Applications of Sulfinate Salts

Pyridine as a Removable Directing Group for Facile Access to *ortho*-Functionalized Sulfinate Salts

Fei Chen

A Thesis

In the Department

of

Chemistry and Biochemistry

Presented in Partial Fulfillment of the Requirements

For the Degree of

Doctor of Philosophy (Chemistry) at

Concordia University

Montréal, Québec, Canada

October 2019

CONCORDIA UNIVERSITY

SCHOOL OF GRADUATE STUDIES

This is to certify that the thesis prepared

By: Fei Chen

Entitled: Applications of Sulfinate Salts: Pyridine as a Removable Directing Group for Facile Access to ortho-Functionalized Sulfinate Salts

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Doctor Of Philosophy (Chemistry)

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_____ External Examiner
Dr. Shawn Collins

_____ External to Program
Dr. Steve Shih

_____ Examiner
Dr. John Capobianco

_____ Examiner
Dr. Xavier Ottenwaelder

_____ Thesis Supervisor
Dr. Pat Forgione

Approved by _____
Dr. Yves Gelinas, Graduate Program Director

December 10, 2019

_____
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ABSTRACT

Applications of Sulfinate Salts: Pyridine as a Removable Directing Group for Facile Access to *ortho*-Functionalized Sulfinate Salts

Fei Chen, Ph.D.
Concordia University, 2019

Palladium catalysis is a salient synthetic methodology for carbon-carbon bond formation for which the classical procedures have been powerful tools in chemistry for decades. Due to certain limitations, alternative methods for palladium catalyzed cross couplings have been developed, rendering the approach more environmentally sustainable. Notably, the desulfinative cross coupling reaction avoids stoichiometric organometallic waste production. Furthermore, sulfinate salts are functionally versatile as they can act both as an electrophilic or nucleophilic cross coupling partner, and at the same time they are also bench stable and easy to handle. However, as sulfinate salts can undergo self-disproportionation in solution, it limits their further synthetic applications. To overcome the issue, we propose to introduce a removable multiuse moiety to maintain the sulfinic acid. We explore pyridine as a multi-purpose option, due to its directing impact on palladium catalyzed *ortho*-halogenation. The methodology also translates to *ortho*-deuteration for the synthesis of useful isotopic compounds with potential value for pharmaceutical research. After *ortho*-functionalization, the pyridine group can be removed to regain the sulfinic acid moiety for subsequent cross couplings. Combined, these approaches complement existing methodologies in accessing multi-functionalized arene systems.

Acknowledgements

First, I would like to thank Dr. Pat Forgione for accepting me to do my Ph.D. in his group and guiding me through the past few years. He gave me exceptional support and helped me with not only the research project itself, but also with scientific thinking, writing and organizing. Pat provided me the opportunity to improve my presentation skills by sending me to multiple conferences. Presenting my work to other chemists in talks or posters was a great experience during my graduate studies. I truly appreciate the group meetings in different subjects that enhanced our sight on research and chemistry. The “ideas” opened our mind, “literature” enriched our knowledge, “research” allowed us to communicate our research within team, and “question” provided us the chance to review and discuss mechanistic problems for better understanding on the basis of organic reaction.

I would also like to thank my committee members Dr. Xavier Ottenwaelder and Dr. John Capobianco for being on my committee and for offering all the valuable advices and opinions during the past few years.

I greatly appreciate the help provided by Cynthia Messina, Franklin Chacón Huete, Peter Liu and Dr. Kashif Tanveer for proofreading this document and help me improve my thesis. It has been a pleasure to work with all my past and present members of the fORGione Group; former graduate students: Avid Hassanpour, Dirk Ortgies, Nicholas Wong, Stephane Sevingy, Daniel Mangel and Fadil Taç; graduate student: Franklin Chacón Huete, Cindy Buonomano, Cynthia Messina and Peter Liu; undergraduates: Roger Chakkal, Nga Vu, Joyce Zaftis, Gowsic Thevendran, Dustin Ng, Edip Tac, Sydney Sullivan, Hassan El-Husseini, Ernesto Armando Cuadra Foy, Xue Bin, and Leila Khelghatybana. I really enjoyed the time that we spend working in the lab. My gratitude also goes to my family; my parents supported me all the time and thanks for always being there for me, and my daughter, who is my angle and gave me courage to face every challenge in my life.

The research presented was funded by the Natural Sciences and Engineering Research Council (NSERC) of Canada and Le Fonds de recherche du Québec, nature et technologies (FQR-NT). Support was also kindly provided by Centre for Green Chemistry and Catalysis (CGCC), and Concordia University.

Contributions of Authors:

Chapter 2 includes a published work of “A Convenient and Inexpensive Route to Access Sulfonylated Pyridines via a SNAr Reaction of Electron-Rich Pyridines through Iron Catalyst” (https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0036-1591541 Copyright © Georg Thieme Verlag Stuttgart · New York). Major work include optimization and most of the reaction scopes were performed by the author. Co-authors Franklin Chacon-Huete and Hassan El-Husseini contributed mainly on the reproducible of the reaction scope and few substrates.

The manuscript of Chapter 3 is in preparation as “Using Pyridine as Removable Ortho-Directing Group to Access *Ortho*-Halogenated Sulfinate Salts”. The content includes the directed *ortho*-halogenation *via* palladium catalyzed C-H activation and the removal of the pyridine functional groups. The reaction optimization and reaction scopes were all contributed by the author. Visiting scientist Dr. Mohammad S. Askari performed the KIE work in mechanism study part and most of the characterization spectra and HRMS were done by Ph.D. candidate Cindy Buonomano.

Chapter 4 is an in progress work and it describes the directed deuteration on sulfonylated pyridines. The optimization and all the preliminary results were contributed by the author. Visiting scientist Dr. Mohammad S. Askari initiated the research and the reaction on *meta*-toluenesulfonylated pyridine substrate was contributed by Ph.D. candidate Cynthia Messina.

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List of Schemes

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List of Abbreviations

δ	chemical shift in ppm
μw	microwave heating
i	iso
*i*Pr	2-propyl
Bu	butyl
J	coupling constant in Hz
m	*meta*
o	*ortho*
p	*para*
t	tert
n-Bu	normal butyl
acac	acetylacetonate
Ac	acetate
ADME	absorption, distribution, metabolism, and excretion
AMBN	2,2'-Azobis(2-methylbutyronitrile)
Ar	aryl
Boc	*tert*-butyloxycarbonyl
Cp	cyclopentadienyl
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DavePhos	2-(dicyclohexylphosphino)-2'-(*N,N*-dimethylamino)-biphenyl
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
DMA	*N,N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N,N* -dimethylformamide
DOI	Digital Object Identifier
DoM	Directed *ortho* metalation
dppf	1,1'-bis(diphenylphosphino)ferrocene
EI	Electron ionization
equiv.	equivalents
Et	ethyl
FQRNT	Le Fonds de Recherche du Québec, Nature et Technologies
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
HetAr	heteroaryl
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry
KIE	Kinetic Isotope Effect
Me	methyl
NBS	N-bromosuccinamide
NCS	N-chlorosuccinamide
NIS	N-iodosuccinamide
NMP	N -methyl-2-pyrrolidone
NMR	nuclear magnetic resonance

NSERC	Natural Sciences and Engineering Research Council
OTf	trifluoromethanesulfonyl
OTs	4-toluenesulfonyl
PPh_3	triphenylphosphine
Ph	phenyl
phen	1,10-phenanthroline
PivOH	pivalic acid
ppm	parts per million
S_EAr	electrophilic aromatic substitution
S_NAr	nucleophilic aromatic substitution
TFA	trifluoroacetic acid
TFA-D	deuterated trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
Ts	*p*-toluenesulfonyl
triflate	trifluoromethanesulfonate

Chapter 1: Introduction

1.1 Carbon-Carbon Bonds

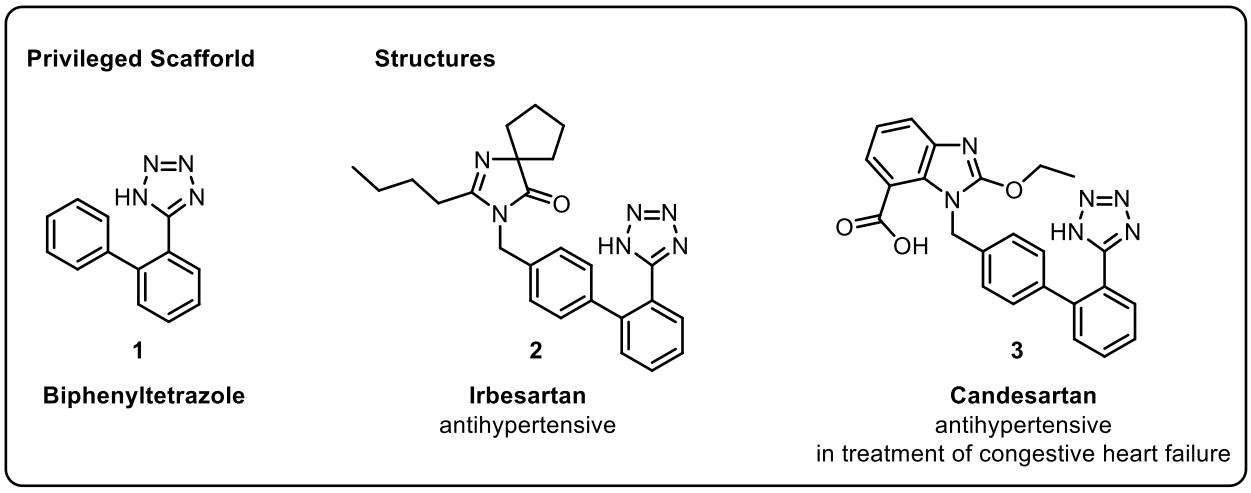
Carbon is a non-metallic element belonging to group 14 in the 2nd period of the periodic table, and is the 4th most abundant element in the universe by mass. Its ability to form long chains of carbon atoms, which is also known as catenation, enabled it to become a common element of all known life on Earth and is the 2nd most abundant element in the human body by mass[1]. As it serves such an important role in everyday life, the formation of carbon-carbon bonds continues to be of interest in synthetic chemistry.

Nowadays with the fast development of technology and population explosion, the living standard is higher than ever, which has increased the demands on both materials and nature. Therefore, with the finite nature of available resources, efficient and environmentally friendly transformations are necessary. The ideal synthetic pathway is the one where each step contributes to the final molecule's framework or its functional groups.[2] Additionally, if the synthetic route could avoid using protection/deprotection or oxidation/reduction steps, it would be even more desirable.[3] Since carbon-carbon bonds are the basic framework of the majority of the organic compounds, rapid and efficient C-C bond formation could be critical.

Surveys have been done for reactions on C-C bond formation and reveal the importance of the formation of C-C bonds in chemistry.[4] In 2006, Carey completed a survey with three pharmaceutical companies, GlaxoSmithkline, AstraZeneca and Pfizer, and found that of the 1039 reactions performed in their R&D departments, 11% of the reactions are C-C bond formations.[4a] Subsequently. Roughley and Jordan did another survey of 139 papers in three medicinal journals and reported that 62.3% of the 7315 reactions are C-C bond formations.[4c] Interestingly, palladium catalyzed C-C formation also weighed heavily in the C-C bond formation. Carey's survey[4a] indicated that 22% of the C-C bond formation reactions are palladium catalyzed reactions and 11.5 % of the 7315 reactions that were evaluated by Roughley and Jordan[4c]. In addition, 17% of the 4800 reactions used towards the development of drug candidates for respiratory diseases at GlaxoSmithkline, are palladium catalyzed reactions.[4b] Those surveys indicated the importance of the C-C bonds in organic synthesis and noticeably both in academic and industrial settings, chemists are interested in C-C bond formation. Furthermore, palladium seems to be a valuable tool towards C-C bond formation.

1.2 Importance of Biaryls

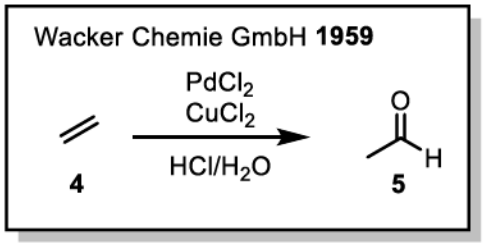
Aromatic systems due to their unique properties such as planar geometry and π stacking abilities are important motifs for pharmaceuticals, materials and fine molecules. Due to their stability and thermal properties, they have been used as insulators and heat-conductors.[5] Biphenyls are also known as *privileged structures* (Scheme 1) as they can be a template motif that could be lead to discovery of novel compounds for binding to proteins.[6] Biphenyl cores have been used to identify a binding pocket of a subclass of G protein-coupled receptors (GPCRs).[7] In addition biphenyls are known to allow aromatic and hydrophobic interactions within protein binding pockets.[8]



Scheme 1: Examples of Privileged Scaffold in Medicine Candidates.

1.3 Classic Palladium Catalyzed Reactions

Palladium (Pd) was discovered in 1802 by Wollaston and reported in 1805[9], however the metal didn't generate much attention until post-World War II, when it was first developed as a catalyst for the industrial scale Wacker process (Scheme 2). The reaction was initially reported in 1894, and has been used to produce large quantities of acetaldehyde from ethylene since 1956.[10] Once the unique properties of Pd metal came into focus, it became widely used in coupling reactions for various bond formations, including C-C bonds. Palladium has become one of the most useful transition metal catalysts in organic synthesis.

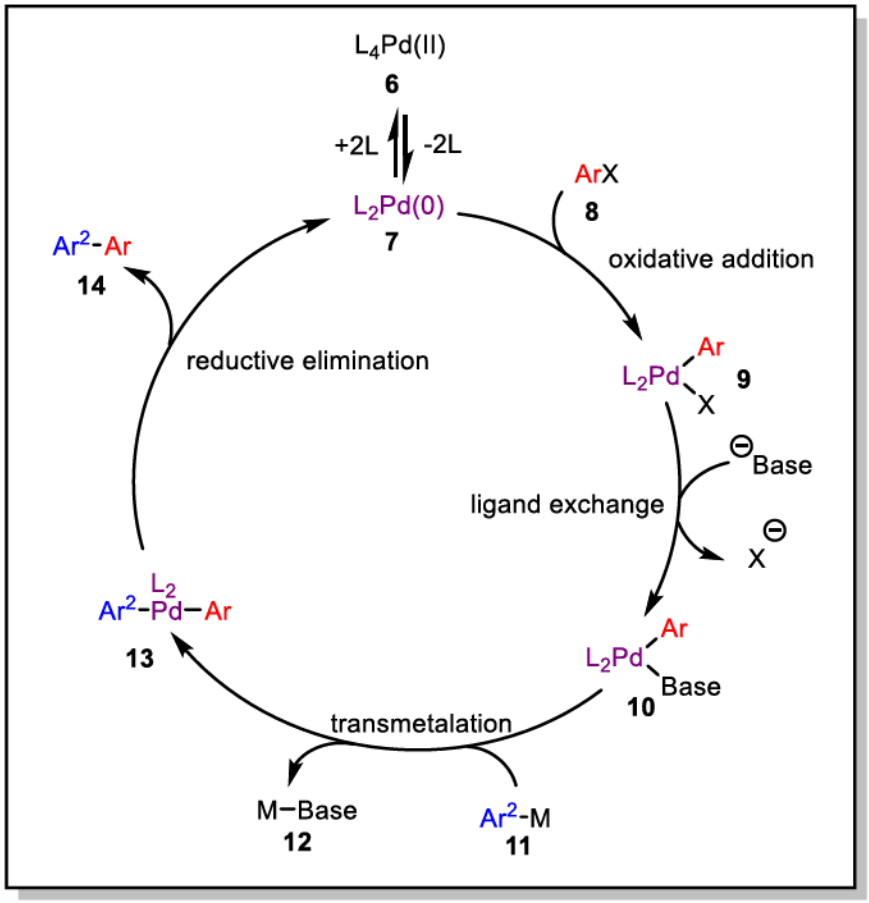


Scheme 2: Wacker process.

Palladium is a group 10 element in the 5th period of the periodic table with an atomic number of 46. Its ability to efficiently shuttle between Pd(0)/Pd(II) or Pd(II)/Pd(IV) makes it a very good transition metal catalyst for two electrons transfer reactions. To highlight the importance of Pd-catalyzed C-C bond formation, the Nobel Prize was awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki in 2010 "for palladium catalyzed cross coupling in organic synthesis".[11] Noticeably, Dr. Negishi and Dr. Suzuki were focused on the cross coupling of two aromatic moieties and the Suzuki reaction is widely used in the pharmaceutical industry, where the moieties are in high demand.

1.3.1 Commonly Accepted Catalytic Cycle

Most of the palladium catalyzed cross coupling reactions involve a Pd(0)/Pd(II) cycle, for which the active species is Pd(0). There are a wide range of Pd(0) complexes that are commercially available and have reported uses , such as $Pd(PPh_3)_4$ or $Pd(dba)_2$.[12] In the complexes, the phosphine ligands coordinate with the metal center and form a tetrahedral 18 electron complex. When the complex is in solution, the dissociation of a ligand liberates the coordination site and forms a 16 electron complex, which promotes reactivity. The Pd(0) catalytic species could also be generated *in situ* from a more stable Pd(II) pre-catalyst. In the reaction mixture, Pd(II) can be thermally reduced to the active Pd(0) catalyst. In most cases however, the phosphine ligand will act as the reductant. It has also been suggested that lone pairs of heteroatoms within a coupling reagent or in solution could play the same role. The processes are thought to generate the active Pd(0) in the catalytic cycle below (Scheme 3).



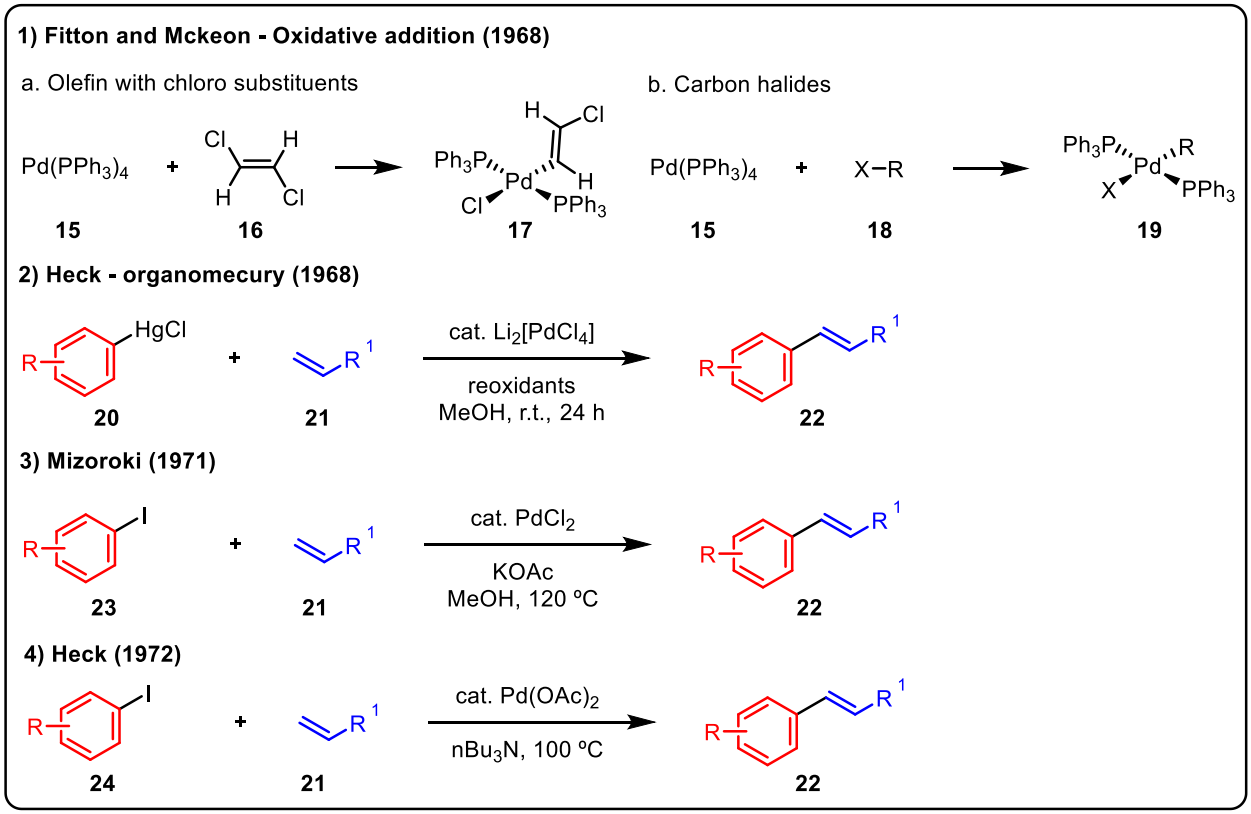
Scheme 3: Commonly accepted palladium catalytic cycle.

The catalytic cycle starts with active species (**7**) undergoing an oxidative addition into the aryl-halide bond, forming the Pd(II) intermediate (**9**). Most of the Pd catalyzed reactions involve a base that is known to act as a ligand to replace the halide and coordinate to the metal center. Next, the palladium complex (**10**) can undergo transmetalation with the coupling partner organometallic/metalloid reagent **11** (except in the Heck type coupling reactions – detailed Mizoroki-Heck reactions and different coupling partners will be discussed later). In order to generate the desired product, the key intermediate (**13**) goes through a cis/trans isomerization to orient the two aromatic systems into the *syn* position. Reductive elimination is the last step of the catalytic cycle – it produces the desired bi-aryl while regenerating the active Pd(0) catalyst.

1.3.2 Mizoroki-Heck

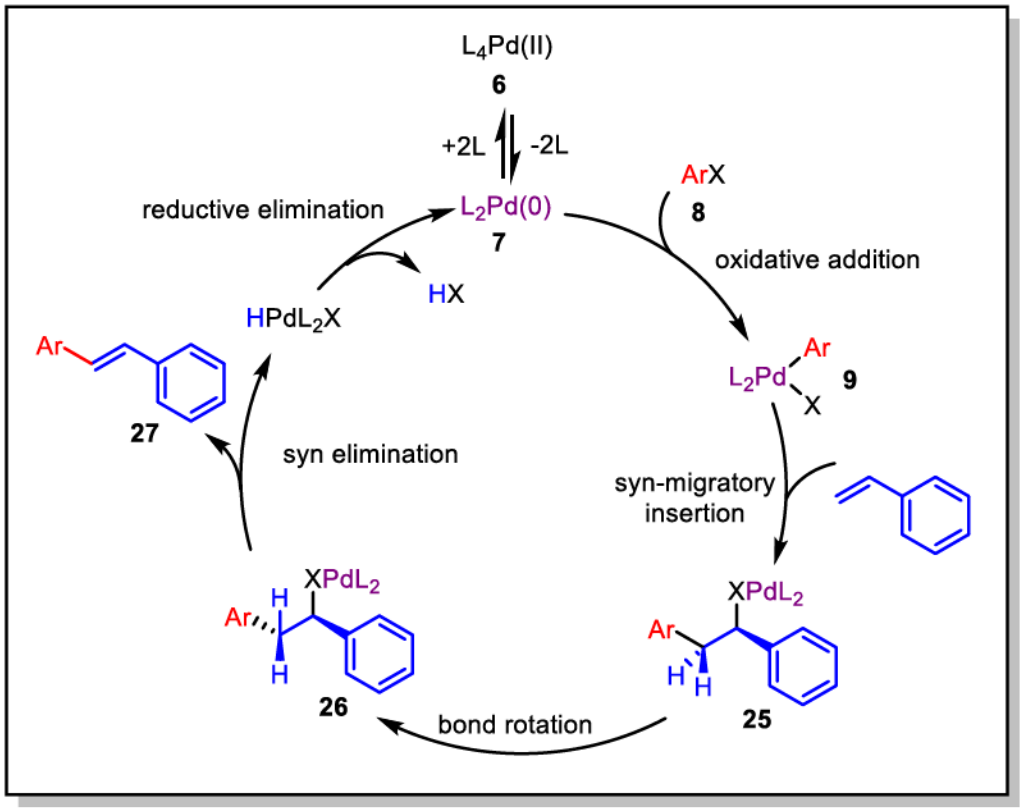
In early 1968, Fitton and Mckeon published papers demonstrating that palladium could insert into the vinyl chloride and aryl halide bond through oxidative addition to form Pd(II) complexes, which is the first step of the catalytic cycle summarized in Scheme 4 – 1).[13] That same

year, Richard Heck[14] discovered that using stoichiometric Pd(II) salts could produce coupling reactions between organo-mercury compounds and olefins. He later optimized the reaction to use only catalytic amounts of Pd with a stoichiometric amount of $CuCl_2$ as the oxidant. In 1971 and 1972, Mizoroki[15] and Heck[16] both independently published coupling reactions between iodobenzene and styrene under different conditions, without a transmetalation step.



Scheme 4: Palladium couplings with vinyl substrates.

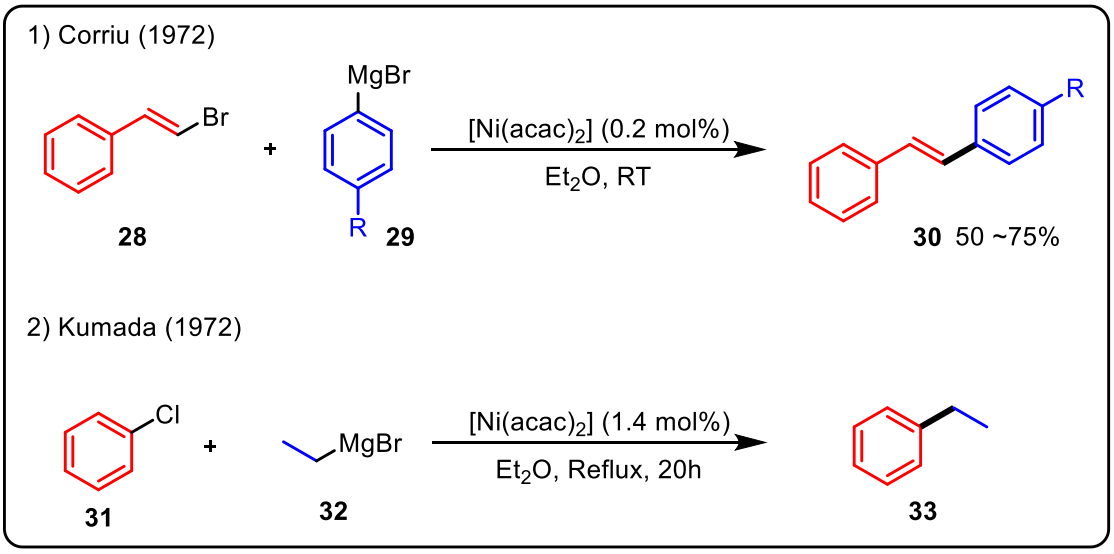
As mentioned earlier, Heck type reactions do not follow the commonly accepted catalytic cycle (see Scheme 5). The nucleophilic partner of Mizoroki-Heck is not an organometallic reagent, but rather an unsaturated carbon-carbon bond (double or triple bonds). After oxidative addition into an aryl-halide, an unsaturated C-C bond acts as a L-ligand to coordinate with the Pd(II) center. Next, the bond will rotate to allow a β-hydride syn-elimination. This step replaces transmetalation and reductive elimination steps in the general cycle. Later, the development of phosphine ligands and the advent of different Pd catalysts increased reaction yields and expanded the reaction scopes, and Mizoroki-Heck type reaction became widely used in the formation of C-C bonds from aryl-halides and unsaturated C-C bonds (the systems must have at least one adjacent hydrogen to allow for β-hydride elimination).



Scheme 5: Palladium catalytic cycle of Heck type reaction.

1.3.3 Kumada-Corriu

In 1972, Kumada[17] discovered nickel-catalyzed cross couplings between Grignard reagents and aryl halides, and Corriu[18] demonstrated a very similar reaction for vinyl halides (Scheme 6). The reaction conditions for those reaction greatly improved the reaction scopes, as long as the functional groups could be tolerated by the Grignard reagent, the reactions will tolerate them.[19] Noticeably, the widely used phosphine ligands for regulating the metal catalysts were also first introduced by the Kumada group.[20] Although nickel is more reactive with aryl-chlorides and pseudo-halides, palladium catalysts offer several advantages compared to nickel catalysts.[21] First, palladium catalysts are easier to prepare and access, and second, they are less sensitive to air and moisture. Additionally, palladium catalysts shuttle well between their most stable oxidation states, Pd(0) and Pd(II), through two electron transfers, while nickel could be stabilized in a greater variety of oxidation states, such as Ni(I) and Ni (III), therefore promoting radical reactions, which can lead to unwanted side reactions or homo-coupling[22].



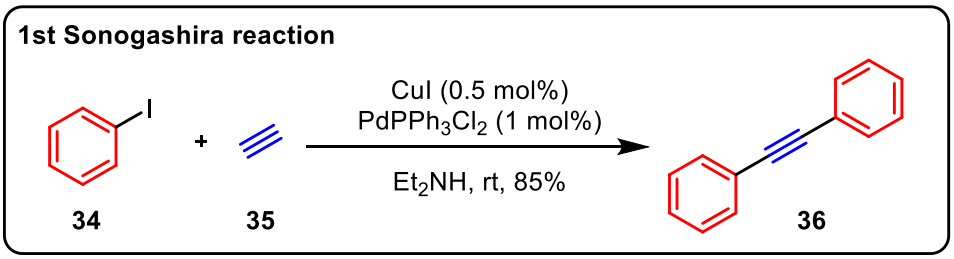
Scheme 6: Kumada reactions.

The discovery of the reactions reveals the capability of palladium to catalyze coupling reactions, especially in C-C bond formation. Palladium catalyzed reactions could tolerate various functional groups, such as aryl, alkenyl and alkyl from other metals (in transmetalation step) such as Mg or Li in this reaction. In addition, the desire to investigate more stable and functional group tolerant organometallic reagents as coupling partners for Pd-catalyzed reactions was established in the chemical community.[10c] Recently, there were reactions developed using more readily available and cheap first row metals – nickel, iron or cobalt to replace the second row or third row metals.[23] Various Ni-catalyzed reactions have been published, as well as iron and cobalt, even though they required more specific functional groups and conditions than Pd-catalyzed equivalents.[24]

1.3.4 Sonogashira

Copper is a first row transition metal element located adjacent to nickel, and it is another well-known and widely used metal catalyst for aryl couplings such as in the Ullmann reaction[25], and alkyne couplings such as the Glaser[26], Cadiot-Chodkiewicz[27] and Castro-Stephens[28] couplings. Cassar[29] and Heck[30] altered the alkyne couplings using catalytic palladium to reduce temperature requirements and to avoid the use of dangerous copper acetylides. Sonogashira[31] further improved this coupling with the re-addition of copper as a co-catalyst, which allowed for the reaction to be performed at room temperature and with a lower loading of palladium (see Scheme 7). The Sonogashira reaction generates active copper acetylides *in situ*, avoiding handling of the dangerous reagent while retaining the milder reaction conditions afforded by the

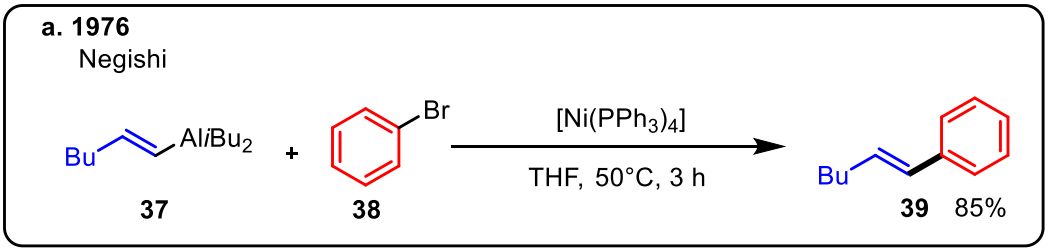
use of palladium. It has becomes an important reaction in the introduction of alkynyl groups into molecular scaffolds.

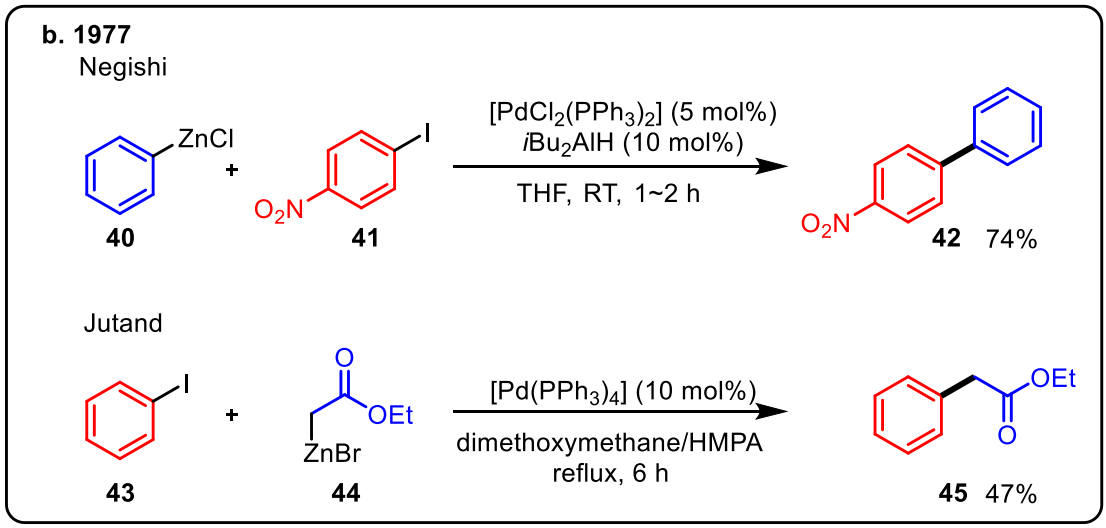


Scheme 7: 1st Sonogashira reaction.

1.3.5 Negishi

The Negishi reaction is now a well-known class of coupling reactions for the formation of C-C bonds utilizing organozinc reagents with aryl halide and Pd catalysts.[25a] Even though Negishi reactions are now inextricably linked to organozinc reagents, the first cross coupling reaction published by Negishi was a coupling between organo-aluminum reagents and aryl halides with nickel catalysts in 1976 (see Scheme 8-a).[22] Later, both Negishi[22, 32] and Jutand[33] independently reported the use of organozinc reagents as the nucleophilic coupling partner using palladium as catalyst (see Scheme 8-b). Organozinc compounds need much milder conditions for coupling when compared to Grignard reagents. The fully occupied d-orbits of zinc metal facilitate the transmetallation. Similar to Grignard reagents, organozincates, organozinc salts and zinc halides are also in equilibrium in solution. As such, different species may result in slightly different transmetallation events, as organozincate has the fastest transmetallation in trans-palladium complexes and organozinc salts lead to cis-palladium complexes. One of the major side products of the Negishi reaction is the homo-coupling product of the zincate, due to the easy exchange of the substrate binding with zinc atom and palladium center.[34] Overall, the Negishi reaction employs a wide range of substrates and occurs in milder conditions compared to Kumada reactions.

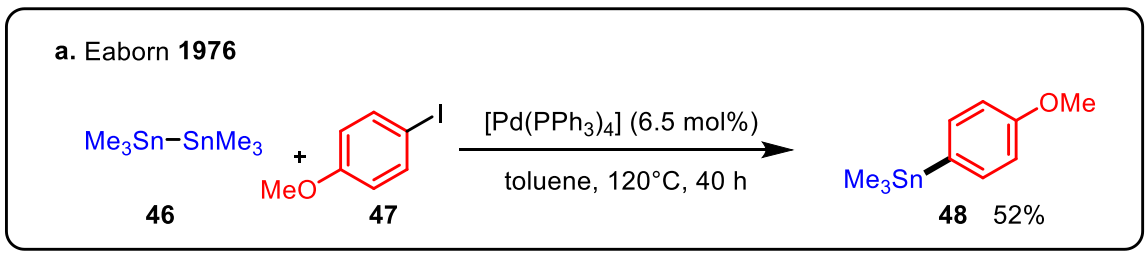


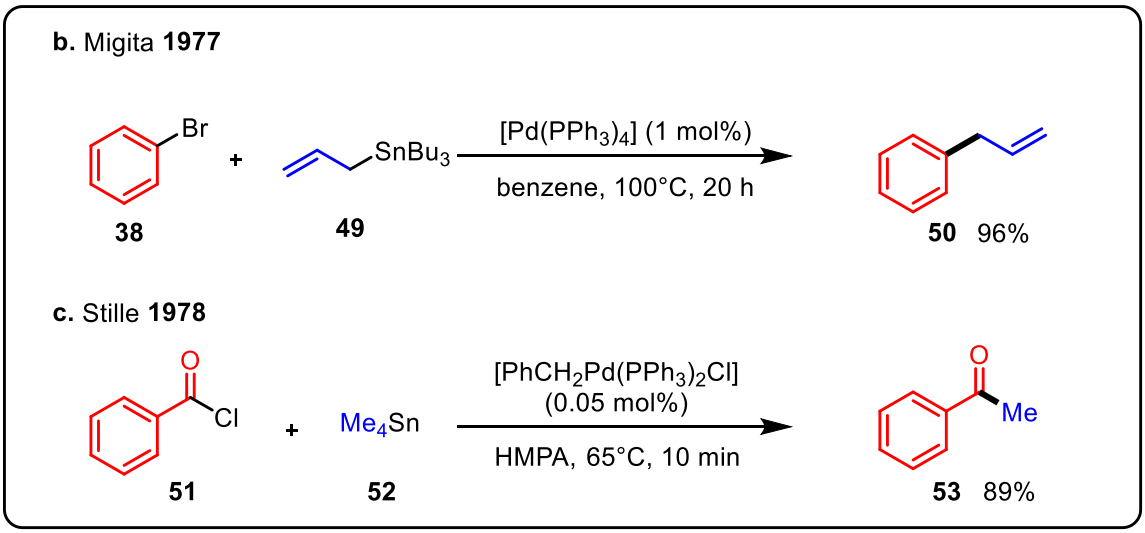


Scheme 8: a. Ni-catalyzed Negishi couplings; b. Pd-catalyzed Negishi couplings.

1.3.6 Stille

The first palladium catalyzed cross coupling between organodistannanes and aryl iodides was reported by Eaborn's group in 1976 (see Scheme 9-a).[35] Subsequently, Migita also reported the palladium catalyzed cross coupling of organotin reagents with aryl bromides (see Scheme 9-b).[36] The first palladium catalyzed coupling was published by Stille and Milstein in 1978 towards the synthesis of ketones under mild reaction conditions through acyl chlorides and organostannanes (see Scheme 9-c).[37] From there, Stille further developed the method in order to tolerate a broad range of functional groups, provided by the small electronegativity differences between carbon and tin.[38] The Stille reaction has become one of the most versatile and applicable methods to construct C-C bonds. To highlight the importance of the method - since its discovery, the Stille coupling is the fourth most published and patented named C-C coupling reaction.[10c] However, the drawback of the method is also very significant; the toxicity of stannanes and the by-products generated due to the organostannanes are problematic for purification and the environment. The drawbacks did not prevent the using of Stille couplings in industry, but did prompt further developments in improving organometallic coupling partners.[39]

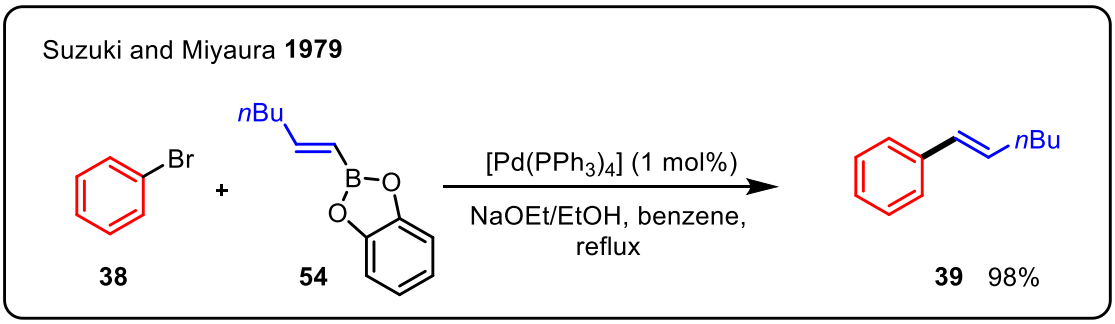




Scheme 9: Examples of Stille couplings.

1.3.7 Suzuki – Miyaura

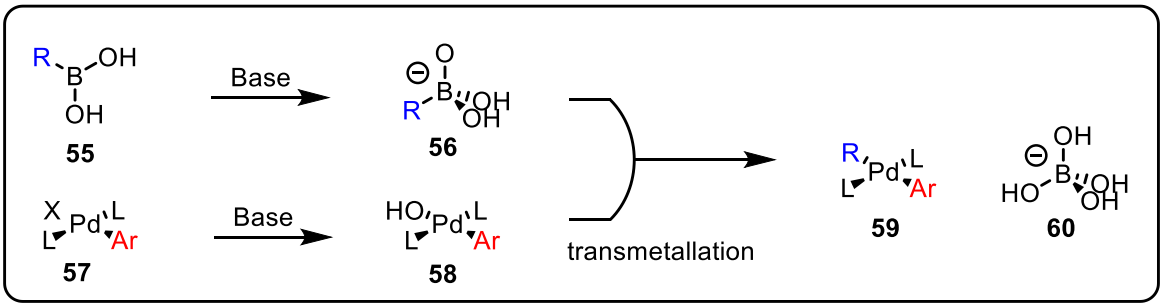
In 1975, Heck published the first cross coupling between boronic acids and aryl halides using stoichiometric palladium, but didn't develop the methodology further.[40] It was Suzuki and Miyaura in 1979 who expanded the use of organoboron reagents for cross couplings with catalytic palladium (Scheme 10).[41] The reaction is now known as the Suzuki-Miyaura cross coupling.[42]



Scheme 10: 1st Suzuki coupling reaction.

Compared with other organometallic starting materials of classic Pd catalyzed reactions, organoboronates and boronic acids are more stable and more easily handled nucleophilic partners, and the resulting by-products are also less toxic. Given the advantages of the Suzuki reaction, further methods for the preparation of various organoboranates and boronic acids were also developed. Suzuki also highlighted the importance of the base in coupling reactions, hypothesizing that the negative charge produced due to the fully coordinated boron centre enhances the nucleophilicity of the coordinated organic groups and promotes the transmetalation step.[42b, 43] Later, Hartwig suggested that a palladium hydroxo complex could undergo

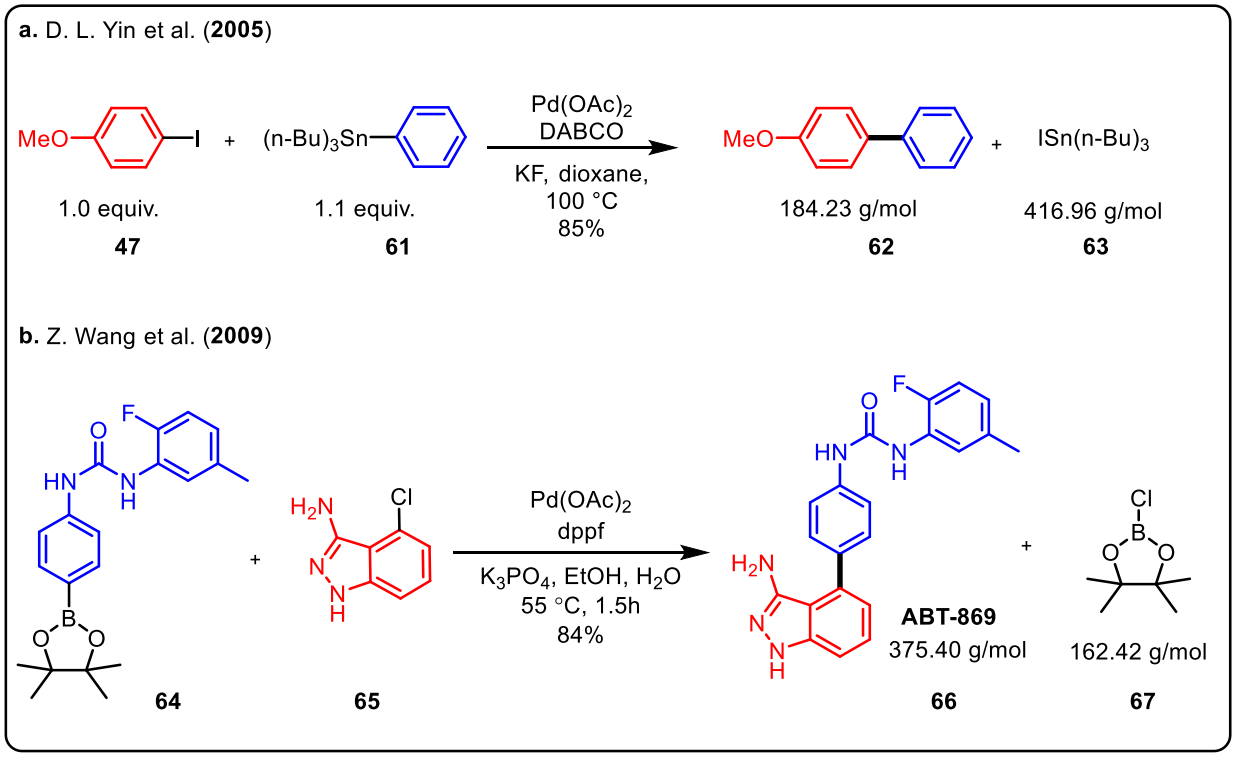
transmetalation with the boronic acid (Scheme 11).[44] His findings indicated that when an appropriate activating agent (presumably, a base) is involved, transmetalation could occur with other type of organo-element reagents that have a much lower electronegativity difference between the organic moiety and the element. Additionally, the lower electronegativity indicates a much more stable and greater functional group compatibility for nucleophilic partners in coupling reactions. Currently, the Suzuki reaction is one of the most widely used reactions in industry.[45]



Scheme 11: Proposed key mechanistic step for the Suzuki reaction.

1.4 Alternative Palladium Catalyzed Cross Couplings

Even though the classic palladium catalyzed cross couplings are powerful methods, chemists are also searching for new alternatives. Different nucleophilic coupling partners have been explored, such as organometallic compounds of indium[46] and bismuth[47]. One of the most utilized is the Hiyama-coupling reaction with organosilanes.[48] The methods using palladium catalysis are complementary and versatile, however, they all involve the organometallic or organometalloids as coupling partners. The coupling partners have limitations, such as sensitivity to air and moisture, as well as toxicity in some cases. Additionally, they generate heavy metal by-products, and, in order to access the pre-functional group needed, more reactions are required that produces more waste. Two examples of a Stille coupling and a Suzuki-Miyaura reaction illustrate the problem (see Scheme 12). With Stille couplings, due to the tributyltin group, the mass of by-product (**63**) generated is doubled compared with the desired product (**62**).[49] Another example is a late-stage Suzuki reaction, but the waste (**67**) produced still accounts for around half of the desired product (**66**).[50] This facet is increasingly significant in light of environmental concerns.[51] As we have only one Earth and limited natural resources, environmentally friendly methodologies are therefore in high demand.[52] As such, alternative palladium catalyzed methods that are increasingly environmentally benign have been developed.



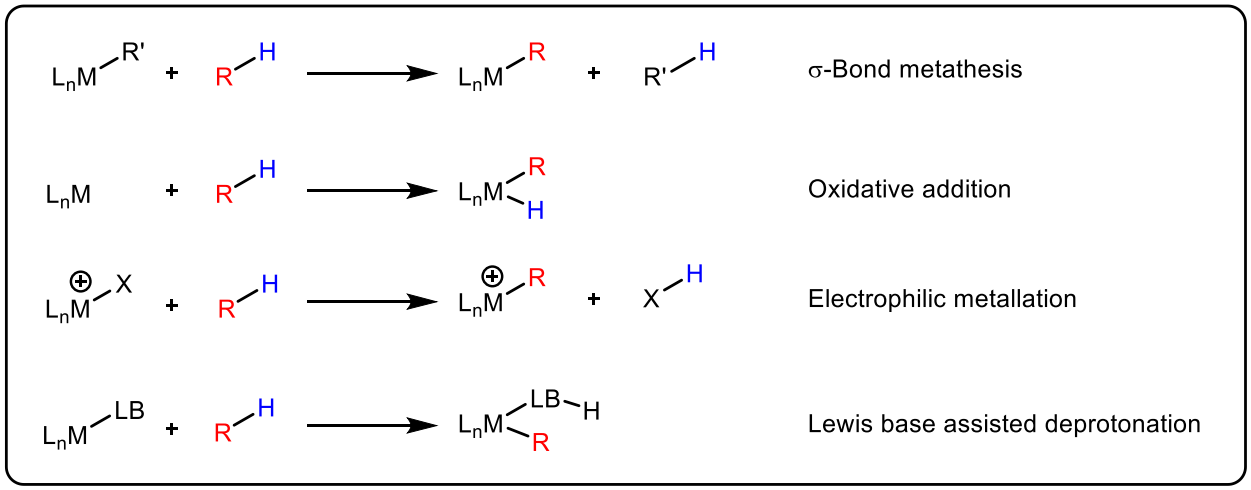
Scheme 12: Examples of by-products generated by classic Pd-catalyzed coupling reactions.

1.4.1 C-H Activation

C-H activation reduces the mass of by-products in cross coupling reactions significantly as there is no need for pre-functionalization to form an organometallic partner. The only by-products of the coupling reaction generated are hydrogen halides and H_2 gas. Therefore, the method is an environmentally friendly alternative reactions in the formation of desired C-C bonds.[53]

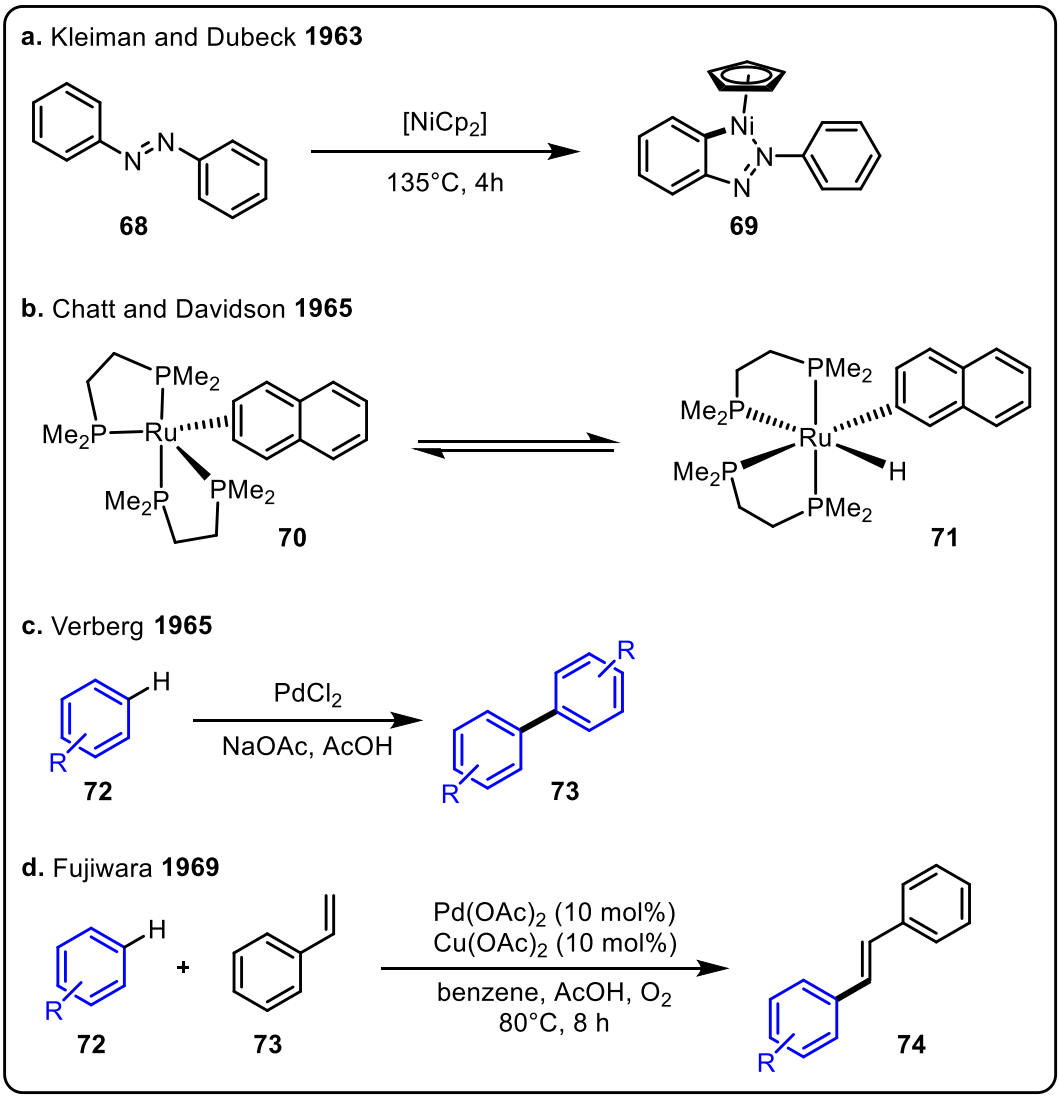
The C-H bond is highly inert and the strength of it is approximately 115 kcal/mol.[54] As such, the activation of a C-H bond normally involves metal catalysts. While several factors, including metal, ligand, solvent, and additives affect the activation step, the metal involved is really the critical element for the reaction pathway. Several proposed C-H bond activation mechanisms can occur depending on the nature of the catalytic metal. For the high oxidation early transition metals, the σ-bond metathesis is the predominate mechanistic route, and with electron-rich and electron-poor mid to late transition metals such as palladium, oxidative addition, electrophilic metalation, and Lewis-base assisted deprotonation are all common pathways (see Scheme 13).[55] Palladium is one of the few catalysts that could be used in various bond formation reactions such as C-O, C-S, C-N, and C-C bonds, and its different complexes have good compatibilities with oxidants as well as different ligands that could promote both sp^2 and sp^3 C-H functionalization. Additionally,

most palladium catalyzed C-H activation reactions can tolerate ambient air and moisture, which makes the reaction much more practical.



Scheme 13: Various commonly accepted C-H activation pathways.

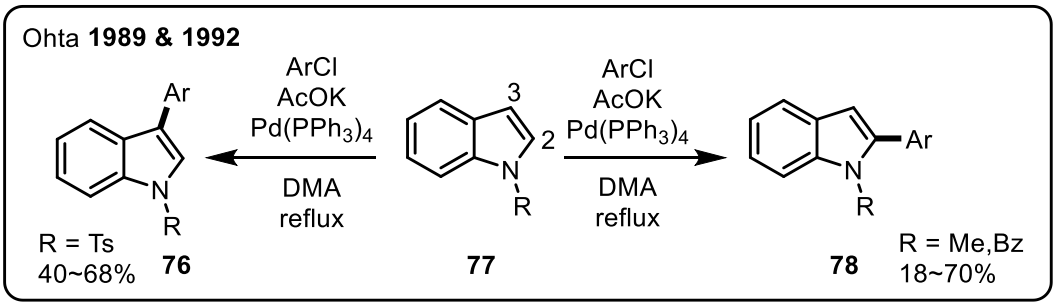
C-H activation is a much broader concept than C-H arylation, and for C-H activation, the earliest examples could be found in 1963, as Kleiman and Dubeck observed a successful *ortho* C-H activation of azobenzene on nickel and the formation of the organometallic Ni(II) complex (see Scheme 14-a).[56] Not long after, Chatt and Davidson also reported that Ru could activate the C-H bond and form a Ru complex (Scheme 14-b).[57] The first C-H arylation was a homo-coupling of aryl compounds reported by Verberg in 1965 using a stoichiometric amount of palladium (Scheme 14-c).[58] In 1969, Fujiwara illustrated the first palladium catalyzed cross coupling of benzene derivatives with styrene (Scheme 14-d). The reaction involved copper(II) acetate and air as an oxidant.[59] Notably, the reaction was observed even before the Heck reaction. The main limitations of the reaction involve the necessary large excess of arenes and the poor regioselectivity of C-H activation. Due to the high abundance of the C-H bonds in most aryl coupling partners, regioselectivity is always an important issue. To overcome the limitation, the target C-H bond has to be differentiated from the remaining C-H bonds of reagent, and can normally be achieved though varying pKa values, placing directing groups, or blocking other active sites.



Scheme 14: Examples of early C-H activation reactions.

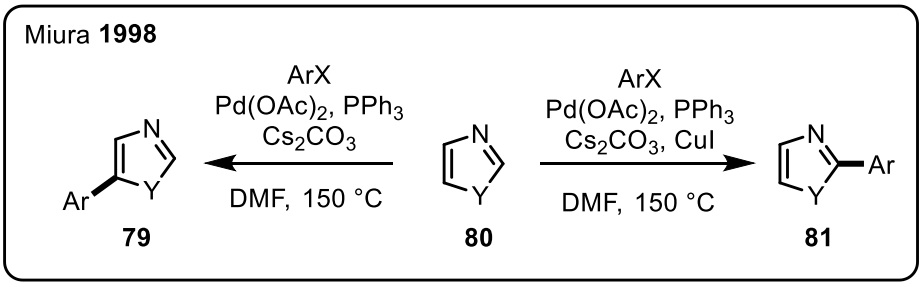
C-H arylation with electron-rich arenes

Heteroarenes could be more suitable substrates in directed C-H activation due to the heteroatoms that confer a difference in acidity of the protons on the ring, or due to directing effects from the heteroatom.[60] Ohta reported a series of C-H arylation reactions with protected indole under Pd(0) catalyst that gave moderate to good yields. Remarkably, with the different nature of the substituents on the nitrogen atom of the indoles, two different C-H bonds are active, therefore the N-functional groups controlled regioselectivity of the reaction (Scheme 15). When the N-functional group is an alkyl or benzyl group, the C2 position is favored and with N-tosyl indole, and the reaction occurs at the C3 position.[61]



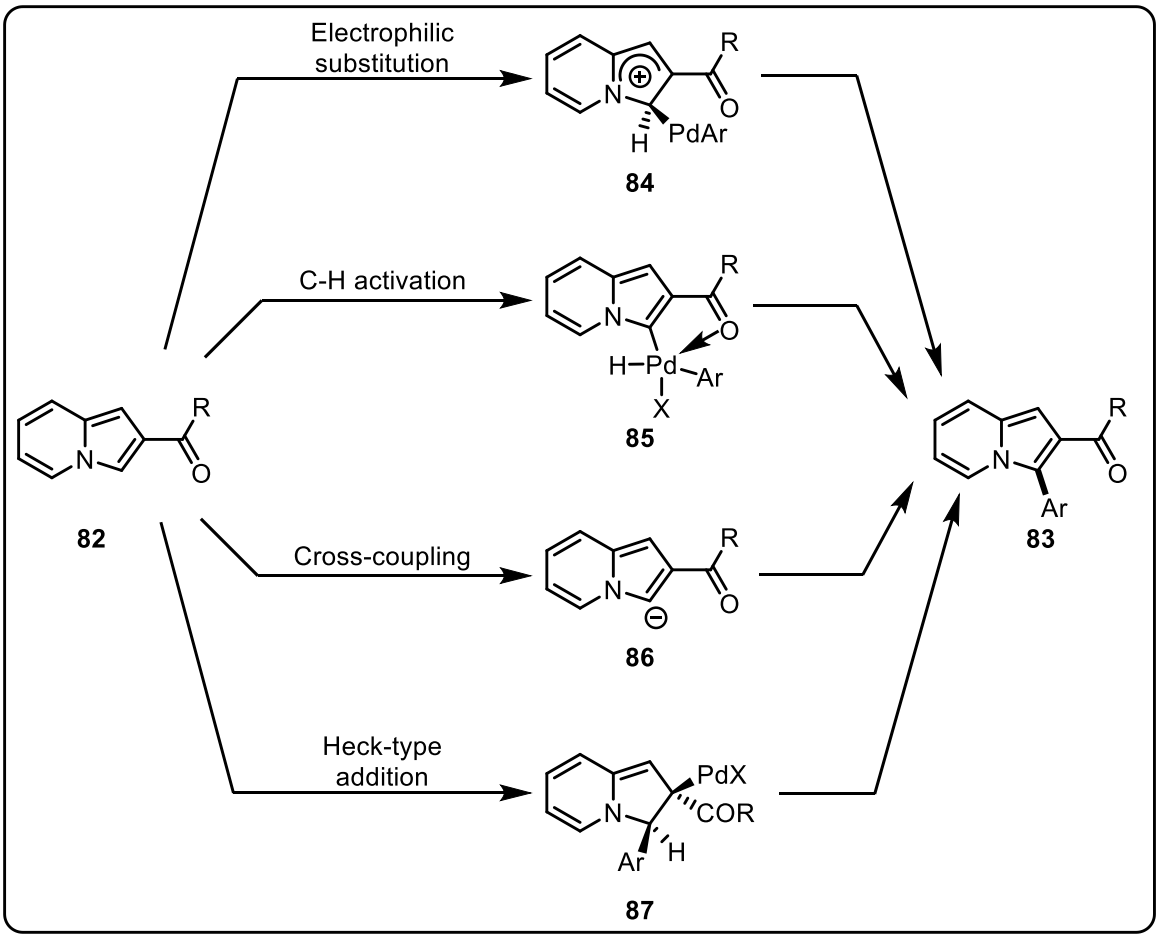
Scheme 15: Different regioselectivity with different protected indoles.

The Miura group also investigated the C-H arylations of electron-rich heteroarenes and halo arenes. Electron-rich heteroarenes, such as imidazoles, oxazoles, thiazoles and thiophenes, have several active C-H bonds and different reaction conditions can favour regioselective coupling (see Scheme 16).[62] At the same time, Lemaire also demonstrated the C-H arylation of thiophenes with a blocking group installed at the C2 position allowing for selective C5 arylation.[63] In addition, intramolecular C-H arylation of heteroarenes and halo arenes has attracted a lot of attention with Grigg[64], Kozikowski[65], Suzuki[66] and Merour[67] having contributing to the topic.

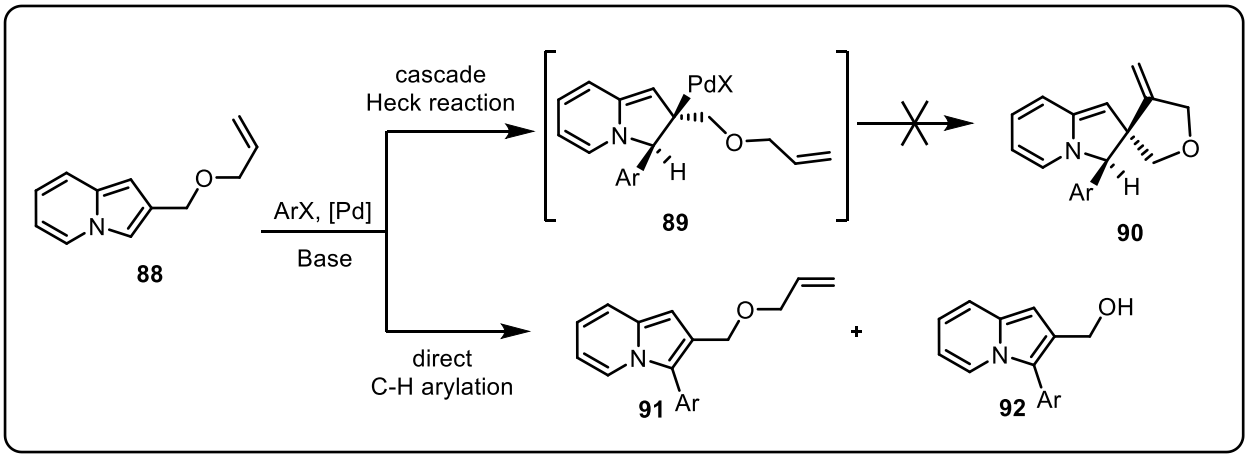


Scheme 16: Examples of regioselective couplings by Miura group.

