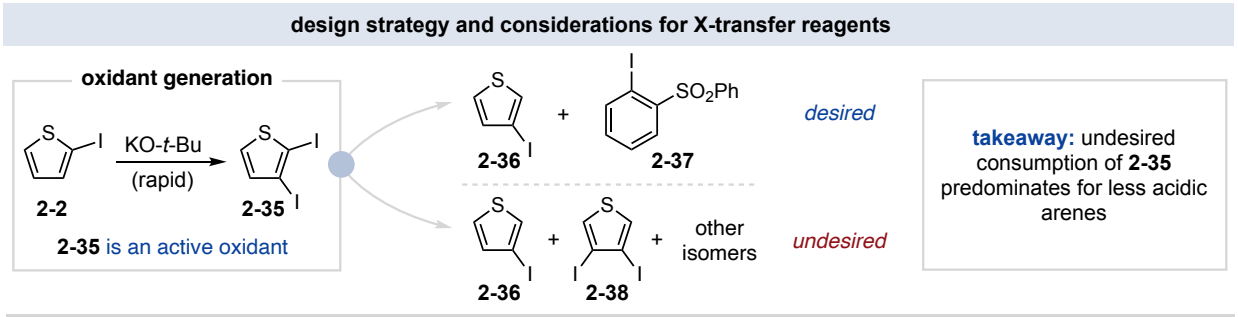
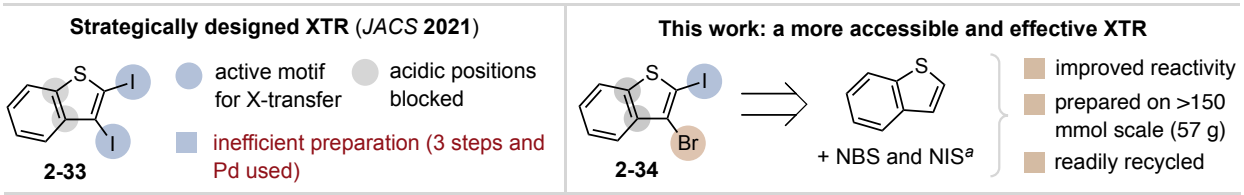


Figure 2-16: Disproportionation pathway of **2-2** when used with less-acidic arene substrate.

Based on this hypothesis, previously developed 2,3-diiodobenzothiophene (**2-33**), wherein a 2,3-dihalo motif is preinstalled and the 4- and 5-positions of the thiophene are substituted to prevent disproportionation (Figure 2-17, right). This reagent has improved stability under basic conditions and increases the C−H hydroxylation yield for diphenyl sulfone (**2-32**) to 46%. Modifying the substituent at the 3-position to a bromine improves the yield to 55%, likely due to enhanced inductive effects (Figure 2-17, left). Notably, 3-bromo-2-iodobenzothiophene (**2-34**) was prepared on >150 mmol scale in 75% yield by treatment of benzothiophene ($120/mol) with *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS) (Figure 2-17, left). This is a marked improvement over the three-step synthesis of 2,3-diiodobenzothiophene (**2-33**) that requires a Pd catalyst and more costly 2-iodothioanisole ($1600/mol) starting material. This reagent is a bench stable free flowing powder, adding to its ease of use and practicality.

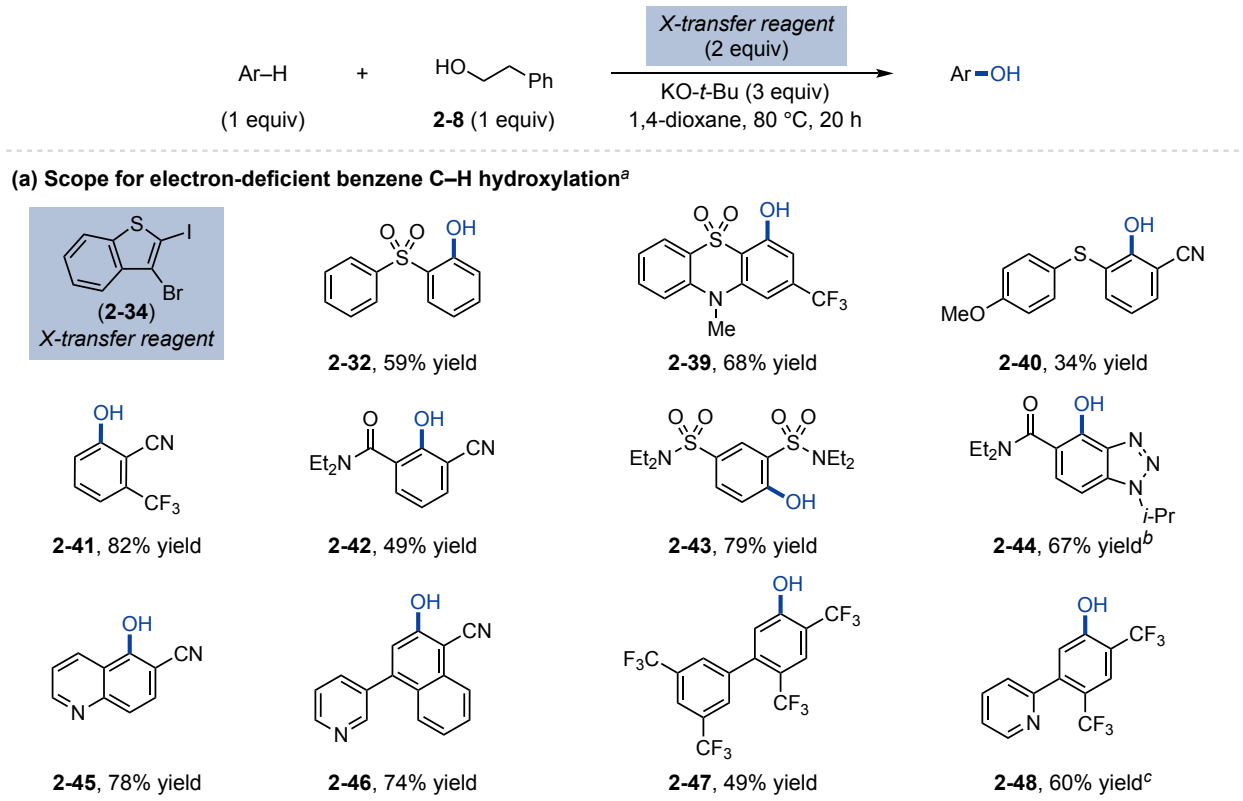


[a]Two-step 75% yield (167 mmol) using NBS (step 1) and NIS (step 2) halogenation reactions as detailed in appendix 1.

Figure 2-17: X-transfer reagent development for benzene C–H hydroxylation.

Using 3-bromo-2-iodobenzothiophene (**2-34**) as a more stable, robust reagent under the hydroxylation conditions allows for the direct hydroxylation of a diverse set of electron-deficient

benzenes (Figure 3-18). Sulfonyl- and cyano groups with a variety of substitution patterns effectively activate benzenes for C−H hydroxylation (**2-32**, **2-39**-**2-42**). Benzenes with other acidifying substituents, such as amides (**2-42**, **2-44**), sulfonamides (**2-43**), and trifluoromethyl groups (**2-47**, **2-48**) also undergo hydroxylation. Hydroxylation of compounds with multiple aryl rings occurs selectively on the more electron-deficient arene, a trend that contrasts electrophilic aromatic substitution and hydroxylation methods.[18-24] High selectivity is also observed for substrates with multiple acidic C−H sites, including biaryl systems (**2-46**-**2-48**) and those with potentially coordinating pyridyl substituents (**2-48**).[25a] For substrates in Figure 2-17, the remaining mass balance is primarily unfunctionalized benzene substrate with the moderate yields likely caused by a lower acidity or a relatively challenging S_NAr step. The S_NAr step challenge is demonstrated by this control experiment where preiodinated diphenylsulfone undergoes 68% hydroxylation under pseudoreaction conditions with 13% competing protodeiodination. Overall, strategic modification of the halogen transfer reagent structure enabled significant yield improvements for the more challenging benzene systems.



[a]Isolated yields of 1 mmol scale reactions, >10:1 site-selectivity as determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [b]2 equiv of KO-*t*-Bu. [c]DME and 18-crown-6 (3 equiv) used.

Figure 2-18: Substrate Scope for electron-deficient benzene C–H Hydroxylation.

2.8. Studies on the Site-Selectivity of X-Transfer-Enabled C−H Hydroxylation

The high positional selectivity observed for the products in Figures 2-14 and 2-18 motivated us to investigate the origin of selectivity in X-transfer-mediated C−H functionalization, a subject not addressed in our initial report. This protocol employs a relatively weak and noncoordinating alkoxide base for deprotonation, so we initially presumed that selectivity is simply obtained for the most acidic site on the arene.[31,45] This appears to be true for the few deprotonative C−H functionalization protocols of acidic (hetero)arenes facilitated by alkoxide bases, such as halogenation with common electrophilic halogen sources and carboxylation with CO_2.[46,47] However, these reported methods are distinct from this X-transfer-mediated strategy as they do not extend to less acidic (di)azines or benzene substrates reported in Figures 2-14 and 2-

18, respectively.[48] Therefore, we investigated the factors that regulate site-selectivity on each class of (hetero)arene. We began by conducting deuterium exchange experiments to ascertain the most favorable site of deprotonation under the optimized conditions.[49] These experiments were performed by mixing the (hetero)arene substrate with deuterated methanol (CD_3OD) and KO-*t*-Bu (Figure 2-19). The percentage of deuterium incorporation at each position of the (hetero)arene was then assessed by ^1H NMR spectroscopy. Initial studies were carried out with benzothiazole (**2-49**) as the C−H bond at the 2-position is more acidic (pK_a 27.3 in DMSO) than those at positions 4−7 (pK_a > 38 in DMSO), thus providing a simple model system (Figure 2-19, top).[31] Predictably, deuteration occurs exclusively at the 2-position. In this case, the most favorable deuteration site is also the position of C−H functionalization *via* X-transfer, a scenario we describe as "matched".

We next conducted deuterium exchange experiments on two distinct pyridine substrates (Figure 3-19, bottom). For pyridine itself, the order of positional acidity is 4-position >3-position >2-position.[31] This pK_a trend is reinforced on pyridines with acidifying substituents at the 3-position, as seen on 3-bromopyridine (**2-1**) where deuterium incorporation occurs exclusively at the 4-position, another case of matched selectivity. In contrast, 2,6-bis(trifluoromethyl)pyridine (**2-50**) undergoes deuteration fastest at the 3- and 5-positions, although the 4-position is selectively functionalized *via* X- transfer. We define this scenario as "mismatched". Representative examples of matched (**2-51**) and mismatched (**2-52**) benzene substrates are also shown in Figure 2-19, bottom. These results are consistent with aryl activation proceeding through alkoxide- mediated deprotonation as the deuterium exchange sites reflect C−H acidity trends.[31,50,51]

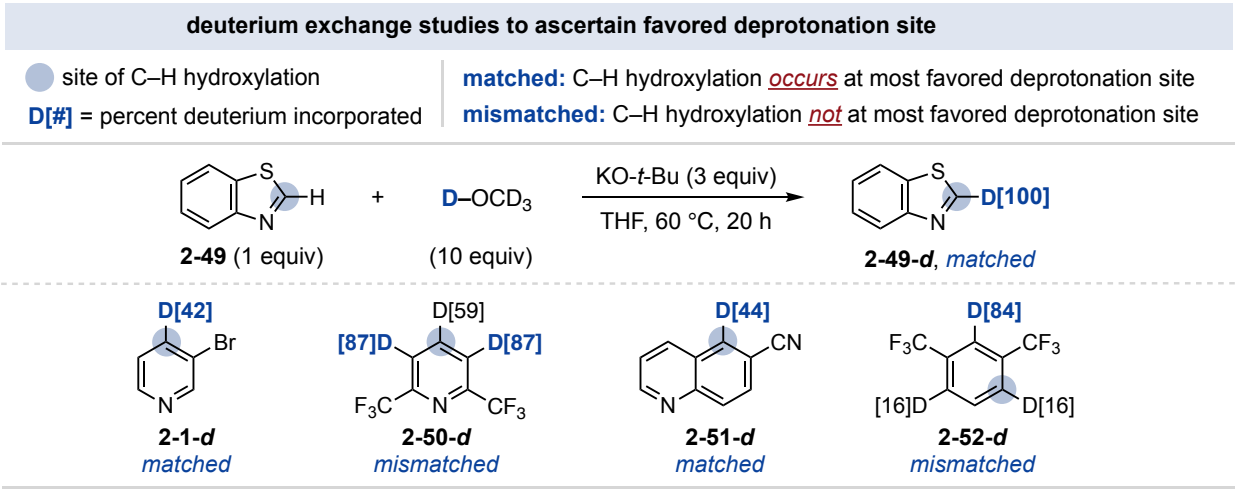


Figure 2-19: Deuterium exchange studies on each class of arene.

To better understand the mismatched cases, we studied the potential interplay among the deprotonation, X-transfer, and substitution steps on the reaction selectivity. We first examined 2,6-bis(trifluoromethyl)pyridine (**2-50**), an arene for which there is no reported 4-selective metalation protocol but undergoes C−H hydroxylation in 83% yield with >10:1 4-selectivity (Figure 2-20a).[52] We subjected 3-iodo-2,6-bis(trifluoromethyl)-pyridine (**2-53**), a potential intermediate that is halogenated at the most acidic position, to hydroxylation pseudoreaction conditions (Figure 2-20b). Using KO-*t*-Bu and 2-phenylethanol, the 3- and 4-hydroxylated products form in similar quantities, initially suggesting that compound **2-53** is not an intermediate under the X-transfer conditions.[53] However, conducting the same control experiment with **2-53** in the presence of 2-iodothiophene (**2-2**) or 3-iodothiophene (**2-36**, an X-transfer byproduct) led to 4-hydroxylation as the major product. We propose that a reversible X-transfer mechanism can explain these observations and the high 4-selectivity for **2-50**. Specifically, if the acidic pyridyl 3-position is halogenated, S_NAr of the 3-iodinated intermediate xx is relatively slow, allowing for reversible X-transfer and halogen migration to the more S_NAr-active 4-position (Figure 2-20c).[54,55]

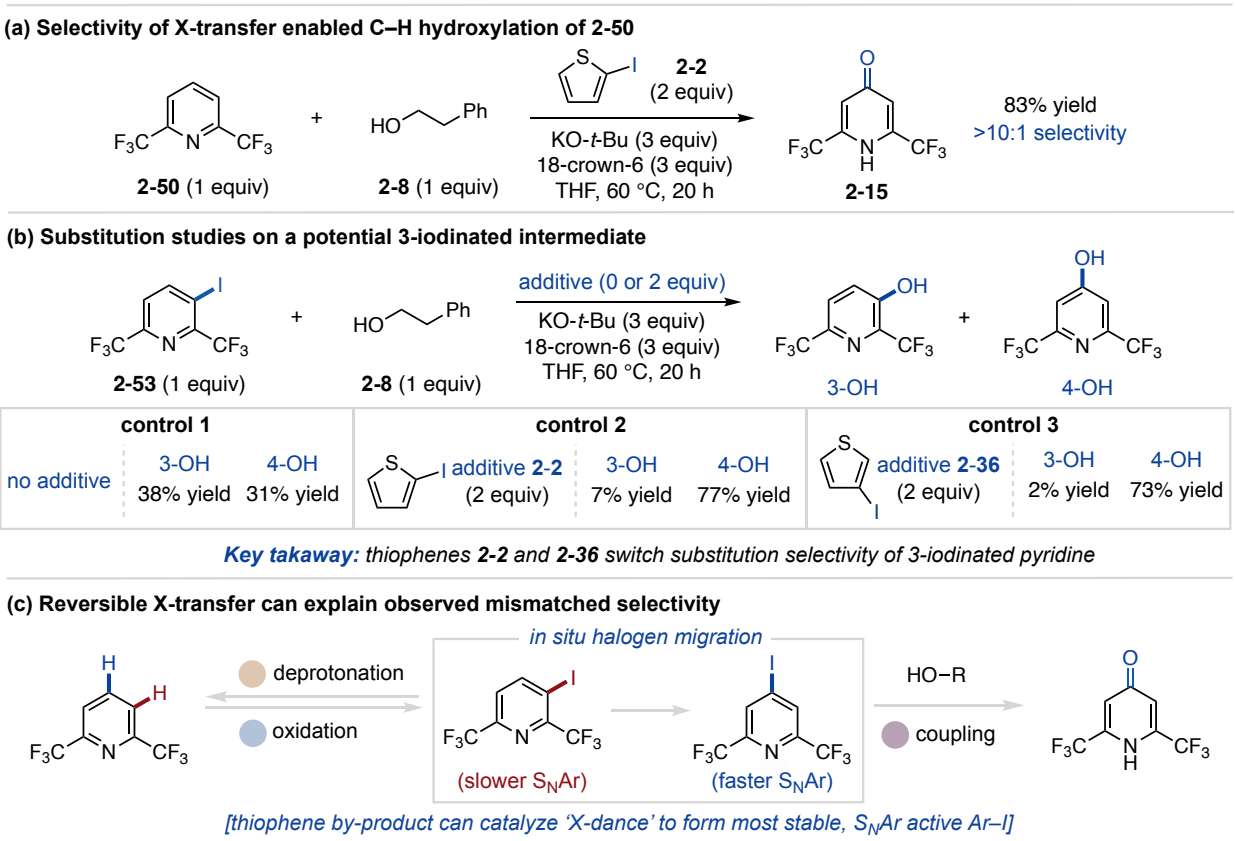


Figure 2-20: Selectivity studies on 2,6-bis(trifluoromethyl)pyridine (**2-50**), a mismatched case study.

Further evidence of a reversible X-transfer process was observed in studies on 1,3-bis(trifluoromethyl)benzene (**2-55**), a mismatched substrate that undergoes hydroxylation with >10:1 4-selectivity (31% yield, Figure 2-21a).[56] 2-Iodo-1,3-bis-(trifluoromethyl)benzene (**2-55**), a potential intermediate halogenated at the most acidic position, was subjected to pseudoreaction conditions using KO-*t*-Bu and 2-phenyl-ethanol. Without a thiophene additive present, an 82% yield of the 2-hydroxy product (**2-56**) is observed, indicating that *ipso*- S_NAr occurs on the 2-iodo isomer (Figure 2-21). In a separate control reaction with X-transfer byproduct **2-57** as an additive, after 10 min, removal of the iodine to give **2-52** (88% yield) and formation of the iodinated X-transfer reagent **2-34** is observed (43% yield).[57] Subsequent heating of the solution for 20 h gives the 4-hydroxy isomer (**2-54**) in 33% yield with >10:1 selectivity. This indicates X-transfer from **2-55** to 3-bromobenzothiophene (**2-57**) is faster than S_NAr at the 2-position, likely due to steric

hindrance of the two *ortho*-trifluoromethyl groups. Accordingly, under the authentic reaction conditions (Figure 2-21), if 2-iodination occurs, S_NAr is slower than reversible halogen transfer and migration to the 4-position.[55] This also helps to explain the high regioselectivity obtained for biaryl phenol product **2-47** in Figure 2-17 that possesses four $-CF_3$ groups and multiple similarly acidic sites.

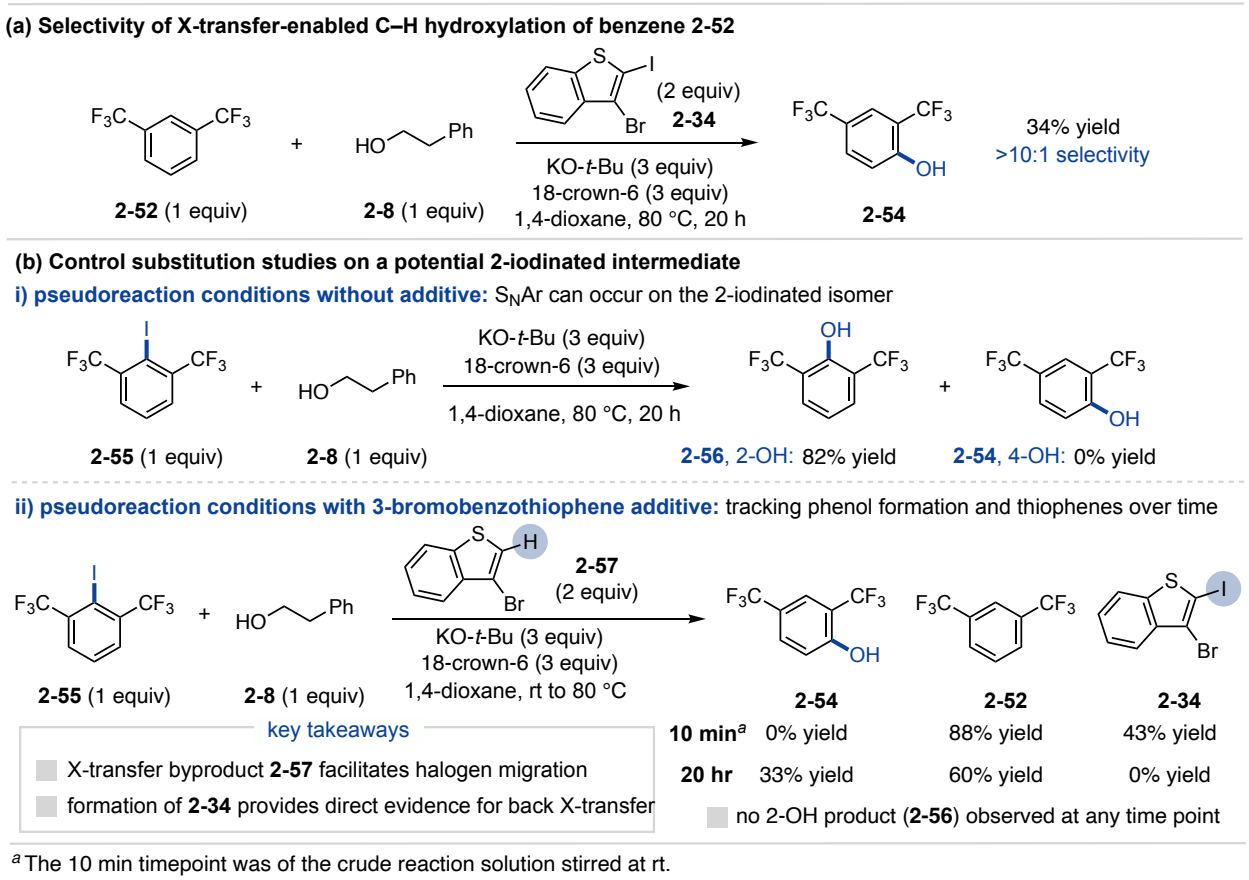


Figure 2-21: Selectivity studies 1,3-bis(trifluoromethyl)benzene (**2-52**), a mismatched case-study.

In summary, these studies indicate that reversible X-transfer and S_NAr reactivity trends can rationalize the high C−H substitution selectivity even if halogenation occurs at multiple positions.[55] However, for substrates that generate multiple equilibrating anions, it is also possible that selective halogen transfer occurs from the 2-halothiophene due to either steric considerations or relative anion nucleophilicities.[58] Given the rapid and dynamic nature of the deprotonation and

X-transfer steps, we have not been able to fully track halogen movement throughout an ongoing reaction.[59] Nonetheless, the compatibility and synergy of deprotonation, halogenation, and substitution represent a new means for controlling deprotonative arene functionalization selectivity. This mechanistic sequence is general to arenes with broad structural diversity so long as they are within an approximate 25−38 pK_a window (in DMSO) and generate S_NAr-active intermediates.[31] The suitable scope of *N*-heteroarenes includes those with electron-withdrawing and -donating groups, provided that they are within this acidity range.[60] Future efforts will survey a larger range of (hetero)arenes to generate a quantitative selectivity model and guide C−H functionalization to alternative positions. Predictably, some base-sensitive functional groups are not currently tolerated, such as esters and alkyl halides. Additionally, compounds with alternative acidic C−H bonds (*e.g.*, methylpyridines and acidic ketones) can interfere with X-transfer, a subject we are exploring in other ongoing work.

2.9. Applications and Utility of the C−H Hydroxylation Protocol.

With insight into the selectivity and scope, we next sought to demonstrate how this C−H hydroxylation reaction provides unique capabilities compared to existing chemistry. This protocol uses inexpensive reagents to directly obtain hydroxyarenes that are inaccessible via alternative direct C−H hydroxylation methods. This advantage is illustrated in the multigram scale preparation of **2-59**, a hydroxylated imidazopyridazine building block where the starting material is inexpensive and the corresponding halogenated precursors are not commercial (Figure 2-22a). An analogous application is shown for the hydroxylation of benzene **2-60** (Figure 2-22b), where 3-bromobenzothiophene (**2-57**) was also recovered and recycled to the active X-transfer reagent **2-34** (72% overall regeneration, Figure 2-22b).

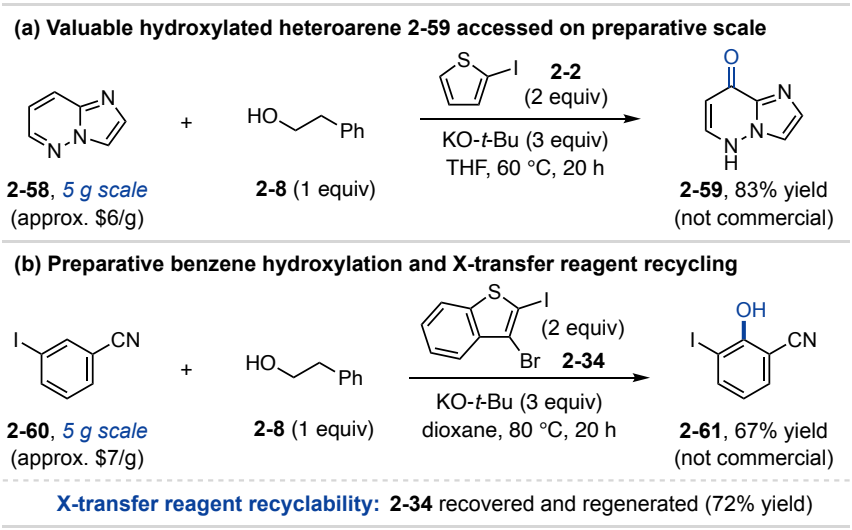


Figure 2-22: Multigram scale C–H hydroxylation and X-transfer reagent recyclability.

Halogenated phenols are frequently prepared *via* electrophilic halogenation of the corresponding phenol; however, this approach can suffer from regioselectivity issues for nonsymmetrical arenes.[61] This limitation is observed for the electrophilic halogenation of 2-(trifluoromethyl)-4-pyridone (**2-62**) that gives an inseparable mixture of the 3- and 5-bromo isomers (**2-63** and **2-64**, Figure 2-23). In contrast, C−H hydroxylation of either inexpensive 3- or 5-bromo-2-(trifluoromethyl)pyridine isomer gives exclusive access to each 4-pyridone (Figure 2-23). This comparison illustrates the value of switching the order of halogenation and hydroxylation steps enabled by this protocol.

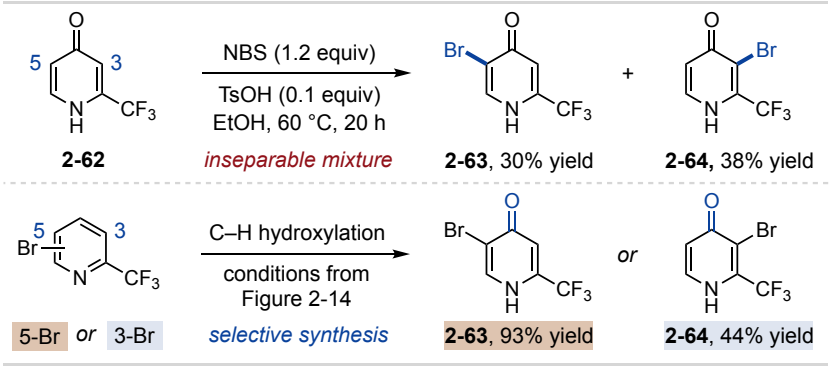
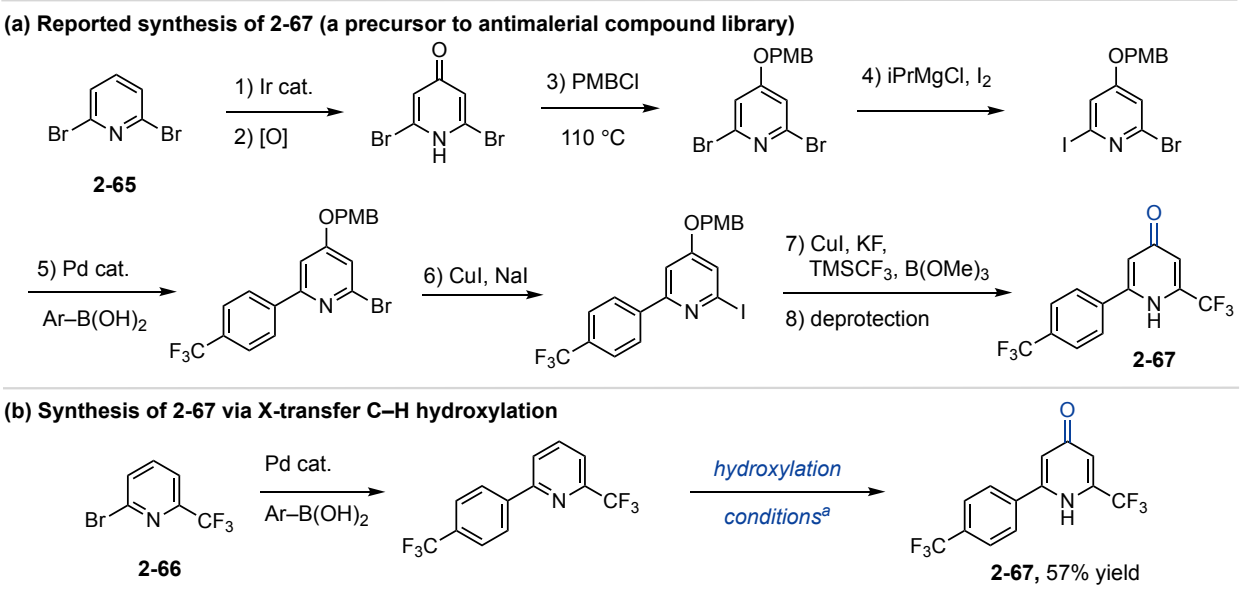


Figure 2-23: Hydroxylation comparison to electrophilic halogenation of hydroxypyridines.

This method can also streamline the synthesis of specific targets. For example, there is a long-standing challenge in accessing 2,4,6-trisubstitued pyridines where functional handles with distinct reactivities at each position of the pyridine are needed to perform selective sequential functionalization. This challenge is typified in the synthesis of **2-67** which was reported in a 2019 investigation of antimalarial drug candidates (Figure 2-24a).[62] First, an iridium-catalyzed borylation/oxidation sequence followed by a challenging protection step was used to give protected pyridone intermediate. A Grignard reaction was then done to give desymmetrized pyridine intermediate and a subsequent Suzuki cross-coupling afforded biaryl intermediate. A copper mediated aryl Finkelstein reaction followed by a nucleophilic copper-mediated trifluoromethylation and subsequent deprotection furnished the final product (**2-67**). Meanwhile our X-transfer hydroxylation protocol provides access to **2-66** from inexpensive **2-67** (~$2/ gram) in two practical and scalable steps in 57% yield (Figure 2-24b).



[a]Hydroxylation conditions use 2.0 eq 2-iodothiophene, 3.0 eq of KO-*t*-Bu and 18-crown-6 in THF at 60 °C for 20 hours.

Figure 2-24: Comparison of reported route to **2-67** versus X-transfer enabled C–H hydroxylation.

Inspired by the route comparisons in Figure 2-24, we next show how C–H hydroxylation can improve access to polysubstituted phenols more broadly. In general, access to such compounds requires the use of polyhalogenated arenes that can be prohibitively expensive and challenging to selectively synthesize or functionalize (Figure 2-25).[63] In contrast, cross-coupling of inexpensive monohalobenzenes followed by X-transfer C–H hydroxylation provides a new route to multisubstituted phenols. These concepts are illustrated in Figure 2-25 for access to biaryl phenols (**2-68**-**2-71**) built from the inexpensive 3-(trifluoromethyl)benzonitrile scaffold. We note that hydroxylation occurs on the more electron-deficient aryl ring in a complementary fashion to other benzene C–H hydroxylation and halogenation protocols. Here, our site-selectivity studies help to explain the regioisomeric outcomes. In brief, substitution at the 4-position is favored (i.e. adjacent to the nitrile), but this preference can be overridden if the position is sterically encumbered or blocked by a preexisting substituent.

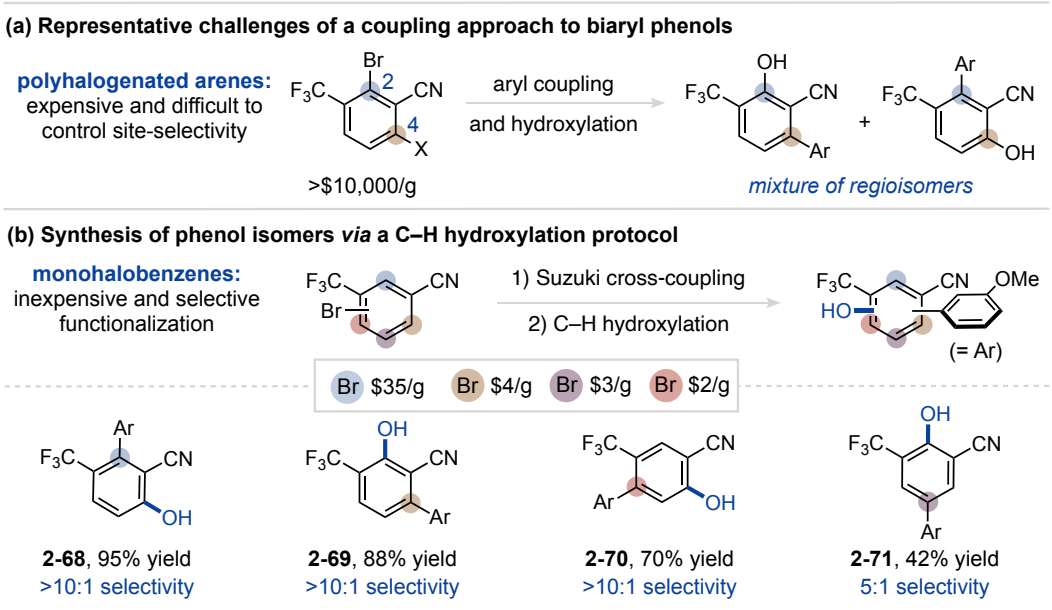
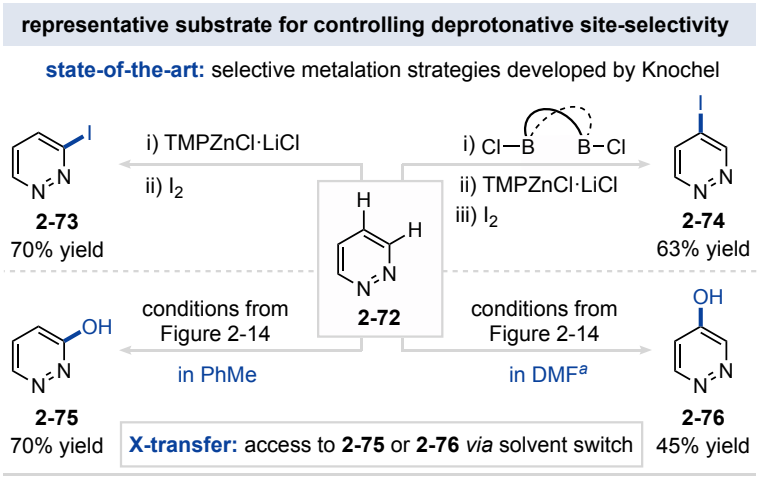


Figure 2-25: Demonstration of improved access to polyfunctionalized phenols using X-transfer-mediated C–H hydroxylation.

This C–H hydroxylation method is unique in that it uses alkoxide bases, as compared to traditional arene metalation that relies on substantially stronger bases (e.g. LiTMP) and whose selectivity has been the subject of much research. Here, alkoxide-promoted hydroxylation occurs with high regioselectivity on arenes with multiple acidic sites (e.g. **2-15**, **2-18**, **2-39**, **2-43**, **2-47**, **2-59**, **2-63**, **2-70**) or potentially competitive directing groups (e.g. **2-14**, **2-17**, **2-48**, **2-67**) and tolerance of base-sensitive functional groups (e.g. nitriles, carboxylic acids, halogens and azoles). An additional striking contrast was observed while investigating pyridazine, a challenging benchmark for metalation chemistry where selectivity control has only recently been achieved by Knochel using 'ate' bases in conjunction with Lewis acids (Figure 2-26, top).[64,65] In our studies, we found site-selectivity for pyridazine C–H hydroxylation switches simply by a change of solvent and use of 18-crown-6 additive (Figure 2-26, bottom). Here, 3-hydroxylation occurs in PhMe while 4-hydroxylation occurs in DMF with 18-crown-6 additive. We speculate the reaction in PhMe promotes coordination between the pyridazine *N*-atom and the potassium alkoxide for 3-deprotonation, whereas the noncoordinating DMF/18-crown-6 conditions lead to deprotonation at the more acidic 4-position. In this sense, the unique reagents, conditions and mechanistic features of X-transfer offers new opportunities over traditional metalation for regulating deprotonative arene functionalization.



[a]18-crown-6 used (3.0 equiv).

Figure 2-26: Comparison of methods for selective pyridazine deprotonative functionalization.

2.10. Expansion of Amenable Nucleophile Coupling Partner to Enable Direct C–H (Hetero)arene Amination

(Hetero)aryl amine motifs are widely present in bioactive molecules, agrichemicals, and other important organic materials.[66] The most practical method to access these products is through direct C–H amination, thereby avoiding the need for access to prefunctionalized materials and providing streamlined access to the desired products. A variety of direct (hetero)aryl amination protocols have been developed, but these methods either require steric or electronic bias to achieve site-selectivity, are limited in the types of amine nucleophiles, or require harsh reaction conditions.[67,68] Thus, it would be of great interest to the scientific community to develop a robust protocol that could selectively couple a broad range of amines with electron deficient (hetero)arenes.

To address this issue, we aimed to continue expansion of the X-transfer platform regarding the nucleophile scope where we sought to engage amine nucleophile coupling partners in place of the alcohol pronucleophiles employed in our previous methods. In initial attempts to achieve this reactivity, a variety of amines were screened using (hetero)arene substrates that were suitable in the etherification and hydroxylation reaction using iodine X-transfer reagents. Low-yields of the

aminated products were observed using the iodine X-transfer reagents under a variety of conditions (Figure 2-27).

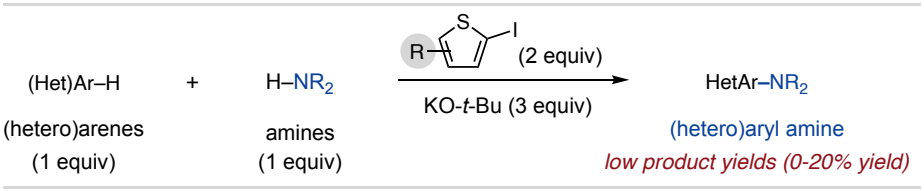


Figure 2-27: Initial attempts at (hetero)aryl amination *via* X-transfer.

To probe the challenge in this reactivity, control reactions to test the feasibility of the S_NAr step for the brominated and iodinated intermediates of diphenyl sulphone were performed. It was determined that S_NAr from the iodinated intermediate was not facile, but that amination *via* an S_NAr pathway was possible from the brominated diphenyl sulfone intermediate (Figure 2-28, top). Based on this result, I screened the X-transfer enabled amination on (hetero)arenes that were amenable in the C–H etherification and hydroxylation protocols using a library of bromine X-transfer reagents that a post-doc in our lab, Dr. Mike DeLost, recently developed. These substrates furnished the respective aminated products using variety of primary and secondary alkyl and aniline amine nucleophiles with moderate yields (Figure 2-28, bottom). This reaction is in its early stages of development and these results can serve as a platform for a future student to further develop.

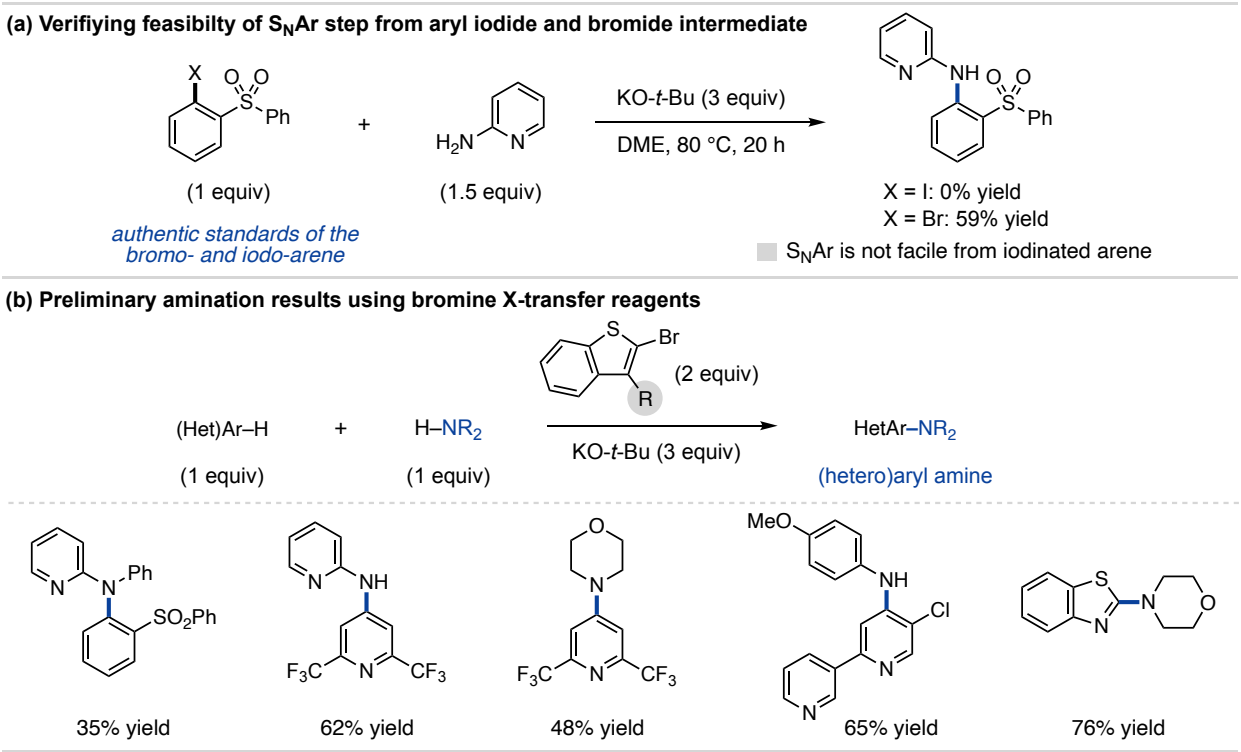


Figure 2-28: Progress made on in expanding the X-transfer reactivity toward (hetero)aryl amination.

2.11. Conclusion

The work described in this chapter was published in the *Journal of the American Chemical Society* in 2024.[69] This method effectively leverages base-catalyzed X-transfer to establish a general aromatic C−H functionalization process by means of hydroxylation. Thus, a broad range of mildly acidic *N*-heteroarenes and benzenes can be combined with simple reagents to obtain valuable hydroxylated synthons. This deprotonative approach addresses limitations of existing aromatic C−H hydroxylation methods as it is ideally suited for all classes of electron-deficient arenes without the need for directing groups. The key to this direct protocol is the ability of X-transfer chemistry to merge deprotonation, oxidation, substitution, and elimination into compatible processes. Our studies suggest that these steps are dynamic and operate in synergy, a fact that manifests in distinct selectivity trends compared to traditional multistep metalation protocols.

Chapter two will describe the expansion of the X-transfer enabled approach to benzylic C(sp^3)–H bonds.

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[38] Prices obtained from www.emolecules.com on 10/30/2023. (a) 2-Phenylethanol (CAS #60-12-8) is an inexpensive commercial reagent (1 kg available for $33 USD). (b) 2,3-Diiodobenzothiophene (**2-33**) is prepared from 2-iodothioanisole (CAS #33775-94-9), a commercially available but costly starting material ($150/25g).

[39] The 5-iodinated isomer (**2-10**) is likely formed from the 4-iodinated isomer (**2-9**) *via* a "halogen dance" process. We describe this process to be enabled by base-catalyzed halogen transfer, as demonstrated in Figure 5c. However, it is not always possible to readily track the formation of halogenated intermediates using this simple control experiment given the instability of the (hetero)aryl halides under the basic conditions. Thus, we note that it is possible for certain substrates the X-transfer step is base-promoted rather than -catalyzed. In general, 3 equiv of KO-*t*-Bu provides the highest yields for this C–H hydroxylation protocol given that the S_NAr and elimination steps both consume an equivalent of base.

[40] For example, the starting material for substrate **2-13** costs ~$2/g, whereas the corresponding aryl halides and hydroxylated product (C–X or C–OH) are not commercially available. This trend is retained for all starting materials used to access products in Figure 2-14 except **2-19**, **2-22** and **2-23**. Prices obtained from www.emolecules.com on 12/04/2023.

[41] For example, substrates **2-17**, **2-22**, **2-24**, **2-28, 2-32** and **2-40** have >25% remaining starting material; this is consistent with these substrates having lower acidity that causes less-efficient deprotonative X-transfer. Two additional causes of yield loss are product volatility during isolation (e.g., **2-15** has 83% ^{1}H NMR yield and 56% isolated yield) and competing S_NAr side reactions on halogenated substrates (e.g., 15% 2-hydroxylation observed for substrate **2-13**). For less electron-deficient benzene substrates, S_NAr of the iodinated intermediate is more challenging (e.g., **2-32**); a control experiment showed 2-iododiphenylsulfone undergoes 68% hydroxylation under pseudoreaction conditions with 13% competing protodeiodination. A discussion of these considerations is provided in the Supporting Information.

[42] 2-Iodothiazole does not undergo high-yielding S_NAr under similar conditions using alcohol pronucleophiles; see ref 2.

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[46] For alkoxide-promoted halogenation of acidic arenes, see: (a) Do, H.-Q.; Daugulis, O. A Simple Base-Mediated Halogenation of Acidic sp2 C−H Bonds under Noncryogenic Conditions. *Org. Lett.* **2009**, *11*, 421−423. (b) Popov, I.; Do, H.-Q.; Daugulis, O. In Situ Generation and Trapping of Aryllithium and Arylpotassium Species by Halogen, Sulfur, and Carbon Electrophiles. *J. Org. Chem.* **2009**, *74*, 8309–8313. (c) Shi, Q.; Zhang, S.; Zhang, J.; Oswald, V. F.; Amassian, A.; Marder, S. R.; Blakey, S. B. KOtBu-Initiated Aryl C–H Iodination: A Powerful Tool for the Synthesis of High Electron Affinity Compounds. *J. Am. Chem. Soc*. **2016**, *138*, 3946−3949.

[47] For alkoxide-promoted carboxylation of acidic benzenes, see: Shigeno, M.; Hanasaka, K.; Tohara, I.; Izumi, K.; Yamakoshi, H.; Kwon, E.; Nozawa-Kumada, K.; Kondo, Y. Direct C–H Carboxylation Forming Polyfunctionalized Aromatic Carboxylic Acids by Combined Brønsted Bases. *Org. Lett.* **2022**, *24*, 809−814.

[48] The alkoxide-promoted halogenation methods in ref 46 apply to arenes substantially more acidic than those in Tables 1a and 2, such as such as polyfluorobenzenes and 1,3-azoles.

[49] (a) Tortajada, A.; Hevia, E. Alkali-metal bases in catalytic hydrogen isotope exchange processes. *Catal. Sci. Technol.* **2023**, *13*, 4919–4925. (b) Kopf, S.; Liu, J.; Franke, R.; Jiao, H.; Neumann, H.; Beller, M. Base-Mediated Remote Deuteration of *N*-Heteroarenes – Broad Scope and Mechanism. *Eur. J. Org. Chem*. **2022**, e202200204. (c) Li, Y.; Zheng, C.; Jiang, Z.-J.; Tang, J.; Tang, B.; Gao, Z. Potassium *tert*-butoxide promoted regioselective deuteration of pyridines. *Chem. Commun.* **2022**, *58*, 3497-3500. (d) Gu, J.-G.; Wang, C.-X.; Hu, G.-Q.; Shen, K.; Zhang, H.-H. K_2CO_3/18-Crown-6-Catalyzed Selective H/D Exchange of Heteroarenes with Bromide as a Removable Directing Group. *Org. Lett.* **2023**, *25*, 3055-3059.

[50] This observation is consistent with prior mechanistic studies on alkoxide-mediated aryl C–H deuterium exchange reactions that have studied the possibility of single electron pathways but routinely support activation *via* deprotonation (see ref 49). An extensive discussion is provided by Jiao, Neuman, Beller and coworkers in 49b. The results in Figure 3-19 also indicate that halothiophenes are not necessary for KO-*t*-Bu to deprotonate (hetero)arene substrates; further, no interactions between *N*-heteroarenes and 2-halothiophenes are observed in UV-Vis spectroscopy experiments, suggesting there is no interaction between these arenes prior to deprotonation.

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[53] High 4-selectivity would be expected if substitution occurred solely *via* an aryne pathway. Additionally, we do not observe 3-hydroxylation under C–H functionalization conditions. See: (a) Goetz, A. E.; Garg, N. K. Regioselective reactions of 3,4-pyridynes enabled by the aryne distortion model. *Nat. Chem.* **2013**, *5*, 54–60. (b) Benkeser, R. A.; Severson, R. G. The Reaction of Sodium Amide with *o*- and *m*-Chlorotrifluoromethylbenzene. *J. Am. Chem. Soc.* **1949**, *71*, 3838–3839.

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[55] This process is akin to a catalytic halogen dance, where halogen migration is driven by the thermodynamic stability of the resulting aryl anionic (or metallic) species; see ref 36. For an example of base-promoted halogen dance on compound **1-55**, see: Cottet, F.; Marull, M.; Lefebvre, O.; Scholosser, M. Recommendable Routes to Trifluoromethyl-Substituted Pyridine- and Quinolinecarboxylic Acids. *Eur. J. Org. Chem.* **2003**, *2003*, 1559–1568.

[56] For metalation studies of 1,3-bis(trifluoromethyl)benzene, see: (a) Schlosser, M.; Katsoulos, G.; Takagishi, S. Superbase reactions: the expedient and selective metalation of fluorine- or trifluoromethyl-substituted benzenes. *Synlett* **1990**, *12*, 747–748. (b) Castelló-Micó, A.; Herbert, S.; León, T.; Bein, T.; Knochel, P. Functionalizations of Mixtures of Regioisomeric Aryllithium Compounds by Selective Trapping with Dichlorozirconocene. *Angew. Chem. Int. Ed.* **2016**, *55*, 401–404.

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[59] Aryl halide intermediates can be observed in low quantities if the pronucleophile is left out of solution.

[60] To illustrate this trend and the tolerance of electron-donating groups, we examined several simple 3-substitute pyridines under the standard conditions from Tables 1a and 2. Pyridine itself is not sufficiently acidic (0% yield and 100% starting material) and 3-methylpyridine displays competing reactivity at the more acidic benzylic site (0% hydroxylation yield and

52% starting material). 3-Methoxypyridine (8% yield and 67% starting material) gives low yield while 3-bromo-5- methoxypyridine (47% yield) provides increased yield, consistent with acidity being the key factor. See appendix 1 for details.

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[65] For other studies on selective pyridazine deprotonative functionalization, see: (a) Imahori, T.; Kondo, Y. A New Strategy for Deprotonative Functionalization of Aromatics: Transformations with Excellent Chemoselectivity and Unique Regioselectivities Using *t*-Bu-P4 Base. *J. Am. Chem. Soc*. **2003**, *125*, 8082–8083. (b) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. A *J. Am. Chem. Soc.* **2008**, *130*, 15185–15192.

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CHAPTER THREE

DIRECT BENZYLIC C–H ETHERIFICATION ENABLED BY BASE-PROMOTED HALOGEN TRANSFER

3.1. Chapter Overview

My studies showed that X-transfer-mediated aromatic functionalization chemistry can be applied toward mildly acidic C–H bonds, where the postulated halogenated intermediate is active toward substitution. Therefore, we posited that this methodology could be expanded beyond sp^2-hybridized systems to provide a protocol for direct benzylic C–H functionalization. This would aid in addressing the surging demand for mechanistically distinct direct benzylic functionalization protocols.

This chapter describes our efforts in accomplishing this through the development of a X-transfer enabled benzylic C–H oxidative coupling reaction with alcohols that proceeds through a synergistic deprotonation, halogenation and substitution sequence (Figure 3-1). This reactivity gives rise to new synthetic capabilities, including the ability to functionalize diverse methyl(hetero)arenes, tolerance of oxidizable and nucleophilic functional groups, precision regioselectivity for polyalkylarenes and use of a double benzaldehydes. The complementary nature of this approach to existing radical-based pathways for C–H functionalization will be presented throughout the chapter.

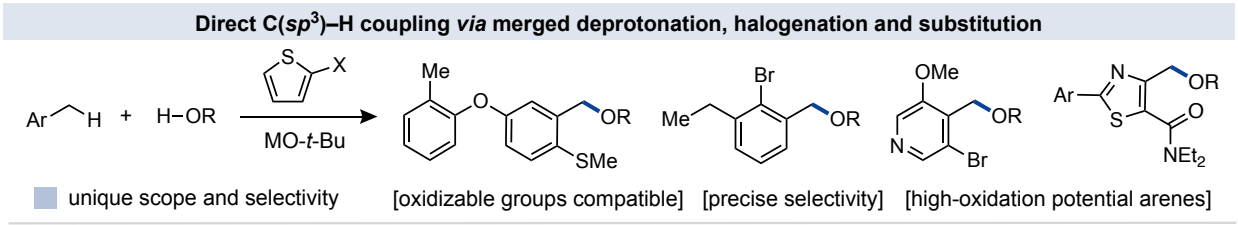


Figure 3-1: Direct benzylic etherification reaction that will be covered in Chapter 3.

3.2. Value and Methods to Access Benzylic Coupled Products

3.2.1. Importance of Benzylic Ethers

The benzylic ether motif is widely employed across many industries, including in pharmaceutical agrochemicals and materials.[1,2] Owing to their use in the pharmaceutical industry is their ability to act as H-bond acceptors, decrease lipophilicity thereby potentially enhancing aqueous solubility and reducing metabolic liabilities.[3] Figure 3-2 displays several benzylic ethers that are important pharmaceuticals.

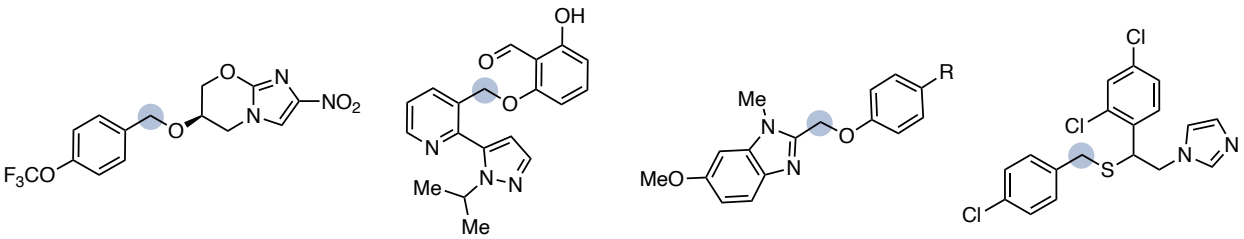


Figure 3-2: Examples of benzyl (thio)ethers in pharmaceuticals and bioactive compounds.

3.2.2. Methods to Access Benzylic Ethers

The widely valued benzyl ether motif is commonly produced by alcohol substitution reactions of benzylic electrophiles, especially benzyl halides.[4] As such, benzylic C–H radical halogenation methods are widely relied upon for the net coupling of alkylarenes with alcohols as a two-step route to benzyl ethers (Figure 3-3). In addition to the use of hazardous initiators, these routes require independent preparation and handling of toxic benzyl halides.[5] Furthermore, the C–H halogenation step is prone to undesired dihalogenation, is not site-selective for compounds with multiple weak C–H bonds and can be incompatible with nucleophilic or oxidizable functional groups.[6] While some of these concerns have been addressed through modern approaches to C–H radical halogenation[7], direct oxidative coupling of abundantly available alkylarenes with alcohols represents a more efficient and modular approach to benzyl ethers.[8,9]

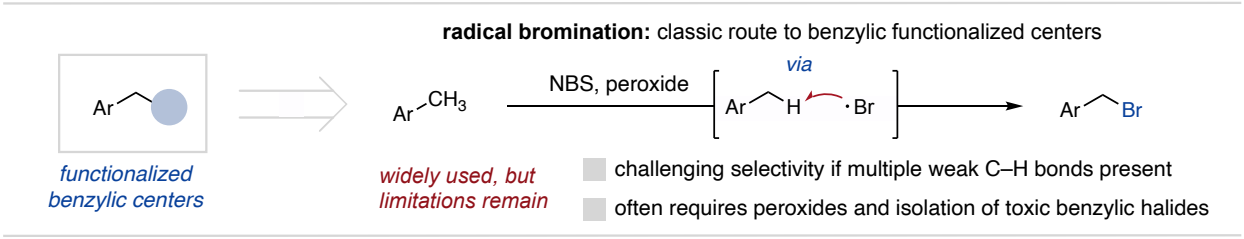


Figure 3-3: Accessing functionalized centers *via* benzylic radical halogenation.

These advantages have motivated developments in benzylic C–H etherification reactions that proceed *via* initial alkylarene activation by single electron oxidation or hydrogen atom abstraction.[10-12] In these reactions, C–O bond formation is ultimately accomplished by alcohol addition to benzylic carbocations or metal-mediated coupling of benzylic radicals. Specifically, there are electrochemical methods to do single-electron transfer, such as this etherification method developed by the Lei group where two-iterative single-electron transfers by the anode provides a benzylic radical that is then coupled with an alcohol nucleophile (Figure 3-4, right).[11b] A disadvantage with etherification by electrochemical methods however is that the substrate scope is limited to simple arenes with low oxidation potentials. Another example of a single-electron transfer pathway was described by Yoon, where they reported benzylic etherification by photoredox catalysis (Figure 3-4, right).[11a] In this method, single-electron transfer followed by deprotonation furnishes a benzylic radical. Further oxidation gives a benzyl cation that is the coupled with an alcohol nucleophile *in situ*. In terms of benzylic radical formation, Stahl developed a copper catalyzed radical relay method where hydrogen atom abstraction of an alkyl arene C–H bond followed by copper-mediated coupling furnishes the benzyl coupled product (Figure 3-4, left).[10a]

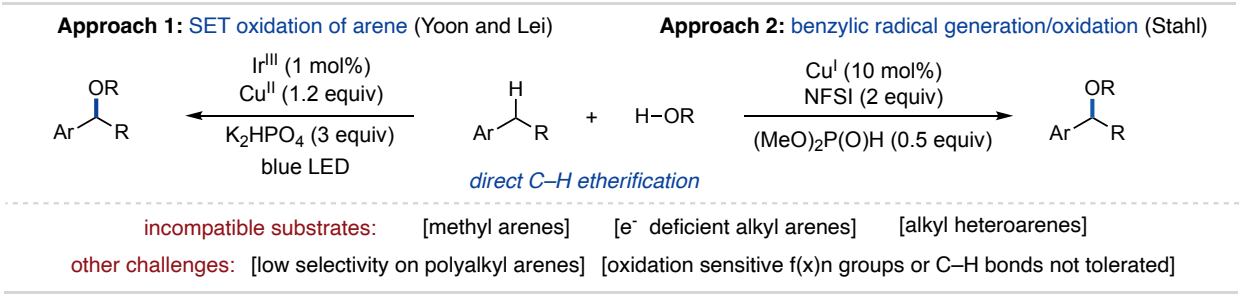


Figure 3-4: Established mechanistic approaches for direct benzylic C–H etherification.

Overall, these each of these methods are limited in the fact that they are not amenable to methyl arenes, electron-deficient alkyl arenes, and alkyl heteroarenes. These protocols also struggle to provide selectivity on polyalkyl systems and demonstrate chemoselectivity challenges when oxidation sensitive functionality or other weak C–H bonds are present. Thus, there is a demand for a mechanistically distinct method for benzylic C–H etherification that can address these limitations.

3.3. Reaction Design and Optimization

We herein describe a new approach to benzylic oxidative coupling reactions that proceeds *via* a base-promoted C–H halogenation/substitution sequence with unique scope, selectivity and utility that are distinct from existing C–H functionalization routes. Although seemingly simple, deprotonative benzylic C–H halogenation is undeveloped due to the incompatibility of strong bases and halogen oxidants. For example, the deprotonative halogenation of weakly acidic benzylic C–H bonds would require a two-step protocol consisting of metalation followed by electrophilic halogenation.[13] In practice, however, the benzyl halide generated upon addition of the halogen electrophile reacts with the pre-generated metalated alkylarene, causing benzylic dimerization (Figure 3-5a).[14,15] We note these challenges can be overcome for the C–H fluorination and chlorination of relatively acidic alkyl-*N*-heteroarenes (e.g., 4-alkylpyridines) using weak bases in conjunction with *N*-atom activation, as developed by the Britton and Stahl

groups.[16] We realized that the key to productively leverage deprotonative benzylic halogenation more generally is to devise a process wherein the base, halogen oxidant and desired benzyl halide functionalization event (e.g., substitution) are all compatible (Figure 3-5b).

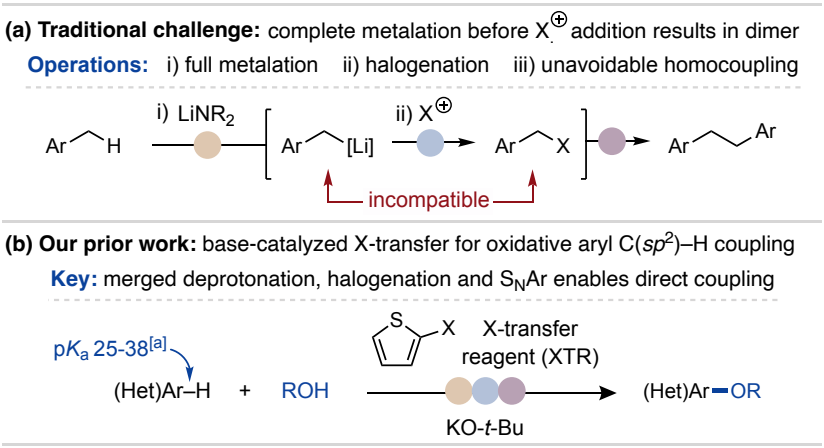


Figure 3-5: Considerations and outline of a deprotonative approach to the generation and use of benzyl halides.

Inspired by the X-transfer enabled aryl hydroxylation discussed in the last chapter, we questioned if X-transfer could be applied to other types of weakly acidic C–H bonds, including C(sp^3)–H variants.[17] We reasoned that if X-transfer to benzylic C–H bonds is possible, the compatibility of deprotonation, oxidation and substitution processes could enable a new means for benzylic C–H coupling with heteroatom pronucleophiles (Figure 3-6).[18,19,20] Specifically, use of an alkoxide base would generate low concentrations of a benzylic carbanion such that, upon halogenation, rapid S_N2 with an anionic heteronucleophile would provide the coupled product and avoid benzylic dimerization.[21] Given that the pK_a of primary and secondary alcohols is lower than *t*-BuOH, we anticipated large concentrations of the desired alkoxide nucleophile would be generated to selectively capture the benzyl halide when *tert*-butoxide bases are used.[22-24]

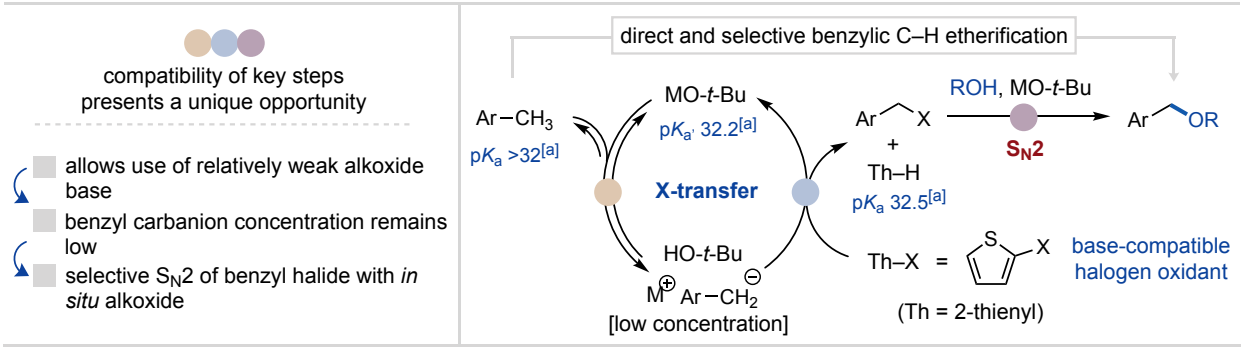


Figure 3-6: Our proposal to use X-transfer to C(sp^3)–H bonds for benzylic C–H oxidative coupling.

In collaboration with my coworker Tom Puleo, we tested this proposal for the C–H etherification of 2,6-dichlorotoluene (Figure 3-7a), a precursor to benzyl ether pharmaceuticals that has been studied for radical benzylic halogenation improvement.[21] We found the desired coupling occurs readily with KO-*t*-Bu and 2-iodothiophene (**3-XTR 1**, XTR = X-transfer reagent) under numerous conditions (e.g., 62% yield in DMPU and 97% in THF).[22] We next investigated 1-methylnaphthalene as a less acidic model substrate (Figure 3-7b).[23] Use of KO-*t*-Bu and 2-iodothiophene (**3-XTR 1**) for this substrate gives 39% yield and could not be increased using other bases or conditions, suggesting improvement would need to come through X-transfer reagent modification.

In our aryl C(sp^2)–H functionalization work, we found 2-iodothiophene undergoes base-promoted disproportionation to form 2,3-diiodothiophene that can act as an oxidant or rearrange further to inactive 3-iodothiophenes. This previously led us to create 2,3-dihalobenzothiophenes as more effective X-transfer reagents that cannot rearrange. However, use of 2,3-diiodo-benzothiophene (**3-XTR 3**) gives only 34% C–H etherification of 1-methylnaphthalene (**3-4**), indicating the 2,3-diiodothiophene motif is not an improved oxidant for this reaction. We therefore investigated 2-halobenzothiophenes with non-halogen 3-substituents, including 2-iodo-3-phenylbenzothiophene (**3-XTR 3**) which gives an improved 59% yield. Structural variations did

not increase the yield further, including 3-aryl substituent derivatives or replacement of iodine with bromine (**3-XTR 4**).

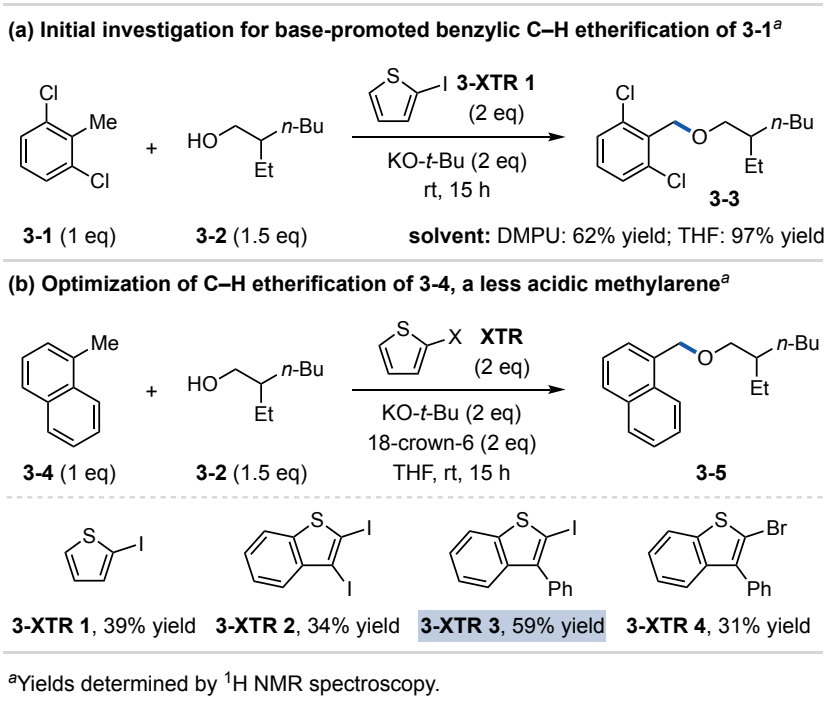


Figure 3-7: Benzylic C–H etherification optimization.

A post-doctoral researcher in our lab, Dr. Mike DeLost, subsequently developed a scalable synthesis of 2-iodo-3-phenylbenzothiophene (**3-XTR 3**), where thiophenol substitution of bromoacetophenone to produce xx followed by a cyclization/halogenation sequence furnished the reagent on scale (Figure 3-8).[24] We found that other classes of electrophilic iodoarenes (e.g., 1,3-dichloro-2-iodobenzene) can also promote C–H etherification of **3-1** and **3-4** but in lower yields, with a summary XTRs and conditions examined shown in the appendix 2. These results indicate that 2-iodothiophenes strike the right balance of compatibility and electrophilicity to be most effective for this method; more comprehensive analyses on structure activity relationships of haloarenes as potential XTRs are ongoing. We note that the postulated benzyl halide intermediates are not observable under the reaction conditions, likely due to their high reactivity towards

substitution. However, ethylarene substrates provide mixtures of C–H etherification and elimination products that are known to arise from secondary benzyl halides; these results are fully consistent with benzyl halides serving as the key intermediates.[25]

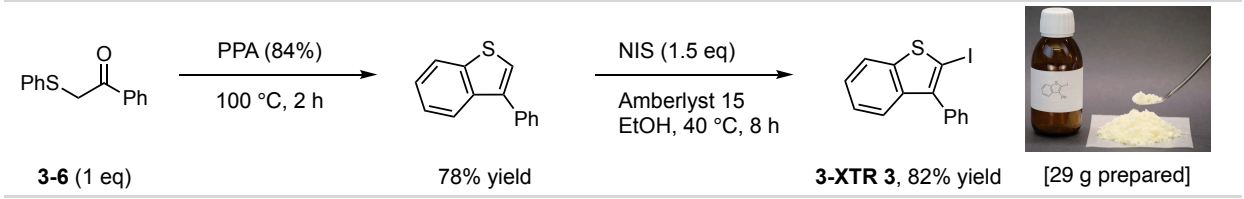
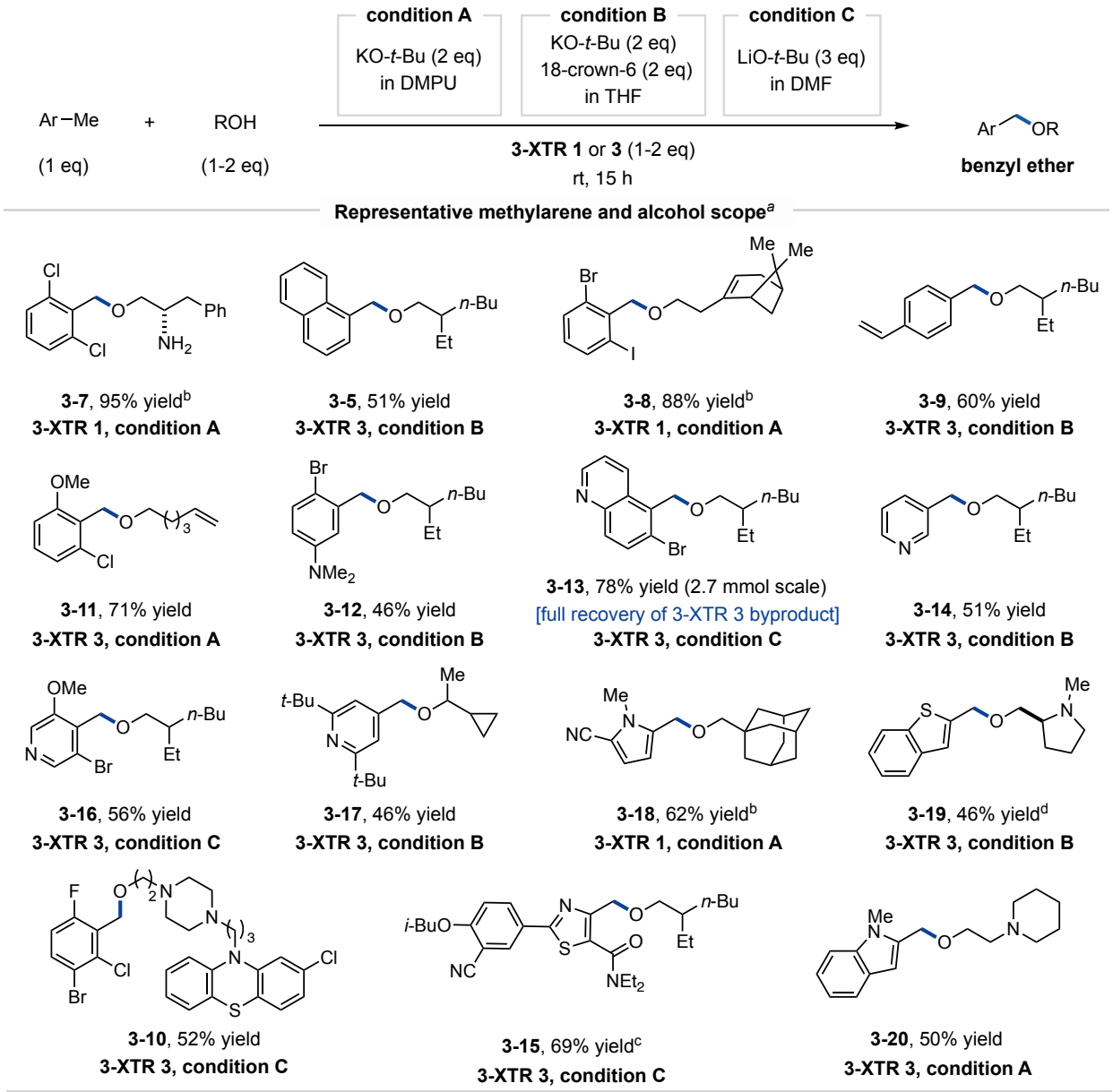


Figure 3-8: Multigram preparation of XTR 3 from simple reagents.

3.4. Methyl Arene and Nucleophile Substrate Scope

A representative scope of benzyl ethers accessible *via* this method is shown in Figure 3-9. Our optimization studies indicated multiple metal *tert*-butoxide bases and solvents promote C–H etherification; during our substrate scope studies, we identified three combinations (Conditions A-C) to be the most general using **3-XTR 1** or **3-XTR 3**.[26] Methylarenes with diverse and potentially base-sensitive functional groups, including all halogens, ethers, primary amines, alkenes and nitriles provide 45-90% yield (**3-7**-**3-12**); here, *ortho*-substitution is well-tolerated but not necessary.[27] A wide range of methylheteroarenes also engage in this process (**3-31**-**3-20**), including pyridines with methyl groups in all positions and methylpyrimidines, -pyrroles, -quinolines, -indoles and -thiophenes. Under the current conditions, toluene itself does not undergo C–H etherification, likely due to lower acidity, while ethylarenes undergo X-transfer but with competing S_N2 and E2 pathways; these challenges are being addressed in ongoing work. We note in Figure 3-9 that primary and secondary alcohols perform well, including unprotected aminoalcohols (**3-7**), the pharmaceutical perphenazine (**3-10**), an alkenol (**3-11**) and other bulky alcohols (**3-17** and **3-18**). While use of benzothiophene **3-XTR 3** is not ideal from an atom

economy perspective, we note that the 3-phenylbenzothiophene byproduct can be recovered and recycled as shown in its gram-scale use for **3-13**.

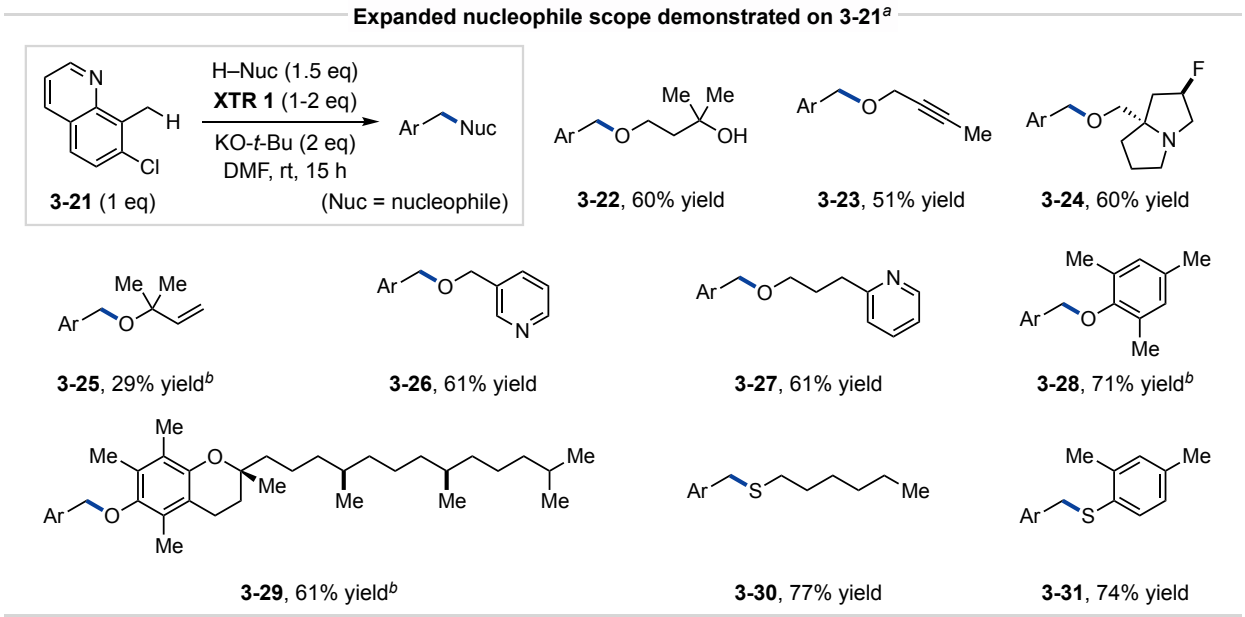


[a]Isolated yields of 0.25-1 mmol scale reactions. [b]10 min reaction time. [c] ^{1}H NMR yield reported due to coelution with methylarene; 32% isolated. [d]18-crown-6 (0.5 eq) used.

Figure 3-9: Methyl arene substrate scope of the benzylic C–H etherification.

We reasoned this approach to oxidative coupling would be readily transferrable to a broader scope of *O*- and *S*-pronucleophiles. Using 7-chloro-8-methylquinoline (**3-21**) as a model substrate, we found that effective coupling occurs with a wide range of alcohols, phenols, thiols and

thiophenols using **3-XTR 1** (Figure 3-10). We also studied polyfunctionalized pronucleophiles to assess the coupling selectivity and found that desired etherification occurs for a variety of more complex substrates. This includes an unprotected diol where benzylation occurs at the primary alcohol (**3-22**), a tertiary alkenol (**3-25**), and pyridine-containing alcohols that have acidic C–H bonds (**3-26** and **3-27**).[28] Additionally, methyl-substituted phenols (**3-28**) and thiophenols (**3-31**), including vitamin E (**3-29**), do not undergo competing functionalization at their benzylic positions. Amines are generally not effective pronucleophiles under the current reaction conditions, an opportunity that is being currently under development.[29]



[a]Isolated yields of 0.25-1 mmol scale reactions. [b]KOH and 18-crown-6 (2.5 eq) used.

Figure 3-10: Nucleophile scope of the benzylic C–H etherification.

The scalability and utility of this protocol is further demonstrated in Figure 3-11 where the antifungal isoconazole (**3-33**) was prepared on a 10-gram scale (80% yield) in 20 minutes using **3-XTR 1**.[30] This reaction was conducted open to air, an unusual capability for a process that proceeds *via* a benzyl carbanion intermediate.[31] Thus, the inclusion of inexpensive 2-iodothiophene (**3-XTR 1**) enables rapid C–H substitution under conditions that parallel traditional

base-promoted alcohol alkylation reactions with benzyl halides. This obviates the need to prepare, purchase or handle benzyl halides and streamlines access to analogues where the benzyl halide is not commercial. These advantages are shown for the gram-scale production of isoconazole halogen analogues **3-34** and **3-35**.[32]

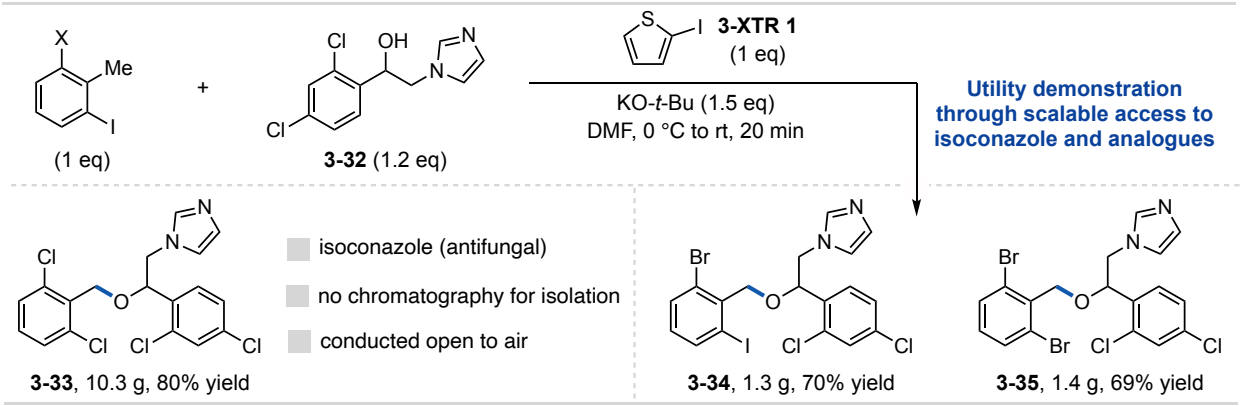


Figure 3-11: Scaled synthesis of isoconazole and analogues.

This oxidative coupling reaction is initiated by deprotonation and is thus guided by acidity trends.[33] This contrasts existing benzylic C–H etherification methods that are dependent on C–H bond strengths or substrate oxidation potentials as they proceed *via* hydrogen atom abstraction or arene oxidation, respectively. This distinction makes the X-transfer mechanistic approach complementary as it is well suited for substrates that are not within the scope of alternative methods, such as methylarenes.[10,11,34] This includes electron-deficient substrates and N-heteroarenes (e.g., **3-8**-**3-10** and **3-13**-**3-18**) that possess high oxidation potentials or substrates with oxidatively-sensitive C–H bonds or functional groups (e.g., **3-8**-**3-11**, **3-26**, **3-30**, **3-31**).[35]

3.5. Site-Selective Benzylic C–H Etherification of Polyalkylarenes

The site-selective functionalization of polyalkylarenes that contain multiple benzylic positions represents an important goal for selective synthesis.[36] This mechanistic and synthetic challenge is exemplified by radical C–H halogenation of polymethylarenes that routinely gives isomeric benzyl halide mixtures that are difficult to separate.[37] Although radical-based C–H

etherification reactions provide selectivity in certain contexts (e.g., for a weaker ethyl over methyl C–H bond or functionalization para to an alkoxy group), no general solution to distinguish between C–H bonds of similar strength or substrates devoid of strong directing groups has been disclosed.[34] In this regard, we proposed that the unique reagent combination of an X-transfer approach could drive selectivity for the most acidic position of polyalkylarenes in a broadly transferrable manner.

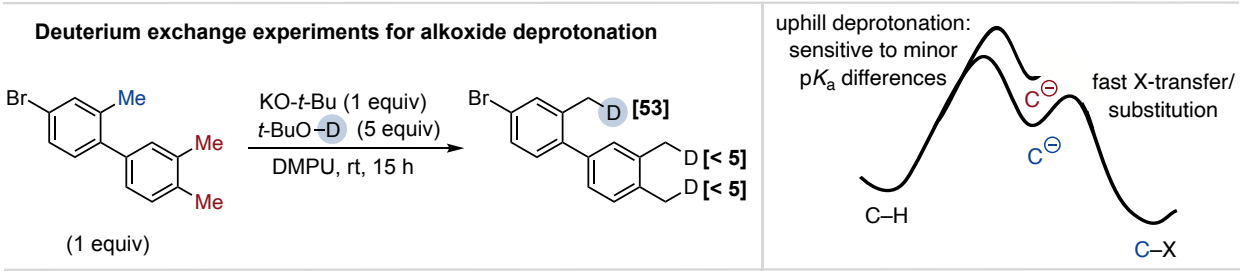
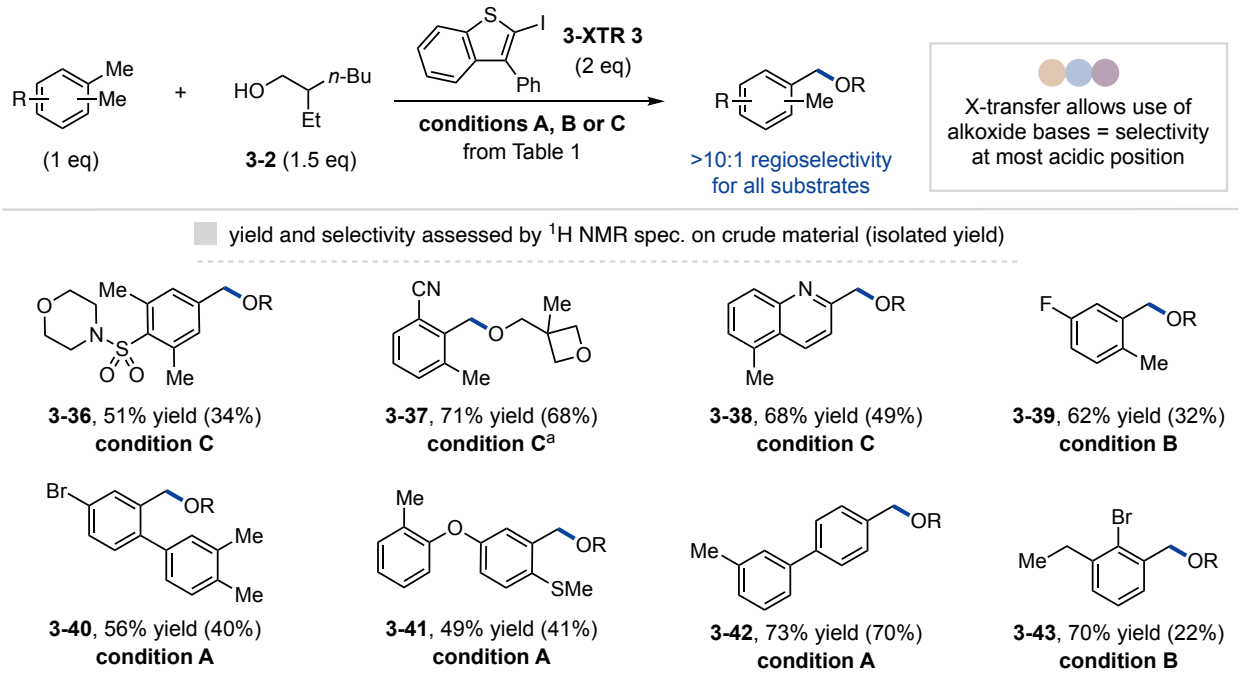


Figure 3-12: Premise of regioselective benzylic functionalization *via* X-transfer on polyalkylarenes.

The X-transfer protocol uses alkoxide bases that facilitate energetically uphill benzylic deprotonation and, consequently, is sensitive to subtle differences in substituent acidity.[38] This is demonstrated on the bromomethylbiaryl substrate, where, under deuterium exchange conditions, deuteration is observed only at the methyl on the more electron-deficient aryl group (Figure 3-12). We therefore reasoned if X-transfer is fast enough, oxidative coupling would occur at the most acidic position of polyalkylarenes. Figure 3-13 demonstrates the efficacy and generality of this principle where the standard coupling conditions promote >10:1 site-selective C–H etherification across a broad range of polyalkylarenes. For polymethyl systems, the position that can form an anion in conjugation with a stabilizing group is preferentially functionalized (**3-36**-**3-38**), although minor electronic disparities can also guide high selectivity (**3-39**-**3-41**). Subtle structural differences are also sufficient for positional precision, as seen for 3,4'-dimethylbiphenyl (**3-42**) and etherification of a methyl over an ethyl group in **3-43**.



[1]H NMR yields reported to assess selectivity on crude reaction material; isolated yields are lower due to coelution. [a]XTR 1 used.

Figure 3-13: Site-selective polyalkylarene C–H etherification.

3.6. Study of the Acetal Formation

During our substrate studies, we found that several relatively acidic methylarenes can undergo a competitive over-oxidation process under conditions A and B. This is represented by 2-methylbenzotrifluoride (**3-45**) that readily undergoes C–H etherification (**3-46**) but with competing formation of an acetal (**3-47**) (Figure 3-14). To probe this side-pathway, a reaction profile analysis of 2-methylbenzotrifluoride (**3-45**) as a representative substrate was conducted (Figure 3-14). At the 30 min time point, 65% of the monofunctionalized benzyl ether product xx is present, at which point the over-oxidized acetal product **3-47** begins to form. At the 60 min time point the maximum yield of xx is formed and, from that time point on, the yield of the monoether product goes down synchronously with the increase of the acetal. This is consistent with X-transfer preferentially occurring to the toluene over the benzyl ether until approximately 60% of benzyl ether has formed. From this study, it was determined that, for substrates that engage in acetal formation, optimal

yields may be obtained at shortened reaction times or through the use of LiO-*t*-Bu that is slower at promoting the second oxidation event (Condition C).

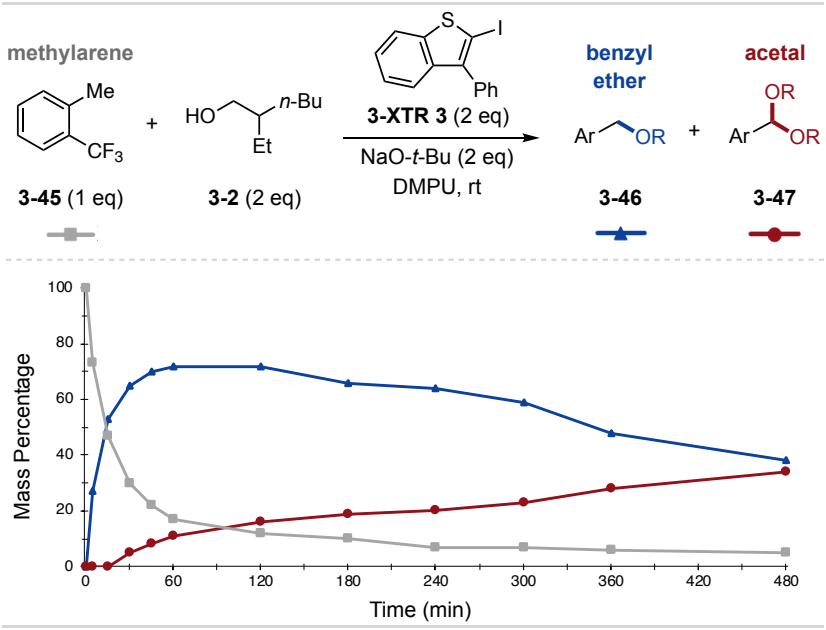


Figure 3-14: Identification of an overoxidized side product and reaction profile for 45.

3.7. Controlling Oxidation to Provide Direct Access to Aryl Aldehydes

The identification of a double C–H etherification side process inspired us to apply this reactivity towards a controlled methylarene oxidation protocol.[39] Conducting this overall transformation is known for 2-methylpyridine substrates, where a four-step protocol involving oxidation to the pyridine *N*-oxide, treatment with acetic anhydride, acetate hydrolysis, and oxidation finally provides the desired product (Figure 3-15, right).[40] Alternatively, methods that could directly afford the carboxaldehyde directly on a broader range of methyl (hetero)arenes would be highly advantageous. To this end, there are several methods that harness chemical and electrochemical oxidation for direct oxidation of methyl arenes to the corresponding aldehydes.[39] For example, the Baran group developed a benzylic oxidation protocol of electron-rich methyl arenes using 2-iodoxybenzoic acid via a single-electron transfer pathway (Figure 3-15, left).

Despite these developments, direct methods to access the benzaldehyde are limited in the fact that they are prone to overoxidation (i.e. acid formation), are best-suited for electron-rich to -neutral methyl arenes, often fail on heteroarene substrates, and provide low-selectivity on polymethyl arenes. In contrast, achieving selectivity based on acidity and not needing strong oxidant, as is true in the X-transfer work, would streamline access and provide selectivity in cases that were previously impossible using established methodology for benzylic oxidation.

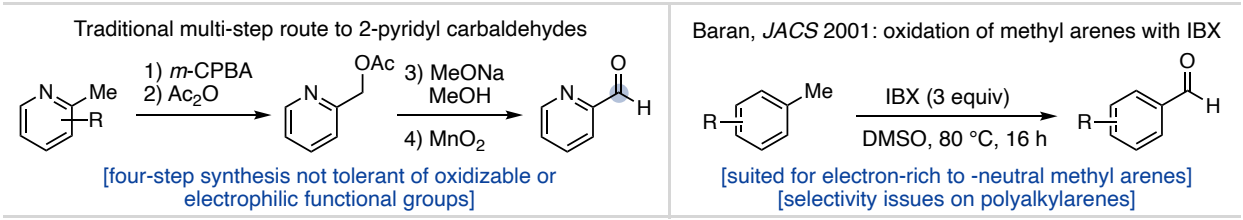
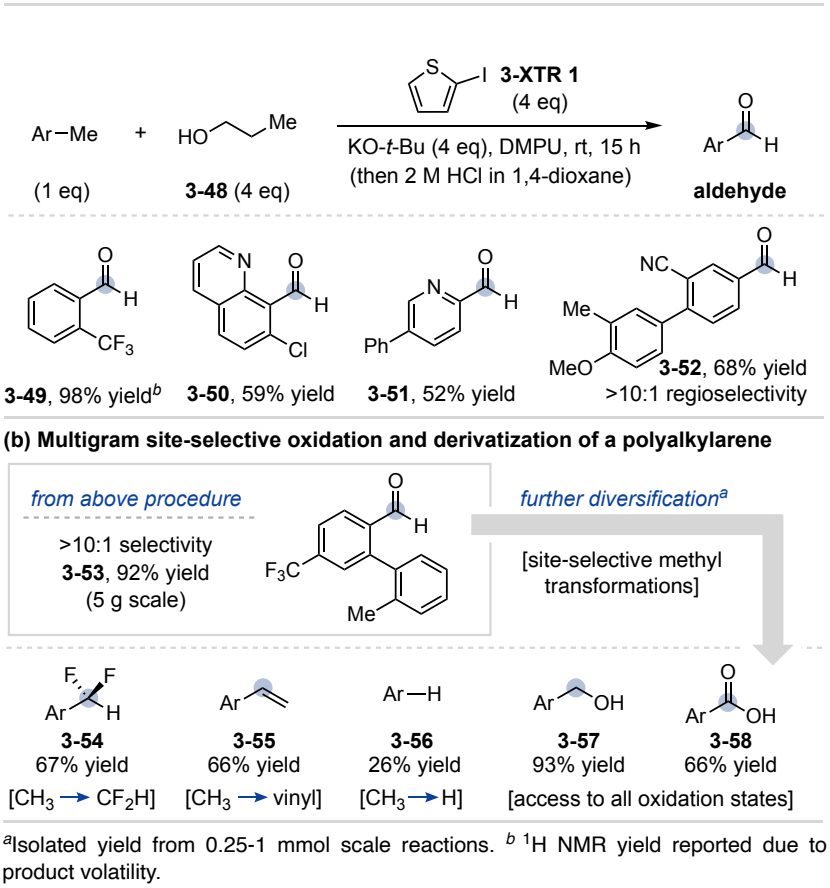


Figure 3-15: Established protocols for the oxidation of methyl arenes.

Thus, we next set-out to develop conditions where X-transfer could be harnessed toward direct benzylic oxidation. To this end, we ultimately found that simply adjusting the optimized conditions from Figure 3-9 to include excess base and X-transfer reagent with *n*-propanol promotes high-yielding acetal formation. Subsequent addition of acid provides the aldehydes in a one-pot process (Figure 3-16). This procedure can be applied to substrates previously shown in Figure 3-9 and Figure 3-13 (e.g., **3-50**). This method also works on 2-methylpyridines (**3-51**) as a streamlined alternative to frequently used but tedious four-steps route previously mentioned (Figure 3-15). Site- and oxidation-state selectivity is also observed for polyalkylarenes (**3-52**). This includes the 5-gram scale synthesis of benzaldehyde **3-53**. Subsequent derivatization achieves site-selective methyl oxidations to all oxidation states (**3-57** and **3-58**), formal conversions of the methyl substituent to difluoromethyl (**3-54**) and vinyl (**3-55**) groups, or methyl removal to a hydrogen atom (**3-56**). This application demonstrates this protocols potential application in library build-up for medicinal chemists where a wide-range of methyl groups can be rapidly modified.



[a]Isolated yield from 0.25-1 mmol scale reactions. [b] ^{1}H NMR yield reported due to product volatility.

Figure 3-16: Substrate scope for controllable methyl arene oxidation via X-transfer and subsequent derivatization of 3-53.

3.8. Conclusion

The work described in this chapter was uploaded onto *ChemRxiv preprint* in 2024. As described throughout the chapter, the base-promoted X-transfer reactivity detailed in chapter one was expanded to enable direct oxidative coupling reactions of benzylic C–H bonds with heteroatom pronucleophiles. The merger of deprotonation, halogenation and substitution steps is a critical design feature that enables in situ generation and use of benzyl halides under basic conditions. In turn, deprotonative activation provides new capabilities for benzylic C–H etherification, such as the ability to functionalize high-oxidation potential and oxidatively-sensitive substrates, to guide selectivity to the most acidic position and to regulate the number of oxidation events. We anticipate this mechanistic platform can bring similar advantages to other

realms of C–H functionalization given that X-transfer is now shown to be general to both C(sp^3)–H and C(sp^2)–H bonds.[42]

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[19] For pK_a values, see: (a) K. Shen, Y. Fu, J.-N. Li, L. Liu, Q.-X. Guo, *Tetrahedron* **2007**, *63*, 1568–1576. (b) M. Balkenhohl, H. Jangra, I. S. Makarov, S.-M. Yang, H. Zipse, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 14992–14999. (c) F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463.

[20] For a base-promoted benzylic C–H etherification reaction under O_2 that is specific to *para*-hydroxytoluenes, see: X. Zhang, W. Li, Y. Yu, M. Luo, H. Bai, L. Shi, H. Li, *Green Chem.* **2024**, *26*, 2207–2212.

[21] (a) A. Steiner, P. M. C. Roth, F. J. Strauss, G. Gauron, G. Tekautz, M. Winter, J. D. Williams, C. O. Kappe, *Org. Process Res. Dev.* **2020**, *24*, 2208–2216. (b) A. Steiner, J. D. Williams, O. de Frutos, J. A. Rincón, C. Mateos, C. O. Kappe, *Green Chem.* **2020**, *22*, 448–454.

[22] 2-Iodothiophene (**2-XTR 1**) is commercially available and inexpensive (~$100 per mole according to emolecules.com). For reviews on 2-halothiophene oxidants, see: (a) T. R. Puleo, J. S. Bandar, 2,3-Diiodobenzo[*b*]thiophene. *e-EROS Encyclopedia of Reagents in Organic Synthesis*. **2022**, DOI: 10.1002/047084289X.rn02468. (b) T. R. Puleo, J. S. Bandar, 2-Iodothiophene. *e-EROS Encyclopedia of Reagents in Organic Synthesis*. **2022**, DOI: 10.1002/047084289X.rn02467. (c) Puleo, T. R.; Bandar, J. S. 2,5-Dibromothiophene. *e-EROS Encyclopedia of Reagents in Organic Synthesis*. **2022**, DOI: 10.1002/047084289X.rn02466.

[23] For experimental and theoretical benzylic pK_a values, see: (a) B. A. Sim, D. Griller, D. D. M. Wayner, *J. Am. Chem. Soc.* **1989**, *111*, 754–755. (b) F. G. Bordwell, D. Algrim, N. R. Vanier, *J. Org. Chem.* **1977**, *42*, 1817–1819. (c) B. D. Groff, B. Koronkiewicz, J. M. Mayer, *J. Org. Chem.* **2023**, *88*, 16259–16269. (d) F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. J. McCollum, M. Van Der Puy, N. R. Vanier, W. S. Matthews, *J. Org. Chem.* **1977**, *42*, 321–325.

[24] Full synthetic details for preparing **2-XTR 3** are provided in the Supporting Information. The synthesis was inspired by: R. M. P. Dias, A. C. B. Burtoloso, *Org. Lett.* **2016**, *18*, 3034–3037.

[25] For example, 2-ethylpyridine, 3-ethylpyridine and 1-ethylnaphthalene provide up to 20%, 11% and 8% C–H etherification yields under these reaction conditions. In these cases, and when tertiary benzylic substrates are studied (e.g., 2-isopropylpyridine), competitive elimination to the aryl alkene is also observed. These studies are consistent with a benzyl halide serving as the key reaction intermediate and indicate that secondary and tertiary benzylic C–H bonds can undergo halogen transfer.

[26] **XTR 1** and **XTR 3** can promote effective C–H etherification of **3-1** and **3-4** using a variety of base, solvent, and additive combinations. Therefore, most substrates in Table 1 and Figure 4 were tested with **3-XTR 1** and **3-XTR 3** under Conditions A and B. More electron rich methylarenes work best with KO-*t*-Bu in either DMPU or THF (e.g., **3-7**, **3-8**, **3-20**), where use of 18-crown-6 can give increased yields for some substrates (e.g., **3-5**, **3-9**, **3-12**). It was found that more acidic substrates (e.g., **3-10**, **3-13**, **3-15**, **3-16**) are overoxidized under Conditions A and B, but this side reaction is minimized under Condition C or by

decreasing reaction time. Thus, for most substrates in Figure 3-7 that have less than 75% yield, the remaining mass balance is primarily unreacted methylarene substrate.

[27] We note that highly electrophilic functional groups are not tolerated, such as preexisting benzyl halides. For example, when 2-chloromethyl-6-methylpyridine is used as a substrate, direct S_N2 of the chloromethyl group is observed as the major product; see Supporting Information. However, we note that selective C–H etherification of polymethylarenes could be sequenced with a radical benzyl halogenation protocol to prepare benzyl ethers with an additional benzyl halide functional group; for an example of selective radical halogenation of a methyl-containing benzyl ether, see: add reference here.

[28] For **3-25**, KOH is used as base and the dibenzyl ether is observed as a side product. It is likely that for the pyridine alcohols used for substrates **3-26** and **3-27**, the presence of both an alcohol O–H and pyridyl benzylic C–H bond prevents C–H deprotonation and X-transfer to the alcohol coupling partner.

[29] The potential for the use of amine pronucleophiles in related coupling reactions is under investigation and will be reported in due course.

[30] S. Veraldi, *Mycoses* **2013**, *56*, 3–15.

[31] Metalated benzylic intermediates are typically prepared under inert atmosphere at low temperatures; see: T. Rathman, J. A. Schwindeman, *Org. Process Res. Dev.* **2014**, *18*, 1192–1210.

[32] Isoconazole analogues **3-34** and **3-35** were obtained from methylarenes that are available in larger quantities and significantly cheaper than their corresponding benzyl bromide analogues (approximately 5-10 fold cost advantage according to emolecules.com).

[33] See the Supporting Information for C–H etherification control experiments conducted in the presence of TEMPO additive that are consistent with a deprotonative pathway and not with benzylic radicals as active intermediates.

[34] Methylarenes are either not shown or prone to overoxidation in the methods in refs 10 and 11. For other recent protocols that are specific to *p*-toluidine or *p*-cresol derivatives, see: (a) S. Chowdhury, S. A Pandey, *Asian J. Org. Chem.* **2021**, *10*, 2902–2906. (b) Z.-W. Hou, M.-M. Zhang, W.-C. Yang, L. Wang, *J. Org. Chem.* **2022**, *87*, 7806–7817. (c) Y. Zhang, P. K. Sahoo, P. Ren, Y. Qin, R. Cauwenbergh, P. Nimmegeers, G. SivaRaman, S. V. Passel, A. Guidetti, S. Das, *Chem. Commun.* **2022**, *58*. 11454–11457.

[35] (a) H. G. Roth, N. A. Romero, D. A. Nicewicz, *Synlett* **2016**, *27*, 714–723. (b) L. K. Sviatenko, L. Gorb, F. C. Hill, J. Leszczynski, *J. Comput. Chem.* **2013**, *34*, 1094–1100. (c) X.-S. Xue, P. Ji, B. Zhou, J.-P Cheng, *Chem. Rev.* **2017**, *117*, 8622–8648. (d) Y.-R. Luo, *Comprehensive Handbook of Chemical Bond Energies*; CRC Press: Boca Raton, FL, 2007.

[36] For discussions of the importance of site-selectivity in C(sp^3)–H functionalization methodology, see: (a) T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 3362–3374. (b) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546–576. (c) M. C. White, J. Zhao, *J. Am. Chem. Soc.* **2018**, *140*, 13988–14009. (d) L. Ping, D. S. Chung, J. Bouffard, S.-G. Lee, *Chem. Soc. Rev.* **2017**, *46*, 4299–4328.

[37] Control studies for radical benzylic bromination were conducted on polyalkylarene starting materials for **3-36** and **3-40** in Figure 3-13; in both cases, more than four distinct products formed in significant quantities and could not be readily separate. See appendix 2 for details.

[38] Consistent with this proposal, control studies with deuterated alcohol showed that metal alkoxide bases promote site-selective deuterium exchange of polyalkylarene starting

materials for **3-36** and **3-40** in Figure 3-13 under similar reaction conditions. See Supporting Information for details.

[39] For representative alternative methods for methylarene oxidation to aldehydes, see: (a) P. Xiong, H.-B. Zhao, X.-T. Fan, L.-H. Jie, H. Long, P. Xu, Z.-J. Liu, Z.-J. Wu, J. Cheng, H.-C. Xu, *Nature Commun.* **2020**, *11*, 2706. (b) E. Gaster, S. Kozuch, D. Pappo, *Angew. Chem. Int. Ed.* **2017**, *56*, 5912–5915. (c) K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, *J. Am. Chem. Soc.* **2001**, *123*, 3183–3185. (d) M. A. Hoque, J. Twilton, J. Zhu, M. D. Graaf, K. C. Harper, E. Tuca, G. A. DiLabio, S. S. Stahl, *J. Am. Chem. Soc.* **2022**, *144*, 15295–15302. (e) P. Hu, M. Tan, L. Cheng, H. Zhao, R. Feng, W.-J. Gu, W. Han, *Nature Commun.* **2019**, *10*, 2425. (f) M. L. Tedder, F. O. Dzeagu, M. M. Mason, D. A. Dixon, J. D. Carrick, *Tetrahedron* **2022**, *116*, 132805.

[40] For example routes for acidic methylarene oxidation that involve Boekelheide oxidation or oxidative alkene cleavage, see: (a) G. Brooks, S. Dabbs, D. T. Davies, A. J. Hennessy, G. E. Jones, R. E. Markwell, T. J. Miles, N. A. Owston, N. D. Pearson, T. W. Peng, *Tetrahedron Lett.* **2010**, *51*, 5035–5037. (b) Y. Aoyama, T. Hakogi, Y. Fukui, D. Yamada, T. Ooyama, Y. Nishino, S. Shinomoto, M. Nagai, N. Miyake, Y. Taoda, H. Yoshida, T. Yasukata, *Org. Process Res. Dev.* **2019**, *23*, 558–564.

[41] **Bone, K. I.‡,** Puleo, T. R.‡, Delost, M. D., Shimizu, Y., Bandar, J. S.*, **2024**, *ChemRxiv Preprint*: 10.26434/chemrxiv-2024-fvrc1.

[42] For the substrates shown in this section, their benzylic C–H bonds are more acidic than their aryl C–H bonds according to known pK_a trends. We are currently investigating selectivity trends for compounds that possess similarly acidic C(sp^2)–H and C(sp^3)–H bonds.

CHAPTER FOUR

CONCLUSION

I have leverage X-transfer to enable direct functionalization of mildly acidic C(sp^2)–H and C(sp^3)–H bonds with a wide variety of nucleophiles. Underpinning the success of this work, is the synergy of the merged deprotonation, oxidation, and coupling steps which ultimately provides a base-promoted approach to conduct reactivity that would be impossible *via* traditional deprotonative chemistry. This synergy also provides distinct selectivity and scope compared to methods based off other platforms for oxidative C–H functionalization, where it is best-suited for electron deficient systems and selectivity is achieved for strong, weakly acidic C–H bonds with no need for directing groups. Overall, the reactivity described herein offers a distinct practical advance in synthetic chemists' enduring challenge of viewing C–H bonds as completely diversifiable and general coupling partners to enable ideal syntheses

The work and knowledge described in this dissertation has also served as the foundation for the development of new projects in the Bandar group. For example, the preliminary heteroaryl amination results (Chapter 2.10) showcased that X-transfer enabled substitution is amenable to amine nucleophiles, and, from this, several benzylic amination projects have arisen. Beyond this, the selectivity studies from both Chapter 2 and 3 indicated that switching the selectivity of X-transfer could be possible, and achieving this is the current focus of several ongoing project in the Bandar lab.

APPENDIX ONE

DIRECT C−H HYDROXYLATION OF *N*-HETEROARENES AND BENZENES *VIA* BASE-CATALYZED HALOGEN TRANSFER

A1.1. General Information

General Reagent Information: All reactions were performed under a nitrogen (N_2) atmosphere unless otherwise noted. 3-Bromopyridine (Chem-Impex catalog #27044), diphenyl sulfone (MilliporeSigma catalog #P35359), 2-phenethyl alcohol (MilliporeSigma catalog #285811), 2,5-dibromothiophene (Matrix Scientific catalog #004596), 2-iodothiophene (CombiBlocks catalog #OR-1024), 2,3-dibromobenzo[*b*]thiophene (CombiBlocks catalog #QJ-0797), and 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6, Chem-Impex catalog #03901) were purchased from the indicated vendors and used as received. Potassium *tert*-butoxide (KO-*t*-Bu, Chem-Impex catalog #27317) was purchased as a 99.8% pure powder and used as received. KO-*t*-Bu and 18-crown-6 were stored at room temperature (rt) inside a N_2 filled glovebox and used immediately if brought outside the glovebox. Tetrahydrofuran (THF) was deoxygenated and dried by passage over packed columns of neutral alumina and copper (II) oxide under positive pressure of N_2. All other solvents and reagents were purchased from Millipore Sigma, Combi-Blocks, TCI, Acros Organics, Matrix Scientific, AlfaAesar, or Synthonix and used as received unless otherwise noted. Flash chromatography was performed on 40-63 μm silica gel (SiliaFlash® F60 from Silicycle). Preparative thin-layer chromatography (PTLC) was performed on silica gel 60 Å F254 plates (20 x 20 cm, 1000 μm, SiliaPlate from Silicycle, #TLG-R10011B-341) and visualized with UV light (254 nm). Celite® 545 (Product #CX0574-3) was purchased from Millipore Sigma.

General Analytical Information: All reported compounds were characterized by ^{1}H, ^{13}C, and ^{19}F (if applicable) NMR spectroscopy, FTIR spectroscopy, and mass spectrometry. Melting point analysis was conducted if the compound was solid. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were obtained on a Bruker NEO400, Bruker US400, Bruker Ascend 400, or Varian Inova 400 spectrometers. ^{1}H NMR data is reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, br s = broad singlet, d =doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, dq = doublet of quartets, qd = quartet of doublets, m = multiplet), coupling constant (Hz), and integration. All ^{1}H NMR signals are reported as chemical shifts (δ ppm) relative to residual $CHCl_3$ at 7.26 ppm, or $(CH_3)_2SO$ at 2.50 ppm, $(CH_3)_2CO$ at 2.05 ppm, CH_2Cl_2 at 5.32 ppm or CH_3CN at 1.94 ppm.[1] ^{13}C NMR data is reported as follows: chemical shift (δ ppm), multiplicity (if applicable, d = doublet, quin = quintet, q = quartet, dq = doublet of quartets, qd = quartet of doublets, m = multiplet), and coupling constant (Hz). ^{13}C NMR signals are reported as chemical shifts (δ ppm) relative to $CDCl_3$ at 77.16 ppm, $(CD_3)_2SO$ at 39.52 ppm, $(CD_3)_2CO$ at 206.26 ppm, CH_2Cl_2 at 53.84 ppm, or CD_3CN at 1.32 ppm.[1] Chemical shifts for ^{19}F NMR are reported in terms of chemical shift in reference to an internal standard (1,2-difluorobenzene set to δ -138.18 ppm); reported ^{19}F NMR data are for proton-decoupled spectra.[2] High resolution mass spectra (HRMS) were recorded on an Agilent 6210 TOF interfaced to a DART 100 source or an Agilent 6230 LC-MS B-TOF equipped with a dual ESI source provided by Colorado State University Analytical Resource Core – Molecular and Materials

Analysis Center. IR spectra were recorded using a Thermo Scientific Nicolet iS-50 FTIR Spectrometer and reported as frequency of absorption (cm^{-1}). Samples were sent to Atlantic Microlab in Norcross, GA for combustion elemental analysis and analyzed for carbon, hydrogen, and nitrogen composition. Melting point analyses were conducted using a MelTemp capillary melting point apparatus. Thin-layer chromatography analysis was performed on silica gel 60 Å F254 plates (250 μm, SiliaPlate from Silicycle, #TLG-R10014B323) and interpreted using UV light (254 nm) or $KMnO_4$ stain. Preparatory thin-layer chromatography purification was performed on silica gel 60 Å (1000 μm, Silicycle, #TLG-R10011B-341) and interpreted using UV light (254 nm).

Nomenclature Note: The names provided for the structures in this document were obtained from ChemDraw Professional 20.1.

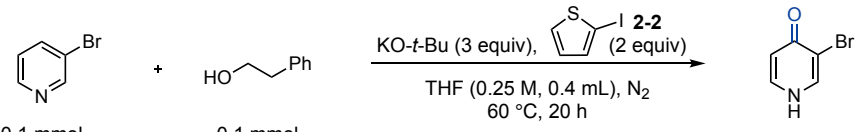
Product Structure Note: The major tautomeric form of most 2- and 4-hydroxylated *N*-heteroarenes is the carbonyl tautomer. [3] This is supported by the ^{1}H NMR and ^{13}C NMR spectral data and thus all structures are depicted accordingly in this report.

A1.2. Optimization of C–H Hydroxylation of *N*-Heteroarenes and Benzenes

(a) Evaluation of changes in optimal base, halogenating agent, solvent, reaction time, and temperature for selective heteroarene C–H hydroxylation.

Preliminary experiments varying base and solvent indicated that KO-*t*-Bu in THF could promote 4-hydroxylation of 3-bromopyridine using 2-phenethyl alcohol. The optimized conditions are provided in the table below in comparison to specific changes of reagents or conditions used to inform readers of these effects.

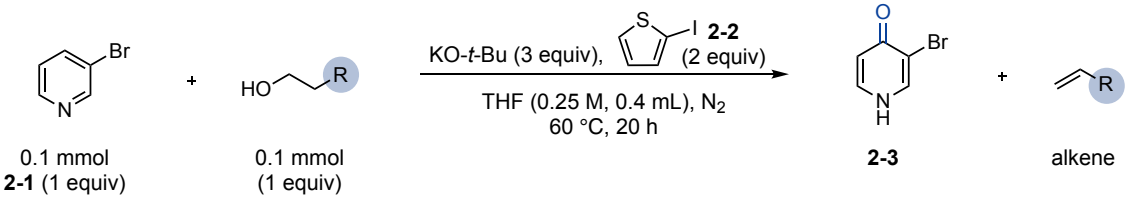
General procedure for condition variation: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE® , #60910-1) was charged with a magnetic stir bar, 3-bromopyridine (15.8 mg, 1 equiv, 0.1 mmol), 2-phenethyl alcohol (12.2 mg, 0.1 mmol, 1 equiv), halogenating agent (0.2 mmol, 2 equiv), anhydrous solvent (0.25 M, 0.4 mL), and base (0.3 mmol, 3 equiv) in successive order (see Table A1-1 below). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), removed from the glovebox, and placed into a preheated 60 °C aluminum reaction block. The reaction solution was stirred for 20 h at 60 °C and then allowed to cool to rt. 1,3,5-Trimethoxybenzene standard was then measured into the reaction solution. For each experiment, the mass of 1,3,5-trimethoxybenzene weighed into the vial was recorded separately. The crude solution was then homogenized with MeOH (1 mL). A small aliquot was removed and injected into an NMR tube and constituted in $(CD_3)_2SO$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, $(CD_3)_2SO$) was used to determine the yield of 3-bromopyridin-4(1H)-one (**2-3**). The aromatic C–H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the aromatic C–H signal of 3-bromopyridin-4(1H)-one (**2-3**) at 6.05 ppm (d, J = 5.8 Hz, 1H) to determine the yield. The results are summarized in Table A1-1 below. **Note:** for the optimized procedure (entry 1), no *tert*-butyl aryl ether (3-bromo-4-(tert-butoxy)pyridine) was observed by ^{1}H NMR spectroscopy or MS analysis of the crude reaction mixture.



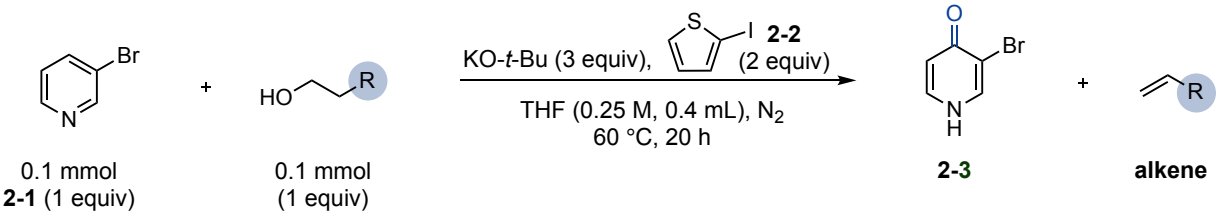
Entry	Change from the "standard conditions"	Yield
1	none	71%
2	25 °C instead of 60 °C	57%
3	80 °C instead of 60 °C	58%
4	DMF used as solvent instead of THF	48%
5	PhMe used as solvent instead of THF	7%
7	KOH instead of KO-*t*-Bu	28%
8	NaO-*t*-Bu used instead of KO-*t*-Bu	0%
9	KOMe instead of KO-*t*-Bu	25%
10	2.0 eq KO-t-Bu instead of 3.0 eq KO-*t*-Bu	50%
11	4.0 eq KO-t-Bu instead of 3.0 eq KO-*t*-Bu	46%
12	no 2-iodothiophene	0%
13	3.0 eq used instead of 2.0 eq 2-iodothiophene	64%
14	2-bromothiophene used instead of 2-iodothiophene	14%
15	3-bromo-2-iodobenzo[*b*]thiophene used instead of 2-iodothiophene	48%
16	30 min instead of 20 h	36%
17	5 h instead of 20 h	50%
18	reaction run open to air instead of under N_2	49%
19	3.0 equiv 18-crown-6 added	37%
20	0.1 molar instead of 0.25 molar	51%
21	1.0 molar instead of 0.25 molar	49%
22	KO-t-Bu (97%) from Thermo Fisher Scientific (Product #A13947-14) instead of KO-t-Bu from Chem-Impex	76%
23	KO-t-Bu (99.99%) from Millipore Sigma (Product #659878) instead of KO-t-Bu from Chem-Impex	73%
24	KO-t-Bu (98%) from Millipore Sigma (Product #156671) instead of KO-t-Bu from Chem-Impex	75%
25	*N*-iodosuccinimide used instead of 2-iodothiophene	0%
26	iodine used instead of 2-iodothiophene	0%
27	carbon tetrabromide used instead of 2-iodothiophene	0%
28	*N*-bromosuccinimide used instead of 2-iodothiophene	0%
29	*N*-chlorosuccinimide used instead of 2-iodothiophene	0%

Table A1-1. Condition variation for the C–H hydroxylation of 3-bromopyridine.

(b) Effect of water surrogate identity on yield



Procedure: Inside a N_2 filled glovebox, a 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 3-bromopyridine (15.8 mg, 1 equiv, 0.1 mmol), water surrogate (0.1 mmol, 1 equiv), 2-iodothiophene (42.0 mg, 2 equiv, 0.2 mmol), anhydrous THF (0.4 mL), and KO-*t*-Bu (33.6 mg, 0.3 mmol, 3 equiv) in successive order (see Table A1-2 below). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, and placed into a preheated 60 °C aluminum reaction block. The reaction solution was stirred for 20 h at 60 °C and then allowed to cool to rt. For each experiment, 1,3,5-trimethoxybenzene was weighed into the vial and the mass added was recorded. The crude solution was then homogenized with MeOH (1 mL). A small aliquot was then removed and injected into an NMR tube and constituted in $(CD_3)_2SO$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, $(CD_3)_2SO$) was used to determine the yield of the resulting alkene and 3-bromopyridin-4(1H)-one (**2-3**). The results are summarized in Table A1-2 below. A representative example ^1H NMR spectrum for the crude reaction solution using the model alkene is shown in Figure A1-1 to show how the yield was determined.



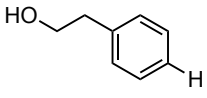
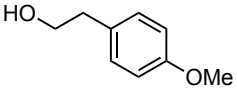
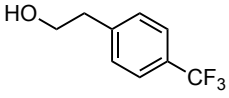
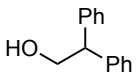
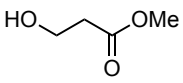
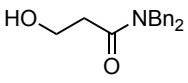
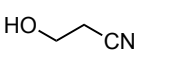
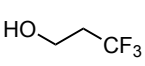
			
alkene, 84% yield **2-3**, 65% yield	**alkene**, 81% yield **2-3**, 60% yield	**alkene**, 30% yield **2-3**, 17% yield	**alkene**, 88% yield **2-3**, 42% yield
			
alkene, 30% yield **2-3**, 13% yield	**alkene**, 3% yield **2-3**, 8% yield	**alkene**, 0% yield **2-3**, 4% yield	**alkene**, 3% yield **2-3**, 9% yield

Table A1-2. Water surrogate variations for 4-selective 3-bromopyridine C-H hydroxylation.

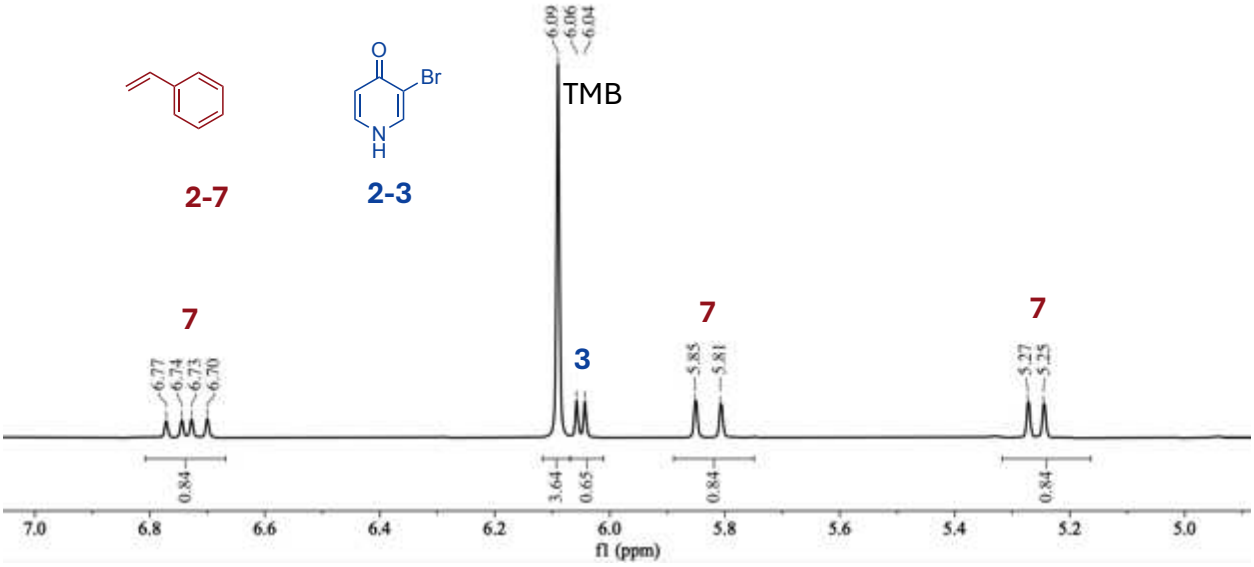


Figure A1-1. ^{1}H NMR spectral window of the crude reaction solution of reaction from the 'Effect of water surrogate identity on yield' study above. 1,3,5-Trimethoxybenzene internal standard (20.4 mg, 0.12 mmol, signal at 6.09 ppm calibrated to 3.64 for 0.1 mmol scale reaction) was used to determine the yield of the styrene (**2-7**, 84% yield) and 3-bromopyridin-4(1H)-one (**2-3**, 65% yield).

(c) Comparison of rate of styrene formation from 2-phenethyl alcohol and 3-bromo-4-phenethoxypyridine.

Purpose: This experiment was performed to evaluate the relative rate of styrene formation from 2-phenethyl alcohol (**2-8**) and the proposed C–H hydroxylation intermediate, 3-bromo-4-phenethoxypyridine (**2-6**).

Procedure: Inside a N_2 filled glovebox, a 4 mL vial (KIMBLE® , #60910-1) was charged with a magnetic stir bar, 3-bromo-4-phenethoxypyridine (27.8 mg, 1 equiv, 0.1 mmol), anhydrous THF (0.4 mL), and KO-*t*-Bu (11.2 mg, 0.1 mmol, 1 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, and placed into a preheated 60 °C aluminum reaction block. The reaction solution was stirred for 5 min at 60 °C and then allowed to cool to rt. The same procedure was conducted with 2-phenethyl alcohol (12.2 mg, 1 equiv, 0.1 mmol) and the reaction solution was placed into a preheated 60 °C aluminum reaction block. The reaction solution was stirred for 20 h at 60 °C and then allowed to cool to rt. For each experiment, 1,3,5-trimethoxybenzene was weighed into the vial and the mass added was recorded. The crude solution was then homogenized with MeOH (1 mL). A small aliquot was then removed and injected into an NMR tube and constituted in $(CD_3)_2SO$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, $(CD_3)_2SO$) was used to determine the yield of styrene (**2-7**) and 3-bromopyridin-4(1H)-one (**2-3**). The results are summarized in Figure A1-2 below.

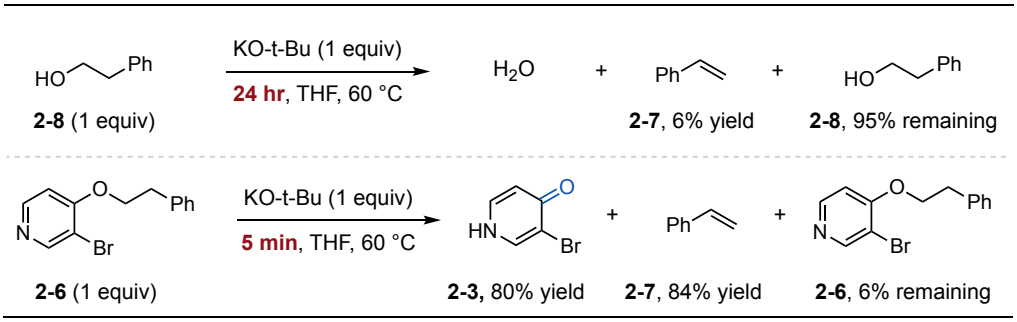
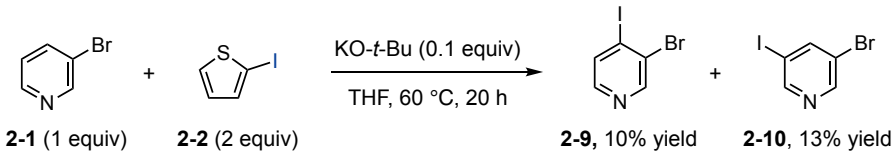


Figure A1-2. Base-promoted styrene elimination of **2-8** (top) and of **2-6** (bottom).

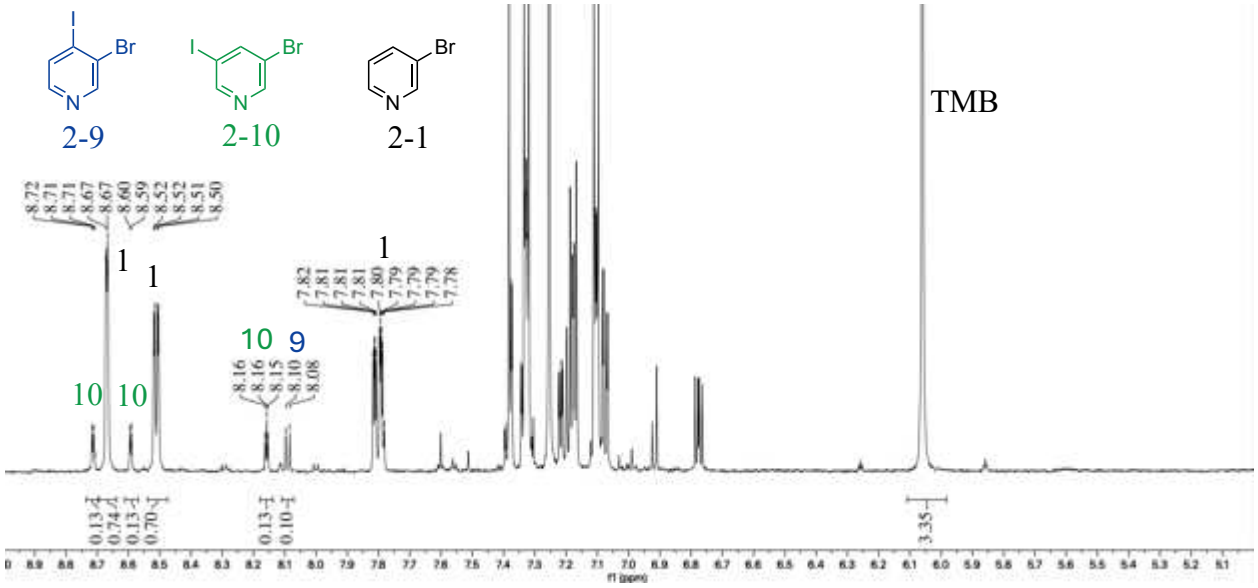
(d) Evidence of KO-*t*-Bu-catalyzed iodine transfer to 3-bromopyridine (2-1)

A control experiment for the independent X-transfer step was conducted to assess the catalytic potential of KO-*t*-Bu for iodine transfer from 2-iodothiophene to substrate **2-1**. Using 10 mol% KO-*t*-Bu under the pseudo-reaction conditions led to 23% iodine transfer to make the 4- and 5-iodinated pyridine products. This experiment confirms the catalytic nature of X-transfer and also illustrates how the X-transfer step needs to be paired with S_NAr to drive the process into a high-yielding and selective C–H functionalization process. We note that the 5-iodo isomer (**2-10**) likely forms from the 4-iodo isomer through a base-catalyzed halogen dance process.

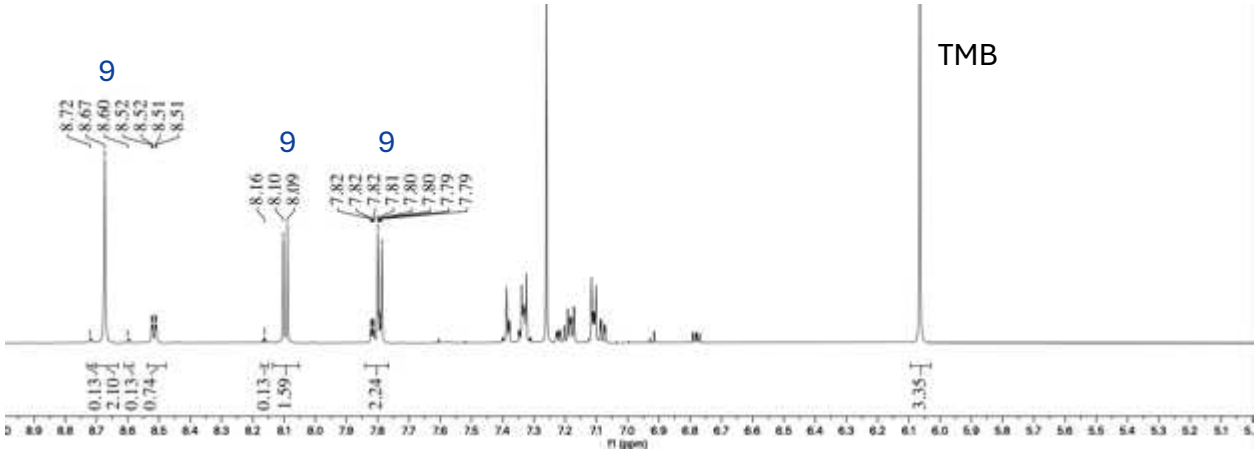


Procedure: Inside a N_2 filled glovebox, a 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 3-bromopyridine (39.5 mg, 1 equiv, 0.25 mmol), 2-iodothiophene (105.0 mg, 2 equiv, 0.5 mmol), anhydrous THF (1.0 mL), and KO-*t*-Bu (2.8 mg, 0.1 equiv, 0.025 mmol) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, and placed into a preheated 60 °C aluminum reaction block. The reaction solution was stirred for 20 h at 60 °C and then allowed to cool to rt. 1,3,5-Trimethoxybenzene internal standard was measured into the crude solution (30.2 mg, 0.18 mmol). A small aliquot of the organic layer was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of 3-bromo-4-iodopyridine (**2-9**) and 3-bromo-5-iodopyridine (**2-10**). The aromatic C–H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the aromatic C–H signal of **2-9** at 8.09 ppm (d, J = 5.1 Hz, 1H) and **2-10** at 8.60 ppm (d, J = 1.7 Hz, 1H) to determine the yields. The ^1H NMR spectrum for the crude reaction solution stacked alongside the ^1H NMR spectrum of authentic standards of 3-bromo-4-iodopyridine (CombiBlocks catalog #OS-7784) and 3-bromo-5-iodopyridine (Ambeed catalog # A136702) are shown below (Figure A1-3).

(a) ^{1}H NMR spectral window of the crude reaction solution:



(b) ^{1}H NMR spectrum of the crude reaction solution spiked with 3-bromo-4-iodopyridine:



(c) ^{1}H NMR spectrum of the crude reaction solution spiked with 3-bromo-5-iodopyridine:

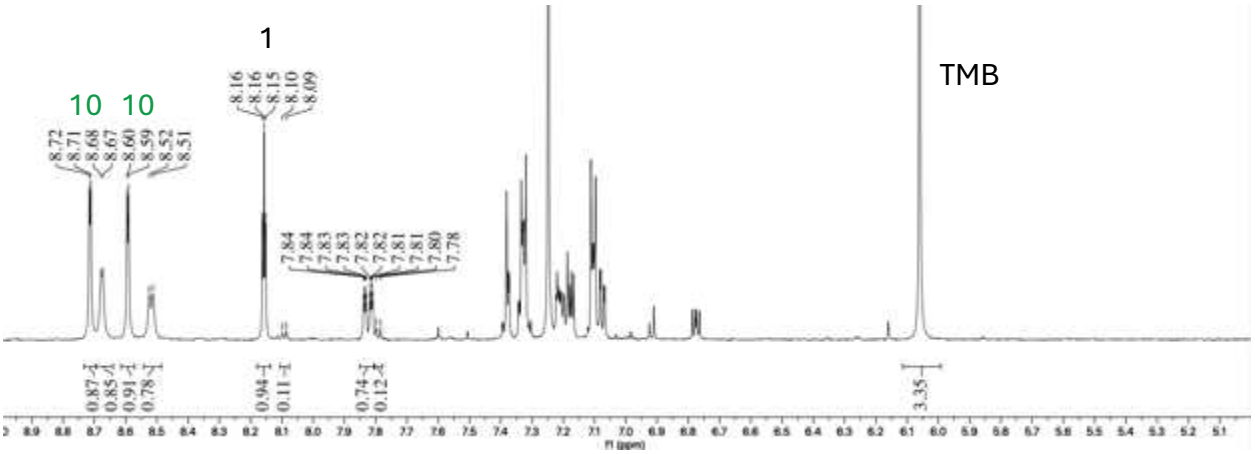
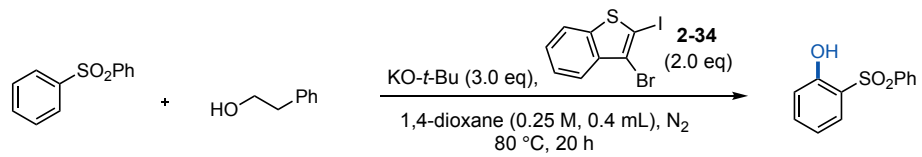


Figure A1-3. ^{1}H NMR spectral window of the crude reaction solution of reaction from the "Evidence of KO-*t*-Bu-catalyzed iodine transfer to 3-bromopyridine (**2-1**)" study above (Figure A1-3, a). 1,3,5-Trimethoxybenzene internal standard (30.2 mg, 0.18 mmol, signal at 6.09 ppm calibrated to 2.15 for 0.25 mmol scale reaction) was used to determine the yield of 3-bromo-4-iodopyridine (10% yield) and 3-bromo-5-iodopyridine (13% yield). ^{1}H NMR spectral window of the crude reaction solution spiked with 3-bromo-4-iodopyridine (Figure A1-3, b). ^{1}H NMR spectral window of the crude reaction solution spiked with 3-bromo-5-iodopyridine (Figure A1-3, c).

(e) Evaluation of changes in optimal base, halogenating agent, solvent, reaction time, and temperature for benzene C–H hydroxylation.

Optimization of the reaction conditions for benzene C–H hydroxylation on diphenyl sulfone indicated that use of 3-bromo-2-iodobenzo[*b*]thiophene and KO-*t*-Bu in 1,4-dioxane was most effective at promoting reactivity with 2-phenethyl alcohol. The optimized conditions are provided in the table below in comparison to specific changes of reagents or conditions used to document these effects for readers.

General procedure for condition variation: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE® , #60910-1) was charged with a magnetic stir bar, diphenyl sulfone (21.8 mg, 1 equiv, 0.1 mmol), 2-phenethyl alcohol (12.2 mg, 0.1 mmol, 1 equiv), halogenating agent (0.2 mmol, 2 equiv), anhydrous solvent (0.25 M, 0.4 mL), and base (0.3 mmol, 3 equiv) in successive order (see Table A1-3 below). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, and placed into a preheated 60 °C aluminum reaction block. The reaction solution was stirred for 20 h at 80 °C and then allowed to cool to rt. 1,3,5-Trimethoxybenzene internal standard was measured into the crude solution and the mass weighed into the vial was recorded. Several drops of 1M HCl were added to the crude solution to ensure protonation of 2-(phenylsulfonyl)phenol. A small aliquot of the organic layer was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of 2-(phenylsulfonyl)phenol (**2-32**). The aromatic C–H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the aromatic C–H signal of **2-32** at 6.85 ppm (d, J = 8.3 Hz, 1H) to determine the yield. The results are summarized in Table A1-3 below. We note that an over-iodinated phenol side-product is observed in small quantities (0-15% yield) for the reactions listed in Table A1-3; this is readily separated upon chromatographic purification.



0.10 mmol **2-31** (1.0 eq)

0.10 mmol **2-8** (1.0 eq)

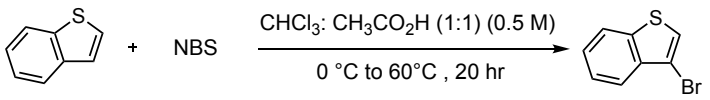
2-32

Entry	Change from the "standard conditions"	Yield
1	none	55%
2	40 °C instead of 80 °C	46%
3	100 °C instead of 80 °C	47%
4	DMF used as solvent instead of dioxane	0%
5	PhMe used as solvent instead of dioxane	39%
6	DMSO used as solvent instead of dioxane	0%
7	KOH instead of KO-*t*-Bu	23%
8	NaO-*t*-Bu used instead of KO-*t*-Bu	34%
9	KOMe instead of KO-*t*-Bu	31%
10	2.0 eq KO-t-Bu instead of 3.0 eq KO-*t*-Bu	47%
11	4.0 eq KO-t-Bu instead of 3.0 eq KO-*t*-Bu	48%
12	3.0 eq used instead of 2.0 eq 2-iodo-3-bromobenzo[*b*]thiophene	55%
13	2-iodothiophene used instead of 2-iodo-3-bromobenzo[*b*]thiophene	35%
14	2,3-diiodobenzo[*b*]thiophene used instead of 2-iodo-3-bromobenzo[*b*]thiophene	46%
15	2,3-dibromobenzo[*b*]thiophene used instead of 2-iodo-3-bromobenzo[*b*]thiophene	26%
16	30 min instead of 20 h	39%
17	5 h instead of 20 h	50%
18	reaction run open to air instead of under N_2	47%
19	0.1 molar instead of 0.25 molar	53%
20	1.0 molar instead of 0.25 molar	54%
21	*N*-iodosuccinimide used instead of 2-iodo-3-bromobenzo[*b*]thiophene	0%
22	iodine used instead of 2-iodo-3-bromobenzo[*b*]thiophene	0%
23	carbon tetrabromide used instead of 2-iodo-3-bromobenzo[*b*]thiophene	0%
24	*N*-bromosuccinimide used instead of 2-iodo-3-bromobenzo[*b*]thiophene	0%
25	*N*-chlorosuccinimide used instead of 2-iodo-3-bromobenzo[*b*]thiophene	0%

Table A1-3. Condition variation for diphenyl sulfone C–H hydroxylation.

A1.3. Synthesis of 3-Bromo-2-iodobenzo[*b*]thiophene

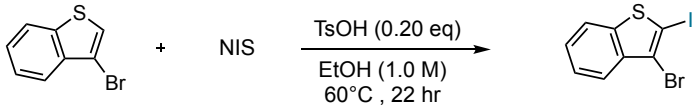
Step 1: 3-bromobenzo[*b*]thiophene (2-57)



(1 eq) (1.2 eq) **2-57**, 100% yield

This procedure was adapted from a literature report.[4] An oven-dried 1 L round bottom flask was charged with a magnetic stir bar, benzo[*b*]thiophene (30.0 g, 224 mmol, 1 equiv), and 1:1 ratio of chloroform:acetic acid (total volume 447 mL, 0.5 M). The flask was inserted into a 0 °C ice-bath and *N*-bromosuccinimide (47.7 g, 268 mmol, 1.2 equiv) was added portion-wise over 5 min while stirring. The reaction flask was then inserted into a 60 °C silicon oil bath and stirred for 3 h. The reaction mixture was cooled to rt and transferred to a separatory funnel containing H_2O (300 mL). $Na_2S_2O_3$ (20 g, 112 mmol) was added to the separatory funnel and the solution was agitated until it became light-yellow in color. The aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL). The organic layer was dried over Na_2SO_4, filtered, and then concentrated *in vacuo* to yield the title compound as a brown oil (47.6 g, 224 mmol, 100% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.80 (m, 2H), 7.55 – 7.33 (m, 3H). Spectroscopic characterization is consistent with a previous report.[4] This material was used directly in the next step for 2-iodination.

Step 2: 3-bromo-2-iodobenzo[*b*]thiophene (2-34)



2-57 (1 eq) (2.2 eq) **2-34**
75% overall yield, 56.7 g isolated

An oven-dried 1 L round bottom flask was charged with a magnetic stir bar, 3-bromobenzo[*b*]thiophene (47.6 g, 223 mmol, 1 equiv), and ethanol (220 mL, 1.0 M). The flask was inserted into a 0 °C ice-bath and stirred. The solution was then charged with *p*-toluenesulfonic acid monohydrate (4.25 g, 22.3 mmol, 0.1 equiv). Next, *N*-iodosuccinimide (55.3 g, 246 mmol, 1.1 equiv) was added portion-wise over 5 min. The flask was then inserted into a 60 °C silicon oil bath and the solution was stirred for 20 h. A second addition of *p*-toluenesulfonic acid monohydrate (4.25 g, 22.3 mmol, 0.1 equiv) and *N*-iodosuccinimide (55.3 g, 246 mmol, 1.1 equiv, added over portion-wise over 5 min) were then added. The reaction mixture was stirred for an additional 2 h at 60 °C. The solution was cooled to rt and transferred to a separatory funnel containing H_2O (300 mL). $Na_2S_2O_3$ (70 g, 491 mmol) was added to the separatory funnel and the solution was agitated until it became light-yellow in color. The aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL). The organic layer was dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. Silica gel chromatography (hexanes) followed by recrystallization (3% CH_2Cl_2/hexanes) yielded the title compound as a crystalline yellow solid (56.7 g, 167 mmol, 75% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 – 7.68 (m, 2H), 7.38 – 7.29 (m, 2H). **^{13}C NMR** (101 MHz, ($CDCl_3$) δ 143.0, 137.9, 134.5, 125.6, 123.8, 121.8, 118.4, 82.2. The spectroscopic data is consistent with a previous report.[5]

A1.4. General Procedures for *N*-Heteroarene and Benzene C–H Hydroxylation

Note: The reaction optimization studies were conducted inside a N_2 filled glovebox, while the general procedure for 1 mmol scale isolation reactions was developed using a standard manifold Schlenk line. The crude ^{1}H NMR yields observed during optimization are comparable to those for the 1 mmol isolation procedure.

General *N*-Heteroarene C–H Hydroxylation Procedure: Open to air, an 8 mL oven-dried vial (Thermo Fischer Scientific, #033405P) was charged with a magnetic stir bar and the following liquid reagents: 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv) or 2,5-dibromothiophene (483.9 mg, 2 mmol, 2 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), and (if liquid) *N*-heteroarene substrate (1 mmol, 1 equiv). **Note:** 2-iodothiophene was used for 6-membered *N*-heteroarenes (Section 4a, below) and 2,5-dibromothiophene was used for the 1,3-azoles (Section 4b, below). The vial was sealed with a screw cap (Thermo Fisher Scientific, #03392A) lined with a PTFE septum (Thermo Fisher Scientific, #B799515), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 on a manifold Schlenk line. The solid reagents were then charged into a separate 8 mL oven-dried vial (Thermo Fischer Scientific, #033405P): KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), 18-crown-6 (if required, as noted in Section 4a-b, 792.4 mg, 3 mmol, 3 equiv), and (if solid) *N*-heteroarene substrate (1 mmol, 1 equiv). This vial was sealed with a screw cap (Thermo Fisher Scientific, #03392A) lined with a PTFE septum (Thermo Fisher Scientific, #B799515), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 on a manifold Schlenk line. Anhydrous THF (4.0 mL, 0.25 M) was added to the vial containing the liquid reagents and the entire contents were promptly transferred to the vial containing the solid reagents *via* syringe. The reaction vial was placed into a preheated 60 °C silicon oil bath and the mixture was stirred under N_2 for 20 h for the 6-membered *N*-heteroarenes (Section 4a) and 3 h for the 1,3-azoles (Section 4b). The reaction mixture was cooled to rt and one of the following isolation procedures was followed. Notably, a trend was observed wherein a solid precipitated during successful reactions conducted in THF.

Isolation Procedure 1: Upon cooling to rt, the crude reaction solution was directly subjected to silica gel flash chromatography (specific conditions given per compound in Section A1-4a-b). **Note:** products isolated using this procedure were found to be soluble in water from pH 1-14, and thus not amenable to an aqueous wash.

Isolation Procedure 2: Upon cooling to rt, the reaction solution was poured into a 250 mL separatory funnel containing water (40 mL). The pH of the water layer was adjusted to pH 14 using 1M NaOH and the organic impurities were extracted with ethyl acetate (EtOAc) (3 x 40 mL). The pH of the water layer was then adjusted to pH 5 using 1M HCl and the product precipitated. The precipitate was collected and dried *in vacuo*.

Isolation Procedure 3: Upon cooling to rt, the reaction solution was poured into a 250 mL separatory funnel containing water (40 mL). The pH of the water layer was adjusted to pH 14 using 1M NaOH and the organic impurities were extracted with EtOAc (3 x 40 mL). The pH of the water layer was then adjusted to pH 5 using 1M HCl and the product was extracted with dichloromethane (CH_2Cl_2) (3 x 40 mL). The CH_2Cl_2 organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo*.

Other Considerations: The yields determined from the ^{1}H NMR spectrum of the crude reaction mixture of styrene and the hydroxylated *N*-heteroarene product were typically similar to the isolated yield of the corresponding hydroxylated product. Hydroxylated *N*-heteroarenes are known to be hygroscopic, so elemental analysis was conducted on several isolated products to ensure that no significant amount of water was contributing to the calculated isolated yield. Additionally, water was not typically observed in significant quantities in the ^{1}H NMR spectrum of the isolated material.

General Benzene C–H Hydroxylation Procedure: Open to air, an 8 mL oven-dried vial (Thermo Fischer Scientific, #033405P) was charged with a magnetic stir bar and any liquid reagents: 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv.) and (if liquid) benzene substrate (1 mmol, 1 equiv). The vial was sealed with a screw cap (Thermo Fisher Scientific, #03392A) lined with a PTFE septum (Thermo Fisher Scientific, #B799515), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 on a manifold Schlenk line. The solid reagents were then charged into a separate 8 mL oven-dried vial (Thermo Fischer Scientific, #033405P): KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), 18-crown-6 (if necessary, as noted in Section 4c, 792.4 mg, 3 mmol, 3 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), and (if solid) benzene substrate (1 mmol, 1 equiv). This vial was sealed with a screw cap (Thermo Fisher Scientific, #03392A) lined with a PTFE septum (Thermo Fisher Scientific, #B799515), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 on a manifold Schlenk line. Anhydrous 1,4-dioxane (4.0 mL, 0.25 M) was added to the vial containing the liquid reagents and the entire contents were promptly transferred to the vial containing the solid reagents *via* syringe. The reaction vial was placed into a preheated 80 °C silicon oil bath and the mixture was stirred for 20 h. The reaction solution was cooled to rt and one of the following isolation procedures was followed.

Isolation Procedure 4: Upon cooling to rt, the crude solution was poured into a 250 mL separatory funnel containing water (40 mL). The pH of the water layer was adjusted to pH 14 using 1M NaOH and the organic impurities were extracted with EtOAc (3 x 40 mL). The pH of the water layer was then adjusted to pH 5 using 1M HCl and the product was extracted with dichloromethane (3 x 40 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo*. The crude material was purified *via* silica gel chromatography (specific conditions given per compound in Section A1-4c).

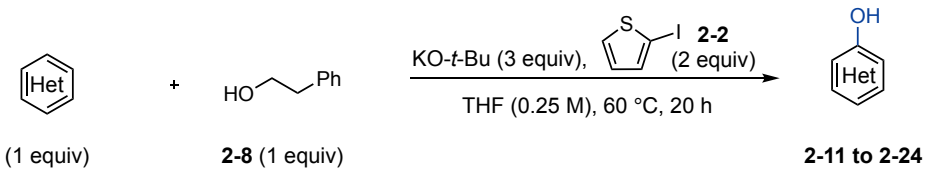
Isolation Procedure 5: Upon cooling to rt, the crude solution was poured into a 250 mL separatory funnel containing water (40 mL). The pH of the water layer was adjusted to pH 14 using 1M NaOH and the organic impurities were extracted with EtOAc (3 x 40 mL). The pH of the water layer was then adjusted to pH 5 using 1M HCl and the product precipitated. The precipitate was collected and dried in *vacuo*.

Verification of Product Regioselectivity: The regioselectivity of the C–H hydroxylation reaction could usually be determined through analysis of the ^{1}H NMR spectrum of each compound. The ^{1}H NMR spectrum of the crude reaction mixture for each compound was analyzed to determine if the major product was formed in high selectivity. An example of this analysis is included for the first substrate (**2-11**) in Figure A1-4. We note that the selectivity appeared to be less than 10:1 only for substrates **2-13** and **2-32**, where more details are included below their characterization data. For

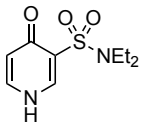
compounds where the regioselectivity of the major product is more ambiguous, additional NMR experiments or crystallographic characterization are provided below the characterization data.

A1.4. Characterization Data of Hydroxylated *N*-Heteroaryl and Phenol Products

(a) Products shown in Figure 2-14a.



***N*,*N*-diethyl-4-oxo-1,4-dihydropyridine-3-sulfonamide (2-11)**



The title product was prepared according to the general procedure for *N*-heteroarene C–H hydroxylation using *N*,*N*-diethylpyridine-3-sulfonamide (214.3 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 1, wherein silica gel chromatography (5% to 10% MeOH/CH_2Cl_2) afforded the title compound as a light-yellow solid (173.3 mg, 0.75 mmol, 75% yield). **Mp**: 168-170 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 11.83 (br s, 1H), 8.20 (d, J = 1.7 Hz, 1H), 7.71 (dd, J = 7.4, 1.7 Hz, 1H), 6.24 (d, J = 7.4 Hz, 1H), 3.26 (q, J = 7.1 Hz, 4H), 1.04 (t, J = 7.1 Hz, 6H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 173.0, 141.5, 138.5, 127.4, 120.0, 42.0, 14.6. **IR** (neat, cm^{-1}) 3055, 2920, 1636, 1506, 1345, 1070, 922, 785, 667. **EA:** Anal. Calcd for $C_9H_{14}N_2O_3S$: C, 46.94; H, 6.13; N, 12.17. Found: C, 47.08; H, 6.32; N, 11.96.

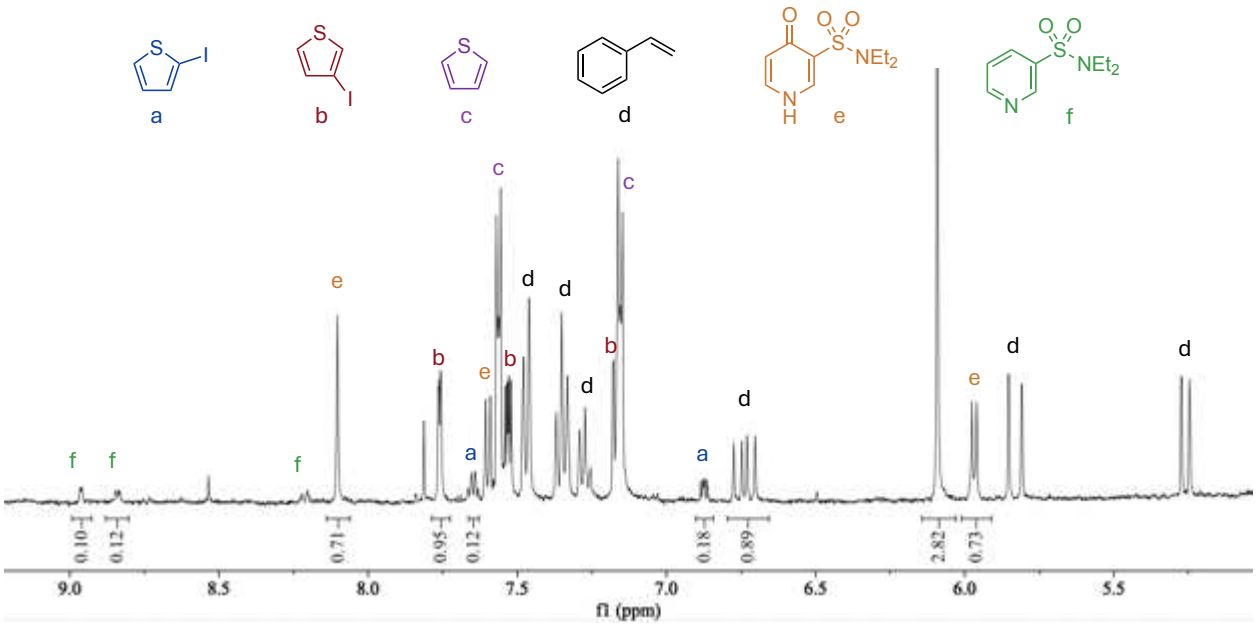
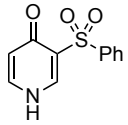


Figure A1-4. The interpretation of all the signals in the ^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$) of the crude reaction solution of the hydroxylation of *N*,*N*-diethylpyridine-3-sulfonamide is shown

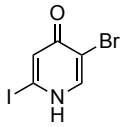
above. Typically seen byproducts from the hydroxylation reaction are marked as such: 2-iodothiophene (**2-2**, marked with a), 3-iodothiophene (**2-36**, marked with b), thiophene (marked with c), styrene (**2-7**, marked with d), and *N,N*-diethyl-4-oxo-1,4-dihydropyridine-3-sulfonamide (**2-11**, marked with e), *N,N*-diethylpyridine-3-sulfonamide (marked with f).

3-(phenylsulfonyl)pyridin-4(1H)-one (2-12)



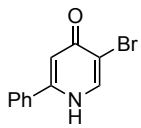
The title product was prepared through slight modification of the general procedure for the C–H hydroxylation of *N*-heteroarenes, where the reaction mixture was stirred at 40 °C instead of 60 °C. Thus, 3-(phenylsulfonyl)pyridine (219.3 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (629.7 mg, 3 mmol, 3 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL) were added according to the general procedure. The product was purified *via* the general *N*-heteroarene isolation procedure 1, wherein silica gel chromatography (5% to 10% MeOH/CH_2Cl_2) afforded the title compound as a pale-yellow solid (190.4 mg, 0.81 mmol, 81% yield). **Mp**: 279-283 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 12.11 (br s, 1H), 8.48 (d, *J* = 1.7 Hz, 1H), 8.02 – 7.93 (m, 2H), 7.75 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.71 – 7.61 (m, 1H), 7.58 – 7.54 (m, 2H), 6.20 (d, *J* = 7.4 Hz, 1H).**^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 172.3, 142.0, 140.7, 139.1, 133.2, 128.7, 128.0, 126.5, 120.6. **IR** (neat, cm^{-1}) 2629, 1630, 1583, 1528, 1309, 1288, 1142, 1094, 867. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{11}H_{10}NO_3S]^+$ = 236.0376, 236.0390 found.

5-bromo-2-iodopyridin-4(1*H*)-one (2-13)



The title product was prepared according to the general procedure for *N*-heteroarene C–H hydroxylation using 5-bromo-2-iodopyridine (282.9 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), 18-crown-6 (793.0 mg, 3 mmol, 3 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The general *N*-heteroarene isolation procedure 1 was followed, wherein silica gel chromatography (3% to 5% MeOH/CH_2Cl_2) provided the title product with residual impurities. Subsequent purification *via* washing with cold CH_2Cl_2 over a fritted funnel was performed and the collected solid material yielded the title compound as a pale-yellow solid (114.5 mg, 0.38 mmol, 38% yield). **Mp**: 238-240 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 12.13 (br s, 1H), 8.24 (s, 1H), 7.19 (s, 1H).**^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 162.3, 151.3, 122.4, 116.0, 110.4. **IR** (neat, cm^{-1}) 2775, 2355, 1603, 1500, 1477, 1077, 1033. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_5H_4BrINO]^+$ = 299.8515, 299.8511 found. **Note on reaction regioselectivity:** Direct 2-substitution on 5-bromo-2-iodopyridine occurred to give 15% of the 5-bromopyridin-2(1H)-one side product, as detected by crude ^{1}H NMR spectroscopy. This material was readily separated from the desired isomer by silica gel chromatography.

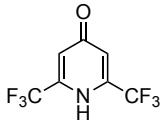
5-bromo-2-phenylpyridin-4(1*H*)-one (2-14)



The title product was prepared according to the general procedure for *N*-heteroarene C–H hydroxylation using 5-bromo-2-phenylpyridine (234.1 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (629.7 mg, 3 mmol, 3 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 3 to afford the title compound as a white solid (99.7 mg, 0.40 mmol, 40% yield). **Mp**: 277-278 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 12.08 (br s, 1H), 8.32 (s, 1H), 7.80 (dd, J = 7.2, 2.4 Hz, 2H), 7.51- 7.48 (m, 3H), 6.90 (s, 1H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 168.0, 151.6, 144.2, 135.0, 129.8, 128.9,

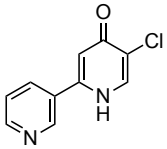
126.6, 111.1, 111.0. **IR** (neat, cm^{-1}) 2900, 2847, 1619, 1498, 1386, 1200, 1054, 851, 731. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{11}H_9BrNO]^+$ = 249.9862, 249.9859 found.

2,6-bis(trifluoromethyl)pyridin-4(1*H*)-one (2-15)



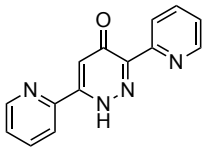
The title product was prepared according to the general procedure for *N*-heteroarene C–H hydroxylation using 2,6-bis(trifluoromethyl)pyridine (215.0 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), 18-crown-6 (793.0 mg, 3 mmol, 3 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 1, wherein silica gel chromatography (70% hexane/EtOAc) afforded the title compound as a brown oil (128.7 mg, 0.56 mmol, 56% yield). **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 10.96 (br s, 1H), 7.50 (s, 2H). **^{13}C NMR** (101 MHz, $(CD_3)_2CO$) δ 168.0, 150.6 (q, *J* = 35.3 Hz), 121.8 (q, *J* = 273.7 Hz), 112.2 (q, *J* = 2.8 Hz). **^{19}F NMR** (376 MHz, $(CD_3)_2SO$) δ -66.1. **IR** (neat, cm^{-1}) 3071, 2927, 1700, 1619, 1415, 1270, 1085, 912, 751. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_7H_4F_6N_3O]^+$ = 232.0192, 232.0186 found. The spectroscopic data is consistent with a previous report.[6] **Note:** The ^{1}H NMR yield was 83% and isolation provided a slightly reduced 56% yield.

5-chloro-[2,3'-bipyridin]-4(1H)-one (2-16)



The title product was prepared according to the general procedure for *N*-heteroarene C–H hydroxylation using 5-chloro-2,3'-bipyridine (190.6 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 1, wherein silica gel chromatography (5% to 10% $MeOH/CH_2Cl_2$) afforded the title compound as a purple solid (190.0 mg, 0.92 mmol, 92% yield). **Mp**: 190-194 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 12.63 (br s, 1H), 9.03 (s, 1H), 8.62 (d, *J* = 4.7 Hz, 1H), 8.34 (s, 1H), 8.20 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.50 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.15 (s, 1H).**^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 150.5, 150.3, 147.6, 134.3, 134.22, 134.18, 131.6, 123.8, 120.0, 111.1. **IR** (neat, cm^{-1}) 2745, 1622, 1518, 1235, 1078, 1024, 873, 810, 661. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{10}H_8N_2OCl]^+$ = 207.0320, 207.0319 found.

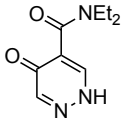
3,6-di(pyridin-2-yl)pyridazin-4(1H)-one (2-17)



The title product was prepared using a slight modification of the general procedure for the C–H hydroxylation of *N*-heteroarenes, where 3-bromo-2-iodobenzo[*b*]thiophene was used as the X-transfer reagent in place of 2-iodothiophene. Thus, 3,6-di(pyridin-2-yl)pyridazine (234.3 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL) were added according to the general procedure. The product was purified *via* the general *N*-heteroarene isolation procedure 1, wherein silica gel chromatography (1% Et_3N in 10% $MeOH/CH_2Cl_2$) afforded the title compound as a brown solid (128.8 mg, 0.51 mmol, 51% yield). **Mp**: 180-187 °C. **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 14.95 (br s, 1H), 8.90 (dt, *J* = 8.1, 1.1 Hz, 1H), 8.73 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 8.68 (dt, *J* = 7.9, 1.1 Hz, 1H), 8.61 (ddd, *J* = 5.1, 1.8, 0.9 Hz, 1H), 8.13 – 8.00 (m, 2H), 7.90 (td, *J* = 7.7, 1.8 Hz, 1H), 7.52 (ddd, *J* = 7.6, 5.1, 1.2 Hz, 1H), 7.41 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 160.2, 159.5, 156.5,

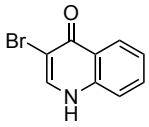
153.9, 149.9, 146.1, 143.9, 139.0, 137.3, 125.0, 124.9, 121.9, 121.5, 111.6. **IR** (neat, cm^{-1}) 2360, 575, 514, 505, 498, 487, 472. **HRMS** (ESI) $[M+NH_4]^+$ calcd. for $[C_{14}H_{14}N_5O]^+$ = 268.1193, 268.1193 found.

_N_,_N_-diethyl-5-oxo-2,5-dihydropyridazine-4-carboxamide (2-18)



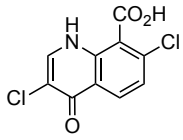
The title product was prepared according to the general procedure for *N*-heteroarene C–H hydroxylation using *N*,*N*-diethylpyridazine-4-carboxamide (179.2 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (629.7 mg, 3 mmol, 3 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous DMF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 1, wherein silica gel chromatography (3% to 5% $MeOH/CH_2Cl_2$) afforded the title compound as an off-white solid (169.5 mg, 0.87 mmol, 87% yield). **Mp**: 84-87 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 13.43 (br s, 1H), 8.35 (s, 1H), 7.86 (s, 1H), 3.38 (q, *J* = 7.1 Hz, 2H), 3.15 (q, *J* = 7.1 Hz, 2H), 1.18 – 0.91 (m, 6H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 166.7, 164.1, 150.0, 139.0, 125.2, 42.4, 38.7, 14.3, 12.9. **IR** (neat, cm^{-1}) 2923, 2776, 1615, 1456, 1260, 1214, 1094, 882, 637. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_9H_{14}N_3O_2]^+$ = 196.1081, 196.1082 found.

3-bromoquinolin-4(1*H*)-one (2-19)



The title product was prepared according to the general procedure for *N*-heteroarene C–H hydroxylation using 3-bromoquinoline (208.1 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 2 to afford the title compound as an off-white solid (185.7 mg, 0.83 mmol, 83% yield). **Mp**: 284-285 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) 12.29 (br s, 1H), 8.48 (s, 1H), 8.14 (d, *J* = 9.6 Hz, 1H), 7.76 – 7.65 (m, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H).**^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 171.4, 140.2, 139.3, 131.9, 125.3, 124.2, 124.0, 118.5, 104.2. **IR** (neat, cm^{-1}) 2784, 1625, 1558, 1474, 1354, 1300, 1191, 689. **EA**: Anal. Calcd for C_9H_6BrNO: C, 48.25; H, 2.70; N, 6.25. Found: C, 48.26; H, 2.66; N, 6.24. The spectroscopic data is consistent with a previous report.[7]

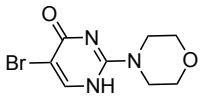
3,7-dichloro-4-oxo-1,4-dihydroquinoline-8-carboxylic acid (2-20)



The title product was prepared according to the general procedure for *N*-heteroarene C–H hydroxylation using 3,7-dichloroquinoline-8-carboxylic acid (242.1 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), 18-crown-6 (793.0 mg, 3 mmol, 3 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 2 followed by silica gel chromatography (1% Et_3N in 10% $MeOH/CH_2Cl_2$) to afford the title compound as the triethylamine salt. This material was then constituted in water (20 mL) and the pH was adjusted to 5 using 1 M HCl. The product was extracted with dichloromethane (CH_2Cl_2) (2 x 20 mL). The CH_2Cl_2 organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo* to provide the title compound as a pale green solid (144.9 mg, 0.56 mmol, 56% yield). **Mp**: 279-280 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) 14.42 (br s, 1H), 11.86 (br s, 1H), 8.24 – 8.21 (m, 2H), 7.51 (d, *J* = 8.6 Hz, 1H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 170.5, 165.4, 139.1, 136.7, 134.5, 128.5, 125.2, 123.6, 123.3, 115.1. **IR** (neat, cm^{-1})

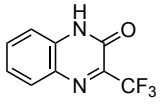
3234, 3070, 2007, 1607, 1497, 1352, 1171, 972, 906. **EA**: Anal. Calcd for $C_{10}H_5Cl_2NO_3$: C, 46.54; H, 1.95; N, 5.43. Found: C, 46.28; H, 2.04; N, 5.24.

5-bromo-2-morpholinopyrimidin-4(1*H*)-one (2-21)



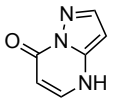
The title product was prepared according to the general procedure for *N*-heteroarene C–H hydroxylation using 4-(5-bromopyrimidin-2-yl)morpholine (244.1 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 3 to afford the title compound as a pale green solid (128.1 mg, 0.49 mmol, 49% yield). **Mp**: 210-215 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) 11.83 (br s, 1H), 7.88 (s, 1H), 3.62 – 3.59 (m, 4H), 3.54 – 3.52 (m, 4H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 160.0, 155.1, 154.9, 97.3, 65.5, 44.8. **IR** (neat, cm^{-1}) 2921, 1641, 1549, 1446, 1314, 992, 754, 653. **EA**: Anal. Calcd for $C_8H_{10}BrN_3O$: C, 36.94; H, 3.88; N, 16.16. Found: C, 37.05; H, 3.74; N, 15.88.

3-(trifluoromethyl)quinoxalin-2(1H)-one (2-22)



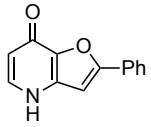
The title product was prepared through slight modification of the general procedure for the C–H hydroxylation of *N*-heteroarenes, where 3-bromo-2-iodobenzo[*b*]thiophene was used as the X-transfer reagent in place of 2-iodothiophene. Thus, 2-(trifluoromethyl)quinoxaline (198.2 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL) were added according to the general procedure. The product was purified *via* the general *N*-heteroarene isolation procedure 1, wherein silica gel chromatography (3% to 5% MeOH/CH_2Cl_2) afforded the title compound as an orange solid (128.3 mg, 0.61 mmol, 61% yield). **Mp**: 197-203 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 11.71 (br s, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 151.7, 144.0 (q, J = 32.0 Hz), 133.7, 133.5, 129.9, 129.87, 124.2, 120.1 (q, J = 276.2 Hz), 115.9. **^{19}F NMR** (376 MHz, $(CD_3)_2CO$) δ -68.0. **IR** (neat, cm^{-1}) 2845, 1672, 1610,1367, 1313, 1141, 1055, 759, 544. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_9H_6F_3N_2O]^+$ = 215.0427, 215.0425 found. The spectroscopic data is consistent with a previous report.[8]

pyrazolo[1,5-a]pyrimidin-7(4H)-one (2-23)



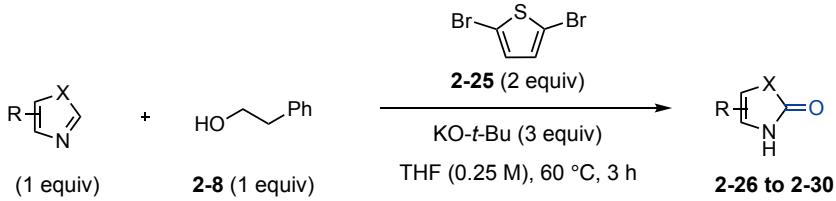
The title product was prepared according to the general procedure for *N*-heteroarene C–H hydroxylation using pyrazolo[1,5-*a*]pyrimidine (119.1 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (629.7 mg, 3 mmol, 3 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 1, wherein silica gel chromatography (5% to 10% MeOH/CH_2Cl_2) provided the title product with residual impurities. This material was resubjected to silica gel chromatography (100% EtOAc to 6% MeOH/CH_2Cl_2) and the obtained material was washed with cold EtOAc to afford the title compound as a pale green solid (61.8 mg, 0.50 mmol, 50% yield). **Mp**: 230-235 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 12.38 (br s, 1H), 7.95 – 7.77 (m, 2H), 6.18 (d, J = 2.0 Hz, 1H), 5.68 (d, J = 7.4 Hz, 1H).**^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 156.7, 142.6, 141.9, 139.6, 95.3, 89.0. The spectroscopic data is consistent with a previous report.[9]

2-phenylfuro[3,2-*b*]pyridin-7(4*H*)-one (2-24)

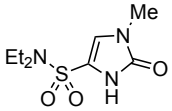


The title product was prepared according to the general procedure for *N*-heteroarene C–H hydroxylation using 2-phenylfuro[3,2-*b*]pyridine (195.2 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 2 to afford the title compound as an off-white solid (86.4 mg, 0.41 mmol, 41% yield). **Mp**: 304-306 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) 12.04 (s, 1H), 7.94 – 7.93 (m, 2H), 7.70 (d, J = 6.6 Hz, 1H), 7.55 – 7.52 (m, 2H), 7.47 – 7.43 (m, 1H), 7.29 (br s, 1H), 6.13 (d, J = 6.6 Hz, 1H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 165.8, 156.1, 142.4, 136.9, 135.8, 129.6, 129.1, 129.0, 125.0, 113.9, 97.5. **IR** (neat, cm^{-1}) 2568, 2362, 1632, 1529, 1507, 1419, 918, 808. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{13}H_{10}NO_2]^+$ = 212.0712, 212.0726 found.

(b) Products shown in Figure 2-14b.

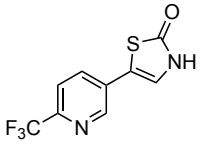


***N*,*N*-diethyl-1-methyl-2-oxo-2,3-dihydro-1H-imidazole-4-sulfonamide (2-26)**



The title product was prepared according to the general procedure for *N*-heteroarene C–H hydroxylation using *N*,*N*-diethyl-1-methyl-1H-imidazole-4-sulfonamide (217.3 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2,5-dibromothiophene (483.9 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 2 to afford the title compound as a beige solid (178.2 mg, 0.76 mmol, 76% yield). **Mp**: 296-300 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 11.01 (br s, 1H), 7.22 (s, 1H), 3.15 (m, 7H), 1.09 (t, J = 6.5 Hz, 6H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 155.2, 119.7, 118.5, 42.1, 29.7, 14.4. **IR** (neat, cm^{-1}) 3675, 2924, 2518, 2363, 2158, 2028, 1050. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_8H_{16}N_3O_3S]^+$ = 234.0907, 234.0910 found.

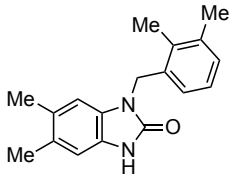
5-(6-(trifluoromethyl)pyridin-3-yl)thiazol-2(3H)-one (2-27)



The title product was prepared through slight modification of the general procedure for the C–H hydroxylation of *N*-heteroarenes, where 2,3-dibromobenzo[*b*]thiophene was used as the X-transfer reagent in place of 2,5-dibromothiophene. Thus, 5-(6-(trifluoromethyl)pyridin-3-yl)thiazole (230.2 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2,3-dibromobenzo[*b*]thiophene (584.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL) were added according to the general procedure. The product was purified *via* the general *N*-heteroarene isolation procedure 2 to afford the yield the title compound as a white solid (236.2 mg, 0.96 mmol, 96% yield). **Mp**: 207-210 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 11.83 (br s, 1H), 8.89 (d, J = 2.5 Hz, 1H), 8.04 (dd, J = 8.3, 2.5 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.83 (s, 1H).**^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 171.5, 145.6, 144.1 (q, J = 35.1 Hz), 132.9, 131.4, 122.5, 121.6 (q, J = 274.4 Hz), 120.9 (q, J = 3.0 Hz), 113.3. **^{19}F NMR** (376 MHz,

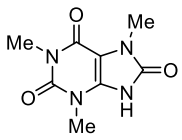
$(CD_3)_2SO$) δ -65.3. **IR** (neat, cm^{-1}) 3154, 2360, 1673, 1635, 1594, 1344, 1130, 515. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_9H_6F_3N_2OS]^+$ = 247.0147, 247.0149 found.

1-(2,3-dimethylbenzyl)-5,6-dimethyl-1,3-dihydro-2H-benzo[*d*]imidazol-2-one (2-28)



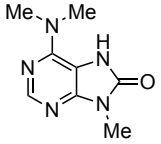
The title product was prepared according to the general procedure for *N*-heteroarene C–H hydroxylation using 1-(2,3-dimethylbenzyl)-5,6-dimethyl-1H-benzo[*d*]imidazole (264.4 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2,5-dibromothiophene (483.9 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 1, wherein silica gel chromatography (70% EtOAc/hexanes to 100% EtOAc) afforded the title compound as a yellow solid (145.6 mg, 0.52 mmol, 52% yield). **Mp**: 261-263 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 10.75 (s, 1H), 7.06 (d, *J* = 7.3 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.81 (s, 1H), 6.67 – 6.56 (m, 2H), 4.94 (s, 2H), 2.24 (d, *J* = 8.5 Hz, 6H), 2.18 (s, 3H), 2.11 (s, 3H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 154.4, 136.6, 134.59, 133.9, 128.6, 128.5, 128.4, 128.0, 126.4, 125.3, 123.7, 109.9, 109.2, 42.1, 20.0, 19.5, 19.4, 14.3. **IR** (neat, cm^{-1}) 2913, 2360, 1687, 1491,1398, 843, 713. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{18}H_{21}N_2O]^+$ =281.1648, 281.1647 found.

