

The Design and Investigation of Sulfur-based Reagents for Cross-Coupling Processes

Xinlan Aloise Ford Cook



Wadham College
University of Oxford
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Supervisor: Professor Michael C. Willis

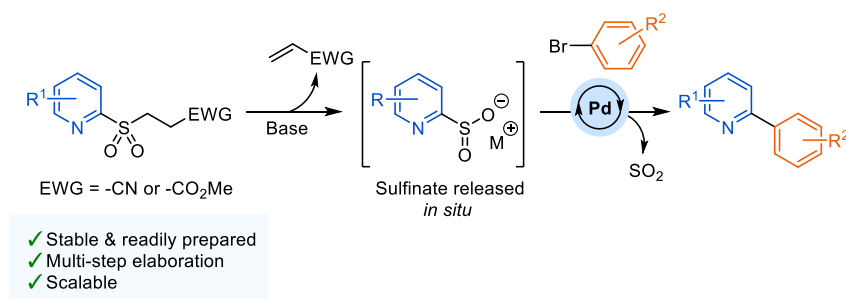
A thesis submitted in partial fulfilment of the requirements for the degree of
Doctor of Philosophy in Organic Chemistry

Abstract

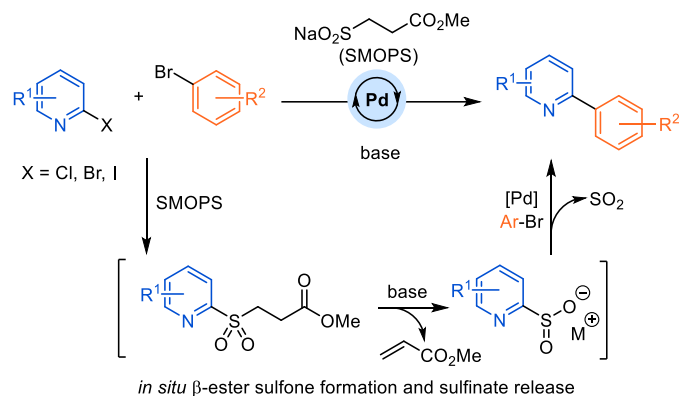
Described in this thesis are new methodologies for the synthesis of important biaryl structures, with a focus on 2-arylpyridines and heteroaryls. This is achieved through the development and application of two novel sulfur-based reagents in palladium-catalysed cross-coupling reactions: firstly, heteroaromatic base-activated latent sulfinates, and secondly, primary aryl sulfinamides.

Chapter 1 is a literature review detailing the challenges and the recent strategies developed to access industrially important 2-(hetero)arylpyridine compounds. The use of (hetero)aryl sulfinates in palladium-catalysed desulfonative cross-coupling reactions is also discussed, as this forms the groundwork for the research described in this thesis.

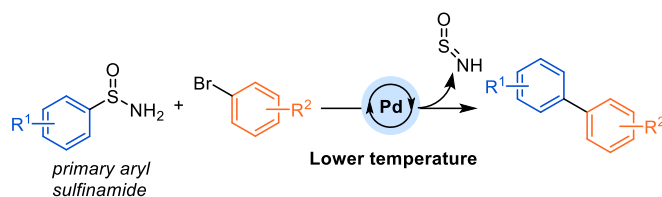
Chapter 2 describes the development and use of base-activated latent sulfinate reagents, notably heteroaromatic β -nitrile and β -ester sulfones, in palladium-catalysed desulfonative ($-\text{SO}_2$) cross-coupling arylation reactions. In this approach, neutral, masked reagents are activated under the basic cross-coupling conditions to give the heteroaryl sulfinate *in situ*, which then reacts with readily available aryl bromides to access a broad range of pyridine biaryls. The robustness of these latent sulfinate reagents is demonstrated and exploited through multi-step transformations to give complex pyridine structures.



Chapter 3 discusses the extension of the latent sulfinate approach from Chapter 2, towards the development of a palladium-catalysed cross-electrophilic coupling of two (hetero)aryl halides, *via* the *in situ* formation of masked sulfinate nucleophilic partner. Initial investigation has demonstrated the feasibility of this process and highlighted strategies for further optimisation.



Chapter 4 details the investigation of primary aryl sulfinamide reagents as nucleophiles in a novel desulfinamidative $C(sp^2)$ - $C(sp^2)$ cross-coupling reaction (-SONH). The use of sulfinamide reagents allows cross-coupling to proceed at a lower temperature than the aryl sulfinate reactions. The viability of carbocyclic aryl sulfinamides in these processes have been established, with the potential for extension to heteroaryl nucleophiles in the future.



Chapter 5 summaries the research in this thesis and suggests potential areas for future work.

Chapter 6 presents the experimental data and procedures for this research.

Declaration

I, Xinlan Cook, hereby declare that the work described in this thesis is entirely my own work, except where specifically indicated. This thesis has not previously been submitted for a degree, diploma or any other qualification at the University of Oxford or elsewhere.

A handwritten signature in black ink, reading 'Xinlan Cook'. The signature is written in a cursive style with a large initial 'X' and a stylized 'C'.

Xinlan Cook

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First, and foremost, I would like to give the biggest thanks to Prof. Michael Willis (aka Mike or M) for being a wonderful supervisor, offering continued guidance, encouragement, and support (especially during these ‘unprecedented times’). I am forever grateful for having had the opportunity to be a part of this research team, and these last four years have been instrumental in my development as a chemist. Thank you!

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Abbreviations and acronyms

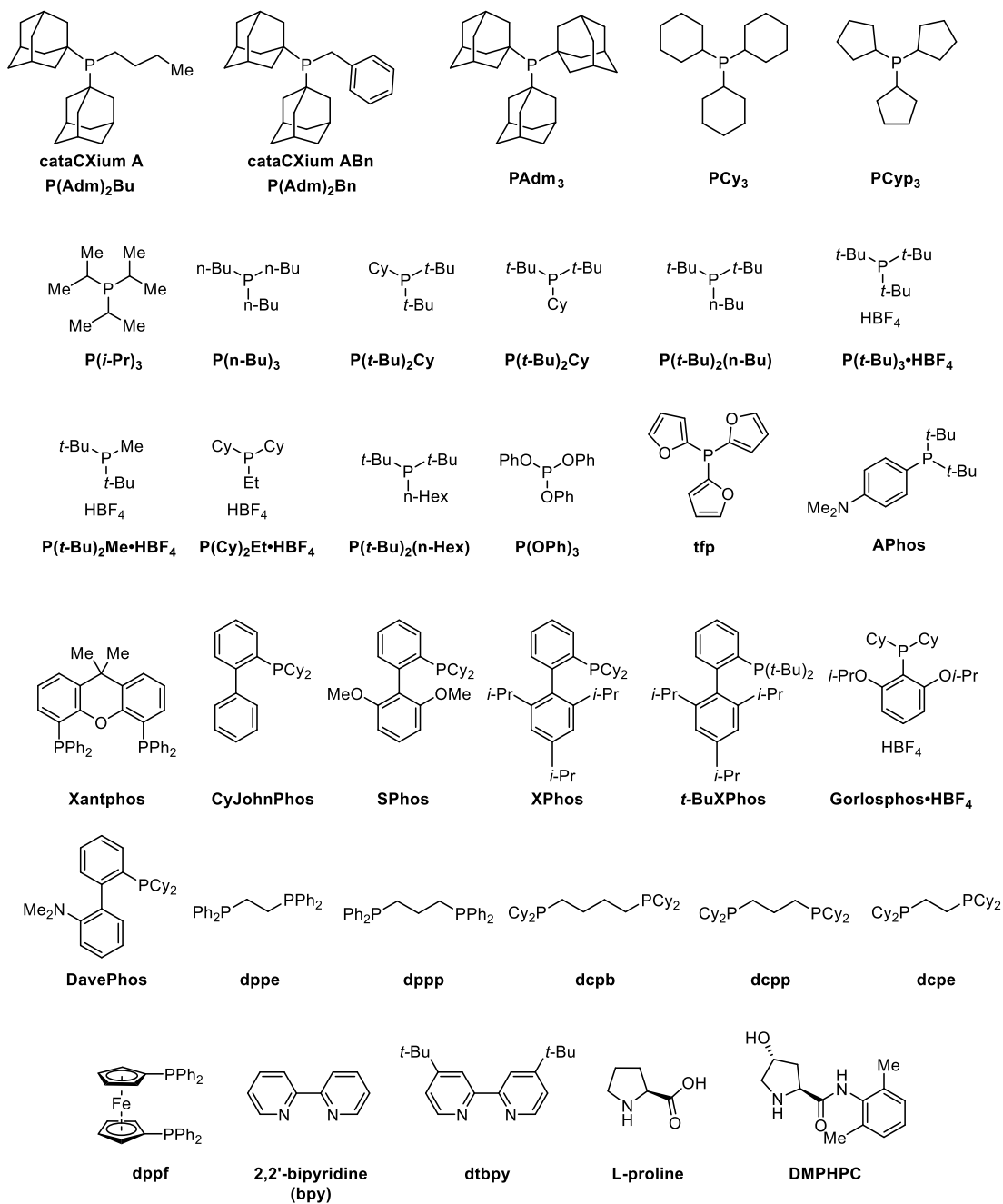
Ac	Acetyl
Adm.	Adamantyl
app.	Apparent
aq.	Aqueous
Ar	Aryl
BMS	Borane dimethylsulfide complex
Boc	<i>tert</i> - Butyloxycarbonyl
bp	Boiling point
br	Broad
Bu	Butyl
cat	Catalyst
cod	1,5-cyclooctadiene
Cy	Cyclohexyl
Cyp	Cyclopentyl
d	Doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DABSO	DABCO- <i>Bis</i> (SO ₂) adduct
DCM	Dichloromethane
DIPEA	<i>N, N'</i> -Diisopropylethylamine
DMA	<i>N, N</i> -Dimethylacetamide
DMEDA	1,2-dimethylethylenediamine
DMF	<i>N, N</i> -Dimethylformamide
DMP	Dess-Martin periodinane

DMSO	Dimethyl sulfoxide
E ₁ CB	Elimination (unimolecular) conjugate base
EI	Electron ionisation
equiv.	Equivalent(s)
Et	Ethyl
ESI	Electrospray Ionisation
EWG	Electron-withdrawing group
g	Gram(s)
h	Hour(s)
Het	Heteroaryl
HRMS	High Resolution Mass Spectrometry
HPLC	High Performance Liquid Chromatography
HTS	High throughput screening
Hz	Hertz
<i>i</i>	<i>iso</i>
IR	Infrared Spectrometry
<i>J</i>	Coupling constant (Hz)
LRMS	Low resolution mass spectrometry
<i>m</i>	<i>meta</i>
m	Multiplet or Mili (10 ⁻³)
M	Molar
Me	Methyl
MIDA	<i>N</i> -methyiminodiacetic acid
mol	Mole
mp	Melting point

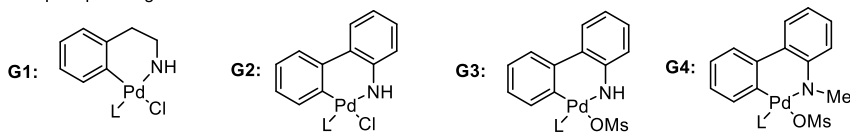
<i>m/z</i>	Mass to charge ratio
NBD	Norbornadiene
NMP	<i>N</i> -methyl pyrrolidone
NMR	Nuclear magnetic resonance
nr	No reaction
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
PDEA	<i>N</i> -phenyldiethanolamine
PET	Positron emission tomography
Petrol	Petroleum ether (40 – 60 °C)
pin	Pinacol
ppm	Parts per million
Ph	Phenyl
Pr	Propyl
Pyr	Pyridine
R	Generic group/ substituent
rbf	Round bottom flask
RDS	Rate determining step
rt	Room temperature
s	Singlet
sat.	Saturated
SCES	Sodium 2-cyanoethane-1-sulfinate
SEM	Trimethylsilylethoxymethyl
SMC	Suzuki-Miyaura cross-coupling
SMOPS	Sodium 3-methoxy-3-oxopropane-1-sulfinate

S _N 2	Nucleophilic bimolecular substitution
S _N Ar	Nucleophilic aromatic substitution
t	Triplet
<i>t</i>	Tertiary
TBA	Tetrabutylammonium
TBDMS	<i>tert</i> -Butyldimethylsilyl
Temp	Temperature
Tf	Triflate
THF	Tetrahydrofuran
TIMSO	SO ₂ -1-methylpyrrolidine adduct
TMS	Trimethylsilyl
TLC	Thin Layer Chromatography
TLS	Turnover limiting step
Tol	Tolyl
vs.	<i>versus</i>
X	(Pseudo)halide (<i>unless specifically stated otherwise</i>)
XEC	Cross-electrophile coupling

Ligand Structures



Pd-GX refers to the 'X' generation of the Buchwald palladium precatalysts, with the general structures below.
L = phosphine ligand.



for example, L = cataCXium A or P(Cy)₃

Chapter 1. Introduction

1.1. Prevalence of 2-arylpyridines and introduction to the 2-pyridyl problem

Pyridine-containing biaryls, such as 2-arylpyridines, are important structures in a diverse range of chemical fields,^[1] such as natural products,^[2] medicinal chemistry,^[3] functional materials (photovoltaics, dyes, cages),^[4] agrichemistry^[5] and ligands for metal catalysis^[6] (**Figure 1.1**). On a survey of the most used ring systems in small molecule drugs from 2014, the pyridine core ranked second, after only the benzene ring.^[7] Due to their ubiquitous nature, efficient methods for synthesis of (hetero)arylpyridine frameworks are continually in demand.^[8] Nevertheless, the arylation of pyridines, particularly next to the nitrogen (2-position), remains challenging. The use of 2-pyridyl reagents as nucleophilic coupling partners in transition metal-catalysed cross-coupling is notoriously difficult, with the challenge coined ‘the 2-pyridyl organometallic cross-coupling problem’ by Fagnou and co-workers in 2005.^[1a, 9]

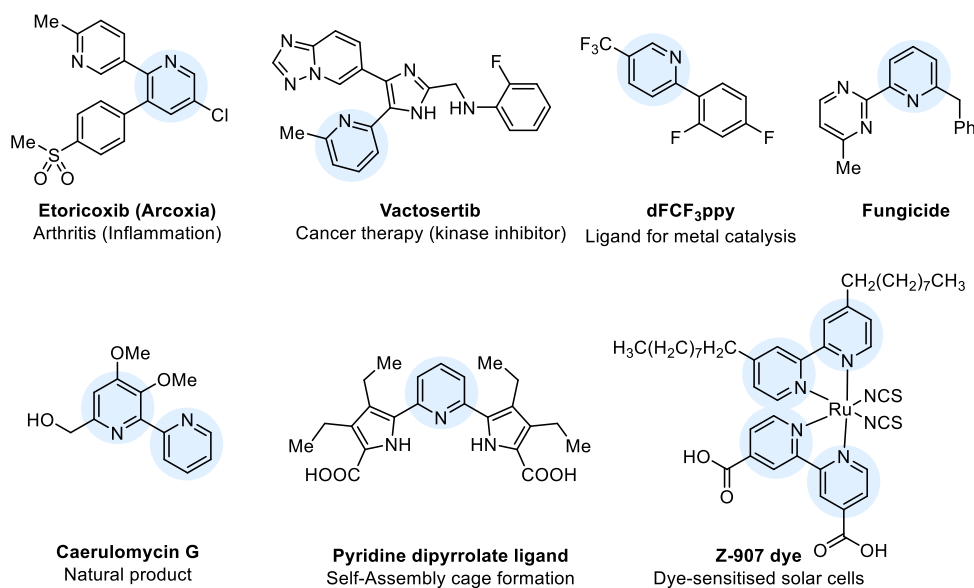


Figure 1.1 A representative selection of industrially and academically important 2-arylpyridine structures.

Transition metal-catalysed processes have revolutionised the formation of carbon(sp²)-carbon(sp²) linkages, due to their tuneability, amenability to modular synthesis, generally broad functional group tolerance and the continually expanding body of research. The popular Suzuki-Miyaura cross-coupling (SMC), which favourably uses less-toxic organoboron reagents under mild conditions, is the most widely employed Pd-catalysed coupling reaction in the pharmaceutical industry.^[10] However, 2-pyridyl boronic acids are infamously difficult to couple, as a result of their instability under cross-coupling conditions. The extent of this challenge is exemplified by the results of a survey of Pfizer's internal electronic laboratory notebook, where less than 8% of all the SMC reactions that used 2-pyridyl boron reagents (358 reactions), gave at least 20% yield of the desired product.^[11] Due to the notoriety of this poor reaction success, methodologies that successfully react 2-pyridyl nucleophiles are generally considered robust. Hence, 2-pyridyl nucleophiles can be viewed as bench-mark substrates, as the strategies developed to enable efficient coupling of these reagents are largely translatable to other challenging heteroaromatic arylations.^[1a]

Regarding terminology used throughout this thesis, transition-metal cross-coupling processes are not conventional nucleophile/electrophile reactions, so instead the electrophilic coupling partner is known as the substrate that undergoes oxidative addition (**A**) and the nucleophilic partner is the species that transmetalates with metal complex (**B**) (**Figure 1.2**). Therefore, the organometallic component ($\text{Ar}'\text{-[M]}$) is referred to as the nucleophile, and the aryl (pseudo)halide (Ar-X) as the electrophile.

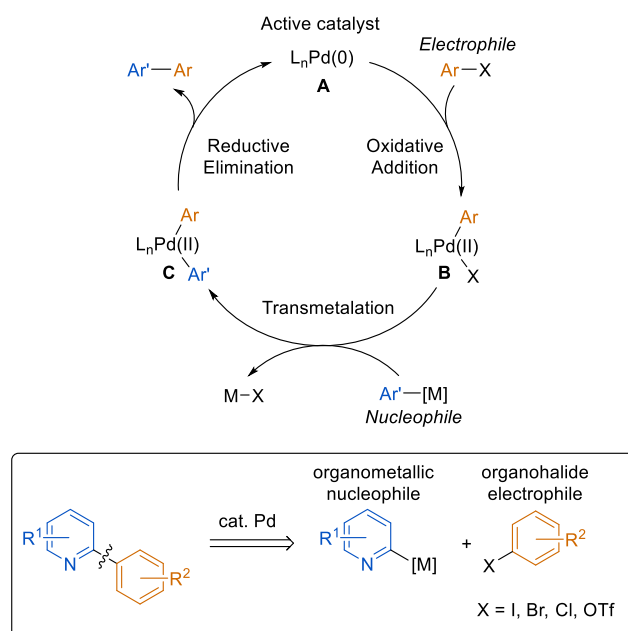


Figure 1.2 Typical catalytic cycle for palladium-catalysed cross-coupling.

In contrast to 2-pyridyl nucleophiles, 2-halopyridines are efficient electrophiles in cross-coupling reactions.^[12] Thus, in some instances, reversing the reagent polarity is favourable to evade the 2-pyridyl problem (**Figure 1.3 A**). Ultimately this is a less attractive strategy, as it does not utilise the vast library of aryl halides that are commercially available. Additionally, without efficient 2-pyridyl nucleophiles, the synthesis of non-symmetrical 2,2'-bipyridines, and other bisazines, remains problematic.

It is worth noting there are other methods for the construction of non-symmetrical bipyridines, albeit less general routes, that circumvent the use of 2-pyridyl nucleophiles

entirely, such as radical mechanisms,^[13] cross-dehydrogenative coupling of pyridines^[14] and Ullmann-type cross-electrophile coupling reactions (**Figure 1.3 B**). Metal-catalysed homocouplings of heteroaryl electrophiles in particular, based on the classical Ullmann reaction, are an established synthetic route to symmetrical 2,2'-bipyridines.^[8, 15] In recent decades interest has grown in cross-electrophile coupling (XEC) arylation reactions, where two electrophiles, commonly aryl halides, react to give the biaryl product.^[16] XEC reactions circumvent many of the stability/ toxicity issues of nucleophilic organometallic reagents, and mostly avoid pre-functionalisation of substrates.^[16] However, a large challenge of XEC reactions is controlling selectivity between the electrophilic partners, particularly when distinguishing between two heteroaryl halides. Weix and co-workers recently advanced this field, overcoming selectivity issues through the innovative development of a bimetallic (Ni/Pd) cross-Ullmann coupling reaction of (hetero)aryl halides and aryl triflates.^[17] In 2021, this approach was extended to the synthesis of unsymmetrical biheteroaryls with the addition of a zinc reductant.^[18] Although many bisazines were synthesised, the scope consisted mainly of moderate to low yields and 2,2'-bipyridine examples were scarce. The synthesis of non-symmetric biheteroaryls and bipyridines *via* cross-electrophile reactions is a promising, yet still developing, area of research, and currently does not provide a general solution to the 2-pyridyl problem.

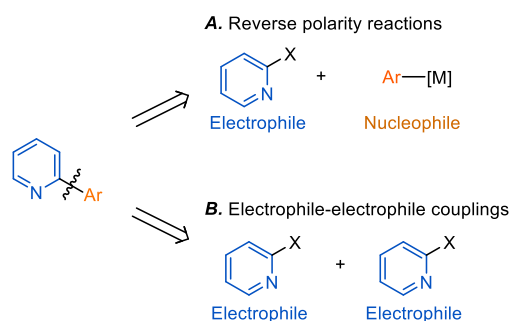


Figure 1.3 Alternative methods to circumvent the use of 2-pyridyl nucleophilic reagents.

Ultimately, transition-metal cross-coupling processes remain unrivalled as swift and tuneable tools for the construction of important unsymmetrical bisazines. As such, continued development of efficient 2-pyridyl reagents is still paramount. Traditional cross-coupling reactions have found varying degrees of success in the synthesis of bipyridines; Stille (Ar-[Sn]), Negishi (Ar-[Zn]), Kumada (Ar-[Mg]) and Hiyama (Ar-SiR₃) processes. There are fewer recent reports using these methods, due to the unfavourable toxicity and/or stability of the organometallic reagents employed, or the development of alternative, more convenient processes. Nonetheless, there is continued innovation towards improving 2-pyridyl arylations using traditional cross-coupling, which are discussed in more detail in three key reviews,^[1a, 8, 19] and consequently will not be covered here.

Detailed in this literature introduction are the main methodologies and recent innovations towards a general solution to the 2-pyridyl organometallic cross-coupling problem. The discussion focuses on the development of 2-pyridyl nucleophiles, application of novel strategies for 2-arylpyridine synthesis, and the advances in Pd-catalysed desulfonative chemistry, framed within this synthetic challenge. For a more detailed discussion, please see a recent review.^[1a]

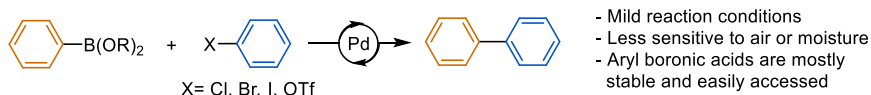
1.2. The Suzuki-Miyaura cross-coupling reaction

1.2.1. The challenges of 2-pyridyl organoboron reagents

The Suzuki-Miyaura cross-coupling (SMC) is one of the most commonly employed tools for C(sp²)-C(sp²) bond formation in both academia and industry.^[20] In SMC arylation reactions, aryl (pseudo)halides are combined with aryl organoboron reagents under palladium-catalysed conditions (**Figure 1.4 A**). The popularity of this process compared

to other cross-coupling reactions, is largely due to the mild reaction conditions, broad functional group tolerance and the use of less toxic, more stable organoboron reagents.^[10] Furthermore, there is a continually growing, extensive body of research into expanding and improving SMC reaction conditions and organoboron reagents.^[21]

A. Suzuki-Miyaura cross-coupling (SMC)



B. Unstable with respect to rapid protodeboronation:

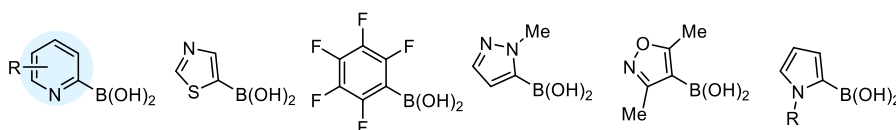


Figure 1.4 (A) The Suzuki-Miyaura cross-coupling and (B) boronic acids that are unstable towards protodeboronation as reported by Lloyd-Jones and co-workers.^[22]

Whereas most boronic acids have found widespread use in SMC reactions, there are several arylboronic acids that exhibit infamously poor reaction success, due to their instability towards protodeboronation (**Figure 1.4 B**).^[22] The most noteworthy of these unstable organoboron nucleophiles are polyfluorinated and heteroaromatic boronic acids, particularly 2-heteroaryl reagents. Indeed, numerous reports using 2-pyridyl boron reagents are plagued with low yields and limited substrate scopes.^[23] Because of the industrial and academic importance of the 2-pyridyl motif, there is particular interest in mitigating the difficulties surrounding the use of 2-pyridyl boron reagents in SMC reactions. Hence, much research has focused on establishing a general approach for the efficient coupling of these reagents, with an emphasis on the development of more stable boron nucleophiles.

The decomposition of unstable arylboronic acids, notably 2-pyridyl boronic acids, has been extensively studied by Lloyd-Jones and co-workers.^[22] In 2016 they reported the

mechanism of 2-pyridyl boronic acid protodeboronation (**Figure 1.5 A**), showing that it proceeds through formation, and subsequent fragmentation, of a key zwitterionic intermediate (**b**).^[22a] The pH-dependence of this process was also studied, with the maximum rate of zwitterion (**b**) formation observed at pH 4 – 8.

When surveying the literature, three primary strategies for circumventing the protodeboronation of 2-pyridyl boronic acids become apparent: (i) addition of a Lewis acid to co-ordinate the pyridine (e.g copper), (ii) using stabilised, masked boronic acids reagents and (iii) substitution at the 6-position of the 2-pyridyl reagent (**Figure 1.5 B**). These approaches are commonly used in conjunction with each other to enable efficient SMC reactions using 2-pyridyl boron nucleophiles, which will be discussed in the following sections **1.2.3 – 1.2.4**.

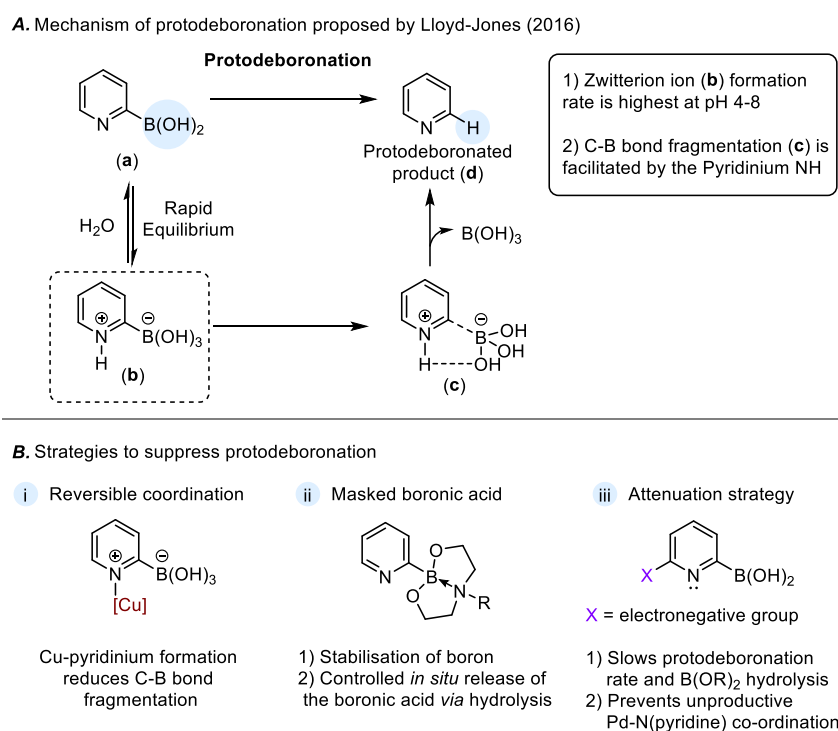
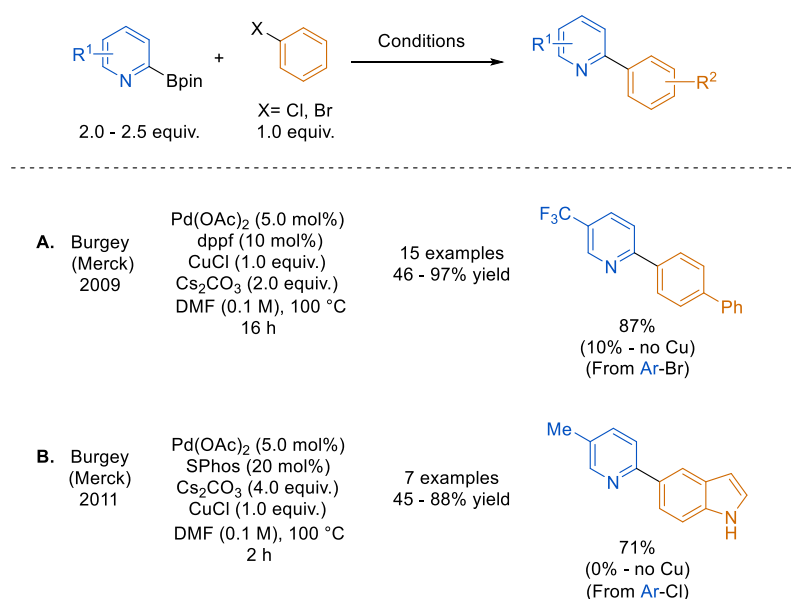


Figure 1.5 (A) Protodeboronation mechanism of 2-pyridyl boronic acids and (B) strategies to attenuate protodeboronation of 2-pyridyl boron nucleophiles.

1.2.2. Copper assisted Suzuki-Miyaura reactions

Deng, Paone and co-workers successfully developed a copper-assisted SMC of 2-pyridyl boronates and aryl halides (**Scheme 1.1 A**).^[24] The use of a cheap, stoichiometric copper(I) chloride was shown to be essential for achieving high yields of 2-aryl pyridines, offering a straightforward solution to the poor reactivity of 2-pyridyl reagents. The scope was further expanded and the reaction time reduced by employing SPhos ligand (**Scheme 1.1 B**).^[25] Studies conducted years later by Lloyd-Jones suggest that the reversible coordination of the copper to the pyridine suppresses the formation of the aforementioned key zwitterionic intermediate (**Figure 1.5**), and thus inhibits the protodeboronation pathway.^[22a]



Scheme 1.1 Copper(I)-assisted SMC reaction of 2-pyridyl boron nucleophiles.