Gevorgyan was the first to report systematic mechanistic studies on palladium catalyzed C-H arylation of one of the most electron-rich heteroarenes – indolizine.[68] There are four proposed mechanisms for the coupling reaction shown in Scheme 17. The control experiment ruled out a Heck-type mechanism (see Scheme 18). In addition, since no kinetic isotope effect (KIE) was observed, C-H activation and cross coupling mechanisms are also thought to be highly unlikely (see Scheme 19-A).[68] Proton-metal exchange pathways, which are usually also involved in the cross coupling mechanism normally exhibit a substantial KIE.[69] Alternatively, with the electrophilic substitution pathway a kinetic isotope effect is normally not observed, as the deprotonation to regain the aromaticity of the ring is normally fast and unlikely to be the rate-limiting step[70]. Therefore, the arylation of indolizine has been proposed to proceed through electrophilic aromatic substitution.



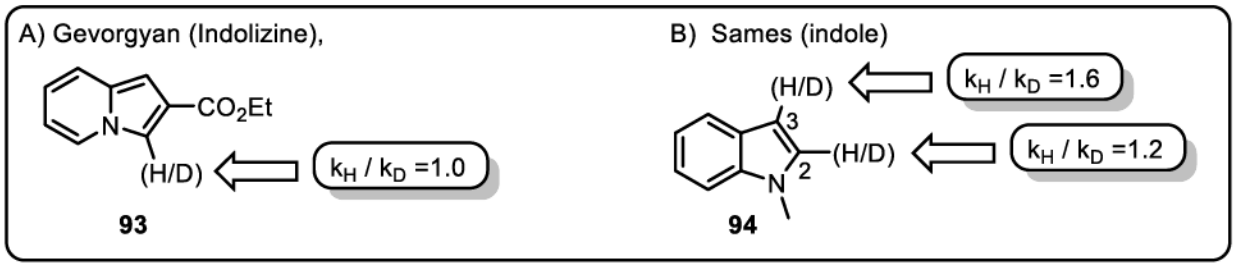
Scheme 17: Proposed mechanism for C-H coupling with indolizine.



Scheme 18: Control experiment: failed cascade Heck reaction on indolizine.

Later, the mechanism of C-H arylation on a less electron-rich substrate – indole, was studied by Sames (see Scheme 19-B).[71] The measured KIEs on the C2 and C3 position of indole were found to be 1.2 and 1.6, respectively. The C3 arylation is most likely due to the electrophilic

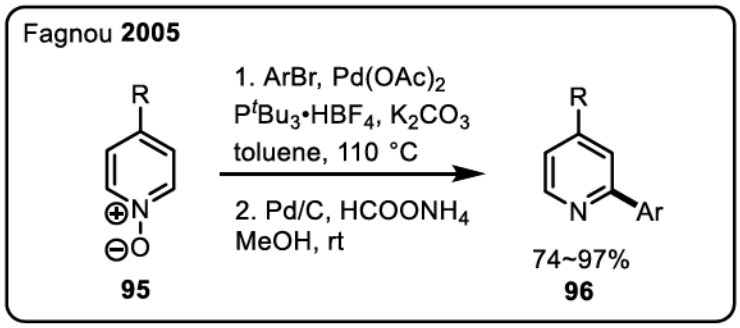
aromatic substitution reactions[72], however there are many examples of C2-selective couplings. The conflicting results indicated that a more complex pathway may have been involved in the arylation of indoles. The KIEs of indole cannot give any conclusive result on the mechanism. Since it is known that the C3 position is more nucleophilic, the electrophilic palladation most likely happens at the C3 position initially, followed by a C3-C2 migration of the organo-palladium complex for C2 arylation. In conclusion, with electron-rich arenes, C-H arylation most likely proceeds through an electrophilic aromatic substitution pathway.



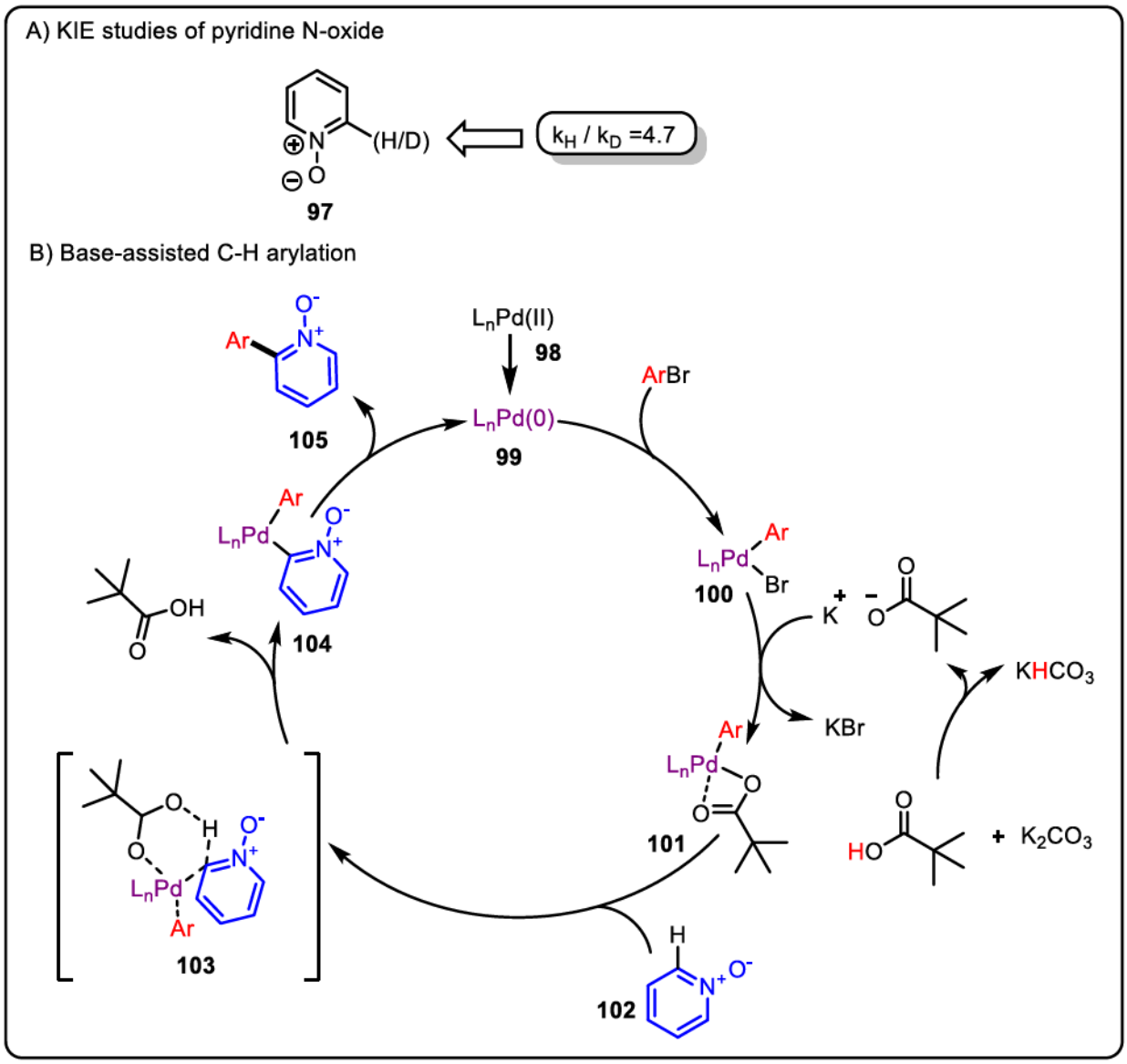
Scheme 19: Kinetic isotopic studies (KIE) on indolizine and indole.

1.4.1.2 C-H arylation with electron-deficient arenes

In contrast to electron-rich heteroarenes, C-H arylation with electron-deficient substrates, such as pyridines, appeared to be much more difficult. In 2005, Fagnou reported an elegant arylation via Pd catalyst is with pyridine N-oxides (**95**) and arylbromides catalyzed in the presence of a base (Scheme 20). The pyridine N-oxides were then reduced to give 2-substituted pyridines in 70 to 80% overall yield.[73] The mechanistic studies conducted by Fagnou suggested that the arylation of electron-poor heteroarenes does not proceed through an electrophilic aromatic substitution (S_EAr) reaction as previously indicated. Unlike the S_EAr mechanism, the kinetic isotope effect studies with pyridine N-oxide arylation resulted in a very high KIE value of 4.7 (see Scheme 21-A). In addition to the KIE studies, a comparison of the reaction rate for the arylation of polyfluorinated arenes was performed and it was found that the more electron-withdrawing, highly fluorinated compounds reacted faster.[74] In contrast, S_EAr mechanisms with electron-rich aromatics are expected to undergo electrophilic substitution reactions faster. Furthermore, the arylation tends to occur at the most acidic proton.[74-75] Therefore Fagnou proposed a concerted mechanism in which the deprotonation and the palladation occur simultaneously. The proposed mechanism is now commonly known as base-assisted C-H activation (see Scheme 21-B).[73, 76] Sharp[77], Mori[78], Gevorgyan[68b], Sames[79], Rossi[80], Lautens[81], Doucet[82] also illustrated several methods for the coupling reaction of heterocycles through the Pd(0) / Pd(II) catalytic cycle. More recently, Sanford[83], Yu[84] and Daugulis[85] have demonstrated coupling reactions that employ a Pd(II) / Pd(IV) manifold.



Scheme 20: Fagnou's C-H arylation with pyridine *N*-oxide.



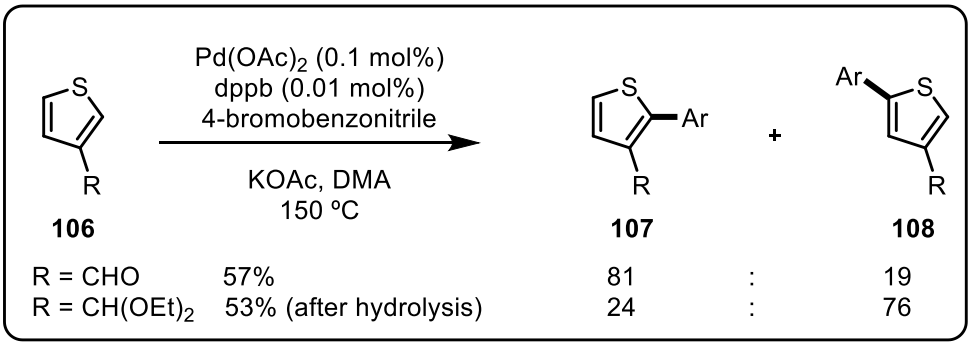
Scheme 21: A) Kinetic isotopic studies on pyridine *N*-oxide; B) Catalytic cycle of base-assisted C-H arylation.

The C-H arylation pathway is highly affected by the nature of the aromatic system and the reaction could occur through a specific pathway, such as in the case of pyridine N-oxides, or it could also go through a combination of different pathways. Sometimes, different substitution pattern could lead to a different regioselectivity such as in Ohta's coupling reactions mentioned earlier (Scheme 15). The different outcome may have resulted from different pathways that have been taken by the reaction due to differences in electronics between the two indoles.

1.4.1.3 Directed C-H activation

As mentioned in discussing electron-rich and deficient aromatic systems, the regioselectivity of C-H activation can be achieved through the pKa difference and electronic differentiation of the C-H bonds. Additionally, blocking groups or directing groups can also lead to regioselectivity.

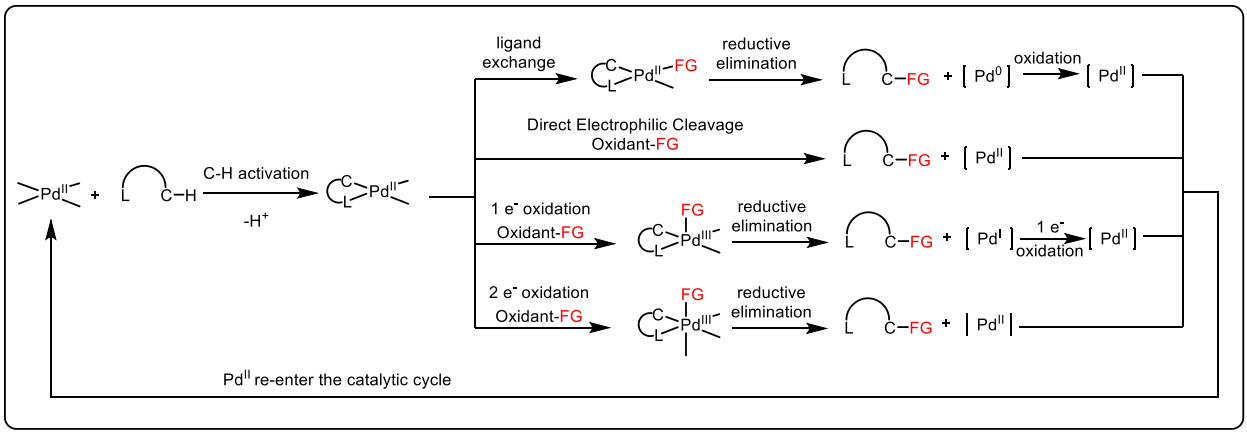
The installation of blocking groups to prevent C-H activation at certain positions could achieve regio-selectivity. The Doucet group affected the regioselectivities of the coupling reaction on thiophene from the C-2 to the C-5 position through the carbonyl group in the 3-position (Scheme 22). In order to favor the C-5 position, a sterically hindered di-ethoxyl acetal was installed on the original aldehyde to block the C-2 position and allow C-5 selectivity.[82, 86] An industrial group from GSK also demonstrated that an ethyl ester in the 3-position could favor arylation at the 2-position with some specific reaction conditions such as an apolar solvent and $Pd(PPh_3)_4$ as catalyst. The selectivity could also be reversed, albeit with a very limited selectivity, by a polar solvent and using Pd/C as the catalyst.[77] Although the blocking group could partially solve the regioselectivity issue associated with C-H activation, the selectivity is normally not very desirable (less than 95%) and required at least two more steps in the synthetic path which is not very atomic and energy economic.



Scheme 22: Regio-selective C-2 or C-5 arylations on thiophene by Doucet group.

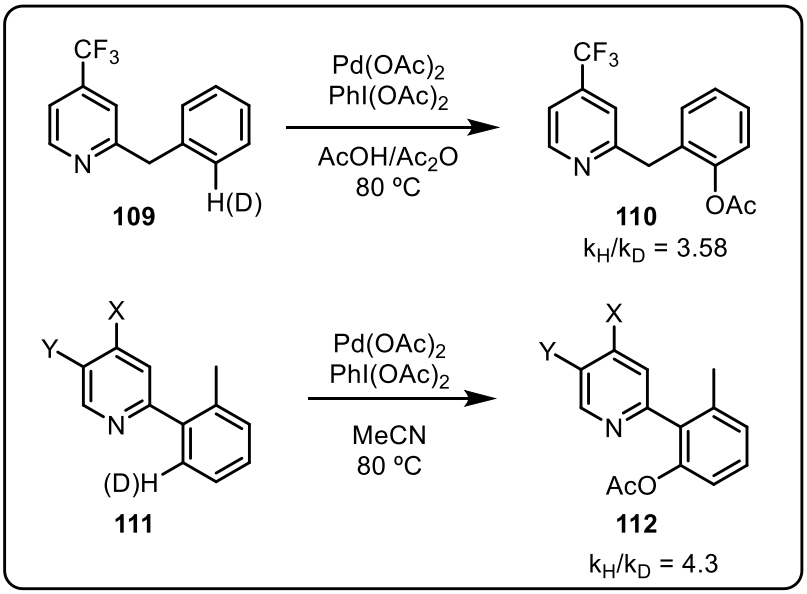
Directed C-H arylation is another alternative method to solve regioselectivity issues and directing groups sometimes can help lower the energy barrier of the C-H activation. Directing groups could be classified in different ways, either as an electronic or ligand type. Here, the focus is primarily on ligand directed C-H functionalization by palladium catalyst. Most ligand type directing groups contain a hetero atom, whose lone pair of electrons can coordinate to the metal center and assist in the key cyclometalation step.

The mechanism of directed C-H functionalization can be generally divided into two parts, the first part is generally accepted as the formation of the cyclo palladated intermediates and usually take place on the Pd(II) center. The second step can potentially proceed through the four following pathways (see Scheme 23). The first proposed mechanism is known as reductive functionalization and follows the general palladium catalytic cycle through ligand exchange and then through reductive elimination to generate the product and Pd(0) species. In order to allow the Pd catalyst to re-enter the cycle, an oxidant is required to oxidize Pd(0) to Pd(II). The other three pathways can all be referred to as electrophilic functionalization. Without altering the oxidation state of the palladium center, the product can be generated through a direct electrophilic cleavage (pathway 2). When the desired compound is produced by a radical pathway, reductive elimination is normally involved, as well as another radical oxidation step (pathway 3). The last mechanism involves a high palladium oxidation state such as Pd(IV) or Pd(III) dimer. In the mechanism, after C-H activation, the coupling partner is coordinated to the metal center through another oxidative addition, which leads to a Pd(IV) center or to a Pd(III) dimer complex. The desired bond formation is through a common reductive elimination and the active Pd(II) species is regenerated. Notably, in the second pathway, direct electrophilic cleavage has no requirement of oxidant, and in the final pathway Pd(II)/Pd(IV) or Pd(III) dimer cycles may not necessarily require an oxidant to promote the palladium center to a higher oxidation state, but in the other two mechanisms, oxidants are required for catalytic cycle.[87]



Scheme 23: Possible pathways of ligand directed C-H activation.

Directed C-H activation could be used in several different bond formation reactions, such as for C-O, C-X, C-N, C-S and C-C bonds. The mechanism varies depending on the type of bond formed. The Sanford group conducted a series of mechanistic studies on the directed functionalization for C-O and C-X bond formation.[83a, 83b, 88] With the KIE studies on the pyridine directed C-H activation with both 5 and 6-membered cyclometalation, large intermolecular KIEs (3.58 and 4.3 see Scheme 24) have been observed, which indicates that cyclopalladation is the rate limiting step in the directed C-H activation.[88b, 89] Since the C-H activation is the turnover limiting step, mechanistic studies for the proposed oxidation step/reductive elimination or direct electrophilic cleavage steps are quite challenging. Studies in the field are thus concentrated on generating model complexes. Sanford's group obtained several model Pd(IV) complexes in C-O, C-X and C-C bond formation, which suggested that a pathway through a high oxidation state palladium complex is possible.[87-90] Later, Ritter's group reported that a more stable Pd(III) dimer (compared with the Pd(IV) complex), might be involved in the reaction.[91] Both mechanistic studies indicated that the reaction occurs through a two electron transfer mechanism and that the high oxidation states of the palladium center lead to fast reductive elimination. Therefore, in most of the five-membered palladation cycles, bis C-H activation is common observed.



Scheme 24: Intermolecular kinetic isotopic studies on pyridine directed C-H activations.

1.4.1.4 Deuteration

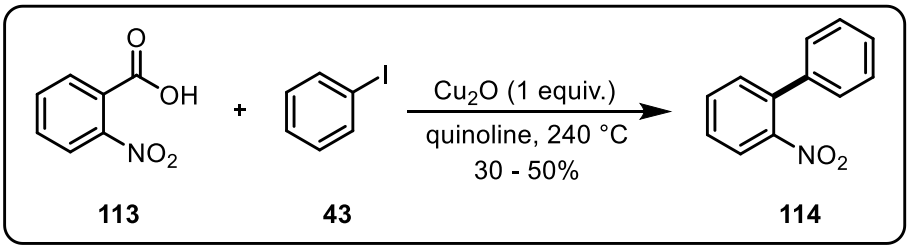
Deuteration has a unique role in chemistry and it is also an important aspect of C-H activation reactions. Deuterium is an isotopic atom of hydrogen and while their chemical properties are identical, deuterium has an exact mass of 2 g/mol. The mass difference leads to a relative

energy difference of +1.2 – 1.5 kcal/mol for the C-D bond relative to the C-H bond.[92] The energy difference between C-D and C-H bonds could provide significant information in understanding the mechanism of C-H bond cleavage reactions that include C-H bond activation as well metabolic processes. Deuteration is mostly used in C-H bond functionalization to determine whether the breaking of the C-H bond is the rate limiting step. The mechanistic studies highlighted in the previous section are an example of understanding the rate limiting step in a reaction through isotopic effects. In drug development, with the help of deuterium, it can be much easier to identify the critical C-H bonds that are subject to oxidation in metabolism by cytochrome P450 or hepatic microsomes[93]. Due to identical chemical properties except the mass, the deuterated drug candidate should have no influence on potency compared to its corresponding non-deuterated candidate, and the changes in the data on pharmacokinetics would indicate the stability and importance of the C-H or C-D bond in the metabolic process. Therefore scientists can better understand how oxidation happens within enzymes and proteins, and develop drugs with structures that are more metabolism resistant and less toxic downstream.[94] Furthermore, there are examples with deuterated drug candidates having fewer side effects and prolonged retention time in blood.[95]

1.4.2 Decarboxylative Cross Coupling

Decarboxylative cross coupling is another approach to Pd-catalyzed cross coupling that avoids the use of a stoichiometric amount of organometallic reagents as the nucleophilic coupling partner. Compared with C-H activation, an additional by-product generated by decarboxylative cross coupling is carbon dioxide gas, which is easy to remove and recycle. An advantage over C-H activation is that the decarboxylative cross coupling is highly chemoselective. An additional advantage is that the carboxylic acid is a very common functional group, and therefore many aromatic carboxylic acids are commercially available.

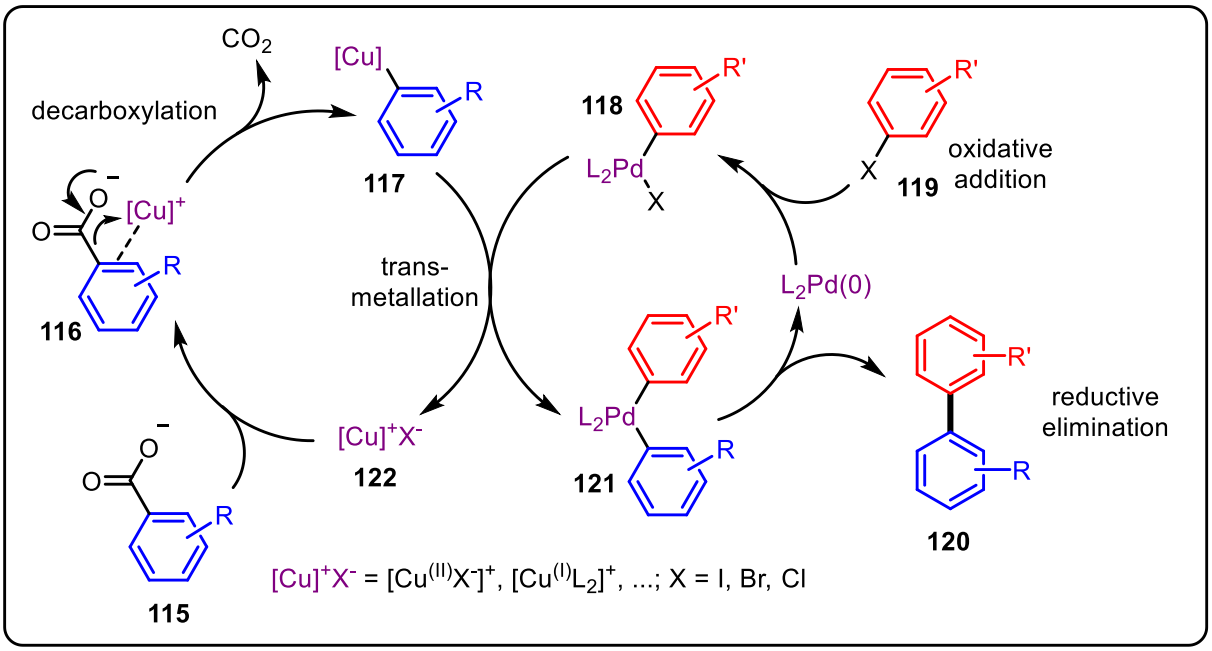
In nature, decarboxylative reactions are performed by enzymes efficiently to extrude CO_2 gas.[96] Even though release of CO_2 is entropically favourable, the aromatic carboxylic acids normally require high temperatures and harsh conditions to extrude CO_2 in the presence of metal catalysts such as copper.[97] The reaction mechanism is proposed to proceed *via* protodecarboxylation, the evidence for which is provided by Nisson through mechanistic studies in the pyrolysis of copper 2-nitrobenzenecarboxylate **113** at 240 °C. In the presence of iodobenzene, bi-aryl compound formation has been observed similar to the Ullmann reaction.[98]



Scheme 25: Decarboxylative cross coupling with copper catalyst by Nisson *et al.*.

1.4.2.1 Decarboxylative cross coupling with arenes

Decarboxylative cross coupling can proceed through protodecarboxylation or Ullmann type reaction, but one of the major drawbacks of the two reactions is that stoichiometric amounts of copper are required. In 2006 Gooßen reported a decarboxylative coupling reaction using catalytic palladium and copper with aryl bromides and chlorides.[97] The proposed mechanism started with the deprotonation of the carboxylic acid by the carbonate salt to form the carboxylate **115**. Intermediate **116** is obtained through binding to the copper(I) source. The copper then inserts into the C-C(O) bond, and with the release of CO_2 gas to form the copper complex **117**. The complex undergoes transmetalation with the palladium arylhalide **118** to regenerate the copper source and the diarylpalladium complex **121**. Then reductive elimination leads to the formation of biaryl **120** and Pd(0) active species (Scheme 26). A variety of functional groups including aromatic aldehydes, amides, and amines have been found to be tolerated in the reaction.[97, 99]

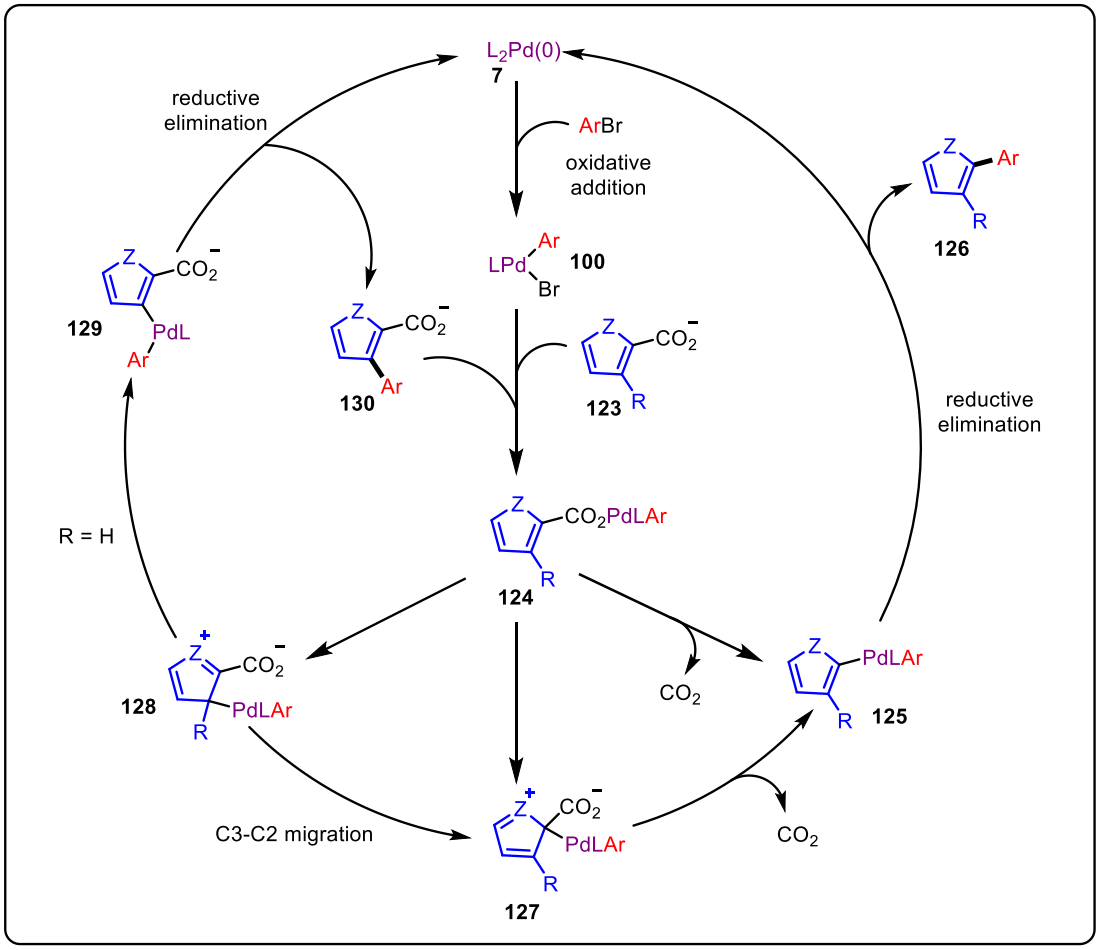


Scheme 26: Proposed catalytic cycle of decarboxylative cross coupling with copper co-catalyst.

1.4.2.2 Decarboxylative cross coupling with hetero-arenes

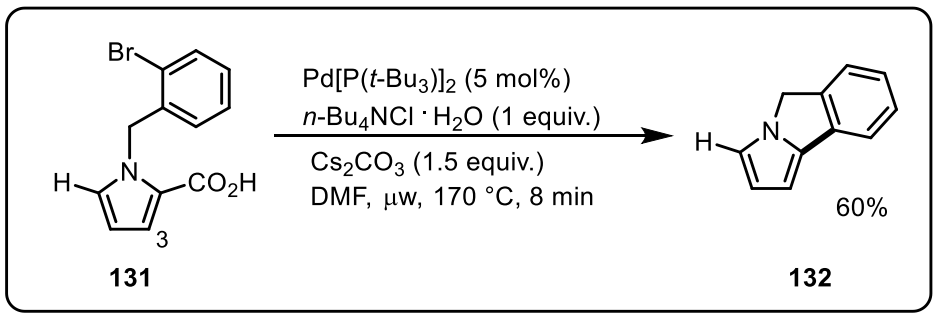
With a heteroarene system, Forgione *et al.* observed an unexpected coupling reaction and then reported decarboxylative coupling reactions with catalytic palladium in 2006.[100] The cross coupling conditions did not require co-catalysts such as copper or silver. The reaction tolerated a variety of heteroarenes, such as oxazoles, pyroles, furans, and thiophenes as nucleophilic partners and its electrophilic coupling partners are also not limited to aryl bromides, but also include aryl chlorides, iodides, and triflates.

One of the major by-products in the reaction observed is the 2,3-disubstituted heterocycle.[101] Based on the observation, and a previously postulated mechanism by Myers[102], a new pathway is proposed (see Scheme 27). The mechanism starts with active palladium catalyst **7** oxidative addition into the aryl-halide forming **100** and produces **124** by coordinating to the carboxylic acid. Then electrophilic palladation can occur at the C2 or C3 positions. In the case of C2-palladation, the decarboxylation occurs either simultaneously or through a stepwise mechanism where the aromaticity of the ring is regained (**125** and **127**). Then the complex reductively eliminates to generate the biaryl **126** while regenerating the active Pd(0). Alternatively, when electrophilic palladation occurrs at the C3 position (**128**), the nature of the R group at the C3 position is important. If R is not a hydrogen atom, C3-C2 migration will occur to form intermediate **127** and continue the catalytic cycle to form the C2-arylation product. When R = H, deprotonation of intermediate **128** will occur to competitively regain the aromaticity and form intermediate **129**. Reductive elimination then yields the C3-arylation product **130**. The C3-arylation product normally reenters the cycle for a second arylation at the C2 position, which is the major side product observed.



Scheme 27: Proposed catalytic cycle of decarboxylative cross coupling on hetero-arenes.

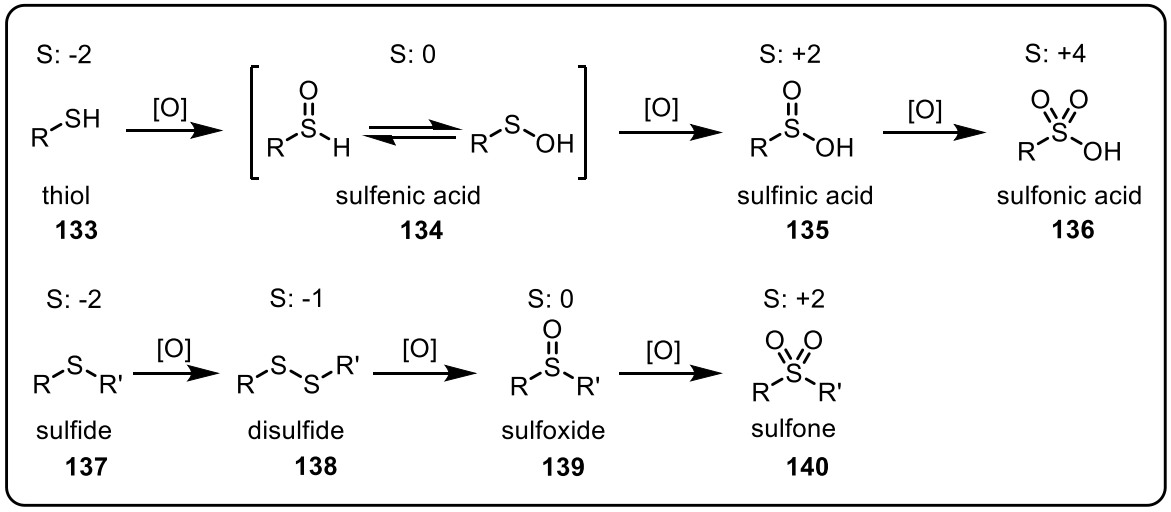
Decarboxylative cross couplings are highly chemoselective and the starting materials are normally commercially available. Different reactions conditions were reported for both arenes and hetero arenes. Indeed, in the intramolecular decarboxylative cross coupling reaction, with the presence of an acidic C-H bond, the decarboxylative coupling prevails over C-H activation (see Scheme 28). Therefore compared with C-H activation, decarboxylative cross coupling is a faster reaction.[101]



Scheme 28: Intramolecular decarboxylative cross coupling.

1.5 Organosulfur chemistry

Organosulfurs have been known for more than a hundred years and most of them are under used by-products of the petroleum industry.[103] One of the most obvious drawbacks of sulfur compounds is that many of them have malodorous smells. Sulfur has various oxidation states in both inorganic and organic compounds from -2 to +4 (see Scheme 29). The sulfur in sulfinate salts are at +2 state and makes them valuable starting materials to access thiols, sulfoxides and sulfones via reduction or oxidation. The organosulfur chemistry has been previously investigated in the 1900s[104], and in the last decade it has been revisited extensively. Organosulfurs have two critical properties that make them very attractive starting materials; they are easily accessible and have versatile reactivity.[105]

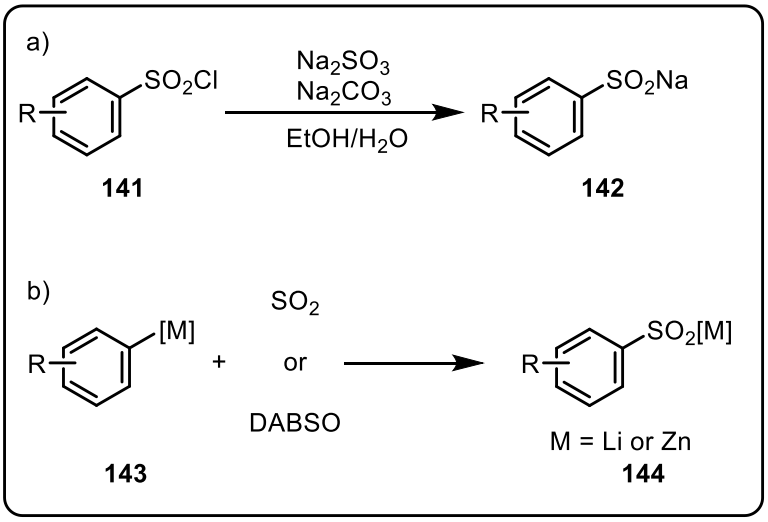


Scheme 29: Organosulfur acids and their alkylated derivatives with various oxidation state above the compounds.

1.5.1 Sulfinate salts preparation

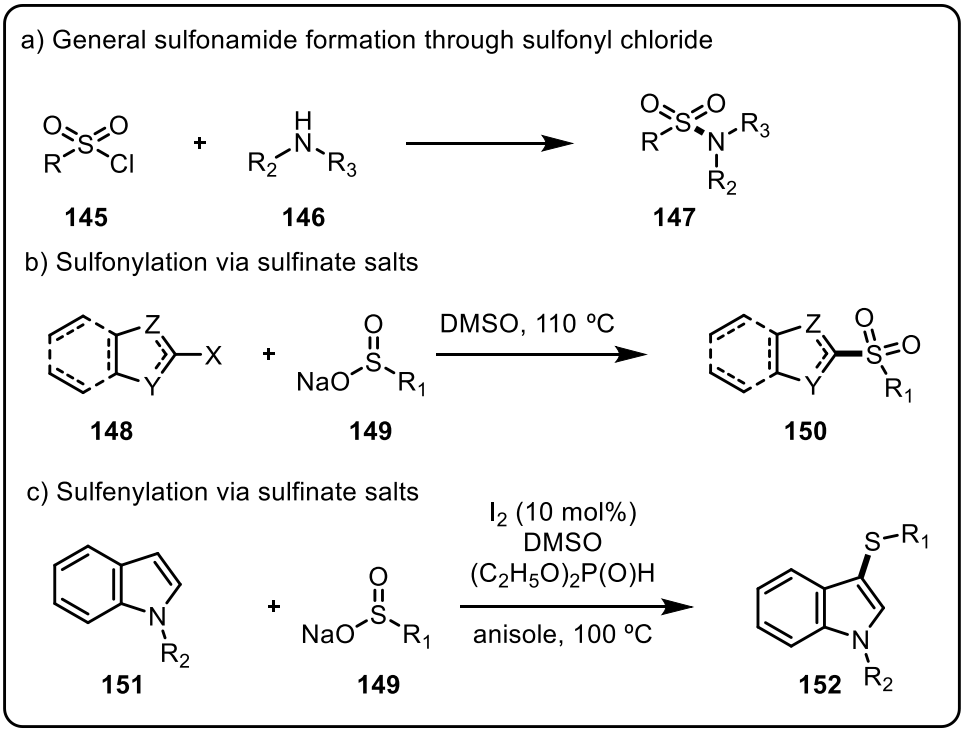
Sulfinic acid is known to undergo radical autoxidation processes[106], therefore when it is exposed to air and moisture, it is not very stable. Once the sulfinic acid is converted to the corresponding sulfinate salt, it is much more stable and moisture insensitive. The common inorganic sulfinate salts are sodium salts, lithium salts and zinc salts. For sodium sulfinate salts, the most common preparation is through the reduction of the corresponding sulfonyl chloride by a mixture of sodium sulfite and sodium bicarbonate in water (Scheme 30-a).[107] Baran's group[108] also illustrated a preparation for sodium 1'1-difluoroethanesulfinate (DFE-Na) from Hu's reagent[109]. In addition, since the sodium salts are the most stable sulfinate salts, the other sulfinate salts could also be transferred to sodium salts through an acid/base counter-ion exchange process. As for lithium sulfinate salts, most are obtained through quenching with an organolithium, which could

be obtained through deprotonation or halogen-metal exchange, with SO_2 gas or complexed SO_2 compounds such as DABSO[110]. Another sulfinate salt is the zinc salt and the groups of Baran and Willis have reported remarkable preparation methods towards zinc sulfinate salts.[111] Compared with other salts, zinc salts have lower reactivity, which has a positive impact on side-product formation and functional group tolerance, and however the use of zinc sulfinate salts is still limited.



Scheme 30: Preparation of sulfinates from sulfonyl chloride (a) or organometallic reagent (b).

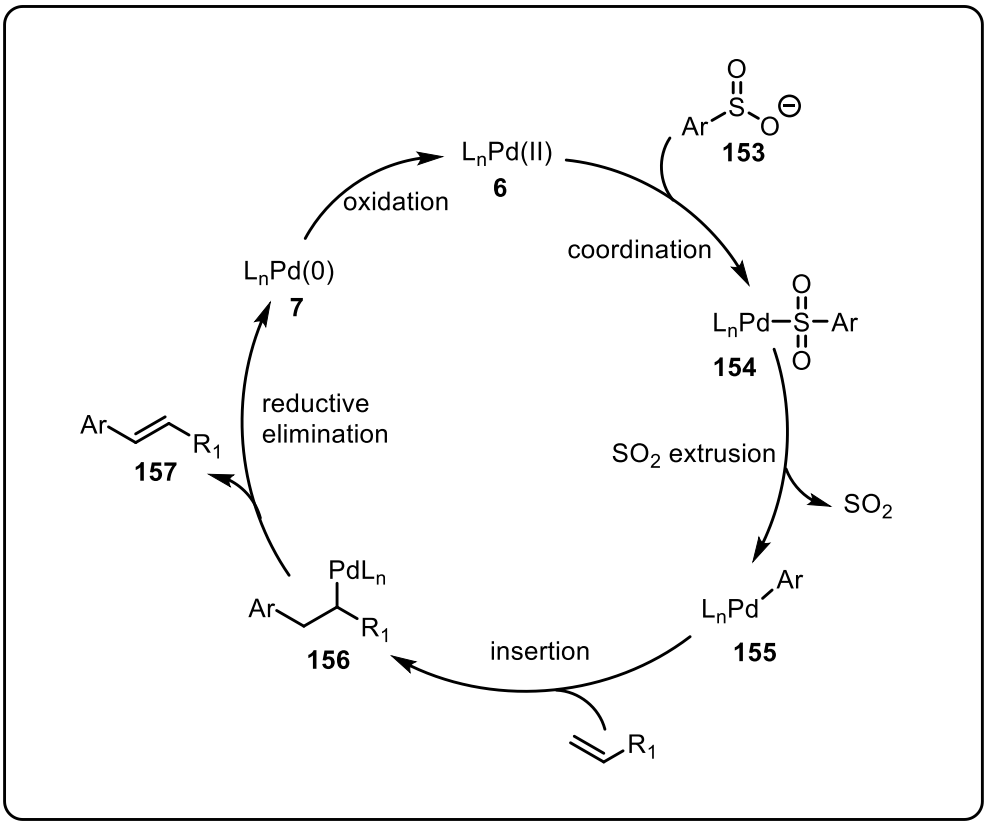
Sulfinate salts, as they already contain a sulfur atom, can be used to easily access various organosulfur compounds such as sulfones or thiols. Most of the sulfonylation reactions occur between a nucleophile and sulfonyl chloride (Scheme 31-a)[112], however sulfinate salts can also act as nucleophilic coupling partners to couple with an electrophile (Scheme 31-b).[113] Therefore the sulfur of the sulfone compounds could come from both nucleophilic[114] and electrophilic[115] partners. In addition to the sulfone, sulfinate salts could also provide access to the thiols through a sulfenylation reaction. Deng's group demonstrated a synthesis of 3-sulfenyl indoles using sodium sulfinate salts as the sulfenylation reagents and the process involved the formation of electrophilic R^3SI in-situ (see Scheme 31-c).[116] Other than sulfur containing products, sulfinate salts have also been used in C-C bond formation.



Scheme 31: Sulfone or thiol formation reaction from sulfonyl chloride (a) or sulfinate salts (b and c).

1.5.2 Sulfinate salts as electrophilic partners

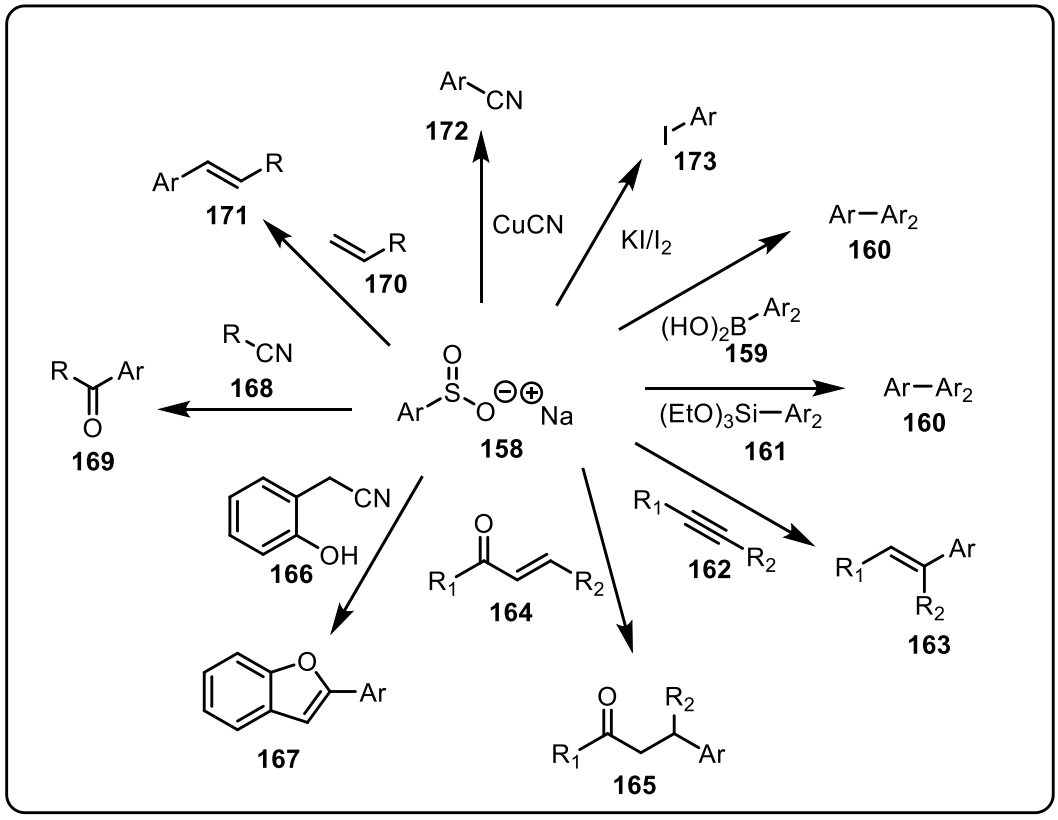
Based on the decarboxylative research, further studies discovered desulfinative cross couplings between aromatic sulfinate salts and nitriles[117], Michael acceptors[118], alkynes[119], arylboronic acids[120] or organosilanes[121]. The first step of the desulfination reaction catalyzed by palladium begins with coordination of the sulfinate salt to the Pd(II) metal center. As Pd(II) salts or complexes are the active species, no oxidative addition is involved in the mechanism. On the other hand, reactions such as the oxidative Mizoroki-Heck[122] or direct arylations[120-121, 123] normally require an oxidant to regenerate Pd(II) active species for the catalytic cycle. While with nitriles[117], Michael acceptors[118] and alkynes[119], the final product is generated through a hydrolysis process and the oxidation state of palladium center remains unchanged in the catalytic cycle (see Scheme 32). The desulfinative reaction conditions are much milder (such as much lower temperature) than the corresponding decarboxylative reactions[124].



Scheme 32: Catalytic cycle of a desulfinative coupling reaction.

In 2011, Larhed[117b] first reported a desulfinative addition to nitriles in the formation of acetophenones with $Pd(TFA)_2$ as the catalyst. With the study of a model reaction with acetonitrile, they proposed a mechanism involving ketamine formation from the hydrolysis of the intermediate and excess of TFA ensured the mechanism could occur. Later the groups of Miao and Wang independently reported mild conditions for the coupling between nitriles and sulfinates, by using $Pd(OAc)_2$ with sulfuric acid and water to promote the hydrolysis reaction.[117c] Other conditions have also been discovered to further utilize the desulfinative addition to nitrile with an intramolecular annulation in formation of benzofuran scaffolds[117e]. Deng's group has been working on using sulfinate salts as starting materials to achieve conjugate addition. They have also demonstrated enones[118a] and alkynes[119] as starting materials. Later, arylalkenes and acrylates have also been employed in Mizoroki-Heck type couplings with sulfinate salts and noticeably, oxygen, air and copper salts can be used as oxidizing agents in the reaction. The Cheng group also demonstrated palladium catalyzed desulfinative cyanation to aryl sulfinates and sulfonyl chlorides by copper cyanide.[125] Even though sulfonyl chlorides give better yield than sodium sulfinates, the sodium sulfinate salts are much more stable. Later, Deng's group reported a palladium catalyzed desulfinative iodination reaction, which is similar to the Sandmeyer reaction, in which a nucleophile,

such as iodide or cyanide, replaces the sulfur dioxide leaving group.[126] Sulfonylhydrazides can also be employed in reactions, and will generate sulfinates *in-situ.*[105, 113] The Qi group has also reported a desulfinative Hiyama-type[121] and Suzuki-type[120] cross coupling, in which sulfinate salts are employed as aryl halide replacements. In the Hiyama-type reaction, a fluoride source is needed to promote silane activation, and air acts as the oxidizing agent. For the Suzuki type reaction, copper acetate is needed to act as a co-catalyst and oxidant.

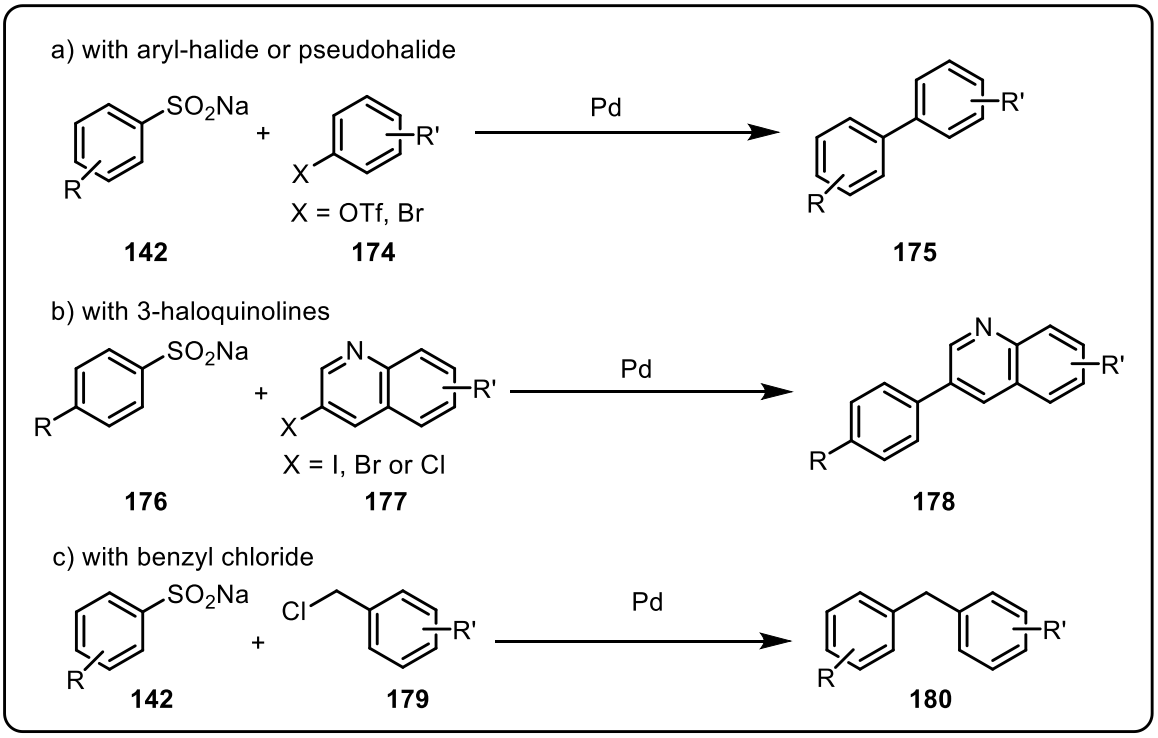


Scheme 33: Coupling reactions with sodium sulfinates as electrophilic partners.

1.5.3 Sulfinate salts as nucleophilic partners

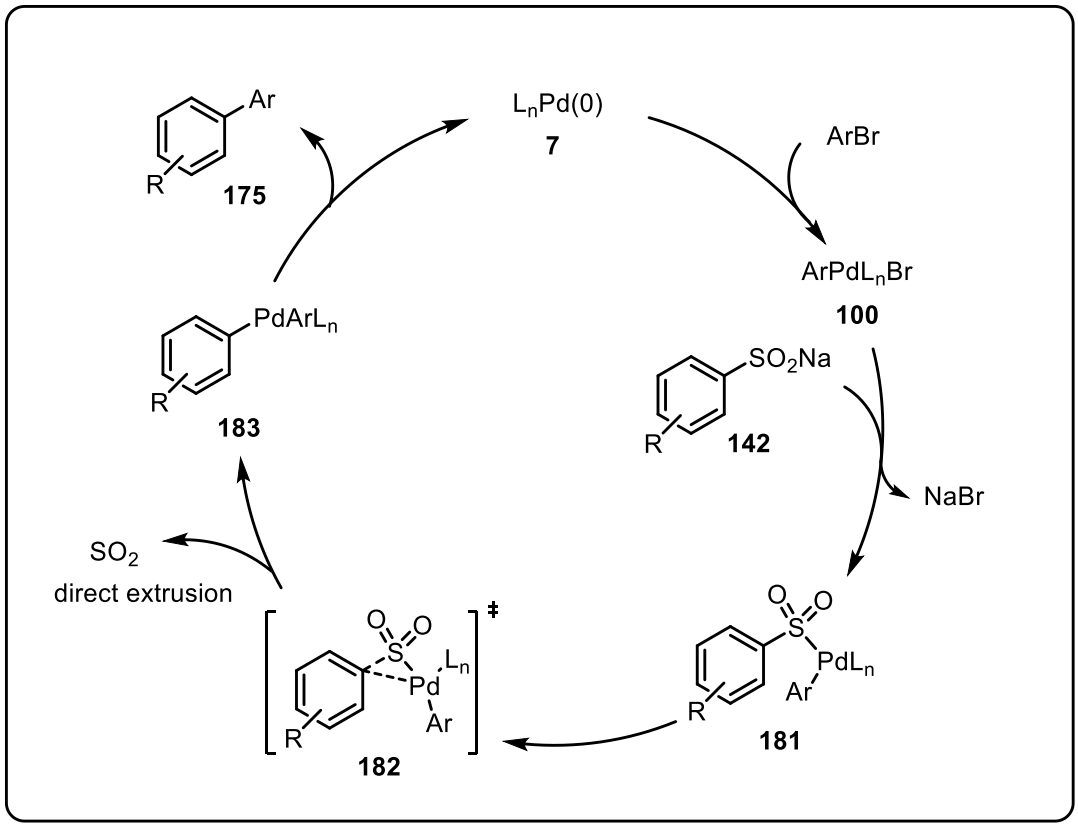
The synthetic use of sulfinate salts is not limited to electrophilic coupling partners and they can also act as a nucleophilic partner in coupling reactions (see Scheme 34). As early as 1905, there was already a report of formation of organometallic reagents by desulfination.[127] At the beginning of the 1970s, Garves[128], and Selke and Thiele[129] also published desulfinative coupling reactions, but there was no further study of the desulfinative reaction until 1992, when Sato and Okoshi reported the desulfinative coupling between aryl sulfinates and aryl bromides in a patent[130]. Using the sulfinate salts as a nucleophilic partner has become much more developed recently decades. The Duan group has published a palladium catalyzed coupling reaction between aryl sulfinate salts and aryl triflates.[131] However, as they used an apolar solvent (toluene) in the

absence of base, the sulfinate salt was insoluble, which has been proposed as the cause of the poor yield with nitro-substituted substrates. Later, the Forgione group extended the scope of desulfinative cross coupling of sulfinate salts to aryl bromides.[132] In the reaction scope, the electron-poor aryl bromide is favored for oxidative addition by the palladium catalyst. Due to the ease of SO_2 extrusion, electron-rich aryl sulfinates were also found to be favored in the reaction. Furthermore, the Wang group demonstrated the application of desulfinative arylation selectively on the C4 position of 5-alkoxy-3,4-dibromo-2(5H) furanone.[133] Billard's group also reported a desulfinative coupling reaction between sodium sulfinate salts and 3-haloquinolines, and they also observed the competitive S_NAr reaction with bromides, and when the substrates are highly suitable for the S_NAr reaction, only the S_NAr product was observed (Scheme 34-b).[134] The Deng group also demonstrated aryl sulfinate salts coupling with benzyl chloride (Scheme 34-c).[135]



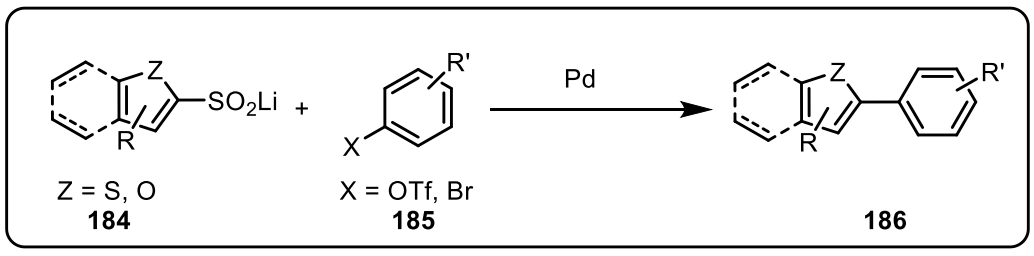
Scheme 34: Pd-catalyzed coupling reactions with sulfinates as nucleophile.

The proposed mechanism with sulfinate salts as the nucleophilic coupling partner is similar to the common palladium catalytic cycles (Scheme 35). The first step is the oxidative addition into the aryl halide or pseudo halide bond. Then the sulfinate will coordinate to the palladium center and lead to formation of the complex (**182**), followed by SO_2 extrusion. After a rearrangement of the ligands coordinated to the palladium center, reductive elimination occurs to generate the product and active Pd(0) species, which re-enter the catalytic cycle.

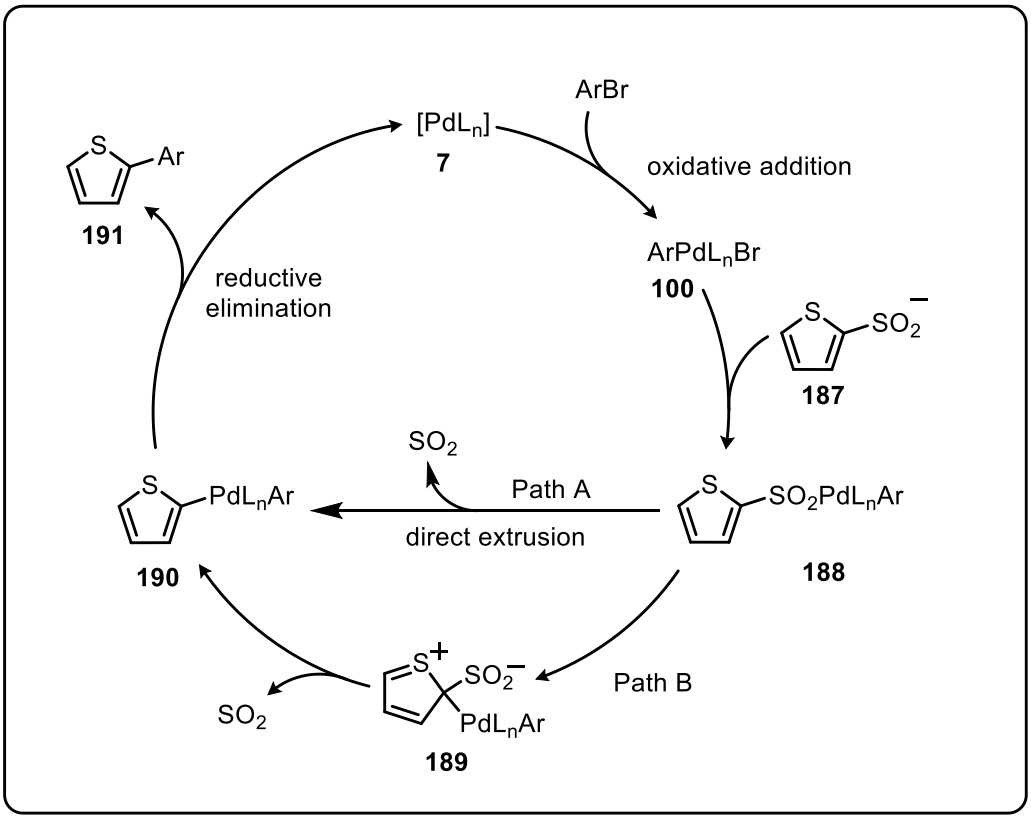


Scheme 35: Proposed catalytic cycle of Pd-catalyzed desulfinative cross coupling with sulfinate salts as nucleophilic coupling partners.

Heteroaromatic sulfinate salts have also been reported as nucleophiles in palladium catalyzed cross coupling reactions by the Forgione group (Scheme 36).[136] They reported coupling of various heteroaromatic sulfinates and with aryl halides and aryl triflates without any base addition and without the need for a large excess of sulfinates. Indeed, the reported desulfinative coupling reaction only required short reaction times with high temperatures in the microwave and was also possible with protic solvents such as water and ethanol. The desulfinative couplings of heteromatic sulfinates involve a different pathway than that of the benzenesulfinate derivatives, and the mechanism might proceed through an electrophilic palladation pathway to the key intermediate **189**, which is impossible for benzene sulfinates (see Scheme 37).

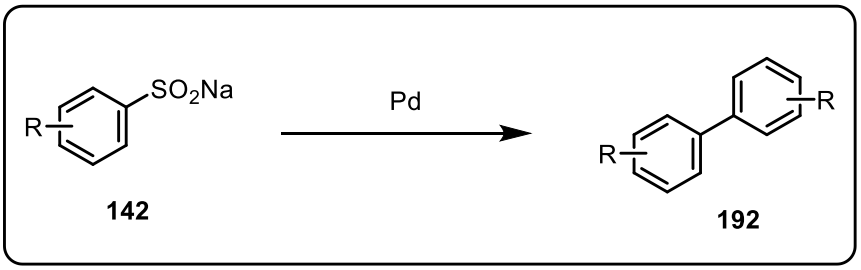


Scheme 36: Pd-catalyzed desulfinative cross coupling with heteroaromatic sulfinate salts.



Scheme 37: Proposed catalytic cycle of Pd-catalyzed desulfinative cross coupling with heteroarenes.

As mentioned before, Selke and Thiele reported stoichiometric palladium catalyzed homo-coupling reactions in 1971. However the catalytic palladium employed in the homo coupling of sulfinate salts has only been revisited recently. In 2012, Rao *et al*. reported homo coupling with sulfinate salts employing catalytic amounts of palladium and copper.[137] The catalytic amount of Cu_2O and molecular oxygen are responsible for re-oxidizing the palladium catalyst. Later the Forgione group also disclosed the homo coupling reaction of sulfinates in the presence of a Buchwald-type ligand with either $CuCl_2$ in water or catalytic TEMPO with oxygen in DMF, which avoided the additional metal in the catalytic system.[138] Furthermore, arylsulfonyl chlorides have been also known to undergo homo coupling under similar conditions by Zhao *et al*.[139].



Scheme 38: Pd-catalyzed homo coupling with sodium sulfinate salts.

1.6 Research goal and thesis organization

As sulfinate salts are such an ideal starting material to use in organic synthesis, we would like to further expand their use in synthesis by overcoming its major limitation, which is that the protonated form could undergo disproportionation. With common reactions, sulfinate salts in basic media could minimize the effect of this drawback, however with several step synthesis, the drawback really limited the usage of the sulfinate salts. Our goal is to mask the sulfinate salts, so they could be used more widely in organic synthesis. However, instead of a protecting group, a directing group could serve a dual function. Directing group installation on the aromatic sulfinate salts could allow the functionality to be carried over numerous synthetic steps and particularly, the directing group could also allow *ortho*-functionalization of the aromatic sulfinate salts, which allows access to some structurally interesting scaffolds. The installed functional group could be removed at a later stage to allowed further functionalization on the sulfinate salts.

Chapter 1 of this thesis is the background information on the carbon-carbon bond formation and mostly focused on palladium catalyzed reactions. The alternative environmentally benign palladium catalyzed coupling reactions have also been introduced as well as the role of organosulfur in modern organic synthesis.