1,3,7-trimethyl-7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione (2-29)



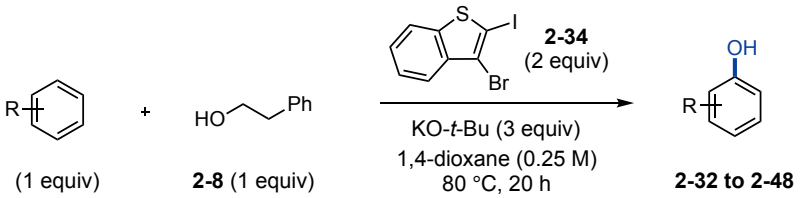
A large amount of solid precipitate forms during this reaction, necessitating use of a larger 50 mL round bottom flask and a relatively large stir bar. Thus, the title product was prepared according to a modified procedure. An oven-dried 50 mL round bottom flask was charged with a magnetic stir bar, 1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (194.1 mg, 1 mmol. 1 equiv), 2-phenylethanol (122.2 mg, 1 mmol, 1 equiv), and 2,5-dibromothiophene (483.9 mg, 2 mmol, 2 equiv). The flask was sealed with a rubber septum (ChemGlass, #CG-3022-93) and evacuated and backfilled three times with N_2 and left under positive pressure on a manifold Schlenk line. A separate oven-dried 2 dram vial was charged with KO-*t*-Bu (336.0 mg, 3 mmol, 3 equiv) and evacuated and backfilled three time with N_2 and left under positive pressure on a manifold Schlenk line. Anhydrous THF (4.0 mL) was added to the vial containing KO-*t*-Bu and the solution was agitated until homogenous. The KO-*t*-Bu solution was then transferred *via* syringe to the 50 mL round bottom flask. The reaction solution was then placed into a preheated 60 °C silicon oil bath and stirred for 3 h. The reaction mixture was cooled to rt and then loaded directly onto a neutralized silica gel column (the silica gel was neutralized by introduction of ca. 10 mL NEt_3 while wet loading the silica gel with 5% $MeOH/CH_2Cl_2$). The solvent line was brought flush with the top face of the silica gel, leaving a small layer of visible solid material. This material was dissolved and brought onto the silica gel column by adding a small amount of H_2O (ca. 1 mL). The title compound was eluted off the column (5% to 12% $MeOH/CH_2Cl_2$). The brown solid obtained was then placed into a fritted funnel and triturated using cold CH_2Cl_2 to yield the purified title compound as a white solid (120.7 mg, 0.57 mmol, 57% yield). **Mp**: 235-237 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 12.09 (br s, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 3.16 (s, 3H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 152.7, 151.7, 149.8, 136.5, 97.8, 30.76, 28.1, 27.4. **IR** (neat, cm^{-1}) 2701, 1660, 1546, 1420, 1322, 1162, 1032, 836. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_8H_{11}N_4O_3]^+$ = 211.0826, 211.0835 found. The spectroscopic data is consistent with a previous report.[10]

6-(dimethylamino)-9-methyl-7,9-dihydro-8H-purin-8-one (2-30)

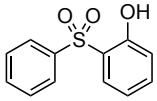


The title product was prepared according to the general procedure for *N*-heteroarene C–H hydroxylation using *N,N,*9-trimethyl-9H-purin-6-amine (193.2 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2,5-dibromothiophene (483.9 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 1, wherein silica gel chromatography (DCM to 3% DCM/MeOH) afforded the title compound as a white solid (150.0 mg, 0.78 mmol, 78% yield). **Sublimation Point**: 275 °C (no melting point observed). **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 10.81 (s, 1H), 8.09 (s, 1H), 3.23 (s, 3H), 3.12 (s, 6H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 153.1, 150.2, 148.7, 147.4, 103.9, 38.1, 25.5. **IR** (neat, cm^{-1}) 3169, 1707, 1611, 1579, 1419, 1343, 883, 775, 613. **HRMS** (ESI) $[M-H]^-$ calcd. for $[C_8H_{12}N_5O]^-$ = 192.0885, 192.0897 found. The spectroscopic data is consistent with a previous report.[11]

(c) Products Shown in Figure 2-18:

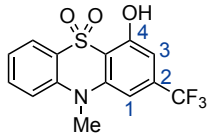


2-(phenylsulfonyl)phenol (2-32)



The title product was prepared according to the general procedure for benzene C–H hydroxylation using diphenyl sulfone (218.3 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,4-dioxane (4.0 mL). The product was purified *via* the general benzene isolation procedure 4, wherein silica gel chromatography (25% EtOAc/hexanes) afforded the purified title compound as a pale-pink solid (139.1 mg, 0.59 mmol, 59% yield). **Mp**: 81-83 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) 9.23 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.71 – 7.57 (m, 2H), 7.55 – 7.51 (m, 2H), 7.45 (t, J = 7.8 Hz, 1H), 7.08 – 6.86 (m, 2H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 155.8, 141.4, 135.7, 133.2, 128.9, 128.9, 127.8, 126.2, 119.0, 117.5. The spectroscopic data is consistent with a previous report.[12] **Note:** Additional iodination occurs on 2-(phenylsulfonyl)phenol to give 8% of a halogenated phenol side product, as detected by crude ^{1}H NMR spectroscopy. This material was readily separated from the desired isomer by silica gel chromatography.

4-hydroxy-10-methyl-2-(trifluoromethyl)-10*H*-phenothiazine 5,5-dioxide (2-39)

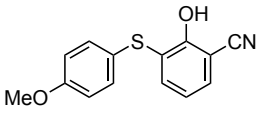


The title product was prepared according to the general procedure for benzene C–H hydroxylation using 10-methyl-2-(trifluoromethyl)-10*H*-phenothiazine 5,5-dioxide (313.3 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,4-dioxane (4.0 mL). The product was purified *via* the general benzene isolation procedure 4, wherein silica gel chromatography (1% Et_3N in 70% EtOAc/hexanes to 3% $MeOH/CH_2Cl_2$) afforded the purified title compound as a pale-purple solid (224.2 mg, 0.68 mmol, 68% yield). **Mp**: 115-119 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$)

7.97 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.71 (ddd, *J* = 8.7, 7.2, 1.6 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.41 – 7.25 (m, 1H), 7.02 (d, *J* = 1.5 Hz, 1H), 6.92 (d, *J* = 1.5 Hz, 1H), 4.38 (br s, 1H), 3.67 (s, 3H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 157.1, 143.8, 140.4, 133.7, 133.2 (q, *J* = 32.0 Hz), 125.0, 123.5 (q, *J* = 274.7 Hz), 122.8, 122.2, 116.7, 115.1, 105.0 (q, *J* = 3.7 Hz), 103.6 (q, *J* = 4.1 Hz), 36.8. **^{19}F NMR** (376 MHz, $(CD_3)_2SO$) δ -61.2. **IR** (neat, cm^{-1}) 3338, 1733, 1600, 1441, 1379, 1184, 1070, 916, 642. **HRMS** (DART) $[M–H]^-$ calcd. for $[C_{14}H_9F_3NO_3S]^-$ = 328.0261, 328.0261 found.

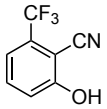
Verification of regioselectivity: Two 2D NMR experiments were used to determine the regioselectivity of C–H hydroxylation for **2-39**. Specifically, a Heteronuclear Single Quantum Coherence (HSQC) experiment indicated that hydroxylation does not occur adjacent to the trifluoromethyl group as the ^{1}H NMR signal δ 6.92 (d, *J* = 1.5 Hz, 1H) correlates to a quartet carbon peak δ 105.0 (q, *J* = 3.7 Hz). This supports that the product is not the other isomer 3-hydroxy-10-methyl-2-(trifluoromethyl)-10H-phenothiazine 5,5-dioxide, as the ^{1}H NMR signal at δ 6.92 (d, *J* = 1.5 Hz, 1H) would then be expected to correlate with a singlet carbon peak. See spectra in Section A1-14. A HMBC (Heteronuclear Multiple Bond Correlation) experiment helped confirmed this assignment as the 3-proton correlates with the carbon at the 2- and 4-position. See spectra in Section A1-14.

2-hydroxy-3-((4-methoxyphenyl)thio)benzonitrile (2-40)



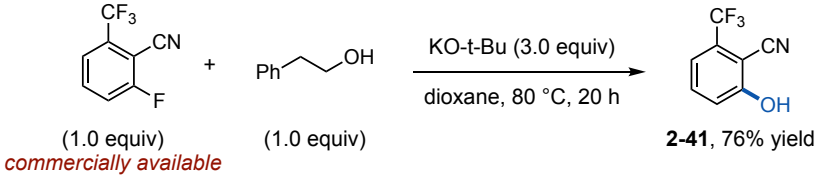
The title product was prepared according to the general procedure for benzene C–H hydroxylation using 3-((4-methoxyphenyl)thio)benzonitrile (241.3 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,4-dioxane (4.0 mL). The product was purified *via* the general benzene isolation procedure 4, wherein silica gel (14% to 20% EtOAc/hexanes) yielded the purified title compound as a purple solid (76.5 mg, 0.34 mmol, 34% yield). **Mp**: 89-91 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.11 (s, 1H), 6.97 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.8, 158.5, 140.2, 134.7, 131.9, 123.9, 122.0, 121.4, 115.8, 115.5, 100.3, 55.6. **IR** (neat, cm^{-1}) 2924, 2230, 1678, 1586, 1492, 1444, 1236, 817, 510. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{14}H_{12}NO_2S]^+$ = 258.0583, 258.0582 found.

2-hydroxy-6-(trifluoromethyl)benzonitrile (2-41)



The title product was prepared according to the general procedure for benzene C–H hydroxylation using 2-(trifluoromethyl)benzonitrile (171.1 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,4-dioxane (4.0 mL). The product was purified *via* the general benzene isolation procedure 4, wherein silica gel chromatography (75% EtOAc/hexanes) yielded the purified title compound as a yellow solid (152.6 mg, 0.82 mmol, 82% yield). **Mp**: 117-124 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 11.93 (s, 1H), 7.70 (t, *J* = 8.4 Hz, 1H), 7.37 – 7.33 (m, 2H). **^{13}C NMR** (101 MHz, CD_3CN) δ 162.2, 135.5, 133.6 (q, *J* = 32.2 Hz), 123.7 (q, *J* = 273.6 Hz), 121.2, 118.9 (q, *J* = 5.2 Hz), 114.1, 97.4 (q, *J* = 2.1 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -60.1. **IR** (neat, cm^{-1}) 3167, 2913, 2244, 1601, 1478, 1116, 925, 632. **EA**: Anal. Calcd for $C_8H_4F_3NO$: C, 51.35; H, 2.15; N, 7.49. Found: C, 51.54; H, 2.01; N, 7.42.

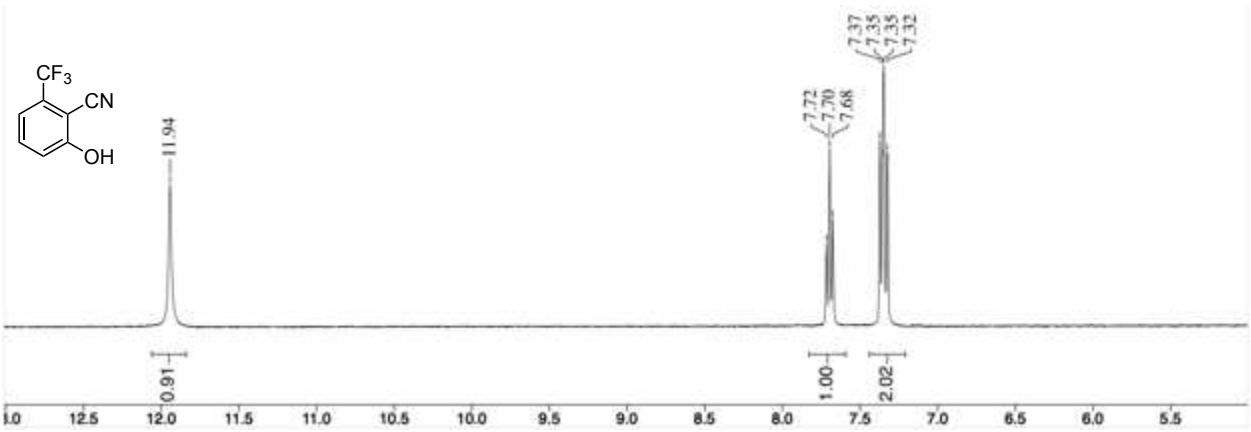
Verification of regioselectivity through preparation of an authentic standard: To verify that substitution occurred *ortho*- to the nitrile substituent, an authentic sample of **2-41** was prepared *via* substitution of 2-fluoro-6-(trifluoromethyl)benzonitrile with 2-phenethyl alcohol.



(1.0 equiv) *commercially available* (1.0 equiv) **2-41**, 76% yield

Procedure: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 2-fluoro-6-(trifluoromethyl)benzonitrile (189.1 mg, 1 equiv, 0.1 mmol), 2-phenethyl alcohol (12.2 mg, 0.1 mmol, 1 equiv), anhydrous 1,4-dioxane (0.25 M, 0.4 mL), and KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, and placed into a preheated 80 °C aluminum reaction block. The reaction solution was stirred for 20 h at 80 °C and then allowed to cool to rt. Upon cooling to rt, the crude mixture was poured into a 25 mL separatory funnel containing water (10 mL). The pH of the water layer was adjusted to pH 14 using 1M NaOH and the organic impurities were extracted with EtOAc (3 x 10 mL). The pH of the water layer was then adjusted to pH 5 using 1M HCl and extracted with EtOAc (3 x 10 mL). The EtOAc extracts were concentrated *in vacuo* to give the title product as a yellow solid (142.9 mg, 0.76 mmol, 76% yield). **Note:** The characterization data from the synthesis of the authentic standard was consistent with that of the C–H hydroxylation reaction on 2-(trifluoromethyl)benzonitrile, as shown below in Figure A1-5. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 11.94 (s, 1H), 7.70 (t, J = 8.1 Hz, 1H), 7.37 – 7.32 (m, 2H).

a) Product (**2-41**) isolated from the C–H hydroxylation



b) Product (**2-41**) isolated from the S_NAr reaction of 2-fluoro-6-(trifluoromethyl)benzonitrile

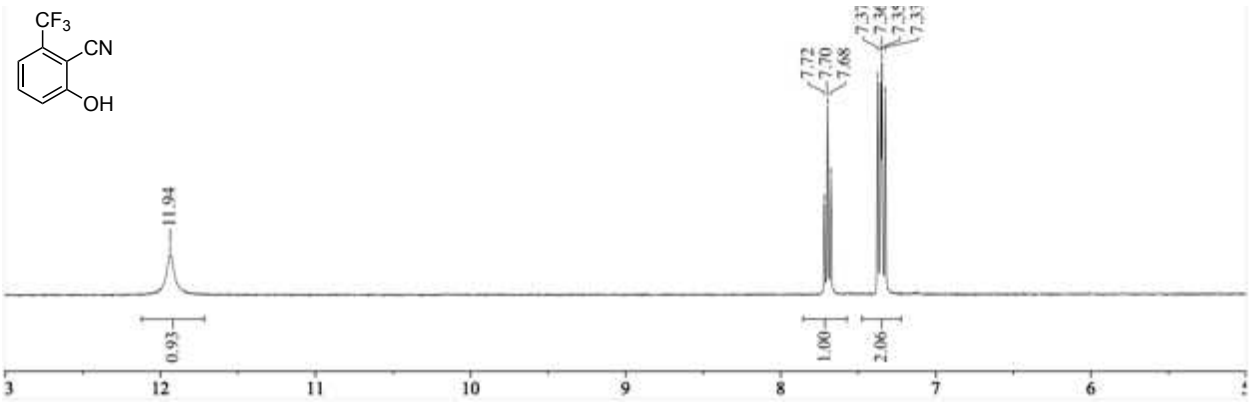
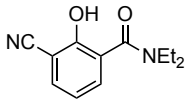


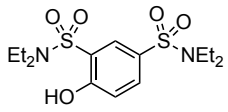
Figure A1-5. ^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$) of 2-hydroxy-6-(trifluoromethyl)benzonitrile (**2-41**) prepared according to the general procedure for benzene C–H hydroxylation (Figure A1-5, a). ^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$) of 2-hydroxy-6-(trifluoromethyl)benzonitrile (**2-41**) prepared according to the S_NAr reaction of 2-fluoro-6-(trifluoromethyl)benzonitrile (Figure A1-5, b).

3-cyano-*N*,*N*-diethyl-2-hydroxybenzamide (2-42)



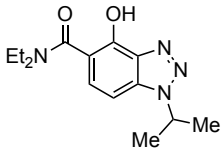
The title product was prepared according to the general procedure for benzene C–H hydroxylation using 3-cyano-*N*,*N*-diethylbenzamide (202.3 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,4-dioxane (4.0 mL). The product was purified *via* the general benzene isolation procedure 4, wherein silica gel chromatography (50% EtOAc/hexanes) yielded the purified title compound as a white solid (107.8 mg, 0.49 mmol, 49% yield). **Mp**: 65-67 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.98 (s, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 6.93 (t, J = 7.8 Hz, 1H), 3.52 (q, J = 7.1 Hz, 4H), 1.30 (t, J = 7.1 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.9, 161.3, 136.0, 131.8, 119.3, 118.9, 115.9, 102.8, 42.5, 13.4. **IR** (neat, cm^{-1}) 2973, 2534, 2228, 1596, 1572, 1454, 1272, 804, 664. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{12}H_{15}N_2O_2]^+$ = 219.1128, 219.1128 found.

N^1,N^1,N^3,N^3-tetraethyl-4-hydroxybenzene-1,3-disulfonamide (2-43)



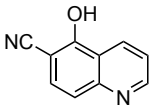
The title product was prepared according to the general procedure for benzene C–H hydroxylation using N^1,N^1,N^3,N^3-tetraethylbenzene-1,3-disulfonamide (348.5 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,4-dioxane (4.0 mL). The product was purified *via* the general benzene isolation procedure 4, wherein silica gel chromatography (50% EtOAc/hexanes to 10% MeOH/CH_2Cl_2) yielded the title compound as a white solid (286.7 mg, 0.79 mmol, 79% yield). **Mp**: 93-95 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.47 (br s, 1H), 8.03 (d, J = 2.2 Hz, 1H), 7.82 (dd, J = 8.8, 2.3 Hz, 1H), 7.11 (d, J = 8.8 Hz, 1H), 3.30 (q, J = 7.2 Hz, 4H), 3.23 (q, J = 7.2 Hz, 4H), 1.17 (t, J = 7.1 Hz, 6H), 1.14 (t, J = 7.1 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.1, 133.1, 132.8, 128.0, 124.0, 119.9, 42.3, 42.2, 14.2, 14.0. **IR** (neat, cm^{-1}) 3244, 2974, 1589, 1322, 1128, 1013, 861, 744, 678. **EA**: Anal. Calcd for $C_{14}H_{24}N_2O_5S_2$: C, 48.25; H, 6.94; N, 8.04. Found: C, 48.20; H, 7.06; N, 7.99.

_N_,_N_-diethyl-4-hydroxy-1-isopropyl-1_H_-benzo[_d_][1,2,3]triazole-5-carboxamide (2-44)



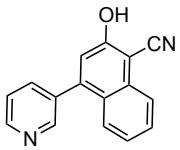
The title product was prepared according to the general procedure for benzene C–H hydroxylation using *N*,*N*-diethyl-1-isopropyl-1*H*-benzo[*d*][1,2,3]triazole-5-carboxamide (260.3 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous 1,4-dioxane (4.0 mL). The product was purified *via* the general benzene isolation procedure 4, wherein silica gel chromatography (50% EtOAc/hexanes to 100% EtOAc) afforded the title compound as a white solid (185.7 mg, 0.67 mmol, 67% yield). **Mp**: 131-135 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) 11.02 (s, 1H), 7.30 (d, J = 8.7 Hz, 1H), 6.91 (d, J = 8.7 Hz, 1H), 5.00 – 4.93 (m, 1H), 3.47 (q, J = 7.1 Hz, 4H), 1.66 (d, J = 6.8 Hz, 6H), 1.23 (t, J = 7.1 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0, 152.1, 138.1, 134.8, 126.8, 111.7, 99.6, 52.0, 42.1, 22.2, 13.4. **IR** (neat, cm^{-1}) 2976, 1625, 1454, 1433, 1255, 1129, 1071, 861, 669. **HRMS** (DART) $[M–H]^-$ calcd. for $[C_{14}H_{19}N_4O_2]^-$ = 275.1513, 275.1515 found.

5-hydroxyquinoline-6-carbonitrile (2-45)



The title product was prepared according to the general procedure for benzene C–H hydroxylation using quinoline-6-carbonitrile (154.2 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,4-dioxane (4.0 mL). The product was purified *via* the general benzene isolation procedure 5 to afford the purified title compound as an orange solid (133.4 mg, 0.78 mmol, 78% yield). **Mp**: 252-257 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 12.07 (br s, 1H), 8.99 (dd, J = 4.3, 1.8 Hz, 1H), 8.75 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.63 (dd, J = 8.5, 4.3 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 159.4, 152.6, 149.8, 132.3, 131.1, 121.4, 120.4, 120.0, 117.5, 94.1. **IR** (neat, cm^{-1}) 2410, 2201, 1600, 1544, 1453, 1311, 1056, 892, 730. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{10}H_7N_2O]^+$ = 171.0553, 171.0553 found.

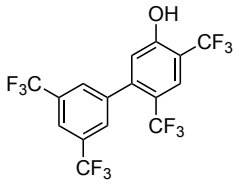
2-hydroxy-4-(pyridin-3-yl)-1-naphthonitrile (2-46)



The title product was prepared according to the general procedure for benzene C–H hydroxylation using 4-(pyridin-3-yl)-1-naphthonitrile (230.3 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,4-dioxane (4.0 mL). The product was purified *via* the general benzene isolation procedure 5 to afford the purified title compound as a brown solid (183.2 mg, 0.74 mmol, 74% yield). **Mp**: 275-280 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 11.95 (br s, 1H), 8.84 – 8.83 (m, 2H), 8.17 (d, J = 7.9 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.22 (s, 1H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 160.4, 146.9, 146.8, 141.8, 140.3, 135.3, 133.5, 129.4, 126.2, 125.3, 125.2, 124.9, 123.4, 119.2, 115.8, 91.9. **IR** (neat, cm^{-1}) 2971, 2547, 2214, 1602, 1397, 1233, 1081, 929, 776. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{16}H_{11}N_2O]^+$ = 247.0866, 247.0863 found.

Verification of regioselectivity: Crystals of compound **2-46** suitable for x-ray analysis were grown *via* vapor diffusion. This was done by charging 5 mg of **2-46** and ethyl acetate (3 mL) into an 8 mL vial, placing the vial in a 25 mL beaker filled with hexanes (15 mL), partially covering the beaker, and waiting 7 days for crystal formation (see Section A1-12 for full crystallographic details).

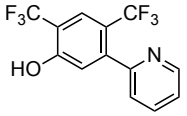
3',4,5',6-tetrakis(trifluoromethyl)-[1,1'-biphenyl]-3-ol (2-47)



The title product was prepared according to the general procedure for benzene C–H hydroxylation procedure using 2,3',4,5'-tetrakis(trifluoromethyl)-1,1'-biphenyl (426.2 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,4-dioxane (4.0 mL). The product was purified *via* the general benzene isolation procedure 4, wherein silica gel chromatography (11% EtOAc/hexanes) yielded the purified title compound as purple solid (206.0 mg, 0.49 mmol, 49% yield). **Mp:** 50-53 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.96 (s, 1H), 7.79 (s, 2H), 6.97 (s, 1H), 6.04 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.4, 143.5, 140.1, 131.8 (q, J = 33.5 Hz), 129.0, 126.3 (m), 123.4 (q, J = 274.5 Hz), 123.2 (q, J = 274.5 Hz), 122.6 (m), 121.1, 121.2 (q, J = 31.7 Hz), 117.0 (q, J = 31.7 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -53.6, -60.3, -60.7. **IR** (neat, cm^{-1}) 3613, 1699, 1631, 1351, 1307, 1120, 1062, 919, 681. **HRMS** (DART) $[M–H]^-$ calcd. for $[C_{16}H_5F_{12}O]^-$ = 441.0154, 441.0152 found.

Verification of regioselectivity: To achieve a more crystalline structure, compound **2-47** was derivatized into 3',4,5',6-tetrakis(trifluoromethyl)-[1,1'-biphenyl]-3-yl 4-iodobenzenesulfonate (**2-47**) *via* sulfonylation with 4-iodobenzenesulfonyl chloride. Thus, crystals of sulfonylated **2-47** suitable for x-ray analysis were grown *via* vapor diffusion. This was done by charging 5 mg of sulfonylated **2-47** and dichloromethane (3 mL) into in an 8 mL vial, placing the vial in a 25 mL beaker filled with hexanes (15 mL), partially covering the beaker, and waiting 7 days for crystal formation (see Section 12 for full crystallographic details).

5-(pyridin-2-yl)-2,4-bis(trifluoromethyl)phenol (2-48)



The title product was prepared through slight modification of the general procedure for the C–H hydroxylation of benzenes, where 18-crown-6 was used as an additive and anhydrous 1,2-dimethoxyethane was used in place of 1,4-dioxane as the solvent. Thus, 2-(2,4-bis(trifluoromethyl)phenyl)pyridine (291.2 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), 18-crown-6 (792.4 mg, 3 mmol, 3 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,2-dimethoxyethane (4.0 mL) were added according to the general procedure. The product was initially purified *via* the general benzene isolation procedure 5 to give an oil that was then suspended in EtOAc and filtered through a plug of silica. The silica plug was washed with 300 mL of EtOAc that was collected and dried *in vacuo* to yield the purified title compound as a white solid (184.7 mg, 0.60 mmol, 60% yield). **Mp**: 160-163 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.50 (br s, 1H), 8.68 – 8.60 (m, 1H), 7.92 (td, J = 7.8, 1.7 Hz, 1H), 7.77 (s, 1H), 7.50 – 7.47 (m, 2H), 6.88 (s, 1H). **^{13}C NMR** (101 MHz, CD_3CN) δ 158.8, 156.7, 149.4, 144.7, 138.6, 126.5 (m), 125.2 (q, J = 2.1 Hz), 124.9, 124.9 (q, J = 272.8 Hz), 124.2 (q, J = 272.8 Hz), 119.7 (q, J = 30.3 Hz), 122.0, 117.5 (q, J = 30.3 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -53.6, -60.5. **IR** (neat, cm^{-1}) 2900, 1627, 1450, 1338, 1166, 1158, 1009, 827, 781. **EA**: Anal. Calcd for $C_{13}H_7F_6NO$: C, 50.83; H, 2.30; N, 4.56. Found: C, 50.37; H, 2.25; N, 4.50.

Verification of regioselectivity: A 2D NMR experiment was used to determine the regioselectivity of C–H hydroxylation for **2-48**. Specifically, a Heteronuclear Single Quantum Coherence (HSQC) experiment indicated that hydroxylation occurs adjacent to the trifluoromethyl group as the ^{1}H NMR signal δ 6.88 (s, 1H) correlates to a singlet carbon peak δ 121.5 ppm. This supports that the product is not the other isomer 2-(pyridin-2-yl)-3,5-bis(trifluoromethyl)phenol

(where hydroxylation would be occurring ortho to the 2-pyridyl group), as the ^{1}H NMR signal at δ 6.88 (s, 1H) would then be expected to correlate with a quartet carbon peak (which it does not). See spectra in Section A1-14.

A1.6. Studies on Reaction Trends and Selectivity

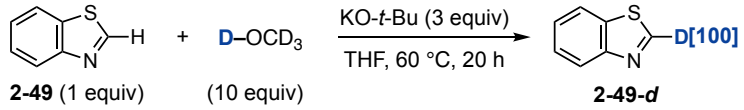
(a) Deuterium Exchange Studies

Purpose: We propose the (hetero)aryl C–H hydroxylation to proceed through halogen transfer to an aryl anionic intermediate. To begin, we performed studies described below to examine the sites of deprotonation and relative rates on a variety of arene substrates.

General Procedure: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, (hetero)arene (1 equiv, 0.1 mmol), methanol-d_4 (36.1 mg, 1 mmol, 10 equiv), anhydrous solvent (0.25 M, 0.4 mL), and KO-*t*-Bu (amount dependent on (hetero)arene) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, and placed into a preheated aluminum reaction block (60 °C or 80 °C, dependent on substrate). The solution was stirred for 2 h at the indicated temperature and then allowed to cool to rt. For substrates **2-50** and **2-52**, trimethoxybenzene (TMB) internal standard was added to the crude reaction mixture. A small aliquot was then removed, injected into an NMR tube, and constituted in deuterated solvent (0.5 mL) for analysis by ^{1}H NMR spectroscopy (400 MHz). **Note:** For some substrates, multiple sites were deuterated quickly. Thus, the equivalence of KO-*t*-Bu and time used were adjusted so that the relative rate could be determined.

Analysis: ^{1}H NMR analysis was conducted on a sample of each (hetero)arene starting material. The spectra of the crude reaction mixture from the deuterium exchange experiment and the corresponding starting material were then overlayed, and each peak was integrated. The percent of deuterium incorporation into the (hetero)arene substrate was calculated based on the reduction of signal integration between the signals in the crude reaction analysis and starting material spectra. The results and stacked spectra for each (hetero)arene assessed are provided below.

Deuterium exchange of benzothiazole (2-49):



2-49 (1 equiv) (10 equiv) **2-49-*d***

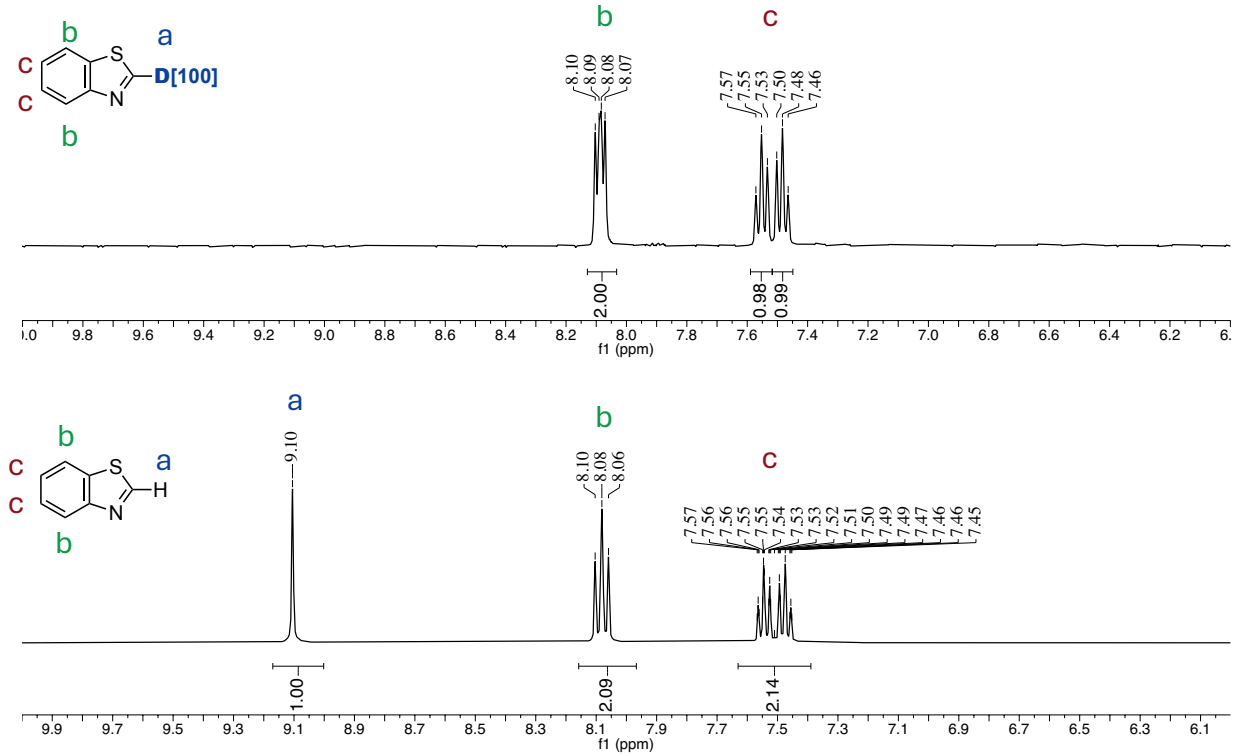


Figure A1-6. ^{1}H NMR spectrum (400 MHz, CD_3CN) of the crude reaction solution of benzothiazole deuteration using CD_3OD and KO-*t*-Bu (top). The signal corresponding to the 2-position disappears completely, indicating full deuterium incorporation at the 2-position. ^{1}H NMR spectrum (400 MHz, CD_3CN) of benzothiazole (bottom).

Deuterium exchange of 3-bromopyridine (2-1):

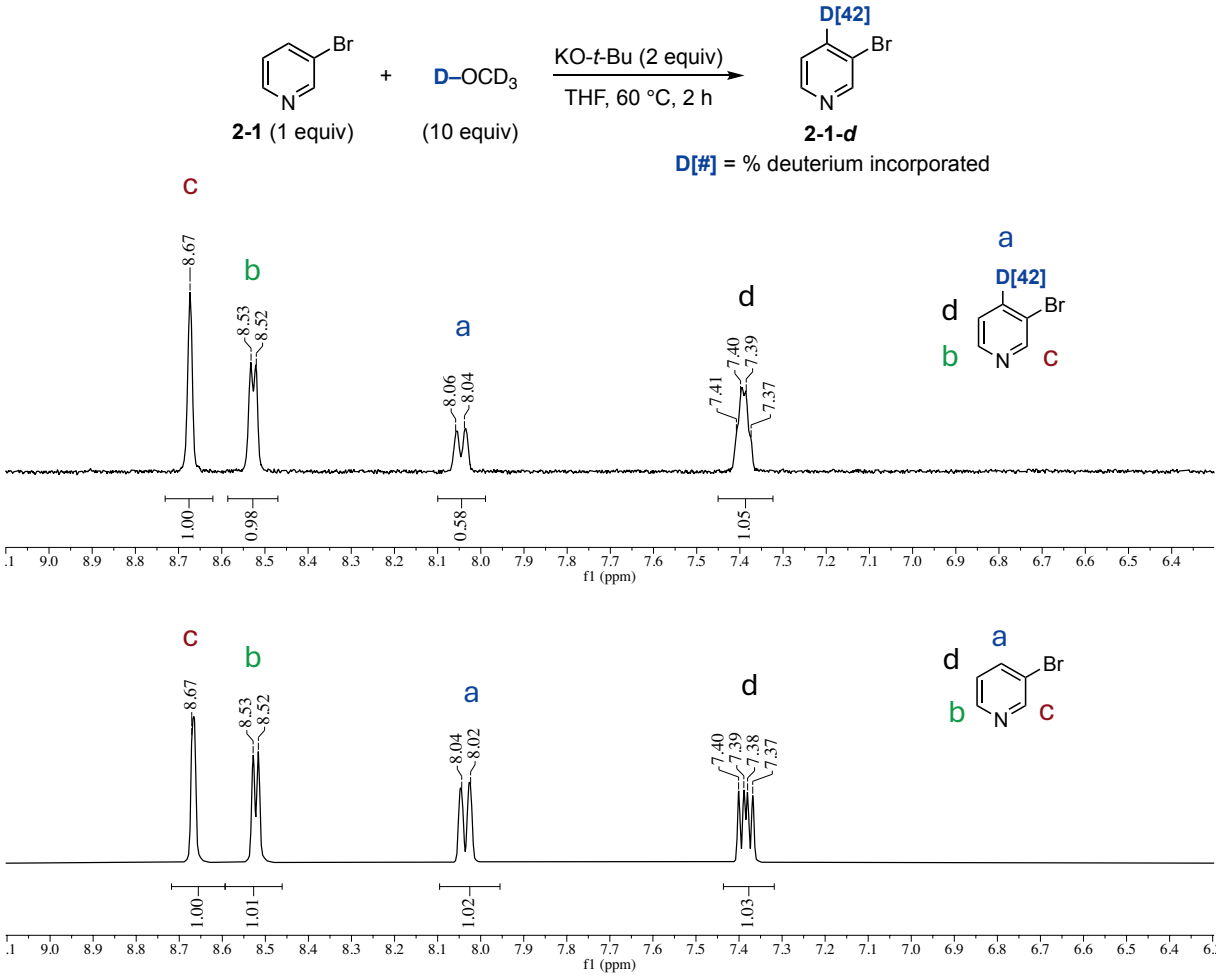
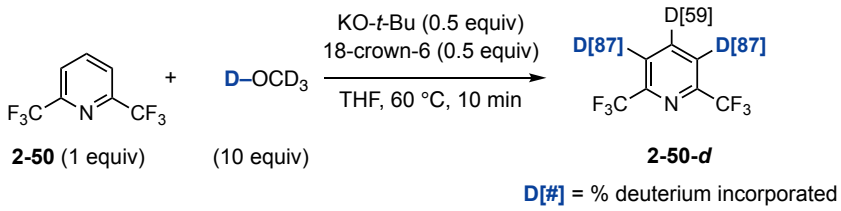


Figure A1-7. ^{1}H NMR spectrum (400 MHz, CD_3OD) of the crude reaction solution of 3-bromopyridine deuteration using CD_3OD and KO-*t*-Bu (top). It was determined that 0.58 H remain at the 4-position, thus 42% of deuteration occurs at the 4-position. ^{1}H NMR spectrum (400 MHz, CD_3OD) of 3-bromopyridine (bottom).

Deuterium exchange of 2,6-bis(trifluoro)methylpyridine (2-50):



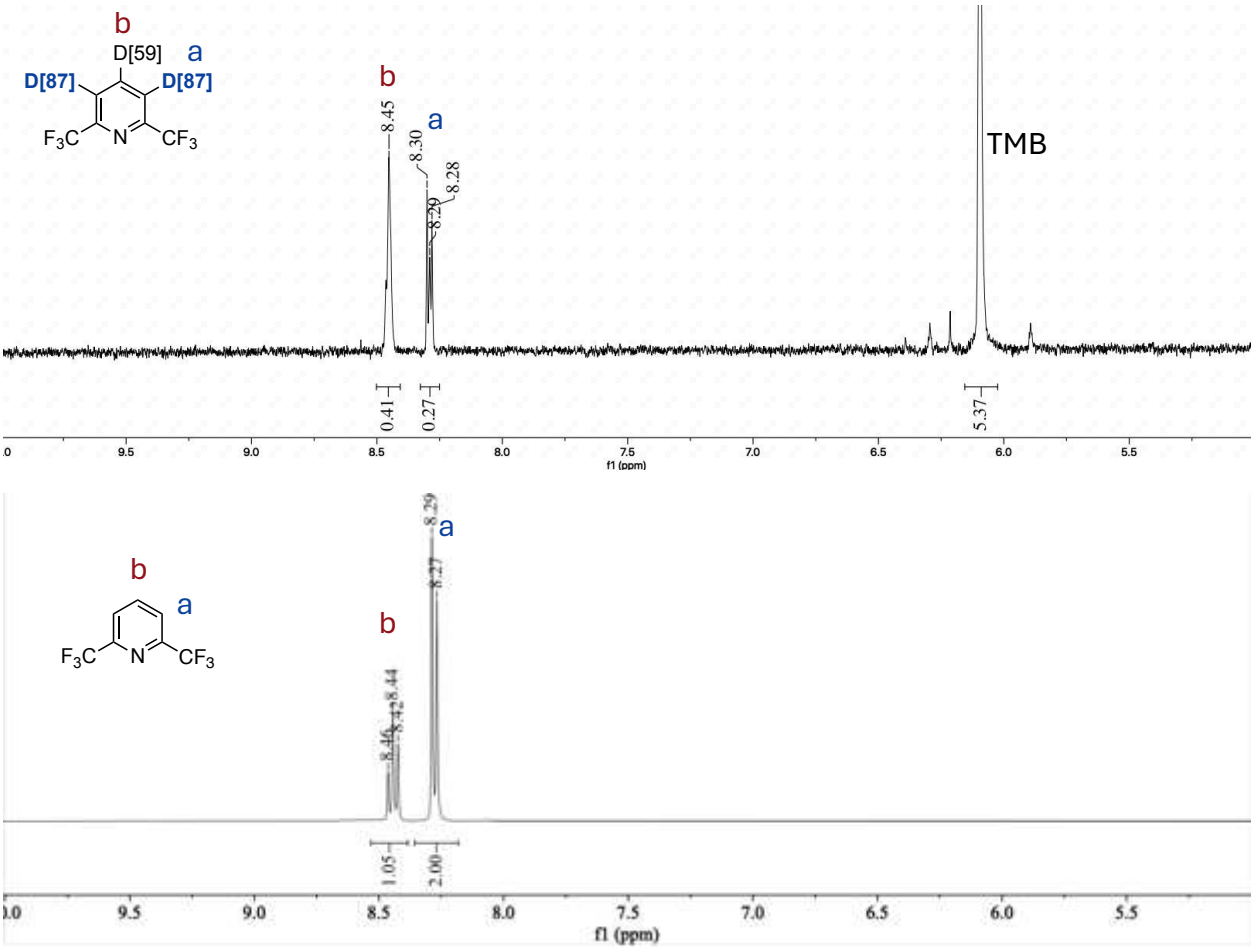
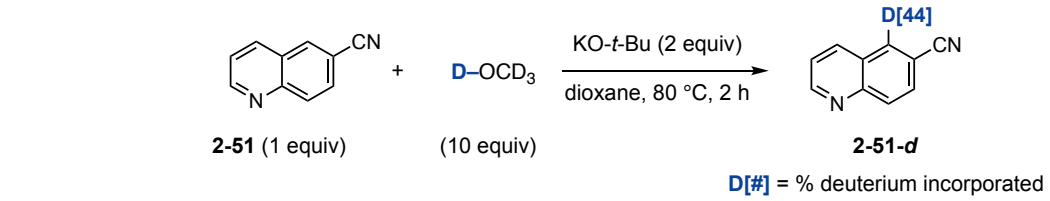


Figure A1-8. ^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$) of the crude reaction solution of 2,6-bis(trifluoro)methylpyridine deuteration using CD_3OD and KO-*t*-Bu (top). 1,3,5-Trimethoxybenzene (TMB) internal standard (20.4 mg, 0.12 mmol, signal at 6.09 ppm calibrated to 5.37 for 0.1 mmol scale reaction) was used to determine the percent deuterium incorporated at each position. It was determined that 0.27 H remain of the 3- and 5-positions combined, and that 0.41 H remains for the 4-position, thus 87% and 59% of deuteration occurs at the 3-/5-positions and 4-position, respectively. ^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$) of 2,6-bis(trifluoro)methylpyridine (bottom).

Deuterium exchange of quinoline-6-carbonitrile (2-51):



2-51 (1 equiv) (10 equiv) **2-51-*d***

D[#] = % deuterium incorporated

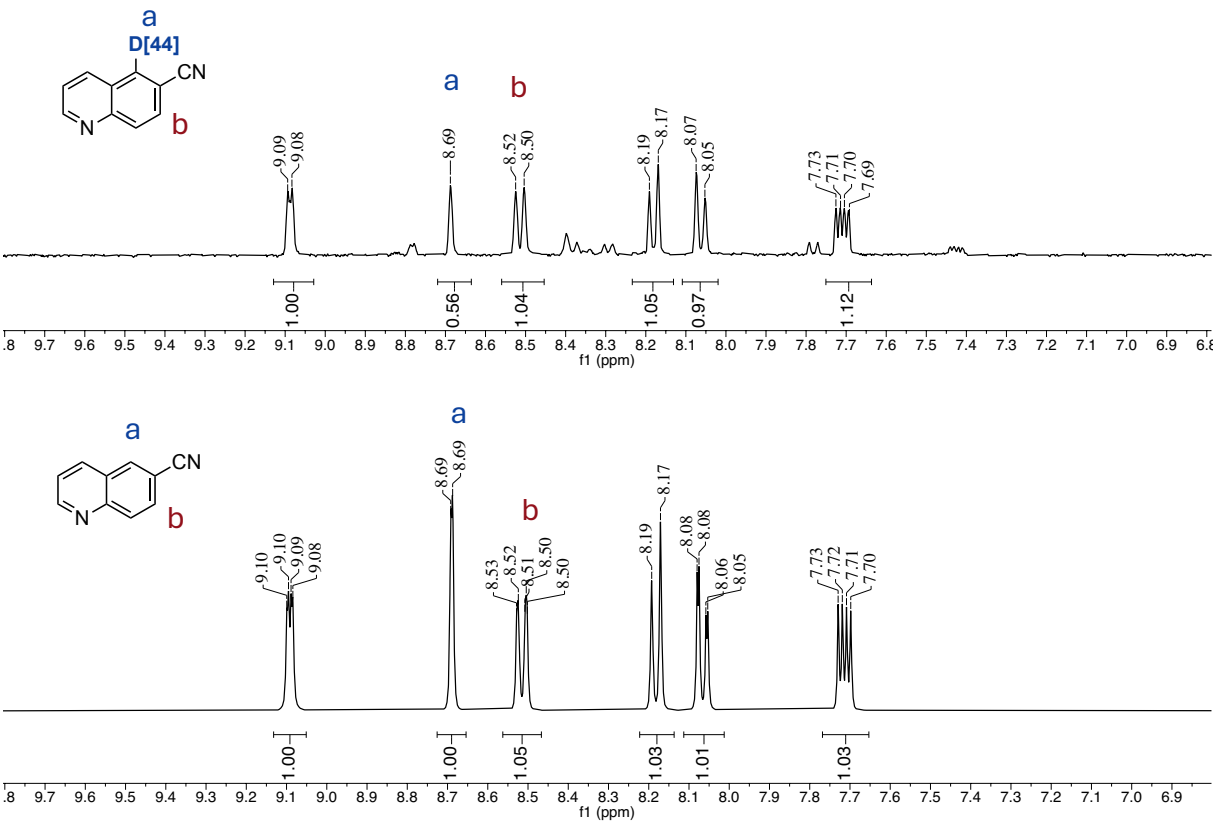
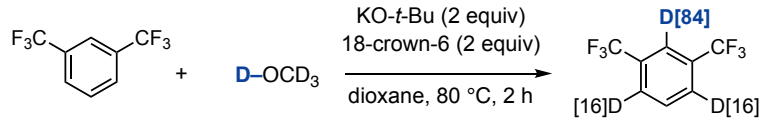


Figure A1-9. ^{1}H NMR spectrum (400 MHz, CD_3CN) of the crude reaction solution of quinoline-6-carbonitrile deuteration using CD_3OD, 18-crown-6, and KO-*t*-Bu (top). It was determined that 0.56 H remain at the 5-position, thus 44% of deuteration occurs at the 5-position. ^{1}H NMR spectrum (400 MHz, CD_3CN) of quinoline-6-carbonitrile (bottom).

Deuterium exchange of 1,3-bis(trifluoro)benzene (2-52):



2-52 (1 equiv) (10 equiv) **2-52-*d***

D[#] = % deuterium incorporated

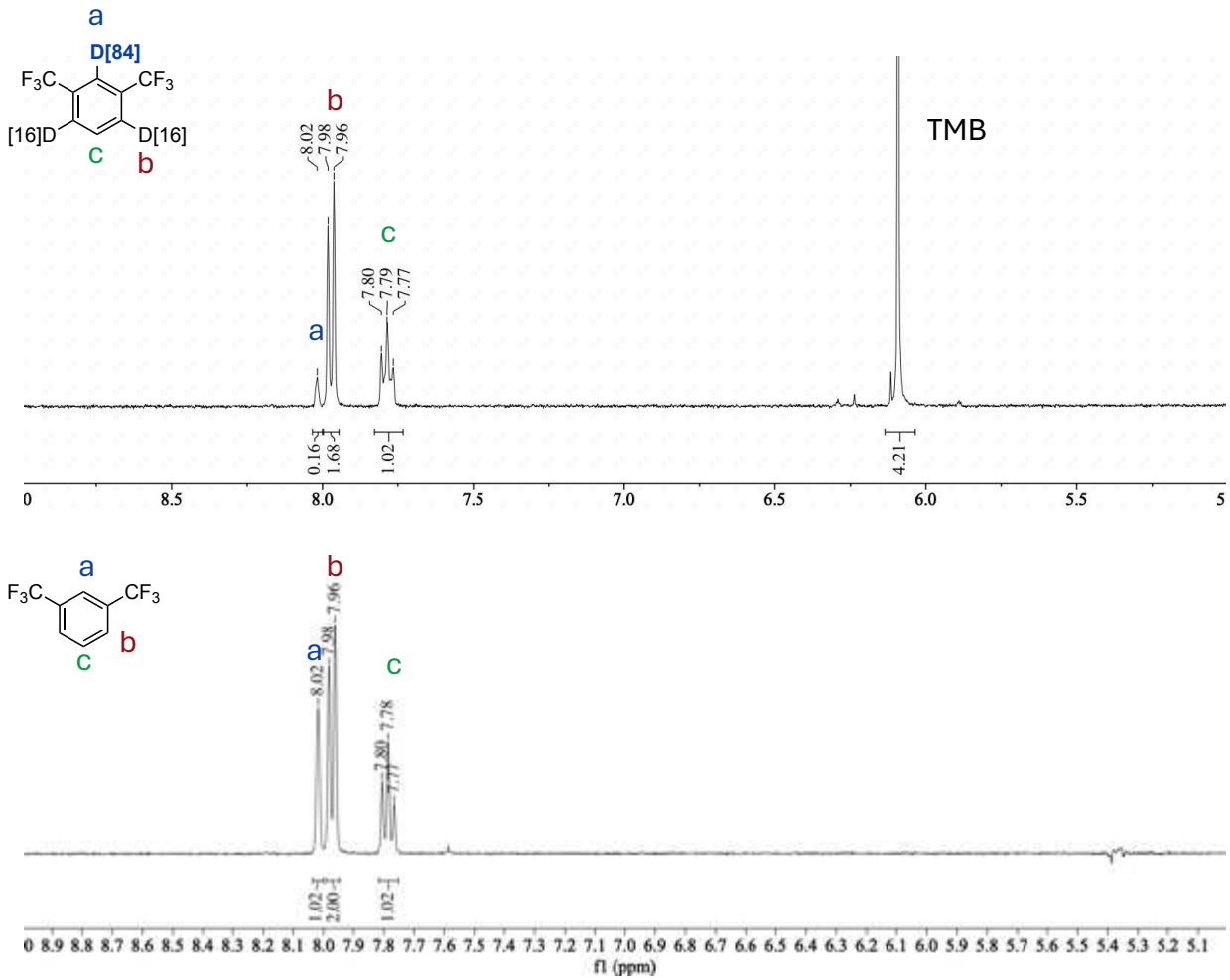
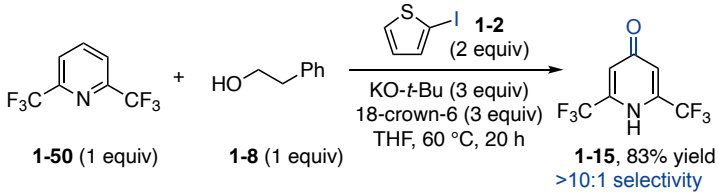


Figure A1-10. ^{1}H NMR spectrum (400 MHz, CD_3CN) of the crude reaction solution of 1,3-bis(trifluoro)benzene deuteration using CD_3OD, 18-crown-6, and KO-*t*-Bu (top). 1,3,5-Trimethoxybenzene (TMB) internal standard (23.6 mg, 0.14 mmol, signal at 6.09 ppm calibrated to 4.21 for 0.1 mmol scale reaction) was used to determine the percent deuterium incorporated at each position. It was determined that 1.68 H remain of the 4- and 6-positions combined, and that 0.16 H remains for the 2-position, thus 16% and 84% of deuteration occurs at the 4-/6-positions and 2-position, respectively. ^{1}H NMR spectrum (400 MHz, CD_3CN) of 1,3-bis(trifluoro)benzene (bottom).

(b) C–H Hydroxylation on Mismatched Substrates 2-15 and 2-54.

Purpose: The crude reaction solutions of substrates **2-15** and **2-54** were analyzed to determine the site-selectivity of the C–H hydroxylation protocol. Unlike other substrates analyzed in the deuterium exchange studies, the following underwent C–H hydroxylation at sites that were not the most favored for deprotonation.

C–H hydroxylation of 2,6-bistrifluoromethylpyridine on 0.1 mmol scale (2-15):



Procedure: The title product was prepared according to the optimization procedure for *N*-heteroarene C–H hydroxylation in a N_2 filled glovebox using 2,6-bis(trifluoro)methylpyridine (21.5 mg, 1 equiv, 0.1 mmol), 2-phenethyl alcohol (12.2 mg, 0.1 mmol, 1 equiv), 2-iodothiophene (42.0 mg, 0.2 mmol, 2 equiv), 18-crown-6 (79.2 mg, 0.3 mmol, 3 equiv), KO-*t*-Bu (33.6 mg, 0.3 mmol, 3 equiv), and anhydrous THF (0.4 mL). 1,3,5-Trimethoxybenzene internal standard was measured into the crude reaction solution and the mass weighed into the vial was recorded. A small aliquot of the solution was then removed and injected into an NMR tube and constituted in $(CD_3)_2SO$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, $(CD_3)_2SO$) was used to determine the yield and selectivity of the 2,6-bis(trifluoro)methylpyridine (83% yield by ^{1}H NMR, >10:1 selectivity for 4-hydroxylation, Figure A1-11). Finally, to confirm the identity of the product, the crude reaction solution was then subjected to purification *via* preparative thin-layer chromatography (33% EtOAc/Hexanes). **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 11.0 (s, 1H), 7.50 (s, 2H). **^{13}C NMR** (101 MHz, $(CD_3)_2CO$) δ 168.0, 150.6 (q, J = 35.3 Hz), 121.8 (q, J = 273.7 Hz), 112.2 (q, J = 2.8 Hz). **^{19}F NMR** (376 MHz, $(CD_3)_2SO$) δ -66.1. The spectroscopic data is consistent with a previous report.[6]

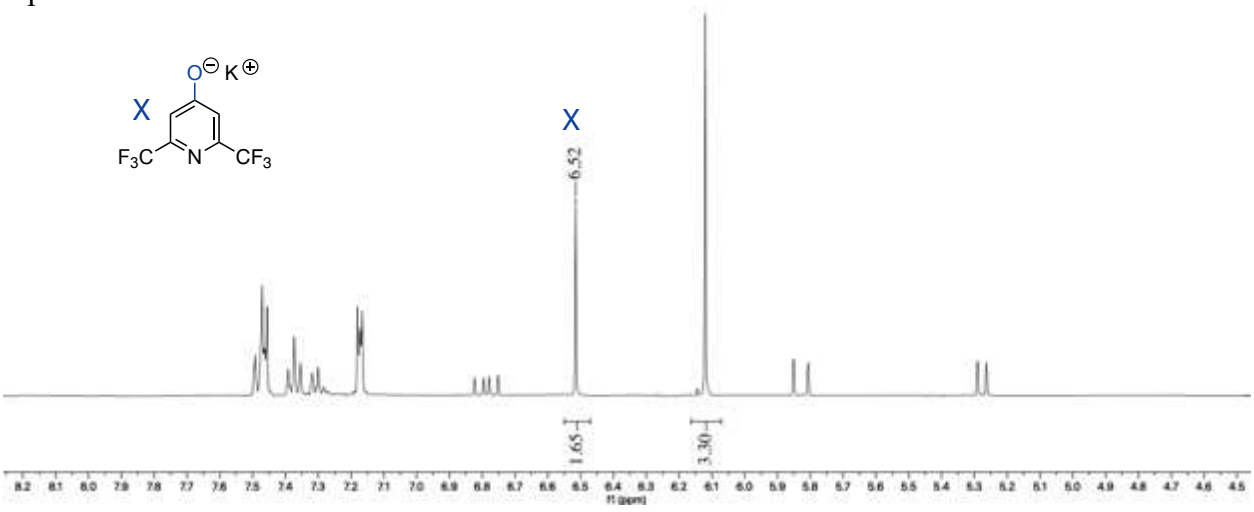
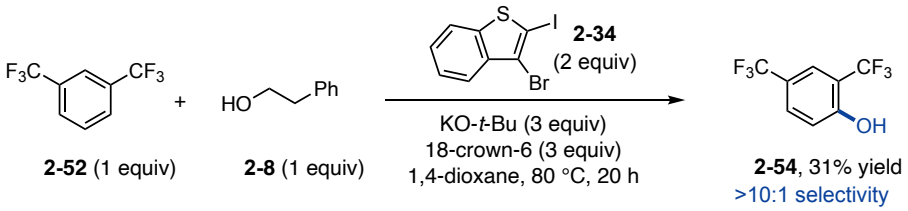


Figure A1-11. ^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$) of the crude reaction solution of 2,6-bis(trifluoro)methylpyridine C–H hydroxylation. The product in the ^{1}H NMR spectra of the crude

reaction solution crude reaction mixture is in the deprotonated form, and thus the product peaks are significantly more shielded in relation to where the neutral pyridone protons are.

C–H hydroxylation of 1,3-bis(trifluoromethyl)benzene (2-54):



Procedure: Inside a N_2 filled glovebox, oven-dried 4 mL vial (KIMBLE® , #60910-1) was charged with a magnetic stir bar, 1,3-bis(trifluoromethyl)benzene (21.5 mg, 1 equiv, 0.1 mmol), 2-phenethyl alcohol (12.2 mg, 0.1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (67.8 mg, 0.2 mmol, 2 equiv), 1,4-dioxane (0.25 M, 0.4 mL), 18-crown-6 (79.2 mg, 0.3 mmol, 3 equiv), and KO-*t*-Bu (0.3 mmol, 3 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, placed into a preheated 80 °C aluminum reaction block, stirred for 20 h at 80 °C, and then cooled to rt. 1,3,5-Trimethoxybenzene internal standard was measured into the crude reaction solution and the mass weighed into the vial was recorded. A small aliquot of the solution was then removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield and selectivity of the 2,4-bis(trifluoromethyl)phenol (31% yield by ^{1}H NMR, >10:1 selectivity for 4-hydroxylation, Figure A1-12). To confirm the identity of the product, the crude reaction solution was then subjected to purification *via* isolation procedure 3 (acidic/base aqueous wash). **^{1}H NMR** (400 MHz, $CDCl_3$) 8.54 (s, 1H), 7.77 (d, J = 1.9 Hz, 1H), 7.62 (dd, J = 8.6, 1.9 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H). The spectroscopic data is consistent with a previous report.[13]

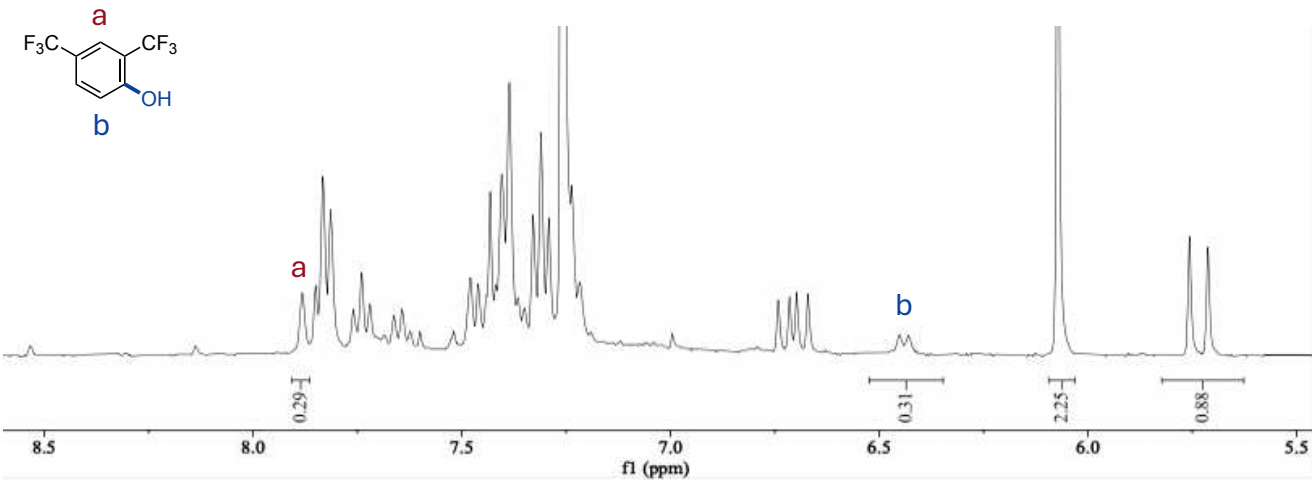


Figure A1-12. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the crude reaction solution of 1,3-bis(trifluoromethyl)benzene C–H hydroxylation. The product in the ^{1}H NMR spectrum of the

crude reaction solution crude reaction mixture is in the deprotonated form, and thus the product peaks are significantly more shielded in relation to where the neutral phenol shifts are.

(c) Selectivity Studies on the Potential (Hetero)aryl Iodide Intermediates 2-52 and 2-55.

Purpose: These experiments were performed to investigate the effects of the X-transfer reagents and byproducts on the selectivity of the substitution step for the potential (hetero)aryl iodide intermediates 3-iodo-2,6-bis(trifluoromethyl)pyridine (**2-52**) and 2-iodo-1,3-bis(trifluoromethyl)benzene (**2-55**).

Selectivity Study Procedure: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE® , #60910-1) was charged with a magnetic stir bar, (hetero)aryl halide (1 equiv, 0.1 mmol), 2-phenethyl alcohol (12.2 mg, 0.1 mmol, 1 equiv), X-transfer reagent additive (0 equiv *or* 0.2 mmol, 2 equiv), anhydrous solvent (0.25 M, 0.4 mL), and KO-*t*-Bu (0.3 mmol, 3 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, placed into a preheated aluminum reaction block, stirred for 20 hr, and then cooled to rt.

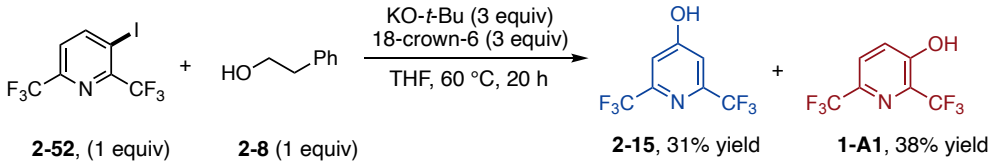
Selectivity Analysis Procedure for Experiments with 2-52: 1,3,5-Trimethoxybenzene internal standard was measured into the crude solution and the mass weighed into the vial was recorded. A small aliquot of the reaction solution was then removed and injected into an NMR tube and constituted in CD_3CN (0.5 mL). ^1H NMR spectroscopy (400 MHz) was used to determine the yields of each product shown in the reaction schemes below. The ^1H NMR spectra of the crude reaction solutions are shown below to illustrate the analysis process. To confirm the peak assignments of 2,6-bis(trifluoromethyl)pyridin-3-ol and 2,6-bis(trifluoromethyl)pyridin-4-ol in the crude ^1H NMR spectra, the crude reaction solution from the reaction of **52** without additive was subjected to purification *via* a preparatory thin layer chromatography plate (1% NEt_3/ 10% MeOH/DCM). Both 2,6-bis(trifluoromethyl)pyridin-3-ol and 2,6-bis(trifluoromethyl)pyridin-4-ol were obtained. For 2,6-bis(trifluoromethyl)pyridin-3-ol: **^{1}H NMR** (400 MHz, $(CD_3)_2SO$): 10.20 (br s, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H). **^{19}F NMR** (376 MHz, (CD_3CN) δ -64.19, -64.69. For 2,6-bis(trifluoromethyl)pyridin-4-ol: **^{1}H NMR** (400 MHz, $(CD_3)_2SO$): δ 11.0 (s, 1H), 7.50 (s, 2H). **^{19}F NMR** (376 MHz, $(CD_3)_2SO$) δ -66.1. The spectroscopic data is consistent with a previous report.[6,13]

Selectivity Analysis Procedure for Experiments with 2-55: 1,3,5-Trimethoxybenzene internal standard was measured into the crude solution and the mass weighed into the vial was recorded. A small aliquot of the reaction solution was then removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz) was used to determine the yields of each product shown in the reaction schemes below. The ^1H NMR spectra of the crude reaction solutions are shown below to illustrate the analysis process. To confirm the peak assignments of 2,6-bis(trifluoromethyl)phenol and 2,4-bis(trifluoromethyl)phenol in the crude ^1H NMR spectra, the crude reaction solutions from the reactions of **55** without additive and with 3-bromobenzo[*b*]thiophene additive were each subjected to purification *via* a preparatory thin layer chromatography plate (33% EtOAc/Hex). Products 2,6-bis(trifluoromethyl)phenol and 2,4-bis(trifluoromethyl)phenol were obtained, respectively. For 2,6-bis(trifluoromethyl)phenol: **^{1}H NMR** (400 MHz, $CDCl_3$): 7.72 (d, J = 7.9 Hz, 2H), 7.12 (t, J = 7.9 Hz, 1H). For 2,4-

bis(trifluoromethyl)phenol: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 7.77 (d, J = 1.9 Hz, 1H), 7.62 (dd, J = 8.6, 1.9 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H). The spectroscopic data is consistent with previous reports.[13,14]

Selectivity experiments with 3-iodo-2,6-bis(trifluoromethyl)pyridine (2-52):

Experiment 1: selectivity study on **2-52** with no additive present



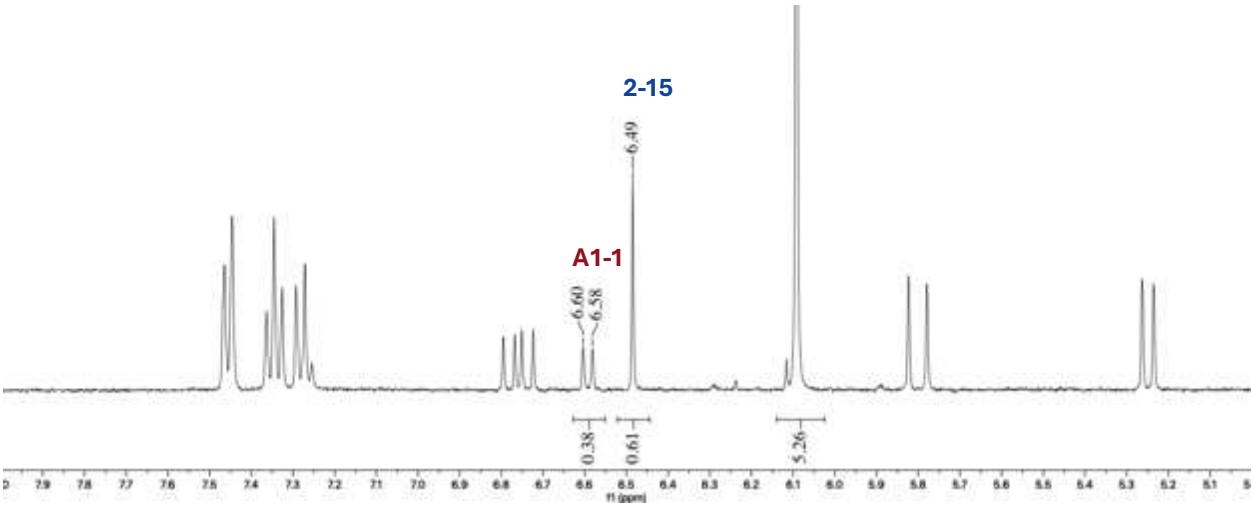
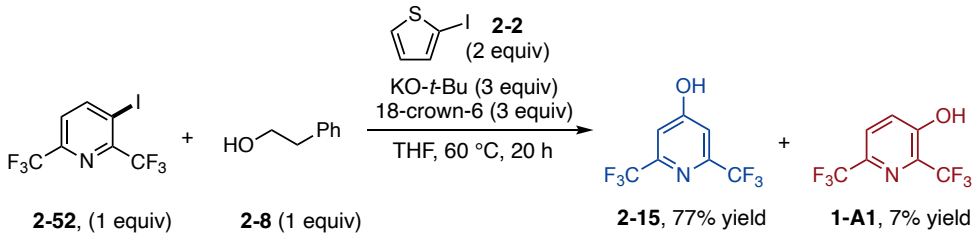


Figure A1-13. ^{1}H NMR spectrum (400 MHz, CD_3CN) of the crude reaction solution of 3-iodo-2,6-bis(trifluoromethyl)pyridine without additive. 1,3,5-Trimethoxybenzene (29.5 mg, 0.18 mmol, signal at 6.09 ppm integrated to 5.26 for 0.1 mmol scale reaction) added as internal standard.

Experiment 2: selectivity study on **2-52** with 2-iodothiophene additive



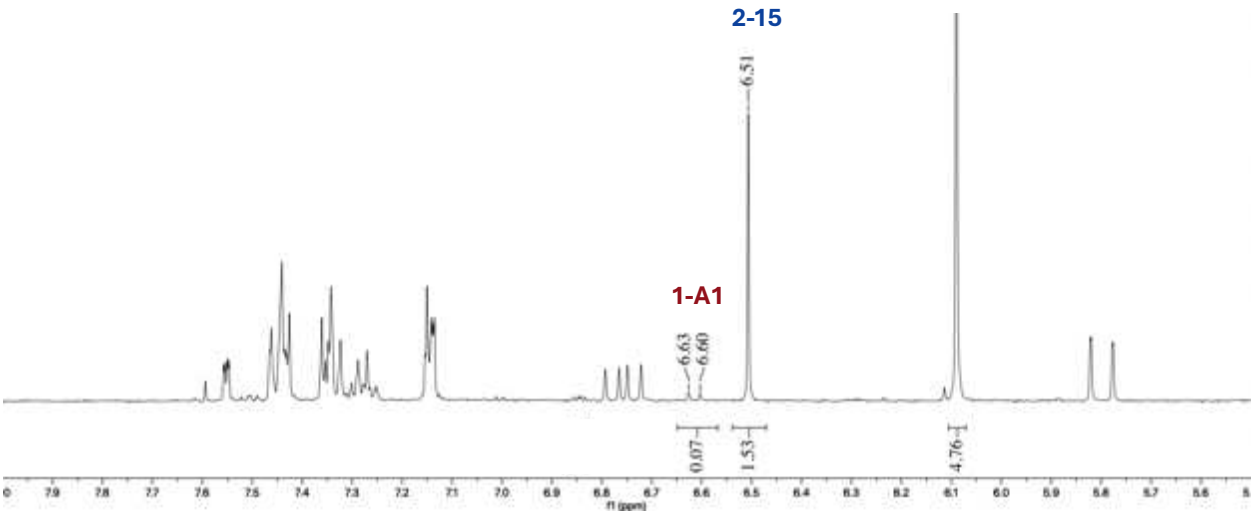
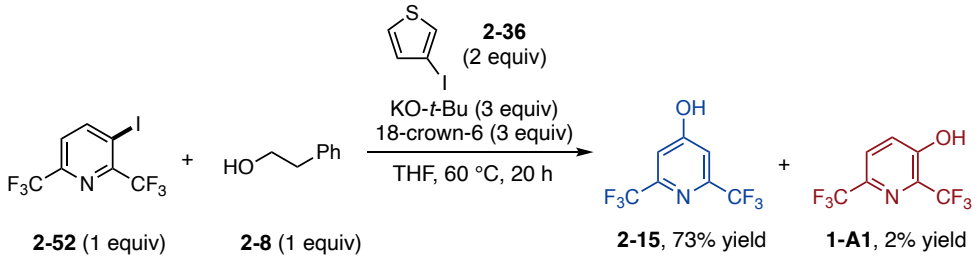


Figure A1-14. ^{1}H NMR spectrum (400 MHz, CD_3CN) of the crude reaction solution of 3-iodo-2,6-bis(trifluoromethyl)pyridine with 2-iodothiophene additive (42.0 mg, 2 equiv). 1,3,5-Trimethoxybenzene (26.7 mg, 0.16 mmol, signal at 6.09 ppm integrated to 4.76 for 0.1 mmol scale reaction) added as internal standard.

Experiment 3: selectivity study on **2-52** with 3-iodothiophene additive



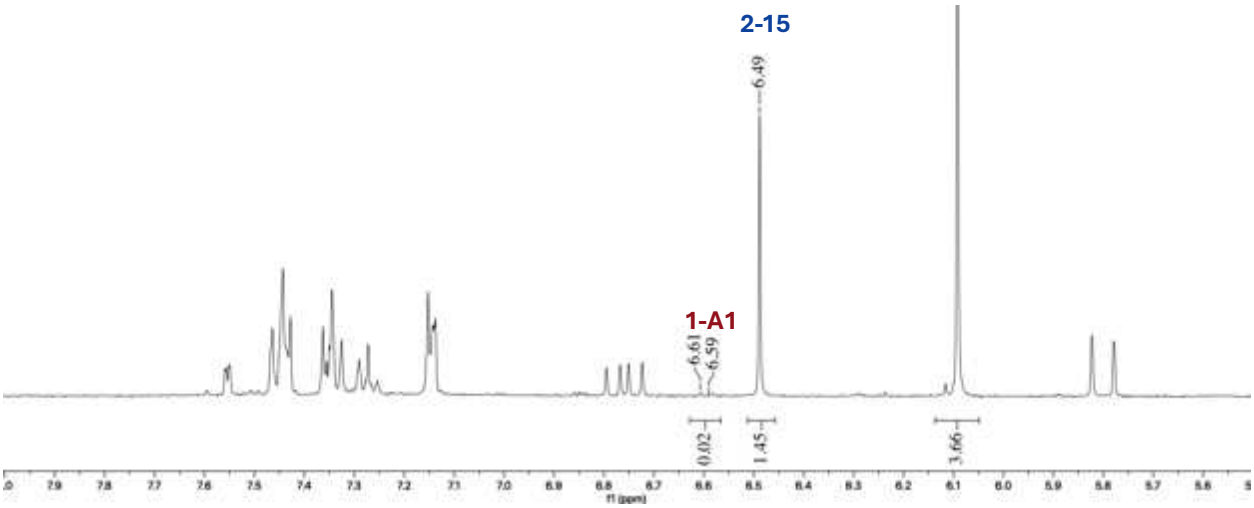
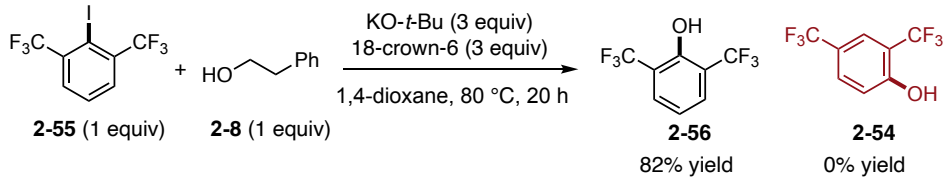


Figure A1-15. ^{1}H NMR spectrum (400 MHz, CD_3CN) of the crude reaction solution of 3-iodo-2,6-bis(trifluoromethyl)pyridine with 3-iodothiophene additive (42.0 mg, 2 equiv). 1,3,5-

Trimethoxybenzene (20.5 mg, 0.12 mmol, signal at 6.09 ppm integrated to 3.66 for 0.1 mmol scale reaction) added as internal standard.

Selectivity experiments with 2-iodo-1,3-bis(trifluoromethyl)benzene (2-55):

Experiment 1: selectivity study on **2-55** without additive present



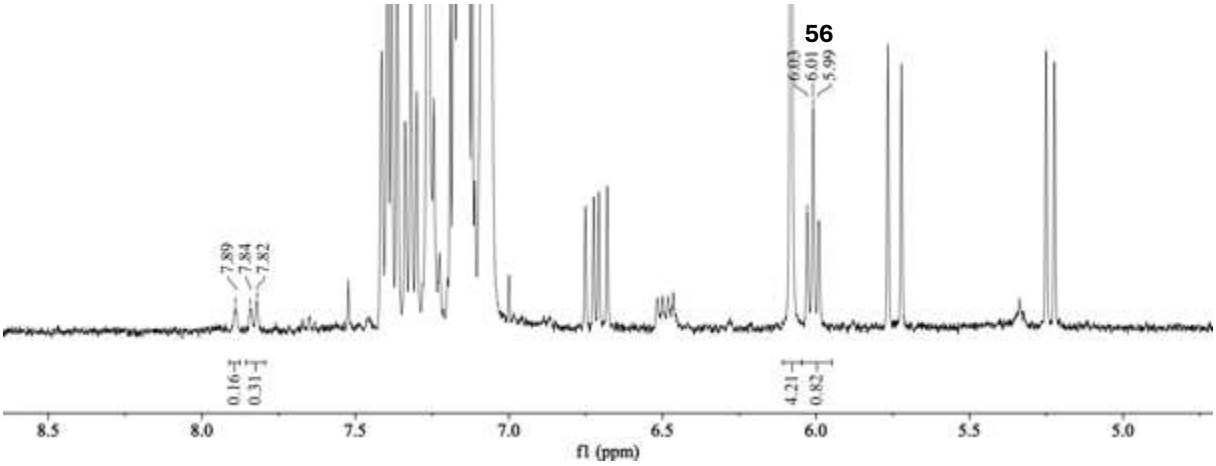
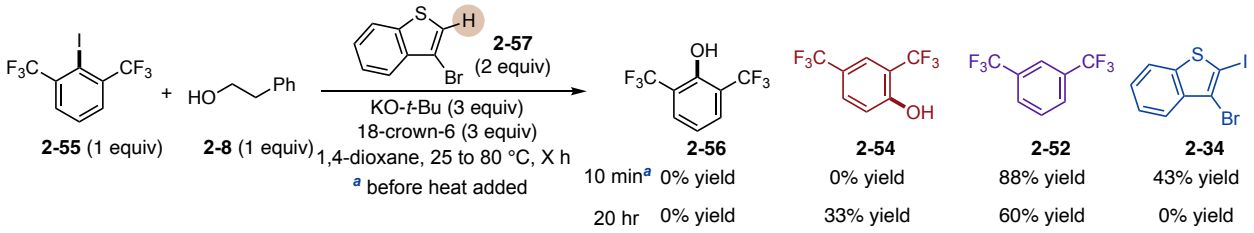
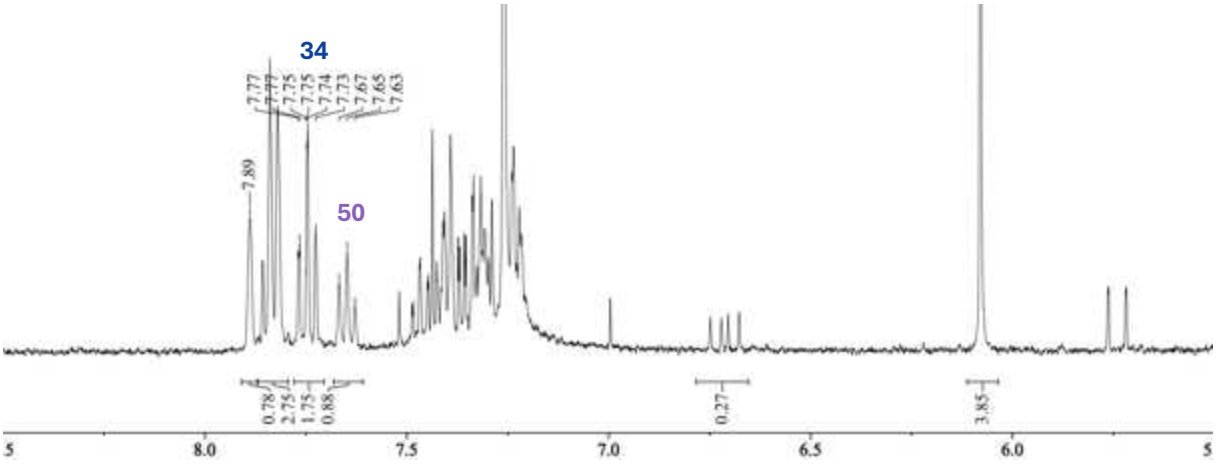


Figure A1-16. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the crude reaction solution of 2-iodo-1,3-bis(trifluoromethyl)benzene without additive. 1,3,5-Trimethoxybenzene (23.6 mg, 0.14 mmol, signal at 6.09 ppm integrated to 4.21 for 0.1 mmol scale reaction) added as internal standard.

Experiment 2: selectivity study on **2-55** with 3-bromobenzo[*b*]thiophene additive



^{1}H NMR spectrum after 10 min (before heat):



^{1}H NMR spectrum after 20 h:

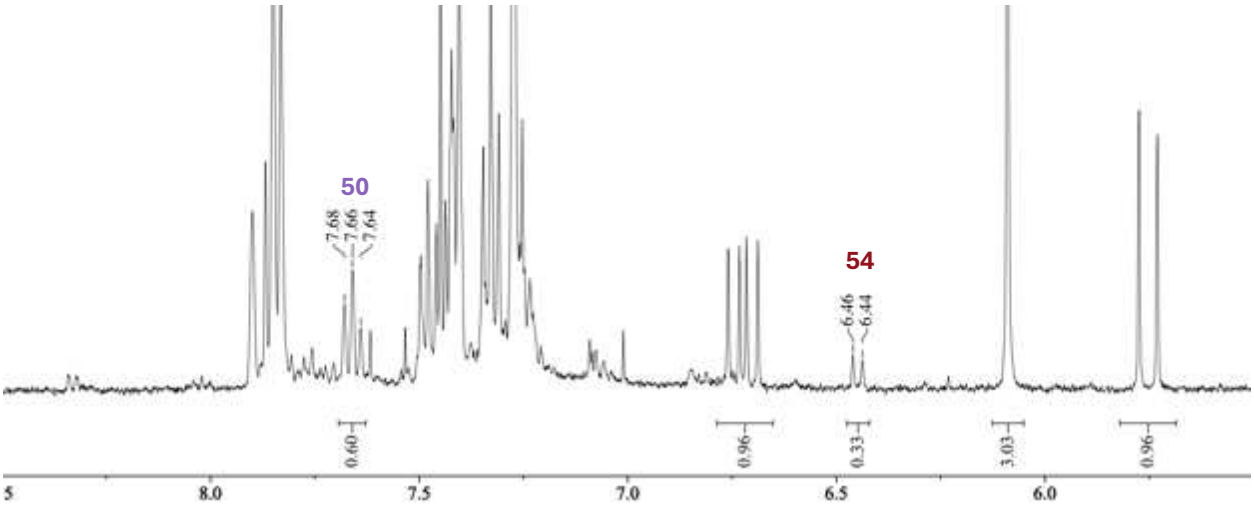


Figure A1-17. Top ^{1}H NMR spectrum (400 MHz, ($CDCl_3$) is the crude reaction solution of 2-iodo-1,3-bis(trifluoromethyl)benzene with 3-bromobenzo[*b*]thiophene additive (42.6 mg, 2 equiv) after 10 min stirring at rt. 1,3,5-Trimethoxybenzene (21.6 mg, 0.1 mmol, signal at 6.09 ppm integrated to 3.85 for 0.1 mmol scale reaction) added as internal standard. Bottom ^{1}H NMR spectrum (400 MHz, ($CDCl_3$) is the crude reaction solution of 2-iodo-1,3-bis(trifluoromethyl)benzene with 3-bromobenzo[*b*]thiophene additive after 20 h stirring at 80 °C.

1,3,5-Trimethoxybenzene (17.0 mg, 0.1 mmol, signal at 6.09 ppm integrated to 3.03 for 0.1 mmol scale reaction) added as internal standard.

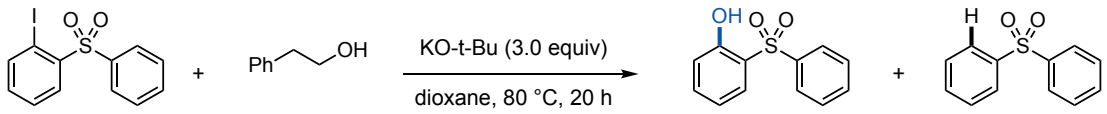
Summary discussion of selectivity: Control reactions of a potential iodinated intermediate where the iodine starts on the most favorable site of deprotonation for heteroarene and benzene mismatched substrates indicate that the X-transfer reagent byproducts (**2-36** and **2-57**) facilitate halogenation migration under the C–H hydroxylation reaction conditions. These experiments support that, regardless of the initial site of deprotonation/halogenation, X-migration can occur to the more S_NAr-active isomer that is substituted to provide unique and high site-selectivity. We note that the more S_NAr-active isomer in these cases is also the one that can generate a more stable (hetero)aryl anion after migration; this is the thermodynamic driving force for traditional "halogen dance" methodology.[16]

(d) Verifying Feasibility of Substitution Step on Corresponding Iodoarenes

Purpose: It is noteworthy that S_NAr reactions with aryl iodides are relatively uncommon compared to other aryl fluorides, chlorides and bromides.[15] The experiments below were performed to demonstrate that several of the proposed (hetero)aryl iodide intermediates can undergo substitution under the reaction conditions. We note that protodehalogenation is observed as a side product and speculate that this process may be the cause of some of the lower yields seen in the benzene substrate scope.

Substitution Control Procedure: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, aryl iodide (1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), anhydrous 1,4-dioxane (0.25 M, 4.0 mL), and KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, and placed into a preheated 80 °C aluminum reaction block. The solution was stirred for 20 h at 80 °C and then allowed to cool to rt. 1,3,5-Trimethoxybenzene internal standard was then measured into the crude solution. Several drops of 1M HCl were added to the reaction solution to ensure protonation of phenol. A small aliquot of the organic layer was then removed and injected into an NMR tube and constituted in $(CD_3)_2SO$ (0.5 mL).

Example 1: substitution control experiment with 1-iodo-2-(phenylsulfonyl)benzene



1-A2 (1.0 equiv) **2-8** (1.0 equiv) **2-32**, 68% yield **2-31**, 13% yield

The substitution control procedure was followed using 1-iodo-2-(phenylsulfonyl)benzene (343.9 mg, 1 mmol, 1 equiv). ^1H NMR spectroscopy (400 MHz, $(CD_3)_2SO$) was used to determine the yield of 2-(phenylsulfonyl)phenol (68% yield). **Note:** unproductive protodehalogenation of 1-iodo-2-(phenylsulfonyl)benzene also occurred to give diphenyl sulfone (**2-31**, 13% yield). The ^1H NMR spectrum of the crude reaction solution is shown below.

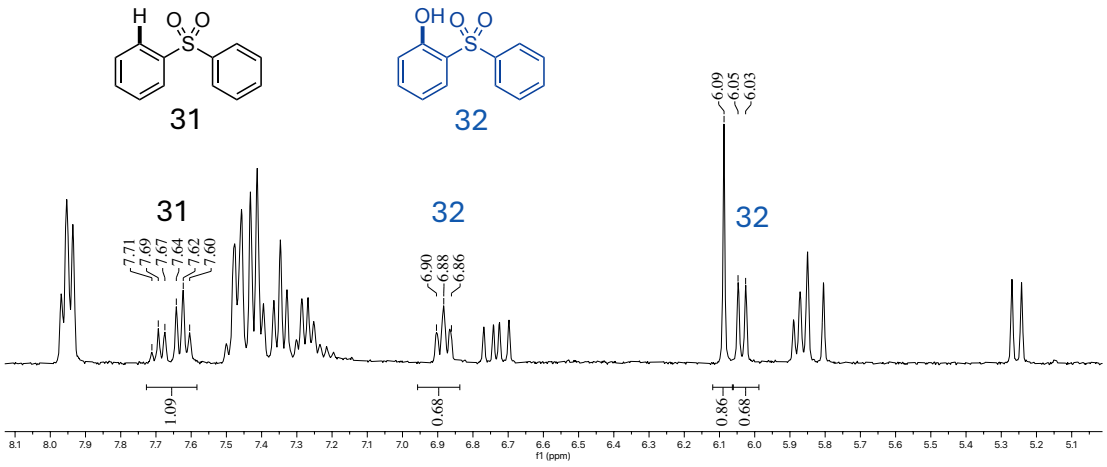
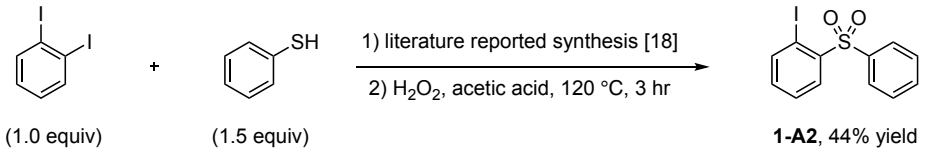


Figure A1-18. ^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$) of the crude reaction solution of 1-iodo-2-(phenylsulfonyl)benzene S_NAr using 2-phenethyl alcohol as the nucleophile. 1,3,5-Trimethoxybenzene (48.4 mg, 0.29 mmol, signal at 6.09 ppm integrated to 0.86 for 1.0 mmol scale reaction) added as internal standard. The ^{1}H NMR signals at 6.88 and 6.05 ppm were used to determine the yield of **2-32**; 68% yield. The ^{1}H NMR signal at 7.64 ppm was used to determine the yield of **2-31**; 13% yield.

1-iodo-2-(phenylsulfonyl)benzene (1-A2)

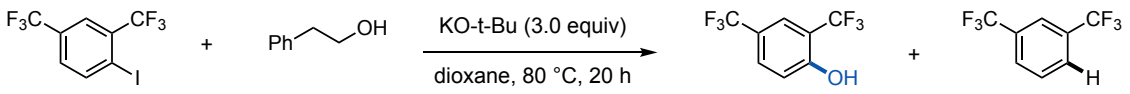


Step 1: (2-iodophenyl)(phenyl)sulfane was prepared according to a literature report using the conditions shown above.[17]

Step 2: 1-iodo-2-(phenylsulfonyl)benzene (1-A2)

Procedure: The title compound was prepared according to a modified literature procedure.[18] An oven-dried 25 mL round-bottom flask was charged with a magnetic stir bar, (2-iodophenyl)(phenyl)sulfane (879.1 mg, 2.82 mmol, 1 equiv) and acetic acid (9 mL). The flask was fitted with a reflux condenser and sealed with a rubber septum (Chemglass, Product #CG-3022-08). The septum was pierced and evacuated and backfilled three times with N_2 and left under positive pressure on a manifold Schlenk line. The reaction mixture was inserted into a 120 °C silicon oil bath and H_2O_2 (30% balanced in water, 2.88 g, 25.34 mmol, 9 equiv) was added *via* syringe in two portions over 15 min. The solution was stirred for 3 hr at 120 °C and then allowed to cool to rt. The reaction mixture was added to a slurry of H_2O and crushed ice. The resulting precipitate was collected and washed with water to afford the title compound as a white solid (422.0 mg, 1.22 mmol, 44% yield). **^{1}H NMR** (400 MHz, (CD_3CN) 8.39 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.98 – 7.88 (m, 2H), 7.72 – 7.53 (m, 4H), 7.38 – 7.29 (m, 1H). **^{13}C NMR** (101 MHz, $(CDCl_3)$ δ 143.1, 134.4, 133.5, 131.4, 129.4, 129.0, 129.0, 128.8, 127.8, 93.4. The spectroscopic data is consistent with a previous report.[19]

Example 2: substitution control experiment with 1-iodo-2,4-bis(trifluoromethyl)benzene (**1-A3**)



1-A3 (1.0 equiv) **2-8** (1.0 equiv) **2-56**, 53% yield **2-52**, 8% yield

The substitution control procedure was completed using 1-iodo-2,4-bis(trifluoromethyl)benzene (34.0 mg, 0.1 mmol, 1 equiv). ^{19}F NMR spectroscopy (376 MHz, $CDCl_3$) was used to determine the yield of 2,4-bis(trifluoromethyl)phenol (53% yield). **Note:** unproductive protodehalogenation of 1-A3 also occurred to give 1,3-bis(trifluoromethyl)benzene (8% yield). The ^{19}F NMR spectrum of the crude reaction solution is shown below. The ^{1}H NMR spectrum is consistent with these results.

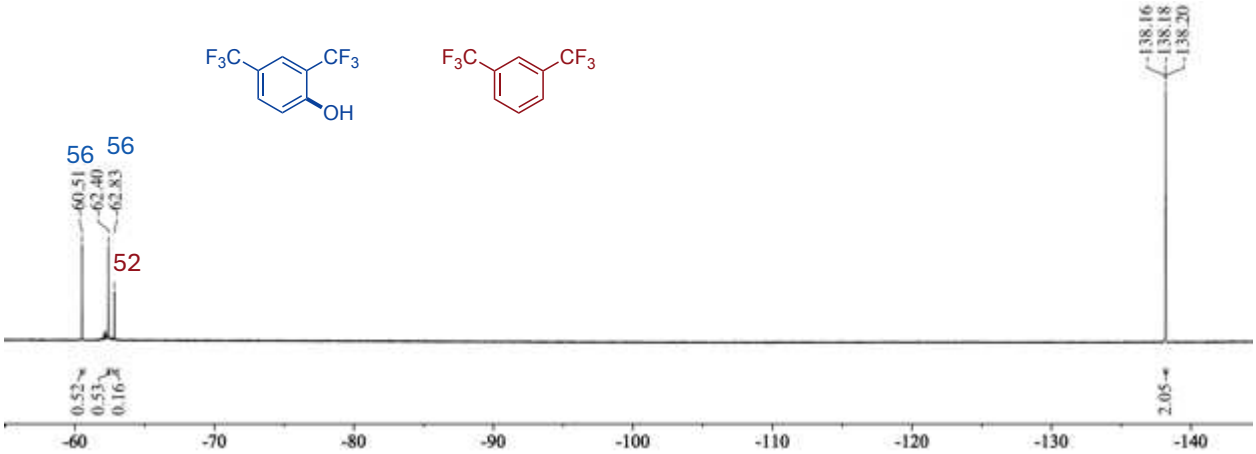
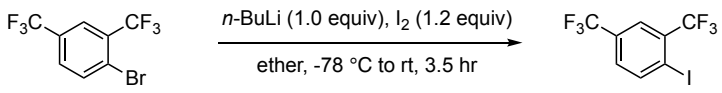


Figure A1-19: ^{19}F NMR spectrum (376 MHz, $CDCl_3$) of the crude reaction solution of 1-iodo-2,4-bis(trifluoromethyl)benzene S_NAr using 2-phenethyl alcohol as the nucleophile. 1,2-Difluorobenzene (70.3 mg, 0.62 mmol, signal at -138.18 ppm integrated to 2.05 for 0.1 mmol scale reaction) added as internal standard. The ^{19}F NMR signals at 60.5 and 62.4 ppm were used to determine the yield of **2-56**; 53% yield. The ^{19}F NMR signal at 62.8 ppm was used to determine the yield of **2-52**; 8% yield.

1-iodo-2,4-bis(trifluoromethyl)benzene (1-A3)



(1.0 equiv) **1-A3**, 28 % yield

Procedure: A 250-mL flame dried round bottom flask was equipped with a magnetic stir-bar and was charged with 1-bromo-2,4-bis(trifluoromethyl)benzene (7.00 g, 23.9 mmol, 1 equiv). The flask was sealed with a rubber septum (Chemglass, Product #CG-3022-08). The septum was pierced and evacuated and backfilled three times with N_2 and left under positive pressure on a

manifold Schlenk line. Anhydrous diethyl ether (59 mL) was then added *via* syringe. The solution was cooled to -78 °C in a dry ice/acetone-bath. An *n*-BuLi solution (14.9 mL, 1.6 M in hexanes, 23.9 mmol, 1 equiv) was added dropwise and stirred for 30 min. A solution of iodine (7.28 g, 28.7 mmol, 1.2 equiv) in ether (20 mL) was added dropwise and the reaction mixture was warmed to rt and stirred for 3 h. The solution was transferred to a separatory funnel containing H_2O (80 mL). Na_2SO_3 was added to the separatory funnel and the solution was agitated until it became light-yellow in color. The aqueous layer was extracted with ether (3 x 80 mL). The organic layer was dried over Na_2SO_4, filtered, and then concentrated *in vacuo* to afford to title compound as orange oil (2.27 g, 6.67 mmol, 28% yield). **Note:** this compound is slightly volatile. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.2 Hz, 1H), 7.88 (s, 1H), 7.49 – 7.42 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1, 134.9 (q, *J* = 31.5 Hz), 131.0 (q, *J* = 34.1 Hz), 129.4 (q, *J* = 4.1 Hz), 124.6 (m), 122.3 (q, *J* = 274.0), 95.8. The spectroscopic data is consistent with a previous report.[20]

(e) Discussion of Reactivity Trends on Pyridines with a Range of Electronic Properties

Purpose: Our studies indicate that C–H bond acidity and S_NAr reactivity trends are the determining factors that govern the scope and selectivity of this hydroxylation protocol. Here, a comparison of simple 3-substituted pyridines is provided to illustrate this trend using 2-iodothiophene (**2-2**) and 3-bromo-2-iodobenzothiophene (**2-36**) as X-transfer reagents (conditions from Figures 2-14 and 2-18, respectively).

Procedure: Inside a N_2 filled glovebox, a 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, *N*-heteroarene (1 equiv, 0.1 mmol), 2-phenethyl alcohol (12.2 mg, 0.1 mmol, 1 equiv), 2-iodothiophene (42.0 mg, 0.2 mmol, 2 equiv) or 3-bromo-2-iodobenzothiophene (67.2 mg, 0.2 mmol, 2 equiv), anhydrous solvent (0.4 mL), and KO-*t*-Bu (33.6 mg, 0.3 mmol, 3 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, and placed into a preheated 60 or 80 °C aluminum reaction block. The reaction solution was stirred for 20 h at 60 or 80 °C and then allowed to cool to rt. For each experiment, 1,3,5-trimethoxybenzene was weighed into the vial and the mass added was recorded. The crude solution was then homogenized with MeOH (1 mL). A small aliquot was then removed and injected into an NMR tube and constituted in $(CD_3)_2SO$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, $(CD_3)_2SO$) was used to determine the yield of the product and remaining starting *N*-heteroarene. The results are summarized in Table A1-4 below.

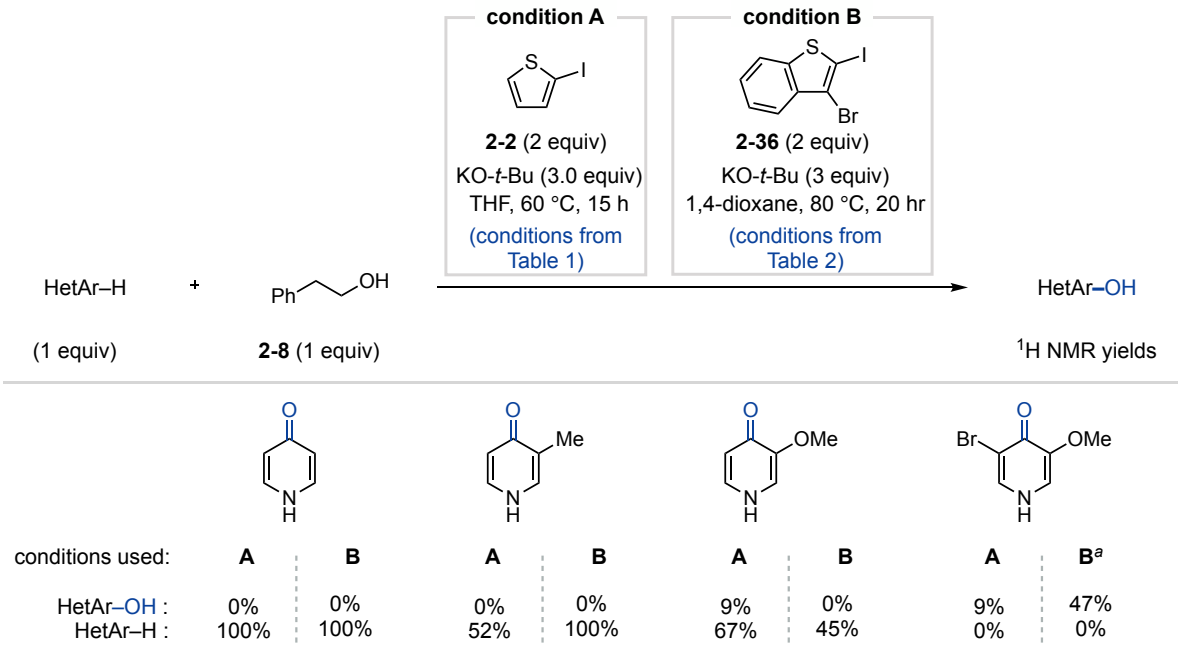
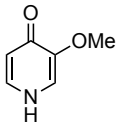


Table A1-4. 3-Substituted pyridine substrates with differing electronic properties under the optimized C–H hydroxylation reaction conditions from Figures 2-14 and 2-18. [a] Reaction run at rt instead of 80 °C.

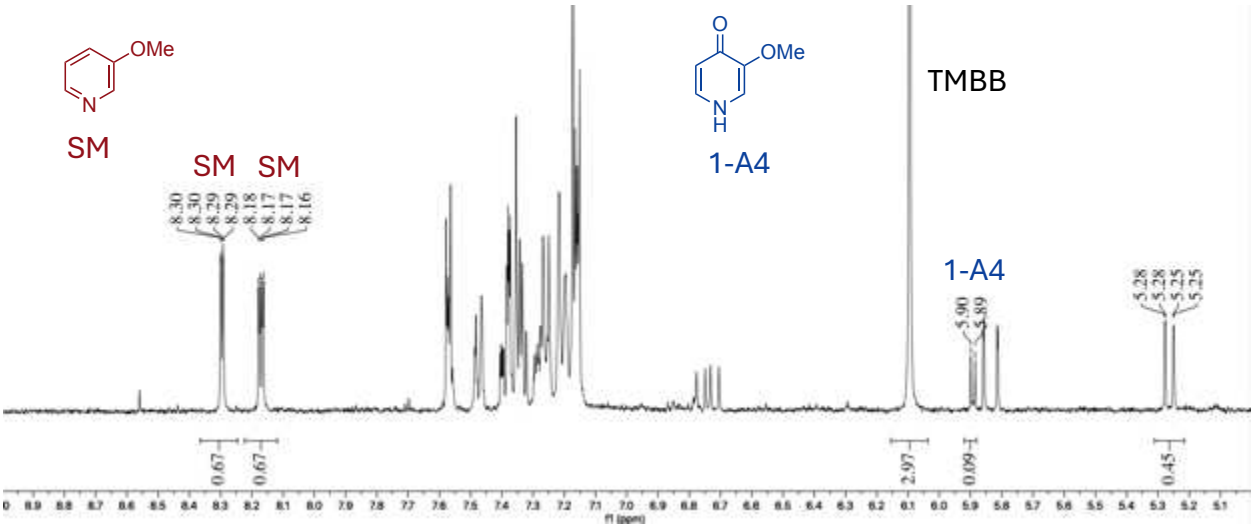
Confirmation of Product Formation from Table A1-4:

3-methoxypyridin-4(1H)-one (1-A4)

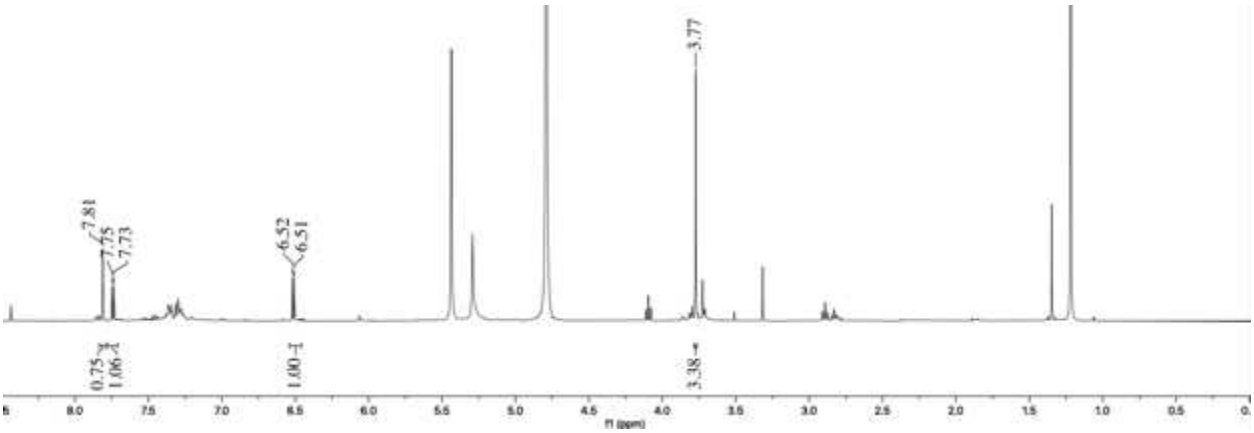


The title product was prepared using the general procedure for the C–H hydroxylation of *N*-heteroarenes on a 1 mmol scale. Thus, 3-methoxypyridine (109.1 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (420.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL) were used according to the general procedure. The yield was determined by ^{1}H NMR spectroscopy. 1,3,5-Trimethoxybenzene (166.5 mg, 0.99 mmol, 0.99 equiv) was added as the internal standard for ^{1}H NMR analysis (9% yield of 1-A4). Next, 2 mL of D_2O was added to the crude reaction and a small aliquot of the D_2O layer was removed, injected into an NMR tube, constituted in D_2O (0.5 mL), and ^{1}H NMR spectroscopy was taken. **^{1}H NMR** (400 MHz, D_2O) 7.81 (s, 1H), 7.74 (d, J = 5.6 Hz, 1H), 6.51 (d, J = 5.6 Hz, 1H), 3.77 (s, 3H). This spectrum was then compared to a ^{1}H NMR spectrum of an authentic commercial standard of the 3-methoxypyridin-4(1H)-one in D_2O (CombiBlocks catalog # QC-5301) to confirm formation of the title product (see Figure A1-20 below).

(a) ^{1}H NMR spectral window of the crude reaction solution in $(CD_3)_2SO$:



(b) ^{1}H NMR spectrum (in D_2O) of the D_2O layer after addition of D_2O into the crude reaction:



(c) ^{1}H NMR spectrum (in D_2O) of the authentic standard of 3-methoxypyridin-4(1H)-one in D_2O:

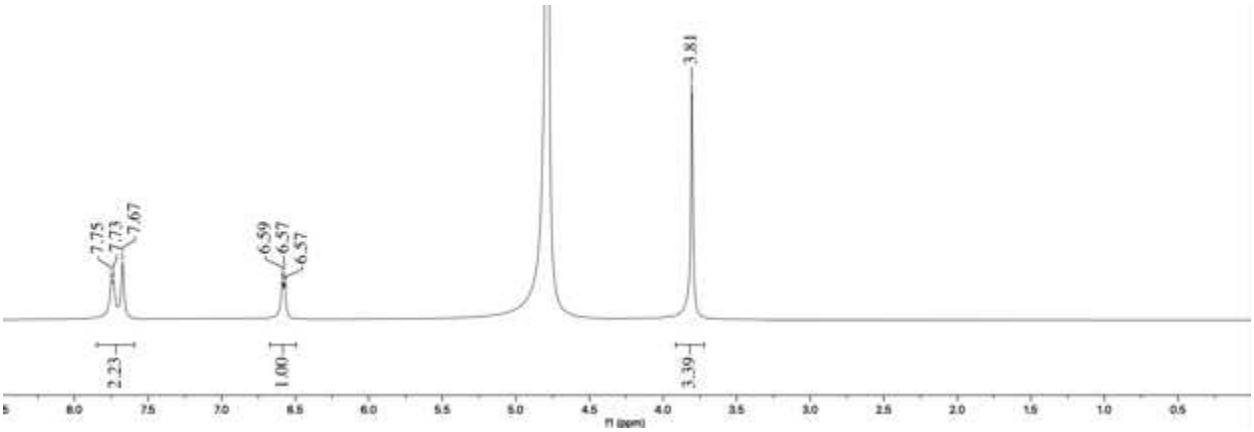
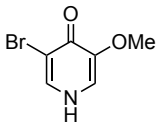


Figure A1-20. ^{1}H NMR spectral window of the crude reaction solution of reaction from the C–H hydroxylation of 3-methoxypyridine (Figure A1-20, a). 1,3,5-Trimethoxybenzene internal

standard (166.5 mg, 0.99 mmol, signal at 6.09 ppm calibrated to 2.97 for 1.0 mmol scale reaction) was used to determine the yield of the 3-methoxypyridin-4(1H)-one (9% yield). ^{1}H NMR spectrum of the of the D_2O layer after addition of D_2O into the crude reaction solution (Figure A1-20, b). ^{1}H NMR spectrum of the authentic standard of 3-methoxypyridin-4(1H)-one in D_2O (Figure A1-20, c).

3-bromo-5-methoxypyridin-4(1H)-one (1-A5)



The title product was prepared through slight modification of the general procedure for the C–H hydroxylation of benzenes, where the reaction was stirred at rt instead of 80 °C. Thus, 3-bromo-5-methoxypyridine (188.0 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (672.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,4-dioxane (4.0 mL) were added according to the general procedure. The product was purified *via* the general *N*-heteroarene isolation procedure 1, wherein silica gel chromatography (10% MeOH/CH_2Cl_2) afforded the title compound as a white solid (96.0 mg, 0.47 mmol, 47% yield). **Mp**: 200-204 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 11.77 (br s, 1H), 8.07 (s, 1H), 7.48 (s, 1H), 3.69 (s, 3H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 166.6, 148.6, 135.6, 119.3, 110.5, 56.4. **IR** (neat, cm^{-1}) 3006, 2625, 1936, 1631, 1535, 1501, 1251, 1028, 764. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_6H_6BrNO_2]^+$ = 203.9660, 203.9659 found.

Discussion: The results above show that electron-donating and -withdrawing groups in the 3-position are tolerated, so long as the pyridine is sufficiently acidic. No product is observed for pyridine with complete mass balance of unreacted substrate. However, 3-methoxypyridine provides some yield, consistent with the acidifying nature of the methoxy substituent; furthermore, under modified conditions, 3-bromo-5-methoxypyridine provides significantly increased yields, likely due to its increased acidity provided by the bromine substituent. In general, this protocol is therefore applicable to (hetero)arenes that contain electron-donating groups so long as they are sufficiently acidic, as seen in substrates **2-21**, **2-30** and **2-39** in Figure 3-14. Acidic methyl groups can undergo competing X-transfer and this explains the low mass balance for 3-methylpyridine under condition A in Table A1-4.

(f) Discussion of Mass Balance for Substrates that Provide Moderate Yields

The substrate tables include several (hetero)arenes that provide only moderate yields of product to illustrate the scope of this protocol. To inform readers of the potential causes of reduced yields, discussions of several representative substrates are provided in this section. The yields reported in this section were determined from the ^{1}H NMR spectra of the corresponding crude reaction materials from the 1 mmol scale general hydroxylation procedures.

(i) Acidity trends: As seen in Section 6 through deuteration experiments and substituent effects on yield (Section A1-6e), C–H bond acidity is a key factor governing productive reactivity. This challenge leads to several substrates giving moderate to low yields but with high mass balance of starting material (i.e., **2-17, 2-22, 2-24, 2-28, 2-32 and 2-40** from Figure 3-14 and 1-18). As specific examples, the mass balance for substrate **2-24** is comprised of 52% product and 42% starting material and the mass balance for substrate **2-40** is comprised of 34% product and 54% starting material.

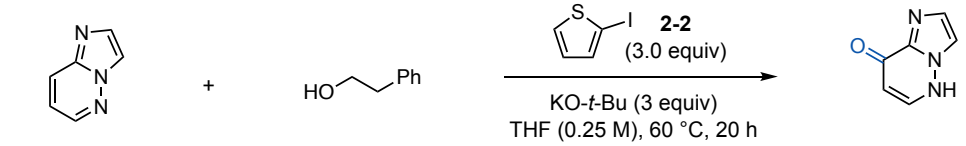
(ii) S_NAr trends: As this C–H hydroxylation protocol proceeds through an S_NAr process, less-electron-deficient substrates may have a more challenging S_NAr step. This challenge is also represented by substrate **2-32** where the mass balance consists of 52% product and 42% starting material. As seen in "Substitution control experiment with 1-iodo-2-(phenylsulfonyl)benzene", 2-(phenylsulfonyl)phenol (**2-32**, 68% yield) and diphenyl sulfone (**2-31**, 13% yield) were the major products of the substitution reaction of 1-iodo-2-(phenylsulfonyl)benzene. Thus, S_NAr reactivity trends of a substrate may lead to reduced yields due to a general lack of reactivity or deiodination of the corresponding (hetero)aryl iodide intermediate. **Note:** the challenges noted for acidity and S_NAr trends generally have similar effects (i.e., a less acidic benzene substrate also generates a less S_NAr active intermediate).

(iii) Product volatility: We reported several products that contain multiple trifluoromethyl groups that can be moderately volatile and thus product loss can occur during isolation. For example, **2-15** gives an 83% yield by ^{1}H NMR spectroscopy (0% starting material) but only 56% isolated yield.

(iv) Functional group compatibility considerations: In certain cases, low mass balance is observed due to potential competing side reactions under the strong base conditions. This occurs for some benzonitriles (e.g., **2-42** has 65% yield, 0% remaining starting material) and polyhalopyridines (e.g., **2-13** has 44% yield, 36% remining starting material, and 15% of 2-substitution side product). The yields of these products indicate good to moderate yields are possible in the presence of these competing functional groups.

A1.7. Multigram Scale Synthesis of Compounds 2-59 and 2-61

(a) Multigram Scale C–H Hydroxylation of 2-59



2-58, 42.0 mmol
5.0 g

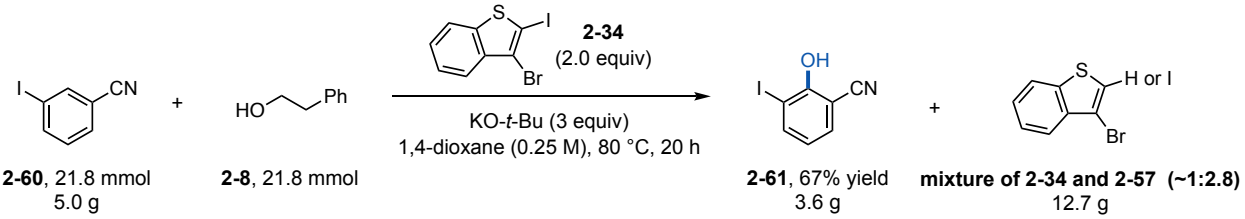
2-8, 42.0 mmol

2-59, 83% yield
4.7 g

Procedure: An oven-dried 500 mL round bottom flask equipped with a magnetic stir-bar was charged with imidazo[1,2-*b*]pyridazine (5.0 g, 42 mmol, 1 equiv) and KO-*t*-Bu (14.1 g, 125.9 mmol, 3 equiv). The flask was fitted with a reflux condenser and sealed with a rubber septum (Chemglass, Product #CG-3022-08). The septum was pierced with a needle connected to a manifold Schlenk line, evacuated and backfilled three times with N_2, and then left under positive pressure of N_2. Concurrently, an oven-dried 250 mL round bottom flask was charged with 2-phenethyl alcohol (5.1 g, 42 mmol, 1 equiv) and 2-iodothiophene (26.5 g, 125.9 mmol, 3 equiv). The 250 mL flask was sealed with a rubber septum (Chemglass, Product #CG-3022-08), pierced with a needle connected to a manifold Schlenk line, evacuated and backfilled with N_2 three times, and then left under positive pressure of N_2. THF (168 mL, 0.25 M) was then charged into the 250 mL flask. Next, the contents of the 250 mL flask were transferred to the 500 mL round bottom flask *via* syringe, no exotherm was detected. The reaction flask was then placed into a preheated 60 °C silicon oil bath and stirred for 20 h under positive pressure of N_2. The reaction solution was

allowed to cool to rt, concentrated *in vacuo*, and then loaded directly onto a silica gel column (100% CH_2Cl_2 to 12% MeOH/CH_2Cl_2) to give the title compound with a small impurity. Further purification *via* recrystallization from 10% MeOH/CH_2Cl_2 yielded the title product as a light-brown solid (4.7 g, 34.8 mmol, 83% yield). **Mp**: 255-260 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 8.12 – 8.10 (m, 2H), 7.69 (s, 1H), 6.24 (s, J = 5.8 Hz, 1H), 4.47 (br s, 1H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 156.3, 146.4, 136.5, 126.8, 117.3, 100.9. **IR** (neat, cm^{-1}) 3385, 3114, 2360, 1902, 1358, 1285, 1029, 885, 746. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_6H_6N_3O]^+$ = 136.0511, 136.0488 found.

(b) Multigram Scale C–H Hydroxylation of 2-61



2-60, 21.8 mmol
5.0 g

2-8, 21.8 mmol

2-61, 67% yield
3.6 g

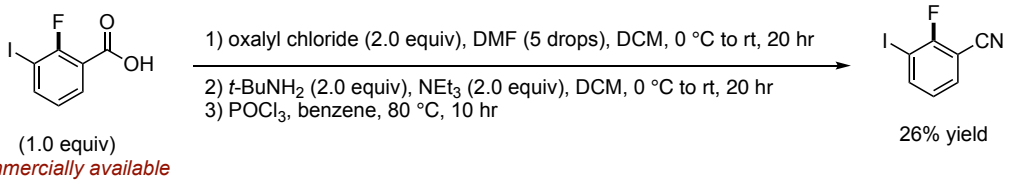
mixture of 2-34 and 2-57 (~1:2.8)
12.7 g

Procedure: An oven-dried 500 mL round bottom flask equipped with a magnetic stir-bar was charged with 3-bromo-2-iodobenzo[*b*]thiophene (14.8 g, 43.7 mmol, 2 equiv) and KO-*t*-Bu (7.3 g, 65.5 mmol, 3 equiv). The flask was then sealed with a rubber septum (Chemglass, Product #CG-3022-08), pierced with a needle connected to a manifold Schlenk line, evacuated and backfilled with N_2 three times, and then left under positive pressure of N_2. Concurrently, an oven-dried 250 mL round bottom flask was charged with 2-phenethyl alcohol (2.7 g, 21.8 mmol, 1 equiv) and 3-iodobenzonitrile (5.0 g, 21.8 mmol, 1 equiv). The flask was sealed with a rubber septum (Chemglass, #CG-3022-08), pierced with a needle connected to a manifold Schlenk line, evacuated and backfilled three times with N_2, and left under positive pressure of N_2. The 250 mL flask was then charged with anhydrous 1,4-dioxane (87 mL, 0.25 M) and its contents were transferred to the 500 mL round bottom flask *via* syringe, no exotherm was detected. The reaction flask was then placed into a preheated 80 °C silicon oil bath and stirred for 20 h. The flask was removed from the oil bath. Upon cooling to rt, the crude reaction solution was poured into a 1 L separatory funnel containing water (200 mL). The pH of the water layer was adjusted to pH 14 using 1M NaOH and the organic impurities were extracted with EtOAc (3 x 200 mL). **Note:** these EtOAc extracts were saved for recovery of **34** (see Section 8). The pH of the water layer was then adjusted to pH 5 using 1M HCl and the product precipitated. The precipitate was collected and triturated with hexanes to yield the title product as a white solid (3.6 g, 14.7 mmol, 67% yield). **Mp**: 117-120 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 6.77 (t, J = 7.9 Hz, 1H), 6.03 (br s, 1H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 158.4, 144.2, 133.6, 122.4, 116.4, 101.1, 88.8. **IR** (neat, cm^{-1}) 3262, 2231, 1594, 1460, 1238, 1216, 1109, 1074, 848. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_7H_5INO]^+$ = 245.9410, 245.9420 found.

Verification of regioselectivity: To verify that 2-substitution of iodine occurred over 3-substitution, an authentic sample of **2-61** was prepared *via* substitution of 2-fluoro-3-iodobenzonitrile with 2-phenethyl alcohol as described below.

Synthesis of authentic standard 2-hydroxy-3-iodobenzonitrile:

Step 1: 2-fluoro-3-iodobenzonitrile

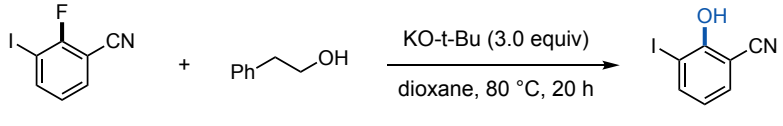


(1.0 equiv)
commercially available

26% yield

Procedure: The title compound was prepared according to a modified literature procedure.[21] An oven-dried 100 mL round bottom flask was charged with a magnetic stir bar, 2-fluoro-3-iodobenzoic acid (1.0 g, 3.8 mmol, 1 equiv), CH_2Cl_2 (14 mL), and 5 drops of *N,N*-dimethylformamide. The solution was cooled to 0 °C in an ice-bath and oxalyl chloride (0.7 mL, 7.5 mmol, 2 equiv) was added dropwise *via* syringe. The reaction solution was warmed to rt and stirred for 20 h. This solution was then concentrated i*n vacuo* and the flask was subsequently charged with DCM (14 mL). This solution was cooled to 0 °C in an ice-bath and 2-methylpropan-2-amine (0.8 mL, 7.5 mmol, 2 equiv) and triethylamine (1.1 mL, 7.3 mmol, 2 equiv) were added dropwise *via* syringe. The reaction solution was warmed to rt and stirred for 20 h. This solution was then concentrated i*n vacuo* and the flask was subsequently charged with benzene (13 mL). The flask was fitted with a reflux condenser, sealed with a rubber septum (Chemglass, product #CG-3022-08), and a N_2 inlet was inserted into septum. Next, phosphoryl chloride (1.8 mL, 18.8 mmol, 5 equiv) was added *via* syringe. The flask was placed into a silicon oil bath preheated to 80 °C and the reaction solution was refluxed and stirred for 10 h. The solution was allowed to cool to rt, then transferred to a separatory funnel containing H_2O (50 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL) and the organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (25% EtOAc/hexanes) yielded the title compound as a yellow solid (246.3 mg, 1.00 mmol, 26% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (ddd, *J* = 7.8, 6.0, 1.6 Hz, 1H), 7.61 (ddd, *J* = 7.6, 5.8, 1.6 Hz, 1H), 7.05 – 7.01 (m, 1H). The spectroscopic data is consistent with a previous report.[22]

Step 2: 2-hydroxy-3-iodobenzonitrile (2-61)



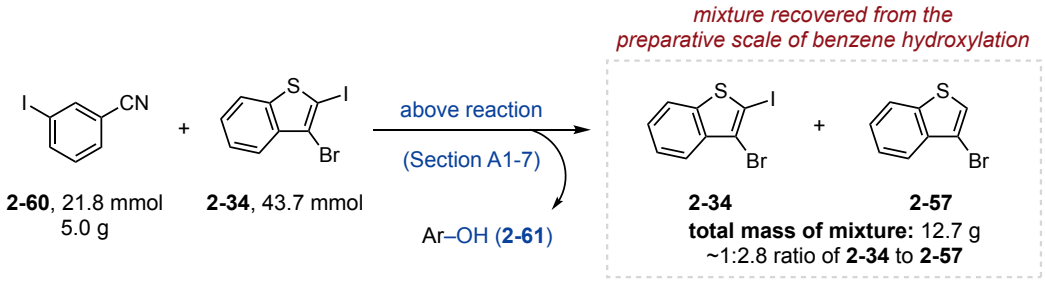
(1.0 equiv) **2-8** (1.0 equiv) **2-61**, 30% yield

Procedure: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 2-fluoro-3-iodobenzonitrile (12.4 mg, 1 equiv, 0.1 mmol), 2-phenethyl alcohol (12.2 mg, 0.1 mmol, 1 equiv), anhydrous 1,4-dioxane (0.25 M, 0.4 mL), and KO-*t*-Bu (33.6 mg, 0.3 mmol, 3 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, and placed into a preheated 60 °C aluminum reaction block. The solution was stirred for 20 h at 80 °C and then allowed to cool to rt. Upon cooling to rt,

the crude reaction solution was poured into a 25 mL separatory funnel containing water (10 mL). The pH of the water layer was adjusted to pH 14 using 1M NaOH and the organic impurities were extracted with EtOAc (3 x 10 mL). The pH of the water layer was then adjusted to pH 5 using 1M HCl and extracted with EtOAc (3 x 10 mL). The organic extracts were concentrated *in vacuo* and loaded onto a preparatory thin layer chromatography plate and developed with 10:1 hexanes/EtOAc to give the title product as a white solid (7.4 mg, 0.30 mmol, 30% yield). **Note:** The characterization data from the synthesis of the authentic standard was consistent with the that of the C–H hydroxylation reaction on 3-iodobenzonitrile. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (dd, J = 7.9, 1.4 Hz, 1H), 7.54 (dd, J = 7.9, 1.4 Hz, 1H), 6.77 (t, J = 7.9 Hz, 1H), 6.03 (s, 1H).

A1.8. Recovery and Regeneration of 3-Bromobenzo[*b*]thiophene from a Multigram Scale Benzene C–H Hydroxylation

(a) Recovery of 3-bromo-2-iodobenzo[*b*]thiophene from the multigram scale C–H hydroxylation of 2-61



Procedure: The EtOAc extracts from the multigram scale reaction of 2-hydroxy-3-iodobenzonitrile from above (Section 7b) were concentrated *in vacuo* to afford a mixture of 3-bromo-2-iodobenzo[*b*]thiophene and 3-bromobenzo[*b*]thiophene (12.7 g total, ~1:2.8 of **2-34** to **2-57**). ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) of this mixture is shown below.

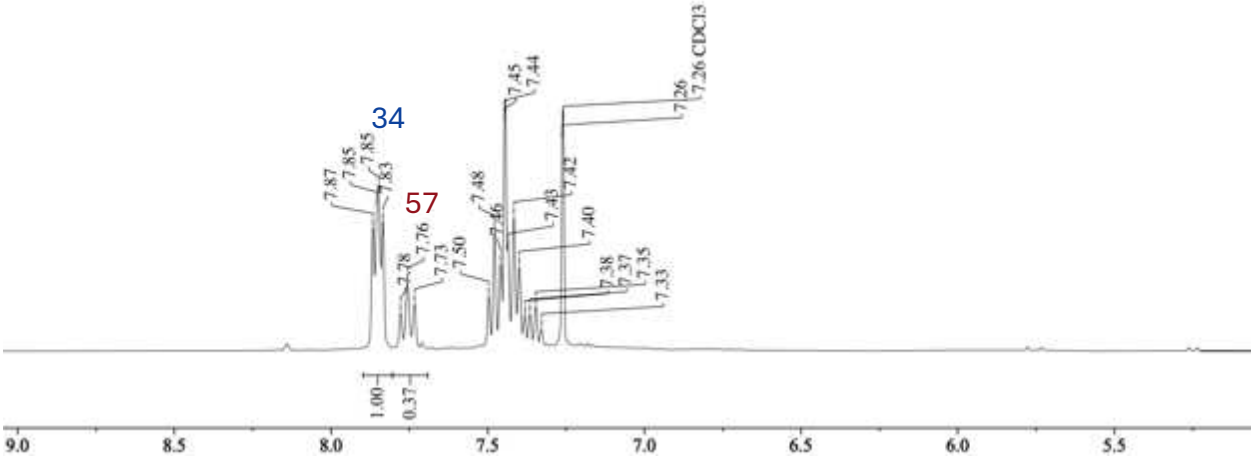
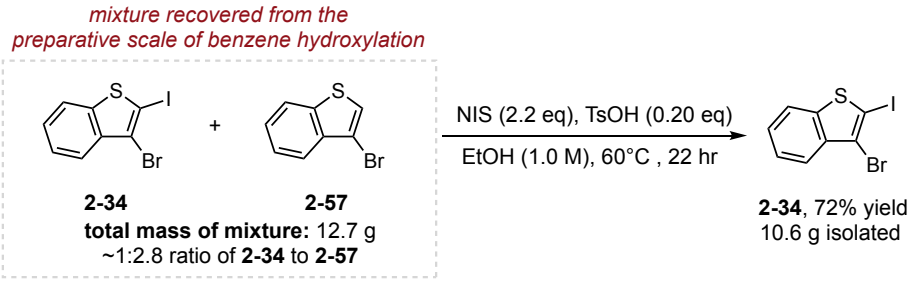


Figure A1-21: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the concentrated EtOAc extracts from the multigram scale of the 3-iodobenzonitrile C–H hydroxylation. The ^{1}H NMR signals at 7.85 ppm and 7.76 ppm represent compounds **2-34** and **2-57**, respectively.

(b) Regeneration of 3-bromo-2-iodobenzo[*b*]thiophene



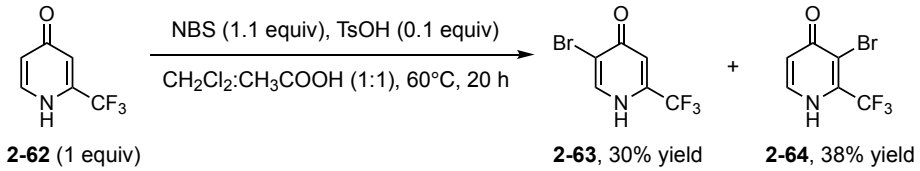
This procedure was adapted from a previous literature report.[5] We note that the stoichiometry for the reagents in this reaction were determined assuming that 74% of the 3-bromobenzo[*b*]thiophene and 3-bromo-2-iodobenzo[*b*]thiophene mixture was comprised of 3-bromobenzo[*b*]thiophene (~9.4 g, 44 mmol). An oven-dried 500 mL round bottom flask was charged with a magnetic stir bar, the mixture of 3-bromobenzo[*b*]thiophene and 3-bromo-2-iodobenzo[*b*]thiophene (12.7 g, ~1:2.8 mixture of **2-34** to **2-57**), from the multigram scale of 2-hydroxy-3-iodobenzonitrile, and ethanol (43 mL, 1.0 molar). The flask was inserted into a 0 °C ice-bath. Subsequently, *N*-Iodosuccinimide (10.9 g, 48.6 mmol, 1.1 equiv) and *p*-toluenesulfonic acid monohydrate (840.4 mg, 4.4 mmol, 0.1 equiv) were added portion-wise. The flask was then placed into a silicon oil bath preheated to 60 °C and the reaction solution stirred for 20 h. A second addition of *N*-iodosuccinimide (10.9 g, 48.6 mmol, 1.1 equiv) and *p*-toluenesulfonic acid monohydrate (836.9 mg, 4.4 mmol, 0.1 equiv) were added and the reaction mixture was stirred for an additional 2 h at 60 °C. The solution was cooled to rt and transferred to a separatory funnel containing H_2O (150 mL). $Na_2S_2O_3$ (20.7 g, 130.9 mmol, 3 equiv) was added to the separatory funnel and the solution was agitated until it became light-yellow in color. The aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL). The organic layer was dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. Silica gel chromatography (hexanes) yielded the title compound. The compound was further purified by recrystallization using 3% CH_2Cl_2/hexanes solvent to give the title product as a light yellow, crystalline solid (10.6 g, 31.3 mmol, 72% yield). **Note:** The reported yield is calculated based on the original quantity of **1-34** (14.8 g, 43.7 mmol) employed in the multigram scale reaction from Section 7. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 – 7.68 (m, 2H), 7.38 – 7.29 (m, 2H). **^{13}C NMR** (101 MHz, ($CDCl_3$) δ 143.0, 137.9, 134.5, 125.6, 123.8, 121.8, 118.4, 82.2. The spectroscopic data is consistent with a previous report.[5]

A1.9. Demonstrations of the Utility of the C–H Hydroxylation Protocol

(a) Comparison to the electrophilic halogenation of hydroxylated *N*-heteroarenes.

Electrophilic halogenation of 2-(trifluoromethyl)-4-pyridone (**2-62**) gives an inseparable mixture of the 3- and 5-bromo isomers. In contrast, the X-transfer C–H hydroxylation protocol on either 3-bromo-2-(trifluoromethyl)pyridine or 5-bromo-2-(trifluoromethyl)pyridine gives exclusive access to each 4-pyridone isomer.

Electrophilic halogenation of 2-(trifluoromethyl)pyridin-4(1H)-one:



Procedure: Open to air, a 4 mL vial (KIMBLE®, #60910-1) was charged with 2-(trifluoromethyl)pyridin-4(1H)-one (16.3 mg, 0.1 mmol, 1 equiv), *N*-bromosuccinimide (0.11 mmol, 1.1 equiv), *p*-toluenesulfonic acid (1.9 mg, 0.01 mmol, 0.1 equiv), CH_2Cl_2 (0.25 mL), and acetic acid (0.25 mL) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13) and placed into a preheated 60 °C aluminum reaction block. The reaction solution was stirred for 20 h at 60 °C and then allowed to cool to rt. 1,3,5-Trimethoxybenzene was weighed into the vial and the mass added was recorded. The crude solution was then homogenized with MeOH (1 mL). A small aliquot was then removed and injected into an NMR tube and constituted in $(CD_3)_2SO$ (0.5 mL). ^{19}F NMR spectroscopy (376 MHz, $(CD_3)_2SO$) was used to determine the yield of each isomer, where it was found that 30% yield of **2-63** formed, 38% yield of **2-64** formed, and that 32% of the starting material (**2-62**) remained (shown below). **Note:** Full characterization of each isomer is provided below where they are synthesized *via* the X-transfer method. The ^{19}F NMR shifts of the purified products and the products in the ^{19}F NMR spectrum of the electrophilic halogenation of 2-(trifluoromethyl)pyridin-4(1H)-one correlate as expected.

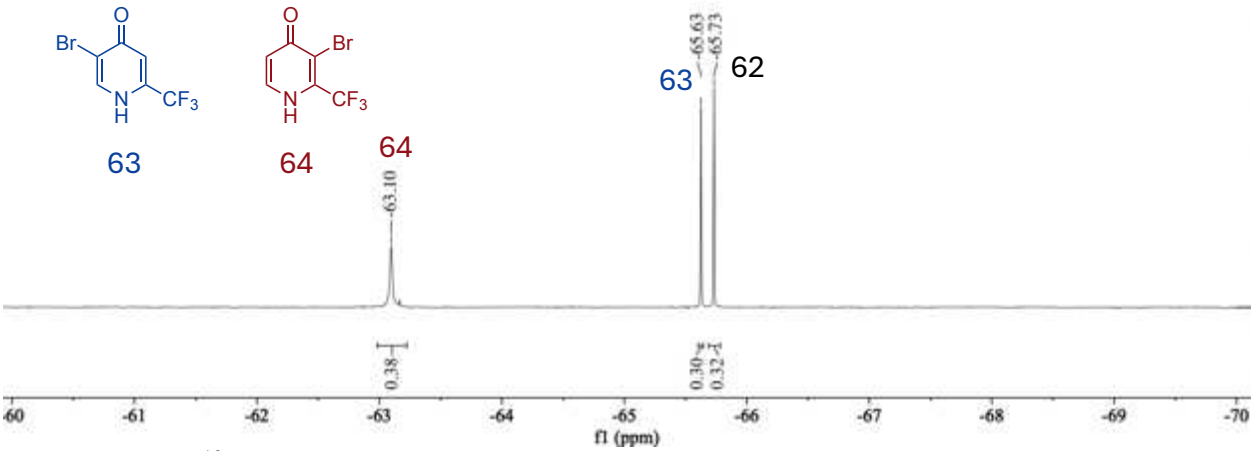
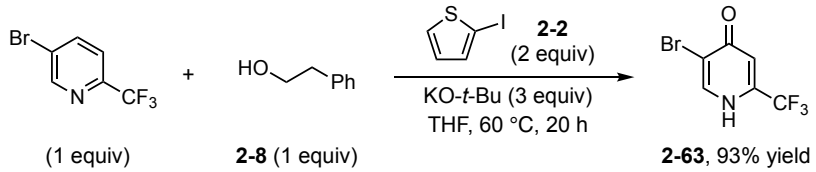
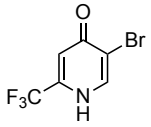


Figure A1-22. ^{19}F NMR spectrum (376 MHz, $(CD_3)_2SO$) of the electrophilic halogenation of 2-(trifluoromethyl)pyridin-4(1H)-one. The ^{19}F NMR signals at -63.1 ppm and -65.6 ppm represent compounds **2-64** and **2-63**, respectively.

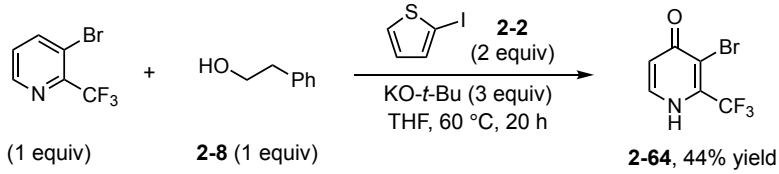
Selective synthesis of both isomers *via* the C–H hydroxylation protocol:



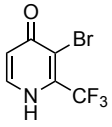
5-bromo-2-(trifluoromethyl)pyridin-4(1H)-one (2-63)



The title product was prepared according to the general procedure for the C–H hydroxylation of *N*-heteroarenes using 5-bromo-2-(trifluoromethyl)pyridine (226.0 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 2 to afford the title compound as a tan solid (226.0 mg, 0.93 mmol, 93% yield). **Mp**: 160-162 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 12.52 (br s, 1H), 8.69 (s, 1H), 7.28 (s, 1H).**^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 162.1, 152.7, 146.7 (q, J = 33.7 Hz), 121.3 (q, J = 275.5 Hz), 111.6, 108.9 (q, J = 2.7 Hz). **^{19}F NMR** (376 MHz, $(CD_3)_2SO$) δ -65.8. **IR** (neat, cm^{-1}) 2972, 2360, 1596, 1425, 1317, 1252, 1139, 1095, 1043, 929. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_6H_4F_3BrON]^+$ = 241.9423, 241.9425 found. **Note:** >10:1 site-selectivity is observed through analysis of the crude reaction mixture by ^{1}H NMR spectroscopy.

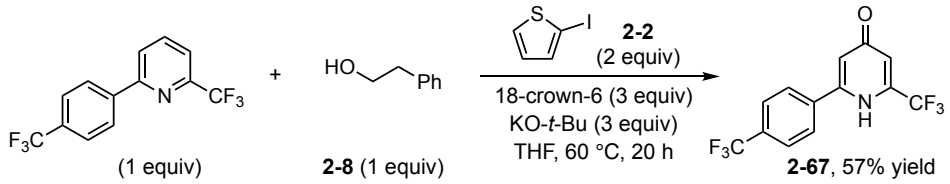


3-bromo-2-(trifluoromethyl)pyridin-4(1*H*)-one (2-64)

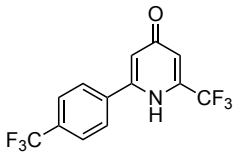


The title product was prepared according to the general procedure for the C–H hydroxylation of *N*-heteroarenes using 3-bromo-2-(trifluoromethyl)pyridine (226.0 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The product was purified *via* the general *N*-heteroarene isolation procedure 1, wherein silica gel chromatography (5% to 10% $MeOH/CH_2Cl_2$) afforded the title compound as a white solid (107.0 mg, 0.44 mmol, 44% yield). **Mp**: 149-152 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 12.38 (br s, 1H), 8.32 (d, J = 5.4 Hz, 1H), 7.16 (d, J = 5.4 Hz, 1H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 163.0, 148.5 (q, J = 28.1 Hz), 121.4 (q, J = 275.6 Hz), 115.0, 114.4, 106.6 (q, J = 3.8 Hz). **^{19}F NMR** (376 MHz, $(CD_3)_2SO$) δ -63.3. **IR** (neat, cm^{-1}) 2920, 2772, 1650, 1565, 1398, 1258, 1032, 848, 777. **EA**: Anal. Calcd for $C_6H_3F_3NBrO$: C, 29.78; H, 1.25; N, 5.79. Found: C, 30.29; H, 1.30; N, 5.65. **Note:** >10:1 site-selectivity is observed through analysis of the crude reaction mixture by ^{1}H NMR spectroscopy.

(b) Streamlined route to hydroxylated pyridine 2-67

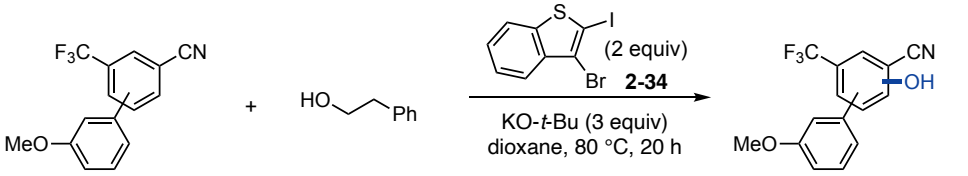


2-(trifluoromethyl)-6-(4-(trifluoromethyl)phenyl)pyridin-4(1*H*)-one (2-67)

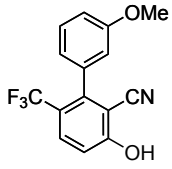


The title product was prepared according to the general procedure for the C–H hydroxylation of *N*-heteroarenes using 2-(trifluoromethyl)-6-(4-(trifluoromethyl)phenyl)pyridine (291.2 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), 18-crown-6 (792.4 mg, 3 mmol, 3 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous THF (4.0 mL). The general *N*-heteroarene isolation procedure 3 was followed by silica gel chromatography (1% Et_3N in CH_2Cl_2 to 1% Et_3N in 5% MeOH/CH_2Cl_2) provided a yellow oil with residual impurities. This oil was further purified *via* silica gel chromatography (100% EtOAc) to afford the pure title compound as a white solid (175.9 mg, 0.57 mmol, 57% yield). **Mp**: 145-148 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) 11.73 (br s, 1H), 8.25 (d, *J* = 8.2 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 2.1 Hz, 1H). **^{13}C NMR** (101 MHz, CD_3OD) δ 168.1, 159.1, 150.7 (q, *J* = 34.3 Hz), 143.0, 132.3 (q, *J* = 32.6 Hz), 128.6, 126.6 (q, *J* = 3.7 Hz), 125.7 (q, *J* = 271.2 Hz), 111.7, 108.8 (q, *J* = 2.8 Hz). **^{19}F NMR** (376 MHz, CD_3OD) δ -61.1, -66.8. The spectroscopic data is consistent with a previous report.[23]

(c) Synthesis of biaryl phenol isomers *via* C–H hydroxylation.



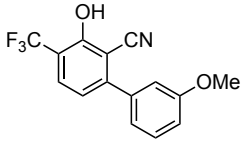
3-hydroxy-3'-methoxy-6-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonitrile (2-68)



The title product was prepared according to the general procedure for the C–H hydroxylation of benzenes using 3'-methoxy-6-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonitrile (277.3 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,4-dioxane (4.0 mL). The product was purified *via* the general benzene isolation procedure 5 to yield the title compound as a brown solid (279.0 mg, 0.95 mmol, 95% yield). **Mp**: 105-110 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 7.97 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.75 – 7.66 (m, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.01 (s, 1H), 6.92 (s, 1H), 4.39 (br s, 1H), 3.67 (s, 3H). **^{13}C NMR** (101 MHz, CD_3CN) δ 162.9, 160.1, 147.2 (q, *J* = 2.0 Hz), 138.1, 132.6 (q, *J* = 5.3 Hz), 130.2, 124.7 (q, *J* = 270.7 Hz), 122.2, 121.6 (q, *J* = 31.8 Hz), 116.0, 115.3, 115.1, 114.3, 104.6, 56.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -54.6. **IR** (neat, cm^{-1}) 3223, 2963, 2840, 2237, 1703, 1578, 1491, 1315, 1122, 833. **HRMS** (DART) $[M–H]^-$ calcd. for $[C_{15}H_9F_3NO_2]^-$ = 292.0591, 292.0588 found.

Verification of regioselectivity: A 2D NMR experiments was used to determine the regioselectivity of C–H hydroxylation for **2-68**. Specifically, a Heteronuclear Single Quantum Coherence (HSQC) experiment indicated that hydroxylation does not occur adjacent to the trifluoromethyl group as the ^{1}H NMR signal δ 7.84 (d, *J* = 8.9 Hz, 1H) correlates to a quartet carbon peak δ 132.6 (q, *J* = 5.3 Hz). This supports that the product is not the other isomer 5-hydroxy-3'-methoxy-6-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonitrile, as the ^{1}H NMR signal at δ 7.84 (d, *J* = 8.9 Hz, 1H) would then be expected to correlate with a singlet carbon peak. See spectra in Section A1-14.

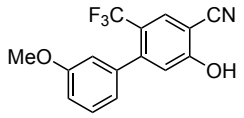
3-hydroxy-3'-methoxy-4-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonitrile (2-69)



The title product was prepared according to the general procedure for the C–H hydroxylation of benzenes using 3'-methoxy-4-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonitrile (277.3 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,4-dioxane (4.0 mL). The product was purified *via* the general benzene isolation procedure 5 to yield the purified title compound as a tan solid (257.3 mg, 0.88 mmol, 88% yield). **Mp**: 172-175 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.15 (dd, *J* = 16.6, 7.3 Hz, 2H), 7.07 (s, 1H), 7.04 (dd, *J* = 8.4, 3.1 Hz, 1H), 6.43 (br s, 1H), 3.88 (s, 3H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 159.2, 158.4, 149.9, 138.4, 131.3 (q, *J* = 4.6 Hz), 129.9, 123.2 (q, *J* = 279.8 Hz), 121.2, 120.8, 118.0 (q, *J* = 31.3 Hz), 115.4, 114.9, 114.2, 102.8, 55.3. **^{19}F NMR** (376 MHz, $(CD_3)_2SO$) δ -61.6. **IR** (neat, cm^{-1}) 3240, 2968, 2360, 2340, 2240, 1573, 1439,1129, 846. **HRMS** (DART) $[M–H]^-$ calcd. for $[C_{15}H_9F_3NO_2]^-$ = 292.0591, 292.0591 found.

Verification of regioselectivity: ^{1}H NMR indicates that hydroxylation occurs at 3-position due to presence of two doublets with 8.4 Hz coupling to each other on the phenol ring. If hydroxylation had alternatively occurred at the 5- or 6- position, then singlet signals or doublet signals with significantly smaller *J*-couplings (W coupling) would be expected in the ^{1}H NMR spectrum.

5-hydroxy-3'-methoxy-2-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile (2-70)

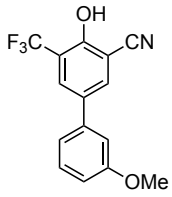


The title product was prepared according to the general procedure for the C–H hydroxylation of benzenes using 3'-methoxy-2-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile (277.3 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,4-dioxane (4.0 mL). The product was purified *via* the general benzene isolation procedure 4, wherein silica gel chromatography (33% EtOAc/hexanes) yielded the title compound as a purple oil (205.4 mg, 0.70 mmol, 70% yield). **^{1}H NMR** (400 MHz, CD_3CN) δ 8.84 (br s, 1H), 7.85 (s, 1H), 7.21 (t, *J* = 8.1 Hz, 1H), 6.86 (dd, *J* = 7.8, 2.1 Hz, 1H), 6.79 (s, 1H), 6.76 (s, 1H), 6.74 (s, 1H), 3.65 (s, 3H). **^{13}C NMR** (101 MHz, CD_3CN) δ 162.2, 160.1, 148.3 (q, *J* = 2.0 Hz), 140.5, 133.1 (q, *J* = 6.2 Hz), 130.2, 124.6 (q, *J* = 270.8 Hz), 121.7, 121.2 (q, *J* = 31.0 Hz), 120.5, 116.1, 115.3 (q, *J* = 1.0), 114.7, 100.0, 56.0. **^{19}F NMR** (376 MHz, CD_3CN) δ -54.2. **IR** (neat, cm^{-1}) 3231, 2942, 2838, 2237,1697, 1600, 1316, 1121, 782. **HRMS** (DART) $[M–H]^-$ calcd. for $[C_{15}H_9F_3NO_2]^-$ = 292.0591, 292.0587 found.

Verification of regioselectivity: A 2D NMR experiments was used to determine the regioselectivity of C–H hydroxylation for **2-70**. Specifically, a Heteronuclear Single Quantum Coherence (HSQC) experiment indicated correlations between each carbon and its attached proton

signals. Based on that information, it was determined that hydroxylation occurs adjacent to the nitrile group as it would be expected that the ^{1}H NMR signal 6.79 (s, 1H) would be significantly more deshielded if the other isomer 2-hydroxy-3'-methoxy-6-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile formed, as ^{1}H NMR signal would then be adjacent to an electron-withdrawing nitrile group. It would also be expected that the ^{1}H NMR signal 6.79 (s, 1H) would be a doublet with a small W coupling if the 2-hydroxy-3'-methoxy-6-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile isomer formed.

4-hydroxy-3'-methoxy-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carbonitrile (2-71)



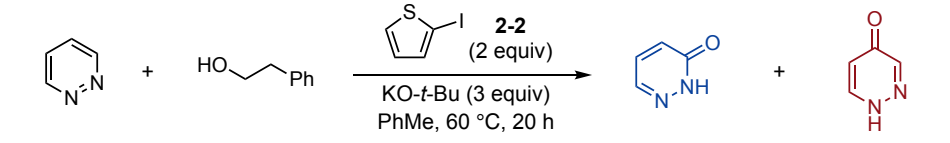
The title product was prepared according to the general procedure for the C–H hydroxylation of benzenes using 3'-methoxy-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carbonitrile (277.3 mg, 1 mmol, 1 equiv), 2-phenethyl alcohol (122.2 mg, 1 mmol, 1 equiv), 3-bromo-2-iodobenzo[*b*]thiophene (678.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (336.6 mg, 3 mmol, 3 equiv), and anhydrous 1,4-dioxane (4.0 mL). The product was purified *via* the general benzene isolation procedure 4, wherein silica gel chromatography (75% hexanes/EtOAc) yielded the title compound as a white solid (124.8 mg, 0.42 mmol, 42% yield). **Mp**: 97-104 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 2.3, 0.7 Hz, 1H), 7.89 (d, *J* = 2.3 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.08 (ddd, *J* = 7.7, 1.8, 0.9 Hz, 1H), 7.01 (t, *J* = 2.1 Hz, 1H), 6.96 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.53 (br s, 1H), 3.88 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.4, 155.8, 138.9, 134.7, 134.6, 130.8 (q, *J* = 4.7 Hz), 130.5, 123.0 (q, *J* = 274.0 Hz), 119.3, 119.2 (q, *J* = 31.9 Hz), 115.0, 113.8, 112.8, 102.8, 55.6. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.3. **IR** (neat, cm^{-1}) 3251, 2242, 1579, 1479, 1270, 1167, 1136, 864, 783. **HRMS** (DART) $[M–H]^-$ calcd. for $[C_{15}H_9F_3NO_2]^-$ = 292.0591, 292.0595 found. **Note on reaction regioselectivity:** The indicated product is obtained as major product, although it forms in a 5:1 ratio to another phenol isomer that was not characterized, as detected by crude ^{1}H NMR spectroscopy. The title product was readily separated from the other isomer *via* silica gel chromatography.

Verification of regioselectivity: A 2D NMR experiment was used to determine the regioselectivity of C–H hydroxylation for **2-71**. Specifically, a 2D Nuclear Overhauser Effect Spectroscopy (NOESY) experiment indicated that hydroxylation occurs at the 2-position as the two other singlet signals corresponding to the 2- and 6- positions on the phenol ring have correlation signals with the 2'- and 6'- positions on the anisole aryl ring. See spectra in Section A1-14.

(d) Site-selective C–H Hydroxylation of Pyridazine.

Note: Hydroxylated pyridazines **2-75** and **2-76** are hygroscopic and thus **^{1}H NMR** yields were used to assess the reactions in Figure 3-26.

Selective synthesis of pyridazin-3(2H)-one *via* the C–H hydroxylation protocol:



2-72 (1 equiv) **2-8** (1 equiv) **2-75**, 70% yield **2-76**, 7% yield

selectivity = 10:1

Procedure: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE® , #60910-1) was charged with a magnetic stir bar, pyridazine (20.0 mg, 1 equiv, 0.25 mmol), 2-phenethyl alcohol (30.6 mg, 1 equiv, 0.25 mmol), 2-iodothiophene (105.0 mg, 2 equiv, 0.5 mmol), toluene (0.25 M, 1.0 mL), and KO-*t*-Bu (84.2 mg, 3 equiv, 0.75 mmol) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, placed into a preheated 60 °C aluminum reaction block, stirred for 20 h at 60 °C, and then cooled to rt. 1,3,5-Trimethoxybenzene internal standard was measured into the crude solution (33.2 mg, 0.16 mmol, signal at 6.09 ppm integrated to 6.83 for 0.1 mmol scale reaction). A small aliquot of the reaction solution was then removed and injected into an NMR tube and constituted in $(CD_3)_2SO$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, $(CD_3)_2SO$) was used to determine the yield and selectivity of the crude reaction (70% yield of pyridazin-3(2H)-one and 7% of pyridazin-4(1H)-one by ^{1}H NMR, shown below). Finally, to confirm the identity of the major product, the crude reaction solution was subjected to purification *via* a preparatory thin layer chromatography plate (6% MeOH/DCM) to provide pyridazin-3(2H)-one. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 13.05 (br s, 1H), 7.85 (d, J = 3.6 Hz, 1H), 7.38 (dd, J = 9.6, 3.8 Hz, 1H), 6.87 (d, J = 9.6 Hz, 1H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 161.0, 136.8, 132.9, 129.7. The spectroscopic data is consistent with a previous report.[24]

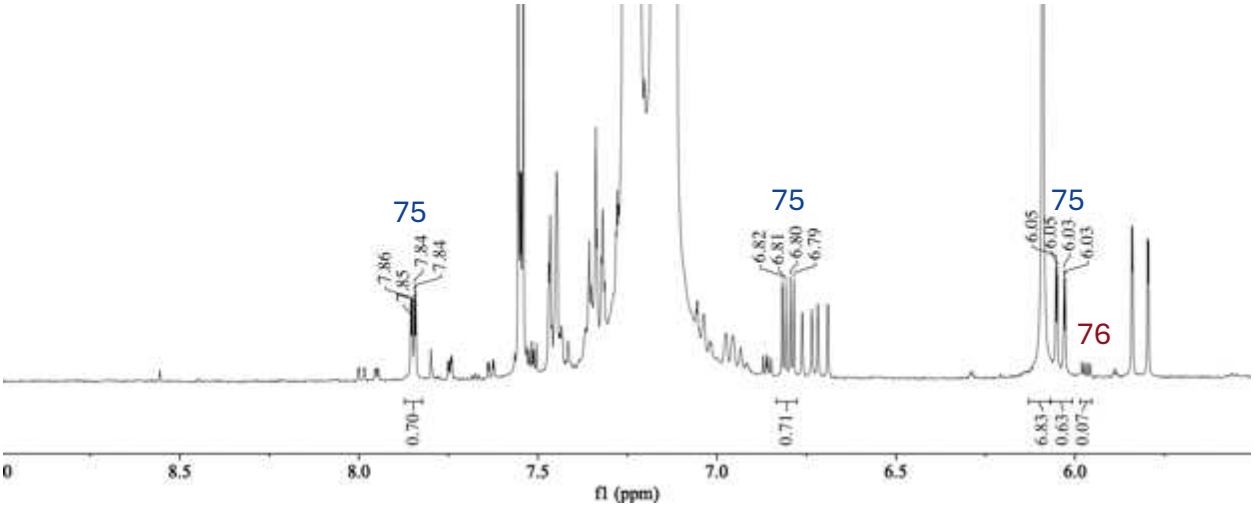
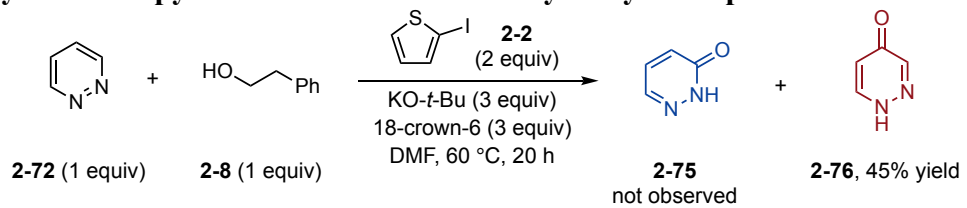


Figure A1-23. Partial ^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$) of the crude reaction solution of the C–H hydroxylation of pyridazine using toluene as the solvent.

Selective synthesis of pyridazin-4-ol *via* the C–H hydroxylation protocol:



Procedure: An identical procedure was used from the above experiment (Selective synthesis of pyridazin-3(2H)-one via the C–H hydroxylation protocol) except dimethylformamide was used as solvent in place of toluene and 18-crown-6 was used as an additive (198.2 mg, 3 equiv, 0.75 mmol).

1,3,5-Trimethoxybenzene internal standard was measured into the crude solution (27.8 mg, 0.13 mmol, signal at 6.09 ppm integrated to 4.95 for 0.1 mmol scale reaction). A small aliquot of the reaction solution was then removed and injected into an NMR tube and constituted in $(CD_3)_2SO$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, $(CD_3)_2SO$) was used to determine the yield and selectivity of the crude reaction (45% yield of pyridazin-4-ol and 0% of pyridazin-3-ol by ^1H NMR, shown below). To confirm the identity of the product, the crude reaction solution was subjected to purification *via* a preparatory thin layer chromatography plate (12% MeOH/DCM) to provide pyridazin-4-ol with some minor impurities. The ^1H and ^{13}C NMR spectra of the partially purified product were included in the Section A1-14 to support product formation. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 13.15 (br s, 1H), 8.17 (d, J = 7.7 Hz, 1H), 7.76 (s, 1H), 6.29 (dd, J = 7.9, 3.1 Hz, 1H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 149.5, 140.5, 115.0, 66.4. The spectroscopic data is consistent with a previous report.[25]

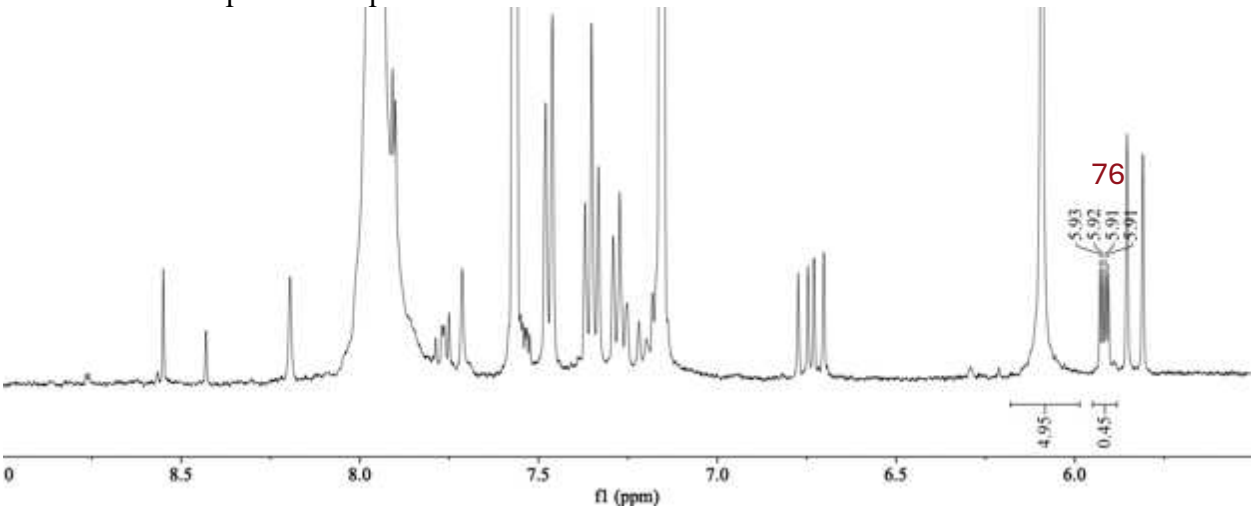


Figure A1-24. Partial ^1H NMR spectrum (400 MHz, $(CD_3)_2SO$) of the crude reaction solution of the C–H hydroxylation of pyridazine using DMF as the solvent.

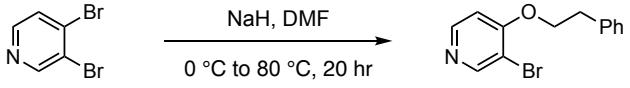
A1.10. Starting Material Syntheses and Characterization

All substrates that are not described below were purchased and used as received. All non-commercial substrates and reagents used are described below.

(a) *N*-Heteroarene starting materials

N,*N*-diethylpyridazine-4-carboxamide,[26] 3-(phenylsulfonyl)pyridine,[26] *N*,*N*-diethylpyridine-3-sulfonamide,[26] 2-(trifluoromethyl)-6-(4-(trifluoromethyl)phenyl)pyridine,[27] *N*,*N*,9-trimethyl-9H-purin-6-amine,[28] and 5-chloro-2,3'-bipyridine[26] were prepared according to reported procedures. Other heteroarenes shown in this report were prepared using the following procedures.

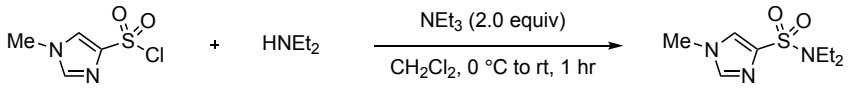
3-bromo-4-phenethoxypyridine (2-6)



2-6, 45% yield

Procedure: An oven-dried 25 mL round-bottom flask was charged with a magnetic stir bar, 2-phenethyl alcohol (458.2 mg, 3.75 mmol, 1.5 equiv) and anhydrous DMF (10 mL). The solution was cooled to 0 °C using an ice water bath, then NaH (60% dispersion in mineral oil, 150.0 mg, 3.75 mmol, 1.5 equiv) was added slowly in small portions. The solution was warmed to rt and stirred for 30 min. 3,4-Dibromopyridine (592.3 mg, 2.5 mmol, 1 equiv) was then slowly added *via* syringe and left under positive pressure with an N_2 filled balloon. The reaction flask was placed into a preheated 80 °C silicon oil bath and stirred for 20 h behind a blast shield. ***Warning:*** this reaction was conducted behind a blast shield as an explosion hazard is associated with heated solutions of DMF and NaH.[29] The reaction solution was cooled to rt, quenched slowly with H_2O (10 mL) and poured into a separatory funnel containing H_2O (20 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo.* The crude reaction mixture was then purified *via* silica gel flash chromatography (30% EtOAc/hexanes) to yield the title compound as a clear oil (310.0 mg, 1.1 mmol, 45% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.32 (d, *J* = 5.6 Hz, 1H), 7.32 (d, *J* = 4.4 Hz, 4H), 7.29 – 7.19 (m, 1H), 6.73 (d, *J* = 5.6 Hz, 1H), 4.24 (t, *J* = 6.8 Hz, 2H), 3.15 (t, *J* = 6.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.1, 152.7, 152.3, 150.1, 149.9, 137.4, 128.6, 129.0, 128.4, 69.7, 35.4. **IR** (neat, cm^{-1}) 3852, 3735, 3628, 2362, 1733, 1684, 1558, 1521, 1507. **HRMS** (ESI) $[M+NH_4]^+$ calcd. for $[C_{13}H_{16}N_2BrO]^+$ = 294.0441, 294.0441 found.

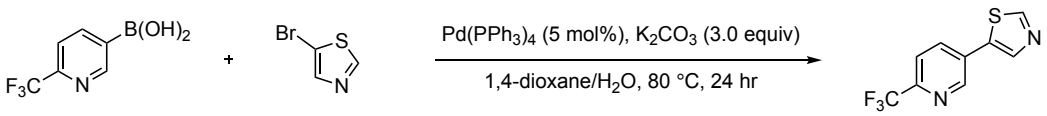
N, N-diethyl-1-methyl-1H-imidazole-4-sulfonamide (1-A6)



(1.0 equiv) (2.0 equiv) **1-A6**, 64% yield

Procedure: An oven-dried 50 mL round bottom flask was charged with a magnetic stir bar, 1-methyl-1H-imidazole-4-sulfonyl chloride (1.0 g, 5.6 mmol, 1 equiv), and anhydrous CH_2Cl_2 (20 mL). The solution was cooled to 0 °C in an ice-bath, then triethylamine (1.6 mL, 11.2 mmol, 2 equiv) and *N,N*-diethylamine (1.2 mL, 11.2 mmol, 2.0 equiv) were added dropwise *via* syringe. The reaction solution was warmed to rt and stirred for 1 h. The solution was then poured into a separatory funnel containing H_2O (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the organic layers were pooled and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (100% EtOAc) yielded the title compound as a white solid (782.2 mg, 3.6 mmol, 64% yield). **Mp:** 62-64 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 1.5 Hz, 1H), 7.39 (d, *J* = 1.5 Hz, 1H), 3.73 (s, 3H), 3.32 (q, *J* = 7.2 Hz, 4H), 1.18 (t, *J* = 7.2 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.1, 139.0, 123.6, 42.8, 34.0, 14.6. **IR** (neat, cm^{-1}) 3112, 2976, 1527, 1381, 1148, 1012, 963, 712, 621. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_8H_{16}N_3O_2S]^+$ = 218.0958, 218.0966 found.

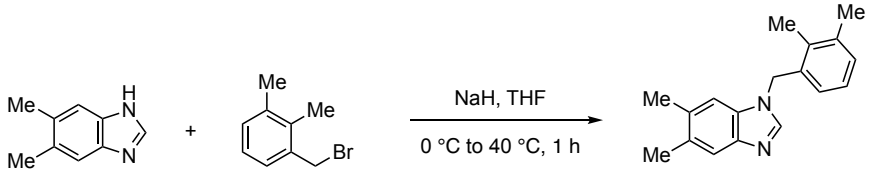
5-(6-(trifluoromethyl)pyridin-3-yl)thiazole (1-A7)



(1.2 equiv) (1.0 equiv) **1-A7**, 86% yield

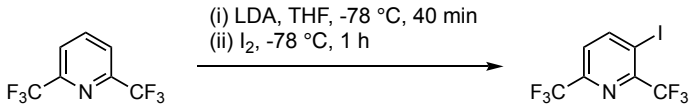
Procedure: Inside an N_2 filled glovebox, a 50 mL round bottom flask was charged with K_2CO_3 (2.53 g, 18.3 mmol, 3 equiv), (6-(trifluoromethyl)pyridin-3-yl)boronic acid (1.49 g, 7.32 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (352.0 mg, 0.3 mmol, 0.05 equiv), 5-bromothiazole (1.0 g, 6.1 mmol, 1 equiv), and 1,4-dioxane (16 mL). The flask was sealed with a rubber septum (Chemglass, #CG-3022-08), removed from the glovebox, and put under positive pressure of N_2 on a manifold Schlenk line. H_2O (8.0 mL) was then added *via* syringe and the flask was inserted into a silicon oil bath preheated to 80 °C. The reaction solution was stirred for 24 h and then cooled to rt. The resulting solution was then poured into a separatory funnel containing H_2O (25 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (25% hexanes/EtOAc) yielded the title compound as a tan solid (1.2 g, 5.2 mmol, 86% yield). **Mp:** 85-87 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 9.27 (s, 1H), 9.14 (s, 1H), 8.61 (s, 1H), 8.39 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.3, 147.9, 147.8 (q, J = 35.2 Hz), 141.4, 135.3, 134.2, 130.4, 121.2 (q, J = 271.9 Hz), 120.9 (q, J = 2.7 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -67.8. **IR** (neat, cm^{-1}) 3154, 2360, 1673, 1635, 1594, 1344, 1130, 515. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_9H_6F_3N_2S]^+$ = 231.0198, 231.0196 found.

1-(2,3-dimethylbenzyl)-5,6-dimethyl-1H-benzo[*d*]imidazole (1-A8)



Procedure: An oven-dried 100 mL round-bottom flask was charged with a magnetic stir bar, 5,6-dimethyl-1H-benzo[*d*]imidazole (1.5 g, 10.26 mmol, 1 equiv) and anhydrous THF (30 mL). The solution was cooled to 0 °C using an ice water bath, then NaH (60% dispersion in mineral oil, 1.0 g, 26 mmol, 2.5 equiv) was added slowly in small portions. 1-(Bromomethyl)-2,3-dimethylbenzene (2.2 g, 11.3 mmol, 1.1 equiv) was then slowly added *via* syringe and left under positive pressure with an N_2 filled balloon. The reaction flask was placed into a preheated 40 °C silicon oil bath and stirred for 1 h. The reaction solution was cooled to rt, quenched slowly with H_2O (10 mL) and poured into a separatory funnel containing H_2O (30 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo.* The crude reaction mixture was then purified *via* silica gel flash chromatography (5% MeOH/DCM) to yield the title compound as a white solid (2.7 g, 10.2 mmol, 100% yield). **Mp:** 91-94 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.59 (s, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.10 (s, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 5.28 (s, 2H), 2.38 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H), 2.19 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.6, 142.4, 137.6, 134.6, 133.3, 132.8, 132.3, 131.2, 130.2, 126.1, 125.9, 120.5, 110.1, 47.5, 20.7, 20.5, 20.4, 14.9. **IR** (neat, cm^{-1}) 2921, 2852, 1493, 1365, 1215, 1004, 844, 761. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{18}H_{21}N_2]^+$ = 265.1699, 265.1696 found.

3-iodo-2,6-bis(trifluoromethyl)pyridine (2-53)

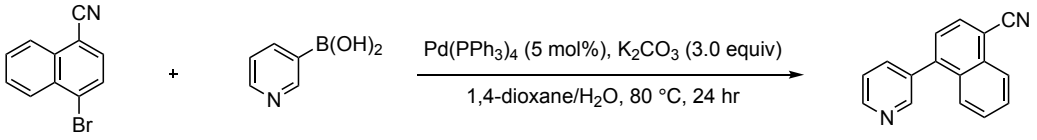


Procedure: An oven-dried 100 mL round bottom flask was charged with a magnetic stir bar, sealed with a red septum stopper (Chemglass, Product #CG-3022-08). The flask was evacuated and backfilled three times with N_2, and left under positive pressure of N_2 on a manifold Schlenk line then diisopropylamine (1.44 mL, 10.2 mmol, 1.1 equiv) and anhydrous THF (32.0 mL) were added *via* syringe. The solution was cooled to -78 °C using a dry ice/acetone bath, then *n*-BuLi (1.6 M in hexanes, 5.84 mL, 9.3 mmol, 1.0 equiv) was added *via* syringe and the solution was stirred for 20 min. 2,6-Bis(trifluoromethyl)pyridine (2.00 g, 9.3 mmol, 1.0 equiv) constituted in 52 mL of anhydrous THF was then added dropwise *via* syringe. The solution was stirred for 20 min at -78 °C and then iodine (2.60 g, 10.2 mmol, 1.1 equiv) constituted in 12 mL of anhydrous THF was added dropwise *via* syringe. The reaction solution was stirred for 1 h at -78 °C and then warmed to rt before being transferred to a separatory funnel containing H_2O (40 mL). Na_2SO_3 was added in portions (ca. 500 mg per portion) with agitation until no discernable color change was observed. The aqueous layer was extracted with EtOAc (3 x 40 mL) and the organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (hexanes) yielded the title product as a yellow oil (2.75 g, 7.5 mmol, 81% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.56 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) 151.9, 148.29 (q, J = 254.7 Hz), 148.28 (q, J = 325.9 Hz), 123.8 (q, J = 2.8 Hz), 120.9 (q, J = 273.9 Hz), 120.6 (q, J = 276.8 Hz), 92.4 **^{19}F NMR** (376 MHz, $CDCl_3$) δ -66.01, -67.92. **IR** (neat, cm^{-1}) 1709, 1412, 1337, 1199, 1132, 1011, 846, 648. **EA**: Anal. Calcd for $C_7H_2NIF_6$: C, 24.66; H, 0.59; N, 4.11. Found: C, 24.91; H, 0.61; N, 4.07. **Note on reaction selectivity:** Both iodination at the 4-position and over iodination occur to give 4-iodo-2,6-bis(trifluoromethyl)pyridine and 3,4-diiodo-2,6-bis(trifluoromethyl)pyridine as side products, respectively. These products were detected by crude ^{1}H NMR spectroscopy in a ~7:2:1 ratio of 3-iodo-2,6-bis(trifluoromethyl)pyridine: 4-iodo-2,6-bis(trifluoromethyl)pyridine: 3,4-diiodo-2,6-bis(trifluoromethyl)pyridine). These products were separated from the desired isomer by silica gel chromatography.

(b) Benzene starting materials

2-(2,4-bis(trifluoromethyl)phenyl)pyridine,[30] 2,3',4,5'-tetrakis(trifluoromethyl)-1,1'-biphenyl,[31] 3-cyano-*N*,*N*-diethylbenzamide,[32] 3-((4-methoxyphenyl)thio)benzonitrile,[33] and 2-iodo-1,3-bis(trifluoromethyl)benzene[34] were prepared according to the reported procedures. Other benzenes shown in this report were prepared using the following procedures.

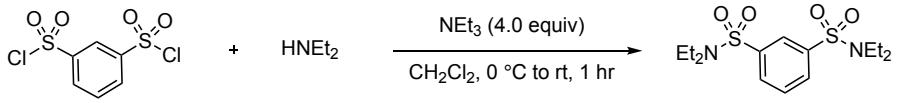
4-(pyridine-3-yl)-1-naphthonitrile (1-A9)



(1.0 equiv) (1.2 equiv) **1-A9**, 76% yield

Procedure: Inside an N_2 filled glovebox, a 50 mL round bottom flask was charged with K_2CO_3 (1.8 g, 12.9 mmol, 3 equiv), pyridine-3-ylboronic acid (636.0 mg, 5.2 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (249.0 mg, 0.2 mmol, 0.05 equiv), 4-bromo-1-naphthonitrile (1.0 g, 4.3 mmol, 1 equiv), and 1,4-dioxane (11 mL). The flask was sealed with a rubber septum (Chemglass, #CG-3022-08), removed from the glovebox, and put under positive pressure of N_2 on a manifold Schlenk line. H_2O (10 mL) was then added *via* syringe and the flask was placed into a silicon oil bath preheated to 80 °C. The reaction solution was stirred 24 h and then cooled to rt. The resulting solution was then poured into a separatory funnel containing H_2O (25 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (50% hexanes/EtOAc) yielded the title compound as a white solid (756.0 mg, 3.3 mmol, 76% yield). **Mp:** 90-93 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 8.75 – 8.72 (m, 2H), 8.33 – 8.17 (m, 2H), 8.03 – 7.92 (m, 1H), 7.92 – 7.83 (m, 2H), 7.79 – 7.70 (m, 1H), 7.71 – 7.65 (m, 1H), 7.66 – 7.58 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.3, 149.7, 142.0, 137.2, 135.0, 133.0, 132.2, 131.5, 128.9, 128.3, 126.6, 126.4, 125.9, 123.5, 117.8, 110.7. **IR** (neat, cm^{-1}) 2218, 1587, 1479, 1388, 1024, 842, 782, 710, 617. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{16}H_{11}N_2]^+$ = 231.0929, 231.0917 found.

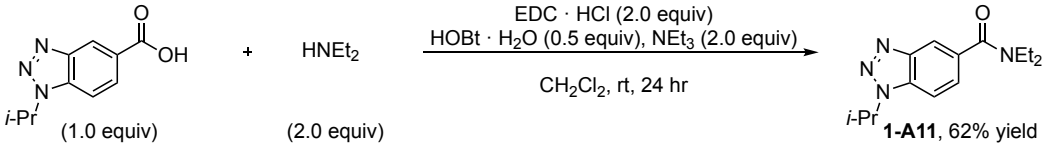
***N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetraethylbenzene-1,3-disulfonamide (1-A10)**



(1.0 equiv) (2.2 equiv) **1-A10**, 62% yield

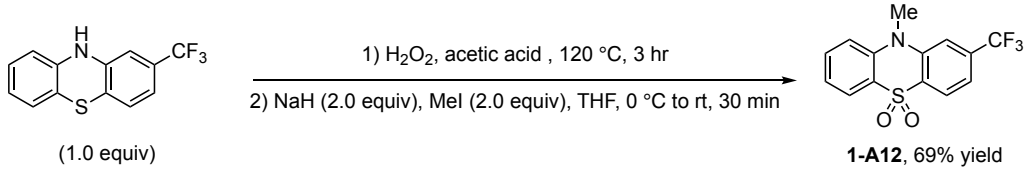
Procedure: An oven-dried 50 mL round bottom flask was charged with a magnetic stir bar, benzene-1,3-disulfonyl dichloride (1.0 g, 3.9 mmol, 1 equiv), and anhydrous CH_2Cl_2 (12 mL). The solution was cooled to 0 °C in an ice-bath, then triethylamine (2.0 mL, 14.5 mmol, 4 equiv) and *N,N*-diethylamine (0.9 mL, 8 mmol, 2.2 equiv) were added dropwise *via* syringe. The reaction solution was warmed to rt and stirred for 1 h. The solution was then poured into a separatory funnel containing H_2O (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the organic layers were pooled and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo* to yield the title compound as an off-white solid (783.0 mg, 2.3 mmol, 62% yield). **Mp:** 93-95 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 (t, *J* = 1.8 Hz, 1H), 7.98 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.64 (t, *J* = 7.9 Hz, 1H), 3.26 (q, *J* = 7.1 Hz, 8H), 1.14 (t, *J* = 7.1 Hz, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.1, 130.4, 130.1, 125.5, 42.3, 14.2. **IR** (neat, cm^{-1}) 2974, 1358, 1333, 1144, 1015, 939, 798, 714. **EA**: Anal. Calcd for $C_{14}H_{24}N_2O_4S_2$: C, 48.25; H, 6.94; N, 8.04. Found: C, 48.20; H, 7.06; N, 7.99.

N,N-diethyl-1-isopropyl-1H-benzo[*d*][1,2,3]triazole-5-carboxamide (1-A11)



Procedure: Open to air, a 50 mL round bottom flask was charged with a magnetic stir bar, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.4 g, 7.3 mmol, 1.5 equiv), 1-hydroxybenzotriazole hydrate (373.1 mg, 2.4 mmol, 0.5 equiv), 1-isopropyl-1*H*-benzo[*d*][1,2,3]triazolets-5-carboxylic acid (1.0 g, 4.9 mmol, 1 equiv), *N,N*-diethylamine (0.8 mL, 7.3 mmol, 1.5 equiv), triethylamine (1.4 mL, 9.7 mmol, 2 equiv), and CH_2Cl_2 (17 mL), in successive order. The solution was stirred 24 h at rt. The solution was then transferred to separatory funnel containing H_2O (50 mL). The organic layer was washed with H_2O (2 x 50 mL) and brine (1 x 30 mL) and then dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (50% hexanes/EtOAc) yielded the title compound as pale-yellow solid (867.0 mg, 3 mmol, 62% yield). **Mp:** 62-63 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 – 8.08 (m, 1H), 7.63 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.55 (dd, *J* = 8.5, 1.4 Hz, 1H), 5.12 (h, *J* = 6.8 Hz, 1H), 3.60 (br s, 2H), 3.36 (br s, 2H), 1.79 (s, 3H), 1.77 (s, 3H), 1.26 (br s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.6, 145.7, 133.1, 132.3, 126.2, 118.0, 110.3, 52.0, 22.3, 14.4. **IR** (neat, cm^{-1}) 2972, 2933, 1620, 1425, 1366, 1231, 1164, 803, 610. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{14}H_{21}N_4O]^+$ = 261.1710, 261.1713 found.

10-methyl-2-(trifluoromethyl)-10H-phenothiazine 5,5-dioxide (1-A12)



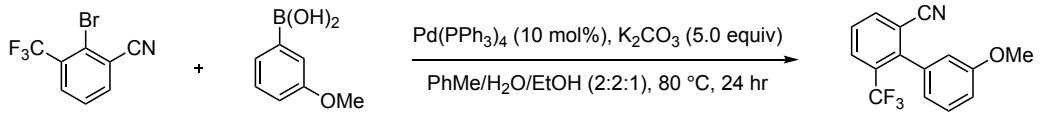
Step 1: 2-(trifluoromethyl)-10H-phenothiazine 5,5-dioxide

Procedure: The title compound was prepared according to a modified literature procedure.[17] An oven-dried 100 mL round-bottom flask was charged with a magnetic stir bar, 2-(trifluoromethyl)-10H-phenothiazine (5.00 g, 18.7 mmol, 1 equiv) and acetic acid (65 mL). The flask was fitted with a reflux condenser and sealed with a rubber septum (Chemglass, #CG-3022-08). Then H_2O_2 (30% balanced in water, 9.55 g, 84 mmol, 4.5 equiv) was added *via* syringe. The flask was placed into a silicon oil bath preheated to 120 °C and the reaction solution was refluxed for 15 min. After 15 min, H_2O_2 (30% balanced in water, 9.55 g, 84 mmol, 4.5 equiv) was added *via* syringe and the reaction was further refluxed for an additional 2.75 hr. The reaction mixture was cooled to rt and added to a slurry of H_2O and crushed ice. The precipitate was collected and washed with water to afford the title compound as an orange solid (4.35 g, 14.5 mmol, 78% yield). **Mp:** 265-267 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 11.28 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 9.3 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.45 – 7.25 (m, 2H). **^{13}C NMR** (101 MHz, $(CD_3)_2SO$) δ 138.4, 137.7, 133.8, 132.9 (q, *J* = 32.2 Hz), 124.6, 123.4, 122.6, 122.4, 121.9, 129.8, 117.4, 117.2 (q, *J* = 3.4 Hz), 114.27 (q, *J* = 4.0 Hz). **^{19}F NMR** (376 MHz, $(CD_3)_2SO$) δ -61.1. **IR** (neat, cm^{-1}) 3303, 1612, 1536, 1357, 1357, 1270, 1143, 1063, 938. **HRMS** (DART) $[M-H]^-$ calcd. for $[C_{13}H_7F_3NO_2S]^-$ = 298.0155, 298.0153 found.

Step 2: 10-methyl-2-(trifluoromethyl)-10H-phenothiazine 5,5-dioxide (1-A12)

Procedure: An oven-dried 50 mL round-bottom flask was charged with a magnetic stir bar, 2-(trifluoromethyl)-10H-phenothiazine 5,5-dioxide (1.3 g, 4.3 mmol, 1 equiv) and anhydrous THF (17 mL). The solution was cooled to 0 °C using an ice water bath, then NaH (60% dispersion in mineral oil, 191.0 mg, 4.78 mmol, 1.1 equiv) was added slowly in small portions. The solution was warmed to rt and stirred for 30 min. The reaction solution was quenched slowly with H_2O and poured into a separatory funnel containing H_2O (20 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were pooled and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo*. Silica gel chromatography (50% hexanes/EtOAc) yielded the title compound as a yellow solid (1.2 g, 3.8 mmol, 88% yield). **Mp:** 119-120 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 8.22 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.89 (s, 1H), 7.82 (t, *J* = 7.9 Hz, 1H), 7.69 (s, 1H), 7.67 (s, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 3.82 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.9, 141.4, 134.0, 133.2 (q, *J* = 32.3 Hz), 126.1, 124.7, 123.4 (q, *J* = 273.3 Hz), 123.3, 122.8, 122.6, 118.1 (q, *J* = 3.7 Hz), 117.2, 114.2 (q, *J* = 4.0 Hz), 36.0. **^{19}F NMR** (376 MHz, $(CD_3)_2SO$) δ -60.4. **IR** (neat, cm^{-1}) 3318, 1733, 1581, 1441, 1256, 1123, 1071, 733, 642. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{14}H_{11}F_3NO_2S]^+$ = 298.0155, 298.0153 found.