1.2.3. Alternative 2-pyridyl boron nucleophiles

Over the last few decades, a variety of novel boron-derived nucleophiles have been developed (**Figure 1.6 B - D**). Many of these alternative organoboron reagents act as

slow-release, masked boronic acids, wherein the boronic acid is stabilised by a protecting group and only released under select cross-coupling conditions (**Figure 1.6 A**). With tailoring of the reaction conditions, this allows a controlled release of the boronic acid *in situ*. Thus, these reagents can circumvent, or at least slow the rate of protodeboronation. Another strategy is to use more stable boron reagents directly in SMC reactions, that do not proceed through hydrolysis to the boronic acid. These reagents will only be discussed in relation to the 2-pyridyl problem; for a more detailed overview of the design, synthesis and application of these species please see reviews from Lennox and Lloyd -Jones.^[21b, 26]

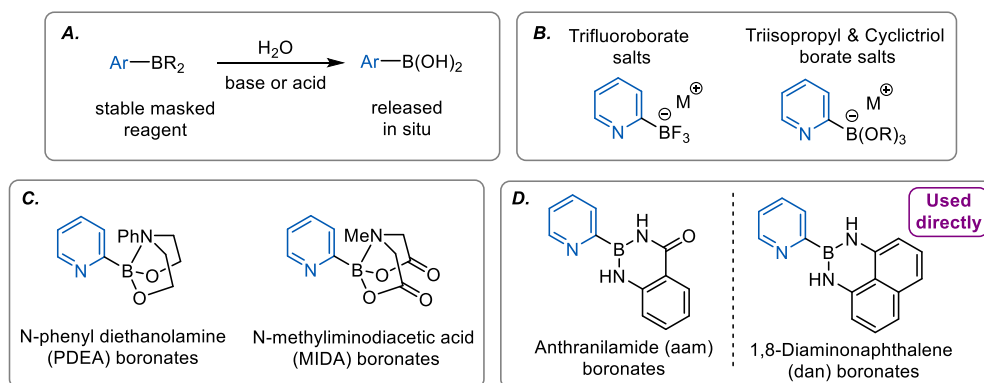


Figure 1.6 Alternative 2-pyridyl boron reagents.

The use of bench-stable cyclic triolborates and triisopropyl borate salts in SMC reactions was pioneered by Miyaura and co-workers, initially focusing on arylborates (**Figure 1.6 B**).^[27] The coupling of 2-pyridyl borate salts and aryl halides has been reported with varying degrees of success, however consistently with the aid of a copper halide or zinc halide additive and/or a phosphine oxide ligand;^[28] as previously discussed, Lewis acidic metals help mitigate protodeboronation. Yamamoto and co-workers explored the effect of the borate counterion, showing that tetrabutylammonium (TBA) borates underwent faster transmetalation than traditionally employed sodium and potassium salts, and were more soluble in organic solvent.^[28b] Using TBA triolborate salts, the authors accessed a

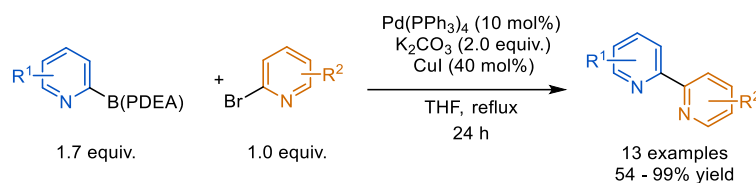
broad range of 2-arylpyridines (28 examples, 56 – 99%) without the need for base; a copper additive was however required.^[28b]

Likewise, Molander and co-workers introduced potassium aryltrifluoroborate salts (Ar-BF₃K) (**Figure 1.6 B**), which were shown to hydrolyse to the boronic acid *in situ* and then react in SMC processes.^[29] A system designed specifically for the cross-coupling of 2-pyridyl trifluoroborate salts was reported by Wu and co-workers in 2012, however the scope was limited by the condition that the pyridyl reagent be 6-substituted,^[30] which is a known strategy to attenuate protodeboronation.^[31] Although bench-stable, both triol- and trifluoro- borate salts are hard to purify and perform sequential transformations. In addition, these reagents are primarily synthesised from the unstable parent boronic acid or *via* lithiation, which limits the functional group tolerance.

Organoboron reagents can also be stabilised by amine-containing ligands, such as *N*-phenyldiethanolamine (PDEA) or *N*-methylinidodiacetic acid (MIDA) (**Figure 1.6 C**). Due to the stabilising intramolecular dative bond between the nitrogen and vacant p-orbital of the boron, these reagents are amenable to prolonged bench storage.

In 2004, Salingue and co-workers introduced the first use of 2-pyridylboronates stabilised by PDEA ligand in SMC reactions with aryl bromides or iodides.^[32] A small scope of 2-arylpyridines was established (9 examples, 10 – 89% yield), with no heteroaryl-heteroaryl linkages shown; again a copper(I) additive was key for reaction success. There are several other reports that expand the substrate scope of 2-pyridyl-B(PDEA) in cross-coupling reactions.^[23a, 33] Notably, in 2010 Lützen and Gütz employed heteroaromatic electrophiles to access a good range of 2,2'-bipyridines and other biheteroaryls (**Scheme 1.2**).^[33a] A copper additive was required in all these reactions, calling into question

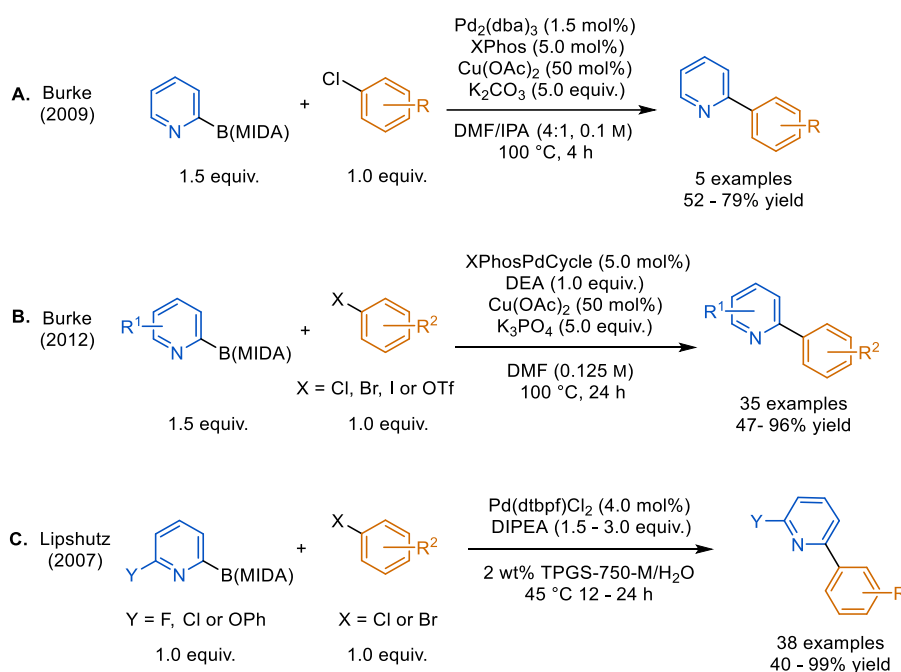
whether the amine-stabilised boronate or the copper additive is responsible for the swifter synthesis of 2-arylpyridines.



Scheme 1.2 Use of 2-pyridyl PDEA boronate reagents in SMC reactions as reported by Lützen and Gütz.

Despite the success of PDEA-masked 2-pyridyl boronic acids, the use of B(MIDA) is vastly more popular. One potential reason is that aryl-aryl ligand exchange can occur when using PDEA and arylphosphine ligands.^[32] Originally developed as masked boronic acids for iterative SMC processes,^[34] MIDA boronates can be selectively hydrolysed to the boronic acids under stepwise treatment with aqueous base, or under cross-coupling conditions.^[34] In 2009, Burke and co-workers used B(MIDA) reagents directly in SMC reactions, and coined the term ‘slow-release’ strategy by studying the rate of B(MIDA) hydrolysis under different conditions (**Scheme 1.3 A**).^[35] They proposed that the improved reaction success with these reagents, compared to the direct use of the boronic acids, is that the slow-release circumvents the competition between *in situ* protodeboronation and cross-coupling, by maintaining a low local concentration of the boronic acid. Further in-depth studies of the rate of hydrolysis of B(MIDA) reagents under varying aqueous conditions have since been reported.^[36] The controllable rate of B(MIDA) ester deprotection has also been leveraged to allow chemoselective SMC reactions in the presence of other organoboron nucleophiles.^[37] In 2012, Burke and co-workers optimised conditions specifically for the cross-coupling of 2-pyridyl B(MIDA) reagents, accessing a wide scope of biheteroaryls with the aid of copper diethanolamine (DEA) (**Scheme 1.3 B**).^[38]

Lipshutz and co-workers showed that using micellar catalysis, the coupling of 2-pyridyl MIDA boronates could proceed without a copper additive under mild aqueous conditions (**Scheme 1.3 C**).^[31] This reaction gave a large scope of 2-hetero(aryl)pyridines, however, only pyridines with electronegative groups in the 6-position were used. The authors describe how using these 6-substituted pyridines slows boronate hydrolysis and subsequently slow protodeboronation. This is further supported by work from Lloyd-Jones and co-workers.^[22a] Furthermore they suggest that a 6-substituent prevents any strong, unproductive Pd-N(pyridine) co-ordination.^[31] This attenuation strategy is commonly employed to ensure cross-coupling efficacy with pyridyl reagents, however it inevitably limits the boronate substrate scope.^[39]

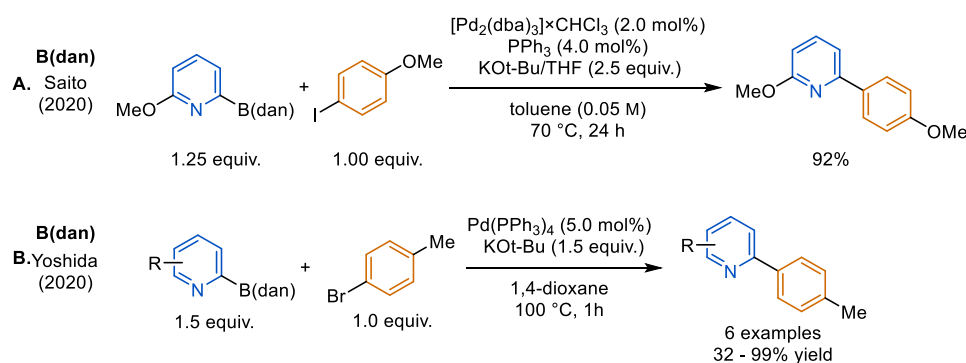


Scheme 1.3 Key reports of 2-pyridyl MIDA boronate reagents in SMC.

Another class of stabilised organoboron reagents, are boranes substituted with arylamine ligands, namely anthranilamide (aam) or 1,8-diaminonaphthalene (dan) (**Figure 1.6 D**). Similar to B(MIDA) esters, B(aam) and B(dan) reagents were originally developed for use in iterative SMC reactions.^[40] Unlike MIDA-stabilised boronates, the bidentate amine

ligand is directly bonded to the boron centre and there is no additional stabilisation into the boron vacant p-orbital. Generally, these groups have been less extensively explored with regards to the use of 2-pyridyl boron nucleophiles. Only one report from Yoshida and co-workers describes the synthesis 2-arylpyridines using 6-substitued-2-pyridyl B(aam) reagents in a microwave-assisted SMC reaction (3 examples, 81 – 99%).^[41]

In contrast to previously discussed organoboron nucleophiles, 1,8-diaminonaphthalene (dan)-protected arylboronic acids are much more stable with regards to hydrolysis,^[41b] and can react directly in SMC reactions instead of acting as masked boronic acids; B(dan) reagents can be transmetalation active.^[42] Known since 2007, the use of aryl-B(dan) reagents directly in SMC reactions was only explored concurrently by the groups of Saito^[43] and Yoshida^[42] in 2020 (**Scheme 1.4 A – B**). Both reports independently found potassium *tert*-butoxide base was essential in assisting transmetalation. The application of these reagents is still in a burgeoning phase, and as such the reaction of 2-pyridyl-B(dan) was not the focus of either paper. Yet these reports establish the potential of these reagents in synthesising 2-arylpyridines.



Scheme 1.4 Direct SMC reaction of 2-pyridyl-B(dan) reagents.

1.3. Direct arylation of pyridyl reagents by C-H activation

Direct C-H arylation reactions are attractive as they do not require pre-formed organometallic reagents, nor suffer the same handling/stability concerns and have innately good atom economies.^[44] Discussed in this section is the research concerning direct arylation of pyridyl reagents *via* single C-H activation of the pyridine reagent, preferentially at the 2-position, and coupling with an electrophilic partner, commonly an aryl halide. A recent review from Soule and co-workers, gives a detailed discussion of alternative C-H activation reactions for the synthesis of bipyridines.^[45] Currently, reports of selective C-H activation and arylation at the 2-position of unfunctionalized pyridine are limited,^[44] with palladium catalysis generally favouring arylation in the 3- or 4-position.^[46] Ellman and co-workers developed a Rh(I)-catalysed direct arylation with aryl bromide to access a small scope of 2-arylpyridines (6 examples, 51 – 78%).^[47] However, the reaction required high temperatures (175 – 190 °C) and the pyridine needed an alkyl substituent in the 6-position to prevent unproductive binding to rhodium.

Due to the challenges of using unfunctionalized pyridine, alternative charged pyridine derivatives have been investigated for the synthesis of 2-arylpyridines: *N*-oxides and other pyridinium reagents (**Figure 1.7**).

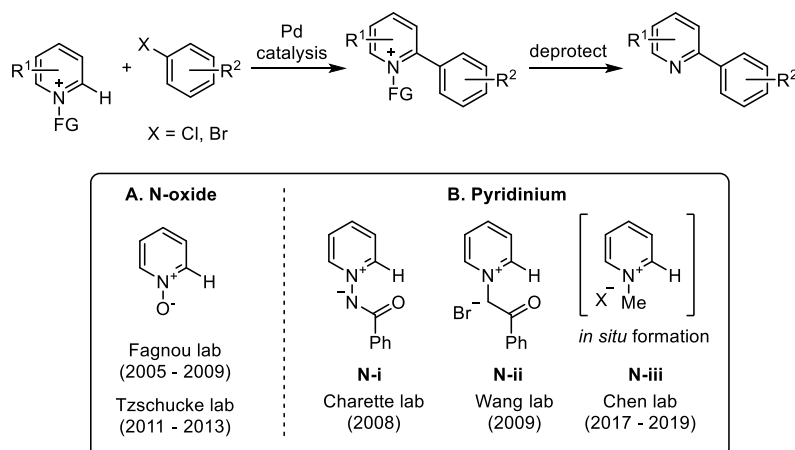
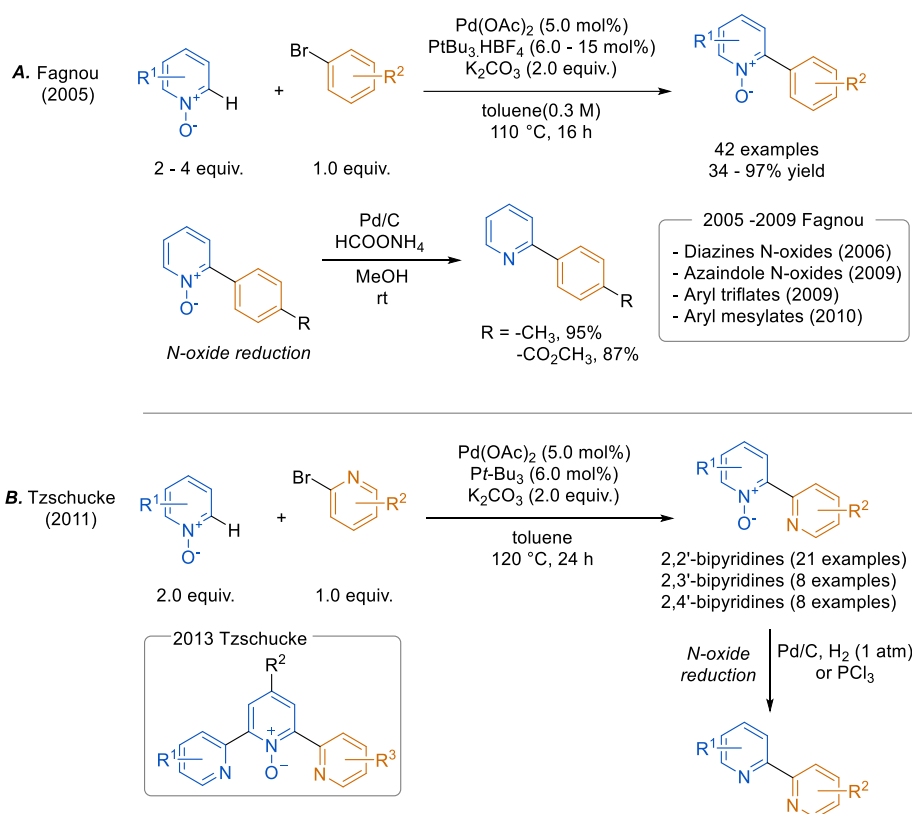


Figure 1.7 Pyridine *N*-oxides and pyridinium reagents for use in direct arylation reactions with aryl halides.

Readily available pyridine *N*-oxides have shown promise as alternative reagents for direct arylation (**Figure 1.7 A**). These reagents are generally bench-stable solids and, owing to the oxide component, have good regioselectivity for the 2-position.^[48] Fagnou and co-workers pioneered the C-H activation of pyridine *N*-oxides in Pd-catalysed cross-coupling with aryl bromides, showing complete regioselectivity for the 2-position (**Scheme 1.5 A**).^[9] The *N*-oxide products could then be reduced using palladium on carbon. Since this seminal 2005 report, Fagnou and co-workers have greatly expanded the scope of *N*-oxides and electrophilic coupling partners (**Scheme 1.5 A**),^[49] and investigated the reaction mechanism.^[50] Other notable contributions to this area come from Duric and Tzschucke, who further expanded the bipyridine scope (**Scheme 1.5 B**).^[51] Although pyridine *N*-oxide chemistry has found success and application to the 2-pyridyl problem, two key limitations are the extra reduction step needed to access the pyridine products, and the need to suppress the generation of 2,6-diarylated by-product.



Scheme 1.5 Selected reports of pyridine *N*-oxides as reagents in cross-coupling reactions.

To overcome the limitations of using pyridine *N*-oxides, alternative pyridinium reagents have been developed (**Figure 1.7 B**). Charette and co-workers successfully investigated the Pd-catalysed reaction of 2-phenyl-*N*-benzoyliminopyridinium ylides (**N-i**) with aryl bromides.^[52] Notably, the increased steric bulk of the *N*-amide component suppressed the formation of the 2,6-diarylated product. Wang, Hu and co-workers introduced pyridinium salts with a modified carbonyl activating group, *N*-phenylacetylpyridinium halides (**N-ii**).^[53] An advantage of these reagents is that after the reaction with aryl bromides, the *N*-activating group can be cleaved *via* enolization, avoiding an additional reduction step. Similarly, Chen and co-workers developed transient methyl pyridinium salts (**N-iii**), which were achieved through *in situ* *N*-methylation and then demethylation. This avoids additional oxidation and reduction steps, albeit the reagents were solely used for accessing diarylpyridines.^[54]

1.4. Contractive main group cross-coupling

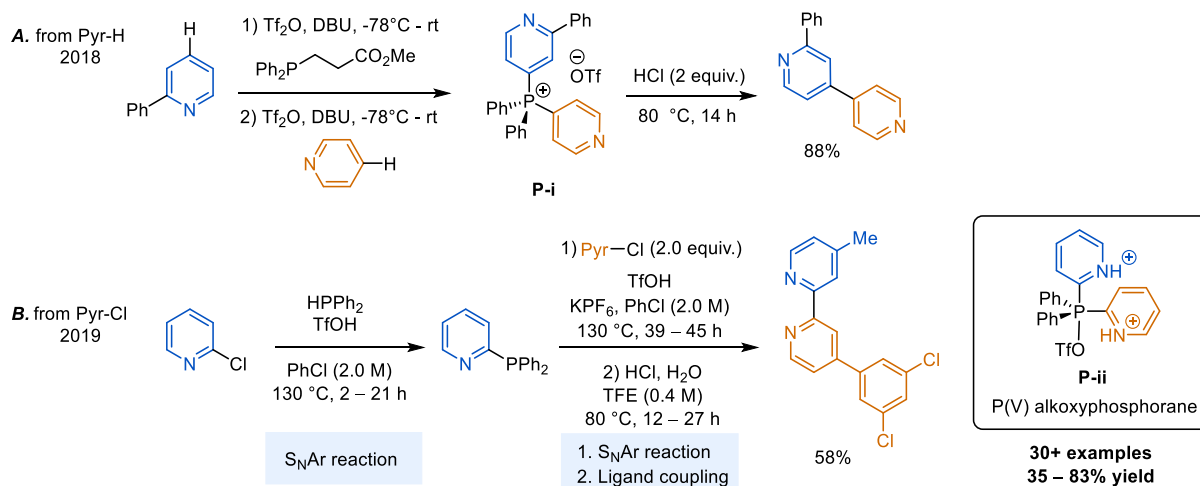
Contractive phosphorous cross-coupling, also known as phosphorus expulsion reactions, offer an alternative to metal-mediated processes and stoichiometric organometallic reagents.^[8] This chemistry was first realised from a phosphine ligand exchange process, which is the scrambling of the aryl coupling reagents and aryl substituents on arylphosphine ligands. Originally an unwanted side reaction leading to mixtures of biaryl products, the synthetic utility of this process was quickly realised and exploited.

The intended formation of 2-2'-bipyridine products, through contractive coupling, *via* a pentacoordinated P(V) intermediate, has been known since 1948,^[55] and further extended decades later by Hager^[56] and Uchida.^[57] However, these reports are limited to the synthesis of dimerised, symmetrical bipyridines, and require harsh conditions for the formation of pyridyl phosphine reagents (*n*-BuLi, PCl₃ / POCl₃).^[55-57] Only with McNally and co-worker's report from 2018 was the potential of these reactions for unsymmetrical bipyridine synthesis realised (**Scheme 1.6 A**).^[58] In this protocol, bis-azine phosphonium salts (**P-i**) were formed *via* step-wise reaction of two C-H pyridyl precursors with a phosphine reagent. Treatment of the resultant phosphorane (**P-ii**) with acid, allowed contractive coupling to give the desired biaryl. Although starting from the C-H precursors is atom-economical, the inherent selectivity for the 4-position of pyridines restricted 2,2'-bipyridine synthesis and the use of strong acids limited the functional group tolerance.

McNally and co-workers resolved this selectivity problem by using two heteroaryl chlorides to form the bis-heteroarylphosphorane intermediate (**P-ii**) *via* tandem S_NAr reactions.^[59] In this strategy heteroaryl phosphines were first formed from the corresponding heteroaryl chloride, and then reacted with a second aryl chloride (**Scheme 1.6 B**). Subsequent acid treatment enabled contractive phosphorous coupling to access a

range of 2-arylpyridines in moderate to good yields. Despite needing strong acids to protonate the pyridines for successful S_NAr , a variety of substrates were tolerated, such as di-halogenated pyridines that would not be compatible with Stille or Negishi reactions.

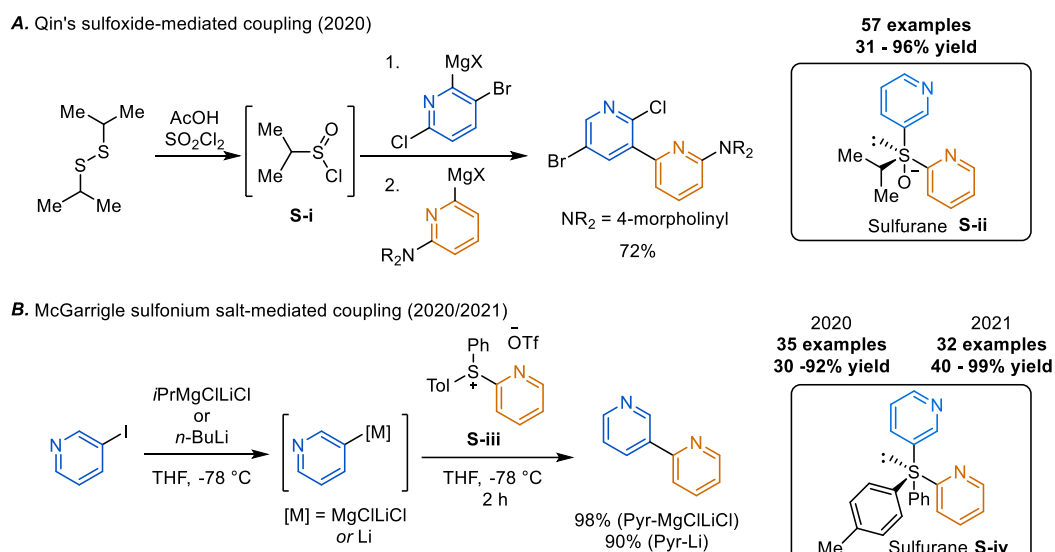
McNally's phosphorous mediated coupling



Scheme 1.6 Contractive phosphorous ligand-coupling reactions by McNally and co-workers.

Sulfur-based contractive coupling for bisazine synthesis is also known, proceeding through a sulfurane intermediate (**Scheme 1.7**). Like early phosphorous couplings, initial reports of this chemistry primarily synthesise simple bipyridine products, by reacting methyl or phenyl 2-pyridyl sulfoxide with organometallic reagents.^[60] This research area has only been revisited recently, with key reports from the groups of Qin and McGarrigle published in 2020 – 2021.^[61] Qin and co-workers pioneered the use of sulfoxide reagent isopropylsulfinyl(IV) chloride (**S-i**) for sulfurane contractive couplings (**Scheme 1.7 A**).^[61a] Thus sulfurane construction (**S-ii**) could proceed through sequential addition of pyridyl Grignard reagents into this sulfoxide (**S-i**), allowing better control and access to unsymmetrical 2,2'-bipyridines. McGarrigle and co-workers concurrently reported the similar use of novel pyridyldiaryl sulfonium salts (**S-iii**), which react directly with lithiated pyridines or 2-pyridyl turbogrignard reagents to form sulfurane intermediate (**S-**

iv), which contractively couples the two aryl fragments to give a range of bipyridines (Scheme 1.7 B).^[61b, 61c]

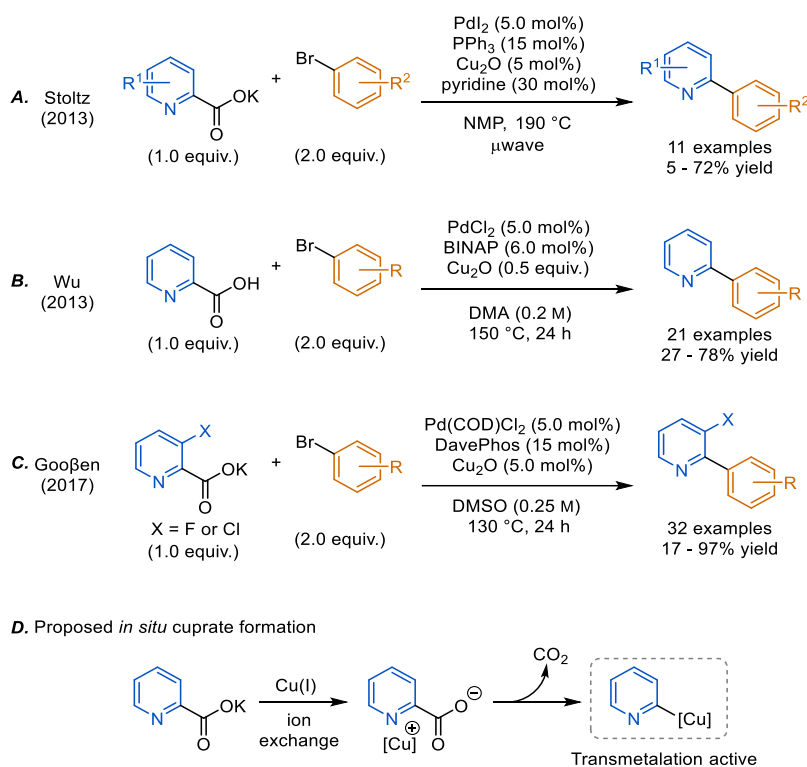


Scheme 1.7 Sulfur(IV)-mediated cross-couplings from the groups of Qin and McGarrigle.^[61]

1.5. Decarboxylative cross-coupling reactions of picolinic acids

Decarboxylative cross-coupling reactions use generally non-toxic, readily available, and largely inexpensive carboxylate reagents, which form the active metalloid nucleophile *in situ*, via extrusion of carbon dioxide. Since the first report of Pd-catalysed decarboxylative cross-coupling by Myers in 2002,^[62] there have been numerous advances in this chemistry.^[63] Nonetheless, the use of 2-pyridyl carboxylates, and heteroaromatic carboxylates in general, has proved challenging. Like 2-pyridyl boronic acids, 2-pyridyl carboxylic acids are unstable with regards to protodecarboxylation, decomposition through the loss of CO₂.^[64] The use of picolinic acid, and its salt derivatives, in decarboxylative arylations has been demonstrated by the groups of Wu,^[65] Stoltz^[66] and Gooßen,^[67] all using a copper (I) co-catalyst (Scheme 1.8 A – C). The proposed role of the copper co-catalyst is the decarboxylative cupration of the aryl carboxylate coupling

partner, which then undergoes transmetalation with the Pd-metal centre and subsequent cross-coupling (**Scheme 1.8 D**).^[63a, 68] There are, however, consistent shortcomings in all these reports, namely requirement of high reaction temperatures and forcing conditions, unsuccessful or limited use of heteroaromatic electrophilic partners, and primarily low to moderate product yields.



Scheme 1.8 Decarboxylative cross-coupling of 2-picolinic acid and salt.

As reported by Hoarau and co-workers, *N*-oxide pyridine carboxylates can be successfully used in decarboxylative cross-coupling under similar bimetallic catalysis.^[69] However, these reagents also exhibit instability towards protodecarboxylation and need similarly high temperatures (150 °C). *N*-oxide pyridine carboxylates also require extra synthetic steps; an oxidation step is required for the preparation of non-commercially available nucleophiles, and an extra step is then needed to deoxygenate the cross-coupling products.

