FORMATION OF ARYL-SUBSTITUTED HETEROAROMATICS *VIA* A PALLADIUM-CATALYZED DESULFINYLATIVE CROSS-COUPLING

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ABSTRACT

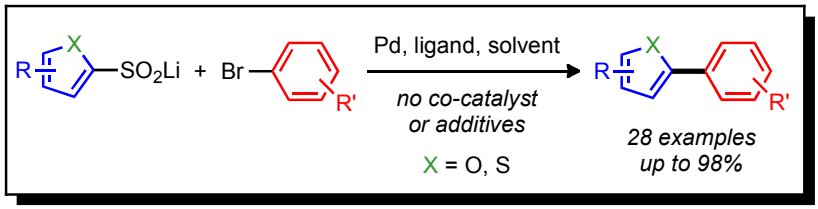
Formation of Aryl-Substituted Heteroaromatics *via* a Palladium-Catalyzed Desulfinylative Cross-Coupling

Stéphane Sévigny

Palladium-catalyzed cross-coupling reactions have found extensive use in the synthesis of biaryls and aryl-substituted heteroaromatics. Although powerful, the classical palladium-catalyzed cross-coupling reactions (*Hiyama, Negishi, Kumada, Stille, Suzuki*) can suffer from common limitations such as extensive reaction times, environmentally unfriendly by-products or reagents, and are atom inefficient. This has generated much attention in the past decades to further improve upon, or expand this type of reactivity, leading to new alternatives. Unfortunately, many newly developed alternatives require the extensive use of co-catalysts and/or additives, or lack selectivity.

Extending upon the decarboxylative cross-coupling protocol previously developed by Forgione and Bilodeau, this work utilizes heteroaromatic sulfinates as nucleophilic coupling partners. Heteroaromatic sulfinates have shown to be readily synthesized by lithiation of the corresponding heteroaromatic followed by quenching with sulfur dioxide gas, requiring little to no purification. Following extensive optimization, an environmentally benign desulfinylative cross-coupling protocol was developed requiring no co-catalyst or additives. The cross-coupling of heteroaromatic sulfinates and aryl bromides occurs in predominantly aqueous media utilizing an inexpensive catalyst system employing a palladium (II) source,

and requires short reaction times. The scope of this newly developed reactivity encompasses thiophene and furan sulfinates, which can be coupled with electron-deficient, electron-neutral and electron-rich aryl bromides in moderate to near quantitative yields.



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LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
Ad	adamantyl
Ar	aryl
CMD	concerted metalation-deprotonation
Cy	cyclohexyl
dba	dibenzylideneacetone
DFT	density-functional theory
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPEphos	bis(2-diphenylphosphinophenyl)ether
dppf	1,1'-bis(diphenylphosphino)ferrocene
eq.	equivalent
EtOAc	ethyl acetate
eV	electron volt
FGA	functional group addition
FGI	functional group interconversion
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
h	hour
(het)Ar	heteroaromatic
HOMO	highest occupied molecular orbital
HRMS	high-resolution mass spectrometry
HSAB	hard-soft acid-base theory
Hz	hertz
IR	infrared
K_a	acid dissociation constant
m	meta
M	molar concentration
min	minute
MS-3Å	3 angstrom molecular sieves
n	normal
N	nitrogen substituted
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidone
NSAID	non-steroidal anti-inflammatory drug
o	ortho
OTf	triflate
OTs	tosylate
ox	oxidation
p	para

petey	$Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$
Ph	phenyl
phen	1,10-phenanthroline
pK_a	negative decadic logarithm acid dissociation constant
ppm	parts per million
R	organic substituent
red	reduction
S_EAr	electrophilic aromatic substitution
S_NAr	nucleophilic aromatic substitution
S_N2	bimolecular nucleophilic substitution
t	time
t	tertiary
T	temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylenediamine
TMS	tetramethylsilane
xs.	excess
Å	angstrom
δ	chemical shift
ºC	degree Celcius
θ	cone angle
$ß_n$	bite angle
η	hapticity
μw	microwave

1 – Introduction

1.1 – Importance of Aryl-Substituted Heteroaromatics

Aryl-substituted heteroaromatics are key motifs that play an important role in a variety of areas, including the pharmaceutical, material, agrochemical and fine chemical industries.[1–6] A study performed by Njardarson *et al.* found that four of the top fifty prescribed drugs in the USA in 2010, Lipitor (#1), Crestor (#6), Celebrex (#21) and Ambien CR (#39) contain this aryl-substituted heteroaromatic motif (**Figure 1**).[7]

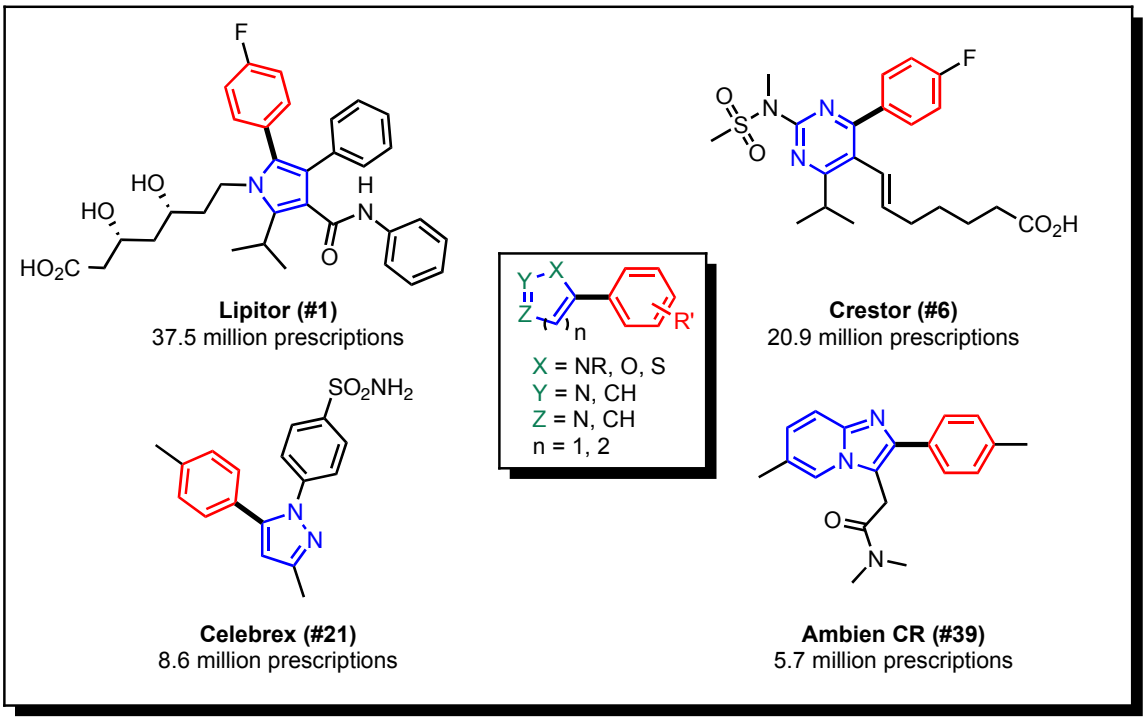


Figure 1: Examples of Aryl-Substituted Heteroaromatics Drugs

The importance of aryl-substituted heteroaromatic and biaryl cores in the pharmaceutical industry is due to the fact that they can provide flat, rigid backbones with aromatic π–systems capable of undergoing non-covalent

interactions. Such interactions can be π–π stacking, using the delocalized π–electrons to interact with amino acids such as phenylalanine, tyrosine and tryptophan that can increase the binding affinity of a drug with a protein active site.[8] The π–systems can also interact with cations (π–cation interactions) or with polarized atoms such as hydrogen in water (π–HO interactions) increasing binding affinity and solubility respectively.[9] Five-membered heteroaromatic rings also form non-covalent interactions but are typically more electron-rich than arenes and have an additional hydrogen bond acceptor. Although there are various strategies to synthesize aryl-substituted heteroaromatic motifs, palladium catalyzed cross-coupling protocols are most commonly employed.[10]

1.2 – Palladium-Catalyzed Cross-Coupling Reactions

Palladium catalysis is made possible due to the facile shuttling between the palladium(0) and palladium(II) oxidation states, typically generating 14 to 18e^- complexes. Catalytic processes shuttling between palladium(II) and palladium(IV) species are also known, but are less common.[11–17]

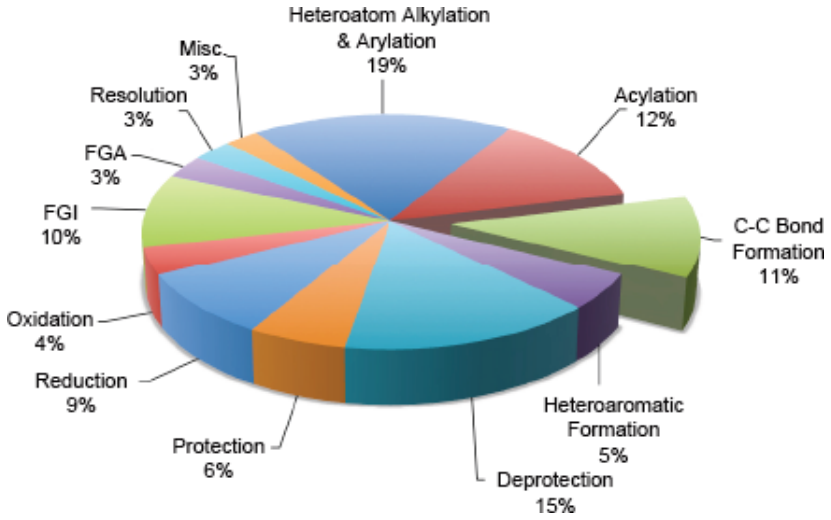


Figure 2: GlaxoSmithKline, Astrazeneca & Pfizer 2005 Reaction Breakdown[10]

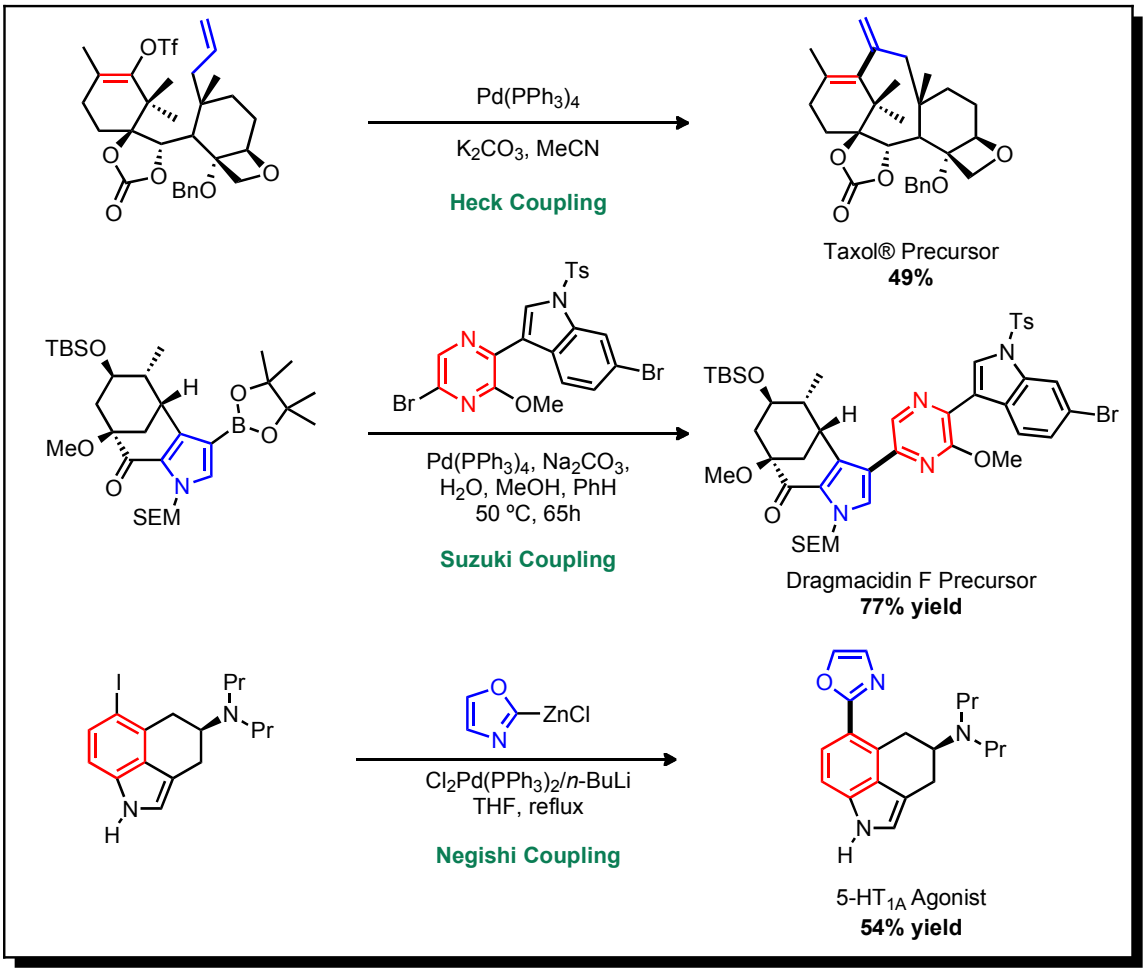
Aryl-substituted heteroaromatics are commonly synthesized by the formation of the carbon-carbon bond between the heteroaromatic and the arene. The most widely accepted strategy to construct this bond is *via* palladium-catalyzed cross-coupling reactions. The importance of these reactions is exemplified by Carey *et al.* who surveyed three major pharmaceutical companies; GlaxoSmithKline, Astrazeneca and Pfizer.[10] In 2005, 1039 reactions were performed for the synthesis of 128 target compounds and these reactions were categorized by type, providing a reaction breakdown (**Figure 2**). From the reactions performed, 11 % were carbon-carbon bond forming and 22% (**Figure 3**) of these were palladium mediated. Although these values appear to be low, the data include modifying reactions (protection/deprotection, functional group inter-conversion (FGI), functional group addition (FGA), reduction and oxidation reactions and reactions for resolution, which makes up a large portion (52%) of the chemical transformations. Chemical transformations contributing to molecular

construction (acylations, aromatic heterocycle formation, heteroatom alkylation & acylation and C-C bond formation) on the other hand, represent only 48% of the chemical transformations analyzed.[10]

Figure 3: GlaxoSmithKline, Astrazeneca & Pfizer 2005 C-C Bond Formation Reaction Breakdown[10]

1.2.1 – Classical Palladium-Catalyzed Cross-Couplings

Carbon–carbon bond formation *via* palladium-catalyzed cross-couplings has played an important role in the pharmaceutical industry,[18] and in the formation of materials, fine and agricultural chemicals and a variety of total syntheses,[19] including that of Taxol®[20] (**Scheme 1**). This led to the recent awarding of the 2010 Nobel Prize to Richard F. Heck, Akira Suzuki and Ei-ichi Negishi for their "pioneering work and development of their respective named reactions".[21]

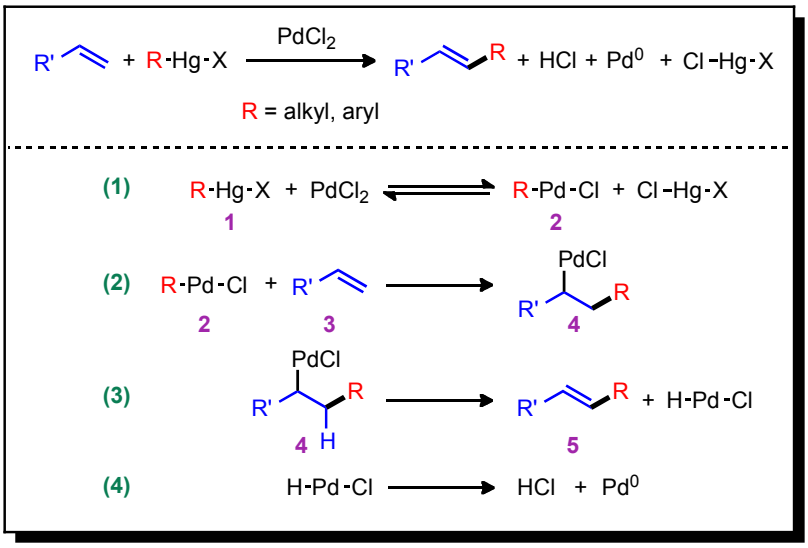


Scheme 1: Examples of Heck[20], Suzuki[22] and Negishi[23] Couplings Used in Total Syntheses

Other related palladium-catalyzed cross-coupling reactions that have had a significant impact include the Stille coupling utilizing organotin reagents,[24,25] the Kumada coupling that uses Grignard reagents[26] and the Hiyama coupling which, employs organosilanes as the organometallic coupling partner[27].

1.2.1.1 – Heck Coupling

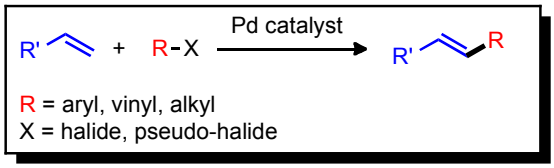
In 1968, Heck released a series of seminal papers describing the alkylation and arylation of olefins at room temperature *via* alkyl or arylpalladium(II) halide intermediates (**Scheme 2**).[28–32]



Scheme 2: Generic Non-Catalytic Heck Cross-Coupling

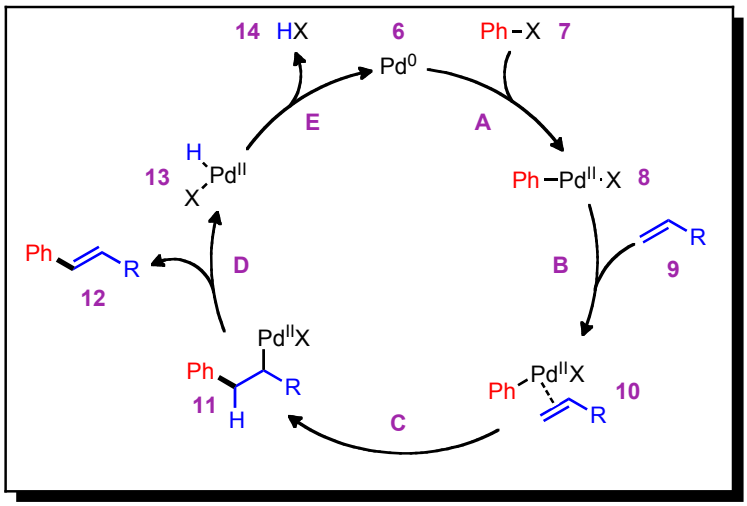
In the original findings, the alkyl- or arylpalladium(II) halide species **2** was generated *via* transmetalation of $PdCl_2$ with primarily alkyl- or arylmercuric halides **1** (eq. **(1)**). The new carbon–carbon bond is generated in intermediate **4** (eq. **(2)**) by a key migratory insertion of the alkyl or aryl (R) group in olefin **3** following the ligand exchange. The presence of a β-hydrogen atom allows for an elimination (eq. **(3)**) that generates the desired alkylated or arylated olefin **5** and a palladium(II) intermediate that undergoes reductive elimination releasing HCl and yielding palladium(0) (eq. **(4)**). This coupling process is non-catalytic as palladium(II) is the active species and following the generation of the product, palladium(II) is reduced to palladium(0). In order to render this process catalytic,

Heck introduced stoichiometric cupric halide in order to oxidize the palladium(0) to palladium(II). Although the catalytic process used stoichiometric mercury, these findings were pivotal as a novel means to alkylate or arylate olefins *via* a migratory insertion followed by β-hydride elimination sequence.



Scheme 3: Generic Example of the Standard Heck Protocol

In 1968, Fitton reported an oxidative addition of a palladium(0) species into aryl-halide bonds generating arylpalladium(II) halides.[33,34] In 1971 and 1972, based on this work, Mizoroki[35] and Heck[36] independently modified his protocol in order to overcome a key limitation, requiring stoichiometric mercury to generate the arylpalladium(II) halide intermediates. This modification revolutionized the protocol, significantly increasing the synthetic utility and becoming the standardized Heck coupling (**Scheme 3**). Employing aryl halides eliminated the need for arylmercuric halides and stoichiometric copper oxidants since the aryl halide acts as oxidant. Based on this, many modifications and improvements have been developed since, allowing for phosphine-assisted catalysis,[37] use of palladacycles,[38–41] carbene complexes,[42–46] under-ligated palladium catalysts and phosphine-free systems,[47,48] use of palladium nanoparticles,[49,50] use of microwave heating,[51] aqueous media,[51–55] supercritical and subcritical fluids,[56–59] fluorous systems,[60] I onic liquids,[39,61,62] use of tosylates,[63] diazonium salts,[64–66] and iodonium salts[67,68] as pseudo-halides, amongst other variants.



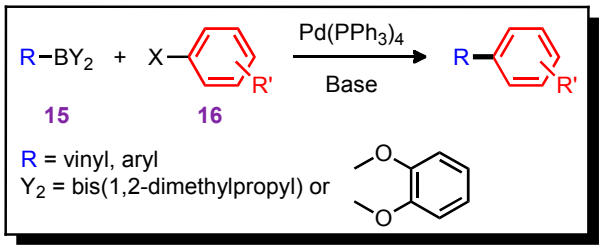
Scheme 4: Generic Heck Catalytic Cycle of a Cross-Coupling between an Aryl Halide with an Olefin

The new protocol follows the same mechanistic pathway as the non-catalytic coupling to generate the new carbon–carbon bond, but varies in catalyst regeneration (**Scheme 4**). Depending on the palladium source being utilized, a pre-activation of the catalyst may be required, typically a reduction of palladium(II) to palladium(0). This reduction of palladium can occur thermally[69] or *via* reducing agents such as phosphine ligands.[70–74] A ligand dissociation to liberate sites on the palladium coordination sphere may be required depending on the steric nature of the ligands employed. Once the active palladium(0) species **6** has been generated, it undergoes the crucial oxidative addition **A** by inserting itself into an R–X bond **7** (R = C or H, X = I, Br, Cl, OTf or H) oxidizing palladium(0) to palladium(II) and generating intermediate **8**.[75–77] Depending on the mechanistic pathway of the oxidative addition, the placement of R and X can be either *cis* or *trans* on the palladium-metal coordination sphere. The rate of the oxidative addition is often governed by ligand basicity, ligand cone angles as well

as the R–X bond strength, with the following relative reactivities; I >> OTf > Br >> Cl.[78] Following the formation of the arylpalladium(II) halide intermediate **8**, the olefin **9** coordinates to the palladium (**B**) generating π–complex **10**, which then undergoes the key migratory insertion **C** yielding palladium intermediate **11**. The olefin inserts into the R–Pd bond in a concerted *syn*-addition, however depending on the electronics and sterics of the system, the reaction path varies and is not always well understood.[37] The regiochemistry favors the formation of the anti-Markovnikov product, although certain strategies have been developed to circumvent this preference.[79] Once arylated, the palladium intermediate **11** undergoes a rotation to relieve torsional strain, placing the substituents *trans* to each other. The migratory insertion onto olefins is often in equilibrium with the reverse process of elimination when β–hydrogen atoms are present, as both processes are closely related. In the Heck coupling, the β–hydride elimination **D** occurs readily to obtain the desired, more highly substituted olefin **12**. In the process, a palladium-hydride complex **13** is generated and a reductive elimination of the palladium(II) occurs regenerating the catalytic species, and releasing HX (**14**). The reductive elimination is the reverse process of an oxidative addition, and its rate is thus affected by the strength of the bond being generated.[80,81] The bond generated in the mineral acid (H–X) is very weak and so the equilibrium does not favor reductive elimination. However, utilizing a base to trap the acid by-product facilitates the reductive elimination process.

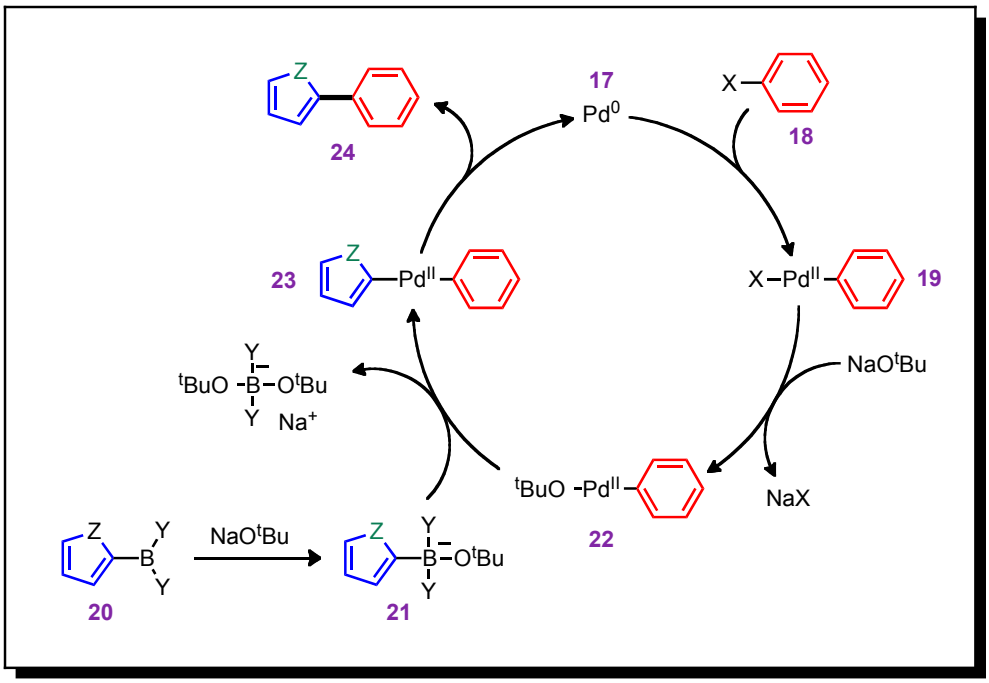
1.2.1.2 – Suzuki Coupling

In 1979, two seminal papers on the cross-coupling of organoboron compounds **15** with aryl and vinyl halides **16** in the presence of base and palladium were reported by Suzuki and co-workers (**Scheme 5**).[82,83]



Scheme 5: Generic Suzuki Cross-Coupling

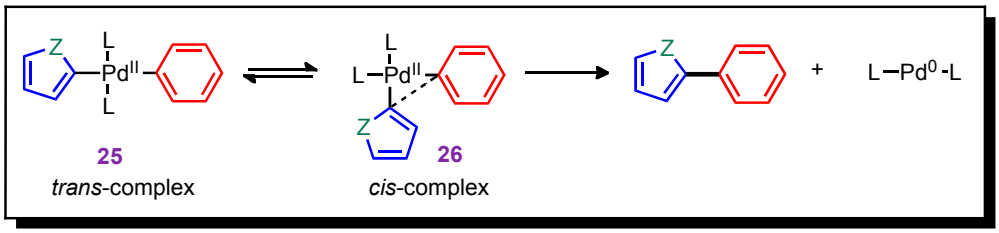
The newfound reactivity proved exciting to the synthetic community, leading to a multitude of publications employing and developing the protocol.[22,84] This has expanded the reactivity of the Suzuki coupling, enabling alkyl–alkyl cross-coupling,[85–91] coupling with aryl and alkyl chlorides,[92–96] coupling in aqueous media,[97–101] solvent free reaction,[102] coupling using phosphine free catalysts,[97,103,104] and coupling at room temperature[89,98,99,105,106] amongst a variety of other improvements.[107,108]



Scheme 6: Catalytic Cycle of the Suzuki Cross-Coupling Between an Aryl Halide and a Heteroaromatic Boronate

The Suzuki coupling begins with an oxidative addition of the palladium(0) species **17** into an aryl halide bond **18**, to generate the organopalladium(II) halide intermediate **19**. The hardness of halides causes weak coordination to the soft palladium metal, and are thus relatively labile ligands.[109] This allows for facile ligand exchange, either *via* transmetalation or nucleophilic ligand displacement, generating a dialkyl- or diaryl-palladium complex **23**. Organoboranes however, are fairly inert to such organopalladium(II) halide species due to the low nucleophilicity of the organic substituent (R–BY_2) on the boron atom.[110,111] The use of bases such as hydroxides, alkoxides, phosphates or carbonates can activate the organoborane **20** by generating a quaternary organoboronate complex **21**, increasing the nucleophilicity of the organic substituent.[112,113] Displacement of the halide ligand on complex **19** with one of the bases,

generating complex **22**, allows facile transmetalation between the palladium(II) species and the organoboronate, leading to the diaryl palladium complex **23**.[82,114,115,116] Once the transmetalation has occurred, an isomerization from the *trans*- **25** to *cis*-complex **26** ensues, placing both aryl and heteroaryl groups adjacent to one another (**Scheme 7**).[117–120] The proximity of the two groups allows the reductive elimination to occur, providing the desired biaryl product **24** and regenerating the palladium(0) catalyst **17**.



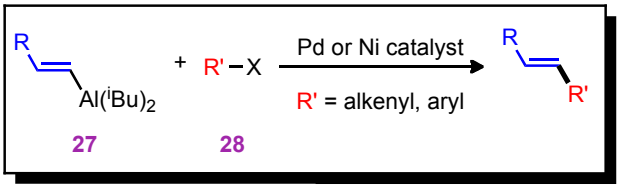
Scheme 7: Palladium(II) Complex Isomerization From *trans* to *cis* for Reductive Elimination

The Suzuki protocol has proven itself invaluable to the synthetic community due to the mild conditions required and the chemoselective nature of the cross-coupling with a high functional group tolerance. Thus, the Suzuki coupling has become one of the most effective industrial processes for aryl–aryl bond formation.[10]

1.2.1.3 – Negishi Coupling

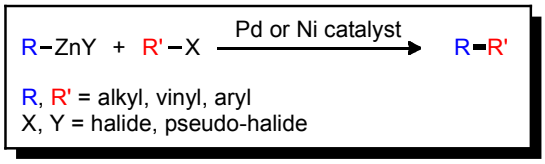
The homo-coupling of arylmagnesium species and cross-coupling with aryl or vinyl halides using transition metals has been known as early as 1941 and described by various groups.[121–126] The limiting factor for these protocols is the poor chemoselectivity due to the high reactivity of the Grignard reagent with a

variety of other functional groups. In 1976, Negishi released the initial articles in search of more chemoselective organometallic species for cross-coupling with organohalides. Using alkenylalanes **27** with alkenyl or aryl halides **28**, employing a palladium or nickel catalyst, a stereoselective cross-coupling tolerating various functional groups was developed (**Scheme 8**).[127,128]



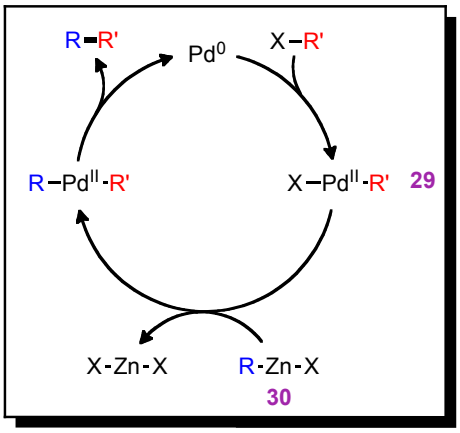
Scheme 8: Initial Negishi Cross-Coupling Reaction Using Alkenylalanes as Nucleophilic Coupling Partners

The success provided by the alkenylalanes lead to the development of the breakthrough protocol in 1977 using organozinc reagents as the nucleophilic coupling partners. These organometallic reagents proved to be even milder than the alanes, yet provided superior yields and demonstrated high selectivity, tolerating a broad range of functional groups.[129,130] Further development of this protocol has generated many improvements, allowing the use of various organozinc reagents to form a variety of carbon-carbon bonds and extend the use of various halides including pseudo-halides, and employing nickel catalysts (**Scheme 9**).[131]



Scheme 9: Standard Negishi Cross-Coupling Using Organozinc Nucleophilic Coupling Partners

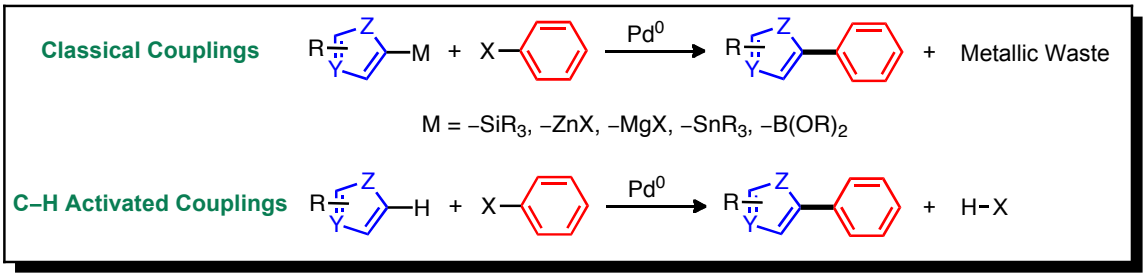
The catalytic cycle for the Negishi cross-coupling is very closely related to the Suzuki mechanism (**Scheme 10**). The transmetalation between the organozinc **30** and the organopalladium(II) halide **29** occurs readily as the organic substituent R is only slightly stabilized by zinc(II). The *d*-orbitals of the zinc metal center are filled, preventing efficient coordination with the organic substituent that consequently increases its nucleophilicity and facilitates transmetalation. Therefore the Negishi coupling does not require pre-activation of either the palladium intermediate or the organometallic coupling partner, as is the case for the Suzuki coupling.



Scheme 10: Generic Catalytic Cycle of the Negishi Cross-Coupling

1.2.2 – C–H Arylations

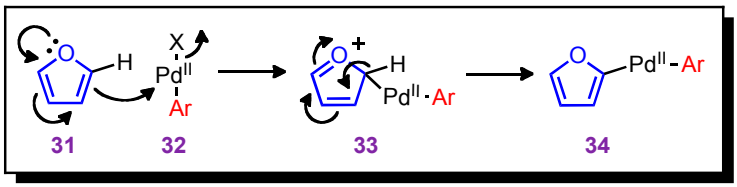
The classical palladium-catalyzed cross-coupling protocols (Suzuki, Neigishi, Stille, Heck, Hiyama and Kumada) are highly efficient and robust processes used extensively for the formation of Ar–Ar bonds in total syntheses and industry. However, they do suffer drawbacks, for example some organometallic reagents (–MgX, –ZnX & $-SnR_3$) cannot be stored for extended periods of time and must be made fresh prior to use. Other processes are atom inefficient, generating large organometallic by-products in stoichiometric amounts, which can be highly toxic in certain cases (Sn)[132] or cause difficulties during purifications. In the past decade, much attention has been dedicated to these issues; leading to the development of C–H activated cross-couplings (**Scheme 11**), eliminating the need for an organometallic coupling partner.



Scheme 11: Comparison of Classical Cross-Coupling Reactions and C–H Activated Cross-Couplings

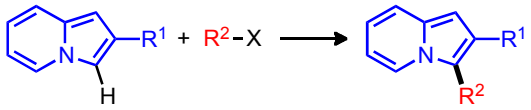
However, C–H functionalization is not without drawbacks or difficulties; the two main challenges include a) the inert nature of the C–H bond and b) chemoselective C–H bond activation within complex molecules. C–H functionalization can be divided into two areas: ligand-directed, and direct

transition metal-catalyzed, with the latter being substantially more challenging. Ligand-directed C–H functionalization uses the proximity of a N or O containing ligand, to direct the palladium to a specific site, enabling the formation of C–O, C–S, C–X, C–N or C–C bonds.[133] Electron-rich systems such as five-membered heteroaromatics undergo the more challenging direct C–H functionalization more readily than electron-poor or electron-neutral rings. The rate of C–H activation is governed by the ability of the coupling partner to undergo an electrophilic aromatic substitution (S_EAr) (**Scheme 12**).[134] The π–system of the heteroaromatic **31** nucleophilically attacks the palladium(II) complex **32**, displacing the labile ligand, rendering this process highly dependent on the π–nucleophilicity of the ring.[134–136] The intermediate **33** then rearomatizes *via* the loss of a proton forming the key intermediate **34**. Five-membered heteroaromatics are especially prone to these types of transformations due to their electron-rich nature (six π–electrons in a five *p*-orbital system).



Scheme 12: Electrophilic Aromatic Substitution (S_EAr) of an Arylpalladium(II) Halide Complex on Furan

Kinetic studies using indolizine (**Table 1**) strongly support this mechanistic pathway as the presence of electron withdrawing groups substantially reduce both the relative rate of direct arylation and Friedel-Crafts acylation.[137,138]

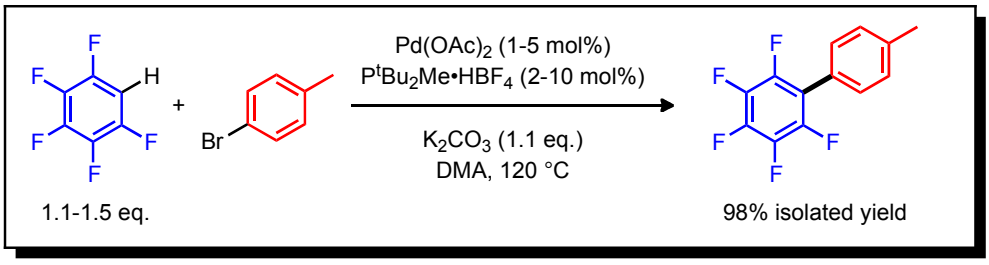


R^1	Relative Rates	
	Direct C–H Arylation	Friedel-Crafts Acylation
H	1.00	1.00
CO_2Et	0.66	0.33

Table 1: Substituent Effects on Relative Rates of Direct C-H Arylation and Friedel-Crafts Acylation

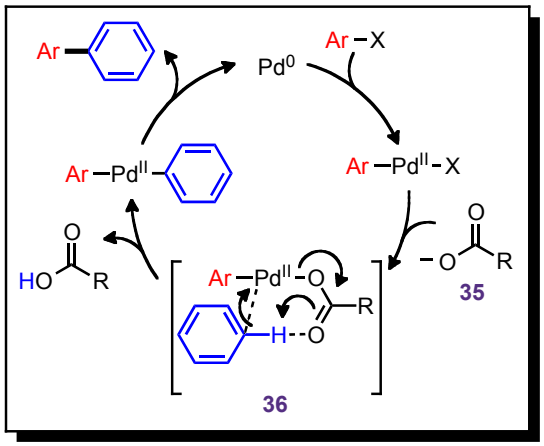
1.2.2.1 – Fagnou Protocol

Advances made by Fagnou *et al.* in the last decade have greatly influenced the field of direct C–H arylation. Traditionally, only systems capable of undergoing S_EAr, i.e. electron rich systems, were capable of direct arylation. This was a highly limiting factor for the field of C–H arylation as electron poor systems or simple arenes could not undergo direct arylation unless aided by a directing group.[11–17,139] The Fagnou group, developed a protocol capable of cross-arylating electron-deficient arenes, such as pentafluorobenzene with 4-bromotoluene in essentially quantitative yields (**Scheme 13**).[140]



Scheme 13: Direct Arylation of Pentafluorobenzene with 4-Bromotoluene

Due to the dependence on π–nucleophilicity of the S_EAr mechanism, electron-deficient systems, such as pentafluorobenzene, cannot undergo coupling *via* this pathway. A concerted metalation-deprotonation (CMD) pathway, a mechanism first proposed by Echavarren and Maseras,[141] was employed to rationalize the observed outcome (**Scheme 14**).



Scheme 14: Concerted Metalation-Deprotonation (CMD) Mechanistic Pathway

After oxidative addition of a palladium(0) species into an Ar–X bond, a carboxylate **35** displaces the halide from the organopalladium(II) halide species, generating complex **36**. This allows for the interaction of the arene with the palladium intermediate where the carboxylate deprotonates the arene as it simultaneously coordinates to the palladium species **36** in a concerted manner. The CMD is of opposite reactivity than the S_EAr pathway, functioning parallel to the acidity of the C–H bond being cleaved. Consequently, electron withdrawing groups activate this pathway whereas they hinder the S_EAr mechanism.[142] This was exemplified with the coupling of the following penta-, tetra-, tri-, di- and monofluorobenzenes (**Figure 4**) with 4-bromotoluene. Increasing electron

richness of the arene by reducing the amount of fluoro substituents present lowers acidity, consequently reducing yields.

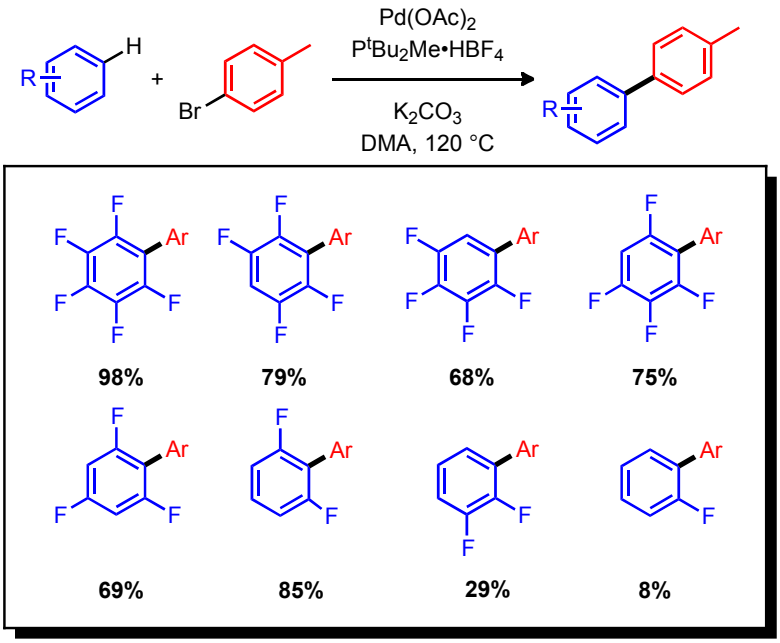
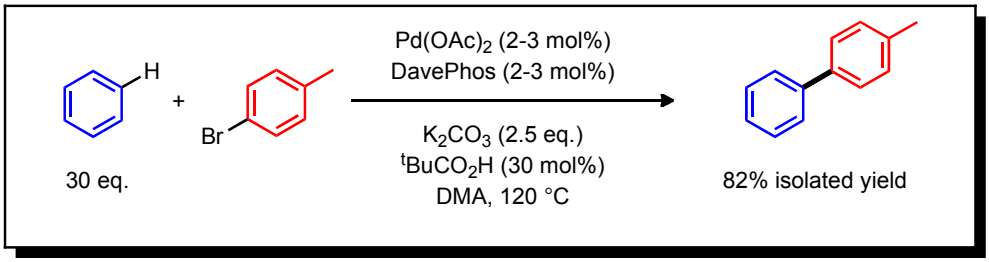


Figure 4: Effect of Electron-Richness on Cross-Coupling Yield in the Direct Arylation of Fluorobenzenes with 4-Bromotoluene

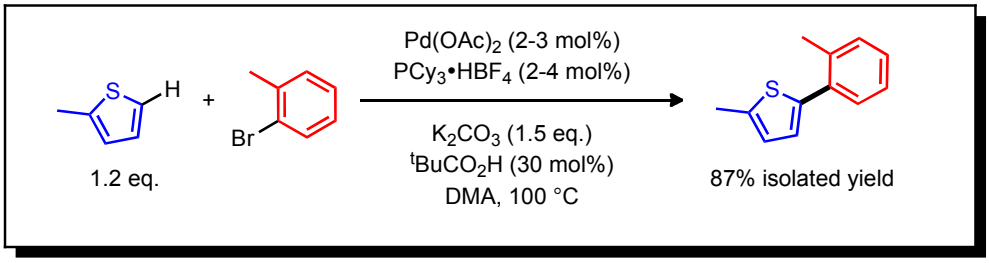
Having developed the first catalytic conditions to couple electron-deficient arenes with a variety of aryl bromides, Fagnou *et al.* evaluated if the process could be extended to the coupling of electron-neutral arenes. They developed a protocol capable of coupling benzene with 4-bromotoluene (**Scheme 15**), however it requires superstoichiometric amounts of benzene (30 eq.).[143] A carboxylic acid additive proved necessary to obtain conversions above 13%, but the best result (82%) was obtained when the carboxylic acid was used in conjunction with an insoluble base such as K_2CO_3 (**Scheme 15**). The steric bulk of the carboxylic acid co-catalyst proved essential in order to render coordination of the benzene to the arylpalladium(II) species competitive, and optimal results

were obtained with pivalic acid (82%). However, employing an even larger acid such as 1-adamantanecarboxylic acid ($AdCO_2H$) proved detrimental (36%).



Scheme 15: Direct Arylation of Superstoichiometric Benzene with 4-Bromotoluene

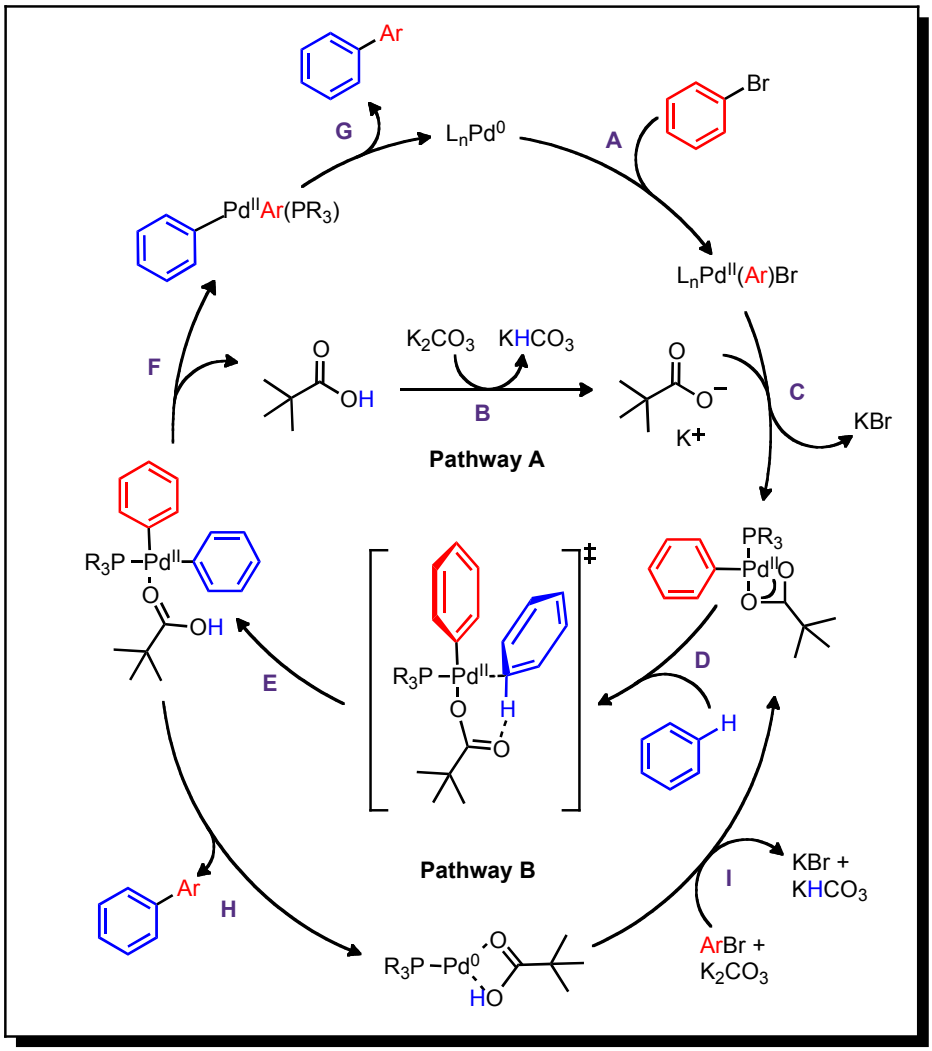
Fagnou *et al.* further demonstrated the value of this approach by cross-coupling electron-rich heteroaromatics using pivalic acid as the proton shuttle in substoichiometric amounts (**Scheme 16**).[144]



Scheme 16: Direct Arylation of Electron-Rich 2-Methylthiophene with 2-Bromotoluene

The catalytic cycle for the direct arylation of arenes and heteroarenes using the CMD pathway was postulated to occur *via* two possible routes (**Scheme 17**).[143] As in all Pd^0/Pd^{II} catalyzed cross-couplings, the Pd^0 first undergoes an oxidative addition in the Ar–X bond generating an aryl-substituted palladium(II) complex. The potassium pivalate, generated *in situ* by treatment of the pivalic acid with potassium carbonate (**B**) coordinates and displaces the bromide on the palladium(II) complex (**C**). The aryl group then coordinates (**D**),

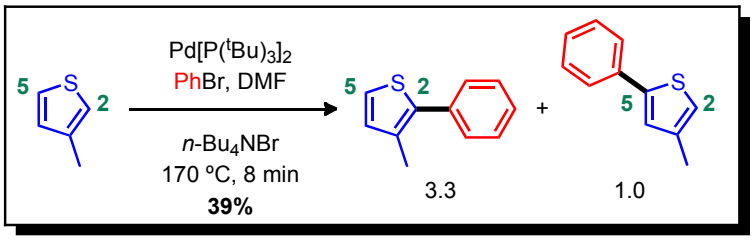
albeit weakly, with the palladium(II) complex allowing for the proton transfer (**E**). The mechanism can then diverge into two possible pathways regarding the role of the pivalic acid. It can dissociate (**F**), which leads to reductive elimination (**G**), generating the product and the palladium(0) catalyst as **Pathway A**. The other possibility is a direct reductive elimination (**H**), forming the desired biaryl and generating the palladium(0) complex but with the pivalic acid still coordinated. It can then undergo an oxidative addition and deprotonation of the pivalic acid (**I**) using K_2CO_3 allowing another CMD as **Pathway B**.