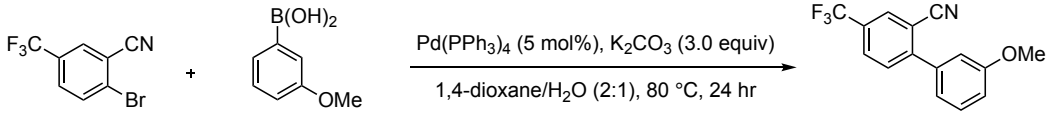
3'-methoxy-6-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonitrile (1-A13)



(1.0 equiv) (1.2 equiv) **1-A13**, 74% yield

Procedure: Inside an N_2 filled glovebox, a 50 mL round bottom flask was charged with K_2CO_3 (2.7 g, 20 mmol, 5 equiv), (3-methoxyphenyl)boronic acid (729.0 mg, 4.8 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (462.0 mg, 0.4 mmol, 0.10 equiv), 2-bromo-3-(trifluoromethyl)benzonitrile (1.0 g, 4 mmol, 1 equiv), toluene (6.5 mL), and ethyl alcohol (3.3 mL). The flask was sealed with a rubber septum (Chemglass, #CG-3022-08), removed from the glovebox, and put under positive pressure of N_2 on a manifold Schlenk line. H_2O (6.5 mL) was then added *via* syringe and the flask was placed into a silicon oil bath preheated to 80 °C. The reaction solution was stirred 24 h and then cooled to rt. The resulting solution was then poured into a separatory funnel containing H_2O (25 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (11% EtOAc/hexanes eluent) yielded the title compound as a yellow solid (825.3 mg, 2.98 mmol, 74% yield). **Mp:** 35-37 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.61 (td, *J* = 8.0, 0.8 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.02 (dd, *J* = 8.5, 0.8 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.84 (s, 1H), 3.84 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.2, 144.9 (q, *J* = 1.9 Hz), 136.3, 135.9, 130.5 (q, *J* = 30.9 Hz), 130.1 (q, *J* = 5.1 Hz), 129.4, 128.4, 123.1 (q, *J* = 273.5 Hz), 121.5 (q, *J* = 1.2 Hz), 116.8, 116.2, 115.0 (q, *J* = 1.2), 114.8, 55.4. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -57.7. **IR** (neat, cm^{-1}) 3096, 3004, 2840, 2359, 2235, 1610, 1458, 1323, 1170, 1019, 883. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{15}H_{11}F_3NO]^+$ = 278.0787, 278.0785 found.

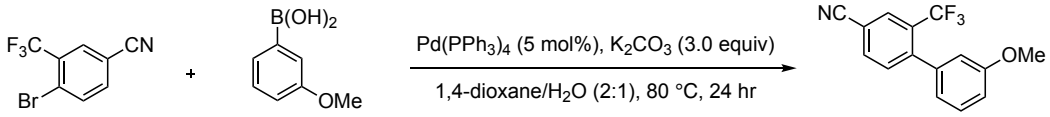
3'-methoxy-4-(trifluoromethyl)-[1,1'-biphenyl]-2-carbonitrile (1-A14)



(1.0 equiv) (1.2 equiv) **1-A14**, 43% yield

Procedure: Inside an N_2 filled glovebox, a 50 mL round bottom flask was charged with K_2CO_3 (3.32 g, 24 mmol, 3 equiv), (3-methoxyphenyl)boronic acid (1.59 g, 9.6 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (462.2 mg, 0.4 mmol, 0.05 equiv), 2-bromo-5-(trifluoromethyl)benzonitrile (2.0 g, 8 mmol, 1 equiv), and 1,4-dioxane (21 mL). The flask was sealed with a rubber septum (Chemglass, #CG-3022-08), removed from the glovebox, and put under positive pressure of N_2 on a manifold Schlenk line. H_2O (11 mL) was then added *via* syringe and the flask was placed into a silicon oil bath preheated to 80 °C. The reaction solution was stirred 24 h and then cooled to rt. The resulting solution was then poured into a separatory funnel containing H_2O (25 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (14% EtOAc/hexanes) yielded the title compound as a white solid (960.2 mg, 3.46 mmol, 43% yield). **Mp:** 60-63 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.81 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.07 (ddd, *J* = 7.6, 1.7, 0.9 Hz, 1H), 7.02 (t, *J* = 2.1 Hz, 1H), 6.97 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 3.81 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.0, 148.8, 138.1, 130.9, 130.8 (q, *J* = 3.8 Hz), 130.4 (q, *J* = 33.1 Hz), 130.2, 129.5 (q, *J* = 3.8 Hz), 123.2 (q, *J* = 273.1 Hz), 121.1, 117.4, 115.3, 114.4, 112.3, 55.5. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.7. **IR** (neat, cm^{-1}) 3240, 2968, 2360, 2340, 2240, 1573, 1439,1129, 846. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{15}H_{11}F_3NO]^+$ = 278.0787, 278.0792 found.

3'-methoxy-2-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile (1-A15)

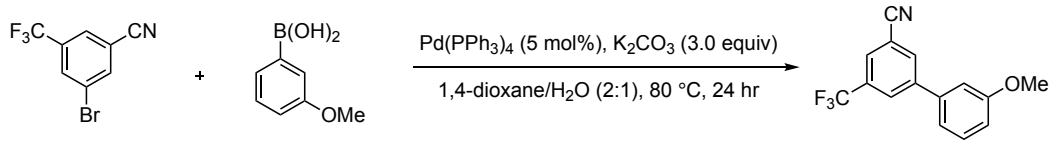


(1.0 equiv) (1.2 equiv) **1-A15**, 78% yield

Procedure: Inside an N_2 filled glovebox, a 50 mL round bottom flask was charged with K_2CO_3 (3.32 g, 24 mmol, 3 equiv), (3-methoxyphenyl)boronic acid (1.46 g, 9.6 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (462.2 mg, 0.4 mmol, 0.05 equiv), 4-bromo-3-(trifluoromethyl)benzonitrile (2.0 g, 8 mmol, 1 equiv), and 1,4-dioxane (21 mL). The flask was sealed with a rubber septum (Chemglass, #CG-3022-08), removed from the glovebox, and put under positive pressure of N_2 on a manifold Schlenk line. H_2O (11 mL) was then added *via* syringe and the flask was placed into a silicon oil bath preheated to 80 °C. The reaction solution was stirred 24 h and then cooled to rt. The resulting solution was then poured into a separatory funnel containing H_2O (25 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (11% EtOAc/hexanes) yielded the title compound as a yellow solid (1.72 g, 6.20 mmol, 78% yield). **Mp:** 44-46 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = Hz, 1H), 7.85 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.35 (t, *J* = 8.3 Hz, 1H), 6.99 (ddd, *J* = 8.4, 2.6, 1.0 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.84 (m, 1H), 3.83 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ

159.2, 146.0 (q, J = 2.0 Hz), 139.2, 135.7, 133.2, 130.1 (q, J = 6.0 Hz), 129.9 (q, J = 31.3 Hz), 129.3, 123.0 (q, J = 273.6 Hz), 121.0 (q, J = 1.4 Hz), 117.6, 114.5 (q, J = 1.5 Hz), 114.2, 112.0, 55.4. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -57.3. **IR** (neat, cm^{-1}) 2968, 2360, 2341, 2234, 1599, 1481, 1463, 1315, 1284, 1170, 1043, 889. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{15}H_{11}F_3NO]^+$ = 278.0787, 278.0787 found.

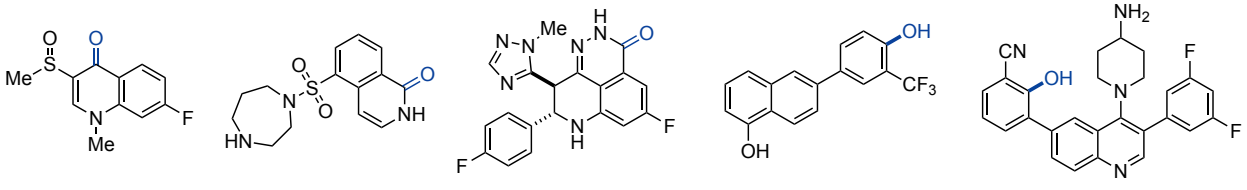
3'-methoxy-5-(trifluoromethyl)-[1,1'-biphenyl]-3-carbonitrile (1-A16)



(1.0 equiv) (1.2 equiv) **1-A16**, 9 % yield

Procedure: Inside an N_2 filled glovebox, a 50 mL round bottom flask was charged with K_2CO_3 (3.32 g, 24 mmol, 3 equiv), (3-methoxyphenyl)boronic acid (1.46 g, 9.6 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (462.2 mg, 0.4 mmol, 0.05 equiv), 3-bromo-5-(trifluoromethyl)benzonitrile (2.0 g, 8 mmol, 1 equiv), and 1,4-dioxane (21 mL). The flask was sealed with a rubber septum (Chemglass, #CG-3022-08), removed from the glovebox, and put under positive pressure of N_2 on a manifold Schlenk line. H_2O (11 mL) was then added *via* syringe and the flask was placed into a silicon oil bath preheated to 80 °C. The reaction solution was stirred 24 h and then cooled to rt. The resulting solution was then poured into a separatory funnel containing H_2O (25 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (10% EtOAc/hexanes) yielded the title compound as a white solid (198.8 mg, 0.72 mmol, 9% yield). **Mp:** 45-47 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (s, 2H), 7.88 (s, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.15 (ddd, J = 7.6, 1.8, 0.9 Hz, 1H), 7.10 – 7.05 (m, 1H), 7.01 (ddd, J = 8.4, 2.6, 1.0 Hz, 1H), 3.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.5, 143.7, 138.9, 133.9, 132.6 (q, J = 34.3 Hz), 130.6, 128.2 (q, J = 3.8 Hz), 127.5 (q, J = 3.8 Hz), 123.1 (q, J = 273.6 Hz), 119.6, 117.5, 114.6, 114.1, 113.1, 55.6. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.9. **IR** (neat, cm^{-1}) 3675, 2980, 2360, 2340, 1066, 527, 518, 505. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{15}H_{11}F_3NO]^+$ = 278.0787, 278.0787 found.

A1.11. References for Bioactive Compounds in Figure 2-2.



vasodilator[a] *ROCK inhibitor*[b] *anticancer*[c] *17β-HSD2 inhibitor*[d] *sST2 agonist*[e]

Bioactive compounds shown in Figure 2-1 of the manuscript are shown above. For more details and discussions, see the footnotes associated with each molecule below:

[a] (1) Satoh, S.; Utsunomiya, T.; Tsurui, K.; Kobayashi, T.; Ikegaki, I.; Sasaki, Y.; Asano, T. Pharmacological profile of hydroxy fasudil as a selective rho kinase inhibitor on ischemic brain damage. *Life Sci.* **2001**, *69*, 1441–1453. (2) Birch, A. M.; Davies, R. V.; Maclean, L.; Robinson, K. Syntheses of flosequinan: a novel 4-quinolone shown to be useful in congestive heart failure. *J. Chem. Soc., Perkin Trans 1.* **1994**, 387–392.

[b] Chen, M.; Liu, A.; Ouyang, Y.; Haung, Y.; Chao, X.; Pi, R. Fasudil and its analogs: a new powerful weapon in the long war against the central nervous system. *Expert Opin. Investig. Drugs*, **2013**, *50*, 537-550.

[c] Wang, B.; Chu, D.; Feng, Y.; Shen, Y.; Aoyagi-Scharber, M.; Post, L. E. Discovery and Characterization of (8*S*,9*R*)-5-Fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3H-pyrido[4,3,2-de]phthalazin-3-one (BMN 673, Talazoparib), a Novel, Highly Potent, and Orally Efficacious Poly(ADP-ribose) Polymerase-1/2 Inhibitor, as an Anticancer Agent. *J. Med. Chem*. **2015**, *59*, 335–357.

[d] Wetzel, M.; Marchais-Oberwinkler, S.; Perspicace, E.; Möller, G.; Adamski, J.; Hartman, R. W. Introduction of an Electron Withdrawing Group on the Hydroxyphenylnaphthol Scaffold Improves the Potency of 17*β*-Hydroxysteroid Dehydrogenase Type 2 (17*β*-HSD2) Inhibitors. *J. Med. Chem*. **2011**, *54*, 7547-7557.

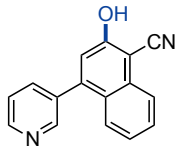
[e] Zhao, J.; Wang, S.; Markison, S.; Kim, S. H.; Han, S.; Chen, M.; Kusnetzow, A. K.; Rico-Bautista, E.; Johns, M.; Luo, R.; Struthers, R. S.; Madan, A.; Zhu, Y.; Betz, S. F. Discovery of Paltusotine (CRN00808), a Potent, Selective, and Orally Bioavailable Non-peptide SST2 Agonist. *ACS Med. Chem. Lett*. **2023**, *14*, 66−74

A1.12. X-Ray Crystallography Experimental Procedure and Data for Compound 2-46 and the Sulfonylated Derivative of Compound 2-47.

Structures were determined for compound **2-46** and the sulfonylated derivative of compound **2-47**. Single crystals were coated with Paratone-N oil and mounted under a cold stream of dinitrogen gas. Single crystal X-ray diffraction data were acquired on a Bruker D8 QUEST diffractometer equipped with a Photon50 CMOS detector and curved graphite monochromator using Mo Kα radiation (λ = 0.71073 Å). Initial lattice parameters were obtained from a least-squares analysis; these parameters were later refined against all data. None of the crystals showed significant decay during data collection. Data were integrated and corrected for Lorentz and polarization effects using Bruker APEX4 software, and semiempirical absorption corrections were applied using SCALE. Space group assignments were based on systematic absences, E statistics, and successful refinement of the structures. Structures were solved using Direct Methods and were refined with the aid of successive Fourier difference maps against all data using the SHELXTL 6.14 software package. Thermal parameters for all non-hydrogen atoms were refined anisotropically. All hydrogen atoms were assigned to ideal positions and refined using a riding model with an isotropic thermal parameter 1.2 times that of the attached carbon atom (1.5 times for methyl hydrogens). Selected bond distances and angles for crystals of compound **2-46** are collected in Tables A6-A12 below. Selected bond distances and angles for crystals of the sulfonylated derivative of compound **2-47** are collected in Tables A13-A19 below. All other metric parameters can be found in the cif files included with the Supporting Information.

Definitions of R_1 and $wR2$.
$R_1 = \mathrm{S}\,||F_o| - |F_c|| \,/\, \mathrm{S}\,|F_o|$; $wR2 = \{\mathrm{S}[w(F_o^2 - F_c^2)^2] \,/\, \mathrm{S}[w(F_o^2)^2]\}^{1/2}$

Data collection details for Compound 2-46



A translucent light-yellow, block-like specimen of $C_{16}H_{10}N_2O_4$, approximate dimensions 0.034 mm x 0.089 mm x 0.102 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a Fixed χ Bruker D8 QUEST system equipped with a Siemens KFF Mo2K- 90 sealed tube (Mo Kα, λ = 0.71073 Å) and a curved graphite monochromator.

The collected frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 38567 reflections to a maximum θ angle of 25.09° (0.85 Å resolution), of which 2147 were independent (completeness = 99.9%, R_{int} = 11.64%, R_{sig} = 3.84%) and 1426 (66.42%) were greater than $2\sigma(F^2)$. The final cell constants of a = 10.8337(3) Å, b = 10.7846(3) Å, c = 11.1588(4) Å, β = 112.060(2)°, volume = 1208.32(7) $Å^3$, are based upon the refinement of the XYZ-centroids of 8256 reflections above 20 σ(I) with 4.469° < 2θ <49.962°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.991 and 0.997. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/n 1, with Z = 4 for the formula unit, $C_{16}H_{10}N_2O_4$. The final anisotropic full-matrix least-squares refinement on F^2 with 175 variables converged at R1 = 4.76%, for the observed data and wR2 = 13.67% for all data. The goodness-of-fit was 1.018. The largest peak in the final difference electron density synthesis was 0.208 $e^-/Å^3$ and the largest hole was -0.185 $e^-/Å^3$ with an RMS deviation of 0.045 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.354 g/cm^3 and F(000), 512 e^-.

Table A1-6. Sample and crystal data for compound 2-46.

Identification code: jb005
Chemical formula: $C_{16}H_{10}N_2O_4$
Formula weight: 246.26 g/mol
Temperature: 149(2) K
Wavelength: 0.71071 Å
Crystal size: 0.102x0.089x0.034 mm
Crystal habit: translucent light-yellow block
Crystal system: monoclinic
Space group: P 1 21/n 1
Unit cell dimensions: a = 10.8337(3) Å α = 90°
b = 10.7846(3) Å β = 112.060(2)°
c = 11.1588(4) Å γ = 90°
Volume: 1208.32(7)
Z: 4
Density (calculated): 1.354 g/cm^3
Absorption coefficient: 0.087 mm^{-1}
F(000): 512

Table A1-7. Data collection and structure refinement for compound 2-46.

Diffractometer: Fixed χ Bruker D8 QUEST
Radiation source: Siemens KFF Mo2K-90 sealed tube (Mo Kα, λ = 0.71073 Å)
Theta range for data collection: 2.73 to 25.09°
Index ranges: -12 <=h<=12, -12<=k<=12, -13<=l<13
Reflections collected: 38567
Independent reflections: 2147 [R(int) = 0.1164]
Coverage of independent reflections: 99.9%
Absorption correction: Multi-Scan
Max. and min. transmission: 0.991,0.997
Structure solution technique: direct methods
Structure solution program: XT, VERSION 2018/2
Refinement method: Full-matrix least-squares on F2, Refined as a 2-component inversion twin
Refinement program: SHELXL-2019/1 (Sheldrick, 2019)
Function minimized: $\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters: 2147/0/175
Goodness-of-fit on F^2 : 1.018
Final R indices: 1406 data; I>2σ(I) R1 = 0.0476, wR2 = 0.1142
all data R1 = 0.0859, wR2 = 0.1367
Weighting scheme: $w=1/[\sigma^2(F_o^2)+(0.0754P)^2+0.1951P]$
where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole: 0.208 and -0.185 eÅ^{-3}
R.M.S. deviation from mean: 0.045 eÅ^{-3}

Table A1-8. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å^2) for compound 2-46.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x/a	y/b	x/c	U(eq)
O1	0.41904(16)	0.69841(15)	0.48135(15)	0.0388(4)
H1A	0.501(3)	0.746(2)	0.512(2)	0.058
N1	0.87680(17)	0.34841(17)	0.97326(17)	0.0339(5)
N2	0.1002(2)	0.5807(2)	0.3490(2)	0.0572(7)
C1	0.9124(2)	0.4286(2)	1.0714(2)	0.0364(6)
H1	0.993543	0.414497	1.142571	0.044
C2	0.8377(2)	0.5308(2)	1.0750(2)	0.0388(6)
H2	0.866737	0.585974	1.146563	0.047
C3	0.7201(2)	0.5510(2)	0.9724(2)	0.0377(6)
H3	0.667406	0.621511	0.971815	0.045
C4	0.7611(2)	0.3684(2)	0.8751(2)	0.0344(5)
H4	0.734039	0.311156	0.805274	0.041
C5	0.6782(2)	0.4685(2)	0.8695(2)	0.0308(5)
C6	0.5520(2)	0.4881(2)	0.75634(19)	0.0293(5)

C7	0.5434(2)	0.5846(2)	0.6746(2)	0.0316(5)
H7	0.617938	0.637845	0.691814	0.038
C8	0.4267(2)	0.6074(2)	0.5651(2)	0.0303(5)
C9	0.3171(2)	0.5325(2)	0.5431(2)	0.0301(5)
C10	0.3200(2)	0.4320(2)	0.6274(2)	0.0310(5)
C11	0.2084(2)	0.3556(2)	0.6092(2)	0.0388(6)
H11	0.126645	0.372332	0.539646	0.047
C12	0.2161(3)	0.2579(2)	0.6898(2)	0.0450(6)
H12	0.140155	0.207227	0.675738	0.054
C13	0.3351(2)	0.2325(2)	0.7927(2)	0.0437(6)
H13	0.340643	0.163377	0.847254	0.052
C14	0.4436(2)	0.3066(2)	0.8155(2)	0.0369(6)
H14	0.523237	0.289553	0.88743	0.044
C15	0.4400(2)	0.4078(2)	0.7344(2)	0.0304(5)
C16	0.1975(2)	0.5585(2)	0.4345(2)	0.0375(6)

Table A1-9. Bond lengths (Å) for compound 2-46.

O1 C8 . 1.336(3)	C7 C8 . 1.412(3)
O1 H1A . 0.97(3)	C7 H7 . 0.950000
N1 C1 . 1.334(3)	C8 C9 . 1.380(3)
N1 C4 . 1.337(3)	C9 C10 . 1.428(3)
N2 C16 . 1.150(3)	C9 C16 . 1.431(3)
C1 C2 . 1.377(3)	C10 C11 . 1.414(3)
C1 H1 . 0.950000	C10 C15 . 1.420(3)
C2 C3 . 1.373(3)	C11 C12 . 1.368(3)
C2 H2 . 0.950000	C11 H11 . 0.950000
C3 C5 . 1.387(3)	C12 C13 . 1.394(3)
C3 H3 . 0.950000	C12 H12 . 0.950000
C4 C5 . 1.390(3)	C13 C14 . 1.364(3)
C4 H4 . 0.950000	C13 H13 . 0.950000
C5 C6 . 1.487(3)	C14 C15 . 1.409(3)
C6 C7 . 1.364(3)	C14 H14 . 0.950000
C6 C15 . 1.435(3)	

Table A1-10. Bond angles (°) for compound 2-46.

C8 O1 H1A . . 109.7(15)	C3 C2 H2 . . 120.900000
C1 N1 C4 . . 117.5(2)	C1 C2 H2 . . 120.900000
N1 C1 C2 . . 123.4(2)	C2 C3 C5 . . 120.1(2)
N1 C1 H1 . . 118.300000	C2 C3 H3 . . 119.900000
C2 C1 H1 . . 118.300000	C5 C3 H3 . . 119.900000
C3 C2 C1 . . 118.3(2)	N1 C4 C5 . . 123.6(2)

N1 C4 H4 . . 118.200000
C5 C4 H4 . . 118.200000
C3 C5 C4 . . 117.1(2)
C3 C5 C6 . . 121.5(2)
C4 C5 C6 . . 121.39(19)
C7 C6 C15 . . 120.38(19)
C7 C6 C5 . . 119.10(19)
C15 C6 C5 . . 120.52(19)
C6 C7 C8 . . 121.7(2)
C6 C7 H7 . . 119.100000
C8 C7 H7 . . 119.100000
O1 C8 C9 . . 118.88(19)
O1 C8 C7 . . 122.24(19)
C9 C8 C7 . . 118.9(2)
C8 C9 C10 . . 121.51(19)
C8 C9 C16 . . 118.7(2)
C10 C9 C16 . . 119.7(2)
C11 C10 C15 . . 118.5(2)
C11 C10 C9 . . 122.8(2)
C15 C10 C9 . . 118.73(19)
C12 C11 C10 . . 121.1(2)
C12 C11 H11 . . 119.400000
C10 C11 H11 . . 119.400000
C11 C12 C13 . . 120.1(2)
C11 C12 H12 . . 119.900000
C13 C12 H12 . . 119.900000
C14 C13 C12 . . 120.3(2)
C14 C13 H13 . . 119.900000
C12 C13 H13 . . 119.900000
C13 C14 C15 . . 121.3(2)
C13 C14 H14 . . 119.300000
C15 C14 H14 . . 119.300000
C14 C15 C10 . . 118.6(2)
C14 C15 C6 . . 122.7(2)
C10 C15 C6 . . 118.7(2)
N2 C16 C9 . . 178.5(3)

Table A1-11. Torsion angles (°) for compound 2-46.

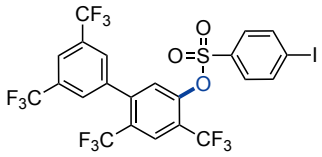
C4 N1 C1 C2 . . . . -1.2(3)
N1 C1 C2 C3 . . . . 0.3(4)
C1 C2 C3 C5 . . . . 1.0(4)
C1 N1 C4 C5 . . . . 1.0(3)
C2 C3 C5 C4 . . . . -1.2(3)
C2 C3 C5 C6 . . . . -179.5(2)
N1 C4 C5 C3 . . . . 0.2(3)
N1 C4 C5 C6 . . . . 178.5(2)
C3 C5 C6 C7 . . . . 68.6(3)
C4 C5 C6 C7 . . . . -109.5(2)
C3 C5 C6 C15 . . . . -110.4(2)
C4 C5 C6 C15 . . . . 71.4(3)
C15 C6 C7 C8 . . . . -1.4(3)
C5 C6 C7 C8 . . . . 179.53(19)
C6 C7 C8 O1 . . . . -177.1(2)
C6 C7 C8 C9 . . . . 2.3(3)
O1 C8 C9 C10 . . . . 178.63(18)
C7 C8 C9 C10 . . . . -0.8(3)
O1 C8 C9 C16 . . . . -2.7(3)
C7 C8 C9 C16 . . . . 177.9(2)
C8 C9 C10 C11 . . . . 178.4(2)
C16 C9 C10 C11 . . . . -0.2(3)
C8 C9 C10 C15 . . . . -1.5(3)
C16 C9 C10 C15 . . . . 179.9(2)
C15 C10 C11 C12 . . . . -2.0(3)
C9 C10 C11 C12 . . . . 178.0(2)
C10 C11 C12 C13 . . . . 0.4(4)
C11 C12 C13 C14 . . . . 1.6(4)
C12 C13 C14 C15 . . . . -1.8(3)
C13 C14 C15 C10 . . . . 0.1(3)
C13 C14 C15 C6 . . . . 179.4(2)
C11 C10 C15 C14 . . . . 1.7(3)
C9 C10 C15 C14 . . . . -178.31(19)
C11 C10 C15 C6 . . . . -177.59(19)
C9 C10 C15 C6 . . . . 2.4(3)
C7 C6 C15 C14 . . . . 179.8(2)
C5 C6 C15 C14 . . . . -1.2(3)
C7 C6 C15 C10 . . . . -0.9(3)
C5 C6 C15 C10 . . . . 178.10(19)

Table A1-12. Anisotropic atomic displacement parameters (Å^2) for compound 2-46.

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{23}
O1	0.0328(9)	0.0357(10)	0.0383(9)	-0.0017(7)	0.0024(7)	0.0046(7)
N1	0.0282(10)	0.0362(11)	0.0334(10)	0.0015(8)	0.0070(8)	0.0022(9)
N2	0.0368(13)	0.0811(18)	0.0433(13)	-0.0031(12)	0.0032(11)	-0.0002(12)
C1	0.0317(12)	0.0420(14)	0.0307(12)	-0.0032(11)	0.0061(10)	0.0030(11)
C2	0.0370(13)	0.0411(14)	0.0319(13)	0.0004(11)	0.0055(10)	-0.0053(10)
C3	0.0351(13)	0.0389(14)	0.0356(13)	0.0032(11)	0.0095(11)	-0.0036(10)
C4	0.0327(13)	0.0347(13)	0.0337(12)	-0.0030(10)	0.0098(10)	-0.0015(10)
C5	0.0286(12)	0.0334(13)	0.0298(12)	-0.0026(9)	0.0102(9)	0.0011(10)
C6	0.0274(12)	0.0291(12)	0.0290(11)	0.0010(9)	0.0080(9)	-0.0033(10)
C7	0.0249(11)	0.0300(12)	0.0363(12)	-0.0016(9)	0.0077(10)	-0.0062(10)
C8	0.0297(12)	0.0300(12)	0.0298(11)	0.0021(9)	0.0095(9)	-0.0012(10)
C9	0.0248(11)	0.0358(13)	0.0269(11)	0.0019(9)	0.0067(9)	-0.0072(10)
C10	0.0306(12)	0.0322(12)	0.0328(12)	-0.0009(10)	0.0147(10)	-0.0084(10)
C11	0.0307(12)	0.0457(15)	0.0413(13)	-0.0058(11)	0.0151(10)	-0.0096(12)
C12	0.0410(14)	0.0494(16)	0.0496(15)	-0.0148(12)	0.0228(12)	-0.0079(13)
C13	0.0490(16)	0.0437(15)	0.0429(14)	-0.0072(12)	0.0225(13)	0.0018(12)
C14	0.0361(13)	0.0394(14)	0.0355(12)	-0.0004(10)	0.0136(10)	0.0004(11)
C15	0.0295(12)	0.0319(13)	0.0311(12)	-0.0003(9)	0.0127(10)	-0.0037(9)
C16	0.0286(13)	0.0493(15)	0.0331(13)	-0.0033(11)	0.0098(11)	-0.0057(11)

b. Crystal Structure Report for sulfonylated derivative of compound 2-47



A clear, colorless needle-like specimen of $C_{22}H_9F_{12}SO_3I$, approximate dimensions 0.023 mm x 0.033 mm x 0.167 mm , was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a Fixed χ Bruker D8 QUEST system equipped with a Siemens KFF Mo2K- 90 sealed tube (Mo Kα, λ = 0.71073 Å) and a curved graphite monochromator.

The collected frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 44435 reflections to a maximum θ angle of 20.81° (0.80 Å resolution), of which 2451 were independent completeness = 99.8%, R_{int} = 10.78%, R_{sig} = 3.42%) and 1832 (74.75%) were greater than $2\sigma(F^2)$. The final cell constants of a = 19.4868(17) Å, b = 4.8407(4) Å, c = 24.927(2) Å, β = 91.269(4)°, volume = 2350.8(3) $Å^3$, are based upon the refinement of the XYZ-centroids of 9881 reflections above 20 σ(I) with 4.456° < 2θ <52.460°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.940 and 0.964.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/c 1, with Z = 4 for the formula unit, $C_{22}H_9F_{12}SO_3I$. The final anisotropic full-matrix least-squares refinement on F^2 with 323 variables converged at R1 = 8.33%, for the observed data and wR2 = 20.47% for all data. The goodness-of-fit was 1.057. The largest peak in the final difference electron density synthesis was 3.697 $e^-/Å^3$ and the largest hole was -1.174 e^-

/Å^3 with an RMS deviation of 0.210 e$^-$/Å^3. On the basis of the final model, the calculated density was 2.001 g/cm^3 and F(000), 1368 e$^-$.

Sample and crystal data for the sulfonylated derivative of compound 2-47.

Identification code: jb008
Chemical formula: $C_{22}H_9F_{12}SO_3I$
Formula weight: 708.25
Temperature: 100(2) K
Wavelength: 0.71071 Å
Crystal size: 0.167x0.033x0.023 mm
Crystal habit: clear, colorless needle
Crystal system: monoclinic
Space group: P 1 21/c 1
Unit cell dimensions: a = 19.4868(17) Å α = 90°
b = 4.8407(4) Å β = 91.269(4)
c = 24.927(2) Å ɣ = 90°
Volume: 2350.8(3)
Z: 4
Density (calculated): 2.001 g/cm^3
Absorption coefficient: 1.572 mm^{-1}
F(000): 1368

Table A1-14. Data collection and structure refinement for the sulfonylated derivative of compound 2-47.

Diffractometer: Fixed χ Bruker D8 QUEST
Radiation source: Siemens KFF Mo2K-90 sealed tube (Mo Kα, λ = 0.71073 Å)
Theta range for data collection: 2.2280 to 26.2300°
Index ranges: -19 <=h<=19, -4<=k<=4, -24<=l<24
Reflections collected: 44435
Independent reflections: 2451 [R(int) = 0.1078]
Coverage of independent reflections: 99.8%
Absorption correction: Multi-Scan
Max. and min. transmission: 0.940, 0.964
Structure solution technique: direct methods
Structure solution program: XT, VERSION 2018/2
Refinement method: Full-matrix least-squares on F2
Refinement program: SHELXL-2019/1 (Sheldrick, 2019)
Function minimized: $\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters: 2451/0/323
Goodness-of-fit on F^2 : 1.057
Final R indices: 1832 data; I>2σ(I) R1 = 0.0833, wR2 = 0.1717
all data R1 = 0.1184, wR2 = 0.2047
Weighting scheme: $w=1/[\sigma^2(F_o^2)+(0.0754P)^2+0.1951P]$

where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole: 3.697 and -1.174 eÅ^{-3}
R.M.S. deviation from mean: 0.210 eÅ^{-3}

Table A1-15. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å^2) for the sulfonylated derivative of compound 2-47.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x/a	y/b	z/c	U(eq)
I1	0.49747(6)	1.3074(3)	0.68676(4)	0.0500(5)
S1	0.3548(2)	0.7264(10)	0.47353(15)	0.0354(12)
F1	0.1094(5)	0.528(2)	0.5812(3)	0.051(3)
F2	0.1819(5)	0.836(2)	0.5619(3)	0.048(3)
F3	0.2176(5)	0.449(2)	0.5933(3)	0.046(3)
F4	0.0187(5)	-0.039(2)	0.4476(3)	0.055(3)
F5	0.0160(4)	0.209(2)	0.3762(3)	0.045(3)
F6	0.0772(4)	-0.158(2)	0.3790(3)	0.043(2)
F7	0.3103(5)	-0.422(2)	0.2873(4)	0.055(3)
F8	0.2723(5)	-0.383(2)	0.2063(4)	0.064(3)
F9	0.3459(5)	-0.098(2)	0.2381(4)	0.061(3)
F10	0.0467(5)	0.545(2)	0.2276(4)	0.058(3)
F11	0.0489(5)	0.165(2)	0.1837(4)	0.050(3)
F12	0.1217(5)	0.482(2)	0.1677(4)	0.055(3)
O1	0.2883(5)	0.595(3)	0.5015(4)	0.046(3)
O2	0.3966(5)	0.514(2)	0.4547(4)	0.039(3)
O3	0.3296(6)	0.931(3)	0.4362(4)	0.045(3)
C1	0.4512(8)	1.130(4)	0.6194(6)	0.0342(17)
C2	0.3819(8)	1.187(4)	0.6048(6)	0.0342(17)
H2	0.355688	1.309713	0.625862	0.041
C3	0.4887(8)	0.935(4)	0.5896(6)	0.0342(17)
H3	0.534372	0.888558	0.600084	0.041
C4	0.3526(8)	1.064(4)	0.5600(6)	0.0342(17)
H4	0.306945	1.108297	0.549015	0.041
C5	0.4594(8)	0.818(4)	0.5467(6)	0.0342(17)
H5	0.485295	0.692203	0.526023	0.041
C6	0.3909(8)	0.875(4)	0.5311(6)	0.0342(17)
C7	0.2316(7)	0.488(4)	0.4738(6)	0.031(4)
C8	0.1733(8)	0.456(3)	0.5036(6)	0.029(4)
C9	0.2340(8)	0.405(4)	0.4201(7)	0.044(5)
H9	0.27374	0.436535	0.399617	0.053
C10	0.1169(8)	0.318(4)	0.4804(6)	0.034(4)

H10	0.076827	0.290789	0.500679	0.04
C11	0.1760(8)	0.275(3)	0.3974(6)	0.030(4)
C12	0.1188(7)	0.223(4)	0.4283(6)	0.034(4)
C13	0.1716(9)	0.563(4)	0.5606(6)	0.035(4)
C14	0.0588(9)	0.062(4)	0.4072(6)	0.044(5)
C15	0.1793(7)	0.202(4)	0.3390(6)	0.034(4)
C16	0.2302(8)	0.013(4)	0.3226(7)	0.038(5)
H16	0.261315	-0.066687	0.348038	0.046
C17	0.1334(8)	0.308(4)	0.3024(6)	0.036(4)
H17	0.098615	0.431624	0.313457	0.044
C18	0.2337(8)	-0.053(4)	0.2682(6)	0.037(4)
C19	0.1380(7)	0.234(4)	0.2483(5)	0.030(4)
C20	0.1869(9)	0.054(4)	0.2313(6)	0.036(4)
H20	0.18875	0.003891	0.194533	0.043
C21	0.2900(8)	-0.233(4)	0.2503(6)	0.041(5)
C22	0.0894(8)	0.351(4)	0.2075(6)	0.038(5)

Table A1-16. Bond lengths (Å) for the sulfonylated derivative of compound 2-47.

O1 C8 . 1.336(3)	C7 C8 . 1.412(3)
O1 H1A . 0.97(3)	C7 H7 . 0.950000
N1 C1 . 1.334(3)	C8 C9 . 1.380(3)
N1 C4 . 1.337(3)	C9 C10 . 1.428(3)
N2 C16 . 1.150(3)	C9 C16 . 1.431(3)
C1 C2 . 1.377(3)	C10 C11 . 1.414(3)
C1 H1 . 0.950000	C10 C15 . 1.420(3)
C2 C3 . 1.373(3)	C11 C12 . 1.368(3)
C2 H2 . 0.950000	C11 H11 . 0.950000
C3 C5 . 1.387(3)	C12 C13 . 1.394(3)
C3 H3 . 0.950000	C12 H12 . 0.950000
C4 C5 . 1.390(3)	C13 C14 . 1.364(3)
C4 H4 . 0.950000	C13 H13 . 0.950000
C5 C6 . 1.487(3)	C14 C15 . 1.409(3)
C6 C7 . 1.364(3)	C14 H14 . 0.950000
C6 C15 . 1.435(3)	

Table A1-17. Bond angles (°) for the sulfonylated derivative of compound 2-47.

C8 O1 H1A . . 109.7(15)	C1 C2 H2 . . 120.900000
C1 N1 C4 . . 117.5(2)	C2 C3 C5 . . 120.1(2)
N1 C1 C2 . . 123.4(2)	C2 C3 H3 . . 119.900000
N1 C1 H1 . . 118.300000	C5 C3 H3 . . 119.900000
C2 C1 H1 . . 118.300000	N1 C4 C5 . . 123.6(2)
C3 C2 C1 . . 118.3(2)	N1 C4 H4 . . 118.200000
C3 C2 H2 . . 120.900000	C5 C4 H4 . . 118.200000

C3 C5 C4 . . 117.1(2)
C3 C5 C6 . . 121.5(2)
C4 C5 C6 . . 121.39(19)
C7 C6 C15 . . 120.38(19)
C7 C6 C5 . . 119.10(19)
C15 C6 C5 . . 120.52(19)
C6 C7 C8 . . 121.7(2)
C6 C7 H7 . . 119.100000
C8 C7 H7 . . 119.100000
O1 C8 C9 . . 118.88(19)
O1 C8 C7 . . 122.24(19)
C9 C8 C7 . . 118.9(2)
C8 C9 C10 . . 121.51(19)
C8 C9 C16 . . 118.7(2)
C10 C9 C16 . . 119.7(2)
C11 C10 C15 . . 118.5(2)
C11 C10 C9 . . 122.8(2)
C15 C10 C9 . . 118.73(19)
C12 C11 C10 . . 121.1(2)
C12 C11 H11 . . 119.400000
C10 C11 H11 . . 119.400000
C11 C12 C13 . . 120.1(2)
C11 C12 H12 . . 119.900000
C13 C12 H12 . . 119.900000
C14 C13 C12 . . 120.3(2)
C14 C13 H13 . . 119.900000
C12 C13 H13 . . 119.900000
C13 C14 C15 . . 121.3(2)
C13 C14 H14 . . 119.300000
C15 C14 H14 . . 119.300000
C14 C15 C10 . . 118.6(2)
C14 C15 C6 . . 122.7(2)
C10 C15 C6 . . 118.7(2)
N2 C16 C9 . . 178.5(3)

Table A1-18. Torsion angles (°) for the sulfonylated derivative of compound 2-47.

C4 N1 C1 C2 . . . . -1.2(3)
N1 C1 C2 C3 . . . . 0.3(4)
C1 C2 C3 C5 . . . . 1.0(4)
C1 N1 C4 C5 . . . . 1.0(3)
C2 C3 C5 C4 . . . . -1.2(3)
C2 C3 C5 C6 . . . . -179.5(2)
N1 C4 C5 C3 . . . . 0.2(3)
N1 C4 C5 C6 . . . . 178.5(2)
C3 C5 C6 C7 . . . . 68.6(3)
C4 C5 C6 C7 . . . . -109.5(2)
C3 C5 C6 C15 . . . . -110.4(2)
C4 C5 C6 C15 . . . . 71.4(3)
C15 C6 C7 C8 . . . . -1.4(3)
C5 C6 C7 C8 . . . . 179.53(19)
C6 C7 C8 O1 . . . . -177.1(2)
C6 C7 C8 C9 . . . . 2.3(3)
O1 C8 C9 C10 . . . . 178.63(18)
C7 C8 C9 C10 . . . . -0.8(3)
O1 C8 C9 C16 . . . . -2.7(3)
C7 C8 C9 C16 . . . . 177.9(2)
C8 C9 C10 C11 . . . . 178.4(2)
C16 C9 C10 C11 . . . . -0.2(3)
C8 C9 C10 C15 . . . . -1.5(3)
C16 C9 C10 C15 . . . . 179.9(2)
C15 C10 C11 C12 . . . . -2.0(3)
C9 C10 C11 C12 . . . . 178.0(2)
C10 C11 C12 C13 . . . . 0.4(4)
C11 C12 C13 C14 . . . . 1.6(4)
C12 C13 C14 C15 . . . . -1.8(3)
C13 C14 C15 C10 . . . . 0.1(3)
C13 C14 C15 C6 . . . . 179.4(2)
C11 C10 C15 C14 . . . . 1.7(3)
C9 C10 C15 C14 . . . . -178.31(19)
C11 C10 C15 C6 . . . . -177.59(19)
C9 C10 C15 C6 . . . . 2.4(3)
C7 C6 C15 C14 . . . . 179.8(2)
C5 C6 C15 C14 . . . . -1.2(3)
C7 C6 C15 C10 . . . . -0.9(3)
C5 C6 C15 C10 . . . . 178.10(19)

Table A1-19. Anisotropic atomic displacement parameters (Å^2) for the sulfonylated derivative of compound 2-47.

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{23}
O1	0.0328(9)	0.0357(10)	0.0383(9)	-0.0017(7)	0.0024(7)	0.0046(7)
N1	0.0282(10)	0.0362(11)	0.0334(10)	0.0015(8)	0.0070(8)	0.0022(9)
N2	0.0368(13)	0.0811(18)	0.0433(13)	-0.0031(12)	0.0032(11)	-0.0002(12)
C1	0.0317(12)	0.0420(14)	0.0307(12)	-0.0032(11)	0.0061(10)	0.0030(11)
C2	0.0370(13)	0.0411(14)	0.0319(13)	0.0004(11)	0.0055(10)	-0.0053(10)
C3	0.0351(13)	0.0389(14)	0.0356(13)	0.0032(11)	0.0095(11)	-0.0036(10)
C4	0.0327(13)	0.0347(13)	0.0337(12)	-0.0030(10)	0.0098(10)	-0.0015(10)
C5	0.0286(12)	0.0334(13)	0.0298(12)	-0.0026(9)	0.0102(9)	0.0011(10)
C6	0.0274(12)	0.0291(12)	0.0290(11)	0.0010(9)	0.0080(9)	-0.0033(10)
C7	0.0249(11)	0.0300(12)	0.0363(12)	-0.0016(9)	0.0077(10)	-0.0062(10)
C8	0.0297(12)	0.0300(12)	0.0298(11)	0.0021(9)	0.0095(9)	-0.0012(10)
C9	0.0248(11)	0.0358(13)	0.0269(11)	0.0019(9)	0.0067(9)	-0.0072(10)
C10	0.0306(12)	0.0322(12)	0.0328(12)	-0.0009(10)	0.0147(10)	-0.0084(10)
C11	0.0307(12)	0.0457(15)	0.0413(13)	-0.0058(11)	0.0151(10)	-0.0096(12)
C12	0.0410(14)	0.0494(16)	0.0496(15)	-0.0148(12)	0.0228(12)	-0.0079(13)
C13	0.0490(16)	0.0437(15)	0.0429(14)	-0.0072(12)	0.0225(13)	0.0018(12)
C14	0.0361(13)	0.0394(14)	0.0355(12)	-0.0004(10)	0.0136(10)	0.0004(11)
C15	0.0295(12)	0.0319(13)	0.0311(12)	-0.0003(9)	0.0127(10)	-0.0037(9)
C16	0.0286(13)	0.0493(15)	0.0331(13)	-0.0033(11)	0.0098(11)	-0.0057(11)

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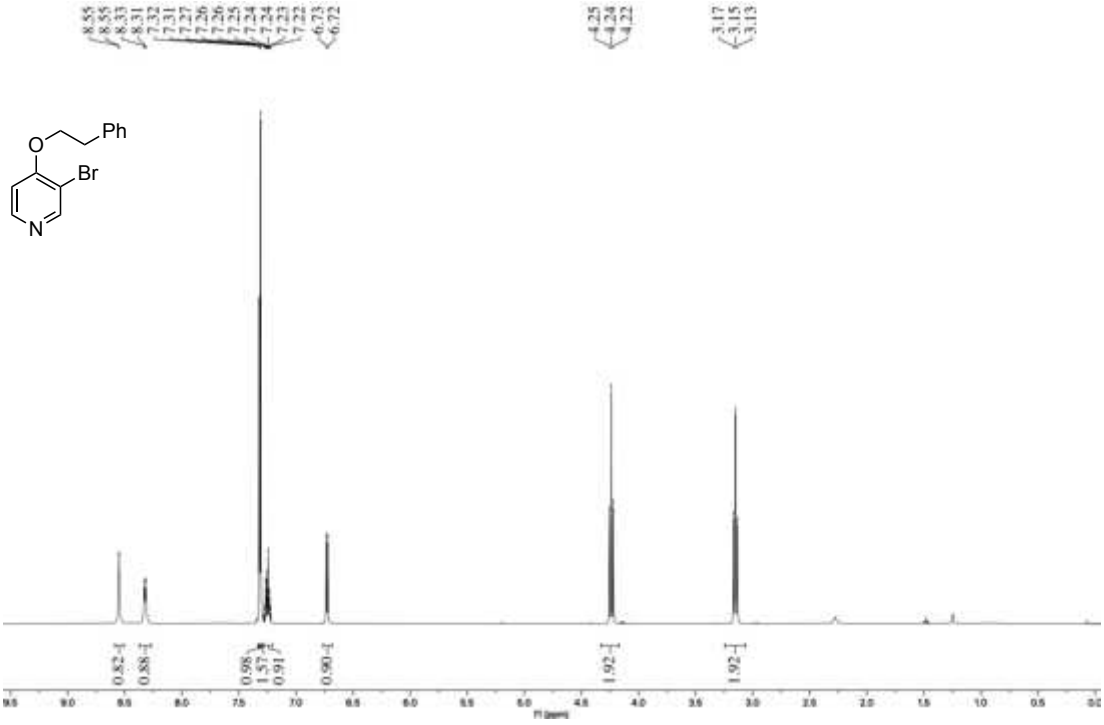
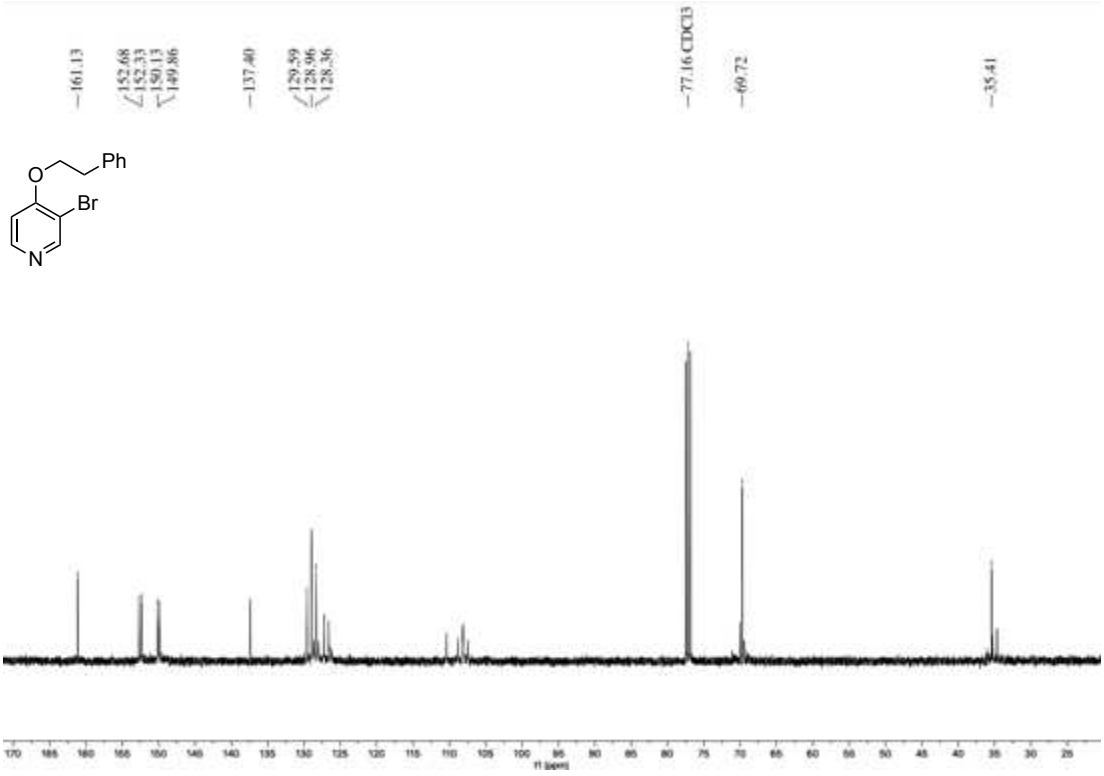
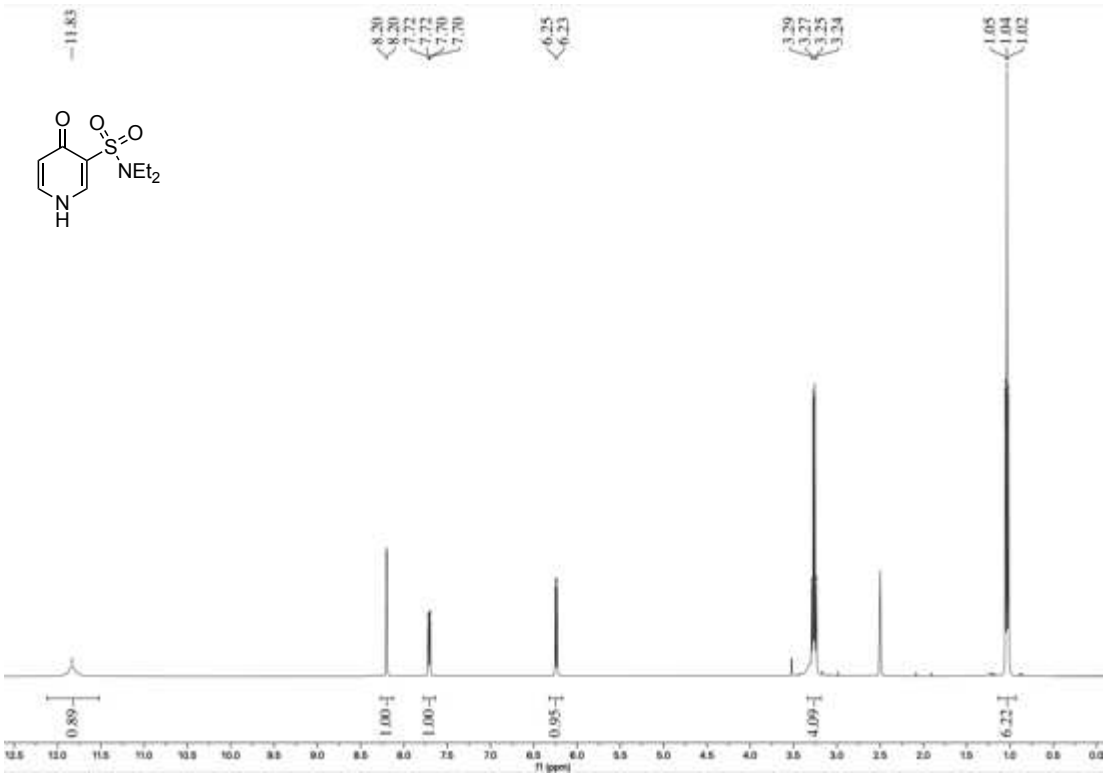
14. NMR Spectra



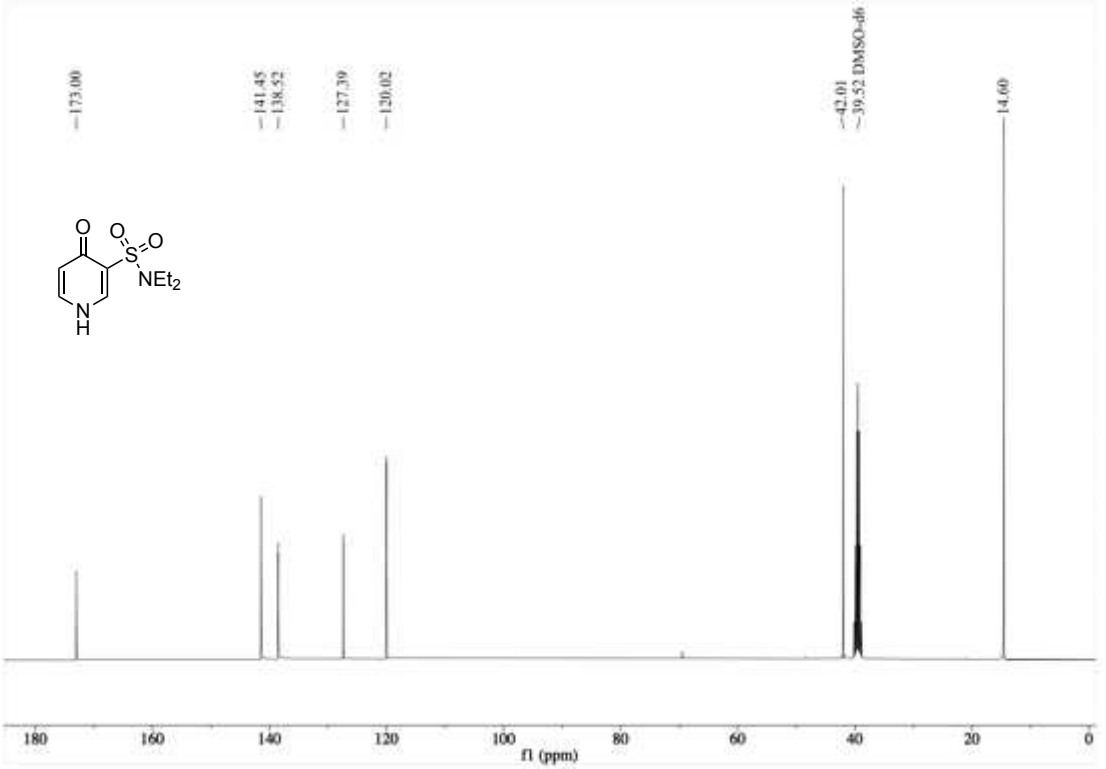
^{1}H NMR spectrum of **2-6** (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of **2-6** (101 MHz, $CDCl_3$)



^{1}H NMR spectrum of **2-11** (400 MHz, $(CD_3)_2SO$)



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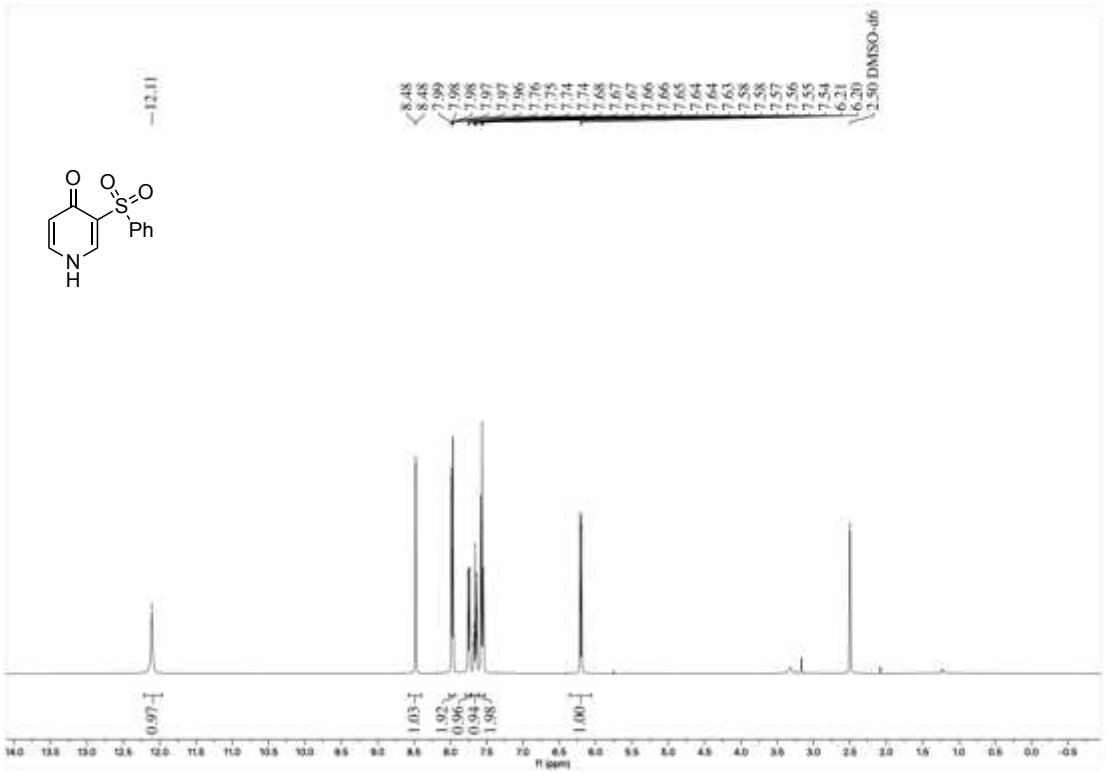

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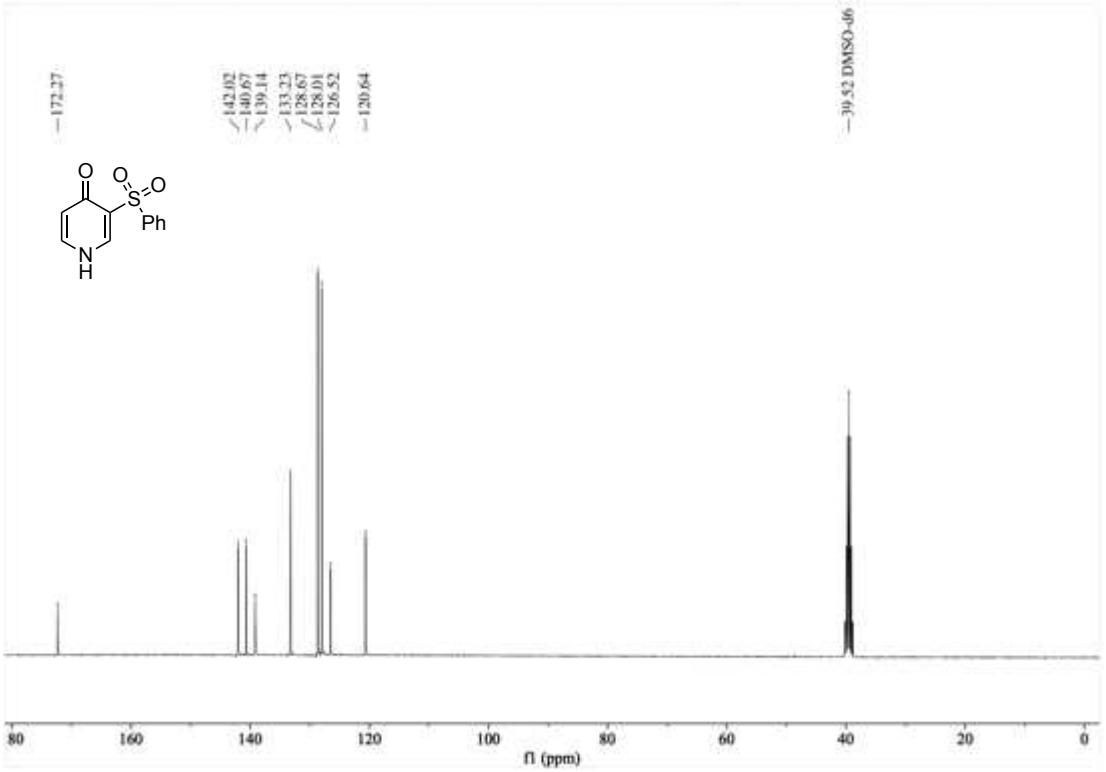
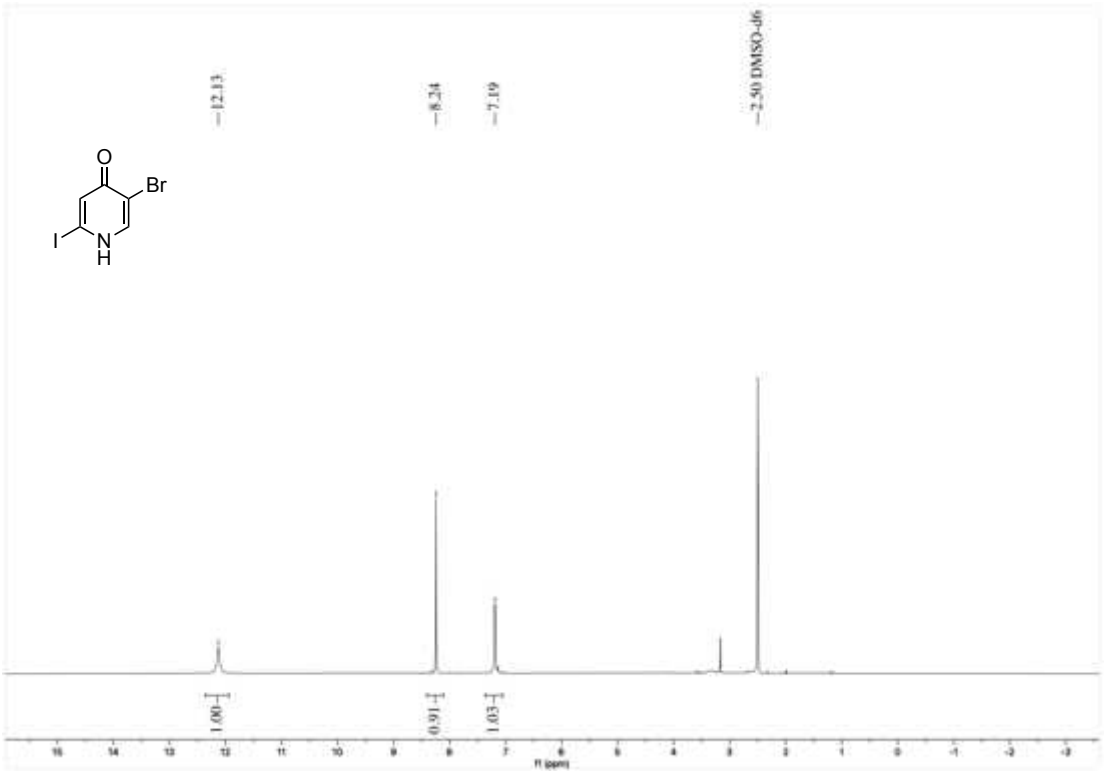


[13]C NMR spectrum of **2-12** (101 MHz, $(CD_3)_2SO$)



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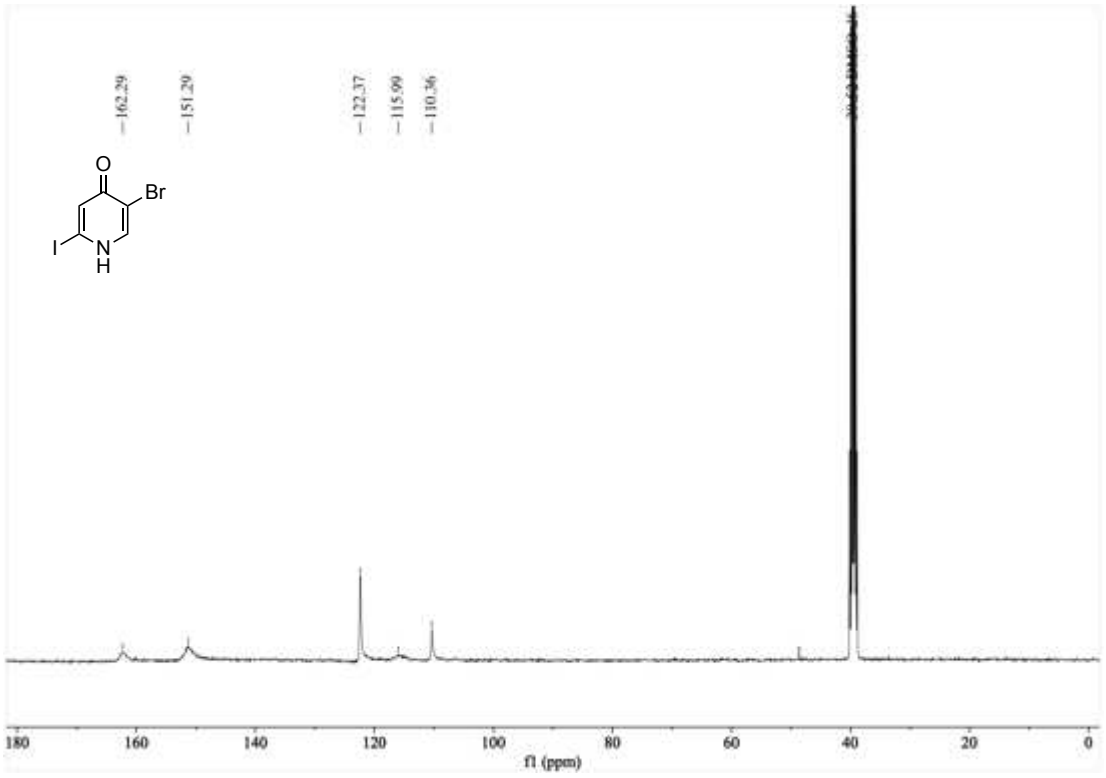

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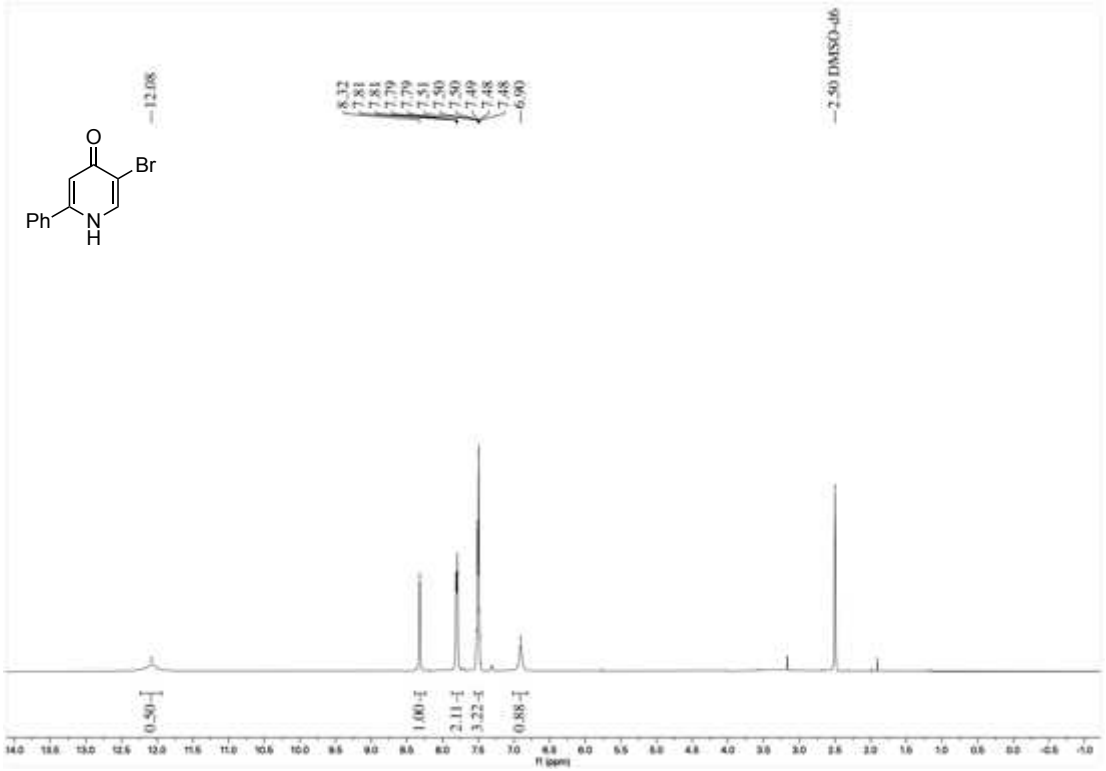

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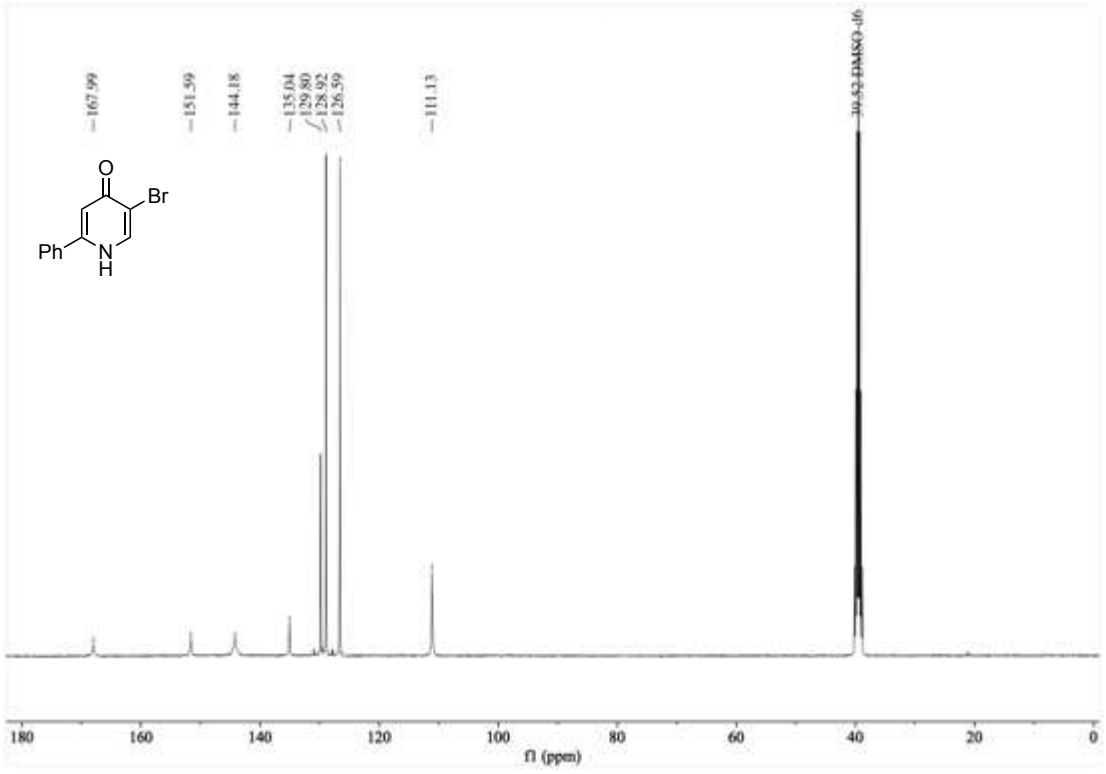

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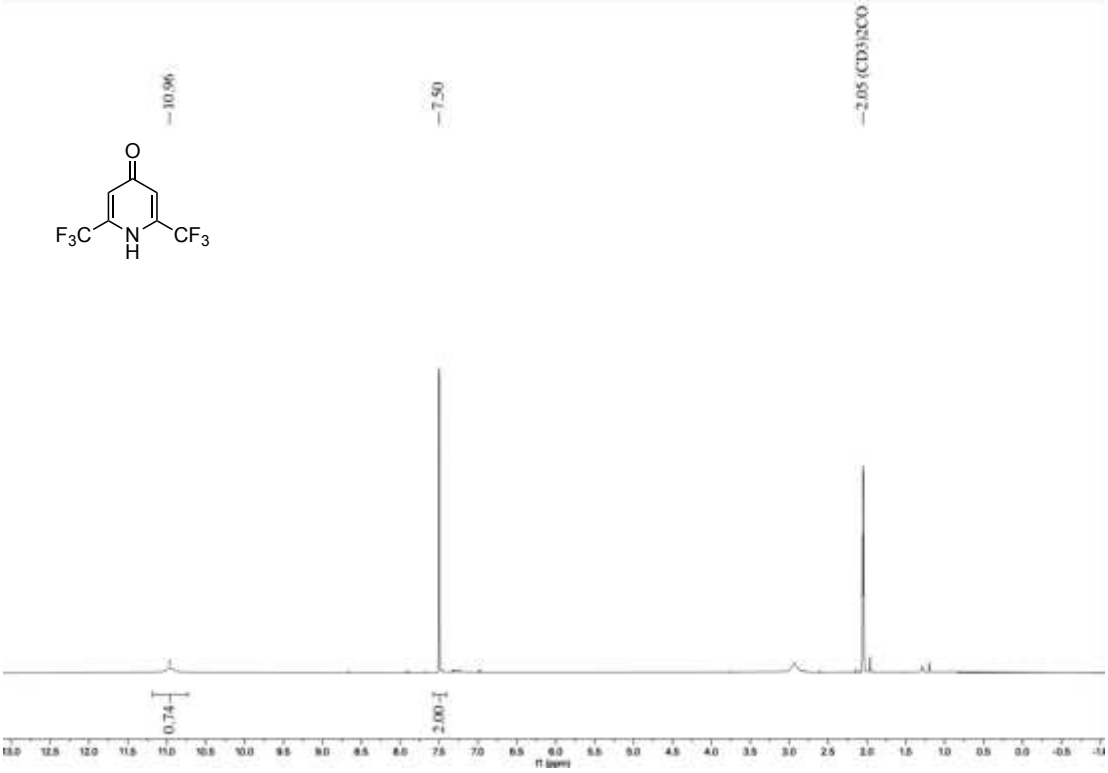

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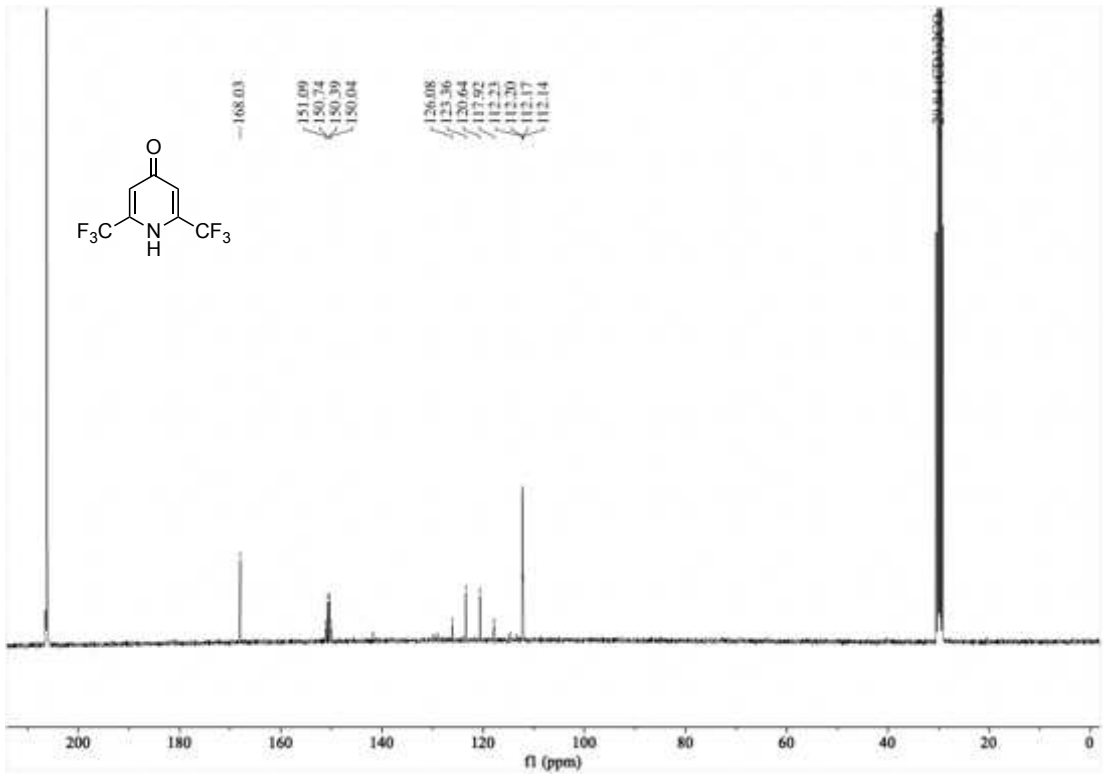

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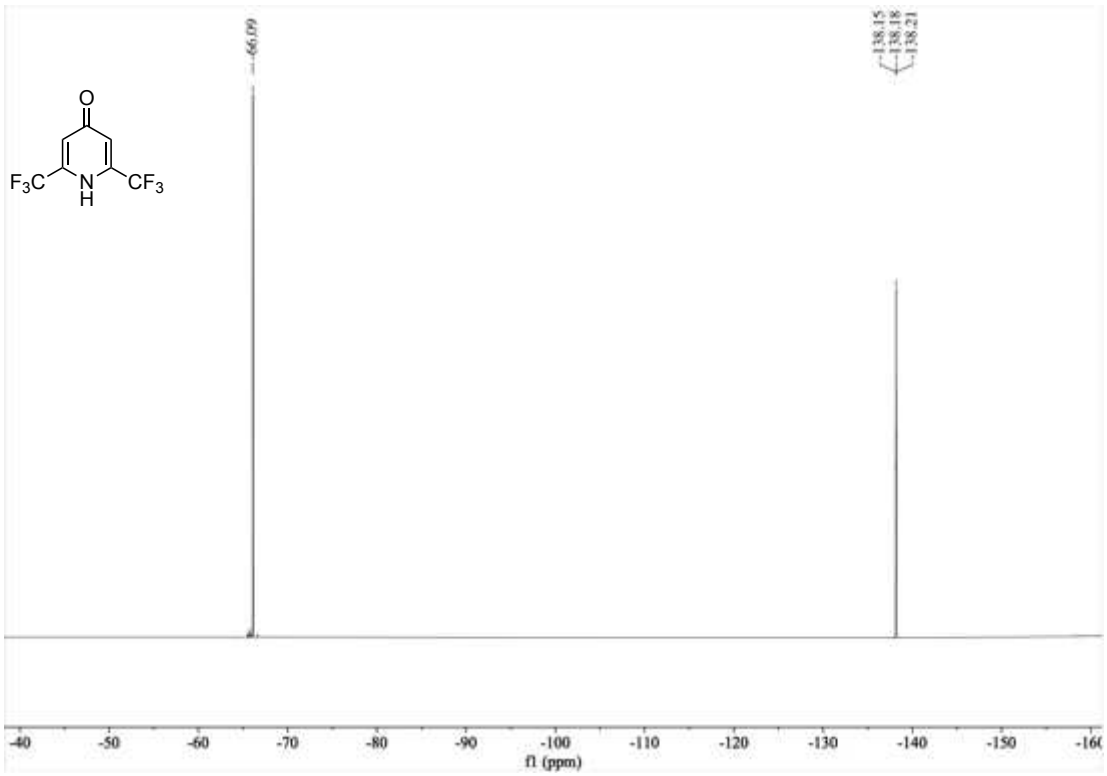
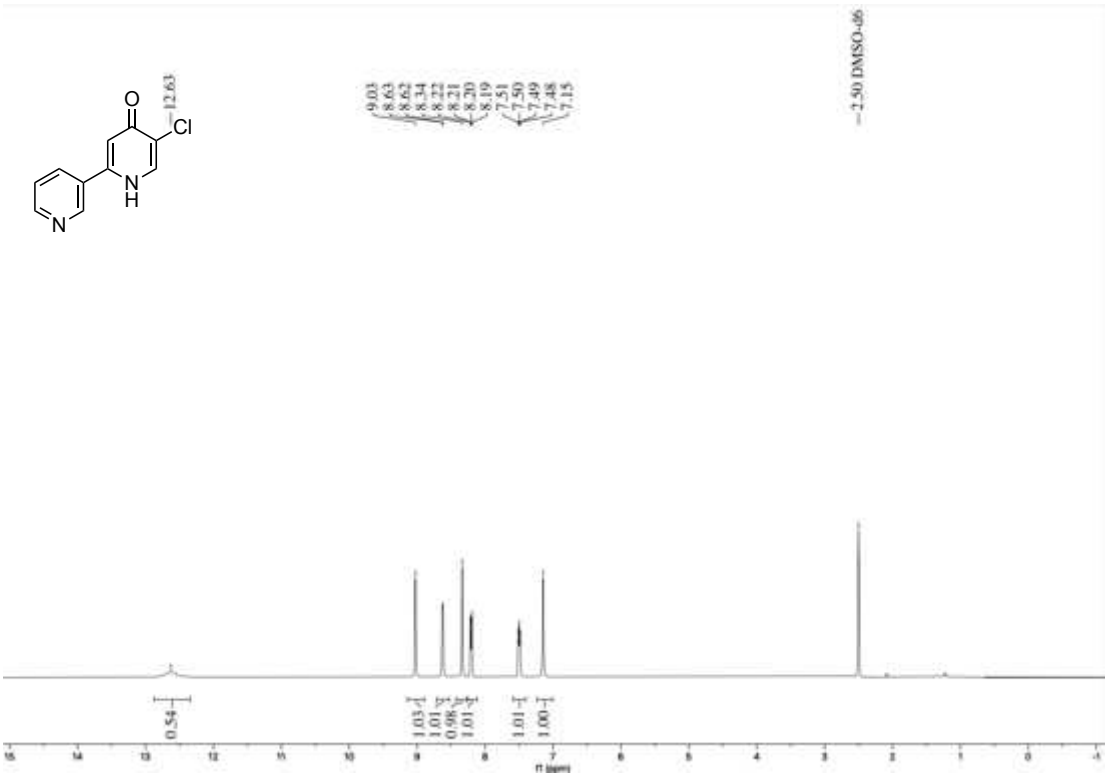


^{19}F NMR spectrum of **2-15** (376 MHz, $(CD_3)_2SO$)



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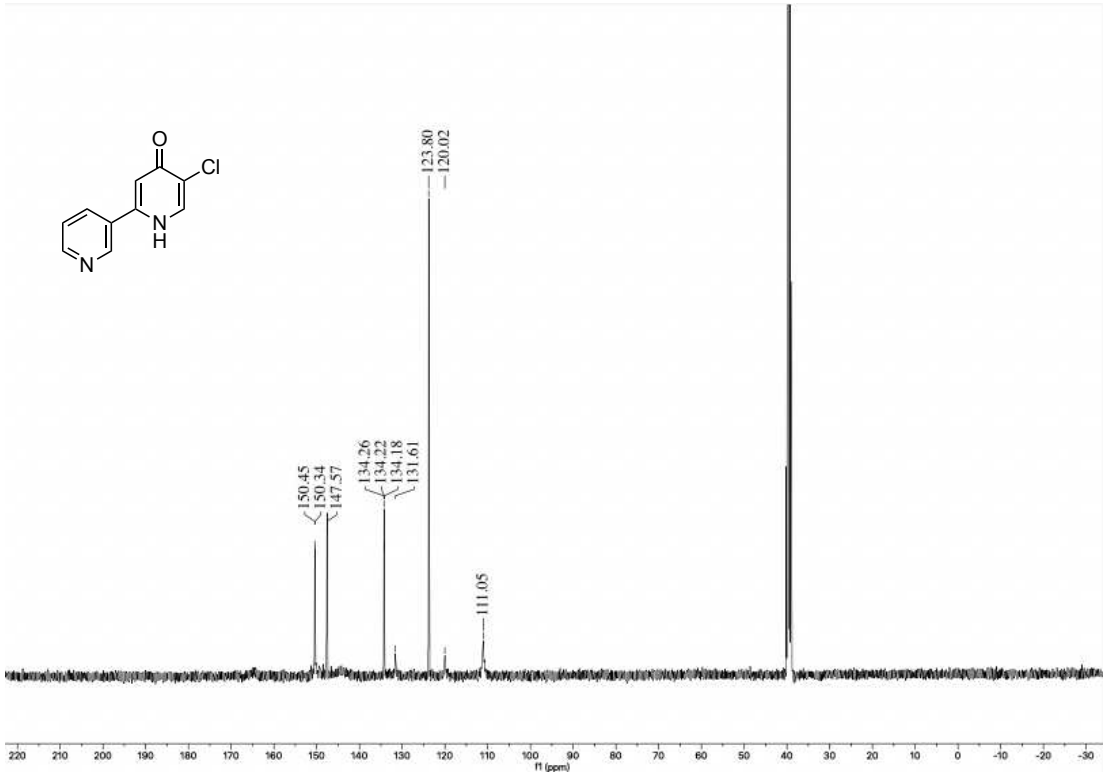
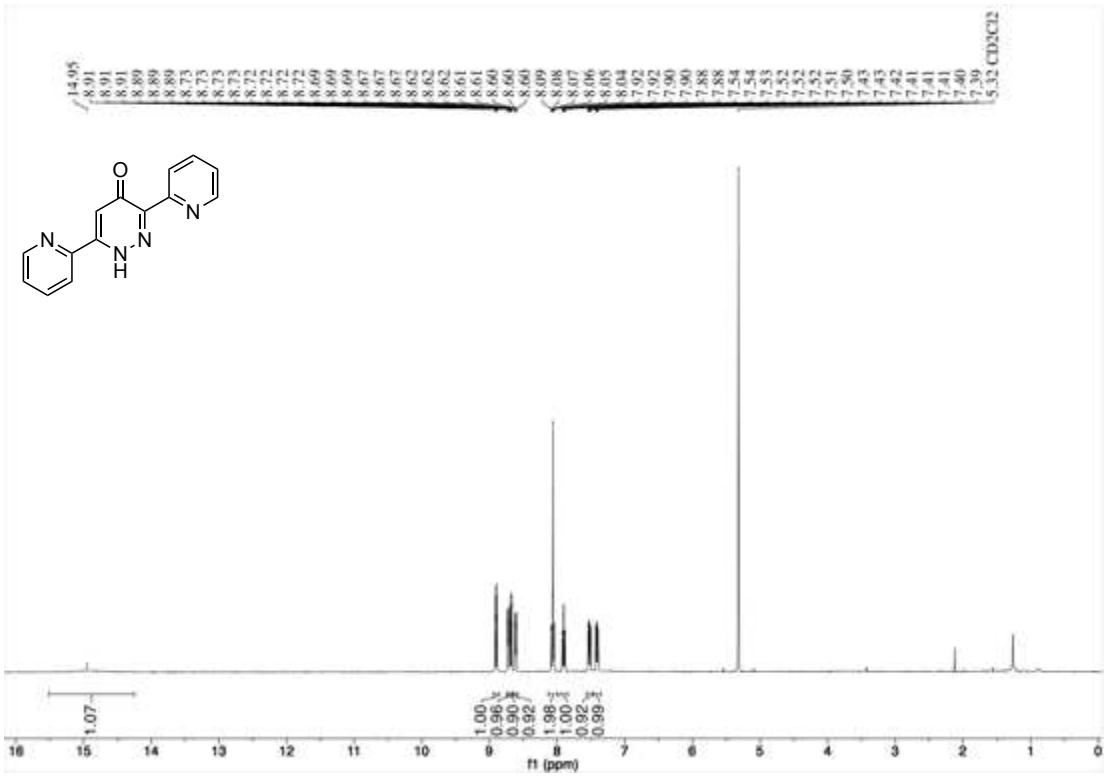
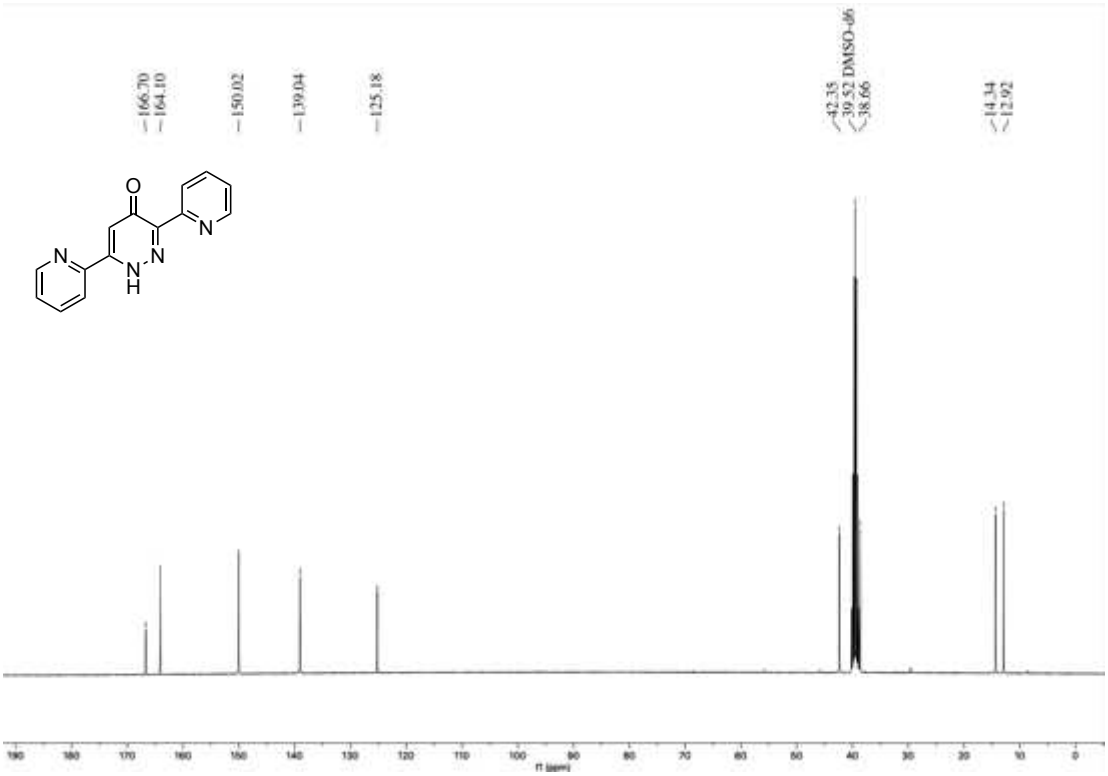


^{13}**C NMR** spectrum of **2-16** (101 MHz, $(CD_3)_2SO$)



^{1}H NMR spectrum of **2-17** (400 MHz, CD_2Cl_2)



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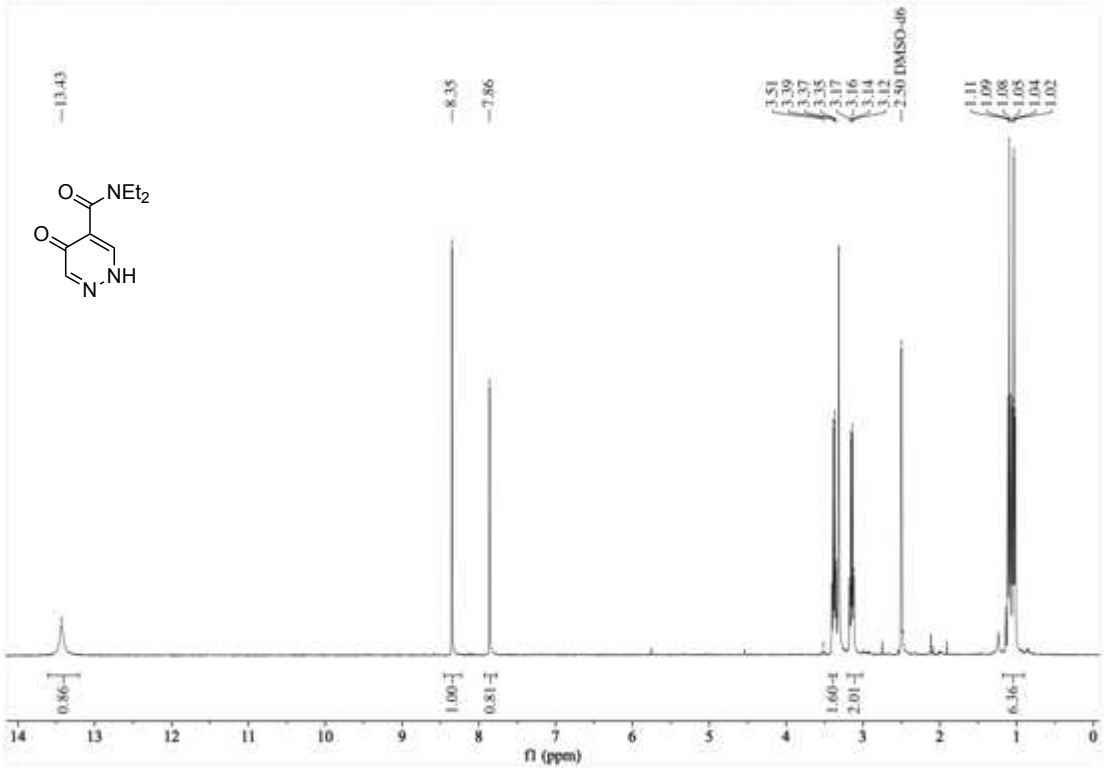
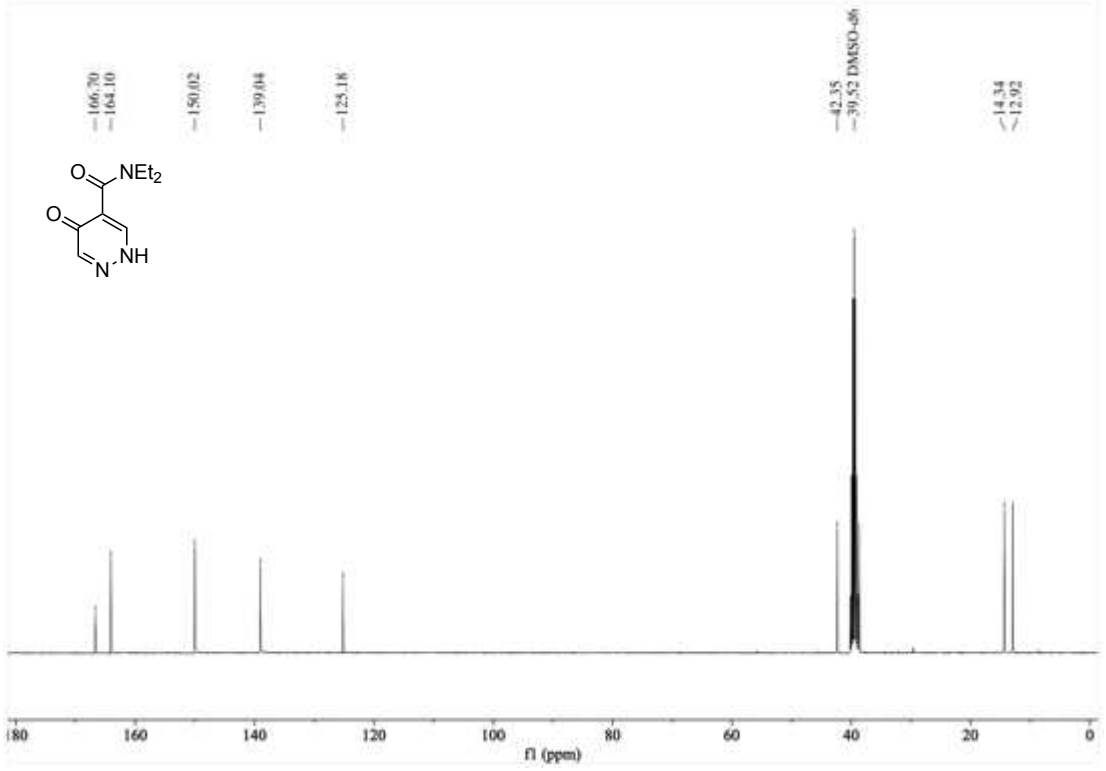
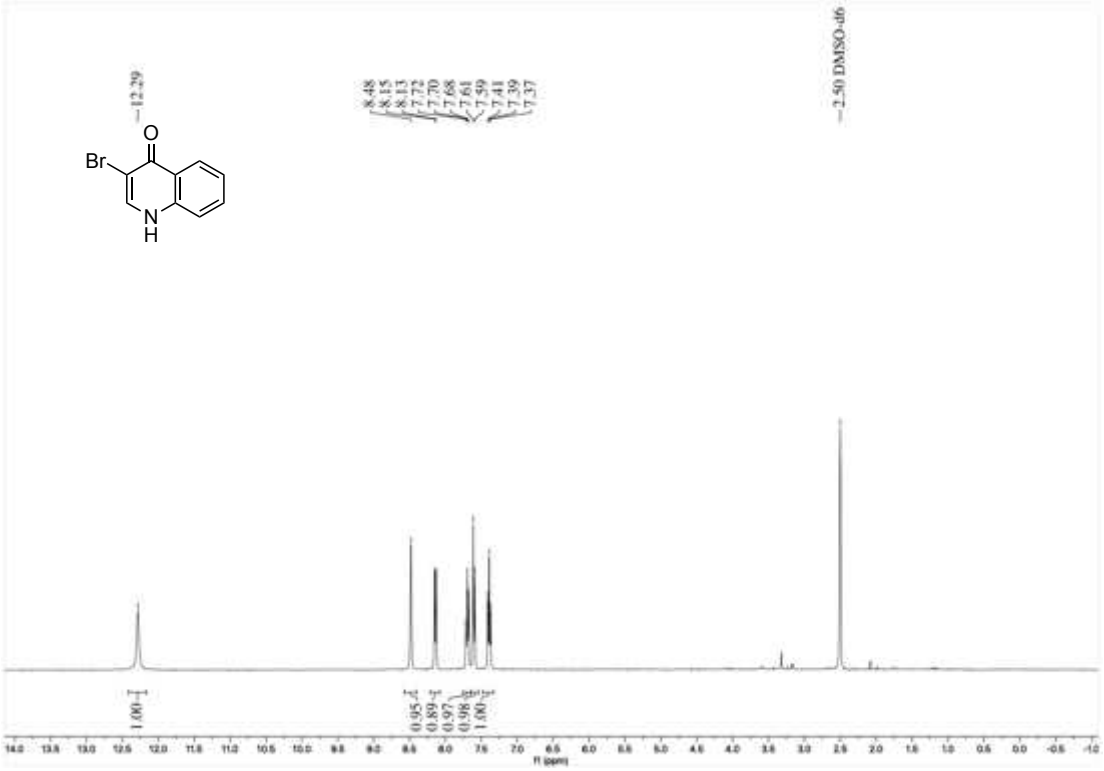


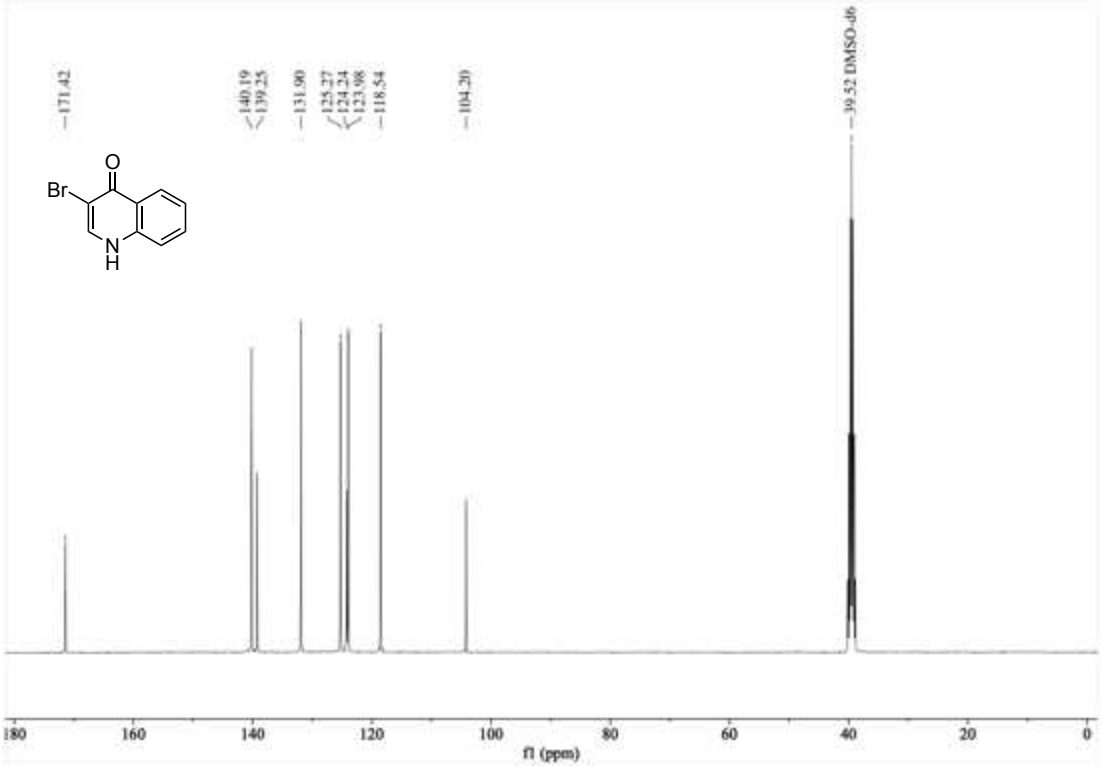
^{1}H NMR spectrum of **2-18** (400 MHz, $(CD_3)_2SO$)



^{13}C NMR spectrum of **2-18** (101 MHz, $(CD_3)_2SO$)



^{1}H NMR spectrum of **2-19** (400 MHz, $(CD_3)_2SO$)



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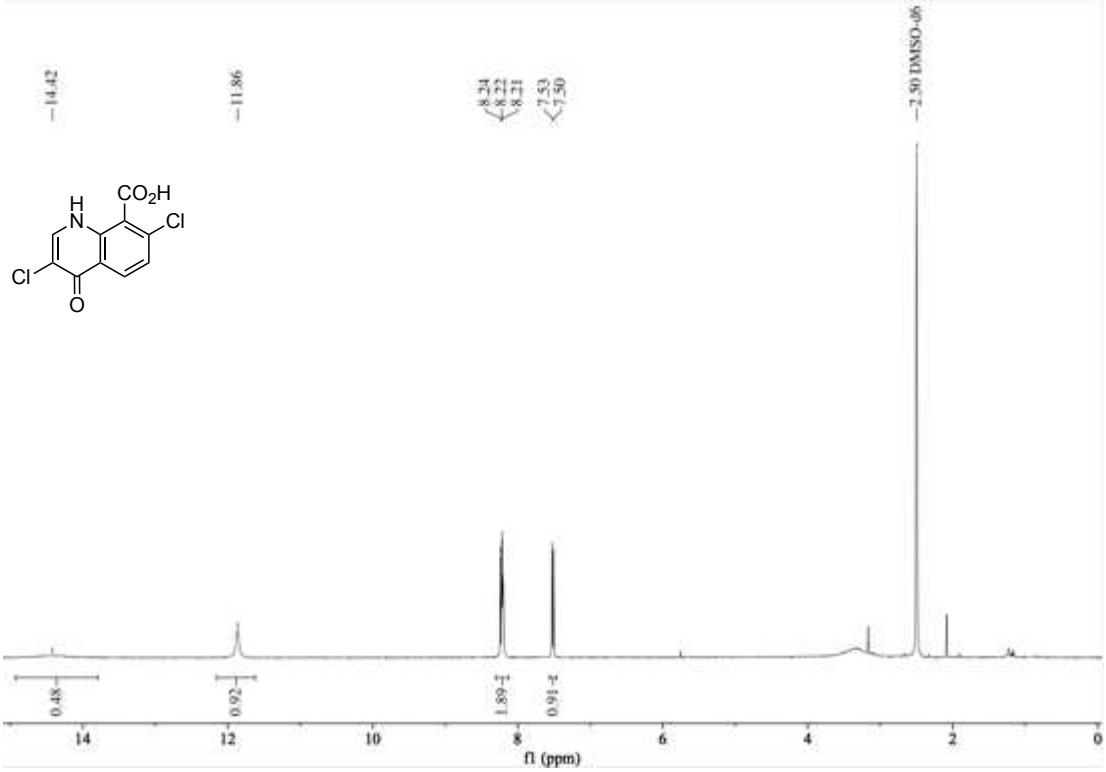

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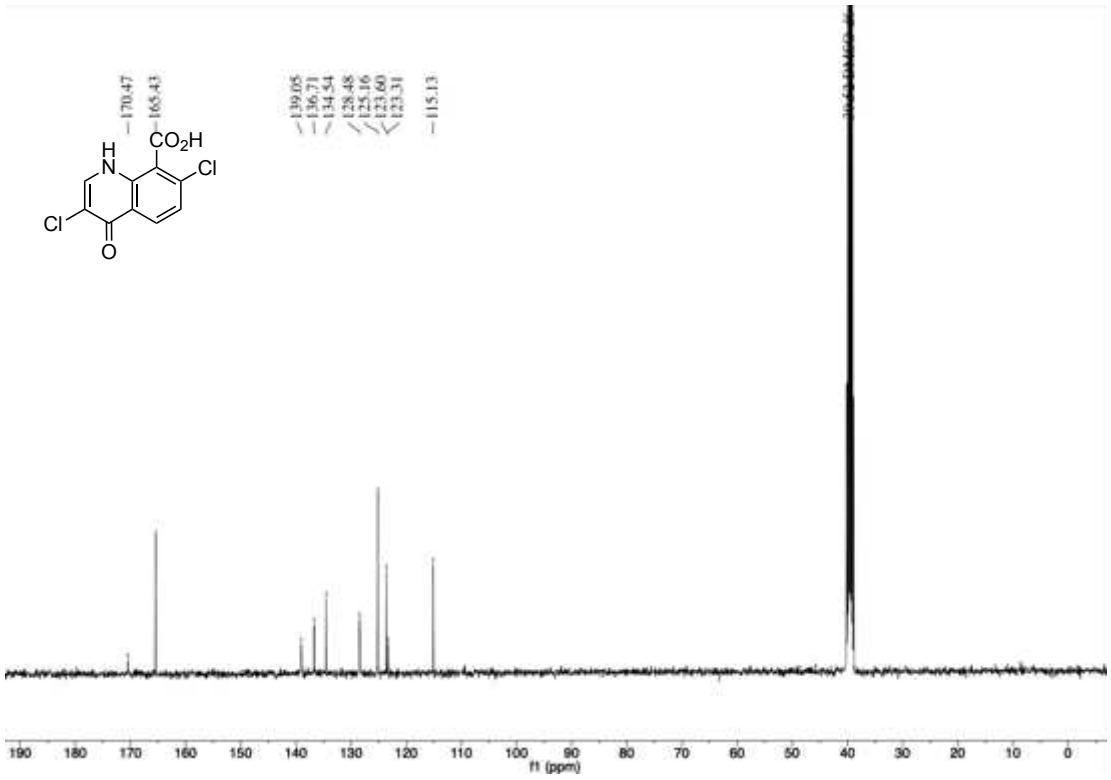

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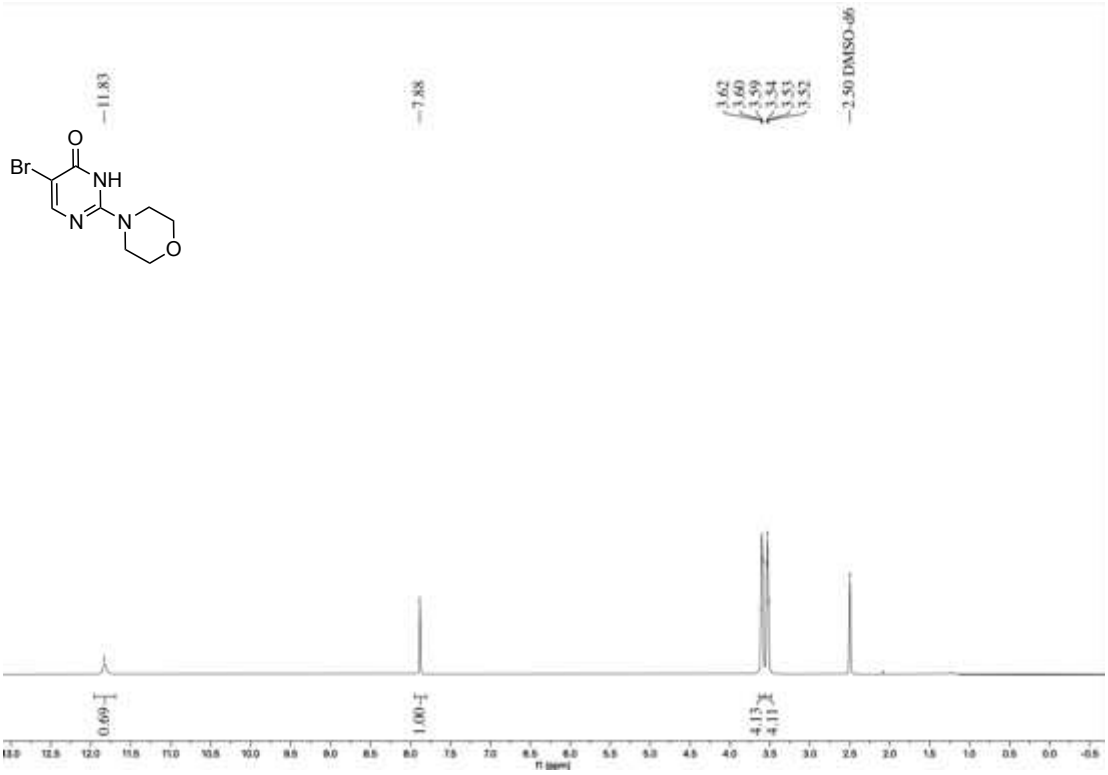

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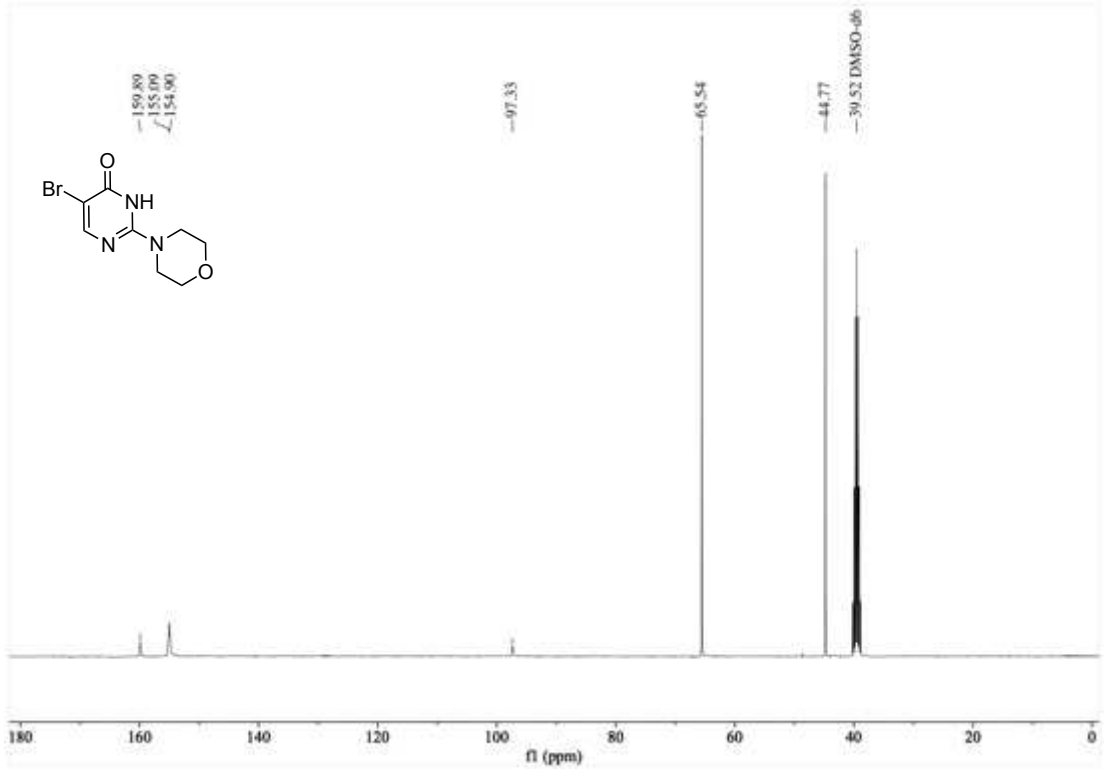

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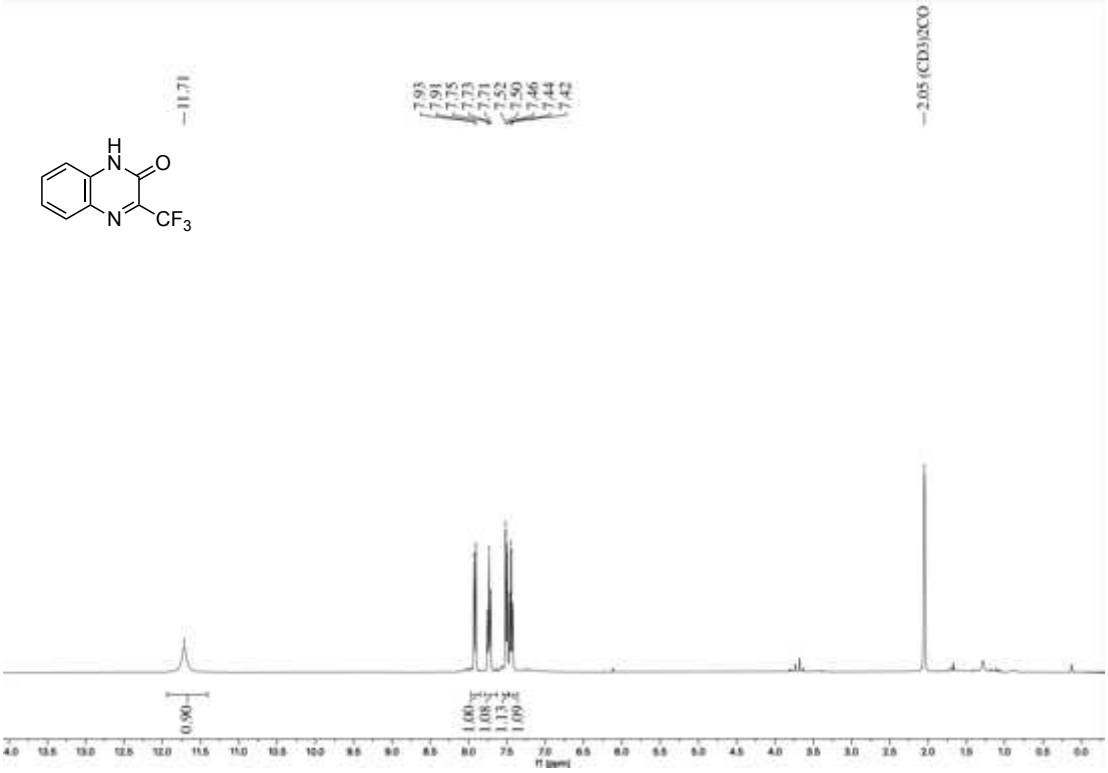

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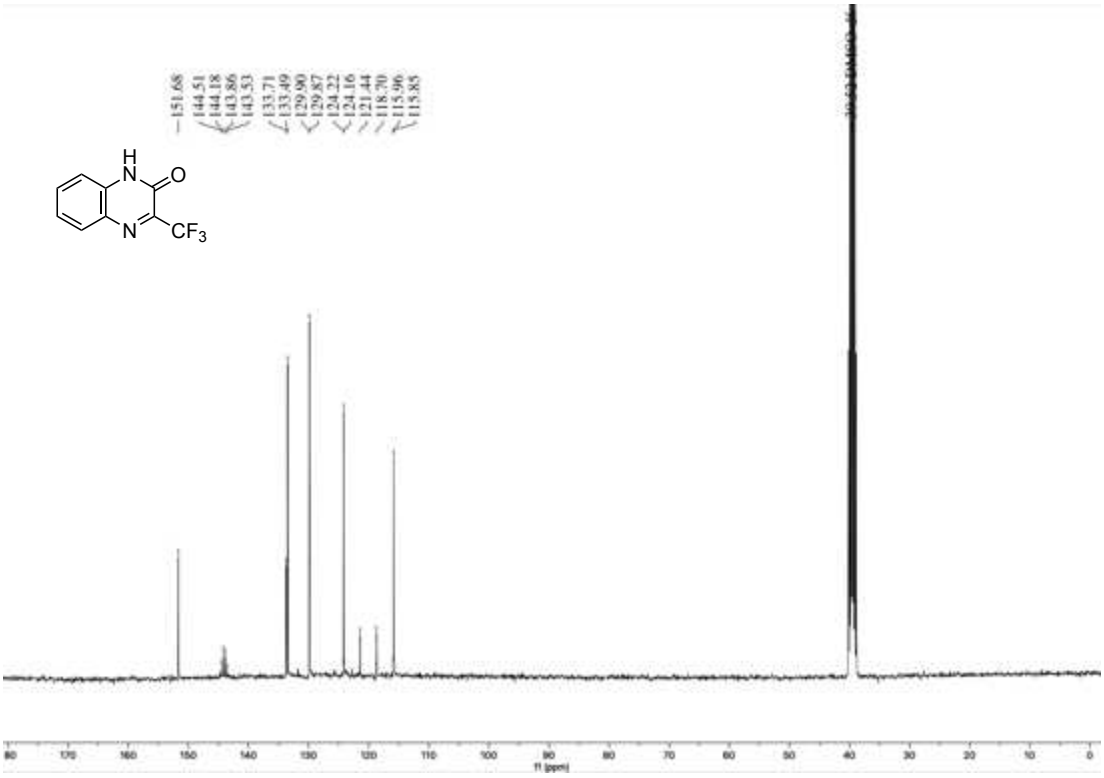

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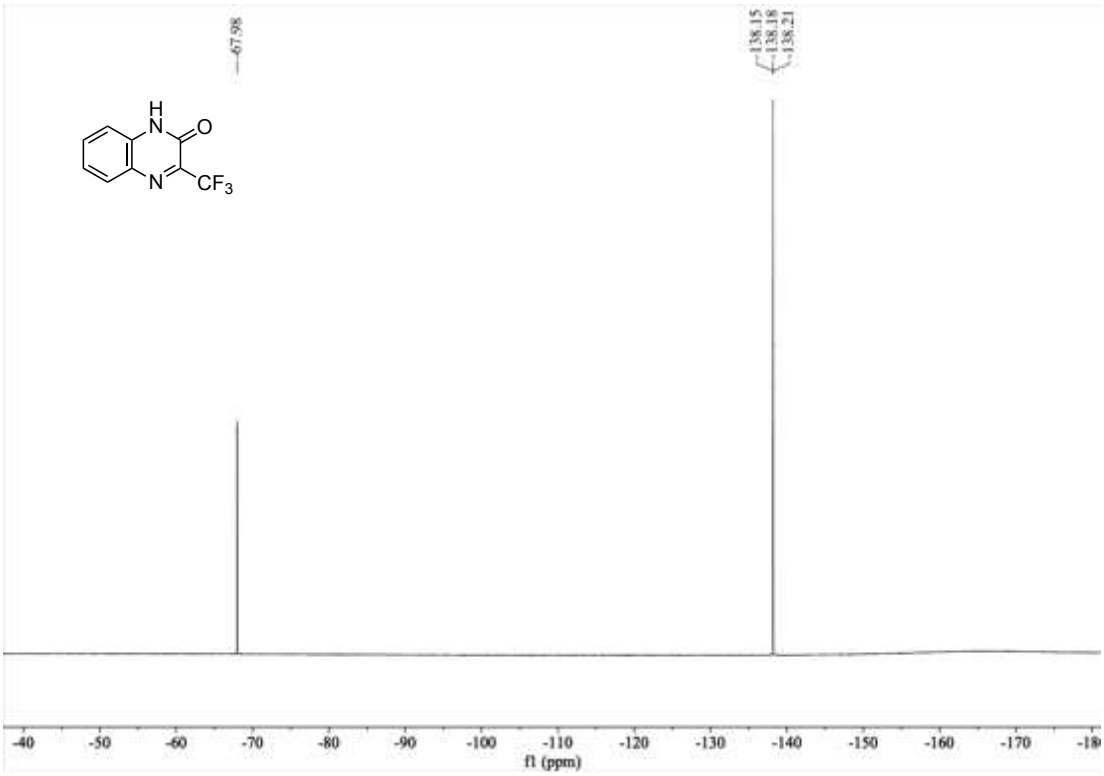
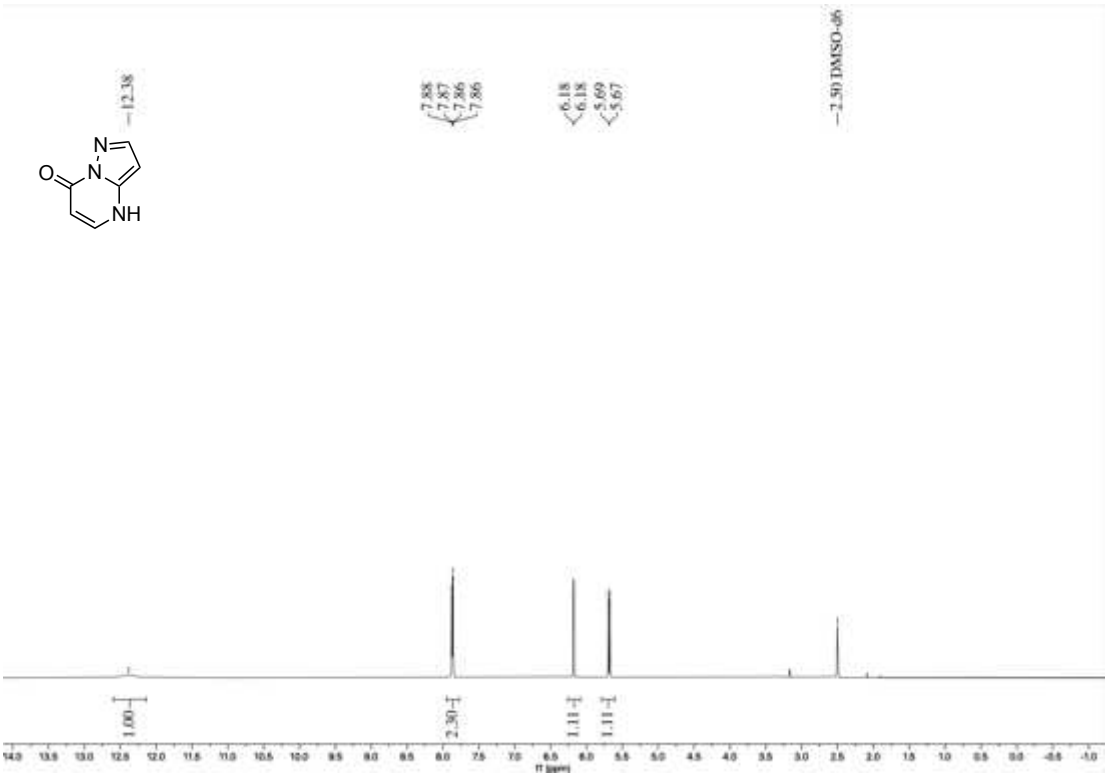


^{19}F NMR spectrum of **2-22** (376 MHz, $(CD_3)_2CO$)



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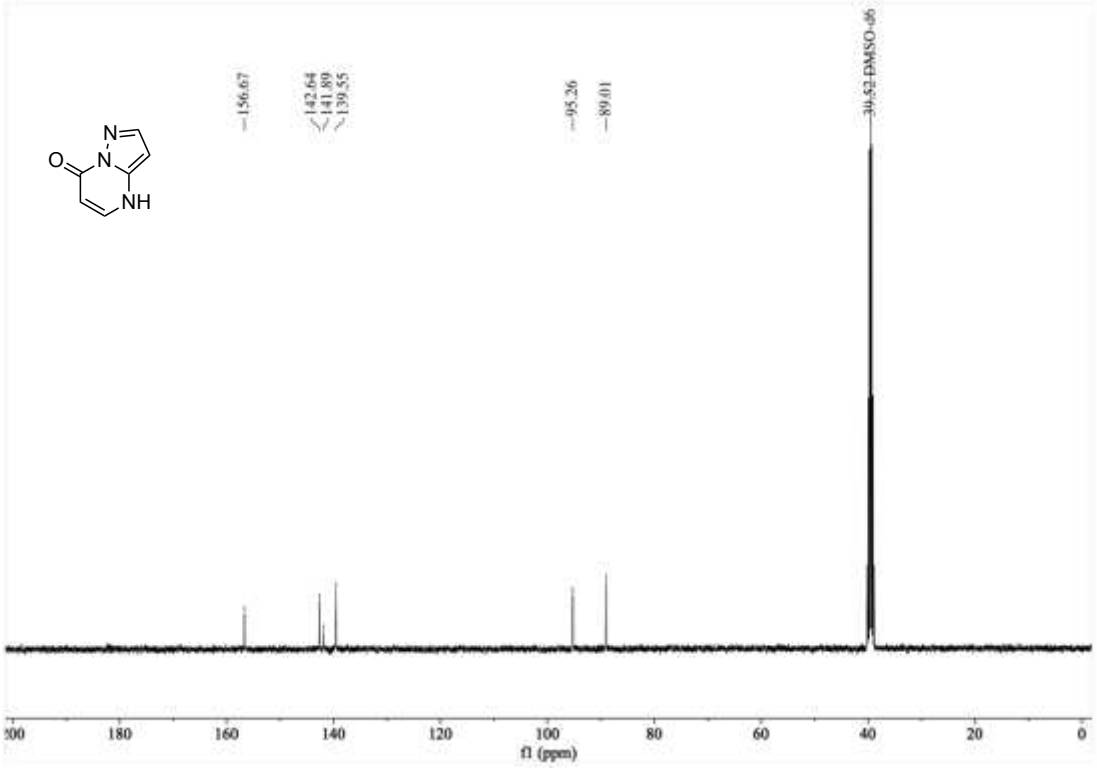

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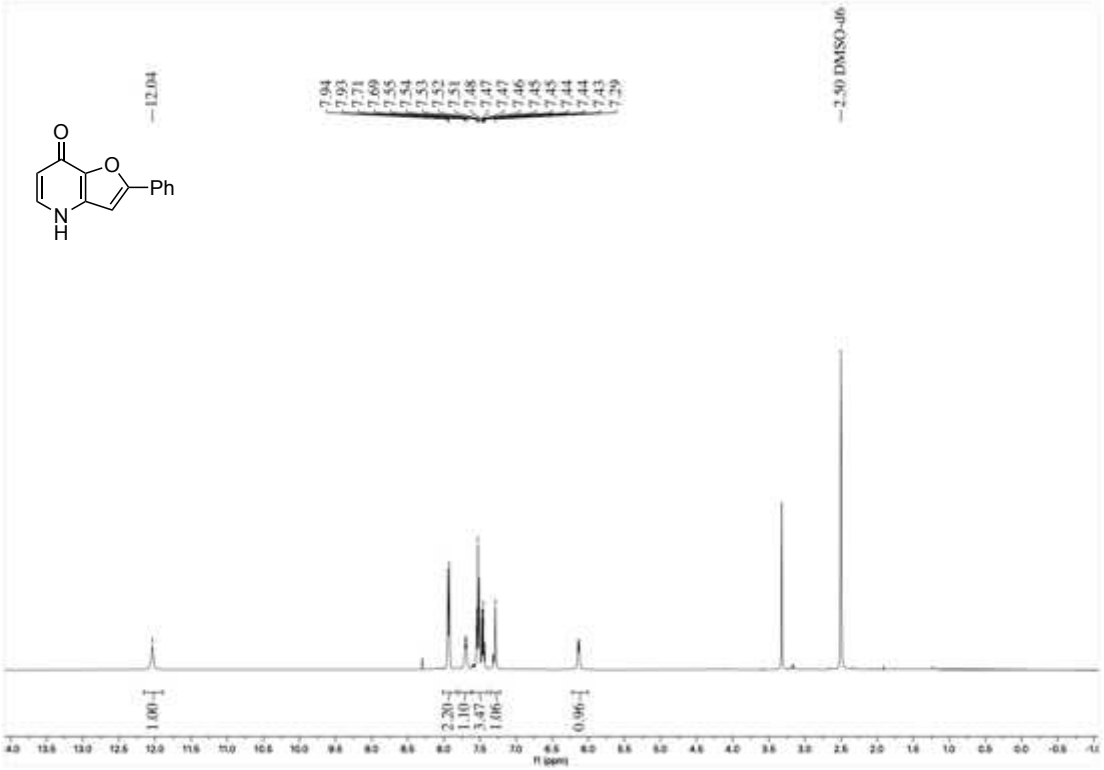
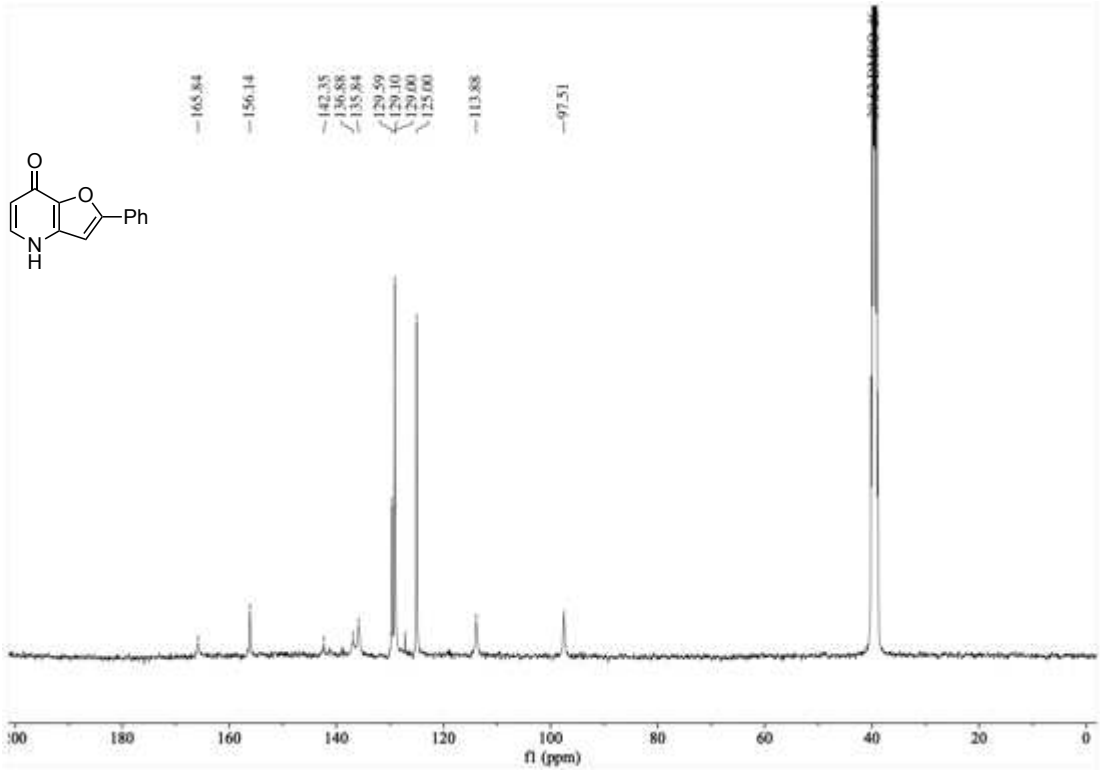


^{1}H NMR spectrum of **2-24** (400 MHz, $(CD_3)_2SO$)



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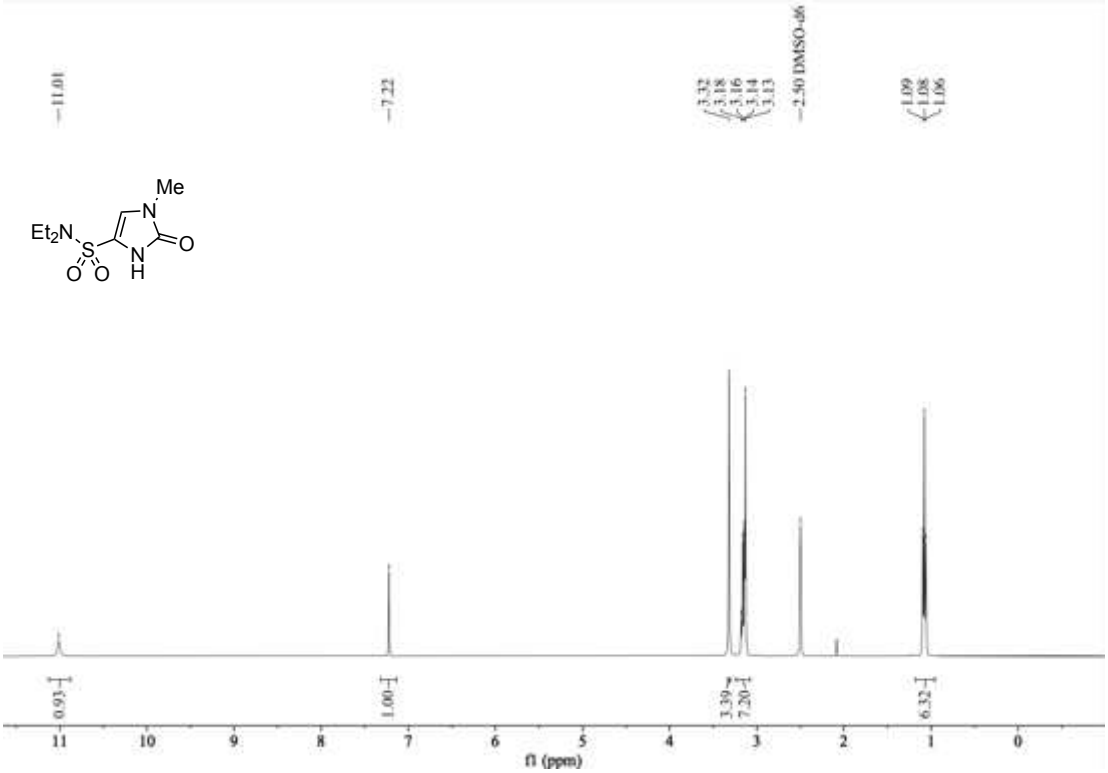

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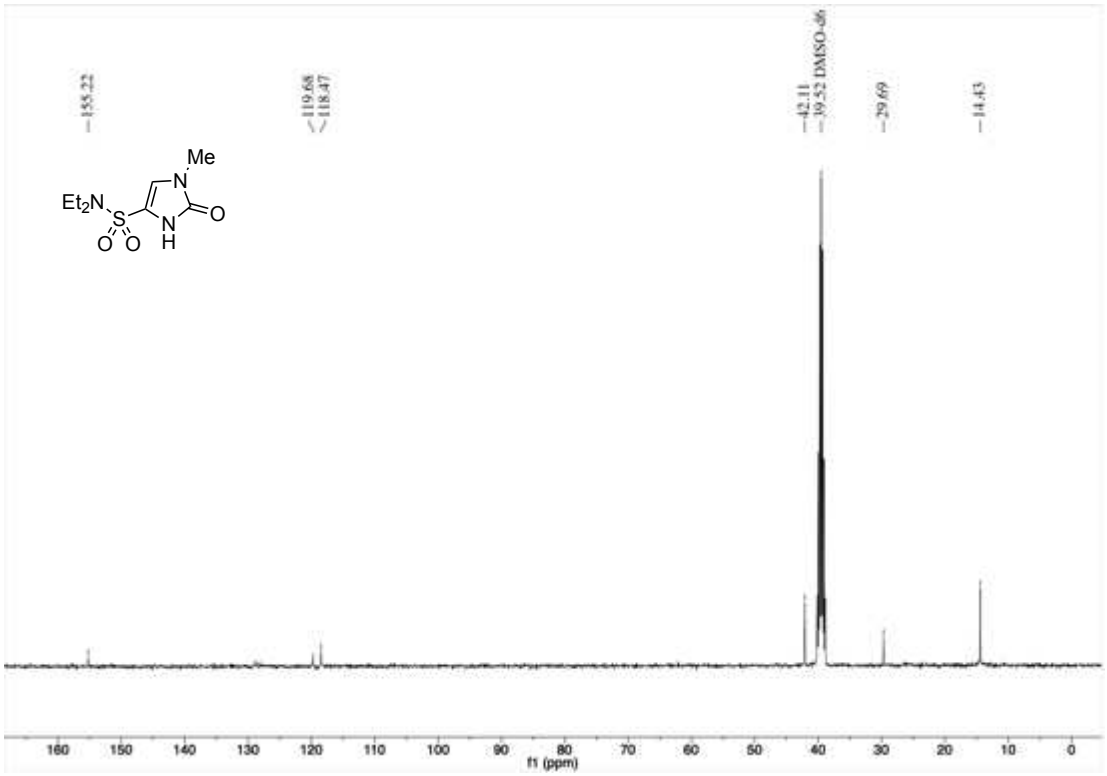

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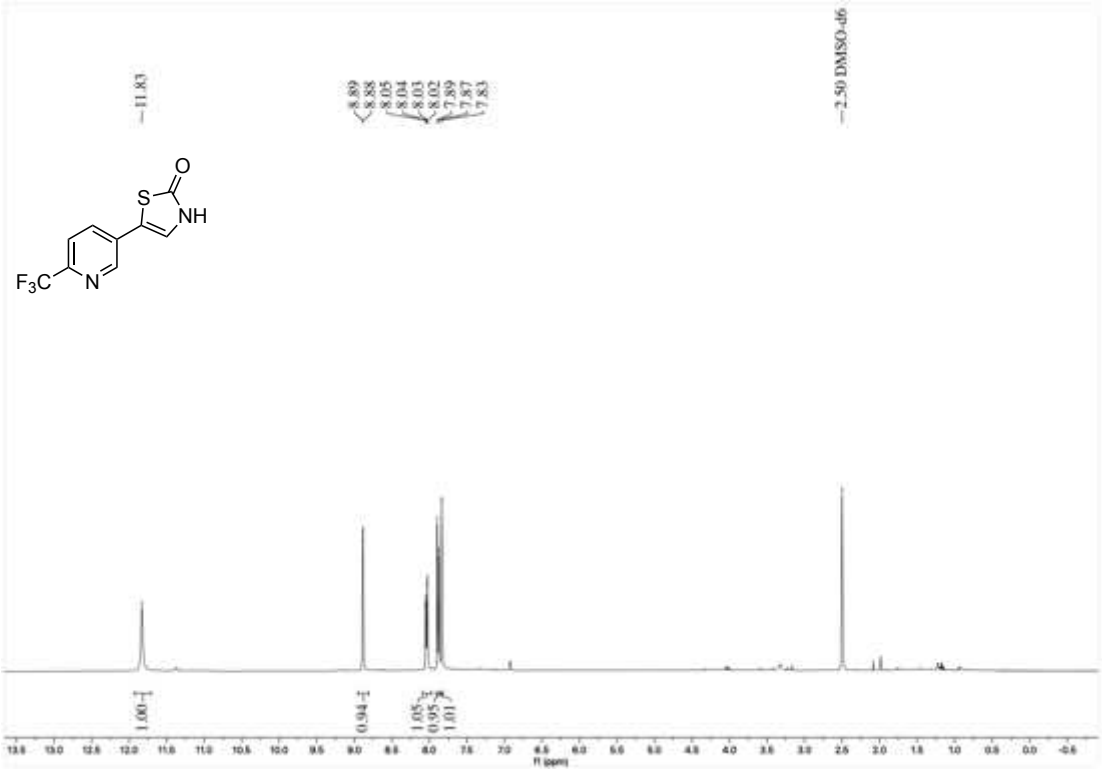

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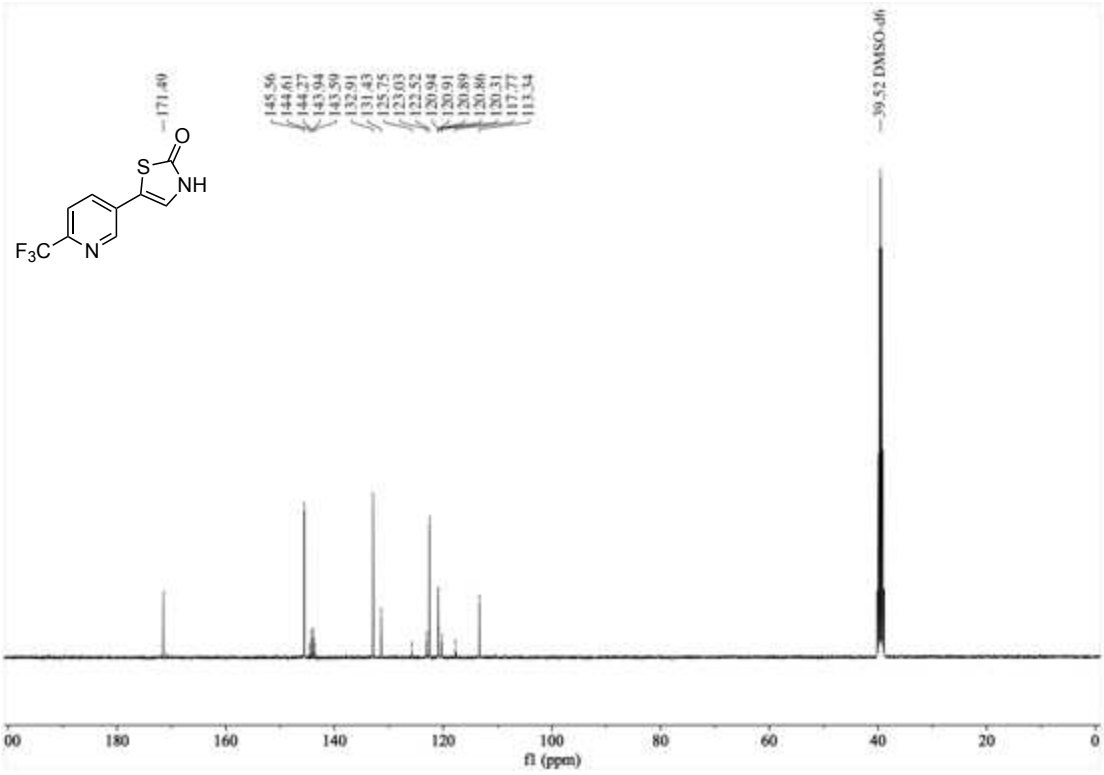

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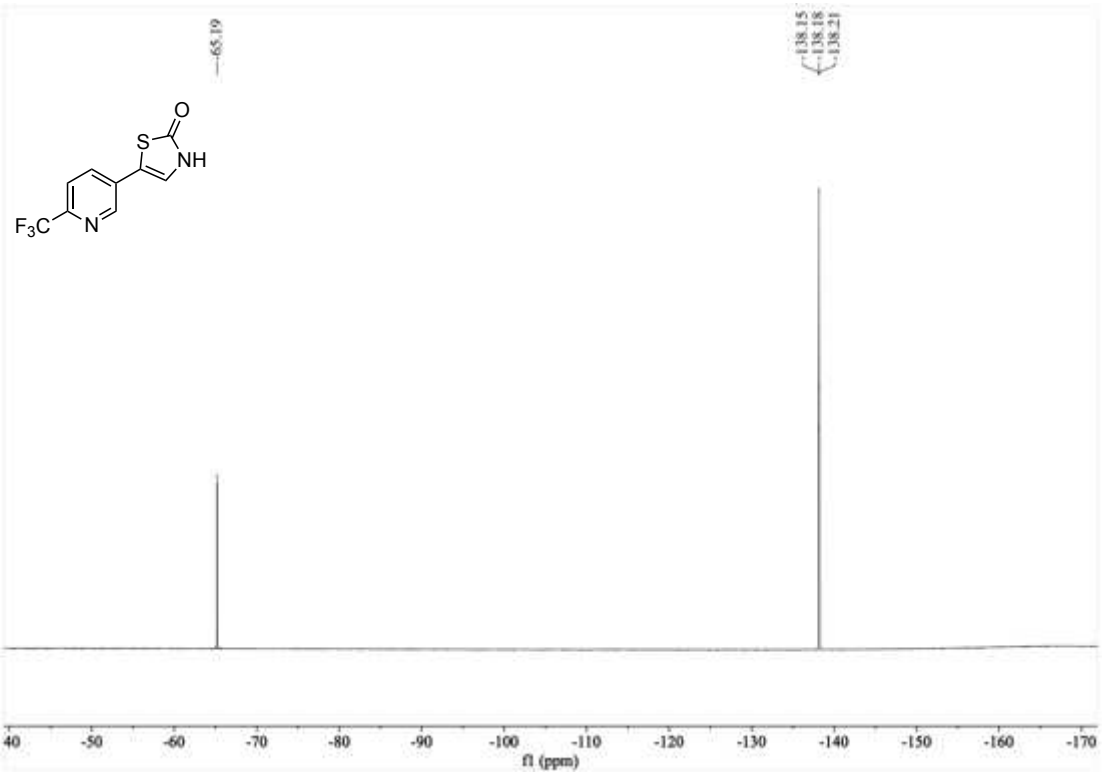
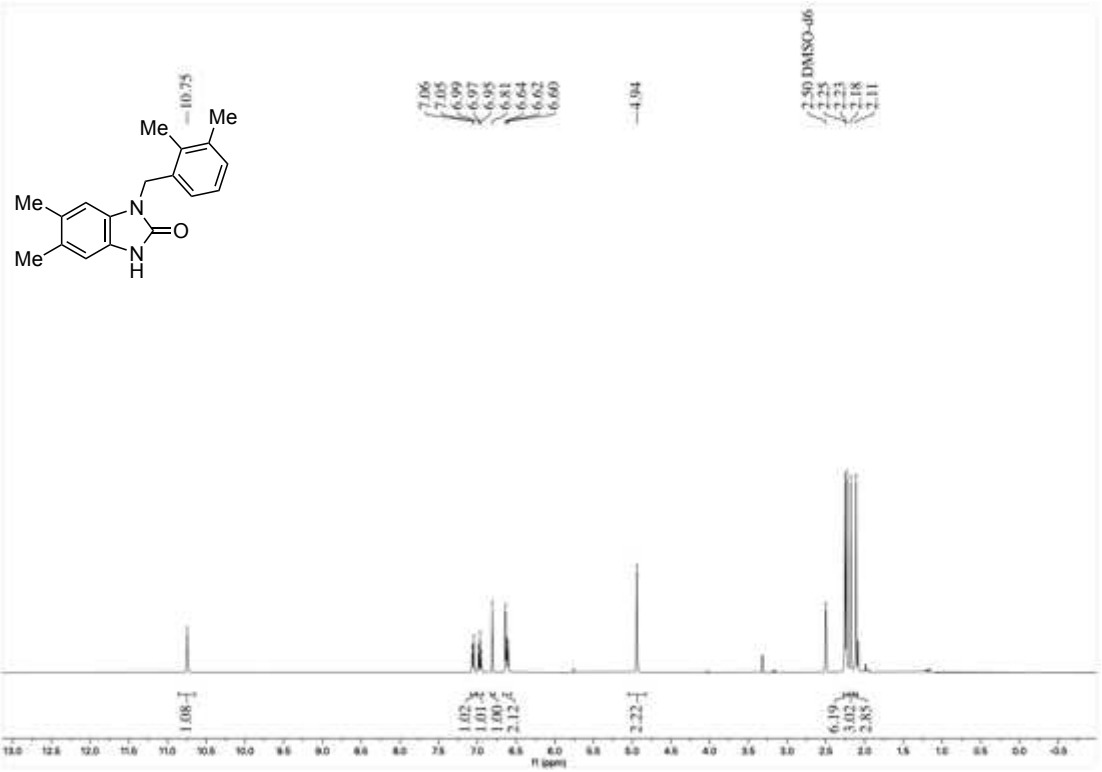
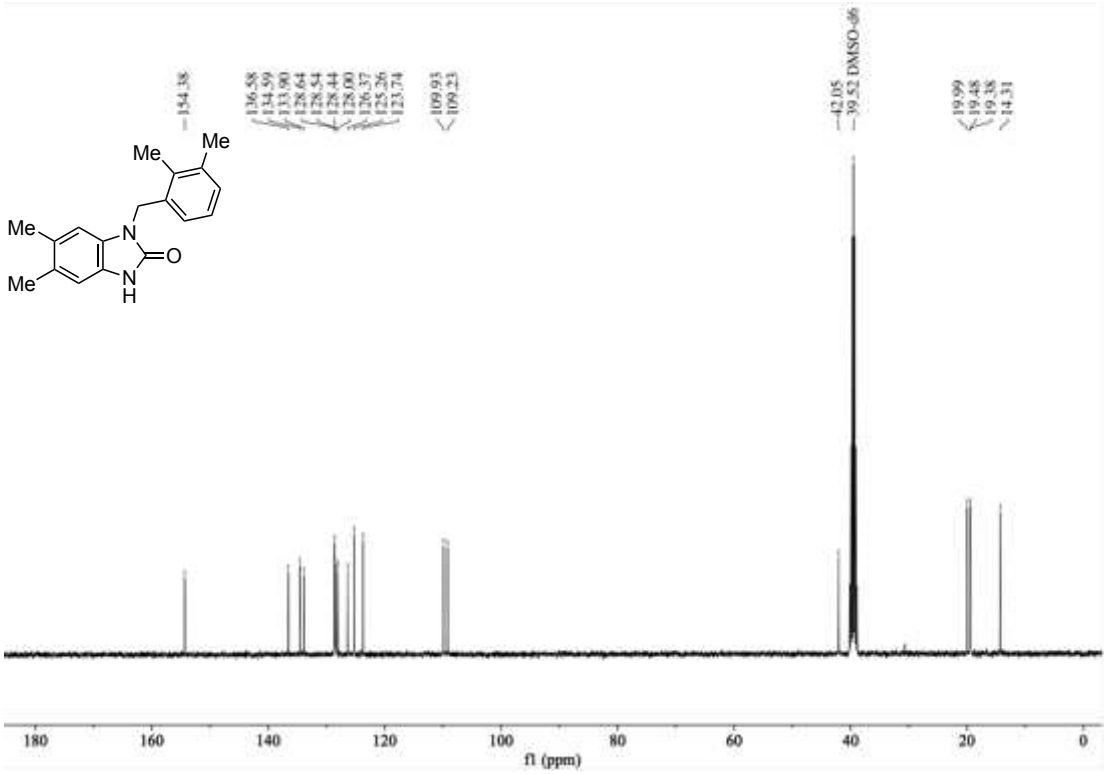


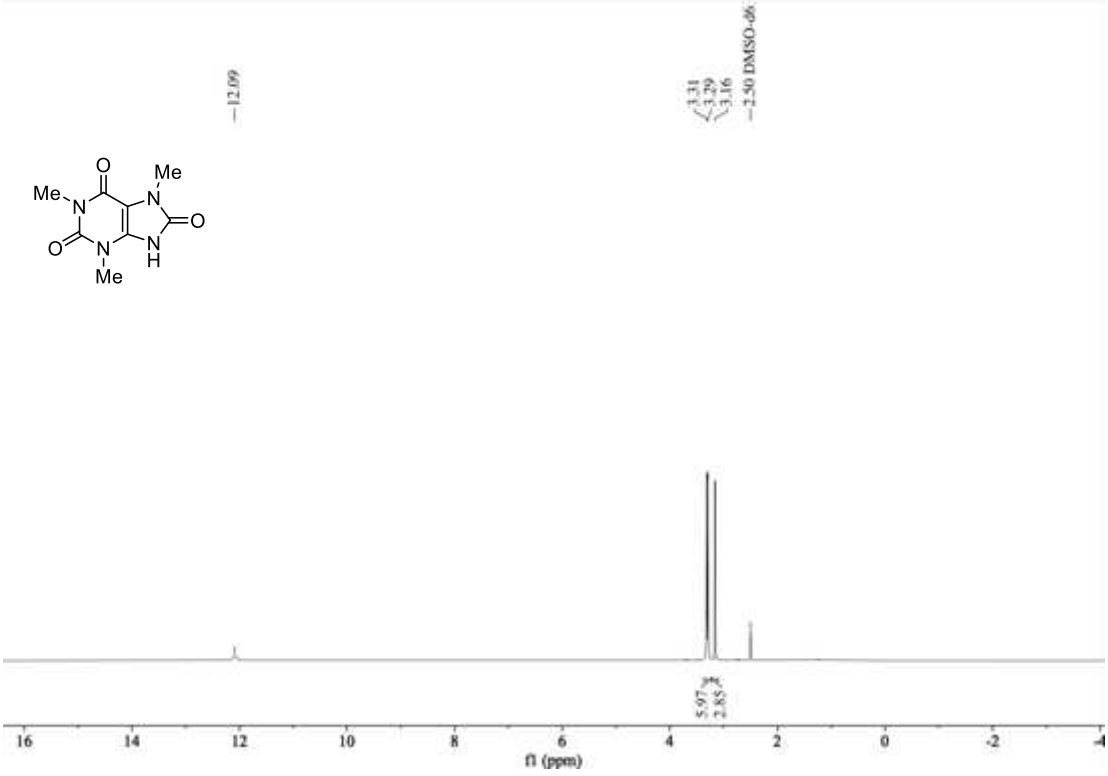
^{19}F NMR spectrum of **2-27** (376 MHz, $(CD_3)_2SO$)



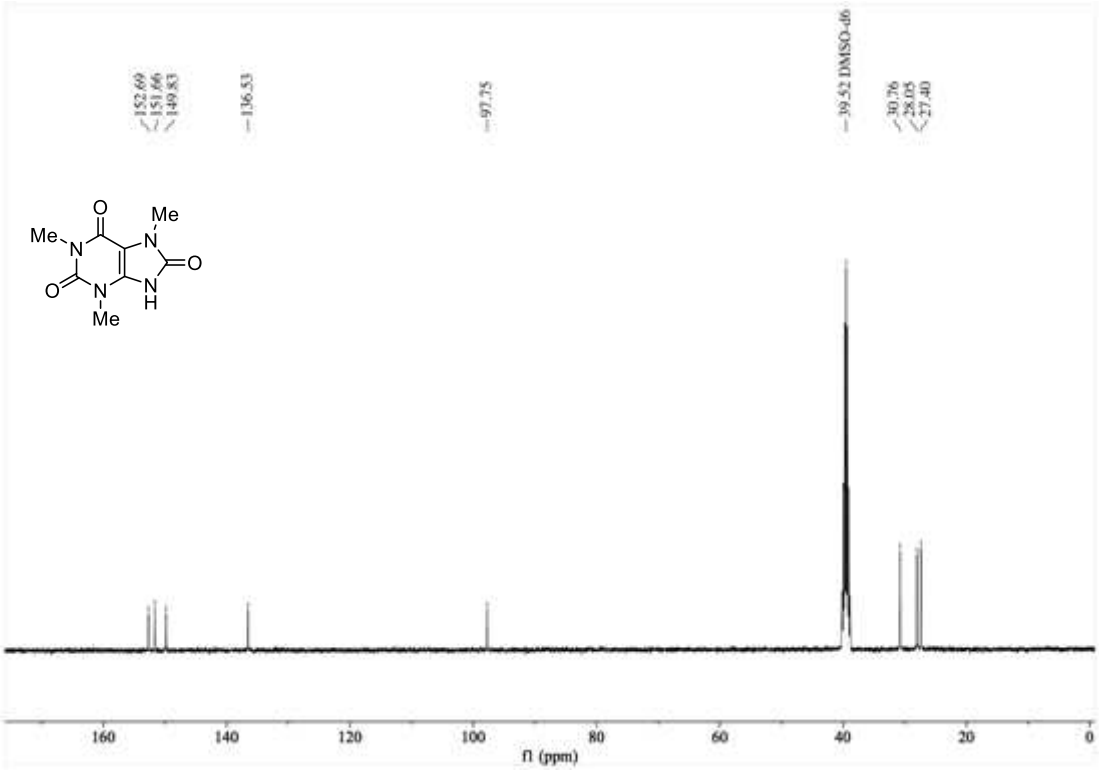
^{1}H NMR spectrum of **2-28** (400 MHz, $(CD_3)_2SO$)



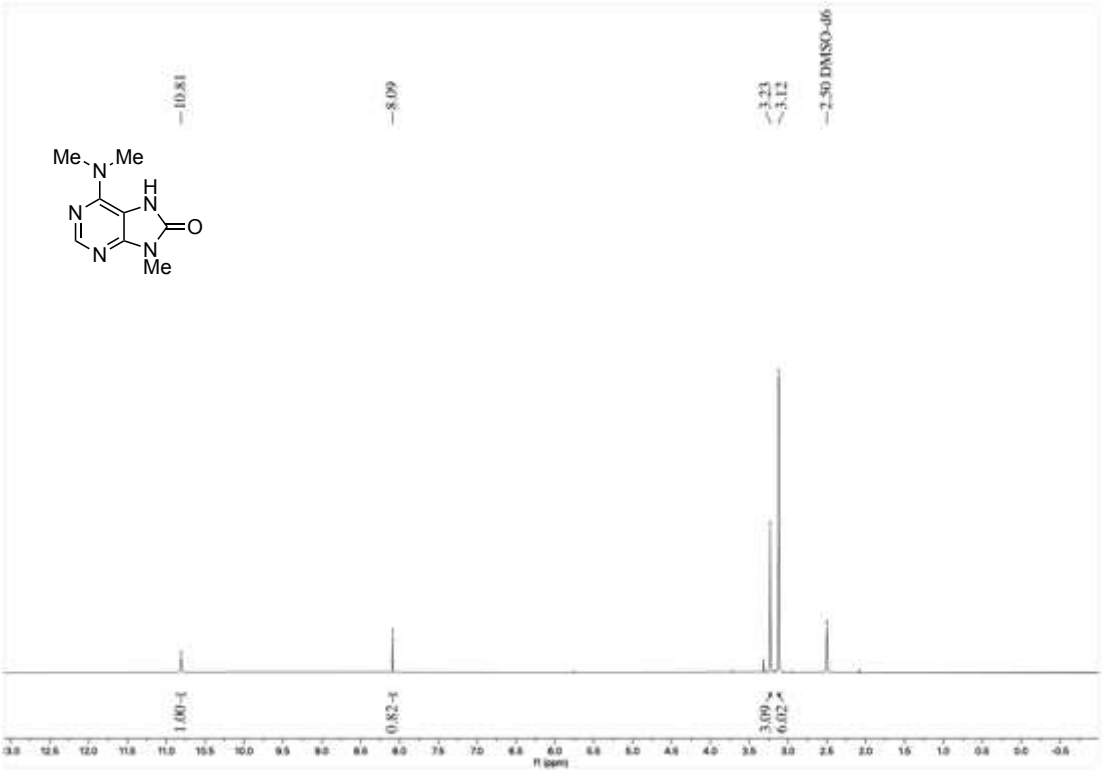
^{13}C NMR spectrum of **2-28** (101 MHz, $(CD_3)_2SO$)



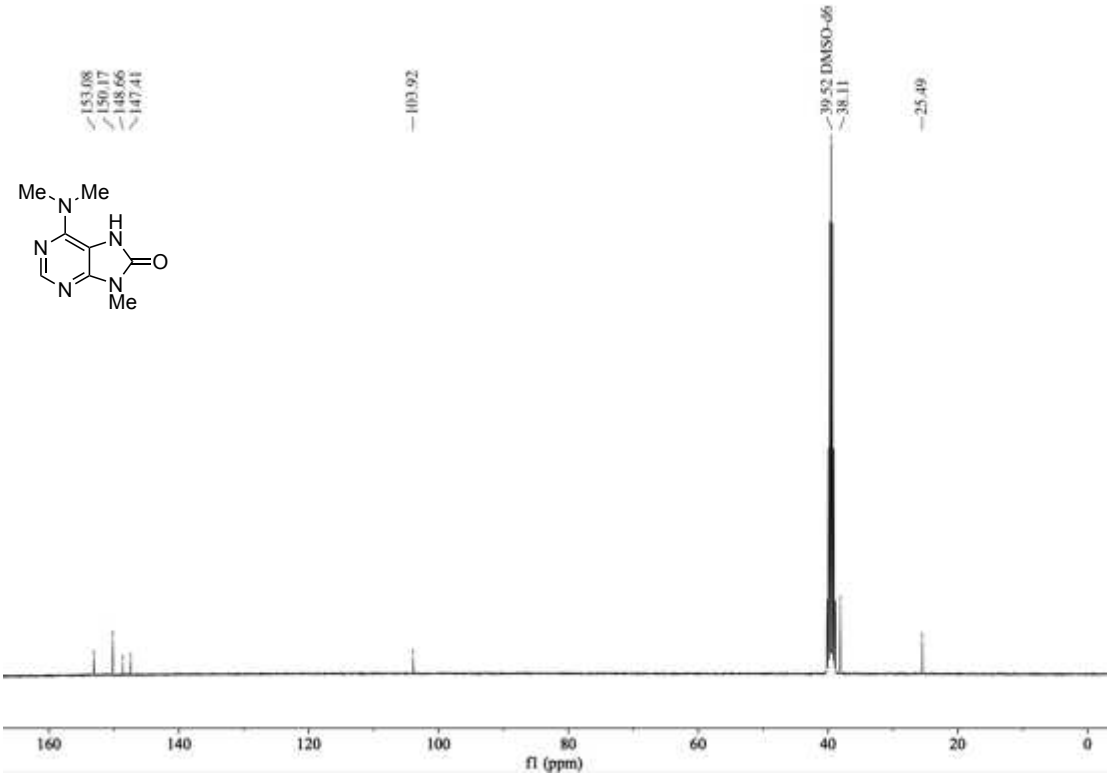
^{1}H NMR spectrum of **2-29** (400 MHz, $(CD_3)_2SO$)



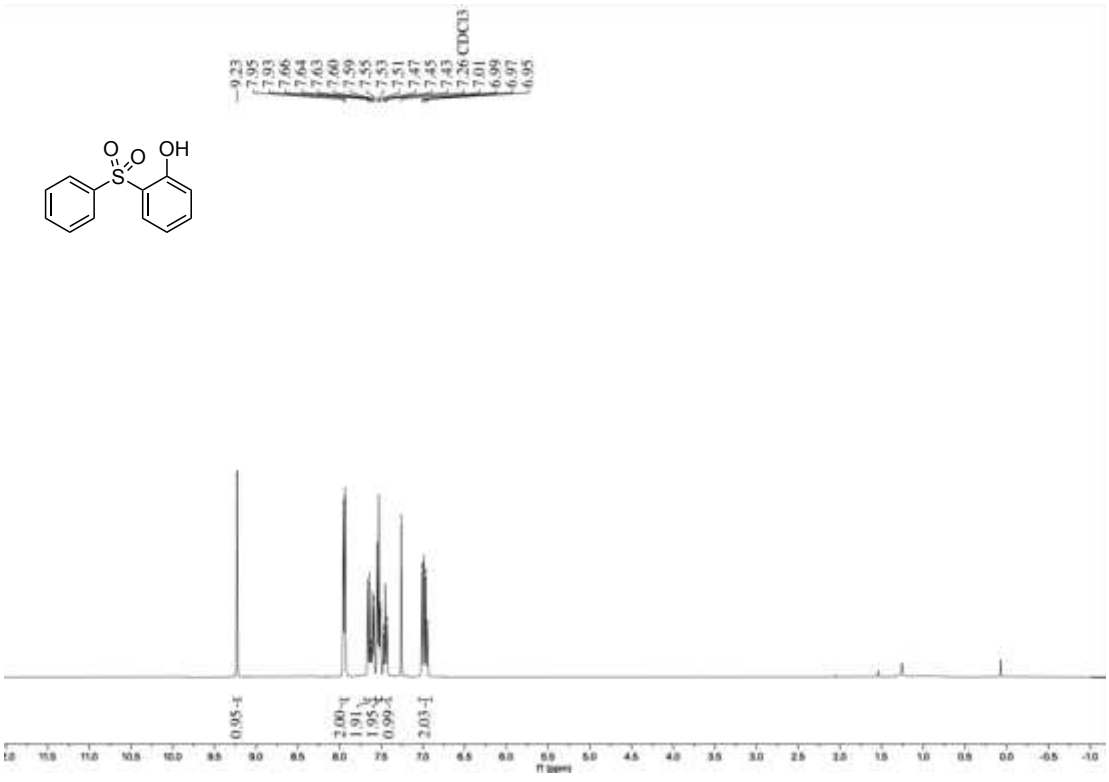
^{13}C NMR spectrum of **2-29** (101 MHz, $(CD_3)_2SO$)



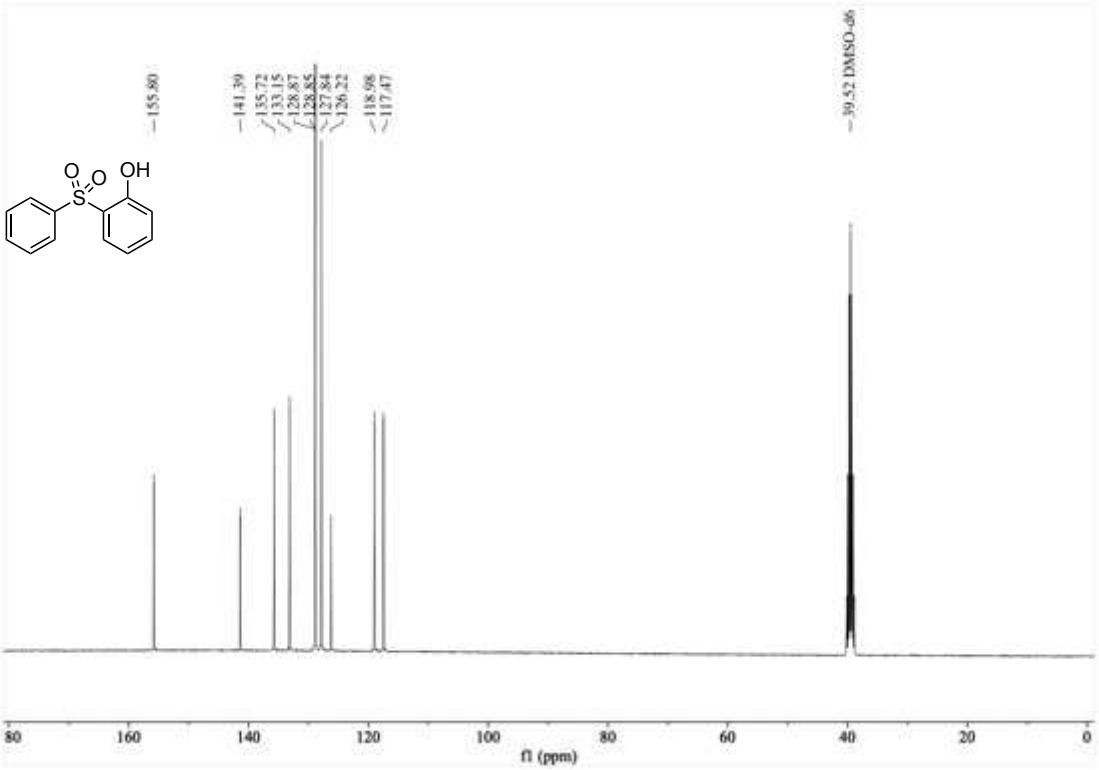
^{1}H NMR spectrum of **2-30** (400 MHz, $(CD_3)_2SO$)



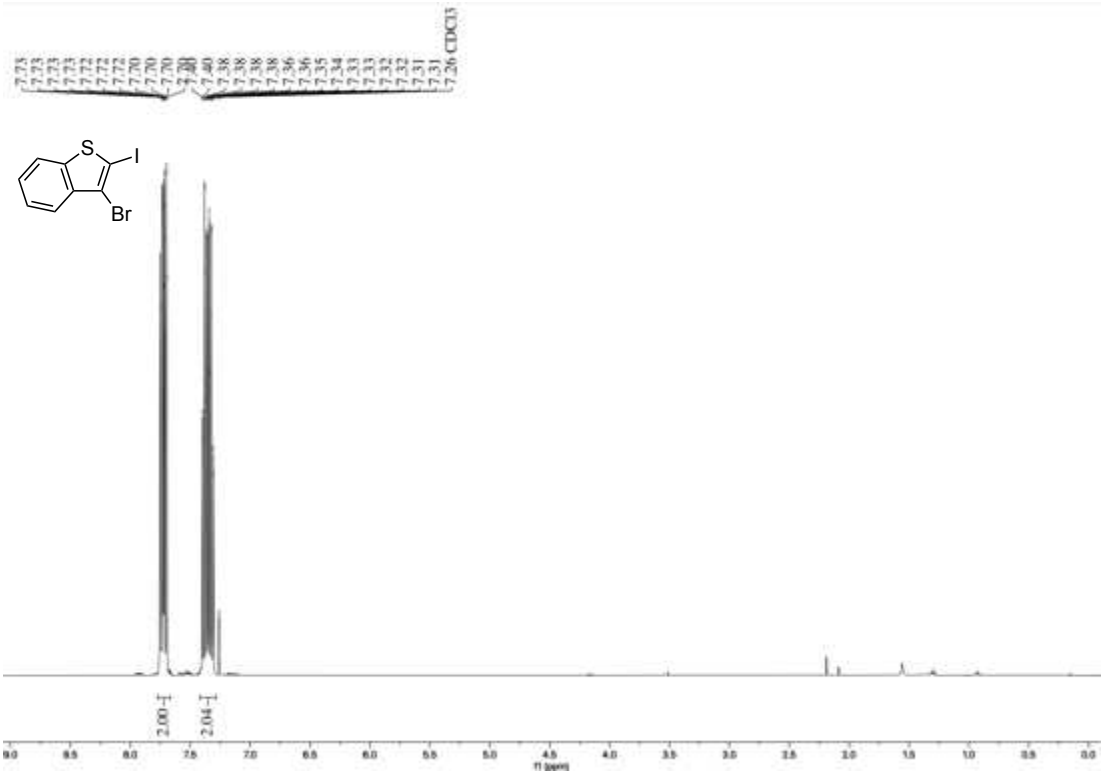
^{13}C NMR spectrum of **2-30** (101 MHz, $(CD_3)_2SO$)



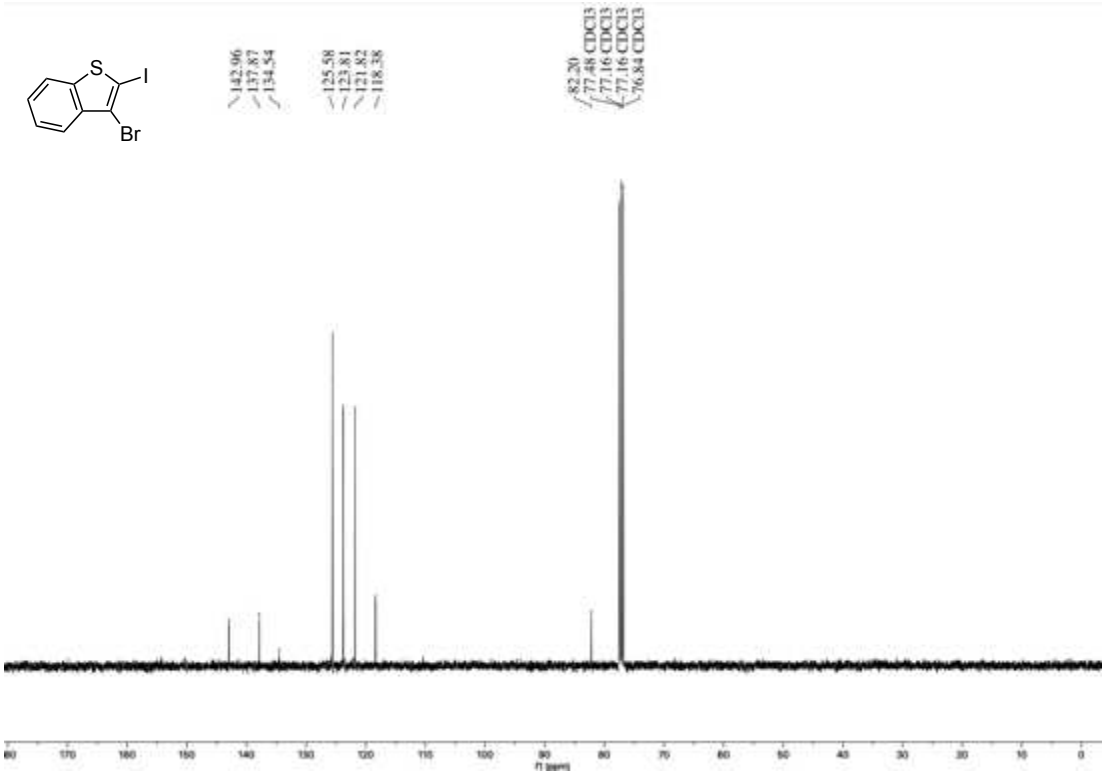
^{1}H NMR spectrum of **2-32** (400 MHz, $CDCl_3$)



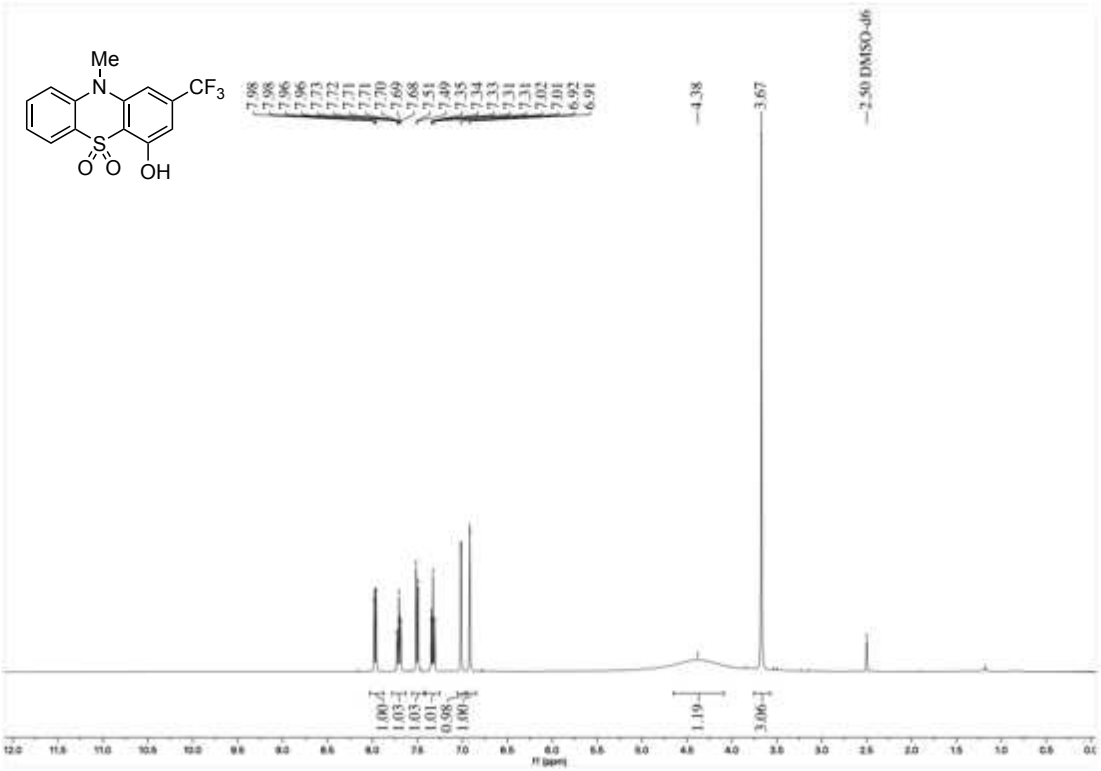
^{13}C NMR spectrum of **2-32** (101 MHz, $(CD_3)_2SO$)



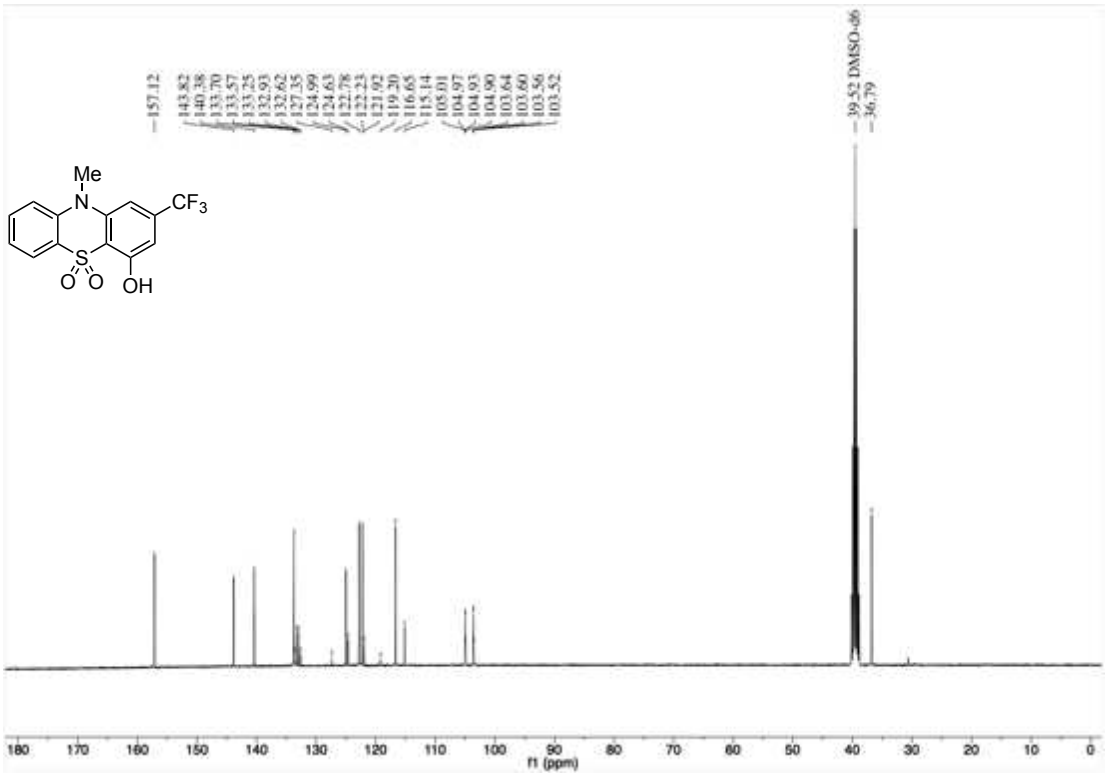
^{1}H NMR spectrum of **2-34** (400 MHz, $CDCl_3$)



