Expanding Benzylic C–H Diversification via C–H Chlorination/Functionalization Strategies

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Marco Antonio Lopez

Under the supervision of Professor Shannon S. Stahl

At the University of Wisconsin-Madison

Abstract

Alkyl chlorides can be employed in a range of C–C, C–O, C–N, and C–S bond forming reactions, making them valuable precursors in the synthesis of diverse drug-like compounds with desirable physiochemical and pharmacokinetic properties. Conventionally, methods for their preparation involve a series of functional group interconversions. Described herein, several methods for the selective chlorination of C(sp^3)–H bonds, with particular emphasis on benzylic positions of alkyl-arenes and azaheterocycles. These technologies provide means by which to structurally diversify benzylic positions with a wide range of oxidatively sensitive functional groups (e.g., amines, azoles, phenols, thiophenols) that are often incompatible with direct C–H oxidation strategies. In addition to the development of a C–H chlorination/nucleophile coupling sequence, Ni-catalyzed cross-electrophile coupling of azaheterobenzyl chlorides has been explored and validated for the synthesis of complex 1,1-diarylalkanes. This work addresses some of the limitations of benzyl chloride arylation, which are constrained to simple alkyl arenes and employ the chloride substrate in excess amount.

Chapter 2 describes efforts toward improving selectivity for benzylic chlorination by leveraging a radical-relay mechanism with a Cu catalyst and *N*-fluorobenzenesulfonimide (NFSI) oxidant. This approach leverages precedents that feature a bis(sulfonyl)imidyl radical (•NSI) that can enact

selective HAT, generating a diffusible benzylic radical that undergoes subsequent functionalization by Cu^{II} and a nucleophilic source. We demonstrate the combination of a CuCl salt, bis(oxazoline) ancillary ligand, potassium chloride, NFSI, and diisopropyl phosphite can affect selective benzylic chlorination with a broad range of C–H substrates. The chloride products derived from this method are then showcased in a coupling step with oxidative sensitive nucleophiles that are incompatible with NFSI.

Chapter 3 discloses complimentary efforts that addresses limitations that are observed when NFSI is applied to chlorination of heterobenzylic positions. In collaboration with Merck, optimization efforts identified new C–H chlorination conditions that feature 1 equiv of the C-H substrate, N-chlorosuccinimide (NCS) or trichloroisocyanuric acid (TCCA) as chlorinating agents, trifluoromethanesulfonyl chloride (TfCl) nitrogen activator, and Li_2CO_3 as a mild base. Contrasting radical C–H chlorination, this method proceeds through a polar mechanism whereby transient *N*-sulfonylation with TfCl is proposed to increase the acidity of the benzylic proton and promote deprotonation with a mild base. The generated alkylidene dihydropyridine intermediates undergo facile reaction with NCS or TCCA to afford the desired chloride. A wide range of 2- and 4-alkylated heterocycles bearing oxidatively sensitive substituents are compatible with this method. The chloride products are seamlessly derivatized, without isolation, in a nucleophilic coupling step with amine and azole building blocks.

Chapter 4 details our recent investigation into hetero(diaryl)alkane synthesis via reductive coupling of heterobenzyl chlorides and (hetero)aryl-halides. Benzylic C–H chlorination has facilitated the rapid expansion of new chemical space though chloride displacement with acidic nucleophiles. However, this strategy is ineffective for rapid formation of diverse C–C bonds at these positions. Ni-catalyzed cross-electrophile coupling (Ni-XEC) presents an alternative and

strategic approach toward benzyl C–C bond derivatization with abundant electrophiles. We proposed that the chloride products described in Chapter 3 are privileged compounds for this type of reactivity and could be further diversified with aryl halides. However, their distinguished reactivity profiles under Ni-XEC conditions necessitated development of new strategies. High-throughput experimentation identified several reaction conditions to promote reductive arylation of heterobenzyl chlorides with aryl-iodides, including those involving the use of cobalt phthalocyanine, iron(tetraphenylporphyrinato) chloride, and $MgCl_2$ as key co-catalysts or additives.

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Although I have pursued chemistry avidly, I owe my personal and scientific development to an incredible collection of mentors, friends, lab mates, and family members.

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Lastly, but certainty, not least, I would like to thank my family. Mom, Dad, Daveed, and Jennifer. You have been my biggest champions in my educational journey and life. Although I know it wasn't easy for you to see me leave California, I cannot be more grateful for the overwhelming support I have received from you these past 4 ½ years. Dad, my journey up to this point could not have been possible if it wasn't for your constant reminder that "no hay nada como la education". Since day one, you have ensured that my academic needs were met, even though I may not have wanted help. Whether it was posting flyers for tutors at East Los Angeles College or meeting with my middle /high school teachers to discuss my coursework, you did everything that you could to equip me with the tools I needed for success. Mom, I look to your educational story as inspiration to mine. I know it must not have been easy to enter high school without knowing any English, but you worked hard and eventually enrolled in college and earned your degree. This will always serve as a reminder to me that nothing is impossible. Daveed, I may be your older brother, but I look up to you in more ways than you think. I have always admired your intellect and your ability to get As in every class you take. Our Facetime chats to talk about politics, the new Marvel films, or share the latest meme were reminders to me that there was life outside of lab. And Jennifer, you have always been one of my biggest advocates. You accept me for who I am and are always there to cheer me on.

This thesis is dedicated to my family.

Abbreviations and Acronyms

•Cl	chlorine radical
•NSI	benzenesulfonimidyl radical
ABDO	azido-1,2-benziodoxole-3-(1H)-one
AIBN	azobisisobutyronitrile
BisOx	bis(oxazoline)
$C(sp^2)$	carbon with sp^2 hybridized orbitals
$C(sp^3)$	carbon with sp^3 hybridized orbitals
Cl_2	elemental chlorine
Co(Pc)	cobalt phthalocyanine
Conv.	percent conversion of the C–H substrate
Cu	copper
CuCl	copper(I)chloride
DBPO	dibenozylperoxide
DFT	density functional theory
DMA	N,N-dimethylacetamide
DMAP	4-(N,N-dimethylamino)pyridine
Dtbbpy	dtbbpy 4,4’-di-tert-butyl-2,2’-bipyridyl
Fe(TPP)Cl	Iron(tetraphenylporphyrinato) chloride
HAT	hydrogen atom transfer
HTE.	high-throughput experimentation
KCl	potassium chloride

LiBr	lithium bromide
LiCl	lithium chloride
Li_2CO_3	lithium carbonate
$MgCl_2$	magnesium chloride
NaOCl	sodium hypochlorite
NCS	N-chlorosuccinimide
NCSI	*N*-chlorobenzensulfonimide
NFSI.	*N*-fluorobenzensulfonimide
NHPI	N-hydroxyphthalimide
$NiBr_2$•dme	Nickel(II) bromide ethylene glycol dimethyl ether
$NiCl_2$•dme	Nickel(II) chloride ethylene glycol dimethyl ether
NMR	nuclear magnetic resonance
$SOCl_2$	thionyl chloride
t-BuOCl	*tert*-butyl hypochlorite
TCCA	trichloroisocyanuric acid
TDAE	tetrakis(dimethylamino)ethylene
TfCl	trifluoromethanesulfonyl chloride
THF.	tetrahydrofuran
TMSCl	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide

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Chapter 1. Radical Strategies Toward Benzylic C–H Bond Chlorination: An Overview

1.1. Introduction

Benzylic chlorides represent highly important synthons in medicinal chemistry and drug discovery efforts because they can streamline rapid diversification of core structures with a broad class of nucleophilic,[1] and more recently, electrophilic coupling partners.[2-5] The outcome of these efforts can increase the likelihood of identifying new drug candidates with improved biological activity. For example, 3-aminoethylquinoline derivative **2,** a potent melanin controlling hormone receptor 1 (hMCHR1) antagonist, showed a significant decrease in cardiovascular risks than the original lead compound, **1** (Figure 1.1).[6]

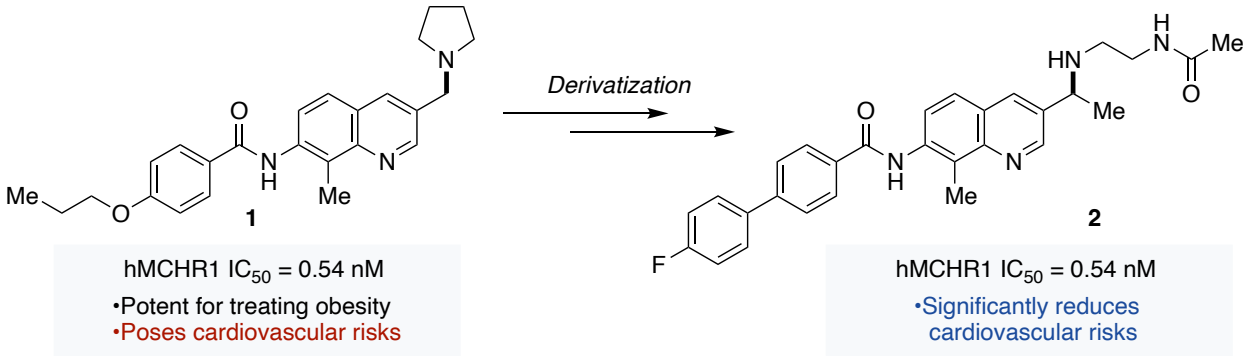

Figure 1.1. Structural modifications of **1** leading to compound **2** with improved biological properties.

Structural modifications of **1**, including a key benzyl chloride derivatization study with cyclic and aliphatic amines, identified the amino(ethyl)acetamide group at the benzylic position to contribute to a significant reduction in undesired human ether-a-go-go related gene K^+ channel inhibitory activity. (Figure 1.2). Moreover, the importance of benzyl chlorides as important synthetic

intermediates is further highlighted in process routes toward drug candidates used to treat asthma[7] psychiatric[8] and immunodeficiency disorders.[9]

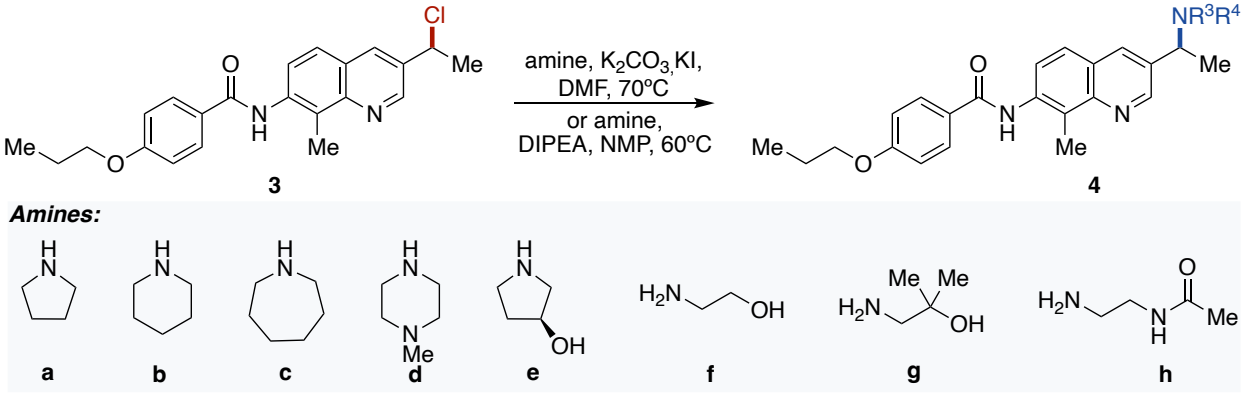

Figure 1.2. Benzylic chloride displacement in drug discovery.

Synthetic approaches toward benzyl chloride preparation traditionally rely on functional group interconversions such as reaction of benzyl alcohols with thionyl chloride ($SOCl_2$)[10]. Alternative strategies using triphenylphosphine in combination with tetrachloromethane have also been reported.[11] While these reactions are appealing, the availability of benzyl alcohols is limited, and by extension, limit the chemical space that can be accessed from the corresponding chlorides. C(sp^3)–H bonds adjacent to alkylated aromatic and heteroaromatics represent a much larger pool of readily available pharmaceutical building blocks and core structures and methods for direct benzylic C–H chlorination could highly benefit drug discovery efforts.[12] The majority of these reactions proceed via various radical mechanisms and can exhibit benzylic selectivity due to the low bond dissociation energy of benzylic C–H bonds (BDE = ~88-92 kcal/mol) [13] over other aliphatic positions.

1.2. Radical Methods for Benzylic C–H Chlorination

Radical-chain strategies are among the most prevalent for direct benzylic C–H bond chlorination and are featured in academic and industrial contexts.[14,15] This reaction includes three general steps: initiation, propagation, and termination. The *initiation* step typically involves the generation of a

radical species through homolytic cleavage of heteroatom-heteroatom bonds such as those found in peroxides, elemental chlorine (Cl_2), and azobisisobutyronitrile (AIBN) under irradiation or thermal conditions. Reduced metal-ions such as Cu^I salts have also been proposed to initiate reactivity. During the propagation steps, most of the benzylic starting material is converted into the corresponding chloride. Radical-radical combination or disproportionation account for the termination step (Figure 1.3 A).

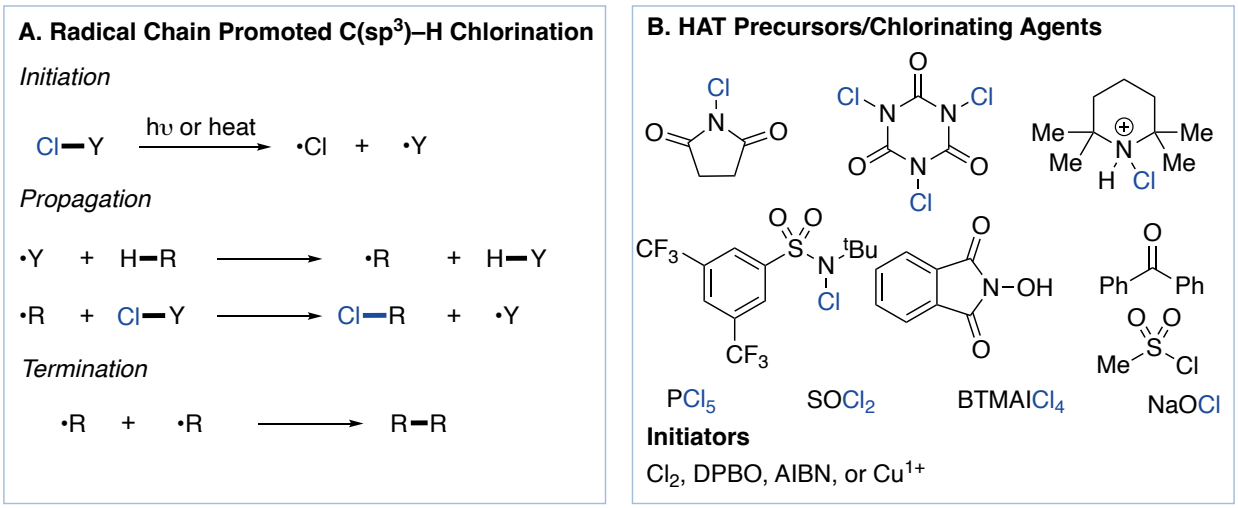

Figure 1.3. (A) Conventional radical-chain mechanism (B**)** Reagents employed in radical-chain promoted benzylic chlorination.

While effective for sp^3 chlorination of simple hydrocarbon feedstocks, traditional radical-chain chlorination protocols are seldom applied to complex targets because they operate under harsh reaction conditions. Moreover, the reagents employed in these reactions can promote chlorine radical (Cl•) formation, a highly reactive and unselective hydrogen atom transfer (HAT) reagent that can result in complex chlorinated product mixtures (Figure 1.4). However, recent efforts toward improving radical-chain chlorination have resulted in new radical precursors with improved reactivity profiles that demonstrate site-selectivity in the HAT and propagation step and expand the scope to more complex molecules (Figure 1.3B).

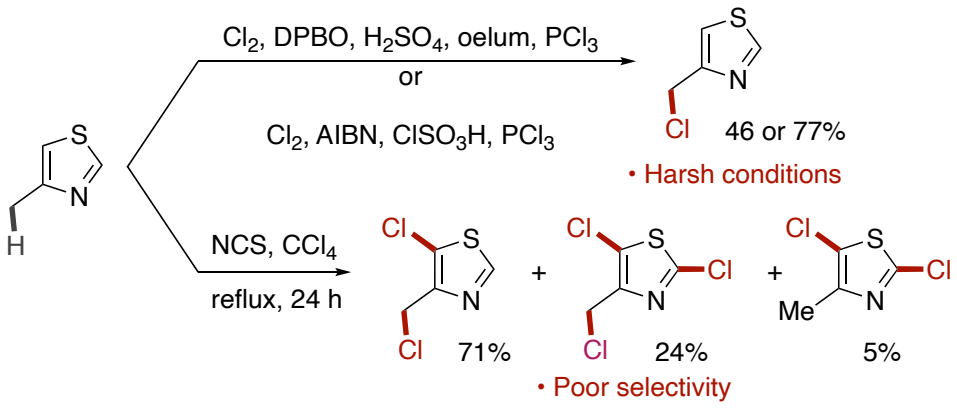

Figure 1.4. Traditional radical chlorination of methylthiazole.

Radical rebound processes can also be effective for benzylic chlorination (Figure 1.5A).[16] These reactions mimic biological C(sp^3)–H activation involving heme enzymes such as cytochrome p450s iron enzymes. These reactions are proposed to proceed through a high-valent metal oxo species that enacts C–H atom cleavage. The generated alkyl-radical undergoes a chloride rebound step to deliver the product. While this strategy is mostly applied to aliphatic chlorination, examples highlighting benzylic chlorination using manganese porphyrin or salen catalysts are reported (Figure 1.5B).

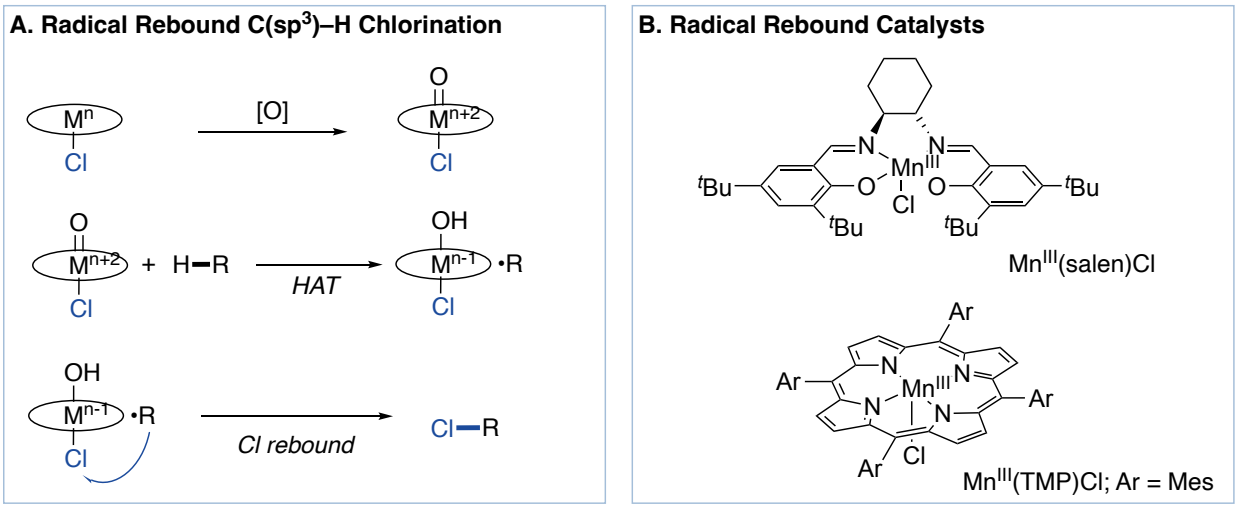

Figure 1.5. (A) Proposed radical-rebound mechanism for C(sp^3)–H chlorination (B) Catalysts employed in radical-rebound benzylic chlorination.

More recently, radical-relay strategies have emerged to affect selective benzylic chlorination (Figure 1.6A). [17] These reactions compliment radical- chain and rebound pathways but are mechanistically distinct and expand the scope of existing chlorination methods. These reactions involve an HAT step that promote formation of a diffusible benzyl-radical that is subsequently functionalized by an external chlorinating reagent. While the nature of the functionalization step is often not understood, three mechanistic hypothesis involving Cu have been proposed and include: 1. Radical-polar cross-over, wherein the radical is oxidized to its corresponding cation and trapped by a chloride nucleophile 2. Radical addition to chloride ligand or 3. Radical trapping at a metal center followed by carbon-chlorine reductive elimination.

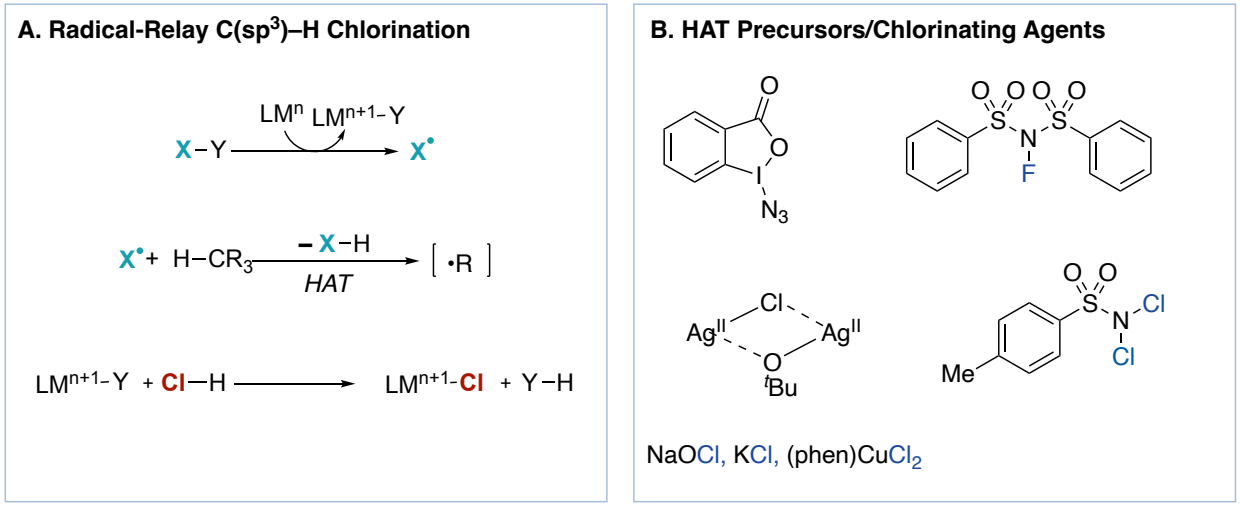

Figure 1.6. (A) Proposed radical-relay mechanism for C(sp^3)–H chlorination (B) HAT precursors and chlorinating reagents employed in radical-relay mediated benzylic chlorination.

The content herein presents a survey of benzylic radical C(sp^3)–H chlorination methods of alkylated arene and heteroarenes. These reactions involve various oxidants and chlorinating agent combinations. Earlier reports demonstrate benzylic chlorination with simple toluene and ethyl benzene derivatives. Recent studies, however, expand the scope to more complex molecular settings by using modified radical precursors that exhibit high levels of benzylic selectivity.

1.3. Radical Chain Approaches to Benzyl Chloride Synthesis

Over 80 years ago, Kharasch and Brown reported the radical chain reaction of sulphuryl chloride and benzoyl peroxide to achieve side-chain chlorination of methyl substituted arenes (Figure 1.7A).[18] This protocol represented an advance over existing radical-chain conditions that relied on irradiation of Cl_2.[19] Further studies by Walling demonstrated that similar results could be obtained by using sodium hypochlorite (NaOCl) as the oxidant and chlorinating agent (Figure 1.7B). [20,21] Strategies using trichloromethane sulfonyl chloride were also shown to be effective for chlorination and expanded scope to secondary benzylic positions (Figure 1.7C) .[22] These reactions commonly feature the chlorinating agent as the limiting reagent and employ the C–H substrate in excess. Indeed, it was commonplace to perform these reactions in neat benzylic substrate. This limitation was addressed by Fujisaki wherein benzyltrimethylammonium tetrachloroiodate was utilized as an alternative reagent to affect benzylic chlorination using 1 equiv of the C–H substrate (Figure 1.7B).[23] This protocol chlorinated toluene derivatives in good to excellent yields; however, secondary benzylic substrates were chlorinated less productively.

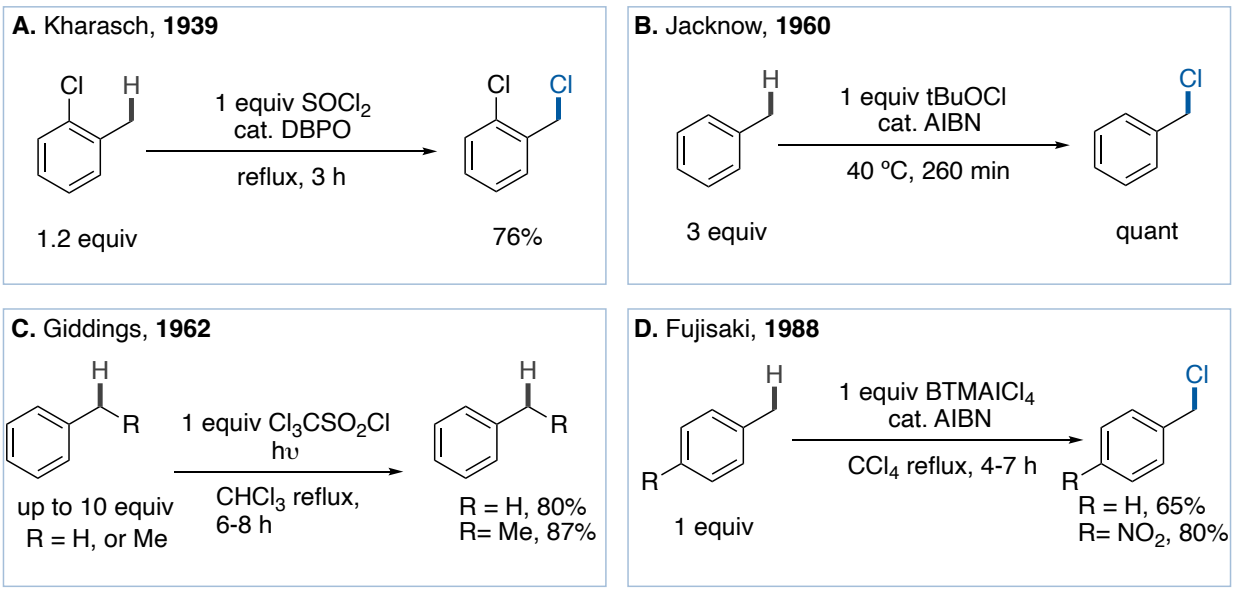

Figure 1.7. Benzylic chlorination using (A) $SOCl_2$ (B) ^tBuOCl (C) Cl_3CSO_2Cl and (D) $BTMAICl_4$

Alkyl substituted heterocycles can also undergo side chain chlorination using N-chlorosuccinimide (NCS) and catalytic amounts of dibenozylperoxide (DBPO).[24] For example, 2-methylpyrazine can undergo radical-chain chlorination to deliver 2-(chloromethyl)pyrazine in 89% yield under these condition (Figure 1.8A). Related heterocycles such as 2- and 3-methylpyrdine, however, are chlorinated less efficiently and polychlorinated side-products account for some of the remaining mass balance (Figure 1.8 B-C). Substituted pyridines with multiple methyl groups undergo poor reactivity and result in a complex mixture of products (Figure 1.8 D).

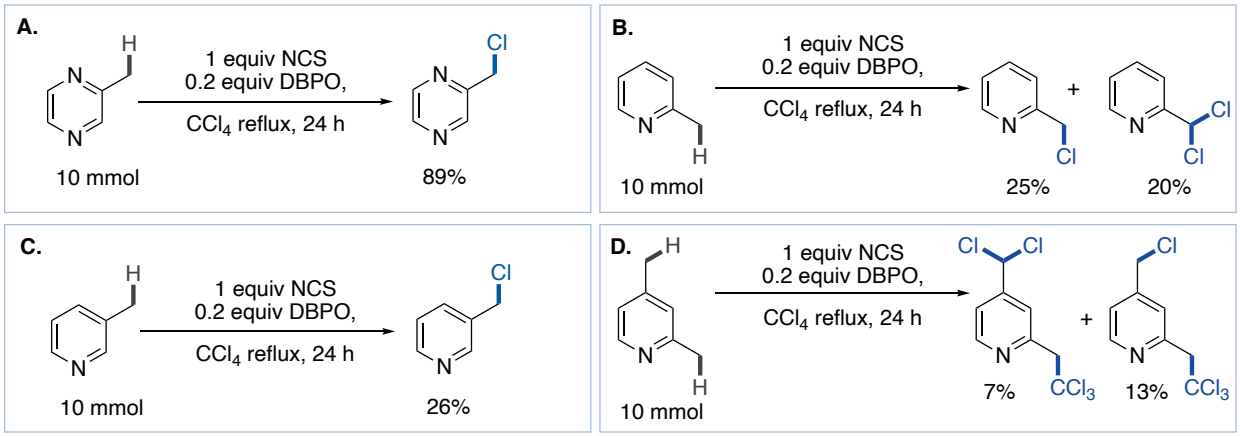

Figure 1.8. Benzylic chlorination of (A) 2-methylpyrazine (B) 2-methylpyridine (C) 3-methylpyridine and(D) 2,4-methylpyridine.

Efforts to improve radical-chain chlorination is demonstrated by Schreiner [25] using a combination of trichloroisocyanuric acid (TCCA), N-hydroxyphthalimide (NHPI) and $Cu(OAc)_2$ (Figure 1.9). Reaction of $Cu(OAc)_2$ and NHPI is proposed to generate a phthalimido-N-oxyl radical that enacts HAT on the benzyl substrate. Catalytic amount of CBr_4 is employed to reduce reaction times due to the formation of chain carrying $\bullet CBr_3$ radicals. The benzylic substrate may also be used as the limiting reagent and is compatible with electron neutral and slightly deficient toluene derivatives. Lower yields were observed when multiple benzylic positions were present, and when ethylbenzene or 2-methylnaphthalene were used as substrates.

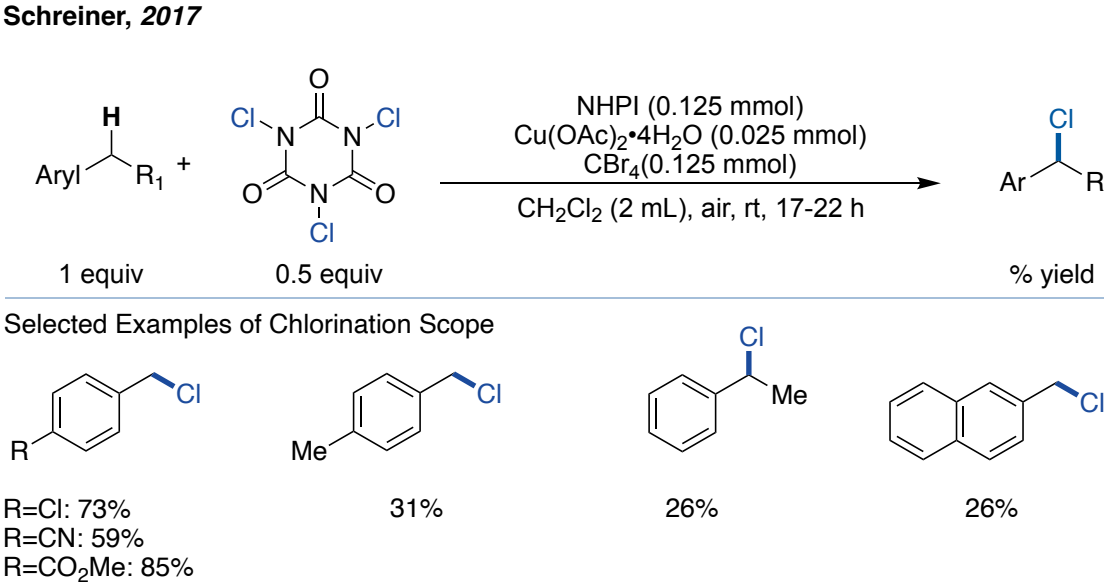

Figure 1.9. Benzylic C–H Chlorination using TCCA, NHPI and $Cu(OAc)_2$.

Concurrently, Kanai reported a silver-catalyzed C(sp^3)–H chlorination method using *tert*-butyl hypochlorite (*t*-BuOCl) as the chlorinating agent and oxidant. Authors proposed that *t*-BuO• or a $Ag^{II}OtBu$ species initiates the HAT step and C–Cl bond formation proceeds via silver-mediate pathway. A radical chain mechanism whereby the carbon-centered reacts with *t*-BuOCl, however, cannot be ruled out. This method is demonstrated on both benzylic and tertiary aliphatic C–H bonds (Figure 1.10). The benzylic scope comprises of various toluene and ethyl benzene derivatives. Para-substituted ethyl-benzenes (60-62%) and alky-substituted arenes featuring electron withdrawing groups at the end of the chain are chlorinated in synthetically useful yields (71-75%). Substrates bearing multiple C–H bonds such as benzylic and α to carbonyl position are exclusively chlorination at the benzylic position, reflecting electronic deactivation at these sites toward an electrophilic *t*-BuO• species.

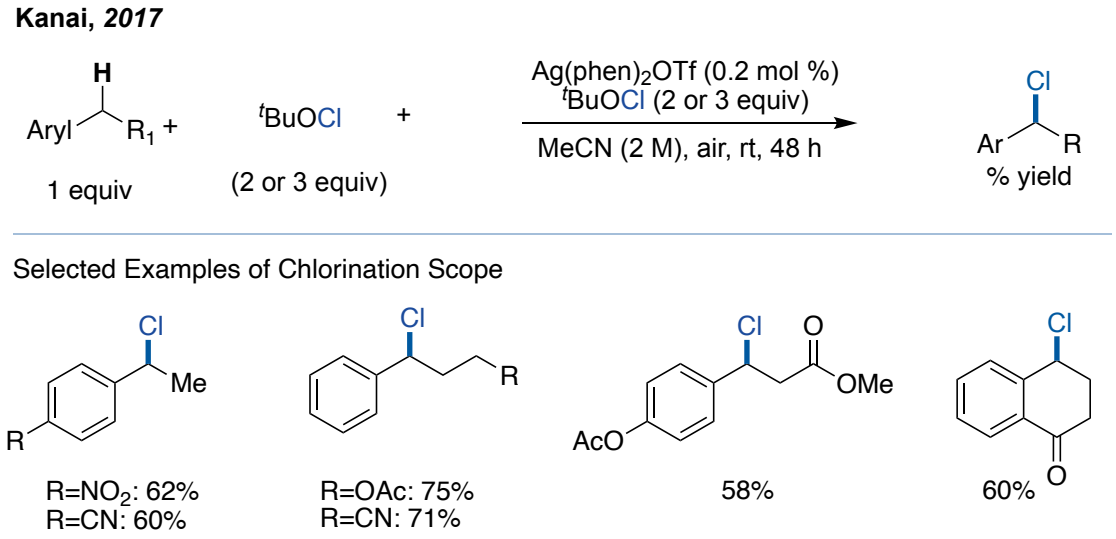

Figure 1.10. Silver-catalyzed benzylic chlorination.

Photochemical strategies have also recently been developed to improve upon radical chain benzylic chlorination. In 2017, Chen reported that photoexcited aryl ketones can be paired with NCS to promote C(sp^3)–H chlorination of both benzylic and unactivatd aliphatic C–H bonds.[26] In this reaction, a triplet-ketone can promote HAT on the substrate and subsequent chlorine atom donation by NCS functionalizes the benzyl radical (Figure 1.11). Primary benzyl substrates such as 4-methyl-1,1'-biphenyl are chlorinated in excellent yields. Ethyl benzene undergoes monochlorination at the benzylic position in 72% yield with 7% of primary aliphatic chlorination and 24% geminal di-chlorination at the benzylic position. A methyl propionate derivative undergoes chlorination exclusively at the benzylic position in 79%. An example of tertiary benzylic functionalization was also reported with a substrate featuring a benzyl azido group.

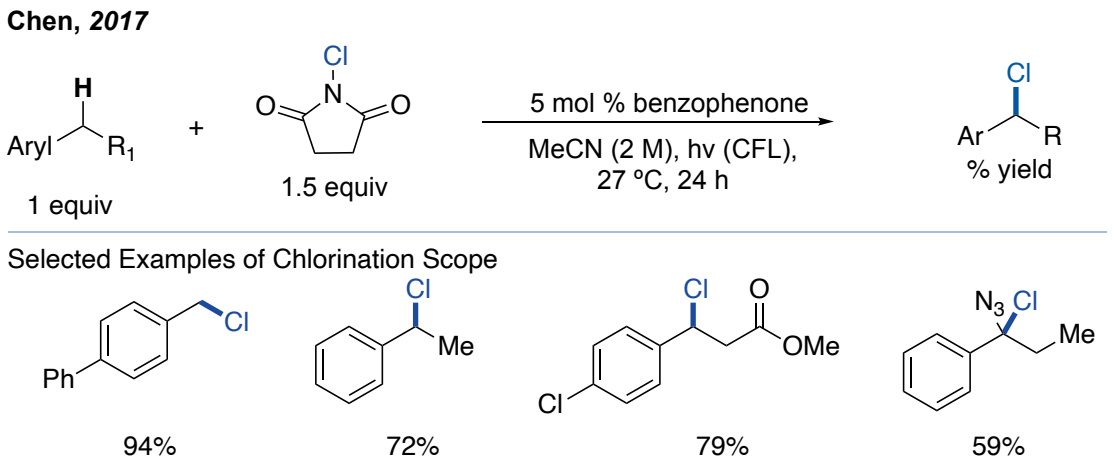

Figure 1.11. Ketone-catalyzed benzylic chlorination.

Similarly, in 2020, Wu demonstrated that benzylic chlorination could be achieved using a photoexcited acridinium catalyst to promote reductive activation of NCS.[27] Succinamidyl radicals are proposed to initiate the HAT step. However, Cl• cannot not be ruled out. The scope of this method is demonstrated on electronically diverse methyl and ethyl-benzene derivatives with neutral and slightly deficient groups contributing to the best yields (64-78%) (Figure 1.12). Para-nitro-toluene reacts less efficiently and delivers the product in 21% yield. Chlorination of the aromatic ring was observed for electron-rich substrates, such as 1,3,5, trimethoxybenzene derivatives.

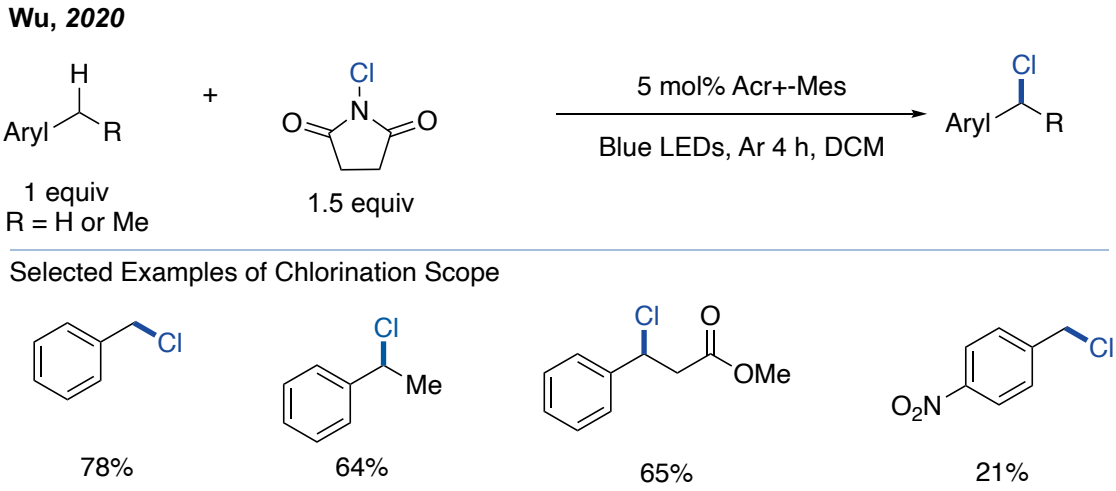

Figure 1.12. Benzylic chlorination promoted by reductive activation of NCS.

Recent efforts by Leonori demonstrated a breakthrough in radical chain chlorination by leveraging a (2,2,6,6,tetramethylpiperidinium)-chloroamine reagent for selective HAT.[28] This photochemical strategy exhibits remarkable selectivity for the most electron rich and accessible C–H bonds, owing to the electrophilicity and steric hindrance of the aminium radical. While the scope of this method is demonstrated on unactivatd C(sp^3)–H bonds, some benzylic examples are reported (Figure 1.13). In the case of 1-phenylpentane, benzylic chlorination was the only product observed. Unprotected carboxylic acids were also compatible with this method. This strategy was also utilized in an unrelated study to access diverse benzyl chlorides from their corresponding C–H substrates, highlighting its utility and practicality.[2] For example, methyl dehydroabietate, a diterpene natural product was chlorinated at the benzylic position in 76% yield. This method however is ineffective for benzylic chlorination of alkylated pyridines. In fact, aliphatic chlorination was primarily observed when these substrate classes were employed, reflecting deactivation of the benzylic position toward HAT by protonation of the pyridine under $HClO_4$ conditions.

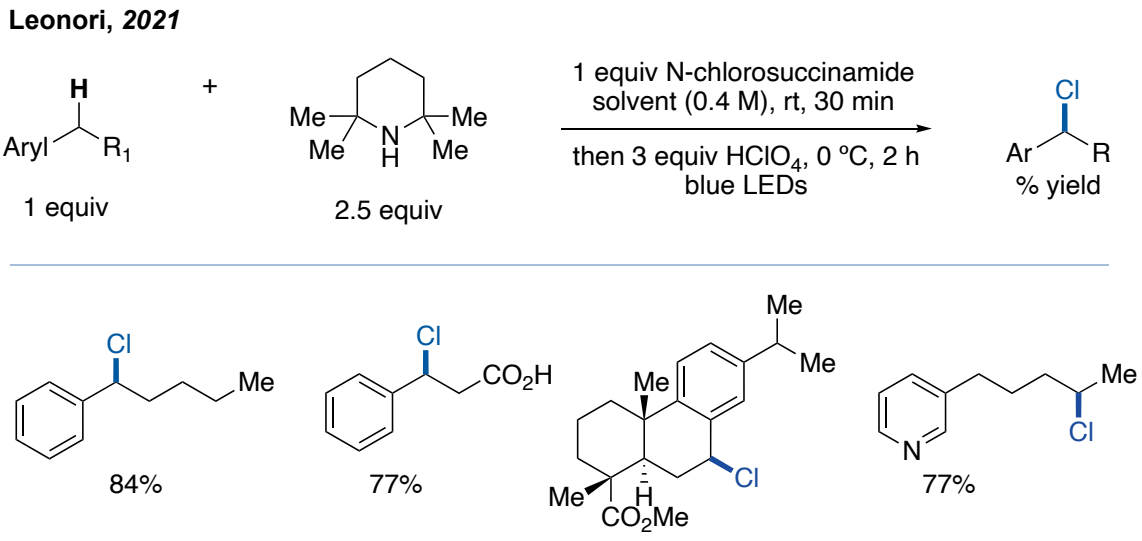

Figure 1.13. Benzylic chlorinating using 2,2,6,6-tetramethylpiperidinium N–Cl reagent.

Efforts toward identifying radical-chain strategies to affect benzylic chlorination of alkyl-substituted heteroarenes have resulted in the use *N*-(*tert*-butyl)-*N*-chloro-3,5-bis(trifluoromethyl)benzenesulfonamide as a radical precursor. [29] Stahl and co-workers have recently shown that this reagent can promote selective benzylic chlorination of 3-alkyl substituted pyridines and related heterocycles. This reaction proceeds via a photo-initiated N–Cl homolysis followed by HAT from the sulfonamidyl radical. DFT calculations support favorable HAT and Cl-atom transfer for the benzylic position when compared to NCS, TCCA, or other N–Cl reagents.[30] Moreover, selectivity studies comparing this strategy over other radical methods displayed higher 2º benzylic over 3º aliphatic selectivity when 3-isobutylpyridine was used. The scope of this method covers a broad range and Figure 1.14 demonstrates some examples. A 5.0 mmol example using 2-chloro-5-ethylpyrimidine delivered the corresponding benzyl chloride in 86% isolated yield.

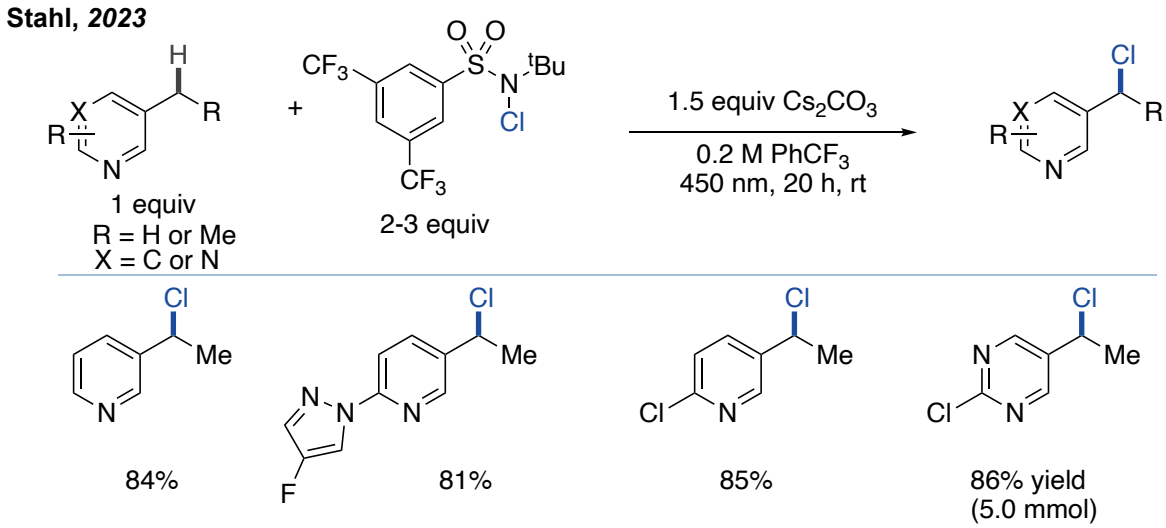

Figure 1.14. Heterobenzylic chlorination of 3-alkyl substituted aromatic heterocycles.

1.4. Radical Rebound Approaches to Benzyl Chloride Synthesis

The radical rebound mechanism may also be leveraged for benzylic chlorination. This mechanistic framework has been mostly demonstrated with functionalization of strong aliphatic C–H bonds (>93 kcal/mol) such as those found in cyclohexane and cyclopentane. Earlier reports from Groves demonstrated that a manganese porphyrin can promote chlorination of various classes of C–H bonds.[31,32] A single example of benzylic chlorination using toluene as the substrate was reported and delivered the benzyl chloride in 38% yield. Complimentary efforts by Maity demonstrated that a Mn(salen) catalyst may also be used for radical-rebound benzylic chlorination.[33] The reaction uses sodium hypochlorite (NaOCl) as both the chlorine source and the oxidant and is compatible with a variety of simple benzylic substrates (Figure 1.15). However, the yields of the product chlorinated low to modest yield (12-38%yield). Overall, these results demonstrate that radical-rebound strategies may not be efficient for benzylic chlorination, leaving significant room for development.

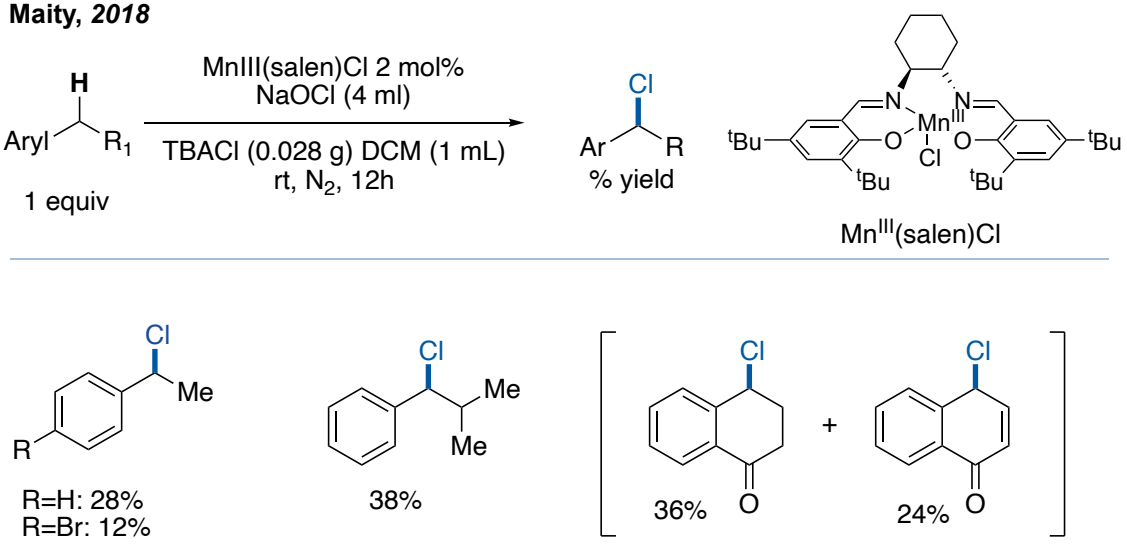

Figure 1.15. Mn-salen catalyzed benzylic chlorination.

1.5. Radical Relay Approaches to Benzyl Chloride Synthesis

Radical-relay strategies have recently emerged for selective benzylic C–H chlorination. Recently, Hartwig disclosed a C–H chlorination strategy that targets benzylic and tertiary aliphatic positions.[34] This reactions employs Zhdankins azidoiodinane (1-azido-1,2-benziodoxole-3-(1H)-one, ABDO) as the oxidant and HAT precursor with a phenanthroline ligated copper-chloride complex ((phen)$CuCl_2$) as the chloride source. The mechanism proposed to affect chlorination is proposed to initiate with N–I bond homolysis. C–H atom absraction by benzoyloxy radical generates an alkyl radical that is then intercepted by (phen)$CuCl_2$. The benzylic substrates demonstrated in this study undergo effective chlorination in good to high yields (Figure 1.16). For example, alkyl-substituted arenes with electron withdrawing groups appended to end of the alkyl-chain proceeded to give the desired benzylic chloride product in good to excellent yields (55-95%). Natural products like Celestolide can furnish the chloride in 91% yield, although authors note that this product undergoes hydrolysis under silica gel chromatography. A tertiary benzylic substrate can deliver the desired chloride in 75% yield, suggesting that the o-iodobenzoyloxyl radical undergoes indiscriminate HAT for both benzylic and tertiary C–H bonds.

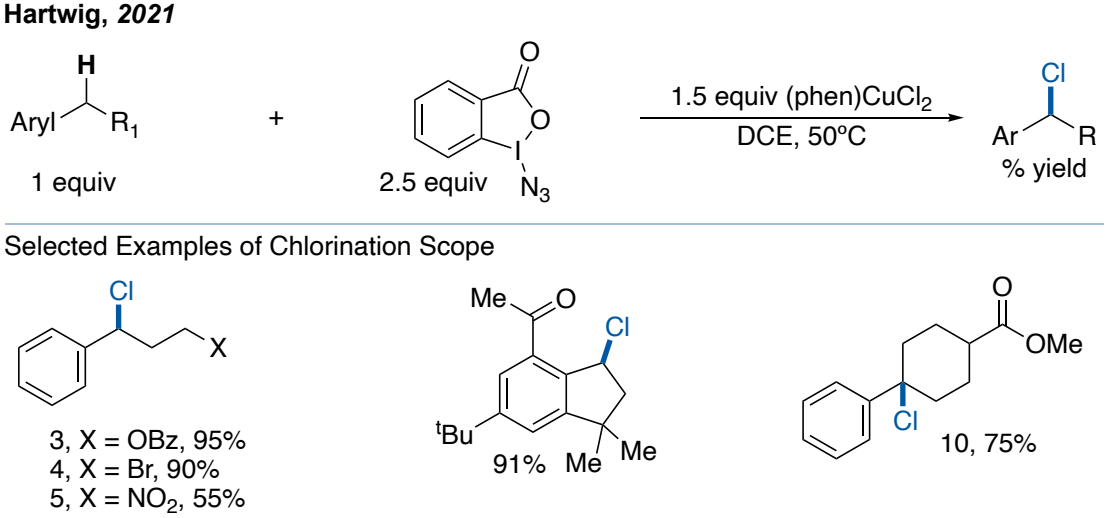

Figure 1.16. Benzylic chlorinating using Zhdankins reagent and (phen)$CuCl_2$.

In 2022, Stahl demonstrated that a redox-buffered radical relay mechanism mediated by the reaction of copper(I)chloride (CuCl) and N-fluorobenzesulfonimide (NFSI) can be used to broaden the scope of benzylic C–H chlorination.[35] This study demonstrated that a bis(sulfonyl)imidyl radical can be harnessed for selective HAT of benzylic C–H bonds over other reactive sites. The use of diisopropyl phosphite proved critical to the success of this reaction to maintain a balanced redox state of the copper catalyst. Selectivity studies using isobutyl- and isopentyl-benzene showed high chlorination selectivity over other established radical chlorination methods with with benzyic:tertiary ratios of 10:1 20:1, respectivley. Building block structures such as a bromo-substituted chroman derivative and a dronedarone core structure are chlorinated in good to excellent yields (Figure 1.17).

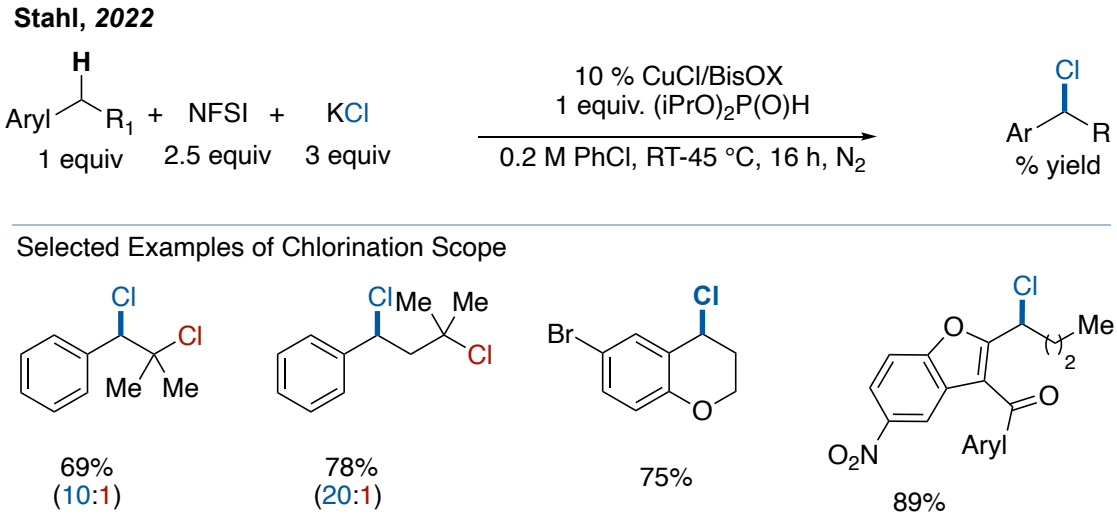

Figure 1.17. Cu/NFSI mediated benzylic chlorination.

Complimentary efforts by Chan et al demonstrated a Cu-catalzed dichloroamine-T as the oxidant to selectively functionalize C(sp^3–H) bonds in ketones, enones, and alkylbenznes.[36] This strategy displays high functional group compatibility and is remarkably selective for the most

electron-rich and sterically accessible C–H bond (Figure 1.18). [TsNCl]• is proposed to enact HAT in this reaction. Toluene derivatives featuring electron withdrawing groups on the arene displayed good reactivity. Secondary benzylic positions on various substrates were also chlorinated in good. When isopentyl benzene was used as a selectivity probe, secondary benzylic chlorination was exclusively observed. Other substrates like 3-phenylpropylbenzoate and Celestolide underwent chlorination in good yields.

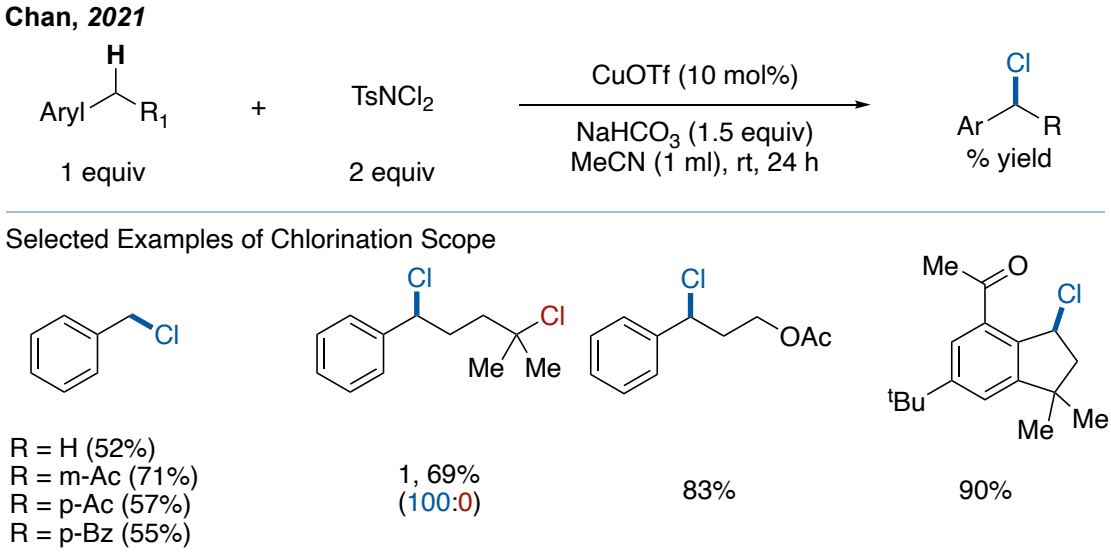

Figure 1.18. Cu-catalyzed benzylic chlorination by dichloroamine-T.

Collectivity, the studies highlighted above represent versatile approaches toward the synthesis of benzyl chlorides. Early methods required harsh reaction conditions and due to the reactivity of •Cl, demonstrated poor selectivity even with simple substrates. Recent methods, however, have expanded the practicality and utility of this reaction class by harnessing new HAT precursors with improved reactivity profiles for selective functionalization. These results have allowed the use of the benzylic substrate as reaction limiting and expand the scope to more complex molecular settings.

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Chapter 2.

Cu-Catalyzed Site-Selective Benzylic Chlorination Enabling Net C−H Coupling with Oxidatively Sensitive Nucleophiles

2.1. Abstract

Site-selective chlorination of benzylic C–H bonds is achieved using a $Cu^{I}Cl$/bis(oxazoline) catalyst with *N*-fluorobenzenesulfonimide as the oxidant and KCl as a chloride source. This method exhibits higher benzylic selectivity relative to established chlorination protocols and is compatible with diverse alkyl arenes. Sequential benzylic C–H chlorination/nucleophilic substitution affords C–O, C–S, and C–N coupling products with oxidatively sensitive coupling partners.

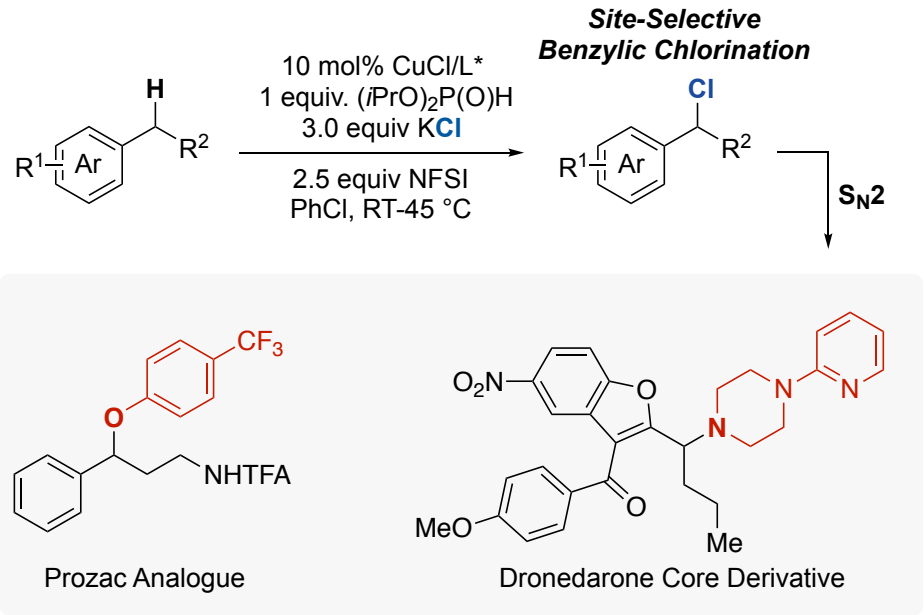


Figure 2.1. Cu-Catalyzed Benzylic C–H Chlorination Summarization of Reactivity

2.2. Introduction

Benzylic chlorides are versatile synthetic intermediates that react readily with heteroatom- and carbon-based nucleophiles in conventional substitution[1] and catalytic cross-coupling reactions.[2–6] These compounds may be accessed via radical-chain chlorination,[7,8] leveraging the comparatively low bond dissociation energy and higher reactivity of benzylic C–H bonds (Figure 1A). Radical-chain chlorination methods that involve chlorine radical (Cl•) as the hydrogen-atom transfer (HAT) reagent, however, often exhibit poor C–H site selectivity. Consequently, benzylic chlorides are commonly prepared by the reaction of benzylic alcohols with $SOCl_2$ or via other functional-group

interconversion methods.[2,3,6,9,10] C–H chlorination methods that employ species other than Cl• for the HAT step can show improved selectivity.[11–22] In this context, Cu catalysts in combination with *N*-fluorobenzenesulfonimide as the oxidant (Cu/NFSI) promote diverse C–H functionalization and oxidative cross-coupling reactions (e.g., Figure 1B)[23–35] that exhibit high benzylic site selectivity. These methods involve a radical-relay mechanism, in which HAT generates a diffusible benzylic radical that undergoes subsequent functionalization by Cu^{II} and a nucleophilic coupling partner. Here, we report the development of a Cu/NFSI method for benzylic chlorination that uses KCl as the source of chloride (Figure 1C). A comparison with other chlorination reactions highlights the unique benzylic selectivity of Cu/NFSI reactivity. The method uses the C–H substrate as the limiting reagent, and it may be paired with a subsequent nucleophilic substitution step to achieve net C–H coupling with nucleophiles that are not compatible with direct oxidative C–H functionalization.

Several mechanistic considerations contributed to initial efforts in this study. A possible C–H chlorination mechanism, shown in Figure 2, reflects insights from other Cu/NFSI C–H functionalization reactions.[30,32] Copper(I) reacts with NFSI to generate a bis(sulfonyl)imidyl radical (•NSI) that can promote HAT. The resulting benzylic radical could undergo Cu^{II}-mediated functionalization via one of several possible mechanisms (inner-sphere[24,26,29] or outer-sphere[30,31] coupling with a coordinated ligand, or radical-polar crossover involving a benzylic cation intermediate[30,31,34,35]). Cu/NFSI C–H functionalization reactions often require a sacrificial reductant or "redox buffer," such as a dialkylphosphite[30,34,35]) to support catalytic turnover. The reductant provides a means to regenerate Cu^{I} if all of the Cu^{I} catalyst is oxidized to Cu^{II} via undesired reaction of •NSI (see red/blue pathways in Figure 2).

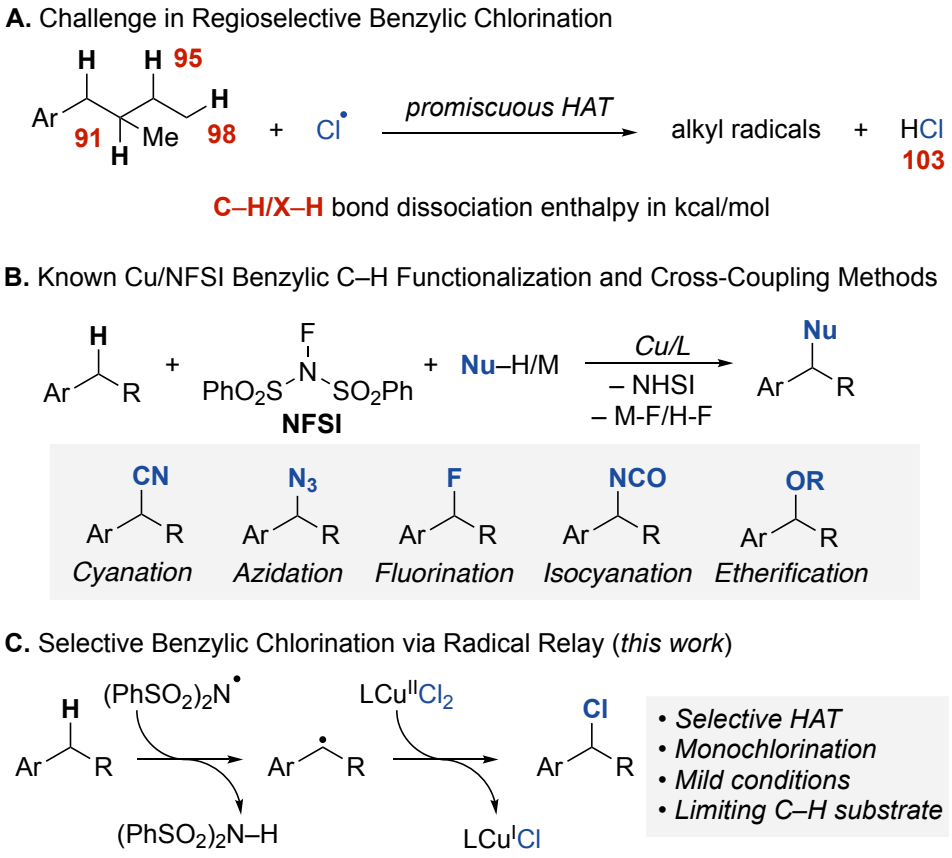


Figure 2.2. Chlorine radical as an unselective HAT agent (A), representative Cu/NFSI benzylic functionalization methods (B), and reaction sequence illustrating Cu/NFSI benzylic chlorination (C).

2.3. Results and Discussion

Initial screening studies were initiated with isobutyl benzene (**1a**) as the substrate and reaction conditions incorporating a Cu salt, ancillary ligand, NFSI, and a chloride source (Table 1). Trimethylsilyl (TMS)-substituted nucleophiles have been used in previous Cu/NFSI reactions, including those with TMSCN,[24] $TMSN_3$,[31] TMSNCO.[34] These reagents are expected to transfer anionic ligands to Cu^{II}, promoted by Si–F bond formation; however, TMSCl proved rather ineffective. No reactivity was observed in the absence of a phosphite additive (Table 1, entry 1), and only 22% yield of the benzylic chloride was observed in the presence of phosphite (entry 2).

Chlorination of the phosphite additive was observed under these conditions (see Figure 2A.3 in Appendix A). Use of alkali metal chlorides improved the reaction outcome (entries 3-

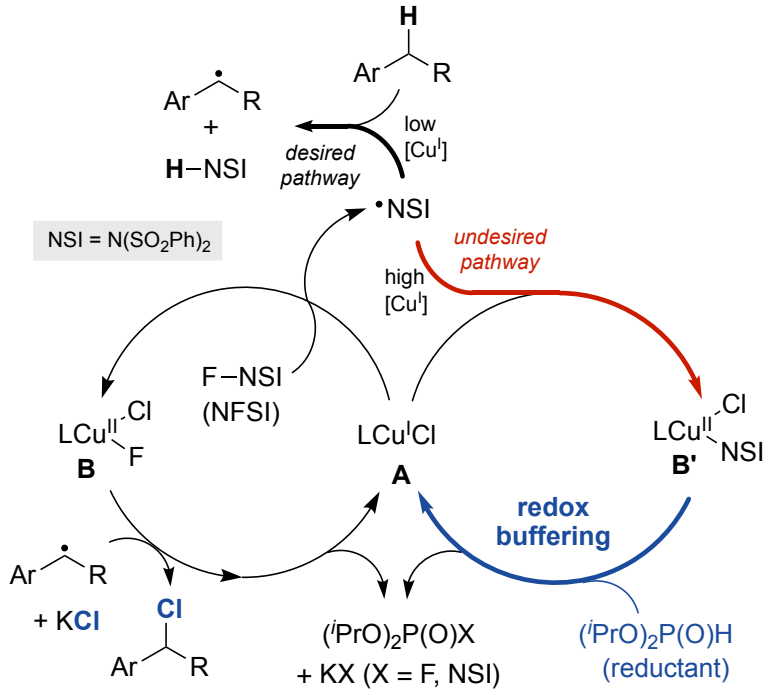


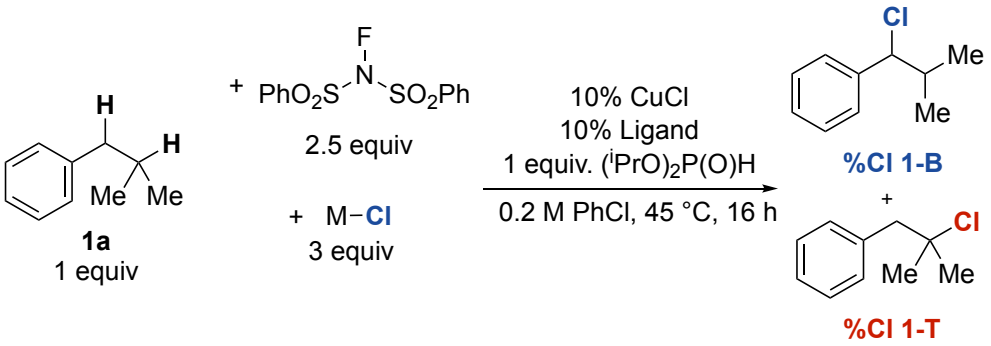
Figure 2.3. Proposed mechanistic cycle for benzylic chlorination leveraging redox-buffering.

7), with use of KCl contributing to the best yield (entry 7). Soluble chloride sources, such as Nbu_4Cl, inhibit the reaction (see Table 2A.8 in Appendix A). The identity of the ancillary ligand influenced the reaction outcome (entries 7-10; see Table 2A.3 in Appendix A for other ligands). The best yields were obtained with bathophenantroline **L1** and the bis(oxazoline) (BisOx) ligand **L4** (entries 7 and 10); however, the latter generally led to higher yields for different substrates (see Figure 2A.2 in Appendix A).[36] Thus, **L4** was selected for subsequent studies, even though no enantioselectivity was observed from the reactions. The latter observation is rationalized by a radical-polar crossover mechanism in which the intermediate benzylic radical is oxidized by Cu^{II} to a benzylic cation, which then reacts with the chloride nucleophile. The latter mechanism is consistent with the seminal early studies of Kochi,[37] which showed that Cu^{II} salts promote

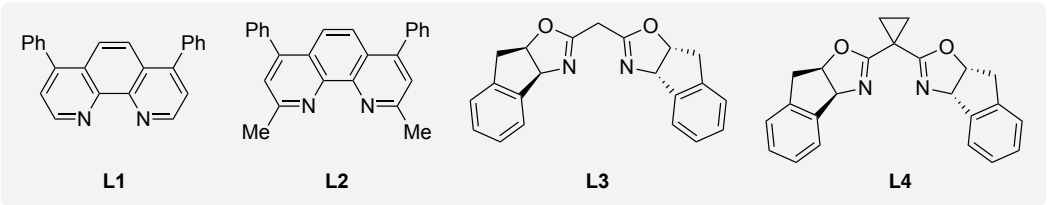
oxidation of organic radicals to the corresponding cations. This mechanism resembles other recently reported Cu/NFSI C–H functionalization reactions.[30,31,34,35]

Bond dissociation energies for the benzylic and tertiary C–H sites (~89 and ~93 kcal/mol, respectively[38]) suggest that reactivity should be strongly favored at the benzylic position. The data

Table 2.1. Cu/NFSI Benzylic Chlorination Reaction Optimization.



entry	ligand (mol%)	M–Cl	Conv. (%)	yield **1-B**:**1-T** (%)[b]
1	L1	TMSCl	0	0:0[c]
2	L1	TMSCl	22	17:1
3	L1	LiCl	29	14:2
4	L1	NaCl	39	28:2
5	L1	RbCl	53	39:4
6	L1	CsCl	72	57:5
7	L1	KCl	75	59:7
8	L2	KCl	68	56:4
9	L3	KCl	65	58:6
10	L4	KCl	80	66:5



in Figure 3, however, reveal a wide range of outcomes from the different chlorination methods. Cu/NFSI conditions support benzylic chlorination in good yield and selectivity, with benzylic:tertiary (B:T) ratios of 10:1 and 20:1 for **1a** and **2a**. Ag(phen)/^{t}BuOCl affords the highest yields and selectivities among the other seven conditions, with benzylic chlorination yields of 37% and 53% for **1a** and **2a**, respectively, and B:T ratios of ~2:1, relative to Cu/NFSI. Conventional radical-chain chlorination conditions (methods c, f, and g) afford lower yields and B:T selectivities, and even slightly favoring tertiary over benzylic chlorination in some cases (see methods f with **1a** and method g with **1a** and **2a**). All reaction conditions generate side products corresponding to dichlorination and/or oxygenation of the substrate (in gray).

The results In Figure 3 highlight the unique benzylic selectivity of •NSI-mediated HAT and provide a starting point for testing of Cu/NSFI C–H chlorination with a series of other substrates (Figure 4). *Para*-substituted alkyl benzenes and 2-ethyl naphthalene, **3**-**5**, **9**, **10**, undergo chlorination in good-to-excellent yields (69-97%), with the exception of the 4-ethyl anisole **5** (24%), which generates the benzylic bis(sulfonyl)imide as a significant byproduct (~50%). Propyl arenes with various substituents at the terminal position lead to benzylic chlorination products in good yield (75-84%, **6**-**8**), providing versatile bifunctional electrophilic building blocks. 3-Phenylpropanoic acid methyl ester and alkyl trifluoroacetamides are chlorinated solely at the benzylic position in good yields (**11**-**14**, 70-74%).[39] The lack of functionalization next to the carbonyl or trifluoroacetamide groups is consistent with electronic deactivation of these sites toward reaction with the electrophilic •NSI species. A bromo-substituted fluorene derivative reacts effectively (**15**, 79%). Common pharmacophores 6-bromochroman **16** and alpha-tetralone **17** afford chlorination products in good yield (75% and 60%, respectively), while pyridine-containing substrates exhibit lower yields (**20**, 34%; **21**, 38%). Benzylic chlorination of more complexes

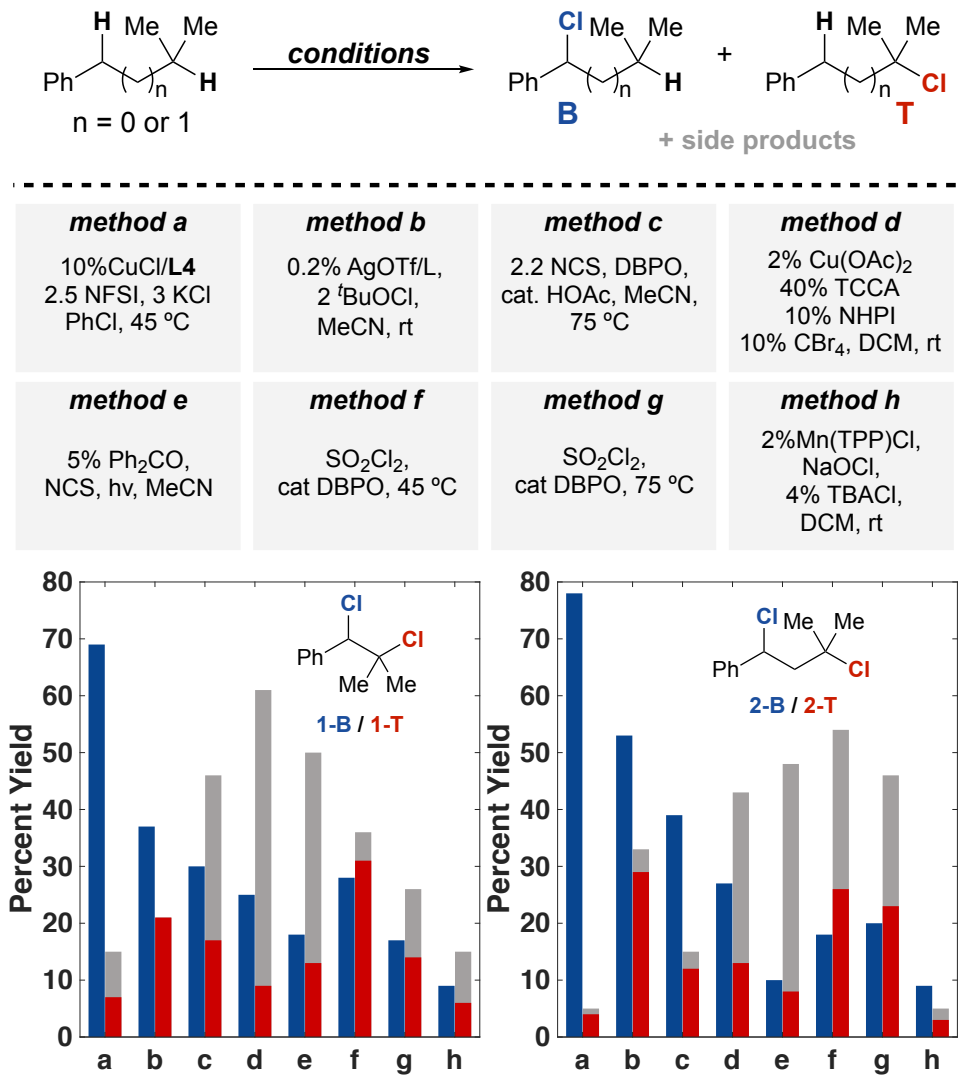


Figure 2.5. Applications of varied C–H chlorination methods on isobutylbenzene and isopentylbenzene. Yields determined by ^{1}H NMR spectroscopy (external std. = mesitylene).

Structures also proved effective (cf. **18**, **19**, **22-26**), including successful reaction of Celestolide (**18**, >99%), Ibuprofen methyl ester (**19**, 52%), the tetrahydroquinoline precursor to a GnRH antagonist (**22**, 40%), the xanthine oxidase inhibitor, benzbromarone (**23**, 68%), and a dronedarone derivative (**24**, 89%). The data in Figure 4 reflect isolated yields, with product volatility accounting for ^{1}H NMR yields in a few cases (**1**, **3-5**). In addition, separation challenges resulted in several products being isolated as a mixture with unreacted C–H substrate (**2**, **6**, **7**, **12**, **13**, **20**, **21**). This

issue is not considered problematic because the substrate will be inert in the subsequent reactions of the benzylic chloride and is readily separated at that stage (see below).

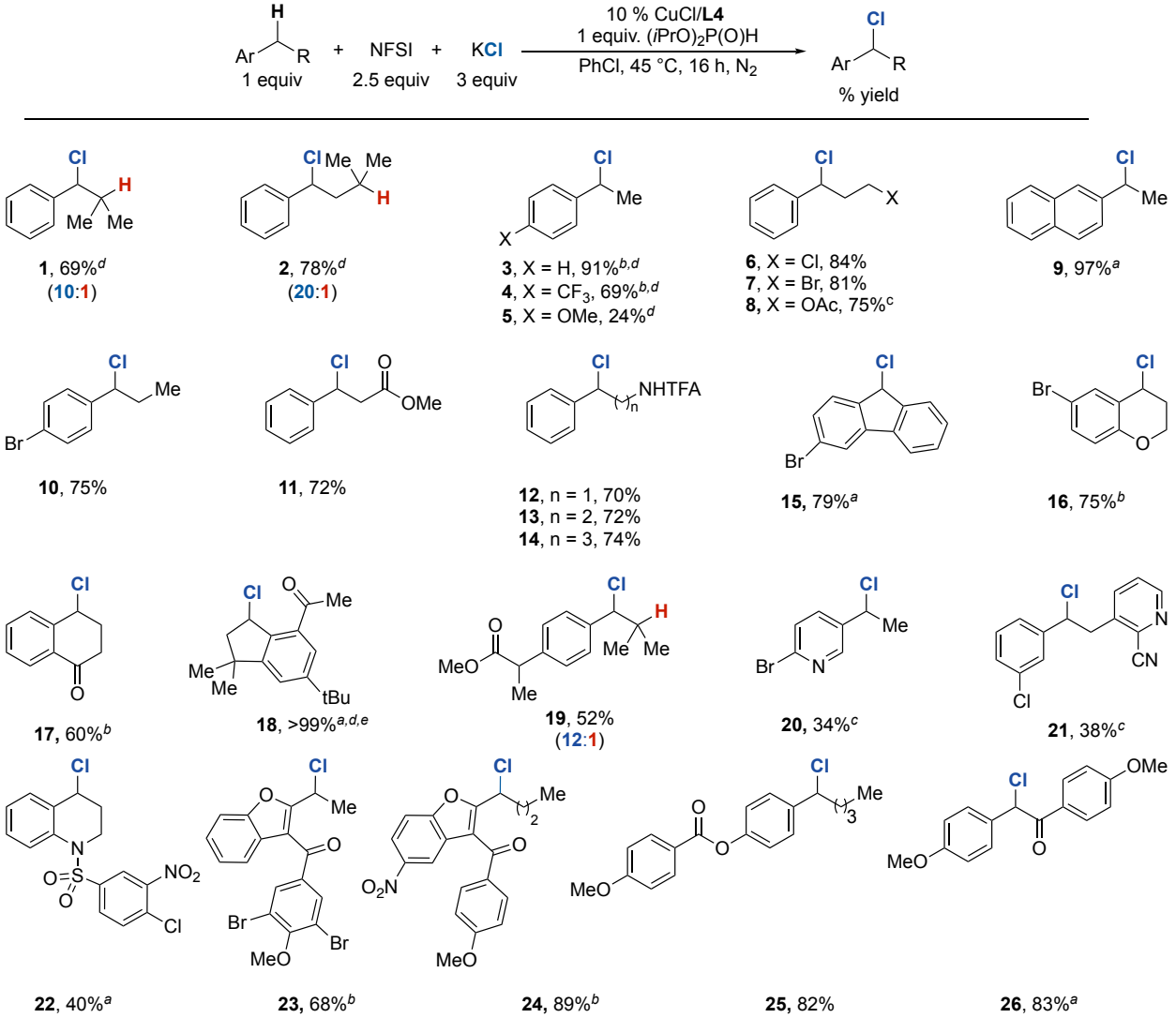


Figure 2.6. Scope of alkylarene benzylic chlorination. Reactions were run on a 0.2, 0.5, or 1.2 mmol scale. [a]Reaction run at RT. [b]Reaction run at 35 °C. [c]Reaction run at 70 °C. [c]10 mol% TMSCl added. [d]Yields determined by ^{1}H NMR spectroscopy (ext. std. = mesitylene). [e]Isolated as the alcohol.

The data in Figure 4 complement previously reported Cu/NFSI methods for C–H functionalization (cf. Figure 1B), but they also introduce new synthetic opportunities. Cu/NFSI oxidative coupling methods are not compatible with oxidatively sensitive nucleophiles, such as phenols, thiophenols, and alkylamines, due to undesirable side reactivity between these

nucleophiles and NFSI. The reactivity here provides a means to bypass this limitation via sequential C–H chlorination/diversification in which the benzylic chlorides are used in subsequent coupling reactions. This concept is illustrated in Figure 5, using benzylic chlorides derived from the trifluoroacetyl-protected aminopropylbenzene (**12**) and the dronedarone derivative (**26**). Coupling of **12** with a series of phenols and thiophenols affords analogues of the antidepressant drug, fluoxetine (i.e., Prozac) (**27-30**). The observed C–O coupling products **27** and **28** are noteworthy because a recently reported[33] C–H fluorination/substitution sequence leads to C–C coupling (i.e., Friedel-Crafts alkylation) in reactions with phenol nucleophiles. The different outcome reflects the different reaction conditions employed to support phenol displacement of the halide leaving group: basic conditions (chloride) versus acidic (fluoride). A complementary set of nucleophilic substitution reactions were carried out with **26**, using thiophenol and cyclic secondary amines coupling partners.

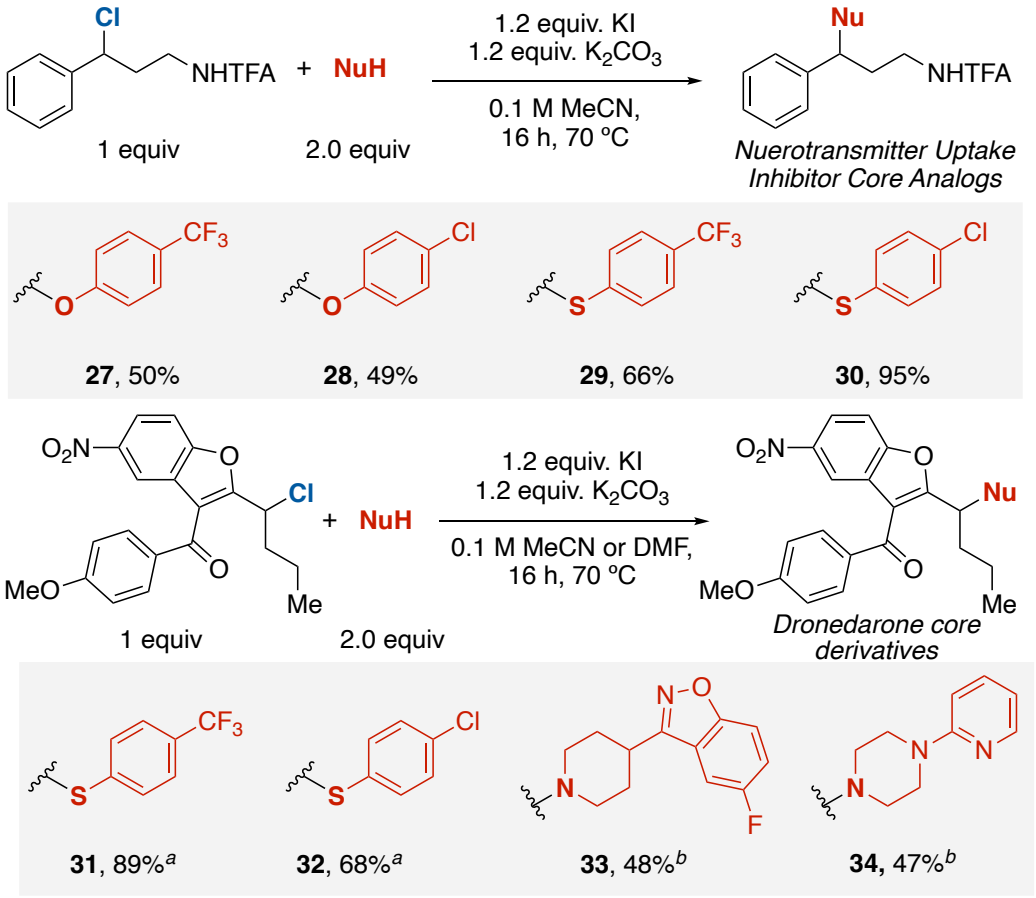


Figure 2.7. Benzylic chloride displacement. Reactions were run on a 0.2 mmol scale. [a]Reaction run with DMF. [b]Reaction run with MeCN.

2.4. Conclusion

Overall, the reactions presented herein establish a new Cu/NFSI-based method for benzylic C–H chlorination, with KCl as the source of chloride. The •NSI HAT species contributes to very high benzylic site selectivity, relative to a broad cross section of other C–H chlorination methods. The ability to pair C–H chlorination in sequence with nucleophilic substitution or cross-coupling steps provide a strategy to achieve rapid diversification of core structures bearing benzylic C–H bonds.

2.5. Acknowledgements

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supported by the NIH (1S10 OD020022-1), the NSF (CHE-1048642), and by a generous gift from Paul J. and Margaret M. Bender.

2.6. Author Contributions

Lopez, M.A. performed the experimental work including optimization studies, substrate synthesis, product isolation, characterization, and contributed to preparation of the manuscript.

Buss, J.A. performed the experimental work including preliminary results and selectivity studies.

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39. The effect of *N*-protecting groups, evaluated with a series of tetrahydroquinoline derivatives (cf. **22**), show that groups with increased electron-withdrawing character (e.g., electron-deficient sulfonamides) are more effective than carbamates, such as Boc and Cbz groups (see Figure 2A.4 in Appendix A).

Chapter 3.

Polar Heterobenzylic Chlorination C(sp^3)–H Chlorination Pathway Enabling Efficient Diversification of Aromatic Nitrogen Heterocycles

3.1. Abstract

Site-selective radical reactions of benzylic C–H bonds are now highly effective methods for C(sp^3–H) functionalization and cross-coupling. The existing methods, however, are often ineffective with heterobenzylic C–H bonds in alkyl-substituted pyridines and related aromatic heterocycles that are prominently featured in pharmaceuticals and agrochemicals. Here, we report new synthetic methods that leverage polar, rather than radical, reaction pathways to enable selective heterobenzylic C–H chlorination of 2- and 4-alkyl-substituted pyridines and other heterocycles. Catalytic activation of the substrate with trifluoromethanesulfonyl chloride promotes formation of enamine tautomers that react readily with electrophilic chlorination reagents. The resulting heterobenzyl chlorides may be used without isolation or purification in nucleophilic coupling reactions. This chlorination-diversification sequence provides an efficient strategy to achieve heterobenzylic C–H cross-coupling with aliphatic amines and a diverse collection of azoles, among other coupling partners.

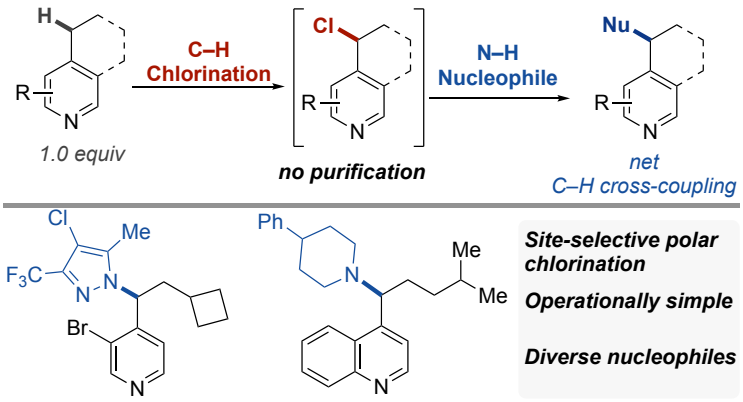

Figure 3.1. Polar Chlorination of Heterobenzylic C–H Bonds Summarization of Reactivity

3.2. Introduction

C(sp^3)–H functionalization reactions provide streamlined access to diverse biologically active molecules, offering strategic value to pharmaceutical and agrochemical discovery efforts.[1-3] Benzylic C–H bonds represent strategic sites for these methods, owing to their innate reactivity and the prevalence of alkyl-substituted aromatic subunits in building blocks and bioactive molecules.[4,6] Recent advances have led to radical-relay benzylic C–H cross-coupling reactions[4-6] that are effective with broad classes of coupling partners, including alcohols,[7] boronic esters, [8]amides,[9] alkynes,[10] and azoles.[11] While these oxidative coupling reactions continue to expand, the catalyst systems and radical mechanisms exhibit limitations that restrict their scope and utility, particularly with heterocyclic substrates (Figure 1A). Aromatic heterocycles, such as pyridines, are prevalent in pharmaceuticals and agrochemicals (Figure 1B), but these structures show limited compatibility with the existing benzylic C–H coupling methods. The oxidants used in these reactions include organic peroxides, *N*-fluorobenzensulfonimide (NFSI), and other reagents that often undergo side reactions with basic heterocycles and/or do not tolerate many appealing coupling partners, such as amines or thiols. In addition, heterobenzylic C–H bonds in these structures are more electron-deficient than benzylic C–H bonds and react poorly in hydrogen-atom transfer reactions involving electrophilic radicals.[12] We postulated that new protocols for heterobenzylic chlorination could overcome these limitations by enabling tandem C–H functionalization/diversification methods (Figure 1C). Such methods would avoid the presence of oxidant in the functionalization step, thereby tolerating electron-rich and/or basic coupling partners that would not be compatible with direct oxidative C–H coupling methods.[13]

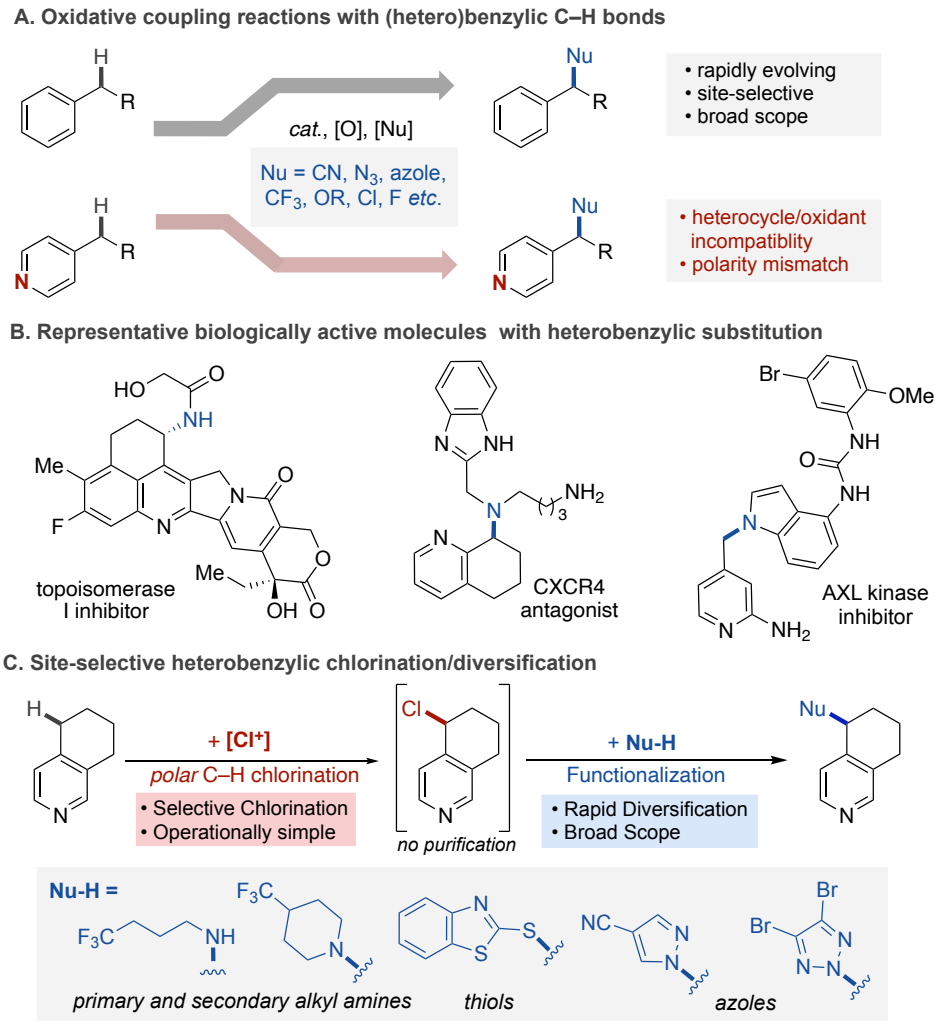

Figure 3.2. Effective C–H functionalization methods at heterobenzylic sites face key challenges relative to benzylic C–H positions (A). Substituted heterobenzylic structures are common in bioactive molecules (B), and selective heterobenzylic chlorination/diversification (C) provide a key strategy to access such target structures.

Successful implementation of this chlorination/diversification strategy, however, requires the development of improved heterocycle-compatible chlorination methods. For example, we recently showed that a Cu/NFSI catalyst system could be paired with KCl as the source of chloride to achieve benzylic C–H chlorination; however, the method showed limited compatibility with pyridines and related heterocycles.[13c] The heteroarene undergoes nucleophilic attack at one of the sulfonyl groups of NFSI to generate an *N*-sulfonyl pyridinium species, electronically deactivating

the heterobenzylic C–H bonds toward HAT.[14] Although this reactivity is deleterious in the Cu/NFSI reactions, Britton has exploited this reactivity to achieve heterobenzylic fluorination (Figure 2A),[15] One example of C–H chlorination using *N*-chlorobenzensulfonimide (NCSI) was also demonstrated.[15b] These observation prompted us to consider a general strategy for chlorination of alkyl-substituted heteroarenes through in situ formation of alkylidene dihydropyridine intermediates (Figure 2C, gray box). Resonant activation of heterobenzylic C–H bonds has been promoted in other transformations[16] by using Lewis acids;[17] electrophiles, such as alkyl chloroformates[18] and sulfonyl chlorides;[19] additional electron-withdrawing substituents; [20] and transition-metal catalysis.[21,22] Here, we develop a complement of methods to achieve site-selective polar chlorination of 2- and 4-alkylpyridines and related heterocycles, setting the stage for tandem C–H chlorination/cross-coupling with amines, azoles, and other important nucleophiles.

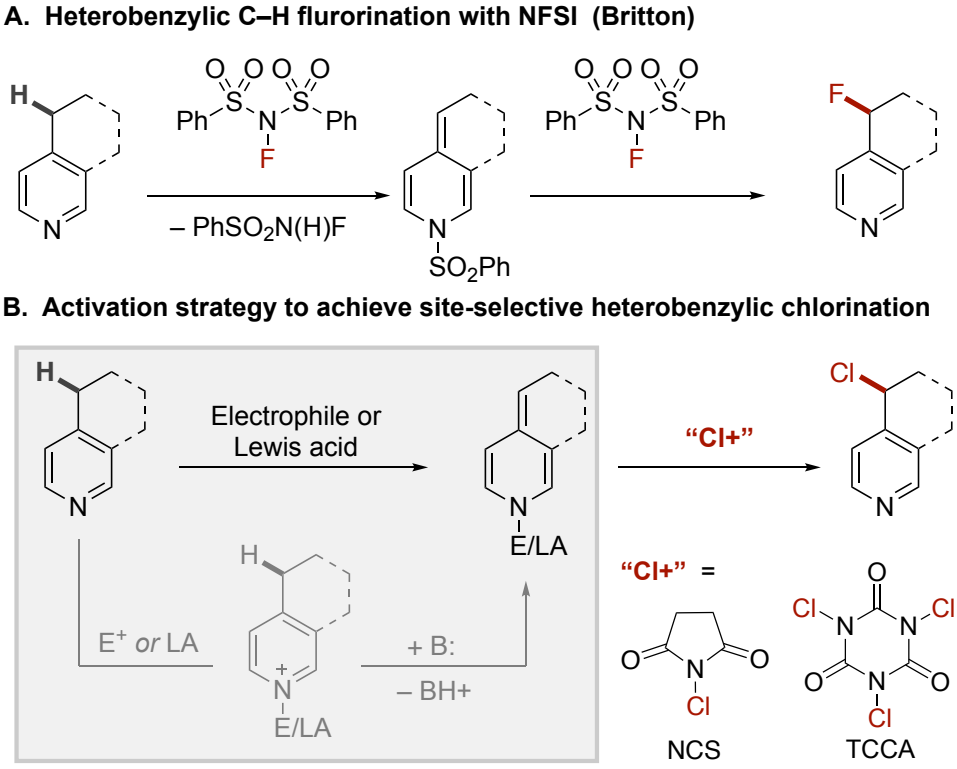

Figure 3.3. Precedent for heterobenzylic fluorination with NFSI, involving in situ formation of an alkylidene dihydropyridine intermediate (A) and strategy to expand on this concept through in situ pyridine activation of chlorination via a polar reaction pathway (B).

3.3. Results and Discussion

Computational analysis of resonance contributions to site selectivity. Resonant activation of alkyl-substituted heteroarenes takes advantage of the relative stability of certain tautomeric enamines. As a foundation for the synthetic methods outlined below, density function theory (DFT) methods were used to probe the energetic differences among different ethylpyridine-derived resonance structures.[23] Results of the DFT calculations (B3LYP, 6-311+G(2d,p) basis set, CH_3CN polarizable continuum model) show that 2- and 4-ethylpyridine can access alkylidene dihydropyridine isomers that are 6.4–11.6 kcal/mol more stable than the isomers derived from 3-ethylpyridine (Figure 3A). Several of the methods reported feature trifluoromethanesulfonyl chloride (TfCl) as a stoichiometric or catalytic promoter. As shown in Figure 3B, formation of *N*-Tf derivatives amplifies the energetic differences between the resonant 2-/4-ethyl and non-resonant 3-ethyl isomers. The lower energetic cost in forming 2- and 4-ethylpyridine isomers relative to the 3-ethylpyridine is manifested in the chlorination methods below, which show high site-selective reactivity at the 2- and 4-position of pyridines and analogous resonance-stabilized position of other heterocycles.

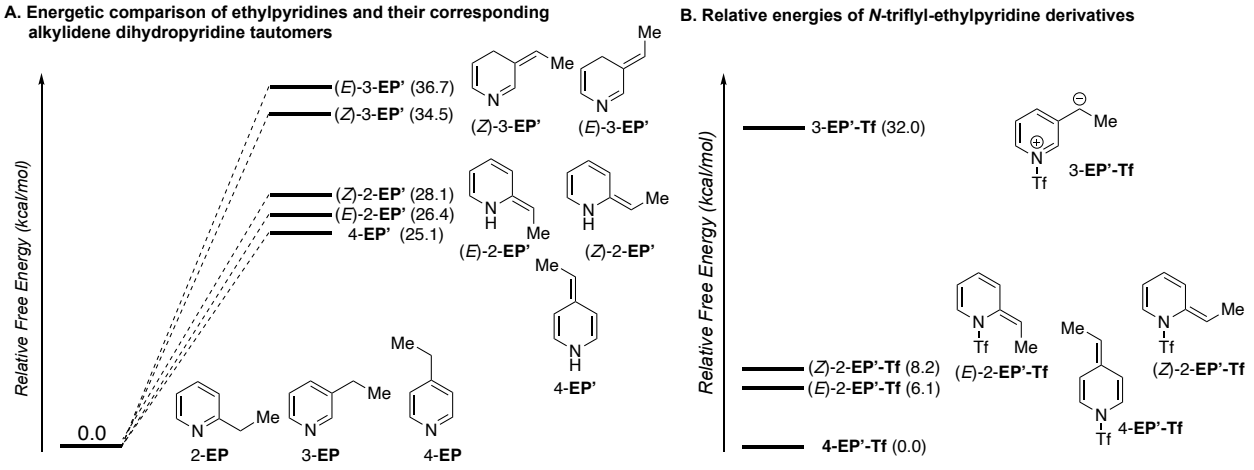

Figure 3.4. Relative free energies among 2-, 3-, and 4-ethylpyridines (**EP**) and their corresponding alkylidene dihydropyridine isomers (**EP'**) (A) and among deprotonated *N*-triflyl derivatives of 2-, 3-, and 4-ethylpyridine (**EP'-Tf)**.

Development of heterobenzylic C(sp^3)–H chlorination conditions and comparison to other methods. Some precedents exist for polar chlorination of alkyl-substituted heteroarenes. Chlorination at the 8-position of 5,6,7,8-tetrahydroquinoline (**1a**) has been achieved with trichloroisocyanuric acid (TCCA) in refluxing dichloromethane (Figure 4A).[24] These conditions had limited utility with other substrates, however. Good results were observed in the reaction of TCCA with 7,8-dihydroquinolin-5(6H)-one, affording **2** in 58% yield when chlorobenzene was used as the solvent (method A, Figure 4B, method a). But, 4-alkylpyridine substrates were unsuccessful, affording trace or low yield of **3** and **4**, respectively (Figure 4B). Use of TfCl as a stoichiometric activator led to modest improvement in the yield of **2**, but negligible impact on the formation of **3** and **4** (method b, Figure 4B).

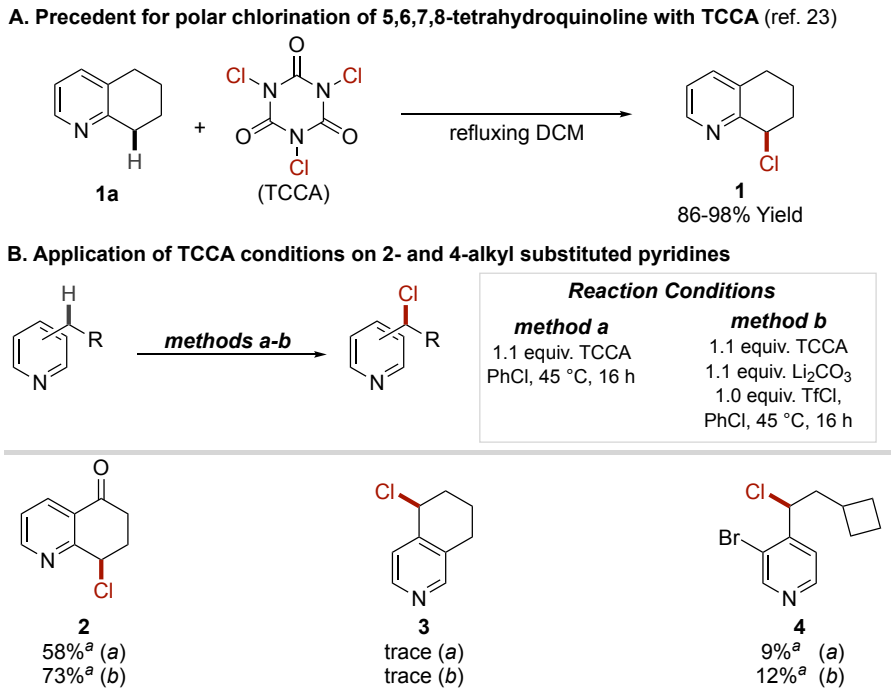

Figure 3.5. Precedent for polar chlorination of 7,8-dihydroquinolin-5(6H)-one with trichloroisocyanuric acid (TCCA) (A), and preliminary assessment of optimized TCCA conditions to other substrates (B). Reactions conducted 0.05 mmol scale. Yields determined by ^{1}H NMR spectroscopy (ext. std. = dibromoethane).

These results prompted broader assessment of other reagents and conditions, including both polar and radical reaction methods (Figure 5). The most effective alternatives to the TCCA methods in Figure 4 feature *N*-chlorosuccinimide (NCS) as the chlorination reagent. Direct use of NCS in acetonitrile (methods *c*) led to significantly improved yields of **3** and **4** (30% and 45%, respectively) relative to that observed with TCCA, but the best results were obtained with catalytic quantities of TfCl when paired with basic additives, 10 mol% 4-(-(dimethylamino)pyridine and 1.1 equiv of $LiCO_3$ (method *d*, 85% and 84% yield of **3** and **4**, respectively). The data in Figure 5 reflect results obtained with six different polar reaction conditions (methods *a–f*), including the original conditions reported for the preparation of **1** (method *e*)[24] and the NCSI conditions of Britton et al. (method *f*).[15b] The latter method led to a notable yield of **4** (35%), showing the best performance aside from the NCS-based conditions. Comparatively poor results were obtained with methods *g–i*,[13c,25,26] which are expected to involve radical reactivity (for additional screening data see Table 3A.I in Appendix 3 in the Supporting Information). These conditions include conventional radical chain conditions (method *g*), and two Cu-catalyzed radical relay conditions (method *h* and *i*). The ineffectiveness of these methods highlights the complications commonly encountered when attempting to extend benzylic C–H chlorination conditions to heterobenzylic substrates.

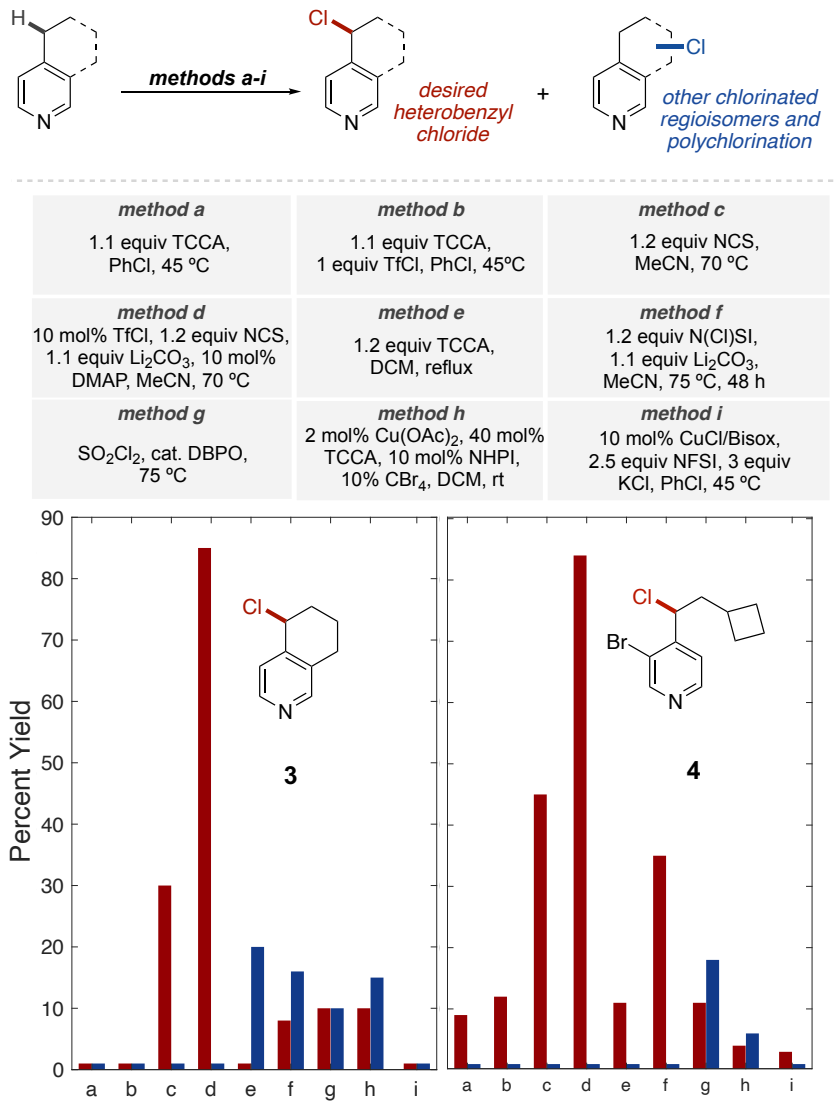

Figure 3.6. Heterobenzylic C–H chlorination data obtained with different polar and radical chlorination methods *a* – *i* to access **3** and **4**. Yields determined by ^{1}H NMR spectroscopy (ext. std. = dibromoethane) and or UPLC area percentages of chloride products.

Assessment of reaction scope for heterobenzylic C–H chlorination. The chlorination conditions identified above provided a starting point to test an array of heterobenzylic substrates (Figure 6). The TCCA methods *a* and *b* are effective with 2-alkyl-substituted pyridine derivatives, in addition to a 3-alkylpyridazine derivative, affording chlorination products **1**, **2**, **5–8** in good-to-excellent yields (57-86%). Alkyl groups at the non-resonant 3-position are completely unreactive

under the polar chlorination conditions (e.g., 3-ethylpyridine, **9**), enabling excellent site-selectivity in the chlorination of dialkylpyridines when one of the substituents is present in the 3-position. This behavior is evident in the selective formation of **3** (cf. Figure 5) and **10**, which is obtained in 94% yield with no evidence of reactivity at the 3-methyl group (Figure 6). Methods *c* and *d* exhibit broad scope with a diverse collection of 4-alkylpyridines (**10-28**) and other 4-alkylheteroarenes (**29**–**34**). The reaction also tolerate a number of C–H sites that would be susceptible to side reactions under radical reaction conditions, including C–H bonds in tertiary (**10**, **18, 19, 23**); benzylic (**12**); propargylic (**13**, **20**); and allylic (**21**) positions, and those adjacent to carbonyl (**14**), ether (**22**), ester (**27**), silylether (**28**), or protected amine (**23**–**26**) groups. The reaction proceeds well with pyridines bearing a 3-cyano (**15**) and 3-bromo (**16-23**) substituents, which provide an effective site for further elaboration of the core structure. In some cases, attempts to improve the yield, for example, by using excess NCS in the reaction to form **14** and **25**, resulted in formation of geminal dichlorination products. As this product was of less interest in the present study, little effort was directed toward optimizing this outcome.

These reaction conditions also support heterobenzylic chlorination of other classes of heteroarenes including alkyl-substituted quinolines (**29**, **30**), pyrimidine (**31**), pyridazines (**32**), and quinazolines (**33**, **34**). The pyridazine derivatives **6** and **32** show interesting complementarity in their reaction selectivity. Pyridazine **6** was accessed in high yield and showed high selectivity for chlorination adjacent to nitrogen (i.e., the 3-position, which resembles the 2-position of pyridine). Good reactivity at the 4-position in the formation of **32** suggests that either nitrogen atom can react

with TfCl to support chlorination via resonant activation of the alkyl group. Overall, this collection

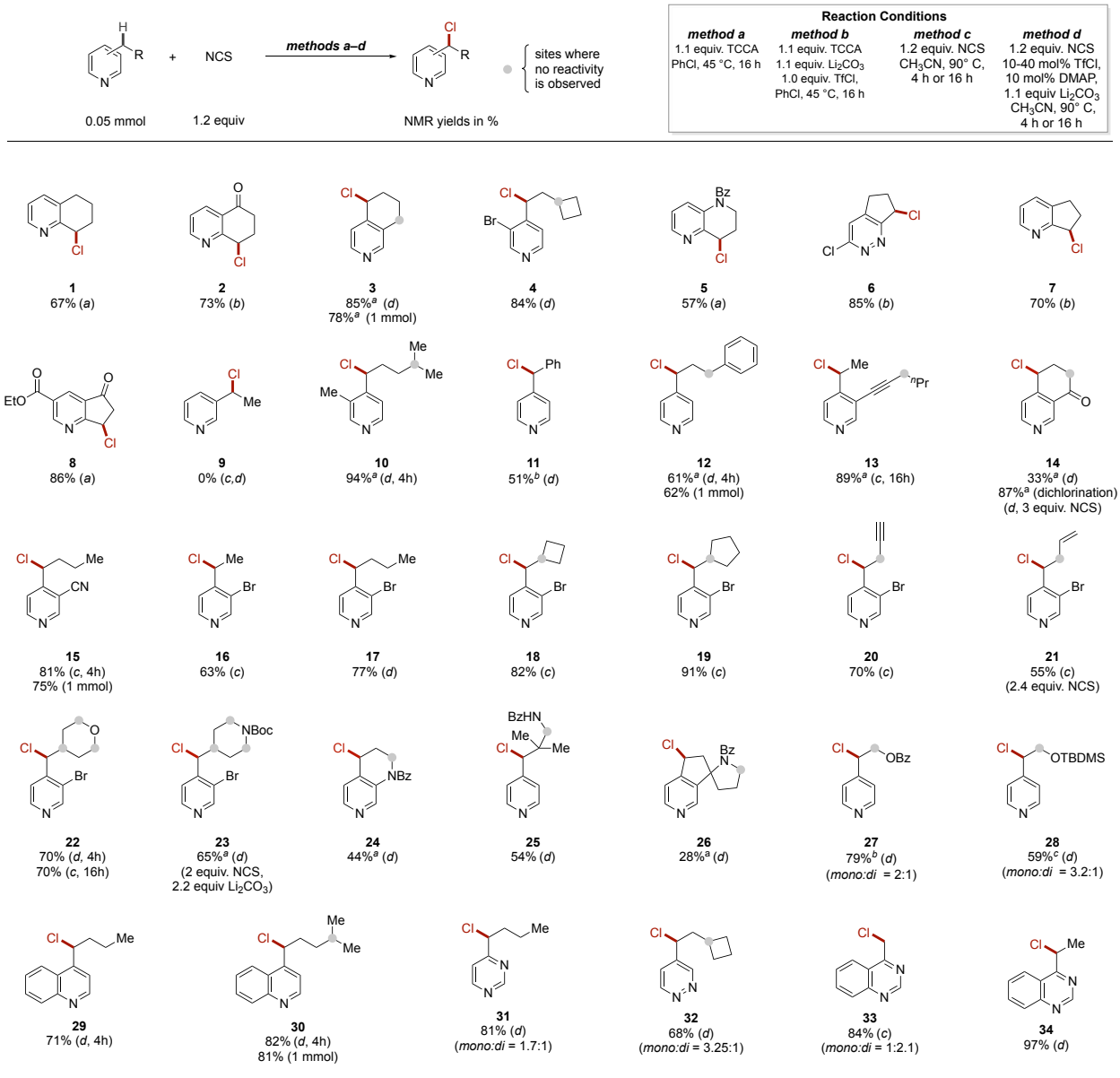

Figure 3.7. Scope of heterobenzylic chlorination under polar conditions. Reactions were run on a 0.05 or 1 mmol scale. Yields determined by ^{1}H NMR spectroscopy (ext. std. = dibromoethane). *a* Reactions run at 70 ºC. *b* Reaction run at 45 ºC *c* Reaction run at 65 ºC. See Section 3B.VI in Appendix 3 for deviation from standard conditions. Mono- versus dichlorination ratios are mentioned in parenthesis (*mono:di*).

of results in Figure 6 of substrates showcase the versatility of these polar chlorination conditions to access heterobenzylic chlorides from pharmaceutically relevant heteroarene core structures.

Notably, a majority of the products benefit from conditions that use TfCl as a catalytic activator. The heterobenzylic chlorides shown in Figure 6 often have polarity nearly identical to their C–H substrates. This feature complicates product purification, but it poses no complication for the goals of this study because these compounds are designed to be used as non-isolated intermediates in tandem chlorination/substitution reactions, as elaborated below.

Demonstration of C–H chlorination/diversification methods with amine, azole, and other nucleophilic coupling partners. In spite of the appeal of direct oxidative C–H cross-coupling methods, existing protocols show very limited reactivity with heterobenzylic coupling partners. Moreover, many important coupling partners, such as primary and secondary amines and thiols, are not compatible with oxidants typically used to support C–H activation. The chlorination method outlined above provide a strategy to bypass this limitation by generating a reactive intermediate that can undergo reaction with a nucleophile when the oxidant is no longer present in reaction mixture. To establish this concept, we selected four representative alkyl-substituted heteroarenes (**3a**, **4a**, **15a**, **30a**) for testing in tandem chlorination/diversification reactions. In addition, we selected 12 primary and secondary amine coupling partners (**Am1**–**Am12**), consisting of cyclic and acyclic alkyl amines and an aniline, and a complementary set of azoles (**Az1**–**Az12**), including pyrazoles, triazoles and imidazoles (Figure 7).

Each C–H substrate was subjected to the relevant chlorination conditions on 1.0 mmol scale. For coupling reactions with amines, the crude MeCN solution of the heterobenzylic chloride was distributed in 0.05 mmol aliquots into an array of vials the different amines and other components used in the displacement reaction and heated for 16 h. The product yield and identity were established by ^{1}H NMR spectroscopy and ultra-high performance liquid chromatography-mass spectrometry (UPLC-MS). A modified process was used with the azole nucleophiles shown in

Figure 7B, reflecting improved substitution yields when the coupling step was conducted in DMF rather than MeCN. Briefly, the crude chlorination product was subjected to a minimal work-up and solvent concentration, prior to dissolving in DMF and distribution into the array of vials containing the azole and other reaction components. The heat maps depicting the outcome of the

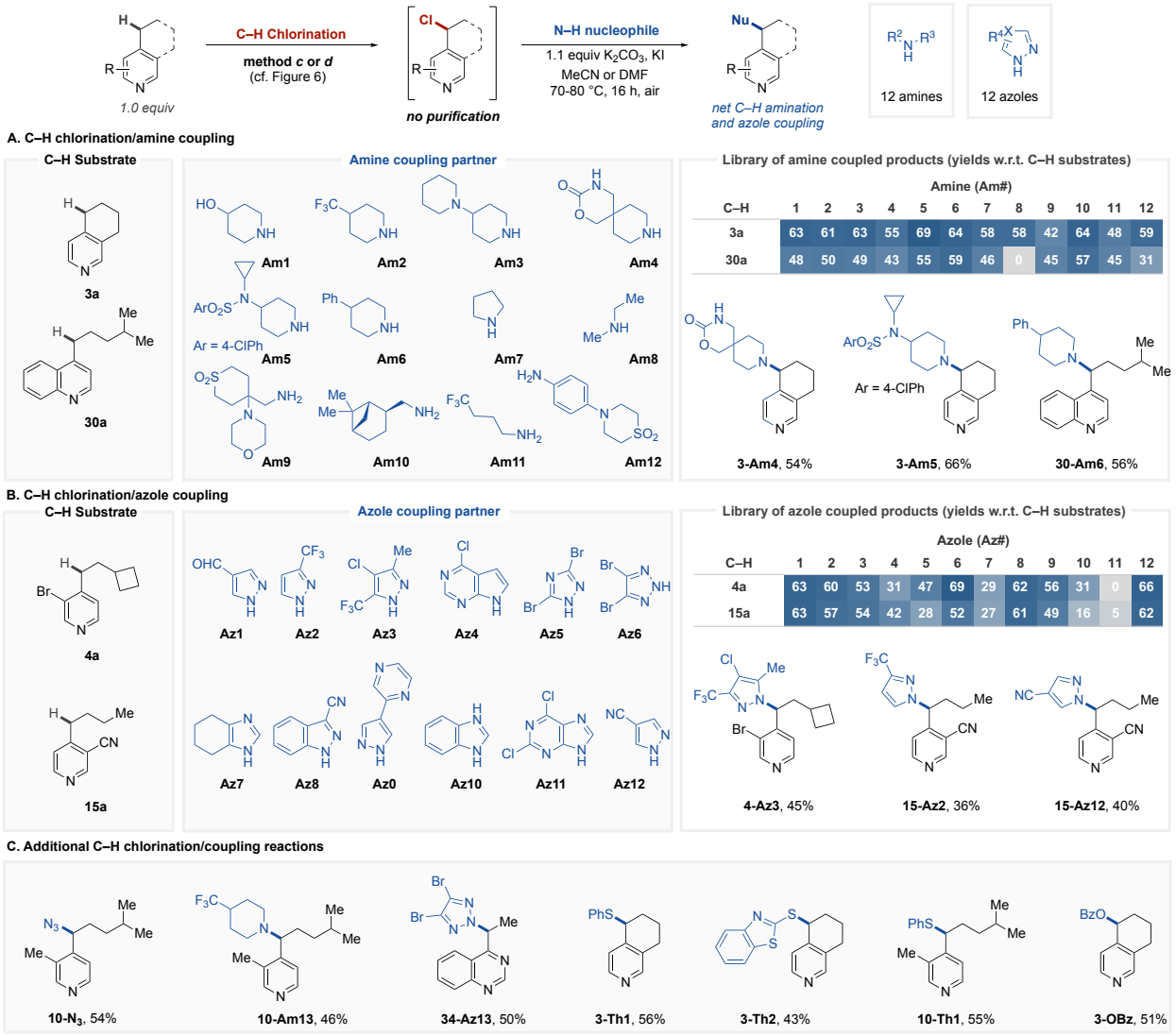

Figure 3.8. Diversification of heterobenzylic C–H bonds through tandem C–H chlorination/functionalization, including C–H chlorination and coupling with amine nucleophiles (**A**), azole nucleophiles, (**B**), in addition to other nucleophiles (**C**). For full experiment details, see Sections 3B.VIII and 3B.IX in Appendix 3.

chlorination/coupling reactions with amines (Figure 7A) and azoles (Figure 7B) reveal excellent performance with most C–H substrates/coupling pairs. All but a few of the reactions generate the desired products in yields that would be very useful in a medicinal chemistry context (i.e., ≥20%), and a majority proceed in >50% yield with respect to the C–H substrate. Six of the reactions were conducted on 0.2 mmol scale to facilitate purification and full characterization (**3-Am4**, **3-Am5**, **30-Am6**, **4-Az3**, **15-Az2**, **15-Az12**), and the isolated yields in these cases were also very good.

As a final demonstration, we evaluated the tandem sequence with other C–H substrates (**10a** and **34a**) and nucleophiles, include azide, a 1,2,3-triazole, thiols, and benzoate. The products of these reactions were obtained in 43–56% isolated yields with respect to the C–H substrate. Direct C–H azidation, benzoyloxylation, and azolylation reactions have been reported previously; however, none of the existing methods show broad scope with heteroarene substrates. Furthermore, the good reactivity observed with thiol coupling partners expands the range of coupling partners compatible with this method that would not be effective in conventional oxidative coupling protocols.

3.4. Conclusion

The work outlined herein represents a major advance in C(sp^3)–H cross coupling methods, enabled by the development of conditions that support site-selective chlorination of resonance-activated heterobenzylic C–H bonds, including those present in alkyl-substituted pyridine, pyrimidine, and pyridazine core structures. The tandem chlorination/diversification strategy implemented herein is operationally simple and does not require isolation or purification of the intermediate heterobenzylic chloride. These methods offer several advantages over direct C–H oxidative coupling reactions. The C–H bond is cionverted into a reactive lynchpin that can undergo effective coupling with many coupling partners, including oxidatively sensitive amines and thiols, that would not be compatible direct C–H functionalization approaches. The versatility of S_N2

substitution reactions allows diverse coupling partners to be employed, without requiring development of new catalyst systems to employ different classes of nucleophiles. The simplicity and synthetic utility of this method will make it highly appealing for integration in high-throughput experimentation platforms that are now widely used in medicinal chemistry and other venues.

3.5. Acknowledgements

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3.6. Author Contributions

Maity, S. performed the experimental work including finding preliminary results, substrate synthesis, optimization studies, data interpretation and analysis, and contributed to preparation of the manuscript.

Lopez, M.A. performed the experimental work including substrate synthesis, isolation of products, data interpretation and analysis, and contributed to preparation of the manuscript.

D.M.B. performed DFT calculations.

S.W.K. and S.L. served as consultants and provided compounds from Merck's library.

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Chapter 4.

Efforts Toward Streamlining Heterobenzylic C–C Bond Formation via Sequential C–H Chlorination/Reductive Coupling

4.1. Abstract

Ni-catalyzed reductive cross-coupling of heterobenzyl chlorides and (hetero)aryliodides has been developed to access novel 1,1,-diarylalkane structures. As part of these studies, two new reaction conditions were developed to promote productive cross-coupling, including a dual Ni/Fe(TPP)Cl and Ni/$MgCl_2$ catalyst systems. The reaction tolerates a wide range of both heterobenzylic chlorides including pyridines pyrazine, and pyrimidines. Lastly, preliminary efforts to pair these reactions with C–H chlorination is demonstrated to affect net heterobenzylic C–H arylation.

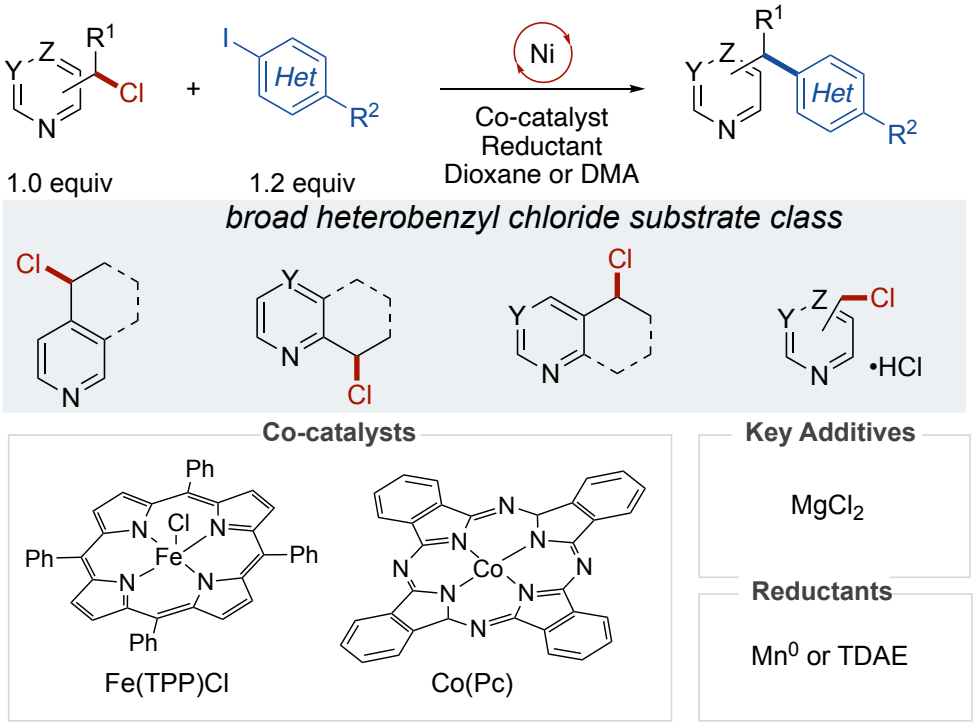


Figure 4.1. Reductive Coupling of Heterobenzylic Chlorides Summary of Reactivity

4.2. Introduction

Heteroaromatic C(sp^2)–H functionalization methods that rapidly forge new C–C bonds (e.g., radical reactions, deprotonative-metalation strategies, and metal catalyzed C–H functionalization) are highly enabling because they provide practical routes toward biological drug targets with improved physiochemical properties.[1-3] While these strategies are now widely adapted in pharmaceutical synthesis, methods involving related benzylic sp^3 C–H functionalization are less available. Alkyl substituted arenes are abundant structural features in building block and core structures and heterobenzylic C–H arylation strategies would provide efficient routes to an important class of pharmacophores known as diarylalkanes and diarylmethanes (Figure 4.2.A).[4-5] Leading strategies involve heterobenzylic C–H cross coupling with aryl halides that involve nitrogen-atom activation with Lewis acids in combination with Pd- or Ni- catalysis (Figure 4.2.B.)[6-9] These reactions, however, are often limited to simple picoline derivatives or other contrived aromatic nitrogen heterocycles, capable of generating transient alkylidene dihydropyridine intermediates that undergo facile reaction with a metal-catalyst at the benzylic position. Recent efforts from our lab have begun prioritizing the development of heterobenzylic C–H functionalization methods by sequential chlorination/functionalization strategies. [10-11] These approaches are appealing because they allow rapid derivatization of resonant and non-resonant heterobenzylic C–H bonds with a wide pool of electron rich functional groups (e.g., amine, phenol, azoles, etc.) that would otherwise be incompatible with direct oxidative methods and may proceed without isolation of the chloride intermediate. We postulated that this approach could be expanded to library synthesis of new diarylalkanes and diarylmethanes structures by pairing the chlorination step with Ni-catalyzed cross-electrophile (Ni-XEC).

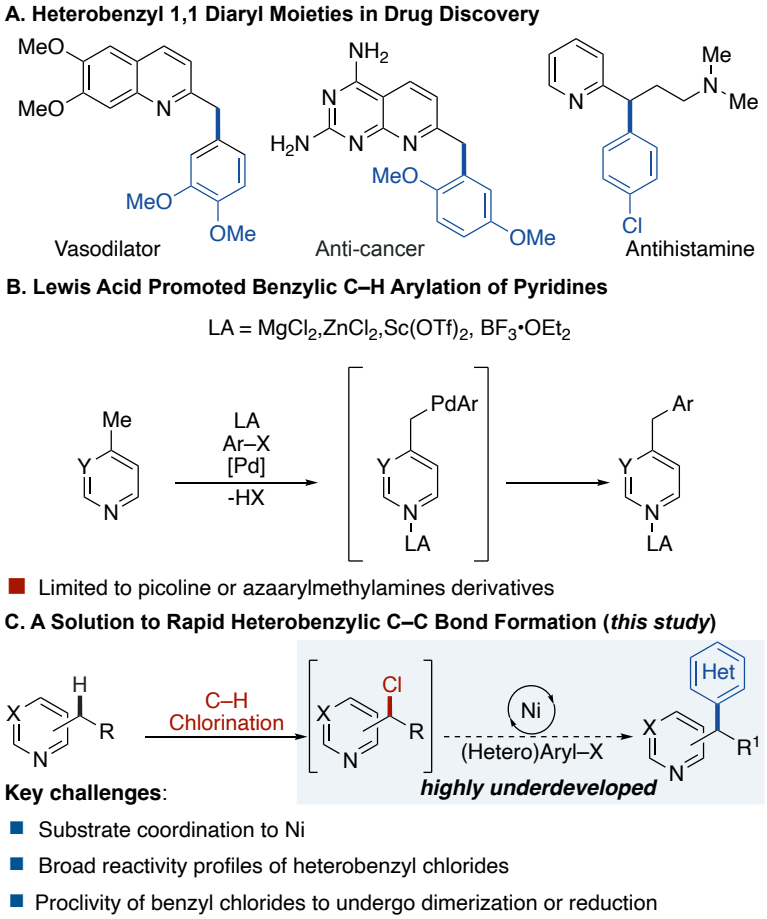


Figure 4.2. 1,1 Hetero(diaryl)-alkanes and -methanes in drug discovery (A). Lewis acid activation of resonance stabilized heterobenzylic positions and cross-coupling (B), Sequential C–H chlorination/reductive coupling sequence (C).

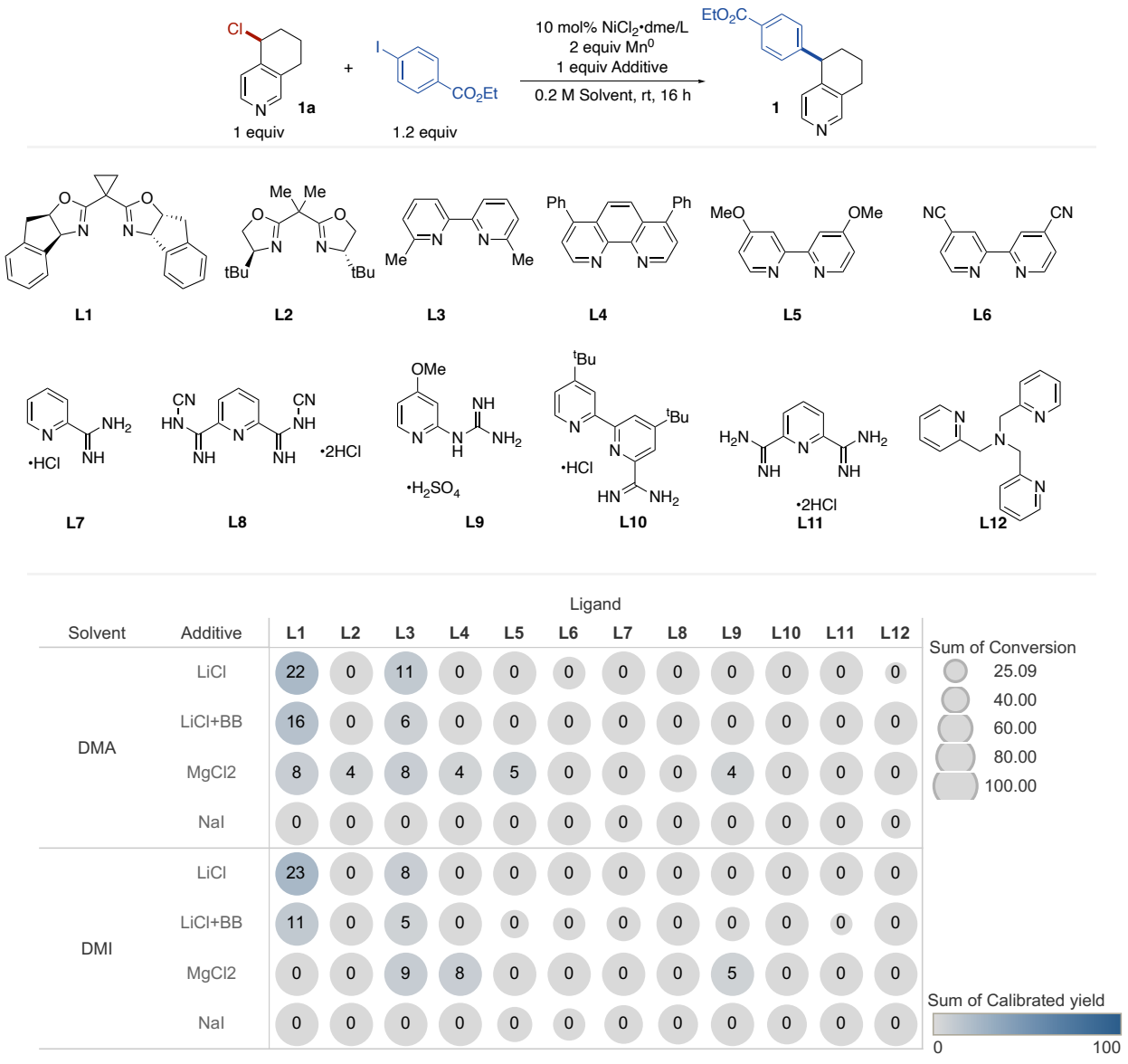
Over the past decade, Ni-XEC has emerged as an enabling strategy to generate new Csp^2–Csp^3 bonds from the abundant pool of readily available alkyl and aryl electrophiles. [12-14] While the majority of the XEC literature is demonstrated with unactivatd alkyl electrophiles[15-19] (i.e., primary halides, tertiary halides), recent efforts from Weix, Reisman, Hazari, and Gong have shown the efficacy of benzyl chlorides in these reactions to undergo reductive arylation with aryl halides. [20-23] However, the benzyl chlorides used in these studies are limited to simple alkyl arene derivatives and often employed in excess. The latter reflects reactivity mismatched effects between highly reactive benzyl and sp^2-electrophiles, resulting in dimerization of the benzyl coupling partner.

Moreover, subtle structural modifications to either coupling partner can also result in less efficient reactions, highlighting a central challenge in XEC methods development. To date, methods to productively affect azaheterobenzyl chlorides in reductive coupling have not been demonstrated.[24] This could be due reactivity challenges that azaheteroaromatic benzyl chlorides may pose such as competitive substrate binding to Ni, broad reactivity profiles, and facile activation. Herein, we report new methods for cross-electrophile coupling of diverse heterobenzyl chlorides and aryl halides for complex 1,1, diarylmethanes and- diarylalkane synthesis. The nuance in this work is the development of new reaction conditions that rely on Fe(TPP)Cl, Co(Pc) and $MgCl_2$ to productively engage a broad range of heterobenzylic chlorides in reductive coupling. Preliminary assessment of net heterobenzylic C–H (hetero)arylation is explored and validated by merging heterobenzylic C–H chlorination strategies with the Ni-XEC coupling methods described herein.

4.3. Results and Discussion

Initial screening studies evaluated the coupling of 5-chloro-5,6,7,8-tetrahydroisquinoline (**1a**), derived from C–H chlorination, and commercially available 4-iodoethylbenzoate. High-throughput experimentation surveying, nitrogen-donor ancillary ligands, halide additives, and amide-based solvents identified possible starting points for optimization (Figure 4.3). We found that combination of $NiCl_2$•dme pre-catalyst, a bis(oxazoline) ligand, LiCl, and Mn^0, in *N*-dimethylacetamide (Conditions A) delivered **1** in 22% yield with significant amount of alkyl-chloride reduction byproduct and unreacted aryl iodide. Empirical screening to improve upon this result, however, led to no significant improvement of the desired product yield. (See Section 4C.111. in Appendix C for additional screening data). Control experiments without the Ni-catalyst indicated background benzyl chloride consumption by Mn^0 or a Zn^0 reductant (See Table 4C.3 in Appendix C). Milder reductants such as tetrakis(dimethylamino)ethylene (TDAE; E^o=-1.11 vs Fc

in DMA) in combination with a cobalt-phthalocyanine (CoPc) co-catalyst have been used previously Ni-XEC reactions between alkyl halides and aryl halides (Conditions B).[22] The role of the Ni catalyst is expected to promote



Solvent	Additive	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12
DMA	LiCl	22	0	11	0	0	0	0	0	0	0	0	0
	LiCl+BB	16	0	6	0	0	0	0	0	0	0	0	0
	MgCl2	8	4	8	4	5	0	0	0	4	0	0	0
	NaI	0	0	0	0	0	0	0	0	0	0	0	0
DMI	LiCl	23	0	8	0	0	0	0	0	0	0	0	0
	LiCl+BB	11	0	5	0	0	0	0	0	0	0	0	0
	MgCl2	0	0	9	8	0	0	0	0	5	0	0	0
	NaI	0	0	0	0	0	0	0	0	0	0	0	0

Figure 4.3. HTE assessment of Ni-catalyzed reductive cross-coupling of 5-chloro-5,6,7,8-tetrahydroisoquinoline (**1a**) and 4-iodoethylbenzoate. of Yields were determined as percent of product relative to all known species derived from the benzyl chloride.

aryl halide activation while a reduced Co^{I}(Pc) activates the alkyl halide. However, these conditions proved rather ineffective. Complete consumption of the benzyl chloride was observed leading to 18% yield of **1** with chloride elimination/reduction/dimerization and unreacted aryl-iodide accounting for the remaining mass balance. Minor improvements in yield were observed in the absence of the Co(Pc). Additive screening studies identified $MgCl_2$ to improve the reaction outcome without the need of a co-catalyst, delivering **1** in 67% yield (Conditions C). We then applied these conditions to 8-chloro-5,6,7,8-tetrahydroquinoline (**2a)**, a regioisomers of **1a**, which furnishes **2** in 72% yield with 10% unreacted benzyl chloride. We hypothesized that this substrate could benefit from the addition of Co(Pc) to promote complete benzyl halide consumption; however, a decrease in reaction yield was observed. Fe-porphyrins have been previously reported to generate alkyl-radicals from activated halides and we postulated they could serve as milder alkyl-halide activators in these reactions to enable full consumption of the alkyl chloride without promoting dimerization.[25-26] Indeed, when Fe(TPP)Cl is used as a co-catalyst the desired product is delivered in 85% yield (Conditions D). We then assessed 8-chloro-5,6,7,8-tetrahydroquinoline (**3a**), a 3-alkyl substituted heterobenzyl chloride, under conditions A-D . The best yield of **3** was obtained with Conditions C (35)%; however, later scope studies will demonstrate improved reactivity with other examples of 3-alkyl substituted pyridines.

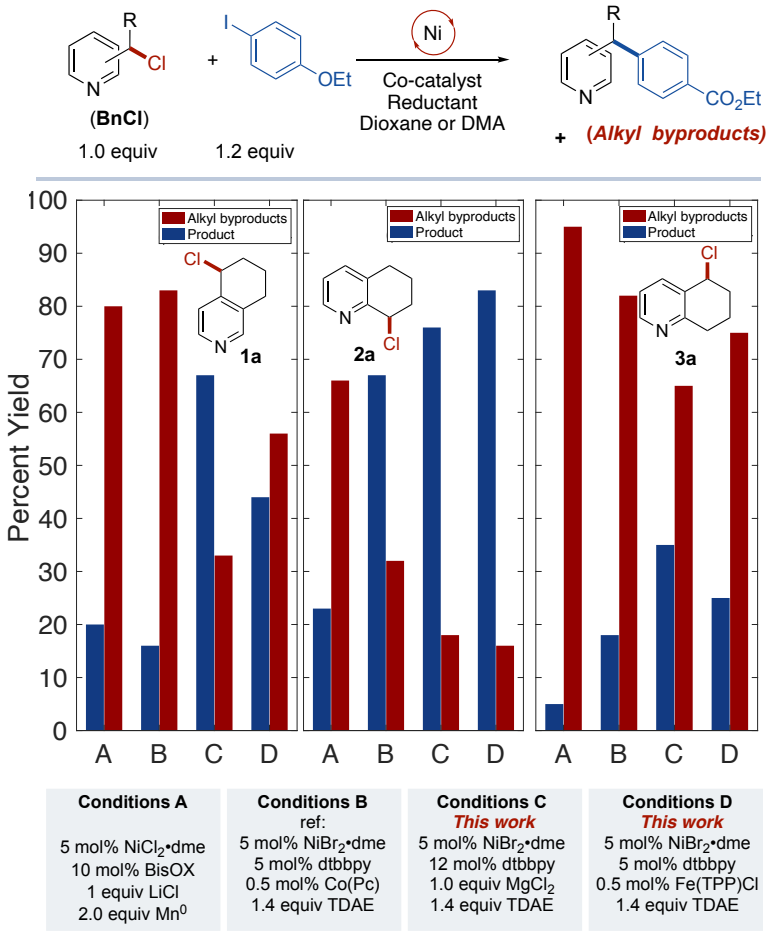


Figure 4.4. Summary of optimization results and literature precedent to access **1**, **2** and **3.** Yields were determined as percent of product relative to all known species derived from the benzyl chloride.

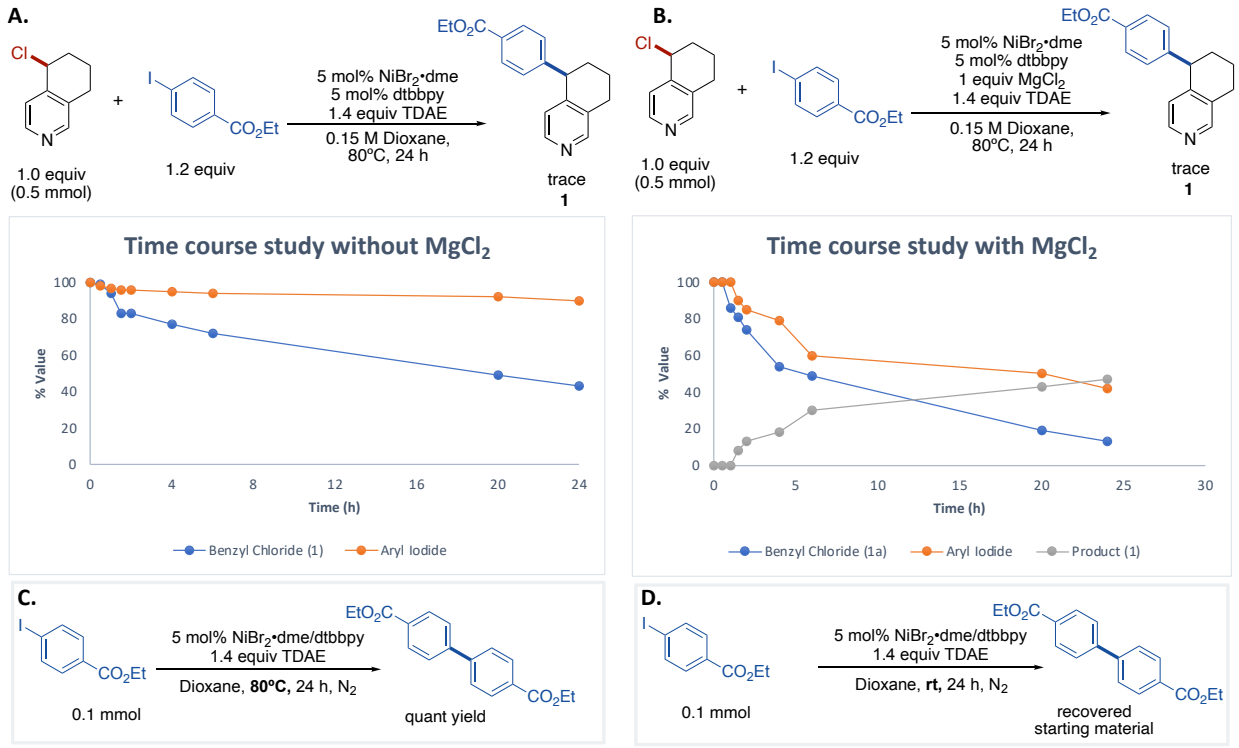


Figure 4.5. Time course studies on of substrate **1a** without (A) and with (B) magnesium chloride and control experiments without benzyl chloride substrate at 80ºC (C) and room temperature (D).

Next, we probed the effect of $MgCl_2$ on the reaction between **1a** and 4-iodoethylbenzoate. The time course data in Figure 4.5A demonstrate that the benzyl chloride is preferentially consumed over the aryl-iodide in the absence of $MgCl_2$, reflecting reactive mismatching between these two coupling partners. However, the addition of $MgCl_2$ promotes aryl halide consumption, leading to productive product formation (Figure 4.5B). We also note that complete consumption of the aryl iodide is observed in the absence of $MgCl_2$ and substrate **1a** (Figure 4.6.C.). These results could reflect a poisoning effect by the benzyl chloride to the Ni species responsible for aryl-halide activation. While $MgCl_2$ has been proposed to accelerate the rate reduction of Ni by heterogenous reductants in previous studies,[27][28] we hypothesize that $MgCl_2$ could be serving as a Lewis acid to the nitrogen-atom on the benzyl substate to attenuate binding at Ni. Almost no consumption of

the iodide was observed at room temperature and may reflect a kinetic barrier toward the Ni pre-catalyst reduction by TDAE (Figure 4.6.D).

To probe whether the reduced Fe(TPP)Cl can react with alkyl-electrophiles, CVs of Fe(TPP)Cl in the presence of **1a** were acquired. Scanning in the negative direction, the CV of a mixture of Fe(TPP)Cl and **1a** shows an increase in current relative Fe(TPP)Cl alone (Figure 4.6). The results demonstrate that upon reduction, an Fe^{I} species is responsible for the activation of the heterobenzyl chloride. Several modes of benzyl chloride activation are possible including, halogen atom transfer (XAT), an outer-sphere single-electron transfer (SET), or S_N2. However, the nature of the activation step cannot be determined.

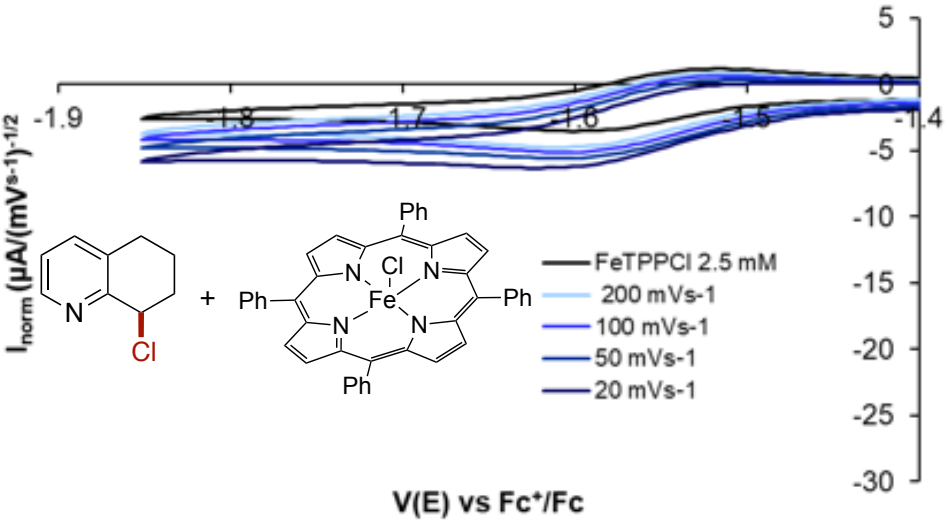


Figure 4.6. CV of a 2.5 mM solution of FeTPPCl in DMA, LiBr 0.2 M alone (black trace) and in presence of 8-Cl-5,6,7,8-tetrahydroquinoline 25 mM at various scan rates 20 to 200 mVs^{-1} (blue traces). CV recorded in the -1.40 V to -1.85 V region to monitor the Fe(II/I) reduction.

Substrate Scope

The reductive coupling conditions identified above provide a starting point to evaluate an array of heterobenzyl chloride substrates. 4-substituted secondary heterobenzyl chlorides undergo efficient cross-coupling only under $MgCl_2$ conditions (Conditions C). For example, good results were obtained when 4-(1-chloroethyl)pyridine and 4-(1-chloro-4-methylpentyl)-3-methylpyridine, demonstrating tolerance of simple and branched alkyl substituent to afford products **5** and **7**. Heterobenzyl chlorides with appended functional groups such as 3-phenylpropyl and tetrahydropyran are also compatible under these conditions providing products **4** and **6** in good yields. Notably, 2-chloro-4-(1-chloroethyl) pyridine underwent cross-coupling without the need for $MgCl_2$ and delivered **8** in 81% isolated yield. This result demonstrates the benefit of a substrates bearing a substituent adjacent to the nitrogen atom on the pyridine. We then assessed the generality of the dual Ni/Fe catalytic system (Conditions D) on other 2-alkyl substituted secondary heterobenzyl chlorides. This method proved effective for mono- and di-substituted substrates to deliver products **9** and **10** in excellent yields. 3-alkyl substituted heterocycles benefit from either dual Ni/Co (Conditions B) or Ni/Mn^0 (Conditions A) catalyst systems. Product **11** can be accessed from Conditions A or Conditions B in good yields. However, application of Conditons B to 3-(1-chloropropyl) pyridine resulted in significant amount of elimination. The reaction conditions also support reductive coupling of other classes of heterocycles including pyrazine (**13**) and pyrimidines (**14, 15**).

We then evaluated a range primary heterobenzyl chlorides under conditions A-D. We found, however, that this substrate class can be engaged in productive cross-coupling without the need of an additional co-catalyst or additive (Conditions E). The position of the benzylic chloride on the heterocycle also did not appear to influence the reactivity, as shown previously with secondary

substrates. Primary chloromethyl pyridines bearing electron deficient (**17**-**18**,**22**,**24**,**26**) or electron donating groups (**19**) showed good reactivity. The strongly electron-withdrawing trifluoromethyl group on substrate **18a** reduces the yield reduces of the product yield (**21%**, **18**). Electron deficient pyrimidine (**27**), pyrazine (**28**), quinazoline (**29**), and tetrahydrobenzofuropyrimidine (**30**) represent other heterocycles that showed efficient reactivity.

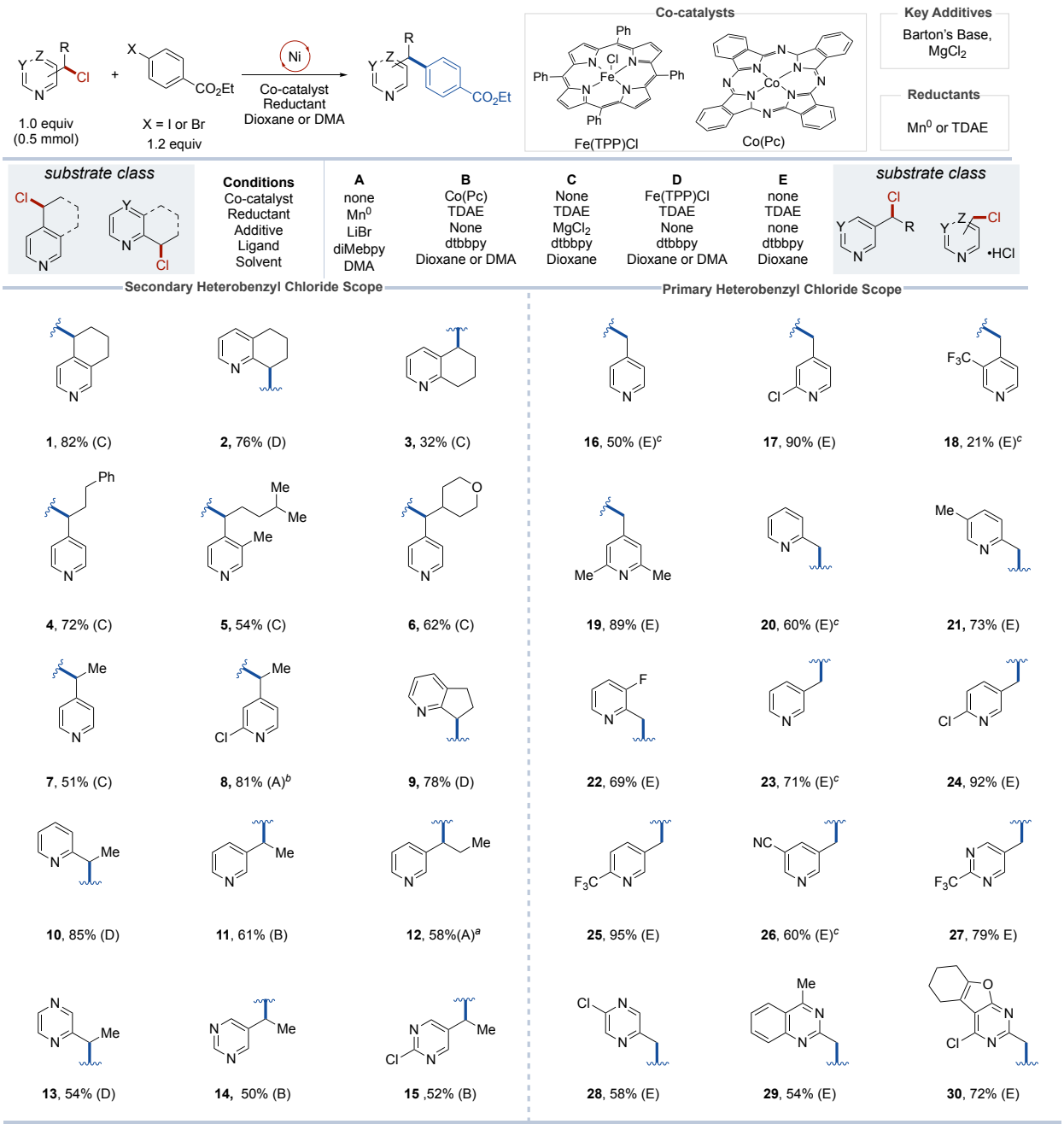


Figure 4.7. Reductive coupling scope of heterobenzyl chlorides. Reactions were run on a 0.5 mmol scale. Yields reflect isolated amount. [a]Reactions run at 40 ºC. [b]Conducted without $MgCl_2$. [c]Conducted with Barton's base.