Chapter 2 presents the installation of a dual functional group on the sulfinate salts and a paper published as “A Convenient and Inexpensive Route to Access Sulfonylated Pyridines via a SNAr Reaction of Electron-Rich Pyridines through Iron Catalyst” (https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0036-1591541 Copyright © Georg Thieme Verlag Stuttgart · New York). The main work is conducted by the author, and some of the reaction scope has been contributed by the co-authors Franklin Chacon-Huete and Hassan El-Husseini. The manuscript was prepared with the supervisor and additional mechanism work is the sole work of the author.

Chapter 3 is a continuation of the work described in chapter 2. It includes the directed *ortho*-halogenation *via* palladium catalyzed C-H activation and the removal of the dual functional groups. The KIE work was contributed by visiting scientist Dr. Mohammad S. Askari. Most of the characterization spectra and HRMS were done by Ph.D. candidate Cindy Buonomano. The manuscript is in preparation as “Using Pyridine as Removable Ortho-Directing Group to Access *Ortho*-Halogenated Sulfinate Salts”.

Chapter 4 describes the directed deuteration on sulfonylated pyridines. Most of optimization is done by author. Visiting scientist Dr. Mohammad S. Askari initiated the research

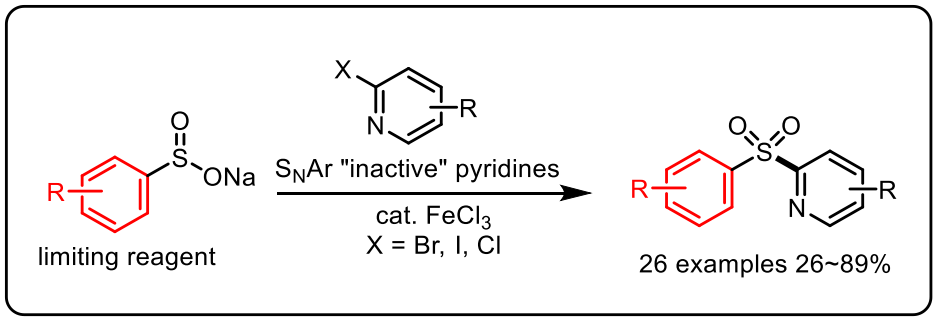
and some of reaction scope were contributed by Ph.D. candidate Cynthia Messina. The manuscript is in preparation.

Chapter 5 describes the major conclusions of the research results in the thesis and it will also include future work and possible research directions.

Chapter 2: A Convenient and Inexpensive Route to Access Sulfonylated Pyridines via a SNAr Reaction of Electron-Rich Pyridines through Iron Catalyst

2.1 Abstract

Sulfonylated pyridines were synthesized in moderate to excellent yields, with a wide scope of substituted pyridines and sulfinate salts through an iron-catalyzed S_NAr reaction. This new methodology exhibits advantages for the synthesis of these useful substrates, such as the use of readily available, inexpensive catalyst, prevents the disproportionation of the sulfinate salts, and more importantly, provides access to electron-rich pyridine substrates.



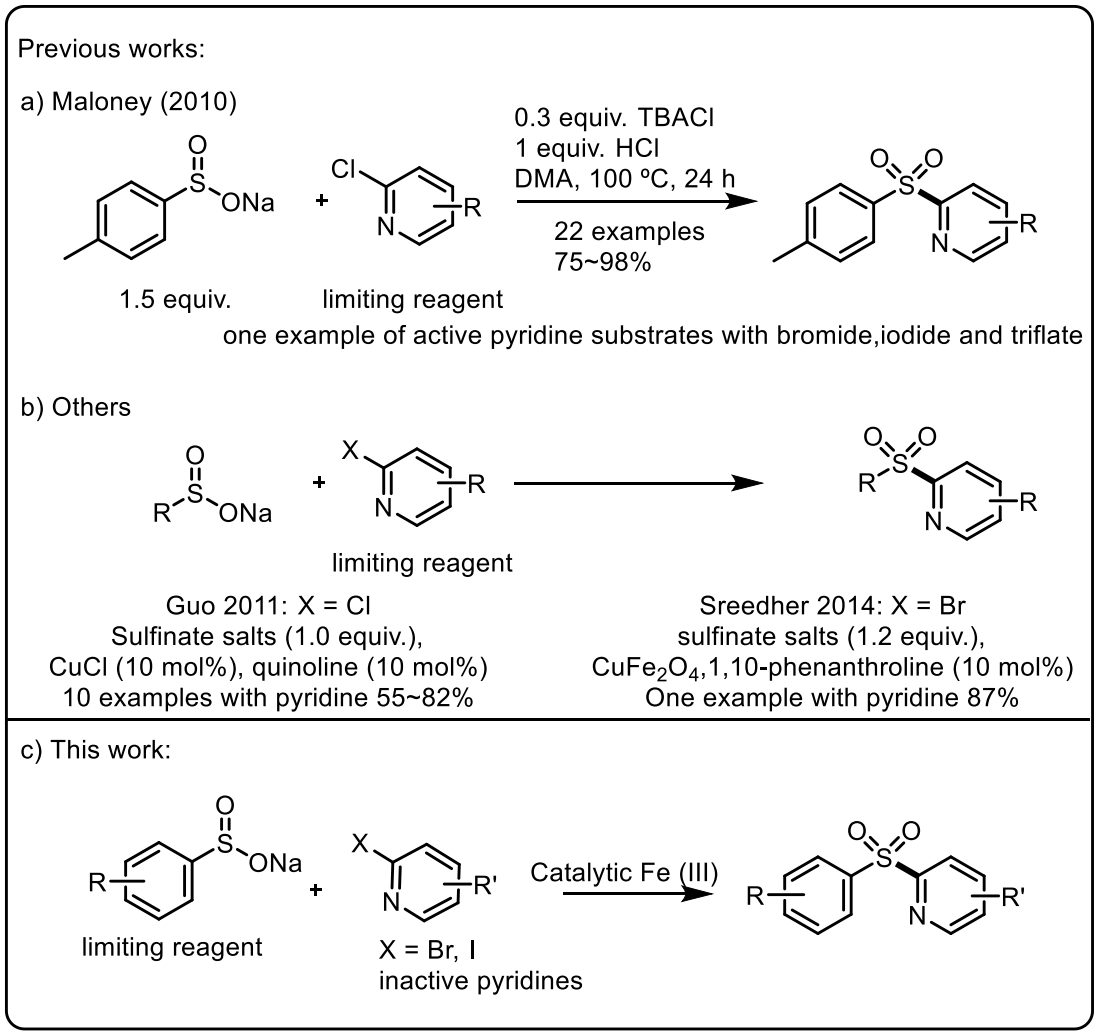
Scheme 39: Graphic abstract.

2.2 Introduction

Aryl sulfones are interesting moieties in various fields including the pharmaceutical industry, agrochemicals, and polymer synthesis.[140] Among these, aryl sulfones and sulfonylated pyridines are highlighted as an important class of versatile and useful compounds.[141] Additionally, these pyridines play an important role as directing groups for further functionalization as applied to complex molecule synthesis.[83a, 83b, 142]

General methods to access the sulfonylated pyridines include the oxidation of thiol ethers[143], coupling reactions[144] and S_NAr chemistry[114a, 145]. The most common oxidation method involves the use of odoriferous thiols that result in the production of a large quantity of hazardous waste.[143a] Metal-catalyzed cross coupling of sulfinate salts with halo-pyridines[146] and pyridyl boronic acids[147] have also been reported, but yields are generally low for the formation of the corresponding sulfonylated pyridines. Sulfone formation through a S_NAr reaction was reported in 1989 by Ulman and co-workers.[148] Employing this method required electron-poor arene substrates, which limits the scope of the reaction. The synthesis of sulfonylated pyridines through a S_NAr

reaction was reported in 2009 using a modified household microwave.[149] In 2011, the group of Guo reported a copper (I) catalyzed reaction between several chloro-pyridines and sodium sulfinate salts using a household microwave reflux apparatus with good yields.[144a] In the same year, Maloney's group reported a metal-free nucleophilic S_NAr reaction to access sulfonylated pyridines mostly with activated, electron-poor chloropyridines employing stoichiometric amounts of HCl. Bromo-, iodo- and triflate- pyridines have only been reported once for the synthesis of these sulfones, and their use was limited to activated, electron-deficient pyridines.[114a] One major limitation of these reported methodologies is that they require an excess of the potentially valuable sulfinate salt. Recently Srinivas and co-workers expanded sulfone formation by using copper ferric nanoparticles, however the 2-bromo-pyridines remained the limiting reagents (Scheme 40).[144b]

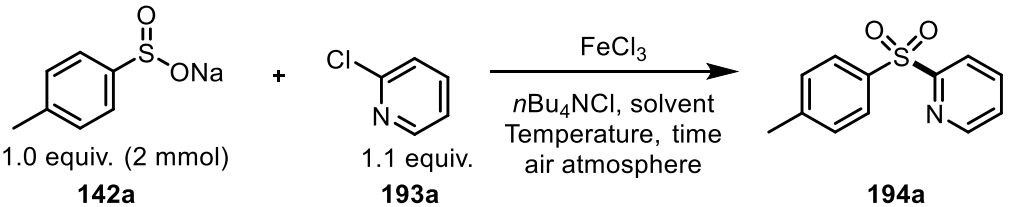


Scheme 40: Reported methods for the synthesis of sulfonylated pyridines and the present work.

2.3 Results and discussion

In this work, we explore the use of sulfinate salts as the limiting reagent through an S_NAr reaction with inactivated pyridines (electron rich and neutral). The starting point for the optimization route were the conditions reported by Maloney's group;[114a] with 2-chloropyridine (**193a**) resulted in a dramatic drop from the 89% reported to 37% when sulfinate **142a** was used as the limiting reagent (Table 1, entry 1). To expand the scope and robustness of the reactions, we evaluated the use of $FeCl_3$ as Lewis acid to replace HCl, which would be useful for substrates that are Brønsted acid sensitive. Initially replacing the HCl (1 equiv.) with $FeCl_3$ (1 equiv.) resulted in complete decomposition of the starting materials (entry 2). Formation of the desired sulfonylated pyridine was observed when catalytic amounts of $FeCl_3$ and increased temperature were employed (entries 3 and 4). Modification of the solvent system to DMSO-H_2O (3:1) dramatically increased the formation of the desired product (entry 5). Further lowering of the catalyst loading and adjusting the additive equivalents and concentration of the reaction further improved the yields (entries 6 to 12). A 66% yield of the desired product **194a** was obtained on a 2 mmol reaction scale (entry 12), however, larger reaction scales (10 to 30 mmol) employing the same conditions resulted in an increase in the yield to 78% (entry 15). $Fe(acac)_3$ was also evaluated as the catalytic iron source and provided similar yields (entry 16). The absence of the additive has a negligible effect when $FeCl_3$ is employed (entry 13) but reduces the yield by 10% with $Fe(acac)_3$ as the catalyst (entry 17). With these newly optimized conditions, we revisited the use of stoichiometric HCl (entry 18), but only a 38% yield of the corresponding product was obtained. The known disproportionation of the sulfinic acids in acidic conditions[150] is the likely cause of these reduced yields, highlighting the value in employing Lewis acids like $FeCl_3$ in these reactions.

Table 1: Optimization of the Conditions for the formation of sulfonylated pridine **194a**[a].



1.0 equiv. (2 mmol) **142a** + 1.1 equiv. **193a** → **194a**

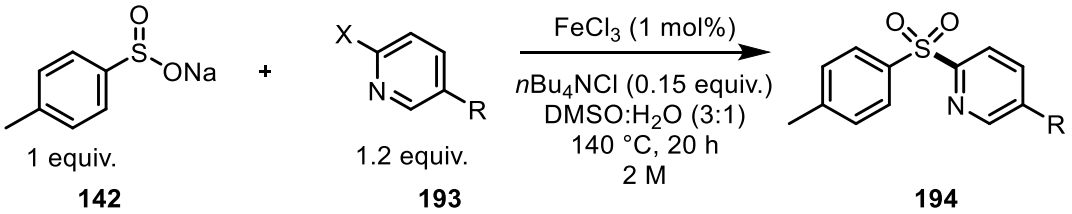
Entry	Catalyst (equiv.)	*n*Bu$_4$NCl (equiv.)	Solvent (2M)	Temperature and time	Yield (%)
1	HCl (1)	0.15	DMA	100 °C, 24 h	37
2	$FeCl_3$ (1)	0.15	DMA	100 °C, 24 h	-
3	$FeCl_3$ (0.3)	0.15	DMA	120 °C, 24 h	8[b]
4	$FeCl_3$ (0.1)	0.15	DMSO	140 °C, 24 h	12
5	$FeCl_3$ (0.1)	0.15	DMSO:H_2O (3:1)	140 °C, 20 h	44
6	$FeCl_3$ (0.2)	0.15	DMSO:H_2O (3:1)	140 °C, 20 h	40
7	$FeCl_3$ (0.3)	0.15	DMSO:H_2O (3:1)	140 °C, 20 h	38

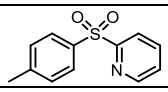
8	-	0.15	DMSO:H_2O (3:1)	140 °C, 20 h	trace
9	$FeCl_3$ (0.01)	1.0	DMSO:H_2O (3:1)	140 °C, 20 h	44
10	$FeCl_3$ (0.01)	0.3	DMSO:H_2O (3:1)	140 °C, 20 h	57
11	$FeCl_3$ (0.01)	0.15	DMSO:H_2O (3:1) 0.5 M	140 °C, 20 h	35
12	$FeCl_3$ (0.01)	0.15	DMSO:H_2O (3:1)	140 °C, 20 h	66
13	$FeCl_3$ (0.01)	-	DMSO:H_2O (3:1)	140 °C, 20 h	60
14	$FeCl_3$ (0.01)	0.15	DMSO:H_2O (3:1) 4 M	140 °C, 20 h	52
15[c]	$FeCl_3$ (0.01)	0.15	DMSO:H_2O (3:1)	140 °C, 20 h	78
16	$Fe(acac)_3$ (0.01)	0.15	DMSO:H_2O (3:1)	140 °C, 20 h	64
17	$Fe(acac)_3$ (0.01)	-	DMSO:H_2O (3:1)	140 °C, 20 h	45
18	HCl (1)	0.15	DMSO:H_2O (3:1)	140 °C, 20 h	38

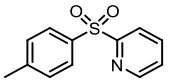
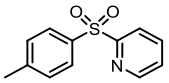
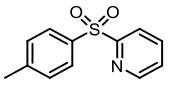
[a] Reaction condition: **142a** (2 mmol, 1.0 equiv.), **193a** (1.1equiv.), $FeCl_3$, $n$$Bu_4NCl$, in air.
[b] Yield determined by ^1H NMR.
[c] Reaction carried out on 10-30mmol scale.

With the concern that our optimized conditions of using $FeCl_3$ in DMSO/H_2O could act as an HCl source, we replaced the water portion of the solvent with buffer solution (phosphate buffer, pH 7.2, 7.8 and 8.3) and obtained similar yields (62%, 71% and 70%, respectively compared with 66% when using just water, Table 1, entry 12). Furthermore, when 0.03 equiv. of Et_3N was added to neutralize the possible acid generated, a 77% yield was obtained that again is in agreement with the iron catalyst not acting as an acid source. $FeCl_3$ was selected over $Fe(acac)_3$ to proceed with the investigation, based on the broad availability and price in bulk for this catalyst. We evaluated a variety of halo-pyridines with a focus on challenging S_NAr substrates including inactive bromo- or iodo-pyridines (Table 2). Impressively, the bromo- (entry 3) and iodo-pyridine (entry 4) provided the corresponding product in equal or better yield than the more electron-poor chloropyridine (entry 1) used during our intial optimization. Further increasing the electronegativity by employing 2-fluoropyridine had a dramatic decrease on the yield (entry 2). Our hypothesis is that as the electronegativity of the halogen atom decreases, there is an increased coordination of pyridine to the iron catalyst that facilitates the addition of the sulfinate, while simultaneously avoiding disproportionation reactions in comparison to using HCl.

Table 2: Halopyridine Scope[a]



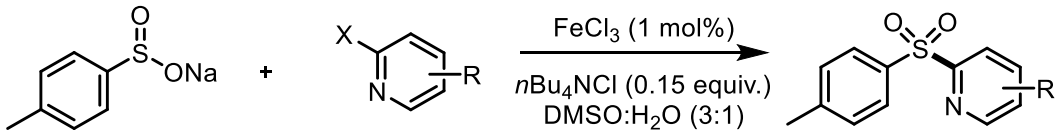
Entry	Substrate **142**	Product **193**	Isolated Yield (%)
1			66

	193a	194a	
2	 193b	 194a	12
3	 193c	 194a	69
4	 193d	 194a	85

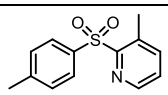
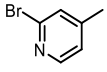
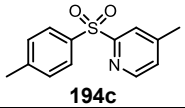
[a] Reaction conditions: **142** (2 mmol, 1.0 equiv.), **193** (1.1equiv.), $FeCl_3$ (1 mol%), *n*Bu_4NCl (0.15 equiv.), DMSO-H_2O (3:1, 2 M), 140 ºC, 20 h.

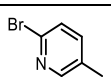
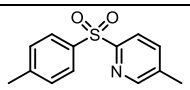
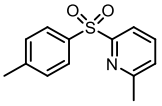
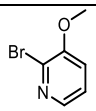
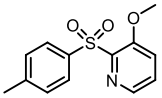
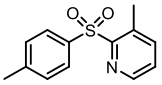
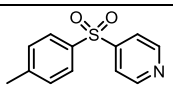
We evaluated this methodology employing a range of electron-rich pyridine substrates. Since the identified main side product is the sulfonic acid of the corresponding sulfinate salt, we initiated investigations under an argon atmosphere and degassing the solvent to avoid oxygen in the reaction medium.[151] Methyl substituents on 2-bromo pyridines in various positions, has no significant steric influence on the yield (68% to 78%, Table 3, entries 1 to 4). However, when a methoxy group is at the 3 position of 2-bromopyridine the yield is reduced to 48%. 3-methyl-2-iodo pyridine provides the corresponding product in higher yield than the equivalent brominated analogue, which is in agreement with the coordination hypothesis (85% vs 78%, entries 6 vs 1). Additionally, the 4-iodo-pyridine analogue also participates in the reaction under these conditions and produces 61% yield of the corresponding sulfonylated pyridine (entry 7). Overall, generally inactive electron-rich pyridines are well suited with iron catalysis and small substituents have limited steric effect.

Table 3: Scope of electron-rich pyridines[a]



1 equiv. **142a** + 1.2 equiv. **193** → **194**

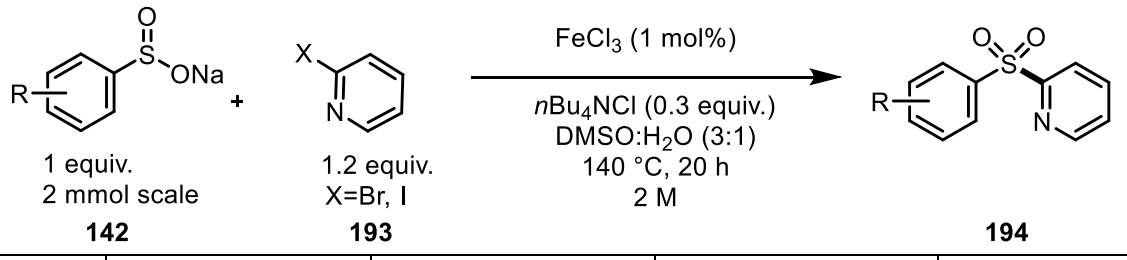
Entry	Substrates	Products	Isolated Yield (%)
1	 193e	 194b	78
2	 193f	 194c	77

3	 **193g**	 **194d**	68
4	 **193h**	 **194e**	72
5	 **193i**	 **194f**	48
6	 **193j**	 **194b**	85
7	 **193k**	 **194g**	61

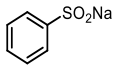
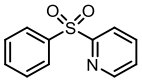
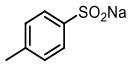
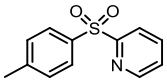
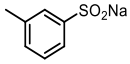
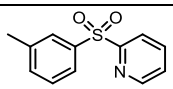
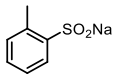
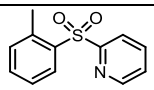
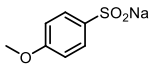
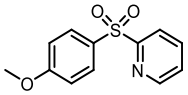
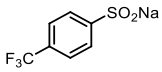
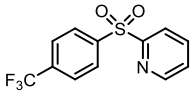
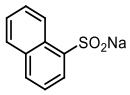
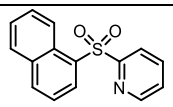
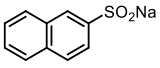
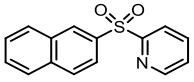
[a] Reaction conditions: **142** (2 mmol, 1.0 equiv.), **193** (1.1equiv.), $FeCl_3$ (1 mol%), *n*Bu_4NCl (0.15 equiv.), DMSO-H_2O (3:1, 2 M), 140 ºC, 20 h.

Various sulfinate salts were studied in the reactions with both 2-bromopyridine and 2-iodopyridine. The results demonstrate that 2-iodopyridines provides the corresponding product in better yields compared with 2-bromopyridines, and various electron-rich to electron-deficient sulfinates are well tolerated in the reaction. This reaction provided higher yields with electron-neutral sulfinate substrates, such as benzene sulfonylated pyridine **194f** that has a yield of 71% starting from 2-bromopyridine in comparison to 82% with 2-iodopyridine (Table 4, entry 1) and *para*-toluene sulfinate salt yielded 79% and 89% of product **194a** (entry 2). To evaluate the effect of the position of substituents, *para*, *meta* and *ortho*-toluene sulfinates were examined. *Ortho*-substituted toluene sulfinate resulted in a lower yield (entry 4) when compared to its *para* isomer (entry 2) presumably due to higher steric hindrance while m*eta*-toluene sulfinate has a slightly lower yield (70% and 78%, entry 3). Both electron-rich and electron-deficient sulfinate substrates are well tolerated in this reaction. With 2-bromopyridine, the electron-rich anisole sulfinate has a lower yield (62%, entry 5) than the electron-deficient benzotrifluoro sulfinate (77%, entry 6). However, with 2-iodopyridine the benzotrifluoro sulfinate has a lower yield than the anisole sulfinate (78% and 88% respectively, entries 5 and 6). Modest results were obtained with naphthalene sulfinates (entries 7 and 8), with a higher yield for the 1-naphthalene isomer. Overall this reaction tolerates a range of sulfinate substrates, including electron-rich, electron-neutral, and electron-deficient as well as sterically hindered sulfinates.

Table 4: Scope of sodium sulfinate salts[a]



142 **193** **194**

Entry	Substrates	Products	X=Br, Yield (%)	X=I, Yield (%)
1	 **142b**	 **194h**	71	82
2	 **142a**	 **194a**	79	89
3	 **142c**	 **194i**	70[b]	78[b]
4	 **142d**	 **194j**	42[b]	46[b]
5	 **142e**	 **194k**	62[b]	88[b]
6	 **142g**	 **194l**	77[a]	78[b]
7	 **142h**	 **194m**	41	59
8	 **142i**	 **194n**	26[b]	27

[a] Reaction conditions: **142** (2 mmol, 1.0 equiv.), **193** (1.1equiv.), $FeCl_3$ (1 mol%), nBu$_4$NCl (0.15 equiv.), DMSO-H_2O (3:1, 2 M), 140 ºC, 20 h.
[b] $FeCl_3$ (10 mol%) used.

2.4 Summary

In conclusion, we have developed an iron-catalyzed reaction for the synthesis of sulfonylated pyridines in good to excellent yields. In this method, inexpensive and readily available $FeCl_3$ has been used to replace HCl, which increases the robustness of the reaction towards acid-sensitive substrates. With this in mind, this methodology uses sulfinate salts as the limiting

reagents since its acid-catalyzed disproportionation is avoided. An examination on the effect of small substituents on the pyridine ring led to the conclusion that little to no steric effect was reflected in the yields. Moreover, it was also demonstrated that electron-rich, electron-neutral and electron-deficient sulfinate substrates can be employed with this methodology with good to excellent yields. Finally, this new methodology allows access to the challenging electron-rich sulfonylated pyridines, which have proven to be versatile building blocks in modern organic synthesis.

2.5 Experimental section

All reactions were performed in round bottom flask containing a Teflon-coated stir bar unless more specific conditions are stated. Chemicals were purchased from Aldrich, Alfa Aesar, or AK Scientific and used without further purification. All solvents were purchased as ACS grade from Fisher Scientific or JT Baker and distilled water was obtained from an in-house water distillery prior to use. Flash chromatography was carried out using 40-63μm silica gel (Silicycle). Melting points were obtained using a Stuart SMP30 bench apparatus. NMR spectra were recorded with Varian Inova 500MHz spectrometer and were referenced to the residual solvent signal or TMS signal. High resolution mass spectra (HRMS) were obtained using a LC-TOF ESI positive mode mass spectrometer.

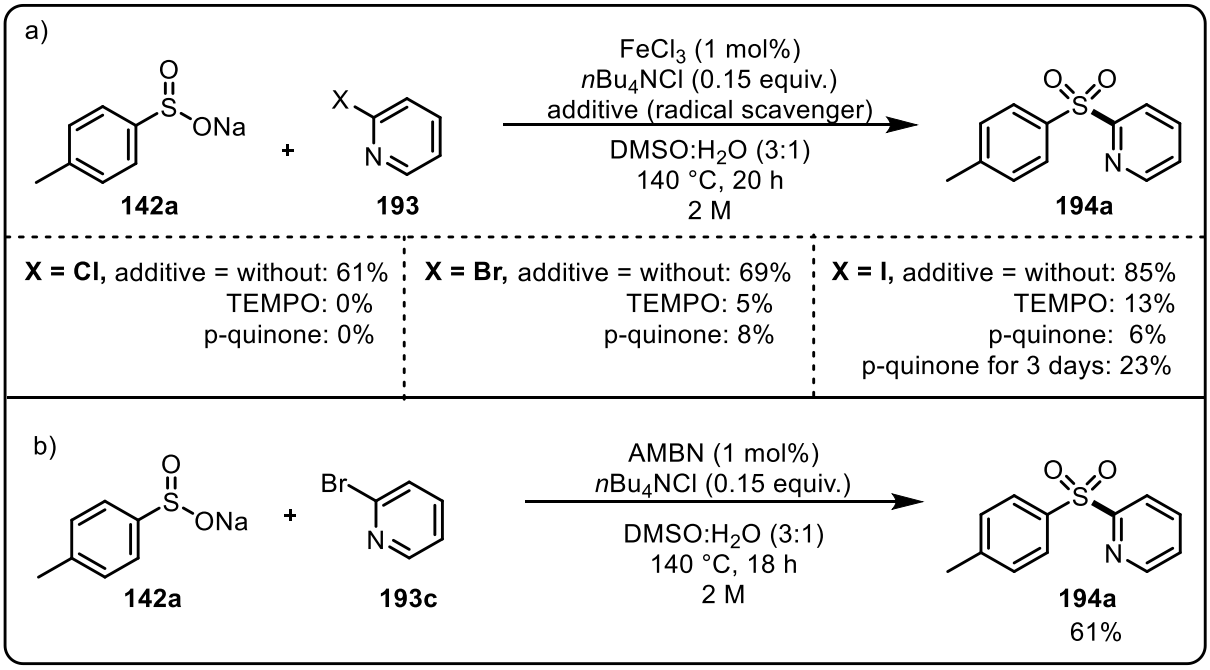
General procedure to prepare sulfonylated pyridine:

The sulfinate salt **142** (1 equiv., 2 mmol scale) and halo-pyridine **193** (1.2 equiv.) in DMSO:H_2O (3:1, 2 M) were added to a round bottom flask containing *n*Bu_4NCl (0.3 equiv.) and $FeCl_3$ (0.01 equiv.). The mixture was degassed for 30 minutes in a sonicator under argon atmosphere, and then heated to 140 ^oC and stirred for 20 h. The resulting mixture was cooled to room temperature and neutralized with 2M NaOH solution, then extracted with EtOAc (3X). The combined organic phases was washed with distilled water, followed by brine solution and then was dried over sodium sulfate and filtered. The solvent was then removed under reduced pressure. The residue was purified by column chromatography with 5% EtOAc, 45% hexanes and 55% DCM to give the desired product sulfonylated pyridine **194**.

2.6 Additional studies

Since iron is a common known Fenton reagent, and the results with the pyridine halide substrates are consistent with a S_NAr reaction mechanism, therefore we suspected the reaction

might involve a radical mechanism. To validate the hypothesis, 1 equiv. of radical scavengers were added into the reaction, such as 1 equiv. of TEMPO and *p*-benzoquinone. Both of them are well known radical scavengers and able to inhibit radical reactions. We performed reactions on chloro-, bromo- and iodo-pyridine substrates (**193**) with additions of both radical scavengers, and observed dramatic decreases in the reaction yields (see Scheme 41a). To further validate the radical mechanism, a known radical initiator—2,2'-azodi(2-methylbutyronitrile) (AMBN) was used to replace $FeCl_3$ under the same condition, a yield of 61% was obtained (see Scheme 41b). All the results seems to support the radical mechanism, however the by-products resulted from radical scavengers were never observed. In addition, when extended the reaction of iodo-pyridine substrate with *p*-benzoquinone scavenger for 3 days, the yield was actually increased slightly from 6% at 20 h to 23% for 3 days. The ambiguous results suggest that the reaction mechanism could be quite complicated, multiple pathways might be involved in the reaction (Scheme 41).



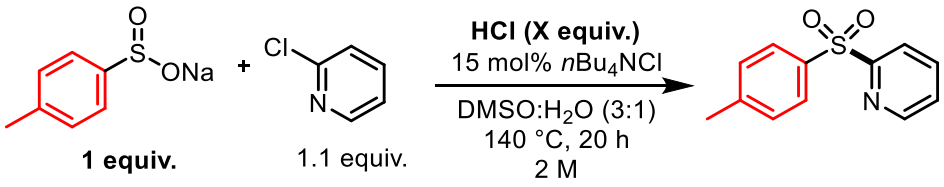
Scheme 41: Reaction with radical scavengers or initiator.

Furthermore, we examined various loading of HCl acids in influence of the reaction yields. With 1 equiv. HCl, the reaction yield was dropped dramatically, but within 0.01 to 0.03 equiv. HCl, the reaction worked as the same as using iron catalyst (see Table 5-a). To further identify whether the iron catalyst is just functioning as an acid source or the results are due to the iron contamination in acid, we also did pH identification with before and after the reactions. With the comparison, we can observe that with 1 equiv. HCl, the reaction mixture before and after reaction

were much more acidic compare with 0.03 equiv. and $FeCl_3$ catalyst. With $FeCl_3$ catalyst, the reaction mixture was more basic than trace HCl loading before the reaction, but after the reaction, the reaction mixtures gave similar pH values (see Table 5-b). The results suggested that over acidic conditions decreased the reaction yield, but it didn't provide enough information to differentiate trace HCl and Fe catalyst. Therefore we also performed the reaction with buffer systems to be able to identify the roles of HCl and Fe catalyst in the reaction. When the reaction performed with the buffer system, with neutral or slight basic buffer systems, such as 7.8 and 8.4, the yields of trace HCl loading showed clearly a decrease with the increase of basicity but still tolerated, while the yields of $FeCl_3$ catalyst almost had no influence by the buffer system. When the solution goes to a more basic level such as 11.40, the reaction with trace HCl loading stopped and the yield of $FeCl_3$ catalyst was dropped dramatically but it still gave 37% (see Table 5-c). The results supported that the iron catalyst played a special role, such as Lewis acid, in this reaction rather than alternative HCl source.

Table 5: Reactions under various acidic environments

a) With HCl loading instead of $FeCl_3$.



1 equiv. 1.1 equiv.

Entry	HCl (X equiv.)	Yield (%)
1	1 equiv.	38%
2	0.01 equiv.	70%
3	0.02 equiv.	69%
4	0.03 equiv.	69%

b) pH values measured with different catalysts.

Entry	HCl (1 equiv.)	HCl (0.03 equiv.)	$FeCl_3$ (0.01 equiv.)
Before	4.50	6.80	7.60
After	0.64	2.08	1.81

c) Reaction with the buffer systems under acid or iron catalysts.

Buffer (pH)	HCl (0.03 equiv.)	$FeCl_3$ (0.01 equiv.)

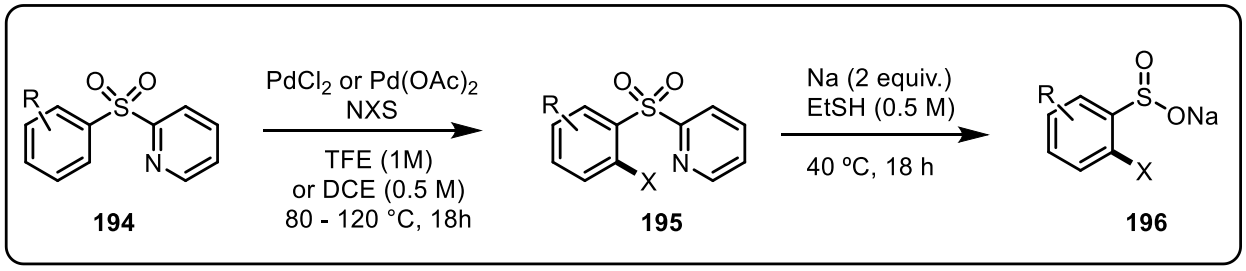
7.8	60%	71%
8.3	51%	70%
11.40	-	37%

Overall, the results of mechanism studies, such as radical scavenger reactions and acid-buffer reactions, indicated the reaction could proceed through several pathways. Both acid assisted and radical reaction routes cannot be excluded, but it is also clearly indicated that the iron catalyst behaved more than just an HCl source. The iron catalyst could played two possible roles in the reaction such as Lewis acid or possible radical initiator. We provided a supplementary method for S_NAr reaction under slightly acidic condition with readily available catalyst.

Chapter 3: Using Pyridine as a Removable *Ortho*-Directing Group to Access the *Ortho*-Halogenated Sulfinate Salts

3.1 Abstract

Sulfinate salts are interesting starting materials but are prone to self-proportionation. *Ortho*-halogenated sulfinate salts can be obtained from sulfonylated pyridines through pyridine directed halogenation followed by a S_NAr reaction to remove the pyridine functional group on the sulfonylated pyridine. In this paper we demonstrate a method to achieve *ortho*-halogenated sulfinate salts (**196**) from the sulfonylated pyridine precursors (**194**) in good to excellent yields. The method provides a pathway to access the aromatic systems with bis-actived functional groups consisting of halogen and sulfinate salts.



Scheme 42: Pyridine directed *ortho*-halogenation on sulfinate salts

3.2 Introduction

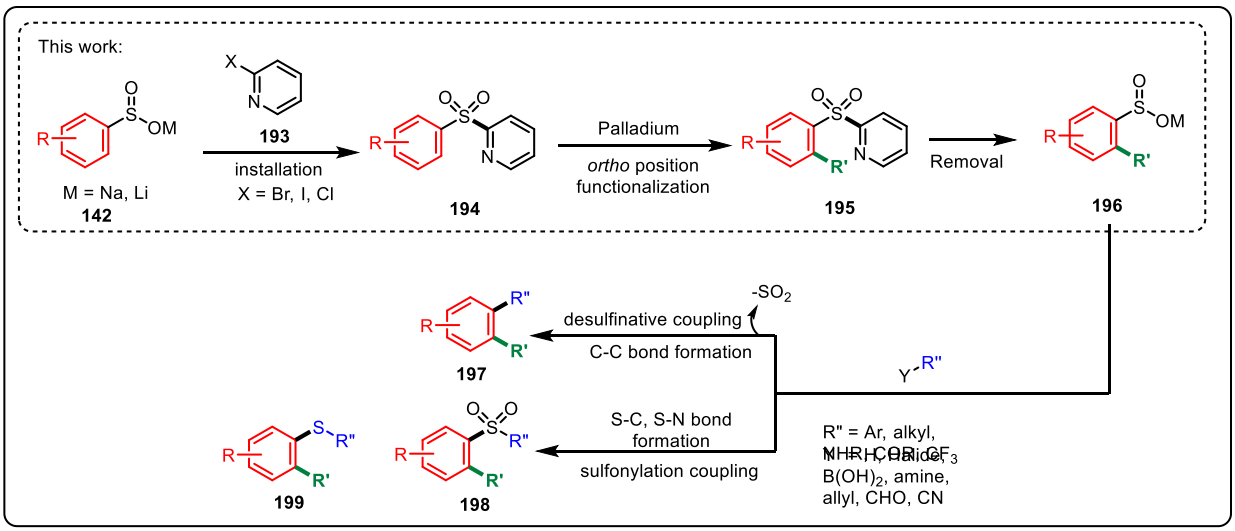
Efficient access to complex molecules is always of interest in organic synthesis. Therefore, developing starting materials that undergo simple and sustainable transformations is desirable. Organosulfur compounds have been known for more than a hundred years[103], such as the tosyl group that is commonly used to protect alcohols and amines.[152] However using them as starting materials has been actively developed relatively recently. Sulfinates are a subset of organosulfur compounds that are versatile coupling partners and enable access to various important building blocks in the pharmaceutical[141, 153] and material[154] industries through formation of S-C[114b, 146a, 147, 155], S-N[115, 156] and C-C[105, 113] bonds

Metal sulfinate salts, which can be used both as a nucleophilic[111b, 111e, 118, 132, 136c] or electrophilic[111a, 120-122, 123c, 123g, 157] coupling partners in palladium catalyzed reactions have been the focus of attention for many research groups lately, mainly because most of the metal sulfinate

salts are commercially available or easily accessible[107, 110a, 158], are bench stable, non-hygroscopic and easy to handle solids, making them ideal starting materials. However, it is also known that the protonated form of these salts can undergo self-disproportionation[106, 159] and is the most critical drawback that limits their usage. In order to diversify their utility in multi-step syntheses, we were interested in using a removable *ortho*-directing functional group that could promote the *ortho* directed functionalization and after deprotection, generate the sulfinate salt functionality. We decided to focus on developing methods to access the *ortho*-halogenated sulfinate salts *via* a removable directing group. Both halogen and sulfinate salt functional groups could provide access to different bonds formation such as C-C, C-N, C-O as well as S-C, S-S, and S-N bonds.

We were interested in synthesizing the *ortho*-halogenated sulfinates as they can be used as precursors or coupling partners for a wide scope of derivatives, and provide an accessible pathway to different functional groups for applications in pharmaceutical, agrochemical and material science industries. Formation of carbon-halogen bonds has always been of great interest to synthetic chemists. From a synthetic point of view, activation of a C-H bond and its transformation to a C-X bond provides access to a wide range of functional groups and developing methods that promote the transformation is valuable and critical. Recently, transition metal catalyzed halogenation has been developed to ensure more environmentally friendly and efficient transformations. However, to overcome the regioselectivity issue, a directing group is normally involved. Most of the directing groups are permanently connected and therefore integrated into the final structures, therefore removable directing groups would be very valuable and have also attracted increasing attention recently.[142c, 142d, 160]

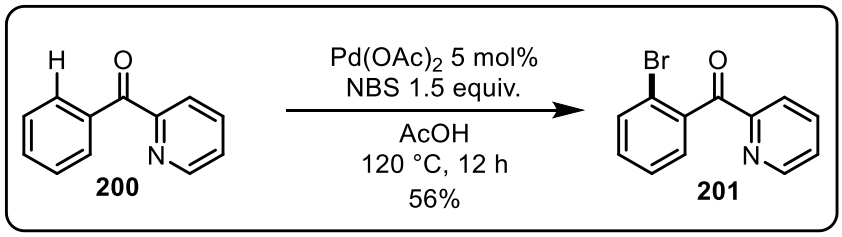
2-Pyridine (**194**) could be employed as an *ortho*-directing group for a palladium catalyzed halogenation reaction (see Scheme 43). Subsequent removal of the pyridine would regenerate the sulfinate salt that is *ortho*-halogenated (**196**), which could be used to access the different building blocks in the formation of C-C (**197**), S-C or S-N bonds (**198 or 199**).



Scheme 43: Using pyridine as removal directing group in synthesis *via* sulfonylated pyridines.

3.3 Results and discussion

Previously the Sanford group reported using pyridine as directing group for *ortho*-halogenation with 2-benzoylpyridine (**200**) as an example with a yield of 56% (see Scheme 44).[83a] Sulfone can be deemed as a replacement of the carbonyl functional group and sulfonylated pyridines are similar to 2-benzoylpyridine, therefore our system could be a suitable substrates for directed halogenation reactions. Inspired by the bromination reaction of the Sanford group, initial attempts started by using 2-tosylpyridine (**194a**) as substrate and under similar reaction conditions with slightly higher NBS loading, and we observed the desired product (**195a**) with 38% yield (see Table 6 entry 1). Further optimization of the reaction conditions were focused on bromination.

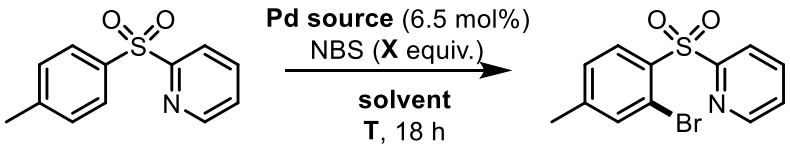


Scheme 44: Pd-catalyzed *ortho*-halogenation: specific condition for 2-benzoylpyridine.

In order to verify the importance of palladium catalyst, a control experiment without catalyst was performed and only a trace amount of desired product was observed (Table 6, entry 2), which highlighted the significance of the palladium in the reaction. Increasing the reaction temperature over 120 °C led to decomposition. Decreasing reaction temperature to 100 ºC and lowering the NBS loading to 1.3 equiv. resulted a dramatic increase in yield to 59% (entry 3). Different palladium

catalysts including palladium (0) were also examined, and generally Pd(II) catalysts worked better in the reaction. Palladium halides gave the highest yields (59% for $PdCl_2$ and 60% for PdI_2, see entries 4-7). Among palladium (II) catalysts, $Pd(OAc)_2$ gave higher conversions as there was no remaining starting material observed, while with palladium halides, there were still trace starting material could be monitored by NMR. Using Pd(0) catalyst such as $Pd_2(dba)_3$, lower yield was obtained (see entry 8). Further lowering of the reaction temperature to 80 ºC and NBS loading to 1.2 equiv. had almost no influence on reaction outcome as 61% yield was observed (entry 9). Below 80 °C, the reaction gave only trace amounts of product with very low conversion. In order to further optimize the reaction, different solvents were screened as important factor for the reaction yield. We examined different solvents in this reaction (see entries 10-16), and solvents that contained halogens and were slightly acidic were favored such as trifluoroethanol (TFE), dichloroethane (DCE) and chloroform. TFE was the prefered solvent that provided the corresponding product in 80% yield, followed by the DCE (75%) and chloroform (70%). The other solvents gave much lower yields from 34% to 56% and when EtOH was used as the solvent, no product was obtained.

Table 6: Optimization route of bromination on 2-tosylpyridine (**194a**).



194a **195a**

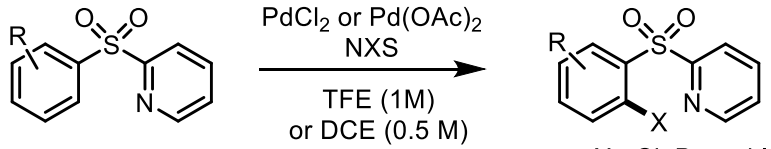
Entry	Pd source	NBS (equiv.)	Temperature	Solvent	%Yield[a]
1	$Pd(OAc)_2$	2	120 °C	AcOH	38%
2	-	1.5	120 °C	AcOH	6%
3	$Pd(OAc)_2$	1.3	100 °C	AcOH	59%
4	$PdCl_2$	1.3	100 °C	AcOH	60%
5	$Pd(TFA)_2$	1.3	100 °C	AcOH	50%
6	$Pd(acac)_2$	1.3	100 °C	AcOH	53%
7	PdI_2	1.3	100 °C	AcOH	59%
8	$Pd_2(dba)_3$	1.3	100 °C	AcOH	41%
9	$PdCl_2$	1.2	80 °C	AcOH	61%
10	$PdCl_2$	1.2	80 °C	MeCN	34%
11	$PdCl_2$	1.2	80 °C	TFA	52%
12	$PdCl_2$	1.2	80 °C	TFE	84%[b]

13	$PdCl_2$	1.2	80 °C	$CHCl_3$	70%
14	$PdCl_2$	1.2	80 °C	DCE	74% [b]
15	$PdCl_2$	1.2	80 °C	$C_2H_2Cl_4$	56%
16	$PdCl_2$	1.2	80 °C	EtOH	-

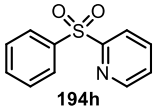
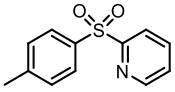
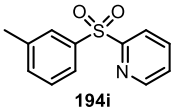
Note: [a] Yields calculated by ^1H NMR with TMB (1,3,5-trimethoxybenzene) as internal standard. [b] Isolated yields.

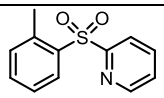
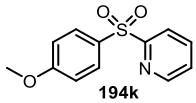
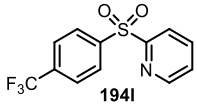
For the reaction to proceed with different halogen functional groups from various N-halide succinimide, we had to modify the optimized bromination conditions in order to achieve maximum chlorination and iodination yields. With the chlorination and iodination, employing DCE as solvent provided superior results, and the equivalents of N-halide succinamides were also increased, as chlorination required double the amount of the corresponding succinamide. Additionally, the temperature of the reactions had to be increased on the less reactive starting materials such as electron-deficient and sterically hindered sulfonylated pyridines and the higher conversion catalyst $Pd(OAc)_2$ was employed. The most common side-products with the reaction were the bis-halogenated products. The bis-halogenated side products were unavoidable in most of the reactions, but could be limited to very small amount.

Table 7: Scope of pyridine directed halogenation.



194 **195**

Entry	Substrate	NCS[1] (yield)	NBS[2] (yield)	NIS[3] (yield)
1	 **194h**	88%	84%	77%
2	 **194a**	66%	88%	70%
3	 **194i**	83%	86%[a]	73%[a]

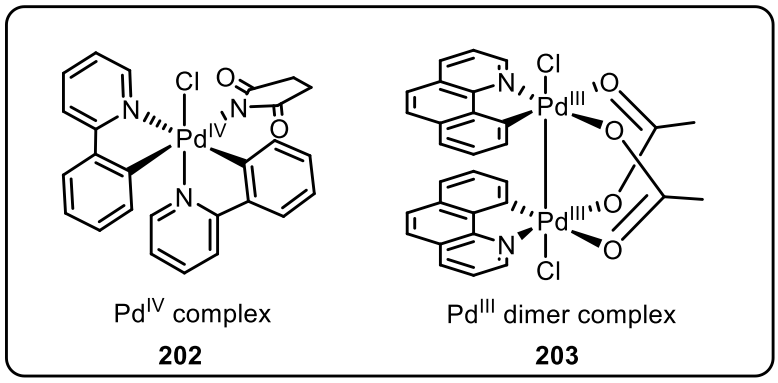
4	 **194j**	80%	66%[a]	43%[a]
5	 **194k**	65%	67%	79%
6	 **194l**	53%[b]	74%[a]	40%[b]

Note: [1] condition: $Pd(OAc)_2$ at 100 °C, 18h with 2 equiv. NCS in DCE (0.5 M). [2] condition: $PdCl_2$ at 80 °C with 1.2 equiv. NBS in TFE (1 M). [3] condition: $PdCl_2$ at 100 °C, 18h with 1.3 equiv. NIS in DCE (0.5 M). [a]: Using $Pd(OAc)_2$ as catalyst. [b]: Using $Pd(OAc)_2$ at 120 °C.

The *ortho*-halogenation reaction gives moderate to excellent yields for a variety of sulfonylated pyridines. For electron-neutral sulfonylated pyridines such as benzene sulfonylated pyridine, and *ortho*, *meta*, & *para* toluene sulfonylated pyridines, all the halogenating reactions were well tolerated (see Table 7 entries 1-4). Due to the steric influence, the most sterically hindered *ortho*-toluene sulfonylated pyridine led to a lower yield in bromination and iodination even when more reactive conditions were employed, and with higher loading of NCS, chlorination had successful results as no bis-halogenation side product was observed (entry 4). For electron-rich – methoxylated benzene sulfonylated pyridine, the halogenations were well tolerated, but iodination was definitely the most successful reaction (entry 5). While the electron-deficient system such as *p*-trifluoro-benzene sulfonylated pyridine was generally less reactive and required higher temperatures as well as the more reactive palladium catalyst $Pd(OAc)_2$, and poor yields were still observed for chlorination and iodination (entry 6). Overall, the bromination reaction seems to be less affected by variations in the electronic and steric properties of the sulfonylated pyridines substrates.

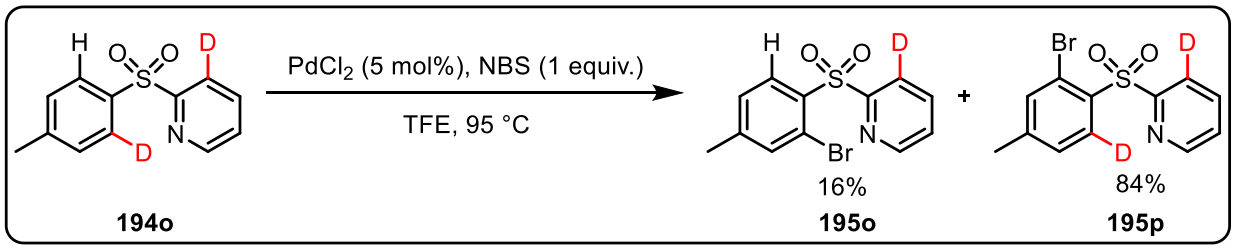
Recently, a concurrent publication from the group of Hierso[161] that reported *ortho*-directed halogenation *via* palladium catalysis and proposed a mechanism through a palladium catalyzed C-H insertion followed by a nucleophilic substitution to form the carbon-halogen bond. While Sanford[83a, 88a, 88b, 90a] and Ritter[91] studied directed palladium catalyzed halogenation with analysis of the crystal structures that mimic the transition states (Scheme 45), they proposed pathways through higher oxidation states of palladium such as a palladium(III) dimer (**203**) or palladium(IV) complex (**202**). In addition, Sanford also performed kinetic isotopic effect (KIE) studies and the

results were consistent with the activation of the C-H bond as the rate-limiting step for directed halogenation reactions.



Scheme 45: Higher oxidation states of palladium complexes.

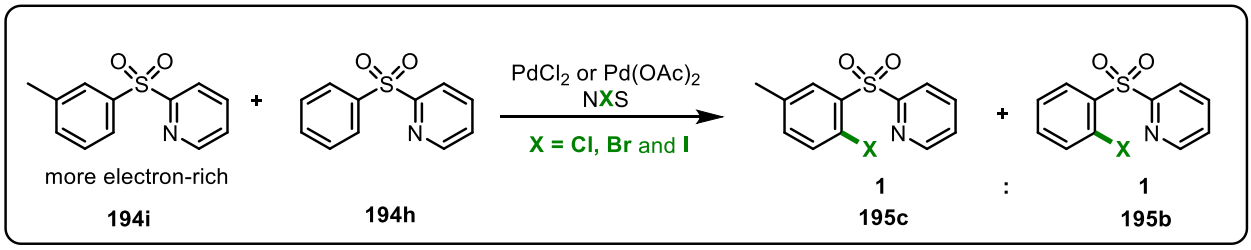
We believe that the halogenation pathway is more likely to proceed through higher oxidation states of palladium complex. Our preliminary mechanistic studies on the palladium catalyzed halogenation reaction for the sulfonylated pyridine system gave a KIE value of 3 for chlorination, which is consistent with previous findings supporting C-H bond activation as the rate-limiting step (Scheme 46). Furthermore, lower yields have been observed when the catalysts are the palladium(0) species and the palladium(II) catalysts, especially palladium(II) halides and acetates are more suitable for this reaction. The observations suggested that palladium(II) is the active catalyst in the reaction rather than palladium(0), as is generally observed for palladium catalyzed cross coupling reactions. Furthermore, the reaction seems to have no special requirement for oxidants even though air is tolerated in the reaction.



Scheme 46: Preliminary KIE studies of pyridine directed halogenation on deuterated sulfonylated pyridine.

To further rule out the nucleophilic substitution, we performed another competition experiments between 2-(*m*-tolylsulfonyl)pyridine (**194i**) and 2-(phenylsulfonyl)pyridine (**194h**) in halogenation reactions (see Scheme 47). If the reaction undergoes nucleophilic substitution, the more electron-rich toluenesulfonylated pyridine should be favored. Indeed, the reactions showed no preference with all the halogenation reactions between the two sulfonylated pyridines, the

desired product obtained is in a 1:1 ratio. The observations indirectly suggested that the reaction more likely to proceed *via* a mechanism that involved higher oxidized palladium center, as it ruled out the nucleophilic substitution pathway.



Scheme 47: Competition studies of halogenation with 2-(*m*-tolylsulfonyl)pyridine and 2-(phenylsulfonyl)pyridine.

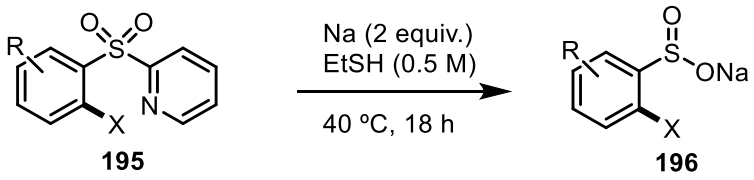
Directed *ortho*-halogenation on the sulfonylated pyridines provided possible further functionalization on the *ortho* position to the sulfur, and furthermore the removal of the pyridine directing group would allow further transformations to occur with the sulfinate salts. As an alternative, the removal of the pyridine group prior to the halogen mediated functionalization, could lead to a reactive core with both sulfinate salt and halogen functionalities, available for further derivatization.

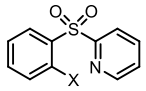
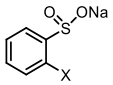
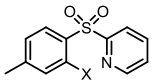
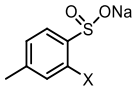
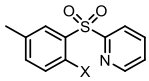
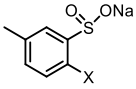
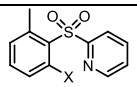
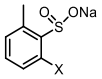
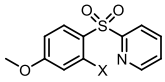
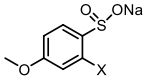
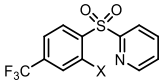
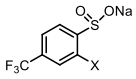
We were interested in preparing *ortho*-halogenated aromatic sulfinate salts, as they could be potentially valuable building blocks for the pharmaceutical and material industries. However, the removal of the pyridine on the halogenated sulfonylated pyridine is very challenging. A method to remove the pyridine is through a S_NAr reaction, as pyridine is the more electron-deficient heteroarene and is a more reactive functional group for S_NAr reactions. However, once the halogen functional group is installed on the aromatic system, the electronic difference between the arenes and pyridine is reduced by the electron-withdrawing effect of the halide. Secondly, the halogen functional groups could undergo S_NAr reaction as well, which complicates the deprotection of the ortho-halogenated sulfonylated pyridines. We need to explore reaction conditions that promote the S_NAr reaction on the pyridine site, but also keep the halogen functionality intact.

Several reaction conditions were tested in the pyridine removal process. Small and nucleophilic sodium salts, such as methoxide and ethoxide; in their corresponding alcohol as solvent, proved to be too reactive, as both the removal of the pyridine and the halogen functional group was observed. The premade ethanethiolate sodium salt was also employed but no reaction was observed. However, when the ethanethiolate was generated *in situ* (sodium metal in

ethanethiol solvent), the desired product was obtained. To maximize the yield, the reaction was heated to 40 ºC for 18 h.

Table 8: Reaction scope of pyridine removal.



Entry	Substrate	Products	Yield X = Cl	Yield X = Br
1	 195b	 196b	91%	90%
2	 195a	 196a	93%	83%
3	 195c	 196c	87%*	80%
4	 195d	 196d	43%*	75%*
5	 195e	 196e	74%*	97%
6	 195f	 196f	mixture	mixture

Note: * reactions performed at 50 ºC.

Pyridine removal on the chlorinated and brominated compounds was accomplished successfully to access the electron-neutral sulfinate salts (see Table 8 entries 1-4). For some chlorinated sulfonylated substrates, in order to achieve a better yield, higher temperatures were employed. With *ortho*, *meta* and *para* toluene sulfonylated pyridine, the S_NAr reaction seems to be influenced by steric effects. *Meta* and *para* toluene sulfonylated pyridines had good to excellent yields (all above 80%, entries, 3 & 4) and o*rtho*-toluene sulfonylated pyridines had lower yields, even when higher temperatures were employed (see Table 8 entry 4). With electron-rich

sulfonylated pyridine such as *p*-methoxylated substrates, we obtained good to excellent yields (74% yield with chlorinated compound and 97% yield for brominated sulfonylated pyridine, see Table 8 entry 5). Despite the unsatisfactory results with electron-deficient sulfonylated pyridines such as trifluoromethyl sulfonylated pyridine, the S_NAr reactions were observed to occur at both phenyl side and pyridine side of the sulfone functional group, to give the desired product and pyridine sulfinate salts (see Table 8 entry 7). Additionally, due to the high lability of the iodo functional group, both desired products and dehalogenation products have been observed. Overall, this method is well-tolerated with electron-rich and neutral sulfonylated pyridines and can be employed with both chlorinated and brominated substrates.

3.4 Summary

In conclusion, sulfonylated pyridines act as a dual functionality as an *ortho*-directing group as well as a protecting group for sulfinate salts. In the chapter, we demonstrated a parallel *ortho*-halogenated methodology in different solvents that complements Hierso's methodology. Furthermore, the preliminary mechanistic studies suggested that the halogenation on the sulfonylated pyridines seems to occur through the high oxidation states of palladium, which Sanford and Ritter also proposed, rather than nucleophilic substitution. Additionally, we also demonstrated that the pyridines on the sulfonylated pyridines could be removed to access the sulfinate salt functionality for further functionalization through S_NAr reactions. Electron-deficient sulfonylated pyridines did not tolerate the S_NAr reactions. As well, the method cannot be used to access iodinated sulfinate salts due to the lability of iodol functional groups. Electron-rich and electron-neutral chlorinated and brominated sulfonylated pyridines were well tolerated and generated the corresponding sulfinate salts. For electron-deficient and iodo substrates, *ortho*-functionalization on the halogen functional groups and then removal of pyridine for further functionalization can be a well suitable alternative pathway. With the method, we can access aromatic moieties that have two active functional groups, such as halogen functional groups and sulfinate salts. Moreover, the halogen functional group could be transformed into more electron-rich or stable functional groups prior to the removal of the pyridine.

Overall, we provided a convenient pathway to access the *ortho*-halogenated sulfinate salts. With the methodology, access to some really rigid ortho-functionalized aromatic systems is allowed, which could be potentially useful for the material and pharmaceutical industries.

3.5 Experimental section

All reactions were performed in round bottom flask containing a Teflon-coated stir bar unless more specific conditions are stated. Chemicals were purchased from Aldrich, Alfa Aesar, or AK Scientific and used without further purification. All solvents were purchased as ACS grade from Fisher Scientific or JT Baker and distilled water was obtained from an in-house water distillery prior to use. Flash chromatography was carried out using 40-63μm silica gel (Silicycle). Melting points were obtained using a Stuart SMP30 bench apparatus. NMR spectra were recorded with Varian Inova 500MHz spectrometer and were referenced to the residual solvent signal or TMS signal. High resolution mass spectra (HRMS) were obtained using a LC-TOF ESI positive mode mass spectrometer.

General procedure of *ortho*-bromination on sulfonylated pyridine:

The sulfonylated pyridine **194** (1 equiv., 2 mmol scale) and NBS (1.2 equiv.) in TFE (2 mL, 1 M) were added to a round bottom flask containing $PdCl_2$ (6.5 mol%) under argon atmosphere. The mixture was heated to 80 ^oC and stirred for 18 h. The resulting mixture was cooled to room temperature and diluted with H_2O and EtOAc, then the organic portion was extracted with EtOAc (3X). The combined organic phases was washed with sat. $NaHCO_3$ solution, followed by brine solution and then was dried over sodium sulfate and filtered. The solvent was then removed under reduced pressure. The residue was purified by column chromatography with 5% EtOAc, 45% hexanes and 55% DCM to give the desired product *ortho*-bromosulfonylated pyridine **195-Br**.

General procedure of *ortho*-chlorination on sulfonylated pyridine:

The sulfonylated pyridine **194** (1 equiv., 2 mmol scale) and NCS (2 equiv.) in DCE (4 mL, 0.5 M) were added to a round bottom flask containing $Pd(OAc)_2$ (6.5 mol%) under argon atmosphere. The mixture was heated to 100 ^oC and stirred for 18 h. The resulting mixture was cooled to room temperature and diluted with H_2O and EtOAc, then the organic portion was extracted with EtOAc (3X). The combined organic phases was washed with sat. $NaHCO_3$ solution, followed by brine solution and then was dried over sodium sulfate and filtered. The solvent was then removed under reduced pressure. The residue was purified by column chromatography with 5% EtOAc, 45% hexanes and 55% DCM to give the desired product *ortho*-chlorosulfonylated pyridine **195-Cl**.

General procedure of *ortho*-iodination on sulfonylated pyridine:

The sulfonylated pyridine **194** (1 equiv., 2 mmol scale) and NIS (1.3 equiv.) in DCE (4 mL, 0.5 M) were added to a round bottom flask containing $PdCl_2$ (6.5 mol%) under argon atmosphere. The mixture was heated to 100 ^oC and stirred for 18 h. The resulting mixture was cooled to room temperature and diluted with H_2O and EtOAc, then the organic portion was extracted with EtOAc (3X). The combined organic phases was washed with sat. $NaHCO_3$ solution, followed by brine solution and then was dried over sodium sulfate and filtered. The solvent was then removed under reduced pressure. The residue was purified by column chromatography with 5% EtOAc, 45% hexanes and 55% DCM to give the desired product *ortho*-iodosulfonylated pyridine **195-I**.

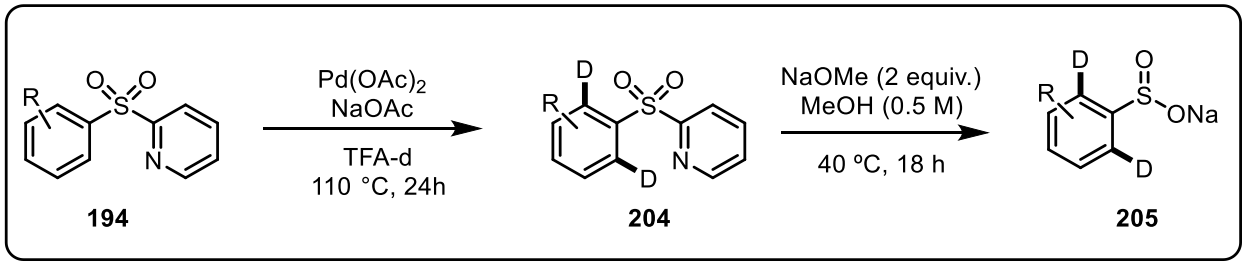
General procedure of pyridine removal method:

The *ortho*-halosulfonylated pyridine **195** (1 equiv., 0.25 mmol scale) was added to a round bottom flask containing Na (2 equiv., 0.5 mmol) in EtSH (1 mL, 0.5 M) under argon atmosphere. The mixture was heated to 40 ^oC and stirred for 18 h. The resulting mixture was set down for 30 minutes and filtered through filter paper. The solid filter cake contained desired product was then washed with Et_2O (5X) and air dried to give the desired product halogenated sulfinate salts **196**.

Chapter 4: Selective *ortho*-deuteration on sulfonylated pyridine *via* Pd catalyzed directed C-H deuteration

4.1 Abstract

Deuterated compounds are useful tools for revealing metabolic pathways or reaction mechanisms. Therefore, methods to access deuterated compounds are always of interest in organic synthesis. In this paper, we demonstrate a pyridine directed *ortho*-deuteration of sulfonylated aromatics with full-deuterium incorporation and good yields. Additionally, the directing group can be transformed into sulfinate salts that have a variety of further applications.