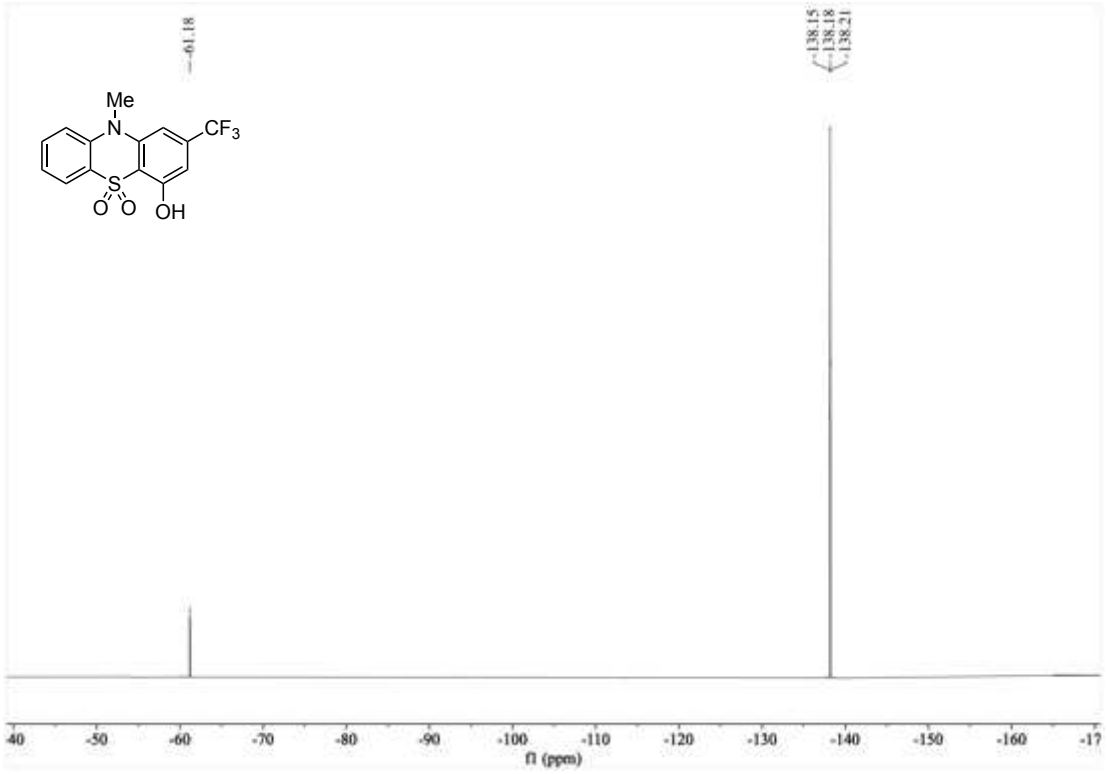
^{13}C NMR spectrum of **2-34** (101 MHz, $(CD_3)_2SO$)



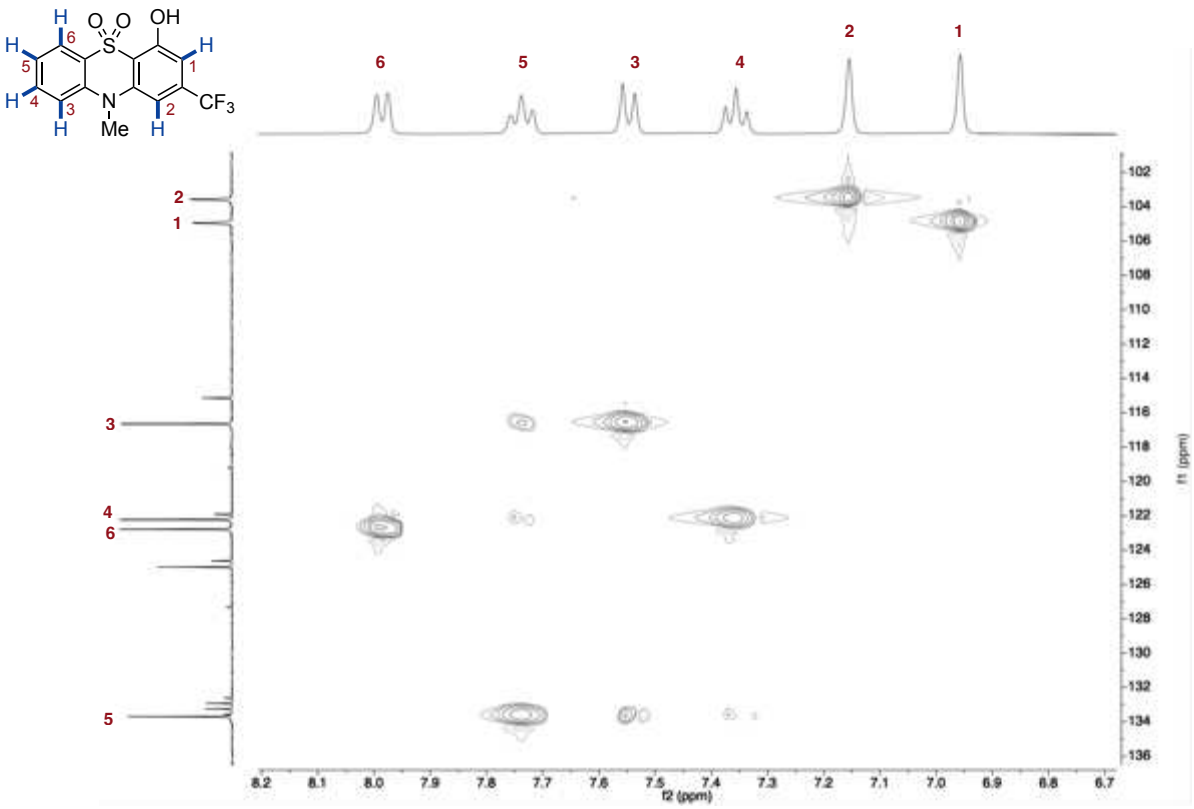
^{1}H NMR spectrum of **2-39** (400 MHz, $(CD_3)_2SO$)



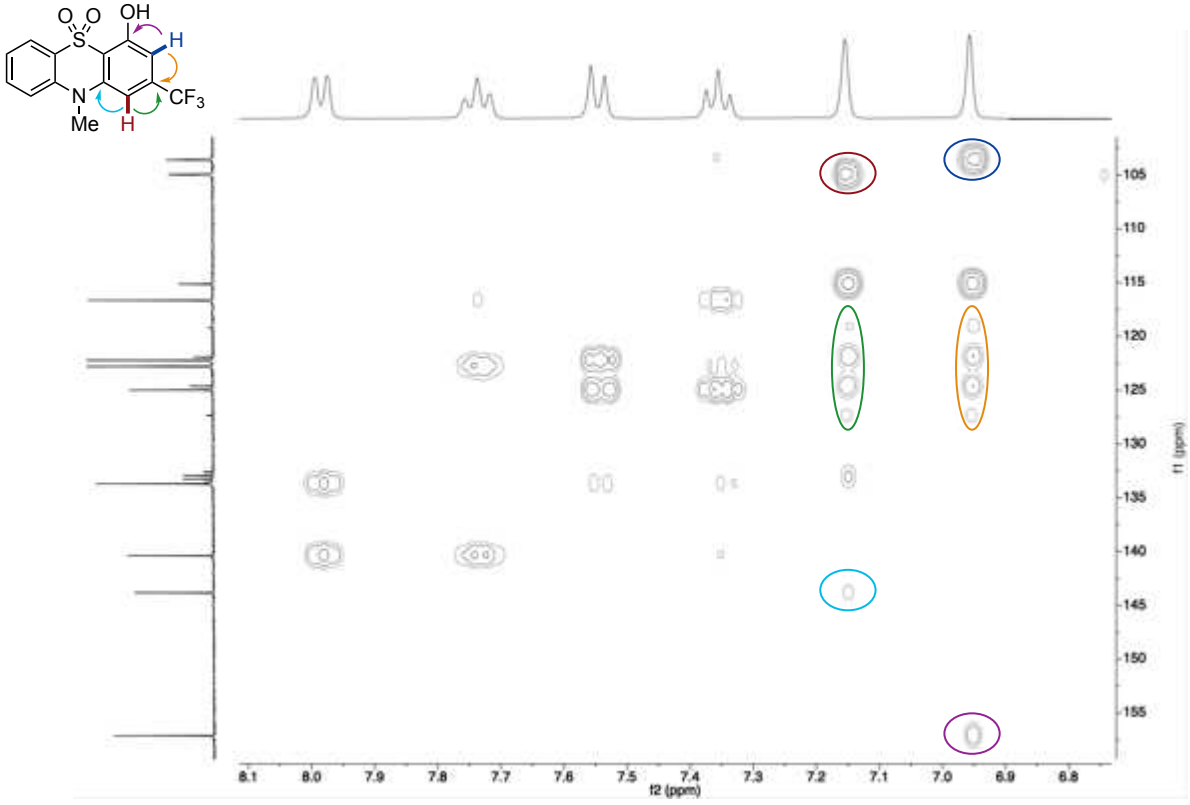
^{13}C NMR spectrum of **2-39** (101 MHz, $(CD_3)_2SO$)



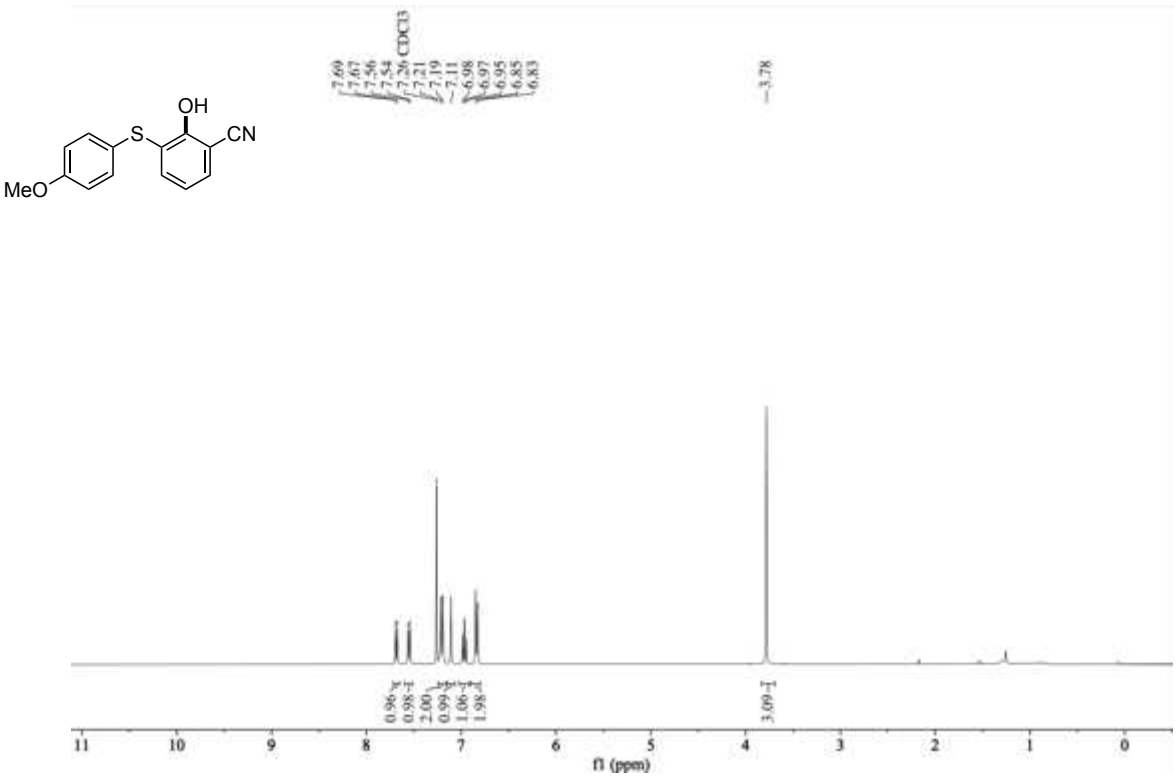
^{19}F NMR spectrum of **2-39** (376 MHz, $(CD_3)_2SO$)



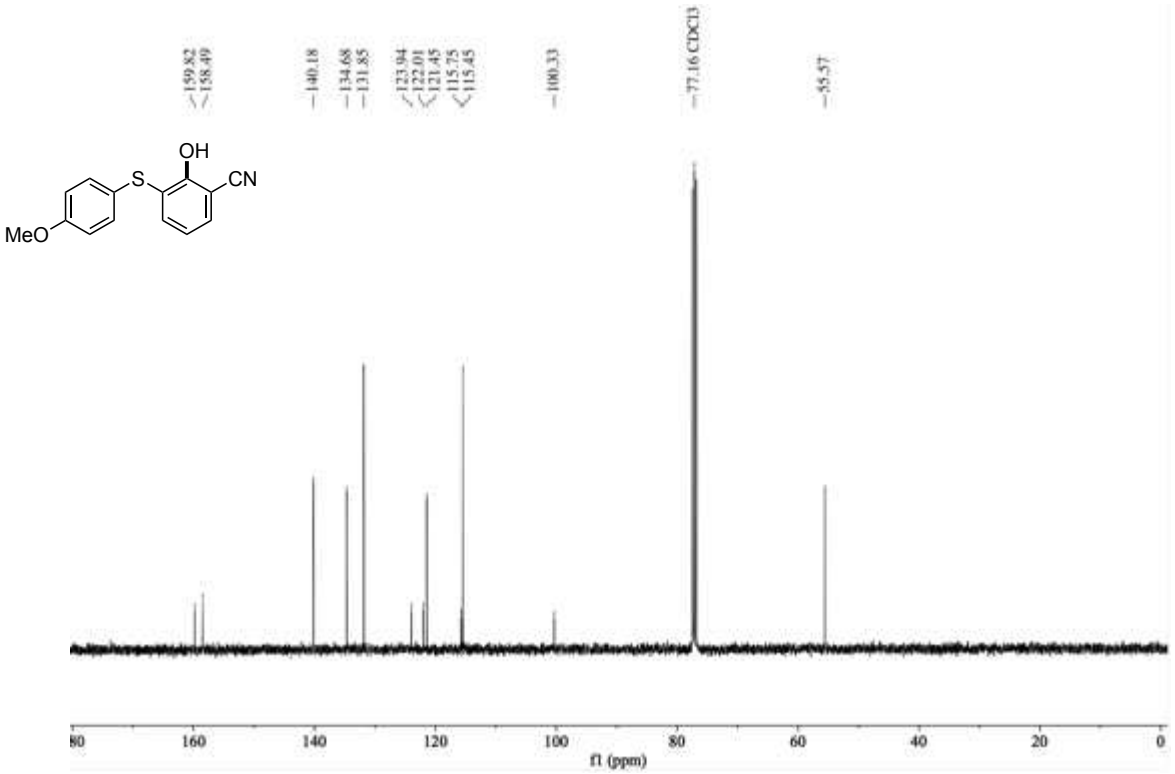
HSQC spectrum of **2-39** $(CD_3)_2SO$



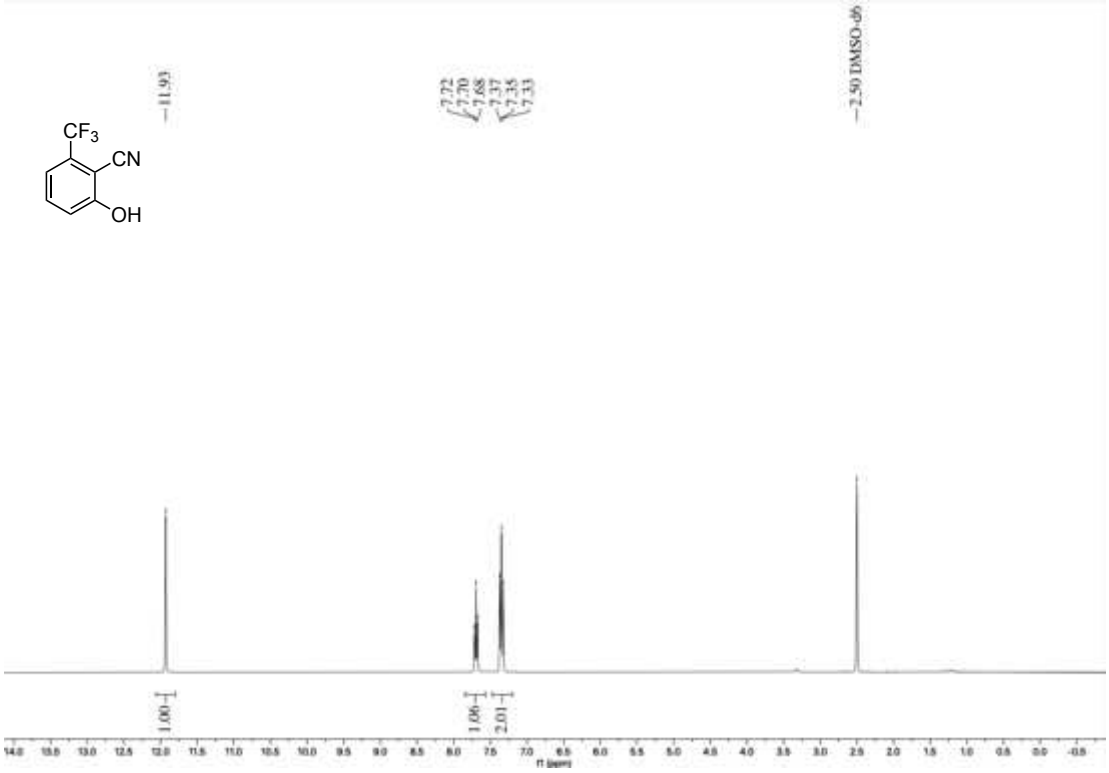
HMBC spectrum of **2-39** $(CD_3)_2SO$



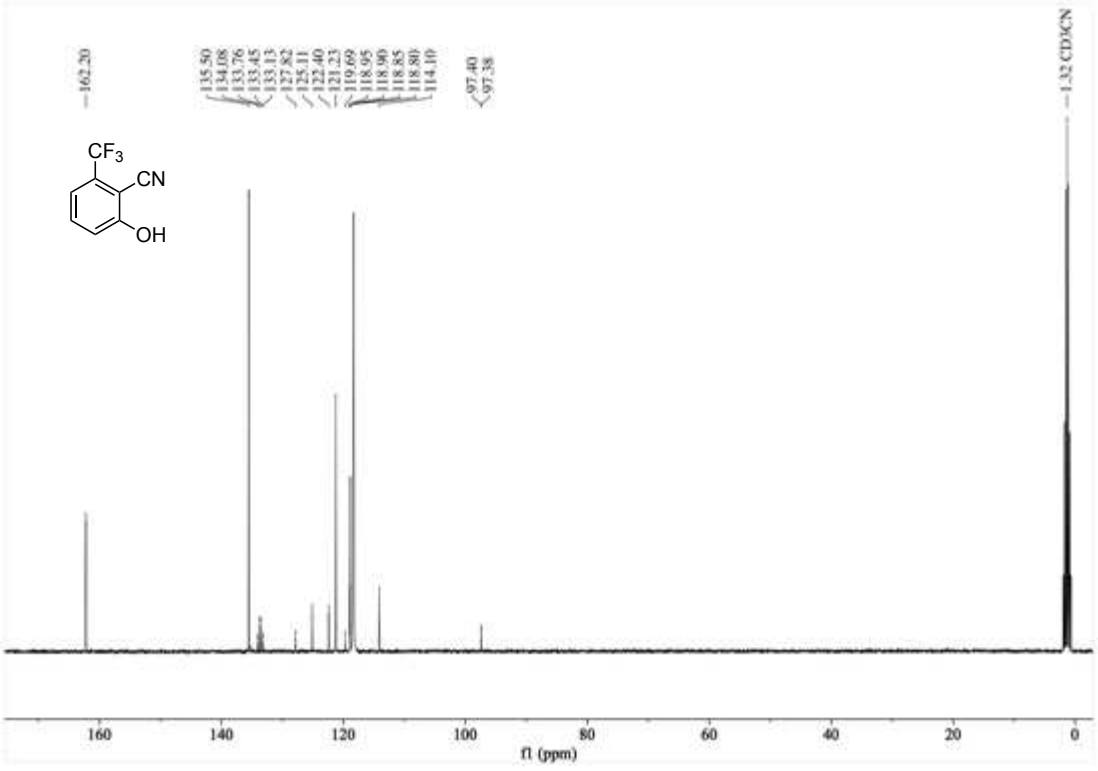
^{1}**H NMR** spectrum of **2-40** (400 MHz, $CDCl_3$)



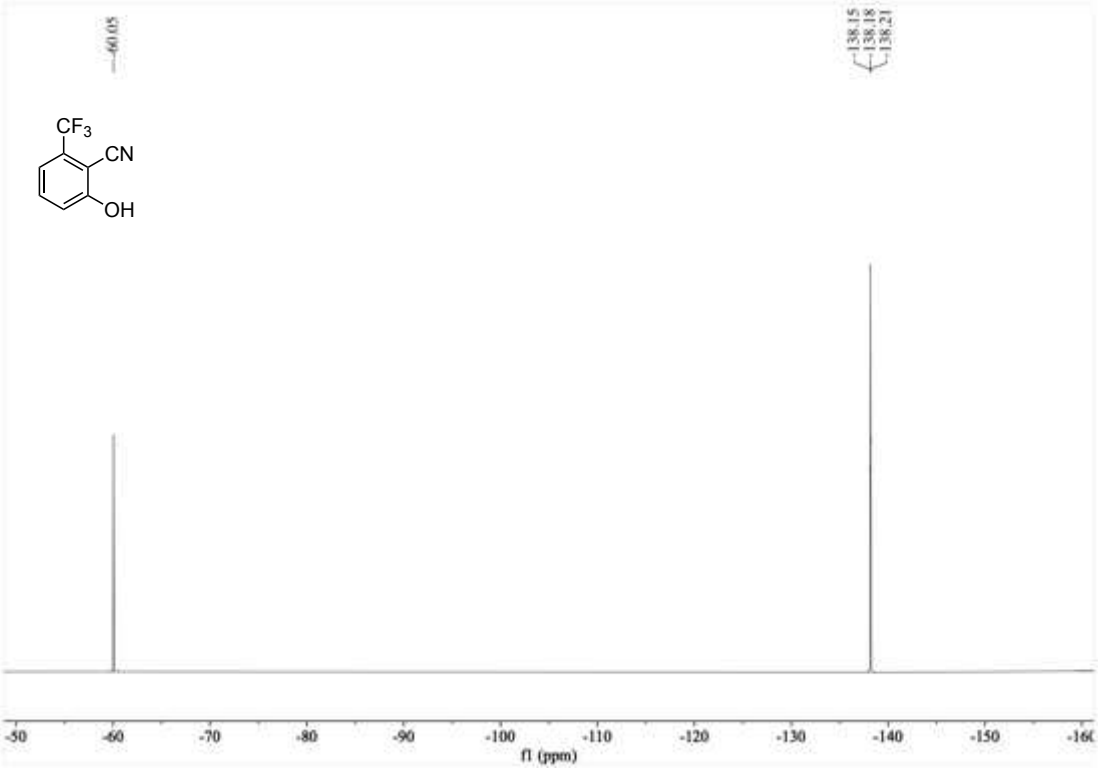
^{13}**C NMR** spectrum of **2-40** (101 MHz, $CDCl_3$)



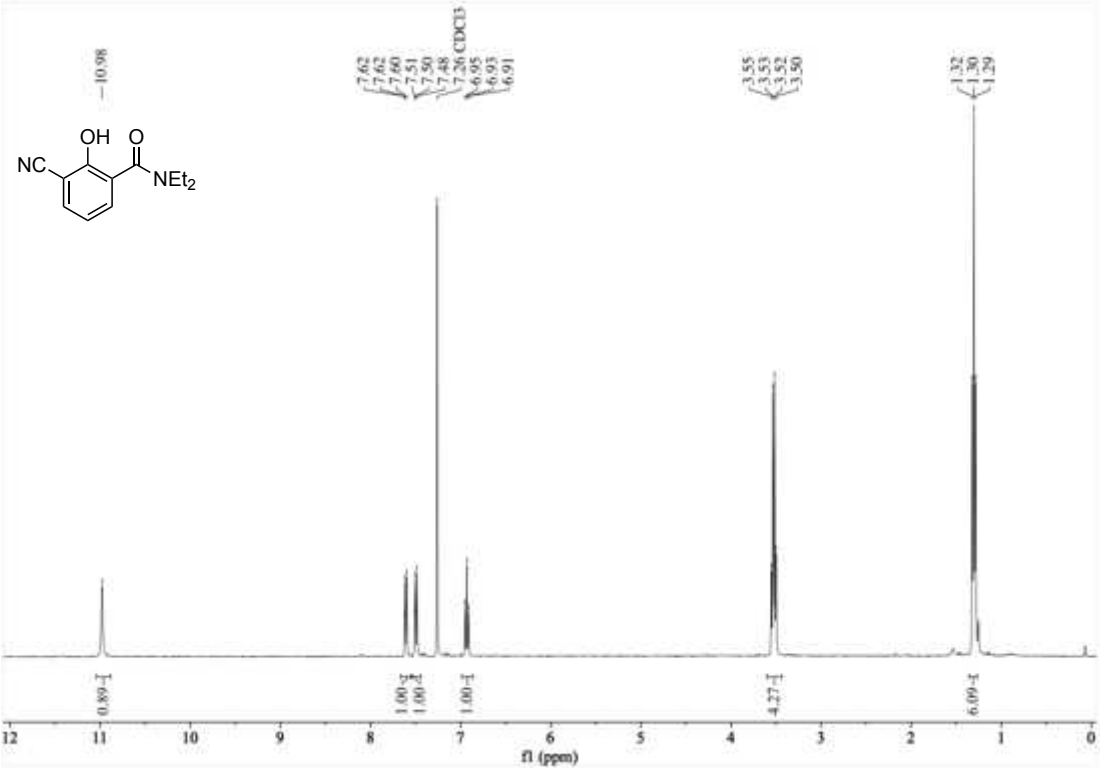
^{1}**H NMR** spectrum of **2-41** (400 MHz, $CDCl_3$)



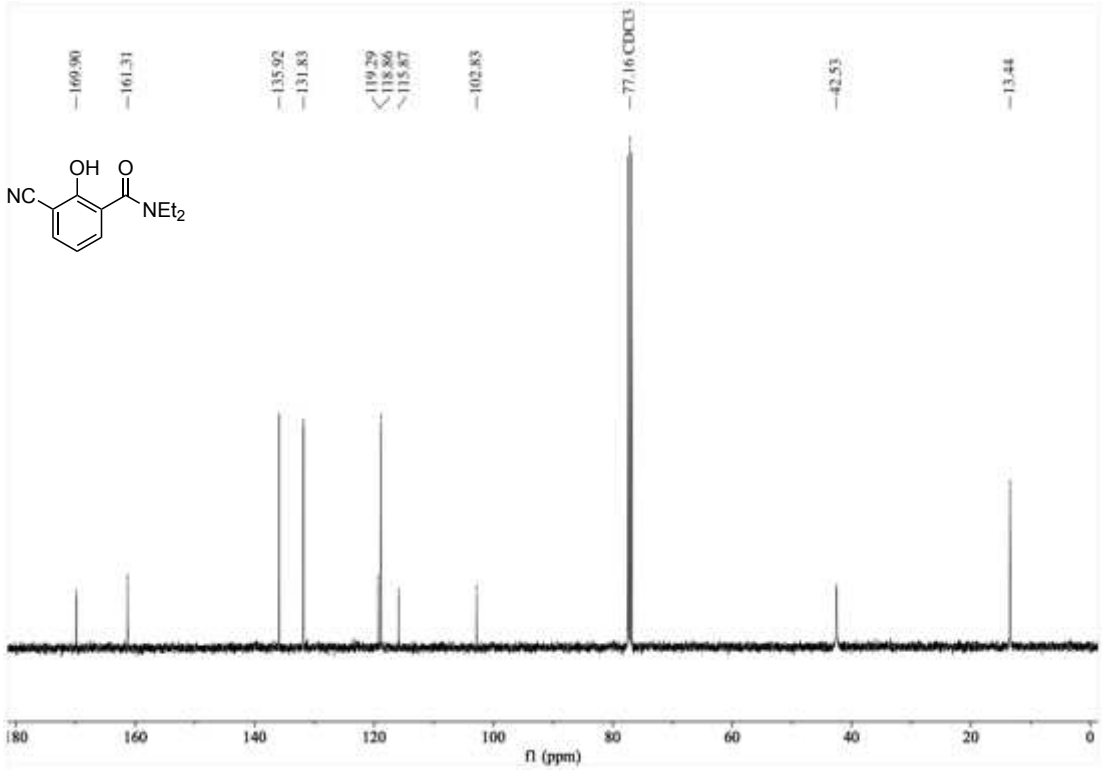
^{13}**C NMR** spectrum of **2-41** (101 MHz, CD_3CN)



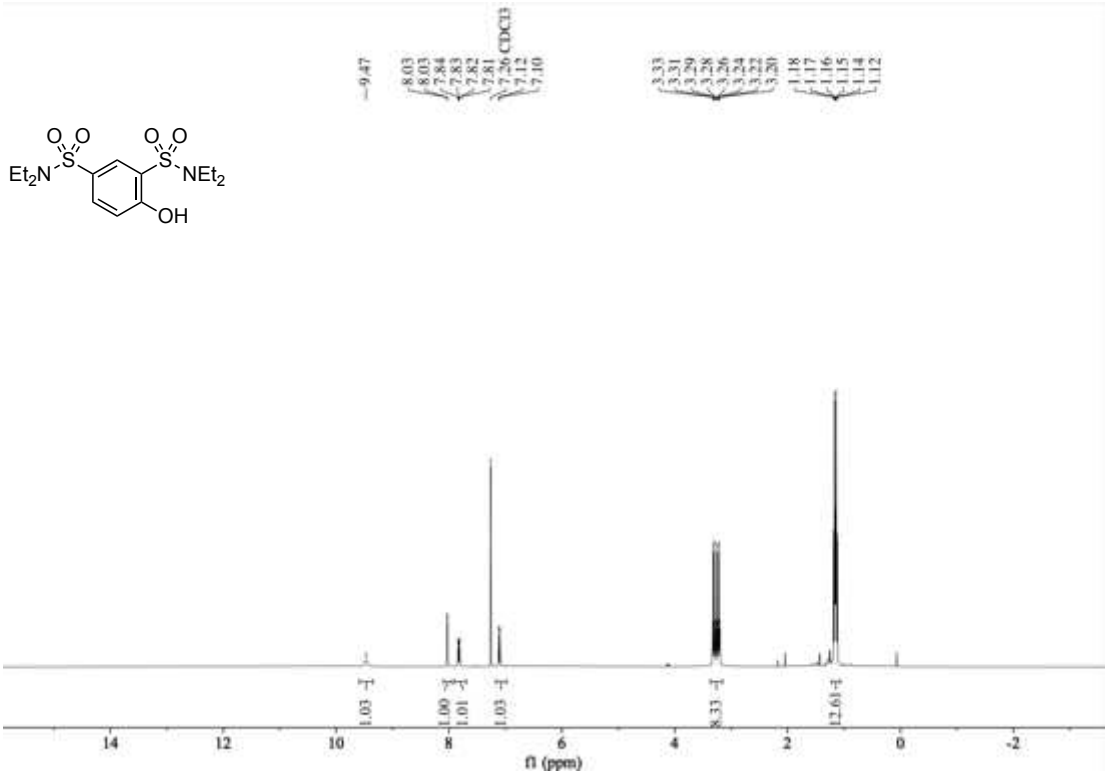
^{19}F NMR spectrum of **2-41** (376 MHz, $CDCl_3$)



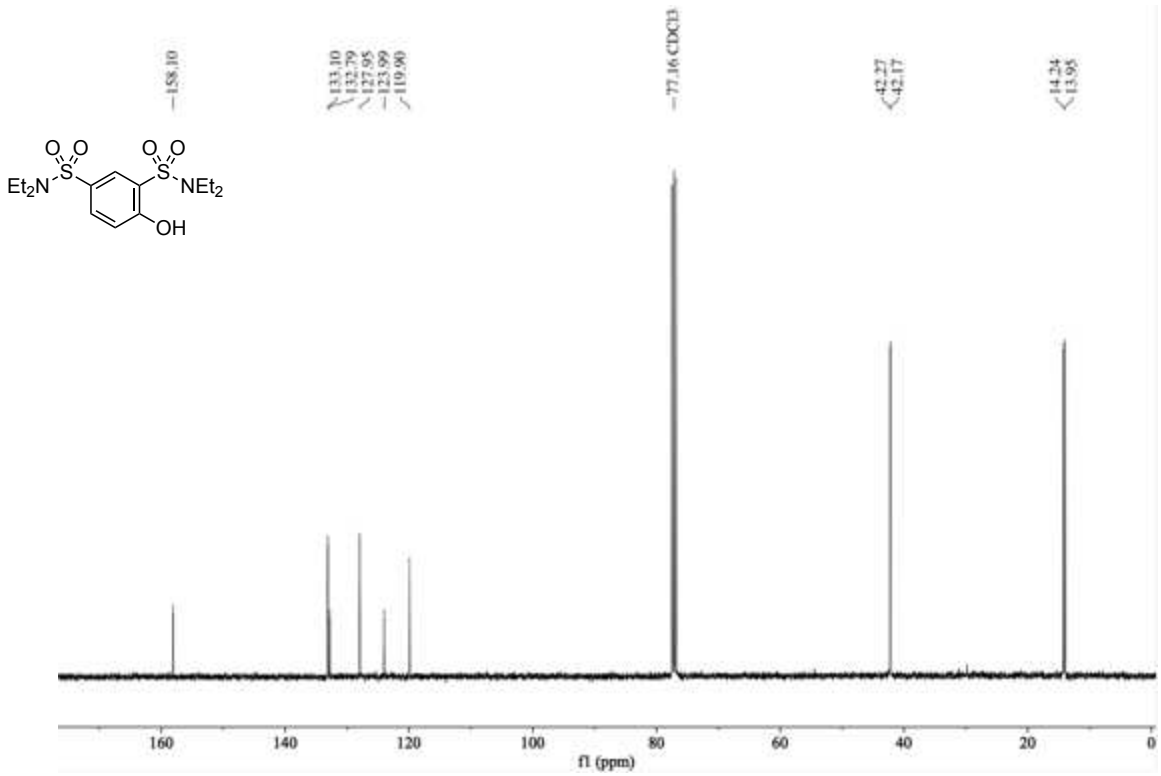
^{1}H NMR spectrum of **2-42** (400 MHz, $CDCl_3$)



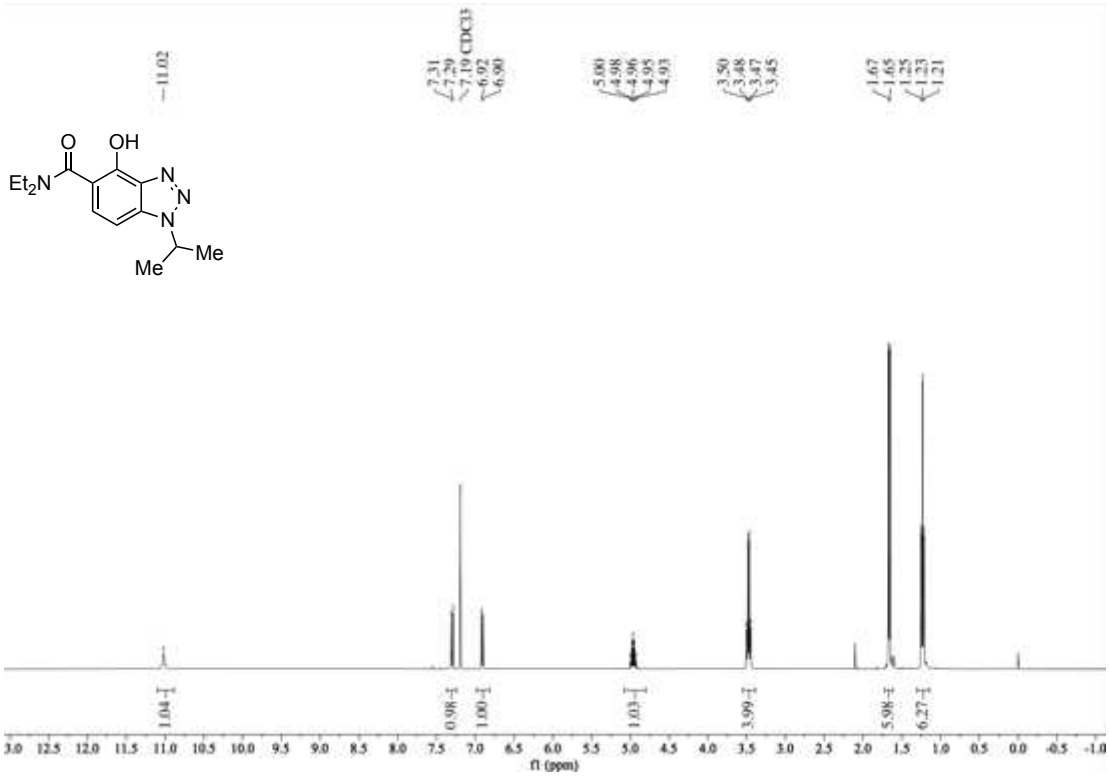
^{13}C NMR spectrum of **2-42** (101 MHz, $CDCl_3$)



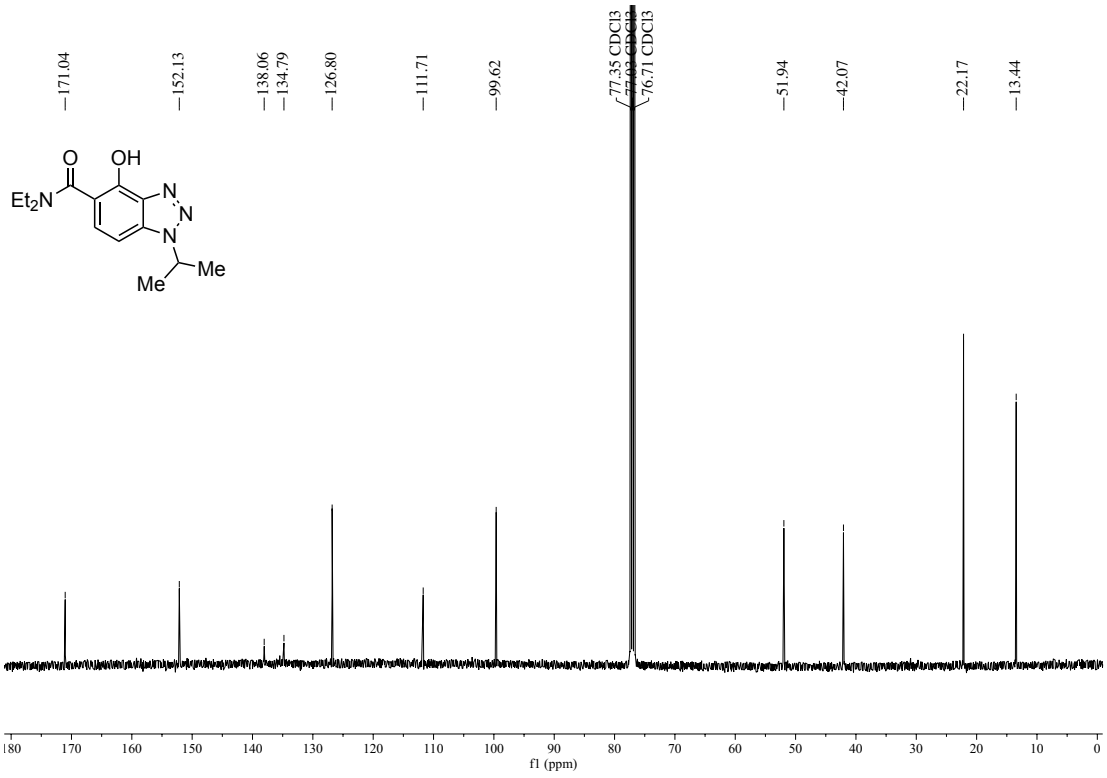
^{1}H NMR spectrum of **2-43** (400 MHz, $CDCl_3$)



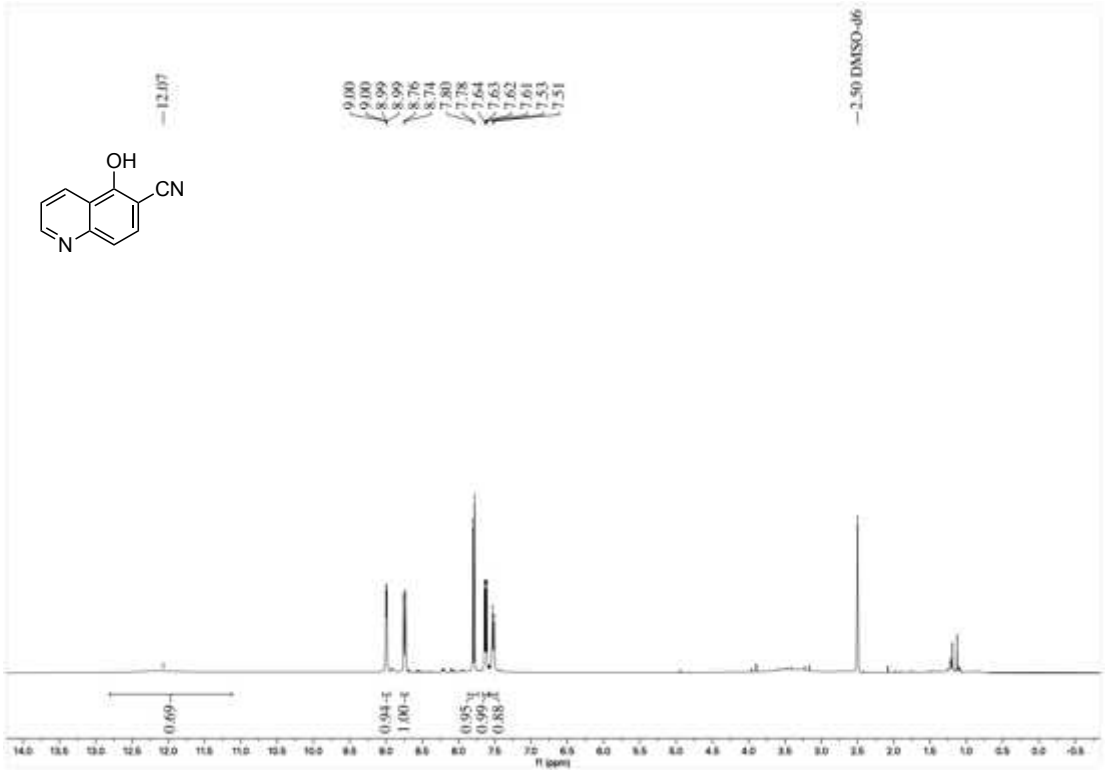
^{13}C NMR spectrum of **2-43** (101 MHz, $CDCl_3$)



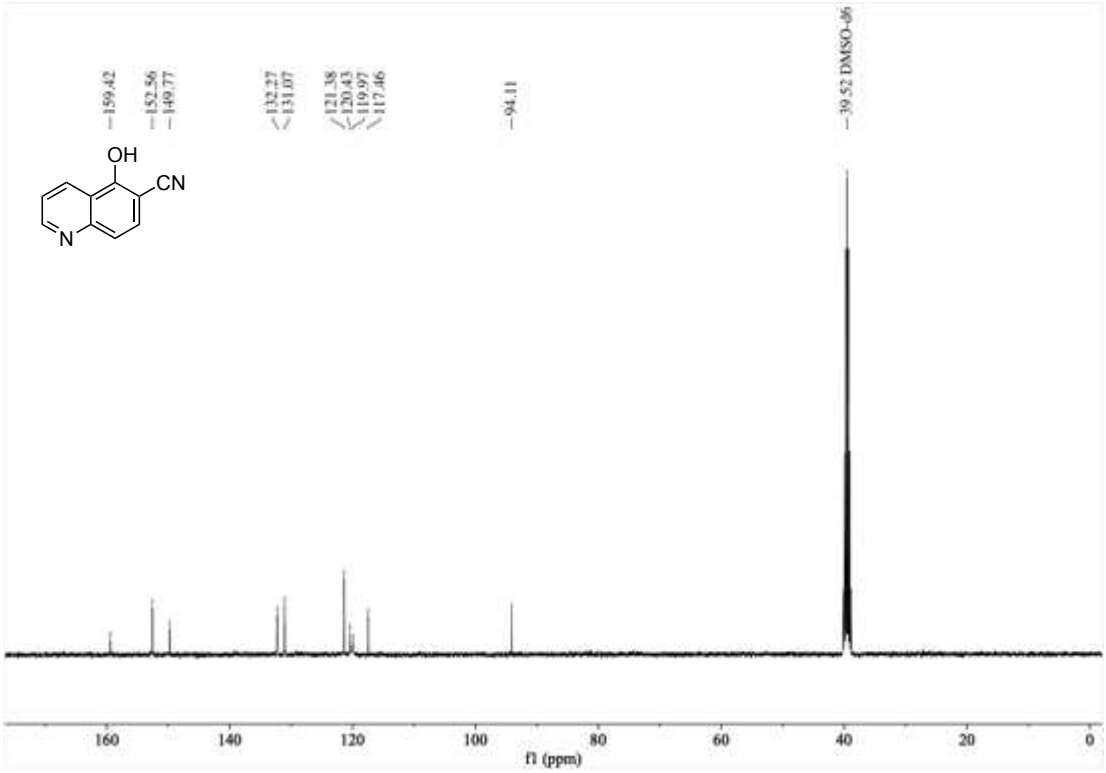
^{1}H NMR spectrum of **2-44** (400 MHz, $CDCl_3$)



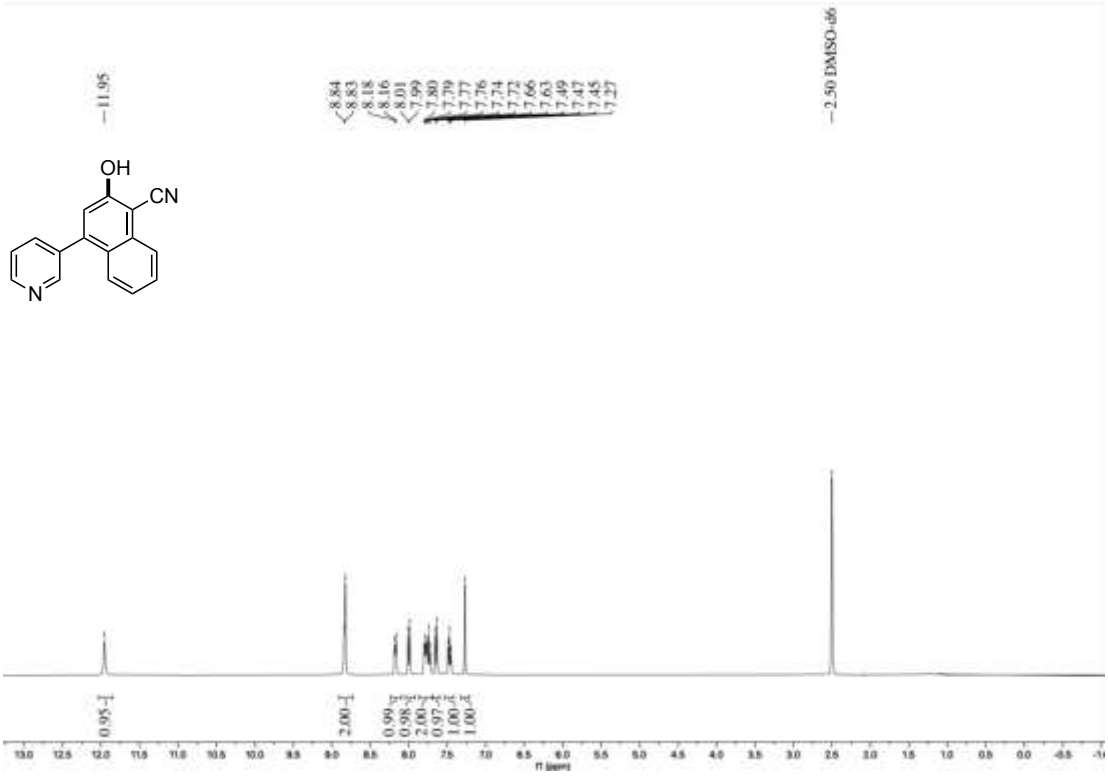
^{13}C NMR spectrum of **2-44** (101 MHz, $CDCl_3$)



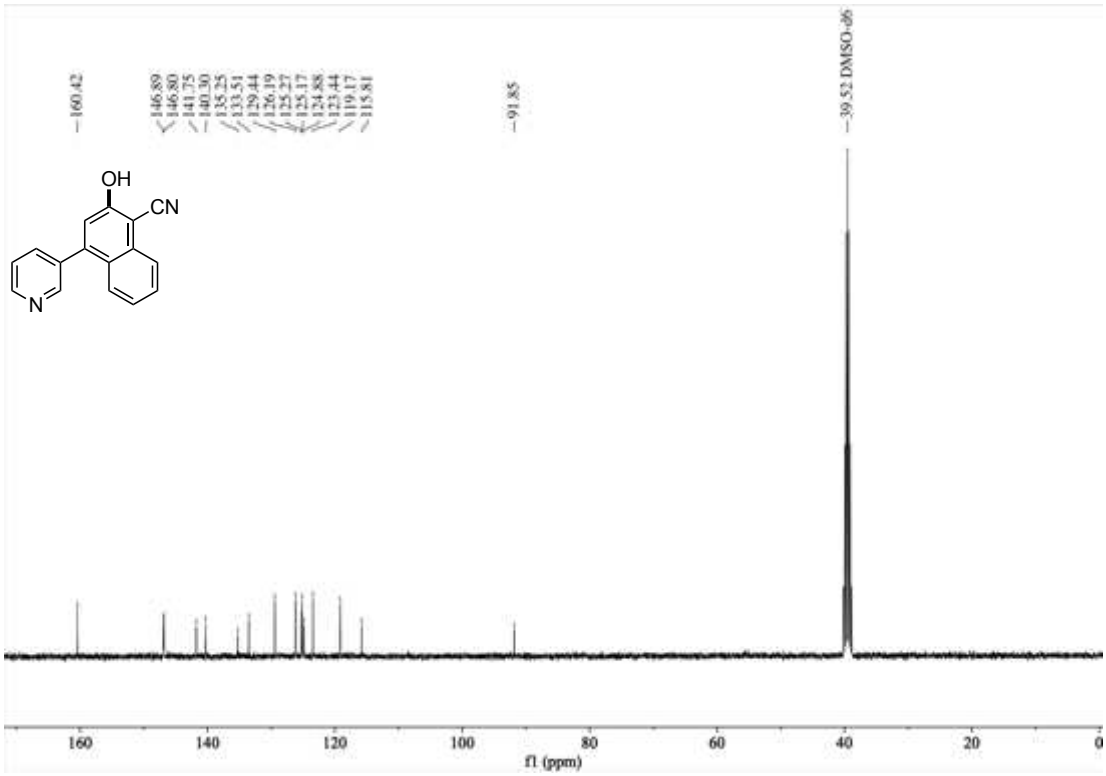
^{1}H NMR spectrum of **2-45** (400 MHz, $(CD_3)_2SO$)



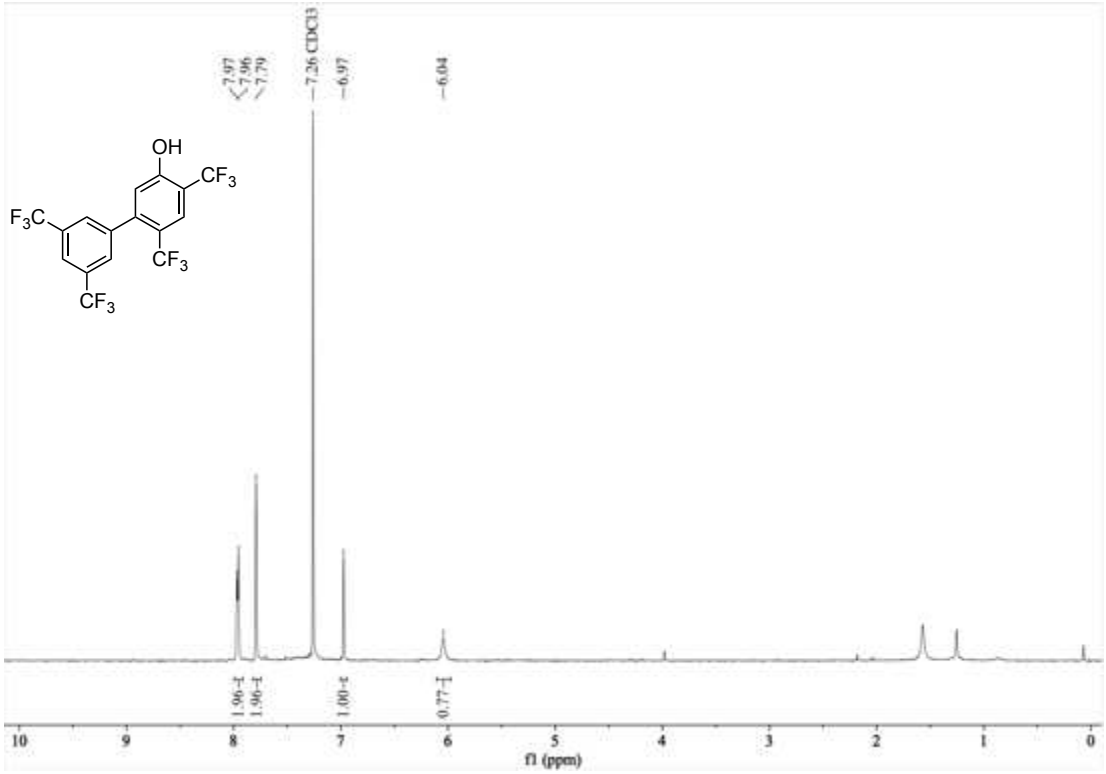
^{13}C NMR spectrum of **2-45** (101 MHz, $(CD_3)_2SO$)



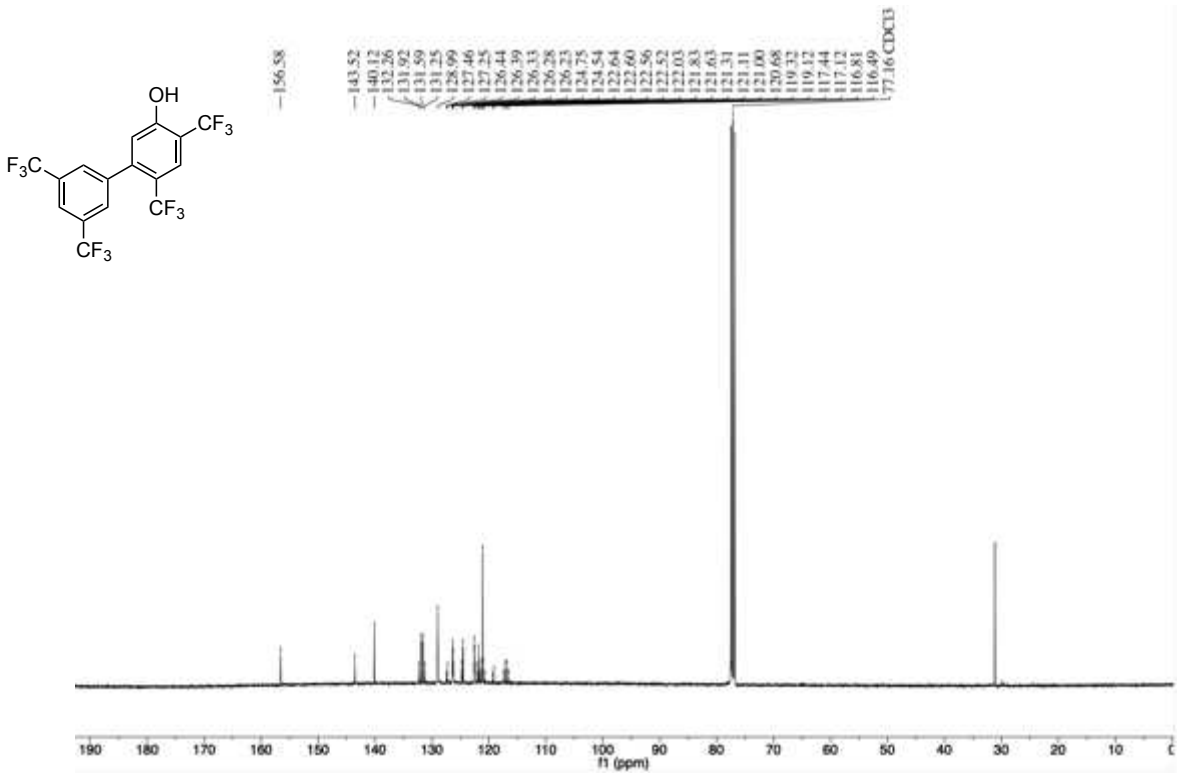
^{1}H NMR spectrum of **2-46** (400 MHz, $(CD_3)_2SO$)



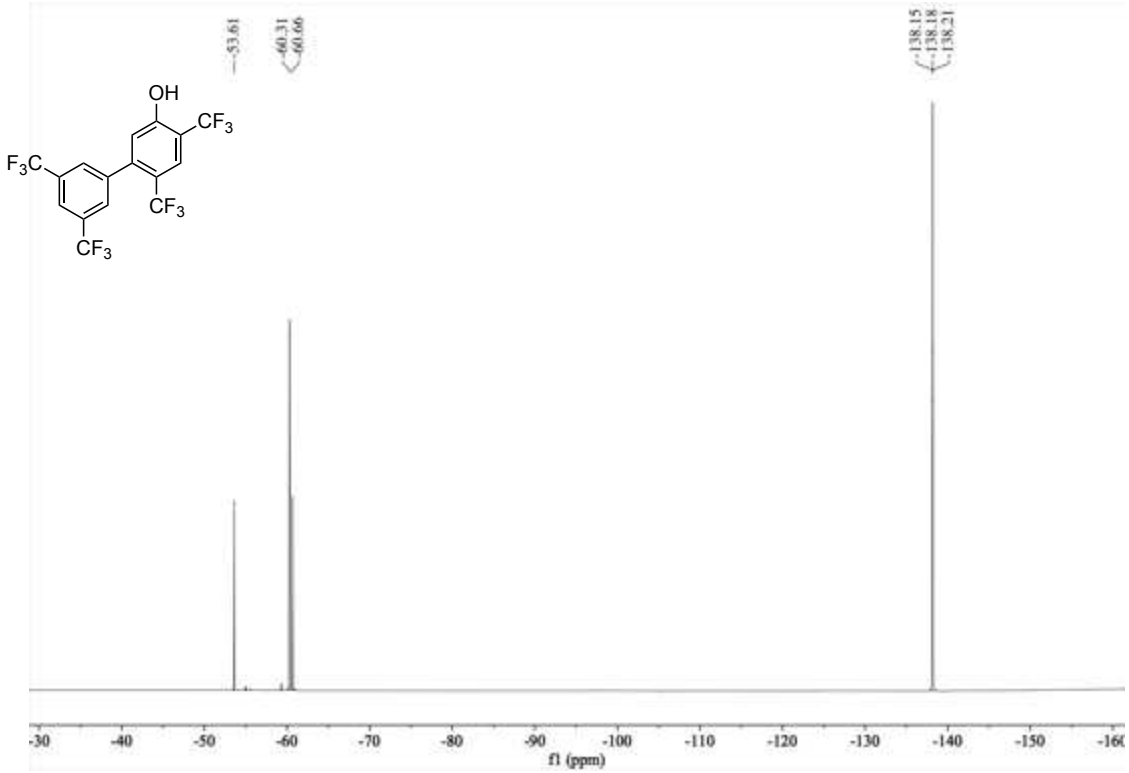
^{13}C NMR spectrum of **2-46** (101 MHz, $(CD_3)_2SO$)



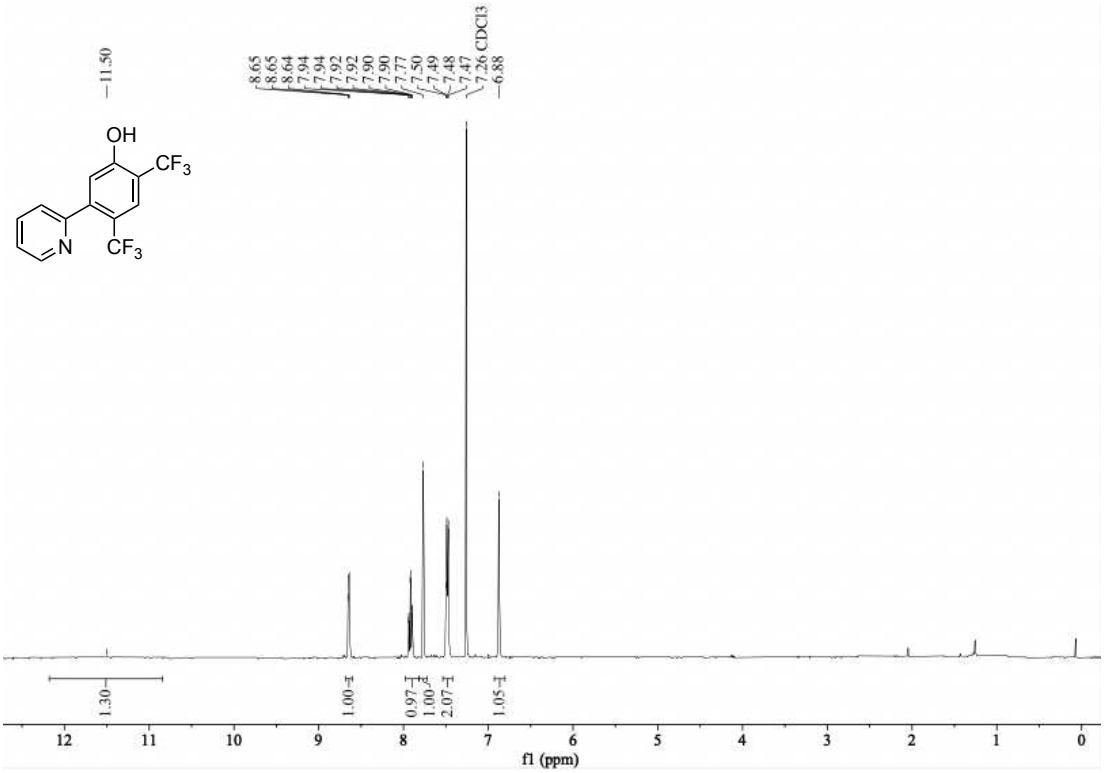
^{1}H NMR spectrum of **2-47** (400 MHz, $CDCl_3$)



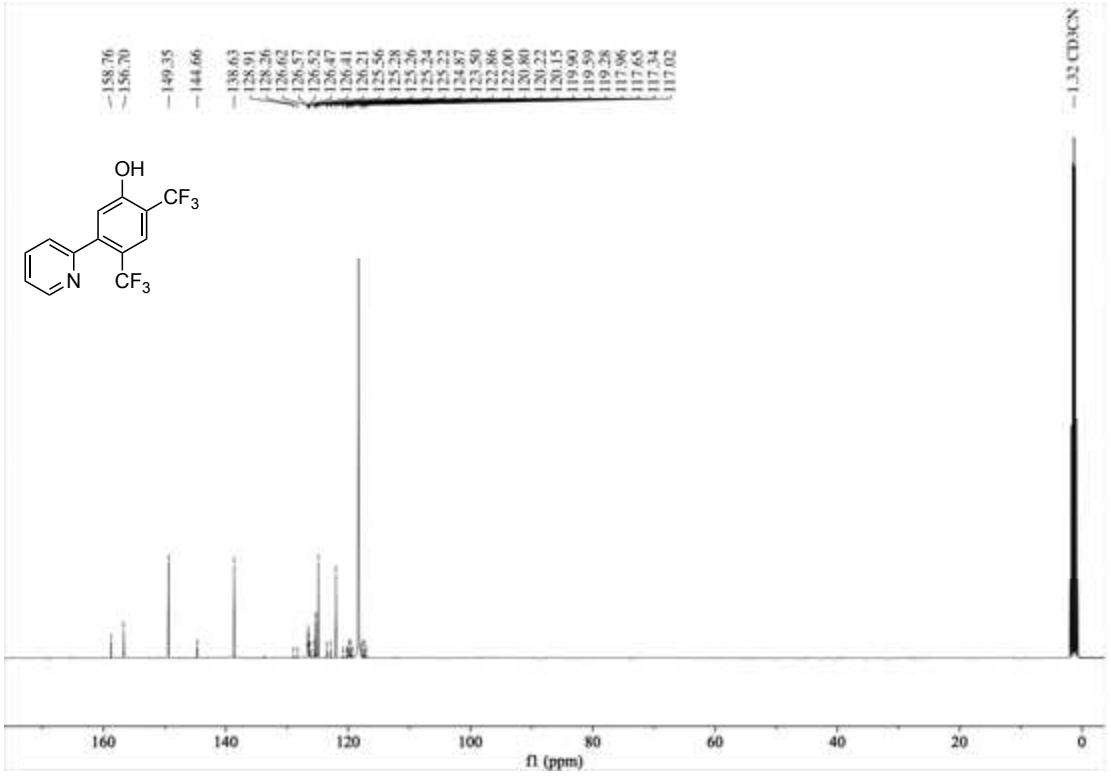
^{13}C NMR spectrum of **2-47** (101 MHz, $CDCl_3$)



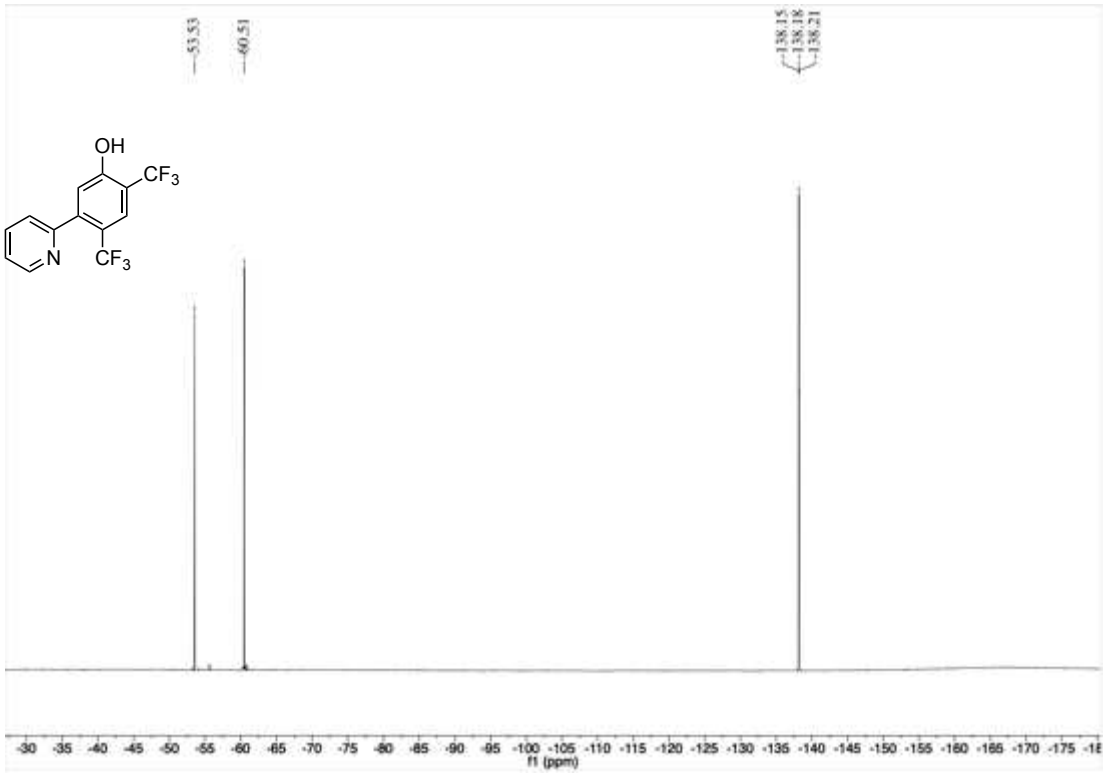
^{19}F NMR spectrum of **2-47** (376 MHz, $CDCl_3$)



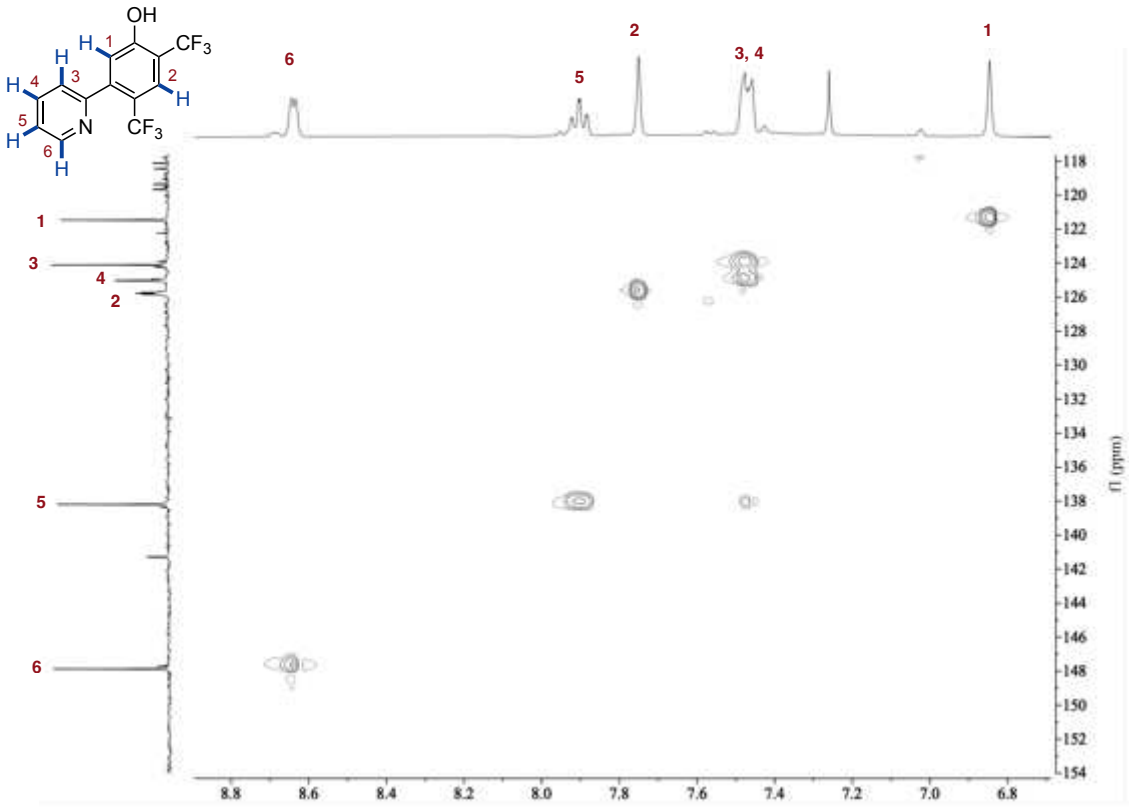
^{1}**H NMR** spectrum of **2-48** (400 MHz, $CDCl_3$)



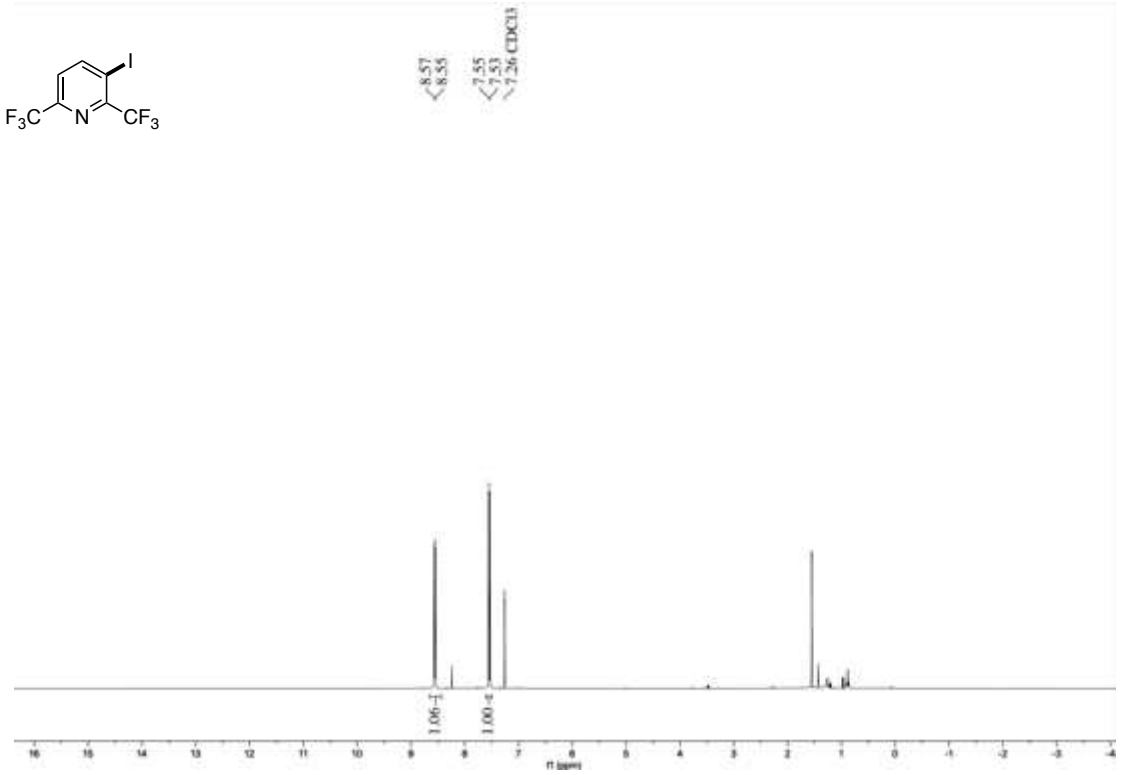
^{13}**C NMR** spectrum of **2-48** (101 MHz, CD_3CN)



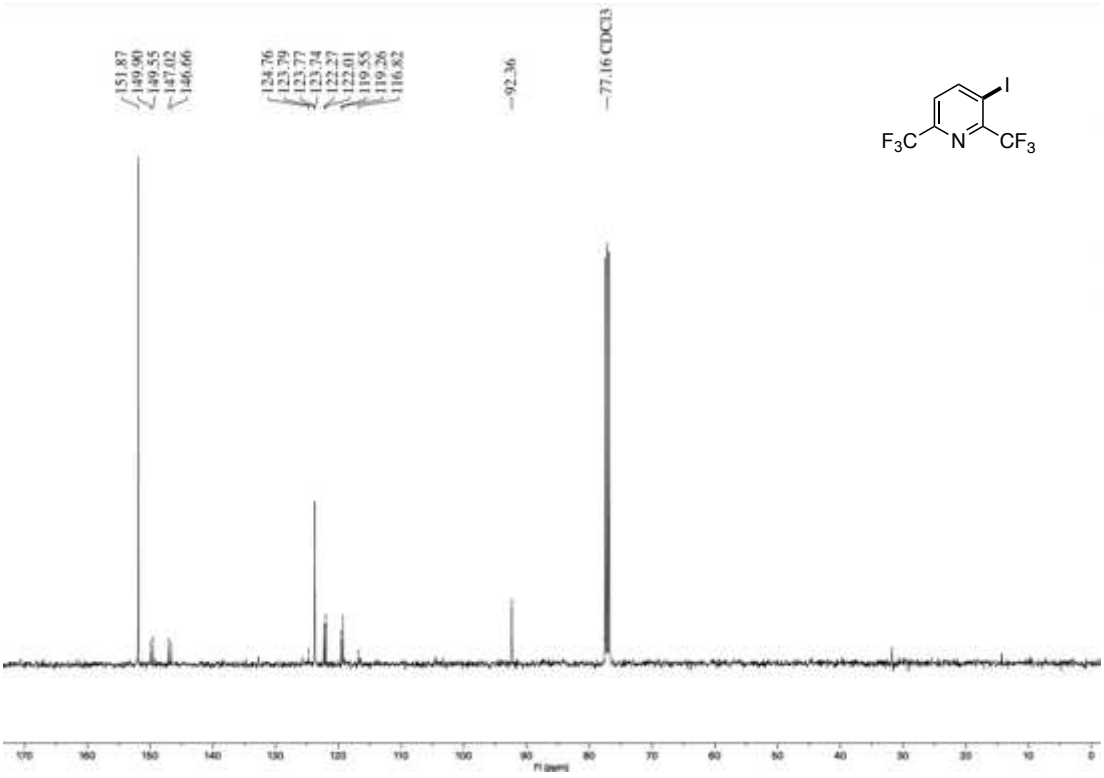
^{19}F NMR spectrum of **2-48** (376 MHz, $CDCl_3$)



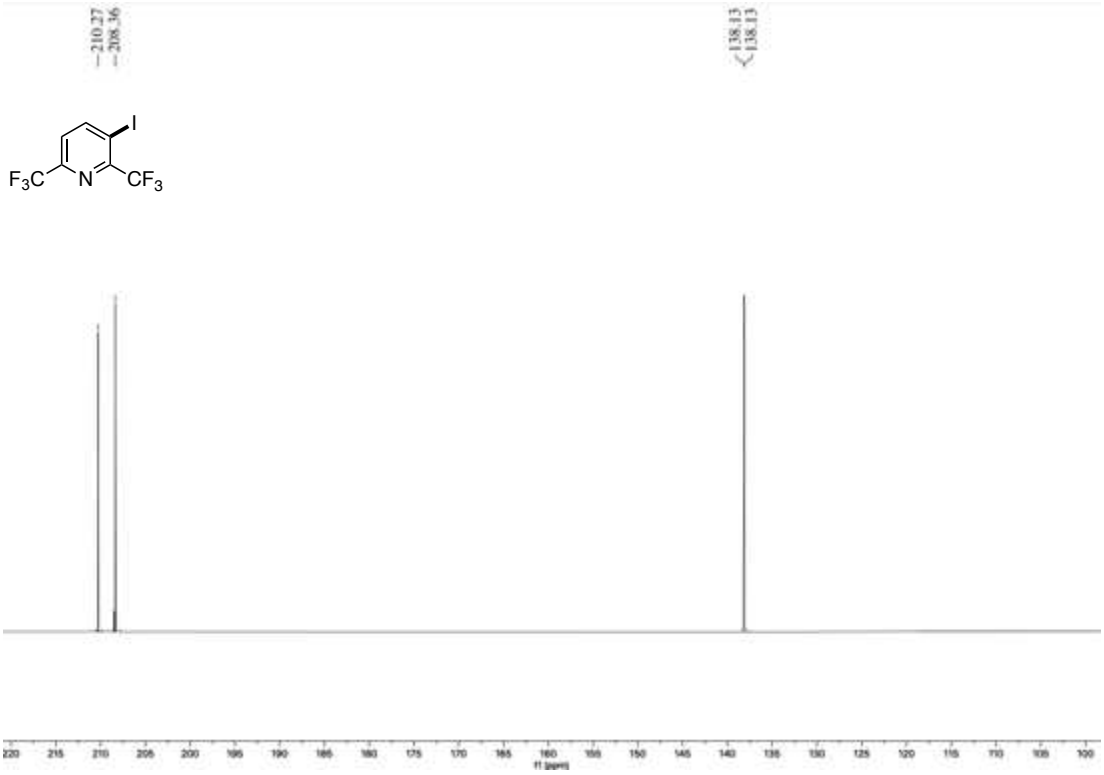
HSQC spectrum of **1-48** ($CDCl_3$)



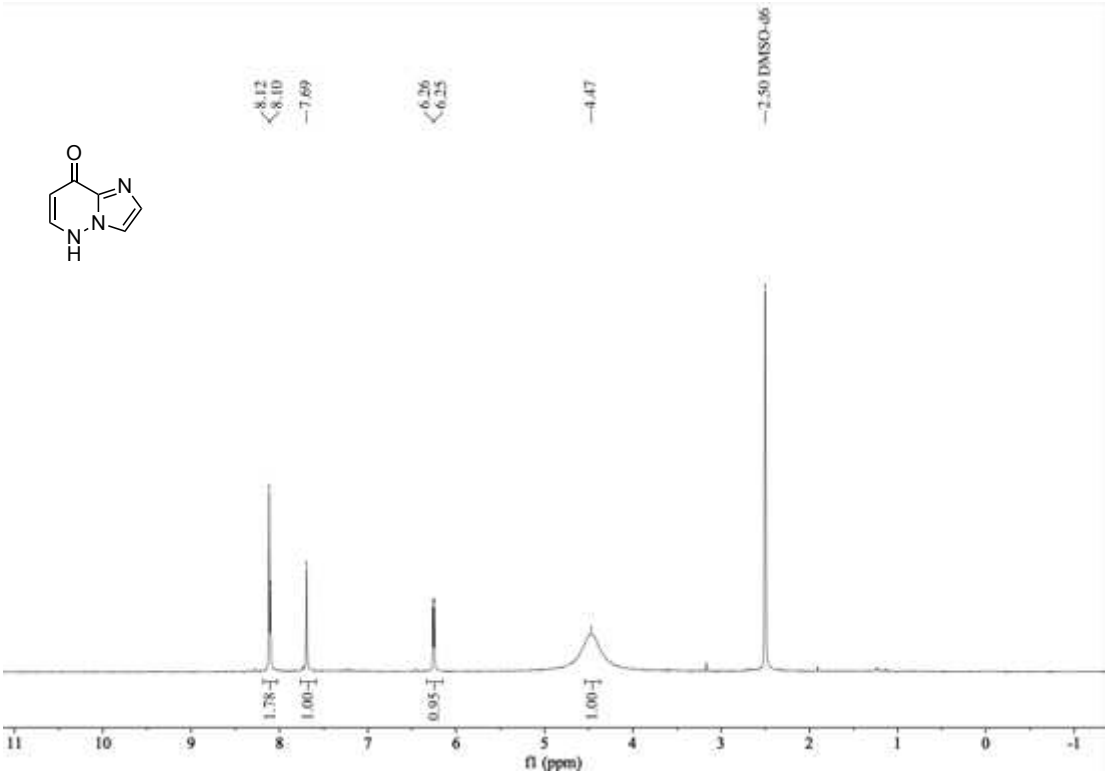
^{1}**H NMR** spectrum of **2-53** (400 MHz, $CDCl_3$)



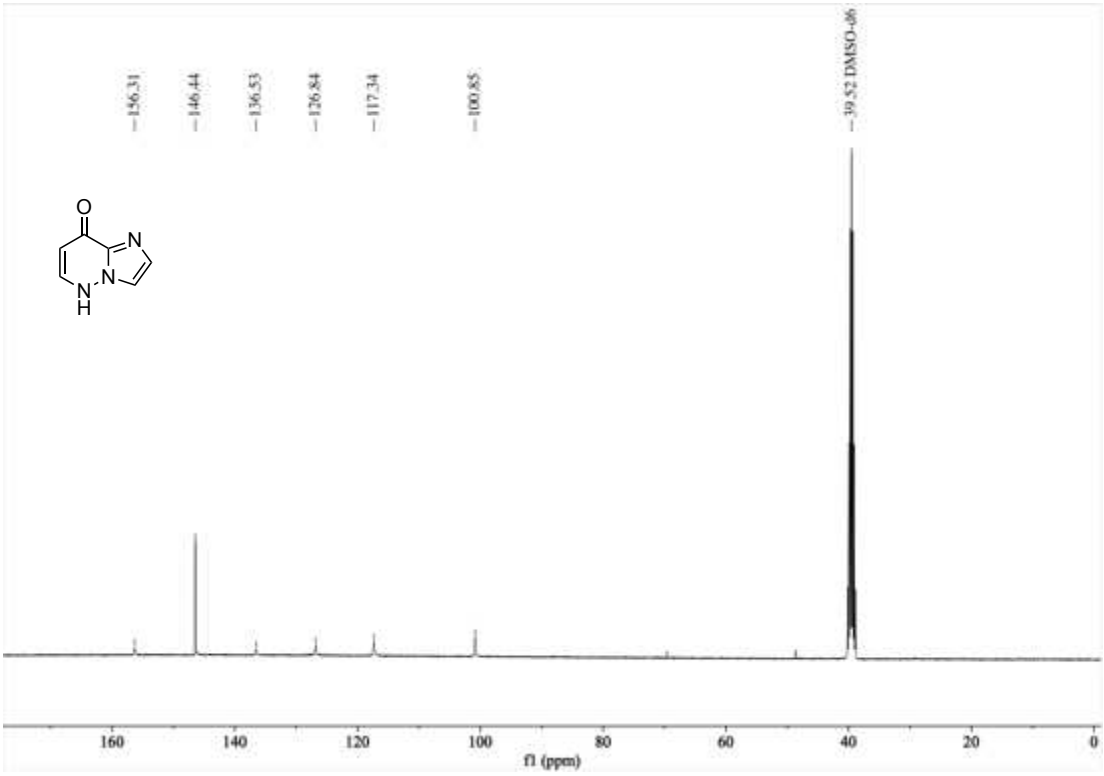
^{13}**C NMR** spectrum of **2-53** (101 MHz, $CDCl_3$)



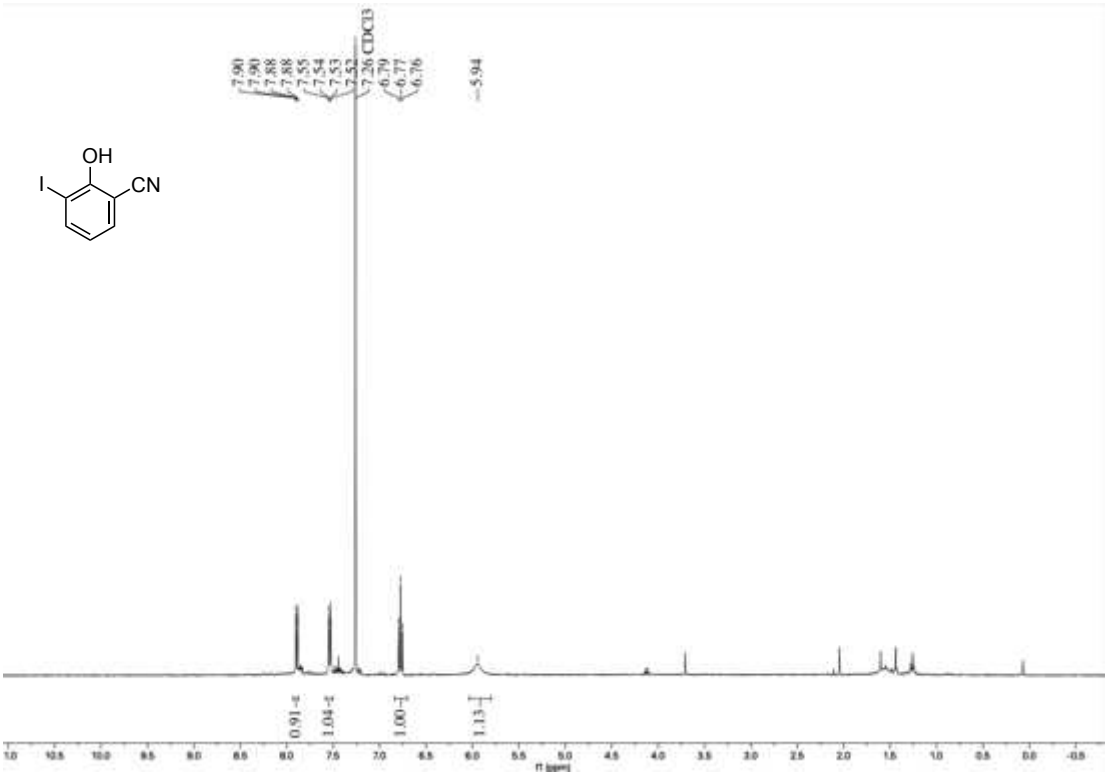
^{19}F NMR spectrum of **2-53** (376 MHz, $CDCl_3$)



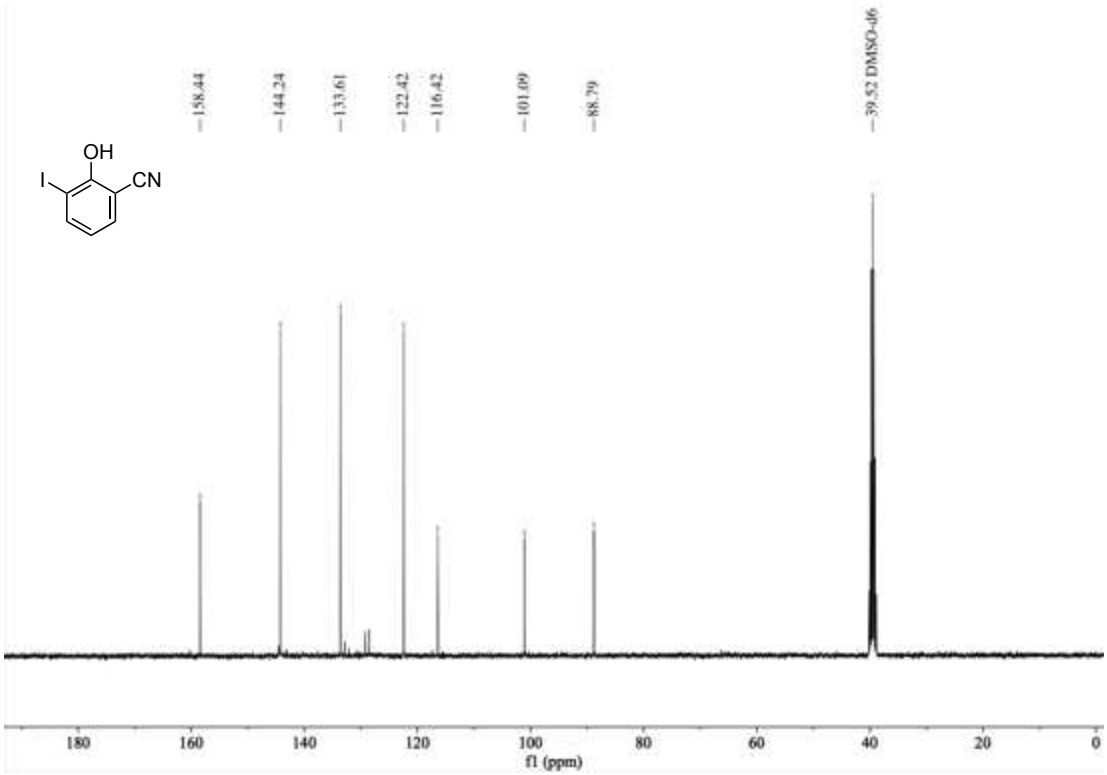
^{1}H NMR spectrum of **2-59** (400 MHz, $(CD_3)_2SO$)



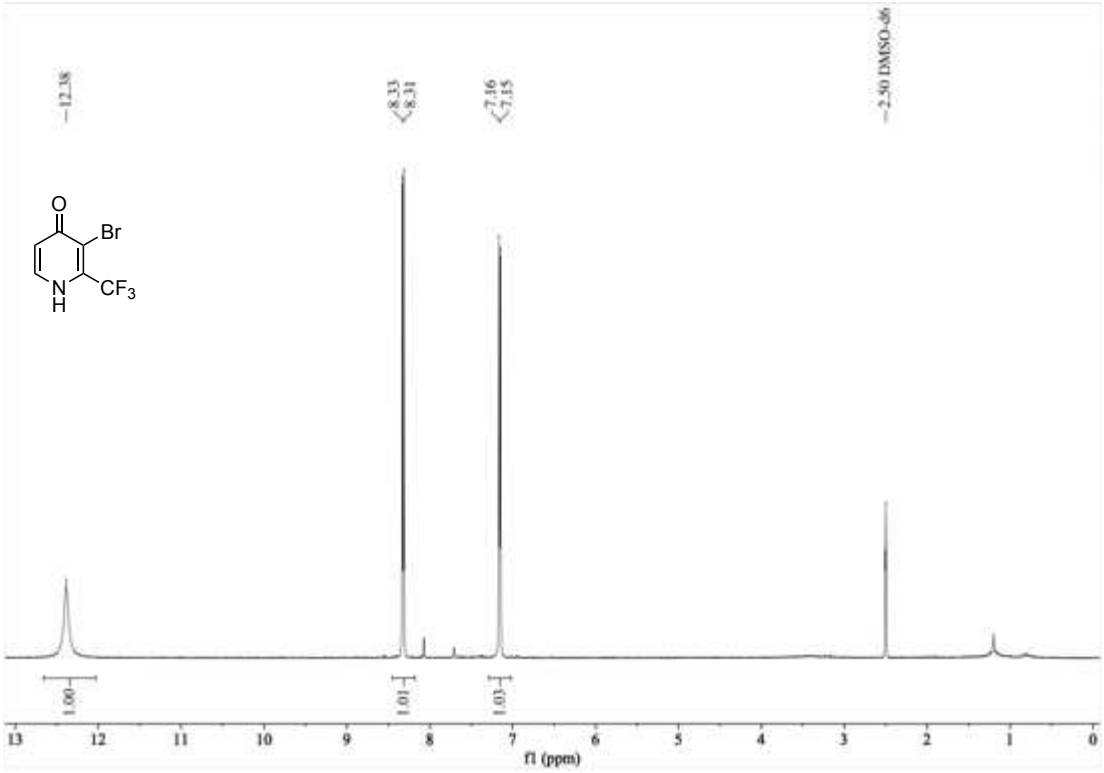
^{13}C NMR spectrum of **2-59** (101 MHz, $(CD_3)_2SO$)



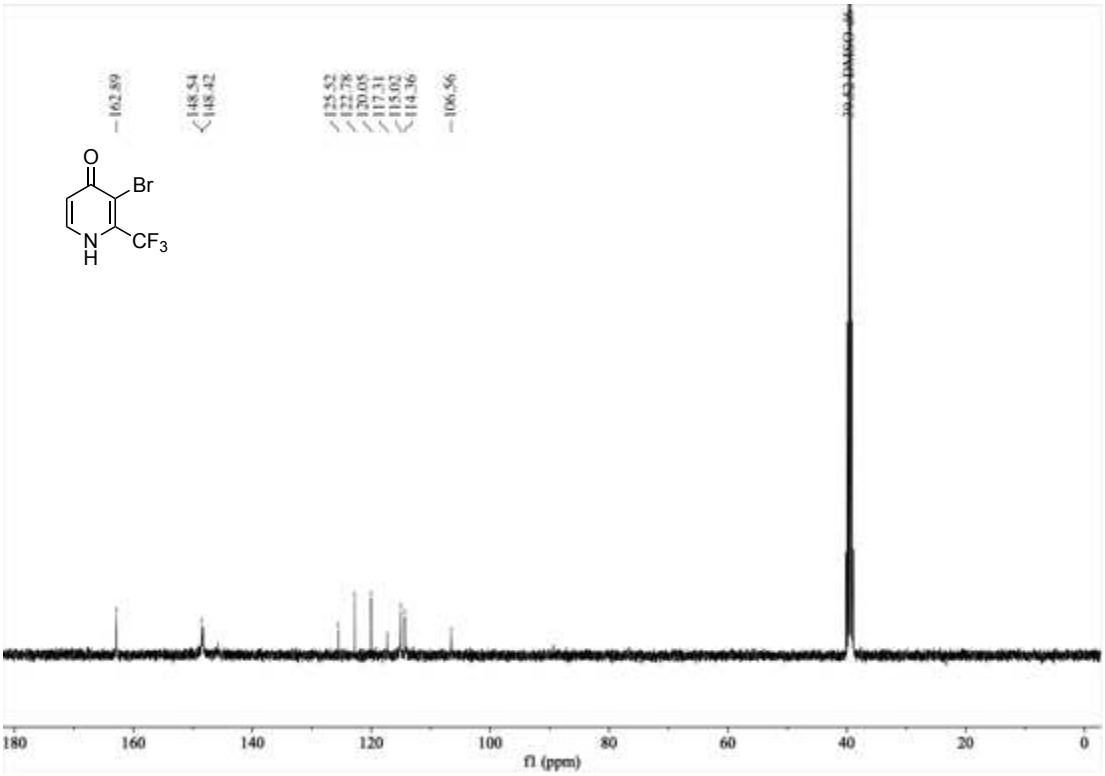
^{1}H NMR spectrum of **2-61** (400 MHz, $CDCl_3$)



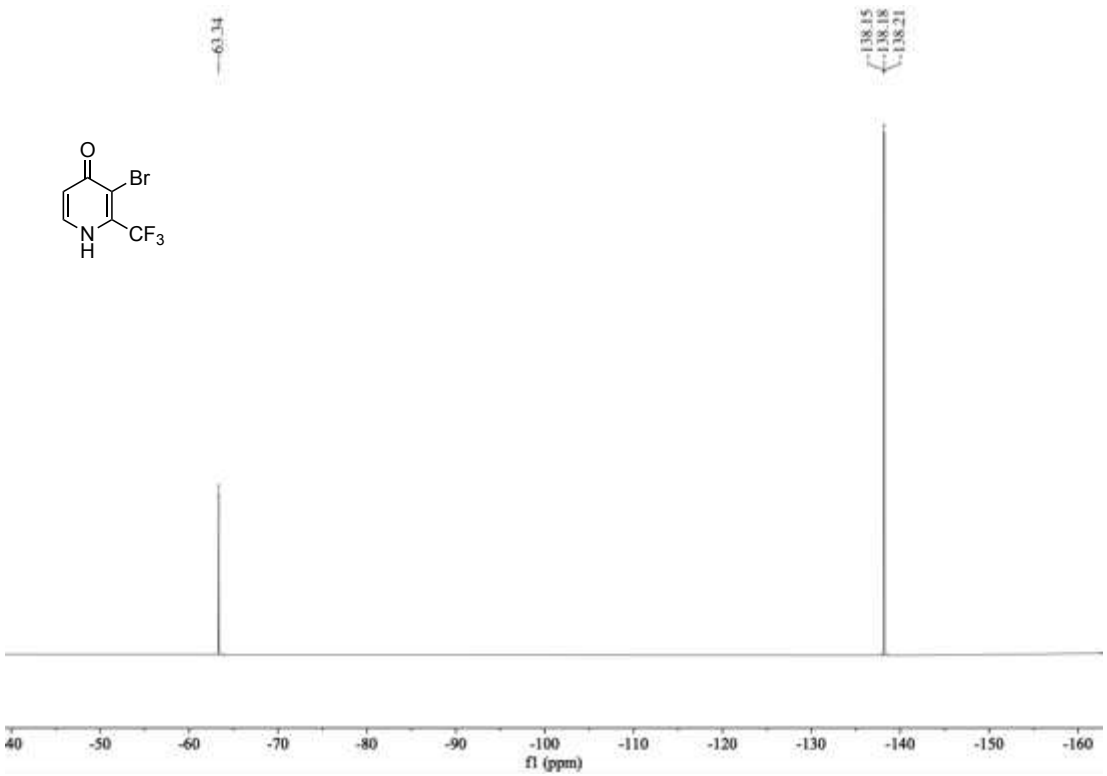
^{13}C NMR spectrum of **2-61** (101 MHz, $(CD_3)_2SO$)



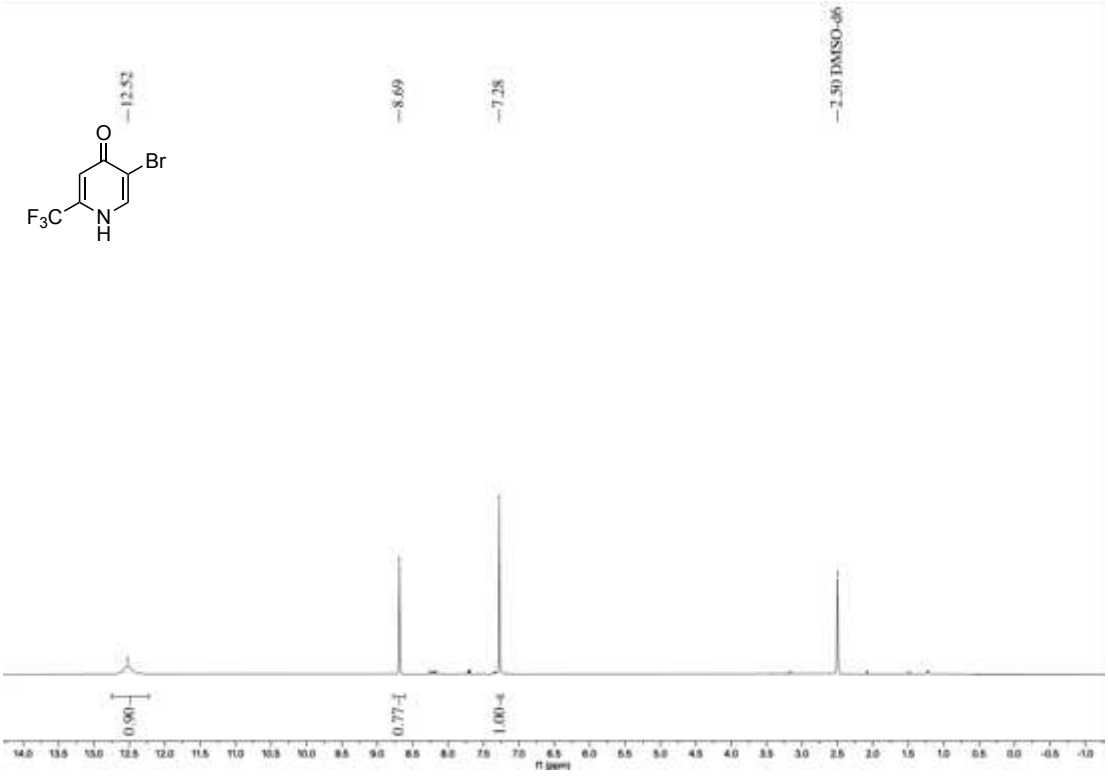
^{1}H NMR spectrum of **2-64** (400 MHz, $(CD_3)_2SO$)



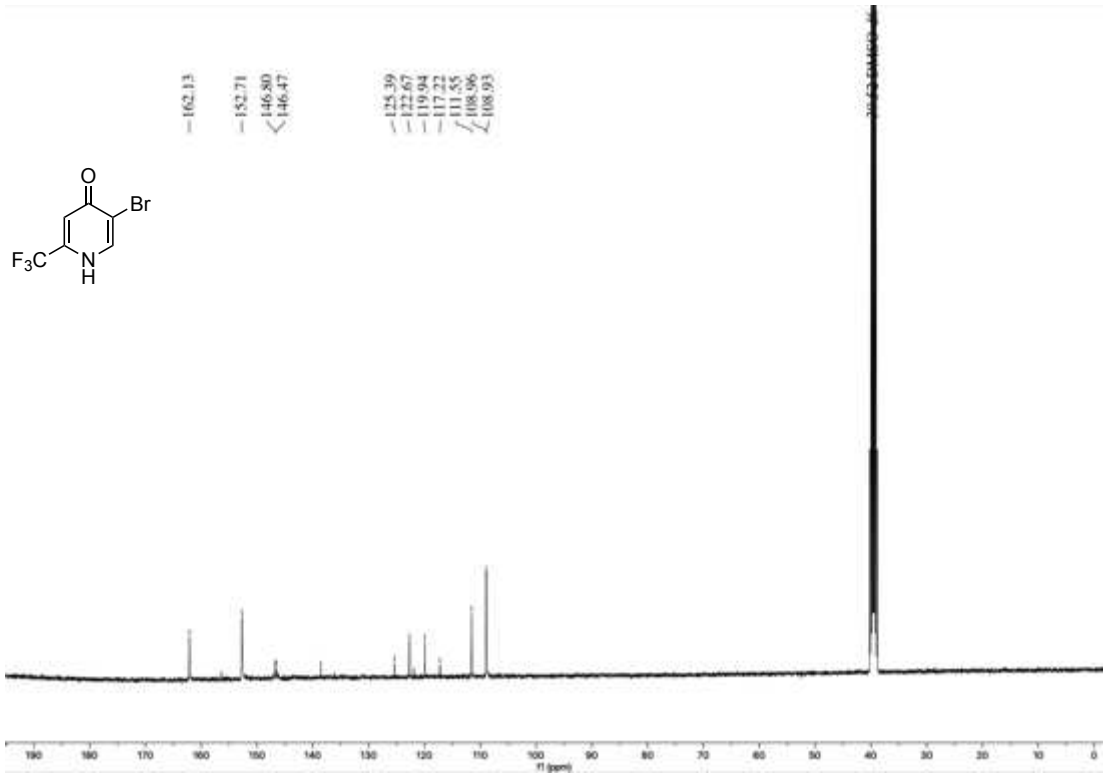
^{13}C NMR spectrum of **2-64** (101 MHz, $(CD_3)_2SO$)



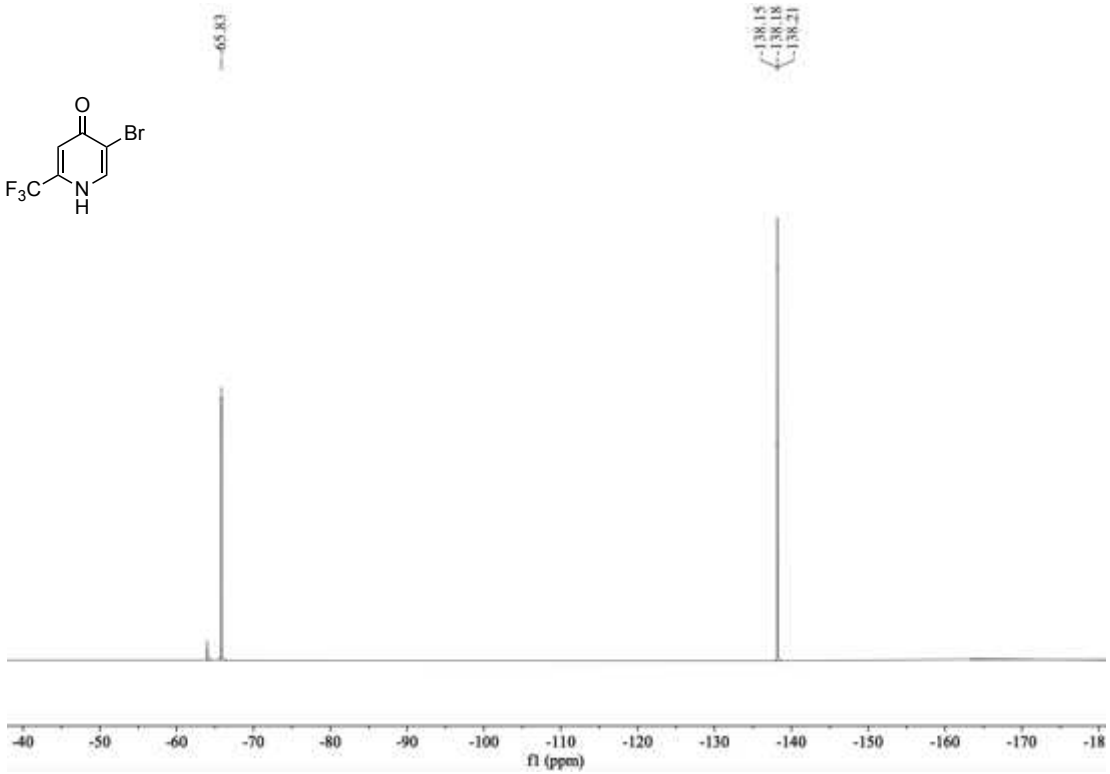
^{19}F NMR spectrum of **2-64** (376 MHz, $(CD_3)_2SO$)



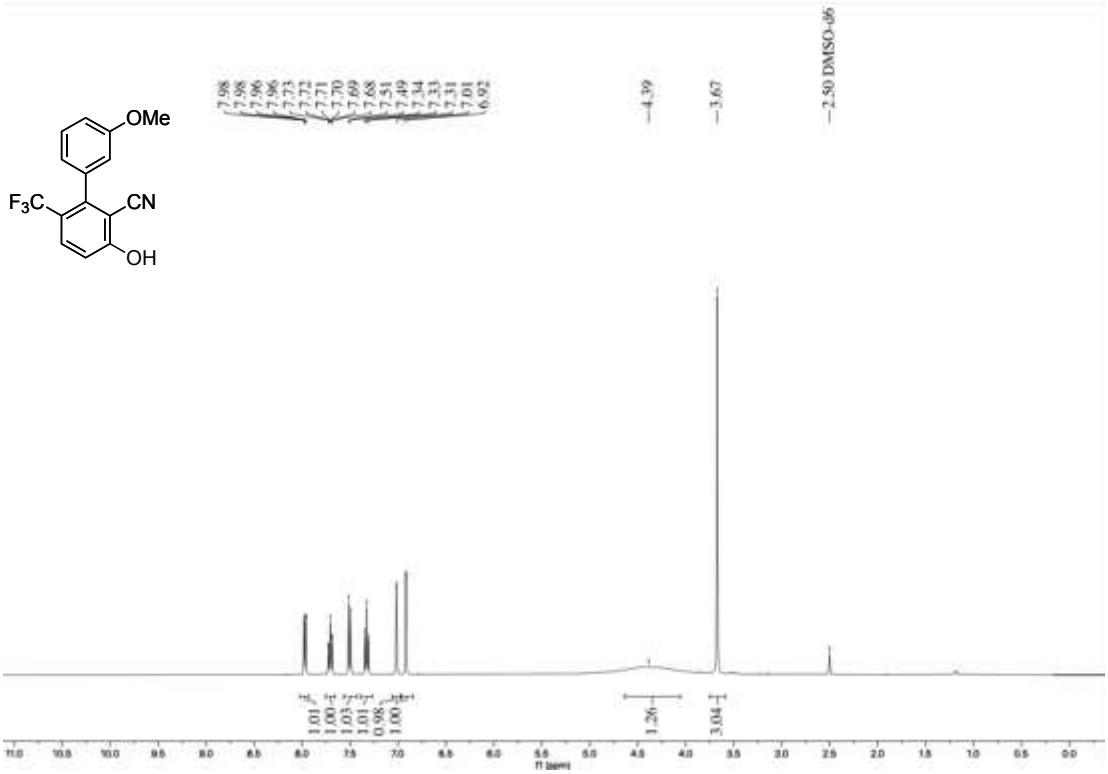
^{1}H NMR spectrum of **2-63** (400 MHz, $(CD_3)_2SO$)



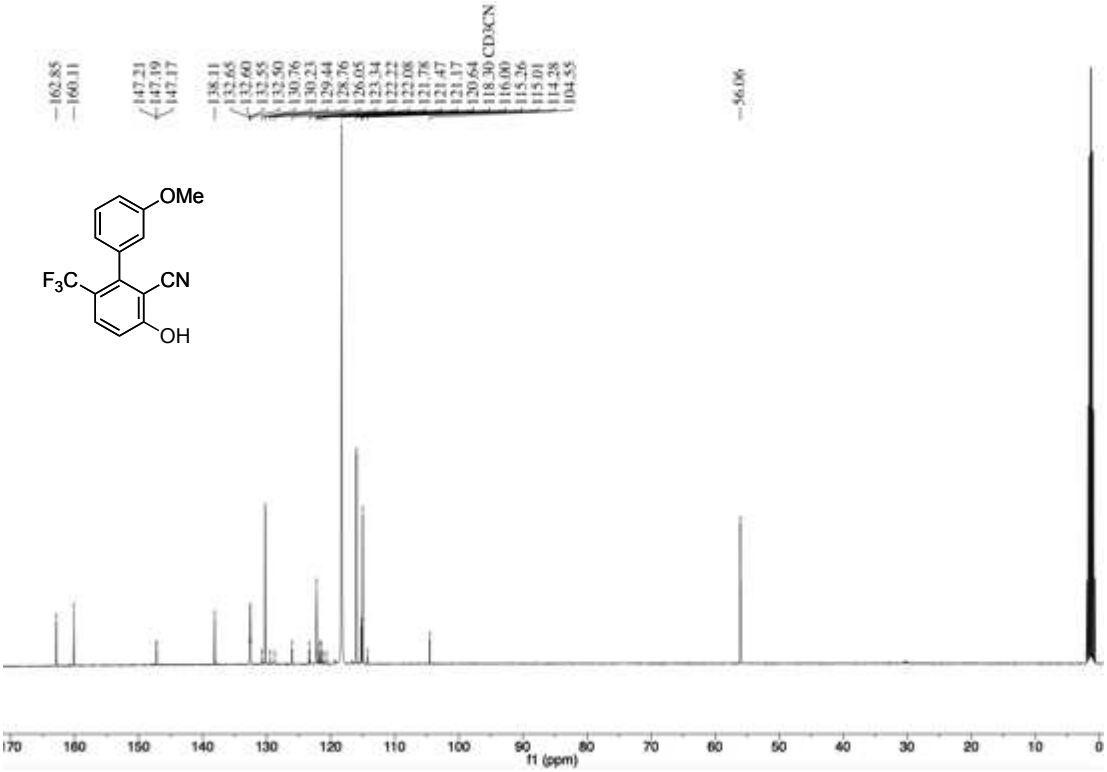
^{13}C NMR spectrum of **2-63** (101 MHz, $(CD_3)_2SO$)



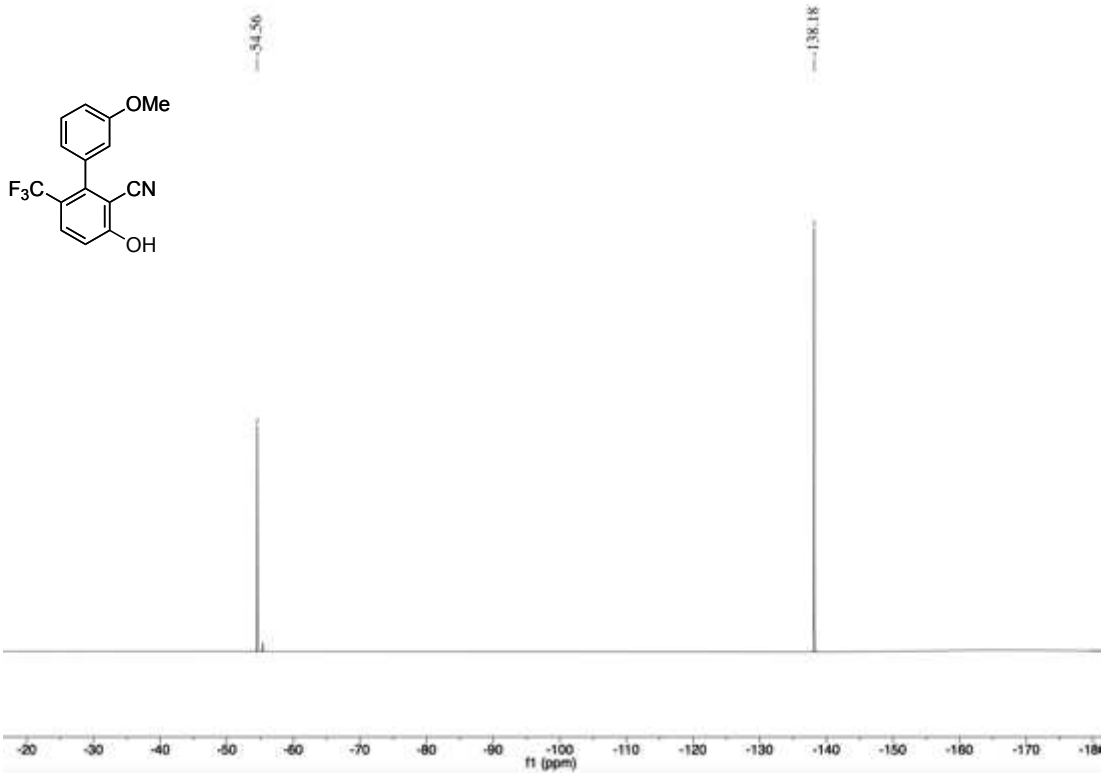
^{19}F NMR spectrum of **2-63** (376 MHz, $(CD_3)_2SO$)



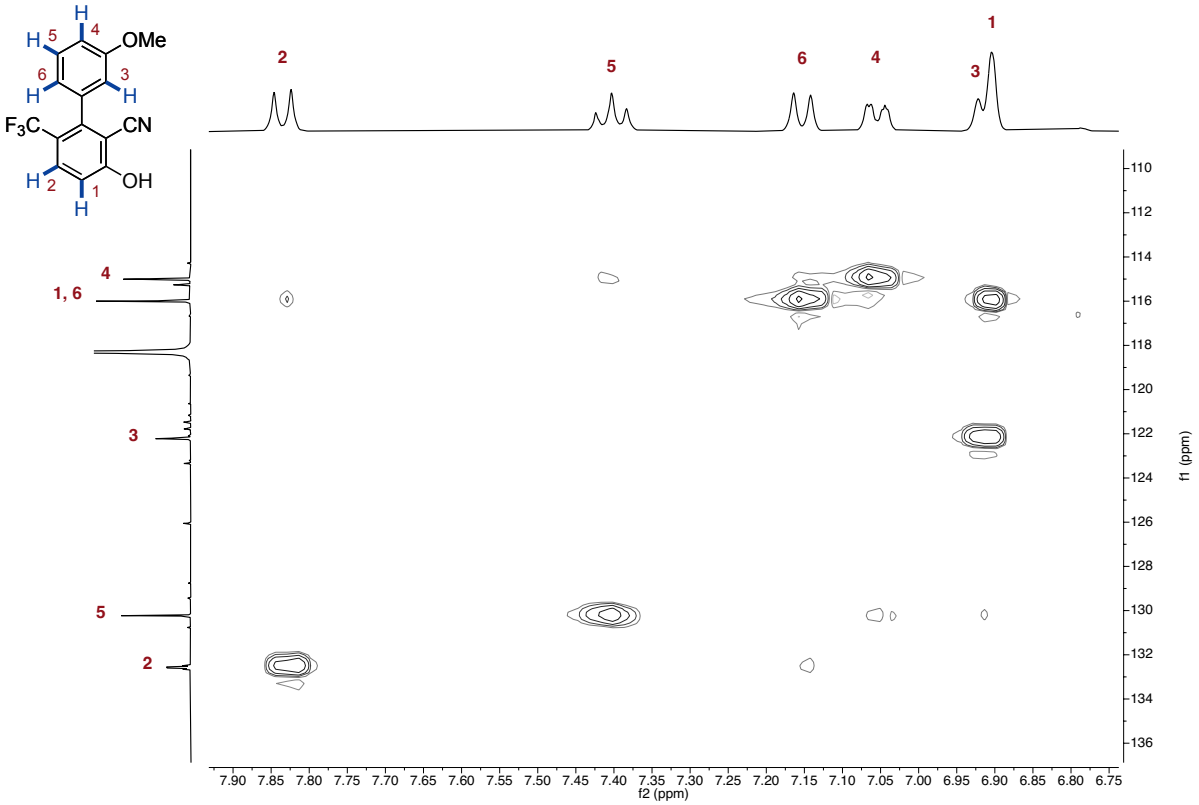
^{1}**H NMR** spectrum of **2-68** (400 MHz, $(CD_3)_2SO$)



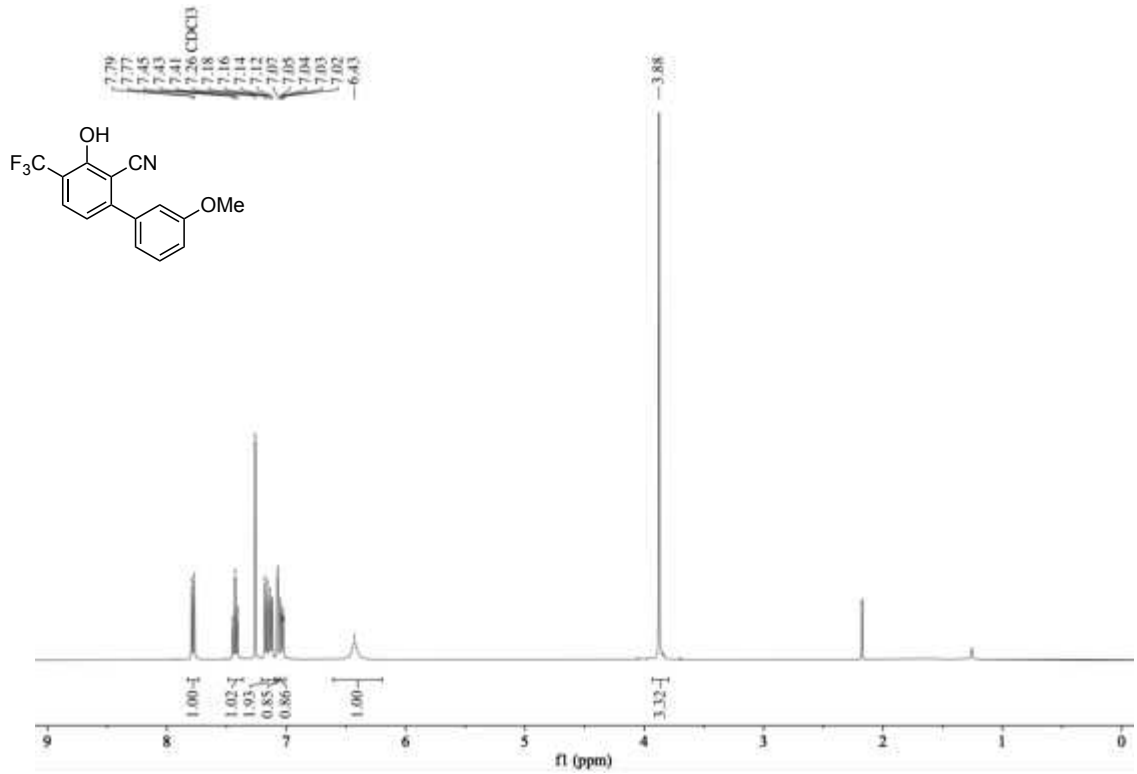
^{13}**C NMR** spectrum of **2-68** (101 MHz, CD_3CN)



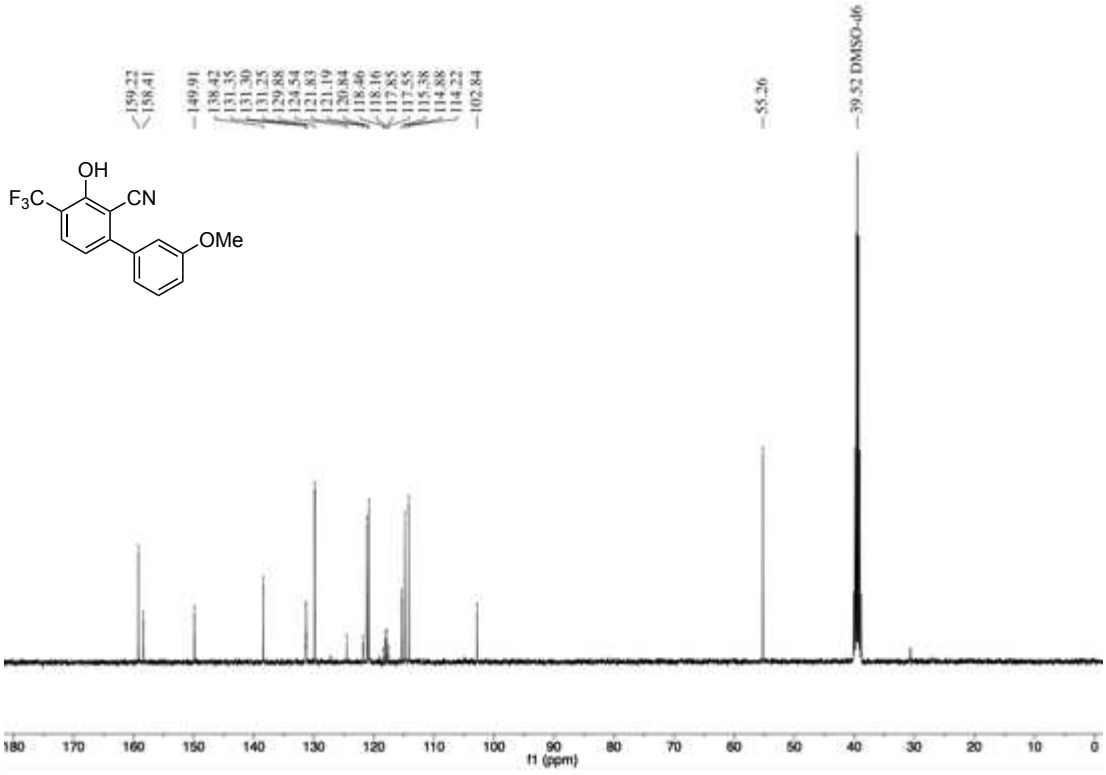
^{19}F NMR spectrum of **2-68** (376 MHz, CD_3CN)



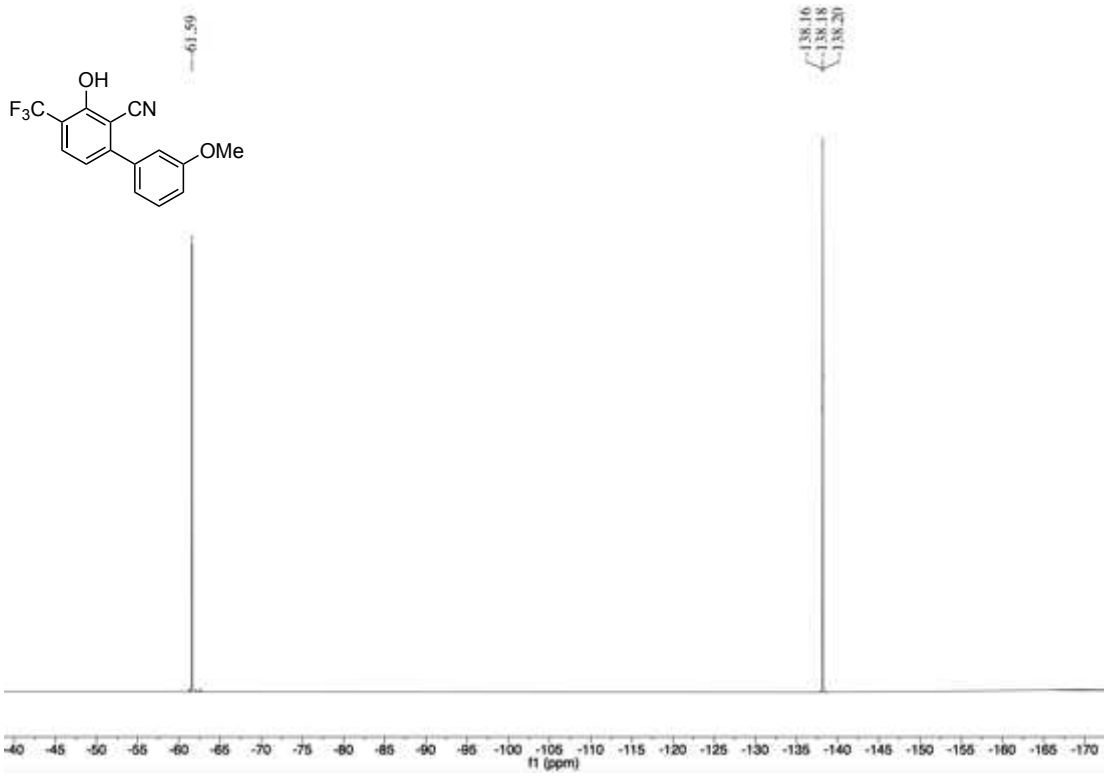
HSQC spectrum of **2-68** (CD_3CN)



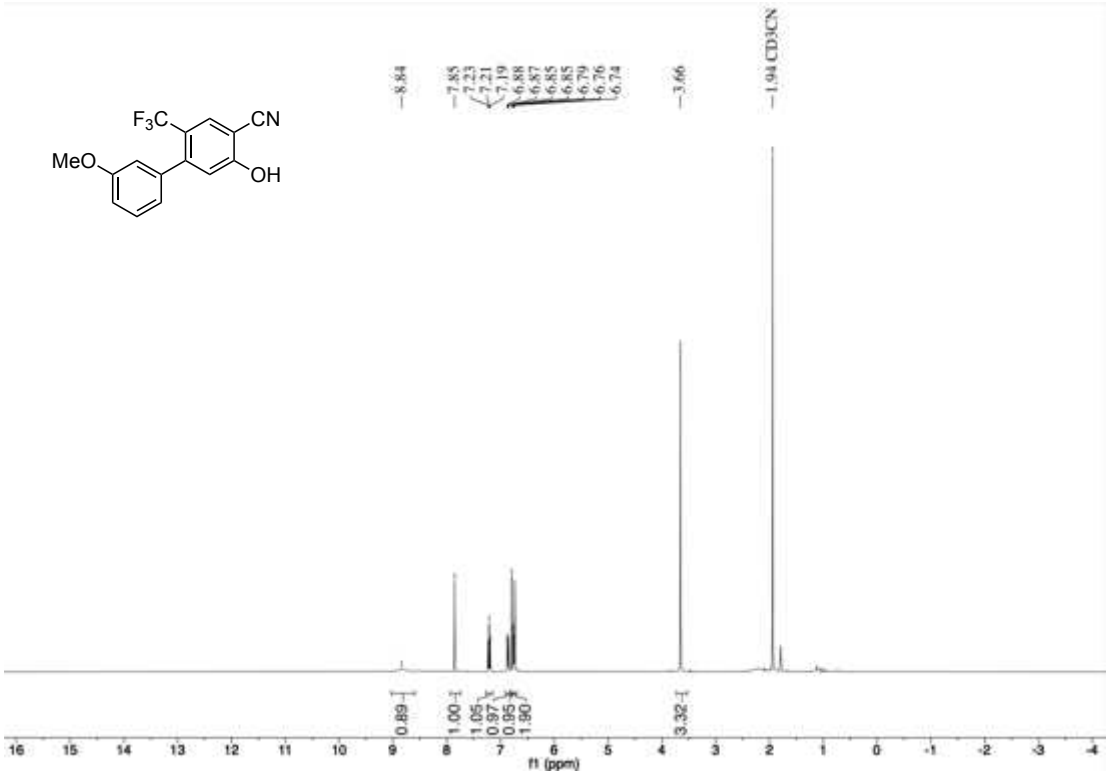
^{1}H NMR spectrum of **2-69** (400 MHz, $CDCl_3$)



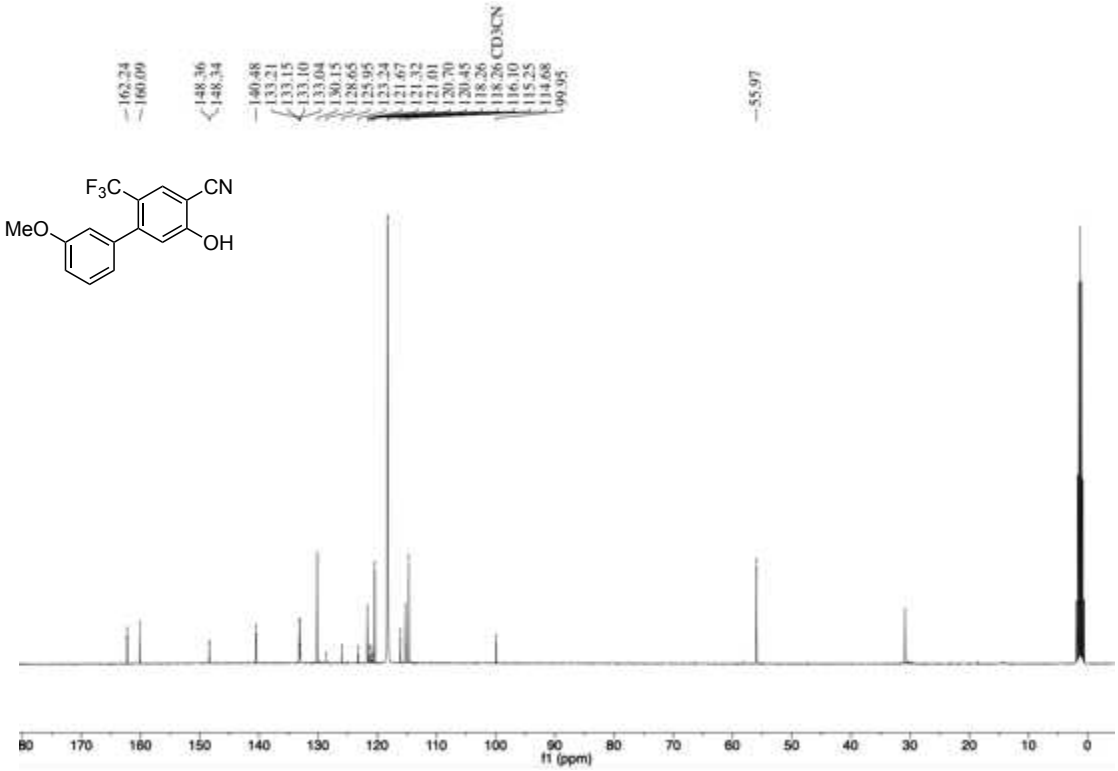
^{13}C NMR spectrum of **2-69** (101 MHz, $(CD_3)_2SO$)



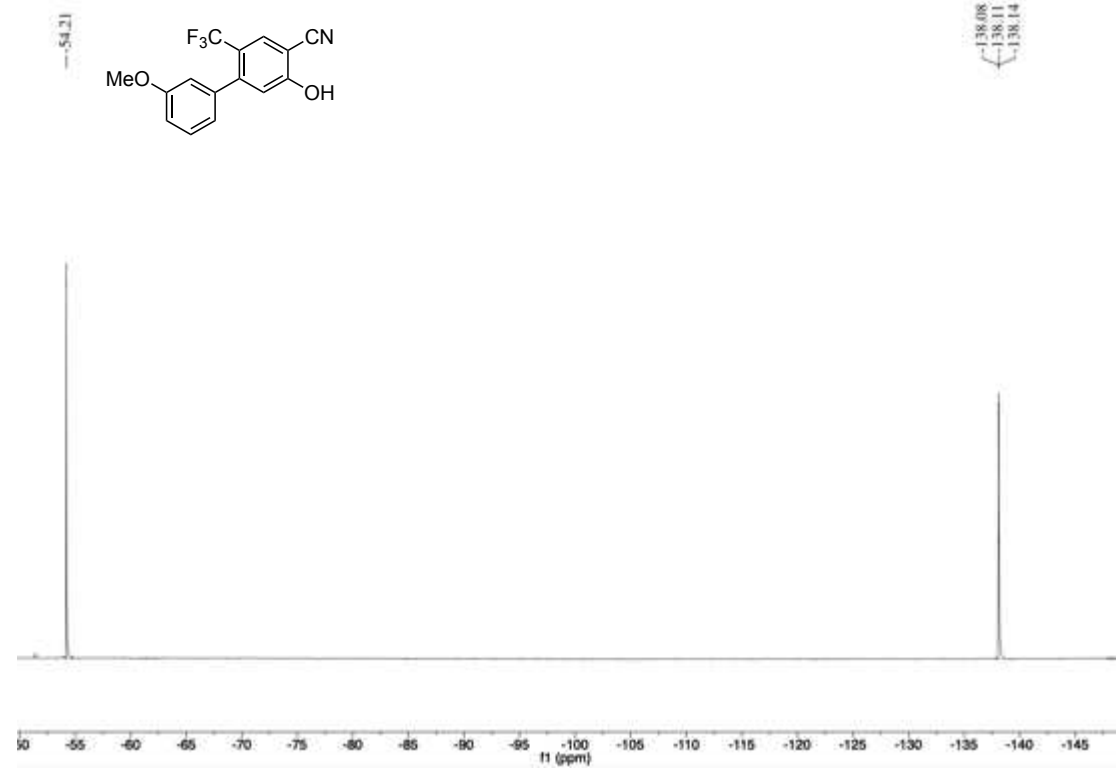
^{19}F NMR spectrum of **2-69** (376 MHz, $(CD_3)_2SO$)



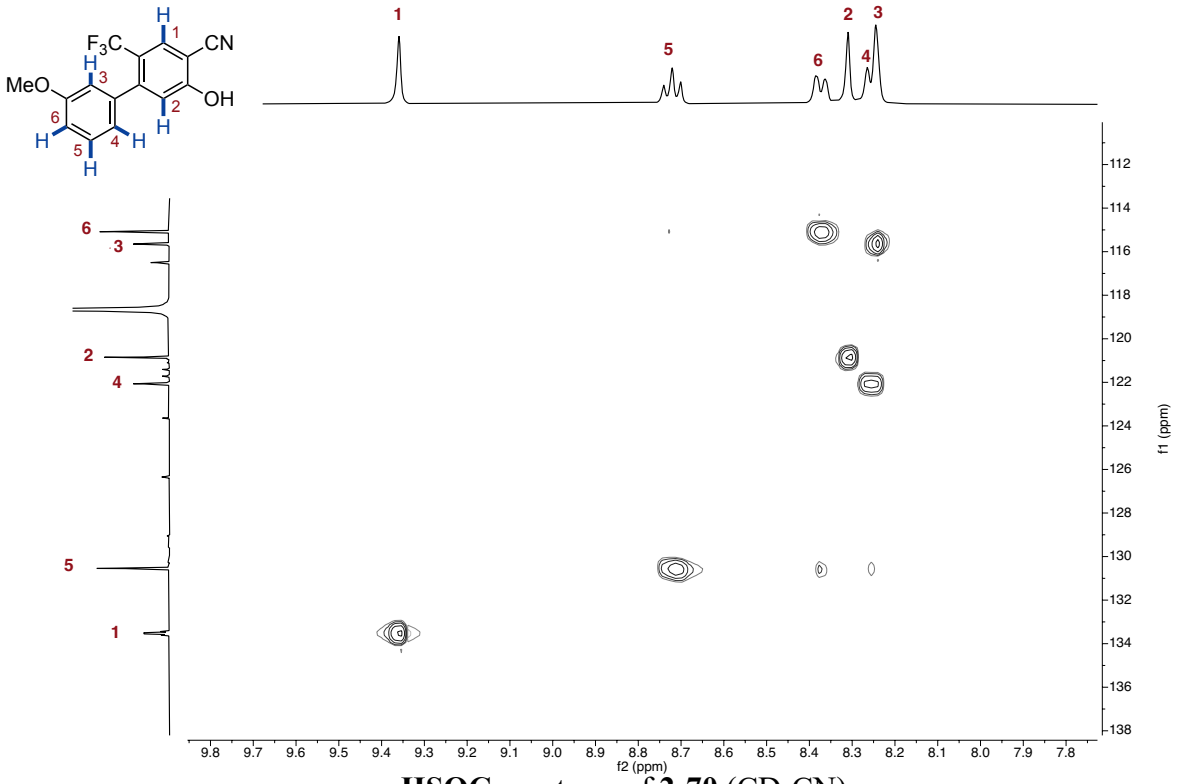
^{1}H NMR spectrum of **2-70** (400 MHz, CD_3CN)



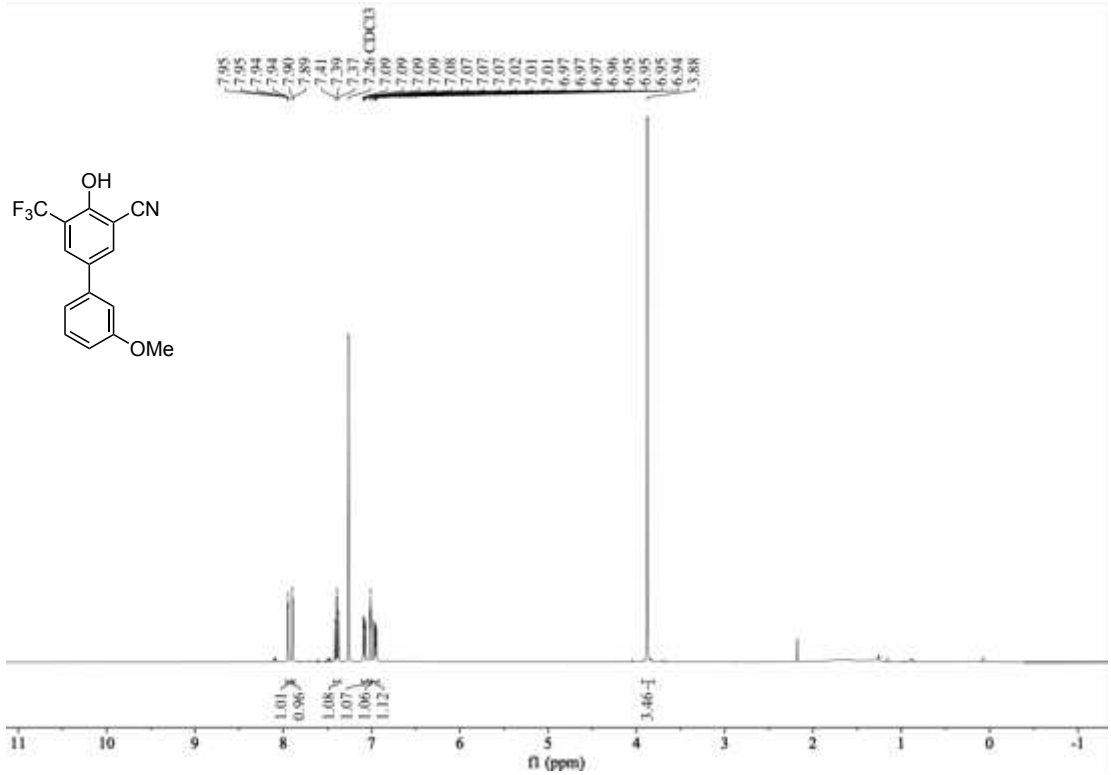
^{13}C NMR spectrum of **2-70** (101 MHz, CD_3CN)



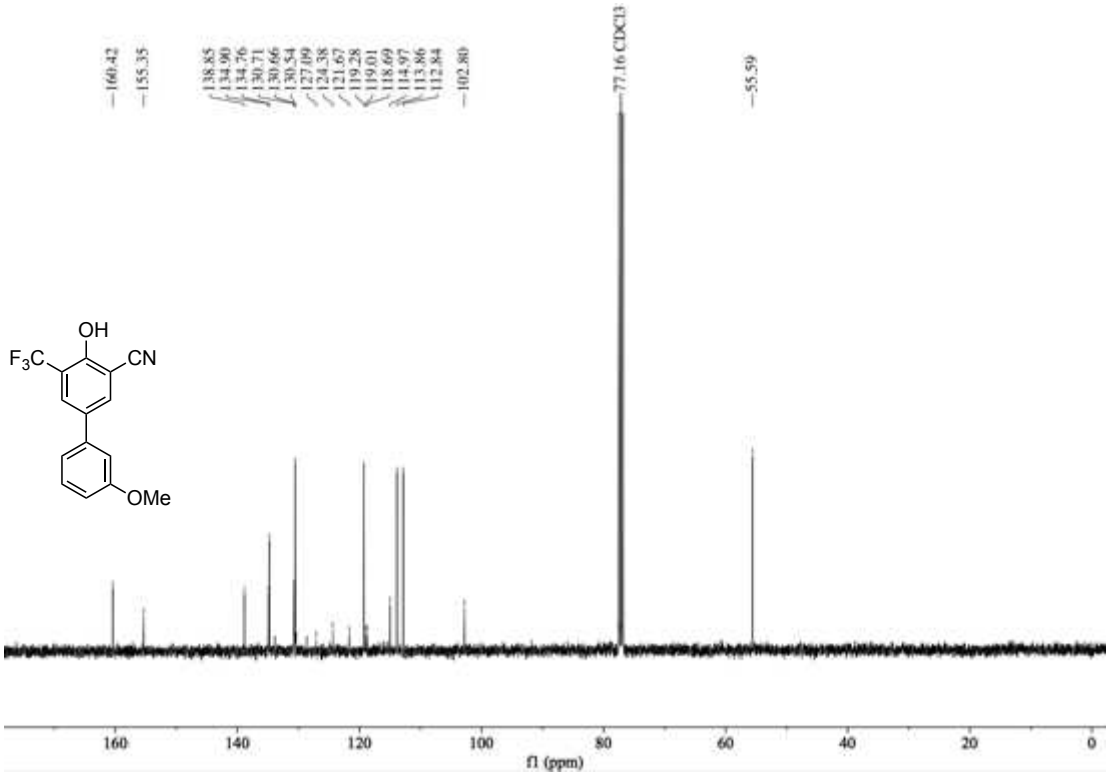
^{19}F NMR spectrum of **2-70** (376 MHz, CD_3CN)



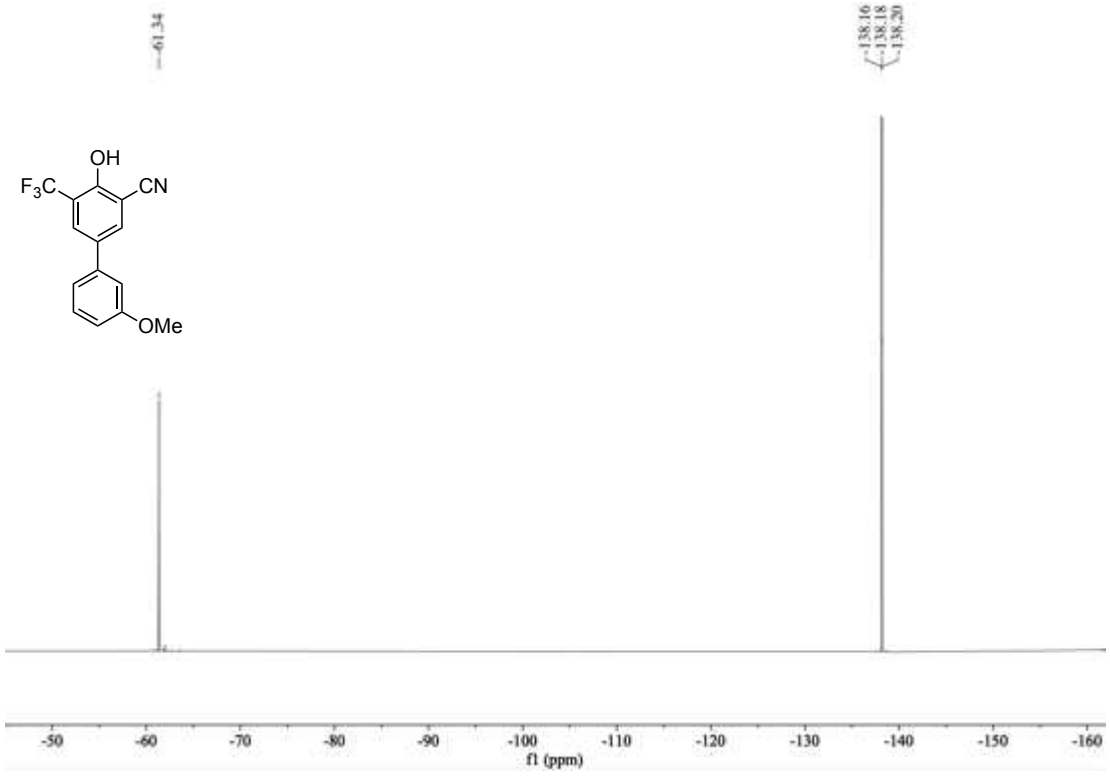
HSQC spectrum of **2-70** (CD_3CN)



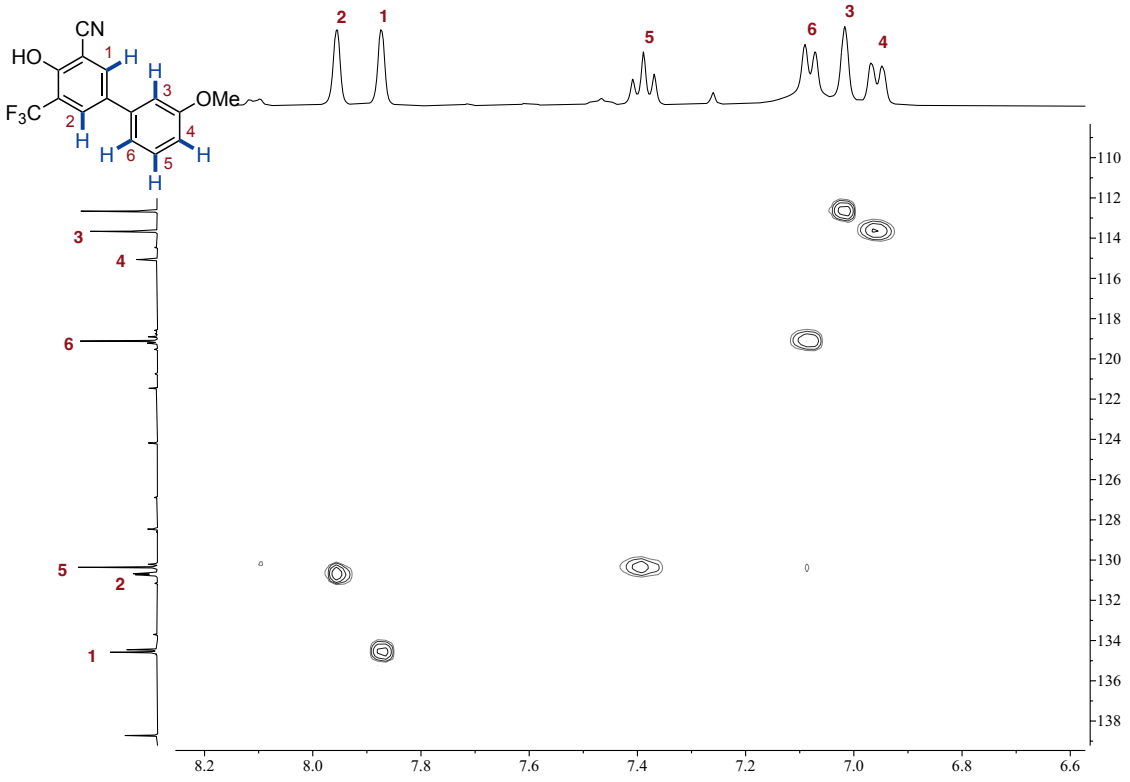
^{1}H NMR spectrum of **2-71** (400 MHz, $CDCl_3$)



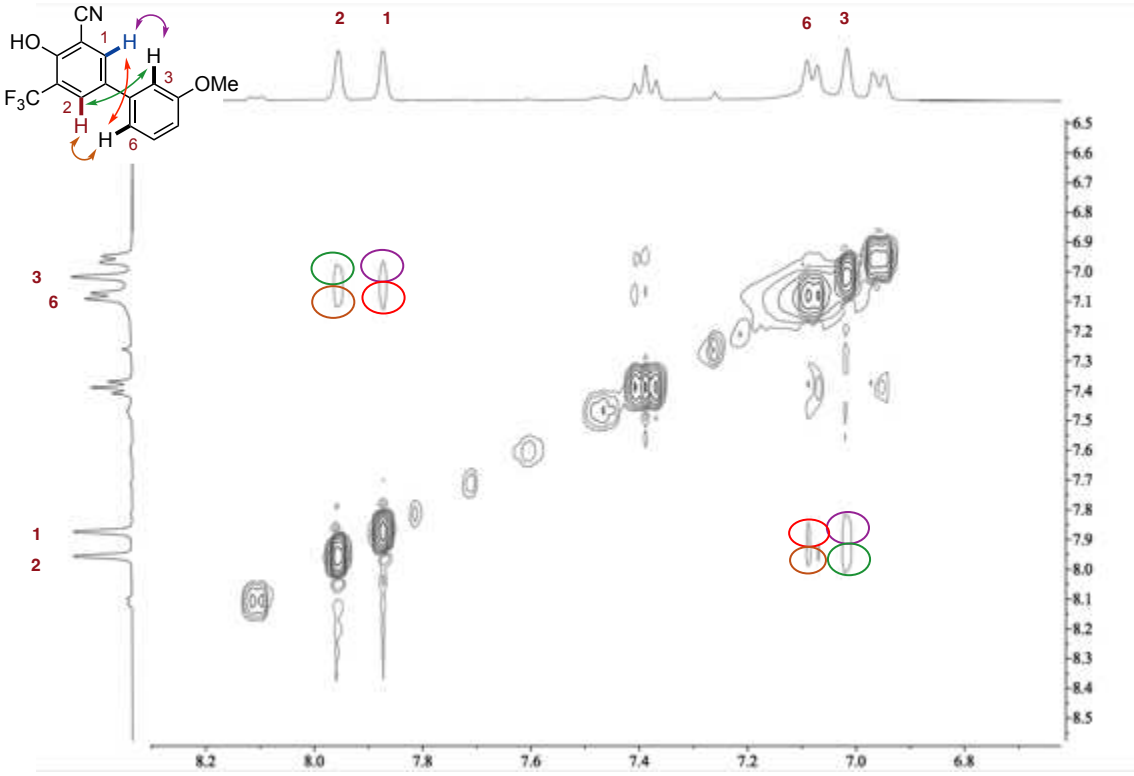
^{13}C NMR spectrum of **2-71** (101 MHz, $CDCl_3$)



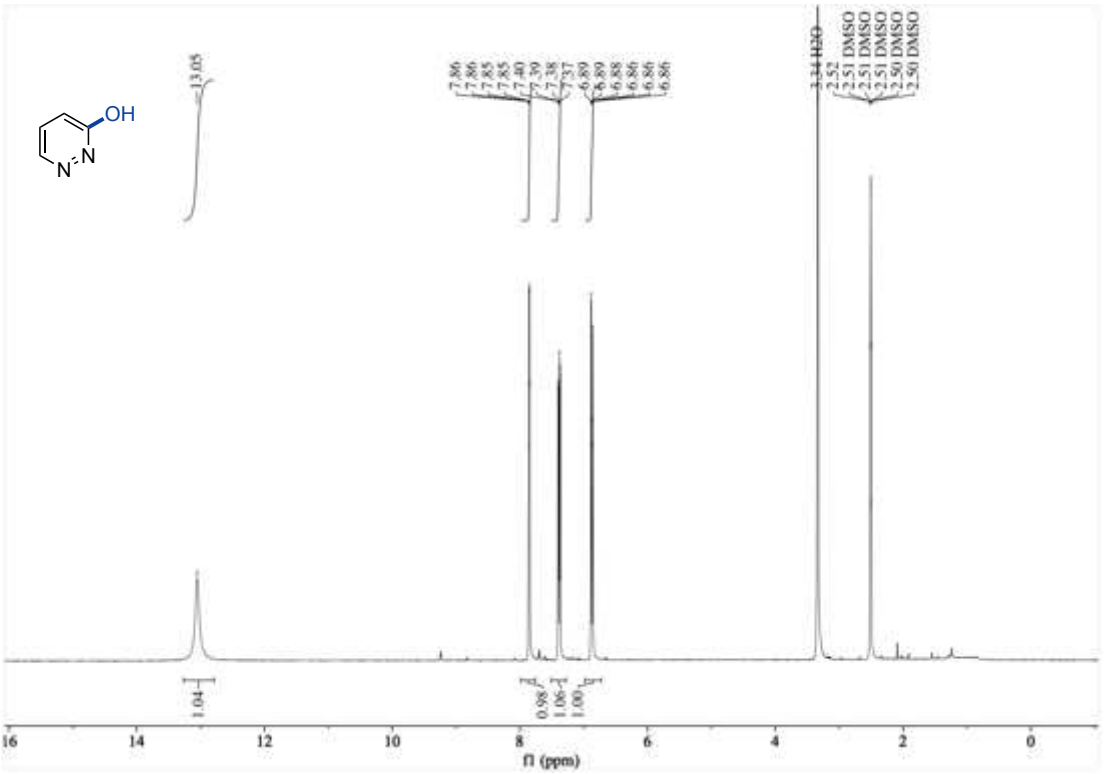
^{19}F NMR spectrum of **2-71** (376 MHz, $CDCl_3$)



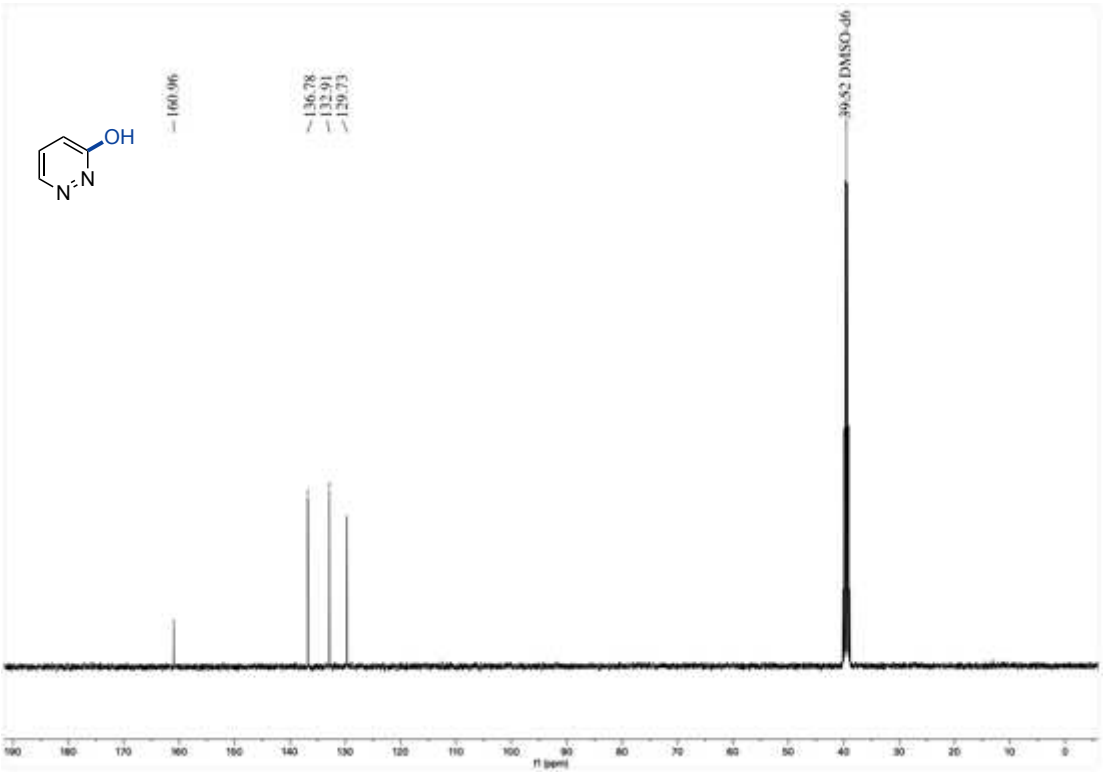
HSQC spectrum of **2-71** ($CDCl_3$)



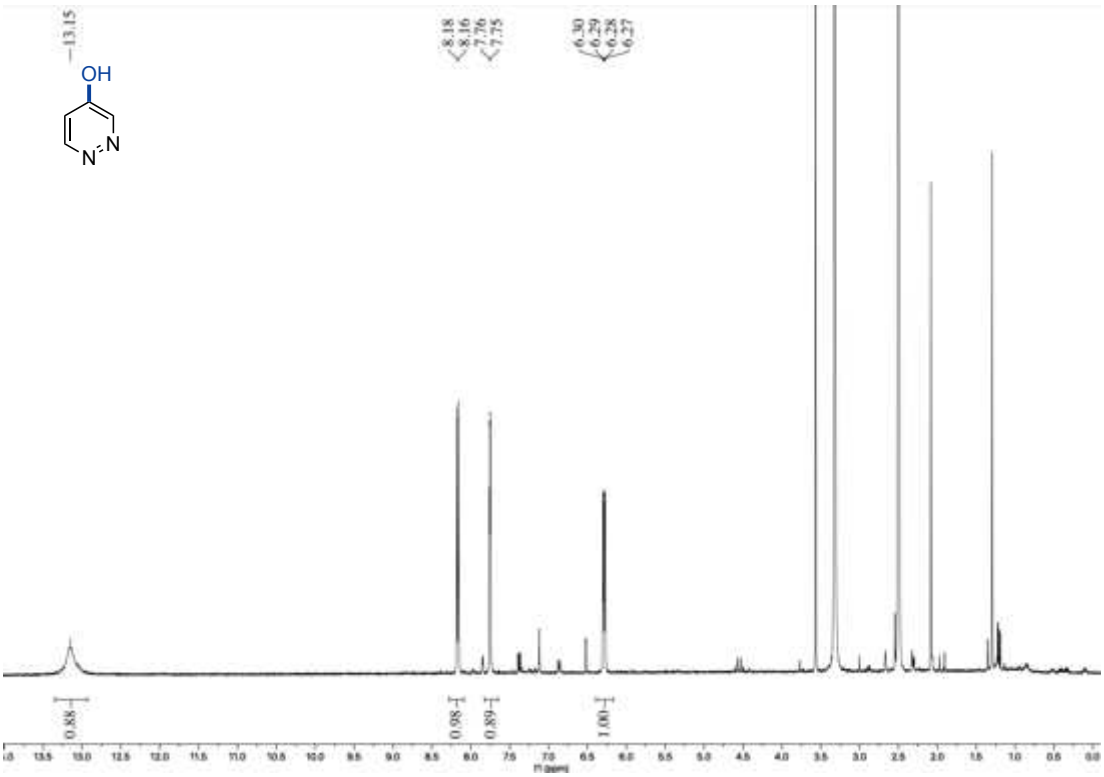
2D NOESY spectrum of **2-71** ($CDCl_3$)



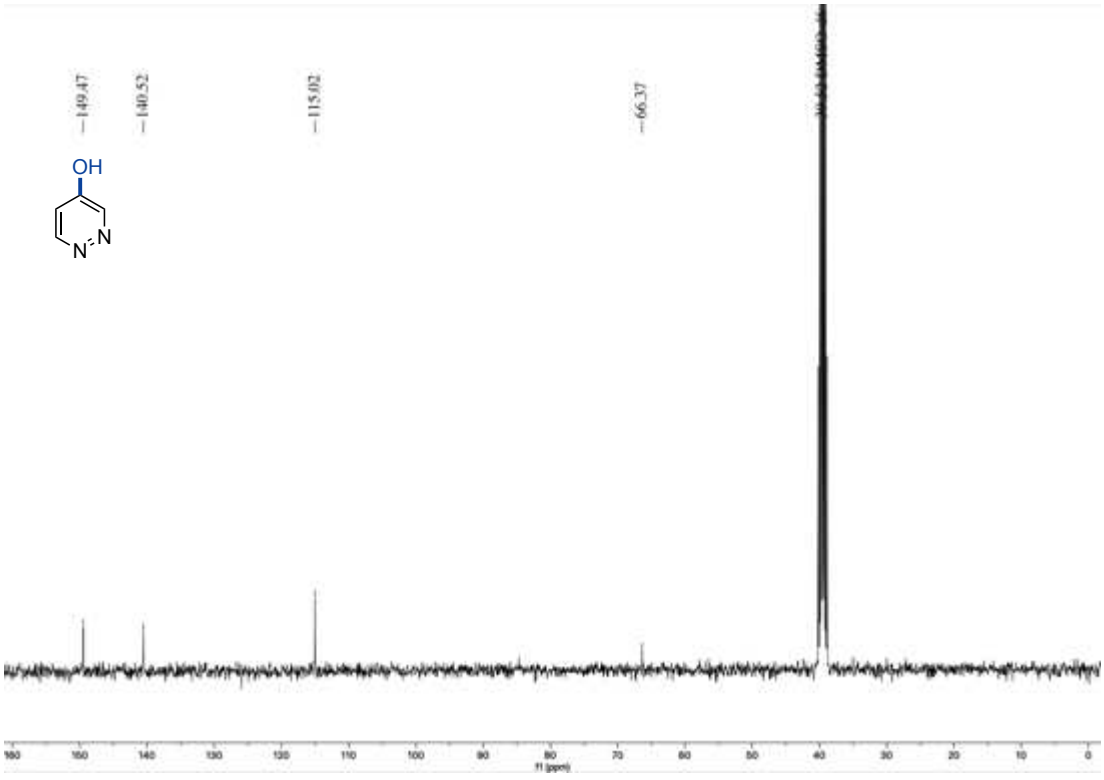
^{1}H NMR spectrum of **2-75** (400 MHz, $(CD_3)_2SO$)



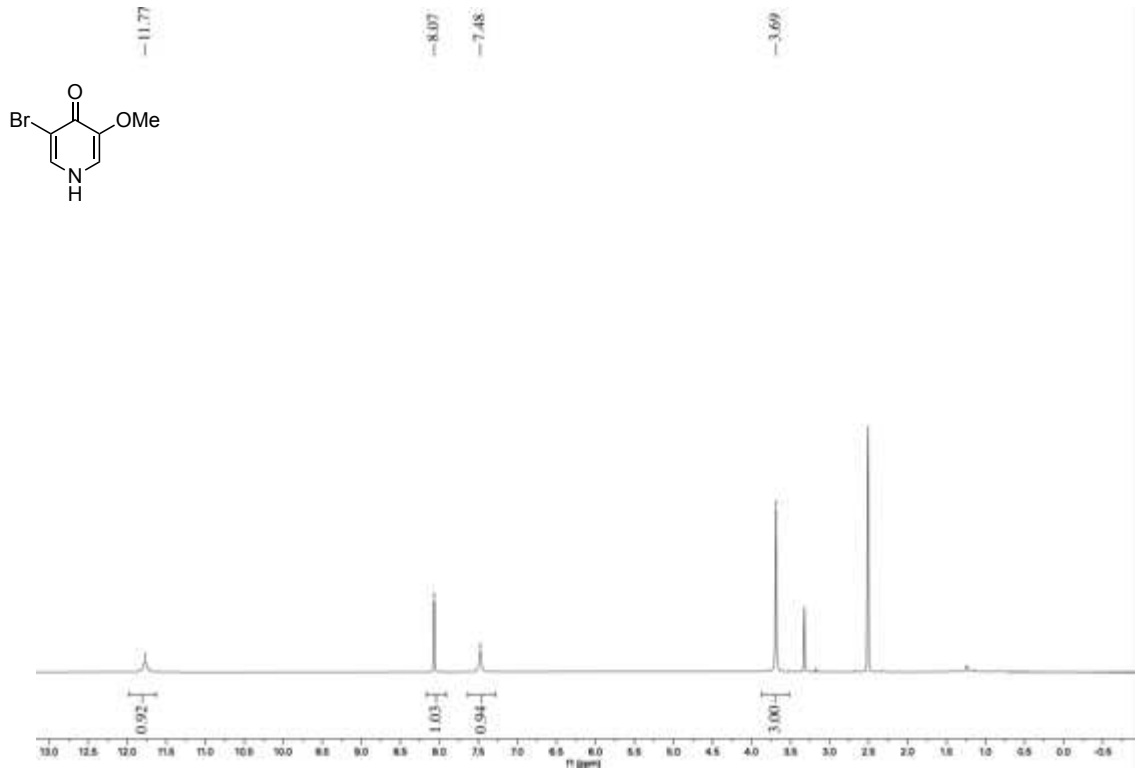
^{13}C NMR spectrum of **2-75** (101 MHz, $(CD_3)_2SO$)



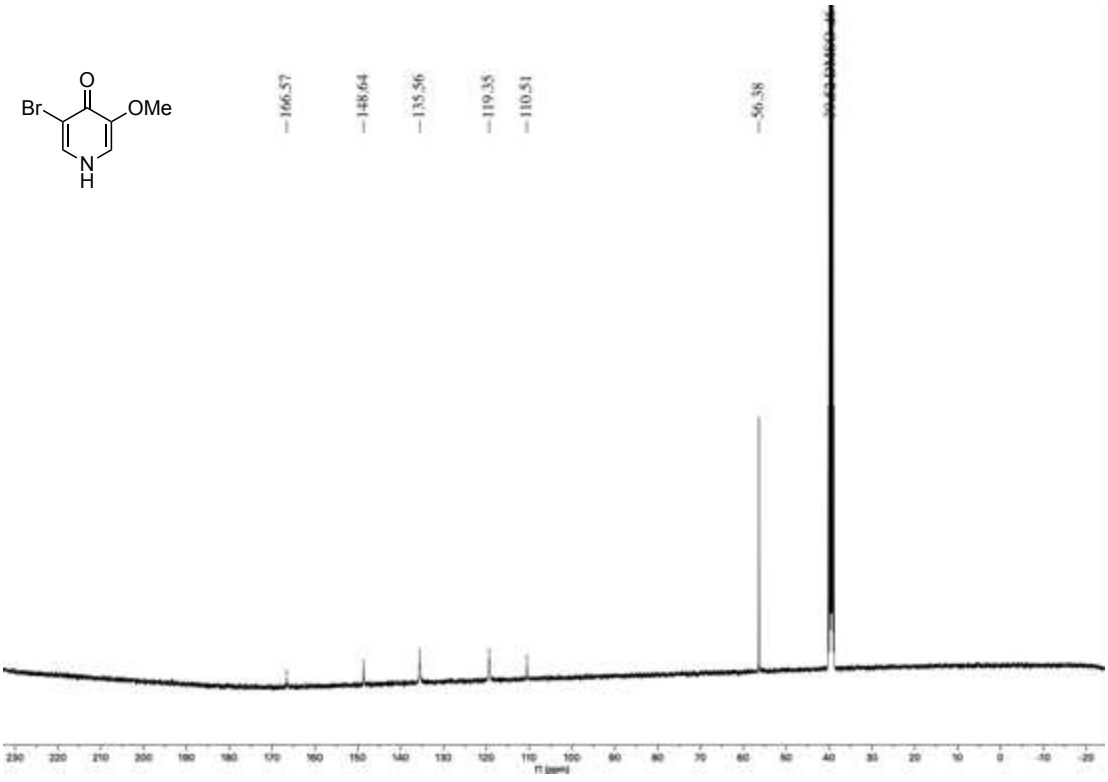
^{1}H NMR spectrum of **2-76** (400 MHz, $(CD_3)_2SO$)



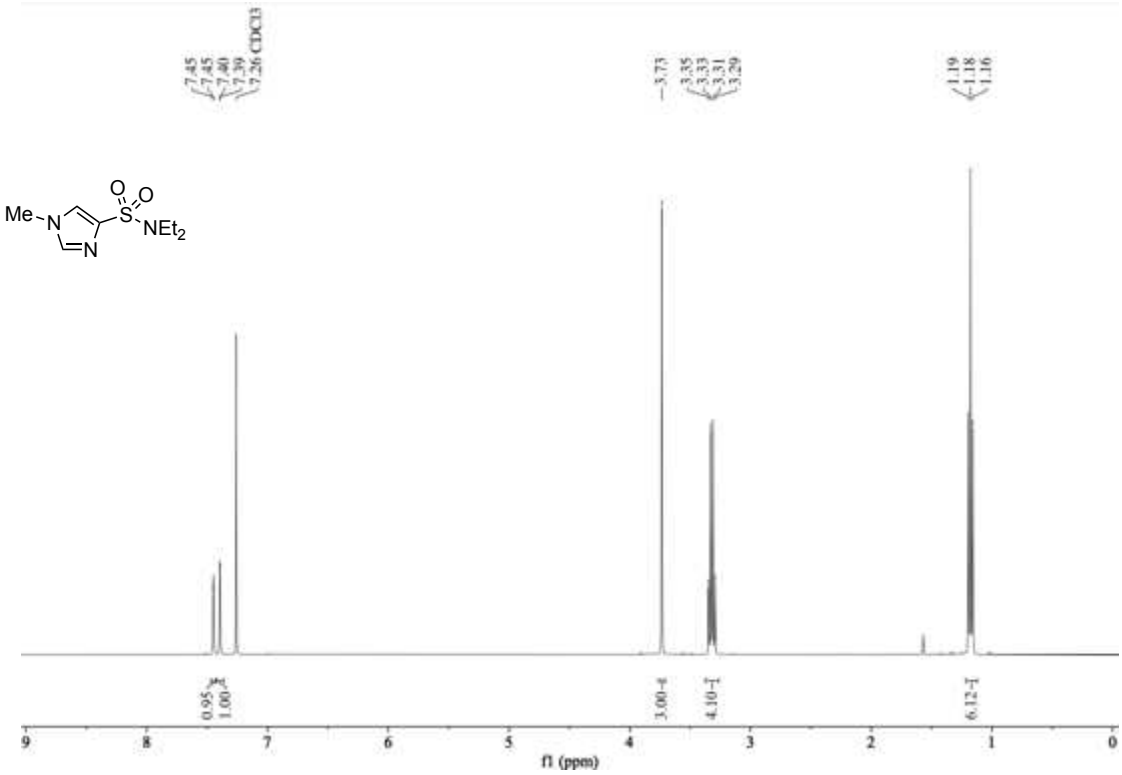
^{13}C NMR spectrum of **2-76** (101 MHz, $(CD_3)_2SO$)



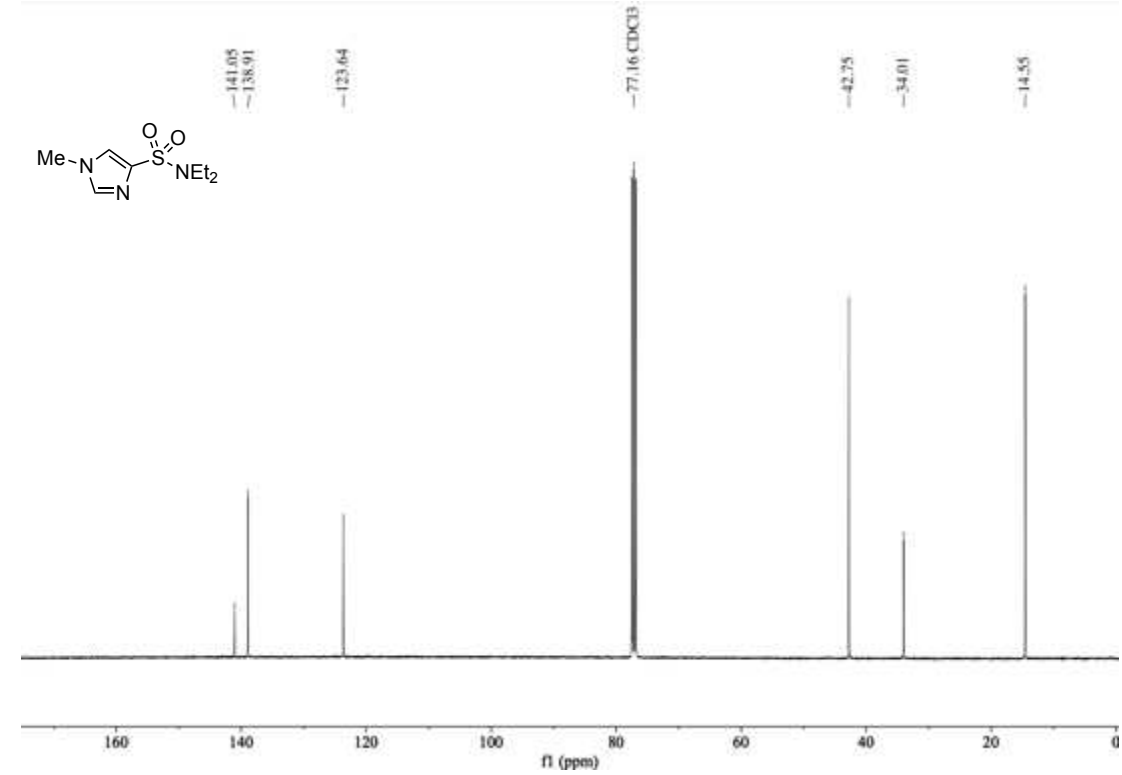
^{1}H NMR spectrum of **1-A5** (400 MHz, $(CD_3)_2SO$)



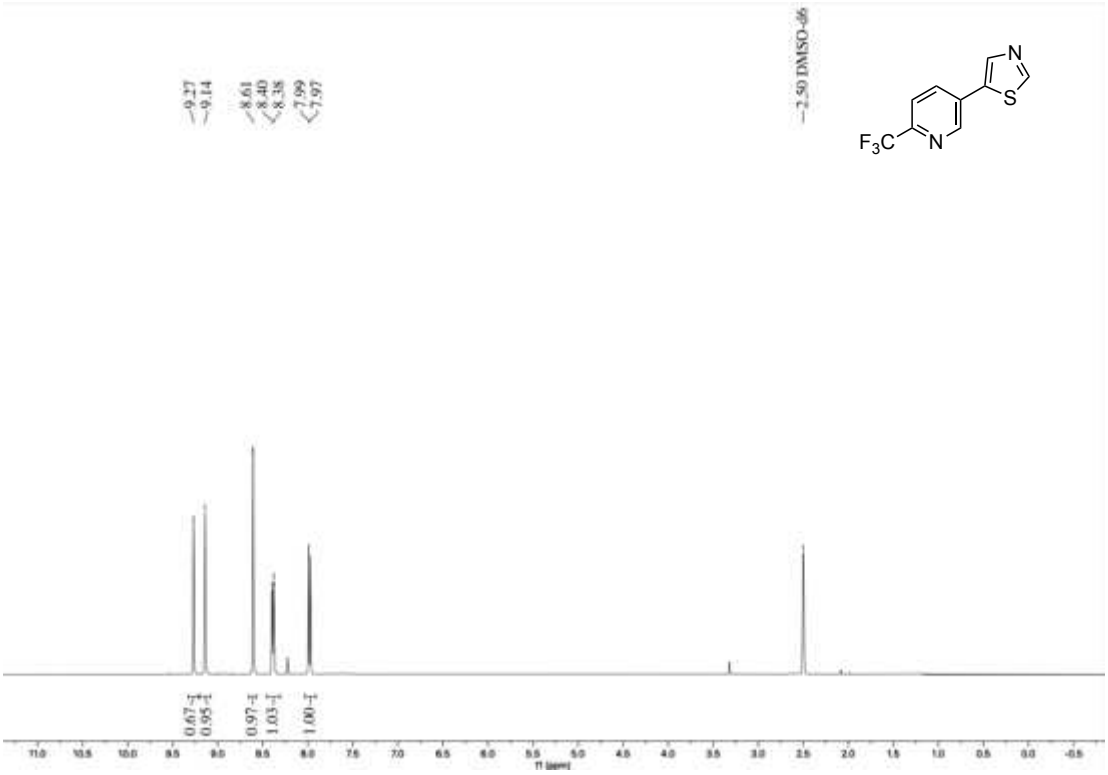
^{13}C NMR spectrum of **1-A5** (101 MHz, $(CD_3)_2SO$



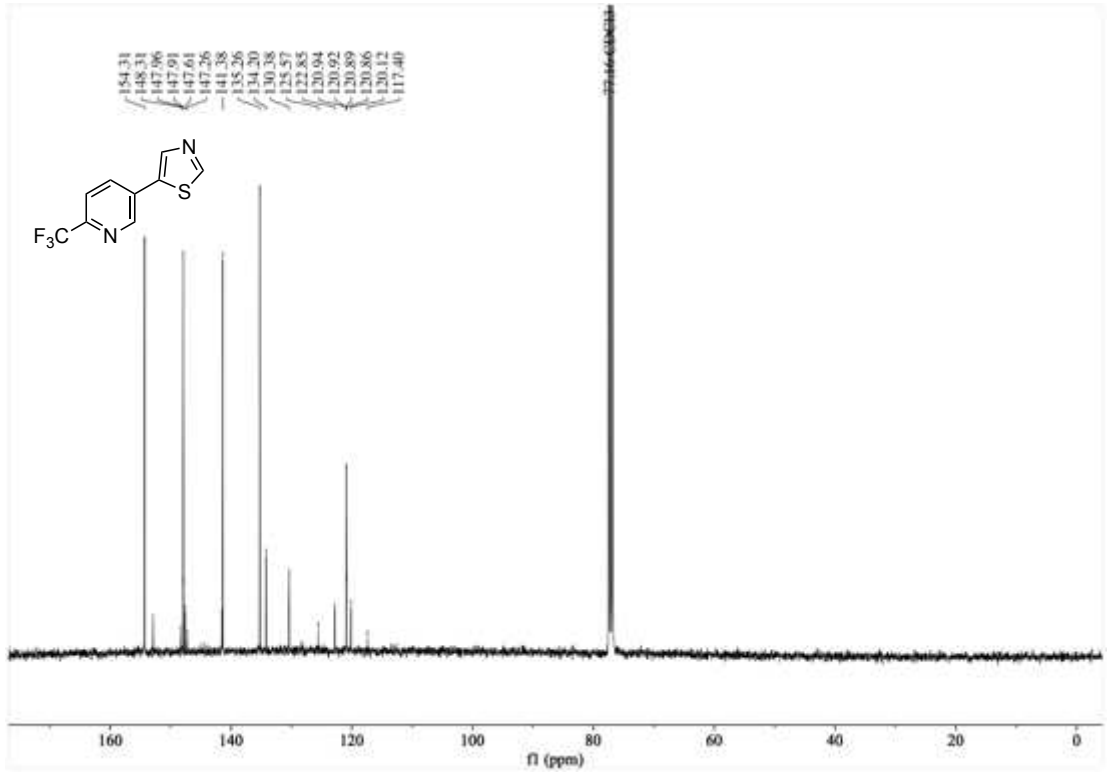
^{1}H NMR spectrum of **1-A6** (400 MHz, $CDCl_3$)