The potential utility of these reductive strategies for library synthesis of di(hetero)arylalkanes is demonstrated when evaluating the coupling of 7-chloro-6,7-dihydro-5H-cyclopenta[b]pyridine (**9a**) and -2-chloro-5-(1-chloroethyl)pyrimidine (**15a)** with a broad collection of hetero(aryl)iodes. The iodide electrophiles assessed in this study feature diverse functional groups that are highly relevant to those commonly found in drug discovery efforts. These include arene structures with electron withdrawing (**1A-1C**) and electron donating groups (**1D-2A**) that could be used as further diversification handles. Further, heteroaryl iodides were also selected for evaluation and include pyridines, (**2C-3E**), a uracil-based electrophile (**3D**) substituted quinolines (**4A-4B**), quinazoline derivatives (**4C**), azaindole (**4D**), Boc-protected indole (**4E**), iodothienopyrmidine (**4F**) benzoxazole (**5A**), benzimidazole (**5B**), triazole (**5C**), isoxoazole (**5D**), and thiazole-indazole substrate (**5E**).

Under the Ni/Fe conditions, the coupling of **9a** with the 30 aforementioned aryl halides afforded the desired arylation products in a 93% hit rate (using a threshold of 10% UPLC-MS assay yield). Generally, electron deficient aryl iodides gave the best results. We note, however, that no product was observed when 2-iodopydine (3C) or the triazole derivative (5C) was tested. Chloride **15a**, however, provided a lower hit rate (66%). Nonetheless the products that can be derived from this study represent new chemical space that has not been currently accessed. In this case, electron deficient aryl iodides seem to react well and trace product is observed when electron donating groups are featured on the arene.

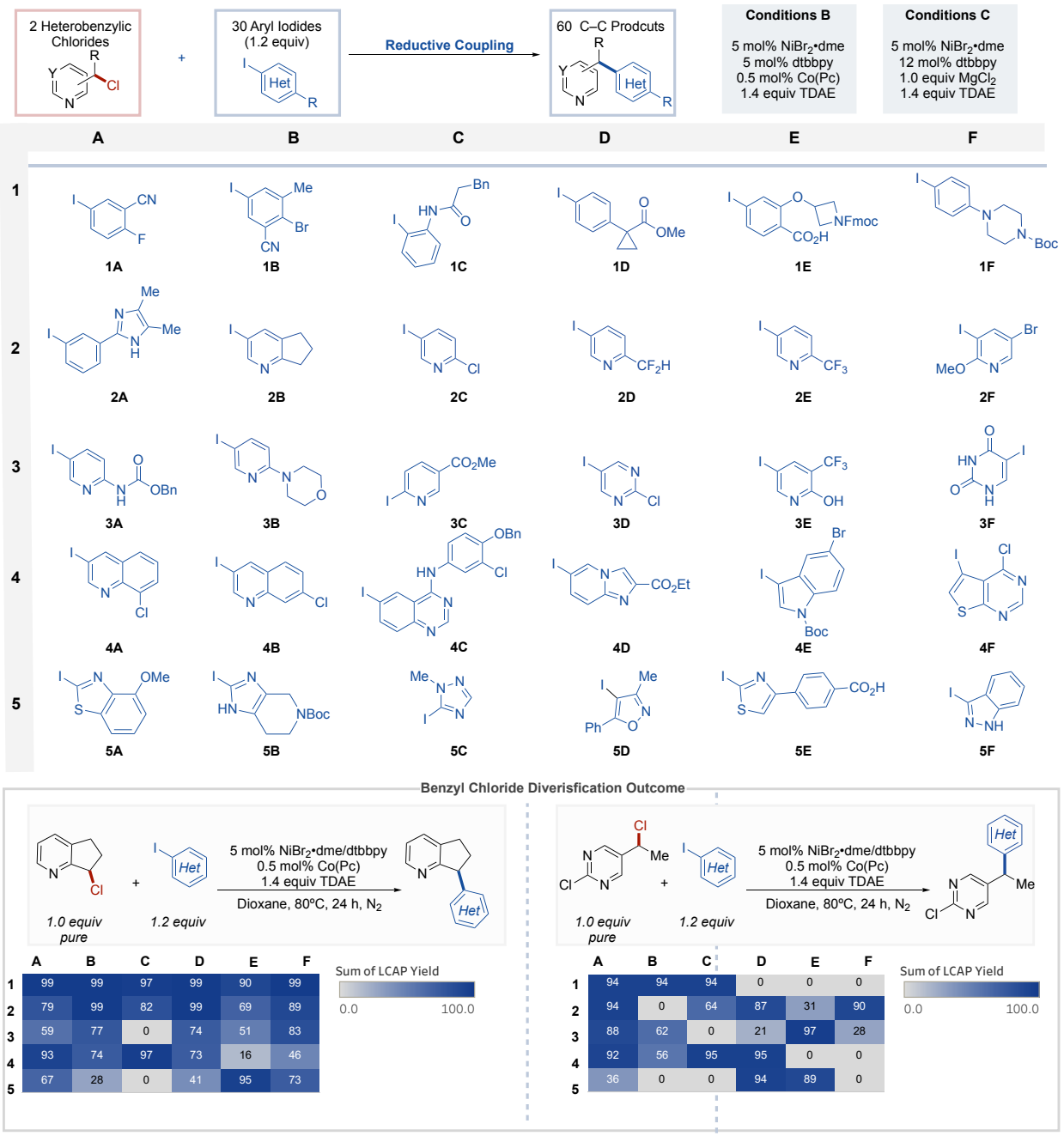


Figure 4.8. Assessment of hetero(aryl)iodides with **9a** under conditions D and 15 a under conditions B for library synthesis of 1,1-hetero(diaryl)alkanes. Yields were determined as percent of product relative to all known species derived from the benzyl chloride.

Preliminary efforts have begun exploring the pairing of the developed reductive coupling conditions with heterobenzylic C–H chlorination strategies (Figure 4.9). 6,7-dihydro-5*H*-

cyclopenta[*b*]pyridine (**9b**) can underdo benzylic chlorination exclusively at the 2-positions using TCCA under refluxing dichloromethane. At 2.0 mmol scale, the reaction affords a 68% ^{1}H NMR yield of the corresponding benzyl chloride. After minimal work up without requiring the need for chromatography, aliquots that correspond to 0.2 mmol of chloride was dosed into 4 different reaction vials containing iodides (1D, 2E, 2C, and 3D). The data in Figure 4.9 demonstrates a powerful proof-of-concept for net C–H heteroarylation with medicinally relevant aryl electrophiles. Moreover, products 9-2E, 9-2C, and 9-3D represent incredibly rare hetero-hetero(diaryl)methanes that could find application in medicinal chemistry.

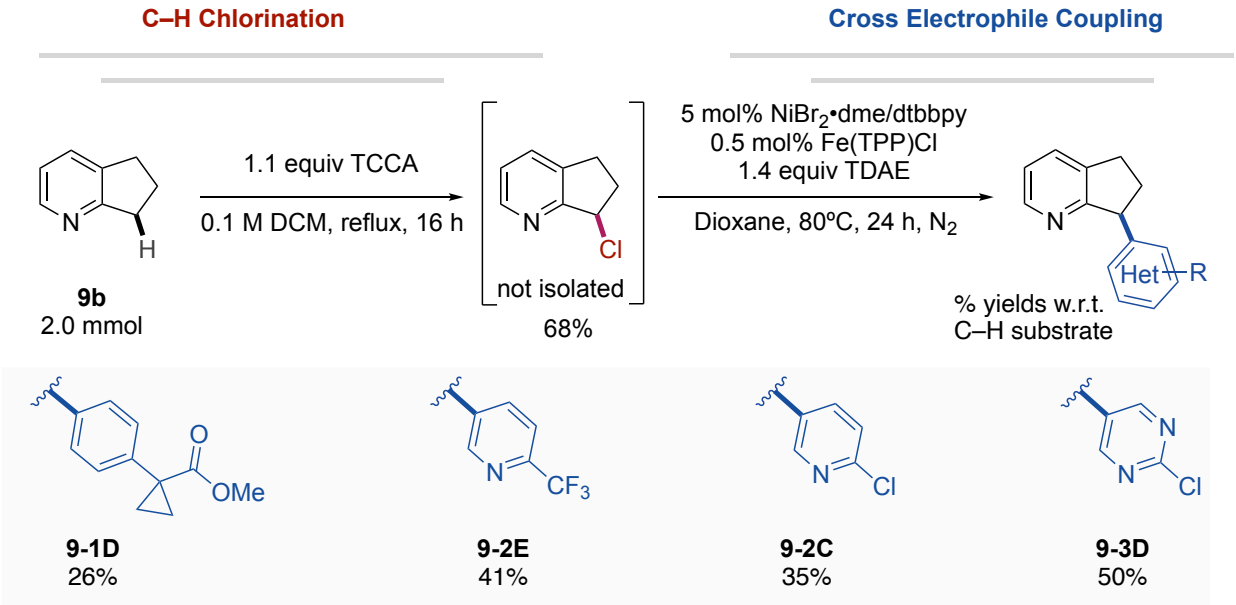


Figure 4.9. Synthesis of hetero-hetero(diaryl)alkanes **via** Sequentual C–H Chlorination/ Reductive Coupling. Values are isolated yields with respect to the C–H substrate.

4.4. Conclusion

Overall, this study unlocks heterobenzyl chlorides as highly underexplored electrophiles for Ni-catalyzed reductive arylation. The distinguished reactivity profiles of this class of substrates can lead to unproductive and often unpredictable reactivity. However, the use of a mild reductant like TDAE, appropriate co-catalyst (Fe(TPP)Cl or CoPc), or $MgCl_2$ provide solutions such that

efficient reactivity is achieved. Preliminary efforts to affect net heterobenzylic arylation via C–H chlorination/reductive coupling sequence holds promise to expand this approach to other classes of heterobenzylic C–H substrates.

4.5. Acknowledgments

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4.6. Author Contributions

Lopez, M.A. led experimental work including substrate synthesis, HTE studies, isolation of products, time courses, data interpretation, and analysis.

Floreancig, J.T performed experiment work including synthesis of substrates, HTE optimization studies, and isolation of compounds.

Dick, A.R. performed initial HTE studies and contributed to isolation of products.

Cardinale, L. performed cyclic voltammogram experiments.

Poole D. L. and Goodwin, N.C. served as consultants and provided compounds from GSK library.

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Appendix A: Supporting Information Chapter 2

2A.I. General Considerations

All reagents were purchased from commercial sources and used without any further purification. Benzylic C–H substrates were purchased from Aldrich, Alfa Aesar, Ark-Pharm, AstraTech, Chem-Impex, Combi-Blocks, Enamine, Fischer-Scientific, TCI America, or Toronto Research Chemicals Inc, and were used without any further purification. ACS grade chlorobenzene was purchased from Aldrich, was dried over calcium hydride, then was degassed via three freeze-pump-thaw cycles prior to use. NFSI was purchased from Ark-Pharm and Oakwood. Crystalline potassium chloride was ground into a powder with a mortar and pestle. The purity of the phosphite reductant is critical to the success of the reaction and should be stored under inert atmosphere.

Ligand **L4**, (3aR,3a'R,8aS,8a'S)-2,2'-(cyclopropane-1,1-diyl)bis(3a,8a-dihydro-8H-indeno[1,2-d]oxazole) was synthesized according to a literature procedure.[1] CuCl was prepared according to a literature procedure[2] and stored in a N_2 filled glovebox. (3,5-dibromo-4-methoxy-phenyl)-(2-ethyl-benzofuran-3-yl)-methanone, precursor to **23**, was synthesized according to the literature procedure.[3] Trifluoroacetyl-protected amines, precursors to **12**-**14**, were synthesized from the corresponding primary amines according to a literature procedure.[4]

Proton (^{1}H), carbon (^{13}C), and fluorine (^{19}F) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz at 25 °C (^{1}H 400.1 MHz, ^{13}C 100.6 MHz, ^{19}F 376.5 MHz), Bruker 500 MHz at 25 °C (^{1}H 500.1 MHz, ^{13}C 125.7 MHz, ^{19}F 470.6 MHz), or a 600 MHz at 25 °C (^{1}H 600.1 MHz, ^{13}C 151.1 MHz). All spectrometers and chemical shifts are reported in parts per million (ppm). NMR spectra are referenced to residual solvent $CHCl_3$ at 7.26 ppm (^{1}H) and $CDCl_3$ at 77.16 ppm (^{13}C). All ^{19}F NMR spectra were absolutely referenced to their respective solvent peaks in the ^{1}H NMR spectrum. High resolution mass spectrometry spectra were obtained on a Thermo Q Exactive™ Plus by the mass spectrometry facility at the University of Wisconsin-Madison. Automatic normal phase column chromatography was performed using reusable 25g Sfär Silica HC D cartridges on a Biotage Isolera®. Preparative thin-layer chromatography was performed using 20 cm x 20 cm glass-backed silica preparative thin-layer chromatography plates (1000 um, layer thickness) from Miles Scientific.

2A.II. General Procedure for Benzylic C–H Chlorination Reaction

General Procedure: On the benchtop, a disposable vial was charged with benzylic substrate (1 equiv), N-Fluorobenzenesulfonimide (NFSI; 2.5 equiv), potassium chloride (KCl; 3 equiv), and a Teflon stir bar. The vial was sealed by a PTFE-lined pierceable cap. Bis(oxazoline) ligand **L4** was weighed into a secondary vial with a Teflon stir bar*. Both vials were sparged with N_2 then transferred into a purging glovebox under N_2. In the glovebox, CuCl was weighed into the vial containing Bis(oxazoline) ligand. Chlorobenzene was added to this vial and the vial was stirred for 15 min to form a clear light yellow stock solution of copper catalyst. To the vial containing benzylic substrate, NFSI, KCl, and the Teflon stir bar was added diisopropyl phosphite (1 equiv) and the copper catalyst stock solution to form a green solution. The reaction vial was then sealed,

removed from the glovebox, and set to stir at 750 rpm on an aluminum block at the specified temperature for 16 h.
Work Up: After 16 h, mesitylene (30 μL, 0.215 mmol) or dibromethane CH_2Br_2 (0.427 mmol, 30 μL 2.36 equiv) was added to the crude heterogenous reaction mixture as an external NMR standard. The crude reaction mixture was filtered through a pad of silica using $CHCl_3$. An aliquot (30 μL) from the now homogenous solution was withdrawn for NMR analysis to detect formation of product and consumption of starting material. After NMR analysis, the crude reaction mixture was concentrated on the rotovap at 30 °C to remove solvent (chlorobenzene and chloroform). The obtained residue was purified by flash column chromatography.
Procedure A (0.2 mmol).
Vial 1: a disposable 1 dram vial, benzylic substrate (0.2 mmol, 1 equiv), NFSI (157.7 mg, 0.5 mmol, 2.5 equiv), KCl (44.7 mg, 0.6 mmol, 3 equiv), and a Teflon stir bar*.
Vial 2: Bis(oxazoline) ligand (**L2**, 21.4. mg, 0.06 mmol), CuCl (6.0 mg, 0.06 mmol), and chlorobenzene (3 mL) combined to form a clear light yellow 0.02 M stock solution of copper catalyst.
To Vial 1 was added diisopropyl phosphite (33 μL, 0.2 mmol, 1 equiv) and 1 mL of the copper catalyst stock solution. The reaction was conducted at room temperature.
Work Up: Mesitylene (30 μL, 0.215 mmol) was added to the crude heterogenous reaction mixture and worked up as outlined in the General Procedure.

Procedure B (0.2 mmol). Adopting Procedure A, the reaction was performed at 35 °C.

Procedure C (0.2 mmol). Adopting Procedure A, the reaction was performed at 45 °C.

Procedure D Adopting Procedure A, benzylic C–H substrate was added inside the glovebox after all reaction components were added. The reaction was performed at 75 °C.
Procedure E (0.5 mmol).
Vial 1: a disposable 24 mL glass vial, benzylic substrate (0.5 mmol, 1 equiv), NFSI (394.2 mg, 1.25 mmol, 2.5 equiv), KCl (111.8 mg, 1.5 mmol, 3 equiv), and **two** Teflon stir bars (see note on stir bars below).
Vial 2: Bis(oxazoline) ligand (**L2**, 53.5 mg, 0.15 mmol), CuCl (14.8 mg, 0.15 mmol), and chlorobenzene (7.5 mL) combined to form a clear light yellow 0.02 M stock solution of copper catalyst.
To Vial 1 was added diisopropyl phosphite (83 μL, 0.5 mmol, 1 equiv) and 2.5 mL of the copper catalyst stock solution. The reaction was conducted at room temperature.
Work Up: Mesitylene (30 μL, 0.215 mmol) was added to the heterogenous solution and worked up as outlined in the General Procedure.

Procedure F (0.5 mmol). Adopting Procedure D, the reaction was performed at 35 °C.

Procedure G (0.5 mmol). Adopting Procedure D, the reaction was performed at 45 °C.

Procedure H (1.2 mmol; used for products 13 and 24).
Vial 1: a disposable 24 mL glass vial benzylic substrate (1.2 mmol, 1 equiv), NFSI (946.0 mg, 3 mmol, 2.5 equiv), KCl (268.4 mg, 3.6 mmol, 3 equiv), and two Teflon stir bars.

Vial 2: Bis(oxazoline) ligand (**L2**, 42.77 mg, 0.12 mmol, 0.1 equiv), CuCl (11.99 mg, 0.12 mmol, 0.1 equiv), and chlorobenzene (5 mL) to form a clear light yellow 0.24 M stock solution of copper catalyst.
To Vial 1 was added diisopropyl phosphite (199 µL, 1.2 mmol, 1 equiv), and 5 mL of the copper catalyst stock solution. The reaction was conducted at 35 °C.
Work up: After 16 h, mesitylene (30 µL, 0.215 mmol) was added to the heterogenous solution and worked up as outlined in the General Procedure.

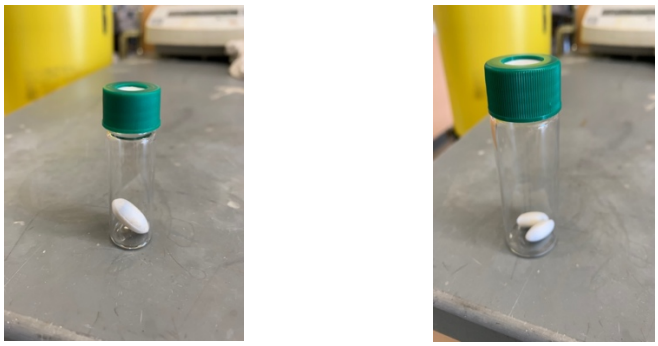


Figure 2A.1. A 1 dram vial for 0.2 mmol reaction with small stir bar (left), and a 24 mL vial for 0.5 and 1.2 mmol reaction with two stir bars (right).

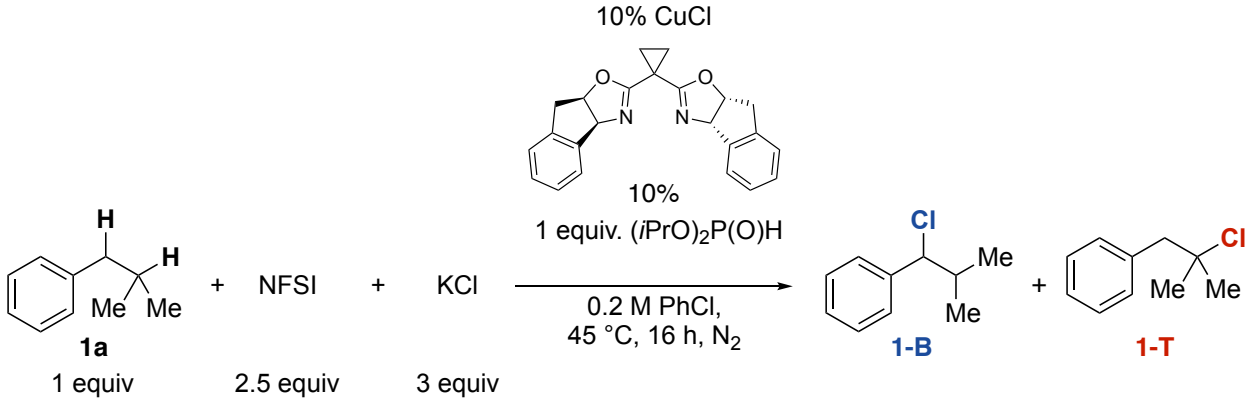
2A.III. Selected Optimization Experiments

General Procedure for Optimization of Reaction Parameters.

Set up: On the benchtop, a disposable 1 dram vial was charged with isobutyl benzene (1a) (0.2 mmol, 1 equiv), NFSI, chloride source, Cu salt, ligand, reductant, and a Teflon stir bar. The vial was sealed by a PTFE-lined pierceable cap and then transferred into a purging glovebox under N_2. In the glovebox, chlorobenzene (1 mL) was added to this vial to form a green solution. The reaction vial was then sealed, removed from the glovebox, and stirred at 750 rpm on an aluminum block at 45 ºC for 16 h.

Work Up: After 16 h, mesitylene (30 µL, 0.215 mmol) was added to the crude heterogenous reaction mixture as an external NMR standard. The crude reaction mixture was filtered through a pad of silica directly into a test tube using $CHCl_3$. An aliquot (30 µL) from the now homogenous solution was taken for NMR analysis to detect formation of product and consumption of starting material.

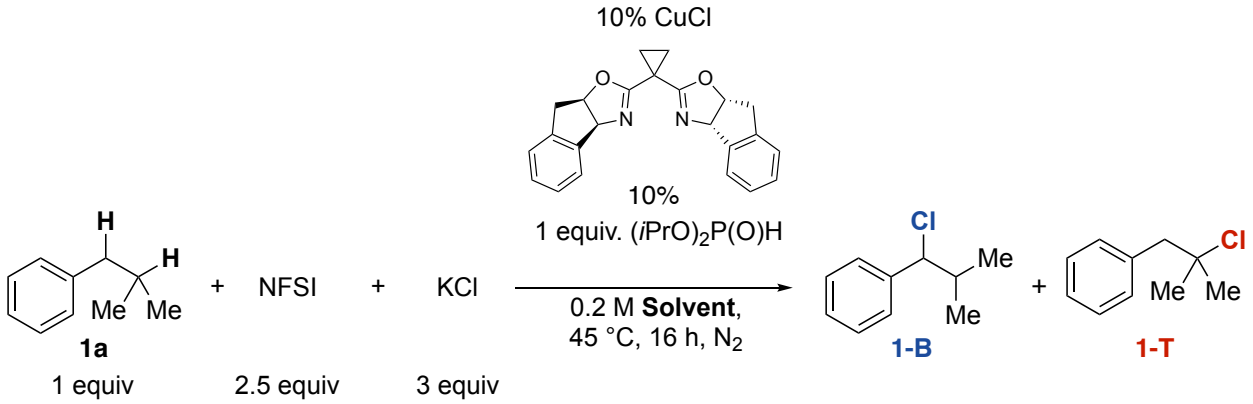
Table 2A.1. Control Experiments.



entry[a]	Variation	Conversion of **1a**	% 1-B	% 1-T
1	No CuCl	0	0	0
2	No NFSI	0	0	0
3	No (^{i}PrO)$_2$P(O)H	0	0	0
4	No KCl	59	2	0
5	No Ligand	69	39	3
6	Under air	54	45	7

[a]Reactions were run on a 0.2 mmol scale. Calibrated ^{1}HNMR yields were determined versus mesitylene as the external standard.

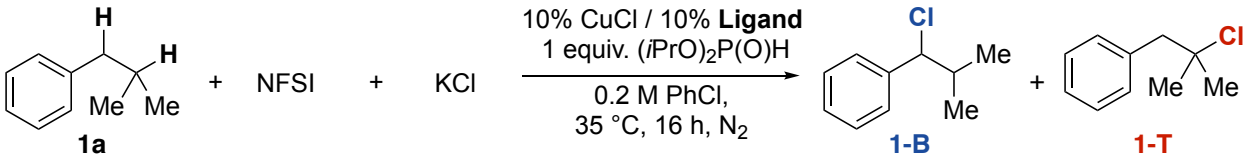
Table 2A.2. Evaluation of Solvent.

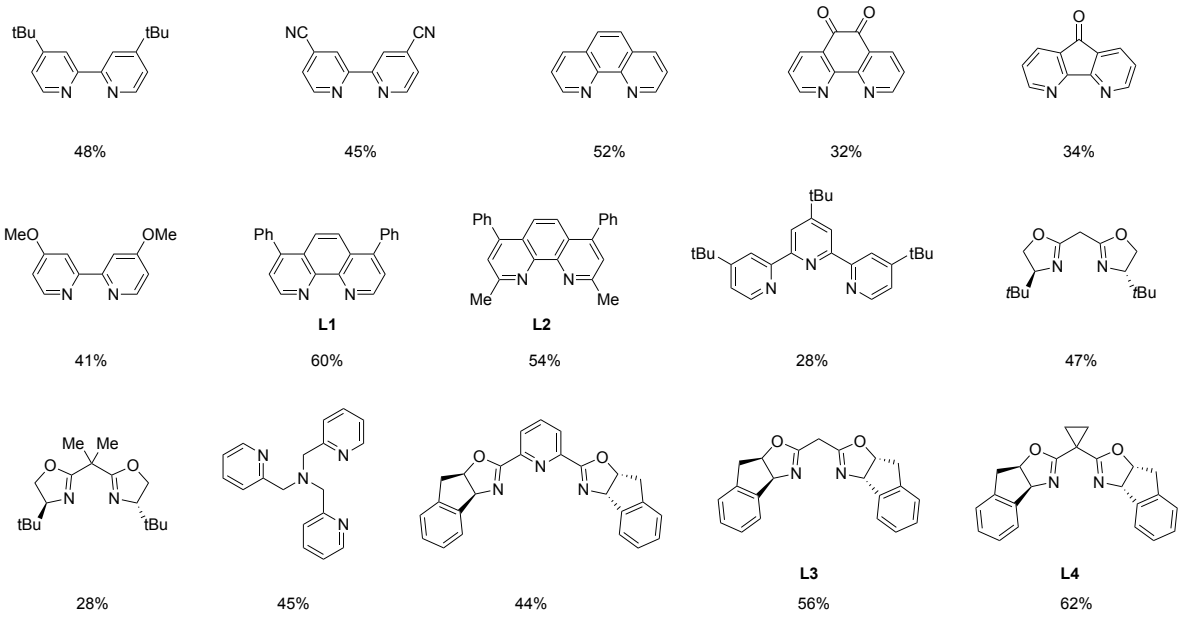


Entry[a]	**Solvent**	Conversion of **1a**	**% 1-B**	**% 1-T**
1	Acetone	85	20	3
2	MeCN	38	25	2
3	EtOAc	42	31	6
4	DCM	42	35	6
5	PhF	77	58	10
6	$PhCF_3$	77	65	10
7	DCE	78	69	6
8	**PhCl**	**78**	**70**	**8**
9	3 PhCl:1 HFIP	94	4	6
10	3 PhCl :1 DMA	16	8	0
11	3 PhCl: 1 TFE	72	26	3
12	3 PhCl: 1 MeCN	50	38	3

[a]Reactions were run on a 0.2 mmol scale. Calibrated ^{1}H NMR yields were determined versus mesitylene as the external standard. DCM, Dichloromethane; DCE, 1,2-dichloroethane; ACN, acetonitrile; EtOAc, ethyl acetate; PhF, Fluorobenzene; $PhCF_3$, Trifluorotoluene; PhCl, Chlorobenzene; HFIP, Hexafluoroisopropanol; TFE, Trifluoroethanol; DMA, N,N-dimethylacetamide.

Table 2A.3. Evaluation of Ancillary Ligands.

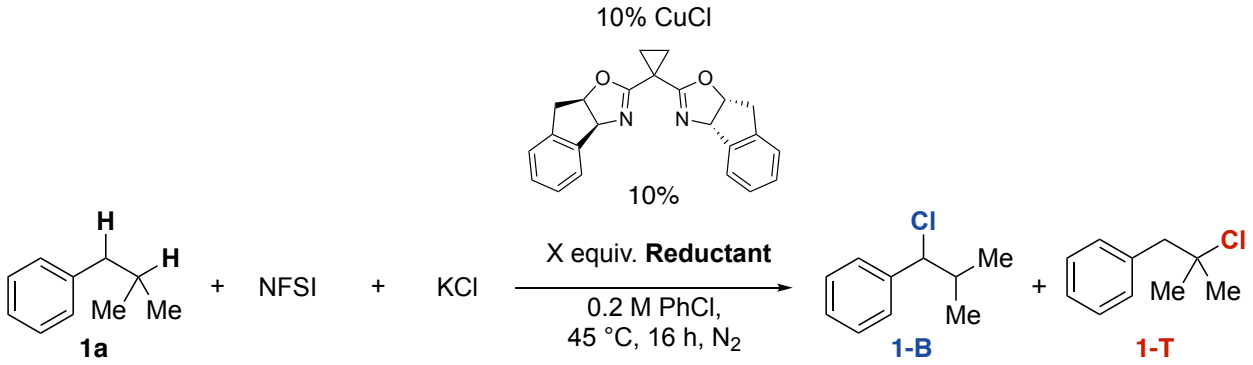




[a]Reactions were run on a 0.2 mmol scale. Calibrated ^{1}H NMR yields were determined versus mesitylene as the external standard.

Discussion: The results reported in **Table S3** shows the chlorination reaction outcome with various ancillary ligands. While bathophenanthroline (**L1**) and bathocuproine (**L2**) demonstrated to be effective ligands for the chlorination reaction on isobutylbenzene, Bis(oxazoline) ligand (**L4**) proved to be slightly more effective in this screen. Evaluation of **L1**, **L2**, and **L4** (see **Figure S2**) on different substrates demonstrates improved reactivity with **L4**

Table 2A.4. Evaluation of Reductants

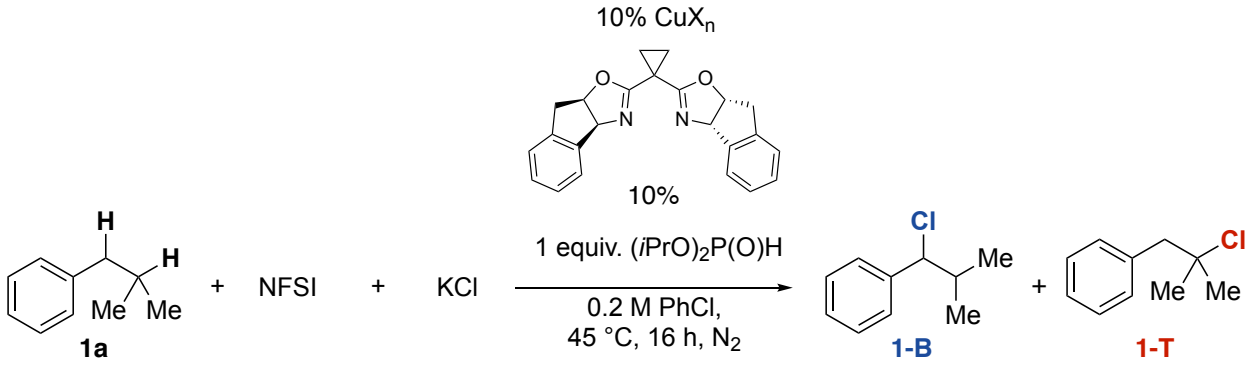


Entry[a]	**Reductant**	Conversion of **1a**	**%Cl 1-B**	**%Cl 1-T**
1	0.5 equiv $(iPrO)_2P(O)H$	85	59	6
2	**1 equiv $(iPrO)_2P(O)H$**	**85**	**63**	**5**
3	1.5 equiv $(iPrO)_2P(O)H$	73	57	4
4	2.0 equiv $(iPrO)_2P(O)H$	69	59	5
5	1 equiv $(PhO)_2P(O)H$	0	0	0
6	1 equiv $(MeO)_2P(O)H$	72	52	6
7	1 equiv $(EtO)_2P(O)H$	65	55	8
8	1 equiv $(tBuO)_2P(O)H$	35	28	3
9	1 equiv $(MeO)_2MeSiH$	25	20	2
10	1 equiv $(EtO)_2MeSiH$	20	14	3

[a]Reactions were run on a 0.2 mmol scale. Calibrated ^1H NMR yields were determined versus mesitylene as the external standard.

Discussion: The results reported in **Table S4** shows the chlorination reaction outcome with various silane and phosphite based reductants. Diisopropyl phosphite (1 equiv) proved to be the most effective for this transformation.

Table 2A.5. Evaluation of Cu Salts

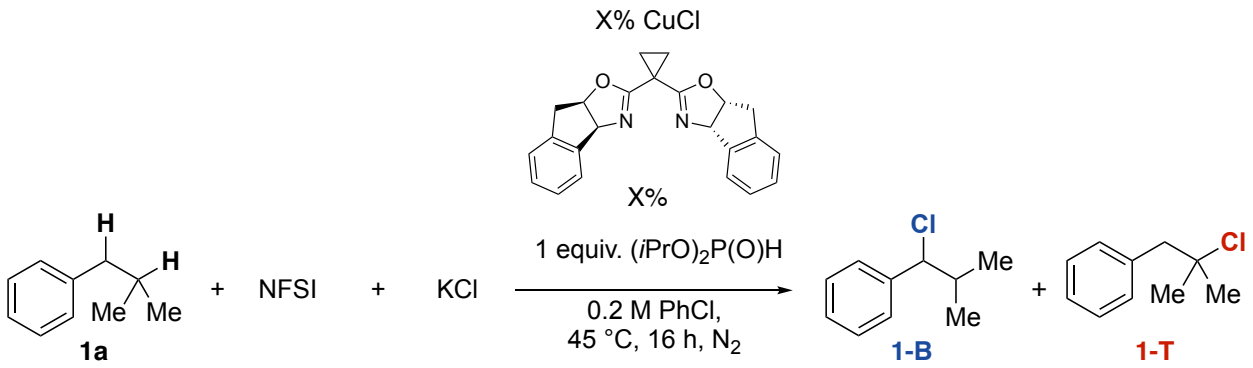


Entry[a]	**Cu Salt**	Conversion of **1a**	**%Cl 1-B**	**%Cl 1-T**
1	CuOTf•Toluene	45	40	3
2	$Cu(OTf)_2$	47	43	3
3	CuOAc	65	52	6
4	$Cu(OAc)_2$	60	54	8
5	$Cu(MeCN)_4PHF_3$	69	56	7
6	CuBr•DMS	65	58	5
7	CuI•DMS	66	60	7
8	$CuCl_2$	68	60	5
9	CuCN	72	63	9
10	**CuCl**	**78**	**69**	**6**

[a]Reactions were run on a 0.2 mmol scale. Calibrated ^{1}H NMR yields were determined versus mesitylene as the external standard.

The results reported in **Table S#** shows the chlorination reaction outcome with various Cu salts.

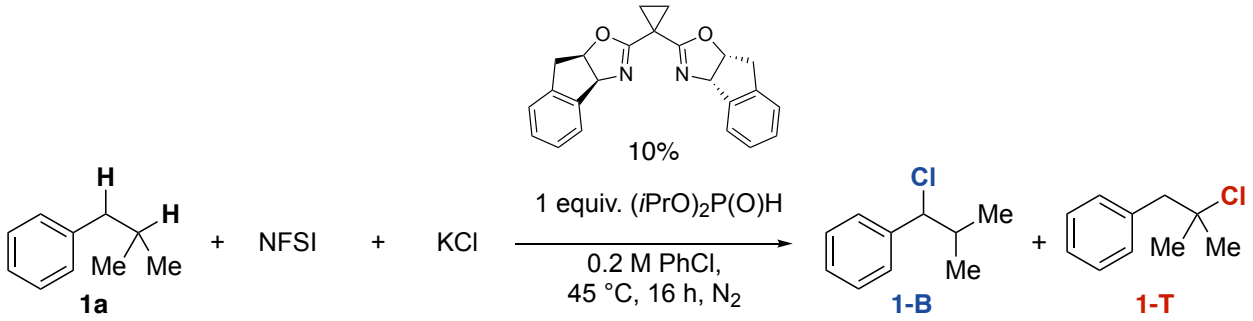
Table 2A.6. Evaluation of Cu/Ligand Loading.



Entry[a]	**CuCl (%)**	**Ligand(%)**	Conversion of **1a**	**%Cl 1-B**	**%Cl 1-T**
1	**10**	**10**	**77**	**62**	**6**
2	5	5	63	56	6
3	15	15	78	60	4
4	10	20	65	57	5
5	20	10	89	63	7
6	10	0	70	35	2
7	10	15	62	55	5
8	10	5	94	56	7

[a]Reactions were run on a 0.2 mmol scale. Calibrated ^{1}HNMR yields were determined versus mesitylene as the external standard.

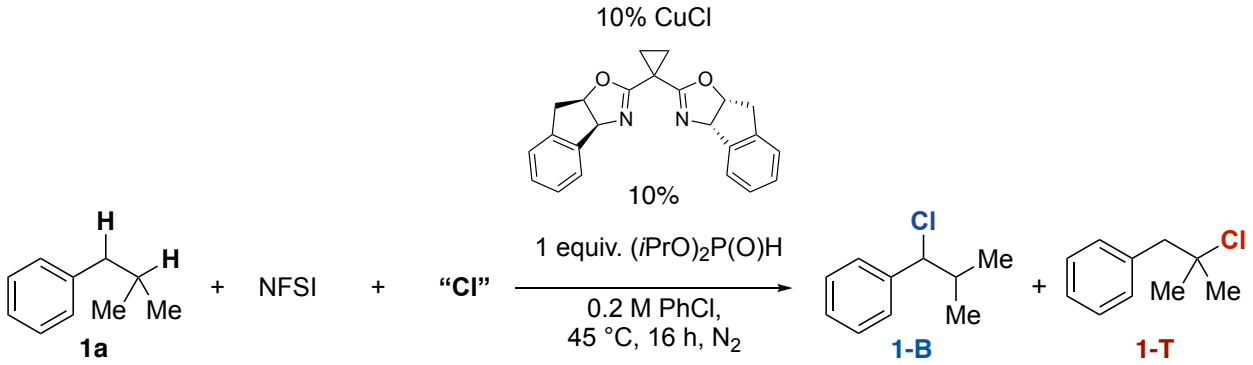
Table 2A.7. Evaluation of NFSI Loading



Entry[a]	**NFSI Equiv**	Conversion of **1a**	**%Cl 1-B**	**%Cl 1-T**
1	1	35	30	3
2	1.5	52	46	5
3	2	76	67	7
4	**2.5**	**80**	**69**	**7**
5	3	91	68	6
6	3.5	88	60	8
7	4	99	59	6
8	5	89	63	8

[a]Reactions were run on a 0.2 mmol scale. Calibrated ^{1}H NMR yields were determined versus mesitylene as the external standard.

Table 2A.8. Evaluation of Chloride Sources.



Entry[a]	**"Cl"**	Conversion of **1a**	**%Cl 1-B**	**%Cl 1-T**
1	TBACl	0	0	0
2	LiCl	25	18	4
3	TMSCl	24	23	1
4	NaCl	35	30	2
5	RbCl	39	34	2
6	CsCl	55	48	3
7	NCS	68	49	9
8	**KCl**	**75**	**70**	**6**

[a]Reactions were run on a 0.2 mmol scale. Calibrated ^{1}H NMR yields were determined versus mesitylene as the external standard. TBAC, Tetrabutylammonium chloride; TMSCl, Trimethylsilyl chloride, NCS, N-Chlorosuccinimide

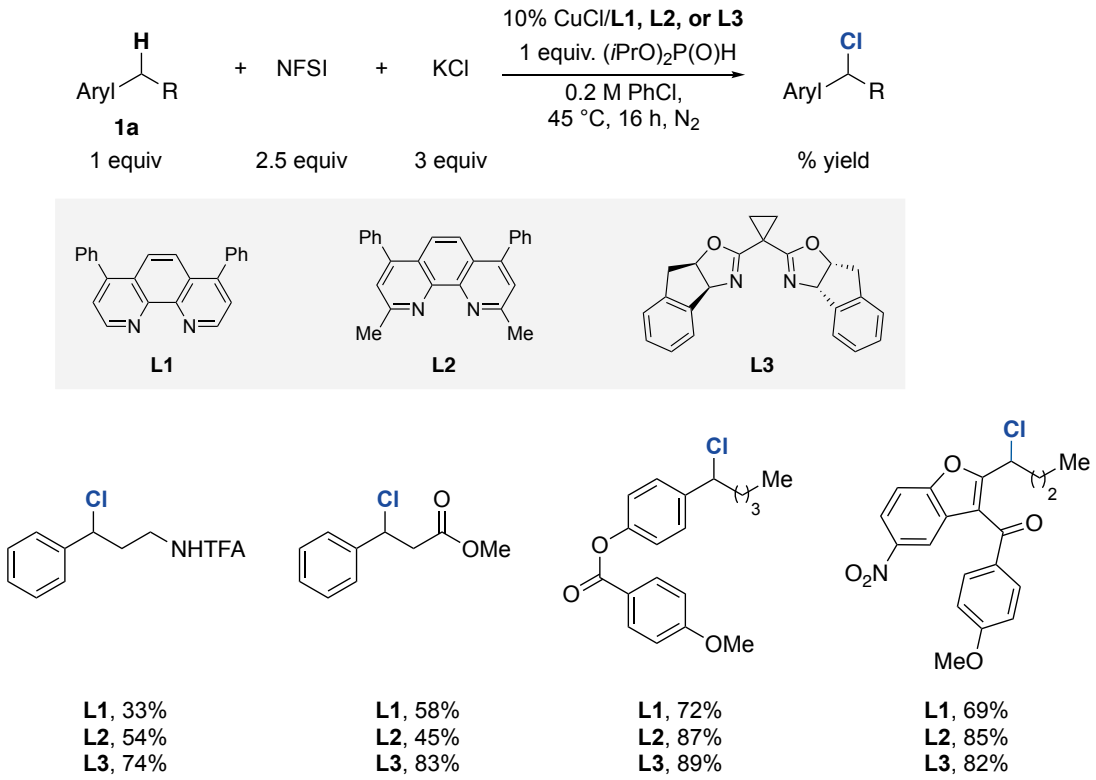
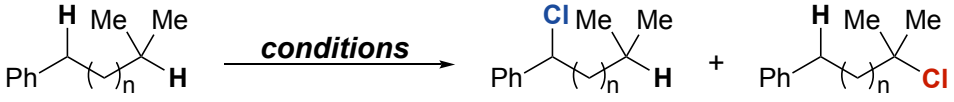


Figure 2A.2. Comparative study of **L1**, **L2**, and **L4** with various C–H substrate. [a]Reactions were run on a 0.2 mmol scale. Calibrated ^{1}H NMR yields were determined versus mesitylene as the external standard.

Table 2A.9. Comparative Data with Known Chlorination Methods



n = 0 or 1

Conditions a-h	%Cl-1-B n = 0	%Cl-1-T n = 0	%Cl 2-B n = 1	%Cl 2-T n = 2
a. 10%CuCl/L, 2.5 NFSI, 3 KCl,	69	7	78	4
b.[5] AgOTf/phen, tBuOCl	37	21	53	29
c.[6] NCS, DPBO, cat. HOAc	30	17	39	12
d.[7] $Cu(OAc)_2$ 40%TCCA, 10% NHPI	25	9	27	13
e.[8] 5% Ph_2CO, NCS, *hv*	18	13	10	8
f.[9] SO_2Cl_2, cat. DBPO, 45 ºC	17	14	18	26
g.[9] SO_2Cl_2, cat. DBPO, 75 ºC	28	31	20	23
h.[10] 2% Mn(TPP)Cl, NaOCl, 4%TBACl	9	6	9	3

[a] Site-selectivity studies were performed on a 0.2 mmol scale according to the literature procedures. The site-selectivity was determined by ^{1}HNMR spectroscopy using mesitylene (0.215 mmol, 30 µL, 1.07 equiv) as the external standard.

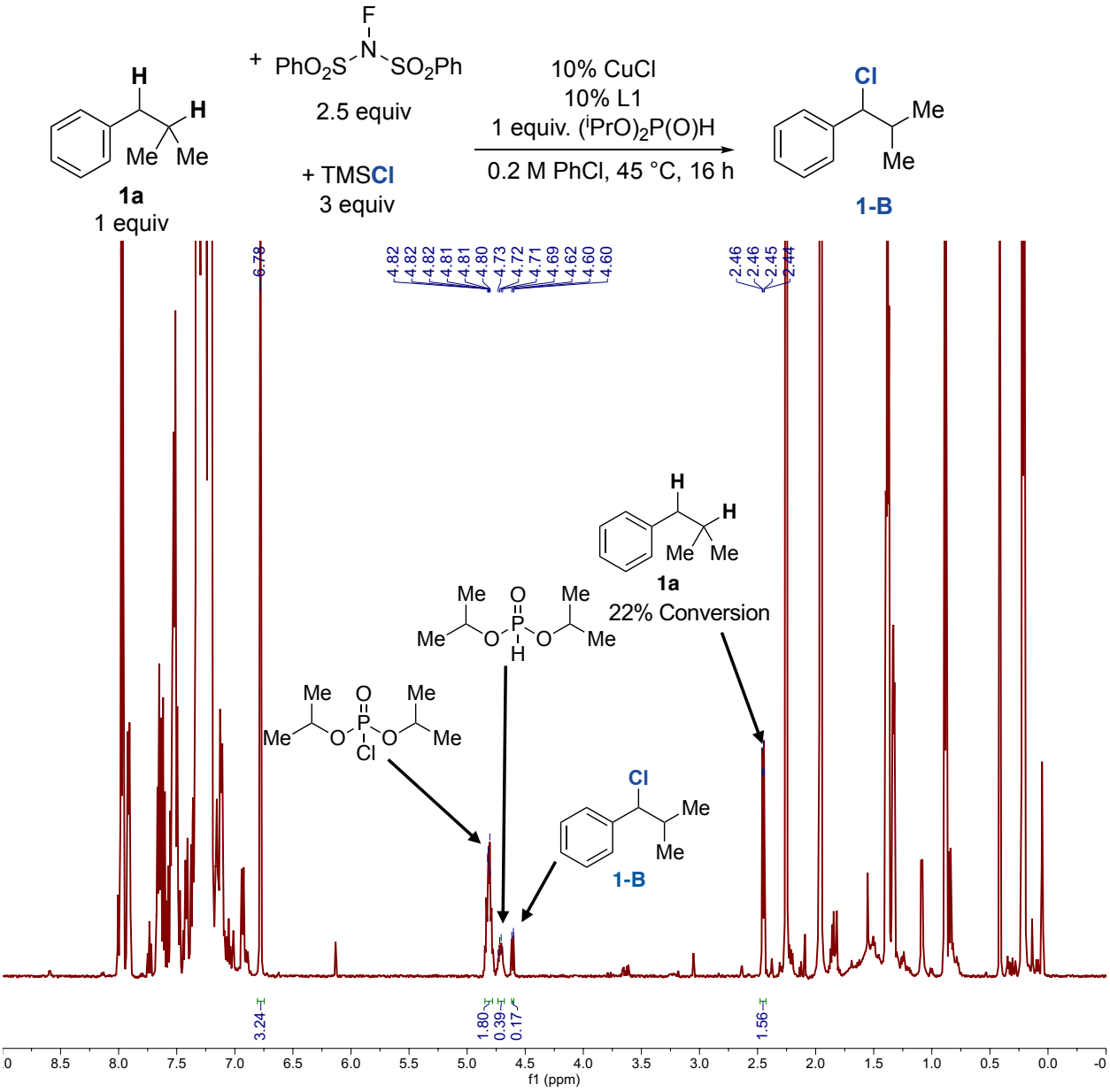


Figure 2A.3. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture for **1-B** following the addition of 0.215 mmol (30 µL) of mesitylene as an external standard (6.78 ppm). The resolved methine protons for diisopropyl chlorophosphate[11] (4.83 ppm, m) and diisopropyl phosphite[12] (4.71 ppm, m) are labeled and integrated. The resolved benzylic protons for both **1-B** (4.62 ppm, d) and 1a (2.45 ppm, d) chlorides are labeled and integrated. [a]Reactions were run on a 0.2 mmol scale. Calibrated ^{1}H NMR yields were determined versus mesitylene as the external standard.

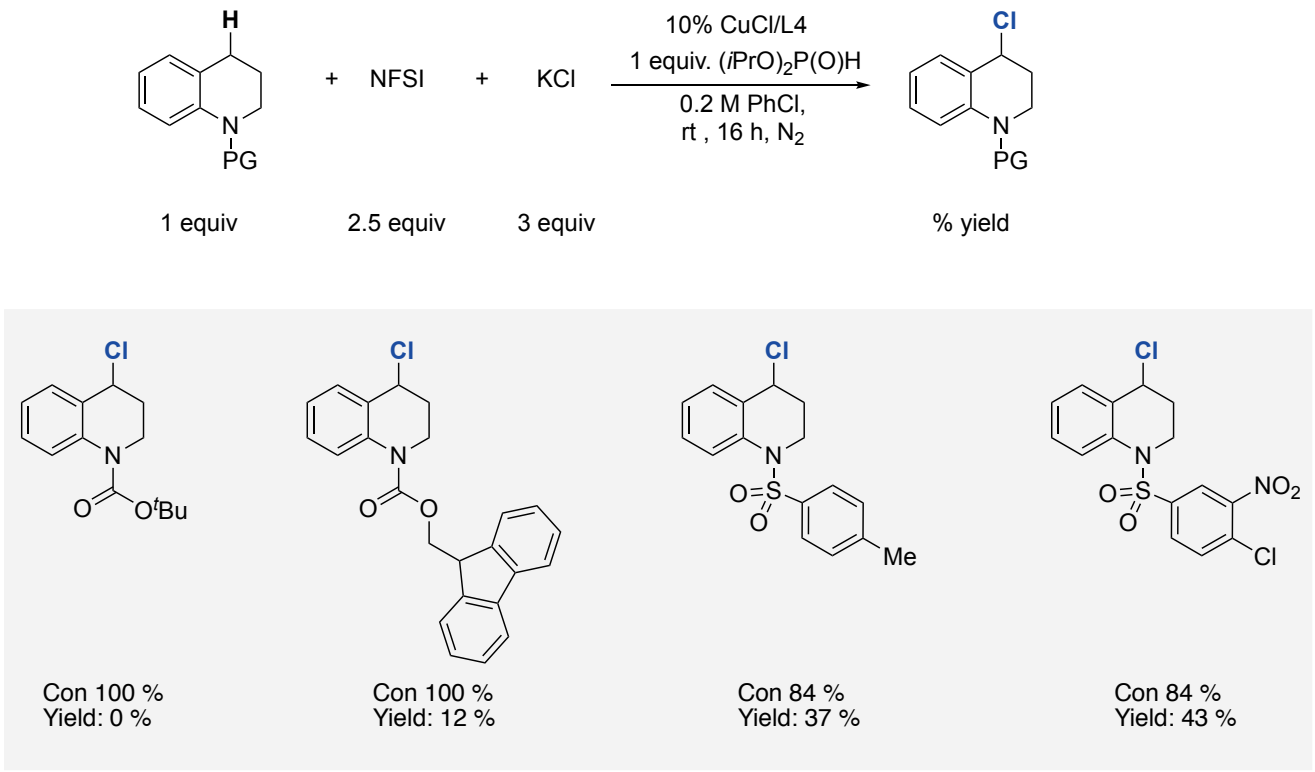


Figure 2A.4. Comparative study of protecting groups on the tetrahydroquinoline substrate. [a]Reactions were run on a 0.2 mmol scale. Calibrated ^{1}H NMR yields were determined versus mesitylene as the external standard.

2A.IV. Procedures for Benzylic Chloride Displacment Experiments

General Procedure I for Chloride Displacement with Phenols and Thiophenols: In the fume hood, a disposable 1 dram vial was charged with (thio)phenol (0.4 mmol, 2 equiv), potassium iodide (KI; 0.21 mmol, 34.9 mg, 1.05 equiv), potassium carbonate (K_2CO_3; 0.41 mmol, 56.7 mg, 2 equiv) and a Teflon stir bar. The vial was subsequently charged with 2 mL of a 0.1 M benzylic chloride stock solution in DMF. The vial was sealed by a PTFE-lined pierceable cap and set to stir at on an aluminum block at 70 ºC and stirred at 750 rpm for 16 h.

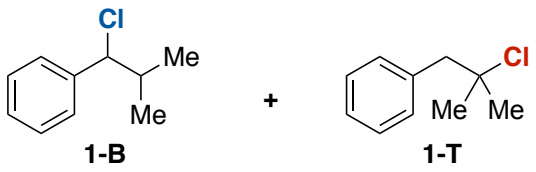
Work Up: After 16 h, mesitylene (0.215 mmol, 30 μL) was added to the crude heterogenous reaction mixture as the external NMR standard. The crude reaction mixture was filtered through a pad of silica directly into a 24 mL vial using dichloromethane (5 mL). An aliquot (30 μL) from the now homogenous solution was taken for NMR analysis to detect formation of product and consumption of starting material. After NMR analysis, crude reaction solution was washed with a 1.0 M NaOH solution (3x). The organic layer was dried with sodium sulfate, filtered through a pad of celite, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography.

General Procedure J for Benzylic Chloride Displacement with Amines: In the fume hood, a disposable 1 dram vial was charged with amine (0.4 mmol, 2 equiv), potassium iodide (KI; 0.21 mmol, 34.9 mg, 1.05 equiv), and a Teflon stir bar. The vial was subsequently charged with 2 mL of a 0.1 M benzylic chloride stock solution in MeCN. The vial was sealed by a PTFE-lined pierceable cap and set to stir at on an aluminum block at 70 ºC and stirred at 700 rpm for 16 h.

Work Up: After 16 h, mesitylene (0.215 mmol, 30 μL) was added to the crude heterogenous reaction mixture as the external NMR standard. The crude reaction mixture was filtered through a pad of silica directly into a 24 mL vial using dichloromethane (5 mL). An aliquot (30 μL) from the now homogenous solution was taken for NMR analysis to detect formation of product and consumption of starting material. After NMR analysis, crude reaction solution was washed with a 1.0 M NaOH solution (3x). The organic layer was dried with sodium sulfate, filtered through a pad of celite, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography.

2A.V. Product Synthesis and Characterization

(1-chloro-2-methylpropyl)benzene **(1-B)**



Reaction conducted using **Procedure G** with isobutylbenzene (67.1 mg, 78.6 µL, 0.5 mmol, 1 equiv). Following workup, crude ^{1}H NMR analysis indicated a mixture composed of 69% yield of the desired chloride (**1-B**), 7% yield of (**1-T**), and complete consumption of starting material (**Figure 2A.5**).

Spectral data for **1** was consistent with reported data.[13]

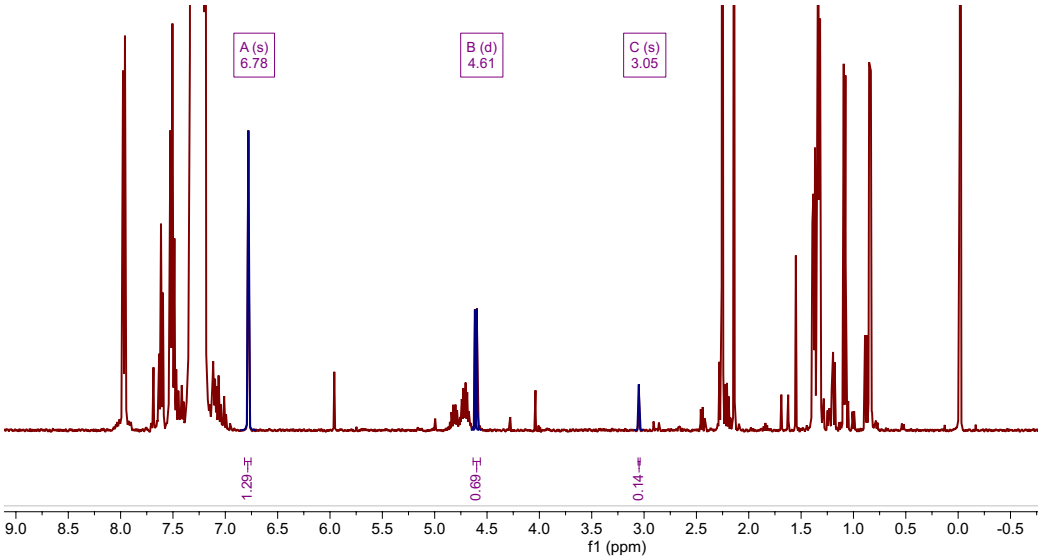
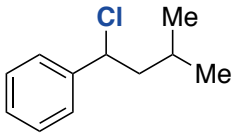


Figure 2A.5. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture for 1 following the addition of 0.215 mmol (30 µL) of mesitylene as an external standard (6.78 ppm). The resolved benzylic protons for both 2-B (4.61 ppm, d) and 2-T (3.05ppm, s) chlorides are labeled and integrated.

(1-chloro-3-methylbutyl)benzene (**2**)



2-B

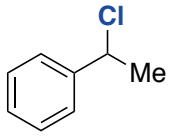
Reaction conducted using **Procedure C** with isopentylbenzene (29.6 mg, 34.7 µL, 0.2 mmol, 1 equiv)

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with 100% heptane to afford a mixture composed of 28.5 mg (78 % yield) of **2-B** and 1.46 mg (4% yield) of **2-T** as a colorless oil. Spectral data for **2-B**. matched those reported in the literature. [14]

NMR Data for **2-B**
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.27 (m, 5H), 4.93 (dd, *J* = 8.8, 6.3 Hz, 1H), 2.07 (ddd, *J* = 13.9, 8.8, 6.2 Hz, 1H), 1.85 (ddd, *J* = 14.0, 7.6, 6.4 Hz, 1H), 1.79 – 1.69 (m, 1H), 0.94 (dd, *J* = 6.6, 4.7 Hz, 6H) ppm

^{13}C NMR (126 MHz, Chloroform-*d*) δ 142.1, 128.6, 128.2, 126.9, 62.1, 48.8, 25.6, 22.4, 21.8 ppm.

(1-chloroethyl)benzene **(3)**



3

Reaction conducted using **Procedure B** with ethylbenzene (0.2 mmol, 21.2 mg, 24.4 µL, 1 equiv). Following workup, crude ^{1}H NMR analysis indicated the product was isolated as a mixture comprised of 13% of remaining C–H starting material and 91% of the desired chloride **3** (**Figure S4**).

Spectral data for **3** was consistent with reported data.[15]

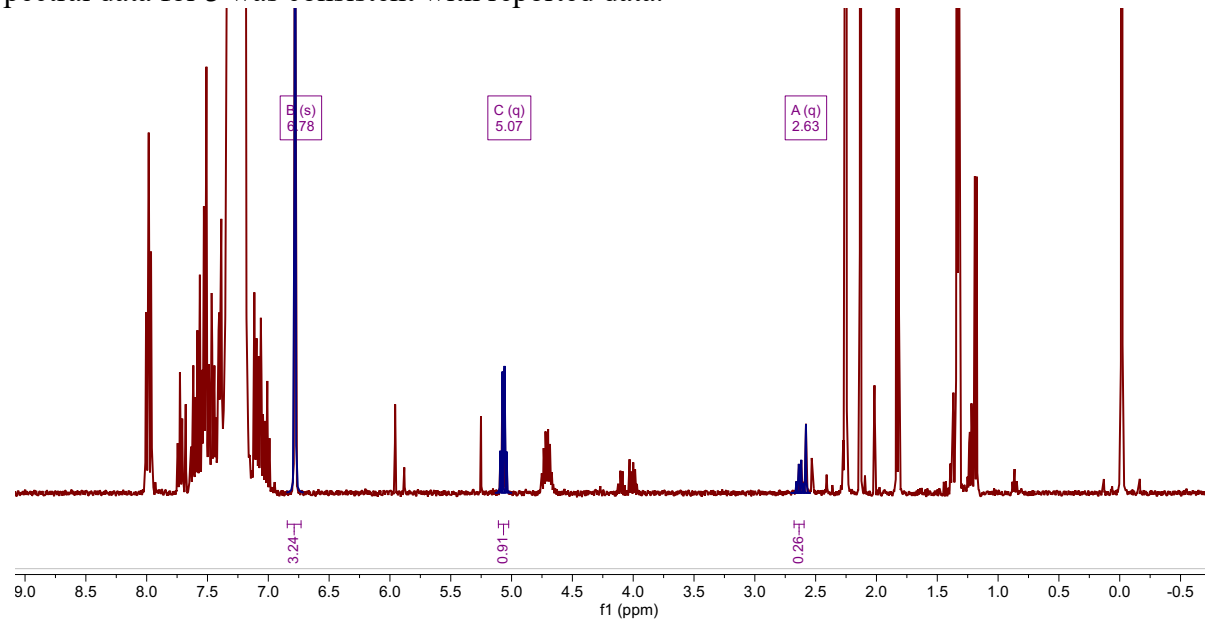
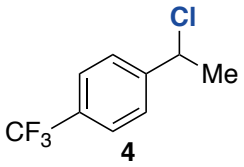


Figure 2A.6 Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture for **3** following the addition of 0.215 mmol (30 µL) of mesitylene as an external standard (6.78 ppm). The resolved benzylic protons of product (5.07 ppm) and starting material (2.63 ppm) are labeled and integrated.

1-(1-chloroethyl)-4-(trifluoromethyl)benzene **(4)**



4

Reaction conducted using **Procedure G** with 4-ethylbenzotrifluoride (0.5 mmol, 87.0 mg, 1 equiv). Following workup, crude ^{1}H NMR analysis indicated the product was isolated as a mixture comprised of 12% of remaining C–H starting material and 69% of the desired chloride **4** (**Figure S5**).

Spectral data for **4** was consistent with reported data.[16]

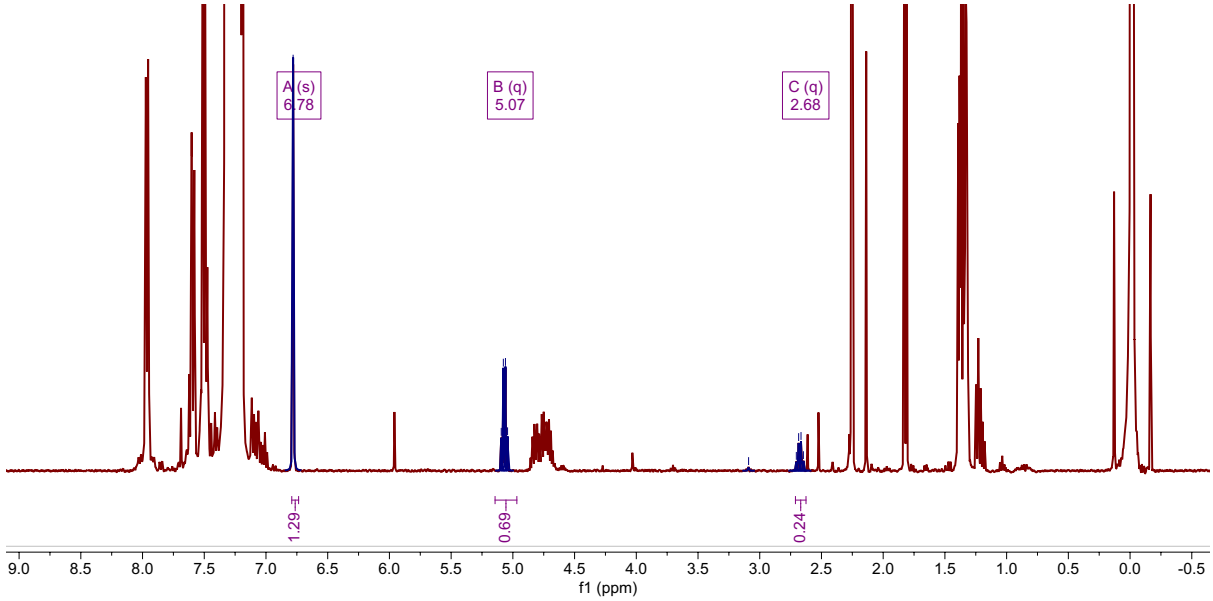
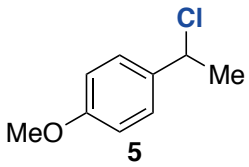


Figure 2A.7 Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture for **4** following the addition of 0.215 mmol (30 µL) of mesitylene as an external standard (6.78 ppm). The resolved benzylic protons of product (5.07 ppm) and starting material (2.68 ppm) are labeled and integrated.

1-(1-chloroethyl)-4-methoxybenzene **(5)**



5

Reaction conducted using **Procedure A** with 4-ethylanisole (34.8 mg, 36.3 µL, 0.2 mmol, 1 equiv). Following workup, crude ^{1}H NMR analysis indicated 24% yield of the desired chloride **5**, 50% yield of the sulfonimide side-product, and complete consumption of starting material (**Figure S6**).

Spectral data for **5** was consistent with reported data.[17]

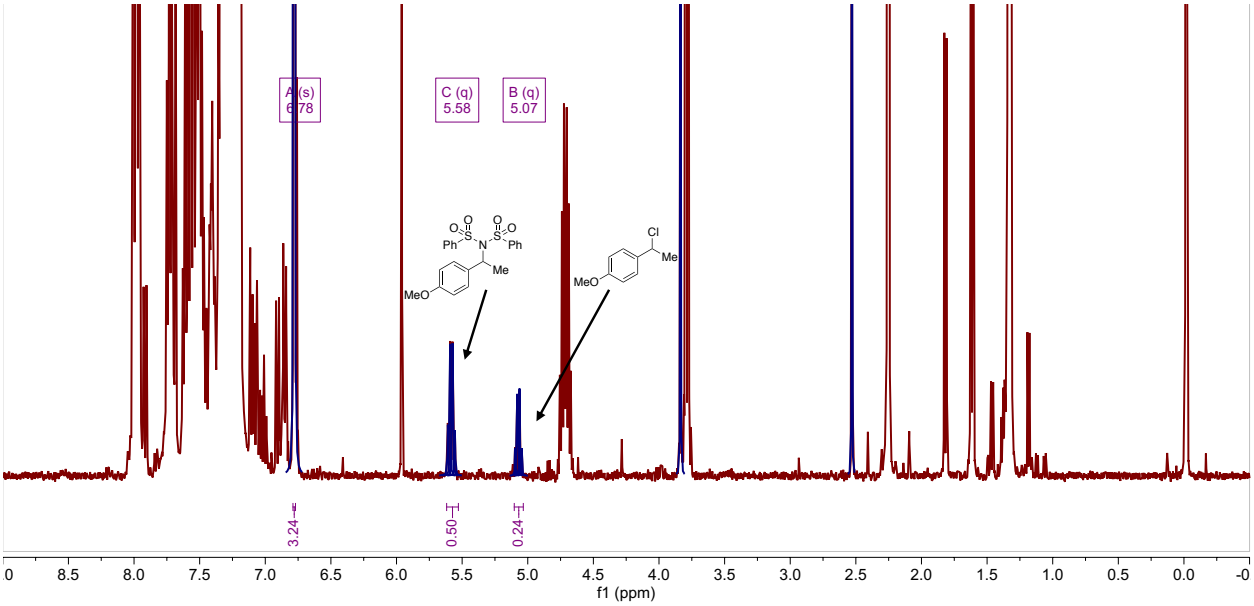
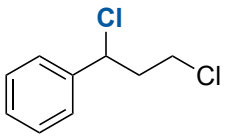


Figure 2A.8 Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture for **5** following the addition of 0.215 mmol (30 µL) of mesitylene as an external standard (6.78 ppm). The resolved benzylic protons (5.07 ppm) of product and sulfonamide side-product (5.58 ppm) are labeled and integrated.

(1,3-dichloropropyl)benzene **(6)**



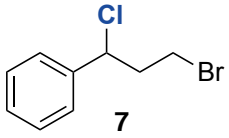
6

Reaction conducted using **Procedure G** with (3-chloropropyl)benzene (77.4 mg, 74.4 µL, 0.5 mmol, 1 equiv)

The obtained residue was purified by column chromatography on silica gel eluting with 100% heptane to afford a mixture comprised of 78 mg (84 % yield) of **6** and 5.4 mg (7% recovered) of unreacted C–H starting material as a clear light-yellow oil. Spectral data matched those reported in the literature.[18]

NMR Spectroscopy:
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43–7.28 (m, 5H), 5.14 (dd, *J* = 9.0, 5.4 Hz, 1H), 3.75 (ddd, *J* = 11.1, 8.1, 5.1 Hz, 1H), 3.55 (ddd, *J* = 11.1, 8.1, 5.1 Hz, 1H), 2.55 (ddt, *J* = 14.6, 9.0, 5.5 Hz, 1H), 2.41 (ddt, *J* = 14.6, 8.1, 5.5 Hz, 1H) ppm.
^{13}C NMR (101 MHz, Chloroform-*d*) δ 140.5, 128.9, 128.7, 127.0, 60.0, 42.3, 41.8 ppm.

(3-bromo-1-chloropropyl)benzene **(7)**



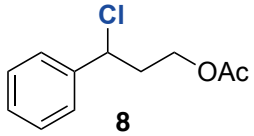
7

Reaction conducted using **Procedure G** with (3-bromopropyl)benzene (99.5 mg, 75.9 µL, 0.5 mmol, 1 equiv)

The obtained residue was purified by column chromatography on silica gel eluting with 100% heptane to afford 94.3 mg (81 % yield) of **7** and 7.84 mg (9% yield) of unreacted C–H starting material as a clear light-yellow oil. Spectral data matched those reported in the literature.[5]

NMR Spectroscopy:
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45–7.28 (m, 6H), 5.12 (dd, *J* = 8.8, 5.4 Hz, 1H), 3.59 (ddd, *J* = 10.3, 8.0, 5.5 Hz, 1H), 3.46–3.36 (m, 1H), 2.63 (ddt, *J* = 14.7, 8.9, 5.8 Hz, 1H), 2.48 (ddt, *J* = 14.8, 8.0, 5.6 Hz, 1H) ppm.
^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.5, 128.9, 128.7, 127.0, 61.1, 42.4, 30.1 ppm.

3-chloro-3-phenylpropyl acetate **(8)**



8

Reaction conducted using **Procedure C** with 3-phenylpropyl acetate (35.6 mg, 0.2 mmol, 1 equiv).

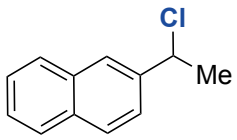
The obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (10:90 (v:v)) to afford 79.8 mg (75 % yield) of **8** as a clear light-yellow oil. Spectral data matched those reported in the literature.[5]

NMR Spectroscopy:

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.30 (m, 5H), 5.00 (dd, *J* = 8.7, 5.9 Hz, 1H), 4.24 (ddd, *J* = 11.3, 7.6, 5.4 Hz, 1H), 4.14 (dt, *J* = 11.4, 5.8 Hz, 1H), 2.50 – 2.28 (m, 2H), 2.05 (s, 3H) ppm.

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.9, 141.0, 128.8, 128.6, 126.9, 61.6, 59.9, 38.7, 20.9 ppm.

2-(1-chloroethyl)naphthalene (**9**)



9

Reaction conducted using **Procedure E** with 2-ethylnaphthalene (78.1 mg, 78.7 µL, 0.5 mmol, 1 equiv).

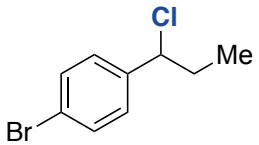
The crude residue was purified by column chromatography on silica gel eluting with a 100% heptane to afford 92.5 mg (97 % yield) of **9** as a white solid. Spectral data matched those reported in the literature[17]

NMR Spectroscopy:

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.88 – 7.80 (m, 4H), 7.57 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.51 – 7.45 (m, 2H), 5.27 (q, *J* = 6.8 Hz, 1H), 1.94 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.1, 133.1, 133.1, 128.7, 128.1, 127.7, 126.4, 126.4, 125.2, 124.5, 59.1, 26.4 ppm.

Bromo-4-(1-chloropropyl)benzene **(10)**



10

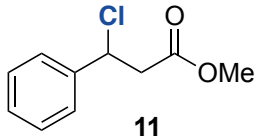
Reaction conducted using **Procedure C** with 1-bromo-4-propylbenzene (38.8. mg, 30.9 µL, 0.2 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with 100% hexanes to afford 35.0 mg (75 % yield) of **10** as a colorless oil.

NMR Spectroscopy:
^{1}H NMR (500 MHz, Chloroform-d) δ 7.47 (d, 2H), 7.24 (d, 2H), 4.72 (dd, J = 7.9, 6.5 Hz, 1H), 2.15 – 1.97 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H) ppm.
^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.8, 131.8, 128.8, 122.1, 64.5, 33.2, 11.7 ppm.

HRMS (ESI) m/z: [M-Cl]+ Calcd for C9H10Br, 196.9960; Found 196.9961.

Methyl 3-chloro-3-phenylpropanoate **(11)**



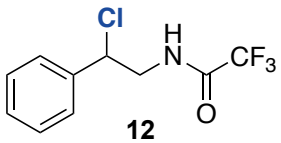
11

Reaction conducted using **Procedure C** with methyl 3-phenylpropanoate (0.2 mmol, 32.8 mg, 31.6 µL, 1 equiv)

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with with a solvent mixture of ethyl acetate:hexanes (10:90 (v:v)) to afford 28.6 mg (72 % yield) of **11** as a clear colorless oil. Spectral data matched those reported in the literature.[19]

NMR Spectroscopy:
^{1}H NMR (400 MHz, Chloroform-d) δ 7.43 – 7.29 (m, 5H), 5.36 (dd, J = 9.1, 5.7 Hz, 1H), 3.71 (s, 3H), 3.20 (dd, J = 16.0, 9.1 Hz, 1H), 3.04 (dd, J = 16.0, 5.7 Hz, 1H) ppm.
^{13}C NMR (101 MHz, Chloroform-d) δ 170.1, 140.3, 128.8, 128.8, 126.9, 58.0, 52.1, 44.7 ppm.

N-(2-chloro-2-phenylethyl)-2,2,2-trifluoroacetamide **(12)**



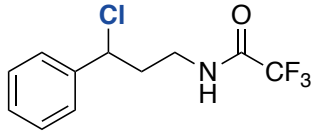
12

Reaction conducted using **Procedure C** with 2,2,2-trifluoro-N-phenethylacetamide (0.2 mmol, 43.4 mg, 1 equiv)

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (7:93 (v:v)) to afford 35.2 mg (70 % yield) and 1.74 mg (4%) of C–H starting material as a white solid.

NMR Spectroscopy:
^{1}H NMR (400 MHz, Chloroform-d) δ 7.40 – 7.30 (m, 5H), 6.64 (s, 1H), 5.01 (dd, J = 9.0, 4.9 Hz, 1H), 3.94 (ddd, J = 14.3, 7.0, 4.9 Hz, 1H), 3.69 5(ddd, J = 14.2, 9.0, 5.3 Hz, 1H) ppm.
^{13}C NMR (101 MHz, Chloroform-d) δ 157.3 (q, J = 37.7 Hz), 137.5, 129.3, 129.1, 127.0, 114.2 (q, J = 288.2), 60.8, 47.1 ppm.
^{19}F NMR (377 MHz, Chloroform-*d*) δ -75.92 ppm.
HRMS (ESI) m/z: [M+Na]+ Calcd for C10H9ClF3NONa 274.0217; Found 274.0213.

N-(3-chloro-3-phenylpropyl)-2,2,2-trifluoroacetamide **(13)**



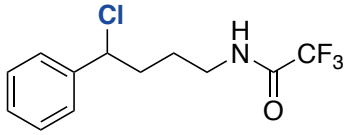
13

Reaction conducted using **Procedure H** with 2,2,2-trifluoro-N-(3-phenylpropyl)acetamide (0.2 mmol, 46.2 mg, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (10:90 (v:v)) to afford a mixture comprised of 283.7 g (72 % yield) of **13** and 47.2 mg (17%) of recovered C–H starting material as a white solid.

NMR Spectroscopy:
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.25 (m, 5H), 6.41 (s, 1H), 4.92 (dd, *J* = 7.7, 6.6 Hz, 1H), 3.66-3.44 (m, 2H), 2.43 – 2.27 (m, 2H) ppm.
^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.4 (q, *J* = 37.1 Hz), 140.5, 129.0, 128.9, 126.8, 115.7 (q, *J* = 287.8 Hz), 60.9, 38.7, 37.9 ppm.
^{19}F NMR (377 MHz, Chloroform-*d*) δ -75.96 ppm.
HRMS (ESI) m/z: [M-H]- Calcd for C11H10ClF3NO 264.0409; Found 264.0409.

N-(4-chloro-4-phenylbutyl)-2,2,2-trifluoroacetamide **(14)**



14

Reaction conducted using **Procedure C** with 2,2,2-trifluoro-*N*-(4-phenylbutyl)acetamide (0.2 mmol, 49.1 mg, 1 equiv)

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (15:85 (v:v)) to afford a mixture of **14**, C–H starting material, and diisopropyl chlorophosphate. The mixture was further purified by preparatory thin layer chromatography eluting with a solvent mixture of ethyl acetate:hexanes (10:90 (v:v)) to afford 41.4 mg (74%) of **14** as a white solid.

NMR Spectroscopy:

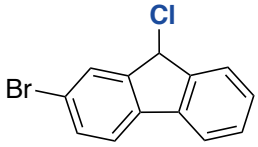
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39-7.29 (m, 5H), 6.27 (s, 1H), 4.88 (dd, *J* = 8.4, 5.9 Hz, 1H), 3.46-3.34 (m, 2H), 2.22 – 2.12 (m, 1H), 2.11 – 2.02 (m, 1H), 1.88 – 1.75 (m, 1H), 1.73 – 1.60 (m, 1H) ppm.

^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.1 (q, *J* = 37.0 Hz), 141.1, 128.8, 128.5, 115.8 (q, *J* = 288.0 Hz), 62.8, 39.3, 37.0, 26.7 ppm.

^{19}F NMR (377 MHz, Chloroform-d) δ -75.90 ppm.

HRMS (ESI) m/z: [M+Na]+ Calcd for C12H13ClF3NONa 302.05300; Found 302.0527.

2-bromo-9-chloro-9*H*-fluorene **(15)**



15

Reaction conducted using **Procedure E** with 2-bromo-9H-fluorene (0.5 mmol, 49.0 mg, 1 equiv)

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with 100% heptane to afford 110.4 mg (79 % yield) of **15** as a white solid.

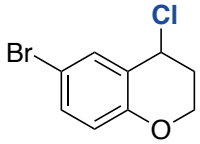
NMR Spectroscopy:

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.81 (s, 1H), 7.67 (t, *J* = 7.1 Hz, 2H), 7.57 (d, *J* = 1.2 Hz, 2H), 7.47-7.38 (m, 2H), 5.79 (s, 1H) ppm.

^{13}C NMR (126 MHz, Chloroform-*d*) δ 145.8, 143.5, 139.0, 132.5, 129.6, 129.2, 128.4, 125.9, 121.6, 121.4, 120.2, 56.8 ppm.

HRMS (ESI) m/z: [M-Cl]+ Calcd for C13H8Br 242.9804; Found 242.9804.

6-bromo-4-chlorochromane **(16)**



16

Reaction conducted using **Procedure F** with 6-bromochroman (0.5 mmol, 106.5 mg, 1 equiv)

Following workup, the obtained residue was purified by column chromatography on silica gel luting with ethyl acetate:hexanes (5:95 (v:v)) to afford 92.8 mg (75 % yield) of **16** as a colorless oil.

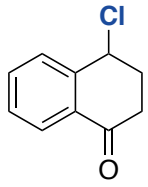
NMR Spectroscopy:

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 2.5 Hz, 1H), 7.34 – 7.27 (m, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 5.17 (t, *J* = 3.7 Hz, 1H), 4.45 (td, *J* = 11.5, 2.2 Hz, 1H), 4.39 – 4.28 (m, 1H), 2.49-2.39 (m, 1H), 2.34 – 2.26 (m, 1H) ppm.

^{13}C NMR (101 MHz, Chloroform-*d*) δ 153.2, 133.1, 133.1, 124.0, 119.3, 112.5, 61.8, 51.9, 31.6 ppm.

HRMS (ESI) m/z: [M+H]+ Calcd for C9H9BrClO 245.9442; Found 245.043.

4-chloro-3,4-dihydronaphthalen-1(2*H*)-one **(17)**



17

Reaction conducted using **Procedure F** with 3,4-dihydronaphthalen-1(2H)-one (0.5 mmol, 73.1 mg, 1 equiv)

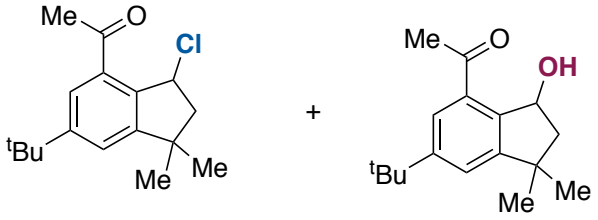
Following workup, the obtained residue was purified by column chromatography on silica gel eluting with ethyl acetate:hexanes (10:90 (v:v)) to afford 54.2 mg (60 % yield) of **17** as a light yellow oil. Spectral data matched those reported in the literature.[5]

NMR Spectroscopy:

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 7.8, 1H), 7.62-7.55 (m, 1H), 7.51 – 7.41 (m, 2H), 5.38 (t, *J* = 3.8 Hz, 1H), 3.16 (m, 1H), 2.81 – 2.42 (m, 3H) ppm.

^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.3, 142.2, 134.2, 131.1, 129.3, 129.0, 127.4, 56.6, 33.96, 31.8 ppm.

1-(6-(*tert*-butyl)-3-chloro-1,1-dimethyl-2,3-dihydro-1*H*-inden-4-yl)ethan-1-one **(18)** and 1-(6-(*tert*-butyl)-3-hydroxy-1,1-dimethyl-2,3-dihydro-1*H*-inden-4-yl)ethan-1-one **(18-OH)**



18
Quantitative
(^{1}H-NMR Yield)

18a

Reaction conducted using **Procedure A** with 1-(6-(tert-butyl)-1,1-dimethyl-2,3-dihydro-1H-inden-4-yl)ethan-1-one (0.2 mmol, 48.9 mg, 1 equiv) Due to the instability of **18**, it was converted and isolated as the alcohol.

Work Up/Hydroxylation: After 16 h, mesitylene (0.215 mmol, 30 µL) was added to the green-colored heterogenous solution as an external NMR standard. The crude reaction mixture was filtered through a pad of celite directly into a 10 mL test tube using $CHCl_3$. An aliquot (30 µL) from the now clear light-green solution was taken for NMR analysis to detect formation of product and consumption of starting material. After NMR analysis, the crude reaction mixture was concentrated on the rotovap at room temperature to remove solvent (chlorobenzene and chloroform). NMR analysis indicated quantitative yield of the desired chloride (**Figure 2A.9.**). To the concentrated residue was added SiO_2 (0.6 mmol, 36.0 mg, 3 equiv) and H_2O:Acetone (1:1 (v:v), 1 mL, c = 0.2 M). The reaction mixture was stirred for 1 h on an aluminum heat block at 30 ºC. The reaction mixture was concentrated on the rotovap and purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (10:90 (v:v)) to afford 49.4 mg of **18-OH** as a colorless solid (95% yield). Spectral data matched those reported in the literature.[20]

NMR Spectroscopy for **18a**

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 1.7 Hz, 1H), 7.43 (d, *J* = 1.7 Hz, 1H), 5.38 (ddd, *J* = 7.6, 3.9, 1.9 Hz, 1H), 4.52 (d, *J* = 2.0 Hz, 1H), 2.68 (s, 3H), 2.29 (dd, *J* = 13.5, 7.6 Hz, 1H), 2.05 (dd, *J* = 13.5, 3.9 Hz, 1H), 1.40 (s, 3H), 1.37 (s, 8H), 1.26 (s, 3H) ppm.

^{13}C NMR (151 MHz, Chloroform-*d*) δ 202.8, 154.4, 152.3, 142.3, 133.7, 126.7, 124.9, 73.2, 48.8, 42.9, 34.9, 31.4, 31.0, 29.9, 28.0 ppm.

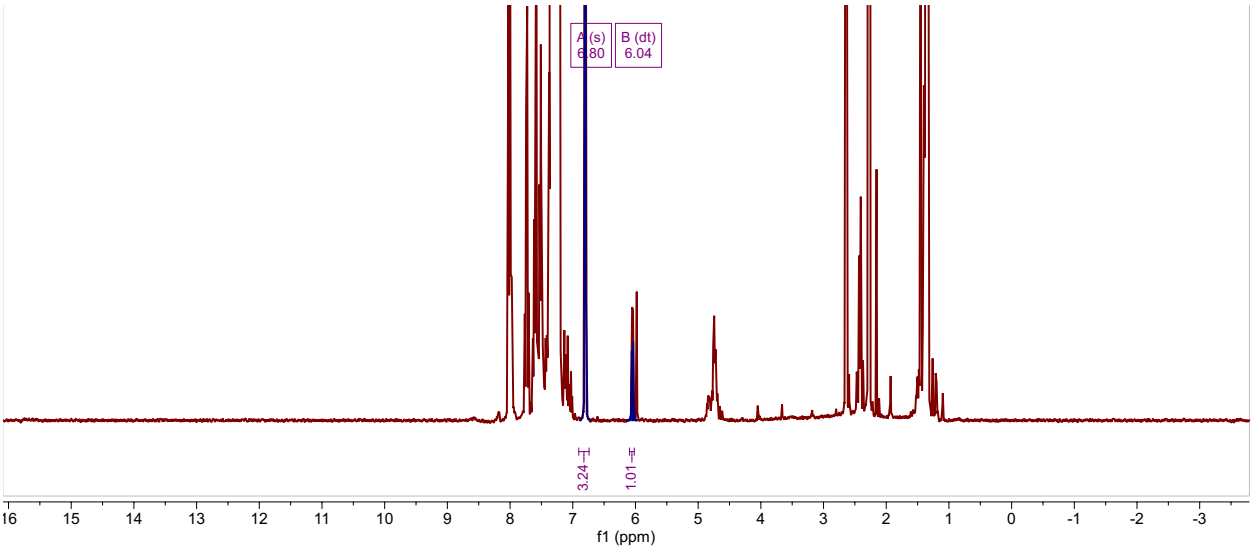
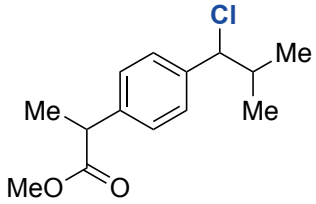


Figure 2A.9. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture for **18** following the addition of 0.215 mmol (30 µL) of mesitylene as an external standard (6.80 ppm). The resolved benzylic protons of product (6.04 ppm) are labeled and integrated.

Methyl 2-(4-(1-chloro-2-methylpropyl)phenyl)propanoate **(19)**



19

Reaction conducted using **Procedure C** with methyl 2-(4-isobutylphenyl)propanoate (0.2 mmol, 44.0 mg, 1 equiv)

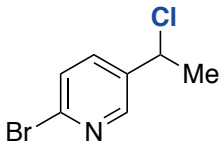
Following workup, the obtained residue was purified by column chromatography on silica gel eluting with ethyl acetate:hexanes (10:90 (v:v)) to afford 26.5 mg (52 % yield) of 19 as a colorless oil. Spectral data matched those reported in the literature. [21]

NMR Spectroscopy:

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.18 (m, 5H), 4.62 (d, *J* = 7.6 Hz, 1H), 3.72 (q, *J* = 7.2 Hz, 1H), 3.66 (s, 3H), 2.28 – 2.17 (m, 1H), 1.49 (d, *J* = 7.2 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H) ppm.

^{13}C-NMR (101 MHz, Chloroform-d) δ 174.9, 140.2, 139.9, 127.7, 127.6, 70.5, 52.09, 45.1, 36.6, 20.2, 19.6, 18.6 ppm.

(2-bromo-5-(1-chloroethyl)pyridine **(20)**



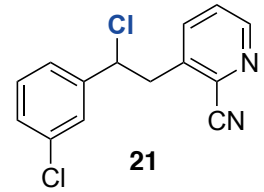
20

Reaction conducted using **Procedure D** with 2-bromo-5-ethylpyridine (0.2 mmol, 40.8 mg, 1 equiv)

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with ethyl acetate:hexanes (5:95 (v:v)) to afford 14.9 mg (34 % yield) of **21** as a colorless oil.

NMR Spectroscopy:
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.38 (d, *J* = 2.6 Hz, 1H), 7.65 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.53 – 7.41 (m, 1H), 5.06 (q, *J* = 6.8 Hz, 1H), 1.84 (d, *J* = 6.9 Hz, 3H) ppm.
^{13}C NMR (126 MHz, Chloroform-*d*) δ 148.2, 141.8, 137.8, 128.2, 54.7, 26.2 ppm.
HRMS (ESI) m/z: [M+H]+ Calcd for C7H8BrClN 219.9523; Found 219.9523.

3-(2-chloro-2-(3-chlorophenyl)ethyl)picolinonitrile **(21)**



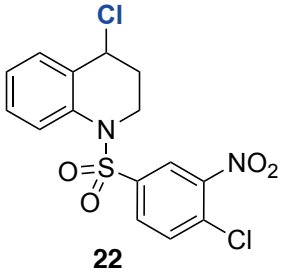
21

Reaction conducted using **Procedure D** with 3-(3-chlorophenethyl)picolinonitrile (0.2 mmol, 48.5 mg, 1 equiv)

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with hexane: ethyl acetate (90:10 (v:v)) to afford 21.2 mg (38% yield) of **21** and 5.82 mg (12%) of remaining starting material as a yellow solid.

NMR Spectroscopy:
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.64 (dd, *J* = 4.7, 1.6 Hz, 1H), 7.69 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.47 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.45 (q, *J* = 1.5 Hz, 1H), 7.34 – 7.29 (m, 3H), 5.12 (dd, *J* = 9.4, 5.1 Hz, 1H), 3.57 (dd, *J* = 14.5, 5.0 Hz, 1H), 3.48 (dd, *J* = 14.5, 9.4 Hz, 1H) ppm.
^{13}C NMR (126 MHz, Chloroform-*d*) δ 149.8, 141.8, 138.8, 137.7, 134.8, 134.4, 130.2, 129.1, 127.1, 126.5, 125.1, 116.0, 61.2, 43.3 ppm.
HRMS (ESI) m/z: [M+H]+ Calcd for C14H11Cl2N2; 277.0293 Found 277.0291.

4-chloro-1-((4-chloro-3-nitrophenyl)sulfonyl)-1,2,3,4-tetrahydroquinoline **(22)**



22

Reaction conducted using **Procedure B** with 1-((4-chloro-3-nitrophenyl)sulfonyl)-1,2,3,4-tetrahydroquinoline (0.2 mmol, 70.5 mg, 1 equiv)

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with ethyl acetate:hexanes (5:95 (v:v)) to afford 31.0 mg (40 % yield) of **22** as a colorless oil.

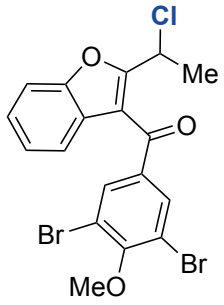
NMR Spectroscopy:

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 2.1 Hz, 1H), 7.87 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.71 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.34 (ddd, *J* = 8.6, 7.3, 1.7 Hz, 1H), 7.29 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.18 (td, *J* = 7.6, 1.2 Hz, 1H), 5.07 (t, *J* = 3.6 Hz, 1H), 4.24 (dtd, *J* = 13.1, 3.8, 3.2, 1.0 Hz, 1H), 2.25 (dq, *J* = 14.7, 3.4 Hz, 1H), 2.12 (ddt, *J* = 14.7, 12.1, 4.3 Hz, 1H) ppm.

^{13}C NMR (126 MHz, Chloroform-*d*) δ 147.7, 138.7, 134.9, 132.9, 132.1, 131.0, 130.6, 130.0, 128.9, 125.7, 124.5, 123.3, 54.1, 42.5, 31.0 ppm.

HRMS (ESI) m/z: [M+H]+ Calcd for C15H13Cl2N2O4S; 386.9968; Found 386.9961.

(2-(1-chloroethyl)benzofuran-3-yl)(3,5-dibromo-4-methoxyphenyl)methanone **(23)**



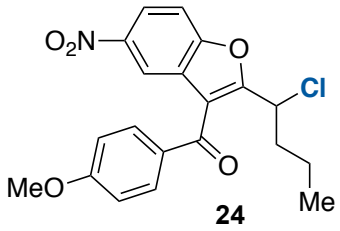
23

Reaction conducted using **Procedure B** with (3,5-dibromo-4-methoxyphenyl)(2-ethylbenzofuran-3-yl)methanone (0.2 mmol, 87.6.6 mg, 1 equiv)

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with hexane: ethyl acetate (93:7 (v:v)) to afford 62.3 mg (68 % yield) of **23** and 8 mg (8%) of elimination side product as a colorless solid.

NMR Spectroscopy:
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.02 (s, 2H), 7.60 – 7.51 (m, 1H), 7.42 – 7.34 (m, 2H), 7.26 (td, *J* = 7.4, 1.0 Hz, 1H), 5.36 (q, *J* = 6.9 Hz, 1H), 3.96 (s, 3H), 1.93 (d, *J* = 6.9 Hz, 3H) ppm.
^{13}C NMR (126 MHz, Chloroform-*d*) δ 186.2, 159.3, 157.3, 153.0, 135.2, 132.9, 125.2, 124.5, 123.4, 120.7, 117.7, 115.0, 110.9, 59.9, 47.5, 22.1 ppm.
HRMS (ESI) m/z: [M+H]+ Calcd for C18H14Br2ClO3 470.8993; Found 470.8997.

(2-(1-chlorobutyl)-5-nitrobenzofuran-3-yl)(4-methoxyphenyl)methanone **(24)**



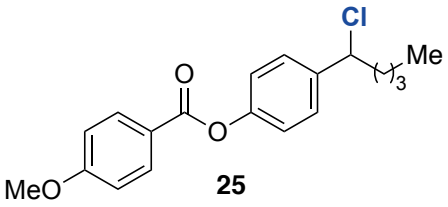
24

Reaction conducted using **Procedure H** with (2-butyl-5-nitrobenzofuran-3-yl)(4-methoxyphenyl)methanone (0.2 mmol, 70.6 mg, 1 equiv)

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with hexane: ethyl acetate (90:10 (v:v)) to afford 414.2 mg (89 % yield) of **24** as a sticky/oily residue.

NMR Spectroscopy:
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.38 (d, *J* = 2.3 Hz, 1H), 8.31 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.67 (d, *J* = 9.1 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 5.21 (t, *J* = 7.6 Hz, 1H), 3.93 (s, 3H), 2.35 – 2.16 (m, 3H), 1.53 – 1.45 (m, 1H), 1.33 (ddt, *J* = 13.5, 8.2, 6.8 Hz, 1H), 0.92 (t, *J* = 7.4 Hz, 3H) ppm.
^{13}C NMR (126 MHz, Chloroform-*d*) δ 187.9, 164.5, 161.2, 156.5, 144.9, 132.0, 130.3, 127.0, 121.6, 118.6, 118.4, 114.3, 112.2, 55.7, 52.4, 38.5, 20.0, 13.2 ppm.
HRMS (ESI) m/z: [M+Na]+ Calcd for C20H18ClNO5Na 410.0766; Found 410.0766.

4-(1-chloropentyl)phenyl 4-methoxybenzoate methoxybenzoate **(25)**



25

Reaction conducted using **Procedure B** with 4-pentylphenyl 4-methoxybenzoate (0.2 mmol, 59.6 mg, 1 equiv)

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with hexane: ethyl acetate (90:10 (v:v)) to afford 54.6 mg (82 % yield) of **25** as a white solid.

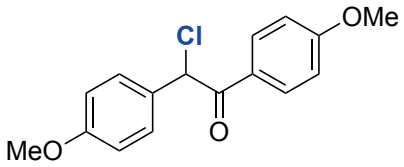
NMR Spectroscopy:

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 8.9 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 2H), 4.88 (dd, *J* = 8.1, 6.5 Hz, 1H), 3.90 (s, 3H), 2.18 – 2.09 (m, 1H), 2.05 (dddd, *J* = 13.8, 9.9, 6.5, 5.2 Hz, 1H), 0.91 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.77, 163.99, 150.75, 139.46, 132.33, 128.10, 121.90, 121.74, 113.89, 63.24, 55.54, 39.84, 29.21, 22.14, 13.91 ppm.

HRMS (ESI) m/z: [M+Na]+ Calcd for C19H21ClO3Na 355.10714; Found 355.106.

2-chloro-1,2-bis(4-methoxyphenyl)ethan-1-one **(26)**



26

Reaction conducted using **Procedure A** with 1,2-bis(4-methoxyphenyl)ethan-1-one (0.2 mmol, 51.3 mg, 1 equiv)

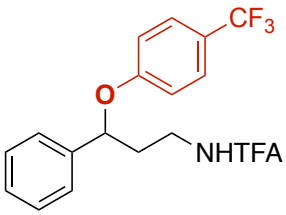
Following workup, the obtained residue was purified by column chromatography on silica gel eluting with dichloromethane: ethyl acetate (90:10 (v:v)) to afford 48.2 mg (83 % yield) of **27** as a colorless oil. Spectral data matched those reported in the literature.[22]

NMR Spectroscopy:

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.90 (m, 2H), 7.44 – 7.36 (m, 2H), 6.93 – 6.85 (m, 4H), 6.28 (s, 1H), 3.84 (s, 3H), 3.79 (s, 3H) ppm.

^{13}C NMR (101 MHz, Chloroform-*d*) δ 190.0, 163.9, 160.1, 131.5, 129.8, 128.3, 127.2, 114.6, 114.0, 62.1, 55.5, 55.3 ppm.

2,2,2-trifluoro-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)acetamide **(27)**



27

Reaction conducted using **Procedure I** with p 4-Trifluoromethylphenol (0.4 mmol, 64.8 mg 2 equiv) Following workup, the obtained residue was purified by column chromatography on silica gel eluting with eluting with a solvent mixture of ethyl acetate:hexanes (08:92 (v:v)) to afford 39.13 mg of **27** as a light-yellow oil (50% yield).

NMR Spectroscopy:

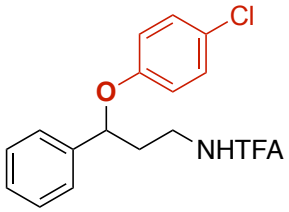
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 8.7 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.32-7.28 (m, 3H), 6.88 (d, J = 8.6 Hz, 2H), 6.76 (s, 1H), 5.33 (dd, J = 6.6, 5.3 Hz, 1H), 3.66 – 3.51 (m, 2H), 2.28 – 2.23 (m, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7 (d, J = 1.5 Hz), 156.0 (q, J = 36.9 Hz), 138.4, 128.1, 127.4, 126.0 (q, J = 3.8 Hz), 124.5, 123.2 (q, J = 271.63 Hz), 122.6 (q, J = 32.8 Hz), 114.9 (q, J = 287.12 Hz), 114.6, 78.3, 36.2, 36.0 ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ -61.71, -76.01 ppm.

HRMS (ESI) m/z: [M+Na]+ Calcd for C18H15F6NO2Na 414.0899; Found 414.0895.

N-(3-(4-chlorophenoxy)-3-phenylpropyl)-2,2,2-trifluoroacetamide (**28**)

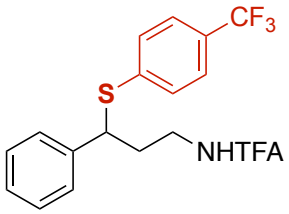


28

Reaction conducted using **Procedure I** with 4-chlorophenol (0.4 mmol, 51.42 mg, 2 equiv) Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (08:92 (v:v)) to afford 35.06 mg of **28** as a light-yellow oil (49% yield).

NMR Spectroscopy:
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 2H), 7.32 – 7.28 (m, 3H), 7.16 – 7.11 (m, 2H), 6.75 – 6.71 (m, 2H), 5.24 (t, *J* = 6.0 Hz, 1H), 3.65-3.48 (m, 2H), 2.21 (q, *J* = 6.5 Hz, 2H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0 (q, *J* = 36.8 Hz), 154.7, 138.7, 128.4, 128.0, 127.3, 125.4, 124.6, 114.8 (q, *J* = 288.17 Hz), 116.0, 78.6, 36.3, 35.9. (q, *J* = 271.63 Hz), 122.6 (q, *J* = 32.8 Hz), 114. (q, *J* = 287.12 Hz), 114.6, 78.3, 36.2, 36.0 ppm.
^{19}F NMR (377 MHz, $CDCl_3$) δ -76.02 ppm.
HRMS (ESI) m/z: [M+Na]+ Calcd for C17H15ClF3NO2Na 380.0636; Found 380.0632.

2,2,2-trifluoro-*N*-(3-phenyl-3-((4-(trifluoromethyl)phenyl)thio)propyl)acetamide (**29**)

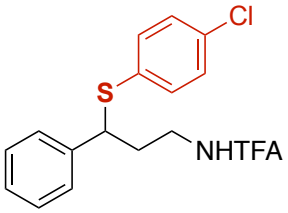


29

Reaction conducted using **Procedure I** with 4-trifluoromethylbenzenethiol (0.4 mmol, 71.27 mg 2 equiv). Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (10:90 (v:v)) to afford 53.77 mg of **29** as a white solid (66% yield).

NMR Spectroscopy:
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.1 Hz, 2H), 7.33 – 7.22 (m, 7H), 6.24 (s, 1H), 4.24 (dd, *J* = 8.4, 6.5 Hz, 1H), 3.48 (dq, *J* = 13.5, 6.7 Hz, 1H), 3.35 (dq, *J* = 13.4, 6.6 Hz, 1H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.3 (q, *J* = 37.0 Hz), 140.3, 139.5 (d, *J* = 1.4 Hz), 131.3, 129.2 (q, *J* = 32.73 Hz), 129.2, 128.3, 127.7, 125.8 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 272.08 Hz) ppm.
^{19}F NMR (377 MHz, $CDCl_3$) δ -62.65, -75.99 ppm.
HRMS (ESI) m/z: [M+Na]+ Calcd for C18H15F6NOS Na 430.0670; Found 430.0668.

N-(3-((4-chlorophenyl)thio)-3-phenylpropyl)-2,2,2-trifluoroacetamide (**30**)



30

Reaction conducted using **Procedure I** with p-Chlorothiophenol (0.4 mmol, 57.85 mg 2 equiv). Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (10:90 (v:v)) to afford 71.02 mg of **30** as a white solid (95% yield).

NMR Spectroscopy:

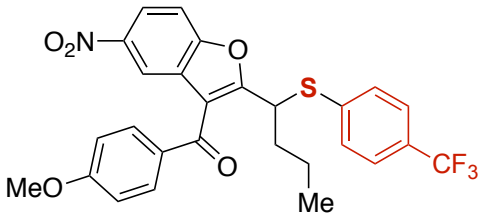
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 3H), 7.20 – 7.11 (m, 6H), 6.23 (s, 1H), 4.10 (dd, *J* = 8.3, 6.7 Hz, 1H), 3.47 (dq, *J* = 13.4, 6.7 Hz, 1H), 3.35 (dq, *J* = 13.4, 6.6 Hz, 1H), 2.26 – 2.14 (m, 2H) ppm.

^{13}C NMR (126 MHz, CDCl3) δ 157.1 (q, J = 37.0 Hz), 140.4, 134.5, 134.1, 132.1, 129.1, 128.9, 127.9, 127.6, 115.7 (q, J = 287.9 Hz), 51.9, 38.5, 35.0 ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ -75.98 ppm.

HRMS (ESI) m/z: [M+NH4]+ Calcd for C17H19ClF3N2OS 391.0850; Found 391.0850.

(4-methoxyphenyl)(5-nitro-2-(1-((4-(trifluoromethyl)phenyl)thio)butyl)benzofuran-3-yl)methanone (**31**)



31

Reaction conducted using **Procedure I** with 4-trifluoromethylbenzenethiol (0.4 mmol, 71.27 mg 2 equiv),Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (07:93 (v:v)) to afford 94.2 mg of **31** as a clear glassy solid (89% yield).

NMR Spectroscopy:

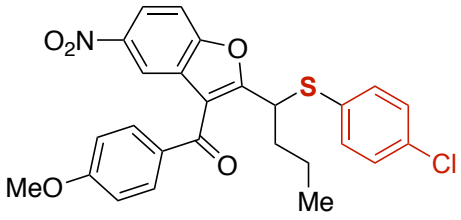
^{1}H NMR ((500 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 9.1, 2.4 Hz, 1H), 8.05 (d, *J* = 2.3 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.32 (s, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.89 – 6.86 (m, 2H), 5.01 (dd, *J* = 8.9, 6.5 Hz, 1H), 3.89 (s, 3H), 2.24-2.16 (m, 1H), 2.12-2.03 (m, 1H), 1.66 – 1.53 (m, 1H), 1.47-1.38 (m, 1H), 1.00 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.3, 164.5, 164.1, 156.3, 144.9, 138.5 (d, *J* = 1.5 Hz), 132.2, 131.8, 130.2, 129.7 (q, *J* = 32.7 Hz), 127.1, 124.9, 122.8, 120.6 (q, J = 272. 29 Hz), 126.9, 125.9, 125.9, 125.8 (q, *J* = 3.7 Hz), 121.1, 119.3, 118.1, 114.2, 112.1, 55.7, 44.4, 35.0, 21.1, 13.8 ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.67 ppm.

HRMS (ESI) m/z: [M+H]+ Calcd for C27H23F3NO5S 530.1244; Found 530.1241.

(2-(1-((4-chlorophenyl)thio)butyl)-5-nitrobenzofuran-3-yl)(4-methoxyphenyl)methanone (**32**)



32

Reaction conducted using **Procedure I** with p-Chlorothiophenol (0.4 mmol, 57.85 mg 2 equiv). ,Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (07:93 (v:v)) followed by a second column eluting with solvent mixture of dichloromethane/cyclohexane (60:40 (v:v)) to afford 67.45 mg **32** as a clear glassy solid (68% yield).

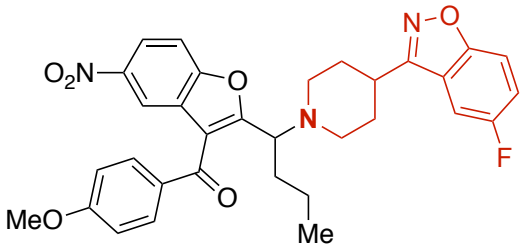
NMR Spectroscopy:

^{1}H NMR 500 MHz, CDCl3) δ 8.24 (dd, J = 9.1, 2.4 Hz, 1H), 8.06 (d, J = 2.3 Hz, 1H), 7.62 (d, J = 9.1 Hz, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.14 – 7.10 (m, 2H), 6.96 – 6.93 (m, 2H), 6.92 – 6.88 (m, 2H), 4.84 (dd, J = 8.9, 6.4 Hz, 1H), 3.91 (s, 3H), 2.21 (dtd, J = 13.6, 9.3, 5.7 Hz, 1H), 2.09 (ddt, J = 13.6, 9.6, 6.2 Hz, 1H), 1.63 – 1.53 (m, 1H), 1.49 – 1.39 (m, 1H), 0.99 (t, J = 7.4 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.1, 164.3, 164.3, 156.3, 144.8, 135.1, 134.7, 131.8, 131.5, 130.1, 129.3, 127.1, 121.0, 119.4, 118.0, 114.1, 112.0, 55.7, 45.4, 34.7, 21.1, 13.8 ppm.

HRMS (ESI) m/z: [M+H]+ Calcd for C26H23ClNO5S 496.0980; Found 496.0981.

(2-(1-(4-(5-fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl)butyl)-5-nitrobenzofuran-3-yl)(4-methoxyphenyl)methanone (**33**)



33

Reaction conducted using **Procedure J** 5-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (0.4 mmol, 88.1 mg 2 equiv). ,Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate: hexanes (10:90 (v:v)) to afford 54.87 mg of **33** as a clear glassy solid (48% yield).

NMR Spectroscopy:

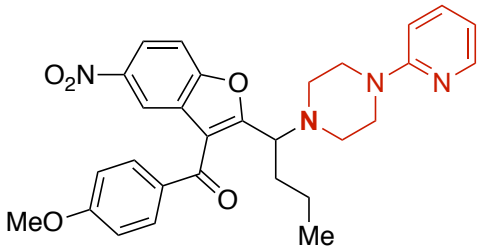
^{1}H NMR (500 MHz, CDCl3) δ 8.30 (d, J = 2.3 Hz, 1H), 8.27 (dd, J = 9.0, 2.3 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 9.0 Hz, 1H), 7.58 (dd, J = 8.7, 5.1 Hz, 1H), 7.21 (dd, J = 8.5, 2.1 Hz, 1H), 7.00 (dd, J = 9.7, 2.6 Hz, 3H), 4.17 (dd, J = 8.5, 6.7 Hz, 1H), 3.92 (s, 3H), 3.22 (dd, J = 11.5, 4.7 Hz, 1H), 2.91 (tt, J = 7.0, 3.8 Hz, 2H), 2.30 (td, J = 11.1, 3.3 Hz, 1H), 2.21 (td, J = 11.4, 2.8 Hz, 1H), 2.10-1.90 (m, 6H), 1.43 (tdd, J = 9.4, 7.6, 6.1 Hz, 1H), 1.37 – 1.26 (m, 1H), 0.95 (t, J = 7.3 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 189.1, 164.5, 164.2 (d, *J* = 250.75 Hz), 164.4, 164.0 (d, *J* = 13.6 Hz), 163.2, 156.4, 144.9, 132.1, 131.0, 127.6, 122.6, 122.5, 120.8, 118.1, 117.4 (d, *J* = 1.3 Hz), 114.4, 112.5 (d, *J* = 25.3 Hz), 112.1, 97.6 (d, *J* = 26.7 Hz), 60.7, 55.8, 52.1, 48.4, 34.7, 32.3, 31.1, 31.0, 19.9, 14.1 ppm.

^{19}F NMR (377 MHz, CDCl3) δ -109.61 ppm.

HRMS (ESI) m/z: [M+H]+ Calcd for C32H31FN3O6 572.2191; Found 572.2185.

(4-methoxyphenyl)(5-nitro-2-(1-(4-(pyridin-2-yl)piperazin-1-yl)butyl)benzofuran-3-yl)methanone (**34**)



34

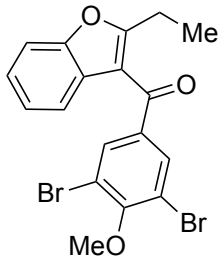
Reaction conducted using **Procedure J** with 1-(2-pyridyl)piperazine (0.4 mmol, 65.29.1 mg 2 equiv). ,Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of DCM: Diethylether (40:60 (v:v)) to afford 48.37 mg of **34** as a light yellow oil (47% yield).

NMR Spectroscopy:

^{1}H NMR (500 MHz, CDCl3) δ 8.24 (dd, J = 9.0, 2.4 Hz, 1H), 8.21 (d, J = 2.3 Hz, 1H), 8.13 (ddd, J = 4.9, 2.1, 0.9 Hz, 1H), 7.86 – 7.82 (m, 2H), 7.62 (d, J = 9.0 Hz, 1H), 7.42 (ddd, J = 8.9, 7.1, 2.0 Hz, 1H), 7.00 – 6.96 (m, 2H), 6.63 – 6.52 (m, 2H), 4.24 (dd, J = 8.9, 6.3 Hz, 1H), 3.92 (s, 3H), 3.54 (ddd, J = 12.3, 7.0, 3.2 Hz, 2H), 3.42 (ddd, J = 12.4, 7.0, 3.3 Hz, 2H), 2.70 (ddd, J = 10.6, 6.9, 3.2 Hz, 2H), 2.58 (ddd, J = 10.8, 7.0, 3.4 Hz, 2H), 2.14 – 1.93 (m, 2H), 1.50 – 1.35 (m, 1H), 1.36-1.26 (m, 1H), 0.95 (t, J = 7.3 Hz, 3H) ppm.

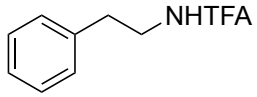
^{13}C NMR (126 MHz, $CDCl_3$) δ 188.9, 164.4, 164.3, 159.5, 156.4, 148.1, 144.8, 137.6, 132.0, 130.9, 127.4, 120.7, 120.6, 118.1, 114.4, 113.5, 112.1, 107.1, 60.4, 55.8, 49.8, 45.7, 32.2, 19.8, 14.1 ppm.

HRMS (ESI) m/z: [M+H]+ Calcd for C29H31N4O5 515.2289; Found 515.2290.



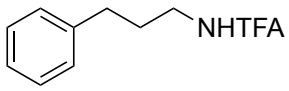
Compound **36**:

Compound **36** was prepared following the literature procedure[3] To a 25 mL round-bottom flask containing a magnetic stir bar was added benzobromarone (842.2 mg, 2.0 mmol). The flask was subsequently charged with a mixture of acetonitrile and methanol (9:1, 8 mL), followed by diisopropylethylamine (0.72 mL, 0.75 equiv) and stirred for 10 min. To the stirring reaction mixture, trimethylsilyldizaomethane (2.0 M Hexane solution, 1.5 mL, 0.75 equiv) was added dropwise. A funnel was placed upside down on top of the flask to ensure minimal solvent evaporation. The reaction was allowed to stir at room temperature overnight. The reaction was concentrated under vacuum and the reside was purified by column chromatography eluting with a solvent mixture pentane:ethylacetate (80:20 (v:v)) to afford .753.7 mg of 36 (86% yield.) Spectra data matched those in the literature.[3]



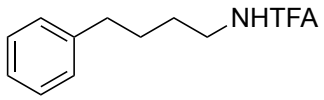
Compound **37**

To a flame-dried 100 mL round-bottom flask containing magnetic stir bar at 0 °C under nitrogen was added phenylethylamine (2 g, 0.016 mol, 1 equiv), anhydrous dichloromethane (40 mL, 0.4M to substrate), and pyridine (3.9 g, 4.0 mL, 3 equiv) followed by dropwise addition of trifluoroacetic anhydride (6.9 g, 4.6 mL, 2 equiv). After stirring at room temperature overnight, the reaction was slowly quenched with water, then extracted with dichloromethane (2x). The organic extracts were combined and washed with H_2O (2 x 100 mL) then brine (1 x 100 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered and concentrated under vacuum. Purification of the desired compound was performed by flash chromatography. a solvent mixture pentane:ethylacetate (90:10 (v:v)) to afford 3.1 g (90% yield) of the product as a white solid. Spectra data matched those in the literature.[23]



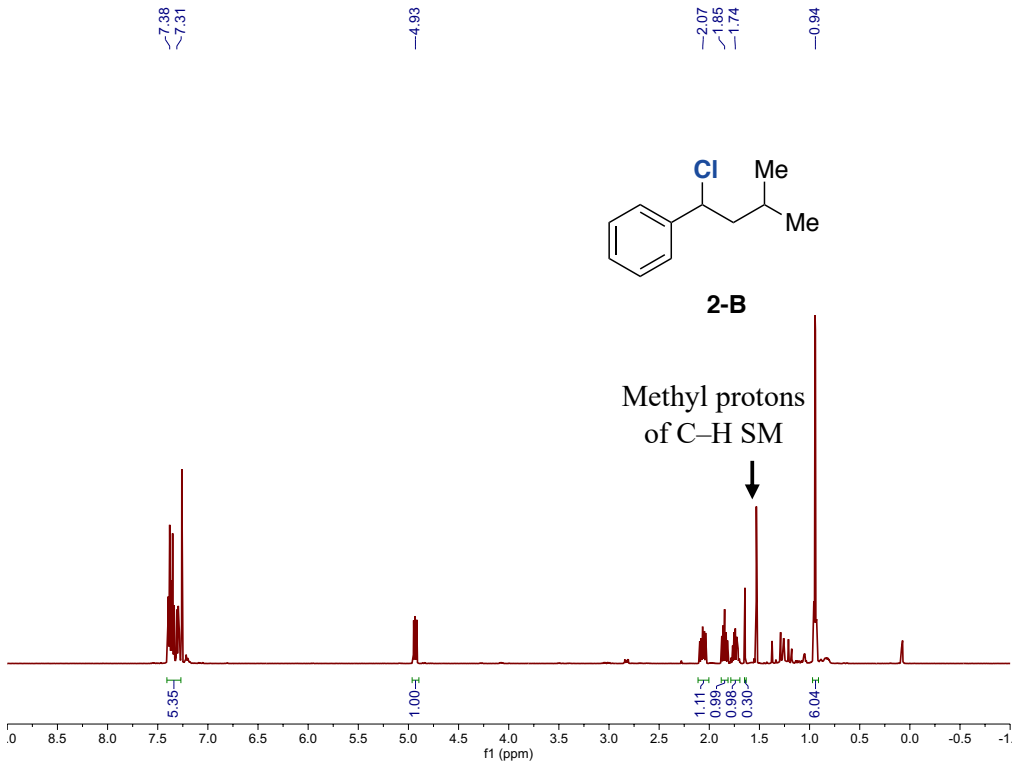
To a flame-dried 100 mL round-bottom flask containing magnetic stir bar at 0 °C under nitrogen was added 3 phenyl propylamine (2 g, 0.015 mol, 1 equiv), anhydrous dichloromethane (40 mL, 0.4M to substrate), and pyridine (3.5 g, 3.6 mL, 3 equiv) followed by dropwise addition of trifluoroacetic anhydride (6.21 g, 4.1 mL, 2 equiv). After stirring at room temperature overnight, the reaction was slowly quenched with water, then extracted with dichloromethane (2x). The organic extracts were combined and washed with H_2O (2 x 100 mL) then brine (1 x 100 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered and concentrated under vacuum. Purification was of the desired compound was performed by flash chromatography. a solvent mixture

pentane:ethylacetate (90:10 (v:v)) to afford 3.2 g (92% yield) of the product as a light-yellow solid. Spectra data matched those in the literature.[23]

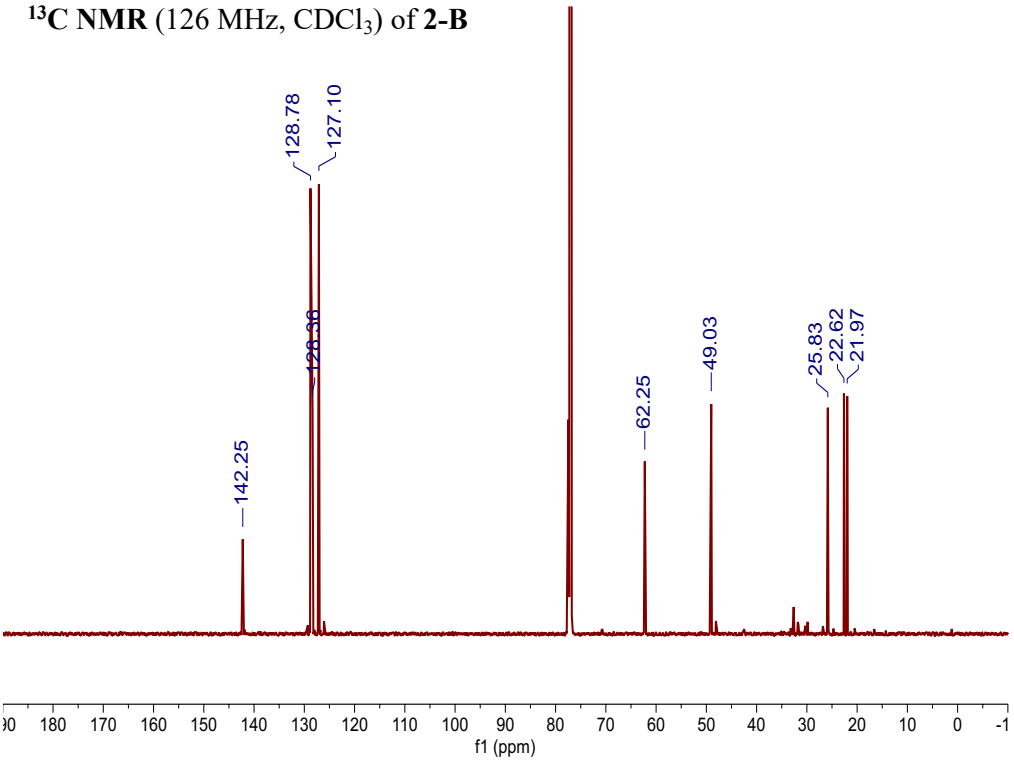


To a flame-dried 100 mL round-bottom flask containing magnetic stir bar at 0 °C under nitrogen was added 3 butyl propylamine (2 g, 0.013 mol, 1 equiv), anhydrous dichloromethane (33 mL, 0.4M to substrate), and pyridine (3.1 g, 3.25 mL, 3 equiv) followed by dropwise addition of trifluoroacetic anhydride (5.6g, 3.7 mL, 2 equiv). After stirring at room temperature overnight, the reaction was slowly quenched with water, then extracted with dichloromethane (2x). The organic extracts were combined and washed with H_2O (2 x 100 mL) then brine (1 x 100 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered and concentrated under vacuum. Purification was of the desired compound was performed by flash chromatography. a solvent mixture pentane:ethylacetate (90:10 (v:v)) to afford 2.86 g (90% yield) of the product as a light-yellow solid. Spectra data matched those in the literature.[24]

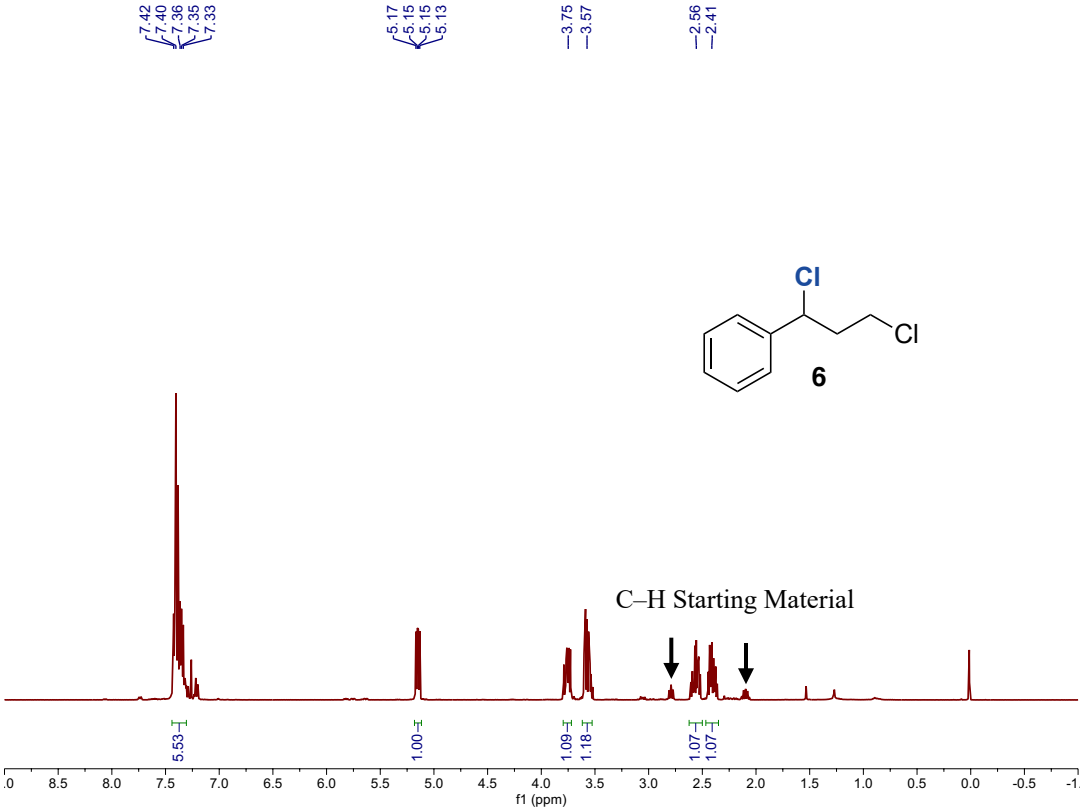
^{1}H NMR (500 MHz, $CDCl_3$) of **2-B**



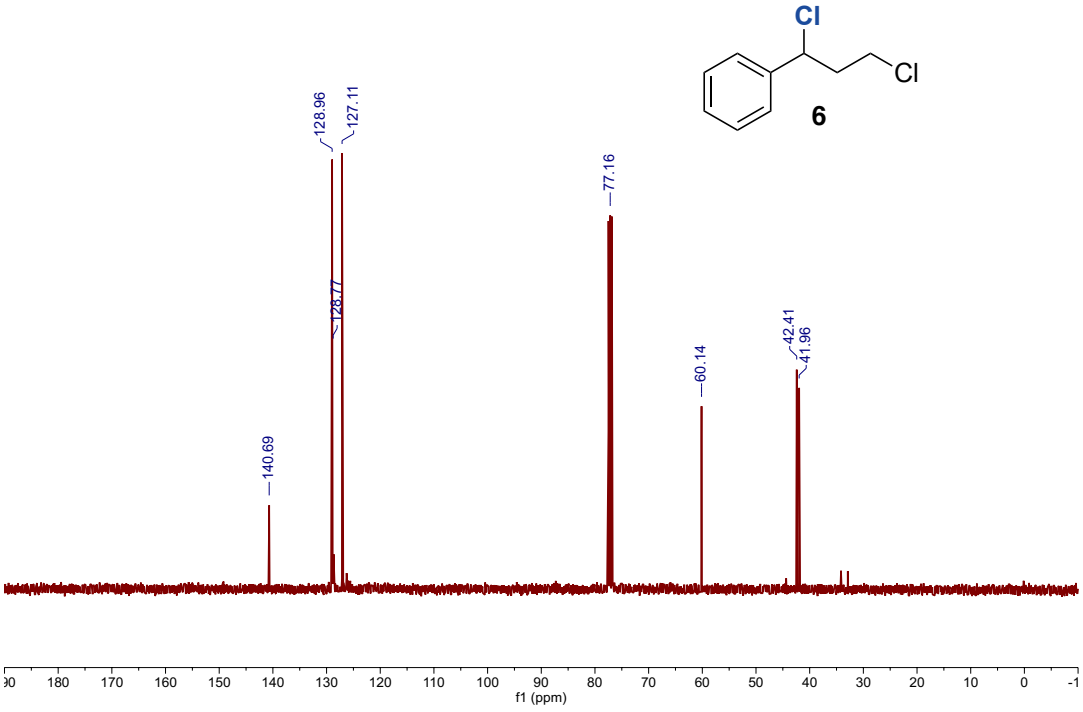
^{13}C NMR (126 MHz, $CDCl_3$) of **2-B**



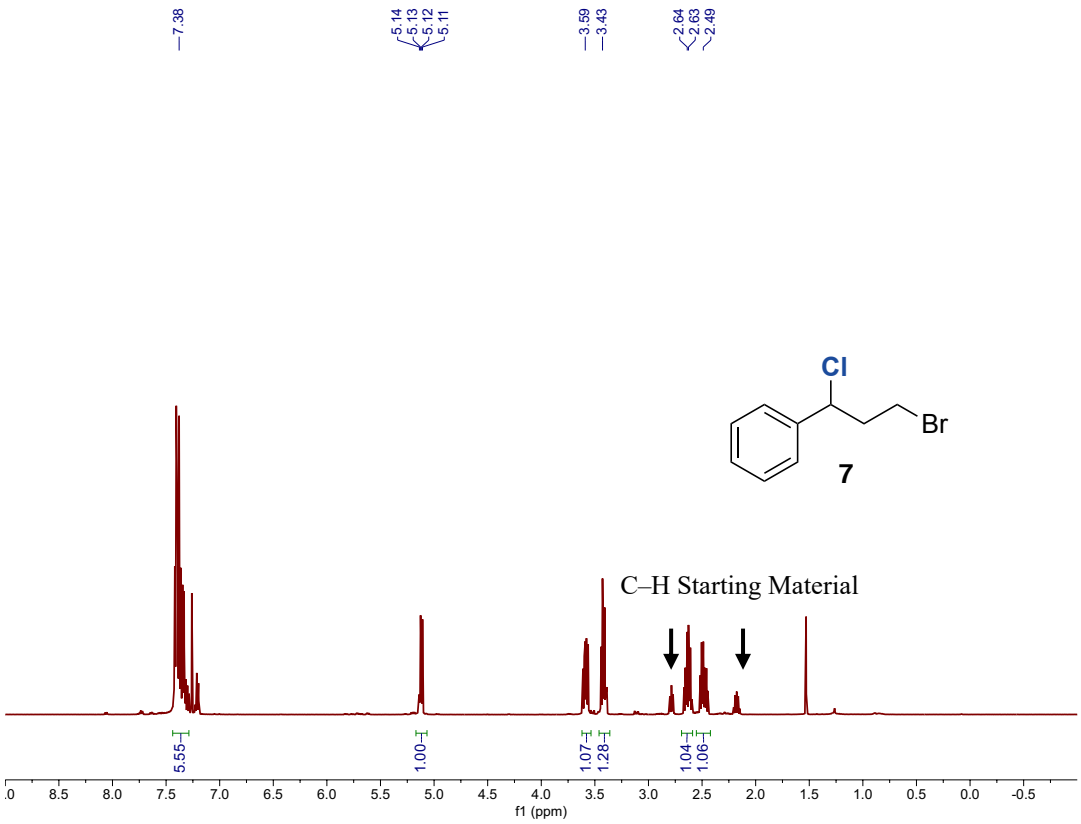
^{1}H NMR (400 MHz, $CDCl_3$) of **6**



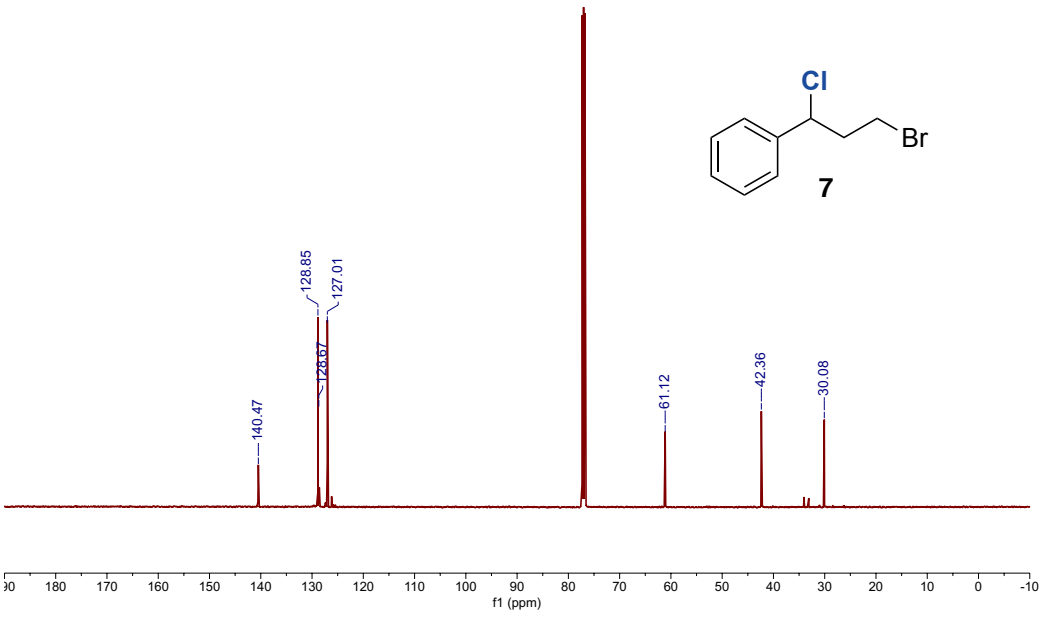
^{13}C NMR (101 MHz, $CDCl_3$) of **6**



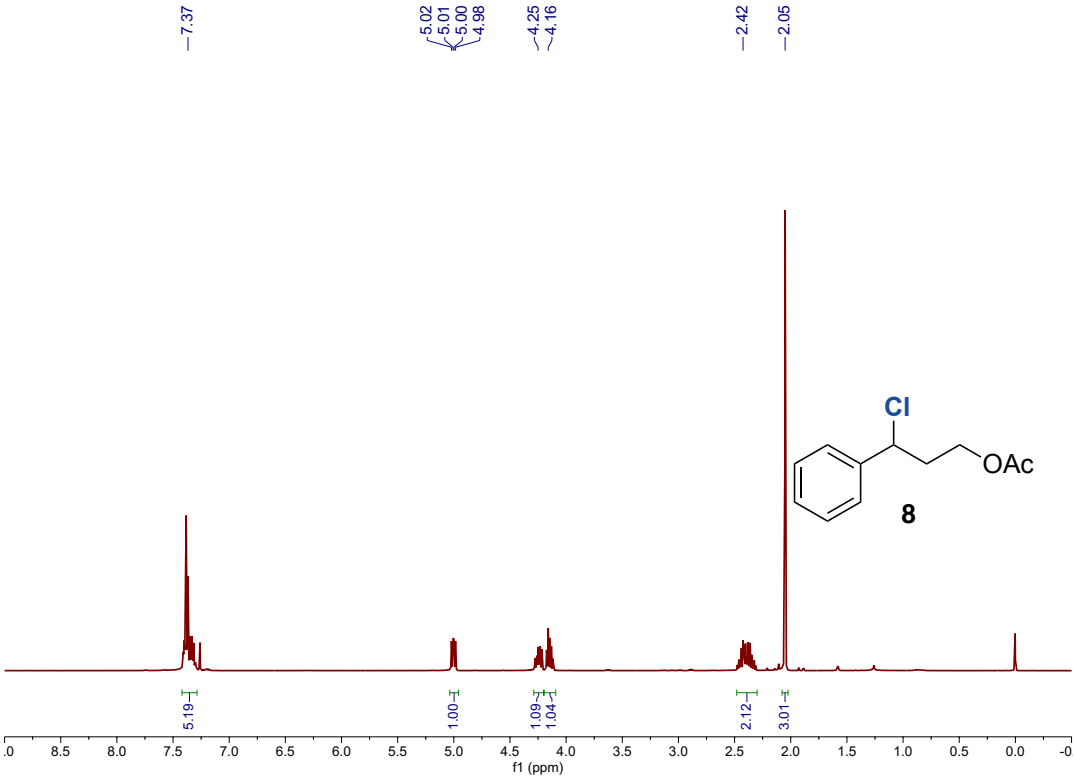
^{1}H NMR (500 MHz, $CDCl_3$) of **7**



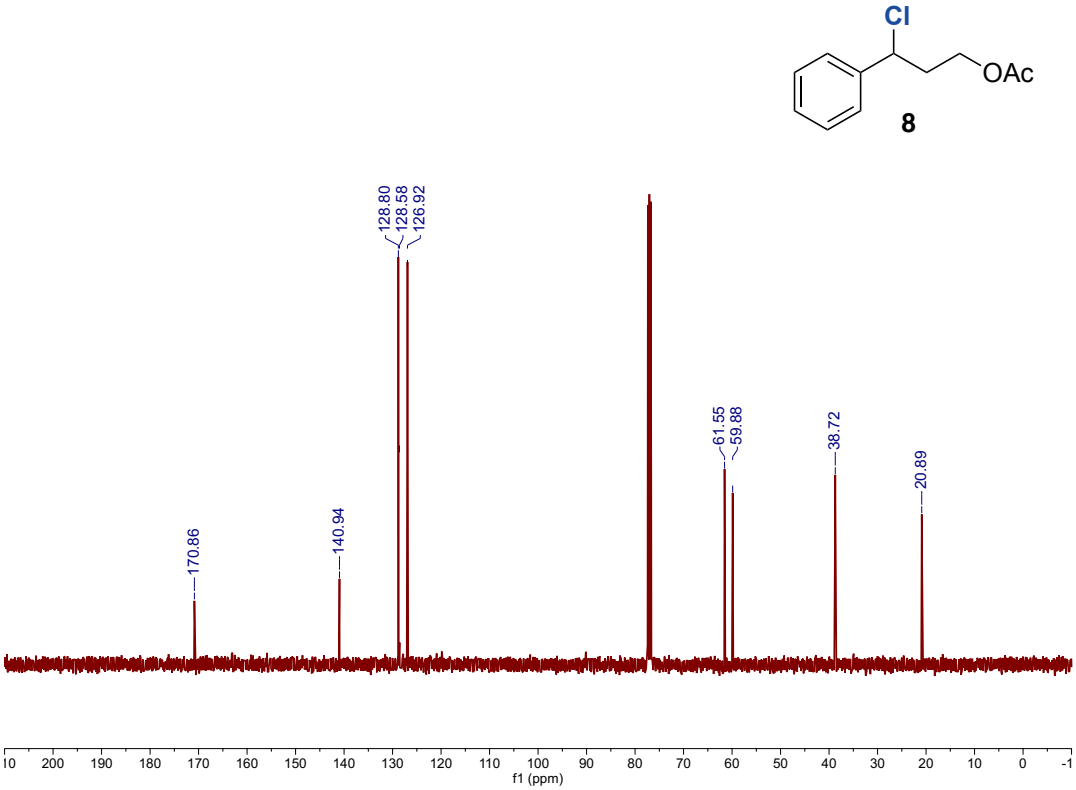
^{13}C NMR (126 MHz, $CDCl_3$) of **7**



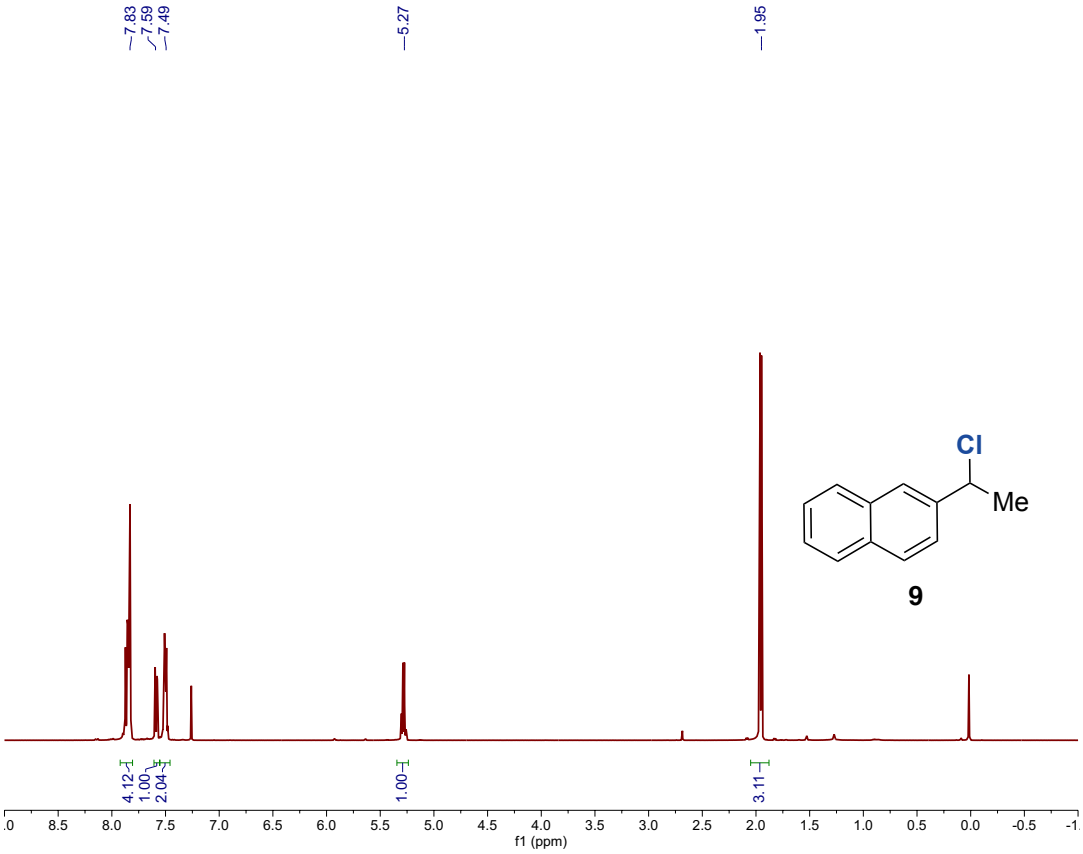
^{1}H NMR (400 MHz, $CDCl_3$) of **8**



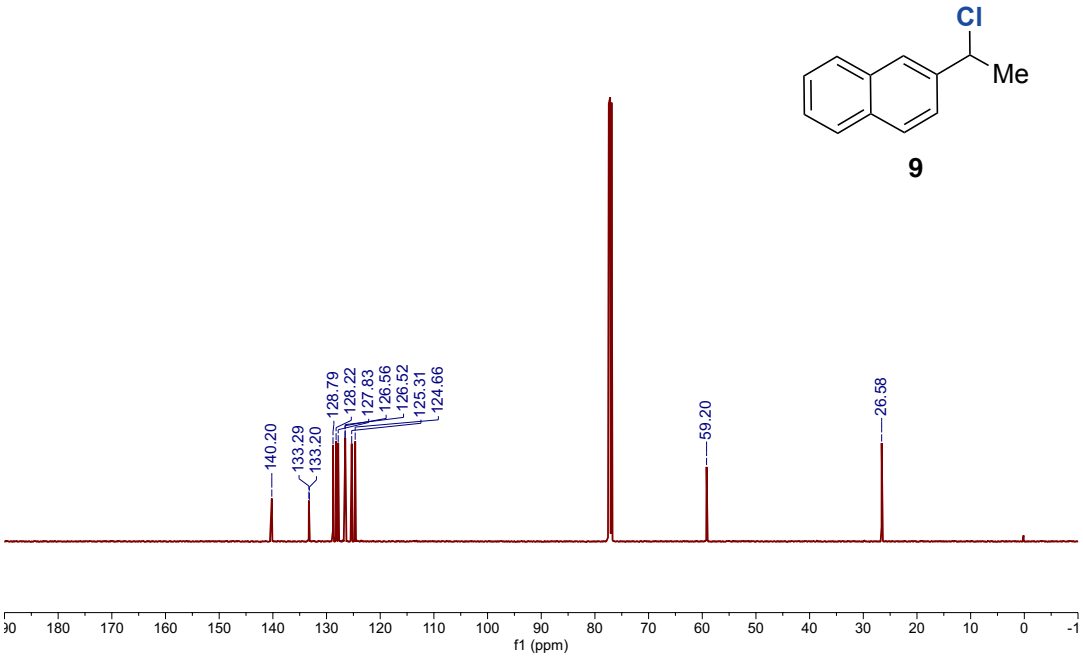
^{13}C NMR (101 MHz, $CDCl_3$) of **8**



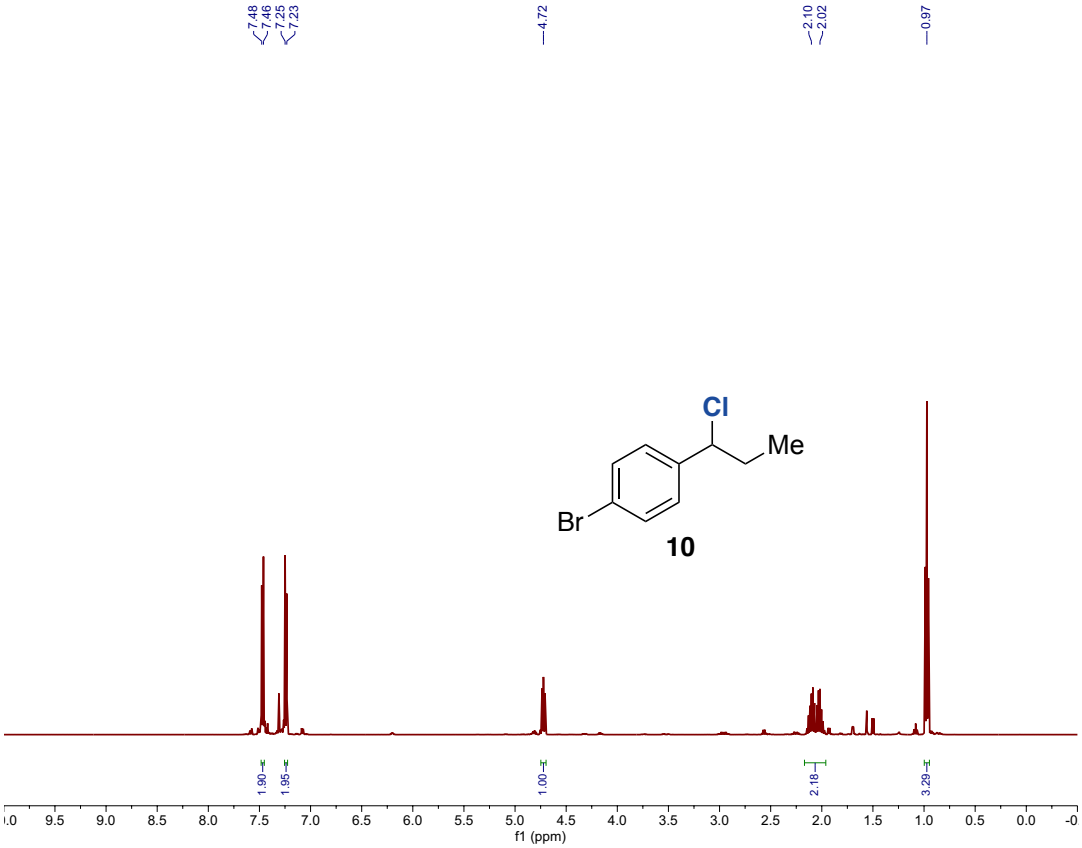
^{1}H NMR (500 MHz, $CDCl_3$) of **9**



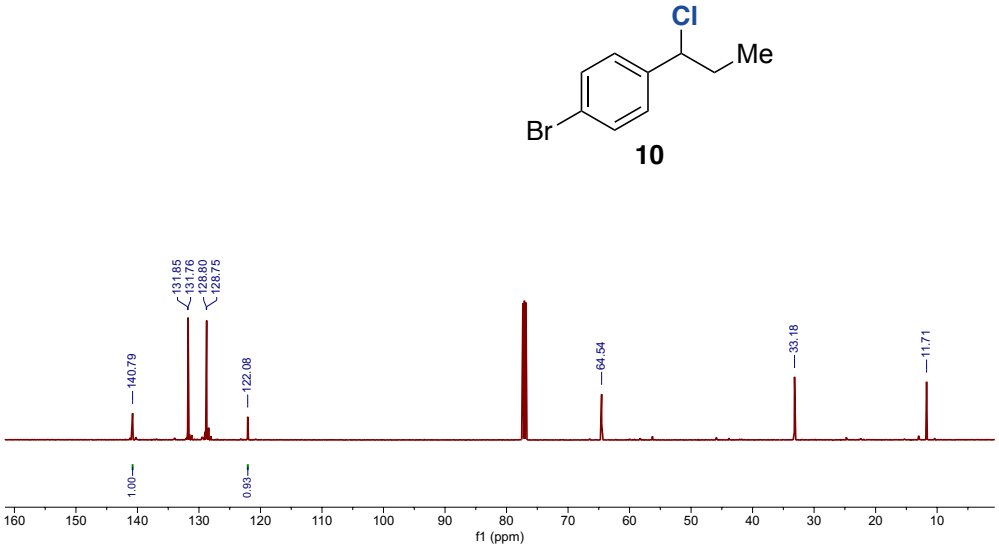
^{13}C NMR (126 MHz, $CDCl_3$) of **9**



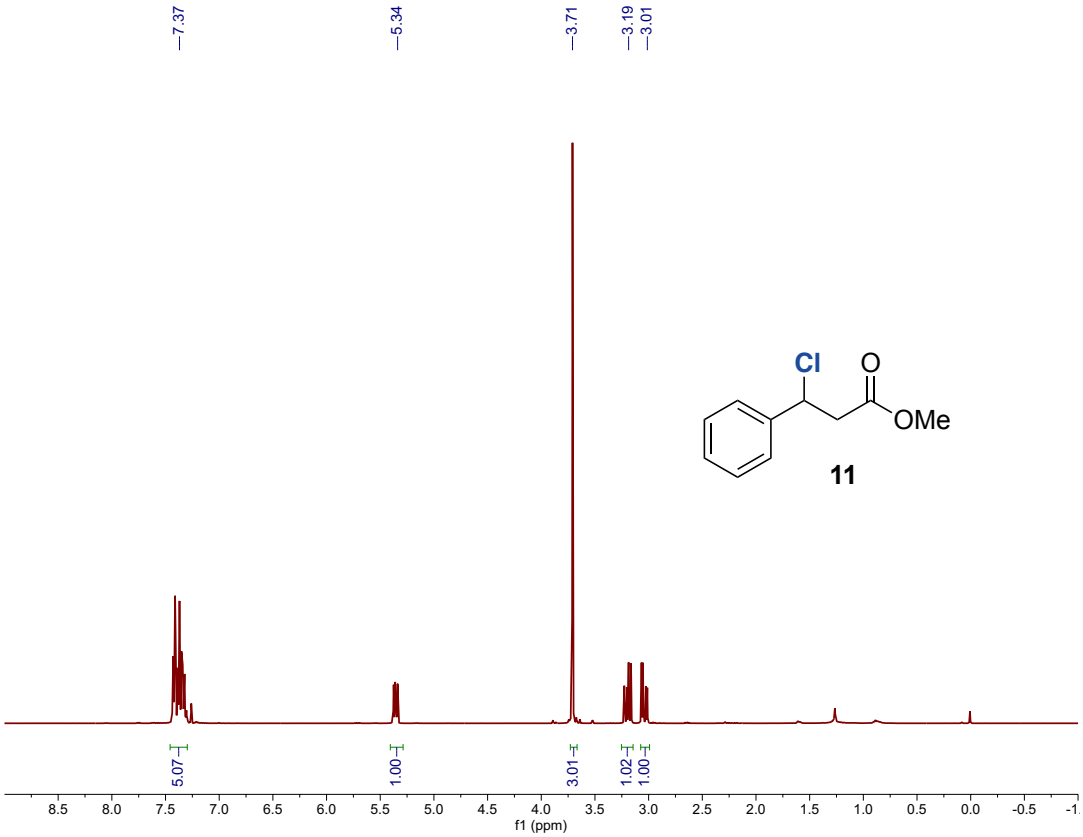
^{1}H NMR (500 MHz, $CDCl_3$) of **10**



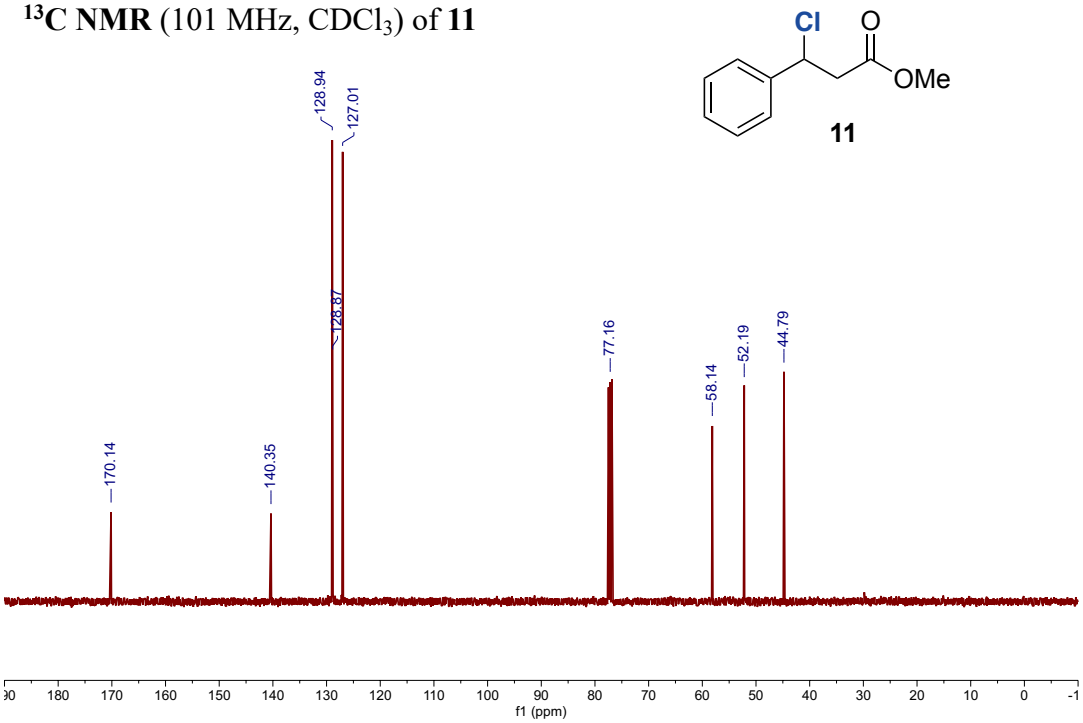
^{13}C NMR (126 MHz, $CDCl_3$) of **10**