1.6. Desulfinate cross-coupling of sulfur nucleophiles

1.6.1. Introduction to metal sulfinate salts

Metal sulfinate salts (RSO_2M), also known as sulfinic acid salts, have been studied since the early 1900s,^[70] however, the popularity of sulfinate salt chemistry has had a resurgence in the past two decades.^[71] The growing interest in sulfinate chemistry is due to improved routes for synthesis,^[71c] the continued interest in sulfur pharmacophores,^[72] and their versatile ability to react as either electrophilic or nucleophilic coupling partners in cross-coupling reactions.^[71a, 71b] Sulfinate salts are easy to handle bench-stable solids and are generally odourless and non-hygroscopic. Resultantly, they have become useful building blocks in the synthesis of important organosulfur functionalities,^[73] such as aryl/alkyl sulfones (**A**), sulfonyl fluorides or chlorides (**B**), sulfonamides (**C**) and thiosulfonates (**D**), and also for use in C-C bond forming reactions *via* SO_2 extrusion (**E**) (**Figure 1.8**). The preparation and uses of sulfinate salts in organic synthesis are extensively discussed in three recent reviews from 2020 – 2021.^[71a, 73]

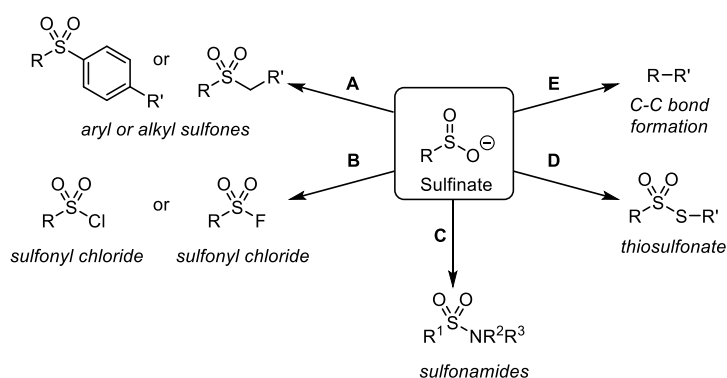


Figure 1.8 Key uses of sulfinate salts in organic synthesis.

There are numerous routes for preparing sulfinate salts (**Figure 1.9**).^[73b] Traditionally, metal sulfinate salts were synthesised *via* oxidation of thiols (**A**), reduction of sulfonyl chlorides reagents (**B**), or SO_2 insertion into organometallic reagents (**E**). Historically,

insertion of SO₂ unattractively used toxic sulfur dioxide gas.^[73b] However, development of easy-to-handle SO₂-surrogates,^[74] such as DABSO^[75] (**Figure 1.9**), has transformed and simplified SO₂ insertion reactions. As well as addition to organometallic reagents,^[76] SO₂-surrogates can be used in conjunction with transition-metal catalysis to form the sulfinate from aryl halides and boronic acids.^[77] Sulfinate salts can also be accessed by cleavage of a sulfinate protecting group (**C**)^[78] or radical reactions (**D**).^[79]

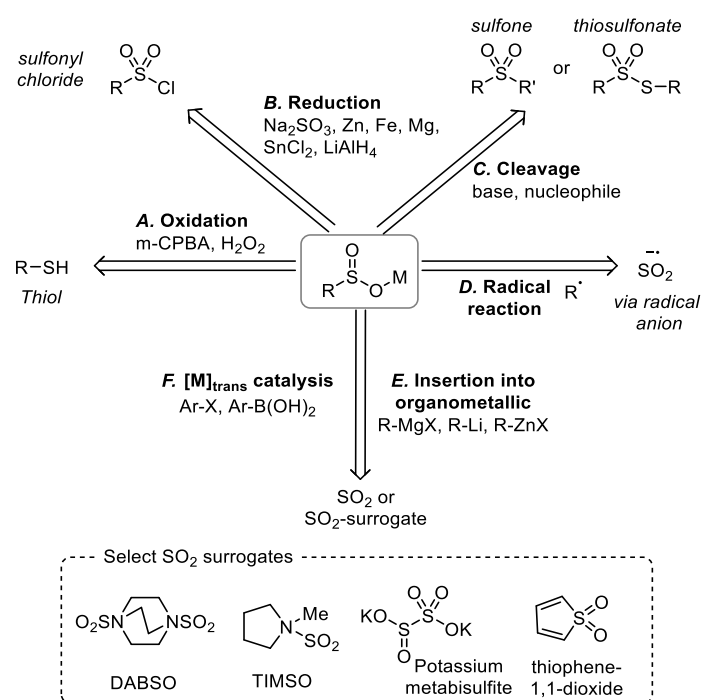
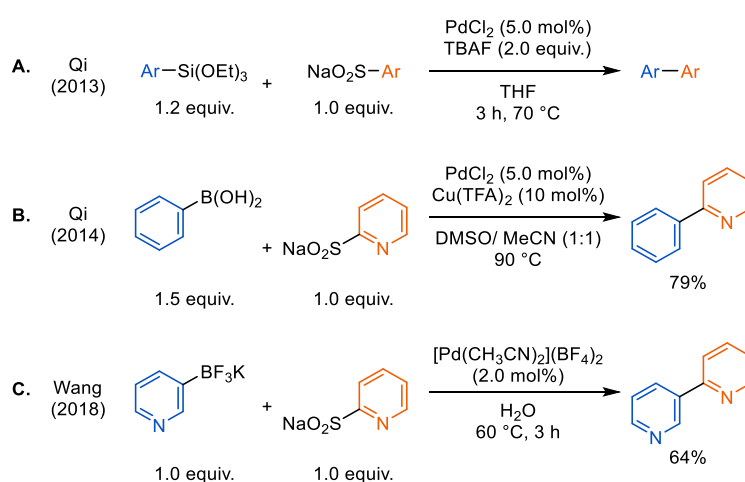


Figure 1.9 Summarised routes to synthesise metal sulfinate salts.

1.6.2. Aryl sulfinate salts in desulfinative Pd- catalysed arylations

Desulfinative C(sp²)-C(sp²) cross-coupling involves the formation of a C-C bond *via* the metal-catalysed reaction of sulfinate salts with the generation of SO₂ gas. Advantageously, aryl sulfinate salts can act as electrophilic or nucleophilic partners in these reactions. Although Pd-catalysed cross-coupling of aryl sulfinate salts was reported 1970s,^[80] it was only in the 2010s that these reactions garnered much synthetic interest.^[81]

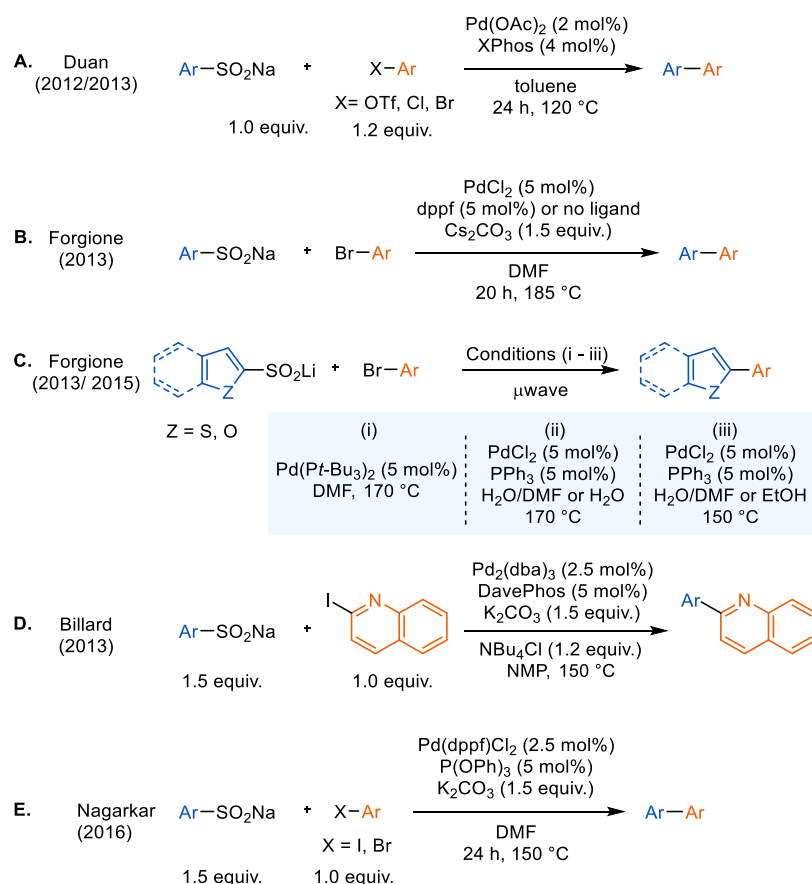
The use of aryl sulfinate reagents as electrophilic partners has been reported in Hiyama-type and SMC reactions (**Scheme 1.9 A – C**).^[82] Notably, reports of Suzuki-Miyaura cross-coupling of arylsulfonates with aryl boron nucleophiles, included examples of 2-pyridyl sulfinate salts as electrophiles (**Scheme 1.9 B – C**).^[82b, 82c] Although not a transition-metal catalysed cross-coupling, 2-pyridyl sulfonates have also been reacted with Grignard reagents to access a range of 2-arylpyridines *via* a desulfinate mechanism.^[83]



Scheme 1.9 Use of aryl sulfinate salts as electrophiles in palladium cross-coupling reactions.

Only in the last decade have arylsulfonates been exploited as nucleophilic partners in cross-coupling arylations with aryl (pseudo)halides (**Scheme 1.10**). Between 2012 – 2013, the groups of Duan and Forgione both contributed to the development of the Pd-catalysed coupling of arylsulfonates and aryl (pseudo)halides for the synthesis of biaryls (**Scheme 1.10 A – B**).^[84] Forgione and co-workers further developed systems for the use of heteroaromatic sulfonates, reporting three different protocols for the cross-coupling of (benzo)furan and (benzo)thiophene sulfonates with aryl bromides and triflates, heating to 150 °C or 170 °C with microwave irradiation (**Scheme 1.10 C**).^[84d, 85] The Billiard and Nagarkar laboratories broadened the scope of electrophilic coupling partners to the use

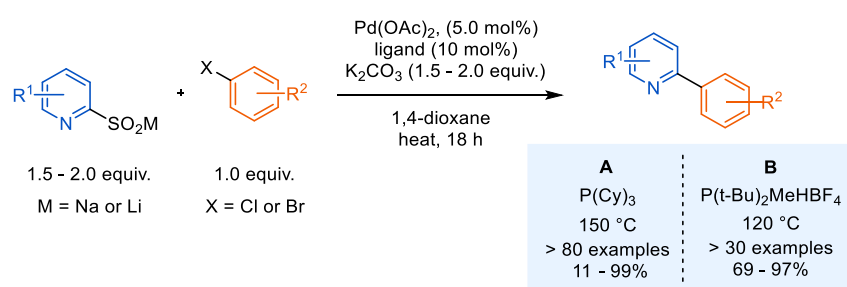
of aryl iodides (**Scheme 1.10 D - E**),^[86] with Billiard and co-workers using 3-iodoquinolines with the assistance of tetrabutylammonium chloride additive.^[86b] Although these reports laid the groundwork for sulfinate nucleophiles in desulfinative arylation reactions, the scope of heteroaryl sulfinate salts was limited, with no *N*-heteroaryl substrates used.



Scheme 1.10 Desulfinative cross-coupling of aryl sulfinate salts and aryl (pseudo)halides.

Work within the Willis group established the use of 2-pyridyl sulfinate salts in cross-coupling reactions, showing efficient reactions using both aryl chlorides and bromides (**Scheme 1.11**). In the first reported system, an extensive range of 2-(hetero)arylpyridines were synthesised using a $\text{Pd(OAc)}_2/\text{P(Cy)}_3$ catalytic system, a carbonate base and a reaction temperature of 150 °C (**Scheme 1.11 A**). Willis and co-workers showcased the industrial relevance of this methodology through modular derivatisation of two drug

structures, varenicline and mepyramine.^[11] Further optimisation of the catalytic system through high throughput screening (HTS), found that changing the phosphine ligand to $P(t\text{-Bu})_2\text{Me}\cdot\text{HBF}_4$ enabled successful cross-coupling at a reduced temperature of 120 °C (**Scheme 1.11 B**). Under these improved reaction conditions, a wider range of heteroaromatic sulfinate salts were tolerated, including pyridine, pyrazine and pyrazole sulfonates. Both reports translate this chemistry from milligram to multigram scale. It is also notable that heteroaromatic sulfinate synthesis has also been reported using continuous flow technology on a multigram scale.^[87] Markedly, cross-coupling of 2-pyridyl sulfinate salts can be achieved at lower temperatures than the corresponding decarboxylative reaction of picolinic acids and salts (130 – 190 °C), and does not require a copper co-catalyst.^[65-67]



Scheme 1.11 Desulfonative cross-coupling of 2-pyridyl sulfinate salts and aryl halides by the Willis lab.^[11, 88]

The mechanism of the Pd-catalysed desulfonative cross-coupling of (hetero)aryl sulfinate salts and aryl bromides has been studied by the Willis laboratory, and the determined catalytic cycle for sodium 2-pyridine sulfinate is shown in **Figure 1.10**.^[89] The turnover limiting step (TLS) was found to be different for the reaction of 2-pyridine sulfinate versus carbocyclic sulfonates. For 2-pyridine sulfinate, the TLS is the extrusion of SO_2 from the chelated sulfinate complex (**iii-a**). Whereas the TLS when using carbocyclic substrates is the transmetalation of the metal sulfinate with the oxidative addition complex

(ii). Notably the Pd(II) pyridyl sulfinate chelate (**iii-a**) that forms, is more thermodynamically stable than the Pd-carbocyclic sulfinate complex (**iii-b**), and as such slows the extrusion of SO₂. This $\kappa^2_{\text{N,O}}$ -binding mode of the pyridine sulfinate can be disrupted by installing steric bulk in the 6-position of the sulfinate and forming a dimeric complex (**iii-c**), like what is observed with carbocyclic sulfonates (**iii-b**). Alternatively, using electron-poor pyridines weakens the Pd-N co-ordination. This helps to explain the challenges of cross-coupling 2-pyridine sulfonates, and the requirement of high temperatures. Regardless of the sulfinate substrate, potassium carbonate base was found to have dual purpose; the base removes free SO₂ from the reaction media to stop deactivation of the Pd-catalyst (**A**), and the potassium cation accelerates transmetalation (**B**).

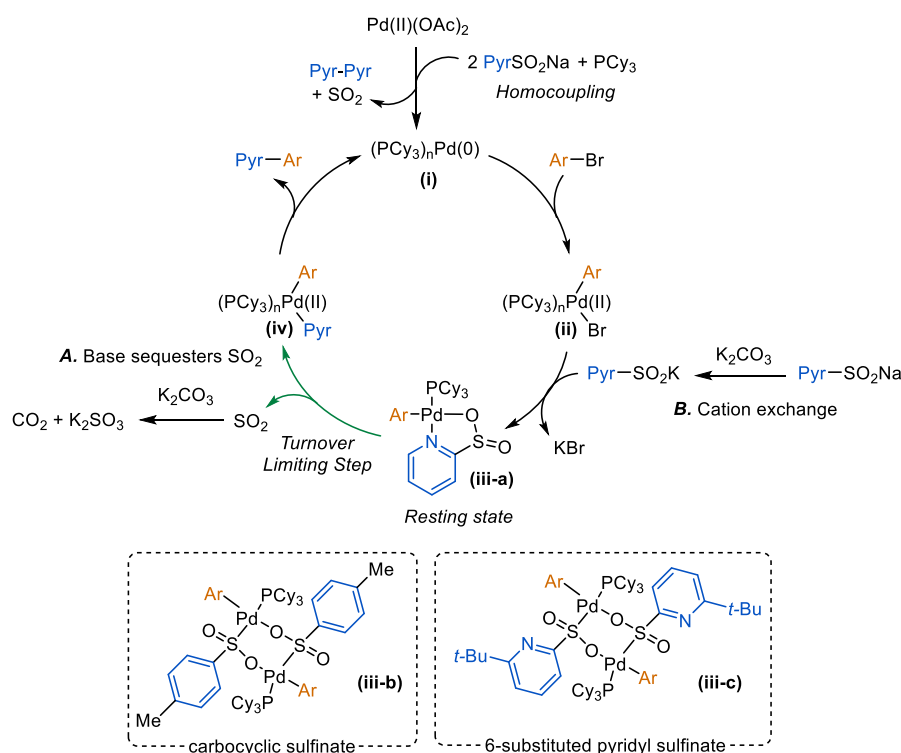


Figure 1.10 Mechanism of the Pd-catalysed cross-coupling of 2-pyridyl sulfinate salts with aryl bromides as studied by de Gombert *et. al.* ^[89a]

1.6.3. Masked sulfonates in desulfonative cross-coupling reactions

Although heteroaromatic sulfonate salts are efficient nucleophilic coupling partners, the purification and preparation of sulfonate reagents can be hindered by their poor organo-solubility and incompatibility with multi-step synthetic sequences. Therefore, the Willis laboratory pioneered the use of allylsulfones, which are Pd-labile, masked sulfonate reagents that release the active sulfonate salt under coupling conditions (**Figure 1.11**).^[90] Allylsulfones are accessible by numerous routes and as organic, neutral substrates are easier to purify than sulfonate salts. The activation of allylsulfone by palladium goes *via* the generation of a π -allyl-Pd intermediate and release of the sulfonate salt, which then proceeds to cross-couple with the aryl halide (**Figure 1.11 A**).

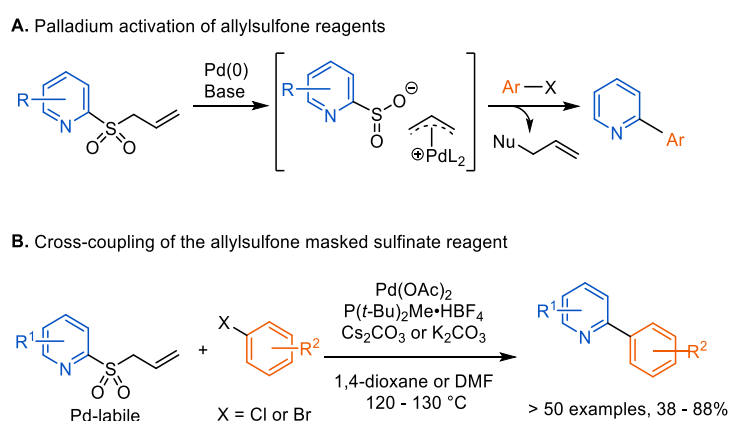


Figure 1.11 Allylsulfones as masked sulfonate salt reagents in cross-coupling processes.

Allylsulfones react under similar conditions used for sulfonate salts at 120 – 130 °C, using $\text{P}(t\text{-Bu})_2\text{Me}\cdot\text{HBF}_4$ ligand (**Figure 1.11 B**). The reaction scope of 2-arylpyridines was diverse and broad (>50 examples), showing a good functional group tolerance. This reaction was successfully extended to the use of other heteroaryl allylsulfones, including pyrazines, pyrimidines, imidazoles and pyrazoles, giving moderate to high yields of the resulting heteroarenes.^[90] Despite the broad reaction scope, it is worth noting that there

was a degree of reaction condition tailoring of the base, solvent and temperature needed depending on the nature of the substrate: 1) Cs_2CO_3 or K_2CO_3 , 2) 1,4-dioxane or DMF, 3) 120 °C or 130 °C.

1.7. Research aims

This literature review has discussed the challenges in accessing important 2-pyridyl-containing structures through cross-coupling processes and shown how this synthetic challenge has proved a springboard for innovation, leading to the development of novel methodologies and 2-pyridyl reagents. Desulfinative cross-coupling reactions, and the seminal use of heteroaryl sulfinate salts and allylsulfones by the Willis laboratory, are useful contributions to this area. Thus, the development of novel 2-pyridyl nucleophilic reagents continues to be an area of chemical interest.

The objective of the research described in this thesis, was to design and develop novel sulfur-based reagents for the synthesis of biaryls, namely 2-arylpiperidines, through palladium-catalysed, desulfinative cross-coupling processes (**Figure 1.12**). Initial focus was the development of next-generation, more robust latent sulfinate reagents, envisioned to be base-activated rather than palladium-activated. Building on this work, this research aimed to establish a formal cross-electrophile coupling of two (hetero)aryl halides, where the sulfinate nucleophile is formed *in situ*. Thirdly, nucleophiles containing alternative sulfur (IV) functionalities were explored, with the goal of improving cross-coupling conditions, such as lowering the reaction temperature.

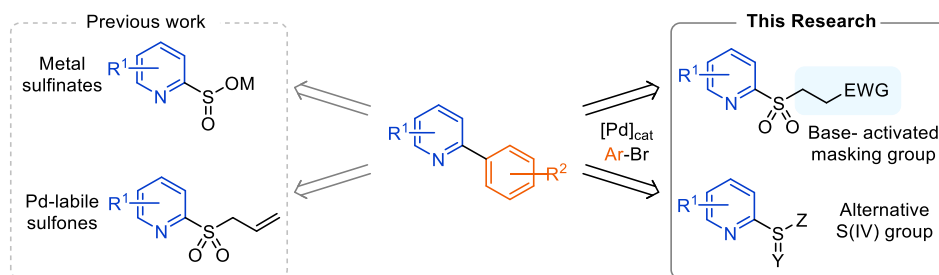


Figure 1.12 The key aims of this research.

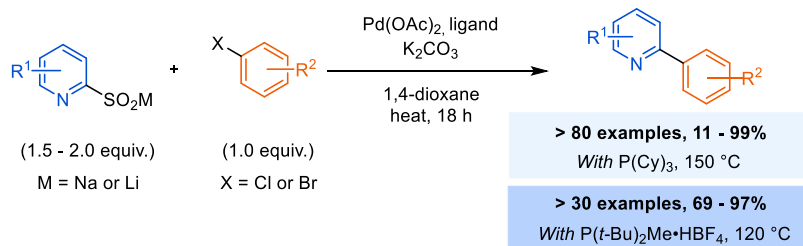
Chapter 2. Base-activated latent sulfinates as nucleophilic coupling partners in Pd-catalysed cross-coupling reactions

2.1. Introduction to base-activated latent sulfinates

As established in **Chapter 1**, 2-arylpyridines are important structures for a range of chemical applications, and resultantly there is an extensive body of research towards developing nucleophilic 2-pyridyl reagents for use in arylation reactions.^[1a] As previously discussed in **Section 1.6.2 – 1.6.3**, the Willis group contributed to this research, pioneering the use of 2-pyridyl sulfinate salts as nucleophilic coupling partners in desulfonative cross-coupling reactions (**Figure 2.1 A**).^[11, 88] Although efficient coupling partners, metal sulfinate salts are hard to purify and are poorly soluble in organic media. Further, these factors hinder their ability to be carried through multi-step synthetic sequences, and for more complex substrates to be formed.

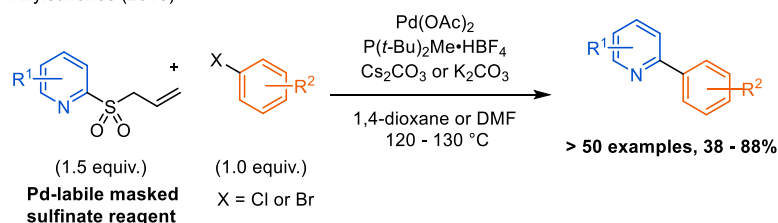
To overcome these drawbacks, our laboratory established the use of latent sulfinate reagents in cross-coupling reactions. This strategy masks the anionic sulfinate with a small organic moiety, providing an organosoluble, neutral and readily accessible reagent that can be selectively deprotected under the coupling conditions. The first generation of latent sulfinate reagents developed were the palladium-labile allylsulfone reagents (**Figure 2.1 B**).^[90] Allylsulfones worked well under similar cross-coupling conditions as the metal sulfinate salts, and were amenable to multi-step elaboration. However, this sulfinate masking strategy limited the use of these reagents in other palladium-catalysed reactions, and in alkene transformations. Additionally, substrate-specific tuning of conditions was needed to achieve high yields.

A. Metal sulfonates (2017)



Metal sulfonate salts	
✓	Robust cross-coupling
✗	Insoluble salts
✗	Difficult to purify and isolate
✗	Not suitable for multistep elaboration

B. Allylsulfones (2018)



Allylsulfones	
✓	Efficient coupling via <i>in situ</i> sulfinate
✓	Stable & organic soluble
✓	Suitable for multistep elaboration
✗	Sensitive to Pd-mediated chemistry
✗	Incompatible with alkene transformations

Figure 2.1 Previous use of (A) metal sulfinate salts and (B) allylsulfones in Pd-catalysed cross-coupling.

To mitigate these issues, we designed a new generation of latent *N*-heteroaromatic sulfinate reagents: β -nitrile (**1**) and β -ester sulfones (**2**) (**Figure 2.2**). These reagents are base-activated, releasing the active sulfinate reagent *via* E1cB elimination under the basic cross-coupling conditions. The electron-withdrawing groups control the acidity of the α -proton and help to stabilise the conjugate base, promoting efficient sulfinate unmasking. Mechanistically, this un-masking was envisaged to occur off-cycle, with the free sulfinate salt undergoing transmetalation in the Pd-catalytic cycle. Thus, the Pd-catalysed cross-coupling would proceed through the same established mechanism of using sulfinate salts directly.^[89a] In contrast to Pd-labile allylsulfones, these base-labile latent sulfonates are more amenable to orthogonal transition metal-catalysed processes and typical alkene functionalisation reactions (see **Section 2.5**).

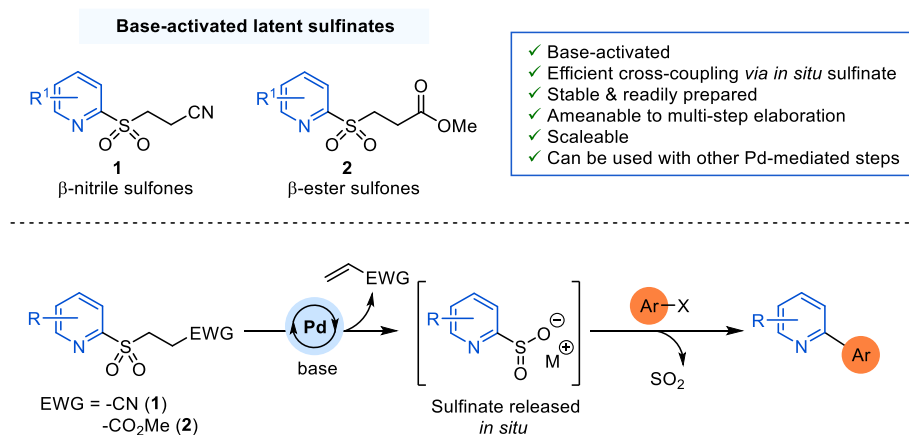


Figure 2.2 Introduction to base-activated latent sulfonate reagents.

In Pd-catalysed cross-coupling chemistry, a protecting group strategy has been widely applied to organoboron reagents (**Chapter 1, Section 1.2.3**).^[21b] Many masked boronate species, such as B(MIDA), B(dan) and B(aam) reagents, were originally developed for use in iterative Suzuki-Miyaura cross-coupling to construct oligomers and more complex structures.^[34, 40] In parallel to the proposed masked sulfonates, the release of the parent boronic acid from masked boronates, such as B(MIDA) esters, can be controlled through selection of cross-coupling reaction conditions.^[35-38] One consideration with masking groups is their molecular weight, which should be minimised in order to maximise the atom-economy of a reaction.^[91] Hence, the proposed masked sulfonates were designed to contain leaving groups that have comparable, if not lower, molecular weights than boron-masking groups.

In this chapter the use of second generation, base-activated masked sulfonates as nucleophilic coupling reagents in desulfonative cross-coupling reactions is investigated. As such, the reactivity and scope of β-nitrile and β-ester sulfonates in arylation reactions is established. A key aim is to explore the scalability of these methods, and extension of this strategy to other base-activated sulfonate masking groups. Furthermore, the robustness of

these reagents with regards to multi-step elaboration is demonstrated, with a particular focus on alkene and palladium-mediated chemistry.

2.2. Heteroaromatic β -nitrile sulfones

Although the aryl β -nitrile sulfone functionality is not widely found in the literature, it does feature in a handful of bioactive molecules (**Figure 2.3 A**).^[92]

The β -ethylnitrile functionality has precedent for use as an alcohol protecting group in nucleotide synthetic chemistry, where it is known as a '2'-O-cyanoethyl' group.^[93] However, the use of β -nitrile sulfones as latent sulfinates is not well established. Only a couple of reports document β -nitrile sulfones as precursors for sulfinates. In these instances the sulfinate is released from the sulfone by treatment with a strong alkoxide base, such as NaOEt or NaOMe (**Figure 2.3 B**).^[94] Furthermore, to the best of our knowledge, the use of β -nitrile sulfones as nucleophilic reagents in metal-mediated reactions is not known.