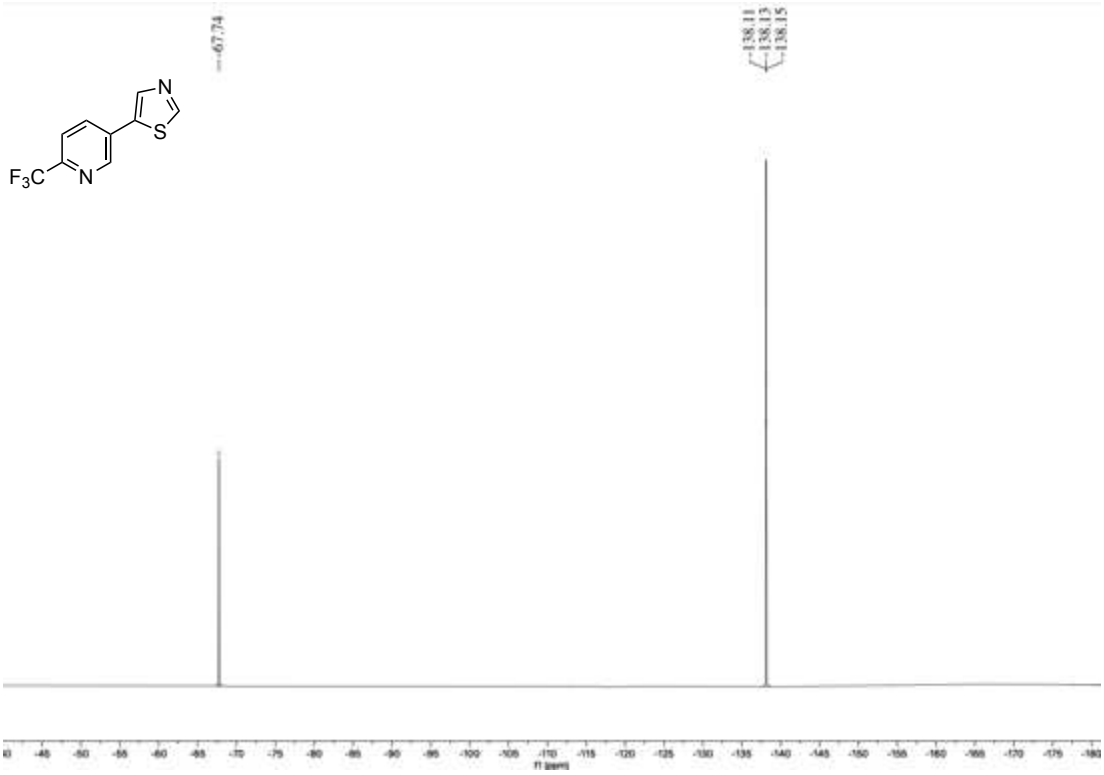
^{13}C NMR spectrum of **1-A6** (101 MHz, $CDCl_3$)



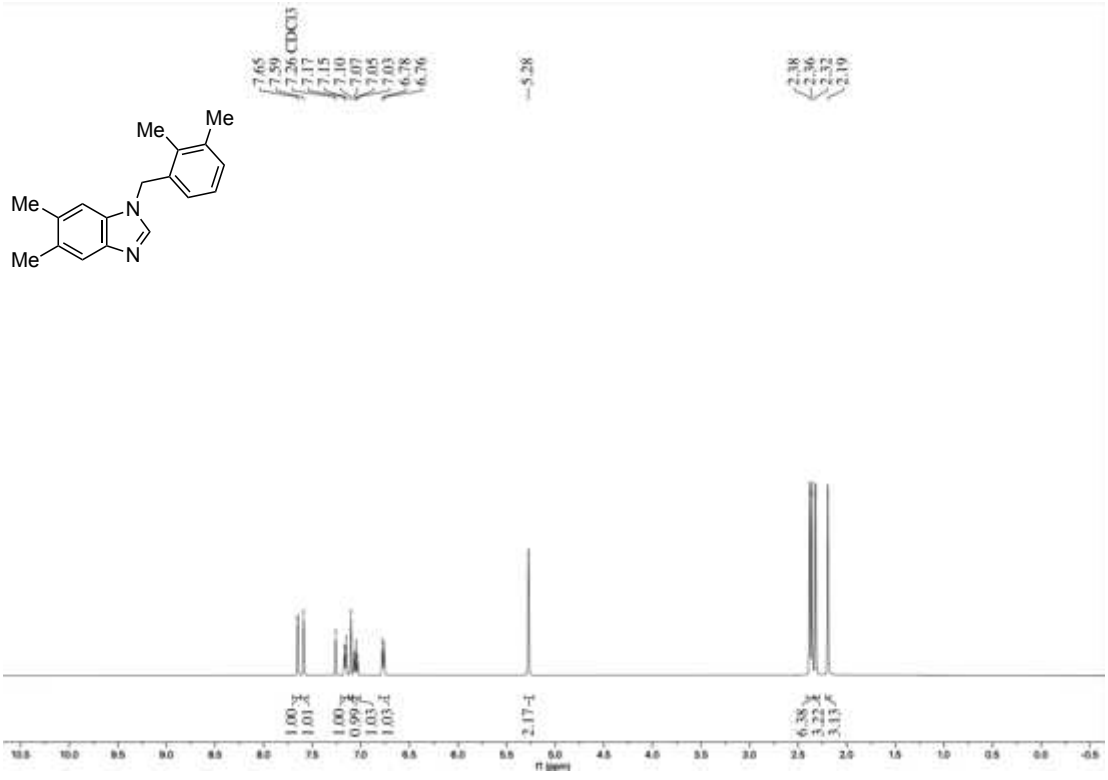
[1]H NMR spectrum of **1-A7** (400 MHz, $(CD_3)_2SO$)



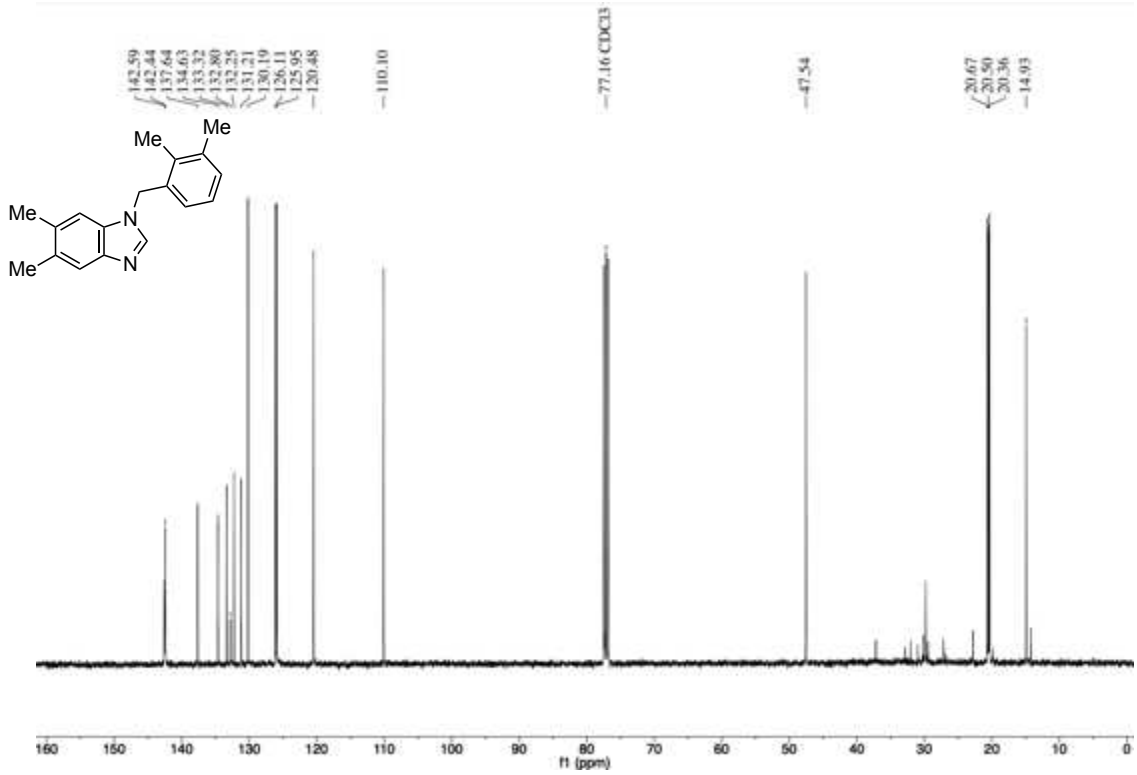
[13]C NMR spectrum of **1-A7** (101 MHz, $CDCl_3$)



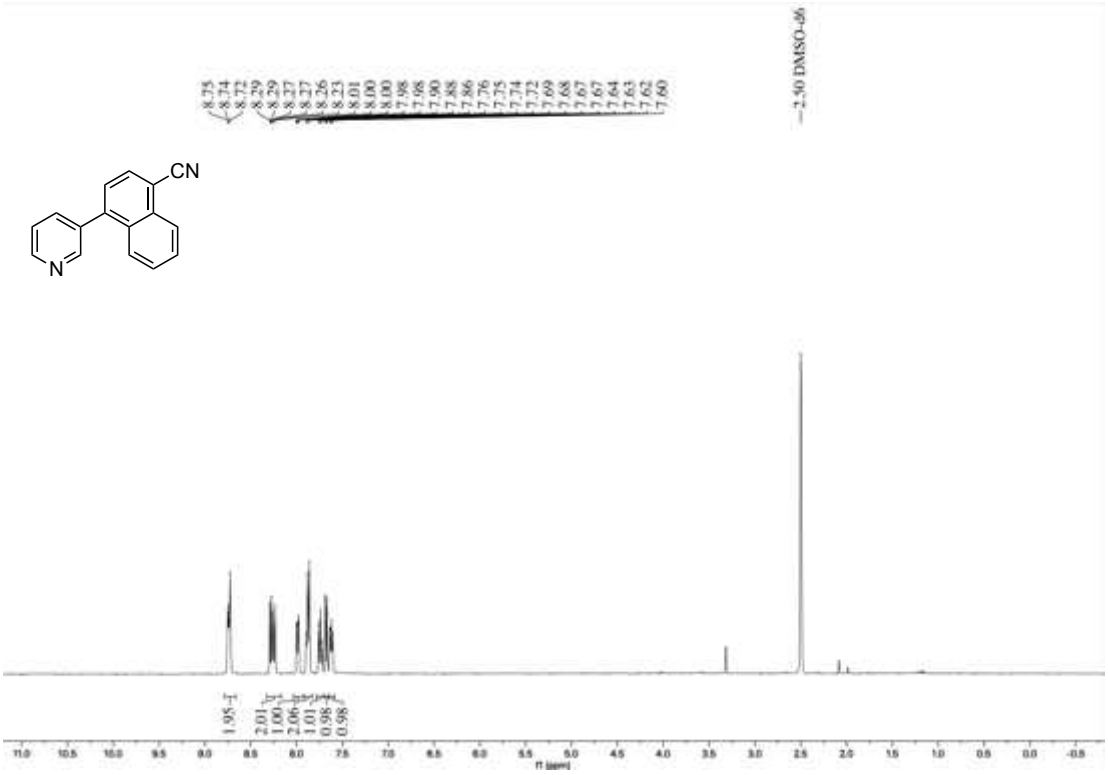
^{19}F NMR spectrum of **1-A8** (376 MHz, $CDCl_3$)



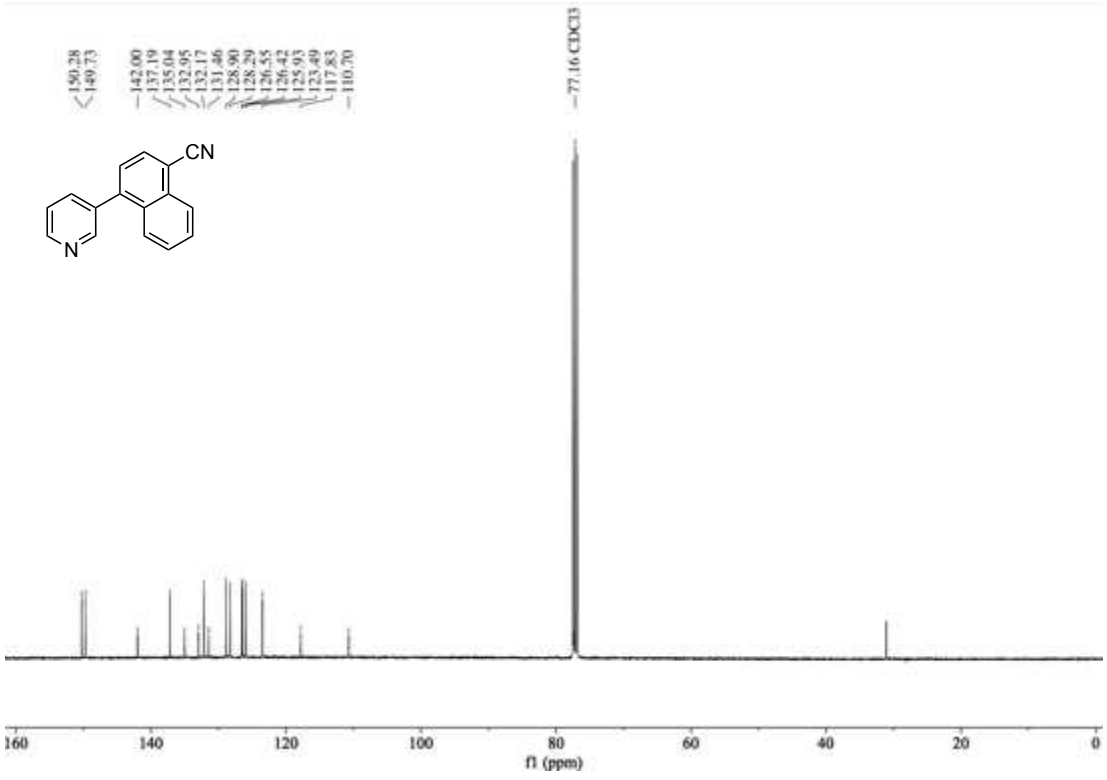
^{1}H NMR spectrum **1-A8** (400 MHz, $CDCl_3$)



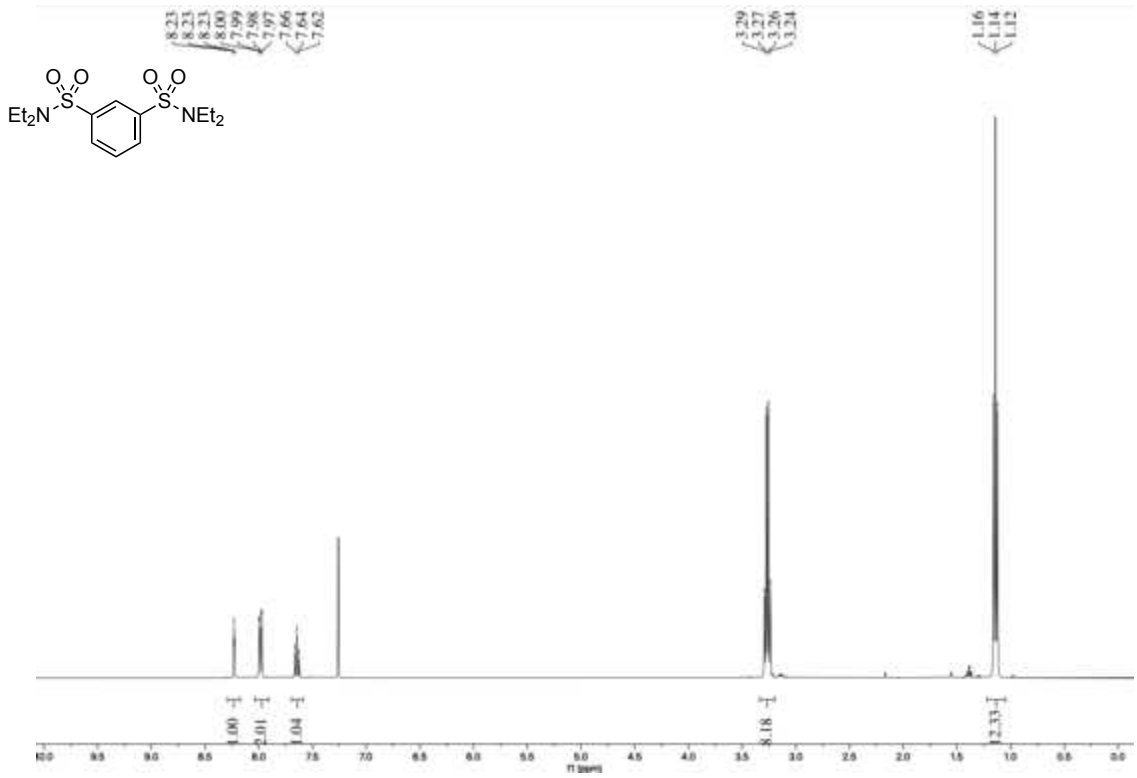
^{13}C NMR spectrum of **1-A8** (101 MHz, $CDCl_3$)



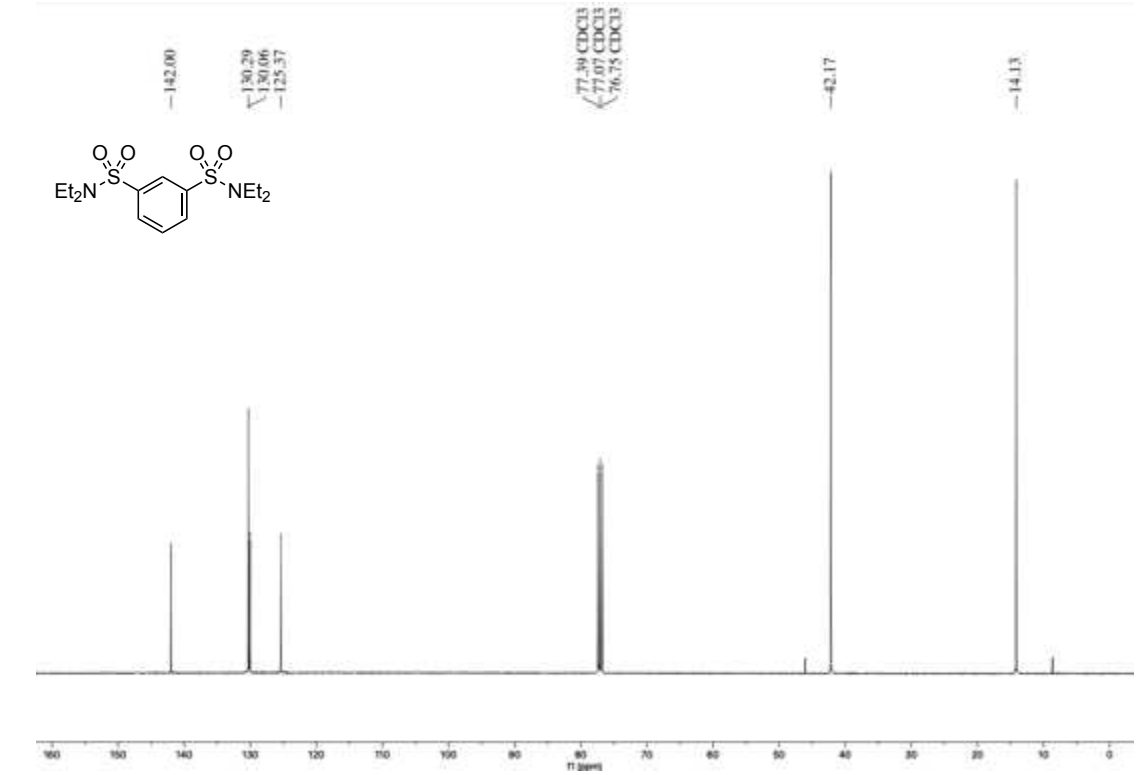
^{1}H NMR spectrum of **1-A9** (400 MHz, $(CD_3)_2SO$)



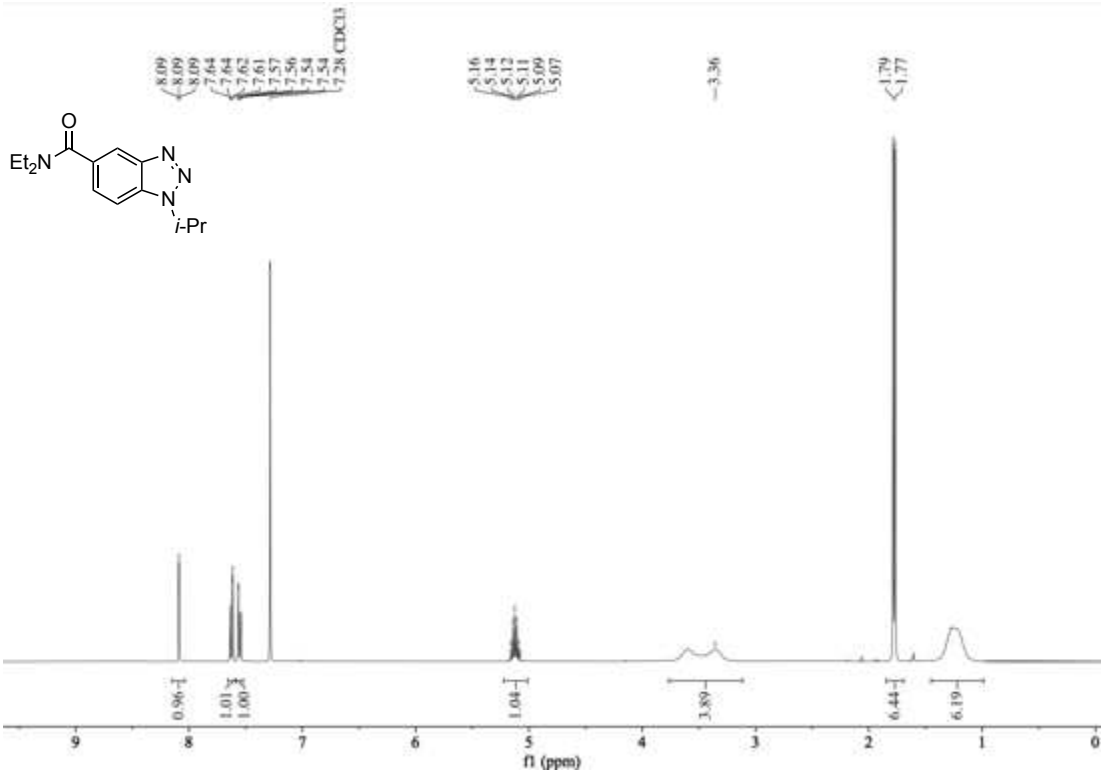
^{13}C NMR spectrum of **1-A9** (101 MHz, $CDCl_3$)



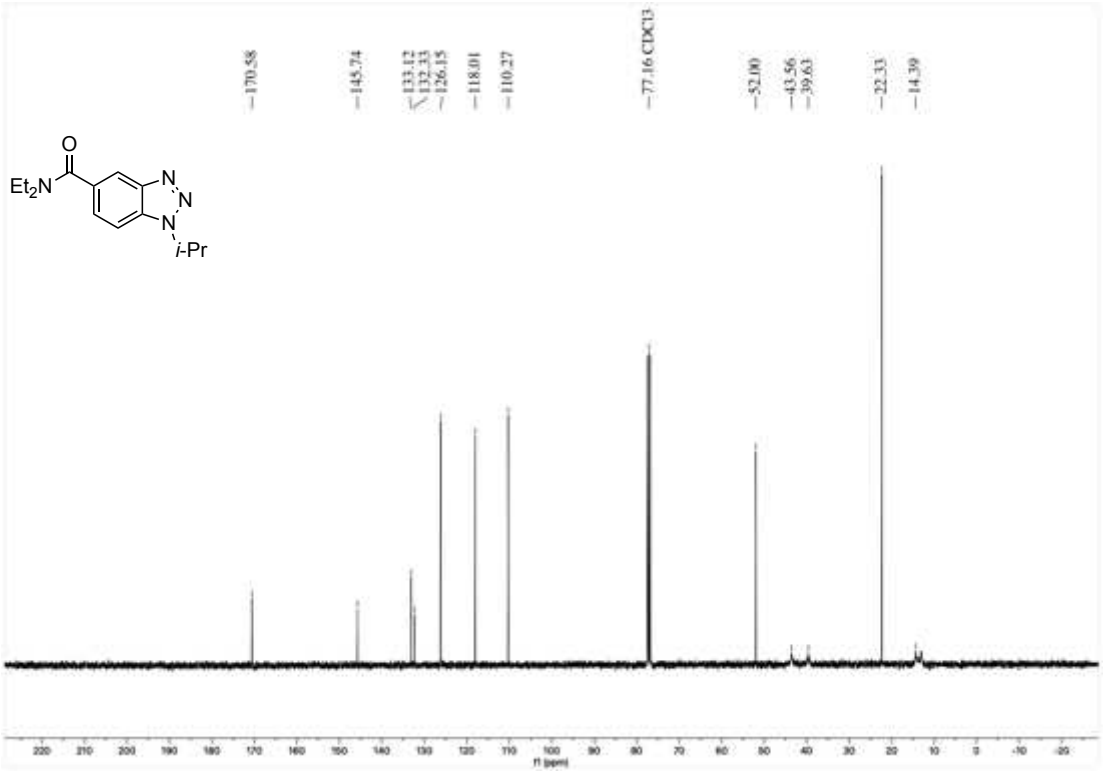
^{1}H NMR spectrum of **1-A10** (400 MHz, $CDCl_3$)



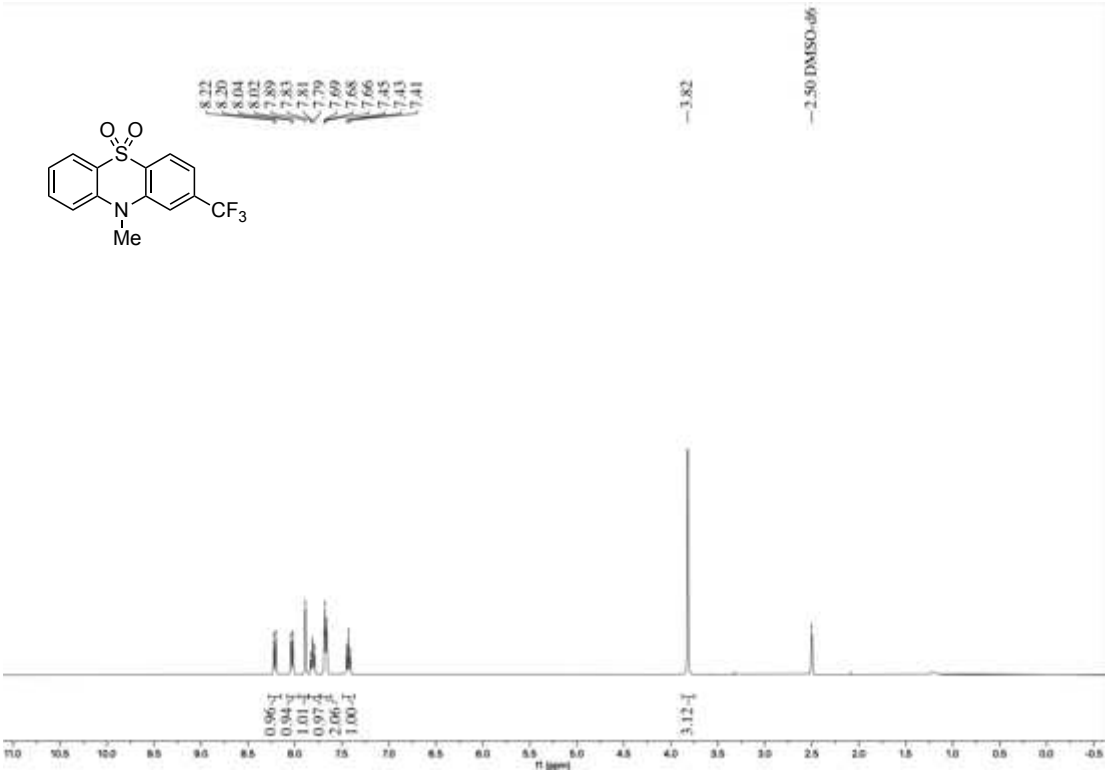
^{13}C NMR spectrum of **1-A10** (101 MHz, $CDCl_3$)



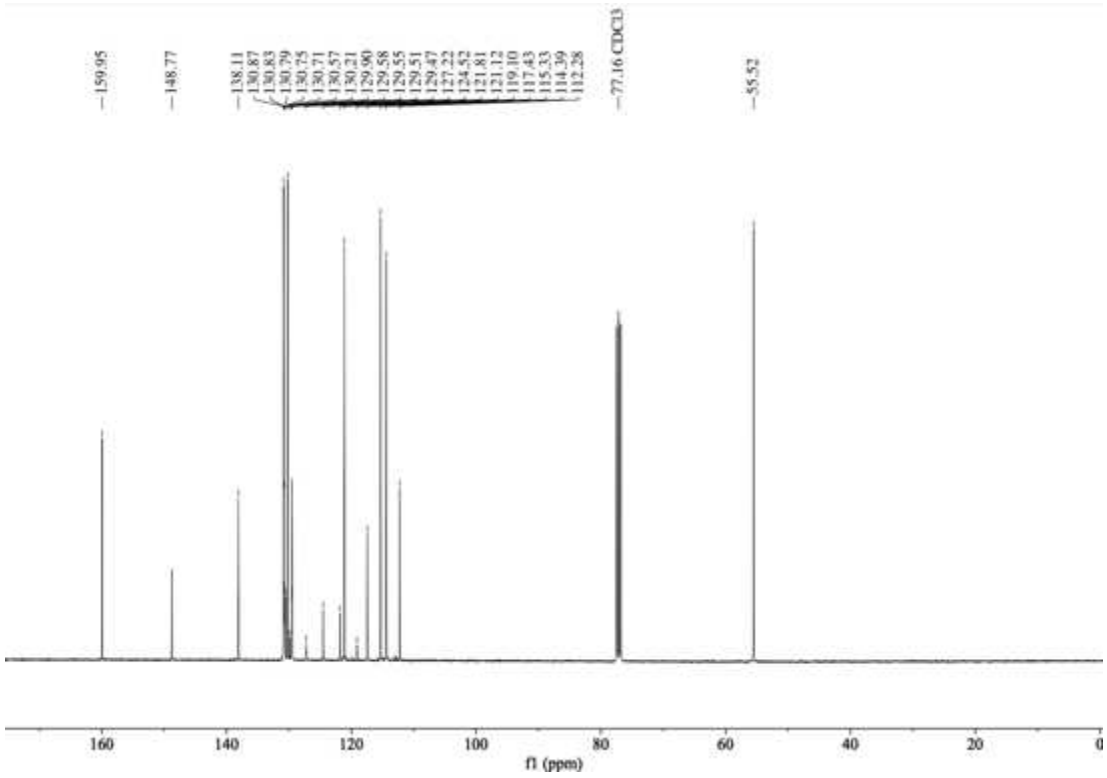
^{1}H NMR spectrum of **1-A11** (400 MHz, $CDCl_3$)



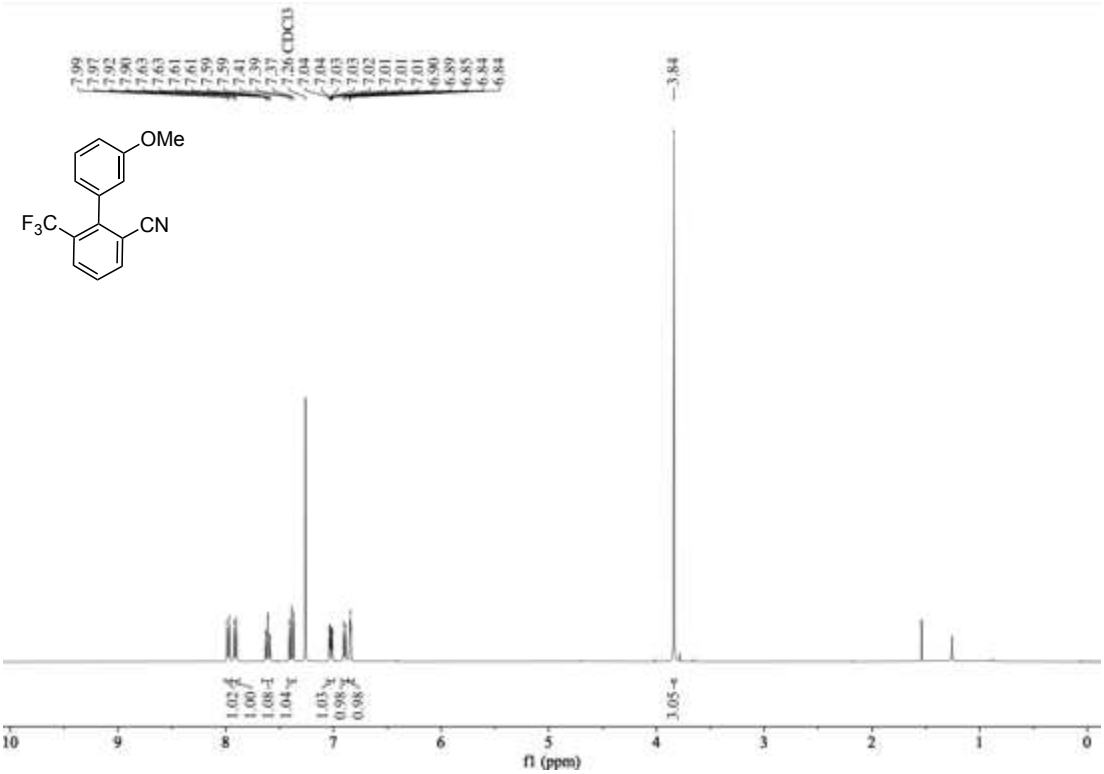
^{13}C NMR spectrum of **1-A11** (101 MHz, $CDCl_3$)



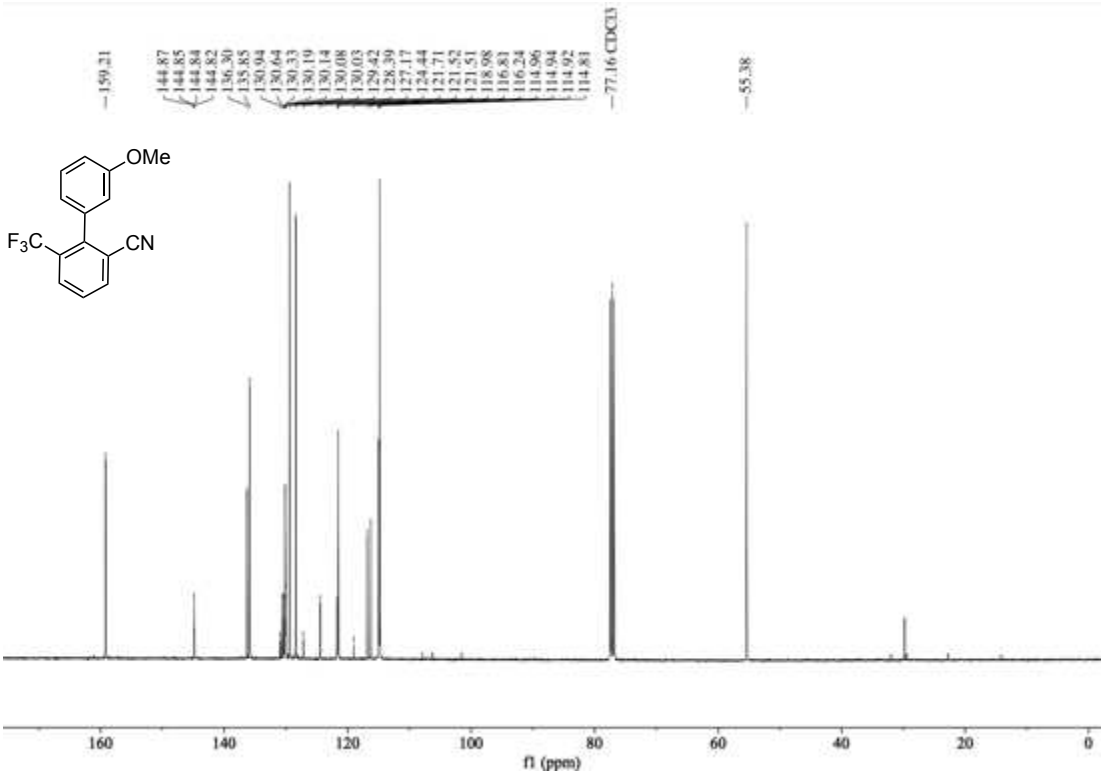
^{1}H NMR spectrum of **1-A12** (400 MHz, $(CD_3)_2SO$)



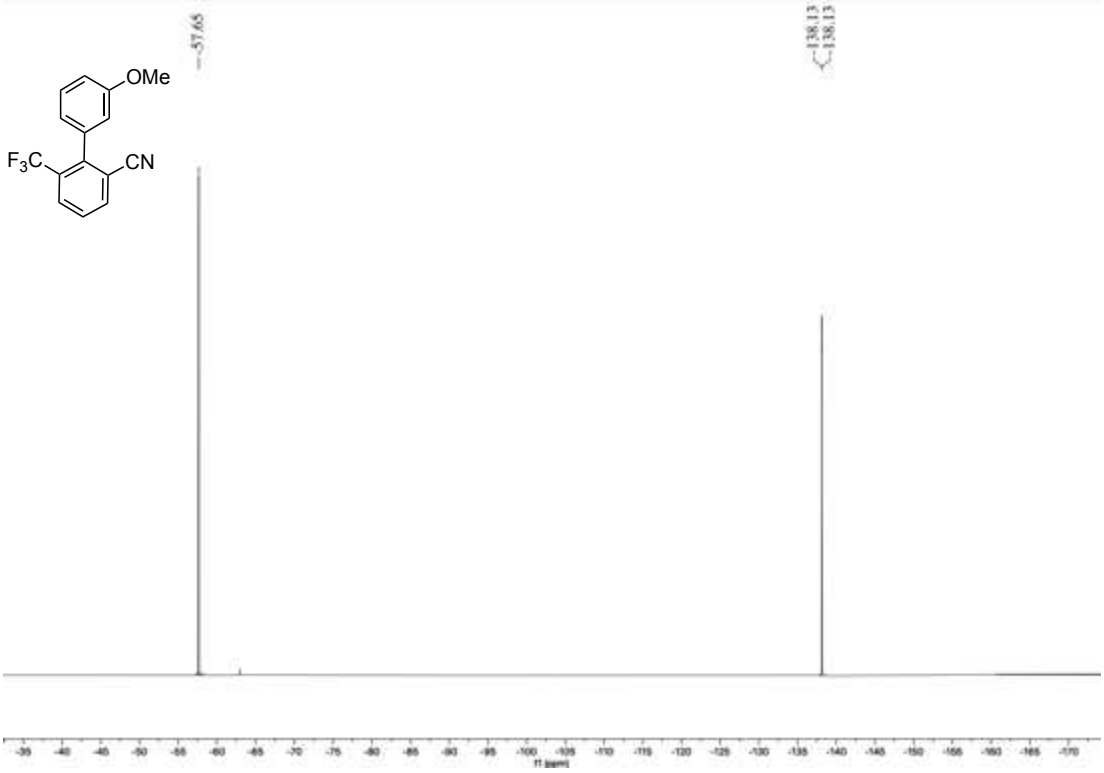
^{13}C NMR spectrum of **1-A12** (101 MHz, $CDCl_3$)



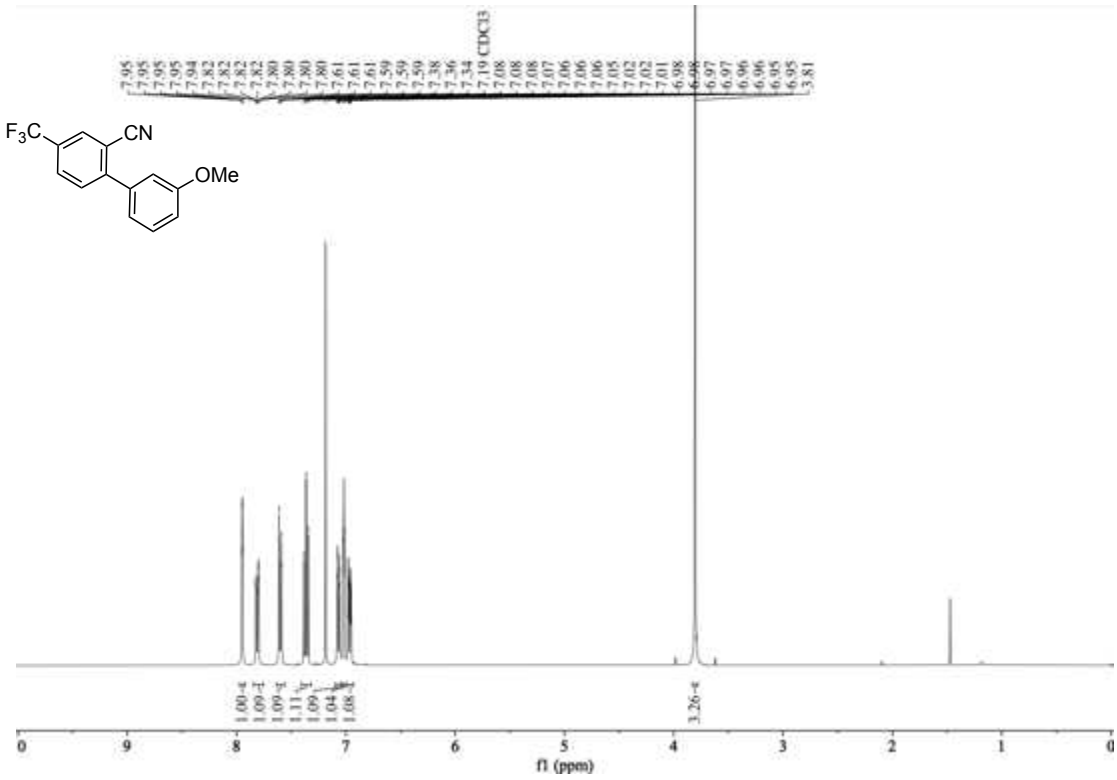
^{1}H NMR spectrum of **1-A13** (400 MHz, $CDCl_3$)



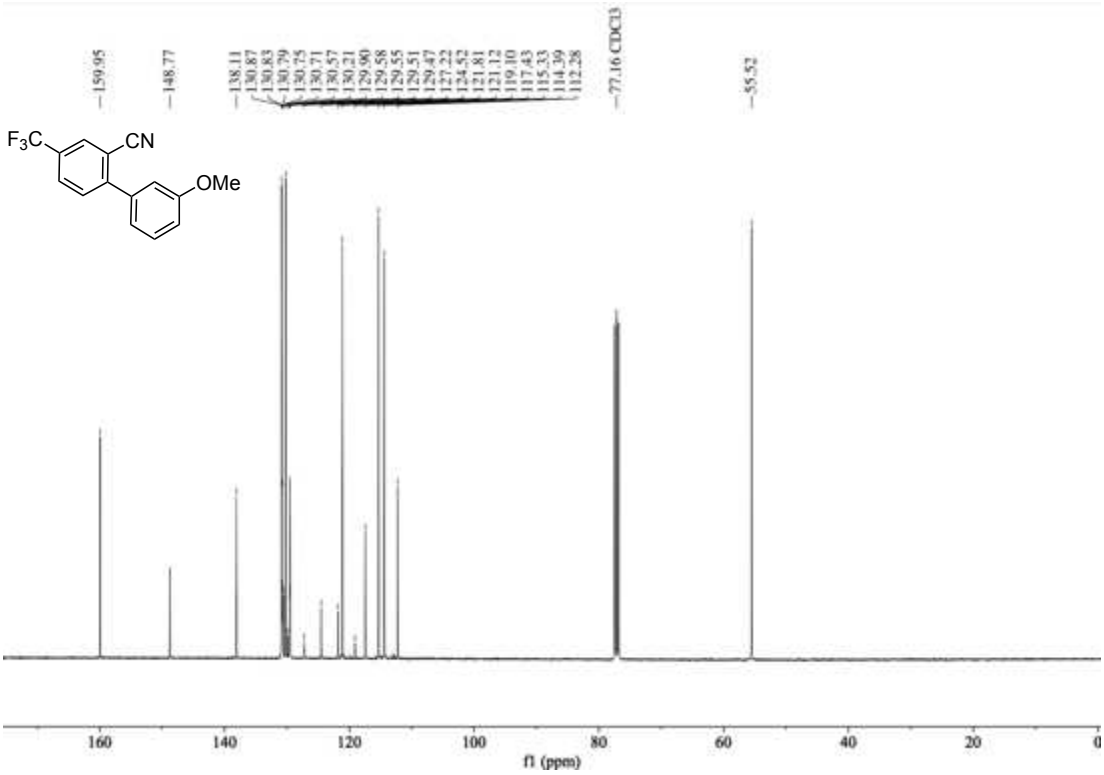
^{13}C NMR spectrum of **1-A13** (101 MHz, $CDCl_3$)



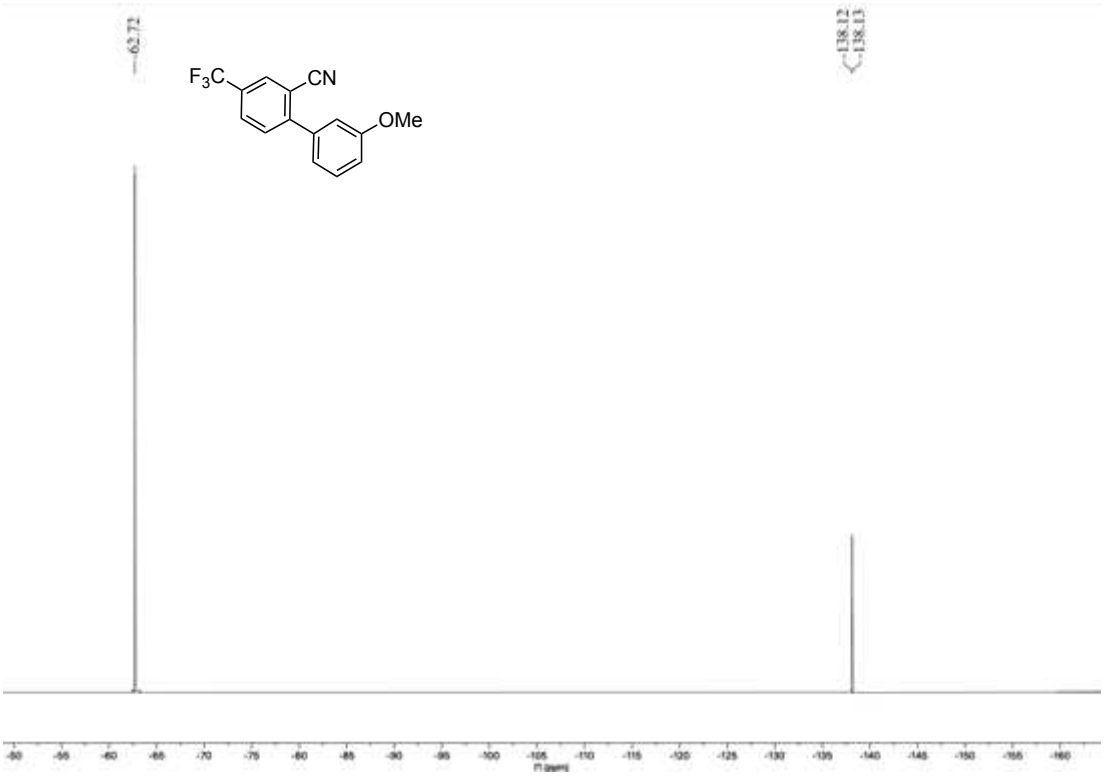
^{19}F NMR spectrum of **1-A13** (376 MHz, $CDCl_3$)



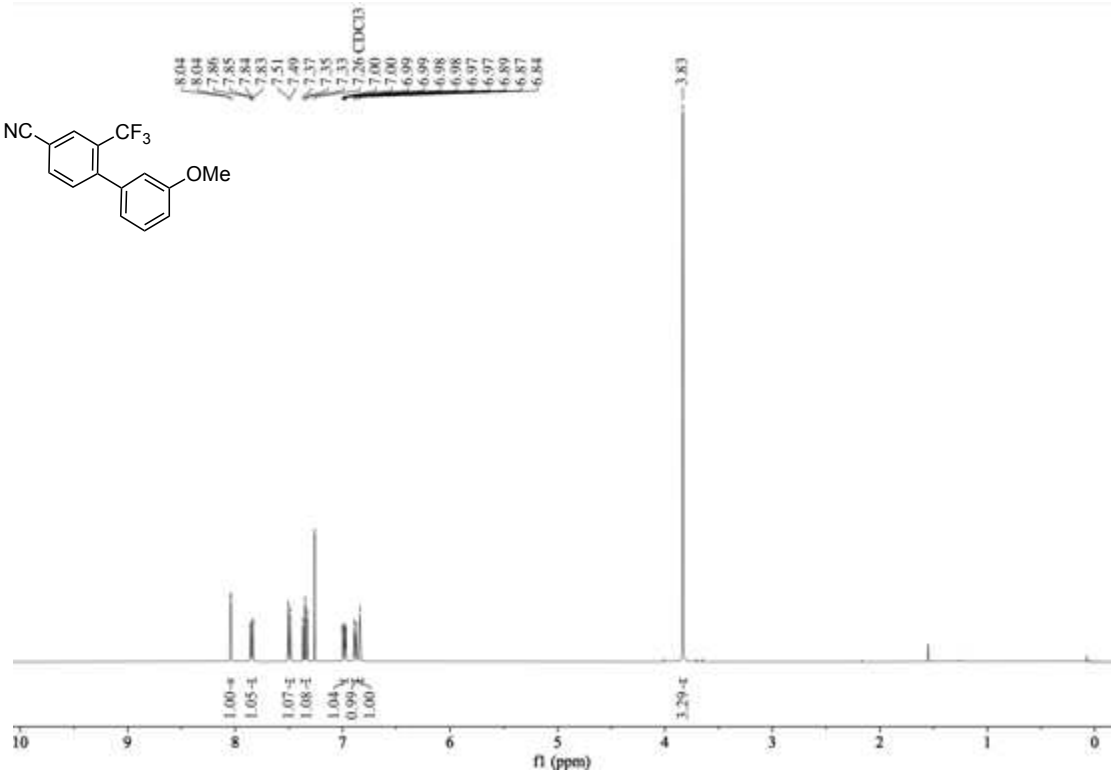
^{1}H NMR spectrum of **1-A14** (400 MHz, $CDCl_3$)



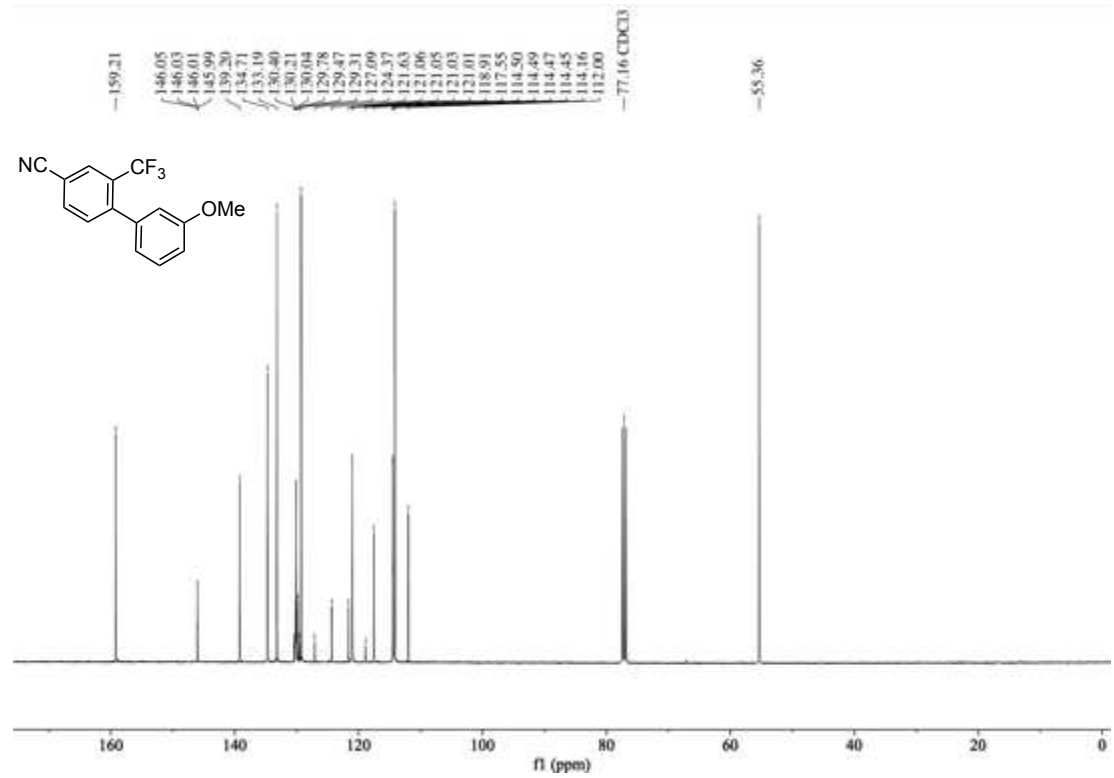
^{13}C NMR spectrum of **1-A14** (101 MHz, $CDCl_3$)



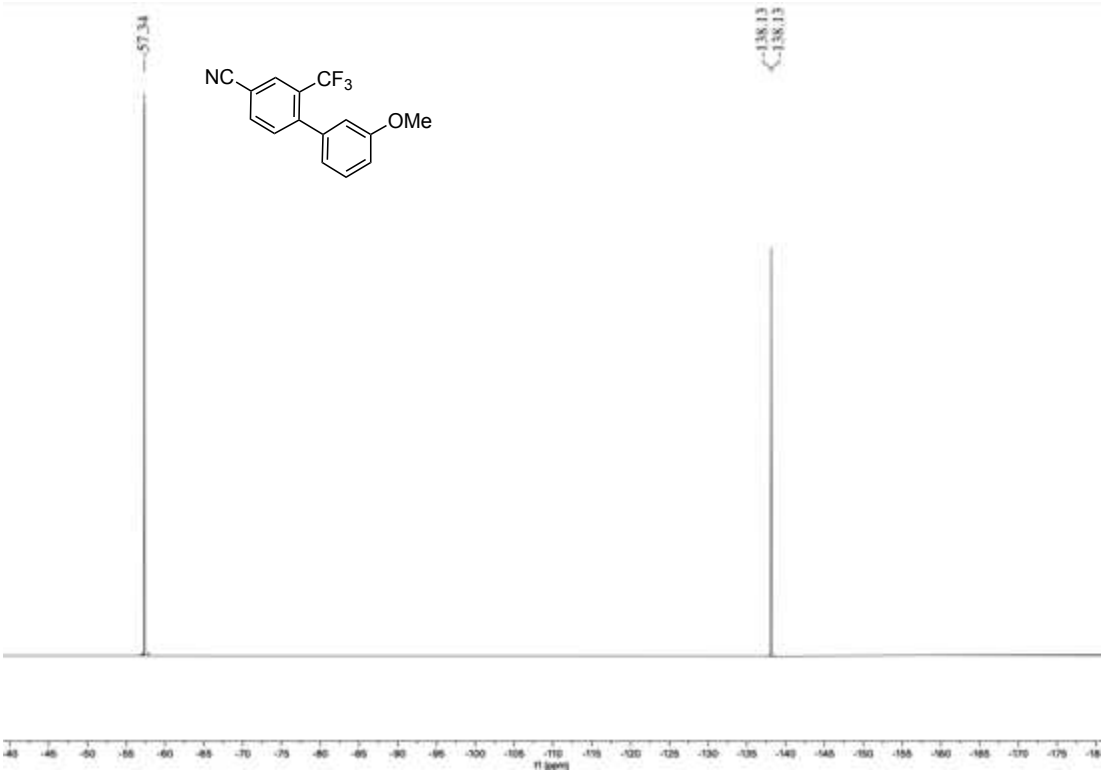
^{19}F NMR spectrum of **1-A14** (376 MHz, $CDCl_3$)



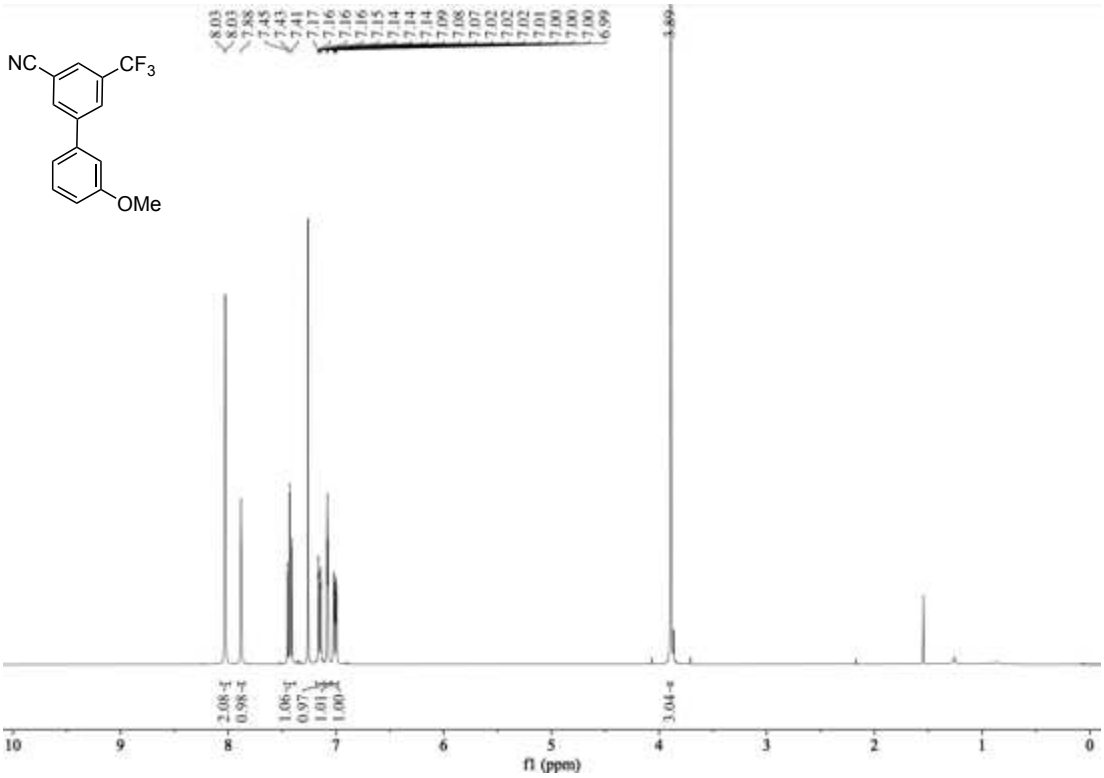
^{1}H NMR spectrum of **1-A15** (400 MHz, $CDCl_3$)



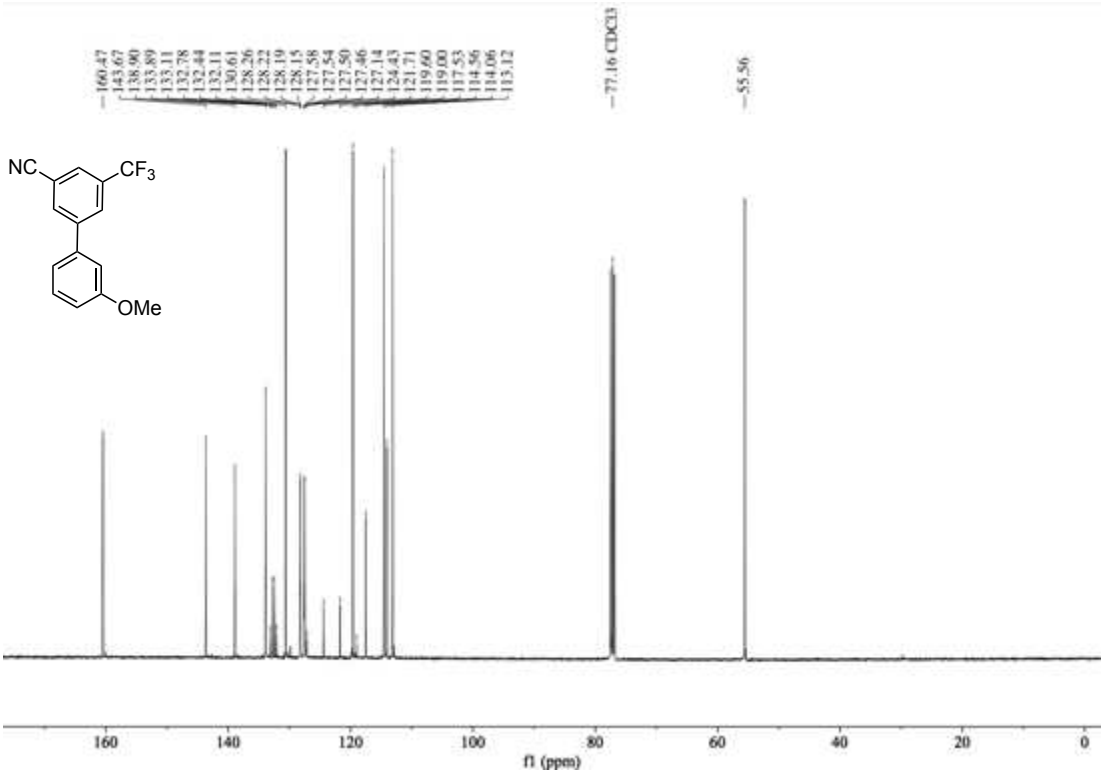
^{13}C NMR spectrum of **1-A15** (101 MHz, $CDCl_3$)



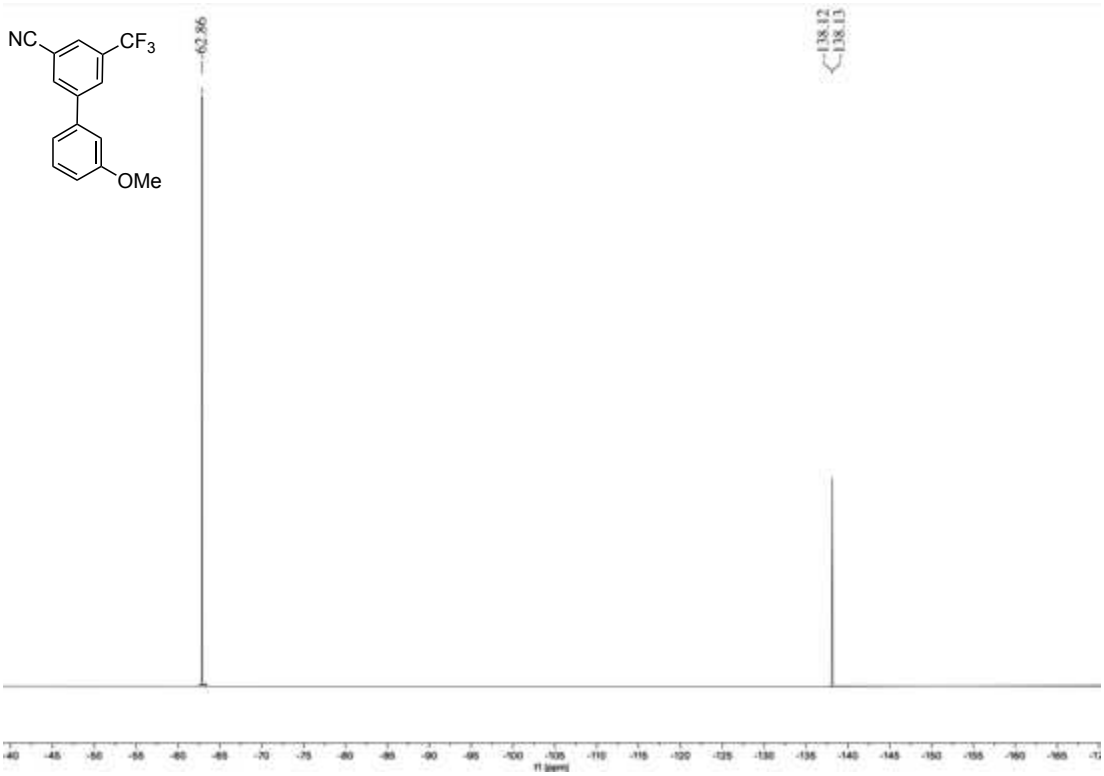
^{19}F NMR spectrum of **1-A15** (376 MHz, $CDCl_3$)



^{1}H NMR spectrum of **1-A16** (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of **1-A16** (101 MHz, $CDCl_3$)



^{19}F NMR spectrum of **1-A16** (376 MHz, $CDCl_3$)

APPENDIX TWO

DIRECT BENZYLIC C–H ETHERIFICATION ENABLED BY BASE-PROMOTED HALOGEN TRANSFER

A2.1. General Information

General Reagent Information: All reactions were performed under a nitrogen (N_2) atmosphere unless otherwise noted. 2,6-Dichlorotoluene (Thermo Scientific Chemicals #10590371), 1-methylnaphthalene (Alfa Aesar #S04F011), 2-ethyl-1-hexanol (Millipore Sigma #538051), 2-iodothiophene (CombiBlocks #OR-1024), lithium *tert*-butoxide (LiO-*t*-Bu, Millipore Sigma #400173), sodium *tert*-butoxide (NaO-*t*-Bu, Millipore Sigma #359270), and 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6, Chem-Impex #03901) were purchased from the indicated vendors and used as received. Potassium *tert*-butoxide (KO-*t*-Bu, Oakwood Chemical #075285) was purchased as a 99% pure powder and used as received. NaO-*t*-Bu, LiO-*t*-Bu, and KO-*t*-Bu and 18-crown-6 were stored at room temperature (rt) inside a N_2 filled glovebox and used immediately if brought outside the glovebox. Anhydrous dimethylformamide (DMF, Millipore Sigma #227056) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU, TCI Chemicals #D2014) were purchased from the indicated vendors and used as received. Tetrahydrofuran (THF) was deoxygenated and dried by passage over packed columns of neutral alumina and copper (II) oxide under positive pressure of N_2. All other solvents and reagents were purchased from Millipore Sigma, Combi-Blocks, TCI, Thermo Scientific Chemicals, Matrix Scientific, Alfa Aesar, Oakwood Chemical, or Synthonix and used as received. Flash chromatography was performed on 40-63 μm silica gel (SiliaFlash® F60 from Silicycle). Preparative thin-layer chromatography (PTLC) was performed on silica gel 60 Å F254 plates (20 x 20 cm, 1000 μm, SiliaPlate from Silicycle, #TLG-R10011B-341) and visualized with UV light (254 nm) or $KMnO_4$. Celite® 545 (Product #CX0574-3) was purchased from Millipore Sigma.

General Analytical Information: All reported compounds were characterized by ^{1}H, ^{13}C, and ^{19}F (if applicable) NMR spectroscopy, FTIR spectroscopy, and mass spectrometry. Melting point analysis was conducted if the compound is a solid. NMR spectra were obtained on a Bruker NEO400, Bruker U2A-400, or Bruker Ascend 400 spectrometers. ^{1}H NMR data is reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, br s = broad singlet, d =doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, dq = doublet of quartets, qd = quartet of doublets, m = multiplet), coupling constant (Hz), and integration. All ^{1}H NMR signals are reported as chemical shifts (δ ppm) relative to residual $CHCl_3$ at 7.26 ppm, $(CH_3)_2SO$ at 2.50 ppm, $(CH_3)_2CO$ at 2.05 ppm, CH_2Cl_2 at 5.32 ppm or CH_3CN at 1.94 ppm.[1] ^{13}C NMR data is reported as follows: chemical shift (δ ppm), multiplicity (if applicable, d = doublet, quin = quintet, q = quartet, dq = doublet of quartets, qd = quartet of doublets, m = multiplet), and coupling constant (Hz). ^{13}C NMR signals are reported as chemical shifts (δ ppm) relative to $CDCl_3$ at 77.16 ppm, $(CD_3)_2SO$ at 39.52 ppm, $(CD_3)_2CO$ at 206.26 ppm, CH_2Cl_2 at 53.84 ppm, or CD_3CN at 1.32 ppm.[1] Chemical shifts for ^{19}F NMR are reported in terms of chemical shift in reference to an internal standard (1,2-difluorobenzene set to δ -138.18 ppm); reported ^{19}F NMR data are for proton-decoupled spectra.[2] High resolution mass spectra (HRMS)

were recorded on an Agilent 6210 TOF interfaced to a DART 100 source, an Agilent 6230 LC-MS B-TOF equipped with a dual ESI source, or an Agilent GC coupled to Xevo G2 QTOF *via* APGC ionization source provided by Colorado State University Analytical Resource Core – Molecular and Materials Analysis Center. IR spectra were recorded using a Thermo Scientific Nicolet iS-50 FTIR Spectrometer and reported as frequency of absorption (cm^{-1}). Samples were sent to Atlantic Microlab in Norcross, GA for combustion elemental analysis and analyzed for carbon, hydrogen, and nitrogen composition. Melting point analyses were conducted using a MelTemp capillary melting point apparatus. Thin-layer chromatography analysis was performed on silica gel 60 Å F254 plates (250 μm, SiliaPlate from Silicycle, #TLG-R10014B323) and interpreted using UV light (254 nm) or $KMnO_4$ stain. Preparatory thin-layer chromatography purification was performed on silica gel 60 Å (1000 μm, Silicycle, #TLG-R10011B-341) and interpreted using UV light (254 nm).

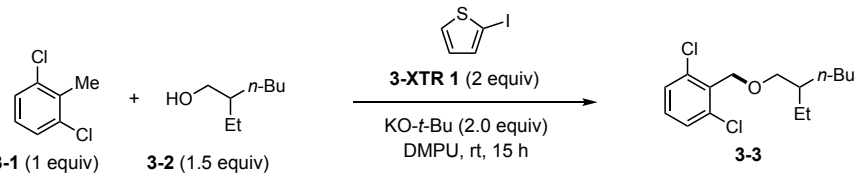
Nomenclature Note: The names provided for the structures in this document were obtained from ChemDraw Professional 20.1.

A2.2. Optimization of Benzylic C–H Etherification

(a) Evaluation of changes in optimal base, halogenating agent, solvent, reaction time, and temperature for direct etherification of 2,6-dichlorotoluene (3-1).

Preliminary experiments varying base and solvent indicated that numerous combinations could promote the benzylic etherification of 2,6-dichlorotoluene using 2-ethyl-1-hexanol as a model alcohol. The set of conditions provided in Table 2A-1 offer a benchmark for comparison to inform readers of the effect that specific changes of reagents or conditions have on yield.

General procedure for condition variation: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE® #60910-1) was charged with a magnetic stir bar, 2,6-dichlorotoluene (16.1 mg, 1 equiv, 0.1 mmol), 2-ethyl-1-hexanol (19.5 mg, 0.15 mmol, 1.5 equiv), halogenating agent (0.2 mmol, 2 equiv), anhydrous solvent (0.25 M, 0.4 mL), and base (0.2 mmol, 2 equiv) in successive order (see Table 2A-1 below). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13) and removed from the glovebox. The reaction solution was stirred for 15 h at rt. 1,3,5-Trimethoxybenzene internal standard was measured into the crude solution and the mass weighed into the vial was recorded. A small aliquot of the crude reaction solution was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of 1,3-dichloro-2-(((2-ethylhexyl)oxy)methyl)benzene (**3-3**). The aromatic C–H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the benzylic methylene C–H signal of **3-3** at 4.71 ppm (s, 2H) to assess the yield. The results are summarized in Table A2-1 below. A representative example ^1H NMR spectrum for the crude reaction solution from the optimization of **3-3** is shown in Figure A2-1 to show how the yield was determined.



3-1 (1 equiv) **3-2** (1.5 equiv) **3-3**

Entry	Change from the "benchmarked conditions"	Yield
1	none	62%
2	THF used as solvent instead of DMPU and w/ 2 equiv 18-crown-6	55%
3	2 equiv of 18-crown-6 used as additive	46%
4	40 °C instead of 25 °C	44%
5	60 °C instead of 25 °C	51%
6	THF used as solvent instead of DMPU	97%
7	DMF used as solvent instead of DMPU	59%
8	DMSO used as solvent instead of DMPU	0%
9	PhMe used as solvent instead of DMPU	0%
10	NaO-*t*-Bu used instead of KO-*t*-Bu	64%
11	LiO-*t*-Bu instead of KO-*t*-Bu	62%
12	KOH instead of KO-*t*-Bu	7%
13	KHMDS instead of KO-*t*-Bu	77%
14	LiTMP instead of KO-*t*-Bu	23%
15	1.0 eq KO-t-Bu instead of 2.0 eq KO-*t*-Bu	44%
16	3.0 eq KO-t-Bu instead of 2.0 eq KO-*t*-Bu	47%
17	KO-*t*-Bu (97%) from Thermo Fisher Scientific (Product #A13947-14) instead of KO-*t*-Bu from Oakwood	61%
18	KO-*t*-Bu (99.99%) from Millipore Sigma (Product #659878) instead of KO-*t*-Bu from Oakwood	58%
19	KO-*t*-Bu (98%) from Millipore Sigma (Product #156671) instead of KO-*t*-Bu from Oakwood	60%
20	3.0 eq used instead of 2.0 eq 2-iodothiophene	66%
21	1.0 eq used instead of 2.0 eq 2-iodothiophene	54%
22	2-bromothiophene used instead of 2-iodothiophene	0%
23	2,5-dibromothiophene used instead of 2-iodothiophene	50%
24	30 min instead of 15 h	63%
25	reaction run open to air instead of under N_2	46%
26	0.1 molar instead of 0.25 molar	41%
27	1.0 molar instead of 0.25 molar	58%
28	*N*-iodosuccinimide used instead of 2-iodothiophenene	0%
29	iodine used instead of 2-iodothiophene	0%
30	carbon tetrabromide used instead of 2-iodothiophene	0%
31	*N*-bromosuccinimide used instead of 2-iodothiophene	0%
32	*N*-chlorosuccinimide used instead of 2-iodothiophene	0%

Table A2-1. Condition variation for the benzylic C–H etherification of 2,6-dichlorotoluene.

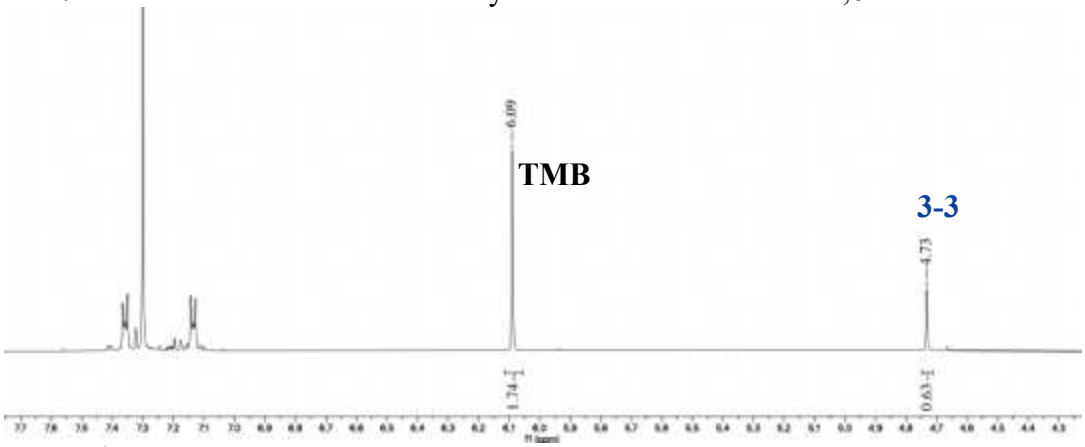
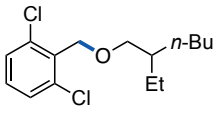


Figure 2A-1. ^{1}H NMR spectral window of the crude reaction solution of reaction 1 from Table 2A-1 above. 1,3,5-Trimethoxybenzene internal standard (27.5 mg, 0.16 mmol, signal at 6.09 ppm calibrated to 1.74 for 0.1 mmol scale reaction) was used to determine the yield of 1,3-dichloro-2-(((2-ethylhexyl)oxy)methyl)benzene **3-3**, 63% yield).

1,3-dichloro-2-(((2-ethylhexyl)oxy)methyl)benzene (3-3)



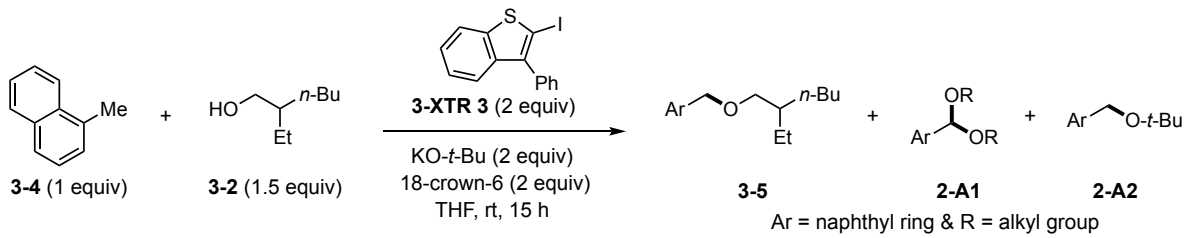
The title product was prepared according GP1 (see Section 4) using 2,6-dichlorotoluene (161.0 mg, 1 mmol, 1 equiv), 2-ethylhexan-1-ol (195.3 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (420.0 mg, 2 mmol, 2 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous THF (4.0 mL). The title product was purified *via* silica gel chromatography (Hex to 10% EtOAc/Hex) to afford the title compound as a colorless oil (182.6 mg, 0.63 mmol, 63% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.0 Hz, 2H), 7.17 (t, J = 8.0 Hz, 1H), 4.73 (s, 2H), 3.41 (d, J = 6.0 Hz, 2H), 1.60 – 1.47 (m, 1H), 1.45 – 1.17 (m, 9H), 0.91 – 0.80 (m, 7H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.1, 134.0, 129.8, 128.5, 73.5, 67.4, 39.7, 30.5, 29.1, 23.8, 23.3, 14.3, 11.1. **IR** (neat, cm^{-1}) 2958, 2817, 1564, 1436, 1098, 1066, 766, 727. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{15}H_{23}OCl_2]^+$ = 289.1120, 289.1136 found.

(b) Evaluation of changes in optimal base, halogenating agent, solvent, reaction time, and temperature for direct etherification of 1-methylnaphthalene (3-4).

Purpose: 1-Methylnaphthalene was selected as a candidate for further optimization as it represents a more challenging substrate for deprotonative X-transfer due to its lower C–H acidity. The optimized conditions are provided in Table 2A-2 below in comparison to specific changes of reagents or conditions used to document these effects for readers.

General procedure for condition variation: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE® , #60910-1) was charged with a magnetic stir bar, 1-methylnaphthalene (14.2 mg, 1 equiv, 0.1 mmol), 2-ethyl-1-hexanol (19.5 mg, 0.15 mmol, 1.5 equiv), halogenating agent (0.2 mmol, 2 equiv), anhydrous solvent (0.25 M, 0.4 mL), and base (0.2 mmol, 2 equiv) in successive order (see Table 2A-2 below). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13) and removed from the glovebox. The reaction solution was stirred for 15 h at rt. 1,3,5-Trimethoxybenzene internal standard was then measured into the crude solution and the mass weighed into the vial was

recorded. A small aliquot of the organic layer was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of 1-(((2-ethylhexyl)oxy)methyl)naphthalene (**3-5**). The aromatic C–H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the benzylic C–H signal of **3-5** at 4.92 ppm (s, 2H) to determine the yield. The results are summarized in Table 2A-2 below. We note that a double C–H etherification acetal side product (1-(bis((2-ethylhexyl)oxy)methyl)naphthalene (**2-A1**) and 1-(*tert*-butoxymethyl)naphthalene (**2-A2**) are observed in small quantities (0-20% yield) for the reactions listed in Table 2A-2; these are readily separated upon chromatographic purification. A representative example ^1H NMR spectrum for the crude reaction solution from the optimization of **3-5** is shown in Figure 2A-2 to show how the yield was determined.



3-4 (1 equiv) + **3-2** (1.5 equiv) → **3-5** + **2-A1** + **2-A2**

Ar = naphthyl ring & R = alkyl group

Entry	Change from the "standard conditions"	Yield 3-5	Yield 2-A1	Yield 2-A2
1	none	59%	8%	5%
2	no 18-crown-6 additive	0%	0%	0%
3	DMPU with no 18-crown-6 additive	41%	6%	4%
4	DMF used as solvent instead of THF	33%	9%	5%
5	DMSO used as solvent instead of THF	4%	2%	2%
6	PhMe used as solvent instead of THF	16%	0%	2%
7	LiO-*t*-Bu used instead of KO-*t*-Bu	0%	0%	0%
8	NaO-*t*-Bu used instead of KO-*t*-Bu	9%	0%	0%
9	KOH instead of KO-*t*-Bu	25%	0%	0%
10	KHMDS instead of KO-*t*-Bu	9%	0%	0%
11	LiTMP instead of KO-*t*-Bu	0%	0%	0%
12	1.0 eq KO-t-Bu instead of 2.0 eq KO-*t*-Bu	24%	0%	0%
13	3.0 eq KO-t-Bu instead of 2.0 eq KO-*t*-Bu	23%	20%	0%
14	1.0 eq **3-XTR 3** instead of 2.0 eq	45%	6%	6%
15	3.0 eq **3-XTR 3** instead of 2.0 eq	59%	9%	0%
16	2-iodothiophene instead of **3-XTR 3**	39%	9%	4%
17	2,3-diiodobenzo[*b*]thiophene instead of **3-XTR 3**	34%	0%	7%
18	2-bromo-3-phenylbenzo[*b*]thiophene instead of **3-XTR 3**	31%	0%	7%
19	reaction run open to air instead of under N_2	14%	0%	0%
20	0.1 molar instead of 0.25 molar	45%	14%	5%
21	1.0 molar instead of 0.25 molar	44%	8%	4%
22	*N*-iodosuccinimide used instead of **3-XTR 3**	0%	0%	0%
23	iodine used instead of **3-XTR 3**	0%	0%	0%
24	carbon tetrabromide used instead of **3-XTR 3**	0%	0%	0%
25	*N*-bromosuccinimide used instead of **3-XTR 3**	0%	0%	0%
26	*N*-chlorosuccinimide used instead of **3-XTR 3**	0%	0%	0%

Table 2A-2. Condition variation for the benzylic C–H etherification of 1-methylnaphthalene.

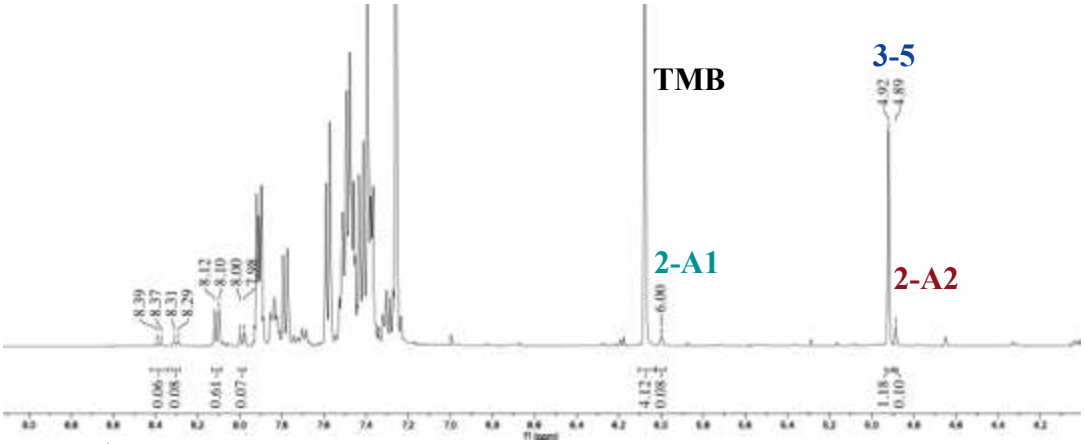


Figure 2A-2. ^{1}H NMR spectral window of the crude reaction solution of reaction 1 from Table 2A-2 above. 1,3,5-Trimethoxybenzene internal standard (27.5 mg, 0.16 mmol, signal at 6.09 ppm calibrated to 1.74 for 0.1 mmol scale reaction) was used to determine the yield of 1-(((2-ethylhexyl)oxy)methyl)naphthalene (**3-5**, 59% yield), acetal side-product (1-(bis((2-ethylhexyl)oxy)methyl)naphthalene (**2-A1**, 8% yield), and 1-(*tert*-butoxymethyl)naphthalene (**2-A2**, 5% yield).

(c) Effect of the X-transfer Reagent Identity on the Benzylic C–H Etherification of Model Substrate 3-1 and 3-4.

Purpose: The condition variation study for substrate **3-4** revealed the most effective halogenation reagent was 2-iodo-3-phenylbenzo[*b*]thiophene (**3-XTR 3**). Below, we tested alternative 3-arylbenzothiophenes under the optimal conditions for the benzylic C–H etherification of **3-4** (Table 2A-3) where no improved yields were observed. It is possible that future work could lead to improved 3-arylbenzothiophene X-transfer reagents; however, given the simplicity of **3-XTR 3** and its initial efficacy, we moved forward with this reagent for substrate scope studies for this report.

Additionally, exploration of halogenation reagents with more diverse structures were tested on model substrates **3-1** and **3-4** under the corresponding optimal conditions for the benzylic C–H etherification (Table 2A-4). Although no improvement was observed, we note that other classes of electrophilic iodoarenes can also promote C–H etherification.

General procedure for X-transfer reagent variation: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE® , #60910-1) was charged with a magnetic stir bar, 2,6-dichlorotoluene (161.0 mg, 0.1 mmol, 1 equiv) or 1-methylnaphthalene (14.2 mg, 1 equiv, 0.1 mmol), 2-ethyl-1-hexanol (19.5 mg, 0.15 mmol, 1.5 equiv), 18-crown-6 additive (if used, 52.8 mg, 0.2 mmol, 2 equiv), halogenating agent (0.2 mmol, 2 equiv), THF (0.25 M, 0.4 mL), and KO-*t*-Bu (22.4 mg, 0.2 mmol, 2 equiv) in successive order (see Table 2A-3 below). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13) and removed from the glovebox. The reaction solution was stirred for 15 h at rt. 1,3,5-Trimethoxybenzene internal standard was then measured into the crude solution and the mass weighed into the vial was recorded. A small aliquot of the organic layer was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of 1,3-dichloro-2-(((2-ethylhexyl)oxy)methyl)benzene (**3-3**) or 1-

(((2-ethylhexyl)oxy)methyl)naphthalene (**3-5**). The aromatic C–H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the benzylic C–H signal of **3-3** at 4.71 ppm (s, 2H) or of **3-5** at 4.92 ppm (s, 2H) to determine the yield. The results are summarized in Table 2A-3 and 2A-4 below.

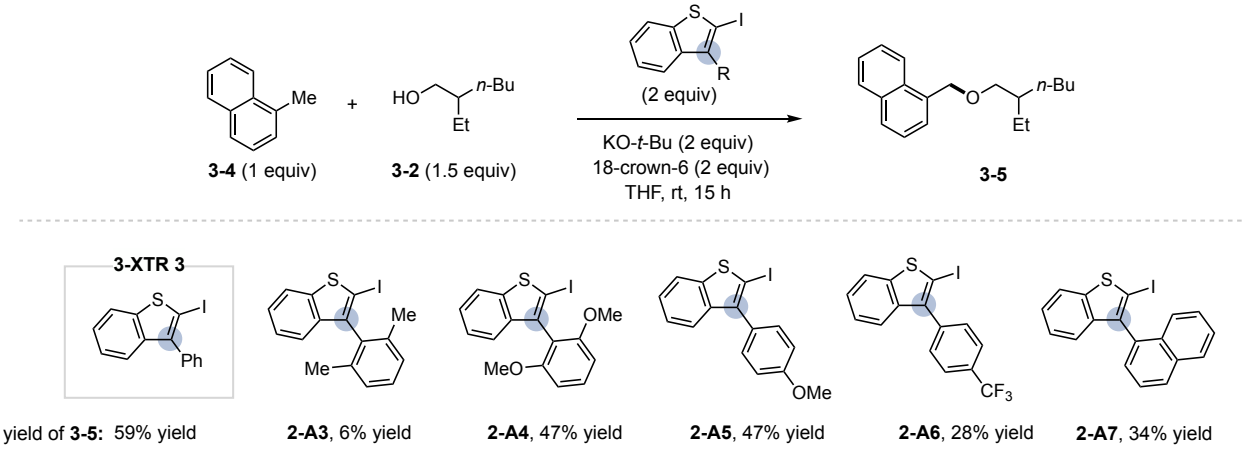


Table 2A-3. Effect of the 3-aryl substituent of the benzothiophene X-transfer reagent for the benzylic C–H etherification of 1-methylnaphthalene.

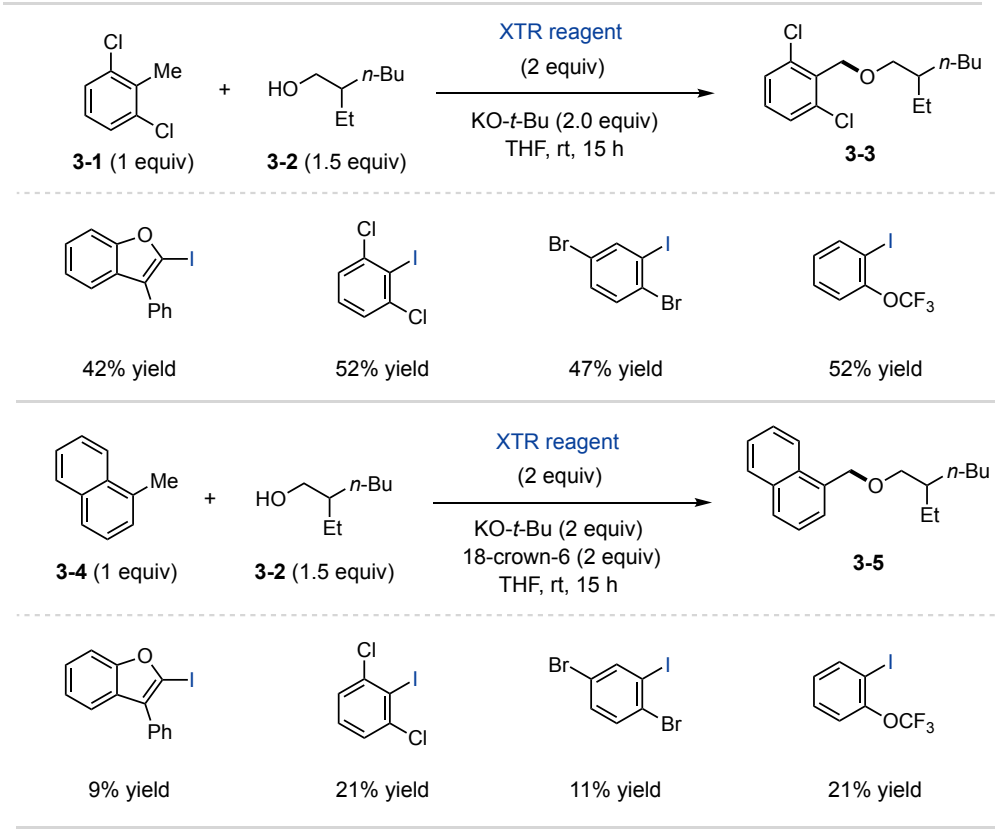
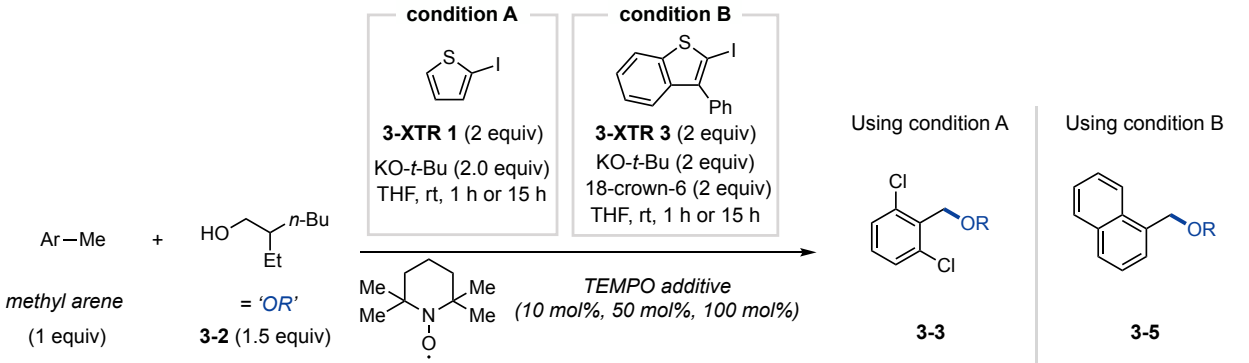


Table 2A-4. Exploration of alternative X-transfer reagents for the benzylic C–H etherification of model substrates **3-1** and **3-4**.

(d) Effect of TEMPO on the Benzylic C–H Etherification of Model Substrates 3-1 and 3-4

Procedure: The following experiments were conducted as a control to test for the possibility of a radical-based mechanism for C–H etherification (i.e., to see if benzylic radicals are generated under these conditions). As such, the highest yielding conditions for substrates **3-1** and **3-4** from the condition variation experiments above (Section 2a-b) were used in the dark with 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, Sigma Aldrich #426369) additive. Thus, **3-1** or **3-4** (1 equiv, 0.1 mmol), 2-ethyl-1-hexanol (19.5 mg, 0.15 mmol, 1.5 equiv), halogenating agent (0.2 mmol, 2 equiv), TEMPO (0.01 - 0.1 mmol, 0.1 - 1 equiv), anhydrous solvent (0.25 M, 0.4 mL), and base (0.2 mmol, 2 equiv) were added according to the general procedure for condition variation and stirred in the dark. The results for each experiment are listed in Figure 2A-3 below.



		Using condition A				Using condition B			
1 hr	mol% TEMPO	0	10	50	100	0	10	50	100
	% Yield	45	43	51	52	15	20	13	18
15 hr	mol% TEMPO	0	10	50	100	0	10	50	100
	% Yield	98	98	46	55	62	67	50	57

Figure 2A-3. The effect of TEMPO on the benzylic C–H etherification of **3-1** and **3-4**.

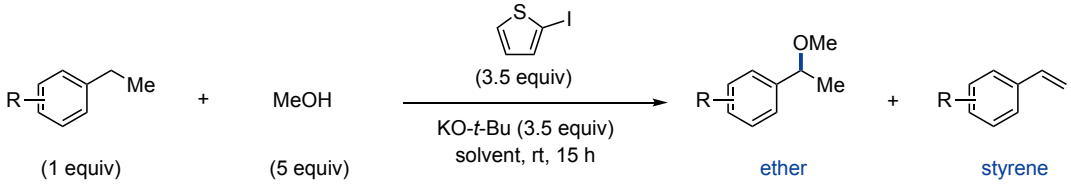
Discussion: Although the productive benzylic C–H etherification of **3-1** predominates with up to 100% TEMPO additive, a decrease in yield does occur with 50% and 100% TEMPO after 15 h. There is no effect on the yield of the benzylic C–H etherification of **3-1** with up to 100% TEMPO after 1 hr. We note that a small amount (less than 10%) of the benzylic-TEMPO product (1-((2,6-dichlorobenzyl)oxy)-2,2,6,6-tetramethylpiperidine) is present when 50-100% TEMPO additive is used in the reaction with **3-1**. There is no impact on the yield for the formation of **3-5** with up to 100% TEMPO additive, and in no condition did we observe any benzylic-TEMPO product in the crude reaction solutions. These results are consistent with a benzyl radical not being involved in the C–H etherification process as the yields for **3-3** are only affected at long durations and with 50% or higher TEMPO additive while the yields for **3-5** are unaffected by TEMPO. We note it is possible that benzyl radicals may be generated under these conditions but are unlikely to be intermediates in route to the benzyl ether products. Similarly, the yields are not affected when the reactions are run in the dark, indicating that the reaction is not promoted by light.

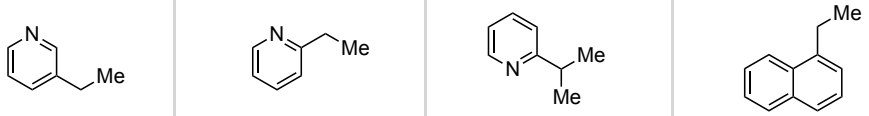
(e) Mechanistic Evidence to Support Benzyl Halide Intermediate Formation

Purpose: We propose that a benzyl halide intermediate is formed through the course of the X-transfer mediated benzylic C–H etherification. In effort to directly observe this intermediate *in situ*, reaction profiles with model substrates **3-1** and **3-4** were performed. These profiles were done using the optimal conditions for each substrate without nucleophile and with 10-20 mol% of base. Despite these efforts, no benzyl halide intermediate was directly observed. This is likely due to the highly reactive nature of the intermediate and its proclivity to react with alkoxide/hydroxide bases.

When testing a variety of ethyl(hetero)arenes under several conditions (Table 2A-5), we observed mixtures of C–H etherification and elimination products, albeit in low-yields. These products are known to arise from secondary benzyl halides, so these results are fully consistent with benzyl halides serving as the key intermediates. We note that condition variation for these ethyl(hetero)arenes did not lead to higher etherification yields, and further exploration of these types of substrates is ongoing in our lab.

Procedure: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE® , #60910-1) was charged with a magnetic stir bar, ethyl(hetero)arene (0.1 mmol, 1 equiv), methanol (16.0 mg, 0.5 mmol, 5 equiv), halogenating agent (0.35 mmol, 3.5 equiv), solvent (0.25 M, 0.4 mL), and KO-*t*-Bu (39.2 mg, 0.35 mmol, 3.5 equiv) in successive order (see Table 2A-5 below). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13) and removed from the glovebox. The reaction solution was stirred for 15 h at rt. 1,3,5-Trimethoxybenzene internal standard was then measured into the crude solution and the mass weighed into the vial was recorded. A small aliquot of the organic layer was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of ether and styrene products, all of which have been previously reported in the literature.[3]





	% ether	% styrene	% ether	% styrene	% ether	% styrene	% ether	% styrene
DME	11	4	20	0	0	35	3	2
DMF	0	2	13	0	0	19	8	4

Table 2A-5. X-transfer enabled benzylic C–H etherification on a variety of ethyl(hetero)arenes.

(f) Benzylic etherification of methyl benzyl halide

Purpose: To determine if selectivity could be achieved for a benzylic C–H bond in the presence of a preexisting benzyl halide, 2-(chloromethyl)-6-methylpyridine was subjected to the optimized conditions for benzylic C–H etherification (Figure 2A-4). It was found that reactivity at the chloromethyl group predominates.

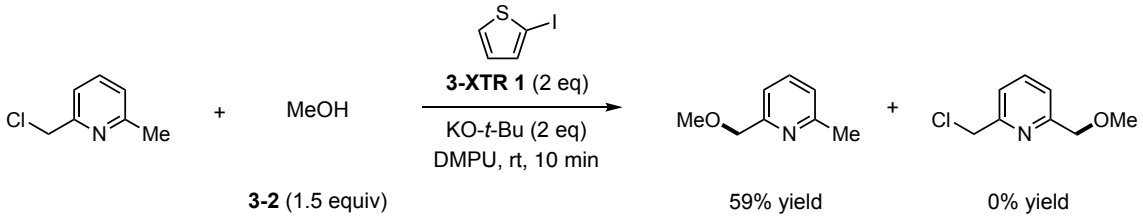
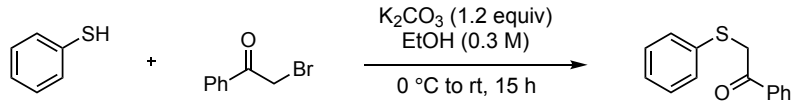


Figure 2A-4. Subjection of 2-(chloromethyl)-6-methylpyridine to the optimized conditions for benzylic C–H etherification. The product formation was determined by ^{1}H NMR and the spectroscopic data is consistent with a previous report.[4]

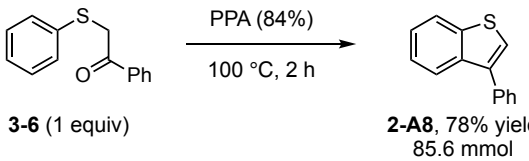
A3. Synthesis of 2-Iodo-3-phenylbenzo[*b*]thiophene

Step 1: 1-phenyl-2-(phenylthio)ethan-1-one (3-6)



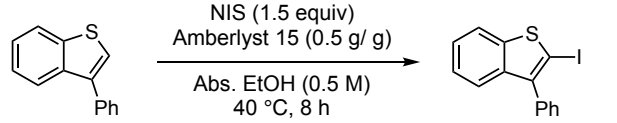
Procedure: An oven-dried 2 L Erlenmeyer flask was charged with a magnetic stir bar, anhydrous K_2CO_3 (75.3 g, 544.6 mmol, 1.2 equiv), and absolute ethanol (1.5 L, ~0.3 M). The solution was cooled to 0 °C using an ice-water bath and thiophenol (50.0 g, 453.8 mmol, 1 equiv) was added. After stirring for 10 min at 0 °C, 2-bromoacetophenone (90.3 g, 453.8 mmol, 1 equiv) was added portion wise. The reaction mixture was warmed to rt and stirred for 15 h open to air. Next, ice (~ 500 g) was added to the reaction mixture and stirred until the ice melted (30 min). The resulting precipitate was collected *via* filtration and washed with deionized water (300 mL) to provide the title product as a white solid (102.0 g, 446.8 mmol, 98% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.61 (td, *J* = 7.4, 1.6 Hz, 1H), 7.49 (td, *J* = 7.8, 1.6 Hz, 2H), 7.44 – 7.40 (m, 2H), 7.35 – 7.19 (m, 3H), 4.30 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.2, 135.6, 135.0, 133.7, 130.7, 129.3, 128.9 (2C), 127.3, 41.4. The spectroscopic data is consistent with a previous report.[5]

Step 2: 3-phenylbenzo[*b*]thiophene (2-A8)



Procedure: An oven-dried 500 mL Erlenmeyer flask was charged with a magnetic stir bar and 84% polyphosphoric acid (PPA, 125 g, 62.5 mL). The flask was inserted into a silicon oil bath preheated to 100 °C and stirring was initiated. Next, 1-phenyl-2-(phenylthio)ethan-1-one (25 g, 109.6 mmol, 1 equiv) was added portion wise and the reaction mixture turned orange. We note that the stir bar must be smoothly stirring PPA before adding **3-6** to obtain the cleanest reaction. If **3-6** is added when the stir bar is not thoroughly mixing PPA, decomposition of starting material may be observed. Once all of **3-6** was added, the reaction mixture was stirred at 100 °C for 2 h. The reaction mixture was cooled to rt and poured into a 1 L Erlenmeyer flask containing a magnetic stir bar with equal parts ice (~ 300 g) and EtOAc (300 mL). The resulting mixture was stirred vigorously until PPA dissolved and two layers were cleanly formed. The resulting mixture was then poured into a separatory funnel containing H_2O (200 mL) and the aqueous layer was extracted with EtOAc (3 x 200 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (100% hexanes) yielded the title compound as a colorless oil (18.0 g, 85.6 mmol, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 – 8.04 (m, 1H), 7.80 – 7.72 (m, 1H), 7.69 – 7.61 (m, 1H), 7.59 – 7.46 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.8, 138.2, 138.0, 136.1, 128.8, 128.8, 127.6, 124.5, 124.4, 123.6, 123.0. The spectroscopic data is consistent with a previous report.[6]

Step 3: 2-iodo-3-phenylbenzo[*b*]thiophene (3-XTR 3)



2-A8 (1 equiv) — **3-XTR 3**, 82% yield, 86.3 mmol

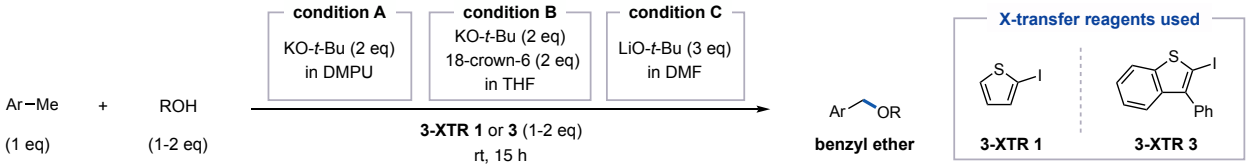
Procedure: An oven-dried 500 mL round-bottom flask charged with a magnetic stir bar, 3-phenylbenzothiophene (22 g, 104.6 mmol, 1 equiv), and absolute ethanol (209 mL, 0.5 M). While stirring at rt, dry amberlyst 15 (11 g used, 0.5 g of amberlyst per g of 3-phenylbenzothiophene) and *N*-iodosuccinimide (35.3 g, 156.9 mmol, 1.5 equiv) were added successively. The flask was inserted into a silicon oil bath preheated to 40 °C and stirred for 8 h open to air. (**Note:** reaction solution turns dark orange/red color). The reaction mixture was then cooled to rt and saturated sodium thiosulfate (~100 mL) was added until a light-yellow color persisted. The mixture was then diluted with ethyl acetate (250 mL) and filtered through celite. The celite cake was washed with additional ethyl acetate (~250 mL) until the organic layer was colorless. The organic filtrate was then poured into a separatory funnel containing H_2O (200 mL) and the aqueous layer was extracted with EtOAc (3 x 200 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo* to afford the title compound with residual succinimide impurity. The mixture was dissolved in diethyl ether (200 mL) and brine (200 mL), poured into a separatory funnel, and washed with brine (2 x 200 mL). The diethyl ether layer was collected and dried over Mg_2SO_4. The Mg_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo* to afford the title compound as a light yellow solid (29.0 g, 86.3 mmol, 82% yield). **Note:** this compound can be recrystallized from 100% hexanes if required. Purification by recrystallization is recommended for highest yields in C–H etherification reactions. **Mp**: 55-57°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, J = 7.9 Hz, 1H), 7.49 – 7.40 (m, 3H), 7.41 – 7.30 (m, 3H), 7.26 – 7.13 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$)

δ 144.0, 142.9, 138.7, 135.8, 130.2, 128.7, 128.3, 124.7 (2C), 123.0, 121.6, 80.9. **IR** (neat, cm^{-1}) 1732, 1597, 1479, 1422, 1157, 1028, 878, 604. **HRMS** (APGC-TOF) [M+] calcd. for $[C_{14}H_9IS]^+$ = 335.9470, 335.9484 found. The spectroscopic data is consistent with a previous report.[7]

2A.4. General Procedure and Isolation of Benzylic C–H Etherification

For the substrates isolated using general procedure 1 (GP1), the general procedure was conducted on a 1 mmol scale of alkylarene using a standard manifold Schlenk line outside of a glovebox. The crude ^1H NMR yields observed before isolation are comparable to the isolated yield unless otherwise noted.

Note on condition selection: In Section 2a-b, it was found that **3-XTR 1** and **3-XTR 3** can promote effective C–H etherification of **3-1** and **3-4** using a variety of base, solvent, and additive combinations. Thus, substrates in Figure 3-9 and Figure 3 were tested with **3-XTR 1** and **3-XTR 3** under Condition A and Condition B shown below to quickly identify effective conditions. In general, electron rich methylarenes work best with KO-*t*-Bu in either DMPU or THF (e.g., **3-7**, **3-8**, **3-20**), where using 18-crown-6 was, in some cases (e.g., **3-5**, **3-9**, **3-12**), found to give increased yields. When using phenol pronucleophiles, the best reactivity is achieved using a KOH and 18-crown-6 base system in DMF. When overoxidation to acetal side-products under Conditions A and B occurs, then a shorter reaction time or Condition C can be used (e.g., **3-10**, **3-13**, **3-15**, **3-16**) to minimize this pathway.



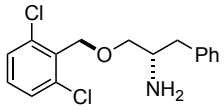
General Benzylic C–H Etherification Procedure (GP1): Open to air, an 8 mL oven-dried vial (Thermo Fischer Scientific, #033405P) was charged with a magnetic stir bar and the following liquid reagents: 2-iodothiophene (if used, 1 - 2 equiv), nucleophile (if liquid, 1 - 1.5 equiv), and alkylarene substrate (if liquid, 1 equiv). The vial was sealed with a screw cap (Thermo Fisher Scientific, #03392A) lined with a PTFE septum (Thermo Fisher Scientific, #B799515), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 on a manifold Schlenk line. The solid reagents were then charged into a separate 8 mL oven-dried vial (Thermo Fischer Scientific, #033405P): KO-*t*-Bu (1.5 - 2 equiv) or LiO-*t*-Bu (3 equiv), 18-crown-6 (if required, 2 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (if used, 2 equiv), nucleophile (if solid, 1 - 1.5 equiv), and alkylarene substrate (if solid, 1 equiv). This vial was sealed with a screw cap (Thermo Fisher Scientific, #03392A) lined with a PTFE septum (Thermo Fisher Scientific, #B799515), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 on a manifold Schlenk line. Anhydrous solvent (0.25 M) was added to the vial containing the liquid reagents and the entire contents were promptly transferred to the vial containing the solid reagents *via* a syringe under N_2. The reaction vial was stirred for 15 h at rt. The reaction mixture was subsequently transferred into a separatory funnel containing H_2O (40 mL) and the aqueous mixture was extracted with EtOAc (3 x 40 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered

off and the organic layer was concentrated *in vacuo*. The crude material was purified *via* silica gel chromatography.

2A.5. Characterization Data for the Benzylic Functionalized Products in Figure 3-9.

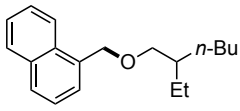
(a) Products shown in Figure 3-9.

(*S*)-1-((2,6-dichlorobenzyl)oxy)-3-phenylpropan-2-amine (3-7)



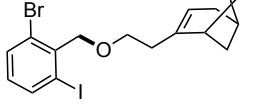
The title product was prepared according to GP1 with a 10 min reaction time instead of 15 h to reduce formation of an acetal side product. Thus, 1,3-dichloro-2-methylbenzene (161.0 mg, 1 mmol, 1 equiv), (*S*)-2-amino-3-phenylpropan-1-ol (226.7 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous DMPU (4.0 mL) were used according to GP1. The product was purified *via* silica gel chromatography (1% Et_3N in 80% EtOAc/hexanes) to afford the title compound as an orange oil (293.4 mg, 0.95 mmol, 95% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.20 (m, 4H), 7.18 – 7.03 (m, 4H), 4.74 (q, *J* = 10.6 Hz, 2H), 3.51 (dd, *J* = 9.0, 4.0 Hz, 1H), 3.33 (dd, *J* = 9.0, 7.1 Hz, 1H), 3.24 – 3.16 (m, 1H), 2.74 (dd, *J* = 13.4, 5.5 Hz, 1H), 2.51 (dd, *J* = 13.4, 8.1 Hz, 1H), 1.51 (br s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.0, 137.0, 133.5, 130.0, 129.4, 128.5, 128.5, 126.4, 75.2, 67.5, 52.4, 40.7. **IR** (neat, cm^{-1}) 2922, 2853, 1645, 1581, 1563, 1436, 1362, 1100, 992, 766, 699. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{16}H_{18}Cl_2NO]^+$ = 310.0765, 310.0782 found.

1-(((2-ethylhexyl)oxy)methyl)naphthalene (3-5)



The title product was prepared using a slightly modified general procedure wherein the 2-iodo-3-phenylbenzo[*b*]thiophene was added last to the final solution in order to reduce the formation of a *tert*-butyl benzyl ether side product. Thus, 1-methylnaphthalene (142.2 mg, 1 mmol, 1 equiv), 2-ethylhexan-1-ol (195.3 mg, 1.5 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (672.4 mg, 2 mmol, 2 equiv), 18-crown-6 (528.2 mg, 2 mmol, 2 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous THF (4.0 mL) were used as described above. The product was purified *via* silica gel chromatography (100% hexanes) to afford the title compound as a white solid (137.6 mg, 0.51 mmol, 51% yield). **Mp**: 73-76 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 7.4 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.45 (m, 3H), 7.43 (t, *J* = 7.6 Hz, 1H), 4.94 (s, 2H), 3.44 (d, *J* = 5.8 Hz, 2H), 1.55 (m, 1H), 1.48 – 1.17 (m, 8H), 0.92 – 0.78 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.4, 133.9, 131.9, 128.6, 128.5, 126.3, 126.1, 125.8, 125.3, 124.3, 73.3, 71.8, 39.9, 30.7, 29.2, 24.0, 23.2, 14.2, 11.2. **IR** (neat, cm^{-1}) 3047, 1598, 1511, 1459, 1266, 1094, 1073, 1020, 791, 773. **EA**: Anal. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69 Found: C, 84.25; H, 9.76.

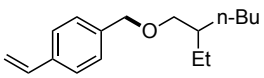
(1*R*)-2-(2-((2-bromo-6-iodobenzyl)oxy)ethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene (3-8)



The title product was prepared according to GP1 with a 10 min reaction time instead of 15 h to reduce formation of an acetal side product. Thus, 1-bromo-3-iodo-2-methylbenzene (296.9 mg, 1 mmol, 1 equiv), (1*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-ethanol (249.2 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and

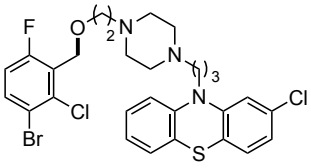
anhydrous DMPU (4.0 mL) used according to GP1. The product was purified *via* silica gel chromatography (0% to 3% to 10% EtOAc/hexanes) to afford the title compound as a colorless liquid (406.3 mg, 0.88 mmol, 88% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.55 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.80 (t, *J* = 7.9 Hz, 1H), 5.34 – 5.20 (m, 1H), 4.79 (s, 2H), 3.59 (t, *J* = 7.4 Hz, 2H), 2.37 – 2.30 (m, 3H), 2.29 – 2.14 (m, 2H), 2.11 – 1.99 (m, 2H), 1.27 (s, 3H), 1.17 (d, *J* = 8.5 Hz, 1H), 0.84 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.0, 139.3, 139.1, 133.5, 131.1, 125.3, 118.0, 102.2, 76.7, 69.5, 46.0, 40.9, 38.1, 37.2, 31.8, 31.5, 26.5, 21.4. **IR** (neat, cm^{-1}) 2914, 1572, 1549, 1426, 1363, 1192, 1095, 769. **HRMS** (APGC-TOF) [M+H] calcd. for = $[C_{18}H_{23}BrIO]^+$ = 460.9977, 461.0020 found.

1-(((2-ethylhexyl)oxy)methyl)-4-vinylbenzene (3-9)



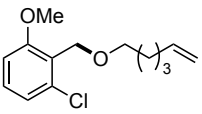
The title product was prepared according GP1 using 1-methyl-4-vinylbenzene (118.2 mg, 1 mmol, 1 equiv), 2-ethylhexan-1-ol (195.3 mg, 1.5 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (672.4 mg, 2 mmol, 2 equiv), 18-crown-6 (528.2 mg, 2 mmol, 2 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous THF (4.0 mL). The product was purified *via* silica gel chromatography (100% hexanes) to afford the title compound as a yellow liquid (146.4 mg, 0.60 mmol, 60% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 6.72 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.74 (d, *J* = 17.6 Hz, 1H), 5.23 (d, *J* = 10.8 Hz, 1H), 4.48 (s, 2H), 3.34 (d, *J* = 5.9 Hz, 2H), 1.61 – 1.48 (m, 1H), 1.46 – 1.19 (m, 8H), 0.95 – 0.82 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.7, 136.9, 136.8, 127.8, 126.3, 113.7, 73.3, 72.9, 39.9, 30.7, 30.3, 29.2, 24.0, 23.2, 23.1, 14.2, 14.2, 11.2, 11.0. **IR** (neat, cm^{-1}) 2957, 2927, 2857, 1743, 1459, 1361, 1095, 988, 904. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{17}H_{27}O]^+$ = 247.2056, 247.2036 found.

10-(3-(4-(2-((3-bromo-2-chloro-6-fluorobenzyl)oxy)ethyl)piperazin-1-yl)propyl)-2-chloro-10H-phenothiazine (3-10)



The title product was prepared according to GP1 using 1-bromo-2-chloro-4-fluoro-3-methylbenzene (221.1 mg, 1 mmol, 1 equiv), 2-(4-(3-(2-chloro-10*H*-phenothiazin-10-yl)propyl)piperazin-1-yl)ethan-1-ol (484.7 mg, 1.2 mmol, 1.2 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (672.4 mg, 2 mmol, 2 equiv), LiO-*t*-Bu (240.2 mg, 3 mmol, 3 equiv), and anhydrous DMF (4.0 mL). The product was purified *via* silica gel chromatography (3% to 6% $MeOH/CH_2Cl_2$) to afford the title compound as an orange oil (325.9 mg, 0.52 mmol, 52% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.7, 5.6 Hz, 1H), 7.19 – 7.08 (m, 2H), 7.01 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.97 – 6.80 (m, 5H), 4.70 (s, 2H), 3.89 (t, *J* = 6.9 Hz, 2H), 3.63 (t, *J* = 6.0 Hz, 2H), 2.66 – 2.35 (m, 12H), 1.93 (t, *J* = 7.1 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.0 (d, *J* = 251.2 Hz), 146.6, 144.6, 137.0 (d, *J* = 5.6 Hz), 134.1, 134.0, 133.3, 125.8, 125.6, 124.9, 123.6, 123.0, 122.3, 118.4 (d, *J* = 4.0 Hz), 116.0, 115.9, 115.5, 115.3, 68.4, 64.5 (d, J = 3.1 Hz), 57.7, 55.6, 53.6, 53.3, 45.5, 24.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.1. **IR** (neat, cm^{-1}) 2938, 2808, 1676, 1592, 1565, 1454, 1278, 1160, 1096, 909. **HRMS** (DART) $[M-H]^-$ calcd. for $[C_{28}H_{28}Cl_2BrFN_3OS]^-$ = 622.0503, 622.0460 found.

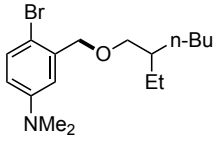
1-chloro-2-((hex-5-en-1-yloxy)methyl)-3-methoxybenzene (3-11)



The title product was prepared according to GP1 using 1-chloro-3-methoxy-2-methylbenzene (156.0 mg, 1 mmol, 1 equiv), hex-5-en-1-ol (150.6 mg, 1.5 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (672.4 mg, 2 mmol, 2

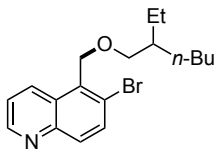
equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous DMPU (4.0 mL). The product was purified *via* silica gel chromatography (0% to 2% to 5% EtOAc/hexanes) to afford the title compound as a colorless liquid (181.4 mg, 0.71 mmol, 71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 8.2 Hz, 1H), 7.00 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 5.80 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.05 – 4.86 (m, 2H), 4.66 (s, 2H), 3.84 (s, 3H), 3.52 (t, *J* = 6.6 Hz, 2H), 2.14 – 1.97 (m, 2H), 1.65 – 1.58 (m , 2H), 1.51 – 1.40 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.5, 139.0, 136.7, 129.8, 124.7, 121.9, 114.5, 109.4, 70.4, 63.8, 56.2, 33.6, 29.3, 25.5. **IR** (neat, cm^{-1}) 3075, 2934, 1640, 1591,1578, 1435, 1265, 1189, 1043, 908, 728. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{14}H_{20}ClO_2]^+$ = 255.1146, 255.1159 found.

4-bromo-3-(((2-ethylhexyl)oxy)methyl)-*N*,*N*-dimethylaniline (3-12)



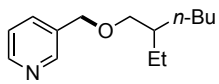
The title product was prepared according to GP1 using 4-bromo-*N*,*N*,3-trimethylaniline (53.5 mg, 0.25 mmol, 1 equiv), 2-ethylhexan-1-ol (48.8 mg, 0.38 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (168.1 mg, 0.5 mmol, 2 equiv), 18-crown-6 (132.1 mg, 0.5 mmol, 2 equiv), KO-*t*-Bu (56.1 mg, 0.5 mmol, 2 equiv), and anhydrous THF (1.0 mL). The product was purified *via* a preparatory thin layer chromatography plate (1% EtOAc/hexanes) to afford the title compound as an orange oil (39.2 mg, 0.11 mmol, 46% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.9 Hz, 1H), 6.88 (d, *J* = 3.1 Hz, 1H), 6.51 (dd, *J* = 8.8, 3.2 Hz, 1H), 4.50 (s, 2H), 3.44 (d, *J* = 5.8 Hz, 2H), 2.93 (s, 6H), 1.59 (m, 1H), 1.49 – 1.26 (m, 8H), 0.92 – 0.86 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.0, 138.1, 132.5, 112.9, 112.8, 108.7, 73.7, 72.5, 40.6, 39.9, 30.8, 29.2, 24.0, 23.1, 14.1, 11.2. **IR** (neat, cm^{-1}) 3369, 2927, 2856, 1596, 1488, 1350, 1205, 1096, 795. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{17}H_{29}BrNO]^+$ = 342.1427, 342.1458 found.

6-bromo-5-(((2-ethylhexyl)oxy)methyl)quinoline (2-13)



The title product was prepared according to GP1 using 6-bromo-5-methylquinoline (222.1 mg, 1 mmol, 1 equiv), 2-ethylhexan-1-ol (195.3 mg, 1.5 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (672.4 mg, 2 mmol, 2 equiv), LiO-*t*-Bu (240.2 mg, 3 mmol, 3 equiv), and anhydrous DMF (4.0 mL). The product was purified *via* silica gel chromatography (10% to 20% EtOAc/hexanes) to afford the title compound as colorless oil (276.2 mg, 0.79 mmol, 79% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.9 (dd, *J* = 4.0, 1.9 Hz, 1H), 8.6 (d, *J* = 8.6 Hz, 1H), 7.9 (d, *J* = 9.0 Hz, 1H), 7.8 (d, *J* = 9.0 Hz, 1H), 7.5 (dd, *J* = 8.6, 4.3 Hz, 1H), 5.1 (d, *J* = 1.5 Hz, 2H), 3.4 (d, *J* = 4.3 Hz, 2H), 1.5 (m, 1H), 1.4 – 1.1 (m, 8H), 0.9 – 0.7 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.5, 147.8, 133.7, 133.5, 133.5, 131.5, 129.0, 123.9, 121.8, 72.9, 69.3, 39.8, 30.6, 29.0, 23.9, 23.2, 14.2, 11.1. **IR** (neat, cm^{-1}) 2926, 1586,1490, 1457, 1319, 1089, 830, 804. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{18}H_{25}BrNO]^+$ = 350.1114, 350.1099 found. **Note:** See Section 7 for a larger scale version of this reaction with recover of 2-XTR 3 and its byproduct.

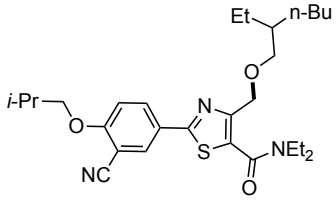
3-(((2-ethylhexyl)oxy)methyl)pyridine (3-14)



The title product was prepared according GP1 using 3-methylpyridine (93.1 mg, 1 mmol, 1 equiv), 2-ethylhexan-1-ol (195.3 mg, 1.5 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (672.4 mg, 2 mmol, 2 equiv), 18-crown-6 (528.2 mg, 2 mmol, 2 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous THF (4.0 mL). The product was purified *via* silica gel chromatography (25% EtOAc/hexanes) to afford the title compound as a yellow oil (112.8 mg, 0.51 mmol, 51% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ

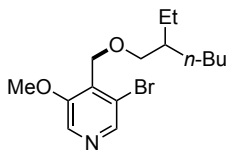
8.65 – 8.39 (m, 2H), 7.64 (d, J = 7.9 Hz, 1H), 7.26 – 7.23 (m, 1H), 4.47 (s, 2H), 3.34 (d, J = 5.9 Hz, 2H), 1.52 (m, 1H), 1.46 – 1.12 (m, 8H), 0.88 – 0.82 (m, Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.1, 148.9, 135.2, 134.3, 123.4, 73.6, 70.5, 39.8, 30.6, 29.1, 23.9, 23.1, 14.1, 11.1. **IR** (neat, cm^{-1}) 2957, 2928, 1577, 1465, 1426, 1093, 1027, 787. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{14}H_{24}NO]^+$ =222.1852, 222.1840 found.

2-(3-cyano-4-isobutoxyphenyl)-*N*,*N*-diethyl-4-(((2-ethylhexyl)oxy)methyl)thiazole-5-carboxamide (3-15)



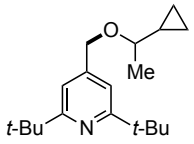
The title product was prepared according to GP1 using 2-(3-cyano-4-isobutoxyphenyl)-*N*,*N*-diethyl-4-(hydroxymethyl)thiazole-5-carboxamide (92.8 mg, 0.25 mmol, 1 equiv), 2-ethylhexan-1-ol (48.8 mg, 0.38 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (167.6 mg, 0.5 mmol, 2 equiv), LiO-*t*-Bu (60.0 mg, 0.75 mmol, 3 equiv), and anhydrous DMF (1.0 mL). The ^{1}H NMR yield was determined by adding 4-(trifluoromethyl)pyridine internal standard (42.1 mg, 0.29 mmol) into the crude solution before transfer into the separatory funnel. A small aliquot of the organic layer was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of the benzyl etherified product (69% yield). The product was purified *via* a preparatory thin layer chromatography plate (5% EtOAc/hexanes) to afford the title compound with residual impurity. This material was resubjected to another preparatory thin layer chromatography plate (30% EtOAc/hexanes) to afford the pure title compound as a colorless oil (40.5 mg, 0.08 mmol, 32% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (d, J = 2.4 Hz, 1H), 8.06 (dd, J = 8.8, 2.5 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 4.58 (s, 2H), 3.89 (d, J = 6.4 Hz, 2H), 3.67 – 3.23 (m, 6H), 2.20 (sept, J = 6.7 Hz, 1H), 1.57 – 1.51 (m, 1H), 1.43 – 1.17 (m, 14H), 1.08 (d, J = 6.7 Hz, 6H), 0.88 – 0.83 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.6, 162.3, 162.3, 152.8, 132.6, 132.1, 127.9, 126.2, 115.6, 112.7, 103.0, 75.8, 74.4, 67.4, 39.6, 30.5, 29.2, 28.3, 23.7, 23.2, 19.2, 14.3, 11.1. **IR** (neat, cm^{-1}) 2959, 2930, 2872, 2228, 1630, 1452, 1277, 1097, 849. **HRMS** (APGC-TOF) [M+] calcd. for $[C_{28}H_{41}N_3O_3S]^+$ = 499.2869, 499.2873 found. **Note:** The ^{1}H NMR yield (69% yield) was higher than the isolated yield due to co-elution issues with the starting methylarene.

3-bromo-4-(((2-ethylhexyl)oxy)methyl)-5-methoxypyridine (3-16)



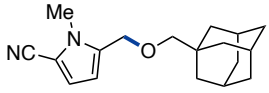
The title product was prepared according to GP1 using 3-bromo-5-methoxy-4-methylpyridine (202.1 mg, 1 mmol, 1 equiv), 2-ethylhexan-1-ol (195.3 mg, 1.5 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (672.4 mg, 2 mmol, 2 equiv), LiO-*t*-Bu (240.2 mg, 3 mmol, 3 equiv), and anhydrous DMF (4.0 mL). The product was purified *via* silica gel chromatography (25% EtOAc/hexanes) to afford the title compound as a yellow liquid (183.7 mg, 0.56 mmol, 56% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.20 (s, 1H), 4.61 (s, 2H), 3.94 (s, 3H), 3.37 (d, J = 6.0 Hz, 2H), 1.61 – 1.45 (m, 1H), 1.46 – 1.13 (m, 8H), 0.95 – 0.78 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.1, 144.9, 134.1, 132.5, 124.1, 73.8, 65.3, 56.9, 39.6, 30.5, 29.1, 23.8, 23.2, 14.2, 11.1. **IR** (neat, cm^{-1}) 2957, 2927, 2858, 1460, 1408, 1275, 1090, 1030. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{15}H_{25}O_2NBr]^+$ = 330.1063, 330.1054 found.

2,6-di-*tert*-butyl-4-((1-cyclopropylethoxy)methyl)pyridine (3-17)



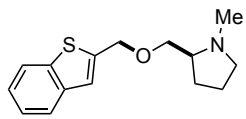
The title product was prepared according to GP1 using 2,6-di-*tert*-butyl-4-methylpyridine (51.4 mg, 0.25 mmol, 1 equiv), 1-cyclopropylethan-1-ol (43.1 mg, 0.38 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (167.6 mg, 0.5 mmol, 2 equiv), 18-crown-6 (132.1 mg, 0.5 mmol, 2 equiv), KO-*t*-Bu (56.1 mg, 0.5 mmol, 2 equiv), and anhydrous THF (1.0 mL). The product was purified *via* a preparatory thin layer chromatography plate (100% hexanes) to afford the title compound as a yellow oil (33.4 mg, 0.12 mmol, 46% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.07 (s, 2H), 4.68 – 4.46 (m, 2H), 2.86 (dq, *J* = 8.3, 6.2 Hz, 1H), 1.34 (s, 18H), 1.31 (d, *J* = 6.3 Hz, 3H), 0.98 – 0.83 (m, 1H), 0.67 – 0.56 (m, 1H), 0.54 – 0.42 (m, 1H), 0.42 – 0.31 (m, 1H), 0.15 – 0.02 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.8, 148.0, 114.0, 79.9, 69.7, 37.7, 30.3, 27.8, 20.4, 16.6, 4.9, 1.2. **IR** (neat, cm^{-1}) 2954, 2865, 1602, 1569, 1458, 1360, 1103, 936, 857. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{19}H_{32}NO]^+$ = 290.2478, 290.2462 found. **Note on reaction side product:** Overoxidation of the benzyl ether product occurs to give 24% of 4-(bis(1-cyclopropylethoxy)methyl)-2,6-di-tert-butylpyridine side product, as detected by ^{1}H NMR spectroscopy of the crude reaction mixture. This material was readily separated from the desired isomer by silica gel chromatography.

5-(((adamantan-1-yl)methoxy)methyl)-1-methyl-1*H*-pyrrole-2-carbonitrile (3-18)



The title product was prepared using a modified version of the general procedure where the 2-iodothiophene was added last to the final solution to reduce formation of a *tert*-butyl benzyl ether side product and the reaction mixture was stirred for 10 min instead of 15 h to reduce formation of an acetal side product. Thus, 1,5-dimethyl-1*H*-pyrrole-2-carbonitrile (120.2 mg, 1 mmol, 1 equiv), (adamantan-1-yl)methanol (249.4 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous DMPU (4.0 mL) were used according to GP1. The product was purified *via* silica gel chromatography (2% EtOAc/hexanes) to afford the title compound as a white solid (176.3 mg, 0.62 mmol, 62% yield). **Mp**: 73-76 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.70 (d, *J* = 4.0 Hz, 1H), 6.10 (d, *J* = 4.0 Hz, 1H), 4.39 (s, 2H), 3.75 (d, *J* = 1.2 Hz, 3H), 2.95 (s, 2H), 1.95 (s, 3H), 1.77 – 1.58 (m, 6H), 1.51 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.7, 118.6, 114.1, 110.7, 105.7, 81.2, 64.8, 39.8, 37.3, 34.1, 32.9, 28.3. **IR** (neat, cm^{-1}) 2899, 2846, 2214, 1463, 1350, 1200, 1081, 1015, 777. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{18}H_{25}N_2O]^+$ =285.1961, 285.1948 found.

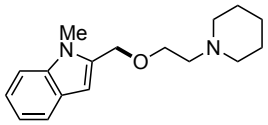
(*S*)-2-((benzo[*b*]thiophen-2-ylmethoxy)methyl)-1-methylpyrrolidine (2-19)



The title product was prepared according to GP1 using 2-methylbenzo[*b*]thiophene (148.2 mg, 1 mmol, 1 equiv), (*S*)-(1-methylpyrrolidin-2-yl)methanol (230.4 mg, 2 mmol, 2 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (672.4 mg, 2 mmol, 2 equiv), 18-crown-6 (132.1 mg, 0.5 mmol, 0.5 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous THF (4.0 mL). The product was purified *via* silica gel chromatography (1% Et_3N in 0% to 5% MeOH/DCM) to afford the title compound as a yellow oil (120.0 mg, 0.46 mmol, 46% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 6.5, 0.9 Hz, 1H), 7.62 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.25 – 7.17 (m, 2H), 7.09 (d, *J* = 1.1 Hz, 1H), 4.69 (s, 2H), 3.45 (dd, *J* = 9.3, 5.2 Hz, 1H), 3.38 (dd, *J* = 9.3, 5.3 Hz, 1H), 2.97 (ddd, *J* = 9.2, 7.0, 2.0 Hz, 1H), 2.32 (s, 3H), 2.32 (m, 1H), 2.15 – 2.08 (m, 1H), 1.88 – 1.76 (m, 1H), 1.74 – 1.49 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.6, 140.3, 139.6, 124.6, 123.5, 122.5, 73.2, 68.7, 64.9, 57.9, 41.7, 28.7, 22.9. **IR** (neat, cm^{-1}) 2940, 2848, 2775, 1457, 1436, 1156,

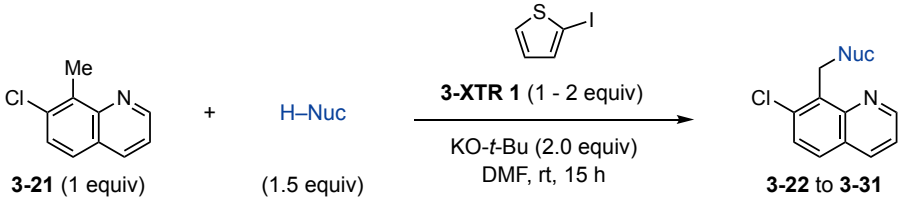
1082, 1014, 825, 726. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{15}H_{20}NOS]^+$ = 262.1260, 262.1251 found.

1-methyl-2-((2-(piperidin-1-yl)ethoxy)methyl)-1*H*-indole (3-20)

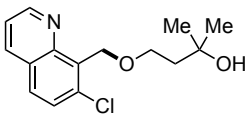


The title product was prepared according to GP1 using 1,2-dimethyl-1*H*-indole (222.1 mg, 1 mmol, 1 equiv), 2-(piperidin-1-yl)ethan-1-ol (195.3 mg, 1.5 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (672.4 mg, 2 mmol, 2 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous DMPU (4.0 mL). The product was purified *via* silica gel chromatography (3% to 7% MeOH/DCM) to afford the title compound as orange solid (135.6 mg, 0.50 mmol, 50% yield). **Mp**: 43-45 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.31 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.22 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.47 (s, 1H), 4.69 (s, 2H), 3.78 (s, 3H), 3.64 (t, *J* = 5.8 Hz, 2H), 2.62 (s, 2H), 2.50 (br s, 4H), 1.64 (br s, 4H), 1.44 (br s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.1, 135.7, 127.2, 121.9, 120.7, 119.5, 109.2, 103.0, 66.5, 65.1, 58.3, 54.8, 29.9, 25.4, 23.9. **IR** (neat, cm^{-1}) 2940, 2821, 1467, 1340, 1319, 1143, 1085, 1005, 981, 748, 734. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{17}H_{25}N_2O]^+$ = 273.1961, 273.1987 found.

(b) Products shown in Figure 3-10



4-((7-chloroquinolin-8-yl)methoxy)-2-methylbutan-2-ol (3-22)

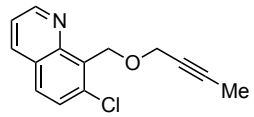


The title product was prepared according to GP1 using 7-chloro-8-methylquinoline (177.6 mg, 1 mmol, 1 equiv), 3-methylbutane-1,3-diol (156.2 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous DMF (4.0 mL). The product was purified *via* silica gel chromatography (2% MeOH/DCM) to afford the title compound as a colorless oil (166.9 mg, 0.60 mmol, 60% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.98 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.33 (s, 2H), 3.92 (t, *J* = 5.7 Hz, 2H), 3.61 (s, 1H), 1.79 (t, *J* = 5.7 Hz, 2H), 1.18 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.0, 147.6, 136.7, 136.2, 133.1, 129.2, 128.3, 126.9, 121.4, 70.4, 68.3, 65.1, 41.5, 29.4. **IR** (neat, cm^{-1}) 3447, 2967, 2929, 2972, 1606, 1589, 1360, 1147, 858, 724. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{15}H_{19}ClNO_2]^+$ = 280.1099, 280.1097 found.

Verification of nucleophile selectivity: Two 2D NMR experiments were used to determine that the primary alcohol of 3-methylbutane-1,3-diol reacted over the tertiary alcohol in the benzylic C–H etherification for **3-22**. Specifically, a Heteronuclear Single Quantum Coherence (HSQC) experiment determined that the ^{1}H NMR signals corresponding to the benzylic ether methylene δ 5.33 (s, 2H) and the unsubstituted methylene peak adjacent to ether alcohol δ 3.92 (t, *J* = 5.7 Hz, 2H) are bonded to the carbon with the ^{13}C NMR signals at δ 65.1 and 68.3, respectively. Heteronuclear Multiple Bond Correlation (HMBC) experiment indicated that the benzylic ether

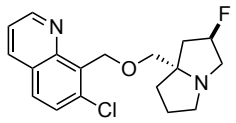
methylene ^{1}H NMR signal δ 5.33 (s, 2H) correlates with ^{13}C NMR signal at δ 68.3. See spectra in Section 17.

8-((but-2-yn-1-yloxy)methyl)-7-chloroquinoline (3-23)



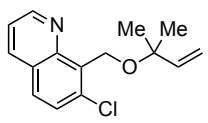
The title product was prepared according to GP1 using 7-chloro-8-methylquinoline (177.6 mg, 1 mmol, 1 equiv), but-2-yn-1-ol (105.1 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (210.0 mg, 1 mmol, 1 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous DMF (4.0 mL). The product was purified *via* silica gel chromatography (15 to 20% EtOAc/hexanes) to afford the title compound as a white solid (125.8 mg, 0.51 mmol, 51% yield). **Mp**: 58-60 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.99 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 5.40 (s, 2H), 4.31 (q, *J* = 2.4 Hz, 2H), 1.87 (t, *J* = 2.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.1, 147.9, 137.3, 136.2, 133.4, 129.3, 128.4, 127.0, 121.3, 82.5, 64.0, 59.1, 3.9. **IR** (neat, cm^{-1}) 2952, 2919, 2850, 2239, 1604, 1491, 1152, 1044, 834. **HRMS** (APGC-TOF) [M+H] calcd. for = $[C_{14}H_{13}ClNO]^+$ = 246.0686, 246.0693 found.

7-chloro-8-((((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)methyl)quinoline (3-24)



The title product was prepared according to GP1 using 7-chloro-8-methylquinoline (177.6 mg, 1 mmol, 1 equiv), ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (238.8 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous DMF (4.0 mL). The ^{1}H NMR yield was determined by adding 4-(trifluoromethyl)pyridine internal standard (42.1 mg, 0.29 mmol) into the crude solution (before transfer into the separatory funnel). A small aliquot of the organic layer was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of product (81% yield). The product was purified *via* silica gel chromatography (1% Et_3N in 25% EtOAc/hexanes) to afford the title compound as a yellow solid (201.6 mg, 0.60 mmol, 60% yield). **Mp**: 64-67 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.03 – 8.89 (m, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.37 (s, 2H), 5.26 – 5.02 (m, 1H), 3.37 (d, *J* = 8.8 Hz, 1H), 3.27 (d, *J* = 8.7 Hz, 1H), 3.19 – 2.97 (m, 3H), 2.92 – 2.79 (m, 1H), 2.16 – 1.90 (m, 3H), 1.89 – 1.66 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.8, 147.8, 137.2, 136.2, 133.7, 129.0, 128.4, 126.9, 121.2, 98.4 (d, *J* = 175.8 Hz), 77.8, 73.2, 65.0, 60.4 (d, *J* = 19.4 Hz), 57.0, 42.8 (d, *J* = 20.0 Hz), 36.1, 25.6. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -172.6 (m, 1F). **IR** (neat, cm^{-1}) 2951, 2857, 1588, 1491, 1257, 1059, 950, 795, 665. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{18}H_{21}ClFN_2O]^+$ = 335.1321, 335.1322 found. **Note:** The ^{1}H NMR yield (81% yield) was higher than the isolated yield due to co-elution challenges with the alcohol pronucleophile.

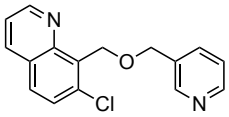
4-((7-chloroquinolin-8-yl)methoxy)-2-methylbutan-2-ol (3-25)



The title product was prepared using a modified GP1 where 2.5 equiv of KOH and 18-crown-6 were used as base system instead of 1.5 equiv KO-*t*-Bu. Thus, 7-chloro-8-methylquinoline (177.6 mg, 1 mmol, 1 equiv), 2-methylbut-3-en-2-ol (129.2 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KOH (140.3 mg, 2.5 mmol, 2.5 equiv), 18-crown-6 (660.3 mg, 1.5, mmol, 1.5 equiv), and anhydrous DMF (4.0 mL) were used according to GP1. The product was purified *via* silica gel

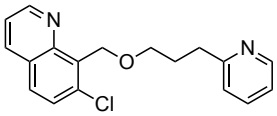
chromatography (5% EtOAc/hexanes) to afford the title compound as a tan solid (75.0 mg, 0.29 mmol, 29% yield). **Mp**: 38-41 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.97 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.09 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.38 (dd, *J* = 8.3, 4.1 Hz, 1H), 6.18 (dd, *J* = 17.7, 10.8 Hz, 1H), 5.32 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.23 (dd, *J* = 10.7, 1.2 Hz, 1H), 5.19 (s, 2H), 1.46 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.8, 147.9, 144.6, 137.2, 136.1, 134.5, 128.8, 128.6, 127.1, 121.1, 113.9, 76.1, 57.6, 26.1. **IR** (neat, cm^{-1}) 3083, 2975, 2880, 1604, 1489, 1370, 1150, 1075, 919, 853. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{15}H_{17}ClNO]^+$ = 262.0993, 262.1018 found. **Note on reaction selectivity:** Competing reaction of the proposed benzyl halide with hydroxide base occurs and leads to 20% of 8,8'-(oxybis(methylene))bis(7-chloroquinoline) side product, as detected by ^{1}H NMR spectroscopy of the crude reaction mixture. This material was readily separated from the desired isomer by silica gel chromatography.

7-chloro-8-((pyridin-3-ylmethoxy)methyl)quinoline (3-26)



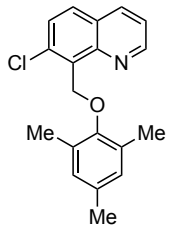
The title product was prepared according to GP1 using 7-chloro-8-methylquinoline (177.6 mg, 1 mmol, 1 equiv), pyridin-3-ylmethanol (163.7 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous DMF (4.0 mL). The product was purified *via* silica gel chromatography (2% MeOH/DCM) to afford the title compound as a tan solid (174.9 mg, 0.61 mmol, 61% yield). **Mp**: 43-45 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.00 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.62 (s, 1H), 8.51 (d, *J* = 2.7 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.80 – 7.70 (m, 2H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.26 – 7.22 (m, 1H), 5.42 (s, 2H), 4.73 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.1, 149.5, 149.1, 147.8, 137.2, 136.2, 135.8, 134.2, 133.3, 129.3, 128.4, 127.0, 123.4, 121.4, 70.4, 64.5. **IR** (neat, cm^{-1}) 3029, 2880, 1577, 1420, 1343, 1083, 831, 794. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{16}H_{14}ClN_2O]^+$ = 285.0789, 285.0817 found.

7-chloro-8-((3-(pyridin-2-yl)propoxy)methyl)quinoline (3-27)



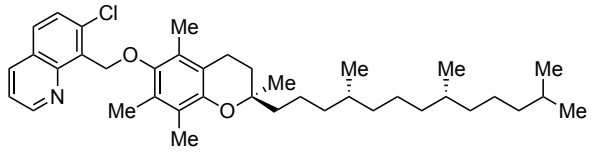
The title product was prepared according to GP1 using 7-chloro-8-methylquinoline (177.6 mg, 1 mmol, 1 equiv), 3-(pyridin-2-yl)propan-1-ol (205.8 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous DMF (4.0 mL). The product was purified *via* silica gel chromatography (0% to 1% to 2% MeOH/DCM) to afford the title compound as a brown oil (191.1 mg, 0.61 mmol, 61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.99 (d, *J* = 6.5 Hz, 1H), 8.50 (d, *J* = 4.9 Hz, 1H), 8.13 (d, *J* = 8.2 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.60 – 7.48 (m, 2H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.07 (dd, *J* = 7.5, 5.0 Hz, 1H), 5.34 (s, 2H), 3.70 (t, *J* = 6.3 Hz, 2H), 2.88 (t, *J* = 7.7 Hz, 2H), 2.14 – 2.00 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.0, 151.0, 149.3, 147.8, 137.2, 136.3, 136.2, 133.8, 129.0, 128.4, 127.0, 123.1, 121.2, 121.0, 70.1, 64.5, 34.9, 29.8. **IR** (neat, cm^{-1}) 3061, 2922, 2854, 1605, 1490,1473, 1350, 1146, 1094, 853, 609. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{18}H_{18}ClN_2O]^+$ = 313.1102, 313.1088 found.

7-chloro-8-((mesityloxy)methyl)quinoline (3-28)



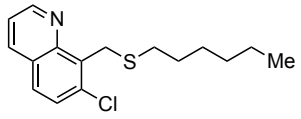
The title product was prepared using GP1 where 2.5 equiv of KOH and 18-crown-6 were used as base system instead of 1.5 equiv KO-*t*-Bu and the reaction was run at 60 ℃. Thus, 7-chloro-8-methylquinoline (177.6 mg, 1 mmol, 1 equiv), 2,4,6-trimethylphenol (204.3 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (210.0 mg, 1 mmol, 1 equiv), KOH (140.3 mg, 2.5 mmol, 2.5 equiv), 18-crown-6 (660.3 mg, 2.5 mmol, 2.5 equiv), and anhydrous DMF (4.0 mL) were used according to GP1. The product was purified *via* silica gel chromatography (3% EtOAc/hexanes) to afford the title compound with residual impurities. The resulting material was subsequently suspended in EtOAc (10 mL) and washed with 2 M NaOH solution (5 mL). The organic layer was collected, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide pure title compound as a yellow solid (221.0 mg, 0.71 mmol, 71% yield). **Mp**: 67-69 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.08 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.36 (dd, *J* = 8.2, 4.2 Hz, 1H), 6.77 (s, 2H), 5.61 (s, 2H), 2.32 (s, 6H), 2.19 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.0, 150.9, 148.0, 137.1, 136.1, 133.2, 133.2, 131.6, 129.5, 129.5, 128.5, 127.1, 121.4, 66.6, 20.9, 16.7. **IR** (neat, cm^{-1}) 2917, 1606, 1485, 1207, 1126, 981, 830, 604. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{19}H_{19}ClNO]^+$ = 312.1150, 312.1146 found.

7-chloro-8-((((*R*)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)methyl)quinoline (3-29)



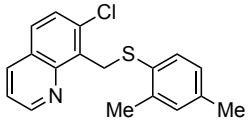
The title product was prepared using GP1 where 2.5 equiv of KOH and 18-crown-6 were used as base system instead of 1.5 equiv KO-*t*-Bu. Thus, 7-chloro-8-methylquinoline (177.6 mg, 1 mmol, 1 equiv), (*R*)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-ol (646.1 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KOH (140.3 mg, 2.5 mmol, 2.5 equiv), 18-crown-6 (660.3 mg, 1.5 equiv, mmol, 1.5 equiv), and anhydrous DMF (4.0 mL) were used according to GP1. A small aliquot of the organic layer was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, CDCl3) was used to determine the yield of the product (88% yield). The product was purified *via* silica gel chromatography (3% EtOAc/hexanes) to afford the title compound with residual impurities. This material was resubjected to silica gel chromatography (1% Et_3N in 2% EtOAc/hexanes) to provide pure title compound as a yellow oil (378.9 mg, 0.61 mmol, 61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.00 (dd, *J* = 4.0, 1.9 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.42 (dd, *J* = 8.2, 4.1 Hz, 1H), 5.57 (d, *J* = 1.4 Hz, 2H), 2.60 (t, *J* = 6.9 Hz, 2H), 2.34 (s, 3H), 2.29 (s, 3H), 2.11 (s, 3H), 1.87 – 1.74 (m, 2H), 1.61 – 0.99 (m, 24H), 0.87 – 0.84 (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.8, 148.7, 148.1, 148.0, 137.1, 136.0, 133.4, 129.4, 128.9, 128.5, 127.1, 126.9, 122.7, 121.3, 117.5, 67.3, 40.2, 39.5, 37.8, 37.6, 37.5, 37.4, 32.9, 32.9, 31.6, 28.1, 25.0, 24.6, 24.0, 22.9, 22.8, 21.2, 20.9, 19.9, 19.8, 19.76 13.3, 12.4, 12.0. **IR** (neat, cm^{-1}) 2923, 2866, 1606, 1590, 1490, 1375, 1249, 1157, 1083, 852, 669. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{39}H_{57}ClNO_2]^+$ = 606.4072, 606.4103 found. **Note:** The ^{1}H NMR yield (88% yield) was higher than the isolated yield due to co-elution challenges with the phenol pronucleophile.

7-chloro-8-((hexylthio)methyl)quinoline (3-30)



The title product was prepared according to GP1 using 7-chloro-8-methylquinoline (177.6 mg, 1 mmol, 1 equiv), hexane-1-thiol (177.4 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous DMF (4.0 mL). The product was purified *via* silica gel chromatography (0% to 3% EtOAc/hexanes) to afford the title compound as a brown oil (225.9 mg, 0.77 mmol, 77% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.96 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.12 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.59 (s, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 1.64 (p, *J* = 7.3 Hz, 2H), 1.38 – 1.21 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.5, 147.1, 136.3, 135.0, 128.4, 127.5, 127.0, 121.2, 32.8, 31.6, 30.1, 28.8, 28.6, 22.6, 14.1. **IR** (neat, cm^{-1}) 2924, 2854, 1605, 1488, 1123, 1038, 832, 801, 506. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{16}H_{21}ClNS]^+$ = 294.1078, 294.1109 found. **Note:** Upon isolation, 5% of an oxidized (at sulfur) impurity derived from **2-30** can be observed in the ^{1}H and ^{13}C NMR spectra. We note that this was not present in crude reaction material and must have occurred during isolation.

7-chloro-8-(((2,4-dimethylphenyl)thio)methyl)quinoline (3-31)

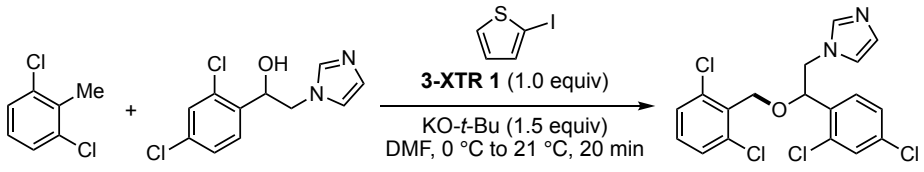


The title product was prepared according to GP1 using 7-chloro-8-methylquinoline (177.6 mg, 1 mmol, 1 equiv), 2,4-dimethylbenzenethiol (207.3 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (210.0 mg, 1 mmol, 1 equiv), KO-*t*-Bu (224.4 mg, 2 mmol, 2 equiv), and anhydrous DMF (4.0 mL). The product was purified *via* silica gel chromatography (3% EtOAc/hexanes) to afford the title compound as a yellow solid (231.2 mg, 0.74 mmol, 74% yield). **Mp**: 67-69 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.90 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.66 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.52 (dd, *J* = 8.9, 1.2 Hz, 1H), 7.42 – 7.33 (m, 2H), 6.97 (s, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 4.89 (d, *J* = 1.2 Hz, 2H), 2.35 (s, 3H), 2.28 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.6, 147.1, 139.6, 136.9, 136.1, 135.5, 134.3, 132.3, 132.2, 130.9, 128.3, 127.8, 127.1, 127.0, 121.2, 32.1, 21.1, 20.6. **IR** (neat, cm^{-1}) 2934, 1588, 1484, 1362, 1123, 920, 834, 520. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{18}H_{17}ClNS]^+$ = 314.0765, 314.0791 found.

A2.6. (Multi)gram Scale Syntheses of Isoconazole and Analogous

(a) Multigram Scale Syntheses of Isoconazole

1-(2-((2,6-dichlorobenzyl)oxy)-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole (3-33)



3-1 (1 equiv)
5.0 grams

3-32 (1.2 equiv)
9.9 grams

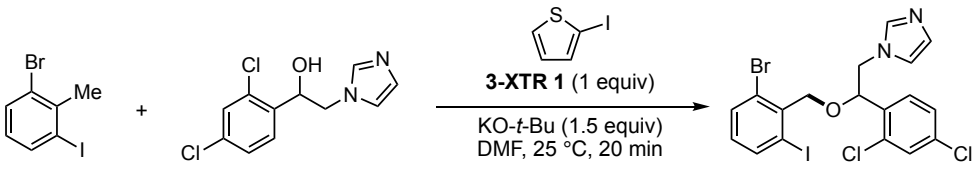
3-33, 80% yield
10.3 grams

Procedure: An oven-dried 500 mL round bottom flask equipped with a magnetic stir bar was charged with 1,3-dichloro-2-methylbenzene (5.0 g, 31.1 mmol, 1 equiv), 1-(2,4-dichlorophenyl)-

2-(1H-imidazol-1-yl)ethan-1-ol (9.6 g, 37.3 mmol, 1.2 equiv), and DMF (125 mL, 0.25 M) open to air. A thermometer was inserted into the reaction flask. The solution was cooled to 0 °C using an ice-water bath, then, also open to air, KO-*t*-Bu (5.2 g, 46.6 mmol, 1.5 equiv) and 2-iodothiophene (6.5 g, 31.1 mmol, 1 equiv) were added in successive order; no exotherm was detected by thermometer. The reaction solution was removed from the ice bath, warmed to rt and stirred for 20 min, quenched slowly with H_2O (50 mL), and poured into a separatory funnel containing H_2O (100 mL). The aqueous mixture was extracted with EtOAc (3 x 100 mL). The organic layers were combined, washed with H_2O (3 x 100 mL), and then dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo.* The resulting mixture was then purified *via* trituration with cold diethyl ether (5 x 75 mL) to yield the title compound as a white powder (10.3 g, 24.8 mmol, 80% yield). **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.55 – 7.51 (m, 2H), 7.43 – 7.39 (m, 2H), 6.98 (s, 1H), 6.83 (s, 1H), 5.21 (dd, *J* = 7.3, 3.2 Hz, 1H), 4.75 (dd, *J* = 24.8, 10.8 Hz, 1H), 4.35 – 4.22 (m, 2H). **^{13}C NMR** (101 MHz, (CD_3CN) δ 138.7, 136.4, 135.6, 135.1, 134.4, 133.5, 132.4, 130.3, 130.0, 129.2, 128.4, 127.2, 120.8, 78.5, 72.3, 51.6. The spectroscopic data is consistent with a previous report.[8]

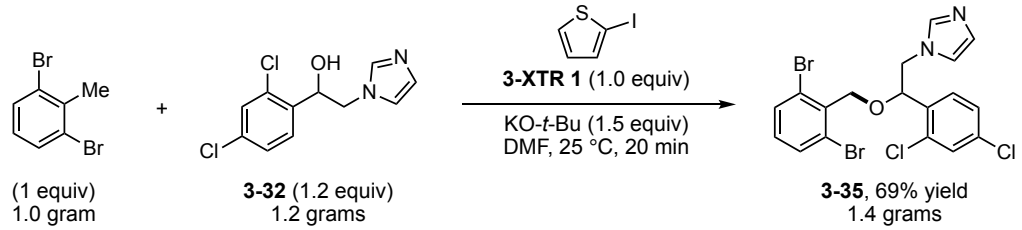
(b) Gram Scale Syntheses of Isoconazole Analogues

1-(2-((2-bromo-6-iodobenzyl)oxy)-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole (3-34)



Procedure: An oven-dried 50 mL round bottom flask equipped with a magnetic stir bar was charged with 1-bromo-3-iodo-2-methylbenzene (1.0 g, 3.4 mmol, 1 equiv), 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethan-1-ol (1.0 g, 4.0 mmol, 1.2 equiv), and DMF (13.5 mL, 0.25 M) open to air. Next, also open to air, KO-*t*-Bu (567 mg, 5.1 mmol, 1.5 equiv) and 2-iodothiophene (707 mg, 3.4 mmol, 1 equiv) were added slowly in successive order. The reaction solution was stirred for 20 min at rt, quenched slowly with H_2O (10 mL), and then poured into a separatory funnel containing H_2O (20 mL). The aqueous mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with H_2O (3 x 20 mL), and then dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo.* The resulting mixture was then purified *via* silica gel chromatography (DCM to 1% MeOH/DCM to 2% MeOH/DCM) to yield the title compound as a tan solid (1.3 g, 2.35 mmol, 70% yield). **Mp**: 70-73 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.92 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.59 – 7.37 (m, 4H), 7.09 – 6.89 (m, 3H), 5.24 (dd, *J* = 6.6, 3.4 Hz, 1H), 4.77 (dd, *J* = 37.8, 10.7 Hz, 1H), 4.38 – 4.26 (m, 2H). **^{13}C NMR** (101 MHz, $(CD_3)_2CO$) δ 140.4, 139.2, 135.7, 135.0, 134.32, 134.28, 132.7, 130.7, 128.9, 128.5, 125.9, 102.8, 78.7, 76.9, 51.5. **IR** (neat, cm^{-1}) 3107, 2360, 1588, 1469, 1427, 1230, 1089, 1042, 819, 696. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{18}H_{15}N_2OBrICl_2]^+$ = 550.8784, 550.8820 found.

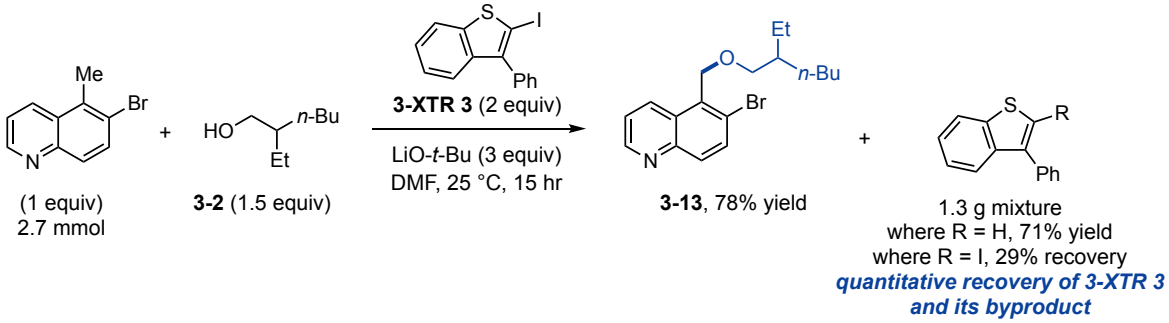
1-(2-((2,6-dibromobenzyl)oxy)-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole (3-35)



Procedure: An identical procedure used for 1-bromo-3-iodo-2-methylbenzene (above protocol) was used with 1,3-dibromo-2-methylbenzene (1.0 g, 4 mmol, 1 equiv), 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethan-1-ol (1.2 g, 4.8 mmol, 1.2 equiv), DMF (16 mL, 0.25 M), KO-*t*-Bu (673 mg, 6 mmol, 1.5 equiv) and 2-iodothiophene (840 mg, 4 mmol, 1 equiv). The product was purified *via* silica gel chromatography (DCM to 1% MeOH/DCM to 2% MeOH/DCM) to yield the title compound as a tan solid (1.4 g, 2.8 mmol, 69% yield). **Mp**: 77-80 °C. **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.64 (d, J = 8.0 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.45 – 7.36 (m, 1H), 7.20 (t, J = 8.0 Hz, 1H), 6.98 (s, 1H), 6.82 (s, 1H), 5.22 (dd, J = 6.9, 3.3 Hz, 1H), 4.81 (d, J = 10.6 Hz, 1H), 4.70 (d, J = 10.6 Hz, 1H), 4.38 – 4.19 (m, 1H). **^{13}C NMR** (101 MHz, $(CD_3)_2CO$) δ 138.7, 136.5, 135.8, 135.0, 134.3, 133.5, 132.5, 130.5, 129.9, 129.4, 128.5, 127.3, 120.5, 78.8, 72.3, 51.5. **IR** (neat, cm^{-1}) 2361, 2341, 1579, 1468, 1378, 1223, 1192, 1089, 856. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{18}H_{15}N_2OBr_2Cl_2]^+$ = 502.8923, 502.8911 found.

A2.7. Demonstration of the Recovery of 3-Phenylbenzo[*b*]thiophene and 3-XTR 3

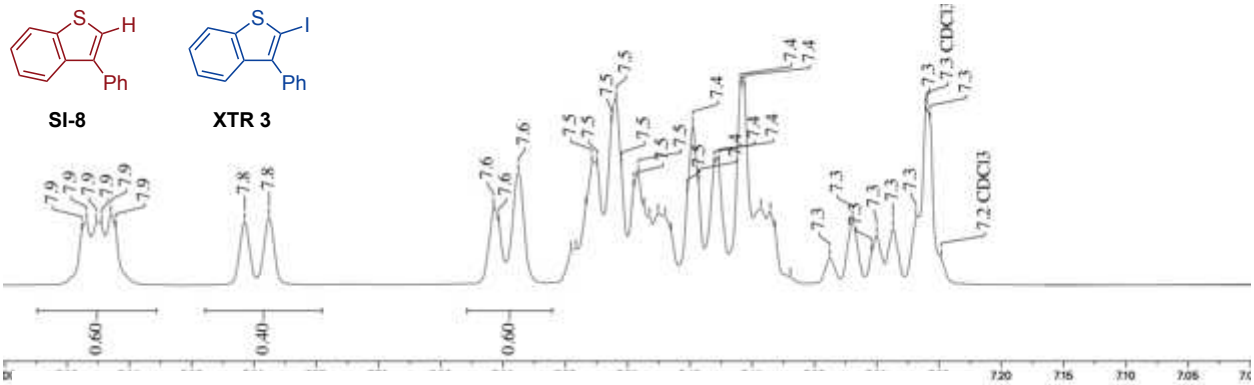
6-bromo-5-(((2-ethylhexyl)oxy)methyl)quinoline (3-13)



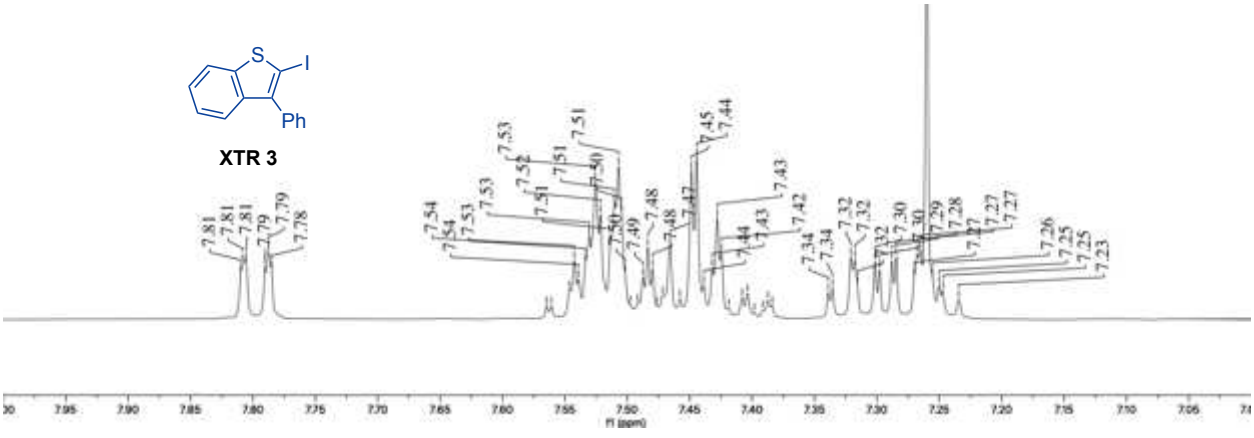
Procedure: An oven-dried 25 mL round bottom flask charged with a magnetic stir bar, 6-bromo-5-methylquinoline (600 mg, 2.7 mmol, 1 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (1.8 g, 5.4 mmol, 2.0 equiv) and LiO-*t*-Bu (649.0 mg, 8.1 mmol, 3.0 equiv). The flask was then sealed with a rubber septum (Chemglass, Product #CG-3022-08), pierced with a needle connected to a manifold Schlenk line, evacuated and backfilled with N_2 three times, and then left under positive pressure of N_2. Concurrently, an oven-dried 8 mL vial (Thermo Fischer Scientific, #033405P) was charged with 2-ethylhexan-1-ol (528.0 g, 4.1 mmol, 1.5 equiv). The vial was sealed with a screw cap (Thermo Fisher Scientific, #03392A) lined with a PTFE septum (Thermo Fisher Scientific, #B799515), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 on a manifold Schlenk line. The 8 mL vial was then charged with anhydrous DMF (6 mL) and its contents were transferred to the 25 mL round bottom flask *via* syringe; no exotherm was detected

by touch. An additional portion of DMF (5 mL, total 11 mL, 0.25 M) was quickly added to the 25 mL flask *via* syringe. The reaction mixture was stirred for 15 h at rt. Next, the crude reaction solution was poured into a 250 mL separatory funnel containing water (20 mL). The aqueous mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with H_2O (3 x 20 mL), and then dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo*. The resulting mixture was then purified *via* silica gel chromatography (10% EtOAc/hexanes to 20% EtOAc/hexanes) to yield the title compound as a colorless oil (735.4 mg, 2.1 mmol, 78% yield). The characterization data of this isolated material is consistent with information reported in Section 5a. A mixture of **3-XTR 3** and **2-A8** was also recovered from the column as a white solid (1.34 g). The percent composition of this mixture was determined by ^{1}H NMR spectroscopy and corresponds to the 2 equiv of **3-XTR 3** originally added to the reaction, where 60% is **3-XTR 3** (799.1 mg, 3.8 mmol, 71% yield) and 40% is **2-A8** (537.9 mg, 1.6 mmol, 29% recovery) (Figure 2A-5, below). We note that this mixture could be subjected to the iodination conditions described in Section 3 to regenerate the active X-transfer reagent **3-XTR 3**.

(a) ^{1}H NMR spectrum of the mixture of **3-XTR 3** of **2-A8** collected from the preparative scale of **3-XTR 3**



(b) ^{1}H NMR spectrum of **3-XTR 3**



(c) ^{1}H NMR spectrum of **2-A8**

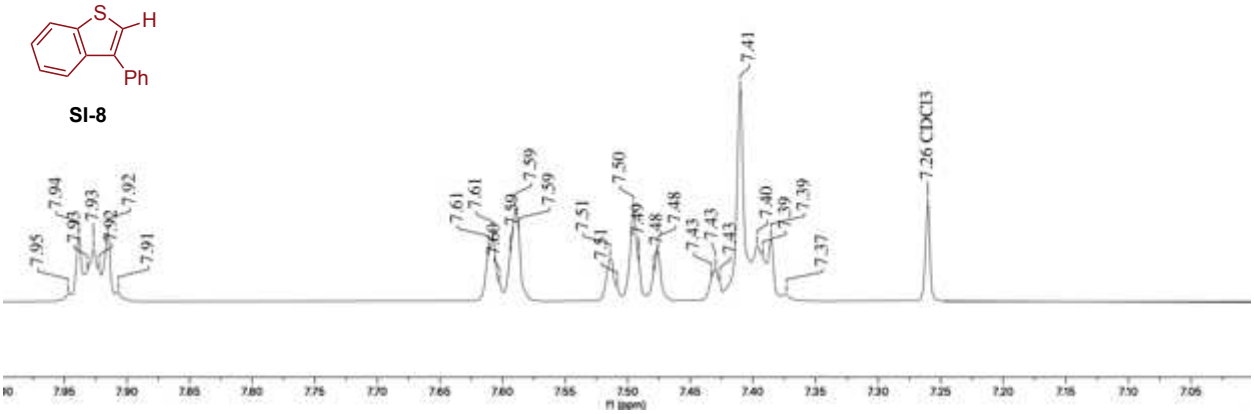
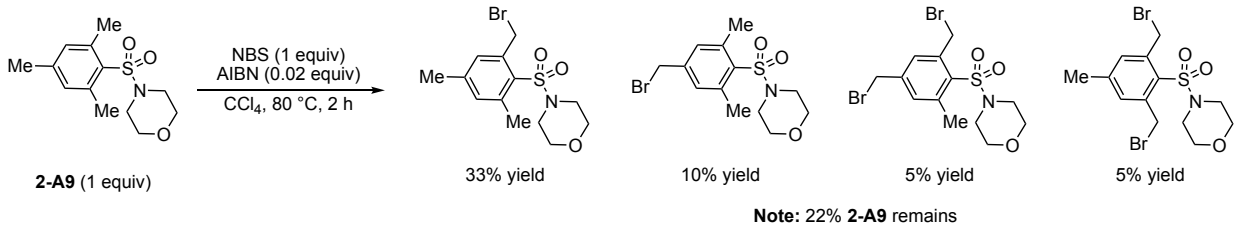


Figure 2A-5. ^{1}H NMR spectral window (400 MHz, $CDCl_3$) of the mixture of **3-XTR 3** and **2-A8** collected from the C–H etherification of 6-bromo-5-methylquinoline (5a). ^{1}H NMR spectral window of **3-XTR 3** (5b). ^{1}H NMR spectral window of **2-A8** (5c).

A2.8. Site-Selectivity Studies of 2-A9 and 2-A10

Purpose: To study the regioselectivity trends for radical C–H functionalization of polyalkylarenes, we subjected 4-(mesitylsulfonyl)morpholine (**2-A9**) and 4-bromo-2,3',4'-trimethyl-1,1'-biphenyl (**2-A10**) to common conditions for radical halogenation.[9] Next, to gain further insight into the selectivity of the X-transfer mediated benzylic C–H etherification protocol, we studied the selectivity of MO-*t*-Bu deprotonation of **2-A9** and **2-A10** using deuterium exchange experiments. We note that LiO-*t*-Bu is used as the base for **2-A9** and KO-*t*-Bu is used as the base for **2-A10** as they were the optimal bases for the etherification of the respective substrates (see Section 10).

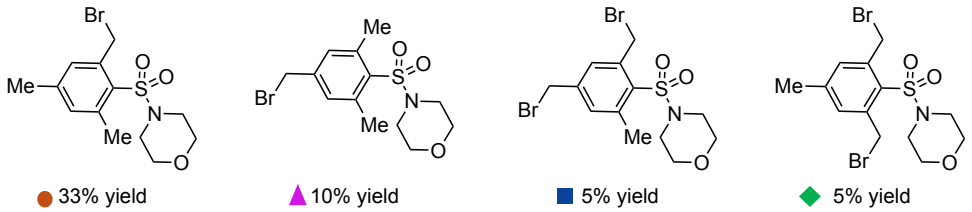
(a) Selectivity of Radical Halogenation of 2-A9 and 2-A10



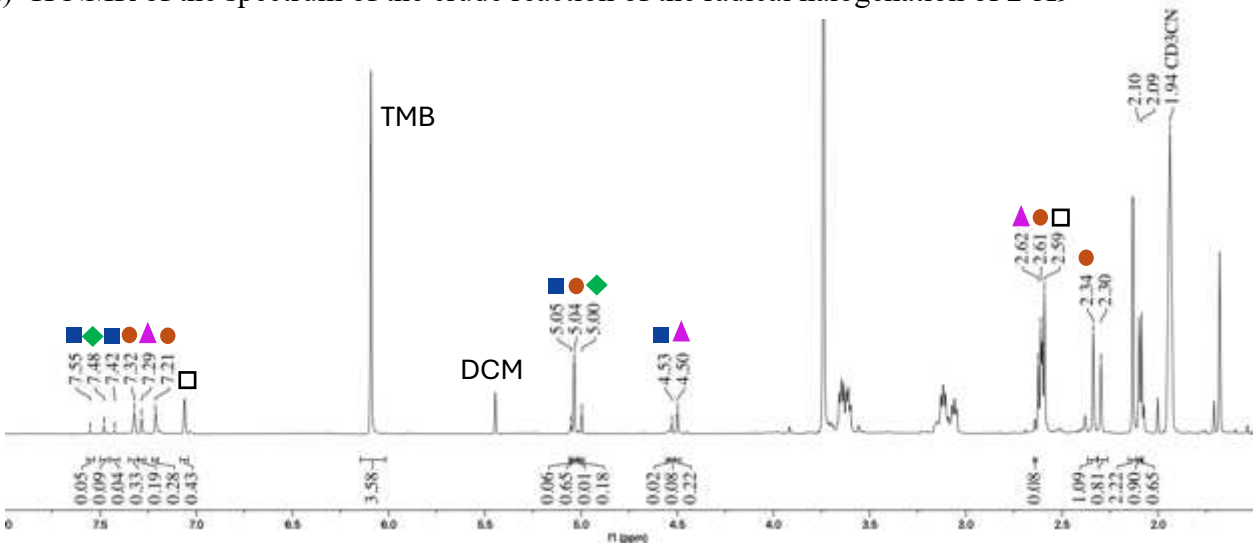
Procedure: This procedure was adapted from a previous literature report.[9] An oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 4-(mesitylsulfonyl)morpholine (67.3 mg, 0.25 mmol, 1 equiv) or 4-bromo-2,3',4'-trimethyl-1,1'-biphenyl (68.8 mg, 0.25 mmol, 1 equiv), *N*-bromosuccinimide (44.5 mg, 0.25 mmol, 1 equiv), and CCl_4 (0.25 M, 0.4 mL). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum

(Thermo Fisher Scientific, #B7995-13), placed into an aluminum reaction block preheated 80 °C, and stirred for 2 min. Next, azobisisobutyronitrile (AIBN, 8.2 mg, 0.05 mmol, 0.2 equiv) was added and the reaction was stirred at 80 °C for 2 h. The solution was cooled to rt. 1,3,5-Trimethoxybenzene (TMB, 50.2 mg, 0.30 mmol) internal standard was added to the crude reaction mixture. A small aliquot was then removed, injected into an NMR tube, and constituted in $CDCl_3$ (0.5 mL) for analysis by ^1H NMR spectroscopy. Further details on the analysis of reaction **2-A9** and **2-A10** are provided below.

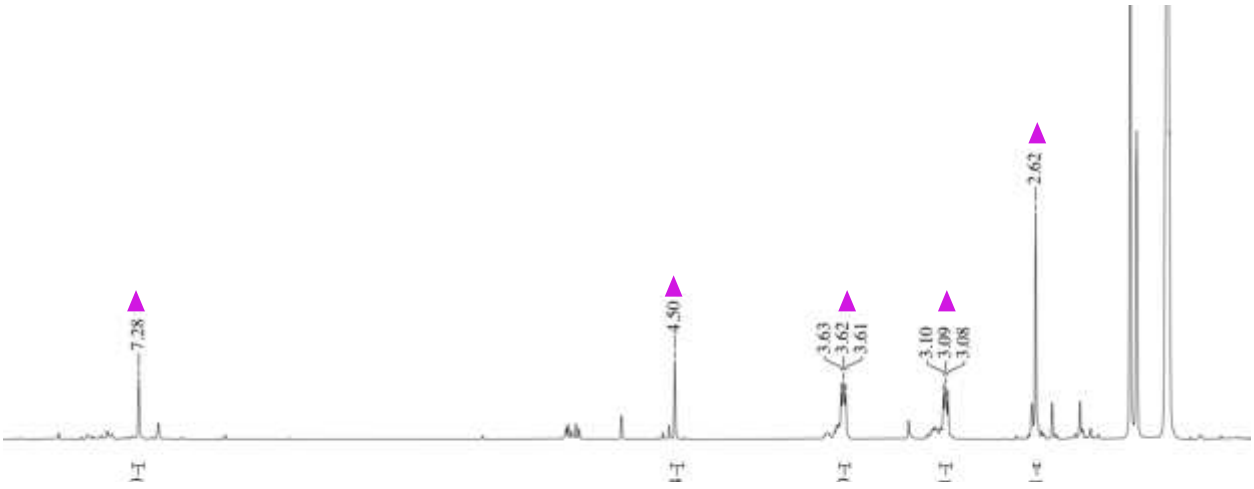
Analysis of 2-A9: The crude reaction solution for the reaction of **2-A9** was poured into a 25 mL separatory funnel containing water (5 mL). The aqueous mixture was extracted with EtOAc (3 x 5 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo*. The resulting mixture was then purified *via* preparatory thin layer chromatography plate (25% acetone/hexanes) to yield several mixtures containing the benzyl halides pictured in Figure 2A-6 with residual impurities. The mixture of benzyl halides formed were not completely isolable from each other, although the preparatory thin layer chromatography plate provided clean enough ^1H NMR spectra for structural assignments to be made and thereby reaction assessment. The spectra of the mixtures the different benzyl halides were overlayed against the crude ^1H NMR spectrum. Based on this, the percent formation of each benzyl halide was determined. The spectra and insights into the analysis are provided below.



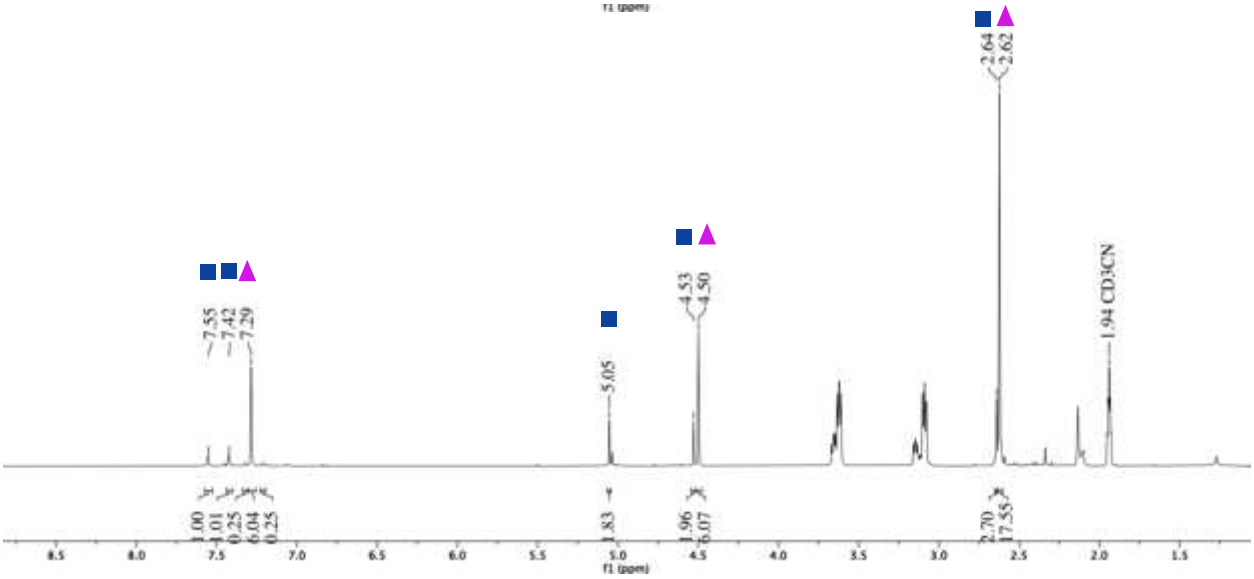
(a) ^1H NMR of the spectrum of the crude reaction of the radical halogenation of **2-A9**



(b) ^{1}H NMR of the spectrum of the first isolated mixture from the radical halogenation of **2-A9**



(c) ^{1}H NMR of the spectrum of the second isolated mixture from the radical halogenation of **2-A9**



(d) ^{1}H NMR of the spectrum of the third isolated mixture from the radical halogenation of **2-A9**

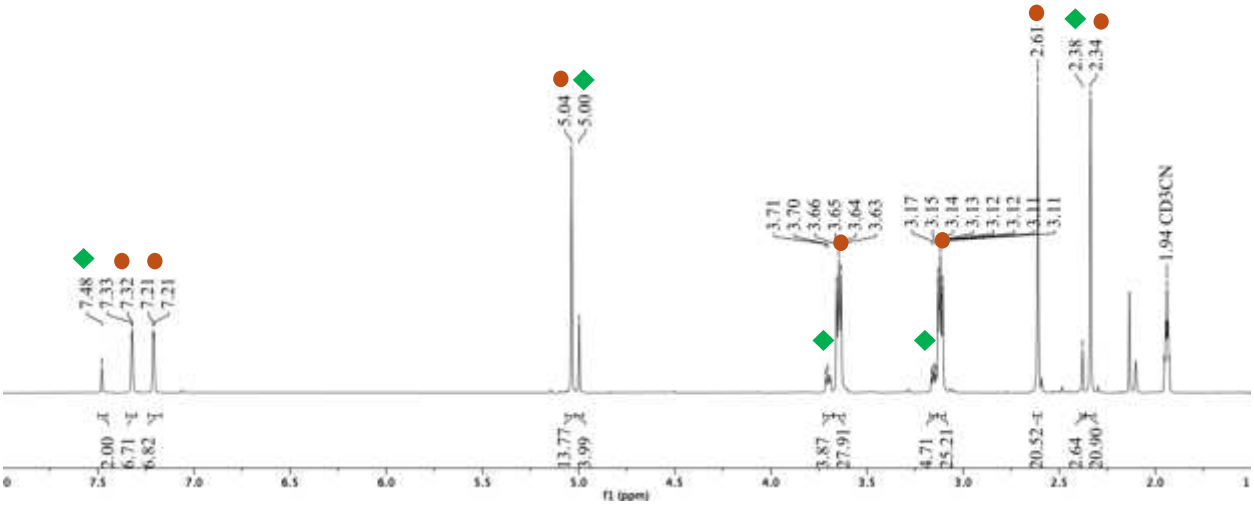


Figure 2A-6. ^{1}H NMR spectrum (400 MHz, CD_3CN) of the crude reaction solution of 4-(mesitylsulfonyl)morpholine using NBS and AIBN (6a). ^{1}H NMR spectrum (400 MHz, CD_3CN) of the first preparatory thin layer chromatography plate band from the radical halogenation of **2-A9 (**6b). ^{1}H NMR spectrum (400 MHz, CD_3CN) of the second preparatory thin layer chromatography plate band from the radical halogenation of **2-A9** (6c). ^{1}H NMR spectrum (400 MHz, CD_3CN) of the third preparatory thin layer chromatography plate band from the radical halogenation of **2-A9** (6d).