4.2 Introduction

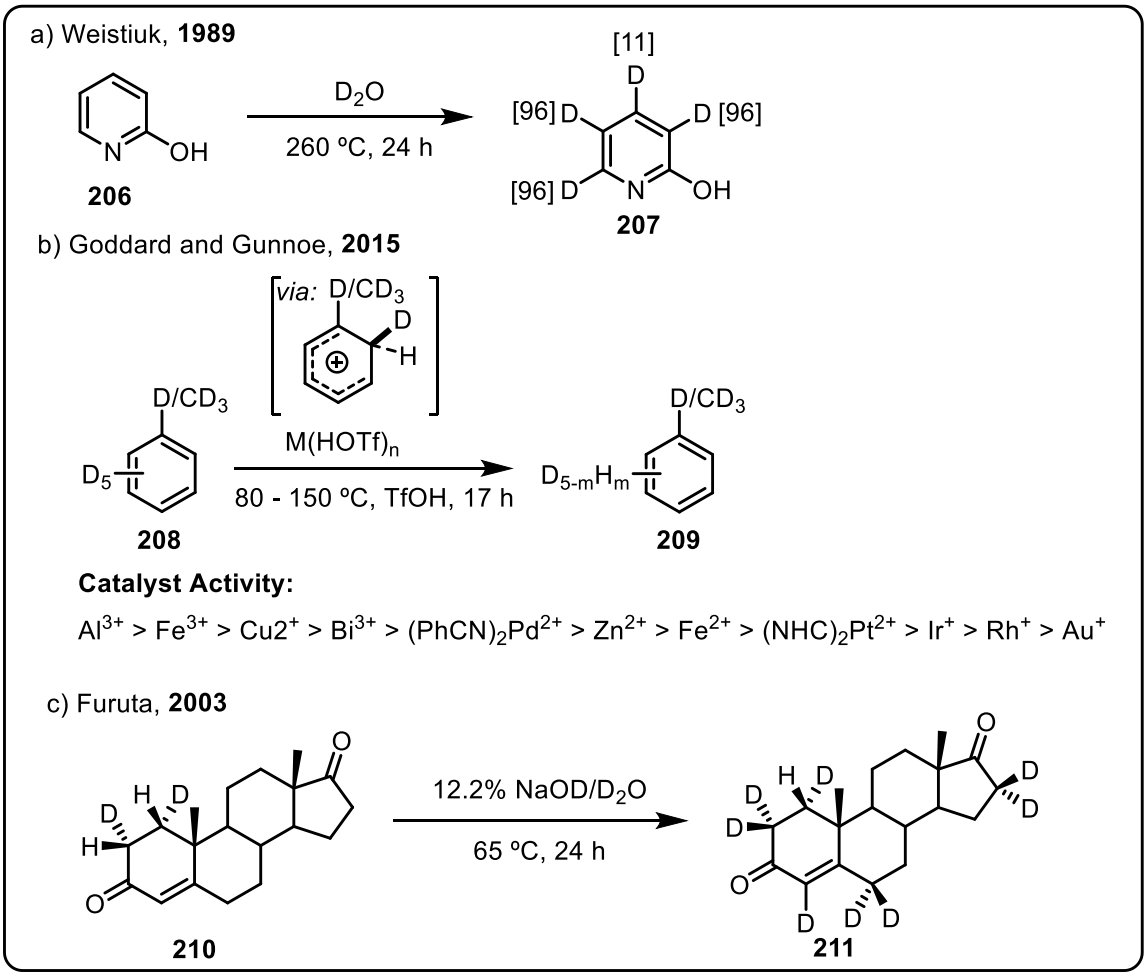
Deuterium is the isotopic atom of hydrogen with double the atomic mass, and therefore, deuterium labeled compounds can be easily identified with mass spectrometry. Furthermore, the relative energy to cleave a C-D bond is +1.2–1.5 kcal/mol with respect to a C-H bond, and this energy difference in the activation barrier could provide key insights in C-H activation processes.[92] Use mass spectrometry and liquid chromatography-mass spectrometry (LCMS), deuterium-labeled compounds are widely used in mechanistic and metabolic studies to provide a insight on biosynthetic and metabolic systems for biomedical research.[162] The principle of KIE is based on the difference of the vibrational frequency due to the mass difference, and deuterium compared to proton has a 100% increase on the mass, therefore the energy difference that is required in breaking the C-H bond relative to the C-D bond is the highest among all the other elements with their corresponding isotopes. Moreover, selective deuteration has now attracted increasing interest as it has been shown to alter the ADME properties of certain drug candidate[163]. For example, the deuterium incorporated drugs venlafaxine and paroxetine have demonstrated fewer side effects and prolonged retention time in blood.[164]

The preparation methods for deuterium labelled compounds can be generally divided into two principal routes: Multiple-step synthesis *via* isotopic labelled starting materials; and direct hydrogen isotope exchange (HIE). In the case of the former, the synthesis of the desired isotopic

labelled compound could be extremely time and resource consuming, based on the availability of starting material, and can also be highly wasteful. On the other hand, HIE is a quicker and greener approach, as the modification is done on the final molecules themselves.

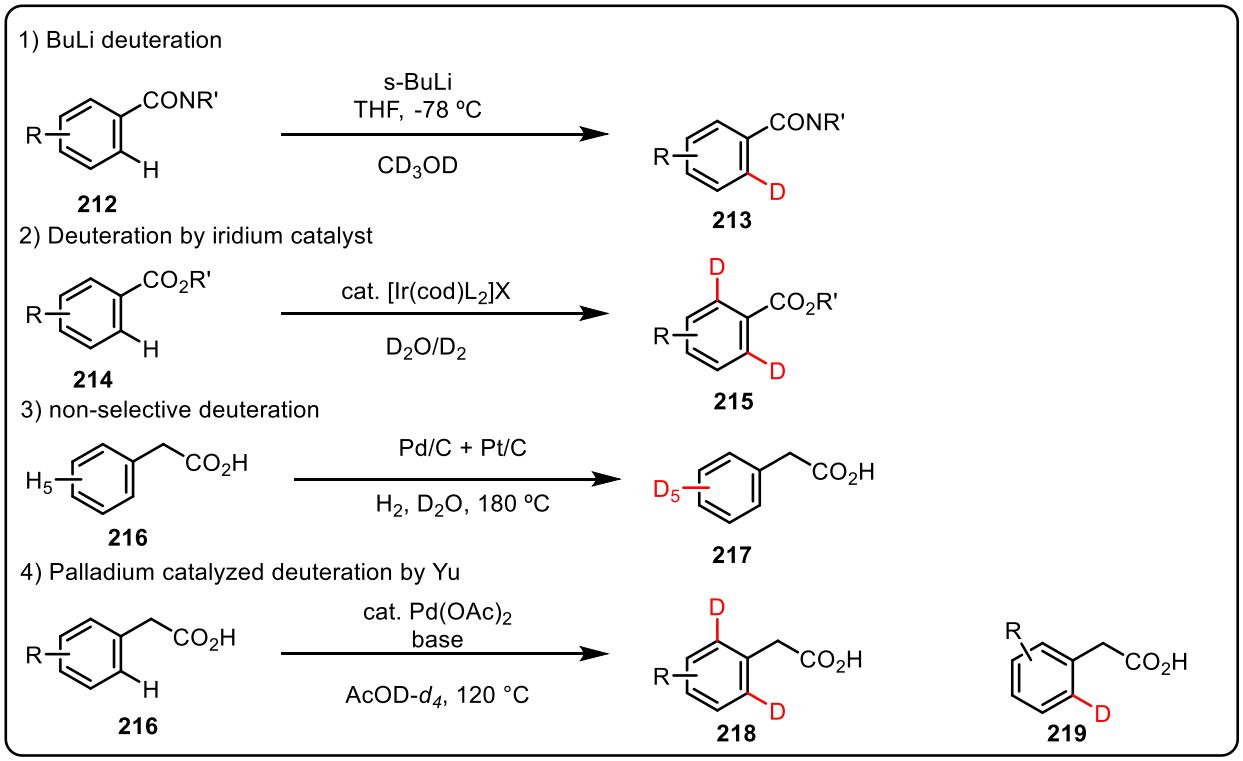
The existing HIE methods can be briefly separated into two classes: pH-dependent H/D exchange or metal-catalyzed H/D exchange. The H/D exchange depending on pH-variations is one of the oldest methods in the field. It is based on the acidity of target C-H bonds in the molecules in order to access enolization under acid or base assistance, followed by a deuteration with D_2O or D_2 for H/D exchange. The acid or base catalyst is not required with certain substrates in H/D exchanges, however without catalyst, the reactions required high temperature (over 200 ºC) and long times (24 h). The advantage is that the H/D exchange is normally associated with high selectivity (see Scheme 48-a). Deuteration can also now be achieved much faster with microwave assistance.[165]

For aromatic systems, deuterated Bronsted acids or deuterium sources combined with Lewis acids can be used in H/D exchange reactions. Goddard, Gunnoe and co-workers completed intensive studies on the mechanisms and demonstrated that an oxidative addition mechanism is not involved, and the reaction most likely proceeds through electrophilic aromatic substitution[166] (Scheme 48-b). Therefore, for activated positions, high deuteration and good yields can be achieved. With acid-assisted H/D exchange, the regioselectivity is modest and it is also highly affected by the substitutions on the system - protons on the *para* and *ortho* positions relative to electron donors are most suitable for the method. Additionally, microwave irradiation can also be utilized in order to shorten the reaction time.[165b] Base-catalyzed H/D exchange reactions can be used to provide facile access to the deuteration of acidic protons. High selectivity, high deuterium incorporation, and good yields have been observed with ketones, aldehydes, esters and carboxylic acids substrates. Furthermore, γ-hydrogen atoms in α,β-unsaturated ketones can also be deuterated (see Scheme 48-c)[167]. Lithium bases are also very useful for deuterations through Li/D exchange, and one of the most representative examples is the *ortho*-selective methods through DoM methods, followed by quenching with D_2O.[168]



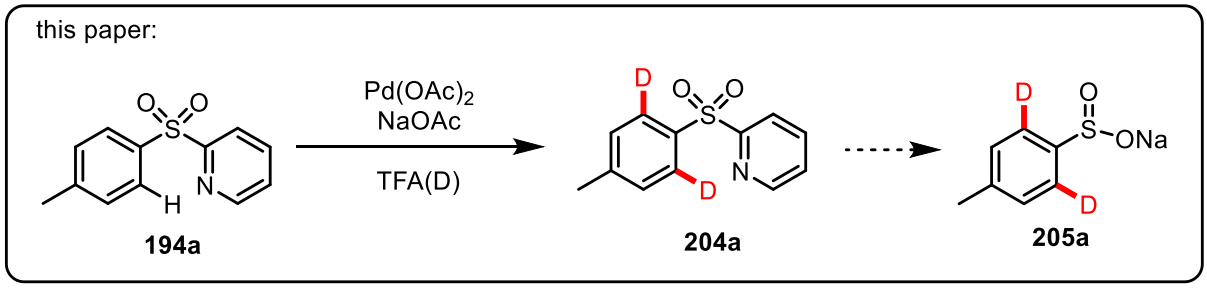
Scheme 48: Previously reported H/D exchange methods.

Transition metal catalyzed H/D exchange has many advantages, including mild reaction conditions and a high tolerance towards various functional groups. Various metals can be used in various H/D exchange protocols, such as Ir, Pt, Ru and Pd. In the area of homogenous metal catalysis on H/D exchange, cationic iridium complexes has received the most focus, mostly concentrating on *ortho*-deuteration of aryl ketones and acetanilides, such as using the Crabtree catalyst[169]. For non-selective deuteration, heterogeneous mixed-transition-metal catalysts with D_2 as the deuterium sources can be used (Scheme 49-3).[170] Highly selective deuteration can be achieved using a directing group within the substrates that differentiates the *ortho* C-H bond from the rest of the C-H bonds in the molecule. Recently, Yu's group demonstrated a Pd-catalyzed *ortho*-deuteration using phenyl acetic acids as directing groups (Scheme 49-4).[171]



Scheme 49: Transition metal catalyzed H/D exchange methods.

In this paper, we demonstrated a HIE method of *ortho*-deuteration using pyridine on aromatic sulfonylated aromatics as a directing group *via* palladium catalyzed proton/deuterium exchange. The pyridine group can be removed later to allow for further functionalization with the resulting sulfinate salts.



Scheme 50: H/D exchange method of this work.

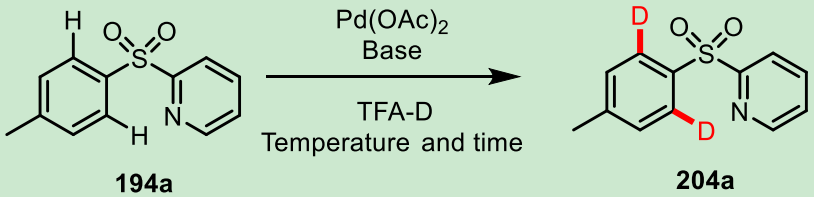
4.2 Results and discussion

Inspired from Yu's *ortho*-deuteration reactions[171], we used our previously reported sulfonylated pyridine (**194a**) as a directing group. Using AcOD-d_4 as the solvent, we observed 29% of deuterium incorporation in to the ortho position of sulfonylated pyridine – **204a** (Table 9, entry 1). As the reaction is an H/D exchange reaction, all the undersigned proton source involved in the

reaction would influence the deuterium incorporation on the molecule and can lead to no H/D exchange. Therefore the reaction is highly sensitive to the moisture and all potential hydrogen sources in the reaction. First we used AcOD-d1 to replace AcOD-d4 and surprisingly found that the non-active proton in the molecule had no influence on deuterium incorporation. Therefore, we surmise that the deuterium incorporation is primarily affected by the acidity of the acidic deuterium in the solvent, or deuterium source. To optimize the deuterium incorporation, we extended the reaction time to 24h, and the deuterium incorporation was increased to 43% with a sacrifice of the yield to 53% (see Table 9 entry 2). Higher $Pd(OAc)_2$ loading up to 30 mol% in AcOD with sodium carbonate as base were also examined, and the deuterium incorporation improved slightly to 50% with 57% yield (Table 9 entry 3). Changing the catalyst to $PdCl_2$ resulted in no deuterium incorporation and the starting material was decomposed and only 37% has been recovered (entry 4). To monitor the solvent influence, when the solvent was modified to the more acidic deuterated trifluoroacetic acid (TFA), deuterium is fully incorporated into both *ortho*-positions, but the yield is only about 50%. At the same time, when the solvent was changed to deuterated chloroform, no deuteration occurred. Furthermore, when the solvent changed to the mixture of 10% TFA in deuterium oxide to see whether TFA could be used as a catalyst, and there was also no observed proton-deuterium exchange (see Table 9 entries 5 and 6). Previous observations revealed that the acidity of acidic deuterium sources is the key for the reaction. Then, to examine the importance of the catalyst, a control experiment without the palladium catalyst was performed that resulted in no observed proton-deuterium exchange (entry 7), which indicated the palladium catalyst is critical for this reaction. With deuterated acetic acids, the acetylation of the *ortho*-position was observed in the crude ^{1}H NMR as a by-product, but with TFA as the solvent, there is no other observable product in the crude ^{1}H NMR, which suggests that the reduction in yield is mainly due to decomposition. Therefore, a first attempt to decrease the decomposition was to reduce the reaction time to 18 h, which led to an incomplete di-deuteration as estimated 78% deuterium incorporation, with only a slight improvement on the yield at 57% (Table 9 entry 9). Instead of shortening the reaction time, the reaction was performed at a lower temperature at 110 ºC, which resulted in a 25% increase in yield to 75% while maintaining complete deuterium incorporation (entry 10). Further reduction of the temperature to 90 ºC provided almost quantitative yield, but dramatically decreased deuterium incorporation to only 50% (entry 12). A range of inorganic bases were also examined for the catalytic system, such as sodium carbonate, lithium acetate, and sodium acetate. As shown in Table 9, sodium acetate as the base in the reaction resulted 100% deuterium incorporation at 110ºC, which led to the best yield. Conditions with sodium carbonate

needed higher temperatures to achieve 100% deuterium incorporation, and therefore presumably led to a higher rate of decomposition and lower yield.

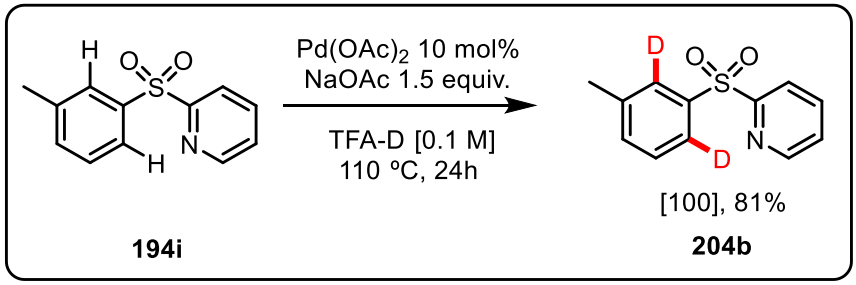
Table 9: Optimization of palladium catalyzed *ortho*-deuteration.



194a **204a**

Entry	Pd	Loading (mol%) & Hour	Temp (°C)	Base Loading	Solvent (Conc.)	% D	NMR Yield (%)
1	$Pd(OAc)_2$	10 & 18 h	120	Na_2CO_3 (1.5 equiv.)	AcOD-d4 (0.1 M)	29	70
2	$Pd(OAc)_2$	10 & 24 h	120	Na_2CO_3 (1.5 equiv.)	AcOD (0.1 M)	42	53
3	$Pd(OAc)_2$	30 & 24 h	120	Na_2CO_3 (1.5 equiv.)	AcOD (0.1 M)	50	57
4	$PdCl_2$	10 & 24 h	120	Na_2CO_3 (1.5 equiv.)	AcOD (0.1 M)	0	37
5	$Pd(OAc)_2$	10 & 24 h	120	Na_2CO_3 (1.5 equiv.)	$CDCl_3$ (0.1 M)	0	-
6	$Pd(OAc)_2$	10 & 24 h	120	Na_2CO_3 (1.5 equiv.)	D_2O & TFA	0	-
7	$Pd(OAc)_2$	10 & 24 h	120	Na_2CO_3 (1.5 equiv.)	TFA-D (0.1 M)	100	50
8	-	10 & 24 h	120	Na_2CO_3 (1.5 equiv.)	TFA-D (0.1 M)	0	-
9	$Pd(OAc)_2$	10 & 18 h	120	Na_2CO_3 (1.5 equiv.)	TFA-D (0.1 M)	78	57
10	**$Pd(OAc)_2$**	**10 & 24 h**	**110**	**NaOAc (1.5 equiv.)**	**TFA-D (0.1 M)**	**100**	**75**
11	$Pd(OAc)_2$	10 & 24 h	100	NaOAc (1.5 equiv.)	TFA-D (0.1 M)	70	78
12	$Pd(OAc)_2$	10 & 24 h	90	NaOAc (1.5 equiv.)	TFA-D (0.1 M)	50	98

Overall, at 110 ºC for 24 h, we obtained a 100% D incorporation into the both *ortho* positions with a yield of 75% estimated by ^1H NMR yield. The method has also been applied on *meta*-toluenesulfonylated pyridine (**194i**), and afforded a 100% deuterium incorporation with a yield of 81%. (Scheme 51).

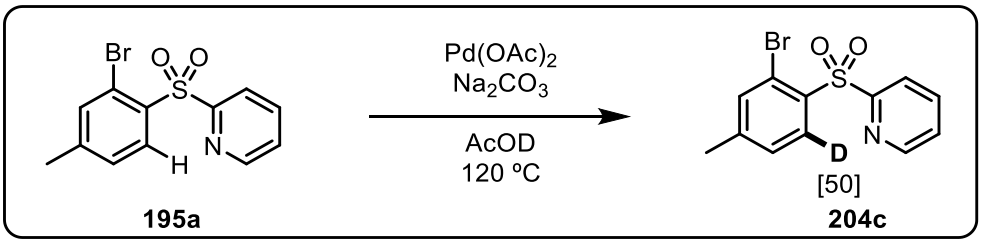


194i **204b**

Scheme 51: Deuteration with *meta*-toluenesulfonylated pyridine.

Another interesting preliminary observation was that 50% deuterium incorporation occurred when we applied the initial reaction conditions ($Pd(OAc)_2$, Na_2CO_3, AcOD at 120 ºC for 24 hours) on the brominated toluenesulfonylated pyridine (**195a**), with the bromine on the other *ortho*-position (see Scheme 52). The result is not yet optimized but offers intriguing potential, as

it indicates that the methods tolerates aryl bromides, and provides potentially access to more complex deuterated systems.



Scheme 52: Deuteration with brominated toluenesulfonylated pyridine (**195a**).

In the future, the conditions will be applied to other sulfonylated pyridines in order to verify functional group tolerance and steric influences. So far, bromine seems well tolerated, and therefore the next step is to test iodine, a more labile halogen functional group. More electron-rich and deficient systems will also be subject to examination. In terms of steric influences, the *meta* and *para* toluenesulfonylated pyridines seem to have the same results, and so *ortho* toluenesulfonylated pyridine will also be investigated.

The pyridine on the sulfonylated aromatics can be removed in order to access the sulfinic salts for the purpose of further functionalization. Overall, the method is highly selective, as we only observed deuterium on the ortho-positions. With such mild conditions, high deuterium incorporation and good yields have been observed. In the future, we would like to explore microwave irradiation, which could potentially reduce reaction times towards a more efficient strategy. The method complements existing H/D exchange protocols, and is potentially useful for later stage deuterium incorporation.

4.3 Experimental section

All reactions were performed in round bottom flask containing a Teflon-coated stir bar unless more specific conditions are stated. Chemicals were purchased from Aldrich, Alfa Aesar, or AK Scientific and used without further purification. All solvents were purchased as ACS grade from Fisher Scientific or JT Baker and distilled water was obtained from an in-house water distillery prior to use. Flash chromatography was carried out using 40-63μm silica gel (Silicycle). Melting points were obtained using a Stuart SMP30 bench apparatus. NMR spectra were recorded with Varian Inova 500MHz spectrometer and were referenced to the residual solvent signal or TMS signal. High resolution mass spectra (HRMS) were obtained using a LC-TOF ESI positive mode mass spectrometer.

General procedure of deuteration on sulfonylated pyridine:

The sulfonylated pyridine **194** (1 equiv., 0.1 mmol scale) in TFA-D was added to a microwave vial containing $Pd(OAc)_2$ (10 mol%, 0.01 mmol) and NaOAc (1.5 equiv. 0.2 mmol) under argon atmosphere. The mixture was heated to 110 ^oC and stirred for 24 h. The resulting mixture was cooled to room temperature and diluted with H_2O and EtOAc, then the organic portion was extracted with EtOAc (3X). The combined organic phases was washed with distilled water, followed by brine solution and then was dried over sodium sulfate and filtered. The solvent was then removed under reduced pressure to give the desired product *bis*-*ortho*-deuterated sulfonylated pyridine **204**.

Chapter 5: General Conclusion and Future Work

5.1 General Conclusion

The work presented in this thesis is aimed forward the development of new tools to access two adjacent functional groups on aromatic systems through sulfinate salts. Sulfinate salts as a starting material have many beneficial features, such as being bench stable and easy to manipulate experimentally. Most importantly, sulfinate salts are common coupling partners in a series of organic reactions and could be used either as an electrophilic or a nucleophilic coupling partner depending on the conditions employed. However, the major limitation restricting the use of sulfinate salts in organic synthesis, especially in multi-step synthesis, is their instability in solution. When the sulfinates are protonated to the corresponding sulfinic acid, these can undergo self-disproportionation leading to undesired side-products such as sulfonic acid and sulfonothioate. In this thesis, we proposed to install a directing group for *ortho*-functionalization and then removal of this additional group to reveal the sulfinate salts. Towards this end, sulfonylated pyridine was chosen. The pyridine functional groups on the sulfonylated pyridines acted as a directing group for *ortho*-functionalization and the subsequent corresponding sulfinate salts were obtained by removal of the pyridine group.

Previously reported methods for the formation of sulfonylated pyridines employed pyridine halides as the limiting reagents, and in order to use pyridine substituent as a directing tool, suitable reaction conditions using sulfinate salts as limiting reagents was explored. For this purpose, we used a cheap and readily available Lewis acid $FeCl_3$ as the catalyst and obtained the desired products—sulfonylated pyridines with good to excellent yields. Interestingly, reaction yield increased when the reaction was performed at larger scale (10 to 30 mmol). Different pyridine halides and sulfinate salts were used as substrates for the reaction. The small substituents, such as methyl substituents, at various positions on the pyridine, has no significant steric influence on the yield. Alternatively for the sulfinate salts, we observed yields decreasing with *ortho*-toluene sulfinate salt. In addition, the mechanism of the reaction was also investigated and ruled out that $FeCl_3$ act as hydrochloric acid source. Preliminary results suggested a potential radical mechanism but there was no definitive proof, and the reaction could undergo multiple pathways. Overall the method provides a complementary route to access sulfonylated pyridines using sulfinate salts as the limiting reagents.

Once the sulfonylated pyridines were obtained, we utilized the pyridine as a directing group for *ortho* functionalization. In the thesis we demonstrated the palladium catalyzed *ortho*-directed halogenation in chapter 2 and *ortho*-deuteration in chapter 3. With a palladium (II) catalyst,

pyridine-directed halogenation on sulfonylated pyridines resulted in the corresponding *ortho*-halogenated products in good to excellent yields using either trifluoroethanol (TFE) or dichloroethane (DCE) as solvent. Other solvents were also examined in the reaction and most of them resulted in lower yields. Interestingly with ethanol, which is non-fluorinated version of TFE, there was no conversion at all. The results indicated the acidity of solvent may be playing an important role. The optimized temperature for reactions were between 80 º to 120 ºC with a time of 18h. The halogenation reaction tolerated both electron-rich and electron-deficient substituents. The undesired *bis*-halogenation products were always observed but with the optimized conditions, the production of the side products was minimized. We also investigated the mechanism of the reaction and the preliminary studies suggest a nucleophilic substitution is unlikely since the KIE data indicated the C-H bond cleavage is the rate-limiting step. In addition to the *ortho*-halogenation, we also developed a pyridine directed *ortho*-deuteration with $Pd(OAc)_2$ as catalyst. With the deuteration reaction, the TFA-D acts both as a deuterium source and solvent. With the optimized conditions, we were able to achieve 75% yield with full deuterium incorporation. The deuteration is a sensitive reaction, and moisture or any proton source contamination resulted in decreasing deuterium incorporation and could even lead to no deuteration. Deuterated compounds are useful tools in understanding mechanisms of organic reactions or metabolism, and furthermore deuterium was could potentially benefit the profile of drug candidates. In this thesis, we demonstrated a useful method that will be useful to access some *ortho*-deuterated scaffolds.

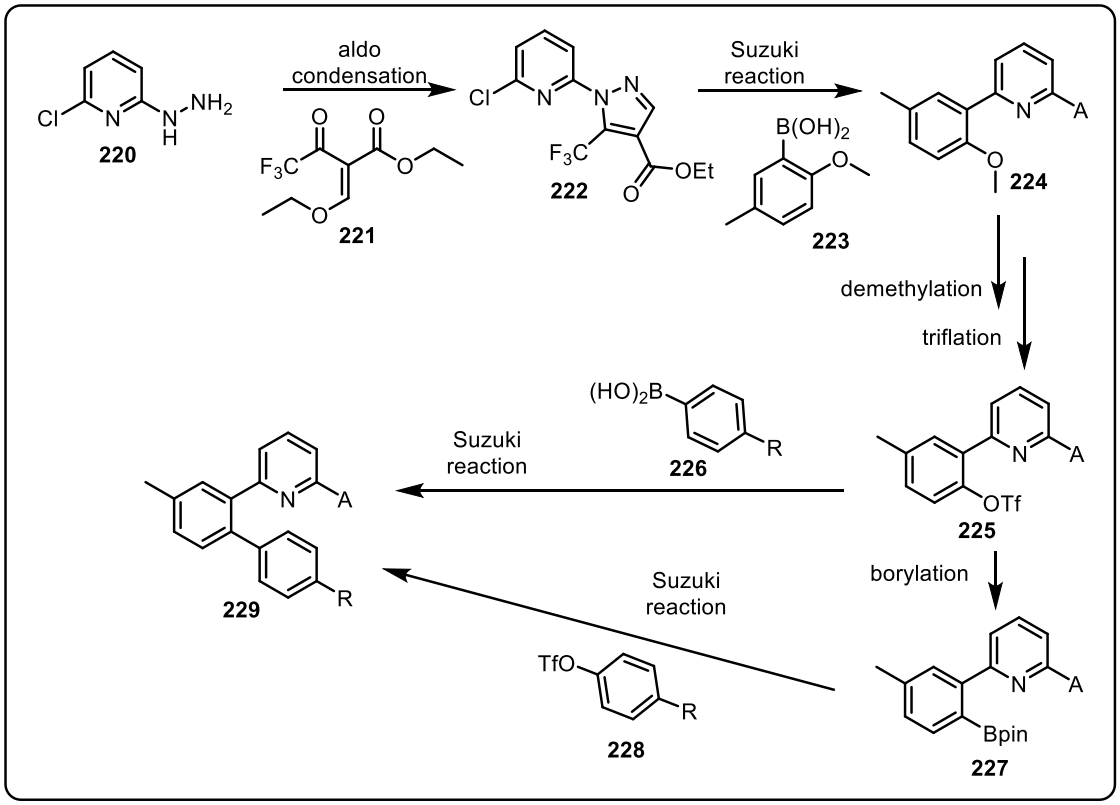
Finally, with *ortho*-functionalized sulfonylated pyridines, removal of the pyridine to regain the properties of sulfinate salts allowed the further functionalization of the sulfinate salts. In this thesis, we demonstrated the removal of pyridine substituent on halogenated sulfonylated pyridine. The electronic differences between pyridine and aromatic ring system allowed us to perform a regioselective S_NAr reaction for the removal the pyridine. With electron-rich or neutral aromatic systems, the strategy worked well and we obtained the corresponding sulfinate salts in good to excellent yields. However with electron-deficient aromatic systems, the electronic difference between the pyridine and arenes is small or negligible, causing poor S_NAr selectivity, especially when a halogen group was installed in the *ortho* position. Furthermore, in order to use the method, the *ortho* functional group needs to be carry through the pyridine removal condition, which means stable with the thiol nucleophile and under the modular temperature. Unfortunately, the removal method did not tolerate iodo functional groups at the *ortho* position, de-iodination was observed in all cases.

Overall, we illustrated a pathway to access *ortho* functionalized sulfinate salts, through installation the pyridine functional group and employing it as a directing group for *ortho* functionalization.

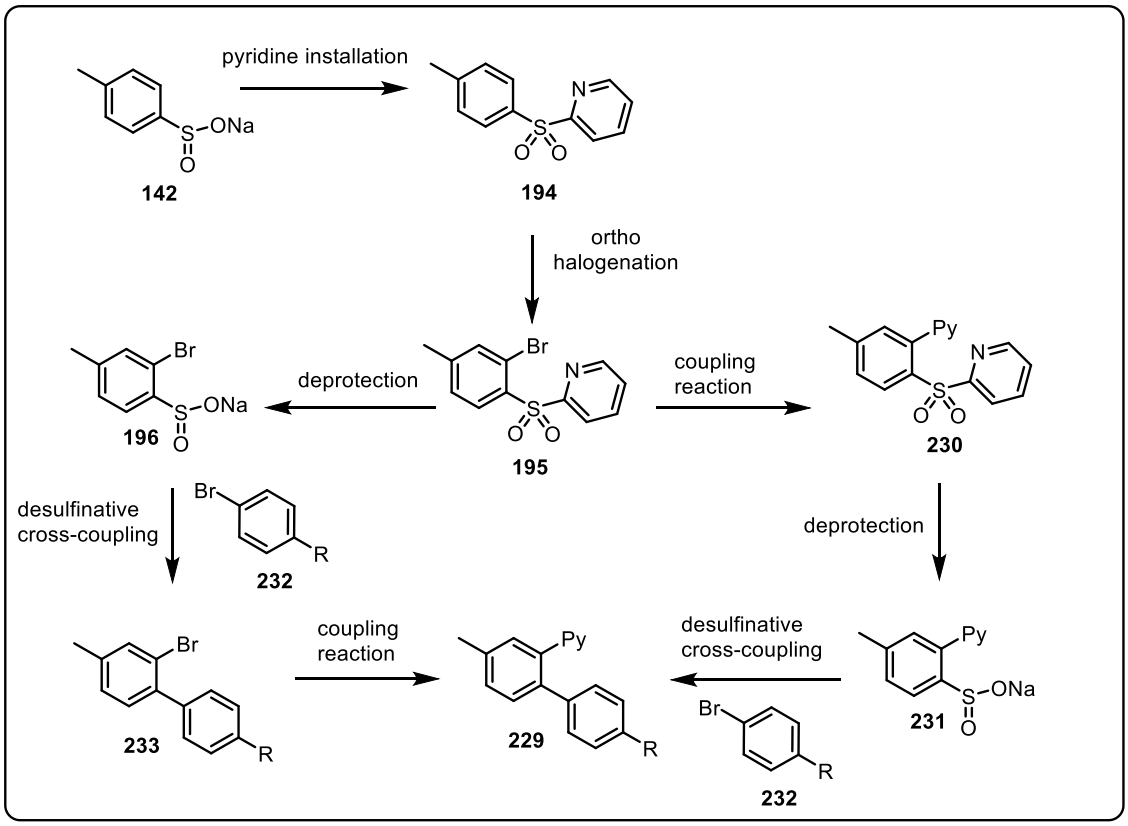
5.2 Future Work

We demonstrated a methodology using pyridine substituted sulfonylated pyridines as directing groups for *ortho* functionalization, such as halogenation and deuteration. An interesting aspect of having halogenated substituents in the *ortho* position is that they could be potentially employed to access other functional groups, as they are commonly used electrophilic coupling partners in various cross coupling reactions. Our halogenated sulfonylated pyridines could be suitable substrates for coupling reactions in order to access more complex *ortho* functionalized scaffolds.

One of the potential targets could be an *ortho*-substituted aromatic compound **229**, which is a potential drug candidate against a number of diseases from heart attack to cancer.[153c] The synthetic route used started from the functionalization of the hydrazide in 2-chloro-6-hydrazinylpyridine **220** through an aldol-condensation. Then the compound **222** undergoes a Suzuki-Miyaura reaction with (2-methoxy-5-methylphenyl)boronic acid **223** through the chloro functional group. In the next step, the methoxyl group (**224**) has been transformed into a triflate (**225**) *via* a demethylation and triflation. In order to access the core structures **229**, a second Suzuki-Miyaura reaction was performed with another boronic acid **226**. Furthermore, in order to perform the Suzuki-Miyaura reaction with electrophilic coupling partners **228**, a borylation had to be performed to access compound **227** (see Scheme 53). The reported pathway functionalized pyridine building block **220** in the first step and then followed with the addition of another two aromatic systems. This synthetic sequence increased the difficulties of SAR studies on pyridine systems. Using our methods to prepare the core structure **229** and depending on the needs of SAR studies, the synthesis could started from key intermediate **195**, and the pyridines or the other aromatic functional groups could be installed accordingly at the last step. For example, to explore the SAR on various pyridine building blocks, the pyridine removal and desulfinative cross coupling could be performed from intermediate **195** to access the compound **233**, then different pyridine functional groups could be installed as in Scheme 54.

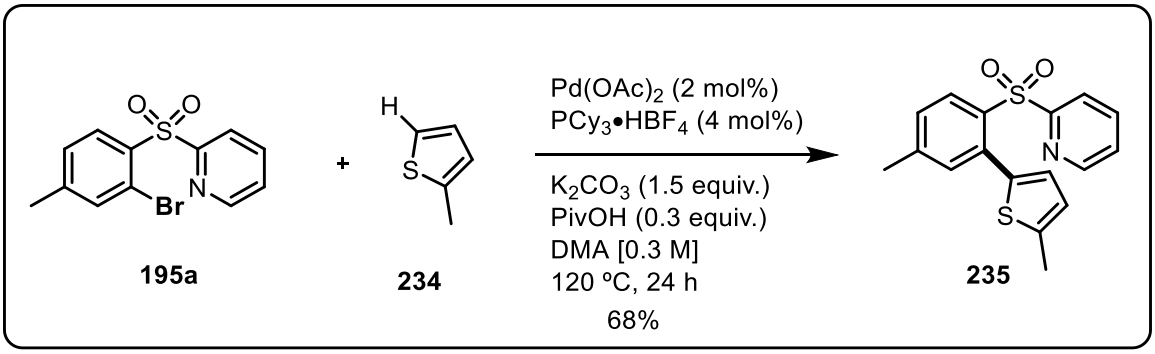


Scheme 53: Reported synthetic pathway in Patent.



Scheme 54: Synthesis using our method.

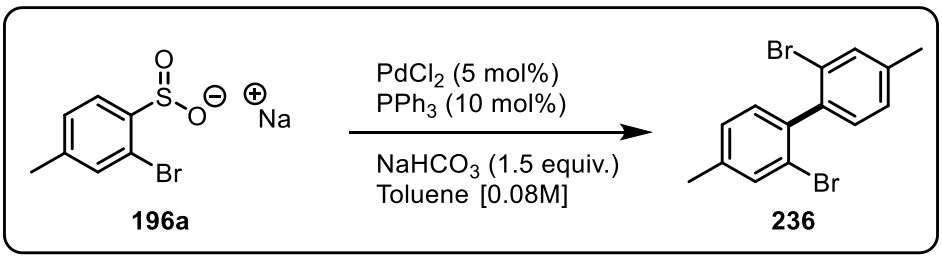
Using our method to access the core **229**, the steps to access the halogenated sulfonylated pyridine **195** were already demonstrated in previous chapters, and the halogen group could be used as electrophilic coupling partners to access other functional groups *via* coupling reactions such as C-H activation, Suzuki-Miyaura reactions, Heck type and Buchwald couplings, for compound (**230**) or final product **229**. A preliminary C-H activation was performed with 2-methylthiophene **234** and the corresponding product **235** with a 68% NMR yield. The promising result indicated the environmentally benign C-H arylation is suitable for further *ortho*-functionalization with halogenated sulfonylated pyridines **195**, and future work on the optimization and scope of this transformation will need to be examined.



Scheme 55: Preliminary result in C-H arylation on halogenated sulfonylated pyridine.

Furthermore after removal of the pyridine functional group, the sulfinate salts could also be used in coupling reactions as proposed in Scheme 54 to access the key intermediate **233** or the final core (**229**) through desulfinative cross coupling. Indeed with compound **196a**, a desulfinative homo-coupling reaction was performed and the major product (**236**) was identified. This homo-coupling reaction indicated that the sulfinate salts are reactive and can undergo desulfinative couplings.

Additionally, as the major product is the homo coupling of the sulfinate salts, the result indicated that the desulfinative homo coupling is faster than desulfinative cross coupling and homo-coupling of the bromide functional groups. The reaction rate difference allowed us to selectivity react sulfinate salts in the presence of halogen functional groups.



Scheme 56: Preliminary result of desulfinative homo-coupling.

Based on the previous results, future work on the project would be the investigation on various reactions with halogen functional group in compound **195** or applying different coupling reactions with sulfinate salts in **196**. Both investigations will allow us to access a library of compounds with an active *ortho*-functional groups, either halogen substituents or sulfinate salts, which could be further diversified. The key core **195** provided discretionary pathways that will be able to meet varied needs in organic synthesis in accessing the bis-*ortho*-functionalized scaffolds, such as for compound **229**.

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Appendices

A Convenient and Inexpensive Route to Access Sulfonylated Pyridines via a S_NAr Reaction of Electron-Rich Pyridines through Iron Catalyst

Fei Chen, Franklin Chacon-Huete, Hassan El-Husseini and Pat Forgione*

Department of Chemistry & Biochemistry, Concordia University, 7141 rue Sherbrooke O. H4B 1R6, Montréal, QC, Canada and Centre for Green Chemistry and Catalysis

Supporting information

2-tosylpyridine (194a) CAS: 51954-53-1

Colorless solid. Prepared following general procedure in chapter 2 unless specified. Synthesized from sulfinate salt **142a** with different halo-pyridines (**193a – d**)

Yield: 308.4 mg, 66% (**193a** with no degassed solvent). Yield: 56.1 mg, 12% (**193b** with no degassed solvent). Yield: 368.6 mg, 79% (**193c**). Yield: 415.2 mg, 89% (**193d**).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.67 (ddd, *J* = 4.7, 1.7, 0.8 Hz, 1H), 8.19 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 2H), 7.92 (td, *J* = 7.9, 1.7 Hz, 1H), 7.45 (ddd, *J* = 7.9, 4.7, 1.0 Hz, 1H), 7.33 (dd, *J* = 8.5, 0.8 Hz, 2H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.13, 150.40, 144.82, 138.04, 135.93, 129.78 (2C), 128.96 (2C), 126.74, 122.01, 21.65.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{11}NO_2S$: 234.0583; found: 243.0583.

3-methyl-2-tosylpyridine (194b) CAS: 1258786-30-9

Colorless solid. Synthesized following general procedure in chapter 2 from sulfinate salt **142a** with halo-pyridine **193e** or **193j**.

Yield: 387.9 mg, 78% (**193e**). Yield: 421.9 mg, 85% (**193j**).

^{1}H NMR (CDCl3, 500 MHz): δ 8.39 (dd, J = 4.6, 1.5 Hz, 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 7.3 Hz, 1H), 7.34 – 7.28 (m, 3H), 2.74 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (CDCl3, 125 MHz): δ 156.76, 146.43, 144.50, 141.31, 136.32, 133.36, 129.50 (2C), 129.02 (2C), 126.53, 21.68, 18.86.

HRMS (EI): m/z $[M + H]^+$ calcd for C13H13NO2S: 248.0740; found: 248.0740.

4-methyl-2-tosylpyridine (194c) CAS: 51954-51-9

Colorless solid. Synthesized following general procedure in chapter 2 from sulfinate salt **142a** with halo-pyridine **193f**.

Yield: 381.8 mg, 77%.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.51 (d, *J* = 4.6 Hz, 1H), 8.02 (s, 1H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 4.6 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.93, 150.14, 149.94, 144.69, 136.10, 129.74 (2C), 128.90 (2C), 127.49, 122.76, 21.65, 21.25.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{13}NO_2S$: 248.0740; found: 248.0735.

5-methyl-2-tosylpyridine (194d) CAS: 51954-52-0

Colorless solid. Synthesized following general procedure in chapter 2 from sulfinate salt **142a** with halo-pyridine **193g**.

Yield: 334.1 mg, 68%.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.49 (d, *J* = 1.7 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.69 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 2.41, 2.39 (2s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.41, 150.92, 144.57, 138.08, 137.41, 136.36, 129.73 (2C), 128.78 (2C), 121.79, 21.63, 18.50.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{13}NO_2S$: 248.0740; found: 248.0740.

6-methyl-2-tosylpyridine (194e)

Colorless solid. Synthesized following general procedure in chapter 2 from sulfinate salt **142a** with halo-pyridine **193h**.

Yield: 357.1 mg, 72%.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.97 (m, 3H), 7.76 (t, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 1H), 2.56 (s, 3H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.21, 158.29, 144.52, 137.83, 136.27, 129.62 (2C), 128.97 (2C), 126.63, 119.13, 24.39, 21.64.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{13}NO_2S$: 248.0740; found: 248.0740.

3-methoxy-2-tosylpyridine (194f) CAS: 1258786-31-0

Colorless solid. Synthesized following general procedure in chapter 2 from sulfinate salt **142a** with halo-pyridine **193i**.

Yield: 255.1 mg, 48%.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.23 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.43 (dd, *J* = 8.4, 4.5 Hz, 1H), 7.33 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 3.87 (s, 3H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 154.02, 146.08, 144.49, 140.50, 136.75, 129.31 (2C), 129.08 (2C), 128.79, 121.14, 56.13, 21.65.

HRMS (EI): *m*/*z* $[M - H]^-$ calcd for $C_{13}H_{13}NO_3S$: 262.05433; found: 262.0545.

4-tosylpyridine (194g) CAS: 66154-65-2

Colorless solid. Synthesized following general procedure in chapter 2 from sulfinate salt **142a** with halo-pyridine **193k**.

Yield: 286.8 mg, 61%.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.81 (d, *J* = 6.0 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 6.0 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 151.13 (2C), 150.12, 145.40, 136.68, 130.26 (2C), 128.18 (2C), 120.47 (2C), 21.65.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{11}NO_2S$: 234.0583; found: 234.0583.

2-(phenylsulfonyl)pyridine (194h) CAS: 24244-60-8

Colorless solid. Synthesized following general procedure in chapter 2 from sulfinate salt **142b** with bromo-pyridine **193c** or iodo-pyridine **193d**.

Yield: 311.5 mg, 71% (**193c**). Yield: 360.0 mg, 82% (**193d**).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.67 (ddd, *J* = 4.7, 1.7, 1.0 Hz, 1H), 8.21 (dt, *J* = 7.9, 1.0 Hz, 1H), 8.10 – 8.04 (m, 2H), 7.93 (td, *J* = 7.9, 1.7 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.57 – 7.51 (m, 2H), 7.46 (ddd, *J* = 7.7, 4.7, 1.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.84, 150.46, 138.95, 138.09, 133.74, 129.10 (2C), 128.92 (2C), 126.90, 122.19.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_9NO_2S$: 220.0427; found: 220.0427.

2-(*m*-tolylsulfonyl)pyridine (194i) CAS: 2139245-00-2

Colorless solid. Synthesized following general procedure in chapter 2 from sulfinate salt **142c** with bromo-pyridine **193c** or iodo-pyridine **193d**.

Yield: 323.6 mg, 70% (**193c**). Yield: 360.5 mg, 78% (**193d**).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.67 (ddd, *J* = 4.7, 1.7, 1.0 Hz, 1H), 8.20 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.93 (td, *J* = 7.9, 1.7 Hz, 1H), 7.89 – 7.82 (m, 2H), 7.46 (ddd, *J* = 7.9, 4.7, 1.0 Hz, 1H), 7.43 – 7.39 (m, 2H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.92, 150.45, 139.38, 138.79, 138.08, 134.58, 129.15, 128.98, 126.86, 126.04, 122.20, 21.30.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{11}NO_2S$: 234.0583; found: 234.0585.

2-(*o*-tolylsulfonyl)pyridine (194j) CAS: 2139245-01-3

Colorless solid. Synthesized following general procedure in chapter 2 from sulfinate salt **142d** with bromo-pyridine **193c** or iodo-pyridine **193d**.

Yield: 197.2 mg, 42% (**193c**). Yield: 216.8 mg, 46% (**193d**).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.64 (ddd, *J* = 4.7, 1.7, 1.0 Hz, 1H), 8.27 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.21 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.96 (td, *J* = 7.9, 1.7 Hz, 1H), 7.50 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.48

(ddd, *J* = 7.6, 4.7, 1.0 Hz, 1H), 7.42 (dddd, *J* = 7.9, 7.6, 1.3, 0.7 Hz, 1H), 7.26 (ddt, *J* = 7.6, 1.3, 0.7 Hz, 1H), 2.48 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.99, 150.25, 138.68, 137.96, 136.82, 133.96, 132.46, 130.68, 126.90, 126.50, 122.27, 20.43.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{11}NO_2S$: 234.0583; found: 234.0584.

2-((4-methoxyphenyl)sulfonyl)pyridine (194k) CAS: 121346-51-8

Colorless solid. Synthesized following general procedure in chapter 2 from sulfinate salt **142e** with bromo-pyridine **193c** or iodo-pyridine **193d**.

Yield: 310.4 mg, 62% (**193c**). Yield: 438.4 mg, 88% (**193d**).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.67 (ddd, *J* = 4.7, 1.7, 1.0 Hz, 1H), 8.18 (d, *J* = 7.9 Hz, 1H), 8.00 (d, *J* = 9.0 Hz, 2H), 7.91 (td, *J* = 7.9, 1.7 Hz, 1H), 7.44 (ddd, *J* = 7.9, 4.7, 1.0 Hz, 1H), 7.00 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.89, 159.41, 150.36, 138.00, 131.19 (2C), 130.28, 126.60, 121.79, 114.40 (2C), 55.64.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{11}NO_3S$: 250.0532; found: 250.0533.

2-((4-(trifluoromethyl)phenyl)sulfonyl)pyridine (194l) CAS: 2139244-99-6

Colorless solid. Synthesized following general procedure in chapter 2 from sulfinate salt **142g** with bromo-pyridine **193c** or iodo-pyridine **193d**.

Yield: 442.4 mg, 77% (**193c**). Yield: 452.9 mg, 78% (**193d**).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.69 (ddd, *J* = 4.7, 1.7, 1.0 Hz, 1H), 8.27 – 8.18 (m, 3H), 7.97 (td, *J* = 7.7, 1.7 Hz, 1H), 7.85 – 7.78 (m, 2H), 7.51 (ddd, *J* = 7.7, 4.7, 1.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.13, 150.63, 142.47, 138.25, 135.35 (q, *J* = 33.1 Hz), 129.61 (2C), 127.28, 126.18 (q, *J* = 3.8 Hz, 2C), 123.13 (q, *J* = 272.68 Hz), 122.36.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_8F_3NO_2S$: 288.0301; found: 288.0299.

2-(naphthalen-1-ylsulfonyl)pyridine (194m)

Colorless solid. Synthesized following general procedure in chapter 2 from sulfinate salt **142h** with bromo-pyridine **193c** or iodo-pyridine **193d**.

Yield: 220.6 mg, 41% (**193c**). Yield: 318.7 mg, 59% (**193d**).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.72 – 8.67 (m, 1H), 8.62 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.60 (ddd, *J* = 4.7, 1.7, 1.0 Hz, 1H), 8.33 (dt, *J* = 7.9, 1.0 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.99 – 7.90 (m, 2H), 7.67 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.62 – 7.50 (m, 2H), 7.43 (ddd, *J* = 7.7, 4.7, 1.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.10, 150.18, 138.05, 135.51, 134.11, 133.98, 131.39, 128.97, 128.94, 128.30, 126.89, 126.81, 124.70, 124.48, 122.32.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{11}NO_2S$: 270.0583; found: 270.0584.

2-(naphthalen-2-ylsulfonyl)pyridine (194n)

Colorless solid. Synthesized following general procedure in chapter 2 from sulfinate salt **142i** with bromo-pyridine **193c** or iodo-pyridine **193d**.

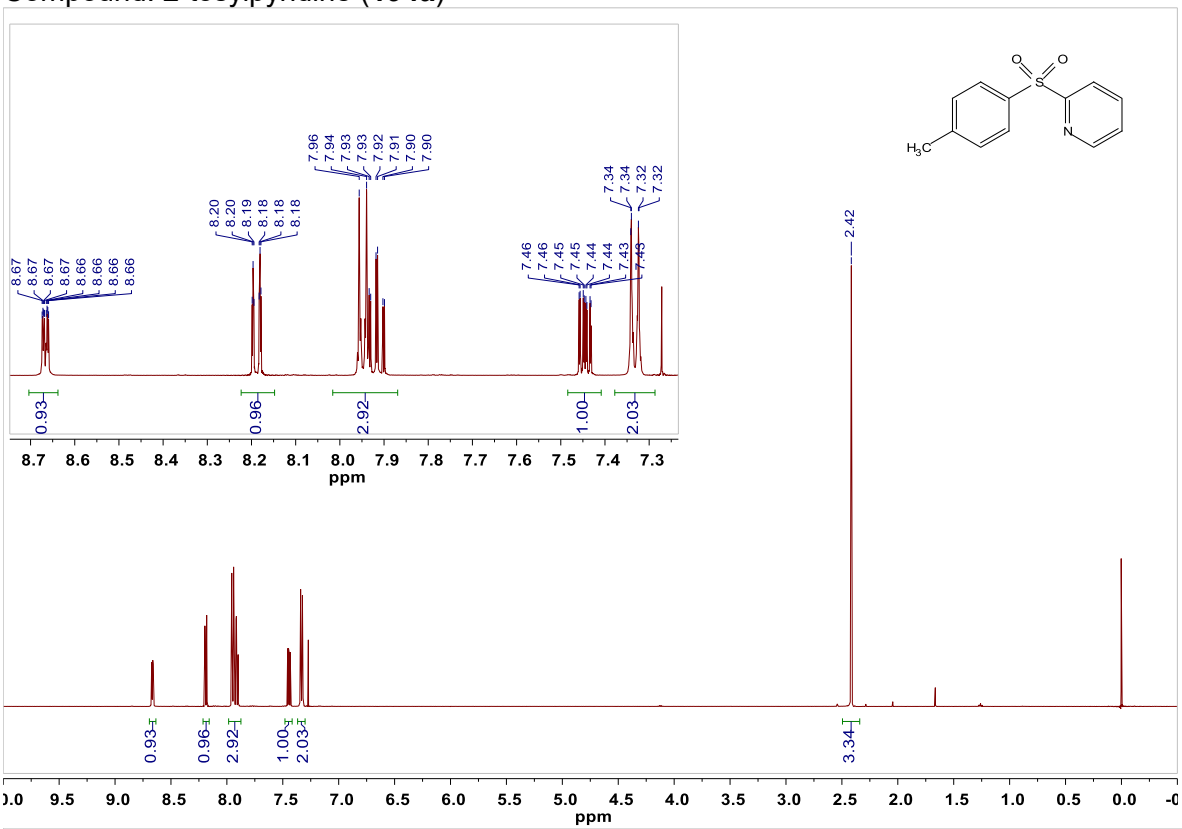
Yield: 140.1 mg, 26% (**193c**). Yield: 144.9 mg, 27% (**193d**).

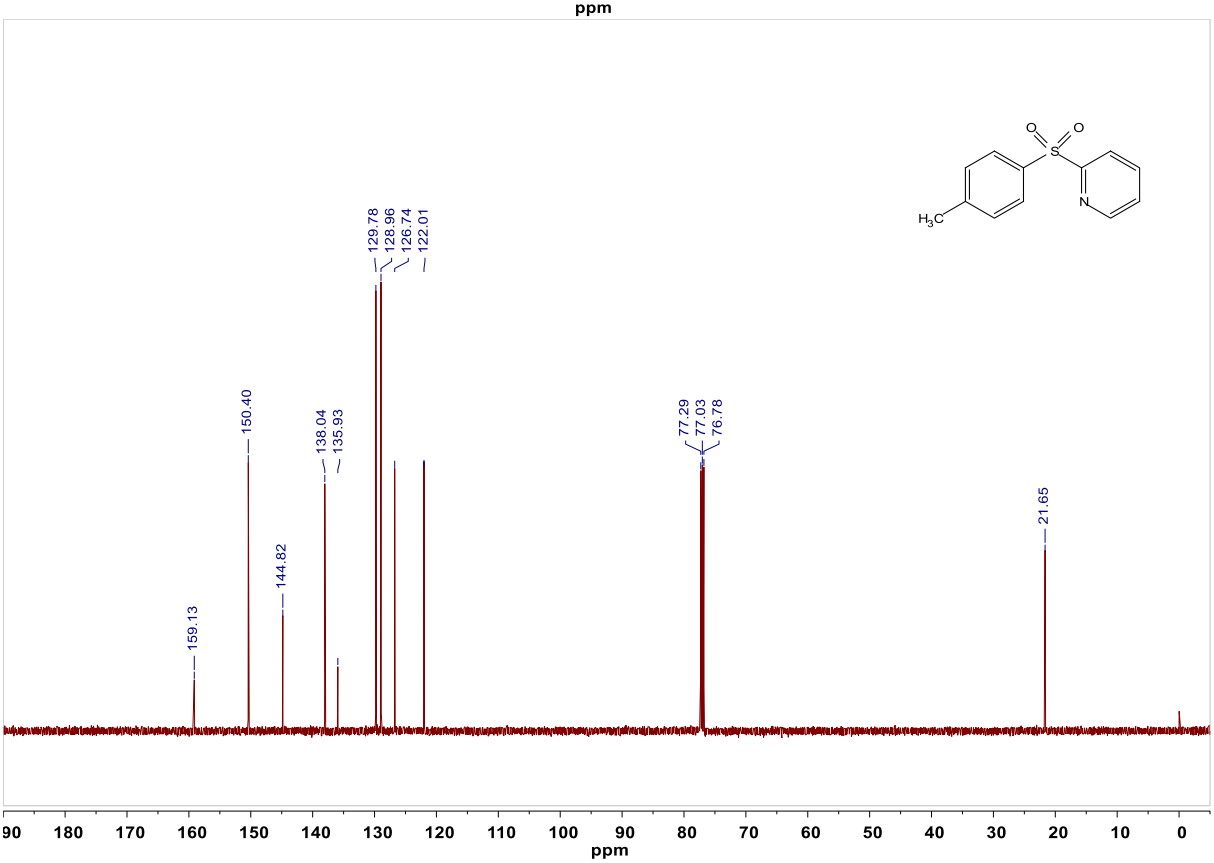
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.70 (s, 1H), 8.67 (d, *J* = 4.7 Hz, 1H), 8.28 (d, *J* = 7.9 Hz, 1H), 8.05 – 7.84 (m, 5H), 7.64 (m, 2H), 7.45 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.95, 150.48, 138.08, 135.84, 135.36, 132.17, 130.82, 129.55, 129.33, 129.31, 127.92, 127.54, 126.84, 123.55, 122.26.

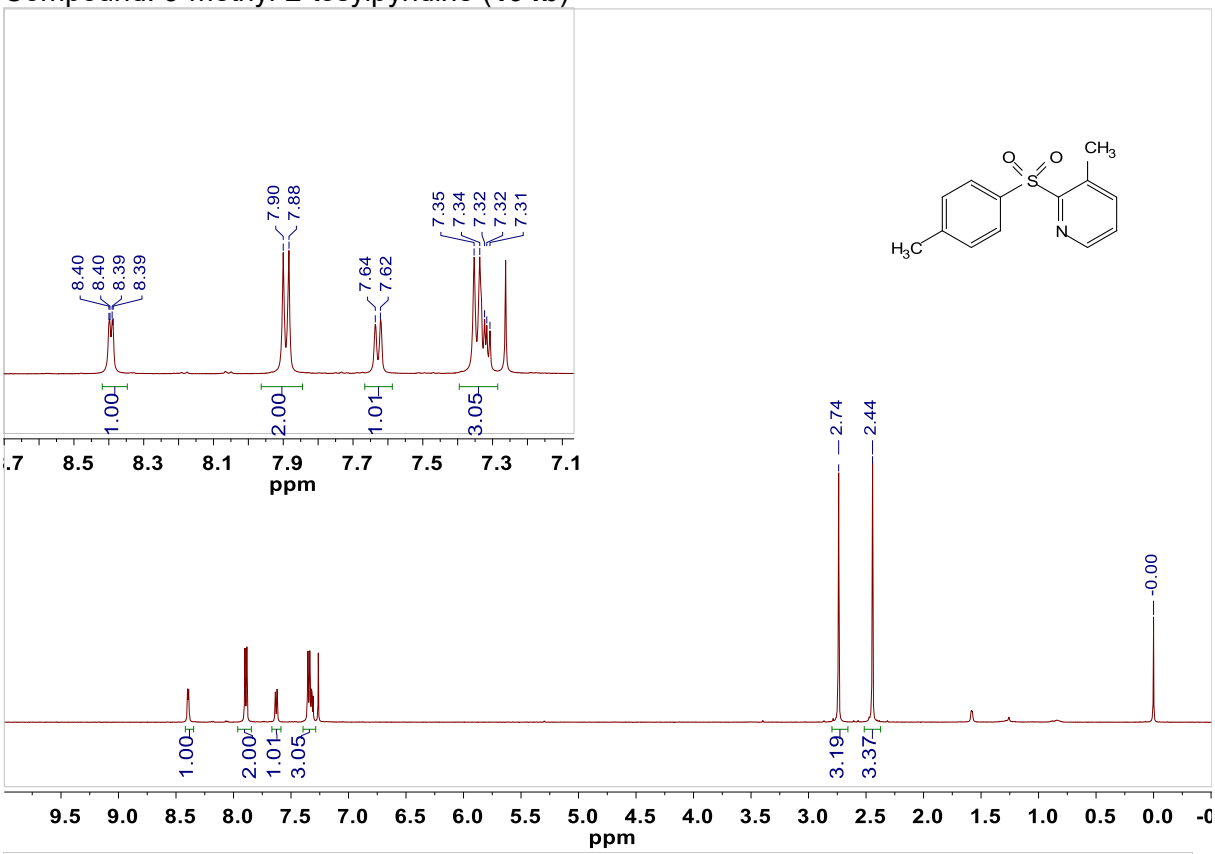
HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{11}NO_2S$: 270.0583; found: 270.0582.