Scheme 17: Proposed Mechanism for Direct Arylation of Benzene

1.2.2.2 – Direct C–H Arylation Regioselectivity

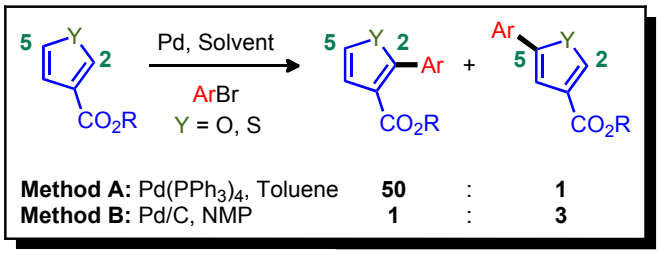
Although direct C–H activated cross-couplings address certain limitations of the classical protocols, such as eliminating the need for generating organometallic partners while generating biaryls in high yields with mild conditions, they still possess restrictions. These protocols are not chemoselective, requiring the arenes to be unsubstituted or contain symmetry so all protons are of equivalent acidity and consequently of equivalent reactivity. Cases with multiple equivalent C–H bonds, such as five-membered heteroaromatics with the C2- and C5- significantly more reactive than the C3- and C4-positions, require the blocking of one of the reactive positions. In unsymmetrical cases where both the C2- and C5-positions are available, a mixture of products is generated. For example, the arylation of 3-methylthiophene occurs at both the C2- and C5-position in a 3.3:1 ratio, respectively (**Scheme 18**).[145]



Scheme 18: C–H Arylation of 3-Methylthiophene with Bromobenzene

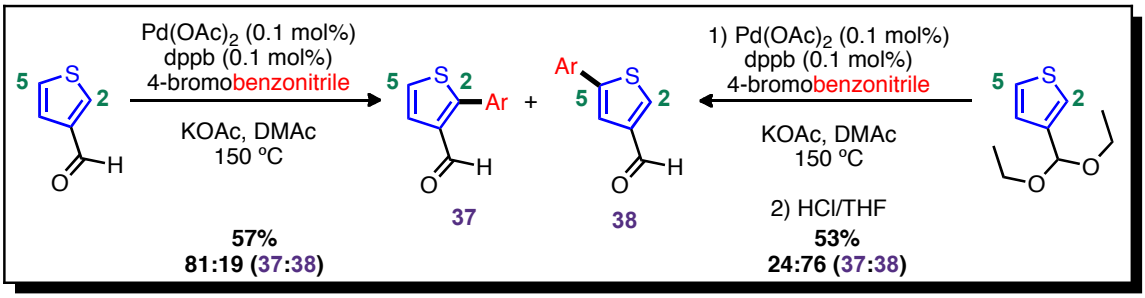
In 2003, Sharp *et al.* developed conditions capable of regioselectively arylating 3-carboalkoxy furans and thiophenes at the C2- or at the C5-position (**Scheme 19**).[134] Using a non-polar solvent, toluene, and $Pd(PPh_3)_4$ as catalyst, a Heck-type α,β–insertion adjacent to the ester is observed yielding a 50:1 ratio of C2:C5-arylation. Conversely, employing Pd/C in a polar aprotic solvent, NMP, a

reversal of selectivity was achieved with C5-arylation (3:1, C5:C2) obtained preferentially *via* an S_EAr mechanism due to ionization of the Pd–X bond.



Scheme 19: Sharp Regioselective Conditions for the Direcy Arylation of C3-Substituted Heteroaromatics with Aryl Bromides

Regioselectivity in C3-substituted thiophenes can also be controlled employing steric bulk. Doucet coupled 3-formylthiophene with electron-deficient 4-bromobenzonitrile, yielding C2-arylation in a 4:1 ratio (**37**: **38**) in moderate yield (**Scheme 20**).[146] The C2-position is favored over the C5-position due to increased acidity caused by the proximity of the electron-withdrawing aldehyde, as well as conjugation. Protecting the aldehyde as a diethyl acetal increases steric bulk, making it more difficult for the palladium complex to access the C2-position and, is consequently more difficult to achieve. After deprotection of the acetal to the aldehyde, the C5-arylated product **38** is obtained, again in moderate yields, in a 1:3 (**37**: **38**) ratio.



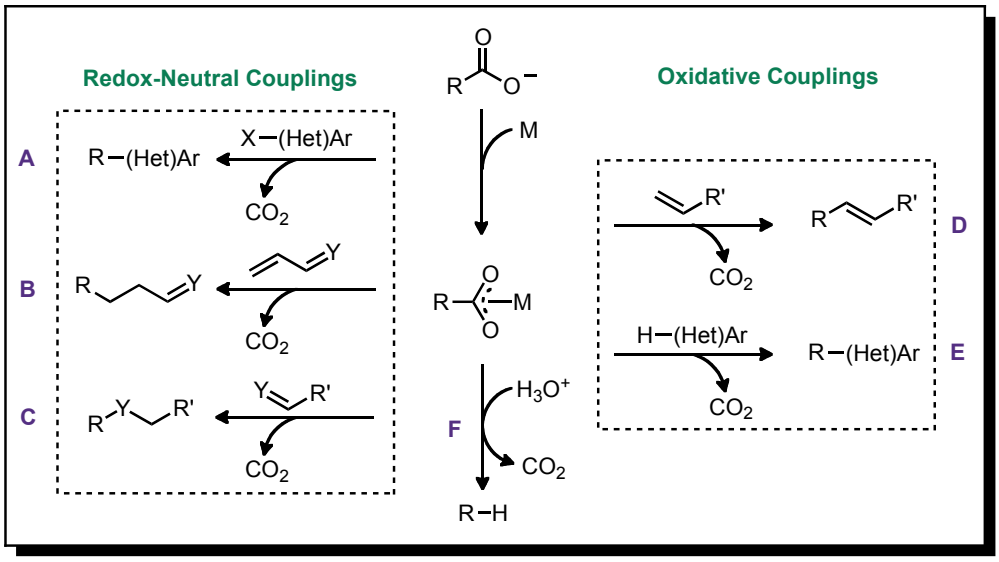
Scheme 20: Regiocontrol of Direct Arylation of C3-Substituted Thiophenes with 4-Bromobenzonitrile

Although Doucet (**Scheme 20**) and Sharp (**Scheme 19**) have demonstrated some degree of control, obtaining complete regiocontrol in direct C–H arylations remains challenging. This is particularly challenging with unsymmetrical five-membered heteroaromatics, where a significant amount of undesired arylation product is generated, reducing the yield of the desired arylation product.

1.2.3 – Decarboxylative Cross-Couplings

In the past decade, carboxylic acids have made a significant impact in the area of transition metal catalyzed couplings.[147] They are powerful coupling partners capable of generating biaryls, aryl-substituted heteroaromatics, 1,3-diaryl-1,3-butadiene derivatives,[148] ketones,[149] azomethines,[150] arenecarboxylate esters,[151] azaarenes,[152] aryl-substituted alkynes,[153–159] γ,δ-unsaturated alkyl ketones,[160–165] vinylarenes,[166–169] aryl-substituted allylic esters,[170] aryl-substituted 1,4-benzoquinone derivatives,[171] (*E*)-β-nitrostyrenes,[172] aryl nitriles,[173] alcohols,[174] α-amino acid derivatives,[175] aryl ketone derivatives,[176] sulfides,[177,178] dialkyl ketones and cyclic alkanones[179,180]. As described by Gooßen, there are

currently five types of decarboxylative couplings (**Scheme 21**); cross-coupling of aryl, vinyl or allyl electrophiles **A**, conjugate additions **B**, carbon-heteroatom bond forming reactions **C**, Heck-type vinylations **D**, and direct arylations **E**.[147] They fall within two mechanistic categories, redox-neutral couplings and oxidative couplings. The metalated carboxylate can also undergo a protodecarboxylation **F** if treated with acid and water, or heated at sufficiently high temperatures.

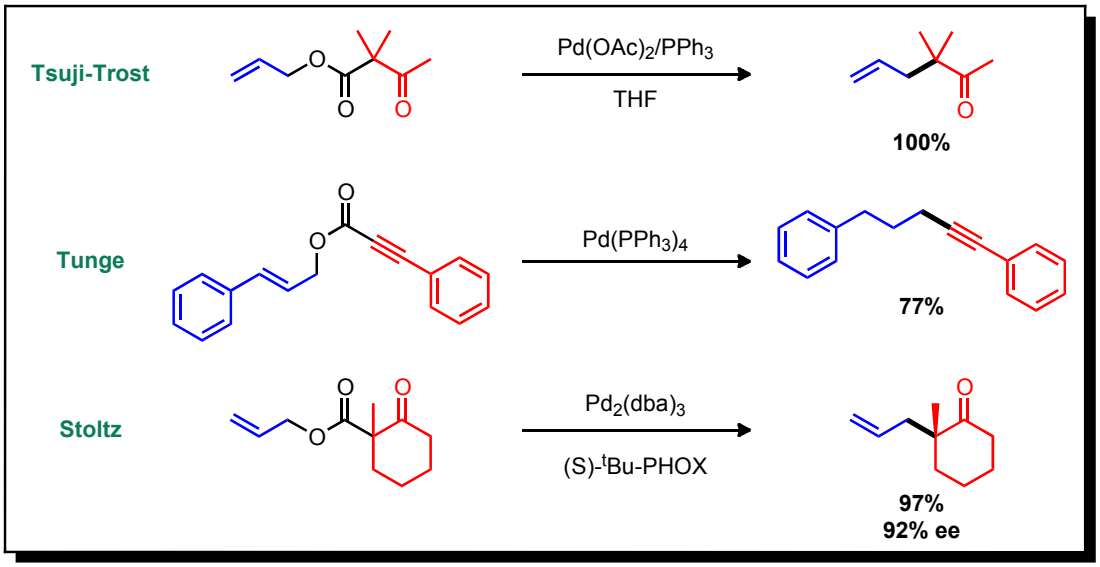


Scheme 21: Types of Decarboxylative Couplings

In redox-neutral couplings, the carboxylic acid provides the nucleophilic coupling partner, replacing organometallic partners from the classical protocols. Alternatively, in oxidative couplings they serve as the electrophilic source for the coupling, but require stoichiometric amounts of oxidant to regenerate the active catalytic species. In palladium-catalyzed couplings, the active catalytic species in redox-neutral couplings is a palladium(0) complex, whereas in oxidative couplings the active catalytic species is a palladium(II) complex.

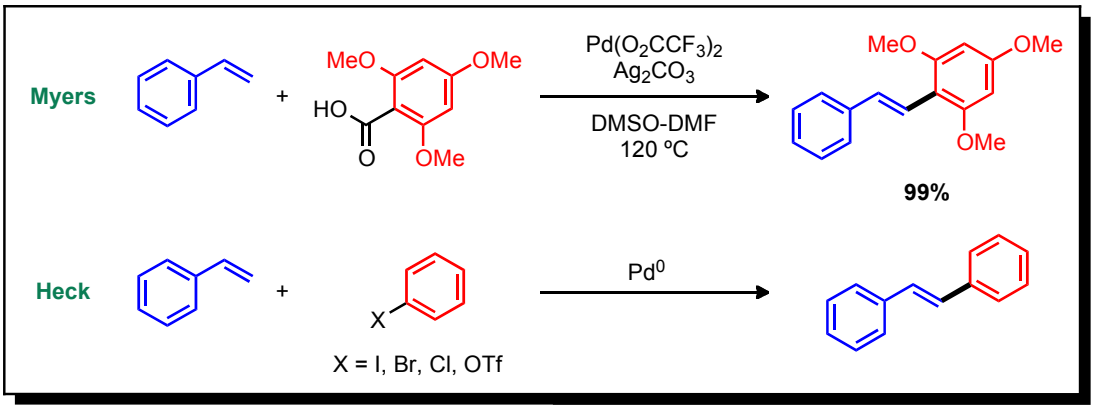
The critical step in any decarboxylative coupling reaction is the extrusion of CO_2, the decarboxylation. This is a relatively difficult process, requiring high temperatures[181] or co-catalysts to facilitate the extrusion,[182] often making this step rate limiting. The resulting harsh thermal conditions can render these processes intolerant of sensitive functionalities. When optimizing such a process employing elevated temperatures, competing protodecarboxylation needs to be taken into consideration. Thus, a primary focus is often to develop milder reaction conditions for decarboxylative couplings.

Palladium-catalyzed decarboxylative couplings made a debut in the 1980s with findings by Tsuji and Trost through the report of a decarboxylative allylic alkylation.[183] These results later led to variations of the protocol, developed by Stoltz[184] for an enantioselective allylation and Tunge[163] for an allyl-acetylide coupling (**Scheme 22**).



Scheme 22: Tsuji-Trost Type Decarboxylative Couplings

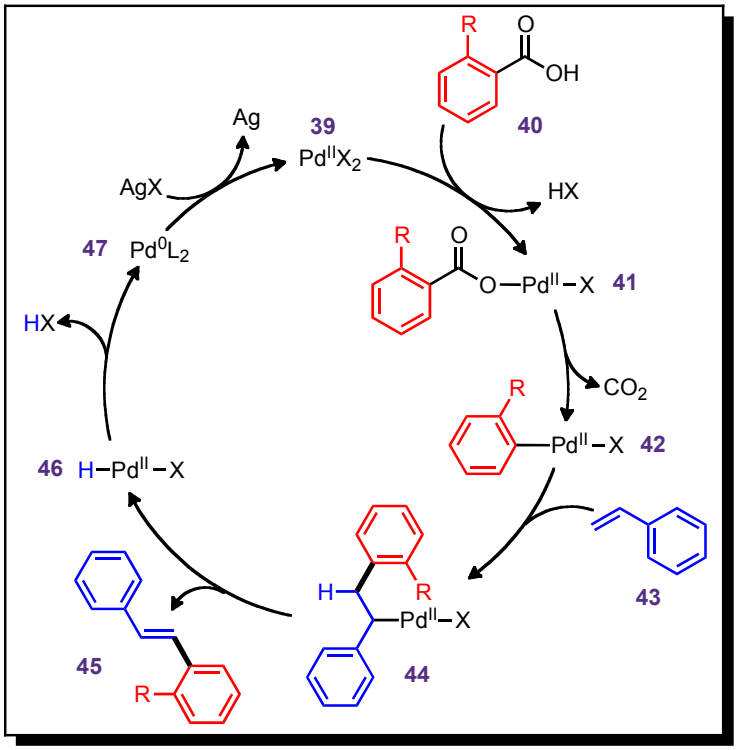
In 2002, Myers *et al.* described a decarboxylative cross-coupling between aryl carboxylic acids and olefins (**Scheme 23**).[166] This chemistry is very closely related to the protocol developed by Heck *et al.* where the carboxylic acid replaces the aryl halide as the electrophilic coupling partner. The protocol developed by Myers *et al.* is not limited to coupling electron-rich carboxylic acids but electron-poor and heteroaromatic acids are also tolerated.[166]



Scheme 23: Myers' Heck-Type Decarboxylative and Heck Cross-Coupling

Based on ^{1}H-NMR studies of the palladium catalyst with the carboxylic acid and X-ray analyses of the intermediate complex, Myers and coworkers were able to propose a mechanism for this Heck-type cross-coupling (**Scheme 24**).[185] Unlike previously mentioned cross-coupling mechanisms, the decarboxylative Heck coupling is not redox-neutral. The catalytic cycle begins with a palladium(II) species **39** that is attacked by the carboxylic acid **40**, generating a palladium(II) carboxylate intermediate **41** and releasing HX in the process. Decarboxylation then occurs, releasing CO_2, and forming the aryl palladium(II) intermediate **42**. The alkene **43** then undergoes the migratory insertion into the aryl–palladium bond analogous to what occurs in the Heck coupling, leading to intermediate **44**.

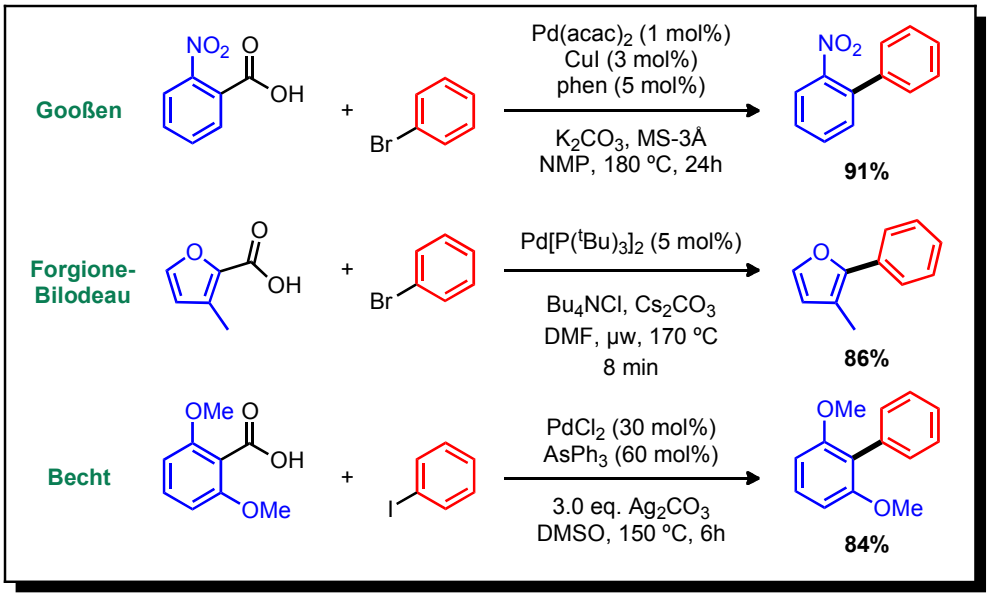
In contrast to previously discussed cross-coupling mechanistic pathways, the desired product **45** is not formed *via* a reductive elimination but rather *via* β–hydride elimination, as in the Heck coupling. The palladium intermediate **46** then undergoes a reductive elimination, releasing HX and forming a palladium(0) complex **47**. The electrophilic coupling partner originates from the carboxylic acid rather than the traditional aryl halide, requiring a palladium(II) complex. Thus an oxidant, which is present in stoichiometric amounts, completes the catalytic cycle by oxidizing the palladium(0) species to the catalytically active palladium(II) complex **39**.



Scheme 24: Myers' Proposed Catalytic Cycle of Decarboxylative Heck Type Cross-Coupling

The first synthesis of biaryls *via* decarboxylative cross-coupling was observed by Nilsson in 1966.[186] Nilsson identified a copper intermediate when treating benzoic acid with 50 mol% Cu_2O and quinoline, which has been previously observed in the Ullmann coupling. Thus, when treating *o*-nitrobenzoic acid with a mixture of aryliodides using the same conditions, a significant amount of unsymmetrical biaryls were isolated. Shortly after these findings, Nilsson applied these conditions to obtain the first aryl-substituted heteroaromatic *via* decarboxylative cross-coupling, albeit in poor yields.[186] What rendered this area of research interesting was the combined use of a two-electron catalyst such as palladium (Pd^0/Pd^{II}) with a copper(I) co-catalyst, facilitating the cross-coupling of the organocopper intermediate with aryl halides.

There are three main protocols for the synthesis of biaryls using palladium catalyzed decarboxylative cross-couplings that have been recently developed; Gooßen's protocol cross-coupling aryl and heteroaryl carboxylic acids with aryl halides and pseudo-halides, a protocol coupling five-membered heteroaromatics with aryl halides and Becht's protocol coupling electron-rich benzoic acids with aryl iodides and diaryliodonium salts (**Scheme 25**).

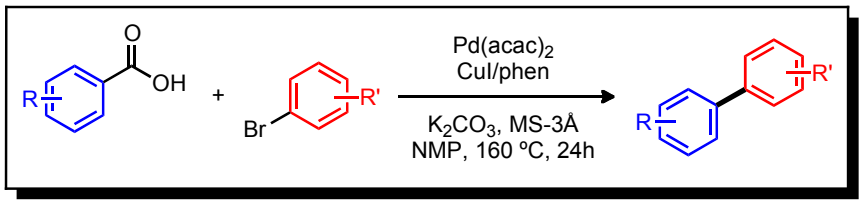


Scheme 25: Decarboxylative Cross-Coupling Protocols for Biaryl Synthesis

Carboxylic acids have proven to be versatile coupling-partners, capable of either replacing organometallic coupling partners, as seen in classical cross-coupling reactions, or aryl halides, as seen in Myers' decarboxylative Heck protocol. Cross-couplings occur at the position of the carboxylic acid, providing the regioselectivity of the classical methods, but produce stoichiometric CO_2 rather than large organometallic waste. There are many strategies to synthesize and to protect carboxylic acids, making them readily available commercially and highly versatile as coupling partners.

1.2.3.1 – Gooßen Protocol

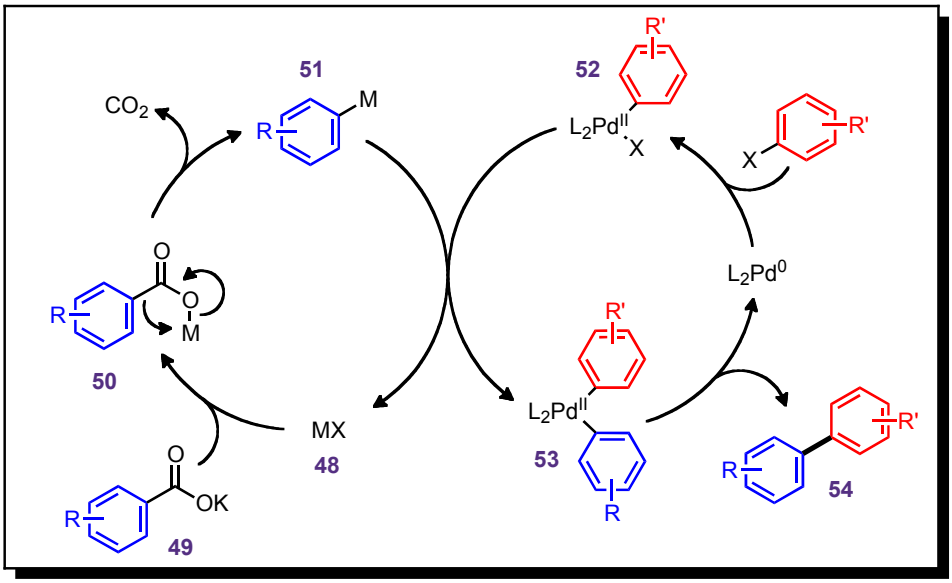
In 2006, Gooßen *et al.* reported the first intermolecular palladium-catalyzed cross-coupling of benzoic acids with aryl bromides (**Scheme 26**).[187]



Scheme 26: Gooßen Cross-Coupling Protocol Using a Copper Co-Catalyst

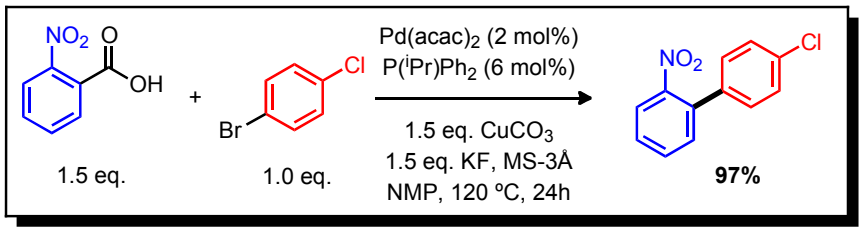
The protocol was inspired from observations made by Nilsson, and the Ullmann reaction.[186,188] The poor capacity of cross-coupling observed in the Ullmann coupling indicated the inability of Cu to mediate a cross-coupling; however, Nilsson observed the necessary arylcopper intermediate generated from a carboxylate. It was hypothesized by Gooßen *et al.* that the addition of a palladium catalyst, capable of shuttling between palladium(II) and palladium(0), could complete the cross-coupling of the arylcopper intermediate with an aryl halide. An attempt to cross-couple with only copper(II) as the catalyst and another with only palladium yielded no biaryl product, however when combining both they observed some cross-coupling product, supporting their hypothesis.

The mechanism proposed by Gooßen (**Scheme 27**) begins with an anion exchange between the copper halide **48** and the benzoate **49**, forming intermediate **50**. The copper, originally coordinated to the carboxylate, shifts to the aryl π–system, followed by insertion into the C–C bond, leading to the release of CO_2 and the organocuprate intermediate **51**. The organocuprate then undergoes a transmetalation with an arylpalladium(II) halide species **52**, which was generated *via* the typical oxidative addition, forming the biarylated palladium(II) intermediate **53**. The biaryl cross-coupling product **54** is then formed by means of reductive elimination, regenerating the palladium(0) species.



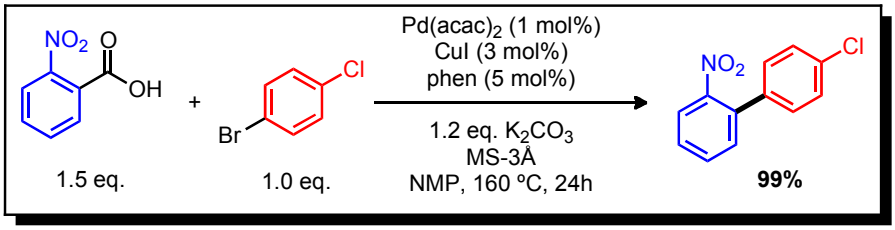
Scheme 27: Proposed Catalytic Cycle for the Gooßen Protocol

Gooßen demonstrated that the efficiency of the transformation can be augmented by addition of KF, which appears to facilitate the decarboxylation process by generating an ArC(O)OCuF intermediate.[187] Water, generated by the carbonate base in the deprotonation of the carboxylic, hinders the reactivity by competing with the decarboxylation by protonating the aryl-copper intermediate, thus addition of molecular sieves (MS) further increased yields. The authors obtained essentially quantitative decarboxylative cross-coupling employing stoichiometric $CuCO_3$ as co-catalyst (**Scheme 28**).



Scheme 28: Gooßen Protocol Using Stoichiometric Copper for the Cross-Coupling of 2-Nitrobenzene-2-Carboxylic Acid and 4-Bromochlorobenzene

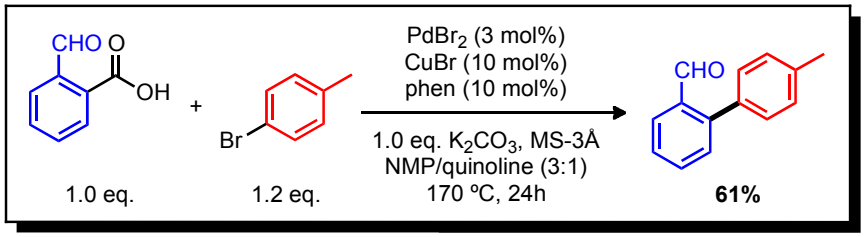
Although the concept of catalyzed decarboxylative cross-coupling had been demonstrated, the use of stoichiometric copper remained limiting. Based on the proposed mechanism, the copper co-catalyst is regenerated after transmetalation with the palladium(II) species, thus theoretically the process should be possible with catalytic amounts of copper. Unfortunately, the reaction produced only trace amounts of product when reducing copper loadings by replacing some $CuCO_3$ with K_2CO_3. As a solution, a new catalytic system was developed using a more stable but less active copper iodide/phenanthroline catalyst. By increasing the temperatures from 120 ºC to 160 ºC comparable results were obtained (**Scheme 29**).



Scheme 29: Gooßen Protocol Using Catalytic Copper for the Cross-Coupling of Nitrobenzene-2-Carboxylic Acid and 4-Bromochlorobenzene

The scope of the protocol proved highly flexible coupling with both electron-rich and electron-poor aryl bromides and chlorides in high yields,[189] and in moderate yields with heteroaromatic carboxylic acids. A limitation, however, was that the catalytic copper conditions only proceeded with *o*-nitrobenzoic acids. A second-generation catalyst system was required for cross-coupling to occur with a variety of other benzoic acids (**Scheme 30**).[189] The addition of a highly

steric, electron-rich (*o*-biphenyl)P^{t}Bu$_2$ phosphine ligand further improved results when coupling with aryl chlorides.[182]



Scheme 30: Gooßen's Second Generation System using Catalytic Copper for the Cross-Coupling of Fluorobenzene-2-Carboxylic Acid and 4-Bromotoluene

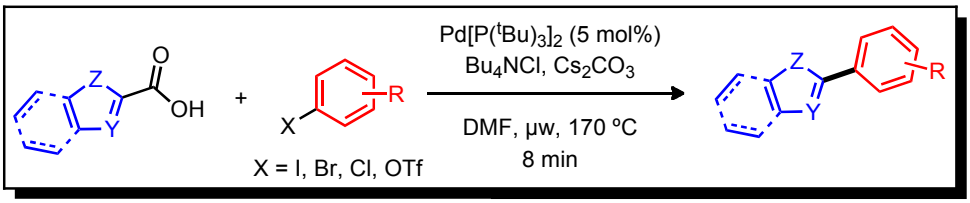
The limitation of this reaction was demonstrated when attempting to cross-couple benzoic acids without *ortho*-coordinating groups, which provided poor yields. The use of aryl halides leads to the generation of copper halide species **48** (**Scheme 27**) after transmetalation of the organocuprate intermediate **51** with arylpalladium(II) halide **52**. However, due to the strong coordinating ability of halides towards copper, an exchange of the halide ligand in the copper halide intermediate **48** for a nonortho-substituted benzoate derivative **49** is thermodynamically unfavourable.[190] Thus, this limitation was circumvented by cross-coupling benzoic acids with aryl triflates, where the TfO^- anion released, post transmetalation, does not hinder coordination of the carboxylate to copper.[191] Further modification of the catalytic conditions allowed for cross-coupling using aryl tosylates as the electrophilic coupling partner.[192] Gooßen *et al.* also observed from previous protodecarboxylation studies and Becht's decarboxylative cross-coupling protocol[193,194] that silver catalysts are capable of undergoing decarboxylation at milder temperatures than copper.[195,196] This led to

the development of a protocol using a silver co-catalyst to cross-couple aryl triflates with aromatic carboxylic acids at lower temperatures.[197]

The protocol developed by Gooßen *et al.* is a powerful tool to cross-couple benzoic acids and heteroaromatic carboxylic acids with aryl halides and pseudo halides. Their methodology was shown to work with thermal conditions and also using microwave irradiation,[198] and was adapted to function in a continuous flow reactor[199].

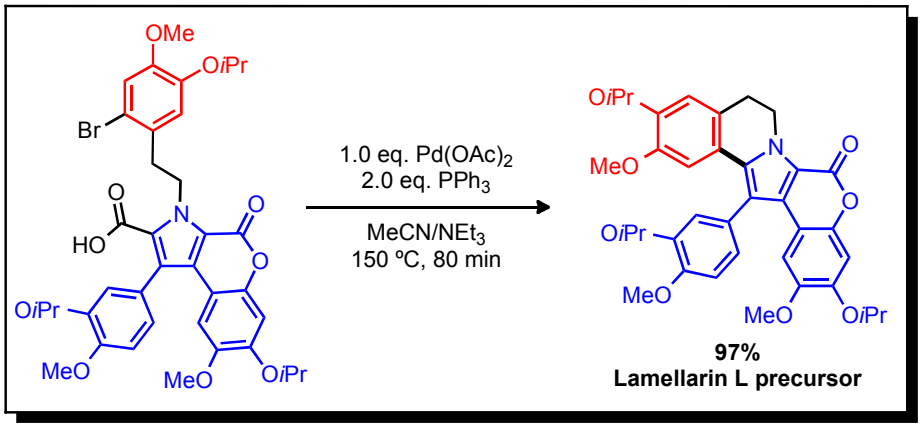
1.2.3.2 – Forgione-Bilodeau Protocol

In 2006, at the same time as Gooßen *et al.* reported their findings, Forgione and Bilodeau reported an intermolecular decarboxylative cross-coupling reaction between heteroaromatic carboxylic acids and aryl bromides (**Scheme 31**).[145]



Scheme 31: Forgione-Bilodeau Decarboxylative Cross-Coupling Protocol of Heteroaromatic Carboxylic Acids with Aryl Bromides

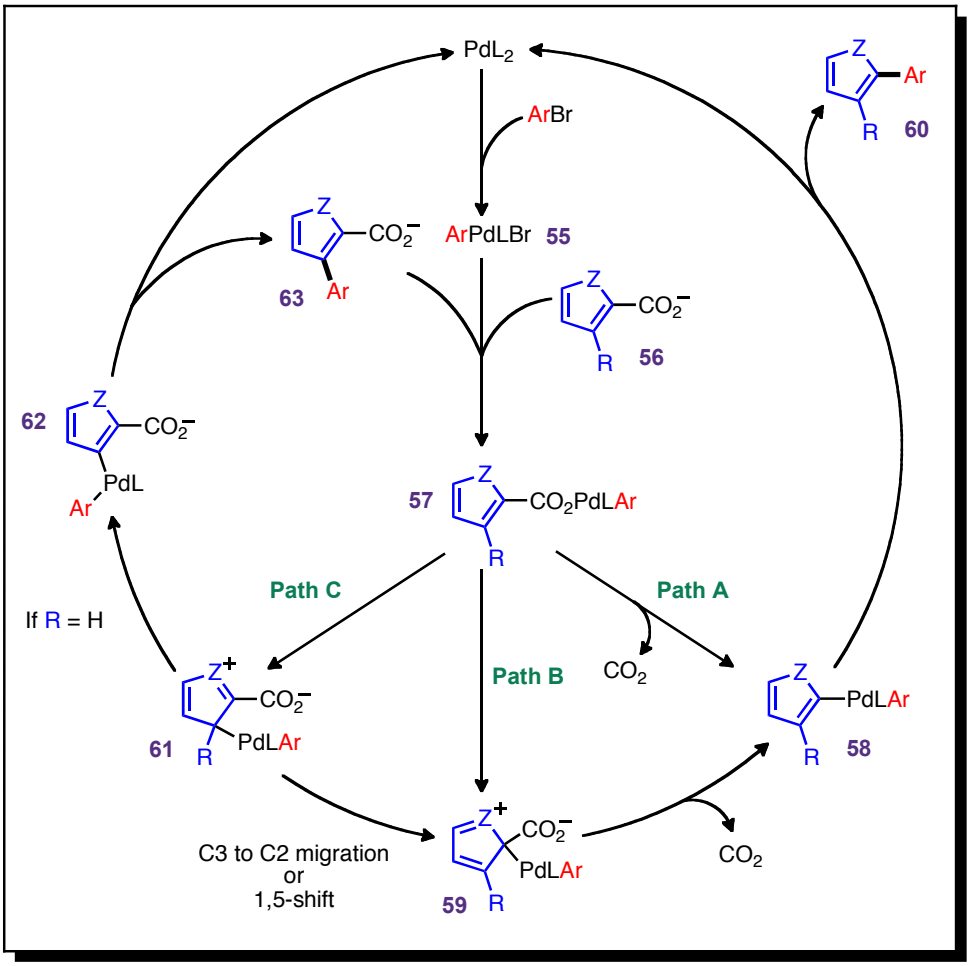
Similar chemistry was described by Steglich *et al.* in 2000 for the total synthesis of Lamellarin L, where a tetrasubstituted pyrrole carboxylic acid was cross-coupled with an aryl bromide intramolecularly, but required stoichiometric amounts of $Pd(OAc)_2$ (**Scheme 32**).[200]



Scheme 32: Intramolecular Decarboxylative Cross-Coupling Using Stoichiometric Palladium for the Synthesis of a Lamellarin L Precursor

The mechanism was proposed as a redox-neutral cross-coupling with a palladium(0) active catalytic species, which generates the arylpalladium(II) intermediate **55** *via* the typical oxidative addition (**Scheme 33**). The palladated carboxylate intermediate **57**, generated from the displacement of the halide by the arylcarboxylate **56**, could undergo three possible routes. **Path A** is a direct decarboxylation releasing CO_2 while leading to the C2-palladated intermediate **58**. **Path B** and **Path C** utilize the electron-richness of the five-membered heteroaromatic to undergo an electrophilic palladation generating intermediate **59** or **61** *via* delocalization of an electron lone-pair on the heteroatom. The direct decarboxylation (**Path A**) was ruled out as a viable pathway due to the failure to cross-couple benzoic acid. The strong aromaticity of the phenyl group and electron-deficiency of benzoic acid prevent an efficient electrophilic palladation, suggesting a mechanistic dependence on the π-nucleophilicity of five-membered heteroaromatics. Further evidence was obtained with the failure to generate cross-coupling product when utilizing furan-3-carboxylic acid. The α-position (C2,

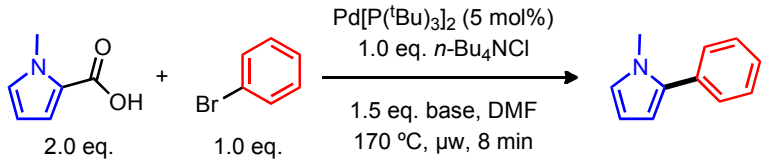
C5) of the heteroaromatic ring is significantly more susceptible to electrophilic attack than the β-position (C3, C4) due to greater mesomeric stabilization of the cationic intermediate. Thus, due to the directing ability of the carboxylic acid, and failure to undergo cross-coupling when substituted at the C3-position **Path B** was hypothesized as the main mechanistic pathway generating key intermediate **59**. Since a co-catalyst is not present to facilitate the decarboxylation process, the driving force for the extrusion of CO_2 is rearomatization of intermediate **59**, which generates the diarylpalladium(II) intermediate **58**. This palladium intermediate then undergoes reductive elimination producing the biaryl product **60**. However, a trace 2,3-biarylated by-product was observed, indicating formation of intermediate **61** *via* C3-electrophilic palladation (**Path C**). If R = H, rearomatization of the ring is obtained *via* deprotonation. Intermediate **62** undergoes reductive elimination, forming a C3-arylated product **63**, which still contains the carboxylic acid functionality at the C2-position, allowing it to re-enter the catalytic cycle to subsequently produce the 2,3-biarylated by-product (**60**, R = Ar).



Scheme 33: Proposed Catalytic Cycle for Forgione-Bilodeau Decarboxylative Cross-Coupling Protocol of Heteroaromatic Carboxylic Acids with Aryl Bromides

Various parameters such as base effects, solvent effects and catalyst effects were studied to evaluate their impact on reactivity.[181] In order to generate the carboxylate ion *in situ*, an excess of non-coordinating base was employed. Carbonate and fluoride bases were screened and provided the biaryl product in good yield, the only exception being with lithium counter ions (**entries 1 and 5**, **Table 2**). Other bases such as K_2CO_3 and KF appear to be beneficial, generating the desired product in good yields, however full conversion of starting materials is not obtained. Thus, Cs_2CO_3 provided the best result, indicating a softer counter-

ion such as Cs^+ is beneficial as it coordinates to the carboxylate more loosely, facilitating attack onto the palladium(II) halide species.



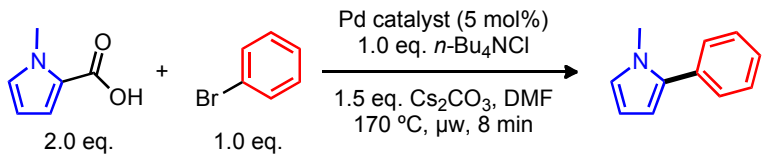
Entry	Base	% Yield
1	Li_2CO_3	14
2	Na_2CO_3	88
3	K_2CO_3	81
4	Cs_2CO_3	88
5	LiF	4
6	KF	75
7	CsF	81

Table 2: Forgione-Bilodeau Decarboxylative Cross-Coupling Protocol Base Screen in the Cross-Coupling of N-Methylpyrrole-2-Carboxylic Acid with Bromobenzene

A solvent screen indicated that the reaction was relatively robust, as good yields were obtained with both highly polar solvents such as DMF, NMP, DMA and non-polar solvents such as xylenes ranging from 74-88%. It was also found that the reaction tolerates the presence of small amounts of polar protic solvents such as EtOH and H_2O when mixed with DMF. However, if the presence of water is too high, such as 1:1 H_2O/DMF, the reaction provides none of the desired products.

Forgione and Bilodeau then evaluated the effects of various catalysts, including the source of palladium and the ligand stoichiometry (**Table 3**). The reference conditions used the highly active $Pd[P(^tBu)_3]_2$ (**entry 1**), which is a palladium(0) source that is relatively sensitive to water and heat, making this

catalyst somewhat difficult to handle. The generation of this catalyst *in situ* using a 2:1 ligand/$PdCl_2$ ratio provided the desired product in comparable yields, 80% (**entry 2**). Reduction of the amount of ligand from 10 mol% to 5 mol% (1:1 ligand/Pd ratio) yielded similar results (**entry 3** *vs.* **entry 2**), indicating a monoligated palladium(0) species as the active catalyst. The use of other pre-formed palladium(0) catalysts such as $Pd(PPh_3)_4$ (**entry 4**) provided only moderate yields, but interestingly, the pre-catalyst, $PdCl_2(PPh_3)_4$ provided substantially better results (**entry 5**).



Entry	Pd catalyst	% Yield
1	$Pd[P(^tBu)_3]_2$	88
2	$PdCl_2 + P(^tBu)_3$ (10%)	80
3	$PdCl_2 + P(^tBu)_3$ (5%)	79
4	$Pd(PPh_3)_4$	43
5	$PdCl_2(PPh_3)_2$	76

Table 3: Forgione-Bilodeau Decarboxylative Cross-Coupling Protocol Catalyst Screen in the Cross-Coupling of N-Methylpyrrole-2-Carboxylic Acid with Bromobenzene

Forgione and Bilodeau demonstrated a diverse substrate scope utilizing developed optimized conditions. They were able to cross-couple *N*-methylpyrrole-2-carboxylic acid with phenyl iodide, bromide, chloride and triflate in good to excellent yields. Both electron-rich and electron-poor aryl halides can be coupled in good yields, yet the best result remains with the electron-neutral bromobenzene. Certain carboxylic acids, however, could not be coupled using

these conditions, such as benzoic acid, thiophene-2-carboxylic acid and furan-3-carboxylic acid.

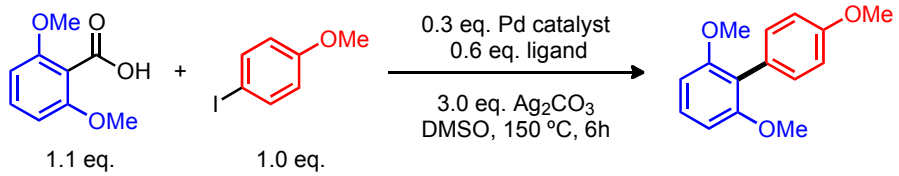
1.2.3.3 – Becht Protocol

In 2007 Becht *et al.* developed a protocol synthesizing biaryls *via* a decarboxylative cross-coupling of aryl iodides with electron-rich benzoic acids (**Scheme 34**).[193]

Scheme 34: Becht Protocol for the Cross-Coupling of Aryl Carboxylic Acids with Aryl Iodides

This work is complimentary to Gooßen's early findings, as mainly electron-poor benzoic acids would couple efficiently with aryl halides. Similar to Gooßen's protocol, Becht requires the use of excess Ag_2CO_3 (3.0 eq.) where it plays a dual role, deprotonating the carboxylic acid, and facilitating decarboxylation. Interestingly, it was found that $PdCl_2$ alone provided better results than with the presence of phosphine ligand, PPh_3, forming the biaryl product in 51% and 37% yield, respectively (**Table 4**). Alterations to the base, solvent, or salt additives also led to a substantial decrease in product yield. It was with the addition of $AsPh_3$ (30 mol%) that yields increased substantially, to 71% and 90% when the benzoic acid was used in slight excess (1.3 eq. *vs.* 1.1 eq.). These optimal

conditions were attempted with aryl bromides, however no cross-coupling product was observed.



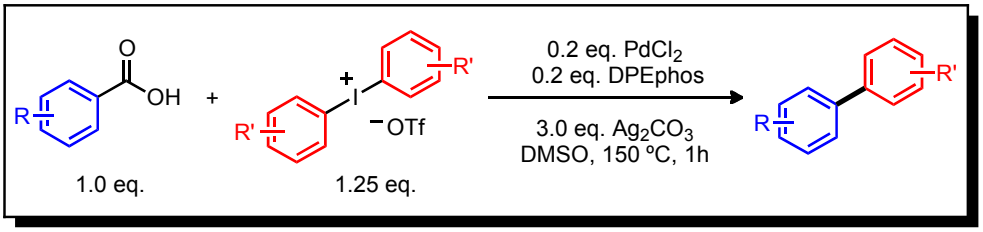
1.1 eq. 1.0 eq.

Pd catalyst	Ligand	% Yield
$PdCl_2$	-	51
$PdCl_2$	PPh_3	37
$PdCl_2$	$AsPh_3$	71 (90)*

* with 1.3 eq. benzoic acid

Table 4: Becht Protocol Condition Screen in the Cross-Coupling of 1,3-Dimethoxybenzene-2-Carboxylic Acid with 4-Iodoanisole

Shortly after their original findings, Becht *et al.* improved their protocol using electron-deficient hypervalent diaryliodonium salts (**Scheme 35**).[194]

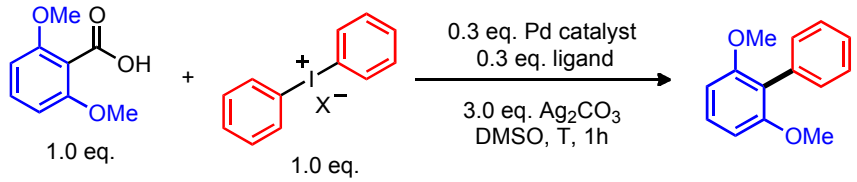


1.0 eq. 1.25 eq.

Scheme 35: Becht Protocol for the Cross-Coupling of Aryl Carboxylic Acids with Diaryliodonium Salts

These iodonium salts act as excellent electrophilic coupling partners due to the strong leaving group ability of Ar–I.[201] Although not very well understood, Becht observed a significant counterion effect on reactivity, where Cl^- provided a poor yield (35%) whereas $CF_3SO_3^-$ and PF_6^- provided the best results, 64% and 65%, respectively (**Table 5**). The use of bidentate phosphine ligands proved

beneficial, increasing biaryl yield to 72% when using DPEphos, and further increasing to 80% when raising the temperature to 150 ºC. The scope of the decarboxylative cross-coupling using hypervalent diaryliodonium salts is not limited to electron-rich benzoic acids, but can also be used with electron-poor, and heteroaromatic carboxylic acids (benzo[*b*]furan) in good yields.