Further notes pertaining to the analysis of Figure 2A-6: (Figure 2A-6, a): 1,3,5-Trimethoxybenzene (TMB) internal standard (50.2 mg, 0.30 mmol, signal at 6.09 ppm calibrated to 3.58 for 0.25 mmol scale reaction) was used to determine the amount of each benzyl halide product. **(Figure 2A-6, b):** The ratio of the aromatic signal δ 7.28 (s, 2H) to the benzylic methylene signal δ 4.50 (s, 2H) to the dimethyl signal δ 2.62 (s, 6H) indicate that this sample is mainly comprised of 4-((4-(bromomethyl)-2,6-dimethylphenyl)sulfonyl)morpholine. **(Figure 2A-6, c):** The ratio of the aromatic signals δ 7.55 (s, 1H) and 7.42 (s, 1H) to the benzylic methylene signals δ 5.05 (s, 2H) and 1.96 (s, 2H) to the methyl signal δ 2.64 (s, 3H) indicate that this sample contains 4-((2,4-bis(bromomethyl)-6-methylphenyl)sulfonyl)morpholine. This band also contains 4-((4-(bromomethyl)-2,6-dimethylphenyl)sulfonyl)morpholine as determined by overlapping with spectrum b above. **(Figure 2A-6, d):** The ratio of the aromatic signal δ 7.48 (s, 2H) to the benzylic methylene signal δ 5.00 (s, 4H) to the methyl signal δ 2.61 (s, 3H) indicate that this sample contains 4-((2,6-bis(bromomethyl)-4-methylphenyl)sulfonyl)morpholine. Additionally, this band also contains 4-((2-(bromomethyl)-4,6-dimethylphenyl)sulfonyl)morpholine as determined through the ratio of the aromatic signals δ 7.32 (s, 1H) and 7.21 (s, 1H) to the benzylic methylene signal δ 5.04 (s, 2H) to the methyl signals δ 2.61 (s, 3H) and 2.34 (s, 3H).

Analysis of 2-A10: The crude ^{1}H NMR spectrum from the radical halogenation of 2-A10 is shown below, where a complex mixture of benzyl halides formed (Figure 2A-7).

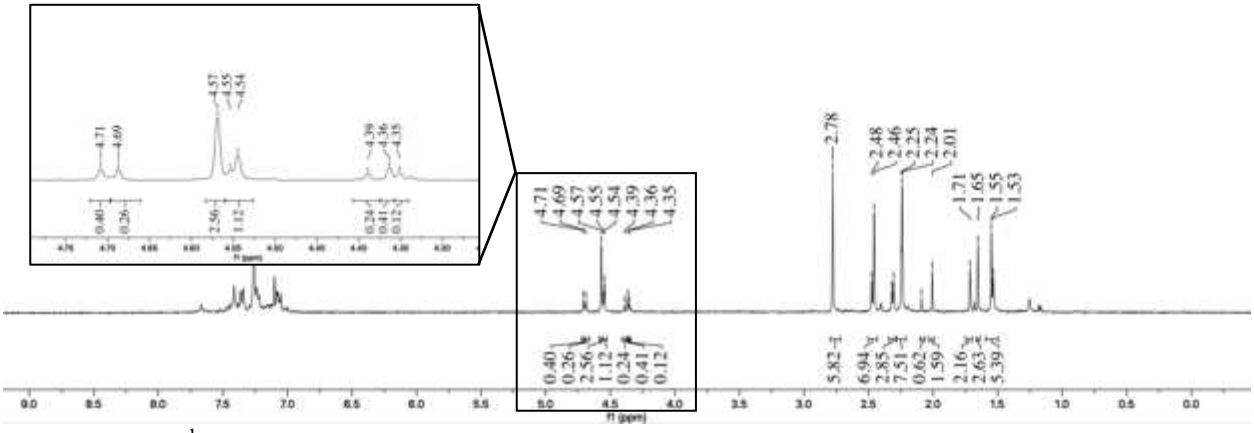
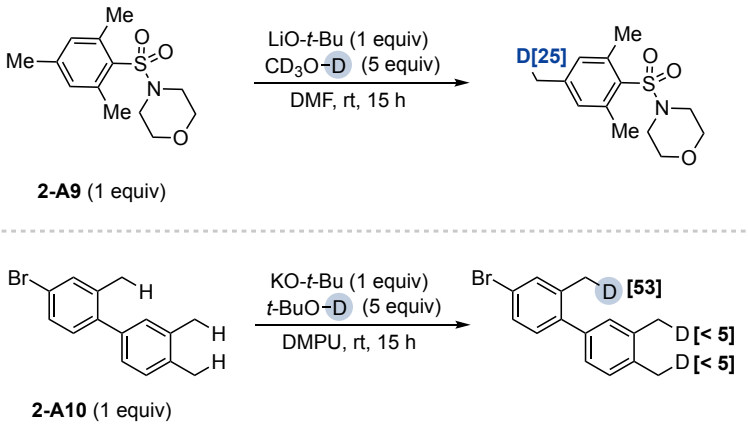


Figure 2A-7. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the crude reaction solution of 4-bromo-2,3',4'-trimethyl-1,1'-biphenyl using NBS and AIBN.

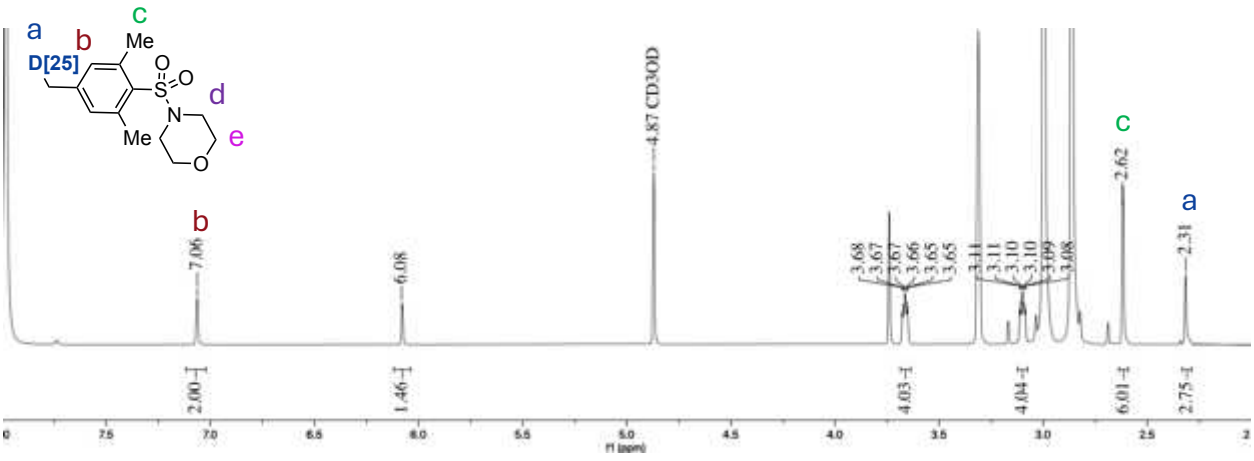
(b) Deuterium Incorporation Studies of 2-A9 and 2-A10



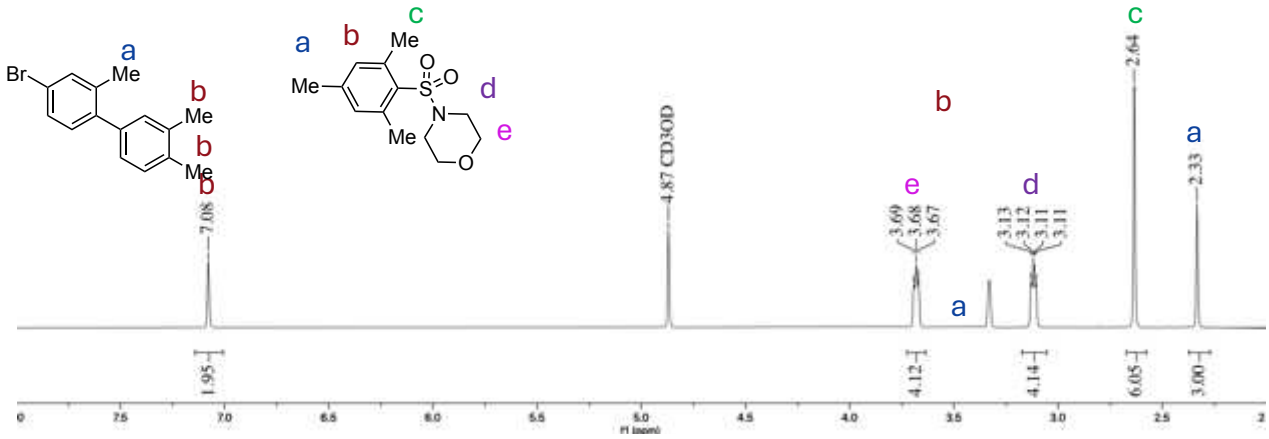
Procedure: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 4-(mesitylsulfonyl)morpholine (67.3 mg, 0.25 mmol, 1 equiv) or 4-bromo-2,3',4'-trimethyl-1,1'-biphenyl (68.8 mg, 0.25 mmol, 1 equiv), methanol-d_4 (45.1 mg, 1.25 mmol, 5 equiv) or *t*-butanol-d_{10} (42.1 mg, 1.25 mmol, 5 equiv), anhydrous solvent (0.25 M, 1 mL), and MO-*t*-Bu (0.25 mmol, 1 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox and stirred for 15 h at rt. 1,3,5-Trimethoxybenzene (TMB) internal standard was added to the crude reaction mixture (20.5 mg, 0.12 mmol). A small aliquot was then removed, injected into an NMR tube, and constituted in CD_3OD (0.5 mL) for analysis by ^{1}H NMR spectroscopy (400 MHz).

Analysis: The ^{1}H NMR spectra of the crude reaction mixtures from the deuterium exchange experiment and the corresponding starting material (**2-A9** or **2-A10**) were then overlayed, and each peak was integrated. The percent of deuterium incorporation into **2-A9** and **2-A10** was calculated based on the reduction of signal integration between the signals in the crude reaction analysis and starting material spectra. The stacked spectra are provided below (Figure 2A-8).

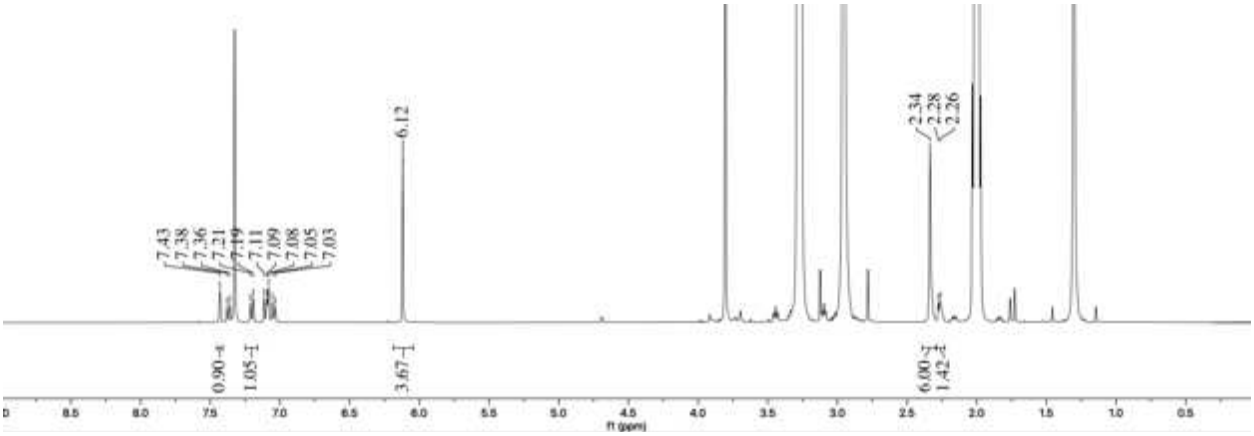
(a) ^{1}H NMR of the reaction solution from the deuterium incorporation of **2-A9** with LiO-*t*-Bu



(b) ^{1}H NMR spectrum of **2-A9**



(c) ^{1}H NMR of the reaction solution from the deuterium incorporation of **2-A10** with KO-*t*-Bu



(d) ^{1}H NMR spectrum of **2-A10**

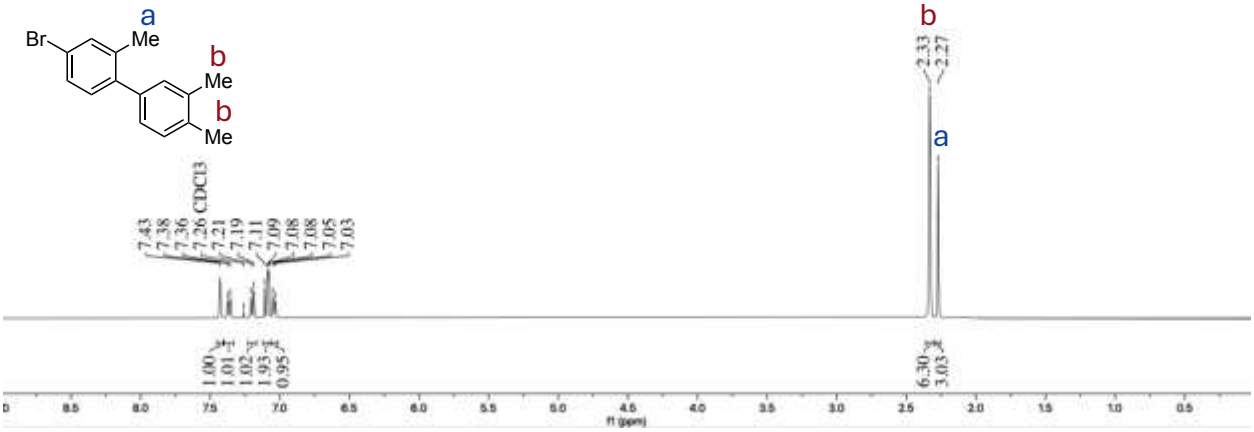


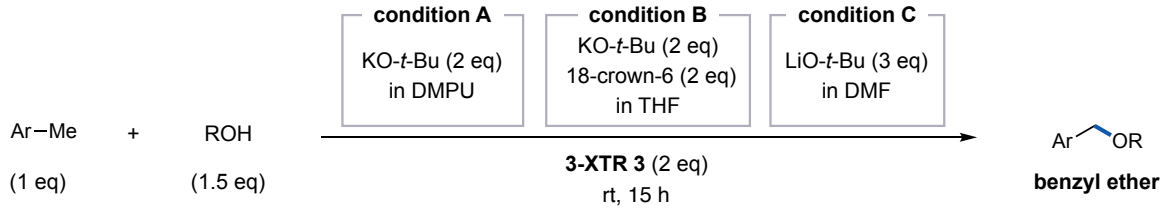
Figure 2A-8. ^{1}H NMR spectrum (400 MHz, CD_3OD) of the crude reaction solution of 4-(mesitylsulfonyl)morpholine using CD_3OD and LiO-*t*-Bu (8a). ^{1}H NMR spectrum (400 MHz, CD_3OD) of 4-(mesitylsulfonyl)morpholine (8b). ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the crude reaction solution of 4-bromo-2,3',4'-trimethyl-1,1'-biphenyl using *t*-butanol-d_{10} and KO-*t*-Bu (8c). ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4-bromo-2,3',4'-trimethyl-1,1'-biphenyl (8d).

Further Notes Pertaining to the Analysis of Figure 2A-8: (Figure 2A-8, a): It was determined that 2.75 H remain at the *para*-methyl position, thus 25% of deuteration occurs at the *para*-methyl position of **2-A9**. Additionally, 6.0 H remains at the other methyl positions of **2-A9**.**(Figure 2A-8, c):** It was determined that 1.42 H remain at the *meta*-bromomethyl position of **2-A10**, thus 53% of deuteration occurs at the *meta*-bromomethyl position. Additionally, 6.0 H remains at the other methyl positions of **2-A10**.

Discussion: Functionalization of **2-A9** and **2-A10** *via* NBS with AIBN gives regioisomeric mixtures. Alternatively, deprotonation with MO-*t*-Bu of **2-A9** and **2-A10** under deuterium exchange conditions results in deuteration at only the most acidic position. We therefore reasoned that, if X-transfer is fast enough, the C–H etherification process using alkoxide bases would display high regioselectivity for the most acidic position.

A2.9. General Procedure for the Selective Benzylic C–H Etherification of Polyalkylarenes

Polyalkylarenes **3-37**, **3-40**, **3-41**, **3-42**, and **3-43** were isolated using GP1, and this general procedure was conducted on a 0.5 - 1 mmol scale of alkylarene using a standard manifold Schlenk line outside of a glovebox. Alternatively, polyalkylarenes **3-36**, **3-38**, **3-39**, and **3-44** were isolated using general procedure 2 (GP2) described below. GP2 was conducted on a 0.25 mmol scale of alkylarene using a glovebox. These substrates give similar yields using GP1, but were isolated on a smaller scale as they were isolated *via* preparatory thin layer chromatography.



General Benzylic C–H Etherification Procedure (GP2): Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE® , #60910-1) was charged with a magnetic stir bar, alkyl arene (1 equiv, 0.25 mmol), alcohol (1.5 equiv), **3-XTR 3** (2 equiv), anhydrous solvent (0.25 M, 0.4 mL), and KO-*t*-Bu or LiO-*t*-Bu (2 equiv) were added in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13) and removed from the glovebox. The reaction solution was stirred for 15 h at rt. The reaction mixture was subsequently transferred into a separatory funnel containing H_2O (10 mL) and the aqueous mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo*. The crude material was purified *via* preparatory thin layer chromatography.

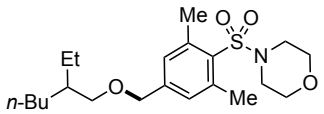
Verification of product regioselectivity and yield: For the substrates reported in Figure 3, there are multiple potential sites of C–H etherification. Thus, the regioselectivity of the benzylic C–H etherification reaction was determined through analysis of the ^{1}H NMR spectrum of each compound. The ^{1}H NMR spectrum of the crude reaction mixture for each reaction was analyzed

to determine if the major product was formed in high selectivity. It was determined that >20:1 selectivity was achieved for each substrate in Figure 3. For compounds where the positional selectivity of the major product is challenging to determine based solely off ^{1}H and ^{13}C NMR spectra, additional NMR experiments on the purified product are provided below the characterization data.

Additionally, the crude ^{1}H NMR yields are provided for the products in Figure 3 to report on the direct efficiency and selectivity of the reaction. The isolated yields can be lower due to separation challenges during purification (e.g., coelution with the starting material or alcohol pronucleophile). Thus, to determine the crude ^{1}H NMR yield, 4-(trifluoromethyl)pyridine internal standard was measured into the crude reaction solution (before transfer into the separatory funnel) and the mass weighed into the vial was recorded. A small aliquot of the organic layer was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of the benzyl ether product. See Section 10, Figure 2A-9 for a description of this analysis process and example crude ^{1}H NMR spectra.

A2.10. Characterization Data of Benzylic Functionalized Polyalkyarene Products

4-((4-(((2-ethylhexyl)oxy)methyl)-2,6-dimethylphenyl)sulfonyl)morpholine (3-36)



The title product was prepared according GP2 using 4-(mesitylsulfonyl)morpholine (67.3 mg, 0.25 mmol, 1 equiv), 2-ethylhexan-1-ol (48.8 mg, 0.38 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (167.6 mg, 0.5 mmol, 2 equiv), LiO-*t*-Bu (60.1 mg, 0.75 mmol, 3.0 equiv), and anhydrous DMF (1.0 mL). The yield and selectivity of the crude material were determined by ^{1}H NMR spectroscopy (51% yield, >20:1 selectivity). The product was purified *via* a preparatory thin layer chromatography plate (17% EtOAc/hexanes) to afford the desired compound with multiple impurities. This material was resubjected to two subsequent preparatory thin layer chromatography plates (33% DCM/hexanes) and (17% EtOAc/hexanes) to afford the title compound as a colorless oil (19.0 mg, 0.05 mmol, 34% yield).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.12 (s, 2H), 4.45 (s, 2H), 3.75 – 3.62 (m, 4H), 3.38 (dd, *J* = 5.9, 1.6 Hz, 2H), 3.21 – 3.08 (m, 4H), 2.67 (s, 6H), 1.62 – 1.52 (m, 1H), 1.47 – 1.23 (m, 8H), 0.94 – 0.83 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.7, 141.0, 132.8, 129.9, 74.0, 72.0, 66.3, 44.5, 39.9, 30.7, 29.3, 24.0, 23.3, 23.2, 14.3, 11.2. **IR** (neat, cm^{-1}) 2924, 2856, 1454, 1323, 1176, 1155 1071, 927, 729. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{21}H_{36}SNO_4]^+$ = 398.2360, 398.2341 found.

Verification of regioselectivity: It was determined that etherification occurred at the *para*-methyl group over the *ortho*-methyl groups as the ^{1}H NMR signal δ 2.67 (s, 6H) corresponding to the two unfunctionalized methyl groups indicates that the product it still symmetrical.

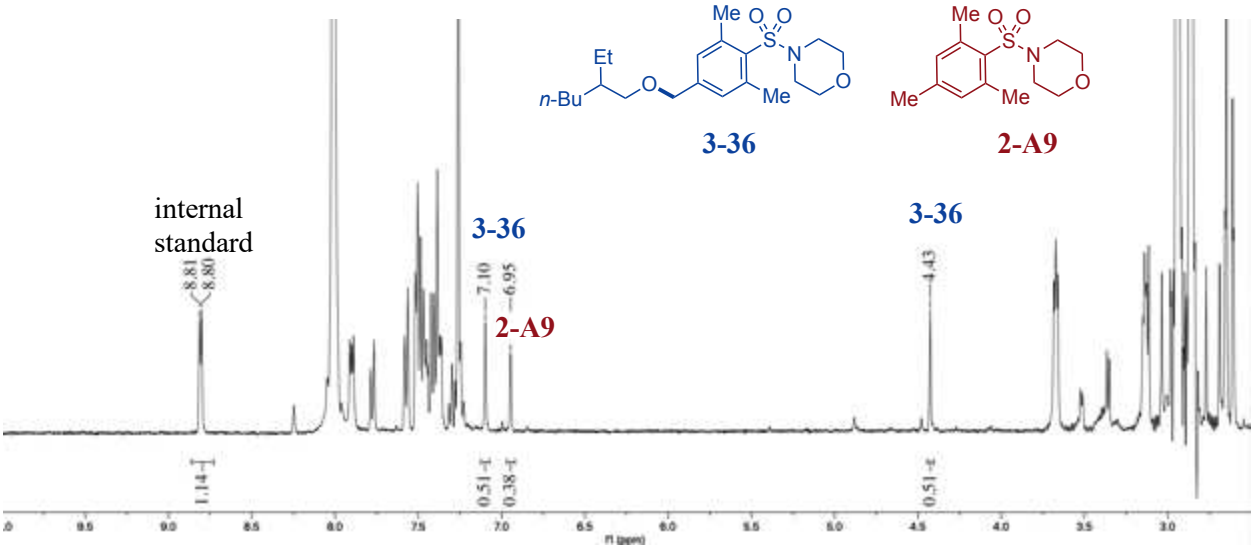
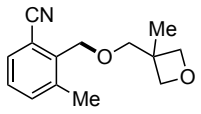


Figure 2A-9. The interpretation of the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the crude reaction solution of the benzylic C–H etherification of 4-(mesitylsulfonyl)morpholine is shown above. 4-(Trifluoromethyl)pyridine internal standard (43.7 mg, 0.3 mmol, signal at 8.80 ppm calibrated to 1.14 for 0.25 mmol scale reaction) was used to determine the yield and selectivity of 4-((4-(((2-ethylhexyl)oxy)methyl)-2,6-dimethylphenyl)sulfonyl)morpholine (51% yield, >20:1 selectivity) and the amount of remaining 4-(mesitylsulfonyl)morpholine (38% remaining).

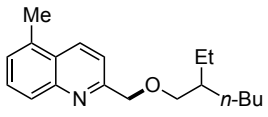
3-methyl-2-(((3-methyloxetan-3-yl)methoxy)methyl)benzonitrile (3-37)



The title product was prepared with GP1 using 2,3-dimethylbenzonitrile (131.1 mg, 1 mmol, 1 equiv), (3-methyloxetan-3-yl)methanol (153.1 mg, 1.5 mmol, 1.5 equiv), 2-iodothiophene (420.1 mg, 2 mmol, 2 equiv), LiO-*t*-Bu (240.3 mg, 3 mmol, 3 equiv), and anhydrous DMF (4.0 mL). The yield and selectivity of the crude material were determined by ^{1}H NMR spectroscopy (71% yield, >20:1 selectivity). The product was purified *via* silica gel chromatography (15% to 20% EtOAc/hexanes) to afford the title compound as a colorless oil (156.8 mg, 0.68 mmol, 68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 4.77 (s, 2H), 4.50 (d, J = 7.5 Hz, 2H), 4.34 (d, J = 7.4 Hz, 2H), 3.59 (s, 2H), 2.45 (s, 3H), 1.31 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.8, 138.9, 135.2, 130.6, 128.8, 118.3, 114.0, 80.2, 69.1, 40.0, 21.5, 19.4. **IR** (neat, cm^{-1}) 2958, 2866, 2224, 1589, 1463, 1095, 977, 788. **HRMS** (APGC-TOF) [M+H] calcd. for $[C_{14}H_{18}NO_2]^+$ = 232.1338, 232.1331 found.

Verification of regioselectivity: Two 2D NMR experiments were used to determine the regioselectivity of benzylic C–H etherification for **3-37**. Specifically, a Heteronuclear Single Quantum Coherence (HSQC) experiment determined that the ^{1}H NMR signals corresponding to the benzylic ether methylene δ 4.77 (s, 2H), the unfunctionalized methyl peak δ 2.45 (s, 3H), and the aromatic signal adjacent to the methyl group δ 7.42 (d, J = 7.7 Hz, 1H) are bonded to the carbon with the ^{13}C NMR signals at δ 69.1, 19.4, and 135.2, respectively. Heteronuclear Multiple Bond Correlation (HMBC) experiment indicated that the benzylic ether methylene ^{1}H NMR signal δ 4.77 (s, 2H) correlates only with aromatic ^{13}C NMR signals that are fully substituted (i.e., δ 114.0 and 139.8). In contrast, the methyl ^{1}H NMR signal δ 2.45 (s, 3H) correlates with the aromatic ^{13}C NMR signal δ 135.2. See spectra in Section 17.

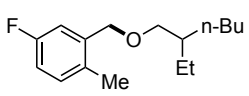
2-(((2-ethylhexyl)oxy)methyl)-5-methylquinoline (3-38)



The title product was prepared according GP2 using 2,5-dimethylquinoline (39.3 mg, 0.25 mmol, 1 equiv), 2-ethylhexan-1-ol (48.8 mg, 0.38 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (167.6 mg, 0.5 mmol, 2 equiv), LiO-*t*-Bu (60.1 mg, 0.75 mmol, 3.0 equiv), and anhydrous DMF (1.0 mL). The yield and selectivity of the crude material were determined by ^{1}H NMR spectroscopy (68% yield, >20:1 selectivity). The product was purified *via* a preparatory thin layer chromatography plate (5% EtOAc/hexanes) to afford the title compound as a colorless oil (34.8 mg, 0.12 mmol, 49% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 7.0 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 4.82 (s, 2H), 3.49 (d, *J* = 5.8 Hz, 2H), 2.80 (s, 3H), 1.67 – 1.55 (m, 1H), 1.55 – 1.23 (m, 8H), 0.95 – 0.83 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.8, 146.7, 137.1, 136.8, 129.6, 127.5, 125.9, 125.7, 119.1, 75.0, 74.0, 40.0, 30.8, 29.3, 24.1, 23.2, 18.0, 14.3, 11.3. **IR** (neat, cm^{-1}) 2924, 2857, 1601, 1501, 1457, 1349, 1318, 1107, 834. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{19}H_{28}NO]^+$ = 286.2165, 286.2176 found.

Verification of regioselectivity: Two 2D NMR experiments were used to determine the regioselectivity of benzylic C–H etherification for **3-38**. Specifically, a Heteronuclear Single Quantum Coherence (HSQC) experiment determined that the ^{1}H NMR signals corresponding to the benzylic ether methylene δ 4.82 (s, 2H) and the adjacent aromatic signal δ 7.60 (d, *J* = 8.4 Hz, 1H) are bonded to the carbon with the ^{13}C NMR signals at δ 75.0 and 119.1, respectively. Heteronuclear Multiple Bond Correlation (HMBC) experiment indicated that the benzylic ether methylene ^{1}H NMR signal δ 4.82 (s, 2H) correlates with the aromatic ^{13}C NMR signal δ 119.1. See spectra in Section 17.

2-(((2-ethylhexyl)oxy)methyl)-4-fluoro-1-methylbenzene (3-39)

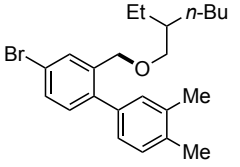


The title product was prepared using GP2 where 4-fluoro-1,2-dimethylbenzene (31.0 mg, 0.25 mmol, 1 equiv), 2-ethylhexan-1-ol (48.8 mg, 0.38 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (167.6 mg, 0.5 mmol, 2 equiv), KO-*t*-Bu (42.1 mg, 0.38 mmol, 1.5 equiv), 18-crown-6 (99.1 mg, 0.38 mmol, 1.5 equiv), and anhydrous THF (1.0 mL) were used as described. The yield and selectivity of the crude material was determined by ^{1}H NMR spectroscopy (62% yield, >20:1 selectivity). The product was then purified *via* preparatory thin layer chromatography plate (100% hexanes) to provide title compound as a colorless oil (20.4 mg, 0.32 mmol, 32% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.14 – 7.01 (m, 2H), 6.86 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.43 (s, 2H), 3.39 (d, *J* = 5.8 Hz, 2H), 2.25 (s, 3H), 1.62 – 1.49 (m, 1H), 1.50 – 1.22 (m, 8H), 0.98 – 0.82 (m, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.4 (d, *J* = 242.5 Hz), 139.1 (d, *J* = 6.8 Hz), 131.4 (d, *J* = 3.1 Hz), 131.3 (d, *J* = 8.0 Hz), 114.7 (d, *J* = 21.7Hz), 113.8 (d, *J* = 20.6 Hz), 73.7, 70.9 (d, *J* = 1.6 Hz), 39.9, 30.8, 29.2, 24.1, 23.2, 18.1, 14.3, 11.2. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.8 (m, 1F). **IR** (neat, cm^{-1}) 1739, 1653, 1559, 1457, 1378, 1232, 1113, 1035, 809. **HRMS** (APGC-TOF) [M+] calcd. for $[C_{16}H_{25}FO]^+$ = 252.1889, 252.1889 found.

Verification of regioselectivity: Two 2D NMR experiments were used to determine the regioselectivity of benzylic C–H etherification for **3-39**. Specifically, a Heteronuclear Single Quantum Coherence (HSQC) experiment determined that the ^{1}H NMR signals corresponding to the benzylic ether methylene δ 4.43 (s, 2H), the unfunctionalized methyl peak δ 2.25 (s, 3H), and the aromatic signal *ortho* to the C–F bond and benzylic methylene δ 7.14 – 7.01 (m, 2H) are bonded to the carbons with the ^{13}C NMR signals at δ 70.9 (d, *J* = 1.6 Hz), 18.1, 114.7 (d, *J* = 21.7Hz), respectively. The benzylic methylene carbon is experiencing long range coupling C–F bond which

supports that C–H etherification occurs at the *meta*-methyl. Further, a Heteronuclear Multiple Bond Correlation (HMBC) experiment indicated that the benzylic ether methylene ^{1}H NMR signal δ 4.77 (s, 2H) correlates strongly with aromatic ^{13}C NMR signals δ 114.7 (d, *J* = 21.7 Hz). See spectra in Section 17.

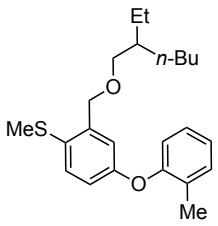
4-bromo-2-(((2-ethylhexyl)oxy)methyl)-3',4'-dimethyl-1,1'-biphenyl (3-40)



The title product was prepared with GP1 on a 0.5 mmol scale using 4-bromo-2,3',4'-trimethyl-1,1'-biphenyl (137.6 mg, 0.5 mmol, 1 equiv), 2-ethylhexan-1-ol (97.6 mg, 0.75 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (335.1 mg, 1 mmol, 2 equiv), KO-*t*-Bu (84.2 mg, 0.75 mmol, 1.5 equiv), and anhydrous DMPU (2.0 mL). Yield and selectivity of the crude material were determined by ^{1}H NMR spectroscopy (56% yield, >20:1 selectivity). The product was then purified *via* a preparatory thin layer chromatography plate (100% hexanes) to afford the title compound as a colorless oil (81.1 mg, 0.21 mmol, 40% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.1 Hz, 1H), 7.44 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.18 (d, *J* = 7.7 Hz, 1H), 7.15 – 7.09 (m, 2H), 7.07 (d, *J* = 7.7 Hz, 1H), 4.35 (s, 2H), 3.31 (d, *J* = 5.8 Hz, 2H), 2.32 (d, *J* = 3.2 Hz, 6H), 1.60 – 1.48 (m, 1H), 1.46 – 1.23 (m, 8H), 0.95 – 0.85 (m, 6H). **^{13}C NMR** (101 MHz, CD_3CN) δ 140.5, 138.4, 137.4, 136.6, 135.9, 131.7, 131.6, 130.39, 130.37, 129.6, 126.6, 121.4, 73.7, 70.5, 39.9, 30.8, 29.3, 24.0, 23.2, 20.0, 19.6, 14.3, 11.2. **IR** (neat, cm^{-1}) 2958, 2360, 2341, 1694, 1473, 1207, 1039, 888. **HRMS** (APGC-TOF) [M+] calcd. for $[C_{23}H_{31}BrO]^+$ = 402.1558, 402.1563 found.

Verification of regioselectivity: Three 2D NMR experiments were used to determine the regioselectivity of benzylic C–H etherification for **3-40**. Specifically, a Heteronuclear Single Quantum Coherence (HSQC) experiment determined that the ^{1}H NMR signals corresponding to the benzylic ether methylene δ 4.35 (s, 2H) and the adjacent aromatic signal δ 7.71 (d, *J* = 2.1 Hz, 1H) are bonded to the carbon with the ^{13}C NMR signals at δ 70.5 and δ 131.7, respectively. Heteronuclear Multiple Bond Correlation (HMBC) experiment indicated that the benzylic ether methylene ^{1}H NMR signal δ 4.35 (s, 2H) correlates with the aromatic ^{13}C NMR signal δ 131.7. The NOESY experiment confirms that the benzylic methylene peak correlates with the aromatic signal *ortho*-to the bromo substituent. See spectra in Section 17.

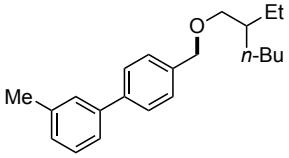
(2-(((2-ethylhexyl)oxy)methyl)-4-(*o*-tolyloxy)phenyl)(methyl)sulfane (3-41)



The title product was prepared with GP1 using methyl(2-methyl-4-(*o*-tolyloxy)phenyl)sulfane (122.1 mg, 0.5 mmol, 1 equiv), 2-ethylhexan-1-ol (97.6 mg, 0.75 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (335.1 mg, 1 mmol, 2 equiv), KO-*t*-Bu (112.2 mg, 1 mmol, 2 equiv), and anhydrous DMPU (2.0 mL). The yield and selectivity of the crude material were determined by ^{1}H NMR spectroscopy (49% yield, >20:1 selectivity). The product was purified *via* a preparatory thin layer chromatography plate (100% hexanes) to afford the title compound as a colorless oil (75.4 mg, 0.20 mmol, 41% yield). **^{1}H NMR** (400 MHz, CD_3CN) δ 7.34 – 7.27 (m, 2H), 7.20 (td, *J* = 7.7, 1.8 Hz, 1H), 7.11 (td, *J* = 7.5, 1.3 Hz, 1H), 6.94 – 6.87 (m, 2H), 6.84 (dd, *J* = 8.5, 2.9 Hz, 1H), 4.48 (s, 2H), 3.36 (d, *J* = 5.7 Hz, 2H), 2.41 (s, 3H), 2.19 (s, 3H), 1.51 – 1.38 (m, 1H), 1.35 – 1.20 (m, 8H), 0.91 – 0.80 (m, 6H). **^{13}C NMR** (101 MHz, CD_3CN) δ 157.3, 155.2, 140.8, 132.5, 130.9, 130.5, 130.4, 125.4, 120.9, 118.3, 117.6, 117.2, 74.0, 70.9, 40.7, 31.4, 29.8, 24.8, 23.8, 17.3, 14.4, 11.5. **IR** (neat, cm^{-1}) 2922, 2857, 1583, 1488, 1437, 1230, 1184, 1098. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{23}H_{33}SO_2]^+$ 373.2196, 373.2138 found.

Verification of regioselectivity: Two 2D NMR experiments were used to determine the regioselectivity of benzylic C–H etherification for **3-41**. Specifically, a Heteronuclear Single Quantum Coherence (HSQC, $CDCl_3$) experiment determined that the ^1H NMR signal corresponding to the benzylic ether methylene is δ 4.48 (s, 2H), the adjacent aromatic signal is δ 6.94 – 6.87 (m, 2H), and the unfunctionalized methyl signal are δ 2.42 (s, 3H) are bonded to the carbon with the ^{13}C NMR signals at δ 70.9, 117.2, and 17.3, respectively. A Heteronuclear Multiple Bond Correlation (HMBC, $CDCl_3$) experiment indicated that the benzylic ether methylene ^1H NMR signal δ 4.48 (s, 2H) correlates with the aromatic ^{13}C NMR signal δ 117.2. It was also determined that this ^1H NMR signal correlates with the carbon bonded to the methyl thioether and the carbon bonded to the benzyl ether. See spectra in Section 17.

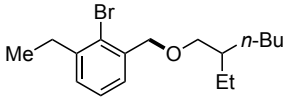
4'-(((2-ethylhexyl)oxy)methyl)-3-methyl-1,1'-biphenyl (3-42)



The title product was prepared with GP1 using 3,4'-dimethyl-1,1'-biphenyl (182.1 mg, 1.0 mmol, 1 equiv), 2-ethylhexan-1-ol (195.0 mg, 1.5 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (670.2 mg, 2 mmol, 2 equiv), 18-crown-6 (132.2 mg, 0.5 mmol, 0.5 equiv), KO-*t*-Bu (60.1 mg, 2 mmol, 2 equiv), and anhydrous DMPU (4.0 mL). The yield and selectivity between methyl groups of the crude material were determined by ^1H NMR spectroscopy (73% yield, >20:1 selectivity). The product was purified *via* silica gel chromatography (0% to 2% to 10% EtOAc/hexanes) to afford the title compound as a colorless oil (218.1 mg, 0.70 mmol, 70% yield). **^1H NMR** (400 MHz, CD_3CN) δ 7.59 (d, J = 8.1 Hz, 2H), 7.46 (s, 1H), 7.42 – 7.38 (m, 3H), 7.32 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 4.48 (s, 2H), 3.38 (d, J = 5.7 Hz, 2H), 2.39 (s, 3H), 1.56 – 1.49 (m, 1H), 1.43 – 1.22 (m, 8H), 0.93 – 0.86 (m, 6H). **^{13}C NMR** (101 MHz, CD_3CN) δ 141.6, 141.1, 139.5, 139.4, 129.8, 129.1, 129.0, 128.6, 127.8, 125.0, 73.7, 73.2, 40.7, 31.5, 29.9, 24.8, 23.8, 21.6, 14.5, 11.5. **IR** (neat, cm^{-1}) 2925, 2857, 1704, 1606, 1093, 822, 779, 698. **EA**: Anal. Calcd for $C_{22}H_{30}O$: C, 85.11; H, 9.74 Found: C, 85.90; H, 9.59. **Note on nucleophile selectivity:** Competing S_N2 of the proposed benzyl halide intermediate with *tert*-butoxide also occurs to give 5% of 4'-(*tert*-butoxymethyl)-3-methyl-1,1'-biphenyl side product (>14:1 selective), as detected by ^1H NMR spectroscopy of the crude reaction mixture. This material remained in the desired isomer in 3% yield after silica gel chromatography.

Verification of regioselectivity: Two 2D NMR experiments were used to determine the regioselectivity of benzylic C–H etherification for **3-42**. Specifically, a Heteronuclear Single Quantum Coherence (HSQC, CD_3CN) experiment determined that the ^1H NMR signals corresponding to the unfunctionalized methyl peak δ 2.39 (s, 3H) and the adjacent aromatic signals δ 7.46 (s, 1H) and δ 7.18 (d, J = 7.27 Hz, 1H) are bonded to the carbon with the ^{13}C NMR signals at δ 21.6, 128.6, and 129.02, respectively. A Heteronuclear Multiple Bond Correlation (HMBC, $CDCl_3$) experiment indicated that the unfunctionalized methyl ^1H NMR signal δ 2.39 (s, 3H) correlates with the aromatic ^{13}C NMR signal δ 128.6 and 129.02. See spectra in Section 17.

2-bromo-1-ethyl-3-(((2-ethylhexyl)oxy)methyl)benzene (3-43)

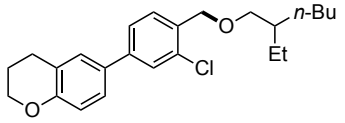


The title product was prepared using GP1, where 1.5 equiv of 18-crown-6 was used as an additive and THF was used as the solvent. Thus, 2-bromo-1-ethyl-3-methylbenzene (49.8 mg, 0.25 mmol, 1 equiv), 2-ethylhexan-1-ol (48.8 mg, 0.38 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (167.6 mg, 0.5 mmol, 2 equiv), KO-*t*-Bu (42.1 mg, 0.38 mmol, 1.5 equiv), 18-crown-6 (99.1 mg, 0.38 mmol, 1.5 equiv) and anhydrous THF (1.0 mL) were used

according to the general procedure. The yield and selectivity of the crude material were determined by ^{1}H NMR spectroscopy (70% yield, >20:1 selectivity). The product was purified *via* a preparatory thin layer chromatography plate (100% hexanes) to afford the title compound as a colorless oil (18.3 mg, 0.09 mmol, 22% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, J = 7.6 Hz, 1H), 7.30 – 7.28 (m, 1H), 7.19 (d, J = 7.5 Hz, 1H), 4.59 (s, 2H), 3.48 (d, J = 5.9 Hz, 2H), 2.83 (q, J = 7.5 Hz, 2H), 1.65– 1.58 (m, 1H), 1.55 – 1.23 (m, 11H), 0.95 – 1.21 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6, 138.9, 128.3, 127.2, 126.3, 124.4, 73.9, 73.1, 40.0, 30.8, 29.9, 29.8, 29.3, 24.1, 23.3, 14.4, 14.3, 11.3. **IR** (neat, cm^{-1}) 2858, 1606, 1491, 1378, 1352, 1241, 1126, 995, 670. **Note:** this compound did not ionize under the various ionization sources attempted.

Verification of regioselectivity: The benzylic ether methylene ^{1}H NMR peak δ 4.59 (s, 2H) indicates functionalization occurred at the methyl group over ethyl group otherwise this ^{1}H NMR signal would be split into a quartet.

6-(3-chloro-4-(((2-ethylhexyl)oxy)methyl)phenyl)chromane (3-44)



The title product was prepared with GP2 using 6-(3-chloro-4-methylphenyl)chromane (64.7 mg, 0.25 mmol, 1 equiv), 2-ethylhexan-1-ol (48.8 mg, 0.38 mmol, 1.5 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (167.6 mg, 0.5 mmol, 2 equiv), LiO-*t*-Bu (80.1 mg, 1 mmol, 4 equiv), and anhydrous DMF (1.0 mL). The yield and selectivity of the crude material was determined by ^{1}H NMR spectroscopy (56% yield, >20:1 selectivity). The title product was then purified *via* preparatory thin layer chromatography plate (4% EtOAc/hexanes) to provide desired compound with residual impurities. This material was resubjected to two subsequent preparatory thin layer chromatography plates (2% MeCN/hexanes) and (2% acetone/hexanes) to afford the title compound as a colorless oil (32.6 mg, 0.34 mmol, 34% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 – 7.48 (m, 2H), 7.43 (dd, J = 8.0, 1.8 Hz, 1H), 7.30 (dd, J = 8.4, 2.3 Hz, 1H), 7.25 (s, 1H), 6.86 (d, J = 8.4 Hz, 1H), 4.61 (s, 2H), 4.23 (t, J = 5.1 Hz, 2H), 3.46 (d, J = 5.9 Hz, 2H), 2.85 (t, J = 6.5 Hz, 2H), 2.12 – 1.93 (m, 2H), 1.67 – 1.53 (m, 1H), 1.52 – 1.22 (m, 8H), 0.91 – 0.87 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.1, 141.7, 134.7, 133.2, 131.7, 129.3, 128.5, 127.3, 126.0, 125.0, 122.7, 117.3, 73.8, 70.0, 66.8, 39.9, 30.7, 29.3, 25.2, 24.1, 23.3, 22.5, 14.3, 11.3. **IR** (neat, cm^{-1}) 2926, 2857, 1607, 1482, 1378, 1264, 1103, 874, 814. **LRMS** (GCMS) $[M+]^+$ calcd. for $[C_{24}H_{32}ClO_2]^+$ = 386.2, 386.2 found. **Note on reaction selectivity:** Overoxidation of the benzyl ether product occurs to give 8% of 6-(4-(bis((2-ethylhexyl)oxy)methyl)-3-chlorophenyl)chromane side product (7:1 selective), as detected by ^{1}H NMR spectroscopy of the crude reaction mixture. This material was readily separated from the desired isomer by silica gel chromatography.

Verification of regioselectivity: The benzylic ether methylene ^{1}H NMR peak δ 4.61 (s, 2H) indicates functionalization occurred at the methyl group over the benzyl methylene in the chromane ring otherwise this ^{1}H NMR signal would be split into a triplet.

A2.11. Reaction Profile Analysis of 3-45

(a) Reaction profile analysis of 3-45

Discussion: Several methylarenes from Table 1a undergo acetal formation under the standard reaction conditions; thus, a reaction profile analysis of 2-methylbenzotrifluoride (**3-45**) as a representative substrate was conducted. At the 30 min time point, 65% of the monofunctionalized

benzyl ether product **3-46** is present, at which point the over-oxidized acetal product **3-47** begins to form. At the 60 min time point the maximum yield of **3-46** is formed and, from that time point on, the yield of the monoether product goes down synchronously with the increase of the acetal (**3-47**). This is consistent with X-transfer preferentially occurring to the toluene over the benzyl ether until approximately 60% of benzyl ether has formed.

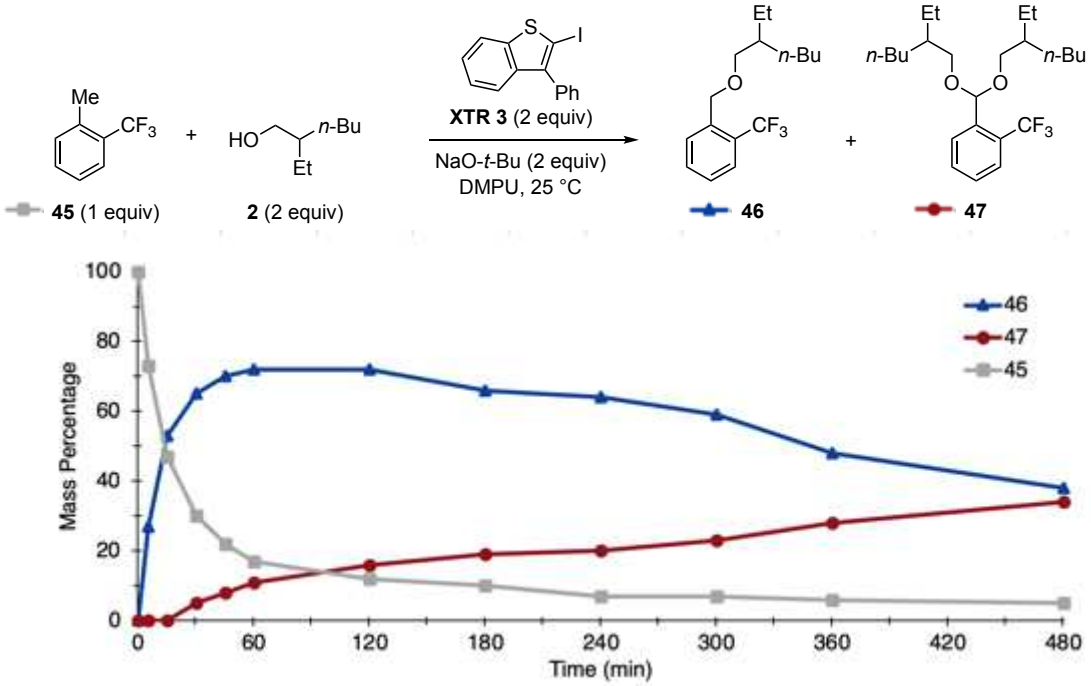


Figure 2A-10. Reaction profile analysis of **3-45** with **2-XTR 3**, 2-ethylhexan-1-ol, and NaO-*t*-Bu.

Procedure: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 1,3,5-trimethoxybenzene internal standard (23.7 mg, 0.13 mmol), 2-ethylhexan-1-ol (26.0 mg, 0.2 mmol, 2 equiv), 1-methyl-2-(trifluoromethyl)benzene (16.0 mg, 0.1 mmol, 1 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (67.2 mg, 0.2 mmol, 2 equiv), anhydrous DMPU (0.25 M, 0.4 mL), and NaO-*t*-Bu (19.2 mg, 0.2 mmol, 2 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13) and stirred at rt in the glovebox. After the time indicated, a small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). The NMR tube was removed from the glovebox and ^1H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of 1-(((2-ethylhexyl)oxy)methyl)-2-(trifluoromethyl)benzene (**3-46**), 1-(bis((2-ethylhexyl)oxy)methyl)-2-(trifluoromethyl)benzene (**3-47**), and the amount of remaining 1-table methyl-2-(trifluoromethyl)benzene (**3-45**). The results are summarized in Table 2A-6 below and in Figure 2A-10 above. Additionally, a representative example ^1H NMR spectrum for the crude reaction solution is shown in Figure 2A-11 to illustrate how the yield of each compound was determined.

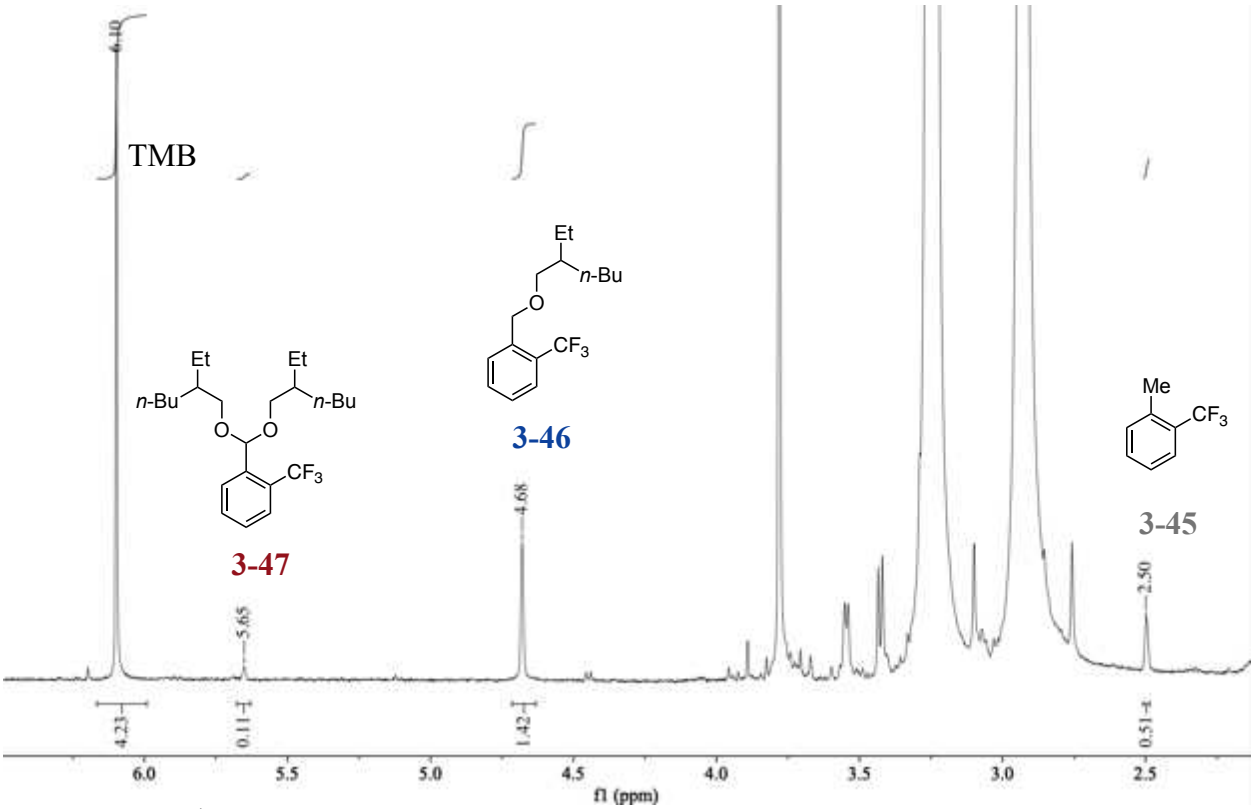


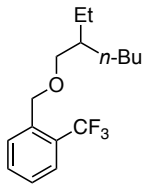
Figure 2A-11. [1]H NMR spectral window of the crude reaction solution from the 60 min time point from the reaction profile analysis study of **3-45**. 1,3,5-Trimethoxybenzene internal standard (23.7 mg, 0.13 mmol, signal at 6.09 ppm calibrated to 4.23 for 0.1 mmol scale reaction) was used to determine the yield of 1-(((2-ethylhexyl)oxy)methyl)-2-(trifluoromethyl)benzene (**3-46**, 72% yield), 1-(bis((2-ethylhexyl)oxy)methyl)-2-(trifluoromethyl)benzene (**3-47**, 11% yield), and the amount of remaining 1-methyl-2-(trifluoromethyl)benzene (**3-45**, 12% yield).

Time (min)	3-46	3-47	3-45	Time (min)	3-46	3-47	3-45
5	27%	0%	73%	180	66%	19%	10%
15	53%	0%	47%	240	64%	20%	7%
30	65%	5%	30%	300	59%	23%	7%
45	70%	8%	22%	360	48%	28%	6%
60	72%	11%	17%	480	38%	34%	5%
120	72%	16%	12%	1440	27%	42%	3%

Table 2A-6. Numerical results for the reaction profile analysis of **3-45**.

(b) Synthesis of 1-(((2-ethylhexyl)oxy)methyl)-2-(trifluoromethyl)benzene (3-46)

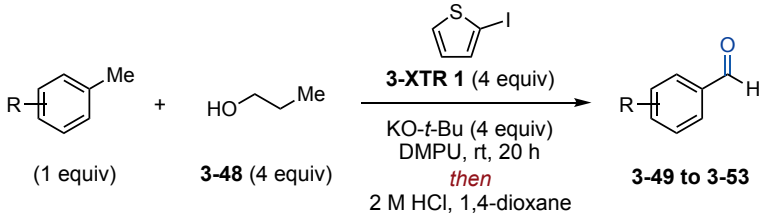
1-(((2-ethylhexyl)oxy)methyl)-2-(trifluoromethyl)benzene (3-46)



The title product was prepared using modified GP1, where the reaction was stirred for 1 hr instead of 15 hr to avoid formation of the acetal side product. Thus, 1-methyl-2-(trifluoromethyl)benzene (160.1 mg, 1 mmol, 1 equiv), 2-ethylhexan-1-ol (260.5 mg, 2 mmol, 2 equiv), 2-iodo-3-phenylbenzo[*b*]thiophene (672.4 mg, 2 mmol, 2 equiv), NaO-*t*-Bu (192.2 mg, 2 mmol, 2 equiv), and anhydrous DMPU (4.0 mL) were added as described. A small aliquot of the organic layer was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, CDCl3) was used to determine the yield of the benzyl etherified product (62% yield). The product was purified *via* silica gel chromatography (100% hexanes) to afford the title compound as a colorless oil (122.0 mg, 0.42 mmol, 42% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ7.72 (d, J = 7.7 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 4.68 (s, 2H), 3.43 (d, J = 5.8 Hz, 2H), 1.58 (dd, J = 11.0, 4.9 Hz, 1H), 1.52 – 1.20 (m, 8H), 0.98 – 0.80 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.1, 132.0, 128.7, 127.4 (q, J = 30.5 Hz), 127.2, 125.7 (q, J = 5.7 Hz), 124.6 (q, J = 274.0 Hz), 73.9, 69.0, 68.9, 68.9, 68.9, 40.0, 30.8, 29.3, 24.1, 23.3, 14.2, 11.2. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -60.1. **IR** (neat, cm^{-1}) 2560, 2930, 2860, 1457, 1312, 1162, 1118, 1059, 1037. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{16}H_{24}F_3O]^+$ = 289.1774, 289.1756 found. **Note:** The title product is moderately volatile and led to reduced isolated yield.

A2.12. General Procedure for Selective Methylarene Oxidation to Aldehydes

The general procedure for 1 mmol scale isolation reactions was developed using a standard manifold Schlenk line.

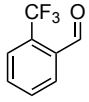


General Procedure for Selective Methylarene Oxidation to Aldehydes (GP3): Open to air, an 8 mL oven-dried vial (Thermo Fischer Scientific, #033405P) was charged with a magnetic stir bar and the following liquid reagents: 2-iodothiophene (840.2 mg, 4 mmol, 4 equiv), propan-1-ol (240.4 mg, 4 mmol, 4 equiv), and alkylarene substrate (if liquid, 1 mmol, 1 equiv). The vial was sealed with a screw cap (Thermo Fisher Scientific, #03392A) lined with a PTFE septum (Thermo Fisher Scientific, #B799515), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 on a manifold Schlenk line. The solid reagents were then charged into a separate 8 mL oven-dried vial (Thermo Fischer Scientific, #033405P): KO-*t*-Bu (448.8 mg, 4 mmol, 4 equiv), and alkylarene substrate (if solid, 1 mmol, 1 equiv). This vial was sealed with a screw cap (Thermo Fisher Scientific, #03392A) lined with a PTFE septum (Thermo Fisher Scientific, #B799515), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 on a manifold Schlenk line. Anhydrous DMPU (4.0 mL, 0.25 M) was added to the vial containing the liquid

reagents and the entire contents were promptly transferred to the vial containing the solid reagents *via* a syringe under N_2. The reaction vial was stirred under N_2 for 15 h at rt. The reaction mixture was allowed to cool to rt and 2 M HCl (10 mL) and 1,4-dioxane (10 mL) were added to the reaction vial open to air. The reaction vial was placed into a preheated 60 °C silicon oil bath and the mixture was stirred for 30 min. The reaction mixture was allowed to cool to rt and subsequently transferred into a separatory funnel containing H_2O (40 mL). The aqueous mixture was then extracted with EtOAc (3 x 40 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo*. The crude material was purified *via* silica gel chromatography.

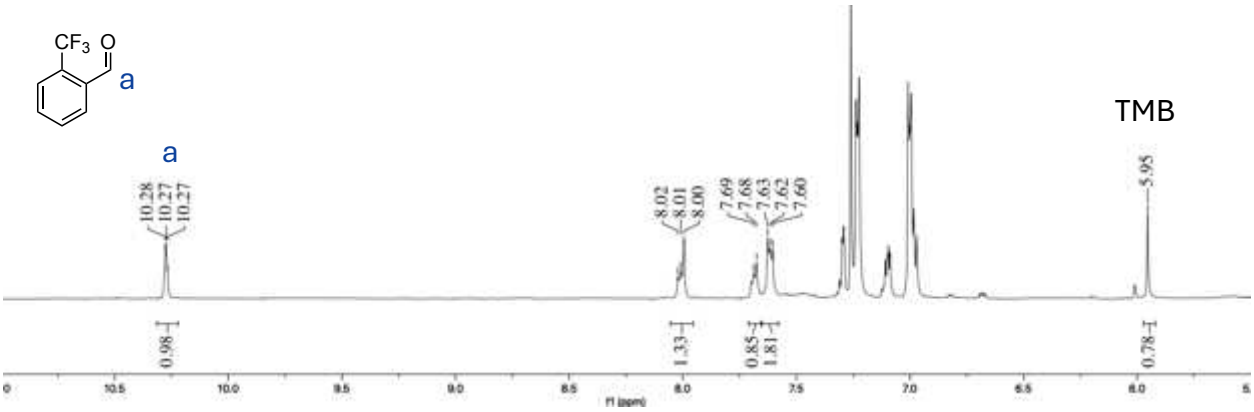
A2.13. Characterization Data of Aldehyde Products

2-(trifluoromethyl)benzaldehyde (3-49)



The title product was prepared according to GP3 using 1-methyl-2-(trifluoromethyl)benzene (160.1 mg, 1 mmol, 1 equiv), propan-1-ol (240.4 mg, 4 mmol, 4 equiv), 2-iodothiophene (840.2 mg, 4 mmol, 4 equiv), KO-*t*-Bu (448.8 mg, 4 mmol, 4 equiv), and anhydrous DMPU (4.0 mL). The yield was determined by ^{1}H NMR due to the volatility of the product. 1,3,5-Trimethoxybenzene (43.9 mg, 0.26 mmol, 0.26 equiv) was added as the internal standard for ^{1}H NMR analysis (98% yield). A commercial standard of the title product (Ambeed, #A546661) was added into the crude sample to confirm the identity of the title product by ^{1}H NMR spectroscopy (see Figure 2A-12 below).

(a) Crude ^{1}H NMR spectrum of the benzylic C–H Oxidation of **3-45**



(b) ^{1}H NMR of the reaction solution from the benzylic C–H oxidation of **3-45** spiked with commercial standard

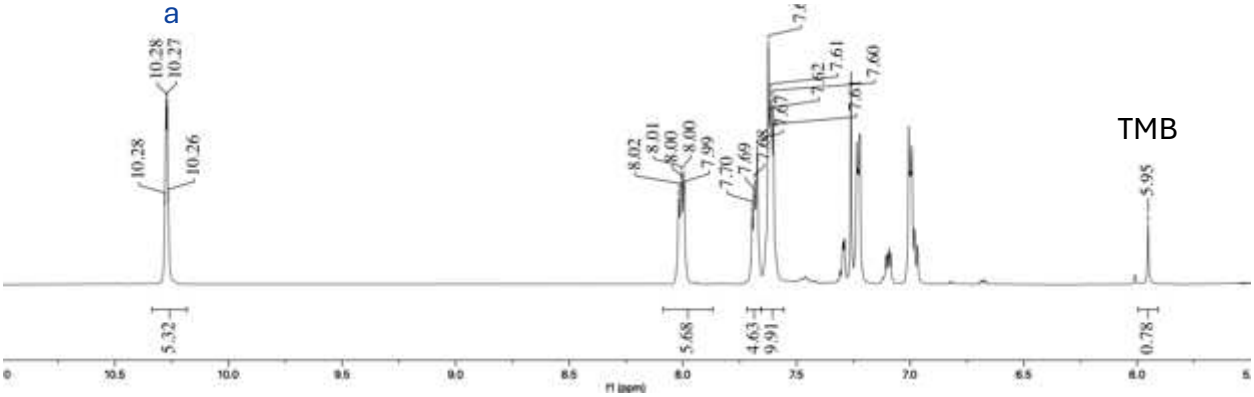
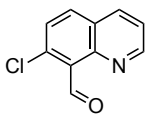


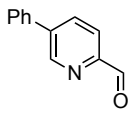
Figure 2A-12. ^{1}H NMR spectral window of the crude reaction solution of the benzylic C–H oxidation of **3-45** (12a). 1,3,5-Trimethoxybenzene internal standard (43.9 mg, 0.36 mmol, signal at 6.09 ppm calibrated to 0.78 for 1 mmol scale reaction) was used to determine the yield of the 2-(trifluoromethyl)benzaldehyde (**3-49**, 98% yield). ^{1}H NMR spectral window of the crude reaction solution of the benzylic C–H oxidation of **3-45** spiked with commercial standard of **3-49** (12b).

7-chloroquinoline-8-carbaldehyde (3-50)



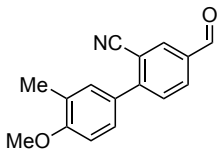
The title product was prepared using modified GP3 where the aqueous layer in the extraction step was adjusted to pH 7 with 1 M NaOH before EtOAc was added. Thus, 7-chloro-8-methylquinoline (177.0 mg, 1 mmol, 1 equiv), propan-1-ol (240.4 mg, 4 mmol, 4 equiv), 2-iodothiophene (840.2 mg, 4 mmol, 4 equiv), KO-*t*-Bu (448.8 mg, 4 mmol, 4 equiv), and anhydrous DMPU (4.0 mL) were used according to the general procedure. The product was purified *via* silica gel chromatography (10% to 40% EtOAc/hexanes) to afford the title compound as a white solid (99.6 mg, 0.59 mmol, 59% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.34 (d, *J* = 0.5 Hz, 1H), 9.03 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.52 (dd, *J* = 8.3, 4.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.3, 151.8, 148.5, 136.3, 136.1, 133.0, 129.8, 129.5, 126.9, 122.1. The spectroscopic data is consistent with a previous report.[10]

5-phenylpicolinaldehyde (3-51)



The title product was prepared according to GP3 using 2-methyl-5-phenylpyridine (169.2 mg, 1 mmol, 1 equiv), propan-1-ol (240.4 mg, 4 mmol, 4 equiv), 2-iodothiophene (840.2 mg, 4 mmol, 4 equiv), KO-*t*-Bu (448.8 mg, 4 mmol, 4 equiv), and anhydrous DMPU (4.0 mL). The product was purified *via* silica gel chromatography (10% EtOAc/hexanes) to afford the title compound as a white solid (94.7 mg, 0.52 mmol, 52% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.95 (t, *J* = 1.5 Hz, 1H), 7.99 (t, *J* = 1.7 Hz, 2H), 7.62 – 7.55 (m, 2H), 7.48 – 7.37 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.2, 151.7, 148.9, 140.9, 136.7, 135.3, 129.5, 129.3, 127.6, 122.0. The spectroscopic data is consistent with a previous report.[11]

4-formyl-4'-methoxy-3'-methyl-[1,1'-biphenyl]-2-carbonitrile (3-52)



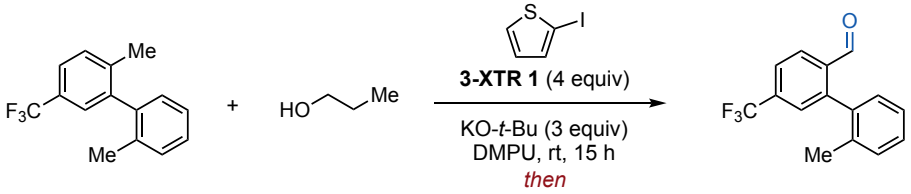
The title product was prepared according to GP3 using 4'-methoxy-3',4-dimethyl-[1,1'-biphenyl]-2-carbonitrile (237.3 mg, 1 mmol, 1 equiv), propan-1-ol (240.4 mg, 4 mmol, 4 equiv), 2-iodothiophene (840.2 mg, 4 mmol, 4 equiv), KO-*t*-Bu (448.8 mg, 4 mmol, 4 equiv), and anhydrous DMPU (4.0 mL). The product was purified *via* silica gel chromatography (20% EtOAc/hexanes) to afford the title compound as a colorless oil (170.4 mg, 0.68 mmol, 68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.23 (d, J = 1.7 Hz, 1H), 8.10 (dd, J = 8.1, 1.7 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.48 (dd, J = 8.5, 2.5 Hz, 1H), 7.39 (dd, J = 2.4, 0.9 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 3.91 (s, 3H), 2.30 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 189.8, 159.3, 150.8, 135.6, 134.7, 132.9, 131.1, 130.8, 128.9, 127.8, 127.7, 118.1, 112.0, 110.2, 55.6, 16.4. **IR** (neat, cm^{-1}) 2872, 2360, 2230, 1703, 1601, 1555, 1253, 1141, 1033. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{16}H_{14}NO_2]^+$ = 252.1019, 252.1000 found.

Verification of regioselectivity: HSQC (Heteronuclear Single Quantum Coherence) and HMBC (Heteronuclear Multiple Bond Correlation) 2D NMR experiments were used to determine the regioselectivity of benzylic C–H oxidation for **3-52**. First, the HSQC experiment was used to correlate the chemical shifts of key ^{1}H NMR signals to the ^{13}C NMR signal of their directly attached carbons. Using this information in tandem with an HMBC experiment, it was determined that the ^{1}H NMR signal corresponding to the aldehydic C–H bond δ 10.05 (s, 1H) correlates with the aromatic ^{13}C NMR signals δ 135.6 and 132.9. Alternatively, if the other methyl peak had been substituted, the aldehydic C–H bond ^{1}H NMR signal would correlate with the aromatic ^{13}C NMR signals at δ 130.8. See spectra in Section 17.

14. Multigram Scale Syntheses and Functional Group Derivatizations of 3-53

(a) Multigram Scale Syntheses of 3-53

2'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde (3-53)



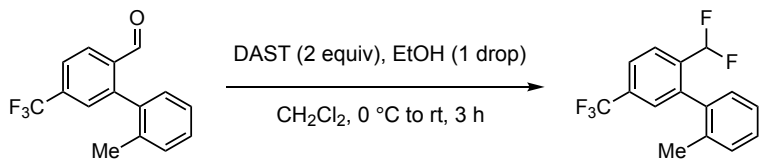
Procedure: An oven-dried 250 mL round bottom flask (Flask A) equipped with a magnetic stir-bar was charged with KO-*t*-Bu (6.73 g, 59.9 mmol, 3 equiv). The flask was fitted with a reflux condenser and sealed with a rubber septum (Chemglass, Product #CG-3022-08). The septum was pierced with a needle connected to a manifold Schlenk line, evacuated and backfilled three times with N_2, and then left under positive pressure of N_2. Concurrently, an oven-dried 250 mL round bottom flask (Flask B) was charged with 2,2'-dimethyl-5-(trifluoromethyl)-1,1'-biphenyl (5.0 g, 20 mmol, 1 equiv), propan-1-ol (4.8 g, 79.9 mmol, 4 equiv), and 2-iodothiophene (16.8 g, 79.9 mmol, 4 equiv). The 250 mL flask was sealed with a rubber septum (Chemglass, Product #CG-3022-08), pierced with a needle connected to a manifold Schlenk line, evacuated and backfilled with N_2 three times, and then left under positive pressure of N_2. DMPU (80 mL, 0.25 M) was then charged into

Flask B. Next, the contents of the Flask B were transferred to Flask A *via* syringe; no exotherm was detected. The reaction mixture was stirred for 15 h at rt under positive pressure of N_2. The reaction mixture was quenched slowly with H_2O (50 mL) and poured into a separatory funnel containing H_2O (50 mL). The aqueous mixture was extracted with PhMe (3 x 100 mL). The organic layers were combined, washed with H_2O (3 x 100 mL), and then dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo.* This material charged into an oven-dried 250 mL flask and then suspended in 1,4-dioxane (50 mL) and 2M HCl (50 mL). The flask was sealed with a rubber septum, a needle connected to N_2 was inserted, and then the flask was placed into a preheated 60 °C silicon oil bath and the then mixture was stirred for 30 min. Next, the reaction mixture was allowed to cool to rt and subsequently transferred into a separatory funnel containing H_2O (10 mL). The aqueous mixture was then extracted with EtOAc (3 x 50 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo*. The crude material was purified *via* silica gel chromatography (0% to 2% to 4% EtOAc/hexanes) to give the title compound as a colorless liquid (4.8 g, 18.2 mmol, 92% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.79 – 7.72 (m, 1H), 7.60 (d, J = 1.7 Hz, 1H), 7.43 – 7.27 (m, 3H), 7.20 (dd, J = 7.4, 1.4 Hz, 1H), 2.11 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.2, 146.1, 136.3, 136.2, 136.1, 135.0 (q, J = 32.3 Hz), 130.5, 130.2, 129.1, 128.0 (q, J = 3.6 Hz), 127.9, 126.2, 124.8 (q, J = 3.6 Hz), 123.6 (q, J = 273.5 Hz), 20.0. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.0. **IR** (neat, cm^{-1}) 3067, 2871, 2360, 2231, 1698, 1601, 1412, 1334, 1270, 1130, 770. **HRMS** (DART) $[M-H]^-$ calcd. for $[C_{15}H_{10}F_3O]^-$ = 263.0689, 263.0667 found.

Verification of regioselectivity: HSQC (Heteronuclear Single Quantum Coherence), HMBC (Heteronuclear Multiple Bond Correlation), and COSY (homonuclear COrrelation SpectroscopY) 2D NMR experiments were used to determine the regioselectivity of benzylic C–H oxidation for **3-53**. First, the HSQC experiment was used to correlate the chemical shifts of key ^{1}H NMR signals to the ^{13}C NMR signal of their directly attached carbons. Using this information in tandem with an HMBC experiment, it was determined that the ^{1}H NMR signal corresponding to the aldehydic C–H bond δ 9.79 (s, 1H) correlates with the aromatic ^{13}C NMR signal δ 127.9 which, in turn, correlates to the carbon adjacent to the trifluoromethyl substituent (i.e., ^{13}C NMR signal δ 127.9 correlates with δ 124.8 (q, J = 3.6 Hz) signal). The COSY experiment confirms that the two most deshielded doublets correlate and are on the trifluoromethyl substituted ring. Overall, these experiments confirms that the methyl on the aryl ring containing the trifluoromethyl group is functionalized. See spectra in Section 17.

(b) Functional Group Derivatizations of 3-53

2-(difluoromethyl)-2'-methyl-5-(trifluoromethyl)-1,1'-biphenyl (3-54)

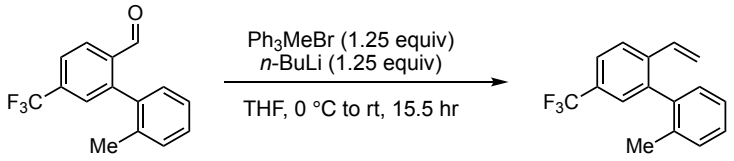


3-53 (1 equiv) **3-54**, 67% yield

Procedure: An oven-dried 8 mL vial (Thermo Fischer Scientific, #033405P) was charged with a magnetic stir bar, 2'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde (66.0 mg, 0.25

mmol, 1 equiv) and anhydrous DCM (0.2 mL). The solution was cooled to 0 °C using an ice water bath, then a solution of *N*,*N*-diethyl-1,1,1-trifluoro-λ4-sulfanamine (81.0 mg, 0.5 mmol, 2 equiv) and DCM (0.2 mL) was added dropwise. A drop of ethanol was then added and the solution was warmed to rt and stirred for 3 hr. The reaction solution was quenched slowly with saturated $NaHCO_3$ (2 mL) and poured into a separatory funnel containing H_2O (5 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo.* The crude reaction mixture was then purified *via* a preparatory thin layer chromatography plate (100% hexanes) to yield the title compound as a colorless oil (48.2 mg, 0.17 mmol, 67% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.2 Hz, 1H), 7.76 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.52 (s, 1H), 7.40 – 7.23 (m, 3H), 7.14 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.34 (t, *J* = 54.8 Hz, 1H), 2.07 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.7 (t, *J* = 6.6 Hz), 136.6, 136.2, 135.8 (t, *J* = 23.1 Hz), 132.6 (q, *J* = 34.1 Hz), 130.5, 129.7, 129.0, 127.5 (q, *J* = 3.6 Hz), 126.4 (t, *J* = 5.2 Hz), 126.0, 124.9 (q, *J* = 4.0 Hz), 122.4, 112.3 (t, *J* = 139.5 Hz), 20.2. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.7 (s, 3F), -110.7 (dq, *J* = 54.4, 308.8 Hz, 2F). **IR** (neat, cm^{-1}) 2360, 2230, 1702, 1601, 1417, 1334, 1280, 1251, 1077, 1033. **HRMS** (APGC-TOF) [M+] calcd. for $[C_{15}H_{11}F_5]^+$ = 286.0781, 286.0785 found.

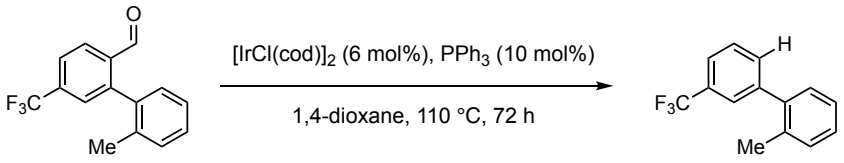
2'-methyl-5-(trifluoromethyl)-2-vinyl-1,1'-biphenyl (3-55)



3-53 (1 equiv) **3-55**, 66% yield

Procedure: An oven-dried 8 mL vial (Thermo Fischer Scientific, #033405P) was charged with a magnetic stir bar and triphenylmethylphosphonium bromide (112.0 mg, 0.31 mmol, 1.25 equiv). The vial was sealed with a screw cap (Thermo Fisher Scientific, #03392A) lined with a PTFE septum (Thermo Fisher Scientific, #B799515), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 on a manifold Schlenk line. THF (1 mL) was added *via* syringe and the vial was cooled to 0 °C in an ice water bath. An *n*-BuLi solution (0.20 mL, 1.6 M in hexanes, 0.31 mmol, 1.25 equiv) was added dropwise and stirred for 30 min. A solution of 2'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde (66.0 mg, 0.25 mmol, 1 equiv) in THF (0.5 mL) was added dropwise *via* syringe and the reaction mixture was warmed to rt and stirred for 15 h. The solution was transferred to a separatory funnel containing H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo.* The crude reaction mixture was then purified *via* a preparatory thin layer chromatography plate (100% hexanes) to yield the title compound as a colorless oil (43.5 mg, 0.17 mmol, 66% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 1H), 7.60 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.43 (s, 1H), 7.34 – 7.23 (m, 3H), 7.12 (dd, *J* = 7.3, 1.5 Hz, 1H), 6.43 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.76 (dd, *J* = 17.5, 0.9 Hz, 1H), 5.24 (dd, *J* = 11.0, 1.0 Hz, 1H), 2.05 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.2, 139.5, 139.3, 136.3, 134.2, 130.2, 129.8, 129.5 (q, *J* = 32.4 Hz), 128.2, 127.0 (q, *J* = 4.0 Hz), 125.9, 125.4, 124.34 (q, *J* = 4.0 Hz), 124.32 (q, *J* = 271.9 Hz), 117.1, 20.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.3. **IR** (neat, cm^{-1}) 2360, 2230, 1702, 1601, 151, 1408, 1333, 1270, 1077, 1022. **HRMS** (APGC-TOF) $[M+H]^+$ calcd. for $[C_{16}H_{14}F_3]^+$ = 263.1048, 263.1050 found.

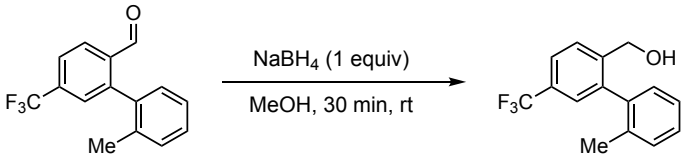
2-methyl-3'-(trifluoromethyl)-1,1'-biphenyl (3-56)



3-53 (1 equiv) **3-56**, 26% yield

Procedure: The title compound was prepared according to a modified literature procedure.[16] An oven-dried 8 mL vial (Thermo Fischer Scientific, #033405P) was charged with a magnetic stir bar, chloro(1,5-cyclooctadiene)iridium(I) dimer ($[IrCl(cod)]_2$, 8.4 mg, 0.006 mmol, 3 mol%), triphenylphosphine (PPh_3, 3.3 mg, 0.012 mmol, 5 mol%), and 1,4-dioxane (0.5 mL). The resulting solution was stirred at rt for 10 min in air. Next, 2'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde (66.0 mg, 0.25 mmol, 1 equiv) was added. The vial was sealed with a screw cap (Thermo Fisher Scientific, #03392A) lined with a PTFE septum (Thermo Fisher Scientific, #B799515) and stirred in an aluminum block preheated to 110 °C for 48 h. The reaction solution was then warmed to rt and charged with the remaining chloro(1,5-cyclooctadiene)iridium(I) dimer ($[IrCl(cod)]_2$, 8.4 mg, 0.006 mmol, 3 mol%) and triphenylphosphine (PPh_3, 3.3 mg, 0.012 mmol, 5 mol%). The reaction mixture was again stirred in an aluminum block preheated to 110 °C for 24 h. The crude reaction mixture was then directly purified *via* a preparatory thin layer chromatography plate (2% EtOAc/hexanes) to yield the title compound as a yellow oil (15.1 mg, 0.06 mmol, 26% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 – 7.59 (m, 2H), 7.56 – 7.50 (m, 2H), 7.33 – 7.21 (m, 4H), 2.27 (s, 3H). The spectroscopic data is consistent with a previous report.[12]

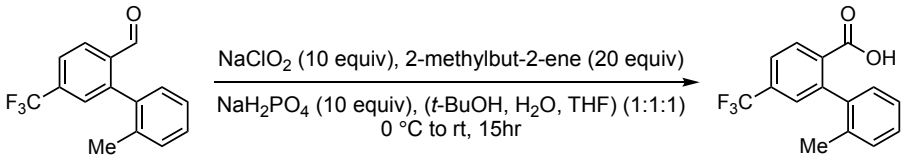
(2'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)methanol (3-57)



3-53 (1 equiv) **3-57**, 93% yield

Procedure: An oven-dried 8 mL vial (Thermo Fischer Scientific, #033405P) was charged with a magnetic stir bar, 2'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde (66.0 mg, 0.25 mmol, 1 equiv) and anhydrous MeOH (0.5 mL, 0.5 M). Next, sodium borohydride (9.5 mg, 0.25 mmol, 1 equiv) was added slowly and the reaction mixture was stirred for 30 min. The solution was transferred to a separatory funnel containing H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo.* The crude reaction mixture was then purified *via* a preparatory thin layer chromatography plate (10% EtOAc/hexanes) to yield the title compound as a colorless oil (62.1 mg, 0.23 mmol, 93% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 1H), 7.66 (dd, J = 8.2, 1.9 Hz, 1H), 7.41 (s, 1H), 7.34 – 7.22 (m, 3H), 7.11 (d, J = 7.3 Hz, 1H), 4.65 – 4.25 (m, 2H), 2.05 (s, 3H), 1.59 (t, J = 5.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.6, 140.8, 138.7, 135.8, 130.4, 129.7 (q, J = 32.8 Hz), 129.2, 128.4, 127.7, 126.5 (q, J = 3.7 Hz), 126.0, 124.6 (q, J = 4.0 Hz), 124.3 (q, J = 271.9 Hz), 62.7, 20.0. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.2. **IR** (neat, cm^{-1}) 3306, 2871, 2360, 2340, 1334, 1163, 1115, 1021, 729. **HRMS** (DART) $[M-H]^-$ calcd. for $[C_{15}H_{12}F_3O]^-$ = 265.0846, 265.0821 found.

2'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid (3-58)



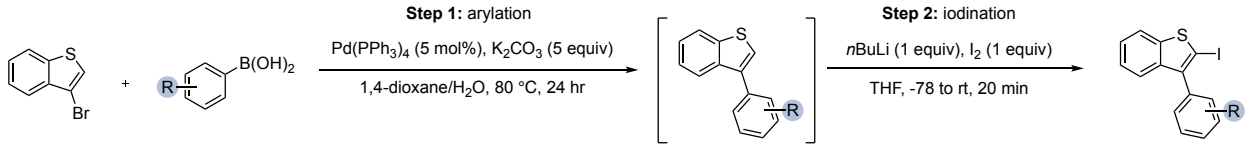
3-53 (1 equiv) **3-58**, 66% yield

Procedure: An oven-dried 8 mL vial (Thermo Fischer Scientific, #033405P) was charged with a magnetic stir bar, 2'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde (66.0 mg, 0.25 mmol, 1 equiv), 2-methylbut-2-ene (351.0 mg, 5 mmol, 20 equiv), *tert*-butanol (0.45 mL), and THF (0.45 mL). The solution was cooled to 0 °C using an ice water bath, then a solution of sodium chlorite (226.0 mg, 2.5 mmol, 10 equiv), NaH_2PO_4 (345.0 mg, 2.5 mmol, 10 equiv) and H_2O (0.45 mL) was added dropwise. The reaction vessel was warmed to rt and stirred for 15 h. The solution was then transferred to a separatory funnel containing H_2O (10 mL). The pH was adjusted to pH 3 with 1 M HCl. The aqueous layer was then extracted with EtOAc (3 x 10 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo.* The crude reaction mixture was then purified *via* a preparatory thin layer chromatography plate (25% EtOAc/hexanes) to yield the title compound as a white solid (43.5 mg, 0.17 mmol, 66% yield). **Mp**: 97-100 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.68 (br s, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.53 (s, 1H), 7.32 – 7.20 (m, 3H), 7.09 (d, J = 7.5 Hz, 1H), 2.08 (d, J = 2.8 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.9, 144.2, 139.7, 135.4, 134.0 (q, J = 32.3 Hz), 132.3, 131.4, 130.0, 128.6, 128.3 (q, J = 3.9 Hz), 128.2, 125.7, 124.2 (q, J = 3.6 Hz), 124.6 (q, J = 273.1 Hz), 20.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.0. **IR** (neat, cm^{-1}) 2542, 1703, 1686, 1406, 1291, 1243, 1168, 1070, 936. **HRMS** (DART) $[M-H]^-$ calcd. for $[C_{15}H_{10}F_3O_2]^-$ = 279.0638, 263.0667 found.

A2.15. Starting Material Syntheses and Characterization

All substrates that are not described below were purchased and used as received. All non-commercial substrates and reagents used are described below.

General Procedure of the X-transfer reagent analogues (2-A3 through 2-A7):



(1 equiv) (1.2 equiv) **2-A3–A7**

Step 1: Arylation of 3-bromobenzo[*b*]thiophene

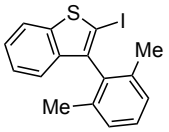
Procedure: Inside an N_2 filled glovebox, a 50 mL round bottom flask was charged with K_2CO_3 (23.5 mmol, 5 equiv), boronic acid (7.1 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (0.14 mmol, 0.03 equiv), 3-bromobenzo[*b*]thiophene (1.0 g, 10.1 mmol, 1 equiv), and 1,4-dioxane (14 mL). The flask was sealed with a rubber septum (Chemglass, #CG-3022-08), removed from the glovebox, and put

under positive pressure of N_2 on a manifold Schlenk line. H_2O (7 mL) was then added *via* syringe and the flask was inserted into a silicon oil bath preheated to 80 °C. The reaction solution was stirred for 24 h and then cooled to rt. The resulting solution was then poured into a separatory funnel containing H_2O (30 mL) and the aqueous layer was extracted with EtOAc (3 x 30 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. The crude reaction mixture was then purified *via* silica gel chromatography to afford the title compounds. This material was used directly in the iodination step.

Step 2: Iodination of 3-arylbenzo[*b*]thiophene analogues

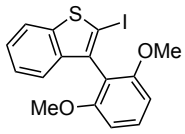
Procedure: An oven-dried 50 mL round bottom flask was charged with a magnetic stir bar and 3-arylbenzo[*b*]thiophene (1 equiv). The flask was sealed with a rubber septum (Chemglass, #CG-3022-08), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 on a manifold Schlenk line. THF (15 mL) was added *via* syringe and the vial was cooled to 0 °C in an ice-water bath. An *n*-BuLi solution (1.6 M in hexanes, 1 equiv) was added dropwise and stirred for 10 min. A solution of iodine (1 equiv) in THF (5 mL) was added dropwise *via* syringe and the reaction mixture was warmed to rt and stirred for 10 min. The solution was transferred to a separatory funnel containing H_2O (30 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was concentrated *in vacuo.* The crude reaction mixture was then purified *via* silica gel chromatography to afford the title compounds. The characterization data for each compound is provided below.

3-(2,6-dimethylphenyl)-2-iodobenzo[*b*]thiophene (2-A3)



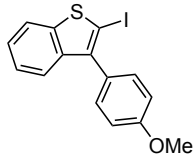
Mp: 80-83 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.16 (m, 6H), 1.99 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.1, 143.3, 138.5, 137.8, 135.1, 128.5, 127.6, 124.8, 124.7, 122.7, 121.8, 81.7, 20.1. **IR** (neat, cm^{-1}) 1772, 1733, 1684, 1559, 1458, 1428, 771, 727. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{16}H_{14}SI]^+$ = 364.9855, 365.0051 found.

3-(2,6-dimethoxyphenyl)-2-iodobenzo[*b*]thiophene (2-A4)



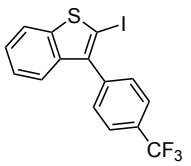
Mp: 106-108 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.87 (m, 1H), 7.48 – 7.28 (m, 6H), 6.73 (d, *J* = 8.4 Hz, 2H), 3.74 (s, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.8, 139.6, 139.4, 129.5, 129.5, 125.5, 123.9, 123.7, 123.5, 122.6, 113.1, 104.3, 56.2. **IR** (neat, cm^{-1}) 1772, 1700, 1653, 1549, 1469, 1428, 1247, 1103, 828, 725. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{16}H_{14}O_2SI]^+$ = 396.9754, 396.9790 found.

2-iodo-3-(4-methoxyphenyl)benzo[*b*]thiophene (2-A5)



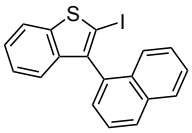
Mp: 94-98 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.35 – 7.26 (m, 2H), 7.12 – 7.03 (m, 2H), 3.92 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 143.8, 142.6, 138.8, 131.3, 128.0, 124.5, 123.0, 121.5, 114.0, 80.6, 55.3. **IR** (neat, cm^{-1}) 1918, 2817, 1675, 1647, 1558, 1490, 1338, 1292. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{15}H_{12}SOI]^+$ = 366.9648, 366.9685 found.

2-iodo-3-(4-(trifluoromethyl)phenyl)benzo[*b*]thiophene (2-A6)



Mp: 60-62 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 3H), 7.60 (d, J = 7.9 Hz, 2H), 7.53 – 7.48 (m, 1H), 7.40 – 7.26 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.1, 141.5, 139.6, 138.5, 130.7, 130.5 (q, J = 32.6 Hz), 125.8 (q, J = 3.9 Hz), 125.03, 125.02, 124.3 (q, J = 272.4 Hz), 122.7, 121.8, 81.4. **IR** (neat, cm^{-1}) 1792, 1750, 1675, 1646, 1521, 1506. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.4. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{15}H_9SF_3I]^+$ = 404.9416, 404.9471 found.

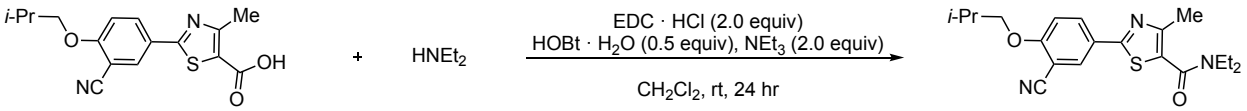
2-iodo-3-(naphthalen-1-yl)benzo[b]thiophene (2-A7)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.93 (m, 2H), 7.86 (d, J = 8.1 Hz, 1H), 7.63 (t, J = 7.7 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.48 – 7.41 (m, 2H), 7.41 – 7.28 (m, 2H), 7.23 – 7.10 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.9, 142.3, 139.8, 133.9, 133.9, 132.1, 129.0, 128.8, 128.5, 126.5, 126.3, 126.1, 125.7, 124.8, 123.4, 121.6, 83.0. The spectroscopic data is consistent with a previous report.[13]

Synthesis of methylarene substrates:

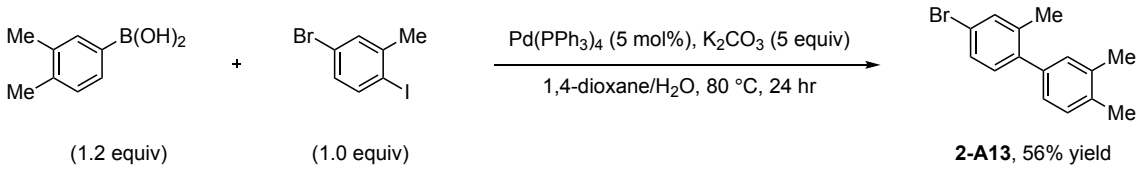
2-(3-cyano-4-isobutoxyphenyl)-*N,N*-diethyl-4-methylthiazole-5-carboxamide (2-A12)



(1.0 equiv) (2.0 equiv) **2-A12**, 37% yield

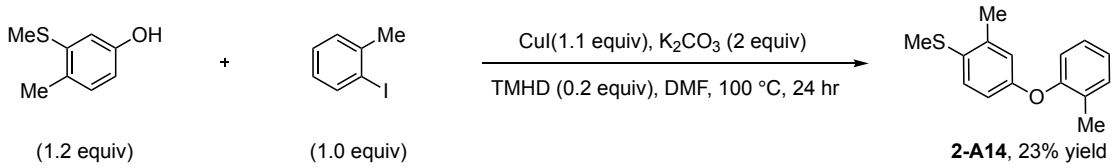
Procedure: Open to air, a 50 mL round bottom flask was charged with a magnetic stir bar, 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid (1.0 g, 3.2 mmol, 1.0 equiv), 1-hydroxybenzotriazole hydrate (242 mg, 1.6 mmol, 0.5 equiv), 1-isopropyl-1*H*-benzo[*d*][1,2,3]triazolets-5-carboxylic acid (1.5 g, 7.9 mmol, 2.5 equiv), *N,N*-diethylamine (0.4 mL, 3.8 mmol, 1.2 equiv), triethylamine (0.9 mL, 6.3 mmol, 2 equiv), and CH_2Cl_2 (12 mL), in successive order. The reaction solution was stirred 24 h at rt. The solution was then transferred to a separatory funnel containing H_2O (50 mL). The organic layer was washed with H_2O (2 x 50 mL) and brine (1 x 30 mL) and then dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (100% EtOAc) yielded the title compound as white solid (437.0 mg, 1.2 mmol, 37% yield). **Mp**: 51-54 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (d, J = 2.3 Hz, 1H), 8.03 (dd, J = 8.8, 2.3 Hz, 1H), 7.00 (d, J = 8.9 Hz, 1H), 3.89 (d, J = 6.5 Hz, 2H), 3.52 – 3.44 (m, 4H), 2.46 (s, 3H), 2.20 (hept, J = 6.7 Hz, 1H), 1.21 (t, J = 7.1 Hz, 6H), 1.08 (d, J = 6.7 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.3, 163.0, 162.2, 152.5, 132.4, 131.9, 126.3, 124.9, 115.7, 112.7, 103.0, 75.8, 28.3, 19.2, 16.3. **IR** (neat, cm^{-1}) 2962, 2937, 2873, 2225, 1618, 1471, 1386, 1277, 1127, 1012. **HRMS** (APGC-TOF) $[M+H]^+$ calcd. for $[C_{20}H_{26}N_3O_2S]^+$ = 372.1746, 372.1756 found.

4-bromo-2,3',4'-trimethyl-1,1'-biphenyl (2-A13)



Procedure: Inside an N_2 filled glovebox, a 100 mL round bottom flask was charged with K_2CO_3 (6.98 g, 50.5 mmol, 5 equiv), (3,4-dimethylphenyl)boronic acid (1.82 g, 12.1 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (584 mg, 0.5 mmol, 0.05 equiv), 4-bromo-1-iodo-2-methylbenzene (3.0 g, 10.1 mmol, 1 equiv), and 1,4-dioxane (27 mL). The flask was sealed with a rubber septum (Chemglass, #CG-3022-08), removed from the glovebox, and put under positive pressure of N_2 on a manifold Schlenk line. H_2O (14 mL) was then added *via* syringe and the flask was inserted into a silicon oil bath preheated to 80 °C. The reaction solution was stirred for 24 h and then cooled to rt. The resulting solution was then poured into a separatory funnel containing H_2O (75 mL) and the aqueous layer was extracted with EtOAc (3 x 60 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (100% hexanes) yielded the title compound as a colorless oil (1.55 g, 5.6 mmol, 56% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 7.11 – 7.08 (m, 2H), 7.04 (d, J = 7.7 Hz), 2.33 (s, 6H), 2.27 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.1, 138.5, 137.8, 136.5, 135.6, 133.0, 131.5, 130.4, 129.6, 128.8, 126.6, 120.9, 20.5, 20.0, 19.6. **IR** (neat, cm^{-1}) 3016, 2918, 1587, 1475, 1446, 1192, 1020, 810. **EA**: Anal. Calcd for $C_{15}H_{15}Br$: C, 65.47; H, 5.49 Found: C, 65.52; H, 5.40.

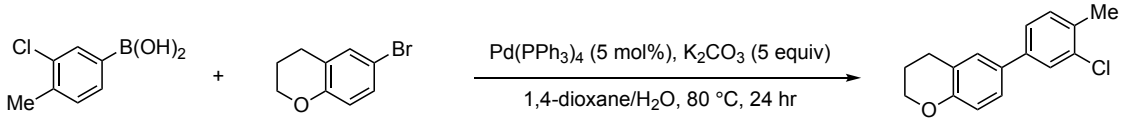
methyl(2-methyl-4-(*o*-tolyloxy)phenyl)sulfane (2-A14)



Procedure: Inside an N_2 filled glovebox, a 20 mL round bottom flask was charged with K_2CO_3 (2.3 g, 11.0 mmol, 2 equiv), 4-methyl-3-(methylthio)phenol (848.0 mg, 5.5 mmol, 1.2 equiv), 1-iodo-2-methylbenzene (1.0 mg, 4.6 mmol, 1 equiv), 2,2,6,6-tetramethyl-3,5-heptanedione (202.7 g, 1.1 mmol, 0.2 equiv), and DMF (27 mL). The flask was sealed with a rubber septum (Chemglass, #CG-3022-08), removed from the glovebox, and put under positive pressure of N_2 on a manifold Schlenk line. The flask was inserted into a silicon oil bath preheated to 100 °C and stirred for 24 h. The reaction mixture was cooled to rt then filtered over a pad of celite. The resulting solution was then poured into a separatory funnel containing H_2O (20 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (1% to 5% EtOAc/hexanes) yielded the title compound as a colorless oil (261.2 mg, 1.07 mmol, 23% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 1H), 7.21 – 7.11 (m, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.78 (s, 1H), 6.74 (d, J = 8.9 Hz, 1H), 2.35 (s, 6H), 2.24 (s, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.0, 154.7, 139.0, 131.6, 130.5, 130.0,

128.5, 127.2, 124.0, 119.6, 119.3, 115.6, 20.4, 16.7, 16.3. **IR** (neat, cm^{-1}) 2920, 2857, 1583, 1489, 1473, 1234, 1159, 1124. **HRMS** (APGC-TOF) [M+] calcd. for $[C_{15}H_{16}OS]^+$ = 244.0922, 244.0919 found.

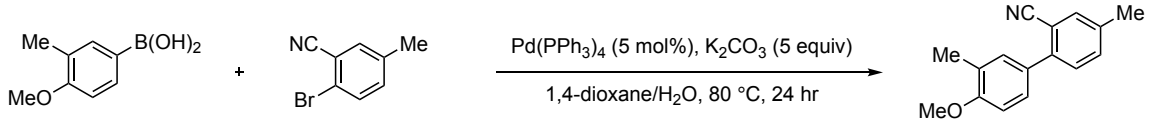
6-(3-chloro-4-methylphenyl)chromane (2-A15)



(1.2 equiv) (1.0 equiv) **2-A15**, 73% yield

Procedure: Inside an N_2 filled glovebox, a 50 mL round bottom flask was charged with K_2CO_3 (1.95 g, 14.1 mmol, 3 equiv), (3-chloro-4-methylphenyl)boronic acid (960.0 mg, 5.6 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (542.0 mg, 0.47 mmol, 0.1 equiv), 6-bromochromane (1.0 g, 4.7 mmol, 1 equiv), and 1,4-dioxane (12.5 mL). The flask was sealed with a rubber septum (Chemglass, #CG-3022-08), removed from the glovebox, and put under positive pressure of N_2 on a manifold Schlenk line. H_2O (6.25 mL) was then added *via* syringe and the flask was inserted into a silicon oil bath preheated to 80 °C. The reaction solution was stirred for 24 h and then cooled to rt. The resulting solution was then poured into a separatory funnel containing H_2O (25 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (1% EtOAc/hexanes) yielded the title compound as a white solid (879.9 mg, 3.4 mmol, 73% yield). **Mp**: 68-70 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 1.9 Hz, 1H), 7.37 – 7.22 (m, 4H), 6.86 (d, *J* = 8.4 Hz, 1H), 4.23 (t, *J* = 5.1 Hz, 2H), 2.86 (t, *J* = 6.5 Hz, 2H), 2.41 (s, 3H), 2.10 – 2.00 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.9, 140.4, 134.8, 134.1, 131.9, 131.3, 128.4, 127.2, 125.9, 124.9, 122.6, 117.3, 66.7, 25.2, 22.5, 19.8. **IR** (neat, cm^{-1}) 2955, 2842, 1609, 1509, 1420, 1286, 1131, 1046, 823. **HRMS** (APGC-TOF) [M+] calcd. for $[C_{16}H_{16}OCl]^+$ = 259.0890, 259.0884 found.

4'-methoxy-3',4-dimethyl-[1,1'-biphenyl]-2-carbonitrile (2-A16)

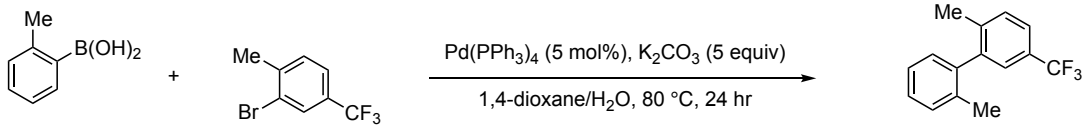


(1.2 equiv) (1.0 equiv) **2-A16**, 17% yield

Procedure: Inside an N_2 filled glovebox, a 50 mL round bottom flask was charged with K_2CO_3 (3.52 g, 25.5 mmol, 5 equiv), (4-methoxy-3-methylphenyl)boronic acid (1.02 g, 6.1 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (294.7 mg, 0.3 mmol, 0.05 equiv), 2-bromo-5-methylbenzonitrile (1.0 g, 5.1 mmol, 1 equiv), and 1,4-dioxane (14 mL). The flask was sealed with a rubber septum (Chemglass, #CG-3022-08), removed from the glovebox, and put under positive pressure of N_2 on a manifold Schlenk line. H_2O (7 mL) was then added *via* syringe and the flask was inserted into a silicon oil bath preheated to 80 °C. The reaction solution was stirred for 24 h and then cooled to rt. The resulting solution was then poured into a separatory funnel containing H_2O (25 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in*

vacuo. Silica gel chromatography (100% hexanes) yielded the title compound as a white solid (238.7 mg, 5.1 mmol, 17% yield). **Mp**: 40-42 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.84 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.43 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.34 (dd, *J* = 2.5, 0.9 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 2.41 (s, 3H), 2.28 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.2, 142.8, 137.1, 134.0, 133.8, 131.1, 130.2, 129.9, 127.4, 127.1, 119.4, 110.9, 110.0, 55.5, 20.8, 16.4. **IR** (neat, cm^{-1}) 3011, 2924, 2223, 1486, 1432, 1240, 1028, 842, 807. **HRMS** (DART) $[M+H]^+$ calcd. for $[C_{16}H_{16}NO]^+$ = 238.1226, 238. 1222 found.

2,2'-dimethyl-5-(trifluoromethyl)-1,1'-biphenyl (2-A17)



(1.2 equiv) (1.0 equiv) **2-A17**, 77% yield

Procedure: Inside an N_2 filled glovebox, a 250 mL round bottom flask was charged with K_2CO_3 (28.9 g, 209.2 mmol, 5 equiv), *o*-tolylboronic acid (6.8 g, 50.2 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (1.45 g, 1.3 mmol, 0.03 equiv), 2-bromo-1-methyl-4-(trifluoromethyl)benzene (10.0 g, 41.8 mmol, 1 equiv), and 1,4-dioxane (111 mL). The flask was sealed with a rubber septum (Chemglass, #CG-3022-08), removed from the glovebox, and put under positive pressure of N_2 on a manifold Schlenk line. H_2O (55.5 mL) was then added *via* syringe and the flask was inserted into a silicon oil bath preheated to 80 °C. The reaction solution was stirred for 24 h and then cooled to rt. The resulting solution was then poured into a separatory funnel containing H_2O (250 mL) and the aqueous layer was extracted with EtOAc (3 x 200 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (100% hexanes) yielded the title compound as a colorless liquid (8.09 g, 32.3 mmol, 77% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 10.1 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.32 – 7.21 (m, 3H), 7.09 (d, *J* = 8.0 Hz, 1H), 2.12 (s, 3H), 2.05 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.3, 140.3 (q, *J* = 1.4 Hz), 140.2, 135.8, 130.4, 130.2, 129.3, 128.2 (q, *J* = 32.3 Hz), 127.9, 126.3 (q, *J* = 3.8 Hz), 125.9, 124.5 (q, *J* = 251.5 Hz), 124.1 (q, *J* = 3.6 Hz), 20.0, 19.9. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.0. **IR** (neat, cm^{-1}) 1408, 1332, 1250, 1164, 1116, 1073, 904, 619. **EA**: Anal. Calcd for $C_{15}H_{13}F_3$: C, 71.99; H, 5.24 Found: C, 71.85; H, 5.13.

A2.16. References

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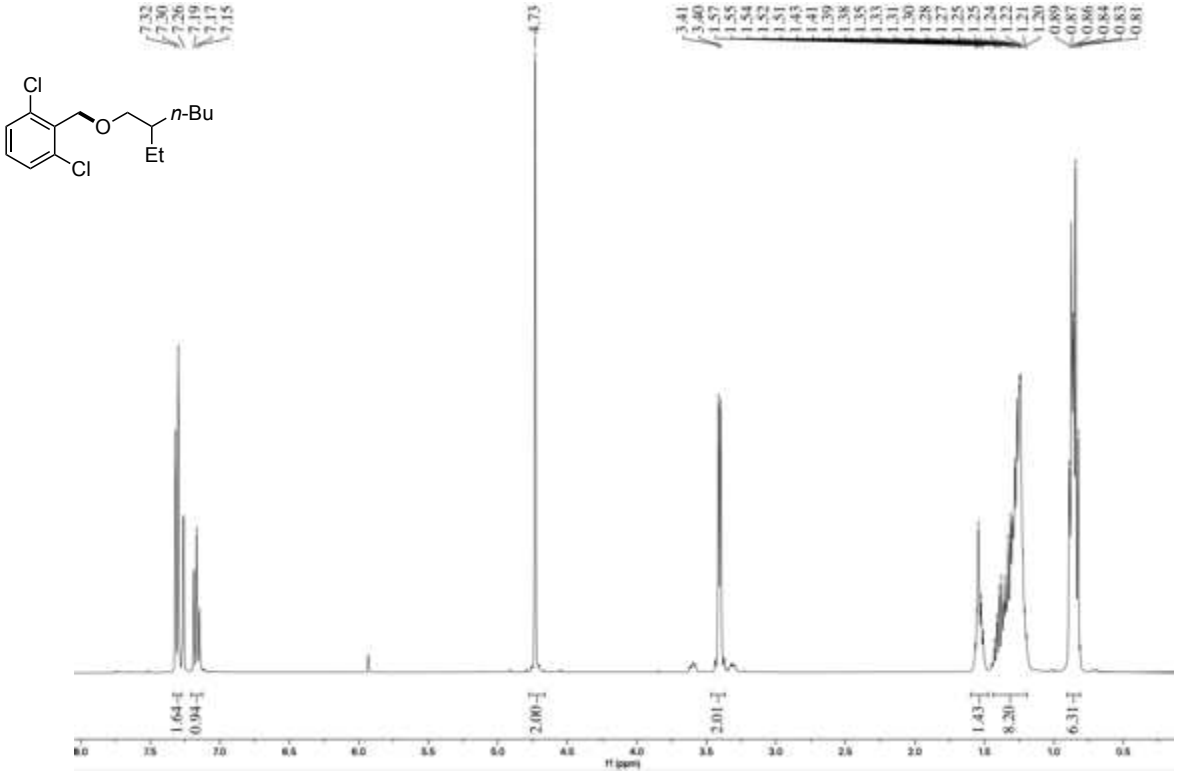
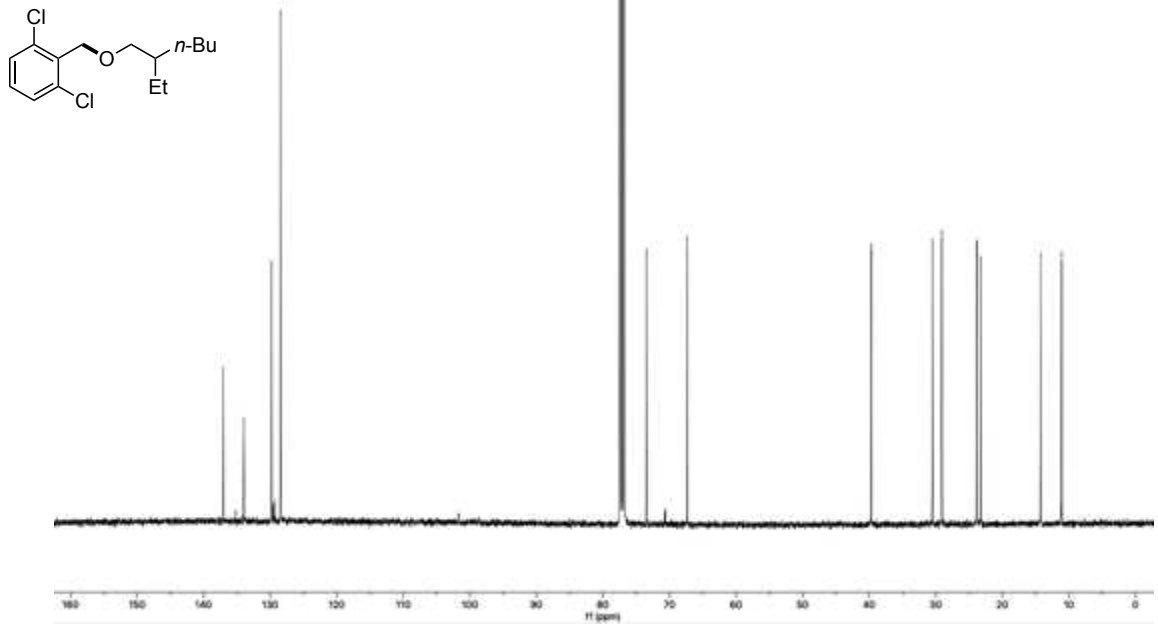
A2.17. NMR Spectra



^{1}H NMR spectrum of **3-3** (400 MHz, $CDCl_3$)



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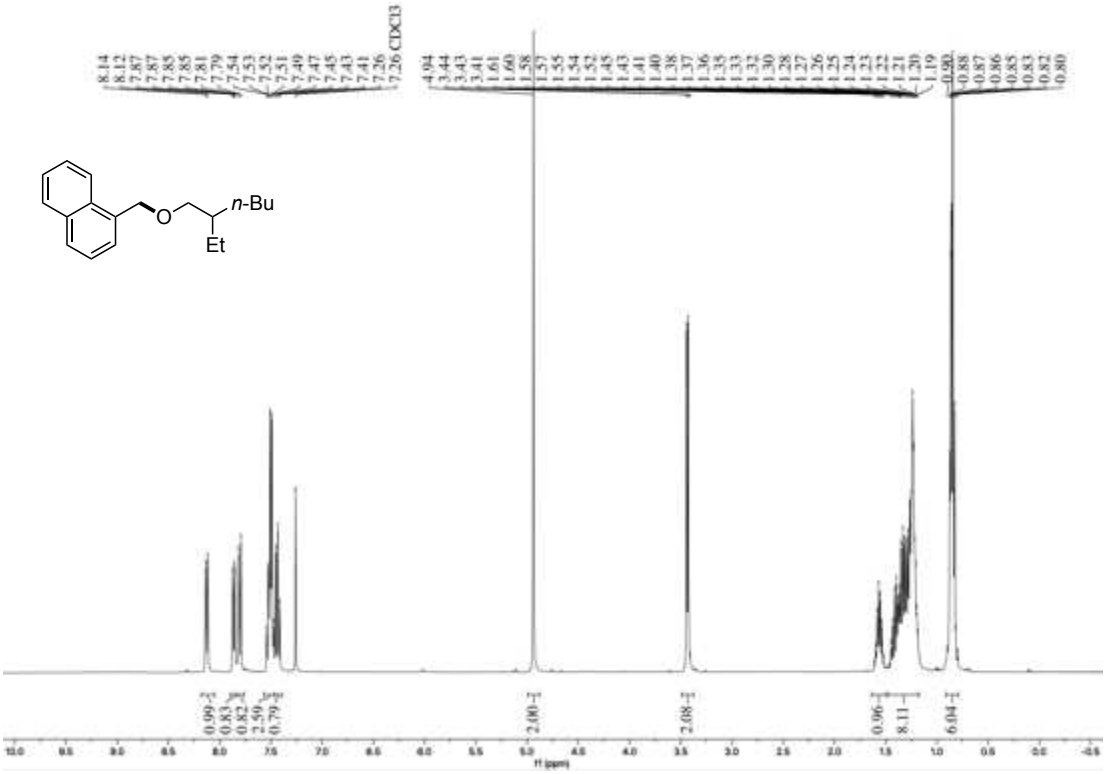

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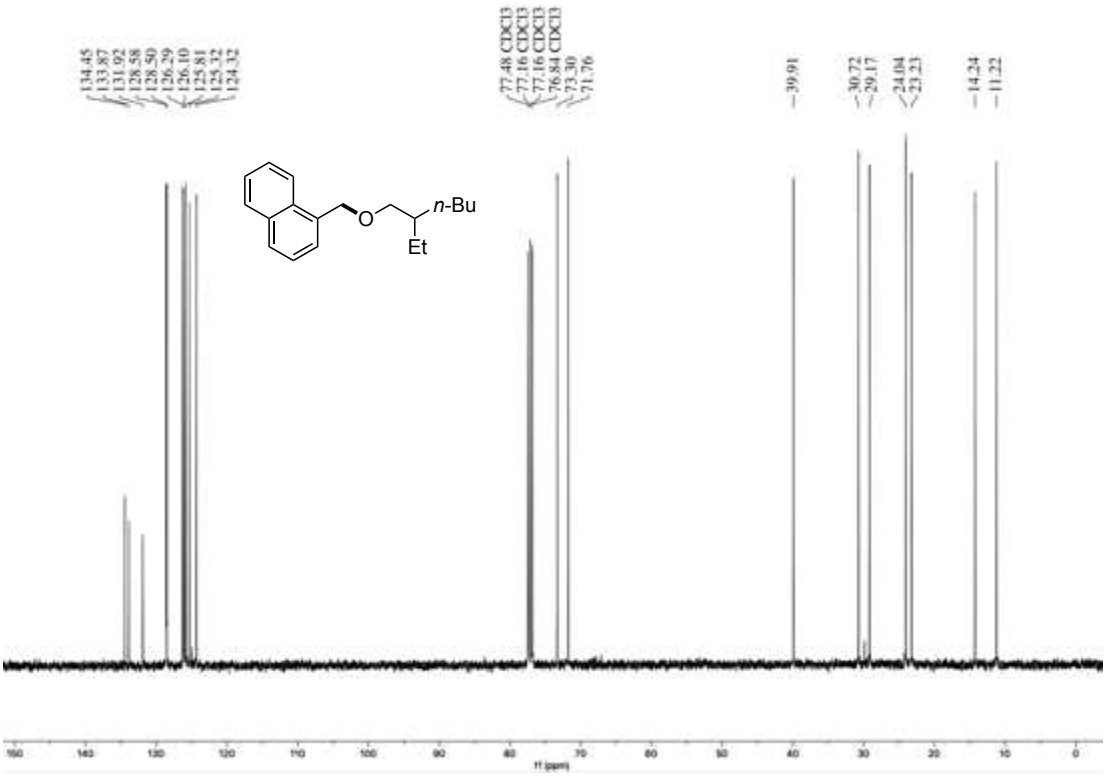
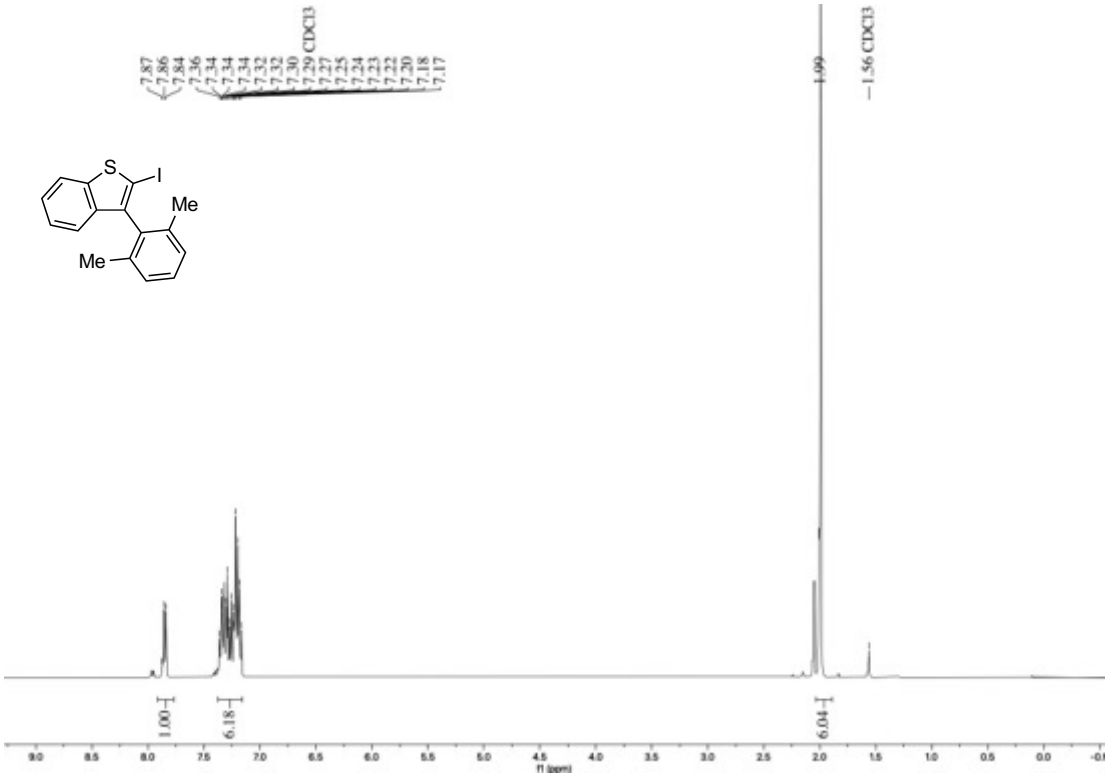


^{13}C NMR spectrum of **3-5** (101 MHz, $CDCl_3$)



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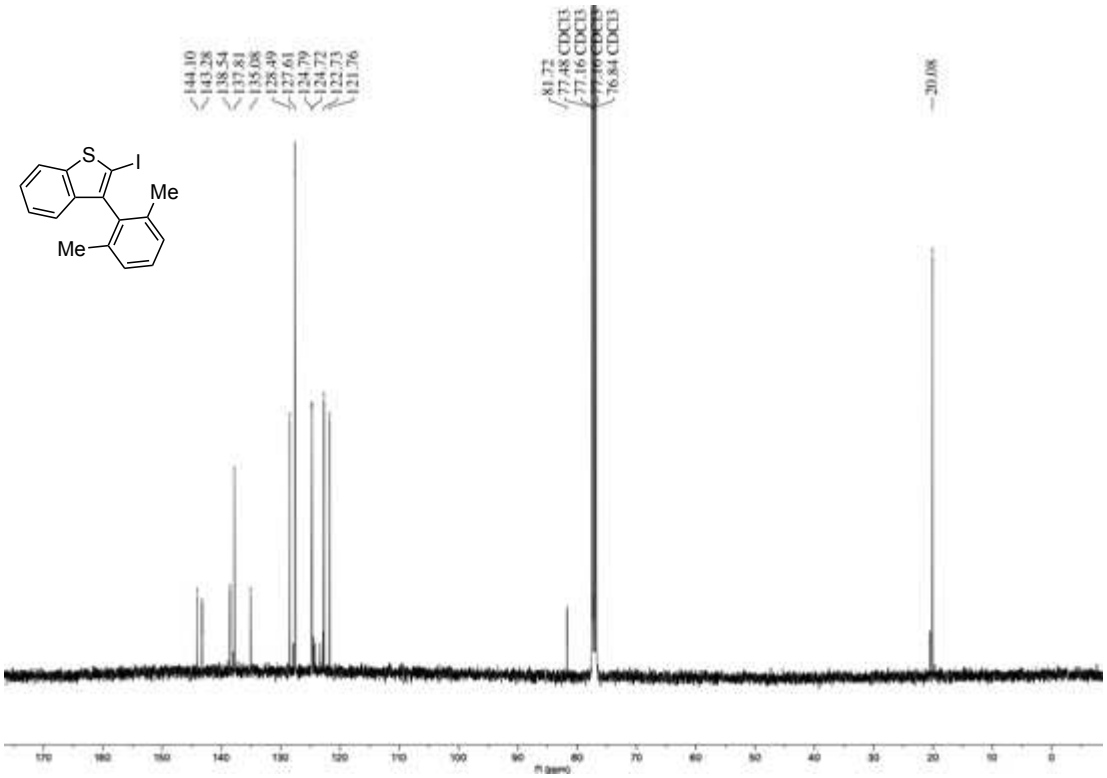
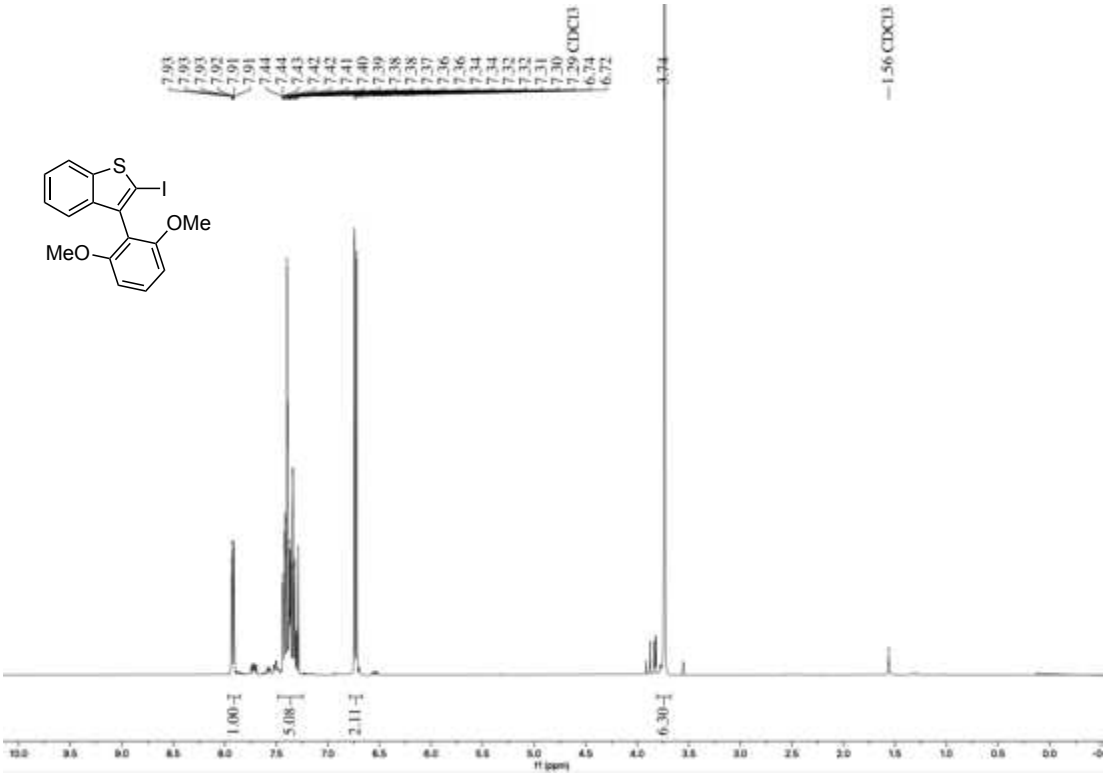


^{13}C NMR spectrum of **2-A3** (101 MHz, $CDCl_3$)



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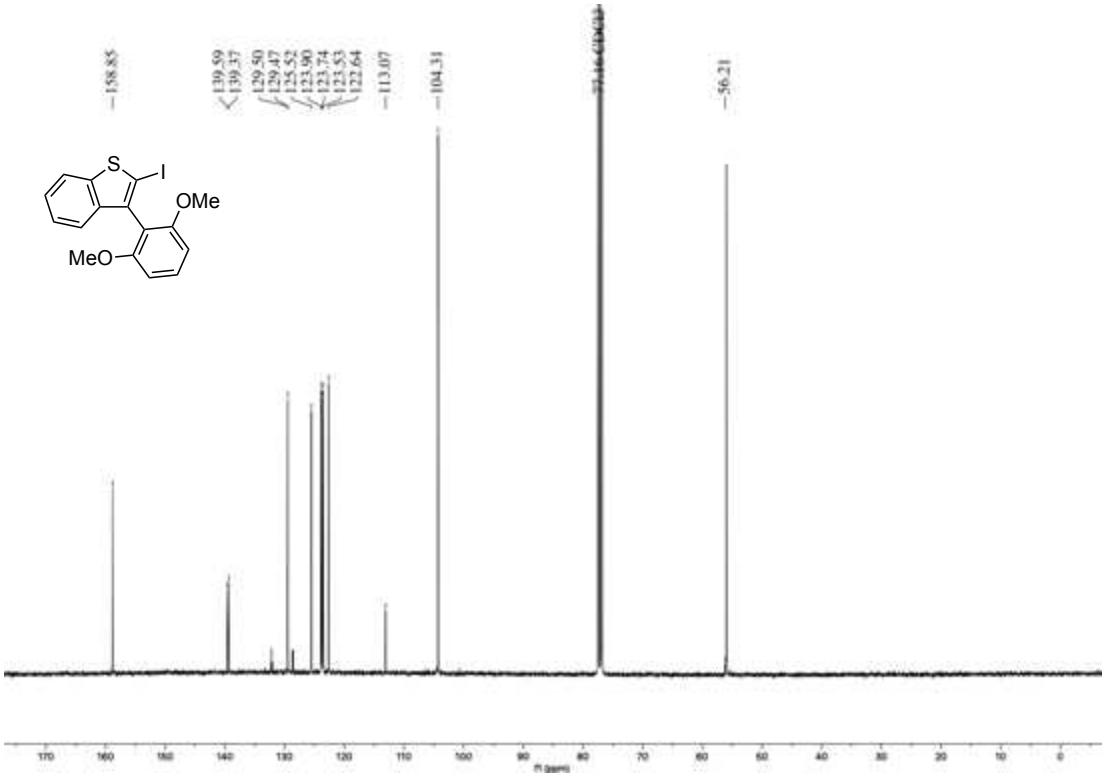

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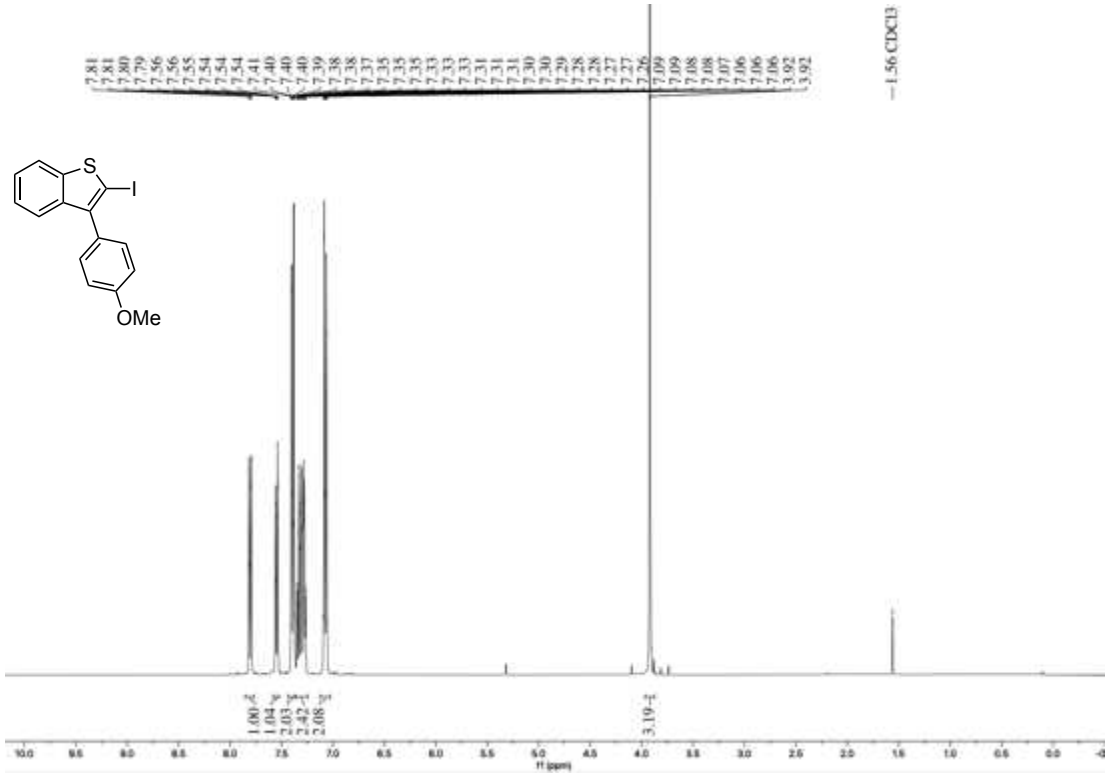
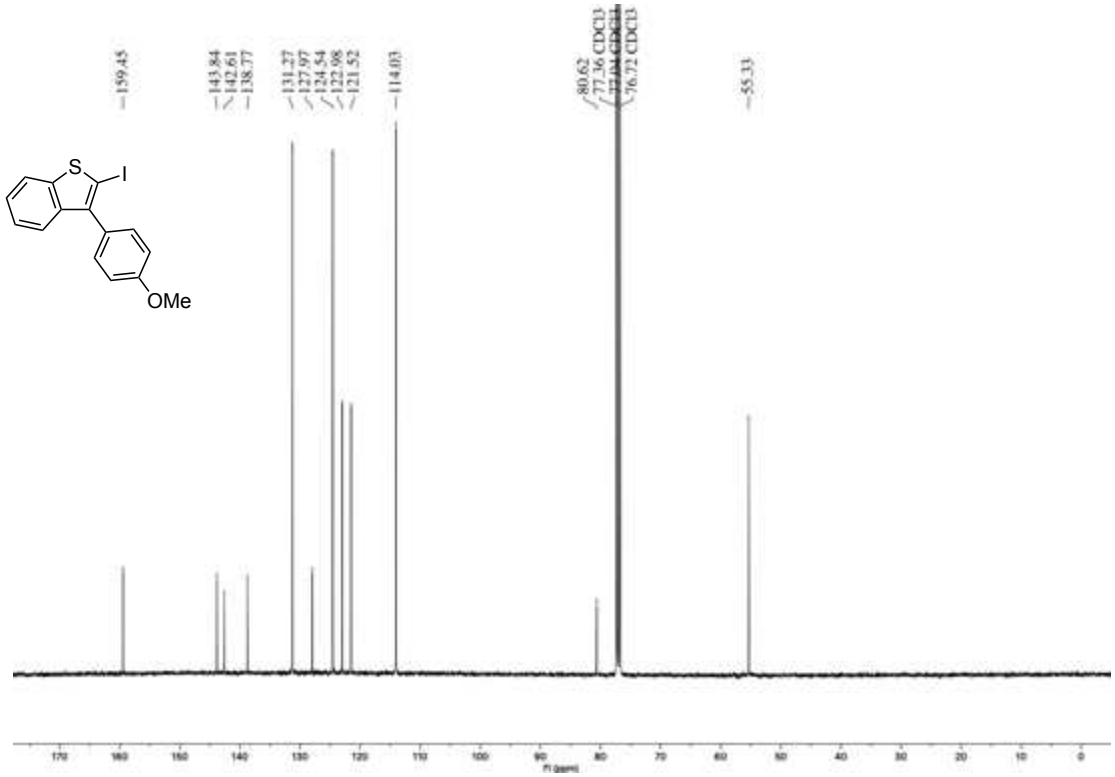


^{1}H NMR spectrum of **2-A5** (400 MHz, $CDCl_3$)



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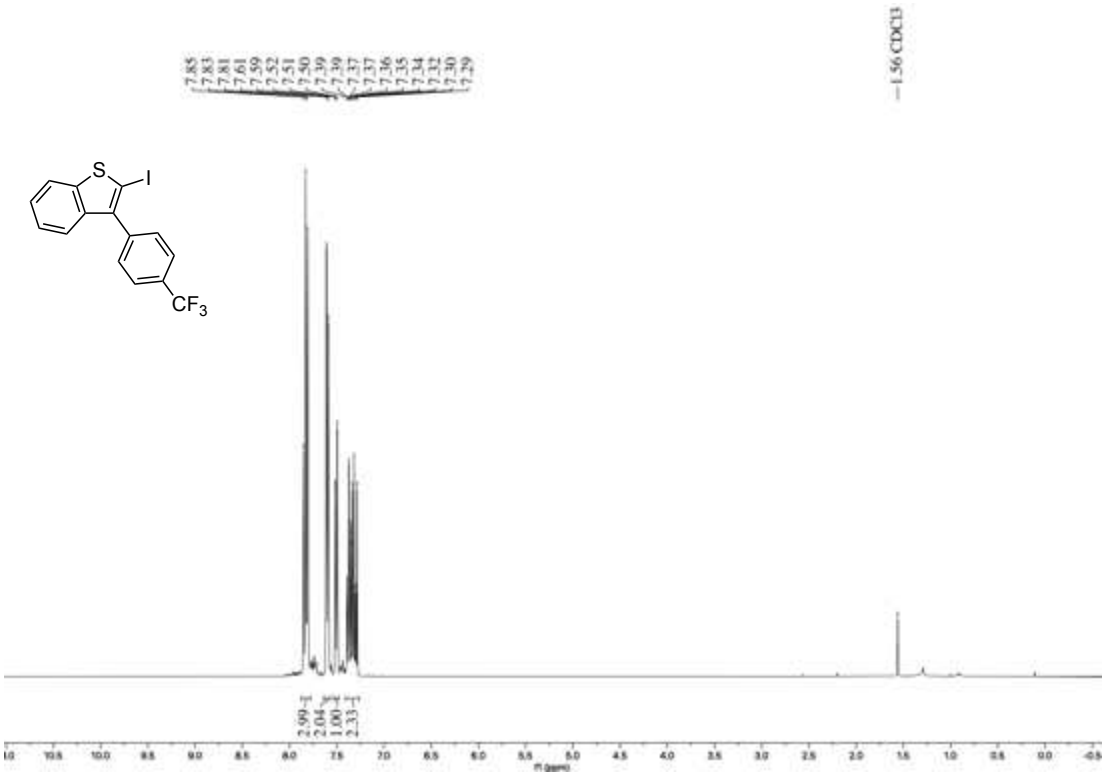
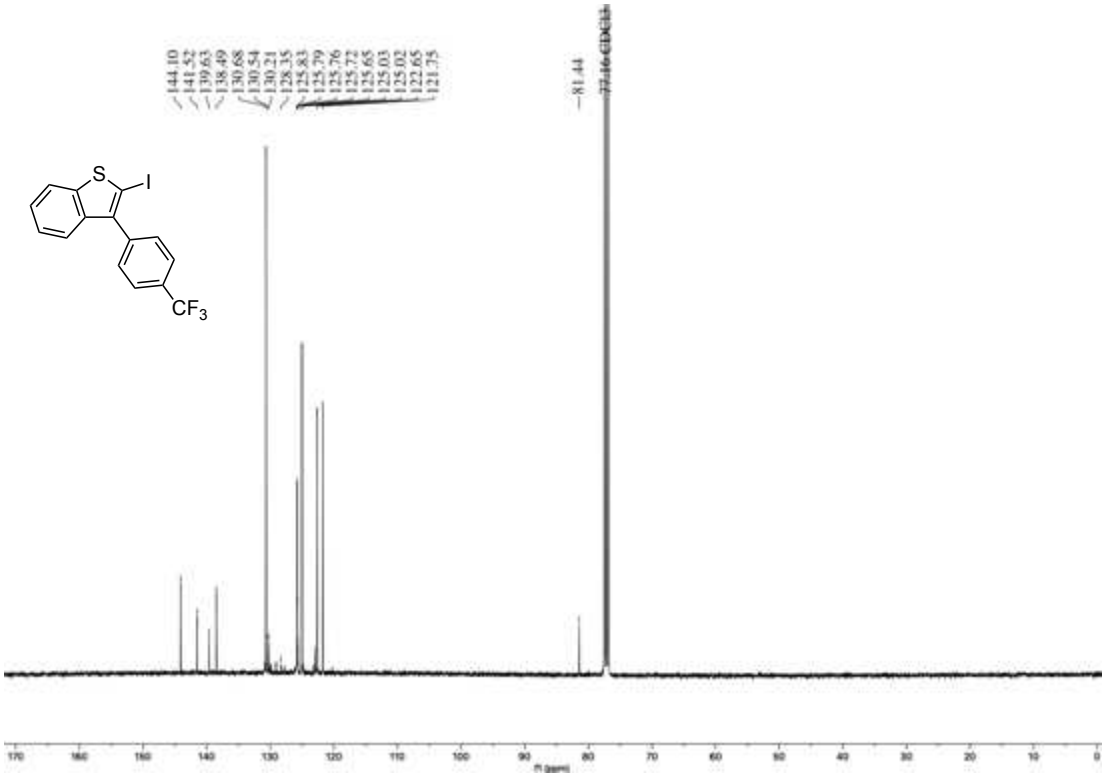
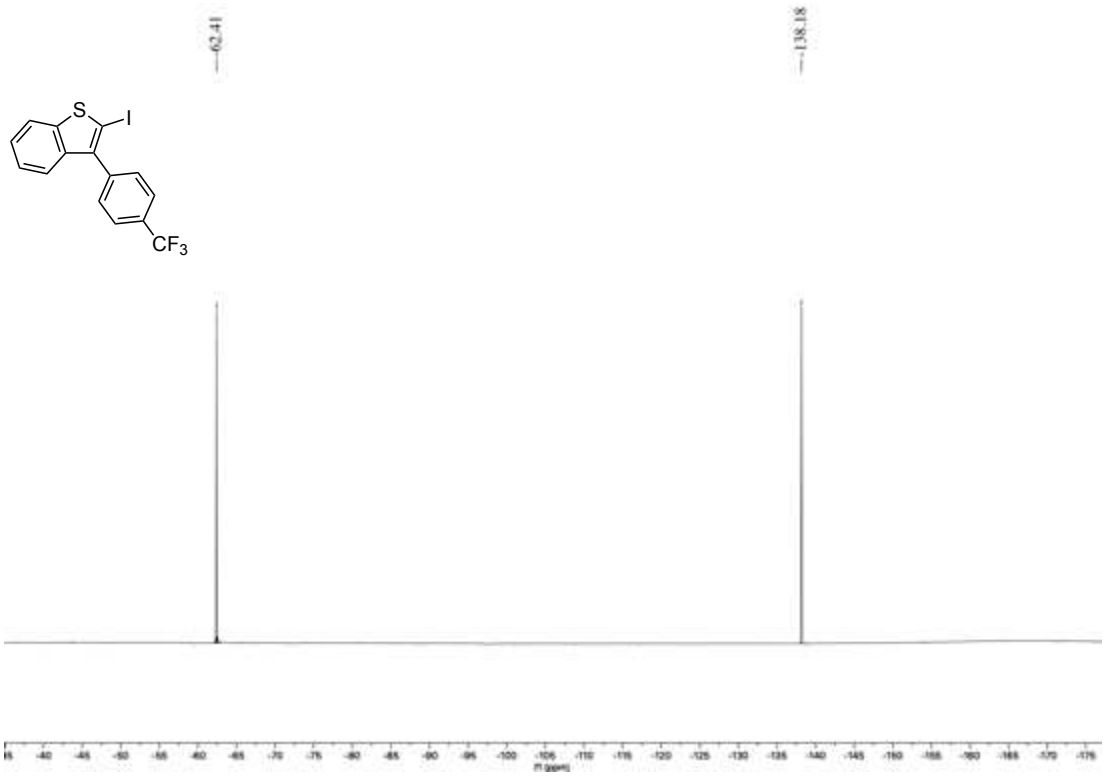


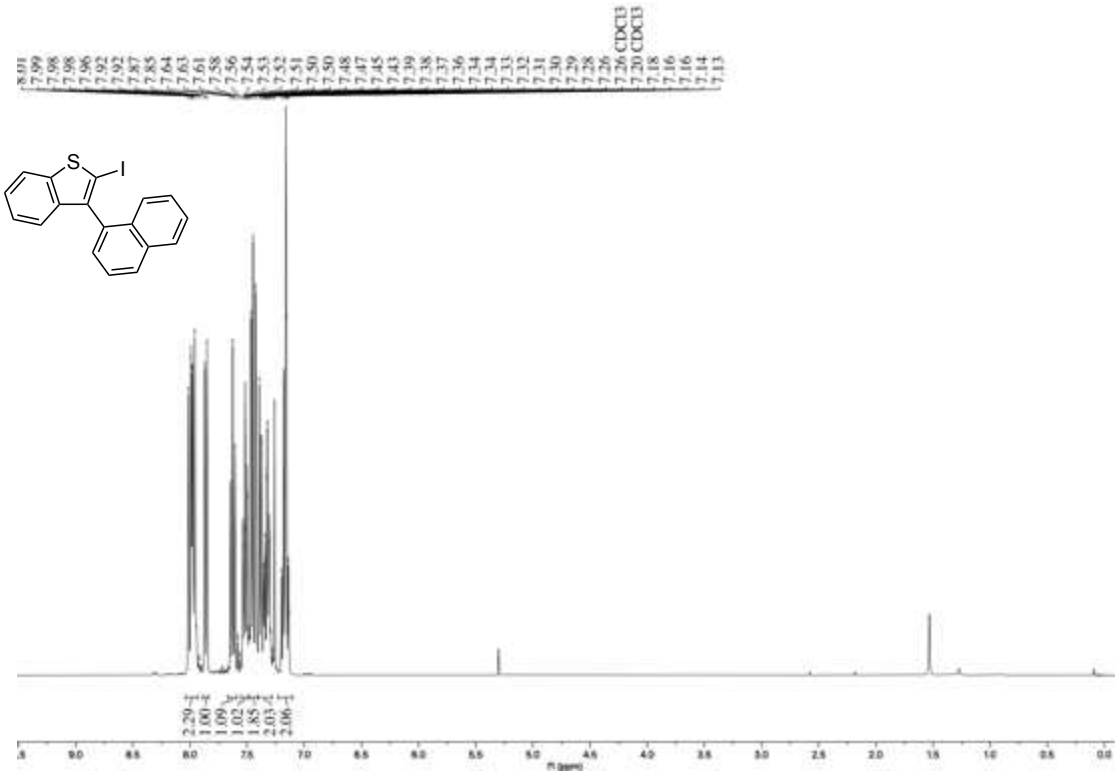
^{1}H NMR spectrum of **2-A6** (400 MHz, $CDCl_3$)



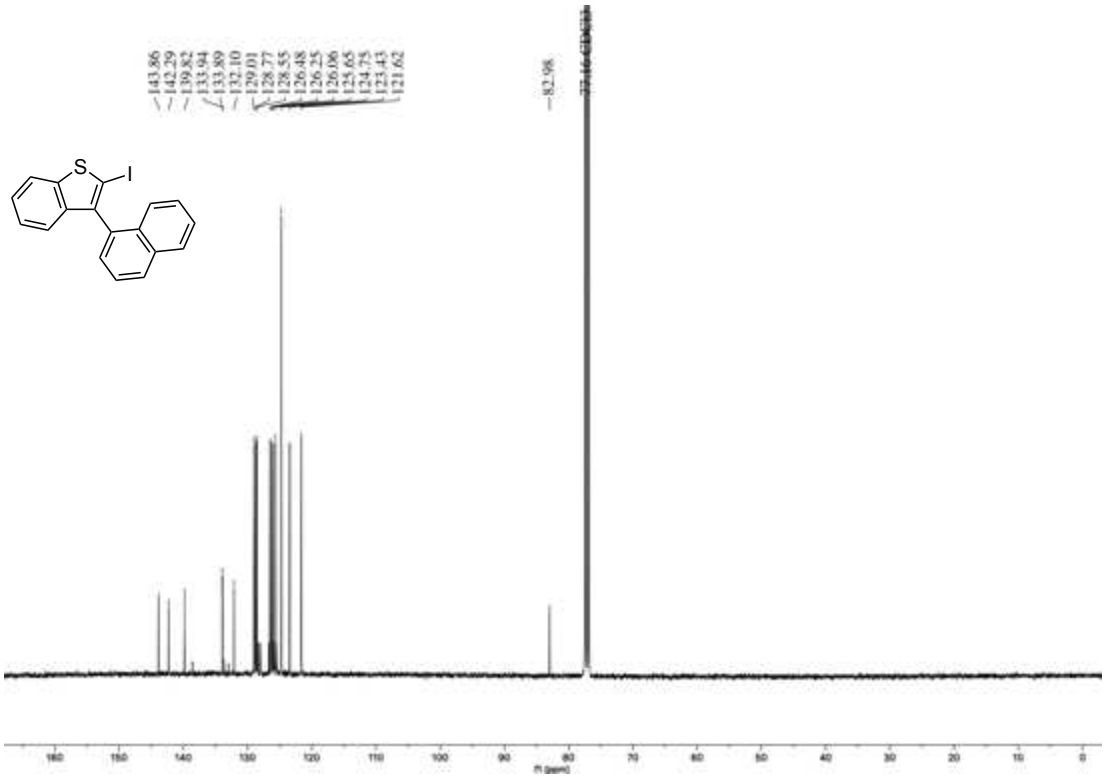
^{13}C NMR spectrum of **2-A6** (101 MHz, $CDCl_3$)



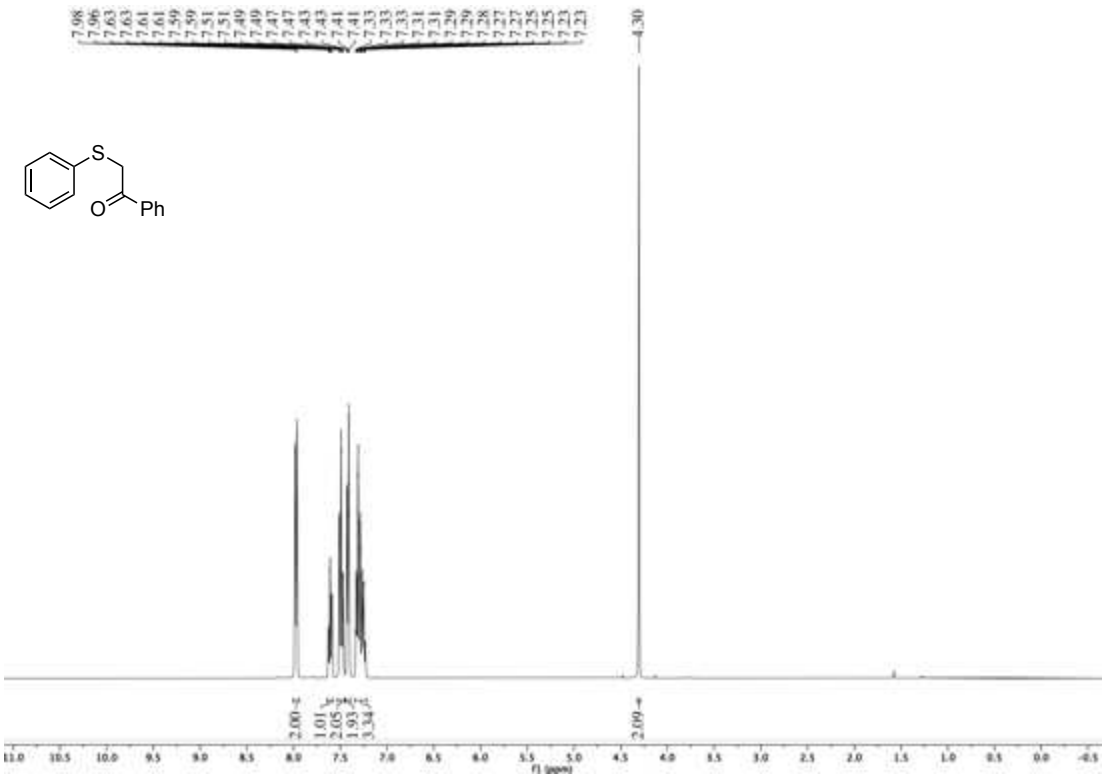
^{19}F NMR spectrum of **2-A6** (376 MHz, $CDCl_3$)



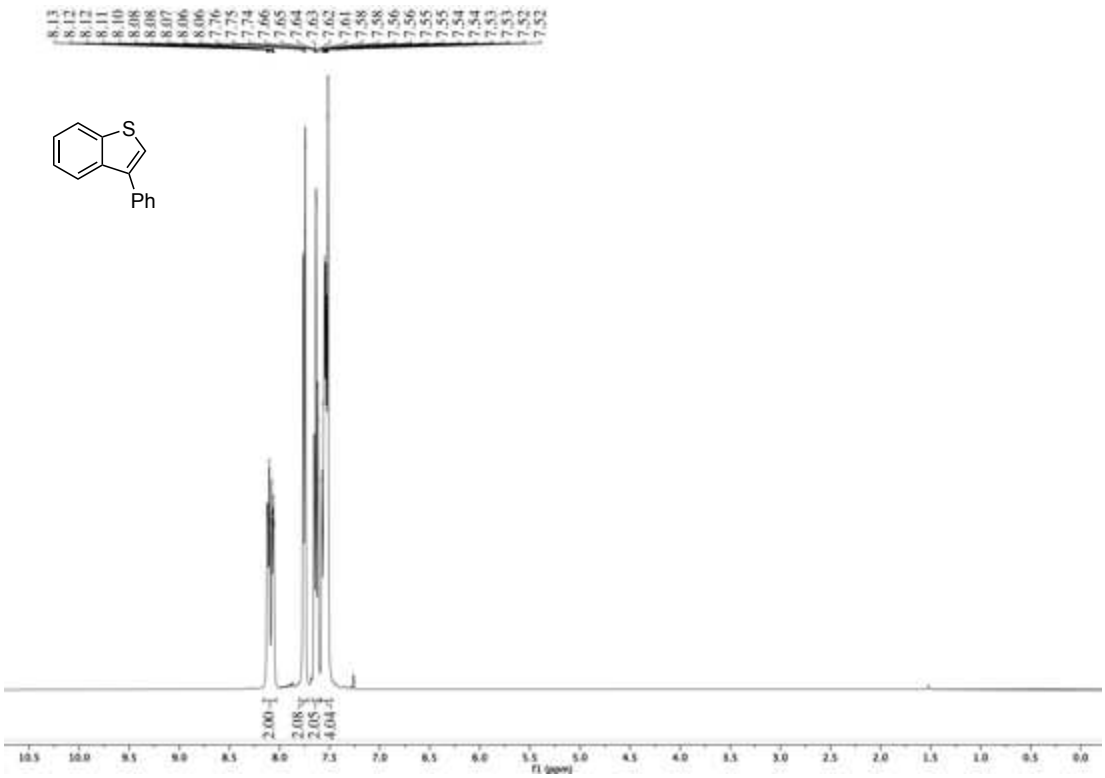
^{1}H NMR spectrum of **2-A7** (400 MHz, $CDCl_3$)



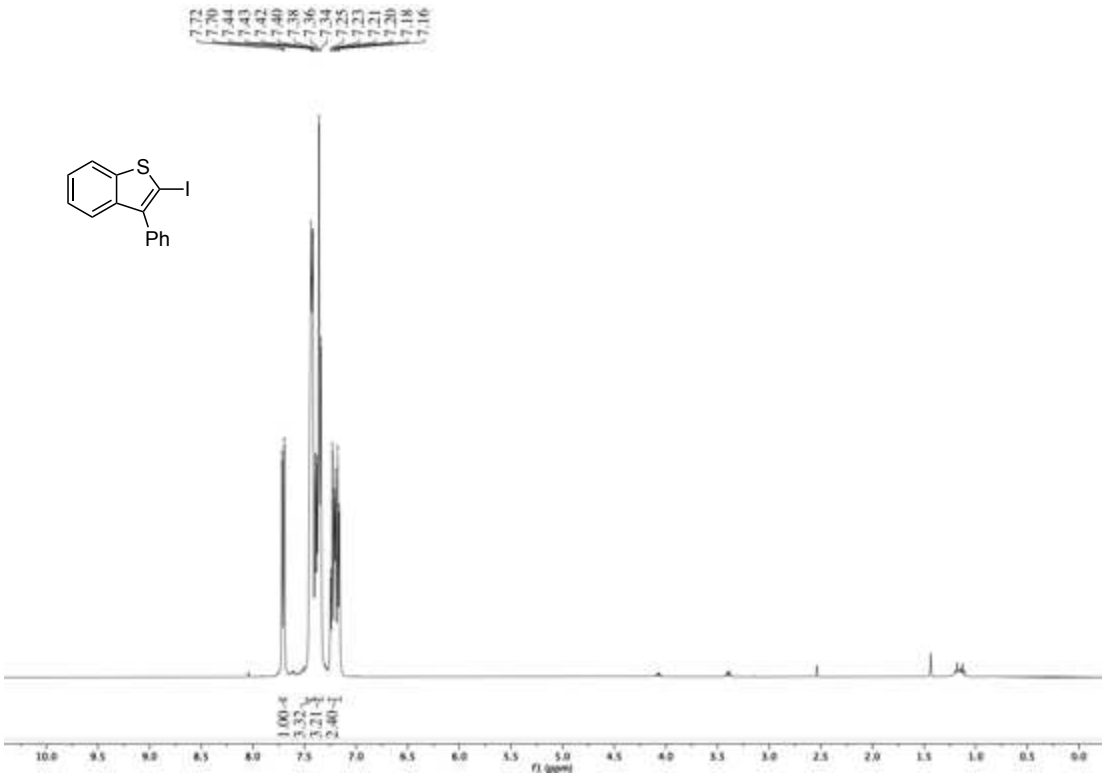
^{13}C NMR spectrum of **2-A7** (101 MHz, $CDCl_3$)



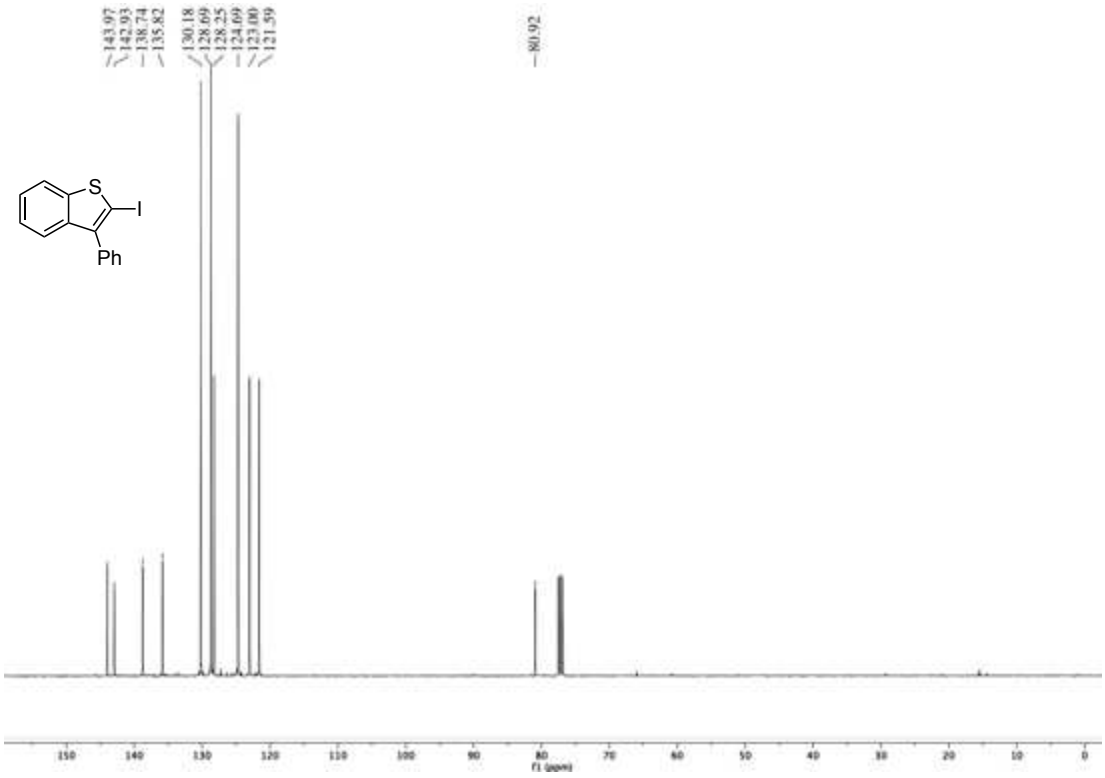
^{1}H NMR spectrum of **2-6** (400 MHz, $CDCl_3$)



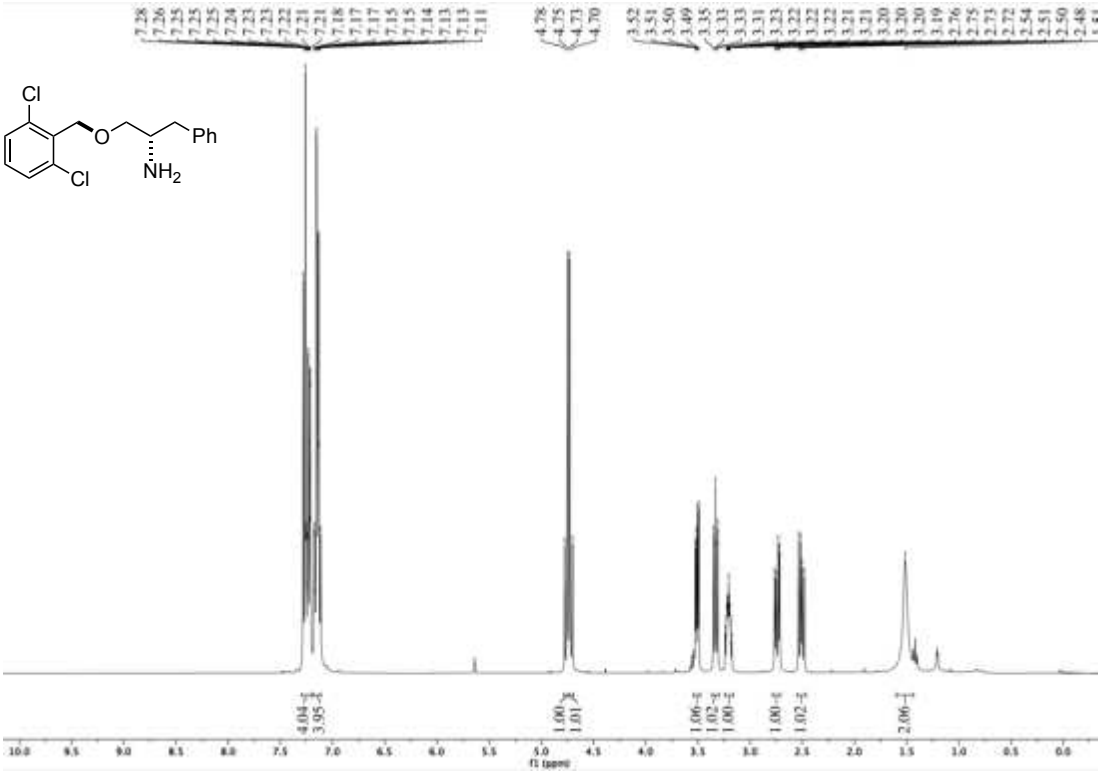
^{1}H NMR spectrum of **2-A8** (400 MHz, $CDCl_3$)



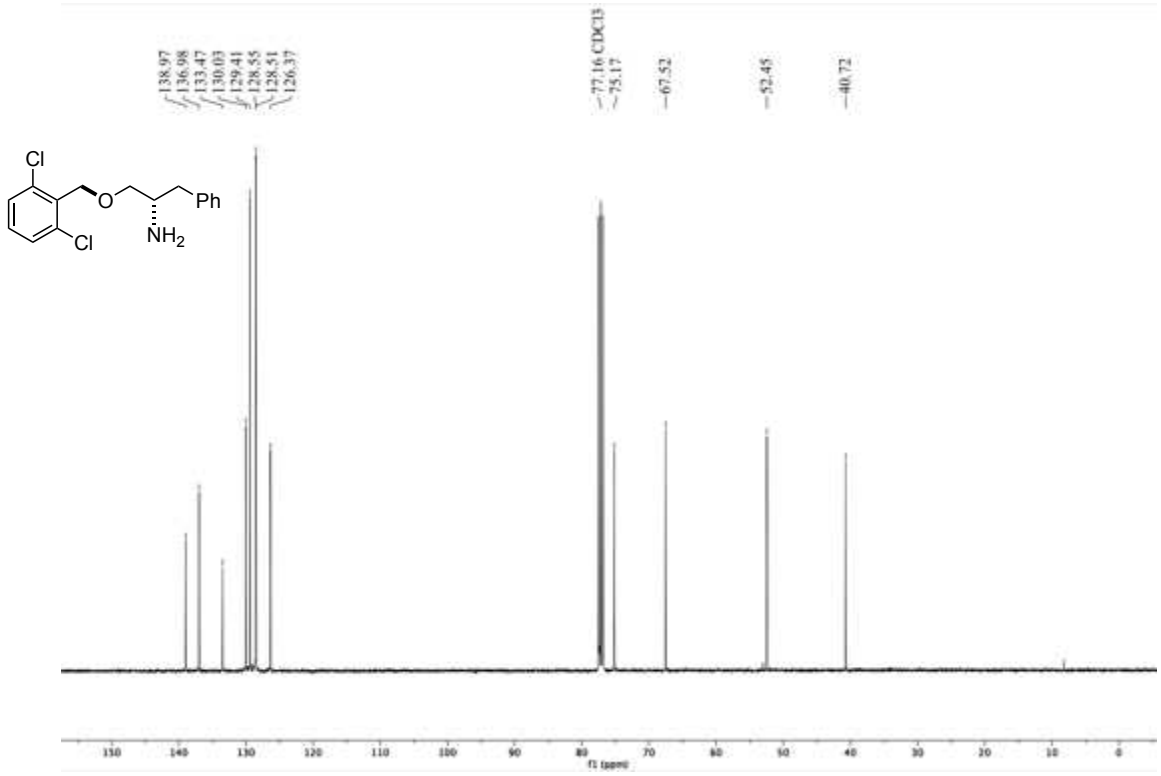
^{1}H NMR spectrum of **3-XTR 3** (400 MHz, $CDCl_3$)



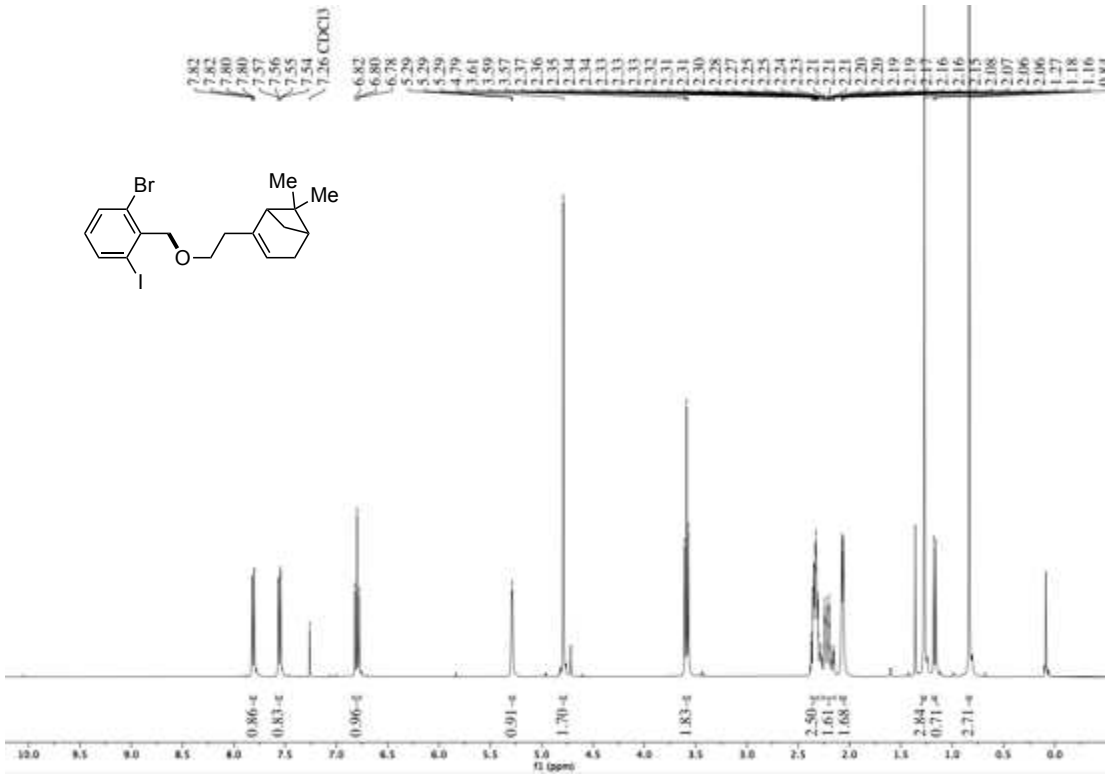
^{13}C NMR spectrum of **3-XTR 3** (101 MHz, $CDCl_3$)



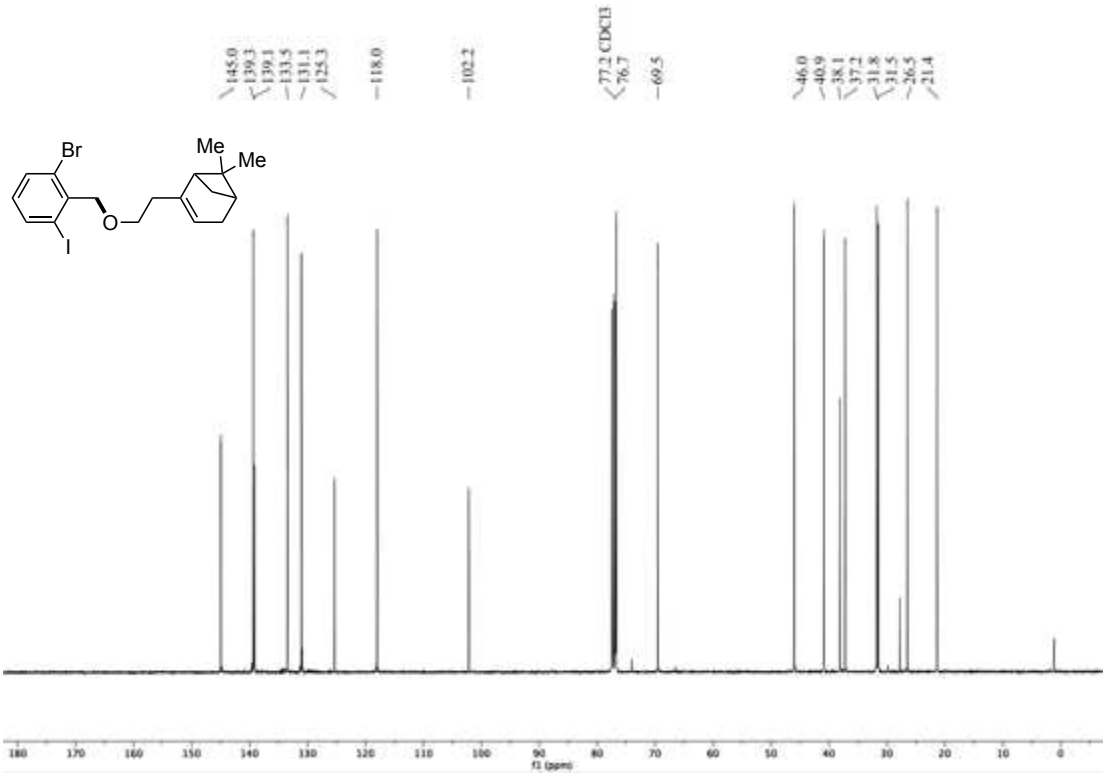
^{1}H NMR spectrum of **3-7** (400 MHz, $CDCl_3$)



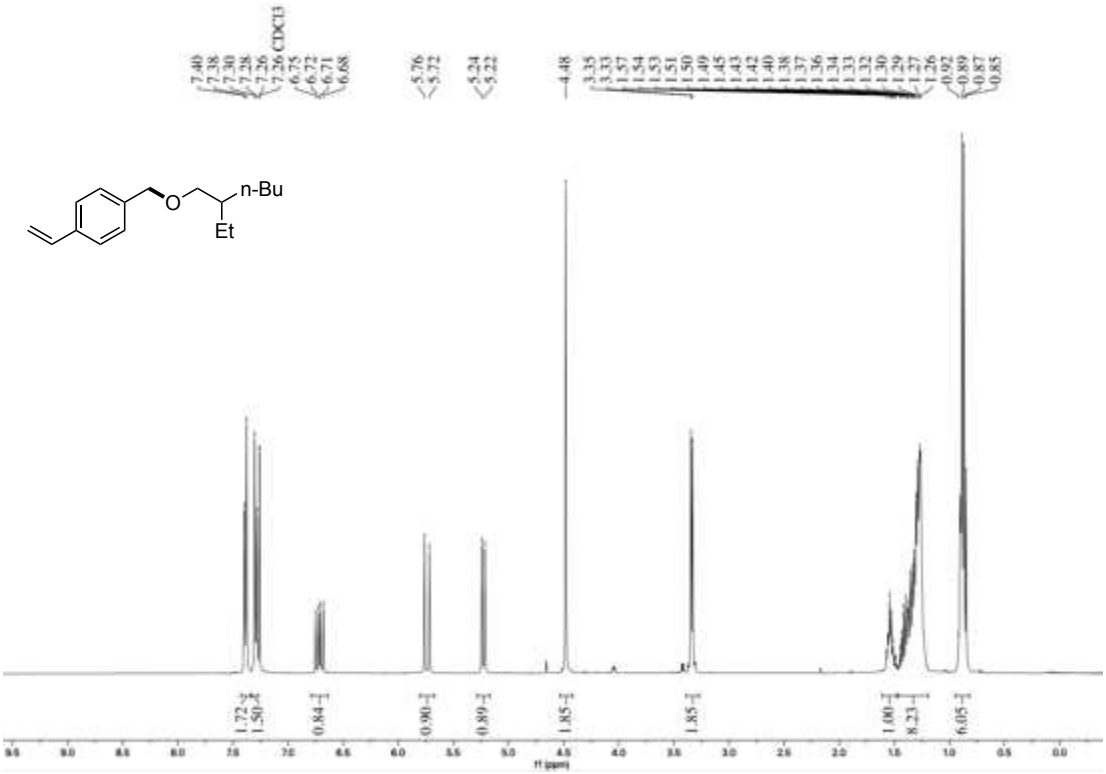
^{13}C NMR spectrum of **3-7** (101 MHz, $CDCl_3$)



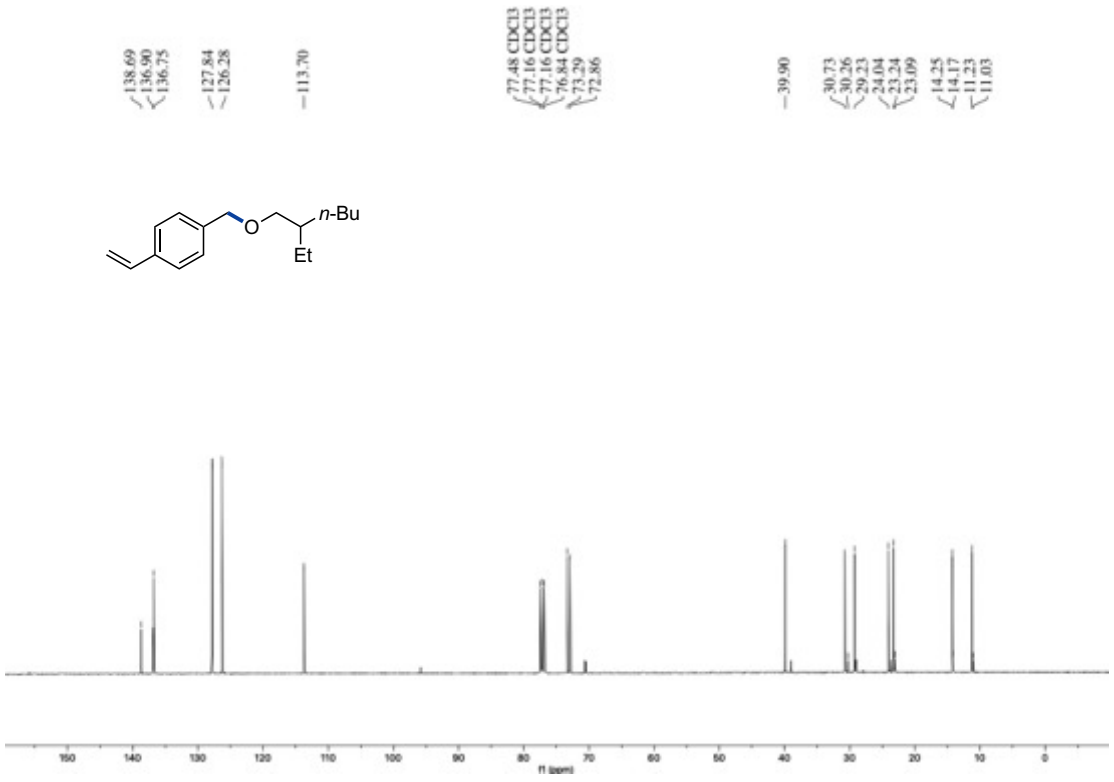
^{1}H NMR spectrum of **3-8** (400 MHz, $CDCl_3$)



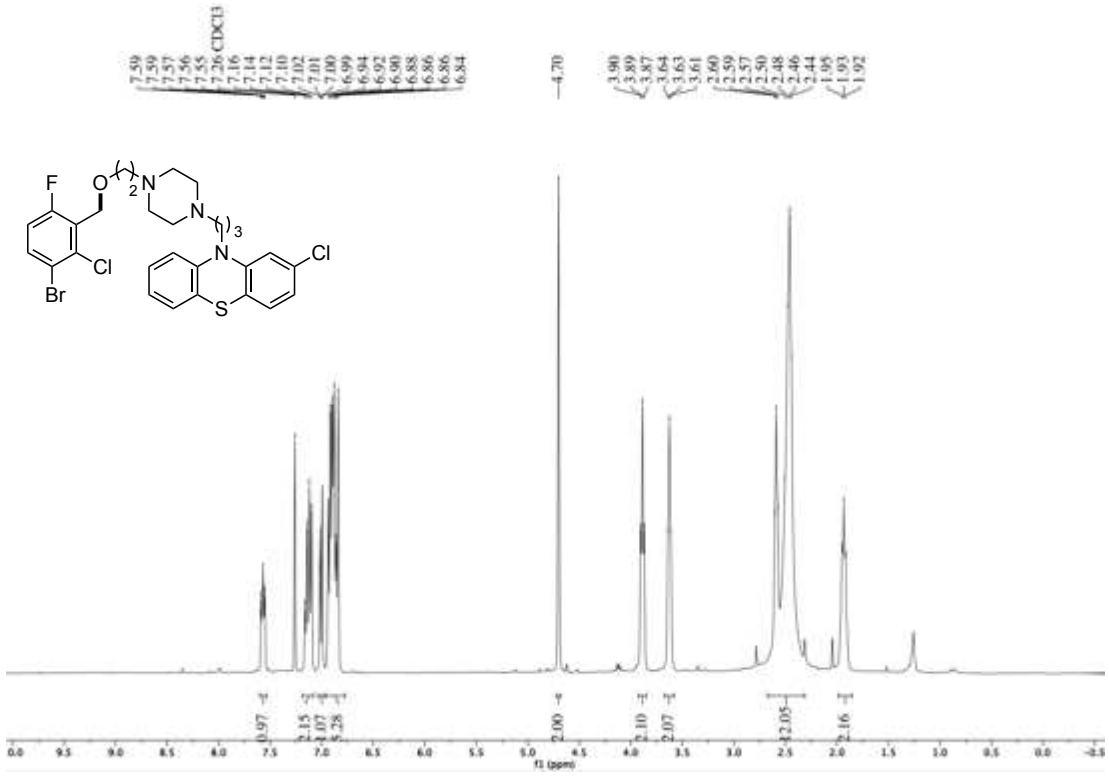
^{13}C NMR spectrum of **3-8** (101 MHz, $CDCl_3$)