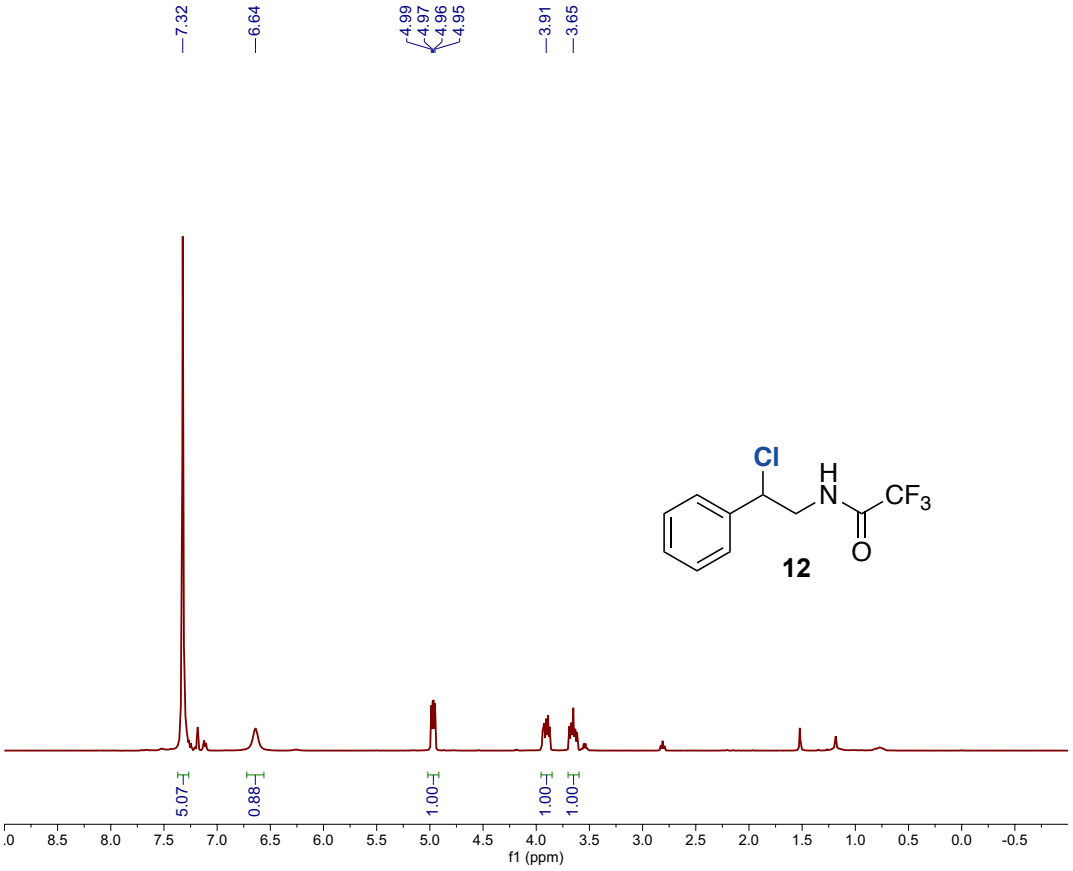
^{1}H NMR (400 MHz, $CDCl_3$) of **11**



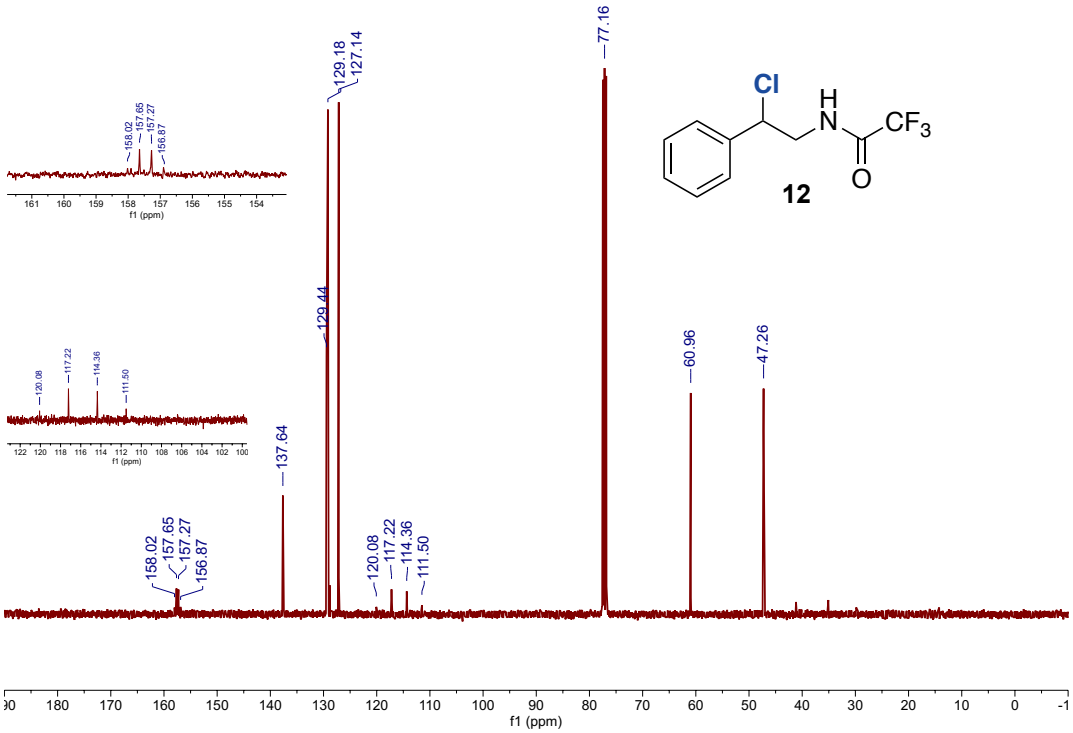
^{13}C NMR (101 MHz, $CDCl_3$) of **11**



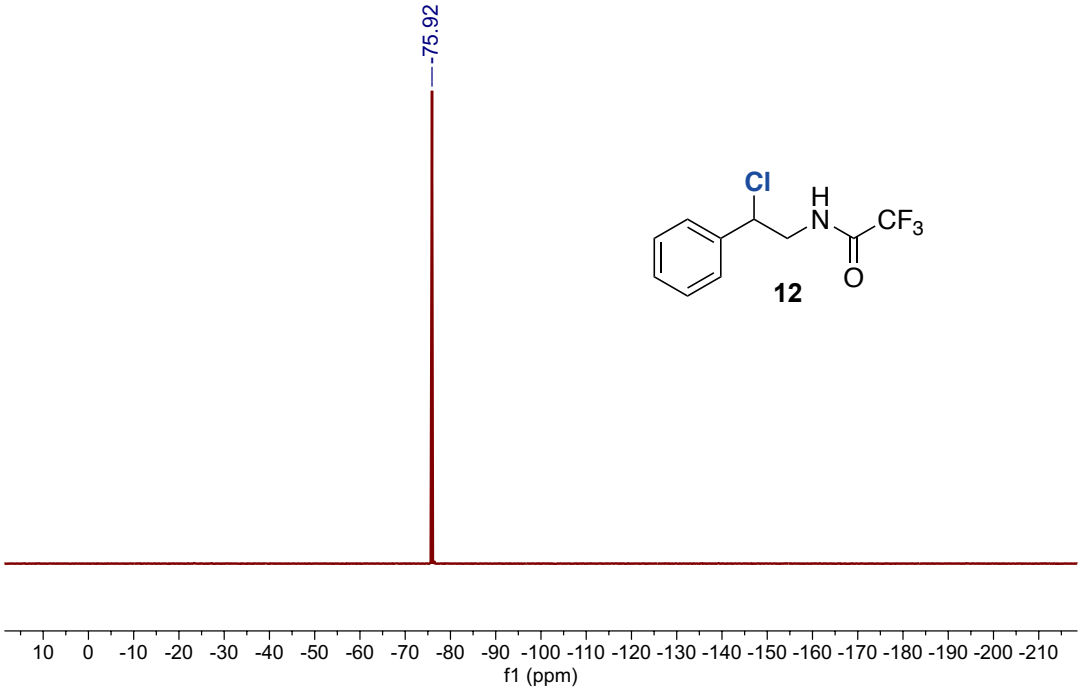
^{1}H NMR (400 MHz, $CDCl_3$) of **12**



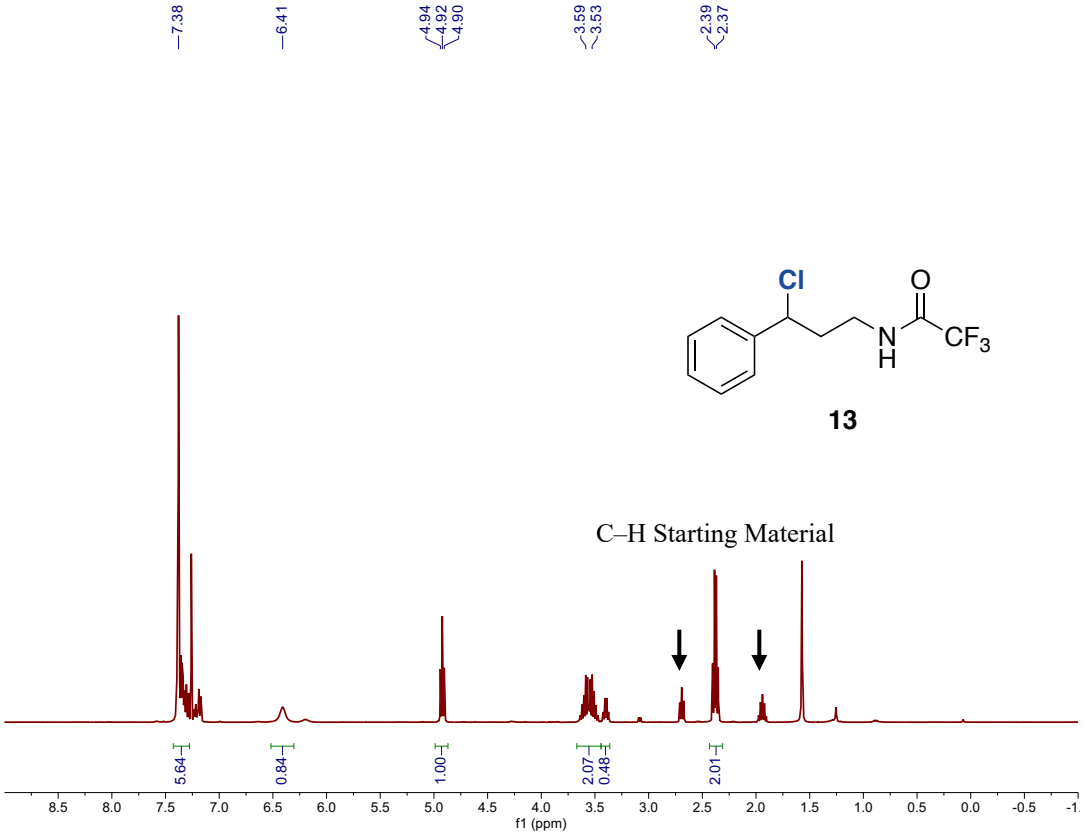
^{13}C NMR (101 MHz, $CDCl_3$) of **12**



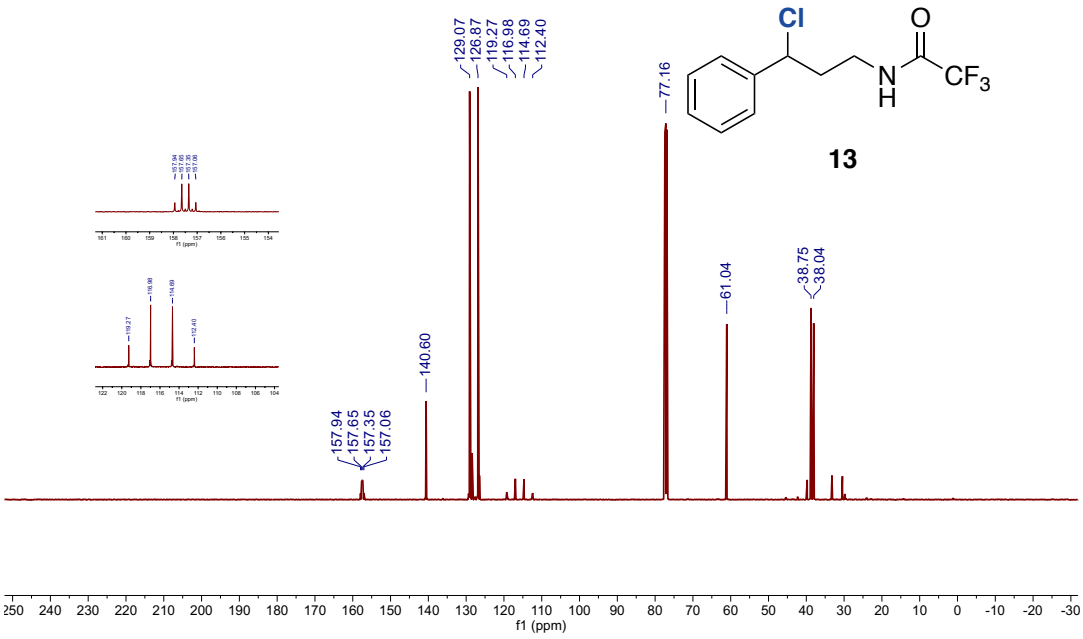
^{19}F NMR (377 MHz, Chloroform-*d*) of **12**



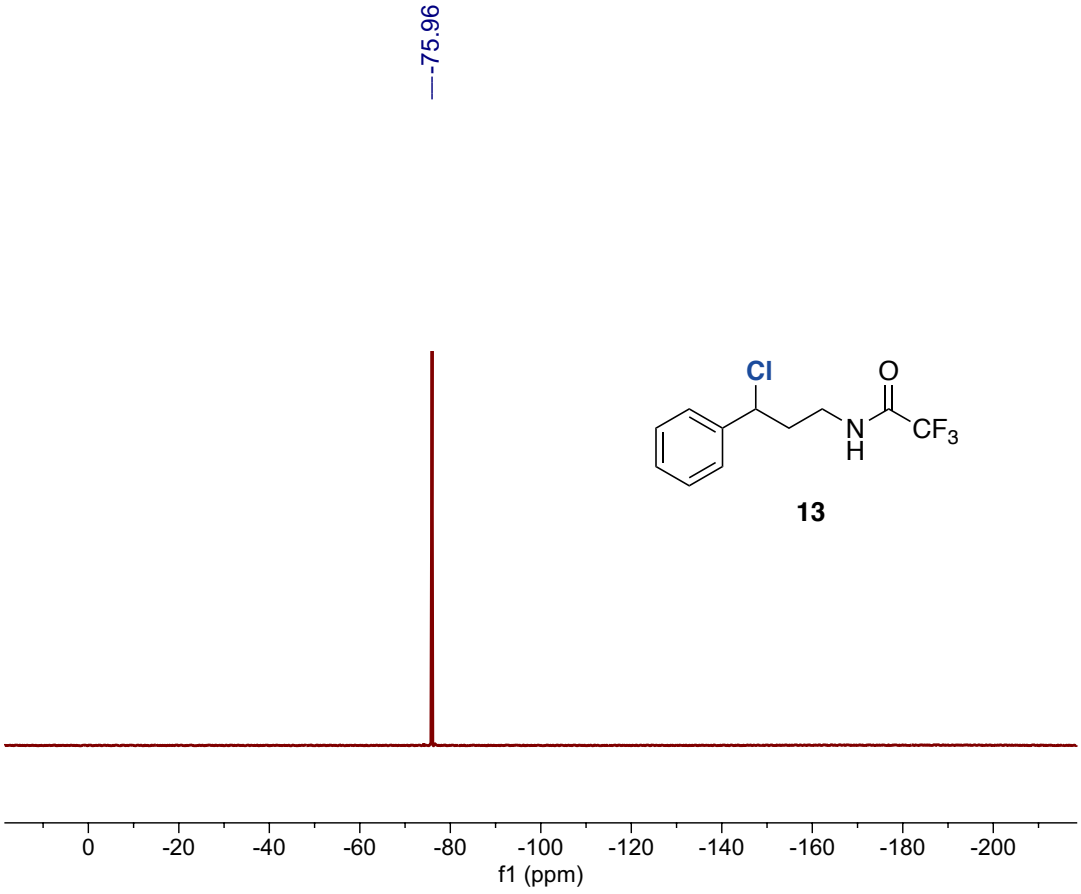
^{1}H NMR (500 MHz, $CDCl_3$) of **13**



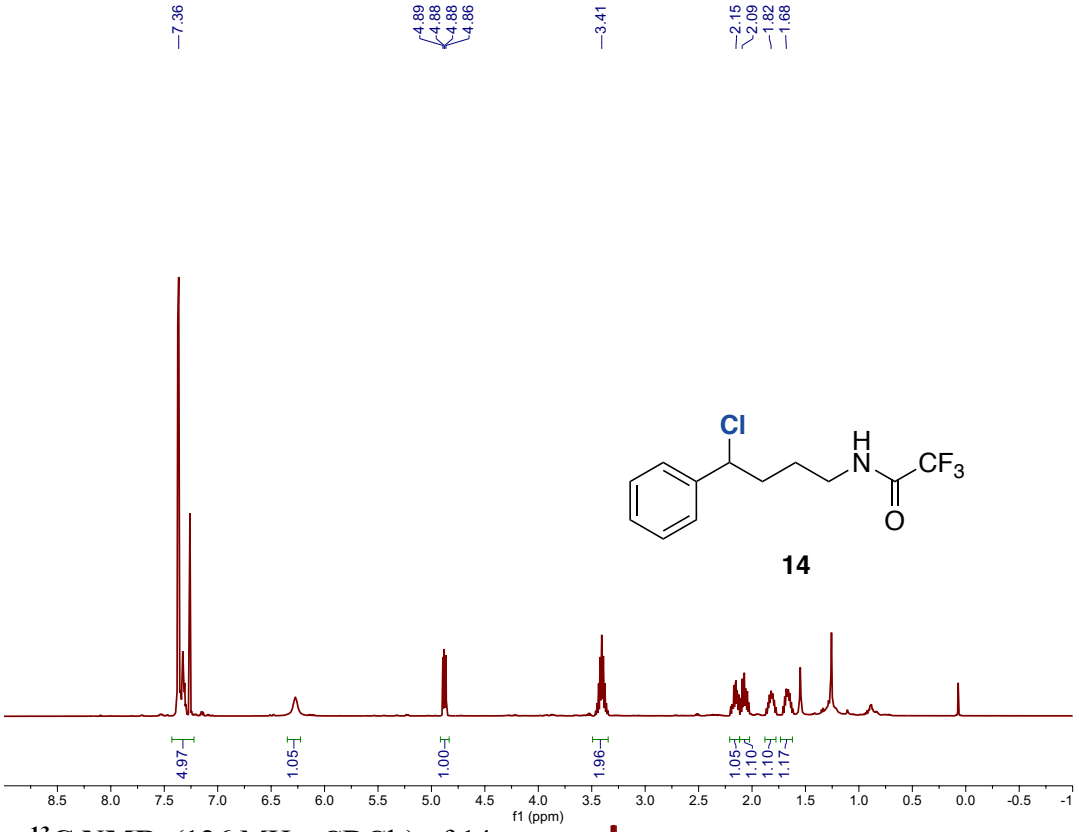
^{13}C NMR (126 MHz, $CDCl_3$) of **13**



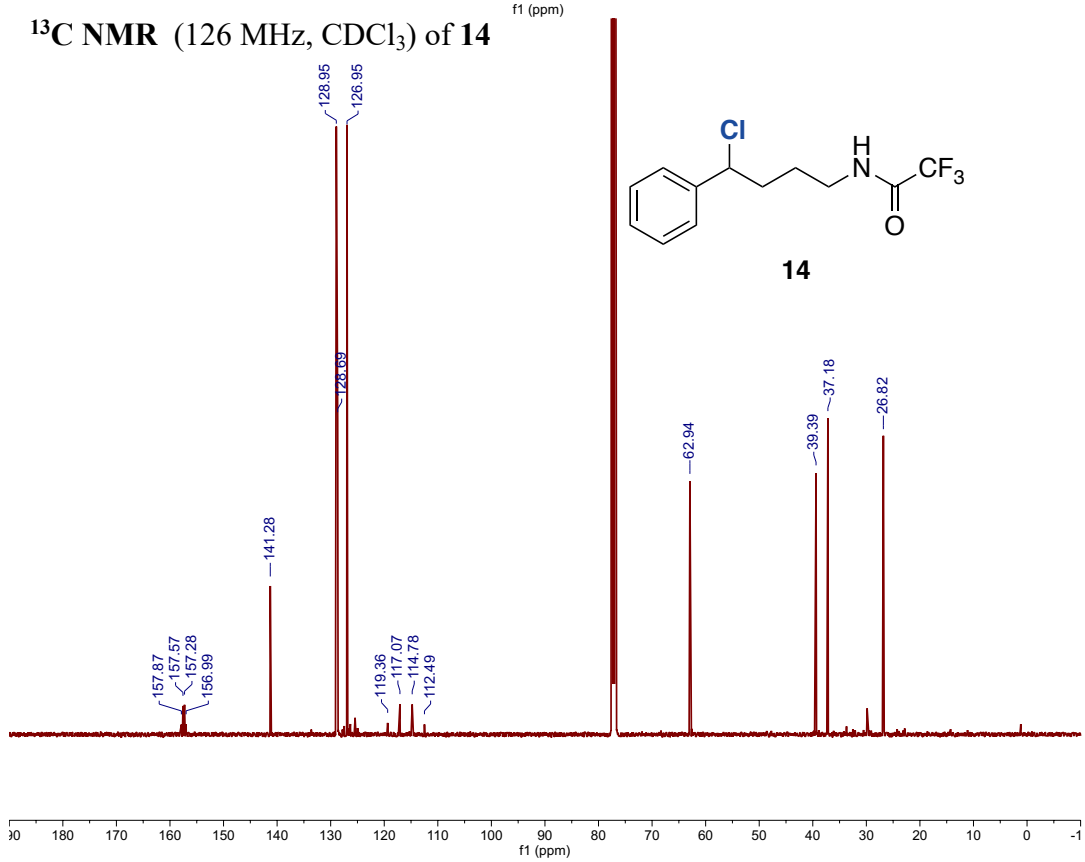
^{19}F NMR (377 MHz, Chloroform-*d*) of **13**



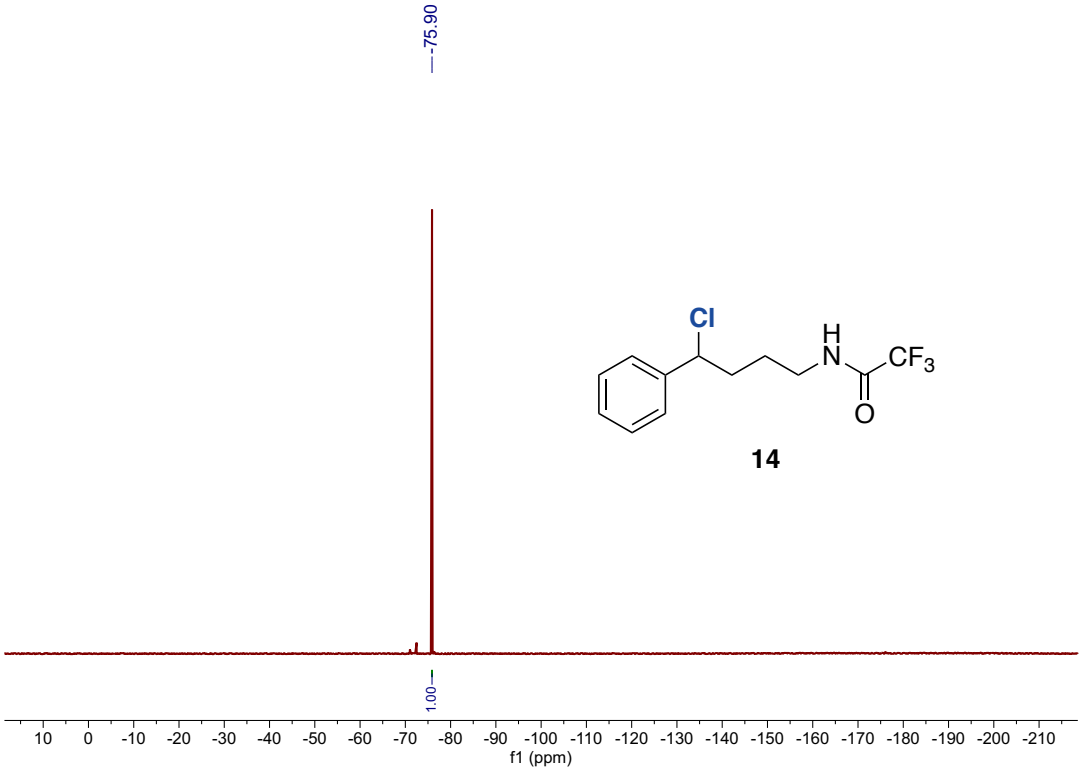
^{1}H NMR (500 MHz, $CDCl_3$) of **14**



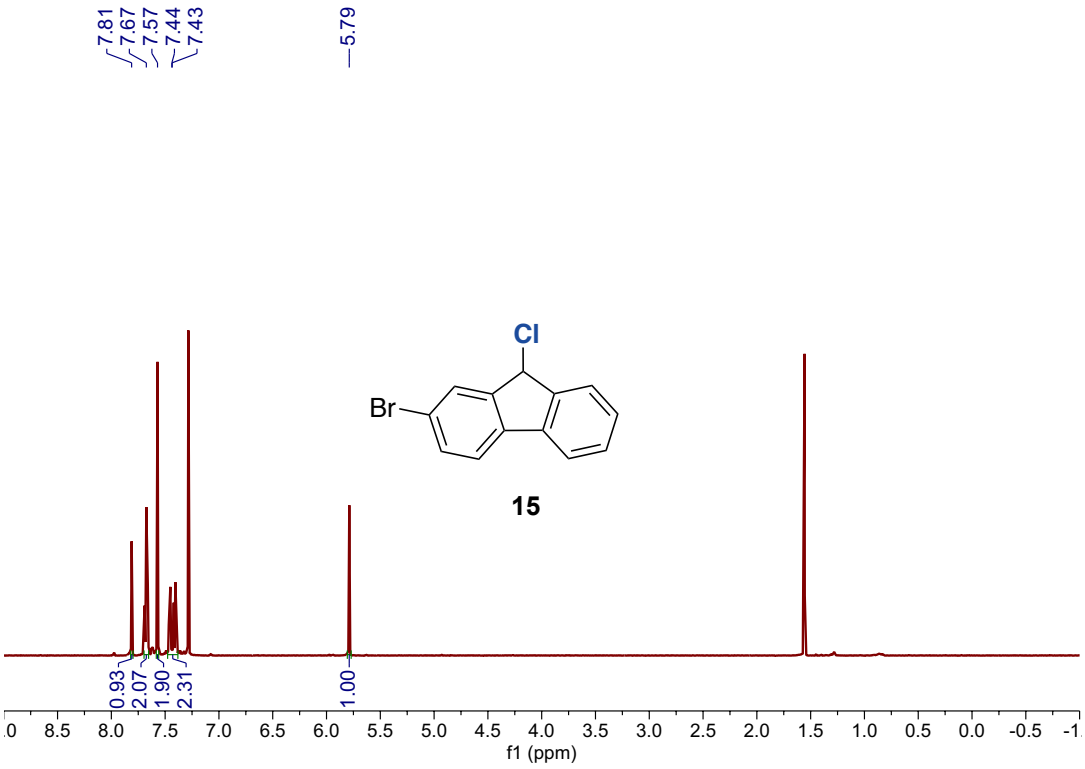
^{13}C NMR (126 MHz, $CDCl_3$) of **14**



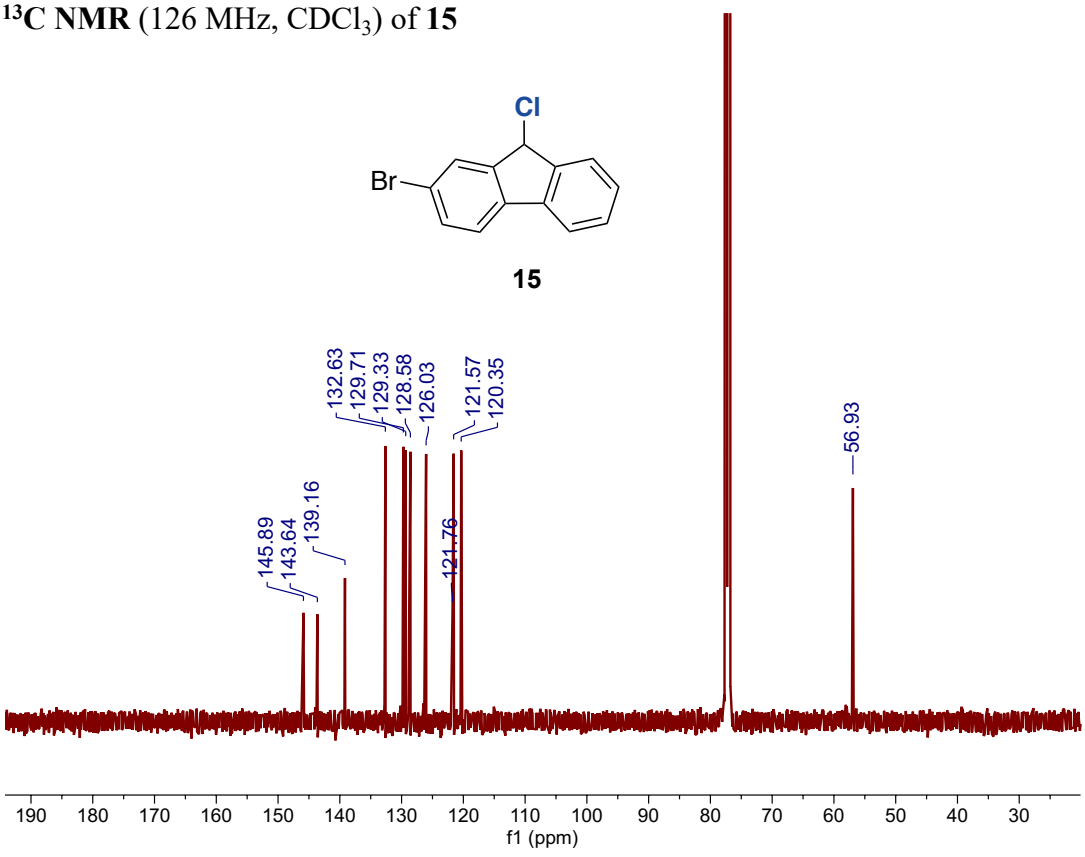
^{19}F NMR (377 MHz, Chloroform-*d*) of **14**



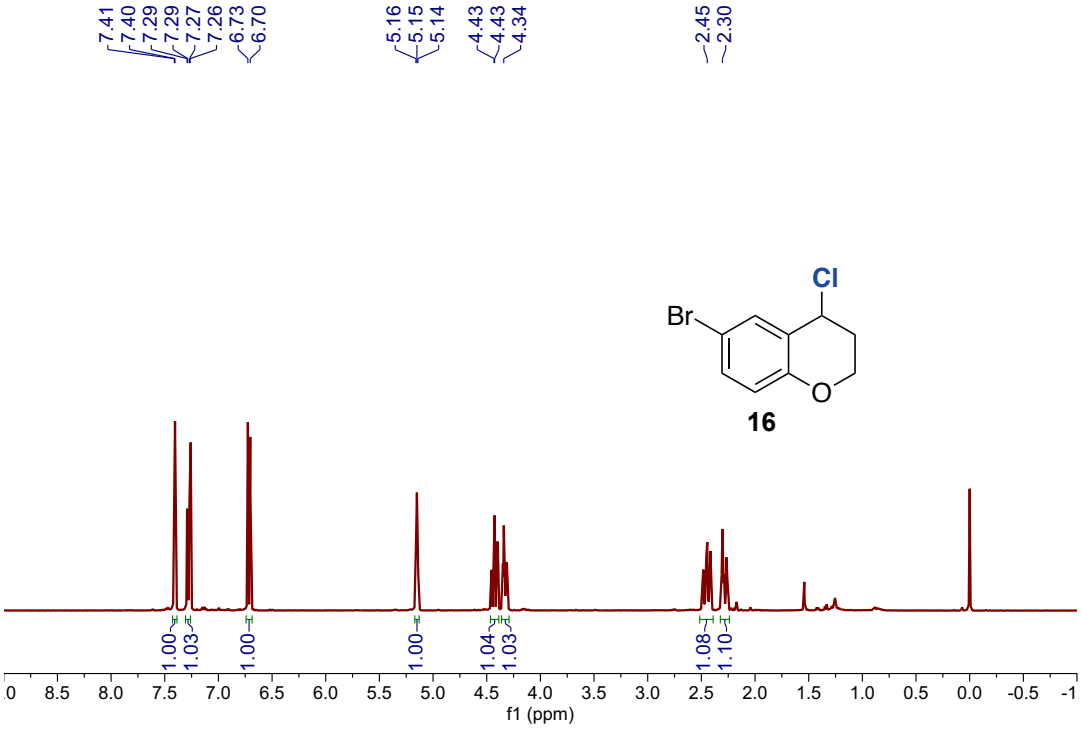
^{1}H NMR (500 MHz, $CDCl_3$) of **15**



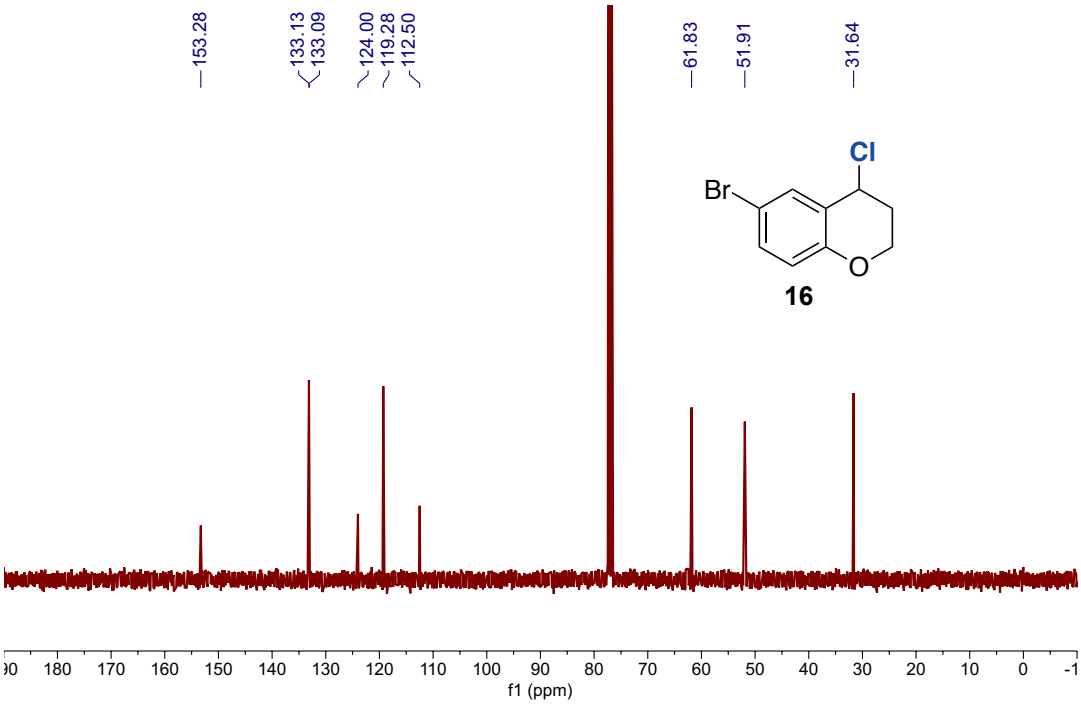
^{13}C NMR (126 MHz, $CDCl_3$) of **15**



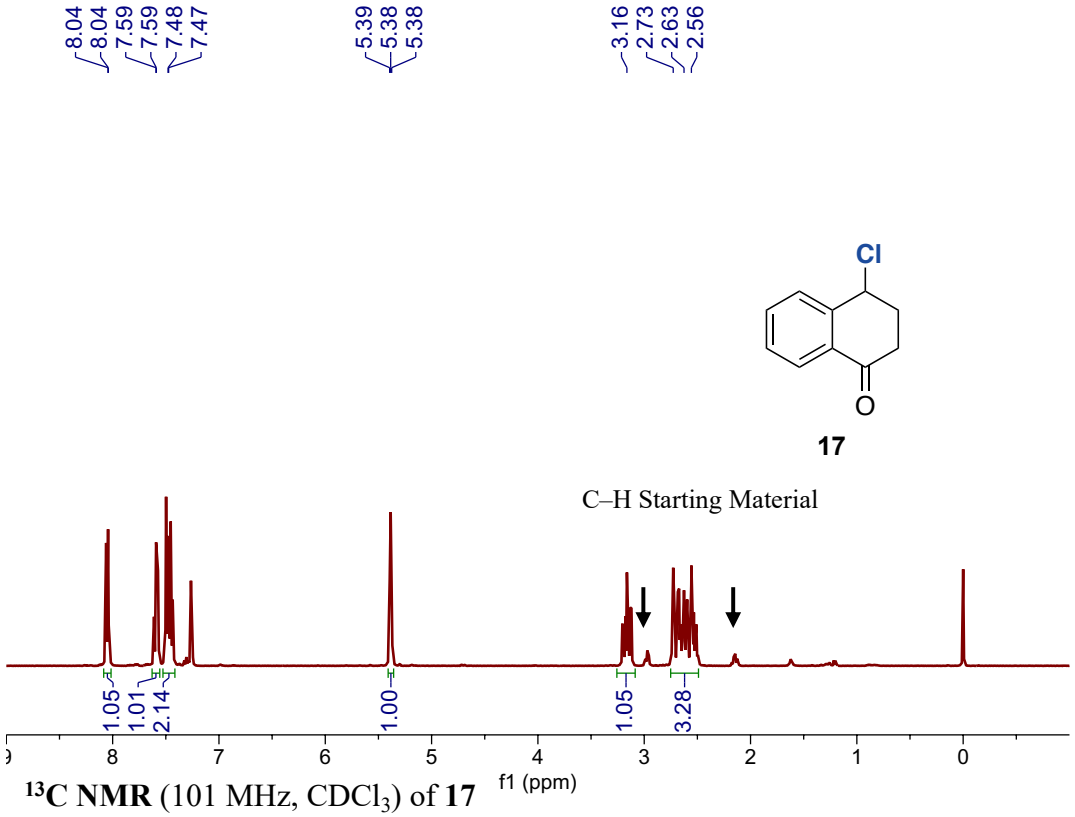
^{1}H NMR (400 MHz, $CDCl_3$) of **16**



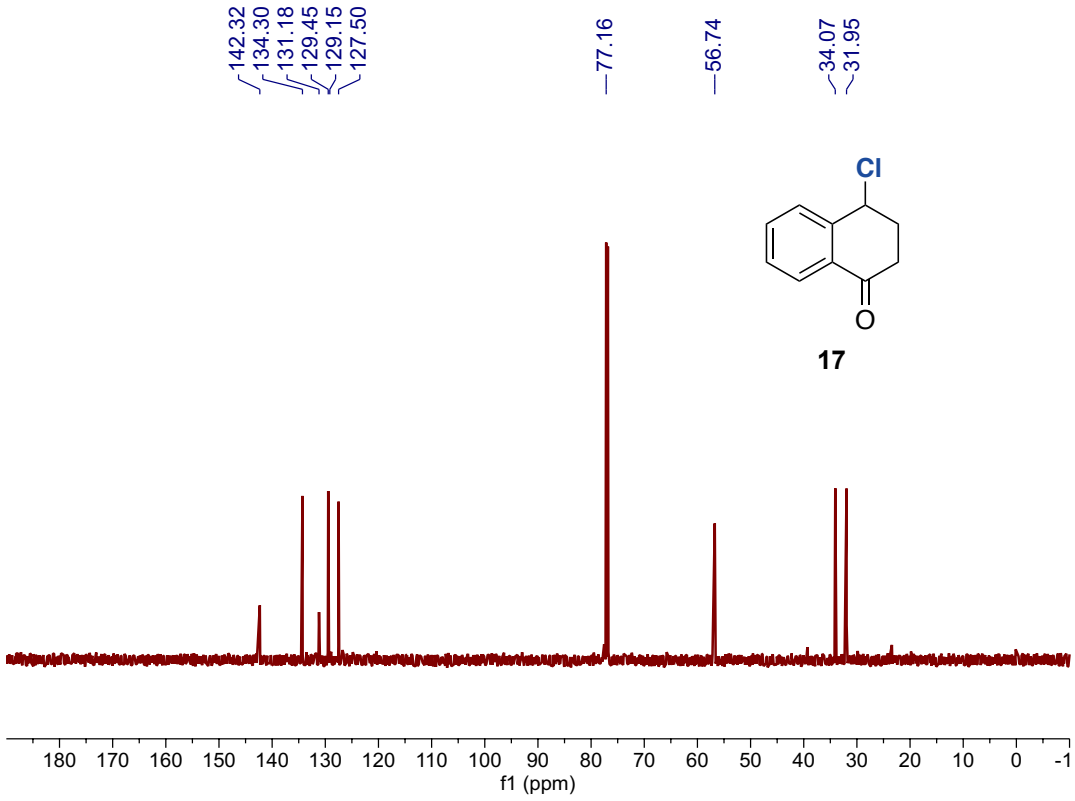
^{13}C NMR (101 MHz, $CDCl_3$) of **16**



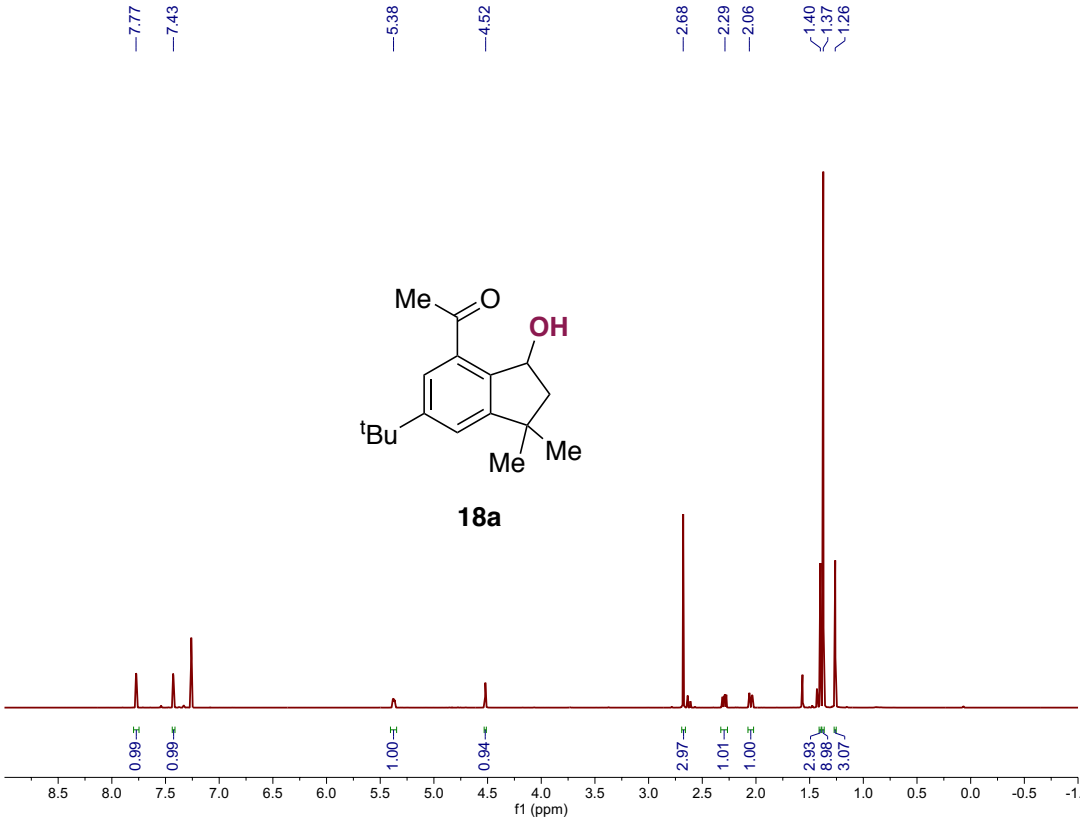
^{1}H NMR (400 MHz, $CDCl_3$) of **17**



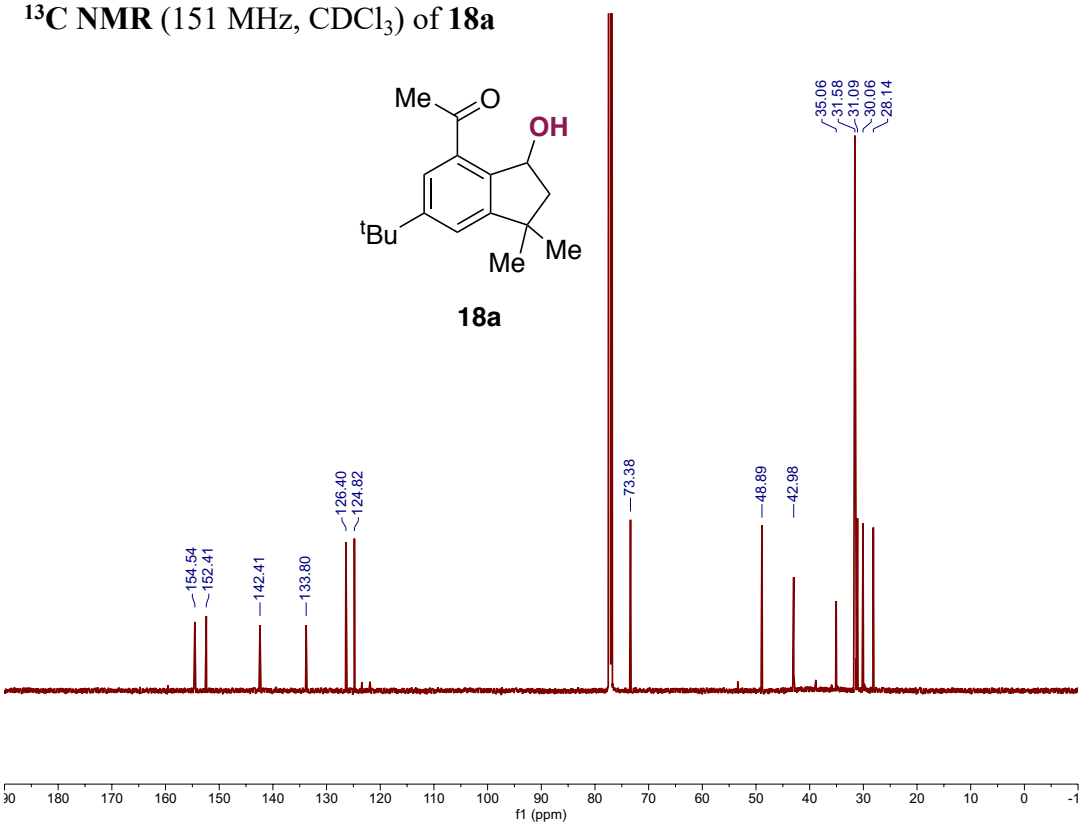
^{13}C NMR (101 MHz, $CDCl_3$) of **17**



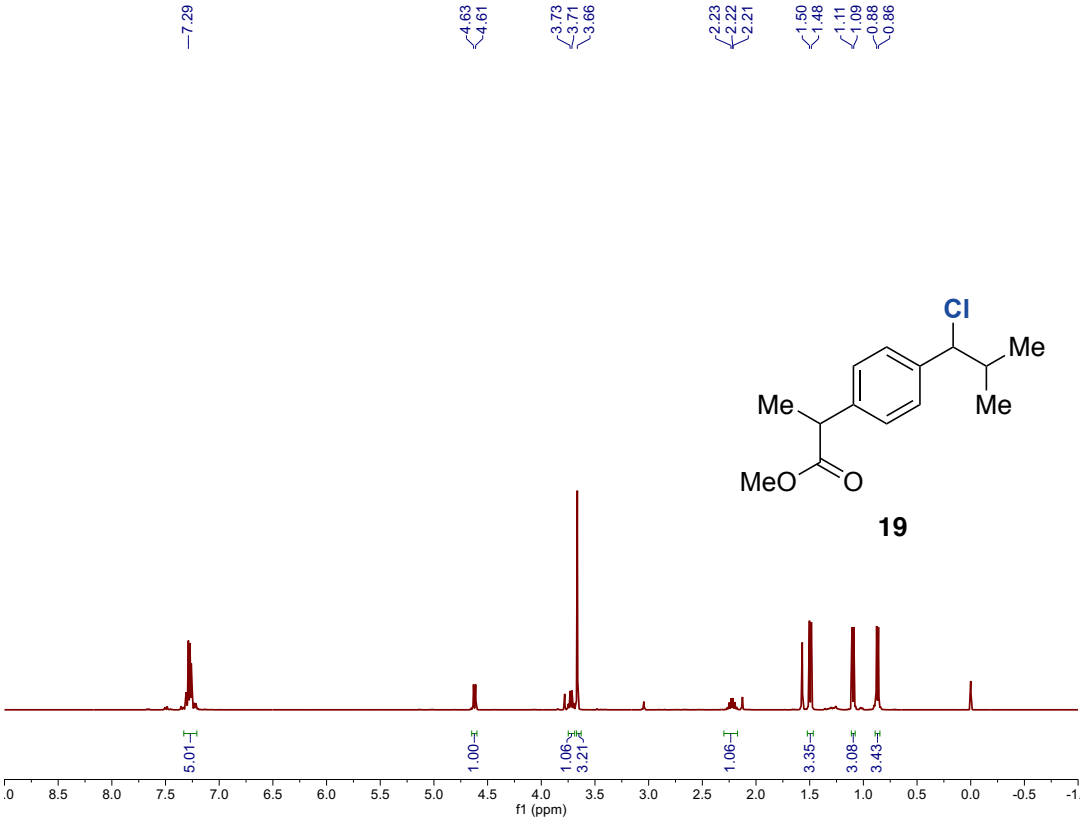
^{1}H NMR (600 MHz, $CDCl_3$) of **18a**



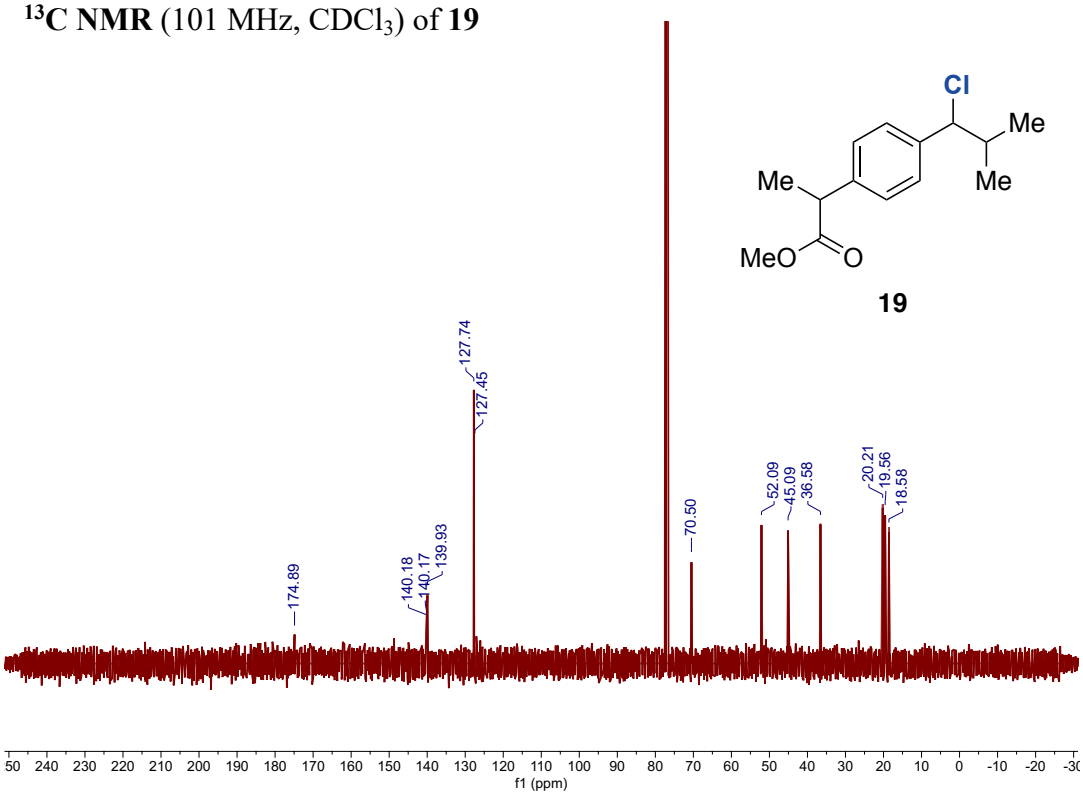
^{13}C NMR (151 MHz, $CDCl_3$) of **18a**



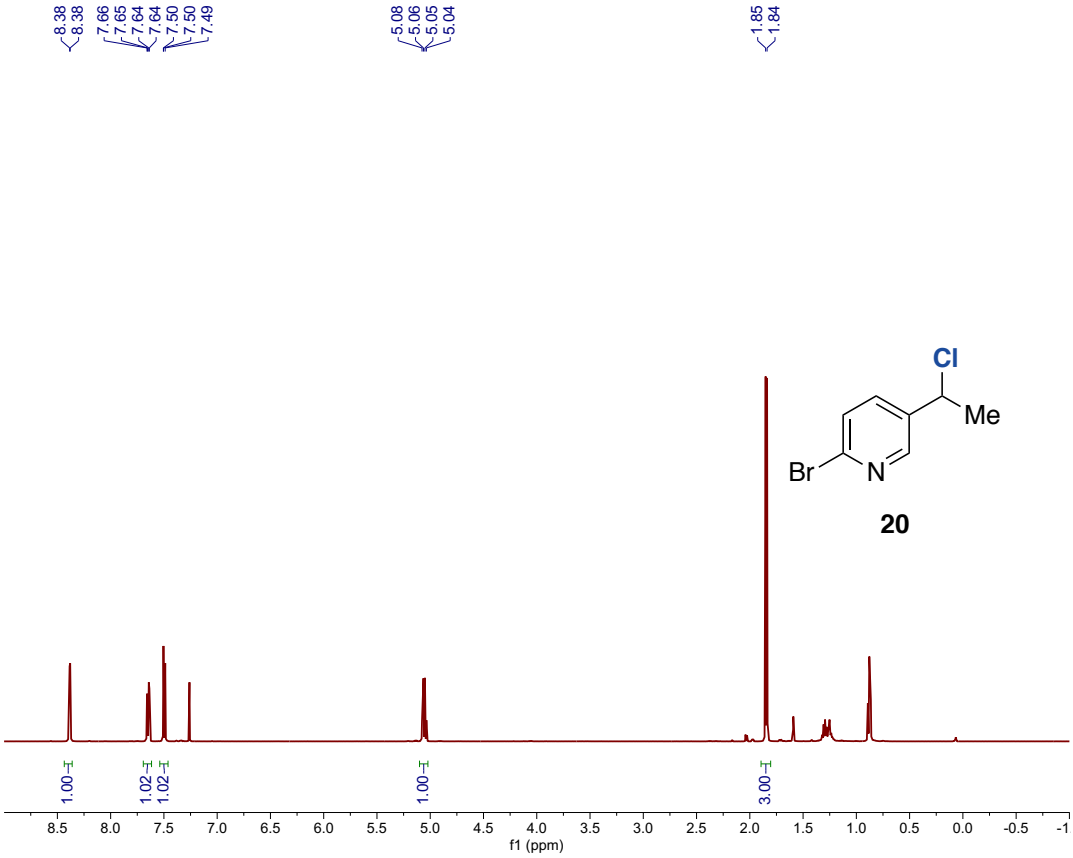
^{1}H NMR (400 MHz, $CDCl_3$) of **19**



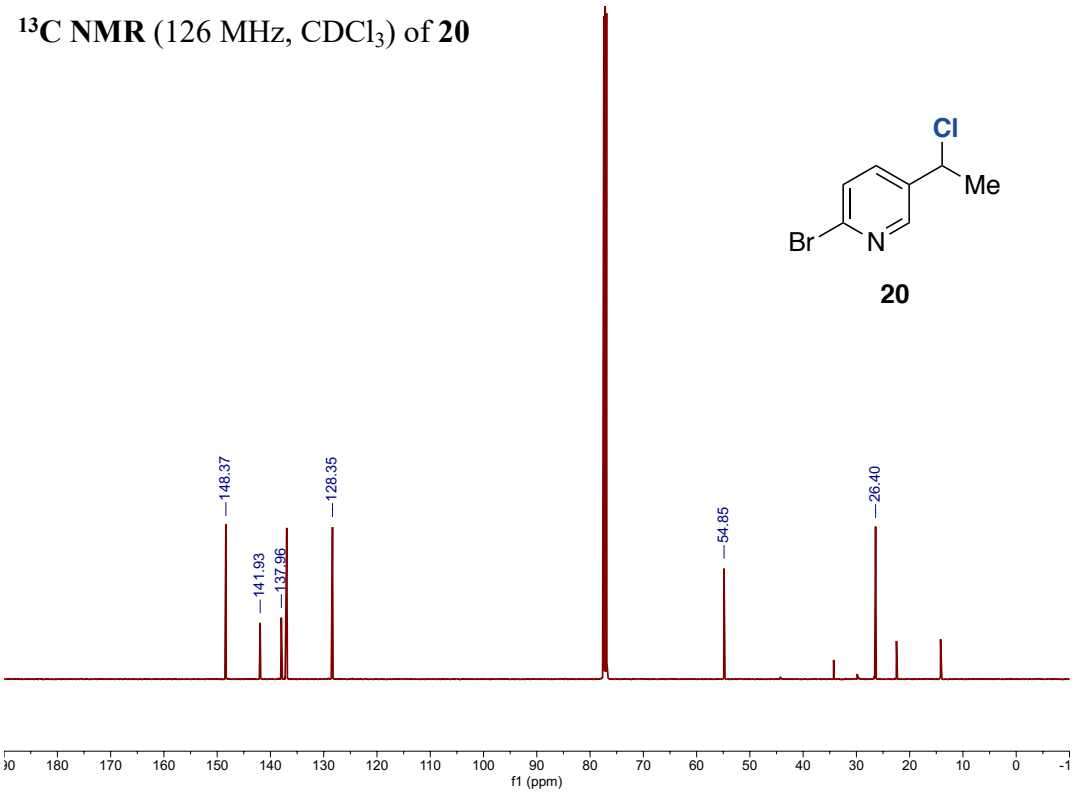
^{13}C NMR (101 MHz, $CDCl_3$) of **19**



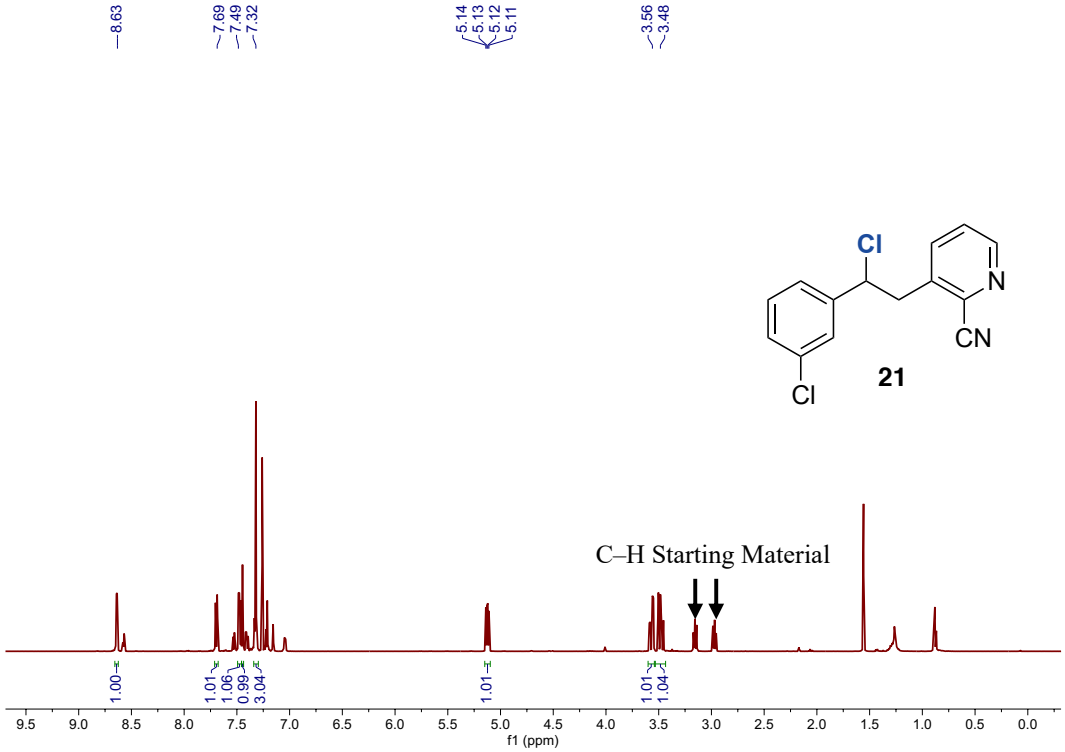
^{1}H NMR (500 MHz, $CDCl_3$) of **20**



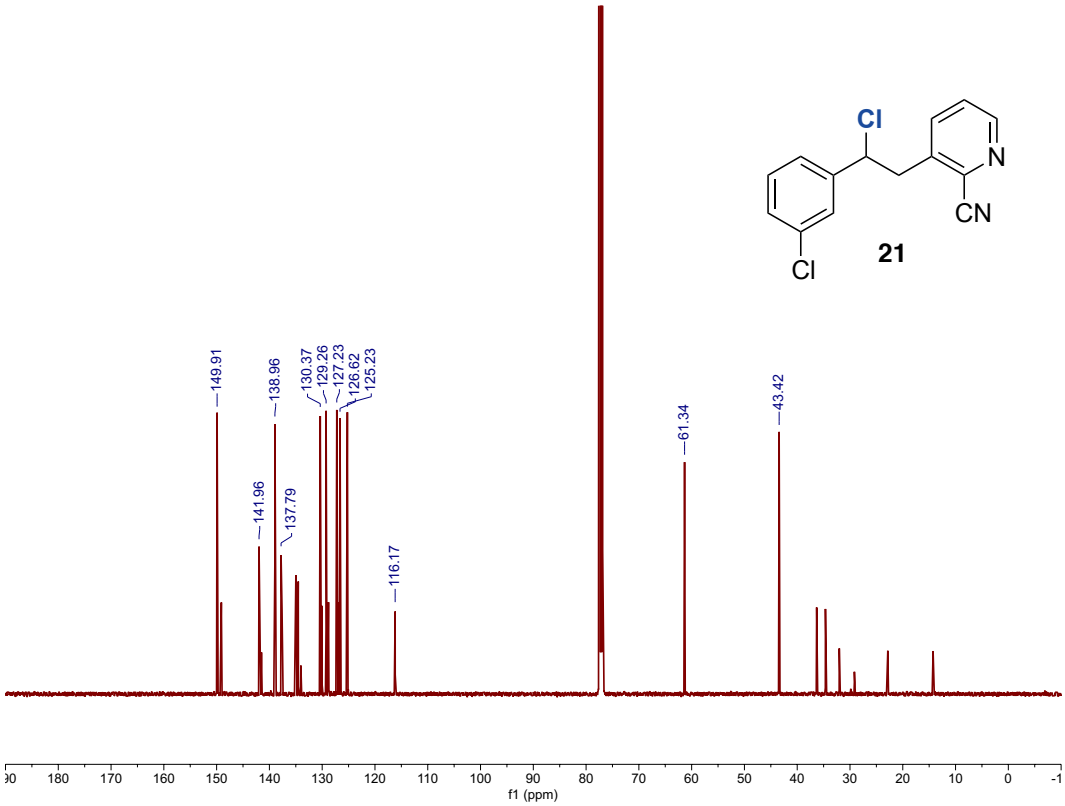
^{13}C NMR (126 MHz, $CDCl_3$) of **20**



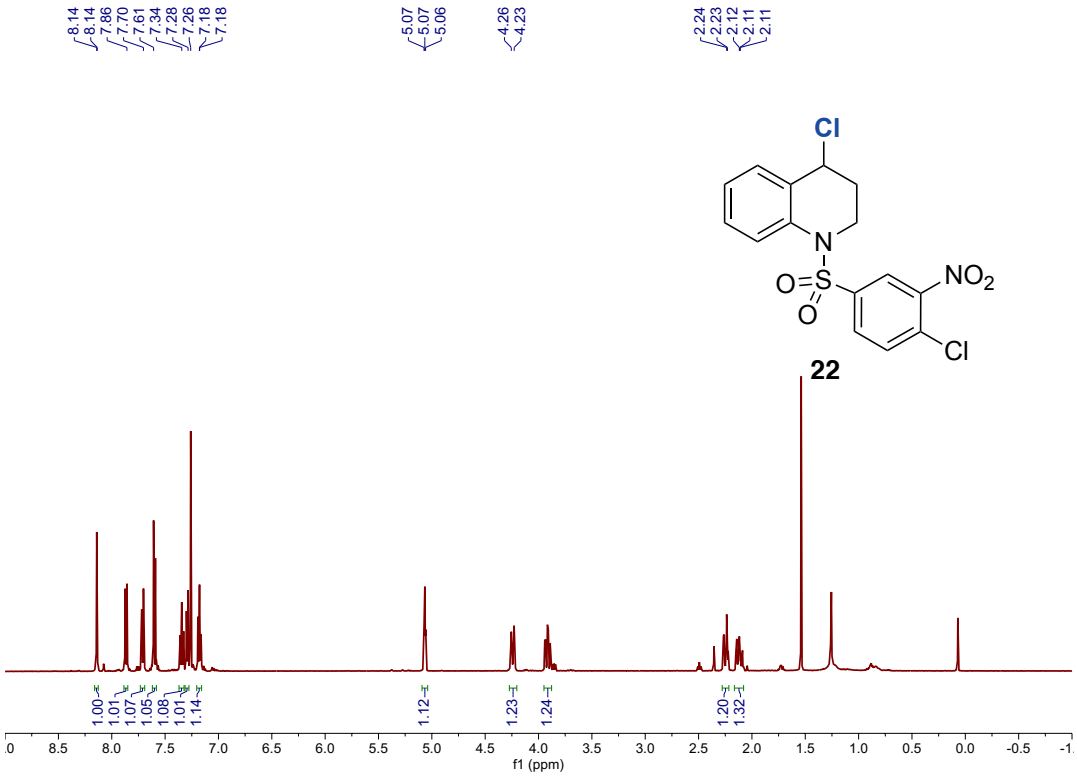
^{1}H NMR (500 MHz, $CDCl_3$) of **21**



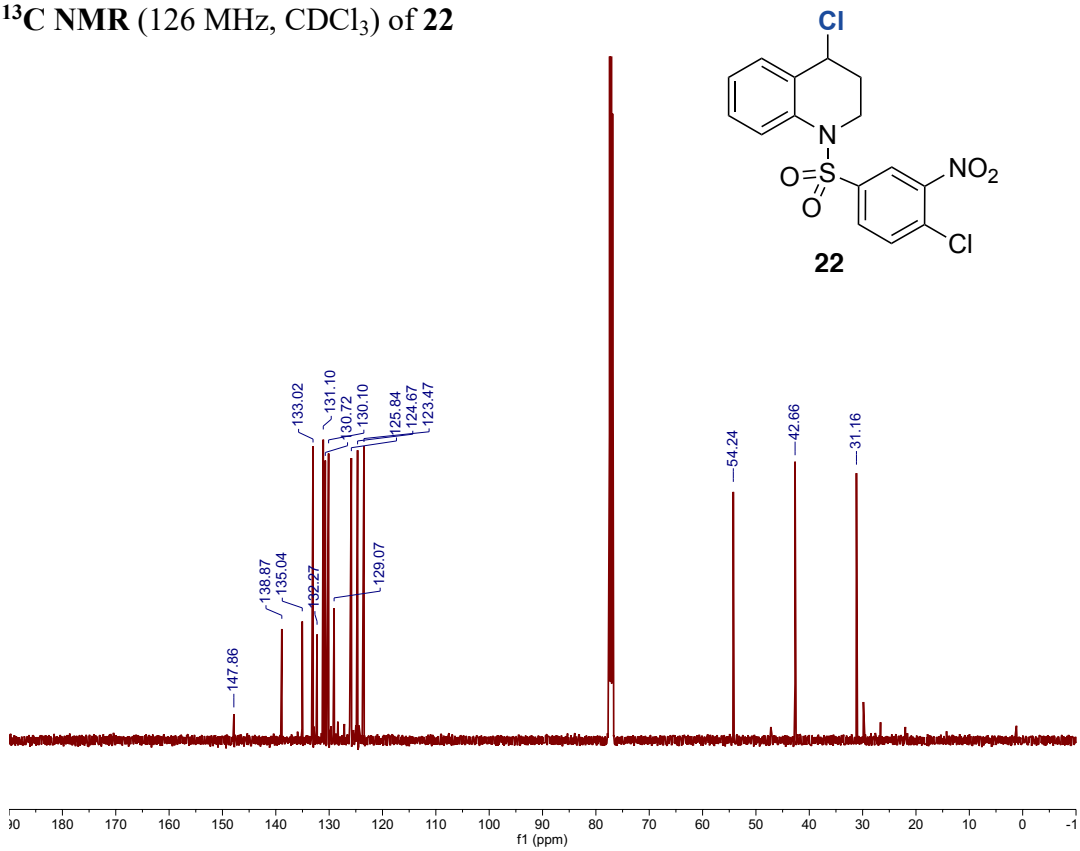
^{13}C NMR (126 MHz, $CDCl_3$) of **21**



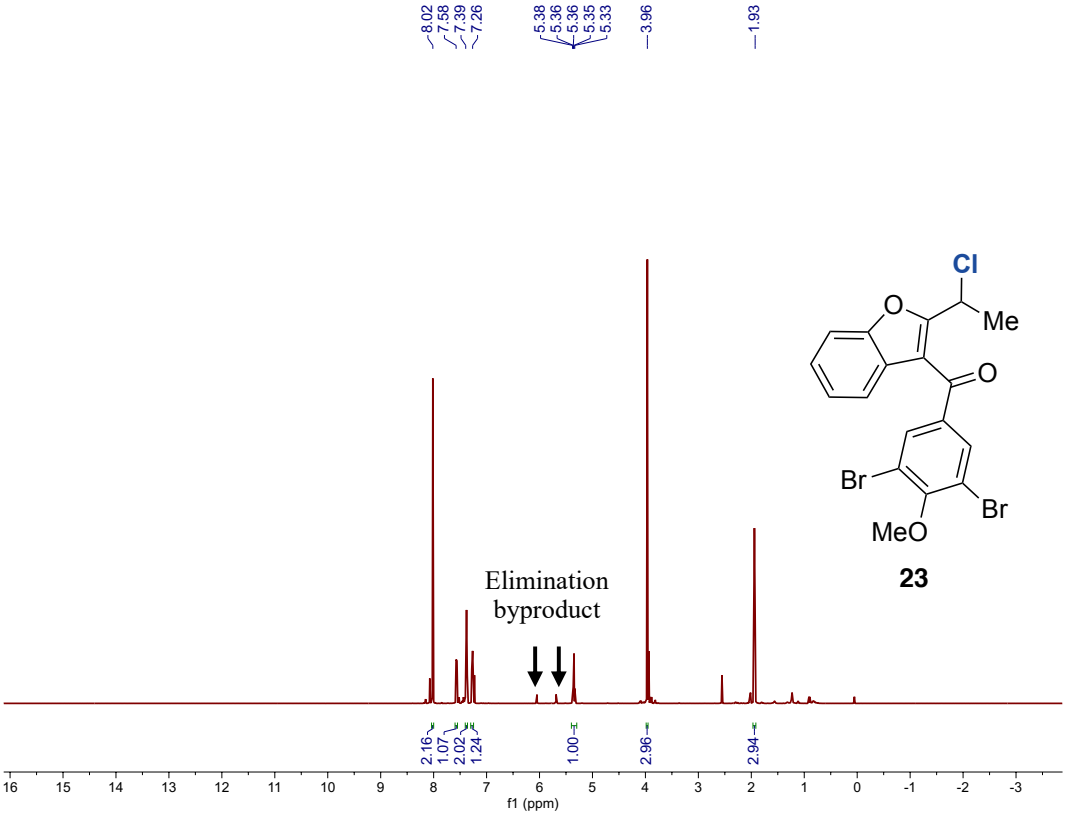
^{1}H NMR (500 MHz, $CDCl_3$) of **22**



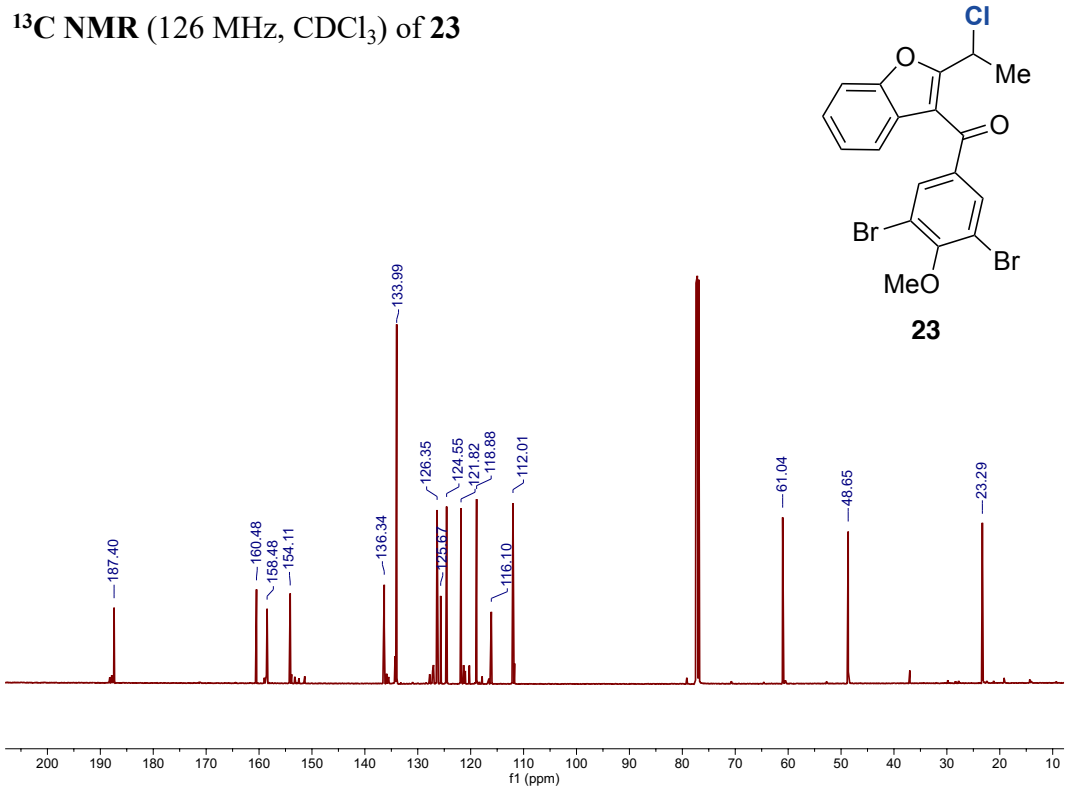
^{13}C NMR (126 MHz, $CDCl_3$) of **22**



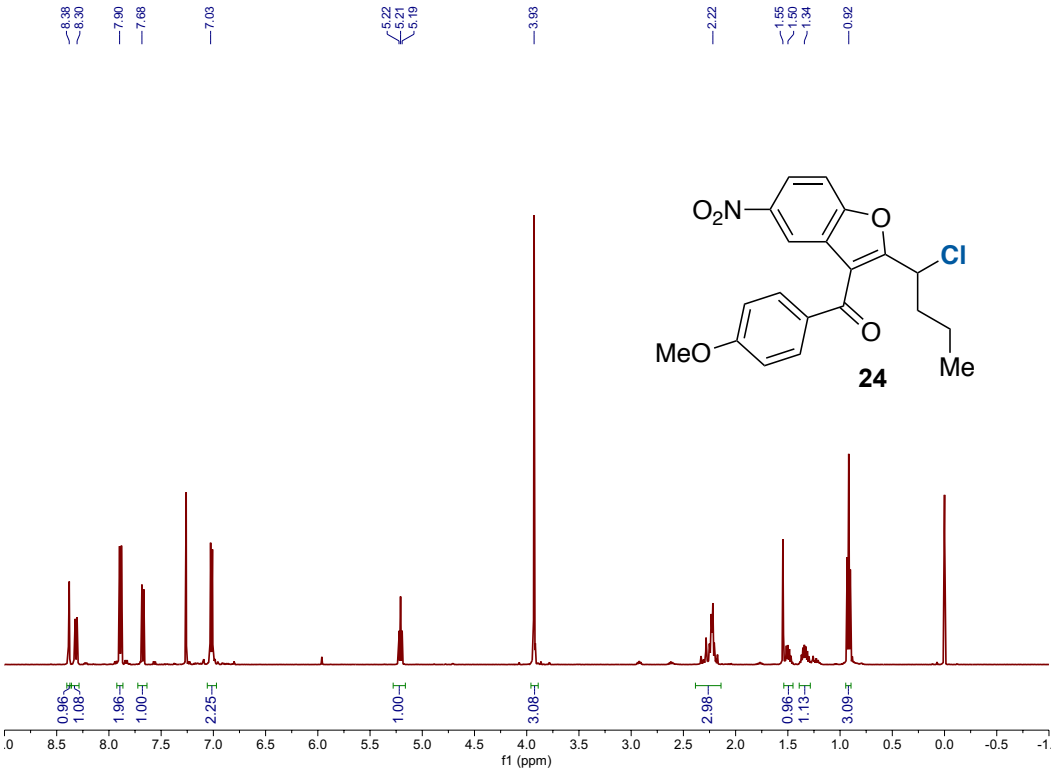
^{1}H NMR (500 MHz, $CDCl_3$) of **23**



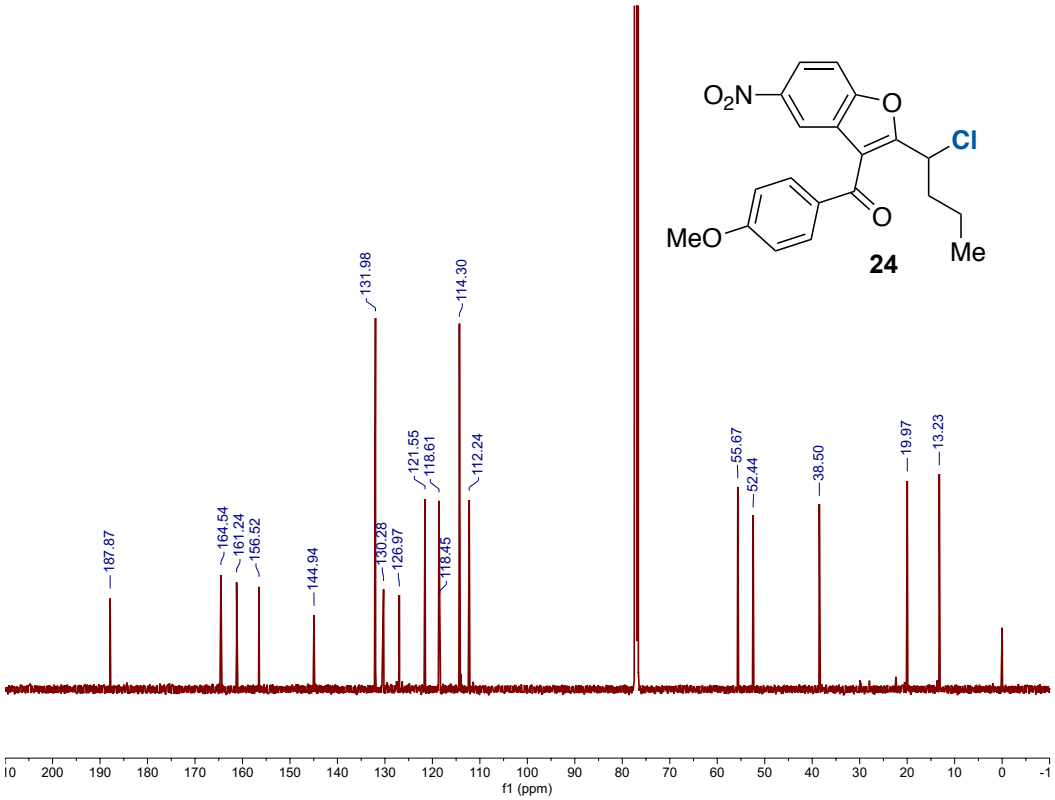
^{13}C NMR (126 MHz, $CDCl_3$) of **23**



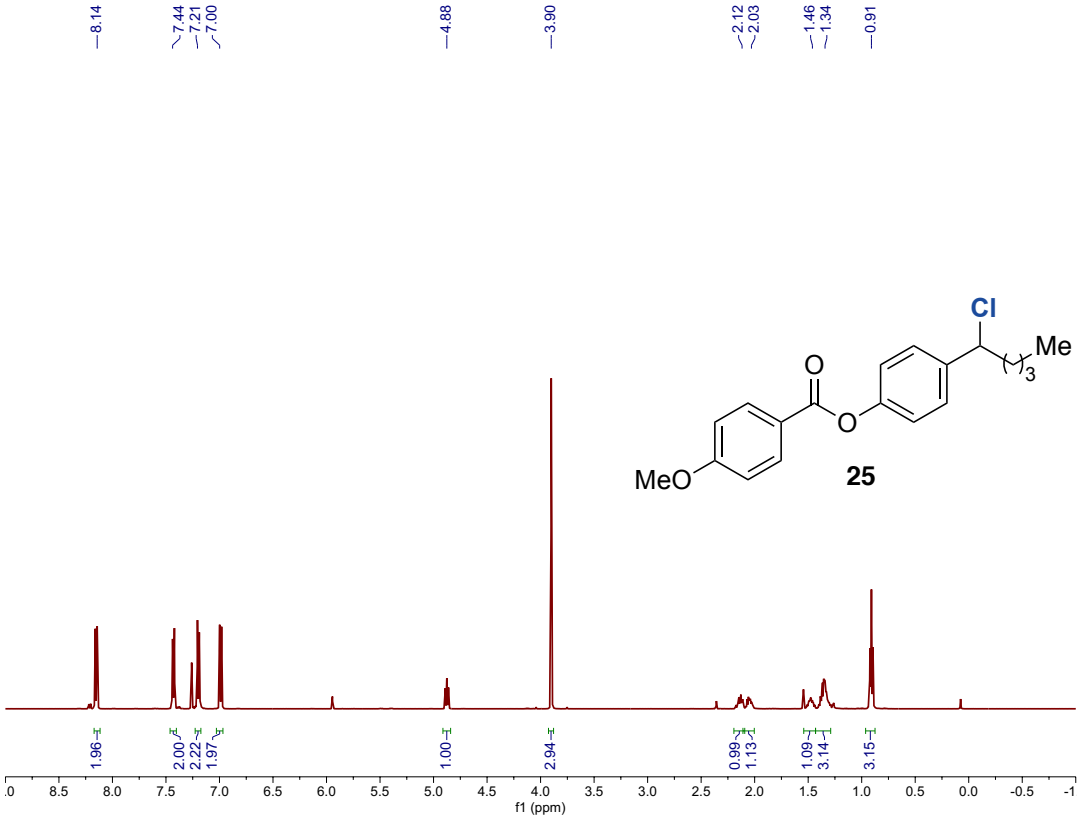
^{1}H NMR (500 MHz, $CDCl_3$) of **24**



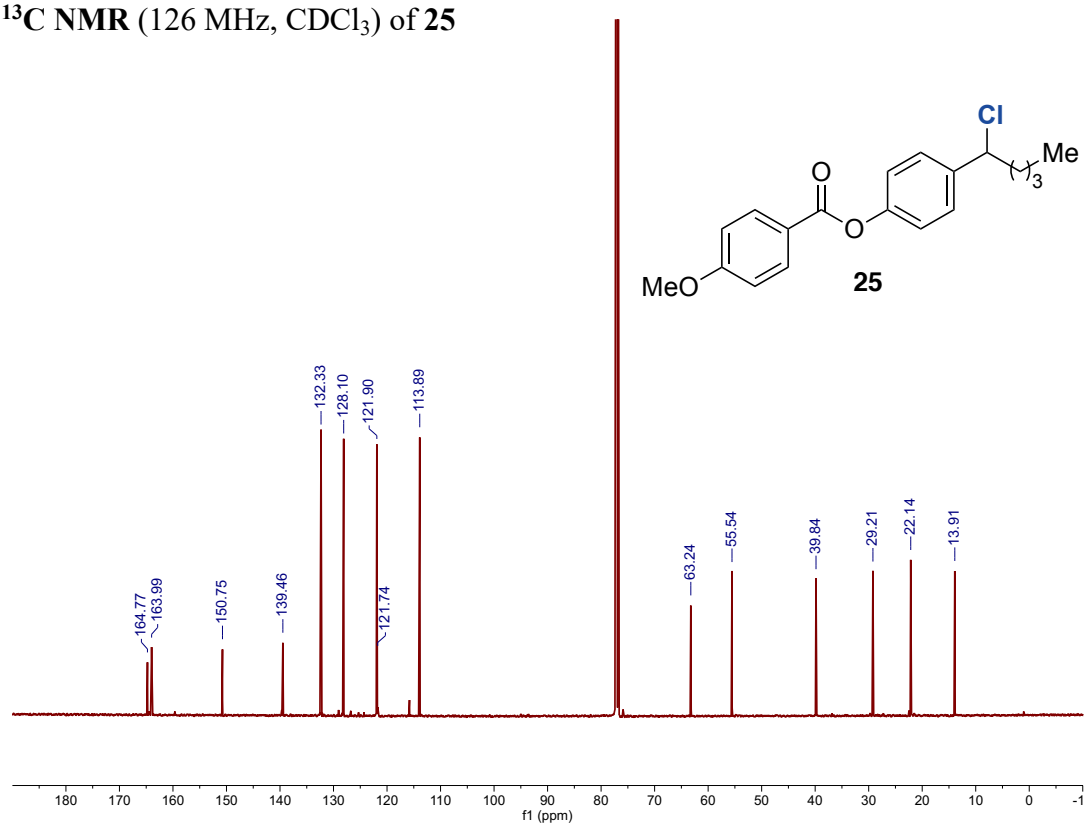
^{13}C NMR (126 MHz, $CDCl_3$) of **24**



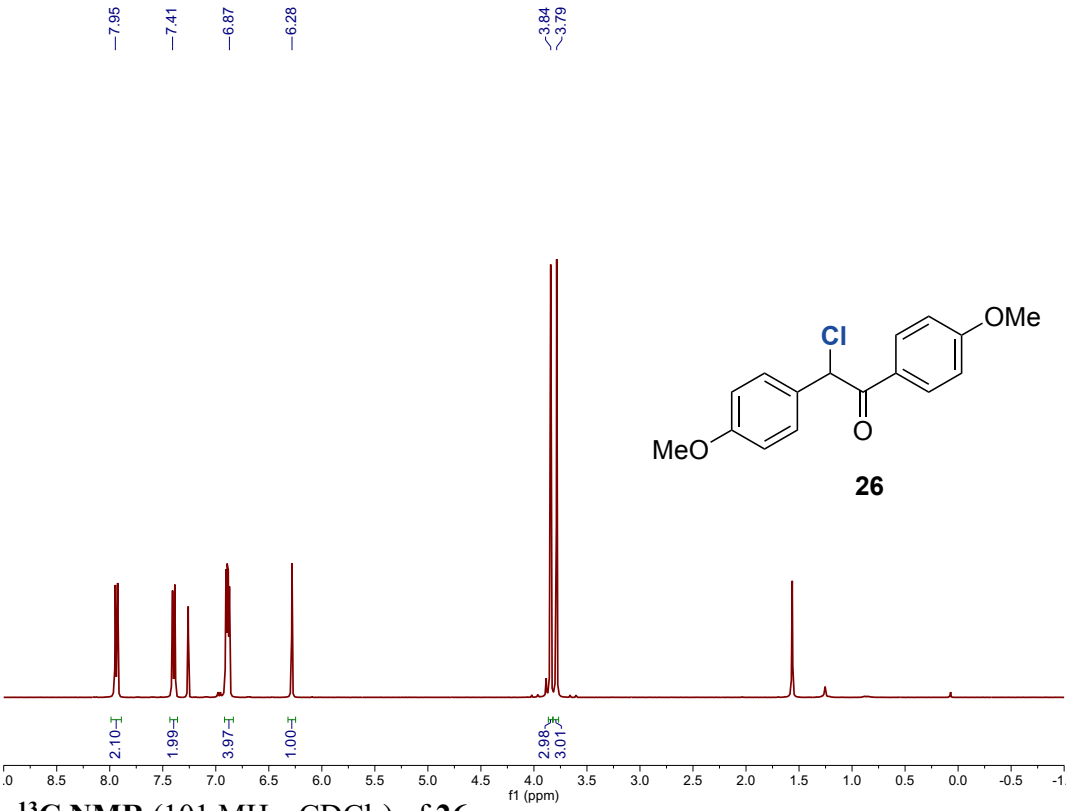
^{1}H NMR (500 MHz, $CDCl_3$) of **25**



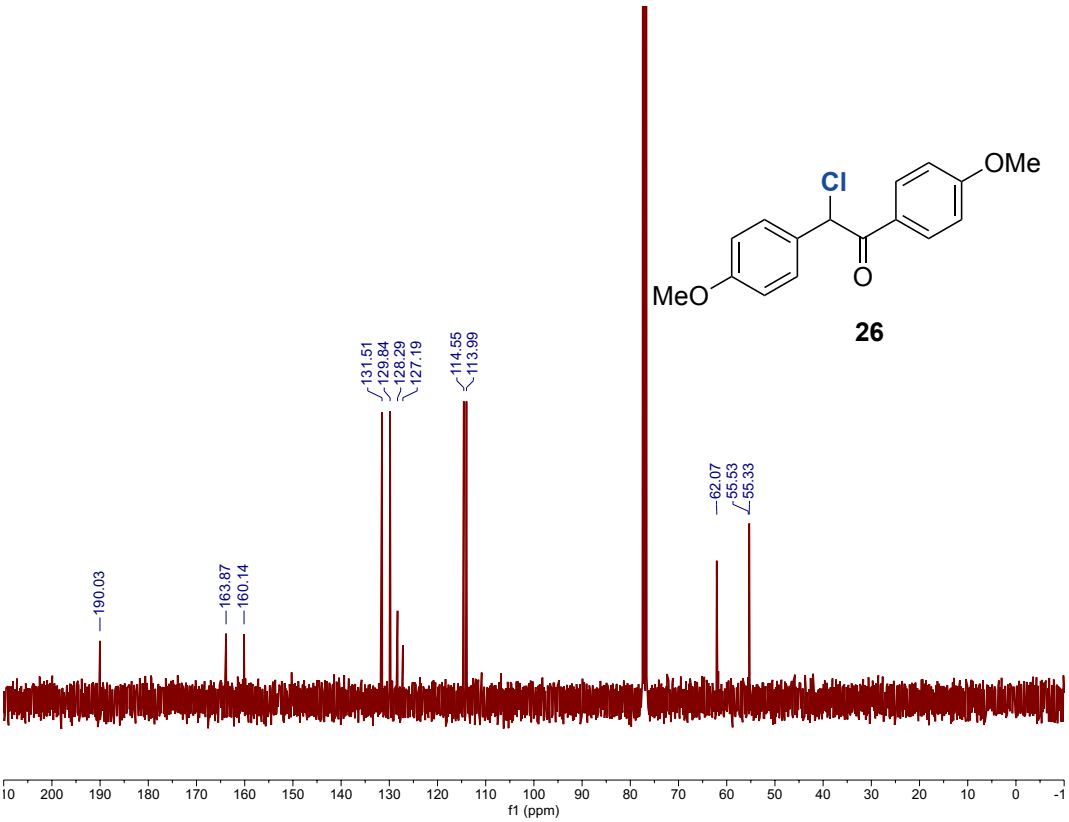
^{13}C NMR (126 MHz, $CDCl_3$) of **25**



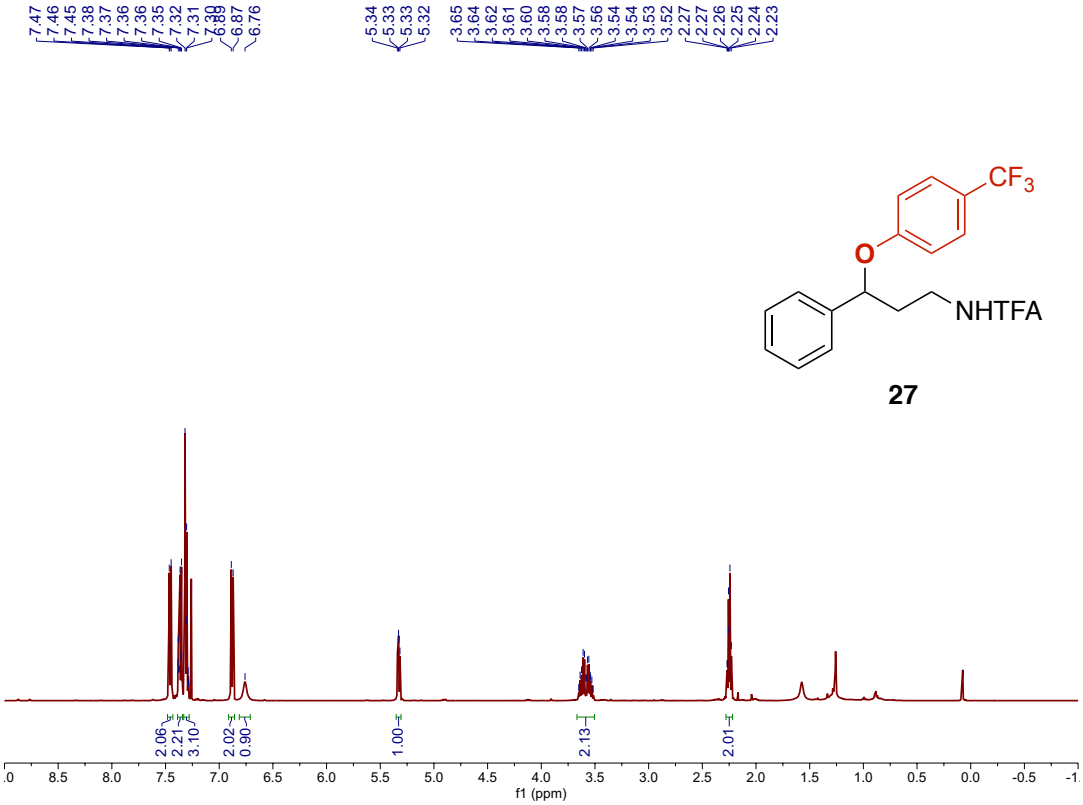
^{1}H NMR (400 MHz, $CDCl_3$) of **26**



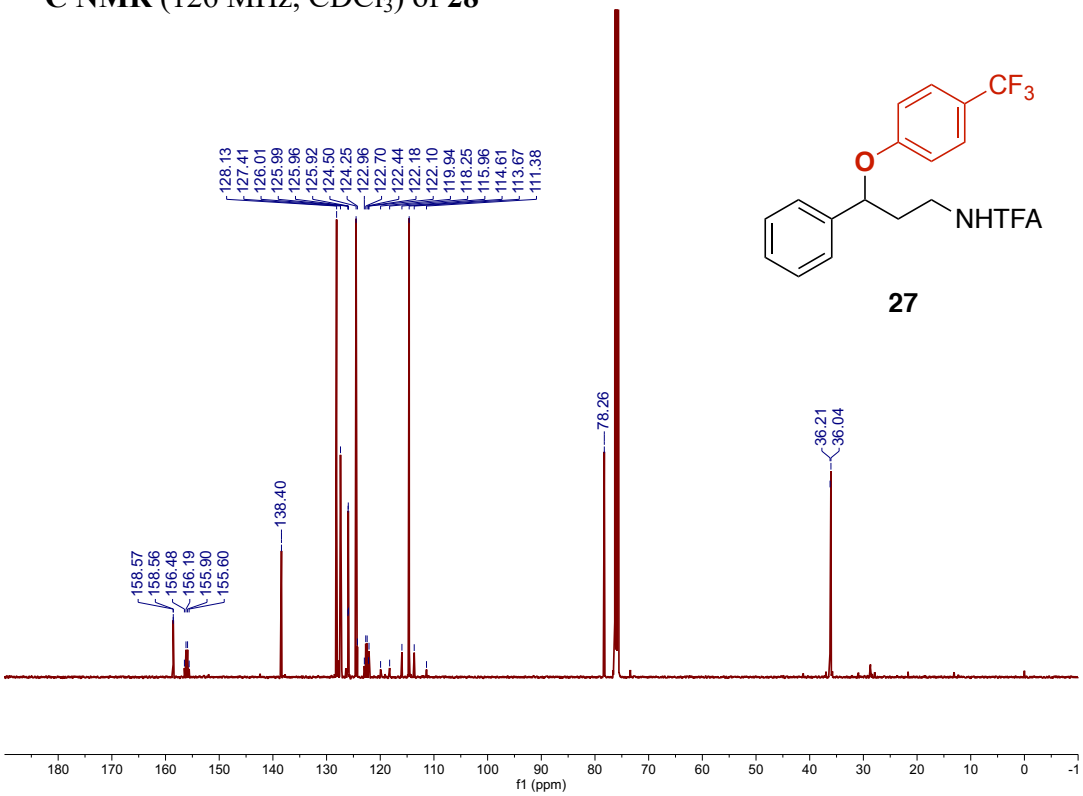
^{13}C NMR (101 MHz, $CDCl_3$) of **26**



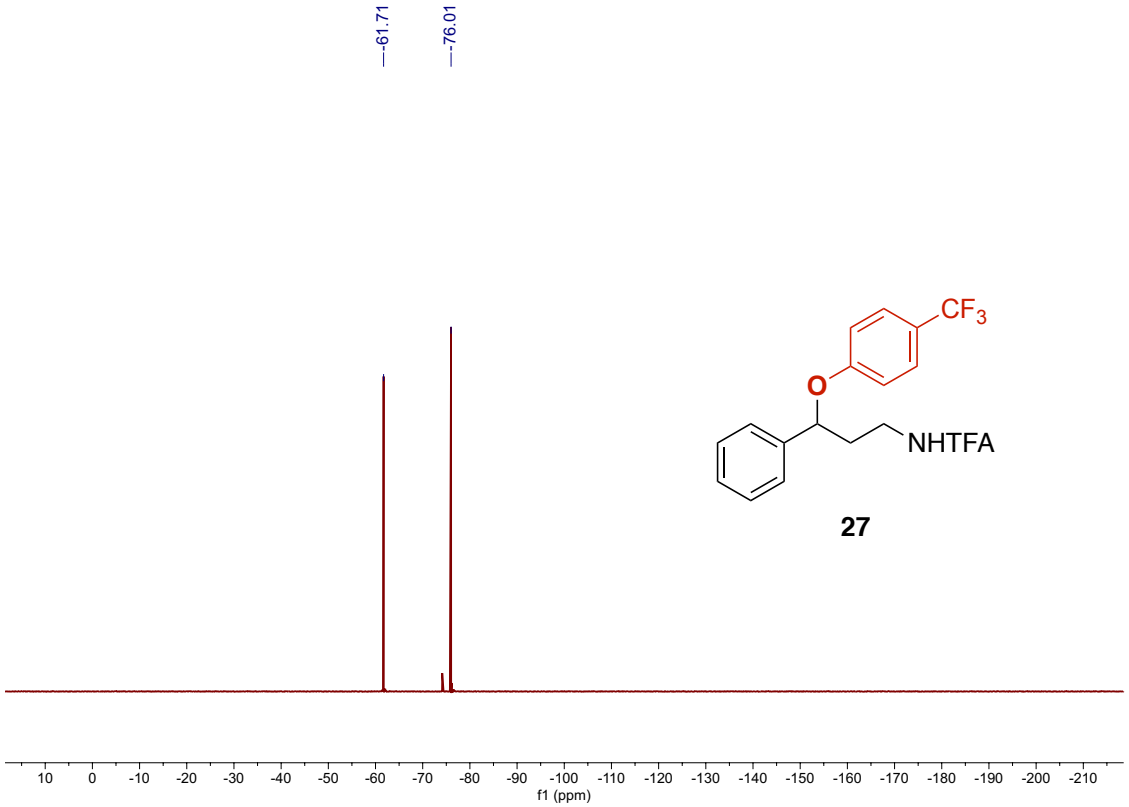
^{1}H NMR (500 MHz, $CDCl_3$) of **27**



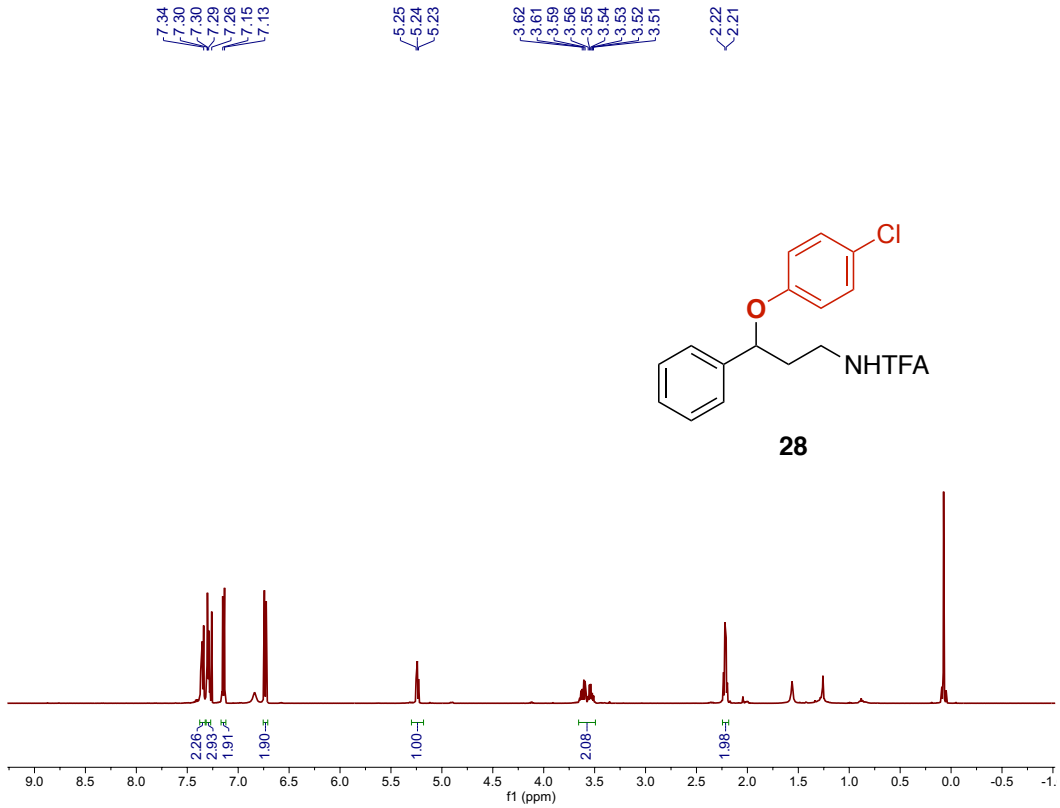
^{13}C NMR (126 MHz, $CDCl_3$) of **28**



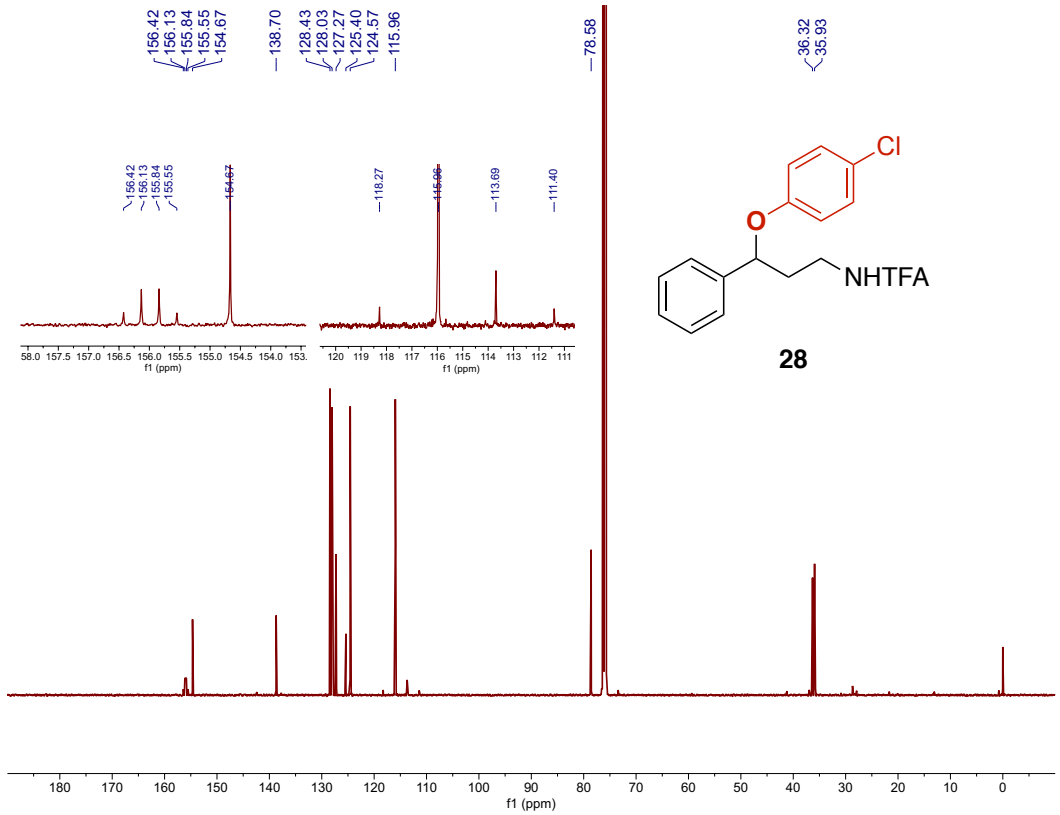
^{19}F NMR (377 MHz, $CDCl_3$) of **27**



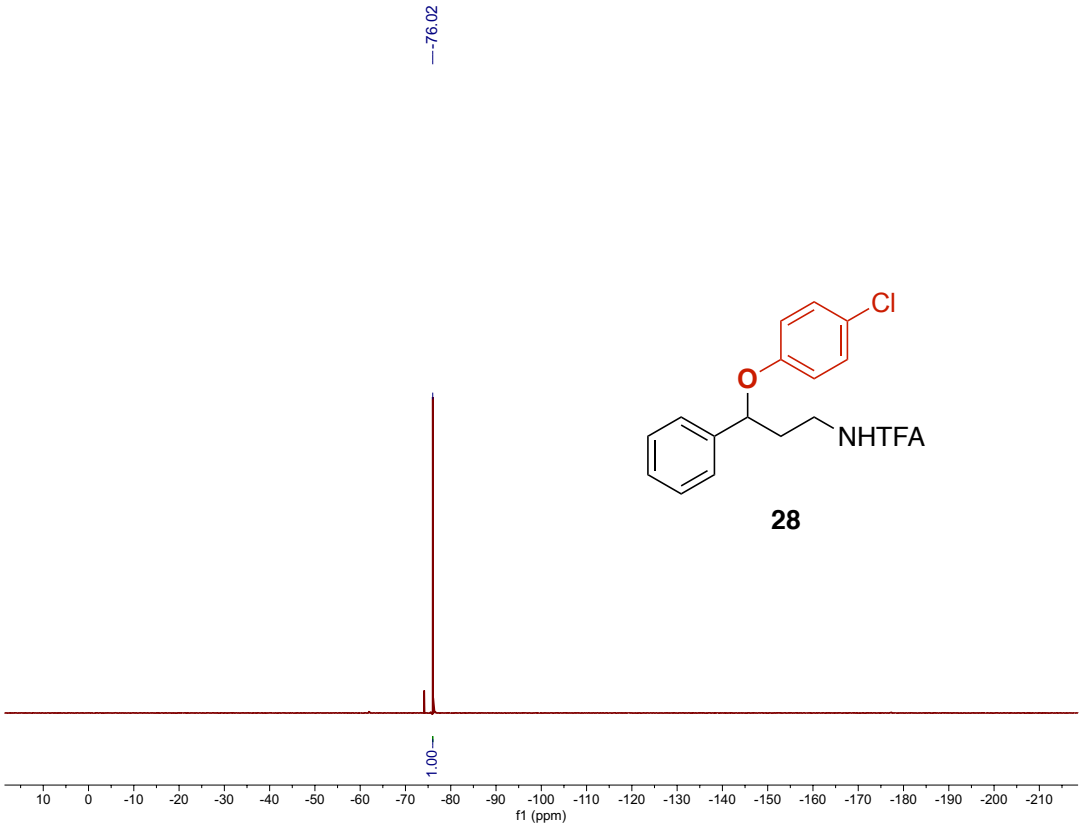
^{1}H NMR (500 MHz, $CDCl_3$) of **28**



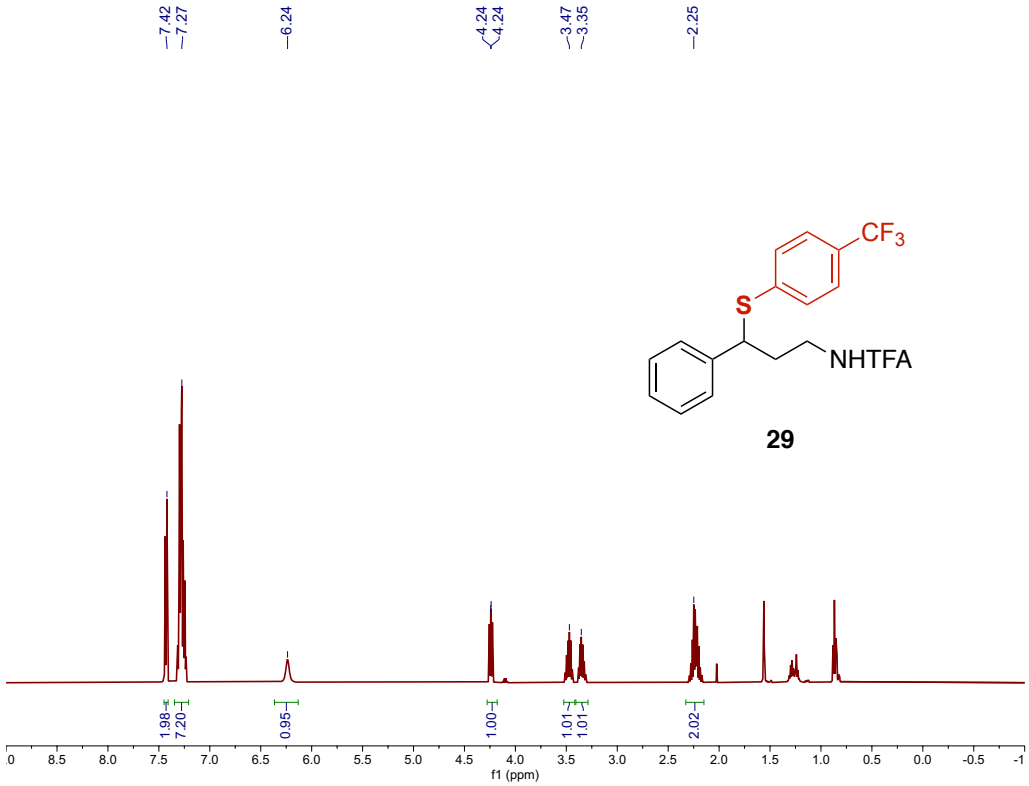
^{13}C NMR (126 MHz, $CDCl_3$) of **28**



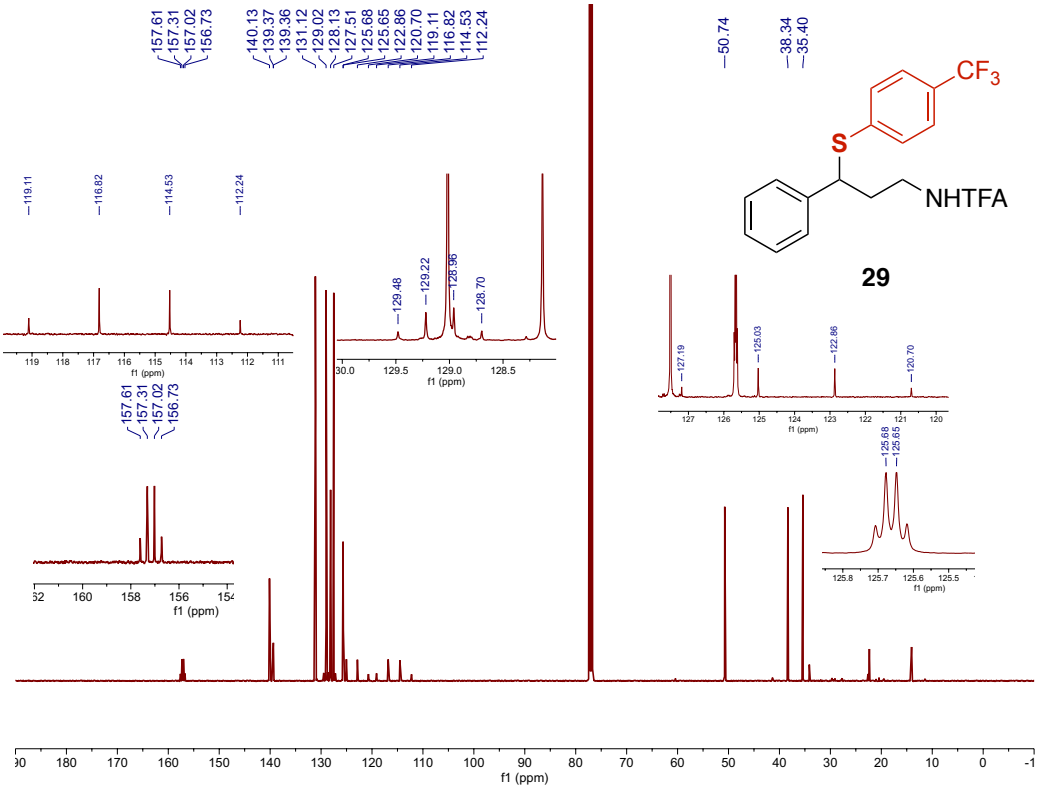
^{19}F NMR (377 MHz, $CDCl_3$) of **28**



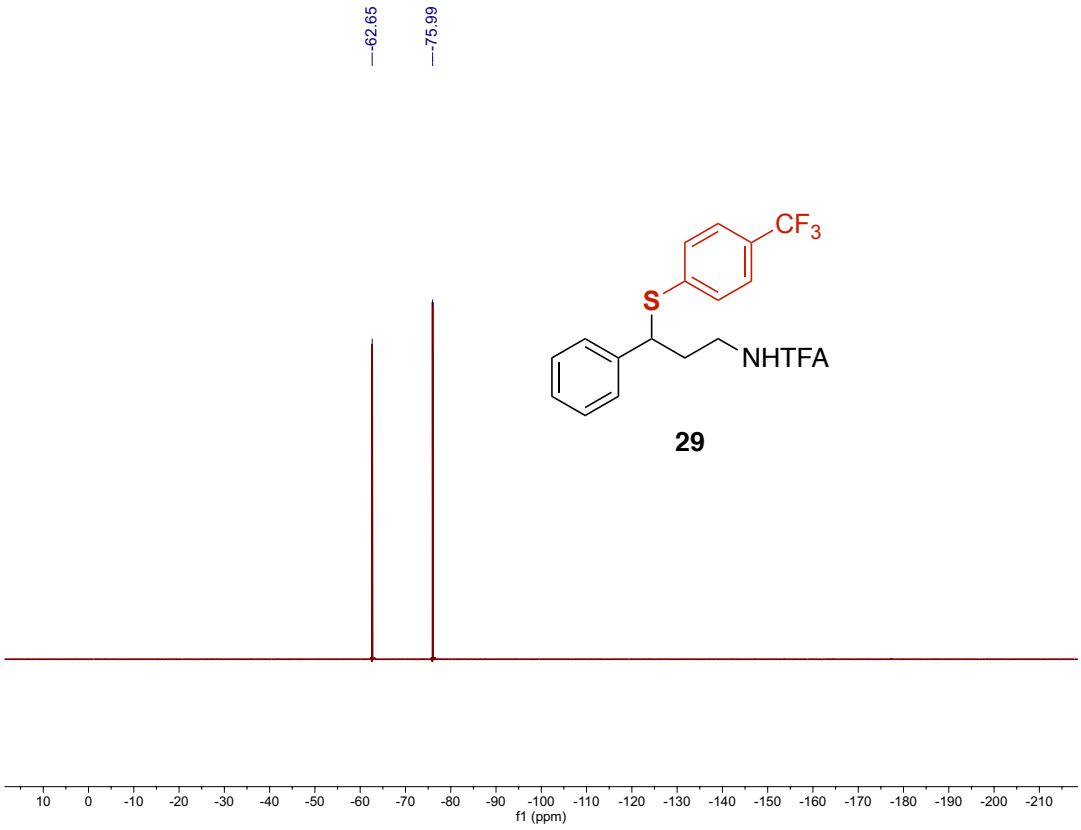
^{1}H NMR (500 MHz, $CDCl_3$) of **29**



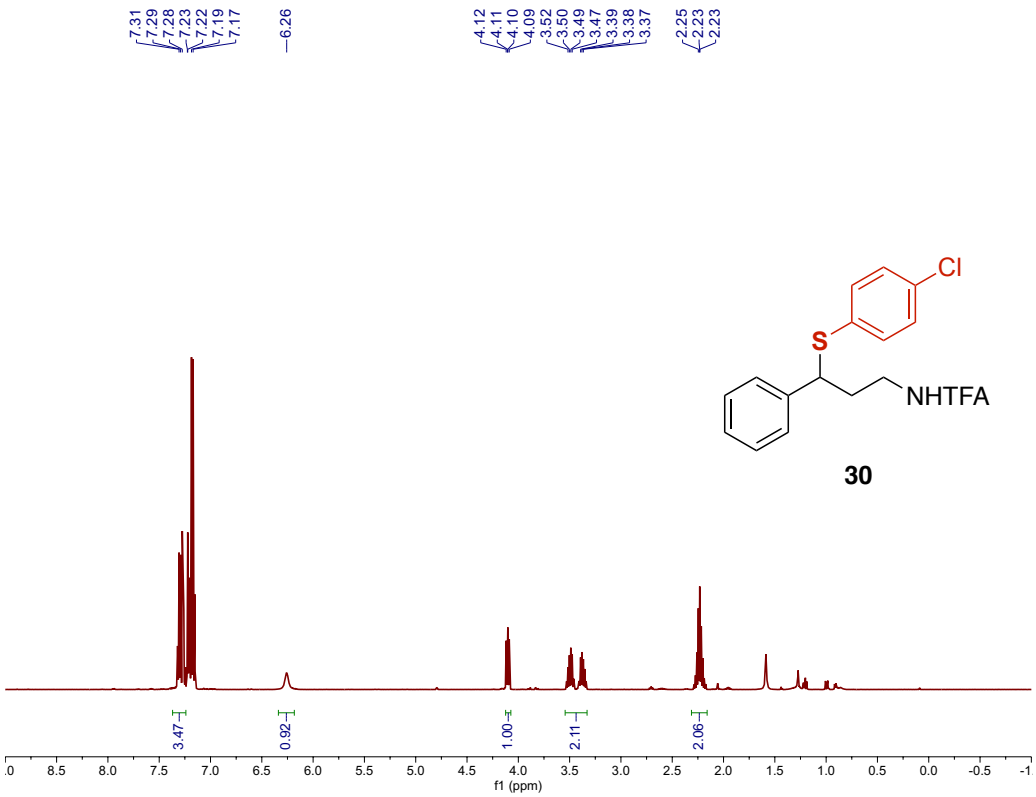
^{13}C NMR (126 MHz, $CDCl_3$) of **29**



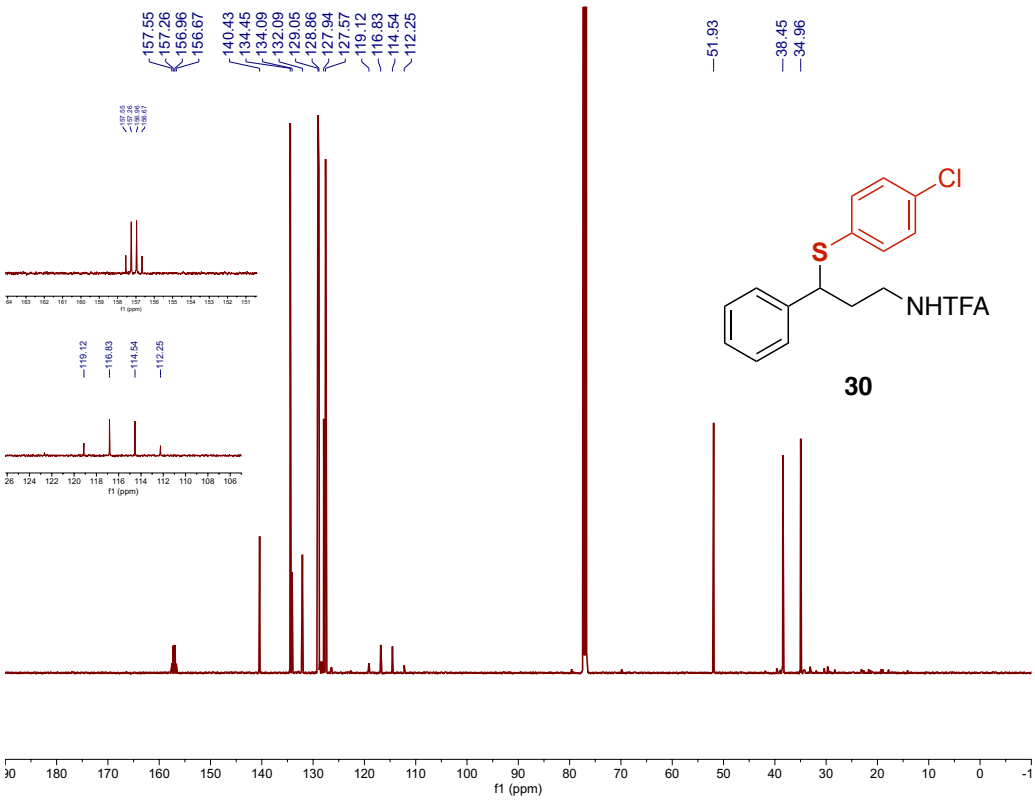
^{19}F NMR (377 MHz, $CDCl_3$) of **29**



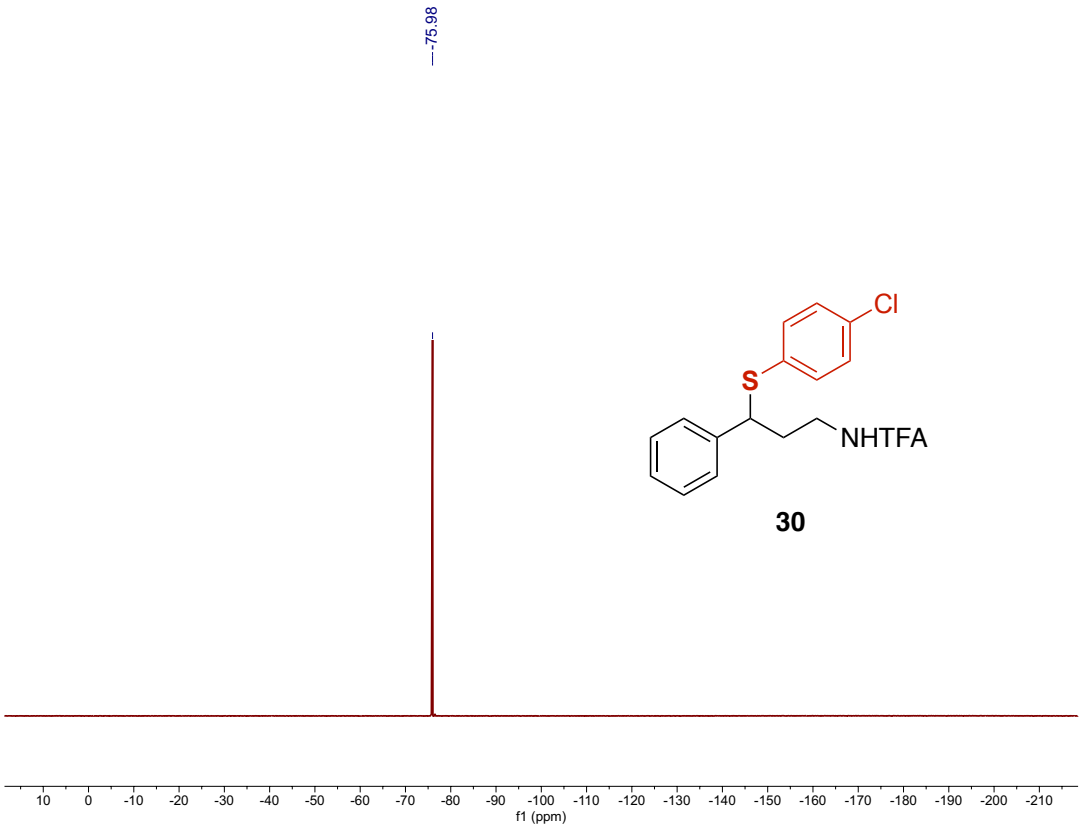
^{1}H NMR (500 MHz, $CDCl_3$) of **30**



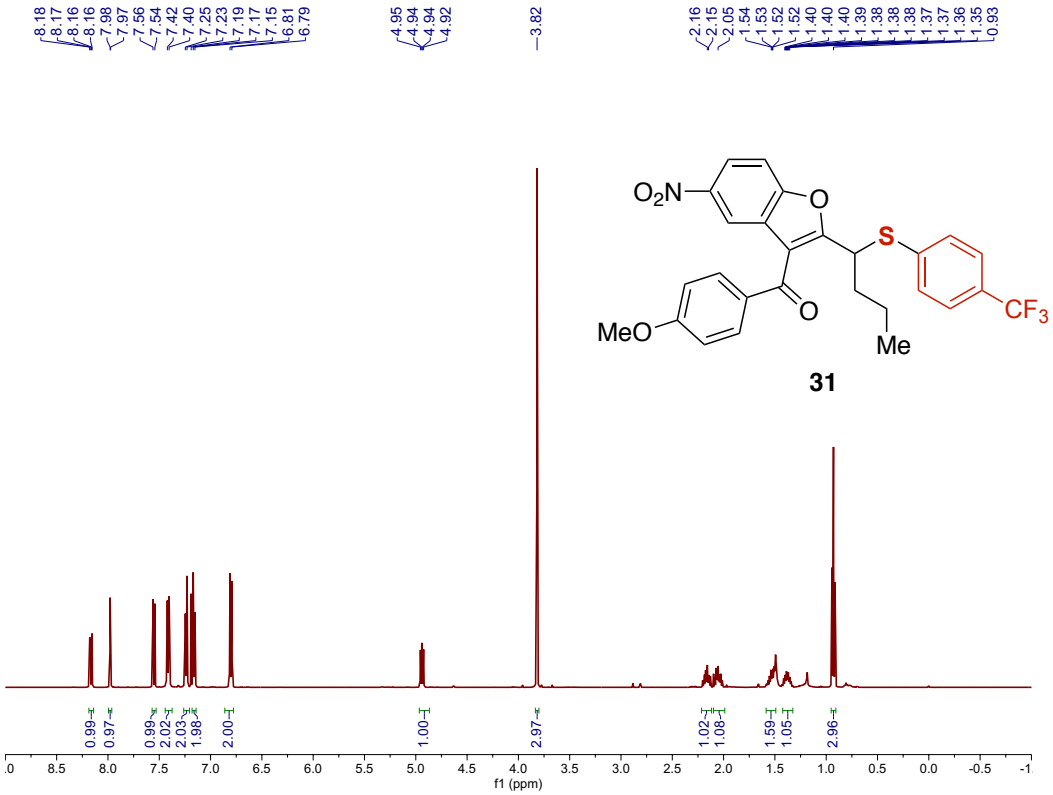
^{13}C NMR (126 MHz, $CDCl_3$) of **30**



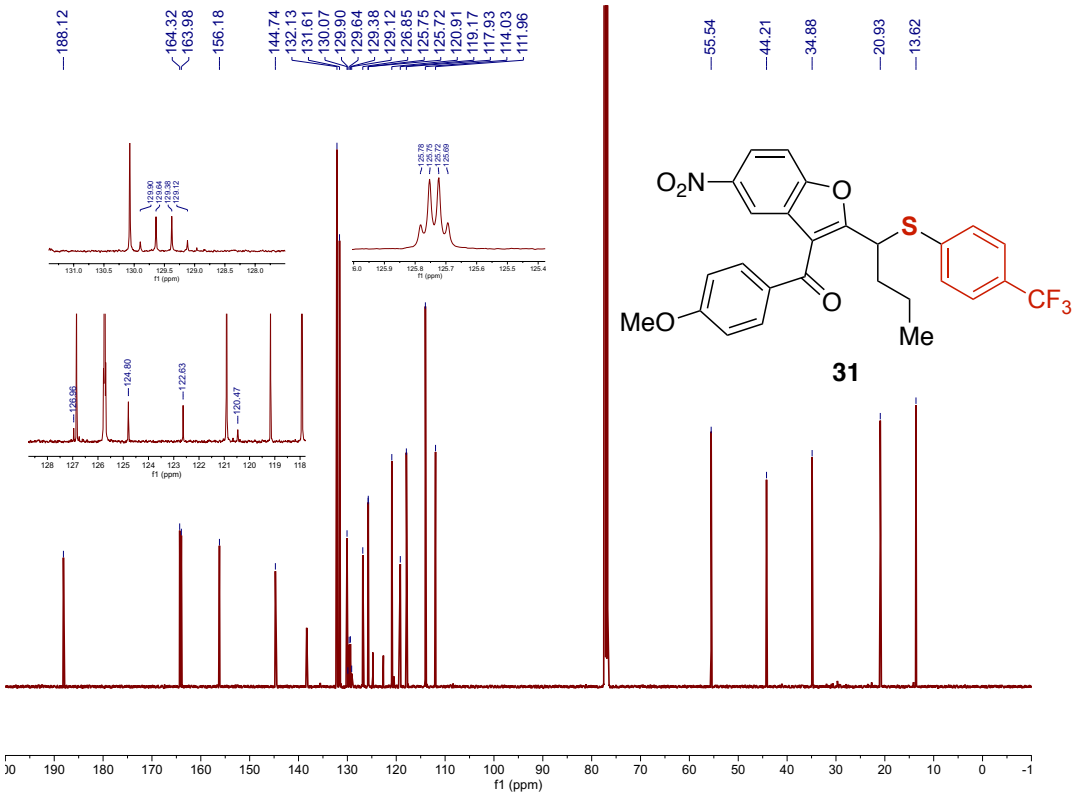
^{19}F NMR (377 MHz, $CDCl_3$) of **30**



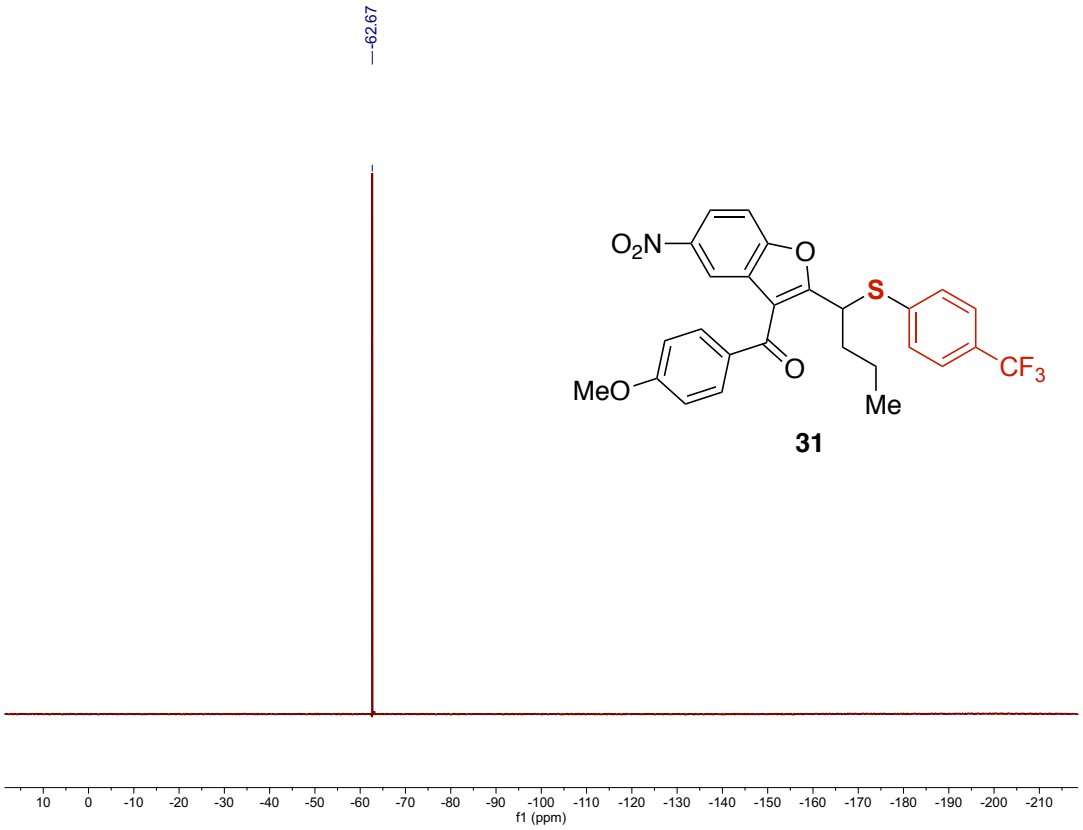
^{1}H NMR (500 MHz, $CDCl_3$) of **31**



^{13}C NMR (126 MHz, $CDCl_3$) of **31**

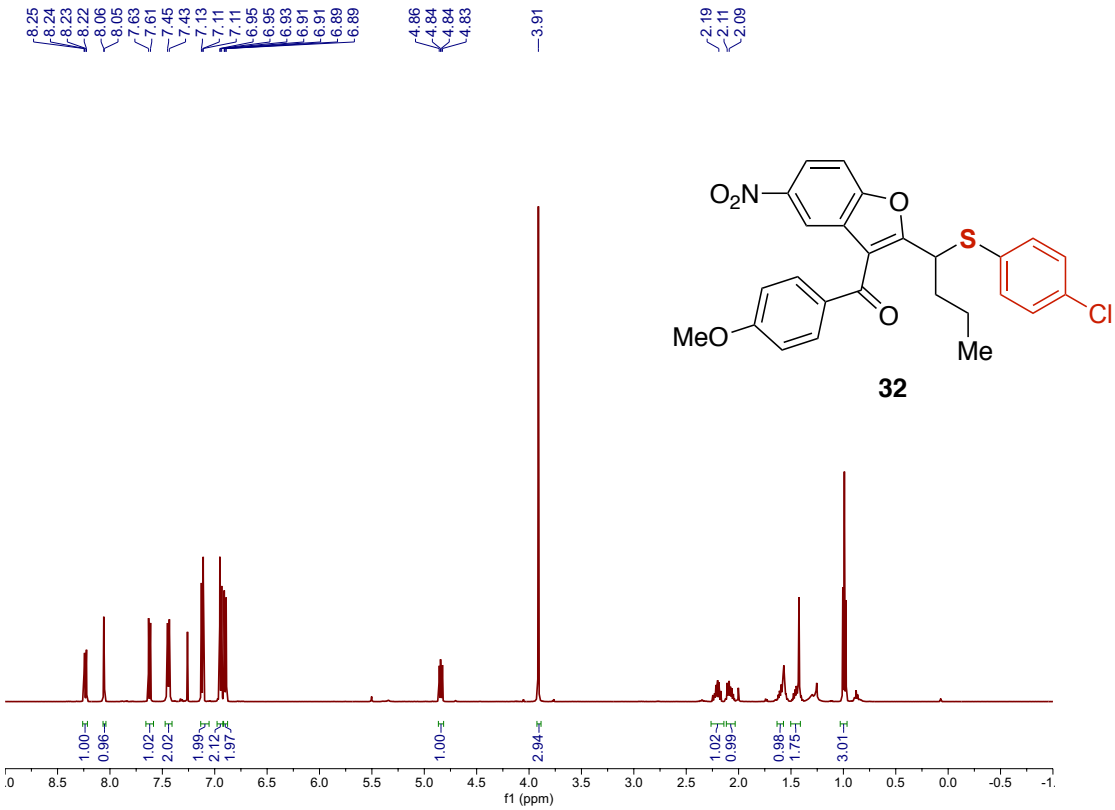


^{19}F NMR (377 MHz, $CDCl_3$) of **31**

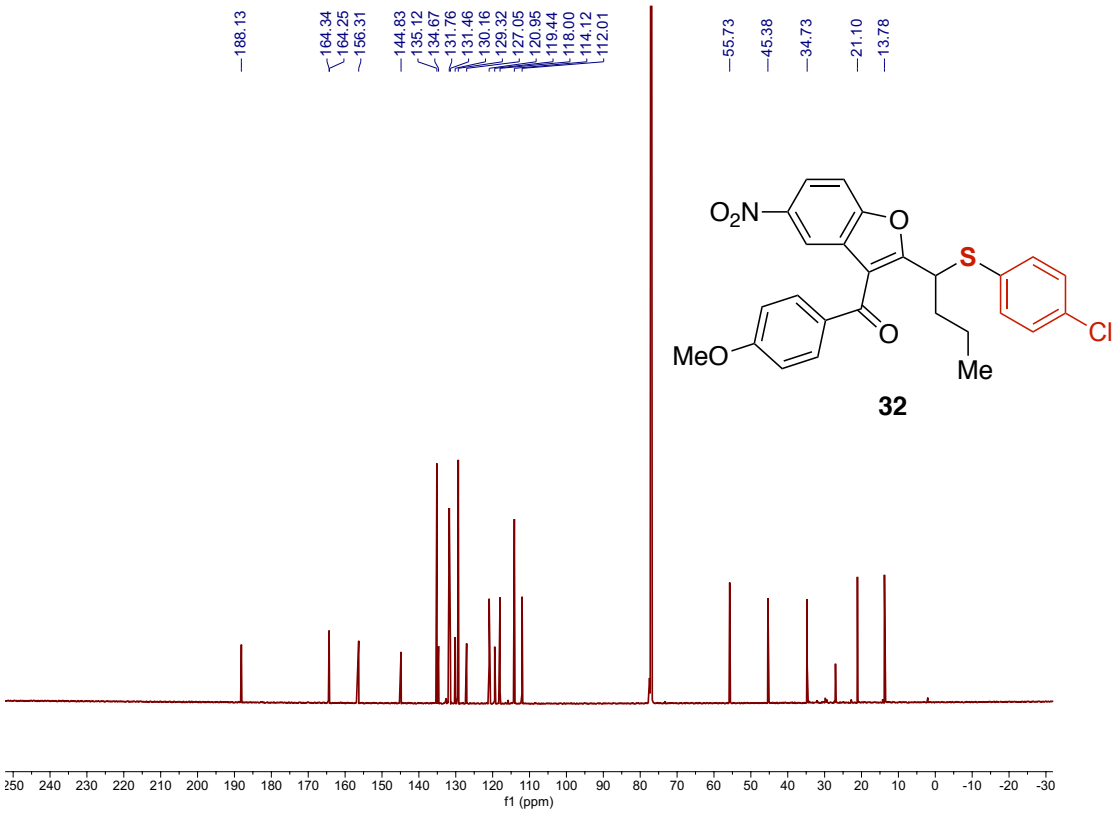


31

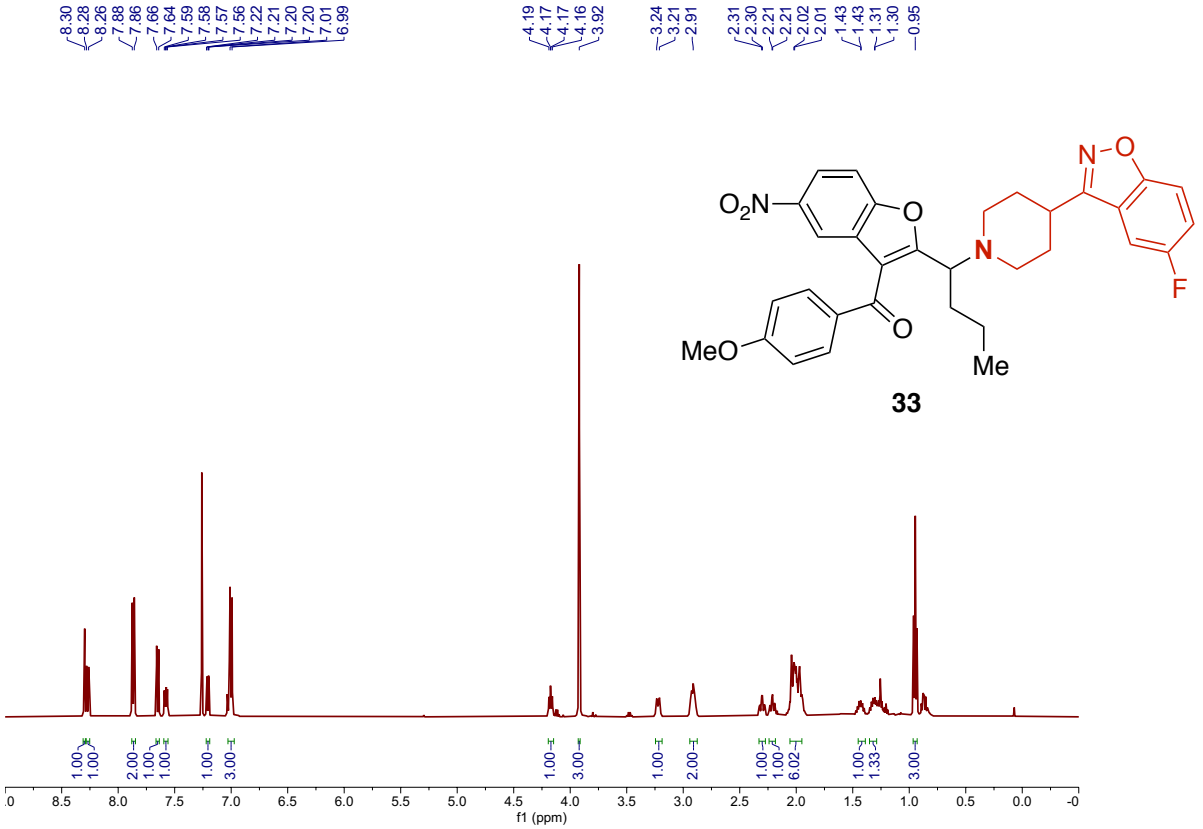
^{1}H NMR (500 MHz, $CDCl_3$) of **32**



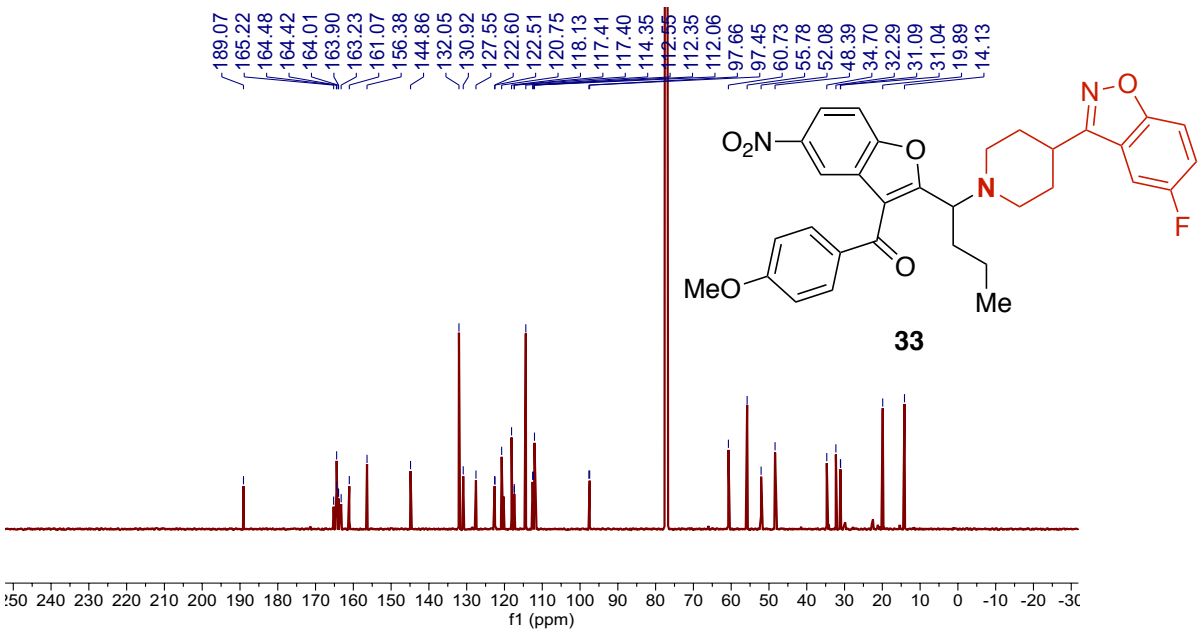
^{13}C NMR (126 MHz, $CDCl_3$) of **32**



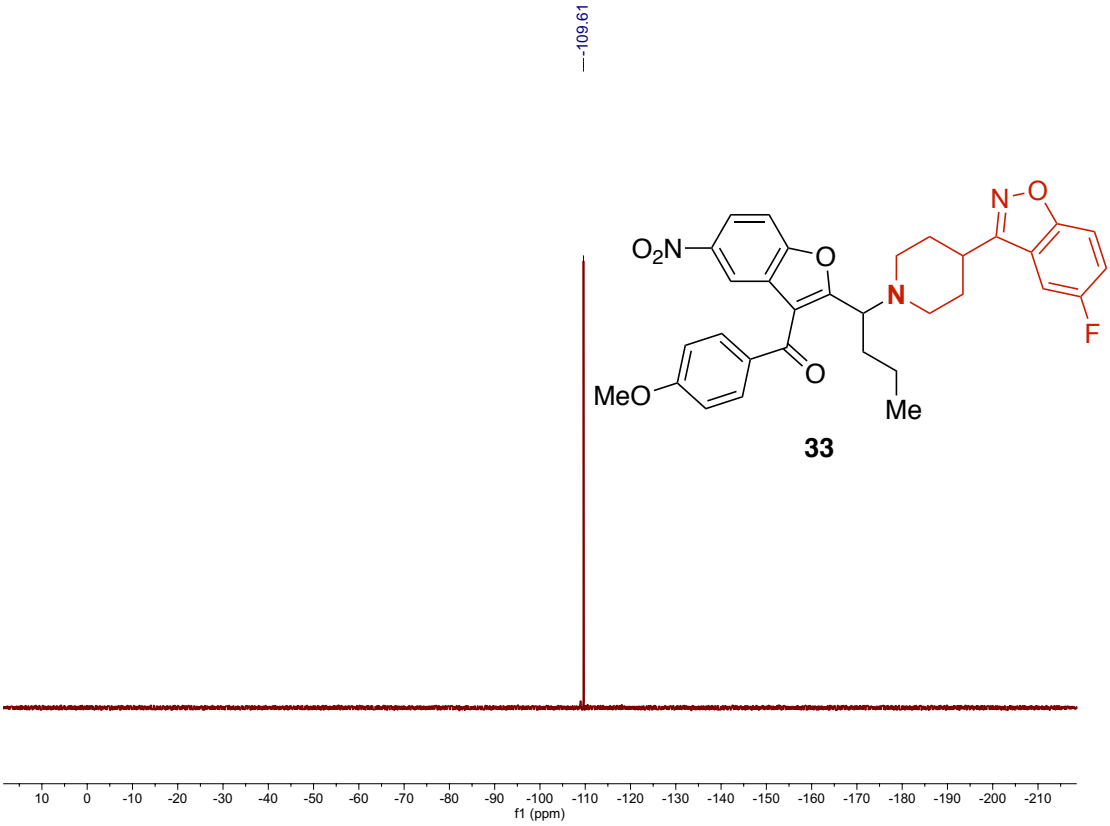
^{1}H NMR (500 MHz, $CDCl_3$) of **33**



^{13}C NMR (126 MHz, $CDCl_3$) of **33**



^{19}F NMR (377 MHz, $CDCl_3$) of **33**



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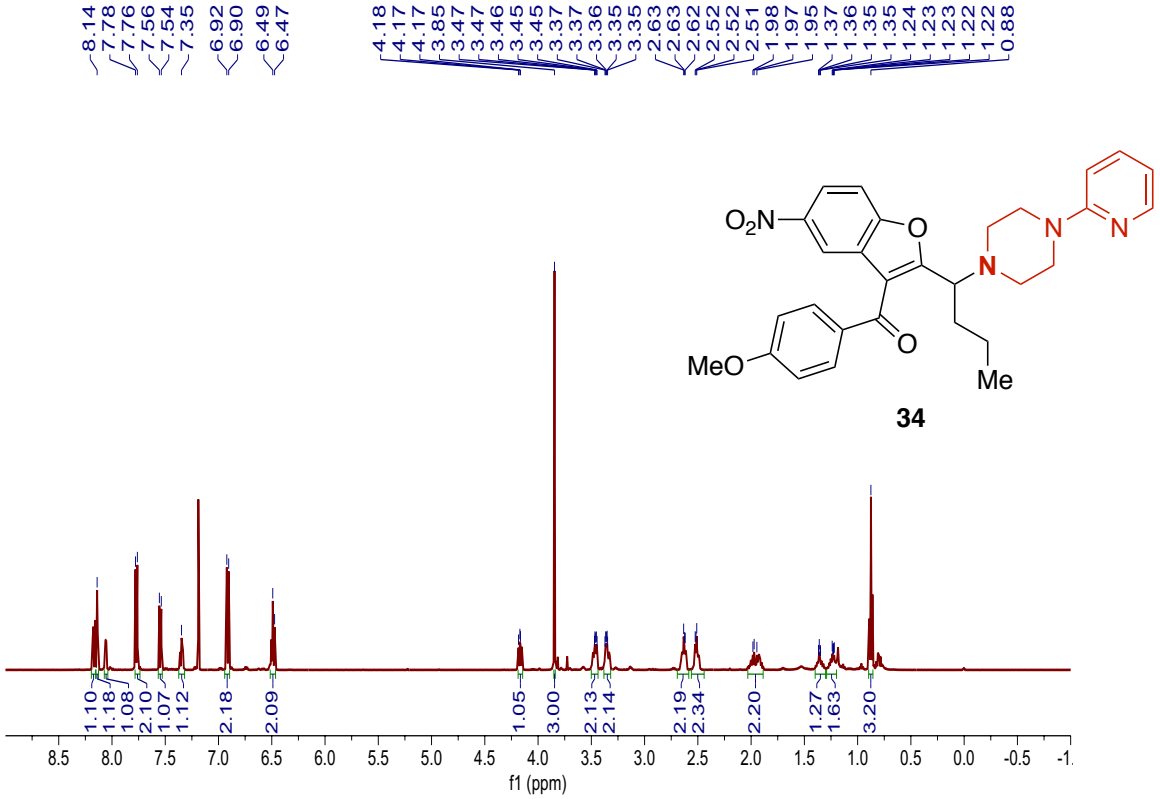
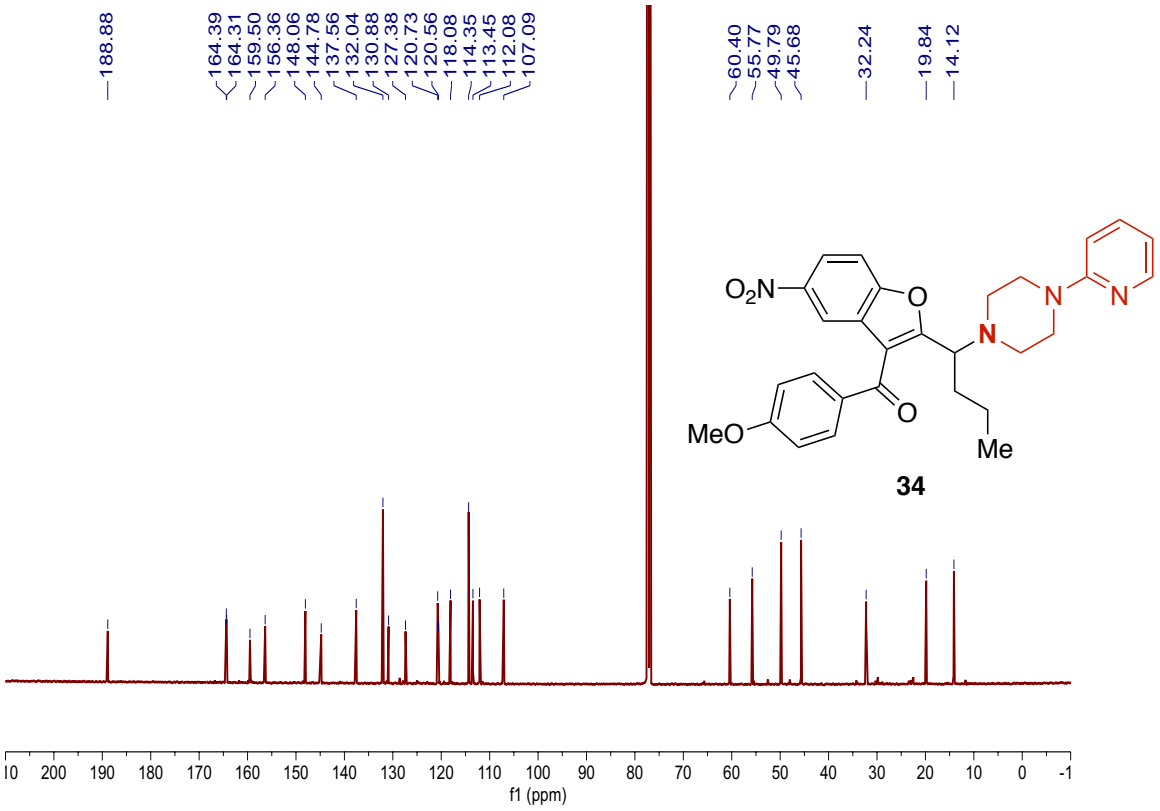


^{13}C NMR (126 MHz, $CDCl_3$) of **34**



2A.VI. References

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Appendix A: Supporting Information Chapter 3

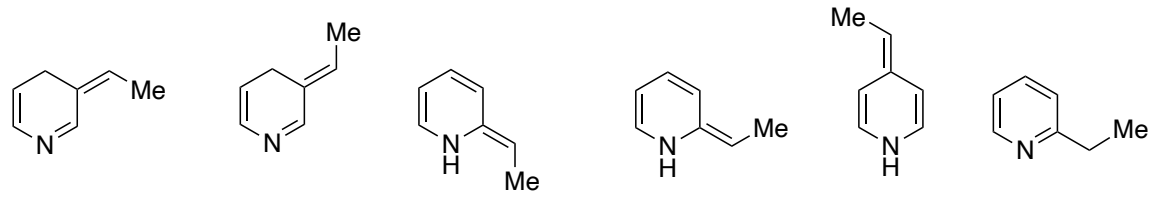
3B.I. General Considerations

Trifluoromethanesulfonyl chloride (TfCl), trichloroisocyanuric acid (TCCA), *N*-chlorosuccinimide, 4-dimethylaminopyridine (DMAP), and Li_2CO_3 were purchased from Sigma Aldrich and used as received. Unless otherwise stated, heterobenzylic C–H substrates and nucleophile coupling partners were acquired from commercial sources (Oakwood, Combi-Blocks, Enamine, AK Scientific, TCI America, Ambeed, and Sigma-Aldrich) and used as received, prepared following literature procedures, or sourced from the Merck Building Block Collection (MBBC) of Merck, Kenilworth, NJ.

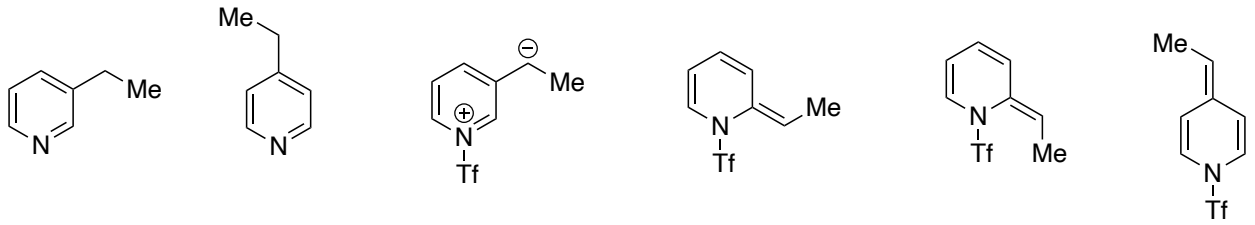
All chlorination reaction solids and liquids were weighed out on the benchtop and set-up under air. Subsequent chloride displacement reactions were also set-up on the benchtop under air. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Advance III 400 MHz spectrometer at 25 °C (^{1}H 400.1 MHz, ^{13}C 100.6 MHz, ^{19}F 376.5 MHz) or a Bruker Advance III 500 MHz spectrometer at 25 °C (^{1}H 500.1 MHz, ^{13}C 125.7 MHz), except where noted otherwise, and chemical shifts are reported in parts per million (ppm). NMR spectra were referenced to residual $CHCl_3$ at 7.26 ppm (^{1}H) and $CDCl_3$ at 77.16 ppm (^{13}C). Chromatography was performed using an automated Biotage Isolera® with reusable 25/80g Biotage®Sfär Silica HC D cartridges for normal phase. High-resolution mass spectra were obtained using a Thermo Q ExactiveTM Plus via (ASAP-MS) by the mass spectrometry facility at the University of Wisconsin-Madison.

3B.II. DFT

All structures were determined using, density functional theory (DFT) using B3LYP functional in conjunction with 6-311+G(2d,p) basis set. Vibrational frequency calculations were performed to determine all structures abre a minima on the potential energy surface. Electronic energies were calculated on optimized structures at MP2/6-311+G(2d,p) level of theory. All calculations used the Polarizable Continuum Model (PCM) to model a solvent. The solvent used is acetonitrile. All calculations were performed using Gaussian 16. All optimized structures, and electronic energies are reported below.