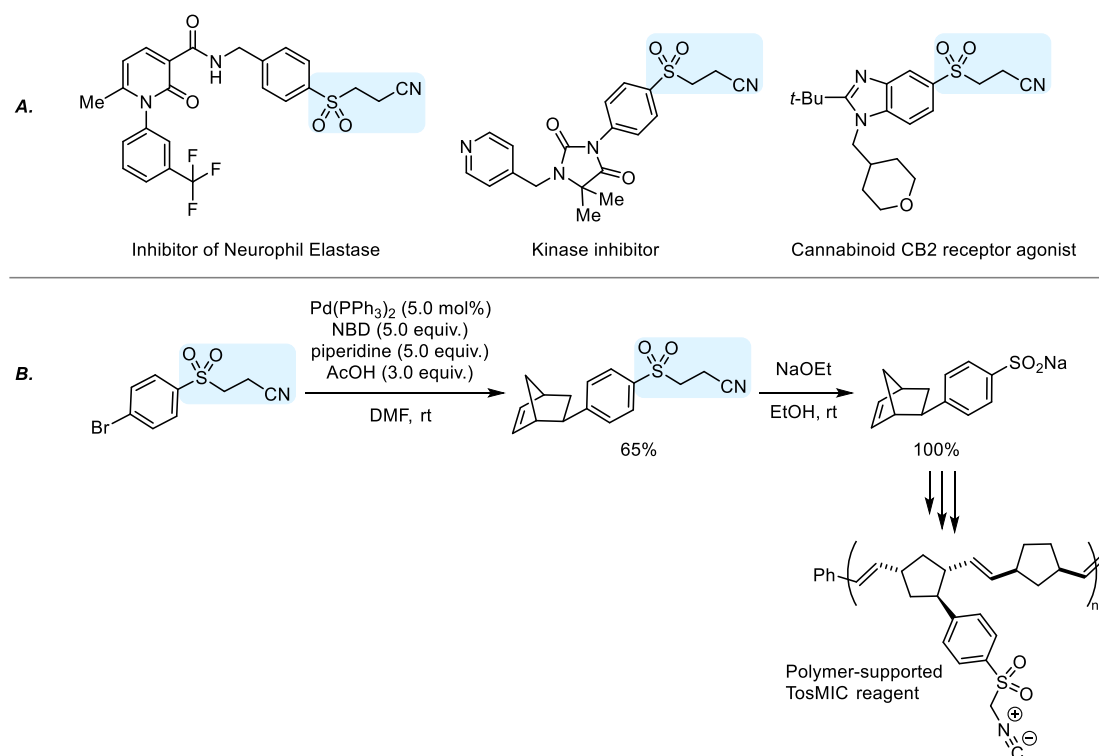


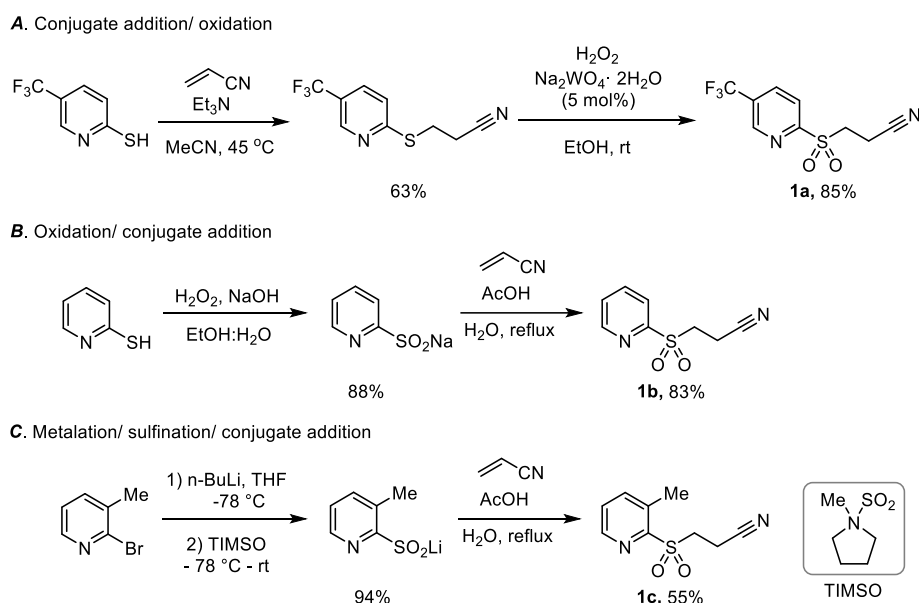
Figure 2.3 Introduction to the β -nitrile sulfone functionality. (A) Therapeutic molecules containing the β -nitrile sulfone motif. (B) Selected example of a β -nitrile sulfone acting as a sulfinate salt intermediate *en route* to the synthesis of a polymer supported TosMIC reagent by Barrett and co-workers.^[94a]

In this section, β -nitrile sulfones are established as base-activated latent sulfinate reagents, and their use in the Pd-catalysed formation of 2-arylpyridines explored.

2.2.1. Synthesis of heteroaromatic β -nitrile sulfones

Heteroaromatic sulfones can be conveniently prepared from commercially available, or readily accessible, thiols, halides, or sulfinate salts.^[73b, 76a, 76c, 78a, 78b, 95] β -Nitrile sulfones were primarily synthesised by conjugate addition of thiols into acrylonitrile and subsequent oxidation (**Scheme 2.1 A**), or by reversing the order of these steps and first forming the sulfinate salt (**Scheme 2.1 B**). Alternatively, heteroaryl halides were sulfinylated using organic SO₂-surrogates,^[11, 75] such as *N*-methyl pyrrolidine-SO₂ adduct

(TIMSO), and the resultant sulfinate salt reacted *via* conjugate addition to give the sulfone (Scheme 2.1 C).



Scheme 2.1 Primary routes for the synthesis of heteroaromatic β -nitrile sulfone reagents, demonstrated through selected examples (see experimental 6.2.3).

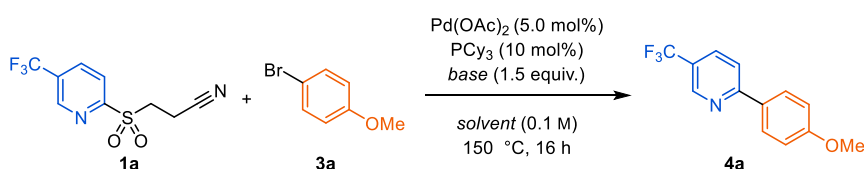
It is worth noting that there is a vast body of work exploring the synthesis of arylalkyl sulfones,^[96] including recent developments in metal catalysis^[77b, 77c, 97] and photocatalysis.^[98] Whilst many of these methods are currently limited in heteroaromatic examples, particularly lacking pyridyl substrates, they will likely influence future synthetic routes to heteroaromatic alkyl sulfones.

2.2.2. Initial optimisation of β -nitrile sulfones in cross-coupling reactions

The potential of β -nitrile sulfones in Pd-mediated cross-coupling reactions was initially investigated through the model reaction of the pyridine sulfone **1a** with 4-bromoanisole **3a** (Table 2.1). Encouragingly, the system gave a 20% yield of the desired biaryl (entry 1) under the conditions used for metal sulfinate salts as nucleophilic coupling partners.^[11]

The system showed a strong solvent dependence, with the yield of biaryl **4a** more than doubling to 67% when substituting 1,4-dioxane for toluene (entry 3 vs. entry 7). The use of potassium carbonate base was observed to be key for reaction success. This is congruent with the reported mechanism of desulfonative cross-coupling, where the carbonate base was shown to sequester SO₂ released into the reaction mixture and prevent palladium de-activation.^[89] In all reactions, the acrylonitrile by-product was not observed and it is assumed to be removed by evaporation.

Table 2.1 Preliminary investigation into the use of β -nitrile sulfone **1a** in cross-coupling processes: base and solvent screening.



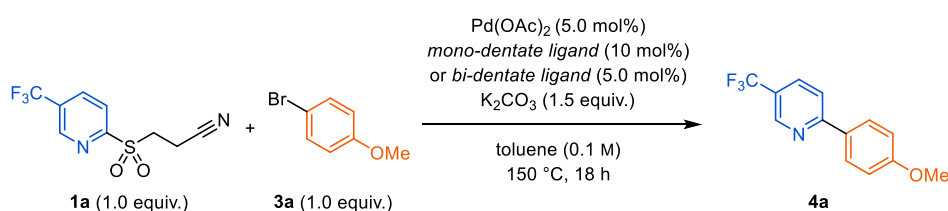
Entry	Sulfone (equiv.)	Ar-Br (equiv.)	Solvent	Base	Isolated yield / %
1	2.0	1.0	1,4-dioxane	K ₂ CO ₃	20
2	2.0	1.0	1,4-dioxane	Cs ₂ CO ₃	13
3	1.0	1.0	1,4-dioxane	K ₂ CO ₃	29 ^[a]
4	1.0	1.5	1,4-dioxane	K ₂ CO ₃	28
5	1.0	2.0	1,4-dioxane	K ₂ CO ₃	19
6	1.0	1.0	1,4-dioxane	<i>t</i> -BuOK ^[b]	7
7	1.0	1.0	toluene	K ₂ CO ₃	67
8	1.0	1.5	toluene	Cs ₂ CO ₃	45
9	1.0	1.0	toluene	Na ₂ CO ₃	13

Reaction conditions: pyridine sulfone, 4-bromoanisole, base (0.3 mmol, 1.5 equiv.), Pd(OAc)₂ (0.01 mmol, 5.0 mol%), PCy₃ (0.02 mmol, 10 mol%) and solvent (0.1 M). Reactions were run on a 0.2 mmol scale unless otherwise stated. ^[a] Run on a 0.4 mmol scale. ^[b] Run with *t*-BuOK (1.0 equiv.).

Next, an array of phosphine ligands were screened (**Table 2.2**). For a complete list of phosphine ligand structures see **page xiii**. Electron-rich, trialkyl phosphine ligands with high steric bulk performed best (entries 1 – 5), albeit there was a limit to how much steric bulk was efficacious (entry 6). Good activity was seen using P(*t*-Bu)₂Me•HBF₄, which was the optimum ligand for the allylsulfone work (entries 3 and 4). However, cataCXium[®] A proved superior for this system, giving a high 84% yield (entry 1). The

reaction did not proceed if either palladium (entry 25) or a phosphine ligand (entry 26) was omitted from the system. Notably, the reaction achieves high yields with only one equivalent of the sulfinate coupling partner; a two-fold excess is needed in the original sulfinate work.^[11, 88] This stoichiometry is advantageous, as the nucleophilic partner is the non-commercially available fragment.

Table 2.2 Screening of phosphine ligands.



Entry	Ligand	Yield ^[a] /%	Entry	Ligand	Yield ^[a] /%
1	cataCXium A	84	17	dppe	57
2	$\text{P}(i\text{-Pr})_3$	80	18	dcpe	39
3	$\text{P}(t\text{-Bu})_2\text{Me}\cdot\text{HBF}_4$	76	19	dcpb	20
4	$\text{P}(t\text{-Bu})_2\text{Me}\cdot\text{HBF}_4$ (6 mol%)	75	20	dppp	16
5	$\text{P}(\text{Cy})_3$	67	21	XantPhos	15
6	$\text{P}(\text{Ph})_3$	56	22	dppf	8
7	$\text{P}(\text{Adm})_3$	12	23	dcpp	5 ^[b]
8	Cy-JohnPhos	13			
9	$\text{P}(t\text{-Bu})_2\text{Cy}$	3	24	$\text{P}(\text{Cy})_3\text{Pd-G3}$	24
10	$\text{P}(t\text{-Bu})_3\cdot\text{HBF}_4$	3	25	No Pd (cataCXium A)	0
11	$\text{P}(n\text{-Bu})_3$	0	26	No ligand	0
12	$\text{P}(\text{OPh})_3$	0			
13	$\text{P}(2\text{-furyl})_3$	0			
14	$\text{P}(\text{Adm})_2\text{Bn}$	4 ^[b]			
15	$\text{P}(\text{Cy})_2\text{Et}$	1 ^[b]			
16	GorlosPhos $\cdot\text{HBF}_4$	34 ^[c]			

Adm = adamantyl

cataCXium A

$\text{P}(\text{Cy})_3\text{Pd-G3}$

Reaction conditions: pyridine sulfone (0.20 mmol, 1.0 equiv.), 4-bromoanisole (0.20 mmol, 1.0 equiv.), K_2CO_3 (0.30 mmol, 1.5 equiv.), $\text{Pd}(\text{OAc})_2$ (0.01 mmol, 5.0 mol%), mono-dentate ligand (0.02 mmol, 10 mol%) or bi-dentate ligand (0.01 mmol, 5.0 mol%) and toluene (0.1 M). ^[a] HPLC yield determined using *p*-ditolylether as an internal standard. ^[b] Run at 130 °C. ^[c] Run at 120 °C. Pd-G3 refers to the third generation of the Buchwald palladium precatalysts.^[99]

2.2.3. Lowering the reaction temperature and investigation of additives

In **Section 2.2.2**, the coupling reaction of β -nitrile sulfones was optimised to be efficient at 150 °C (84%). However, the ability to perform this chemistry at lower reaction temperatures (120 – 130 °C), like the allylsulfone work, would be advantageous.^[90] On reduction of the temperature to 130 °C, the reaction yield of biaryl **4a** disappointingly dropped (Table 2.3).

Table 2.3 Initial results lowering the temperature of the cross-coupling reaction.

1a (1.0 equiv.) + 3a (1.0 equiv.) $\xrightarrow[\text{toluene (0.1 M), 18 h}]{\text{Pd(OAc)}_2 \text{ (5.0 mol\%)}, \text{ligand (5.0 mol\%)}, \text{K}_2\text{CO}_3 \text{ (1.5 equiv.)}}$ 4a

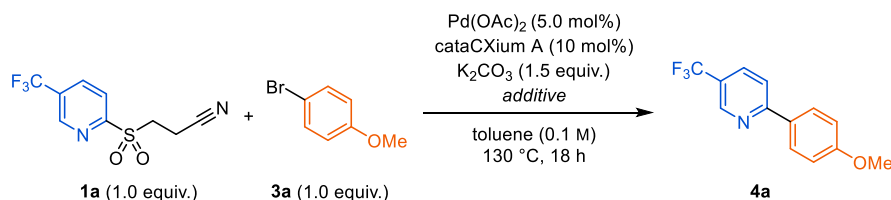
Entry	Ligand	Yield ^[a] / %	
		150 °C	130 °C
1	cataCXium A	84	59
2	P(<i>i</i> -Pr) ₃	80	42
3	P(<i>t</i> -Bu) ₂ Me · HBF ₄	76	48

Reaction conditions: pyridine sulfone (0.20 mmol, 1.0 equiv.), 4-bromoanisole (0.20 mmol, 1.0 equiv.), K₂CO₃ (0.30 mmol, 1.5 equiv.), Pd(OAc)₂ (0.01 mmol, 5.0 mol%), ligand (0.02 mmol, 10 mol%) and toluene (0.1 M). ^[a] HPLC yield determined using *p*-ditolylether as an internal standard.

To improve the reaction efficacy at lower temperatures, the use of additives was investigated (Table 2.4). Some success was found by doping the reaction with triethylamine (entries 2 – 5), which improved the reaction yield by 10 – 15%. Amine additives, such as triethylamine, are known to assist the reduction of Pd(II) precatalysts to the active Pd(0) species for cross-coupling.^[100] Use of acetic acid as an additive also improved the yield (entries 7 – 11), with one equivalent of acetic acid giving a significantly increased 93% yield. Furthermore, the combination of acetic acid and a slight increase in the stoichiometry of the pyridine sulfone (1.1 equiv.) allowed yields

over 90% to be achieved at 130 °C and, most desirably, at 120 °C (entries 18 – 19). These conditions at 120 °C (entry 19) were therefore selected and used to establish the reaction scope.

Table 2.4 Screening of the use of additives in the cross-coupling system.



Entry	Additive	Variations to above system	Yield ^[a] /%
1	-	-	59
2	NEt ₃ (0.05 equiv.)	-	69
3	NEt ₃ (0.10 equiv.)	-	72
4	NEt ₃ (0.20 equiv.)	-	74
5	NEt ₃ (1.0 equiv.)	-	73
6	NEt ₃ (1.5 equiv.)	no K ₂ CO ₃	9
7	AcOH (0.10 equiv.)	-	70
8	AcOH (0.20 equiv.)	-	79
9	AcOH (0.50 equiv.)	-	86
10	AcOH (1.0 equiv.)	-	93 (84)
11	AcOH (1.5 equiv.)	-	79
12	AcOH (1.0 equiv.)	toluene (0.05 M)	78
13	AcOH (1.0 equiv.)	toluene (0.20 M)	58
14	AcOH (1.0 equiv.) + NEt ₃ (0.10 equiv.)	-	70
15	acetic anhydride (0.10 equiv.)	-	81
16	acetic anhydride (0.50 equiv.)	-	85
17	Sulfone (1.1 equiv.)	-	81
18	Sulfone (1.1 equiv.) + AcOH (1.0 equiv.)	-	94
19	Sulfone (1.1 equiv.) + AcOH (1.0 equiv.)	120 °C	96 (88)
20	Sulfone (1.1 equiv.) + AcOH (1.0 equiv.)	100 °C	10
21	Sulfone (1.1 equiv.) + AcOH (1.0 equiv.)	anisole (0.10 M), 120 °C	94
22	Sulfone (1.1 equiv.) + AcOH (1.0 equiv.)	<i>p</i> -xylene (0.10 M), 120 °C	(77)
23	Sulfone (1.1 equiv.) + AcOH (1.0 equiv.)	120 °C, H ₂ O (100 μL)	86
24	Sulfone (1.1 equiv.) + AcOH (1.0 equiv.)	cataCXium A Pd-G3	34
25	Sulfone (1.1 equiv.) + AcOH (1.0 equiv.)	PdCl ₂ (no Pd(OAc) ₂)	86
26	Sulfone (1.1 equiv.) + AcOH (1.0 equiv.)	Pd(TFA) ₂ (no Pd(OAc) ₂)	>99

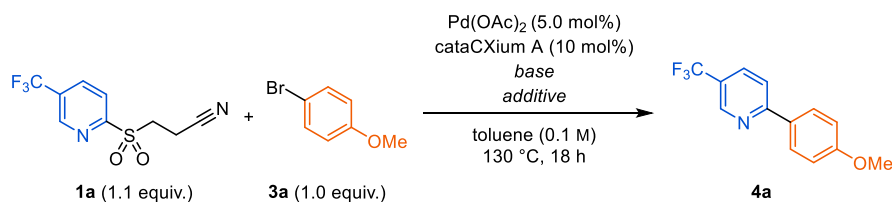
Reaction conditions: pyridine sulfone (0.20 mmol, 1.0 equiv.), 4-bromoanisole (0.20 mmol, 1.0 equiv.), K₂CO₃ (0.30 mmol, 1.5 equiv.), Pd(OAc)₂ (0.01 mmol, 5.0 mol%), cataCXium A (0.02 mmol, 10 mol%) and toluene (0.1 M). ^[a] HPLC yield determined using *p*-ditolylether as an internal standard. Isolated yields are indicated in parentheses.

The additional 10 mol% of sacrificial pyridine sulfone is believed to aid the reduction of the palladium(II) precatalyst to the active palladium(0) species through homo-coupling of the active sulfinato nucleophile. Similar dimerization of two sulfinates is seen to assist the activation of Pd(II) complexes in pyridine sulfinato cross-coupling reactions.^[89a] The role of acetic acid in improving the reaction yield was not well understood, and so further investigation was undertaken (**Section 2.2.4**).

2.2.4. Investigating the role of acetic acid as a reaction additive

To establish if the reaction specifically requires an acetic acid additive, we investigated the use of alternative carboxylic acids (**Table 2.5**, entries 1 – 3). The mixing of acetic acid and potassium carbonate generates other potassium salts (**Table 2.5 A**). Therefore, the use of these potassium salts directly was explored (entries 4 – 7). Furthermore, addition of AcOH will lower the basicity of the reaction. Hence, we alternatively omitted the acid and ran reactions with reduced quantities of potassium carbonate (entries 8 – 10). However, throughout these condition alterations, the optimised conditions still performed best; a combination of an acetic acid additive and potassium carbonate base still gave the highest yield of biaryl product (entry 1). This suggests that the role of the acetic acid is not just the generation of KOAc or KHCO₃, nor to solely reduce the quantity of base in the reaction. Lastly, as sulfinato salts are not readily soluble in toluene, phase transfer agents, such as tetrabutylammonium (TBA) salts, were explored as they could comparably aid the reaction (entries 12 – 13). However, only tetrabutylammonium acetate worked well (entry 12), suggesting that the acetate ion or *in situ* generated acetic acid is key. Therefore, the combination of base and acid is postulated to be buffering the system, and enabling a controlled release of the sulfinato from the latent species.

Table 2.5 Exploring the effect of various acid and salt additives.



Entry	Additive	Base	Yield ^[a] /%
1	AcOH (1.0 equiv.)	K_2CO_3 (1.5 equiv.)	94
2	Pivalic acid (1.0 equiv.)	K_2CO_3 (1.5 equiv.)	42
3	Benzoic acid (1.0 equiv.)	K_2CO_3 (1.5 equiv.)	62
4	-	KHCO_3 (1.5 equiv.)	67
5	AcOH (1.0 equiv.)	KHCO_3 (1.5 equiv.), K_2CO_3 (1.5 equiv.)	56
6	-	KOAc (1.0 equiv.)	34
7	-	KOAc (1.0 equiv.), K_2CO_3 (1.5 equiv.)	76
8	-	K_2CO_3 (0.7 equiv.)	49
9	-	K_2CO_3 (0.5 equiv.)	33
10	-	K_2CO_3 (0.2 equiv.)	11
11	NaOTf (1.0 equiv.)	K_2CO_3 (1.5 equiv.)	35
12	NBu ₄ OAc (10 mol%)	K_2CO_3 (1.5 equiv.)	80
13	NBu ₄ Br (10 mol%)	K_2CO_3 (1.5 equiv.)	23



Reaction conditions: pyridine sulfone (0.22 mmol, 1.1 equiv.), 4-bromoanisole (0.20 mmol, 1.0 equiv.), K_2CO_3 (0.30 mmol, 1.5 equiv.), $\text{Pd}(\text{OAc})_2$ (0.01 mmol, 5.0 mol%), cataCXium A (0.02 mmol, 10 mol%), toluene (0.1 M), 130 °C. ^[a] HPLC yield determined using *p*-ditolylether as an internal standard.

To further investigate the effect of adding acetic acid into the system, the consumption of pyridine sulfone **1a** and formation of cross-coupled product **4a** was monitored under various cross-coupling conditions (**Figure 2.4**). Consumption of pyridine β -nitrile sulfone **1a**, and subsequent sulfinate release, was slower when acetic acid was present than when acetic acid was omitted; consumption of **1a** in *c.a.* 1 hour vs. < 15 mins respectively (**Figure 2.4 A vs. B**). This supports the working hypothesis that the base and acid are buffering the system, enabling a controlled release of the sulfinate from the heteroaromatic sulfone. Although further elucidation of the exact role of acetic acid needs to be conducted, based on initial observations it is apparent that the reaction has a pH dependency and that the rate of release of the sulfinate is linked to the reaction yield. In other words, tailoring the pH of the conditions through the addition of the right amount

of acetic acid allows for control of the rate of sulfinate unmasking. Similar pH-dependencies are seen when using masked organoboron species in Suzuki-Miyaura cross-coupling that undergo slow-release mechanisms of the active boronic acid *in situ*.^[26, 36, 101]

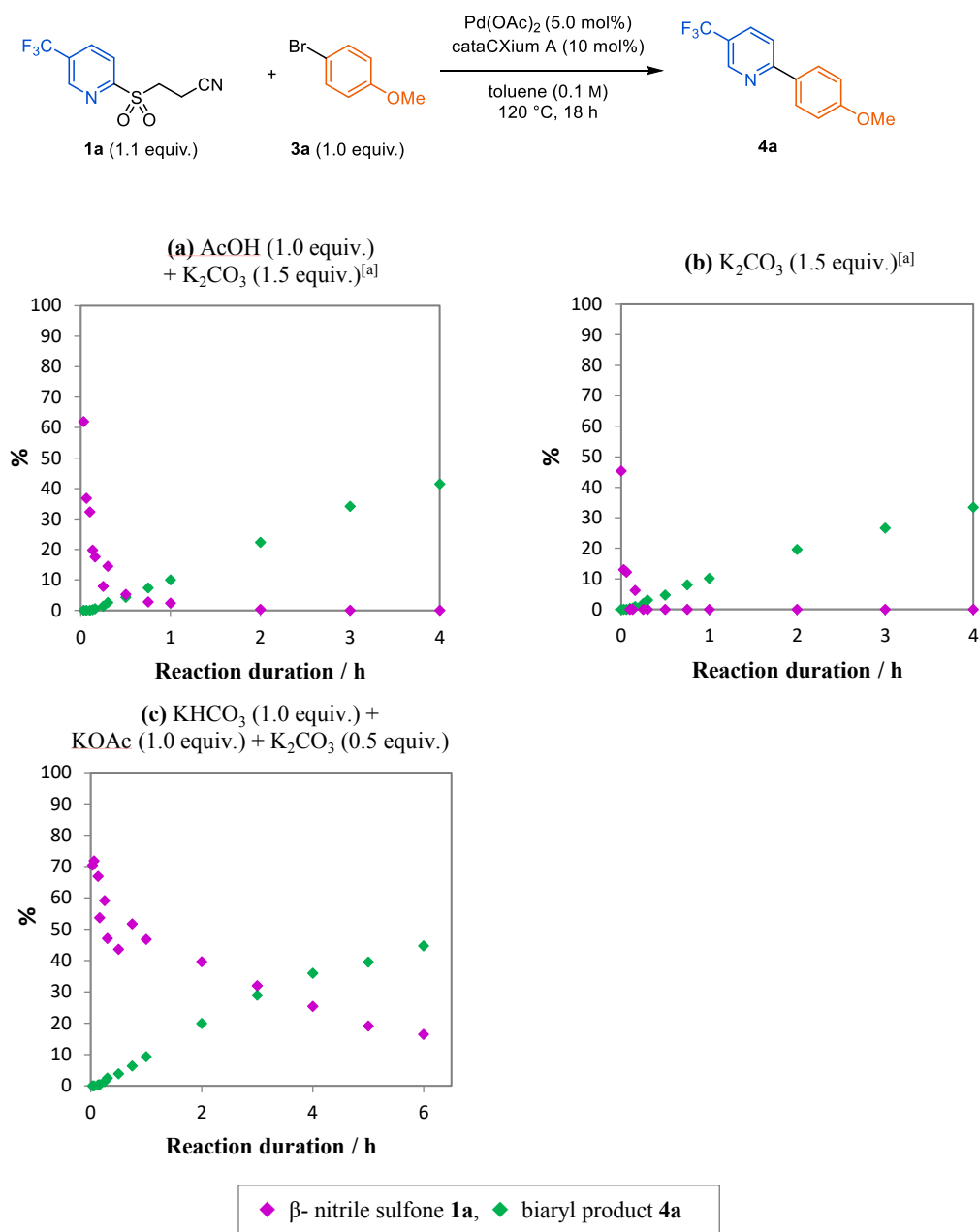


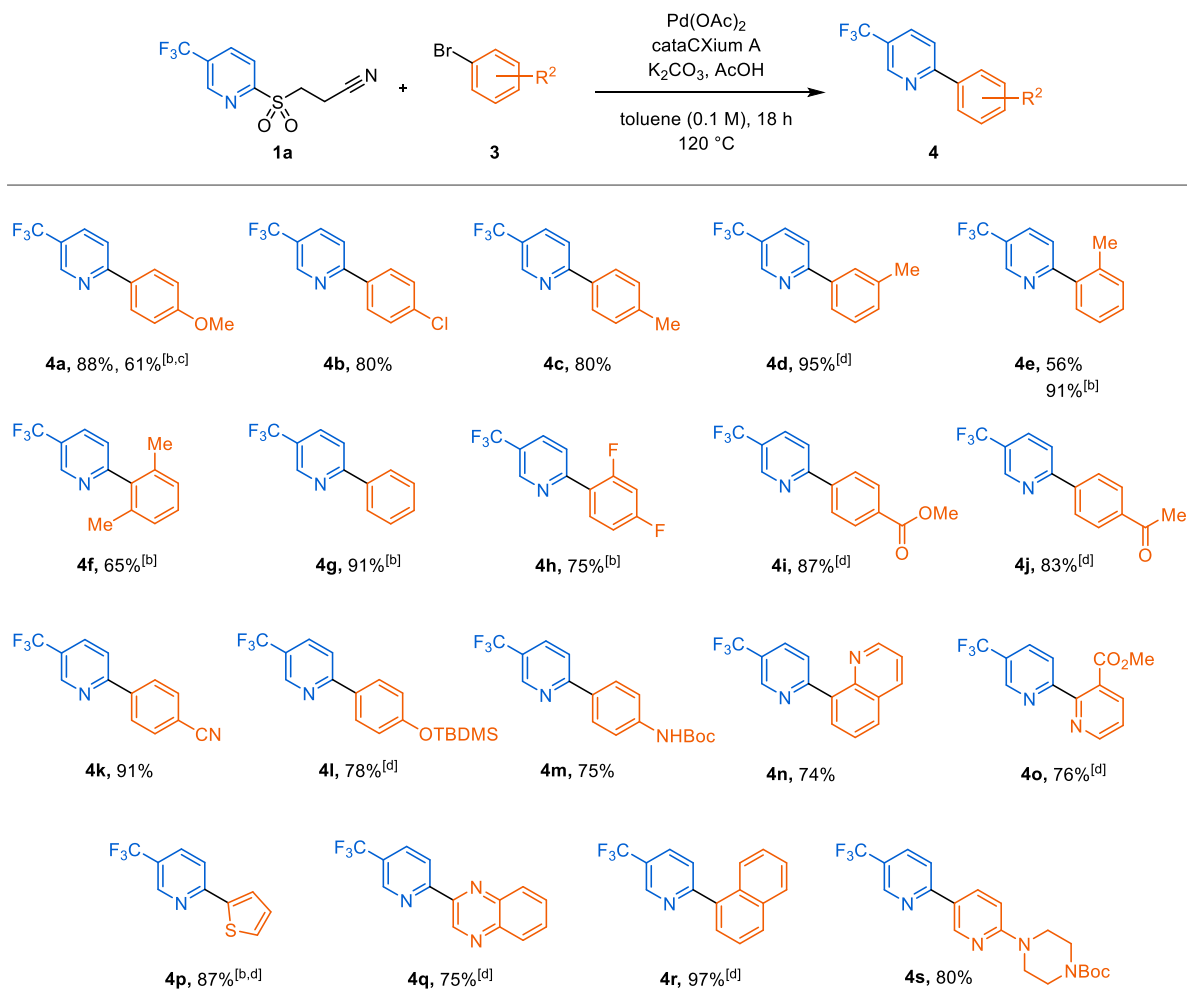
Figure 2.4 HPLC monitoring of the consumption of β-ester sulfone **1a** in purple, and production of biaryl product **4a** in green over the first 4 – 6 hours of the reaction (hours, x-axis). The yield/consumption (% , y-axis) is determined using *p*-ditolylether as an internal standard. Points were calculated by removing reaction aliquots at time intervals and analysing the sample by HPLC analysis. ^[a]These data sets were repeated multiple times (× 3).

2.2.5. Reaction scope of the cross-coupling reaction of heteroaromatic β -nitrile sulfones and aryl bromides

To establish the reaction scope, sulfone **1a** was first reacted with varying aryl halide electrophilic coupling partners (**Table 2.6**). Exploration of the reaction scope was performed in collaboration with a former post-doctorate fellow in the Willis group, Dr. Loïc Pantaine, and the relevant compounds synthesised by him are specifically indicated.