X^-	Pd catalyst	ligand	T (º C)	% Yield
Cl^-	$PdCl_2$	-	120	35
NO_2^-	$PdCl_2$	-	120	62
$CF_3SO_3^-$	$PdCl_2$	-	120	64
PF_6^-	$PdCl_2$	-	120	65
PF_6^-	$PdCl_2$	DPEphos*	120	72
PF_6^-	$PdCl_2$	DPEphos*	150	80

* bidentate ligand used in 0.3 eq.

Table 5: Becht Protocol Condition Screen for the Cross-Coupling of 1,3-Dimethoxybenzene-2-Carboxylic Acid with Diphenyliodonium Salts

It is important to note that unlike other decarboxylative cross-couplings, Becht's protocol demands substantially higher catalyst loadings, requiring at least 20 mol% when coupling with diaryliodonium salts or 30 mol% $PdCl_2$ and 60 mol% $AsPh_3$ when coupling with aryl iodides. Although providing a valuable alternative to the synthesis of biaryls *via* decarboxylative cross-coupling, Becht *et al*. failed to discuss any mechanistic considerations. Albeit, based on the similarities in reaction conditions with Gooßen's protocol, a similar mechanistic pathway seems likely.

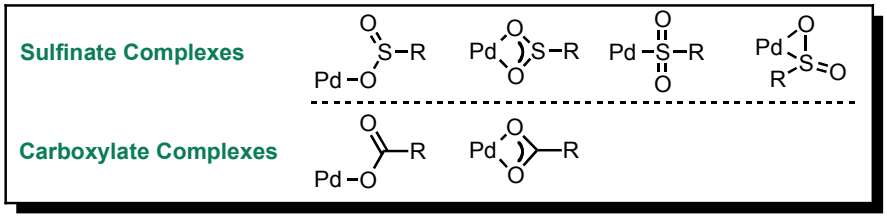
1.3 – Sulfinic Acids as Carboxylic Acid Mimics

The synthesis of biaryls *via* palladium-catalyzed cross-couplings has greatly evolved since the development of the classical protocols. Although powerful techniques, they were limited due to the sensitivity of the organometallic precursors and the generation of stoichiometric amounts of large organometallic by-products. The possibility to cross-couple aryl halides with unactivated arenes and heteroaromatics provides a powerful pathway to biaryls without the need of pre-functionalization or generating stoichiometric amounts of metallic waste. Unfortunately, this alternative suffers from a lack of regioselectivity in cases with multiple reactive but inequivalent C–H bonds, providing a mixture of products. Decarboxylative cross-couplings provide the regioselectivity of the classical protocols but remain green, only evolving CO_2 as a by-product. Carboxylic acids are also readily available commercially and can be synthesized easily. In the synthesis of aryl-substituted heteroaromatics, a co-catalyst such as copper or silver is required to facilitate the decarboxylative process with extensive reaction times using the Gooßen protocol. In the Forgione-Bilodeau protocol, their synthesis occurs rapidly in eight minutes and without a co-catalyst, but fails to couple some carboxylic acids such as thiophene-2-carboxylic acid and benzoic acids.

Decarboxylative cross-couplings have presented many advantages as a synthetic strategy in obtaining biaryl motifs, but are energetically difficult to accomplish. This has been demonstrated with the need for high reaction temperatures and co-catalysts. In order to improve this area of chemistry, new

means of facilitating this step are required. However, other functional groups capable of mimicking the role of the carboxylic acid, while generating the aryl palladium(II) species more easily are also viable options.

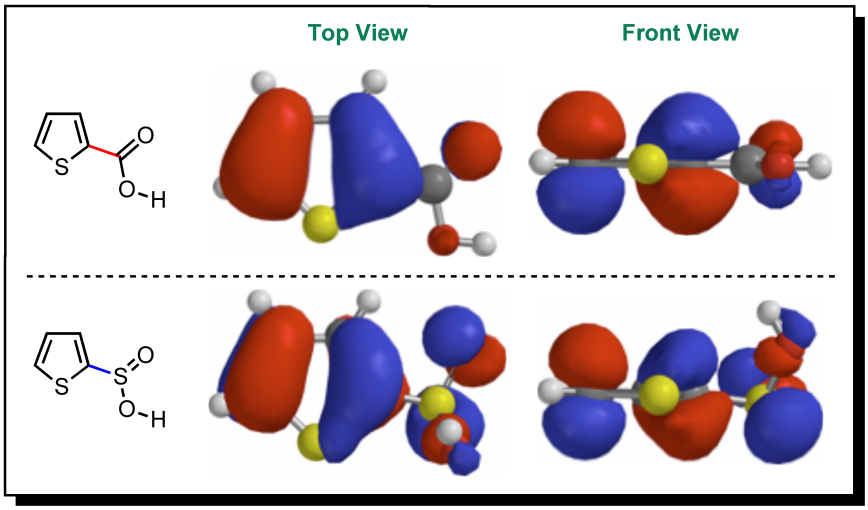
Sulfinic acids ($–SO_2H$), being the sulfur equivalent of carboxylic acids, are expected to undergo similar reactivity. The acidity of sulfinic acids has been found to be greater than that of their carboxylic acid counterparts.[202] This is caused by the additional free *d*-orbital on the sulfur atom and can be demonstrated by comparing phenylsulfinic acid and benzoic acid with pK_a values of 2.76 and 4.20, respectively.[202] Protonated, they undergo disproportionation and redox chemistry forming sulfonic acids, sulfenic acids and thiols in the process, whereas when deprotonated as the sulfinate salt, they appear to be bench stable.[203] Sulfinates have been shown to coordinate to metals, such as palladium, similarly to carboxylic acids but with additional modes of coordination due to the added coordinating sulfur atom, forming sulfinato-complexes (**Scheme 36**).[204] Although sulfinates provide new modes of coordination (sulfinato–*S* complexes), they can theoretically mimic the role of heteroaromatic carboxylates in cross-couplings.



Scheme 36: Modes of Coordination Sulfinates and Carboxylates with Palladium(II)

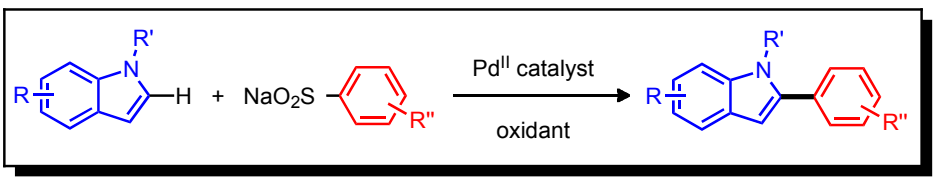
The use of sulfinates rather than carboxylic acids would prove beneficial as extrusion of SO_2[205] appears to occur under milder conditions than the extrusion of CO_2.[181,182,196] This could render the cross-coupling, using the Forgione protocol, of thiophene-2-sulfinic acids and phenyl sulfinic acids with aryl halides possible. This type of chemistry is highly dependent on the π–nucleophilicity of the aromatic system for reactivity and site-selectivity,[181,206] thus changing functional groups from carboxylic acid to sulfinic acid could affect the HOMO of the π–systems. However, from DFT calculations performed,[a] it was found that the change in functionality does not appear to affect the highest occupied molecular orbital (HOMO) significantly, where C2 still retains a probability of holding electron density (**Scheme 37**).[207,208] The model illustrates a slight distortion of thiophene ring when substituted with the sulfinic acid functionality. The distortion in the ring leads to a less efficient overlap of the *p*-orbitals, reducing the aromaticity of the ring and consequently increasing the nucleophilicity of the π-system. This increase in π-nucleophilicity suggests a more facile electrophilic palladation with thiophene-2-sulfinic acid than with thiophene-2-carboxylic acid.

[a] DFT calculations were performed using the Spartan '06 Version 1.0.3 software package. The equilibrium geometries were obtained from the ground states using the B3LYP(2) exchange correlation functional with the 6-311++G** basis set for all atoms.



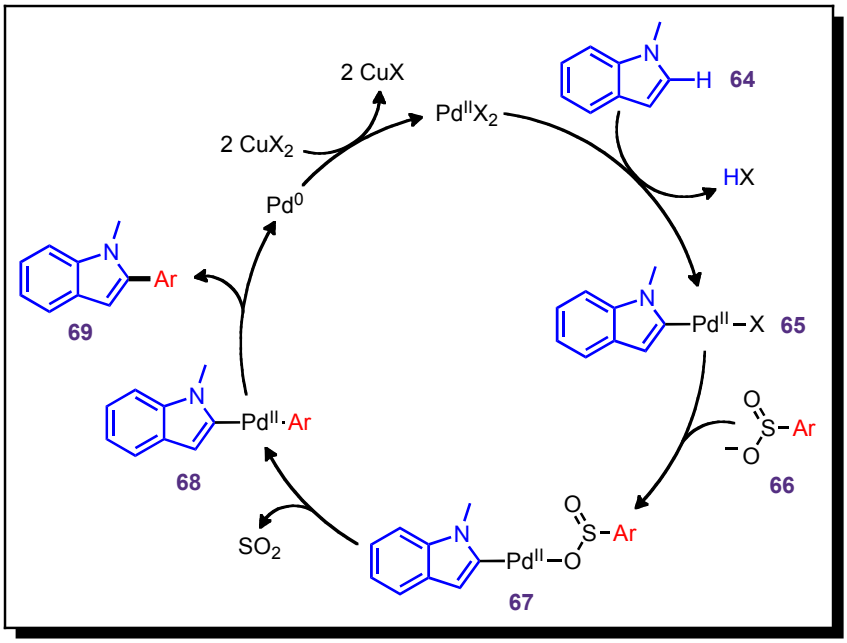
Scheme 37: Two Views of the HOMO for Thiophene-2-Carboxylic Acid and Thiophene-2-Sulfinic Acid

With these considerations, there has also been some literature precedence using this technique for related coupling strategies. In 1970, Garves[209] used stoichiometric palladium salts to homo-couple aryl sodium sulfinate salts, and concurrently, Thiele developed a similar protocol.[210] In 1992, Sato and Okoshi reported, in a patent, the first desulfitative cross-coupling of aryl sulfinates with aryl halides using catalytic palladium.[211] Very recently, Deng and Luo have demonstrated the ability to use aryl sodium sulfinates as an electrophilic aryl source in a desulfitative Heck coupling,[212] and in a direct arylation of indoles (**Scheme 38**)[213].



Scheme 38: Deng and Luo Desulfinylative Arylation of Indoles with Aryl Sodium Sulfinates

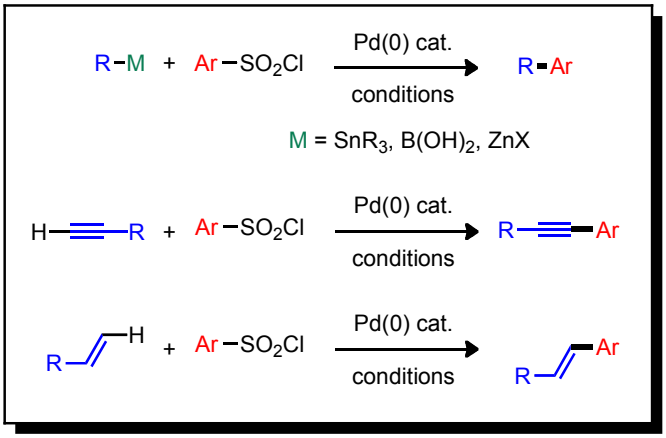
Their proposed mechanism is *via* an oxidative pathway, since the sulfinate is used as an electrophilic source, requiring an oxidant to regenerate the active palladium(II) species (**Scheme 39**). The mechanism is reported to begin with the insertion of $Pd^{II}X_2$ into the indole (**64**) C–H bond leading to the arylated palladium(II) intermediate **65** (X = OAc). The acetate ligand is then displaced by the sulfinate **66** forming sulfinato–*O* complex **67**, which can then undergo desulfinylation forming biarylated palladium(II) complex **68**. The arylated indole **69** is then formed *via* reductive elimination, generating a palladium(0) species, which is oxidized back to palladium(II) by the stoichiometric copper oxidant.



Scheme 39: Deng and Luo Proposed Catalytic Cycle for the Direct Desulfitative Arylation of Indoles with Aryl Sodium Sulfinates

Sulfonyl chlorides have also been known to act as electrophilic coupling partners in desulfitative cross-couplings (**Scheme 40**).[205,214] A palladium(0)

species can undergo an oxidative addition into the Cl–S bond and lead to similar intermediates such as **67** (**Scheme 39**) thereby generating biaryl or aryl-substituted heteroaromatic cross-coupling products.

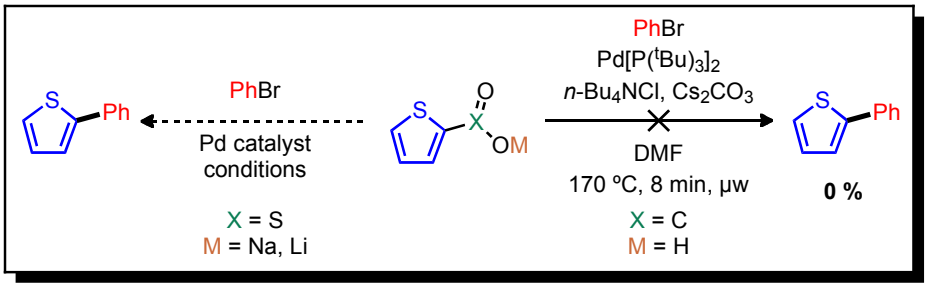


Scheme 40: Desulfitative Cross-Coupling of Sulfonyl Chlorides

1.3.1 – Research Goals

The classical palladium-catalyzed cross-coupling reactions have demonstrated extensive application in various industries based on efficiency and versatility. However, limitations such as the instability of certain organometallic coupling partners and the generation of stoichiometric metallic by-products has created a desire for more environmentally benign processes with bench-stable coupling partners. A very powerful alternative to these processes was developed, utilizing previously thought unreactive C–H bonds to directly arylate. These protocols do not require pre-functionalization and consequently reduce substantially the amount of waste generated. Direct arylation is not without restrictions however, requiring nucleophilic coupling partners be either symmetrical or suffer a mixture of products unless limited to a single reactive C–

H bond. Decarboxylative cross-couplings on the other hand are chemoselective and generate environmentally benign by-products. Unfortunately, the decarboxylation process is inherently difficult, requiring high reaction temperatures or the use of a co-catalyst. The procedure developed by Forgione and Bilodeau is the only reported decarboxylative cross-coupling protocol that does not require the aid of a co-catalyst for the synthesis of biaryls. The coupling of benzoic acid and thiophene-2-carboxylic acid with aryl halides without the use of a co-catalyst has been unsuccessful. Thus with evidence of sulfinates demonstrating similar reactivity as carboxylates in palladium catalyzed cross-coupling reactions, it was hypothesized that heteroaromatic sulfinates could be employed as a new nucleophilic heteroaromatic source. Consequently, the goal of this project was to utilize sulfinates to diversify the reaction scope, enabling the cross-coupling of thiophene-2-sulfinate with aryl halides, where thiophene-2-carboxylic acid previously failed to react (**Scheme 41**).

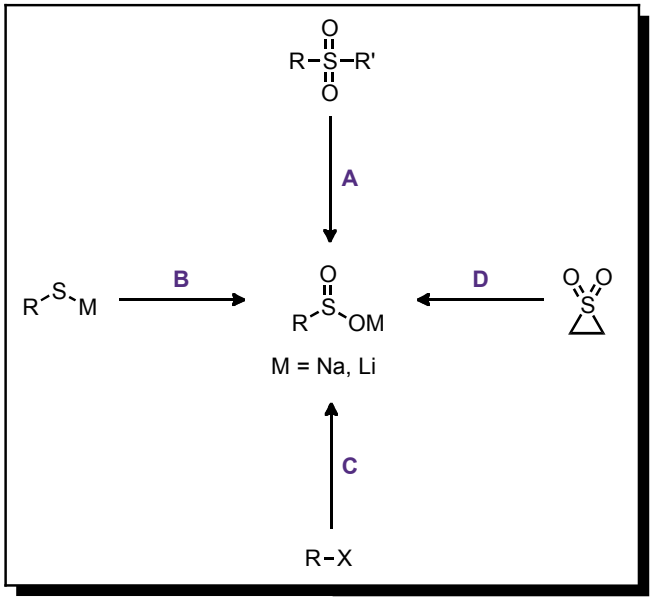


Scheme 41: Model Reaction for the Desulfinylative Cross-Copling of Thiophene-2-Sulfinates with Bromobenzene

2 – Results and Discussion

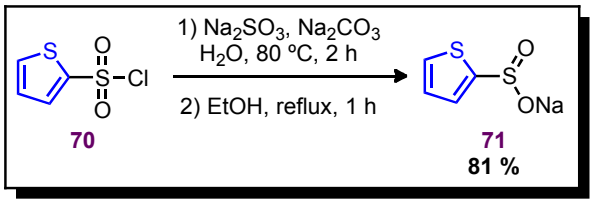
2.1 – Sulfinate Synthesis and Preliminary Results

Sulfinic acids have been known for the better part of a century but have attracted limited attention from the synthetic community until recently. Unlike the analogous carboxylic acids, sulfinic acids have substantially fewer methods for their preparation (**Scheme 42**). The most commonly employed method for the synthesis of sulfinic acids or sulfinates, is the reduction of sulfonyl chlorides, as they are easily prepared and commercially available, or the reduction of sulfones (**A**).[215–217] Other means for their generation is *via* oxidation of thiols or thiolates (**B**),[218,219] quenching of organolithium species (generated by deprotonation or halogen-metal exchange) or reaction of Grignard reagents with sulfur dioxide (SO_2) (**C**),[220] or opening thiirane 1,1-dioxide (**D**)[221].



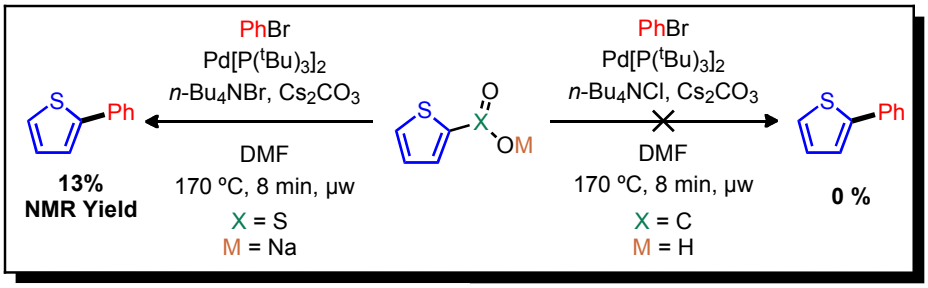
Scheme 42: Methods for the Synthesis of Sulfinates

To obtain proof of concept for the model desulfinylative cross-coupling reaction (**Scheme 41**), thiophene-2-sulfinate (**71**, **Scheme 43**) needed to be prepared as it is not commercially available. Reduction of the sulfonyl chloride was chosen since the protocol was simple, efficient and thiophene-2-sulfonyl chloride **70** is commercially available.[215] Purification of the sulfinate is done by dissolving the sulfinate in 99% ethanol heated at reflux followed by hot filtration through celite to remove the insoluble excess inorganic salts. This method provided the desired thiophene-2-sulfinate pure by ^{1}H-NMR analysis.



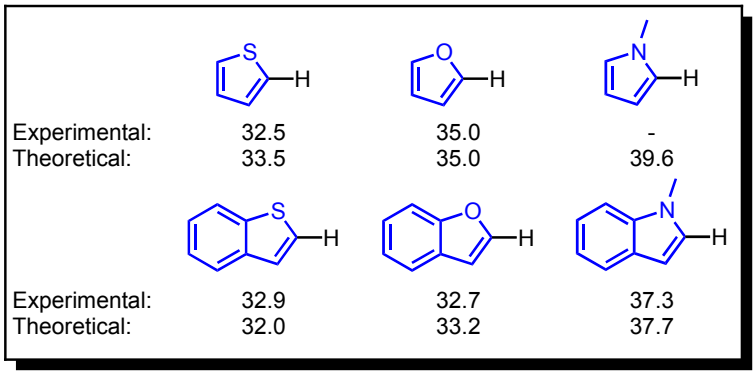
Scheme 43: Reduction of Thiophene-2-Sulfonyl Chloride to Sodium Thiophene-2-Sulfinate

Using the optimal conditions from the Forgione-Bilodeau decarboxylative cross-coupling protocol, the desired cross-coupling product was observed in 13% *via* ^{1}H-NMR using an internal standard (**Scheme 44**). This preliminary result demonstrated that heteroaromatic sulfinates can mimic the role of their carboxylic acid counterparts as a nucleophilic heteroaromatic source in a cross-coupling with aryl bromides.



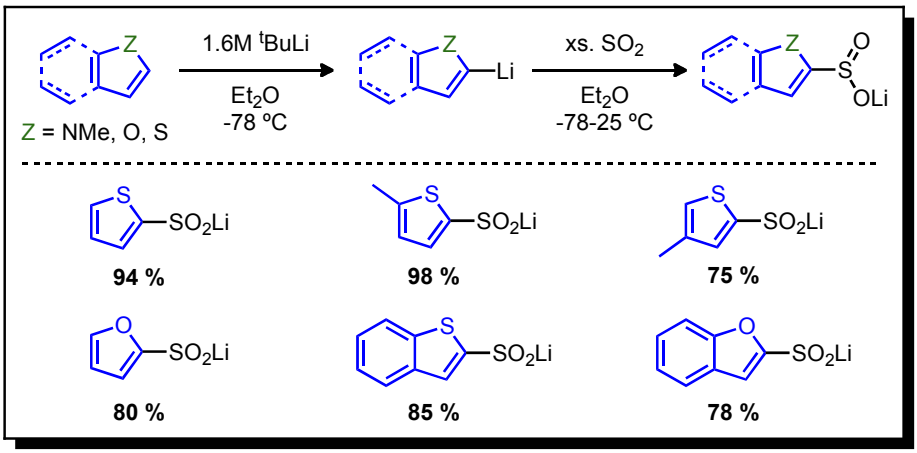
Scheme 44: Proof of Concept for the Desulfinylative Cross-Coupling of Sodium Thiophene-2-Sulfinate with Bromobenzene

In order to synthesize a variety of heteroaromatic sulfinates to study the scope of the desulfinylative cross-coupling, a simpler synthesis was required. Although thiophene-2-sulfonyl chloride is commercially available, substituted thiophenes, as well as other heteroaromatic sulfonyl chlorides are not. Five-membered heteroaromatics are significantly more acidic at the C2- than the C3-position due to the presence of the heteroatom (**Scheme 45**).[222] Thus, a convenient route to sulfinates can be obtained by using strong bases to generate a C2-metalated intermediate, which can then be quenched with SO_2. Unlike carboxylic acids that can be purified by precipitation *via* protonation/deprotonation, sulfinate purification is more problematic. This is due to the relative instability of the protonated sulfinic acids, which tends to lead to polymerization or decomposition. Therefore, the presence of salt contaminants due to by-products or excess presence of base can provide serious purification issues rendering the choice of base highly important.



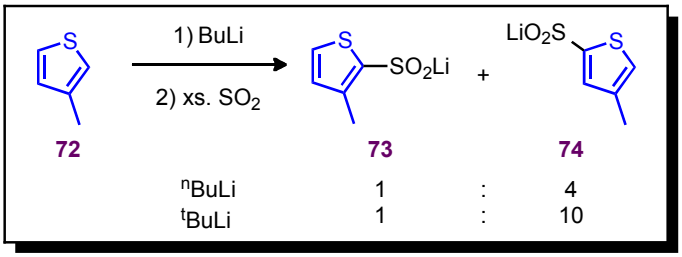
Scheme 45: Experimental and Theoretical pK_a Values of Five-Membered and Benzo-Fused Heteroaromatics in DMSO[222]

Bases such as sodium hydride (NaH) and sodium amide ($NaNH_2$) were considered as they are strong enough to deprotonate the heteroaromatics and generate a gas as by-product, which would facilitate purification, but suffer from solubility issues. Butyl lithium (BuLi), however, proved ideal as it is highly soluble, basic enough to deprotonate heteroaromatics, and produces butane gas as a by-product after proton abstraction. Thus, using butyl lithium, a variety of heteroaromatics were deprotonated in anhydrous ether at reduced temperatures, followed by quenching using excess SO_2 gas, forming the desired sulfinates, which precipitated from the solution (**Scheme 46**). Both *n*-BuLi and *t*-BuLi were used, however the latter provided better results, and in some cases *n*-BuLi proved ineffective. The sulfinates were then purified simply *via* rinsing or trituration with diethyl ether or acetone to remove any excess or unreacted heteroaromatic.



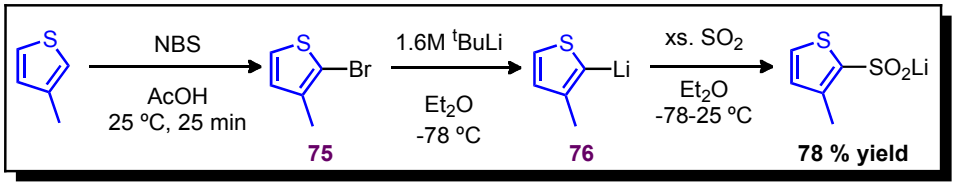
Scheme 46: Sulfinate Synthesis *via* Deprotonation of Heteroaromatic Followed by SO_2 Quenching

For the preparation of lithium 4-methylthiophene-2-sulfinate (**74**, **Scheme 47**) from 3-methylthiophene (**72**), the difference in steric bulk between *t*-BuLi and *n*-BuLi played an important role. The less sterically hindered *n*-BuLi favors deprotonation at the C5- over the C2-position, in a 4:1 ratio of **74**:**73** (*via* ^{1}H-NMR). To further favor deprotonation at the C5-position the more sterically hindered *t*-BuLi proved necessary, where unfavorable interactions with the methyl group at the C3-position lead to an increased 10:1 ratio of C5:C2 deprotonation. Interestingly, after an acetone wash, the ratio of lithium 4-methylthiophene-2-sulfinate (**74**) to lithium 3-methylthiophene-2-sulfinate (**73**) increased from 10:1 to 100:1 ratio. The acetone likely solubilizes the lithium 3-methylthiophene-2-sulfinate more readily than the lithium 4-methylthiophene-2-sulfinate.



Scheme 47: BuLi Regioselectivity in the Deprotonation of 3-Methylthiophene

A halogen-metal exchange of 2-bromo-3-methylthiophene (**75**, **Scheme 48**) was required to exclusively produce the lithiated intermediate **76** and generate lithium 3-methylthiophene-2-sulfinate.



Scheme 48: Synthesis of Lithium 3-Methylthiophene-2-Sulfinate *via* Halogen-Metal Exchange of 2-Bromo-3-Methylthiophene using ^{t}BuLi

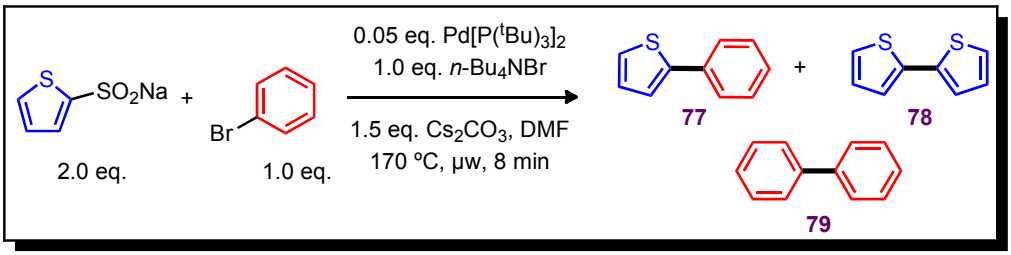
This procedure failed with the nitrogen containing isostere, N-methylpyrrole, which is likely due to the very difficult α–lithiation. The cause for this more difficult α–lithiation is two-fold: nitrogen lacks the presence of a *d*-orbital and is significantly less electronegative than oxygen. The empty *d*-orbital present in sulfur allows for overlap with the σ-orbital of the adjacent, α–carbon, stabilizing the anion generated and consequently increasing acidity.[223,224] The α–lithiation of N-methylpyrrole is possible, however the known protocols require extensive reaction times, elevated temperatures, and excess amounts of lithiating agent, only to obtain the product in poor to moderate yields.[225,226] This was attempted, and clearly the desired lithium N-methylpyrrole-2-sulfinate was generated,

however there proved to be too many contaminants. The issue with synthesizing the sulfinate with these conditions is the limitation in purification. Unlike for carboxylic acids, a protonation-deprotonation purification pathway quickly leads to product decomposition. Thus, a low-yielding α–lithiation that generate salt by-products due to excess lithiating agent is not a viable option. An alternative to this is using chelating agents such as tetramethylethylenediamine (TMEDA) to break apart the butyl lithium clusters, increasing reactivity.[227] This occurs due to the strong affinity of the nitrogen atoms for the lithium cation. With the use of 1 eq. of TMEDA with *n*-butyl lithium, the desired sulfinate was generated in seemingly better yields, yet the product still remained contaminated with various salts and TMEDA. Other sulfinates such as lithium benzo[*b*]furan-2-sulfinate, and its sulfur isostere, were synthesized in the same manner and both remained contaminated with TMEDA in a 1:1 ratio. The TMEDA remains chelated strongly with the lithium ion in the sulfinate and was only removed partially with the use of a soxhlet extractor and THF. The successful preparation of pure lithium *N*-methylpyrrole-2-sulfinate has not yet been achieved.

The source of the SO_2 gas used for quenching proved inconsequential, thus the gas can be either purchased or generated by adding sulfuric acid (H_2SO_4) to sodium metabisulfite ($Na_2S_2O_5$), but both require drying by diffusing into concentrated H_2SO_4. Once scrubbed, the SO_2 can be either bubbled through the solution of lithiated heteroaromatic, or can be condensed at -78ºC so the lithiated intermediate can be added *via* cannulation.

2.2 – Optimization with Electron-Rich 4-Bromoanisole

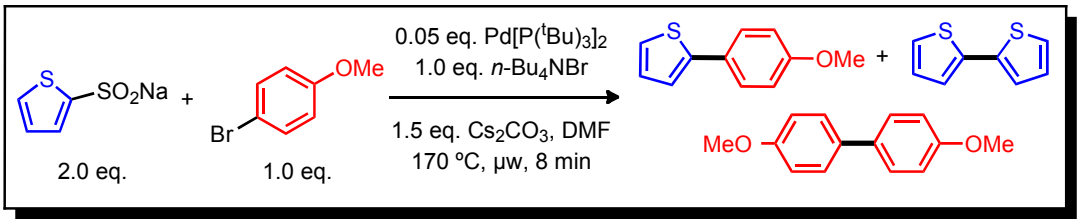
The desired cross-coupling product from sodium thiophene-2-sulfinate and bromobenzene using decarboxylative cross-coupling conditions was observed *via* GC-MS. Unfortunately, isolation of the product *via* column chromatography was not possible due to the presence of by-products generated from homo-coupling of the sulfinate as well as the unreacted aryl bromide (**Scheme 49**). The cross-coupling product (**77**) has the same R_f value as the 2,2'- bisthiophene (**78**) and biphenyl (**79**) due to the similar polarities between thiophene and benzene. The low polarity of the products also proves problematic, and does not allow for many solvent system alternatives, as co-elution occurs in pure hexanes. More polar products do not suffer from this limitation, however, as varying polar co-solvents may be used to facilitate separation.



Scheme 49: Desulfinylative Cross-Coupling Between Sodium Thiophene-2-Sulfinate and Bromobenzene

Due to difficulties in isolating the cross-coupling product, a new model reaction was needed where one of the coupling partners contained a polar functionality. To facilitate purification the cross-coupling was optimized using 4-bromoanisole as the electrophilic aryl source (**Scheme 50**). The desired product would contain only one methoxyl group, whereas the homo-coupling by-product

2,2'-bisthiophene would contain none, and the 4-bromoanisole homo-coupling by-product would contain two, allowing us to isolate the desired product. Although 4-bromoanisole renders isolation of the cross-coupling product possible, it is not an ideal coupling partner for a model reaction, as electron-rich aryl halides are known to undergo slower oxidative addition than electron-deficient aryl halides.[228]



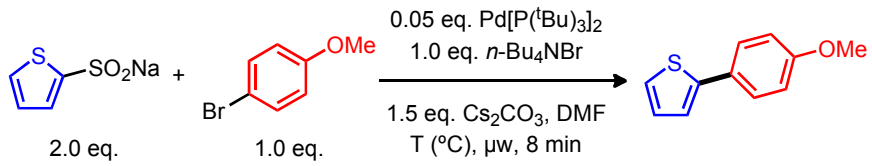
Scheme 50: Desulfinylative Cross-Coupling Between Sodium Thiophene-2-Sulfinate and 4-Bromoanisole

Originally, sodium thiophene-2-sulfinate, which was synthesized *via* reduction of the sulfonyl chloride (**Scheme 43**), was used for the screening experiments. Due to limited availabilities of the various heteroaromatic sulfonyl chlorides, we subsequently opted for the lithium salts, which were generated *via* the deprotonation of the heteroaromatic followed by quenching with SO_2 (**Scheme 46**).

2.2.1 – Reaction Optimization

The decarboxylative cross-coupling from the Forgione-Bilodeau protocol was found to occur optimally at 170 °C, requiring the high temperature for the decarboxylation step since no co-catalyst is present to facilitate the process. Using these conditions, the product from the desulfinylative cross-coupling of

sodium thiophene-2-sulfinate and 4-bromoanisole was obtained in 53% isolated yield (**entry 3**, **Table 6**). This initial result was promising as the desulfinylative cross-coupling between heteroaromatic sulfinates and aryl bromides appears to be more facile than its decarboxylative counter-part. With the more facile desulfinylation step, a reduction in reaction temperature was attempted as it would prove very beneficial. Unfortunately, a substantial decrease was observed in product yield when reducing the temperature to 160 ºC (**entry 2**) or 150 ºC (**entry 1**). On the other hand, increasing the reaction temperature to 190 ºC (**entry 4**) did not appear to provide any significant benefit.

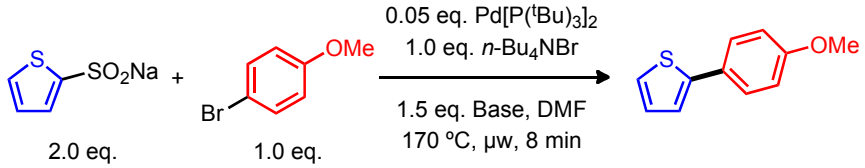


Entry	Temperature (ºC)	% Yield
1	150	19
2	160	23
3	170	53
4	190	56

Table 6: Temperature Effect on the Desulfinylative Cross-Coupling of Sodium Thiophene-2-Sulfinate with 4-Bromoanisole

Previously, coupling between thiophene-2-carboxylic acid and the electron-neutral bromobenzene provided no cross-coupling product. By simply exchanging the carboxylic acid functionality with a sulfinate the cross-coupling product was generated in moderate yields, even with the challenging electron-rich 4-bromoanisole. Thus, although replacing the carboxylic acid functionality with a sulfinate allows for the cross-coupling of thiophene with aryl bromides, it

appears relatively high reaction temperatures are still required. This requirement may be due to the multiple modes of binding of the sulfinate with the palladium complex. As previously mentioned, sulfinates interact with palladium(0) preferentially *via* the sulfur atom due to its softness; thus, changing from a sulfinato–*S* to a less favorable sulfinato–*O* complex may be a difficult process requiring high reaction temperatures.

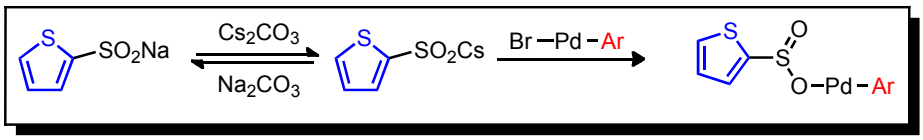


Entry	Base	% Yield
1	Cs_2CO_3	53
2	K_2CO_3	22
3	Na_2CO_3	43
4	Li_2CO_3	29

Table 7: Base Effect on the Desulfinylative Cross-Coupling of Sodium Thiophene-2-Sulfinate with 4-Bromoanisole

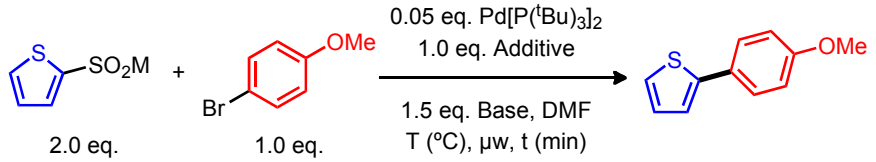
The second variable evaluated was the base effects where various carbonate bases were screened (**Table 7**). Although the nucleophilic coupling partner is a sulfinate, and thus does not require proton abstraction, maintaining a basic environment prevents undesired protonation of the sulfinate and consequently degradation of the starting material. Not unlike the decarboxylative cross-coupling (**Table 2**), the Cs_2CO_3 base provided the best results, with Na_2CO_3 slightly lower at 43% (**entry 3**) and with K_2CO_3 (**entry 2**) and Li_2CO_3 (**entry 4**) both providing substantial reductions in yield with 22% and 29% yields,

respectively. Despite the reaction not requiring a proton abstraction, suggests that the alkali cation may be playing a role in the cross-coupling causing a strong variation in product yield. The carbonate was thought to be undergoing a cation exchange with the sulfinate, exchanging the coordinated sodium for the cesium cation. The large ionic radius of the cesium cation provides a higher polarizability due to greater dispersion of the charge caused by the larger surface making it very soft in comparison to sodium. The sodium cation, concentrating its charge over a smaller surface, should coordinate more strongly to the sulfinate, reducing its nucleophilicity. Palladium(II), being a late transition metal, is also a very soft acid, and thus exchanging the hard sodium cation for a soft cesium cation would allow the sulfinate to more easily attack the arylpalladium(II) halide (**Scheme 51**).



Scheme 51: Hypothesized Cation Exchange between Sodium Thiophene-2-Sulfinate and Cesium Carbonate in the Cross-Coupling of Sodium Thiophene-2-Sulfinate and Aryl Bromides

The sodium-cesium cation exchange may not be occuring since the cross-coupling of lithium thiophene-2-sulfinate with 4-bromoanisole, while using the same conditions, provided a substantially reduced yield (**entry 2**, **Table 8**). The Cs_2CO_3 appeared to hinder reactivity when using the lithium thiophene-2-sulfinate, as a substantially higher yield was obtained without the base (**entry 3).**



Entry	T (ºC)	Metal Ion	t (min)	Base	Additive	GC Yield (%)
1	170	Na^+	8	Cs_2CO_3	*n*-Bu_4NBr	53*
2	170	Li^+	8	Cs_2CO_3	*n*-Bu_4NBr	30*
3	170	Li^+	8	-	*n*-Bu_4NBr	49
4	170	Li^+	8	-	-	51
5	170	Li^+	64	-	-	51
6	160	Li^+	16	-	-	50
7	150	Li^+	32	-	-	43

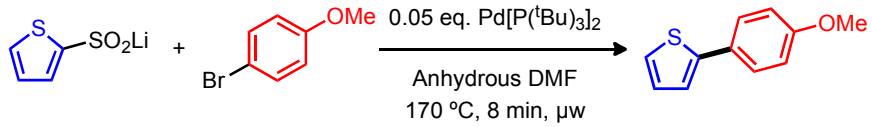
***** Isolated yield

Table 8: Condition Optimizations on the Desulfinylative Cross-Coupling of Sodium Thiophene-2-Sulfinate with 4-Bromoanisole

Without a need for excess base, the additive tetrabutylammonium bromide used in stoichiometric amounts was also evaluated. This quaternary ammonium salt, *n*-Bu_4NBr, is often used in palladium-catalyzed reactions as a halide source for organic media. The presence of these halides helps prevent aggregation of palladium, which precipitates as unreactive, undesired, palladium black. The palladium complexes, which are either coordinated by solvent or have free coordination sites, can be coordinated by halides which stabilize the complex and consequently maintains it in solution.[229,230] It was found that similar cross-coupling product yields were obtained without the additive (**entry 4** *vs.* **entry 3**), which is interesting as this additive was essential in the decarboxylative cross-coupling.

Although moderate yields were obtained, the reaction was not proceeding to completion as a substantial amount of residual 4-bromoanisole was observed

via GC-MS. Therefore increased reaction times were attempted (**entry 5**) but did not provide any change in yield. The catalyst was precipitating as palladium black, regardless of the presence (or absence) of *n*-Bu_4NBr, and the cause was hypothesized to be the elevated reaction temperatures. Control reactions with milder temperatures were considered with elongated reaction times in order to compensate for the reduction in reactivity (**entry 6 & 7**). Unfortunately, palladium black was still obtained and an increase in product yield was not observed.



Entry	Sulfinate eq.	Aryl Brmide eq.	GC Yield (%)
1	2.0	1.0	51
2	1.0	1.0	51
3	1.0	2.0	52
4	1.0	3.0	53

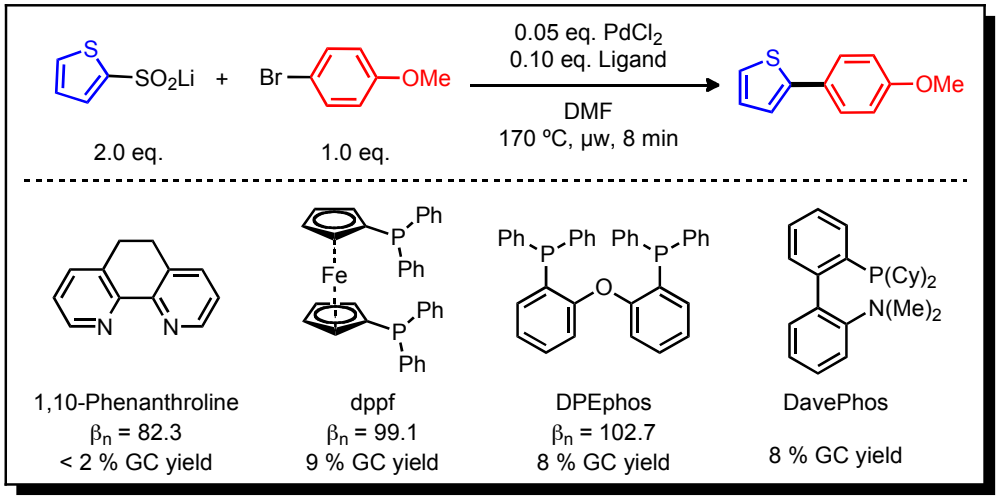
Table 9: Cross-Coupling Partner Equivalent Screen In the Cross-Coupling of Lithium Thiophene-2-Sulfinate and 4-Bromoanisole

A cross-coupling partner equivalent screen was performed (**Table 9**), however, whether altering limiting reagent did not substantially alter the product yield observed by GC-MS.

2.2.2 – Ligand Screen

Although cross-coupling product was being generated without utilizing base or additive, altering the reaction conditions failed to increase product yield. The reaction was not proceeding to completion as substantial amounts of

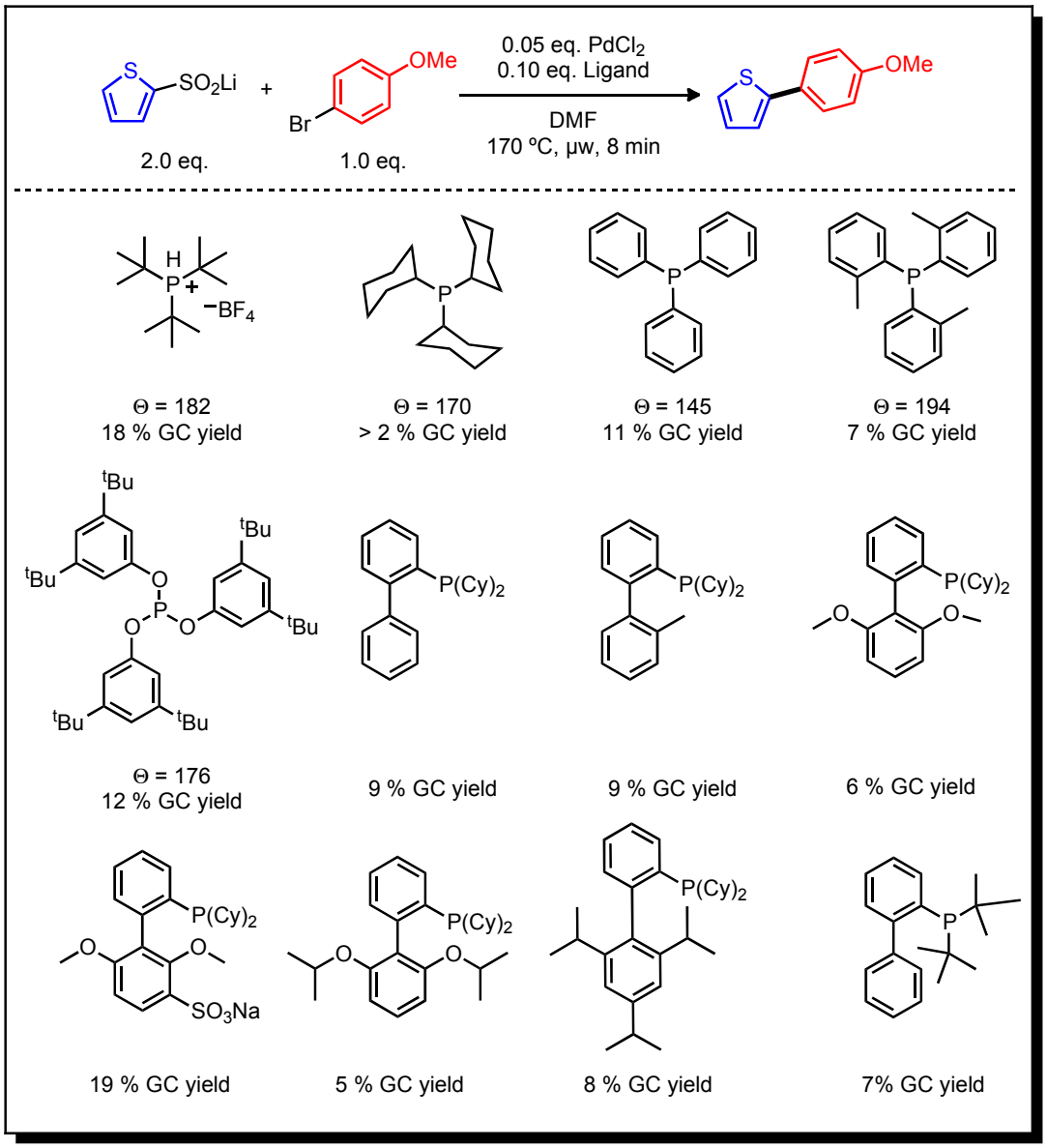
unreacted 4-bromoanisole remained, which may be caused by preliminary catalyst decomposition. At these elevated temperatures and with the thermal sensitivity of $Pd[P(^tBu)_3]_2$, it was apparent that a more stable catalyst may prove beneficial. Bidentate ligands, containing two coordinating atoms, bind the palladium more strongly, rendering these complexes more stable. However, in order to maintain catalytic activity it is important to avoid overly stabilizing the complex, as its capacity to undergo the desired reactivity may be lost. Thus, a balance between complex reactivity and stability must be obtained. By increasing the bite angle (β_n) of bidentate ligands, the rate of the reductive elimination increases, consequently increasing reactivity.[231] With this in mind the cross-coupling was attempted using three common bidentate ligands, 1,10-phenanthroline, dppf and DPEphos (**Scheme 52**). The nitrogen-coordinating 1,10-phenanthroline failed to generate the desired cross-coupling product, with less than 2% yield *via* GC-MS. More surprising were the low yields obtained when using dppf and DPEphos, which are ligands that are typically successful with related palladium-catalyzed cross-coupling reactions.[231,232]



Scheme 52: Bidentate Ligand Screen for the Desulfinylative Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromoanisole

The poor results obtained with the bidentate ligands suggest the complex may be too stable and might require other bulky monodentate ligands. A variety of phosphine monodentate ligands with varying sterics and electronics were screened *via* GC-MS (**Scheme 53**). Using $PdCl_2$ as the palladium source and the tri-*tert*-butylphosphine tetrafluoroborate (BF_4•$HP(^tBu)_3$) salt (with Cs_2CO_3 in a 1:1 ratio with the ligand) we observed a substantially reduced yield of 18%. Triphenylphosphine (PPh_3), with a substantially smaller cone angle (Θ = 145º) provided a very poor yield of 11%, whereas tri-*o*-tolylphosphine (Θ = 194º), which is bulkier than $P(^tBu)_3$ (Θ = 182º), provided even poorer yields (7%).[233] An important aspect of phosphine ligands is the ability to alter their electronics as well as their sterics; thus, bulky electron-rich phosphine ligands were used in order to increase the reactivity of the complex. The higher donor strength of these ligands favors a higher oxidation state, and thus increases oxidative addition rates. However, even such ligands (tris(3,5-di-*tert*-butylphenyl)

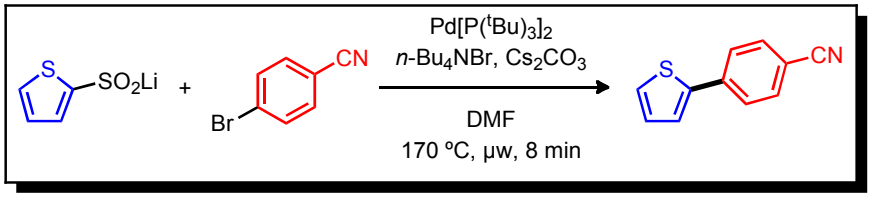
phosphine) provided extremely poor yields, and a variety of other phosphine ligands provided the cross-coupling product in yields ranging from 5 to 19% *via* GC-MS. It became apparent that the *in situ* generation of the catalyst was inefficient in this system. Consequently, attempts to optimize this reaction using 4-bromoanisole as a model were ceased for a more favorable coupling partner.