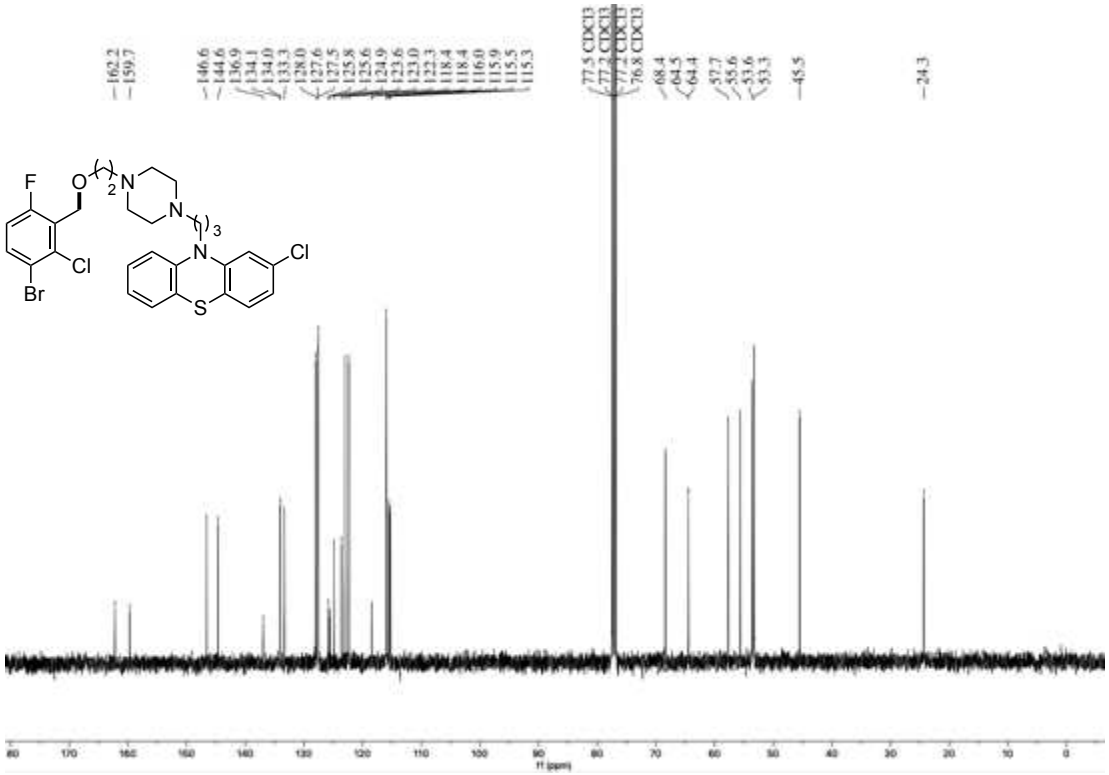
^{1}H NMR spectrum of **3-9** (400 MHz, $CDCl_3$)



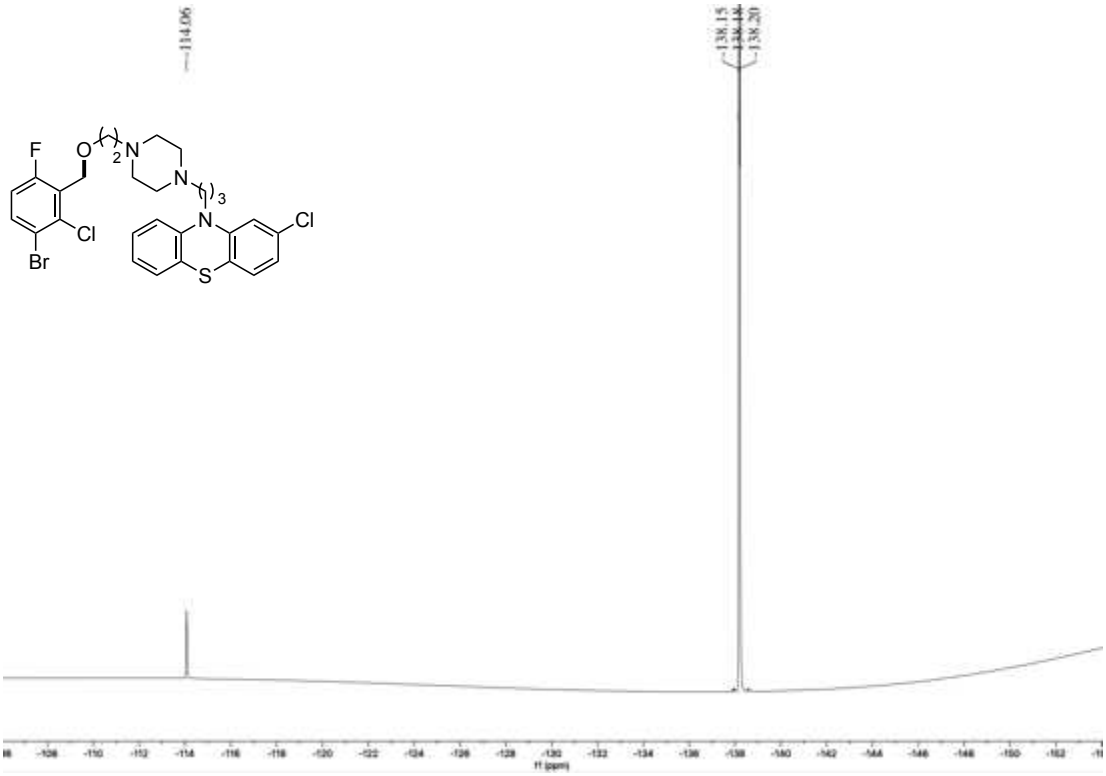
^{13}C NMR spectrum of **3-9** (101 MHz, $CDCl_3$)



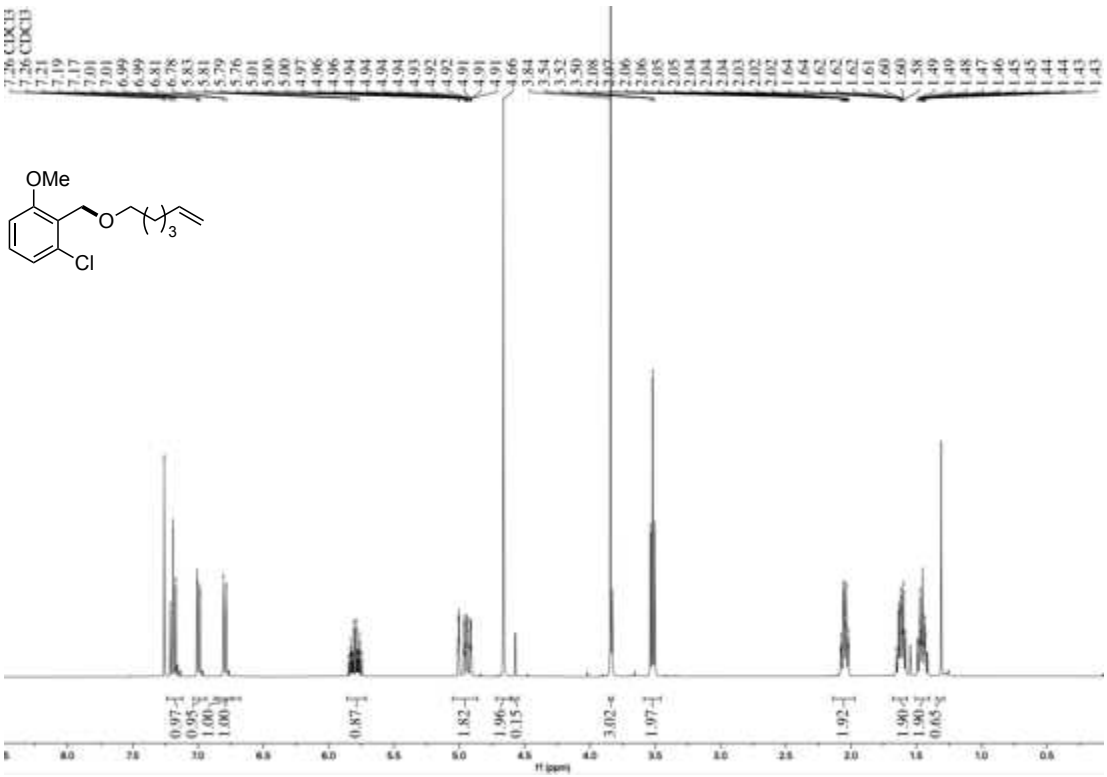
^{1}H NMR spectrum of **3-10** (400 MHz, $CDCl_3$)



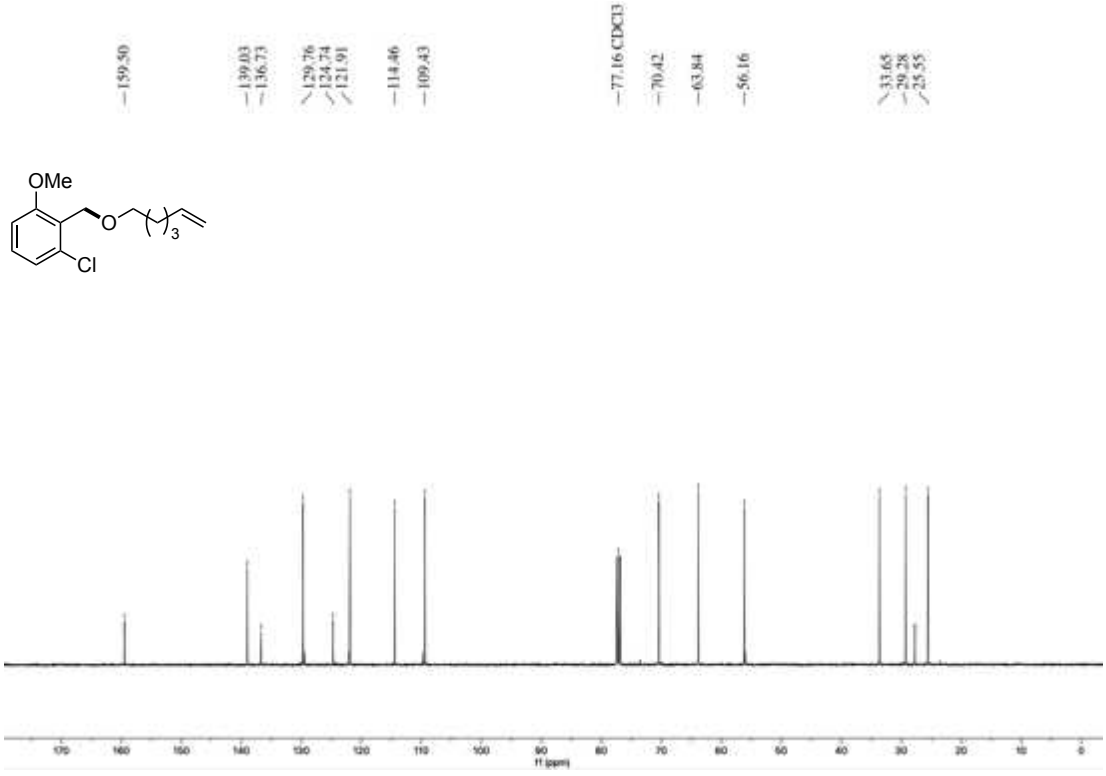
^{13}C NMR spectrum of **3-10** (101 MHz, $CDCl_3$)



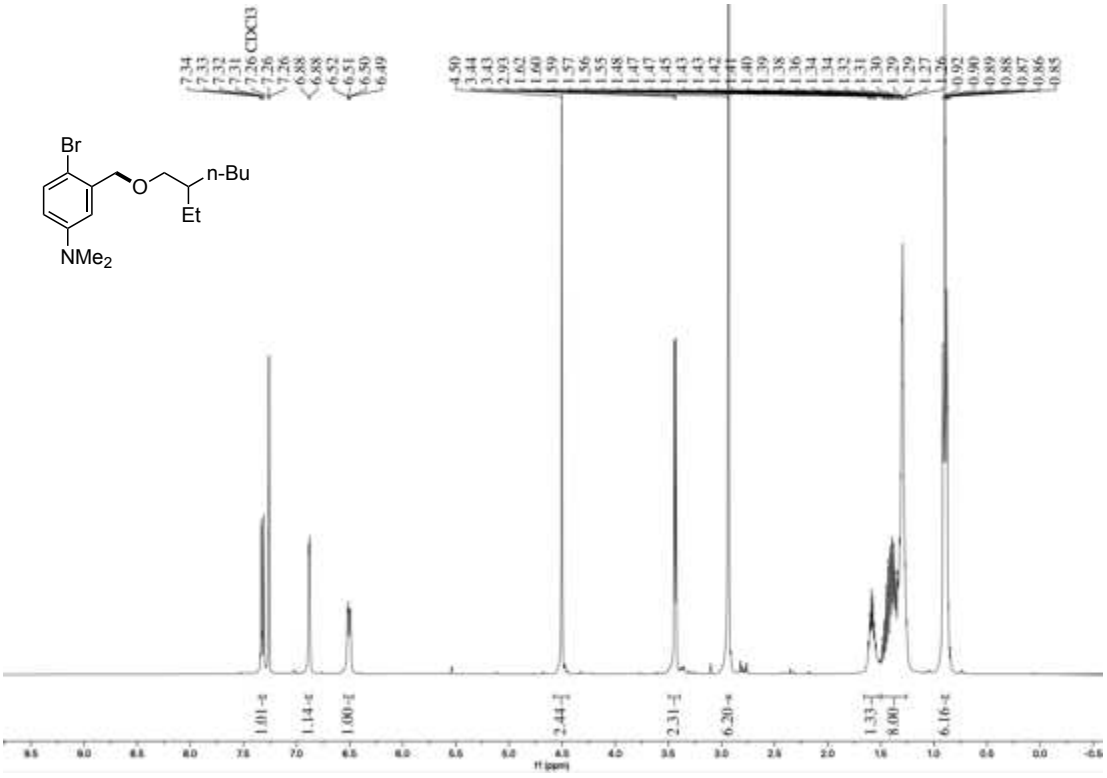
^{19}F NMR spectrum of **3-10** (376 MHz, $CDCl_3$)



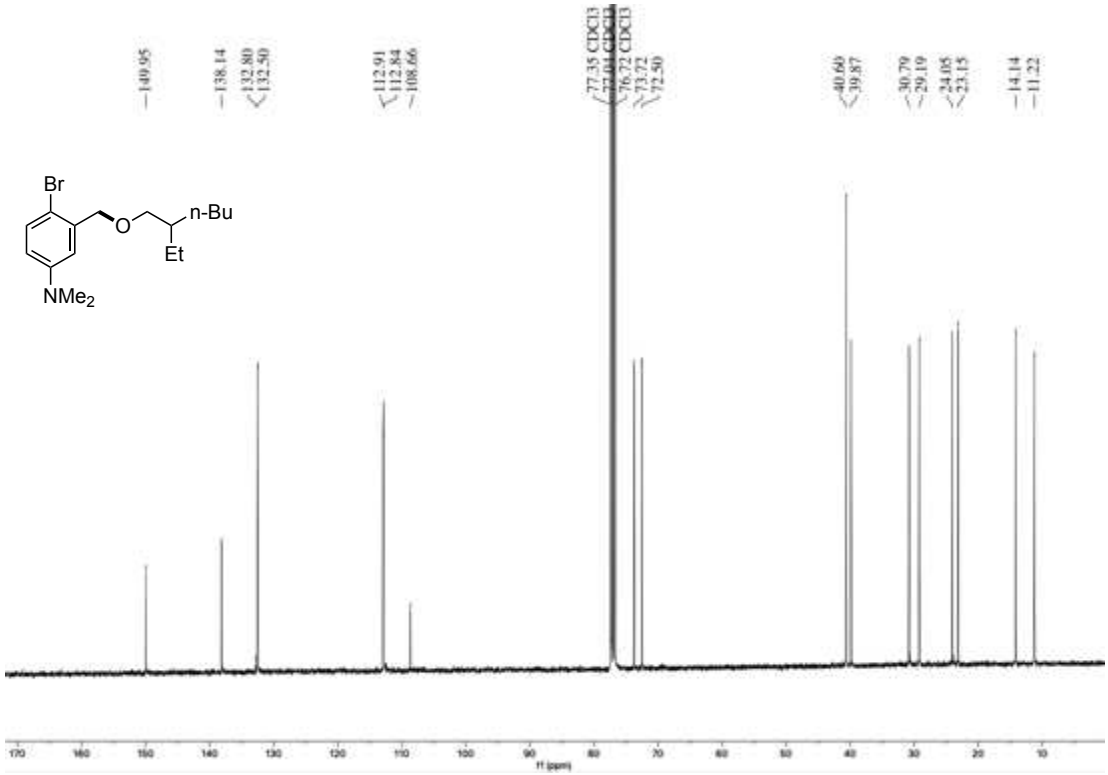
^{1}H NMR spectrum of **3-11** (400 MHz, $CDCl_3$)



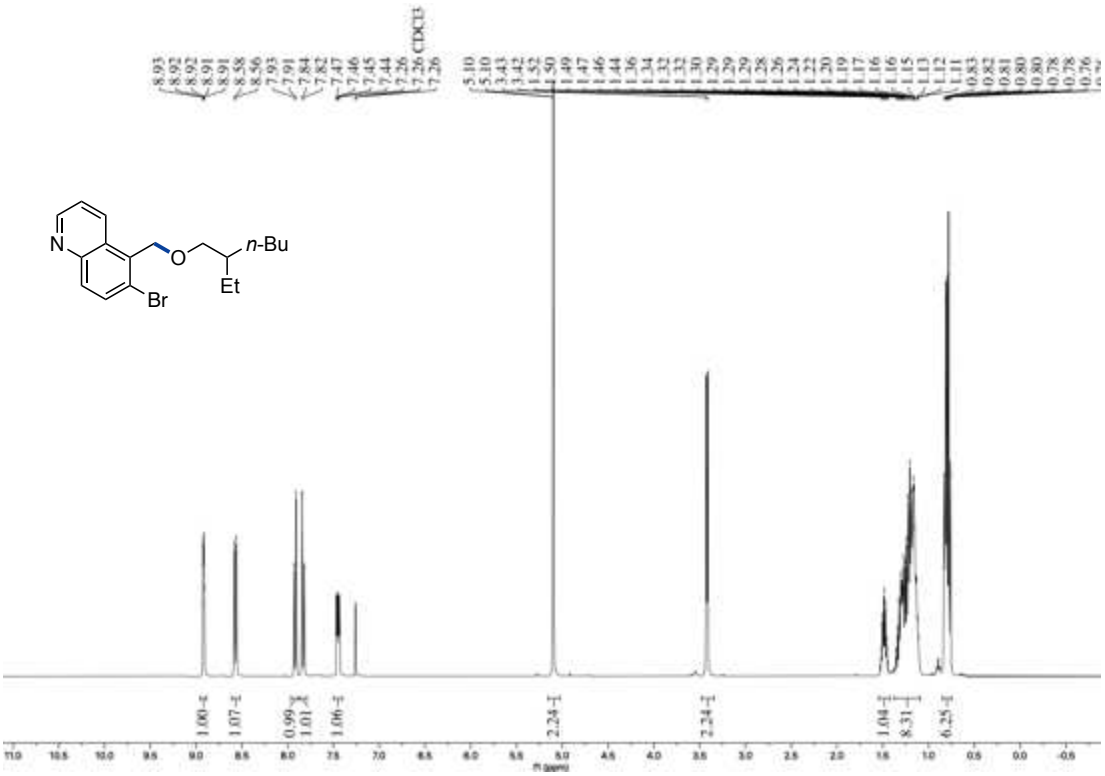
^{13}C NMR spectrum of **3-11** (101 MHz, $CDCl_3$)



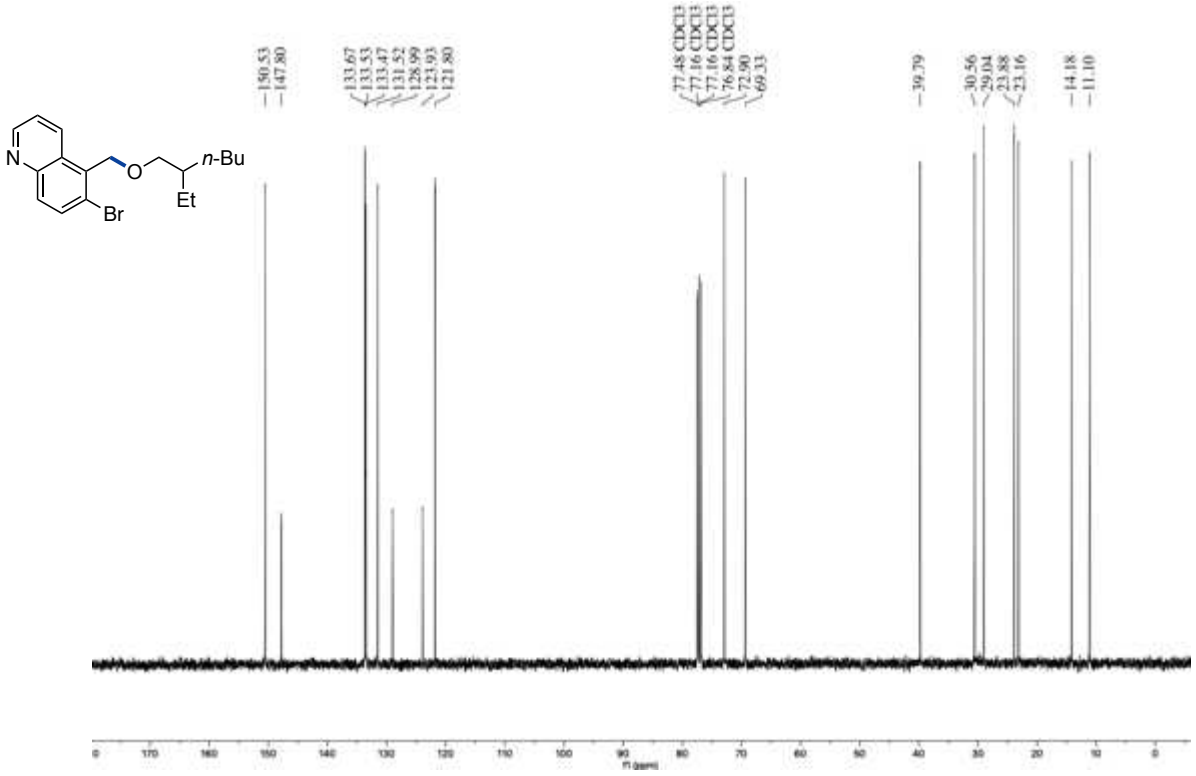
^{1}H NMR spectrum of **3-12** (400 MHz, $CDCl_3$)



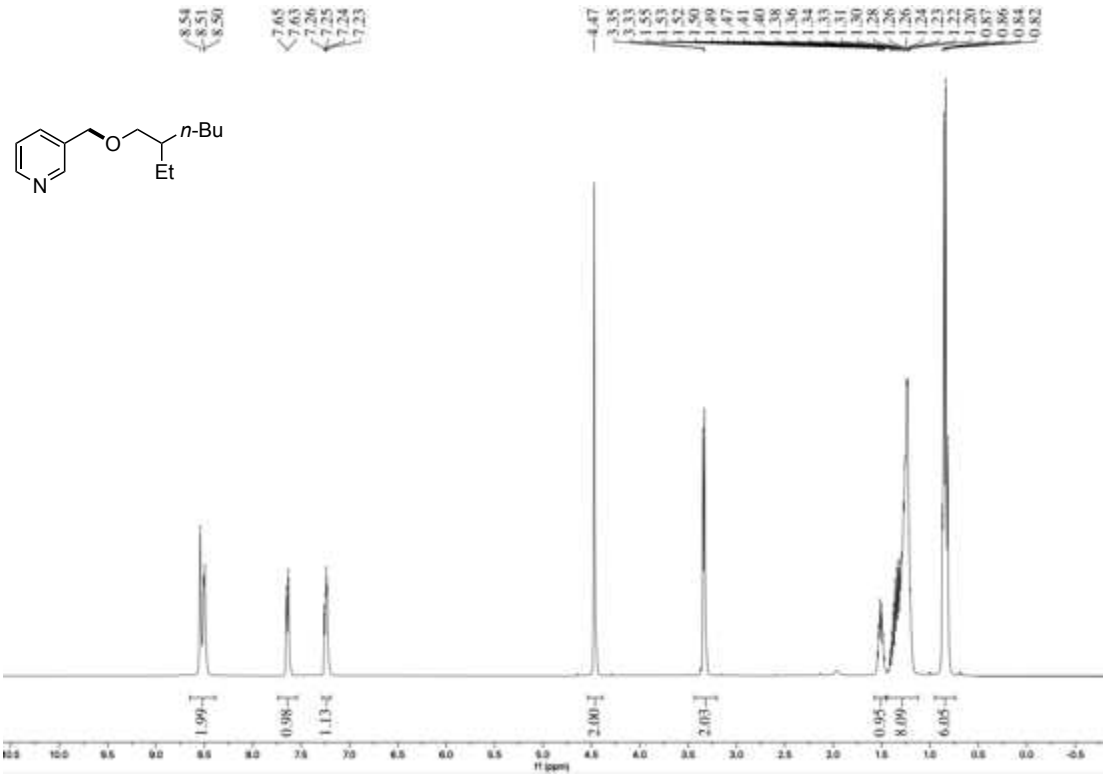
^{13}C NMR spectrum of **3-12** (101 MHz, $CDCl_3$)



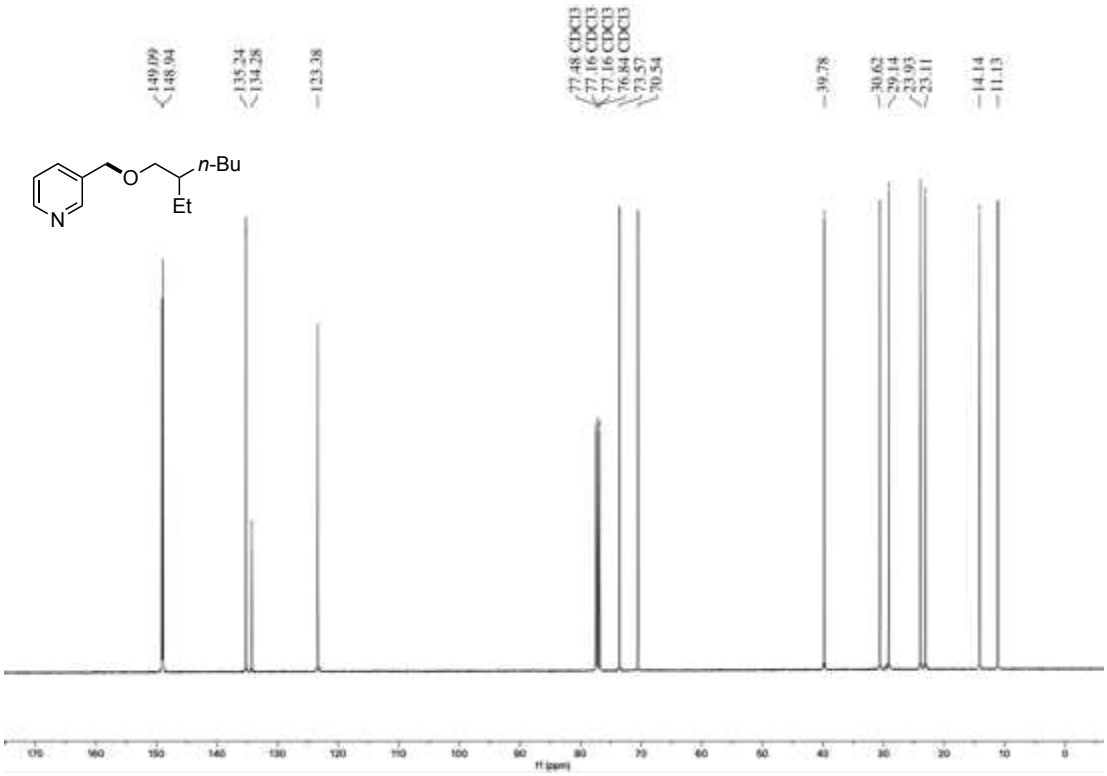
^{1}H NMR spectrum of **3-13** (400 MHz, $CDCl_3$)



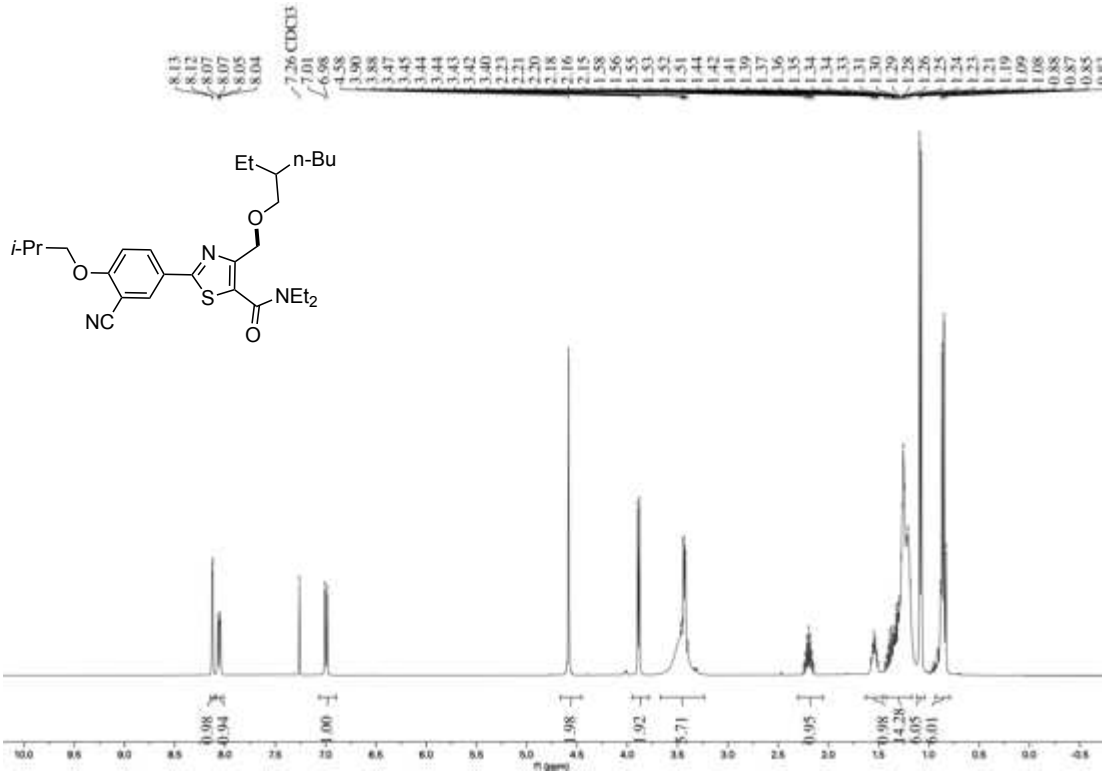
^{13}C NMR spectrum of **3-13** (101 MHz, $CDCl_3$)



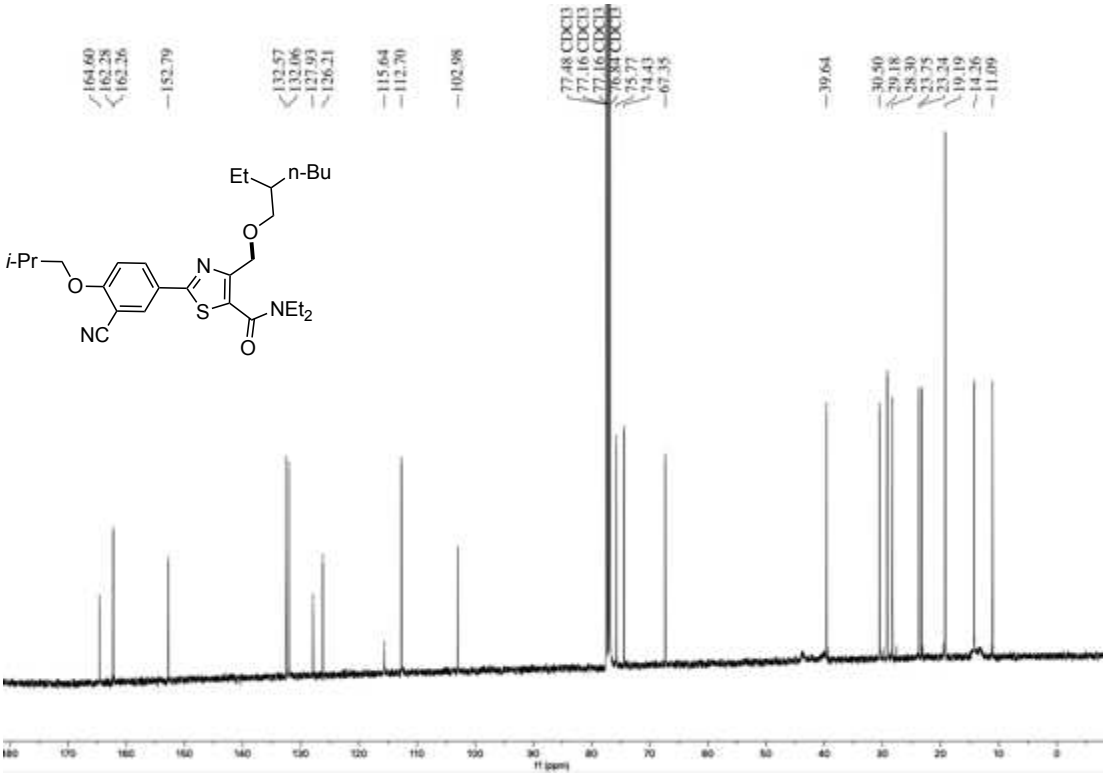
^{1}H NMR spectrum of **3-14** (400 MHz, $CDCl_3$)



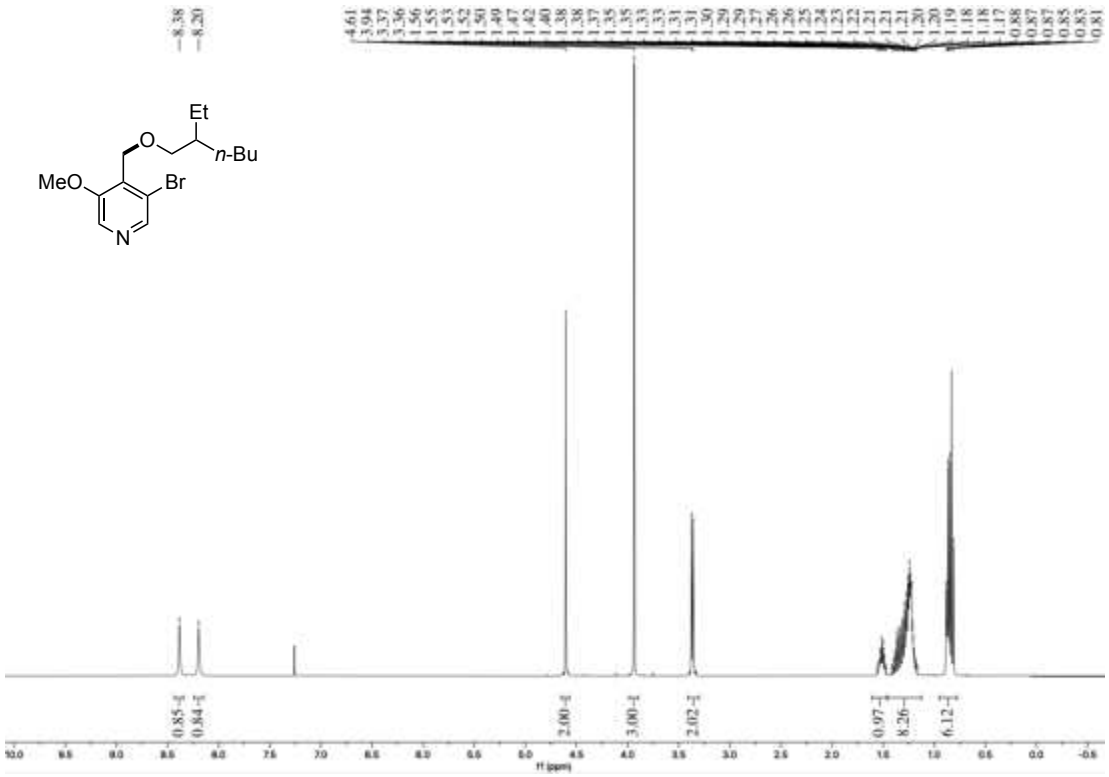
^{13}C NMR spectrum of **3-14** (101 MHz, $CDCl_3$)



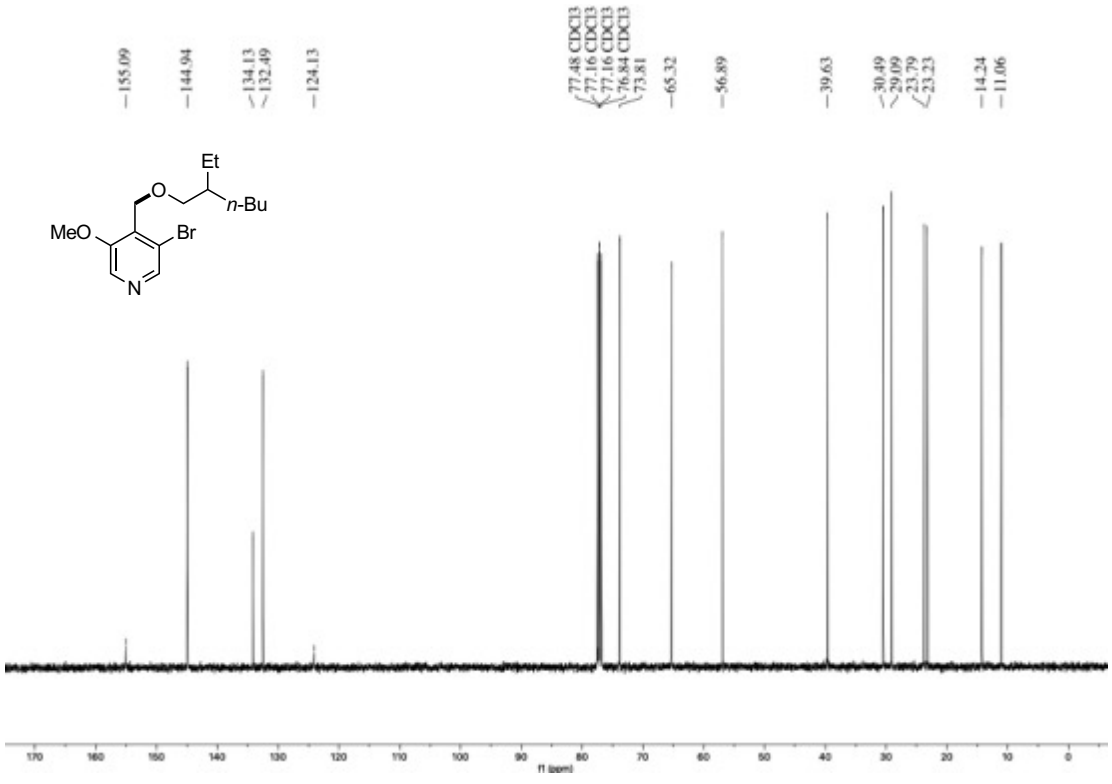
^{1}H NMR spectrum of **3-15** (400 MHz, $CDCl_3$)



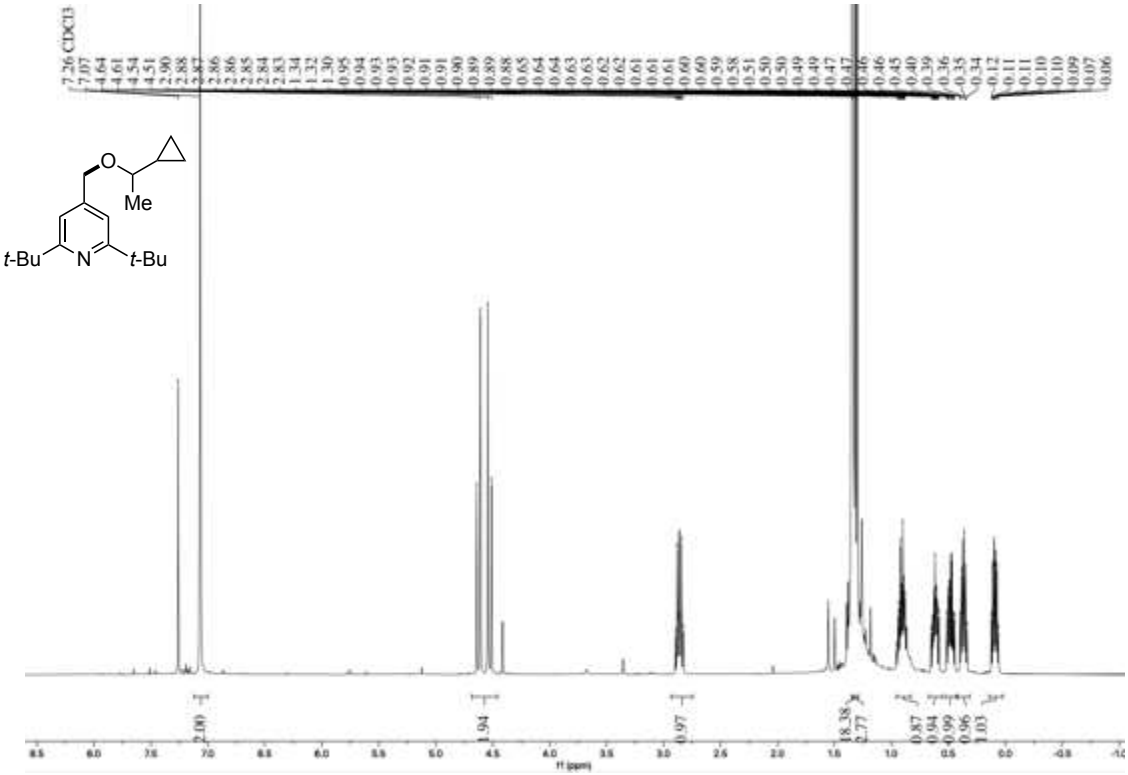
^{13}C NMR spectrum of **3-15** (101 MHz, $CDCl_3$)



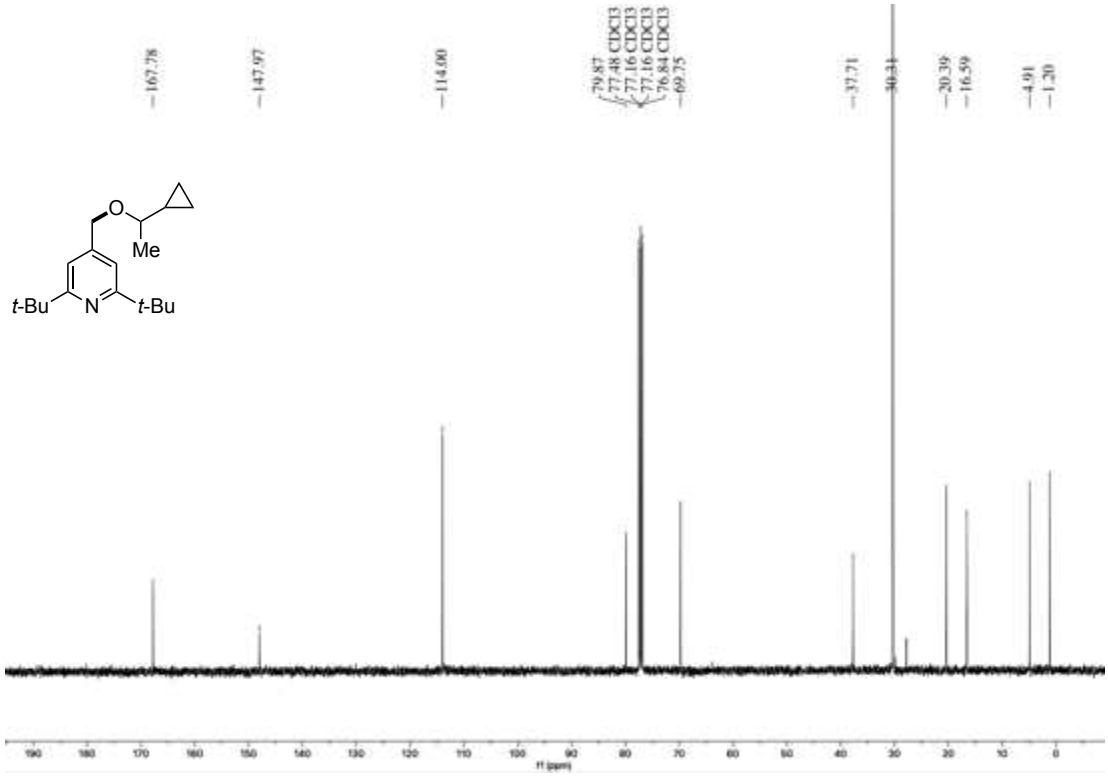
^{1}H NMR spectrum of **3-16** (400 MHz, $CDCl_3$)



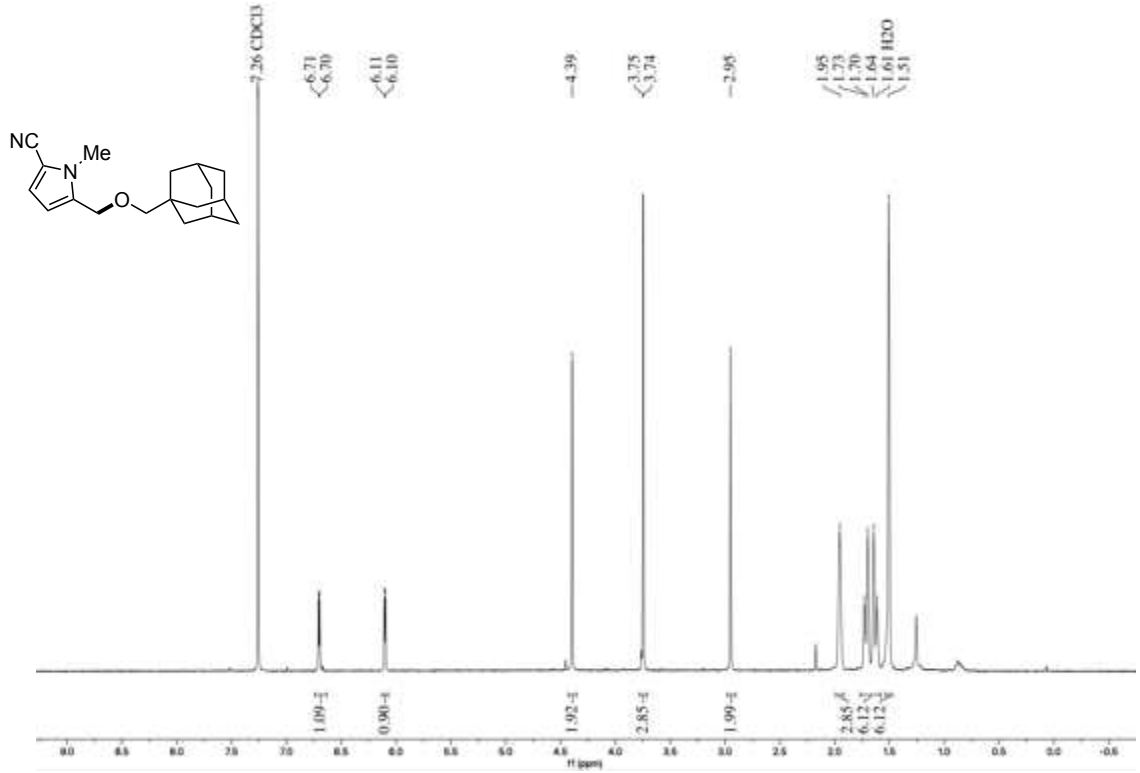
^{13}C NMR spectrum of **3-16** (101 MHz, $CDCl_3$)



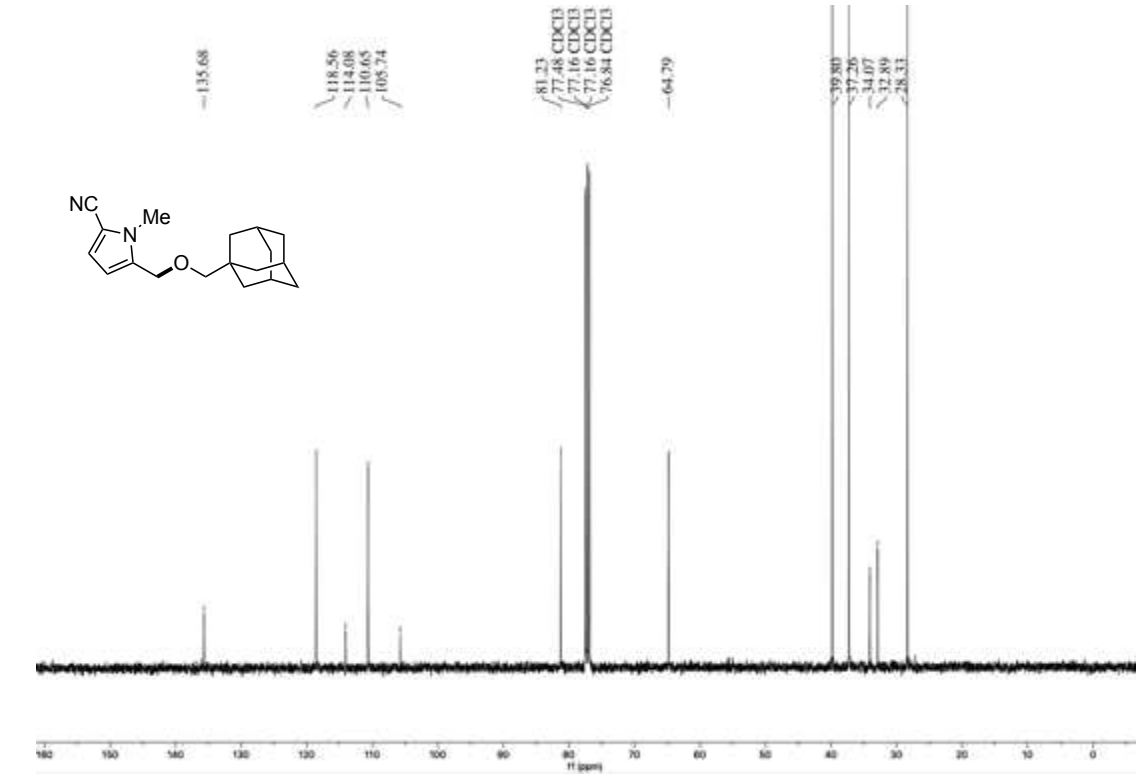
^{1}H NMR spectrum of **3-17** (400 MHz, $CDCl_3$)



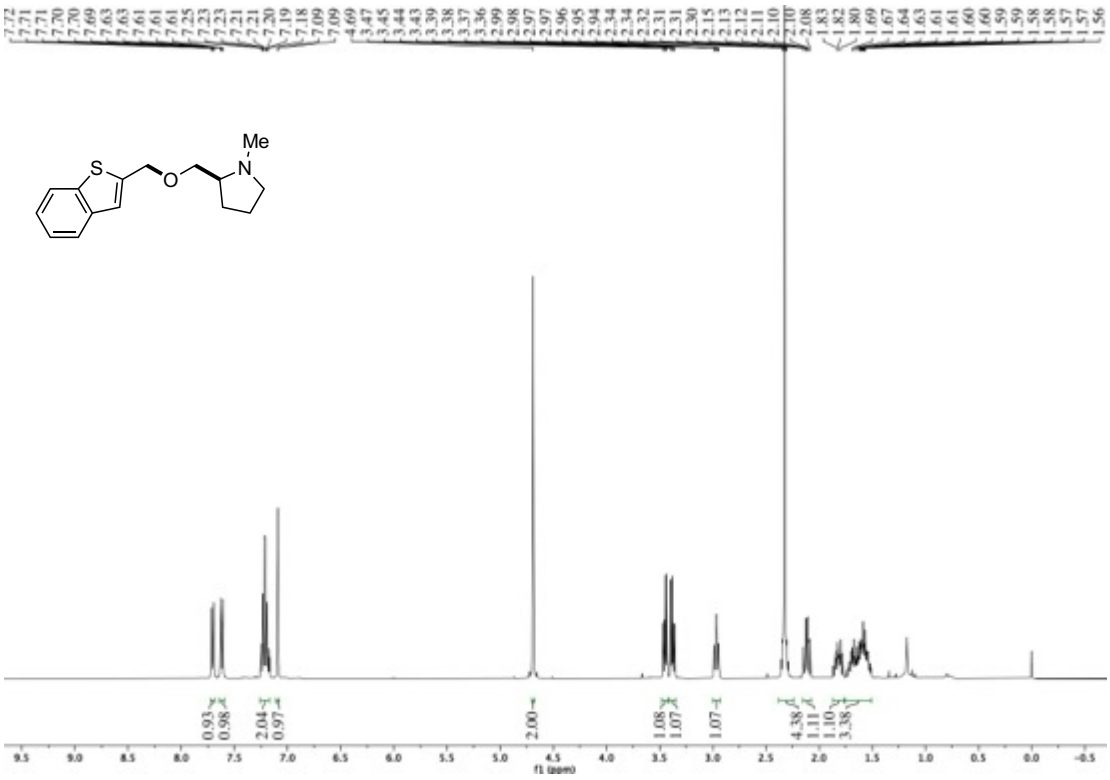
^{13}C NMR spectrum of **3-17** (101 MHz, $CDCl_3$)



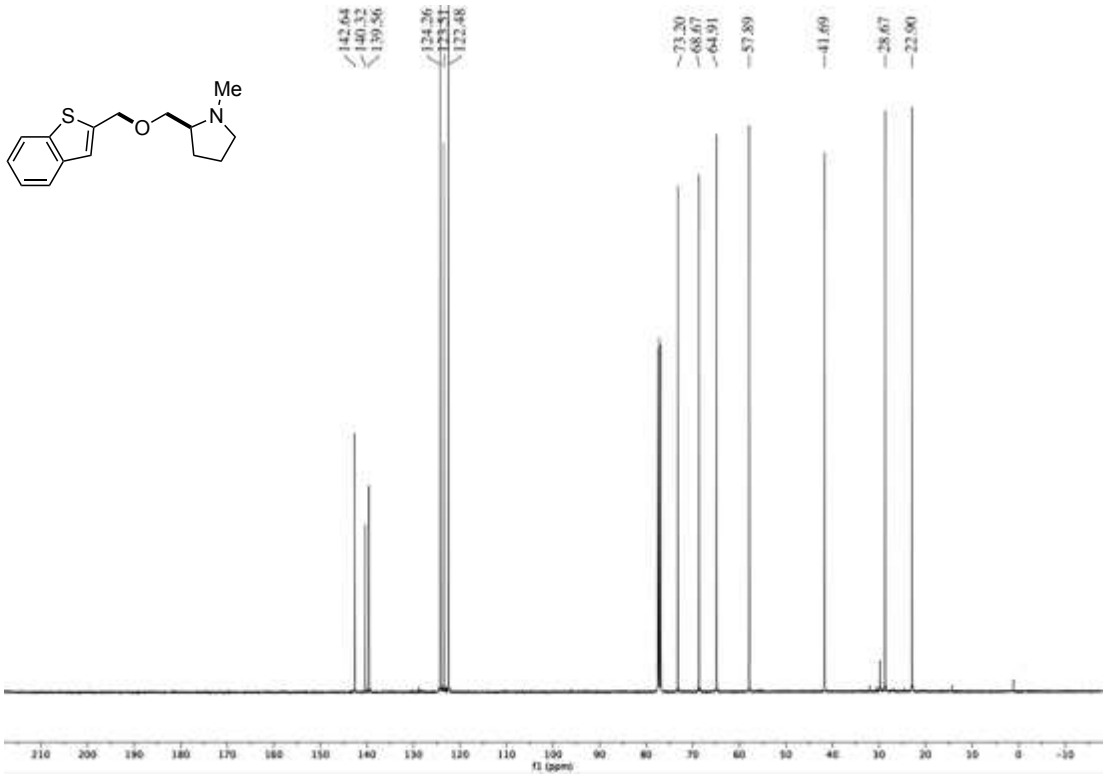
^{1}H NMR spectrum of **3-18** (400 MHz, $CDCl_3$)



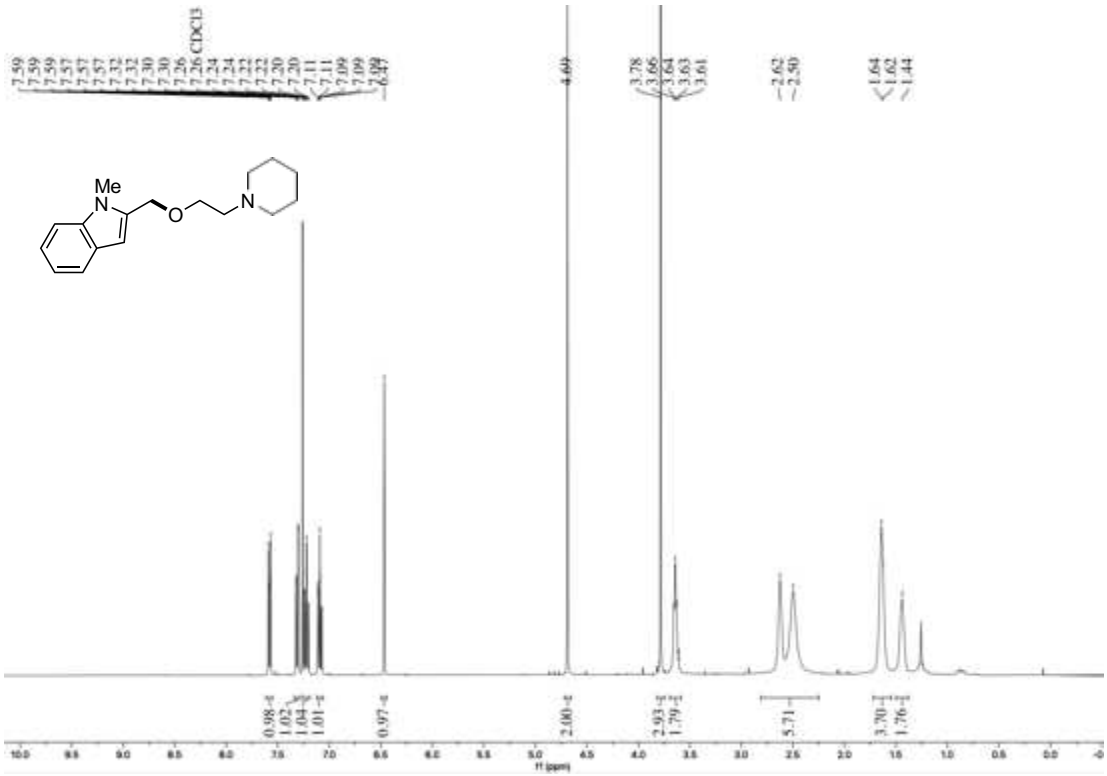
^{13}C NMR spectrum of **3-18** (101 MHz, $CDCl_3$)



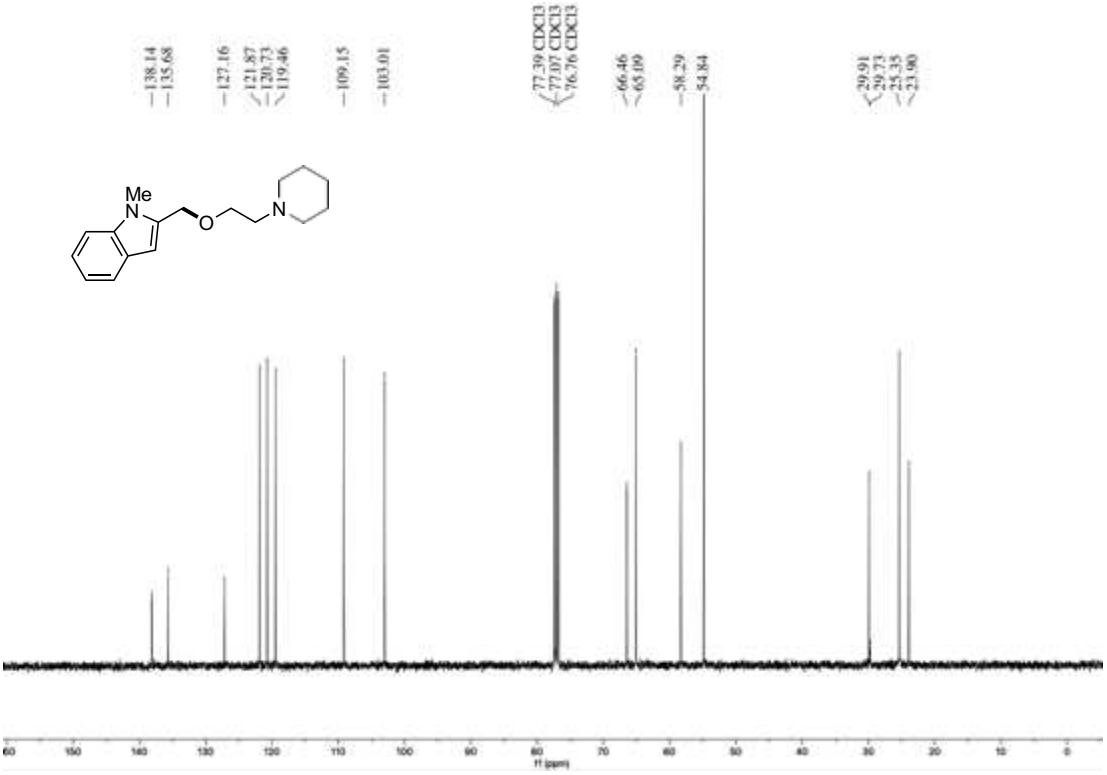
^{1}H NMR spectrum of **3-19** (400 MHz, $CDCl_3$)



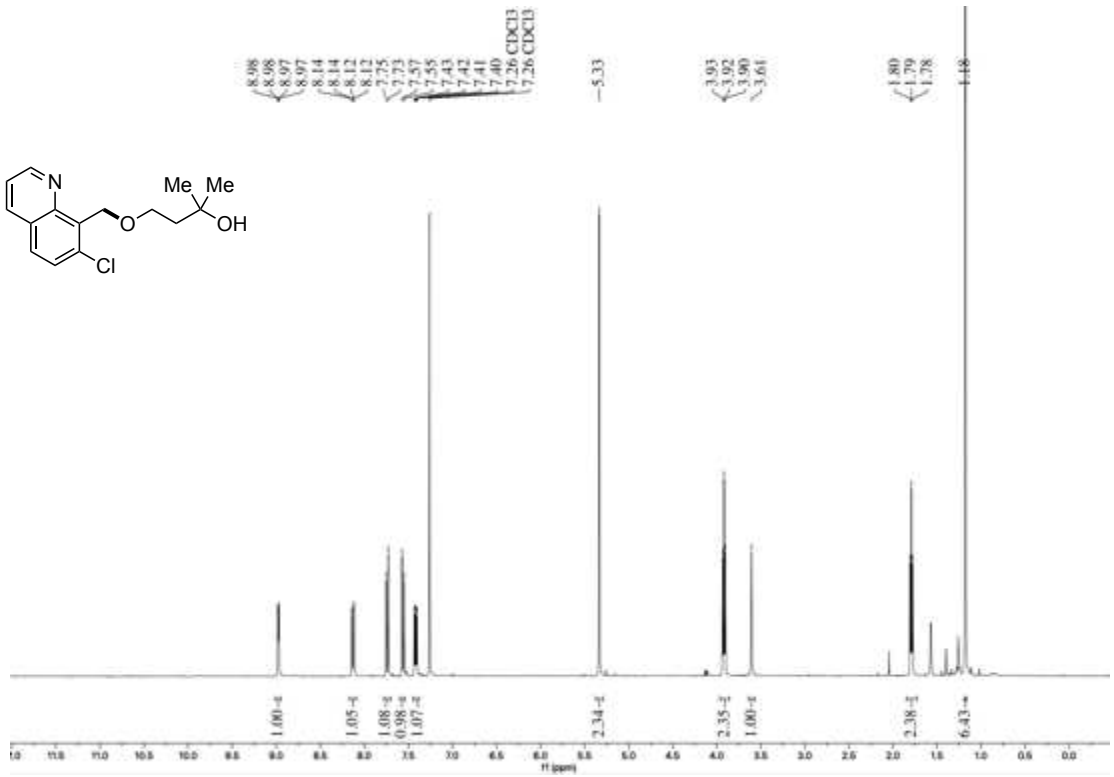
^{13}C NMR spectrum of **3-19** (101 MHz, $CDCl_3$)



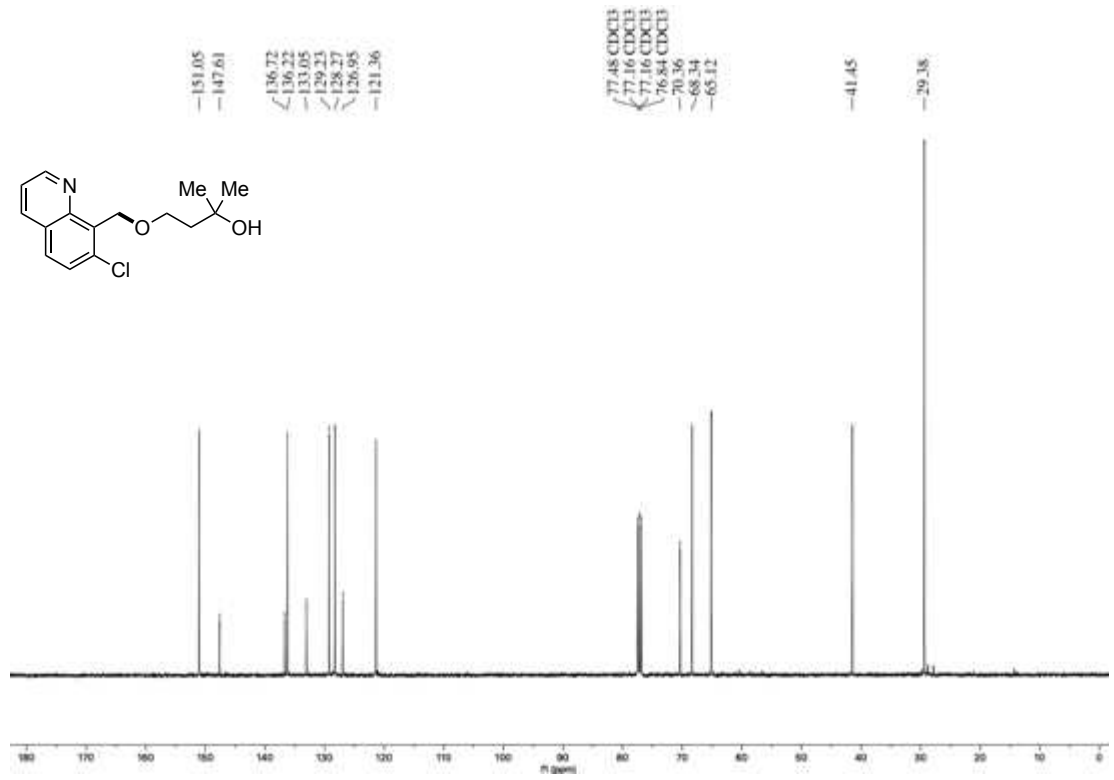
^{1}H NMR spectrum of **3-20** (400 MHz, $CDCl_3$)



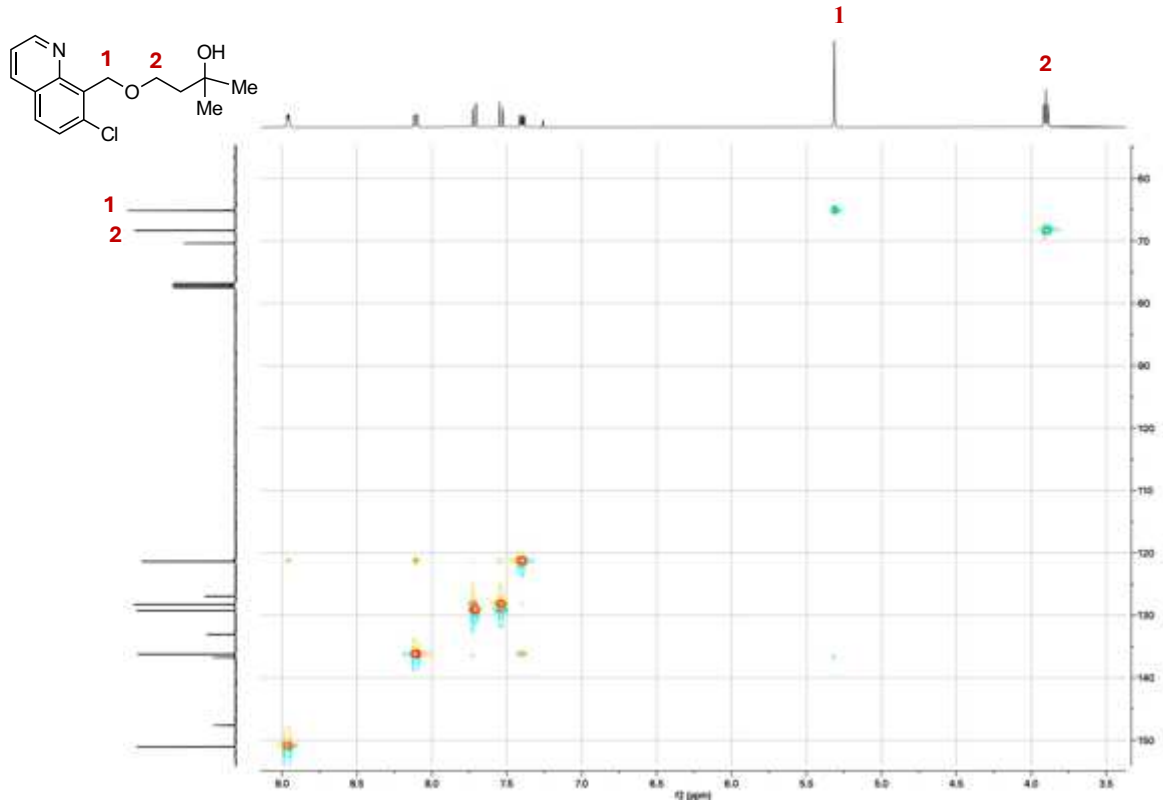
^{13}C NMR spectrum of **3-20** (101 MHz, $CDCl_3$)



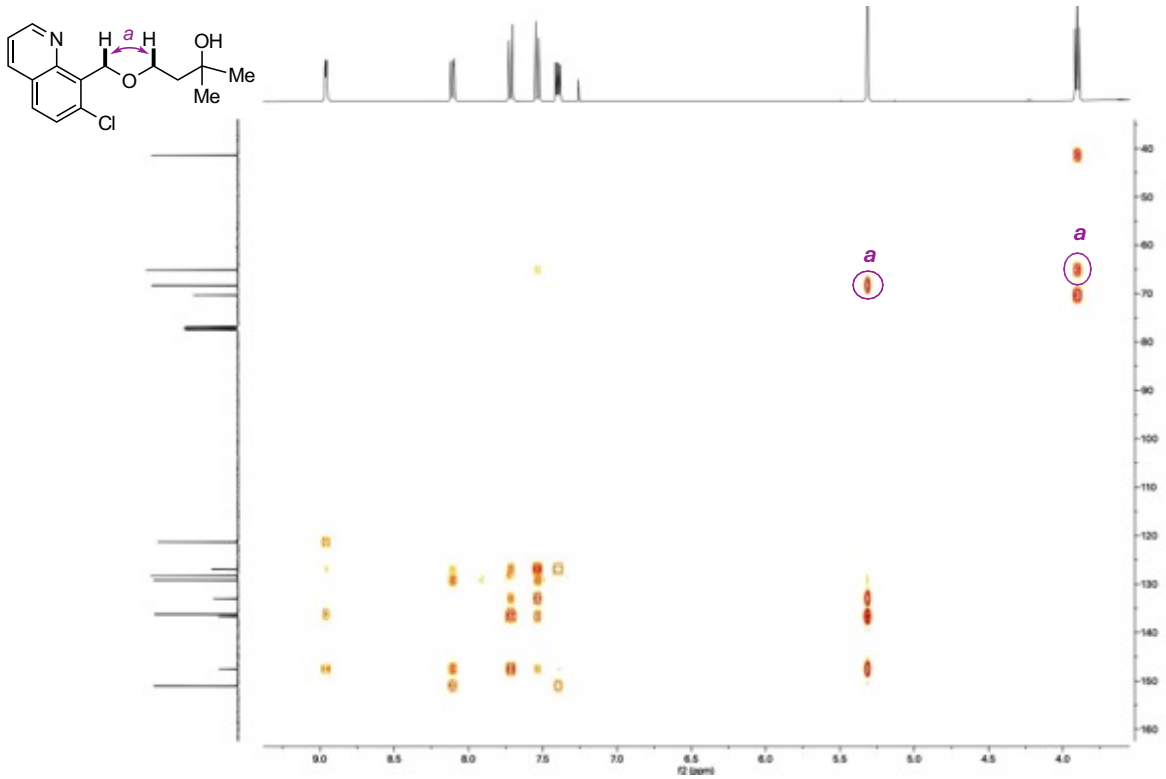
^{1}H NMR spectrum of **3-22** (400 MHz, $CDCl_3$)



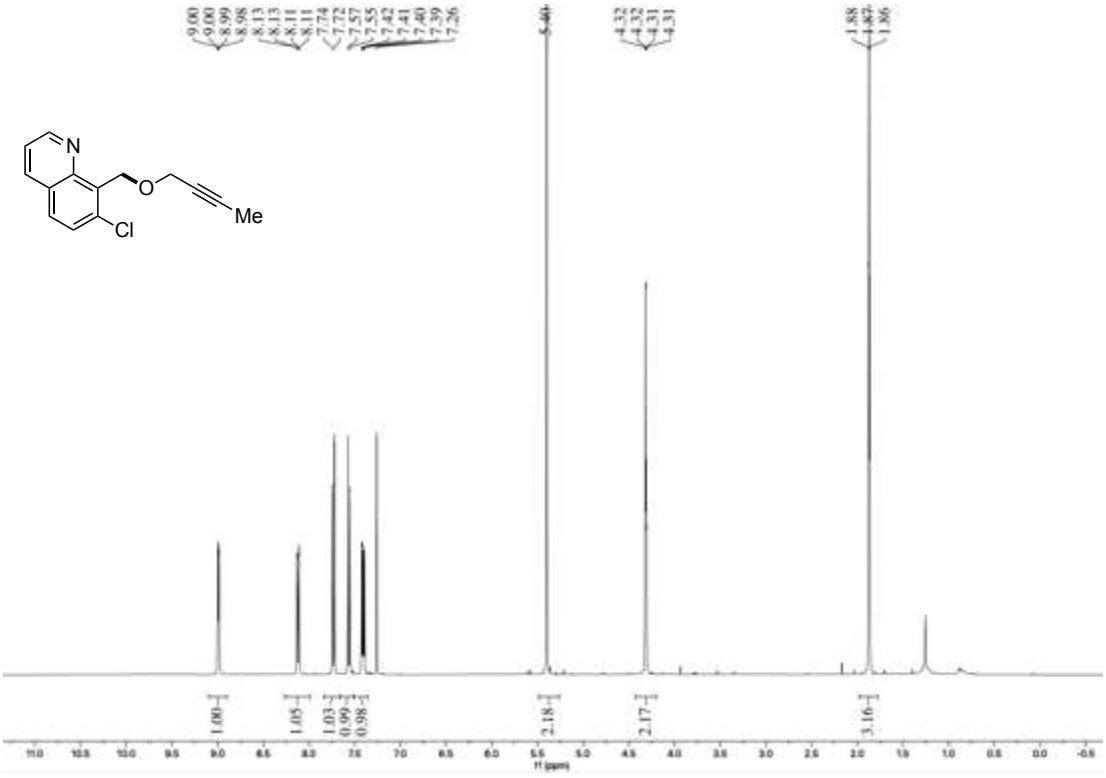
^{13}C NMR spectrum of **3-22** (101 MHz, $CDCl_3$)



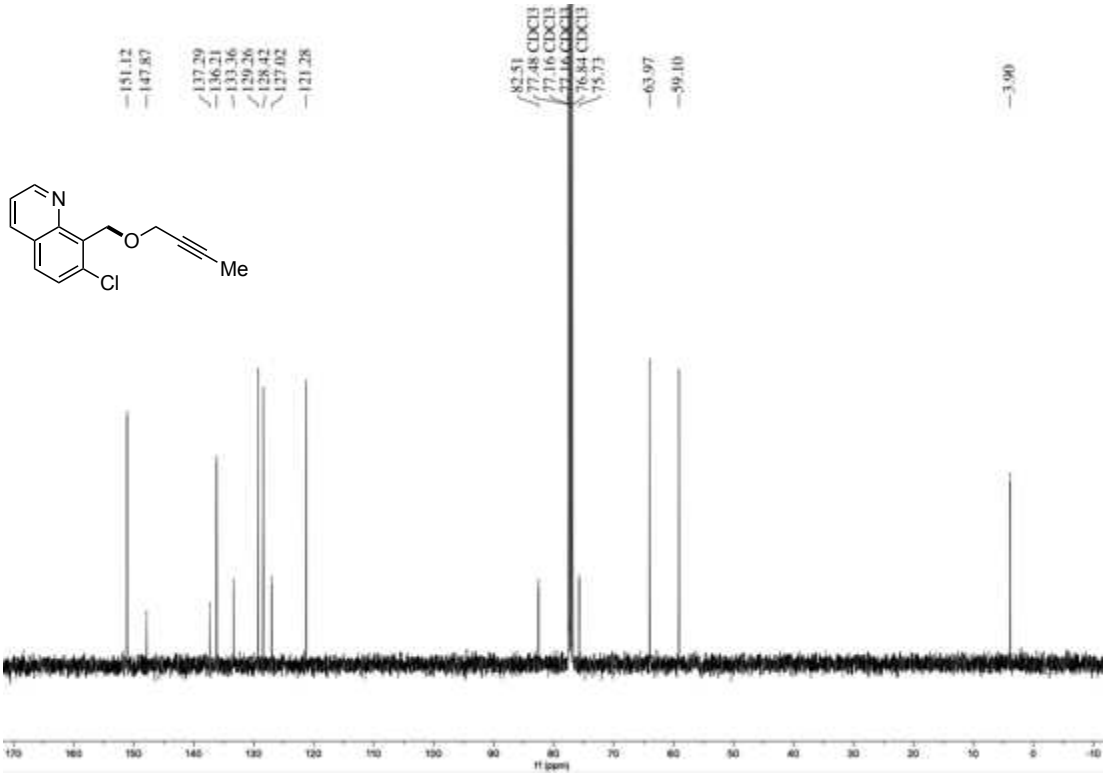
HSQC spectral window of **3-22** ($CDCl_3$)



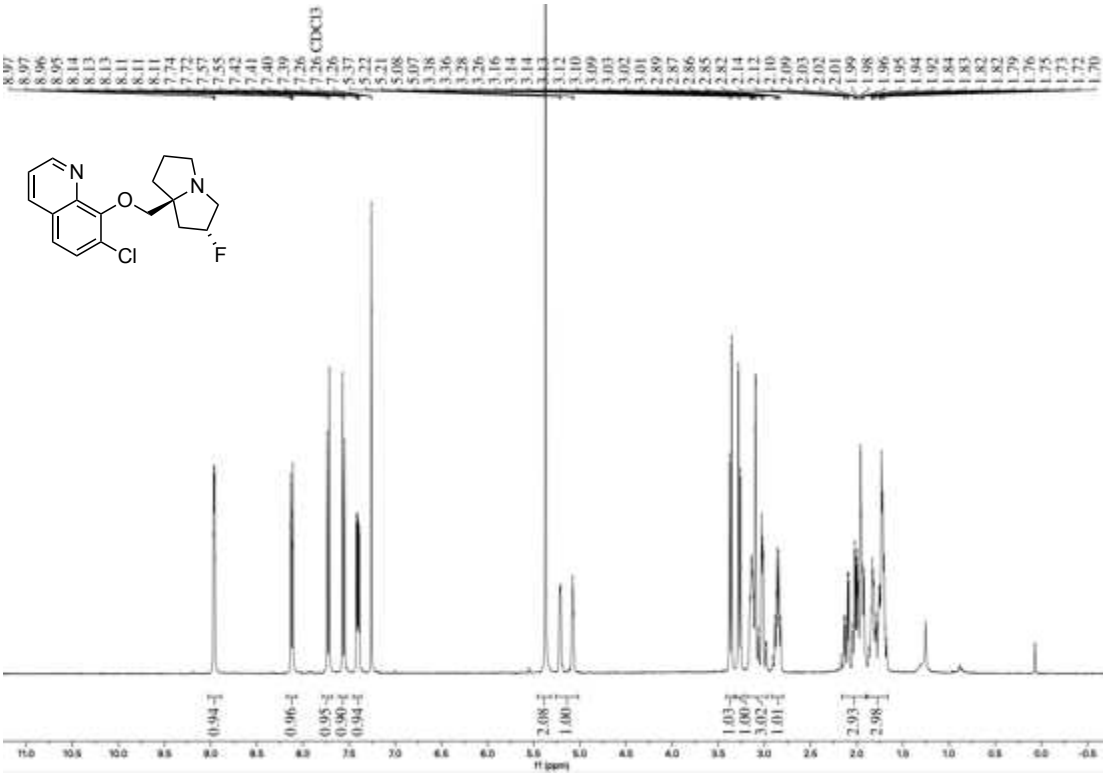
HMBC spectral window of **3-22** ($CDCl_3$)



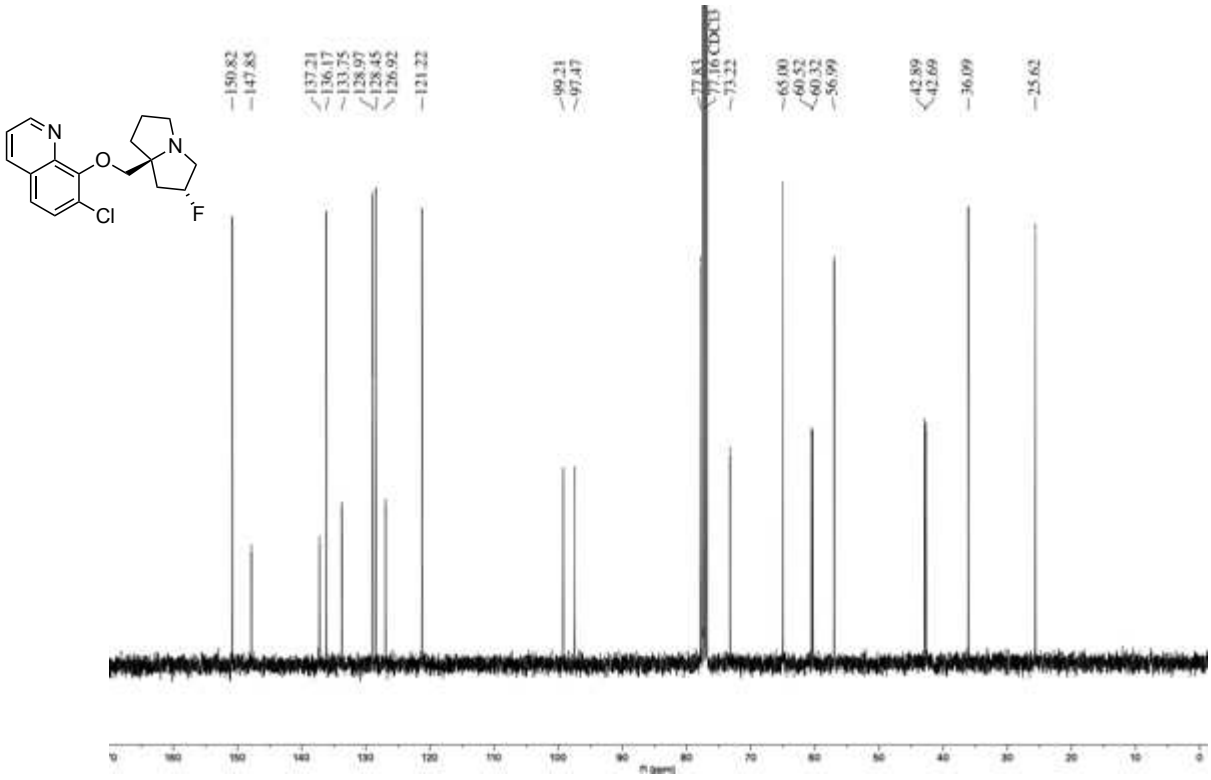
^{1}H NMR spectrum of **3-23** (400 MHz, $CDCl_3$)



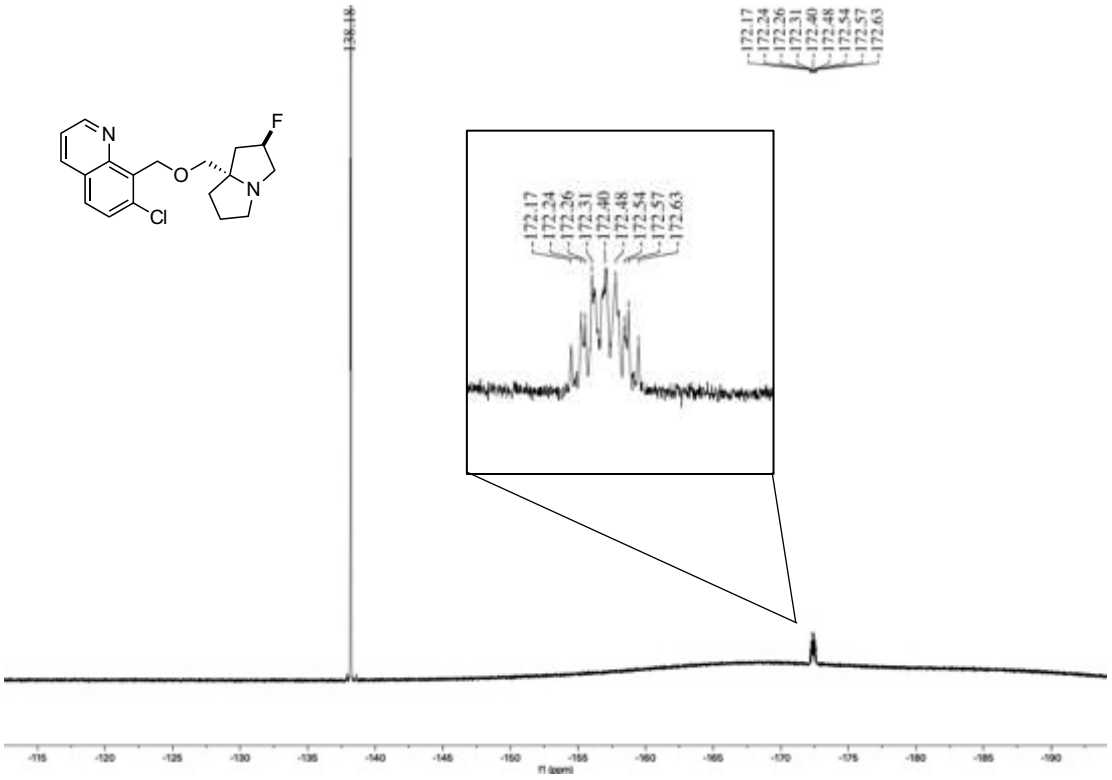
^{13}C NMR spectrum of **3-23** (101 MHz, $CDCl_3$)



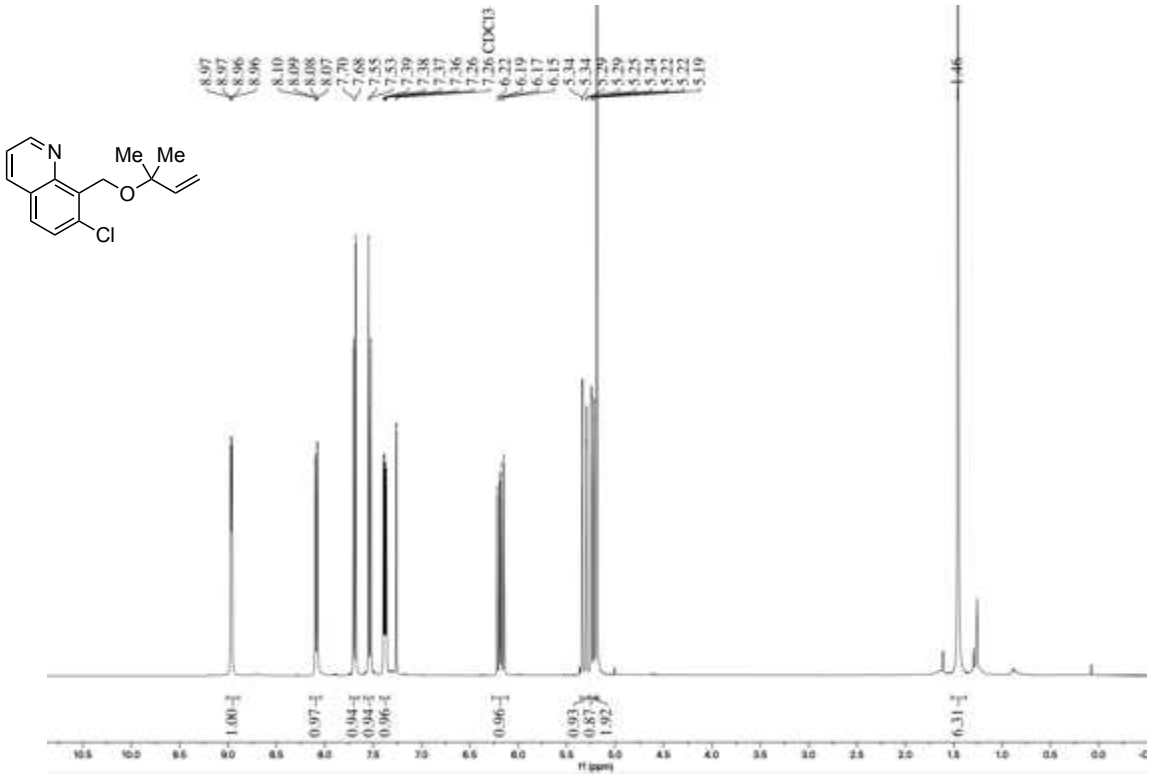
^{1}H NMR spectrum of **3-24** (400 MHz, $CDCl_3$)



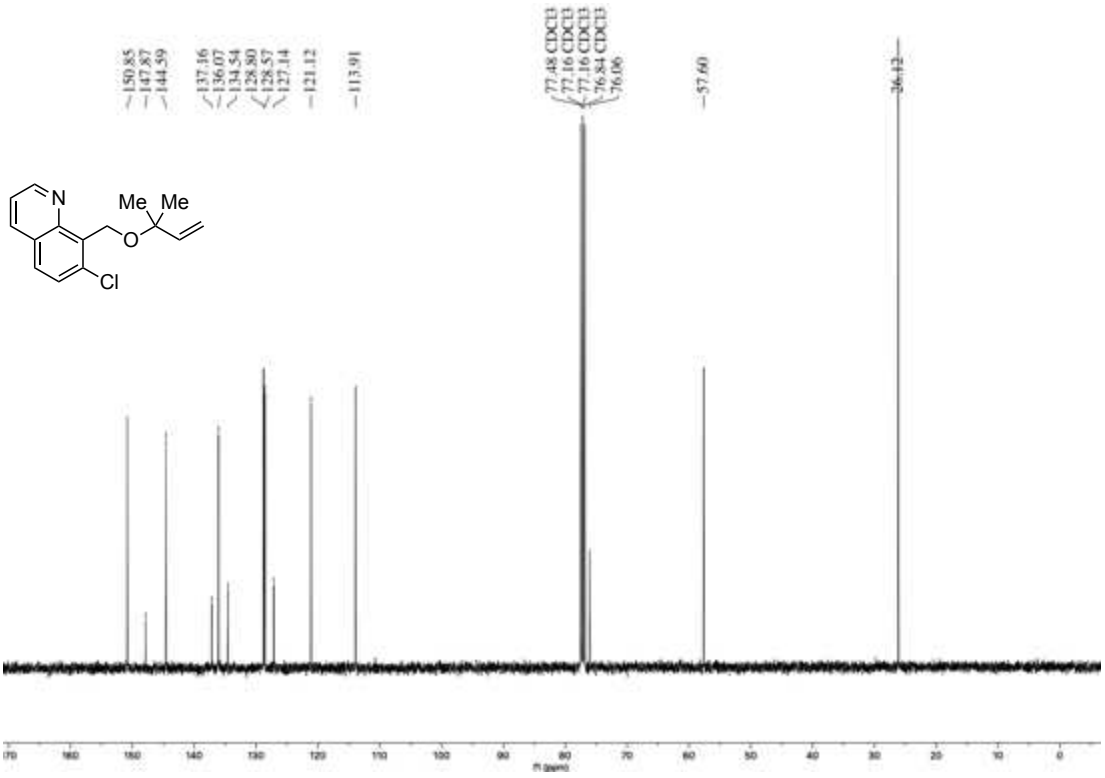
^{13}C NMR spectrum of **3-24** (101 MHz, $CDCl_3$)



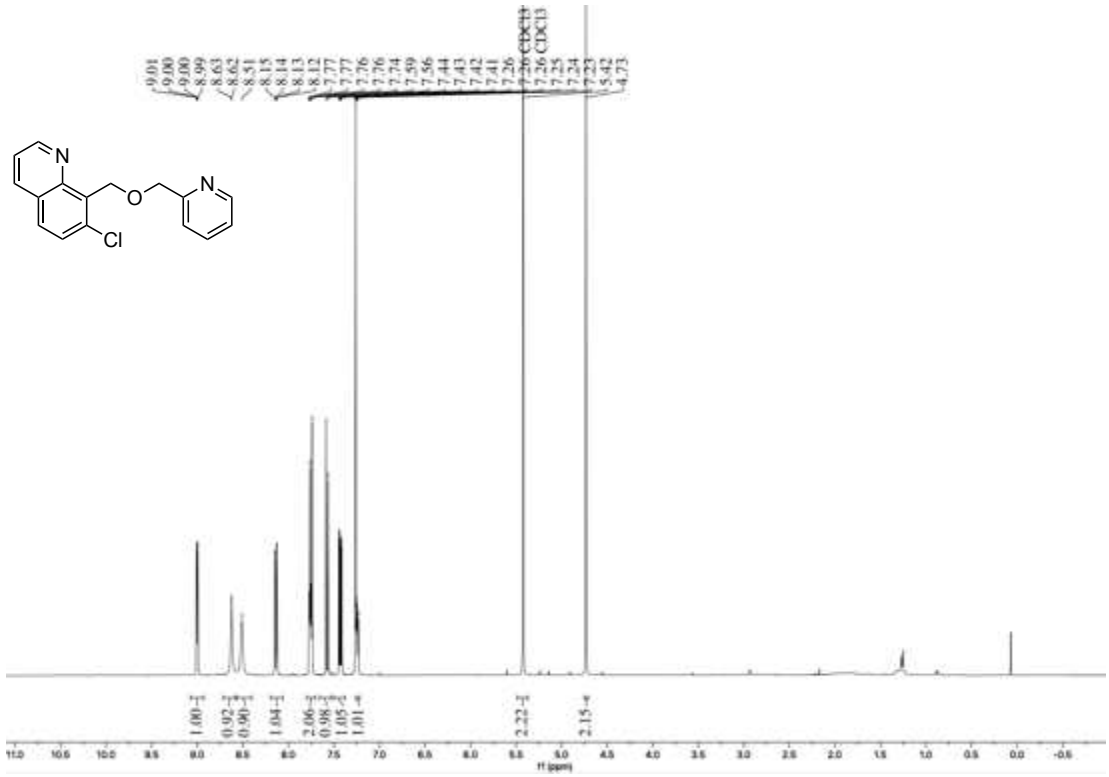
^{19}F NMR spectrum of **3-24** (376 MHz, $CDCl_3$)



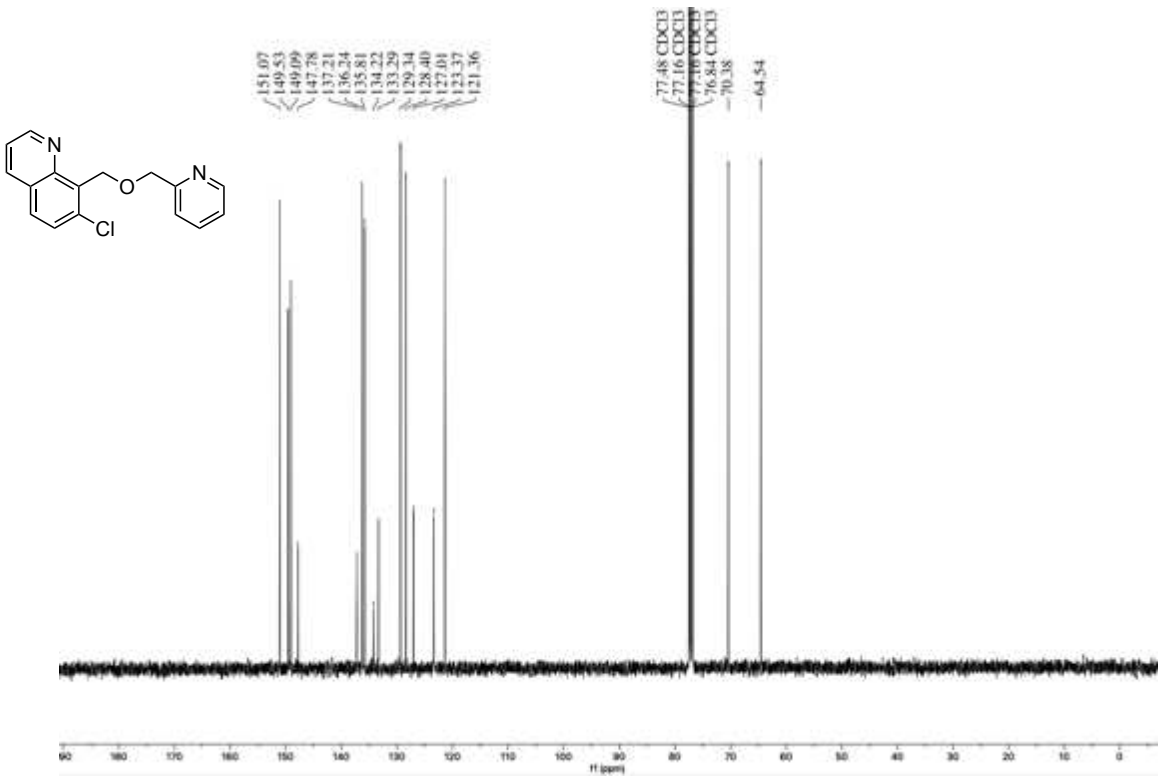
^{1}H NMR spectrum of **3-25** (400 MHz, $CDCl_3$)



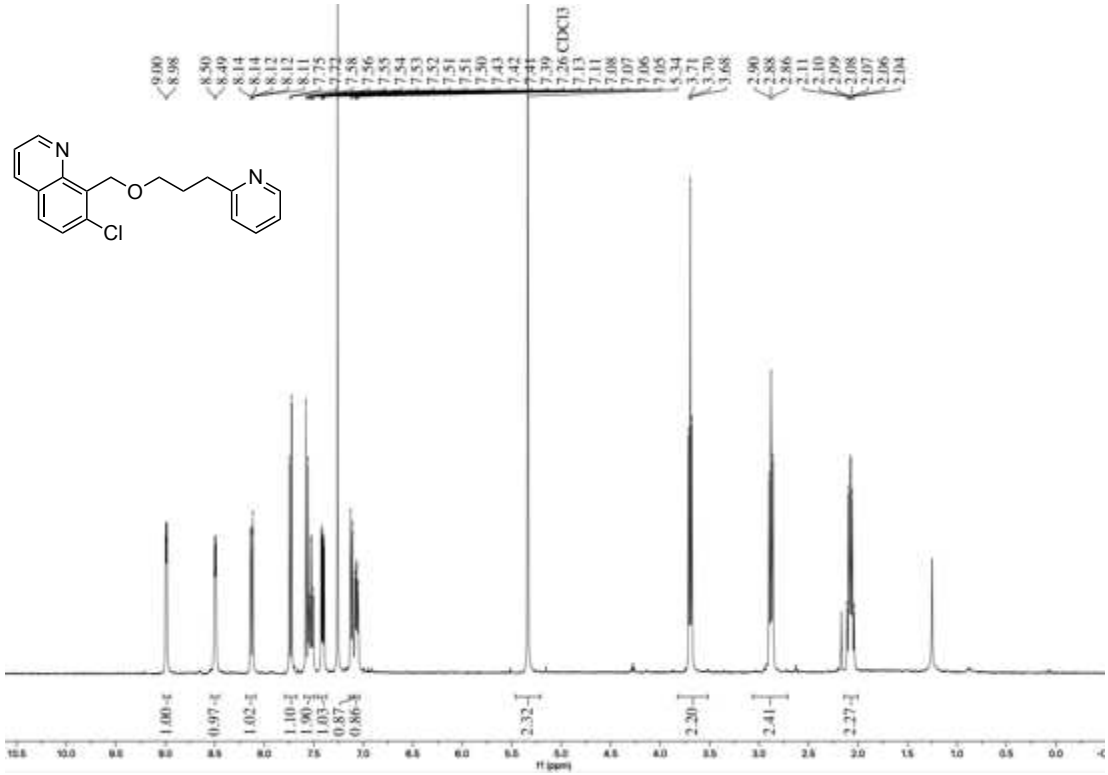
^{13}C NMR spectrum of **3-25** (101 MHz, $CDCl_3$)



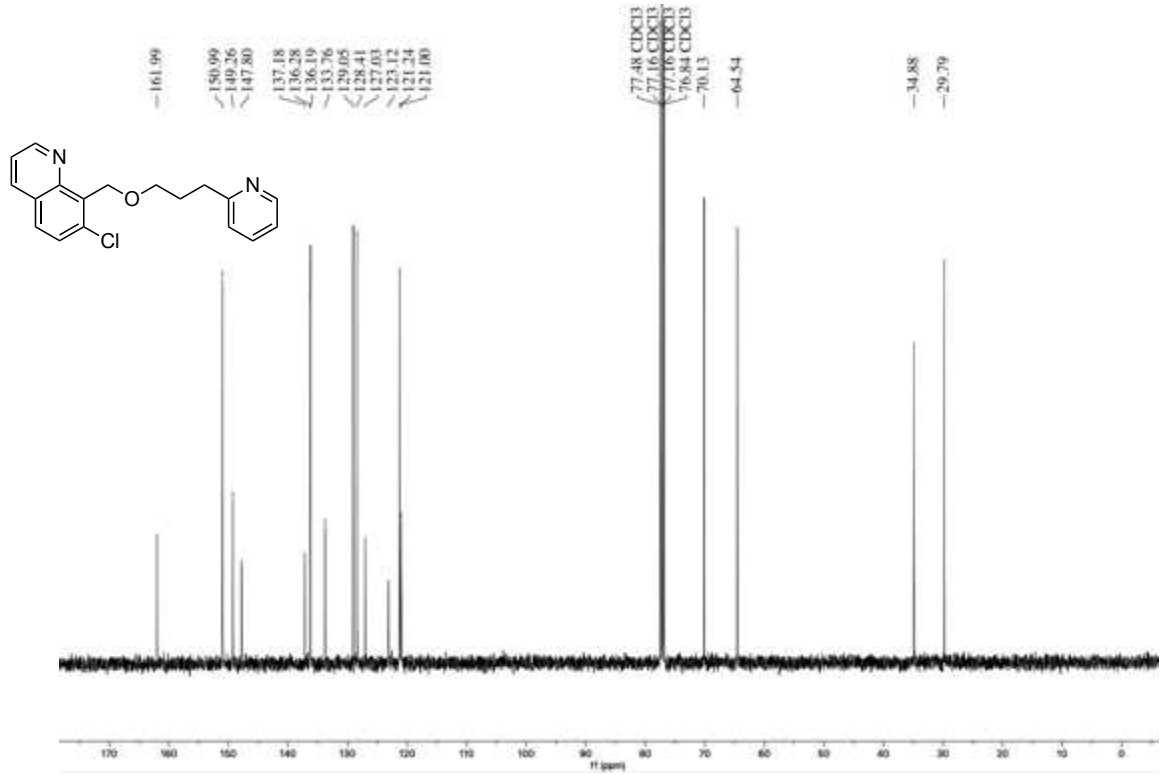
^{1}H NMR spectrum of **3-26** (400 MHz, $CDCl_3$)



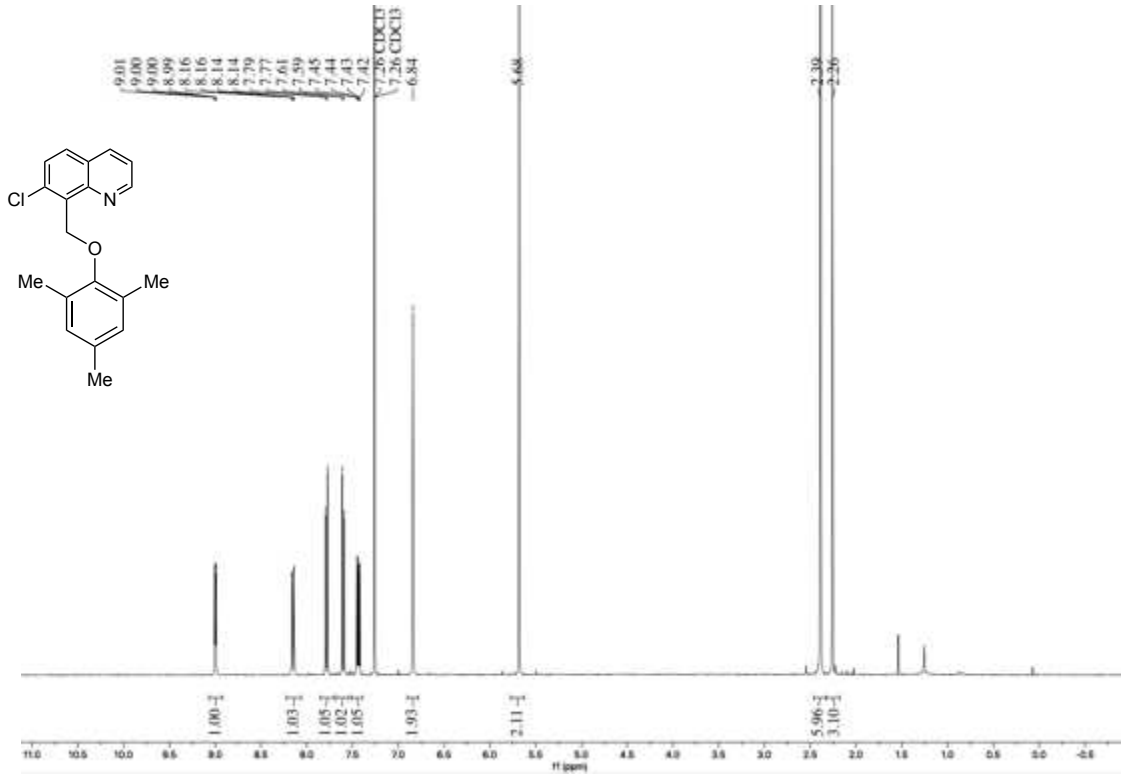
^{13}C NMR spectrum of **3-26** (101 MHz, $CDCl_3$)



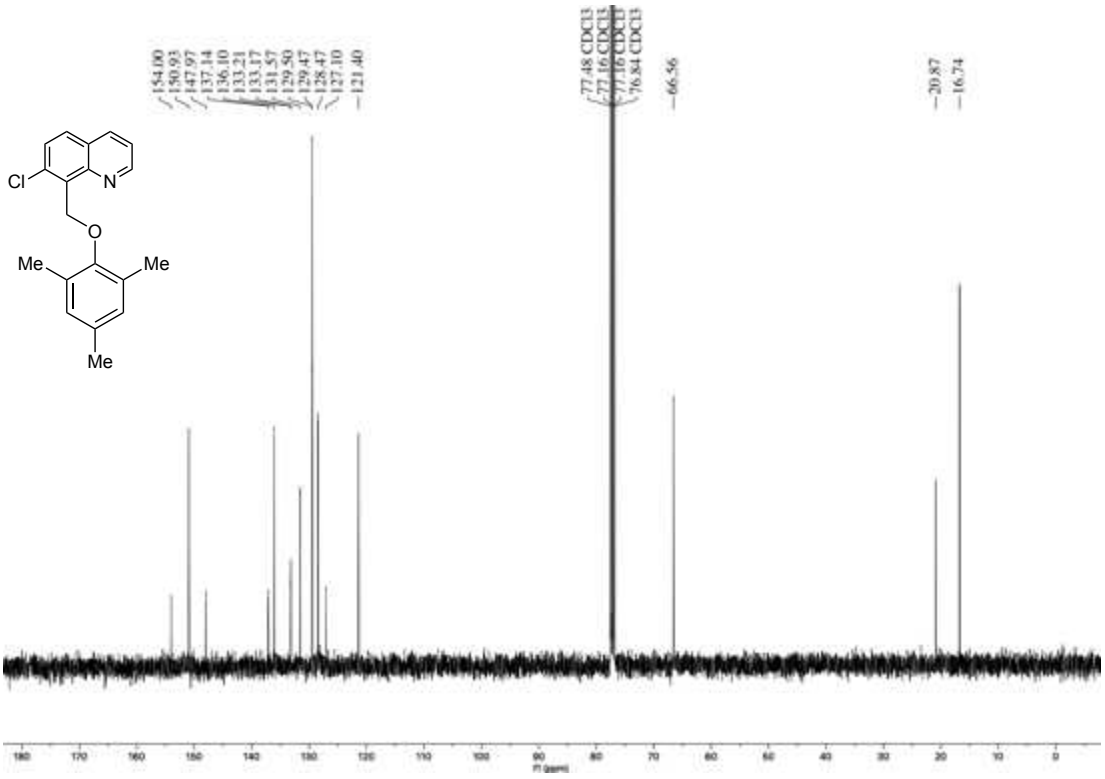
^{1}H NMR spectrum of **3-27** (400 MHz, $CDCl_3$)



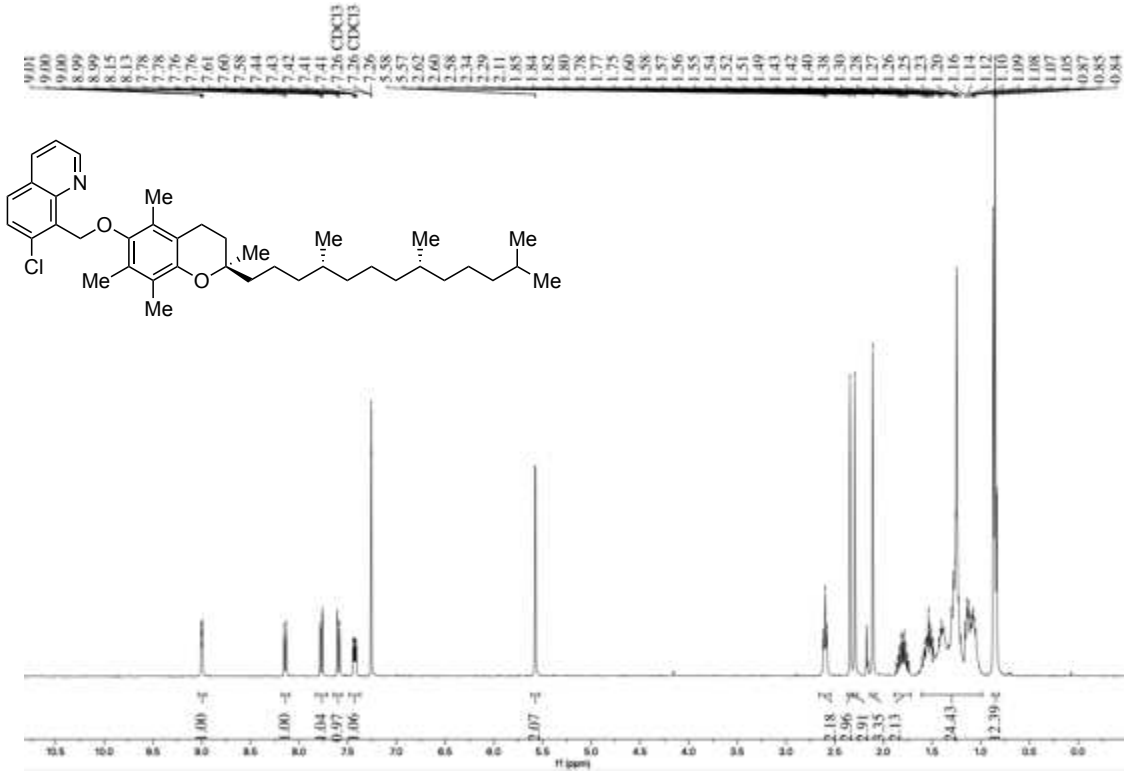
^{13}C NMR spectrum of **3-27** (101 MHz, $CDCl_3$)



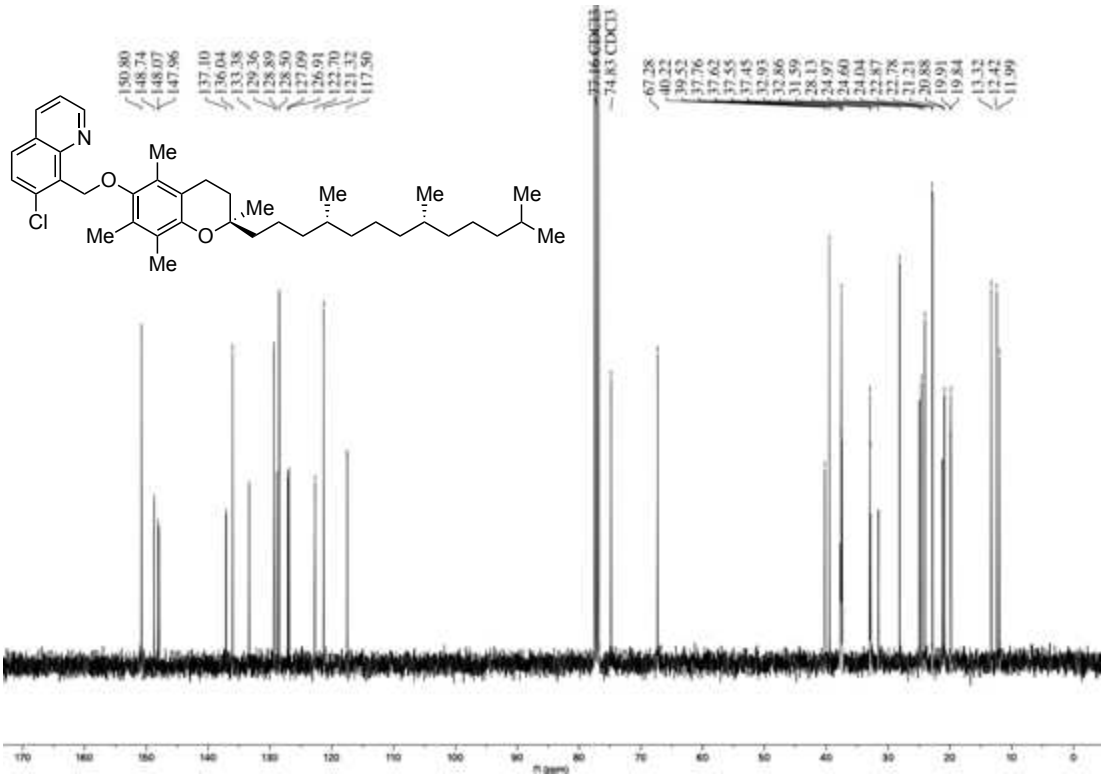
^{1}H NMR spectrum of **3-28** (400 MHz, $CDCl_3$)



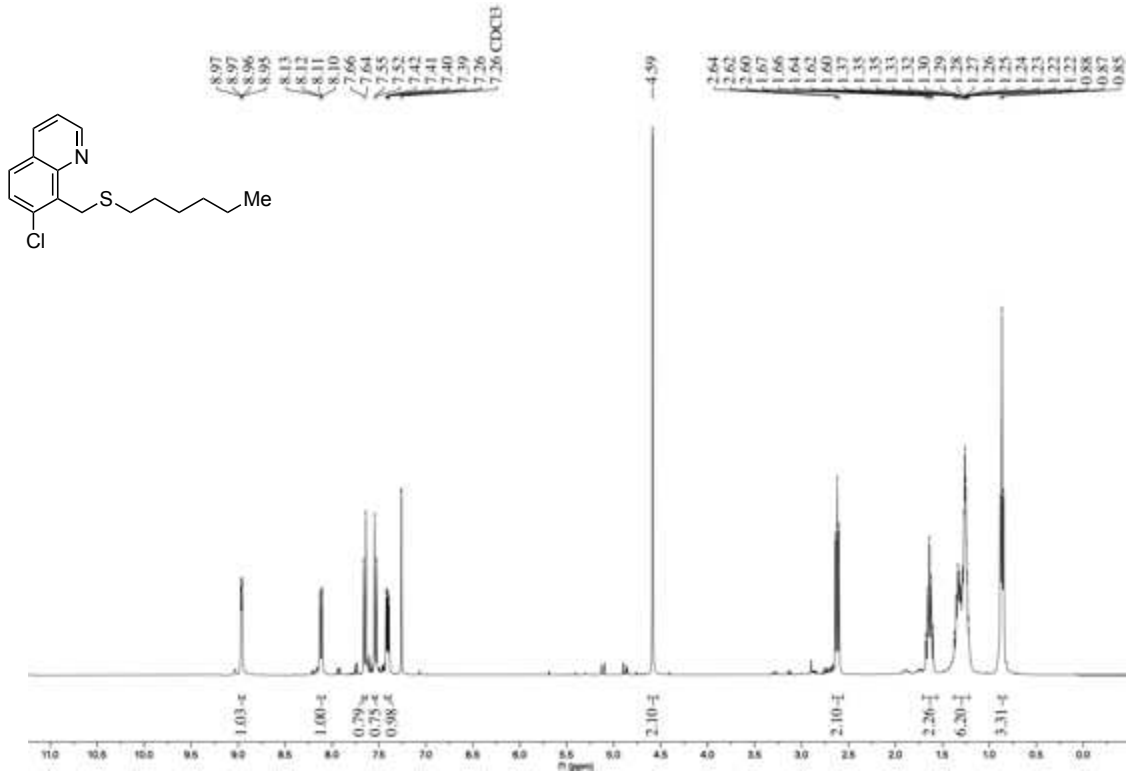
^{13}C NMR spectrum of **3-28** (101 MHz, $CDCl_3$)



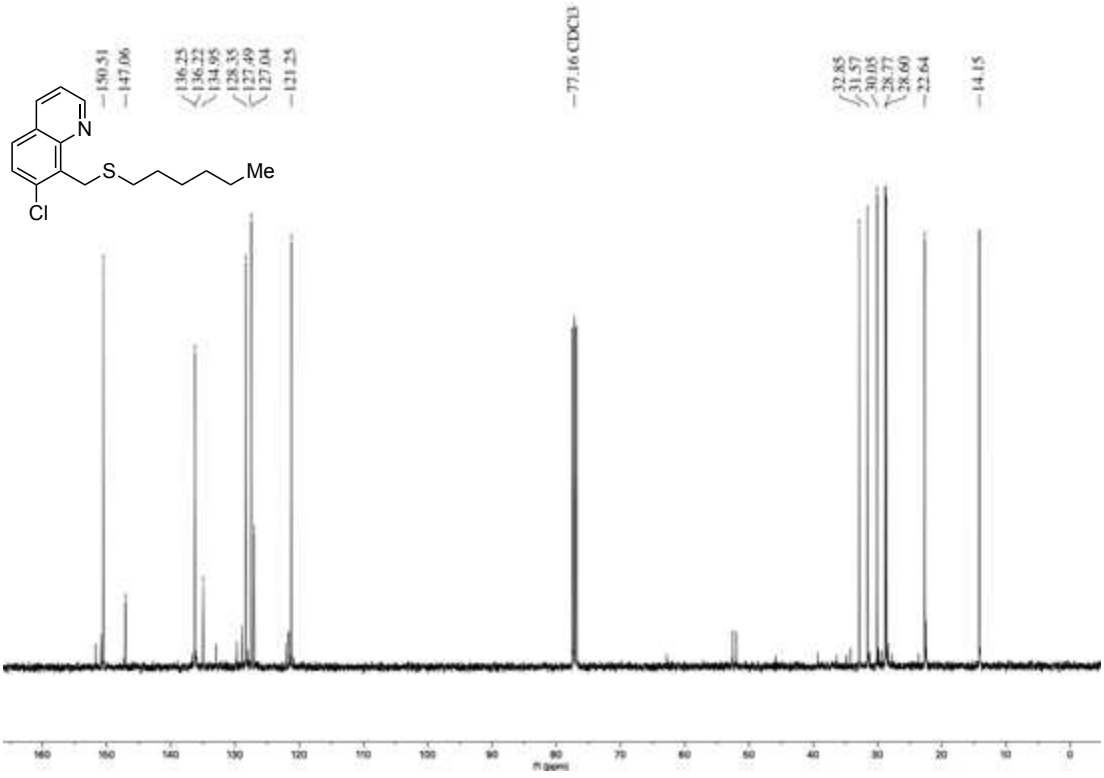
^{1}H NMR spectrum of **3-29** (400 MHz, $CDCl_3$)



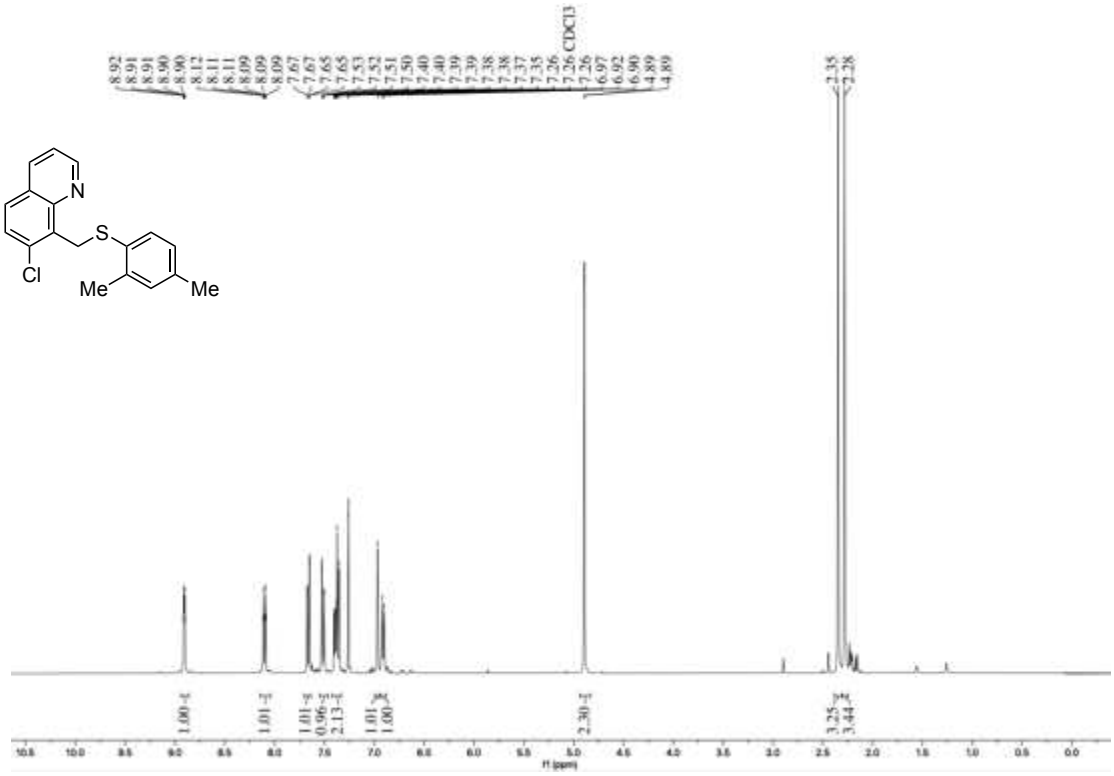
^{13}C NMR spectrum of **3-29** (101 MHz, $CDCl_3$)



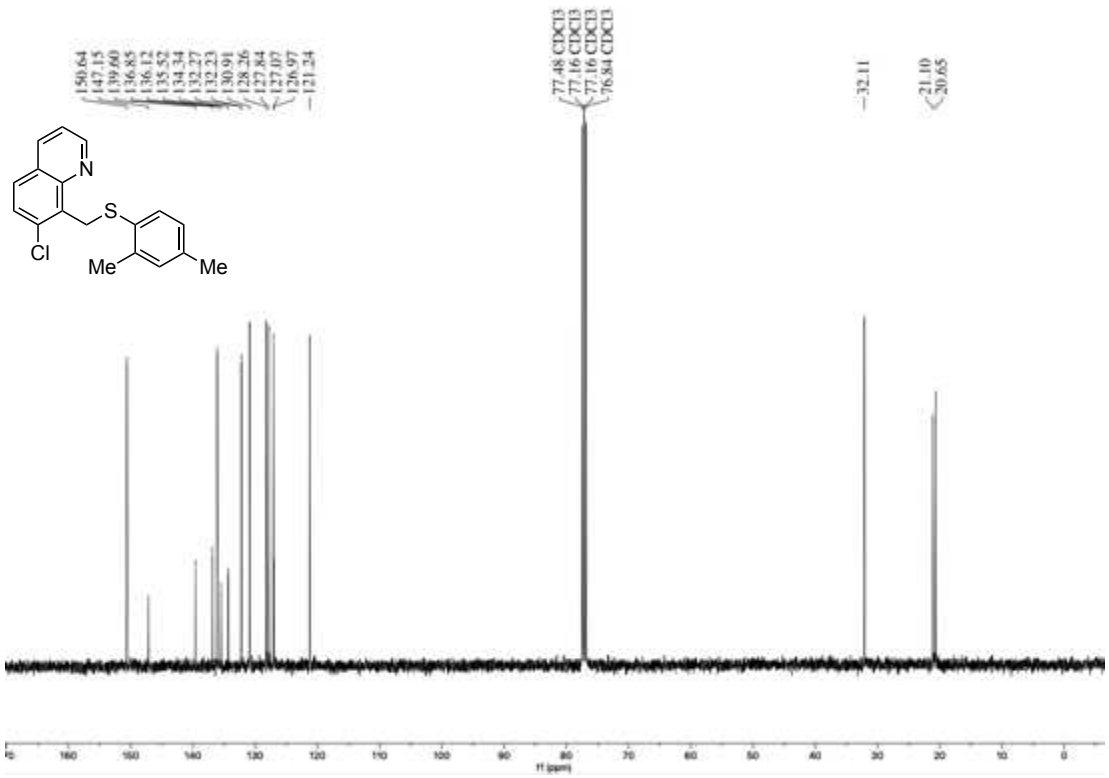
^{1}H NMR spectrum of **3-30** (400 MHz, $CDCl_3$)



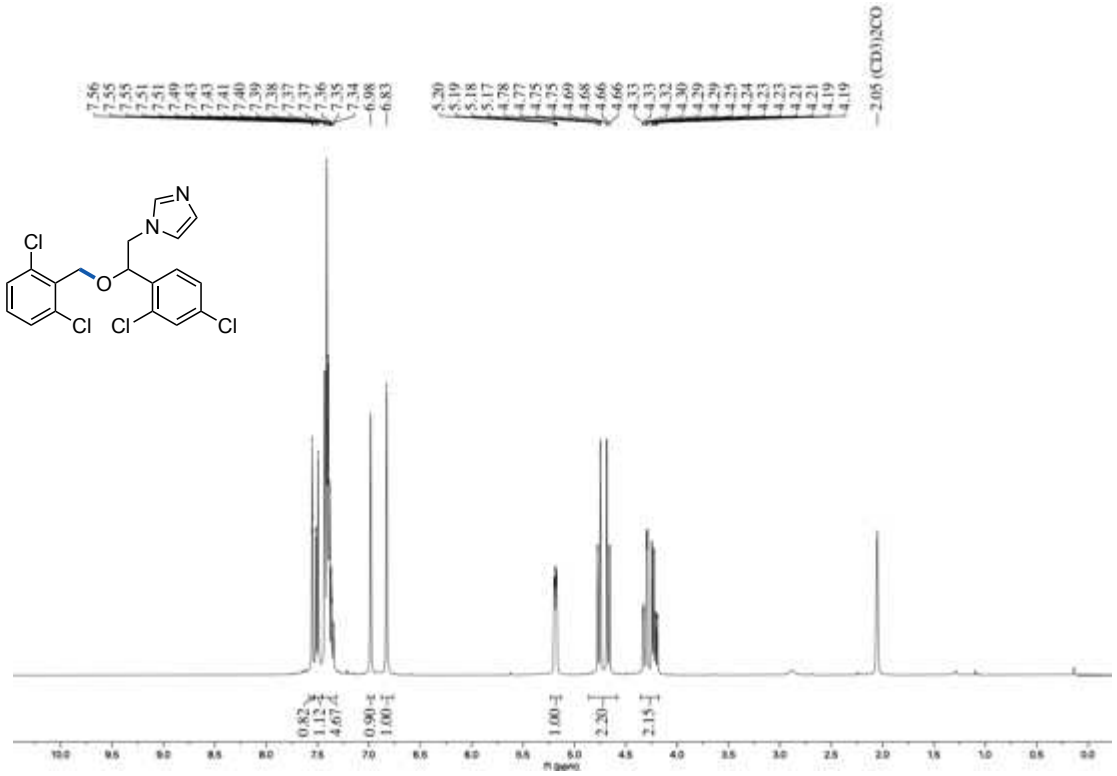
^{13}C NMR spectrum of **3-30** (101 MHz, $CDCl_3$)



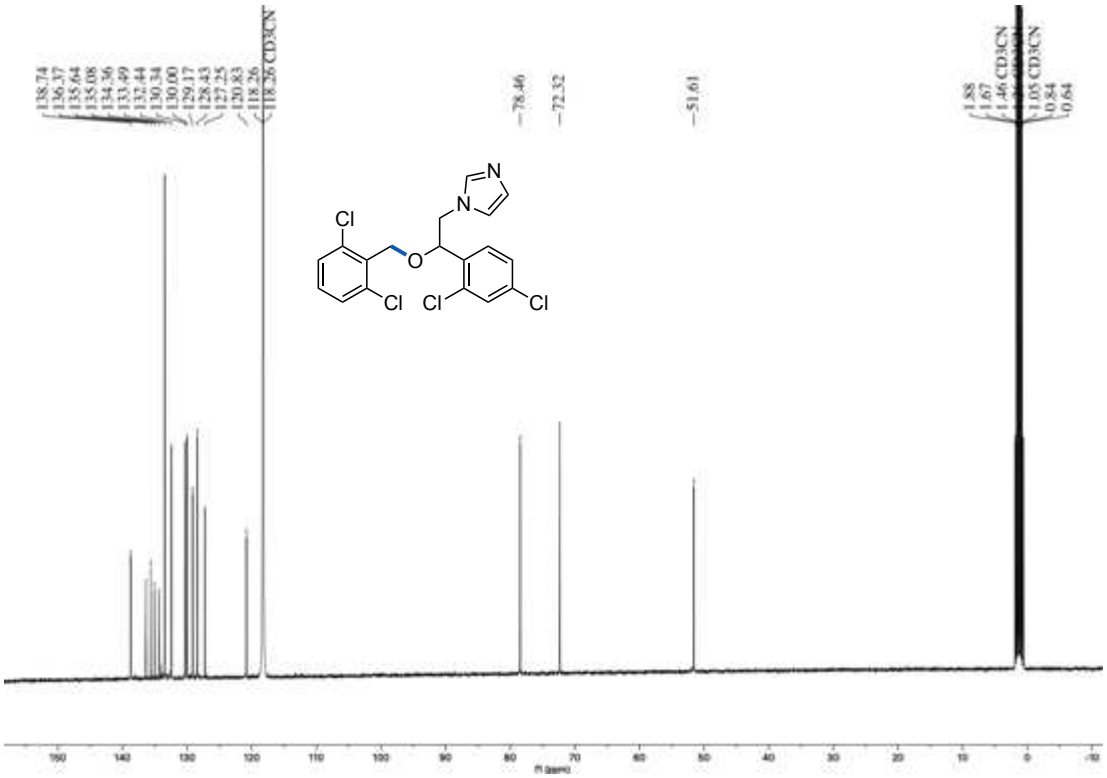
^{1}H NMR spectrum of **3-31** (400 MHz, $CDCl_3$)



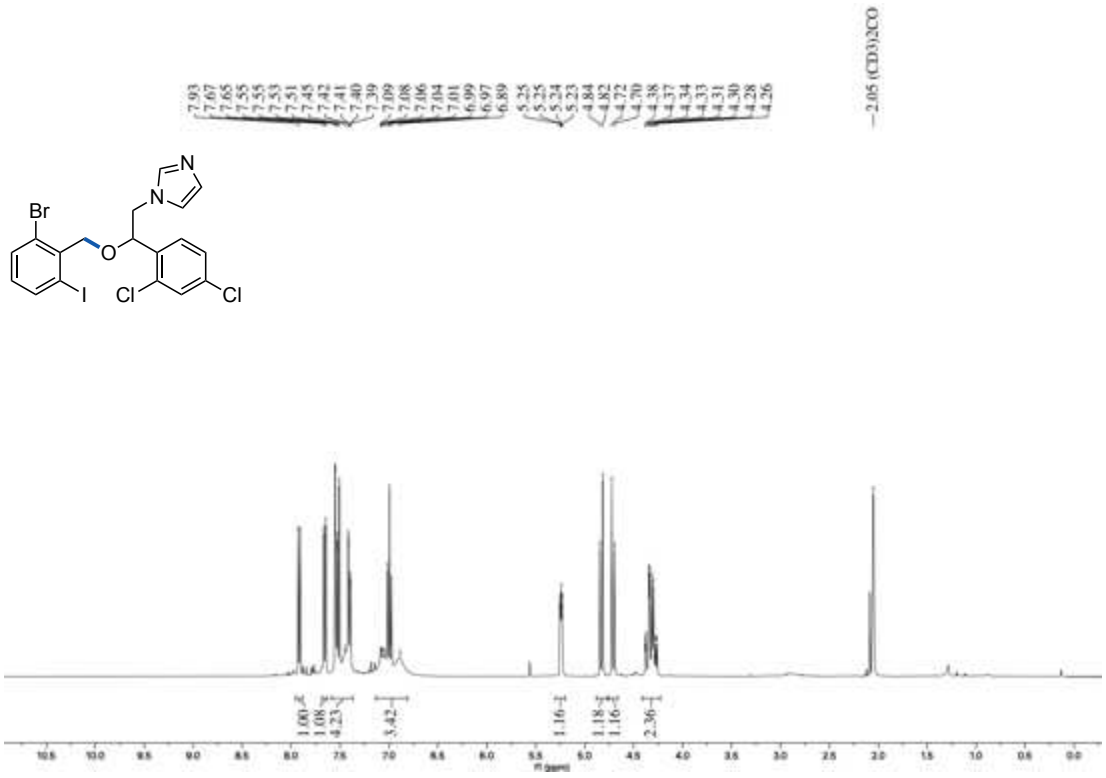
^{13}C NMR spectrum of **3-31** (101 MHz, $CDCl_3$)



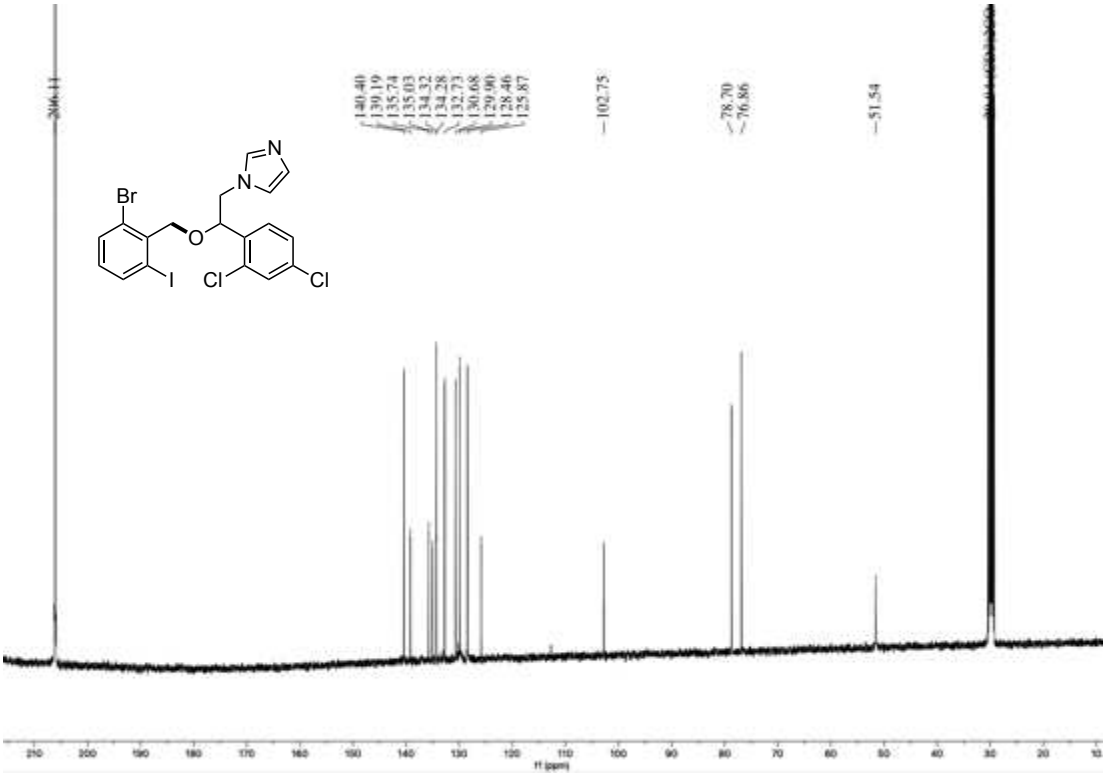
^{1}H NMR spectrum of **3-33** (400 MHz, $(CD_3)_2CO$)



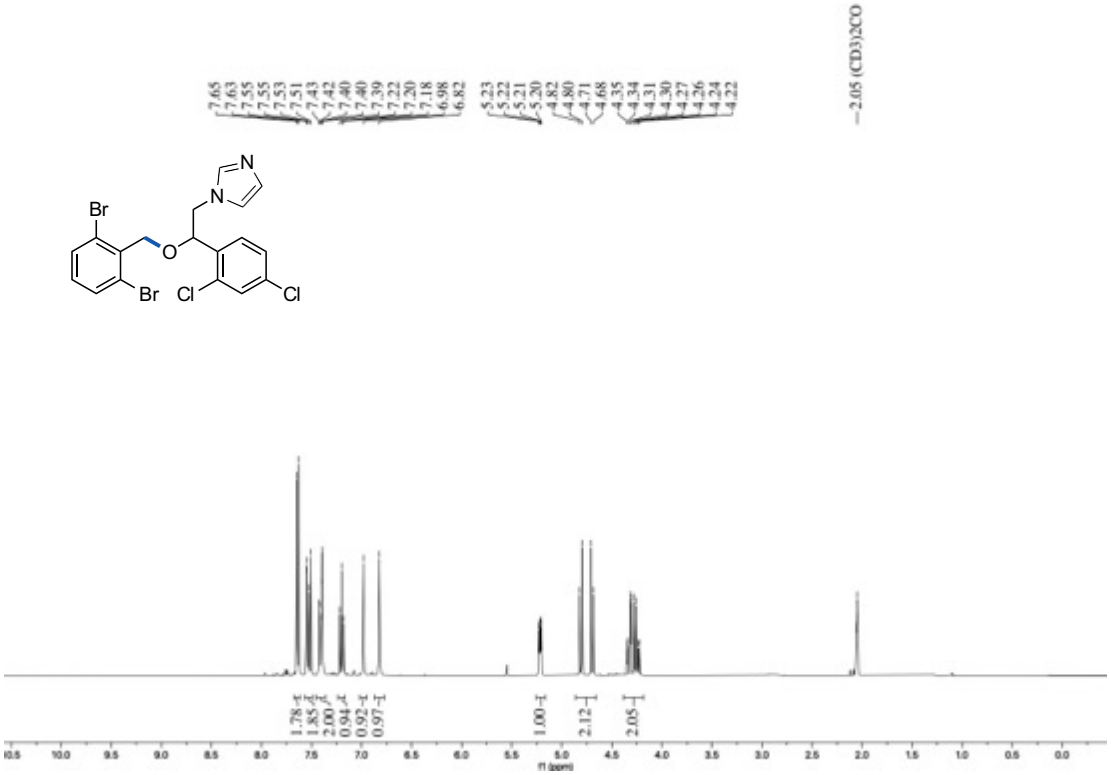
^{13}C NMR spectrum of **3-33** (101 MHz, CD_3CN)



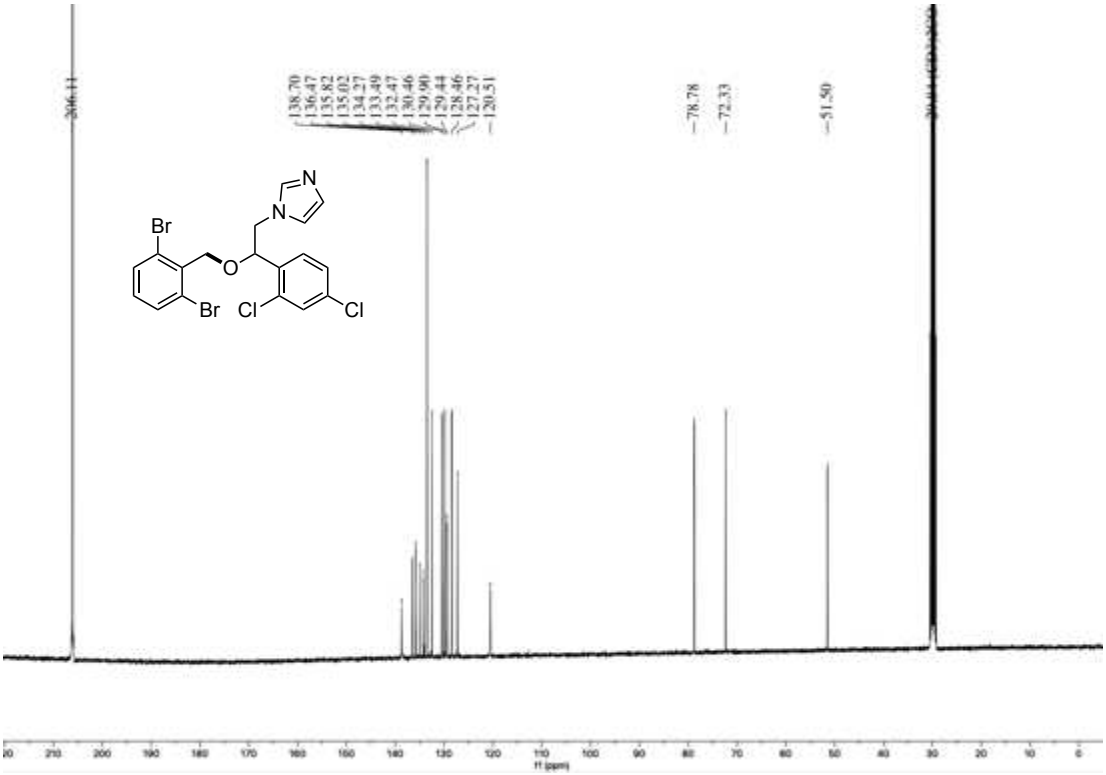
^{1}H NMR spectrum of **3-34** (400 MHz, $(CD_3)_2CO$)



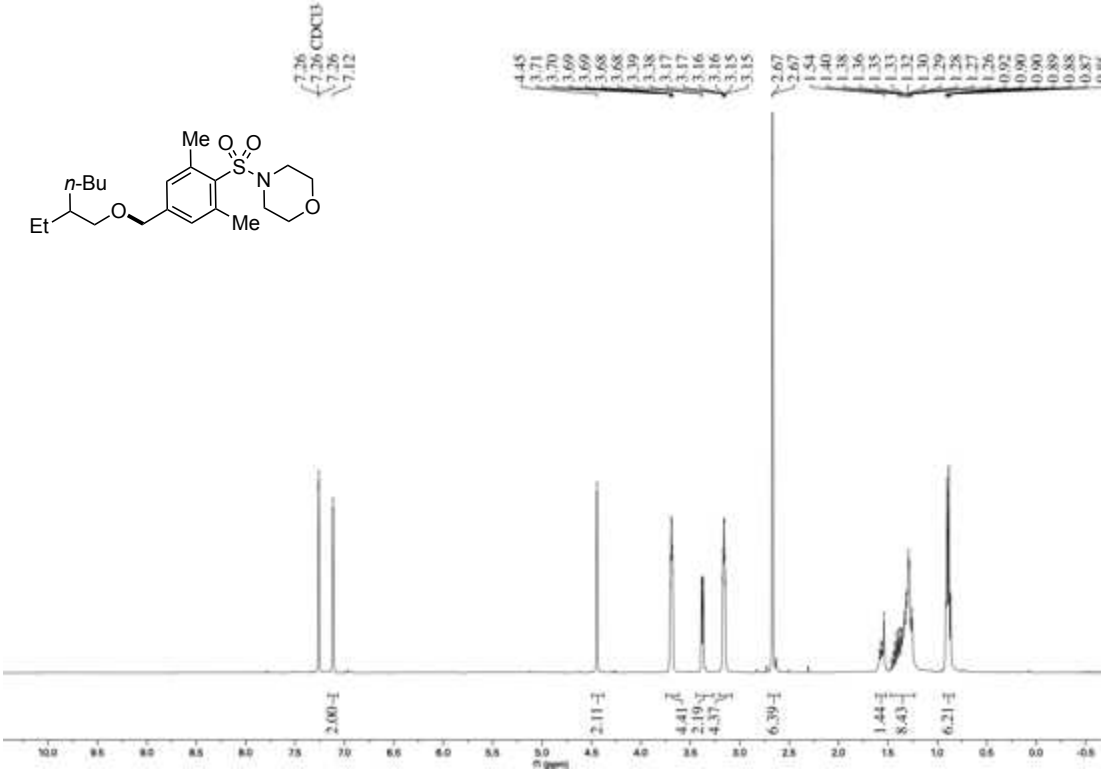
^{13}C NMR spectrum of **3-34** (101 MHz, $(CD_3)_2CO$)



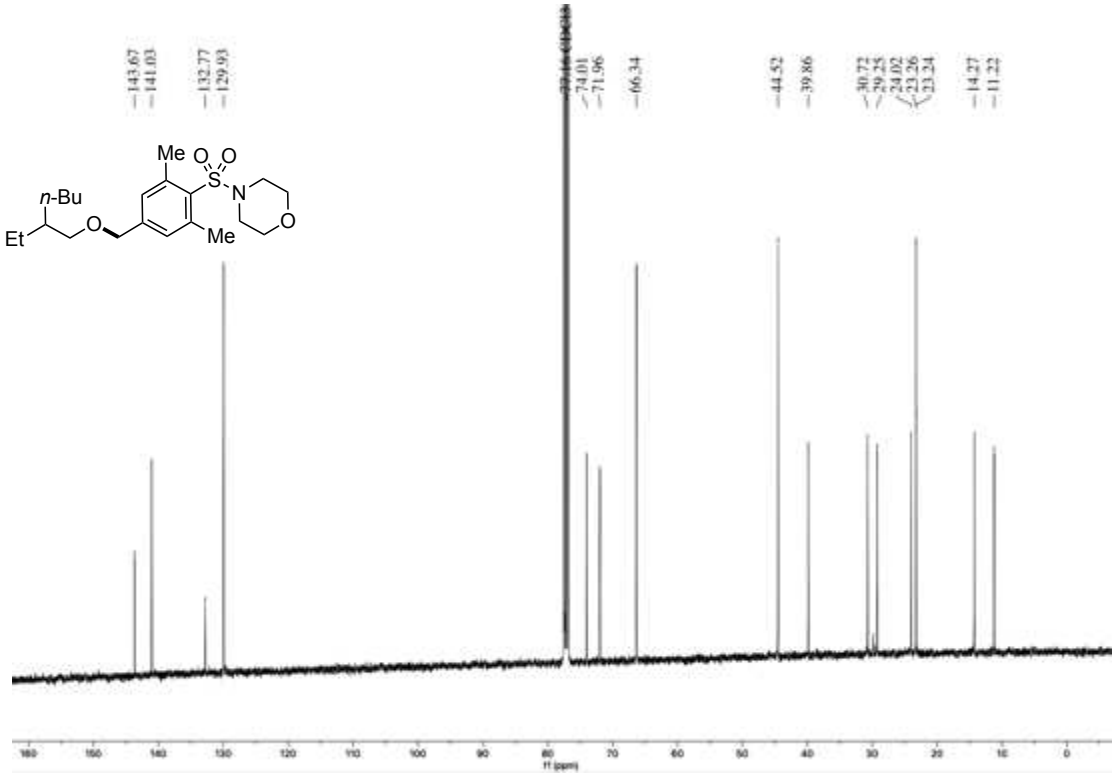
^{1}H NMR spectrum of **3-35** (400 MHz, $(CD_3)_2CO$)



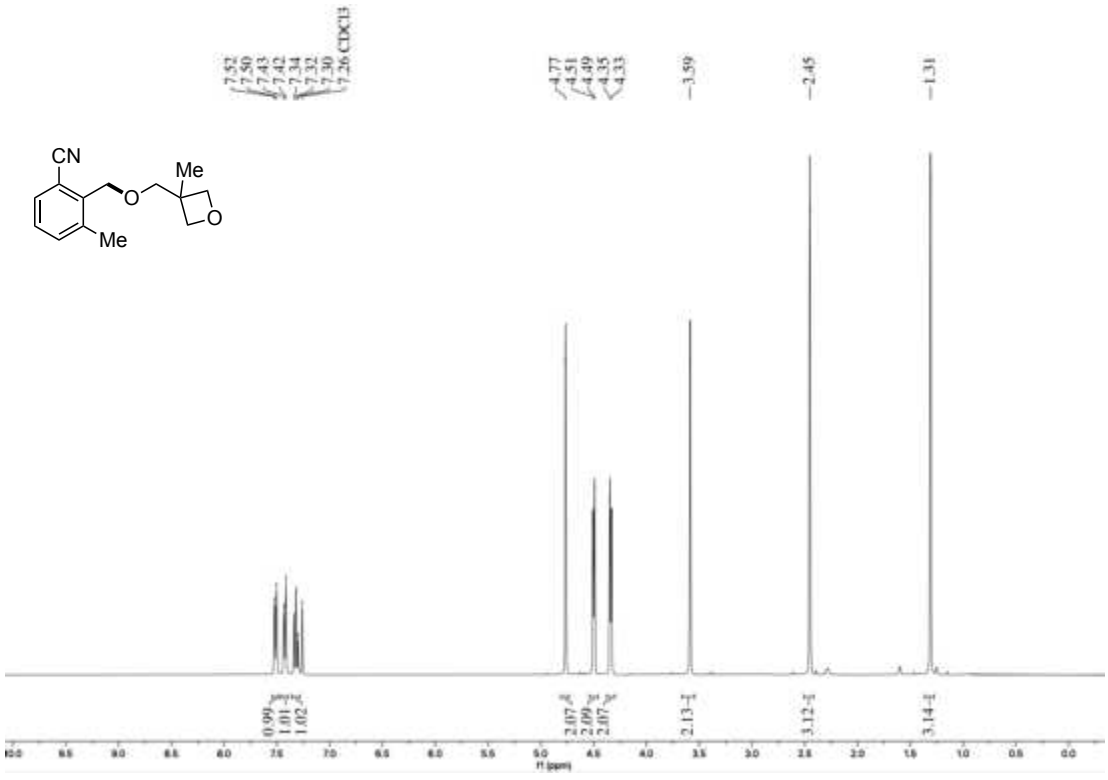
^{13}C NMR spectrum of **3-35** (101 MHz, $(CD_3)_2CO$)



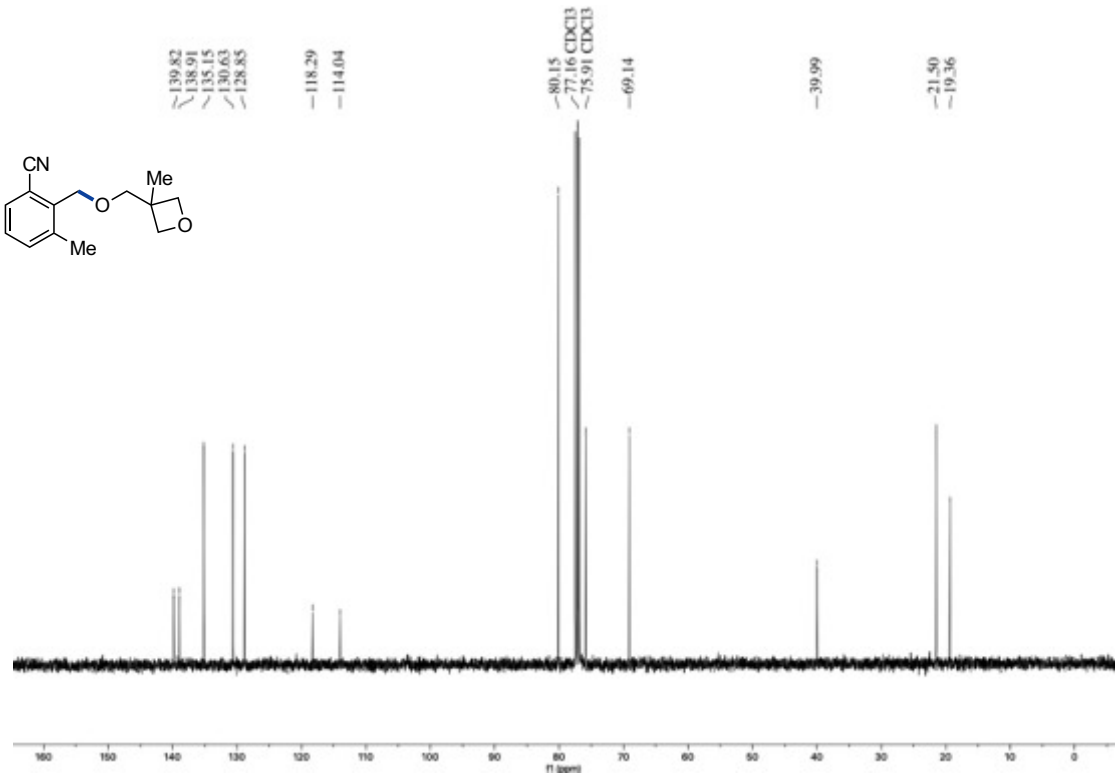
^{1}H NMR spectrum of **3-36** (400 MHz, $CDCl_3$)



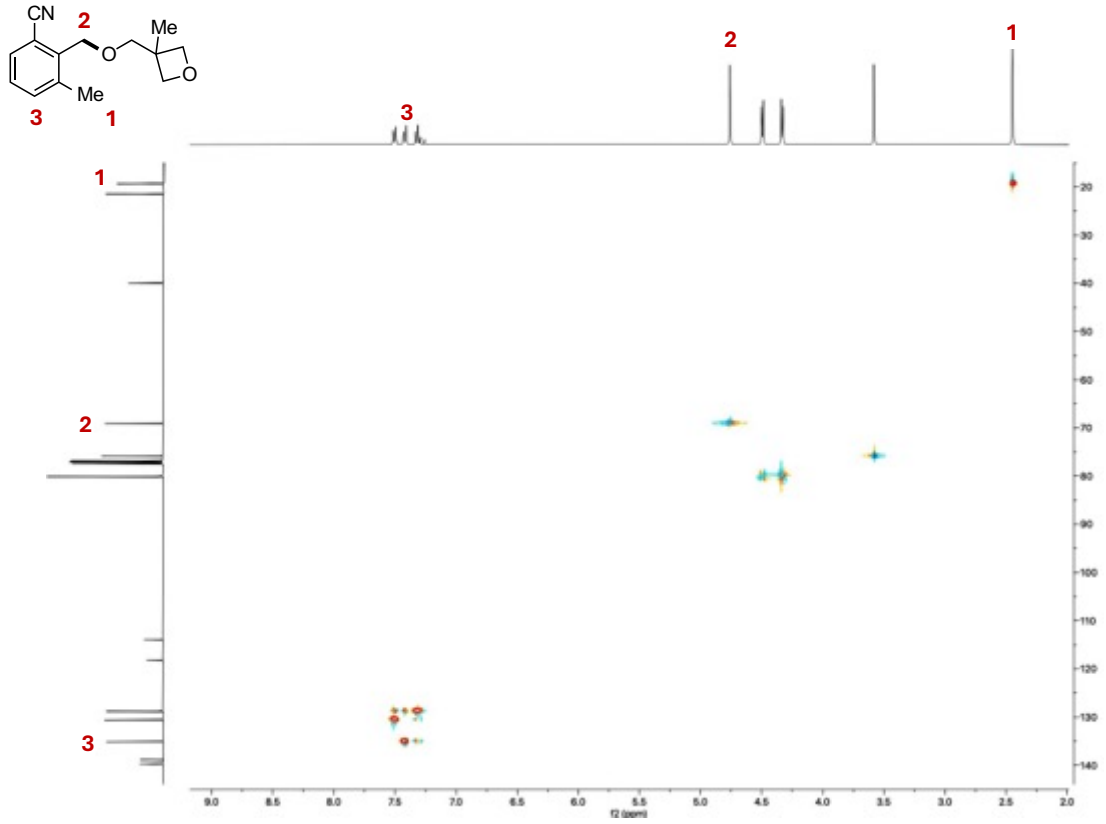
^{13}C NMR spectrum of **3-36** (101 MHz, $CDCl_3$)



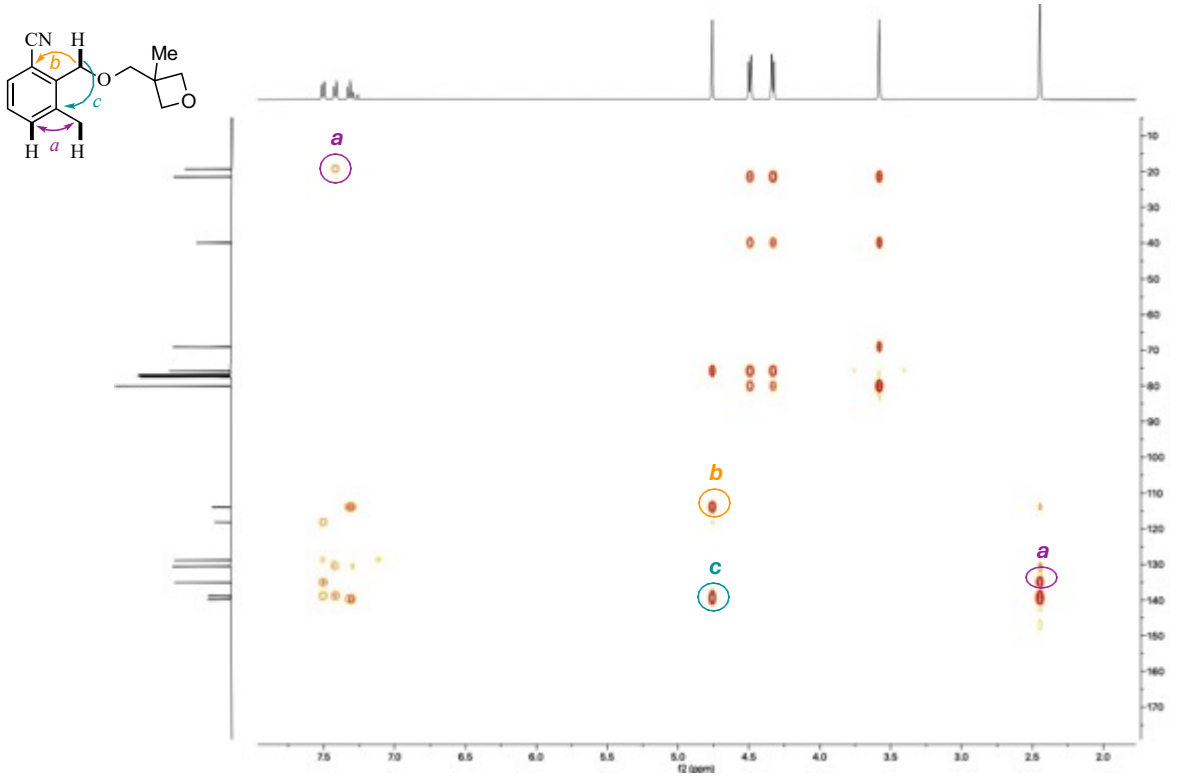
^{1}H NMR spectrum of **3-37** (400 MHz, $CDCl_3$)



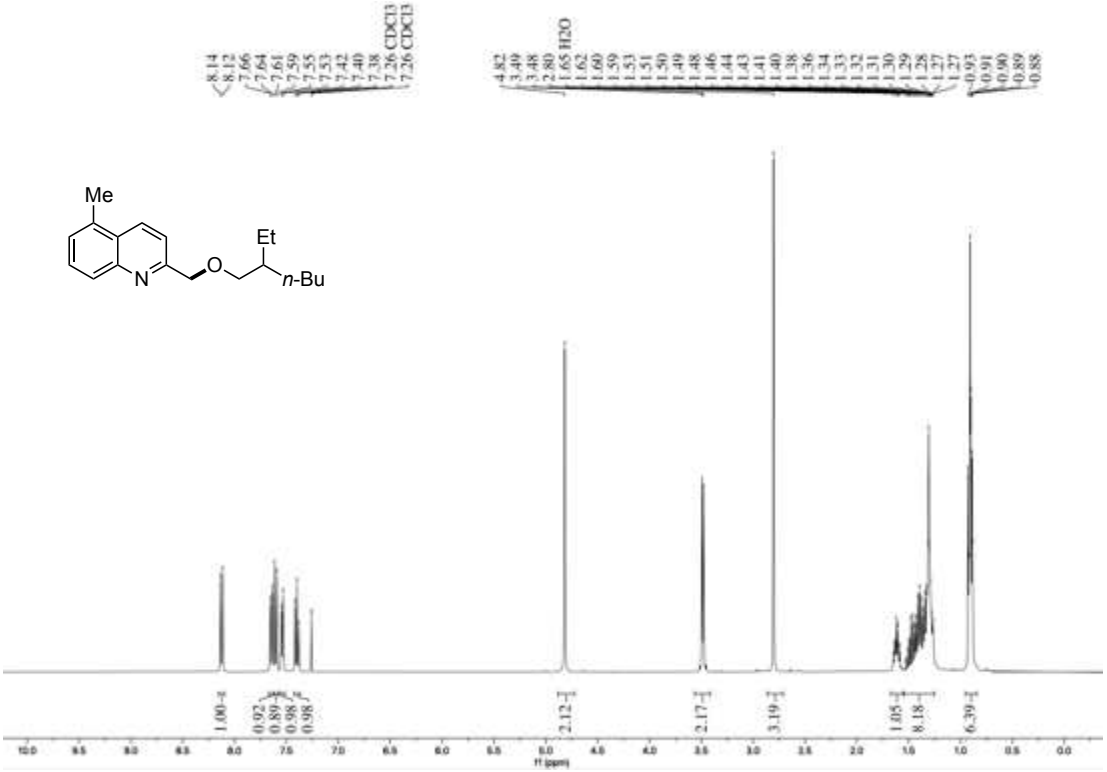
^{13}C NMR spectrum of **3-37** (101 MHz, $CDCl_3$)



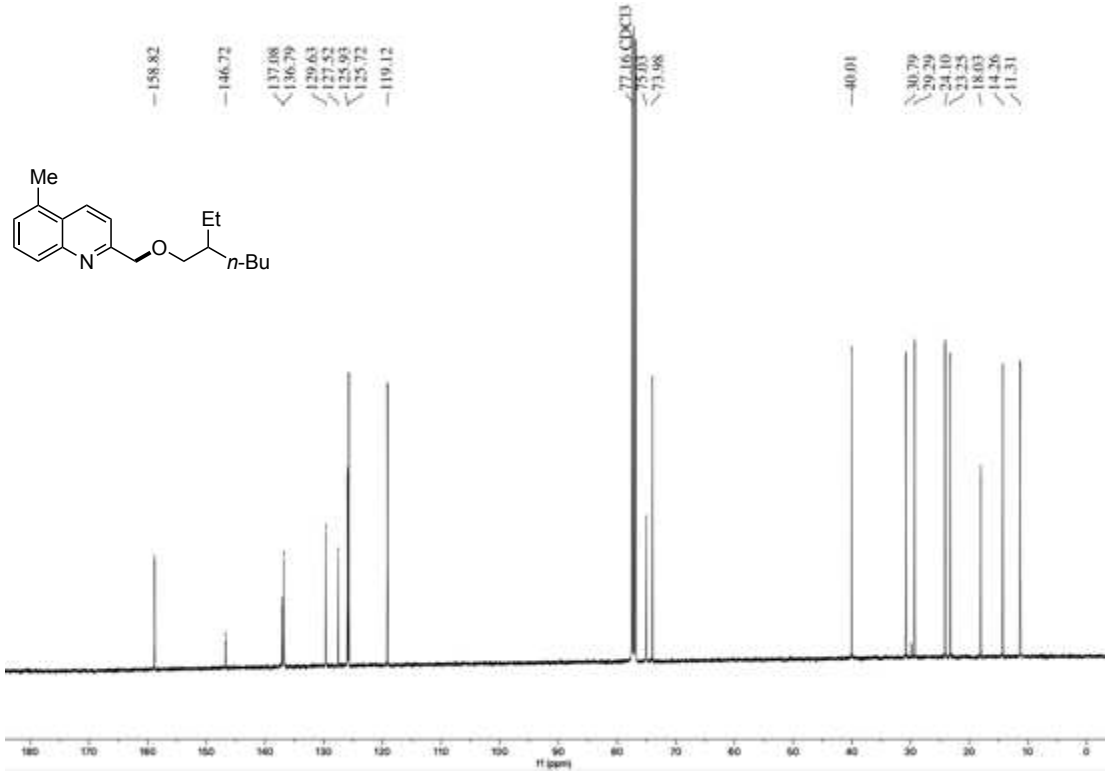
HSQC spectral window of **3-37** ($CDCl_3$)



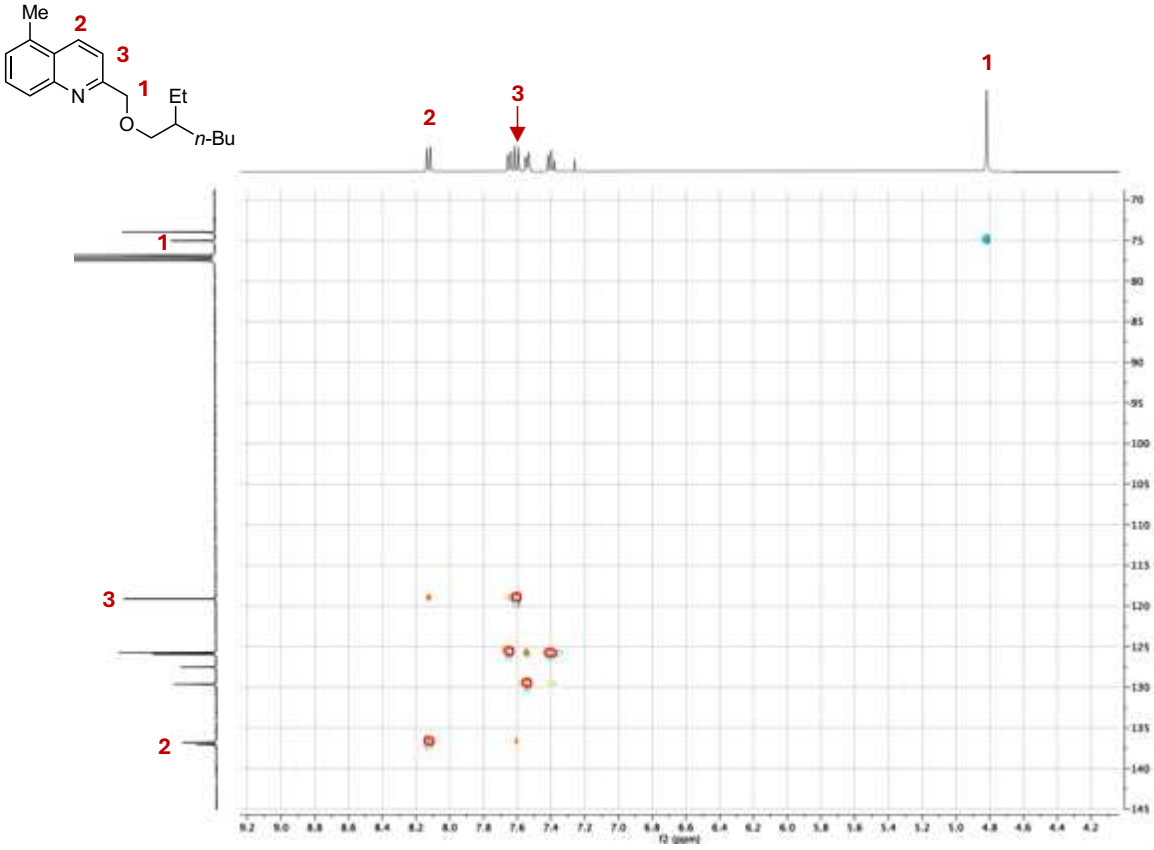
HMBC spectral window of **3-37** ($CDCl_3$)



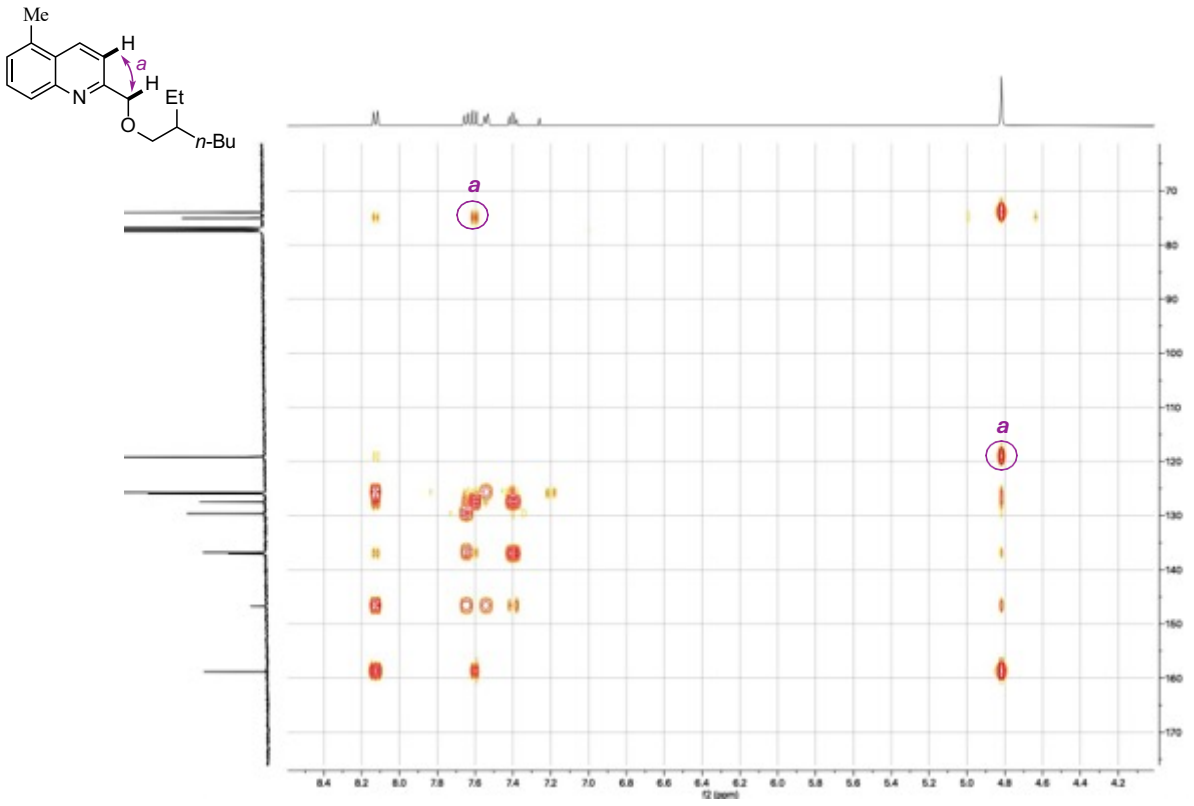
^{1}H NMR spectrum of **3-38** (400 MHz, $CDCl_3$)



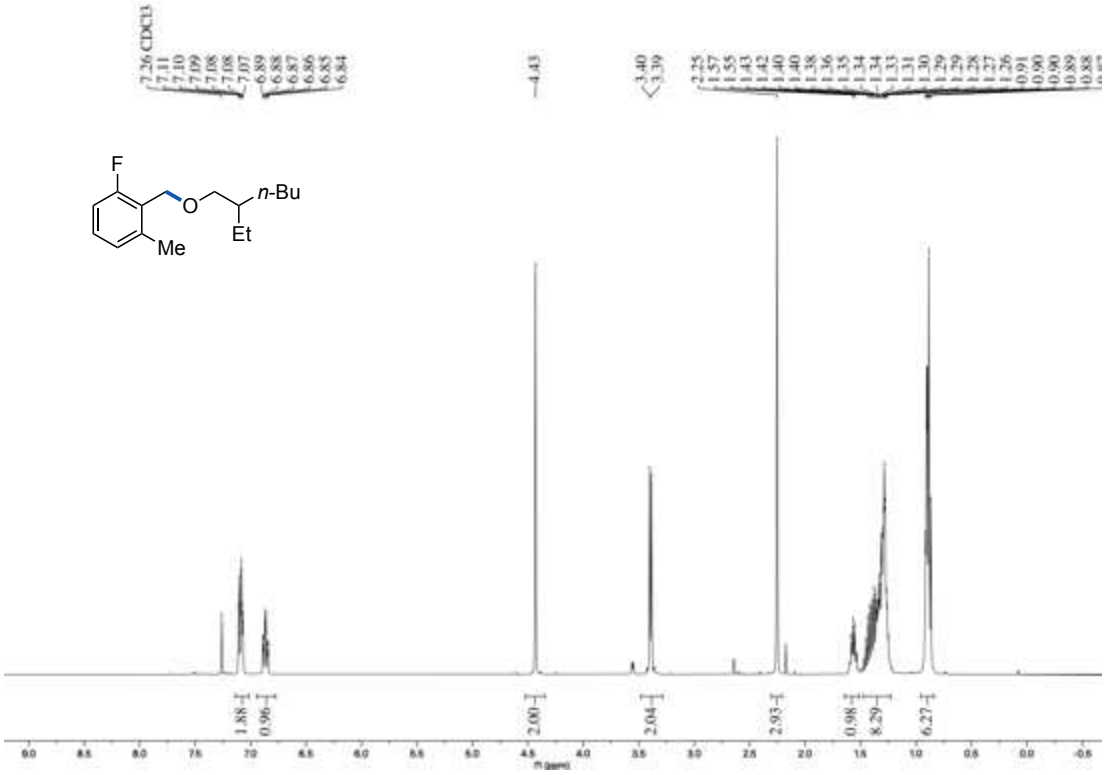
^{13}C NMR spectrum of **3-38** (101 MHz, $CDCl_3$)



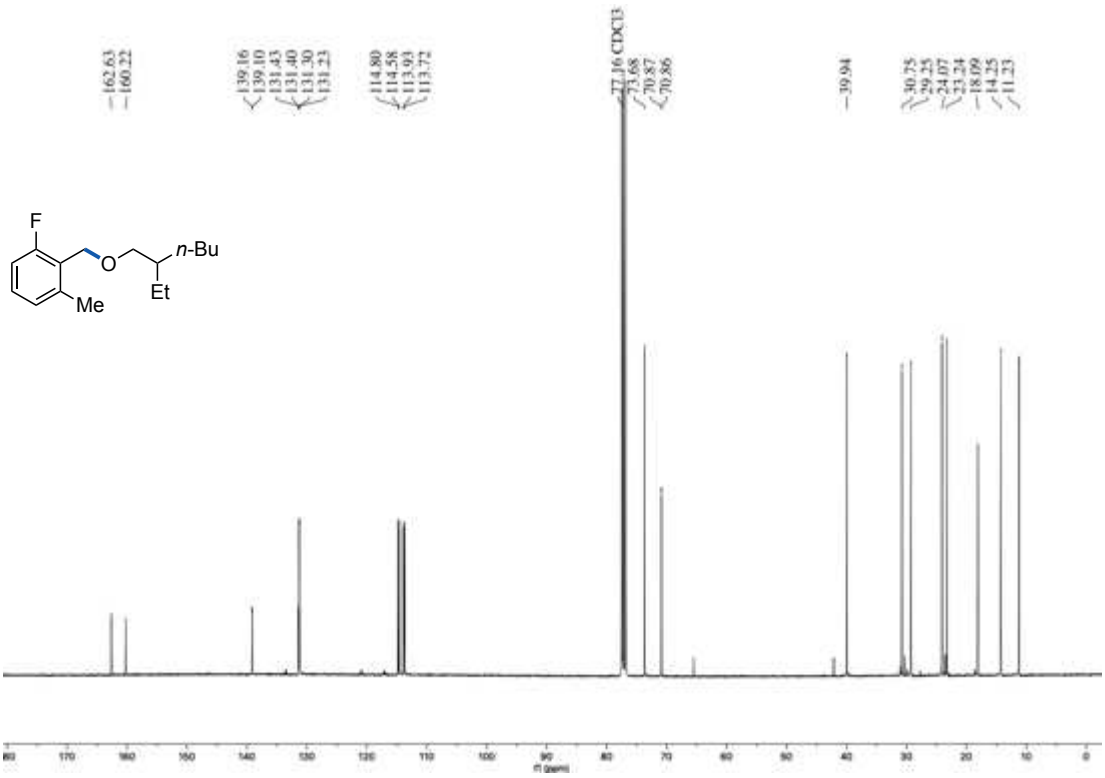
HSQC spectral window of **3-38** ($CDCl_3$)



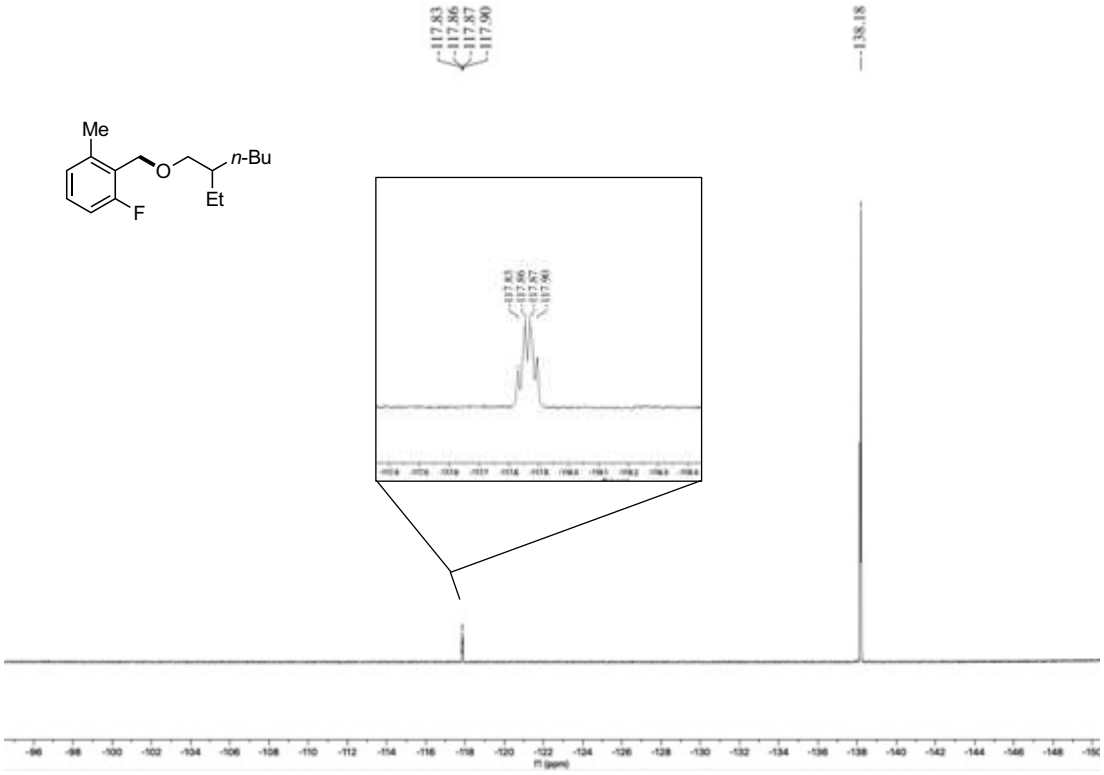
HMBC spectral window of **3-38** ($CDCl_3$)