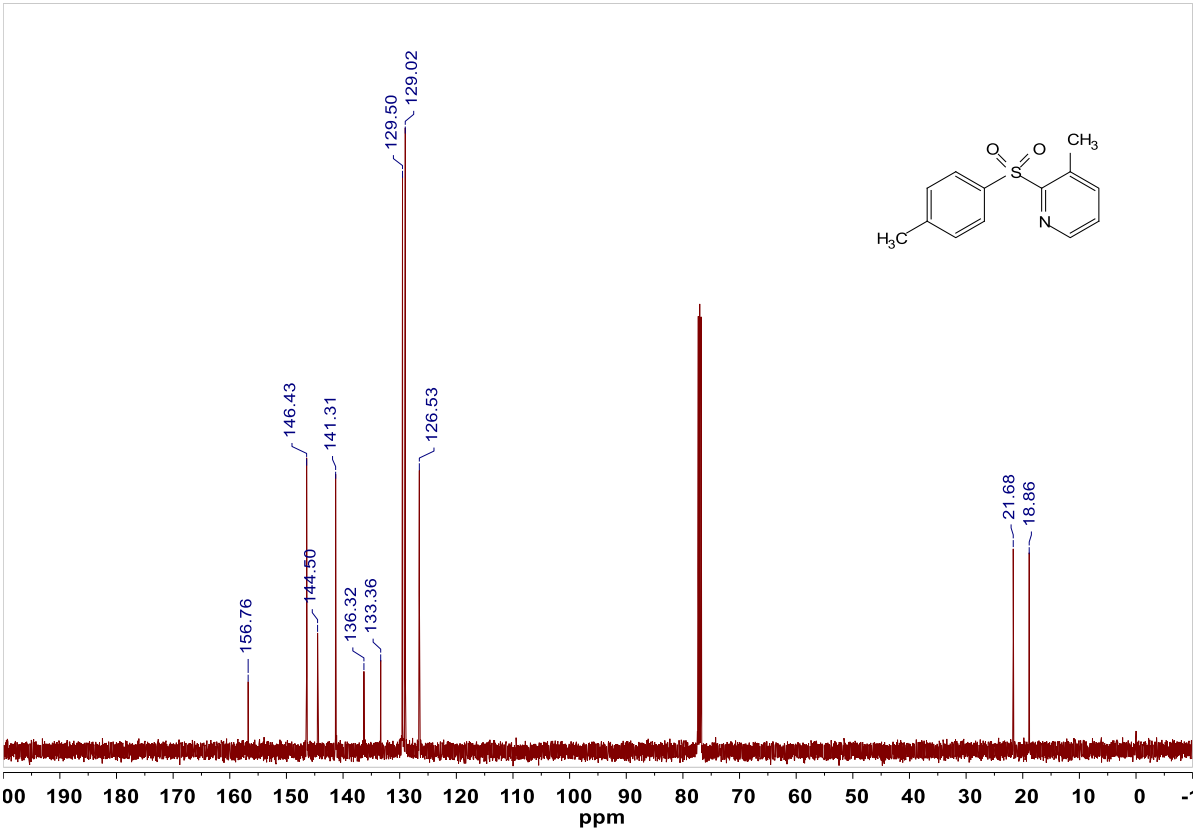
Compound: 2-tosylpyridine (**194a**)



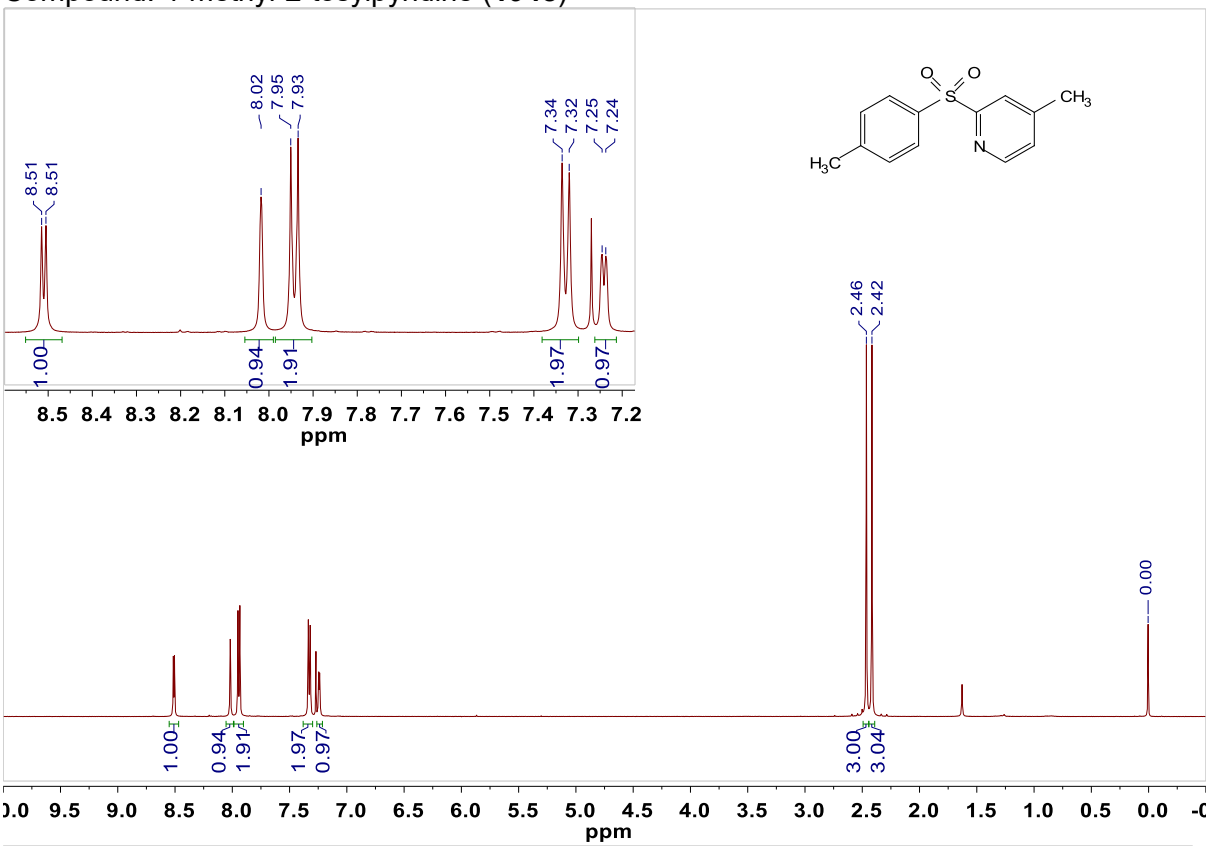


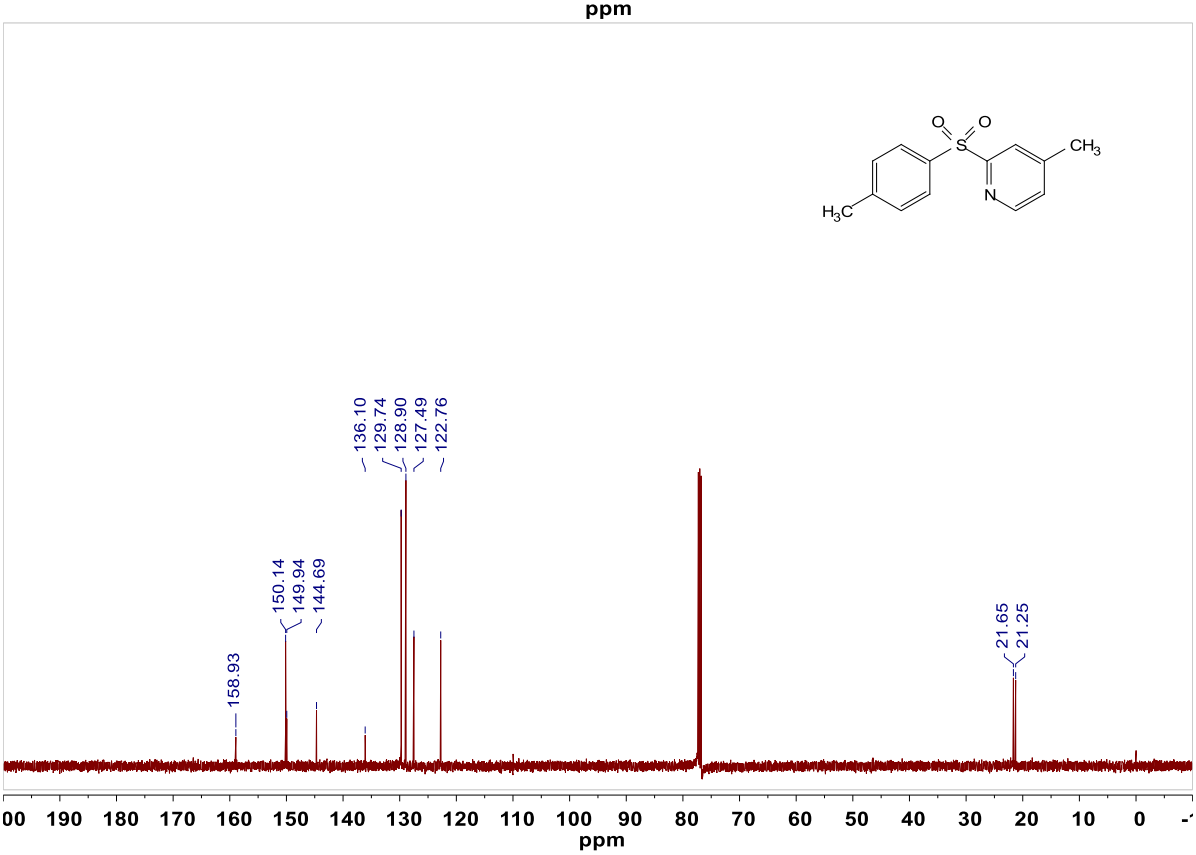
Compound: 3-methyl-2-tosylpyridine (**194b**)



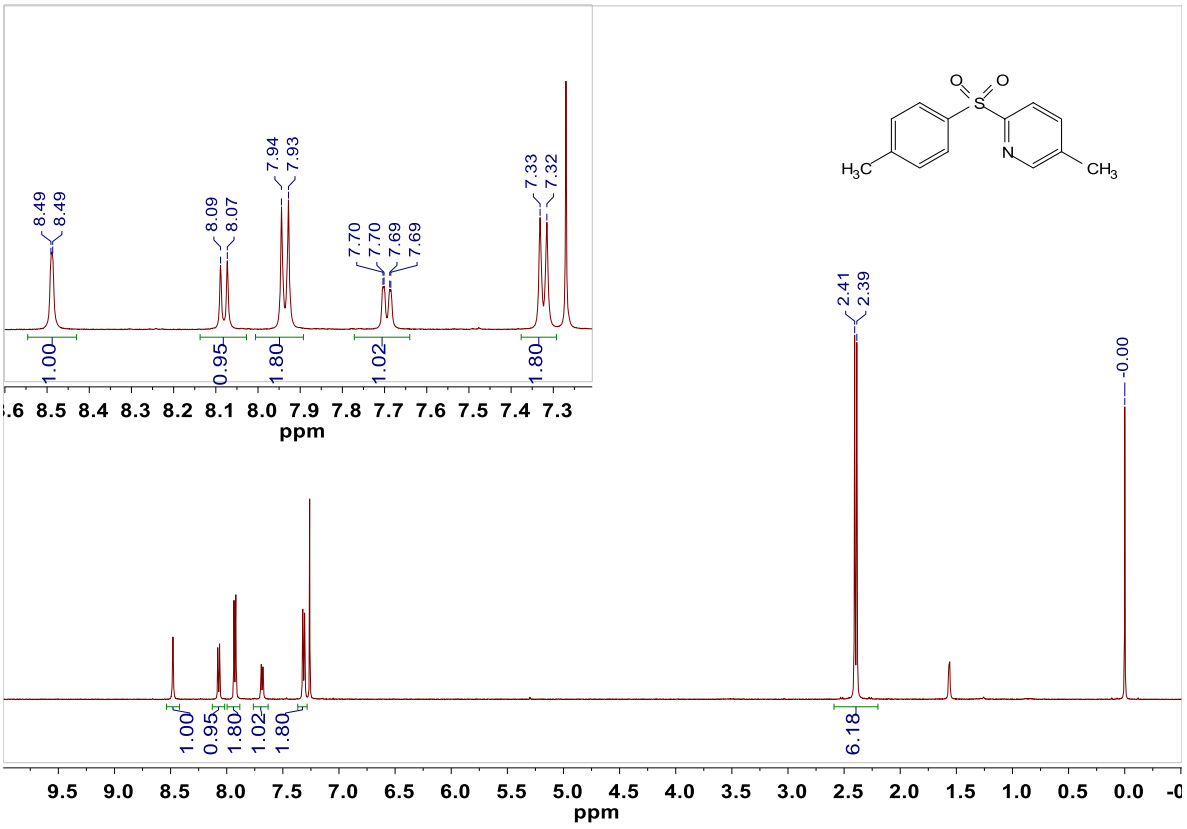


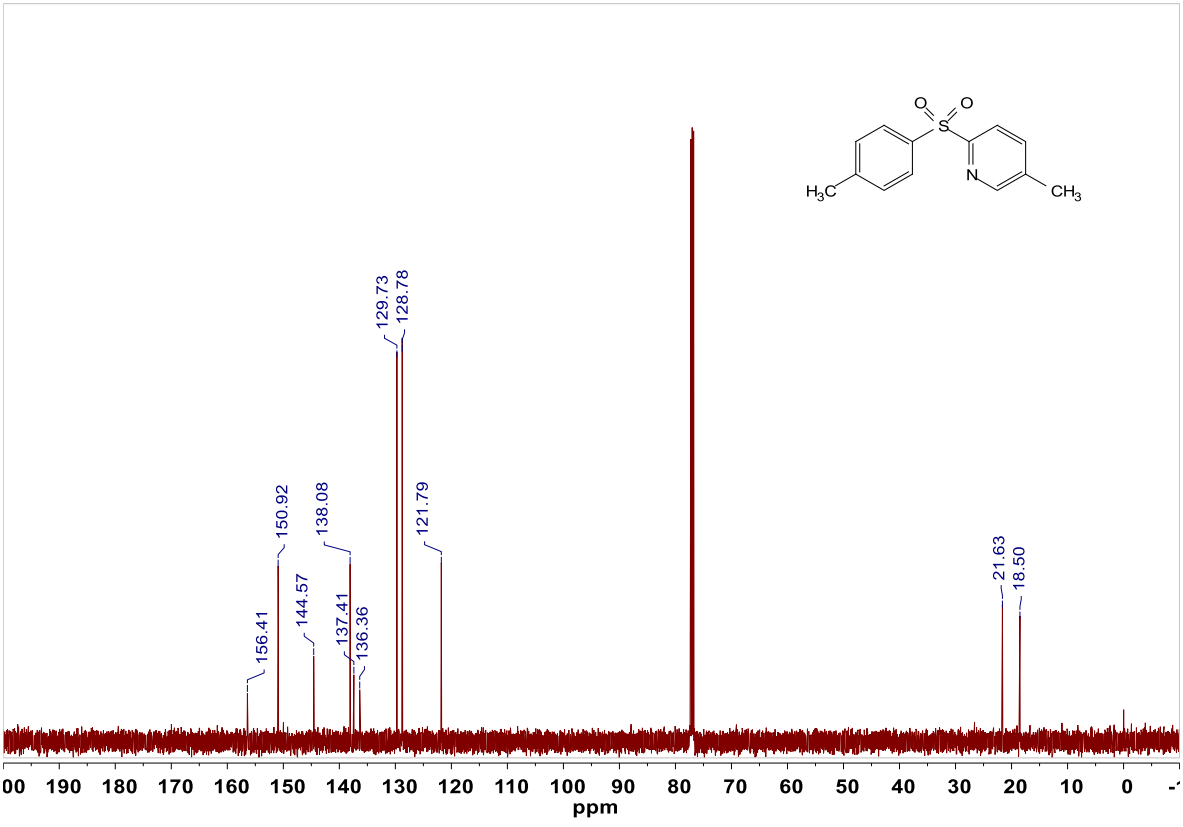
Compound: 4-methyl-2-tosylpyridine (**194c**)



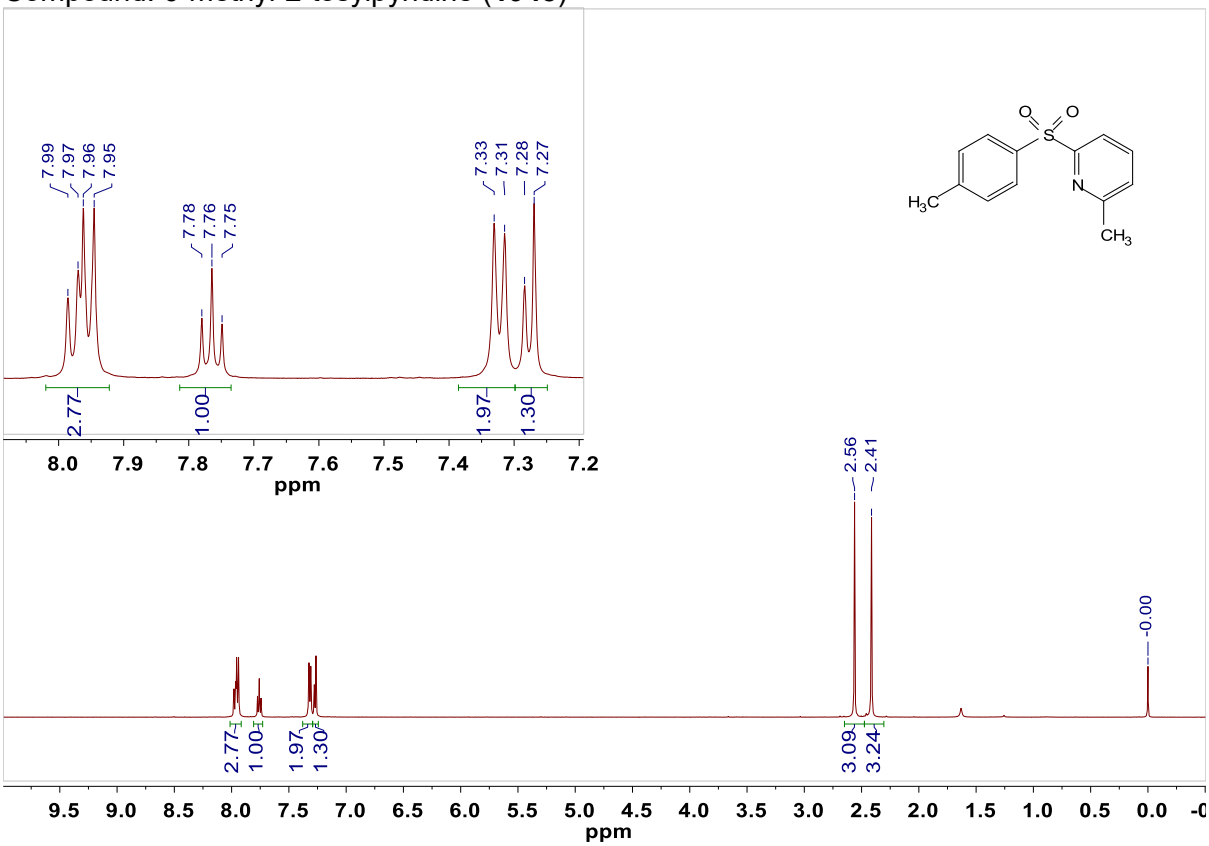


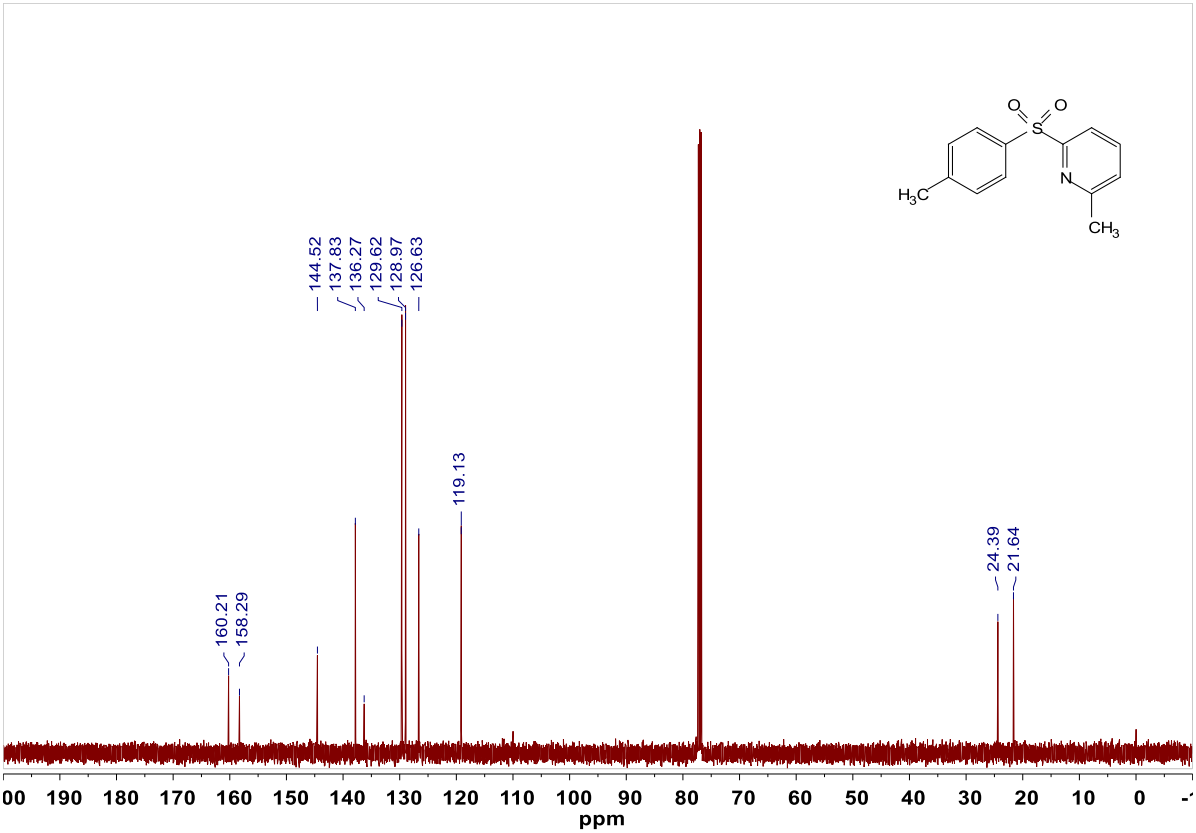
Compound: 5-methyl-2-tosylpyridine (**194d**)



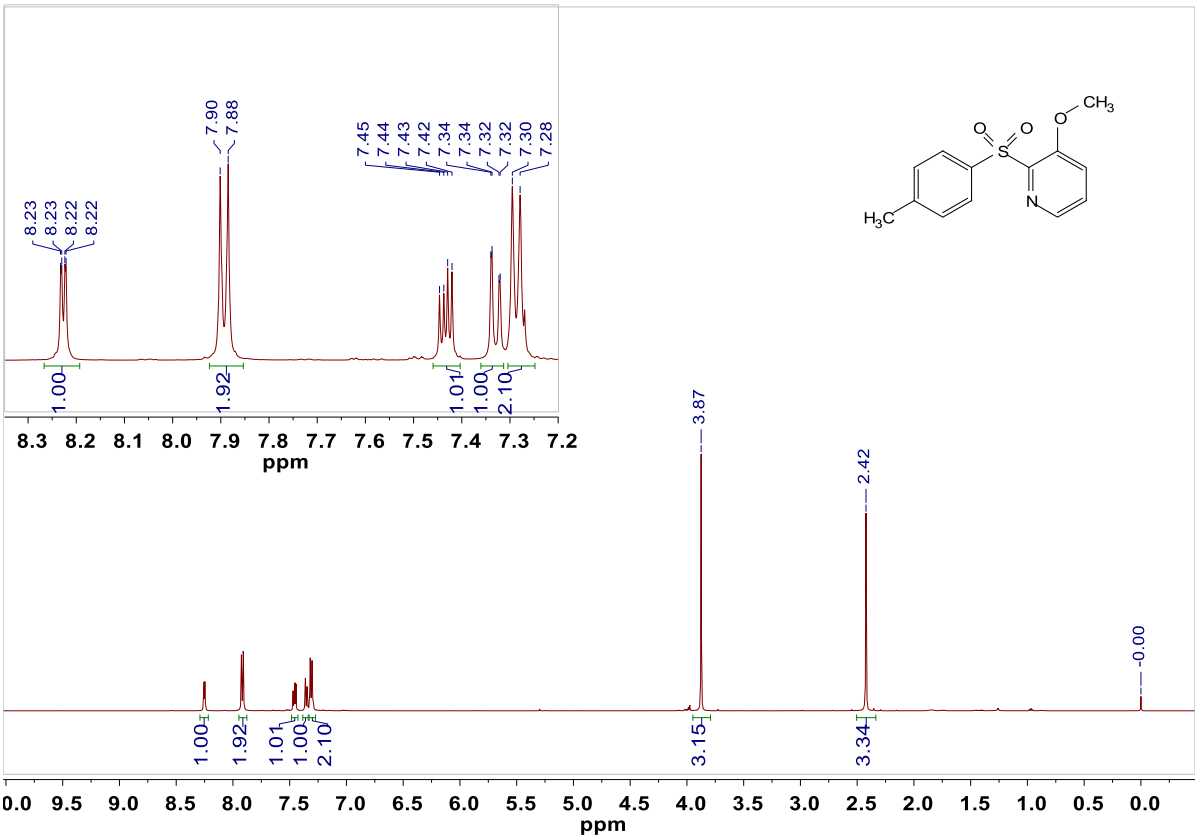


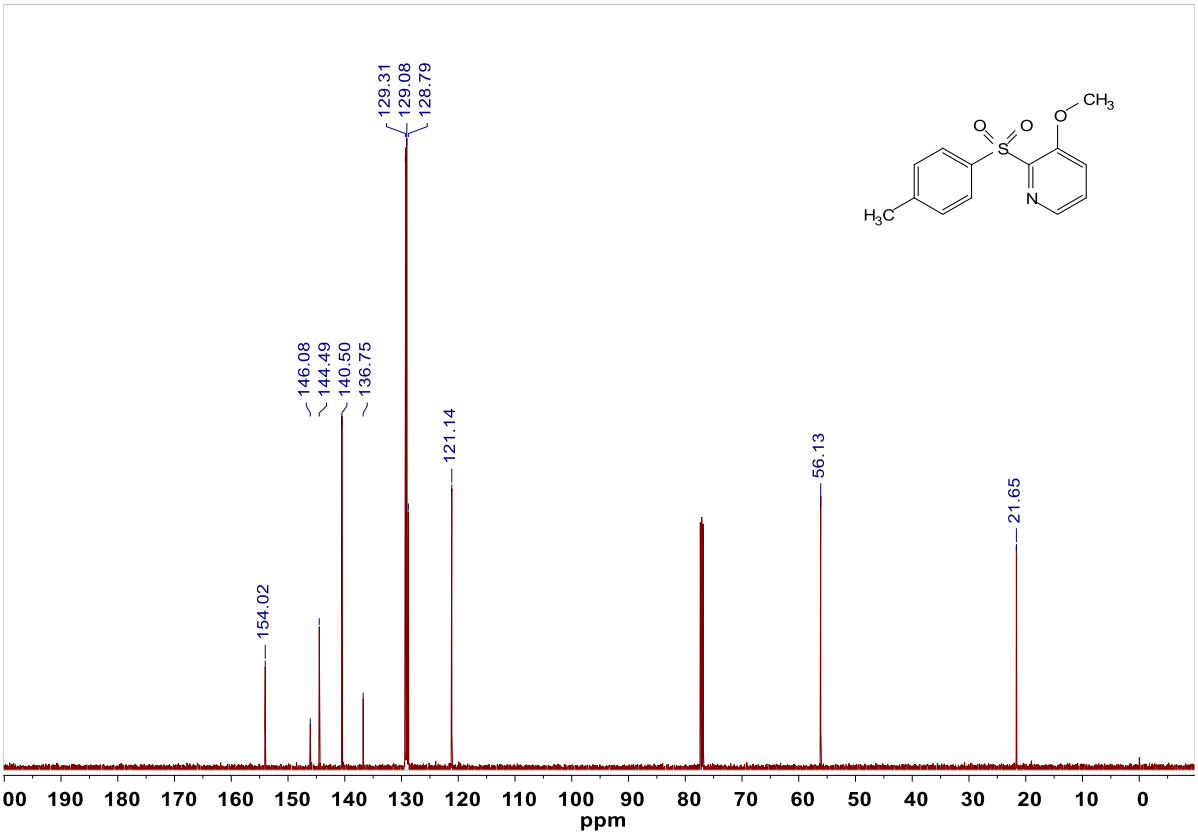
Compound: 6-methyl-2-tosylpyridine (**194e**)



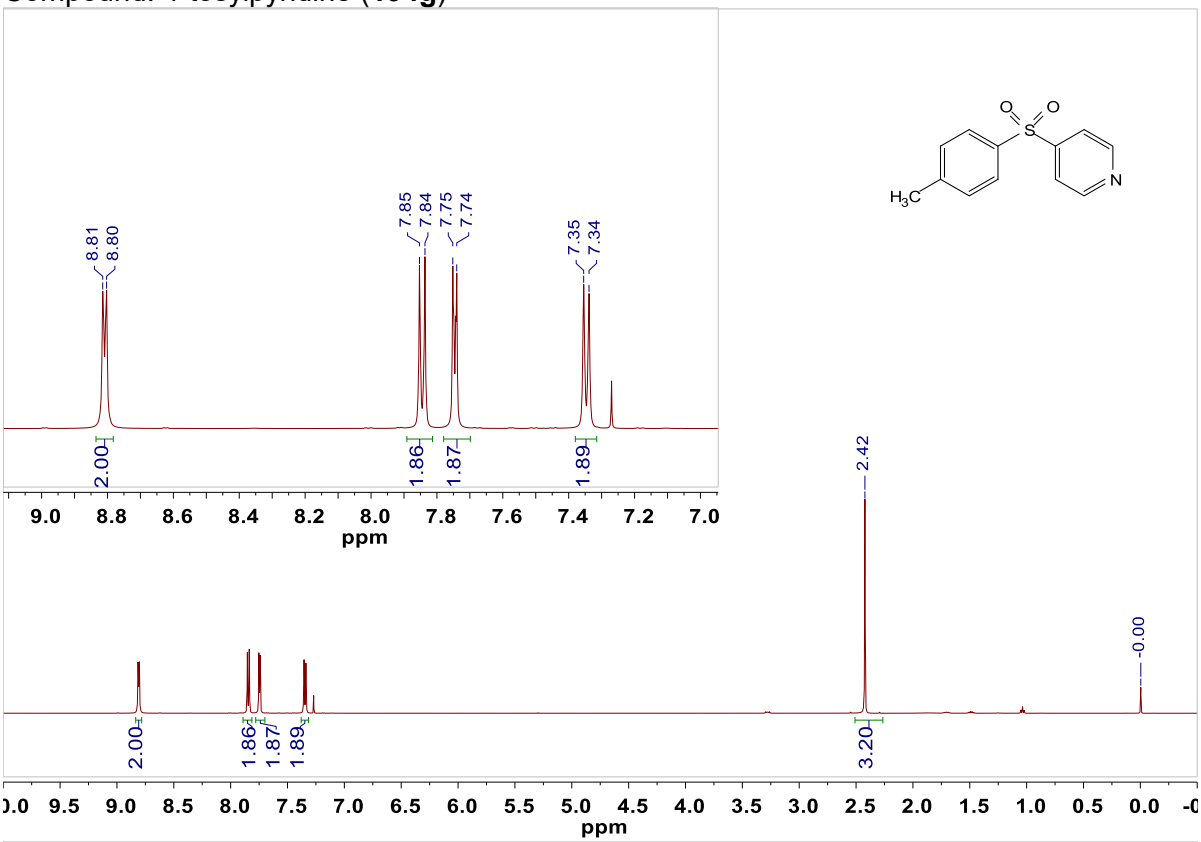


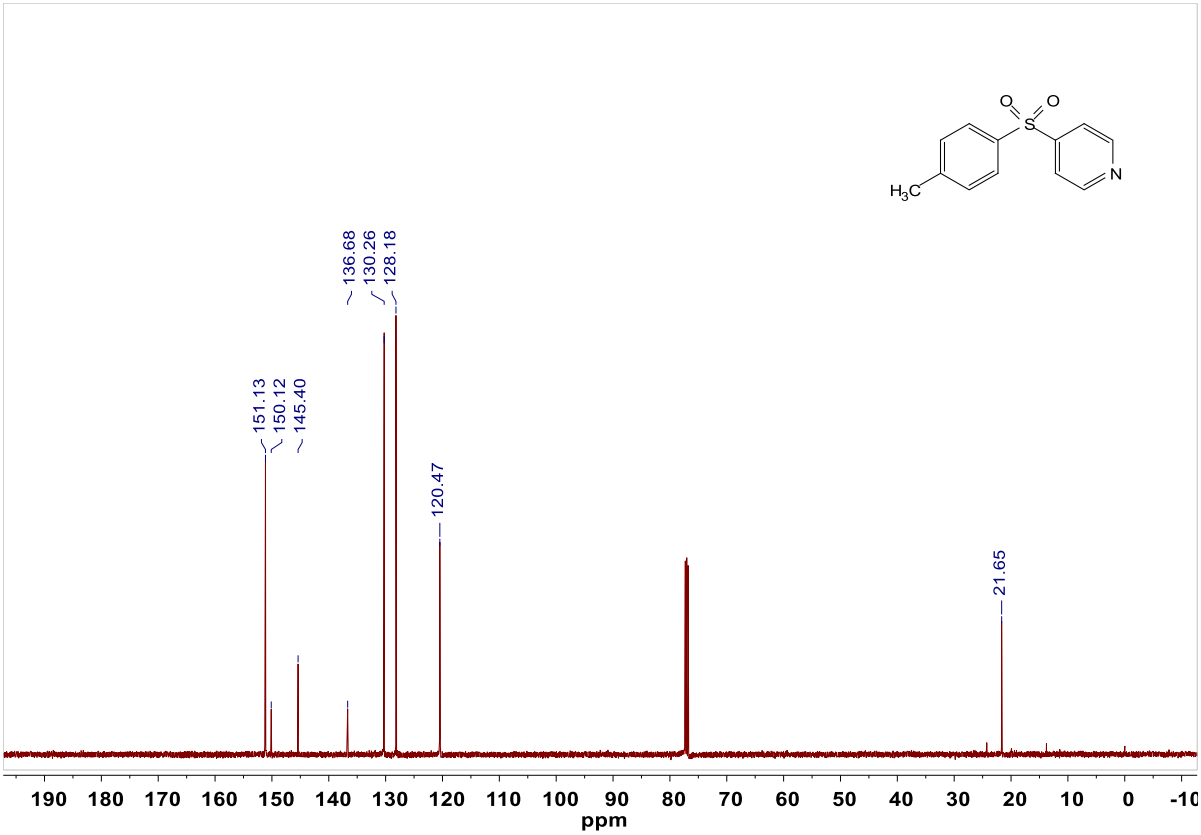
Compound: 3-methoxy-2-tosylpyridine (**194f**)



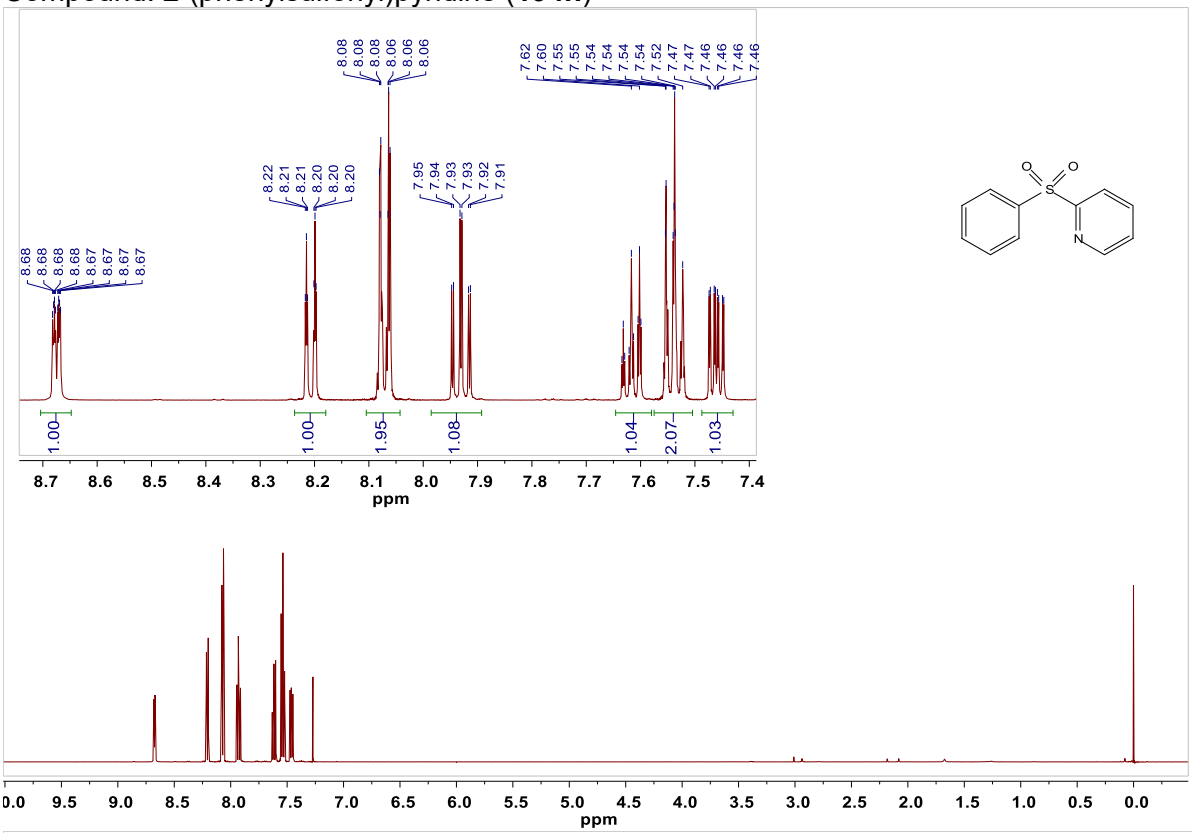


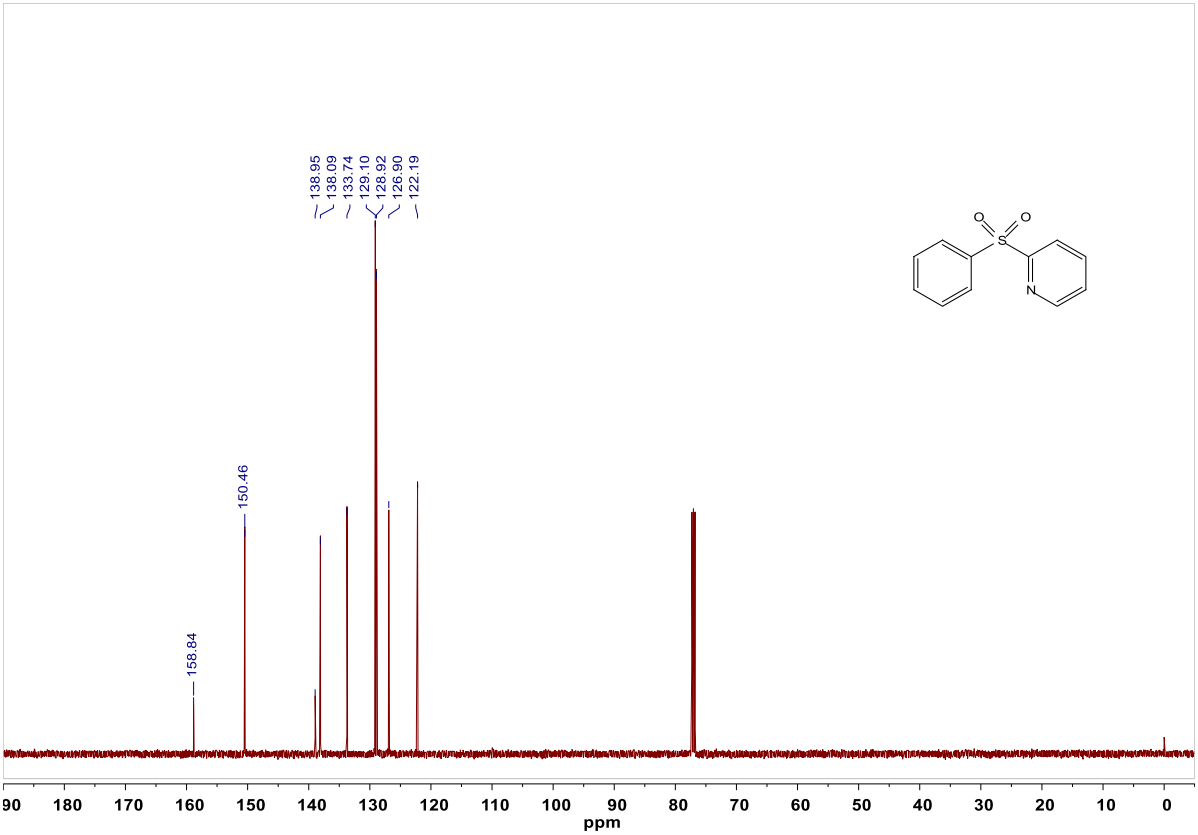
Compound: 4-tosylpyridine (**194g**)



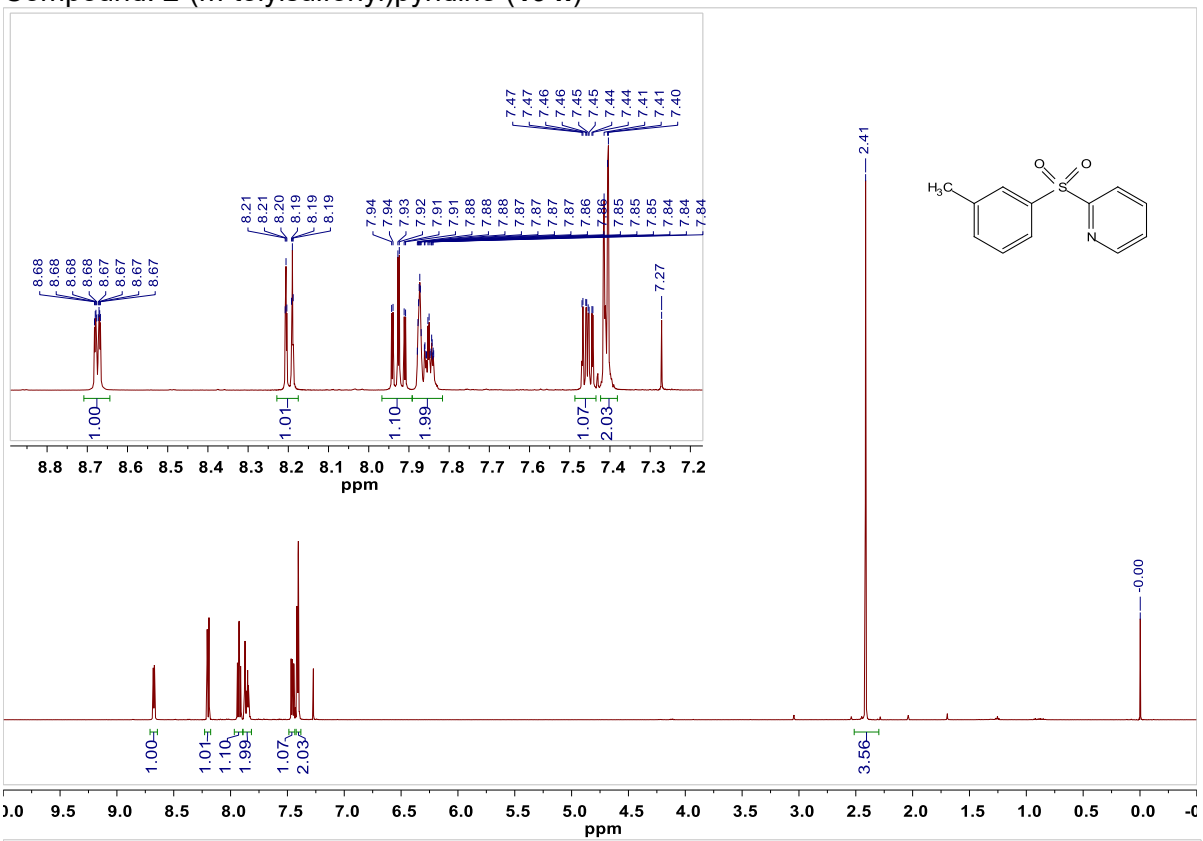


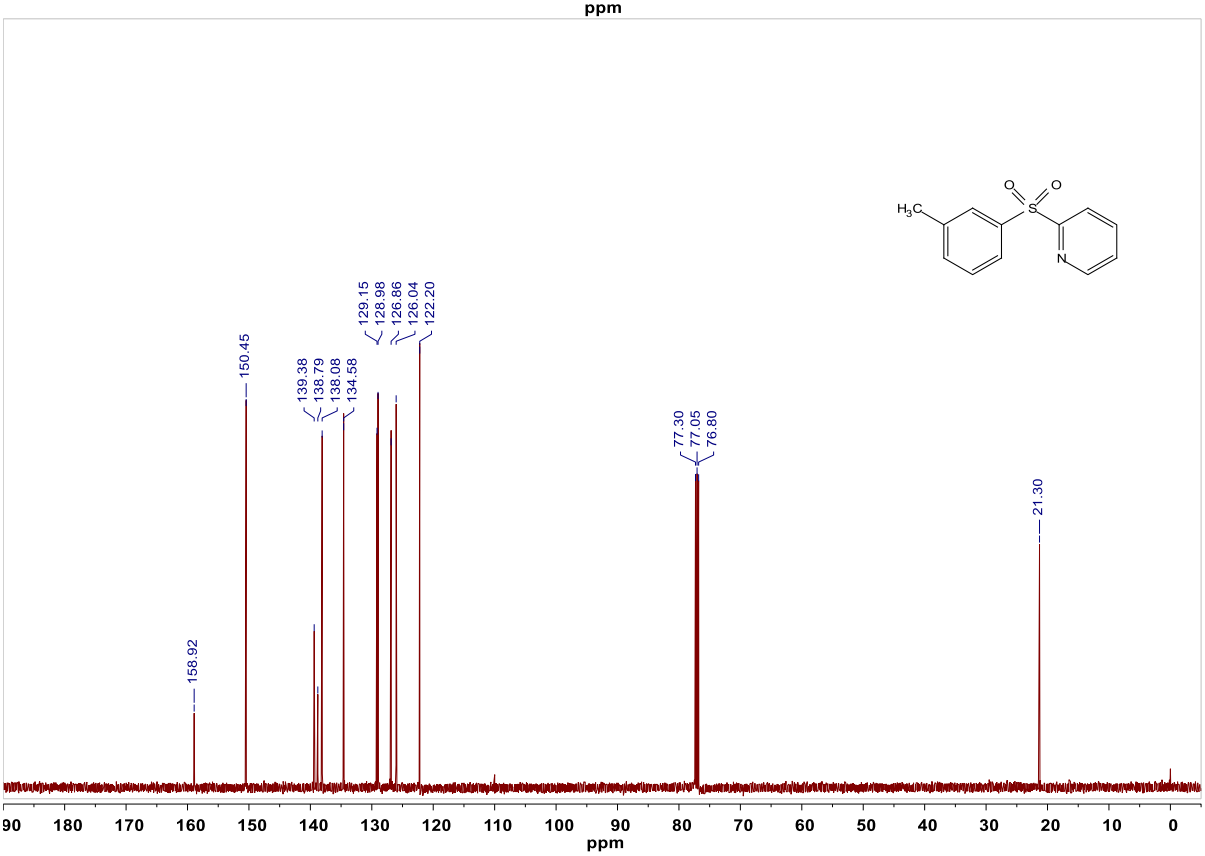
Compound: 2-(phenylsulfonyl)pyridine (**194h**)



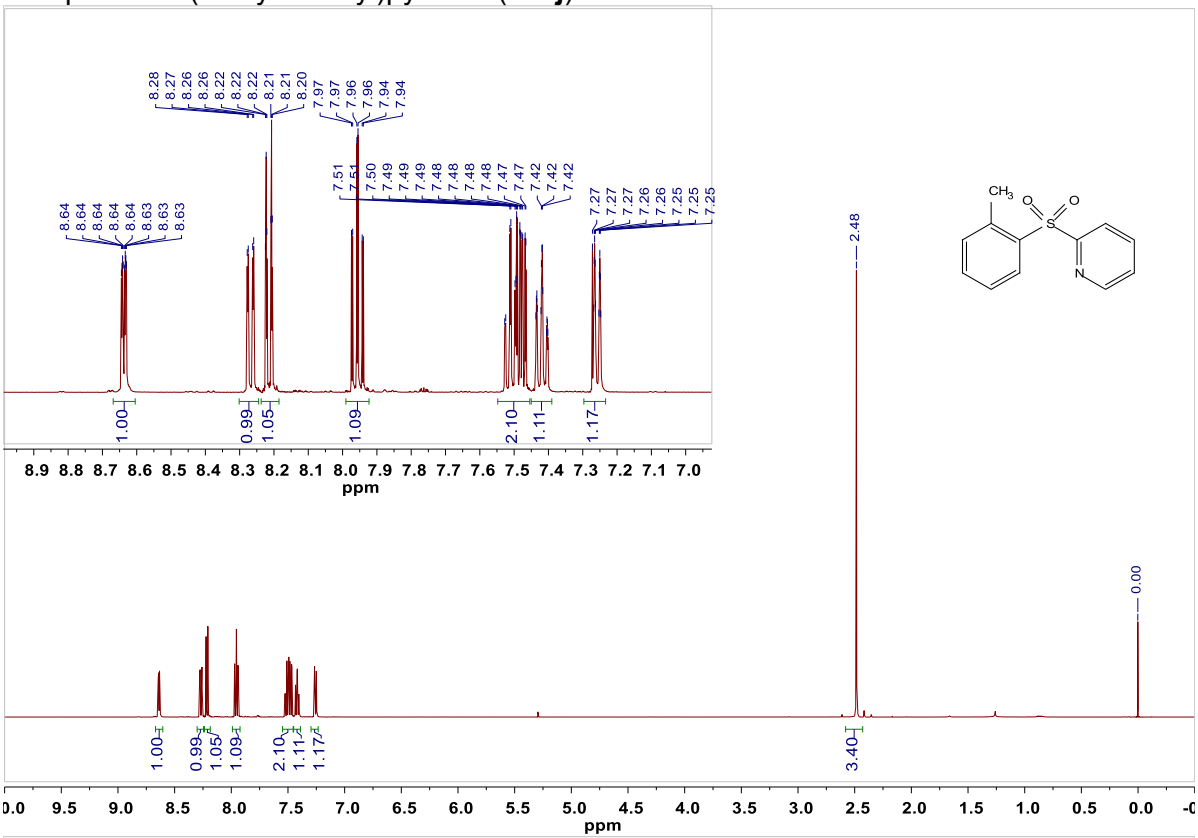


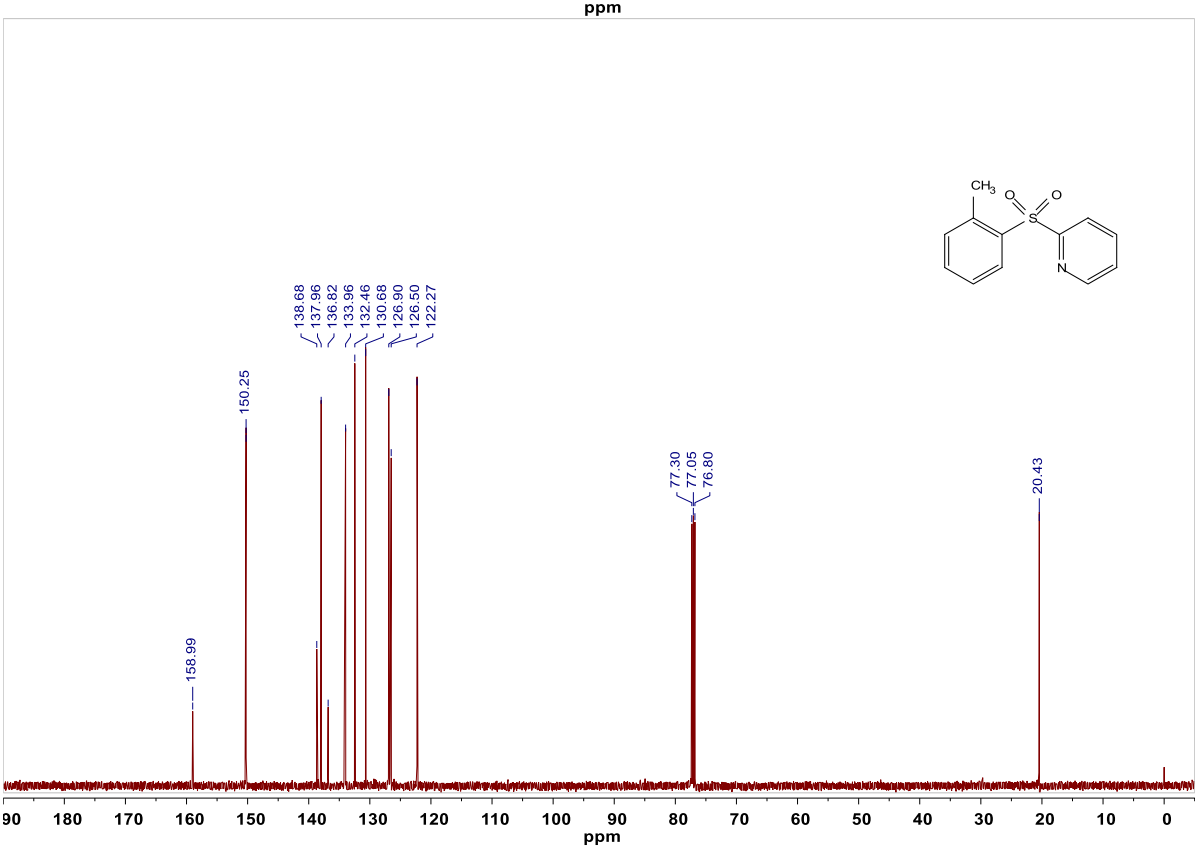
Compound: 2-(m-tolylsulfonyl)pyridine (**194i**)



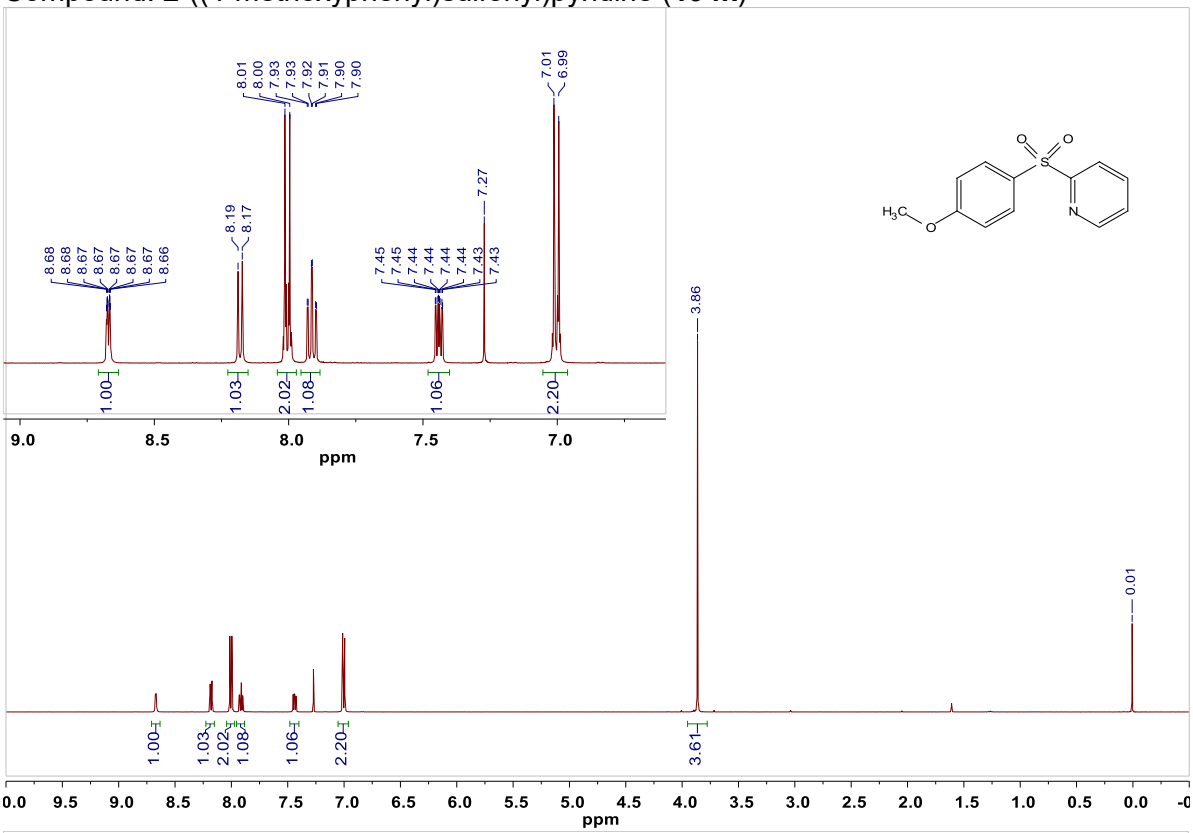


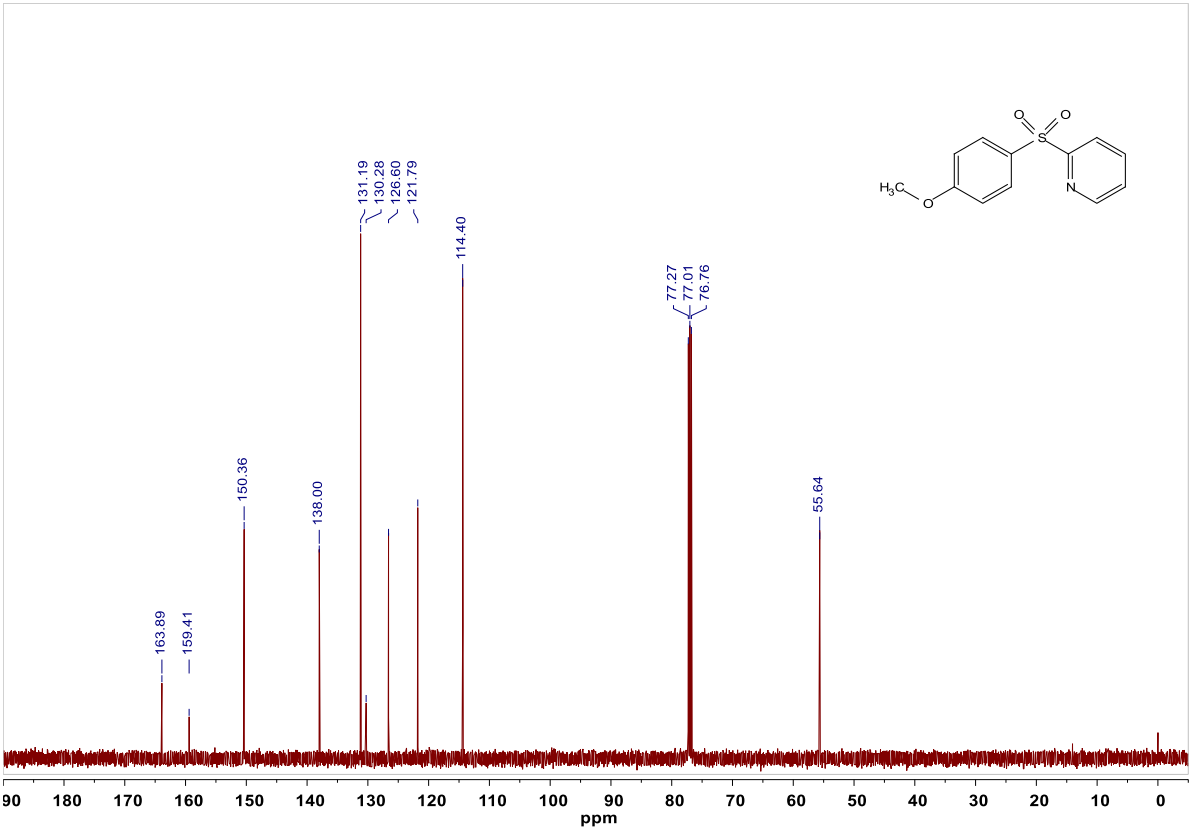
Compound: 2-(o-tolylsulfonyl)pyridine (**194j**)



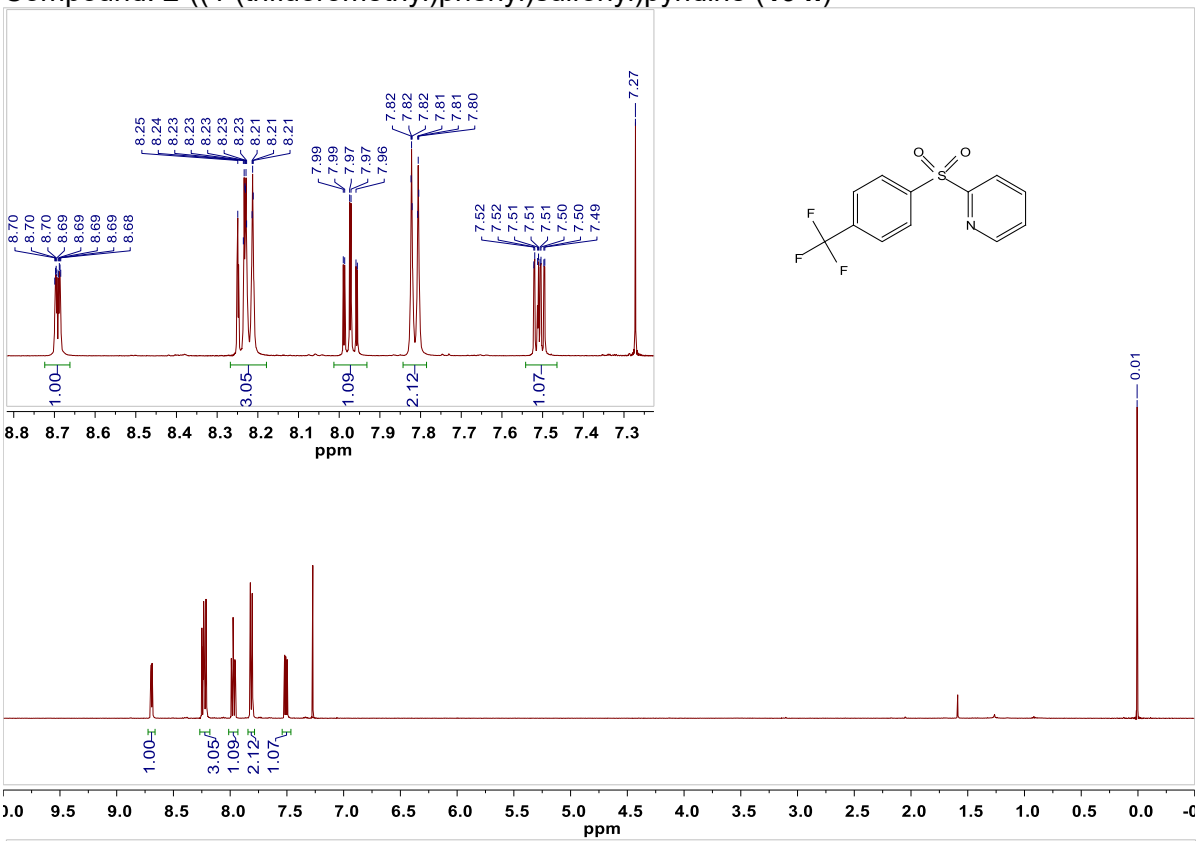


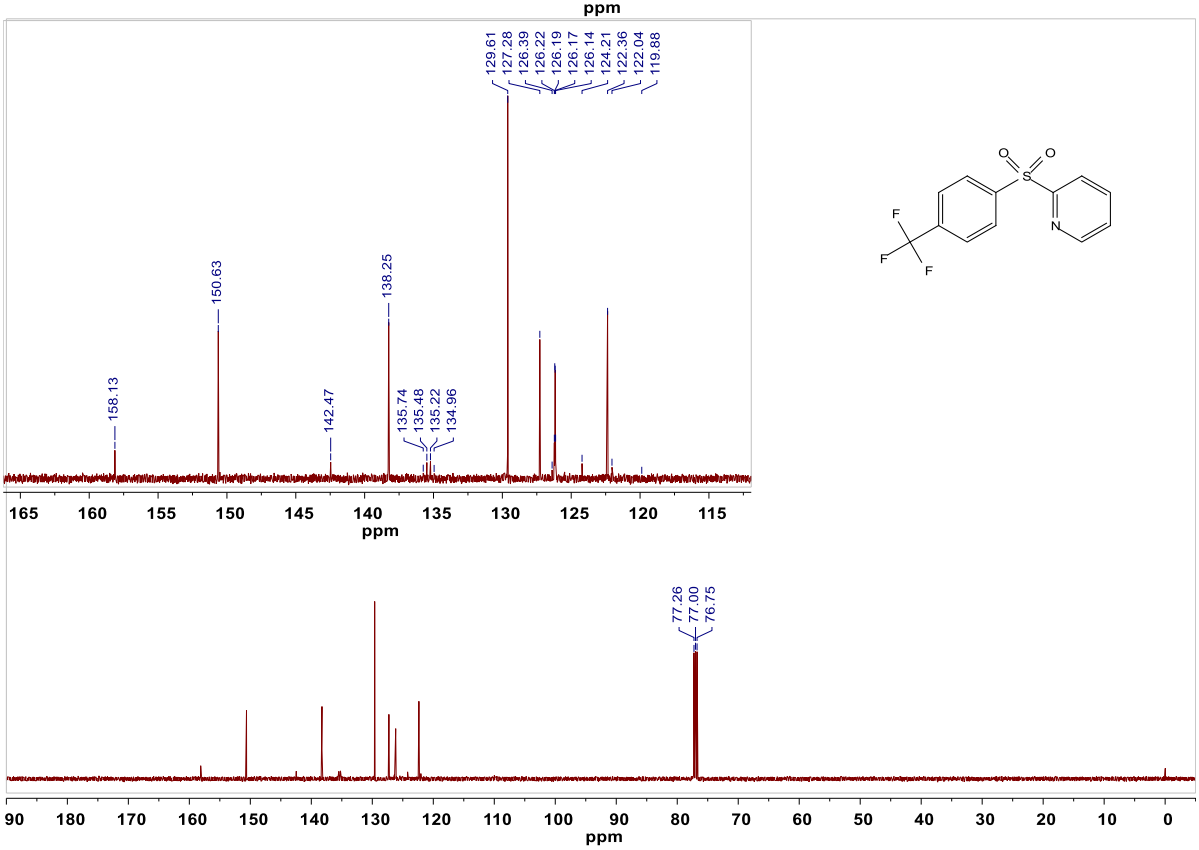
Compound: 2-((4-methoxyphenyl)sulfonyl)pyridine (**194k**)