The reaction worked more efficiently with aryl bromides than with aryl chlorides, exemplified through the 88% yield of biaryl **4a** using 4-bromoanisole, compared to the reduced 61% yield when using 4-chloroanisole. This selectivity for bromides over chlorides could be leveraged to obtain 80% yield of coupling product **4b**. The reaction proceeded in high yields regardless of the position of the methyl substituent on the bromotoluene coupling partner (**4c** - **4f**), however *ortho*-substituted aryl bromides required a slight higher reaction temperature of 130 °C (**4e**, **4f**). Pleasingly, a good 75% yield of difluorinated 2-arylpyridine **4h** was achieved, which is a widely used ligand in iridium photocatalysts and luminescent platinum complexes.^[4c, 6] The reaction exhibited a good tolerance for a range of functionality on the electrophilic partner; high yields were achieved when using aryl halides containing esters, ketones, nitriles, protected alcohols and amines (**4i** - **4m**). Heteroaryl halides were also compatible, giving quinoline (**4n**), substituted pyridine (**4o**, **4s**), thiophene (**4p**) and quinoxaline (**4q**) products in high 74 – 87% yields.

Table 2.6 Scope of the desulfurative cross-coupling of heteroaromatic β -nitrile sulfones with (hetero)aryl halides: Variation of the electrophilic coupling partner with β -nitrile sulfone **1a**.^[a]

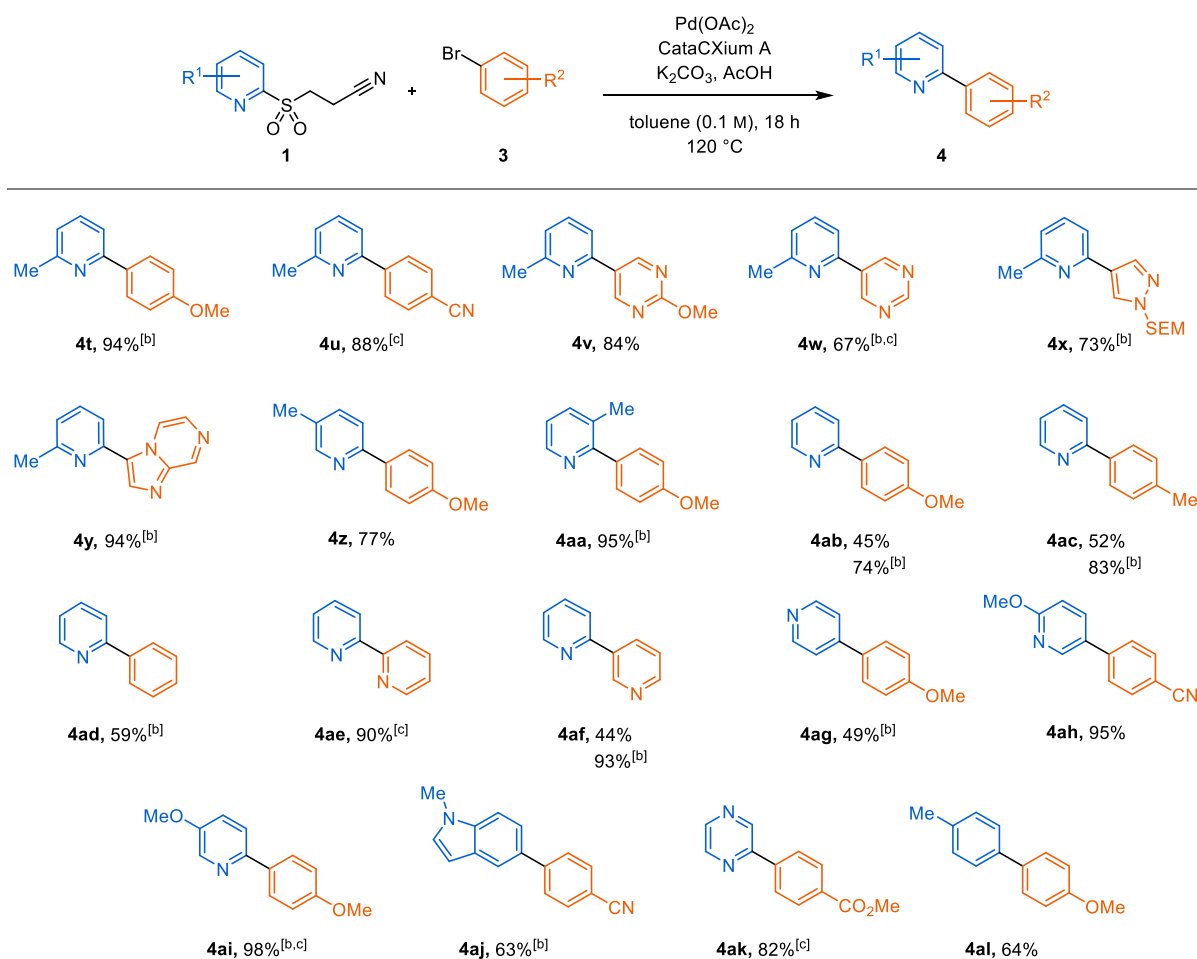


^[a] Isolated yields. Reaction conditions: pyridine sulfone (0.22 mmol, 1.1 equiv.), aryl halide (0.20 mmol, 1.0 equiv.), K_2CO_3 (0.30 mmol, 1.5 equiv.), AcOH (0.20 mmol, 1.0 equiv.), $\text{Pd}(\text{OAc})_2$ (5.0 mol %), cataCXium A (10 mol %), toluene (0.10 M), 120 °C, 18 h. ^[b] Reaction run at 130 °C. ^[c] Using 4-chloroanisole. ^[d] Compounds synthesised by Dr. Loïc Pantaine.

Next, varying the heteroaryl β -nitrile sulfone reagent was explored (**Table 2.7**). Encouragingly, 6- and 5-methyl substituted pyridine sulfones reacted with comparable efficacy to 5-trifluoromethyl pyridine sulfone **1a** (**4t**, **4u**, **4z**), despite being less electron-deficient. More challenging couplings to nitrogen-rich heteroaryl halides were successful, giving pyrimidines (**4v**, **4w**), pyrazole (**4x**) and imidazo[1,2-*a*]pyrazine (**4y**) products in good to high yields. Steric incumbrance vicinal to the masked sulfinate group was well tolerated when the reaction was run at 130 °C, giving 95% of 2-arylpyridine **4aa**.

Moreover, to achieve good to high yields using unsubstituted pyridine sulfones (**4ab** - **4ag**), a raised temperature of 130 °C was often needed; substantially reduced yields were observed when the reactions were run at 120 °C (**4ab**, **4ac**, **4af**). This result is consistent with previous mechanistic study of desulfinative cross-coupling reactions, which demonstrate that extrusion of SO₂ during the catalytic cycle is easier with electron-deficient pyridine sulfinates, as a weaker pyridine *N*-Pd co-ordination in the transmetallation complex is seen (Section 1.6.2, Figure 1.10). This is also the case when using pyridine sulfinates with substituents able to disrupt this co-ordination (6-position). Electron-rich pyridine sulfones were also efficient coupling partners, giving biaryls **4ah** and **4ai** in excellent yields. Markedly, this methodology was extended to other heteroaromatic β-nitrile sulfones, with *N*-methylindole **4aj** and pyrazine **4ak** obtained in 63% and 82% yields respectively. Although not the focus of this work, *p*-tolyl β-nitrile sulfone could be reacted under these conditions to give a 64% yield of carbocyclic biaryl **4al**.

Table 2.7 Scope of the desulfurative cross-coupling of heteroaromatic β -nitrile sulfones with (hetero)aryl halides: Variation of nucleophilic coupling partner.^[a]

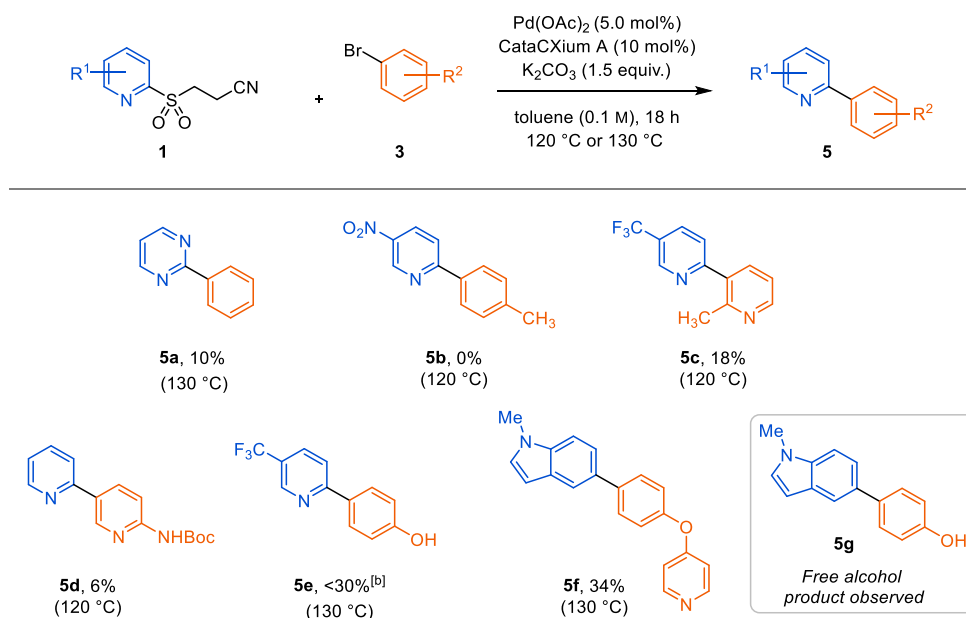


^[a] Isolated yields. Reaction conditions: pyridine sulfone (0.22 mmol, 1.1 equiv.), aryl halide (0.20 mmol, 1.0 equiv.), K_2CO_3 (0.30 mmol, 1.5 equiv.), AcOH (0.20 mmol, 1.0 equiv.), $\text{Pd}(\text{OAc})_2$ (5.0 mol %), cataCXium A (10 mol %), toluene (0.10 M), 120 °C, 18 h. ^[b] Reaction run at 130 °C. ^[c] Compounds synthesised by Dr. Loïc Pantaine.

The substrates that gave low or no yield of the desired biaryl are summarised in **Table 2.8**. Notably, decomposition of the pyrimidine and 5-nitropyridine β -nitrile sulfones were observed under the reaction conditions, leading to the formation of a variety of compounds but trace, or none, of the desired biaryl (**5a**, **5b**). As previously shown, the cross-coupling reaction was compatible with carbocyclic electrophilic partners with an *ortho*-methyl substituent (**4e**) or containing a Boc-protected amine (**4m**). However, using analogous pyridine halides gave comparably poorer results (**5c** – **5d**). This discrepancy in reactivity could be due to the more electron-deficient pyridine halides being more likely

to undergo metal-mediated homo-coupling (pyr-pyr) than the corresponding carbocyclic reagent,^[8] and/or the pyridine nitrogen unproductively binding to palladium. Use of a free alcohol-containing electrophile gave a poor yield (**5e**), possibly due to the buffering nature of the acid/base conditions being incompatible with substrates with an acidic proton. Although only 34% of ether-containing biaryl (**5f**) was isolated, the ether-cleaved free alcohol product was observed (**5g**). Therefore, the lower product yield can likely be attributed to the stability of the electrophilic fragment or final product under the reaction conditions, rather than poor cross-coupling success.

Table 2.8 Poor yielding substrates when using β -nitrile sulfones.



^[a] Isolated yields. Reaction conditions: pyridine sulfone (0.22 mmol, 1.1 equiv.), aryl halide (0.20 mmol, 1.0 equiv.), K₂CO₃ (0.30 mmol, 1.5 equiv.), AcOH (0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (5.0 mol %), cataCXium A (10 mol %), toluene (0.10 M), 18 h. ^[b] Compounds synthesised by Dr. Loïc Pantaine.

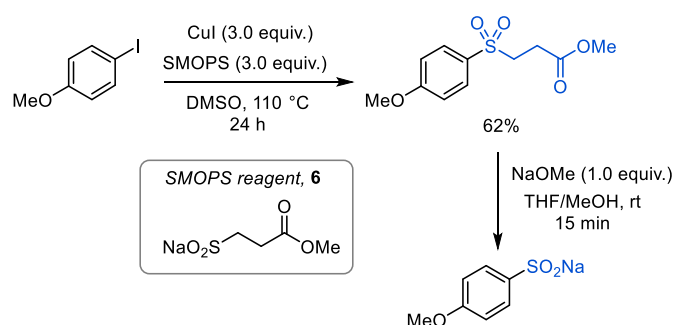
2.3. Heteroaromatic β -ester sulfones

2.3.1. Introduction and synthesis of heteroaromatic β -ester sulfones

Although β -nitrile sulfones have shown to be effective coupling partners, we wanted to establish the generality of the base-activated latent sulfinate strategy. As a result, we

chose to explore other electron-withdrawing groups in place of a nitrile that would undergo a similar mechanism of release. Hence the β -ester sulfone functionality was chosen for investigation, starting with the simple methyl ester **2**.

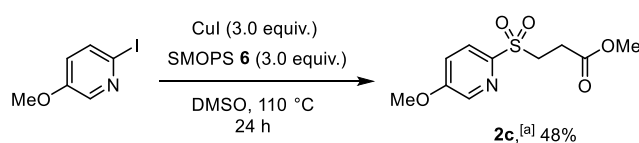
Compared to the β -ethylnitrile group, the β -ethylester functionality is more established as a sulfur protecting group. The β -ester group has been used to protect thiols,^[102] and in the synthesis of sulfinamide salts.^[103] However, the β -ester functionality is most prominently used as a precursor and protecting group for sulfinate salts.^[78a, 83, 104] This masked sulfinate approach was popularised in seminal work by Baskin and Wang in 2002,^[78a] where sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS **6**) was introduced as an organic SO₂-installing reagent. Baskin and Wang reported an efficient synthesis of masked aryl sulfonates *via* a Cu(I)-mediated coupling of the SMOPS reagent **6** with aryl iodides or bromides (**Scheme 2.2**). In this report, the metal sulfinate salt is then freed by treatment of the sulfone with NaOMe. As a consequence of this work, the synthesis of metal sulfonates for use in desulfonative cross-coupling reactions commonly proceeds *via* β -ester sulfone intermediates.^[11, 88, 105] Thus using β -ester sulfones directly as coupling partners in Pd-catalysed arylations is further advantageous, as it reduces the step-count of synthetic sequences.



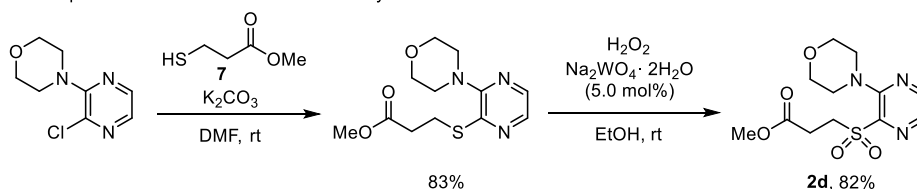
Scheme 2.2 Baskin and Wang's synthesis of sodium arylsulfinate salts *via* β -ester sulfones.

Because they are established masked sulfinate reagents, the synthetic routes to access β -ester sulfones are more straightforward than for β -nitrile sulfones. In addition to being accessible *via* all the routes previously discussed for β -nitrile sulfones (**Scheme 2.2**), the aforementioned SMOPS reagent **6** offers a one-step synthesis of β -methylester sulfones (**Scheme 2.3 A**). Alternatively, commercially available thiol **7** can be readily reacted with heteroaromatic halides, either by nucleophilic aromatic substitution (S_NAr) or by metal-catalysed processes if required,^[83, 104b, 104c, 106] and then oxidised at sulfur (**Scheme 2.3 B**). These additional synthetic methods better exploit the vast libraries of commercially available heteroaryl halides, allowing more diverse β -ester sulfone reagents to be synthesised compared to the β -nitrile reagents.

A. Cu-mediated sulfone formation using SMOPS **6**



B. Nucleophilic aromatic substitution followed by S-oxidation



Scheme 2.3 Additional routes to synthesise β -ester sulfone reagents, demonstrated by select examples.
^[a] Compound synthesised by Dr. Loïc Pantaine.

2.3.2. Optimisation of β -ester sulfones in cross-coupling processes

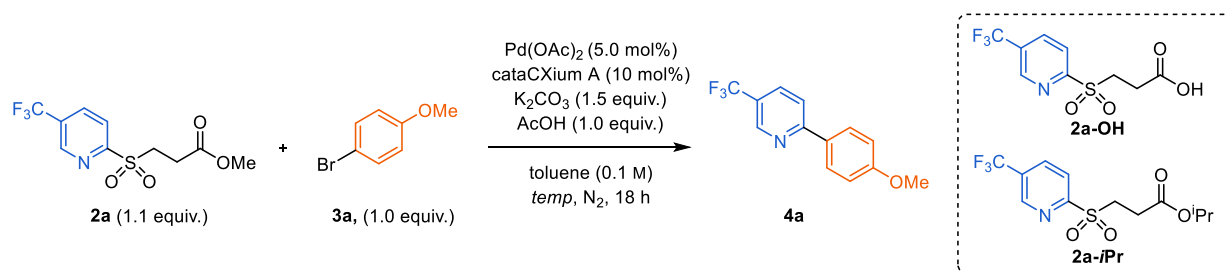
To investigate and compare the reactivity of β -ester sulfones to β -nitrile sulfones, the reaction of β -methylester sulfone **2a** and 4-bromoanisole **3a** was used as a model system (**Table 2.9**).

Promisingly, β -ester sulfone **2a** gave a high 73% yield (entry 1) at 120 °C, using the reaction conditions optimised for the β -nitrile system. Unlike the β -nitrile system,

increasing the temperature did not improve the yield (entry 2). Furthermore, reducing or completely removing the acetic acid additive improved the reaction yield (entries 4 – 7), with an 81% yield of biaryl **4a** obtained when the acetic acid was fully omitted from the system (entry 7).

It was postulated that the ester could be hydrolysing to the corresponding acid *in situ*. To test this, an authentic sample of acid **2a-OH** was synthesised, which expectantly performed poorly as a masked sulfinic acid under the reaction conditions (entries 8 and 9). However, no evolution of the acid **2a-OH** from β -ester sulfone **2a** was seen in the reaction mixture by HPLC or ^1H NMR analysis. The *iso*-propyl ester derivative **2a-i-Pr**, which should be less susceptible to hydrolysis, also gave a slightly reduced yield of coupling product **4a** (entry 10).

Table 2.9 Initial optimisation of the β -ester sulfone system.



Entry	Variation from equation above	Temp / °C	Yield ^[a] / %
1	-	120	73
2	-	130	(65)
3	-	110	56
4	AcOH (0.75 equiv.)	120	77
5	AcOH (0.50 equiv.)	120	72
6	AcOH (0.25 equiv.)	120	78
7	No AcOH	120	81
8	Using 2a-OH instead of 2a	120	2
9	Using 2a-OH instead of 2a , No AcOH	120	1
10	Using 2a-iPr instead of 2a	120	69 ^[b]
11	TMSOK (1.5 equiv.) instead of K ₂ CO ₃	120	41
12	KOPiv (1.5 equiv.) instead of K ₂ CO ₃	120	9
13	KOt-Am (25% in toluene) (1.5 equiv.) instead of K ₂ CO ₃	120	36
14	Cs ₂ CO ₃ (1.5 equiv.) instead of K ₂ CO ₃ (no AcOH)	120	84
15	K ₂ CO ₃ (2.0 equiv.) instead of K ₂ CO ₃ (no AcOH)	120	81
16	PCy ₃ (5.0 mol%) instead of cataCXium A	120	64
17	P(<i>t</i> -Bu) ₂ Me•HBF ₄ (5.0 mol%) instead of cataCXium A	120	81

Reaction conditions: pyridine sulfone (0.22 mmol, 1.1 equiv.), 4-bromoanisole (0.20 mmol, 1.0 equiv.), K₂CO₃ (0.30 mmol, 1.5 equiv.), Pd(OAc)₂ (0.01 mmol, 5.0 mol%), cataCXium A (0.02 mmol, 10 mol%), toluene (0.1 M).^[a] HPLC yield determined using *p*-ditolylether as an internal standard and isolated yields are in parentheses. ^[b] Reaction run on a 0.10 mmol scale.

Reaction monitoring of the consumption of β -ester sulfone **2a**, both with and without acetic acid in the reaction (**Figure 2.5 A - B**), showed that slower consumption of sulfone is observed when acetic acid is present; sulfinate release is faster when no acetic acid additive is used. Therefore, addition of acetic acid affects the rate of sulfinate release from the β -nitrile sulfone and β -ester sulfone to different extents, with the β -ester sulfone system favouring no acetic acid.

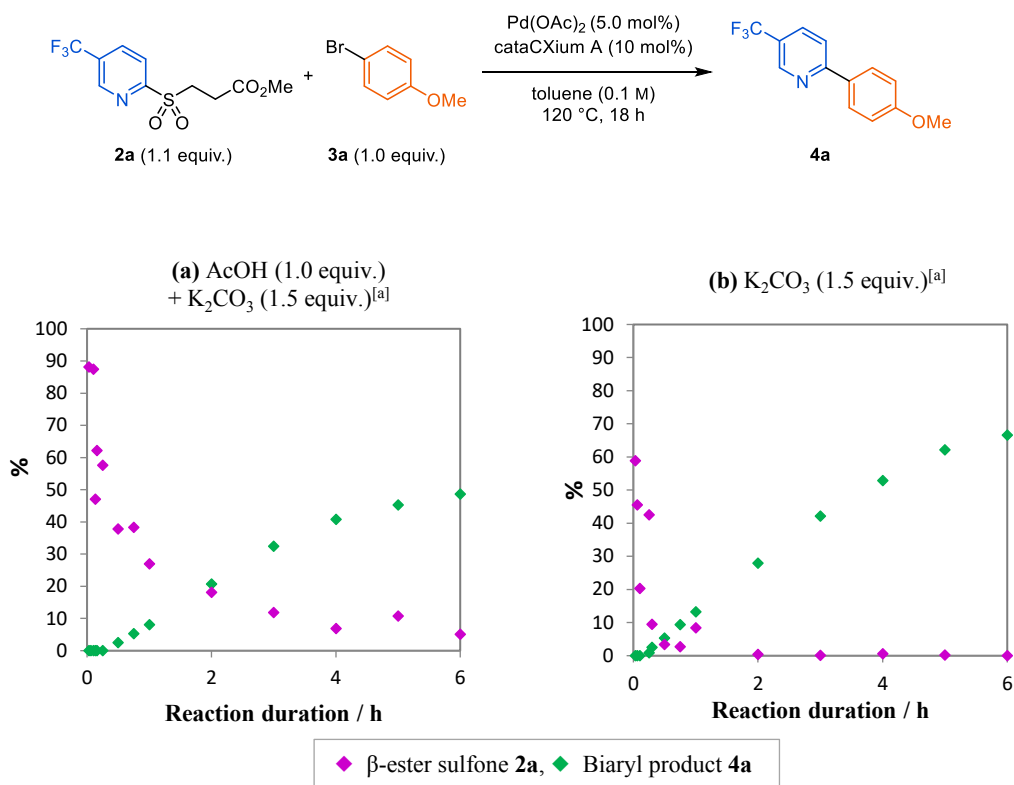
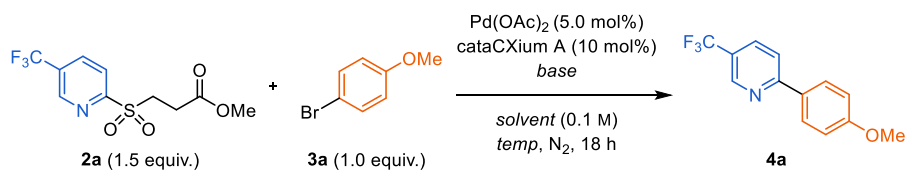


Figure 2.5 HPLC monitoring of the consumption of β-ester sulfone **2a** in purple, and production of biaryl product **4a** in green over the first 6 hours of the reaction (h, x-axis). The yield/consumption (% , y-axis) is determined using *p*-ditolylether as an internal standard. Points were calculated by removing reaction aliquots at time intervals, and analysing the sample by HPLC analysis. ^[a] In subsequent monitored reaction runs the same trends were observed.

Final tuning of the reagent stoichiometry, by slightly increasing the equivalents of pyridine sulfone **2a** and base, provided the best conditions for this system, with an isolated 87% yield of biaryl **4a** (Table 2.10, entry 4). This result is equivalent to the optimised yield of the analogous β-nitrile sulfone system (88% of biaryl **2a**). Carbonate bases performed best (entries 11 – 15), similarly to the previous desulfinative coupling systems (metal sulfinates, allylsulfones and β-nitrile sulfones). Although both potassium and caesium carbonate bases gave comparable yields, potassium carbonate was selected as it is less expensive, less hygroscopic and gave a cleaner reaction. The reaction also worked well with aromatic solvents with higher boiling points (entries 5 – 7). Interestingly, the same yield was obtained when running the reaction at 130 °C (entry 8) instead of 120 °C (entry 4).

Table 2.10 Final optimisation of β -ester sulfones in desulfinative cross-coupling.



Entry	Base	Solvent	Temp / °C	Yield ^[a] / %
1	Cs_2CO_3 (1.5 equiv.)	toluene	120	84
2	Cs_2CO_3 (2.0 equiv.)	toluene	120	88
3	K_2CO_3 (1.5 equiv.)	toluene	120	91 (86)
4	K_2CO_3 (2.0 equiv.)	toluene	120	92 (87)
5	K_2CO_3 (2.0 equiv.)	toluene:sulfolane (1:1)	120	93
6	K_2CO_3 (2.0 equiv.)	anisole	120	91 (91)
7	K_2CO_3 (2.0 equiv.)	<i>p</i> -xylene	120	(89)
8	K_2CO_3 (2.0 equiv.)	toluene	130	88

Reaction conditions: pyridine sulfone (0.30 mmol, 1.5 equiv.), 4-bromoanisole (0.20 mmol, 1.0 equiv.), K_2CO_3 (0.40 mmol, 2.0 equiv.), $\text{Pd}(\text{OAc})_2$ (0.01 mmol, 5.0 mol%), cataCXium A (0.02 mmol, 10 mol%), toluene (0.1 M).^[a] HPLC yield determined using *p*-ditolylether as an internal standard and isolated yields are in parentheses.

2.3.3. Reaction scope of the cross-coupling reaction of heteroaromatic β -ester sulfones and aryl bromides

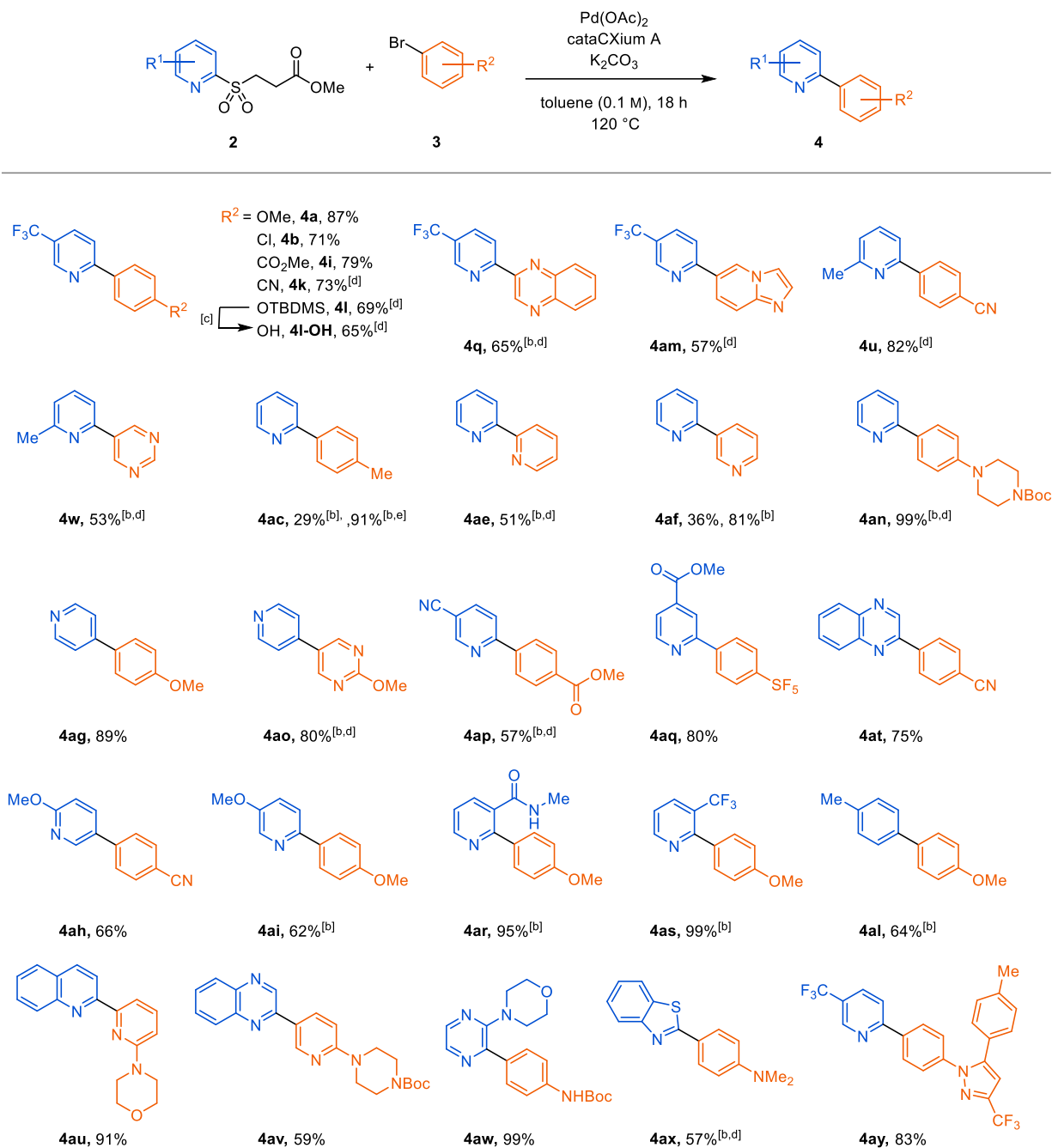
The reaction scope of β -methylester pyridyl reagents was explored in collaboration with my colleague Dr. Loïc Pantaine; the compounds synthesised by Dr. Pantaine are indicated in the table below.