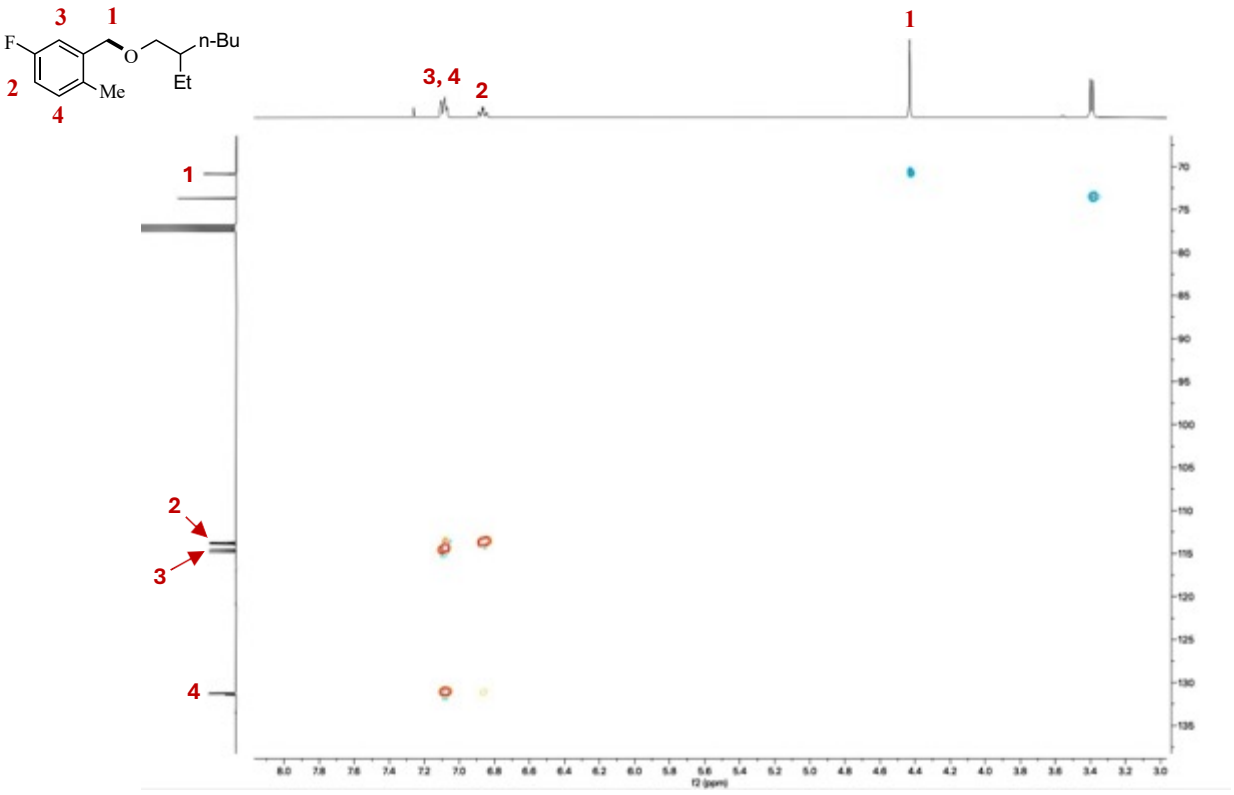
^{1}**H NMR** spectrum of **3-39** (400 MHz, $CDCl_3$)



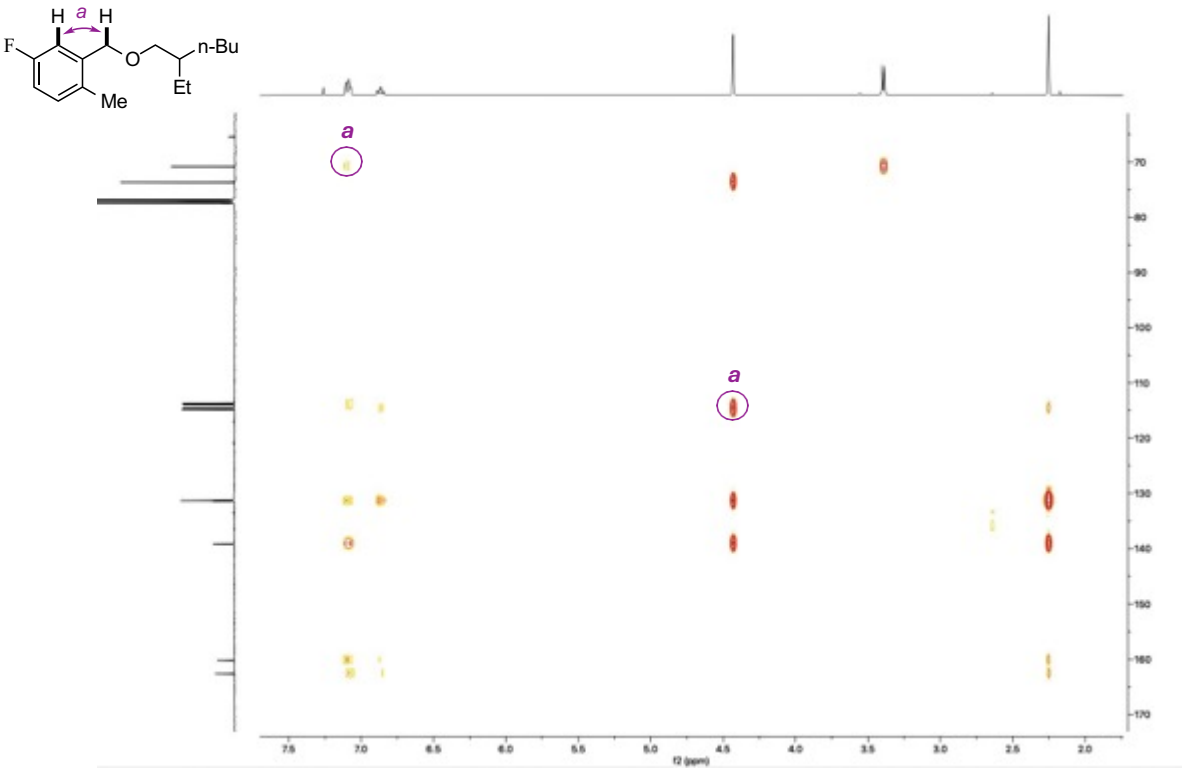
^{13}C NMR spectrum of **3-39** (101 MHz, $CDCl_3$)



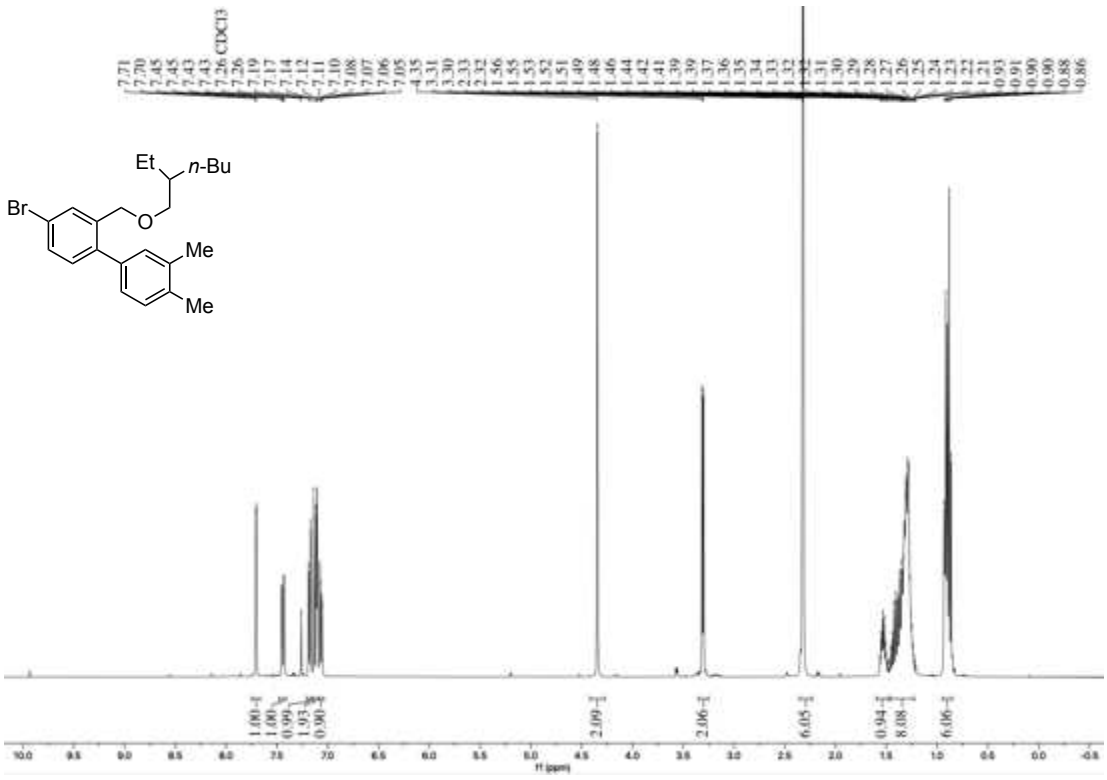
^{19}F NMR spectrum of **3-39** (376 MHz, $CDCl_3$)



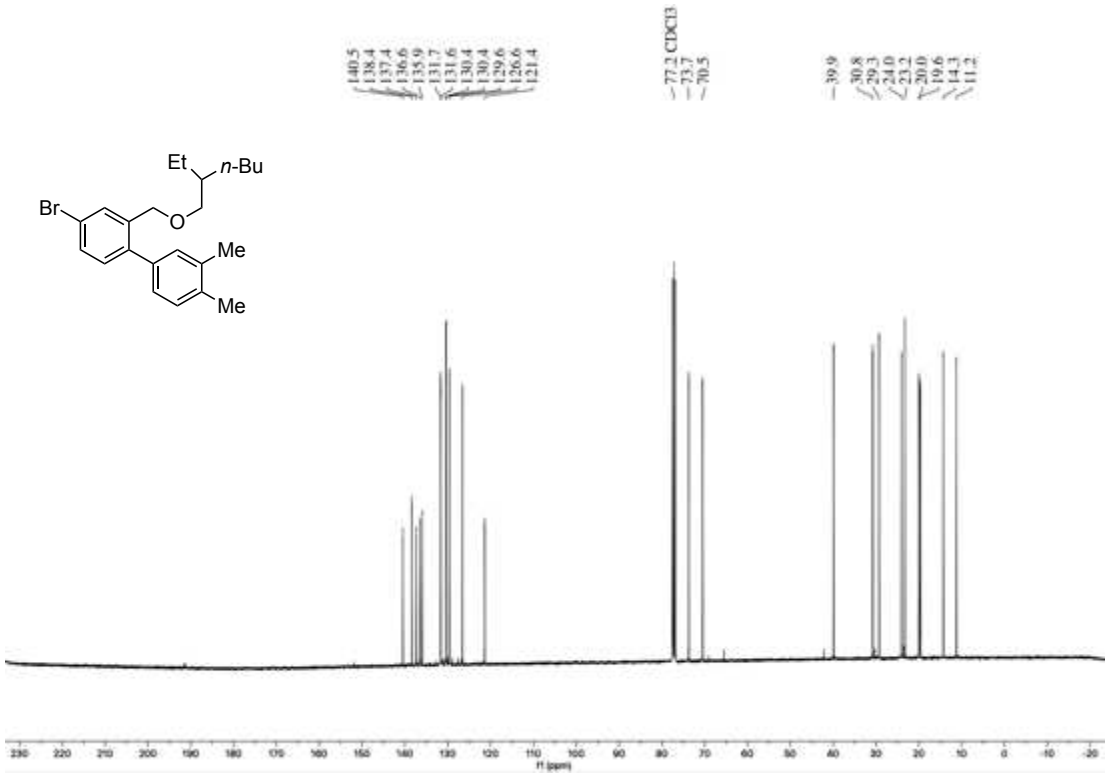
HSQC spectral window of **3-39** ($CDCl_3$)



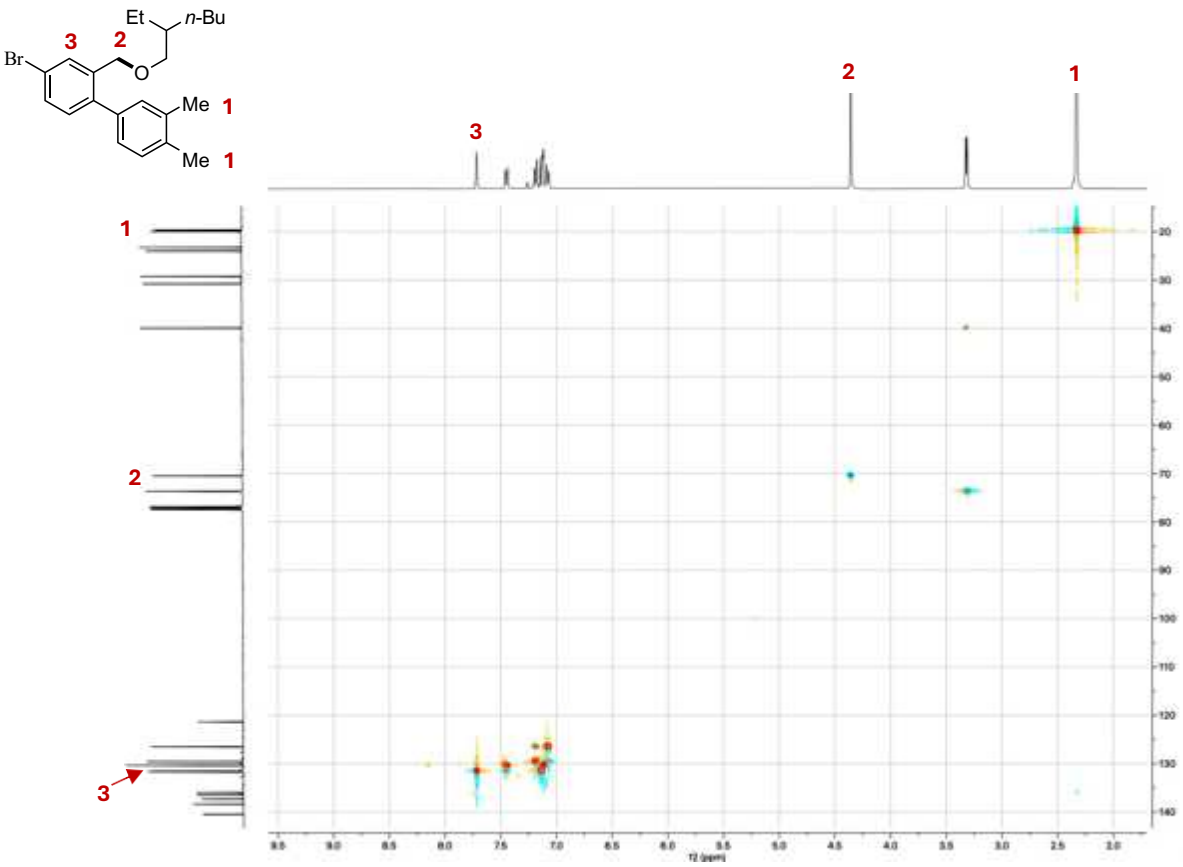
HMBC spectral window of **3-39** ($CDCl_3$)



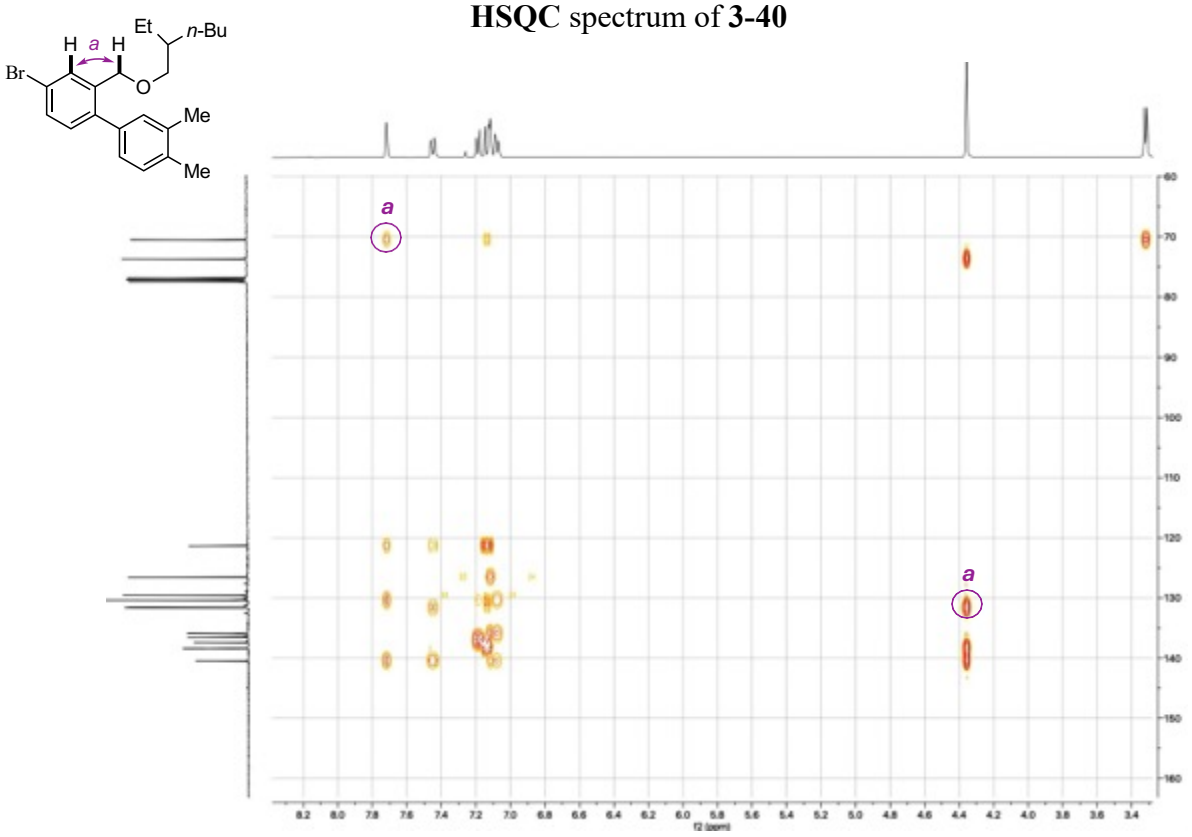
^{1}H NMR spectrum of **3-40** (400 MHz, $CDCl_3$)



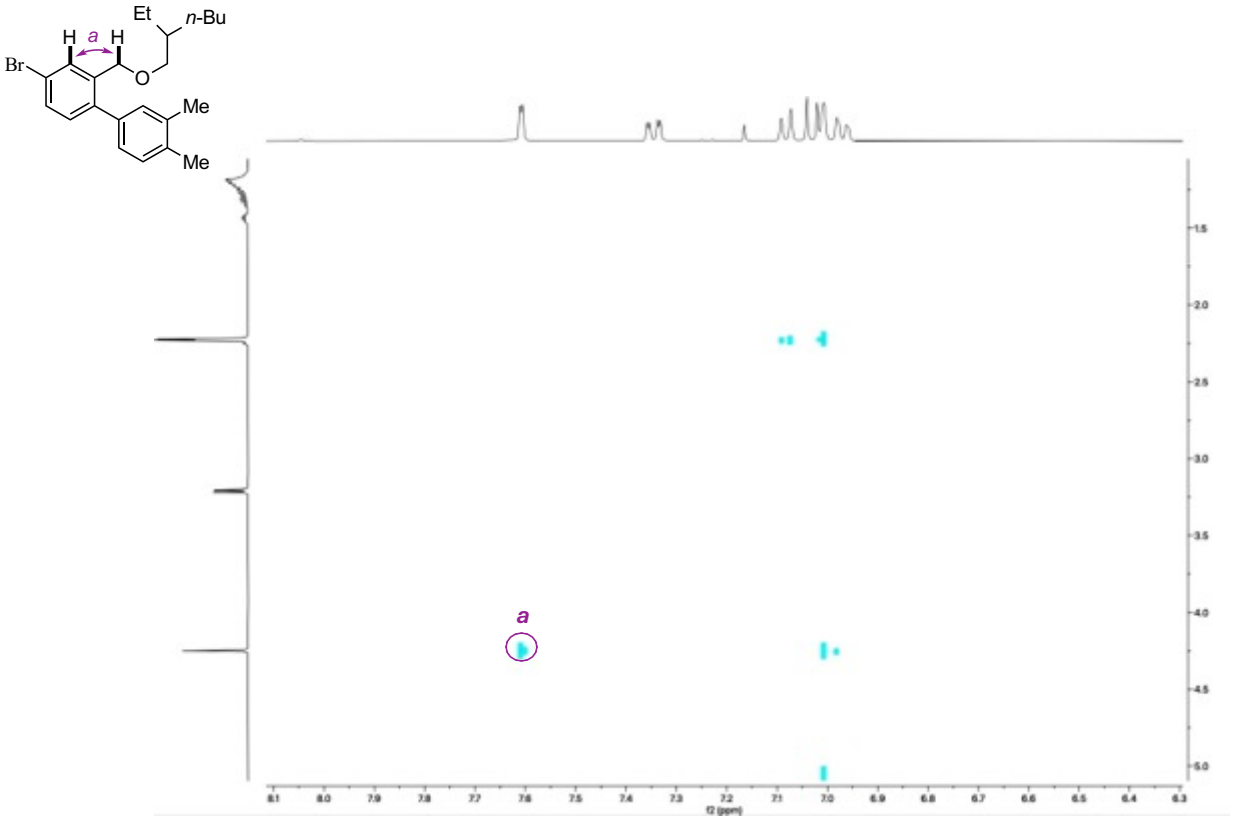
^{13}C NMR spectrum of **3-40** (101 MHz, $CDCl_3$)



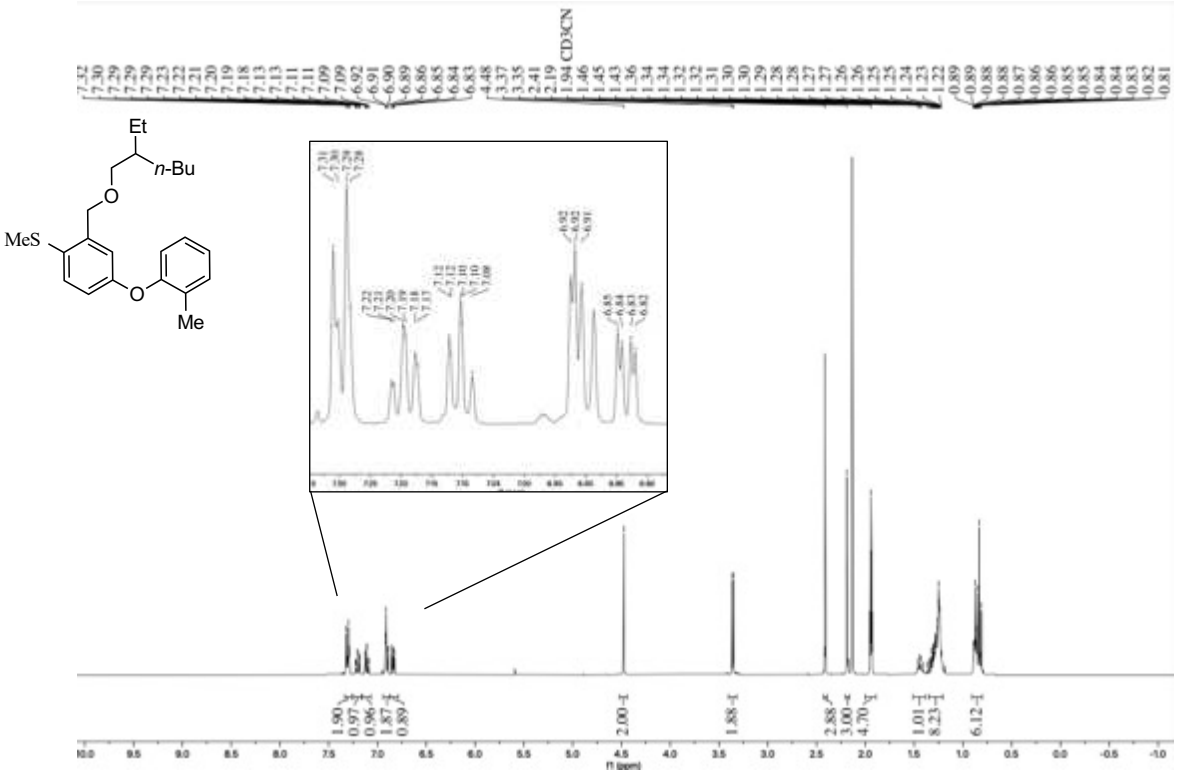
HSQC spectrum of **3-40**



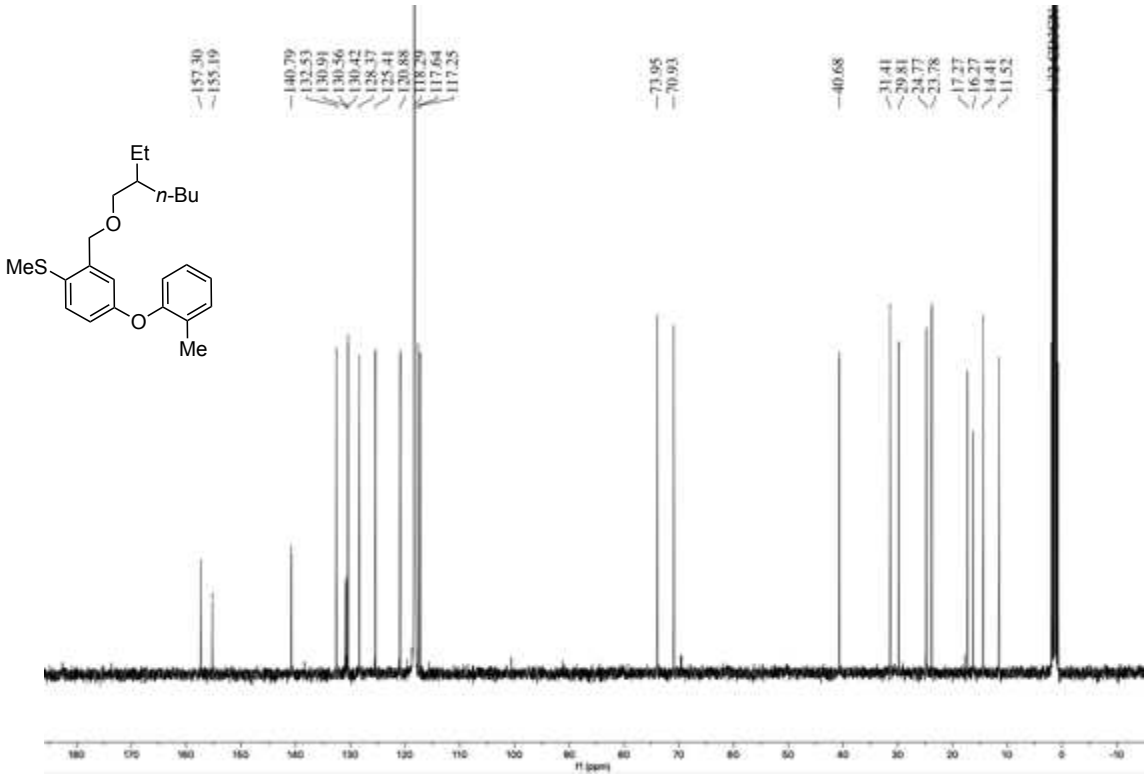
HMBC spectrum of **3-40** ($CDCl_3$)



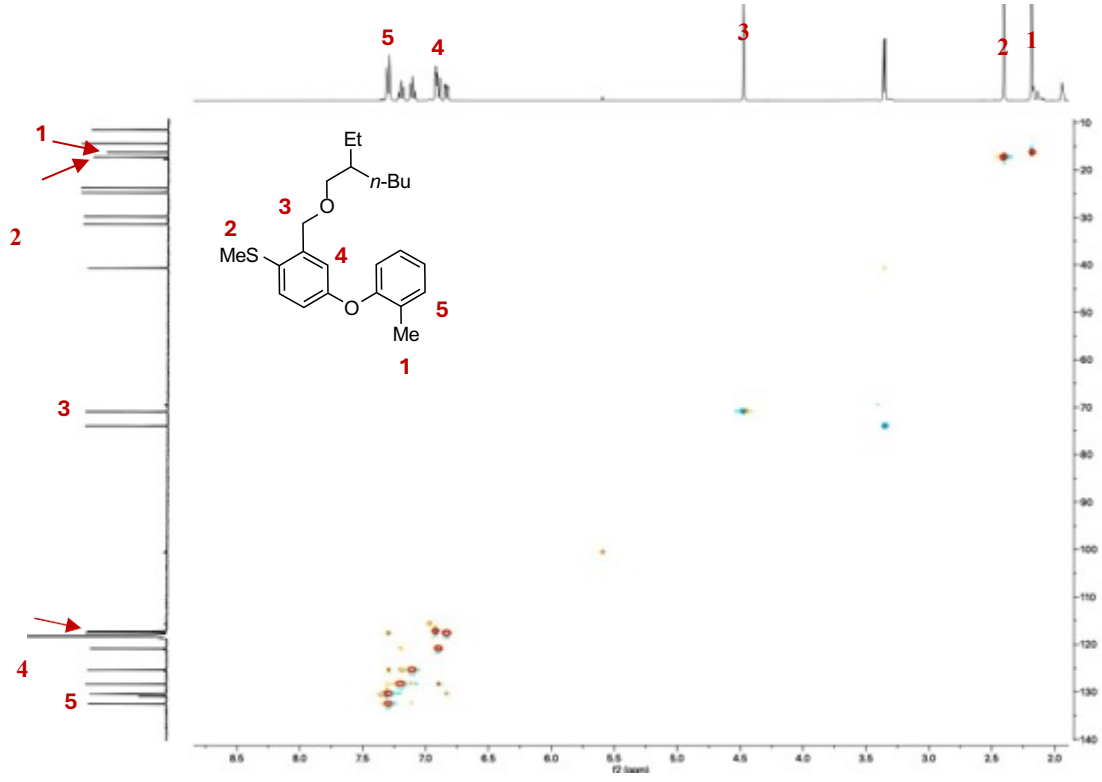
2D NOESY spectrum of **3-40** ($CDCl_3$)



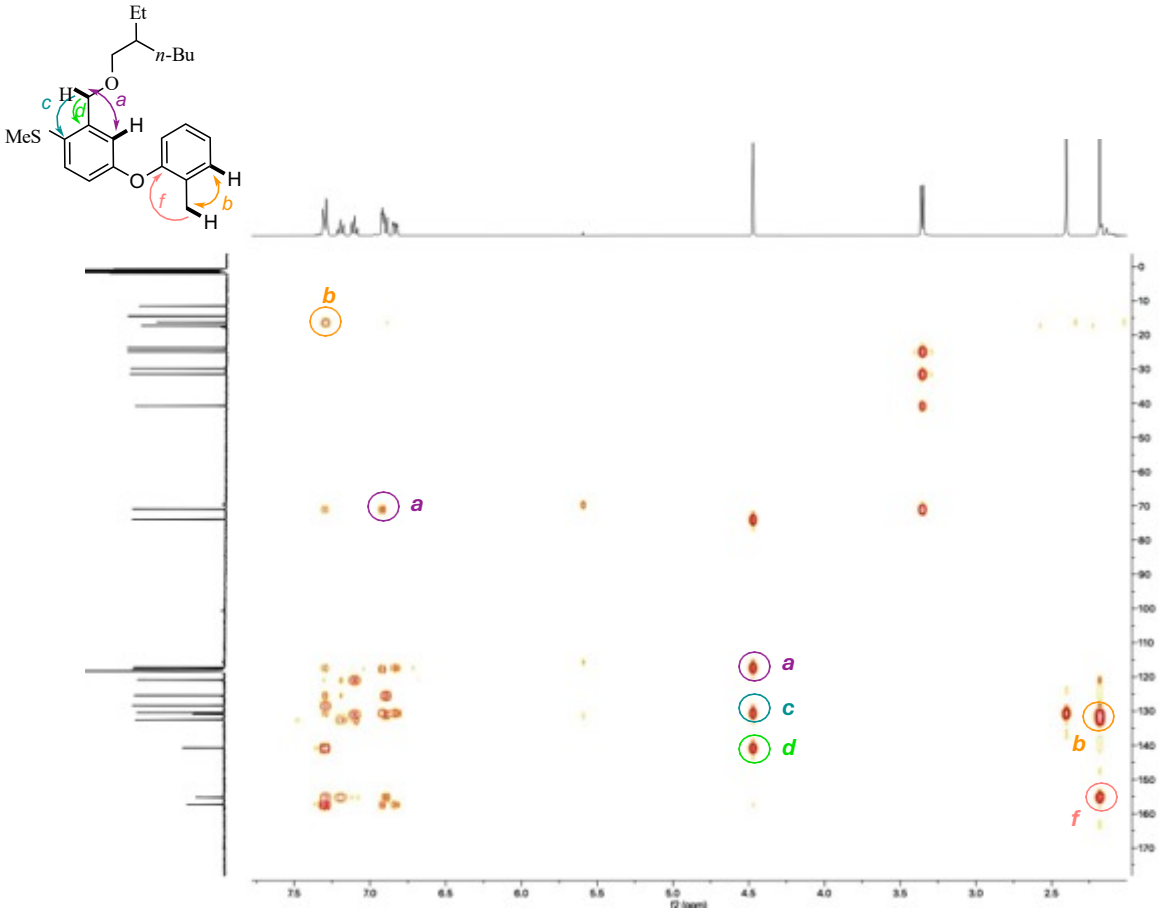
^{1}H NMR spectrum of **3-41** (400 MHz, CD_3CN)



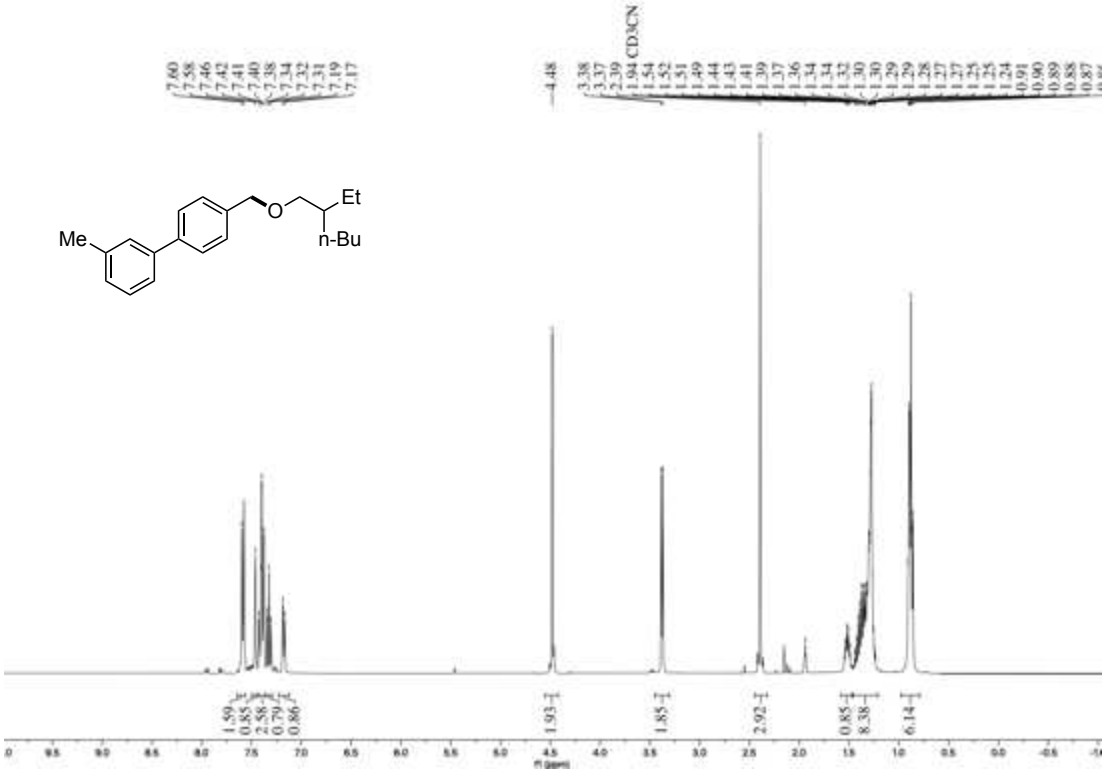
^{13}C NMR spectrum of **3-41** (101 MHz, CD_3CN)



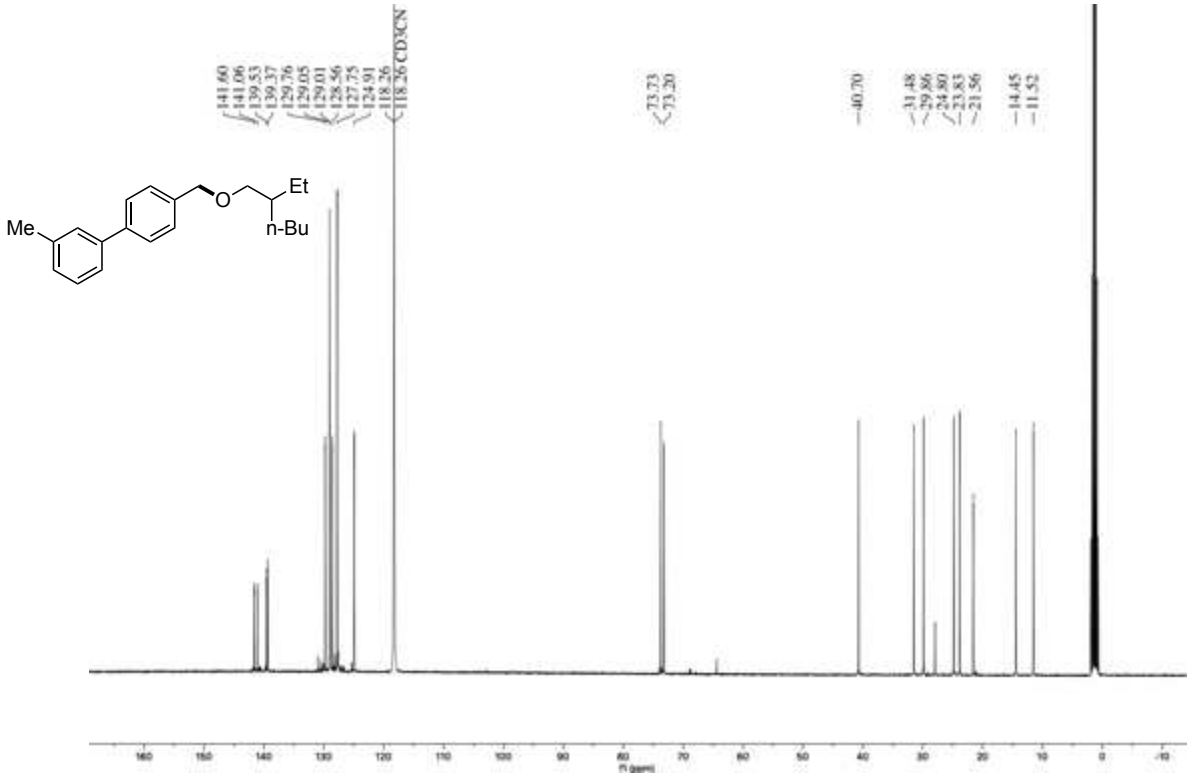
HSQC spectrum of **3-41** (CD_3CN)



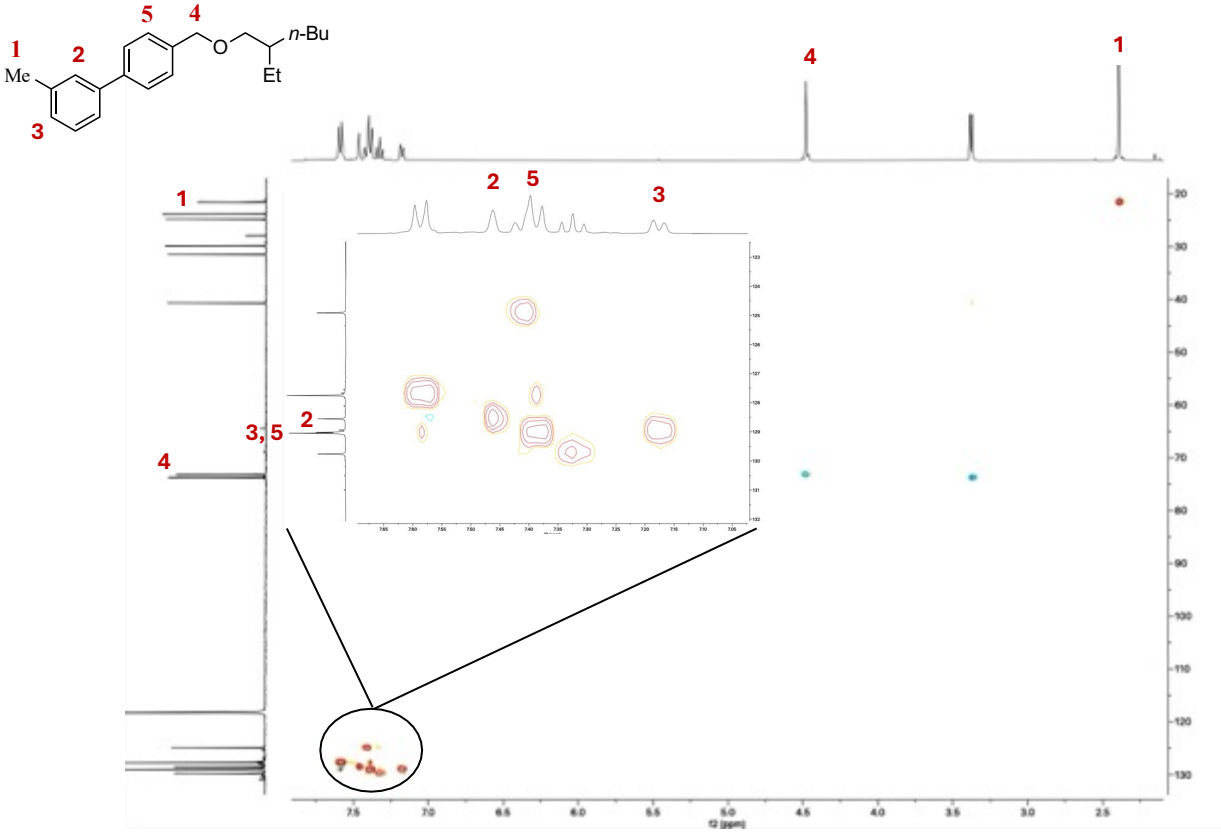
HMBC spectrum of **3-41** (CD_3CN)



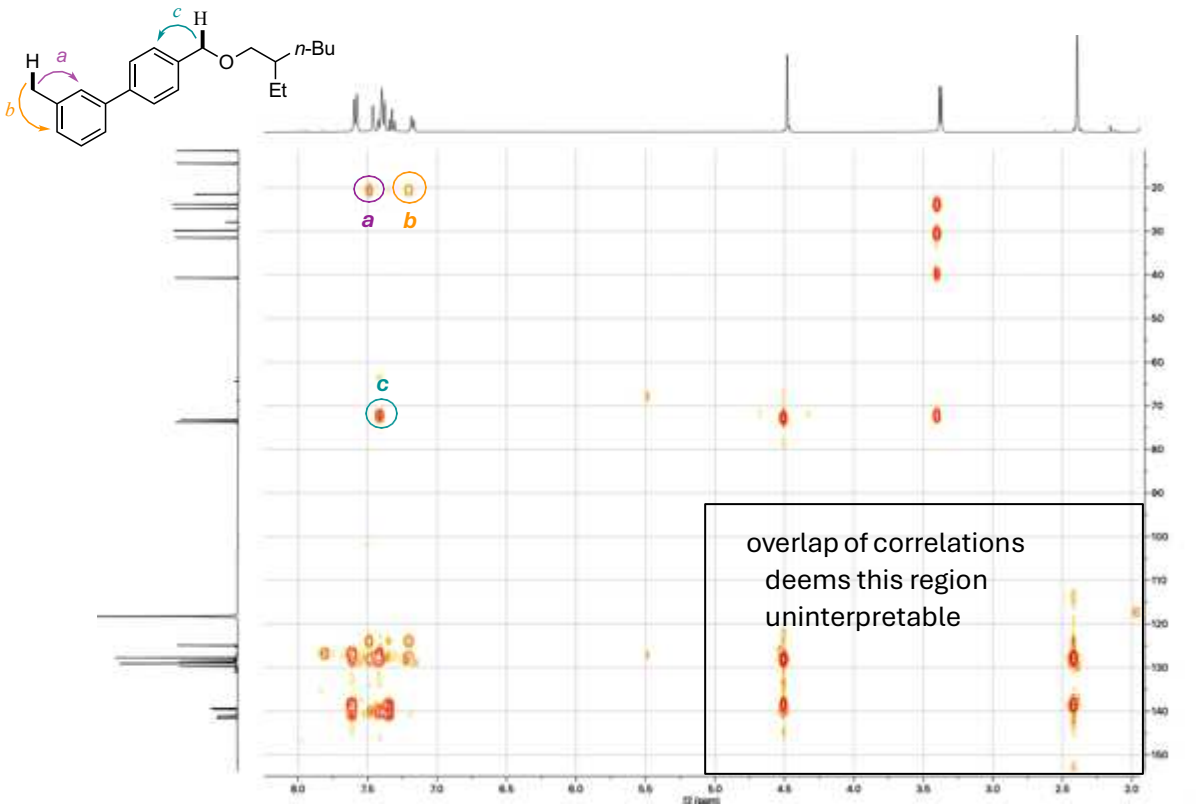
^{1}H NMR spectrum of **3-42** (400 MHz, CD_3CN)



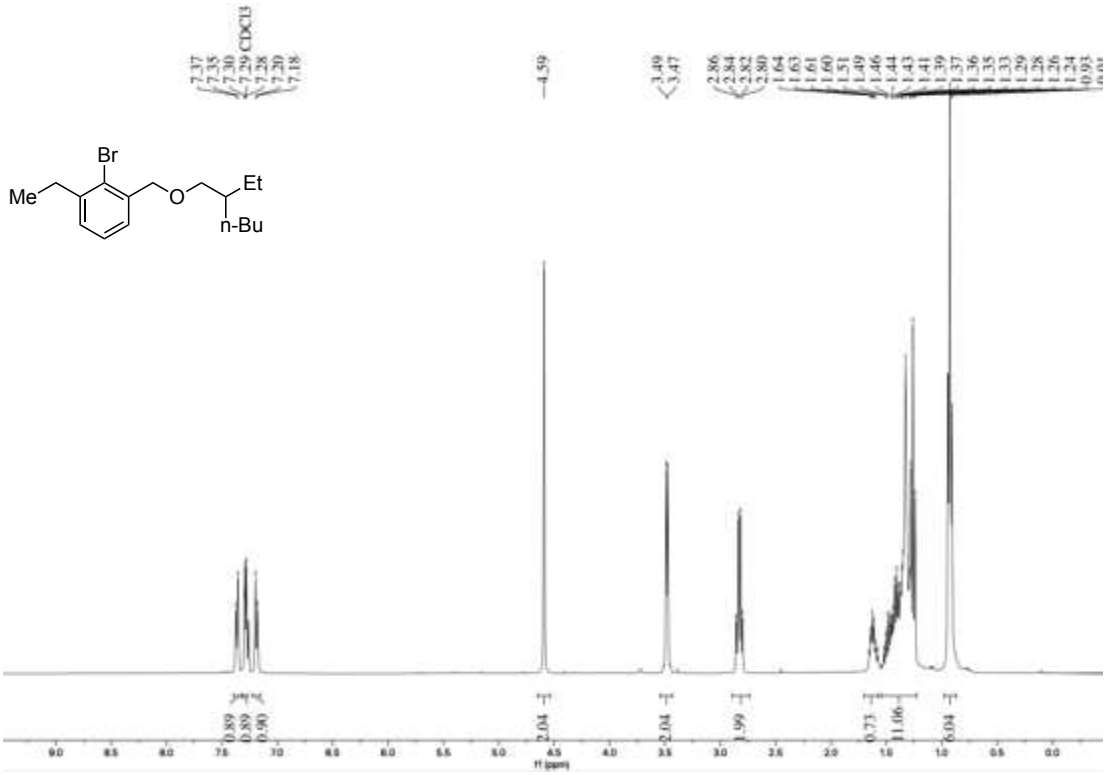
^{13}C NMR spectrum of **3-42** (101 MHz, CD_3CN)



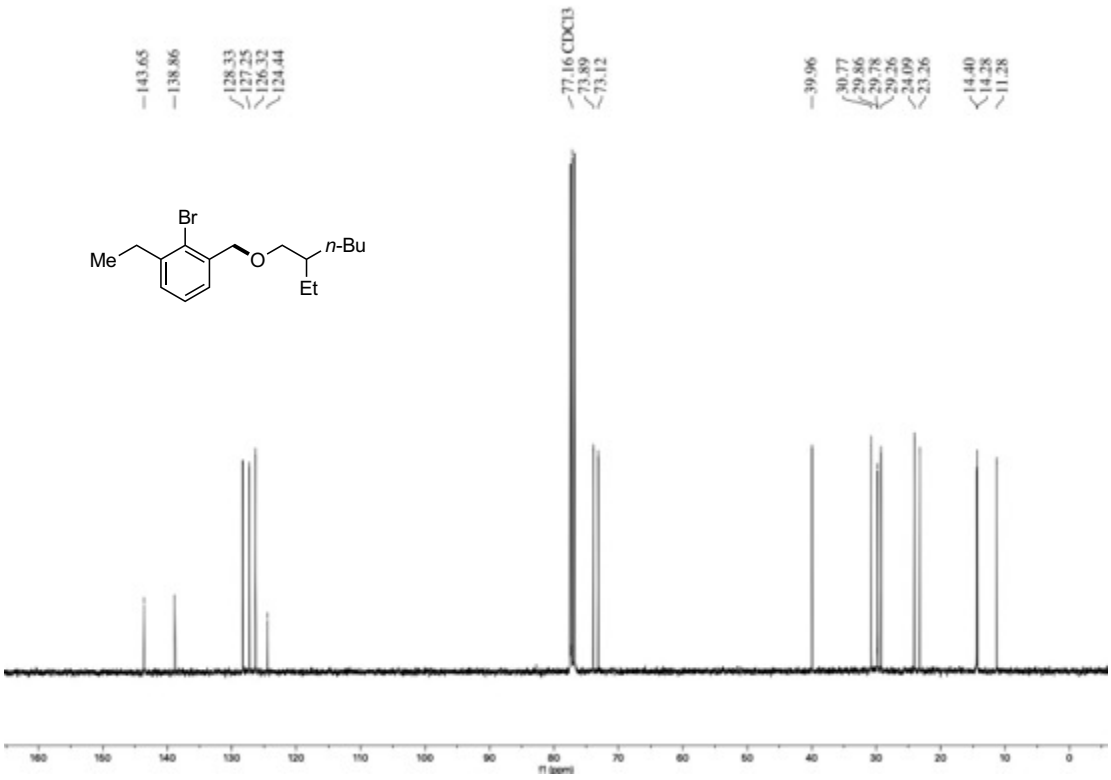
HSQC spectral window of **3-42** (CD_3CN)



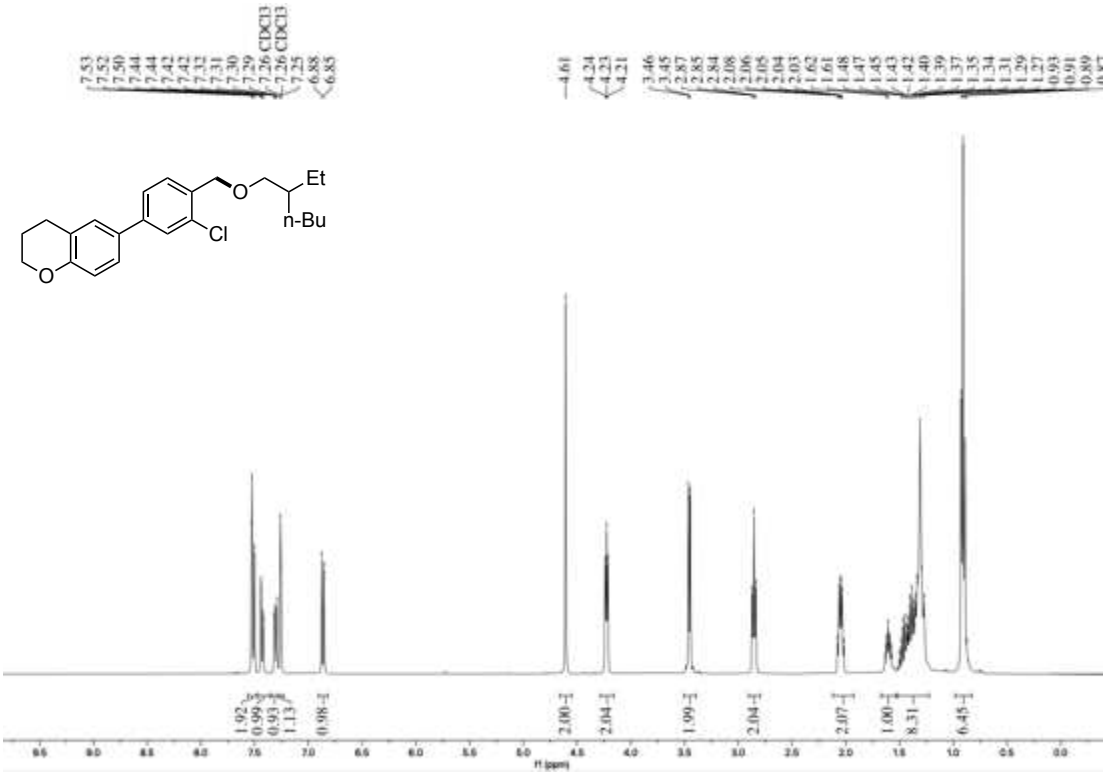
HMBC spectral window of **3-42** (CD_3CN)



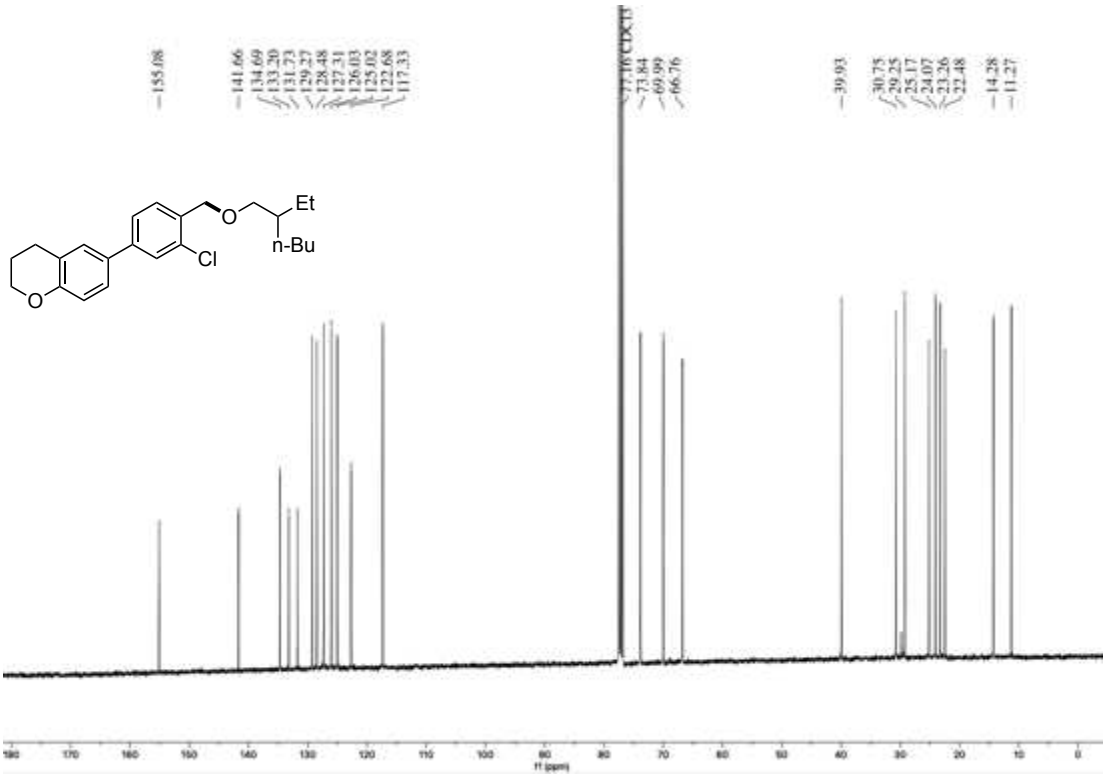
^{1}**H NMR** spectrum of **3-43** (400 MHz, $CDCl_3$)



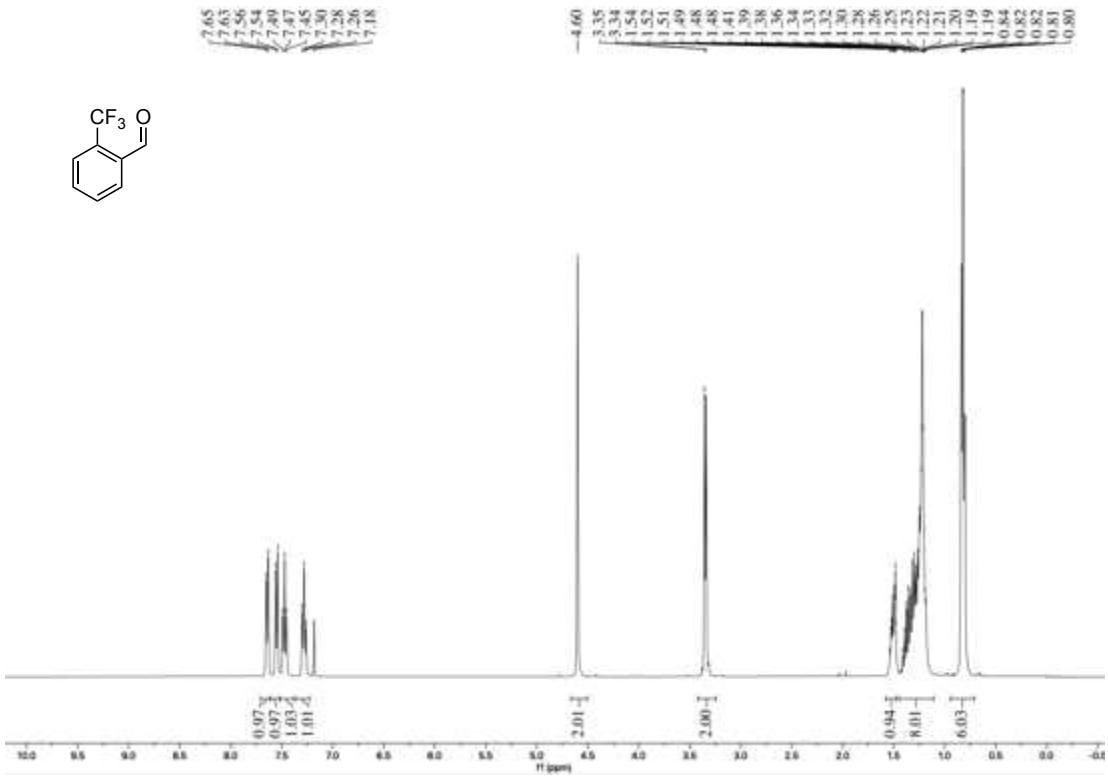
^{13}C NMR spectrum of **3-43** (101 MHz, $CDCl_3$)



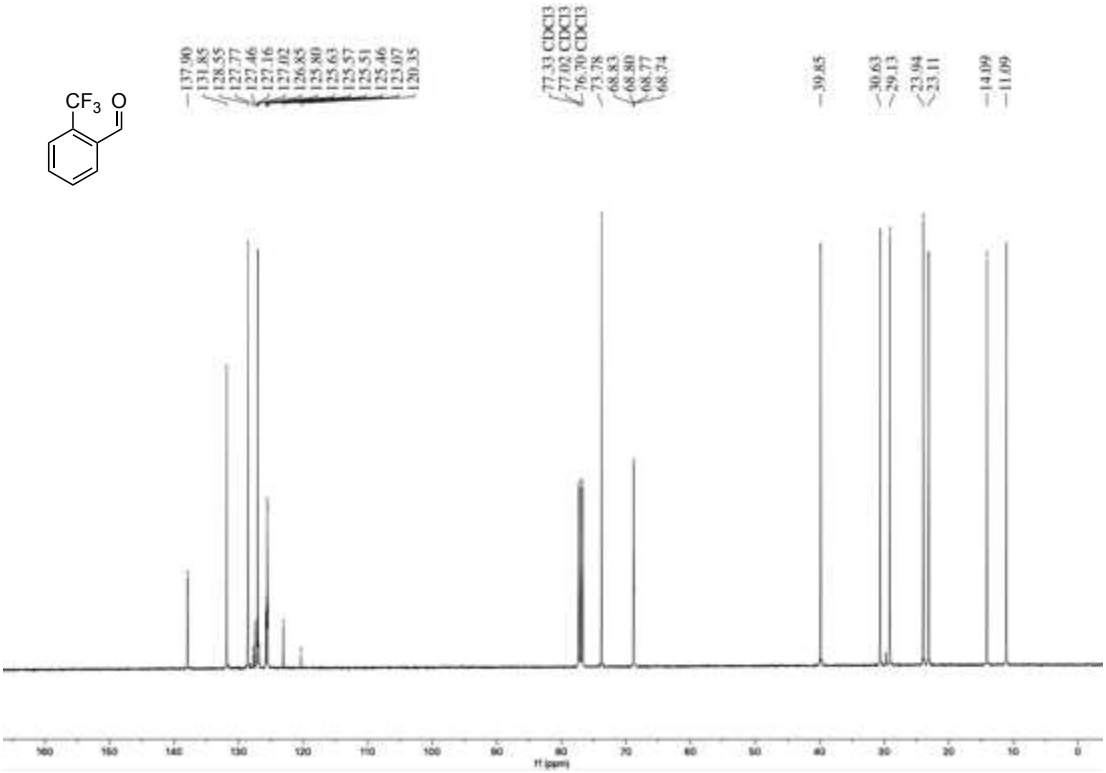
^{1}H NMR spectrum of **3-44** (400 MHz, $CDCl_3$)



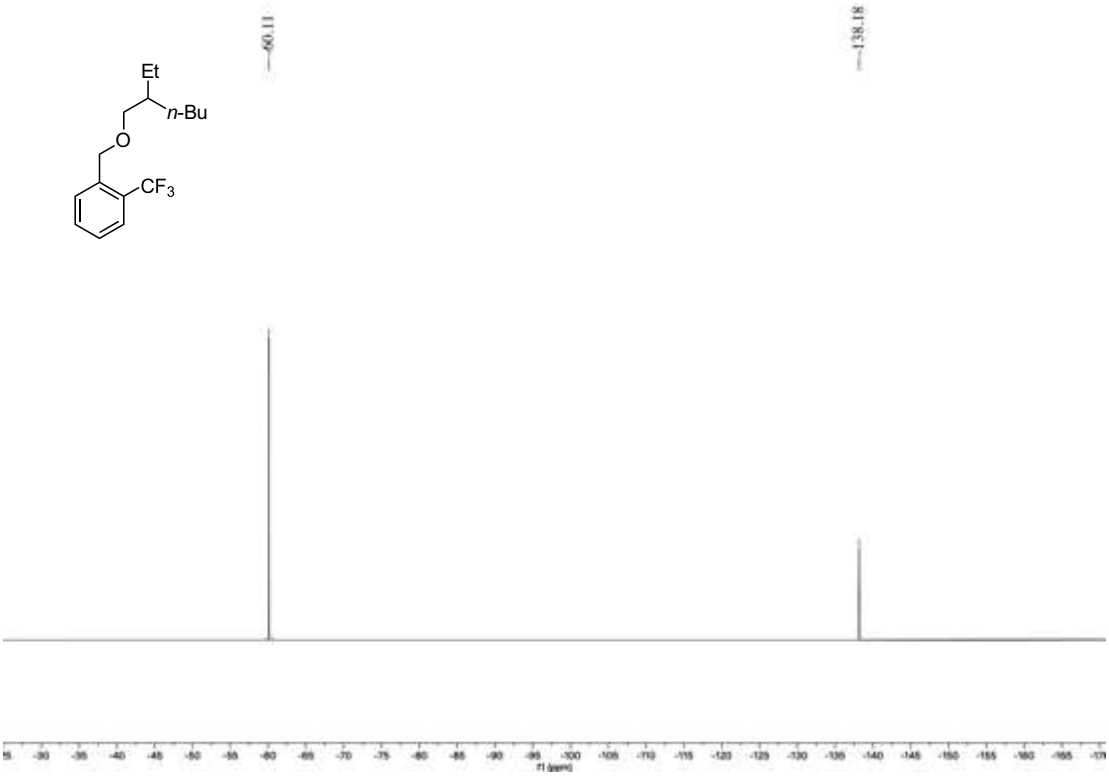
^{13}C NMR spectrum of **3-44** (101 MHz, $CDCl_3$)



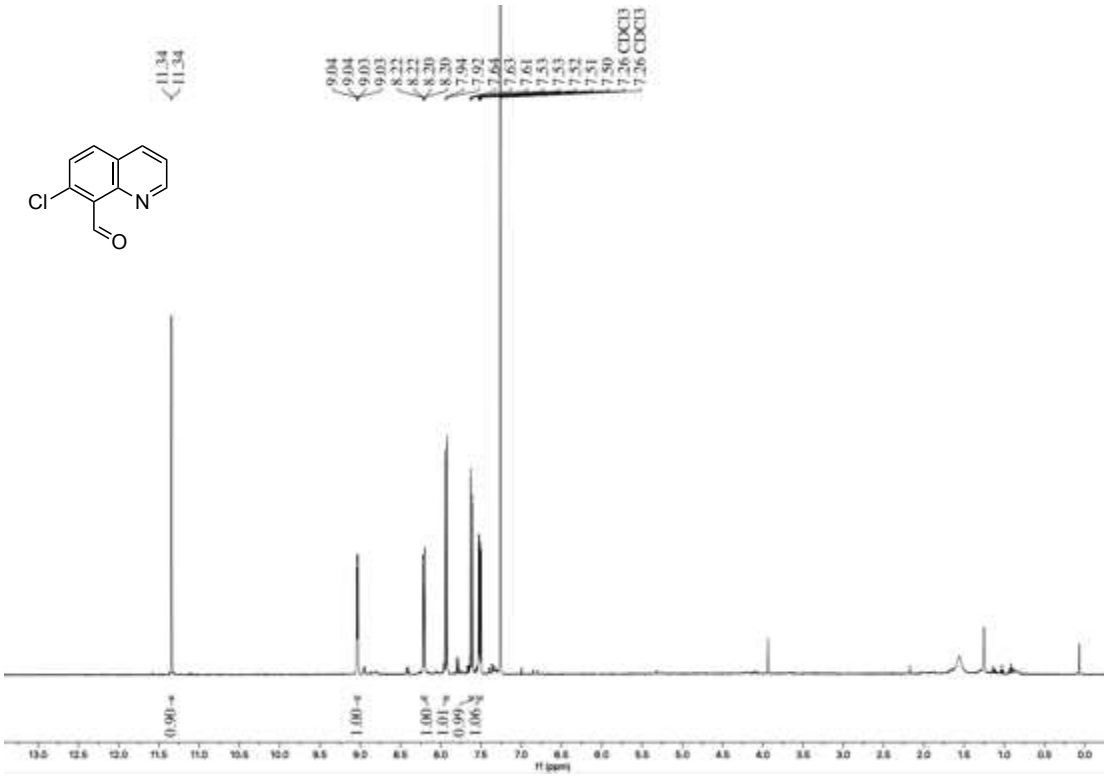
^{1}H NMR spectrum of **3-46** (400 MHz, $CDCl_3$)



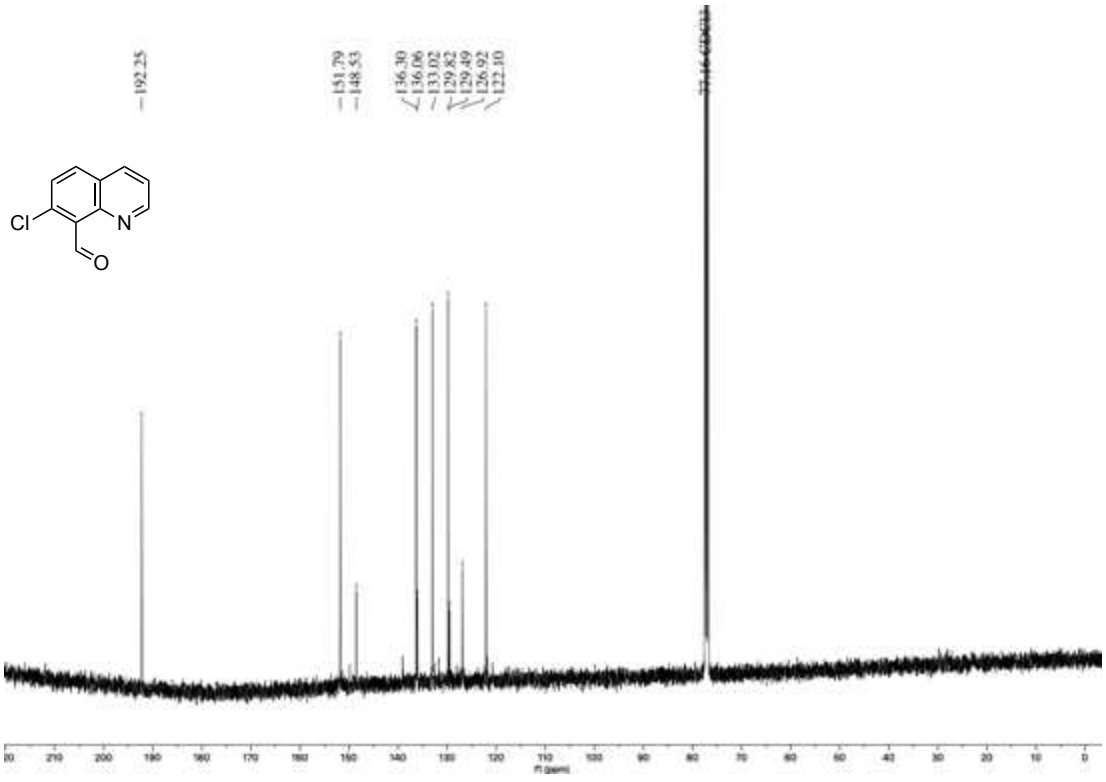
^{13}C NMR spectrum of **3-46** (101 MHz, $CDCl_3$)



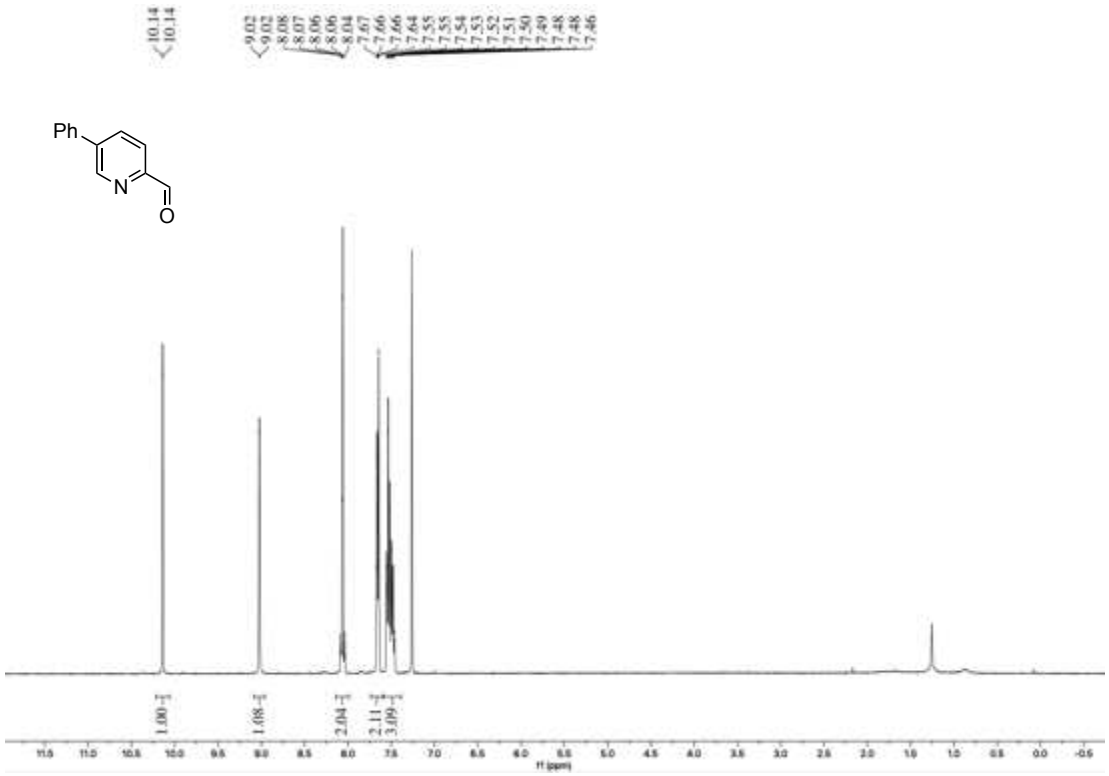
^{19}F NMR spectrum of **3-46** (376 MHz, $CDCl_3$)



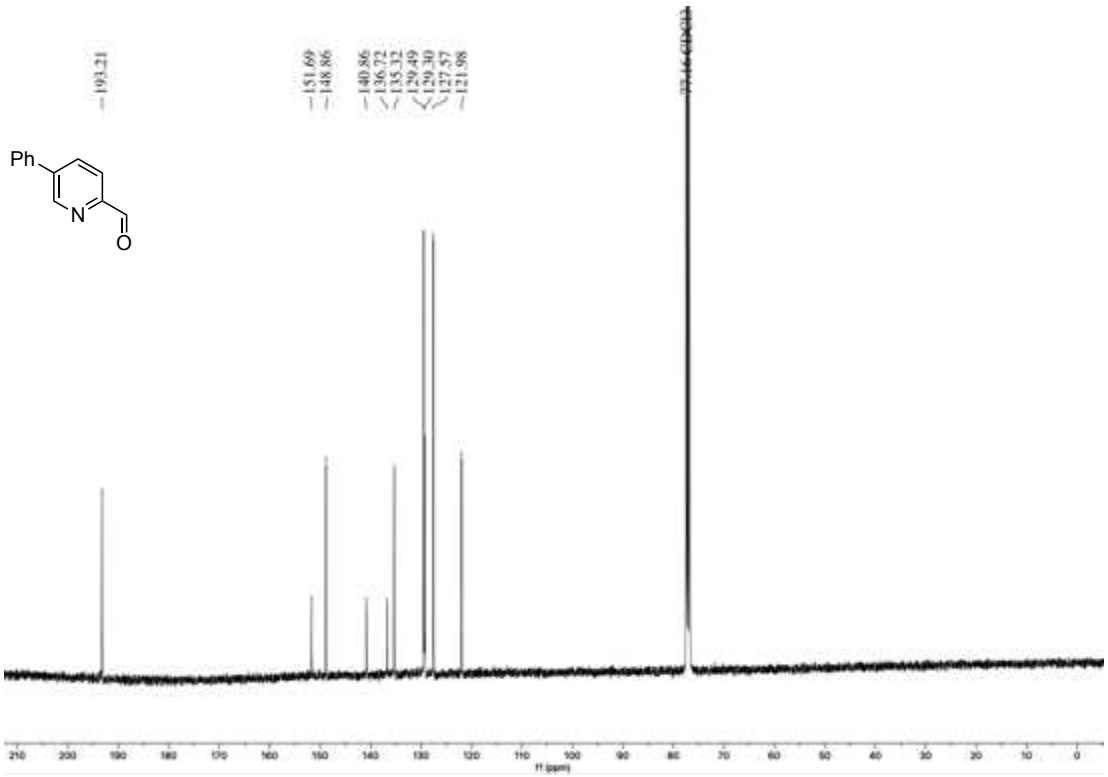
^{1}H NMR spectrum of **3-50** (400 MHz, $CDCl_3$)



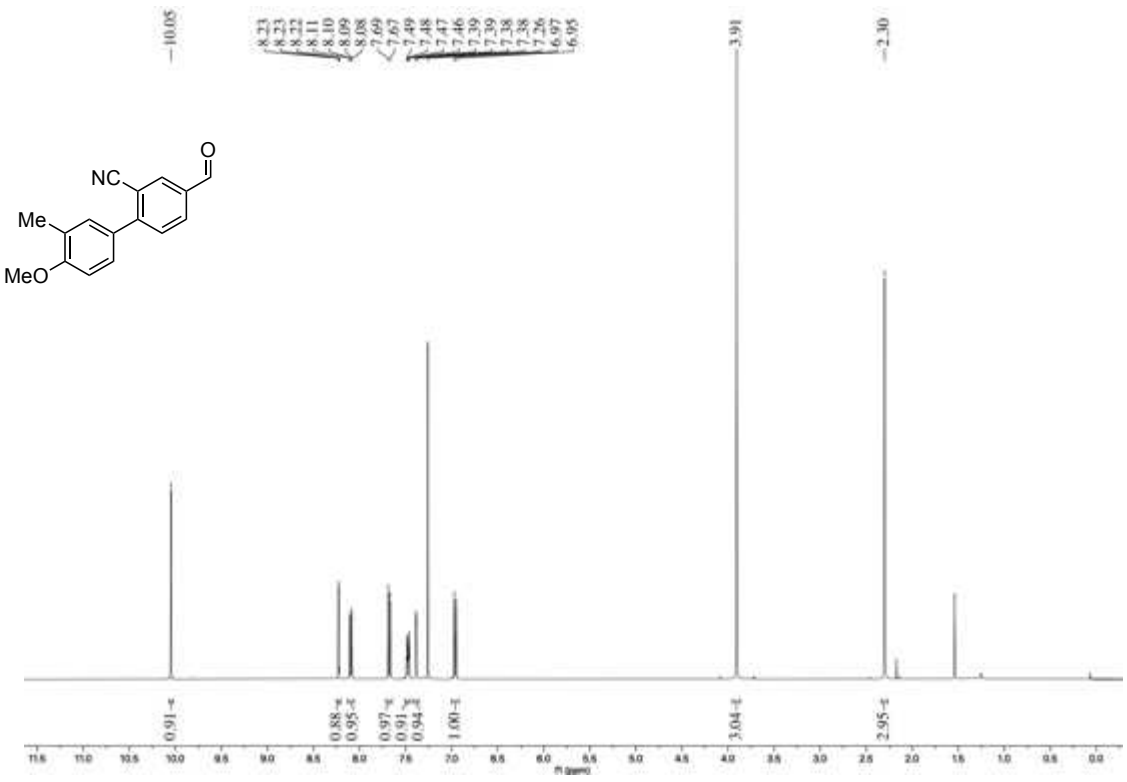
^{13}C NMR spectrum of **3-50** (101 MHz, $CDCl_3$)



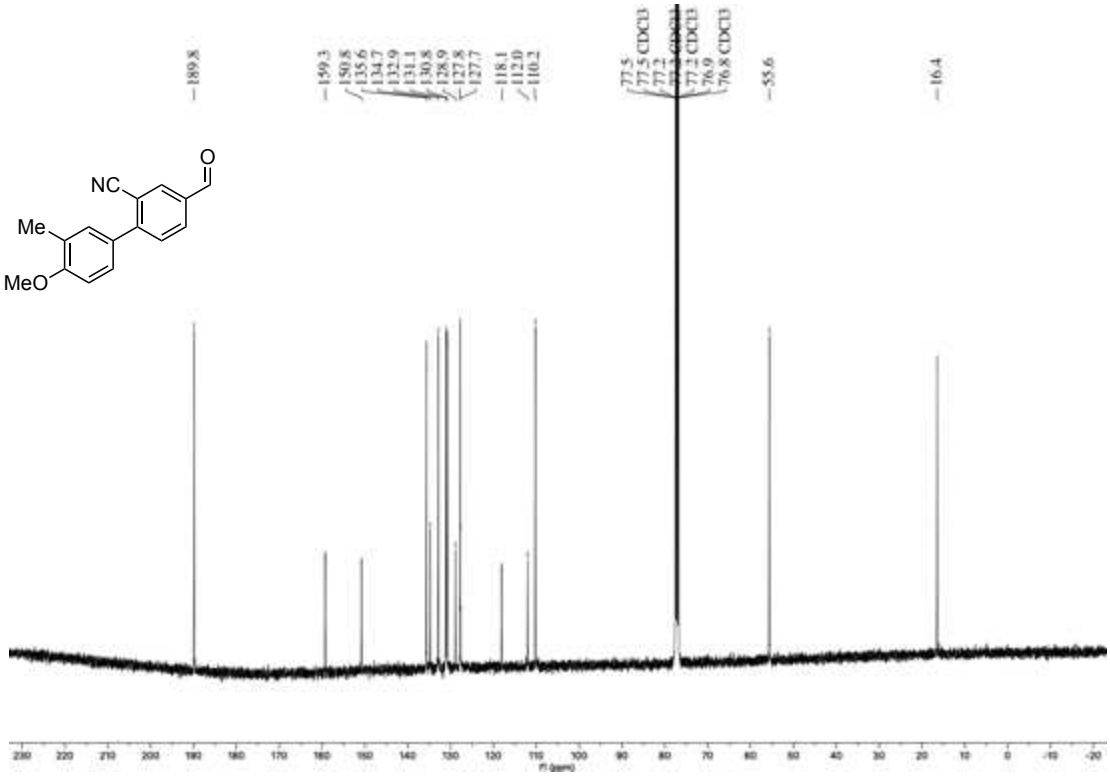
^{1}H NMR spectrum of **3-51** (400 MHz, $CDCl_3$)



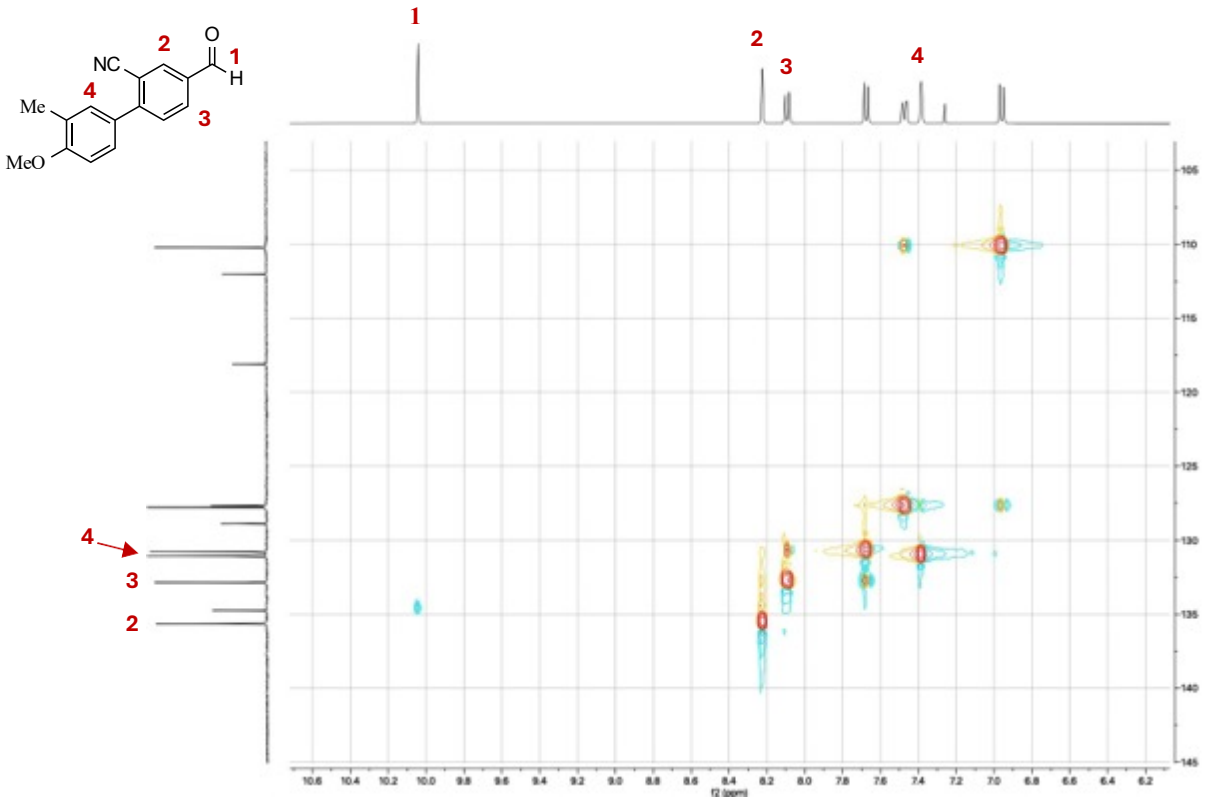
^{13}C NMR spectrum of **3-51** (101 MHz, $CDCl_3$)



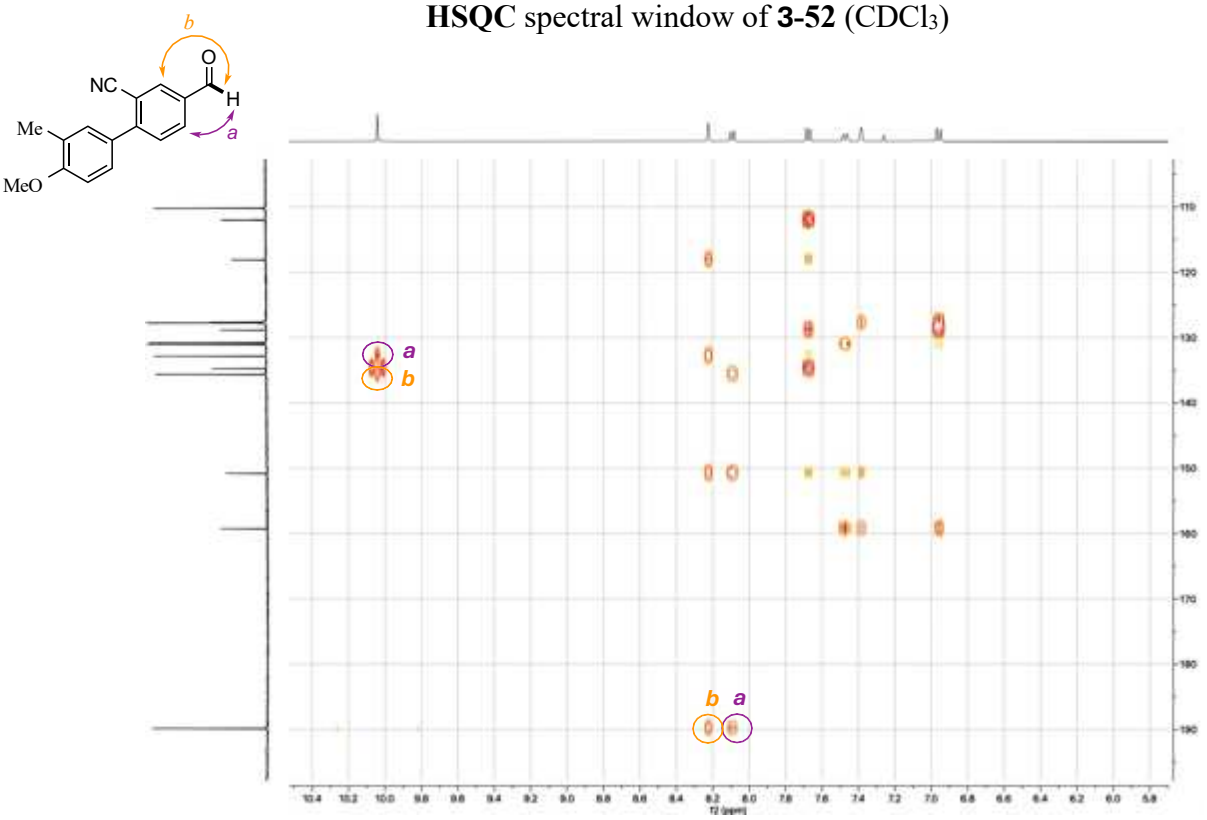
^{1}H NMR spectrum of **3-52** (400 MHz, $CDCl_3$)



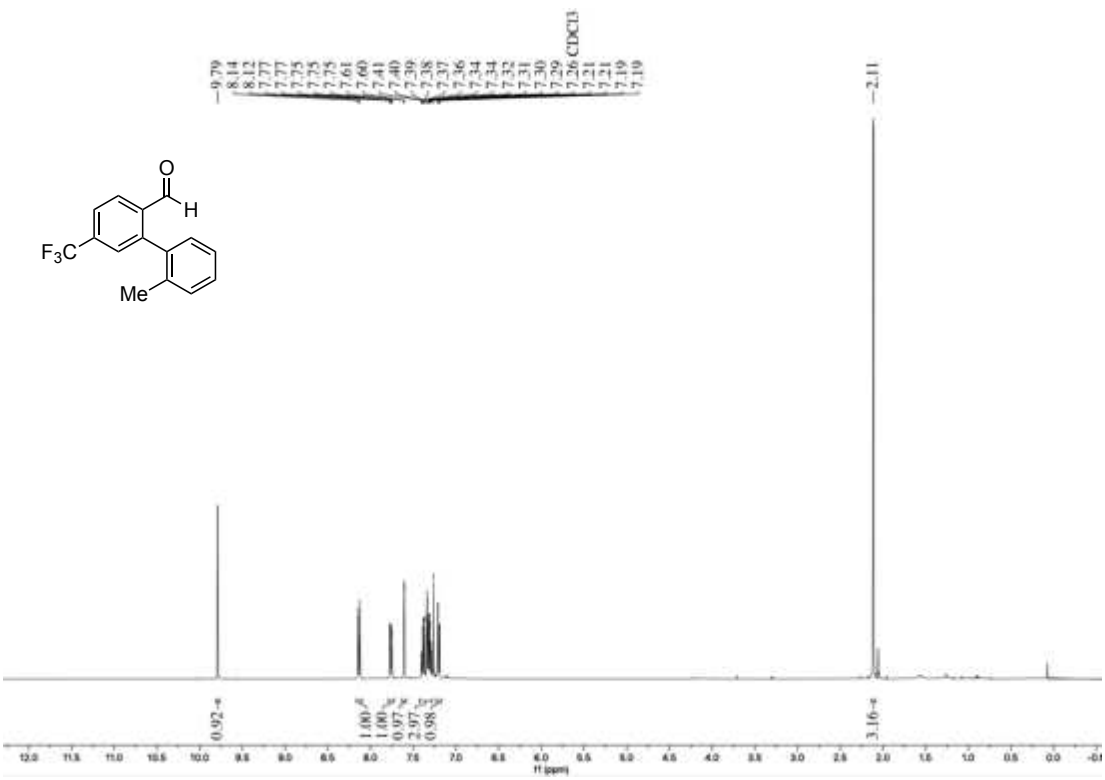
^{13}C NMR spectrum of **3-52** (101 MHz, $CDCl_3$)



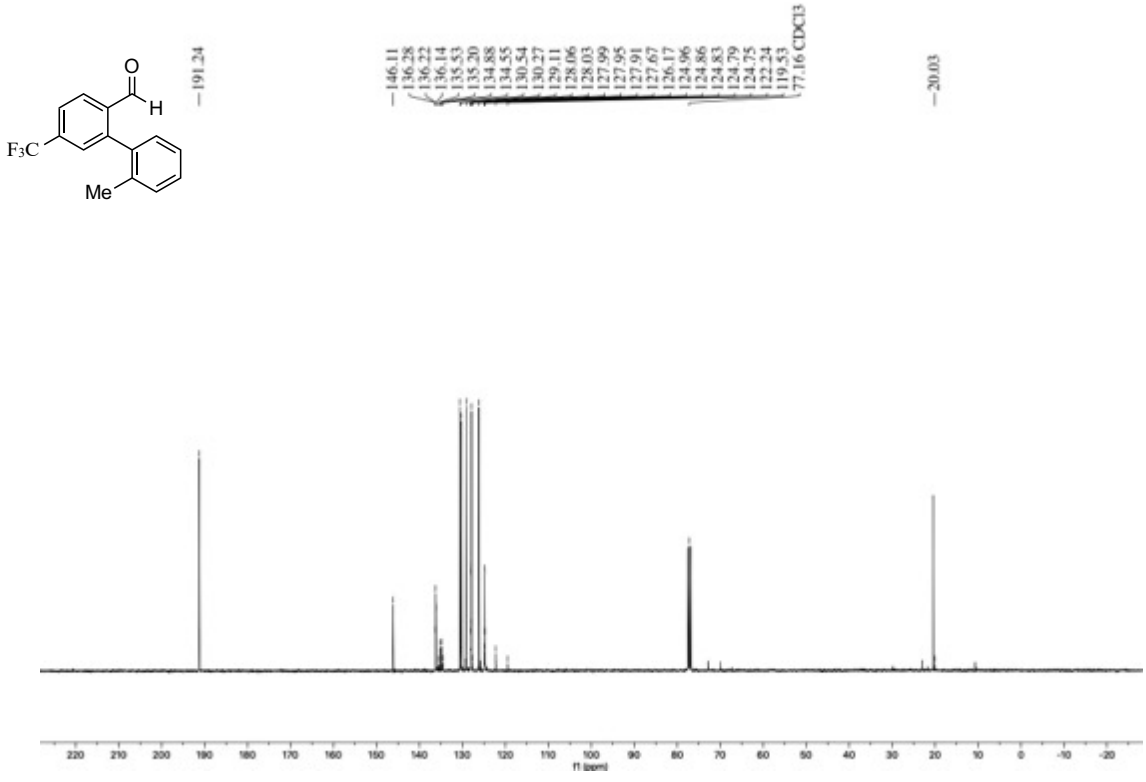
HSQC spectral window of **3-52** ($CDCl_3$)



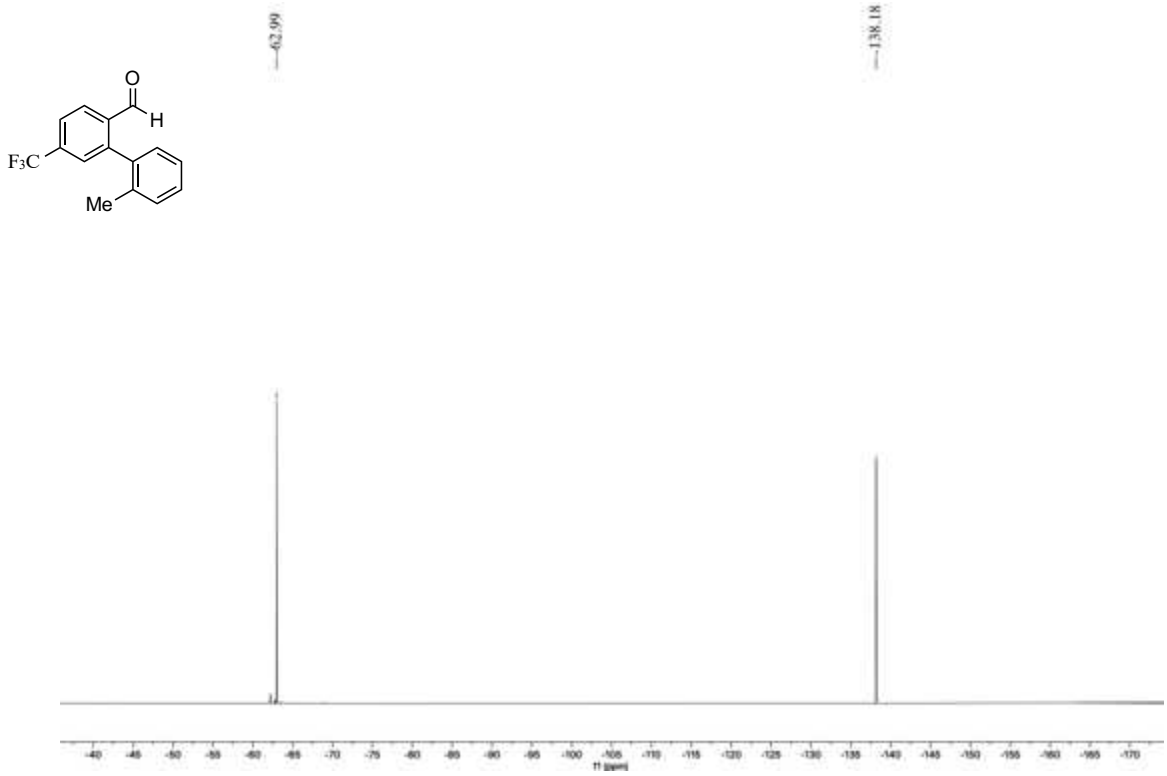
HMBC spectral window of **3-52** ($CDCl_3$)



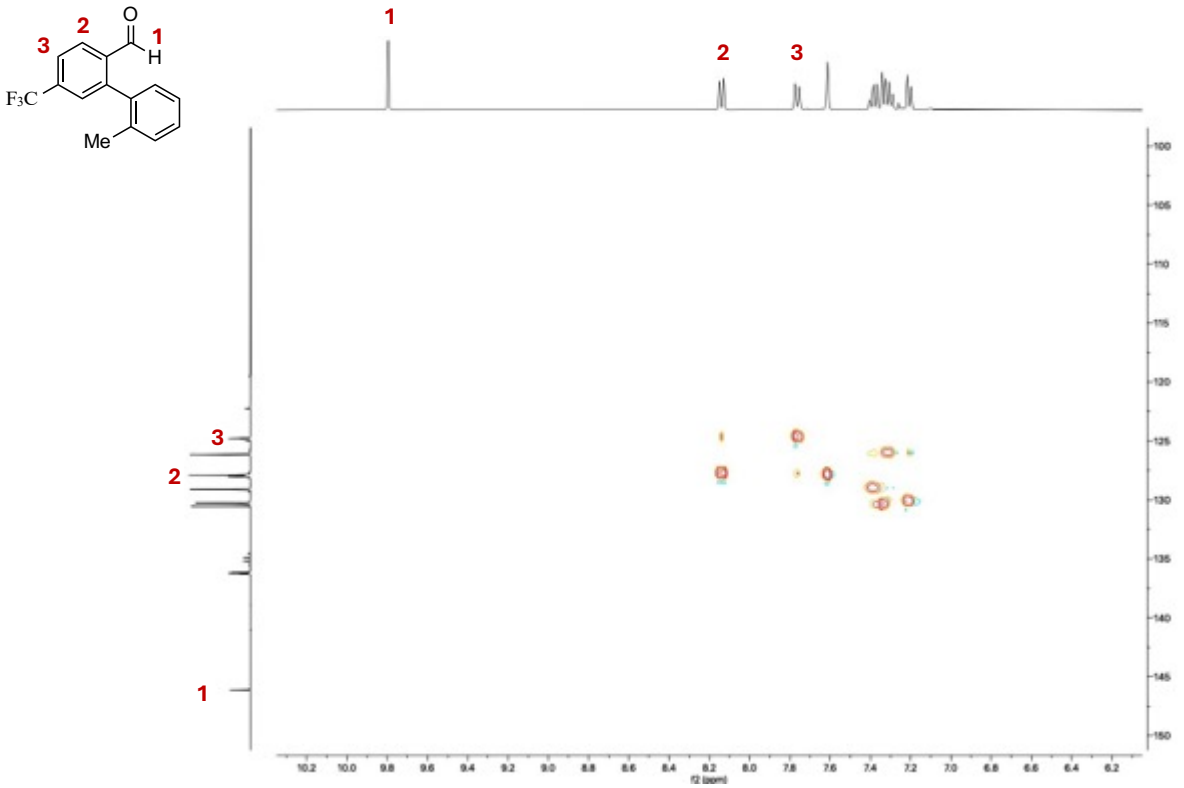
^{1}H NMR spectrum of **3-53** (400 MHz, $CDCl_3$)



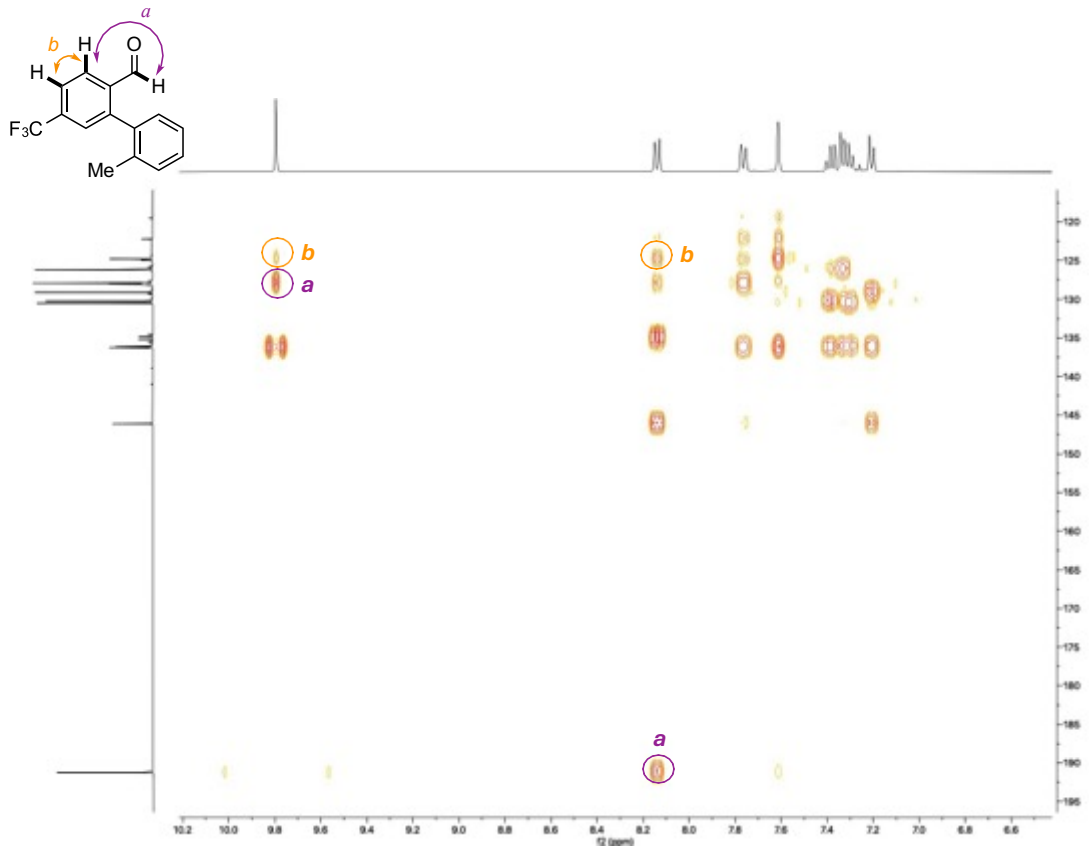
^{13}C NMR spectrum of **3-53** (101 MHz, $CDCl_3$)



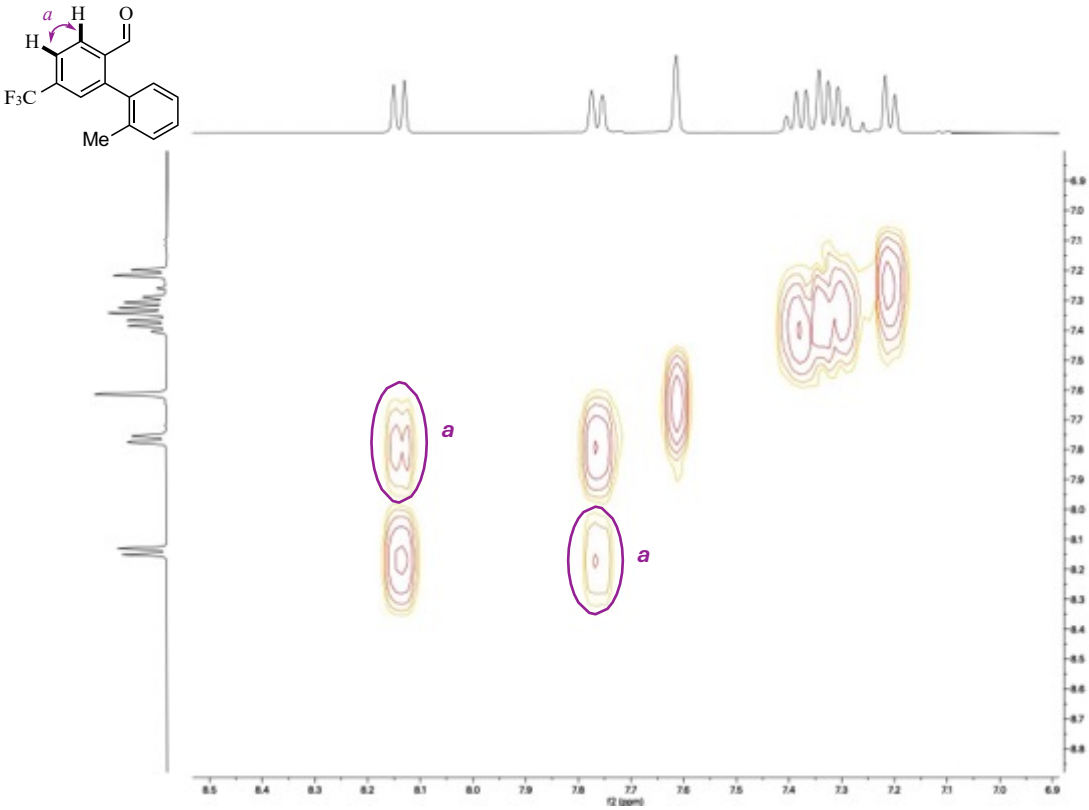
^{19}F NMR spectrum of **3-53** (376 MHz, $CDCl_3$)



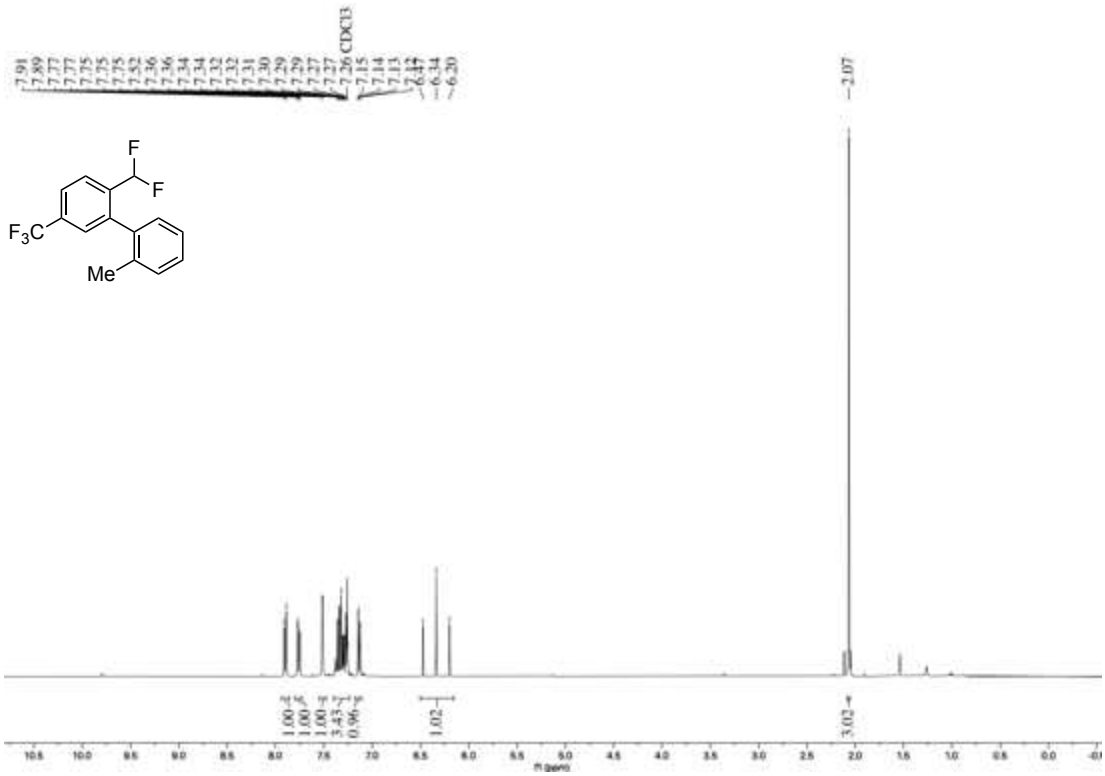
HSQC spectral window of **3-53** ($CDCl_3$)



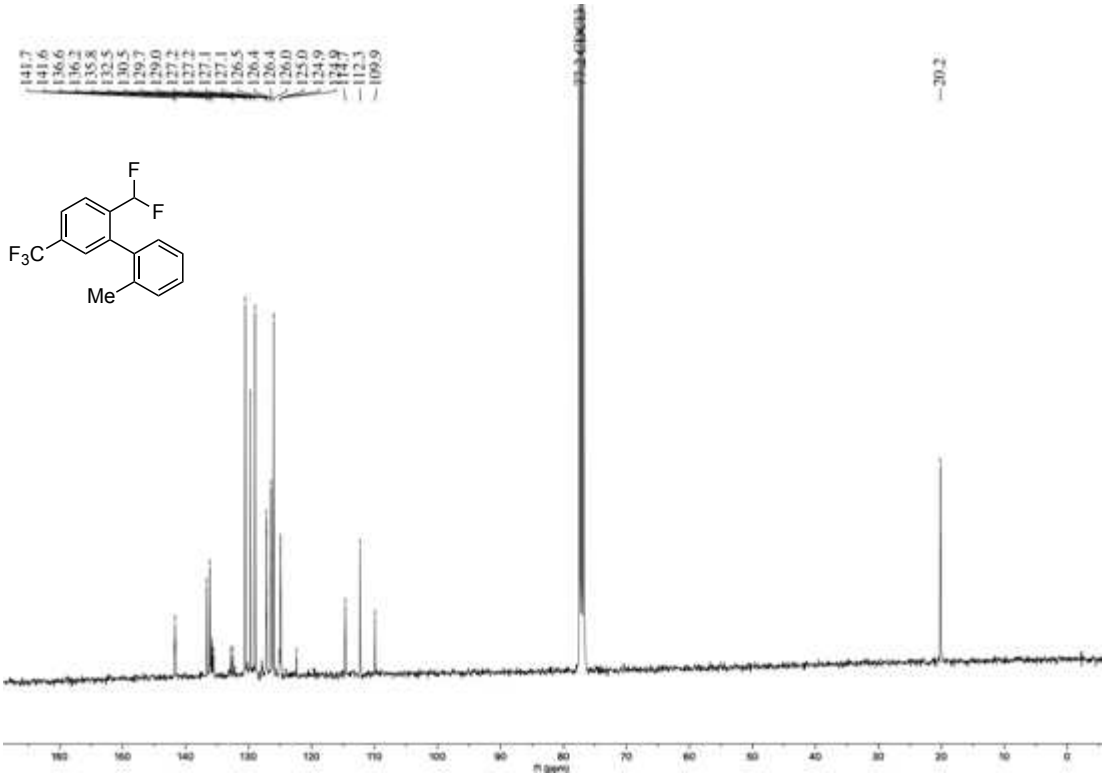
HMBC spectral window of **3-53** ($CDCl_3$)



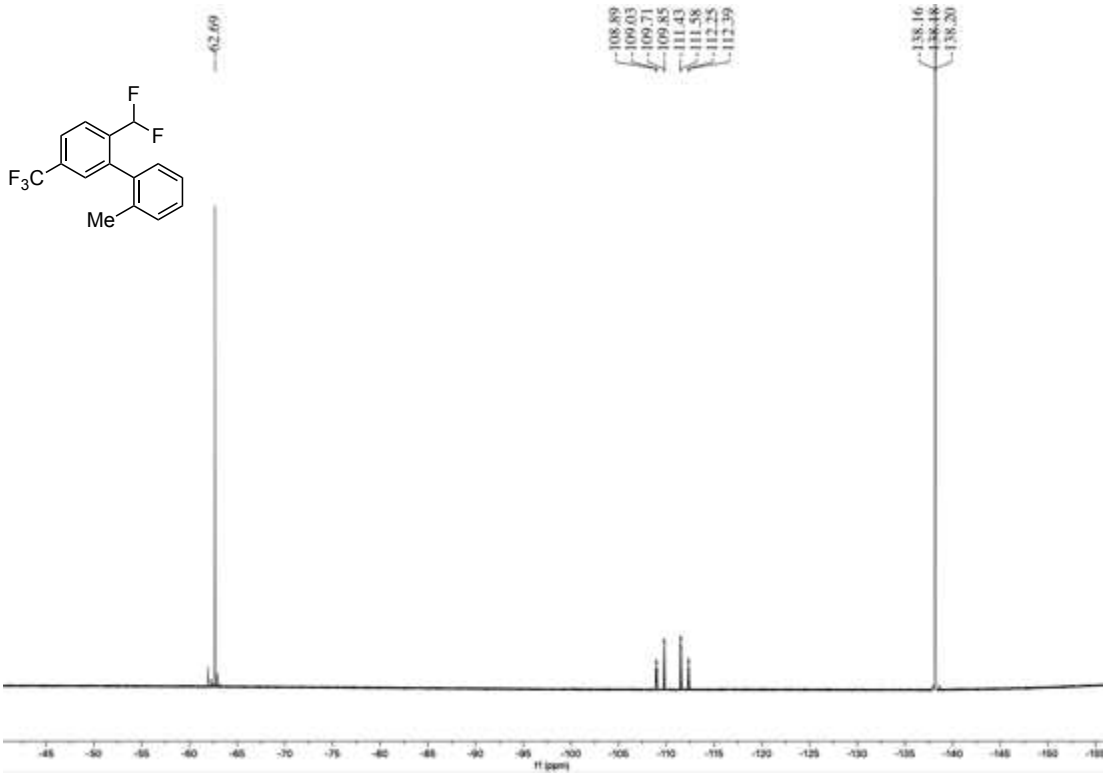
COSY spectral window of **3-53** ($CDCl_3$)



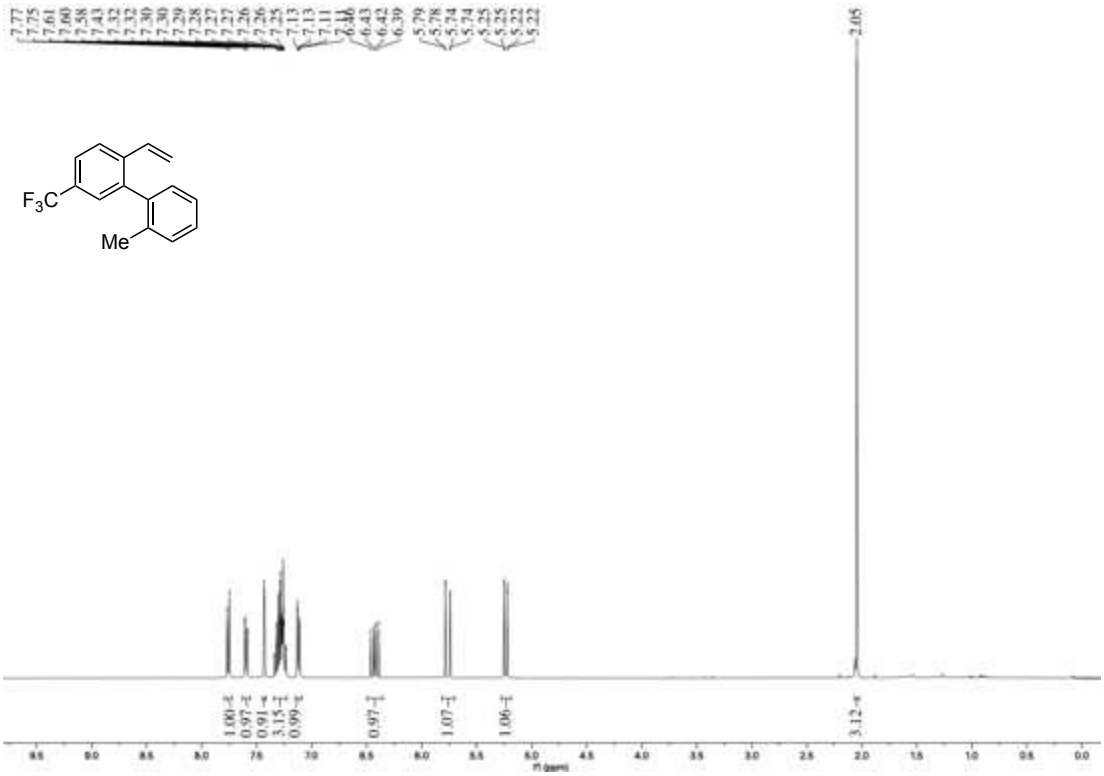
^{1}H NMR spectrum of **3-54** (400 MHz, $CDCl_3$)



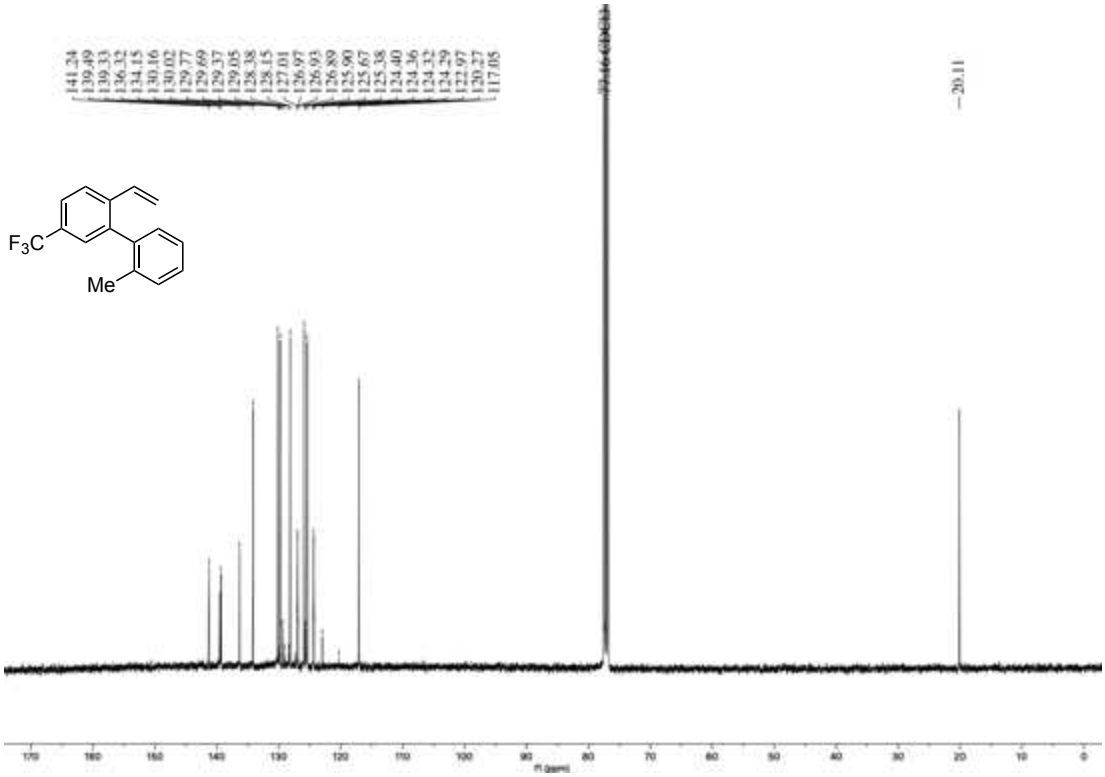
^{13}C NMR spectrum of **3-54** (101 MHz, $CDCl_3$)



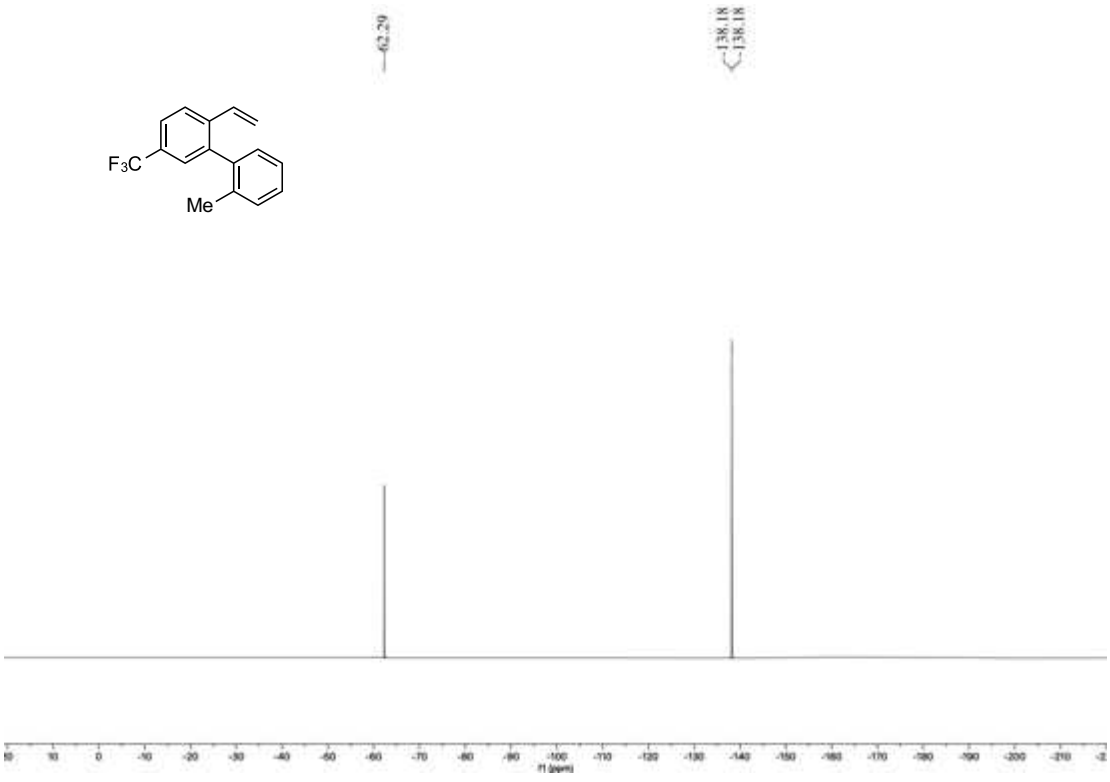
^{19}F NMR spectrum of **3-54** (376 MHz, $CDCl_3$)



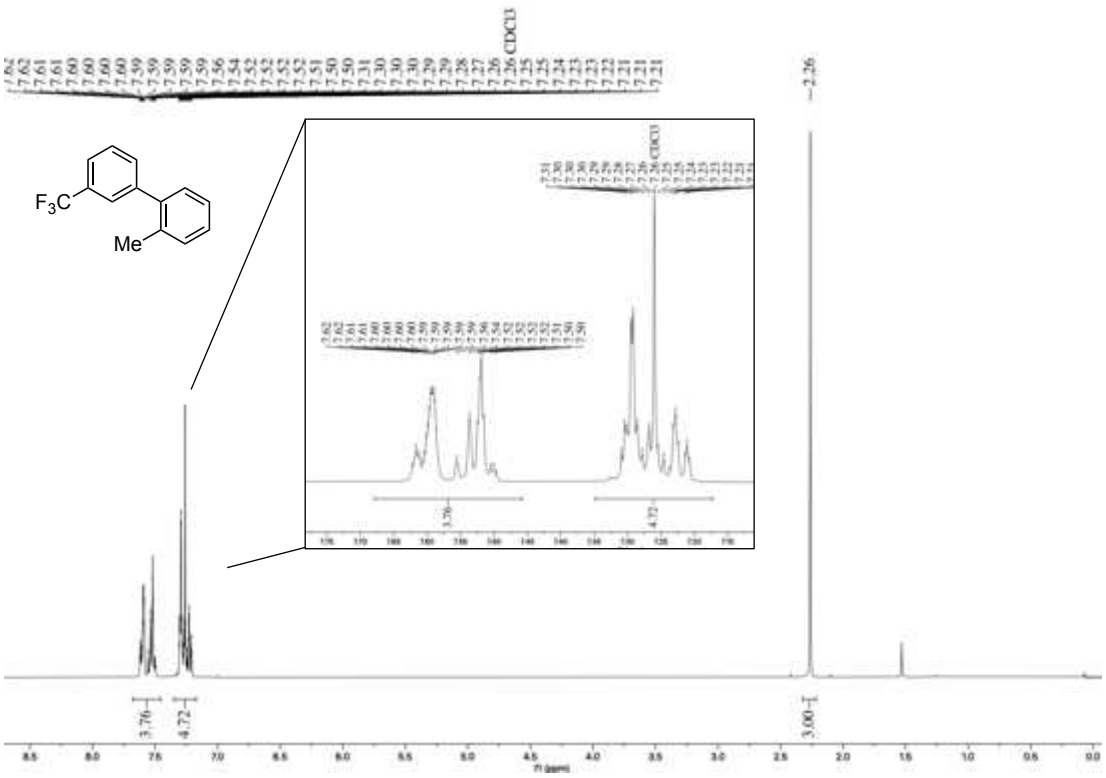
^{1}H NMR spectrum of **3-55** (400 MHz, $CDCl_3$)



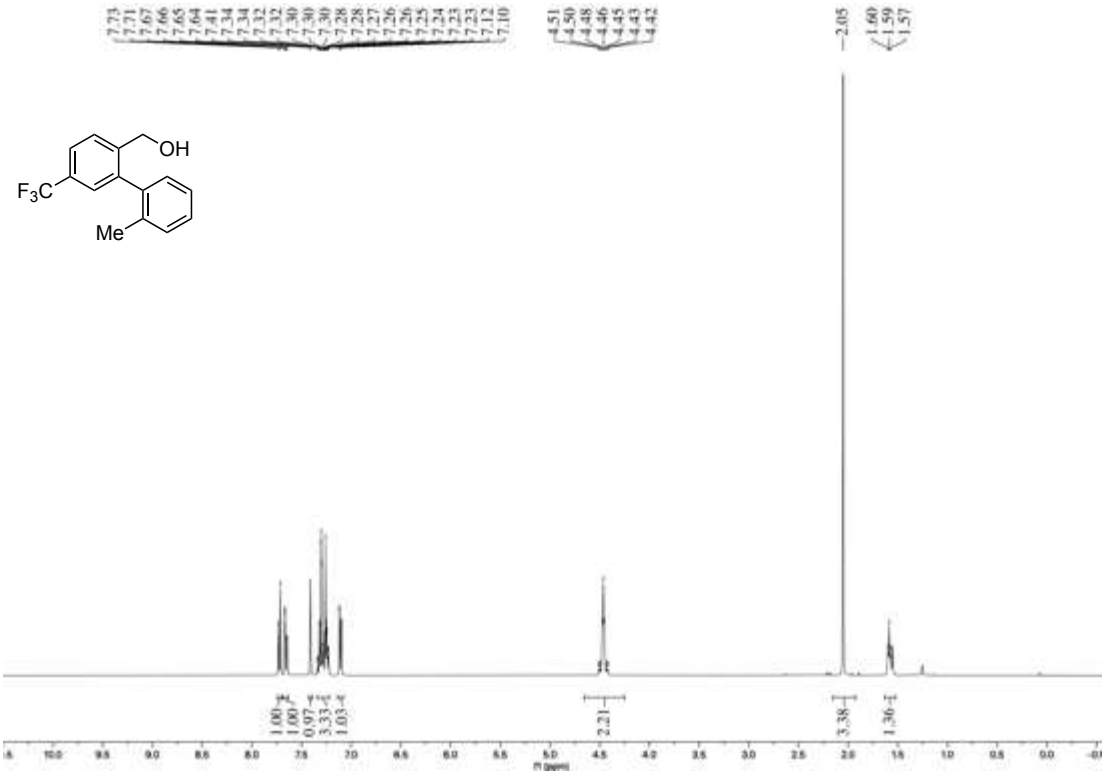
^{13}C NMR spectrum of **3-55** (101 MHz, $CDCl_3$)



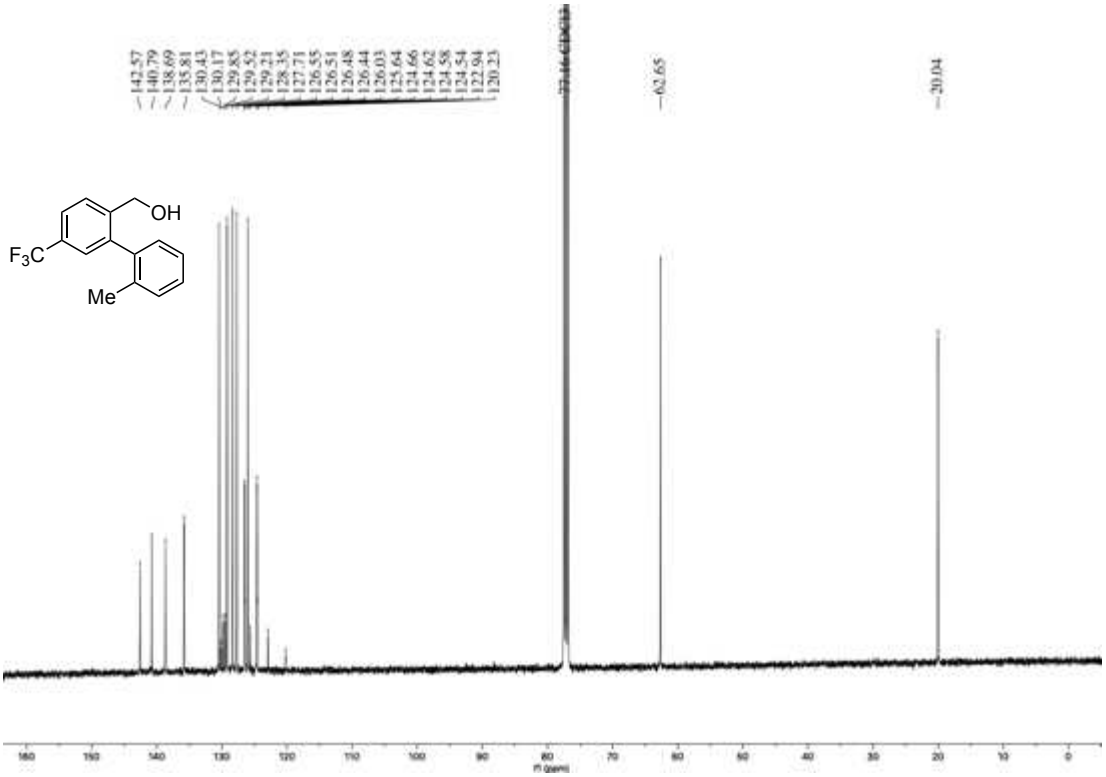
^{19}F NMR spectrum of **3-55** (376 MHz, $CDCl_3$)



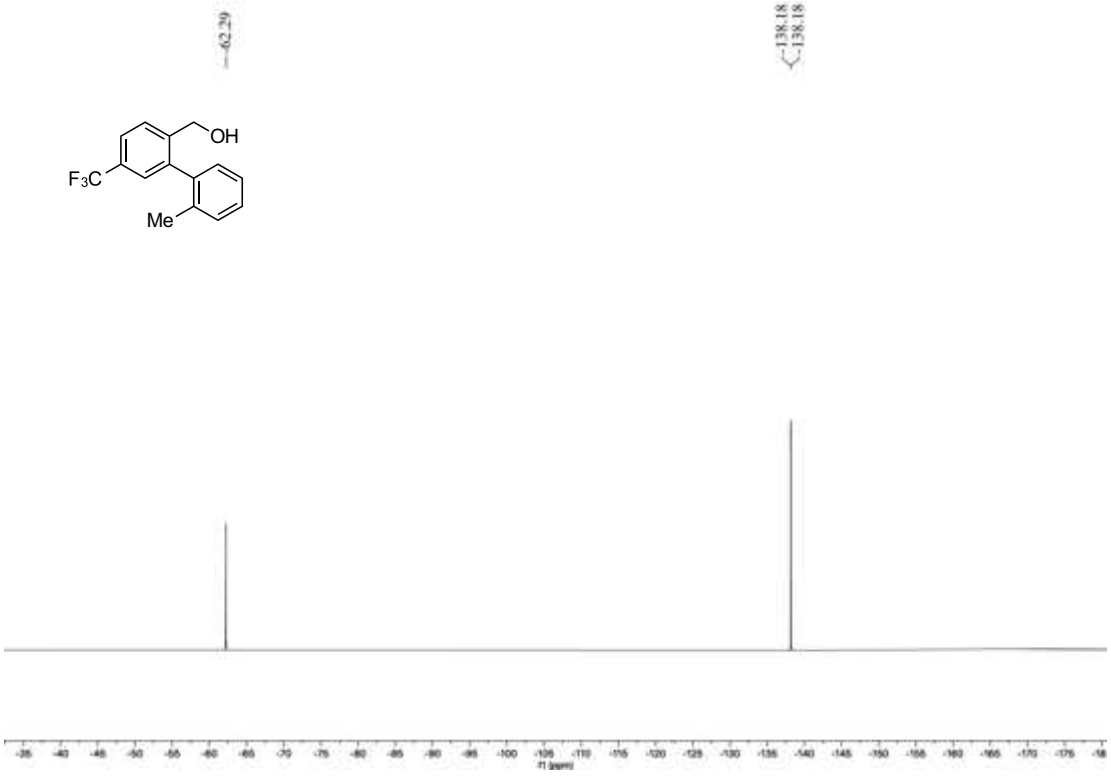
^{1}H NMR spectrum of **3-56** (400 MHz, $CDCl_3$)



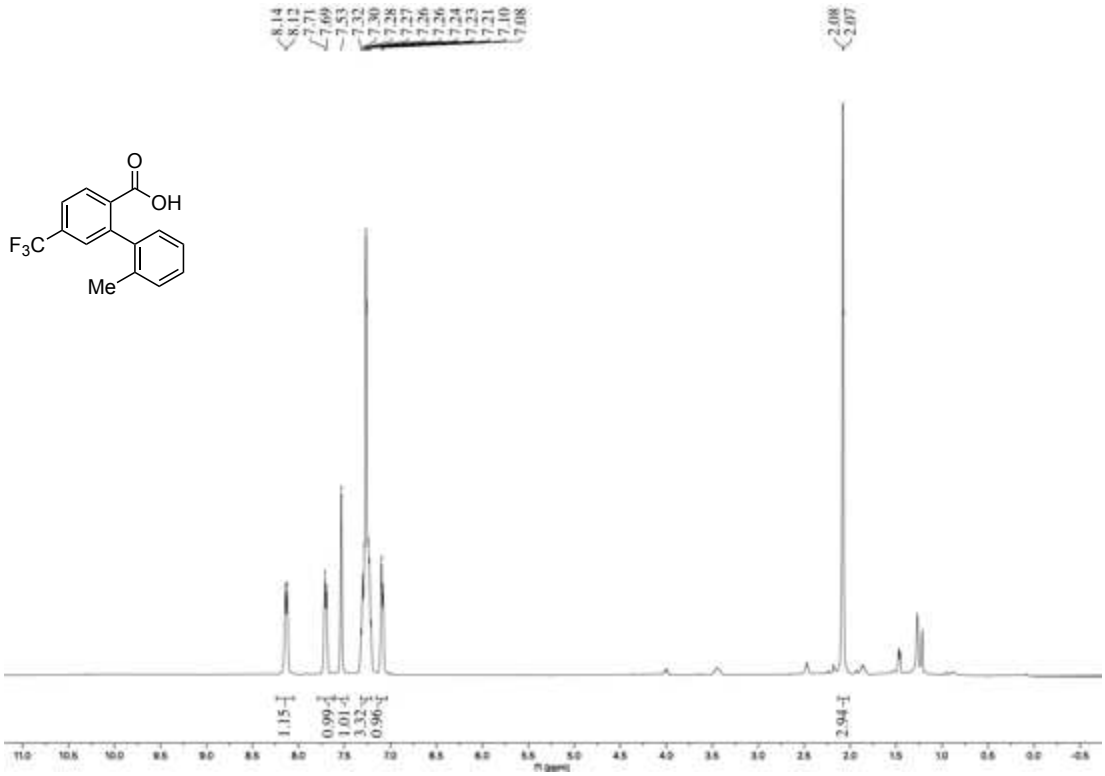
^{1}H NMR spectrum of **3-57** (400 MHz, $CDCl_3$)



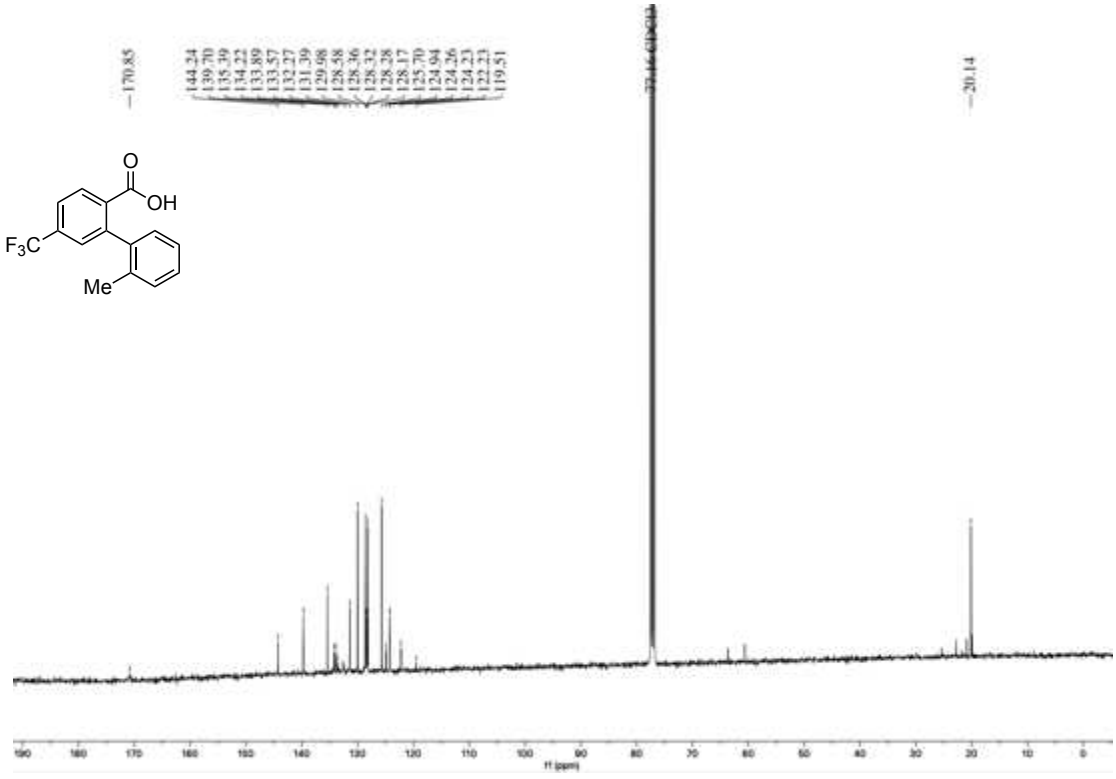
^{13}C NMR spectrum of **3-57** (101 MHz, $CDCl_3$)



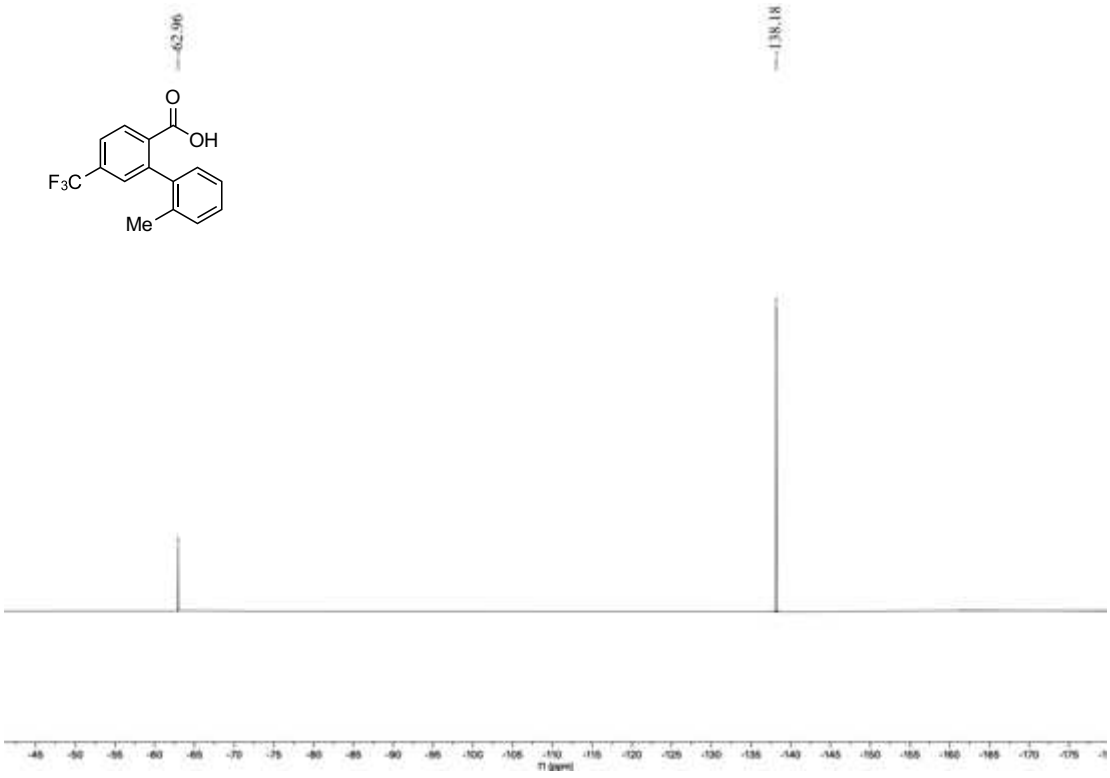
^{19}F NMR spectrum of **3-57** (376 MHz, $CDCl_3$)



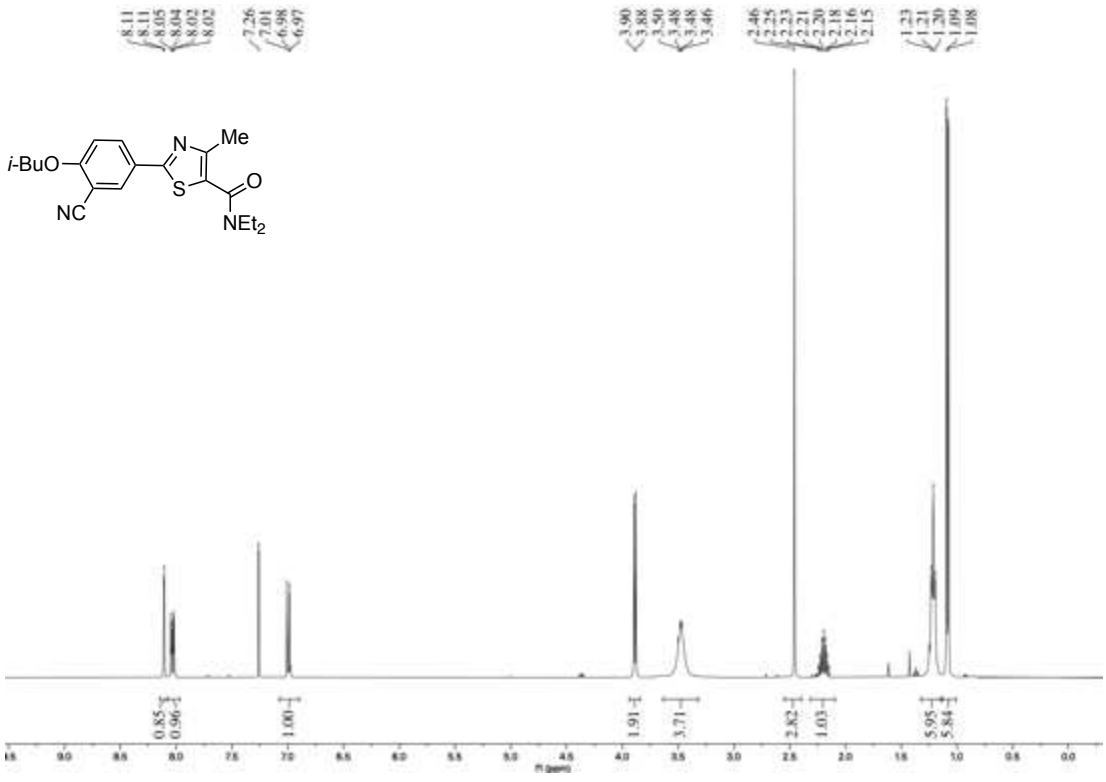
^{1}H NMR spectrum of **3-58** (400 MHz, $CDCl_3$)



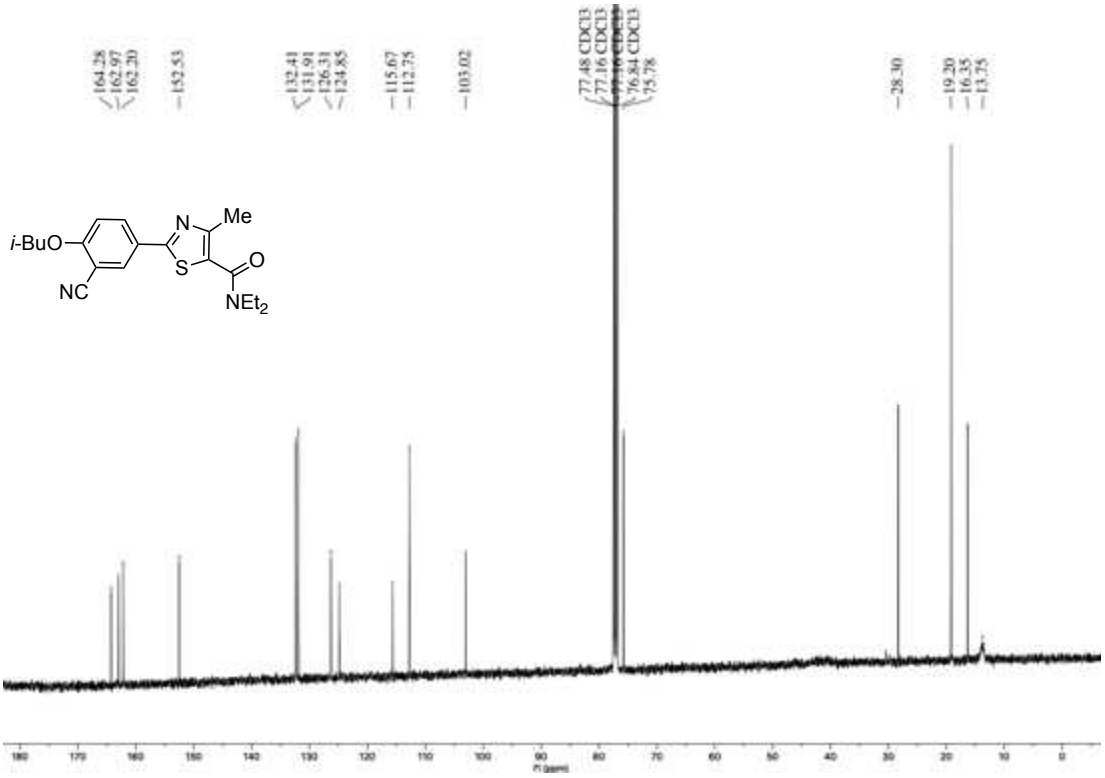
^{13}C NMR spectrum of **3-58** (101 MHz, $CDCl_3$)



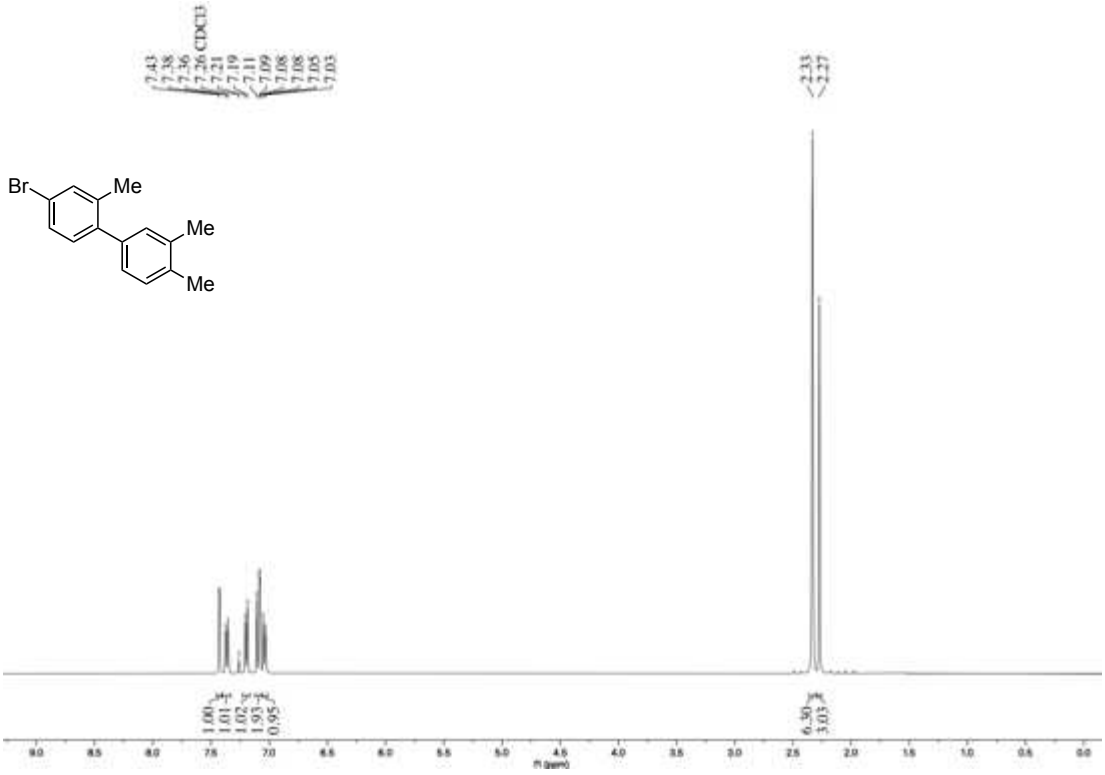
^{19}F NMR spectrum of **33-58** (376 MHz, $CDCl_3$)



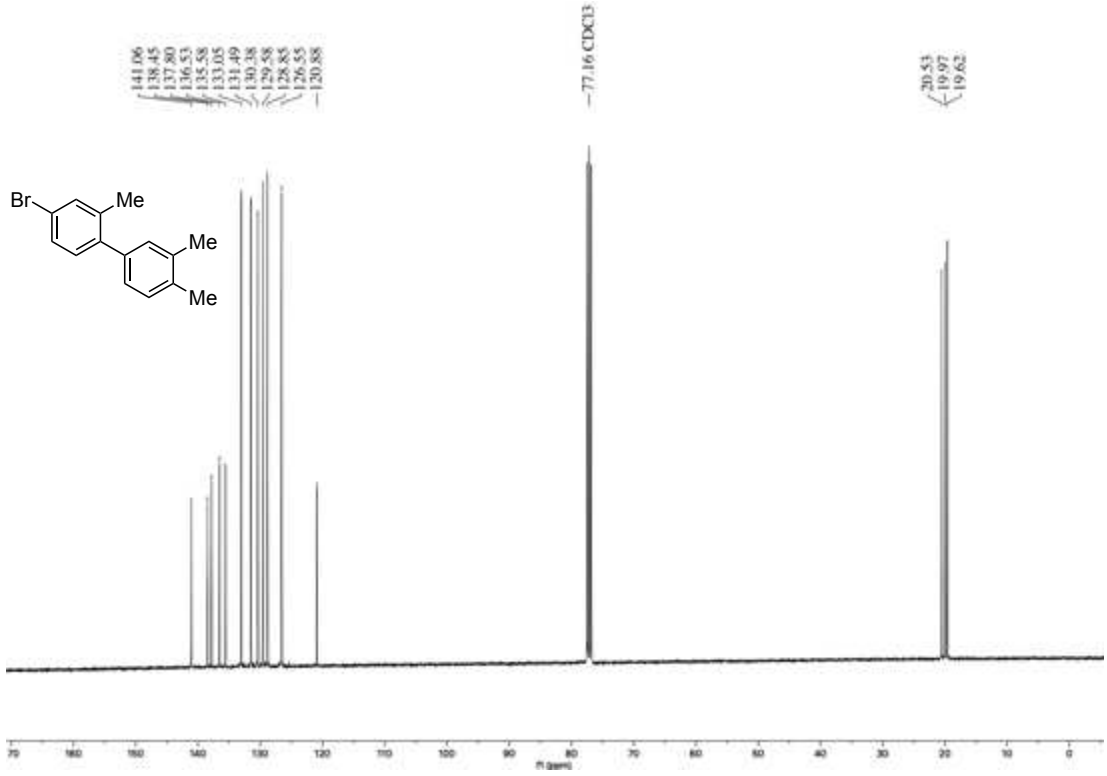
^{1}H NMR spectrum of **2-A12** (400 MHz, $CDCl_3$)



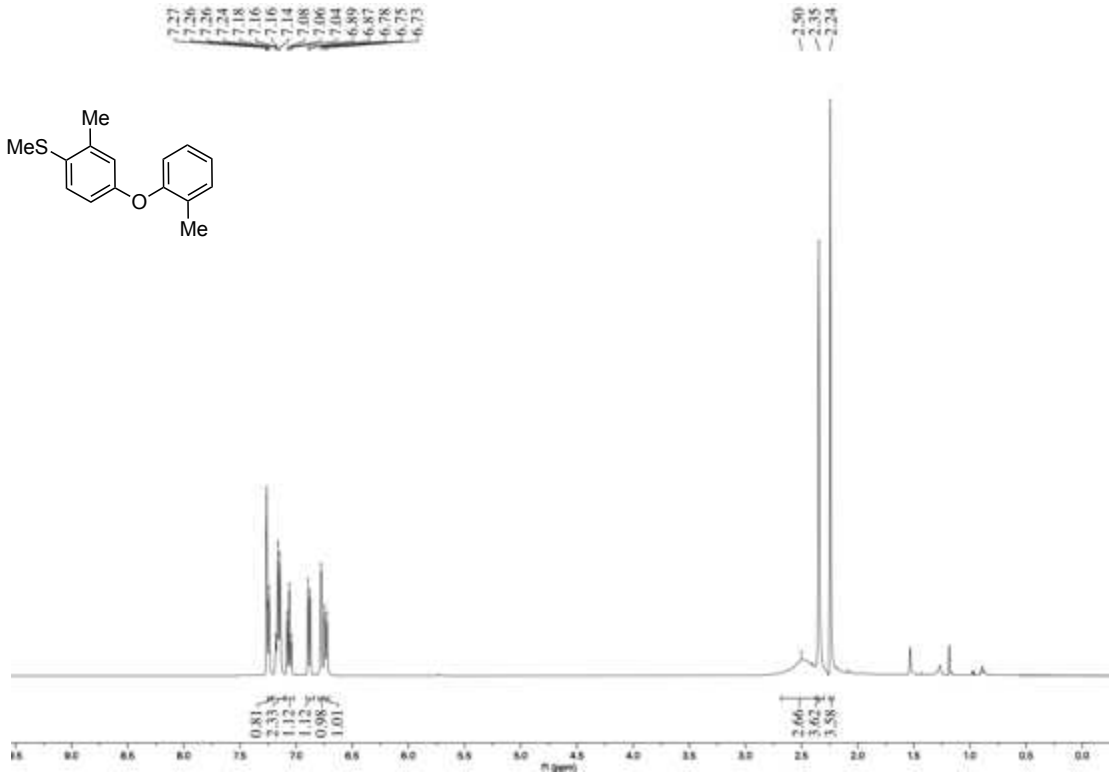
^{13}C NMR spectrum of **2-A12** (101 MHz, $CDCl_3$)



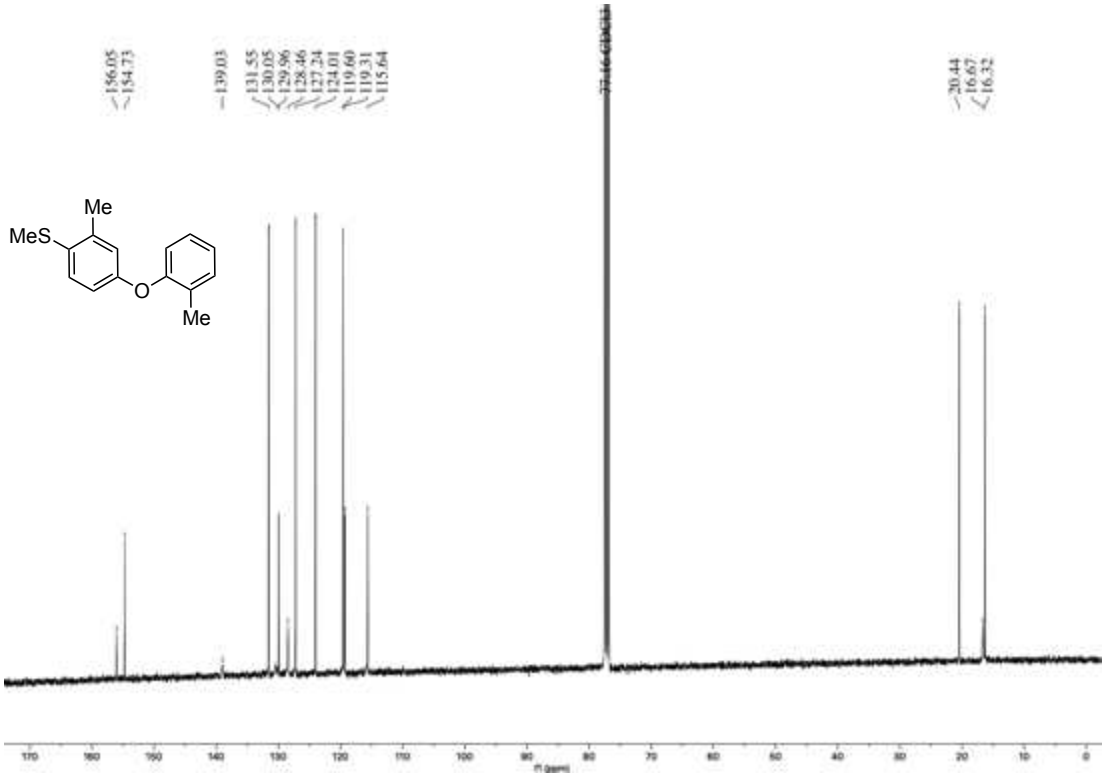
^{1}H NMR spectrum of **2-A13** (400 MHz, $CDCl_3$)



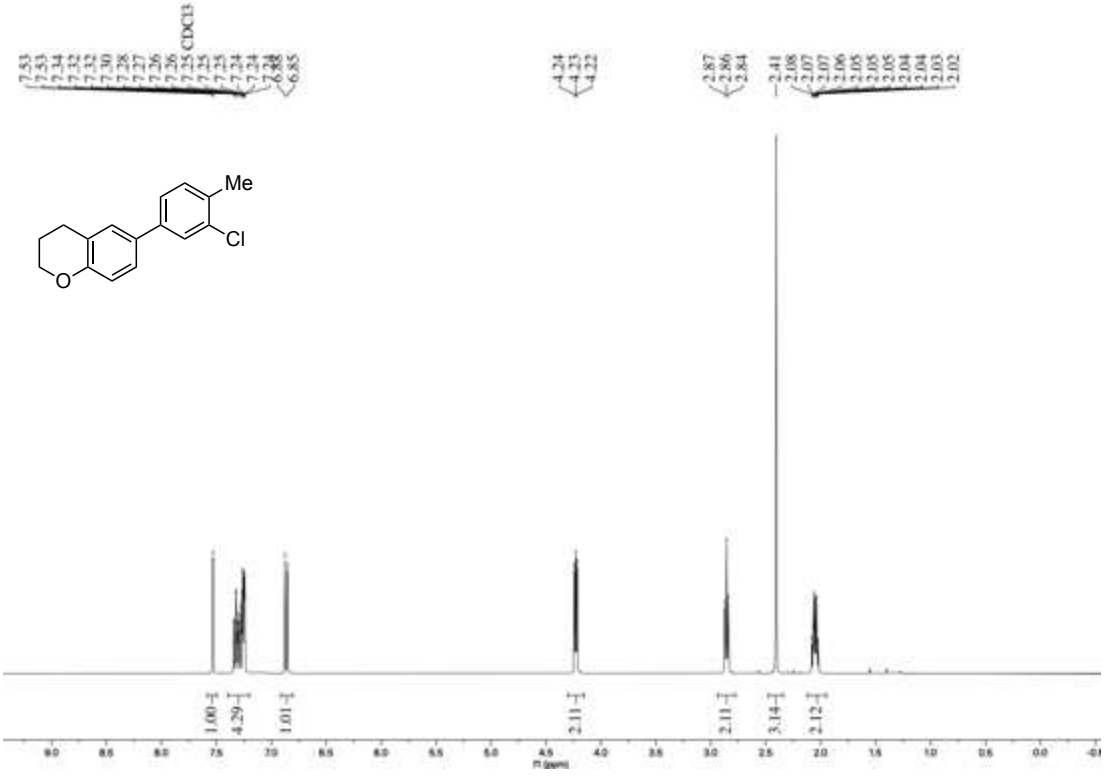
^{13}C NMR spectrum of **2-A13** (101 MHz, $CDCl_3$)



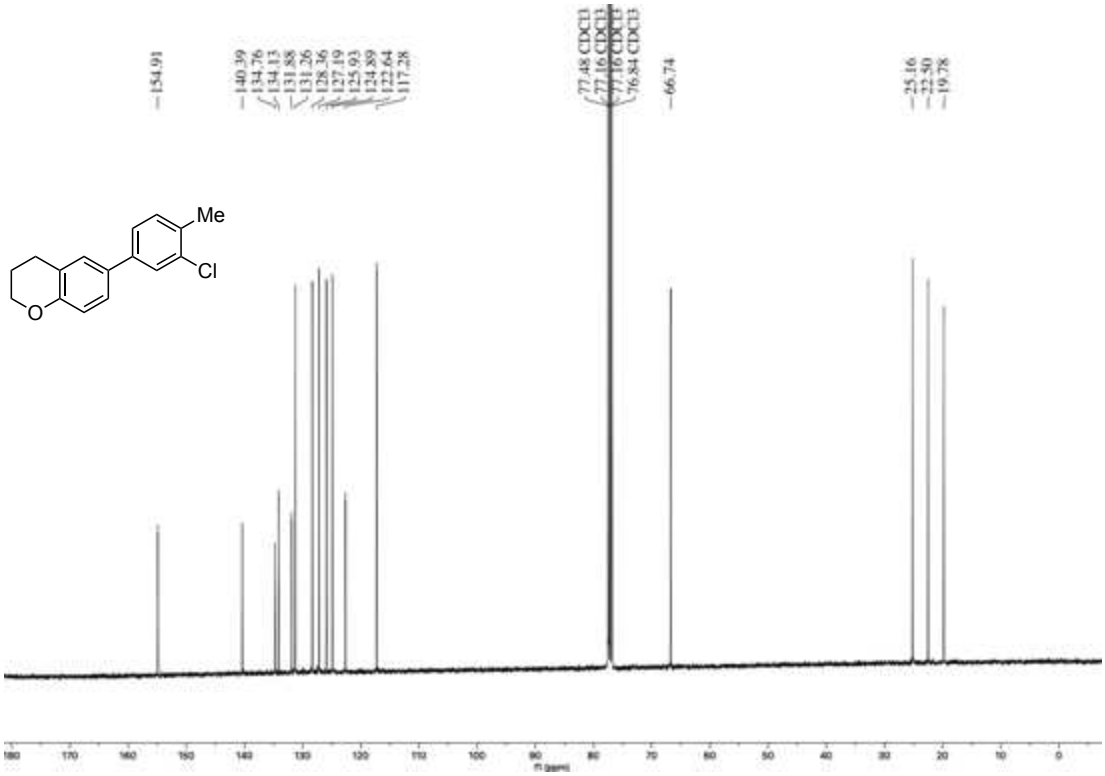
^{1}H NMR spectrum of **2-A14** (400 MHz, $CDCl_3$)



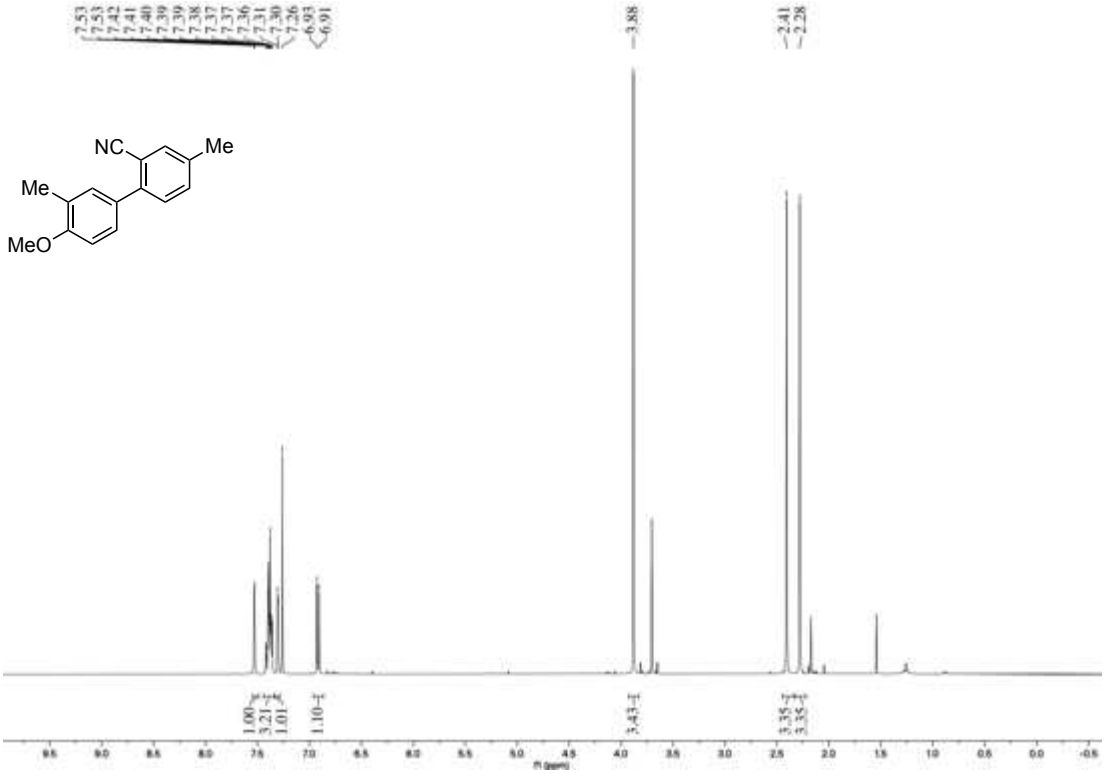
^{13}C NMR spectrum of **2-A14** (101 MHz, $CDCl_3$)



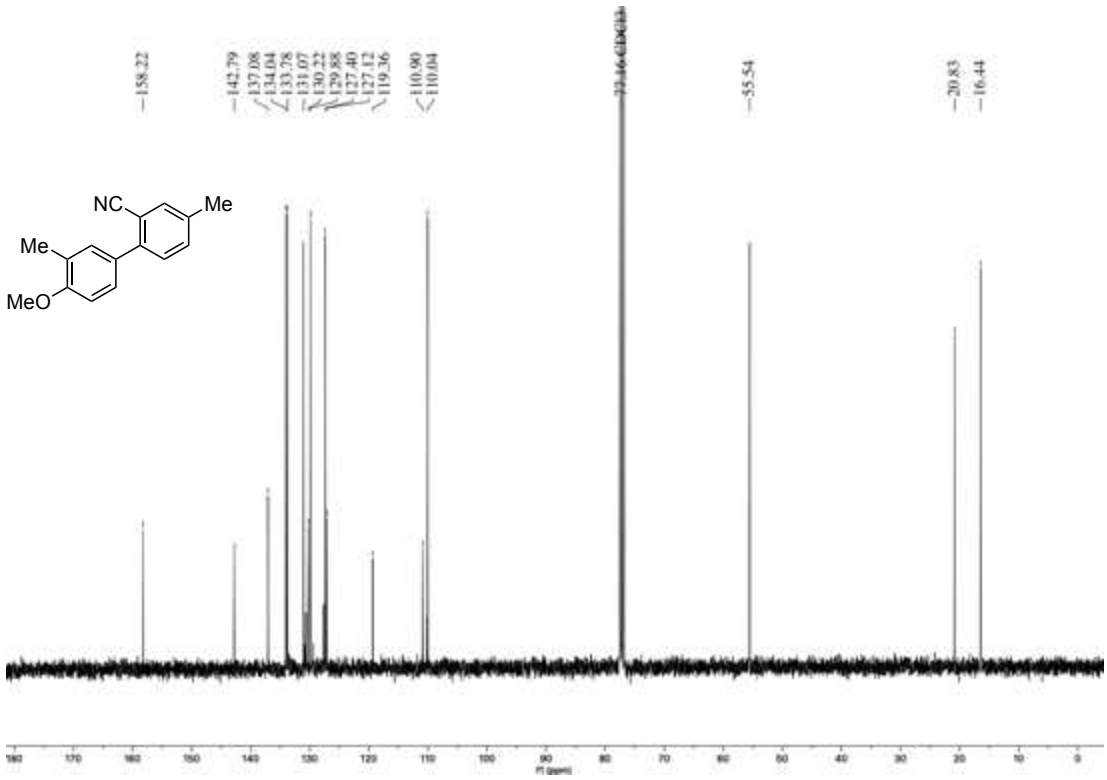
^{1}H NMR spectrum of **2-A15** (400 MHz, $CDCl_3$)



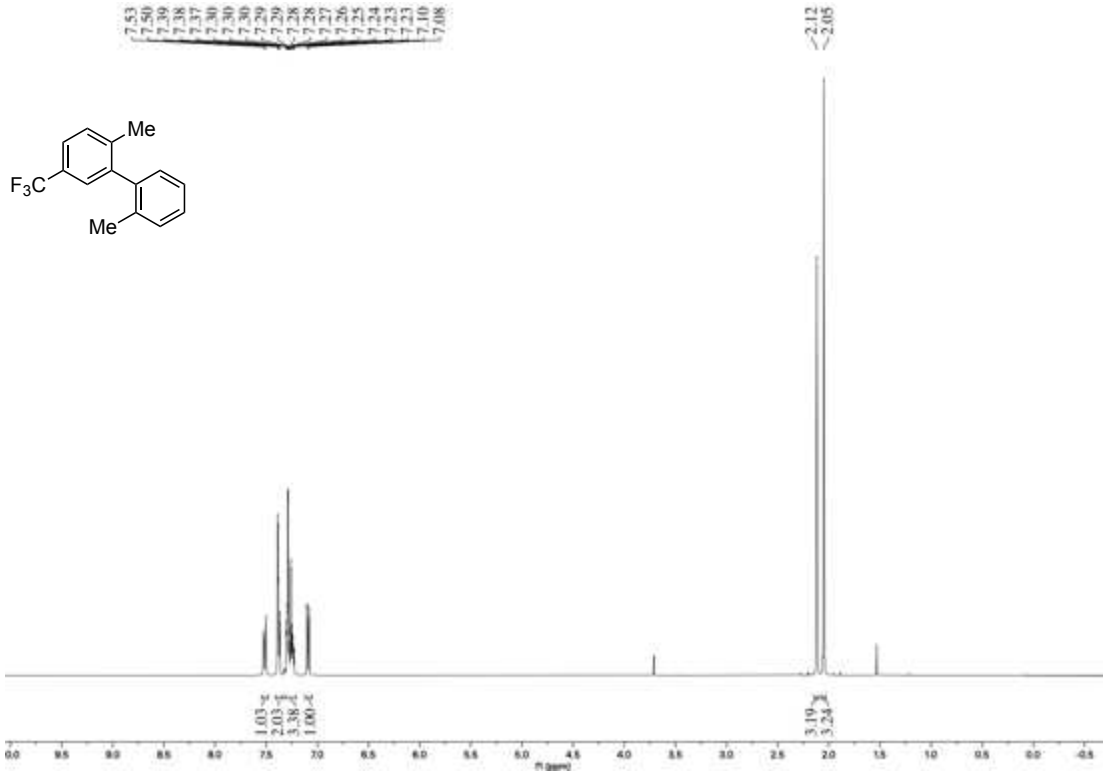
^{13}C NMR spectrum of **2-A15** (101 MHz, $CDCl_3$)



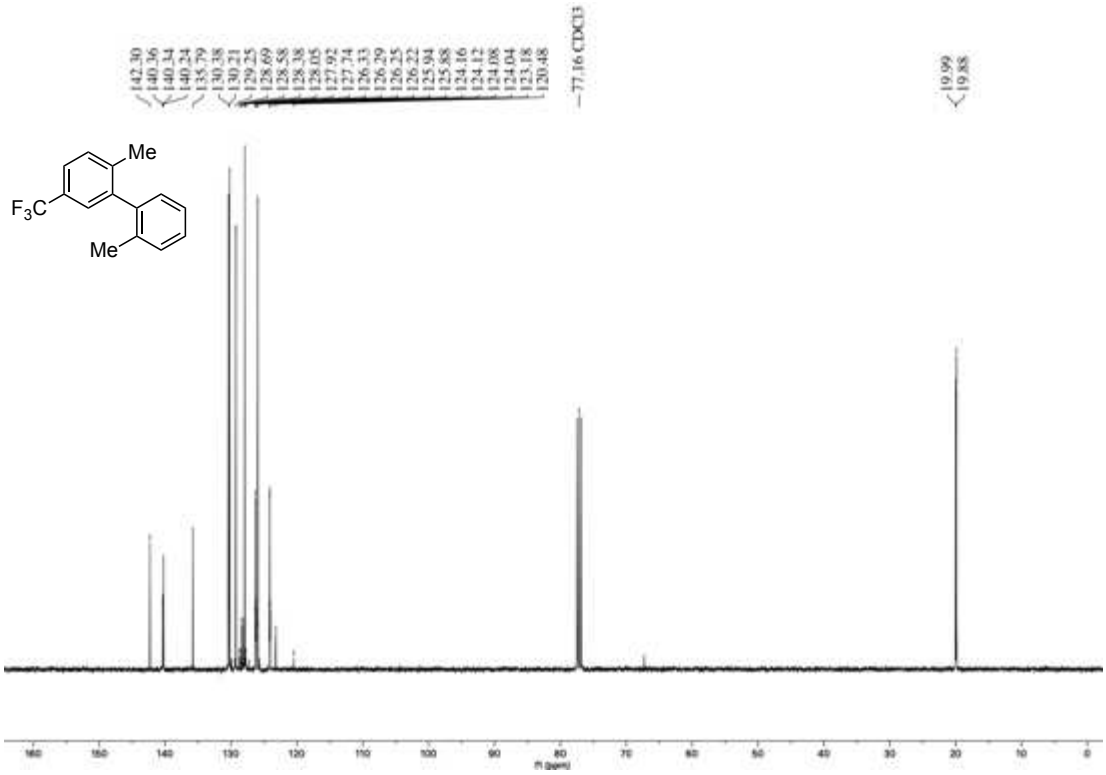
^{1}H NMR spectrum of **2-A16** (400 MHz, $CDCl_3$)



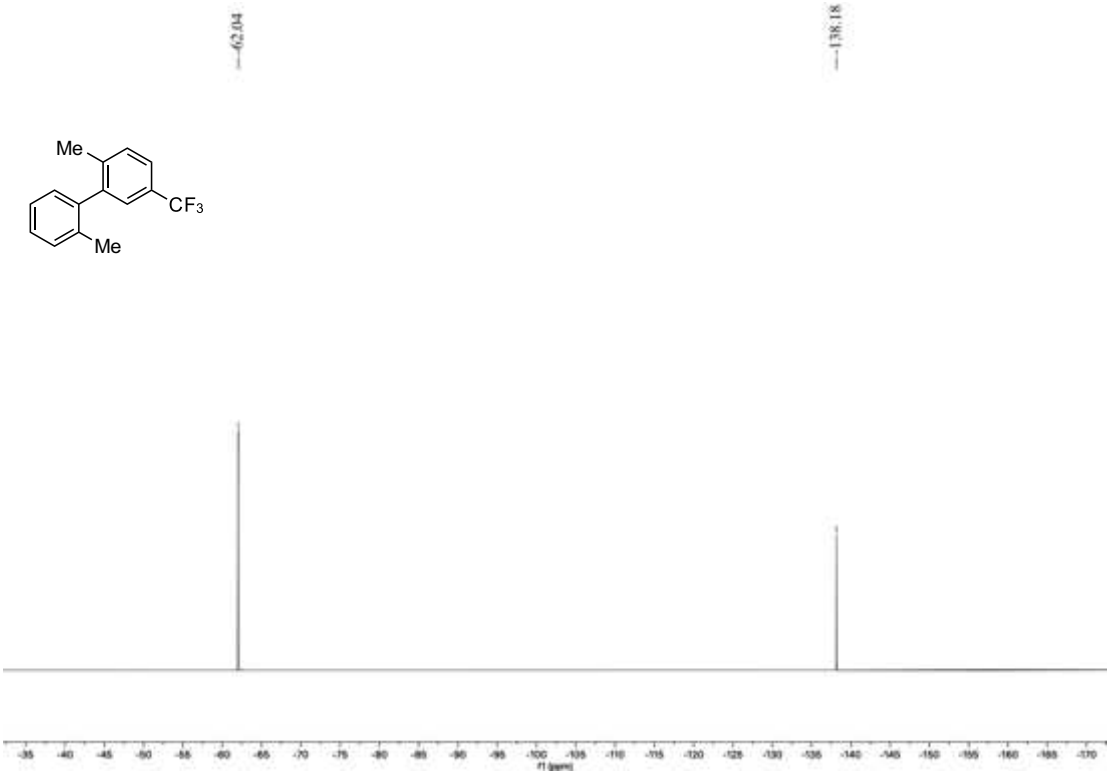
^{13}C NMR spectrum of **2-A16** (101 MHz, $CDCl_3$)



^{1}H NMR spectrum of **2-A17** (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of **2-A17** (101 MHz, $CDCl_3$)



^{19}F NMR spectrum of **2-A17** (376 MHz, $CDCl_3$)

LIST OF ABBREVIATIONS

AIBN	azobisisobutyronitrile
DG	directing group
DMAc	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*′-dimethylpropyleneurea
DMSO	dimethyl sulfoxide
EWG	electron-withdrawing group
g	gram
h	hour
*K*eq	equilibrium constant
LDA	lithium diisopropylamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidine
MeOH	methanol
min	minute
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
Nu-H	nucleophile
S_NAr	nucleophilic aromatic substitution
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
THF	tetrahydrofuran

XTR	halogen transfer reagent
X-Transfer	halogen transfer