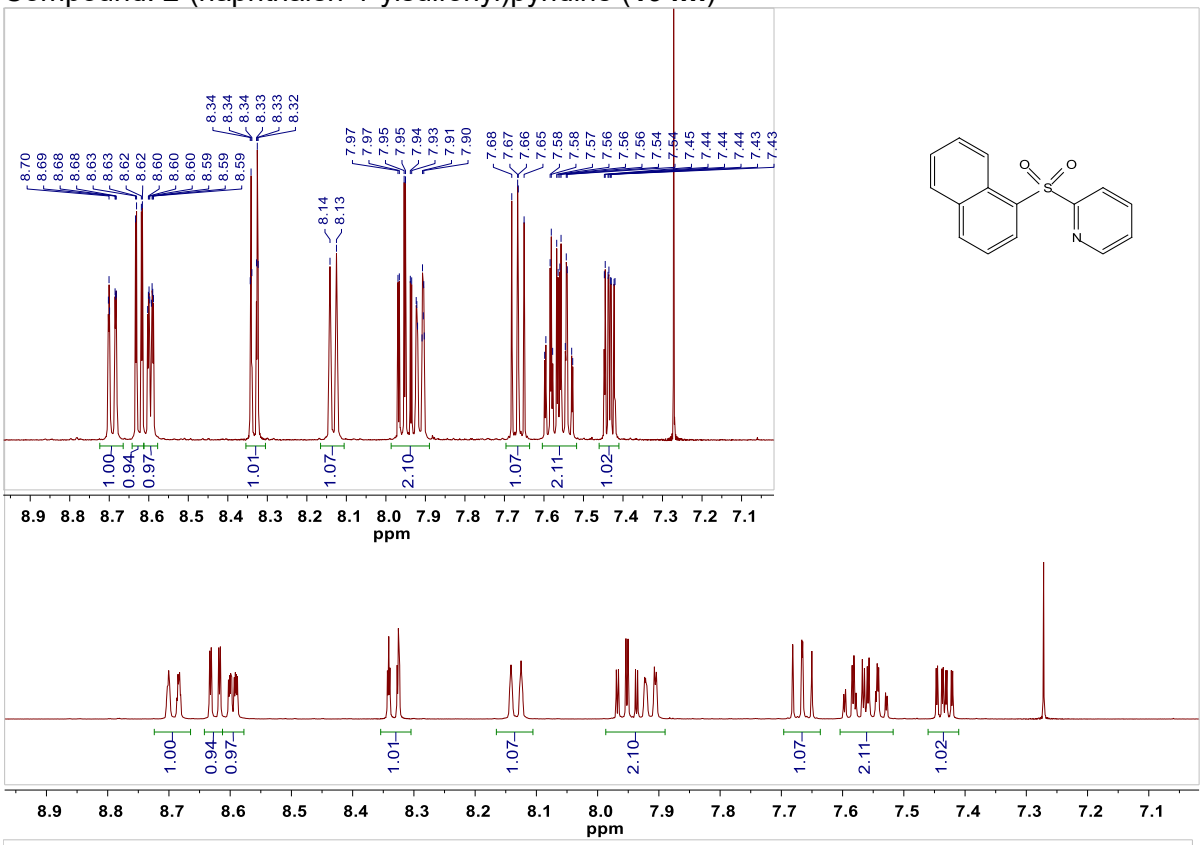


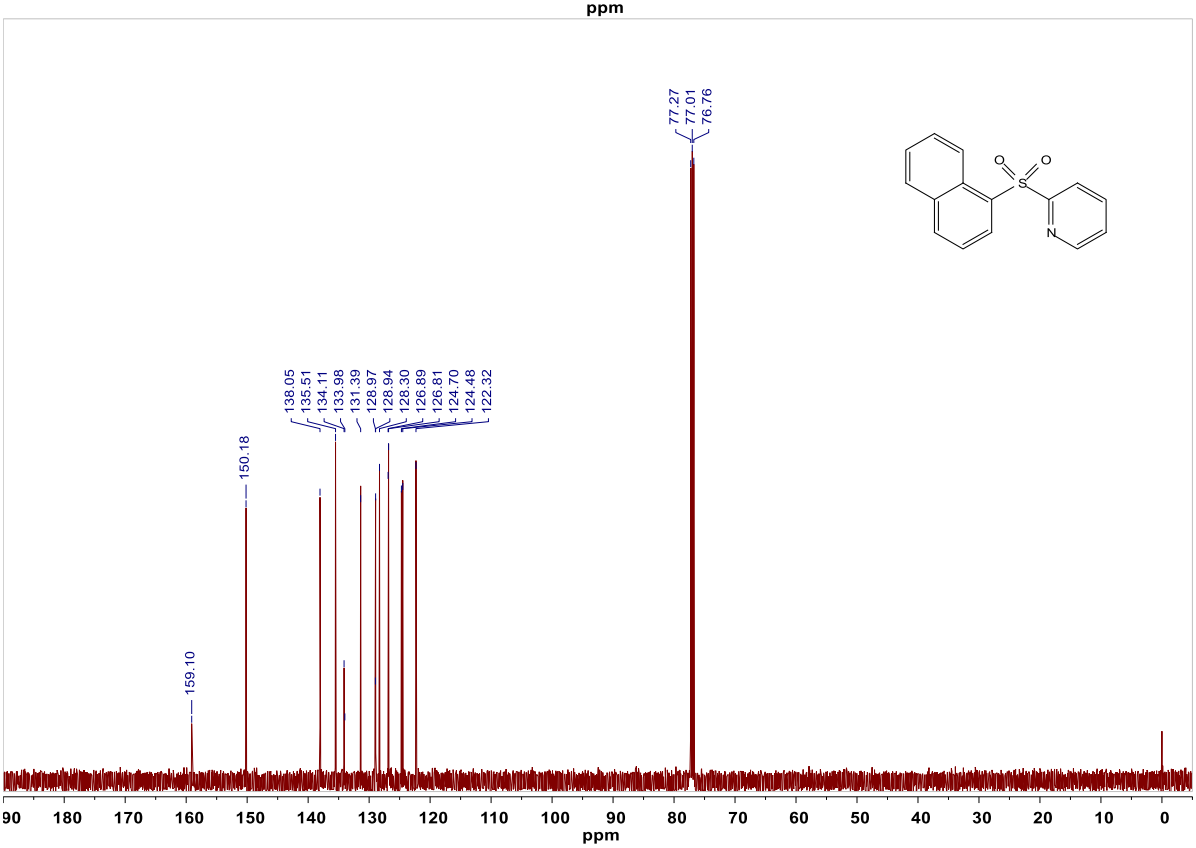
Compound: 2-((4-(trifluoromethyl)phenyl)sulfonyl)pyridine (**194l**)



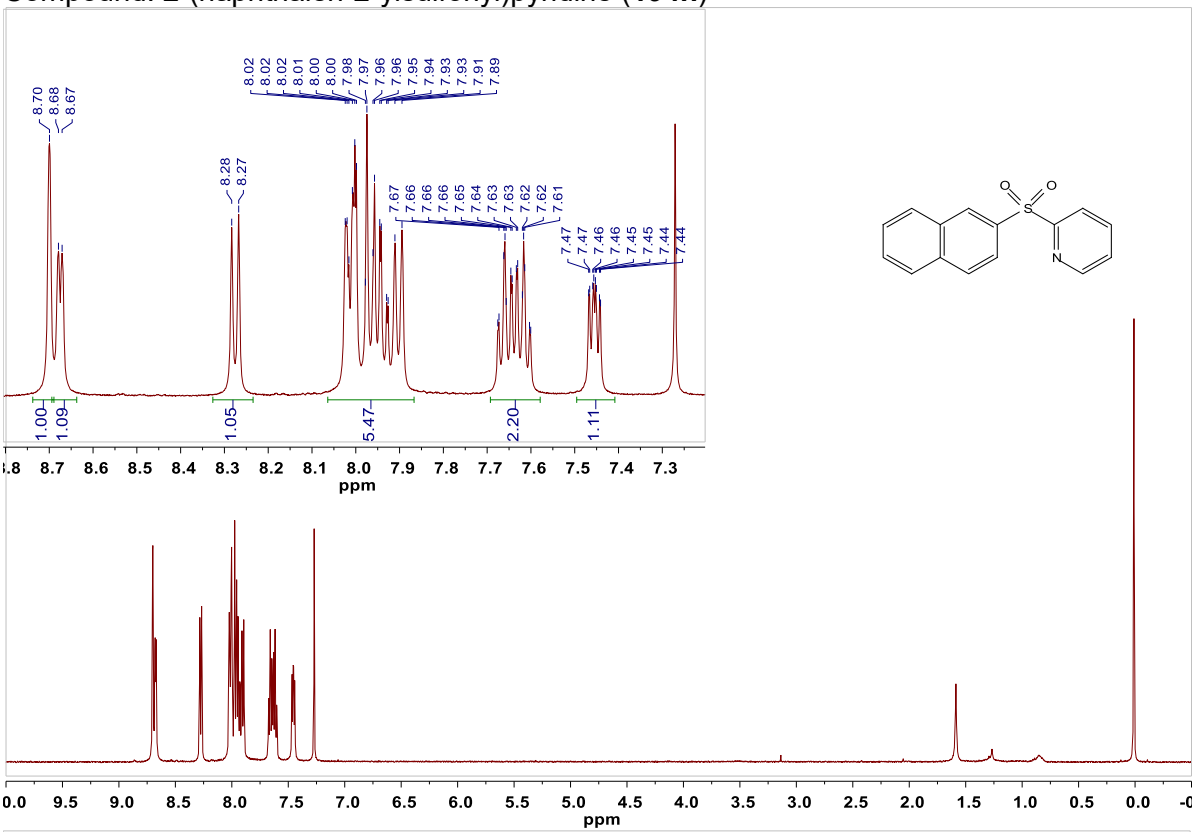


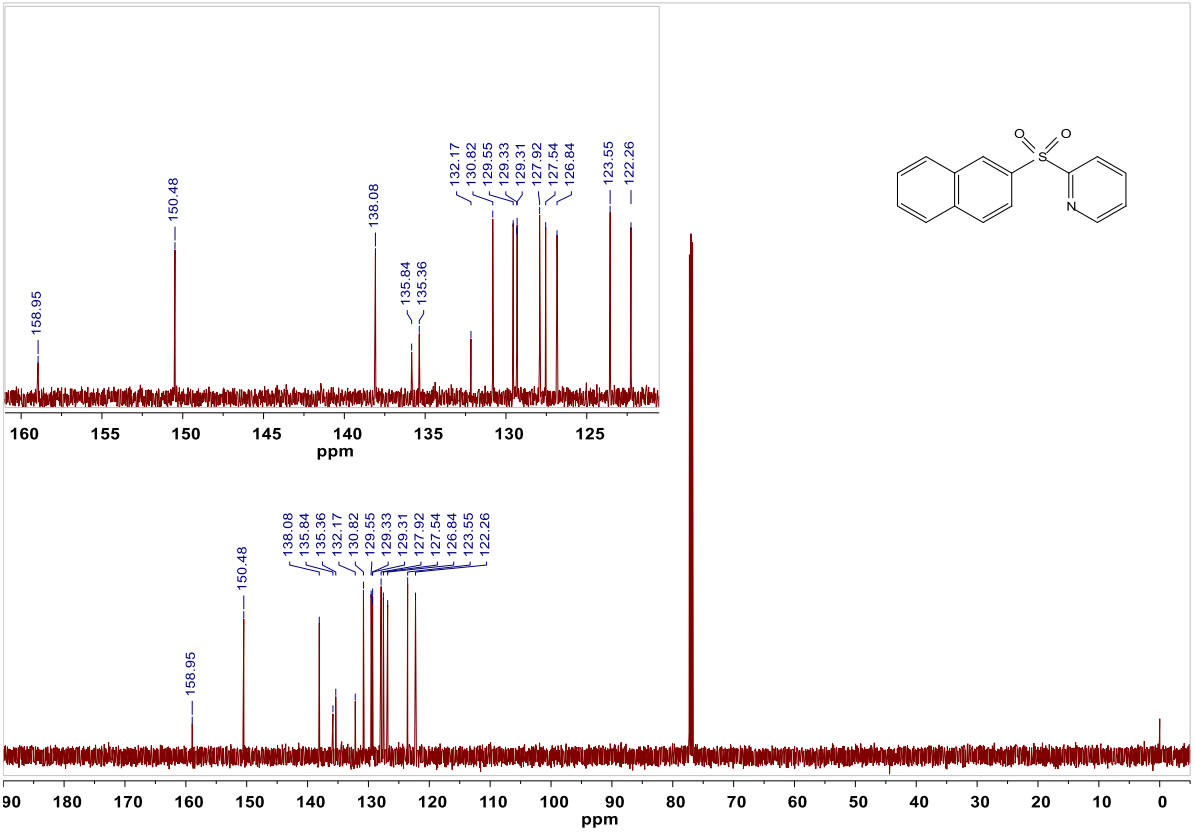
Compound: 2-(naphthalen-1-ylsulfonyl)pyridine (**194m**)





Compound: 2-(naphthalen-2-ylsulfonyl)pyridine (**194n**)





Using Pyridine as a Removable *Ortho*-Directing Group to Access the *Ortho*-Halogenated Sulfinate Salts

Fei Chen, Cindy Buonomano, Mohammad S. Askari and Pat Forgione*

Department of Chemistry & Biochemistry, Concordia University, 7141 rue Sherbrooke O. H4B 1R6, Montréal, QC, Canada and Centre for Green Chemistry and Catalysis

Supporting information

2-((2-bromo-4-methylphenyl)sulfonyl)pyridine (195a-Br):
Synthesized following general procedure of *ortho*-bromination in chapter 3 unless specified.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.60 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.34 (d, *J* = 8.2 Hz, 2H), 7.97 (td, *J* = 7.8, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H), 7.46 – 7.44 (m, 1H), 7.41 – 7.34 (m, 1H), 2.40 (s, 3H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 157.99, 150.02, 146.41, 137.66, 135.60, 134.89, 132.58, 128.59, 126.89, 123.57, 120.91, 21.18.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}BrNO_2S$: 311.9689; found: 311.9691.

2-((2-chloro-4-methylphenyl)sulfonyl)pyridine (195a-Cl):
Synthesized following general procedure of *ortho*-chlorination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.60 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.34 – 8.27 (m, 2H), 7.97 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 7.31 (ddd, *J* = 8.1, 1.7, 0.9 Hz, 1H), 7.24 – 7.21 (m, 1H), 2.40 (s, 3H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 158.15, 150.07, 146.50, 137.75, 133.30, 132.58, 132.14, 132.08, 128.03, 126.96, 123.25, 21.31.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}ClNO_2S$: 268.0194; found: 268.0196.

2-((2-iodo-4-methylphenyl)sulfonyl)pyridine (195a-I):
Synthesized following general procedure of *ortho*-iodination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.59 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.40 – 8.33 (m, 2H), 7.96 (td, *J* = 7.8, 1.7 Hz, 1H), 7.82 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.48 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 7.40 (ddd, *J* = 8.2, 1.7, 0.8 Hz, 1H), 2.36 (s, 3H).
^{13}C NMR (126 MHz, dmso) δ 152.77, 145.27, 141.19, 138.19, 132.98, 132.80, 127.74, 124.60, 122.10, 119.53, 88.62, 16.16.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}INO_2S$: 359.9550; found: 359.9550.

2-((2-bromophenyl)sulfonyl)pyridine (195b-Br)
Synthesized following general procedure of *ortho*-bromination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.60 (ddd, *J* = 4.5, 1.7, 0.9 Hz, 1H), 8.48 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.35 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.98 (td, *J* = 7.8, 1.7 Hz, 1H), 7.64 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.61 – 7.56 (m, 1H), 7.52 – 7.43 (m, 2H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 157.79, 150.06, 137.93, 137.71, 135.11, 134.93, 132.66, 127.88, 127.02, 123.67, 121.15.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_8BrNO_2S$: 297.9532; found: 297.9536.

2-((2-chlorophenyl)sulfonyl)pyridine (195b-Cl)
Synthesized following general procedure of *ortho*-chlorination in chapter 3.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.60 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.43 (dd, *J* = 7.6, 2.1 Hz, 1H), 8.33 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.98 (td , *J* = 7.8, 1.7 Hz, 1H), 7.59 – 7.46 (m, 3H), 7.42 (dd, *J* = 7.5, 1.7 Hz, 1H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 157.95, 150.10, 137.80, 136.35, 134.96, 132.87, 132.21, 131.59, 127.30, 127.08, 123.35.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_8ClNO_2S$: 254.0037; found: 254.0040.

2-((2-iodophenyl)sulfonyl)pyridine (195b-I)
Synthesized following general procedure of *ortho*-iodination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.60 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.50 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.40 (dt, *J* = 7.9, 1.0 Hz, 1H), 8.02 – 7.95 (m, 2H), 7.62 (td, *J* = 7.7, 1.2 Hz, 1H), 7.49 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 7.27 (dt, *J* = 7.6, 1.7 Hz, 1H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 157.28, 150.04, 142.39, 140.73, 137.59, 134.60, 132.61, 128.62, 126.97, 124.40, 93.38.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_8INO_2S$: 345.9393; found: 345.9393.

2-((2-bromo-5-methylphenyl)sulfonyl)pyridine (195c-Br)
Synthesized following general procedure of *ortho*-bromination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.61 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.29 (d, *J* = 2.3 Hz, 1H), 7.98 (td, *J* = 7.8, 1.8 Hz, 1H), 7.49 (dd, *J* = 7.8, 4.1 Hz, 2H), 7.30 – 7.23 (m, 1H), 2.44 (s, 3H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 157.85, 150.04, 138.44, 137.72, 137.36, 135.81, 134.88, 132.98, 127.00, 123.73, 117.59, 20.97.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}BrNO_2S$: 311.9689; found: 311.9693.

2-((2-chloro-5-methylphenyl)sulfonyl)pyridine(195c-Cl)
Synthesized following general procedure of *ortho*-chlorination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.61 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.33 (dt, *J* = 8.0, 1.0 Hz, 1H), 8.27 – 8.21 (m, 1H), 7.98 (td, *J* = 7.8, 1.7 Hz, 1H), 7.49 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 7.35 (ddd, *J* = 8.1, 2.2, 0.8 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 2.45 (s, 3H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 158.03, 150.09, 137.80, 137.78, 135.75, 135.73, 132.42, 131.34, 129.63, 127.03, 123.39, 20.90.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}ClNO_2S$: 268.0194; found: 268.0194.

2-((2-iodo-5-methylphenyl)sulfonyl)pyridine (195c-I)
Synthesized following general procedure of *ortho*-iodination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.61 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.40 (dt, *J* = 7.9, 1.1 Hz, 1H), 8.32 (dt, *J* = 2.2, 0.8 Hz, 1H), 7.98 (td, *J* = 7.8, 1.7 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.49 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H), 7.13 – 7.02 (m, 1H), 2.43 (d, *J* = 0.8 Hz, 4H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 157.36, 150.03, 142.17, 140.28, 139.25, 137.58, 135.67, 133.15, 126.95, 124.46, 89.17, 21.02.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}INO_2S$: 359.9550; found: 359.9550.

2-((2-bromo-6-methylphenyl)sulfonyl)pyridine (195d-Br)
Synthesized following general procedure of *ortho*-bromination in chapter 3.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.58 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.26 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.95 (td, *J* = 7.8, 1.7 Hz, 1H), 7.52 (ddd, *J* = 7.8, 1.4, 0.7 Hz, 1H), 7.47 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 7.32 (ddd, *J* = 7.7, 1.5, 0.7 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 2H), 2.93 (d, *J* = 0.7 Hz, 4H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 159.60, 149.77, 144.56, 137.63, 136.02, 133.90, 133.54, 132.90, 126.80, 123.11, 122.13, 23.63.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}BrNO_2S$: 311.9688; found: 311.9691.

2-((2-chloro-6-methylphenyl)sulfonyl)pyridine (195d-Cl)
Synthesized following general procedure of *ortho*-chlorination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.58 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.23 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.96 (td, *J* = 7.8, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.29 – 7.24 (m, 2H), 2.92 (s, 3H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 159.79, 149.80, 144.06, 137.73, 134.67, 134.38, 133.47, 132.22, 130.08, 126.86, 121.76, 23.13.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}ClNO_2S$: 268.0194; found: 268.0194.

2-((2-iodo-6-methylphenyl)sulfonyl)pyridine (195d-I)
Synthesized following general procedure of *ortho*-iodination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.59 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.29 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.95 (td, *J* = 7.7, 1.7 Hz, 2H), 7.48 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.8 Hz, 1H), 2.89 (s, 3H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 158.93, 149.82, 144.35, 141.85, 138.46, 137.58, 133.69, 133.64, 126.87, 122.88, 95.68, 24.34.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}INO_2S$: 359.9550; found: 359.9550.

2-((2-bromo-4-methoxyphenyl)sulfonyl)pyridine (195e-Br)
Synthesized following general procedure of *ortho*-bromination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.69 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.22 (d, *J* = 2.3 Hz, 1H), 8.19 (dt, *J* = 7.9, 1.0 Hz, 1H), 8.04 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.94 (td, *J* = 7.8, 1.7 Hz, 1H), 7.47 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 3.97 (s, 3H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 160.15, 150.47, 138.12, 133.97, 131.49, 130.34, 126.86, 121.93, 120.81, 112.36, 111.47, 56.66.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}BrNO_3S$: 327.9638; found: 327.9640.

2-((2-chloro-4-methoxyphenyl)sulfonyl)pyridine (195e-Cl)
Synthesized following general procedure of *ortho*-chlorination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.65 – 8.58 (m, 1H), 8.33 (d, *J* = 8.9 Hz, 1H), 8.32 – 8.27 (m, 1H), 7.96 (td, *J* = 7.8, 1.8 Hz, 1H), 7.47 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 6.99 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.92 (d, *J* = 2.5 Hz, 1H), 3.85 (s, 4H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 164.31, 158.31, 150.07, 137.76, 134.32, 133.97, 126.89, 123.15, 117.30, 114.39, 112.46, 55.98.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}ClNO_3S$: 284.0143; found: 284.0143.

2-((2-iodo-4-methoxyphenyl)sulfonyl)pyridine (195e-I)
Synthesized following general procedure of *ortho*-iodination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.61 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.42 – 8.39 (m, 1H), 8.37 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.96 (td, *J* = 7.8, 1.7 Hz, 1H), 7.50 (d, *J* = 2.5 Hz, 1H), 7.48 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 7.08 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.85 (s, 3H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 163.30, 150.01, 137.54, 134.20, 131.18, 128.18, 126.76, 124.13, 114.39, 113.43, 94.29, 55.88.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}INO_3S$: 375.9499; found: 375.9498.

2-((2-bromo-4-(trifluoromethyl)phenyl)sulfonyl)pyridine (195f-Br)
Synthesized following general procedure of *ortho*-bromination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.65 – 8.56 (m, 2H), 8.36 (d, *J* = 7.9 Hz, 1H), 8.02 (td, *J* = 7.8, 1.7 Hz, 1H), 7.89 (d, *J* = 1.8 Hz, 1H), 7.85 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.54 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 157.14, 150.18, 141.55, 137.96, 136.42 (q, J = 33.4 Hz), 133.23, 132.11 (q, *J* = 3.8 Hz), 127.42, 124.81 (q, *J* = 3.6 Hz), 123.69, 123.34, 121.80.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_7BrF_3NO_2S$: 365.9406; found: 365.9406.

2-((2-chloro-4-(trifluoromethyl)phenyl)sulfonyl)pyridine (195f-Cl)
Synthesized following general procedure of *ortho*-chlorination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.61 (s, 1H), 8.57 (d, *J* = 8.0 Hz, 1H), 8.38 – 8.31 (m, 1H), 8.02 (t, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.68 (s, 1H), 7.57 – 7.48 (m, 1H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 157.29, 150.23, 139.91, 138.05, 136.62 (q, *J* = 33.1 Hz), 133.81, 132.93, 128.68 (q, *J* = 3.8 Hz), 127.49, 124.22 (q, *J* = 3.5 Hz), 123.37, 121.29.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_7ClF_3NO_2S$: 321.9911; found: 321.9910.

2-((2-iodo-4-(trifluoromethyl)phenyl)sulfonyl)pyridine (195f-I)
Synthesized following general procedure of *ortho*-iodination in chapter 3.
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.63 – 8.57 (m, 2H), 8.40 (dt, *J* = 7.9, 1.0 Hz, 1H), 8.20 (dd, *J* = 1.7, 0.8 Hz, 1H), 8.01 (td, *J* = 7.8, 1.7 Hz, 1H), 7.88 (ddd, *J* = 8.3, 1.8, 0.8 Hz, 1H), 7.53 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 156.64, 150.15, 144.43, 139.19 (q, *J* = 3.8 Hz), 137.82, 135.86 (q, *J* = 33.6 Hz), 132.92, 127.36, 125.57 (q, *J* = 3.6 Hz), 124.42, 123.08, 93.54.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_7IF_3NO_2S$: 413.9267; found: 413.9265.

Sodium 2-chloro-4-methylbenzenesulfinate (196a-Cl)
Synthesized following general procedure of pyridine removal method in chapter 3.
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.57 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.10 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.03 (s, 1H), 2.25 (s, 3H).
^{13}C NMR (126 MHz, dmso) δ 153.80, 139.40, 131.63, 129.22, 127.86, 124.94, 20.76.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $NaC_7H_6ClO_2S$ without Na: 188.9783; found: 188.9785.

Sodium 2-bromo-4-methylbenzenesulfinate (196a-Br)
Synthesized following general procedure of pyridine removal method in chapter 3.
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56 (d, *J* = 7.5 Hz, 1H), 7.20 (s, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 2.24 (s, 3H).
^{13}C NMR (126 MHz, dmso) δ 155.27, 139.81, 132.27, 128.52, 125.19, 121.24, 20.66.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $NaC_7H_6BrO_2S$ without Na: 232.9272; found: 232.9278.

Sodium 2-chlorobenzenesulfinate (196b-Cl)
Synthesized following general procedure of pyridine removal method in chapter 3.
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.69 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.29 (ddd, *J* = 7.5, 4.5, 3.4 Hz, 1H), 7.20 (d, *J* = 3.4 Hz, 2H).
^{13}C NMR (126 MHz, dmso) δ 156.82, 131.86, 129.64, 129.01, 127.22, 124.95.
HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $NaC_6H_4ClO_2S$ without Na: 174.9626; found: 174.9628.

Sodium 2-bromobenzenesulfinate (196b-Br)
Synthesized following general procedure of pyridine removal method in chapter 3.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 (dd, J = 7.5, 1.8 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.13 (ddd, J = 7.5, 7.2, 1.8 Hz, 1H).
^{13}C NMR (126 MHz, dmso) δ 158.34, 132.10, 130.07, 127.87, 125.28, 121.43.
HRMS (EI): m/z $[M + H]^+$ calcd for $NaC_6H_4BrO_2S$ without Na: 218.9115; found: 218.9122.

Sodium 2-chloro-5-methylbenzenesulfinate (196c-Cl)
Synthesized following general procedure of pyridine removal method in chapter 3.
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.52 – 7.46 (m, 1H), 7.07 (dd, J = 8.0, 1.3 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 2.27 (s, 3H).
^{13}C NMR (126 MHz, dmso) δ 156.12, 136.52, 130.26, 128.82, 128.77, 125.29, 21.06.
HRMS (EI): m/z $[M + H]^+$ calcd for $NaC_7H_6ClO_2S$ without Na: 188.9783; found: 188.9785.

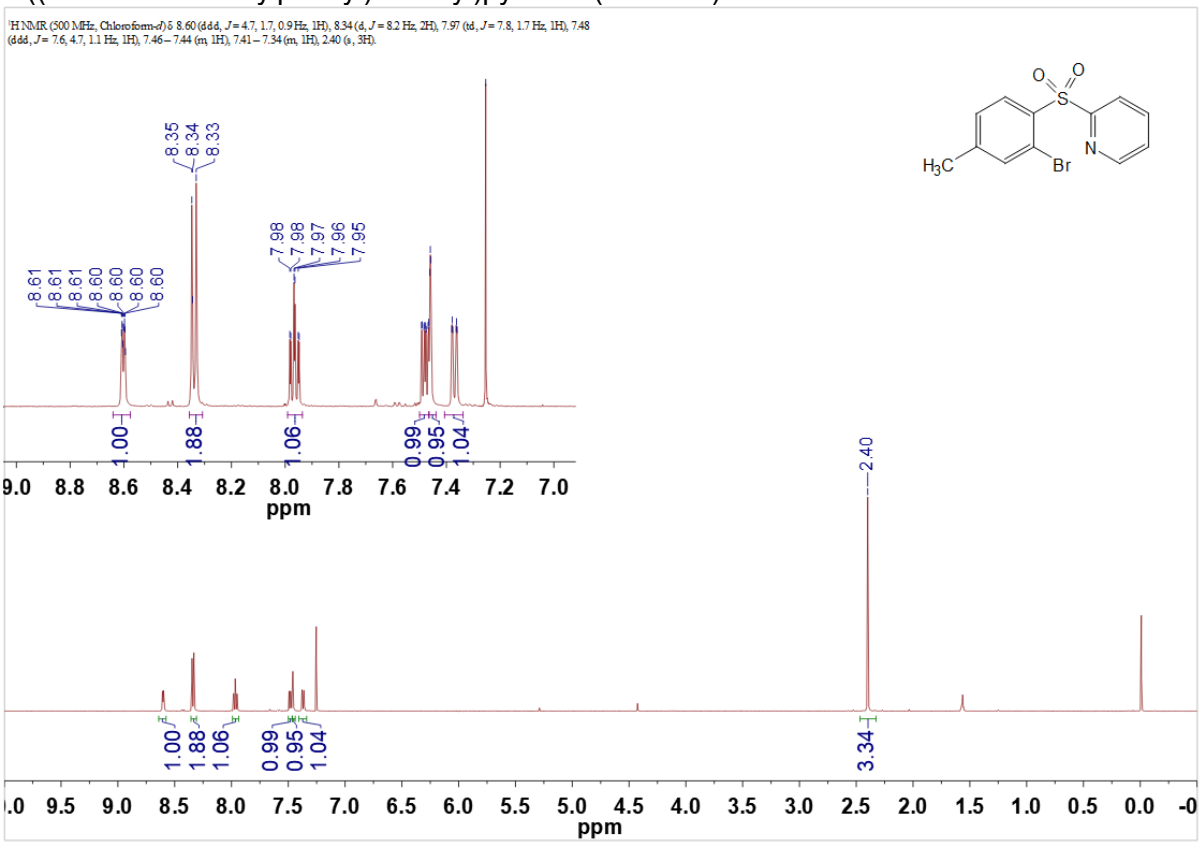
Sodium 2-bromo-5-methylbenzenesulfinate (196c-Br)
Synthesized following general procedure of pyridine removal method in chapter 3.
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.47 (d, J = 2.3 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 6.95 (dd, J = 8.0, 2.3 Hz, 1H), 2.25 (s, 3H).
^{13}C NMR (126 MHz, dmso) δ 157.80, 137.21, 131.84, 130.75, 125.69, 118.10, 21.08.
HRMS (EI): m/z $[M + H]^+$ calcd for $NaC_7H_6BrO_2S$ without Na: 232.9272; found: 232.9278.

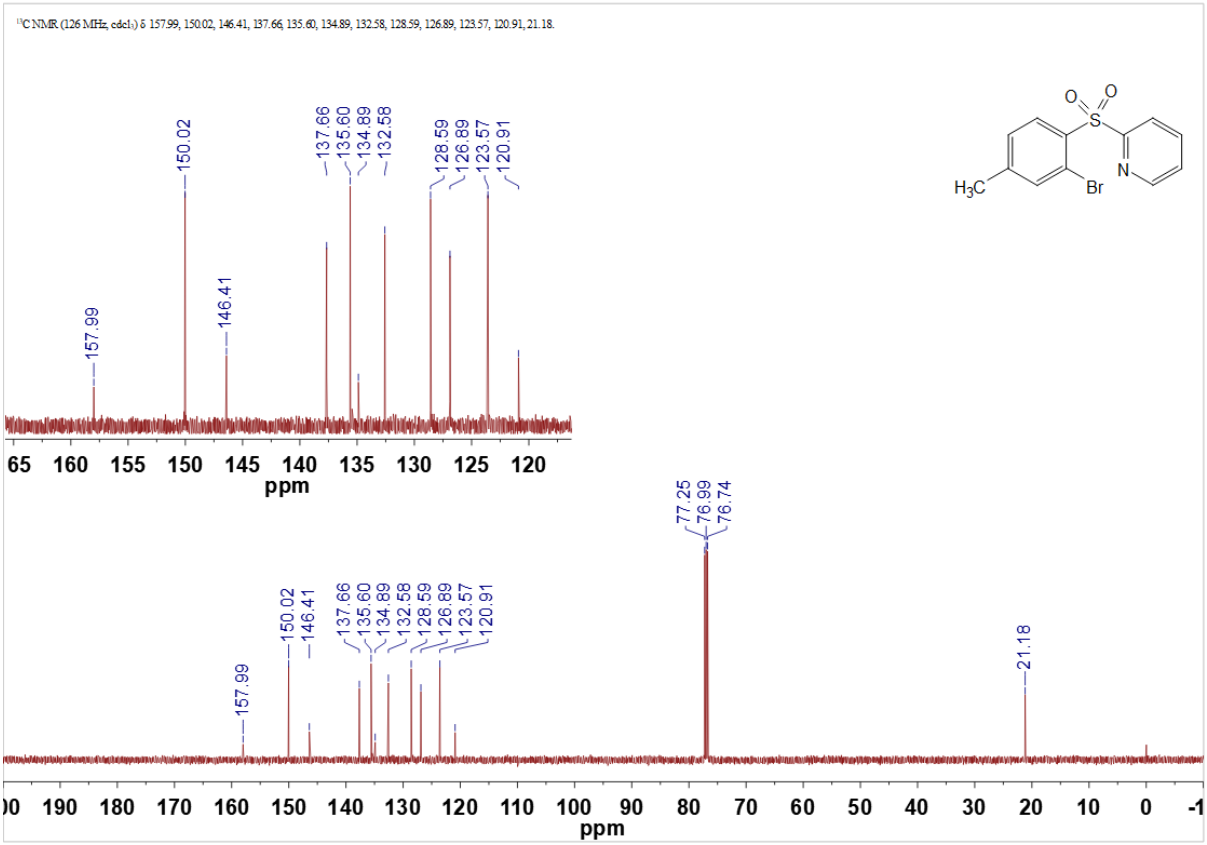
Sodium 2-chloro-6-methylbenzenesulfinate (196d-Cl)
Synthesized following general procedure of pyridine removal method in chapter 3.
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.01 – 6.95 (m, 2H), 6.90 (ddd, J = 6.7, 2.0, 0.9 Hz, 1H), 2.62 (s, 3H).
^{13}C NMR (126 MHz, dmso) δ 153.13, 138.47, 131.52, 130.97, 128.16, 127.05, 17.39.
HRMS (EI): m/z $[M + H]^+$ calcd for $NaC_7H_6ClO_2S$ without Na: 188.9783; found: 188.9785.

Sodium 2-chloro-4-methoxybenzenesulfinate (196e-Cl)
Synthesized following general procedure of pyridine removal method in chapter 3.
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.60 (d, J = 8.4 Hz, 1H), 6.86 (dd, J = 8.4, 2.4 Hz, 1H), 6.77 (d, J = 2.4 Hz, 1H), 3.73 (s, 3H).
^{13}C NMR (126 MHz, dmso) δ 160.00, 148.93, 132.44, 126.09, 113.88, 113.26, 55.96.
HRMS (EI): m/z $[M + H]^+$ calcd for $NaC_7H_6ClO_3S$ without Na: 204.9726; found: 204.9733.

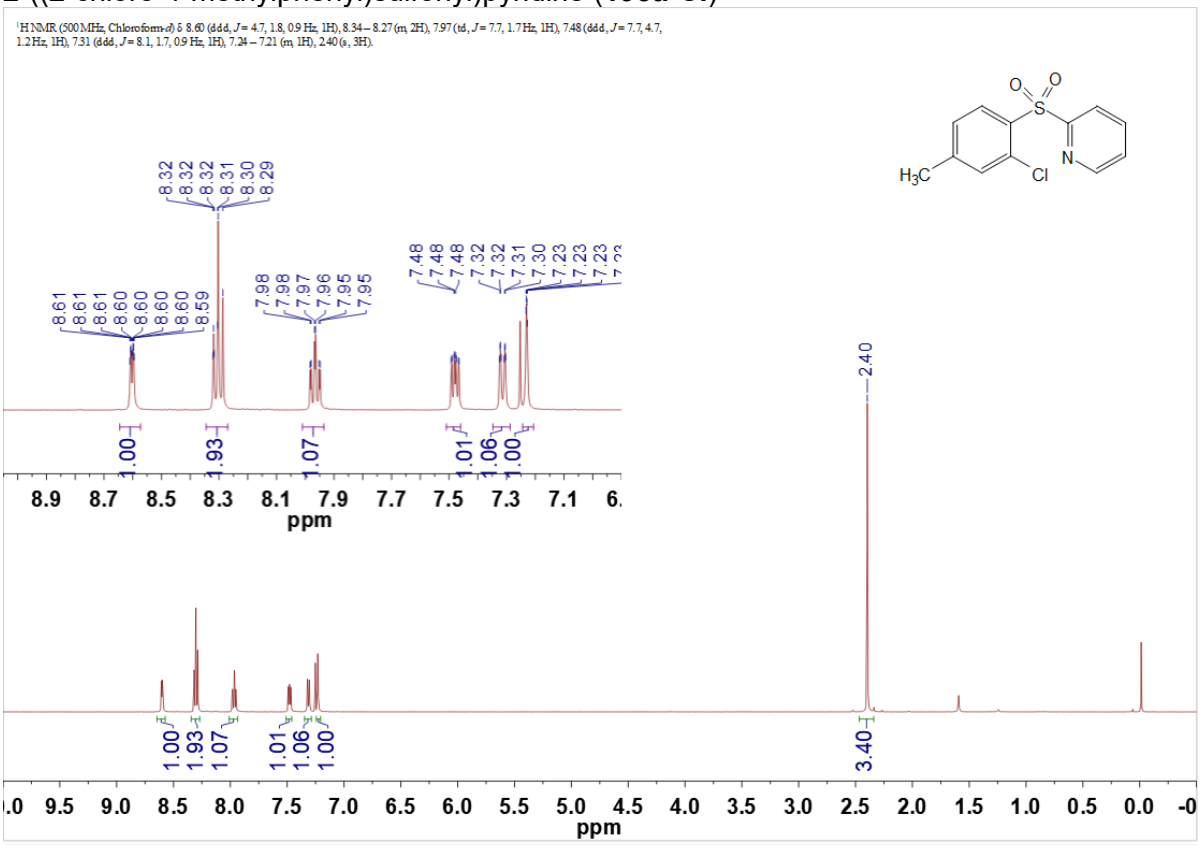
Sodium 2-bromo-4-methoxybenzenesulfinate (196e-Br)
Synthesized following general procedure of pyridine removal method in chapter 3.
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.58 (d, J = 1.8 Hz, 1H), 7.36 (dd, J = 8.3, 1.8 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 3.81 (s, 3H).
^{13}C NMR (126 MHz, dmso) δ 155.24, 154.50, 129.21, 125.63, 112.40, 110.67, 56.71.
HRMS (EI): m/z $[M + H]^+$ calcd for $NaC_7H_6BrO_3S$ without Na: 248.9221; found: 248.9228.

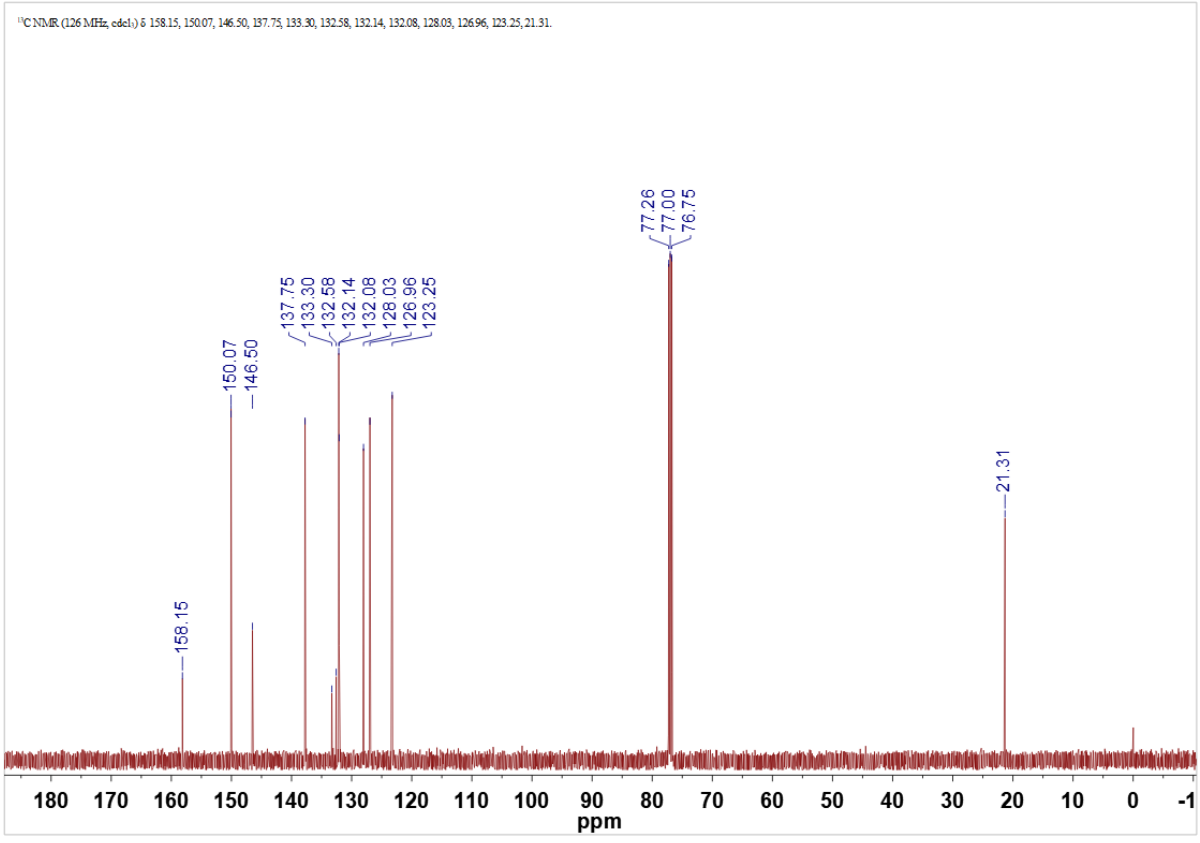
2-((2-bromo-4-methylphenyl)sulfonyl)pyridine (**195a-Br**)



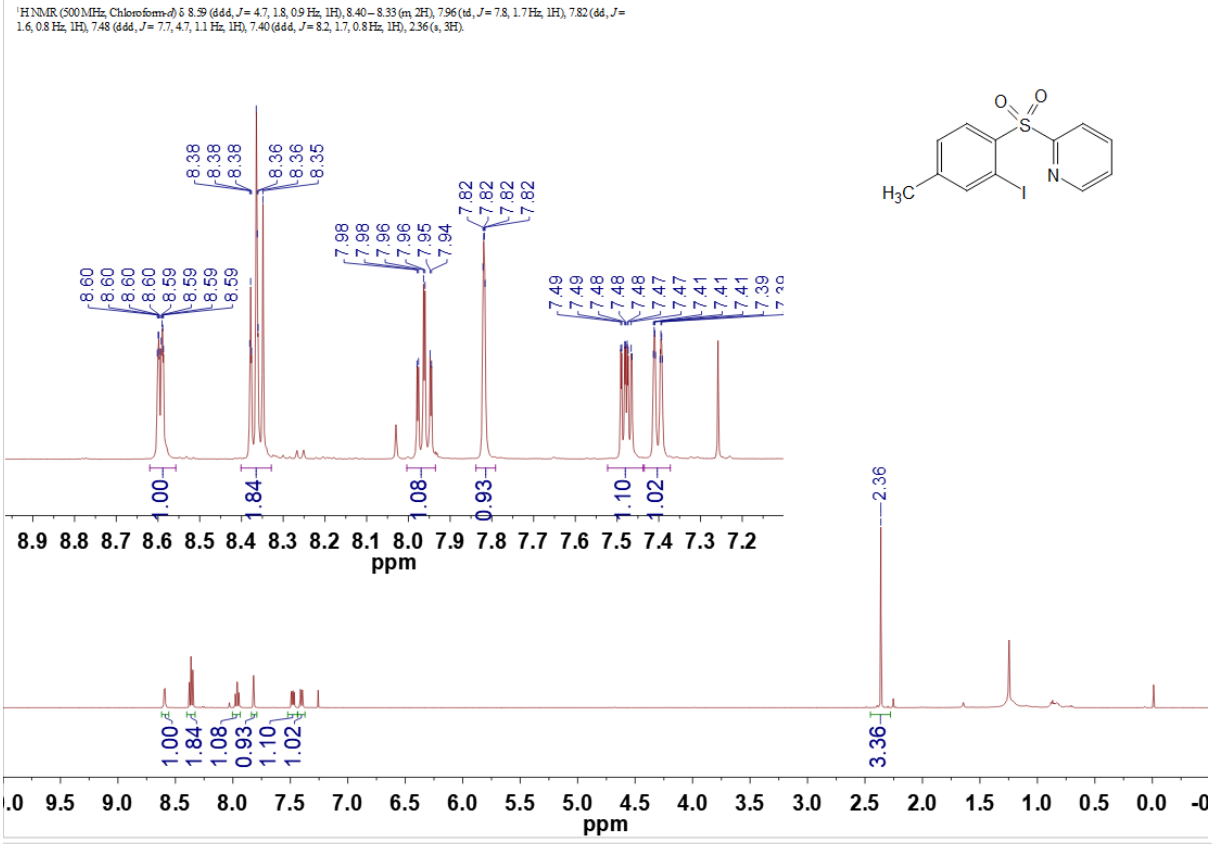


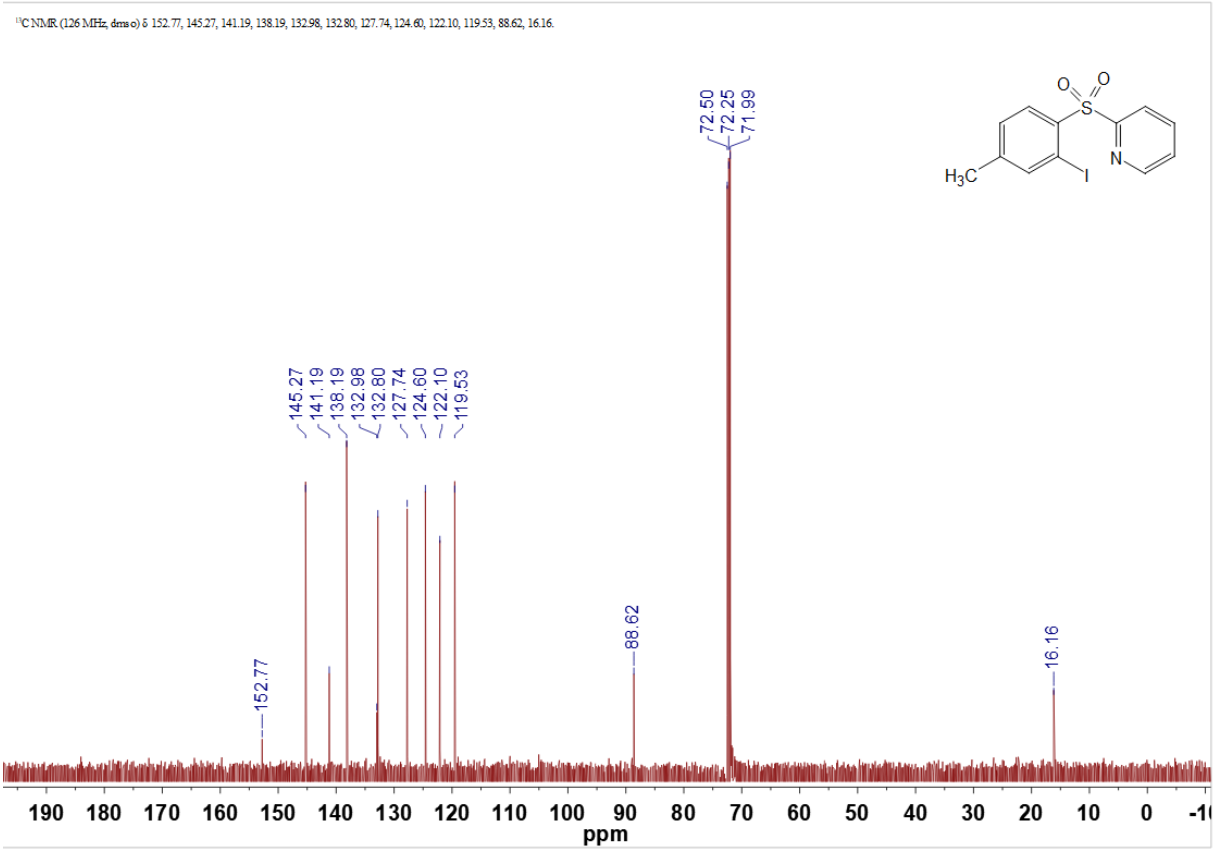
2-((2-chloro-4-methylphenyl)sulfonyl)pyridine (**195a-Cl**)



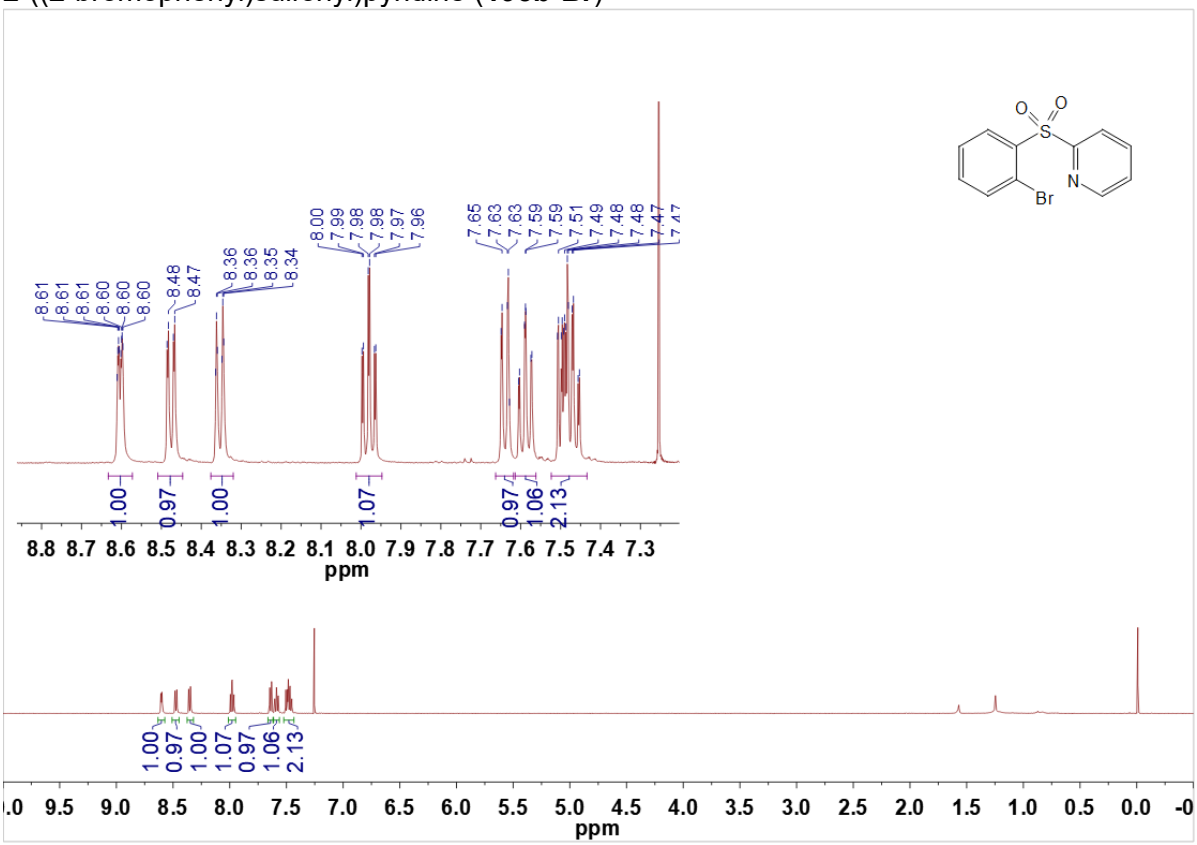


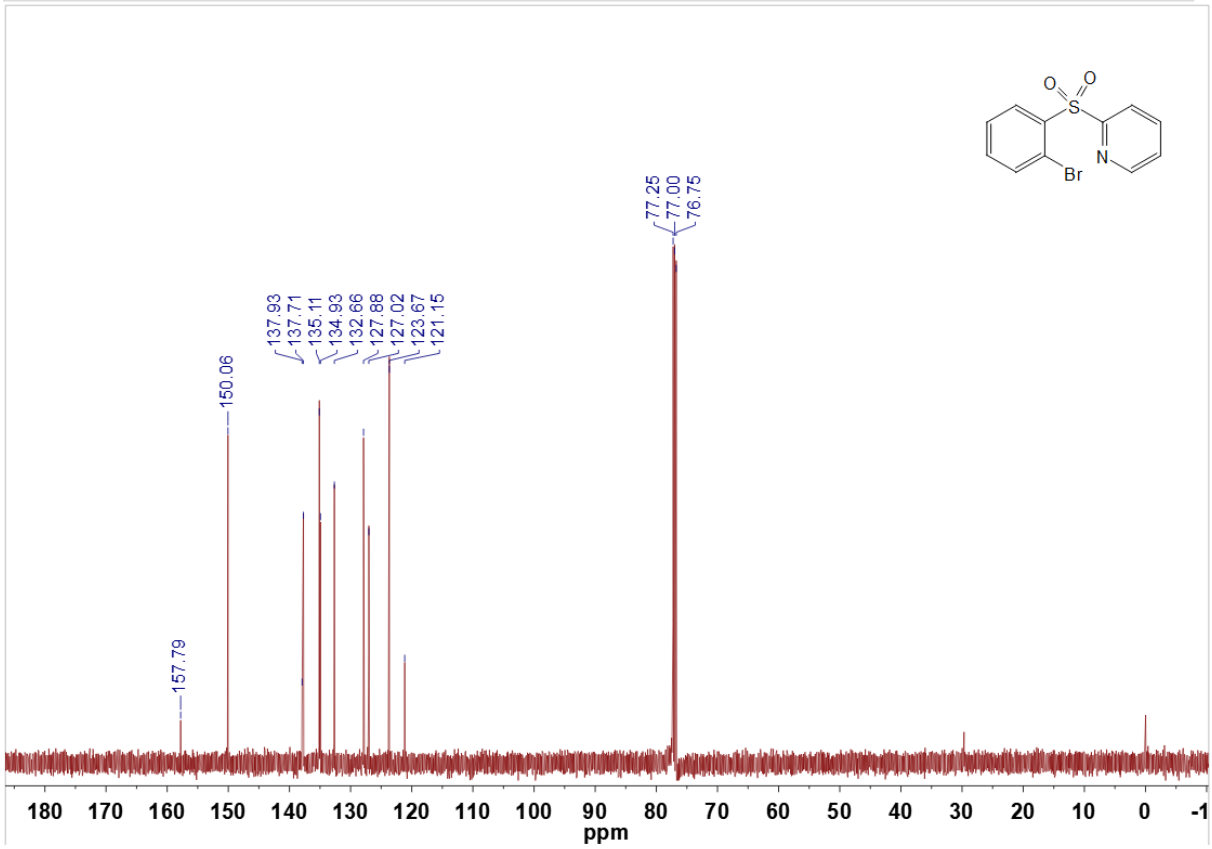
2-((2-iodo-4-methylphenyl)sulfonyl)pyridine (**195a-I**)



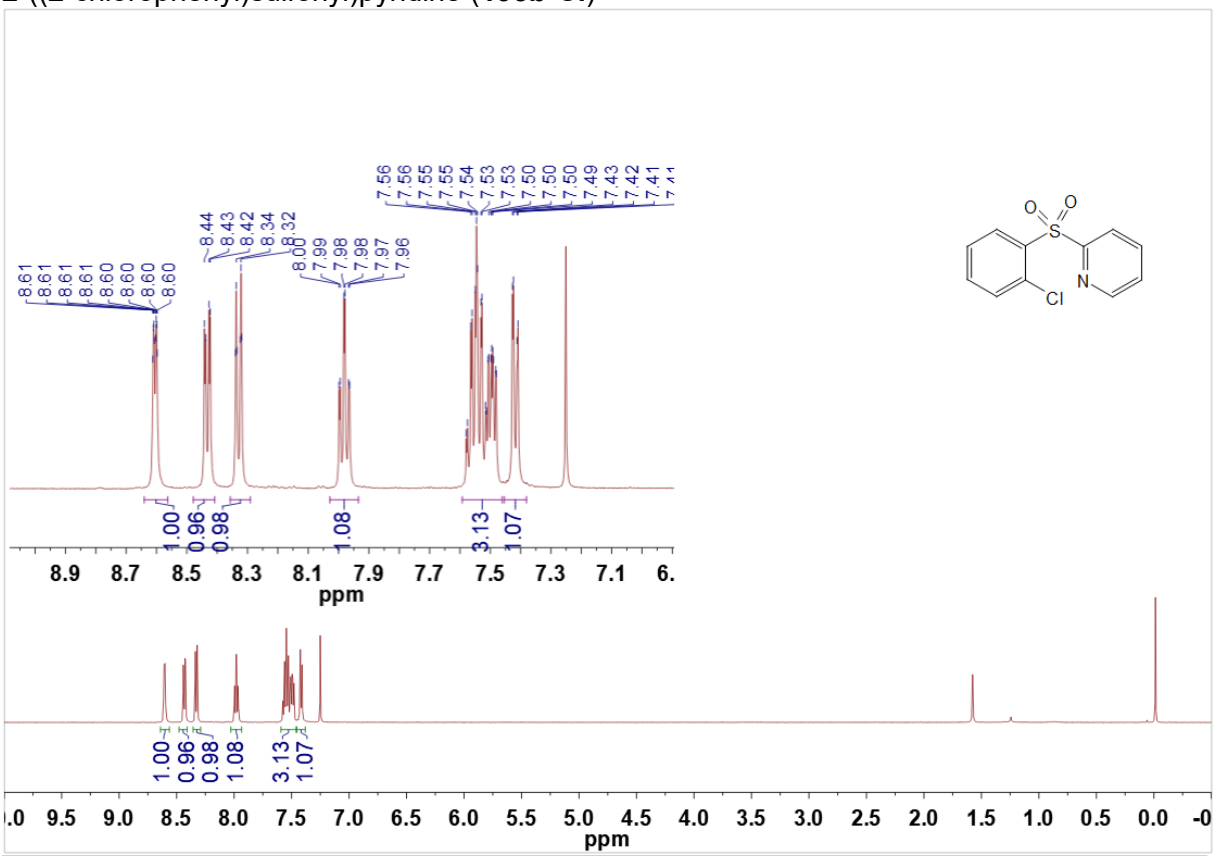


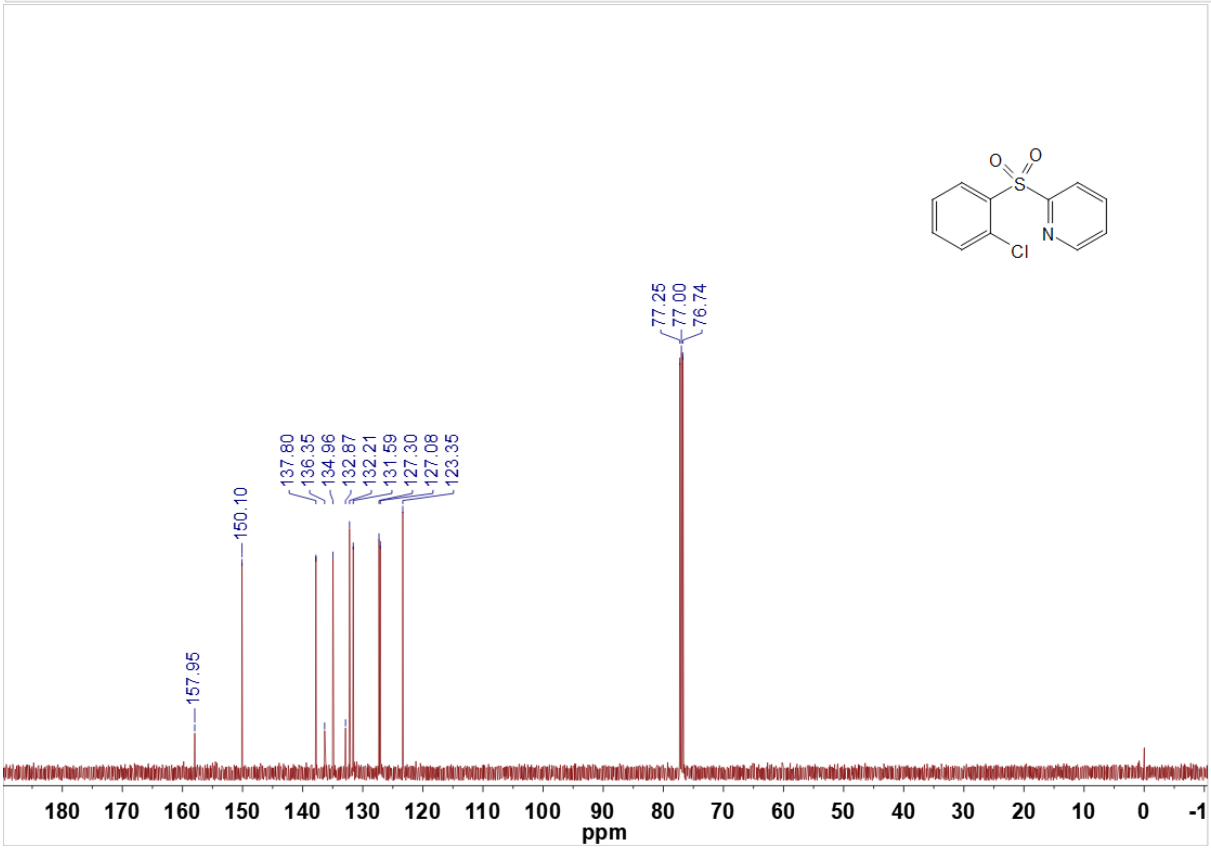
2-((2-bromophenyl)sulfonyl)pyridine (**195b-Br**)