(*Z*)-3-**EP'** (*E*)-3-**EP'** (*E*)-2-**EP'** (*Z*)-2-**EP'** 4-**EP'** 2-**EP**



3-**EP** 4-**EP** 3-**EP'-Tf** (*Z*)-2-**EP'-Tf** (*E*)-2-**EP'-Tf** **3-Tf**

Structure	B3LYP/6-311+G(2d,p)//B3LYP/6-311+G(2d,p)
(*Z*)-3-EP'	-326.0198117
(*E*)-3-EP'	-326.0163504
(*Z*)-2-EP'	-326.0314312
(*E*)-2-EP'	-326.0340536
4-EP'	-326.0353126
4-EP	-326.075346
3-EP	-326.0761952
2-EP	-326.0748169
3-EP'-Tf	-1212.73615022
(*Z*)-2-EP'-Tf	-1212.77413876
(*E*)-2-EP'-Tf	-1212.77740876
3-Tf	-1212.787169

Compound 4-EP'

C 0.00000000 0.00000000 0.00000000
C 1.43371800 0.55542900 0.00000000
H 1.42004200 1.64734900 0.00000000
H 1.98293900 0.22270400 0.88354800
H 1.98293900 0.22270400 -0.88354800
C -0.03509000 -1.50720800 0.00000000
C -0.03608600 -2.23925900 -1.18810300
C -0.03608600 -3.62748700 -1.13935200
N -0.03571300 -4.32956400 -0.00000000
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C -0.03608600 -2.23925900 1.18810300
H -0.04202500 -1.73560800 2.14792300
H -0.04012100 -4.20362800 2.05959400
H -0.04012100 -4.20362800 -2.05959400
H -0.04202500 -1.73560800 -2.14792300
H -0.53167000 0.37326600 -0.87888800
H -0.53167000 0.37326600 0.87888800

Compound 4-EP

C 0.00000000 0.00000000 0.00000000
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C -1.70965900 -1.90546800 -0.00000000
C -0.75495300 -3.01598700 0.00000000
C -1.15930000 -4.30316600 0.00000000
N -2.49146400 -4.64592000 -0.00000000
C -3.44824500 -3.65148900 -0.00000000
C -3.10536800 -2.34898900 -0.00000000
H -3.89337400 -1.60572700 -0.00000000
H -4.47612200 -3.98712600 -0.00000000
H -2.76530300 -5.61402300 0.00000000
H -0.46277800 -5.13057700 0.00000000
H 0.30868300 -2.82282400 0.00000000
H -2.19989200 0.12582300 -0.00000000
H 0.16634900 0.63747400 0.87691200
H 0.78427500 -0.75825200 0.00000000
H 0.16634900 0.63747400 -0.87691200

Compound (*E*)-3-EP'

C 0.00000000 0.00000000 0.00000000
C -1.34966400 -0.52262700 -0.40112200
C -1.58525300 -1.83530500 -0.45459000
N -0.62129800 -2.82394600 -0.15302200
C 0.60216900 -2.44642600 -0.01152900
C 1.07375900 -1.06568900 -0.11981200
C 2.36755100 -0.75264900 -0.31169500
C 3.54828800 -1.66763800 -0.39272900
H 4.03177300 -1.57317200 -1.37065400
H 4.29894400 -1.37805400 0.34951100
H 3.30529400 -2.71743500 -0.23982700
H 2.60521900 0.30326100 -0.42832800
H 1.32998100 -3.22967600 0.18391500
H -2.56049900 -2.22647100 -0.71940700
H -2.14504200 0.18425500 -0.60736900
H 0.26587700 0.88302700 -0.58620900
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Compound (*Z*)-3-EP'

C 0.00000000 0.00000000 0.00000000
C -0.62004500 -1.36792400 0.00000000
C -1.94132900 -1.55004800 0.00000000
N -2.89327400 -0.50301900 -0.00000000
C -2.44491600 0.70237000 -0.00000000
C -1.04197600 1.10457100 -0.00000000
C -0.75817300 2.41960700 -0.00000000
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H 0.66236300 0.09701300 -0.86897800

Compound (*Z*)-2-EP'

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C -1.71273200 -1.86158500 0.00000000
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C -3.43258400 -3.61041900 0.00000000
C -2.52001700 -4.61388500 0.00000000
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H 0.57830800 -0.30876000 -0.87940200

Compound (*E*)-2-EP'

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C -3.07214800 -4.16772600 0.00000000
C -3.95290300 -3.02818700 0.00000000
C -3.45875500 -1.76908400 0.00000000
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H -5.02508300 -3.18621500 0.00000000
H -3.45294600 -5.17822600 0.00000000
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H -0.23496700 -2.55274400 0.00000000
H -2.15905900 0.57991700 0.00000000
H 0.20349500 1.07141200 0.00000000
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H 0.50689800 -0.41898700 -0.88024900

Compound 3-EP

C	0.00000000	0.00000000	0.00000000
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H	0.64196100	0.43817500	2.03875500
H	0.62019000	-1.28546400	1.64564700
C	-1.48248900	-0.07621800	0.26878000
C	-2.24620300	1.07645000	0.46928200
C	-3.60253000	0.95871900	0.74187100
C	-4.16470000	-0.31047100	0.80749800
C	-3.33453400	-1.40420500	0.59402500
N	-2.02805000	-1.30141200	0.33101700
H	-3.73738100	-2.41189300	0.63248600
H	-5.21751100	-0.45374400	1.01439300
H	-4.21031500	1.84214700	0.89760800
H	-1.77801400	2.05135700	0.40824300
H	0.24821900	-0.72403600	-0.78020000
H	0.24827000	0.99194700	-0.38465900

Compound 2-EP

C	0.00000000	0.00000000	0.00000000
C	0.84954500	0.19755100	1.26511600
H	1.91389600	0.14706100	1.02497700
H	0.65210200	1.16933000	1.72354700
H	0.63184700	-0.57422500	2.00705400
C	-1.48272300	0.06703300	0.27031600
C	-2.16156100	1.28142600	0.37329000
C	-3.52171000	1.28598100	0.65247200
C	-4.17198300	0.06889200	0.82232300
N	-3.54720500	-1.10888500	0.72442500
C	-2.23753400	-1.09307200	0.45440800
H	-1.75534700	-2.06384700	0.37423800
H	-5.23468000	0.03744800	1.04065300
H	-4.07331400	2.21429800	0.73374800
H	-1.62976400	2.21607000	0.23093200
H	0.24068600	-0.96692000	-0.44940800
H	0.26638700	0.76383100	-0.73583800

(*Z*)-2-EP'-Tf

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C	-0.99715500	-1.10774000	-0.11803900
C	-0.76172800	-2.41184700	0.08509300
N	-1.84828200	-3.38385500	0.03174100
C	-1.56809900	-4.69676800	-0.44238400
C	-0.30896400	-5.14834300	-0.44910700
C	0.75748800	-4.32322600	0.07437700
C	0.53525200	-3.02302300	0.34280600
H	1.33395200	-2.39049800	0.70477900
H	1.73652300	-4.75788400	0.23012500
H	-0.10512300	-6.13698600	-0.83673000
H	-2.41802700	-5.27615200	-0.76704500
S	-3.23738700	-3.20848800	0.93760500
C	-4.51749500	-2.66753300	-0.33530800
F	-5.71098100	-2.63870500	0.25520200
F	-4.23966400	-1.45639000	-0.81372600
F	-4.54633300	-3.53902200	-1.34374900
O	-3.11535000	-2.11037300	1.85970800
O	-3.70047400	-4.51449200	1.34002100
H	-2.00508900	-0.80079700	-0.36475000
H	0.05602500	0.55805800	-0.93984400
H	-0.31391100	0.71492500	0.76741900
H	1.00356600	-0.34190900	0.24627300

(*E*)-2-EP'-Tf

C	0.00000000	0.00000000	0.00000000
C	0.37668200	-1.40619200	-0.35369600
C	-0.11169700	-2.57771900	0.11677300
N	-1.22957300	-2.71776800	1.00426600
C	-1.41411200	-3.87340200	1.77197100
C	-0.69305300	-4.98111400	1.53957900
C	0.25504700	-4.98326100	0.45191600
C	0.51474300	-3.84707300	-0.22363500
H	1.25339800	-3.82417100	-1.01493800
H	0.76905400	-5.90059800	0.19394900
H	-0.84066400	-5.85599900	2.15658000
H	-2.16899300	-3.79329700	2.54048900
S	-2.49476100	-1.55222300	0.98899600
C	-3.78756000	-2.60948300	0.02678500
F	-4.82517700	-1.80927600	-0.25511200
F	-3.26560000	-3.05179200	-1.12151600
F	-4.23461200	-3.64767200	0.73361300
O	-3.08263000	-1.50313000	2.34789800
O	-0.31530400	0.18564600	1.39162000
H	1.18979000	-1.50658100	-1.06260000
H	0.82222500	0.66323600	-0.28406000
H	-0.88764200	0.34800500	-0.53575000
H	0.42981900	-0.14272300	1.91188000

Compound 3-Tf

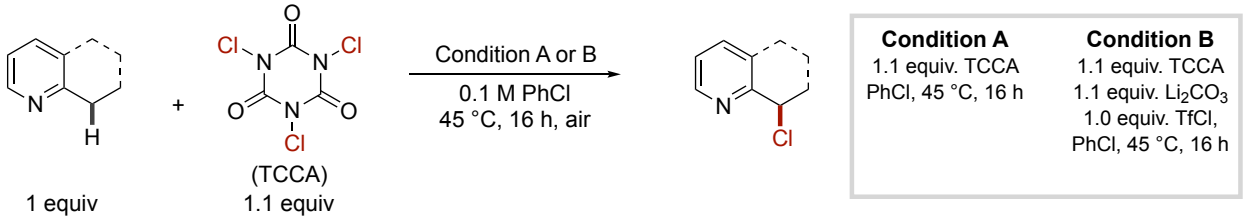
C 0.00000000 0.00000000 0.00000000
C -1.00187100 -0.88073000 -0.67624100
C -2.30210200 -1.05160900 -0.35148800
C -2.98402200 -0.39239700 0.76006500
C -4.27853200 -0.58646400 1.03203800
N -5.06808100 -1.46724800 0.25310000
C -4.45500100 -2.14132400 -0.83493600
C -3.16227100 -1.95365000 -1.11340500
H -2.73799100 -2.51173700 -1.93882600
H -5.09591100 -2.81595800 -1.37912500
S -6.71209800 -1.48636300 0.42650700
C -7.32414100 -0.08028900 -0.67392900
F -8.65174400 -0.01255800 -0.60191200
F -6.79979100 1.07291200 -0.26286700
F -6.96081800 -0.30404900 -1.93540700
O -7.03514000 -1.08108000 1.76924100
O -7.22066800 -2.68895600 -0.17892000
H -4.79122000 -0.11915900 1.85752000
H -2.44021500 0.27429400 1.41440600
H -0.63151400 -1.44393500 -1.52875000
H 0.85374300 -0.58627200 0.35686300
H 0.40566700 0.73619900 -0.70252900
H -0.40801600 0.54459200 0.85102900

Compound 3-EP'-Tf

C 0.00000000 0.00000000 0.00000000
C 1.42962300 -0.19807900 0.41254200
C 2.38142800 0.77879100 0.31781000
C 2.15910600 2.13371400 -0.19102000
C 3.16047200 3.06351100 -0.22451200
C 4.45986700 2.77574300 0.20937100
N 4.66854200 1.49698000 0.66281000
C 3.73356900 0.53729400 0.72496400
H 4.05310200 -0.41926200 1.10825700
S 6.30553100 1.05954600 1.11126600
O 6.97732100 2.25932000 1.51738400
O 6.24091100 -0.12814600 1.91317600
C 7.01757900 0.55124700 -0.57387400
F 8.24461900 0.10133900 -0.34947600
F 6.27180300 -0.40690900 -1.10294600
F 7.05900100 1.59735400 -1.38341600
H 5.28288500 3.46497300 0.24658100
H 2.96572000 4.06290000 -0.59292000
H 1.17349400 2.40299100 -0.54581200
H 1.72230300 -1.16575600 0.80368300
H -0.58542900 -0.90255600 0.18249600
H -0.48908500 0.81841900 0.54657500
H -0.10579800 0.24237400 -1.06689000

3B.III. Procedure for Heterobenzylic C–H Chlorination and ^{1}H-NMR Quantitation

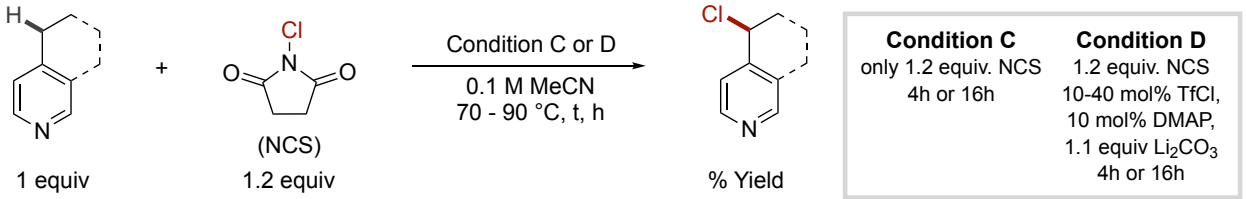
Heterobenzylic Chlorination of 2-Alkylated Heterocycles



General Procedure A Set Up: On the benchtop, a disposable 4 mL glass vial was charged with TCCA (0.055 mmol, 14.0 mg, 1.1 equiv), heterobenzylic substrate (0.05 mmol, 1 equiv), anhydrous chlorobenzene (0.1 M, 0.5 mL), and a Teflon stir bar. The vial was sealed by a PTFE-lined pierceable cap. The reaction vial is then set to stir at 45 ℃ on a stirring hot plate in an aluminum block at 750 rpm for 16 h.

General Procedure B Set Up: On the benchtop, a disposable 4 mL glass vial was charged with TCCA (0.055 mmol, 14.0 mg, 1.1 equiv), Li_2CO_3 (0.05 mmol, 4.1 mg, 1.1 equiv), heterobenzylic substrate (0.05 mmol, 1 equiv), chlorobenzene (0.5 mL), and a Teflon stir bar. The vial was sealed by a PTFE-lined pierceable cap. Trifluoromethanesulfonyl chloride (0.05 mmol, 5.3 µL, 1.0 equiv) was added by a microliter syringe and the pierced PTFE-lined cap was sealed by silicone grease. The reaction vial is then set to stir at 45 ℃ on a stirring hot plate in an aluminum block at 750 rpm for 16 h.

Heterobenzylic Chlorination of 4-Alkylated Heterocycles



General Procedure C Set Up: On the benchtop, a disposable 4 mL glass vial was charged with NCS (0.06 mmol, 8.0 mg, 1.2 equiv), anhydrous acetonitrile (0.5 mL), and a Teflon stir bar. The vial was sealed by a PTFE-lined pierceable cap. The reaction vial is then set to stir at 70 ℃ or 90 ℃ on a stirring hot plate in an aluminum block at 750 rpm for 4 h or 16 h.

General Procedure D Set Up: On the benchtop, a disposable 4 mL glass vial was charged with NCS (0.06 mmol, 8.0 mg, 1.2 equiv), Li_2CO_3 (0.055 mmol, 4.1 mg, 1.1 equiv), DMAP (0.005 mmol, 0.6 mg, 0.1 equiv), the C–H substrate (0.05 mmol, 1 equiv), anhydrous acetonitrile (0.5 mL), and a Teflon stir bar. The vial was sealed by a PTFE-lined pierceable cap. Trifluoromethanesulfonyl chloride (10 or 40 mol%) was added by a microliter syringe and the pierced PTFE-lined cap was sealed by silicone grease. The reaction vial is then set to stir at 70 ℃ or 90 ℃ on a stirring hot plate in an aluminum block at 750 rpm for 4 or 16 h.

Work up for Procedures A-D: After 4 or 16 hours, the reaction was allowed to cool to room temperature. The cap of the vial is loosened slowly to vent the pressure build-up from the reaction. The crude reaction solution is then filtered through a pad of celite plug eluting with acetone or ethyl acetate into a 24 ml glass vial and concentrated on the rotovap. A solution of dibromoethane ($C_2H_4Br_2$) or dibromomethane (CH_2Br_2) in $CDCl_3$ was added into the concentrated reaction mixture as the external standard and analyzed by ^1H NMR to detect formation of product and conversion of starting material.

Additional Comments:

1. The trifluoromethanesulfonyl chloride reagent can also be added prior to capping the vial with the PTFE-line cap.
2. While anhydrous MeCN and moisture sensitive TfCl are used in this procedure, the set-up is conducted under ambient air.
3. It is also advisable to use hot plates with a thermocouple to ensure consistent reaction temperature throughout the duration of the reaction.

Warning: At 1 mmol scale (in 6-dram vials), build-up of vapor pressure from MeCN solvent may pressurize the reaction vial. Be sure to take appropriate safety precautions or conduct the reaction in sealed vials (such as microwave vials). Reactions conducted in smaller scales (0.05 mmol/0.1 mmol/0.5 mmol) do not produce sufficient vapor.

3B.IV. Modification of Reaction Conditions

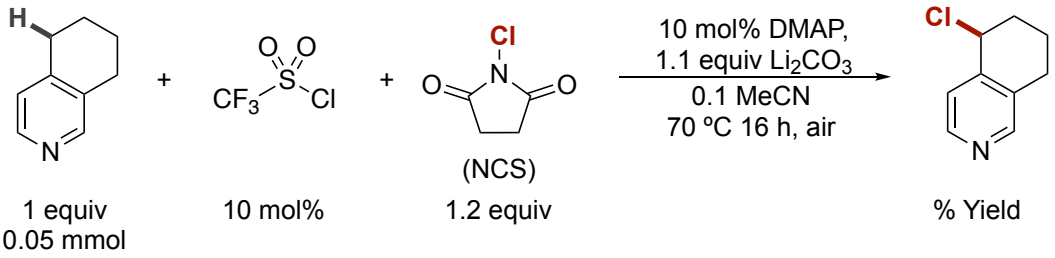


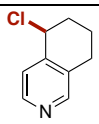
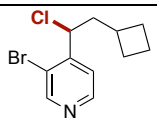
Table 3A.1. Deviation from standard conditions on 5,6,7,8-tetrahydroisoquinoline.

Entry	Variation from standard conditions	Yield (%)
1	None	85
2	No DMAP	52
3	No Li_2CO_3	78
4	No TfCl and DMAP	29
5	0.1 M chlorobenzene instead of MeCN	36
6	0.1 M toluene instead of MeCN	24
7	0.1 M ethyl acetate instead of MeCN	37
8	No TfCl, no DMAP, and 3 equiv. NCS	8
9	1.2 equiv of TCA instead of NCS	28
10	0.4 equiv of TCA instead of NCS	24
11	0.5 M MeCN	24
12	0.2 M MeCN	72
13	1.1 equiv K_2CO_3 instead of Li_2CO_3	17
14	1.1 equiv 3 $NaHCO_3$ instead of Li_2CO_3	41

Discussion: Table 3A.1 describes the importance of each reaction component for obtaining optimal yield. While optimization was performed on 5,6,7,8-tetrahydroisoquinoline, other entries in the substrate scope required slight deviation from the conditions above.

3B.V. Evaluating different polar and radical chlorination methods.

Table 3A.2. Comparative Data with Known Chlorination Methods[a]

Conditions a-i[a]	 (%)	Other chloride products (%)	 (%)	Other chloride Products (%)
a. 1.1 equiv TCCA, PhCl, 45ºC	**1**	**1**	**9**	**0**
b. 1.1 equiv TCCA 1 equiv TfCl, PhCl, 45ºC	**1**	**1**	**12**	**0**
c. 1.2 equiv NCS MeCN, 70ºC	**30**	**0**	**45**	**0**
d 10 mol% TfCl, 1.2 equiv NCS 1.1 equiv Li_2CO_3, 10 mol% DMAP, MeCN, 70ºC	**85**	**0**	**84**	**0**
e. 1.2 equiv TCCA, DCM, reflux	**0**	**20**	**11**	**0**
f. [9] 1.2 equiv N(Cl)SI 1.1 equiv Li_2CO_3 MeCN, 75ºC, 48h	**8**	**16**	**35**	**0**
g. [8] SO_2Cl_2, cat DBPO, 75ºC	**10**	**10**	**11**	**18**
h. [7] 2 mol% Cu(OAc)2, 40 mol% TCCA, 10 mol% NHPI, 10% CBr_4, DCM, rt	**10**	**15**	**4**	**6**
i. [10] 10 mol% CuCl/Bisox 2.5 equiv NFSI, 3 equiv KCl, PhCl, 45ºC	**0**	**1**	**3**	**0**

[a] Performed on a 0.2 mmol scale according to the literature procedures. Yields were determined by ^{1}H-NMR spectroscopy or UPLC area percentages of chloride products.

3B.VI. Quantitative ^{1}H NMR for Heterobenzylic Chloride Products

Processed (phase and baseline corrected) NMR spectra for the crude reaction mixtures of each of the heterobenzyl chloride products are shown below. For several entries, relevant peaks in the aromatic region were selected which were consulted to confirm conversion and yield data. See figure captions for additional details.

(*rac*)-8-Chloro-5,6,7,8-tetrahydroquinoline (1): Prepared from 5,6,7,8-tetrahydroquinoline (0.05 mmol, 6.7 mg, 1.0 equiv) following procedure A (45 °C, 16 h) in Section 3.

Heterobenzylic Chloride C–H Shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.52–5.48 (m, 1H).

Calibrated ^{1}H NMR yield from heterobenzylic proton: 70%.

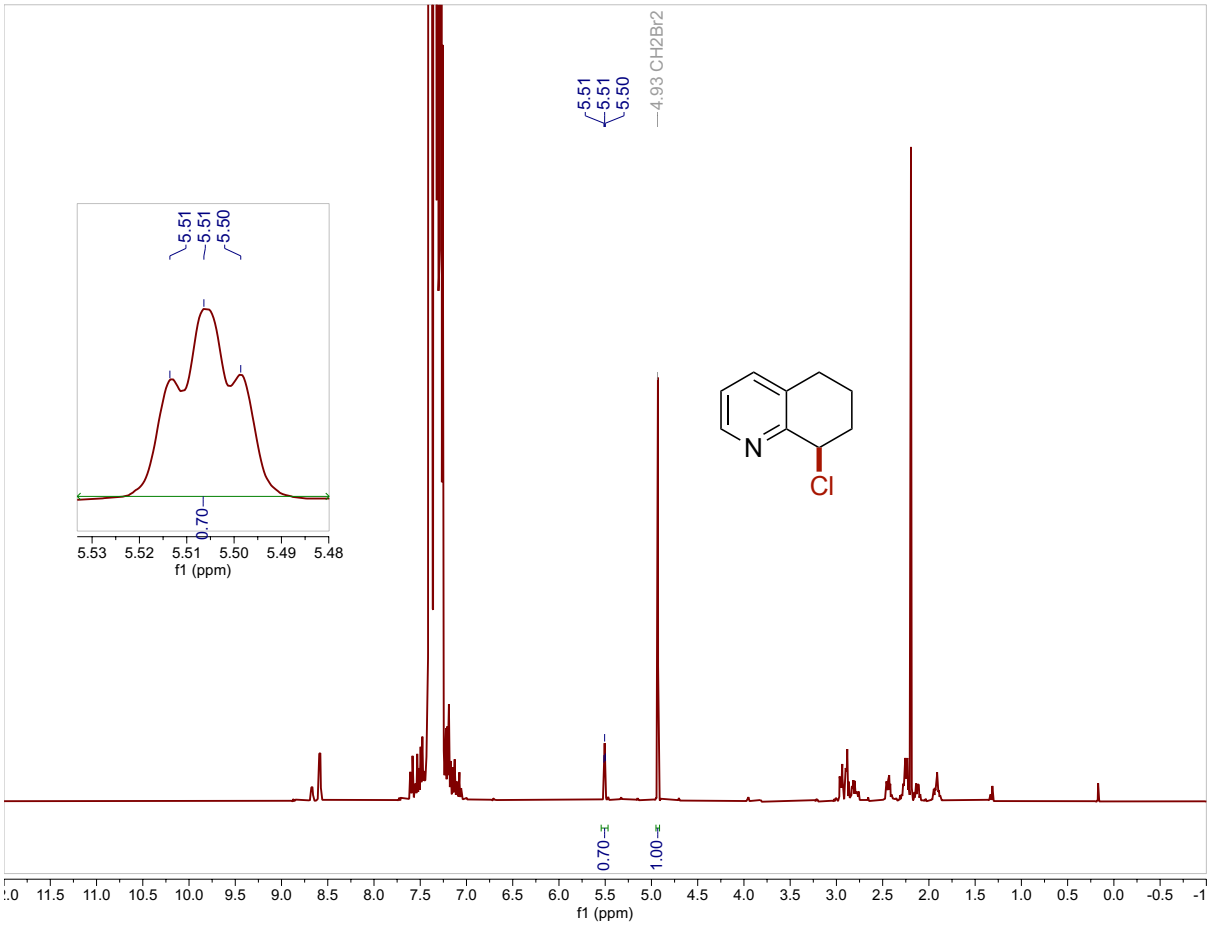


Figure 3B.1. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.92 ppm). The resolved heterobenzylic proton (5.52–5.48 ppm) is labeled and integrated.

(*rac*)-8-Chloro-7,8-dihydroquinolin-5(6*H*)-one (2): Prepared from 7,8-dihydroquinolin-5(6*H*)-one (0.05 mmol, 7.4 mg, 1.0 equiv) following procedure B (45 °C, 16 h) in Section 3.

Heterobenzylic Chloride C–H Shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.48 (broad s).

Calibrated ^{1}H NMR Yield from heterobenzylic and aromatic protons: 71%.

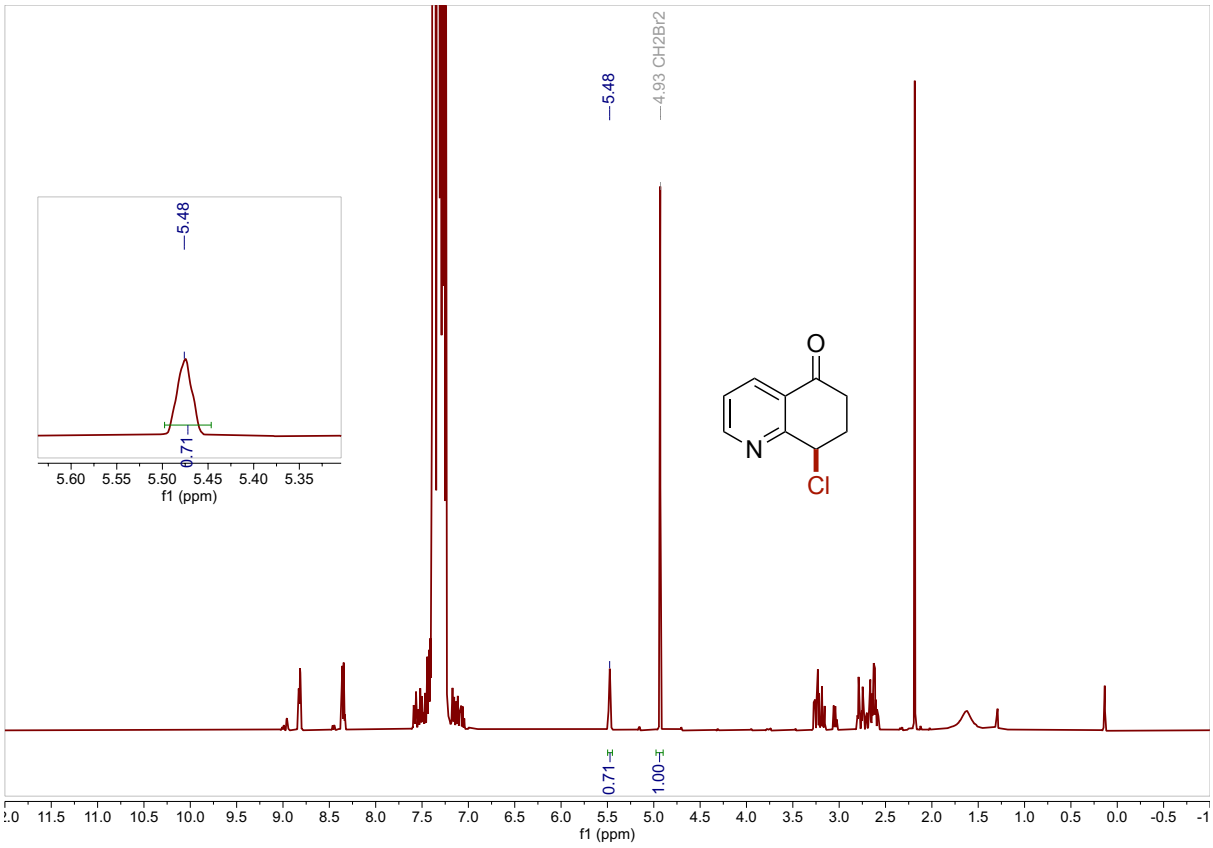


Figure 3B.2. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.92 ppm). The resolved heterobenzylic proton (5.48 ppm) is labeled and integrated.

(*rac*)-5-Chloro-5,6,7,8-tetrahydroisoquinoline (3): Prepared from 5,6,7,8-tetrahydroisoquinoline (0.05 mmol, 6.7 mg, 1.0 equiv) following procedure D (70 ℃, 16 h) in Section 3, using 10 mol% TfCl (0.005 mmol, 0.8 mg, 0.5 µL). Note that, under the standard conditions, a 1 mmol scale reaction resulted in 78-83% NMR yield consistently on many occasions thereby supporting the scalability of the reaction condition.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.14 (t, J = 4.6 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 85%.

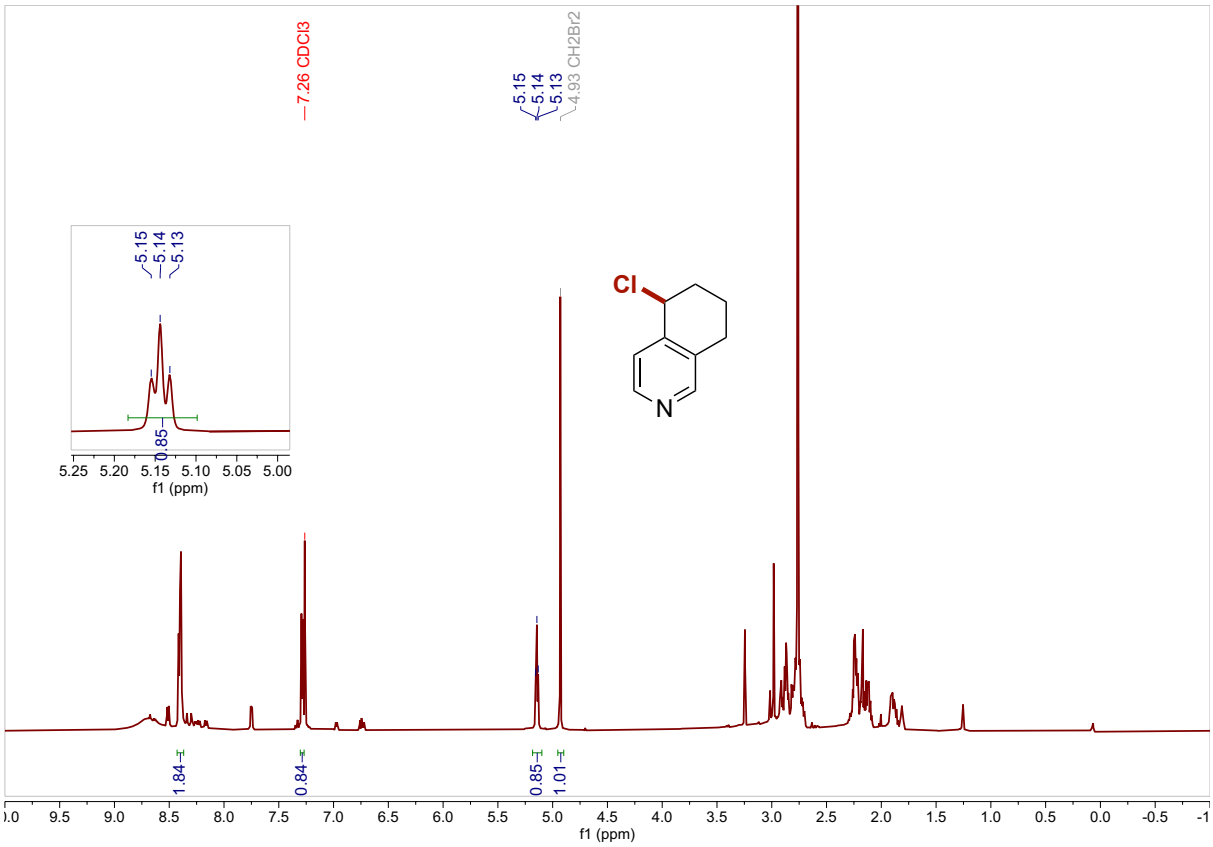


Figure 3B.3. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved heterobenzylic proton (5.14 ppm) is labeled and integrated.

***(rac)*-3-Bromo-4-(1-chloro-2-cyclobutylethyl) pyridine (4)**: Prepared from 3-bromo-4-(2-cyclobutylethyl) pyridine (0.05 mmol, 12.0 mg, 1.0 equiv) following procedure D in Section 3 (90 °C, 16 h.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): 5.16 (dd, J = 8.3, 5.7 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 84% (with 16% unreacted starting material)

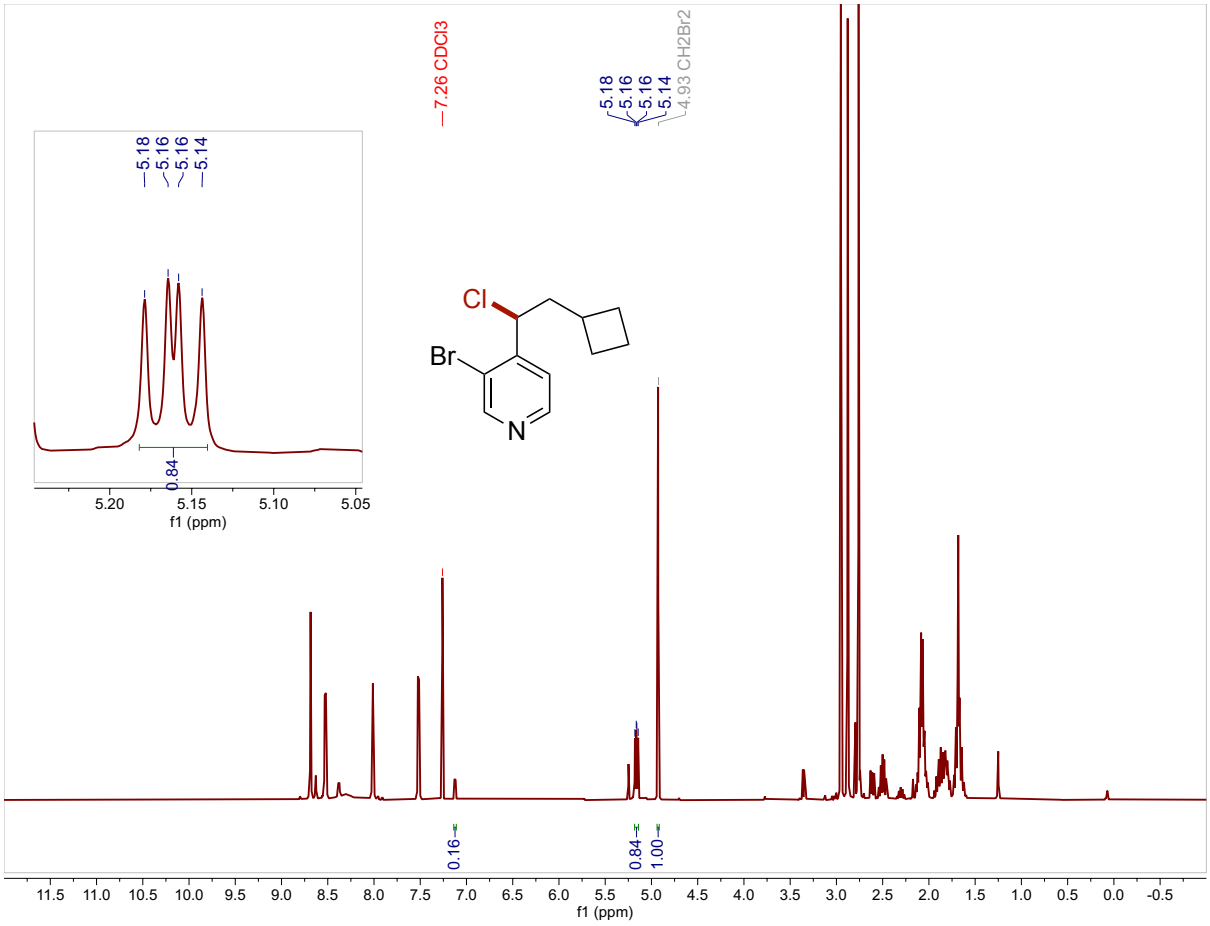


Figure 3B.4. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved heterobenzylic proton (5.16 ppm) is labeled and integrated.

((*rac*)-(4-Chloro-3,4-dihydro-1,5-naphthyridin-1(2*H*)-yl) (phenyl)methanone (5): Prepared from (3,4-dihydro-1,5-naphthyridin-1(2*H*)-yl) (phenyl)methanone (0.05 mmol, 11.9 mg, 1.0 equiv) following procedure A (45 °C, 16 h) in Section 3.

Deviation from procedure A: Reaction was conducted in dichloromethane.

Heterobenzylic Chloride C–H Shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.42 (t, J = 3.5 Hz, 1H).

Calibrated ^{1}H NMR yield from heterobenzylic proton: 57%.

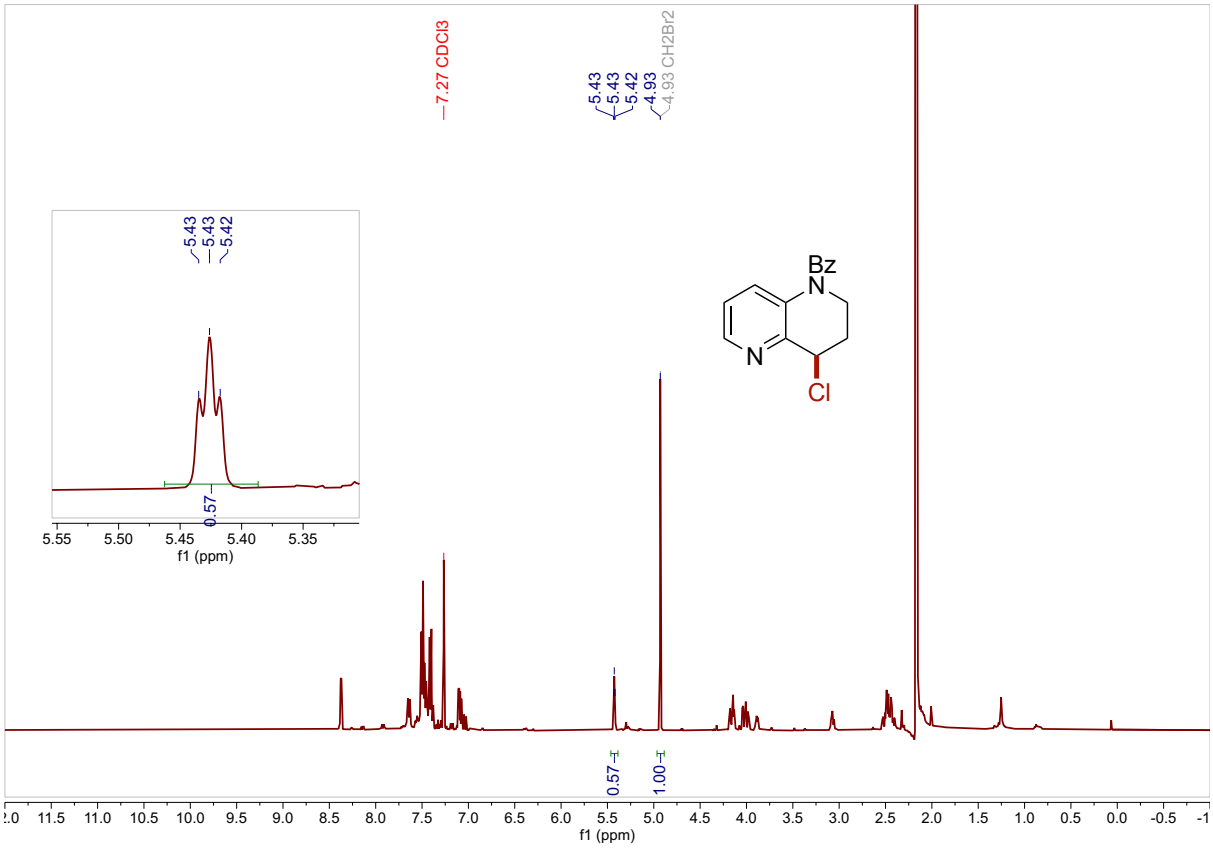


Figure 3B.5. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an external standard (4.92 ppm). The resolved heterobenzylic proton (5.43-5.41 ppm) is labeled and integrated.

(*rac*)-3,7-Dichloro-6,7-dihydro-5*H*-cyclopenta[c]pyridazine (6): Prepared from 3-chloro-6,7-dihydro-5*H*-cyclopenta[*c*]pyridazine (0.05 mmol, 7.7 mg, 1.0 equiv) following procedure B (45 °C, 16 h) in Section 3.

Heterobenzylic Chloride C–H Shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.52 (dd, J = 6.6, 2.2 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 85%.

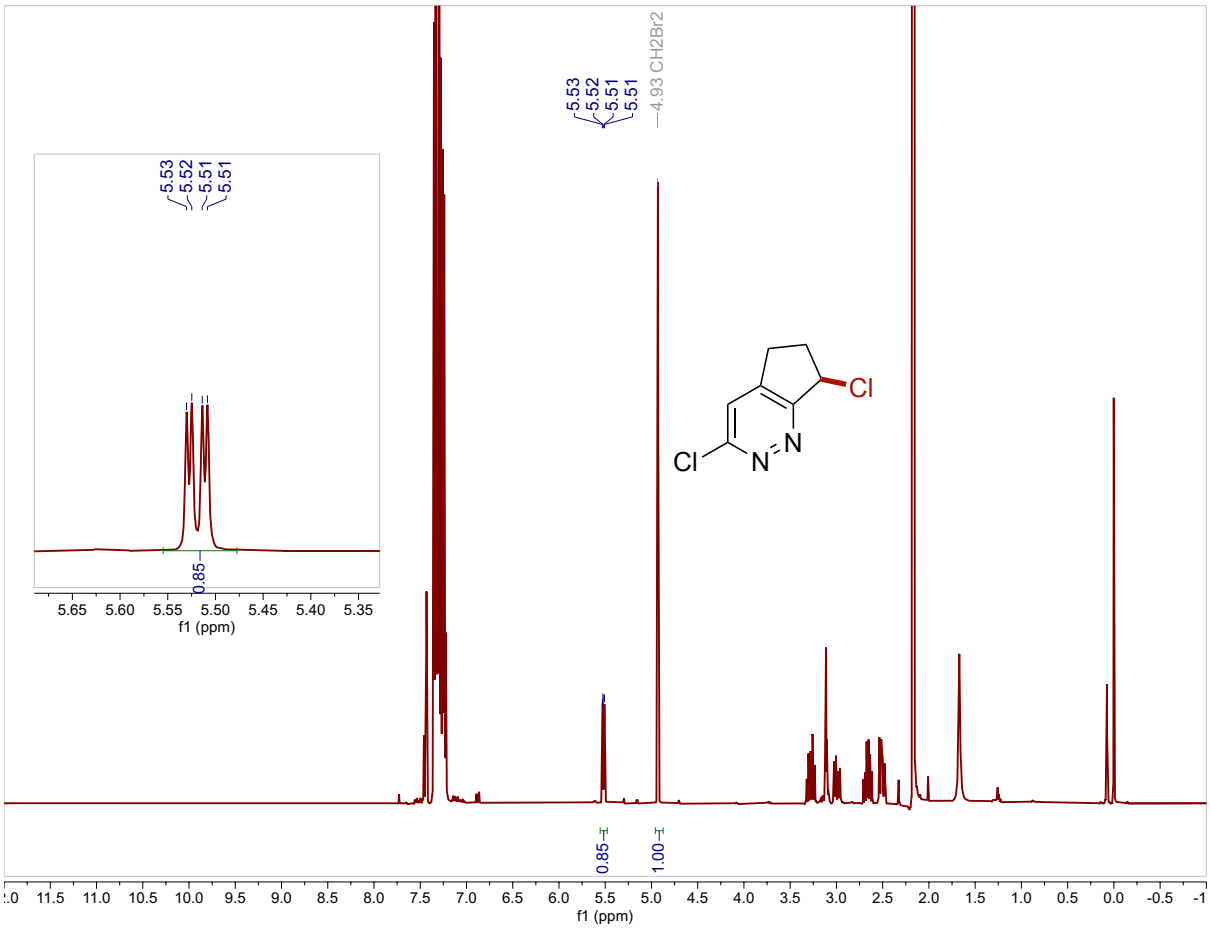


Figure 3B.6. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved heterobenzylic proton (5.54-5.50 ppm) is labeled and integrated.

((*rac*)-7-Chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine(7): Prepared from 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine (0.05 mmol, 5.9 mg, 1.0 equiv) following procedure B (45 °C, 16 h) in Section 3.
Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.41 (dd, J = 6.9, 2.8 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 70%.

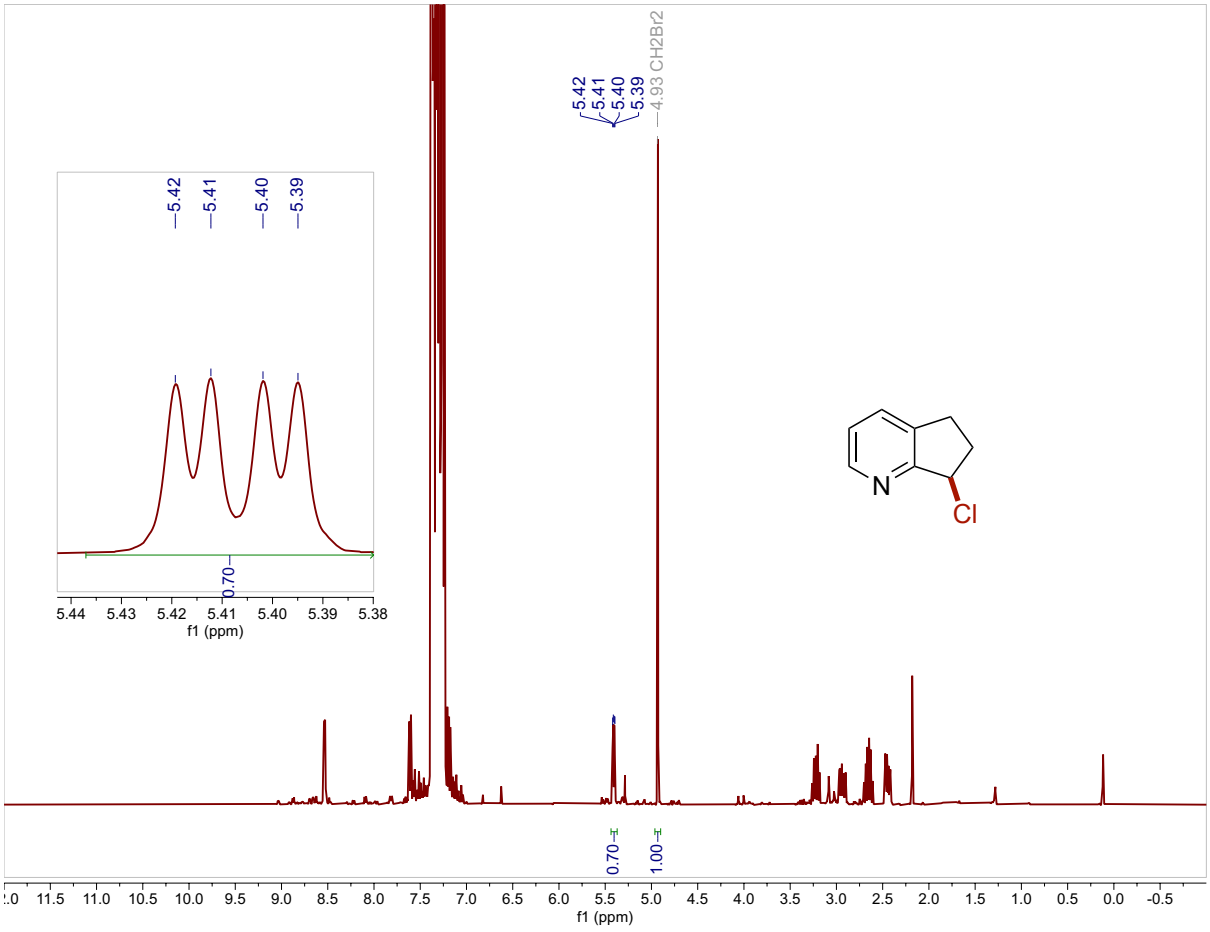


Figure 3B.7. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved heterobenzylic proton (5.41 ppm) is labeled and integrated.

Ethyl-(*rac*)-7-chloro-5-oxo-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carboxylate (8): Prepared from ethyl 5-oxo-6,7-dihydro-5*H*-cyclopenta[b]pyridine-3-carboxylate (0.05 mmol, 10.3 mg, 1.0 equiv) following procedure A (45 °C, 16 h) in Section 3

Heterobenzylic Chloride C–H Shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.55 (dd, J = 7.5, 2.8 Hz, 1H).

Calibrated ^{1}H NMR yield from heterobenzylic proton: 86%.

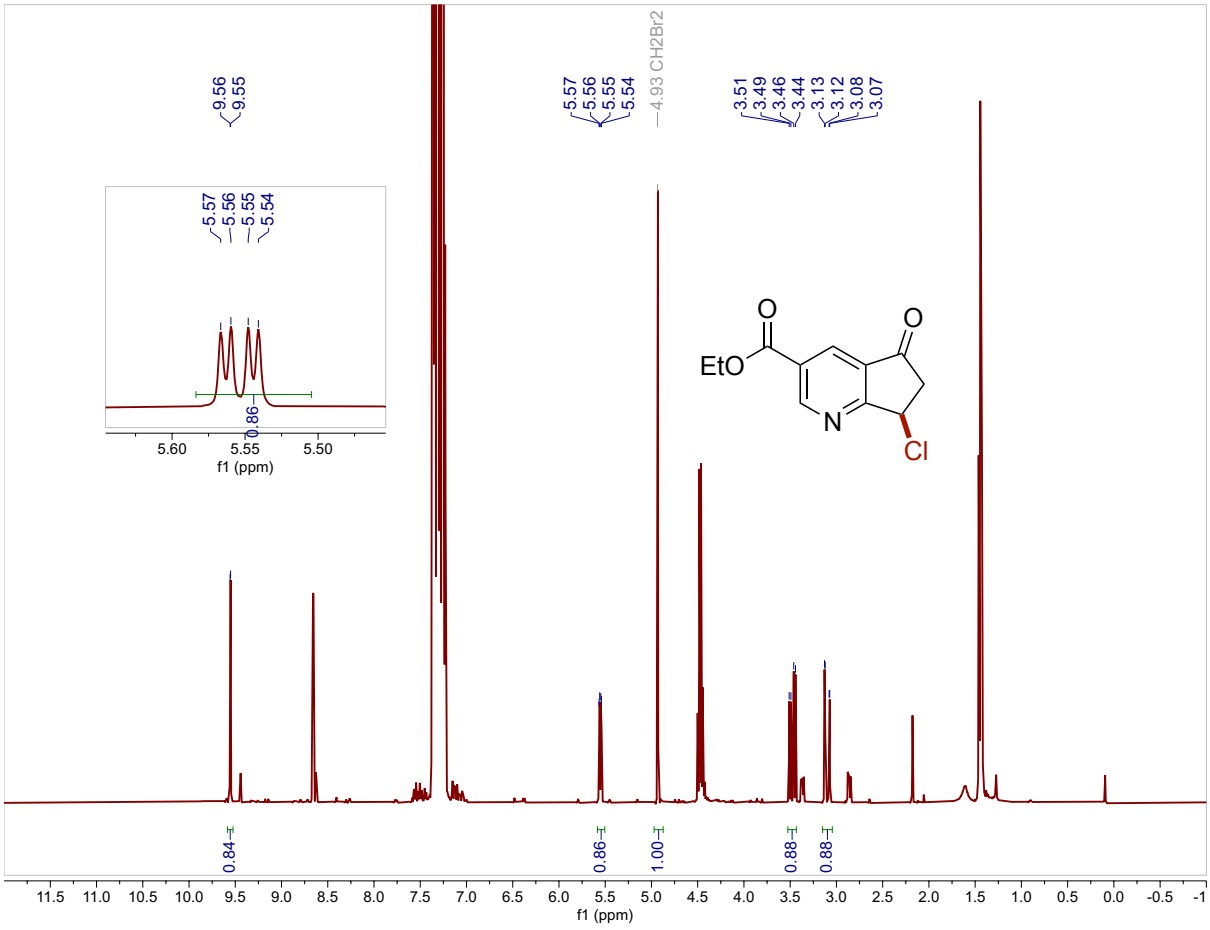


Figure 3B.8. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved heterobenzylic proton (5.57-5.54 ppm) is labeled and integrated.

(*rac*)-4-(1-Chloro-4-methylpentyl)-3-methylpyridine (10): Prepared from 3-methyl-4-(4-methylpentyl) pyridine (0.05 mmol, 8.9 mg, 1.0 equiv) following Procedure D (70 °C, 4 h) in Section 3, using 10% mol% TfCl (0.005 mmol, 0.8 mg, 0.5 µL). Deviation from procedure D is the exclusion of Li_2CO_3 and DMAP.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.98 (dd, J = 8.3, 6.0 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 94%.

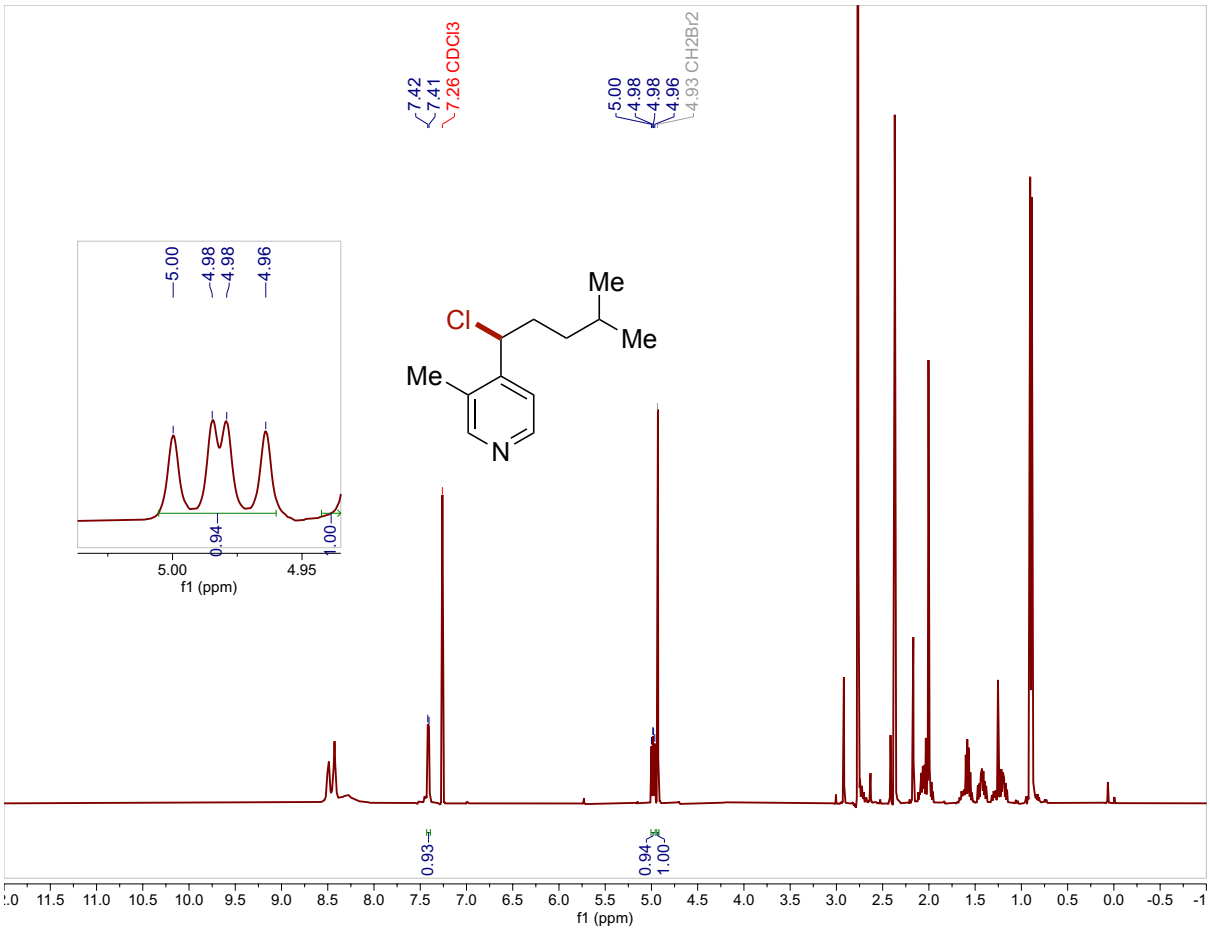


Figure 3B.10. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved heterobenzylic proton (4.98 ppm) is labeled and integrated.

(*rac*)-4-(Chloro(phenyl) methyl) pyridine (11): Prepared from 4-benzylpyridine (0.05 mmol, 8.5 mg, 1.0 equiv) according to a modified version of the general procedure D (45 °C, 16 h) in Section 3.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.03 (s).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 51%. Under this condition, 37% starting material remained unreacted. Efforts to improve yield resulted in more dichlorination and we settled for this acceptable yield of mono-chloride (51%).

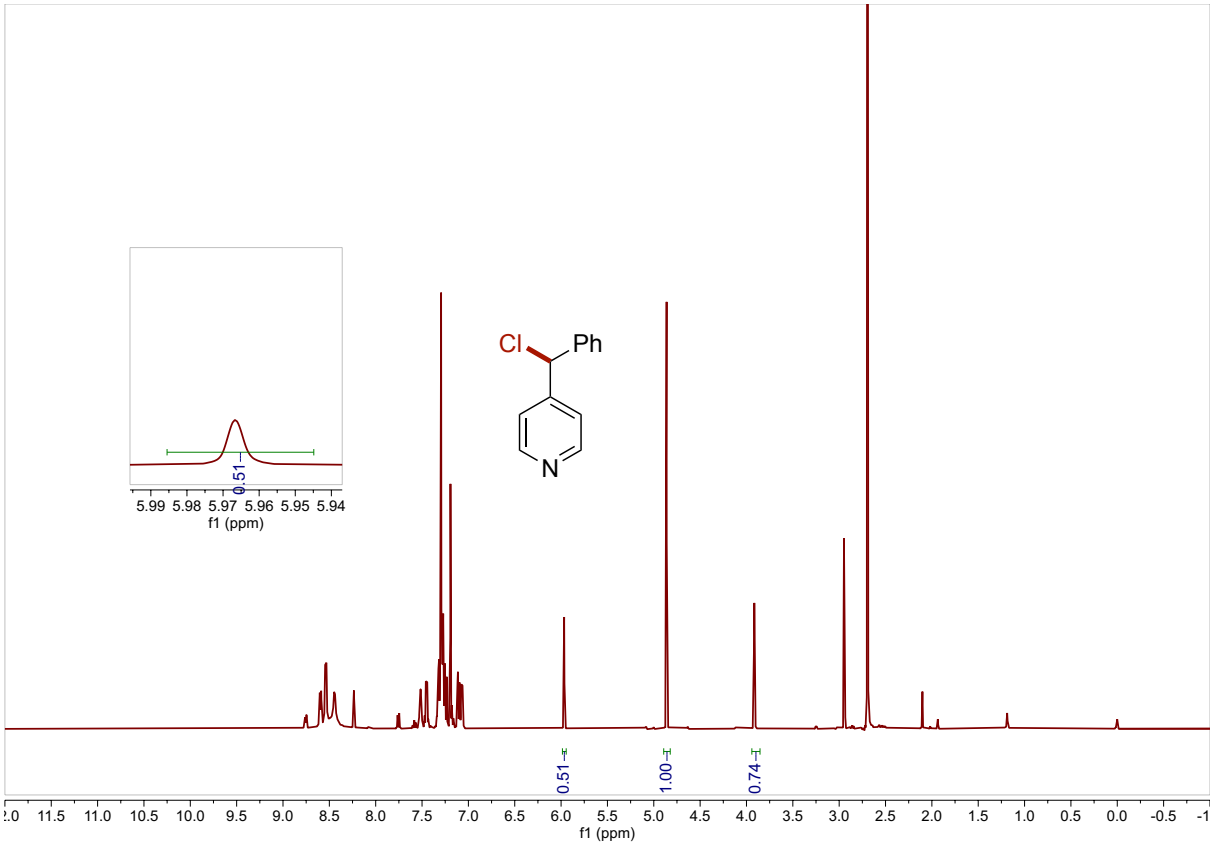


Figure 3B.11. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved hetero benzylic proton is labeled and integrated.

(*rac*)-4-(1-Chloro-3-phenylpropyl) pyridine (12): Prepared from 4-(3-phenylpropyl) pyridine (0.05 mmol, 9.9 mg, 1.0 equiv) following procedure D (70 °C, 4 h) in Section 3, using 40 mol% TfCl (0.02 mmol , 3.37 mg, 2 µL). Deviation from procedure D is the exclusion of DMAP.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.73 (dd, J = 8.8, 5.4 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 61% (with 10-15% *di*-Cl product and 15% unreacted starting material).

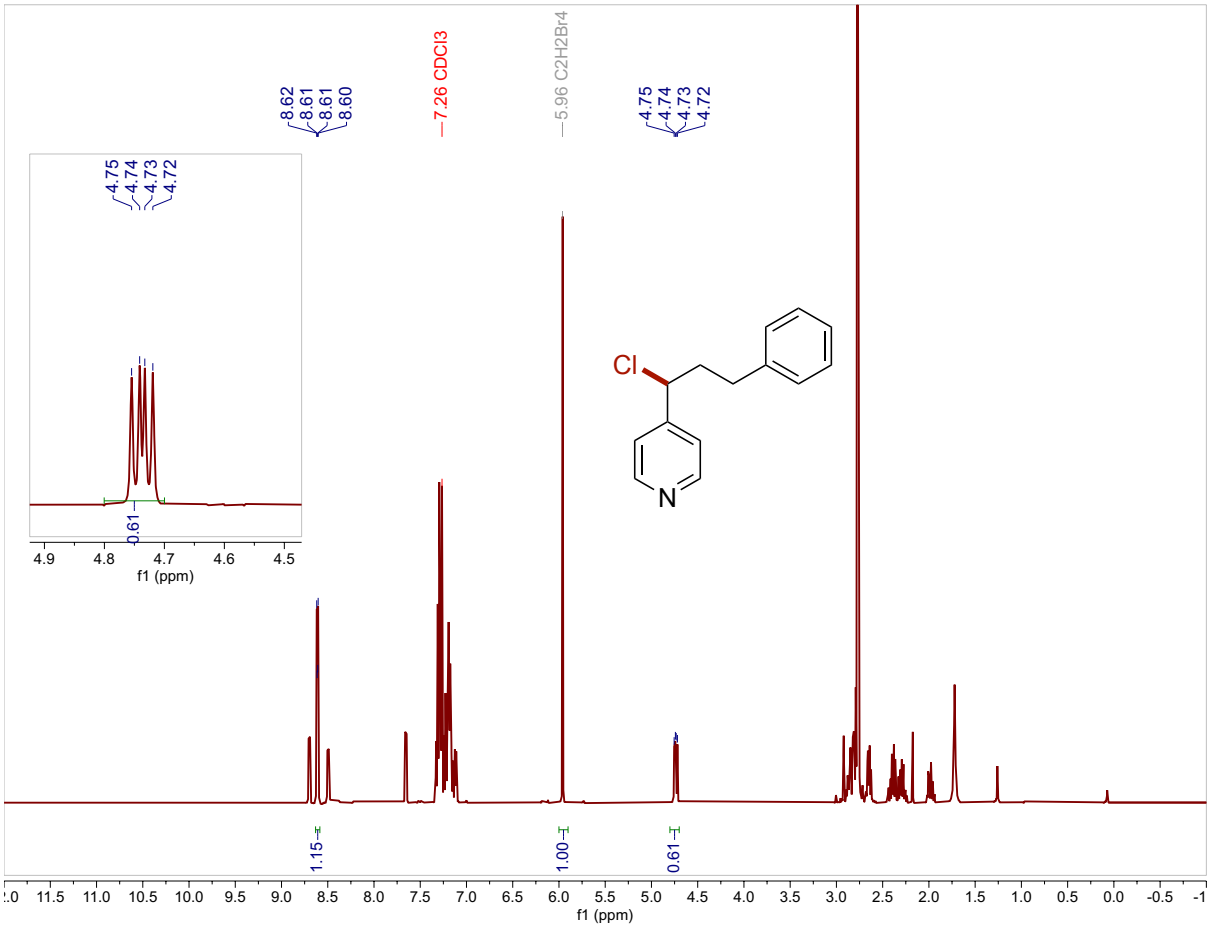


Figure 3B.12. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of $C_2H_2Br_4$ as an internal standard (5.96 ppm). The resolved heterobenzylic proton (4.73 ppm) is labeled and integrated.

(*rac*)-4-(1-Chloroethyl)-3-(hex-1-yn-1-yl) pyridine (13): Prepared from 4-ethyl-3-(hex-1-yn-1-yl) pyridine (0.05 mmol, 9.4 mg, 1.0 equiv) according to the general procedure D (70 °C, 4 h) in Section 3. The substrate seemed to have worked under general procedure C (70 °C, 16 h) as well. Use of TfCl as an additive reduced the reaction time.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.46 (q, J = 6.8 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 80% (GP C, 4 h) and 89% (GP D, 16 h).

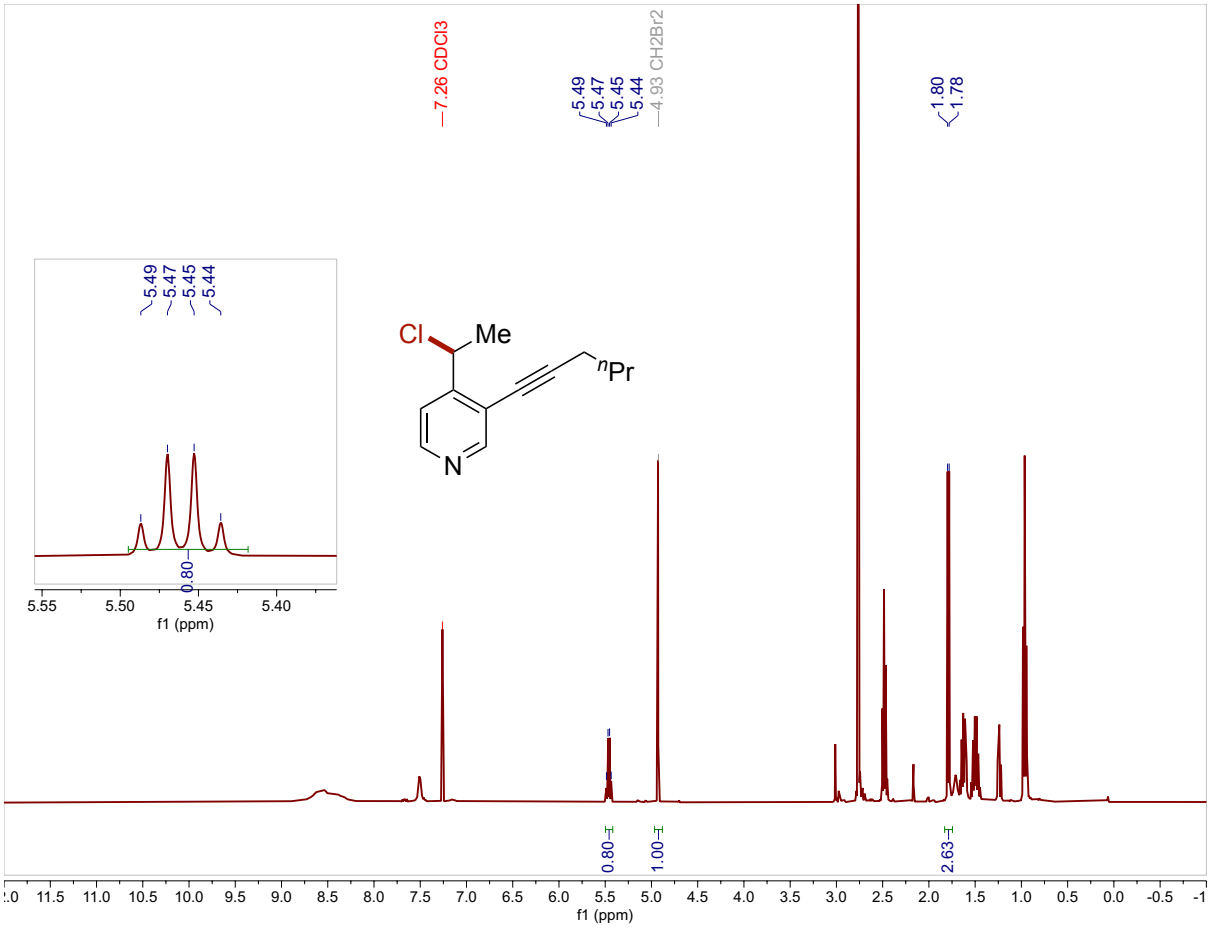


Figure 3B.13. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved hetero benzylic proton (5.47 ppm) is labeled and integrated.

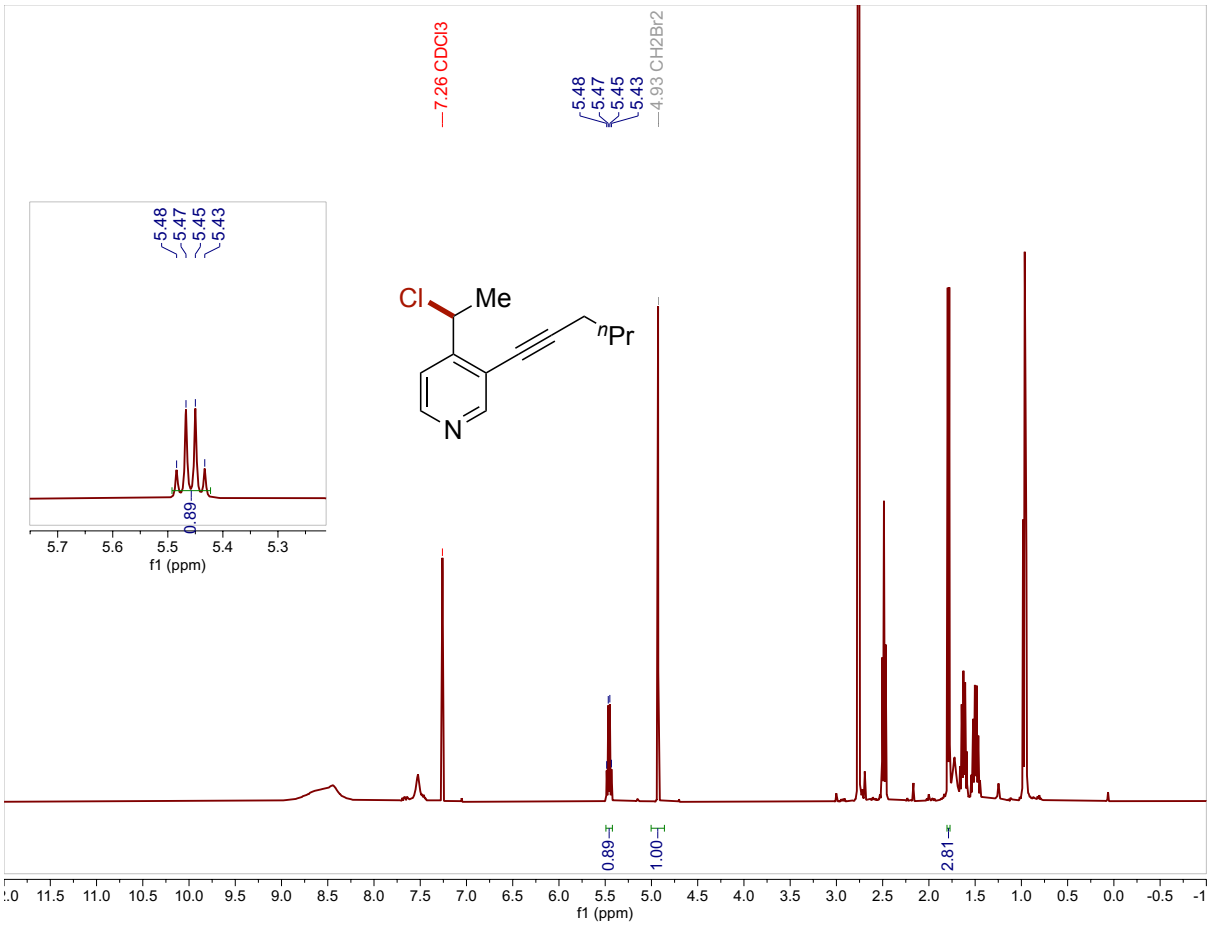


Figure 3B.13.B. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved hetero benzylic proton (5.47 ppm) is labeled and integrated.

(*rac*)-5-Chloro-6,7-dihydroisoquinolin-8(5*H*)-one (14): Prepared from 6,7-dihydroisoquinolin-8(5*H*)-one (0.05 mmol, 7.4 mg, 1.0 equiv) according to the general procedure D (70 °C, 16 h) in Section 3, using 10% mol% TfCl (0.005 mmol, 0.8 mg, 0.5 µL).

Heterobenzyl *mono*-Chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.29 – 5.22 (m, 1H). Under a different condition, exclusively *di*-chlorinated product obtained (see below).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 33%; Under standard conditions of procedure D, 40% remaining starting material was detected.

Attempts to increase the yield of *mono*-chloride product, led to formation of mixture of *mono*- and *di*-chlorinated products. However, using 3 equiv of NCS provided the di-chlorinated product in 87% ^{1}H NMR yield under modified procedure C (70 °C, 16 h).

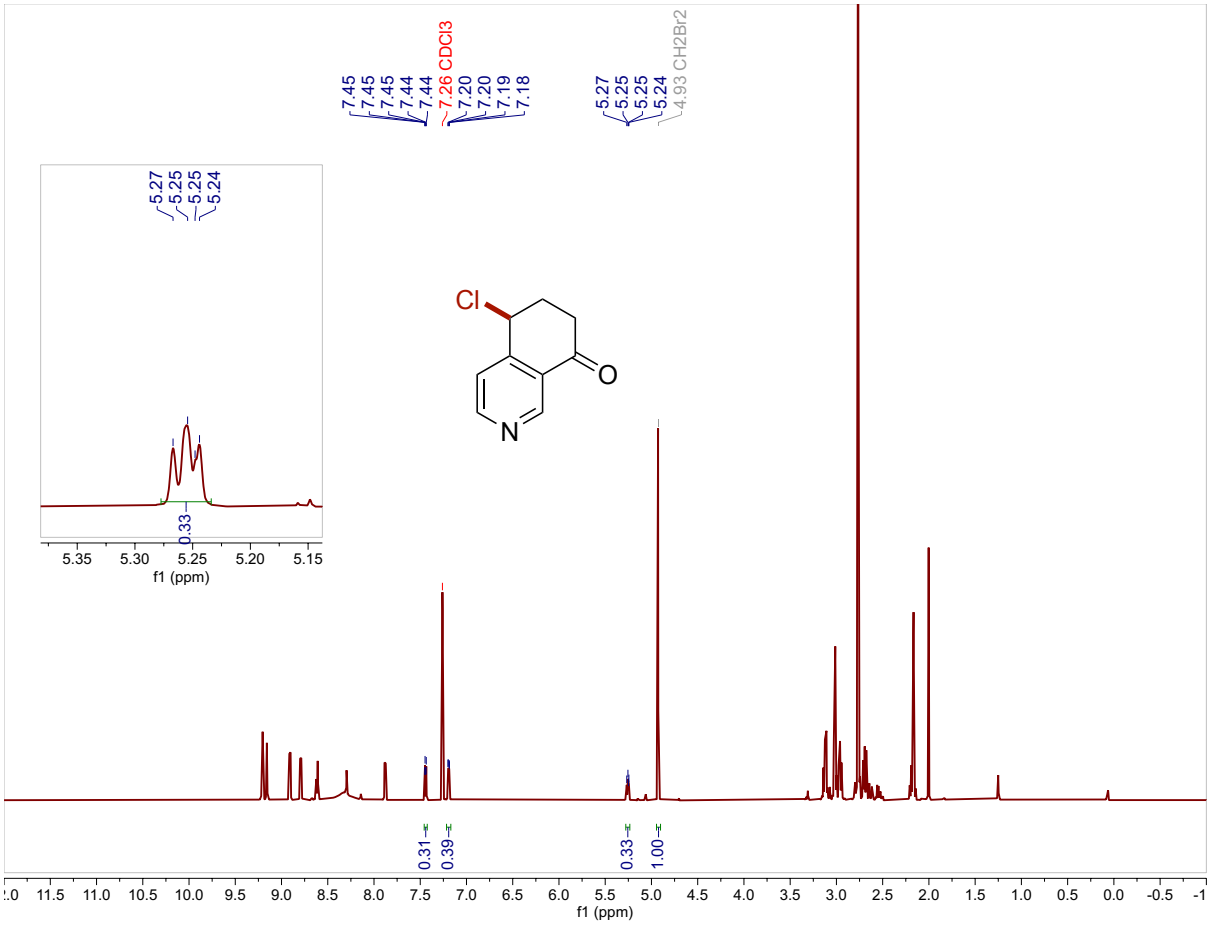


Figure 3B.14.A. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The relevant resolved proton (5.25 ppm) is labeled and integrated.

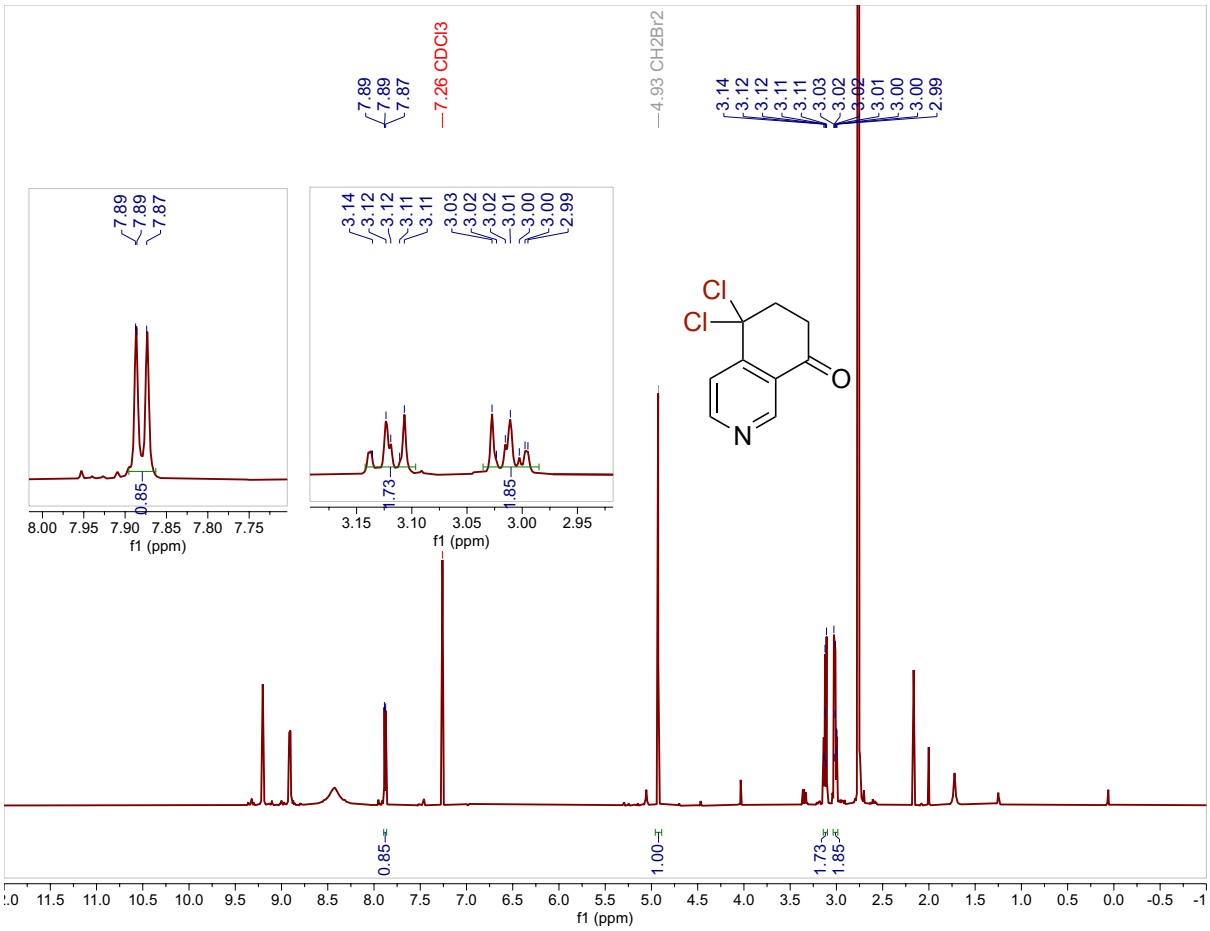


Figure 3B.14.B. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The relevant resolved aromatoc proton (7.89 ppm) is labeled and integrated.

(*rac*)-4-(1-Chlorobutyl) nicotinonitrile (15): Prepared from 4-butylnicotinonitrile (0.05 mmol, 8.0 mg, 1.0 equiv) following procedure C (90 °C, 4 h) in Section 3.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.17 (dd, J = 8.5, 5.7 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 81%.

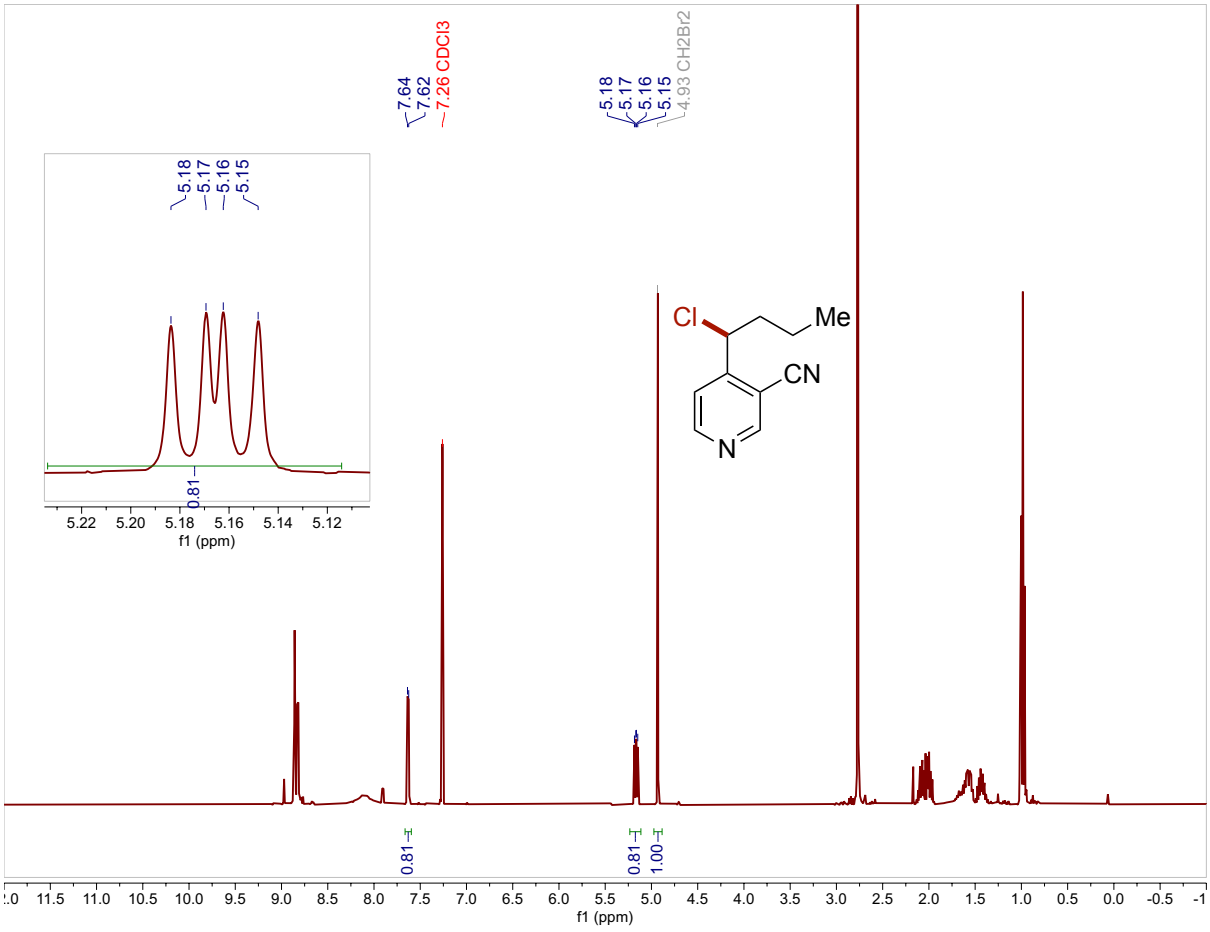


Figure 3B.15. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved heterobenzylic proton (5.17 ppm) is labeled and integrated.

(*rac*)-3-Bromo-4-(1-chloroethyl) pyridine (16): Prepared from 3-bromo-4-ethylpyridine (0.05 mmol, 9.3 mg, 1.0 equiv) following procedure C (90 °C, 16 h) in Section 3.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.38 (q, J = 6.8 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 63% (with 16% unreacted starting material)

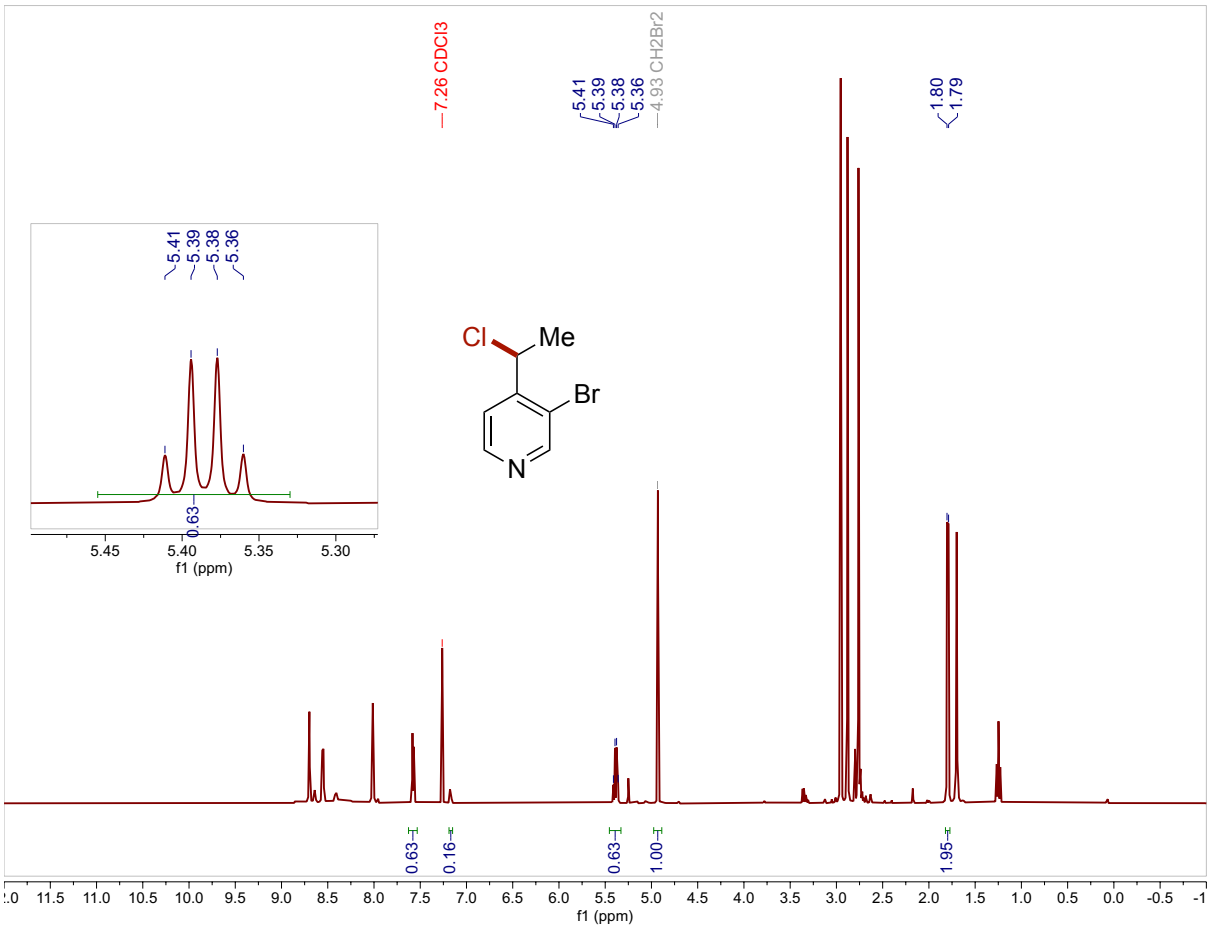


Figure 3B.16. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved heterobenzylic proton (5.38 ppm) is labeled and integrated.

(*rac*)-3-Bromo-4-(1-chlorobutyl) pyridine (17): Prepared from 3-bromo-4-butylpyridine (0.05 mmol, 10.7 mg, 1.0 equiv) following procedure D (90 °C, 16 h) using 10% mol% TfCl (0.005 mmol, 0.8 mg, 0.5 µL).

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.29 – 5.21 (m, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 85%.

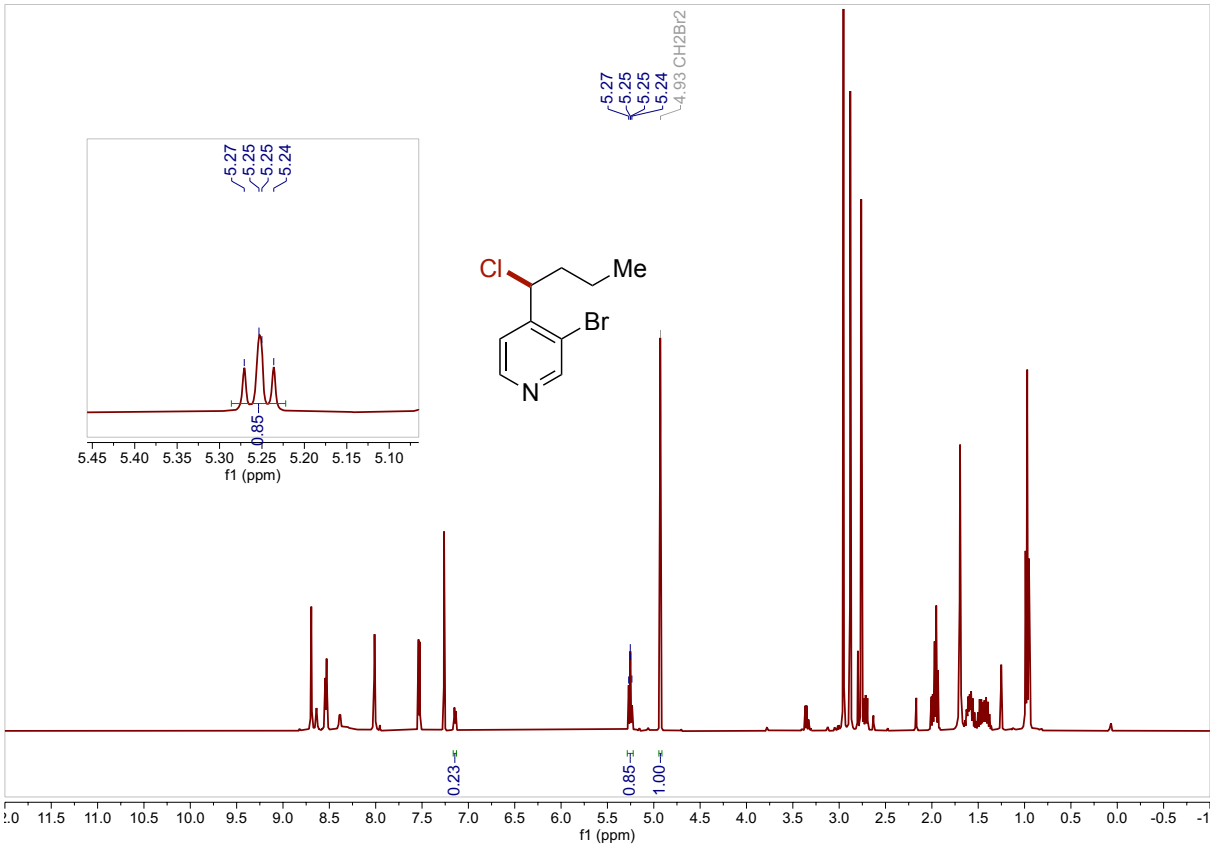


Figure 3B.17. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved heterobenzylic proton (5.29 – 5.21 ppm) is labeled and integrated.

(*rac*)-3-Bromo-4-(chloro(cyclobutyl)methyl) pyridine (18): Prepared from 3-bromo-4-(cyclobutylmethyl) pyridine (0.05 mmol, 11.3 mg, 1.0 equiv) following procedure C (90 °C, 16 h) in Section 3.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.24 (d, J = 8.6 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 82%.

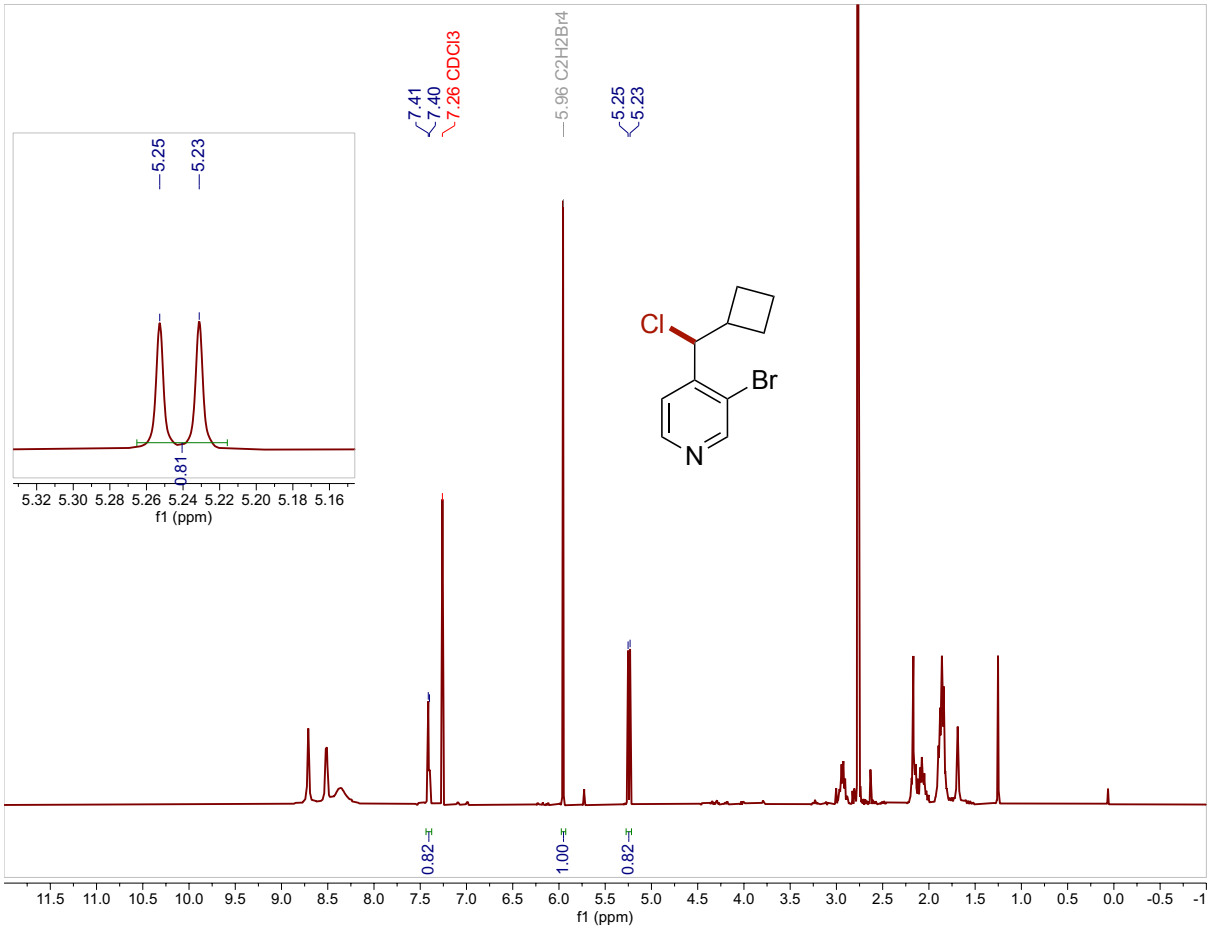


Figure 3B.18. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of $C_2H_2Br_4$ as an internal standard (5.96 ppm). The resolved heterobenzylic proton (5.24 ppm) is labeled and integrated.

(*rac*)-3-Bromo-4-(chloro(cyclopentyl)methyl) pyridine (19): Prepared from 3-bromo-4-(cyclopentylmethyl) pyridine (0.05 mmol, 12.0 mg, 1.0 equiv) following procedure C (90 °C, 16 h) in Section 3.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.16 (d, J = 8.6 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 91%.

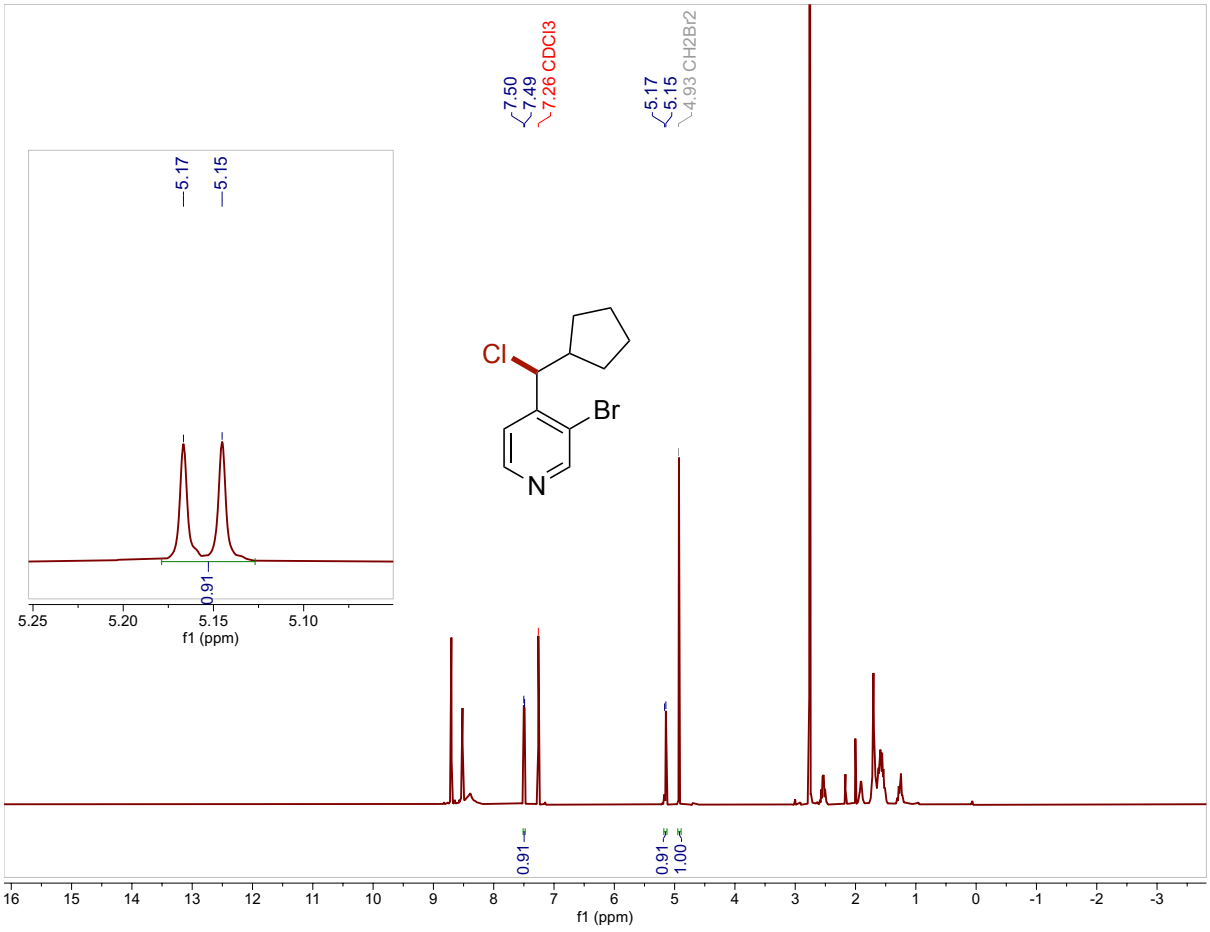


Figure 3B.19. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved heterobenzylic proton (5.16 ppm) is labeled and integrated.

(*rac*)-3-Bromo-4-(1-chlorobut-3-yn-1-yl) pyridine (20): Prepared from 3-bromo-4-(but-3-yn-1-yl) pyridine (0.05 mmol, 10.5 mg, 1.0 equiv) according to the general procedure C (90 °C, 16 h) in Section 3.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.41 (t, J = 6.4 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 70%.

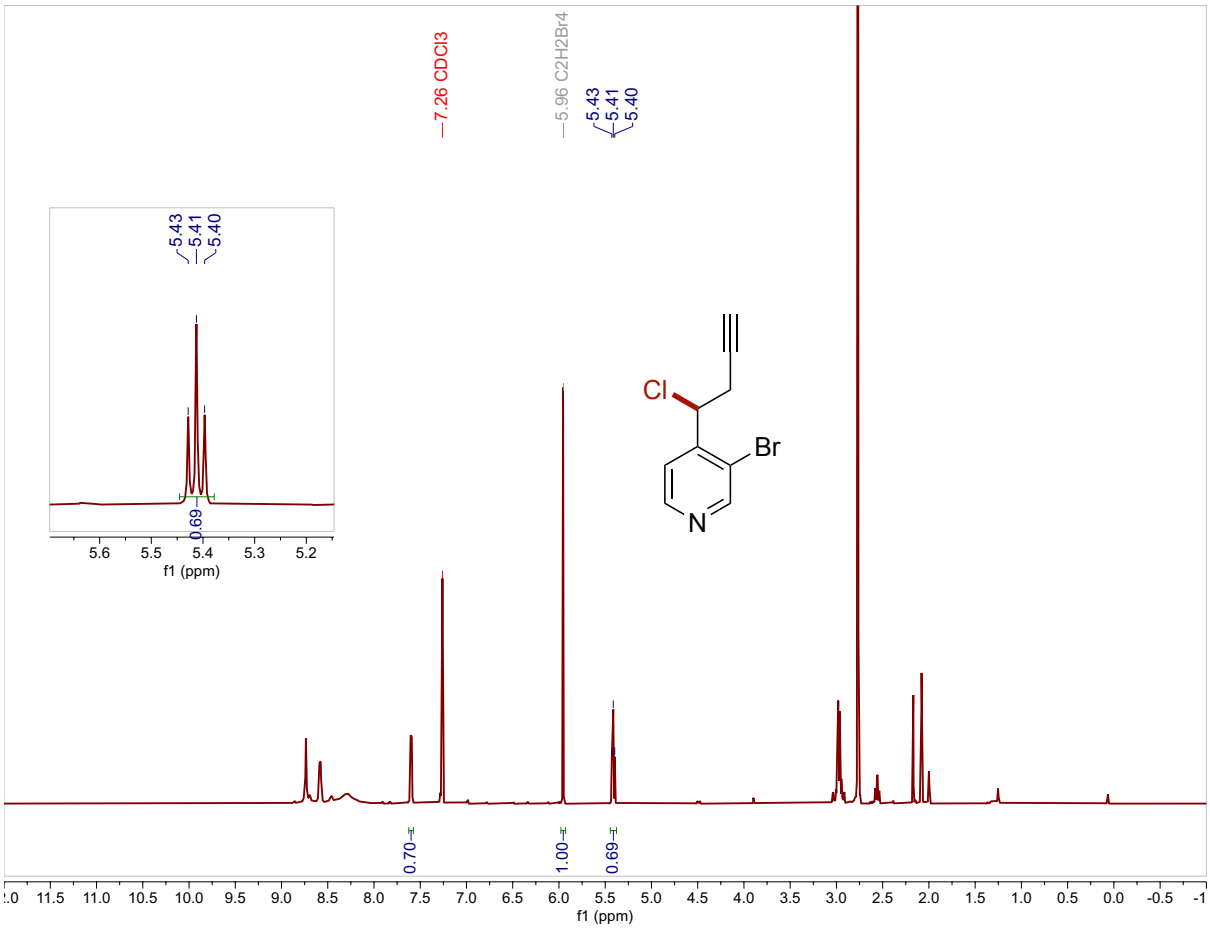


Figure 3B.20. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of $C_2H_2Br_4$ as an internal standard (5.96 ppm). The resolved hetero benzylic proton (5.41) is labeled and integrated.

(*rac*)-3-Bromo-4-(1-chlorobut-3-en-1-yl) pyridine (21): Prepared from 3-bromo-4-(but-3-en-1-yl) pyridine (0.05 mmol, 10.6 mg, 1.0 equiv) according to Procedure C (90 °C, 16 h) in Section 3. Deviation from Procedure C is 2.4 equiv of NCS (0.12 mmol, 16 mg).

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.29 (dd, J = 7.8, 5.8 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 55%. Under this condition ~ 10% di-Cl product was detected in LCMS; however, a cleaner and higher yielding condition was not found.

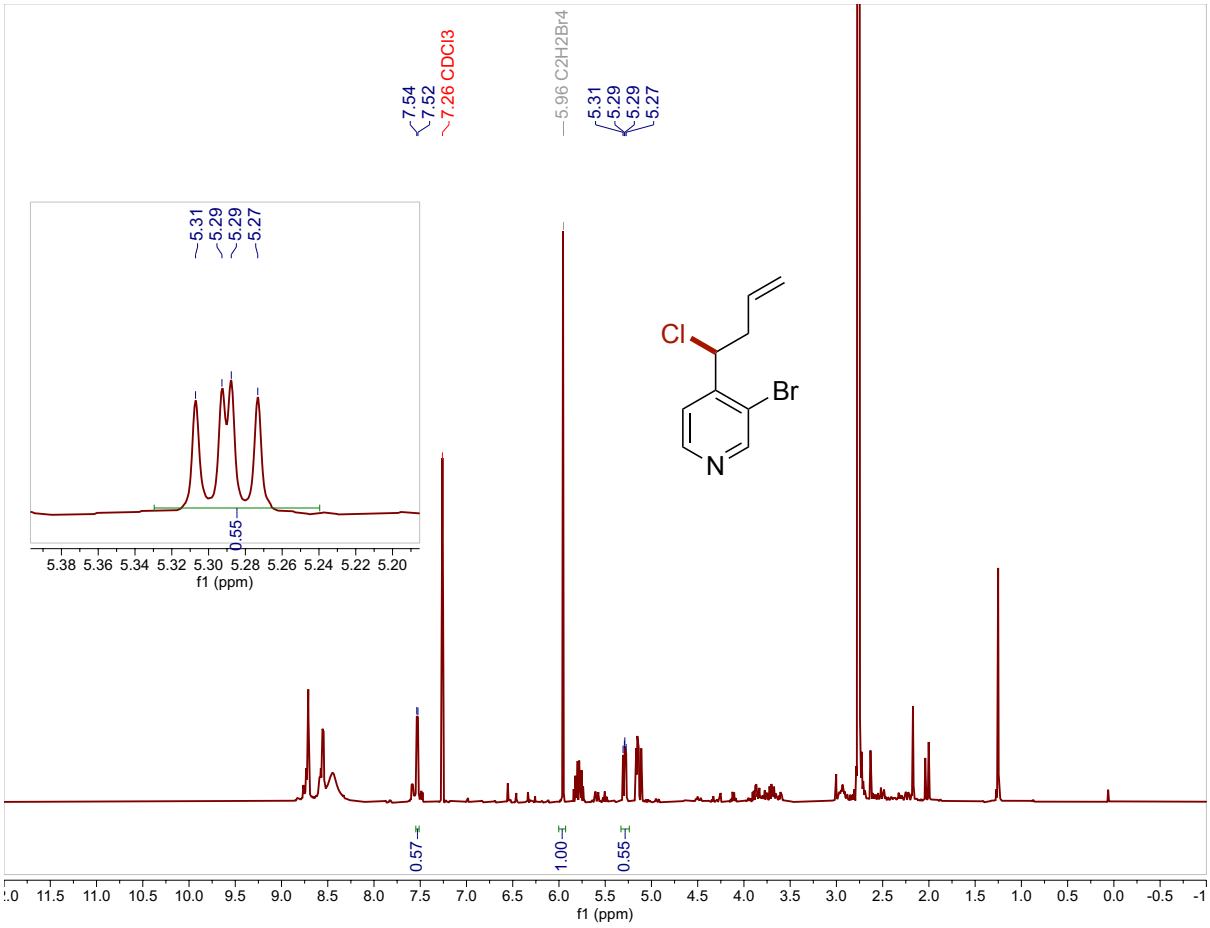


Figure 3B.21. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of $C_2H_2Br_4$ as an internal standard (5.96 ppm). The resolved hetero benzylic proton (5.29 ppm) is labeled and integrated.

(*rac*)-3-Bromo-4-(chloro(tetrahydro-2*H*-pyran-4-yl) methyl) pyridine (22): Prepared from 3-bromo-4-((tetrahydro-2*H*-pyran-4-yl) methyl) pyridine (0.05 mmol, 12.8 mg, 1.0 equiv) according to a general procedure D (90 °C, 4 h) in Section 3, using 40 mol% TfCl (0.02 mmol , 3.37 mg, 2 µL).

Otherwise, comparable yield (70%) can be obtained simply under procedure C (90 °C, 16 h).

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.11 (d, J = 7.6 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 70%. Under this condition, 15% of the starting material remained unreacted.

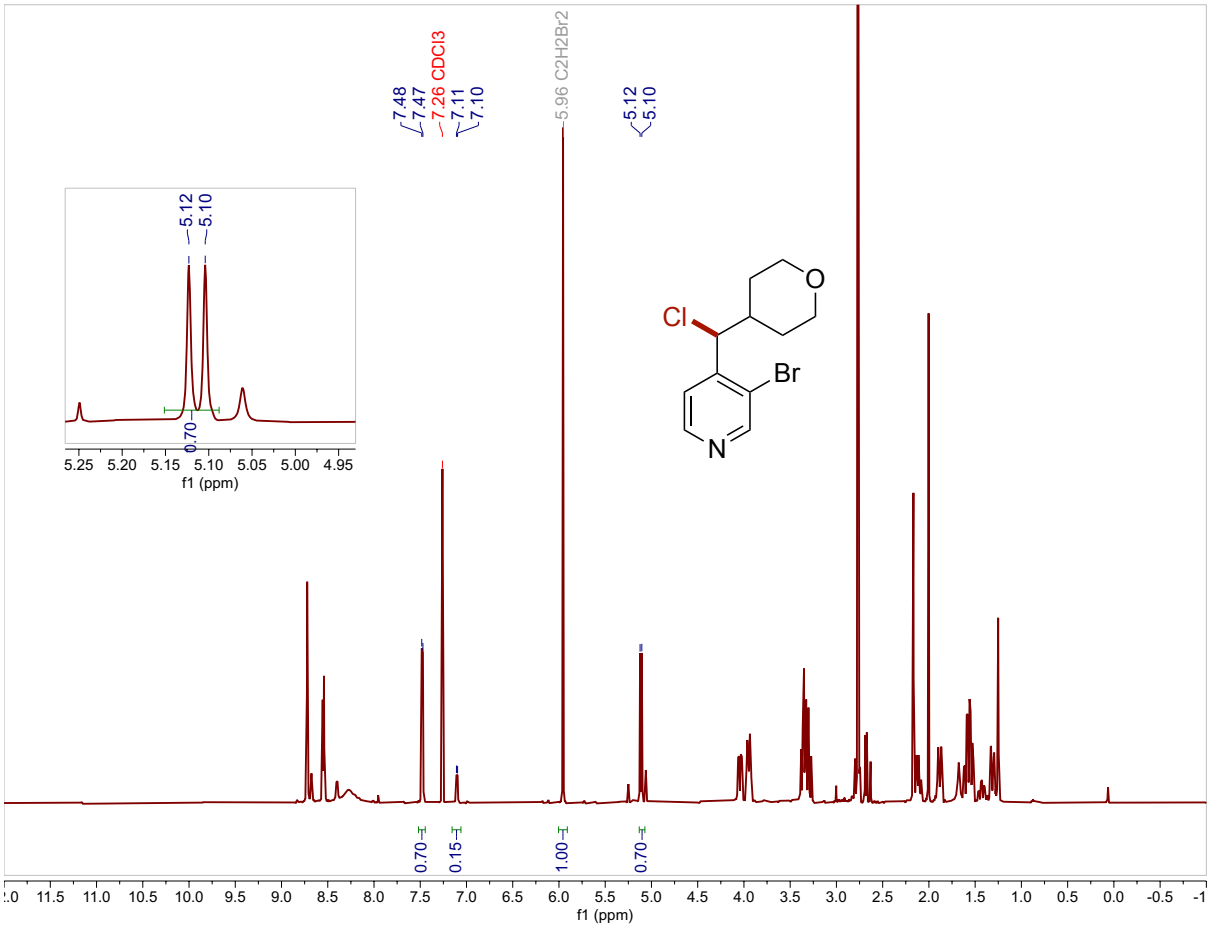


Figure 3B.22. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of $C_2H_2Br_4$ as an internal standard (5.96 ppm). The resolved hetero benzylic proton (5.11 ppm) is labeled and integrated.

(*tert*-Butyl-(*rac*)-4-((3-bromopyridin-4-yl) chloromethyl) piperidine-1-carboxylate (23): Prepared from tert-butyl 4-((3-bromopyridin-4-yl) methyl) piperidine-1-carboxylate (0.05 mmol, 17.8 mg, 1.0 equiv) according to a modified general procedure D (70 °C, 16 h) in Section 3 using 10 mol% TfCl (0.005 mmol, 0.8 mg, 0.5 µL). Deviation from Procedure D is 2.2 equiv NCS (0.11 mmol, 15 mg) and 2.2 equiv. Li_2CO_3 (0.11 mmol, 8 mg).

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.12 (d, J = 7.2 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 65%. Under this condition, 9% of the starting material remained unreacted.

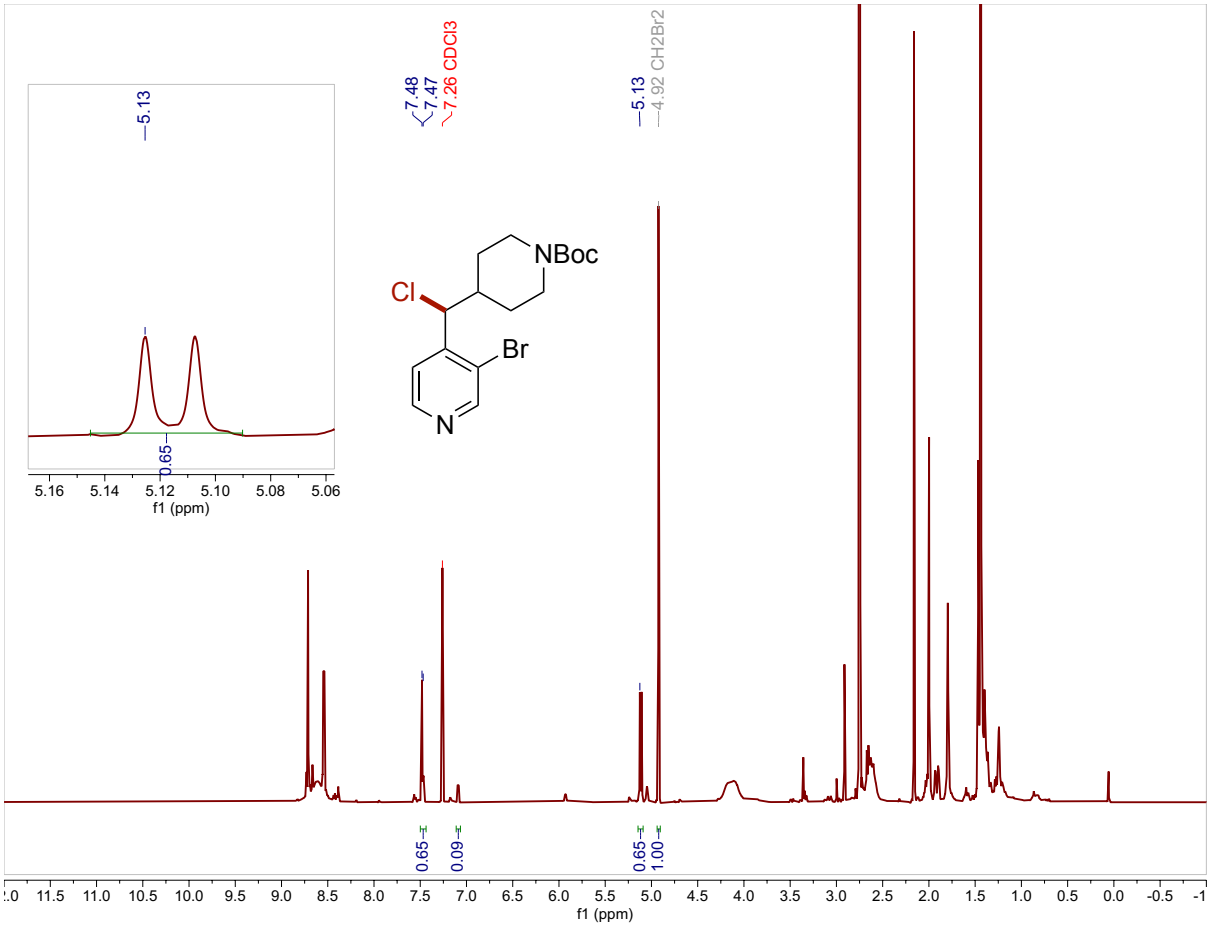


Figure 3B.23. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm, in this case 4.92 ppm). The resolved heterobenzylic proton (5.12) is labeled and integrated.

(*rac*)-(4-Chloro-3,4-dihydro-1,7-naphthyridin-1(2*H*)-yl) (phenyl)methanone (24): Prepared from (3,4-dihydro-1,7-naphthyridin-1(2*H*)-yl) (phenyl)methanone (0.05 mmol, 11.9 mg, 1.0 equiv) according to the general procedure D (70 °C, 16 h) in Section 3, using 10 mol% TfCl (0.005 mmol, 0.8 mg, 0.5 µL).

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.19 (t, J = 4.2 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 44%. Under the reaction conditions, 8% remaining starting material was detected. A cleaner or higher yielding condition was not found.

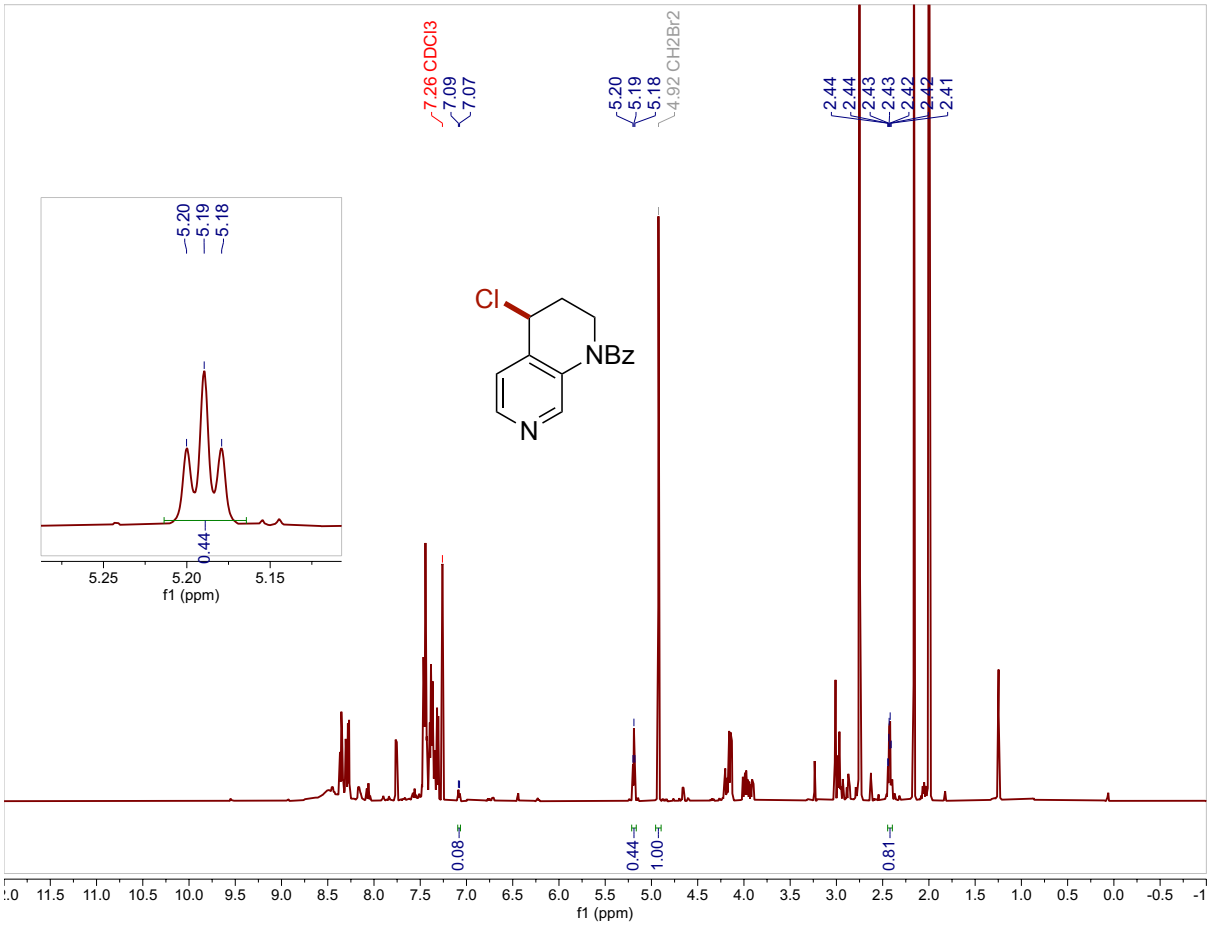


Figure 3B.24. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm, in this case 4.92 ppm). The resolved hetero benzylic proton (5.19 ppm) is labeled and integrated.

(*rac*)-*N*-(3-Chloro-2,2-dimethyl-3-(pyridin-4-yl) propyl) benzamide (25): Prepared from *N*-(2,2-dimethyl-3-(pyridin-4-yl) propyl) benzamide (0.05 mmol, 13.4 mg, 1.0 equiv) according to procedure D (16 h) in Section 3. Deviation from procedure D is 2 equiv NCS (0.1 mmol, 13 mg) 1.1 equiv of 4-trifluorophenylsulfonyl chloride (0.05 mmol, 13.5 mg) and PhCl as the solvent at 95 ºC.

Note that slightly improved yield (~10%) was obtained under this modified condition as compared to general procedure C.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.89 (s, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 54%.

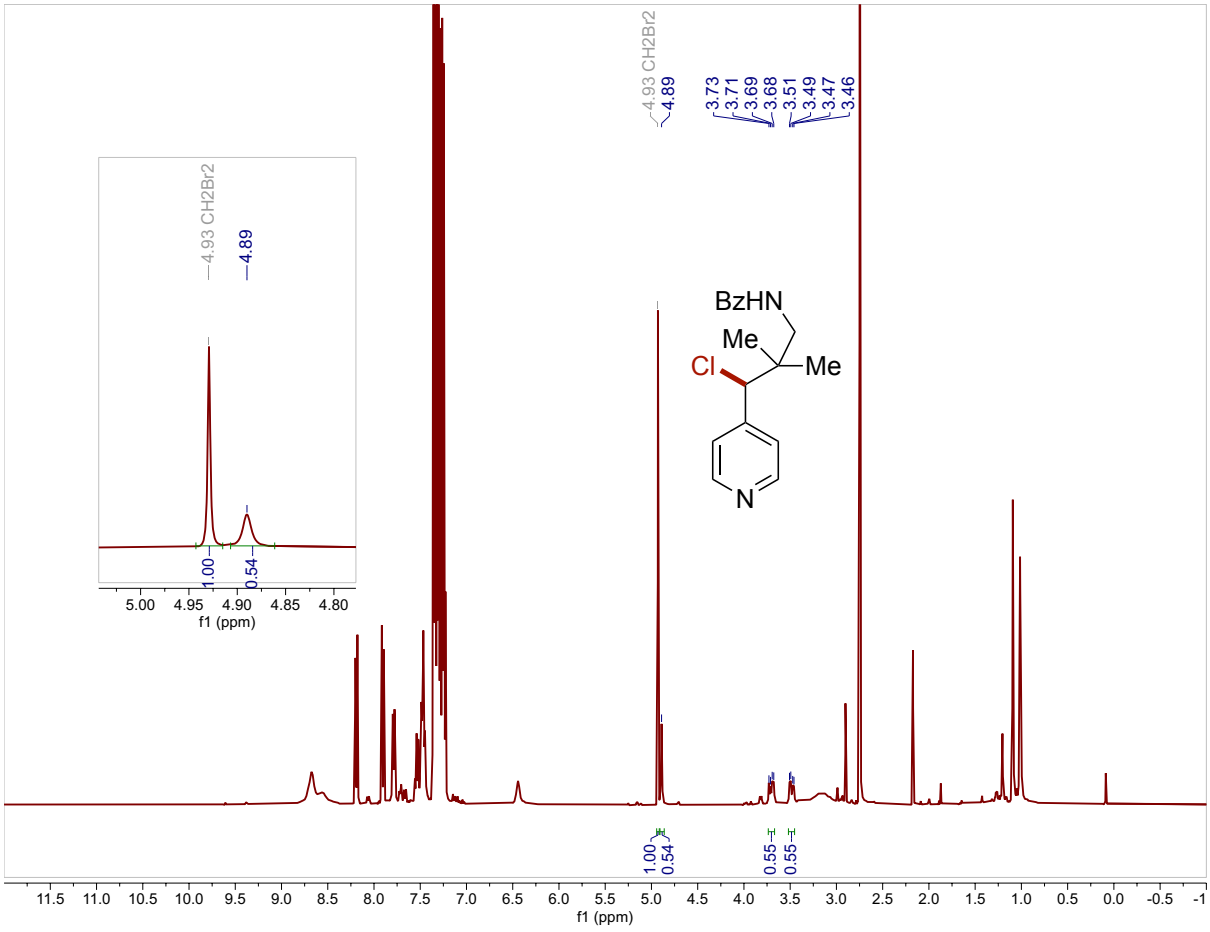


Figure 3B.25. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved hetero benzylic proton (4.89 ppm) is labeled and integrated.

***(rac)*-5-Chloro-5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-pyrrolidin]-1'-yl) (phenyl)methanone (26)**: Prepared from (5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-pyrrolidin]-1'-yl) (phenyl)methanone (0.05 mmol, 13.9 mg, 1.0 equiv.) according to procedure D (70 °C, 16 h) in Section 3, using 10 mol% TfCl (0.005 mmol, 0.8 mg, 0.5 µL).

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.72 (dd, J = 8.0, 3.3 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 27%. This substrate remains lower yielding and an improved condition was not found.

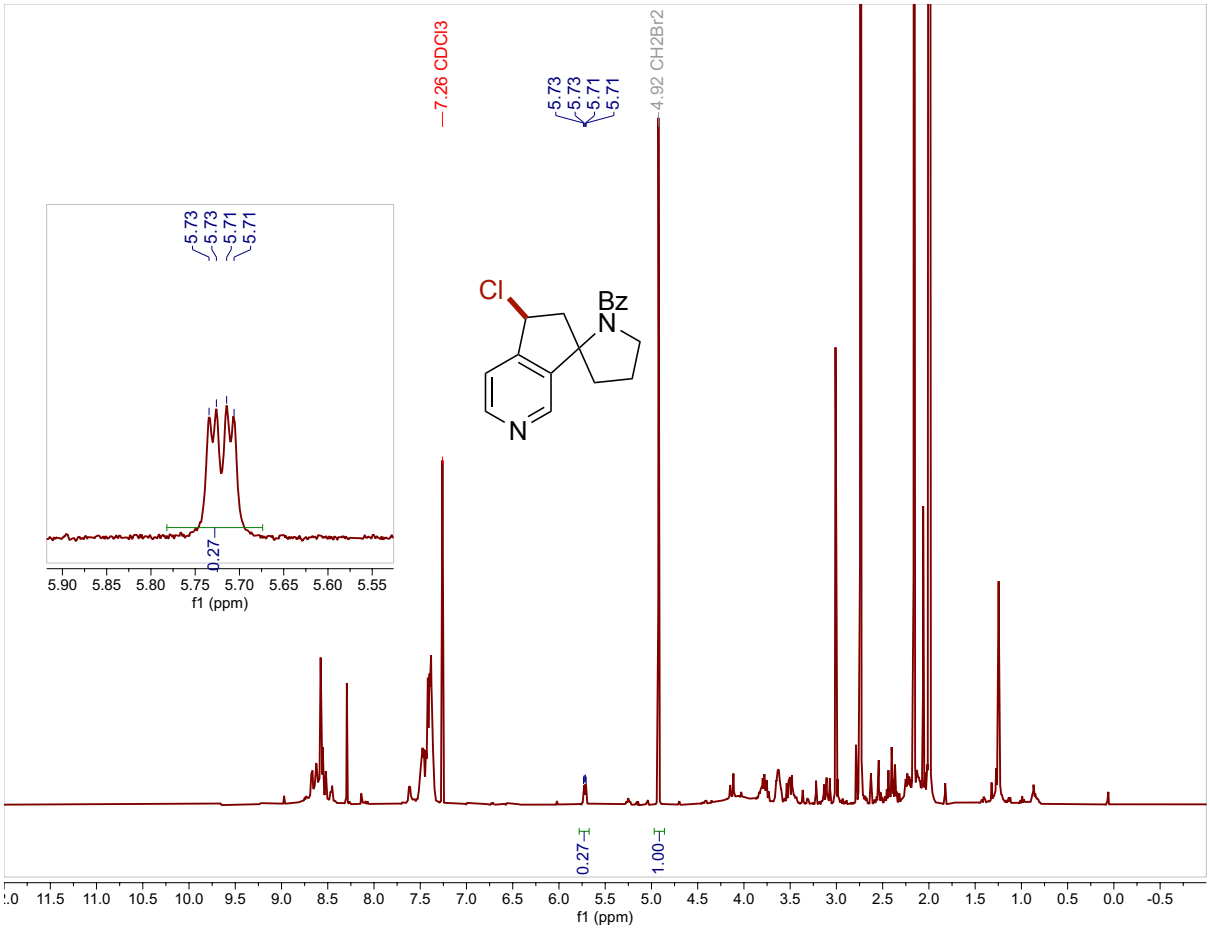


Figure 3B.26. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm, in this case 4.92 ppm). The resolved hetero benzylic proton (5.73 ppm) is labeled and integrated.

(*rac*)-2-Chloro-2-(pyridin-4-yl) ethyl benzoate (27): Prepared from 2-(pyridin-4-yl) ethyl benzoate (0.05 mmol, 11.4 mg, 1.0 equiv) according to a modified procedure D in Section 3. Deviation from Procedure D includes 2 equiv of NCS, DCE as solvent, exclusion of DMAP, at 45 °C for 16 h.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.29 (m, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 79% (*mono*-Cl: *di*-Cl = 2:1).

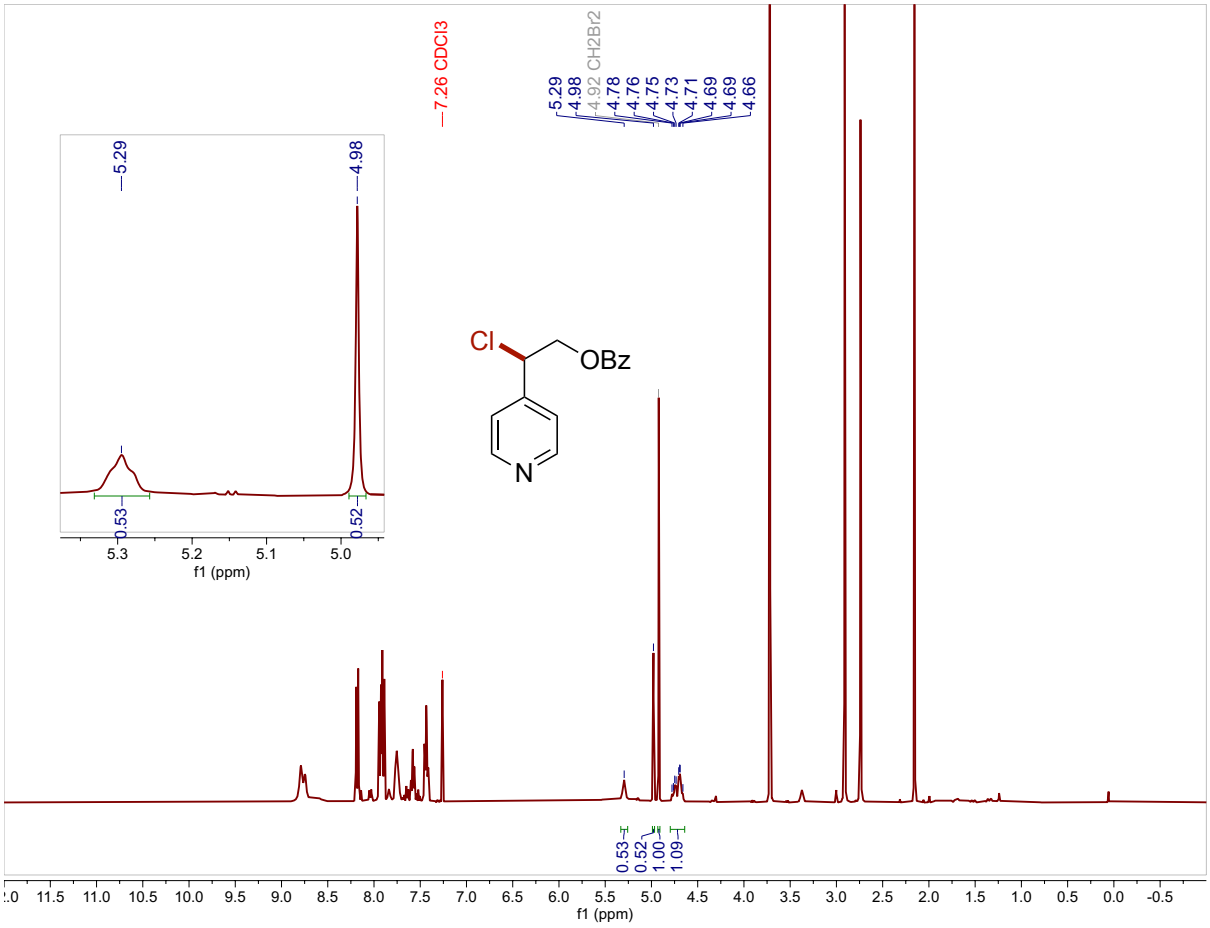


Figure 3B.27. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm, in this case 4.92 ppm). The resolved hetero benzylic proton (5.29 ppm) is labeled and integrated.

(*rac*)-4-(2-((*tert*-Butyldimethylsilyl) oxy)-1-chloroethyl) pyridine (28): Prepared from 4-(2-((*tert*-butyldimethylsilyl) oxy) ethyl) pyridine (0.05 mmol, 11.9 mg, 1.0 equiv) according to a modified version of the procedure D in Section 3. Deviation from Procedure D include 2 equiv. of NCS, PhCl as solvent, exclusion of DMAP, at 65 ℃ for 16 h.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.82 (t, J = 6.5 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 45%. Around 14% *di*-Cl product detected along with another ~15-20% unreacted starting material.

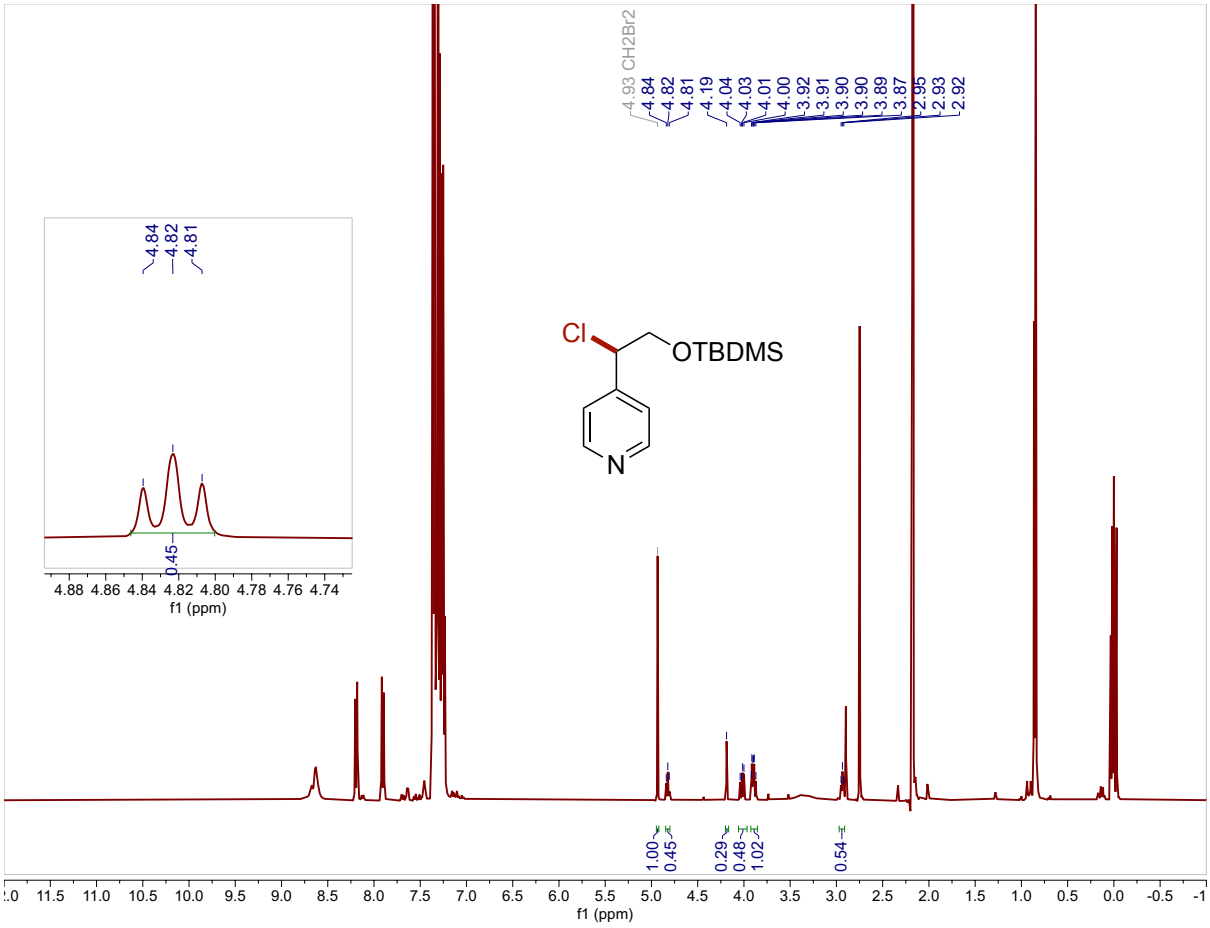


Figure 3B.28. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved hetero benzylic proton (4.84 ppm) is labeled and integrated.

(*rac*)-4-(1-Chlorobutyl) quinoline (29): Prepared from 4-butylquinoline (0.05 mmol, 9.3 mg, 1.0 equiv) according to procedure D in Section 3 (90 °C, 4 h), using 40 mol% TfCl. An additional amount of TfCl (40 mol% in place of 10 mol%) reduced the reaction time from 16 h to 4 h.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.64 (dd, J = 8.6, 5.3 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 71%.

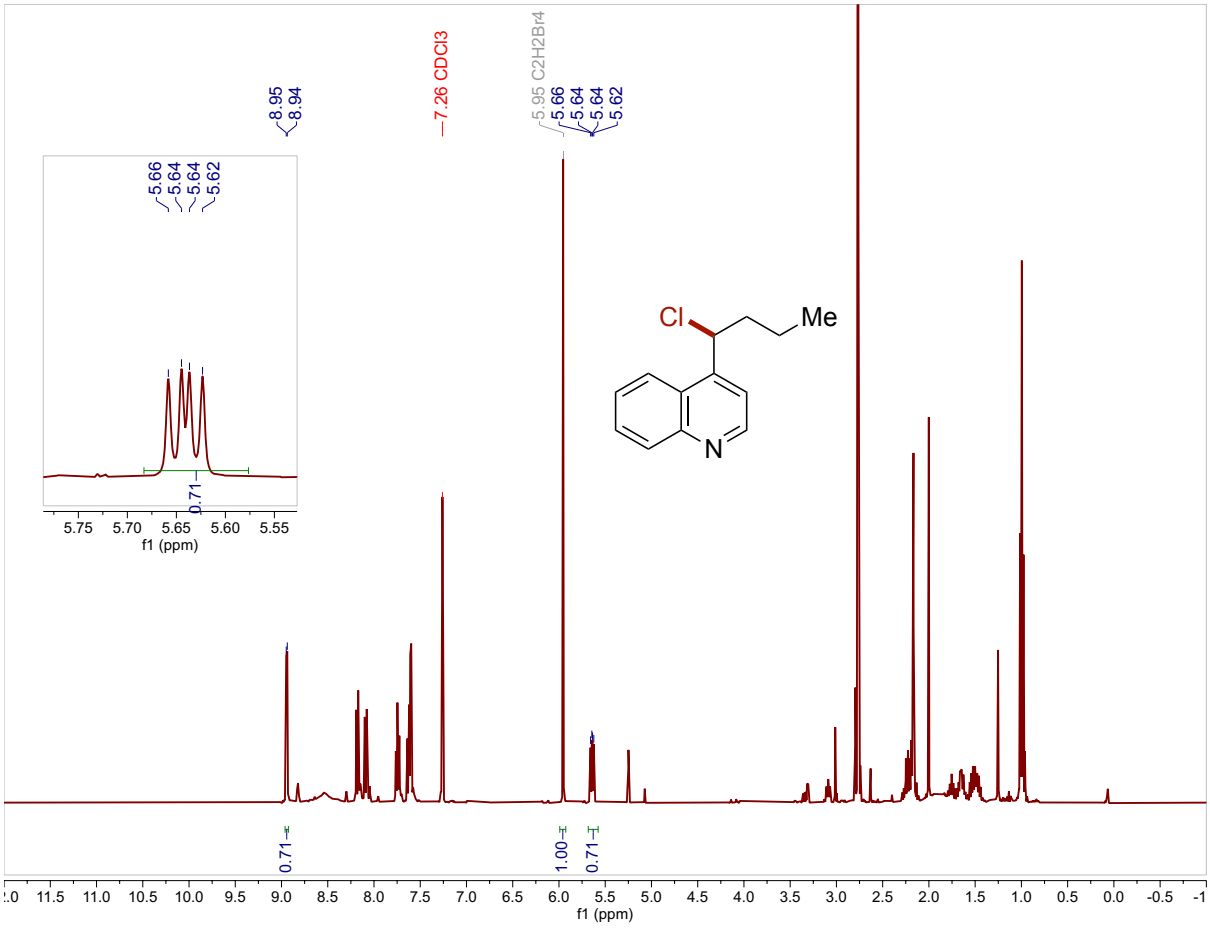


Figure 3B.29. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of $C_2H_2Br_4$ as an internal standard (5.95 ppm). The resolved hetero benzylic proton (5.66 ppm) is labeled and integrated.

(*rac*)-4-(1-Chloro-4-methylpentyl) quinoline (30): Prepared from 4-(4-methylpentyl) quinoline (0.05 mmol, 10.7 mg, 1.0 equiv) according to procedure D (90 °C, 4 h) in Section 3, using 40 mol% TfCl. An additional amount of TfCl (40 mol% in place of 10 mol%) reduced the reaction time from 16 h to 4 h.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.59 (t, J = 7.0 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton: 82%.

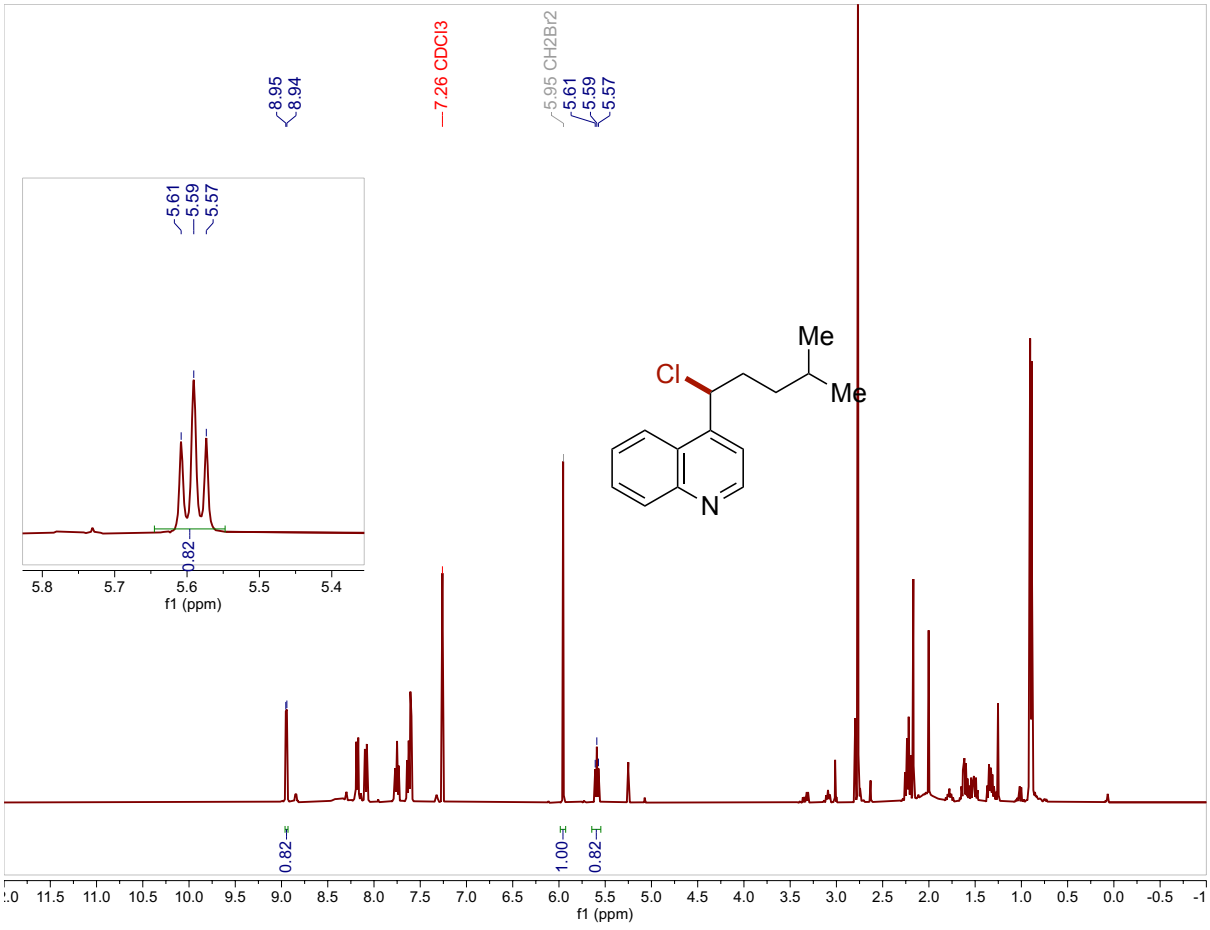


Figure 3B.30. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of $C_2H_2Br_4$ as an internal standard (5.95 ppm). The resolved hetero benzylic proton (5.61 ppm) is labeled and integrated.

(*rac*)-4-(1-Chlorobutyl) pyrimidine(31): Prepared from 4-butylpyrimidine (0.05 mmol, 6.8 mg, 1.0 equiv) procedure D (90 °C, 16 h) in Section 3. Deviation from procedure D is the exclusion of Li_2CO_3.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.88 (dd, J = 8.4, 5.6 Hz, 1H), which corresponds to the yield (50%) of mono-Cl product.

Calibrated ^{1}H NMR Yield from heterobenzylic proton and other relevant protons in aromatic region: 81% (*mono*-Cl: *di*-Cl = 1.7: 1).

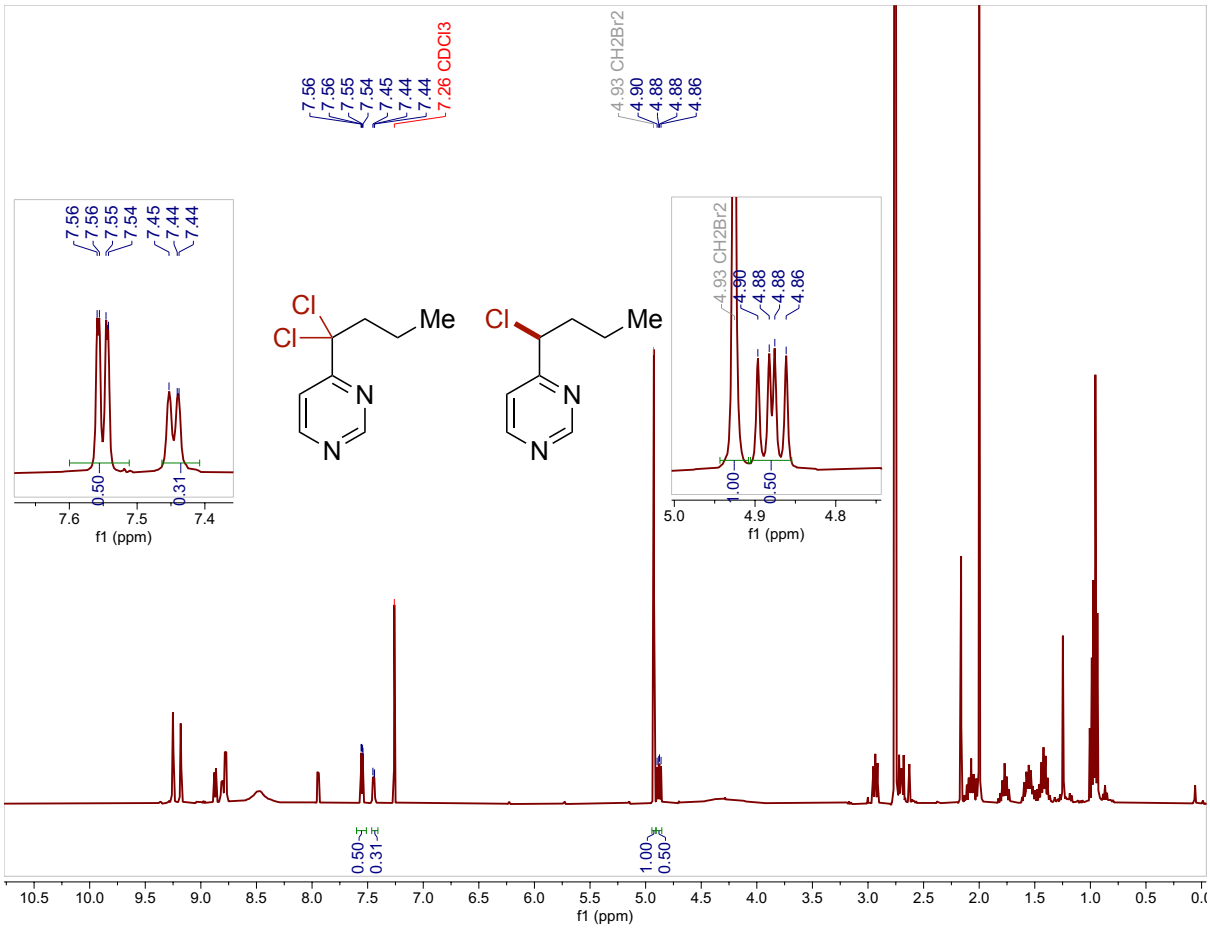


Figure 3B.31. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved hetero benzylic proton (4.90) and aromatic proton for di-chlorination product (7.44 ppm) are labeled and integrated.

(*rac*)-4-(1-Chloro-2-cyclobutylethyl) pyridazine (32): Prepared from 4-(2-cyclobutylethyl) pyridazine (0.05 mmol, 8.1 mg, 1.0 equiv) according to the general procedure D (90 ℃, 16 h) in Section 3.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.72 (dd, J = 8.2, 6.3 Hz, 1H).

Calibrated ^{1}H NMR Yield from Hetero benzylic Proton and other relevant protons in aromatic region: 68% (*mono*-Cl: *di*-Cl = 3.25: 1).

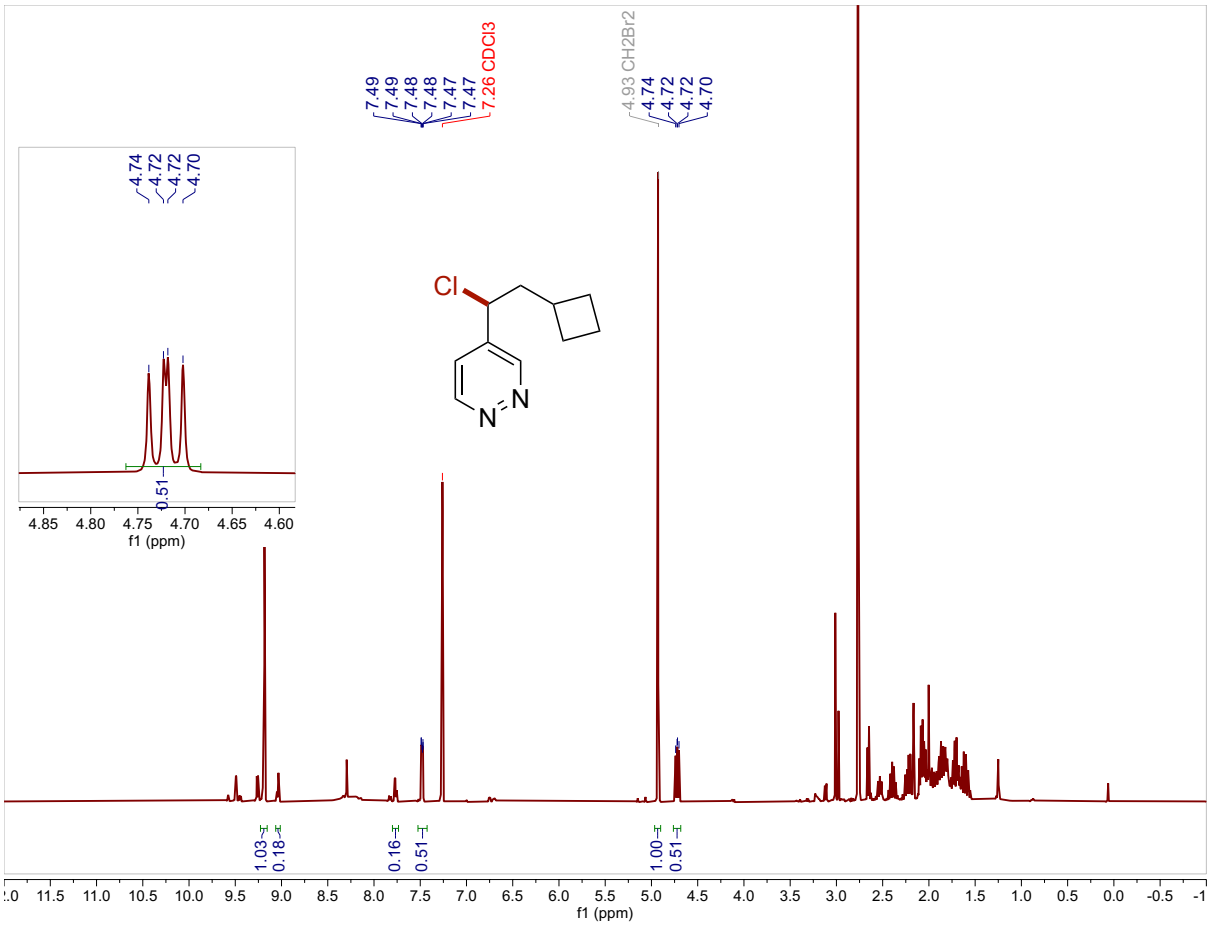


Figure 3B.32. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved hetero benzylic proton (4.72 ppm) is labeled and integrated.