Scheme 53: Monodentate Ligand Screen for the Desulfinylative Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromoanisole

2.3 – Optimization with Electron-Poor 4-Bromobenzonitrile

Unable to obtain good yields when optimizing with an electron-rich 4-bromoanisole in the model reaction, the cross-coupling was attempted with an electron-deficient 4-bromobenzonitril. Thus, optimization began with a screen of additives and coupling partner stoichiometry, beginning with the original decarboxylative conditions (**Scheme 54**). This was followed with a catalyst and solvent screen, which later allowed for a substrate scope.

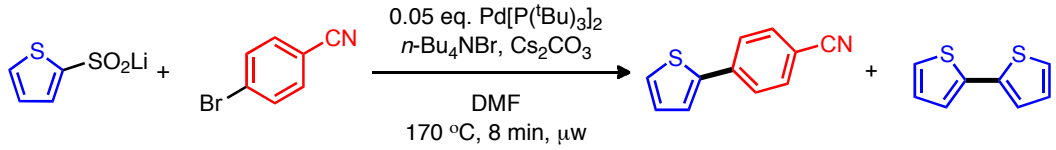


Scheme 54: Model Reaction Using Electron-Deficient 4-Bromobenzonitrile in the Cross-Coupling with Lithium Thiophene-2-Sulfinate

2.3.1 – Additive and Equivalents Screen

Previously the major by-product obtained was homo-coupled aryl bromide, therefore the decarboxylative cross-coupling conditions with the sulfinate as the limiting reagent were used as the starting point (**entry 1**, **Table 10**). The cross-coupling product was obtained in an excellent preliminary yield of 72%, which is 19% higher than with the optimal conditions when using 4-bromoanisole. Since oxidative addition is a process highly affected by the electron-richness of the aryl halide, this result indicates the importance of this step in the mechanism and the electronic effects on the palladium center. As with 4-bromoanisole, the need for the *n*-tetrabutylammonium bromide additive was evaluated, and it was found to

be unnecessary, yielding similar amounts of cross-coupling product (**entry 2**). The need for a mild cesium carbonate base was evaluated as it was hypothesized to be unnecessary due to the use of unprotonated sulfinate salts and an aprotic solvent. Identical yields were obtained without base (**entry 3**) as with base (**entry 2**), and it was thus deemed unnecessary when using sulfinates and pre-formed palladium(0) catalysts. These results were promising since good yields were obtained without the need of additives or base, simply with the coupling partners and the catalyst.



Entry	Eq. Sulfinate	Eq. ArBr	Eq. Cs_2CO_3	Eq. *n*-Bu_4NBr	Cross-coupling % Yield
1	1.0	2.0	1.5	1.0	72
2	1.0	2.0	1.5	-	69
3	1.0	2.0	-	-	69
4	1.0	1.0	-	-	59
5	1.5	1.0	-	-	84
6	2.0	1.0	-	-	91
7	3.0	1.0	-	-	89

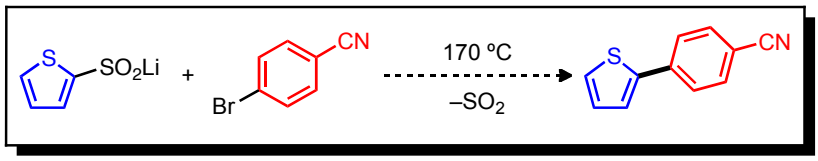
Table 10: Additive and Cross-Coupling Partner Stoichiometry Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile

Although good yields were obtained, a substantial amount of the limiting sulfinate reagent was being consumed to generate the 2,2'-bisthiophene homocoupling by-product. However, little homo-coupling of the aryl-bromide was observed, thus the use of excess sulfinate was evaluated. When using the sulfinate in a 2:1 ratio relative to the aryl bromide (**entry 6**), an excellent 91%

yield of cross-coupling product was obtained. Further increasing the amount of sulfinate to a 3:1 ratio, did not have a substantial impact on the product yield (**entry 7**). Although using the sulfinate in excess at a 2:1 ratio provided the cross-coupling product in excellent yield, using smaller excess is preferable. Requiring the use of excess sulfinate can be problematic when attempting to apply the protocol in a multi-step synthesis, wasting valuable material. This can also be problematic from a green chemistry perspective, where more waste is generated and the reaction is consequently less atom-economical. Thus we were able to reduce the amount of sulfinate to 1.5 eq. and still obtain a very good 84% yield (**entry 5**). The cross-coupling is still viable when using both coupling partners in a 1:1 ratio, however the product was obtained in a moderate yield of 59% (**entry 4**).

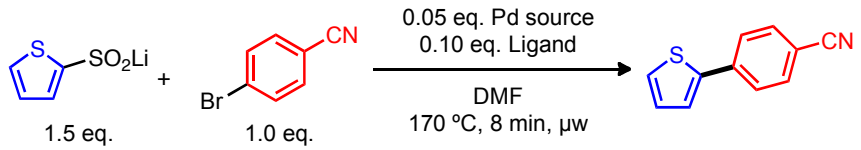
2.3.2 – Catalyst Screen

Having eliminated the need of base and additive, which were both key components to the decarboxylative cross-coupling, the next variable evaluated was the catalyst. The conditions used were again based on the decarboxylative cross-coupling, but employing the sulfinate in a 1.5:1 ratio relative to 4-bromobenzonitrile. The electron-poor 4-bromobenzonitrile has been known to undergo S_NAr reactions, and thus ensuring that the cross-coupling was in fact catalyzed by palladium was pivotal.[234] At 170 ºC a desulfinylation could occur thermally, followed by an S_NAr reaction (**Scheme 55**) to yield the identical product that would be expected *via* palladium-catalyzed cross-coupling.



Scheme 55: Hypothesized Palladium-Free Cross-Coupling *via* S_NAr between Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile

Subjecting the two coupling partners to cross-coupling conditions without a palladium source (**entry 1**, **Table 11**) did not generate cross-coupling product observable by GC-MS, suggesting the S_NAr pathway does not occur. In order to ensure the process proceeds *via* a palladium(0) mechanism, $Pd(OAc)_2$ was utilized without any phosphine ligands. The role of the phosphine ligands is two-fold: stabilizing the palladium(0) complex and reducing the palladium(II) to a palladium(0) complex while being oxidized to a phosphine oxide. As anticipated, when utilizing $Pd(OAc)_2$ without the presence of the reducing and stabilizing $P(^tBu)_3$, cross-coupling product was not observed (**entry 2**) indicating a palladium(0)-dependent mechanism.



Entry	Catalyst	% Yield
1	-	0
2	$Pd(OAc)_2$	0
3	$Pd[P(^tBu)_3]_2$	84
4	$PdCl_2 + HP(^tBu)_3BF_4$ ‡*	66
5	$PdCl_2$(dppf)	76
6	$PdCl_2$ + dppf*	55
7	$Pd(PPh_3)_4$	83
8	$PdCl_2 + PPh_3$ $	70
9	$PdCl_2 + P(^tBu)_2Me$ *	47

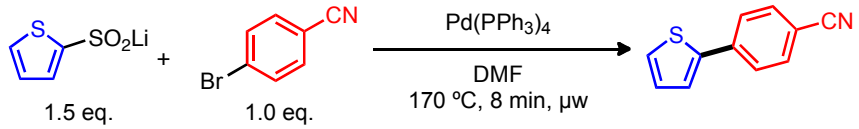
‡0.15 eq. Cs_2CO_3 used *Ligand used in 0.10 eq., $ Ligand used in 0.20 eq.

Table 11: Palladium Catalyst Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile

Palladium black was consistently obtained as a precipitate at the end of the cross-couplings. The $Pd[P(^tBu)_3]_2$ catalyst is considered highly reactive as it is a 14 electron complex, where the bulky ligands block further coordination to the metal center, preventing additional stabilization, which causes the complex to be highly sensitive and consequently, expensive. Thus, other pre-ligated palladium(II) or pre-formed palladium(0) catalysts such as $PdCl_2$(dppf) and $Pd(PPh_3)_4$, respectively, were considered as they are known to be less reactive than $Pd[P(^tBu)_3]_2$, and consequently more stable. We were pleased to observe good yields of 76% when using the bidentate dppf ligand (**entry 5**), and 83% when using $Pd(PPh_3)_4$ (**entry 7**). The less sensitive $Pd(PPh_3)_4$ catalyst provided similar yields as $Pd[P(^tBu)_3]_2$ (**entry 3**), with the latter being considerably less expensive.

Although the cross-coupling product was being generated in good yield using the pre-formed $Pd[P(^tBu)_3]_2$, $Pd(PPh_3)_4$ and pre-ligated $PdCl_2$(dppf) catalysts, generating the catalyst *in situ* would render the protocol more convenient, as well as reduce cost. A substantial reduction in yield (13-21%) was observed when the catalyst was generated *in situ* (**entry 4**, **6**, **8**) when compared to the pre-formed or pre-ligated catalysts (**entry 3, 5, 7**). Although these yields are lower, they still exceed the best result when using the electron-rich 4-bromoanisole as the aryl halide. Generating the catalyst *in situ* provides greater flexibility when optimizing the reaction by adjusting the palladium source, ligand and the ligand-to-palladium ratio.

A series of catalyst loading experiments were performed using $Pd(PPh_3)_4$ in an effort to reduce the amount of palladium used (**Table 12**). When reducing the catalyst loading from 5 mol% (**entry 4**) to 2 mol% (**entry 3**) and 1 mol% (**entry 2**), a substantial reduction in yield was observed, and essentially no product was being formed with 0.1 mol% (**entry 1**). Increasing catalyst loading from 5 mol% to 10 mol% however, produced an increase in yield from 83% (**entry 4**) to 92% (**entry 5**) respectively. The increased yield from higher catalyst loading suggests that the formation and precipitation of palladium black may occur prior to the complete consumption of the aryl bromide.



Entry	Eq. $Pd(PPh_3)_4$	% Yield
1	0.001	7*
2	0.01	31
3	0.02	54
4	0.05	83
5	0.10	92

* Reaction was scaled ten fold

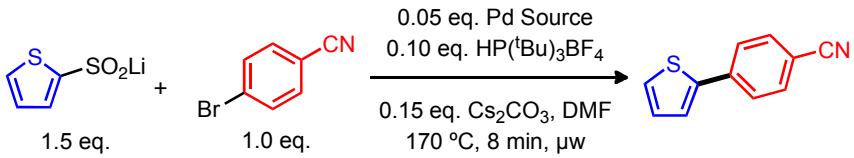
Table 12: Catalyst Loading Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile

Thus, without increasing catalyst loading, the most promising catalytic systems proved to be $Pd[P(^tBu)_3]_2$ and $Pd(PPh_3)_4$ in 5 mol%, both providing the cross-coupling product in similar yields of 84% and 83% respectively.

2.3.2.1 – Palladium Source Screen

In an attempt to optimize the cross-coupling using the *in situ* generation of the palladium catalyst, the palladium source was evaluated (**Table 13**). Originally, $PdCl_2$ (**entry 1**) had been used as the palladium source and provided the cross-coupling product in 66% with a 2:1 ligand-to-palladium ratio, which was 18% lower than with the pre-formed $Pd[P(^tBu)_3]_2$ catalyst (**Table 11**, **entry 3**). Other common sources of palladium(II) were screened, such as PdI_2, $Pd(OAc)_2$ and Pd(acac) (**entry 2-4**), however all provided the cross-coupling product in slightly lower yields. Palladium(0) sources such as $Pd(dba)_2$ (**entry 5**) and "petey"[235] (**entry 6**) were evaluated, but again provided lower yields than using $PdCl_2$. Thus,

since $PdCl_2$ provided the higher yield, was the least expensive and most readily available palladium(II) source, it was employed for all further screenings.



Entry	Pd Source	% Yield
1	$PdCl_2$	66
2	PdI_2	62
3	$Pd(OAc)_2$	55
4	$Pd(acac)_2$	51
5	$Pd(dba)_2$	61
6	petey*	58

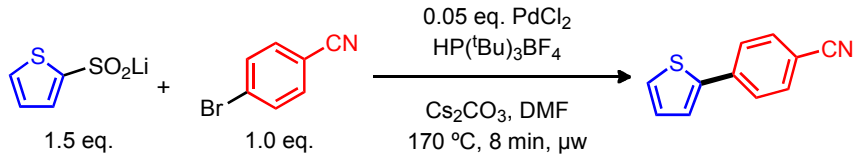
* $Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$

Table 13: Palladium Source Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile

2.3.2.2 – Ligand Equivalent Screen

Generating catalysts *in situ* presents many benefits over utilizing their pre-formed palladium(0) counter-parts. Pre-formed palladium(0) catalysts can pose a financial burden due to high costs, typically proportional to their reactivity. Another inconvenience of using pre-formed palladium(0) catalysts is proper storage in order to avoid decomposition due to thermal or air sensitivity. Palladium(II) sources and $H^+BF_4^-$ phosphonium ligand salts, however are typically air stable and are inexpensive in comparison to palladium(0) sources and phosphine ligands. The limiting factor of *in situ* catalyst generation lies in the reduction of palladium(II) to palladium(0), which can be affected by temperature, as well as phosphine ligand loading.[70] Previously when generating the

$Pd[P(^tBu)_3]_2$ catalyst *in situ*, the ligand was used in a 2:1 ratio relative to the palladium. However, the active palladium species is thought to be the monoligated version, $Pd[P(^tBu)_3]$ which is formed *via* ligand dissociation and has an available coordination site for the oxidative addition to occur.[107,236] Thus, the cross-coupling was attempted with a 1:1 ligand-to-palladium ratio (**entry 1**, **Table 14**) and was found to provide similar results (58 *vs*. 66%). The role of the phosphine ligand, however, is not limited to simple coordination. As mentioned previously palladium(II) must be reduced to palladium(0) and this may occur in two ways, thermally or *via* oxidation of the phosphine ligands. Thus, higher phosphine ligand equivalences may aid the reduction process of the palladium(II) and in order to evaluate this effect, a range of phosphine ligand-to-palladium ratios were examined. A clear trend was observed when increasing phosphine ligand loading, where the optimal result was obtained with a 5:1 ligand-to-palladium ratio (**entry 5**), increasing the cross-coupling product yield from 66% with a 2:1 ratio (**entry 2**) to 80%.



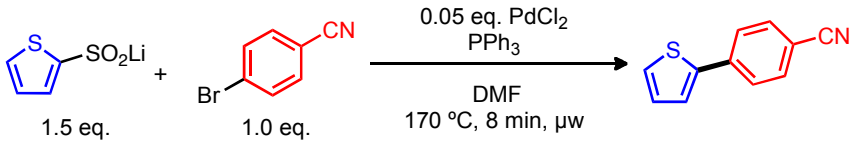
Entry	Eq. $HP(^tBu)_3BF_4$	% Yield
1	0.05	58
2	0.10	66
3	0.15	69
4	0.20	74
5	0.25	80
6	0.40	81

* Cs_2CO_3 used in a 1:1 ratio with $HP(^tBu)_3BF_4$

Table 14: $HP(^tBu)_3BF_4$ Equivalent Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile

Since similar results were obtained with $Pd(PPh_3)_4$ when compared to $Pd[P(^tBu)_3]_2$ (**Table 11**, 83% *vs.* 84%, respectively), the analogous ligand loading screen was performed (**Table 15**). Due to the smaller cone angles of PPh_3 (Θ = 145º) compared to $P(^tBu)_3$ (Θ = 182º),[233] more PPh_3 ligands can interact with the palladium coordination sphere without incurring steric repulsions. One palladium(0) center can coordinate four PPh_3 ligands, generating a stabilized 18-electron complex $Pd(PPh_3)_4$. Thus, the saturated complex is obtained with a 4:1 ratio of phosphine to palladium (**entry 4**), whereas when using $P(^tBu)_3$ the saturated complex is obtained with a 2:1 ratio. Again, similar results were obtained with lower ligand loading in a 3:1 (**entry 3**) and a 2:1 (**entry 2**) ratio providing 75% and 67% yields respectively, *vs*. 70% (4:1). However, using less than a 2:1 ratio reduced reactivity by half, lowering the product yield to 33% (**entry 1**). Similarly to the $HP(^tBu)_3BF_4$ case, higher ligand loading at a 5:1 ratio (**entry 5**) provided the cross-coupling product with an excellent 93% yield. Unlike

$HP(^tBu)_3BF_4$, exceeding a 5:1 ligand to palladium ratio provided reduced reactivity. The cause for this reduction in reactivity is not quite understood, however, a large excess of ligand disfavors the ligand dissociation step, reducing the effective concentration of the active palladium species present. It is also noteworthy that a small excess of PPh_3 relative to palladium (5:1) provided superior results than the required 4:1 ratio to generate the saturated $Pd(PPh_3)_4$ complex. Employing the $HP(^tBu)_3BF_4$ ligand, however, required a large excess of 5:1 compared to the required 2:1 ratio needed to generate $Pd[P(^tBu)_3]_2$. This may be due to their varying ability to reduce palladium(II) to palladium(0), where PPh_3 would appear to be more efficient due to its smaller cone angle.[70]



Entry	Eq. PPh_3	% Yield
1	0.05	33
2	0.10	67
3	0.15	75
4	0.20	70
5	0.25	93
6	0.40	59

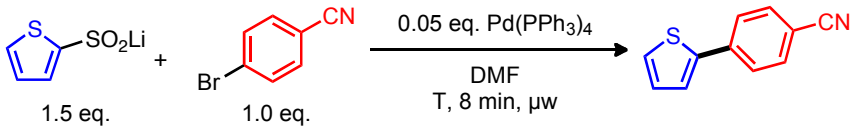
Table 15: PPh_3 Equivalent Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile

It is clear with these results that an excess of phosphine ligand is beneficial, however its effects are not limited to the reduction of palladium. Based on Le Chatelier's principle, an excess amount of phosphine ligand may force the equilibrium to lie more heavily towards a saturated palladium complex, possibly

reducing the rate of oxidative addition. Considering the intermediate oxidation state of sulfinates, an excess presence of phosphine ligand may aid in preventing oxidation to sulfonates.

2.3.3 – Temperature Screen

With the successful cross-coupling of lithium thiophene-2-sulfinate with the electron-deficient 4-bromobenzonitrile in excellent yields, the temperature effects were evaluated in order to reduce the high thermal requirement. The control temperature of 170 ºC *via* microwave irradiation was used in the model reaction (**entry 3**, **Table 16**). Reduced temperatures of 160 ºC (**entry 2**) and 150 ºC (**entry 1**) provided substantial reductions in yields, generating the cross-coupling product in 42% and 53% yield, respectively. It was interesting to note, however, that yields decreased with elevated reaction temperatures (190 ºC) obtaining the product in 68% (**entry 4**). The reduction in yield is hypothesized to be caused by the early formation of palladium aggregates, precipitating as palladium black, which may be accelerated by the exceedingly high reaction temperatures.



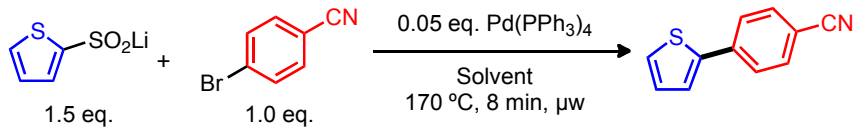
Entry	T (°C)	% Yield
1	150	53
2	160	42
3	170	83
4	190	68

Table 16: Temperature Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile

The reactions performed in the temperature screen were maintained at a constant reaction time of 8 minutes consequently leading to a reduction in reaction rate. Thus, additional control experiments are required to compensate this reduction in reaction rate, caused by lowered temperatures, by elongating the reaction time.

2.3.4 – Solvent Screen

The evaluation of solvent was performed in order to verify the effect of polarity, hydration as well as reagent solubility. Due to the high sensitivity of sulfinic acids, anhydrous DMF had been used previously as the solvent, to prevent the possibility of protonation caused by the presence of water at the elevated temperatures of 170 ºC. However, hydrated DMF from a bottle open to air provided slightly better results than when using anhydrous DMF (**entry 2** *vs*. **entry 1**, **Table 17**), rendering the protocol substantially more practical and potentially applicable for industrial use. A variety of other aprotic polar solvents such as DMA (**entry 3**), NMP (**entry 4**), and DMSO (**entry 5**) were used and also provided very good yields.



Entry	Solvent	% Yield	Entry	Solvent	% Yield
1	DMF (dry)	83	**8**	DMF/H_2O (1:1)	91
2	DMF	87	**9**	DMF/H_2O (1:2)	92
3	DMA	80	**10**	DMF/H_2O (1:3)	98
4	NMP	89	**11**	H_2O (distilled)	63
5	DMSO	89	**12**	H_2O (tap)	59
6	DMF/H_2O (3:1)	97	**13**	H_2O (pacific)	69
7	DMF/H_2O (2:1)	63	**14**	H_2O (3 eq. DMF)	76

Table 17: Solvent Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile

Since the cross-coupling tolerates the presence of water, a series of mixed DMF/H_2O mixtures ranging from 3:1 (**entry 6**) to 1:3 (**entry 10**) ratios were evaluated. Essentially quantitative yields were observed when using 3:1 or 1:3 DMF/H_2O mixtures and excellent yields when used in 1:1 (91%, **entry 8**) and 1:2 ratios (92%, **entry 9**). The sulfinate salt is relatively insoluble in organic solvents, and the DMF/H_2O mixture may solubilize both coupling partners in one phase due to the miscibility of the two solvents, where previously the sulfinate would most likely react at the solid/liquid interface. The presence of water may also increases the rate of reduction of the $PdCl_2$ to generate the palladium(0) complex in the presence of PPh_3 by providing an oxygen source.[70] Intriguingly, when a 2:1 DMF/H_2O mixture (**entry 7**) was used, a 63% yield was obtained, which is substantially lower than the yield for all other DMF/H_2O mixtures. The reason for this decrease in yield remains unknown since all other ratios generate excellent yields, however, the result proved reproducible.

From a green chemistry perspective, organic solvents pose a noteworthy concern as they are used in large excess and are potentially detrimental to the environment. Therefore, recent focus has been devoted to develop new, and adapt known reactions that are compatible in water. Typically, distilled water is used in order to prevent effects caused by minerals or contaminants found in tap water, however this not ideal from a green perspective. Distilled water is commonly produced by distilling drinkable, filtered tap water, which is a valuable resource. Using non-drinkable sea-water would prove the ideal green solvent as it is present in abundance, and does not require energy for filtering or distilling. Since the desulfinylative cross-coupling proceeded almost quantitatively in most DMF/H_2O mixtures, it remained to be determined if the reaction could be conducted in water exclusively. The reaction proceeded with a moderate yield of 63% (**entry 11**), substantially lower than in DMF at 87%. However, this result was promising considering water-soluble ligands were not employed. The robustness of the reaction was evaluated by attempting the cross-coupling in tap water as it contains a variety of minerals. The cross-coupling product was generated in similar yields, 59% (**entry 12**), slightly lower than with distilled water. In an effort to render the reaction “greener”, the cross-coupling was attempted in untreated, pacific ocean water (**entry 13**). Interestingly, the cross-coupling product was obtained in slightly higher yields at 69%, which may be due to the organic contaminants or the high salt concentrations. Since DMF is known to coordinate to palladium complexes, it was hypothesized that it may only be needed in stoichiometric amounts to help stabilize a certain intermediate species.[236,237]

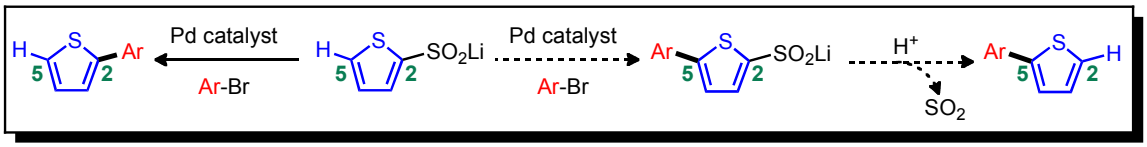
Thus, the cross-coupling was attempted in water with 3 eq. of DMF (**entry 14**) and 6 eq. of DMF and the product was obtained in 76% and 73% yield, respectively. The presence of DMF does appear to aid the cross-coupling, however, whether it stabilizes the catalytic intermediates or aids in solubilizing both cross-coupling partners within one phase remains unknown.

2.4 – Substrate Scope

The optimization of the desulfinylative cross-coupling using both an electron-rich and an electron-poor aryl bromide model reaction has provided two sets of conditions that yield aryl-substituted heteroaromatics from moderate to essentially quantitative yields. The two catalytic systems, using $PdCl_2/PPh_3$ (1:5) in DMF/H_2O (1:3) and $Pd[P(^tBu)_3]_2$ in DMF at 170ºC for 8 minutes in a microwave, were both used to determine the scope of heteroaromatic sulfinates and aryl halides.

2.4.1 – Heteroaromatic Sulfinate Scope

All of the optimization reactions were performed using thiophene-2-sulfinate, as it is the heteroaromatic that undergoes S_EAr type reactivity with the most difficulty. However, with an unsubstituted heteroaromatic sulfinate, a direct C–H arylation, followed by proto-desulfinylation (**Scheme 56**), would yield the same product as a direct desulfinylative cross-coupling.

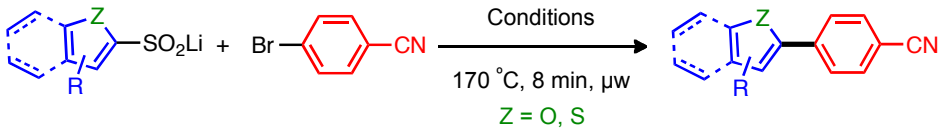


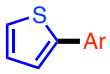
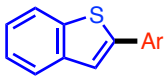
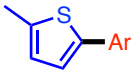
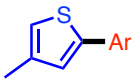
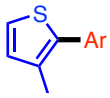
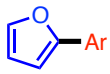
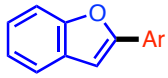
Scheme 56: Hypothesized Direct C–H Arylation, Protodesulfinylation Sequence of Lithium Thiophene-2-Sulfinate with Aryl Bromides

In order to evaluate this possibility, a variety of substituted thiophenes were screened (**entry 2-5**, **Table 18**). Lithium benzo[*b*]thiophene-2-sulfinate (**entry 2**) provided the cross-coupling product, using the $PdCl_2/PPh_3$ (1:5) catalytic system, in poorer yields (86%) than the unsubstituted thiophene sulfinate (98%, **entry 1**). This can be attributed to the reduction in electron-richness of the benzo-fused heteroaromatic, which is due to a greater delocalization of the electrons over a larger ring system, consequently reducing its nucleophilicity required for electrophilic palladation. Lithium 5-methylthiophene-2-sulfinate (**entry 3**) provides further evidence that the sulfinate functionality acts as a directing group, generating the C2-arylated cross-coupling product in an excellent 97% yield. Although lithium 5-methylthiophene-2-sulfinate (**entry 3**) prevents C–H arylation at the C5-position due to the presence of the methyl group, the possibility of a direct arylation at the C5-position when a reactive C–H bond is present cannot be excluded. Therefore lithium 4-methylthiophene-2-sulfinate (**entry 4**) and lithium 3-methylthiophene-2-sulfinate (**entry 5**), both containing a reactive C–H bond at the C5-position and the sulfinate functionality at the C2-position, were evaluated. When subjected to cross-coupling conditions, both sulfinates exclusively provided the C2-arylated cross-coupling product, in 73% (**entry 4**) and 58% (**entry 5**) yield. These two

results further support the directing effect of the sulfinate functionality, as arylation was observed exclusively at the sulfinate position with no C5-arylated products. Consequently, C–H arylation followed by proto-desulfinylation (**Scheme 56**) is not observed. However, the poor 58% cross-coupling yield obtained with lithium 3-methylthiophene-2-sulfinate (**entry 5**) is interesting when compared with the Forgione–Bilodeau decarboxylative cross-coupling reaction. Thiophene-2-carboxylic acid does not undergo C2-arylation when subjected to cross-coupling conditions, whereas 3-methylthiophene-2-carboxylic acid does in 63% yield.[181] The equivalent sulfinates, lithium thiophene-2-sulfinate (**entry 1**) and lithium 3-methylthiophene-2-sulfinate (**entry 5**), however, under cross-coupling conditions generate C2-arylated products in 98% and 58% yields, respectively, indicating complementarity between both protocols. The substantial reduction in cross-coupling yield observed between **entry 1** and **entry 5** may be attributed to the steric effects caused by the methyl group at the C3-position, preventing proper coordination of the palladium complex to the sulfinate. With good to excellent yields obtained from the highly aromatic thiophene isostere, two furan examples, lithium furan-2-sulfinate (**entry 6**) as well as lithium benzo[*b*]furan-2-sulfinate (**entry 7**), were subjected to cross-coupling conditions. Interestingly, their respective arylated products were obtained in a moderate 65% and very good 82% yield. Due to the weaker aromatic nature of the furan isostere a higher yield was anticipated than with thiophene as it is more susceptible to electrophilic addition at the C2-position. Although it is unsure as to why furan sulfinates provide lower cross-coupling yields than thiophene sulfinates,

subjecting lithium 1-methylpyrrole-2-sulfinate and lithium 1-methylindole-2-sulfinate to identical conditions would be crucial in developing a hypothesis.



Entry	Product	% Yield	
		Conditions A	Conditions B
1		98	91
2		86	67
3		97 (82)*	93
4		73	83
5		58	53
6		65 (69)*	85
7		82	73

Conditions A: 1.50 eq. sulfinate, 1.00 eq. 4-bromobenzonitrile, 0.05 eq. $PdCl_2$, 0.25 eq. PPh_3, DMF/H_2O (1:3); **Conditions B**: 2.00 eq. sulfinate, 1.00 eq. 4-bromobenzonitrile, 0.05 eq. $Pd[P(^tBu)_3]_2$, DMF (Anhy.)

* Using $Pd(PPh_3)_4$ pre-made catalyst

Table 18: Scope of Heteroaromatic Sulfinate in the Cross-Coupling with 4-Bromobenzonitrile

The lithium benzo[*b*]thiophene-2-sulfinate and benzo[*b*]furan-2-sulfinate complexed with TMEDA in a 1:1 ratio were subjected to a cross-coupling with 4-bromobenzonitrile, yet a cross-coupling product was not observed *via* GC-MS.

The overwhelming presence of TMEDA (1.5 eq.) is hypothesized to hinder reactivity of the palladium catalyst (0.05 eq.) due to its chelating ability.

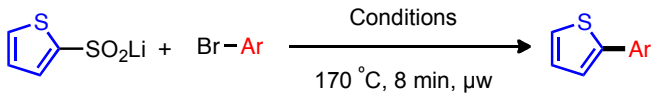
The series of sulfinates were also subjected to cross-coupling utilizing the original catalytic system, using $Pd[P(^tBu)_3]_2$ in anhydrous DMF (**Conditions B**). The cross-coupling product yields obtained remained similar to those using the optimized **Conditions A**, utilizing $PdCl_2/PPh_3$ (1:5) in DMF/H_2O (1:3), with certain exceptions. This catalytic system provided substantially poorer yields when utilizing lithium benzo[*b*]thiophene-2-sulfinate (**entry 2**), with 67% yield *vs*. 86% when using **Conditions A**. On the other hand, when cross-coupling lithium furan-2-sulfinate (**entry 6**) with **Conditions B**, a substantially higher yield was obtained, with 85% *vs*. 65% when using **Conditions A**. The cause of the variation in product yield with these examples remains unknown, however, this catalytic system has demonstrated comparable yields, and may yet prove beneficial with less electronically favorable sulfinate coupling partners.

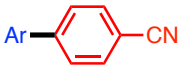
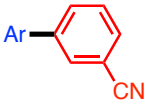
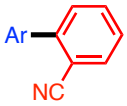
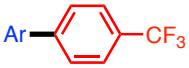
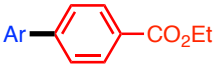
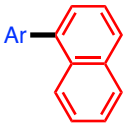
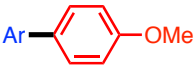
2.4.2 – Aryl Bromide Scope

The scope of the aryl bromide coupling partner was evaluated by performing a systematic analysis using lithium thiophene-2-sulfinate and two catalytic systems (**Table 19**). From the optimizations previously performed, it was apparent that electron-deficient aryl bromides such as 4-bromobenzonitrile achieved better cross-coupling product yields than electron-rich systems. Previously, however, only *para*-substituted aryl bromides were utilized, which is optimal for groups such as nitrile (–CN) that withdraw electron density *via*

mesomeric effects rather than inductivly. Also, *para*-substituted aryl bromides do not incur steric constraints at the bromide position. Thus, varying the nitrile group from the C4- (*para*, **entry 1**) to the C3-position (*meta*, **entry 2**) yielded the cross-coupling product in good, but substantially reduced yield of 70% when using $PdCl_2/PPh_3$ (1:5) in DMF/H_2O (1:3) (**Conditions A**). When incurring steric constraints at the bromide position by using 2-bromobenzonitrile (**entry 3**), a reduced product yield of 81% was observed. With the nitrile group in the *para*- (**entry 1**) and in the *ortho*-position (**entry 3**) a partial positive charge lies at the C1-position, which is not the case when it lies in the *meta*-position. The decrase in electron-richness of the aryl halide can facilitate the generation of the arylpalladium(II) halide complex by lowering the π*-orbital.[225] Moreover, a more thermodynamically stable arylpalladium(II) halide complex can be obtained by π-back donating into the π*-orbital which is lower in energy in electron-poor systems.[235] The increase in complex stability may contribute to an enhanced active catalytic specie lifetime, resulting in the improved cross-coupling product yields. Inductively withdrawing functional groups, such as trifluoromethyl (**entry 4**), may not effect π*-orbital energy level as much, and consequently generate the cross-coupling product in substantially lower yields (25%). Interestingly, other resonance activating groups such as a *para*-substituted ethyl ester (**entry 5**), did not provide as promising yields as the nitrile group, yielding the cross-coupling product in 65%. Since isolation of the bromobenzene cross-coupling product was not achieved, 1-bromonaphthalene was utilized as an electron-neutral example (**entry 6**), and the cross-coupling product was obtained in 43% yield. As

anticipated, the electron-rich 4-bromoanisole provided the least amount of cross-coupling product at 20% yield.



Entry	Product	% Yield	
		Conditions A	Conditions B
1		98	91
2		70	86
3		81	94
4		26	64
5		65	50
6		43	94
7		20	53*

Conditions A: 1.50 eq. sulfinate, 1.00 eq. 4-bromobenzonitrile, 0.05 eq. $PdCl_2$, 0.25 eq. PPh_3, DMF/H_2O (1:3); **Conditions B**: 2.00 eq. sulfinate, 1.00 eq. 4-bromobenzonitrile, 0.05 eq. $Pd[P(^tBu)_3]_2$, DMF (Anhy.)

*Using sodium thiophene-2-sulfinate

Table 19: Scope of Aryl Bromide in the Cross-Coupling with Lithium Thiophene-2-Sulfinate

The same series of aryl bromides were subjected to catalytic **Conditions B**, utilizing the more sterically hindered and electron-deficient palladium catalyst $Pd[P(^tBu)_3]_2$ in anhydrous DMF. Unlike the sulfinate screen, catalytic **Conditions**

B provided improved cross-coupling yields in all entries other than **entry 5**. The improvement is most notable with **entry 4**, **entry 6** and **entry 7,** where poor yields were previously obtained. The higher reactivity of the 14-electron complex is likely required for aryl bromides with more subtle activation, such as 4-bromobenzotrifluoride (**entry 4**) and 1-bromonaphthalene (**entry 6**), or electronically disfavored aryl bromides such as 4-bromoanisole (**entry 7**).

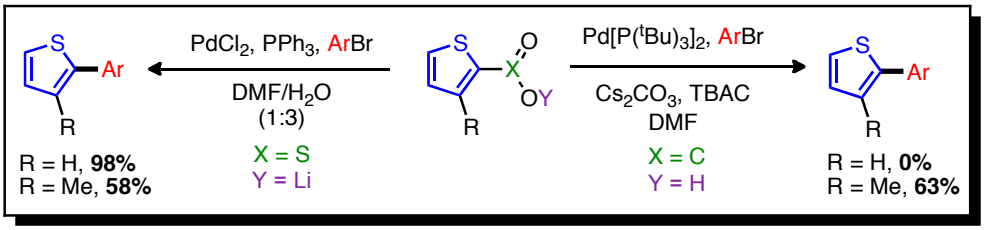
Thus, although the optimized catalytic system in **Conditions A** provides excellent yields in many cases, the more expensive, sterically hindered and electron-deficient catalyst from **Conditions B** is required to obtain superior results with less reactive aryl bromides.

3 – Conclusion

The desire to continually improve existing methods and to develop more efficient or environmentally conscientious protocols has caused the field of palladium-catalyzed cross-coupling to evolve substantially in the past few decades. The very efficient, yet high waste-generating, classical palladium-catalyzed couplings inspired powerful modern alternatives such as direct C–H arylation and decarboxylative cross-couplings that are also high yielding and more environmentally benign. Naturally these procedures suffer limitations as well. While pre-functionalization is not required for direct arylation, it suffers from a lack of regioselectivity when presented with multiple active positions. The extrusion of CO_2 in decarboxylative couplings, on the other hand, is inherently difficult to undergo and typically requires high reaction temperatures and a co-catalyst. Forgione and Bilodeau developed a protocol capable of decarboxylative cross-coupling without the need of a co-catalyst but were unsuccessful with coupling partners such as thiophene-2-carboxylic acid and benzoic acid.

This work has demonstrated that sulfinates are capable carboxylic acid mimics in a desulfinylative cross-coupling, and the cross-coupling of thiophene-2-sulfinate proceeds in excellent yield where its carboxylic acid counter-part does not provide any desired product (**Scheme 57**). The protocol developed allows for a facile and chemoselective cross-coupling of various sulfinates from moderate to essentially quantitative yields with electron-deficient aryl bromides, electron neutral and electron-rich systems. The desulfinylative cross-coupling is an environmentally benign protocol, as it has been shown to excel with a simple

catalytic system using $PdCl_2$ and PPh_3 in a highly aqueous solvent system, without the need of base or additives. Additionally, intriguing preliminary results have been obtained in a purely aqueous solvent and further investigations are currently underway.



Scheme 57: Comparison of Desulfinylatie Cross-Coupling and Decarboxylative Cross-Coupling of Heteroaromatics with Aryl Bromides

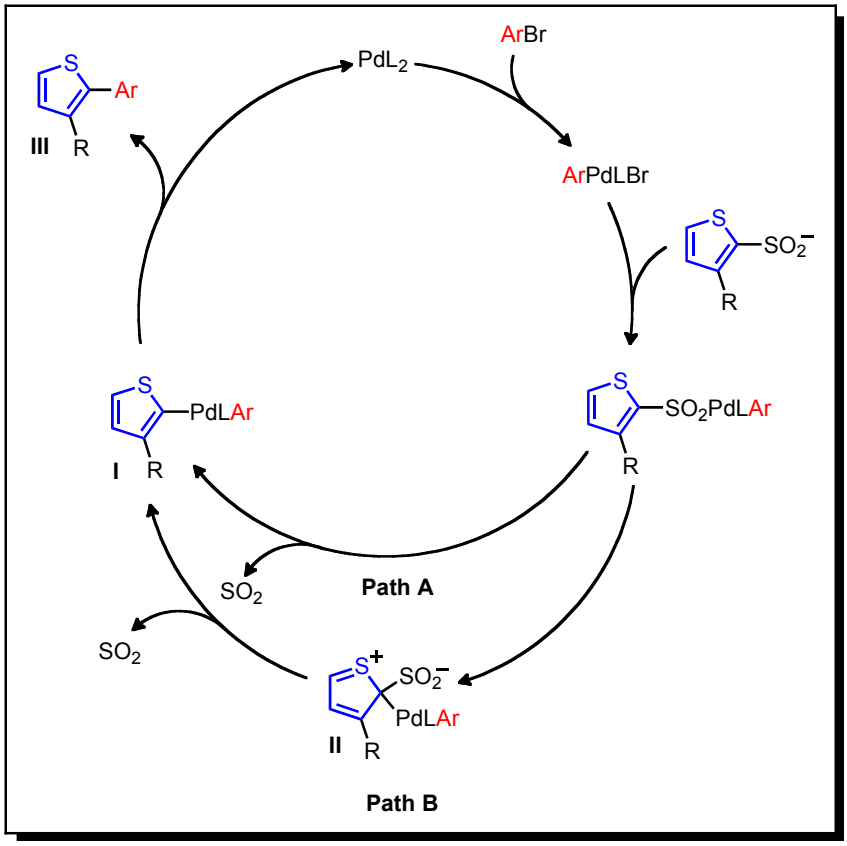
4 – Future Directions

Although the successful cross-coupling of heteroaromatic sulfinates with aryl bromides was achieved from moderate to excellent yields, much remains to be improved and explored. With pyrrole being the most prominent five-membered heteroaromatic in drug development, the inability to readily synthesize pure nitrogen-containing heteroaromatic sulfinates proves to be an important limiting factor of the current protocol. Focusing on means to synthesize pyrrole as well as indole sulfinates would extend the scope of this newly developed protocol, and increase its potential application in industry. Another current limitation of the desulfinylative cross-coupling is its inability to couple heteroaromatic sulfinates with the less reactive aryl chlorides. Developing more reactive catalytic systems capable of undergoing oxidative addition into the less reactive aryl–chloride bond would prove beneficial to further increase the reaction scope.

The use of a microwave reactor can prove beneficial for small scale syntheses as the reaction proceeds with substantially reduced reaction times due to the more efficient heating. Unlike thermal heating, microwave irradiation increases the reaction temperature more uniformly but also more rapidly. Unfortunately, this heating method is not practical from an industrial or large-scale point of view due to the elevated cost of the reactors and limited vessel sizes. Thus, adapting the desulfinylative cross-coupling protocol to a purely thermal process would render the procedure more widely available, and consequently more practical. Naturally, due to the reduction in heating efficiency,

longer reaction times would be required and possibly a more stable catalytic system to extend catalytic activity.

The presented work was based on a previous protocol developed by Forgione and Bilodeau, in order to verify if sulfinates could mimic the role of carboxylic acids. Through successful cross-coupling of the sufinates to aryl bromides, this was implied to be true. Thus, current mechanistic considerations are based on the decarboxylative cross-coupling catalytic cycle, yet the sulfinates do differ in certain aspects from the carboxylic acids. A key distinction of the sulfinates from carboxylates is the variation in coordination modes to the palladium (**Scheme 36**). The sulfur atom contains additional lone pairs of electrons that can coordinate to metals, and it has been shown that with palladium, sulfinato–*S* complexes are preferred to sulfinato–*O* complexes. Nonetheless, the desulfinylative cross-coupling is proposed to occur similarly to the decarboxylative coupling as depicted in **Scheme 58**. As no 2,3-diarylated by-products were observed, a C3-electrophilic palladation is not suspected to occur. A direct desulfinylation is proposed to be a contributing pathway due to the successful coupling of arene sulfinates.[243] Although the model catalytic cycle appears to fit the current results, it is imperative to undergo further mechanistic studies to better understand the active catalytic cycle of the desulfinylative cross-coupling.



Scheme 58: Proposed Mechanism for the Desulfinylative Cross-Coupling of Heteroaromatic Sulfinates with Aryl Bromides

Preliminary results obtained in the solvent screen have indicated very promising reactivity in purely aqueous solutions. The cross-coupling occurs in good yield in not only distilled water, but also tap and sea-water (pacific ocean). Developing these results could prove extremely beneficial from a green chemistry perspective, which would avoid the use of organic solvents, as well as the use of potable water. Naturally the first step in optimizing the aqueous desulfinylative cross-coupling would be to utilize a water-soluble analog of PPh_3, which contains sulfonate groups on the phenyl rings. Other possible alternatives

would be to explore the use of stabilizing agents, similar to DMF as it proved beneficial in stoichiometric amounts.

Naturally, the possibilities for improvements and new directions are endless, yet if these goals are obtained, the desulfinylative cross-coupling could prove to be a highly efficient and practical alternative to other cross-coupling protocols in the synthesis of aryl-substituted heteroaromatics.

5 – Experimental

General: All anhydrous flasks were flame-dried while under high-vacuum and purged with argon unless otherwise stated. Solids were weighed on a balance open to air and added to a round bottom flask or microwave vial unless otherwise noted. Liquids were transferred using a glass syringe with a stainless steel needle or a micropipette for µL volumes unless noted otherwise. Manual flash chromatography columns were carried out using 40-63 µm silica gel from Silicycle.

Materials: All reagents we purchased are from Sigma-Aldrich or Alfa Aesar and used without further purification unless otherwise noted. All solvents were purchased as ACS grade from Fischer Scientific or JT Baker unless otherwise noted. Anhydrous solvents were dried and stored in a flame-dried Schlenk flask using 3 Å molecular sieves, which were activated by heating at 150 ºC under high vacuum overnight. Distilled water was obtained from an in-house distillery.

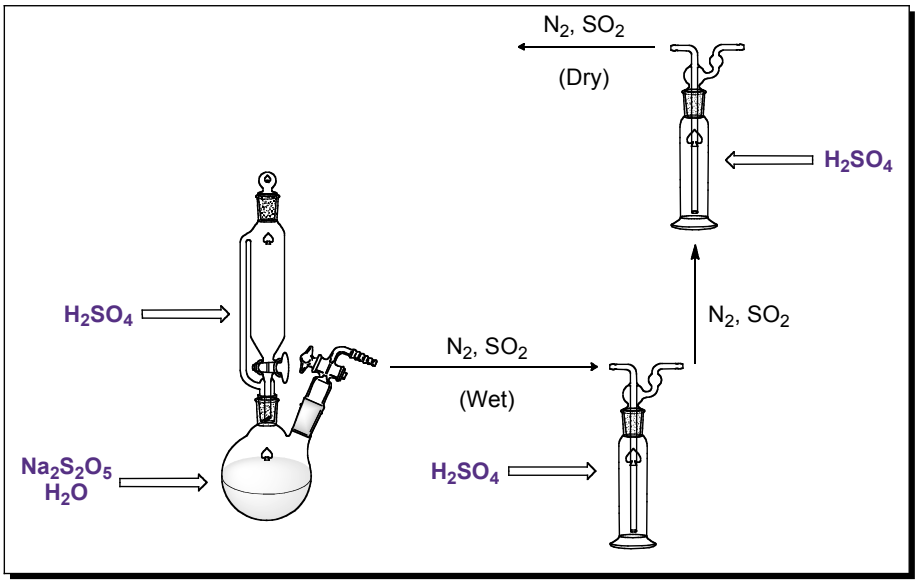
Instrumentation: Unless otherwise noted, reactions were performed using a Biotage Initiator 2.3 build 6250 microwave. Purifications by flash column chromatography were performed using a Teledyne Isco CombiFlash® R_f unless mentioned otherwise. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were measured using a 500 MHz Varian VNMRS-500 in chloroform-d unless stated otherwise. Carbon nuclear magnetic resonance spectra (^{13}C-NMR) were measured at 125 MHz using the Varian VNMRS-500 in chloroform-d unless stated otherwise. The chemical shifts are reported in parts per million (ppm) and

referenced from either residual solvent or tetramethylsilane (TMS) signal. The multiplicity is represented as; s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet which is indicated in parentheses along with the number of protons and coupling constants (in Hz). Gas chromatograph-mass spectral analyses (GC-MS) were obtained using an Agilent 7890A GC system and Agilent 5975C VL MSD with Triple-Axis Detector MS with a HP-588 column coated with (5%-phenyl)-methylpolysiloxane.