The β -methylester sulfone system exhibited good functional group tolerance and reaction success, comparable to that of the β -nitrile sulfones (**Table 2.11**). The reactivity of the two different base-activated masked sulfinate reagents can be readily compared by looking at the reactions of 5-trifluoromethylpyridyl β -ester sulfone (**4a**, **4b**, **4i**, **4k**, **4l**, **4q**) and 6-methylpyridyl β -ester sulfone (**4u**, **4w**), which gave the desired 2-arylpyridines in similarly high yields to the analogous β -nitrile sulfone substrates (see **Table 2.6**). A telescoped base-mediated deprotection of protected alcohol **4l**, accessed free alcohol

product **4l-OH** in 65% yield. As also observed for the β -nitrile sulfone system, efficient coupling of unsubstituted 2-pyridyl β -ester sulfones required a reaction temperature of 130 °C (**4ac** – **4ao**). 2-*p*-Tolylpyridine **4ac** was a poor yielding substrate under the optimised ester conditions, despite full consumption of the masked sulfinate reagent. Interestingly, addition of acetic acid (1.5 equiv.) into the reaction caused a dramatic increase in the product yield from 29% to 91%. Although not further explored, in this instance the acid additive could potentially allow for a more optimal rate of sulfinate release.

Electron-poor β -ester sulfones were compatible with the cross-coupling reaction, giving good to high yields of products containing nitriles (**4ap**), esters (**4aq**) and amides (**4ar**), as well as quinoxaline products (**4at**, **4av**). Electron-rich β -ester sulfones were also employed successfully, albeit they did not perform quite as well as their β -nitrile counterparts (**4ah**, **4ai**). 2-Pyridyl nucleophiles with substituents in the 3-position, adjacent to the sulfinate coupling site, coupled efficiently at 130 °C giving arylpyridines **4ar** and **4s** in $\geq 95\%$ yields. 2-Quinoline and 2-quinoxaline sulfones reacted successfully with pyridyl electrophiles, enabling the construction of more complex bisazines (**4au**, **4av**). Pyrazine containing compound **4aw** was synthesised in a high 99% yield; this motif is a synthetic intermediate for a class of ROR Gamma modulators.^[106] Through the challenging coupling of benzothioazole β -methyl ester sulfone with 4-bromo-*N,N*-dimethylaniline, we achieved 57% yield of benzothiazole **4ax**, an analogue of PET scanning radiopharmaceutical Flutemetamol (¹⁸F).^[107] Finally, the reaction of sulfone **1a** with a halogenated fragment of anti-inflammatory drug celecoxib,^[108] gave 83% of complex product **4ay**.

Table 2.11 Scope of the desulfurative cross-coupling reaction of heteroaromatic β -ester sulfones with (hetero)aryl halides.^[a]



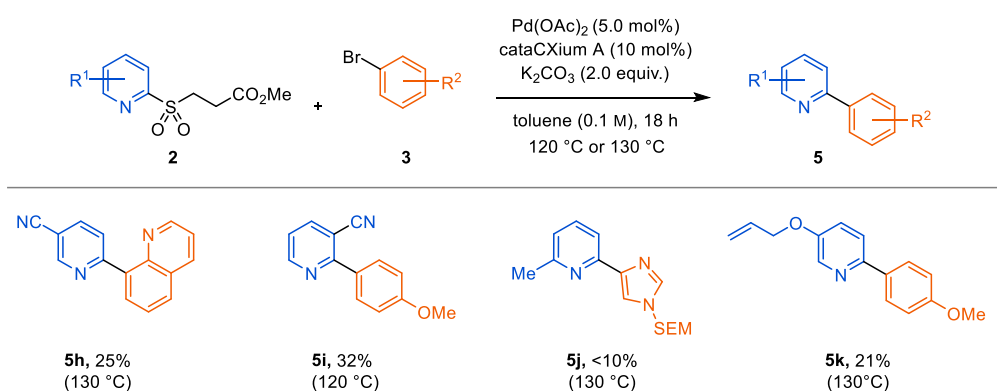
^[a] Isolated yields. Reaction conditions: pyridine sulfone (0.30 mmol, 1.5 equiv.), aryl halide (0.20 mmol, 1.0 equiv.), K_2CO_3 (0.40 mmol, 2.0 equiv.), $\text{Pd}(\text{OAc})_2$ (5.0 mol %), cataCXium A (10 mol %), toluene (0.10 M), 120 °C, 18 h. ^[b] Reaction run at 130 °C. ^[c] Telescoped deprotection of protected phenol product directly after cross-coupling reaction: reaction temperature lowered to 85 °C, ethanol (2 mL), 2 M aq. Solution of K_2CO_3 (0.2 mL, 0.4 mmol), 18 h. ^[d] Compounds synthesised by Dr. Loïc Pantaine. ^[e] Addition of AcOH (1.5 equiv.). SEM = [2-(trimethylsilyl)ethoxy]methyl acetal.

Substrates that gave poor reaction yields in the β -ester sulfone system are summarised in

Table 2.12. Pyridyl nucleophilic partners with nitrile substituents were generally

challenging to couple under desulfinate conditions, even at 130 °C (**5h**, **5i**). This was surprising due to the high yield of biaryls achieved using the similarly electron-poor, 5-trifluoromethyl substituted pyridines. This lack of reaction success may be due to undesired reactivity at the nitrile group under the palladium-catalytic conditions;^[109] however, no major by-product was observed or isolated from the reaction. The SEM-protected imidazole electrophile was not well tolerated, leading to only trace formation of product **5j**. The imidazole nitrogen could potentially co-ordinate to the Pd centre and lead to unproductive pathways. Use of an O-allylpyridine reagent resulted in a low 21% yield of biaryl **5k**. This is likely due to Pd-mediated deallylation, similar to the activation mechanism of allylsulfone reagents.^[90]

Table 2.12 Poor yielding substrates when using β -ester sulfones.



^[a] Isolated yields. Reaction conditions: pyridine sulfone (0.30 mmol, 1.5 equiv.), aryl halide (0.20 mmol, 1.0 equiv.), K₂CO₃ (0.40 mmol, 2.0 equiv.), Pd(OAc)₂ (5.0 mol %), cataCXium A (10 mol %), toluene (0.10 M), 18 h.

2.4. Alternative base-activated latent sulfinates

The success of the β -nitrile and β -ester masked sulfinates encouraged the extension of this strategy to masking groups with higher molecular weight, that have similar modes of base activation. Moreover, the organic by-products formed by unmasking β -nitrile and β -

ester sulfones have low boiling points and poor toxicity profiles, making them less favourable for large-scale chemistry; acrylonitrile (bp = 77 °C), methyl acrylate (bp = 80 °C). Therefore, four potential alternative masking groups were designed, derived from diethyl fumarate **8**, ethyl cinnamate **9**, ethyl crotonate **10** and *N*-methyl maleimide **11** (**Figure 2.6**). Upon treatment with base, it was envisaged that these masked sulfinate reagents would release the sulfinate and high-boiling, less toxic by-products, making them more amenable to larger scale reactions.

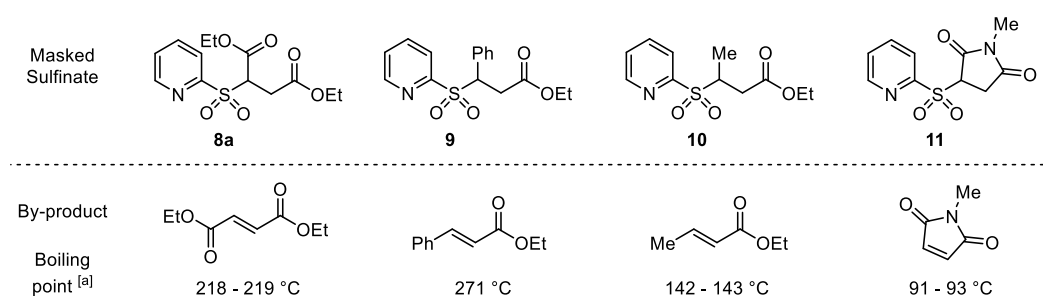


Figure 2.6 Alternative base-activated masked sulfinate reagents **8** – **11**. [a] Boiling points of alkene by-products obtained from Merck's Sigma Aldrich catalogue database, assuming atmospheric pressure.

To assess the reactivity of these alternative masked sulfonates, 2-pyridine sulfones **8a**, **9**, **10** and **11** were synthesised, and reacted with 4-bromotoluene under the β -ester sulfone conditions (**Figure 2.7**). The succinate sulfone **8a**, gave the most promising results, giving 96% of the desired 2-arylpyridine at 130 °C (**Figure 2.7 A**). This is comparable to the yields obtained when using the corresponding β -nitrile sulfone (83%) or the β -ester sulfone (91%). Both the cinnamate-masked sulfinate **9** and crotyl-masked sulfinate **10** showed some promising initial reactivity, giving 22% and 37% of biaryl **4ac** respectively under the β -ester sulfone conditions (**Figure 2.7 B - C**). Performing the cross-coupling of cinnamate masked sulfinate **9** in anisole instead of toluene, boosted the product yield to 30% yield, with a 94% recovery of the cinnamate by-product. A slight increase in yield to 34% was seen when acetic acid was added to the reaction, with 78% recovery of ethyl

cinnamate. The high recovery of cinnamate by-product and remaining 4-bromotoluene indicates that the sulfone is releasing the sulfinate salt, yet the Pd-catalysed arylation is not proceeding. To further investigate this system, it would be worthwhile to screen the reaction in non-aromatic solvents to assess if the by-product is interfering in the reaction.

The maleimide-derived sulfone **11** gave poor results, with low yields of biaryl **4ac**, numerous side-products and no recovery of the sulfone starting material or maleimide by-product (**Figure 2.7 D**). This suggests that sulfone **11** is not stable under the reaction conditions. As a result of the initially poor results, this line of investigation was not further investigated.

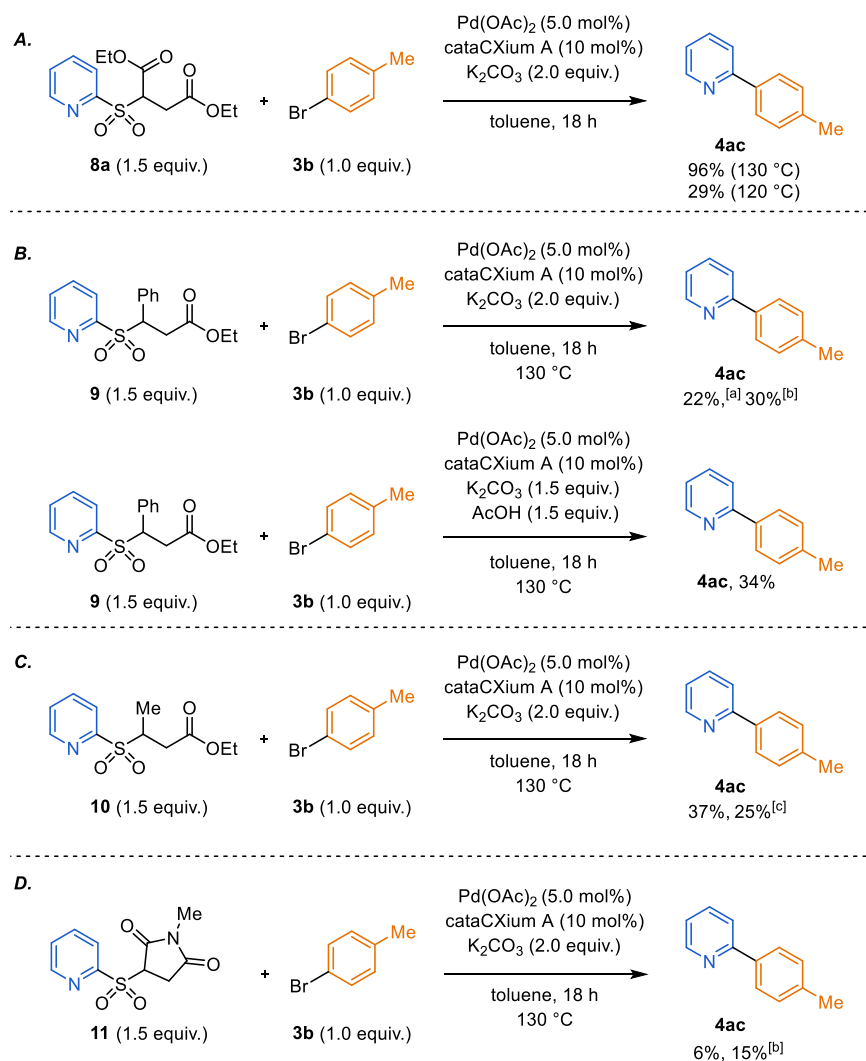
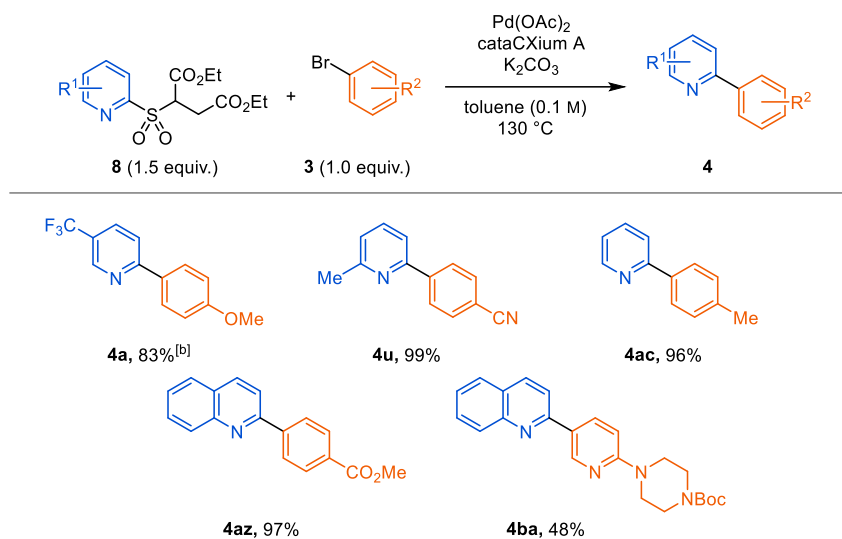


Figure 2.7 Investigation into the reactivity of alternative masked sulfinates **8** – **11**. Isolated yields. ^[a] Run with sulfone (1.4 equiv.), ^[b] Reaction run in anisole (0.1 M) instead of toluene, ^[c] Reaction run in DMF (0.1 M) instead of toluene.

Due to the promising results using the succinate sulfone **8a**, efforts were focused on further exploring this masked sulfinate reagent. Succinate sulfone reagents react with similar efficiency to their β -nitrile and β -ester analogues, as shown through a representative small scope of biaryls (**Table 2.13**). Notably a high 96% of biaryl **4ac** was obtained at 120 °C, whereas the nitrile and ester sulfones afforded 88% and 87% respectively.

Table 2.13 Small scope of the desulfurative cross-coupling of succinate sulfones **8** with aryl bromides.^[a]



^[a] Isolated yields. Reaction conditions: pyridine succinate sulfone (0.3 mmol, 1.5 equiv.), aryl bromide (0.2 mmol, 1.0 equiv.), $\text{Pd}(\text{OAc})_2$ (5.0 mol %), cataCXium A (10 mol %), K_2CO_3 (0.4 mmol, 2.0 equiv.), toluene (0.1 M), 130 °C, 18 h. ^[b] Reaction run at 120 °C

2.5. Desulfurative cross-coupling protocol outside of a sealed vial

The reactions described throughout this chapter so far have been routinely performed in sealed reaction vials on a 0.2 mmol scale (see experimental section 6.2.3 for full procedure). To improve the versatility of this chemistry for larger scale, we set about developing a reaction protocol in a non-pressurised reaction vessel. The investigation commenced by revisiting the reaction of pyridyl sulfones **1a** and **2a** with 4-bromoanisole **3a**. However, this time the reactions were performed on a 0.6 mmol scale in a round bottom flask/ condenser set-up (Table 2.14). The internal reaction temperature was measured by a temperature probe inserted into the reaction mixture.

When the reaction of β -nitrile sulfone **1a** was refluxed in toluene only 25% of biaryl **4a** was observed (entry 1). Changing the reaction solvent to the higher boiling mesitylene allowed the reactions to be run at higher temperatures, and a temperature of 130 °C was found to be key for achieving good yields (entries 2 and 3). Removing the acetic acid

additive marginally reduced the yield (entry 4), whereas substituting acetic acid for the higher boiling propanoic acid more than halved the yield (entry 5). Other high boiling, aromatic solvents that had originally performed well in a sealed vial were explored, with anisole found to be optimum (entries 8 and 9). The use of anisole solvent and a reaction temperature of 130 °C were also key for effective cross-coupling of β -ester sulfone **2a**, giving desired biaryl **4a** in an isolated 85% yield.

Table 2.14 Optimisation of reaction of base-labile masked sulfinates in a non-pressurised system.

EWG = -CN (**1a**)
-CO₂Me (**2a**)

3a

Pd(OAc)₂
cataCXium A
K₂CO₃
(a) or (b)

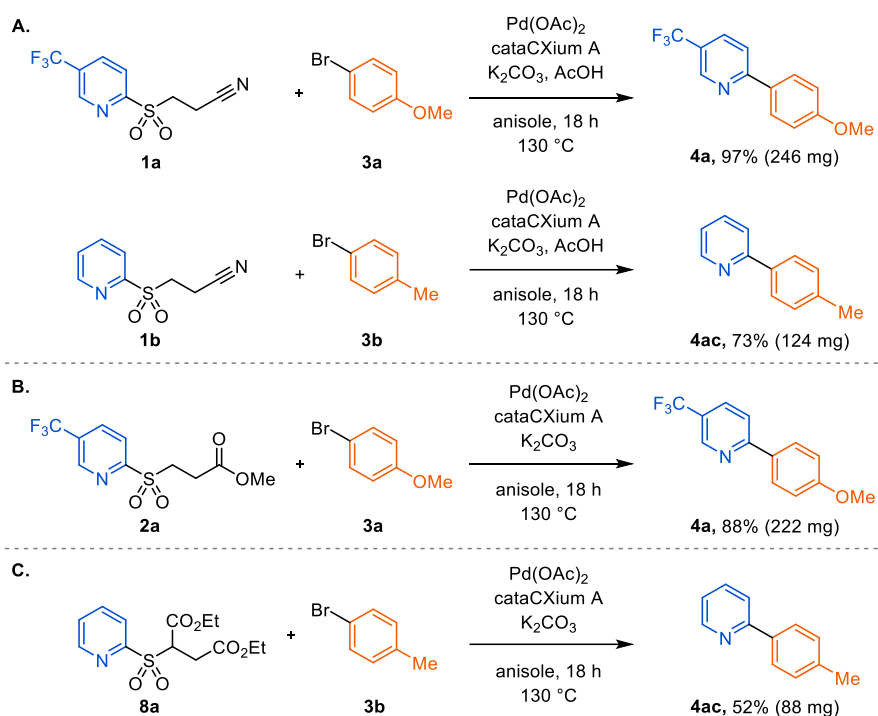
Solvent (0.1 M)
0.6 mmol
50 mL RBF

4a

EWG	Entry	Solvent	Variations to system	Internal Temp. / °C	HPLC yield / %
-CN (a)	1	toluene	-	110	25
	2	mesitylene	-	120	49
	3	mesitylene	-	130	62
	4	mesitylene	no AcOH	130	57
	5	mesitylene	propanoic acid instead of AcOH	130	29
	6	<i>p</i> -xylene	-	130	78 (68)
	7	toluene: sulfolane (1:1)	-	130	55
	8	anisole	-	130	68
	9	anisole	adjusted stoichiometry ^[a]	130	88 (82)
-CO ₂ Me (b)	10	<i>p</i> -xylene	-	130	67
	11	toluene: sulfolane (1:1)	-	130	87 (82)
	12	anisole	-	130	91 (85)
	13	anisole	P(<i>t</i> -Bu) ₂ Me·HBF ₄	130	66
	14	anisole	-	120	47

Reaction conditions: (a) β -nitrile pyridine sulfone (0.66 mmol, 1.1 equiv.), 4-bromoanisole (0.60 mmol, 1.0 equiv.), K₂CO₃ (0.90 mmol, 1.5 equiv.), AcOH (0.60 mmol, 1.0 equiv.), Pd(OAc)₂ (5.0 mol%), cataCXium A (10 mol%), solvent (0.1 M). (b) β -ester pyridine sulfone (0.90 mmol, 1.5 equiv.), 4-bromoanisole (0.60 mmol, 1.0 equiv.), K₂CO₃ (1.2 mmol, 1.5 equiv.), Pd(OAc)₂ (0.03 mmol, 5.0 mol%), cataCXium A (0.06 mmol, 10 mol%), solvent (0.1 M). HPLC yield determined using *p*-ditolylether as an internal standard. Isolated yields are in brackets. ^[a] Adjusted Stoichiometry: pyridine sulfone (0.30 mmol, 1.5 equiv.), AcOH (0.30 mmol, 1.5 equiv.) and K₂CO₃ (0.40 mmol, 2.0 equiv.).

With these new conditions in hand, the reactions of both masked sulfonates were efficiently scaled up to 1.0 mmol in a non-pressurised vessel, giving good to excellent yields of the desired 2-arylpyridines (**Scheme 2.4 A – C**). With no further reaction optimisation, an encouraging 52% of 2-(*p*-tolyl)pyridine **4ac** was obtained from the reaction of succinate sulfone **8a**.



Scheme 2.4 Scaled-up cross-coupling reactions of base-activated latent sulfinate reagents outside of a sealed vial.

2.6. Multi-step elaboration of latent 2-pyridyl sulfinate reagents

In contrast to the palladium labile allylsulfones, an advantage of using base-activated latent sulfonates is that they are more amenable to multi-step functionalisation, particularly regarding alkene transformations and orthogonal Pd-mediated reactions. Therefore, to demonstrate the robustness of these reagents two key goals were set: (1) to achieve sequential Pd-catalysed cross-coupling reactions around the pyridine core of the

sulfinate reagent and (2) to perform alkene chemistry on a substituent on a masked sulfinate reagent. To achieve these goals, three key sulfone reagents were envisioned (**Figure 2.8 A – C**).

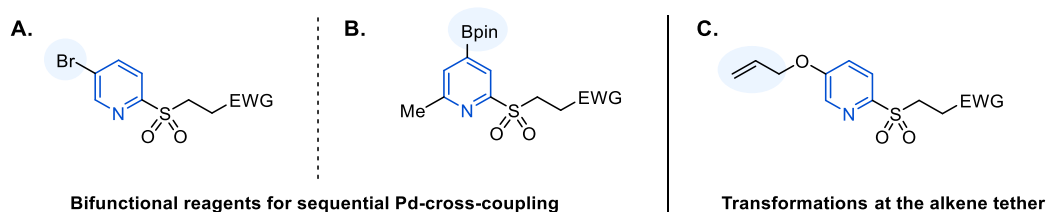
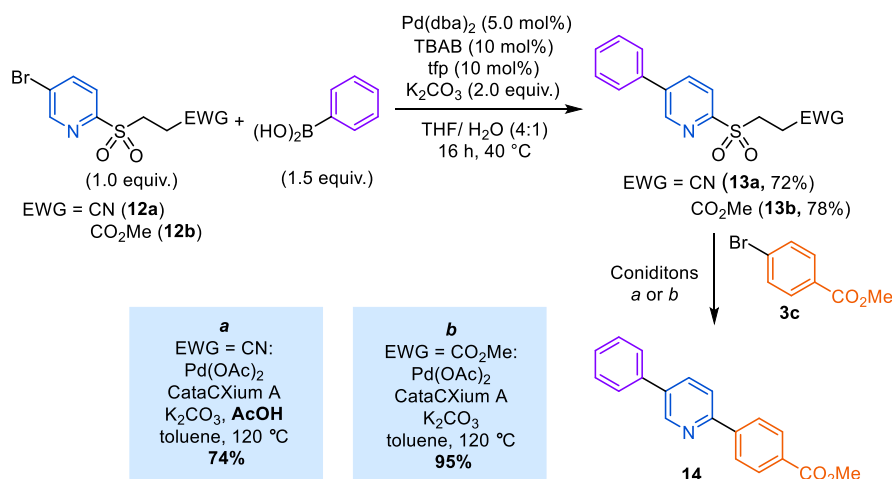


Figure 2.8 Planned substrates to perform multi-step derivatisations.

2.6.1. Bidirectional Pd-catalysed cross-coupling chemistry

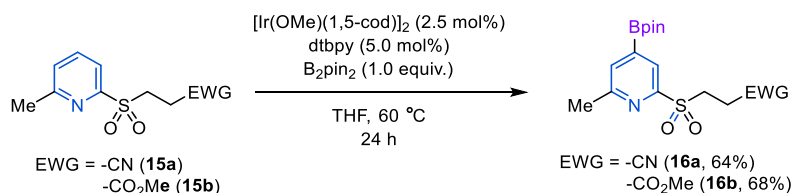
To achieve the first goal, the plan was to use masked sulfinate reagents with a second reactive functionality on the pyridine core, that was either an electrophilic or nucleophilic site. It was intended that these bifunctional reagents would chemoselectively cross-couple under different Pd-mediated conditions to construct more complex heteroaryl structures.

Firstly, 5-bromopyridine sulfones (**12a** and **b**) were synthesised and reacted as the electrophilic coupling partner with phenylboronic acid under typical SMC conditions,^[110] to give the corresponding biaryl sulfones **13a** and **b** in 72% (β -nitrile) and 78% (β -ester) yields respectively (**Scheme 2.5**). Notably, both sulfinate masking groups were stable and did not react under these SMC conditions. Biaryl sulfones **13a** and **b** were then reacted as nucleophiles under the corresponding desulfinate coupling conditions (*a* or *b*) to give high yields (74% and 95% respectively) of diarylpyridine **14**.



Scheme 2.5 Bifunctional pyridine reagents in a Pd-mediated cross-coupling sequence.

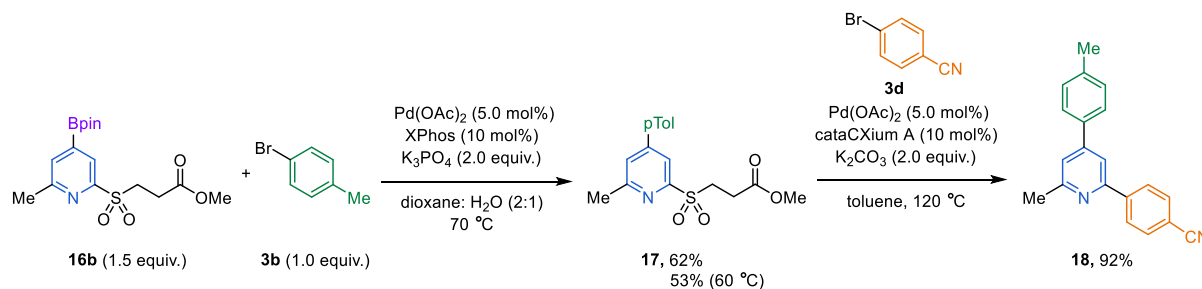
To further establish the compatibility of the base-labile masked sulfinate groups with transition metal-mediated chemistry, boronate esters **15a** and **b** were accessed *via* Ir-catalysed borylation of β -nitrile and β -ester sulfones **16a** and **b** in 64% and 68% yields respectively (**Scheme 2.6**).^[111] To ensure economical product isolation, purification *via* a series of trituration and filtration was favoured over silica column chromatography. This was because hydrolysis of the boronate ester products was observed to occur on silica.



Scheme 2.6 Ir-catalysed borylation of masked sulfinate reagents **15a** and **b**.

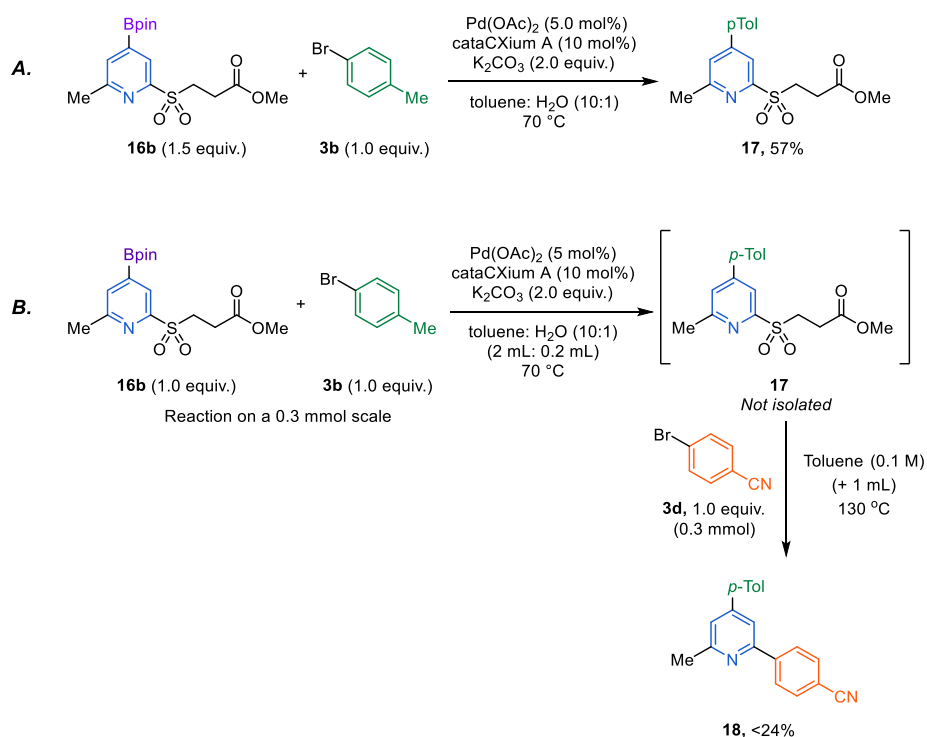
Next, the aim was to react borylated pyridine reagent **16b** selectively as a nucleophilic reagent in tandem cross-coupling reactions: first at the boronate ester functionality and then at the masked sulfinate. The borylated β -ester sulfone **16b** successfully reacted with 4-bromotoluene **3b** under SMC conditions to give 62% of biaryl sulfone **17** (**Scheme 2.7**).^[112] A reaction temperature of 70 °C was needed to achieve good conversion.

Unreacted β -ester sulfone **16b** was observed in the crude reaction mixture, highlighting the stability of masked sulfinate functionality under these conditions. To complete the sequence, diarylpyridine **18** was then obtained in an excellent 92% yield from sulfone **17** under the optimised desulfinate coupling conditions.



Scheme 2.7 Two-step Pd-catalysed cross-coupling sequence, starting from borylated pyridine sulfone **16b**.