4-(Chloromethyl) quinazoline(33): Prepared from 4-methylquinazoline (0.05 mmol, 7.2 mg, 1.0 equiv) according to the general procedure C (90 °C, 16 h) in Section 3.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.08 (s, 2H): corresponds to *mono*-Cl and δ 7.15 (s, 1H): corresponds to *di*-Cl.

Calibrated ^{1}H NMR Yield from heterobenzylic proton and other relevant protons in aromatic region: 84% (*di*-Cl: *mono*-Cl = 2.1:1).

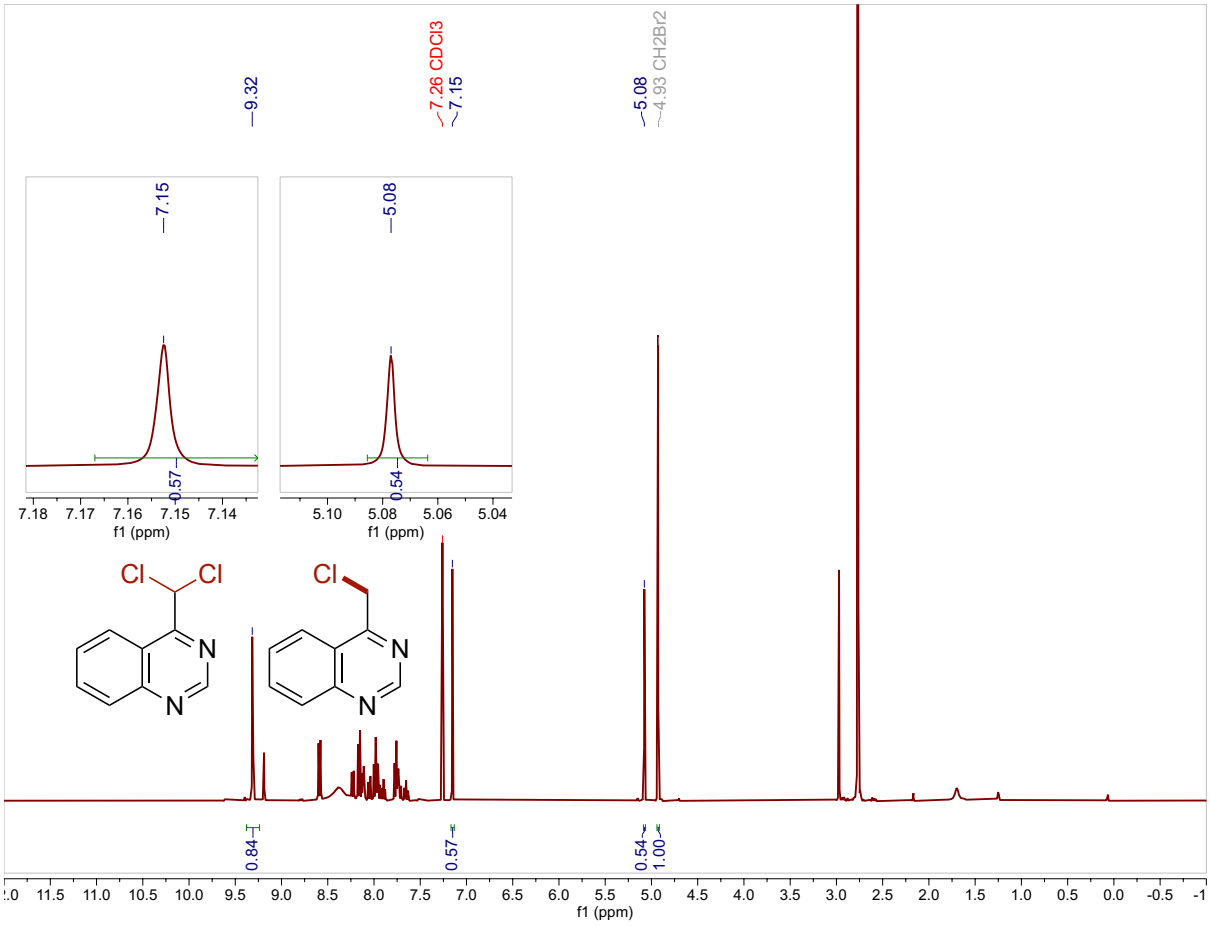


Figure 3B.33. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved hetero benzylic proton (5.08) and aromatic proton for di-chlorination product (7.15 ppm) are labeled and integrated.

(*rac*)-4-(1-Chloroethyl) quinazoline(34): Prepared from 4-ethylquinazoline (0.05 mmol, 7.9 mg, 1.0 equiv) according to the general procedure D (90 °C, 16 h) in Section 3.

Heterobenzylic chloride C–H shift: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.84 (q, J = 6.7 Hz, 1H).

Calibrated ^{1}H NMR Yield from heterobenzylic proton and other relevant protons in aromatic region: 97%.

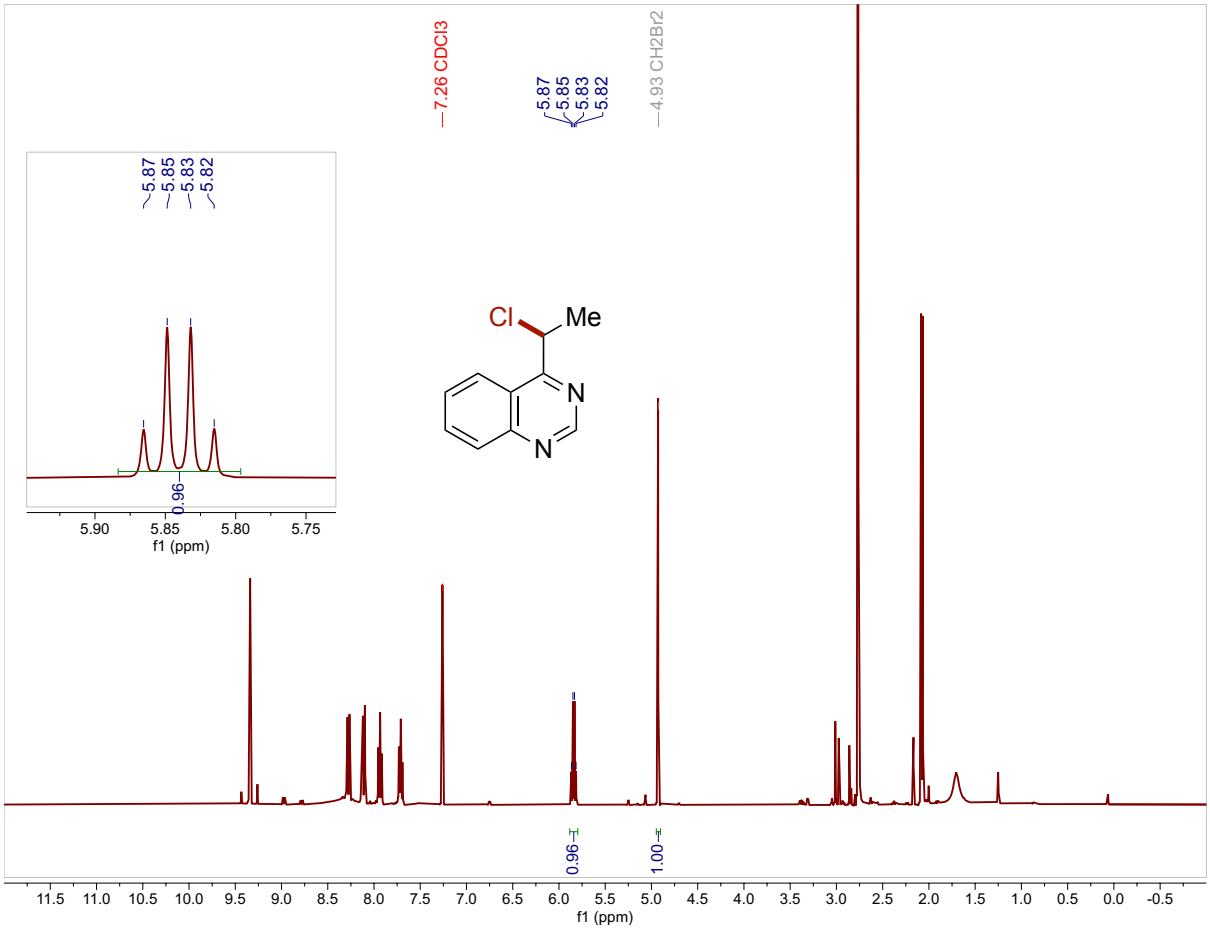
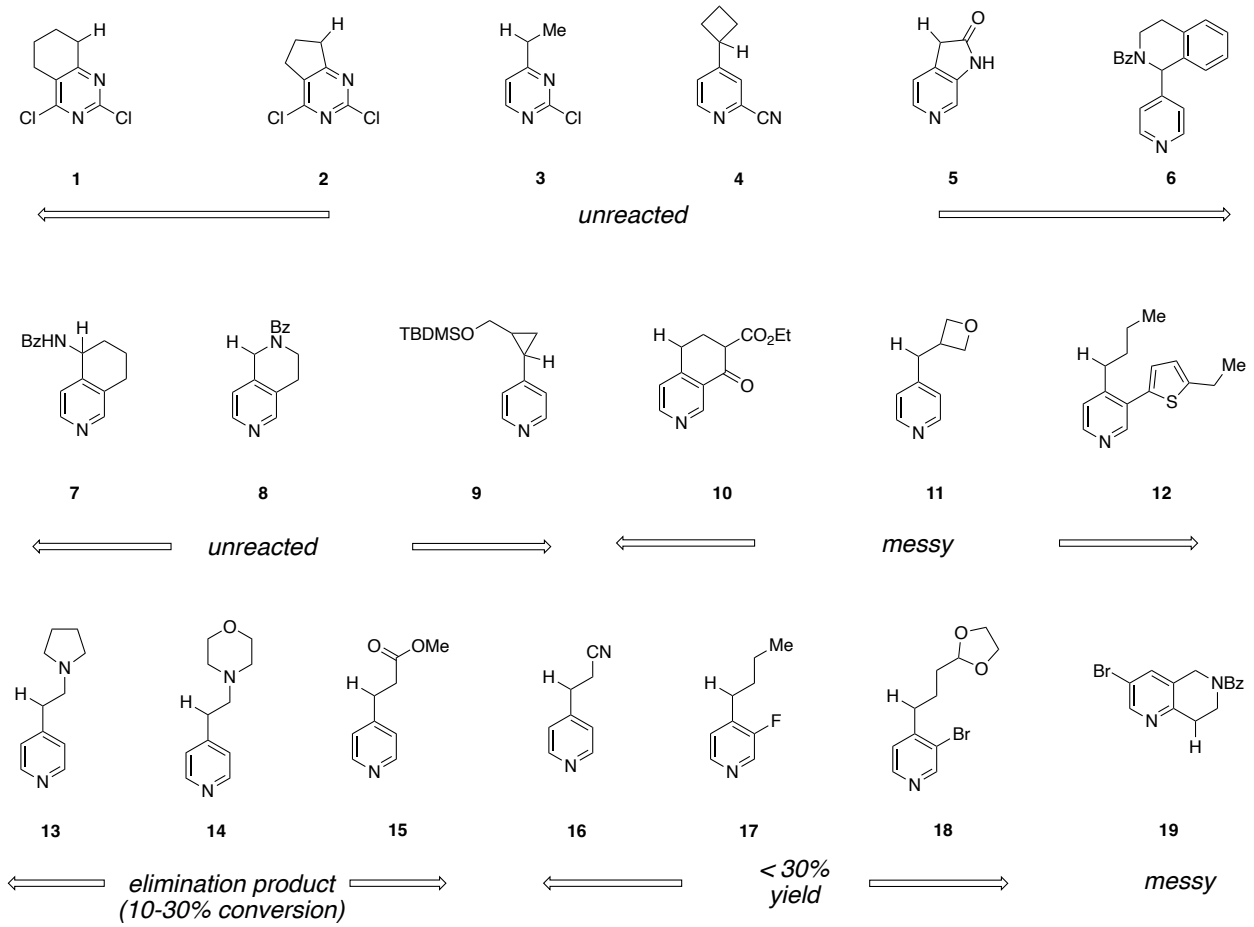


Figure 3B.34. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture following the addition of 0.025 mmol of CH_2Br_2 as an internal standard (4.93 ppm). The resolved hetero benzylic proton (5.85 ppm) ia labeled and integrated.

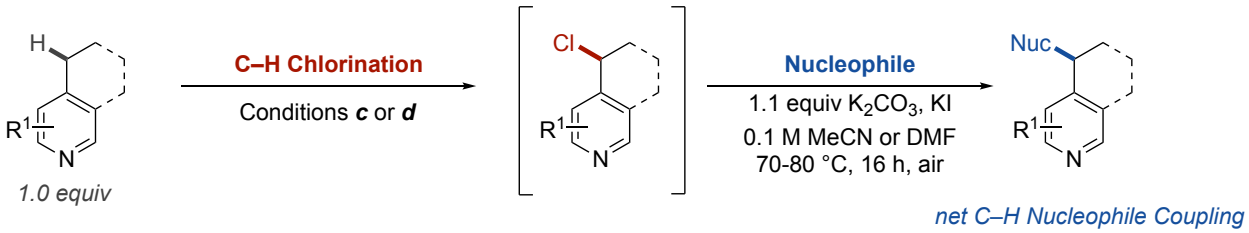
3B.VII. Quantitative ^{1}H NMR for Heterobenzylic Chloride Products



Discussion:

Several substrates were not successful for chlorination. Substrates **1-9** were found to be unreactive under standard conditions. Efforts to increase reaction temperatures up to 120 °C, addition of more equiv of chlorinating agent and other screening efforts failed to afford any productive chemistry. Only entry 3 provided ~10% *mono*-Cl product, while rest of them remained unreacted. Entries **10-12** underwent chlorination but provided multiple chlorinated products as determined by ^{1}H NMR and LCMS analysis. Entries **13-15** exhibited modest level of reactivity in the chlorination step. However, elimination products were primarily observed for these substrates. Entries **16-18** and **19** turned out to be less yielding/sluggish and the reason behind the low reactivity cannot be fully assessed at this point.

3B.VIII. Heterobenzylic Chloride Displacment with Nucleophiles



Heterobenzylic Diversification with Amine Nucleophiles

General Procedure 1: Following chlorination and ^{1}H NMR quantitation, an aliquot of the crude reaction mixture corresponding to a known amount of the heterobenzylic chloride (1.0 equiv) was added to scintillation vial containing the amine nucleophile (3.0 equiv), KI (1.1 equiv), K_2CO_3 (1.1 equiv), and a magnetic stir bar. The vial was sealed by a PTFE-lined pierceable cap and set to stir at 70 °C on a stirring hot plate in an aluminum block at 750 rpm for 12-16 h.

Heterobenzylic Diversification with Azole Nucleophiles

General Procedure 2: Following chlorination and ^{1}H NMR quantitation, the crude reaction mixture was washed with aq. $NaHCO_3$, and the aqueous layer was extracted with DCM. The organic layer was further washed with brine, separated, and dried over Na_2SO_4. The organic extract was concentrated on the rotavap, transferred to scintillation vial, and dissolved in DMF to prepare a stock solution of the heterobenzylic chloride. an aliquot of the crude reaction mixture corresponding to a known amount of the heterobenzylic chloride (1.0 equiv.) was added to scintillation vial containing the azole nucleophile (3.0 equiv), KI (1.1 equiv), K_2CO_3 (1.1 equiv), and a magnetic stir bar. The vial was sealed by a PTFE-lined pierceable cap and set to stir at 70 °C on a stirring hot plate in an aluminum block at 750 rpm 16 h.

Heterobenzylic Diversification with Thiolate Nucleophiles

General Procedure 3: Following chlorination and ^{1}H NMR quantitation, the crude reaction mixture was washed with aq. $NaHCO_3$, and the aqueous layer was extracted with DCM. The organic layer was further washed with brine, separated, and dried over Na_2SO_4. The organic extract was concentrated on the rotavap, transferred to scintillation vial, and redissolved in MeCN to prepare a solution of the heterobenzylic chloride. The vial was then charged with the thiolate nucleophile (3 equiv), and a magnetic stir bar. The vial was sealed by a PTFE-lined pierceable cap and set to stir at 80 °C on a stirring hot plate in an aluminum block at 750 rpm 16 h.

Heterobenzylic Diversification with Azide Nucleophiles

General Procedure 4: Following chlorination and ^{1}H NMR quantitation, the crude reaction mixture was washed with aq. $NaHCO_3$, and the aqueous layer was extracted with DCM. The organic layer was further washed with brine, separated, and dried over Na_2SO_4. The organic extract was concentrated on the rotavap, transferred to scintillation vial, and dissolved in DMF to prepare a 0.1 M solution of the heterobenzylic chloride. The vial was then charged with NaN_3 (3 equiv.),

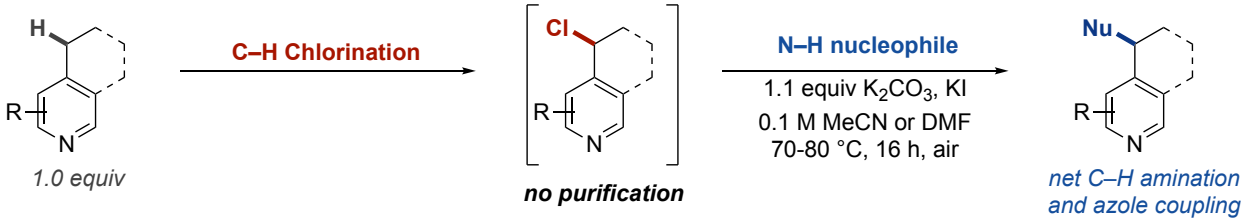
and a magnetic stir bar. The vial was sealed by a PTFE-lined pierceable cap and set to stir at 80 °C on a stirring hot plate in an aluminum block at 750 rpm for 6-8 h.

Benzylic Diversification with Benzoate Nucleophile

General Procedure 5: Following chlorination and ^{1}H NMR quantitation, the crude reaction mixture was washed with aq. $NaHCO_3$, and the aqueous layer was extracted with DCM. The organic layer was further washed with brine, separated, and dried over Na_2SO_4. The organic extract was concentrated on the rotavap, transferred to scintillation vial, and dissolved in DMF to prepare a 0.1 M solution of the heterobenzylic chloride. The vial was then charged with KOBz (3 equiv.), KI (1.1 equiv) and a magnetic stir bar. The vial was sealed by a PTFE-lined pierceable cap and set to stir at 80 °C on a stirring hot plate in an aluminum block at 750 rpm 16 h.

Work up for General Procedures 1-5: After 6-16 hours, the crude reaction mixture was washed with aq. $NaHCO_3$, and the aqueous layer was extracted with DCM. The organic layer was further washed with brine, separated, and dried over Na_2SO_4. The organic extract was concentrated on the rotavap, and the crude residue was purified by silica gel chromatography.

3B.IX. Synthesis of Heterobenzylic Amines and Azoles



Heterobenzylic Diversification with Amine Nucleophiles

Procedure 6: Following chlorination and ^{1}H NMR quantitation, aliquots of the crude reaction mixture corresponding to 0.05 mmol (1.0 equiv.) of the heterobenzylic chloride **3** and **30** were added to a series of 4 mL glass vials containing the **amine nucleophiles (Am#)** (3.0 equiv.), KI (1.1 equiv.), K_2CO_3 (1.1 equiv), and a magnetic stir bar. The vials were sealed by PTFE-lined pierceable caps and set to stir at 70°C on a stirring hot plate in an aluminum block at 750 rpm for 16 h. The reaction was cooled to room temperature, and the crude reaction solution is then filtered through a pad of celite plug eluting with acetone or ethyl acetate into a 6-dram vial and concentrated on the rotavap. A solution of dibromoethane ($C_2H_4Br_2$) or dibromomethane (CH_2Br_2) in $CDCl_3$ (0.05 M) was added into the concentrated reaction mixture as the external standard and analyzed by ^{1}H NMR to detect formation of product.

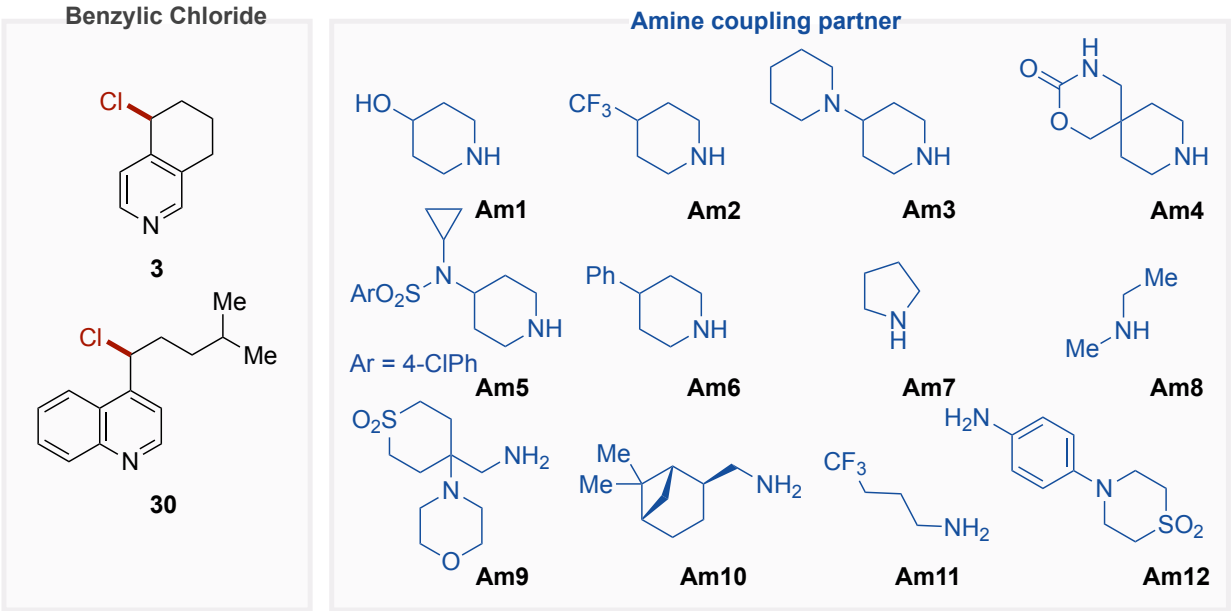


Table 3B.3. Heterobenzylic Diversification Results with Amine Nucleophiles

C-Cl	Amine	^{1}H NMR Yield (Substitution step)	^{1}H NMR Yield (*w.r.t.* to C-H substrate)
3	Am1	74	63
3	Am2	72	61
3	Am3	74	63
3	Am4	68	55
3	Am5	81	69
3	Am6	75	64
3	Am7	68	58
3	Am8	68	58
3	Am9	49	42
3	Am10	75	64
3	Am11	57	48
3	Am12	69	59
30	Am1	59	48
30	Am2	62	50
30	Am3	60	49
30	Am4	53	43
30	Am5	68	55
30	Am6	73	59
30	Am7	56	46
30	Am8	0	0
30	Am9	56	45
30	Am10	70	57
30	Am11	55	45
30	Am12	38	31

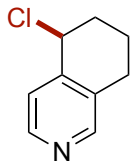
Benzylic Diversification with Azole Nucleophiles

Procedure 7: Following chlorination and ^{1}H NMR quantitation, the crude reaction mixture was washed with aq. $NaHCO_3$, and the aqueous layer was extracted with DCM. The organic layer was further washed with brine, separated, and dried over Na_2SO_4. The organic extract was concentrated on the rotavap, transferred to 24 mL or 6-dram glass vial, and dissolved in DMF to prepare a solution of the heterobenzylic chloride. Aliquots of the DMF stock solution corresponding to 0.05 mmol (1.0 equiv) of the heterobenzylic chloride C and D were added to a series of 4 mL glass vials containing the azole nucleophile (3.0 equiv), KI (1.1 equiv), K_2CO_3 (1.1 equiv), and a magnetic stir bar. The vials were sealed by PTFE-lined pierceable caps and set to stir at 70 ℃ on a stirring hot plate in an aluminum block at 750 rpm for 16 h. The crude reaction solution is then filtered through a pad of celite plug eluting with acetone or ethyl acetate into a 6-dram vial and concentrated on the rotovap. A solution of dibromoethane ($C_2H_4Br_2$) or dibromomethane (CH_2Br_2) in $CDCl_3$ (0.05 M) was added into the concentrated reaction mixture as the external standard and analyzed by ^{1}H NMR to detect formation of product.

Table 3B.4. Heterobenzylic Diversification Results with Azole Nucleophiles

C-Cl	Azole#	^{1}H NMR Yield (Substitution step)	^{1}H NMR Yield (*w.r.t.* to C-H substrate)
4	Az1	72	63
4	Az2	68	60
4	Az3	60	53
4	Az4	35	31
4	Az5	54	47
4	Az6	78	69
4	Az7	33	29
4	Az8	70	62
4	Az9	64	56
4	Az10	35	31
4	Az11	0	0
4	Az12	75	66
15	Az1	77	63
15	Az2	70	57
15	Az3	67	54
15	Az4	52	42
15	Az5	34	28
15	Az6	64	52
15	Az7	33	27
15	Az8	75	61
15	Az9	60	49
15	Az10	20	16
15	Az11	6	5
15	Az12	76	62

3B.X. Product Synthesis and Characterization



(*rac*)-5-Chloro-5,6,7,8-tetrahydroisoquinoline (3)

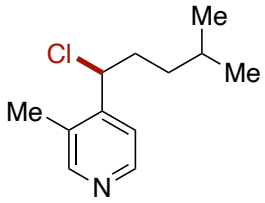
Prepared from 5,6,7,8-tetrahydroisoquinoline (0.5 mmol, 67.5 mg, 1.0 equiv.) according to the general procedure D (10 mol% of trifluoromethylsulfonylchloride, 70 °C, 16 h). After working up, the reaction mixture was purified by silica gel chromatography eluting with 10% acetone in petroleum ether to afford 67 mg of the title compound **7** (70% yield).

^{1}H NMR (400 MHz, CDCl3) δ 8.39 – 8.32 (m, 2H), 7.23 (d, J = 5.1 Hz, 1H), 5.10 (t, J = 4.6 Hz, 1H), 2.83 – 2.66 (m, 2H), 2.23 – 2.15 (m, 2H), 2.12 – 2.03 (m, 1H).

^{13}C NMR (101 MHz, CDCl3) δ 150.92, 147.23, 144.85, 132.05, 124.14, 77.55, 76.91, 55.78, 32.58, 25.83, 18.51.

HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_9H_{11}ClN$ 168.0575; found 168.0574.

(*rac*)-4-(1-Chloro-4-methylpentyl)-3-methylpyridine (10)

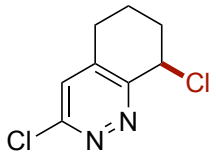


Prepared from 3-methyl-4-(4- methylpentyl) pyridine (0.5 mmol, 89 mg, 1.0 equiv.) according to the general procedure D (10 mol% of trifluoromethylsulfonylchloride, 70 °C, 4 h). After working up, the reaction mixture was purified by silica gel chromatography eluting with 10% acetone in petroleum ether to afford 89 mg of the title compound **16** (74% yield).

^{1}H NMR (400 MHz, CDCl3) δ 8.44 (d, *J* = 5.2 Hz, 1H), 8.37 (s, 1H), 7.33 (d, *J* = 5.1 Hz, 1H), 4.94 (dd, *J* = 8.2, 6.0 Hz, 1H), 2.31 (s, 3H), 2.09 – 1.91 (m, 2H), 1.55 (dt, *J* = 13.3, 6.6 Hz, 1H), 1.44 – 1.33 (m, 1H), 1.21 – 1.10 (m, 1H), 0.86 (dd, *J* = 6.6, 1.1 Hz, 6H). [1]

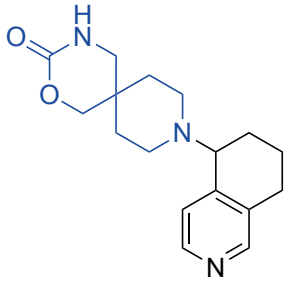
^{3}C NMR (101 MHz, CDCl3) δ 151.49, 148.42, 148.36, 130.16, 120.88, 77.55, 76.91, 58.27, 36.31, 36.04, 27.81, 22.66, 22.46, 16.02.

HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{12}H_{19}ClN$ 212.1201; found 212.1199.



(*rac*)-3,7-Dichloro-6,7-dihydro-5*H*-cyclopenta[*c*]pyridazine (6):
Prepared from 3-chloro-6,7- dihydro-5*H*-cyclopenta[*c*]pyridazine (0.3 mmol, 46.5 mg, 1.0 equiv.) according to procedure B. After working up, the reaction mixture was purified by silica gel chromatography eluting with 10% ethyl acetate in petroleum ether to afford 45 mg of the title compound **5** (79% yield).
^{1}H NMR (400 MHz, CDCl3) δ 7.43 (s, 1H), 5.51 (dd, *J* = 6.6, 2.2 Hz, 1H), 3.27 (dddd, *J* = 16.9, 9.1, 7.8, 1.5 Hz, 1H), 3.00 (dddd, *J* = 17.7, 8.2, 2.6, 1.0 Hz, 1H), 2.66 (dddd, *J* = 14.6, 8.9, 8.1, 6.6 Hz, 1H), 2.50 (ddt, *J* = 14.4, 7.8, 2.4 Hz, 1H).
^{13}C NMR (101 MHz, CDCl3) δ 166.12, 156.35, 144.99, 125.19, 77.55, 76.91, 58.23, 35.34, 28.21.
HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_7H_7Cl_2N_2$ 188.9981; found 188.9978.

9-(5,6,7,8-tetrahydroisoquinolin-5-yl)-2-oxa-4,9-diazaspiro [5.5] undecan-3-one (3-Am4).



Prepared from 5,6,7,8-tetrahydroisoquinoline according to Procedure D (1.0 mmol, 10 mol% TfCl, 70 ºC, 16 h in a 24 mL vial) followed by Procedure 1 (0.2 mmol of benzyl chloride) for benzylic amine formation. The product was purified by silica gel chromatography eluting with 96% DCM, 3% MeOH, and 1% TEA followed by a second flash column eluting with a gradient of 97% DCM, 2% MeOH, and 1% TEA.

Isolated Yield *w.r.t.* C–H Substrate : 40.9 mg (54%).

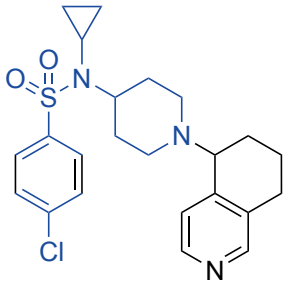
NMR Yield (Chlorination Step): 79%

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 5.2 Hz, 1H), 8.30 (s, 1H), 7.56 (d, *J* = 5.1 Hz, 1H), 5.94 (d, *J* = 8.6 Hz, 1H), 4.08 – 4.00 (m, 2H), 3.80 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.17 (q, *J* = 10.9 Hz, 2H), 2.76 – 2.66 (m, 2H), 2.58 – 2.51 (m, 3H), 2.45 – 2.41 (m, 1H), 2.07 – 1.96 (m, 2H), 1.73 – 1.57 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.18, 150.52, 147.34, 147.32, 133.95, 122.05, 77.48, 76.98, 74.01, 62.79, 49.24, 44.84, 44.23, 31.63, 29.60, 26.64, 21.80, 20.91.

HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{17}H_{24}N_3O_2$ 302.1863; found 302.1860.

4-Chloro-*N*-cyclopropyl-N-(1-(5,6,7,8-tetrahydroisoquinolin-5-yl)piperidin-4 yl)benzenesulfonamide (3-Am5).



Prepared from 5,6,7,8-tetrahydroisoquinoline according to Procedure D (1.0 mmol, 10 mol% TfCl, 70 ºC, 16 h in a 24 mL vial) followed by Procedure 1 (0.2 mmol of benzyl chloride) for benzylic amine formation. The product was purified by silica gel chromatography eluting a 96% DCM, 3% MeOH, and 1% TEA followed by a second flash column eluting with a gradient of 90% DCM, 10% Et_2O.

Isolated Yield *w.r.t.* C–H Substrate : 75.4 mg (66%).

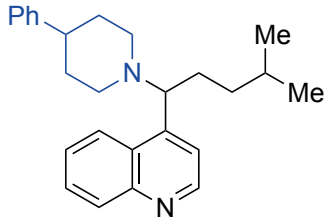
NMR Yield (Chlorination Step): 79%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 5.2 Hz, 1H), 8.29 (s, 1H), 7.82 – 7.79 (m, 2H), 7.54 (d, *J* = 5.1 Hz, 1H), 7.49 – 7.46 (m, 2H), 3.83 – 3.75 (m, 2H), 2.87 – 2.84 (m, 1H), 2.75 – 2.67 (m, 3H), 2.45 – 2.42 (m, 1H), 2.15 – 2.05 (m, 2H), 2.05 – 1.97 (m, 3H), 1.84 – 1.76 (m, 1H), 1.67 – 1.63 (m, 3H), 1.47 – 1.43 (m, 1H), 1.03 – 0.96 (m, 2H), 0.83 – 0.78 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.53, 147.49, 147.35, 139.18, 138.79, 133.90, 129.48, 129.00, 122.07, 77.48, 76.98, 62.58, 59.36, 51.99, 45.65, 32.07, 31.44, 26.68, 26.40, 21.84, 20.93, 7.84, 7.81.

HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{23}H_{29}ClN_3O_2S$ 446.1664; found 446.1662.

4-(4-Methyl-1-(4-phenylpiperidin-1-yl)pentyl)quinoline (3-Am6)



Prepared from 1-methyl-2-(4-methylpentyl)benzene according to Procedure D (1.0 mmol, 40 mol% TfCl, 90 ºC, 4 h) followed by Procedure 1 (0.2 mmol of benzyl chloride) for benzylic amine formation. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.

Isolated Yield *w.r.t.* C–H Substrate

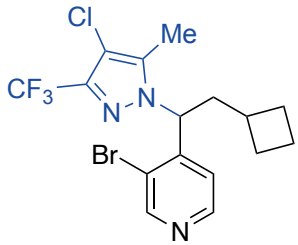
NMR Yield (Chlorination Step): 80%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (d, *J* = 4.5 Hz, 1H), 8.40 (d, *J* = 8.6 Hz, 1H), 8.14 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.71 (ddd, *J* = 8.3, 6.7, 1.3 Hz, 1H), 7.56 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.44 (d, *J* = 4.5 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.16 (m, 3H), 4.10 (s, 1H), 3.30 (d, *J* = 10.9 Hz, 1H), 2.89 (d, *J* = 10.9 Hz, 1H), 2.44 (tt, *J* = 11.7, 4.3 Hz, 1H), 2.25 – 2.00 (m, 3H), 2.00 – 1.90 (m, 1H), 1.88 – 1.77 (m, 2H), 1.76 – 1.64 (m, 2H), 1.45 (dt, *J* = 13.3, 6.6 Hz, 1H), 1.05 (dddd, *J* = 13.4, 11.5, 6.4, 5.1 Hz, 1H), 0.95 – 0.83 (m, 1H), 0.79 (dd, *J* = 6.6, 2.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.1, 148.9, 148.2, 146.54, 130.44, 129.02, 128.22, 126.96, 126.24, 126.21, 124.27, 120.18, 52.18, 51.51, 42.98, 35.41, 34.08, 33.91, 29.83, 28.40, 22.77, 22.50.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{26}H_{33}N_2$ 373.2638; Found 373.2634

3-Bromo-4-(1-(4-chloro-5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-2-cyclobutylethyl) pyridine(4-Az3).



Prepared from 3-bromo-4-(2-cyclobutylethyl)pyridine according to Procedure D (1.0 mmol, 10 mol% TfCl, 70 ºC, 16 h in a 24 mL vial) followed by Procedure 2 (0.2 mmol of benzyl chloride) for benzylic azole formation. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in pentane.

Isolated Yield *w.r.t.* C–H Substrate 51.2 mg (45%)

NMR Yield (Chlorination Step): 76%.

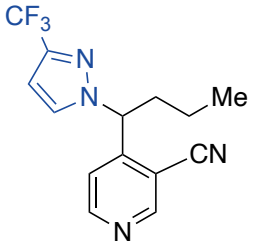
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 7.28 (d, *J* = 5.1 Hz, 1H), 5.54 (dd, *J* = 9.7, 4.8 Hz, 1H), 2.63 (ddd, *J* = 13.8, 9.7, 5.8 Hz, 1H), 2.20 (s, 3H), 2.22 – 2.14 (m, 1H), 2.10 – 2.05 (m, 1H), 2.04 – 1.94 (m, 2H), 1.89 – 1.80 (m, 2H), 1.79 – 1.72 (m, 1H), 1.71 – 1.62 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.28, 149.52, 147.65, 138.90, 138.81, 138.60, 138.31, 138.01, 124.09, 123.21, 121.95, 120.66, 119.80, 117.66, 107.71, 107.70, 77.48, 76.98, 60.16, 41.28, 32.95, 28.38, 27.70, 18.57, 9.33.

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.30.

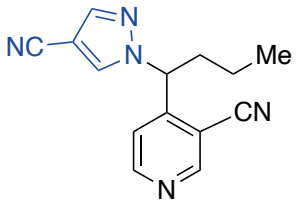
HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{16}H_{17}BrClF_3N_3$ 422.0241; found 422.0240.

4-(1-(4-(Trifluoromethyl)-1H-pyrazol-1-yl) butyl) nicotinonitrile (15-Az2).



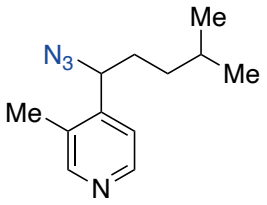
Prepared from 4-butylnicotinonitrile according to Procedure C (1.0 mmol, 90 ºC, 4 h, in a 24 mL vial) followed by Procedure 2 (0.2 mmol of benzyl chloride) for benzylic azole formation. The product was purified by silica gel chromatography eluting with 10% ethyl acetate in pentane.
Isolated Yield *w.r.t.* C–H Substrate 28.2 mg (36%).
NMR Yield (Chlorination Step): 67%.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, *J* = 0.8 Hz, 1H), 8.77 (d, *J* = 5.3 Hz, 1H), 7.61 (dd, *J* = 2.3, 1.0 Hz, 1H), 7.48 (d, *J* = 5.3 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 5.62 (dd, *J* = 9.7, 5.4 Hz, 1H), 2.52 (ddt, *J* = 14.6, 9.6, 4.6 Hz, 1H), 2.17 – 2.09 (m, 1H), 1.39 – 1.28 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.02, 153.20, 152.04, 144.43, 144.13, 143.82, 143.52, 131.70, 124.43, 122.29, 121.63, 120.16, 118.02, 115.40, 108.72, 105.00, 104.98, 104.97, 104.95, 77.48, 76.98, 63.61, 37.01, 19.70, 13.52.
^{19}F NMR (377 MHz, $CDCl_3$) δ -62.04.
HRMS (ESI) m/z: $[M+H]^+$ Calculated for C14H14F3N4 295.1165; found 295.1161

4-(1-(4-Cyano-1H-pyrazol-1-yl)butyl)nicotinonitrile(15-Az12)



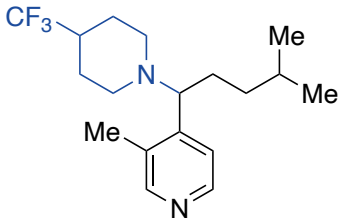
Prepared from 4-butylnicotinonitrile according to Procedure C (1.0 mmol, 90 ºC, 4 h, in a 24 mL vial) followed by Procedure 2 (0.2 mmol of benzyl chloride) for benzylic azole formation. The product was purified by silica gel chromatography eluting with 10% ethyl acetate in pentane.
Isolated Yield *w.r.t.* C–H Substrate 28.2 mg (36%)
NMR Yield (Chlorination Step): 67%
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, *J* = 0.8 Hz, 1H), 8.77 (d, *J* = 5.3 Hz, 1H), 7.61 (dd, *J* = 2.3, 1.0 Hz, 1H), 7.48 (d, *J* = 5.3 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 5.62 (dd, *J* = 9.7, 5.4 Hz, 1H), 2.52 (ddt, *J* = 14.6, 9.6, 4.6 Hz, 1H), 2.17 – 2.09 (m, 1H), 1.39 – 1.28 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.02, 153.20, 152.04, 144.43, 144.13, 143.82, 143.52, 131.70, 124.43, 122.29, 121.63, 120.16, 118.02, 115.40, 108.72, 105.00, 104.98, 104.97, 104.95, 77.48, 76.98, 63.61, 37.01, 19.70, 13.52.
HRMS (ESI) m/z: $[M+H]^+$ Calculated for C14H14N5 252.1244; found 252.1239

4-(1-Azido-4-methylpentyl)-3-methylpyridine (10-N_3).



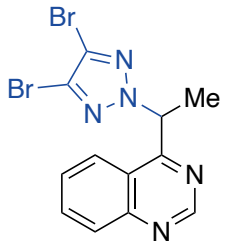
Prepared from 1-methyl-2-(4-methylpentyl)benzene according to Procedure D (0.5 mmol, 10 mol% TfCl, 70 ºC, 16 h, excluding DMAP in a 24 mL vial) followed by Procedure 4 for benzylic azide formation. The product was purified by silica gel chromatography eluting with 10% ethyl acetate in petroleum ether.
Isolated Yield *w.r.t.* C–H Substrate : 58.9 mg (54%).
NMR Yield (Chlorination Step): 90%
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 5.1 Hz, 1H), 8.42 (s, 1H), 7.24 (d, *J* = 5.1 Hz, 1H), 4.59 (m, 1H), 2.33 (s, 3H), 1.73 (m, 2H), 1.55 (m, 1H), 1.39 – 1.28 (m, 1H), 1.24 – 1.13 (m, 1H), 0.88 (m, 6H). **^{13}C ^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.72, 148.41, 147.03, 130.46, 120.70, 77.55, 76.91, 62.14, 35.37, 33.03, 28.03, 22.71, 22.55, 16.27.
HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{12}H_{19}N_4$ 219.1604; found 219.1603.

3-Methyl-4-(4-methyl-1-(4-(trifluoromethyl)piperidin-1-yl)pentyl)pyridine (10-Am13).



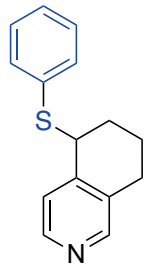
Prepared from 1-methyl-2-(4-methylpentyl)benzene according to Procedure D (0.5 mmol, 10 mol% TfCl, 70 ºC, 16 h, excluding DMAP in a 24 mL vial) followed by Procedure 1 for benzylic amine formation. The product was purified by silica gel chromatography eluting with 20% ethyl acetate in petroleum ether.
Isolated Yield *w.r.t.* C–H Substrate : 58.9 mg (46%).
NMR Yield (Chlorination Step): 80%
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 – 8.31 (m, 2H), 7.20 (d, *J* = 5.1 Hz, 1H), 3.50 (m, 1H), 3.10 (d, *J* = 11.0 Hz, 1H), 2.79 (d, *J* = 11.4 Hz, 1H), 2.30 (s, 3H), 2.02 – 1.88 (m, 2H), 1.85 – 1.76 (m, 2H), 1.75 – 1.64 (m, 2H), 1.62 – 1.47 (m, 2H), 1.45 – 1.38 (m, 1H), 1.04 – 0.94 (m, 1H), 0.92 – 0.85 (m, 1H), 0.80 (d, *J* = 6.7 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.39, 149.33, 147.44, 132.63, 131.78, 129.01, 126.25, 123.48, 122.11, 77.55, 76.91, 64.64, 50.28, 48.84, 41.11, 40.84, 40.57, 40.30, 34.78, 28.72, 28.46, 25.13, 25.11, 22.80, 22.52, 16.80.
^{19}F NMR (377 MHz, $CDCl_3$) δ -73.87.
HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{18}H_{28}F_3N_2$ 329.2199; found 329.2196.

4-(1-(4,5-Dibromo-2*H*-1,2,3-triazol-2-yl)ethyl)quinazoline(34-Az13).



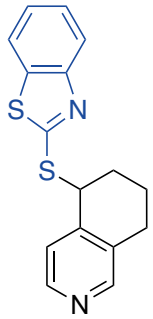
Prepared from 4-ethylquinazoline according to Procedure D (0.5 mmol, 10 mol% TfCl, 90 ºC, 16 h, excluding DMAP in a 24 mL vial) followed by Procedure 7 for benzylic azole product formation. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.
Isolated Yield *w.r.t.* C–H Substrate : 95.3 mg (51%).
NMR Yield (Chlorination Step): 80%
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.13 – 8.10 (m, 2H), 7.95 – 7.92 (m, 1H), 7.71 – 7.68 (m, 1H), 6.66 (q, *J* = 7.0 Hz, 1H), 2.16 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 165.14, 154.82, 151.05, 134.29, 129.91, 128.79, 125.42, 123.40, 122.63, 77.48, 76.98, 62.99, 18.83.
HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{12}H_{10}Br_2N_5$ 381.9298; found 381.9296.

5-(Phenylthio)-5,6,7,8-tetrahydroisoquinoline (3-Th1)



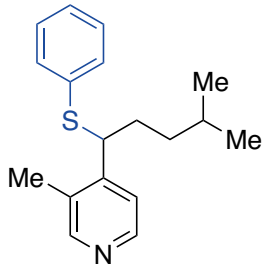
Prepared from 5,6,7,8-tetrahydroisoquinoline according to Procedure D (1.0 mmol, 1 mol% TfCl, 70 ºC, 16 h in a 24 mL vial) followed by Procedure 3 (0.2 mmol of benzyl chloride) for benzylic thiol ether formation. The product was purified by silica gel chromatography eluting with 10% ethyl acetate in petroleum ether.
Isolated Yield *w.r.t.* C–H Substrate: 33.2 mg (56%).
NMR Yield (Chlorination Step): 80%
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.24 (d, *J* = 5.1 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.27 – 7.18 (m, 3H), 7.17 (d, *J* = 5.2 Hz, 1H), 4.34 (t, *J* = 4.6 Hz, 1H), 2.74 (m, 1H), 2.63 (m, 1H), 2.14 – 2.01 (m, 1H), 1.94 (m, 2H), 1.72 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 150.98, 146.95, 144.83, 134.96, 133.09, 132.70, 129.28, 127.81, 124.52, 77.55, 76.91, 46.71, 28.57, 26.20, 18.88.
HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{15}H_{16}NS$ 242.0998; found 242.0996.

2-((5,6,7,8-Tetrahydroisoquinolin-5-yl)thio)benzo[*d*]thiazole (3-Th2).



Prepared from 5,6,7,8-tetrahydroisoquinoline according to Procedure D (0.4 mmol, 1 mol% TfCl, 70 ºC, 16 h in a 24 mL vial) followed by Procedure 3 for benzylic thiol ether formation. The product was purified by silica gel chromatography eluting with 15% ethyl acetate in petroleum ether.
Isolated Yield *w.r.t.* C–H Substrate: 51.2 mg (43%).
NMR Yield (Chlorination Step): 79%
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.36 (d, J = 5.1 Hz, 1H), 7.91 (m, 1H), 7.78 (m, 1H), 7.47 – 7.42 (m, 1H), 7.39 (d, J = 5.2 Hz, 1H), 7.36 – 7.30 (m, 1H), 5.44 (t, J = 4.7 Hz, 1H), 2.89 (m, 1H), 2.78 (m, 1H), 2.40 – 2.27 (m, 2H), 2.08 (m, 1H), 2.01 – 1.91 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.60, 153.29, 151.14, 147.37, 143.89, 135.64, 133.40, 126.38, 124.80, 124.63, 121.91, 121.31, 77.55, 76.91, 46.01, 29.86, 26.20, 19.75.
HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{16}H_{15}N_2S_2$ 299.0671; found 299.0670.

3-Methyl-4-(4-methyl-1-(phenylthio)pentyl)pyridine(10-Th1).



Prepared from 1-methyl-2-(4-methylpentyl)benzene according to Procedure D (0.5 mmol, 10 mol% TfCl, 70 ºC, 16 h, excluding DMAP in a 24 mL vial) followed by Procedure 3 for benzylic thiol ether formation. The product was purified by silica gel chromatography eluting with 10% ethyl acetate in petroleum ether.
Isolated Yield *w.r.t.* C–H Substrate: 78.4 mg (55%).
NMR Yield (Chlorination Step): 87%
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 5.1 Hz, 1H), 8.30 (s, 1H), 7.25 – 7.14 (m, 6H), 4.23 (m, 1H), 2.16 (s, 3H), 2.01 – 1.82 (m, 1H), 1.52 (dp, J = 13.2, 6.7 Hz, 1H), 1.36 – 1.27 (m, 1H), 1.16 – 1.05 (m, 1H), 0.85 (m, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.08, 149.67, 147.95, 133.81, 133.66, 131.37, 129.00, 128.14, 121.70, 77.55, 76.91, 48.92, 36.78, 33.05, 28.14, 22.73, 22.59, 16.35.
HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{18}H_{24}NS$ 286.1624; found 286.1621.

5,6,7,8-tetrahydroisoquinolin-5-yl benzoate(3-OBz).

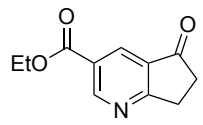
Prepared from 5,6,7,8-tetrahydroisoquinoline according to Procedure D (0.5 mmol, 10 mol% TfCl, 70 ºC, 16 h, in a 24 mL vial) followed by Procedure 5 for benzylic benzoate formation. The product was purified by silica gel chromatography eluting with 10% ethyl acetate in petroleum ether.
Isolated Yield *w.r.t.* C–H Substrate : 65.3 mg (51%).
NMR Yield (Chlorination Step): 70%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.39 (d, *J* = 5.1 Hz, 1H), 8.07 – 8.02 (m, 2H), 7.58 – 7.54 (m, 1H), 7.45 – 7.41 (m, 2H), 7.24 (d, *J* = 5.1 Hz, 1H), 6.17 (t, *J* = 5.6 Hz, 1H), 2.93 – 2.86 (m, 1H), 2.82 – 2.75 (m, 1H), 2.24 – 2.16 (m, 1H), 2.12 – 2.00 (m, 2H), 1.97 – 1.87 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.22, 150.88, 147.49, 143.44, 133.39, 133.24, 130.21, 129.89, 128.61, 122.97, 77.55, 76.91, 69.44, 28.85, 26.01, 19.24.
HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{16}H_{16}NO_2$ 254.1176; found 254.1173.

3B.XI. Substrate Synthesis

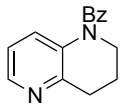
Procedure 8 (LDA Mediated Alkylation) for S8, S10, S11-12, S14-18, S20-21, S25-28
To an oven-dried 250 mL RB flask containing a magnetic stir bar and cooled under nitrogen was added the 4-methyl heteroaryl substrate (10 mmol, 1 equiv), followed by 100 mL of dry THF. With a nitrogen balloon attached, the RB flask was cooled to -78 ℃ in a dry ice/acetone bath and stirred for 10-15 mins. 1.2 equiv of LDA (2 M in THF) was added dropwise while maintaining the temperature of the reaction at -78 ℃. The reaction was left to stir at this temperature for about 45 min-1 h, and then 1.3 equiv of alkyl bromide/iodide was added dropwise. The reaction was slowly warmed to room temperature, left to stir at rt for 4-6 hrs., and quenched with aq. $NaHCO_3$ solution. The reaction mixture was extracted with ethyl acetate and washed with brine. The organic layer was separated, dried over Na_2SO_4, and concentrated on the rotavapor. The residue was then purified by silica gel chromatography.

Procedure 9 (Bz Protection) for S2, S19, S22-23: An oven-dried 250 mL RB flask containing a magnetic stir-bar was added the amine substrate (1 equiv), triethylamine (3 equiv), and anhydrous dichloromethane. Then benzoyl chloride (1.2 equiv) was added dropwise after which the flask was warmed to rt and left to stir at rt for 2-4 hrs or overnight. The organic reaction mixture in DCM was washed with aq. $NaHCO_3$, and then with brine. The organic layer was separated and dried over anhydrous Na_2SO_4, concentrated in rotavapor, and purified by silica gel chromatography with pentane or petroleum ether and ethyl acetate as the eluent.

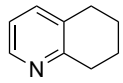
Benzoyl protected alcohol (**S30**) was synthesized from the corresponding alcohol according to a literature procedure.[1] TBS protected alcohol (**S30**) was synthesized from the corresponding alcohol according to a literature procedure.[2] 4-methylquinazoline was synthesized according to a literature procedure.[3] 4-ethylquinazoline was synthesized according to a literature procedure.[4] 4-ethyl-3-(hex-1-yn-1-yl)pyridine (**S29**) was synthesized according to an adapted literature procedure.[6]



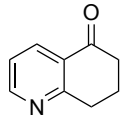
S1
Sourced from MBBC Library



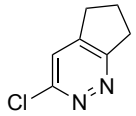
S2
Sourced from MBBC Library then ***Procedure 9***



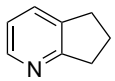
S3
Commerically Availble
Sigma-Aldrich
CAS: 36556-06-6



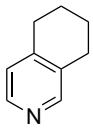
S4
Commercially Available
Sigma-Aldrich
CAS: 53400-41-2



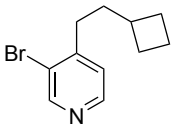
S5
Sourced from MBBC Library



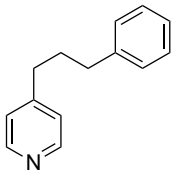
S6
Commerically Availble
Sigma-Aldrich
CAS: 533-37-9



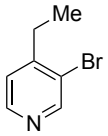
S7
CommericallyAvailble
Sigma-Aldrich
CAS: 10500-57-9



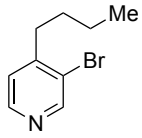
S8
Procedure 8



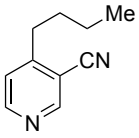
S9
CommericallyAvailble
Sigma-Aldrich
CAS: 2057-49-0



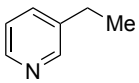
S10
Procedure 8



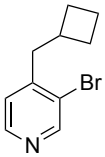
S11
Procedure 8



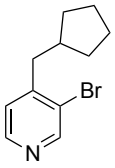
S12
Procedure 8



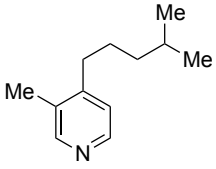
S13
CommericallyAvailble
Sigma-Aldrich
CAS: 536-78-7



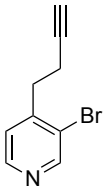
S14
Procedure 8
See Below



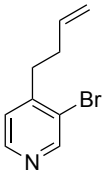
S15
Procedure 8



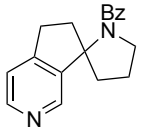
S16
Procedure 8



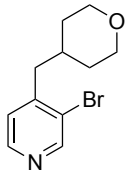
S17
Procedure 8



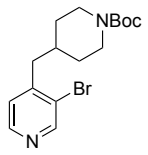
S18
Procedure 8



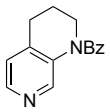
S19
Sourced from MBBC Library then ***Procedure 9***



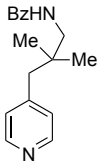
S20
Procedure 8



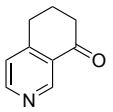
S21
Procedure 8



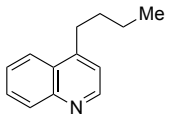
S22
Sourced from MBBC Library then ***Procedure 9***



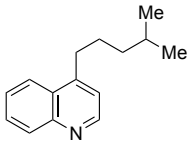
S23
Sourced from MBBC Library then ***Procedure 9***



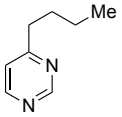
S24
J. Med. Chem.
1993, *36*, 3381–3385.[5]



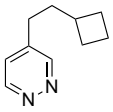
S25
Procedure 8



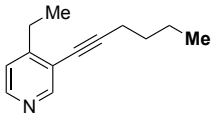
S26
Procedure 8
See Below



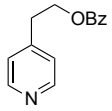
S27
Procedure 8
See Below



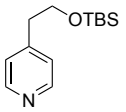
S28
Procedure 8
See Below



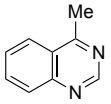
S29
Tetrahedron Lett.
2004, *45*, 8733–8736.[6]



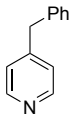
S30
Tetrahedron Lett.
1984, *25*, 1223–1226.[1]



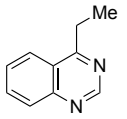
S31
Eur. J. Med. Chem.
2019, *168*, 58–77.[2]



S33
Org. Biomol. Chem.
2019, *17*, 4774–4782.[3]

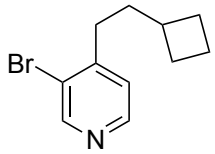


S32
Commerically Availble
Sigma-Aldrich
CAS: 2116-65-6



S34
Angew. Chem. Int. Ed.
2018, *57*, 5134–5138.[4]

3-Bromo-4-(2-cyclobutylethyl)pyridine

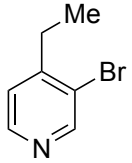


Prepared from 3-bromo-4-methylpyridine (10 mmol) and (bromomethyl)cyclobutane (13 mmol) following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.37 (d, *J* = 4.9 Hz, 1H), 7.11 (d, *J* = 4.9 Hz, 1H), 2.70 – 2.48 (m, 2H), 2.29 (h, *J* = 7.8 Hz, 1H), 2.12 – 1.97 (m, 2H), 1.94 – 1.74 (m, 2H), 1.75 – 1.56 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9, 150.9, 148.2, 125.2, 123.2, 36.2, 35.7, 33.3, 28.2, 18.5.

3-Bromo-4-ethylpyridine

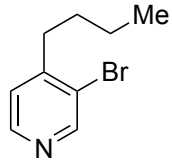


Prepared from 3-bromo-4-methylpyridine (10 mmol) and methyl iodide (13 mmol) following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.40 (d, *J* = 4.9 Hz, 1H), 7.16 (d, *J* = 4.9 Hz, 1H), 2.74 (q, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.5 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0, 151.8, 148.7, 124.4, 123.1, 28.1, 13.1.

3-Bromo-4-butylpyridine

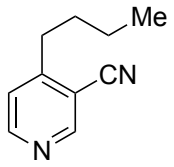


Prepared from 3-bromo-4-methylpyridine (10 mmol) and propyl iodide (13 mmol) following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.38 (d, *J* = 5.0 Hz, 1H), 7.13 (d, *J* = 4.9 Hz, 1H), 2.80 – 2.57 (m, 2H), 1.59 (p, *J* = 7.6 Hz, 2H), 1.40 (h, *J* = 7.4 Hz, 2H), 0.95 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0, 151.0, 148.3, 125.2, 123.3, 35.2, 31.1, 22.1, 14.0.

4-Butylnicotinonitrile



Prepared from 3-cyano-4-methylpyridine (10 mmol) and propyl iodide (13 mmol) following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.59 (d, *J* = 5.2 Hz, 1H), 7.52 – 6.71 (m, 1H), 3.00 – 2.19 (m, 2H), 1.75 – 1.50 (m, 2H), 1.34 (h, *J* = 7.3 Hz, 2H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.48, 153.05, 152.66, 123.98, 116.06, 110.52, 33.89, 32.05, 22.36, 13.80.

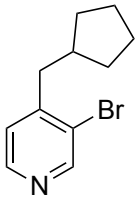
3-Bromo-4-(cyclobutylmethyl)pyridine

Prepared from 3-bromo-4-methylpyridine (10 mmol) and bromocyclobutane (13 mmol) following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.38 (d, *J* = 4.9 Hz, 1H), 7.08 (d, *J* = 4.9 Hz, 1H), 2.82 (d, *J* = 7.5 Hz, 2H), 2.67 (hept, *J* = 7.8 Hz, 1H), 2.12 – 1.96 (m, 2H), 1.95 – 1.81 (m, 2H), 1.80 – 1.67 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9, 149.4, 148.1, 125.1, 123.4, 42.0, 34.8, 28.2, 18.5.

3-Bromo-4-(cyclopentylmethyl)pyridine

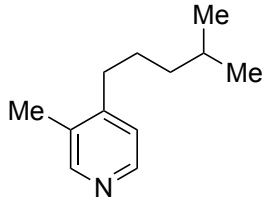


Prepared from 3-bromo-4-methylpyridine and bromocyclopentane following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.38 (d, *J* = 5.0 Hz, 1H), 7.13 (d, *J* = 4.9 Hz, 1H), 2.73 (d, *J* = 7.4 Hz, 2H), 2.19 (tt, *J* = 8.7, 7.2 Hz, 1H), 1.78 – 1.61 (m, 4H), 1.58 – 1.49 (m, 2H), 1.23 (dqd, *J* = 15.1, 6.5, 3.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0, 150.4, 148.1, 125.7, 123.4, 41.2, 39.6, 32.5, 25.0.

3-Methyl-4-(4-methylpentyl)pyridine)

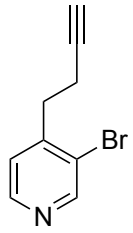


Prepared from 3,4-dimethylpyridine (20 mmol) 3-bromo-4-methylpyridine and 1-iodo-3-methylbutane (26 mmol) following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 2H), 7.03 (d, *J* = 5.0 Hz, 1H), 2.61 – 2.43 (m, 2H), 2.26 (s, 3H), 1.66 – 1.50 (m, 3H), 1.34 – 1.15 (m, 2H), 0.88 (d, *J* = 6.7 Hz, 6H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 149.9, 147.6, 131.6, 123.5, 38.9, 32.8, 28.0, 27.1, 22.6, 16.2.

3-Bromo-4-(but-3-yn-1-yl)pyridine

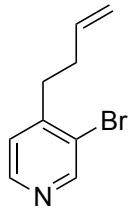


Prepared from 3-bromo-4-methylpyridine (10 mmol) and 3-bromoprop-1-yne (13 mmol) following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.43 (d, *J* = 4.9 Hz, 1H), 7.23 (d, *J* = 4.9 Hz, 1H), 2.94 (t, *J* = 7.3 Hz, 2H), 2.54 (td, *J* = 7.3, 2.7 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.06, 148.38, 148.12, 125.52, 123.07, 82.33, 70.04, 34.25, 17.85.

3-Bromo-4-(but-3-en-1-yl)pyridine

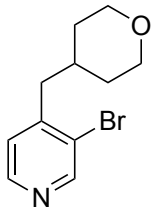


Prepared from 3-bromo-4-methylpyridine (10 mmol) and 3-bromoprop-1-ene (13 mmol) following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.40 (d, *J* = 4.9 Hz, 1H), 7.14 (d, *J* = 4.9 Hz, 1H), 5.84 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.21 – 4.75 (m, 2H), 2.82 (dd, *J* = 8.8, 6.7 Hz, 2H), 2.39 (dtt, *J* = 7.9, 6.6, 1.4 Hz, 2H).

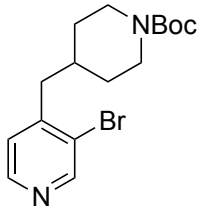
^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0, 149.9, 148.3, 136.7, 125.3, 123.2, 116.1, 34.8, 32.7.

3-Bromo-4-((tetrahydro-2*H*-pyran-4-yl)methyl)pyridine



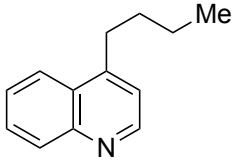
Prepared from 3-bromo-4-methylpyridine (10 mmol) and 4-bromotetrahydro-2*H*-pyran (13 mmol) following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.39 (d, *J* = 4.9 Hz, 1H), 7.10 (d, *J* = 4.9 Hz, 1H), 3.95 (ddt, *J* = 11.7, 3.2, 1.3 Hz, 3H), 3.46 – 3.19 (m, 2H), 2.68 (dd, *J* = 7.2, 1.2 Hz, 3H), 1.90 (ddd, *J* = 11.5, 7.5, 4.0 Hz, 1H), 1.54 (ddd, *J* = 13.0, 4.1, 2.1 Hz, 3H), 1.49 – 1.33 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 152.26, 148.42, 148.04, 126.21, 123.54, 67.94, 42.62, 35.06, 32.88.

***tert*-Butyl 4-((3-bromopyridin-4-yl)methyl)piperidine-1-carboxylate**



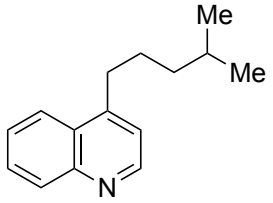
Prepared from 3-bromo-4-methylpyridine (10 mmol) and *tert*-butyl 4-bromopiperidine-1-carboxylate (13 mmol) following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.40 (d, *J* = 4.9 Hz, 1H), 7.09 (d, *J* = 4.9 Hz, 1H), 4.10 (s, 2H), 2.67 (d, *J* = 7.2 Hz, 3H), 1.80 (m, 1H), 1.60 (d, *J* = 13.1 Hz, 2H), 1.45 (s, 9H), 1.24 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 152.3, 148.6, 148.1, 126.2, 123.6, 79.6, 42.3, 36.2, 32.0, 28.6.

4-Butylquinoline



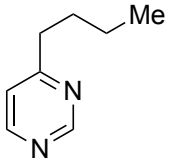
Prepared from 4-methylquinoline (10 mmol) and 1-iodopropane (13 mmol) following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.57 (dd, *J* = 5.1, 1.2 Hz, 2H), 7.15 (d, *J* = 5.2 Hz, 1H), 2.80 – 2.63 (m, 3H), 1.82 – 1.57 (m, 4H), 1.37 (dqd, *J* = 14.5, 7.3, 1.3 Hz, 3H), 0.92 (td, *J* = 7.4, 1.3 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 158.8, 156.7, 120.5, 37.7, 31.0, 22.5, 13.9

4-(4-Methylpentyl)quinoline



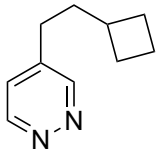
Prepared from 4-methylquinoline (10 mmol) and 1-iodo-3-methylbutane (13 mmol) following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 4.4 Hz, 1H), 8.11 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.04 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.73 – 7.66 (m, 1H), 7.60 – 7.52 (m, 1H), 7.23 (d, *J* = 4.4 Hz, 1H), 3.05 (t, *J* = 7.9 Hz, 2H), 1.81 – 1.69 (m, 2H), 1.60 (dq, *J* = 13.3, 6.6 Hz, 1H), 1.45 – 1.27 (m, 2H), 0.90 (d, *J* = 6.7 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6, 148.9, 148.5, 130.4, 129.1, 127.8, 126.3, 123.7, 120.9, 39.1, 32.5, 28.1, 28.0, 22.7.

4-Butylpyrimidine



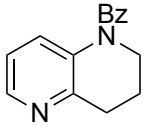
Prepared from 4-methylpyrimidine (10 mmol) and 1-iodopropane (13 mmol) following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.57 (dd, *J* = 5.1, 1.2 Hz, 2H), 7.15 (d, *J* = 5.2 Hz, 1H), 2.80 – 2.63 (m, 3H), 1.82 – 1.57 (m, 4H), 1.37 (dqd, *J* = 14.5, 7.3, 1.3 Hz, 3H), 0.92 (td, *J* = 7.4, 1.3 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 158.8, 156.7, 120.5, 37.7, 31.0, 22.5, 13.9.

4-(2-Cyclobutylethyl)pyridazine



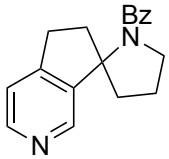
Prepared from 4-methylpyridazine (10 mmol) and (bromomethyl)cyclobutane (13 mmol) following procedure 8 in Section 5. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 – 8.91 (m, 2H), 7.74 – 6.97 (m, 1H), 2.60 – 2.44 (m, 2H), 2.26 (hept, *J* = 7.8 Hz, 1H), 2.15 – 2.00 (m, 2H), 1.93 – 1.77 (m, 2H), 1.73 (q, *J* = 7.6 Hz, 2H), 1.63 (qd, *J* = 8.8, 2.4 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 151.1, 142.1, 126.0., 37.00, 35.4, 30.47, 28.2, 18.4.

(3,4-Dihydro-1,5-naphthyridin-1(2*H*)-yl)(phenyl)methanone



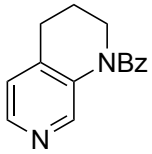
Prepared 1,2,3,4-tetrahydro-1,5-naphthyridine (1 mmol) and benzoyl chloride (1.2 mmol) following procedure 9 in Section 5. The product was purified by silica gel chromatography eluting with 50% ethyl acetate in petroleum ether.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.48 – 7.30 (m, 6H), 6.92 (dd, *J* = 8.4, 4.7 Hz, 1H), 3.98 – 3.70 (m, 2H), 3.07 (t, *J* = 6.8 Hz, 2H), 2.25 – 1.97 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 150.2, 145.3, 135.7, 135.4, 132.0, 130.6, 128.5, 128.3, 120.8, 45.5, 30.3, 23.3.

(5,6-Dihydrospiro[cyclopenta[*c*]pyridine-7,2'-pyrrolidin]-1'-yl)(phenyl)methanone



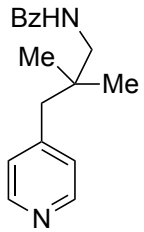
Prepared 5,6-dihydrospiro[cyclopenta[*c*]pyridine-7,2'-pyrrolidine](1 mmol) and benzoyl chloride (1.2 mmol) following procedure 9 in Section 5. The product was purified by silica gel chromatography eluting with 50% ethyl acetate in petroleum ether.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 7.46 (m, 2H), 7.38 (m, 3H), 7.21 (d, *J* = 5.1 Hz, 1H), 3.83 – 3.73 (m, 1H), 3.63 (m, 1H), 3.30 (m, 1H), 2.96 (m, 2H), 2.27 – 2.14 (m, 2H), 2.14 – 2.09 (m, 1H), 2.07 – 2.03 (m, 1H), 2.03 – 1.90 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 153.8, 147.4, 143.2, 142.8, 137.6, 129.9, 128.3, 126.8, 120.5, 73.9, 51.7, 42.6, 37.0, 30.7, 24.6.

3,4-Dihydro-1,7-naphthyridin-1(2*H*)-yl)(phenyl)methanone



Prepared 1,2,3,4-tetrahydro-1,7-naphthyridine (1 mmol) and benzoyl chloride (1.2 mmol) following procedure 9 in Section 5. The product was purified by silica gel chromatography eluting with 50% ethyl acetate in petroleum ether.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 5.0 Hz, 1H), 8.13 (s, 1H), 7.42 – 7.37 (m, 3H), 7.37 – 7.30 (m, 2H), 7.08 (d, J = 4.9 Hz, 1H), 3.92 (td, J = 6.0, 1.1 Hz, 2H), 2.88 (t, J = 6.7 Hz, 2H), 2.10 – 2.02 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 146.1, 144.6, 138.7, 136.5, 135.6, 130.8, 128.6, 128.5, 123.3,44.9, 26.5, 23.4.

***N*-(2,2-Dimethyl-3-(pyridin-4-yl)propyl)benzamide**

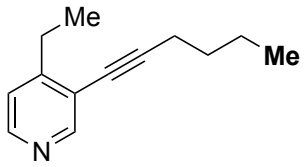


Prepared from 2,2-dimethyl-3-(pyridin-4-yl)propan-1-amine (1 mmol) and benzoyl chloride (1.2 mmol) following procedure 9 in Section 5. The product was purified by silica gel chromatography eluting with 50% ethyl acetate in petroleum ether.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 2H), 7.86 – 7.63 (m, 2H), 7.54 – 7.48 (m, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.17 – 7.03 (m, 2H), 6.19 (s, 1H), 3.38 (d, *J* = 6.4 Hz, 2H), 2.60 (s, 2H), 0.96 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 149.6, 147.4, 134.8, 131.7, 128.8, 126.9, 126.0, 49.9, 45.9, 36.2, 25.0.

4-Ethyl-3-(hex-1-yn-1-yl)pyridine



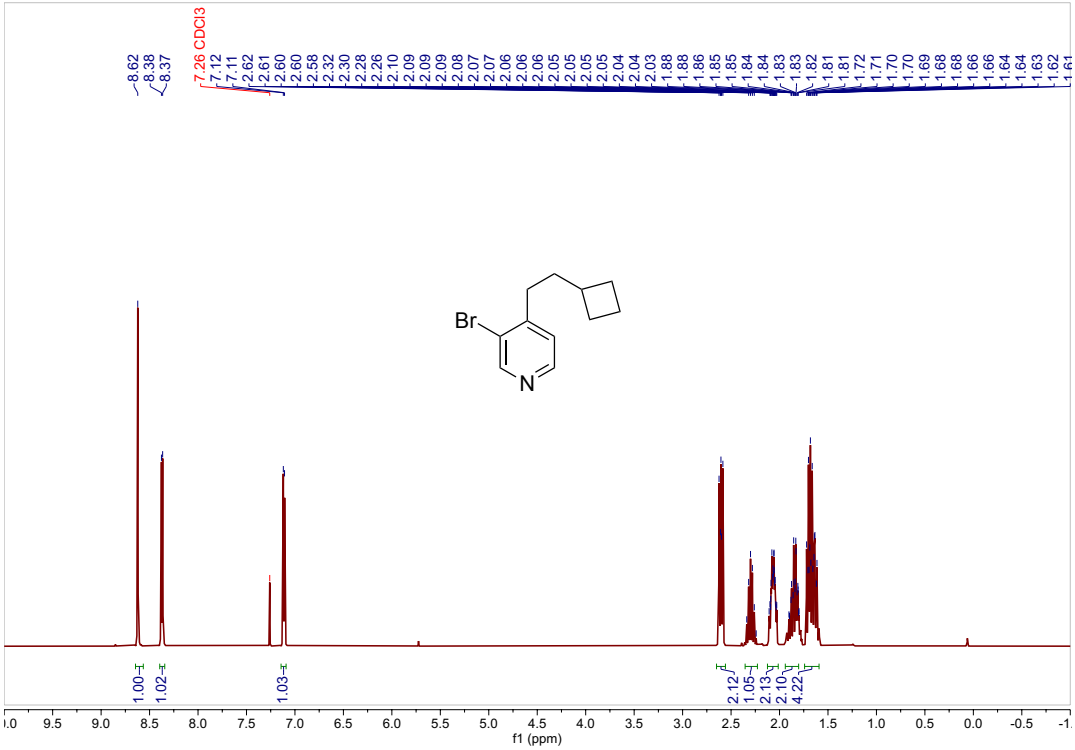
Prepared from 3-bromo-4-ethylpyridine (2 mmol) and 1-hexyne (4 mmol) following a literature protocol. The product was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 68.0 Hz, 2H), 7.12 (s, 1H), 2.75 (q, *J* = 7.6 Hz, 2H), 2.46 (t, *J* = 7.0 Hz, 2H), 1.68 – 1.55 (m, 2H), 1.55 – 1.41 (m, 2H), 1.23 (t, *J* = 7.6 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H).

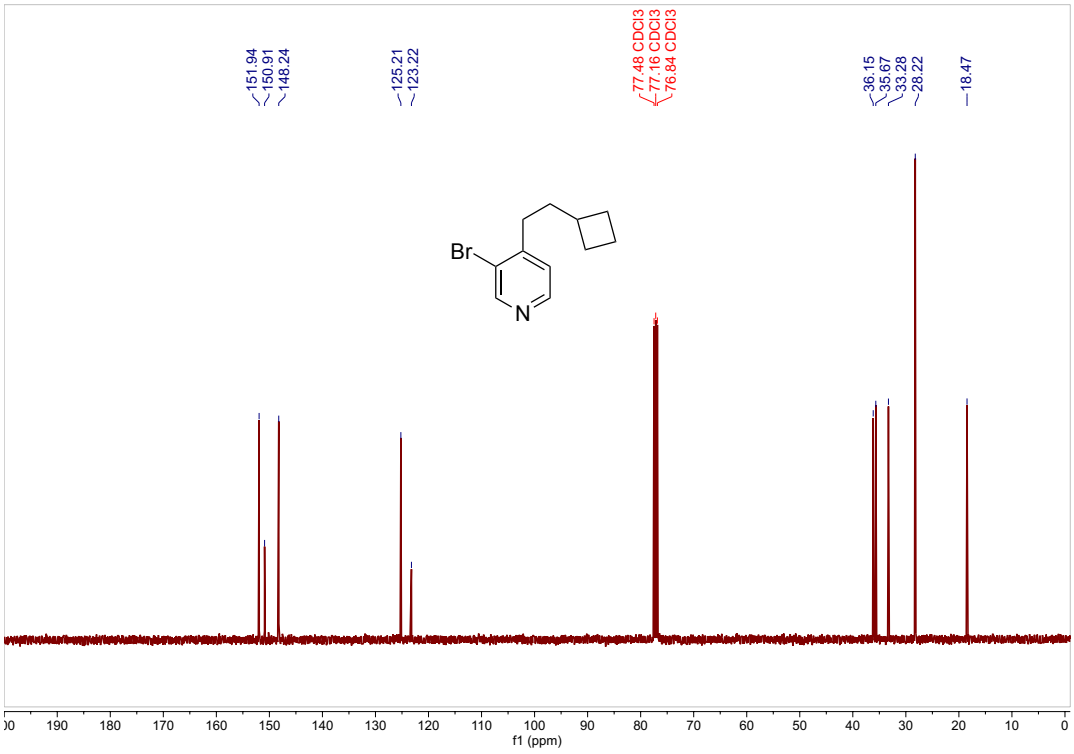
^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 152.6, 148.0, 132.2, 128.6, 97.4, 30.9, 27.2, 22.1, 19.4, 13.7, 13.6.

3B.XII. NMR Spectroscopic Data

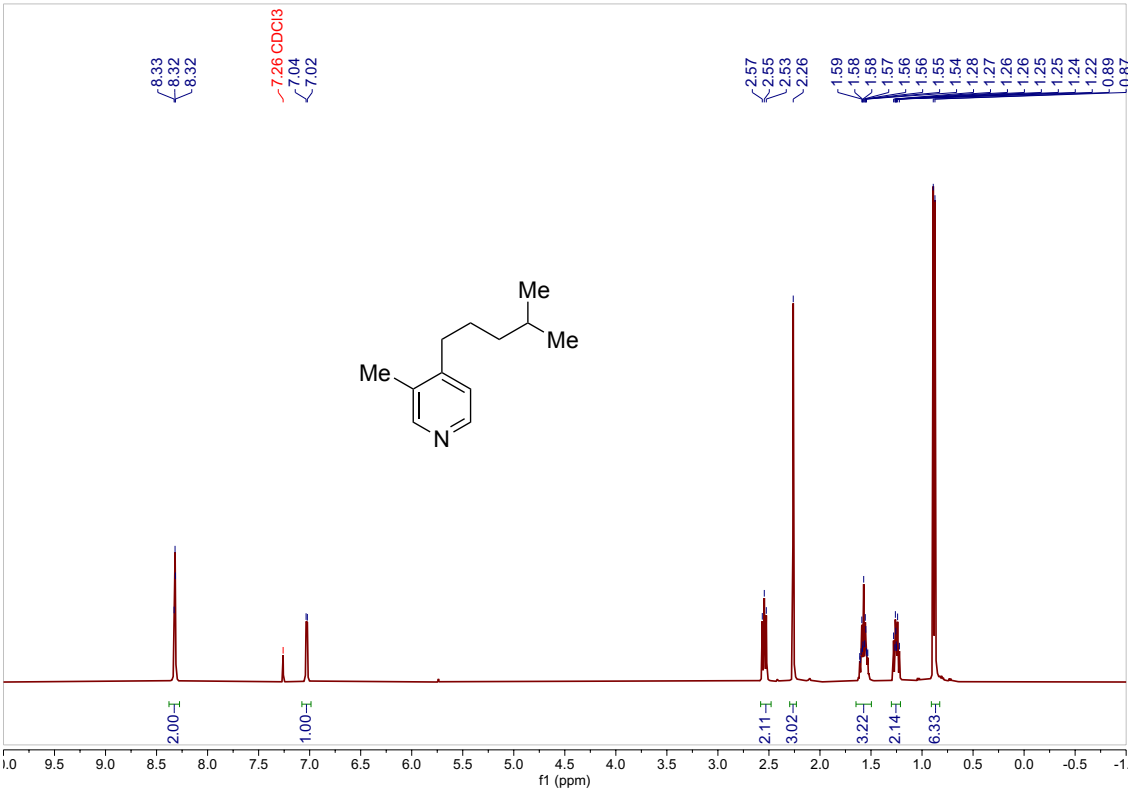
^{1}H NMR (400 MHz, $CDCl_3$) of **4a**



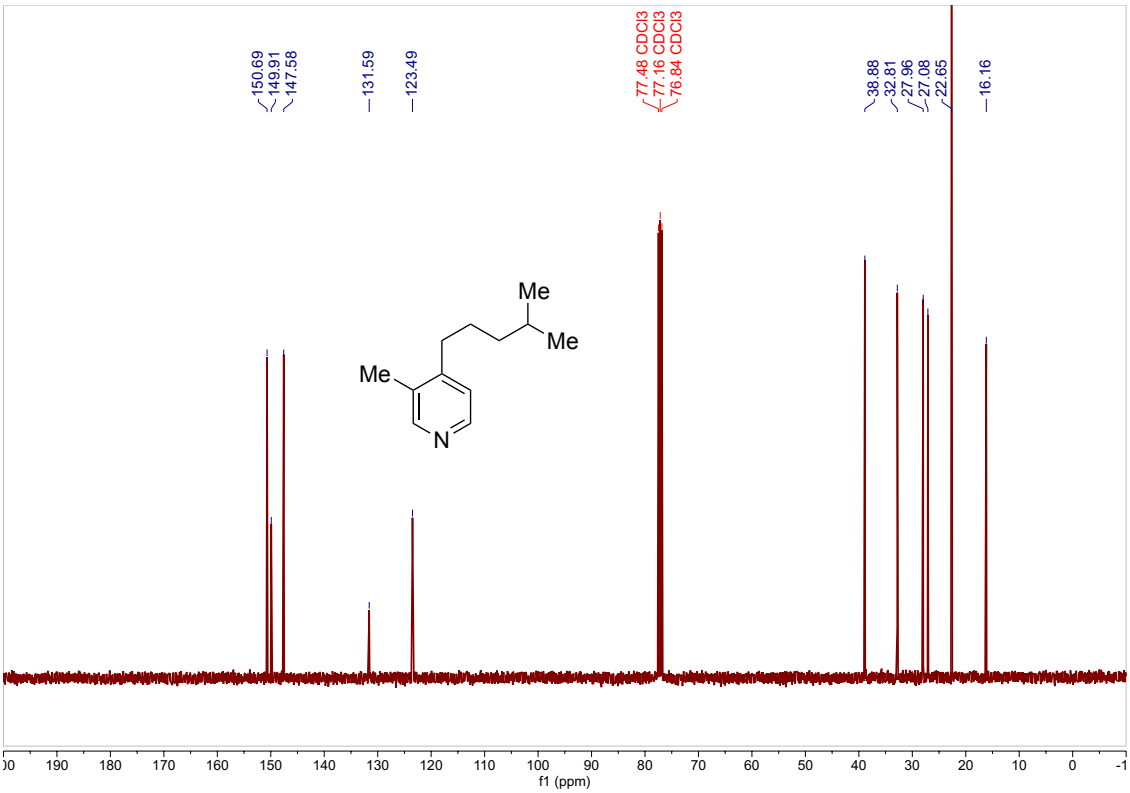
^{13}C NMR (101 MHz, $CDCl_3$) of **4a**



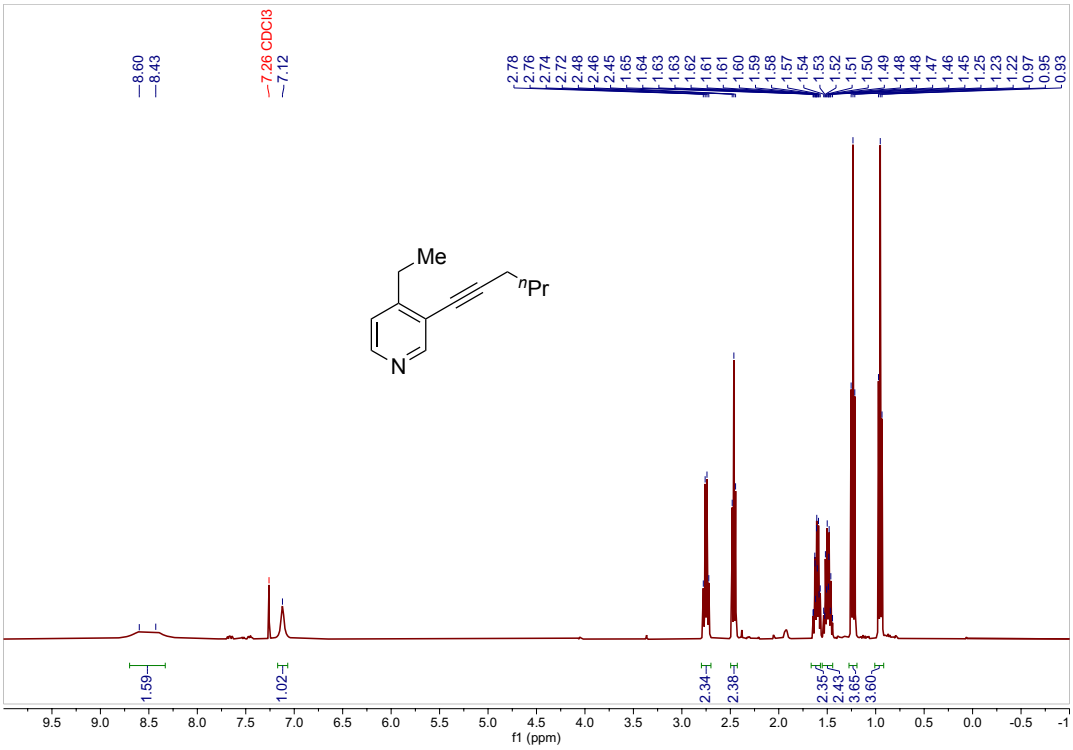
^{1}H NMR (400 MHz, $CDCl_3$) of **10a**



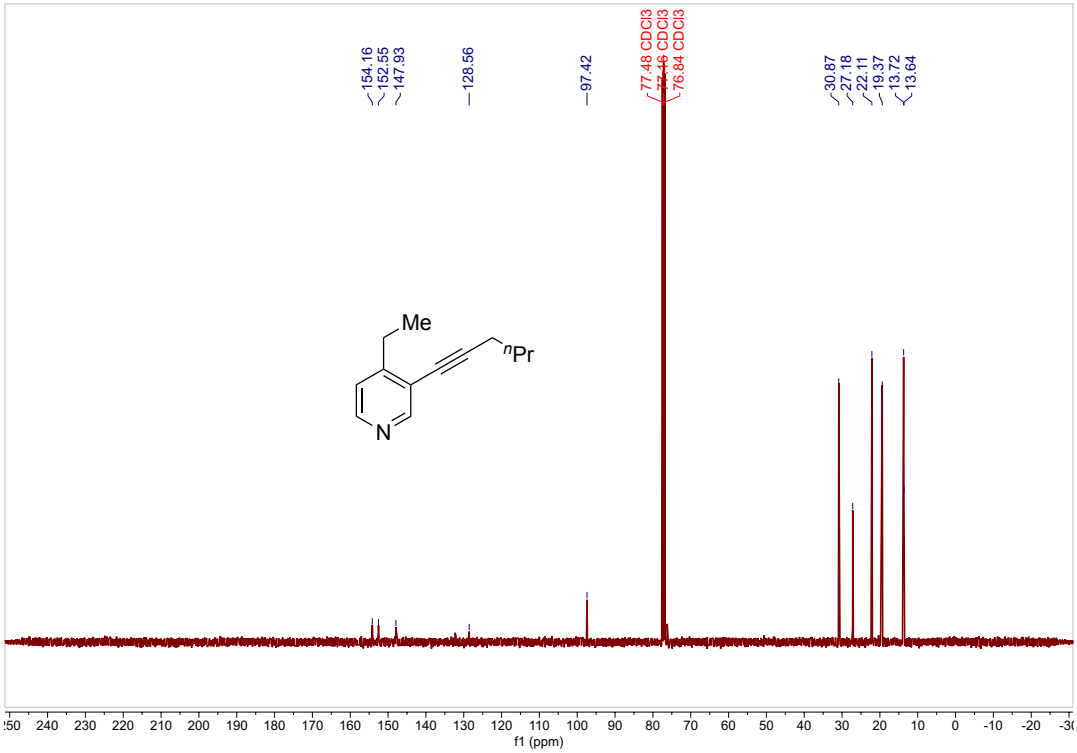
^{13}C NMR (101 MHz, $CDCl_3$) of **10a**



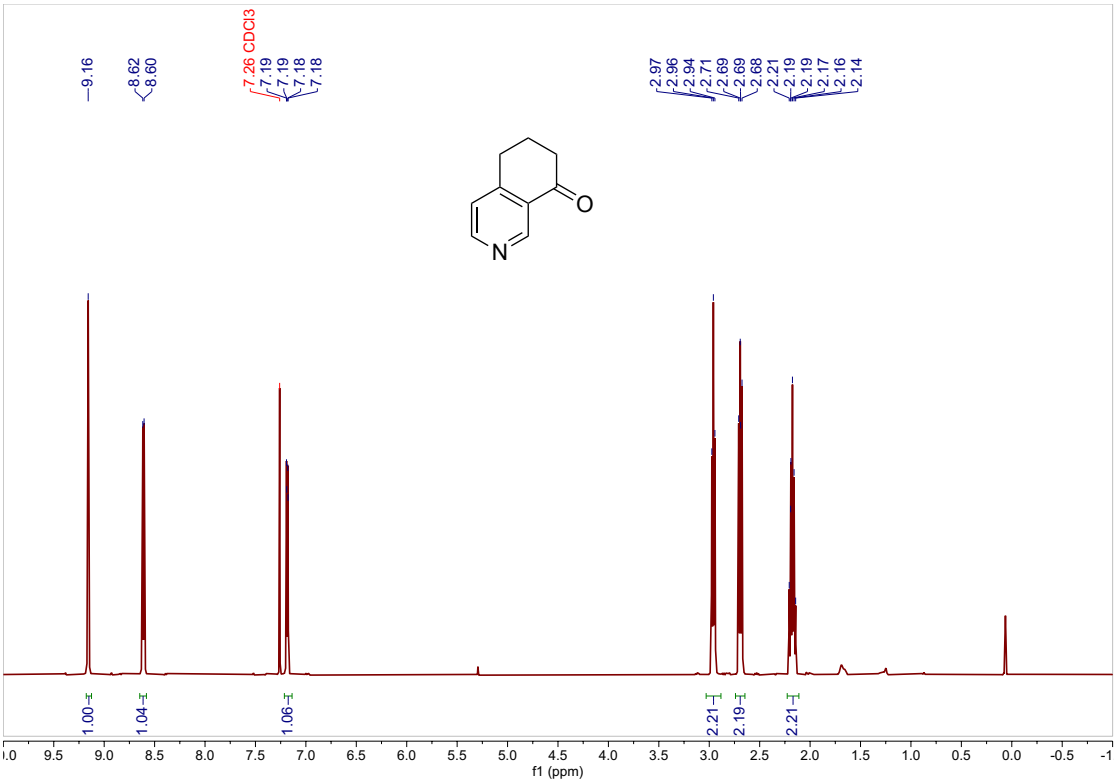
^{1}H NMR (400 MHz, $CDCl_3$) of **13a**



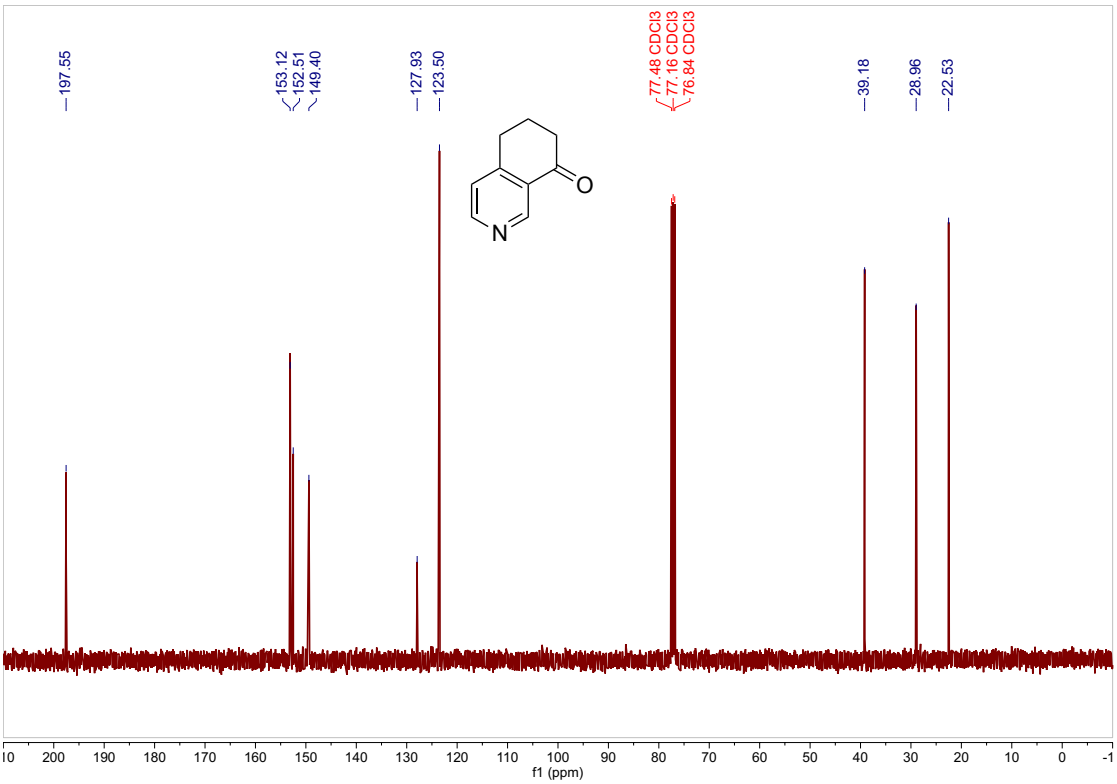
^{13}C NMR (101 MHz, $CDCl_3$) of **13a**



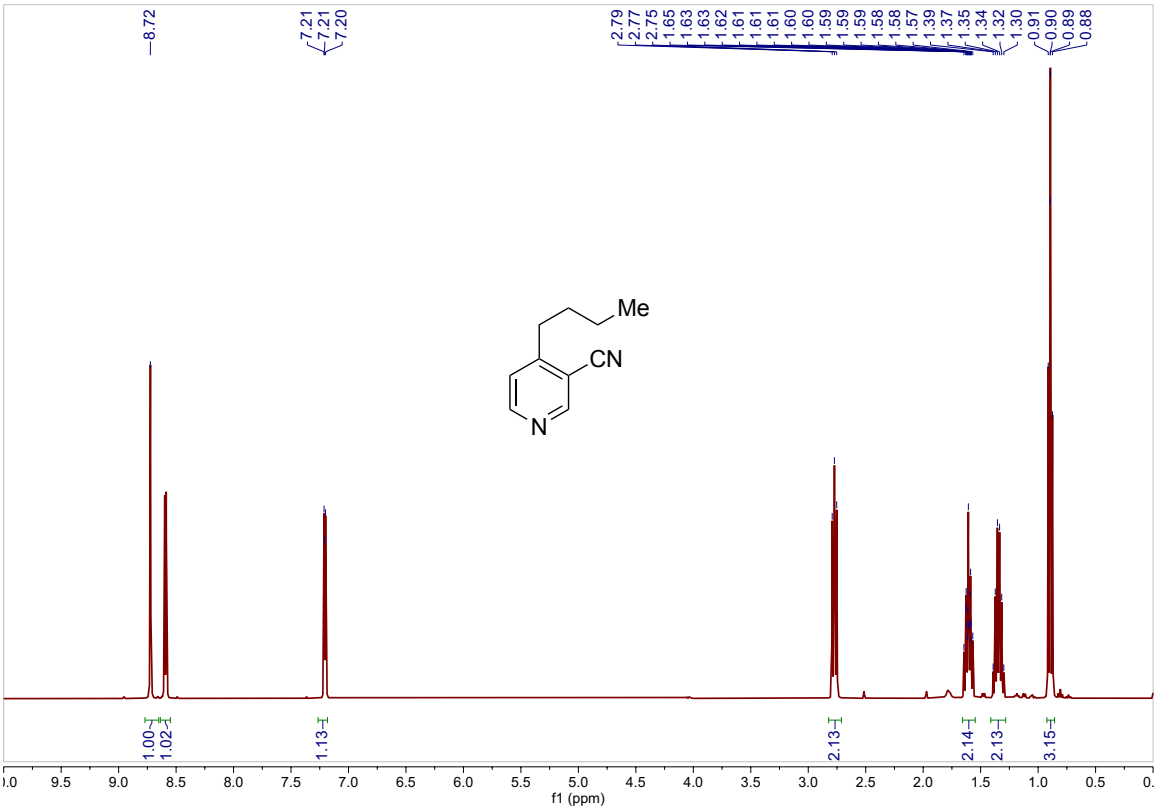
^{1}H NMR (400 MHz, $CDCl_3$) of **14a**



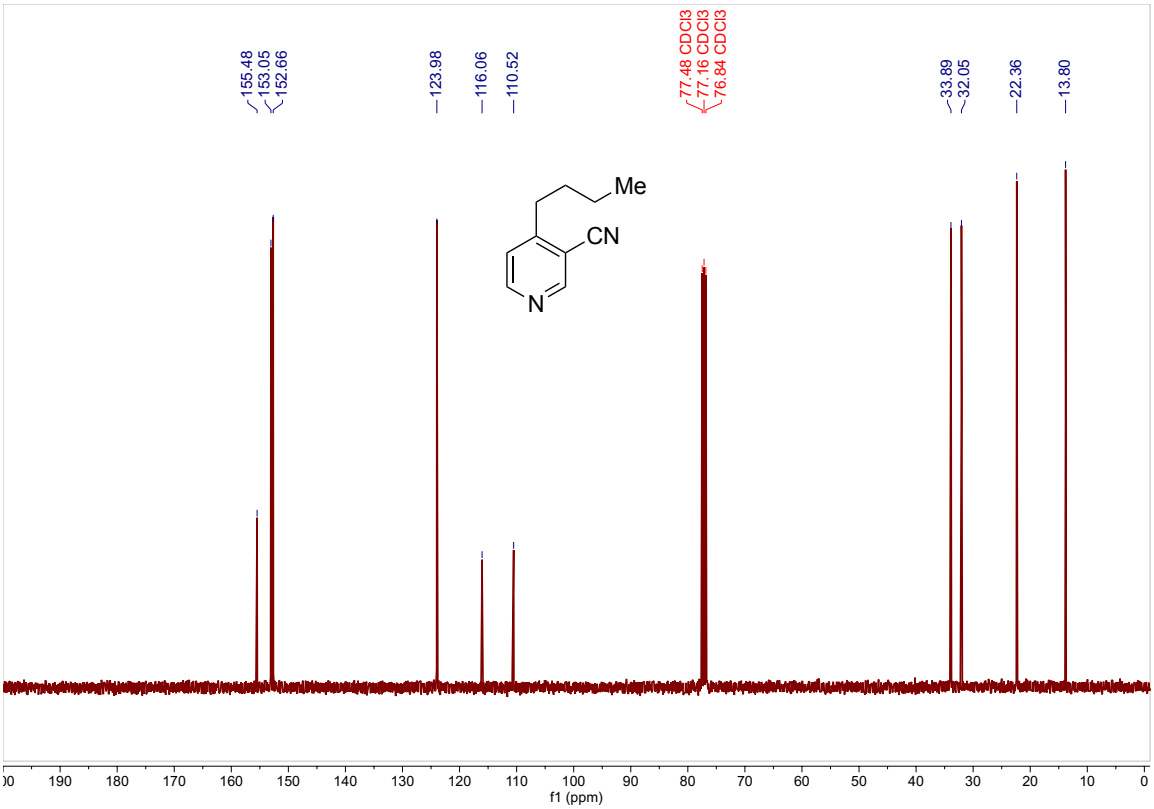
^{13}C NMR (101 MHz, $CDCl_3$) of **14a**



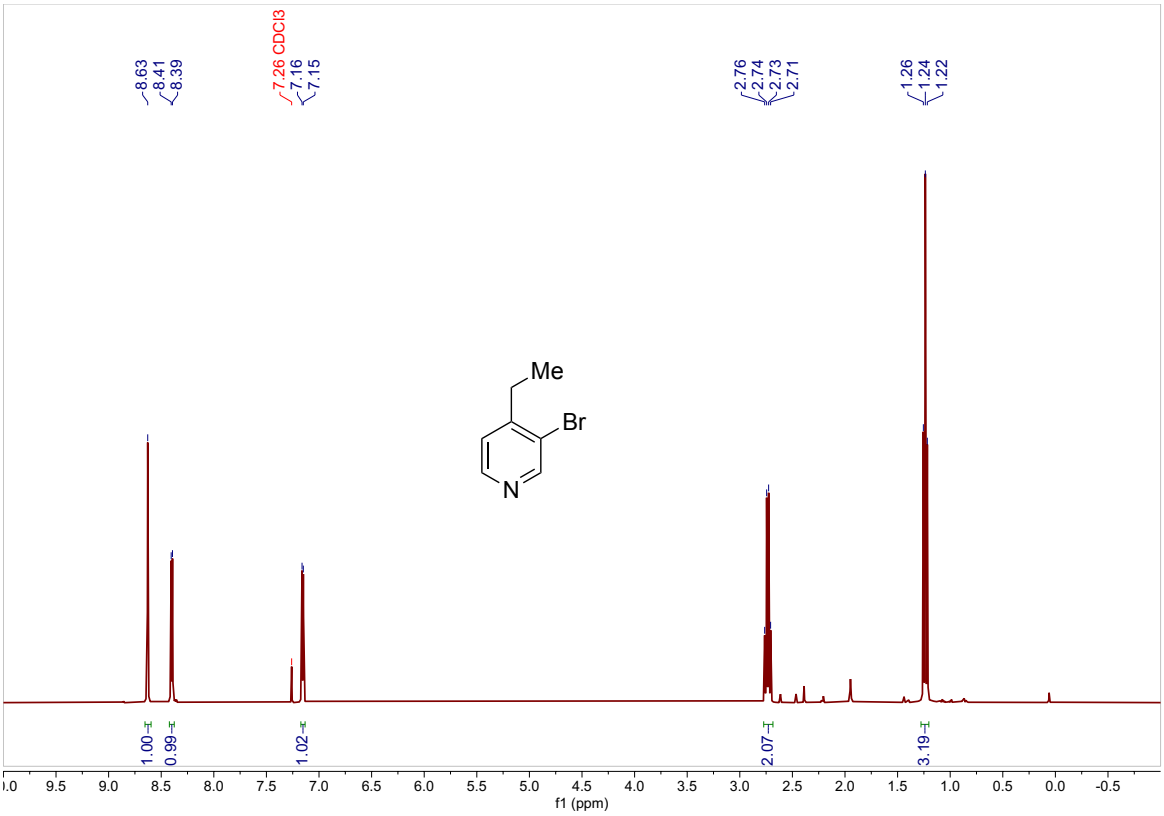
^{1}H NMR (400 MHz, $CDCl_3$) of **15a**



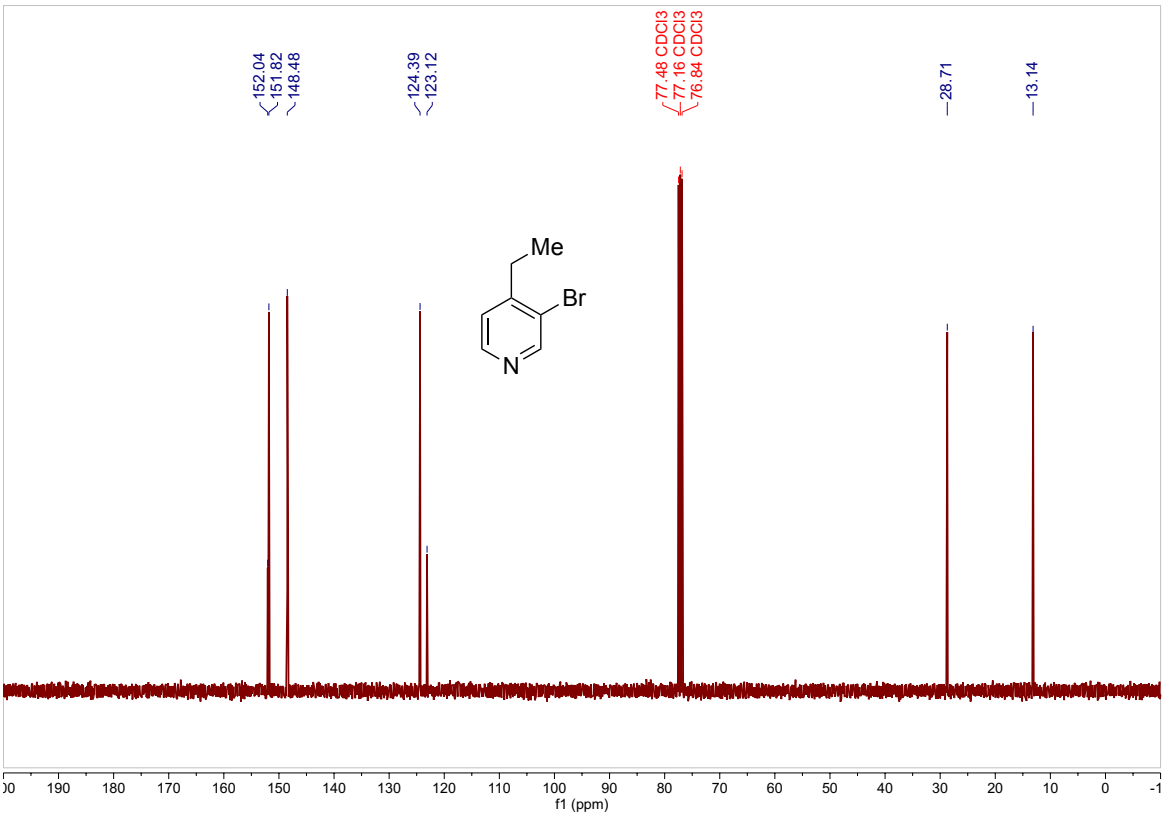
^{13}C NMR (101 MHz, $CDCl_3$) of **15a**



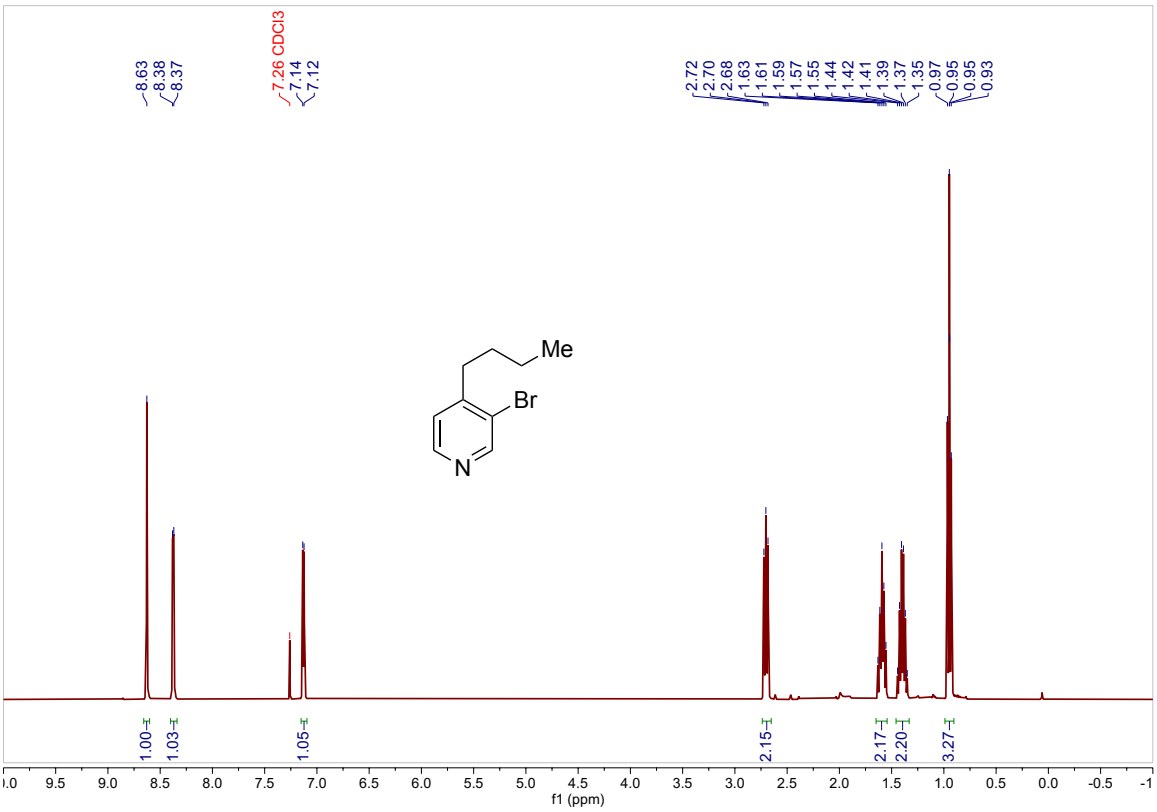
^{1}H NMR (400 MHz, $CDCl_3$) of **16a**



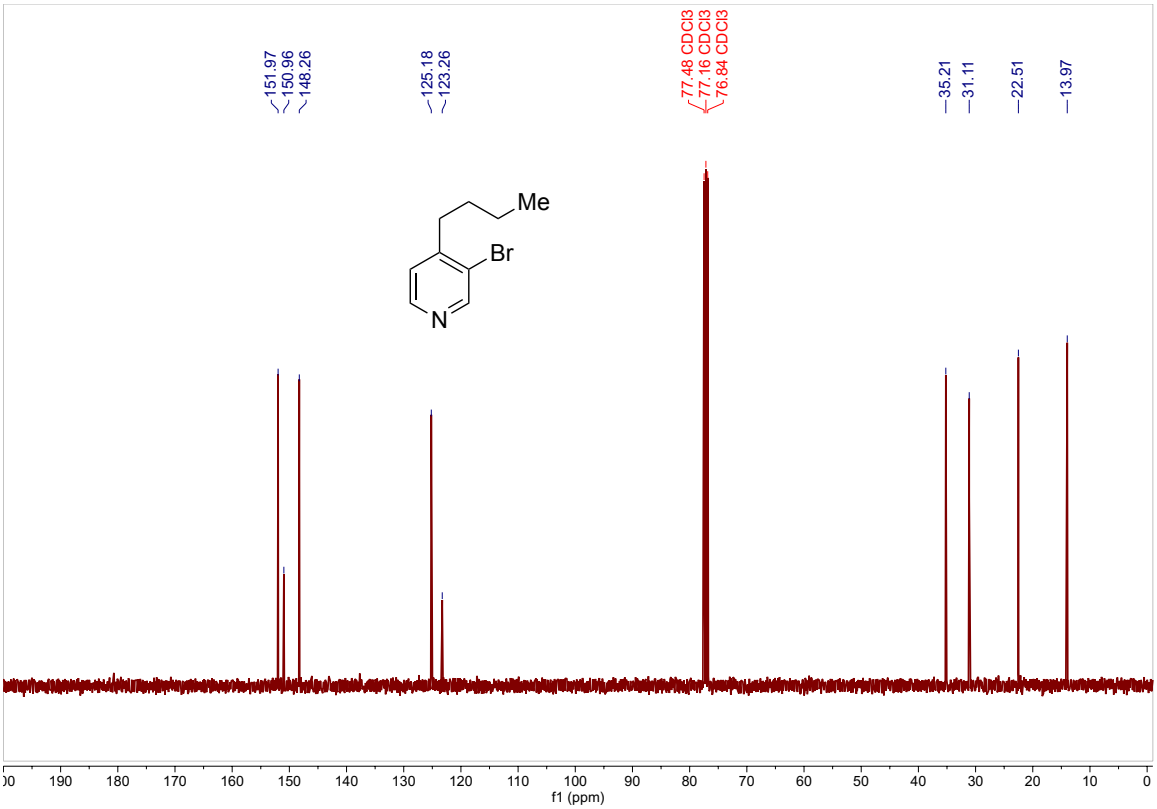
^{13}C NMR (101 MHz, $CDCl_3$) of **16a**



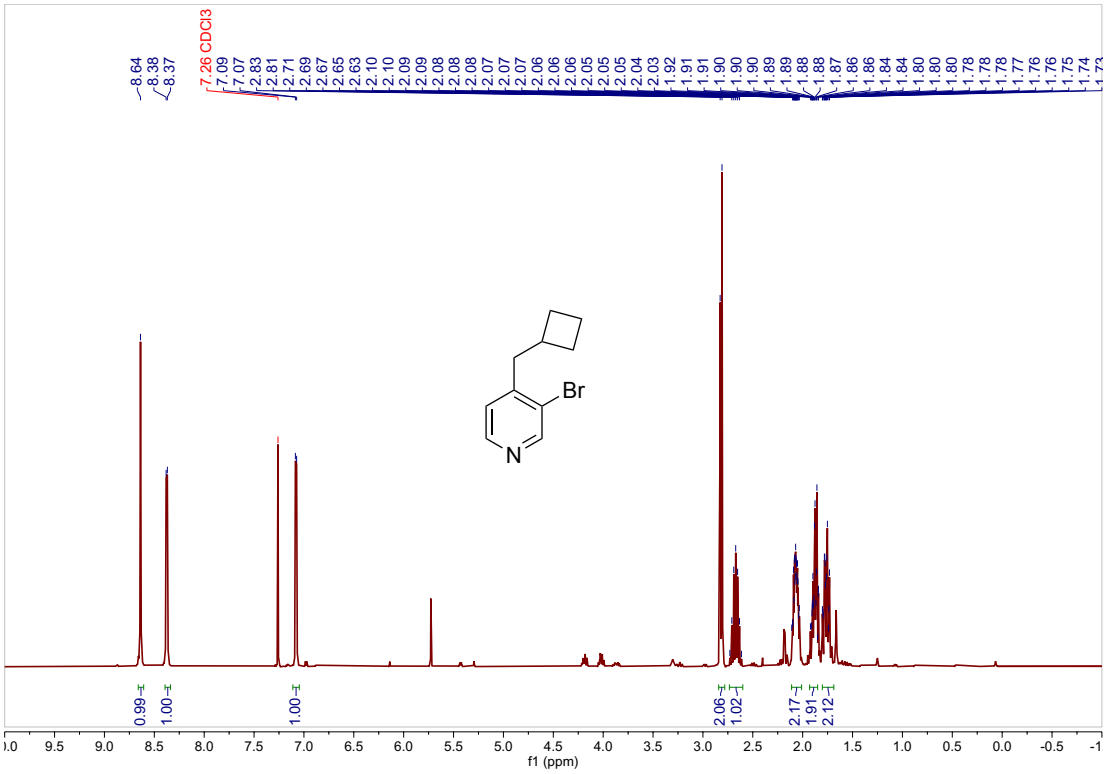
^{1}H NMR (400 MHz, $CDCl_3$) of **17a**



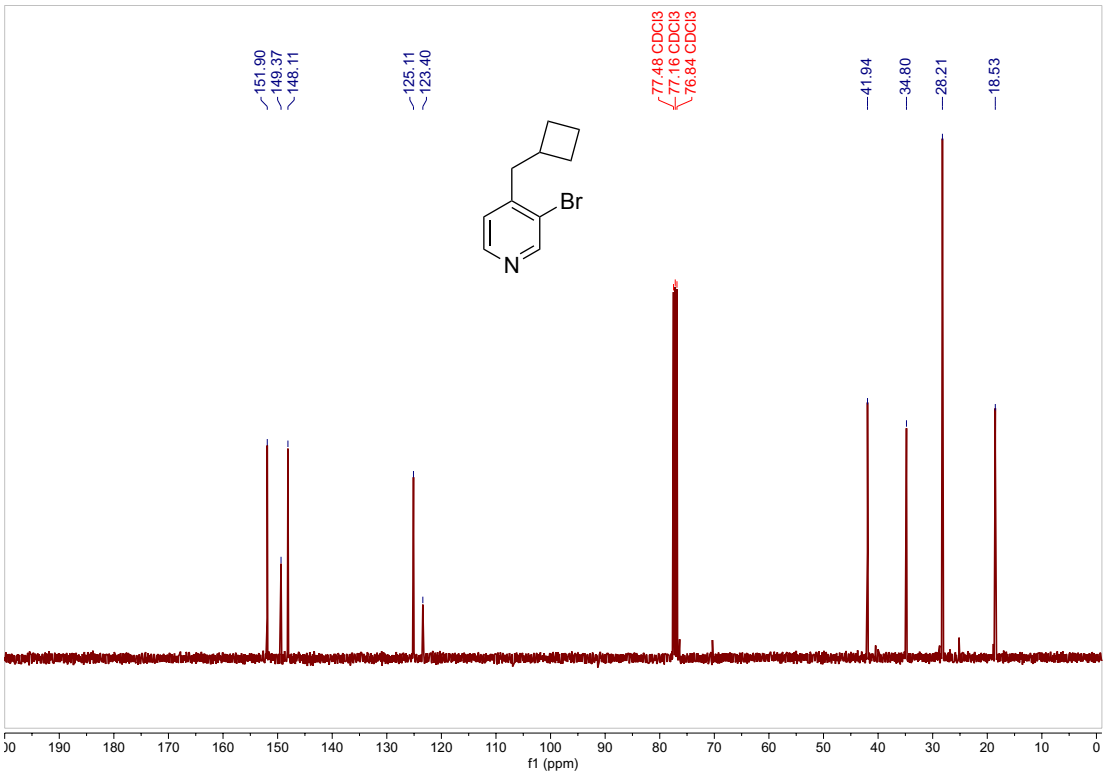
^{13}C NMR (101 MHz, $CDCl_3$) of **17a**



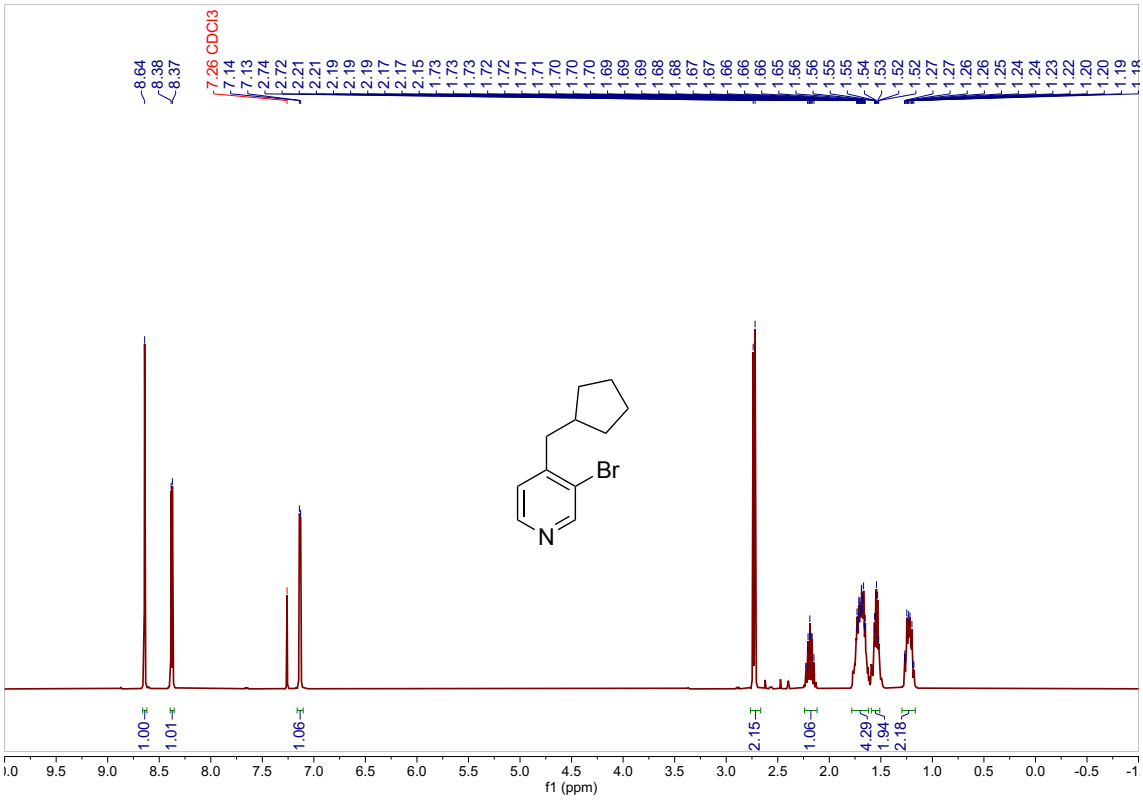
^{1}H NMR (400 MHz, $CDCl_3$) of **18a**



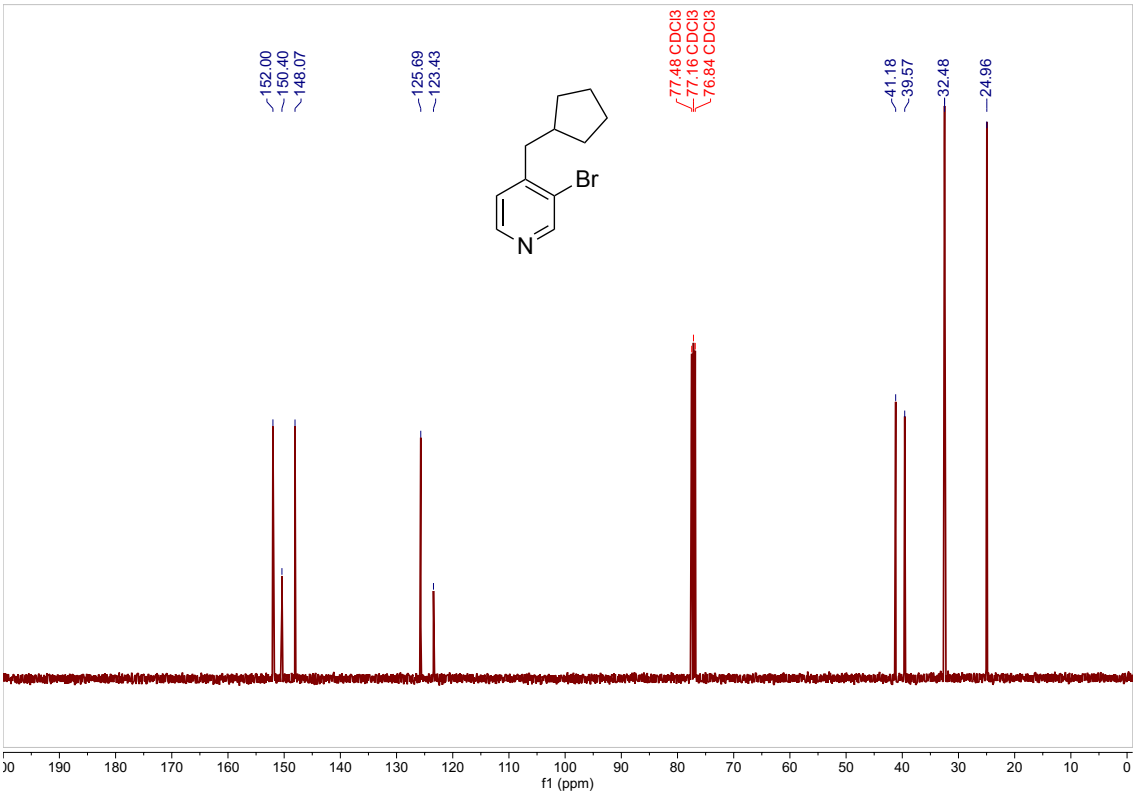
^{13}C NMR (101 MHz, $CDCl_3$) of **18a**



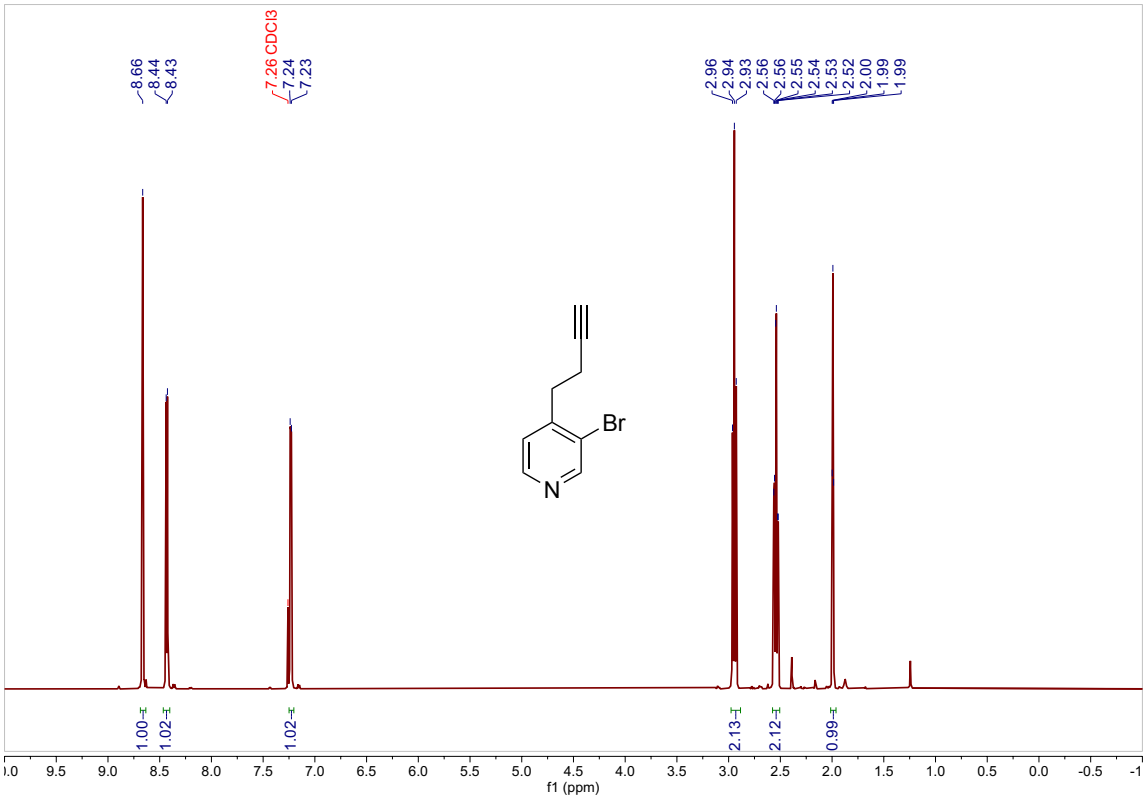
^{1}H NMR (400 MHz, $CDCl_3$) of **19a**



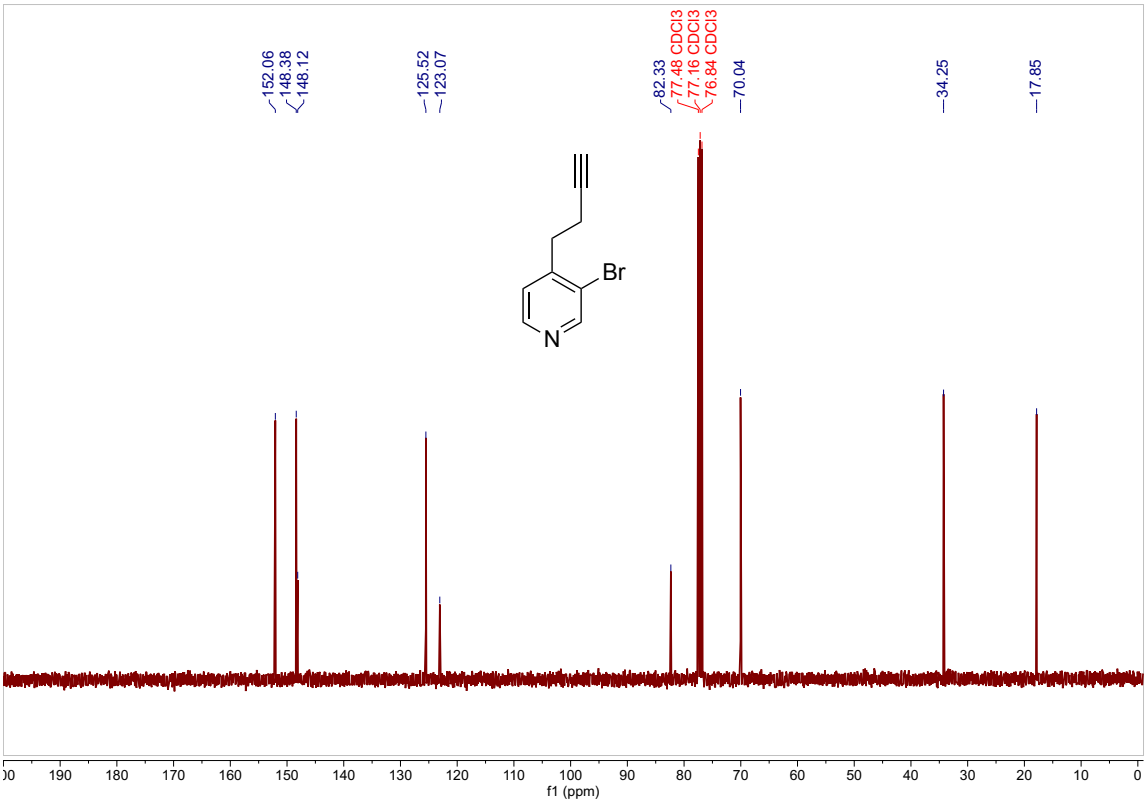
^{13}C NMR (101 MHz, $CDCl_3$) of **19a**



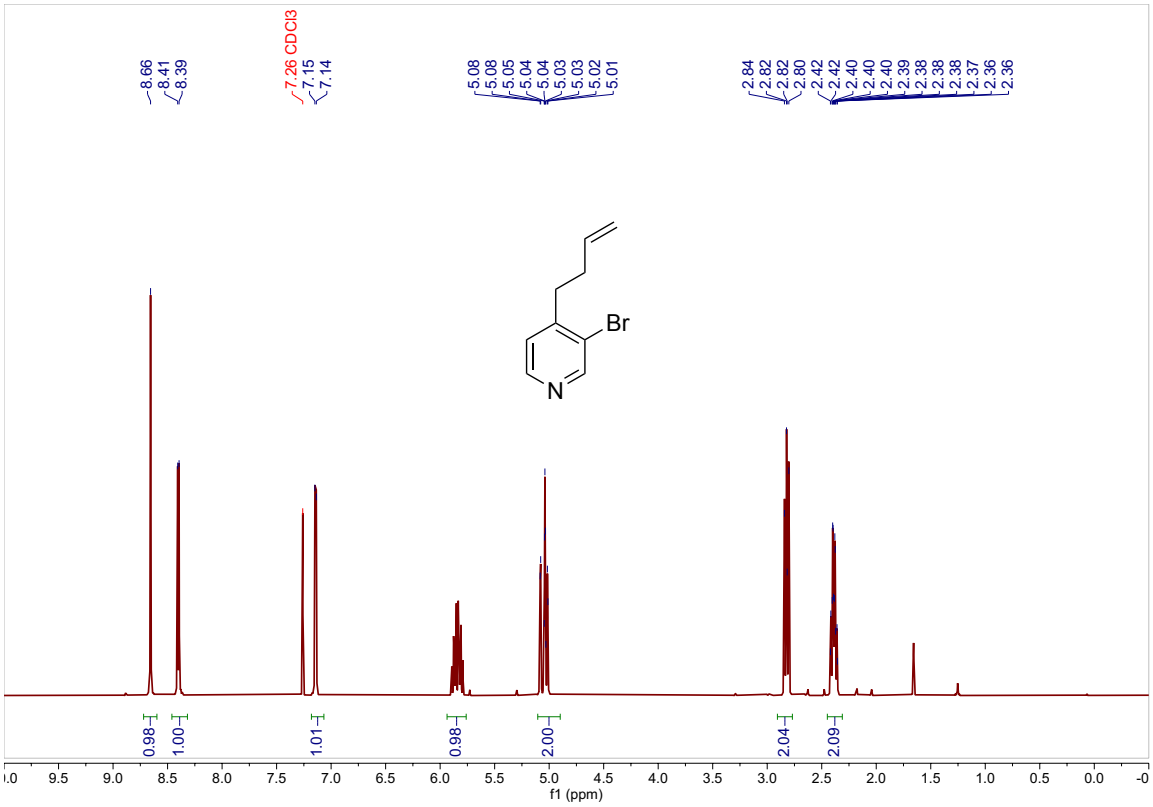
^{1}H NMR (400 MHz, $CDCl_3$) of **20a**



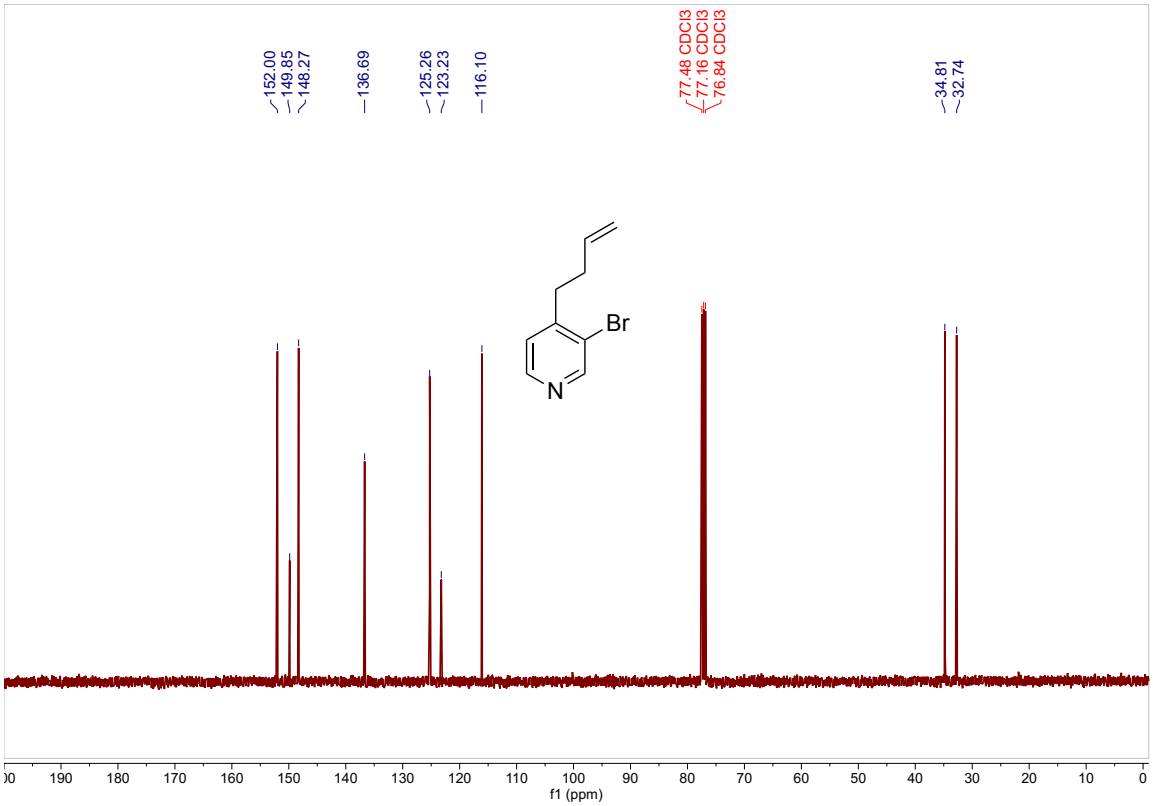
^{13}C NMR (101 MHz, $CDCl_3$) of **20a**



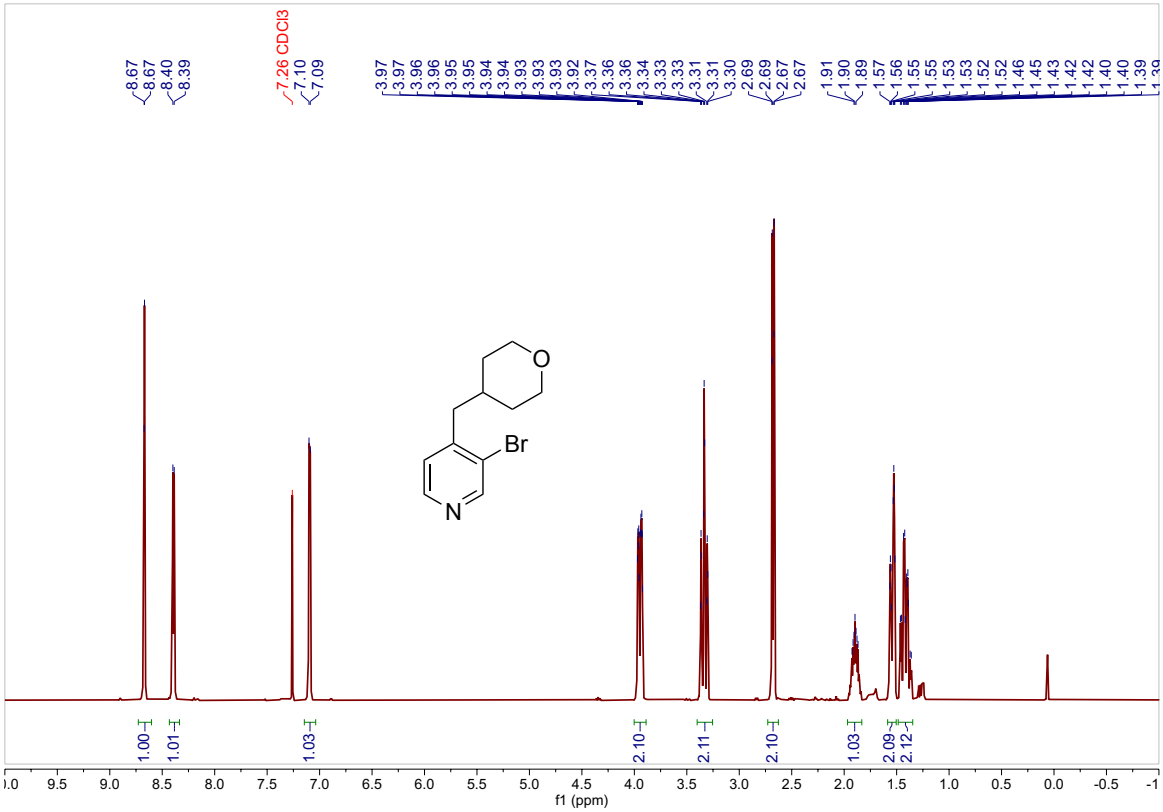
^{1}H NMR (400 MHz, $CDCl_3$) of **21a**



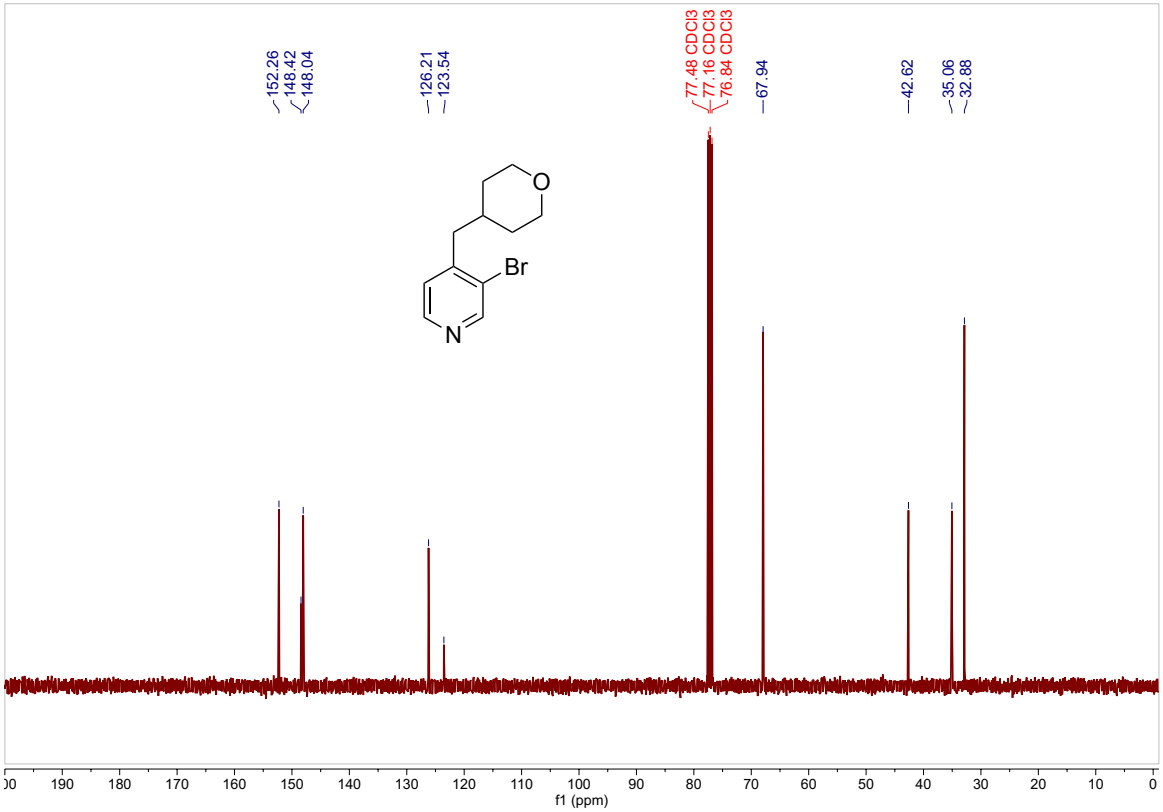
^{13}C NMR (101 MHz, $CDCl_3$) of **21a**



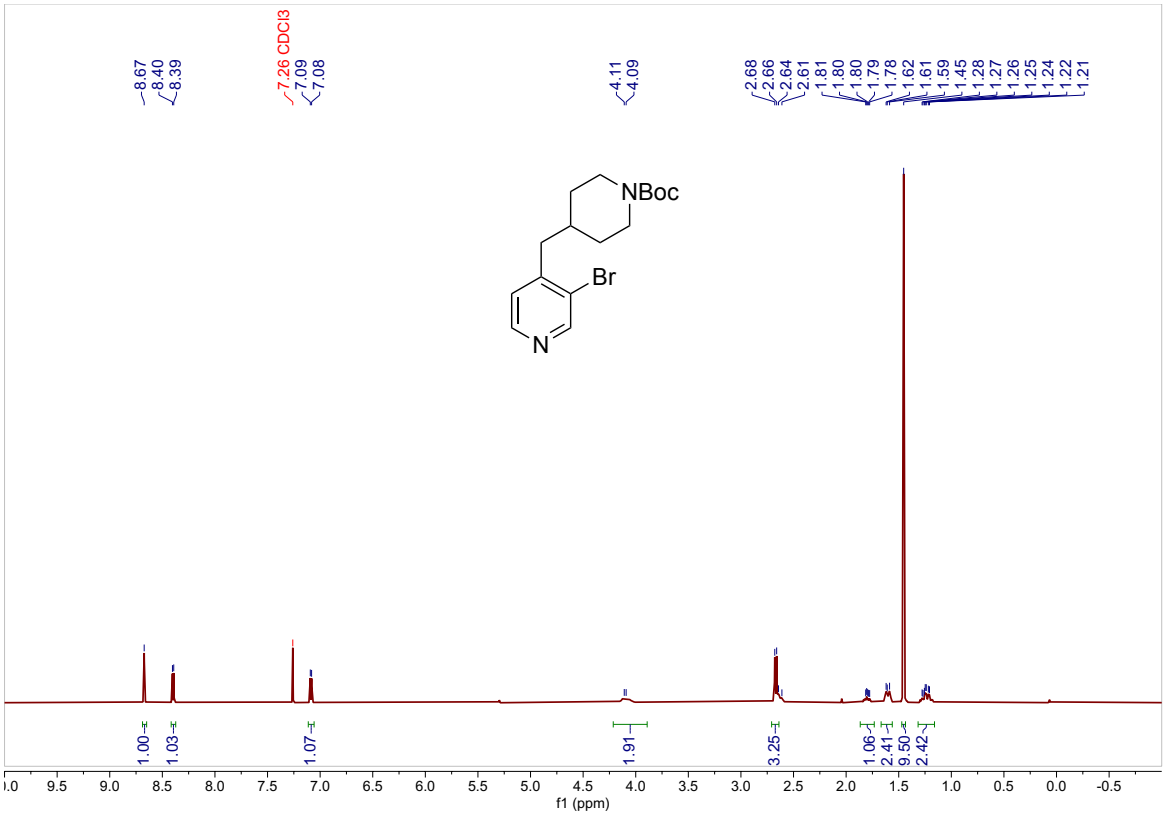
^{1}H NMR (400 MHz, $CDCl_3$) of **22a**



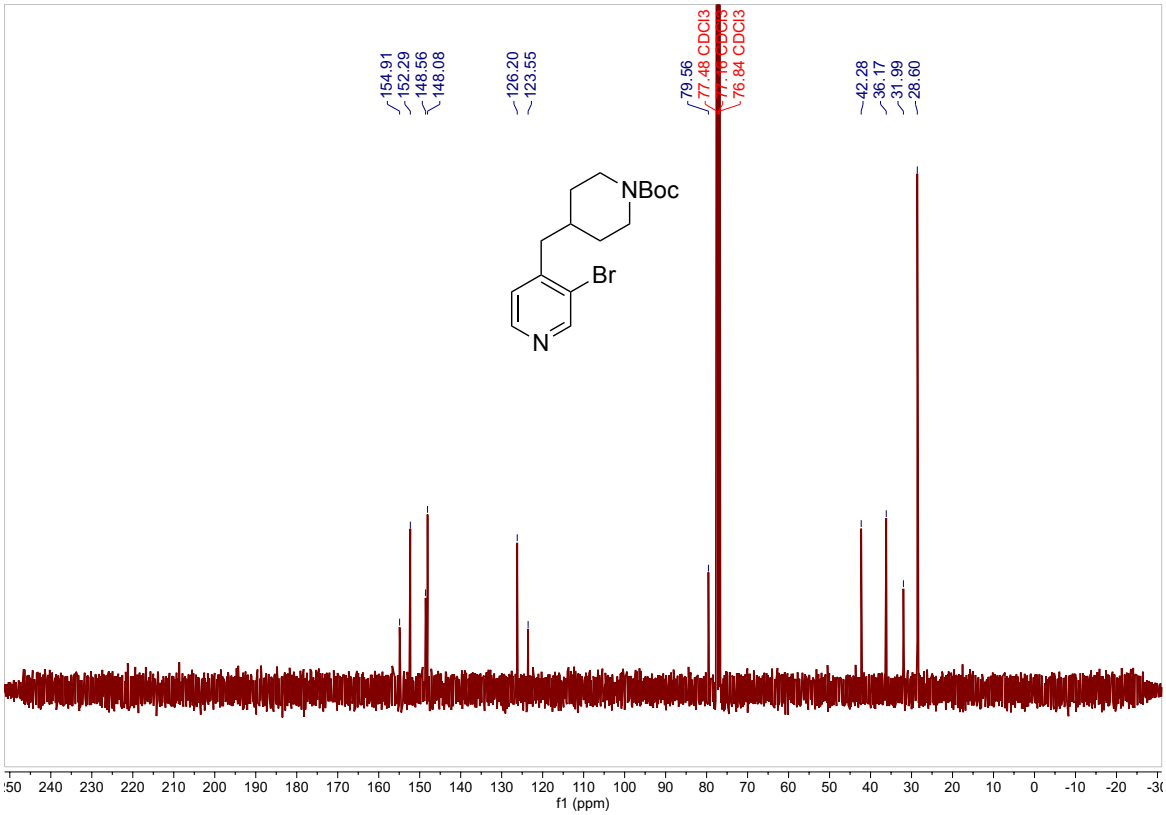
^{13}C NMR (101 MHz, $CDCl_3$) of **22a**



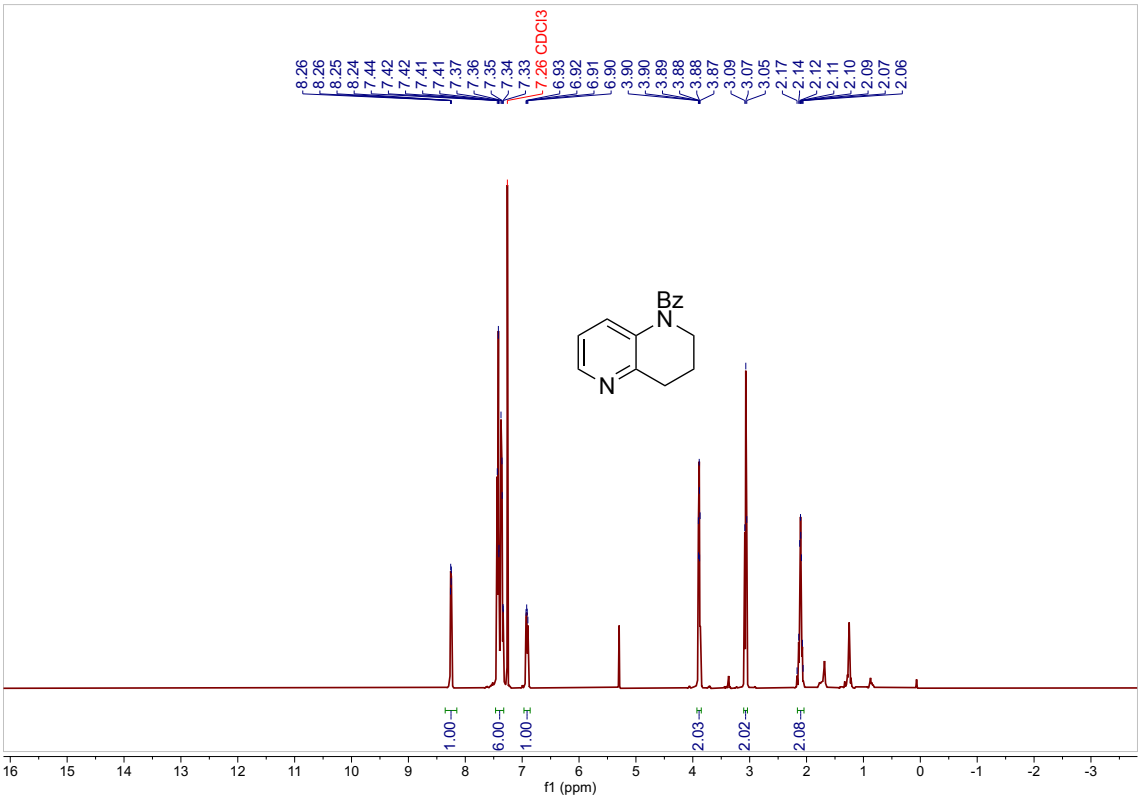
^{1}H NMR (400 MHz, $CDCl_3$) of **23a**



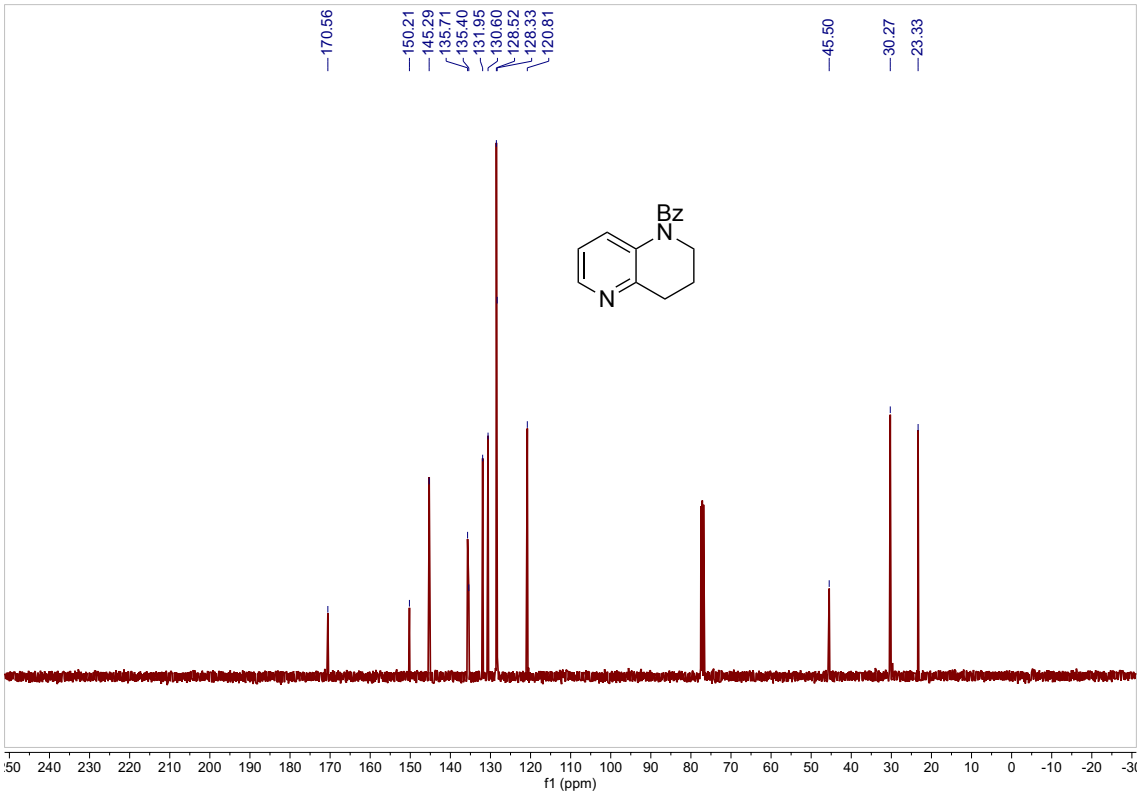
^{13}C NMR (101 MHz, $CDCl_3$) of **23a**