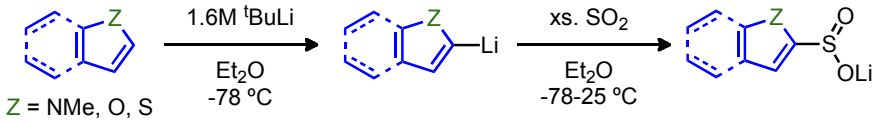
5.1 – General Procedures

General procedure (A) for the generation of anhydrous sulfur dioxide

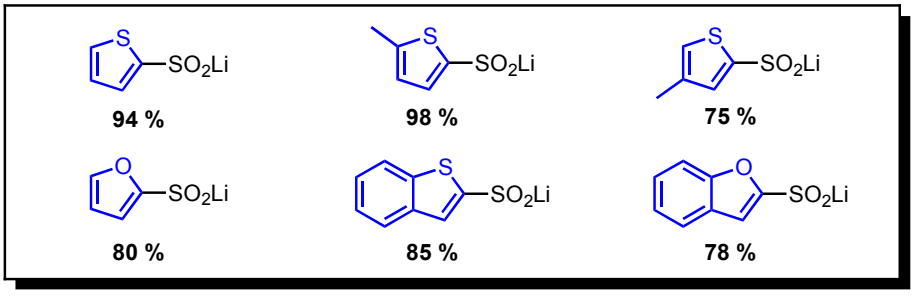
To a three-neck flask equipped with a magnetic stir bar, sodium sulfite or sodium metabisulfite (1.0 eq.) and water were added. Concentrated sulfuric acid (1.0 eq.) was added drop-wise, with stirring, from a capped pressure-equalized addition funnel. The gas generated was then scrubbed twice *via* diffusion through concentrated sulfuric acid.



General procedure (B) for the synthesis of heteroaromatic lithium sulfinates (Scheme 46**)**



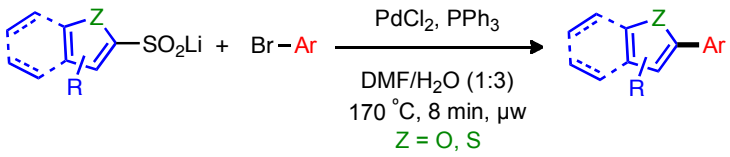
To a dried, rubber septum capped flask, under an argon stream, equipped with a magnetic stir bar and cooled to -78 ºC (in an ethyl acetate–liquid nitrogen bath) was added the heteroaromatic (1.0 eq.) with anhydrous diethyl ether (0.3 M). After 20 minutes, with stirring, *tert*-butyl lithium (0.9 eq.) was added slowly with a glass syringe over 5 minutes. The reaction was stirred for 2 hours while maintaining a temperature of -78 ºC. The reaction was then quenched by bubbling SO_2 produced from general procedure (A) for an hour, while warming to 23 ºC, precipitating the sulfinate salt. The salt was isolated *via* vacuum filtration, washed thoroughly with diethyl ether followed by acetone, and dried under vacuum. The solid was then ground to a fine powder, to which diethyl ether was added, and sonicated for 10 minutes, followed by vacuum filtration and drying under high vacuum.



General procedure (C) for the work-up of cross-coupling reactions

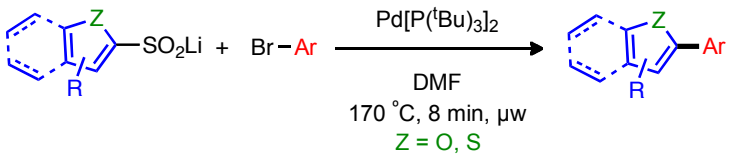
The crude cross-coupling solution was diluted with EtOAc (50 mL). The organic layer was washed with a saturated NaCl aqueous solution (2x 50 mL), saturated $NaHCO_3$ aqueous solution (2x 50 mL), distilled H_2O (1x 50 mL), and saturated NaCl aqueous solution (1x 50 mL). The combined aqueous phases were washed with EtOAc (50 mL). The combined organic phases were dried over Na_2SO_4 and after filtration the solvent evaporated under reduced pressure.

General procedure (D) for the arylation of thiophene and furan-2-sulfinates



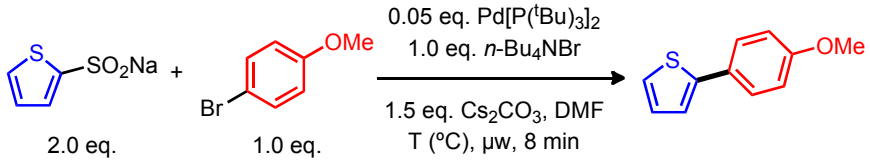
To a 5 mL conical microwave vial equipped with a spin-vein was added heteroaromatic sulfinate (0.30 mmol, 1.5 eq.), aryl halide (0.20 mmol, 1.0 eq.), $PdCl_2$ (0.01 mmol, 0.05 eq.), and PPh_3 (0.05 mmol, 0.25 eq.). A DMF/H_2O (2 mL, 1:3) mixture was then added and the vial was pre-stirred for 30 s at 23 ºC followed by heating at 170 ºC, for 8 min with stirring. The work-up was performed using general procedure (C), and the solid residue was purified by flash column chromatography.

General procedure (E) for the arylation of thiophene and furan-2-sulfinates



To a 5 mL conical microwave vial equipped with a spin-vein was added heteroaromatic sulfinate (0.40 mmol, 2.0 eq.), aryl halide (0.20 mmol, 1.0 eq.), and $Pd[P(^tBu)_3]_2$ (0.01 mmol, 0.05 eq.). DMF (2 mL) was then added and the vial was pre-stirred for 30 s at 23 ºC followed by heating at 170 ºC, for 8 min with stirring. The work-up was performed using general procedure (C), and the solid residue was purified by flash column chromatography.

General procedure (F) for the temperature screen in the synthesis of 2-(4-methoxyphenyl)thiophene (Table 6**)**

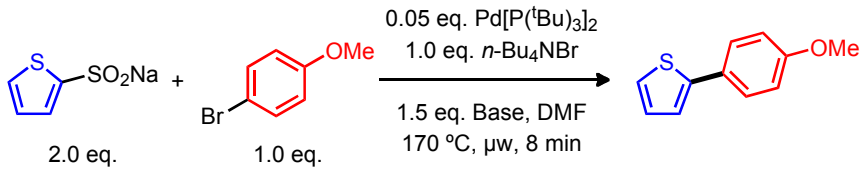


To a 5 mL conical microwave vial equipped with a spin-vein was added sodium thiophene-2-sulfinate (0.40 mmol, 2.0 eq.), 4-bromoanisole (0.20 mmol, 1.0 eq.), $Pd[P(^tBu)_3]_2$ (0.01 mmol, 0.05 eq.), Cs_2CO_3 (0.30 mmol, 1.5 eq.), and *n*-Bu_4NBr (0.20 mmol, 1.0 eq.). Anhydrous DMF (2 mL) was then added and the vial was pre-stirred for 30 s at 23 ºC followed by heating at varying temperatures (150-190 ºC), for 8 min with stirring. The work-up was performed using general procedure (C), and the solid residue was purified by flash column

chromatography using a gradient to 5% EtOAc in hexanes, to obtain a colourless solid.

Entry	Temperature (ºC)	% Yield
1	150	19
2	160	23
3	170	53
4	190	56

General procedure (G) for the base screen in the synthesis of 2-(4-methoxyphenyl)thiophene (Table 7**)**

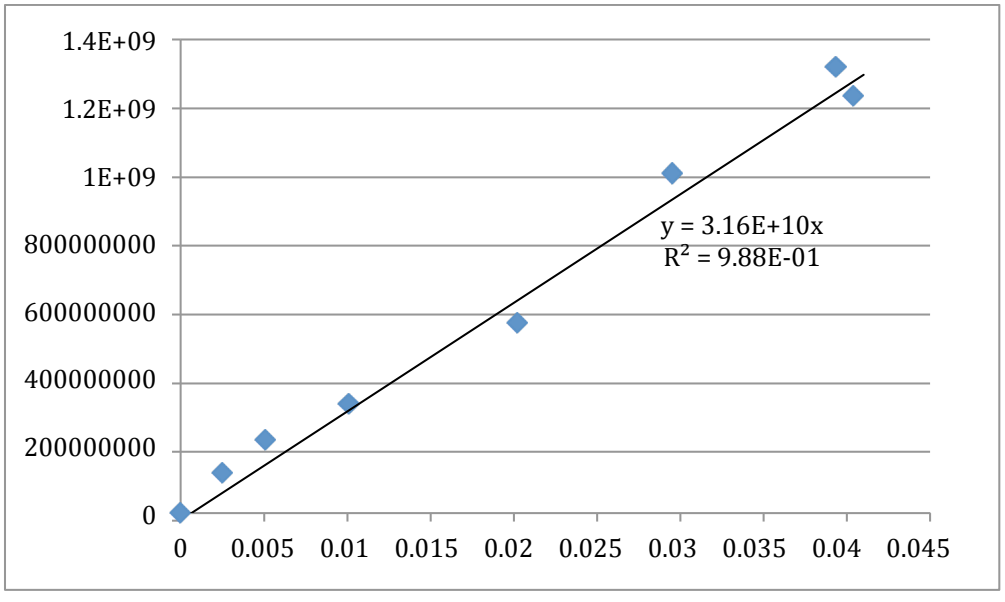


To a 5 mL conical microwave vial equipped with a spin-vein was added sodium thiophene-2-sulfinate (0.40 mmol, 2.0 eq.), 4-bromoanisole (0.20 mmol, 1.0 eq.), $Pd[P(^tBu)_3]_2$ (0.01 mmol, 0.05 eq.), varying carbonate base (0.30 mmol, 1.5 eq.) and *n*-Bu_4NBr (0.20 mmol, 1.0 eq.). Anhydrous DMF (2 mL) was then added and the vial was pre-stirred for 30 s at 23 ºC followed by heating at 170 ºC, for 8 min with stirring. The work-up was performed using general procedure (C), and the solid residue was purified by flash column chromatography using a gradient to 5% EtOAc in hexanes, to obtain a colourless solid.

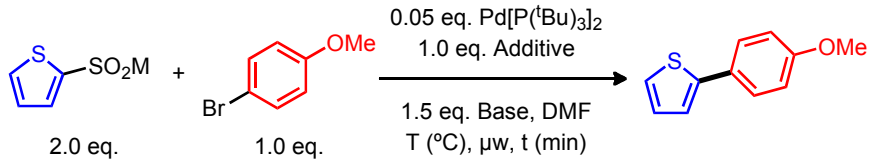
Entry	Base	% Yield
1	Cs_2CO_3	53
2	K_2CO_3	22
3	Na_2CO_3	43
4	Li_2CO_3	29

General procedure (H) for determination of 2-(4-methoxyphenyl)thiophene yield *via* GC-MS

The crude 2 mL reaction mixture was filtered through a plug of silica and celite to remove any solid residue. The sample was diluted four fold, then injected (3 µL) three times into the GC-MS using a splitless method. The resulting areas (y-axis) were utilized to calculate the yield of 2-(4-methoxyphenyl)thiophene using a calibration curve created from known concentrations of product (x-axis).



General procedure (I) for the condition screen in the synthesis of 2-(4-methoxyphenyl)thiophene (Table 8**)**

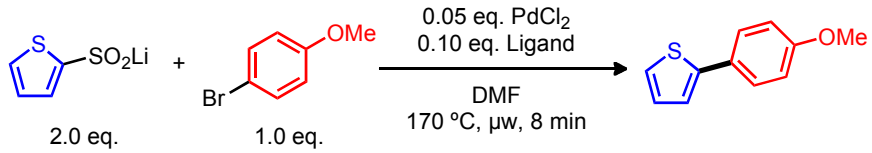


To a 5 mL conical microwave vial equipped with a spin-vein was added thiophene-2-sulfinate (0.20-0.40 mmol, 1.0-2.0 eq.), 4-bromoanisole (0.20-0.40 mmol, 1.0-2.0 eq.), $Pd[P(^tBu)_3]_2$ (0.01 mmol, 0.05 eq.), varying Cs_2CO_3 (0.00 or 0.30 mmol, 0.0 or 1.5 eq.) and *n*-Bu_4NBr (0.00 or 0.20 mmol, 0.00 or 1.0 eq.). Anhydrous DMF (2 mL) was then added and the vial was pre-stirred for 30 s at 23 ºC followed by heating at variable temperature (150-170 ºC), for various times (8-64 min) with stirring. The product yield was determined *via* GC-MS analysis from general procedure (H).

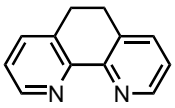
Entry	T (ºC)	Metal	t (min)	Base	Additive	GC Yield (%)
1	170	Na^+	8	Cs_2CO_3	*n*-Bu_4NBr	53*
2	170	Li^+	8	Cs_2CO_3	*n*-Bu_4NBr	30*
3	170	Li^+	8	-	*n*-Bu_4NBr	49
4	170	Li^+	8	-	-	51
5	170	Li^+	64	-	-	51
6	160	Li^+	16	-	-	50
7	150	Li^+	32	-	-	43

***** Isolated yield

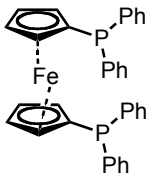
General procedure (J) for the ligand screen in the synthesis of 2-(4-methoxyphenyl)thiophene (Scheme 52**,** Scheme 53**)**



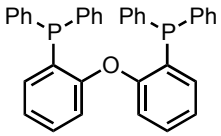
To a 5 mL conical microwave vial equipped with a spin-vein was added lithium thiophene-2-sulfinate (0.20 mmol, 1.0 eq.), 4-bromoanisole (0.20 mmol, 1.0 eq.), $PdCl_2$ (0.01 mmol, 0.05 eq.), and varying ligand (0.02 mmol, 0.10 eq.). Anhydrous DMF (2 mL) was then added and the vial was pre-stirred for 30 s at 23 ºC followed by heating at 170 ºC, for 8 min with stirring. The product yield was determined *via* GC-MS analysis from general procedure (H).



1,10-Phenanthroline
β_n = 82.3
< 2 % GC yield

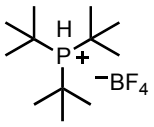


dppf
β_n = 99.1
9 % GC yield

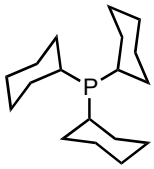


DPEphos
β_n = 102.7
8 % GC yield

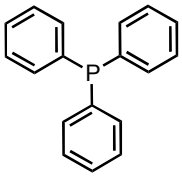
8 % GC yield



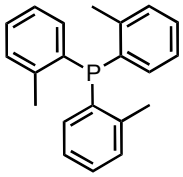
Θ = 182
18 % GC yield



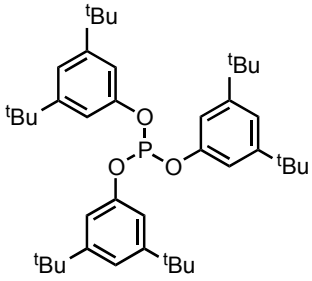
Θ = 170
> 2 % GC yield



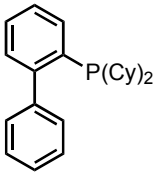
Θ = 145
11 % GC yield



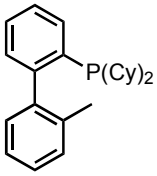
Θ = 194
7 % GC yield



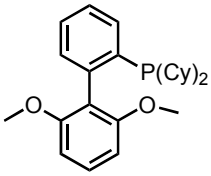
Θ = 176
12 % GC yield



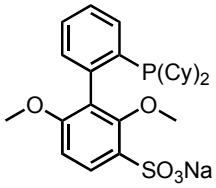
9 % GC yield



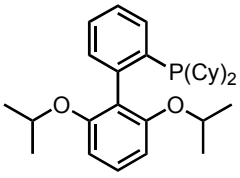
9 % GC yield



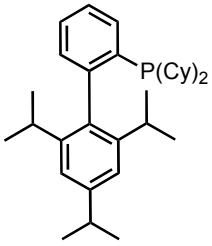
6 % GC yield



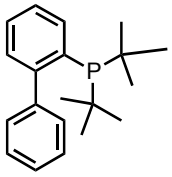
19 % GC yield



5 % GC yield

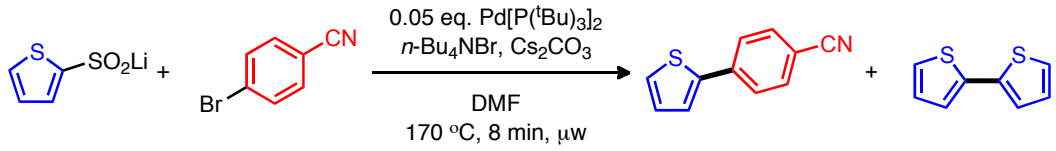


8 % GC yield



7% GC yield

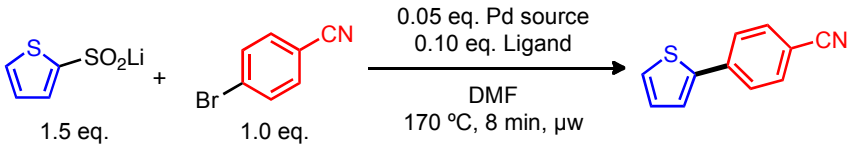
General procedure (K) for the additive and coupling partner stoichiometry screen in the synthesis of 4-(thiophen-2-yl)benzonitrile (Table 10**)**



To a 5 mL conical microwave vial equipped with a spin-vein was added lithium thiophene-2-sulfinate (0.20-0.60 mmol, 1.0-3.0 eq.), 4-bromobenzonitrile (0.20-0.40 mmol, 1.0-2.0 eq.), $Pd[P(^tBu)_3]_2$ (0.01 mmol, 0.05 eq.), varying Cs_2CO_3 (0.00 or 0.30 mmol, 0.0 or 1.5 eq.), and *n*-Bu_4NBr (0.00 or 0.20 mmol, 0.00 or 1.0 eq.). Anhydrous DMF (2 mL) was then added and the vial was pre-stirred for 30 s at 23 ºC followed by heating at 170 ºC, for 8 min with stirring. The work-up was performed using general procedure (C), and the solid residue was purified by flash column chromatography using a gradient to 2.5% EtOAc in hexanes, to obtain a colourless solid.

Entry	Eq. Sulfinate	Eq. ArBr	Eq. Cs_2CO_3	Eq. *n*-Bu_4NBr	% Yield
1	1.0	2.0	1.5	1.0	72
2	1.0	2.0	1.5	-	69
3	1.0	2.0	-	-	69
4	1.0	1.0	-	-	59
5	1.5	1.0	-	-	84
6	2.0	1.0	-	-	91
7	3.0	1.0	-	-	89

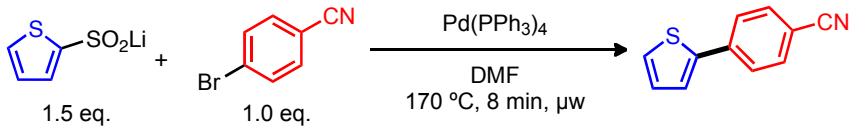
General procedure (L) for the catalyst screen in the synthesis of 4-(thiophen-2-yl)benzonitrile (Table 11**)**



To a 5 mL conical microwave vial equipped with a spin-vein was added lithium thiophene-2-sulfinate (0.30 mmol, 1.5 eq.), 4-bromobenzonitrile (0.20 mmol, 1.0 eq.), and palladium catalyst (0.01 mmol, 0.05 eq.). Anhydrous DMF (2 mL) was then added and the vial was pre-stirred for 30 s at 23 ºC followed by heating at 170 ºC, for 8 min with stirring. The work-up was performed using general procedure (C), and the solid residue was purified by flash column chromatography using a gradient to 2.5% EtOAc in hexanes, to obtain a colourless solid.

Entry	Catalyst	% Yield
1	-	0
2	$Pd(OAc)_2$	0
3	$Pd[P(^tBu)_3]_2$	84
4	$PdCl_2 + HP(^tBu)_3BF_4$ ‡*	66
5	$PdCl_2(dppf)$	76
6	$PdCl_2$ + dppf*	55
7	$Pd(PPh_3)_4$	83
8	$PdCl_2 + PPh_3$ $	70
9	$PdCl_2 + P(^tBu)_2Me$ *	47

General procedure (M) for the catalyst loading screen in the synthesis of 4-(thiophen-2-yl)benzonitrile (Table 12**)**

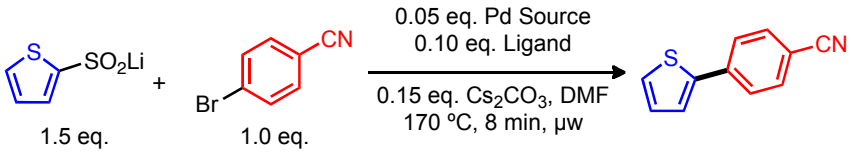


To a 5 mL conical microwave vial equipped with a spin-vein was added lithium thiophene-2-sulfinate (0.30 mmol, 1.5 eq.), 4-bromobenzonitrile (0.20 mmol, 1.0 eq.), and $Pd(PPh_3)_4$ (0.002-0.02 mmol, 0.001-0.10 eq.). Anhydrous DMF (2 mL) was then added and the vial was pre-stirred for 30 s at 23 °C followed by heating at 170 °C, for 8 min with stirring. The work-up was performed using general procedure (C), and the solid residue was purified by flash column chromatography using a gradient to 2.5% EtOAc in hexanes, to obtain a colourless solid.

Entry	Eq. $Pd(PPh_3)_4$	% Yield
1	0.001	7*
2	0.01	31
3	0.02	54
4	0.05	83
5	0.10	92

* Reaction was scaled ten fold

General procedure (N) for the *in situ* catalyst generation screens in the synthesis of 4-(thiophen-2-yl)benzonitrile (Table 13**,** Table 14**,** Table 15**)**



To a 5 mL conical microwave vial equipped with a spin-vein was added lithium thiophene-2-sulfinate (0.30 mmol, 1.5 eq.), 4-bromobenzonitrile (0.20 mmol, 1.0 eq.), a palladium source (0.01 mmol, 0.05 eq.), and phosphine ligand (0.01-0.06 mmol, 0.05-0.30 eq.). Anhydrous DMF (2 mL) was then added and the vial was pre-stirred for 30 s at 23 ºC followed by heating at 170 ºC, for 8 min with stirring. The work-up was performed using general procedure (C), and the solid residue was purified by flash column chromatography using a gradient to 2.5% EtOAc in hexanes, to obtain a colourless solid.

Entry	Pd Source	Ligand	% Yield
1	$PdCl_2$	$HP(^tBu)_3BF_4$	66
2	PdI_2	$HP(^tBu)_3BF_4$	62
3	$Pd(OAc)_2$	$HP(^tBu)_3BF_4$	55
4	Pd(acac)	$HP(^tBu)_3BF_4$	51
5	$Pd(dba)_2$	$HP(^tBu)_3BF_4$	61
6	petey*	$HP(^tBu)_3BF_4$	58

* $Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$

Table 13: Palladium Source Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile

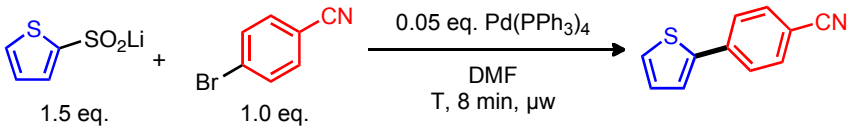
Entry	Pd Source	Eq. $HP(^tBu)_3BF_4$	% Yield
1	$PdCl_2$	0.05	58
2	$PdCl_2$	0.10	66
3	$PdCl_2$	0.15	69
4	$PdCl_2$	0.20	74
5	$PdCl_2$	0.25	80
6	$PdCl_2$	0.40	81

Table 14: $HP(^tBu)_3BF_4$ Equivalent Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile

Entry	Pd Source	Eq. PPh_3	% Yield
1	$PdCl_2$	0.05	33
2	$PdCl_2$	0.10	67
3	$PdCl_2$	0.15	75
4	$PdCl_2$	0.20	70
5	$PdCl_2$	0.25	93
6	$PdCl_2$	0.40	59

Table 15: PPh_3 Equivalent Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile

General procedure (O) for the temperature screen in the synthesis of 4-(thiophen-2-yl)benzonitrile (Table 16**)**

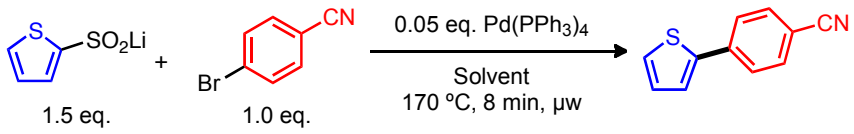


To a 5 mL conical microwave vial equipped with a spin-vein was added lithium thiophene-2-sulfinate (0.30 mmol, 1.5 eq.), 4-bromobenzonitrile (0.20 mmol, 1.0 eq.), and $Pd(PPh_3)_4$ (0.01 mmol, 0.05 eq.). Anhydrous DMF (2 mL) was then added and the vial was pre-stirred for 30 s at 23 ºC followed by heating

at variable temperatures (150-190 ºC), for 8 min with stirring. The work-up was performed using general procedure (C), and the solid residue was purified by flash column chromatography using a gradient to 2.5% EtOAc in hexanes, to obtain a colourless solid.

Entry	T (°C)	% Yield
1	150	53
2	160	42
3	170	83
4	190	68

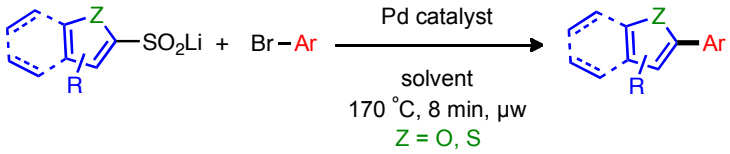
General procedure (P) for the solvent screen in the synthesis of 4-(thiophen-2-yl)benzonitrile (Table 17**)**



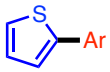
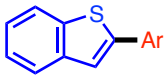
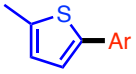
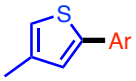
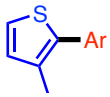
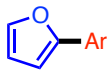
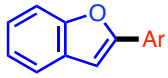
To a 5 mL conical microwave vial equipped with a spin-vein was added lithium thiophene-2-sulfinate (0.30 mmol, 1.5 eq.), 4-bromobenzonitrile (0.20 mmol, 1.0 eq.), and $Pd(PPh_3)_4$ (0.01 mmol, 0.05 eq.). A solvent (2 mL) was then added and the vial was pre-stirred for 30 s at 23 ºC followed by heating at 170 ºC, for 8 min with stirring. The work-up was performed using general procedure (C), and the solid residue was purified by flash column chromatography using a gradient to 2.5% EtOAc in hexanes, to obtain a colourless solid.

Entry	Solvent	% Yield	Entry	Solvent	% Yield
1	DMF (dry)	83	**8**	DMF/H_2O (1:1)	91
2	DMF	87	**9**	DMF/H_2O (1:2)	92
3	DMA	80	**10**	DMF/H_2O (1:3)	98
4	NMP	89	**11**	H_2O (distilled)	63
5	DMSO	89	**12**	H_2O (tap)	59
6	DMF/H_2O (3:1)	97	**13**	H_2O (pacific)	69
7	DMF/H_2O (2:1)	63	**14**	H_2O (3 eq. DMF)	76

General procedure (Q) for the substrate scope in the synthesis of aryl substituted heteroaromatics (Table 18**,** Table 19**)**



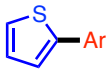
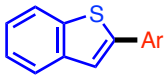
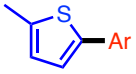
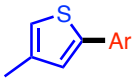
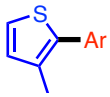
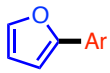
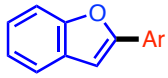
To a 5 mL conical microwave vial equipped with a spin-vein was added heteroaromatic sulfinate (0.30-0.40 mmol, 1.5-2.0 eq.), aryl halide (0.20 mmol, 1.0 eq.), and palladium catalyst (0.01 mmol, 0.05 eq.). A solvent (2 mL) was then added and the vial was pre-stirred for 30 s at 23 ºC followed by heating at 170 ºC, for 8 min with stirring. The work-up was performed using general procedure (C), and the solid residue was purified by flash column chromatography.

Entry	Product	% Yield	
		Conditions A	Conditions B
1		98	91
2		86	67
3		97 (82)*	93
4		73	83
5		58	53
6		65 (69)*	85
7		82	73

Conditions A: 1.50 eq. sulfinate, 1.00 eq. 4-bromobenzonitrile, 0.05 eq. $PdCl_2$, 0.25 eq. PPh_3, DMF/H_2O (1:3); **Conditions B**: 2.00 eq. sulfinate, 1.00 eq. 4-bromobenzonitrile, 0.05 eq. $Pd[P(^tBu)_3]_2$, DMF (Anhy.)

* Using $Pd(PPh_3)_4$ pre-made catalyst

Table 18: Scope of Heteroaromatic Sulfinate in the Cross-Coupling with 4-Bromobenzonitrile

Entry	Product	% Yield	
		Conditions A	Conditions B
1		98	91
2		86	67
3		97 (82)*	93
4		73	83
5		58	53
6		65 (69)*	85
7		82	73

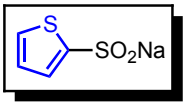
Conditions A: 1.50 eq. sulfinate, 1.00 eq. 4-bromobenzonitrile, 0.05 eq. $PdCl_2$, 0.25 eq. PPh_3, DMF/H_2O (1:3); **Conditions B**: 2.00 eq. sulfinate, 1.00 eq. 4-bromobenzonitrile, 0.05 eq. $Pd[P(^tBu)_3]_2$, DMF (Anhy.)

* Using $Pd(PPh_3)_4$ pre-made catalyst

Table 18: Scope of Heteroaromatic Sulfinate in the Cross-Coupling with 4-Bromobenzonitrile

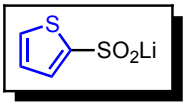
4.2 – Sulfinates

Sodium thiophene-2-sulfinate



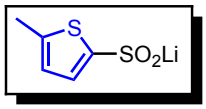
To a 100 mL round bottom flask equipped with a magnetic stir bar was added 4.035 g (22.09 mmol, 1.0 eq.) of thiophene-2-sulfonyl chloride, 7.301 g (68.81 mmol, 3.1 eq.) of sodium sulfite and 10.998 g (86.99 mmol, 3.9 eq.) of sodium bicarbonate in 50 mL H_2O. The solution was heated at 80 ºC for 3 hours with vigorous stirring. The solution was cooled to 23 ºC and the solvent was evaporated under reduced pressure leaving a colourless solid which was then purified by heating at reflux in 99% EtOH for 1 h and filtered, while still hot, through Celite and evaporated. The purification was performed three times. Yield 20% (0.7184 g) colourless solid.

Lithium thiophene-2-sulfinate



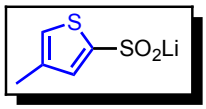
The above compound was synthesized following general procedure (B) on a 128.84 mmol (20.01 g) scale. Yield 94% colourless powder. ^{1}H NMR (500 MHz, DMSO) δ 7.41 (ddd, *J* = 4.9, 1.2, 0.5 Hz, 1H), 7.00 (ddd, *J* = 3.4, 1.3, 0.5 Hz, 1H), 6.95 (ddd, *J* = 4.9, 3.4, 0.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 166.96, 126.56, 125.72, 123.48.

Lithium 5-methylthiophene-2-sulfinate



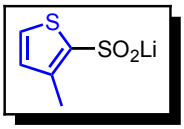
The above compound was synthesized following general procedure (B) on a 20.81 mmol (3.50 g) scale. Yield 98% colourless powder. ^{1}H NMR (500 MHz, DMSO) δ 6.76 (d, *J* = 3.2 Hz, 1H), 6.61 (d, *J* = 1.8 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 164.53, 139.05, 124.79, 123.13, 15.30.

Lithium 4-methylthiophene-2-sulfinate



The above compound was synthesized following general procedure (B) on a 20.70 mmol (4.12 g) scale. Yield 75% colourless powder. ^{1}H NMR (500 MHz, DMSO) δ 6.96 (s, 1H), 6.79 (s, 1H), 2.14 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 166.70, 136.45, 125.61, 120.94, 105.94, 15.55.

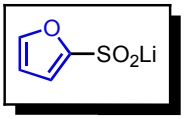
Lithium 3-methylthiophene-2-sulfinate



To a dry flask under argon atmosphere, equipped with a magnetic stir bar, 1.57 g (8.88 mmol, 1 eq.) 2-bromo-3-methylthiophene synthesized by bromination of 3-methylthiophene,[238] was added along with 30 mL anhydrous diethyl ether. The flask was cooled to -78 ºC (using an ethyl acetate–liquid

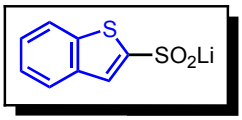
nitrogen bath) and 10.5 mL (17.85 mmol, 2 eq.) 1.7M *tert*-butyl lithium was added drop-wise over 5 minutes, with stirring. The reaction was stirred for two hours at -78 ºC for 2 hours, and then quenched by bubbling SO_2 produced from general procedure (A) for an hour, while warming to 23 ºC, precipitating the sulfinate salt. The salt is isolated *via* vacuum filtration, washed thoroughly with diethyl ether, and dried under vacuum. The solid is then ground to a fine powder, to which diethyl ether is added, and sonicated for 10 minutes, followed by filtration, and drying under high vacuum. Yield 78% colourless powder. ^{1}H NMR (500 MHz, DMSO) δ 7.20 (d, *J* = 4.8 Hz, 1H), 6.71 (d, *J* = 4.8 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 160.55, 132.32, 130.03, 123.32, 13.50.

Lithium furan-2-sulfinate



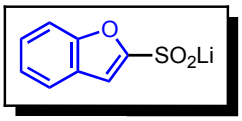
The above compound was synthesized following general procedure (B) on a 34.38 mmol (4.75 g) scale. Yield 80% light yellow powder. ^{1}H NMR (500 MHz, DMSO) δ 7.52 (s, 1H), 6.36 (dd, *J* = 3.1, 1.7 Hz, 1H), 6.31 (d, *J* = 3.1 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 169.63, 152.20, 141.97, 109.86, 105.23.

Lithium benzo[*b*]thiophene-2-sulfinate



The above compound was synthesized following general procedure (B) on a 18.7 mmol (3.82 g) scale. Yield 85% colourless powder. ^{1}H NMR (500 MHz, DMSO) δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.3 Hz, 1H), 7.33 – 7.25 (m, 3H). ^{13}C NMR (126 MHz, DMSO) δ 166.76, 140.09, 140.05, 124.61, 124.52, 124.40, 123.14, 120.27.

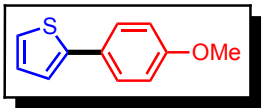
Lithium benzo[*b*]furan-2-sulfinate



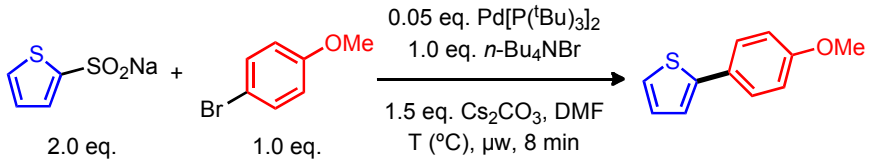
The above compound was synthesized following general procedure (B) on a 18.15 mmol (3.42 g) scale. Yield 78% colourless powder. ^{1}H NMR (500 MHz, DMSO) δ 7.60 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.26 (t, *J* = 7.1 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.75 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 172.11, 154.64, 127.79, 124.06, 122.64, 121.59, 111.35, 101.53.

4.3 – Optimization with Electron-Rich 4-Bromoanisole

2-(4-Methoxyphenyl)thiophene

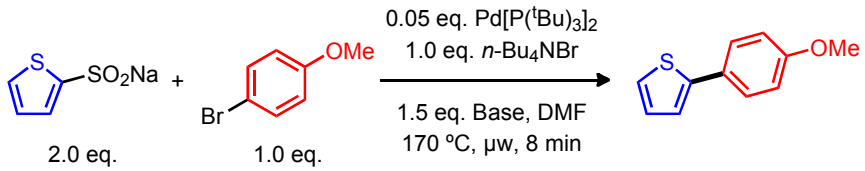


The above compound was prepared from the general procedure (E) on a 0.20 mmol (38.06 mg) scale, starting from lithium thiophene-2-sulfinate and 4-bromoanisole. The target compound was isolated in 53% yield (20.17 mg) as a colourless solid using 5% ethyl acetate in hexanes as the eluent. The NMR spectrum was consistent with that found in the literature,[239] and the mass obtained (m/z: 190.05) by GC-MS matched. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.52 (m, 2H), 7.22 – 7.19 (m, 2H), 7.05 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.94 – 6.90 (m, 2H), 3.84 (s, 3H).



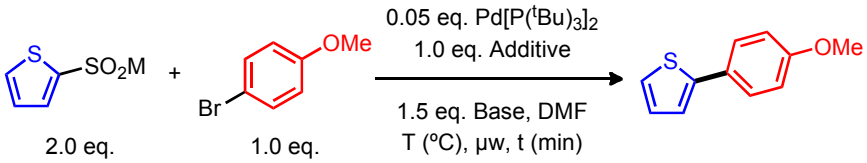
Entry	Temperature (°C)	% Yield
1	150	19
2	160	23
3	170	53
4	190	56

Table 6: Temperature Effect on Desulfinylative Cross-Coupling of Sodium Thiophene-2-Sulfinate with 4-Bromoanisole



Entry	Base	% Yield
1	Cs_2CO_3	53
2	K_2CO_3	22
3	Na_2CO_3	43
4	Li_2CO_3	29

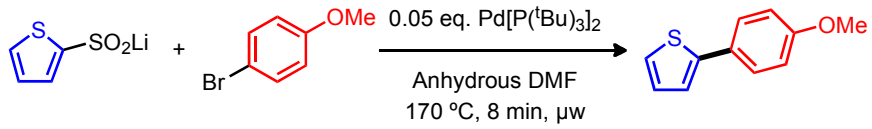
Table 7: Base Effect on Desulfinylative Cross-Coupling of Sodium Thiophene-2-Sulfinate with 4-Bromoanisole



Entry	T (ºC)	Metal	t (min)	Base	Additive	GC Yield (%)
1	170	Na^+	8	Cs_2CO_3	*n*-Bu_4NBr	53*
2	170	Li^+	8	Cs_2CO_3	*n*-Bu_4NBr	30*
3	170	Li^+	8	-	*n*-Bu_4NBr	49
4	170	Li^+	8	-	-	51
5	170	Li^+	64	-	-	51
6	160	Li^+	16	-	-	50
7	150	Li^+	32	-	-	43

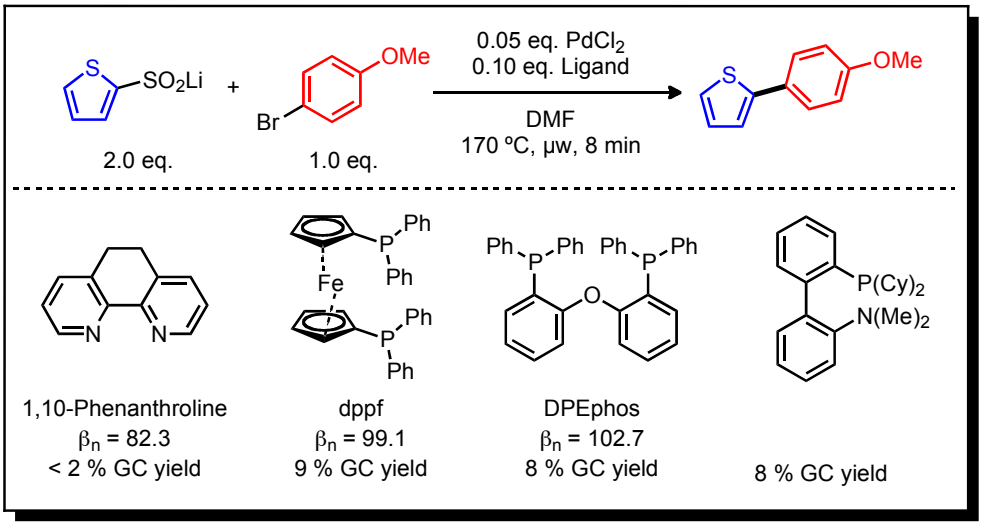
***** Isolated yield

Table 8: Condition Optimizations on Desulfinylative Cross-Coupling of Sodium Thiophene-2-Sulfinate with 4-Bromoanisole

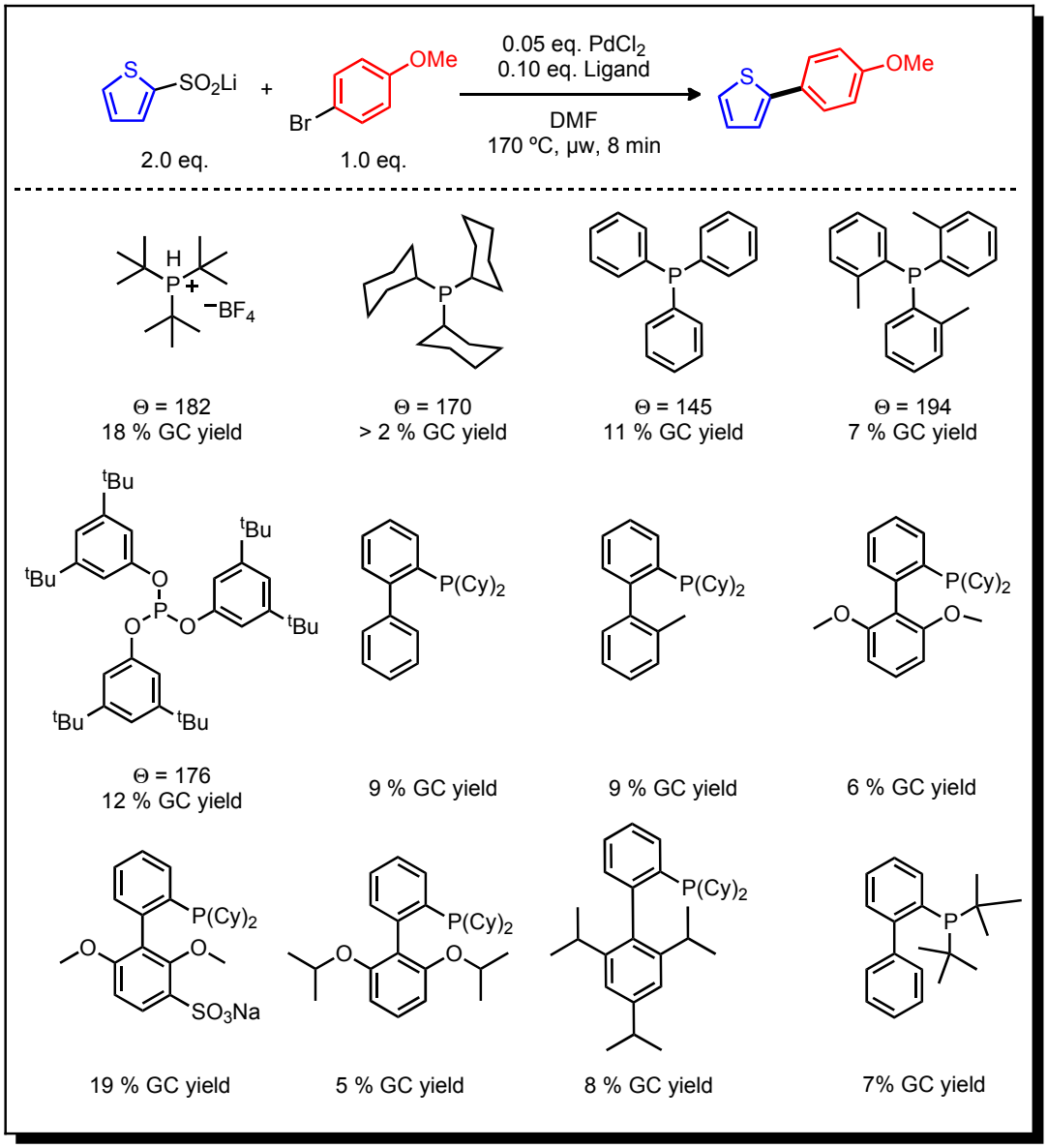


Entry	Sulfinate eq.	Aryl Brmide eq.	GC Yield (%)
1	2.0	1.0	51
2	1.0	1.0	51
3	1.0	2.0	52
4	1.0	3.0	53

Table 9: Cross-Coupling Partner Equivalent Screen In the Cross-Coupling of Lithium Thiophene-2-Sulfinate and 4-Bromoanisole



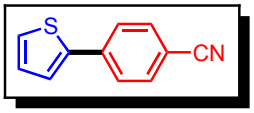
Scheme 53: Bidentate Ligand Screen for the Desulfinylative Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromoanisole



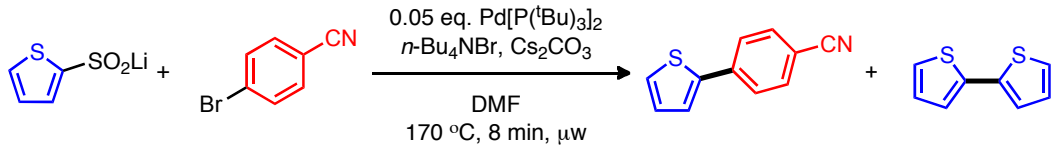
Scheme 54: Monodentate Ligand Screen for the Desulfinylative Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromoanisole

4.4 – Optimization with Electron-Poor 4-Bromobenzonitrile

4-(Thiophen-2-yl)benzonitrile

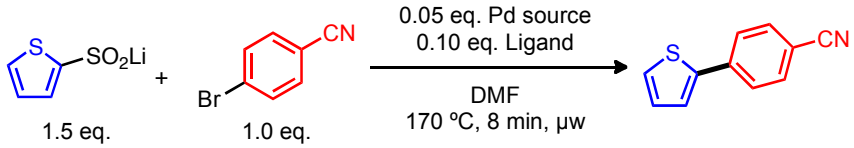


The above compound was prepared from the general procedure (D) on a 0.20 mmol (37.05 mg) scale, starting from lithium thiophene-2-sulfinate and 4-bromobenzonitrile. The target compound was isolated in 98% yield (36.31 mg) as a colourless solid using 1% ethyl acetate in hexanes as the eluent. The NMR spectrum was consistent with that found in the literature,[239] and the mass obtained (m/z: 185.03) by GC-MS matched. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 4H), 7.41 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.39 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.12 (dd, *J* = 5.1, 3.7 Hz, 1H).