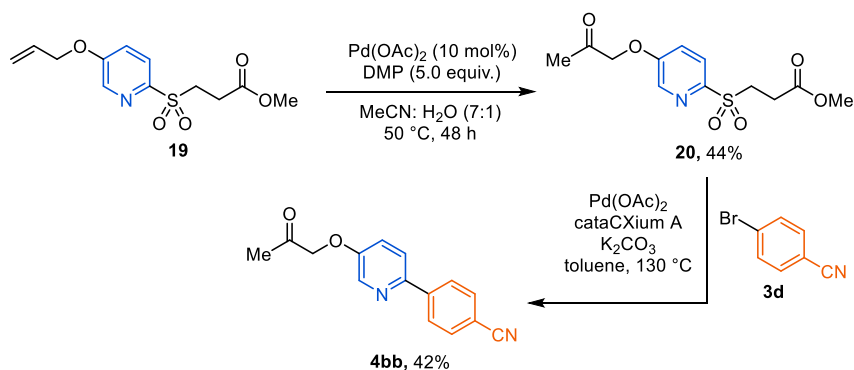
The Suzuki-Miyaura conditions used to react boronate ester **16b** are similar to the desulfinate cross-coupling conditions for base-activated masked sulfinates, albeit not anhydrous and at a lower temperature. Thus, we were curious if using the same catalytic system and base as the desulfinate cross-coupling a chemoselective Suzuki-Miyaura cross-coupling reaction could be achieved (**Scheme 2.8 A**). The reaction proceeded well under these conditions, giving 57% of biaryl sulfone **17**. As already established during optimisation, low quantities of water do not inhibit desulfinate coupling (**Table 2.4**). Hence, a one-pot, telescoped SMC and desulfinate cross-coupling reaction was attempted (**Scheme 2.8 B**). However, as the first step SMC reaction gave only a moderate yield, an array of biaryl products were obtained after the second cross-coupling, with only a low yield of the desired product **18** isolated. Due to the success of the two-step sequence (**Scheme 2.7**), investigation of the one-pot reaction was discontinued.



Scheme 2.8 Investigation into a telescoped Suzuki-Miyaura reaction / desulfonative cross-coupling sequence.

2.6.2. Oxidative alkene transformations

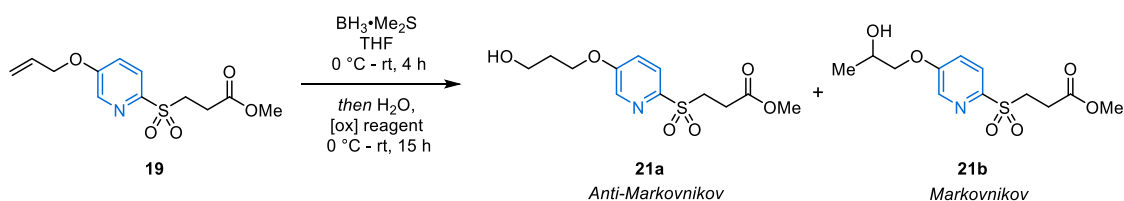
To test the compatibility of the base-labile sulfone functionality with alkene-modifying chemistry, oxidative transformations of the O-allyl tether of pyridine sulfone **19** were explored. Using Dess-Martin periodinane (DMP) as an oxidant and Wacker-type conditions, the allyl group was selectively oxidised to yield 44% of ketone product **20** (**Scheme 2.9**). The ketone-containing pyridine **20** was then reacted *via* desulfonative cross-coupling to give 42% of biaryl **4bb**. The lower yield could be due to potential side reactivity, because of deprotonation of the α -position of the ketone sulfone **20** under the basic reaction conditions.



Scheme 2.9 Wacker-like oxidation of O-allyl pyridine sulfone **19** and subsequent cross-coupling.

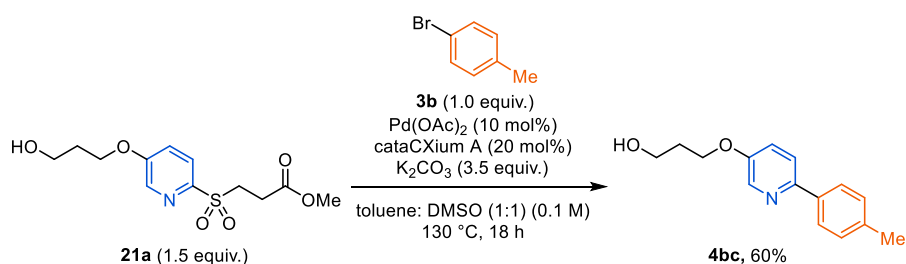
Focus was next shifted to converting the alkene tether on sulfone **19** to an alkyl alcohol, *via* a hydroboration/oxidation sequence. Literature reports of the hydroboration of O-allyl pyridine containing compounds utilise borane dimethyl sulfide complex (BMS) as the borane source.^[113] The first attempt using BMS gave a combined 31% yield of the alcohol products **21**, with a 9:1 selectivity for the primary over the secondary alcohol (Table 2.15, entry 1). Despite the poor yield, there was full consumption of starting material during the hydroboration step. It was hypothesised that the strongly basic oxidation conditions (NaOH/H₂O₂) could decompose the intermediate borylated species or the oxidised products **21**. Indeed, as previously discussed, release of the sulfinate salt from the sulfone can be achieved using NaOH or NaOMe at room temperature.^[78a] Hence the use of sodium perborate tetrahydrate salt (NaBO₃•4H₂O) was investigated, which is a milder oxidising agent than base-generated hydroperoxide anion.^[114] Changing the oxidation conditions resulted in an increased, combined 52% yield of the alcohol products; there was still good selectivity for the anti-Markovnikov product **21a** (entry 2). Reducing the equivalence of BMS improved the yield further (entry 3), and use of a greater excess of sodium perborate in the oxidative quenching step gave a 65% combined yield of alcohol products **21a** and **b** (entry 4).

Table 2.15 Investigation of the hydroboration/oxidation of O-allyl pyridine sulfone **19**.



Entry	BH ₃ ·Me ₂ S	[ox] reagents	Product yield (%)	
			21a	21b
1	1.0 equiv.	NaOH (2.0 equiv.), 30% H ₂ O ₂ in H ₂ O (3.0 equiv.)	28	3
2	1.0 equiv.	NaBO ₃ ·4H ₂ O (2.0 equiv.)	46	6
3	0.6 equiv.	NaBO ₃ ·4H ₂ O (2.0 equiv.)	49	8
4	0.6 equiv.	NaBO ₃ ·4H ₂ O (4.0 equiv.)	55	10

Subsequently, primary alcohol-containing reagent **21a** underwent desulfonative cross-coupling to give 60% of 2-arylpyridine **4bc** (Scheme 2.10). To achieve this good yield, an extra equivalence of carbonate base was used to account for the potential deprotonation of the hydroxyl group. When the reaction is run in toluene alone, product **4ac** was only achieved in a 38% yield, and unreacted pyridine sulfone was observed. Therefore, a dual solvent system was employed to address the poor solubility of the alcohol substrate in toluene.



Scheme 2.10 Desulfonative cross-coupling reaction of primary alcohol containing pyridine sulfone **21a**.

2.7. Project summary and future work

In this chapter, base-labile latent sulfinate reagents, the β -nitrile and β -ester sulfone, have been designed and developed as efficient nucleophilic reagents in palladium-catalysed cross-coupling processes (**Figure 2.9**). Using this methodology, challenging heteroaryl-(hetero)aryl linkages are achieved, allowing construction of a diverse range of 2-arylpiperidines including industrially and biologically relevant structures. These reactions have a broad scope of electrophilic partners, exhibiting good tolerance of varying substitution patterns and numerous functional groups. Moreover, both base-labile sulfinate masking groups are stable towards oxidative and palladium-mediated transformations, allowing multistep elaboration of these reagents. This chemistry has also been shown to be scalable (1.0 mmol), running efficiently outside of a sealed reaction vessel.

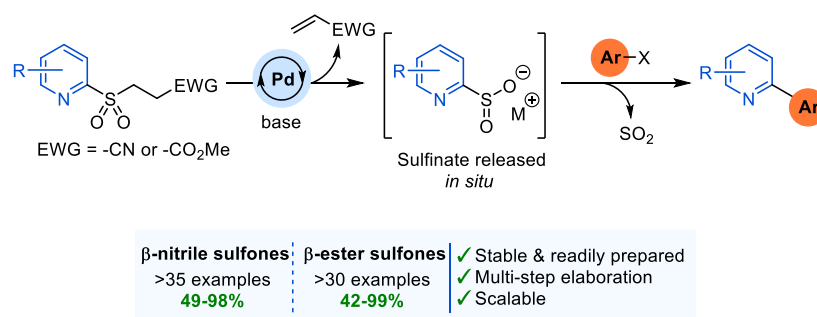
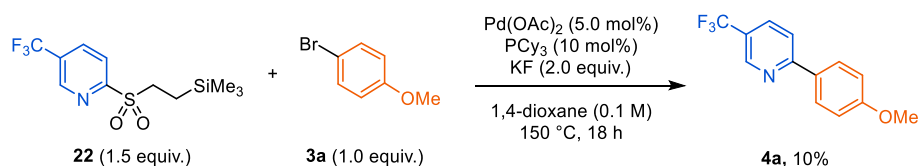


Figure 2.9 Summary of the development and cross-coupling of base-activated heteroaromatic sulfonates.

The base-labile latent sulfinate strategy has been extended to alternative, benign, base-labile masking groups, with succinate sulfones coupling efficiently under our desulfonative conditions. This initial expansion of the base-activated masking groups lends itself to further exploration in the future. Due to the prevalence of the 2-pyridyl motif in medicinal chemistry and the robustness of this chemistry, these reagents offer a complementary and viable alternative to the use of allylsulfones, metal sulfonates and

other organometallic reagents in the construction of these challenging heteroaromatic frameworks.

The observed pH dependency of the rate of sulfinate release from base-activated latent sulfinate reagents warrants further mechanistic study, as this could offer useful information for further development of these systems. Furthermore, masked sulfinate reagents that are activated through different mechanisms could be explored, such as a silyl-containing fluoride-activated masked sulfinate reagents (**Scheme 2.11**). Developing an arsenal of masked sulfinate reagents that are activated by different modes would, like masked boronate reagents, allow a library of suitable reagents for an array of synthetic needs.



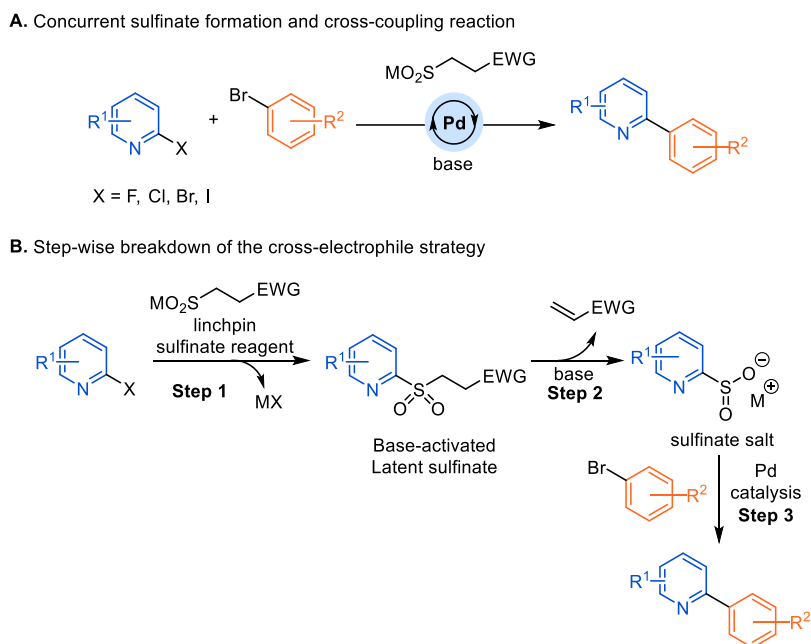
Scheme 2.11 Initial results of the cross-coupling reaction of ethyl TMS sulfone **22**.

Chapter 3. Palladium-catalysed cross-electrophile coupling reactions *via* sulfinates formation

3.1. Introduction to cross-electrophile coupling *via* sulfinates formation

As discussed in **Chapter 2**, multiple routes to synthesise base-activated masked sulfinates commence from the corresponding heteroaryl halides (**Schemes 2.1** and **2.3**).^[83, 115] Therefore, we considered if masked sulfinates reagents could be synthesised from heteroaryl halides *in situ*, before reacting as the nucleophilic partner with another (hetero)aryl halide. This would eliminate the need for preformed sulfone or sulfinates reagents and better exploit the wide range of diverse and commercially available heteroaryl halides, which are plentiful in comparison to heteroaryl sulfinates salts. Thus, the investigation of such a Pd-catalysed cross-electrophile coupling reaction, *via in situ* generated sulfinates salts, was embarked upon.

In this strategy, it was envisaged that a linchpin sulfinates reagent, also known as a sulfinates transfer reagent, could react with a heteroaryl halide to form a masked sulfinates *in situ*, which then releases the sulfinates salt and undergoes Pd-catalysed desulfinate cross-coupling with the other (hetero)aryl bromide (**Scheme 3.1**). This approach of generating and then reacting the active reagent in the cross-coupling reaction, using a transient nucleophile, has been developed for a number of traditional organometallic and next-generation 2-pyridyl nucleophiles (**Chapter 1**).



Scheme 3.1 Introduction to cross-electrophile desulfinate cross-coupling reactions.

Cross-electrophile couplings (XEC) are defined as the reaction of two different electrophiles, often using transition-metal catalysis, and as such circumvents the need for preformed nucleophiles.^[16, 116] In traditional XEC reaction mechanisms, both electrophiles add directly into the transition-metal centre (**Figure 3.1 A**).^[16] However, the proposed strategy relies on the formation of the sulfinate nucleophilic reagent *in situ*, prior to cross-coupling with the other aryl halide; generating a transient nucleophile (**Scheme 3.1**). Although this is formally a cross-electrophile coupling, commencing from two electrophilic reagents, this strategy is therefore distinct from classical XEC and Ullmann-type reactions (**Figure 3.1 B**). An alternative, yet similar approach is a one-pot, two step cross-coupling where there is step-wise synthesis of the nucleophile, then subsequent addition of the second aryl halide for cross-coupling (**Figure 3.1 C**).

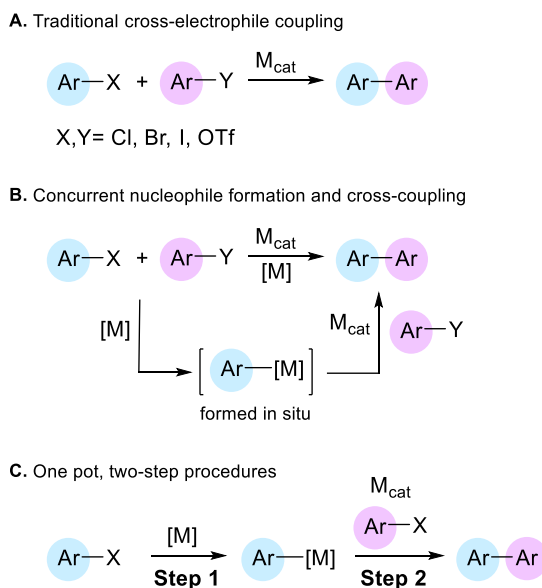
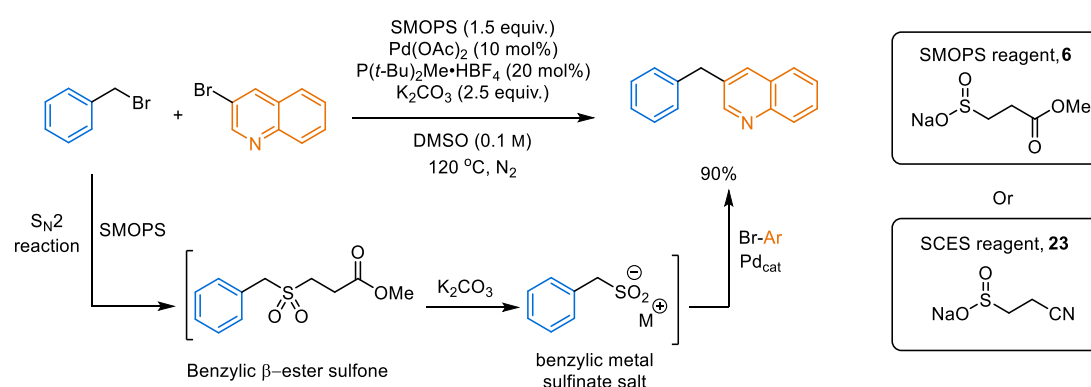


Figure 3.1 Mechanistic strategies of formal cross-electrophile reactions.

The use of transition-metal-mediated cross-electrophile coupling reactions for the synthesis of unsymmetrical biaryls, is a still burgeoning area of research.^[16] Moreover, there are only a handful of reports of formal XEC arylation reactions that use a similar mode of concurrent nucleophile generation as the proposed strategy (**Figure 3.1 B**).^[117] Notable reports are the cobalt-mediated cross-coupling of aryl halides through *in situ* preparation of organozinc reagents (using zinc dust additive),^[117a] and seminal work by Toste and co-workers, who reported a palladium/zirconium catalysed cross-electrophile coupling of aryl halides, occurring through the *in situ* generation of an arylzirconium ‘shuttling’ complex.^[117b] Similarly, as mentioned in **Chapter 1**, Chen and co-workers synthesised diarylpyridines from the Pd-mediated direct arylation of alkyl pyridine through the *in situ* generation and reaction of methyl pyridinium salts.^{[54][118]}

Desulfonative cross-electrophile arylations are not known, however, synthesis of diarylmethanes using Pd-catalysed cross-electrophile reactions is preceded by the Willis group.^[119] McKnight *et. al.* developed a methodology where benzylic sulfinate salts are formed *in situ* by the nucleophilic substitution (S_N2) reaction of benzyl bromide

and sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS) **6**, or sodium 2-cyanoethane-1-sulfinate (SCES) **23** (**Scheme 3.2**). The species evolution was monitored, showing that the cross-coupling proceeds through the proposed generation of the sulfone coupling partner, instead of direct electrophile-electrophile coupling of the aryl halide and benzyl halide starting materials. In other words, throughout the reaction there is formation and consumption of the benzylic β -ester sulfone, and subsequent formation and consumption of the free sulfinate.

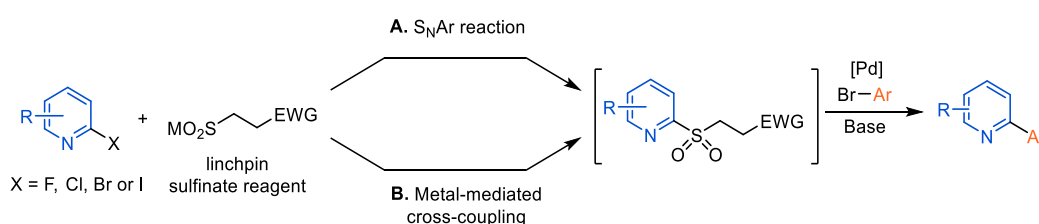


Scheme 3.2 Selected example of desulfative cross-electrophile coupling to access diarylmethane reported by McKnight, Willis and co-workers.^[119]

In this chapter, the Pd-catalysed desulfative XEC of heteroaryl halides through *in situ* generated sulfinate salt nucleophiles is explored. Consequently, the formation of base-activated latent sulfinates, *via* the reaction of a sulfinate linchpin reagent and pyridine halide, was studied. Initial investigation focused on latent sulfinate formation through a nucleophilic aromatic substitution reaction (S_NAr). The potential of using Cu-mediated sulfone formation instead was then explored, with scope towards a dual Pd/Cu system. Ultimately, the development of a straightforward, efficient Pd-catalysed cross-electrophile coupling of two (hetero)aryl halides would be a highly useful methodology, allowing swift synthesis of important 2-arylpyridines and other biheteroaryls.

3.2. Initial optimisation of the cross-electrophile coupling reaction

As documented in **chapter 2**, base-labile latent sulfinate reagents, β -nitrile and β -ester sulfones, are efficient nucleophiles in Pd-catalysed arylation reactions. Therefore the initial challenge in the proposed strategy was to obtain the masked sulfinate reagent from the heteroaryl halide under the coupling conditions. Similar to the work by McKnight *et al.*,^[119] masked sulfinate formation could occur through nucleophilic aromatic substitution (S_NAr) of an alkylsulfinate linchpin with a 2-halopyridine (**Scheme 3.3 A**). With this strategy, the differentiation of the two electrophilic partners is due to their different reactivity towards either S_NAr or oxidative addition. This circumvents one of the key challenges of achieving chemoselective $C(sp^2)$ - $C(sp^2)$ cross-electrophile coupling reactions, which is the electronic differentiation between two aryl halide reagents.^[16, 120]

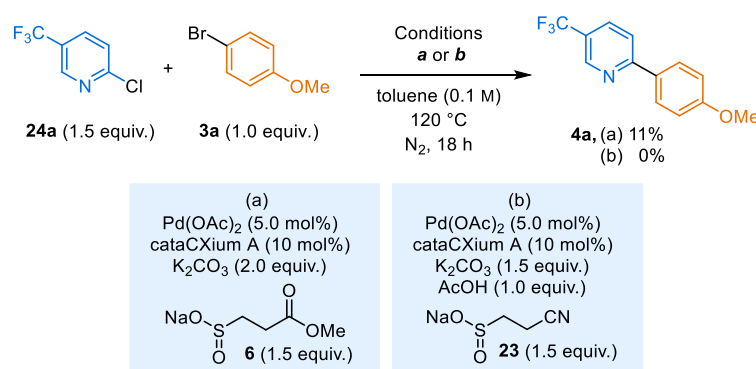


Scheme 3.3 Different routes for the *in situ* synthesis of masked sulfinate reagents.

Alternatively, the *in situ* synthesis of the masked sulfinate reagent could occur through metal-mediated coupling of the alkyl sulfinate with the heteroaryl halide (**Scheme 3.3 B**). There is precedent for the synthesis of unsymmetrical alkyl aryl sulfones through metal mediated reactions, prominently using copper salts.^[78a, 97, 121] Although the use of a dual copper/palladium catalytic system has potential, initial focus was on sulfone formation *via* S_NAr , as it is more straightforward and avoids the use of additional transition-metals.

To establish the feasibility of the proposed cross-electrophile coupling, we initially looked at a system that was analogous to the optimised model reaction used for β -nitrile and β -ester sulfone reagents (**Scheme 3.4**). In these reactions the commercially available (a) sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS) **6** or (b) sodium 2-cyanoethane-1-sulfinate (SCES) **23** were employed as the linchpin reagents to form the β -methylester or β -nitrile sulfones respectively. The attack of alkyl sulfinate reagents into activated aryl (pseudo)halides through aromatic nucleophilic substitution reactions is known,^[122] and has been applied to chloropyridine substrates by Maloney *et. al.*^[95]

Although the initial hit of 11% of biaryl **4a** using SMOPS **6** was promising, we were cautious of optimising a system with a 2-pyridyl halide that is strongly activated towards S_NAr , such as electron-poor 5-trifluoromethyl-2-pyridine, as it may narrow the scope and applicability of such a method. The electron-withdrawing group is 4-substituted relative to the chloride, which helps to stabilise the negative charge build up after attack of the nucleophile, thus assisting the S_NAr reaction.

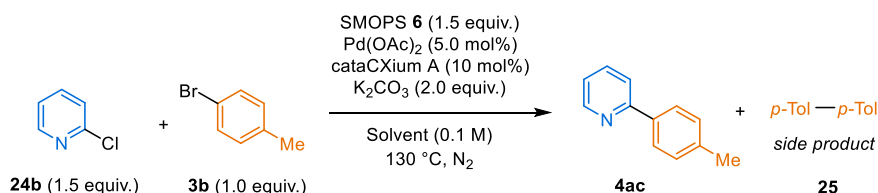


Scheme 3.4 First attempt at cross-electrophile coupling using pyridine chloride **24a** and 4-bromoanisole **3a** to give 2-arylpyridine **4a**.

Therefore the model system was changed, and instead the reaction between 2-chloropyridine **24a** and 4-bromotoluene **3b** was selected, using SMOPS as the sulfinate

transfer reagent (**Table 3.1**). A similar yield of desired biaryl **4a** was obtained with 2-chloropyridine **24b** compared to the 5-trifluoromethyl substrate **24a**, provided that a slight raise in temperature to 130 °C was employed (**Table 3.1**, entry 1). An initial solvent screen showed that polar aprotic solvents with large dipoles, DMA (3.72 D) and DMF (3.86 D),^[123] gave the highest yields (entry 4 – 6), with DMF performing the best (entry 4). Neither increasing nor decreasing the reaction concentration improved reaction efficacy (entries 7 – 8). The reaction did not proceed when the SMOPS reagent was omitted (entry 9), suggesting that the reaction occurs *via* the proposed formation of the sulfinate salt. The mass balance of the reported reactions consisted mainly of unreacted starting material and the major by-product, homocoupling product 4,4'-dimethyl-1,1'-biphenyl **25**. The production of the by-product generally increased as the yield of the desired biaryl **4ac** increased. As observed by HPLC analysis, the majority of 2-chloropyridine **24b** starting material was recovered (51 – 93%).

Table 3.1 Solvent screening of the cross-electrophile coupling reaction.



Entry	Solvent	Yield ^[a] / %	
		4ac	25
1	toluene	11 (9)	6
2	anisole	8	2
3	DMSO	9	34
4	DMA	21	40
5	NMP	13	31
6	DMF	27	41
7	DMF (0.05 M)	17	32
8	DMF (0.20 M)	19	37
9 ^[b]	toluene	0	1

^[a] HPLC yields calculated using *p*-ditolylether as an internal standard. All isolated yields are in parentheses. ^[b] SMOPS reagent was omitted.

The rate determining step (RDS) of the traditional addition-elimination mechanism of a stepwise S_NAr reaction is the addition of the nucleophile into the C-X bond. Hence, as fluorine is more electronegative than chlorine, and C-F bonds are more polarised than C-Cl bonds, 2-fluoropyridine was used instead of 2-chloropyridine in an attempt to promote more efficient S_NAr (**Table 3.2**). However, after 16 hours, 2-fluoropyridine starting material is observed unreacted (entry 2). The major product observed is the aryl bromide homo-coupling product **25**. To mitigate the formation of this side product, 4-chlorotoluene was used (entry 3). Although less homo-coupled product was observed, the yield of the desired biaryl **4ac** was also reduced.

2-Bromopyridine was also employed instead of 2-chloropyridine, which should work better if pyridyl β -ester sulfone formation is occurring through a Pd-mediated pathway instead of an S_NAr reaction. However, 2-bromopyridine gave a yield of biaryl four-fold lower than with 2-chloropyridine (**Table 3.2**, entry 1 vs. entry 4). This suggests that S_NAr , rather a Pd-mediated reaction, is responsible for the 27% yield observed using 2-chloropyridine (entry 1).

Table 3.2 Varying the pyridine halide and aryl halide combination.

Reaction scheme: 2-halopyridine (1.5 equiv.) + 4-methylphenyl halide (1.0 equiv.) $\xrightarrow[\text{DMF (0.1 M), 130 }^\circ\text{C, N}_2]{\text{SMOPS 6 (1.5 equiv.), Pd(OAc)}_2 \text{ (5.0 mol\%), cataCXium A (10 mol\%), K}_2\text{CO}_3 \text{ (2.0 equiv.)}}$ biaryl **4ac** + side product **25** (p-Tol-p-Tol).

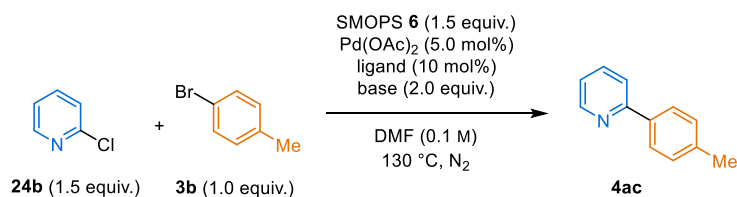
Entry	X	Y	Yield ^[a] /%	
			4ac	25
1	Cl	Br	27	41
2	F	Br	trace	49
3	Cl	Cl	6	<1
4	Br	Br	7	<1

^[a] HPLC yields calculated using *p*-ditolylether as an internal standard.

Both $P(i\text{-Pr})_3\bullet\text{HBF}_4$ and $P(t\text{-Bu})_2\text{Me}\bullet\text{HBF}_4$, which have been employed in other Pd-catalysed cross-couplings of aryl halides and (hetero)aryl sulfinate salts, exhibited good reactivity (**Table 3.3**, entries 1 – 3). Synthesis of diaryl or aryl vinylsulfones through the Pd-catalysed coupling of aryl sulfonates with aryl halides has been reported, using XantPhos or ligands with the XantPhos core.^[76a, 124] We wanted to explore if this catalytic system for sulfone formation could be adapted into the cross-electrophile reaction, to enable palladium mediated β -ester sulfone formation and subsequent cross-coupling. However there was a decrease in reaction yield when XantPhos was used (entry 4 – 5).

Additives that had previously shown compatibility with the β -nitrile and β -ester sulfone systems were evaluated (entries 6 – 10). Interestingly, triethylamine additive doubled the yield of the reaction when run in toluene (entry 8), but was detrimental to the reaction yield when the solvent was DMF (entry 7). A reduced yield was also observed when using TBACl (entry 10), which had proven an essential reagent in the aforementioned $\text{S}_{\text{N}}\text{Ar}$ reactions reported by Maloney *et. al.*^[95] Due to their established efficacy in desulfonative couplings, carbonate bases were primarily evaluated (entries 1, 12 – 13), with caesium carbonate giving a marginally improved 30% yield of the biaryl **4ac** (entry 13). Nonetheless, it is notable that using potassium phosphate tribasic gave a comparable yield to the carbonate bases (entry 11).

Table 3.3 Optimisation of the cross-electrophile arylation reaction.