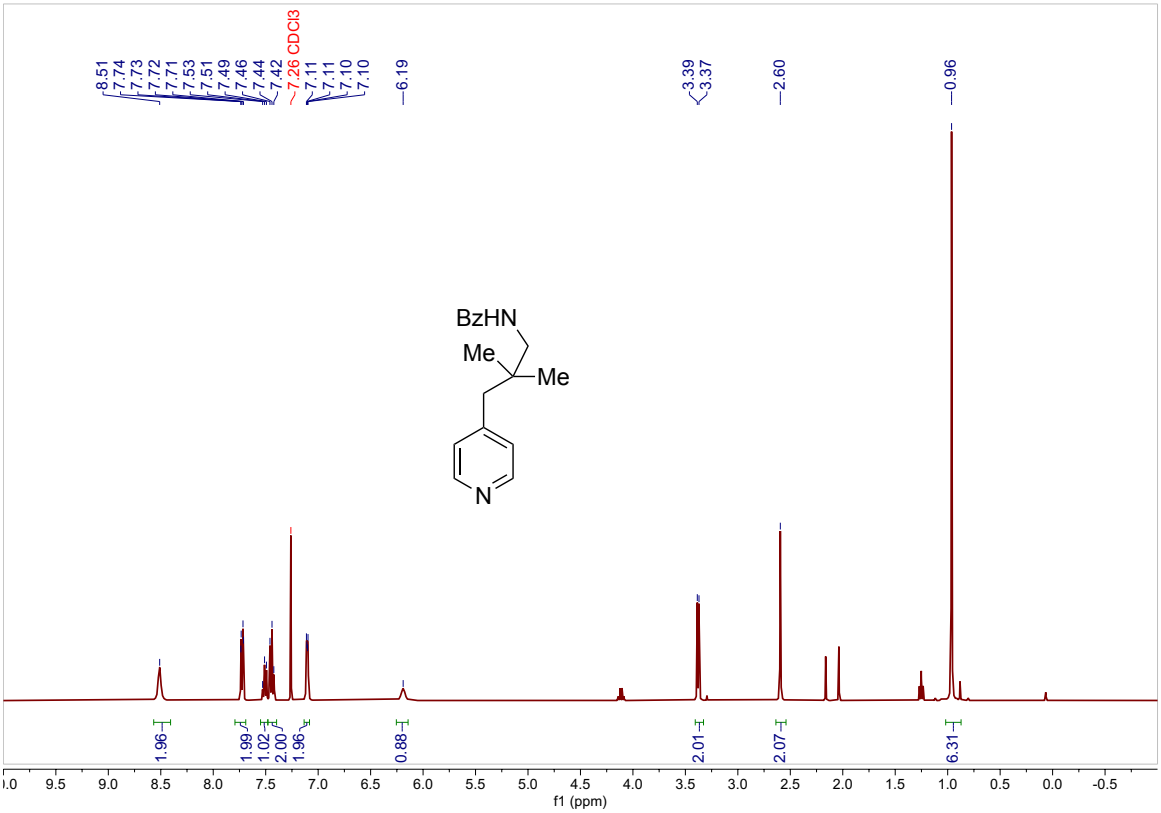
^{1}H NMR (400 MHz, $CDCl_3$) of **24a**



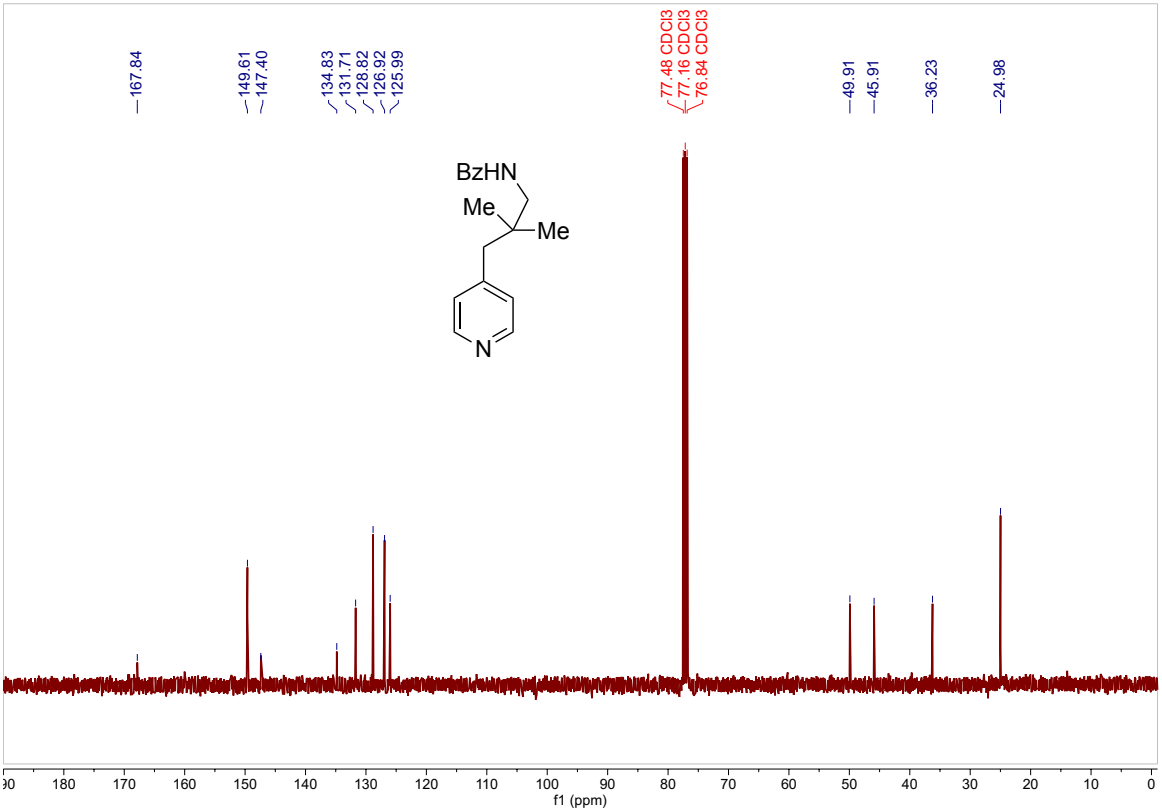
^{13}C NMR (101 MHz, $CDCl_3$) of **24a**



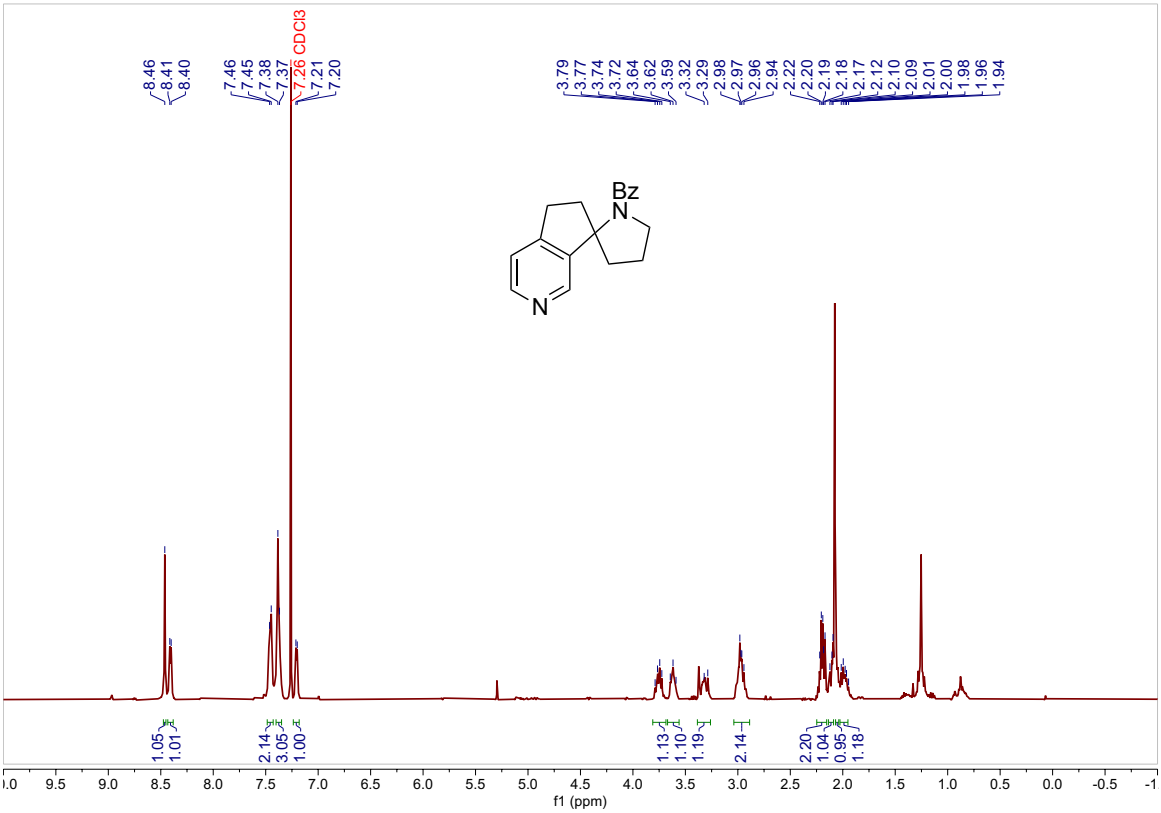
^{1}H NMR (400 MHz, $CDCl_3$) of **25a**



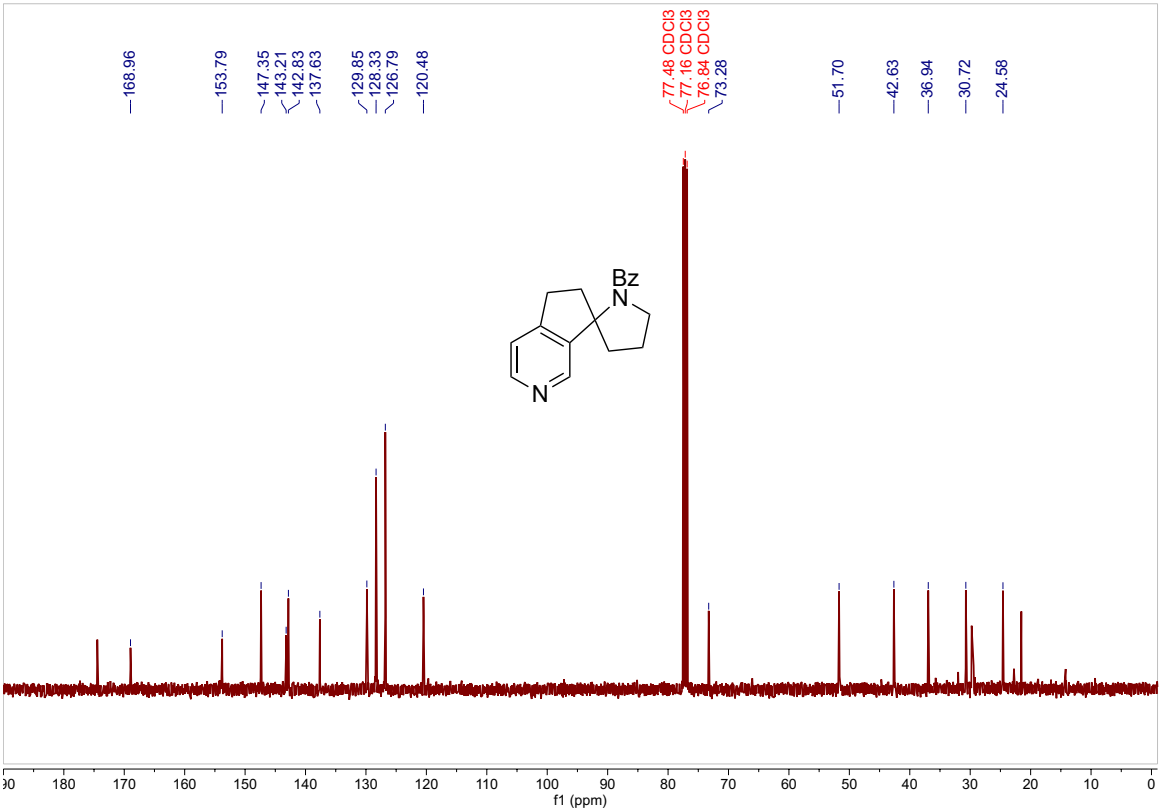
^{13}C NMR (101 MHz, $CDCl_3$) of **25a**



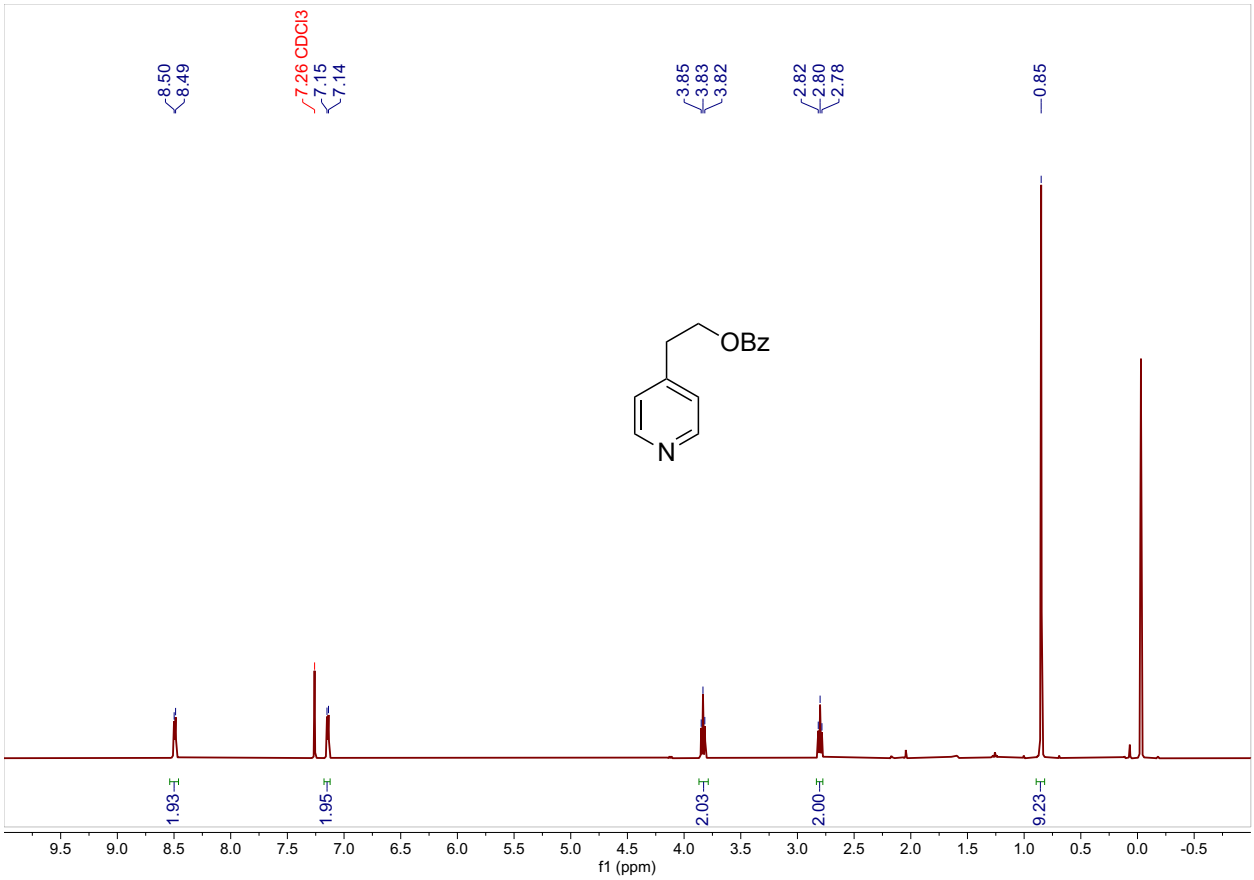
^{1}H NMR (400 MHz, $CDCl_3$) of **26a**



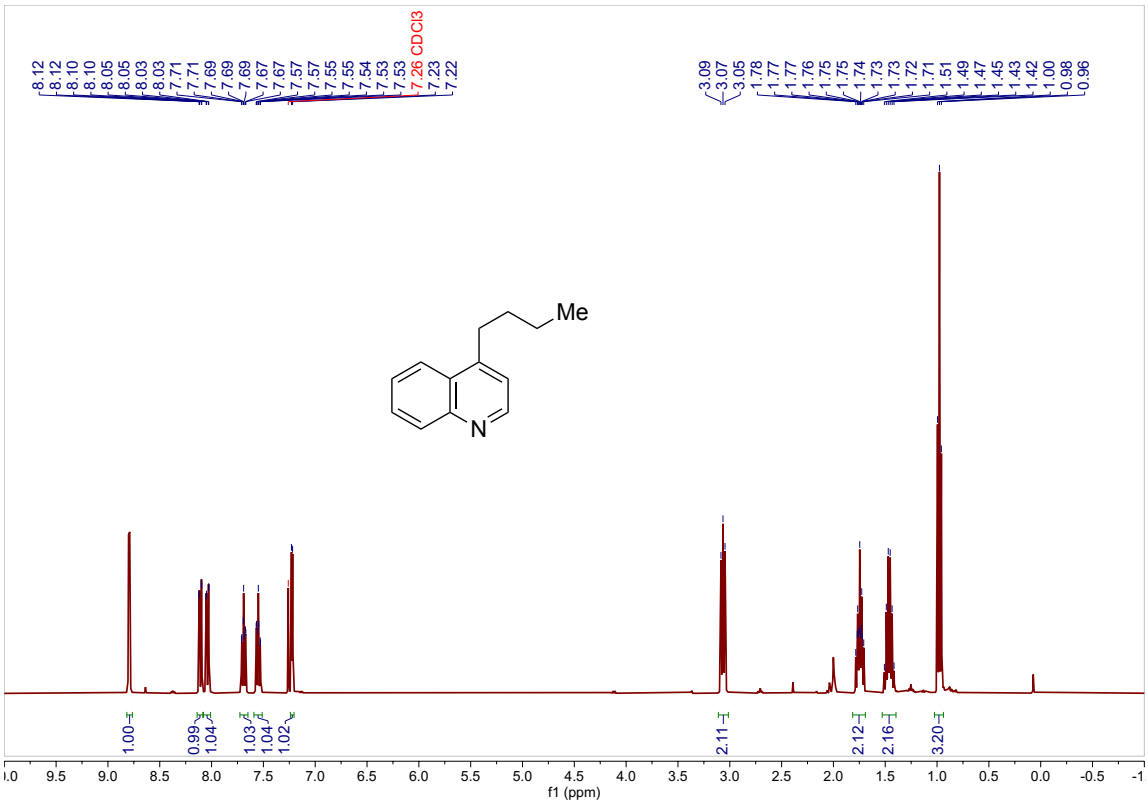
^{13}C NMR (101 MHz, $CDCl_3$) of **26a**



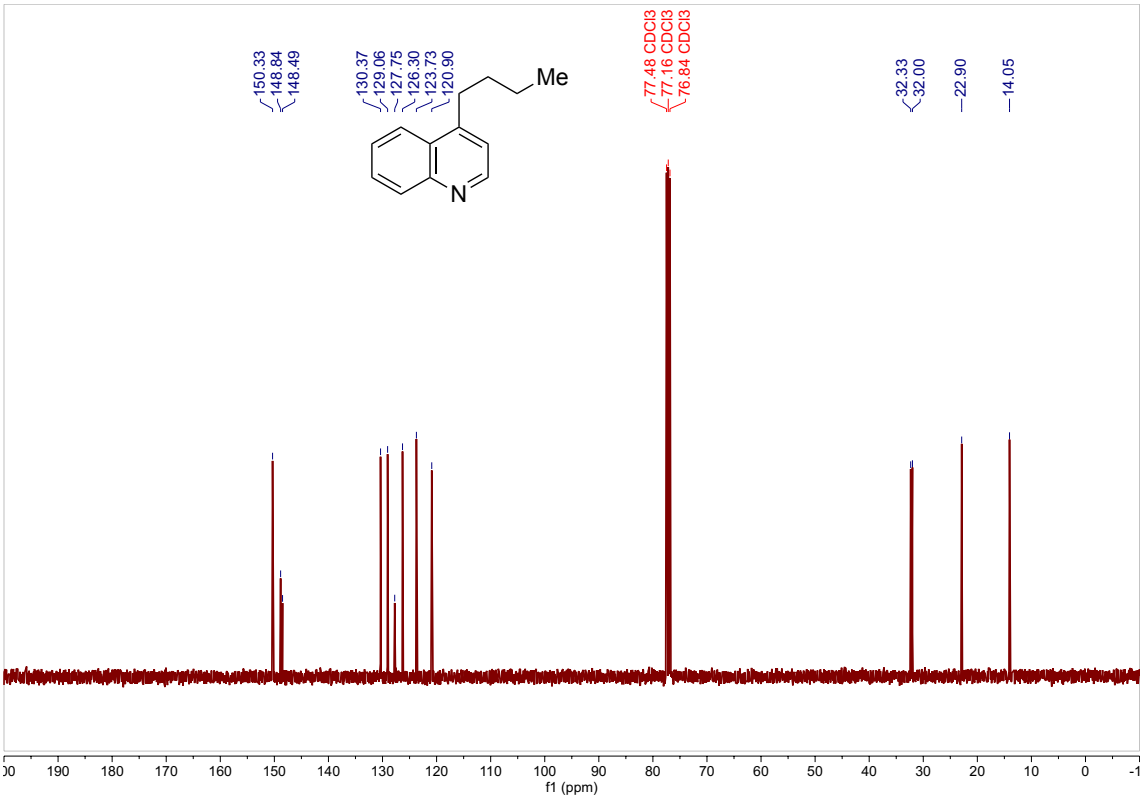
^{1}H NMR (400 MHz, $CDCl_3$) of **27a**



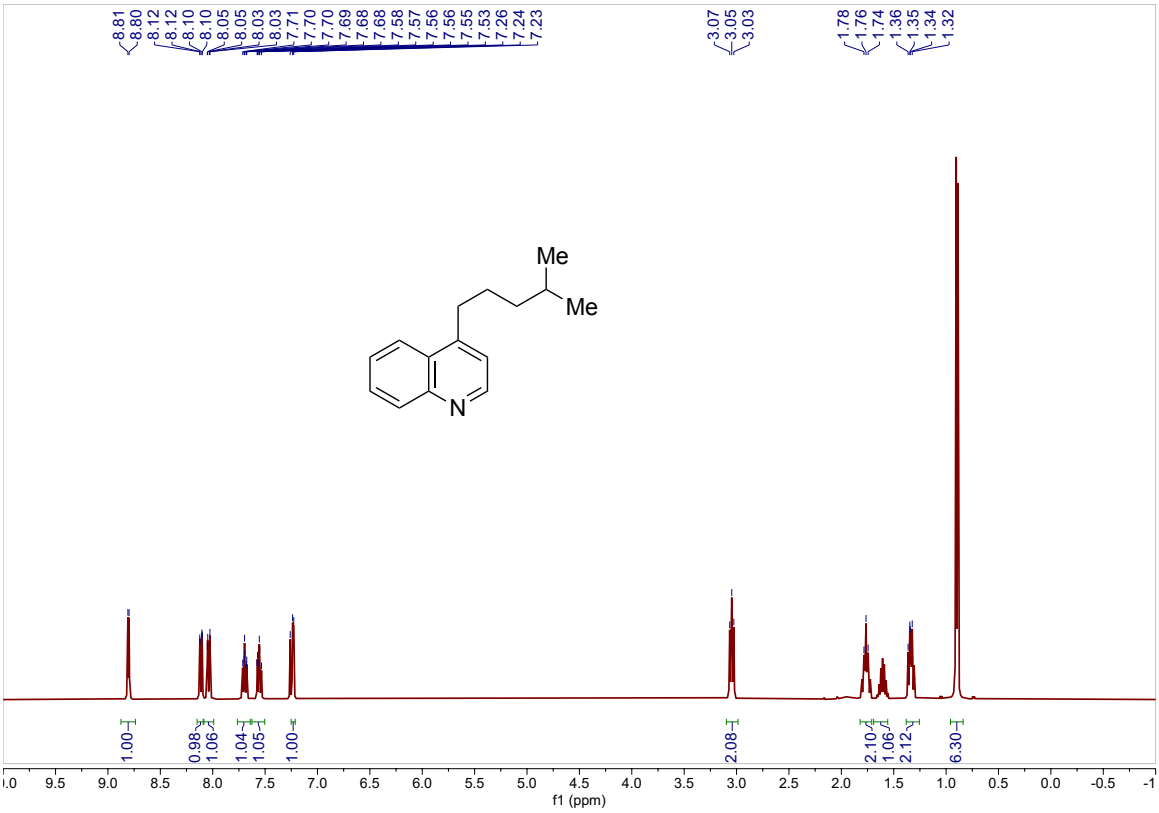
^{1}H NMR (400 MHz, $CDCl_3$) of **29a**



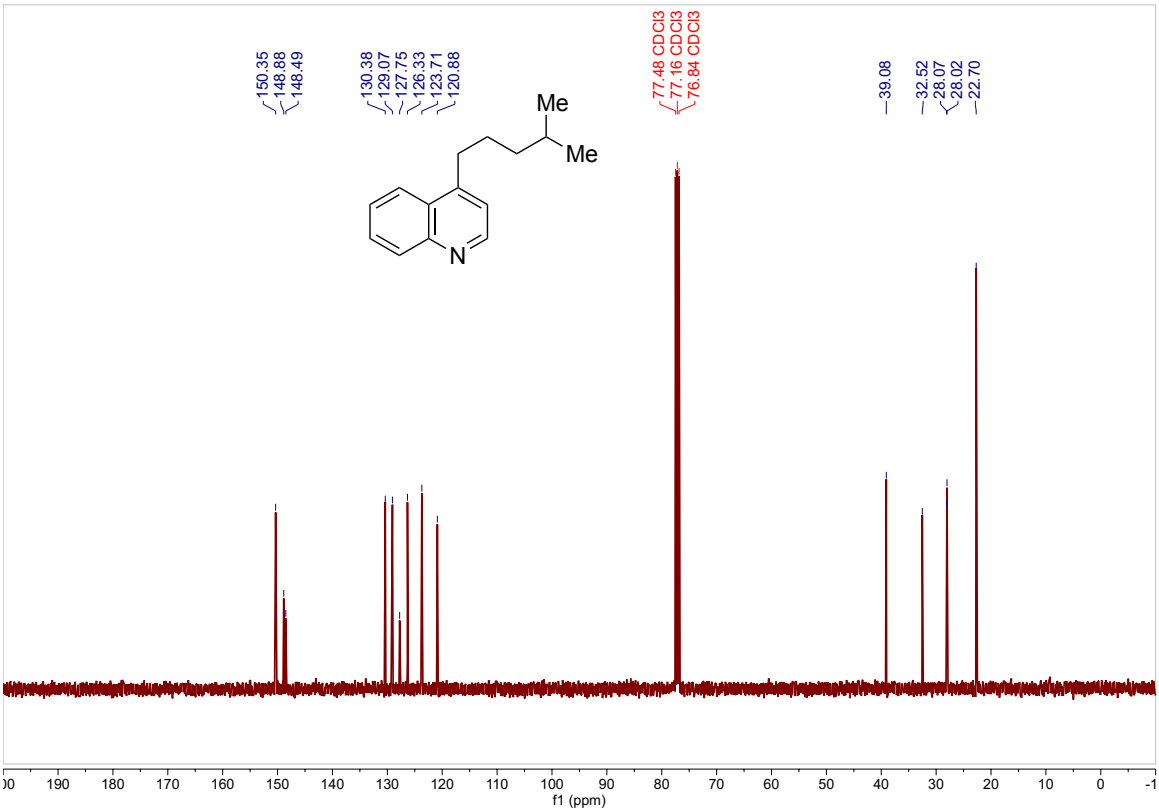
^{13}C NMR (101 MHz, $CDCl_3$) of **29a**



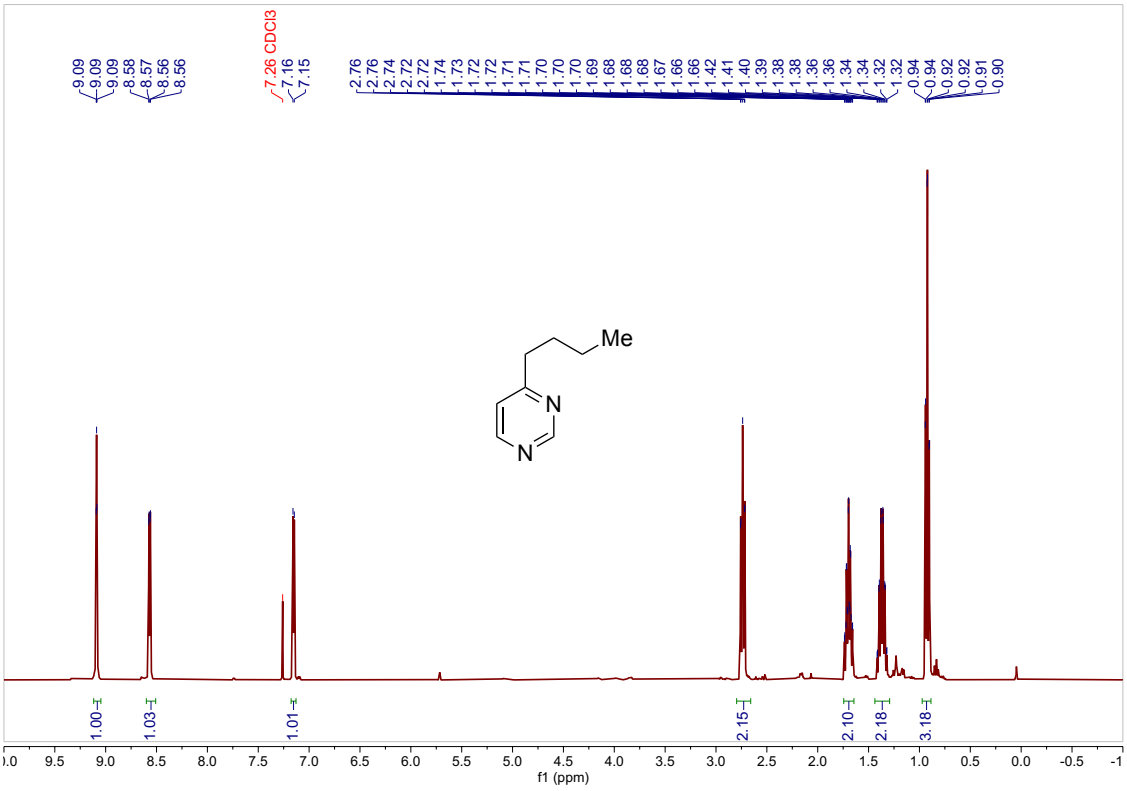
^{1}H NMR (400 MHz, $CDCl_3$) of **30a**



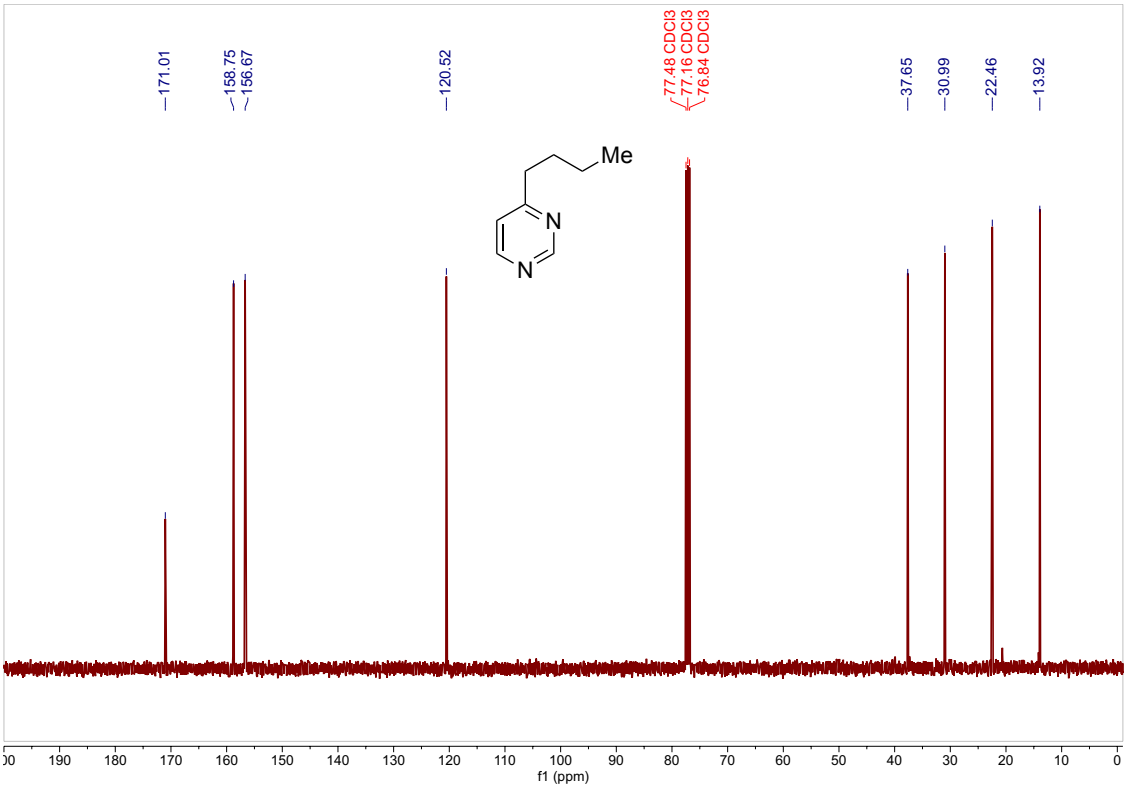
^{13}C NMR (101 MHz, $CDCl_3$) of **30a**



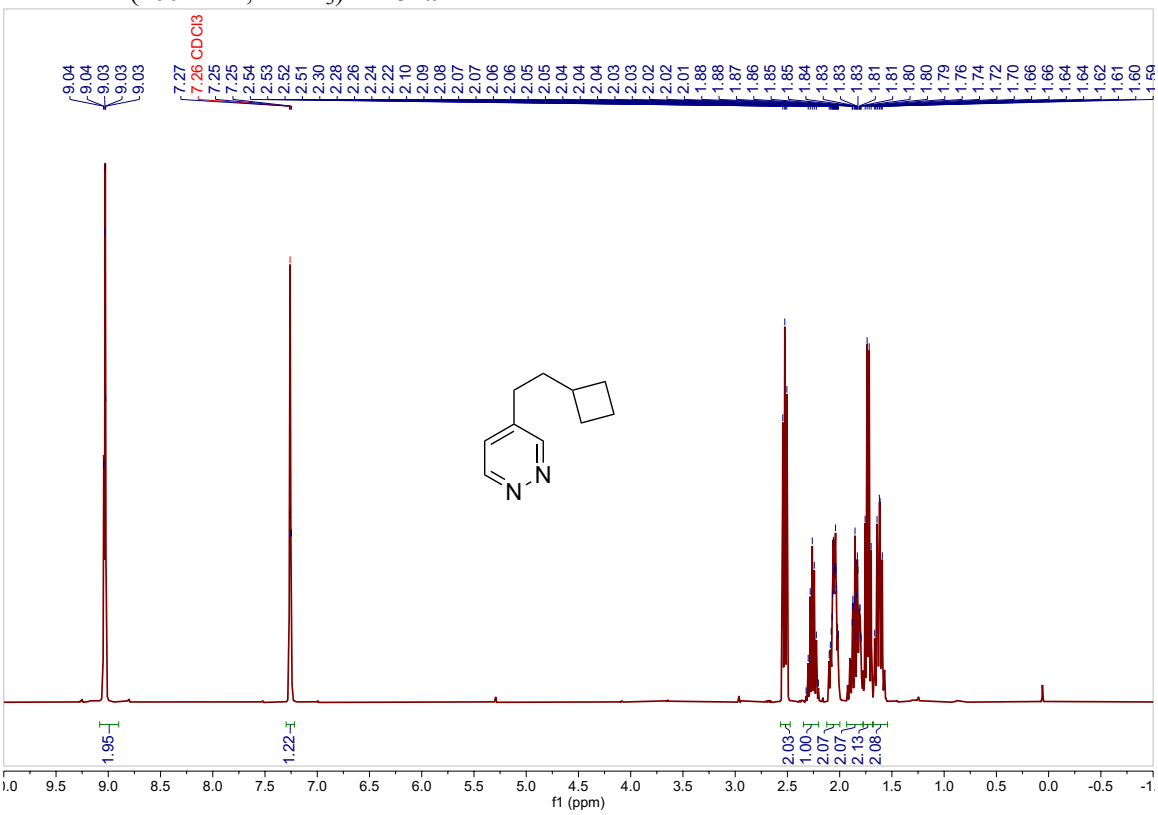
^{1}H NMR (400 MHz, $CDCl_3$) of **31a**



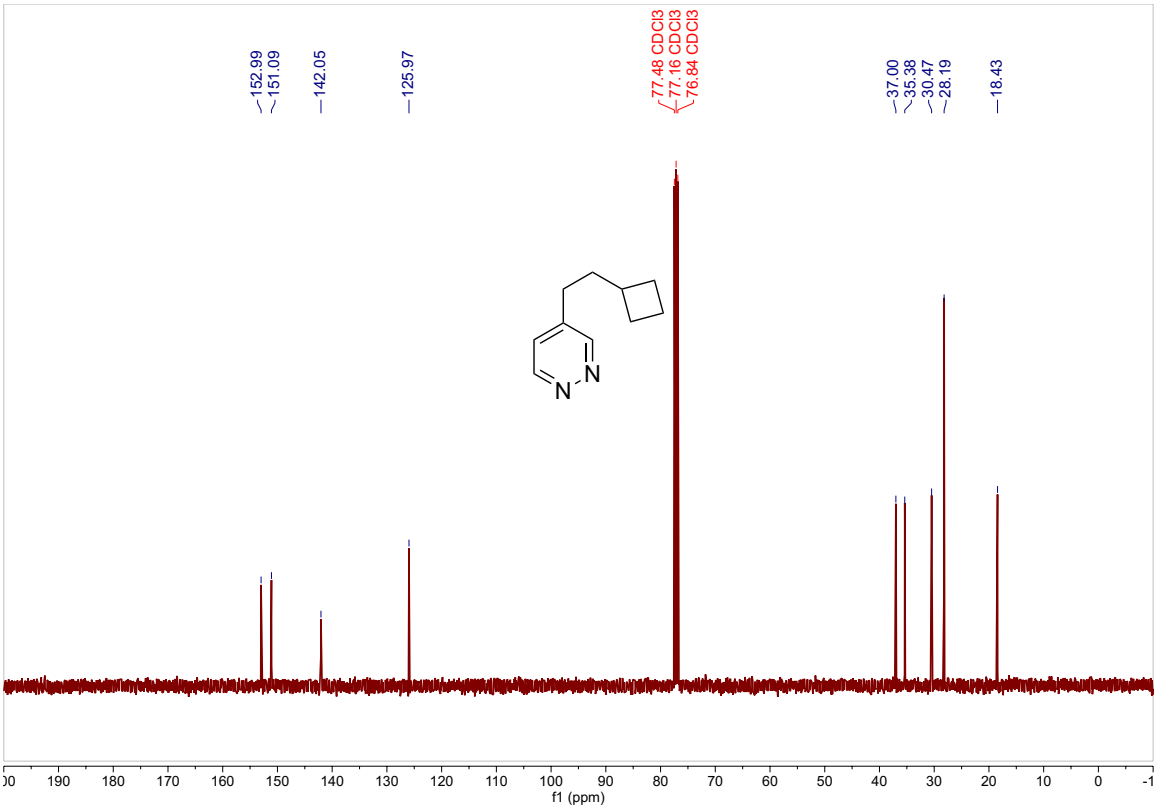
^{13}C NMR (101 MHz, $CDCl_3$) of **31a**



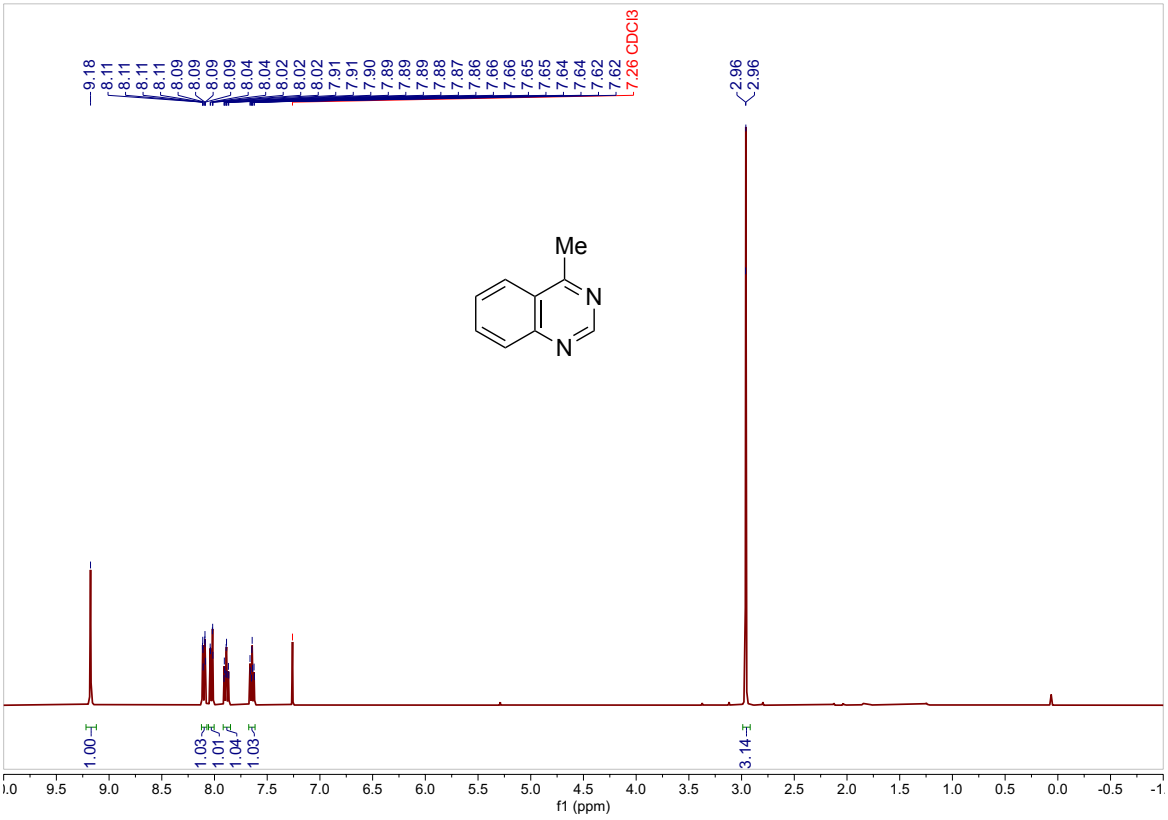
^{1}H NMR (400 MHz, $CDCl_3$) of **32a**



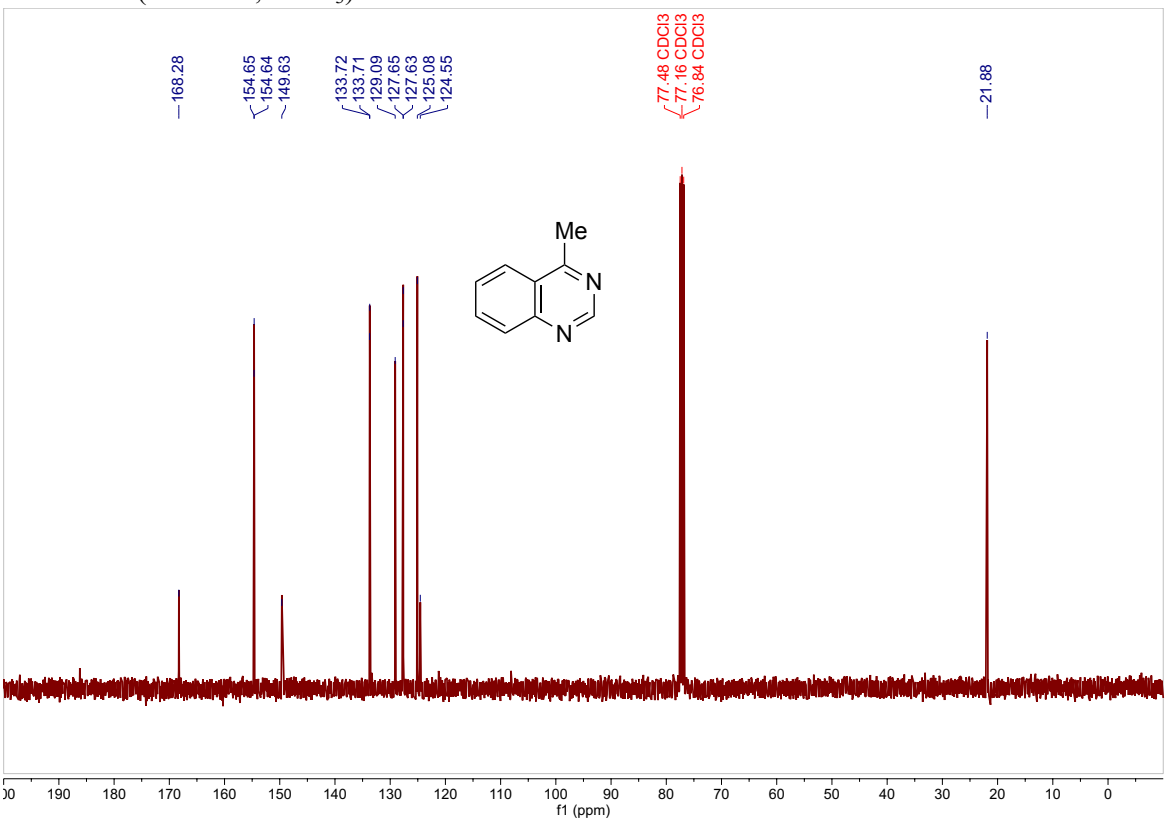
^{13}C NMR (101 MHz, $CDCl_3$) of **32a**



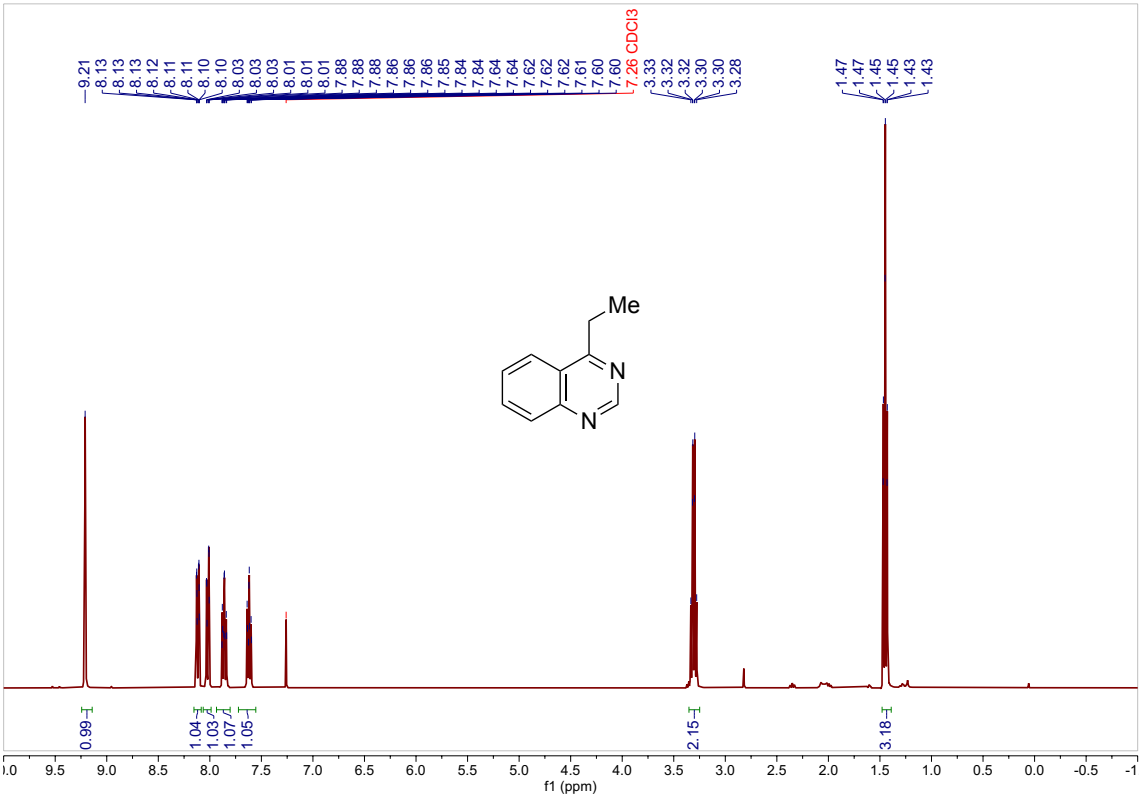
^{1}H NMR (400 MHz, $CDCl_3$) of **33a**



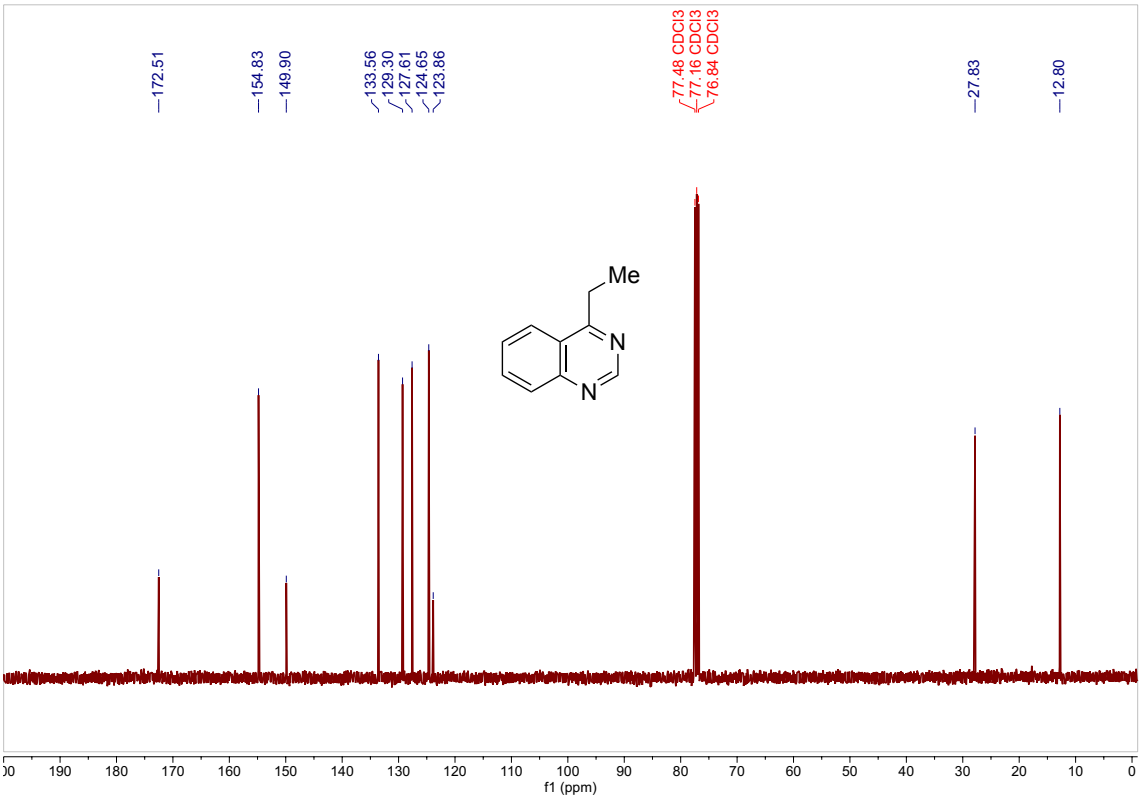
^{13}C NMR (101 MHz, $CDCl_3$) of **33a**



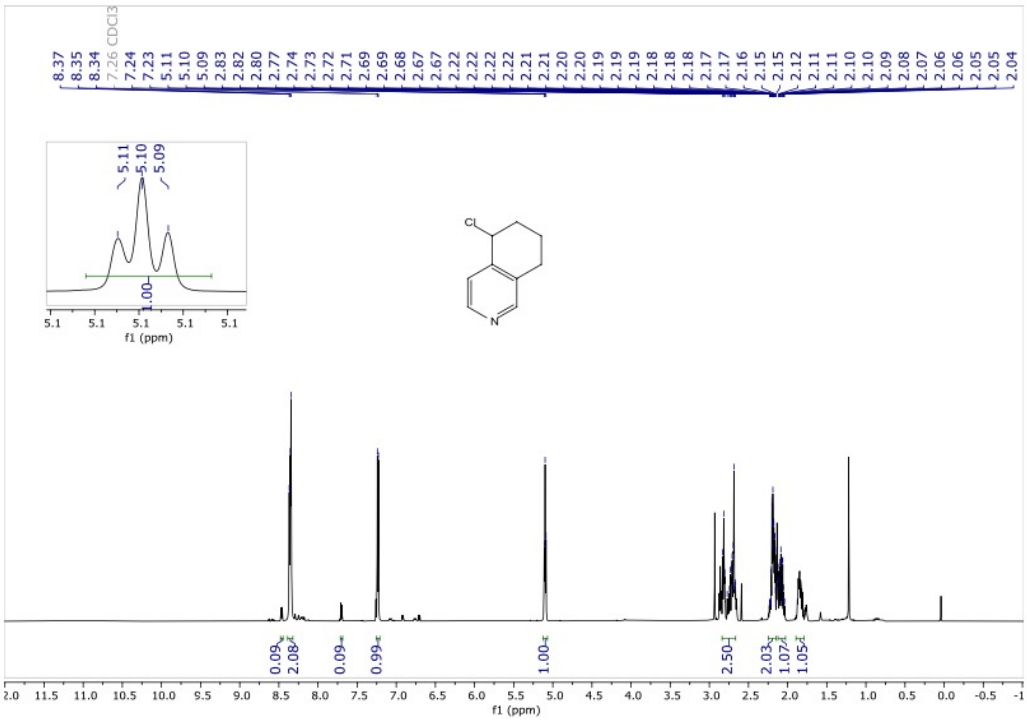
^{1}H NMR (400 MHz, $CDCl_3$) of **34a**



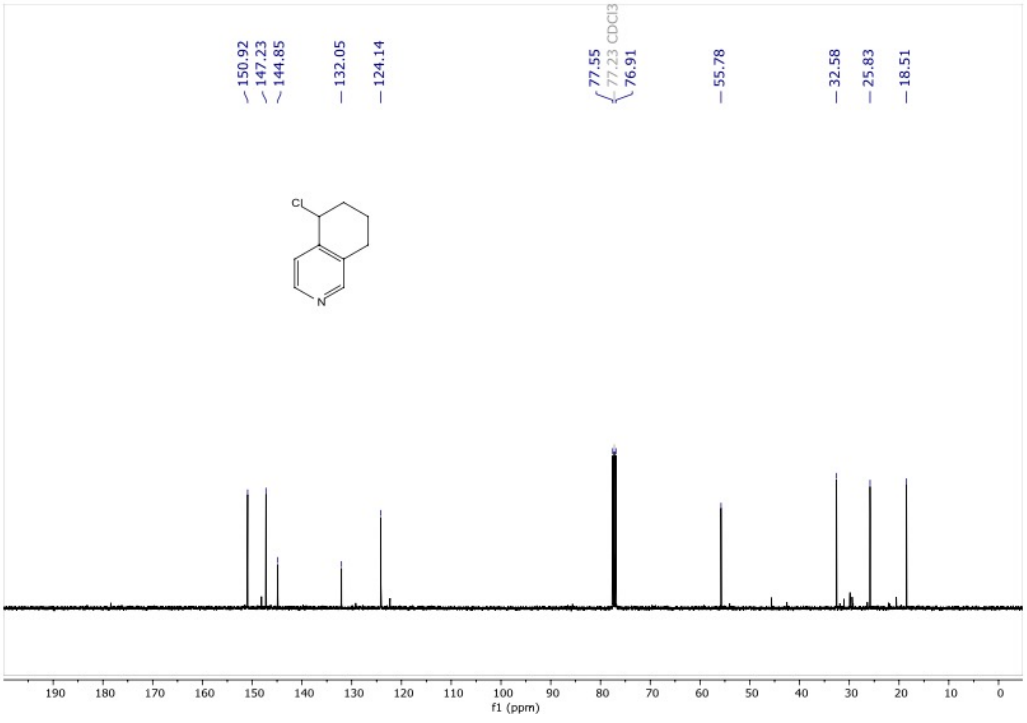
^{13}C NMR (101 MHz, $CDCl_3$) of **34a**



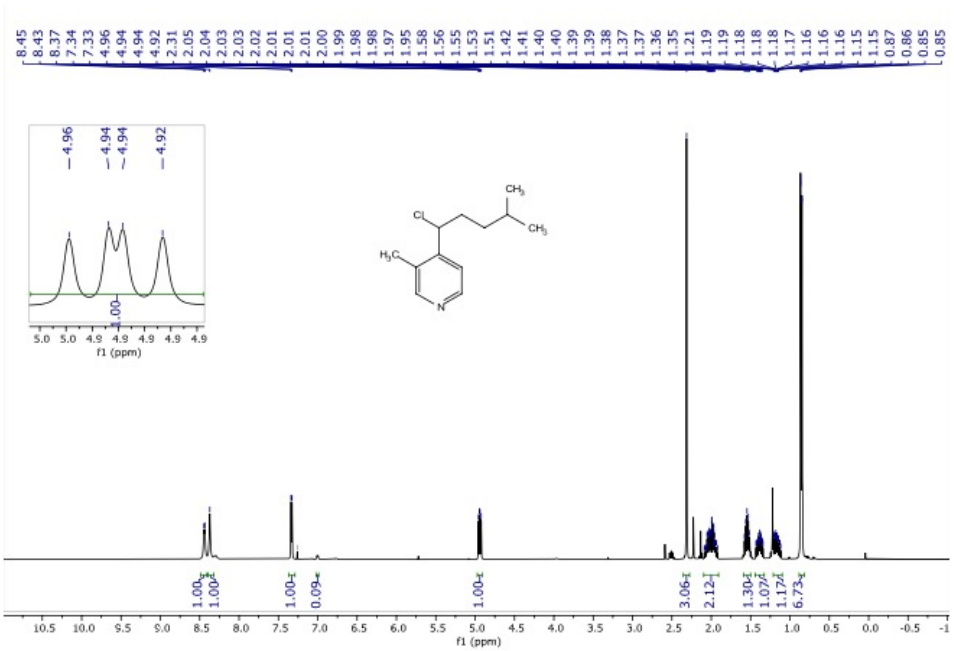
^{1}H NMR (400 MHz, $CDCl_3$) of **3**



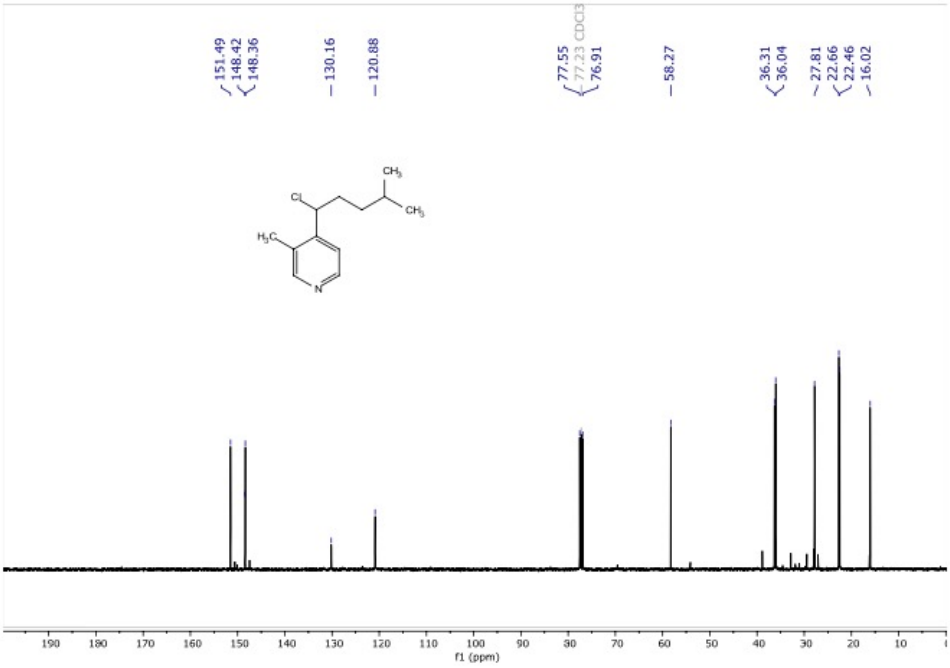
^{13}C NMR (101 MHz, $CDCl_3$) of **3**



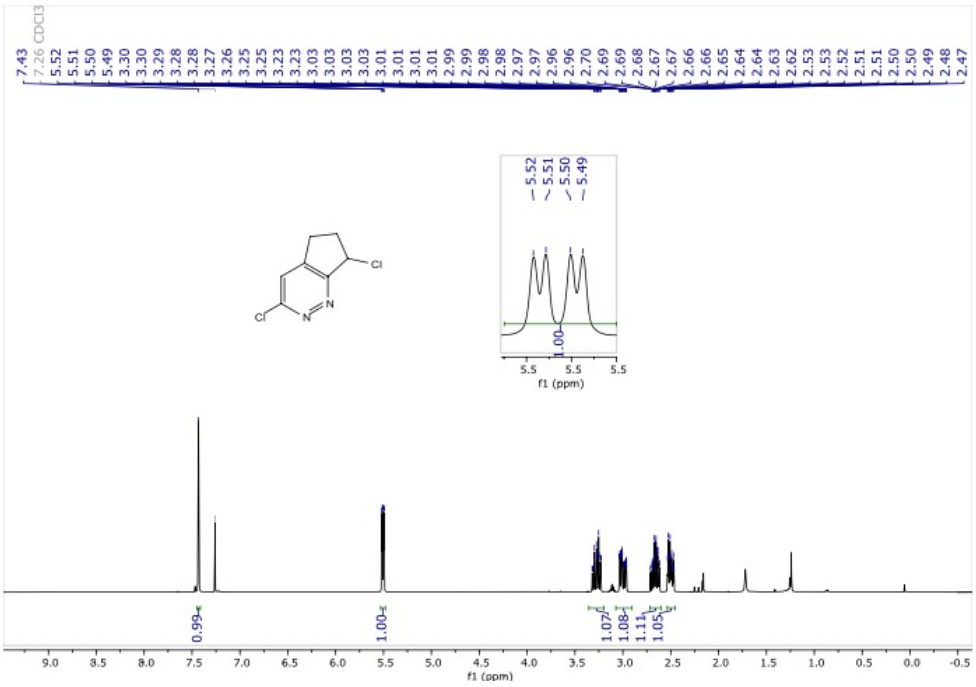
^{1}H NMR (400 MHz, $CDCl_3$) of **10**



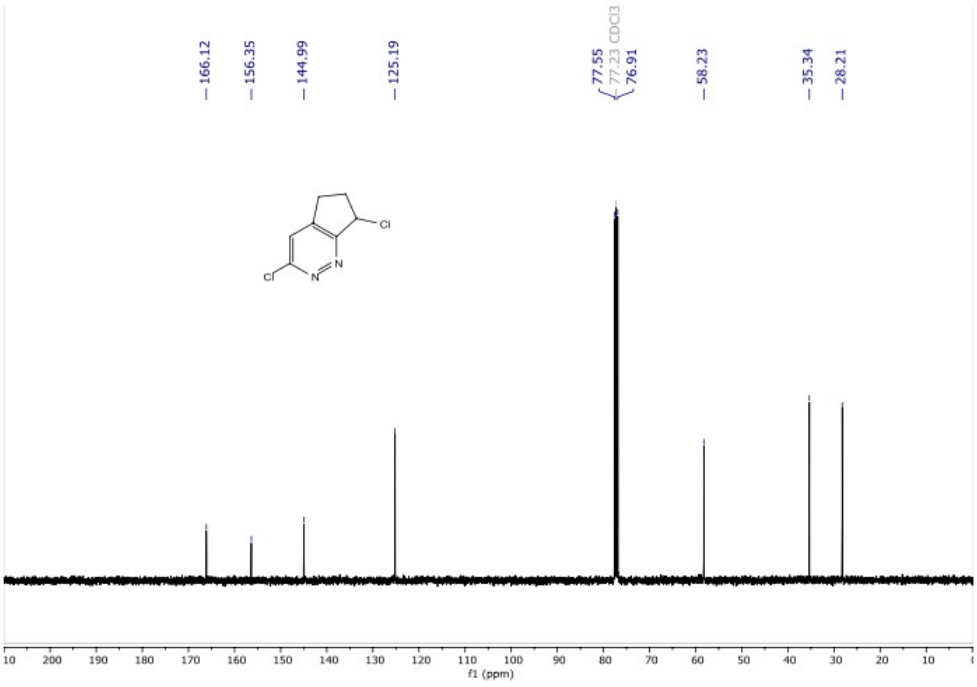
^{13}C NMR (101 MHz, $CDCl_3$) of **10**



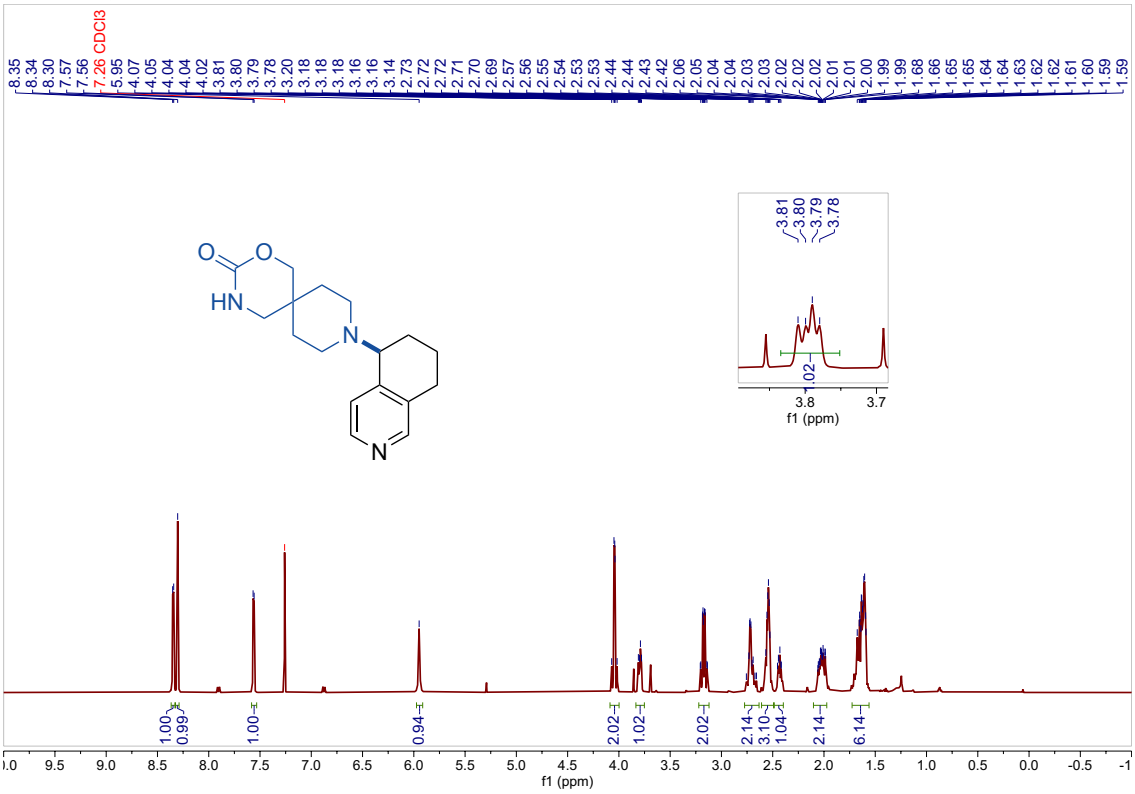
^{1}H NMR (400 MHz, $CDCl_3$) of **6**



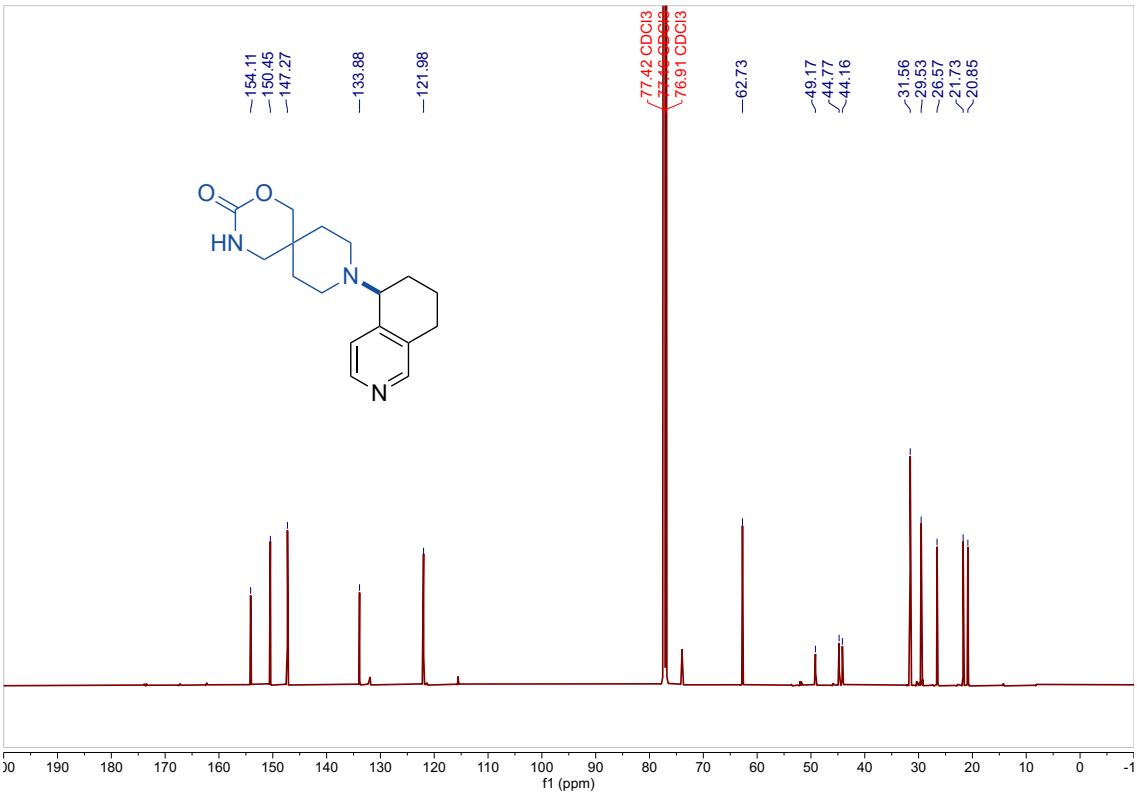
^{13}C NMR (101 MHz, $CDCl_3$) of **6**



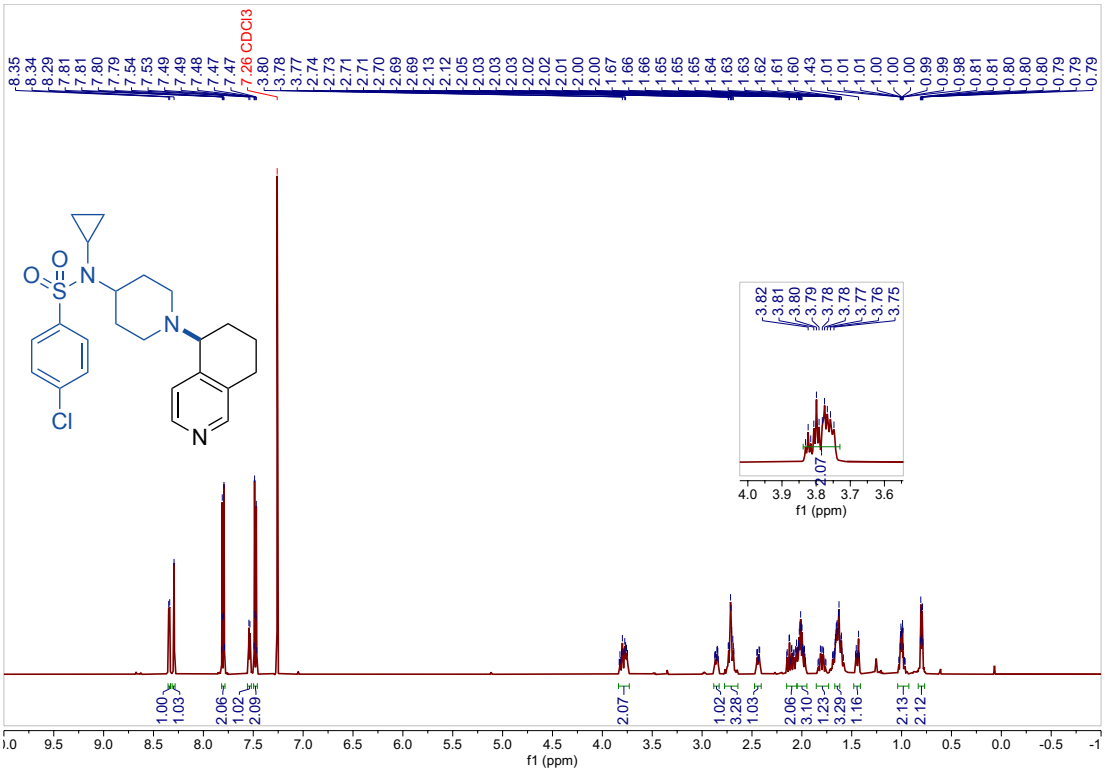
^{1}H NMR (500 MHz, $CDCl_3$) of **3-Am4**



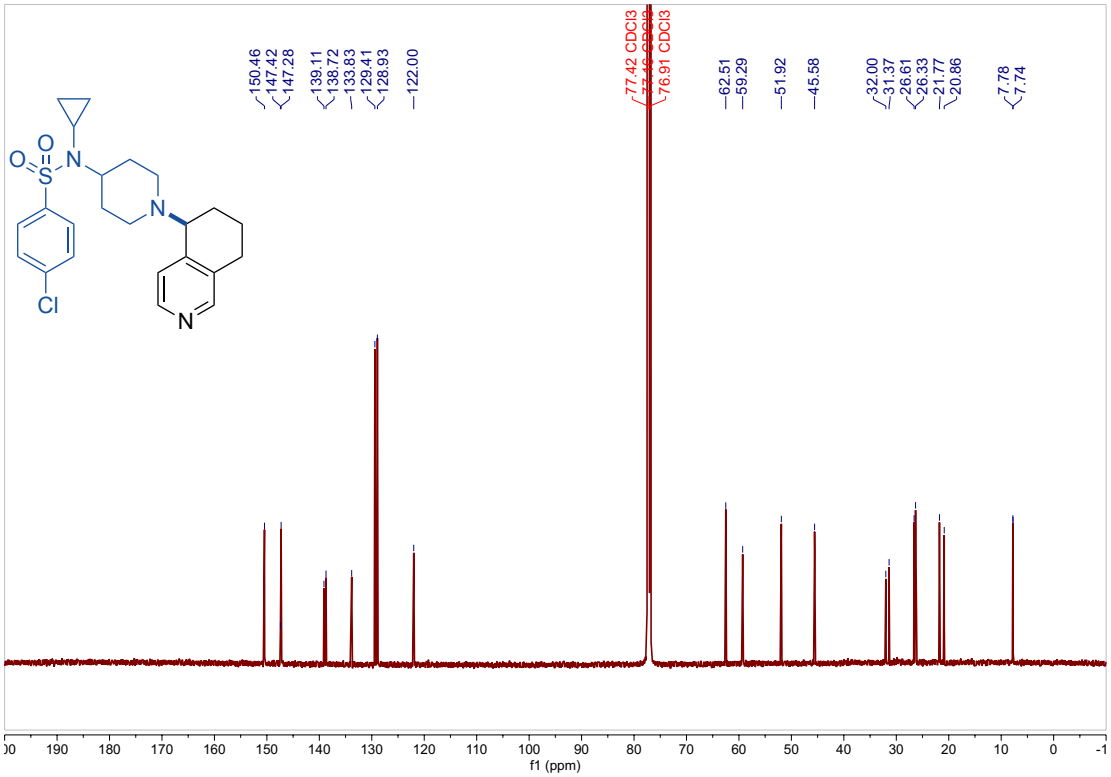
^{13}C NMR (101 MHz, $CDCl_3$) of **3-Am4**



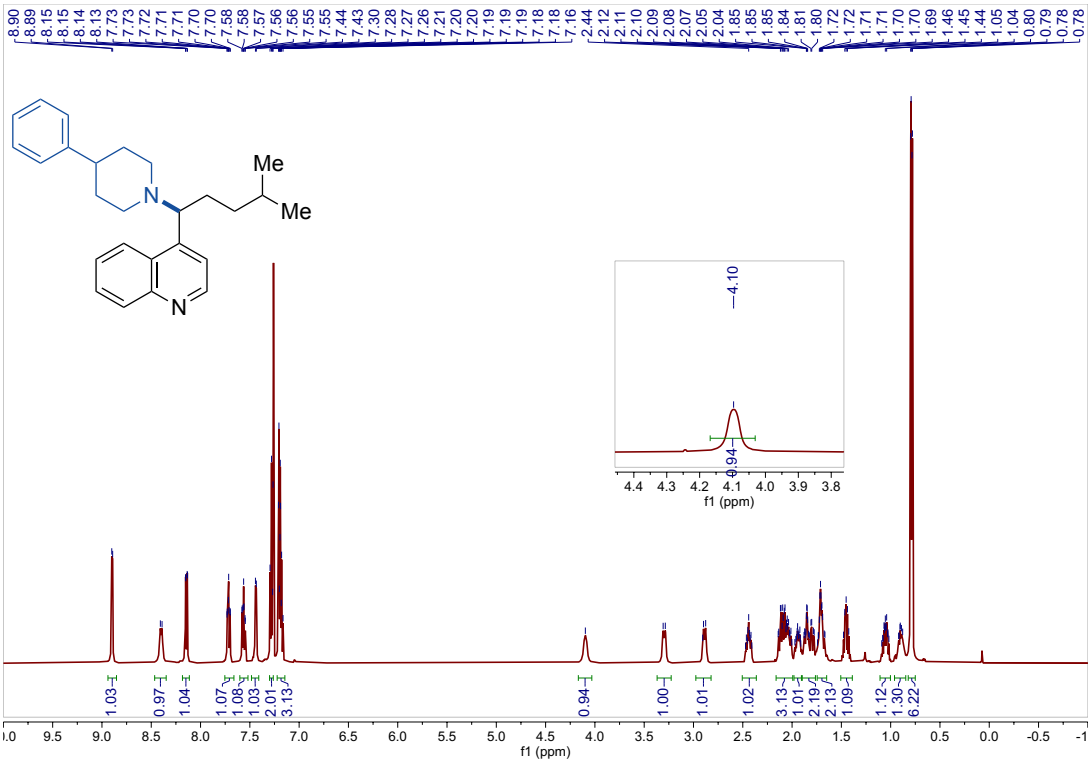
^{1}H NMR (500 MHz, $CDCl_3$) of **3-Am5**



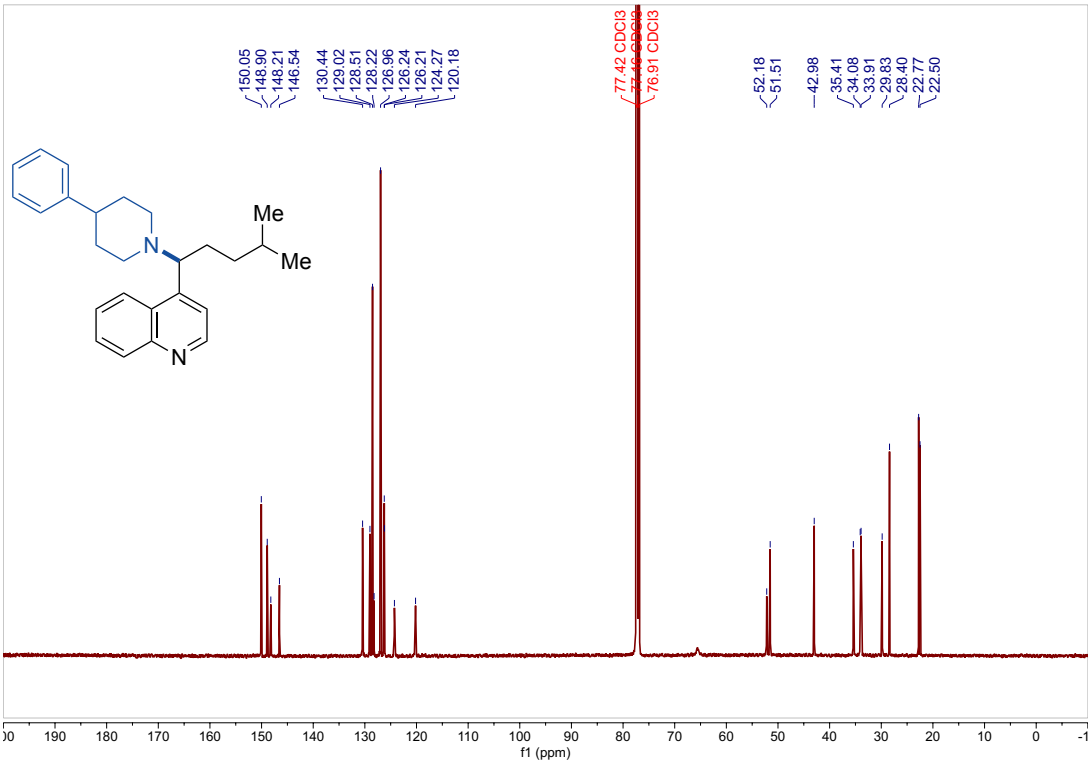
^{13}C NMR (101 MHz, $CDCl_3$) of **3-Am5**



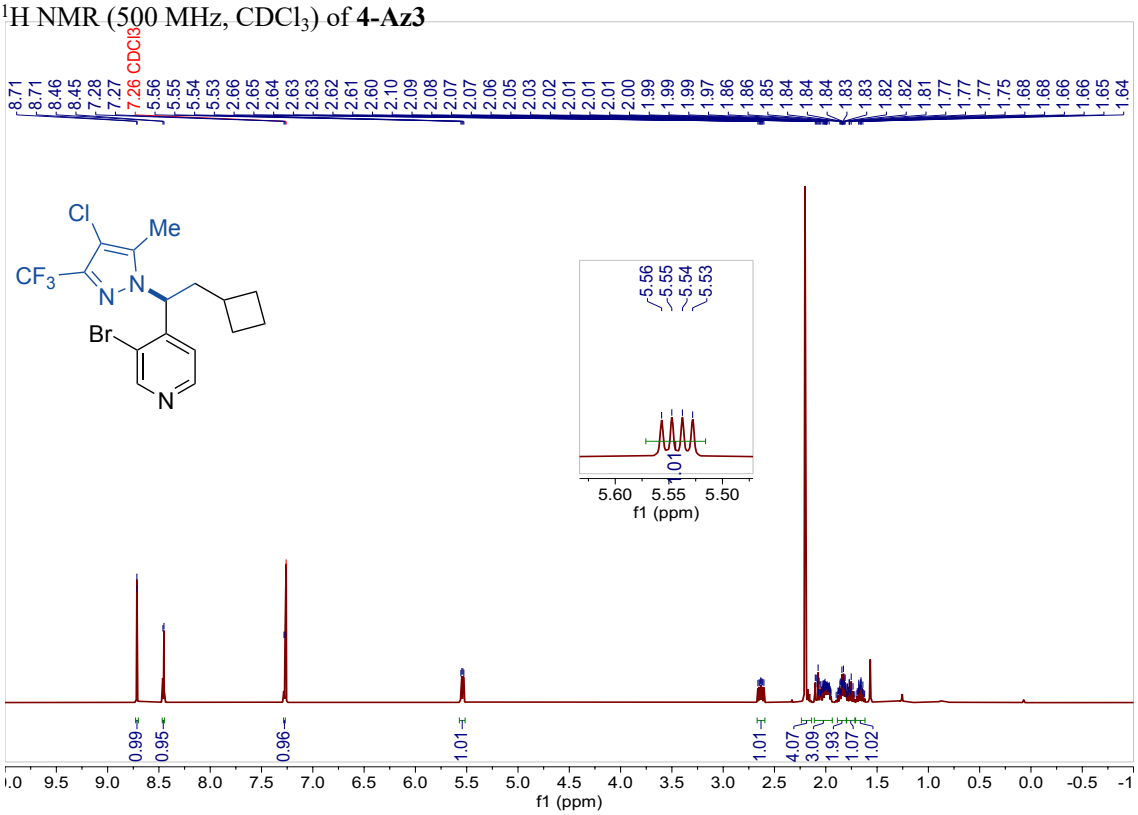
^{1}H NMR (500 MHz, $CDCl_3$) of **30-Am6**



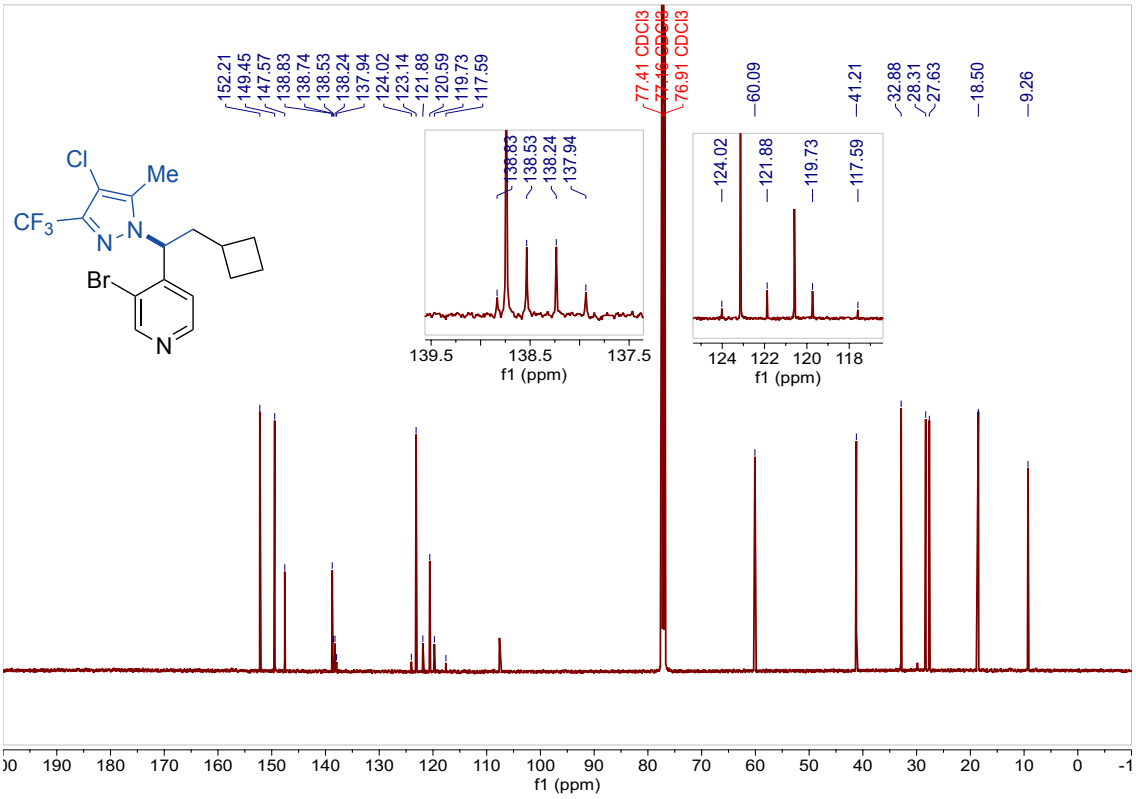
^{13}C NMR (101 MHz, $CDCl_3$) of **30-Am6**



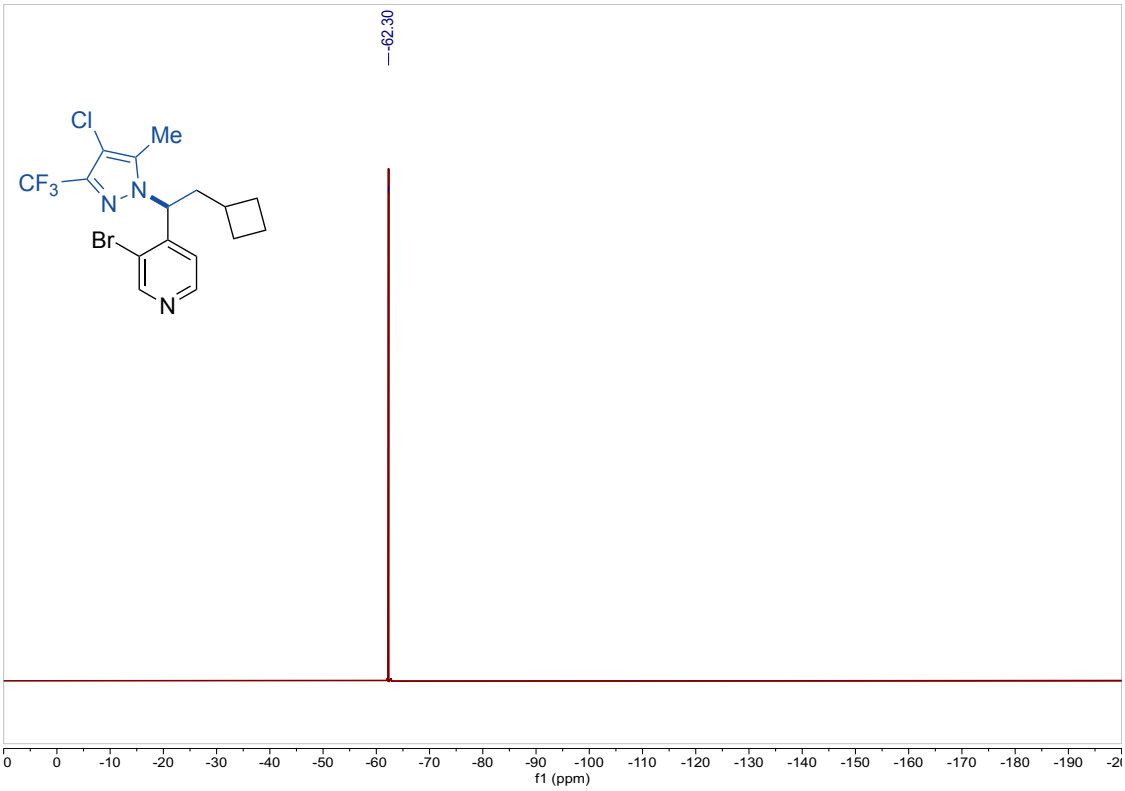
^{1}H NMR (500 MHz, $CDCl_3$) of **4-Az3**



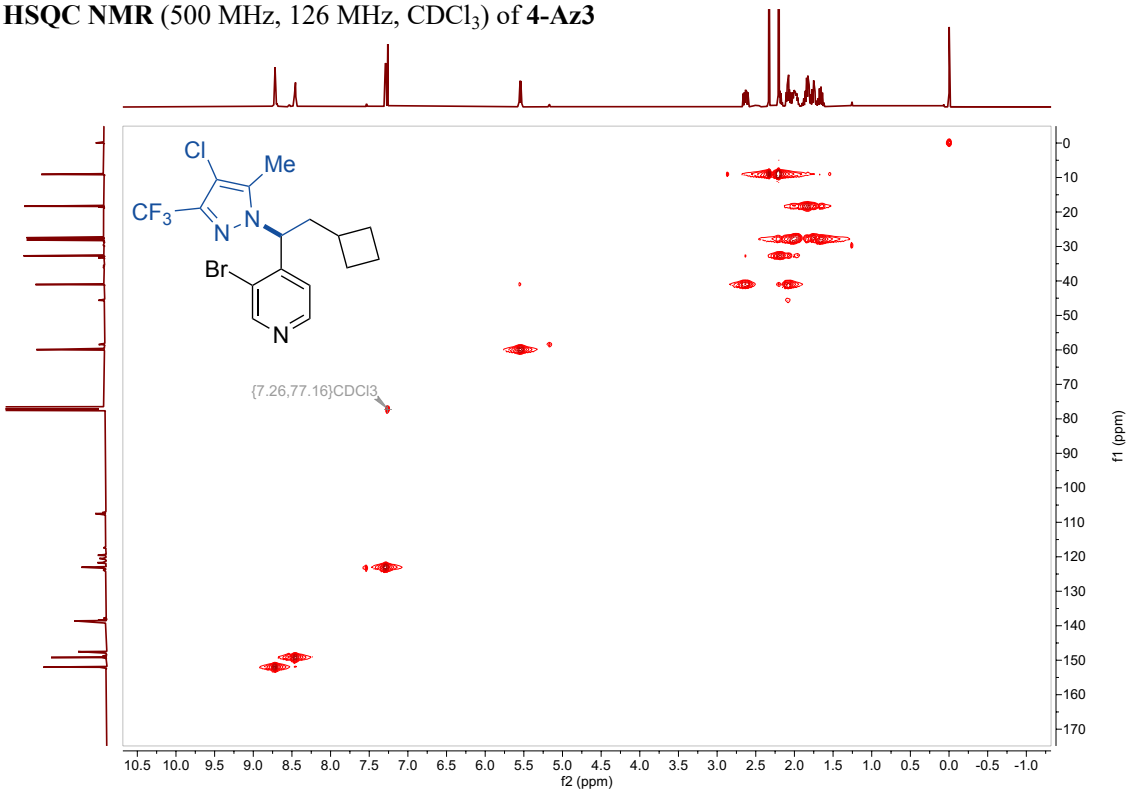
^{13}C NMR (101 MHz, $CDCl_3$) of **4-Az3**



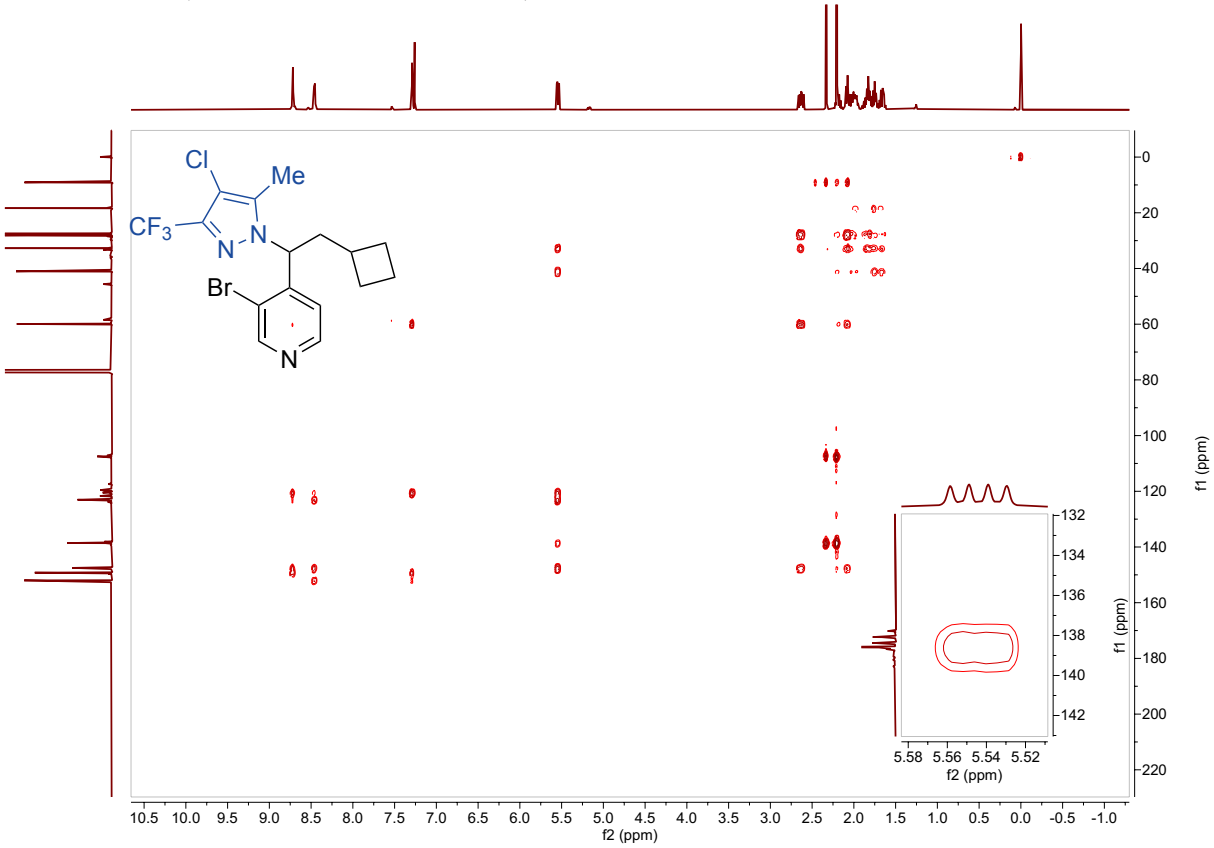
^{19}F NMR (377 MHz, $CDCl_3$) of **4-Az3**



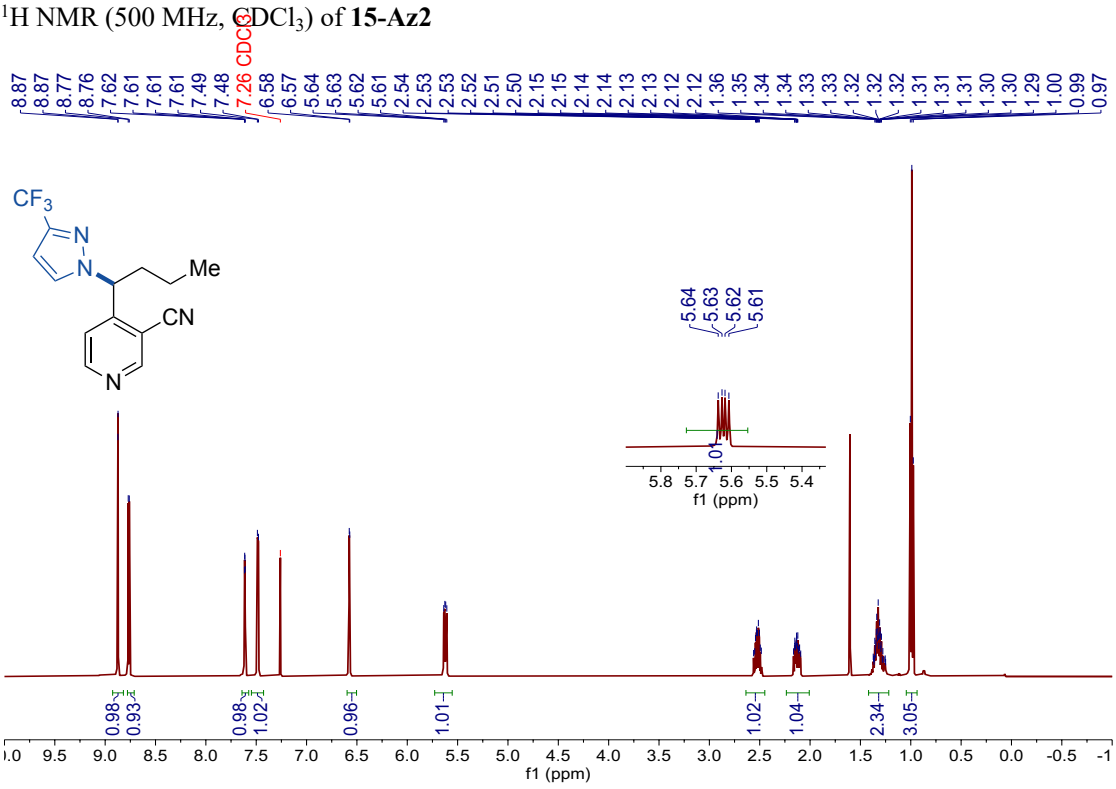
HSQC NMR (500 MHz, 126 MHz, $CDCl_3$) of **4-Az3**



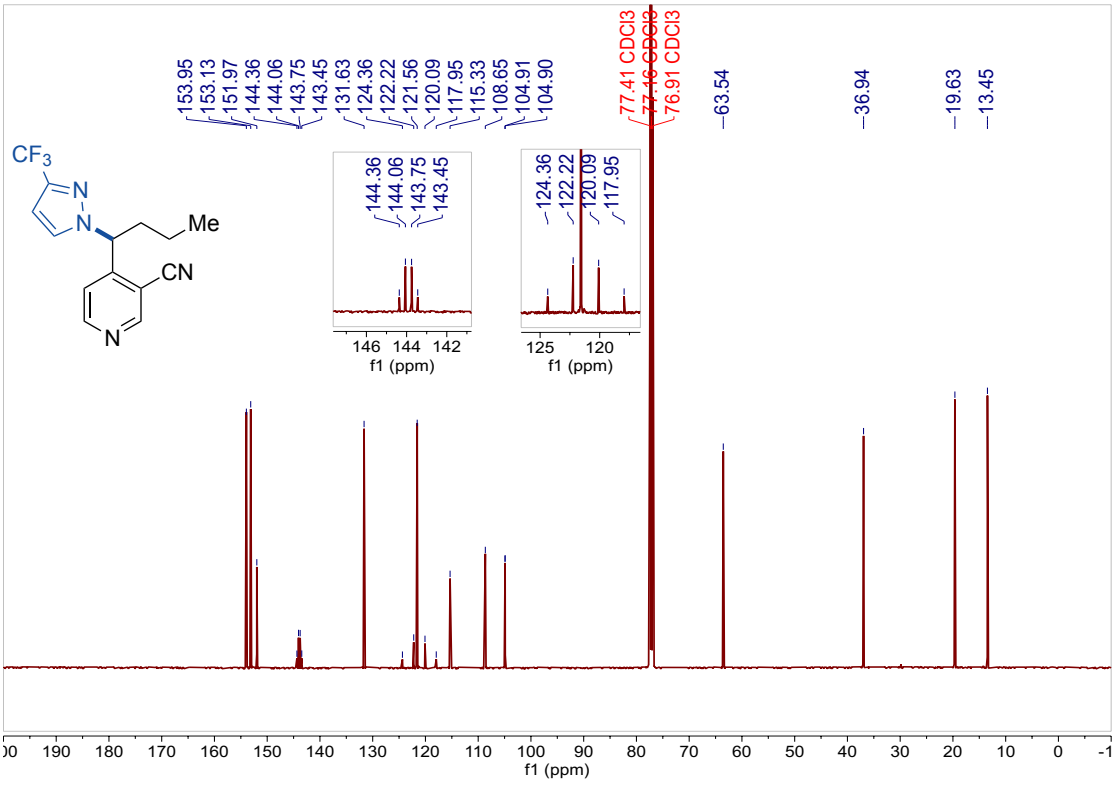
HMBC NMR (500 MHz, 126 MHz, $CDCl_3$) of **4-Az3**



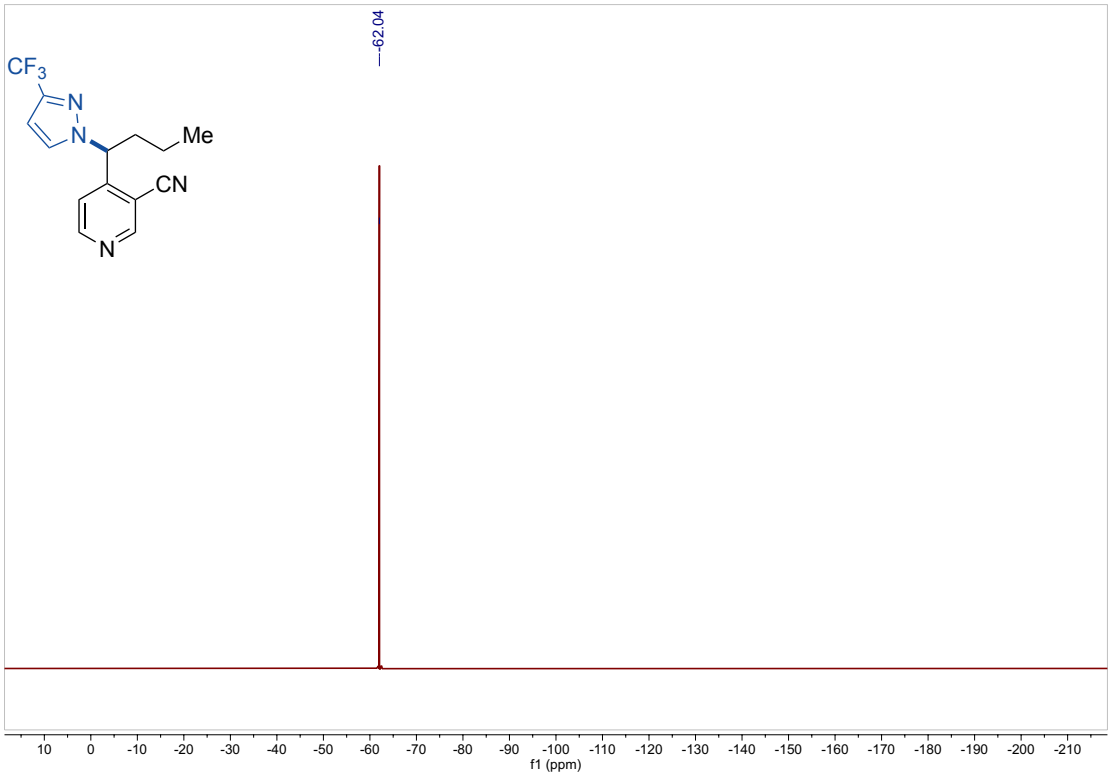
^{1}H NMR (500 MHz, $CDCl_3$) of **15-Az2**



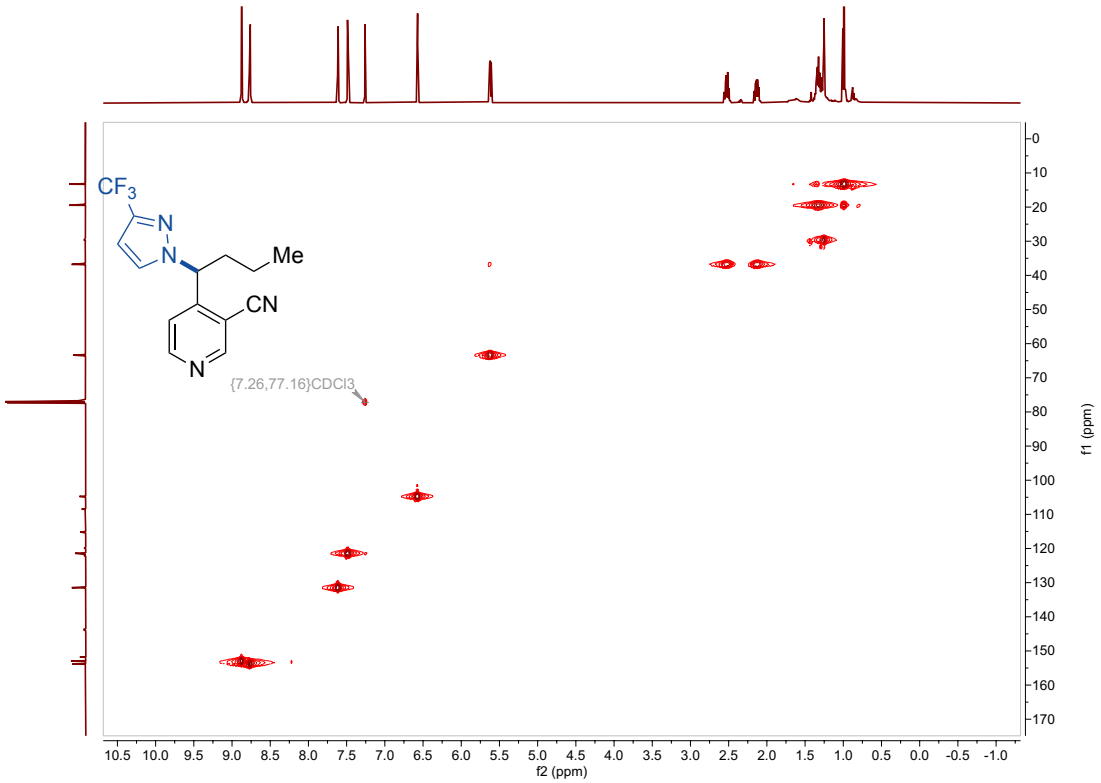
^{13}C NMR (101 MHz, $CDCl_3$) of **15-Az2**



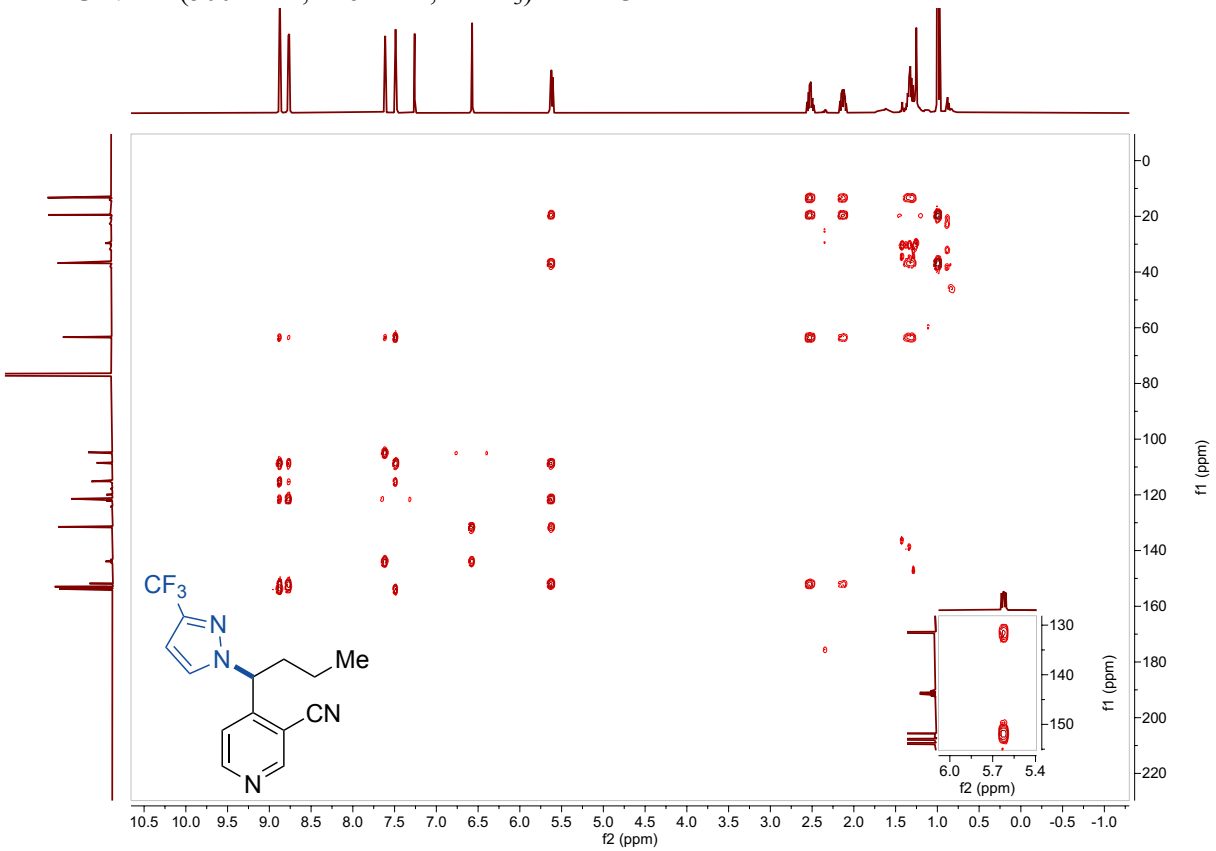
^{19}F NMR (377 MHz, $CDCl_3$) of of **15-Az2**



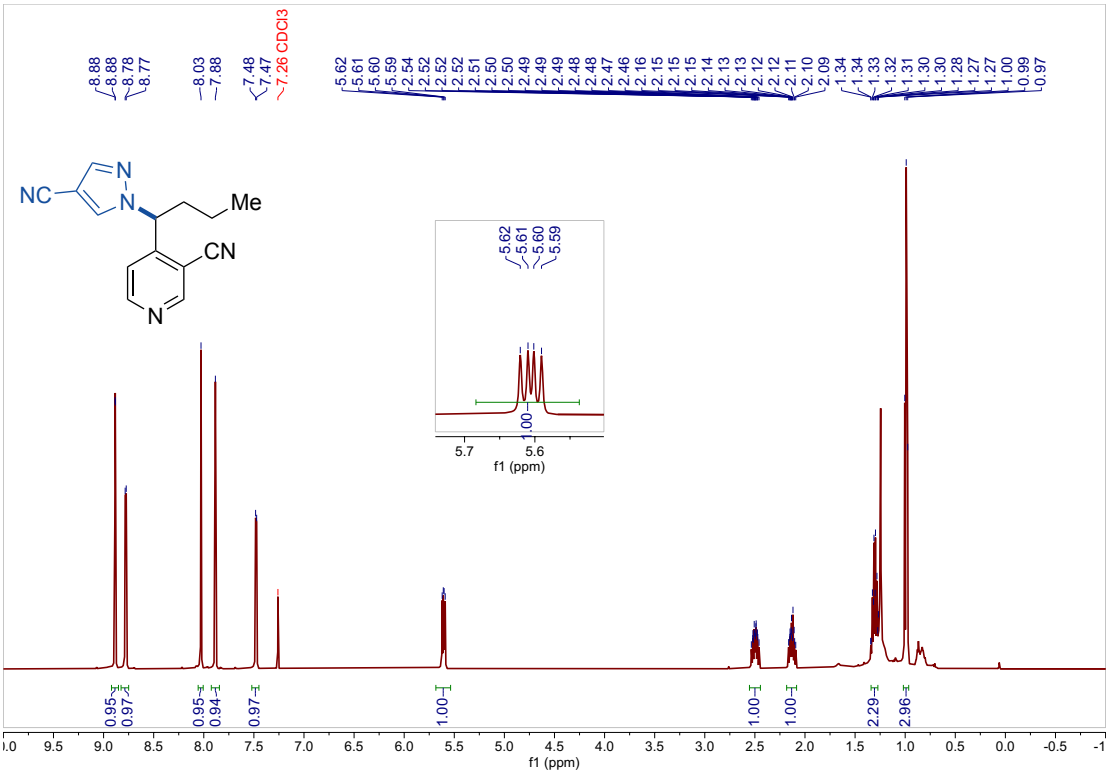
HSQC NMR (500 MHz, 126 MHz, $CDCl_3$) of **15-Az2**



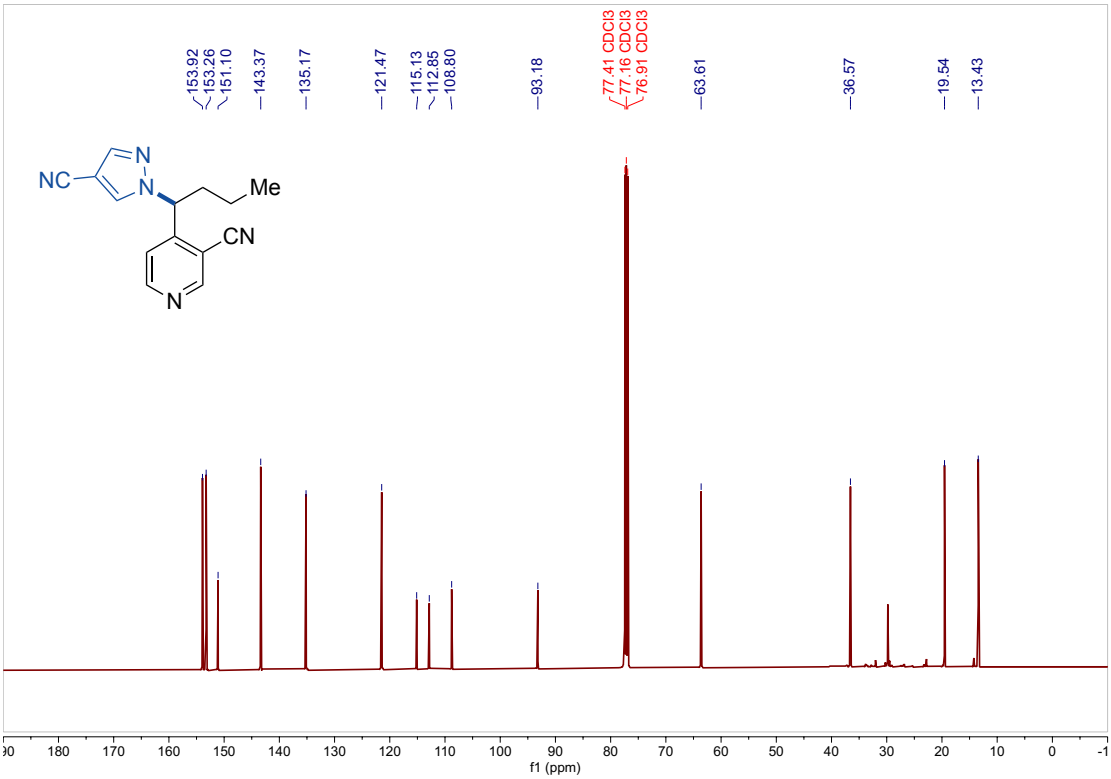
HMBC NMR (500 MHz, 126 MHz, $CDCl_3$) of of **15-Az2**



^{1}H NMR (500 MHz, $CDCl_3$) of **15-Az12**



^{13}C NMR (126 MHz, $CDCl_3$) of **15-Az12**



3B.XI. References

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Appendix C: Supporting Information Chapter 4

4C.I. General Considerations

All reagents were purchased from commercial sources and used without any further purification. Anhydrous *N*,*N*-dimethylformamide (DMF, 99.9%), 1,3-Dimethyl-2-imidazolidinone (DMI, 98%), and 1,4 Dioxane (99.8%) was purchased from Sigma-Aldrich. Solvents were opened and stored in a nitrogen-filled glovebox and used as-is. $NiBr_2$•dme and $NiCl_2$•dme were purchased from Sigma-Aldrich. 5,10,15,20-Tetraphenyl-21H,23H-porphine iron(III) chloride (Fe(TPP)Cl) and Cobalt(II) phthalocyanine (Co(Pc)) were purchased from Sigma-Aldrich or Alfa Aesar. Tetrakis(dimethylamino)ethylene, (TDAE), zinc powder (-140 + 325 mesh, 99%) and manganese powder (-140 + 325 mesh, 99.6%) were purchased from Sigma-Aldrich or Fisher Scientific and stored in the glove box. Ligands used in reaction optimizations and scope investigations were purchased from Sigma-Aldrich, Ambeed or Alfa Aesar. Heterobenzyl chlorides **16a-24a**, **26a,** and **29a** were purchased from Ambeed. Substrate **30a** was purchased from Key Organics. Preparations and characterizations of synthesized starting materials are described in 4C.II.

Proton (^{1}H), carbon (^{13}C), and fluorine (^{19}F) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz at 25 °C (^{1}H 400.1 MHz, ^{13}C 100.6 MHz, ^{19}F 376.5 MHz), Bruker 500 MHz at 25 °C (^{1}H 500.1 MHz, ^{13}C 125.7 MHz, ^{19}F 470.6 MHz), or a 600 MHz at 25 °C (^{1}H 600.1 MHz, ^{13}C 151.1 MHz). All spectrometers and chemical shifts are reported in parts per million (ppm). NMR spectra are referenced to residual solvent $CHCl_3$ at 7.26 ppm (^{1}H) and $CDCl_3$ at 77.16 ppm (^{13}C). All ^{19}F NMR spectra were absolutely referenced to their respective solvent peaks in the ^{1}H NMR spectrum. UPLC-MS analysis was conducted on a Waters-Acquity High resolution mass spectrometry spectra were obtained on a Thermo Q Exactive™ Plus by the mass spectrometry facility at the University of Wisconsin-Madison. Automatic normal phase column chromatography was performed using reusable 25g Sfär Silica HC D cartridges on a Biotage Isolera®.

4C.II. Experimental Procedures for Preparation of Compounds

Reductive Arylation of 4-Alkyl-Substituted Heterobenzyl Chlorides

General Procedure A: On the benchtop, an oven-dried 6-dram borosilicate vial was charged with benzylic chloride (1 equiv), ethyl-4-iodobenzoate (1.2 equiv), and a Teflon stir bar. $NiBr_2$•dme, and dtbbpy was weighed into a secondary 2-dram vial with a cross-shaped stir bar*. Both vials were sparged with N_2 then transferred into a purging glovebox under N_2. In the glovebox, 1,4 Dioxane was added to the vial containing $NiBr_2$•dme and dtbbpy and stirred for 10 min to from a blue-green catalyst stock solution. To the vial containing benzylic chloride, aryl iodide, and the Teflon stir bar was added $MgCl_2$ (1 equiv), the catalyst stock solution and TDAE (1.4 equiv). The reaction vial was then sealed, removed from the glovebox, and set to stir at 750 rpm on an aluminum block at the 80 ºC 24 h.

Vial 1: a disposable 6-dram vial, benzylic chloride (0.5 mmol, 1 equiv), aryl-iodide (0.6 mmol, 1.2 equiv), and a Teflon stir bar*.
Vial 2: a disposable 2-dram vial, cross-shaped stir bar, $NiBr_2$•dme (15.4. mg, 0.05 mmol), dttbpy (32.2 mg, 0.12 mmol), and 1,4-Dioxane (6.5 mL) were combined to form a blue-green 0.007 M stock solution of the Ni catalyst.
To Vial 1 was added $MgCl_2$ (48 mg, 1 equiv). Then vial 1 was slurry doesd with 3.5 mL of the Ni catalyst stock solution followed by and TDAE (163µL, 0.7 mmol, 1.4 equiv). The reaction was conducted 80 ºC.

Work Up: The crude reaction mixture was filtered through a 40 Micron disposable polyethylene frit, washed with ethyl acetate, and concentrated on the rotovap. The obtained residue was diluted with ethyl acetate, transferred to a separatory funnel, washed with $NaHCO_3$ (aq) (3x), dried over sodium sulfate, and concentrated on the rotovap. The obtained residue was purified by flash column chromatography.

Reductive Arylation of 2-Alkyl-Substituted Heterobenzyl Chlorides

General Procedure B: On the benchtop, an oven-dried 6-dram borosilicate vial was charged with benzylic chloride (1 equiv), ethyl-4-iodobenzoate (1.2 equiv), and a Teflon stir bar. $NiBr_2$•dme, Fe(TPP)Cl, and dtbbpy was weighed into a secondary 2-dram vial with a cross-shaped stir bar*. Both vials were sparged with N_2 then transferred into a purging glovebox under N_2. In the glovebox, 1,4 Dioxane was added to the vial containing $NiBr_2$•dme, Fe(TPP)Cl, and dtbbpy and stirred for 10 min to from a dark brown catalyst stock solution. To the vial containing benzylic chloride, aryl iodide, and the Teflon stir bar was added the catalyst stock solution and TDAE (1.4 equiv). The reaction vial was then sealed, removed from the glovebox, and set to stir at 750 rpm on an aluminum block at the 80 ºC 24 h.

Vial 1: a disposable 6-dram vial, benzylic substrate (0.5 mmol, 1 equiv), aryl-iodide (0.5 mmol, 1.2 equiv), and a Teflon stir bar*.

Vial 2: a disposable 2-dram vial, cross-shaped stir bar, $NiBr_2$•dme (15.4. mg, 0.05 mmol), dttbpy (13.4 mg, 0.05 mmol), Fe(TPP)Cl (3.5 mg, 5 μmol) and 1,4-Dioxane (6.5 mL) combined to form a dark brown catalyst stock solution.
Vial 1 was slurry dosed with 3.5 mL of the catalyst stock solution followed by TDAE (163μL, 0.7 mmol, 1.4 equiv). The reaction was conducted 80 ºC

Work Up: The crude reaction mixture was filtered through a 40 Micron disposable polyethylene frit, washed with ethyl acetate, and concentrated on the rotovap. The obtained residue was diluted with ethyl acetate, transferred to a separatory funnel, washed with $NaHCO_3$ (aq) (3x), dried over sodium sulfate, and concentrated on the rotovap. The obtained residue was purified by flash column chromatography.

Reductive Arylation of 3-Alkyl-Substituted Heterobenzyl Chlorides

General Procedure C: On the benchtop, an oven-dried 6-dram borosilicate vial was charged with benzylic chloride (0.5 1 equiv), ethyl-4-iodobenzoate (1.2 equiv), and a Teflon stir bar. $NiBr_2$•dme, Co(Pc), and dtbbpy was weighed into a secondary 2-dram vial with a cross-shaped stir bar*. Both vials were sparged with N_2 then transferred into a purging glovebox under N_2. In the glovebox, 1,4 Dioxane was added to the vial containing $NiBr_2$•dme, Co(Pc), and dtbbpy and stirred for 10 min to from a deep-purple stock solution. To the vial containing benzylic chloride, aryl iodide, and the Teflon stir bar was added the catalyst stock solution and tetrakis(dimethylamino)ethylene (1.4 equiv). The reaction vial was then sealed, removed from the glovebox, and set to stir at 750 rpm on an aluminum block at the specified temperature for 16 h.

Vial 1: a disposable 6-dram vial, benzylic substrate (0.5 mmol, 1 equiv), aryl-iodide (0.5 mmol, 1.2 equiv), and a Teflon stir bar.
Vial 2: a disposable 2-dram vial, cross-shaped stir bar, $NiBr_2$•dme (15.4. mg, 0.05 mmol), dttbpy (13.4 mg, 0.05 mmol), Co(Pc) (2.8 mg, 5 μmol) and 1,4-Dioxane (6.5 mL) combined to form a deep-purple catalyst stock solution.
Vial 1 was slurry dosed with 3.5 mL of the catalyst stock solution followed by TDAE (163μL, 0.7 mmol, 1.4 equiv). The reaction was conducted 80 ºC.

Work Up: The crude reaction mixture was filtered through a 40 Micron disposable polyethylene frit, washed with ethyl acetate, and concentrated on the rotovap. The obtained residue was diluted with ethyl acetate, transferred to a separatory funnel, washed with $NaHCO_3$ (aq) (3x), dried over sodium sulfate, and concentrated on the rotovap. The obtained residue was purified by flash column chromatography.

General Procedure D: On the benchtop, an oven-dried 8-mL borosilicate vial was charged with $NiCl_2$•dme (10 mol%), dttbpy (10 mol%), benzylic chloride (1 equiv), ethyl-4-iodobenzoate (1.2 equiv), and a crossed shaped Teflon stir bar. The vial was sparged with N_2 then transferred into a purging glovebox under N_2. In the glove box, the vial was charged with lithium chloride (1 equiv) and DMA (0.2 M) and allowed to stir for 10 min. Then, magnesium powder (2 equiv) was added to the vial. The reaction vial was then sealed, removed from the glovebox, and set to stir at 1000 rpm on an aluminum block at the specified temperature for 16 h.

Work Up: The crude reaction mixture was diluted with a 10% acetic acid solution in MeCN and transferred to a separatory funnel, washed with 5% LiCl (aq), $NaHCO_3$ and brine, dried over sodium sulfate, and concentrated on the rotovap. The obtained residue was purified by flash column chromatography.

Reductive Arylation of Primary 2-, 3-, and 4-Alkyl Substituted Heterobenzyl Chlorides

General Procedure E: On the benchtop, an oven-dried 24 mL borosilicate vial was charged with $NiBr_2$•dme (7.7 mg, 5 mol%), dttbpy (6.71 mg, 5 mol%), benzylic chloride (1 equiv), ethyl-4-iodobenzoate (1.2 equiv), and a Teflon stir bar. The vial was sparged with N_2 then transferred into a purging glovebox under N_2. In the glove box, the vial was charged 1,4 Dioxane (0.15 M), Barton's base (101 µL, 0.5 mmol, 1 equiv), and TDAE (163µL, 0.7 mmol, 1.4 equiv). The reaction vial was then sealed, removed from the glovebox, and set to stir at 750 rpm on an aluminum block at 80ºC for 24 h.

Work Up: The crude reaction mixture was filtered through a 40 Micron disposable polyethylene frit, washed with ethyl acetate, and concentrated on the rotovap. The obtained residue was diluted with ethyl acetate, transferred to a separatory funnel, and washed with $NaHCO_3$ (aq) (3x), dried over sodium sulfate, and concentrated on the rotovap. The obtained residue was purified by flash column chromatography.

Substrate Preparation

General Procedure F: C–H Chlorination of 4-Alkyl Substituted Pyridines
Set up: On the benchtop, a disposable 24 mL glass vial was charged with NCS (1.2 equiv), Li_2CO_3 (1.1 equiv), DMAP (10 mol%), C–H substrate (1 equiv), anhydrous acetonitrile (0.1 M), a Teflon stir bar, and trifluoromethanesulfonyl chloride (TfCl, 10 or 40 mol%). The reaction vial was then sealed and set to stir at 750 rpm on an aluminum block at the specified temperature. After 4 or 16 hours the reaction was allowed to cool, filtered through a pad of celite, concentrated on the rotovap. The obtained residue was diluted with ethyl acetate, transferred to a separatory funnel, and washed with $NaHCO_3$ (aq). The organic layer was collected, dried over Na_2SO_4, and concentrated on the rotovap. The obtained residue was purified by flash column chromatography on silica gel.

General Procedure G: C–H Chlorination of 2-Alkyl Substituted Pyridines
Set up: An oven-dried 100 mL round-bottom flask containing a magnetic stir bar was charged with 2 g of C–H Substrate (1.0 equiv 15 mmol), 40 mL of anhydrous DCM (0.3 M), and 4.2 g of trichloroisocyanuric acid (1.2 equiv, 18 mmol). The flask was fitted with a Findenser™ and refluxed under air. After 16 hours, the reaction was allowed to cool, filtered through a pad of celite, conctrated on the rotovap. The obtained residue was diluted with ethyl acetate, transferred to a separatory funnel, and washed with $NaHCO_3$ (aq). The organic layer was collected, dried over Na_2SO_4, and concentrated on the rotovap. The obtained residue was purified by flash column chromatography on silica gel.

General Procedure H: C–H Chlorination of 3-Alkyl Substituted Pyridines
On the benchtop, *N*-(*tert*-butyl)-*N*-chloro-3,5-bis(trifluoromethyl)benzenesulfonamide (7674.6 mg, 20 mmol, 4.0 equiv) and benzylic substrate (5.00 mmol, 1.0 equiv) was added to a 250-mL round bottom flask. The flask was then moved to a purging glove box under N_2 atmosphere. Cs_2CO_3 (2443.7 mg, 7.5 mmol, 1.5 equiv), α,α,α-trifluorotoluene (25 mL), and benzylic substrate (5.0 mmol, 1.0 equiv) were added to the reaction flask. The flask was sealed with a septum, secured with electrical tape in the glove box and taken out to photochemical setup. The reaction was carried out under irradiation of two blue LED lamps (~ 450 nm) with stirring for 20 hours. When the reaction finished, mesitylene (70 µL, 0.50 mmol) was added as internal standard. An aliquot (50 µL) was withdrawn and filtered through a celite plug for ^{1}H NMR analysis to detect formation of product and consumption of starting material. After ^{1}H NMR analysis, the crude reaction was filtered through a silica plug using acetonitrile, evaporated under vacuum, and purified by column chromatography.

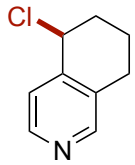
General Procedure I: $NaBH_4$ Reduction

To a solution of ketone (1.0 equiv) dissolved in ethanol (1.0 M) was added sodium borohydride (1.5 equiv) in small portions at 0 °C. The resulting mixture was allowed to stir at room temperature until complete by TLC analysis. When the starting material was consumed, the reaction was quenched with water and extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated on the rotovap. The resulting residue was used without purification.

General Procedure J: Chlorination with $SOCl_2$

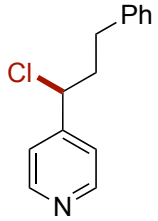
An oven-dried 25 mL round-bottom flask containing a magnetic stir bar was charged with heterobenzyl alcohol (1 equiv) and anhydrous dichloromethane (2.0 M). The flask was capped with a septum, and placed under a positive pressure of nitrogen, and cooled 0 ºC. Thionyl chloride (2 equiv) was added dropwise over a span of 15 min and stirred. After 10 min, the reaction was allowed to warm to room temperature and stirred for an addition 2 hours. The reaction was quenched with water and washed with diethyl ether. The aqueous layer was neutralized with solid $NaHCO_3$, then extracted with 25 mL of diethyl ether (2x). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The obtained residue was purified by column chromatography on silica gel.

(1a) 5-chloro-5,6,7,8-tetrahydroisoquinoline



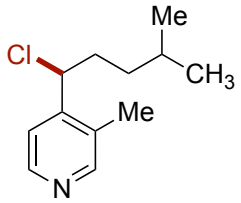
Reaction conducted following **Procedure F** using 5,6,7,8-tetrahydroisoquinoline (133.1 mg, 1.0 mmol, 1 equiv), and 10 mol% TfCl, at 70 ºC for 16 h. Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (70:30 (v:v)) to afford mg 119 mg (71% yield) of **1a** as a yellow oil.
NMR Spectroscopy:
^{1}H-NMR 400 MHz, CDCl3) δ 8.39 – 8.32 (m, 2H), 7.23 (d, J = 5.1 Hz, 1H), 5.10 (t, J = 4.6 Hz, 1H), 2.83 – 2.66 (m, 2H), 2.23 – 2.15 (m, 2H), 2.12 – 2.03 (m, 1H).
^{13}C NMR (101 MHz, CDCl3) δ 150.92, 147.23, 144.85, 132.05, 124.14, 77.55, 76.91, 55.78, 32.58, 25.83, 18.51.

(4a) 4-(1-chloro-3-phenylpropyl)pyridine



Reaction conducted following **Procedure F** using 4-(3-phenylpropyl)pyridine (197.2 mg, 1.0 mmol, 1 equiv), and 40 mol% TfCl, at 70 ºC for 4 h. Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (70:30 (v:v)) to afford mg 83 mg (36% yield) of **4a** as a yellow oil.
NMR Spectroscopy:
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.84 – 8.62 (m, 2H), 7.37 – 7.30 (m, 4H), 7.27 – 7.15 (m, 3H), 4.76 (dd, *J* = 8.8, 5.3 Hz, 1H), 2.96 – 2.66 (m, 2H), 2.41 (dtd, *J* = 14.3, 8.7, 5.6 Hz, 1H), 2.31 (dddd, *J* = 14.2, 8.7, 7.1, 5.4 Hz, 1H).
^{13}C-NMR (126 MHz, $CDCl_3$) δ 150.3, 140.2, 128.8, 128.6, 126.6, 122.0, 60.7, 41.1, 32.8.

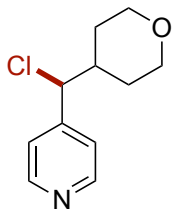
(5a) 3-methyl-4-(4-methylpentyl)pyridine



Reaction conducted following **Procedure F** using 3-methyl-4-(4-methylpentyl)pyridine (177.3 mg, 1.0 mmol, 1 equiv), 10 mol% TfCl, at 70 ºC for 4 h. Deviation from Procedure F is the exclusion of DMAP. Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (70:30 (v:v)) to afford mg 182 mg (86% yield) of **5a** as a yellow oil.

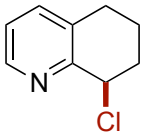
NMR Spectroscopy:
^{1}H-NMR ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, *J* = 5.2 Hz, 1H), 8.41 (s, 1H), 7.37 (d, *J* = 5.2 Hz, 1H), 4.98 (dd, *J* = 8.3, 6.0 Hz, 1H), 2.36 (s, 3H), 2.12 – 2.05 (m, 1H), 2.03 – 1.95 (m, 1H), 1.58 (dt, *J* = 13.3, 6.6 Hz, 1H), 1.42 (dddd, *J* = 13.4, 10.9, 6.9, 4.9 Hz, 1H), 1.23 – 1.12 (m, 1H), 0.89 (dd, *J* = 6.6, 1.4 Hz, 6H).
^{13}C-NMR ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.5, 148.5, 148.4, 130.2, 120.9, 36.4, 36.1, 27.9, 22.7, 22.5, 16.1.

(6a) 4-(chloro(tetrahydro-2*H*-pyran-4-yl)methyl)pyridine
Reaction conducted following **Procedure F** using 34-((tetrahydro-2*H*-pyran-4-yl)methyl)pyridine (177.1 mg, 1.0 mmol, 1 equiv), 40 mol% TfCl, at 90 ºC for 4 h. Deviation from Procedure F is the exclusion of DMAP. Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (70:30 (v:v)) to afford 112.2 mg (52% yield) of **6a** as a clear oil.



4-((tetrahydro-2*H*-pyran-4-yl)methyl)pyridine
NMR Spectroscopy:
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.99 – 8.31 (m, 2H), 7.26 (dd, *J* = 4.3, 1.8 Hz, 2H), 4.53 (d, *J* = 8.2 Hz, 1H), 4.08 – 4.00 (m, 1H), 3.92 (ddd, *J* = 12.5, 4.9, 1.7 Hz, 1H), 3.39 (dd, *J* = 12.0, 2.2 Hz, 1H), 3.34 – 3.20 (m, 1H), 2.19 – 1.90 (m, 2H), 1.60 – 0.97 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ 150.3, 122.6, 67.7, 67.3, 66.6, 43.0, 30.5, 30.1.

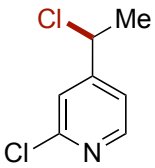
(2a) 8-chloro-5,6,7,8-tetrahydroquinoline



Reaction conducted following **Procedure G** using 5,6,7,8-tetrahydroquinoline (2 g, 15 mmol, 1 equiv). Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:pentane (30:70 (v:v)) to afford 2.1 g (83% yield) of **2a**. Spectral data matched those reported in the literature.
NMR Spectroscopy:
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.54 – 8.45 (m, 1H), 7.43 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.14 (dd, *J* = 7.8, 4.6 Hz, 1H), 5.30 (t, *J* = 3.5 Hz, 1H), 2.94 – 2.84 (m, 2H), 2.84 – 2.69 (m, 1H), 2.40 (dddd, *J* = 11.5, 4.7, 3.1, 1.3 Hz, 1H), 2.31 – 2.17 (m, 3H), 1.90 (m, 1H).
^{13}C-NMR (126 MHz, $CDCl_3$) δ 154.7, 148.0, 137.7, 132.3, 123.4, 59.1, 32.6, 28.2, 17.6.

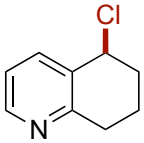
(9a) 7-chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine

(8a) 2-chloro-4-(1-chloroethyl)pyridine



Reaction conducted following **Procedure I** using 1-(2-chloropyridin-4-yl)ethan-1-one (1 g, 7.1 mmol, 1 equiv) and **Procedure J**. Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:pentane (20:80 (v:v)) to afford 81 mg (72% yield) of the of corresponding chloride.
Yield of benzyl alcohol: quantitative (1.0 g)
Yield of benzyl chloride: 72% (81 mg)
NMR Spectroscopy:
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.48 – 8.35 (m, 1H), 7.38 (s, 1H), 7.27 (s, 1H), 4.97 (q, *J* = 6.7 Hz, 1H), 1.82 (d, *J* = 6.7 Hz, 3H).
^{13}C-NMR ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 152.2, 150.5, 122.2, 120.4, 55.7, 26.2.
HRMS (ESI) m/z:

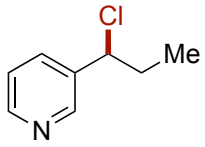
(3a) 5-chloro-5,6,7,8-tetrahydroquinoline



Reaction conducted following **Procedure I** using 17,8-dihydroquinolin-5(6*H*)-one (1 g, 7.5 mmol, 1 equiv) and **Procedure J**. Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:pentane (60:40 (v:v)) to afford 83 mg (58% yield) of the of corresponding chloride.
Yield of benzyl alcohol: 85% (126 mg)
Yield of benzyl chloride: 58% (83 mg)

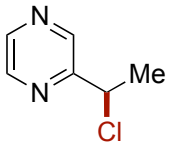
NMR Spectroscopy of chloride:
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.44 – 8.39 (m, 2H), 7.30 (d, *J* = 5.2 Hz, 1H), 5.16 (t, *J* = 4.6 Hz, 1H), 2.91 (dt, *J* = 17.0, 5.2 Hz, 1H), 2.76 (ddd, *J* = 16.8, 9.3, 6.0 Hz, 2H), 2.34 – 2.22 (m, 2H), 2.22 – 2.10 (m, 1H), 1.96 – 1.87 (m, 1H).
^{13}C-NMR (126 MHz, $CDCl_3$) δ 151.1, 147.5, 144.7, 132.0, 124.1, 55.8, 32.6, 25.9, 18.6.

(12a) 3-(1-chloropropyl)pyridine



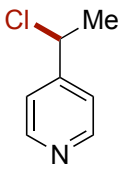
Reaction conducted following **Procedure I** using 1-(pyridin-3-yl)propan-1-one (1 g, 8.3 mmol, 1 equiv) and **Procedure J**. Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:pentane (60:40 (v:v)) to afford 92 mg (62% yield) of the of corresponding chloride.
Yield of benzyl alcohol: 95% (130) mg
Yield of benzyl chloride: 62% (92 mg)
NMR Spectroscopy:
^{1}H-NMR 400 MHz, $CDCl_3$) δ 8.66 – 8.50 (m, 2H), 7.74 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.35 – 7.28 (m, 1H), 4.80 (dd, *J* = 8.0, 6.4 Hz, 1H), 2.24 – 1.93 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ 149.7, 148.6, 134.6, 123.7, 62.5, 33.2, 11.7.

(13a) 2-(1-chloroethyl)pyrazine



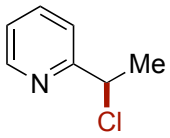
Reaction conducted following **Procedure I** using 1-(pyrazin-2-yl)ethan-1-one (1 g, 8.2 mmol, 1 equiv) and **Procedure J**. Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:pentane (40:60 (v:v)) to afford 81 mg (63% yield) of the of **13a**. Spectral data matched those reported in the literature.[1]
Yield of benzyl alcohol: 90% (112 mg)
Yield of benzyl chloride: 63% (81 mg)

(7a) 4-(1-chloroethyl)pyridine



Reaction conducted following **Procedure J** using 1-(pyridin-4-yl)ethan-1-ol (1 g, 8.1 mmol, 1 equiv) Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (70:30 (v:v)) to afford 118 mg (83% yield) of **7a** as a yellow oil.
NMR Spectroscopy of chloride:
^{1}H-NMR ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 6.2 Hz, 2H), 7.33 (d, *J* = 6.2 Hz, 2H), 5.00 (q, *J* = 6.9 Hz, 1H), 1.82 (d, *J* = 6.9 Hz, 3H).
^{13}C-NMR (126 MHz, $CDCl_3$) δ 151.3, 150.2, 121.3, 56.4, 26.1.

(10a) 2-(1-chloroethyl)pyridine



Reaction conducted following **Procedure J** using 1-(pyridin-2-yl)ethan-1-ol (1 g, 8.1 mmol, 1 equiv), 10 mol% TfCl, at 70 ºC for 4 h. Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (30:70 (v:v)) to afford 120 mg (85% yield) of **10a** as a yellow oil.
NMR Spectroscopy of chloride:
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.59 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.73 (td, *J* = 7.7, 1.8 Hz, 1H), 7.51 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.24 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 5.17 (q, *J* = 6.9 Hz, 1H), 1.90 (d, *J* = 6.8 Hz, 3H).
^{13}C-NMR (126 MHz, $CDCl_3$) δ 161.00, 149.24, 137.20, 123.12, 121.32, 59.06, 25.09.

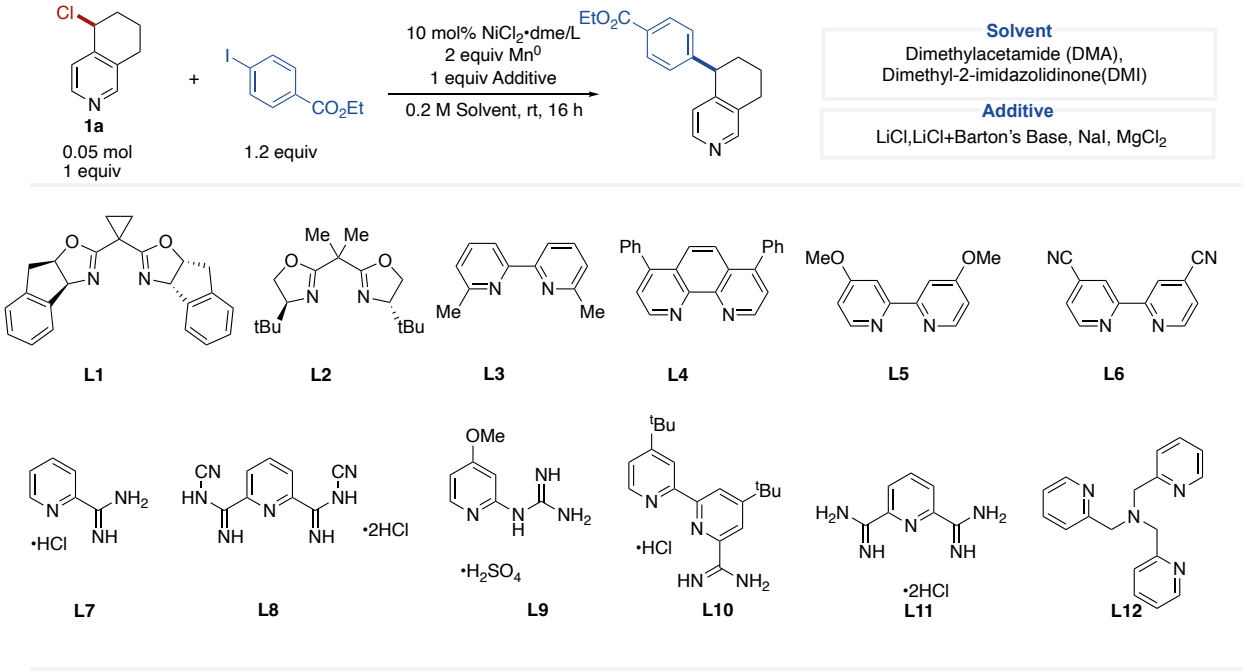
4C.III. Optimization of Reaction Conditions

General Procedure for Optimization of Reaction Parameters (0.1 mmol).
On the benchtop, an oven-dried 1-dram borosilicate vial was charged with benzylic chloride (1 equiv), ethyl-4-iodobenzoate (1.2 equiv), and a Teflon stir bar. Ni pre-catalyst and appropriate ligand was weighed into a secondary 2-dram vial with a cross-shaped stir bar*. Both vials were sparged with N_2 then transferred into a purging glovebox under N_2. In the glovebox, solvent was added to the vial containing Ni and ligand and stirred for 10 min to from a stock solution. To the vial containing benzylic chloride, aryl halide, and the Teflon stir bar was added salt additive, the catalyst stock solution and reductant. The reaction vial was then sealed, removed from the glovebox, and set to stir at 750 rpm on an aluminum block at at the 80 ºC 24 h.
Work Up: After 24 h, an aliquot of the reaction was filtered into an HPLC collection block (Analytical Sales and Services) HPLC collection block. The block was diluted with MeCN (0.001 M) and then analyzed utilizing UPLC-MS (Waters-Acquity) analysis. Yields were determined as percent of product relative to all known species derived from the benzyl chloride or calibrated UPLC-MS yield.

Optimization of heterobenzylic chloride reductive arylation (HTE Optimization)

On the bench top, to individual 2-dram vials fitted with cross-shaped stir bars was added Ni catalyst, appropriate nitrogen-donor ligand, benzylic chloride, and aryl iodide. These vials were then transferred into a nitrogen-filled glove box and solvent was added. In the glove box, separate 2-drams vial fitted with a cross-shaped stir bar was added appropriate salt additive, reductant, and solvent. These stock solutions were stirred for 15 min. To a 96-well optimization block (Analytical Sales and Services) with 1-mL glass vial inserts (Analytical Sales and Services) fitted with stainless-steel stir bars (V&P scientific) in a nitrogen- filled glove box, was dispensed appropriate quantities of the stock solutions in the following order: benzyl chloride, aryl iodide, Ni pre-catalyst, ligand, additive, and reductant (concentrations of stock solutions were adjusted so that around 20 µL of each stock solution was dispensed).The plate was then sealed with a screwdriver and placed in a zip lock bag inside the glove box. The plate was then removed from the glove box and agitated on a tumble stirrer (V&P Scientific) at room temperature ºC for 16 hours. A a 2µL aliquot was filtered and taken into an HPLC collection block (Analytical Sales and Services) and diluted to 0.001 M. and then analyzed utilizing UPLC-MS (Waters-Acquity) analysis. Yields were determined as percent of product relative to all known species derived from the benzyl chloride. Data was then visualized on Tableu®.

Table 4C.1. HTE evaluation of nitrogen-donor ligands, additives, and solvents for reductive coupling of 5-chloro-5,6,7,8-tetrahydroisoquinoline (**1a**) and 4-iodoethylbenzoate[a]



Solvent	Additive	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12
		Ligand											
DMA	LiCl	22	0	11	0	0	0	0	0	0	0	0	0
	LiCl+BB	16	0	6	0	0	0	0	0	0	0	0	0
	MgCl2	8	4	8	4	5	0	0	0	4	0	0	0
	NaI	0	0	0	0	0	0	0	0	0	0	0	0
DMI	LiCl	23	0	8	0	0	0	0	0	0	0	0	0
	LiCl+BB	11	0	5	0	0	0	0	0	0	0	0	0
	MgCl2	0	0	9	8	0	0	0	0	5	0	0	0
	NaI	0	0	0	0	0	0	0	0	0	0	0	0

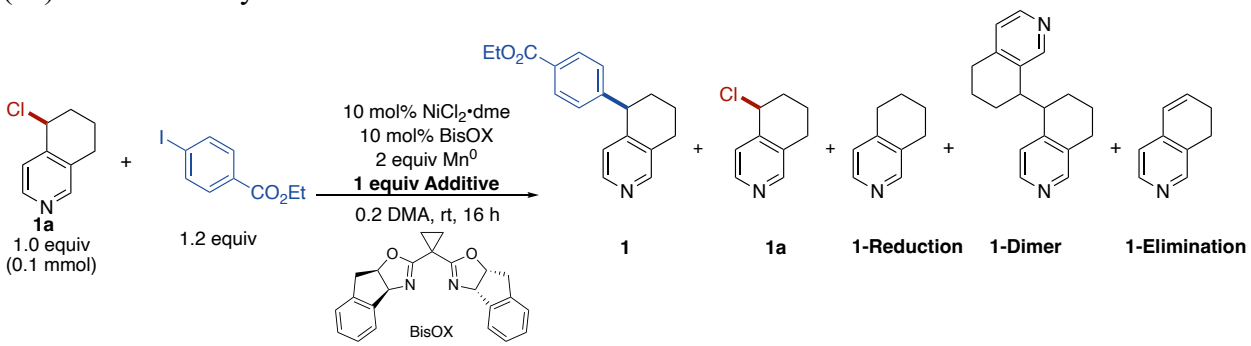
Sum of Conversion
25.09
40.00
60.00
80.00
100.00

Sum of Calibrated yield
0
100

[a]Reactions were run on a 0.03 mmol scale. Values are reported as area percent of product relative to all known species derived from **1a** as determined by UV-Visible spectroscopy.

Discussion: The results reported in **Table 4C.1** shows the reductive coupling reaction outcome when employing different ligand, additives, and solvents. LiCl, bisoxazoline ligand (**L1**), and DMA were selected for initial optimization studies as it afforded the highest yields of the desired product **1**. Benzyl chloride reduction and dimerization, and unreacted aryl iodide accounted for the remaining mass balance.

Table 4C.2. Additive screening for reductive coupling of 5-chloro-5,6,7,8-tetrahydroisoquinoline (**1a**) and 4-iodoethylbenzoate[a]

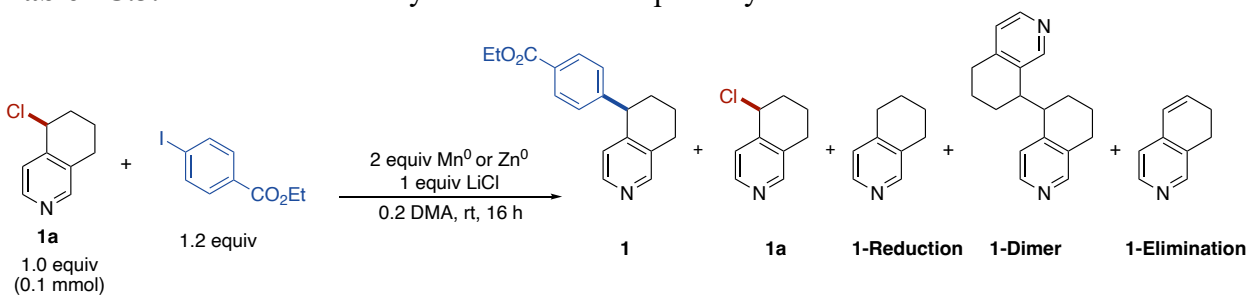


Additive	1	1a	1-Reduction	1-Dimer	1-Elimination
TBACl	8	0	52	40	0
KCl	12	0	35	53	0
LiBr	15	0	60	25	0
TBABr	7	0	42	51	0
KBr	16	0	49	35	0
TBAI	3	0	53	44	0

[a]Reactions were run on a 0.1 mmol scale. Values are reported as area percent of product relative to all known species derived from **1a** as determined by UV-Visible spectroscopy.

Discussion: The results reported in **Table 4C.2**. demonstrate the reductive coupling reaction outcome when employing different additives. However, no significant improvements in reactivity were observed when compared to results in **Table 4C.1.**

Table 4C.3. Evaluation of benzyl chloride consumption by Zn^0 and Mn^0 .[a]

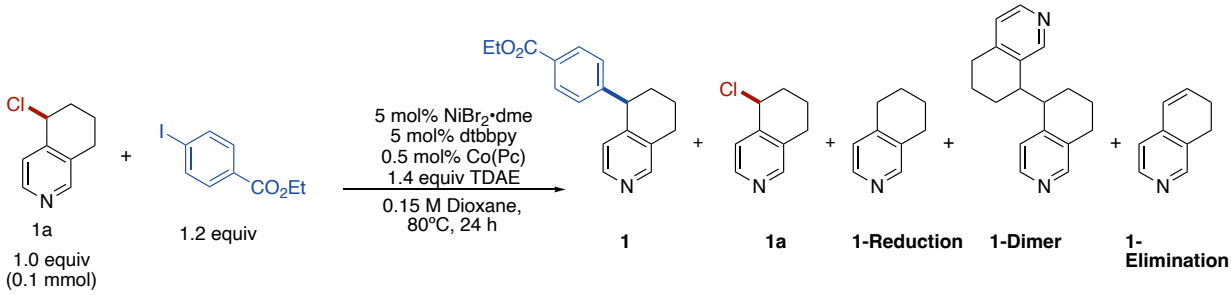


Reductant	1	1a	1-Reduction	1-Dimer	1-Elimination
Zn	0	0	34	37	0
Mn	0	70	30	0	0

[a]Reactions were run on a 0.1 mmol scale. Values are reported as area percent of product relative to all known species derived from **1a** as determined by UV-Visible spectroscopy.

Discussion: The results reported in **Table 4C.3** shows that Zn^0 and Mn^0 can contribute to the consumption of **1a**.

Table 4C.4. Evaluation of C(sp^2)–C(sp^3) reductive coupling strategies using TDAE as the reductant [a]

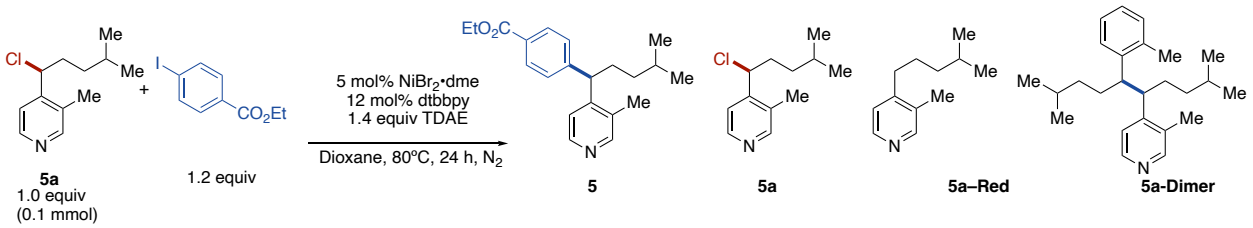


Modification	1	1a	1-Reduction	1-Dimer	1-Elimination
None	18	0	58	24	0
No Co(Pc)	8	0	52	40	0

Table 4C.4 Reactions were run on a 0.03 mmol scale. Values are reported as area percent of product relative to all known species derived from **1a** as determined by UV-Visible spectroscopy

Discussion: The results reported in **4C.4.** shows under established literature protocols reported by the groups of Weix[2] and Hazari,[3] no significant improvements in reaction outcome for the coupling of 1a and 4-iodode ethyl benzoate were observed.