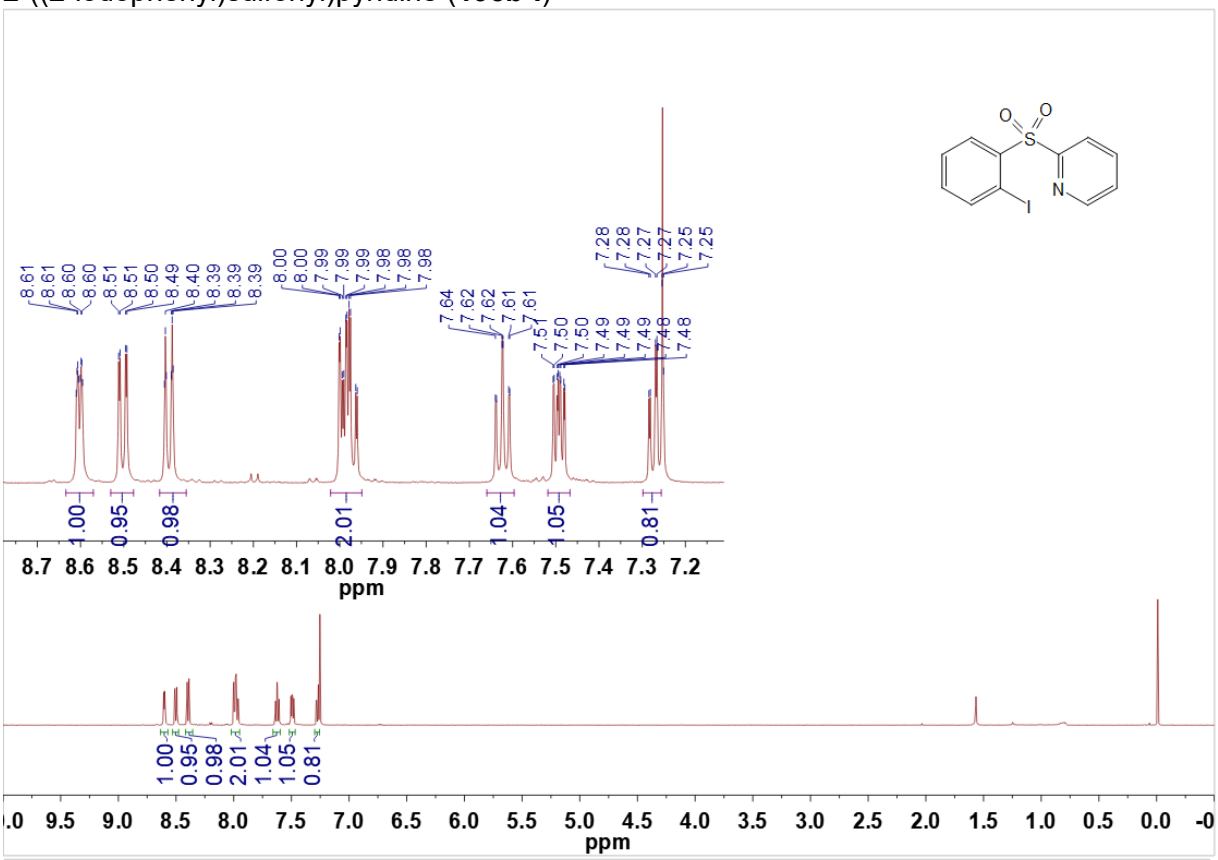


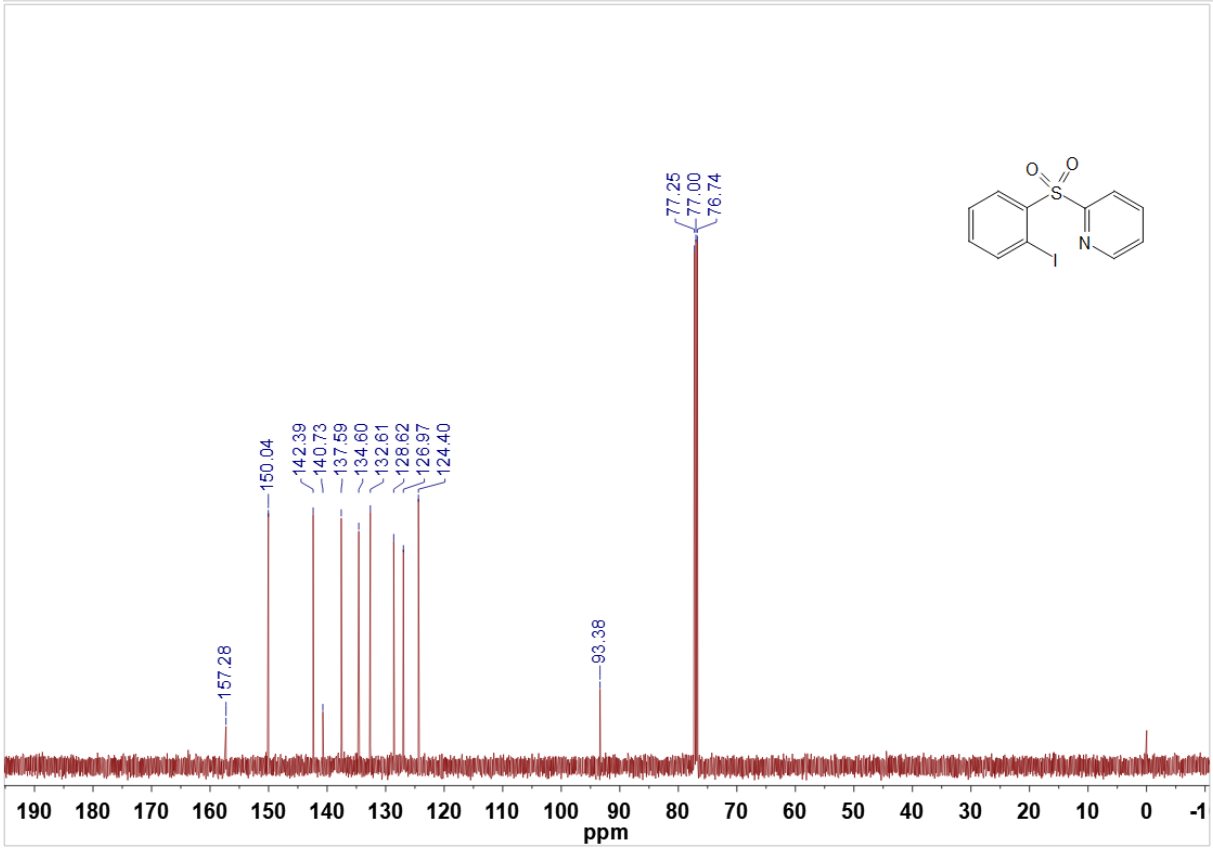
2-((2-chlorophenyl)sulfonyl)pyridine (**195b-Cl**)



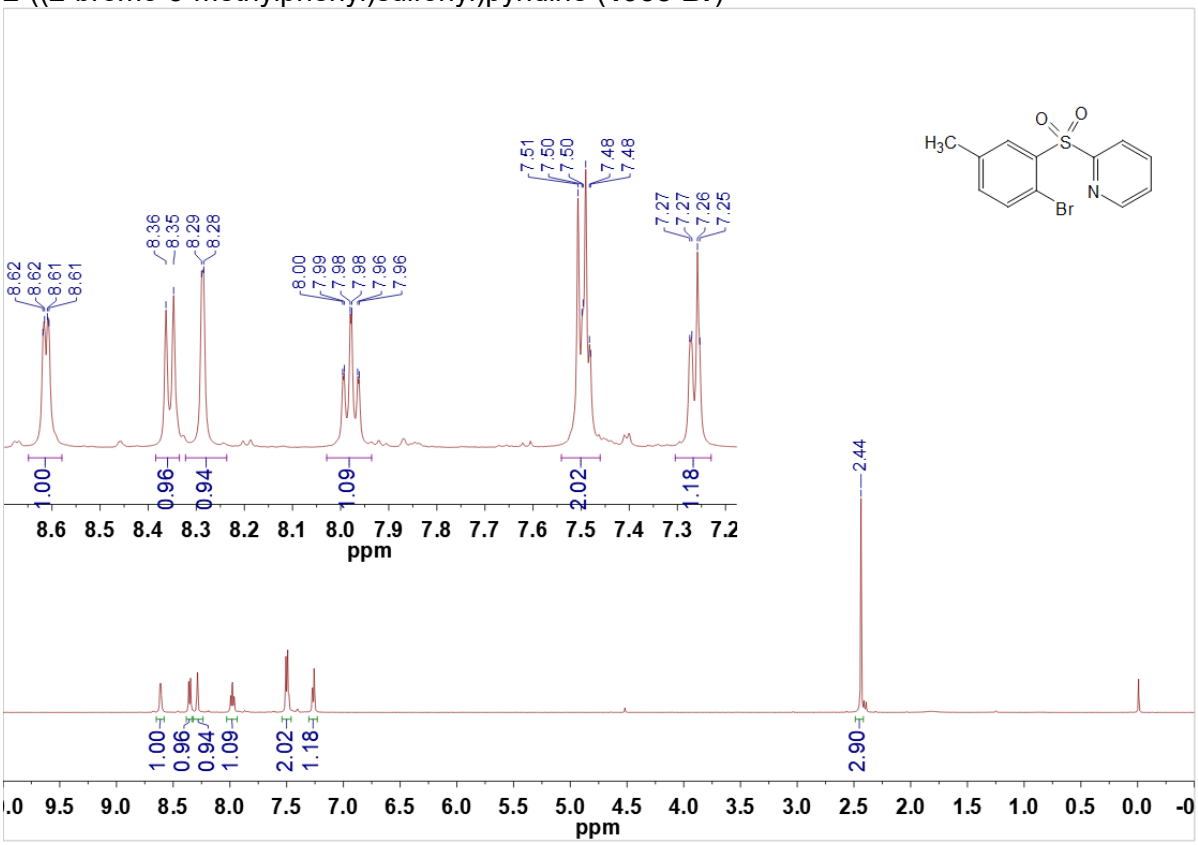


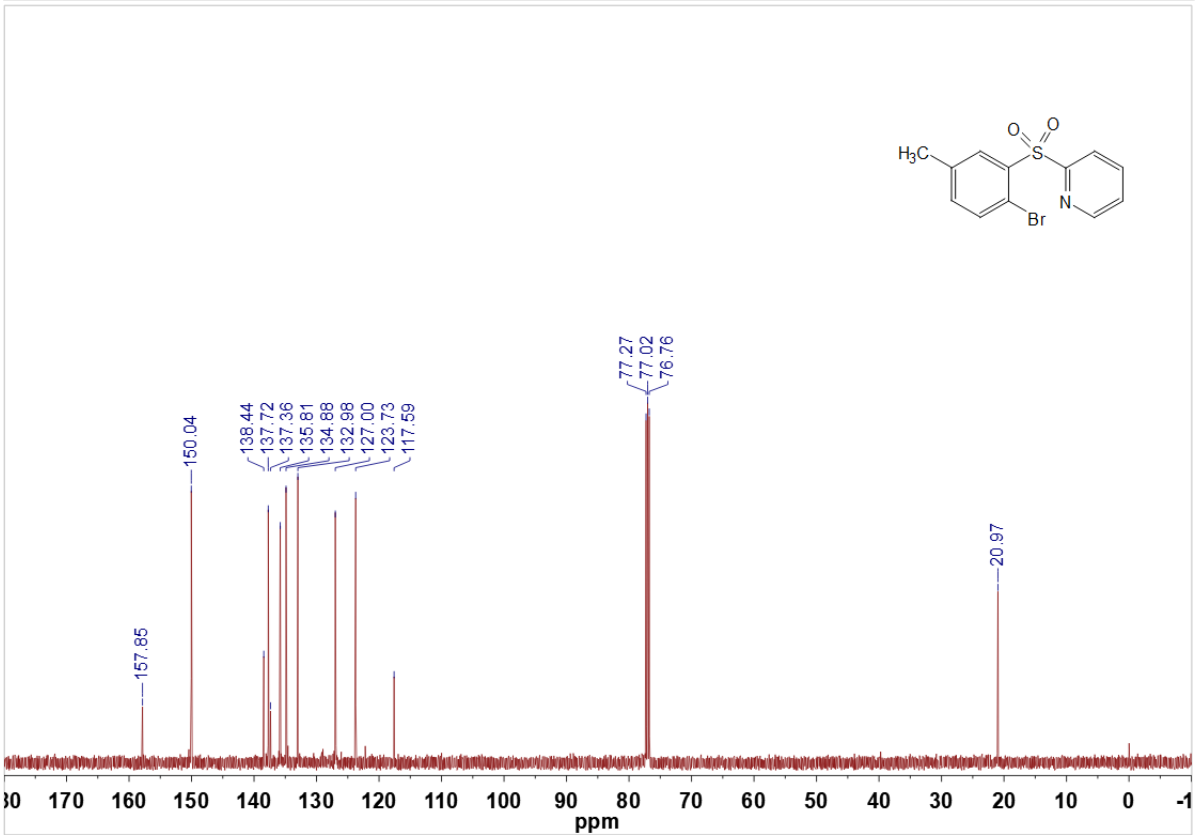
2-((2-iodophenyl)sulfonyl)pyridine (**195b-I**)



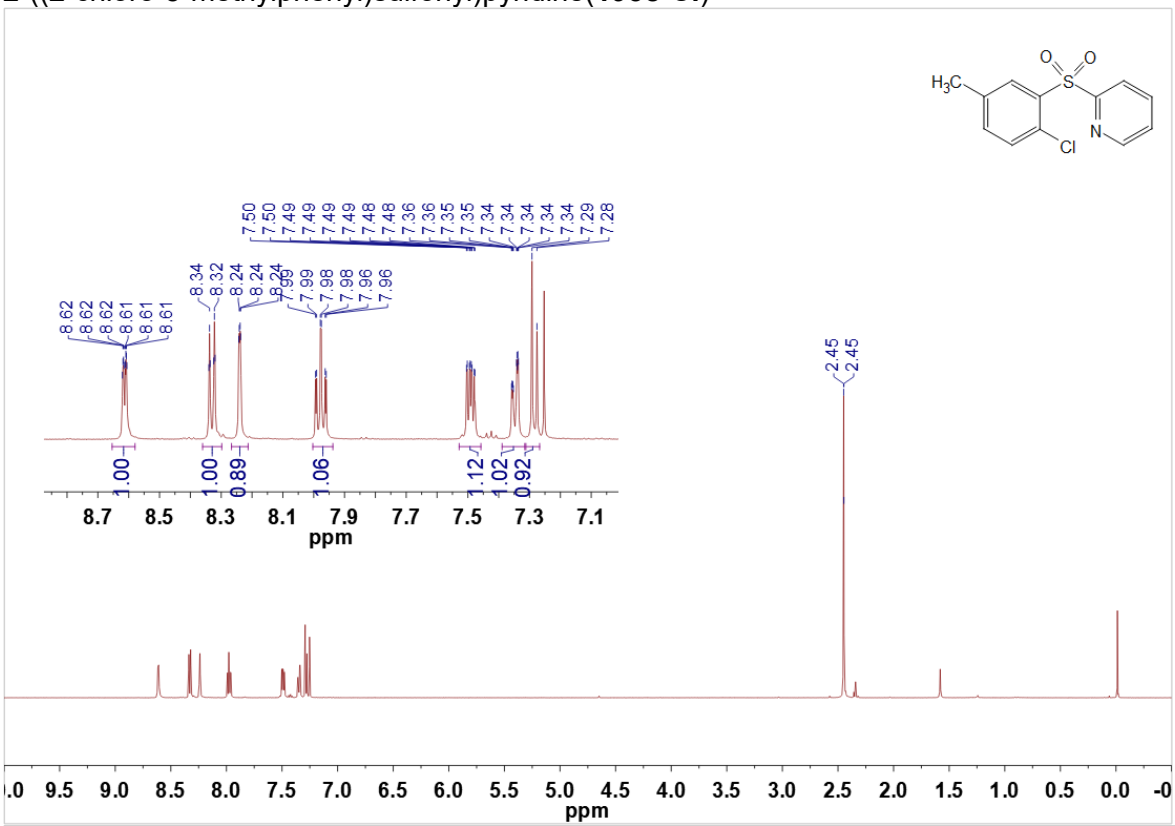


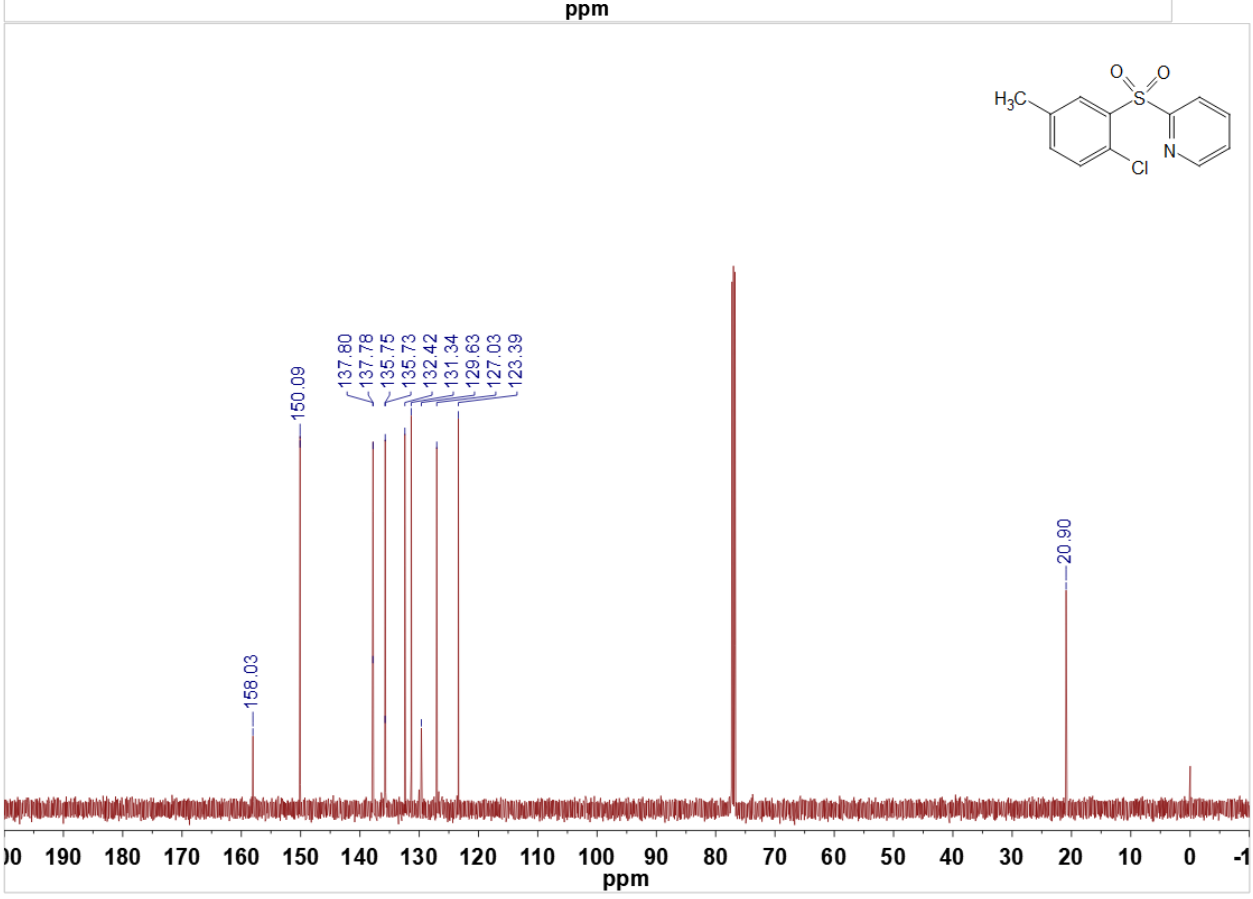
2-((2-bromo-5-methylphenyl)sulfonyl)pyridine (**195c-Br**)



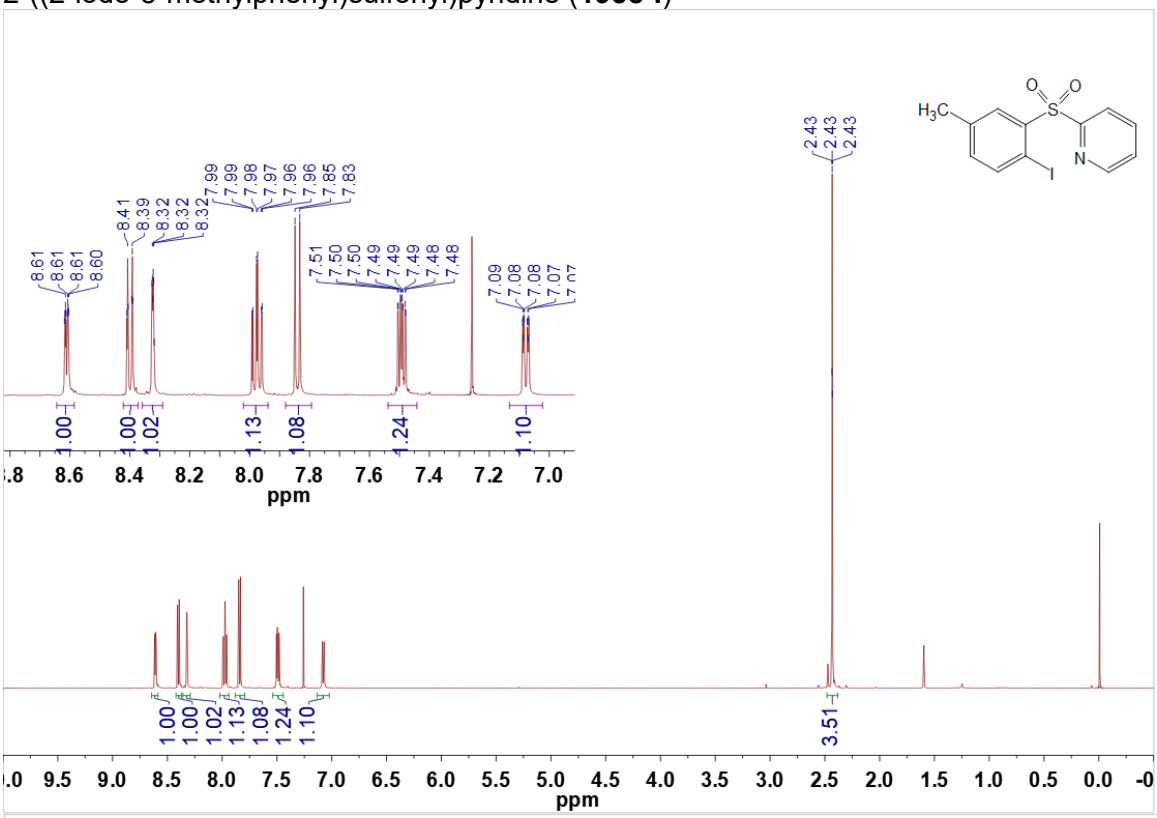


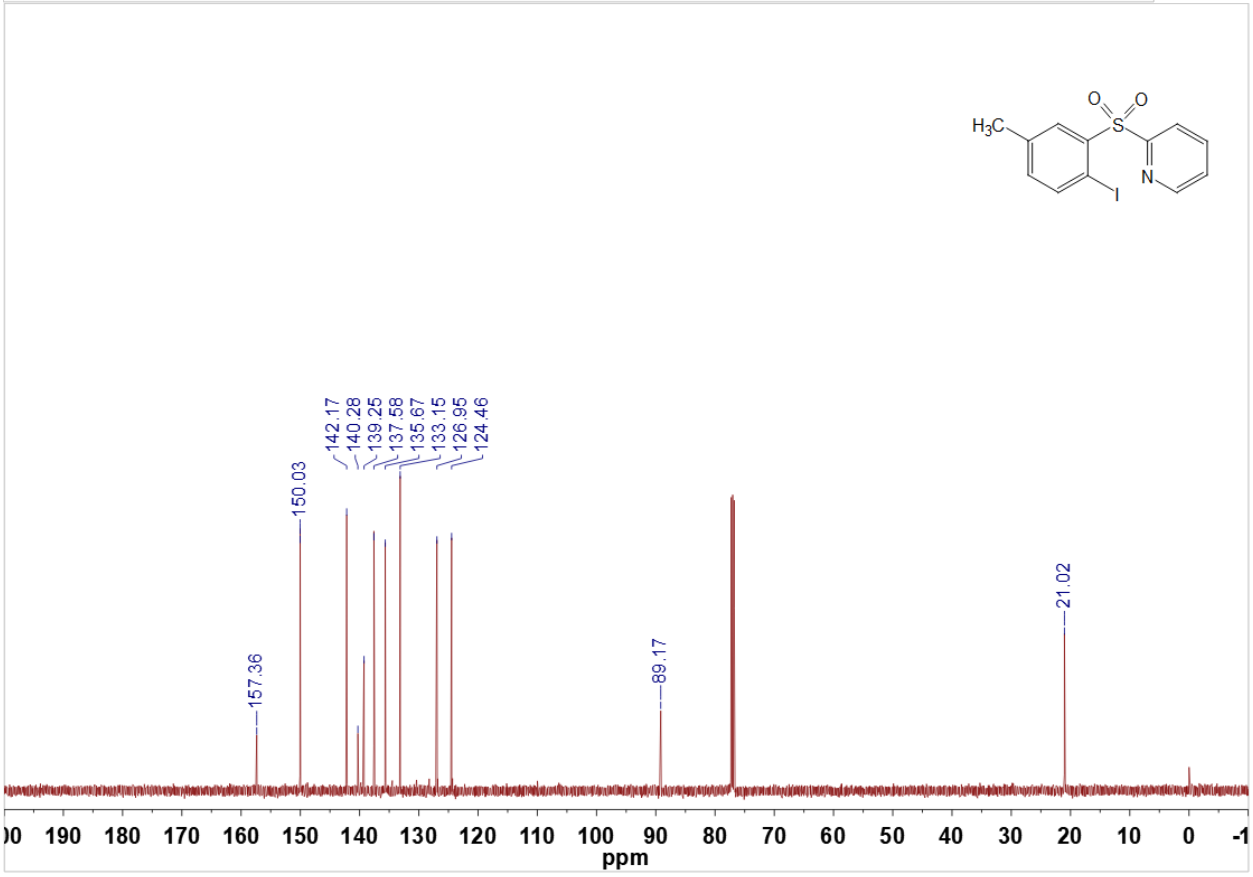
2-((2-chloro-5-methylphenyl)sulfonyl)pyridine(**195c-Cl**)



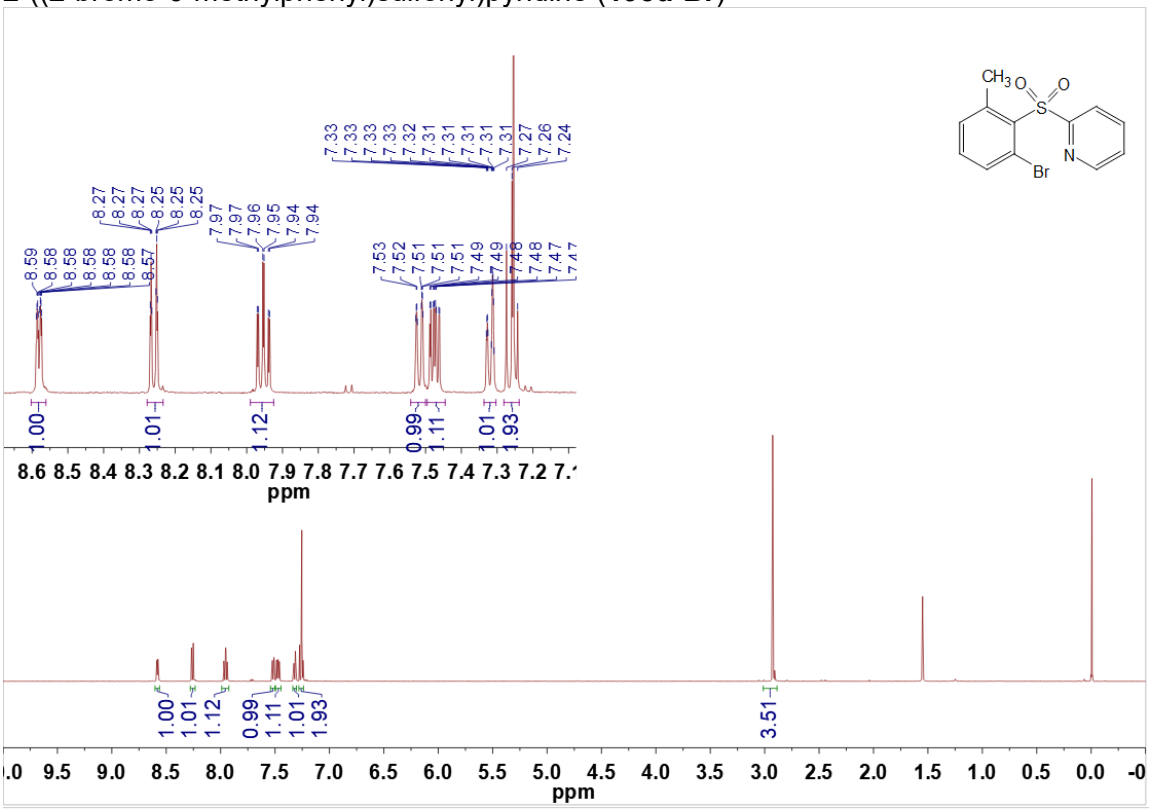


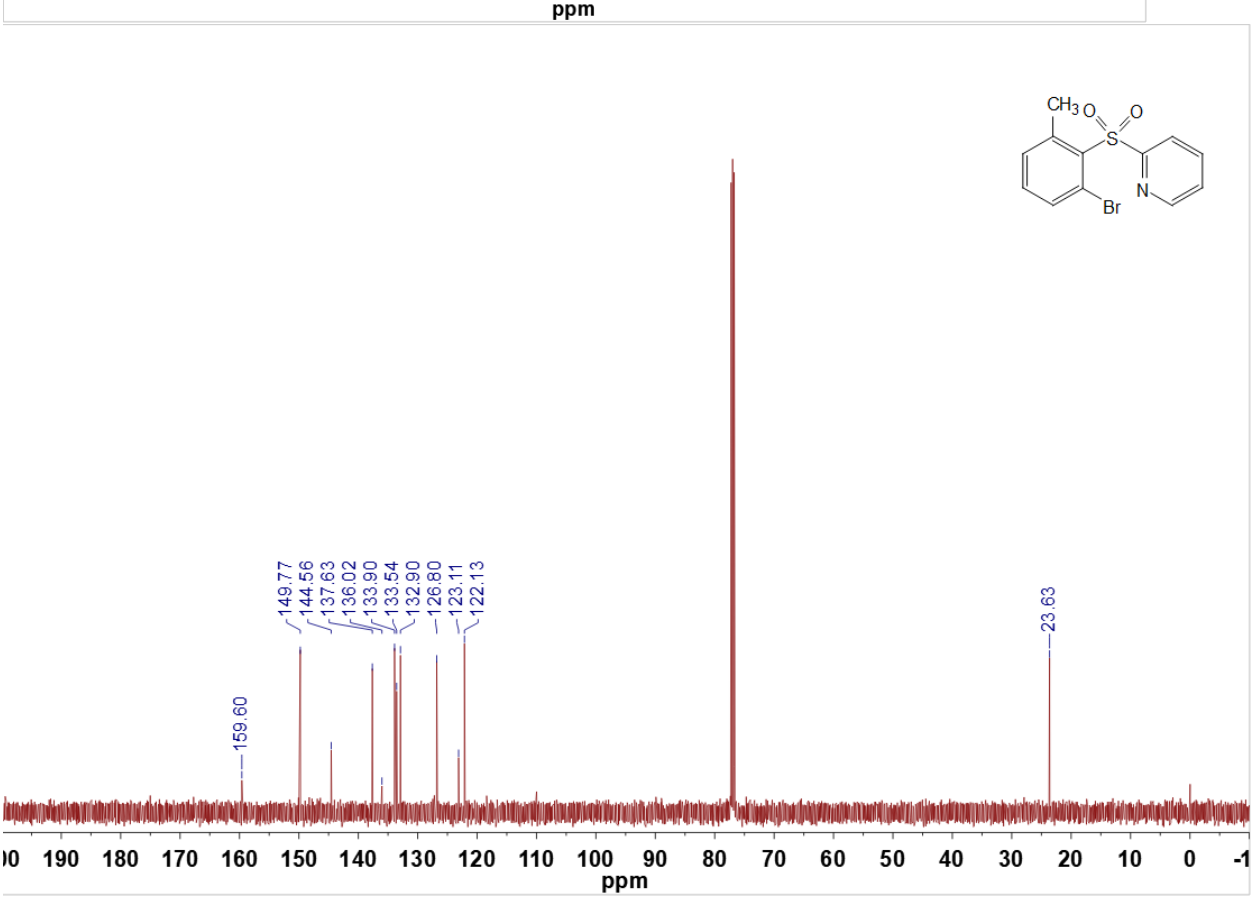
2-((2-iodo-5-methylphenyl)sulfonyl)pyridine (**195c-I**)



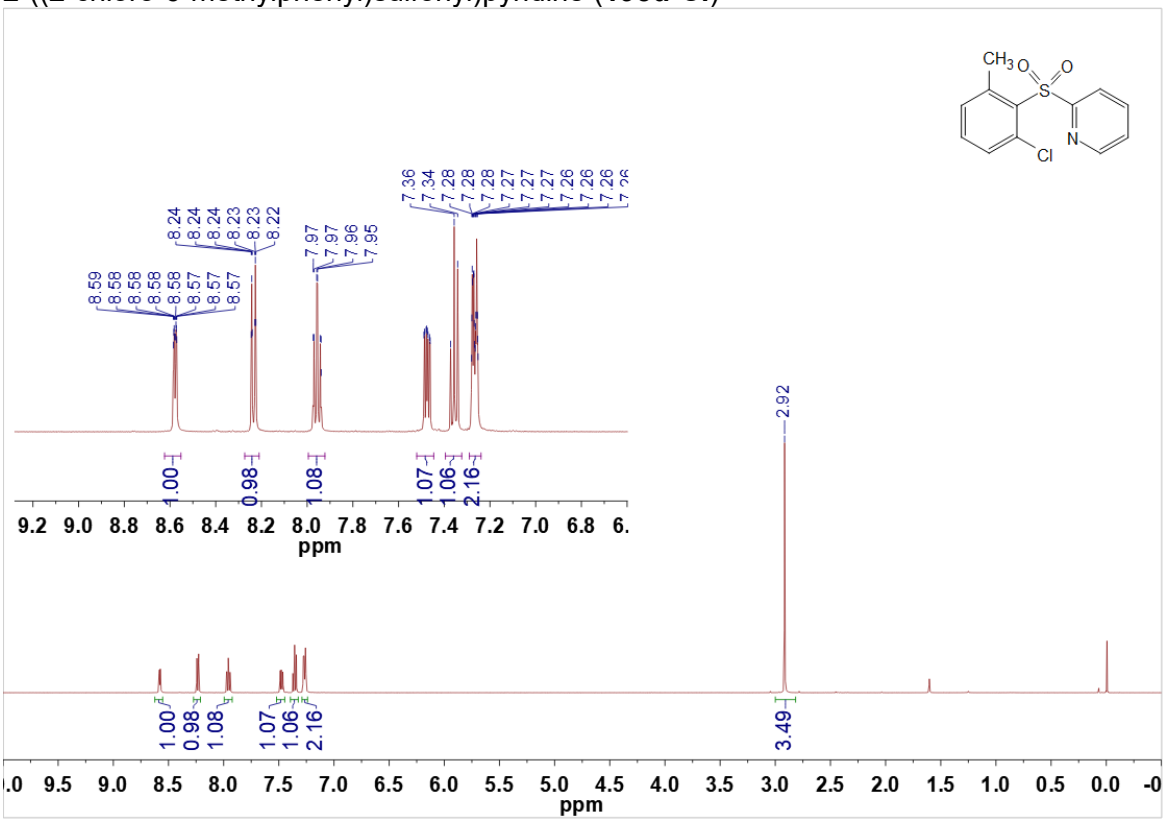


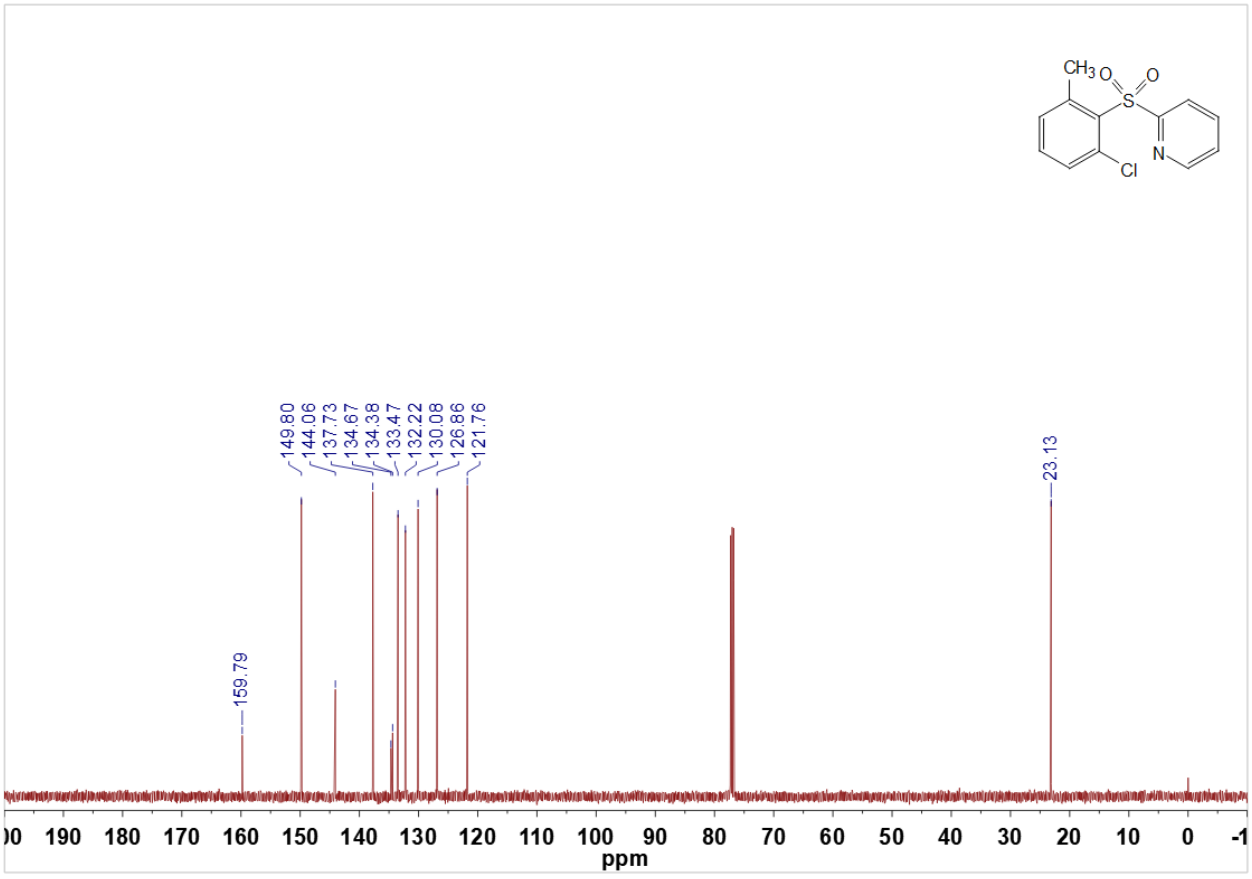
2-((2-bromo-6-methylphenyl)sulfonyl)pyridine (**195d-Br**)



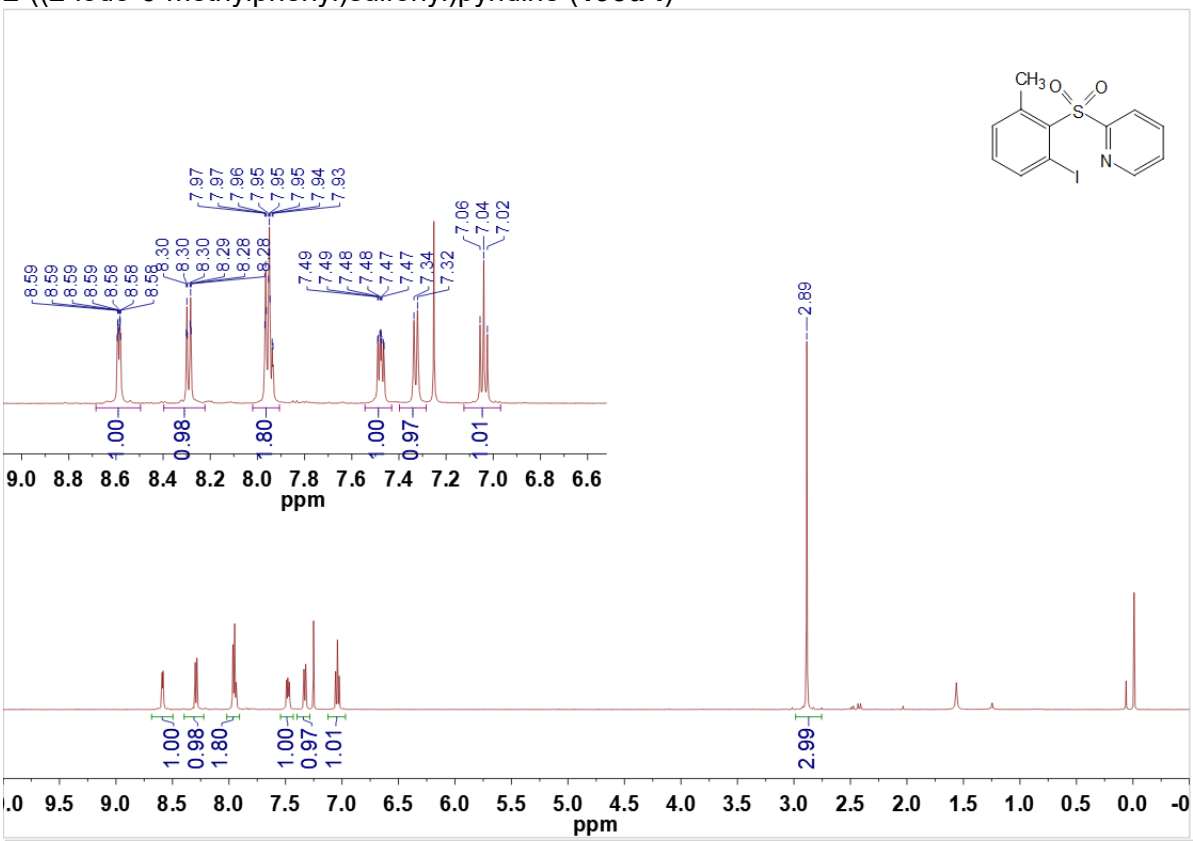


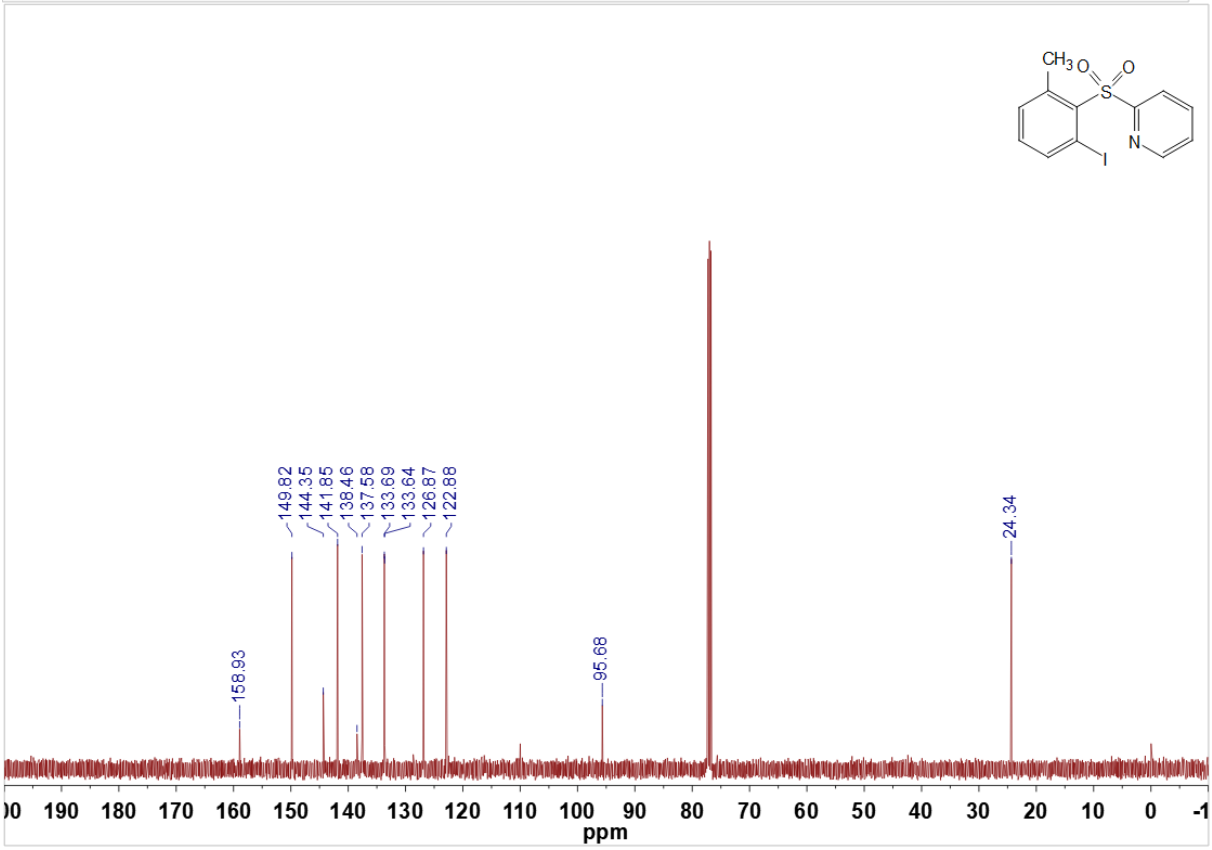
2-((2-chloro-6-methylphenyl)sulfonyl)pyridine (**195d-Cl**)



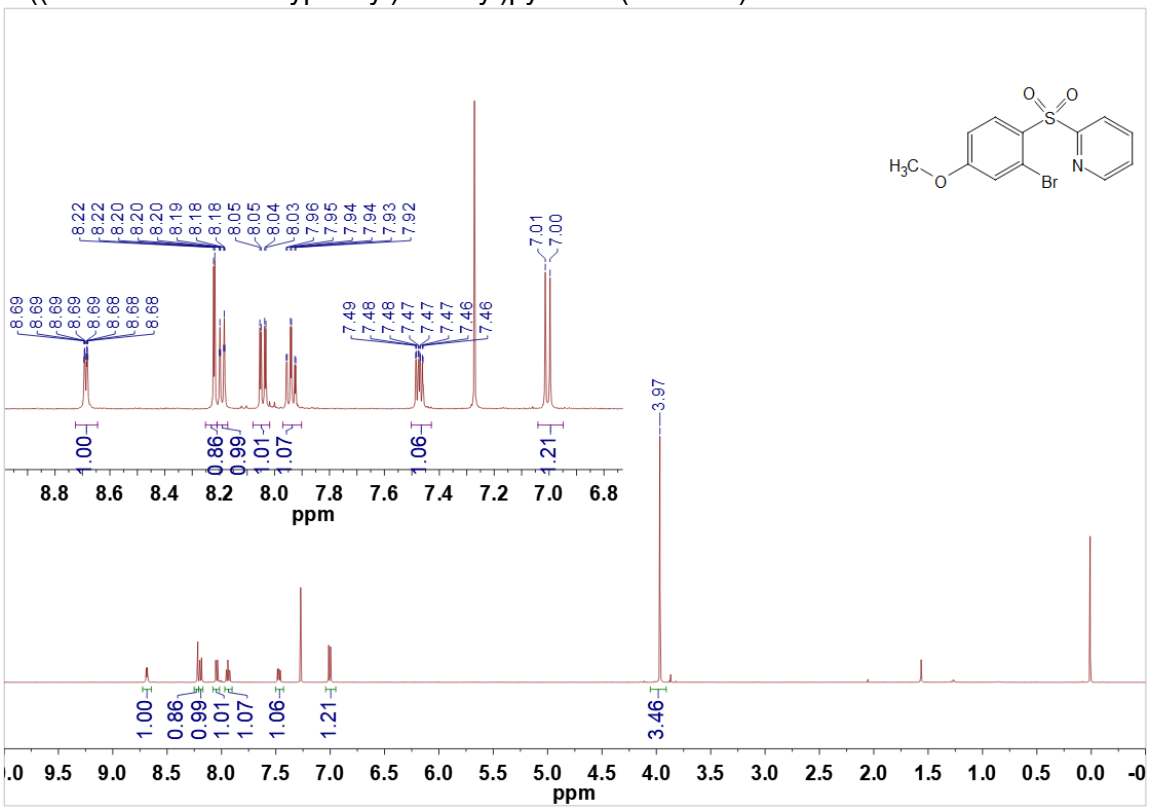


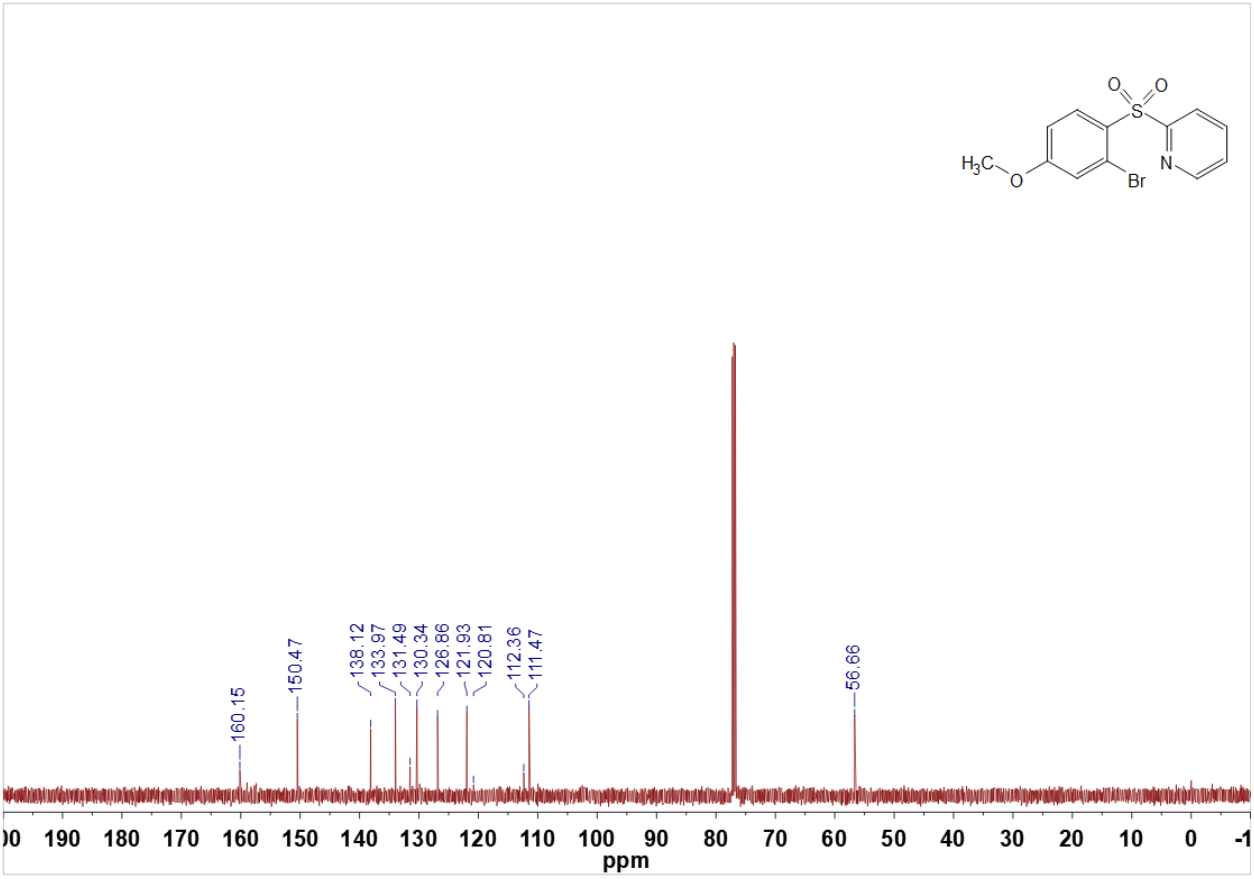
2-((2-iodo-6-methylphenyl)sulfonyl)pyridine (**195d-I**)



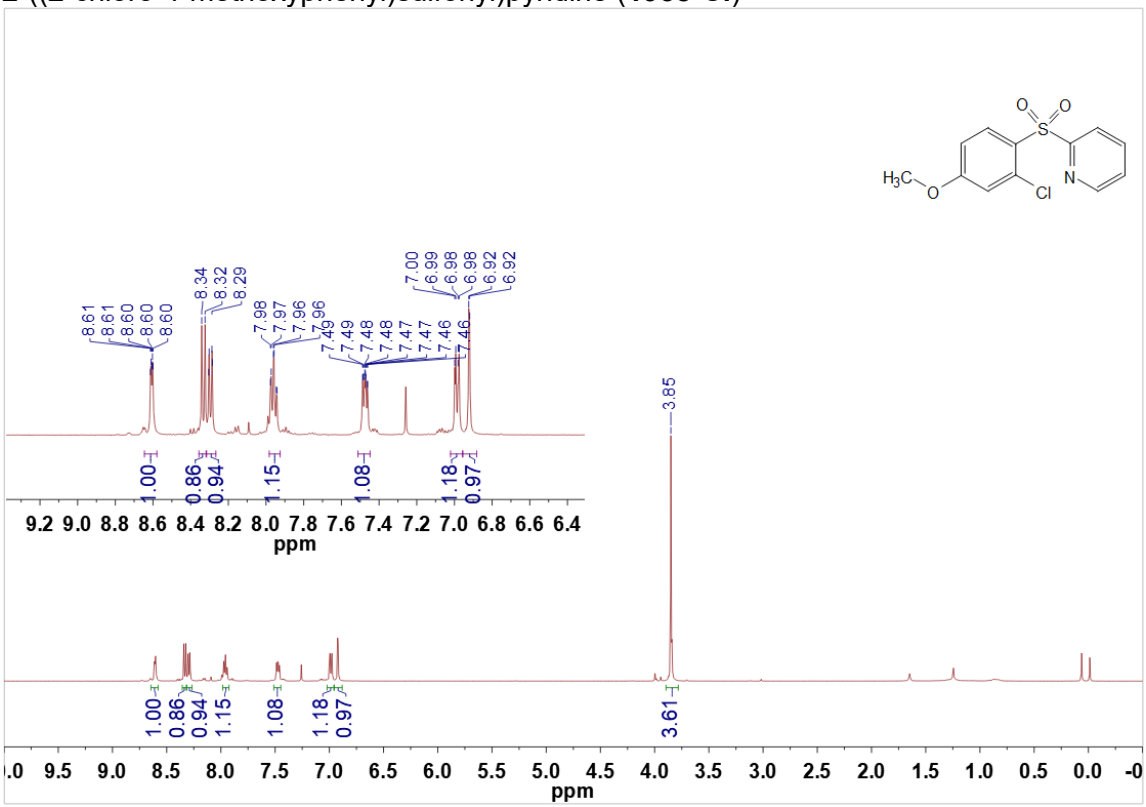


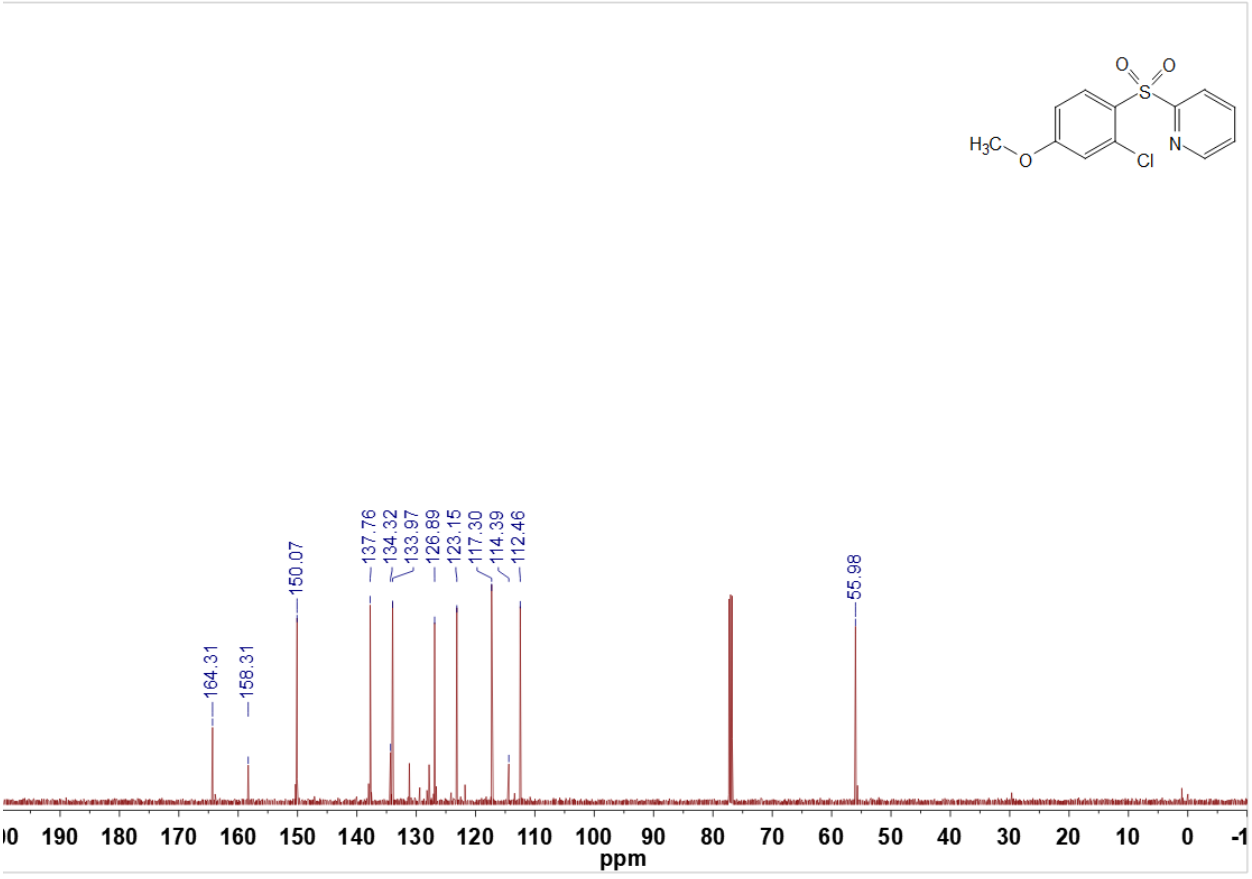
2-((2-bromo-4-methoxyphenyl)sulfonyl)pyridine (**195e-Br**)



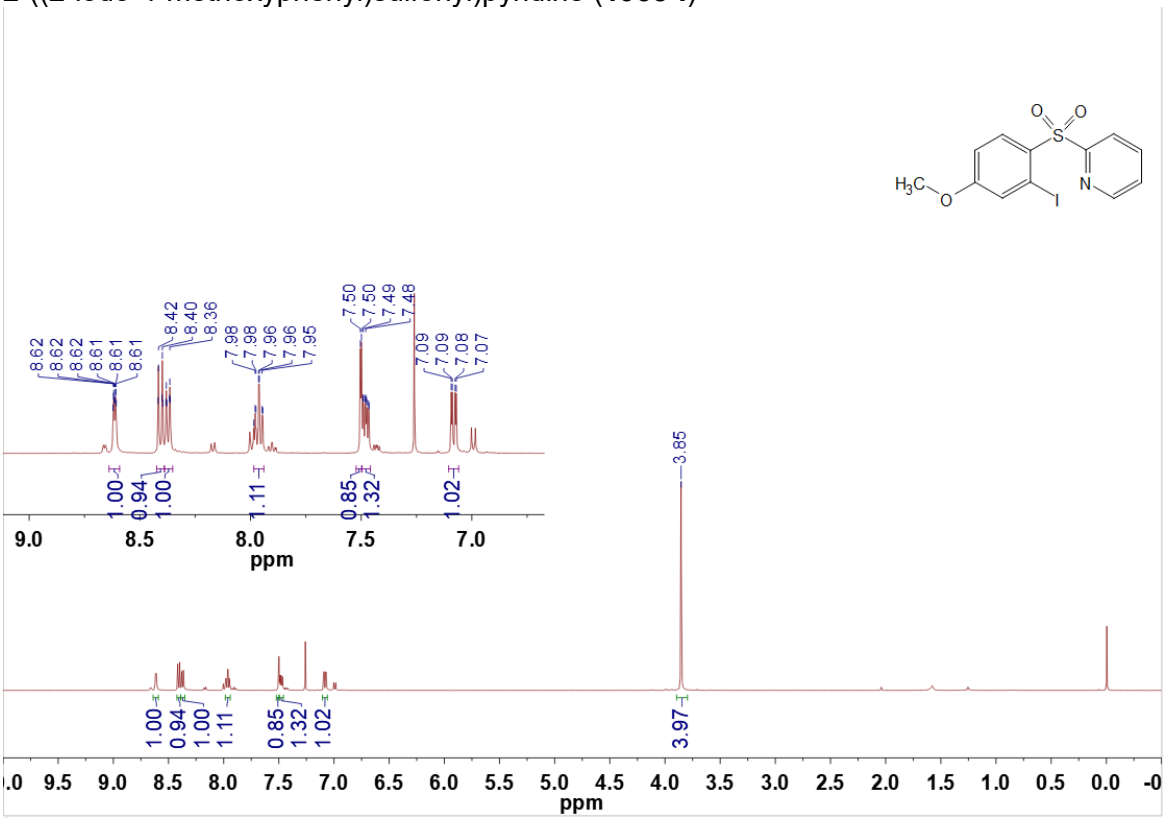


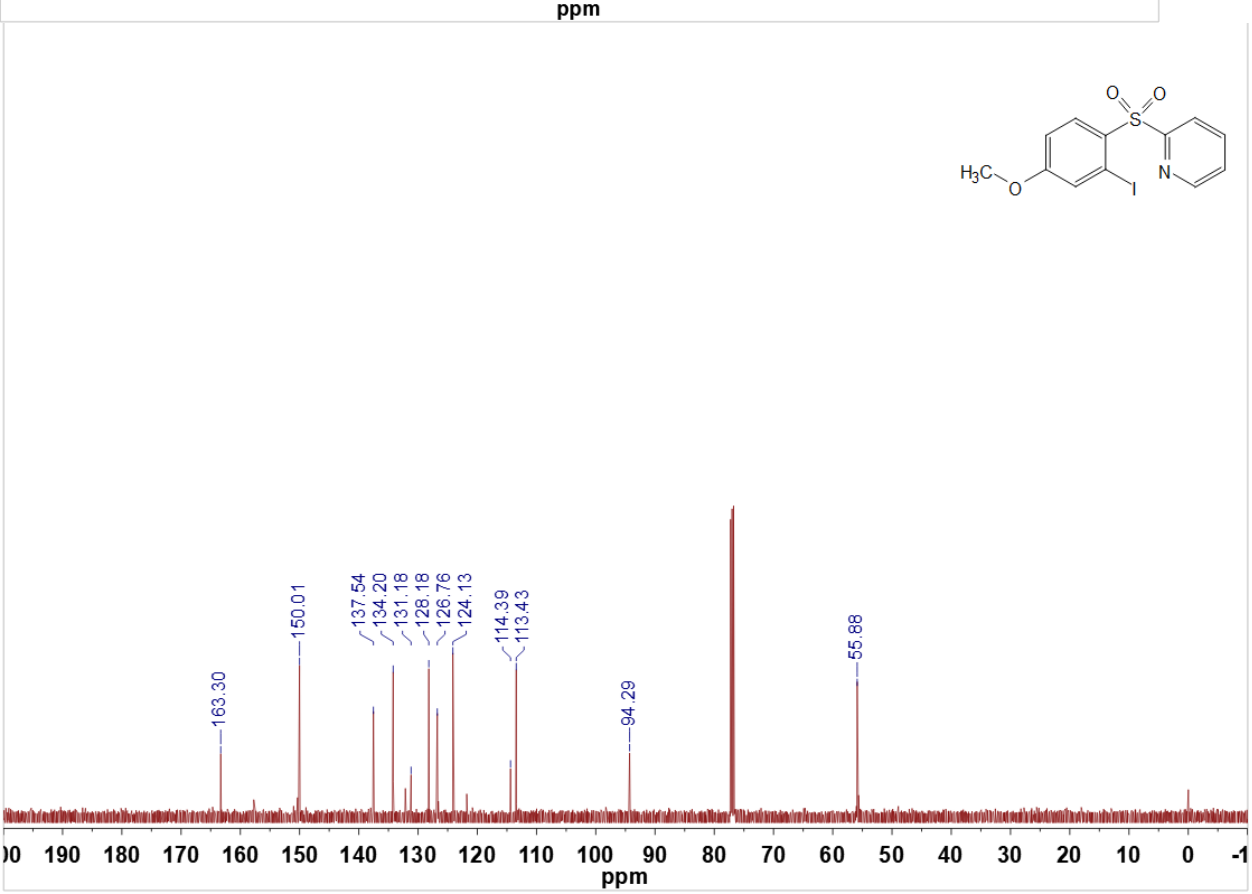
2-((2-chloro-4-methoxyphenyl)sulfonyl)pyridine (**195e-Cl**)