Entry	Eq. Sulfinate	Eq. ArBr	Eq. Cs_2CO_3	Eq. *n*-Bu_4NBr	Cross-Coupling % Yield
1	1.0	2.0	1.5	1.0	72
2	1.0	2.0	1.5	-	69
3	1.0	2.0	-	-	69
4	1.0	1.0	-	-	59
5	1.5	1.0	-	-	84
6	2.0	1.0	-	-	91
7	3.0	1.0	-	-	89

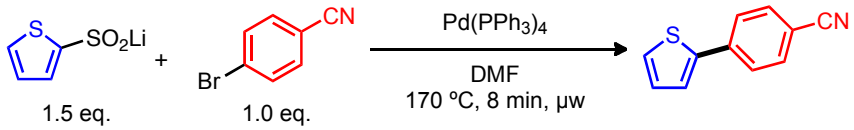
Table 10: Additive and Cross-Coupling Partner Stoichiometry Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile



Entry	Catalyst	% Yield
1	-	0
2	$Pd(OAc)_2$	0
3	$Pd[P(^tBu)_3]_2$	84
4	$PdCl_2 + HP(^tBu)_3BF_4$ ‡*	66
5	$PdCl_2$(dppf)	76
6	$PdCl_2$ + dppf*	55
7	$Pd(PPh_3)_4$	83
8	$PdCl_2 + PPh_3$ $	70
9	$PdCl_2 + P(^tBu)_2Me$ *	47

‡0.15 eq. Cs_2CO_3 used *Ligand used in 0.10 eq., $ Ligand used in 0.20 eq.

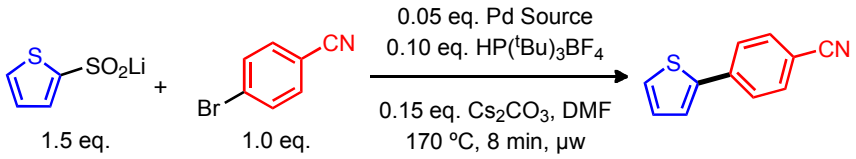
Table 10: Palladium Catalyst Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile



Entry	Eq. $Pd(PPh_3)_4$	% Yield
1	0.001	7*
2	0.01	31
3	0.02	54
4	0.05	83
5	0.10	92

* Reaction was scaled ten fold

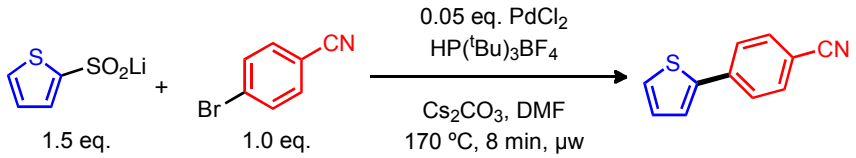
Table 11: Catalyst Loading Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile



Entry	Pd Source	% Yield
1	$PdCl_2$	66
2	PdI_2	62
3	$Pd(OAc)_2$	55
4	Pd(acac)	51
5	$Pd(dba)_2$	61
6	petey*	58

* $Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$

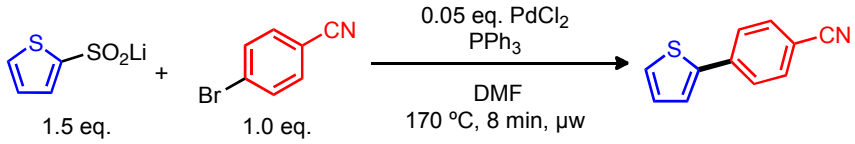
Table 12: Palladium Source Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile



Entry	Eq. $HP(^tBu)_3BF_4$	% Yield
1	0.05	58
2	0.10	66
3	0.15	69
4	0.20	74
5	0.25	80
6	0.40	81

* Cs_2CO_3 used in a 1:1 ratio with $HP(^tBu)_3BF_4$

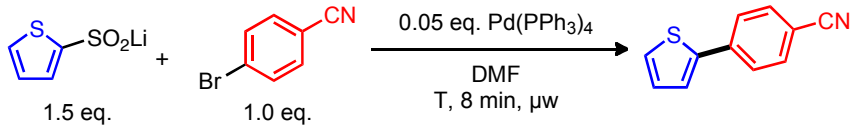
Table 13: $HP(^tBu)_3BF_4$ Equivalent Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile



1.5 eq. 1.0 eq.

Entry	Eq. PPh_3	% Yield
1	0.05	33
2	0.10	67
3	0.15	75
4	0.20	70
5	0.25	93
6	0.40	59

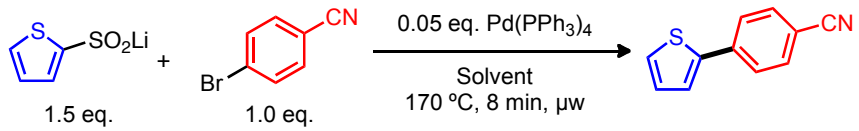
Table 14: PPh_3 Equivalent Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile



1.5 eq. 1.0 eq.

Entry	T (°C)	% Yield
1	150	53
2	160	42
3	170	83
4	190	68

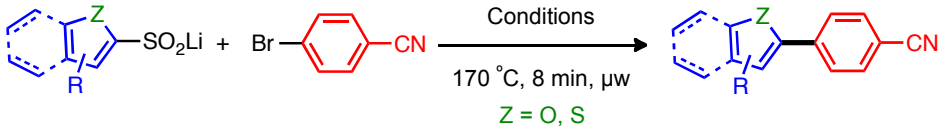
Table 15: Temperature Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile

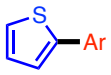
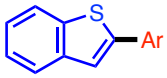
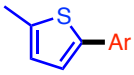
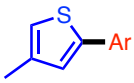
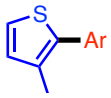
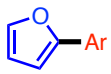
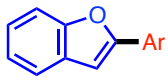


Entry	Solvent	% Yield	Entry	Solvent	% Yield
1	DMF (dry)	83	**8**	DMF/H_2O (1:1)	91
2	DMF	87	**9**	DMF/H_2O (1:2)	92
3	DMA	80	**10**	DMF/H_2O (1:3)	98
4	NMP	89	**11**	H_2O (distilled)	63
5	DMSO	89	**12**	H_2O (tap)	59
6	DMF/H_2O (3:1)	97	**13**	H_2O (pacific)	69
7	DMF/H_2O (2:1)	63	**14**	H_2O (3 eq. DMF)	76

Table 16: Solvent Screen in the Cross-Coupling of Lithium Thiophene-2-Sulfinate with 4-Bromobenzonitrile

4.5 – Heteroaromatic Sulfinate Scope



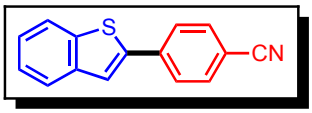
Entry	Product	% Yield	
		Conditions A	Conditions B
1		98	91
2		86	67
3		97 (82)*	93
4		73	83
5		58	53
6		65 (69)*	85
7		82	73

Conditions A: 1.50 eq. sulfinate, 1.00 eq. 4-bromobenzonitrile, 0.05 eq. $PdCl_2$, 0.25 eq. PPh_3, DMF/H_2O (1:3); **Conditions B**: 2.00 eq. sulfinate, 1.00 eq. 4-bromobenzonitrile, 0.05 eq. $Pd[P(^tBu)_3]_2$, DMF (Anhy.)

* Using $Pd(PPh_3)_4$ pre-made catalyst

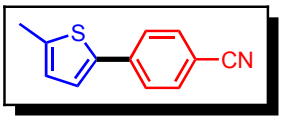
Table 17: Heteroaromatic Sulfinate Scope with 4-Bromobenzonitrile

4-(Benzo[*b*]thiophen-2-yl)benzonitrile



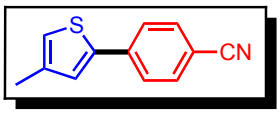
The above compound was prepared from the general procedure (D) on a 0.20 mmol (47.06 mg) scale, starting from lithium benzo[*b*]thiophene-2-sulfinate and 4-bromobenzonitrile. The target compound was isolated in 86% yield (40.47 mg) as a colourless solid using 1% ethyl acetate in hexanes as the eluent. The NMR spectrum was consistent with that found in the literature,[240] and the mass obtained (m/z: 235.05) by GC-MS matched. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.78 (m, 4H), 7.73 – 7.69 (m, 2H), 7.66 (d, *J* = 0.7 Hz, 1H), 7.42 – 7.35 (m, 2H).

4-(5-Methylthiophen-2-yl)benzonitrile



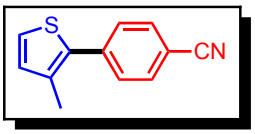
The above compound was prepared from the general procedure (D) on a 0.20 mmol (39.85 mg) scale, starting from lithium 5-methylthiophene-2-sulfinate and 4-bromobenzonitrile. The target compound was isolated in 97% yield (38.66 mg) as a colourless solid using 1% ethyl acetate in hexanes as the eluent. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 4H), 7.22 (d, *J* = 3.6 Hz, 1H), 6.79 – 6.76 (m, 1H), 2.53 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.34, 139,71, 139.06, 132.78, 126.95, 125.63, 125.25, 119.10, 110.05, 15.69.

4-(4-Methylthiophen-2-yl)benzonitrile



The above compound was prepared from the general procedure (E) on a 0.20 mmol (39.85 mg) scale, starting from lithium 4-methylthiophene-2-sulfinate and 4-bromobenzonitrile. The target compound was isolated in 83% yield (33.08 mg) as a colourless solid using 1% ethyl acetate in hexanes as the eluent. The NMR spectrum was consistent with that found in the literature,[240] and the mass obtained (m/z: 199.05) by GC-MS matched. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.23 (s, 1H), 6.98 (s, 1H), 2.30 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.78, 139.34, 138.94, 132.79, 127.51, 125.93, 122.64, 119.00, 110.48, 15.90.

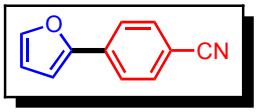
4-(3-Methylthiophen-2-yl)benzonitrile



The above compound was prepared from the general procedure (D) on a 0.20 mmol (39.85 mg) scale, starting from lithium 3-methylthiophene-2-sulfinate and 4-bromobenzonitrile. The target compound was isolated in 58% yield (23.11 mg) as a colourless solid using 1% ethyl acetate in hexanes as the eluent. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.67 (m, 2H), 7.58 – 7.55 (m, 2H), 7.30 (d, *J* = 5.1 Hz, 1H), 6.96 (d, *J* = 5.1 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ

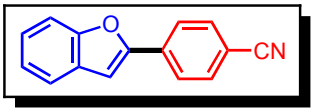
139.69, 135.84, 135.11, 133.53, 132.78, 132.44, 131.83, 129.35, 125.30, 118.97, 110.61, 77.41, 77.16, 76.91, 15.32.

4-(Furan-2-yl)benzonitrile



The above compound was prepared from the general procedure (E) on a 0.20 mmol (33.64 mg) scale, starting from lithium furan-2-sulfinate and 4-bromobenzonitrile. The target compound was isolated in 85% yield (28.59 mg) as a yellow solid using 1% ethyl acetate in hexanes as the eluent. The NMR spectrum was consistent with that found in the literature,[239] and the mass obtained (m/z: 169.05) by GC-MS matched. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.54 – 7.52 (m, 1H), 6.81 (d, *J* = 3.4 Hz, 1H), 6.54 – 6.51 (m, 1H).

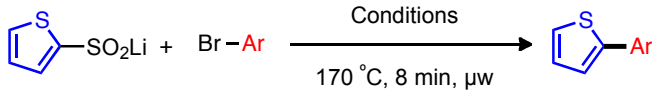
4-(Benzo[*b*]furan-2-yl)benzonitrile

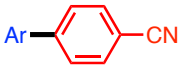
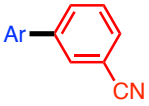
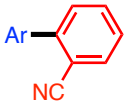
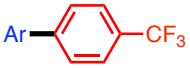
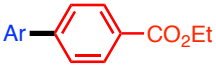
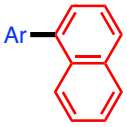
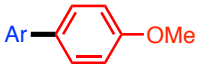


The above compound was prepared from the general procedure (D) on a 0.20 mmol (43.85 mg) scale, starting from lithium benzo[*b*]furan-2-sulfinate and 4-bromobenzonitrile. The target compound was isolated in 82% yield (35.96 mg) as a colourless solid using 1% ethyl acetate in hexanes as the eluent. The NMR spectrum was consistent with that found in the literature,[240] and the mass obtained (m/z: 219.07) by GC-MS matched. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 –

7.92 (m, 2H), 7.74 – 7.71 (m, 2H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.29 – 7.27 (m, 1H), 7.18 (s, 1H).

4.6 – Aryl Bromide Scope



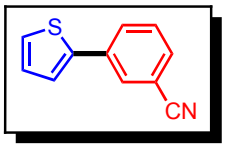
Entry	Product	% Yield	
		Conditions A	Conditions B
1		98	91
2		70	86
3		81	94
4		26	64
5		65	50
6		43	94
7		20	53*

Conditions A: 1.50 eq. sulfinate, 1.00 eq. 4-bromobenzonitrile, 0.05 eq. $PdCl_2$, 0.25 eq. PPh_3, DMF/H_2O (1:3); **Conditions B**: 2.00 eq. sulfinate, 1.00 eq. 4-bromobenzonitrile, 0.05 eq. $Pd[P(^tBu)_3]_2$, DMF (Anhy.)

*Using sodium thiophene-2-sulfinate

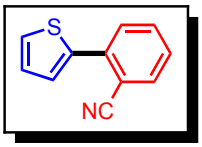
Table 19: Scope of Aryl Bromide in the Cross-Coupling with Lithium Thiophene-2-Sulfinate

3-(Thiophen-2-yl)benzonitrile



The above compound was prepared from the general procedure (E) on a 0.20 mmol (37.05 mg) scale, starting from lithium thiophene-2-sulfinate and 3-bromobenzonitrile. The target compound was isolated in 86% yield (31.86 mg) as a colourless solid using 1% ethyl acetate in hexanes as the eluent. The NMR spectrum was consistent with that found in the literature,[241] and the mass obtained (m/z: 185.03) by GC-MS matched. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.87 (m, 1H), 7.84 – 7.80 (m, 1H), 7.57 – 7.53 (m, 1H), 7.48 (td, *J* = 7.8, 0.5 Hz, 1H), 7.38 – 7.35 (m, 2H), 7.14 – 7.10 (m, 1H).

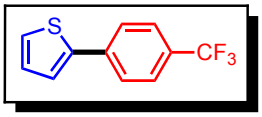
2-(Thiophen-2-yl)benzonitrile



The above compound was prepared from the general procedure (E) on a 0.20 mmol (37.05 mg) scale, starting from lithium thiophene-2-sulfinate and 2-bromobenzonitrile. The target compound was isolated in 94% yield (34.83 mg) as a colourless solid using 1% ethyl acetate in hexanes as the eluent. The NMR spectrum was consistent with that found in the literature,[242] and the mass obtained (m/z: 185.03) by GC-MS matched. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74

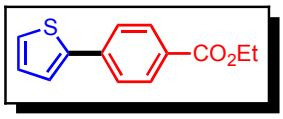
(d, *J* = 7.8 Hz, 1H), 7.66 – 7.57 (m, 3H), 7.44 (d, *J* = 5.1 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.16 (dd, *J* = 5.1, 3.7 Hz, 1H).

2-(4-(Trifluoromethyl)phenyl)thiophene



The above compound was prepared from the general procedure (E) on a 0.20 mmol (45.65 mg) scale, starting from lithium thiophene-2-sulfinate and 4-bromobenzotrifluoride. The target compound was isolated in 64% yield (29.21 mg) as a colourless solid using hexanes as the eluent. The NMR spectrum was consistent with that found in the literature,[239] and the mass obtained (m/z: 228.02) by GC-MS matched. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.40 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.36 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.12 (dd, *J* = 5.1, 3.6 Hz, 1H).

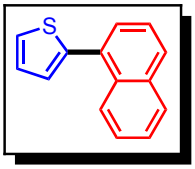
Ethyl 4-(thiophen-2-yl)benzoate



The above compound was prepared from the general procedure (D) on a 0.20 mmol (46.46 mg) scale, starting from lithium thiophene-2-sulfinate and ethyl 4-bromobenzoate. The target compound was isolated in 65% yield (30.20 mg) as a colourless solid using 1-2% ethyl acetate in hexanes as the eluent. The NMR spectrum was consistent with that found in the literature,[239] and the mass obtained (m/z: 232.06) by GC-MS matched. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05

(d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.42 (dd, *J* = 3.6, 0.9 Hz, 1H), 7.36 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.13 – 7.10 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

2-(Naphthalen-1-yl)thiophene



The above compound was prepared from the general procedure (E) on a 0.20 mmol (42.06 mg) scale, starting from lithium thiophene-2-sulfinate and 2-bromonaphthalene. The target compound was isolated in 94% yield (39.53 mg) as a colourless solid using hexanes as the eluent. The NMR spectrum was consistent with that found in the literature,[239] and the mass obtained (m/z: 210.05) by GC-MS matched. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (dd, J = 6.9, 2.6 Hz, 1H), 7.93 – 7.89 (m, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.59 (dd, J = 7.1, 1.2 Hz, 1H), 7.54 – 7.48 (m, 3H), 7.44 (dd, J = 5.1, 1.0 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.20 (dd, J = 5.1, 3.5 Hz, 1H).

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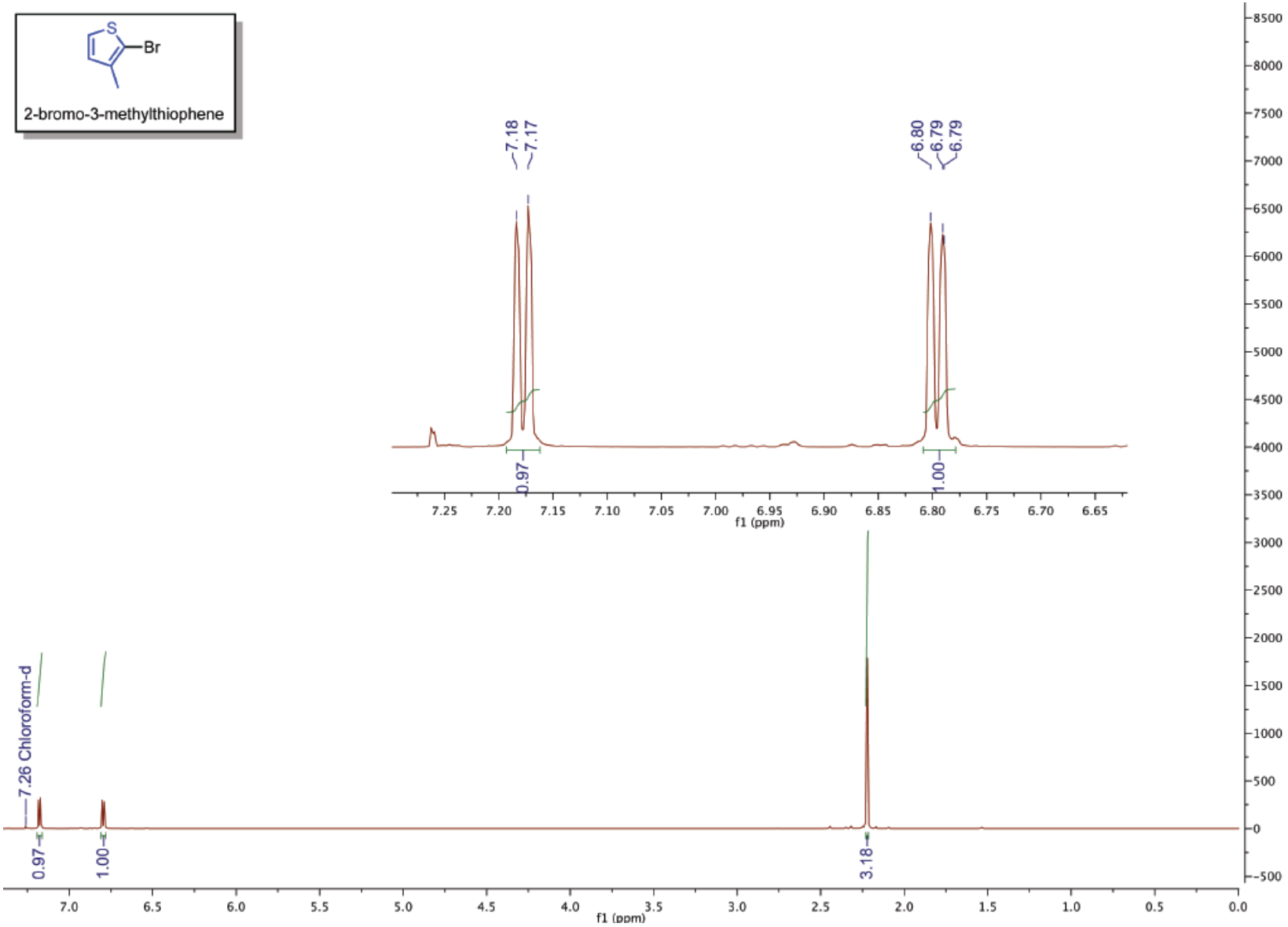
NMR Data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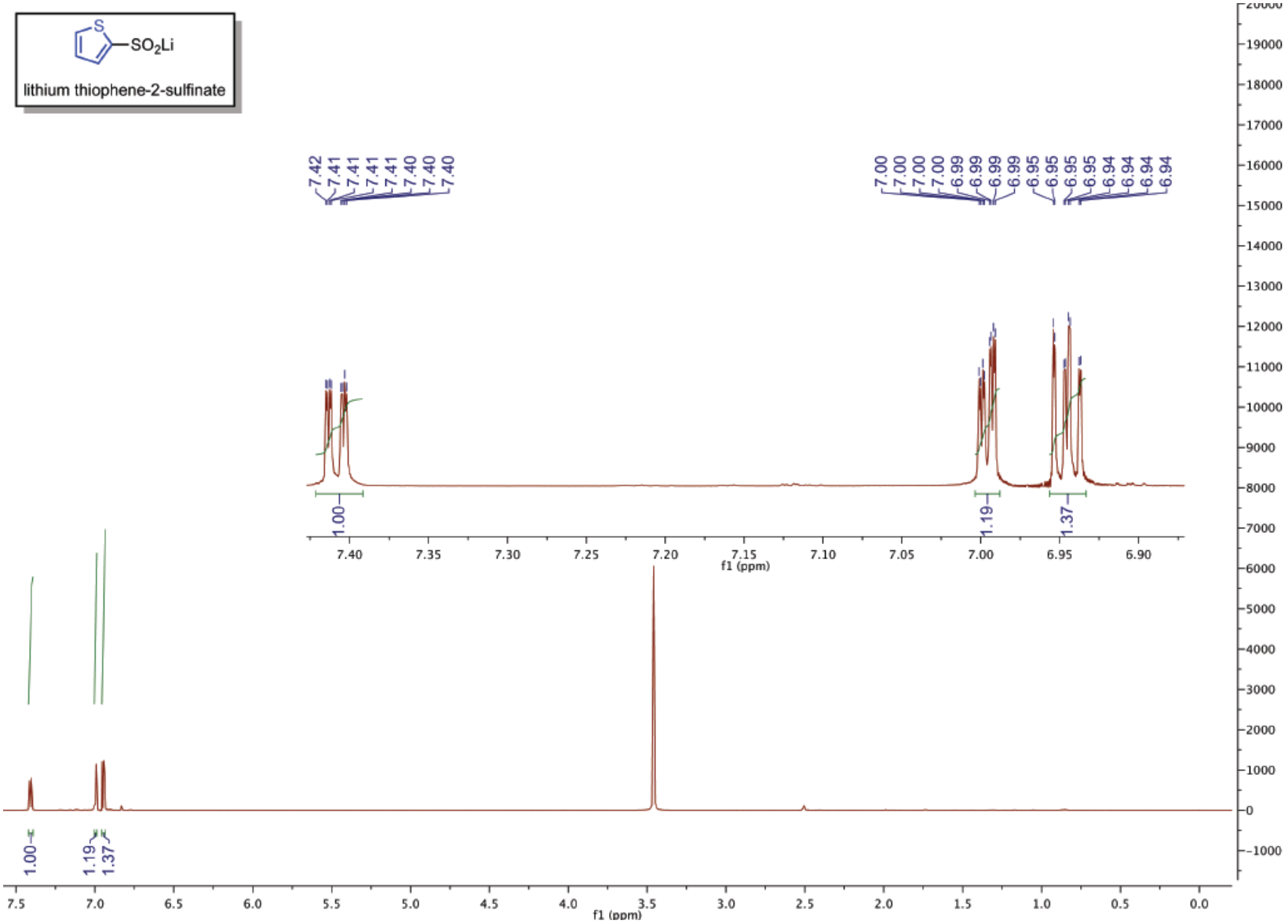
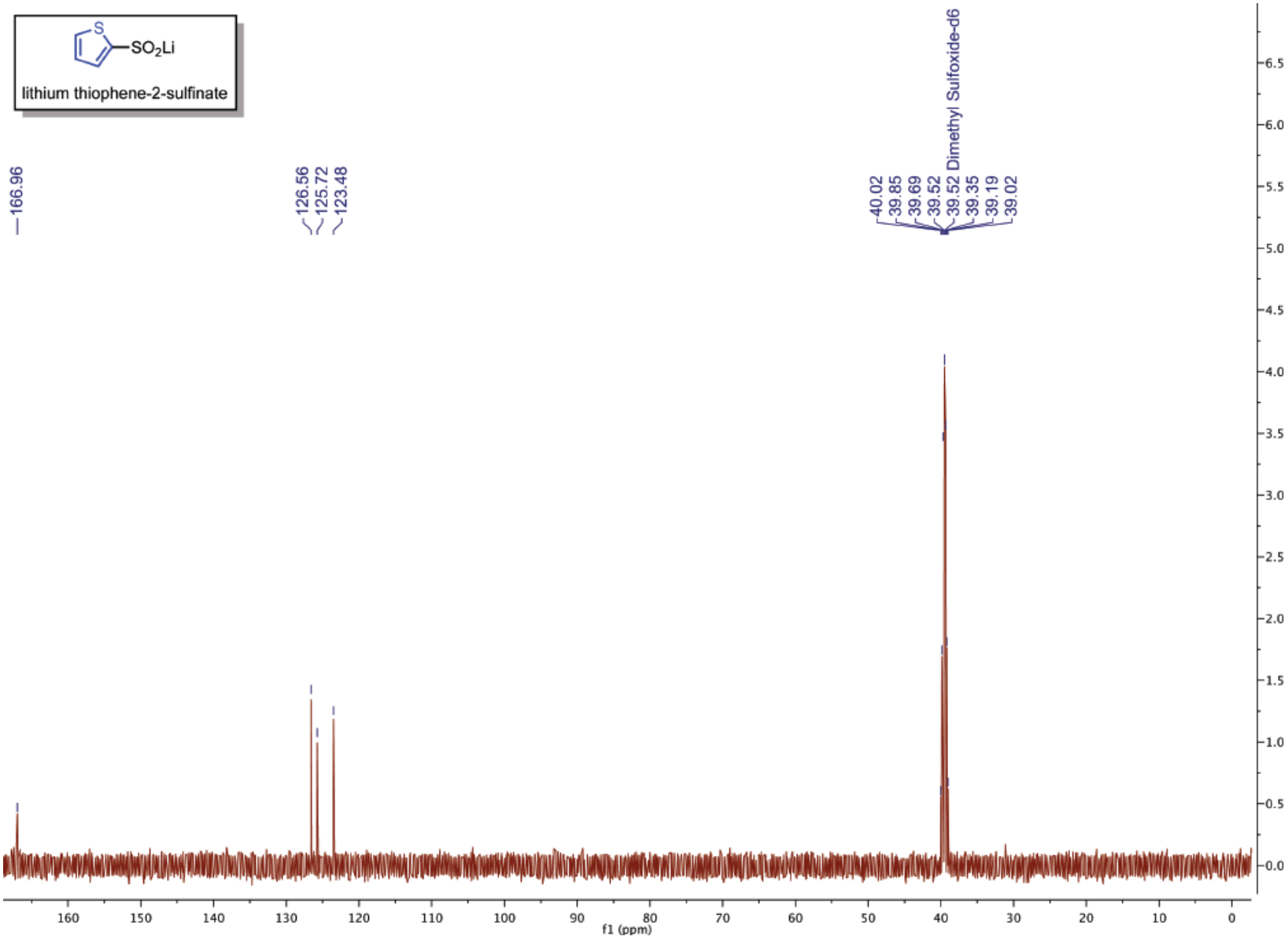
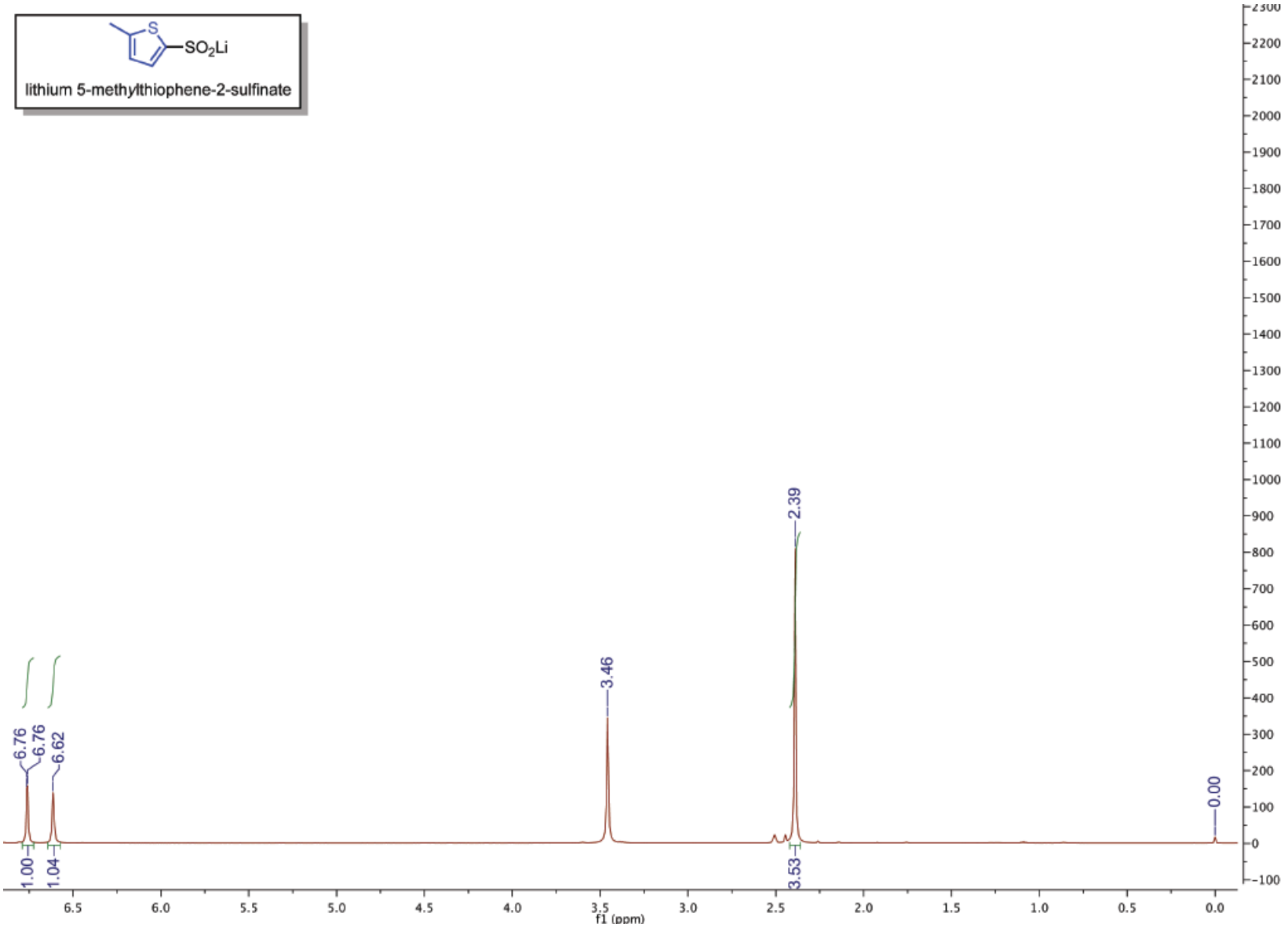
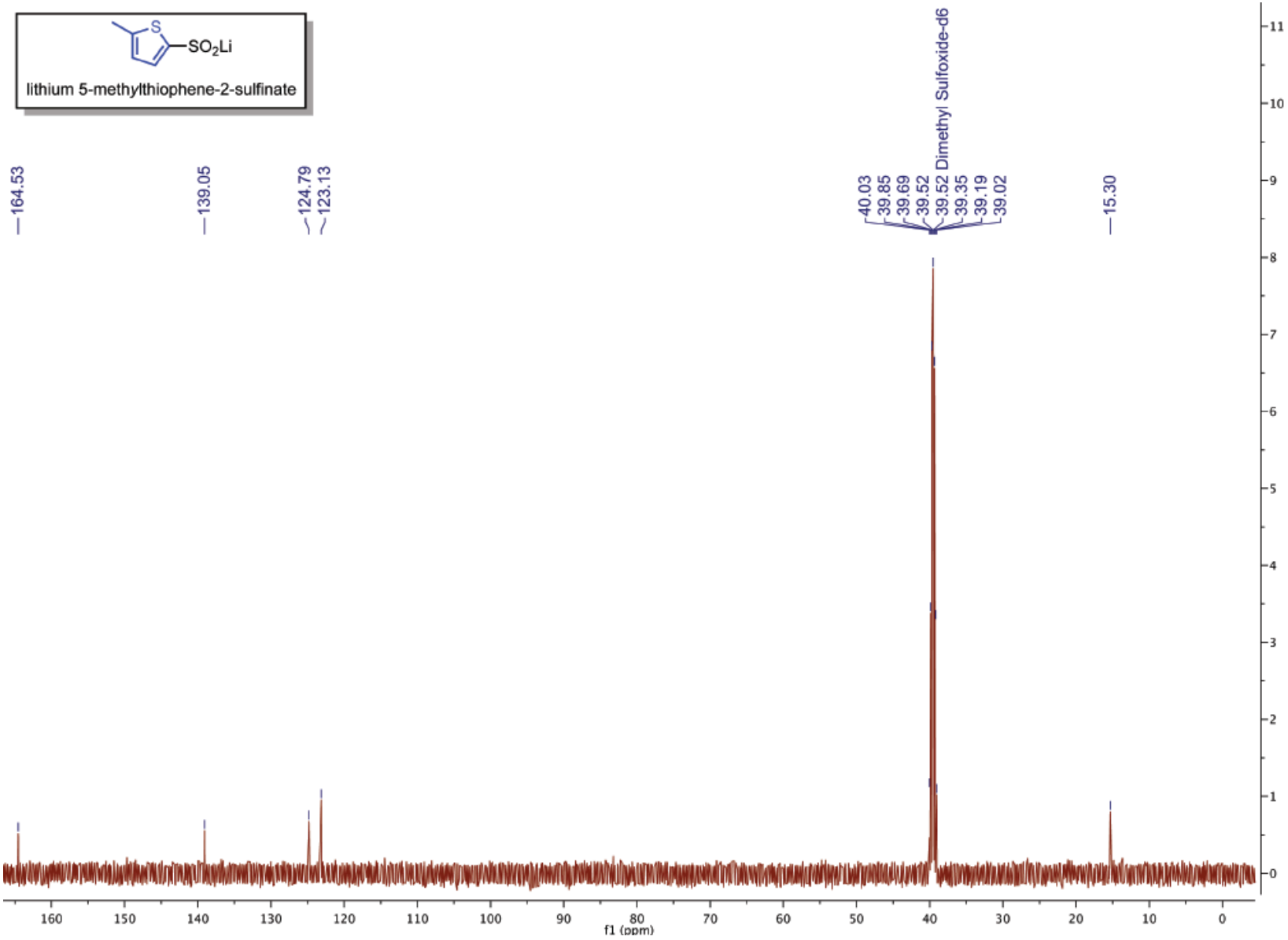
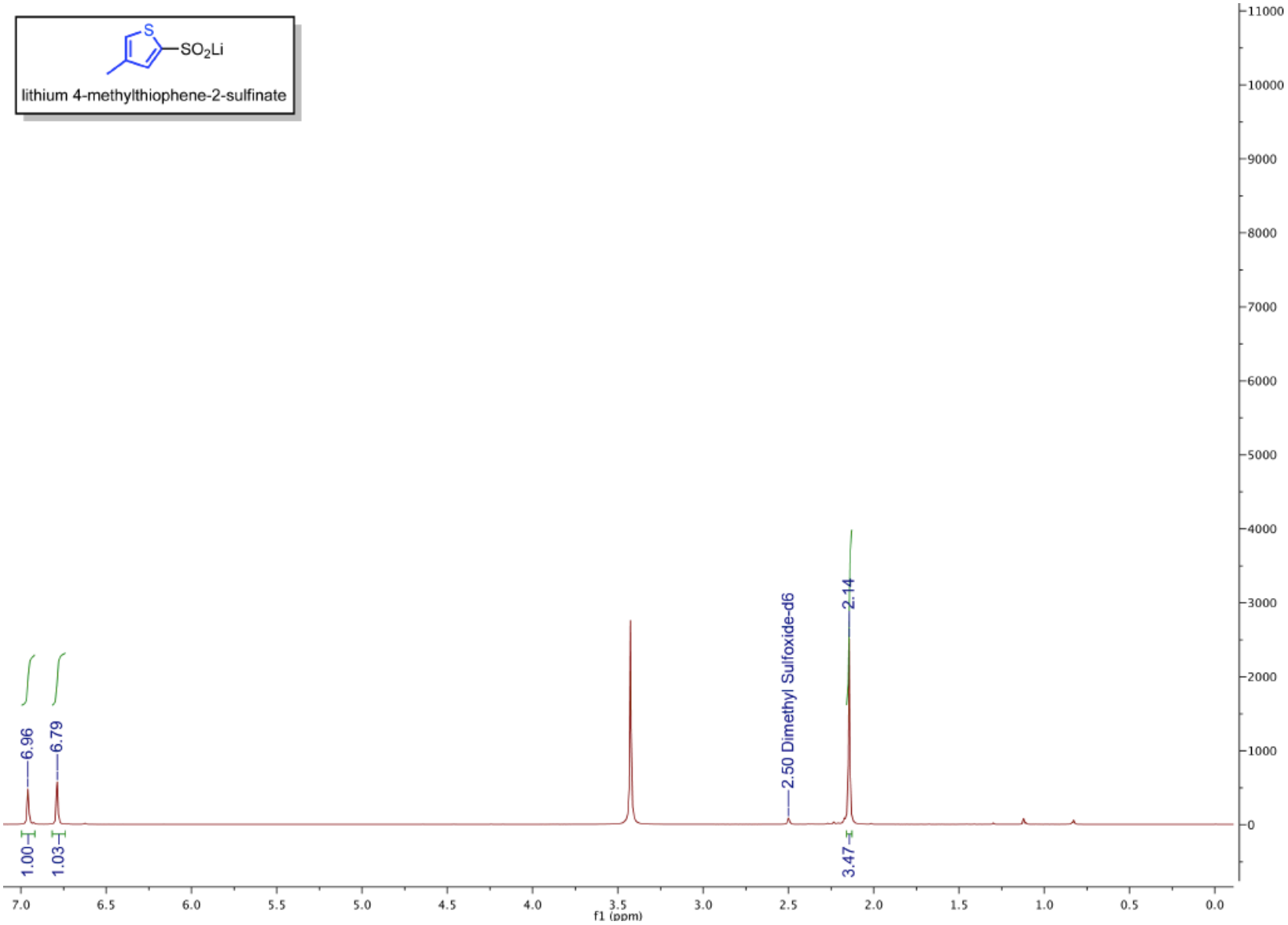
3.18
f1 (ppm)

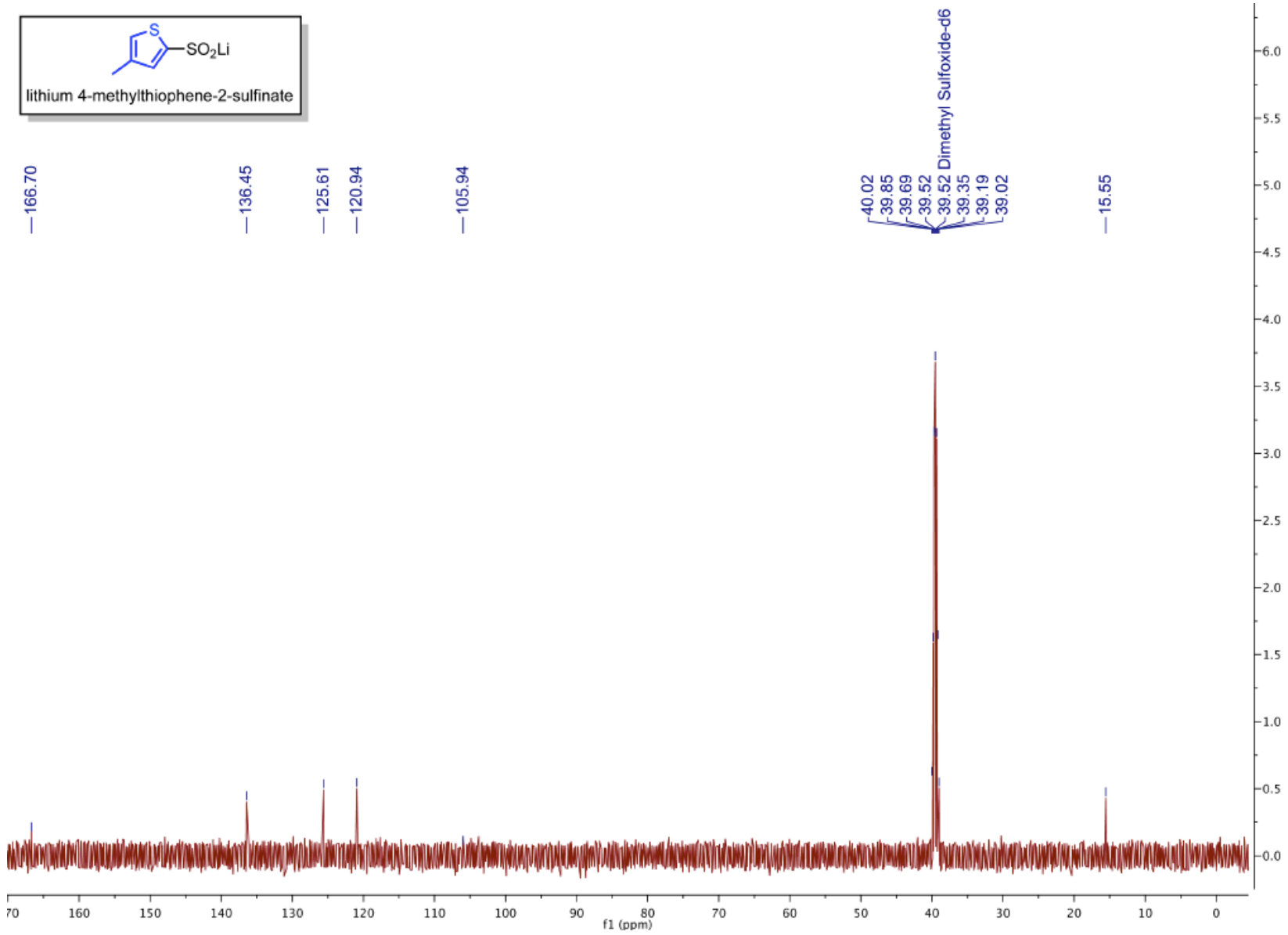

lithium thiophene-2-sulfinate
7.42
7.41
7.41
7.41
7.41
7.40
7.40
7.40
7.00
7.00
7.00
7.00
6.99
6.99
6.99
6.95
6.95
6.95
6.94
6.94
6.94
6.94
1.00
1.19
1.37
f1 (ppm)
1.00
1.19
1.37
f1 (ppm)

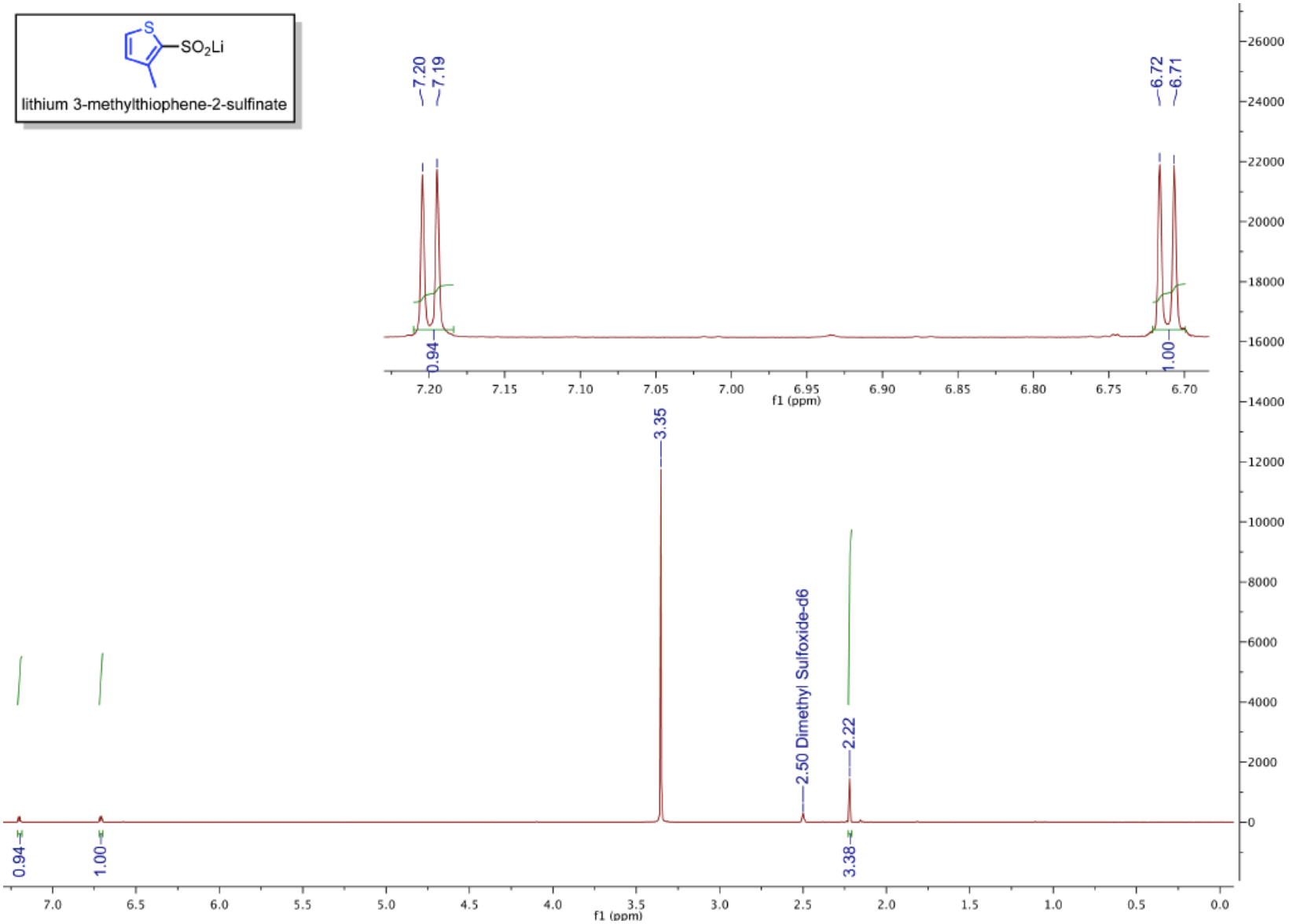

lithium thiophene-2-sulfinate
166.96
126.56
125.72
123.48
40.02
39.85
39.69
39.52
39.52 Dimethyl Sulfoxide-d6
39.35
39.19
39.02
f1 (ppm)