Table 4C.5. Modification of reaction conditions with substrate **5a**[a]

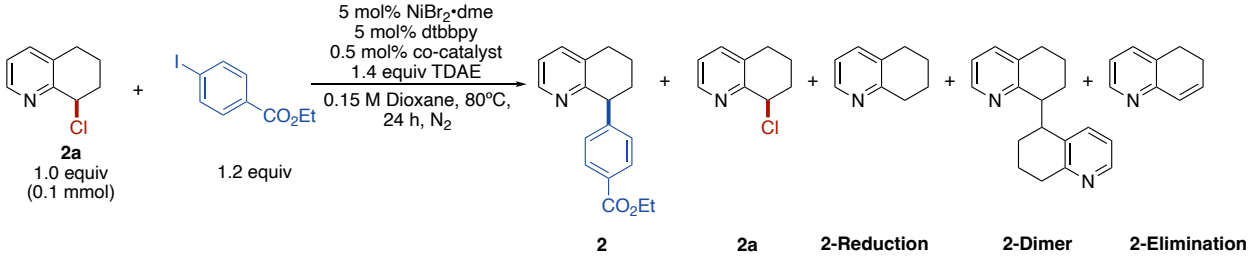


Modification	5	5a	5a-Reduction	5a-Dimer	5a-Elimination
None	17	0	33	50	0
6 mol% dttbppy and 6 mol% BIOX	8	0	0	60	0
1 equiv MgCl2	70	0	16	14	0
0.5 mol% Fe(TPP)Cl	9	0	60	31	0
1 equiv $LiCl_2$	10	0	32	58	0
5 mol% $NiCl_2$•dme	22	0	30	48	0

[a]Reactions were run on a 0.1 mmol scale. Values are reported as area percent of product relative to all known species derived from **5a** as determined by UV-Visible spectroscopy.

Discussion: The results reported in **Table 4C.5** shows the effect of modifying the reaction conditions by on the coupling of **5a** with 4-iodoethylbenzoate. $MgCl_2$ contributes to the best outcome in this experiment.

Table 4C.6. Evaluation of co-catalyst reductive coupling of 8-chloro-5,6,7,8-tetrahydroquinoline (**2a**) and 4-iodoethylbenzoate.[a]

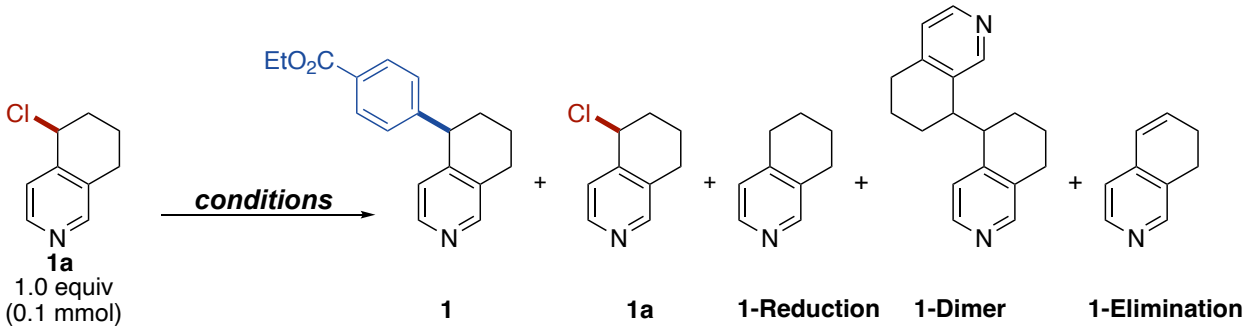


Entry	**Co-Catalyst**	**2**	**2a**	**2-red**	**2-dimer**	**2-elim**
1	None	25	86	2	0	0
2	0.5 mol% Co(Pc)	68	0	20	12	0
3	0.5 mol% Fe(TPP)Cl	85	0	6	9	0

[a]Reactions were run on a 0.1 mmol scale. Values are reported as area percent of product relative to all known species derived from **1a** as determined by UV-Visible spectroscopy.

Discussion: The results reported in **Table 4C.6** shows the outcome when different co-catalysts are added to the reductive coupling reaction of **2a** and 4-iodoethylbenzoate. Fe(TPP)Cl was selected for this class of substrate as it led to higher product yield with less alkyl chloride side product formation.

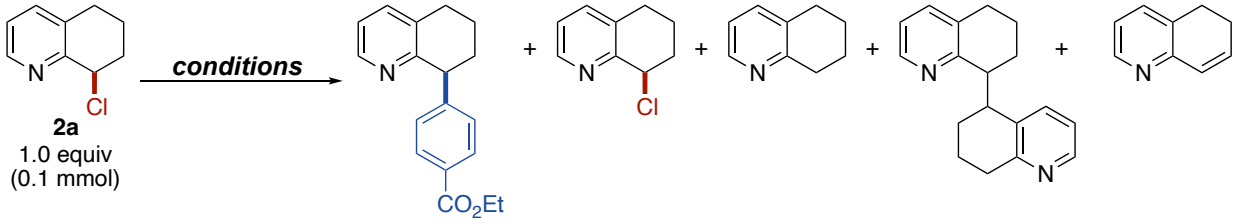
Table 4C.7. Evaluation of reductive coupling of 5-chloro-5,6,7,8-tetrahydroquinoline (**1a**) and 4-iodoethylbenzoate under several reaction conditions.[a]



Conditions a-h	1	1a	1-Reduction	1-Dimer	1-Elimination
a. 10% $NiCl_2$•dme/BisOX 1 equiv LiCl, 2 equiv Mn^0, DMA, rt, 16 h, N_2	20	0	63	17	0
b. 5% $NiBr_2$•dme/dtbbpy 0.5 mol% Co(Pc) 1,4-Dioxane, 80ºC, 24 h, N_2	16	0	25	20	38
c. 5% $NiBr_2$•dme/dtbbpy 0.5 mol% Fe(TPP)Cl 1,4-Dioxane, 80ºC, 24 h, N_2	44	0	27	29	0
d. 5% $NiBr_2$•dme/dtbbpy 1 equiv $MgCl_2$ 1,4-Dioxane, 80ºC, 24 h, N_2	67	0	24	9	0

[a]Reactions were run on a 0.1 mmol scale. Values are reported as area percent of product relative to all known species derived from **1a** as determined by UV-Visible spectroscopy.

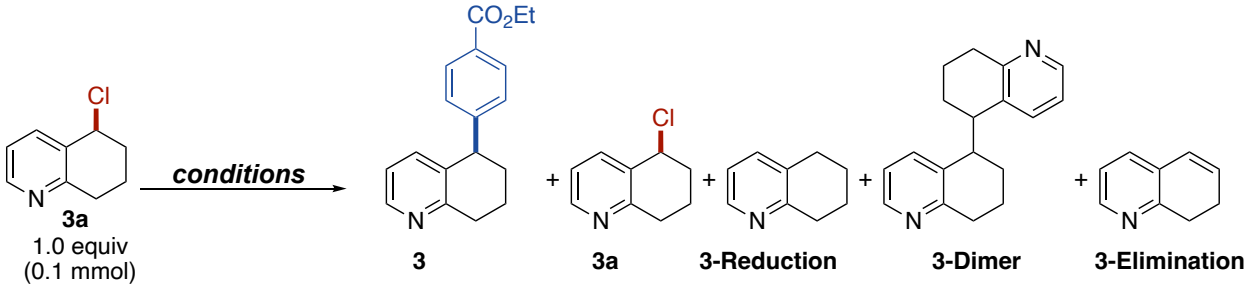
Table 4C.8. Evaluation of reductive coupling of 8-chloro-5,6,7,8-tetrahydroquinoline (**2a**) and 4-iodoethylbenzoate under several reaction conditions.[a]



Conditions a-d	2	2a	1-Reduction	1-Dimer	1-Elimination
a. 10% $NiCl_2$•dme/BisOX 1 equiv LiCl, 2 equiv Mn^0 , DMA, rt, 16 h, N_2	23	11	51	15	0
b. 5% $NiBr_2$•dme/dtbbpy 0.5 mol% Co(Pc) 1,4-Dioxane, 80ºC, 24 h, N_2	67	0	24	8	0
c. 5% $NiBr_2$•dme/dtbbpy 0.5 mol% Fe(TPP)Cl 1,4-Dioxane, 80ºC, 24 h, N_2	83	0	5	11	0
d. 5% $NiBr_2$•dme/dtbbpy 1 equiv $MgCl_2$ 1,4-Dioxane, 80ºC, 24 h, N_2	72	10	13	5	0

[a]Reactions were run on a 0.1 mmol scale. Values are reported as area percent of product relative to all known species derived from **2a** as determined by UV-Visible spectroscopy.

Table 4C.9. Evaluation of reductive coupling of 8-chloro-5,6,7,8-tetrahydroquinoline (**2a**) and 4-iodoethylbenzoate under several reaction conditions.[a]



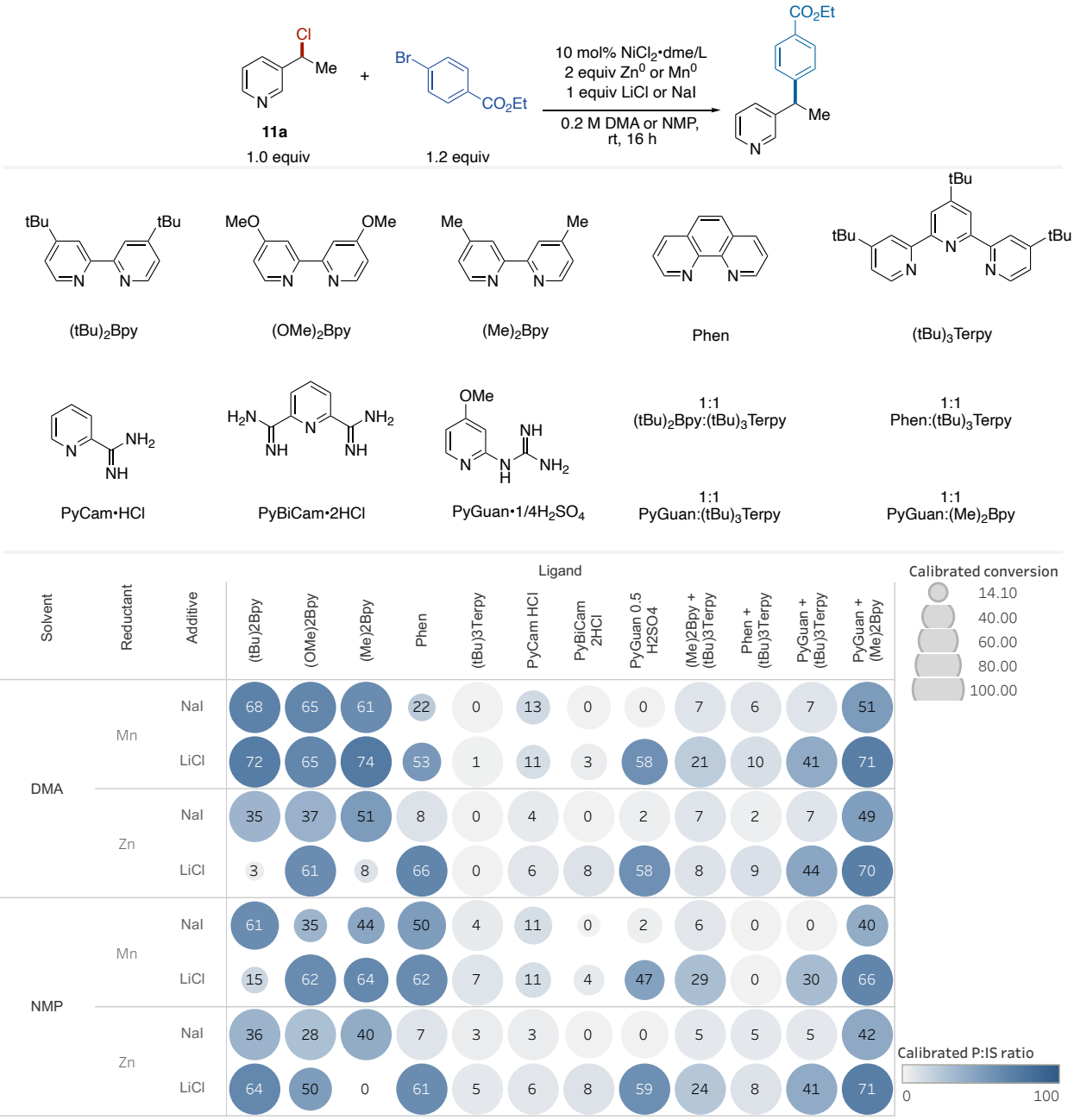
Conditions a-h	3	3a	3-Reduction	3-Dimer	3-Elimination
a. 10% $NiCl_2$•dme/BisOX 1 equiv LiCl, 2 equiv Mn^0, DMA, rt, 16 h, N_2	5	0	27	68	0
b. 5% $NiBr_2$•dme/dtbbpy 0.5 mol% Co(Pc) 1,4-Dioxane, 80ºC, 24 h, N_2	18	0	12	52	18
c. 5% $NiBr_2$•dme/dtbbpy 0.5 mol% Fe(TPP)Cl 1,4-Dioxane, 80ºC, 24 h, N_2	25	0	14	61	0
d. 5% $NiBr_2$•dme/dtbbpy 1 equiv $MgCl_2$ 1,4-Dioxane, 80ºC, 24 h, N_2	35	0	13	52	0

[a]Reactions were run on a 0.1 mmol scale. Values are reported as area percent of product relative to all known species derived from **3a** as determined by UV-Visible spectroscopy.

Table S1. Evaluation of reductive coupling on primary heterobenzyl chlorides

4C.IV. Additional Experiments and Observation

Table 4C.10. HTE evaluation of nitrogen-donor ligands, additives, and solvents for reductive coupling of 3-(1-chloroethyl)pyridine and 4-bromoethylbenzoate.[a]



Solvent	Reductant	Additive	(tBu)2Bpy	(OMe)2Bpy	(Me)2Bpy	Phen	(tBu)3Terpy	PyCam HCl	PyBiCam 2HCl	PyGuan 0.5 H2SO4	(Me)2Bpy + (tBu)3Terpy	Phen + (tBu)3Terpy	PyGuan + (tBu)3Terpy	PyGuan + (Me)2Bpy
DMA	Mn	NaI	68	65	61	22	0	13	0	0	7	6	7	51
		LiCl	72	65	74	53	1	11	3	58	21	10	41	71
	Zn	NaI	35	37	51	8	0	4	0	2	7	2	7	49
		LiCl	3	61	8	66	0	6	8	58	8	9	44	70
NMP	Mn	NaI	61	35	44	50	4	11	0	2	6	0	0	40
		LiCl	15	62	64	62	7	11	4	47	29	0	30	66
	Zn	NaI	36	28	40	7	3	3	0	0	5	5	5	42
		LiCl	64	50	0	61	5	6	8	59	24	8	41	71

[a]Reactions were run on a 0.1 mmol scale. Values are reported as calibrated UPLC-MS yields.

Discussion: HTE experimentation determined that 3-(1-chloroethyl) pyridine and 4-bromoethylbenzoate can engage in reductive cross-coupling using several combinations of bpy ligands and manganese as the reductant. These conditions, however, were not general across a broad range of substrates.

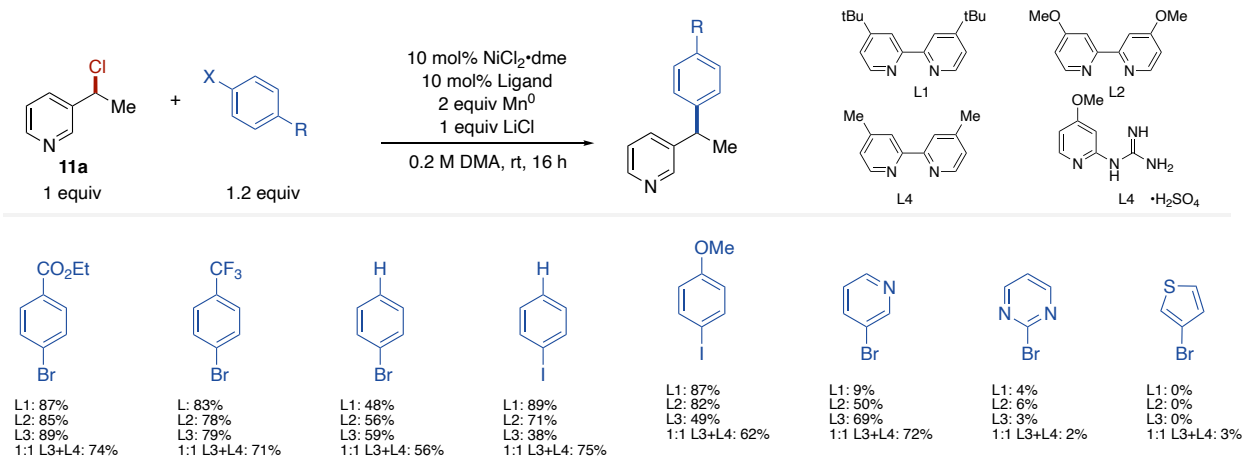


Figure 4C.1. Assessment of reaction 3-(1-chloroethyl)pyridine (11a) with electronically diverse aryl halides under manganese conditions. Values are reported as area percent of product relative to all known species derived from **11a** as determined by UV-Visible spectroscopy.

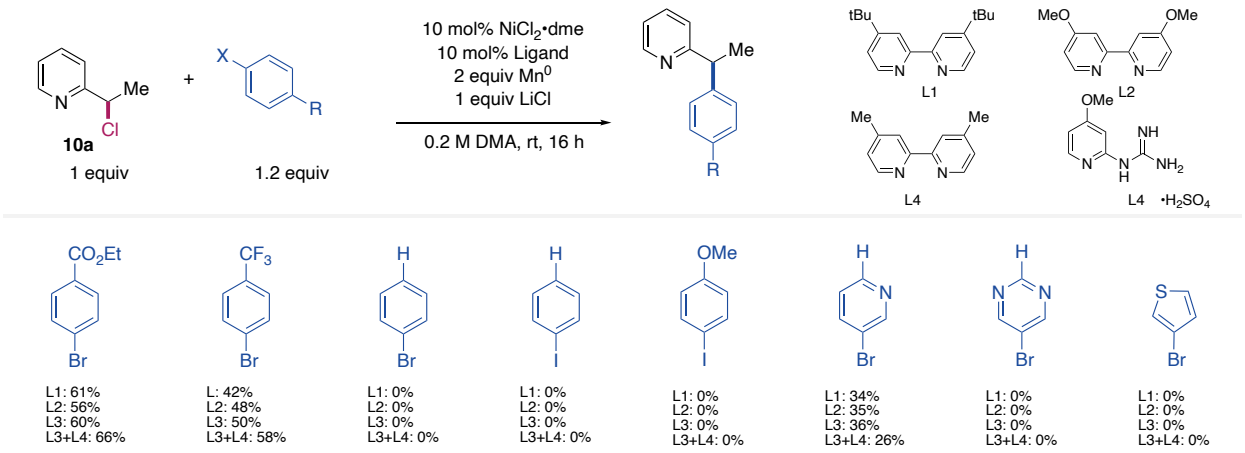


Figure 4C.2. Assessment of reaction 2-(1-chloroethyl)pyridine (10a) with electronically diverse aryl halides under manganese conditions. Values are reported as area percent of product relative to all known species derived from **10a** as determined by UV-Visible spectroscopy.

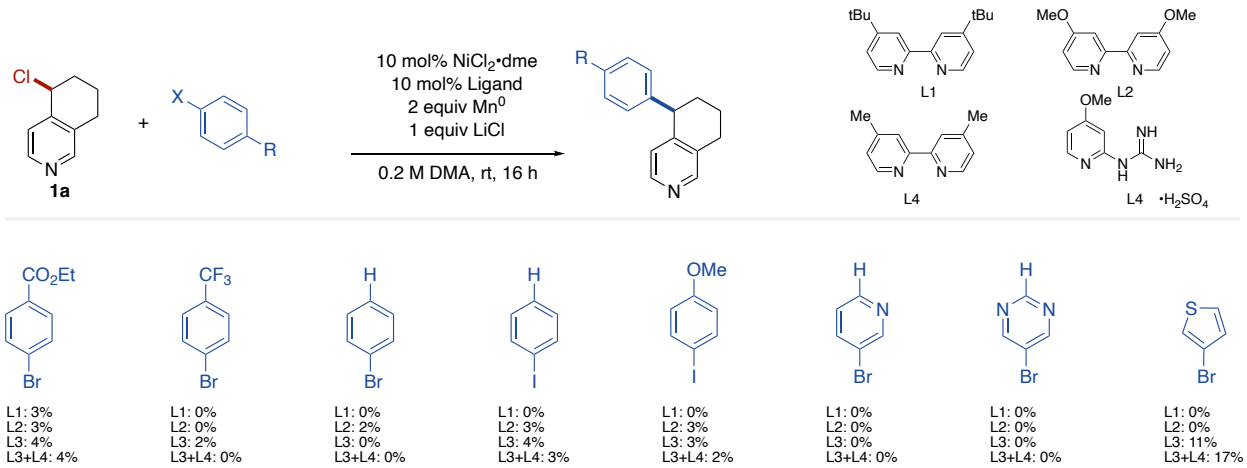


Figure 4C.3. Assessment of reaction 5-chloro-5,6,7,8-tetrahydroisoquinoline with electronically diverse aryl halides under manganese conditions. Values are reported as area percent of product relative to all known species derived from **1a** as determined by UV-Visible spectroscopy.

4C.V. Cyclic Voltammogram Experiments

Electrochemical experiments

All cyclic voltammetry (CV) experiments were performed using a Pine WaveNow PGstat. The CV experiments were carried out in a three-electrode cell configuration with a glassy carbon (GC) working electrode (3 mm diameter), and a platinum wire counter electrode (~ 1.0 cm, spiral wire). The working electrode potentials were measured versus $Ag/AgNO_3$ reference electrode (internal solution, 0.1 M Bu_4NPF_6 and 0.01 M $AgNO_3$ in DMF). The redox potential of ferrocenium/ferrocene (Fc^+/Fc) was measured (under same experimental conditions usually at the end of the same experimental day) and used to provide an internal reference. The potential values were then adjusted relative to Fc^+/Fc, and electrochemical studies in organic solvents were recorded accordingly. The GC working electrode was polished with alumina powder (5 µm) before each experiment. All solutions used for CV analysis were prepared right before the experiments (30 minutes ca.) and kept under nitrogen atmosphere using a thin Teflon tube to allow continuous nitrogen bubbling. All experiments were recorded at r.t unless otherwise noted.

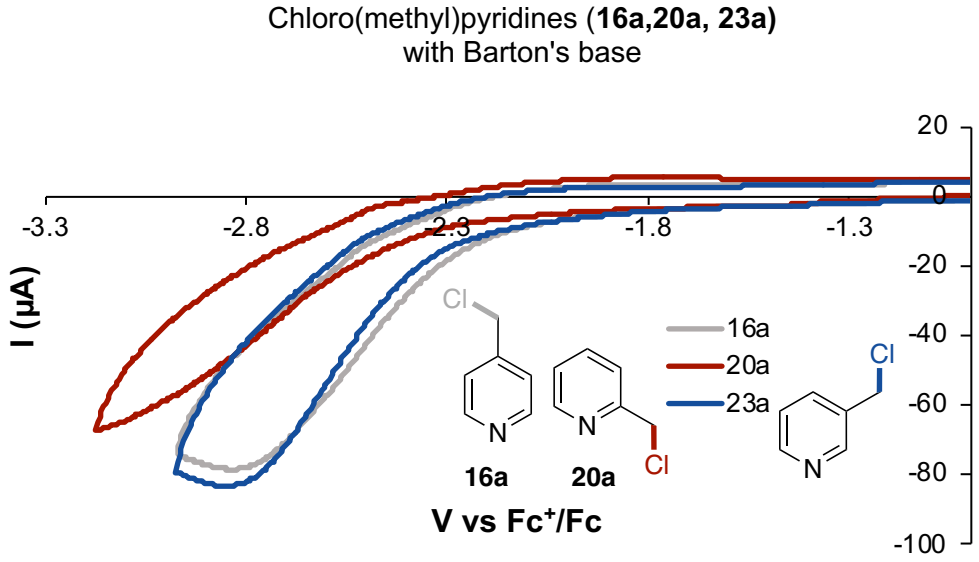


Figure 4C.4. CV of 5 mM solution of compounds 16a, 20a and 23a in DMA, LiBr 0.2 M at 50 mVs^{-1}. The CV traces where independently recorded and then overlaid in this graph.

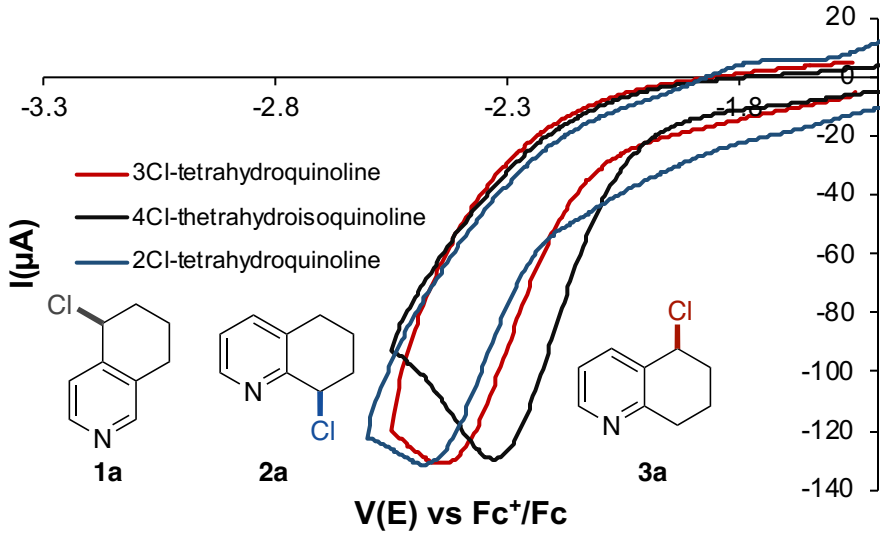


Figure 4C.5. CV of 5 mM solution of compounds **1a**, **2a** and **3a** in DMA, LiBr 0.2 M at 50 mVs^{-1}. The CV traces where independently recorded and then overlaid in this graph.

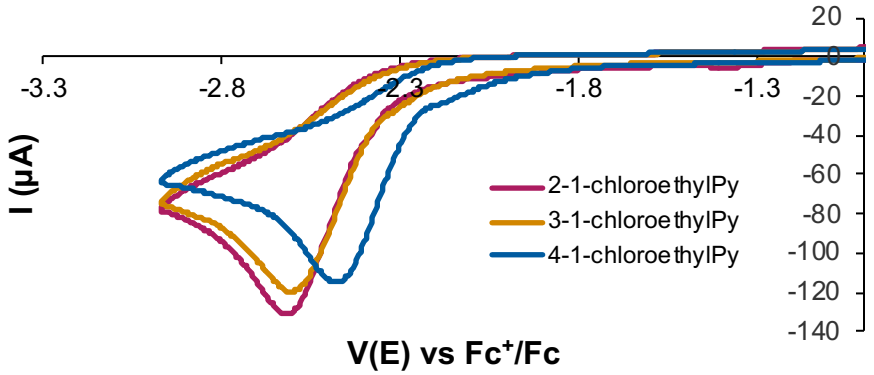


Figure 4C.6. CV of 5 mM solution of compounds **7a**, **10a** and **11a** in DMA, LiBr 0.2 M at 50 mVs^{-1}. The CV traces where independently recorded and then overlaid in this graph.

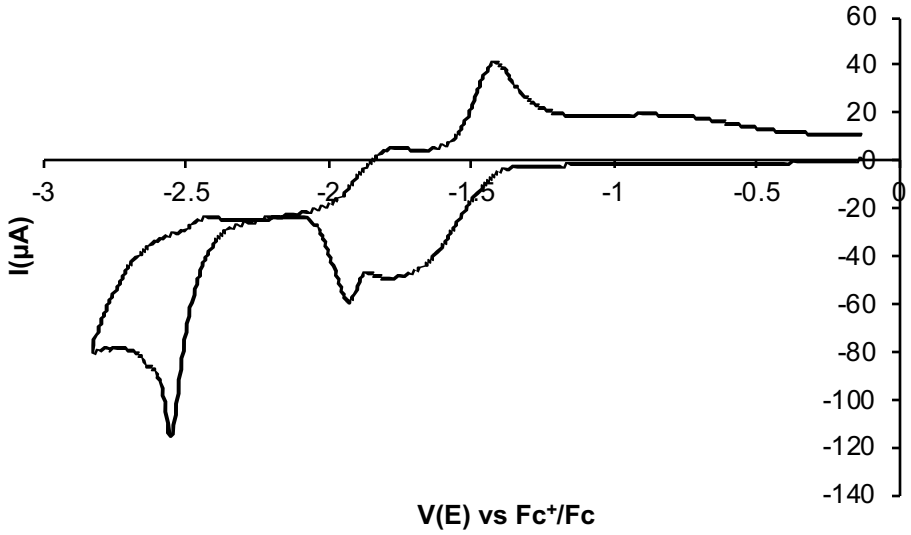


Figure 4C.7. CV of 5 mM solution of $NiCl_2(dtbbpy)_2$ previously prepared in DMA, LiBr 0.2 M at 100 mVs^{-1}. The monoligated species shows a complex trace which hamper the assignment of the identity of the Ni species undergoing reduction.

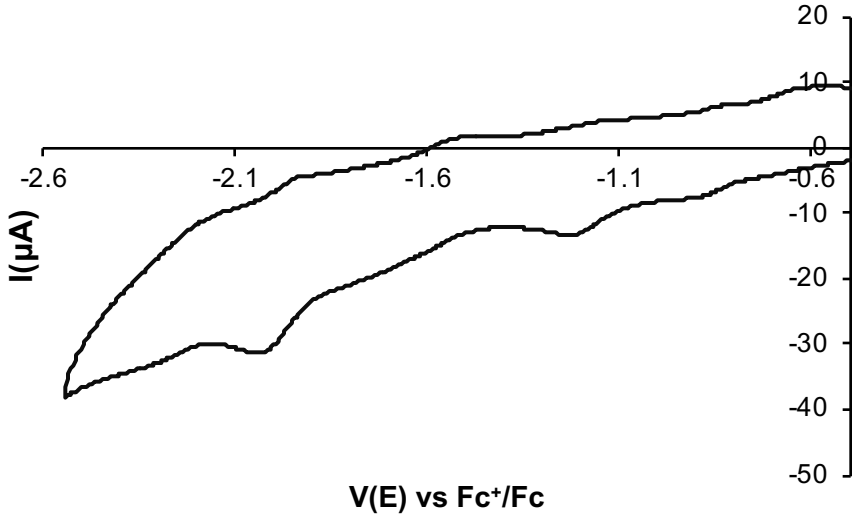


Figure 4C.8. CV of a 2.5 mM solution of cobalt(II) phthalocyanine PcCo(II) in DMA, LiBr 0.2 M at 50 mVs^{-1}. The CV shows several complex quasi-reversible reduction events.

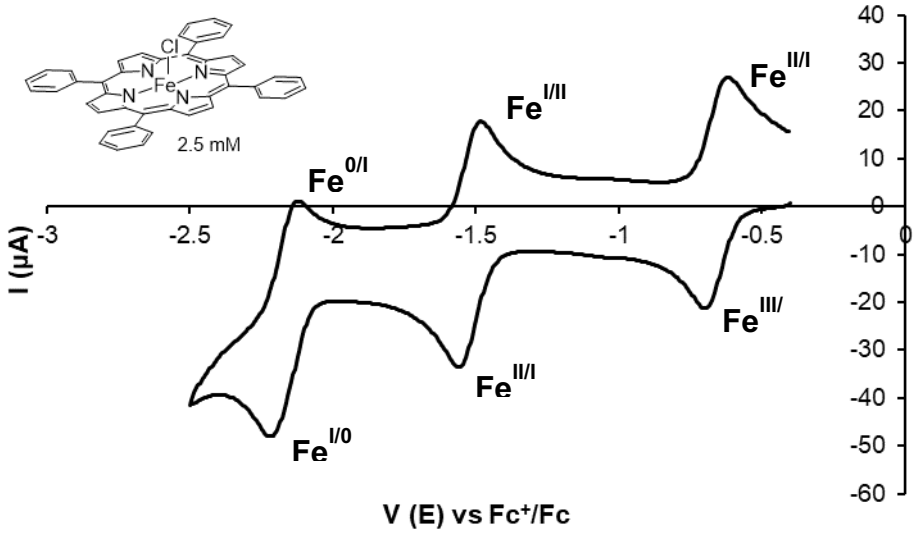


Figure 4C.9. CV of a 2.5 mM solution of FeTPPCl in DMA, LiBr 0.2 M at 50 mVs^{-1}. The CV shows three reversible reductions assigned in order from right to left to the Fe(III/II) reduction, Fe(II/I) reduction and Fe(I/0) reduction.

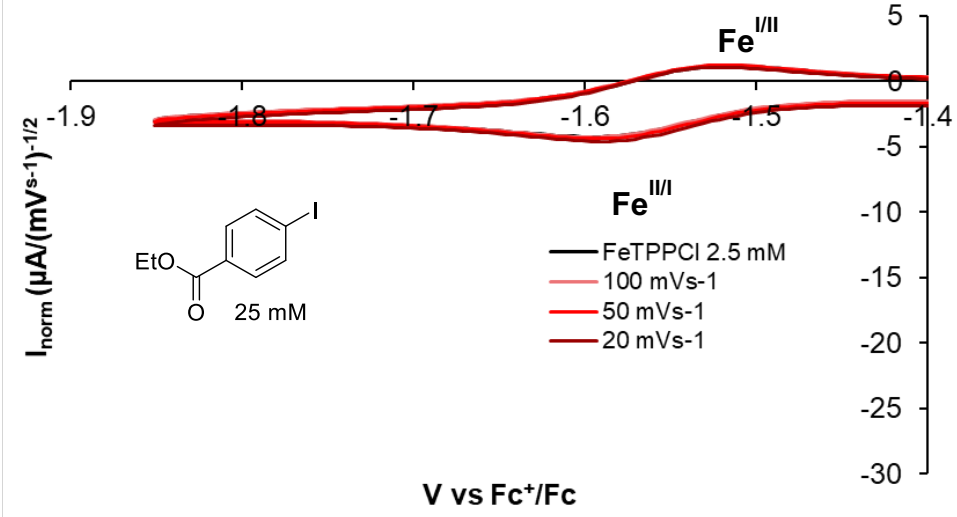


Figure 4C.10. CV of a 2.5 mM solution of FeTPPCl in DMA, LiBr 0.2 M alone (black trace) and in presence of 4-Ethyliodobenzoate 25 mM at various scan rates 20 to 200 mVs^{-1} (red traces). CV recorded in the -1.40 V to -1.85 V region to monitor the Fe(II/I) reduction.

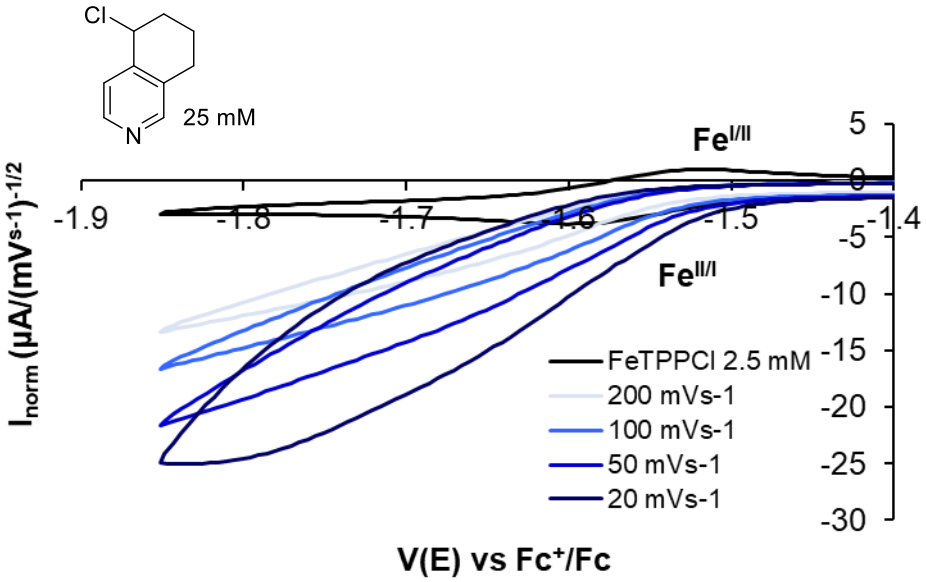


Figure 4C.11. CV of a 2.5 mM solution of FeTPPCl in DMA, LiBr 0.2 M alone (black trace) and in presence of 5-Cl-5,6,7,8-tetrahydroisoquinoline 25 mM at various scan rates 20 to 200 mVs^{-1} (blue traces). CV recorded in the -1.40 V to -1.85 V region to monitor the Fe(II/I) reduction.

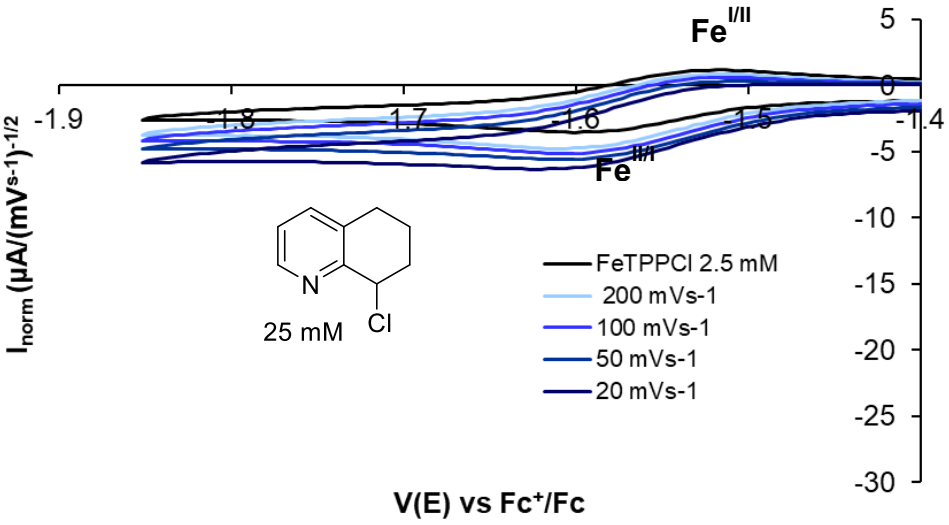


Figure 4C.12. CV of a 2.5 mM solution of FeTPPCl in DMA, LiBr 0.2 M alone (black trace) and in presence of 8-Cl-5,6,7,8-tetrahydroquinoline 25 mM at various scan rates 20 to 200 mVs^{-1} (blue traces). CV recorded in the -1.40 V to -1.85 V region to monitor the Fe(II/I) reduction.

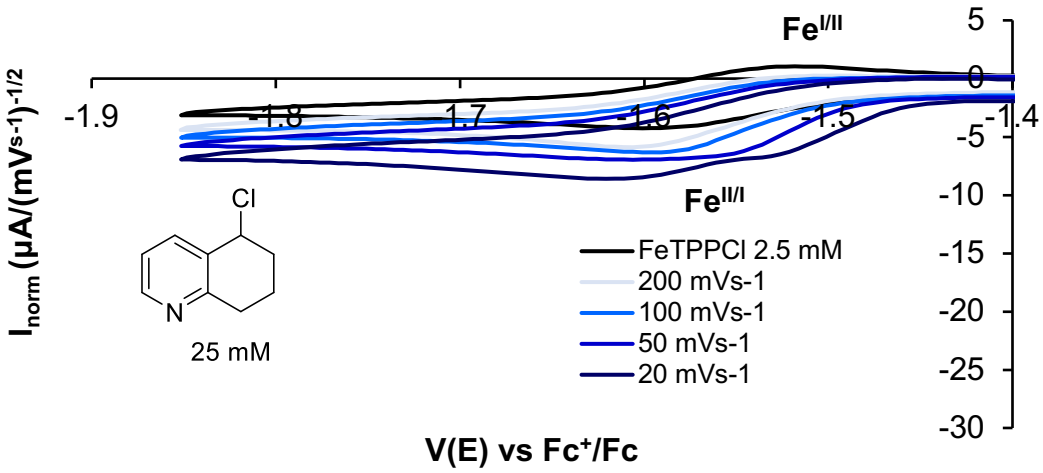


Figure 4C.13. CV of a 2.5 mM solution of FeTPPCl in DMA, LiBr 0.2 M alone (black trace) and in presence of 5-Cl-5,6,7,8-tetrahydroquinoline 25 mM at various scan rates 20 to 200 mVs^{-1} (blue traces). CV recorded in the -1.40 V to -1.85 V region to monitor the Fe(II/I) reduction.

General Procedure for time course: On the benchtop, an oven-dried 50-mL Schlenk tube was charged with benzylic chloride (0.5 mmol, 1 equiv), ethyl-4-iodobenzoate (1.2 equiv), and a cross-shaped stir bar. $NiBr_2$•dme, and dtbbpy was weighed into a secondary 2-dram vial with a cross-shaped stir bar*. Both the vial and Schlenk tube were sparged with N_2 then transferred into a purging glovebox under N_2. In the glovebox, 1,4 Dioxane was added to the vial containing $NiBr_2$•dme and dtbbpy and stirred for 10 min to from a blue-green catalyst stock solution. To the Schlenk tube containing benzylic chloride, aryl iodide, and the cross-shaped stir bar was added $MgCl_2$ (1 equiv), the catalyst stock solution and TDAE (1.4 equiv). The Schlenk tube was then sealed with a rubber septum, removed from the glovebox, and set to stir at 750 rpm on an oil bath at the 80 ºC temperature. Under a positive pressure of nitrogen, an aliquot (2 uL) was taken, filtered, and taken into an HPLC collection block (Analytical Sales and Services) and diluted to 0.001 M. and then analyzed utilizing UPLC-MS (Waters-Acquity) analysis. Yields were determined as percent of product relative to all known species derived from the benzyl chloride. Data was then visualized on Tableu®.

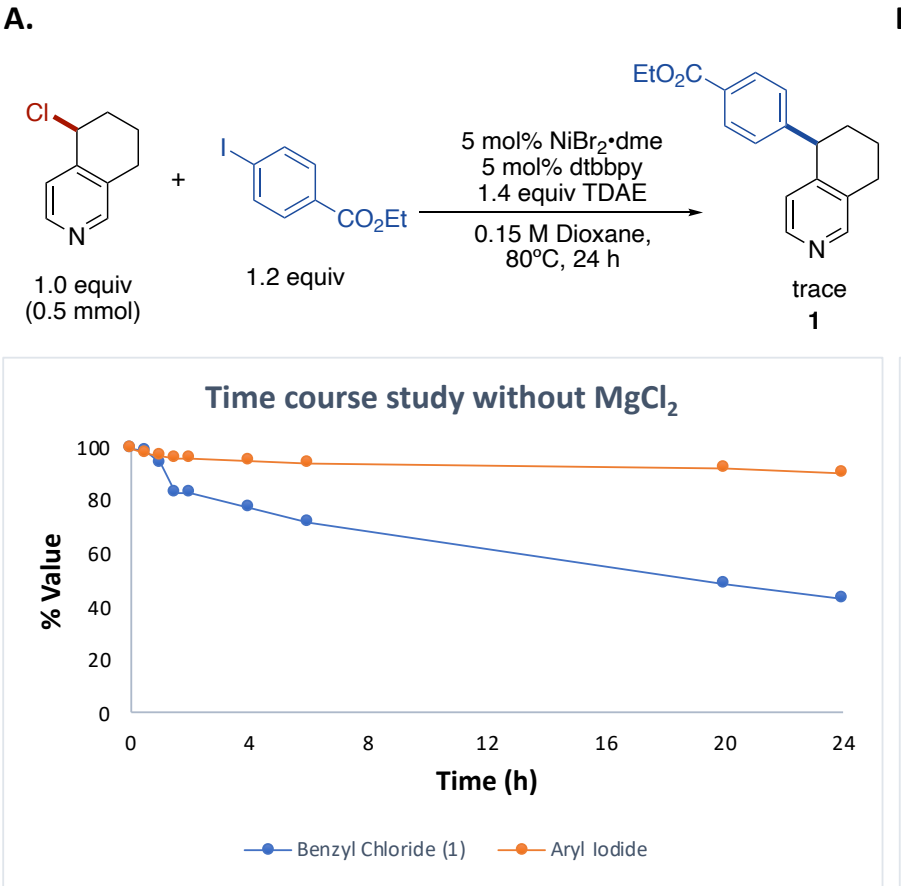


Figure 4C.14. Time course study on the reductive coupling 5-chloro-5,6,7,8-tetrahydroisoquinoline and 4-iodoethylbenzoate without $MgCl_2$..

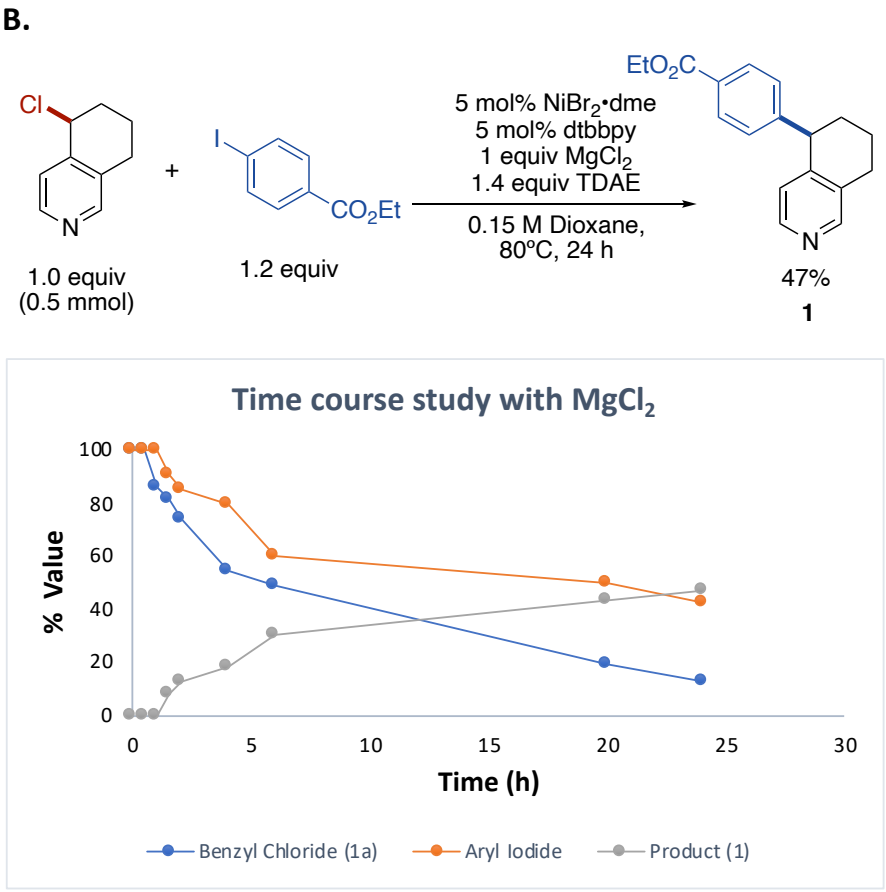


Figure 4C.15. Time course study on reductive coupling 5-chloro-5,6,7,8-tetrahydroisoquinoline and 4-iodoethylbenzoate with $MgCl_2$.

4C.VI. Assessment of Heteroaryl Iodides

General Procedure: On the bench top, to a 6-dram vials fitted with a cross-shaped stir bar was added $NiBr_2$•dme, dtbbpy, and co-catalyst. To a separate induvial 6-dram vials was added benzylic chloride and aryl iodide. These vials were then transferred into a nitrogen-filled glove box and solvent was added. The catalyst stock solution was stirred for 15 min. To a 96-well optimization block (Analytical Sales and Services) with 1-mL glass vial inserts (Analytical Sales and Services) fitted with stainless-steel stir bars (V&P scientific) in a nitrogen- filled glove box, was dispensed appropriate quantities of the stock solutions in the following order: benzyl chloride, aryl iodide, catalyst stock solution, additive, and reductant (concentrations of stock solutions were adjusted so that around 20 μL of each stock solution was dispensed).The plate was then sealed with a screwdriver, agitated on a tumble stirrer (V&P Scientific) at 80ºC for 24 hours. The block was then diluted to 0.1 mM with MeCN and an aliquot (2 μL) was filtered and taken into an HPLC collection block (Analytical Sales and Services). The HPLC collection block was then utilizing UPLC-MS (Waters-Acquity) analysis. Yields were determined as percent of product relative to all known species derived from the benzyl chloride. Data was then visualized on Tableu®.

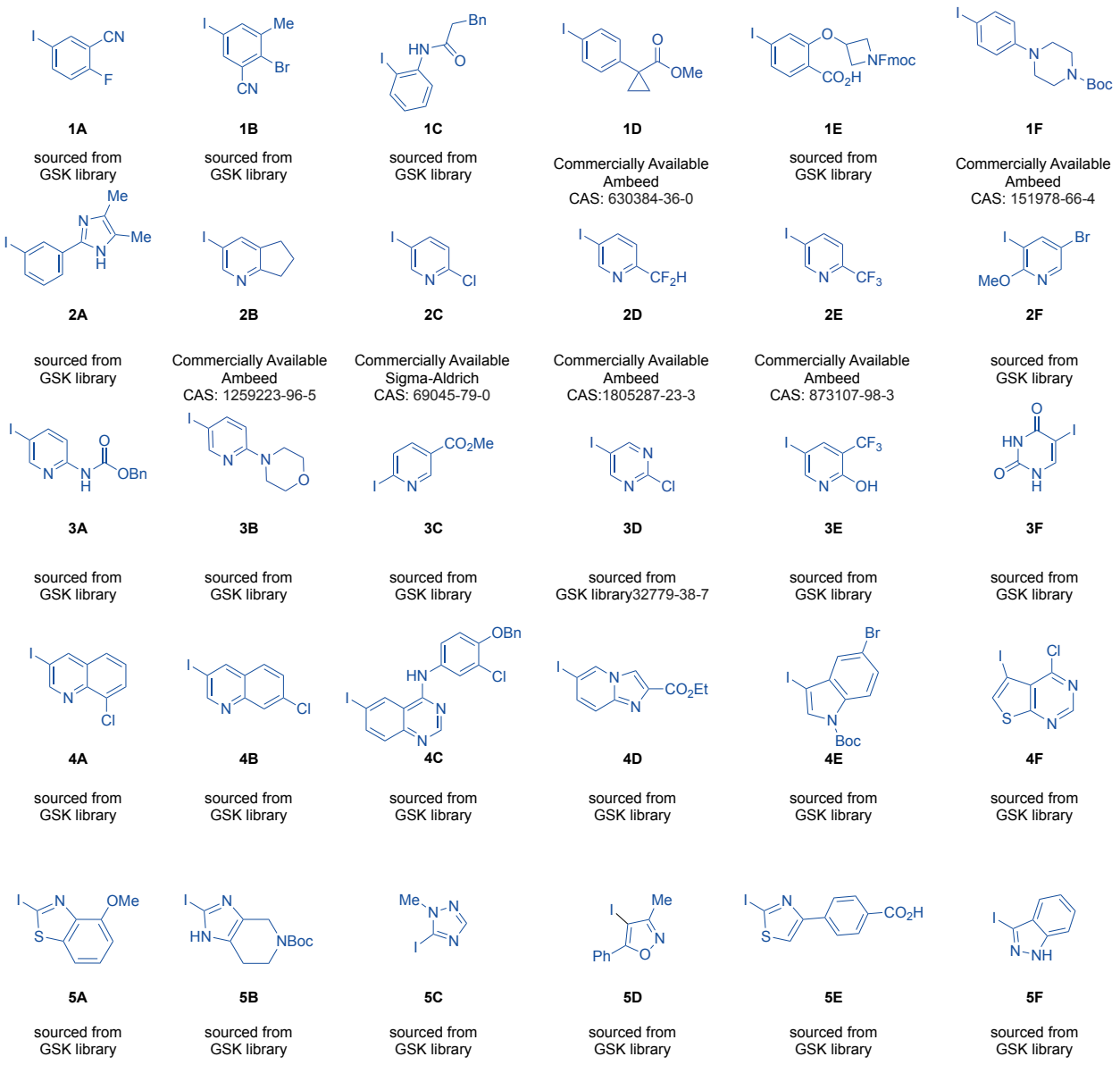
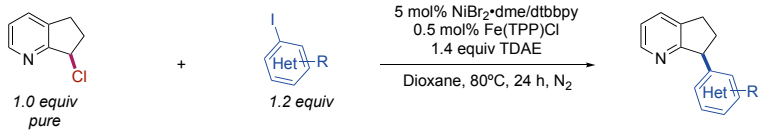
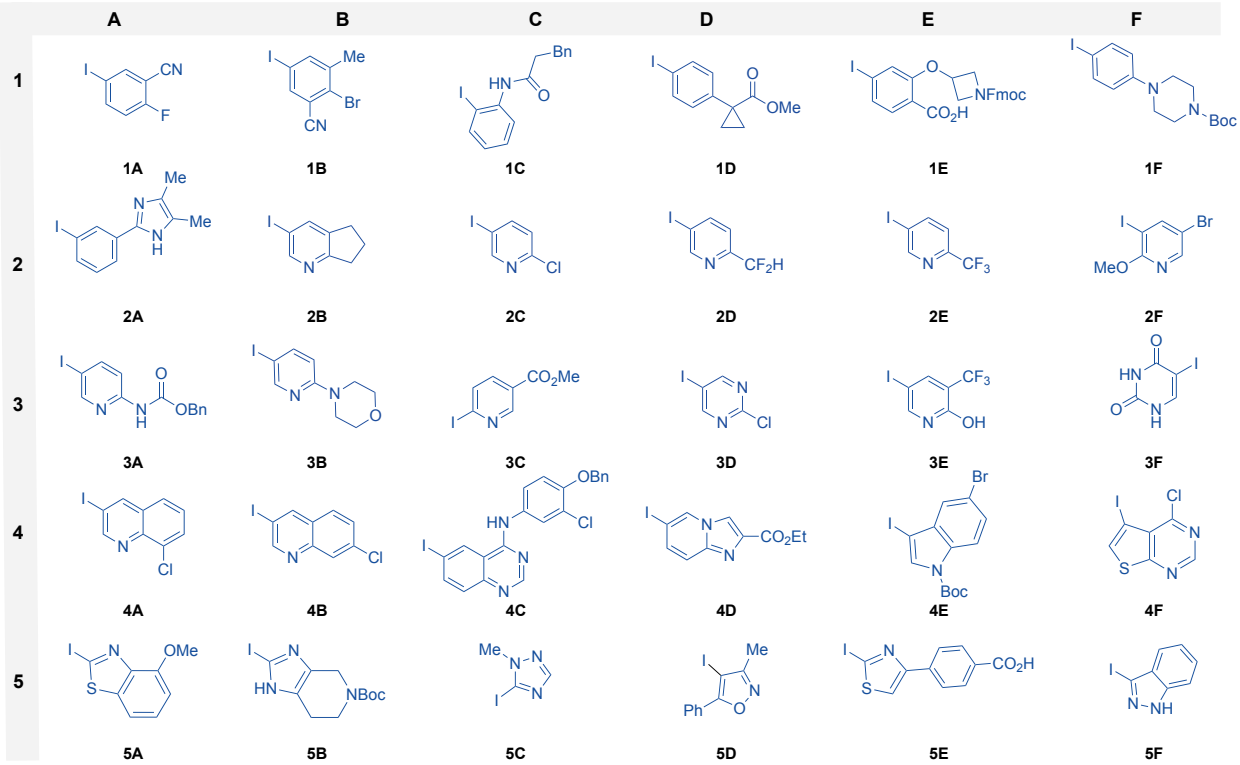


Figure 4C.16. Aryl halide sources

Table 4C.11. Evaluation of aryl halides coupling using (*R*)-7-chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine (**9a**) and various aryl halides.[a]





Row	A	B	C	D	E	F
1	99	99	97	99	90	99
2	79	99	82	99	69	89
3	59	77	0	74	51	83
4	93	74	97	73	16	46
5	67	28	0	41	95	73

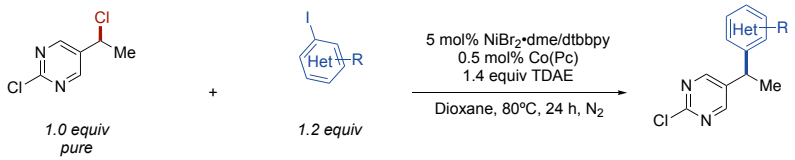
Column

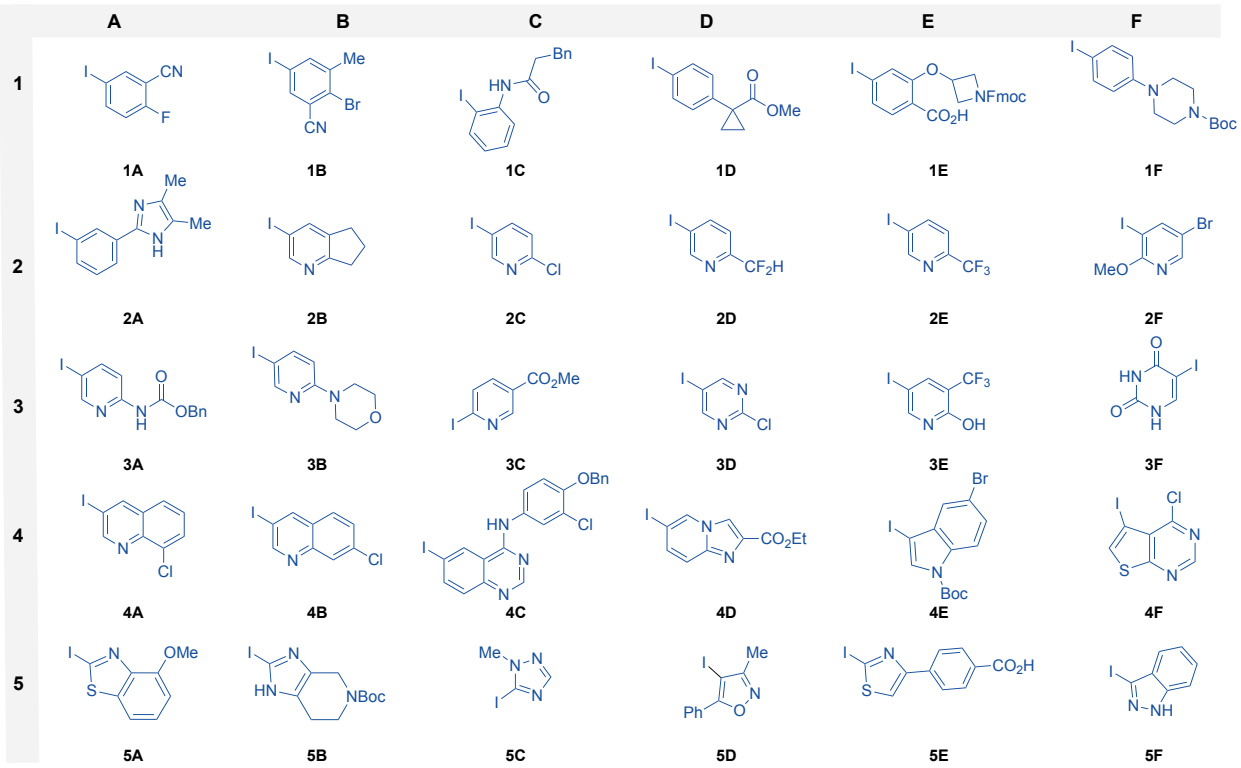
Sum of LCAP Yield

0 100

[a]Reactions were run on a 0.03 mmol scale. Values are reported as area percent of product relative to all known species derived from **9a** as determined by UV-Visible spectroscopy.

Table 4C.12. Evaluation of aryl halides coupling using (2-chloro-5-(1-chloroethyl)pyrimidine (**15a**) and various aryl halides.[a]





Column

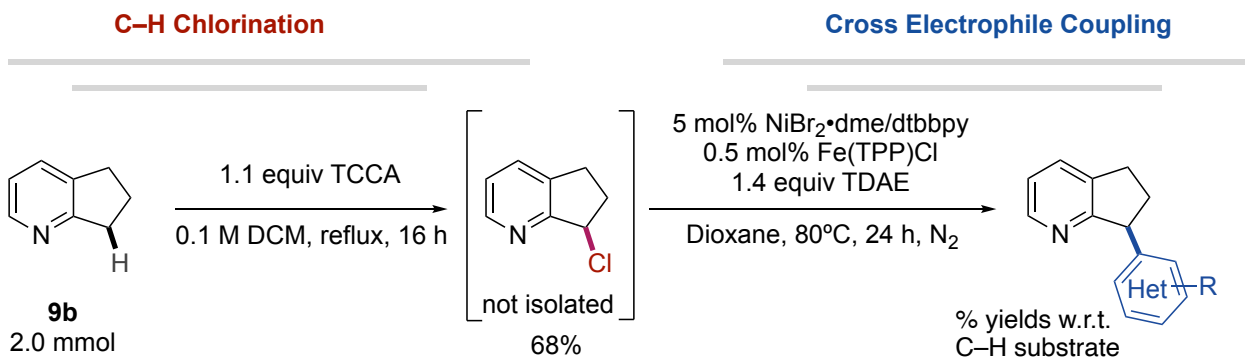
Row	A	B	C	D	E	F
1	94	94	94	0	0	0
2	94	0	64	87	31	90
3	88	62	0	21	97	28
4	92	56	95	95	0	0
5	36	0	0	94	89	0

Sum of LCAP Yield

0 100

[a]Reactions were run on a 0.1 mmol scale. Values are reported as area percent of product relative to all known species derived from **15a** as determined by UV-Visible spectroscopy.

4C.VII. Assessment of Heteroaryl Iodides



An oven-dried 50 mL round-bottom flask containing a magnetic stir bar was charged with 0.24 g of C–H Substrate (1.0 equiv 2.0 mmol), 20 mL of anhydrous DCM (0.1 M), and 0.51 g of trichloroisocyanuric acid (2.2 equiv). The flask was fitted with a Findenser™ and refluxed under air. After 16 hours, the reaction was allowed to cool. To crude reaction mixture was added 20 mL of water and 2.0 equiv of sodium sulfite to quench unreacted N–Cl reagent. The mixture was then allowed to stir for 20 min. The crude reaction mixture was then filtered and concentrated on the rotovap. The obtained residue was diluted with ethyl acetate, transferred to a separatory funnel, and washed with $NaHCO_3$ (aq). The organic layer was collected, dried over Na_2SO_4, and concentrated on the rotovap. The obtained residue was then analyzed by ^{1}H-NMR to obtain a yield of 68% (1.32 mmol) of the desired product. Then a 0.3 M benzyl chloride stock solution in anhydrous 1,4-Dioxane was prepared.

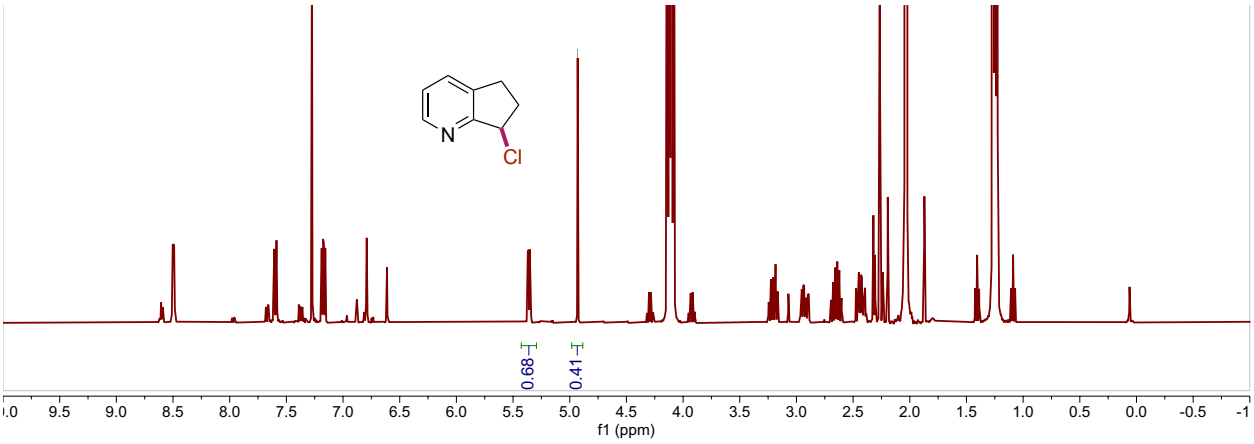


Figure 4C.16. Crude ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 25 °C) of the reaction mixture for **9a** following the addition of 0.215 mmol (30 µL) of dibromomethane as an external standard (4.93 ppm). The resolved benzylic proton (5.36 ppm) of product is labeled and integrated.

Reductive Coupling

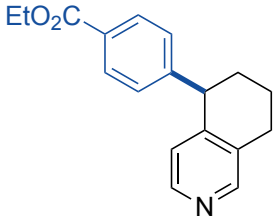
On the benchtop, a 2-dram borosilicate vial was charged with aryl iodide and a Teflon stir bar. $NiBr_2$•dme, Fe(TPP)Cl, and dtbbpy was weighed into a secondary 2-dram vial with a cross-shaped stir bar*. Both vials were sparged with N_2 then transferred into a purging glovebox under N_2. In the glovebox, 1,4 Dioxane was added to the vial containing $NiBr_2$•dme, Fe(TPP)Cl, and dtbbpy and stirred for 10 min to from a dark brown catalyst stock solution. To the vial containing the aryl

iodide, and the Teflon stir bar was added 600 µL of benzyl chloride stock solution (corresponding to 0.2 mmol of the benzyl chloride), catalyst stock solution and TDAE (1.4 equiv). The reaction vial was then sealed, removed from the glovebox, and set to stir at 750 rpm on an aluminum block at the 80 ºC 24 h.

Vial 1: a disposable 2-dram vial, aryl-iodide (0.2 mmol, 1.2 equiv), and a Teflon stir bar*.
Vial 2: a disposable 2-dram vial, cross-shaped stir bar, $NiBr_2$•dme (15.4. mg, 0.05 mmol), dttbpy (13.4 mg, 0.05 mmol), Fe(TPP)Cl (3.5 mg, 5 µmol) and 1,4-Dioxane (3.9 mL) combined to form a dark brown catalyst stock solution.
Vial 1 was slurry dosed with 600 µL of the benzyl chloride stock solution, 780 µL of the catalyst stock solution followed by TDAE (65 µL, 0.28 mmol, 1.4 equiv). The reaction was conducted 80 ºC **Work up:** Reactions were worked up according to Procedure B in Section II.

4C.VIII. Product Synthesis and Characterization

(1) Ethyl 4-(5,6,7,8-tetrahydroisoquinolin-5-yl)benzoate

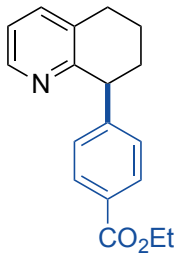


Reaction conducted following **Procedure A** using 5-chloro-5,6,7,8-tetrahydroisoquinoline (83.5 mg, 0.5 mmol, 1equiv)

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (70:30 (v:v)) to afford 115.3 mg (82 % yield) of **1** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.20 (d, *J* = 5.1 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 6.66 (d, *J* = 5.1 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.09 (td, *J* = 6.6, 1.6 Hz, 1H), 2.85 (m, 2H), 2.27 – 2.09 (m, 1H), 2.00 – 1.90 (m, 1H), 1.90 – 1.69 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 150.7, 147.5, 147.0, 133.2, 129.9, 129.0, 128.8, 124.4, 61.0, 45.3, 32.5, 26.6, 20.9, 14.4.
HRMS (ESI) m/z: [M+H]+ Calcd for C18H20NO2, 282.1489; Found 282.1487

(2) ethyl-4-(5,6,7,8-tetrahydroquinolin-8-yl)benzoate



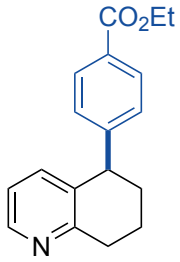
Reaction conducted following **Procedure B** using 8-chloro-5,6,7,8-tetrahydroquinoline pyridine (83.5 mg, 0.5 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (30:70 (v:v)) to afford 106.9 mg (76 % yield) of **8** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 3.6 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.16 – 7.00 (m, 2H), 4.39 – 4.30 (m, 3H), 2.98 – 2.76 (m, 2H), 2.33 – 2.19 (m, 1H), 1.97 (m, 1H), 1.90 – 1.81 (m, 1H), 1.81 – 1.71 (m, 1H), 1.36 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 157.9, 151.9, 147.7, 137.2, 133.3, 129.8, 128.8, 128.4, 121.7, 60.8, 48.0, 33.0, 29.1, 19.8, 14.5.

HRMS (ESI) m/z: [M+H]+ Calcd for C18H20NO2, 282.1489; Found 282.1486

(3) ethyl 4-(5,6,7,8-tetrahydroquinolin-5-yl)benzoate

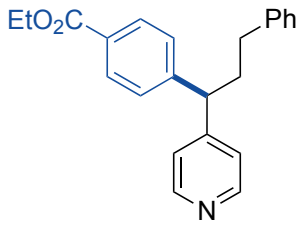


Reaction conducted following **Procedure A** using 5-chloro-5,6,7,8-tetrahydroquinoline (83.5 mg, 0.5 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (60:75 (v:v)) to afford 45.0 mg (32 % yield) of **12** as a clear oil .

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 – 8.41 (d, *J* = 4.7 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.13 – 7.07 (m, 1H), 7.00 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.18 (t, *J* = 7.0 Hz, 1H), 3.15 – 2.99 (m, 2H), 2.29 – 2.14 (m, 1H), 2.10 – 1.97 (m, 1H), 1.88 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 157.6, 151.4, 147.5, 138.1, 134.5, 130.0, 129.0, 128.9, 121.4, 61.1, 45.5, 32.7, 21.1, 14.5.
HRMS (ESI) m/z: [M+H]+ Calcd for C18H20NO2, 282.1489; Found 282.1484

(4) ethyl 4-(3-phenyl-1-(pyridin-4-yl)propyl)benzoate

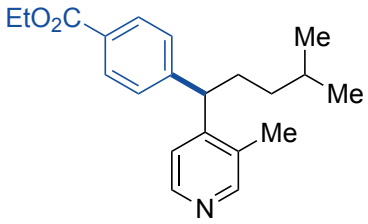


Reaction conducted following **Procedure A** using 4-(1-chloro-3-phenylpropyl)pyridine (115.5 mg, 0.5 mmol, 1 equiv)..

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (60:40 (v:v)) to afford 124.3 mg (72 % yield) of **4** as a clear oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 – 8.44 (m, 2H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.33 – 7.27 (m, 4H), 7.22 – 7.18 (m, 1H), 7.16 – 7.09 (m, 4H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.94 (t, *J* = 7.7 Hz, 1H), 2.57 (m, 2H), 2.41 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR 126 MHz, $CDCl_3$) δ 166.4, 152.9, 150.2, 148.0, 141.2, 130.2, 128.7, 128.5, 128.1, 126.3, 123.3, 61.1, 50.0, 36.45, 33.8, 14.5.
HRMS (ESI) m/z: [M+H]+ Calcd for C23H24NO2, 346.1802; Found 346.1797

(5) ethyl 4-(4-methyl-1-(3-methylpyridin-4-yl)pentyl)benzoate

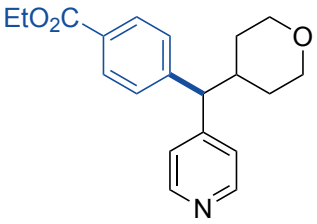


Reaction conducted following **Procedure A** using 4-(1-chloro-4-methylpentyl)-3-methylpyridine (105.6 mg, 0.5 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (60:40 (v:v)) to afford 87.8 mg (54 % yield) of **5** as a clear oil .

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 5.1 Hz, 1H), 8.34 (s, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.24 – 7.18 (m, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.05 (t, *J* = 7.6 Hz, 1H), 2.21 (s, 3H), 2.07 – 1.96 (m, 2H), 1.56 (hept, *J* = 6.6 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.16 (m, 2H), 0.87 (dd, *J* = 9.1, 6.6 Hz, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 151.4, 151.0, 148.3, 148.1, 132.0, 130.0, 129.0, 128.3, 121.5, 61.0, 47.2, 37.1, 33.3, 28.2, 22.7, 16.8, 14.5.
HRMS (ESI) m/z: [M+H]+ Calcd for C21H28NO2, 326.2115; Found 326.2111

(6) ethyl 4-(pyridin-4-yl(tetrahydro-2*H*-pyran-4-yl)methyl)benzoate



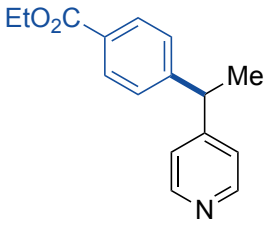
Reaction conducted following **Procedure A** using 4-(chloro(tetrahydro-2*H*-pyran-4-yl)methyl)pyridine
(105.5 mg, 0.5 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (60:40 (v:v)) to afford 100.8 mg (62 % yield) of **6** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 – 8.43 (m, 2H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 6.1 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.98 – 3.80 (m, 2H), 3.56 (d, *J* = 11.0 Hz, 1H), 3.36 (m, 2H), 2.36 (dt, *J* = 11.2, 3.7 Hz, 1H), 1.47 – 1.38 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.31 – 1.22 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.29, 151.28, 150.28, 146.63, 130.26, 129.45, 128.17, 123.53, 67.85 (d, J = 6.3 Hz), 61.07, 58.58, 38.44, 32.00, 31.85, 14.44.
HRMS (ESI) m/z: [M+H]+ Calcd for C20H24NO3, 326.1751; Found 326.1749

(7) Ethyl 4-(1-(pyridin-4-yl)ethyl)benzoate

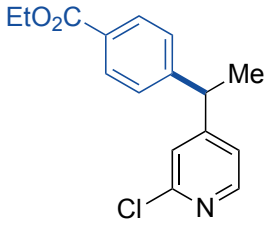


Reaction conducted following **Procedure A** using 4-(1-chloroethyl)pyridine (70.8 mg, 0.5 mmol, 1equiv)

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (70:40 (v:v)) to afford 65.1 mg (49 % yield) of **2** as a clear oil .

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 6.1 Hz, 2H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 6.2 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 1H), 1.66 (d, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 154.4, 150.0, 149.6, 130.1, 129.2, 127.8, 123.1, 61.1, 44.4, 21.0, 14.5.
HRMS (ESI) m/z: [M+H]+ Calcd for C16H18NO2, 256.1332; Found 256.1333

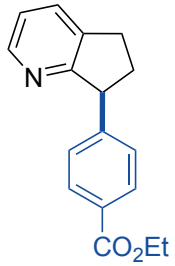
(8) Ethyl 4-(1-(2-chloropyridin-4-yl)ethyl)benzoate



Reaction conducted following **Procedure A** using 2-chloro-4-(1-chloroethyl)pyridine (87.5 mg, 0.5 mmol, 1 equiv). Deviation from Procedure A was the exclusion of $MgCl_2$.

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (30:70 (v:v)) to afford 117.1 mg (81 % yield) of **3** as a clear oil .
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.2, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.16 – 7.15 (m, 1H), 7.03 – 7.02 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 1H), 1.65 (d, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 157.8, 152.1, 149.9, 148.70, 130.2, 129.5, 127.7, 123.4, 121.9, 61.1, 44.2, 20.9, 14.5.
HRMS (ESI m/z: [M+H]+ Calcd for C16H17ClNO2, 290.0942; Found 290.0936

(9) ethyl 4-(6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)benzoate

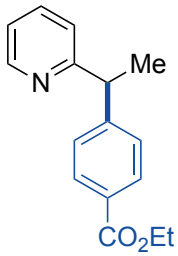


Reaction conducted following **Procedure B** using 7-chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine (76.8 mg, 0.5 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 104.3 mg (78 % yield) of **8** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 5.0 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.30 – 7.25 (d, *J* = 8.3 Hz, 2H), 7.13 (dd, *J* = 7.6, 4.9 Hz, 1H), 4.50 (t, *J* = 8.2 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.12 (m, 1H), 3.02 (m, 1H), 2.71 (m, 1H), 2.18 (m, 1H), 1.39 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 165.9, 149.3, 148.2, 137.3, 132.6, 130.0, 128.8, 128.1, 121.7, 60.8, 51.8, 33.8, 29.4, 14.4.
HRMS (ESI) m/z: [M+H]+ Calcd for C17H18NO2, 268.1332; Found 268.1326

(10) ethyl 4-(1-(pyridin-2-yl)ethyl)benzoate

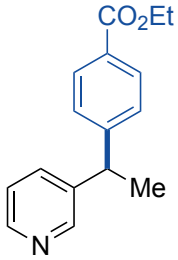


Reaction conducted following **Procedure B** using 2-(1-chloroethyl)pyridine (70.8 mg, 0.5 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 108.5 mg (85 % yield) of **8** as a clear oil .

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 3.4 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.60 – 7.55 (m, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.15 – 7.09 (m, 2H), 4.38 – 4.31 (m 3H), 1.72 (d, *J* = 7.3 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 164.2, 150.4, 149.4, 136.7, 129.9, 128.8, 127.8, 122.3, 121.6, 60.9, 47.5, 20.7, 14.4.
HRMS (ESI) m/z: [M+H]+ Calcd for C16H18NO2, 256.1332; Found 256.1328

(11) ethyl 4-(1-(pyridin-3-yl)ethyl)benzoate

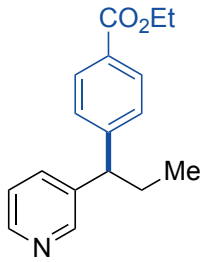


Reaction conducted following **Procedure D** using 3-(1-chloroethyl)pyridine (70.8 mg, 0.5 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 77.9 mg (61 % yield) of **9** as a clear oil .

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 2.4 Hz, 1H), 8.46 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.21 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.23 (q, *J* = 7.2 Hz, 1H), 1.68 (d, *J* = 7.2 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 4H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 150.2, 149.4, 147.9, 140.9, 129.0, 127.7, 123.6, 61.0, 42.6, 21.5, 14.5.
HRMS (ESI) m/z: [M+H]+ Calcd for C16H18NO2, 256.1332; Found 256.1328

(12) ethyl 4-(1-(pyridin-3-yl)propyl)benzoate

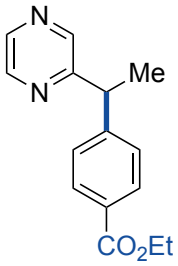


Reaction conducted following **Procedure D** using 3-(1-chloropropyl)pyridine (77.8 mg, 0.5 mmol, 1 equiv). Deviation from Procedure D running the reaction at 40 ºC

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 78.1 (58 % yield) of **12** as a clear oil .

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.45 (d, *J* = 3.2 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.49 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.21 (dd, *J* = 7.9, 4.8 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.87 (t, *J* = 7.8 Hz, 1H), 2.19 – 2.03 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 149.7, 149.1, 148.0, 139.8, 135.2, 130.1, 129.0, 128.0, 123.7, 61.0, 50.9, 28.3, 14.5, 12.7.
HRMS (ESI) m/z: [M+H]+ Calcd for C17H20NO2, 270.1489; Found 270.1488

(13) ethyl 4-(1-(pyrazin-2-yl)ethyl)benzoate

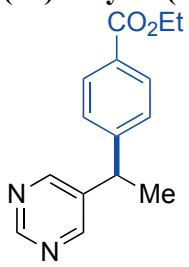


Reaction conducted following **Procedure B** using 2-(1-chloroethyl)pyrazine (71.0 mg, 0.5 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 69.2 mg (54 % yield) of **8** as a clear oil .

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.45 (s, 1H), 8.39 (d, *J* = 2.5 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 4.47 – 4.26 (m, 3H), 1.73 (d, *J* = 7.2 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 159.6, 149.0, 144.3, 144.2, 142.7, 130.1, 129.2, 127.8, 61.0, 45.2, 20.4, 14.4.
HRMS (ESI) m/z: [M+H]+ Calcd for C15H17N2O2, 257.1285; Found 257.1279

(14) ethyl 4-(1-(pyrimidin-5-yl)ethyl)benzoate

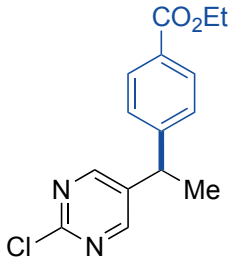


Reaction conducted following **Procedure C** using 5-(1-chloroethyl)pyrimidine (71.3 mg, 0.5 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 64.0 mg (50 % yield) of **8** as a clear oil .

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.59 (s, 2H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.22 (q, *J* = 7.3 Hz, 1H), 1.72 (d, *J* = 7.3 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR 126 MHz, $CDCl_3$) δ 166.2, 157.1, 156.1, 148.6, 138.3, 130.2, 129.4, 127.5, 61.1, 40.6, 21.0, 14.3.
HRMS (ESI) m/z: [M+H]+ Calcd for C15H17N2O2, 257.1285; Found 257.1283

(15) ethyl 4-(1-(2-chloropyrimidin-5-yl)ethyl)benzoate

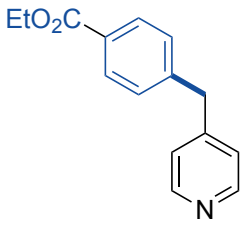


Reaction conducted following **Procedure C** using 2-chloro-5-(1-chloroethyl)pyrimidine (88.0 mg, 0.5 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 150.8 mg (52 % yield) of **8** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 2H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.23 (q, *J* = 7.2 Hz, 1H), 1.71 (d, *J* = 7.2 Hz, 3H), 1.39 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 159.8, 158.9, 148.1, 137.1, 130.4, 129.7, 127.5, 61.2, 40.0, 21.2, 14.4.
HRMS (ESI) m/z: [M+H]+ Calcd for C15H16ClN2O2, 291.0895; Found 291.0893

(16) ethyl 4-(pyridin-4-ylmethyl)benzoate

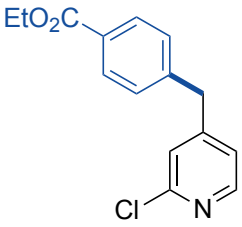


Reaction conducted following **Procedure E** using 3-(chloromethyl)pyridine hydrochloride (82.0 mg, 0.5 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 60.3 mg (50 % yield) of **8** as a clear oil .

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.4 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.09 – 7.08 (d, *J* = 4.9 Hz, 2H), 4.42 – 4.29 (q, *J* = 7.2 Hz, 2H), 4.01 (s, 2H), 1.41 – 1.36 t, *J* = 7.2 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 150.1, 149.2, 144.1, 130.2, 129.2, 129.2, 124.3, 61.1, 41.3, 14.5.
HRMS (ESI) m/z: [M+H]+ Calcd for C15H16NO2, 242.1176; Found 242.1176

(17) ethyl 4-((2-chloropyridin-4-yl)methyl)benzoate

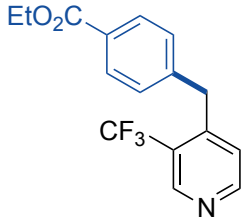


Reaction conducted following **Procedure E** using 2-chloro-4-(chloromethyl)pyridine (116.0 mg, 0.5 mmol, 1 equiv). Deviation from procedure is the exclusion of Barton's base.

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 124.8 mg (90 % yield) of **8** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 5.1 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.12 (s, 1H), 7.01 (d, *J* = 5.3 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 152.6, 152.1, 149.9, 143.1, 130.3, 129.6, 129.2, 124.6, 123.0, 61.2, 41.0, 14.5.
HRMS (ESI) m/z: [M+H]+ Calcd for C15H15ClNO2, 276.0786; Found 276.0787

(18) ethyl 4-((3-(trifluoromethyl)pyridin-4-yl)methyl)benzoate

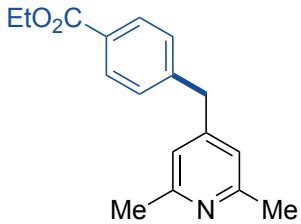


Reaction conducted following **Procedure E** using 4-(chloromethyl)-3-(trifluoromethyl)pyridine hydrochloride (116.0 mg, 0.5 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 32.5 mg (21 % yield) of **8** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.64 (d, *J* = 5.1 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 5.2 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.23 (s, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 152.9, 148.3, 146.9 (q, *J* = 6.3 Hz), 142.5, 130.2, 129.3, 125.6, 125.2, 123.8 (q, *J* = 275.3 Hz), 122.8, 61.1, 37.4 (d, *J* = 2.2 Hz), 14.3.
^{19}F NMR (377 MHz, $CDCl_3$) δ -59.95.
HRMS (ESI) m/z: [M+H]+ Calcd for C16H15F3NO2, 310.1049; Found 310.1051

(18) ethyl 4-((2,6-dimethylpyridin-4-yl)methyl)benzoate

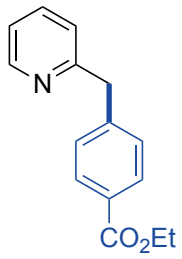


Reaction conducted following **Procedure E** using 4-(chloromethyl)-2,6-dimethylpyridine (77.5 mg, 0.5 mmol, 1 equiv). Deviation from procedure is the exclusion of Barton's base.

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 119.8 mg (89 % yield) of **8** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 6.76 (s, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 2H), 2.47 (s, 6H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 158.1, 149.7, 144.6, 130.1, 129.2, 129.1, 120.9, 61.1, 41.3, 24.5, 14.5.
HRMS (ESI) m/z: [M+H]+ Calcd for C17H20NO2, 270.1489; Found 270.1489

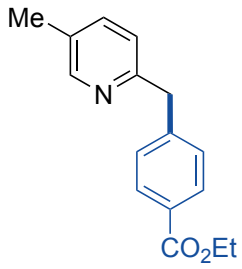
(19) ethyl 4-(pyridin-2-ylmethyl)benzoate



Reaction conducted following **Procedure E** using 2-(chloromethyl)pyridine hydrochloride (82 mg, 0.5 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 144.7 mg (60 % yield) of **8** as a clear oil.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.2 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.59 (td, *J* = 7.6, 1.7 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.17 – 7.06 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.21 (s, 2H), 1.37 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR: (126 MHz, $CDCl_3$) δ 166.53, 160.05, 149.47, 144.68, 136.74, 129.89, 129.08, 128.77, 123.20, 121.52, 60.84, 44.61, 14.34.
HRMS (ESI) m/z: [M+H]+ Calcd for C15H16NO2, 242.1176; Found 242.1176

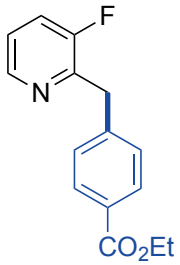


Reaction conducted following **Procedure E** using 2-(chloromethyl)-5-methylpyridine (70.5 mg, 0.5 mmol, 1 equiv). Deviation from procedure is the exclusion of Barton's base.

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 93.1 mg (73 % yield) of **8** as a clear oil .

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (q, *J* = 1.1 Hz, 1H), 7.99 – 7.95 (m, 2H), 7.44 – 7.37 (m, 1H), 7.36 – 7.30 (m, 2H), 7.00 (d, *J* = 7.7 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.16 (s, 2H), 2.29 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 157.3, 150.0, 145.2, 137.4, 131.0, 130.0, 129.1, 128.8, 122.8, 61.0, 44.3, 18.2, 14.5.
HRMS (ESI) m/z: [M+H]+ Calcd for C16H18NO2, 256.1332; Found 256.1330

(22) ethyl 4-((3-fluoropyridin-2-yl)methyl)benzoate

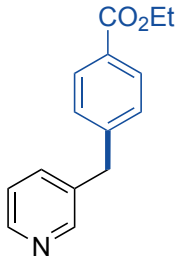


Reaction conducted following **Procedure E** using 2-(chloromethyl)-3-fluoropyridine (72.5 mg, 0.5 mmol, 1 equiv). Deviation from procedure is the exclusion of Barton's base.

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 89.5 mg (69 % yield) of **8** as a clear oil .

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.6, 1H), 8.03 – 7.90 (m, 2H), 7.42 – 7.32 (m, 3H), 7.18 (m, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.25 (d, *J* = 2.6 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 157.8 (d, *J* = 257.0 Hz), 148.4 (d, *J* = 15.2 Hz), 145.4 (d, *J* = 5.5 Hz), 130.0, 129.1, 129.0, 123.3 (d, *J* = 3.6 Hz), 123.2 (d, *J* = 19.1 Hz), 61.0, 38.3 (d, *J* = 2.1 Hz), 14.5.
^{19}F NMR (377 MHz, $CDCl_3$) δ -124.34.
HRMS (ESI) m/z: [M+H]+ Calcd for C15H15FNO2, 260.1081; Found 260.1078

(23) ethyl 4-(pyridin-3-ylmethyl)benzoate

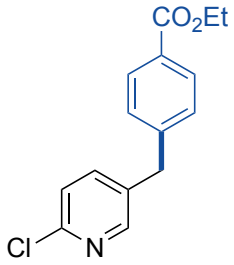


Reaction conducted following **Procedure E** using 3-(chloromethyl)pyridine hydrochloride (82.0 mg, 0.5 mmol, 1 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 85.6 mg (71 % yield) of **8** as a clear oil .

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 2H), 8.00 – 7.79 (m, 2H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.17 (m, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.96 (s, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 145.1, 136.5, 130.1, 129.0, 129.0, 61.0, 39.2, 14.5.
HRMS (ESI) m/z: [M+H]+ Calcd for C15H16NO2, 242.1176; Found 242.1172

(24) ethyl 4-((6-chloropyridin-3-yl)methyl)benzoate



Reaction conducted following **Procedure E** using 2-chloro-5-(chloromethyl)pyridine (80.5 mg, 0.5 mmol, 1 equiv). Deviation from procedure is the exclusion of Barton's base.

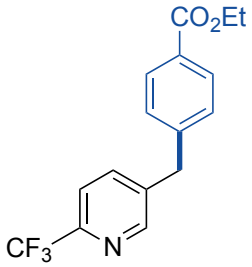
Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 126.5 mg (92 % yield) of **8** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 2.4 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 2H), 7.40 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.23 (m, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, CDCl3) δ 166.4, 150.0, 149.9, 144.4, 139.3, 134.7, 130.4, 129.3, 128.9, 124.4, 61.1, 38.3, 14.5.
HRMS (ESI) m/z: [M+H]+ Calcd for C15H15ClNO2, 276.0786; Found 276.0784

(25) ethyl 4-((6-(trifluoromethyl)pyridin-3-yl)methyl)benzoate

Reaction conducted following **Procedure E** using 5-(chloromethyl)-2-(trifluoromethyl)pyridine (97.5 mg, 0.5 mmol, 1 equiv). Deviation from procedure is the exclusion of Barton's base.

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 147 mg (95 % yield) of **8** as a clear oil .

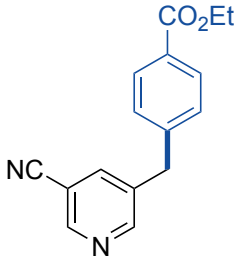


^{1}H NMR (500 MHz, CDCl3) δ 8.61 (s, 1H), 8.00 (d, J = 8.3 Hz, 2H), 7.61 (s, 2H), 7.24 (d, J = 8.3 Hz, H), 4.37 (q, J = 7.1 Hz, 3H), 4.11 (s, 3H), 1.38 (t, J = 7.1 Hz, 4H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 150.5, 146.7 (q, *J* = 34.8 Hz), 143.8, 139.2, 137.6, 130.3, 129.5, 129.0, 121.7 (q, *J* = 273.9 Hz), 120.5 (q, *J* = 2.7 Hz), 61.2, 38.9, 14.5.
^{19}F NMR (377 MHz, CDCl3) δ -67.79.
HRMS (ESI) m/z: [M+H]+ Calcd for C16H15F3NO2, 310.1049; Found 310.1049

(26) ethyl 4-((5-cyanopyridin-3-yl)methyl)benzoate

Reaction conducted following **Procedure E** using 5-(chloromethyl)nicotinonitrile hydrochloride (94.5 mg, 0.5 mmol, 1 equiv).

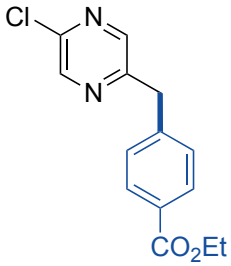
Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 79.8 mg (60 % yield) of **8** as a clear oil .



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.0 Hz, 1H), 8.69 (d, *J* = 2.2 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.70 (t, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.09 (s, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 153.6, 150.6, 143.1, 139.3, 136.5, 130.5, 129.7, 129.1, 116.5, 110.2, 61.2, 38.7, 14.5.
HRMS (ESI) m/z: [M+H]+ Calcd for C16H15N2O2, 267.1128; Found 267.1128
(27) ethyl 4-((5-chloropyrazin-2-yl)methyl)benzoate

Reaction conducted following **Procedure B** using 2-chloro-5-(chloromethyl)pyrazine (81.0 mg, 0.5 mmol, 1 equiv). Deviation from procedure is the exclusion of Barton's base.

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 160.1 mg (58 % yield) of **8** as a clear oil .

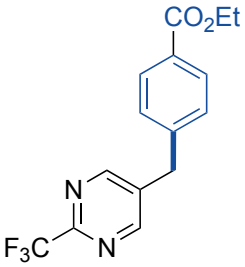


^{1}H NMR (500 MHz, CDCl3) δ 8.52 (d, J = 1.4 Hz, 1H), 8.24 (d, J = 1.5 Hz, 1H), 8.00 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 4.20 (s, 2H), 1.38 (t, J = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, CDCl3) δ 166.4, 153.8, 147.7, 144.3, 143.6, 142.9, 130.3, 129.5, 129.1, 61.1, 41.0, 14.5.
HRMS (ESI) m/z: [M+H]+ Calcd for C14H14ClN2O2, 277.0738; Found 277.0739

(28) ethyl 4-((2-(trifluoromethyl)pyrimidin-5-yl)methyl)benzoate

Reaction conducted following **Procedure E** using 5-(chloromethyl)-2-(trifluoromethyl)pyrimidine
(98 mg, 0.5 mmol, 1 equiv). Deviation from procedure is the exclusion of Barton's base.

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 122.6 mg (79 % yield) of **8** as a clear oil .

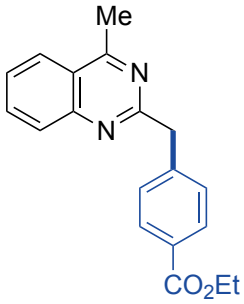


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 2H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.12 (s, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 158.0, 155.4 (q, *J* = 36.9 Hz), 142.3, 136.0, 130.6, 130.0, 129.0, 119.7 (q, *J* = 275.3 Hz), 61.3, 36.5, 14.5.
^{19}F NMR (377 MHz, $CDCl_3$) δ -70.19.
HRMS (ESI) m/z: [M+H]+ Calcd for C15H14F3N2O2, 307.1441; Found 307.1438

(29) ethyl 4-((4-methylquinazolin-2-yl)methyl)benzoate

Reaction conducted following **Procedure E** using 2-(chloromethyl)-4-methylquinazoline (96.3 mg, 0.5 mmol, 1 equiv). Deviation from procedure is the exclusion of Barton's base.

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 82.7 mg (54 % yield) of **8** as a white solid. .

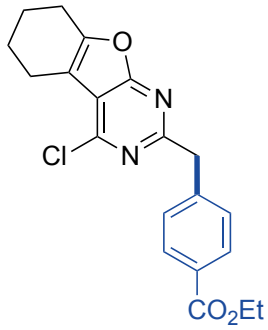


^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (m, 1H), 7.97 (m, 3H), 7.85 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.58 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 4.45 (s, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.91 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$): δ 168.9, 166.8, 164.5, 150.1, 144.0, 133.8, 129.8, 129.4, 128.8, 128.8, 127.2, 125.1, 122.7, 60.9, 46.3, 21.9, 14.5.
HRMS (ESI) m/z: [M+H]+ Calcd for C19H19N2O2, 307.1441; Found 307.1438

(30) ethyl 4-((4-chloro-5,6,7,8-tetrahydrobenzofuro[2,3-*d*]pyrimidin-2-yl)methyl)benzoate

Reaction conducted following **Procedure E** using 4-chloro-2-(chloromethyl)-5,6,7,8-tetrahydrobenzofuro[2,3-*d*]pyrimidine (128.0 mg, 0.5 mmol, 1 equiv). Deviation from procedure is the exclusion of Barton's base.

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (25:75 (v:v)) to afford 133.5 mg (72% yield) of **30** as a clear oil .

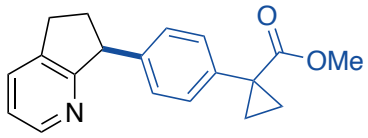


^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 4.39 – 4.33 (m, 4H), 2.80 (tt, *J* = 6.0, 2.1 Hz, 2H), 2.76 (tt, *J* = 6.3, 2.1 Hz, 2H), 1.98 – 1.92 (m, 2H), 1.90 – 1.83 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$):δ 167.13, 166.51, 162.98, 155.30, 151.20, 143.10, 129.76, 129.18, 128.91, 115.73, 111.42, 60.81, 45.19, 23.18, 22.17, 22.13, 21.04, 14.33.
HRMS (ESI) m/z: [M+H]+ Calcd for C20H20ClN2O3, 371.1157; Found 371.1152

(9-1D) methyl 1-(4-(6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl)phenyl)cyclopropane-1-carboxylate

Reaction conducted following the procedure in 4C.VII. using methyl 1-(4-iodophenyl)cyclopropane-1-carboxylate (72.5 mg, 0.24 mmol, 1.2 equiv).

Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (15:85 (v:v)) to afford 15.3 mg (39% yield w.r.t. C–H substrate) of **31** as white solid. .

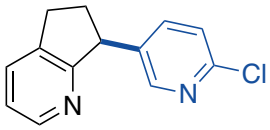


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 – 8.31 (d, *J* = 4.8, 1H), 7.56 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.27 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 7.06 (ddd, *J* = 7.6, 4.9, 0.8 Hz, 1H), 4.39 (t, *J* = 8.2 Hz, 1H), 3.61 (s, 3H), 3.11 – 3.03 (m, 1H), 3.01 – 2.90 (m, 1H), 2.65 (dtd, *J* = 12.9, 8.4, 4.5 Hz, 1H), 2.22 – 2.10 (m, 1H), 1.63 – 1.51 (m, 1H), 1.15 (d, *J* = 3.1 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 166.8, 148.4, 143.0, 137.6, 137.3, 132.5, 130.9, 128.0, 121.5, 52.4, 51.7, 34.1, 29.5, 28.8, 16.8, 16.8.
HRMS (ESI) m/z: [M+H]+ Calcd for C19H20NO2 294.1489; Found 294.1485

(9-2C) 7-(6-chloropyridin-3-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine

Reaction conducted following the procedure in 4C.VII. 2-chloro-5-iodopyridin e(57.4 mg, 0.24 mmol, 1.2 equiv).

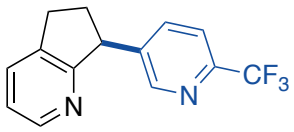
Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (40:60 (v:v)) to afford 16.1 mg (35% yield w.r.t. C–H substrate) of **34** as a tan solid. .



^{1}H NMR δ 8.42 – 8.34 (m, 1H), 8.28 (d, *J* = 2.5 Hz, 1H), 7.60 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.44 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.29 – 7.21 (m, 1H), 7.12 (ddd, *J* = 7.6, 4.9, 0.8 Hz, 1H), 4.41 (t, *J* = 8.4 Hz, 1H), 3.38 – 2.93 (m, 2H), 2.69 (dtd, *J* = 12.5, 8.2, 4.2 Hz, 1H), 2.08 (dq, *J* = 13.0, 8.5 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 149.7, 148.6, 138.5, 138.4, 137.3, 132.8, 124.4, 122.1, 48.7, 34.0, 29.4.
HRMS (ESI) m/z: [M+H]+ Calcd for C13H12ClN2, 231.0684; Found 231.0684

(9-2E) 7-(6-(trifluoromethyl)pyridin-3-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine
Reaction conducted following the procedure in 4C.VII. 5-iodo-2-(trifluoromethyl)pyridine (65.5 mg, 0.24 mmol, 1.2 equiv).

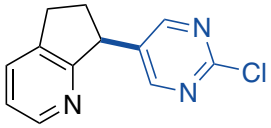
Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (40:60 (v:v)) to afford 21.7 mg (41% yield w.r.t. C–H substrate) of **32** as tan solid. .



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 2.1 Hz, 1H), 8.39 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.68 – 7.59 (m, 3H), 7.14 (ddd, *J* = 7.6, 5.0, 0.8 Hz, 1H), 4.51 (t, *J* = 8.5 Hz, 1H), 3.18 – 2.96 (m, 2H), 2.74 (dtd, *J* = 12.7, 8.2, 4.2 Hz, 1H), 2.13 (dq, *J* = 13.0, 8.5 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 150.1, 148.5, 146.5 (q, *J* = 34.6 Hz), 142.7, 137.2, 136.8, 132.8, 122.1, 121.7 (q, *J* = 273.8 Hz), 120.4 (q, *J* = 2.7 Hz), 49.1, 33.9, 29.4.
HRMS (ESI) m/z: [M+H]+ Calcd for C14H12F3N2 265.0947; Found 265.0945

(9-3D) 7-(2-chloropyrimidin-5-yl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine
Reaction conducted following the procedure in 4C.VII. 2-chloro-5-iodopyrimidine (57.7 mg, 0.24 mmol, 1.2 equiv).

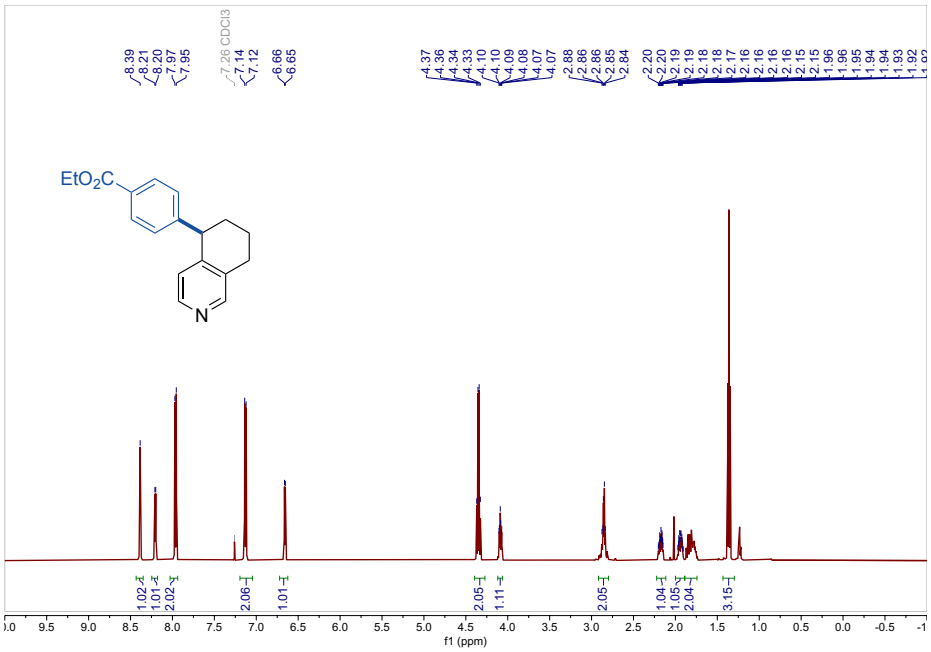
Following workup, the obtained residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate:hexanes (40:60 (v:v)) to afford 23.1 mg (50% yield w.r.t. C–H substrate) of **33** as a white solid. .



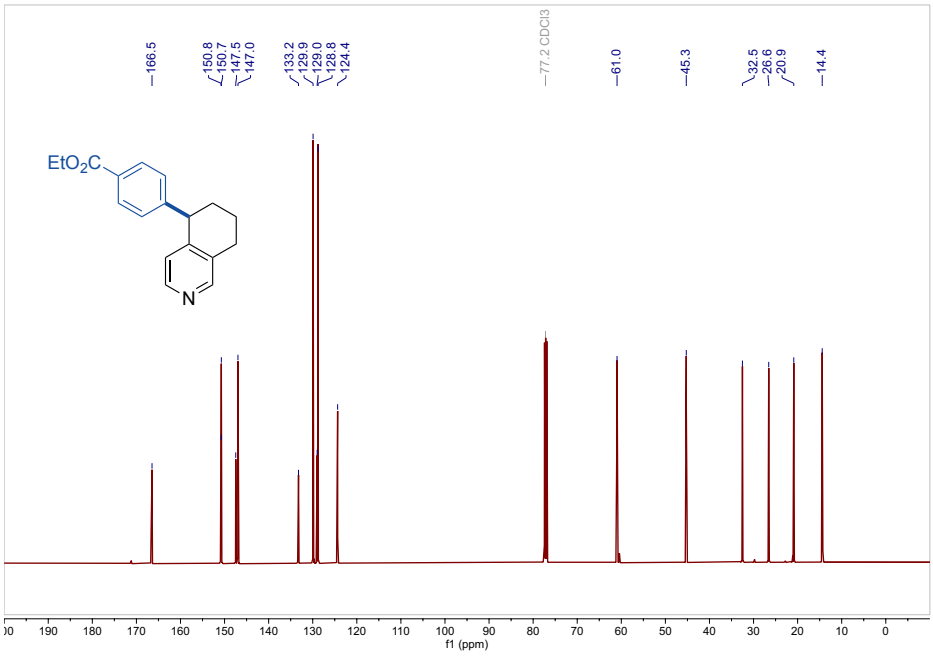
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 2H), 8.39 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.63 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.15 (ddd, *J* = 7.7, 5.0, 0.8 Hz, 1H), 4.41 (t, *J* = 8.6 Hz, 1H), 3.17 – 2.98 (m, 2H), 2.73 (dtd, *J* = 12.4, 8.0, 4.0 Hz, 1H), 2.11 (dq, *J* = 13.0, 8.7 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8, 159.8, 159.5, 148.7, 137.2, 135.7, 133.0, 122.5, 46.4, 33.6, 29.4.
HRMS (ESI) m/z: [M+H]+ Calcd for C13H12ClN2, 232.0636; Found 232.0637

4C.VIX. NMR Spectroscopic Data

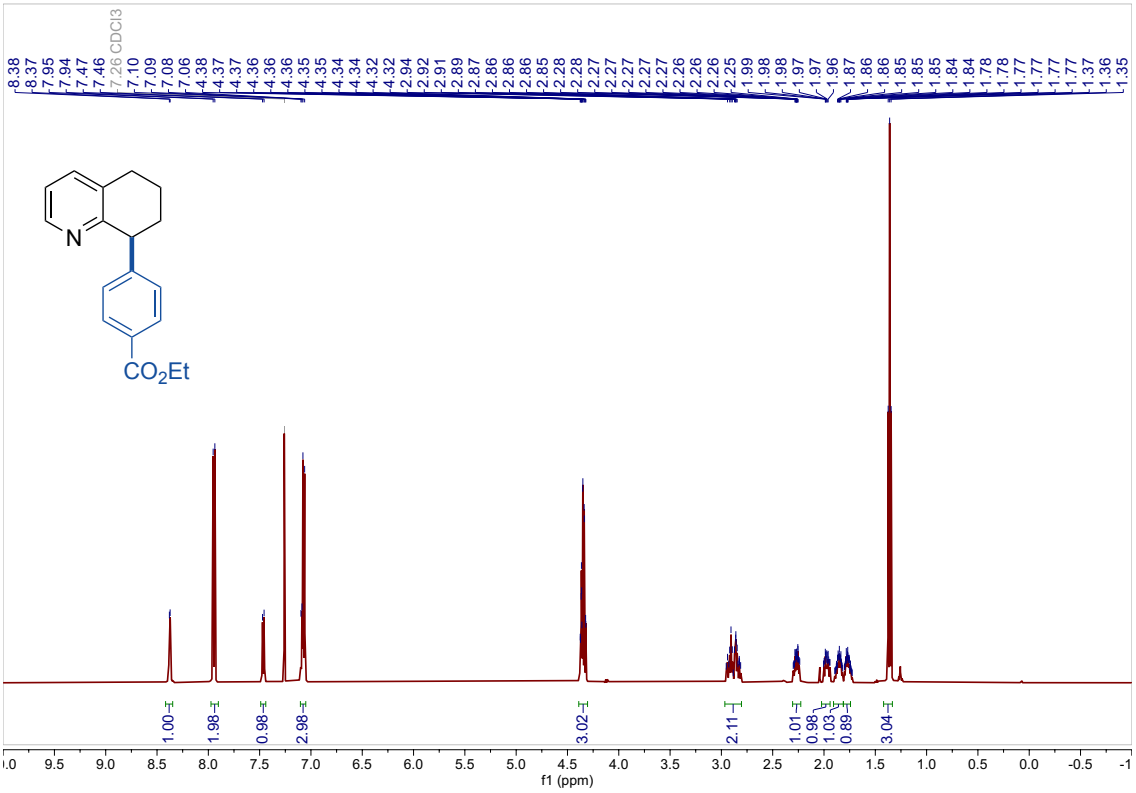
^{1}H NMR (500 MHz, $CDCl_3$) of **1**



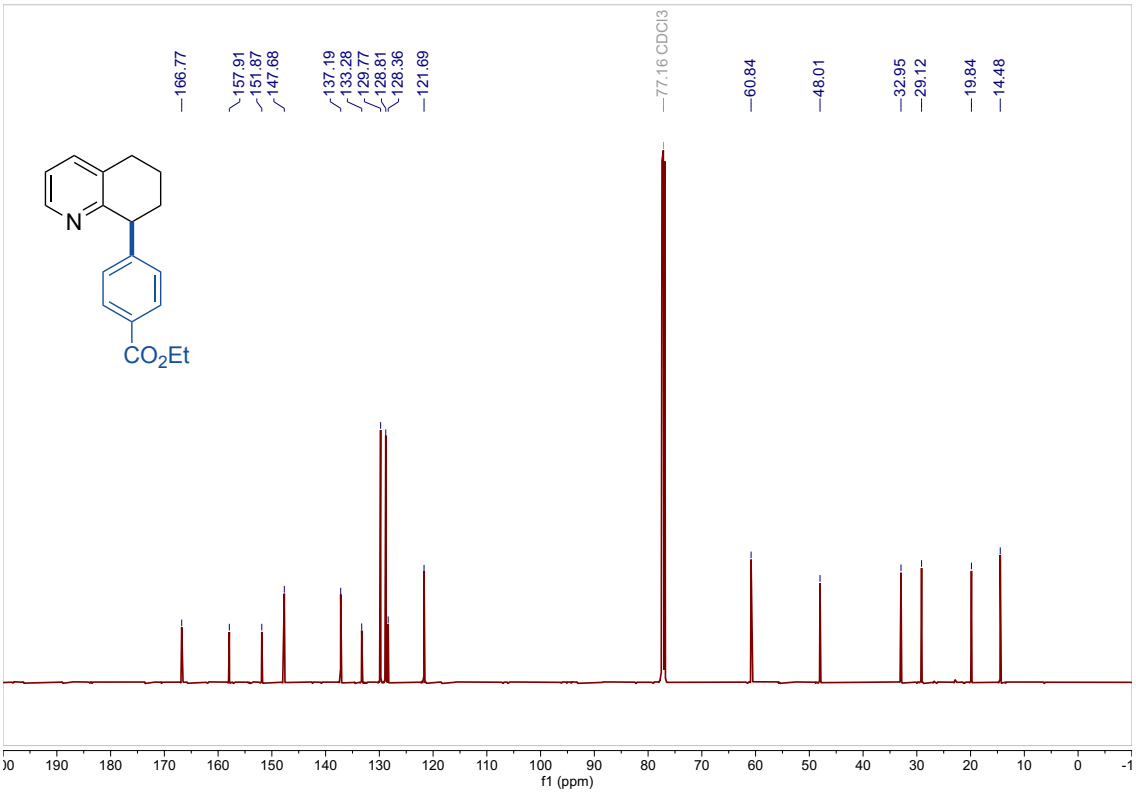
^{13}C NMR: (126 MHz, $CDCl_3$) of **1**



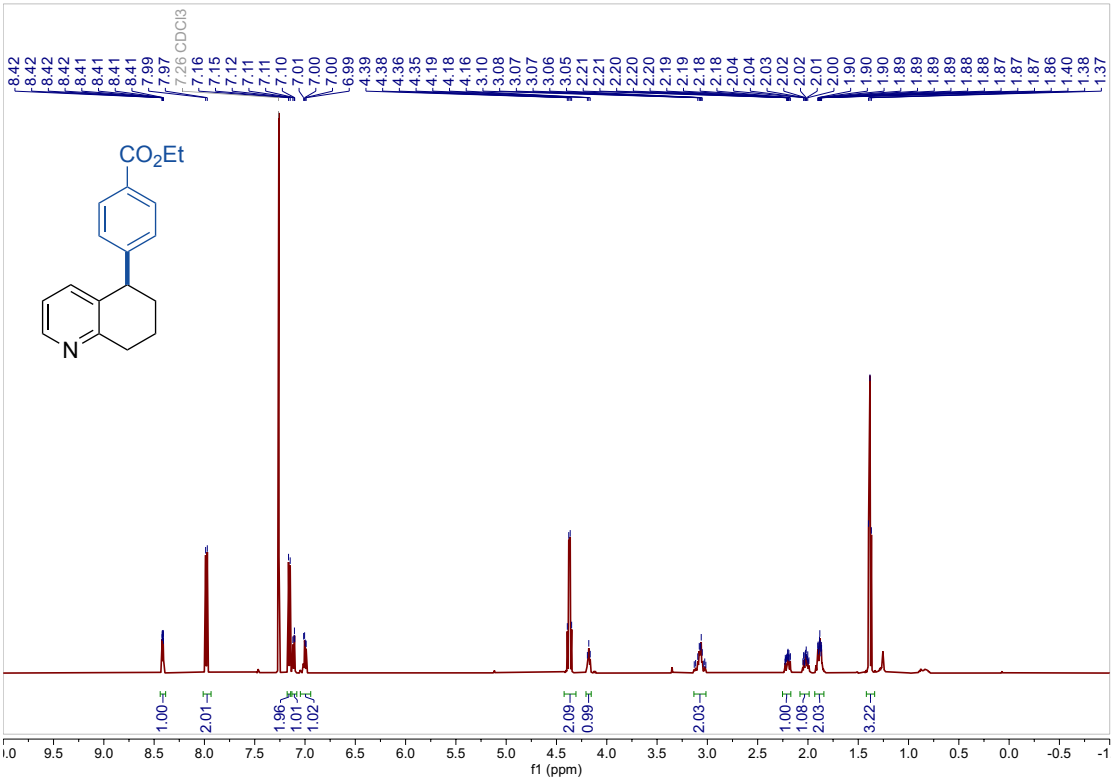
^{1}H NMR (500 MHz, $CDCl_3$) of **2**



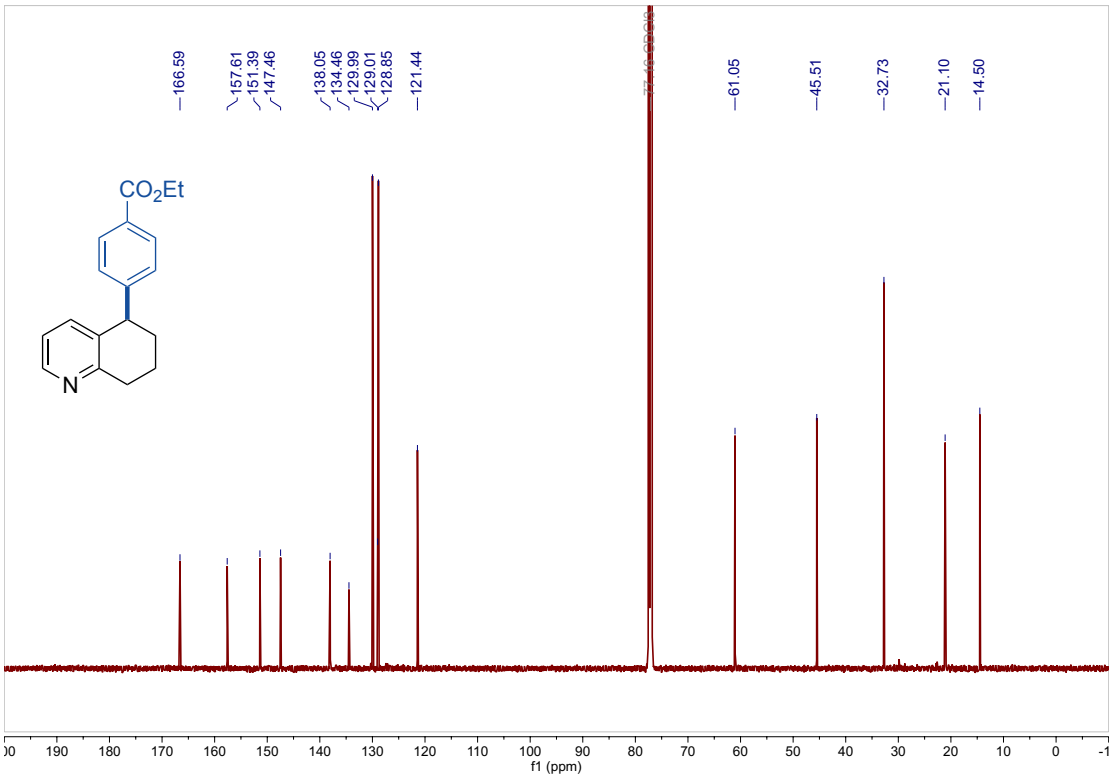
^{13}C NMR: (126 MHz, $CDCl_3$) of **2**



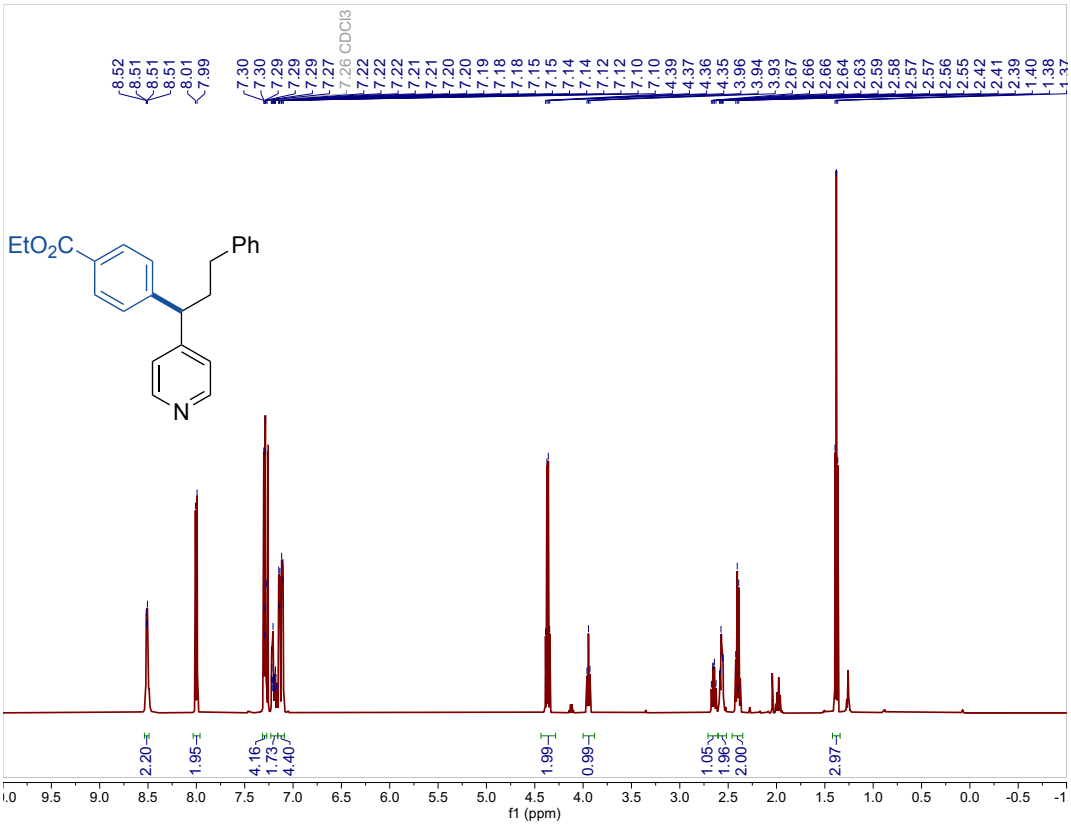
^{1}H NMR (500 MHz, $CDCl_3$) of **3**



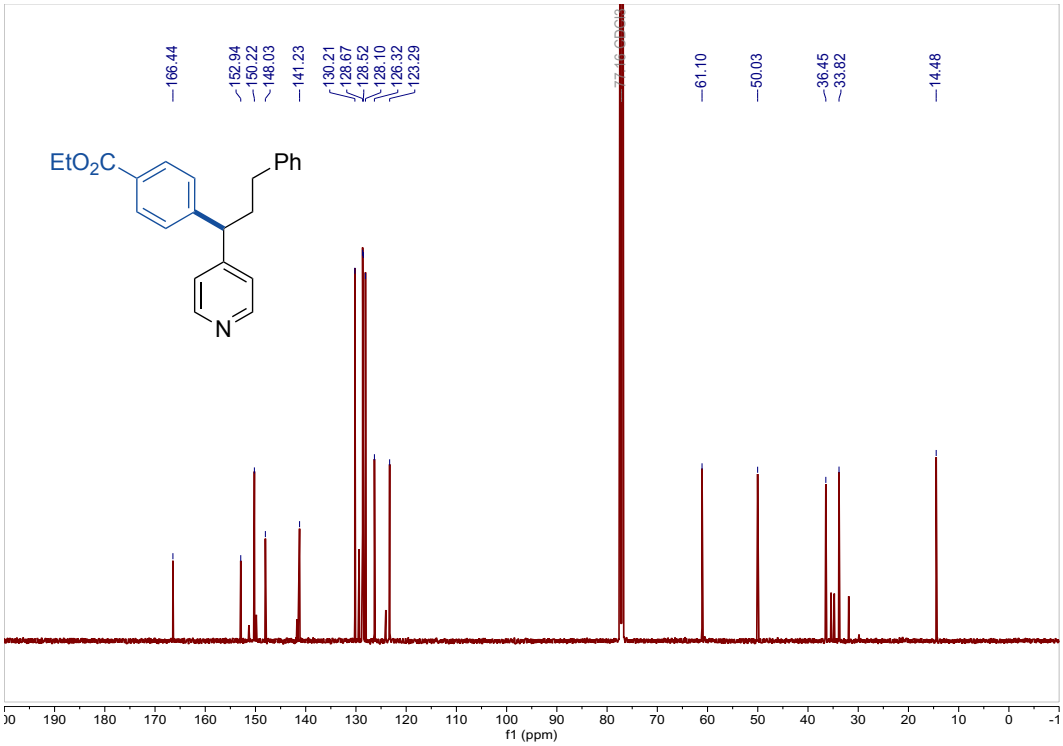
^{13}C NMR: (126 MHz, $CDCl_3$) of **3**



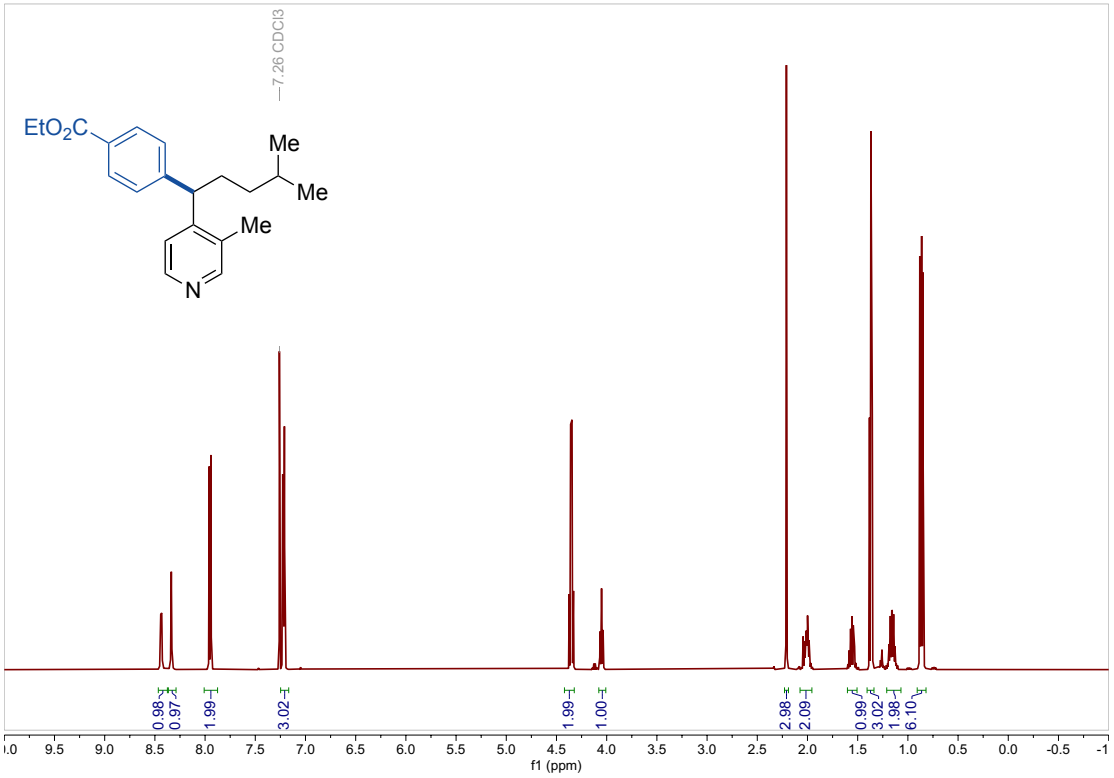
^{1}H NMR (500 MHz, $CDCl_3$) of **4**



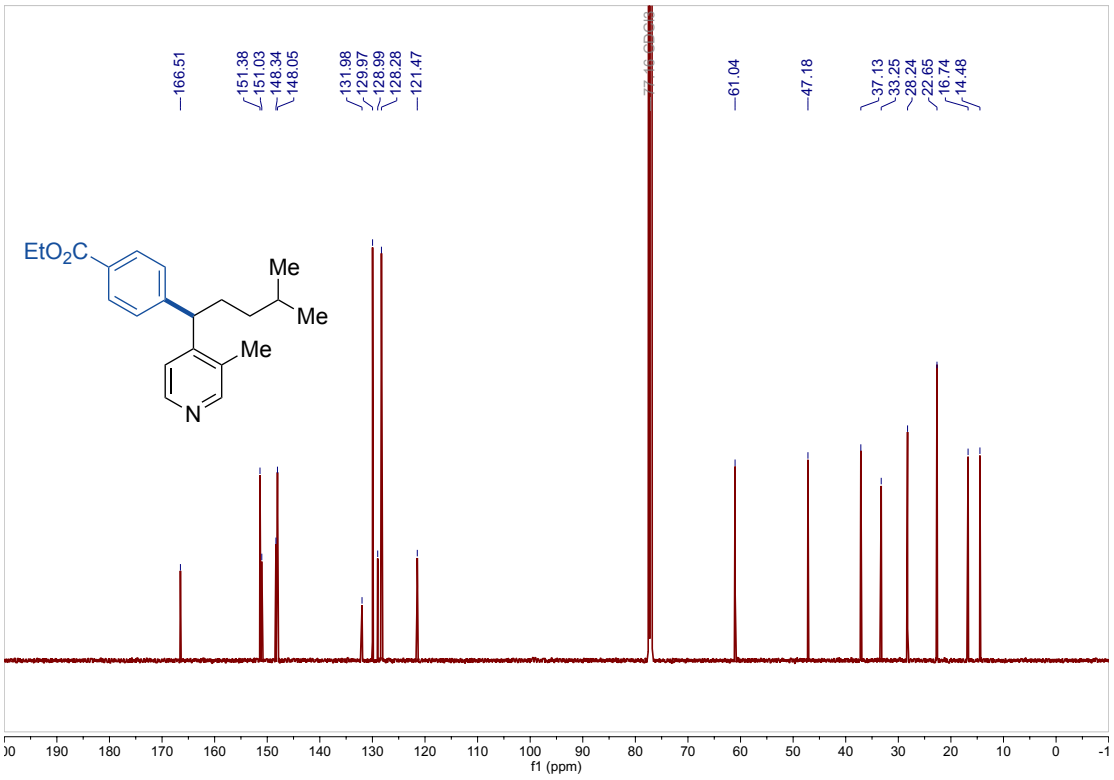
^{13}C NMR: (126 MHz, $CDCl_3$) of **4**



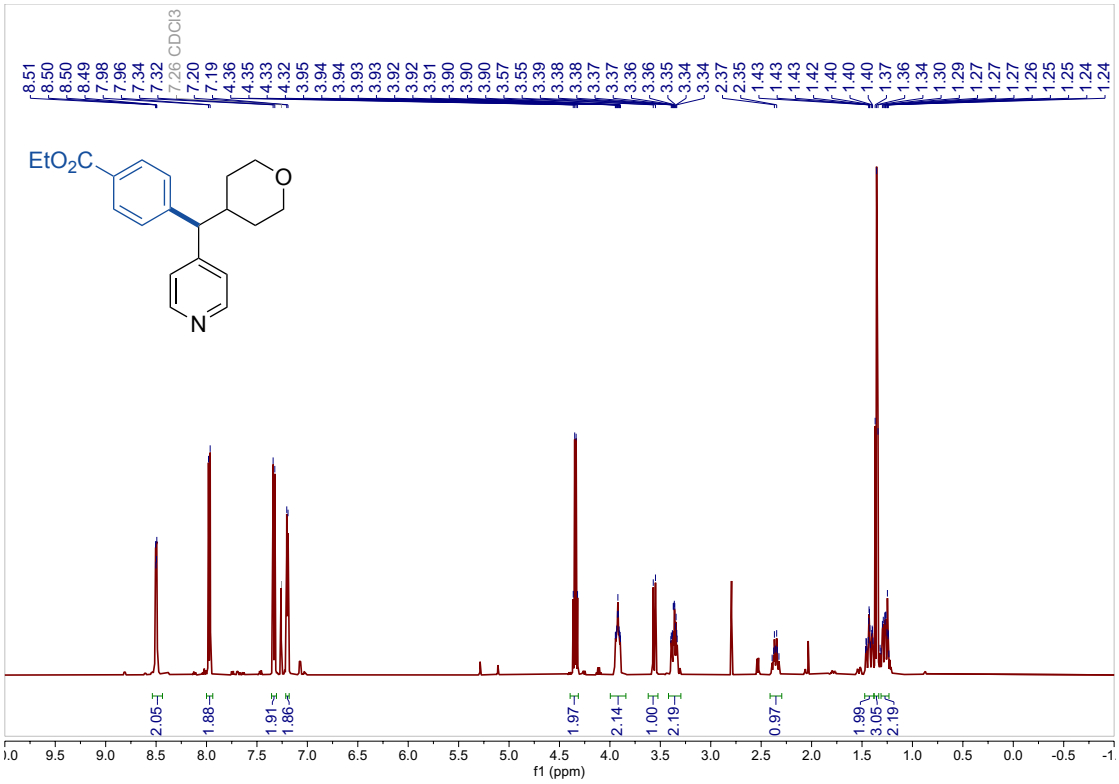
^{1}H NMR (500 MHz, $CDCl_3$) of **5**



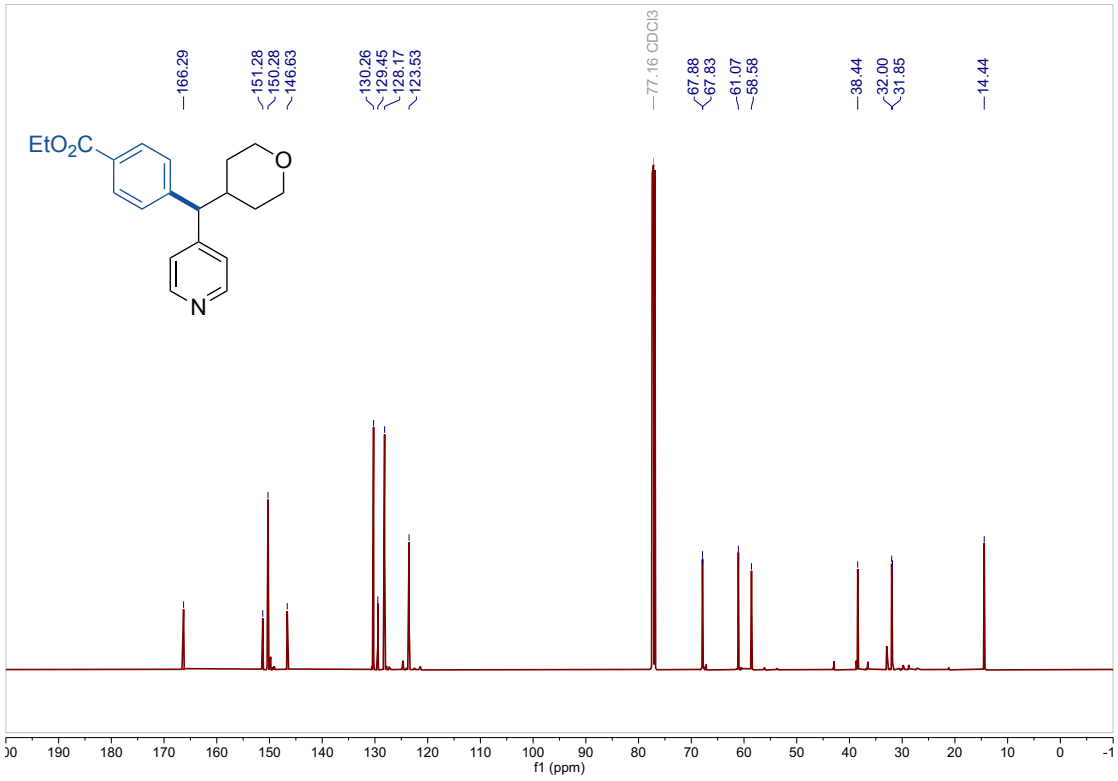
^{13}C NMR: (126 MHz, $CDCl_3$) of **5**



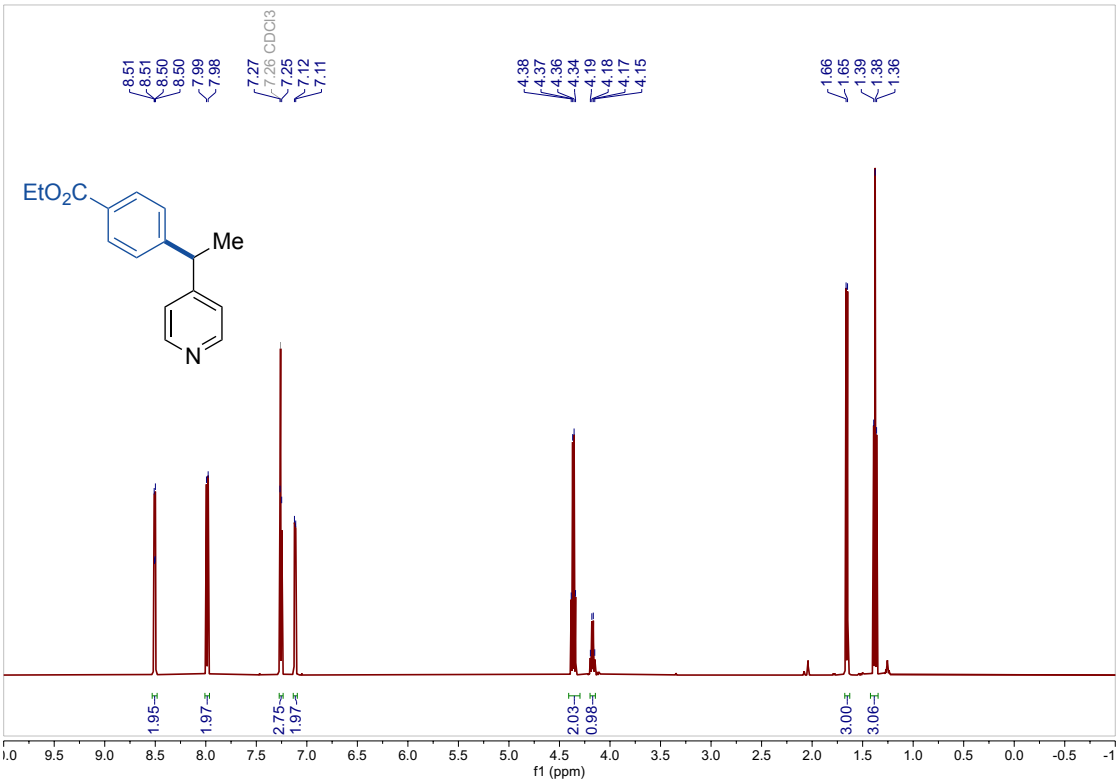
^{1}H NMR (500 MHz, $CDCl_3$) of **6**



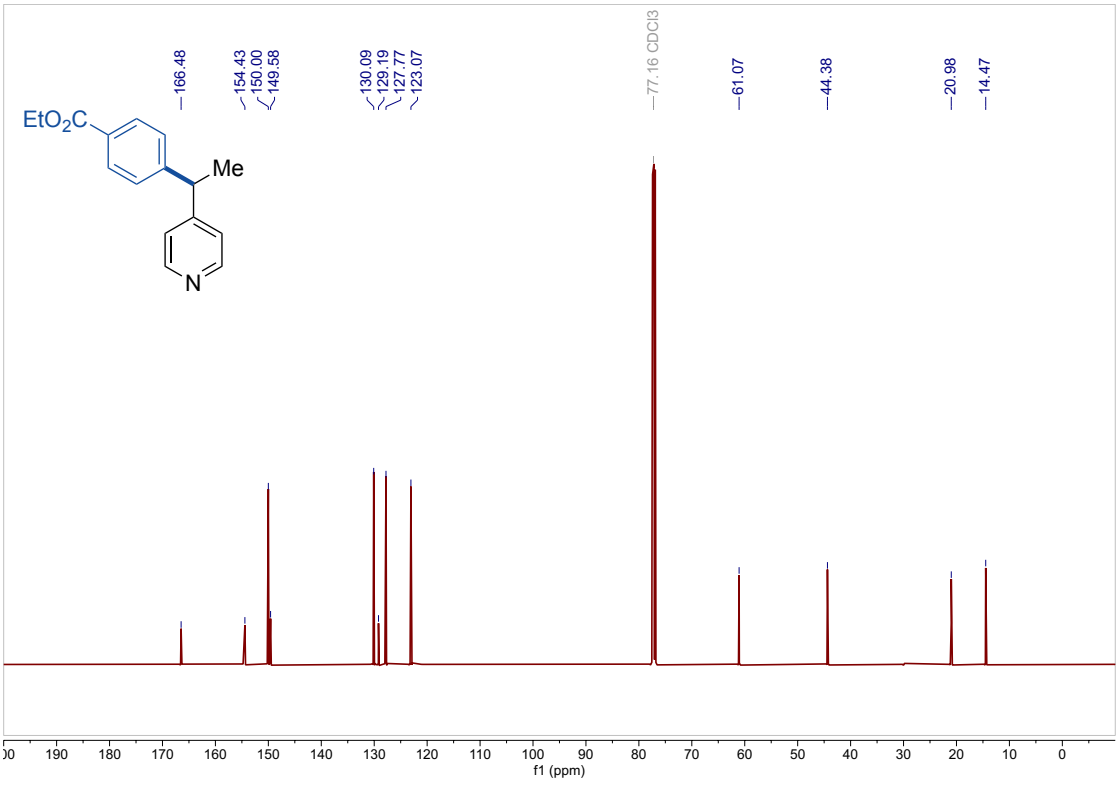
^{13}C NMR: (126 MHz, $CDCl_3$) of **6**



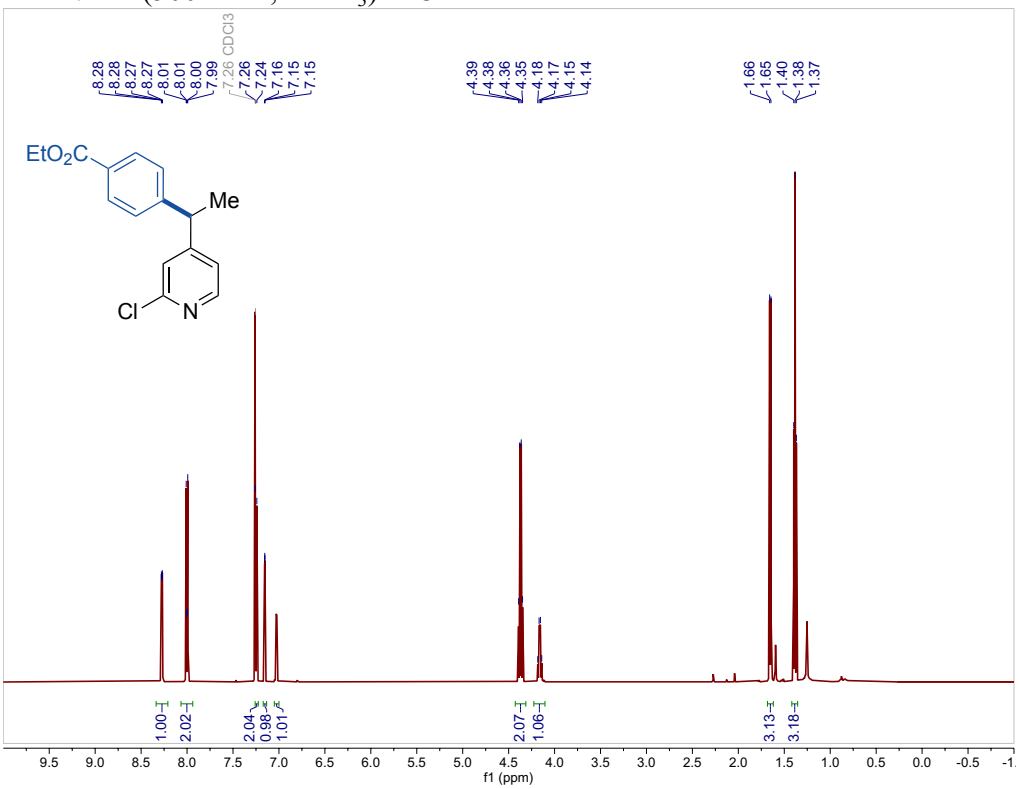
^{1}H NMR (500 MHz, $CDCl_3$) of **7**



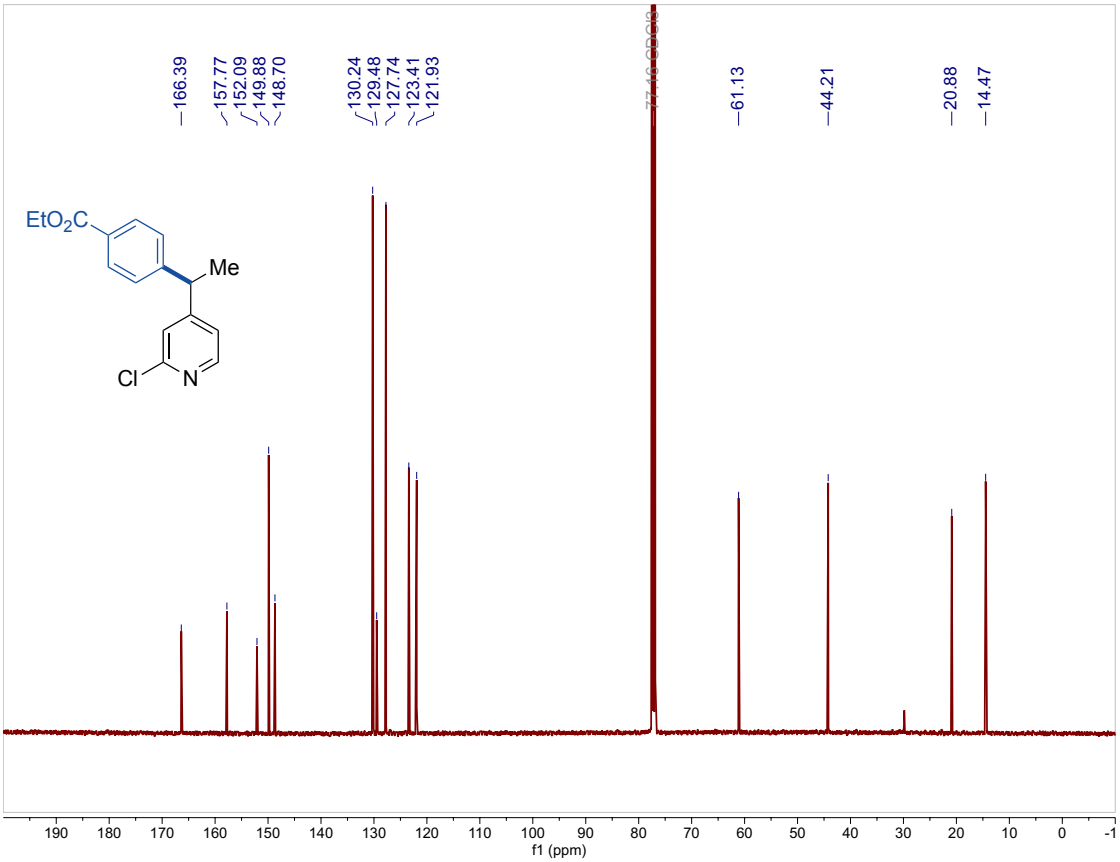
^{13}C NMR: (126 MHz, $CDCl_3$) of **7**



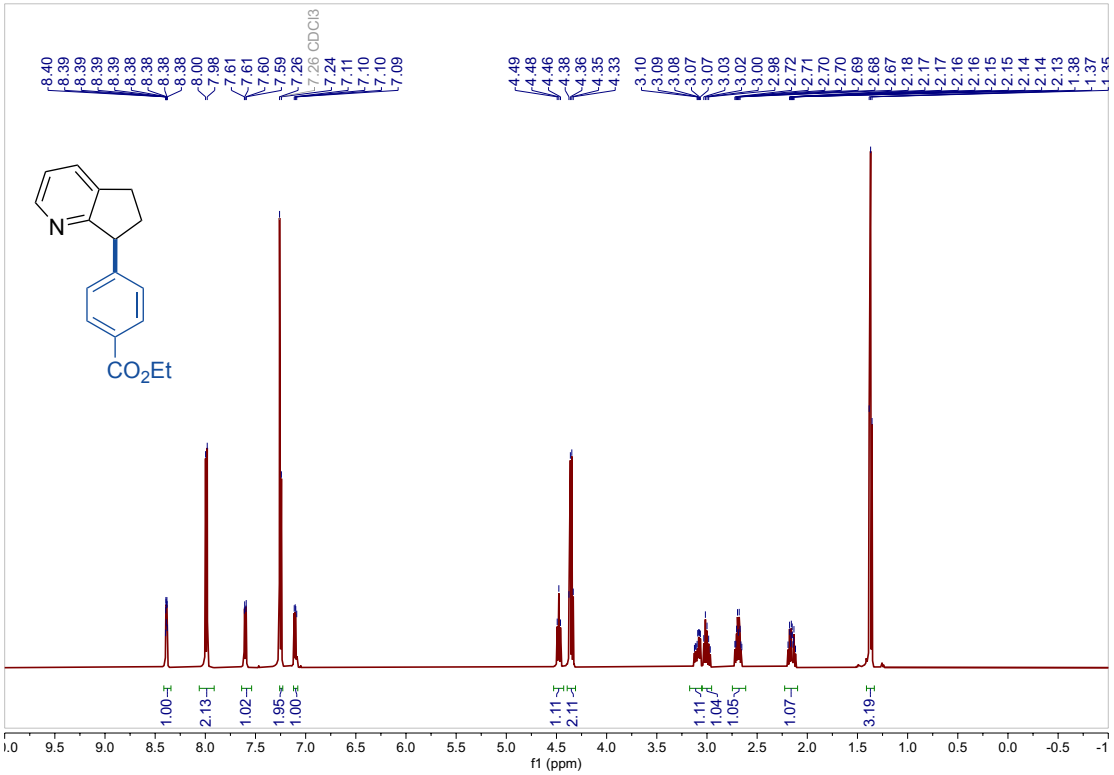
^{1}H NMR (500 MHz, $CDCl_3$) of **8**



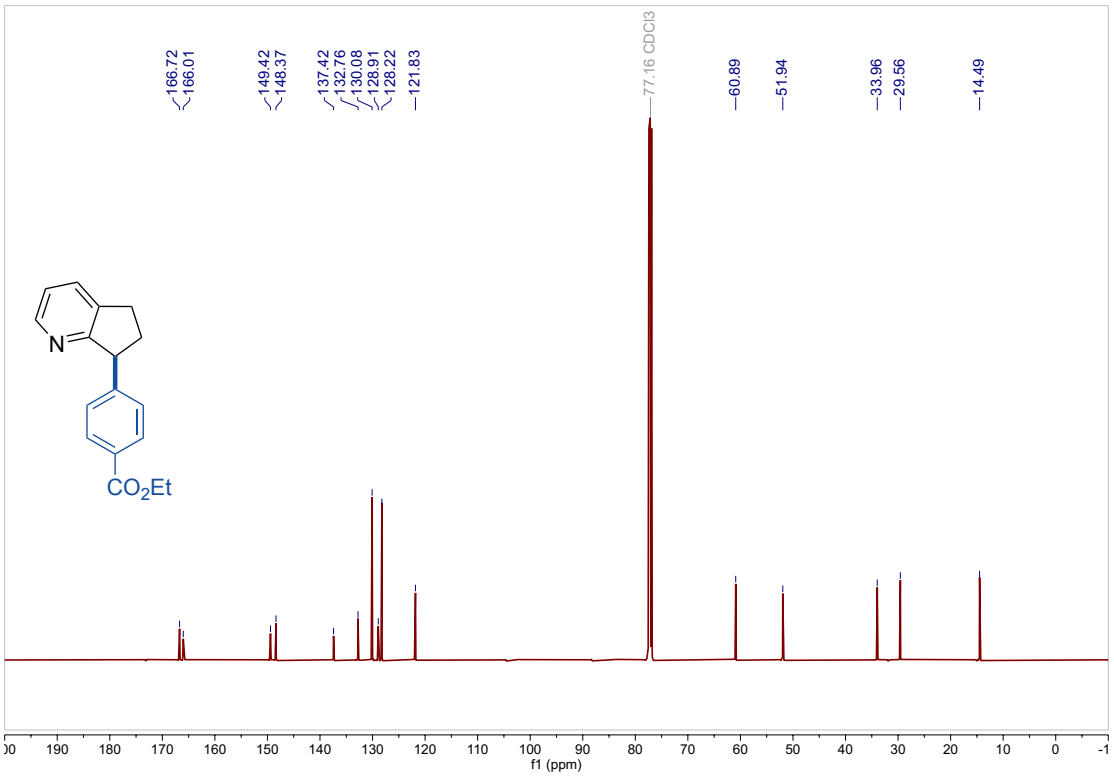
^{13}C NMR: (126 MHz, $CDCl_3$) of **8**



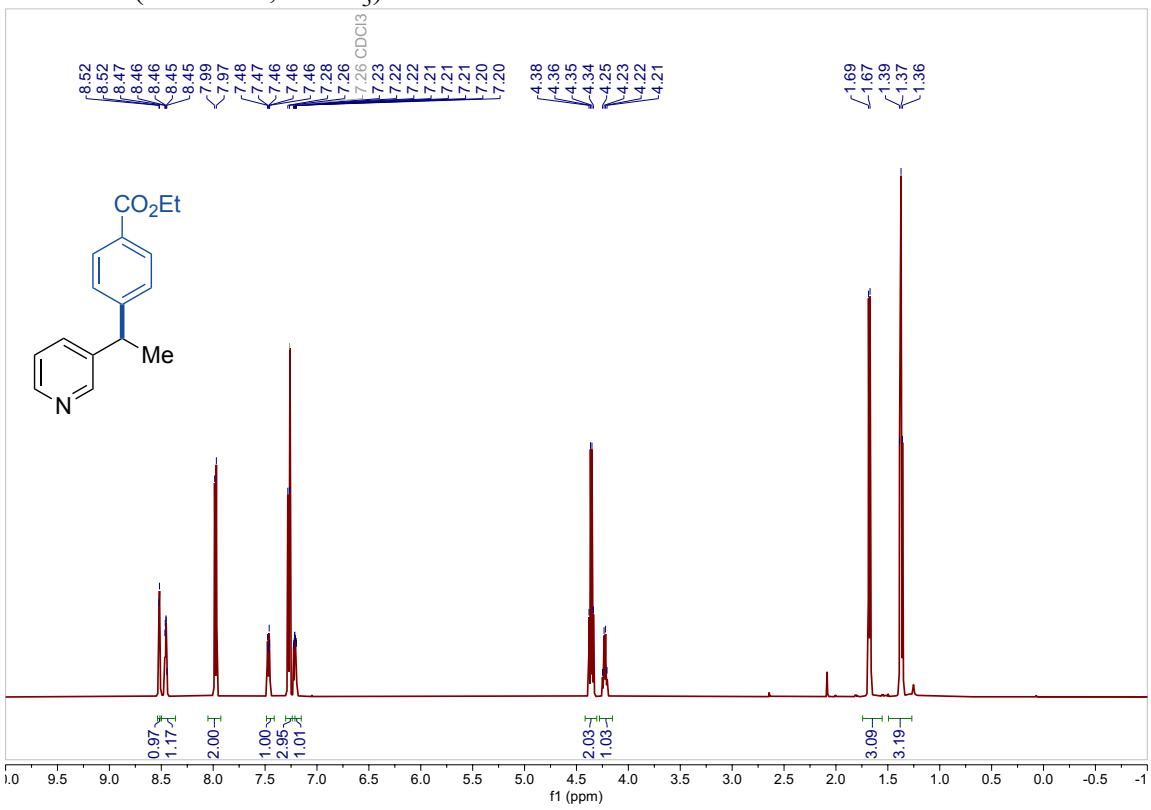
^{1}H NMR (500 MHz, $CDCl_3$) of **9**



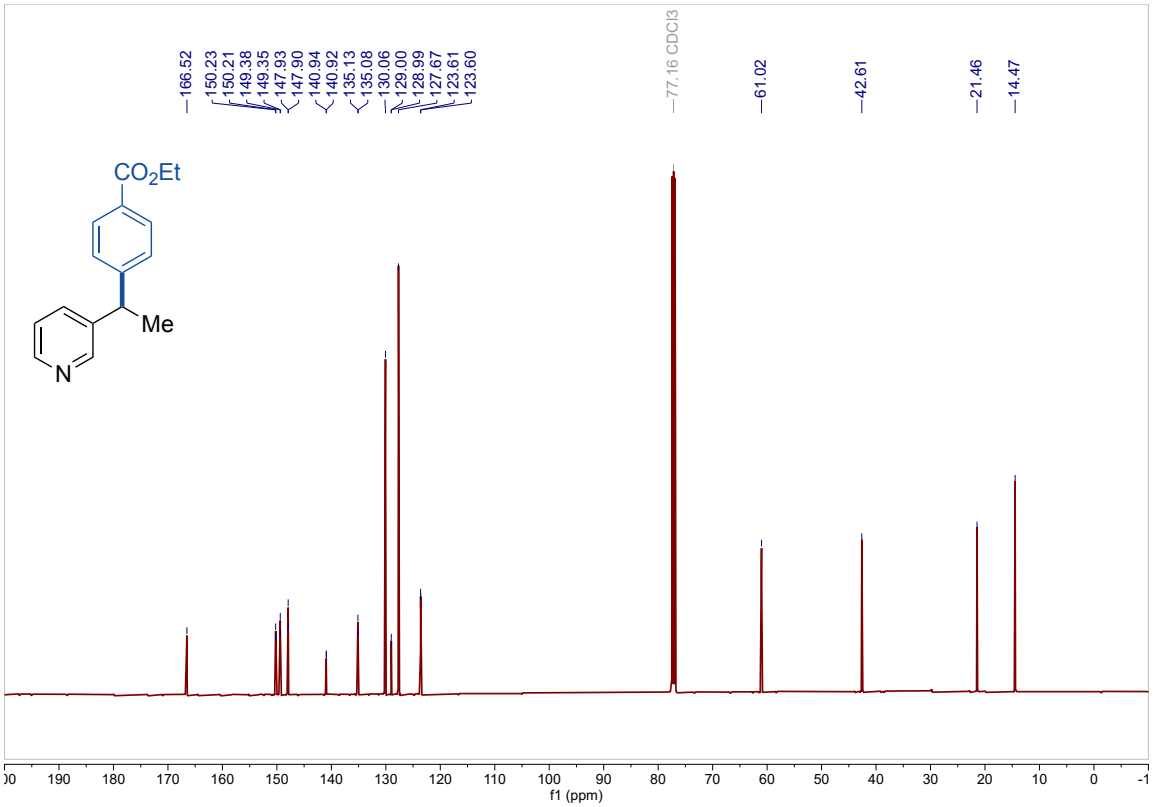
^{13}C NMR: (126 MHz, $CDCl_3$) of **9**