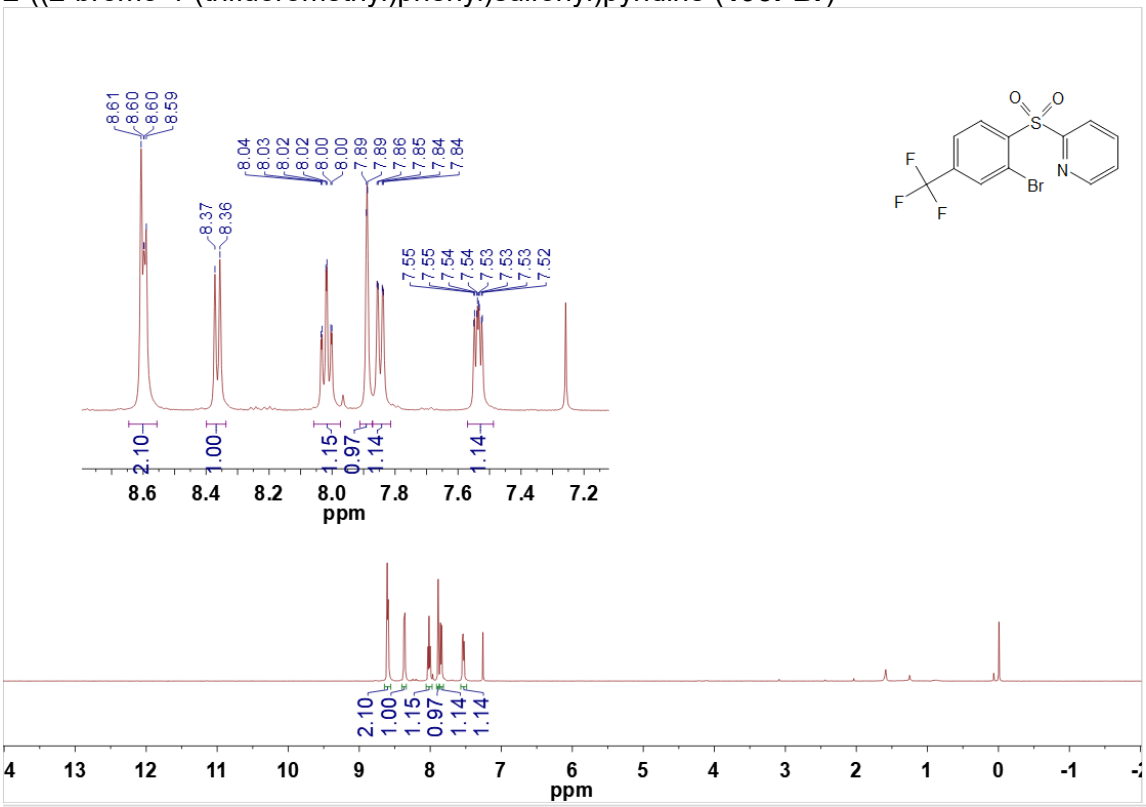


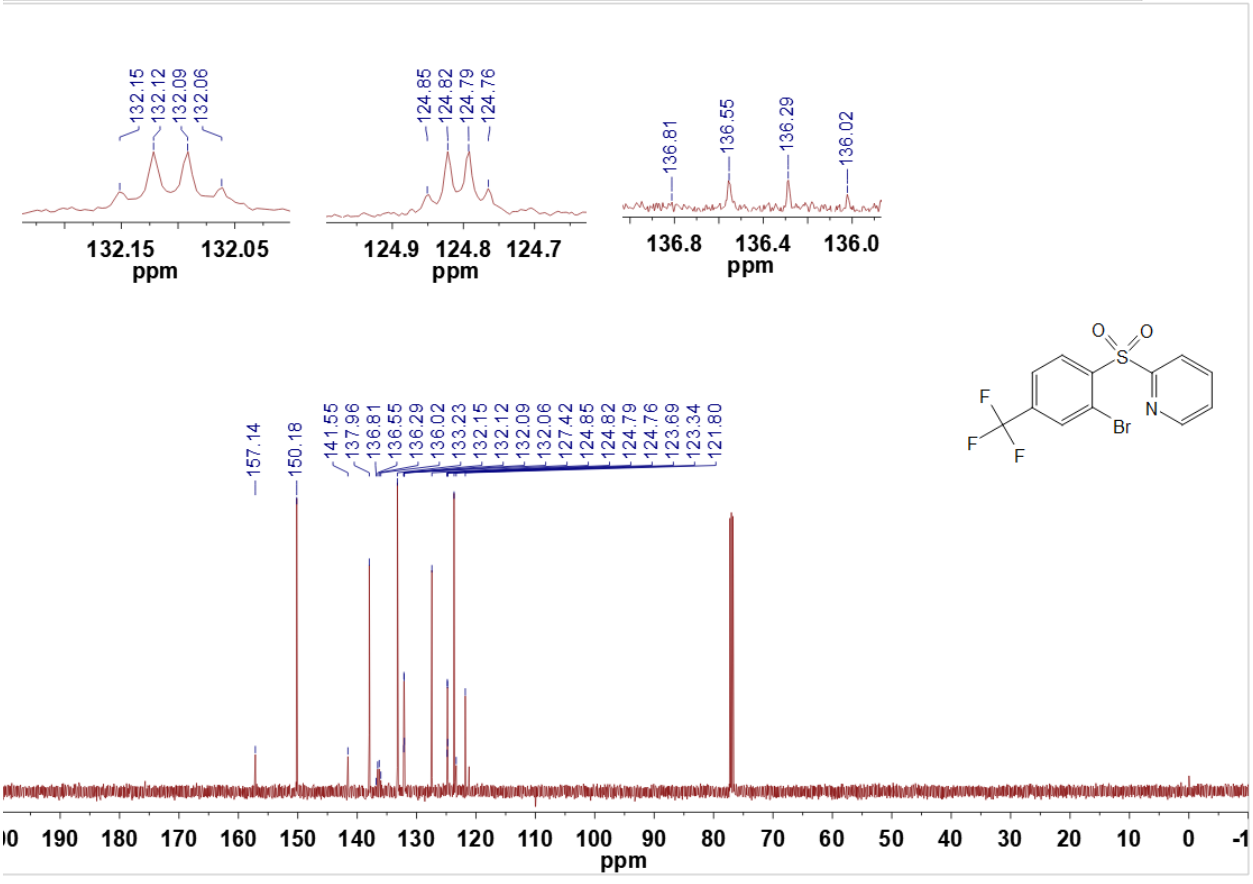
2-((2-iodo-4-methoxyphenyl)sulfonyl)pyridine (**195e-l**)



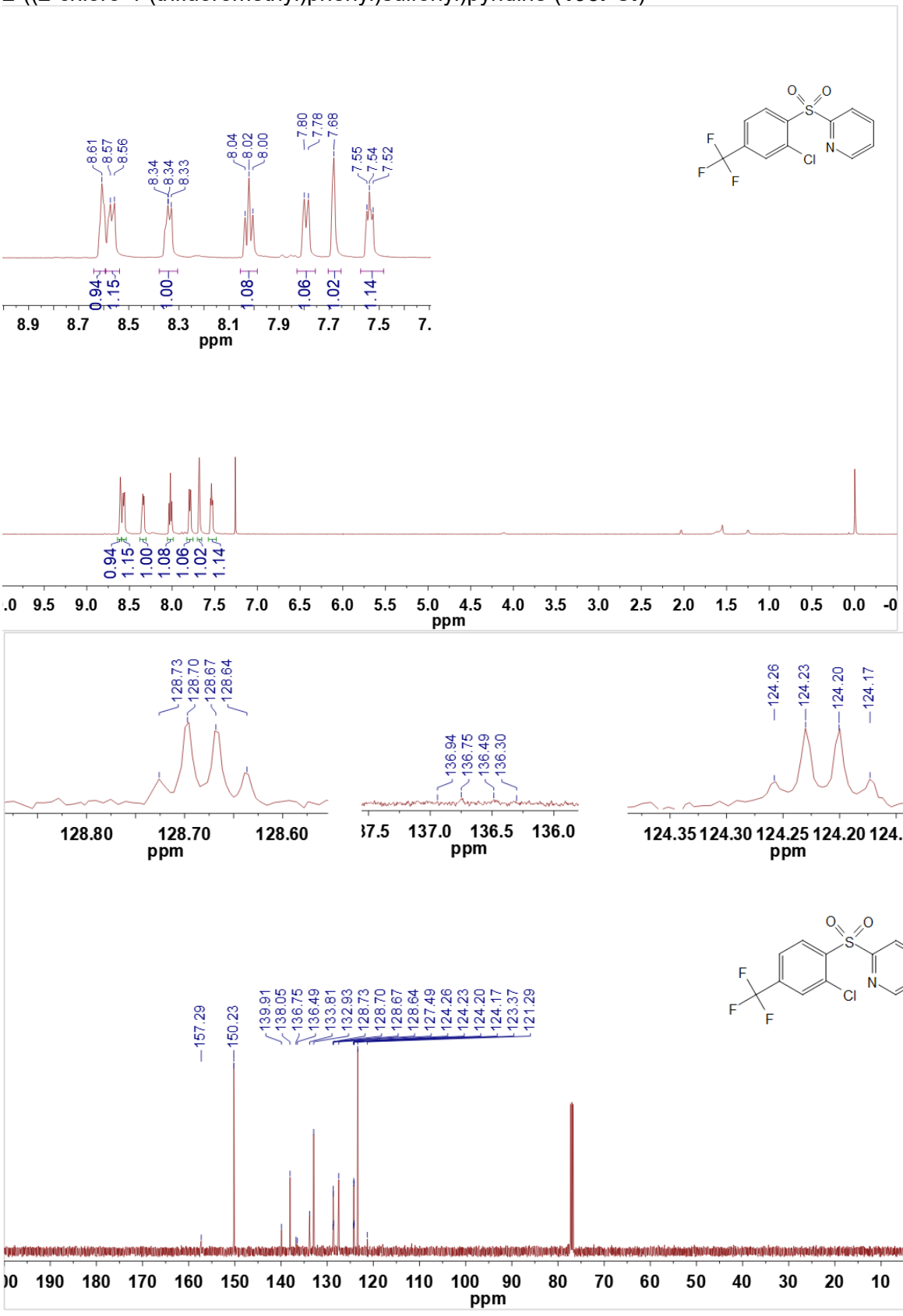


2-((2-bromo-4-(trifluoromethyl)phenyl)sulfonyl)pyridine (**195f-Br**)

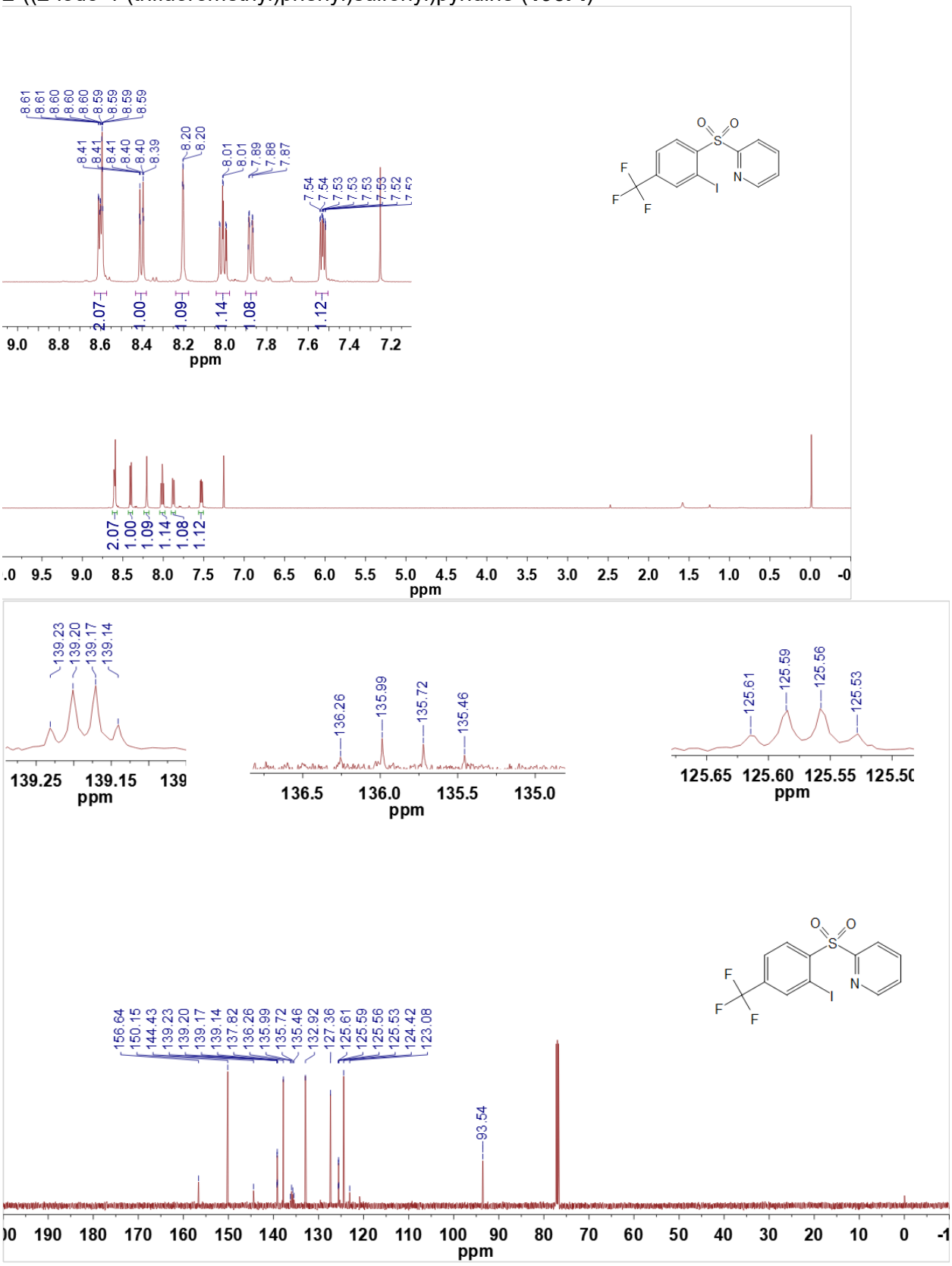




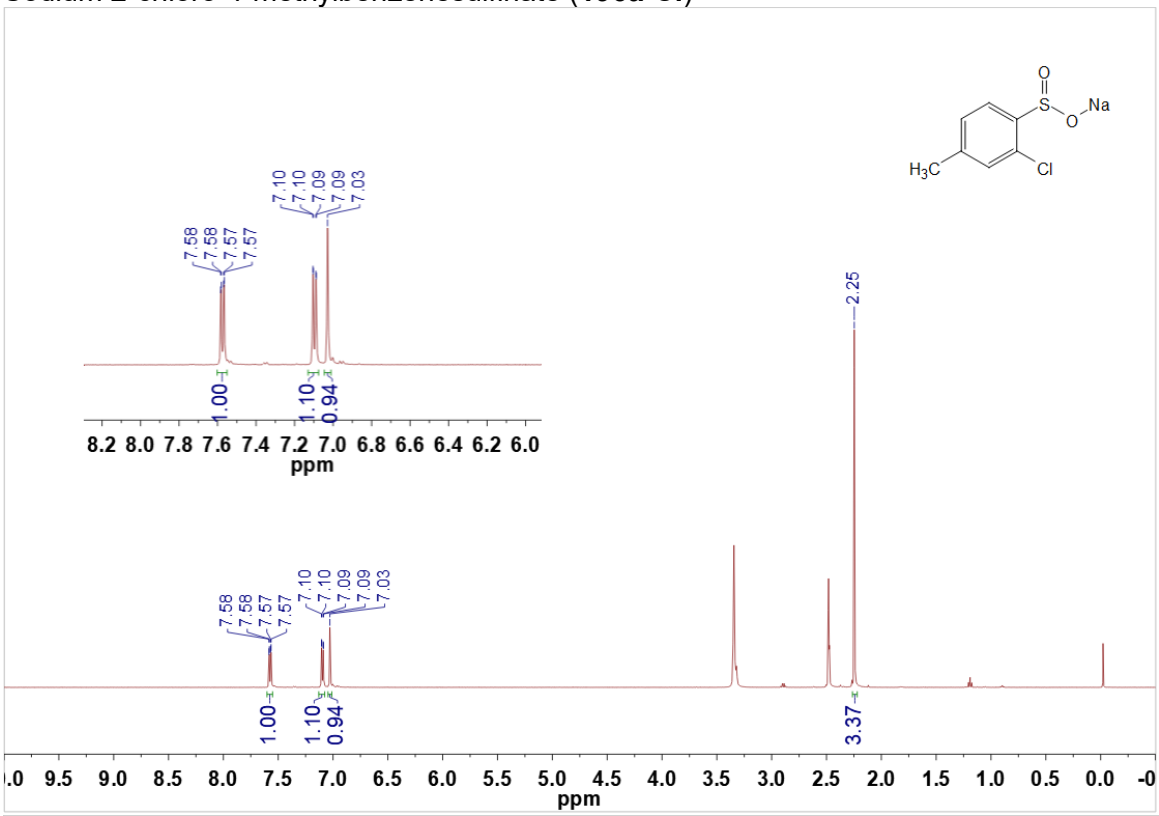
2-((2-chloro-4-(trifluoromethyl)phenyl)sulfonyl)pyridine (**195f-Cl**)

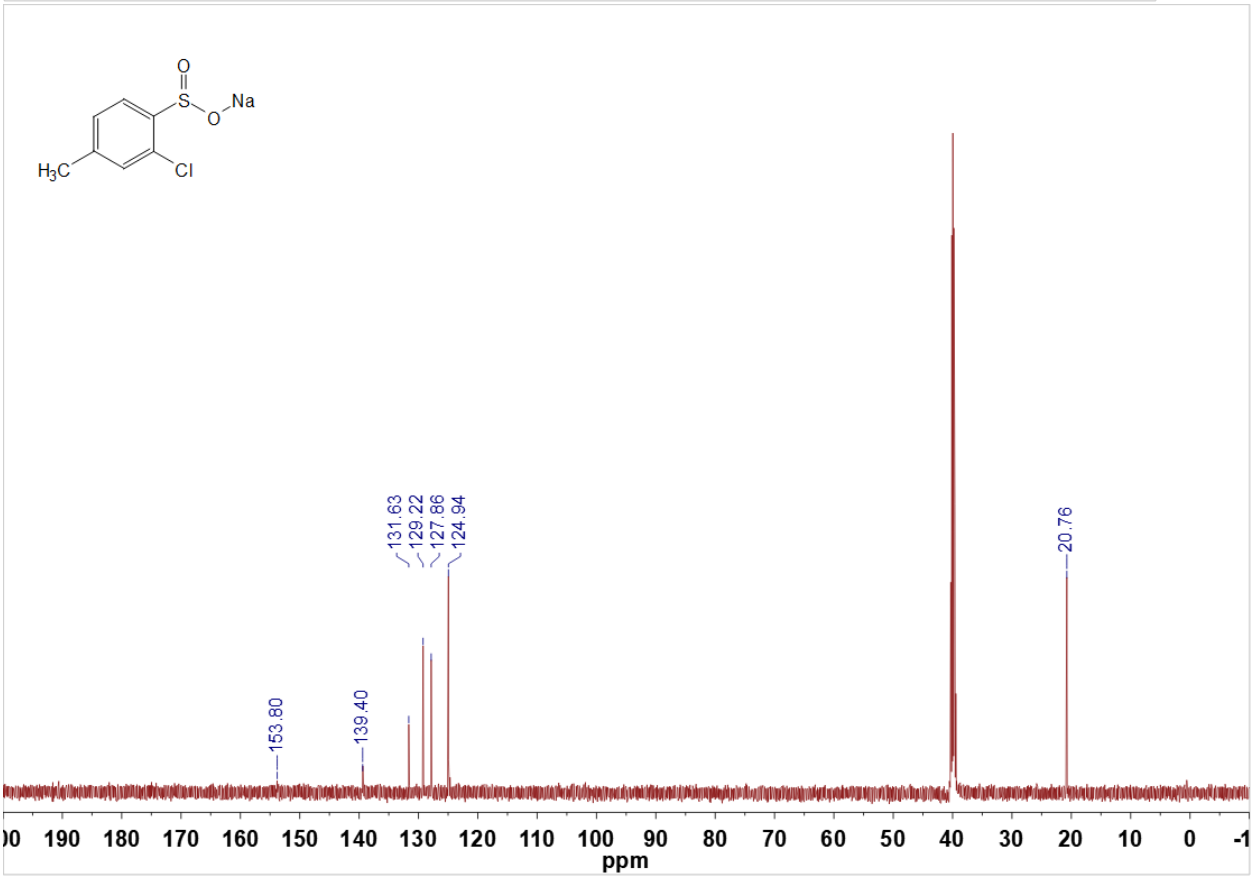


2-((2-iodo-4-(trifluoromethyl)phenyl)sulfonyl)pyridine (**195f-I**)

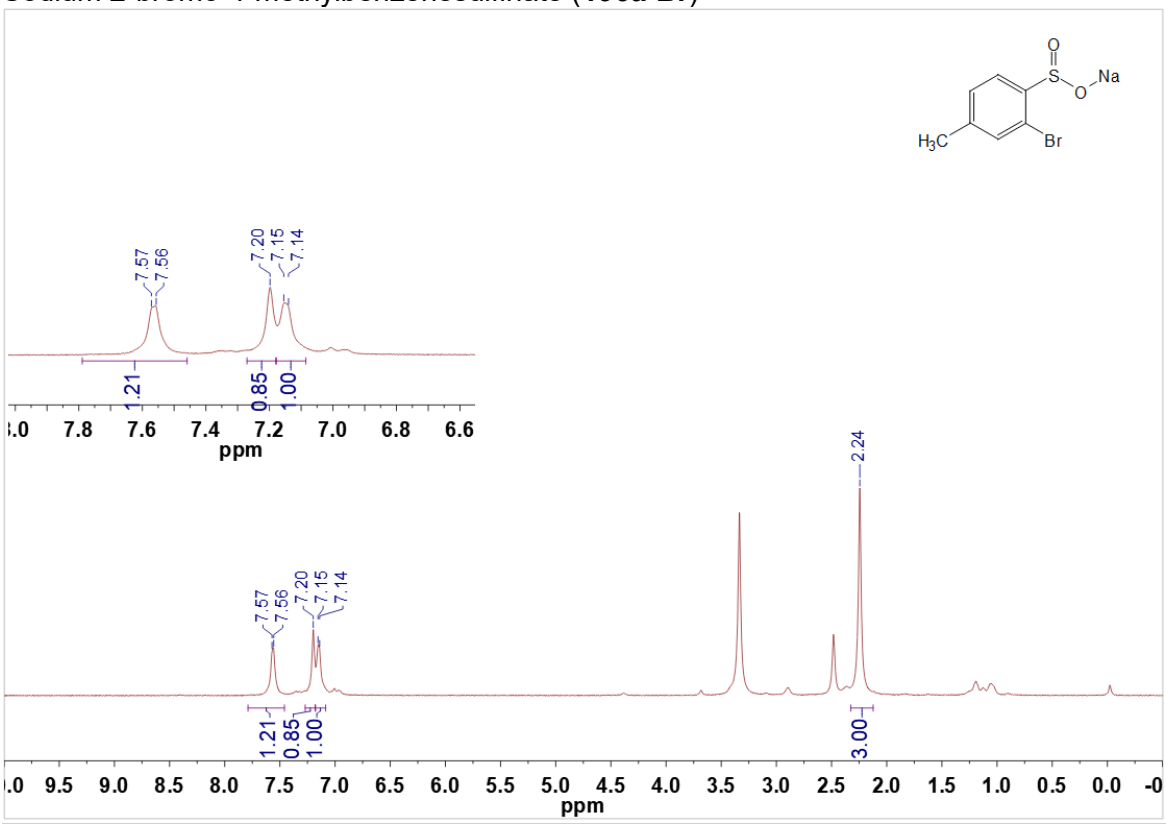


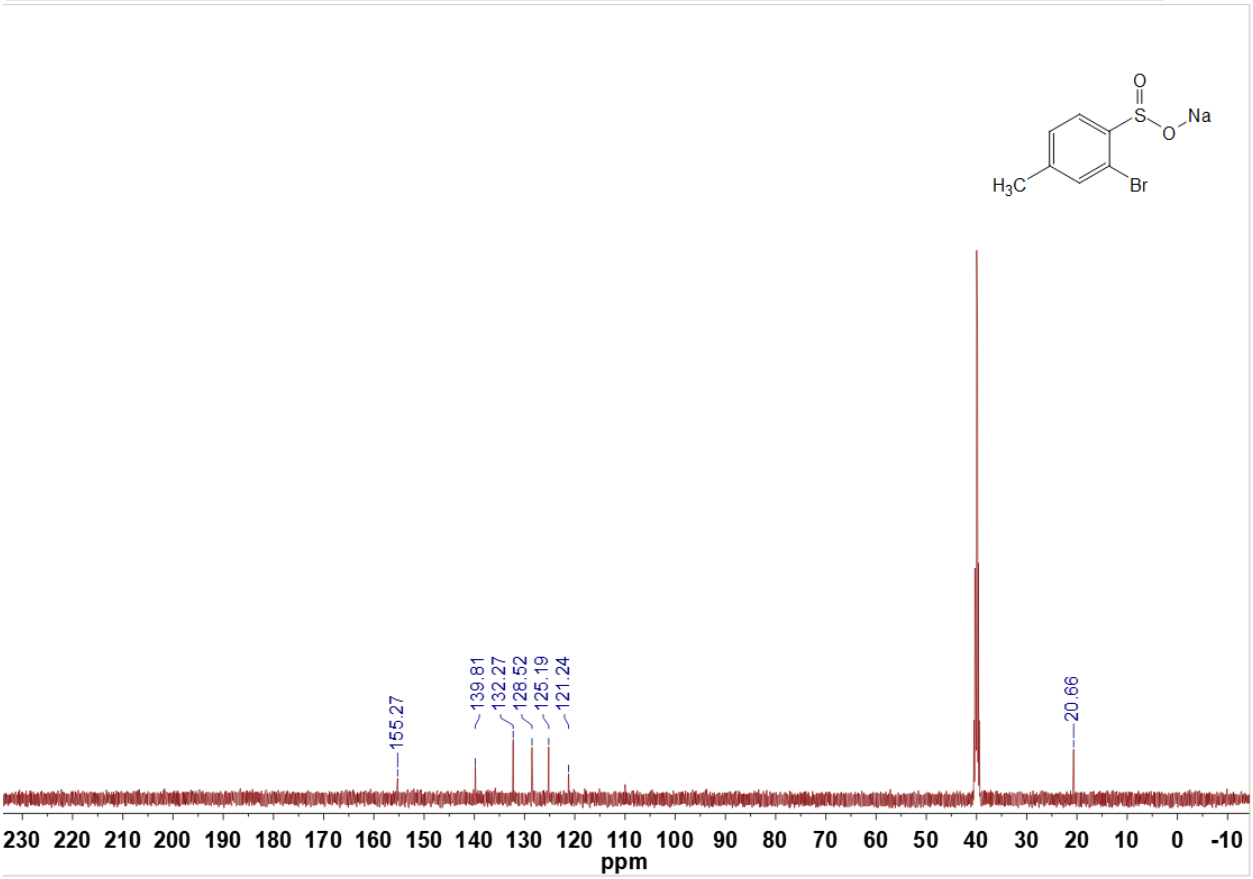
Sodium 2-chloro-4-methylbenzenesulfinate (**196a-Cl**)



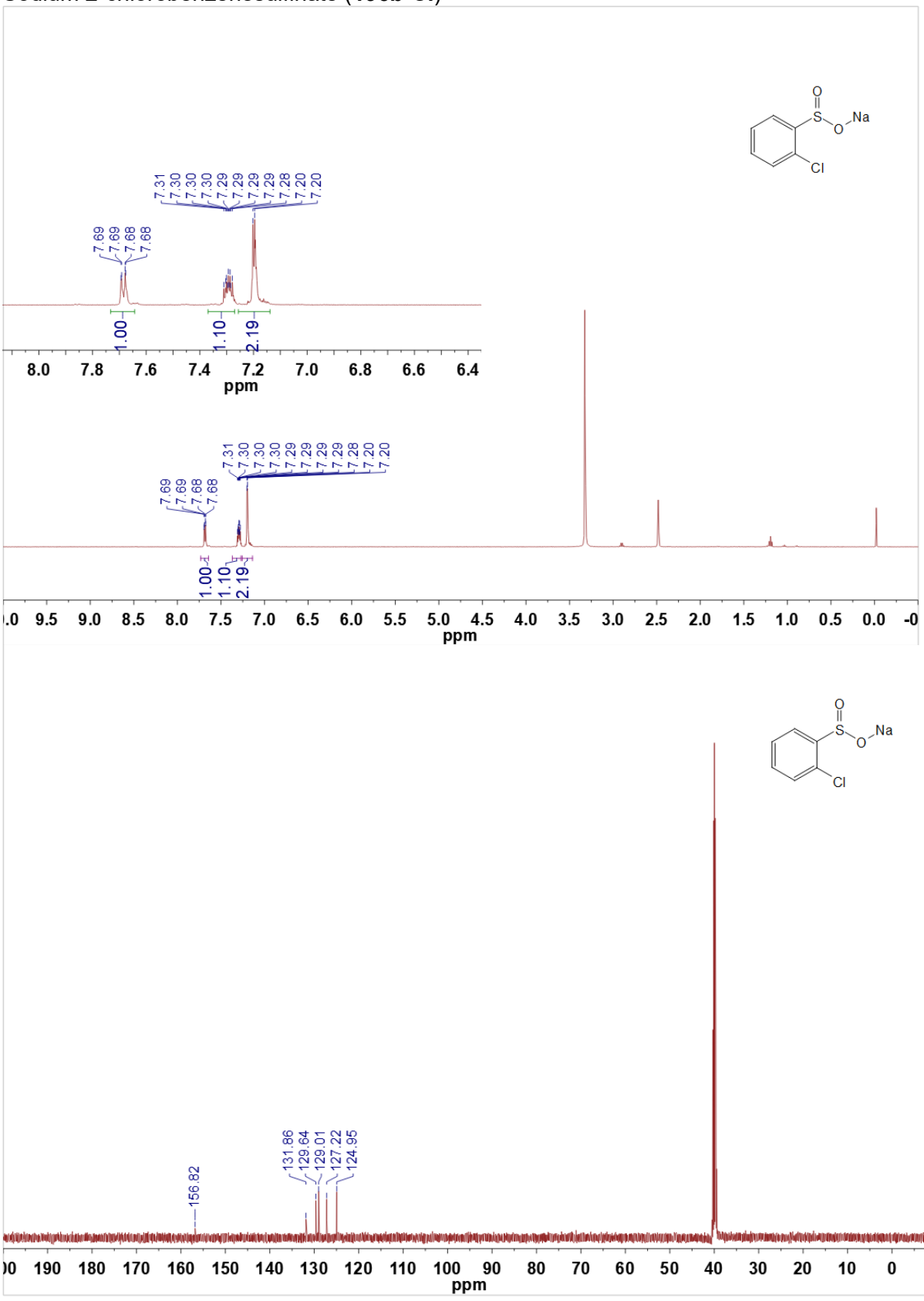


Sodium 2-bromo-4-methylbenzenesulfinate (**196a-Br**)

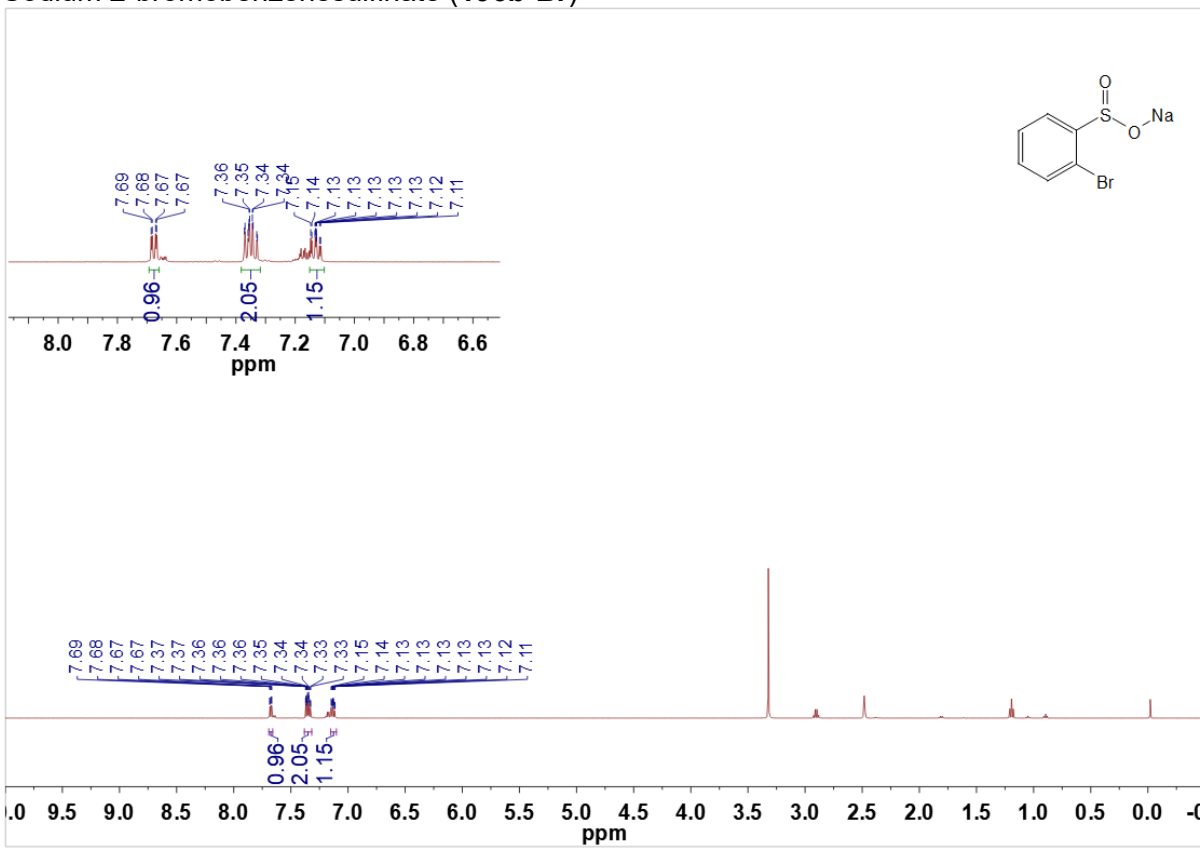


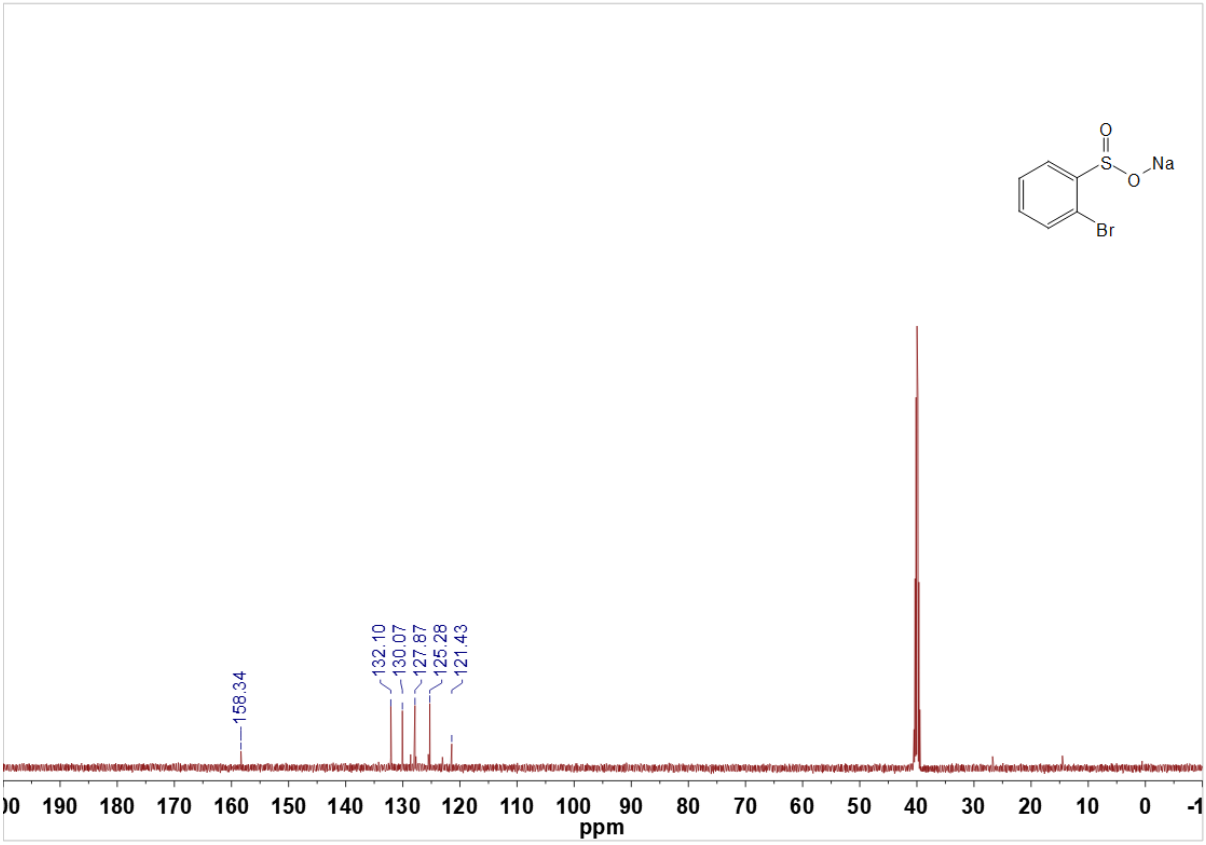


Sodium 2-chlorobenzenesulfinate (**196b-Cl**)

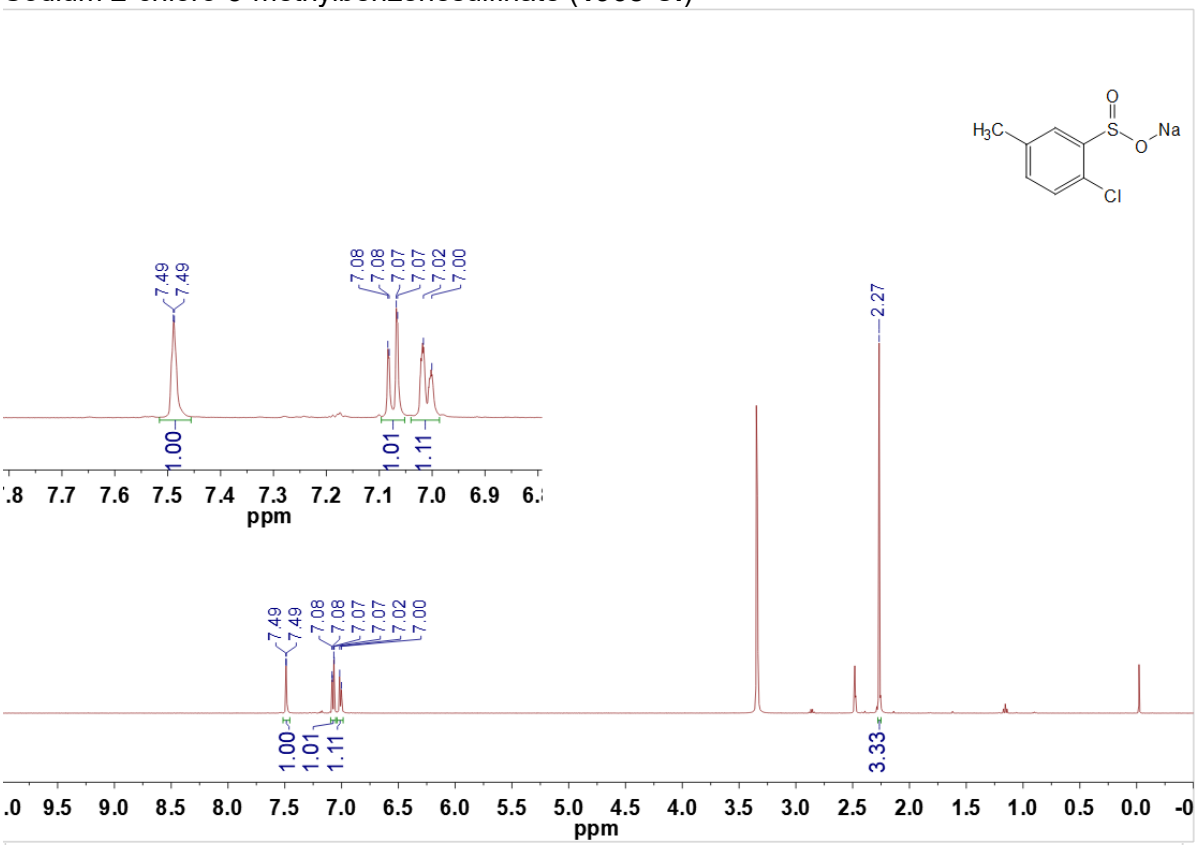


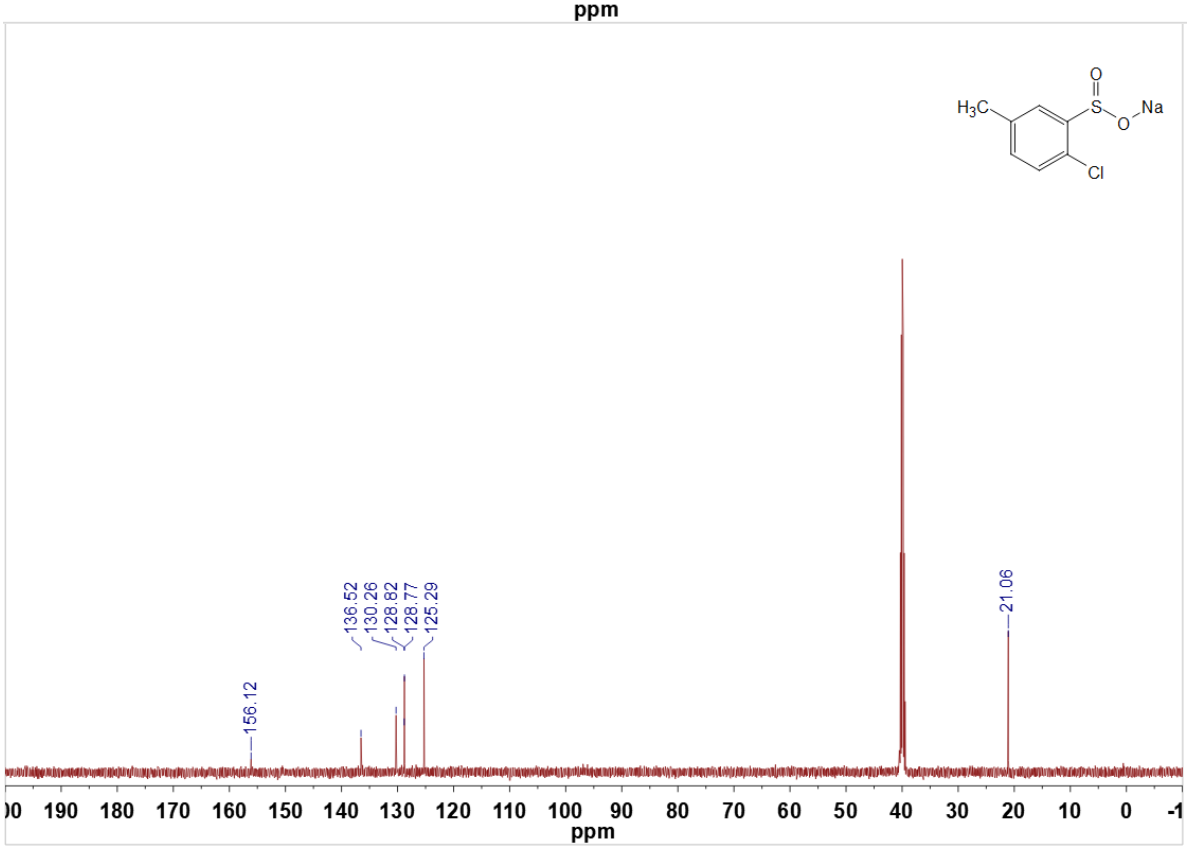
Sodium 2-bromobenzenesulfinate (**196b-Br**)



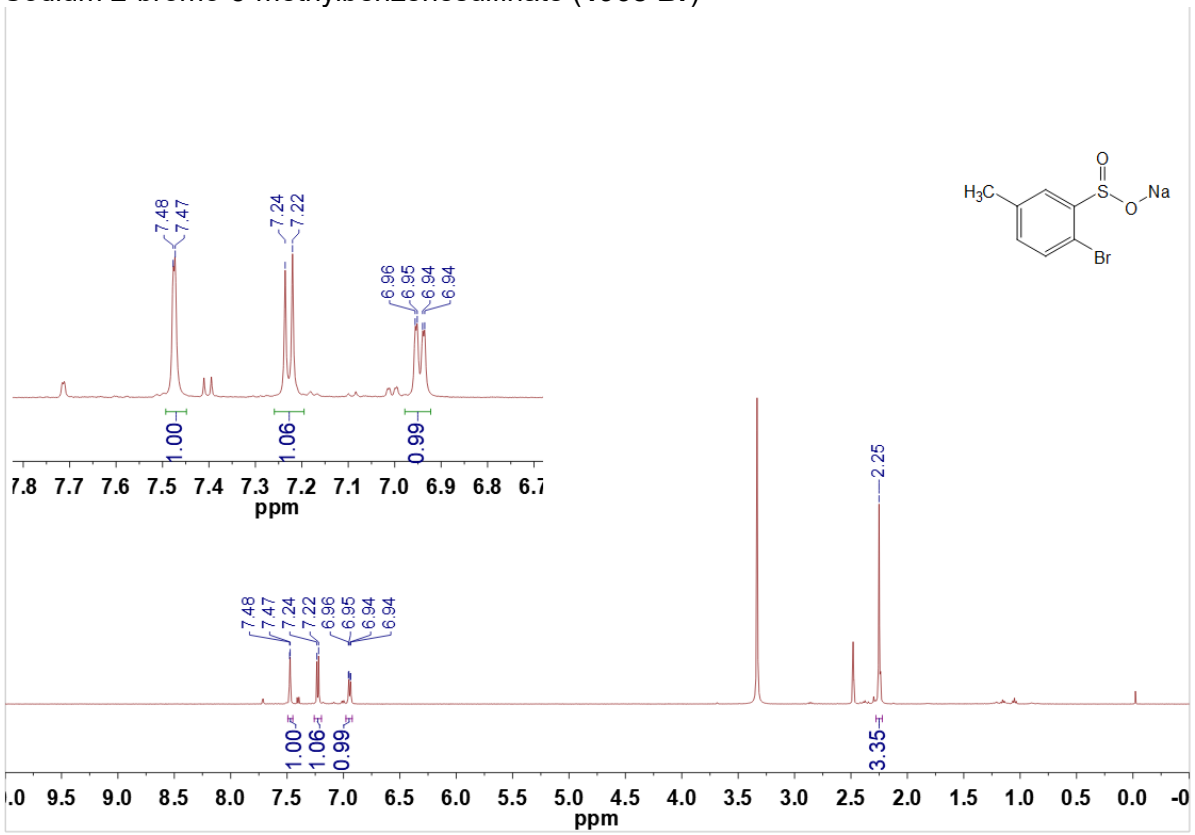


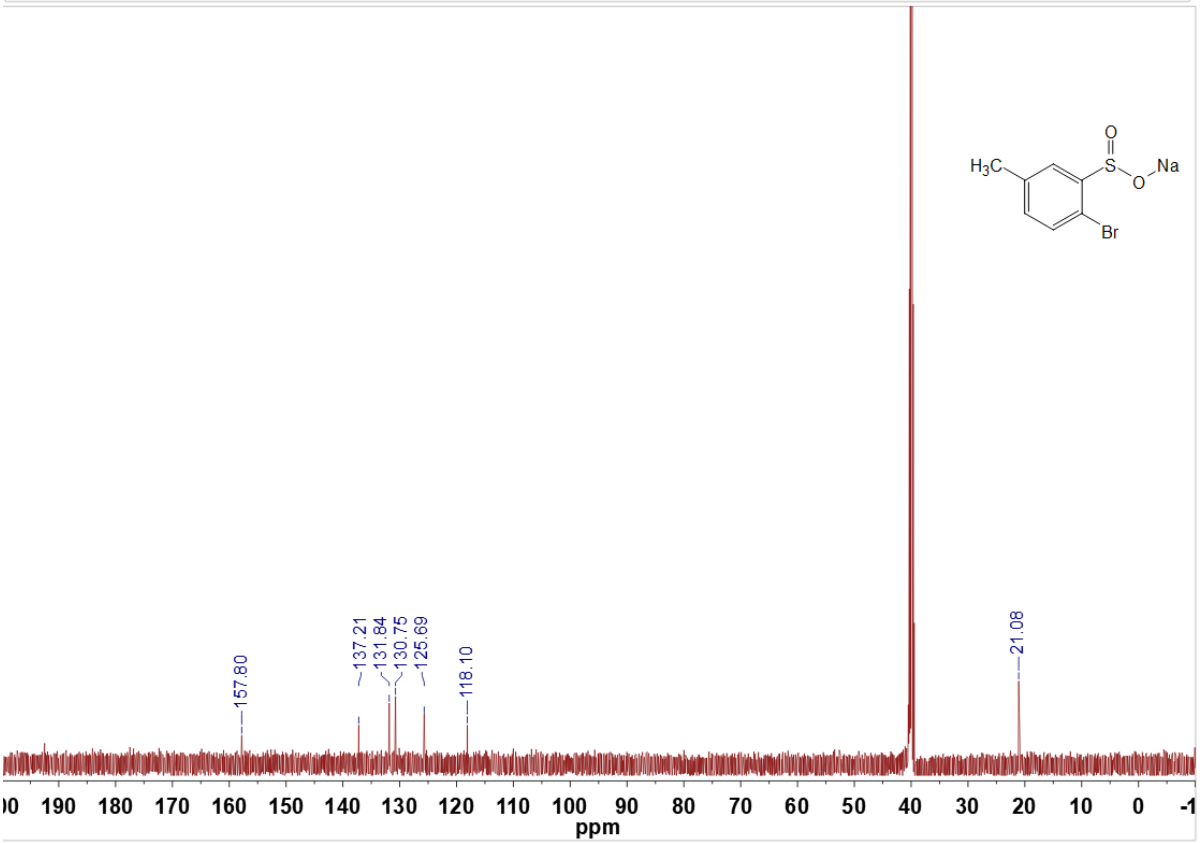
Sodium 2-chloro-5-methylbenzenesulfinate (**196c-Cl**)



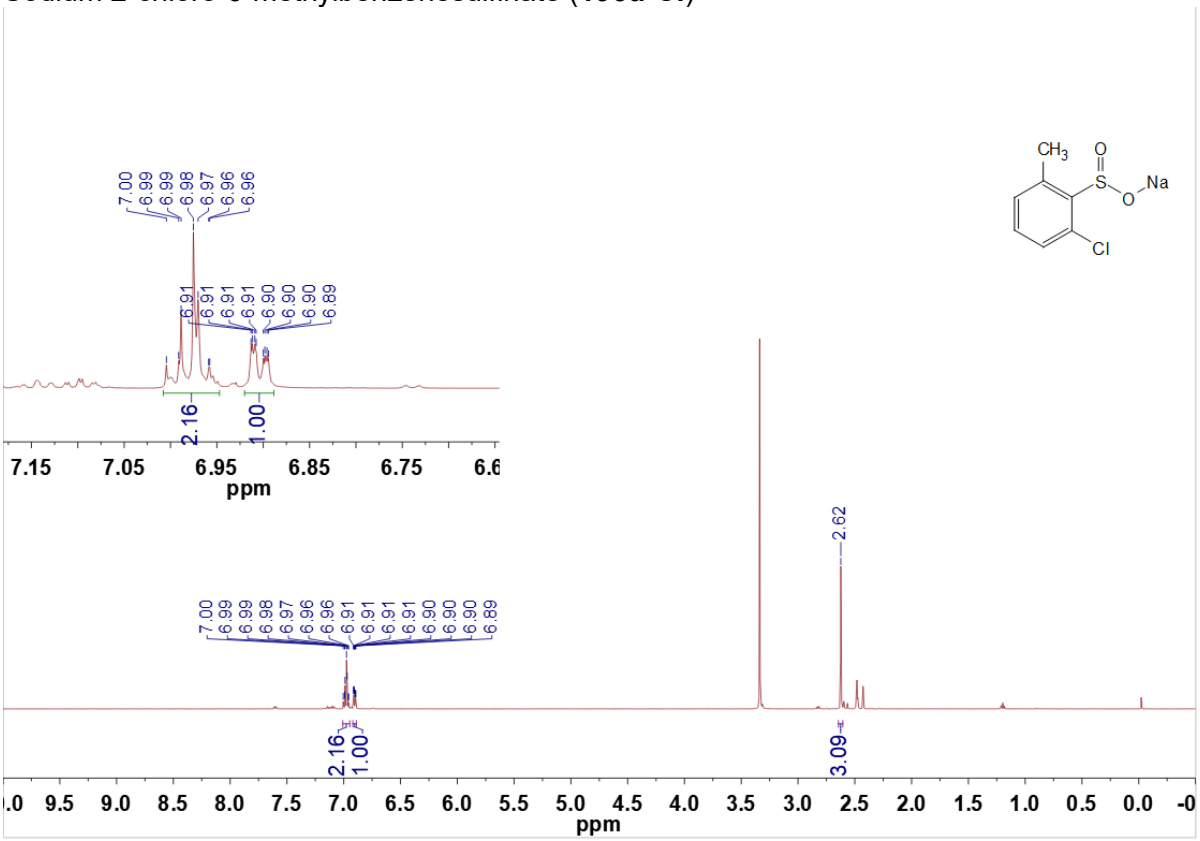


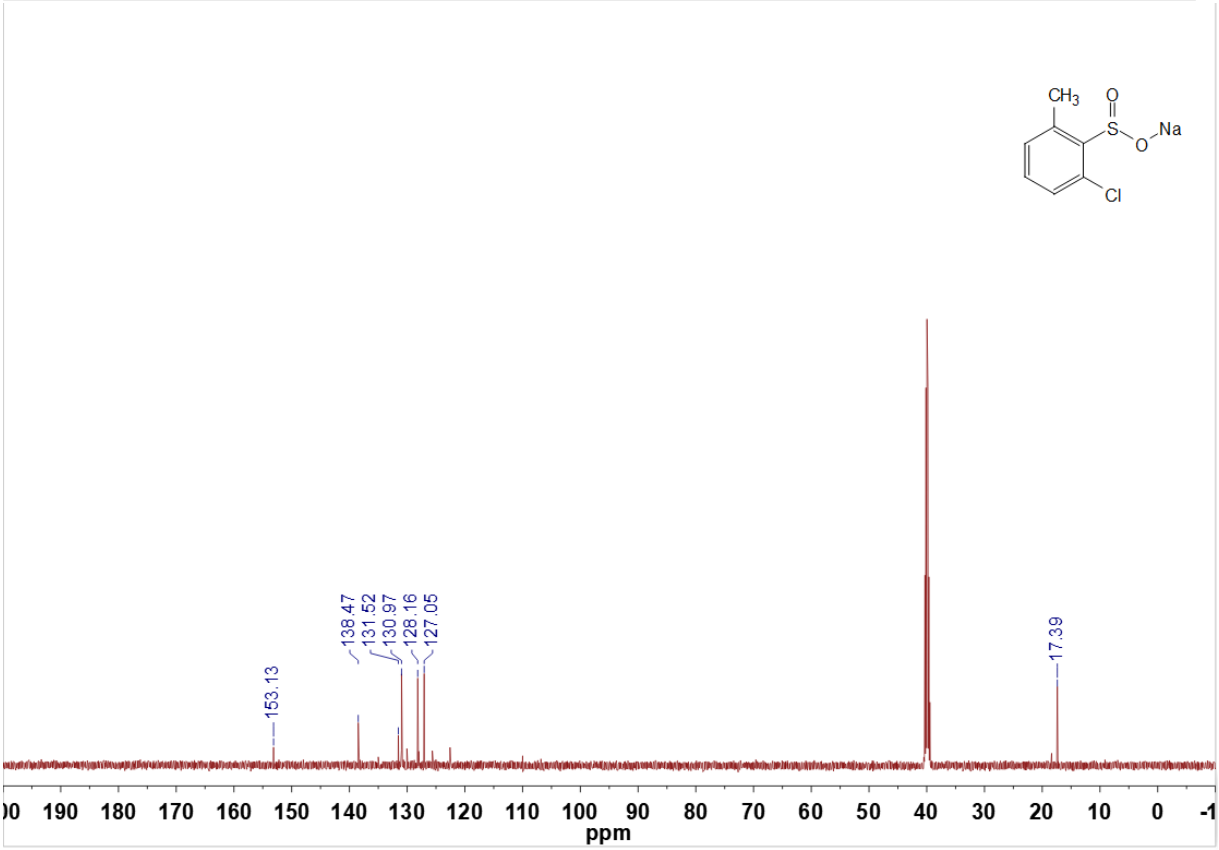
Sodium 2-bromo-5-methylbenzenesulfinate (**196c-Br**)



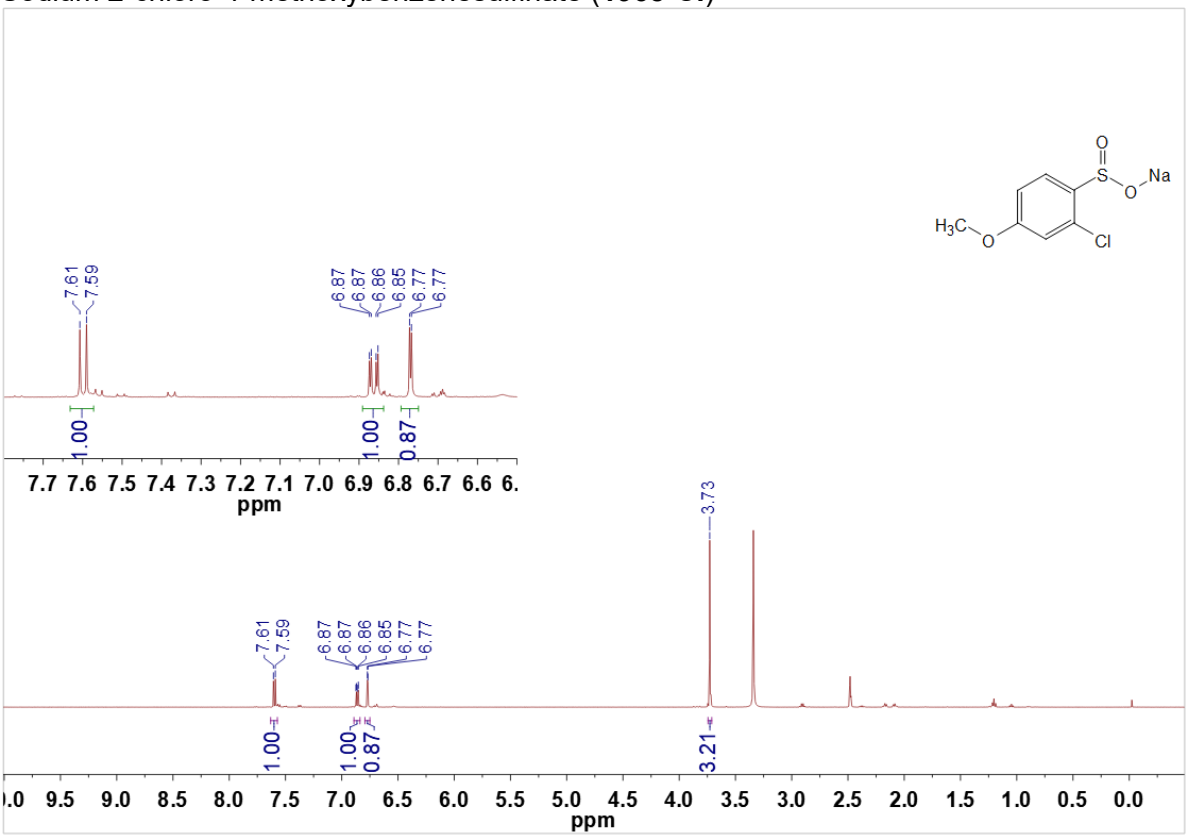


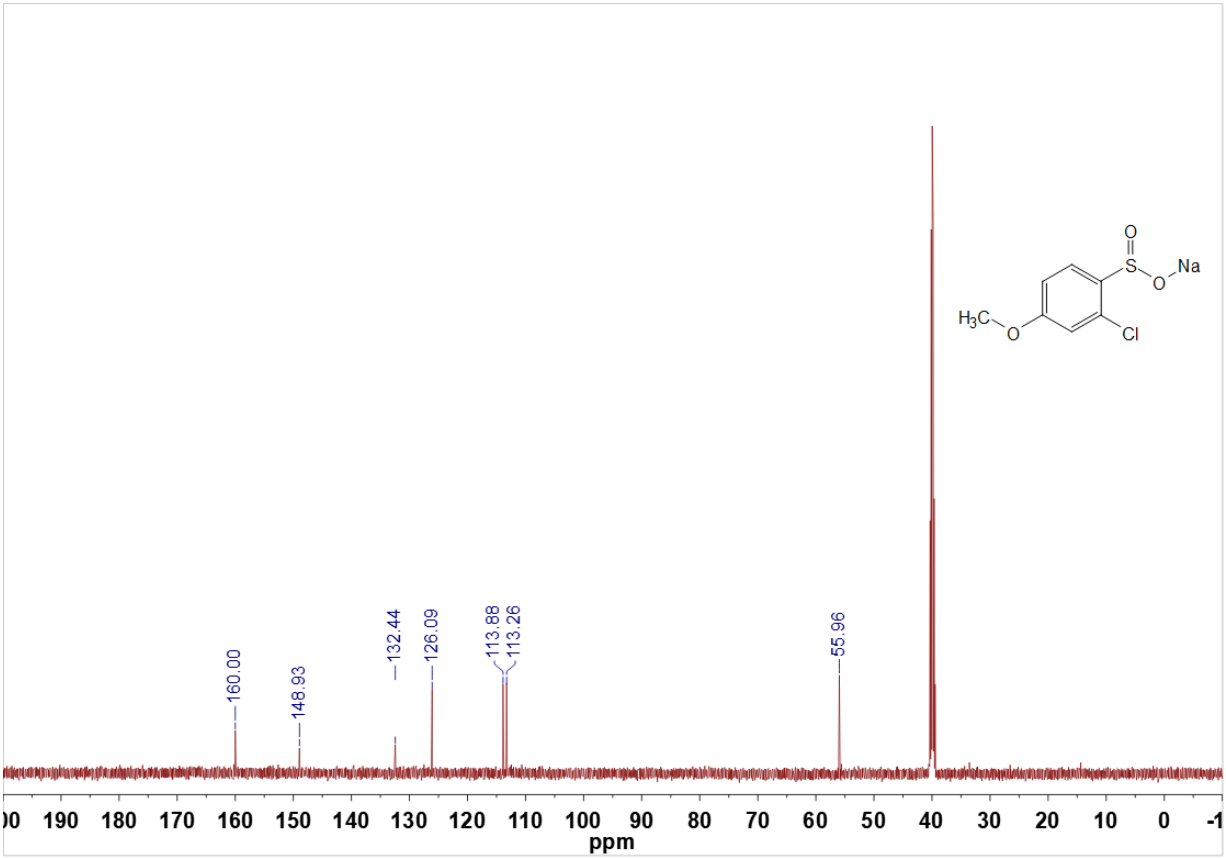
Sodium 2-chloro-6-methylbenzenesulfinate (**196d-Cl**)





Sodium 2-chloro-4-methoxybenzenesulfinate (**196e-Cl**)





Sodium 2-bromo-4-methoxybenzenesulfinate (**196e-Br**)