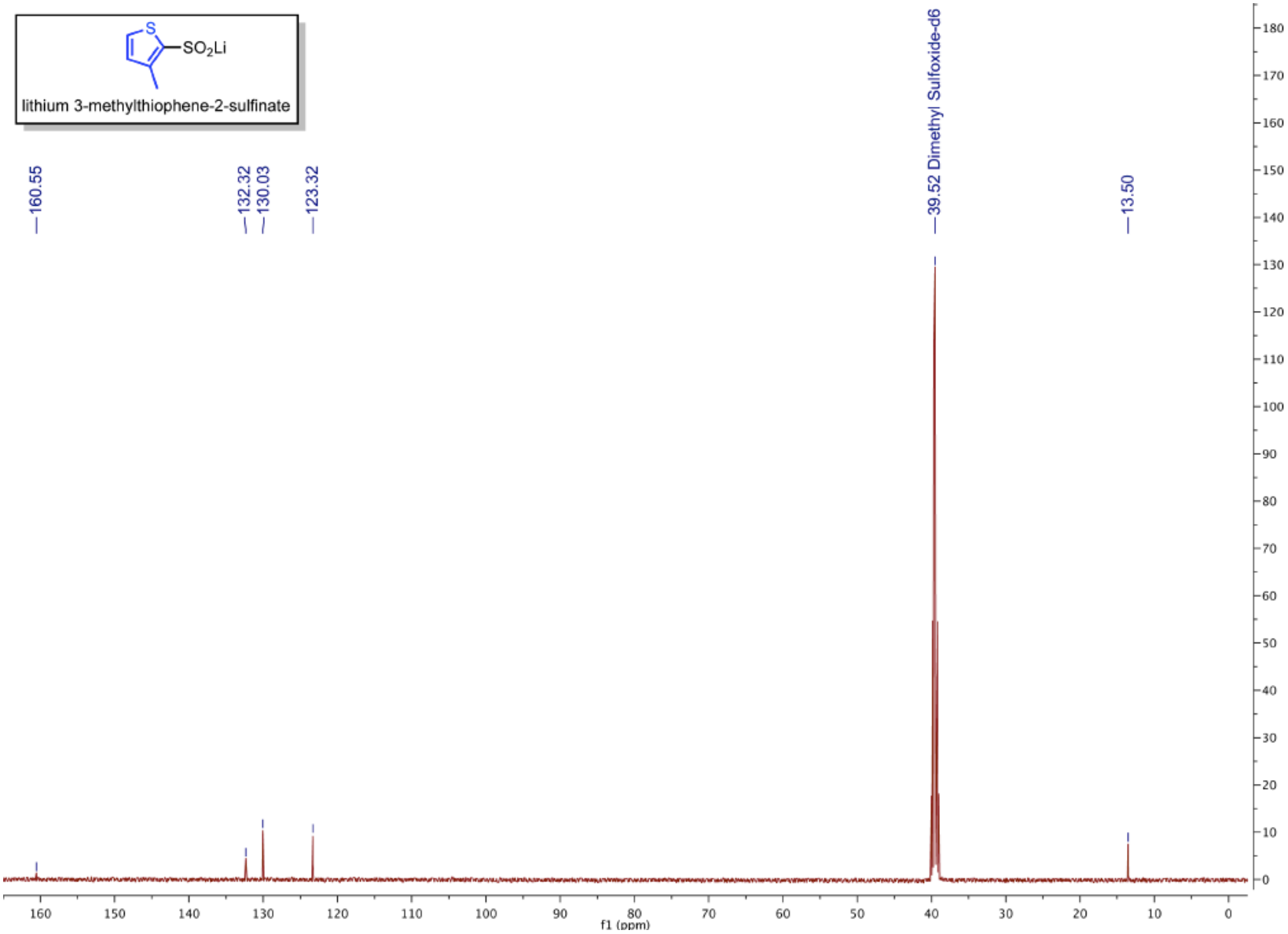

lithium 5-methylthiophene-2-sulfinate
6.76
6.76
6.62
3.46
2.39
0.00
1.00
1.04
3.53
f1 (ppm)


lithium 5-methylthiophene-2-sulfinate
SO2Li
S
164.53
139.05
124.79
123.13
40.03
39.85
39.69
39.52
39.52 Dimethyl Sulfoxide-d6
39.35
39.19
39.02
15.30
f1 (ppm)

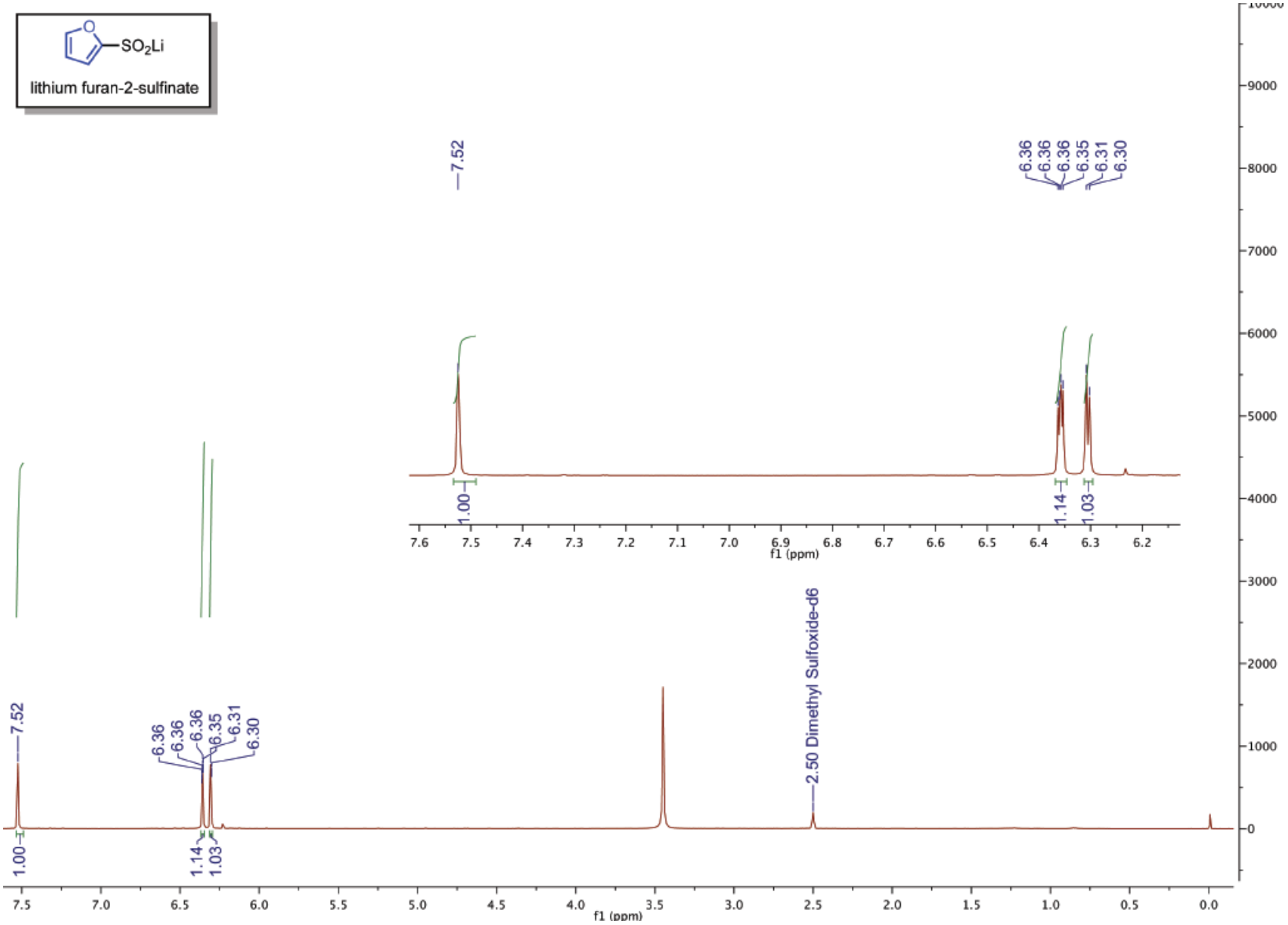

lithium 4-methylthiophene-2-sulfinate
6.96
6.79
2.50 Dimethyl Sulfoxide-d6
2.14
1.00
1.03
3.47
f1 (ppm)

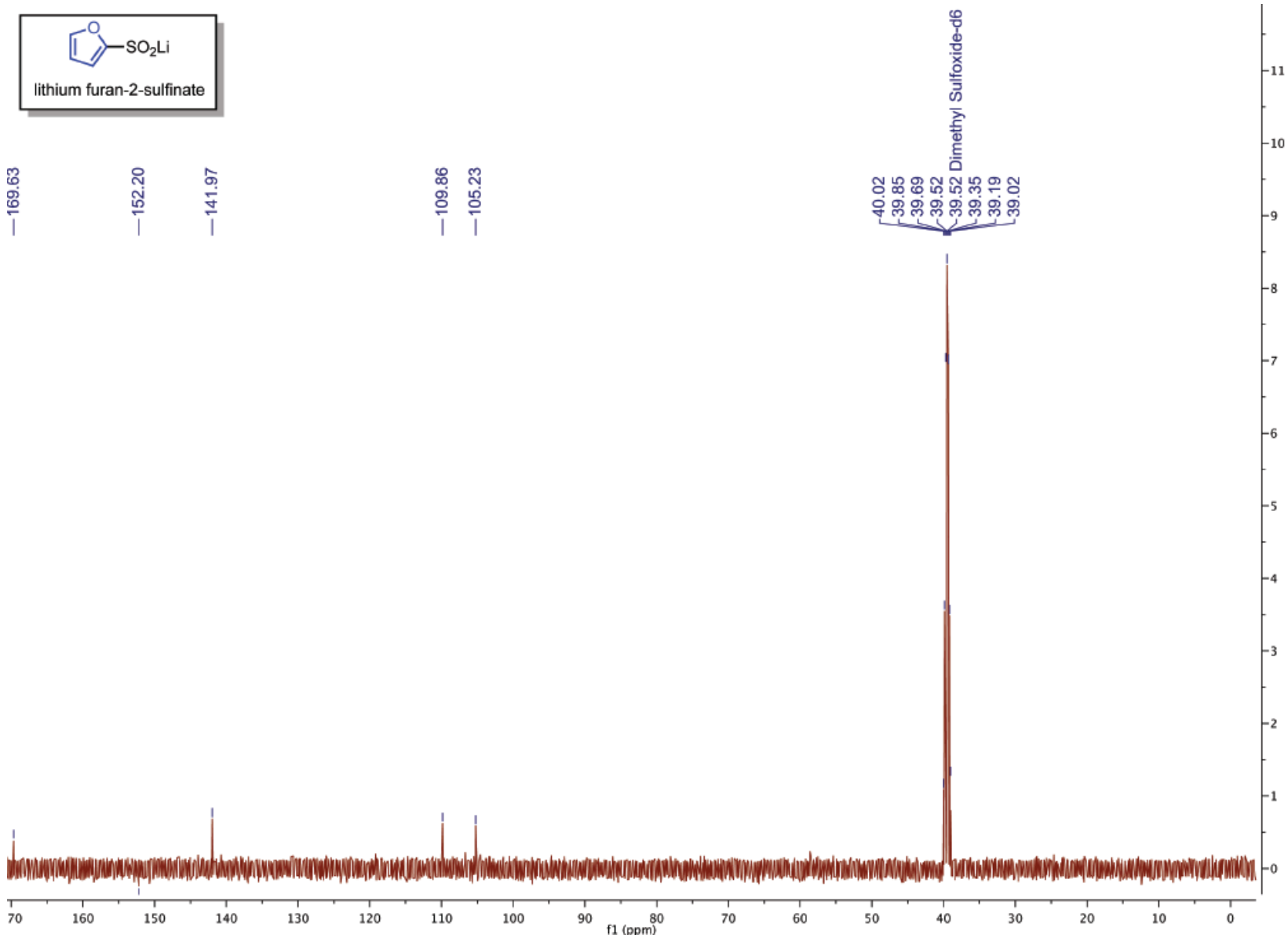

lithium 4-methylthiophene-2-sulfinate
166.70
136.45
125.61
120.94
105.94
40.02
39.85
39.69
39.52
39.52 Dimethyl Sulfoxide-d6
39.35
39.19
39.02
15.55
f1 (ppm)

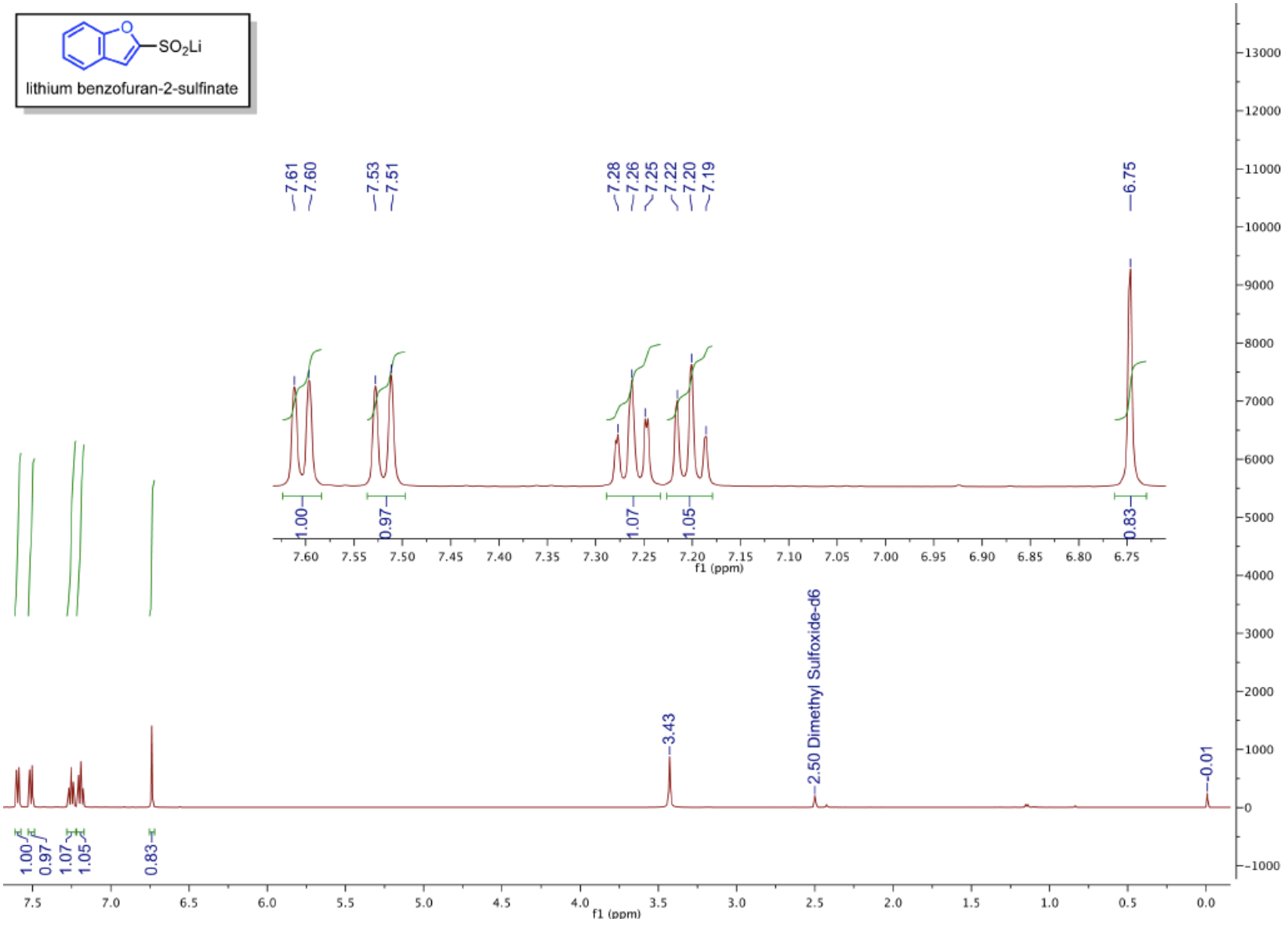

lithium 3-methylthiophene-2-sulfinate
7.20
7.19
6.72
6.71
0.94
1.00
f1 (ppm)
3.35
2.50 Dimethyl Sulfoxide-d6
2.22
0.94
1.00
3.38
f1 (ppm)

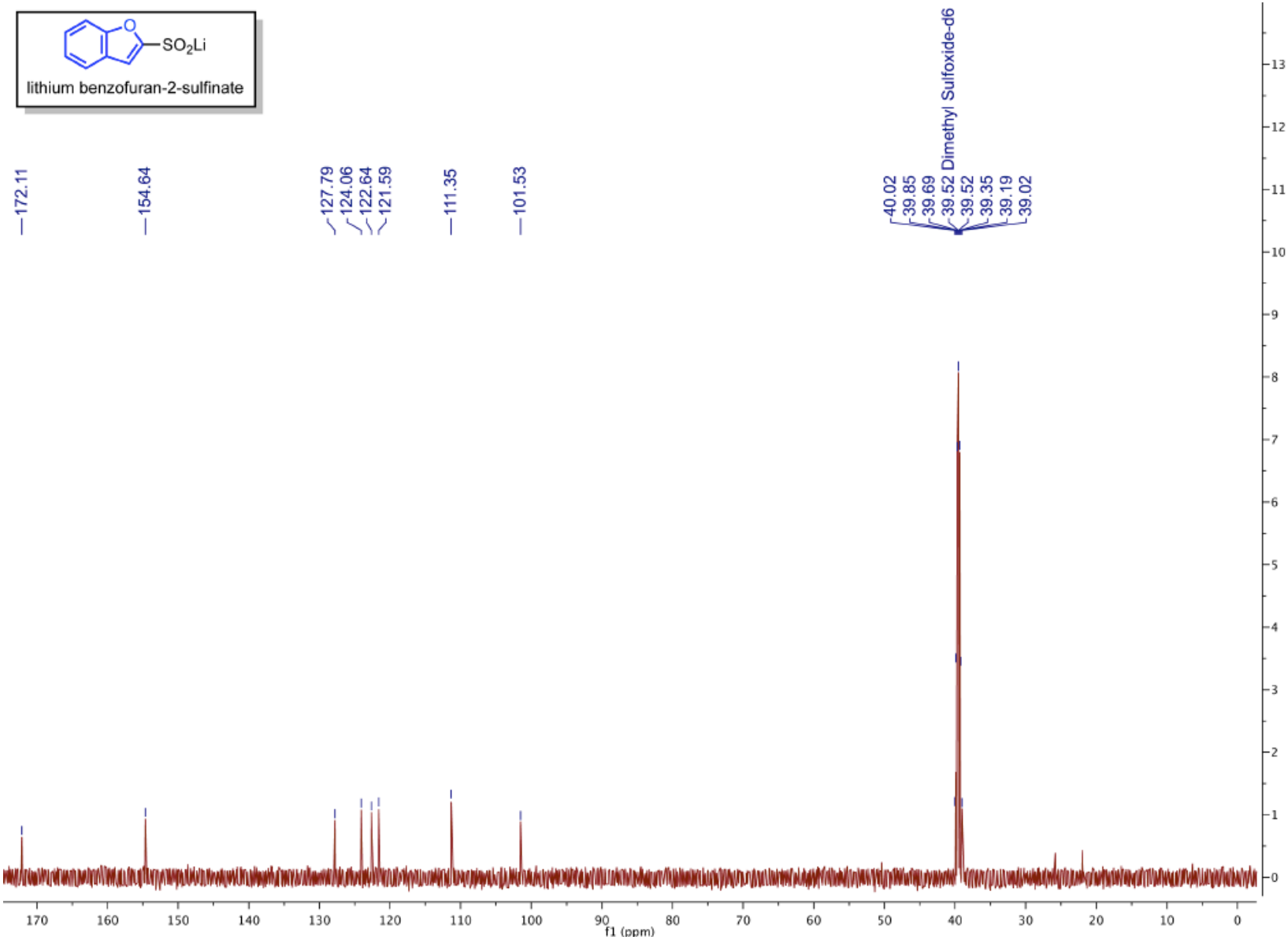

lithium 3-methylthiophene-2-sulfinate
160.55
132.32
130.03
123.32
39.52 Dimethyl Sulfoxide-d6
13.50
f1 (ppm)

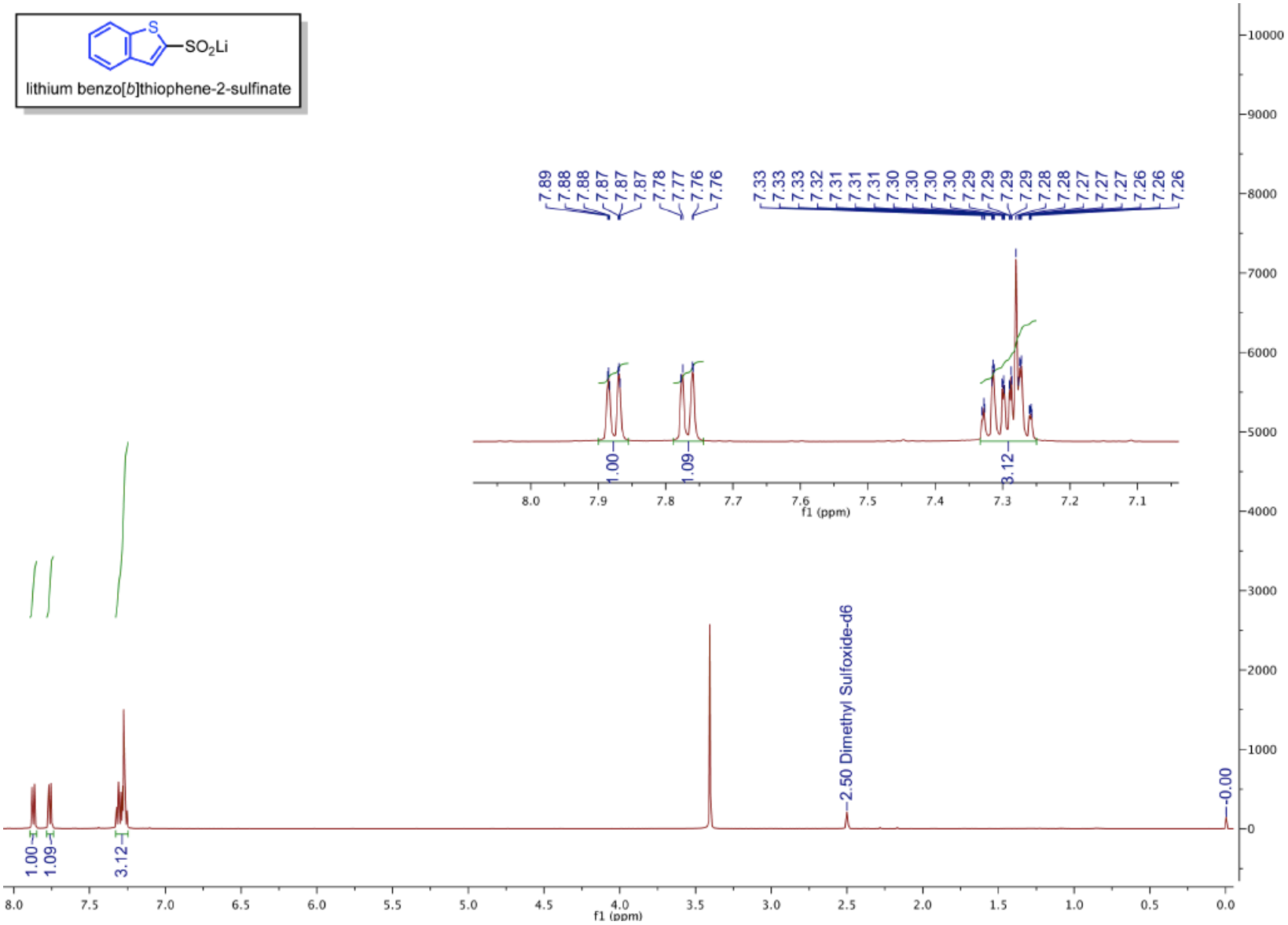
X

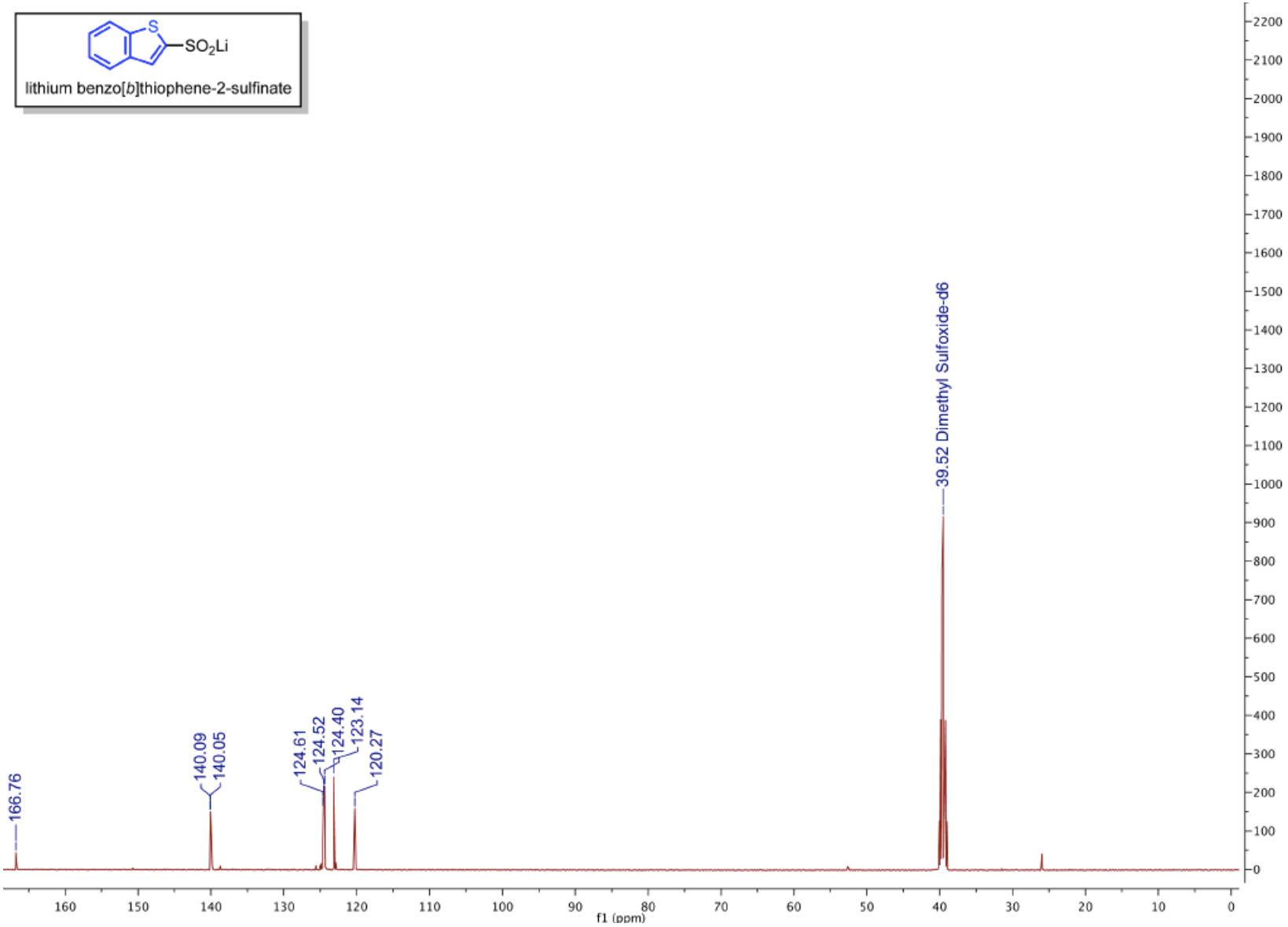

SO2Li
lithium furan-2-sulfinate
7.52
6.36
6.36
6.36
6.35
6.31
6.30
1.00
1.14
1.03
2.50 Dimethyl Sulfoxide-d6
f1 (ppm)

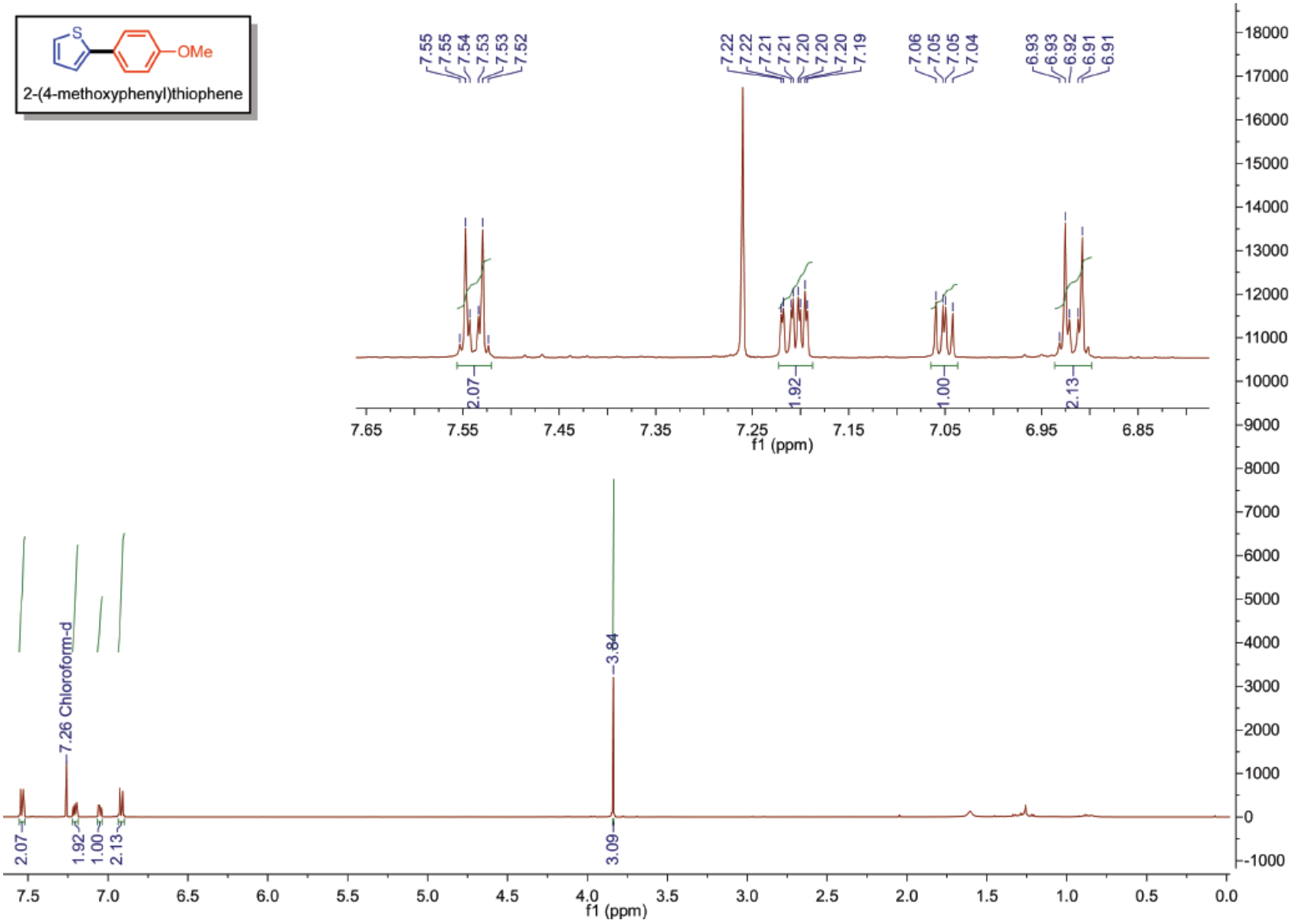

SO2Li
lithium furan-2-sulfinate
169.63
152.20
141.97
109.86
105.23
40.02
39.85
39.69
39.52
39.52
39.35
39.19
39.02
Dimethyl Sulfoxide-d6
f1 (ppm)

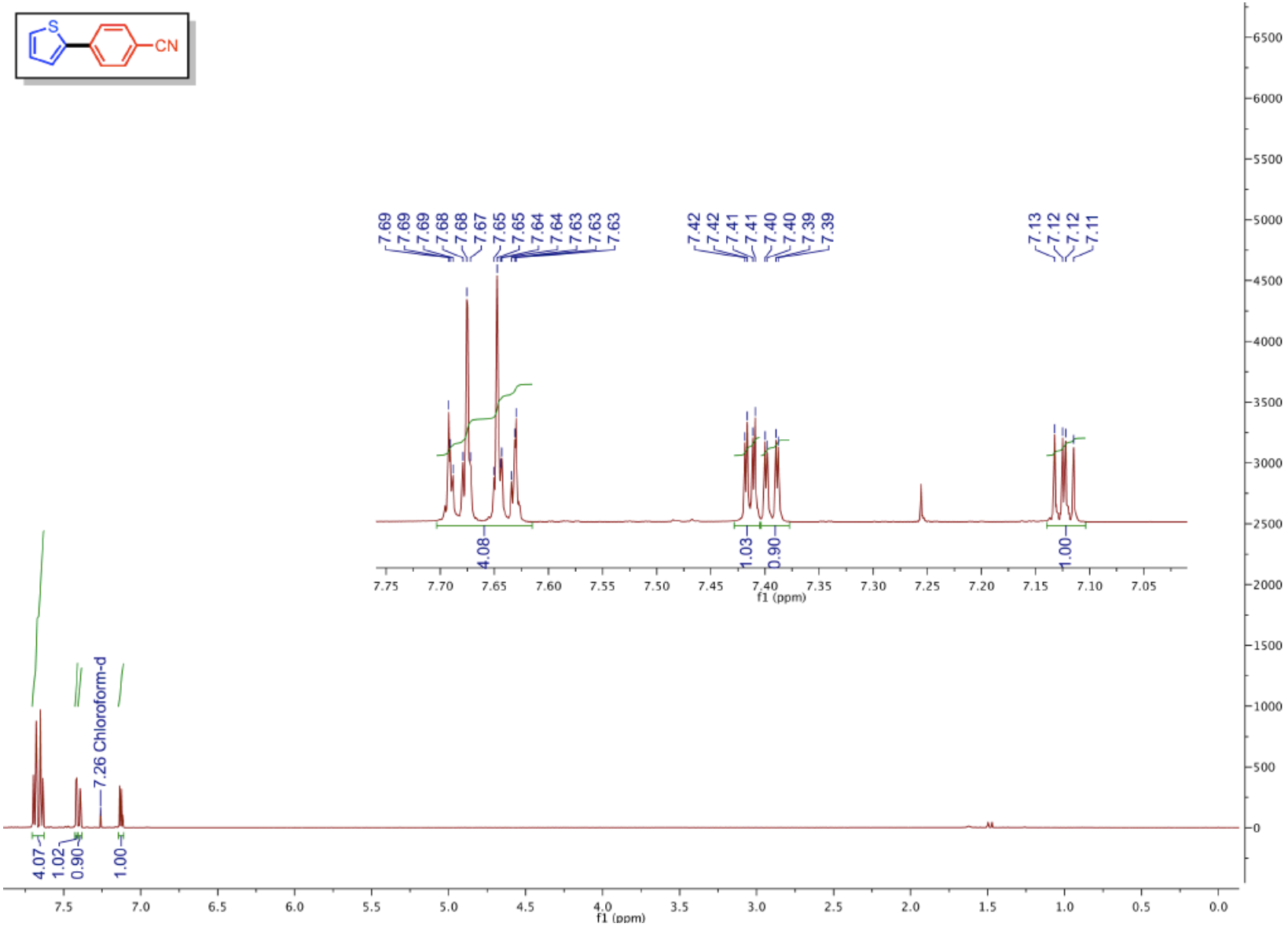

lithium benzofuran-2-sulfinate
7.61
7.60
7.53
7.51
7.28
7.26
7.25
7.22
7.20
7.19
6.75
1.00
0.97
1.07
1.05
0.83
f1 (ppm)
3.43
2.50 Dimethyl Sulfoxide-d6
0.01
f1 (ppm)

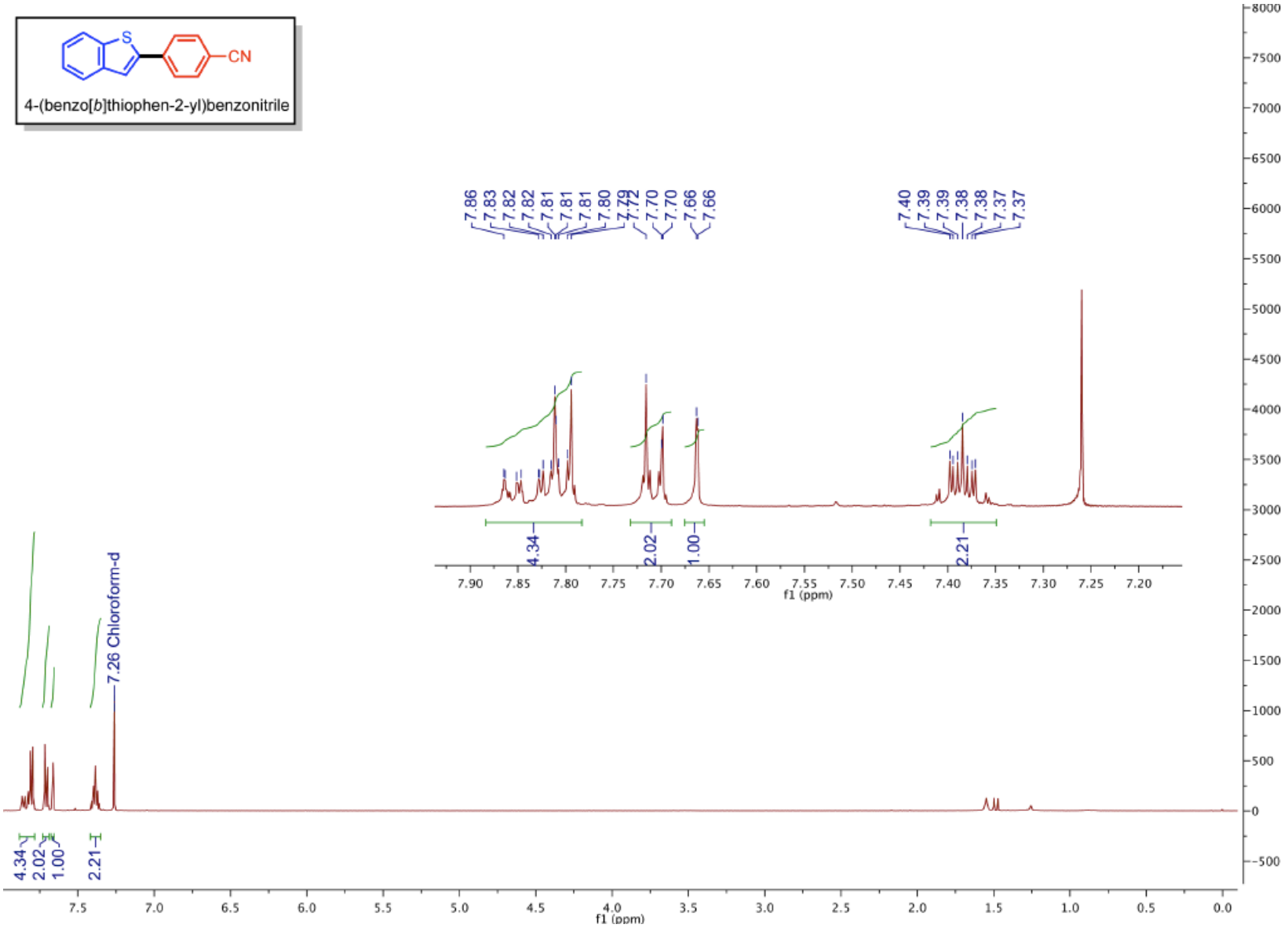

SO2Li
lithium benzofuran-2-sulfinate
172.11
154.64
127.79
124.06
122.64
121.59
111.35
101.53
40.02
39.85
39.69
39.52 Dimethyl Sulfoxide-d6
39.52
39.35
39.19
39.02
f1 (ppm)

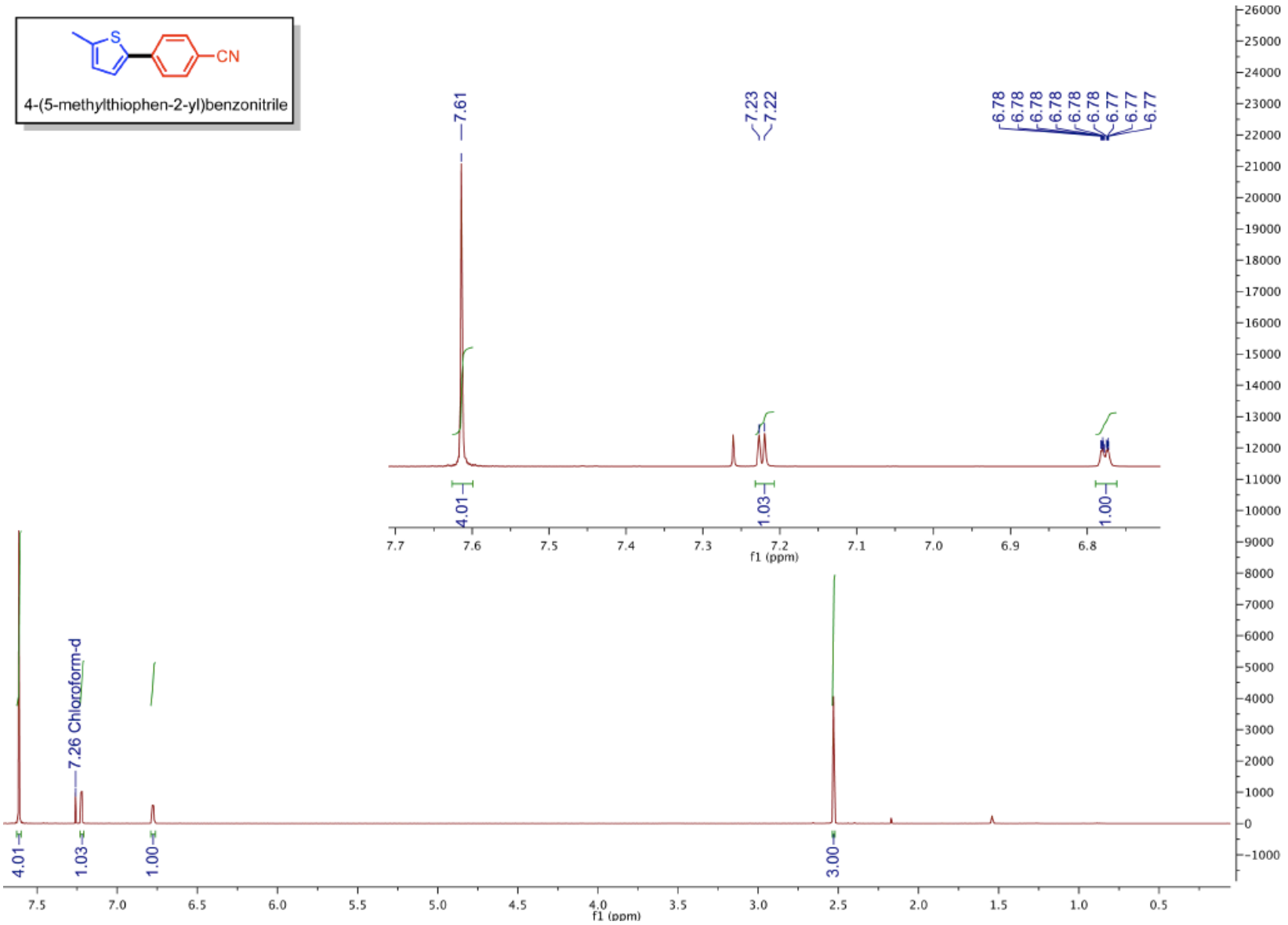

lithium benzo[b]thiophene-2-sulfinate
SO2Li
S
7.89
7.88
7.88
7.87
7.87
7.87
7.78
7.77
7.76
7.76
7.33
7.33
7.33
7.32
7.31
7.31
7.31
7.30
7.30
7.30
7.30
7.29
7.29
7.29
7.29
7.28
7.28
7.27
7.27
7.27
7.26
7.26
7.26
1.00
1.09
3.12
f1 (ppm)
2.50 Dimethyl Sulfoxide-d6
0.00

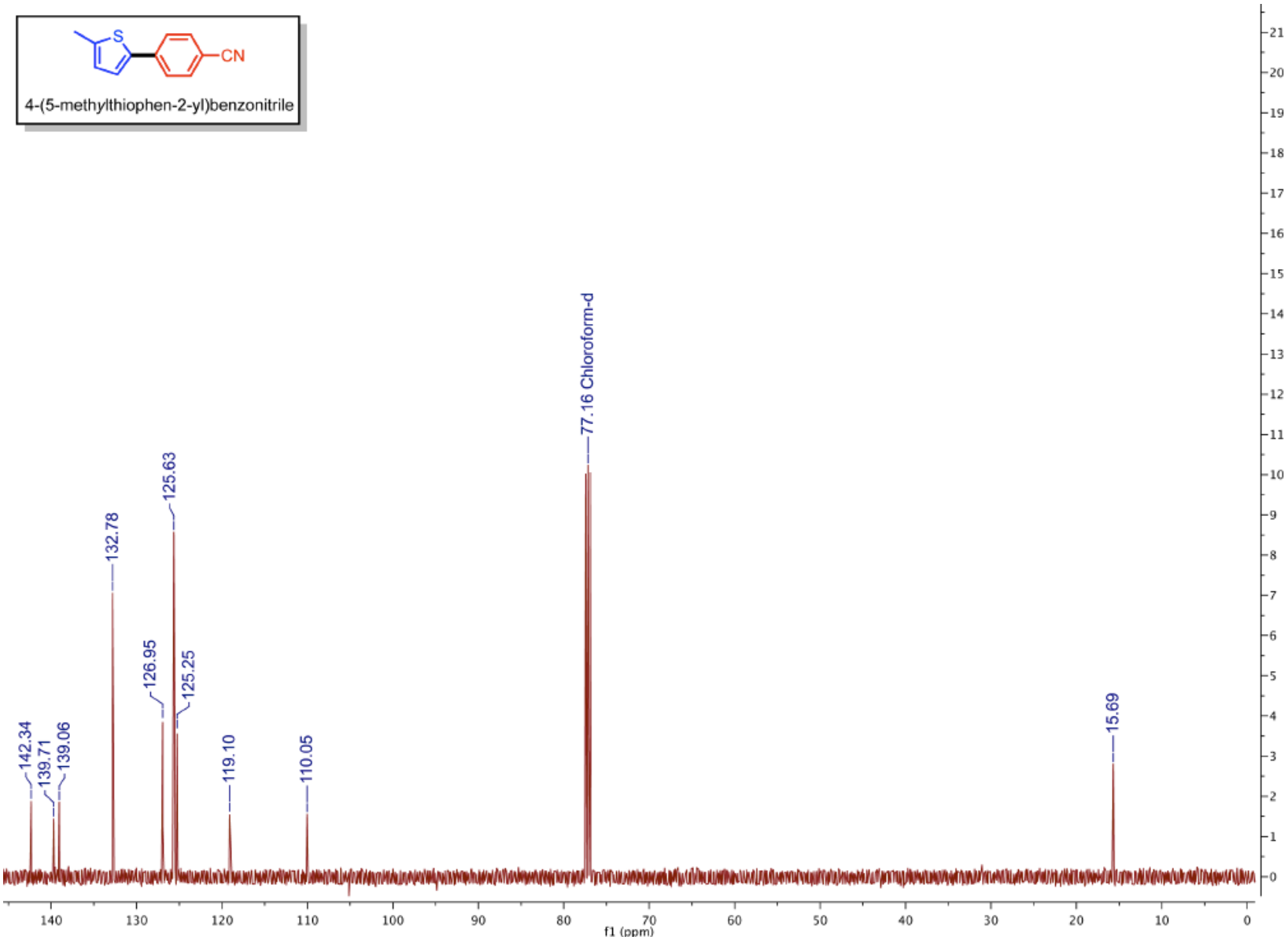

lithium benzo[b]thiophene-2-sulfinate
166.76
140.09
140.05
124.61
124.52
124.40
123.14
120.27
39.52 Dimethyl Sulfoxide-d6
f1 (ppm)