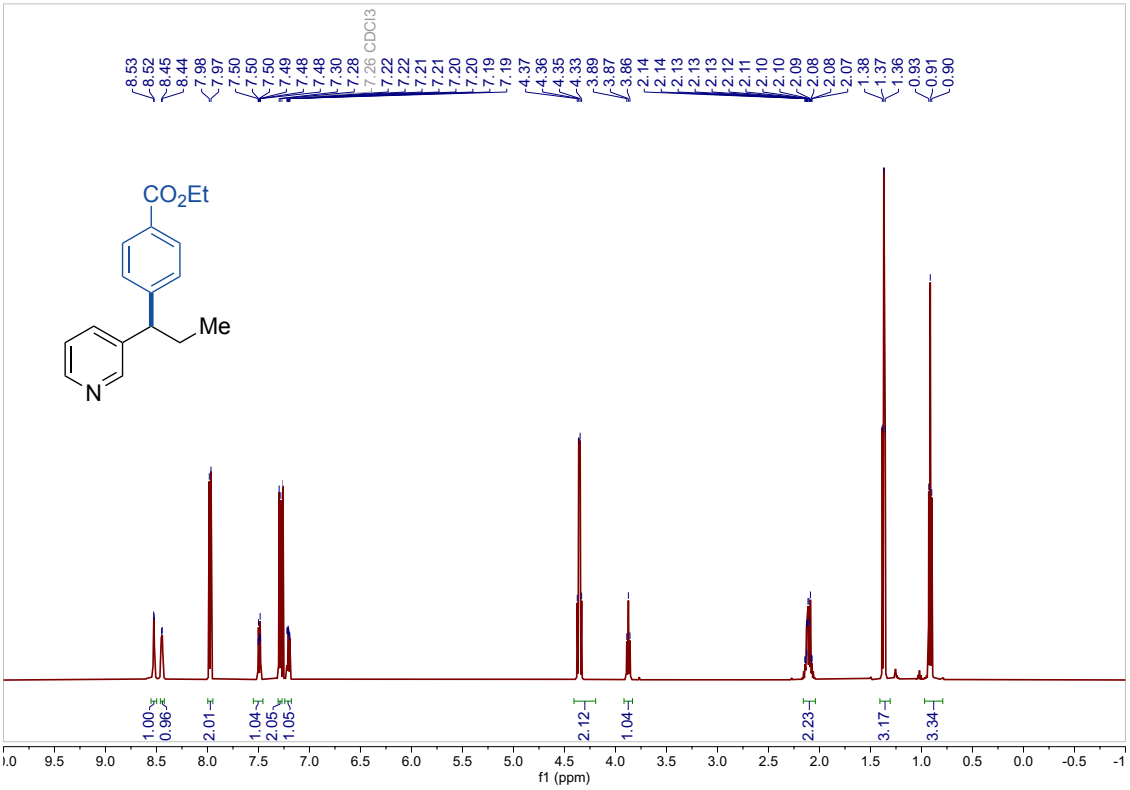
^{1}H NMR (500 MHz, $CDCl_3$) of **10**



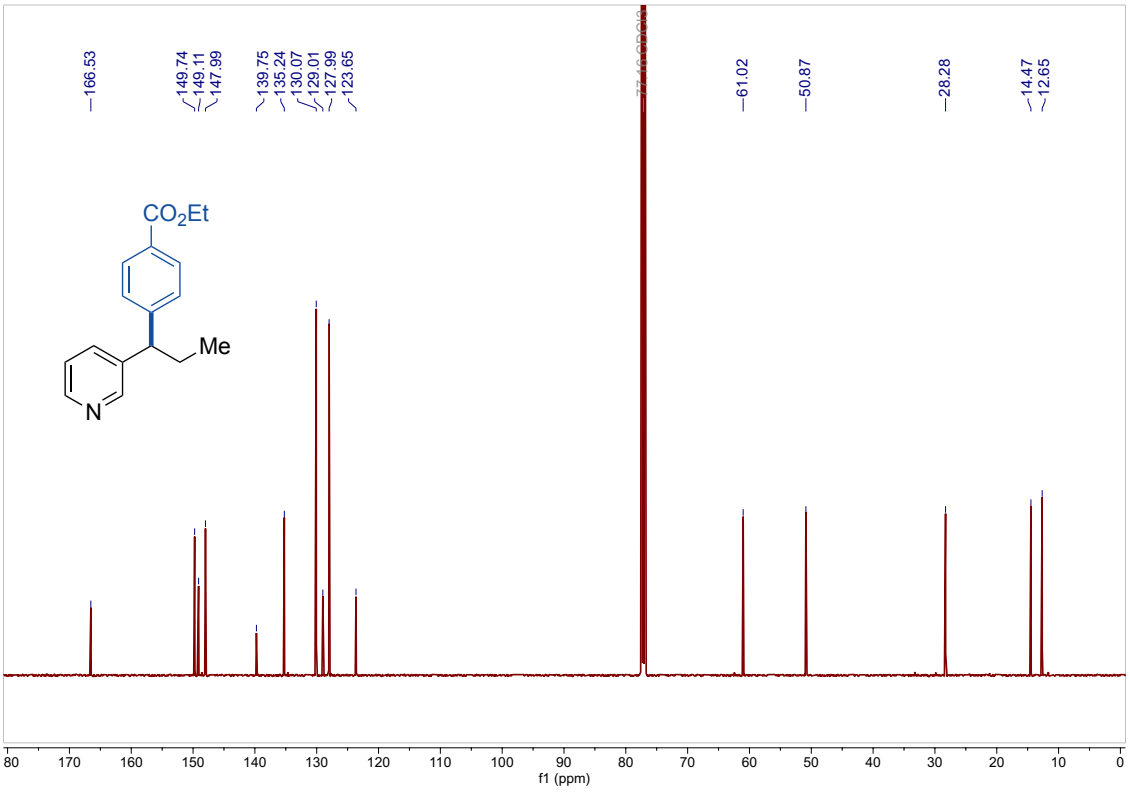
^{13}C NMR: (126 MHz, $CDCl_3$) of **10**



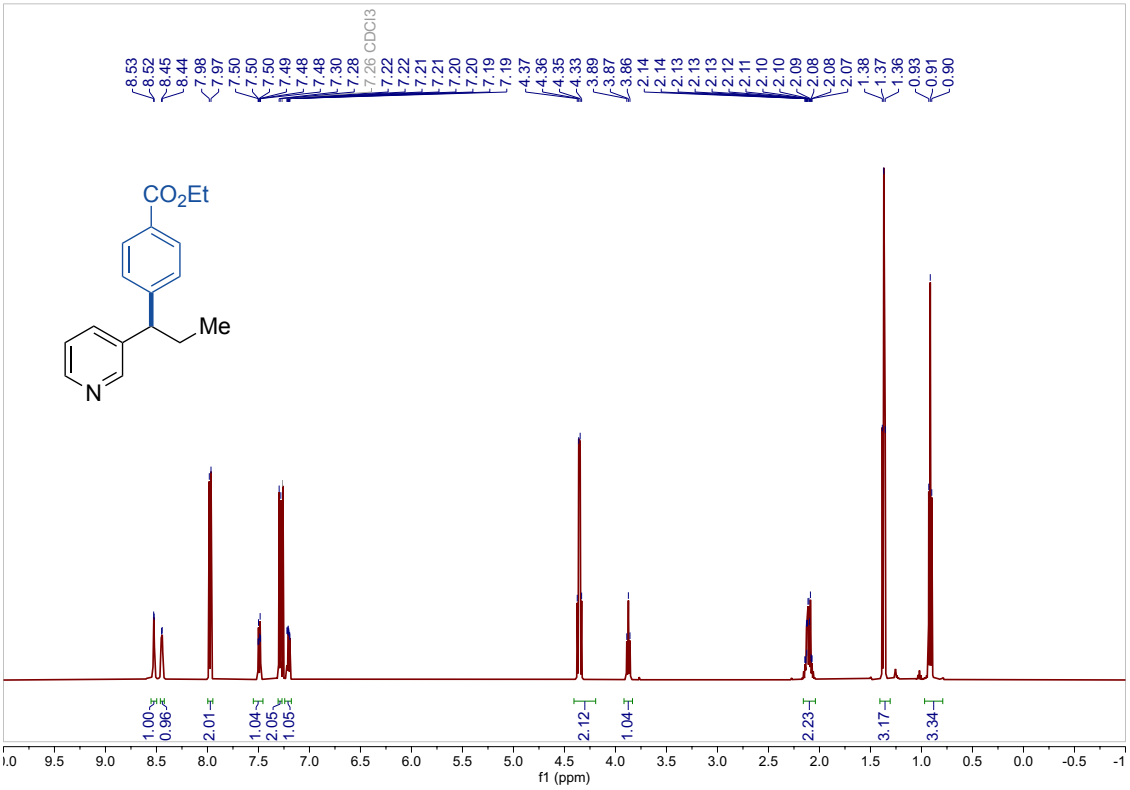
^{1}H NMR (500 MHz, $CDCl_3$) of **11**



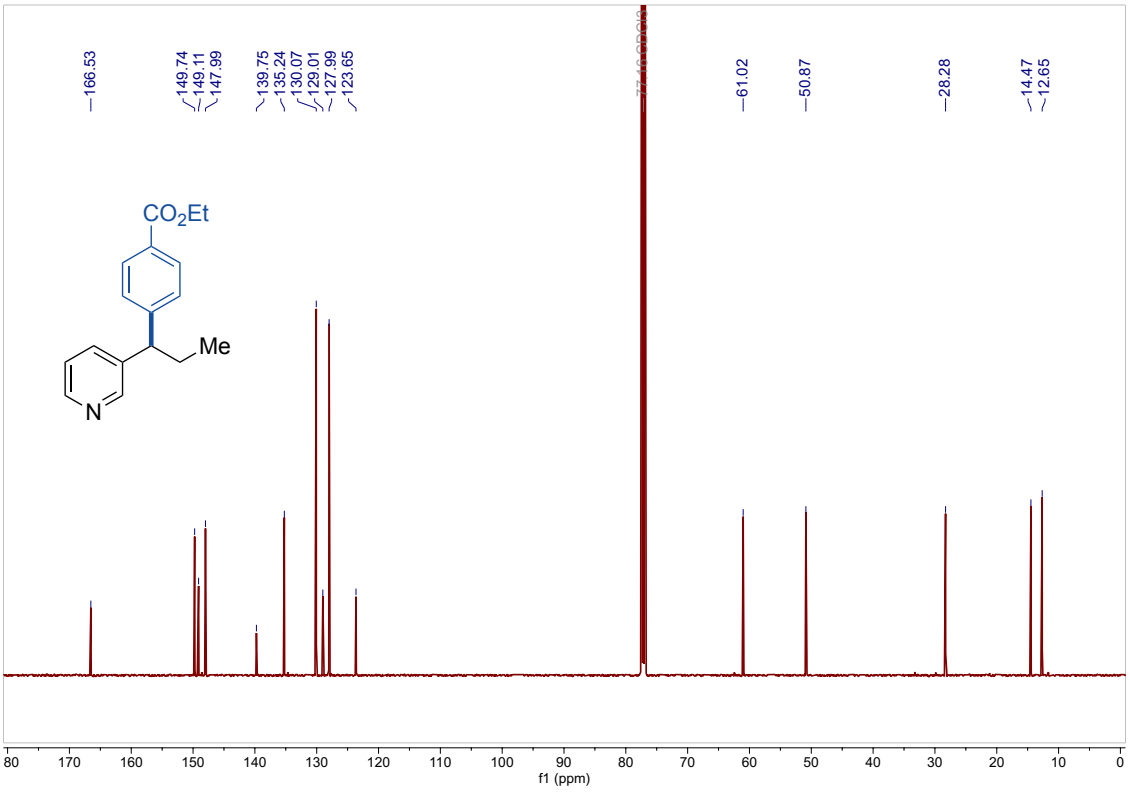
^{13}C NMR: (126 MHz, $CDCl_3$) of **11**



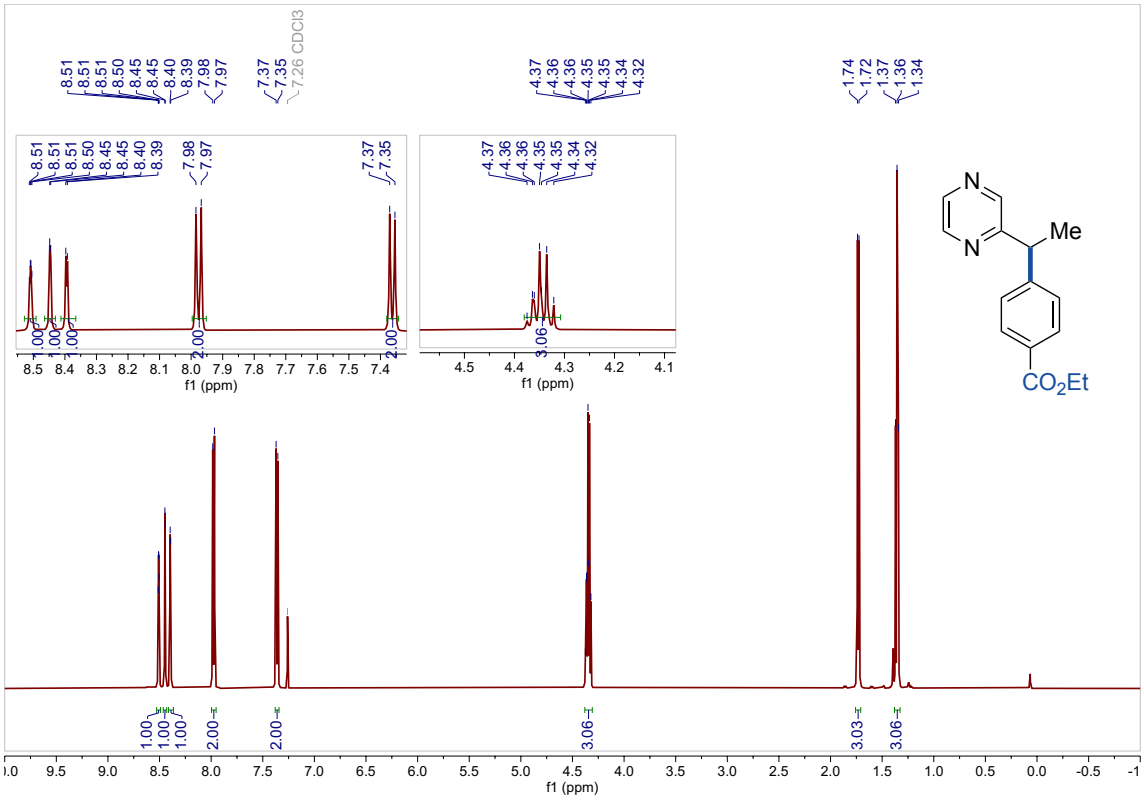
^{1}H NMR (500 MHz, $CDCl_3$) of **12**



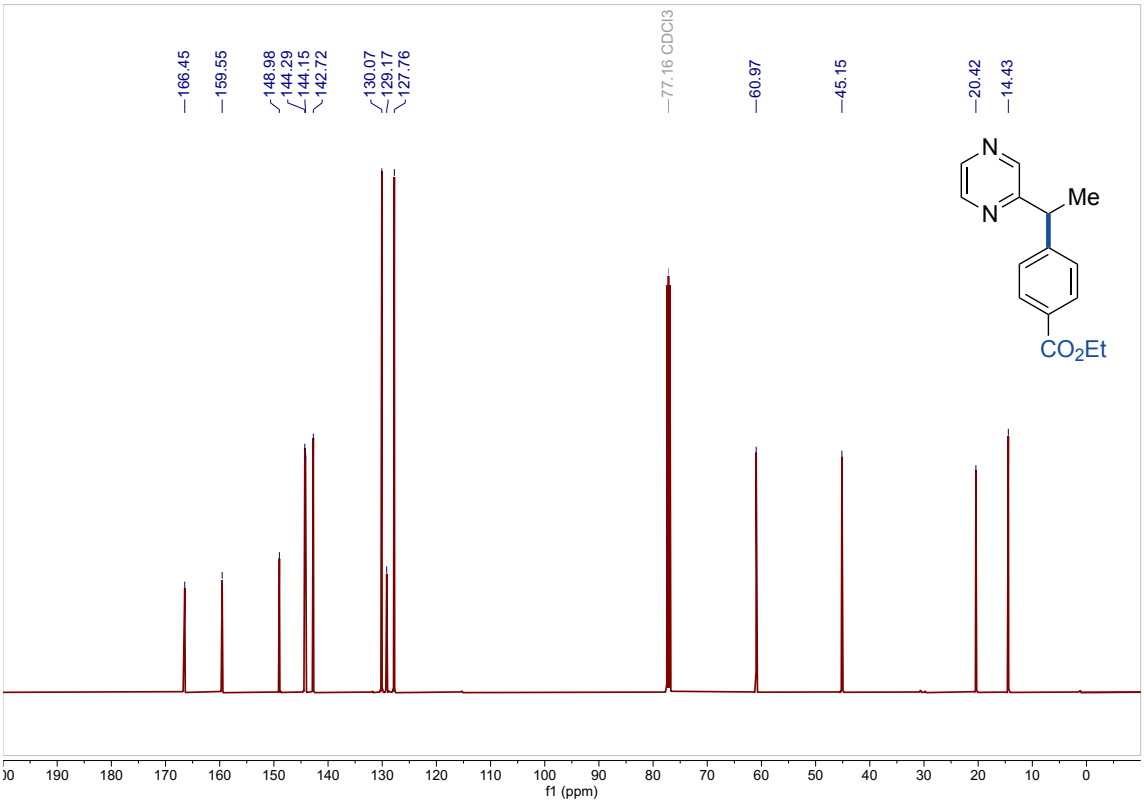
^{13}C NMR: (126 MHz, $CDCl_3$) of **12**



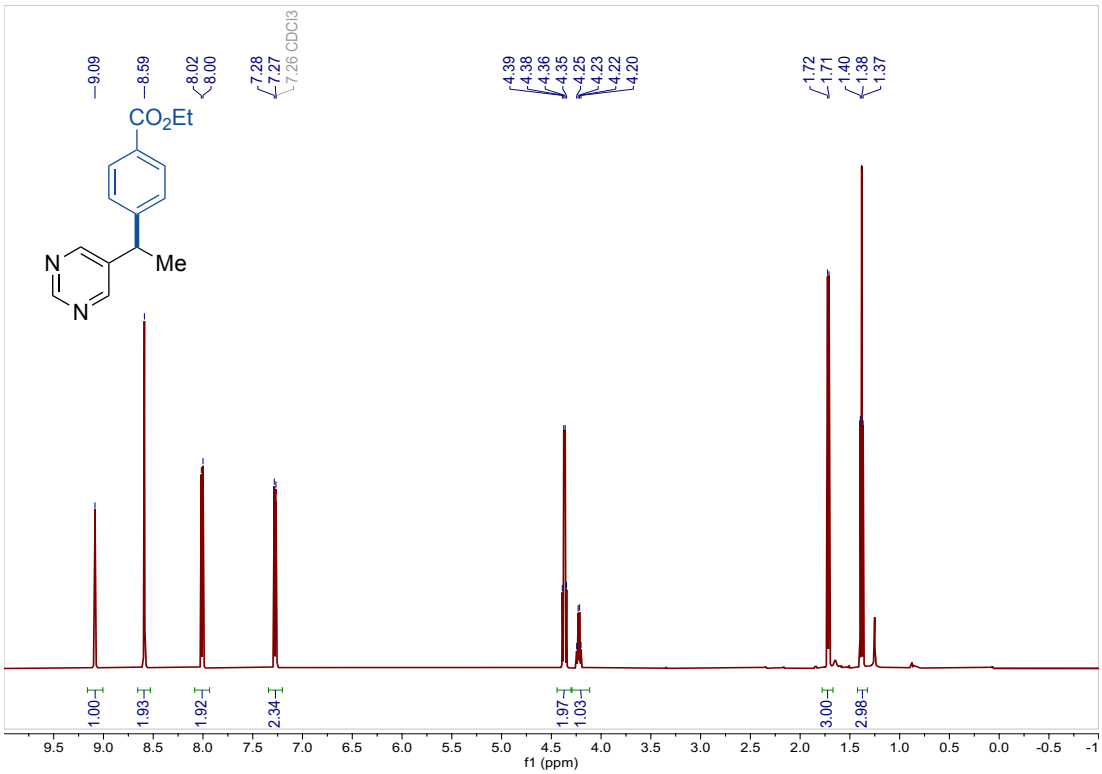
^{1}H NMR (500 MHz, $CDCl_3$) of **13**



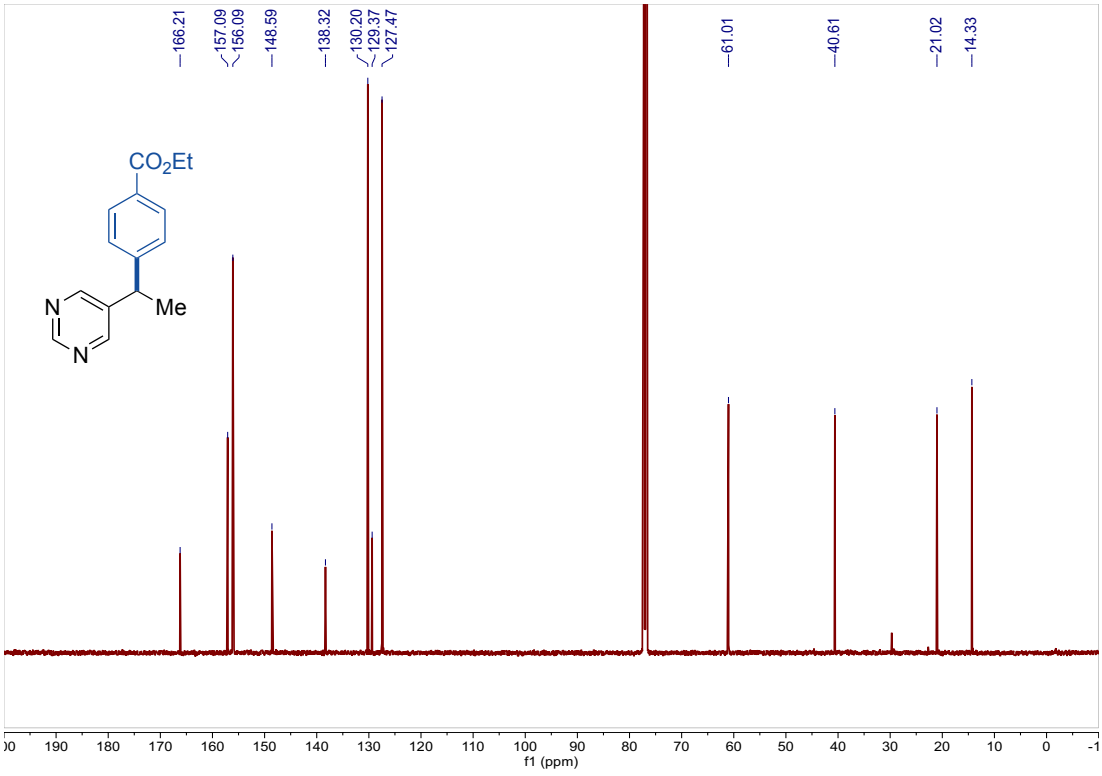
^{13}C NMR: (126 MHz, $CDCl_3$) of **13**



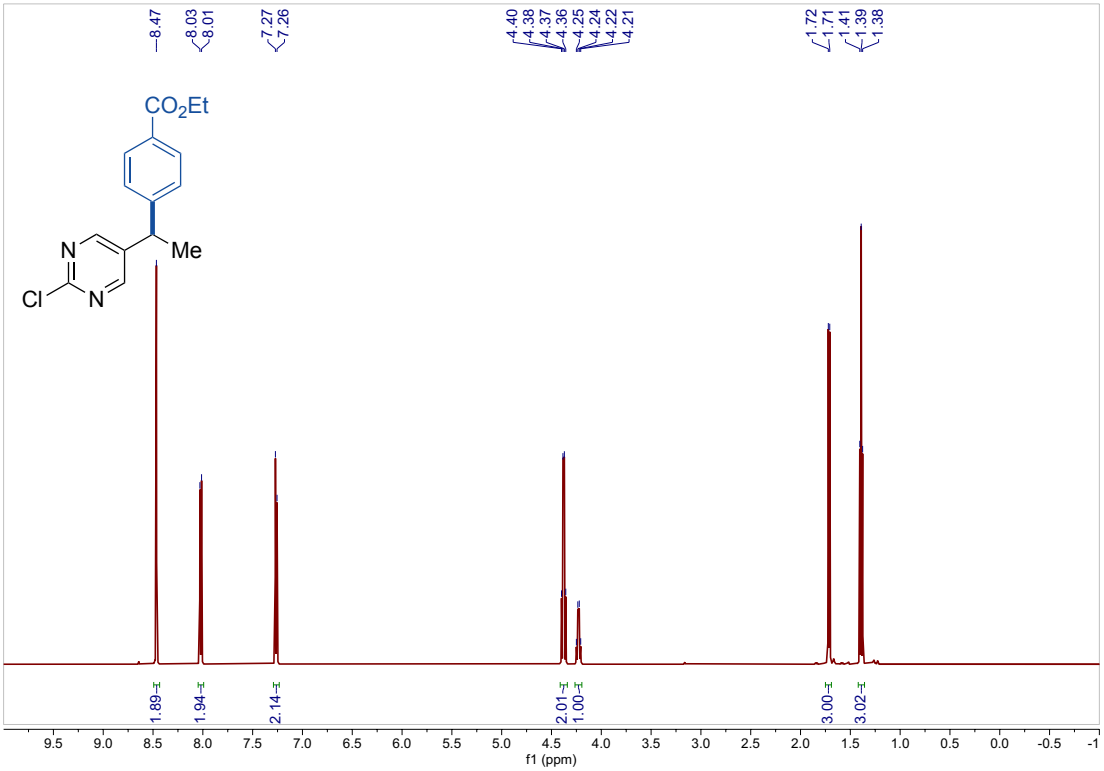
^{1}H NMR (500 MHz, $CDCl_3$) of **14**



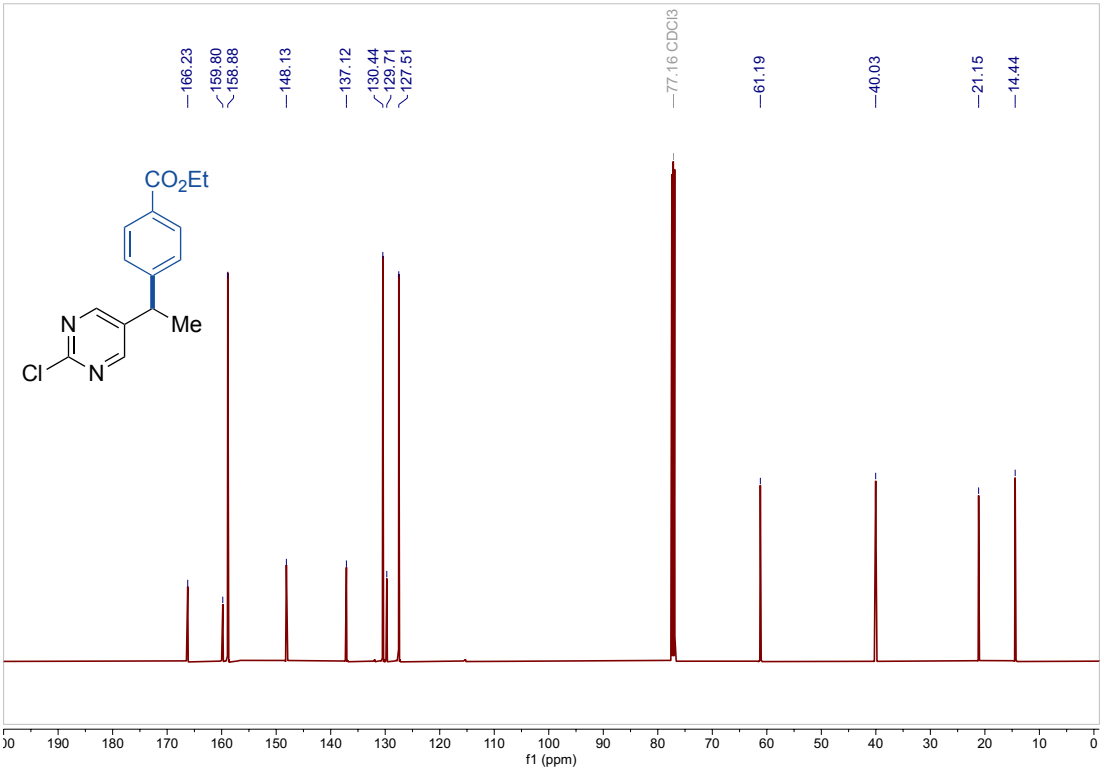
^{13}C NMR: (126 MHz, $CDCl_3$) of **14**



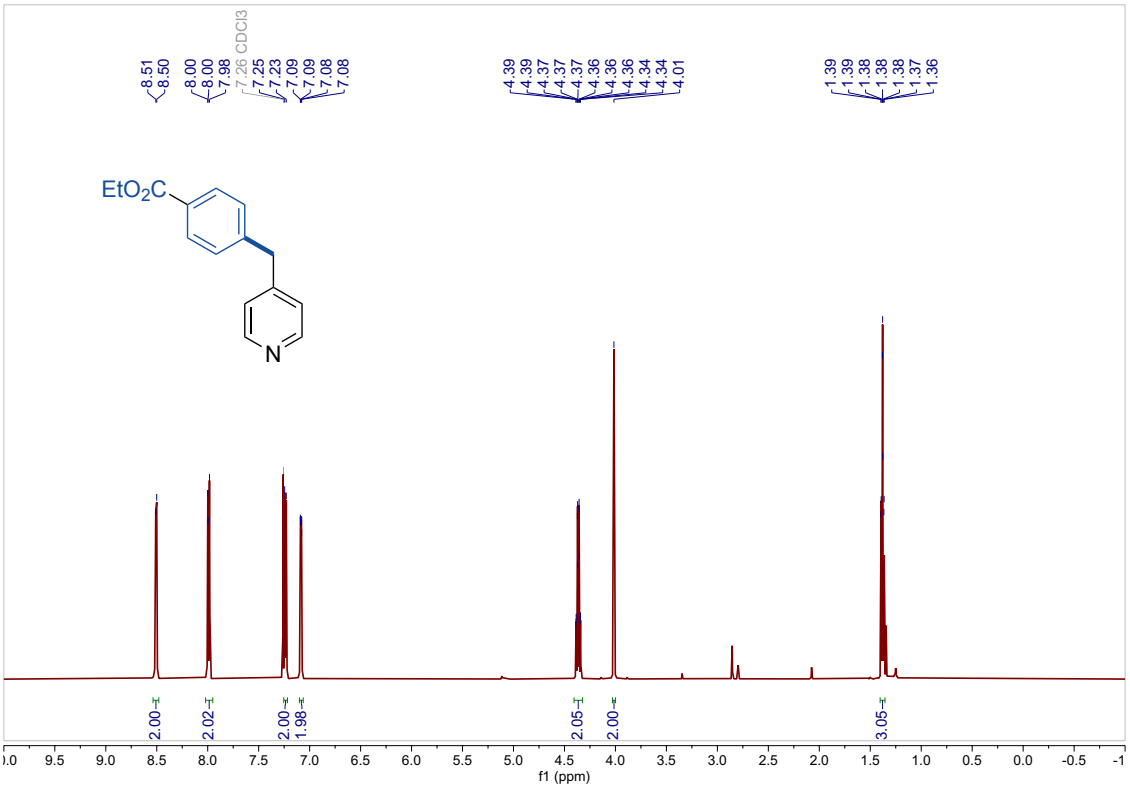
^{1}H NMR (500 MHz, $CDCl_3$) of **15**



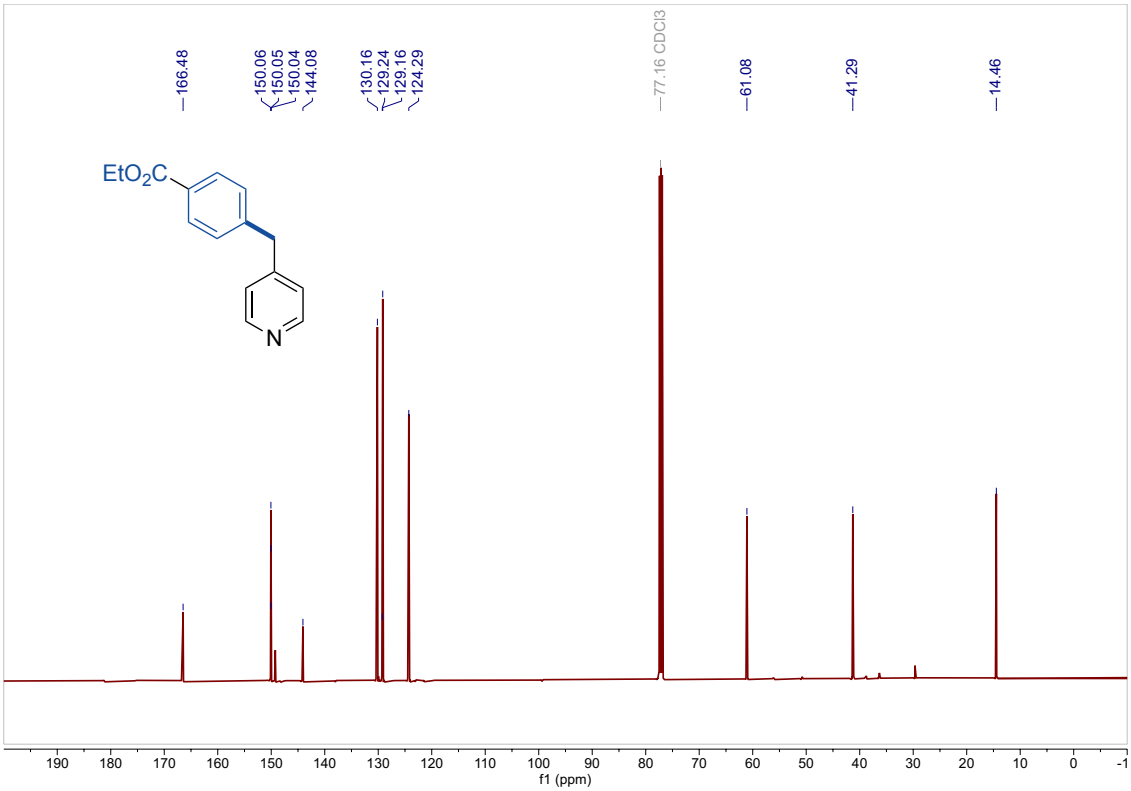
^{13}C NMR: (126 MHz, $CDCl_3$) of **15**



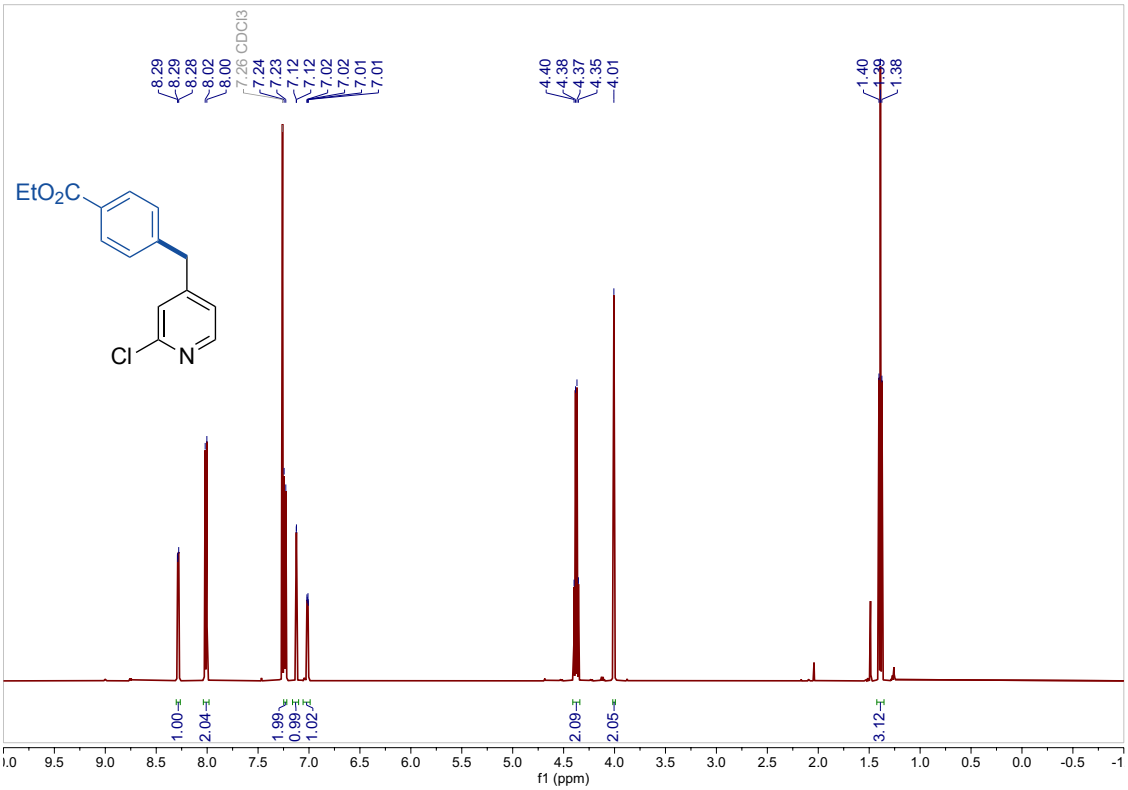
^{1}H NMR (500 MHz, $CDCl_3$) of **16**



^{13}C NMR: (126 MHz, $CDCl_3$) of **16**



^{1}H NMR (500 MHz, $CDCl_3$) of **17**



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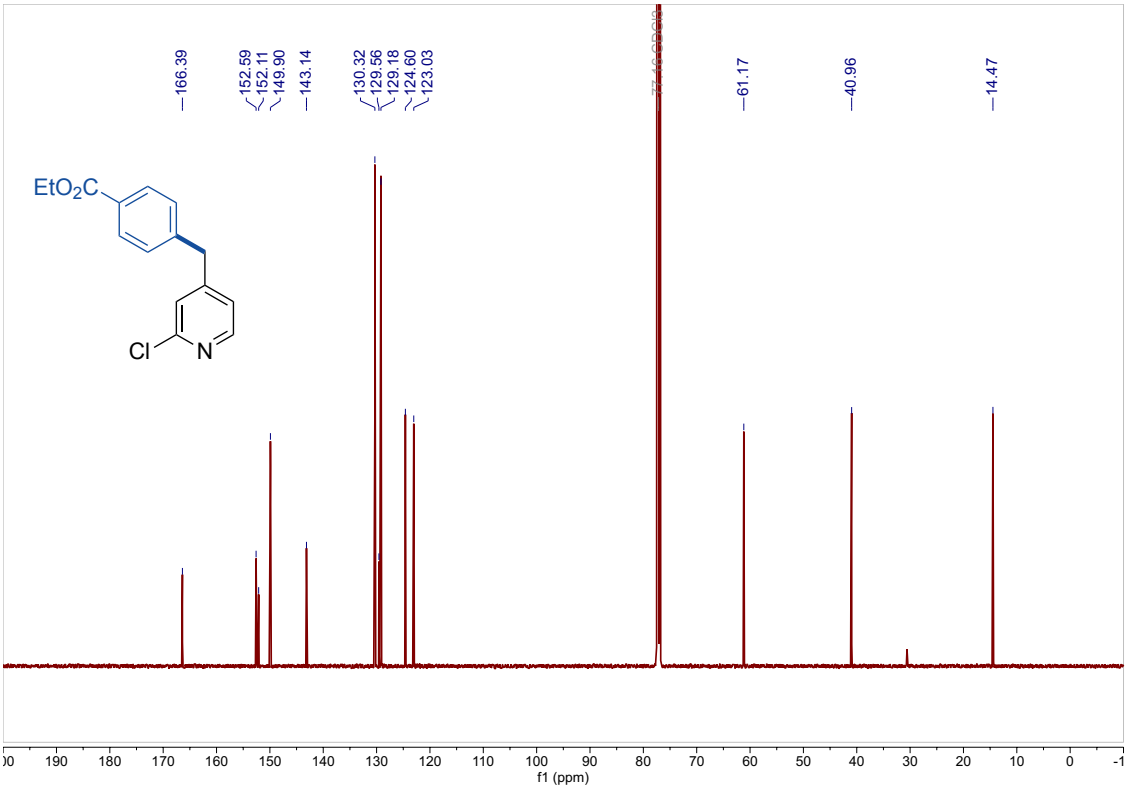
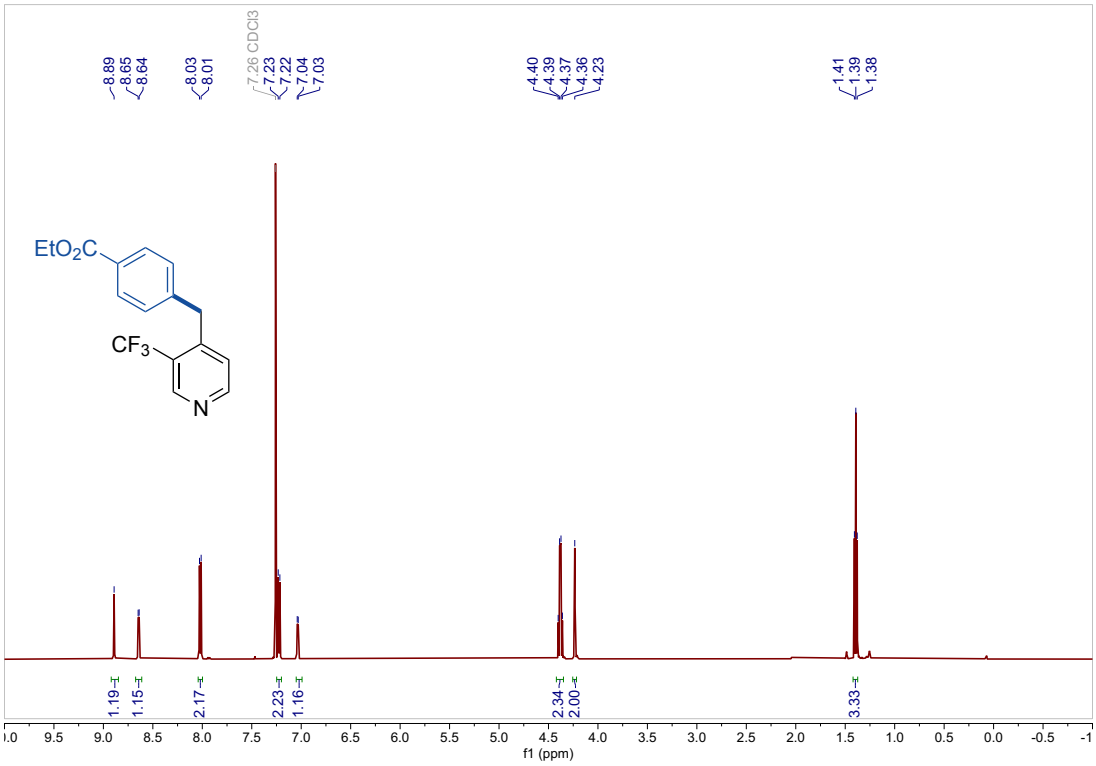
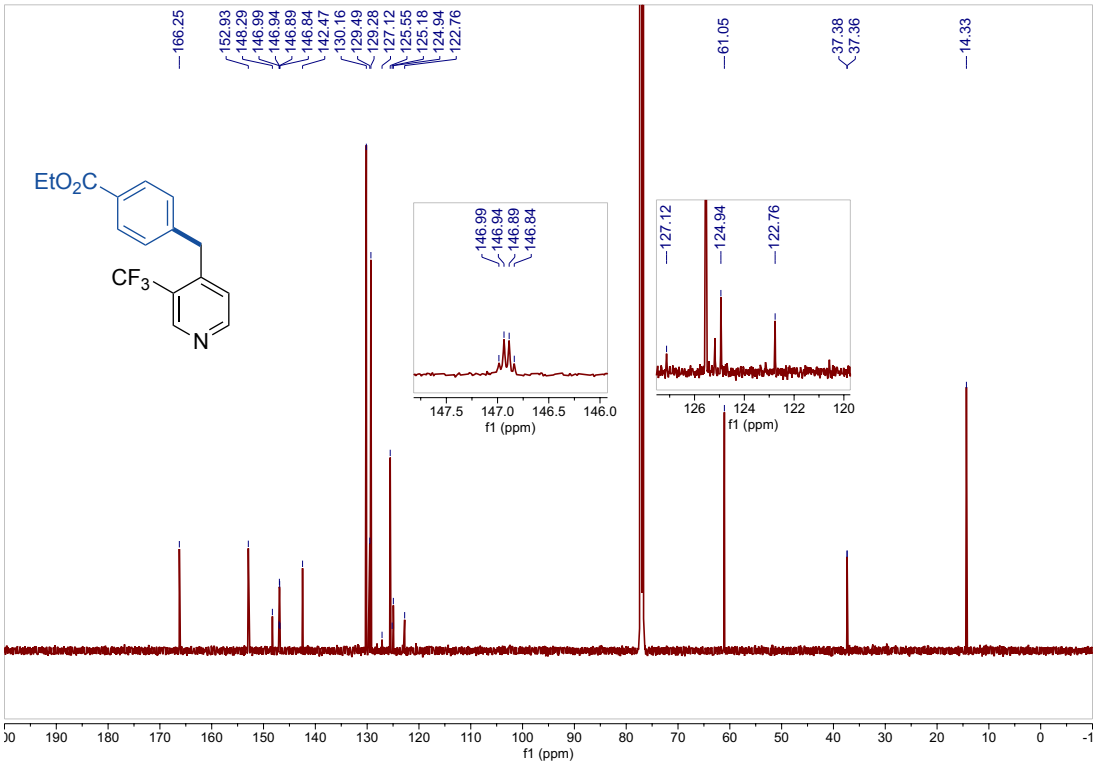


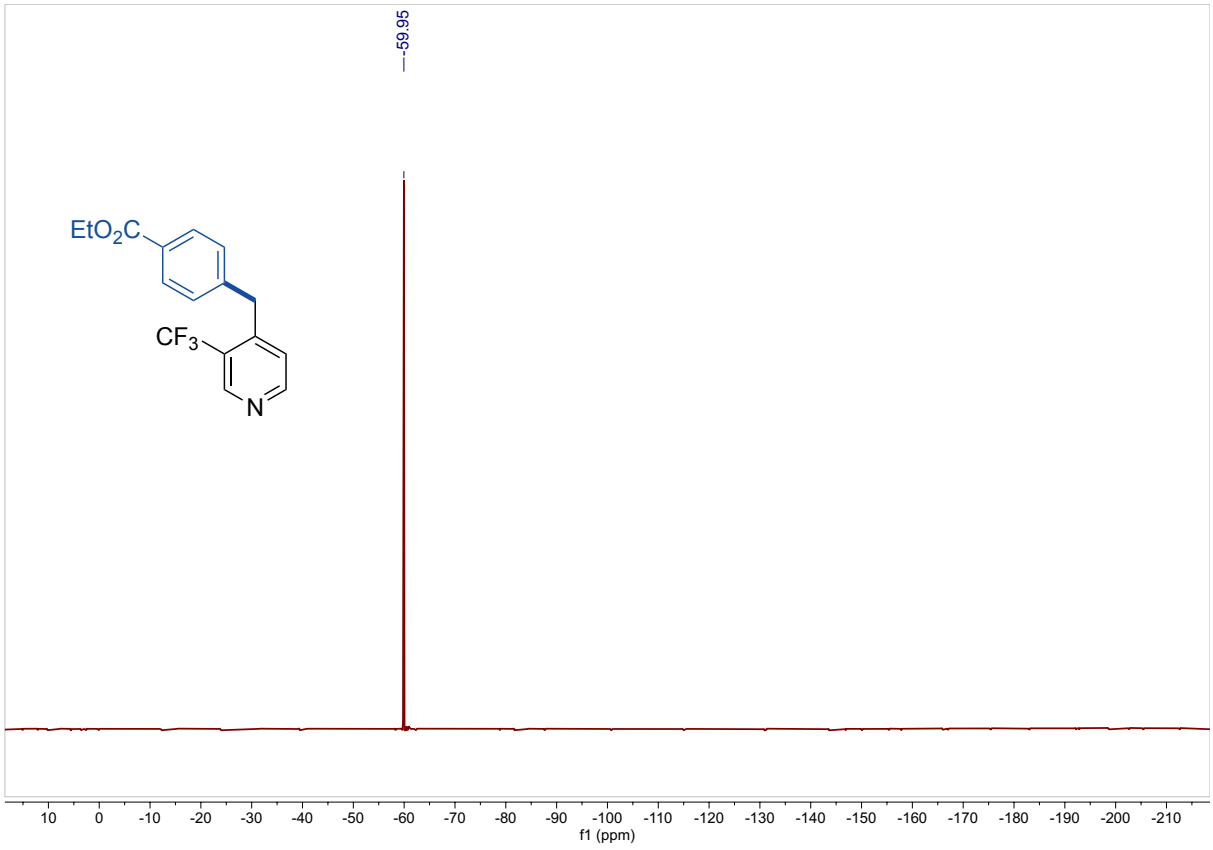
^{1}H NMR (500 MHz, $CDCl_3$) of **18**



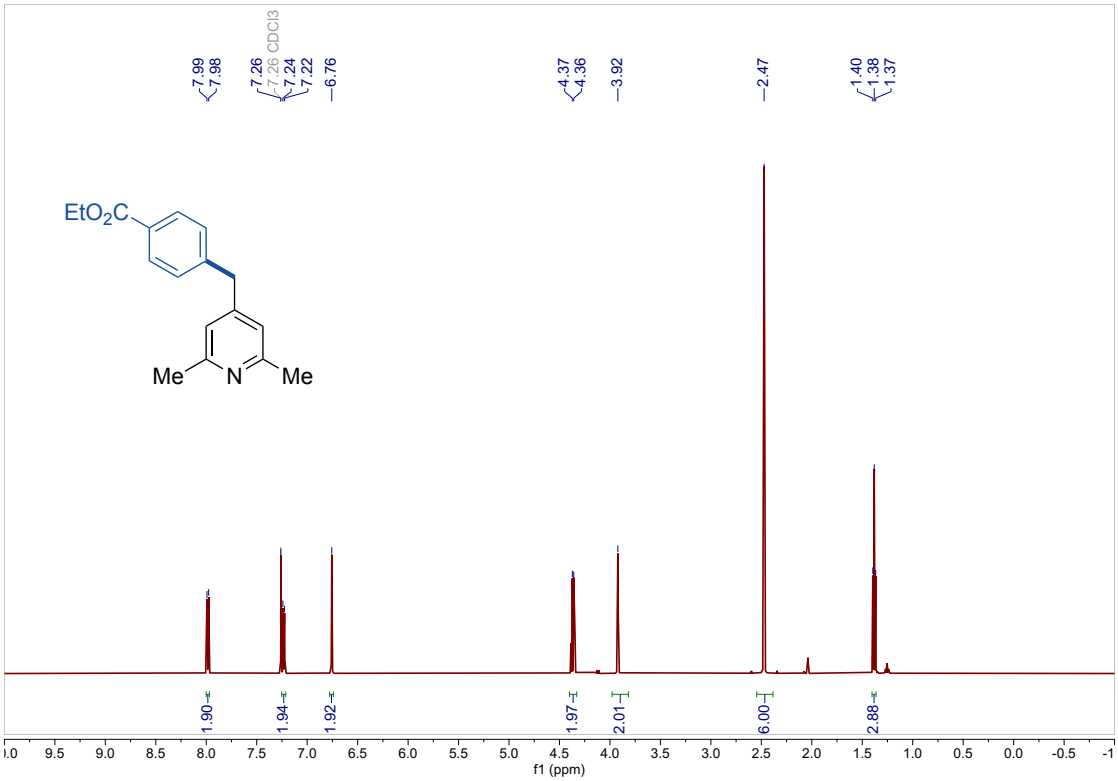
^{13}C NMR: (126 MHz, $CDCl_3$) of **18**



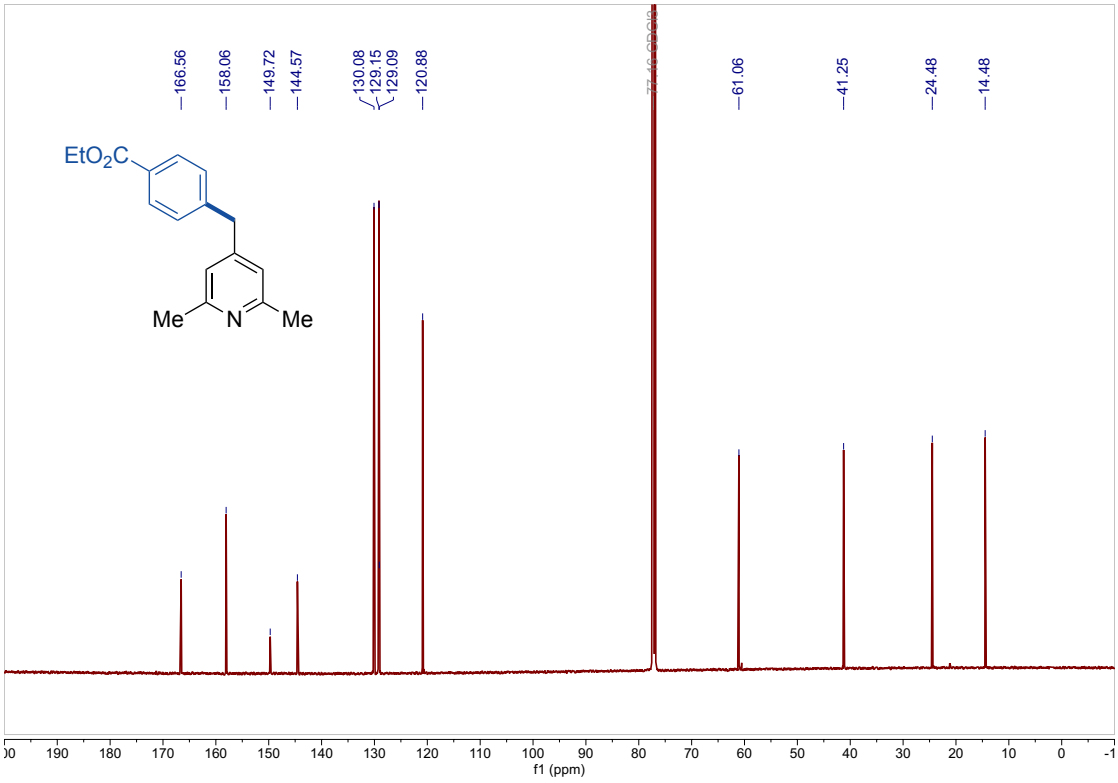
^{19}F NMR (377 MHz, $CDCl_3$) of **18**



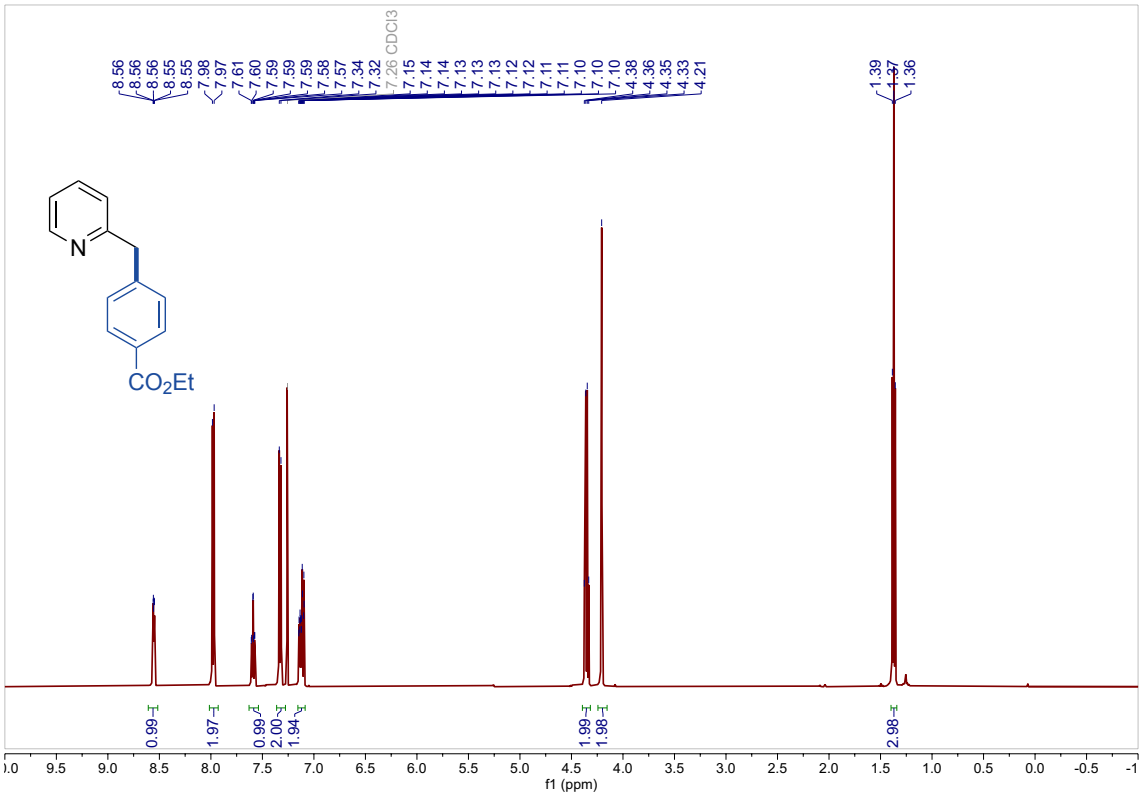
^{1}H NMR (500 MHz, $CDCl_3$) of **19**



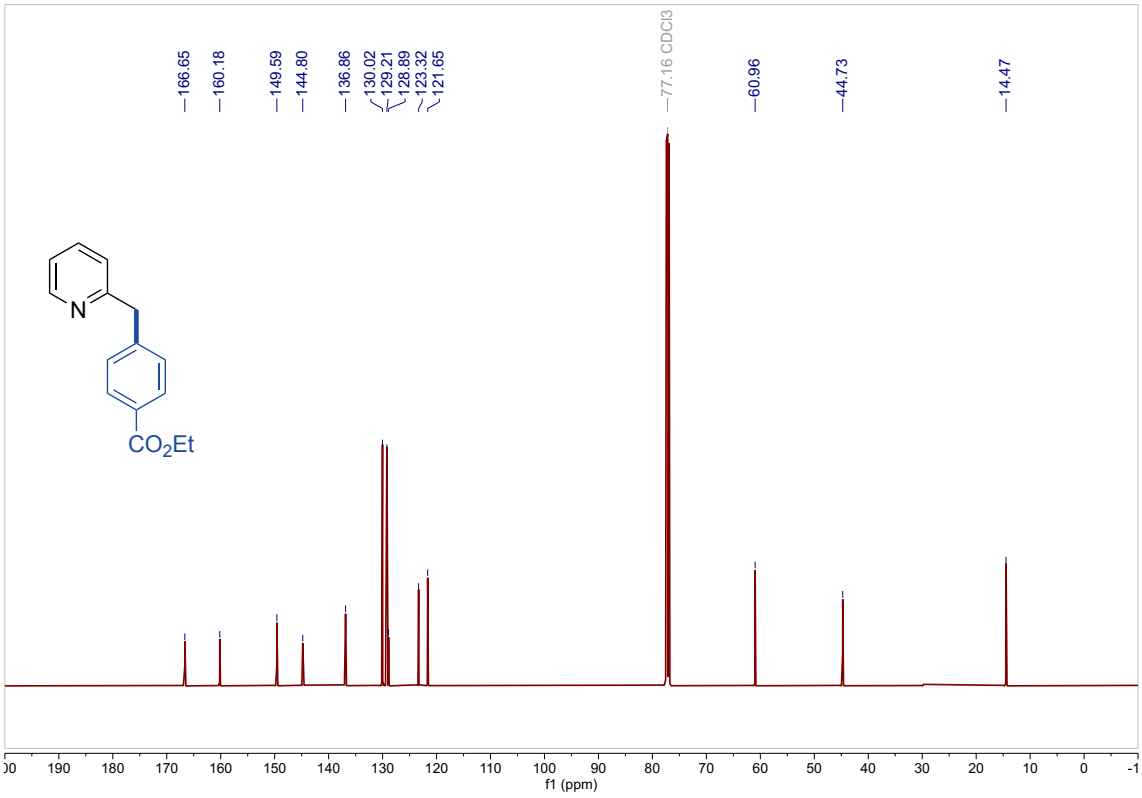
^{13}C NMR: (126 MHz, $CDCl_3$) of **19**



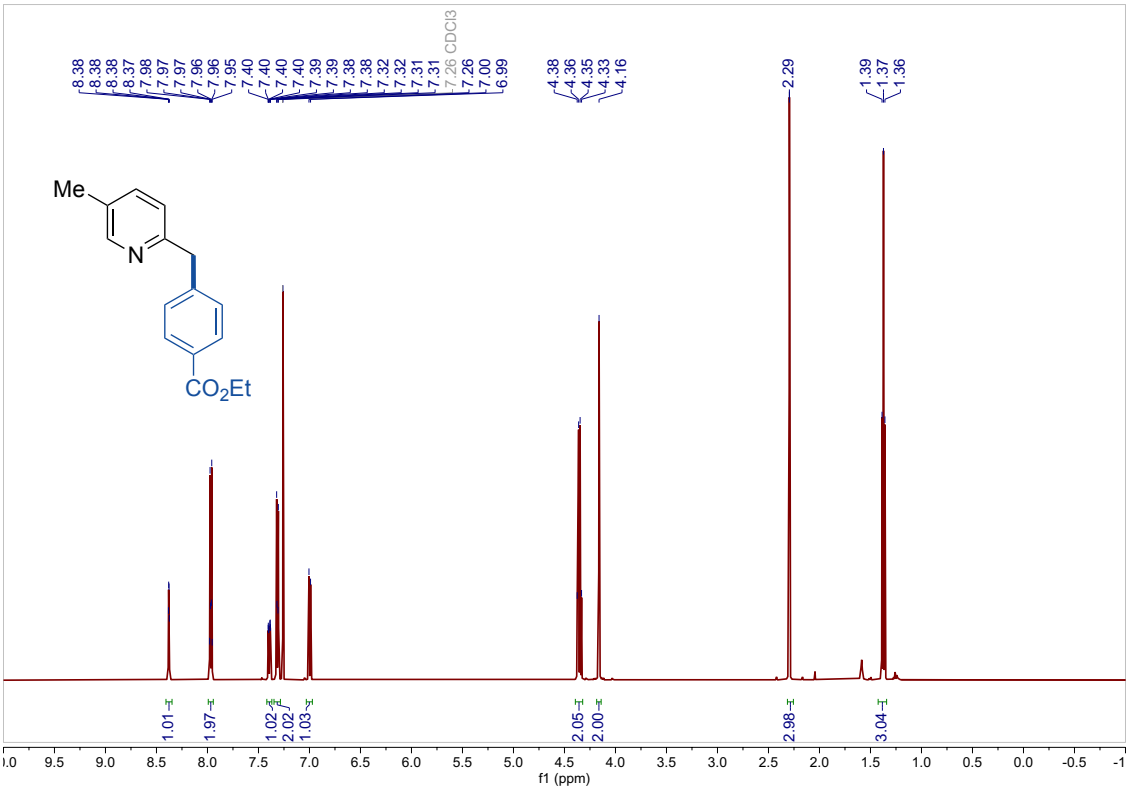
^{1}H NMR (500 MHz, $CDCl_3$) of **20**



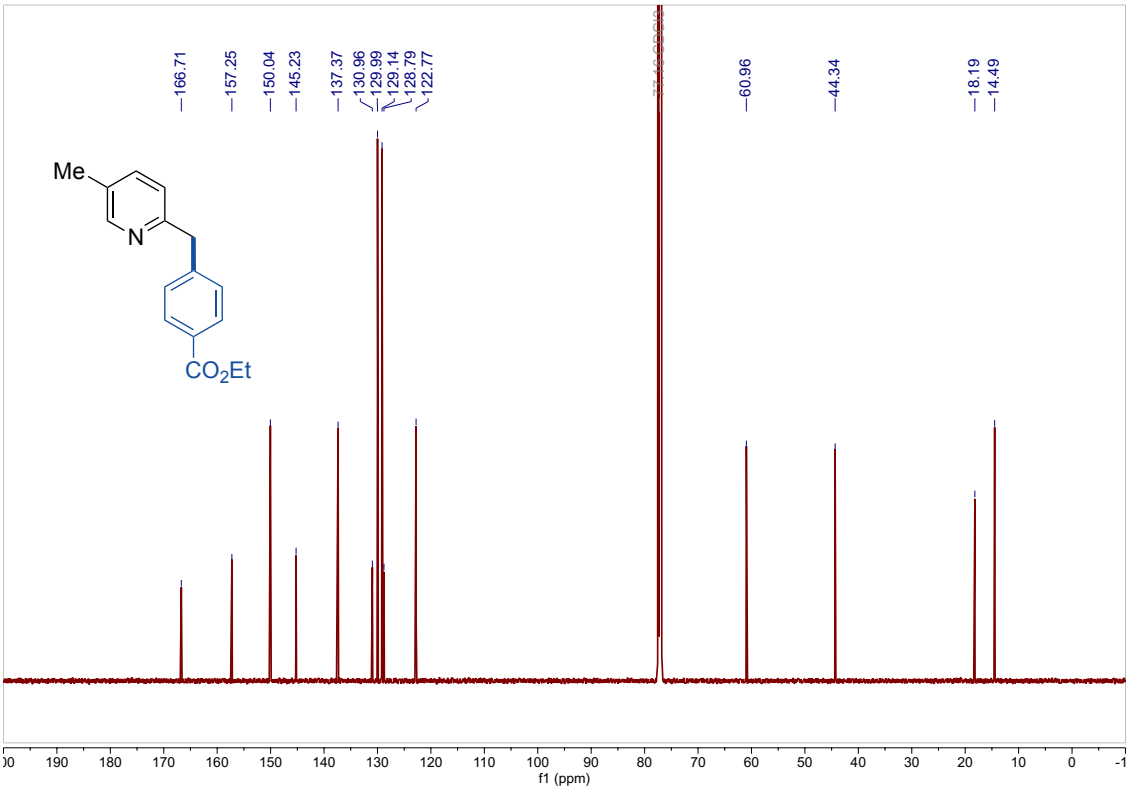
^{13}C NMR: (126 MHz, $CDCl_3$) of **20**



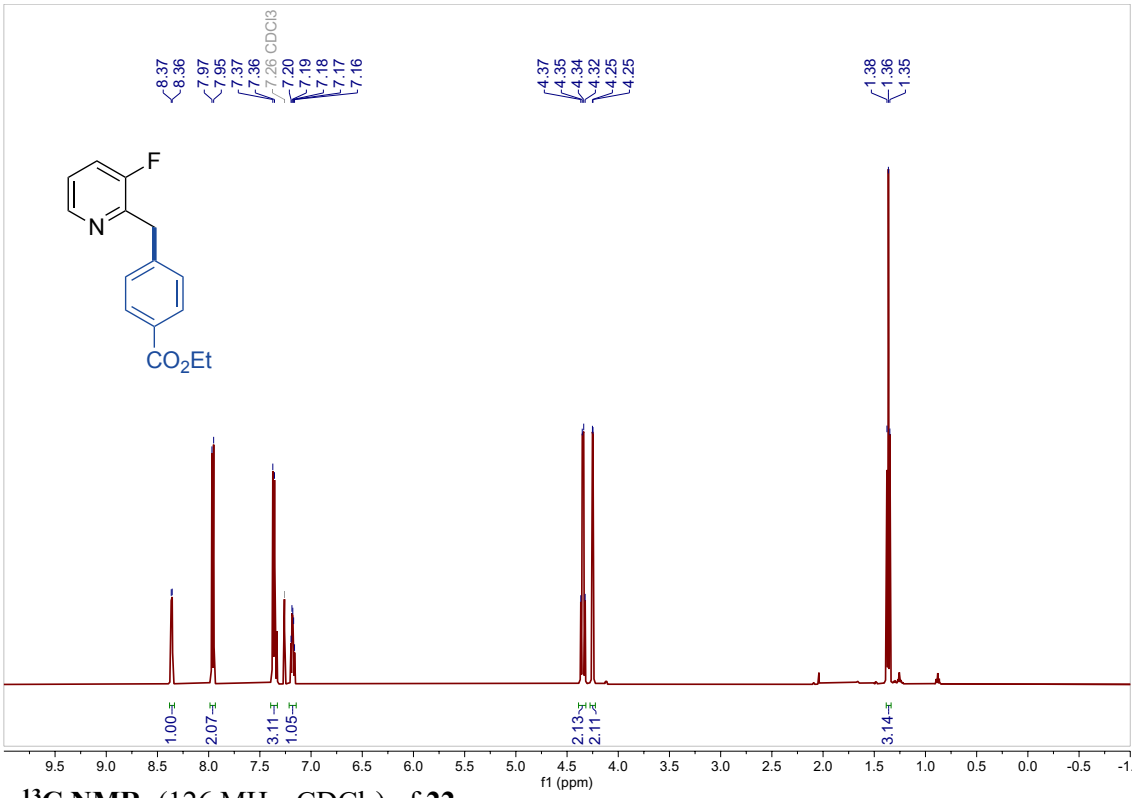
^{1}H NMR (500 MHz, $CDCl_3$) of **21**



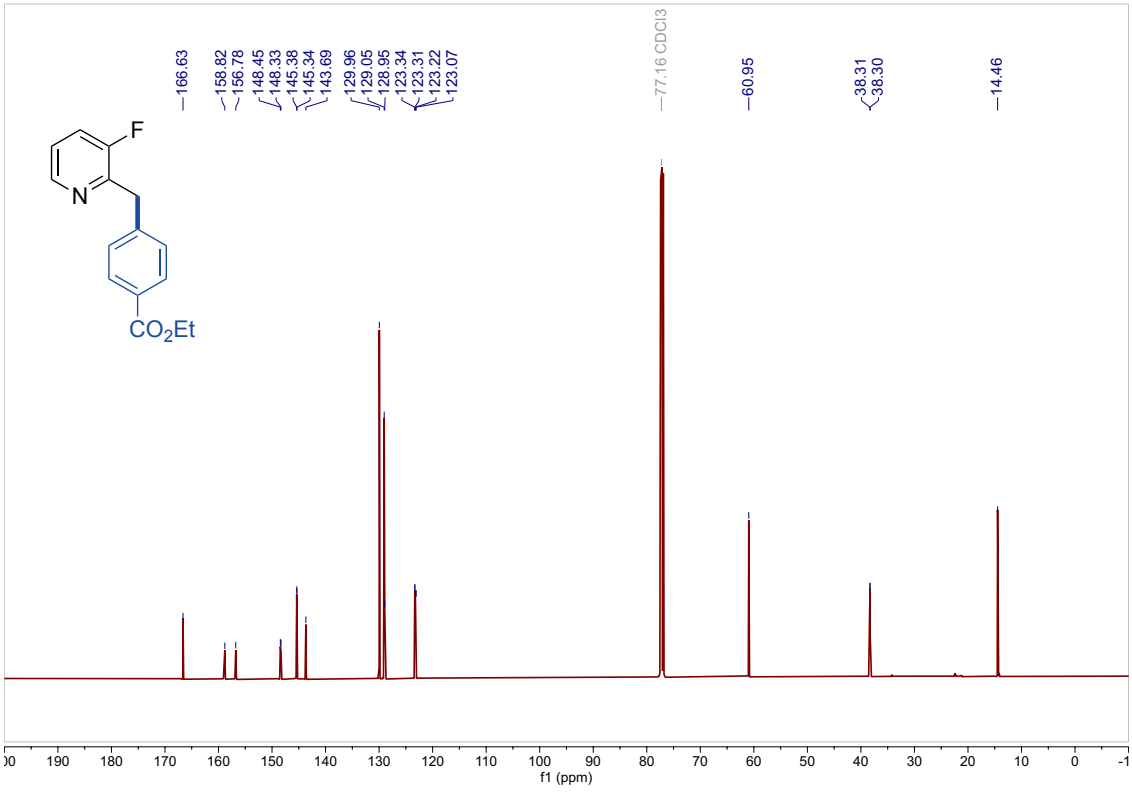
^{13}C NMR: (126 MHz, $CDCl_3$) of **21**



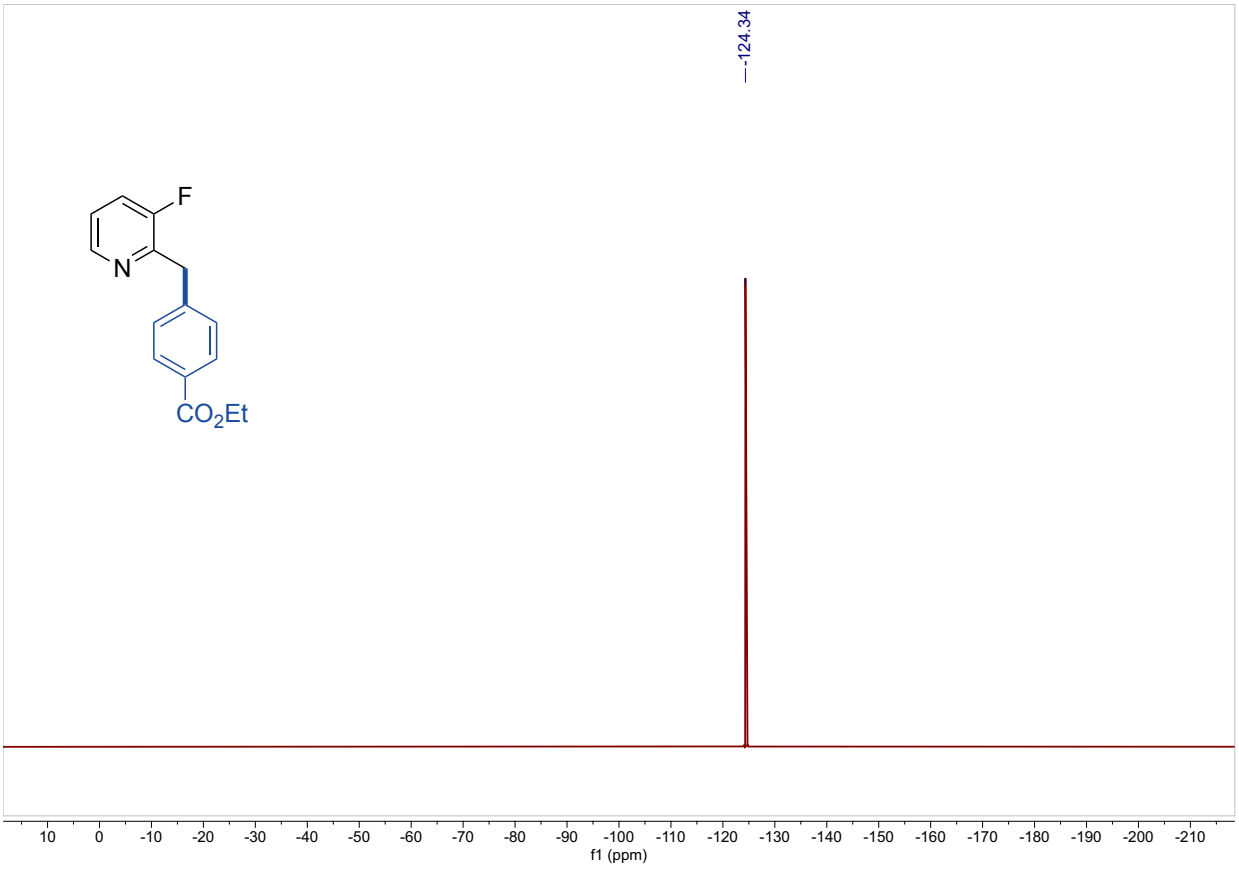
^{1}H NMR (500 MHz, $CDCl_3$) of **22**



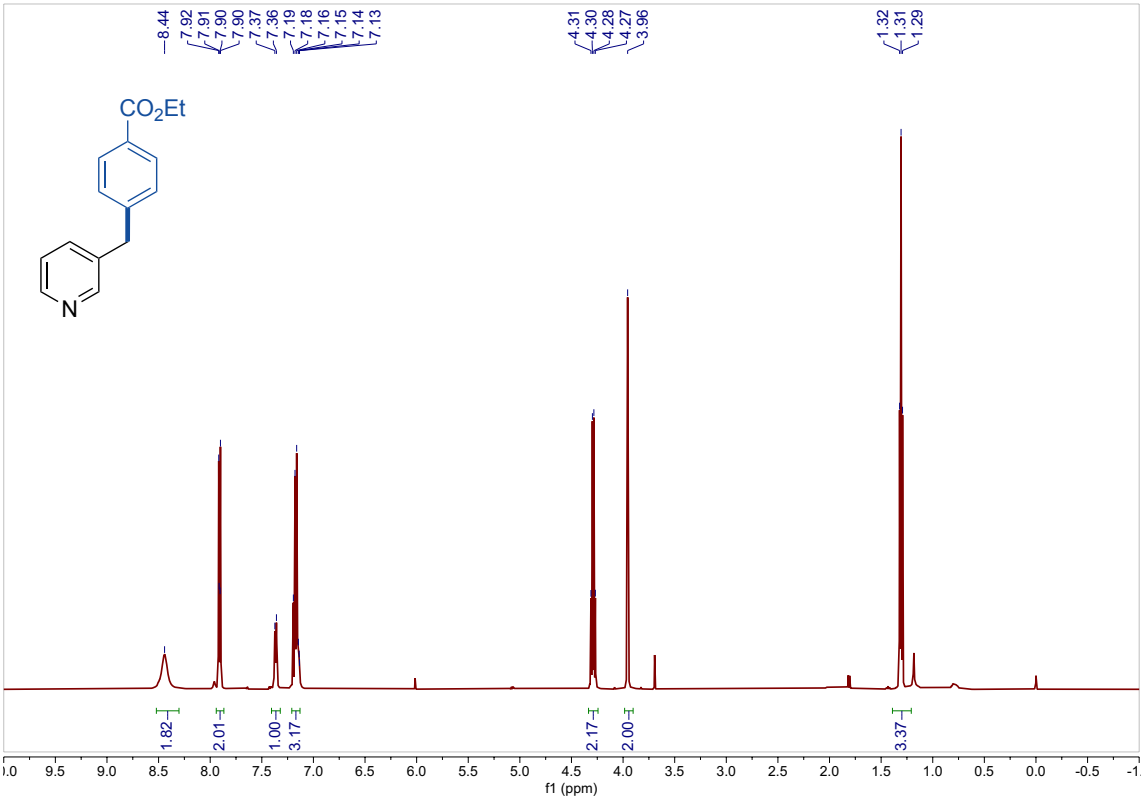
^{13}C NMR: (126 MHz, $CDCl_3$) of **22**



^{1}H NMR (500 MHz, $CDCl_3$) of **22**



^{1}H NMR (500 MHz, $CDCl_3$) of **23**



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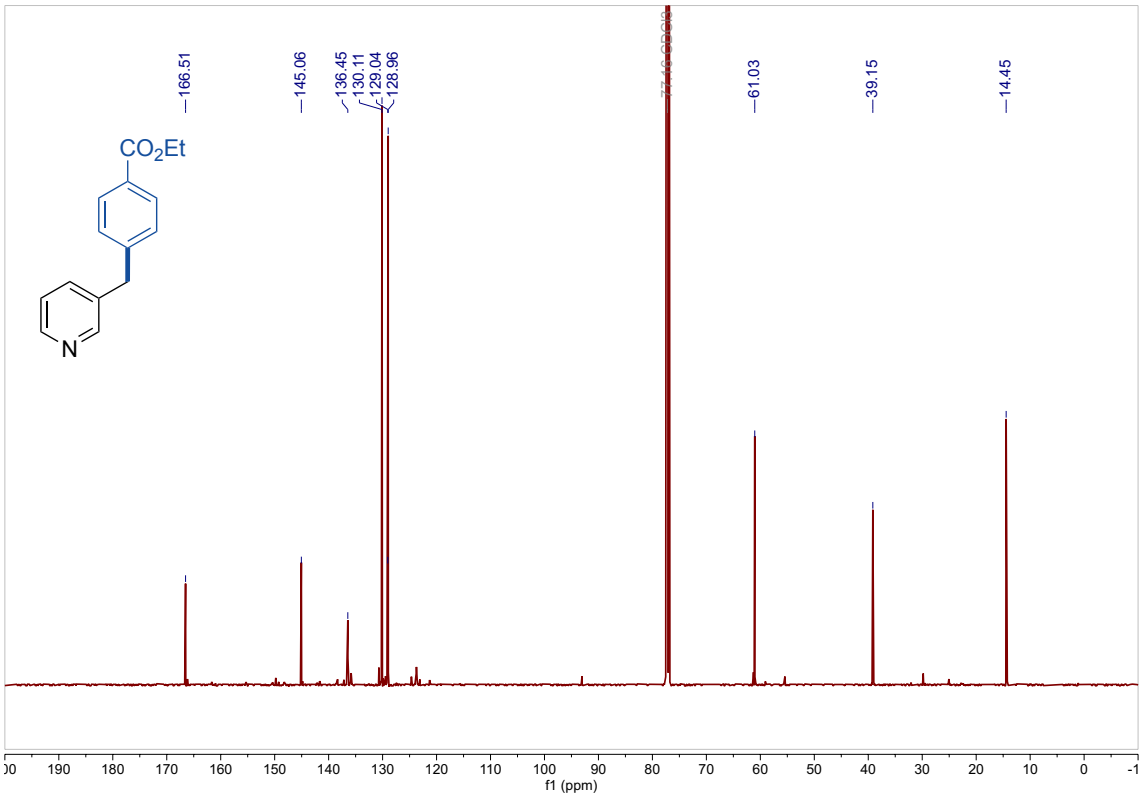
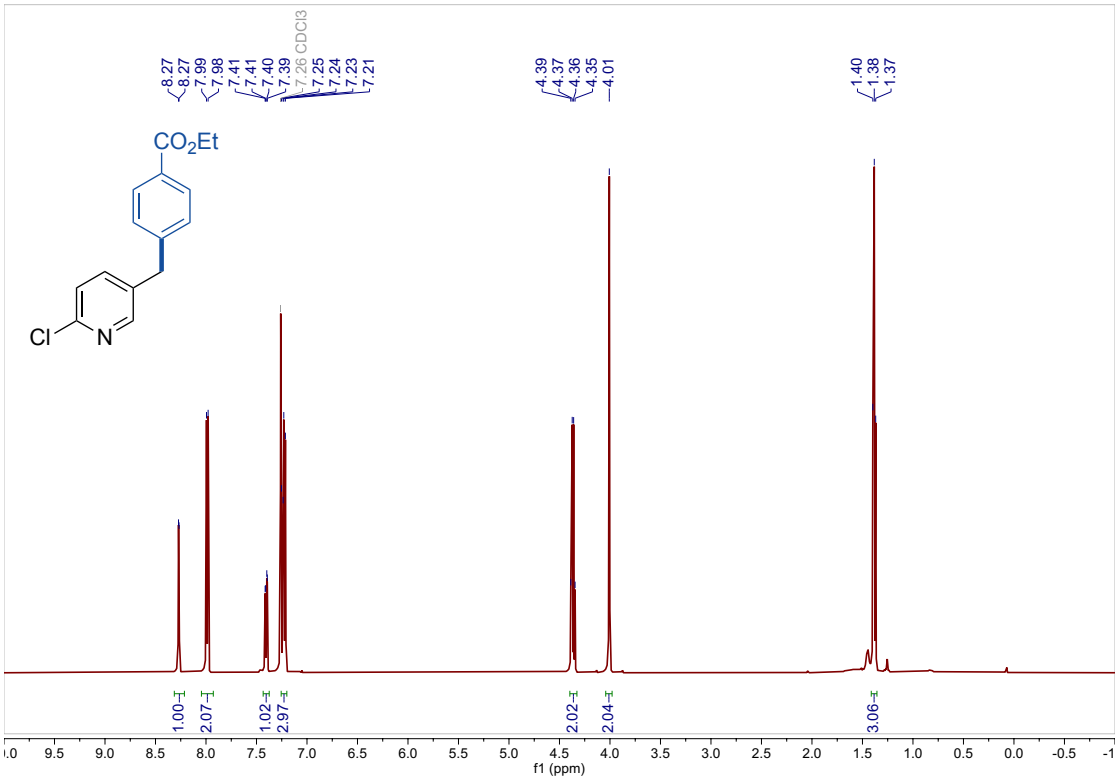
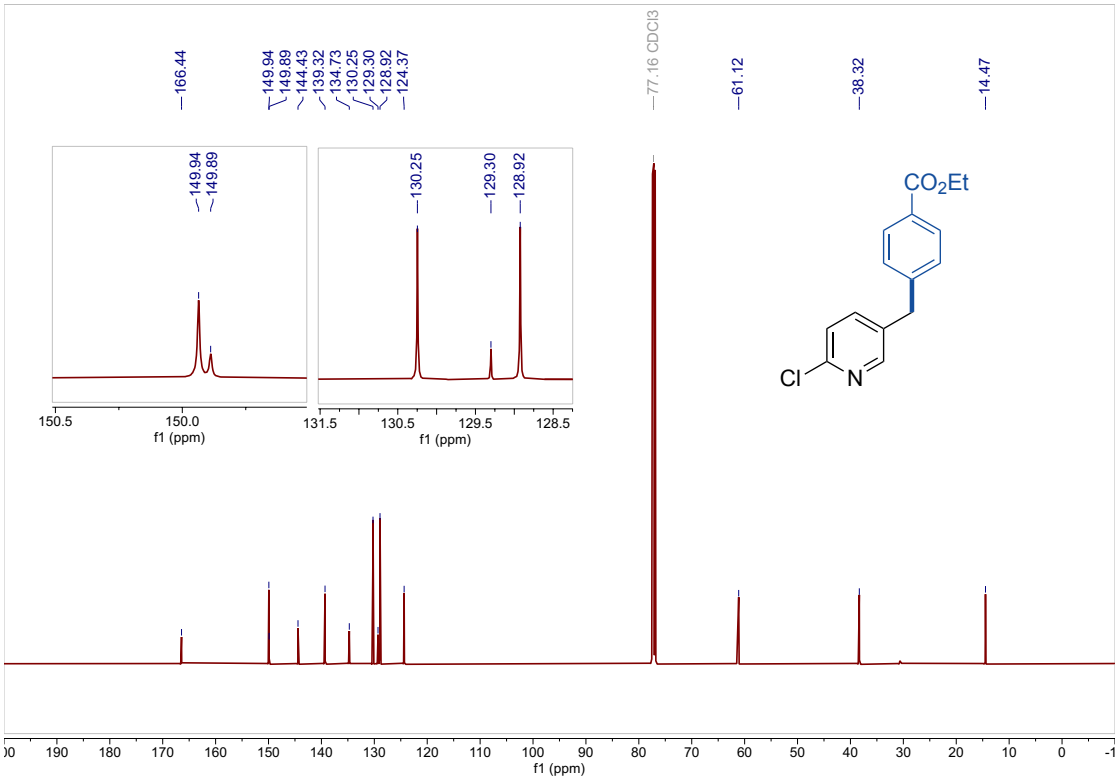


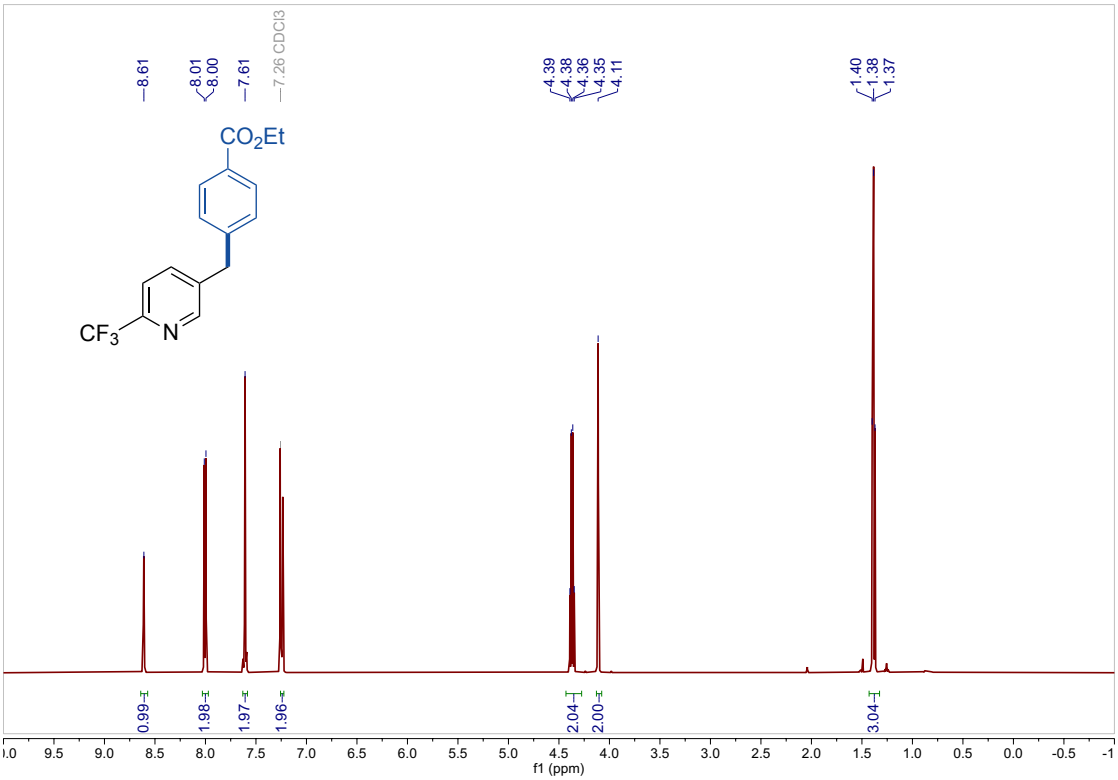
^{1}H NMR (500 MHz, $CDCl_3$) of **24**



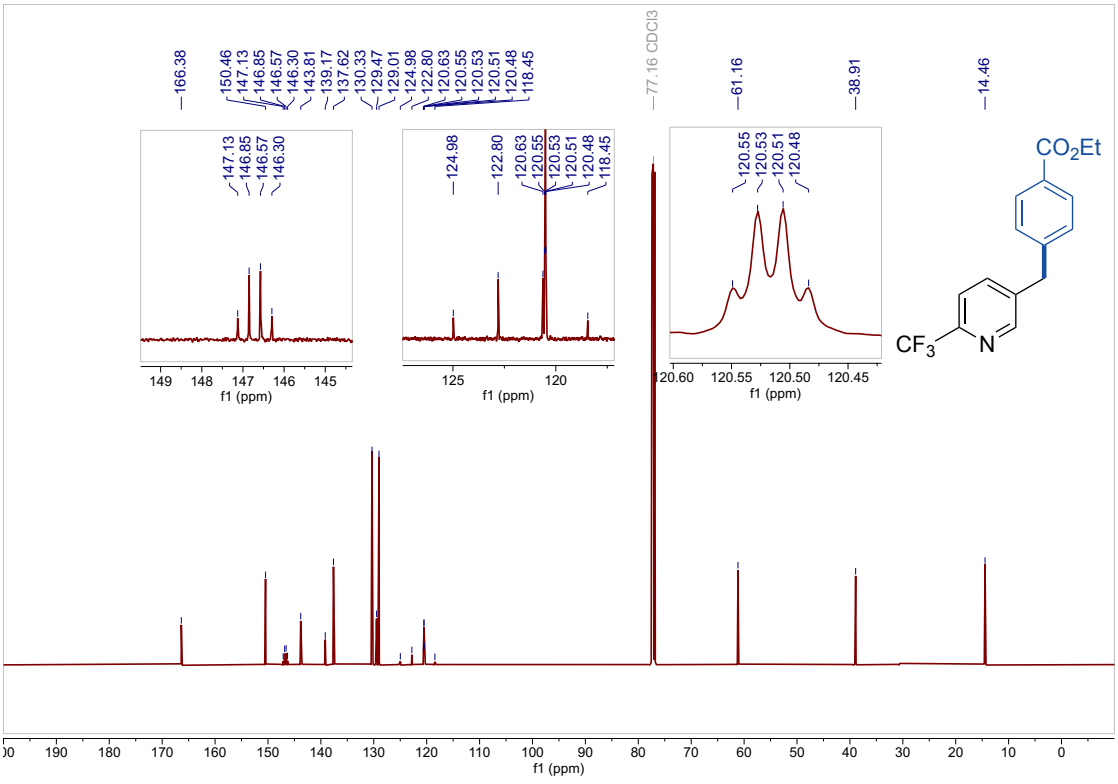
^{13}C NMR: (126 MHz, $CDCl_3$) of **24**



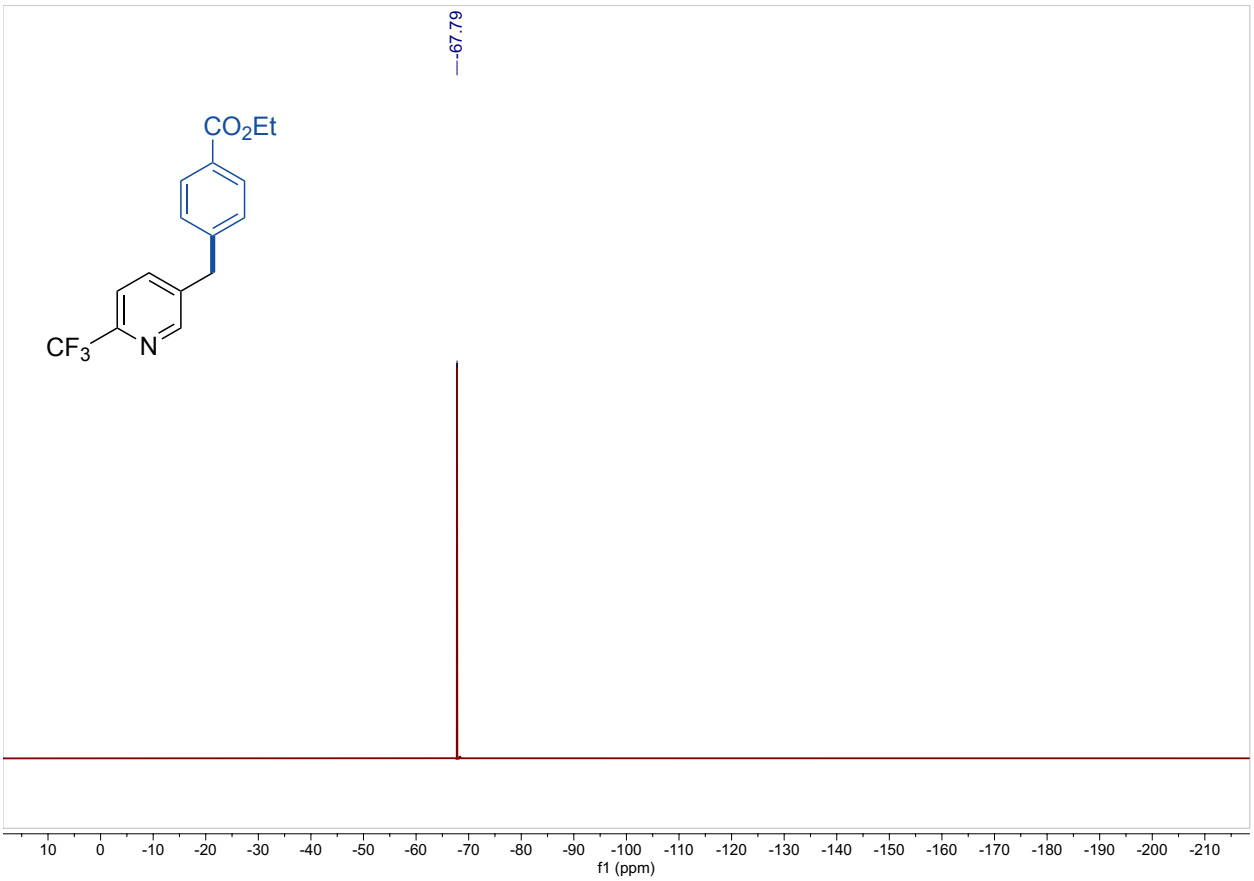
^{1}H NMR (500 MHz, $CDCl_3$) of **25**



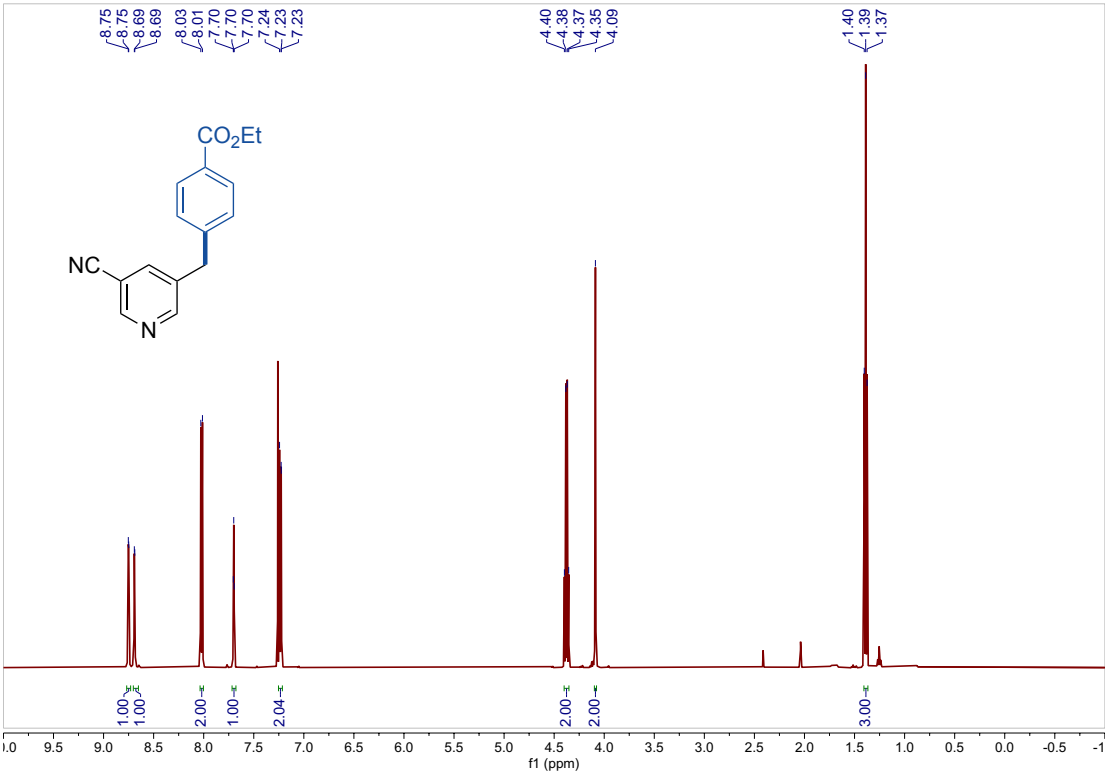
^{13}C NMR: (126 MHz, $CDCl_3$) of **25**



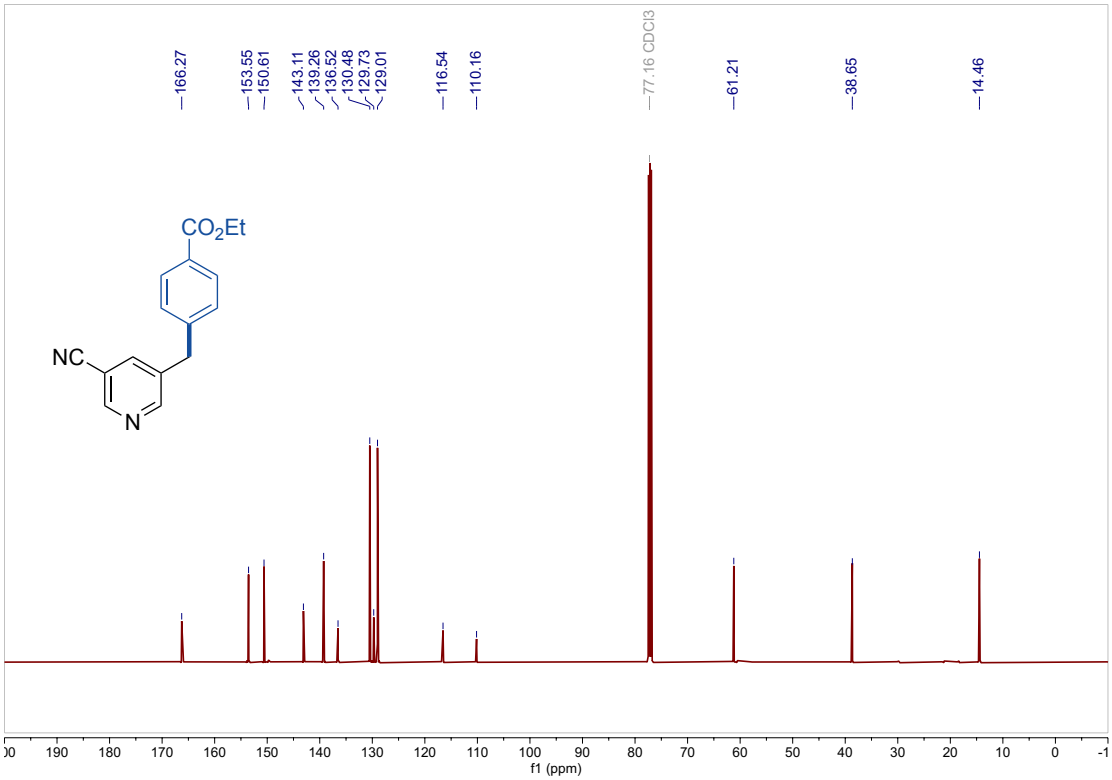
^{19}F NMR (377 MHz, $CDCl_3$) of **25**



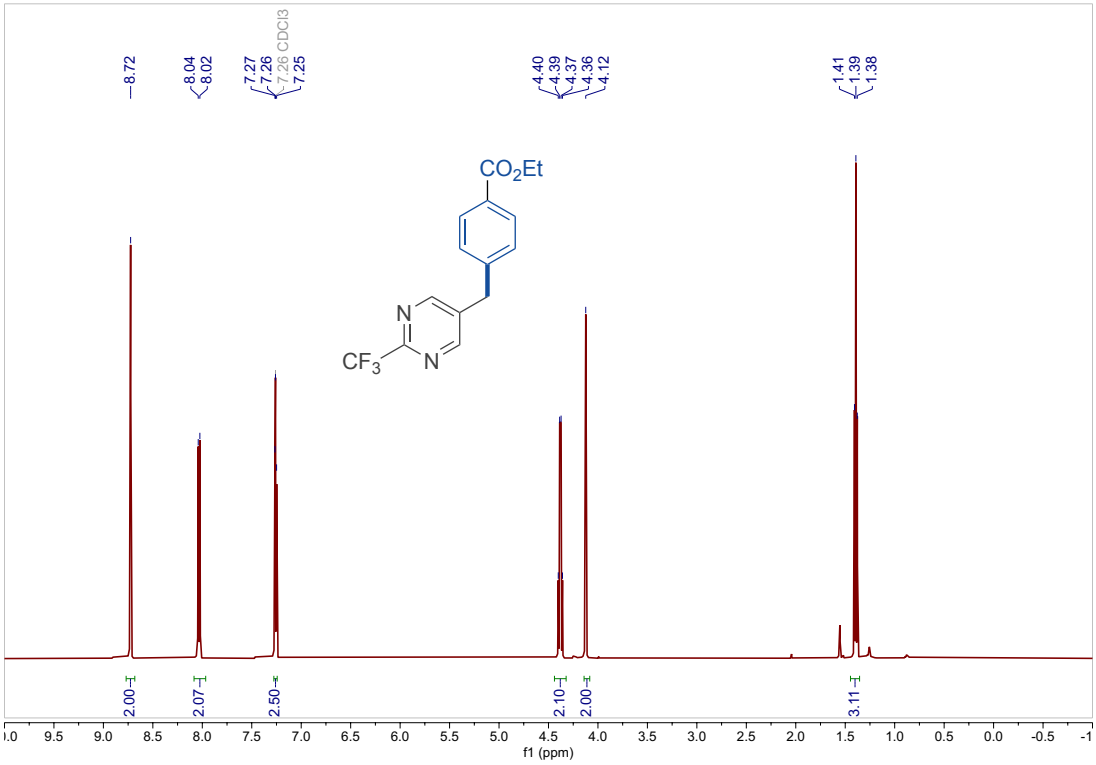
^{1}H NMR (500 MHz, $CDCl_3$) of **26**



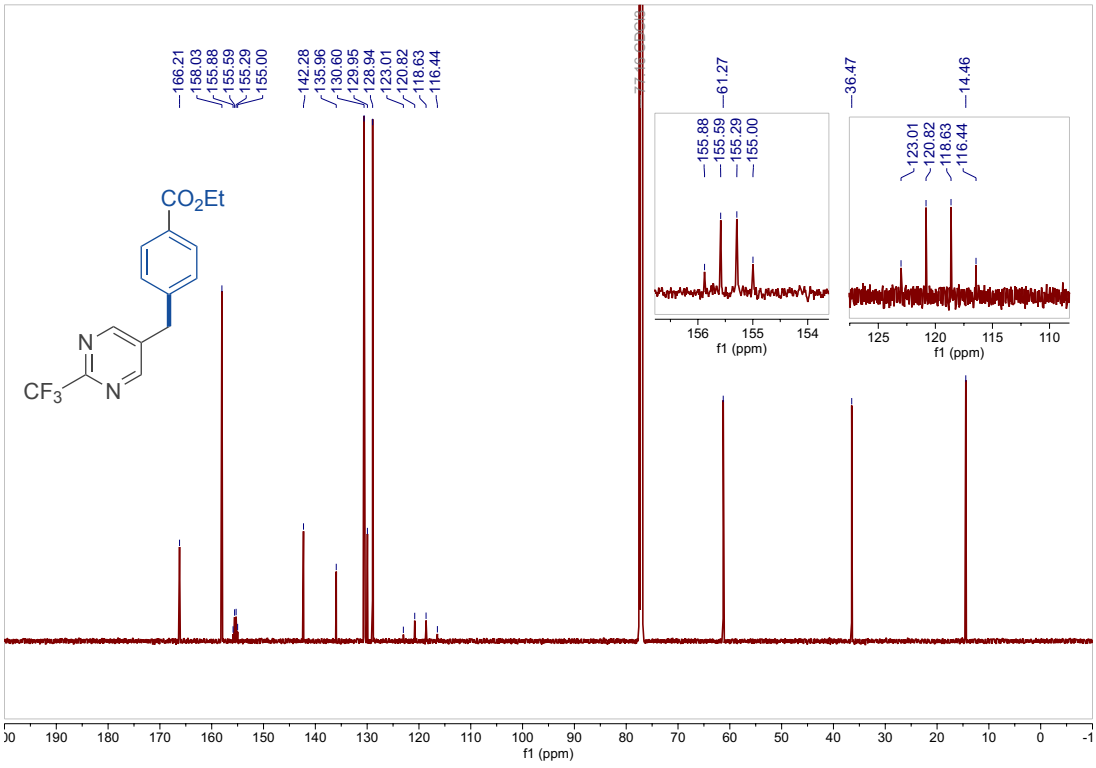
^{13}C NMR: (126 MHz, $CDCl_3$) of **26**



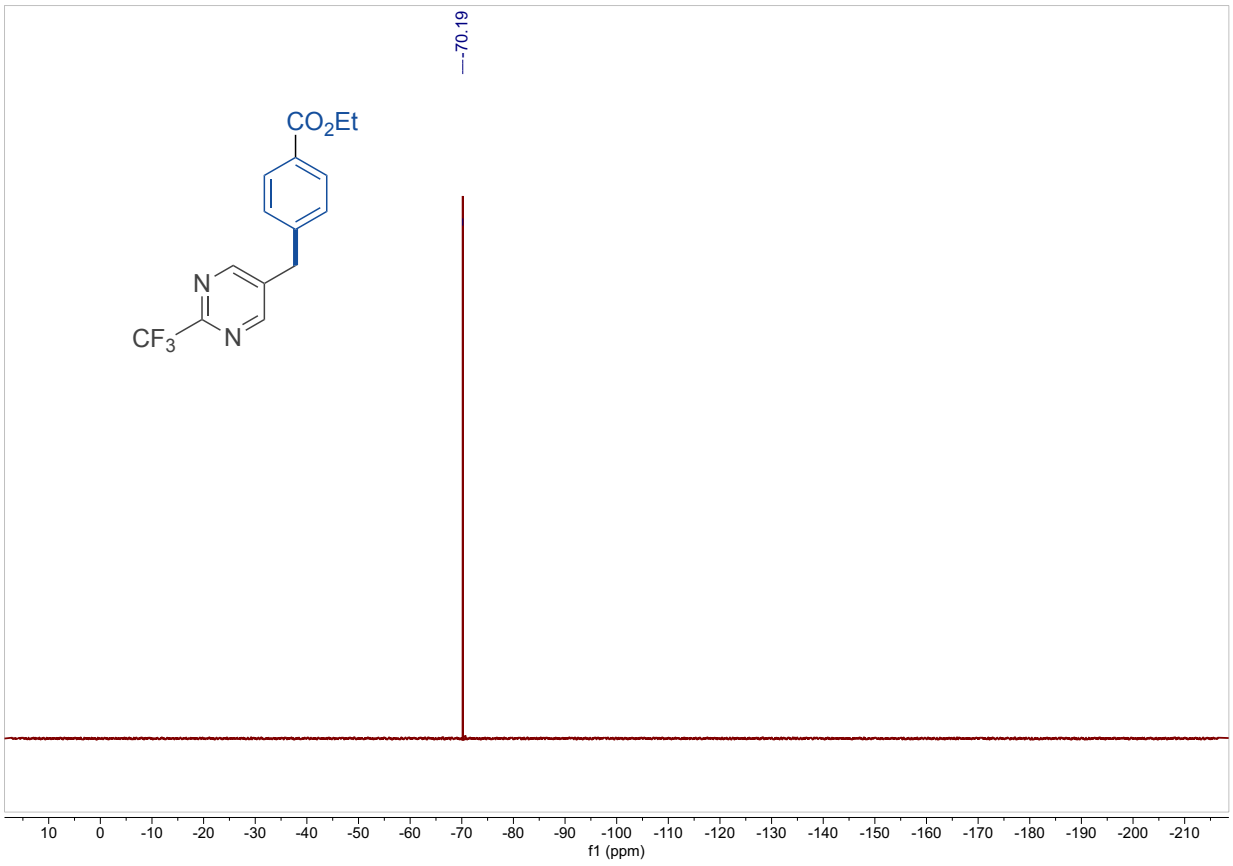
^{1}H NMR (500 MHz, $CDCl_3$) of **27**



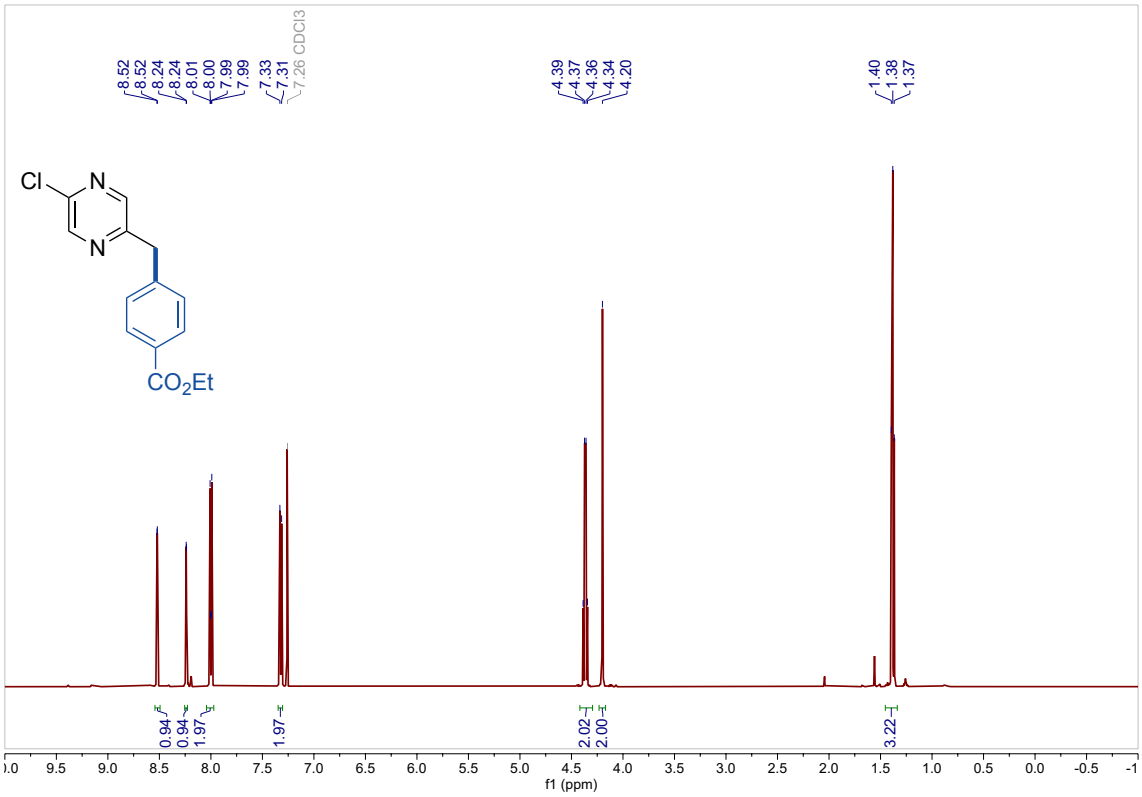
^{13}C NMR: (126 MHz, $CDCl_3$) of **27**



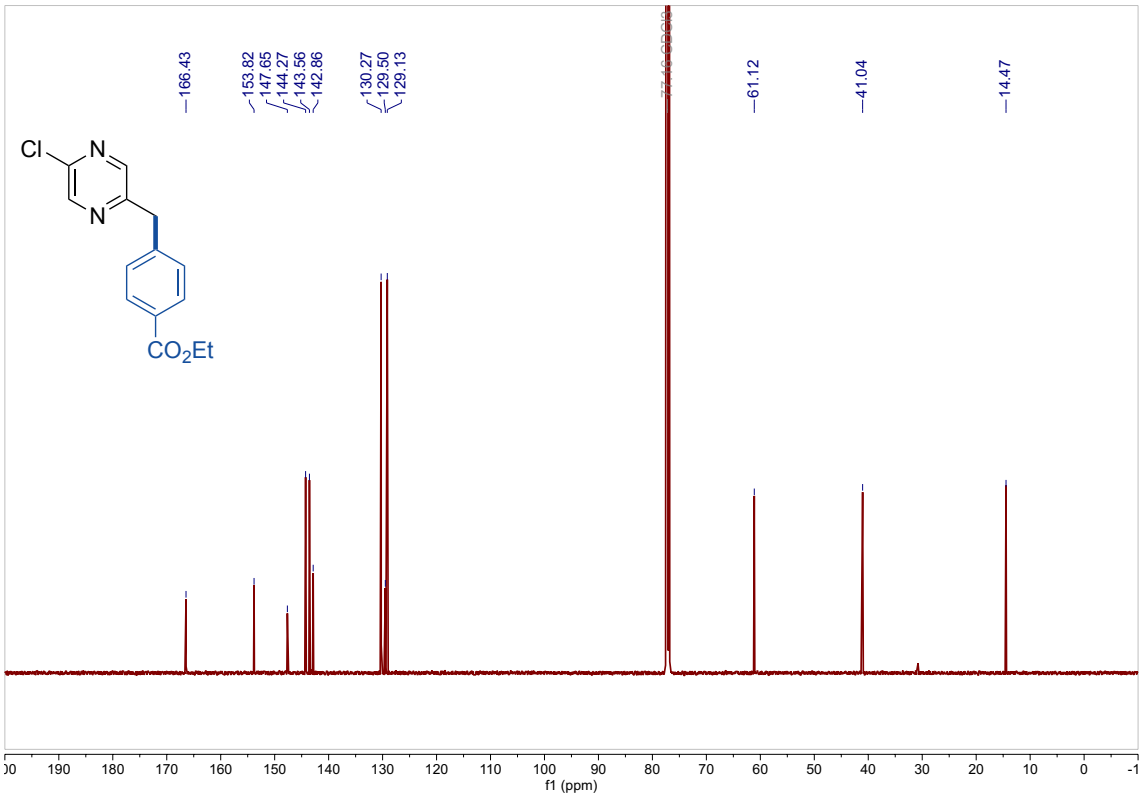
^{19}F NMR (377 MHz, $CDCl_3$) of **27**



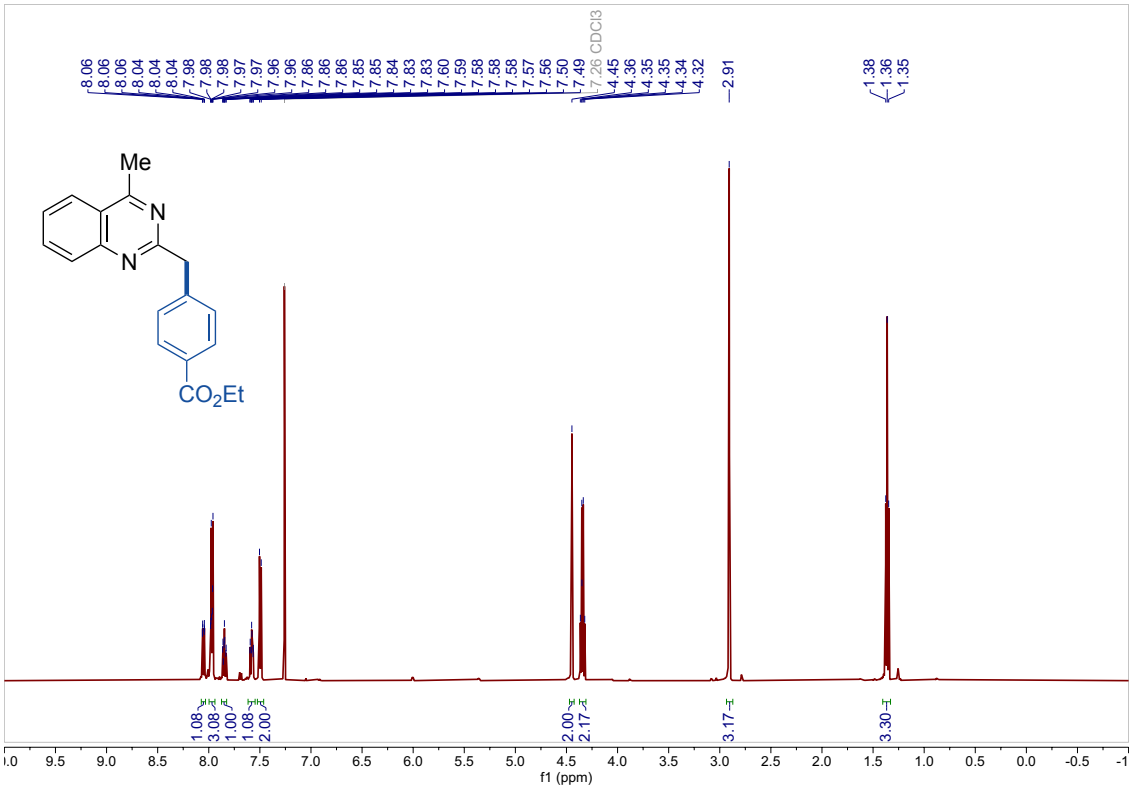
^{1}H NMR (500 MHz, $CDCl_3$) of **28**



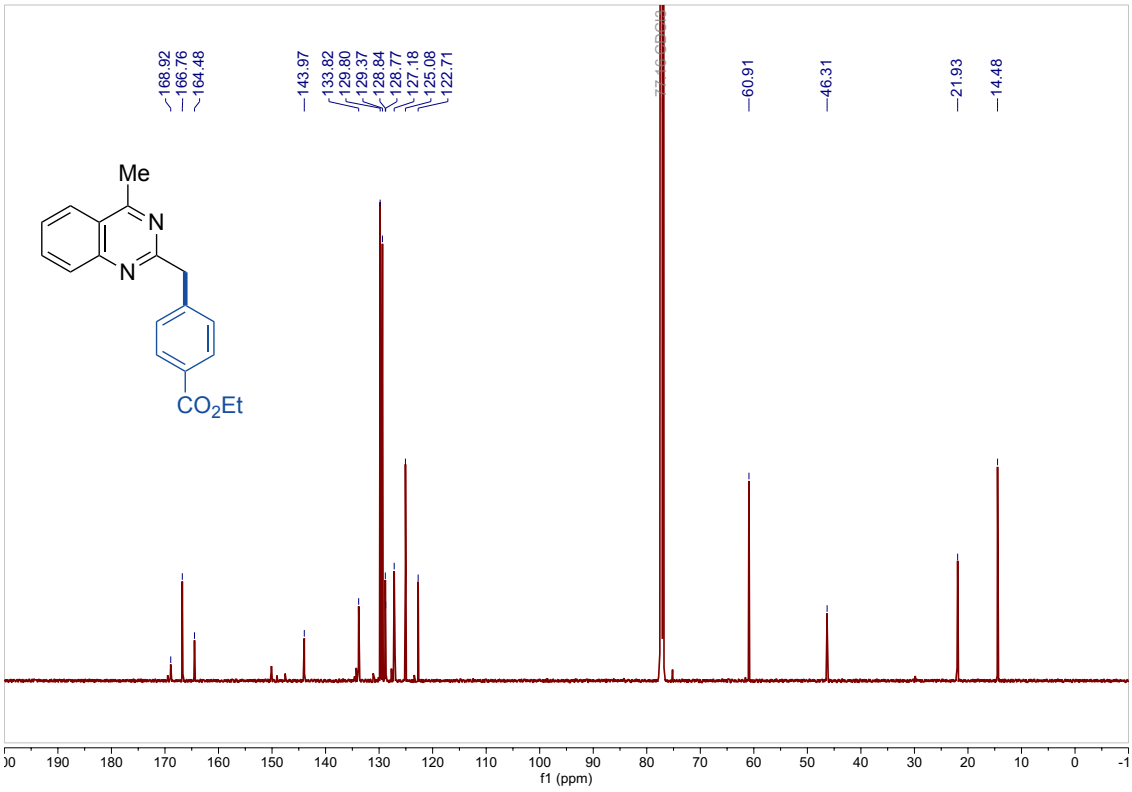
^{13}C NMR: (126 MHz, $CDCl_3$) of **28**



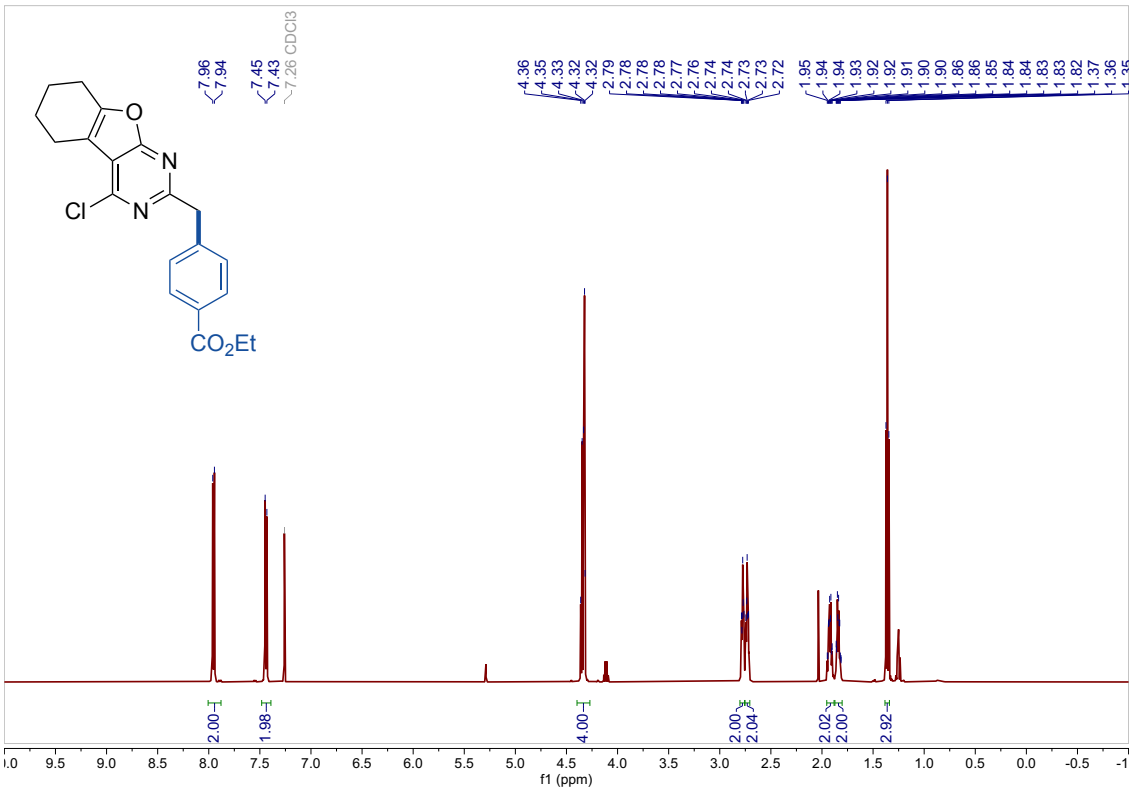
^{1}H NMR (500 MHz, $CDCl_3$) of **29**



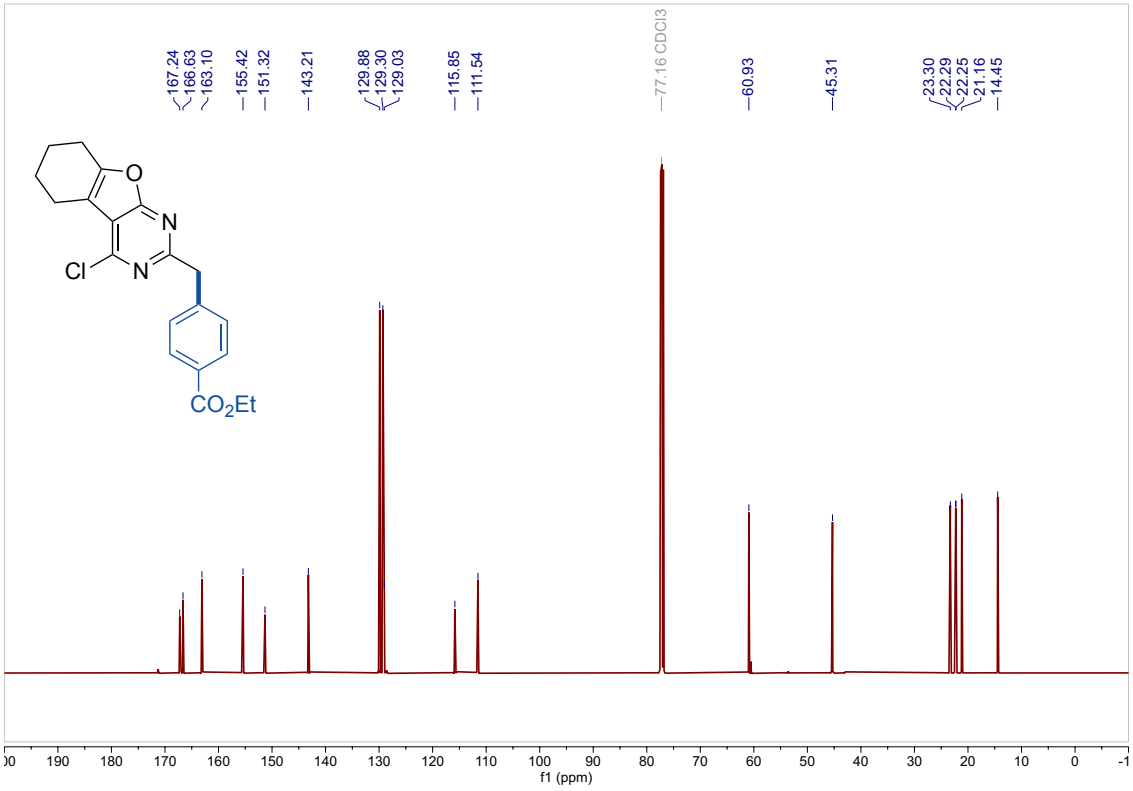
^{13}C NMR: (126 MHz, $CDCl_3$) of **29**



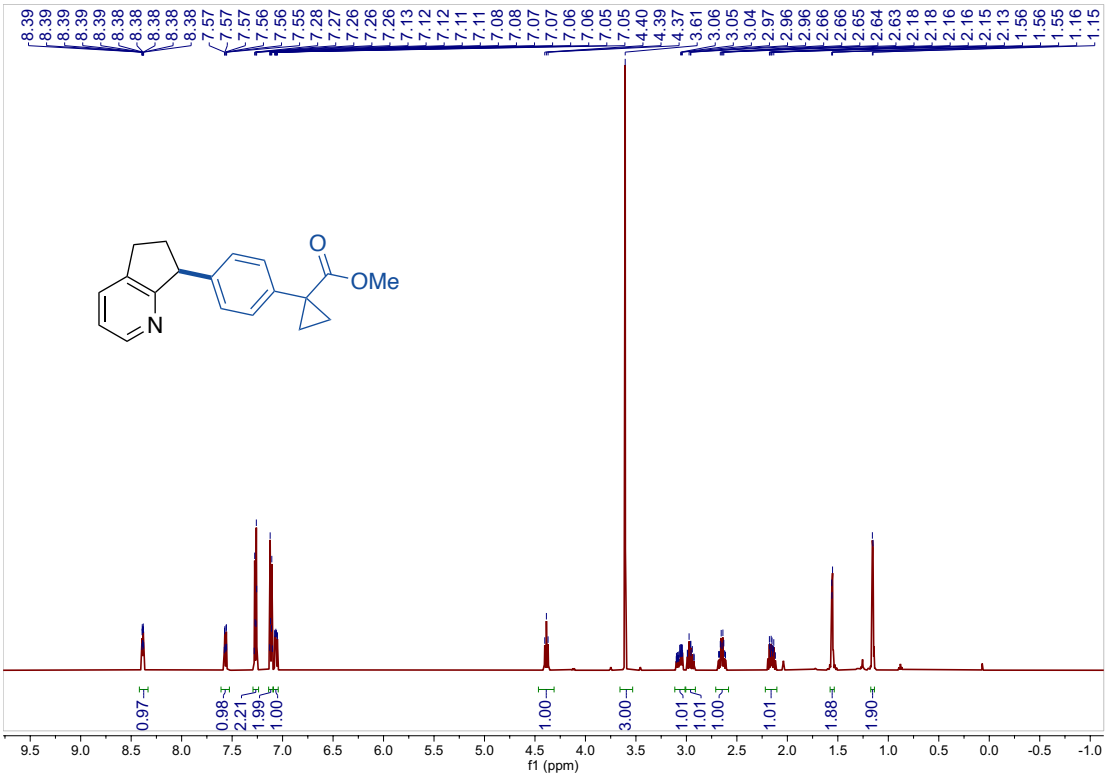
^{1}H NMR (500 MHz, $CDCl_3$) of **30**



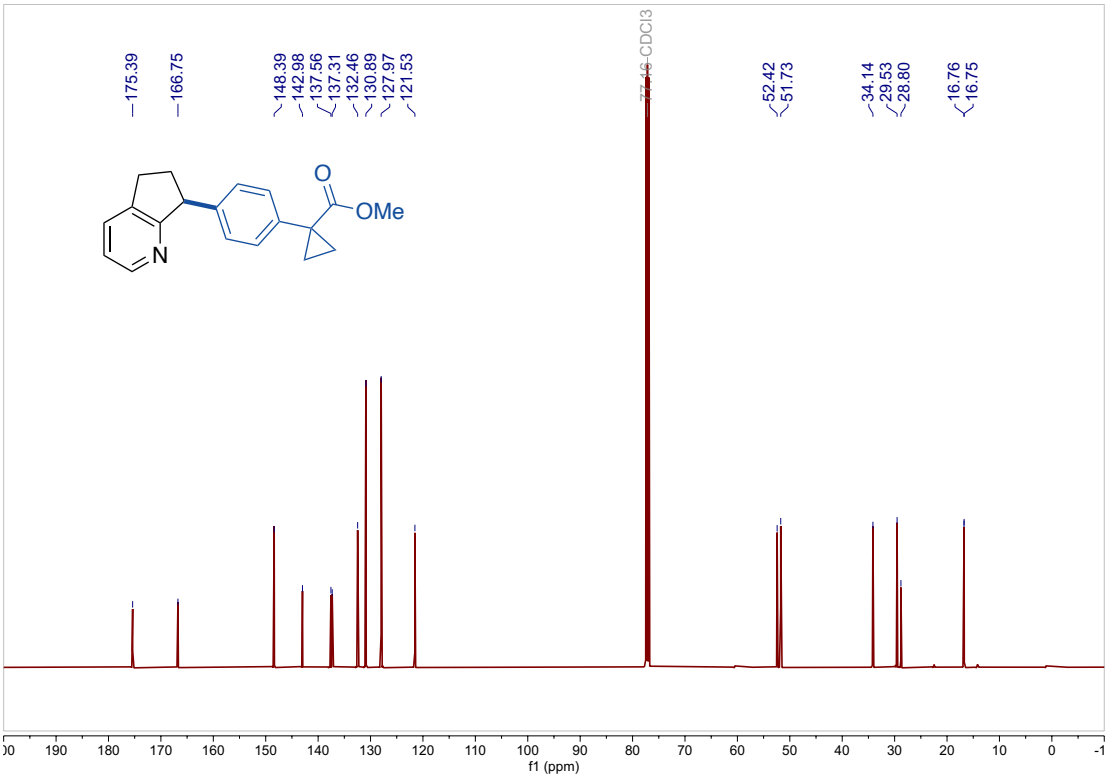
^{13}C NMR: (126 MHz, $CDCl_3$) of **30**



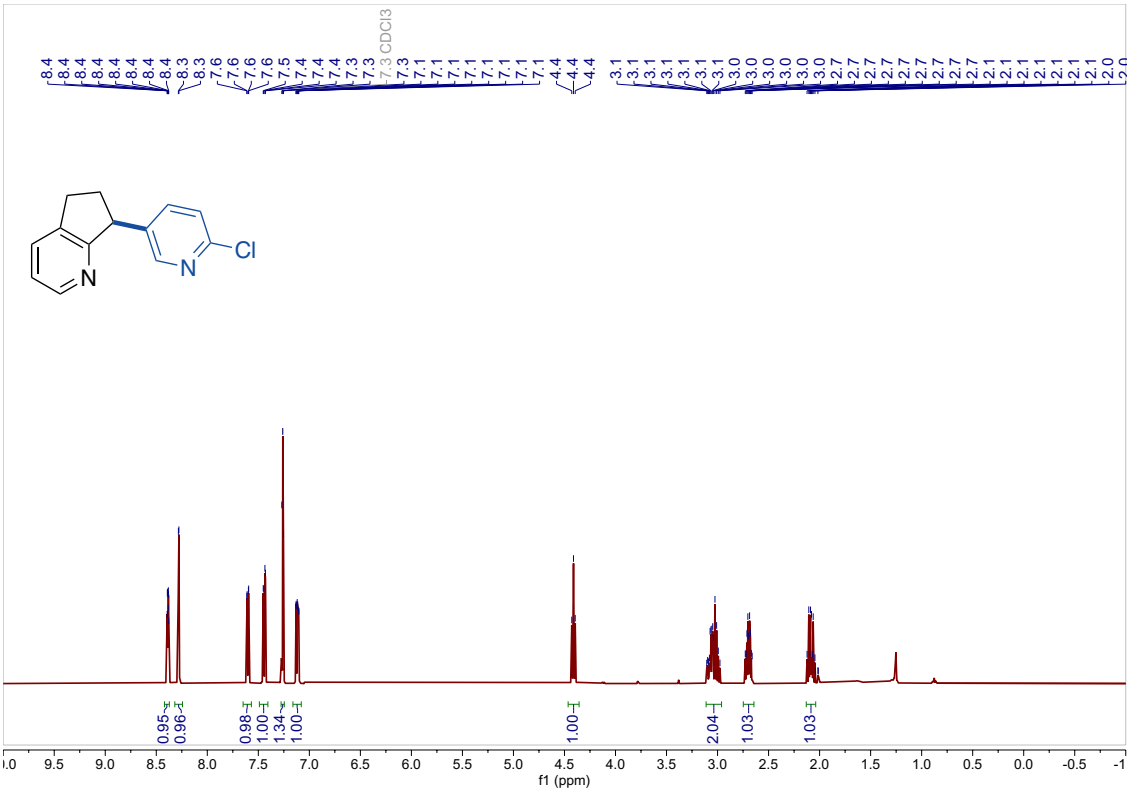
^{1}H NMR (500 MHz, $CDCl_3$) of **9-1D**



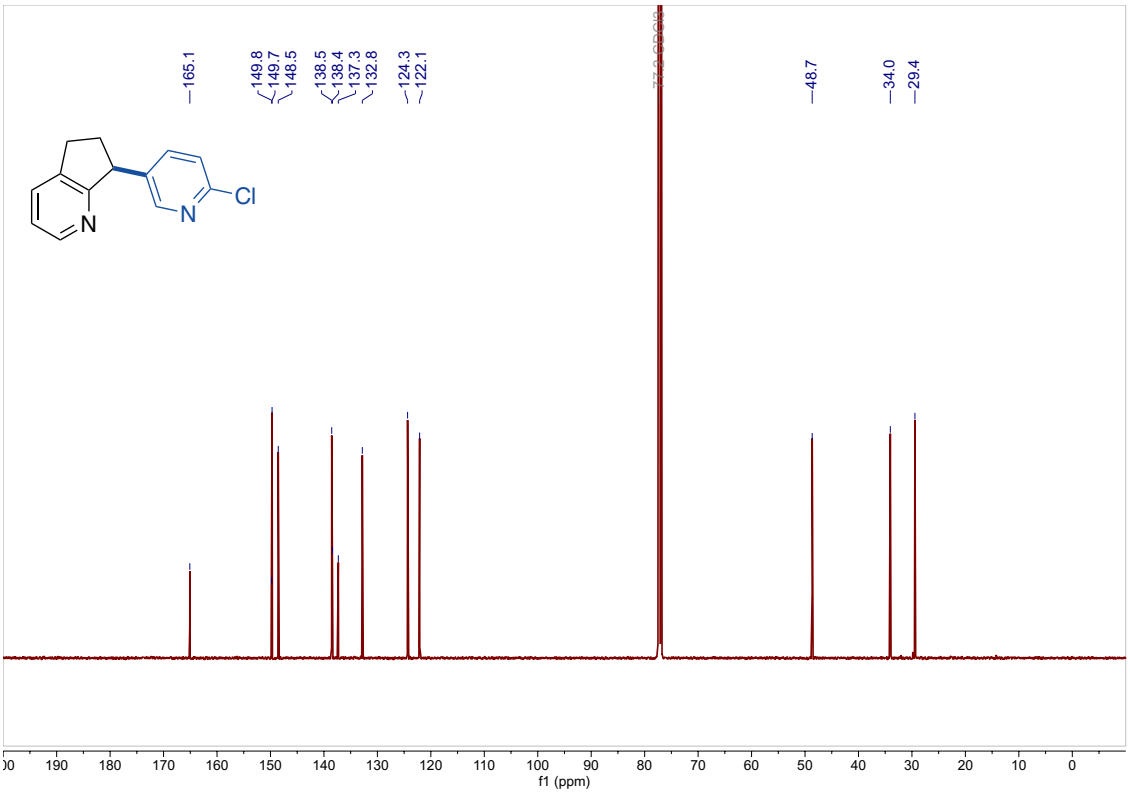
^{13}C NMR: (126 MHz, $CDCl_3$) of **9-1D**



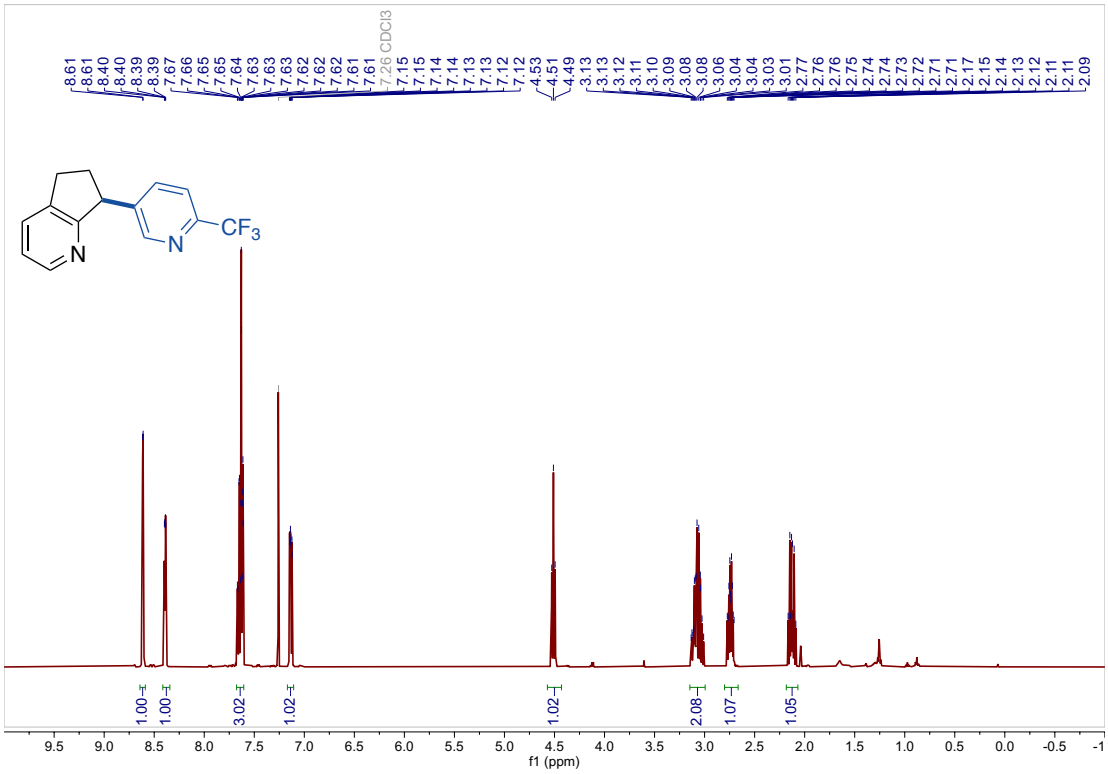
^{1}H NMR (500 MHz, $CDCl_3$) of **9-2C**



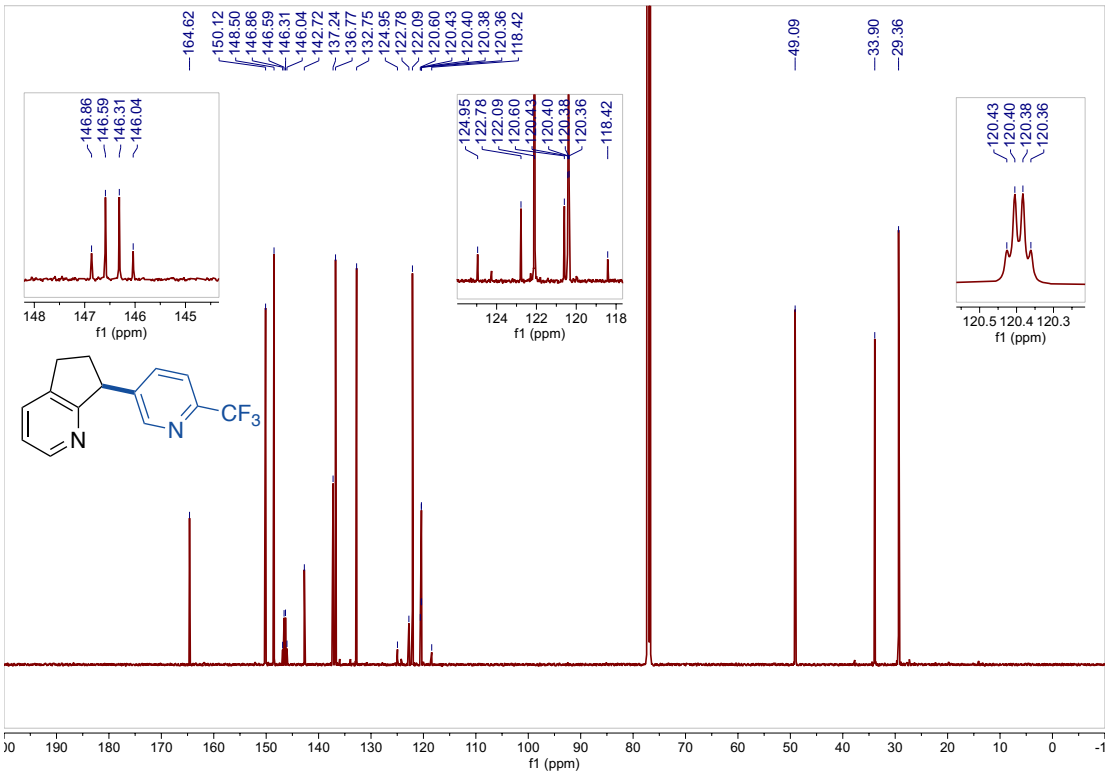
^{13}C NMR: (126 MHz, $CDCl_3$) of **9-2C**



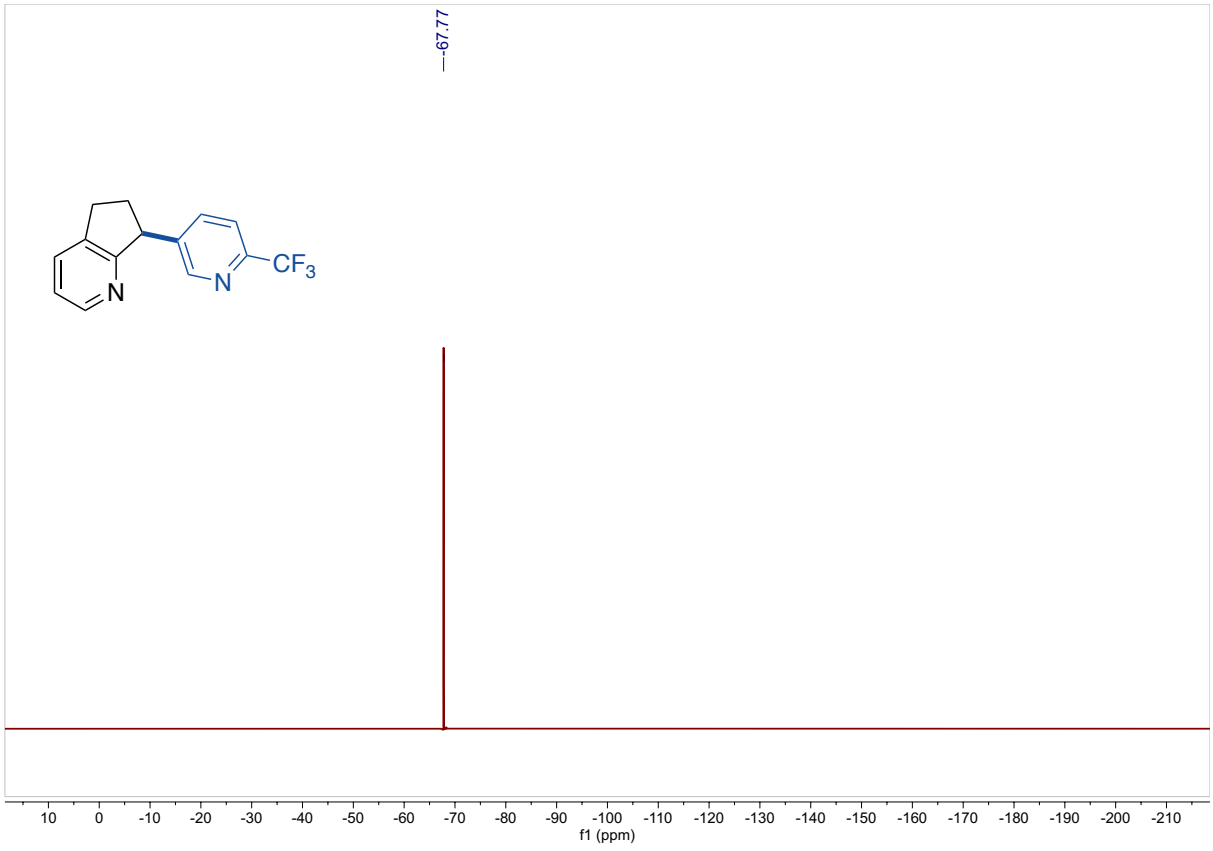
^{1}H NMR (500 MHz, $CDCl_3$) of **9-2E**



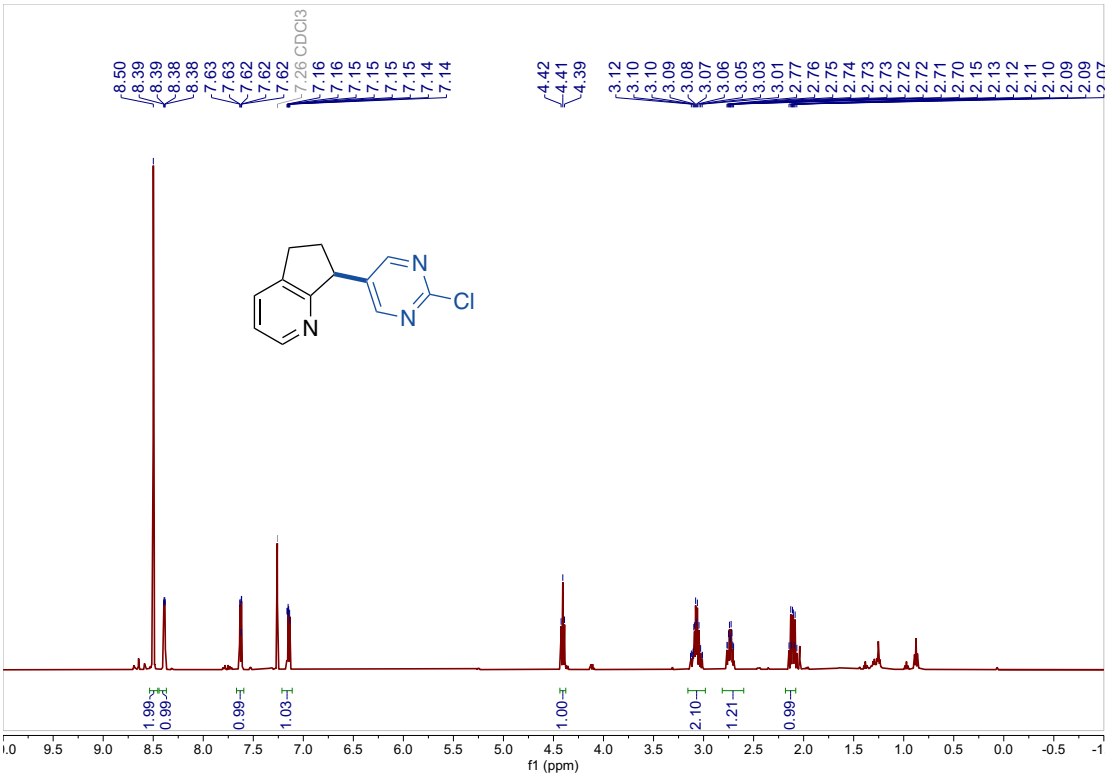
^{13}C NMR: (126 MHz, $CDCl_3$) of **9-2E**



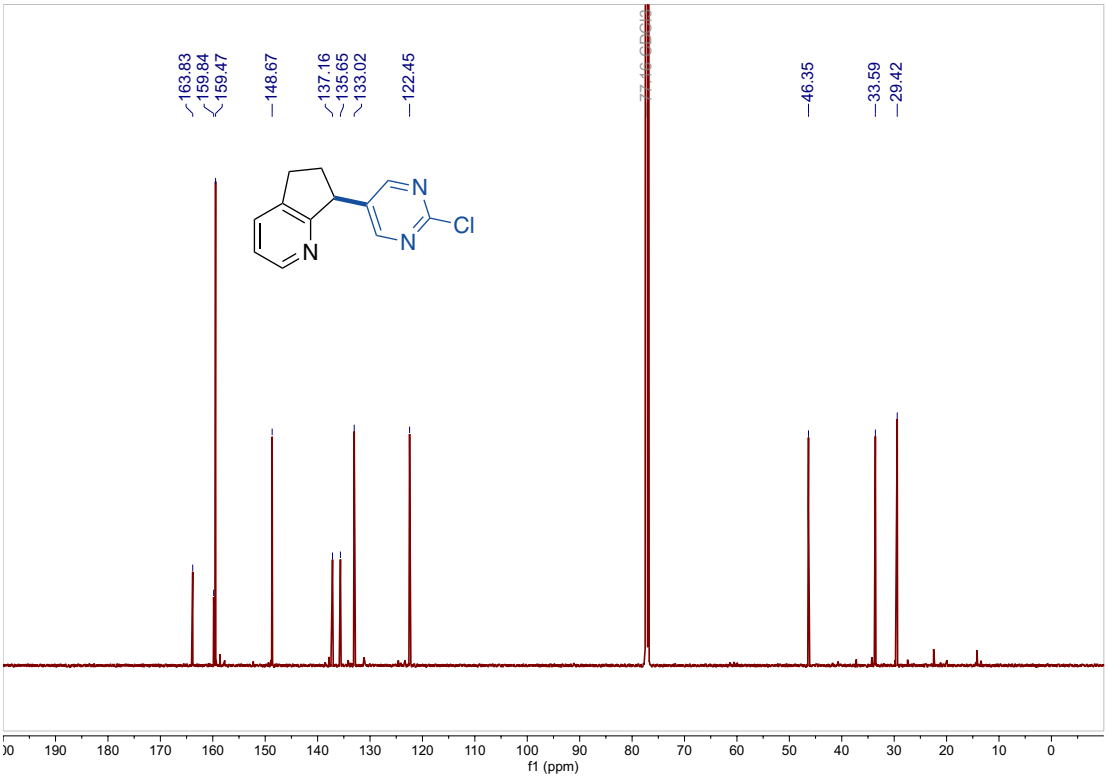
^{19}F NMR (377 MHz, $CDCl_3$) of **9-2E**



^{1}H NMR (500 MHz, $CDCl_3$) of **9-3D**



^{13}C NMR: (126 MHz, $CDCl_3$) of **9-3D**



4C.X. References

1. Huang, W.; Wang, Y.; Weng, Y.; Shrestha, M.; Qu, J.; Chen, Y. Nickel-Catalyzed Formal Aminocarbonylation of Unac- tivated Alkyl Iodides with Isocyanides. Org. Lett. 2020, 22, 3245.

2. Anka-Lufford, L. L.; Huihui, K. M. M.; Gower, N. J.; Ackerman, L. K. G.; Weix, D. J. Nickel-Catalyzed Cross-Electrophile Coupling with Organic Reductants in Non-Amide Solvents. *Chem. - Eur. J.* **2016**, *22*, 11564−11567.

3. Charboneau, D. J.; Barth, E. L.; Hazari, N.; Uehling, M. R.; Zultanski, S. L. A Widely Applicable Dual Catalytic System for Cross- Electrophile Coupling Enabled by Mechanistic Studies. *ACS Catal.* **2020**, *10*, 12642−12656.