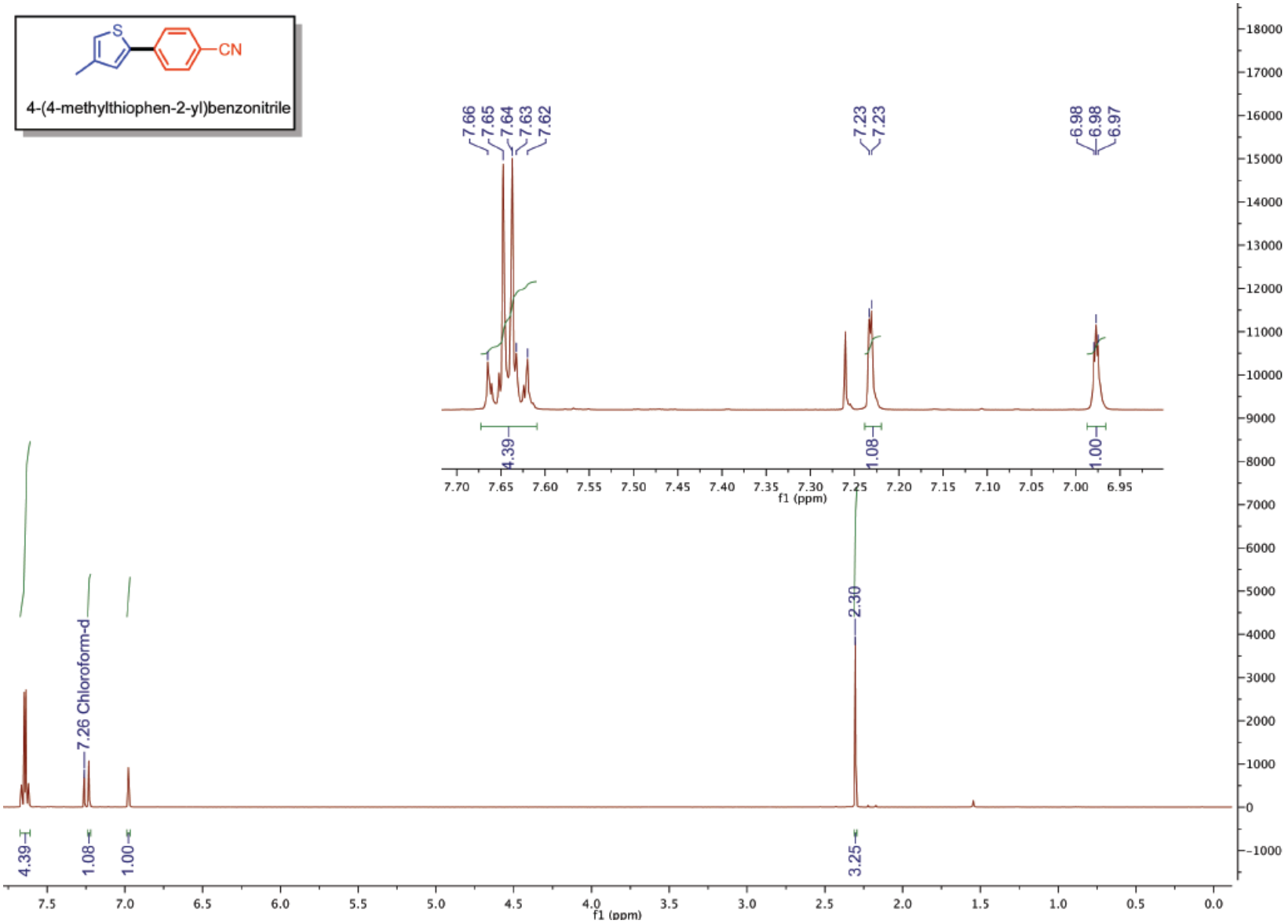

2-(4-methoxyphenyl)thiophene
OMe
S
7.55
7.55
7.54
7.53
7.53
7.52
7.22
7.22
7.21
7.21
7.20
7.20
7.20
7.19
7.06
7.05
7.05
7.04
6.93
6.93
6.92
6.91
6.91
2.07
1.92
1.00
2.13
f1 (ppm)
7.26 Chloroform-d
3.84
2.07
1.92
1.00
2.13
3.09
f1 (ppm)

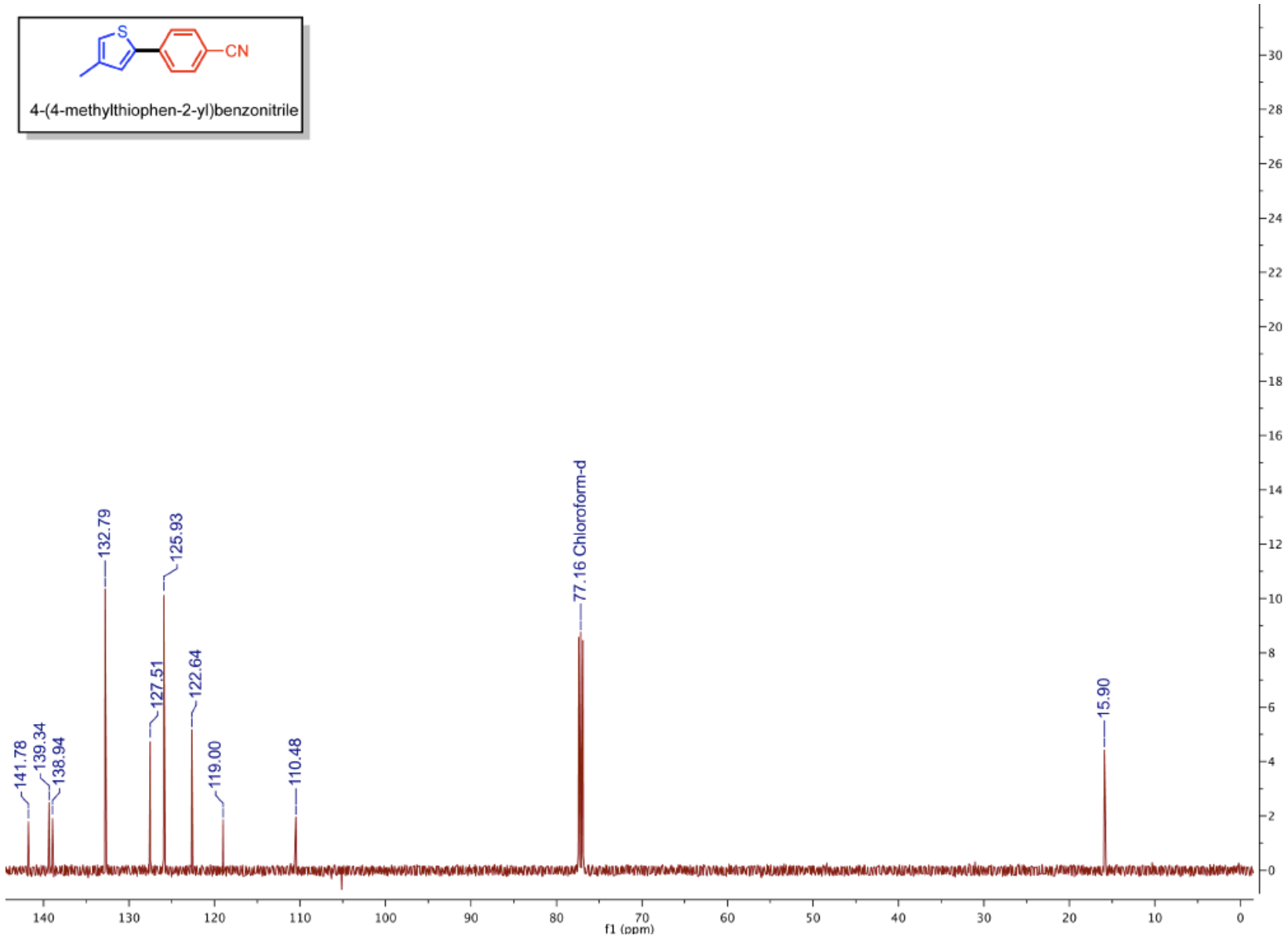

S
CN
7.69
7.69
7.69
7.68
7.68
7.67
7.65
7.65
7.64
7.64
7.63
7.63
7.63
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.39
7.13
7.12
7.12
7.11
4.08
1.03
0.90
1.00
7.75
7.70
7.65
7.60
7.55
7.50
7.45
7.40
7.35
7.30
7.25
7.20
7.15
7.10
7.05
f1 (ppm)
7.26 Chloroform-d
4.07
1.02
0.90
1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0

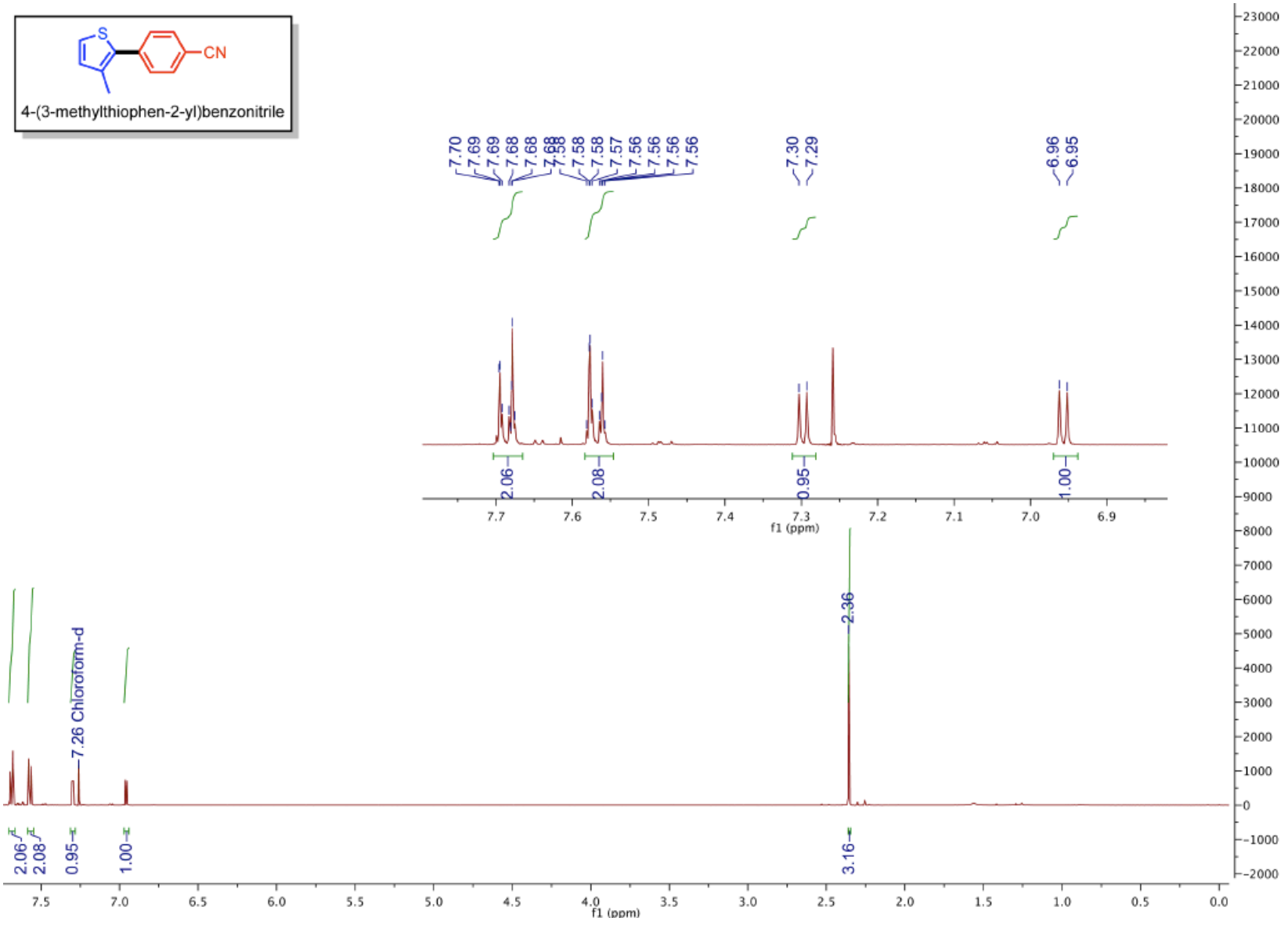

4-(benzo[b]thiophen-2-yl)benzonitrile
S
CN
7.86
7.83
7.82
7.82
7.81
7.81
7.81
7.80
7.70
7.70
7.66
7.66
7.40
7.39
7.39
7.38
7.38
7.37
7.37
4.34
2.02
1.00
2.21
7.26 Chloroform-d
f1 (ppm)

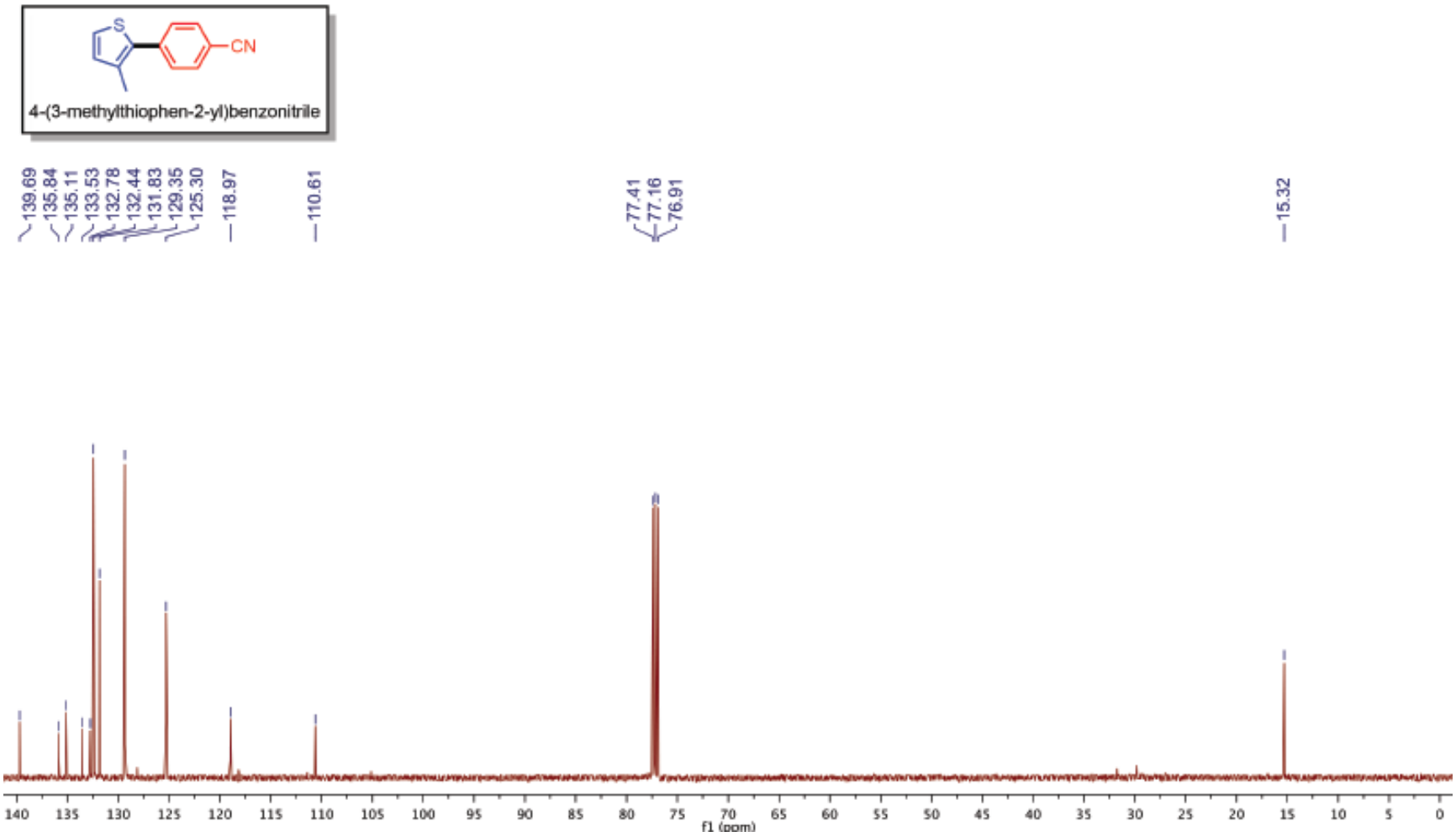

4-(5-methylthiophen-2-yl)benzonitrile
S
CN
7.61
7.23
7.22
6.78
6.78
6.78
6.78
6.78
6.77
6.77
6.77
4.01
1.03
1.00
f1 (ppm)
7.26 Chloroform-d
4.01
1.03
1.00
3.00
f1 (ppm)

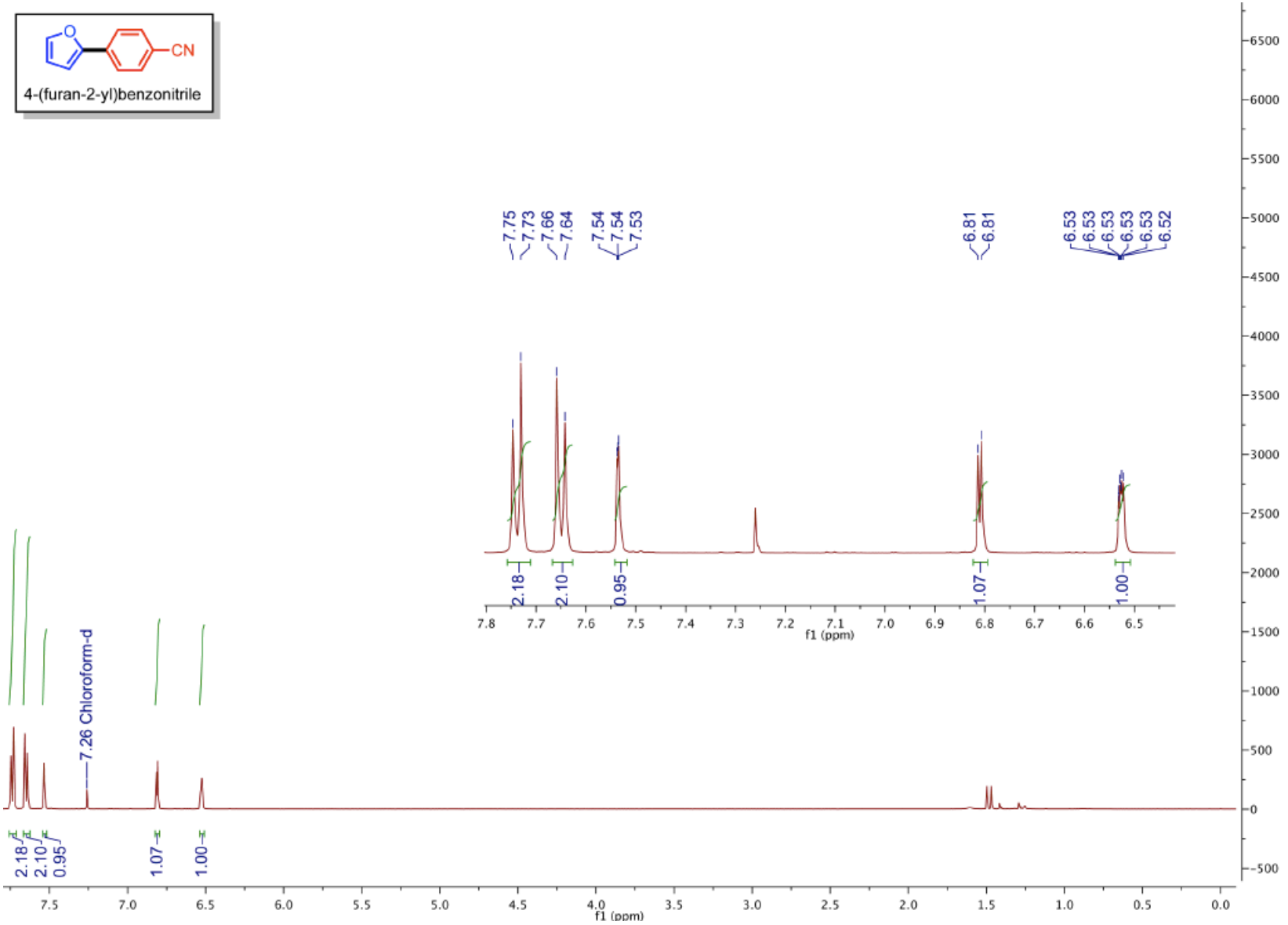

4-(5-methylthiophen-2-yl)benzonitrile
S
CN
142.34
139.71
139.06
132.78
126.95
125.63
125.25
119.10
110.05
77.16 Chloroform-d
15.69
f1 (ppm)

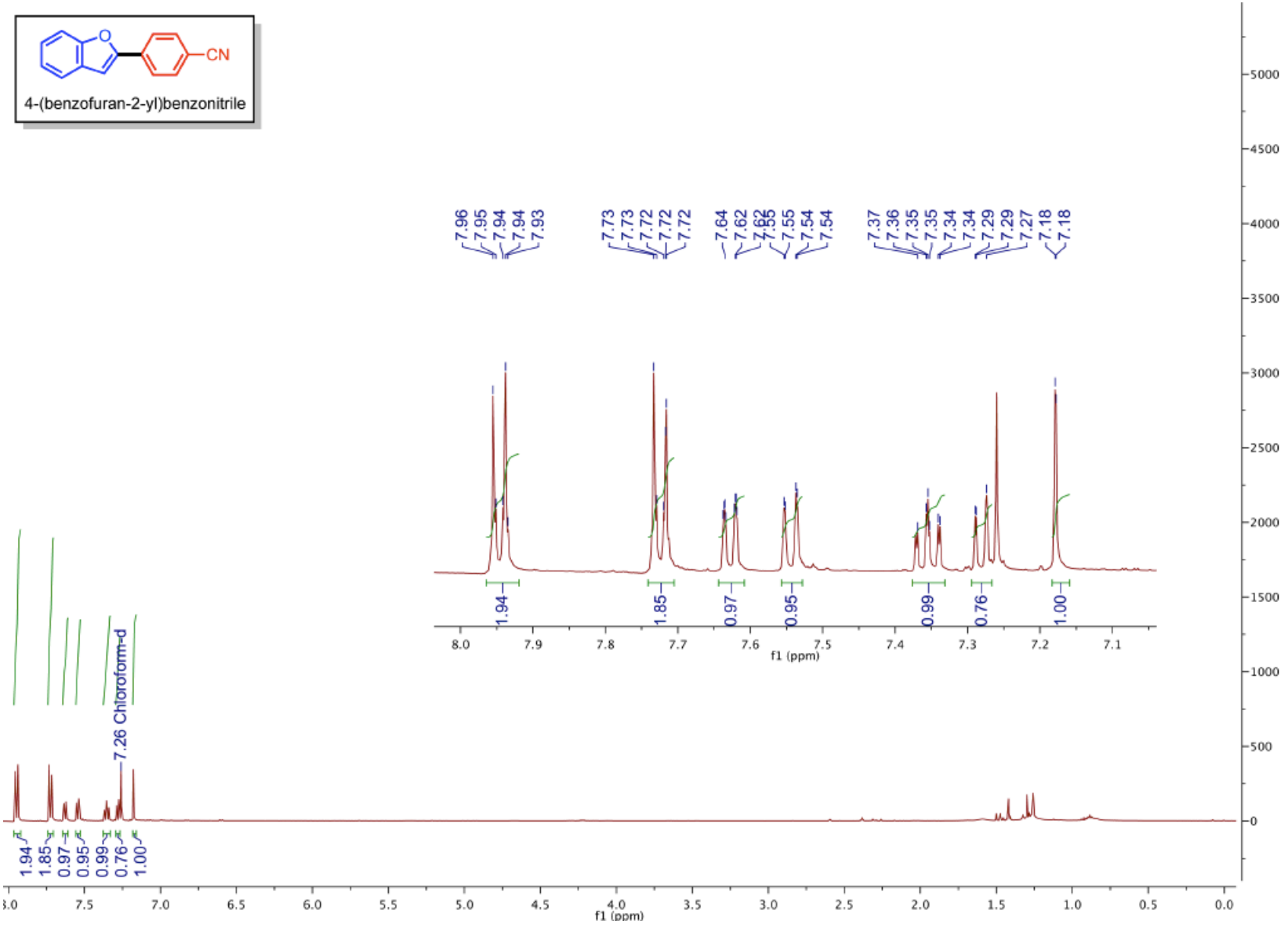

4-(4-methylthiophen-2-yl)benzonitrile
S
CN
7.66
7.65
7.64
7.63
7.62
7.23
7.23
6.98
6.98
6.97
4.39
1.08
1.00
f1 (ppm)
7.26 Chloroform-d
2.30
4.39
1.08
1.00
3.25
f1 (ppm)

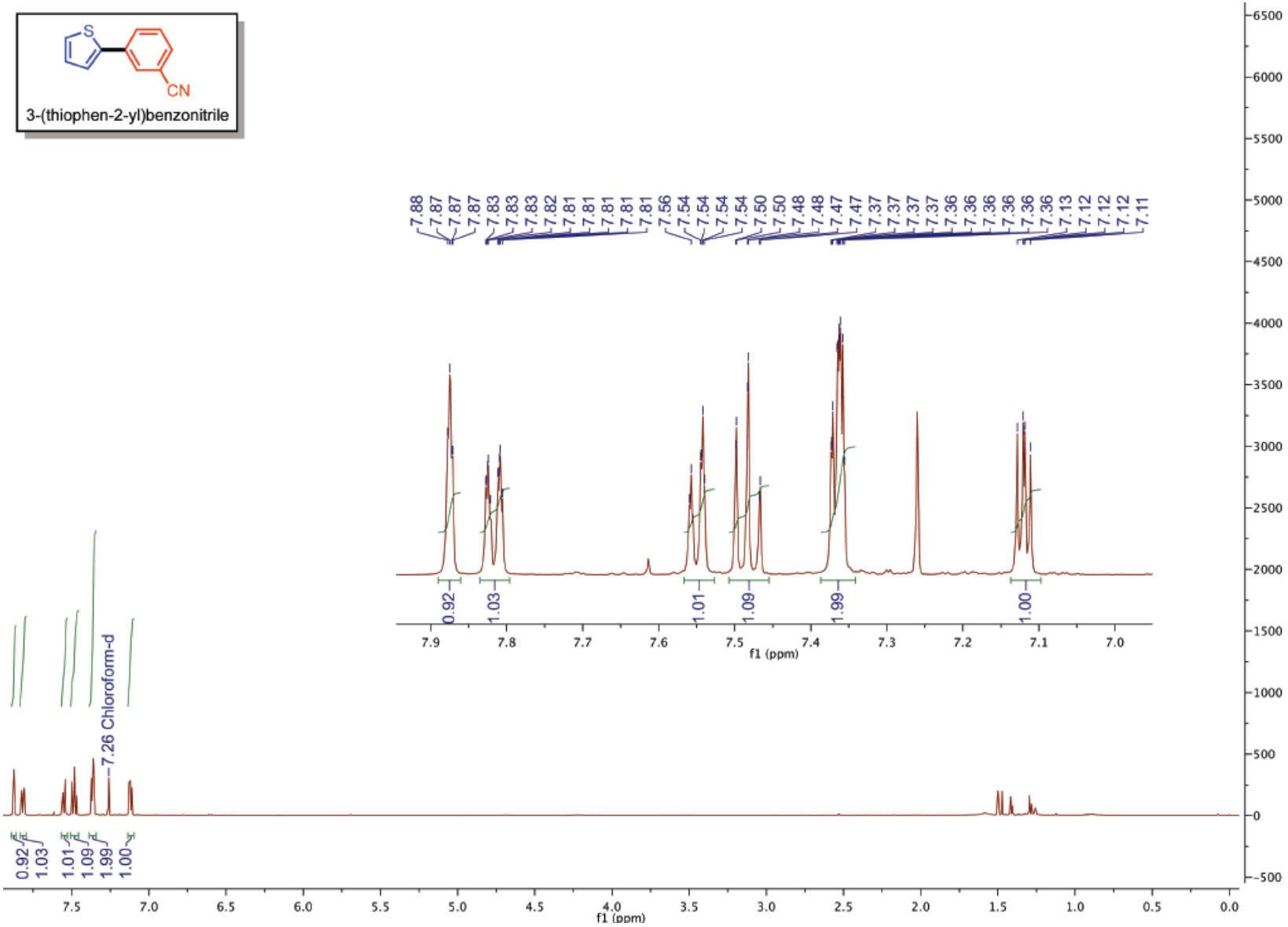

S
CN
4-(4-methylthiophen-2-yl)benzonitrile
141.78
139.34
138.94
132.79
127.51
125.93
122.64
119.00
110.48
77.16 Chloroform-d
15.90
f1 (ppm)

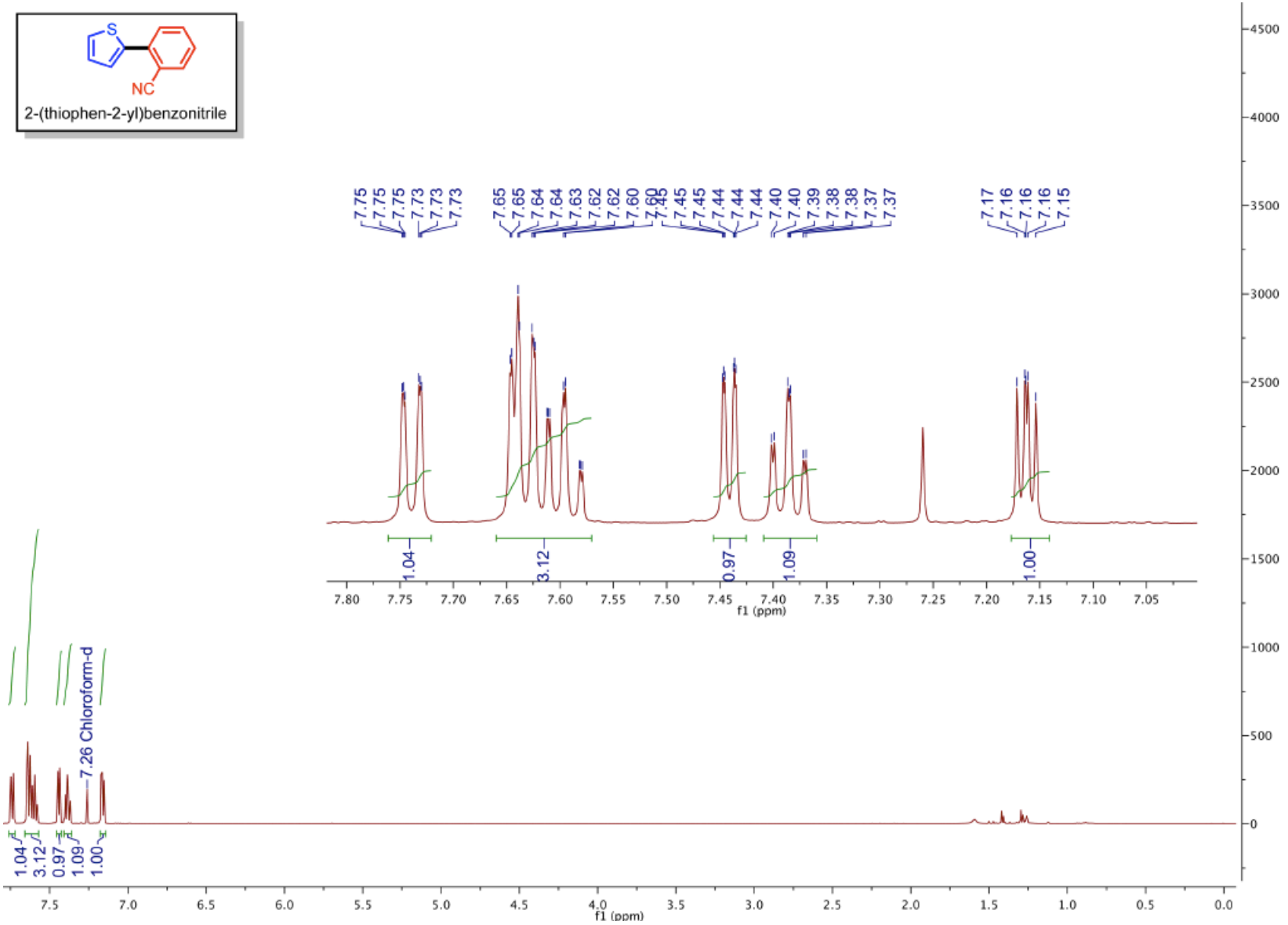

4-(3-methylthiophen-2-yl)benzonitrile
S
CN
7.70
7.69
7.69
7.68
7.68
7.58
7.58
7.57
7.56
7.56
7.56
7.30
7.29
6.96
6.95
2.06
2.08
0.95
1.00
f1 (ppm)
7.26 Chloroform-d
2.36
3.16
f1 (ppm)

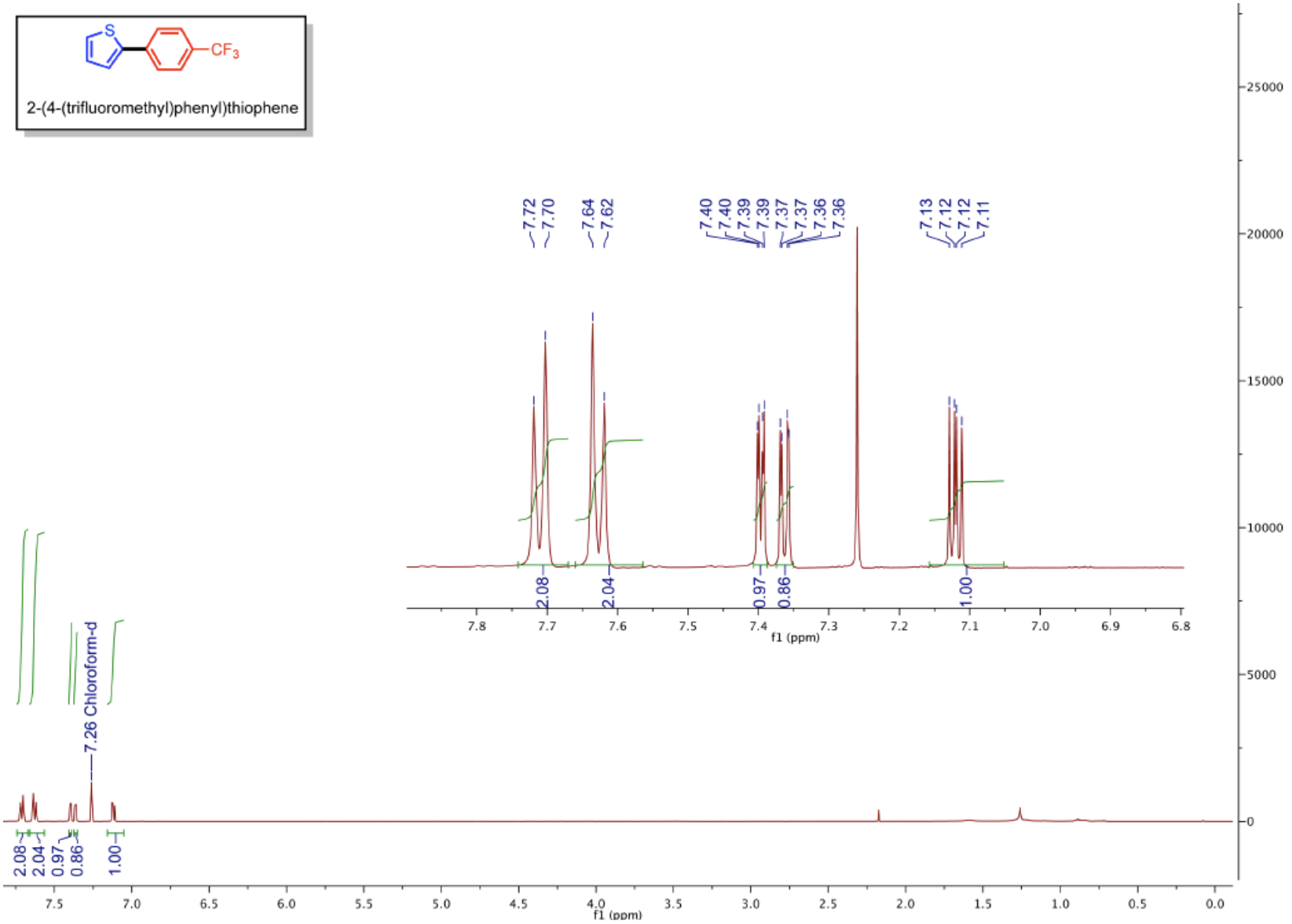

4-(3-methylthiophen-2-yl)benzonitrile
139.69
135.84
135.11
133.53
132.78
132.44
131.83
129.35
125.30
118.97
110.61
77.41
77.16
76.91
15.32
f1 (ppm)

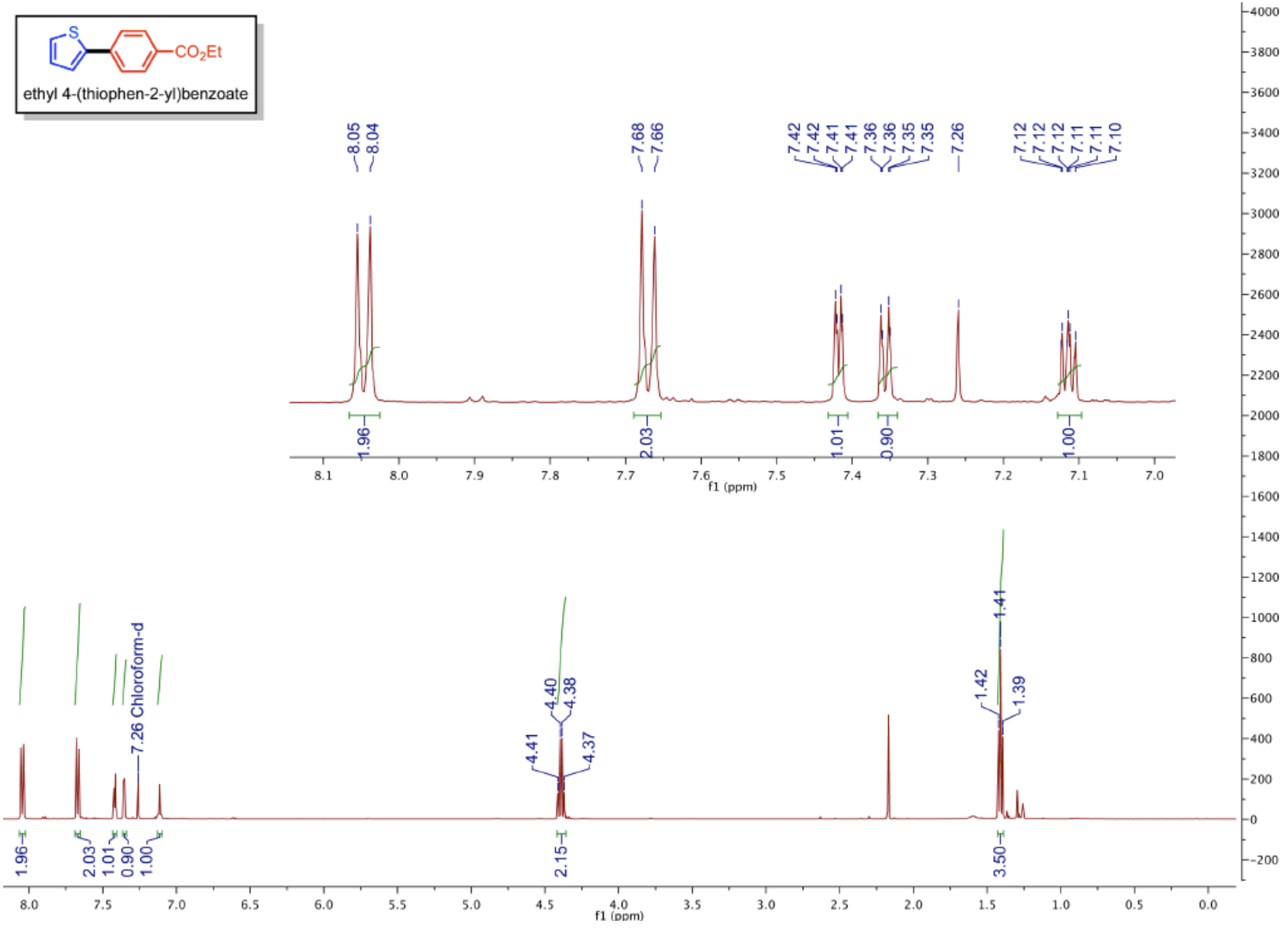

4-(furan-2-yl)benzonitrile
CN
7.75
7.73
7.66
7.64
7.54
7.54
7.53
6.81
6.81
6.53
6.53
6.53
6.53
6.53
6.52
2.18
2.10
0.95
1.07
1.00
f1 (ppm)
7.26 Chloroform-d
2.18
2.10
0.95
1.07
1.00
f1 (ppm)

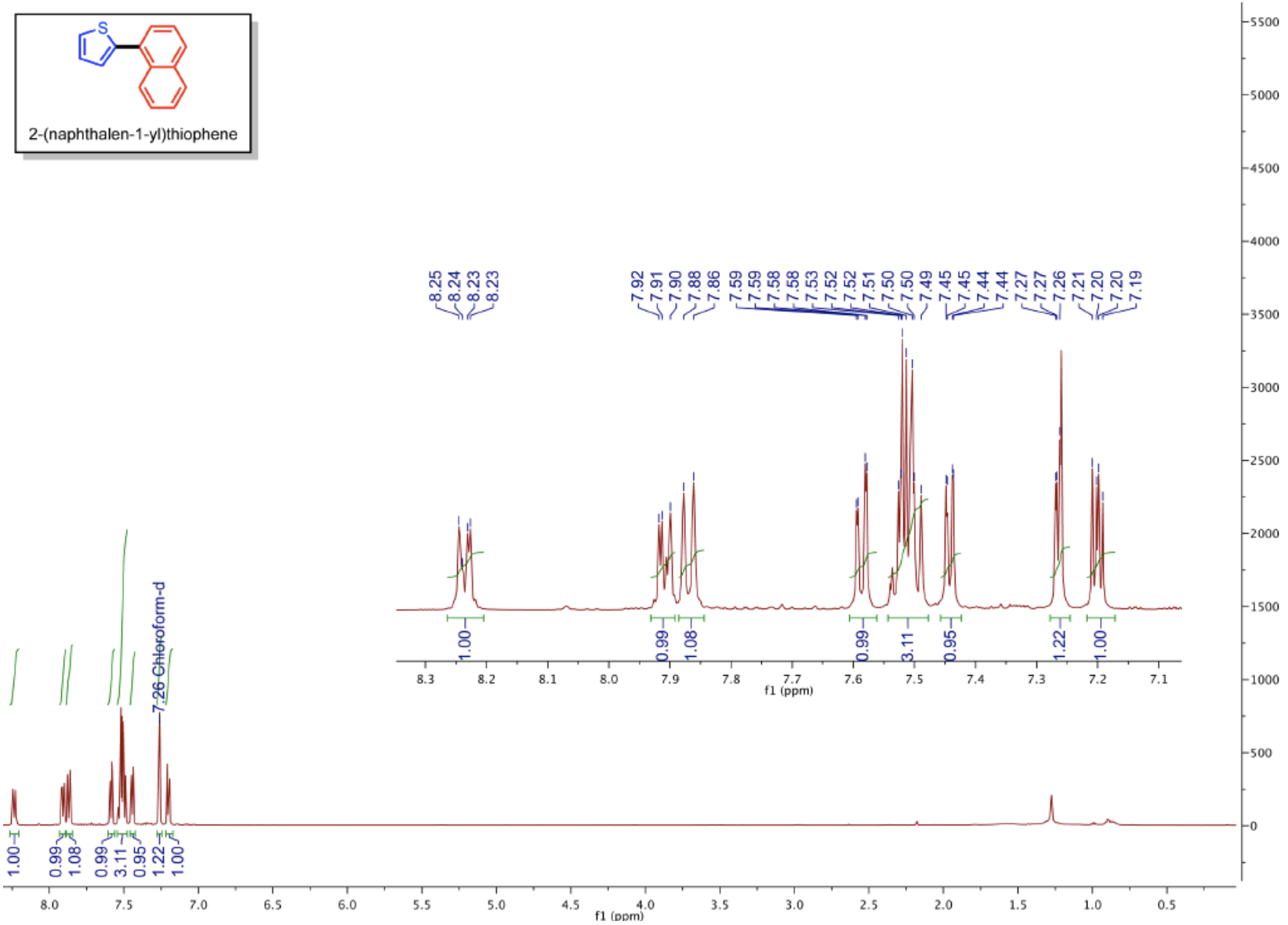

4-(benzofuran-2-yl)benzonitrile
CN
7.96
7.95
7.94
7.94
7.93
7.73
7.73
7.72
7.72
7.72
7.64
7.62
7.55
7.54
7.54
7.37
7.36
7.35
7.35
7.34
7.34
7.29
7.29
7.27
7.18
7.18
1.94
1.85
0.97
0.95
0.99
0.76
1.00
f1 (ppm)
7.26 Chloroform-d
f1 (ppm)


3-(thiophen-2-yl)benzonitrile
S
CN
7.88 7.87 7.87 7.87 7.83 7.83 7.82 7.81 7.81 7.81 7.81 7.56 7.54 7.54 7.54 7.50 7.50 7.48 7.48 7.47 7.47 7.37 7.37 7.37 7.37 7.36 7.36 7.36 7.36 7.36 7.13 7.12 7.12 7.12 7.11
0.92 1.03 1.01 1.09 1.99 1.00
f1 (ppm)
7.26 Chloroform-d
0.92 1.03 1.01 1.09 1.99 1.00
f1 (ppm)


2-(thiophen-2-yl)benzonitrile
S
NC
7.75
7.75
7.75
7.73
7.73
7.73
7.65
7.65
7.64
7.64
7.63
7.62
7.62
7.60
7.60
7.45
7.45
7.44
7.44
7.44
7.40
7.40
7.39
7.38
7.38
7.37
7.37
7.17
7.16
7.16
7.16
7.15
1.04
3.12
0.97
1.09
1.00
7.80
7.75
7.70
7.65
7.60
7.55
7.50
7.45
7.40
7.35
7.30
7.25
7.20
7.15
7.10
7.05
f1 (ppm)
7.26 Chloroform-d
1.04
3.12
0.97
1.09
1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
4500
4000
3500
3000
2500
2000
1500
1000
500
0


2-(4-(trifluoromethyl)phenyl)thiophene
7.72
7.70
7.64
7.62
7.40
7.40
7.39
7.39
7.37
7.37
7.36
7.36
7.13
7.12
7.12
7.11
2.08
2.04
0.97
0.86
1.00
f1 (ppm)
7.26 Chloroform-d
2.08
2.04
0.97
0.86
1.00
f1 (ppm)


ethyl 4-(thiophen-2-yl)benzoate
CO2Et
S
8.05
8.04
7.68
7.66
7.42
7.42
7.41
7.41
7.36
7.36
7.35
7.35
7.26
7.12
7.12
7.12
7.11
7.11
7.10
1.96
2.03
1.01
0.90
1.00
f1 (ppm)
7.26 Chloroform-d
4.41
4.40
4.38
4.37
1.42
1.41
1.39
1.96
2.03
1.01
0.90
1.00
2.15
3.50
f1 (ppm)


2-(naphthalen-1-yl)thiophene
8.25
8.24
8.23
8.23
7.92
7.91
7.90
7.88
7.86
7.59
7.59
7.58
7.58
7.53
7.52
7.52
7.51
7.50
7.50
7.49
7.45
7.45
7.44
7.44
7.27
7.27
7.26
7.21
7.20
7.20
7.19
1.00
0.99
1.08
0.99
3.11
0.95
1.22
1.00
f1 (ppm)
7.26 Chloroform-d
1.00
0.99
1.08
0.99
3.11
0.95
1.22
1.00
f1 (ppm)