Entry	Base	Ligand	Variations to equation	Yield ^[a] / %
1	K ₂ CO ₃	cataCXium A	-	27
2	K ₂ CO ₃	P(<i>i</i> -Pr) ₃ •HBF ₄	-	26
3	K ₂ CO ₃	P(<i>t</i> -Bu) ₂ Me•HBF ₄	-	22
4	K ₂ CO ₃	XantPhos (5.0 mol%)	-	19
5	K ₂ CO ₃	XantPhos (2.5 mol%) + cataCXium A (5.0 mol%)	-	trace
6	K ₂ CO ₃	cataCXium A	Et ₃ N (1.5 equiv.)	20
7	K ₂ CO ₃	cataCXium A	Et ₃ N (1.5 equiv.) toluene (0.1 M) solvent	23
8	K ₂ CO ₃	cataCXium A	AcOH (1.5 equiv.)	4
9	K ₂ CO ₃	cataCXium A	NaOTf (1.5 equiv.)	15
10	K ₂ CO ₃	cataCXium A	TBACl (1.0 equiv.)	16
11	K ₃ PO ₄	cataCXium A	-	21
12	K ₂ CO ₃ (3.0 equiv.)	cataCXium A	-	21
13	Rb ₂ CO ₃	cataCXium A	-	19
14	Cs ₂ CO ₃	cataCXium A	-	30
15	Cs ₂ CO ₃	cataCXium A	SMOPS 6 (2.0 equiv.)	31
16	Cs ₂ CO ₃	cataCXium A	SMOPS 6 (2.0 equiv.) and Pyr-Cl 24b (2.0 equiv.)	31
17	Cs ₂ CO ₃	cataCXium A	NaO ₂ S-CH ₂ CH ₂ CN 23 (1.5 equiv.)	15
18	Cs ₂ CO ₃	cataCXium A	NaO ₂ S-CH ₂ CH ₂ OTBS 26 (1.5 equiv.)	trace
19	Cs ₂ CO ₃	cataCXium A	no Pd source	0
20	Cs ₂ CO ₃	cataCXium A	no base	5
21	Cs ₂ CO ₃	cataCXium A	no ligand	12

^[a] HPLC yields calculated using *p*-ditolylether as an internal standard.

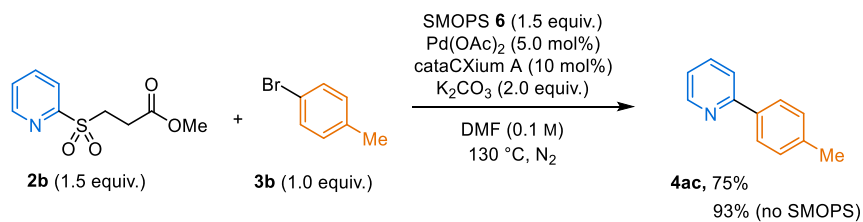
Alternative linchpin reagents, such as the nitrile containing SCES reagent **23** and sodium *tert*-butyldimethylsilyloxymethanesulfinate (TBSOMS-Na) **26**, did not perform as well as SMOPS **6** (entries 17 – 18). Increasing the loading of SMOPS reagent from 1.5 to 2.0 equivalents did not improve the yield further, giving 31% yield of biaryl **4ac** (entries 17 – 18). The presence of both palladium and base proved to be crucial for

reactivity (entries 19 – 20); in contrast 12% product was obtained when the ligand was omitted.

3.3. Deconvolution of the multi-step reaction sequence

The intended cross-electrophile coupling involves a multi-step sequence: (i) sulfone formation, (ii) subsequent sulfinic acid generation, and (iii) Pd-catalysed cross-coupling. Optimising this complex reaction is challenging as there are different factors that affect the success of each step, which in turn affects the success of subsequent steps. After the initial assessment of the feasibility of such a coupling in **Section 3.2**, with an encouraging 31% yield obtained, it was decided to deconvolute the reaction to further optimise it.

Firstly, the β -ester sulfone **2b** and 4-bromotoluene were reacted under the current cross-electrophile conditions, to check the release of the sulfinic acid and cross-coupling still proceeded efficiently with DMF as the solvent (**Scheme 3.5**). Efficient cross-coupling of β -ester sulfone **2b** was observed under these conditions, both with and without additional SMOPS reagent. However, the yield dropped from 93% to 75% when SMOPS reagent was added, suggesting that the presence of free SMOPS reagent impedes the cross-coupling reaction. Therefore, in the cross-electrophile coupling, if the sulfone formation is not going to completion, a high concentration of SMOPS reagent in the reaction mixture could interfere with the cross-coupling process. These results support that the challenging step of cross-electrophile coupling is the initial sulfone formation.



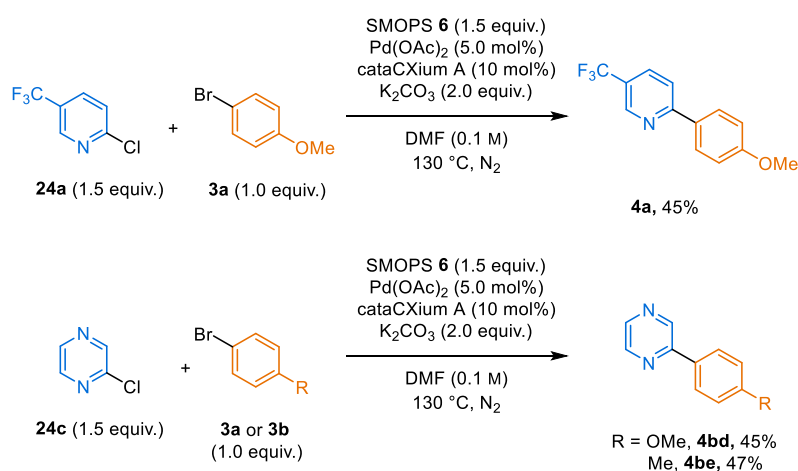
Scheme 3.5 Reaction 2-pyridyl β -ester sulfone **2b** with 4-bromotoluene **3b** under cross-electrophile conditions. HPLC yields given, calculated using *p*-ditolylether as an internal standard.

The cross-coupling of β -ester sulfones and aryl halides only proceeds smoothly at reaction temperatures above 110 °C (**Chapter 2**). Therefore, a potential way to troubleshoot this reaction is to assess if the sulfone formation *via* S_NAr proceeds at a lower temperature. This reaction could then be run step-wise in one-pot through temperature incrementation; first allow the sulfone formation to go to completion at a lower temperature, then raise the temperature to enable cross-coupling. In an initial investigation, formation of 2-(5-trifluoromethyl)pyridyl β -ester sulfone **1a** from the corresponding pyridine chloride **24a**, was observed to occur at a reaction temperature of 70 °C using K₂CO₃, DMF and SMOPS salt; none was observed at 50 °C. As β -ester sulfones were designed to release the corresponding sulfinate salt upon heating under basic reaction conditions, investigating the formation of such sulfone intermediates is challenging. Due to limited time, this line of investigation was not continued, however monitoring the S_NAr reaction at different temperatures would be interesting future work.

3.4. Use of alternative heteroaryl chlorides

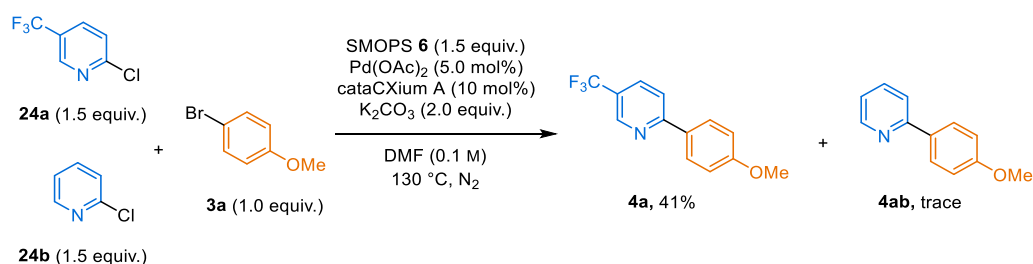
Previous discussion suggests that the low efficacy of the proposed S_NAr reaction may be responsible for the low reaction yields observed for the overall cross-electrophile coupling process. Hence, using heteroaryl chlorides that are more electron-poor, and thus

more activated towards S_NAr than 2-chloropyridine, should give higher reaction yields. Therefore, use of 5-trifluoromethylpyridine **24a** and pyrazine **24c** in the cross-electrophile coupling was investigated (**Scheme 3.6**). Indeed, both gave higher isolated yields of the corresponding biaryls **4a**, **4bd** and **4be** (45 – 47%), than the highest yield observed with 2-chloropyridine. Although these yields are still moderate, the improved yields suggest that β -ester sulfone formation proceeds more efficiently with electron-poor pyridine chlorides.



Scheme 3.6 Cross-electrophile coupling using more activated S_NAr heteroaryl substrates. Isolated yields.

Moreover, these reactions with electron-poor heteroaryl chlorides further support that sulfone formation is currently the weak link in this system, impeding the overall reaction yield. To further investigate this, competition reactions were run; pyridines **24b** and **24a** were combined with aryl bromide **3a** in the same cross-coupling reaction (**Scheme 3.7**).



Scheme 3.7 Competition experiment between chloropyridines **24a** and **24b**. Isolated yield.

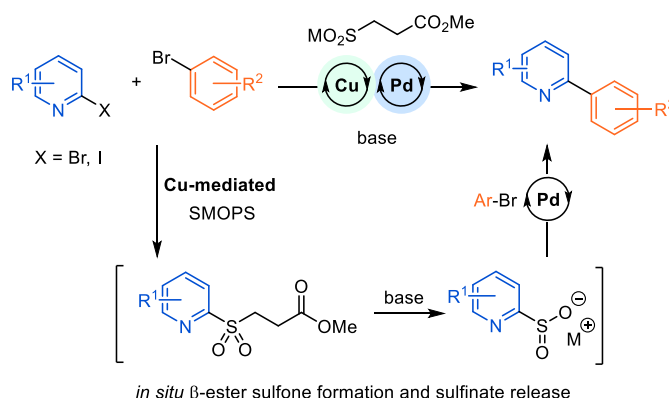
As expected, the electron-poor pyridine **24a** outcompeted unsubstituted pyridine **24b** to give the corresponding biaryl **4a** in a 41% yield, compared to the trace amounts of 2-arylpyridine **4ab**. Further confirming that to optimise the cross-electrophile system, the initial sulfone formation needs to be more efficient.

One way to improve S_NAr reaction efficacy is to further activate the pyridine chloride through protonation. This strategy was employed by Maloney *et.al.* in the aforementioned S_NAr reaction of aryl/alkyl sulfinates into pyridine chlorides, where a HCl additive was necessary when reacting pyridines that did not feature electron-withdrawing substituents.^[95] McNally and co-workers similarly promoted the S_NAr reaction of pyridine chlorides and phosphorus nucleophiles using a combination of HCl and NaOTf.^[59] Hence protonation of the pyridine reagent, either prior or during the reaction, would be worth investigating.

3.5. Copper-assisted routes for concurrent sulfone formation

As a result of the challenges surrounding *in situ* masked sulfinate formation through the proposed S_NAr pathway, alternative strategies were explored. There are several literature reports using copper salts, both stoichiometrically and catalytically, to assist alkyl aryl sulfone formation from metal sulfinate salts and aryl halides.^[78a, 97, 121] As such, a dual

Cu/Pd system was envisaged, wherein the sulfone would be formed *via* a copper mediated process, followed by Pd-catalysed desulfonative cross-coupling (**Scheme 3.8**).



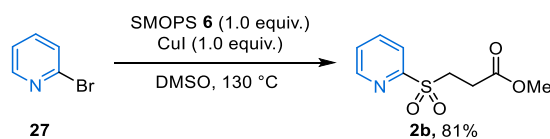
Scheme 3.8 Dual copper/palladium cross-electrophile coupling.

3.5.1. Stoichiometric copper-mediated β -ester sulfone formation

Regarding sulfone synthesis using stoichiometric copper, a key report comes from Baskin and Wang, previously discussed in **Chapter 2**. This ligand-free methodology provides a direct synthesis of aryl β -ester sulfones, using copper(I) iodide, SMOPS **6** reagent and aryl halides.^[78a] In their original report, no heteroaromatic substrates were used. However, the SMOPS coupling procedure has since been extended to heteroaromatic halides with varying degrees of reaction success. Notably, the synthesis of 2-pyridyl β -ester sulfones, or compounds containing this motif, has been achieved using the SMOPS Cu-coupling by both medicinal chemists and the Willis laboratory.^[88, 90, 104b, 105, 115, 125]

To achieve difficult SMOPS-couplings the reaction temperature can be raised from the originally reported 110 °C, or assisted by microwave heating.^[125a, 125e] These conditions are compatible with the desulfonative cross-coupling reaction. The SMOPS coupling uses super stoichiometric amounts of SMOPS **6** and copper iodide. Nonetheless, when the

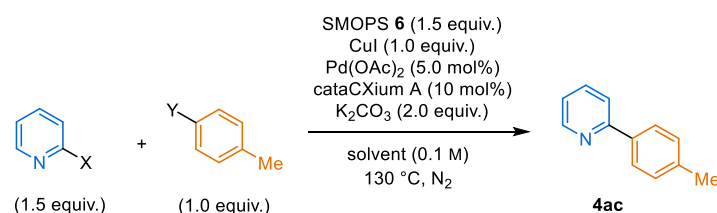
quantities of these reagents were reduced to be equimolar with 2-bromopyridine **27**, 2-pyridyl β -ester sulfone **2b** could be achieved in 81% yield at 130 °C (**Scheme 3.9**).



Scheme 3.9 Lowering the loading of copper iodide and SMOPS at 130 °C.

Having established the efficacy of the SMOPS-coupling using 2-bromopyridine **27**, efforts were focused on incorporating this reaction into the cross-electrophile system (**Table 3.4**). The reaction solvent used for the SMOPS-coupling, DMSO, was employed in these investigations; some cross-coupling success has already been observed in this solvent (entry 2). Ultimately, addition of copper iodide into the reaction mixture attenuated all desired reactivity (entries 3 – 4), giving thick, black suspensions instantly on reaction heating. Interestingly, HPLC analysis of the crude reaction mixture of the reactions with CuI and SMOPS (entries 3 – 4), saw unreacted aryl halide, but no 2-bromopyridine starting material, or pyridyl β -ester sulfone. However, a conclusion cannot be drawn as to whether the sulfone formed, and released to the sulfinate, or if bromopyridine **27** was consumed through a different pathway.

Table 3.4 Investigation of the cross-electrophile coupling with addition of stoichiometric copper(I) iodide.

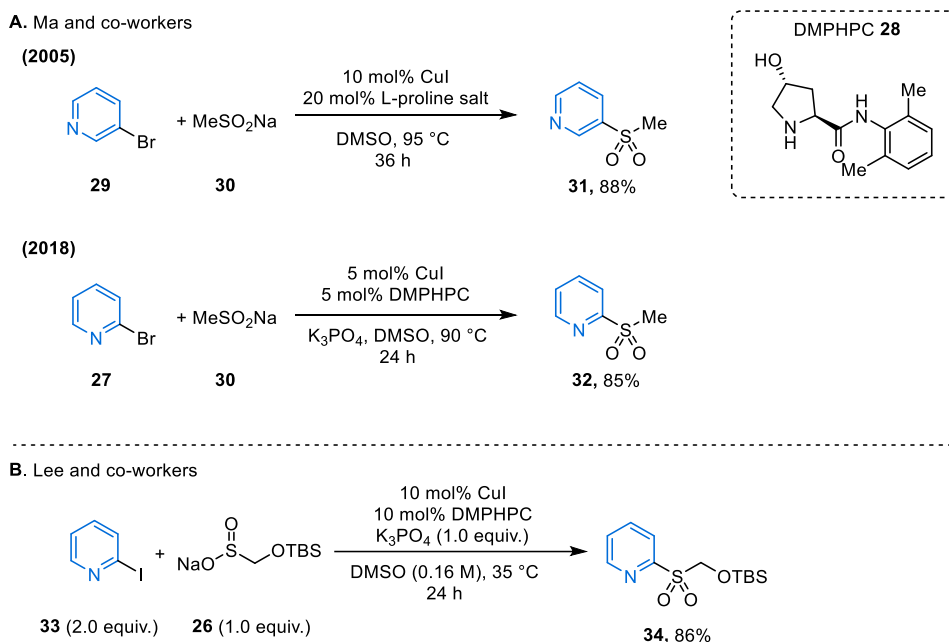


Entry	X	Y	Solvent	Variations from above	Yield ^[a] /%
1	-Cl	-Br	DMF	no CuI	27
2	-Cl	-Br	DMSO	no CuI	9
3	-Br	-Br	DMSO	-	0
4	-Br	-Cl	DMSO	-	0
5	-Br	-Cl	DMSO	no SMOPS 6	0

^[a] HPLC yields calculated using *p*-ditolyether as an internal standard.

3.5.2. Preliminary investigation into Cu-catalysed β -ester sulfone formation

Whilst copper-catalysis is known for the synthesis of diaryl sulfones, *via* reaction of aryl sulfinate salts and aryl halides,^[121a, 126] there are few reports of the copper assisted addition of alkyl sulfinate reagents into aryl halides.^[121a, 121b, 127] The C-S coupling of sulfinate reagents with pyridyl halides is even less known, with key reports from the group of Ma and Lee.^[97, 121c] In 2005, Ma and co-workers used L-proline as a ligand, alongside catalytic copper (I) iodide, to synthesise alkyl aryl sulfones in high yields.^[97] The authors later improved the reaction conditions using a base and a novel proline-based ligand, DMPHPC **28**, which allowed the catalyst loading to be reduced and the scope of heteroaromatic substrates to be expanded (**Scheme 3.10 A**). Similar to the S_NAr literature for 2-pyridyl alkyl sulfone formation,^[95] the predominant alkyl sulfinate reagent used in both these reports was methanesulfinate **30**.

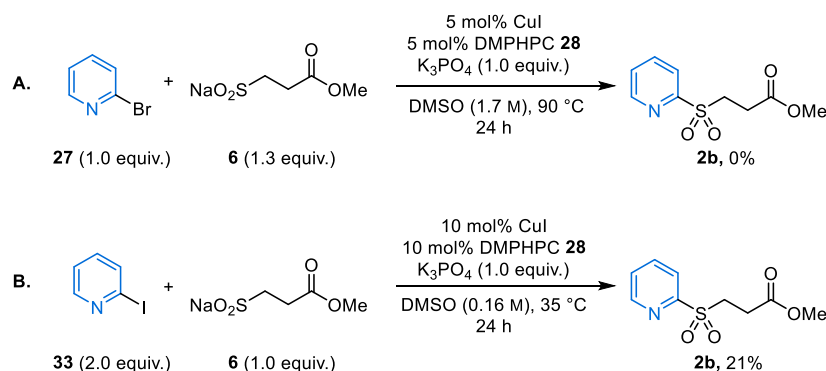


Scheme 3.10 Copper-catalysed coupling of alkyl sulfinate salts with pyridine halides.

In 2020, Lee and co-workers published the mild CuI-mediated coupling of (hetero)aryl iodides with Rongalite derived sodium *tert*-butyldimethylsilyloxymethanesulfonate (TBSOMS-Na) **26** as the alkyl sulfonating agent (**Scheme 3.10 B**).^[121c] The TBSOMS product **34**, is an isolable masked sulfinate species that releases the sulfinate salt on treatment with a fluoride source (TBAF or CsF).

Initial attempts to investigate the Cu-catalysed reaction of SMOPS **6** and 2-bromopyridine **27** using Ma's conditions were unsuccessful (**Scheme 3.11 A**); the primary reagent observed in the reaction mixture was unreacted 2-bromopyridine. However, using 2-iodopyridine **33** and the conditions from Lee and co-workers at room temperature, gave β -ester sulfone **2b** in a 21% isolated yield (**Scheme 3.11 B**). The resulting mass balance consisted of unreacted halide starting material. This was a promising starting point, especially considering the SMOPS reagent is more complex than other alkyl sulfinate reagents that have been used in these copper-catalysed reactions. Indeed, patents that use catalytic copper cross-couplings to install the less functionalised

methyl sulfone (-SO₂Me), opt to use the stoichiometric copper-mediated SMOPS coupling to synthesise 2-pyridyl β-ester sulfones.^[125b-e] Optimisation of this Cu-catalysed system using the SMOPS reagent **6** would therefore also be of interest as a standalone methodology.



Scheme 3.11 Preliminary work to synthesise β-ester sulfone **2b** from the Cu-catalysed reaction of SMOPS reagent and 2-halopyridine, employing a proline-based ligand.

Copper is azaphilic, therefore nitrogen-based ligands are commonly employed in Cu-mediated coupling reactions. Ma's proline-based ligand **28** was initially explored for β-ester sulfone formation, due to its established use in conjunction with pyridyl halides. However there are plethora of N-containing ligands that have shown efficacy in Cu-catalysed sulfone formation that can be explored, such as *N,N'*-dimethylethylene-diamine (DMEDA),^[121a] D-glucosamine,^[127a] 1, 10- phenanthroline^[121b, 127b] and imidazole salts.^[127c] Furthermore, a new class of 6-hydroxypicolinamide ligands have recently been developed by chemists at Pfizer for use in Cu-catalysed couplings.^[128]

There are many avenues of exploration for future optimisation of this Cu-catalysed alkyl heteroaryl sulfone formation, namely alternative ligands, and the study of reaction temperature. Establishing a working sulfone formation would be useful before combination with concurrent Pd-catalysed cross-coupling. Furthermore, there are currently limited commercially available alkyl sulfinate reagents, particularly those

employed in direct sulfone formation from reaction with aryl halides. The most notable functionalised alkyl sulfinate salts are rongalite,^[121b] silyl-protected rongalite (TBSOMSNa) **26**,^[121c] sodium 2-cyanoethane-1-sulfinate (SCES) **23**^[115] and SMOPS reagent **6**.^[78a] Therefore, deployment and development of alternative alkyl sulfinate reagents could be useful for the synthesis of alternative masked sulfinates and to expand the toolbox of alkyl sulfinate salts in general.

3.6. Project summary and future work

In this chapter, the Pd-catalysed formal cross-electrophilic coupling of 2-pyridyl halides and aryl bromides to give 2-arylpyridines has been explored, through *in situ* sulfinate salt formation using a sulfinate linchpin reagent. The initial reactivity of the one-pot reaction was established, obtaining 30% of the desired biaryl when using the SMOPS reagents and 2-chloropyridine. Using more activated azines increased the yield (>45%), suggesting that improving the sulfone formation step is key to better overall reaction success. Due to the complexity of this system, future work into deconvoluting the reaction steps and monitoring the various species evolution would be useful in informing further reaction optimisation.

Consequently, copper-mediated sulfone formation was also explored, with the aim of utilising a dual Cu/Pd system. Stoichiometric CuI-mediated sulfone formation was not compatible with the Pd-catalysed coupling conditions. Preliminary exploration of using copper catalysis in the synthesis of β -ester sulfones gave promising initial results. However, this will need much further investigation, both into the Cu-catalysed synthesis of β -ester sulfones and combination of this chemistry with the Pd-catalysed desulfonative cross-coupling process.

Chapter 4. Primary aryl sulfinamides as novel nucleophiles in Pd-catalysed sp^2 - sp^2 cross-coupling reactions

4.1. Introduction to primary aryl sulfinamide reagents in Pd-catalysed reactions

As previously discussed in **Chapter 1**, the use of sulfinate salts as nucleophilic partners in cross-coupling processes is primarily limited by their poor solubility in organic media, which limits the preparation of complex examples and their ability to be carried through multi-step syntheses. The use of neutral, latent sulfinate species offers an attractive and efficient solution to these problems (**Chapter 2**). However, despite the efficacy of the masked sulfinate approach in accessing a wide range of biaryls, namely 2-arylpyridines, these Pd-catalysed desulfinate sp^2 - sp^2 cross-coupling reactions still require high reaction temperatures: 120 – 130 °C. Previous mechanistic studies by the Willis laboratory on the catalytic cycle of desulfinate coupling reactions, indicates that high reaction temperatures are required for efficient transmetalation of the aryl metal sulfinate salt with the aryl halide palladium oxidation addition complex (**Figure 4.1 A**).^[89a] Furthermore, the rate of transmetalation of the sulfinate salt at 120 °C is affected by the selection of metal cation ($NMe_4 > Cs > K > Na > Li$).^[89a, 129]

As a result, we turned our attention to replacing the metal sulfinate group with an alternative sulfur (IV) functionality. Hence, we decided to investigate primary sulfinamides ($RSONH_2$) as nucleophilic coupling partners in Pd-catalysed arylations (**Figure 4.1 B**). Sulfinamide-containing ligands are known for palladium and other transition-metal catalysis, primarily for use in asymmetric transformations.^[130]

Additionally, there are reports using primary sulfinamides as nucleophiles in palladium^[131] and copper-mediated reactions.^[132] Thus, it was postulated that primary arylsulfinamide reagents would have good affinity for the palladium metal centre and could potentially allow Pd-catalysed C(sp²)-C(sp²) cross-coupling at a lower reaction temperature. Furthermore, like latent sulfonates, sulfinamides are neutrally charged and easier to isolate/purify compared to metal sulfonate salts. They also do not require consideration of the metal counterion. Advantageously, primary aryl sulfinamides have a lower molecular weight than previously developed masked sulfonate reagents and would not require the expulsion of a small organic molecule.

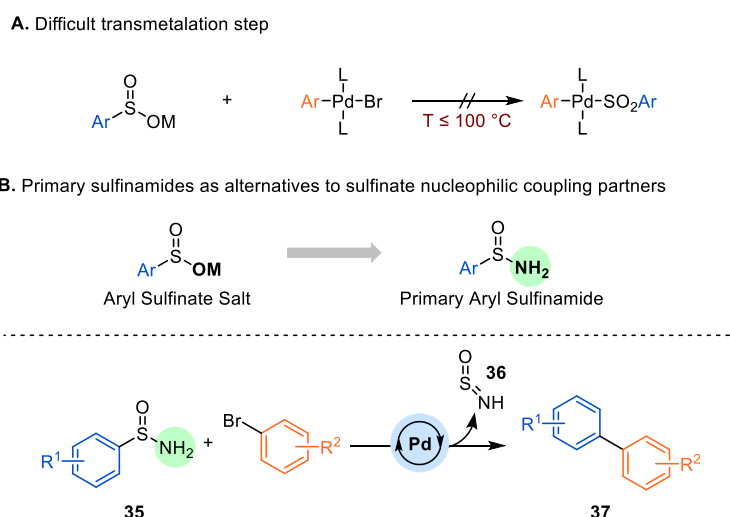


Figure 4.1 Introduction to primary aryl sulfinamides as alternative nucleophilic coupling partners.

The use of primary sulfinamides **35** as nucleophilic coupling partners to form biaryls would entail the extrusion of primary sulfinylamine gas **36** (HNSO), also known as thionylimide, instead of sulfur dioxide, making this a desulfinamidative process (**Figure 4.1 B**). Although *N*-sulfinylamine (R-N=S=O) chemistry is experiencing a resurgence,^[133] thionylimide has limited synthetic applications. The primary reports are preparation and characterisation of HNSO from the gas-phase reaction of ammonia and

thionyl chloride,^[134] and the analysis of its fundamental vibrational modes.^[135] To the best of our knowledge the evolution of this gas in the context of transition metal catalysed cross-coupling has not been reported. The development of a desulfinamidative Pd-catalysed cross coupling process would further the utility of sulfinamides and provide another synthon for C(sp²)-C(sp²) bond disconnection.

Transition-metal catalysed desulfonative cross-coupling (loss of SO₂), is often compared to the analogous carbon-based decarboxylative cross-coupling (loss of CO₂). As such, the use of deamidative cross-couplings (loss of CONR₂) was researched, in order to inform the use of sulfinamides in these processes. However, there are only a few reports of deamidative cross-coupling,^[136] and none that focus on C(sp²)-C(sp²) bond formation. This appears an underdeveloped area, likely due to amide's high bond order, stability and the relative higher molecular weight compared to carboxylic acids.^[137]

Interest in sulfinamide chemistry has greatly grown in the last couple of decades, particularly due to the pioneering use of *N-tert*-butanesulfinamide **38** as a chiral auxiliary,^[138] and use of subsequent derivatives as organocatalysts,^[139] as ligands for metal catalysis,^[140] and as metal directing groups.^[141] The chemistry of primary aryl sulfinamides was revolutionised by Davis and co-workers through their use of readily available *p*-toluenesulfinamide **39** as a versatile building block in accessing enantiopure sulfinimine reagents,^[142] such as Davis auxiliary, that are employed for the asymmetric synthesis of amines and α- or β-amino acid derivatives (**Figure 4.2 A**).^[143]

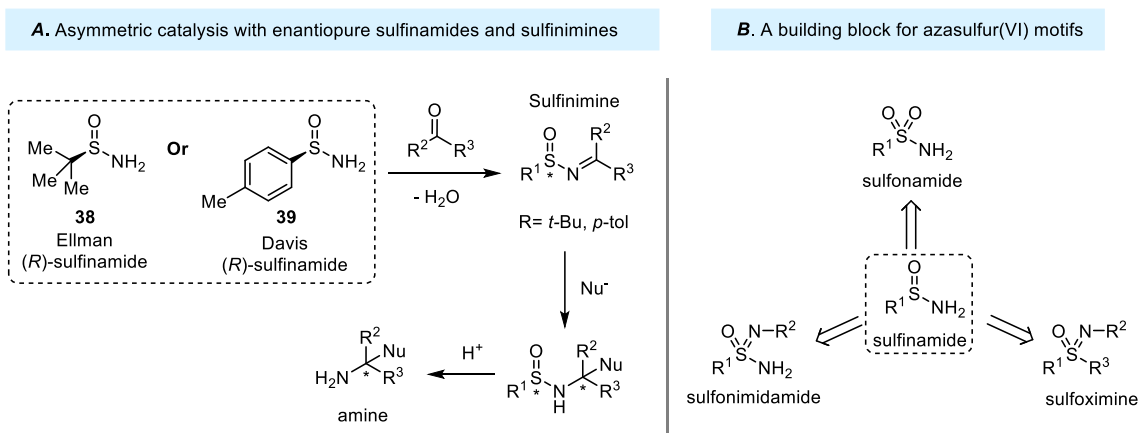


Figure 4.2 Key research areas of sulfinamide chemistry.

Primary aryl sulfinamides are yet to have notable pharmaceutical uses of their own. However, aryl sulfinamide reagents have been used widely as synthetic intermediates to access aza-sulfur(VI) functionalities that are of increasing importance in medicinal chemistry (**Figure 4.2 B**), such as sulfonamides,^[72b, 144] sulfonimidamides,^[145] and sulfoximines.^[146] As a result of their utility, there are numerous and increasing routes to synthesise primary aryl sulfinamides, mainly starting from thiols,^[147] sulfinate esters,^[145a, 148] organometallic reagents,^[149] and boroxines (**Figure 4.3**).^[150]

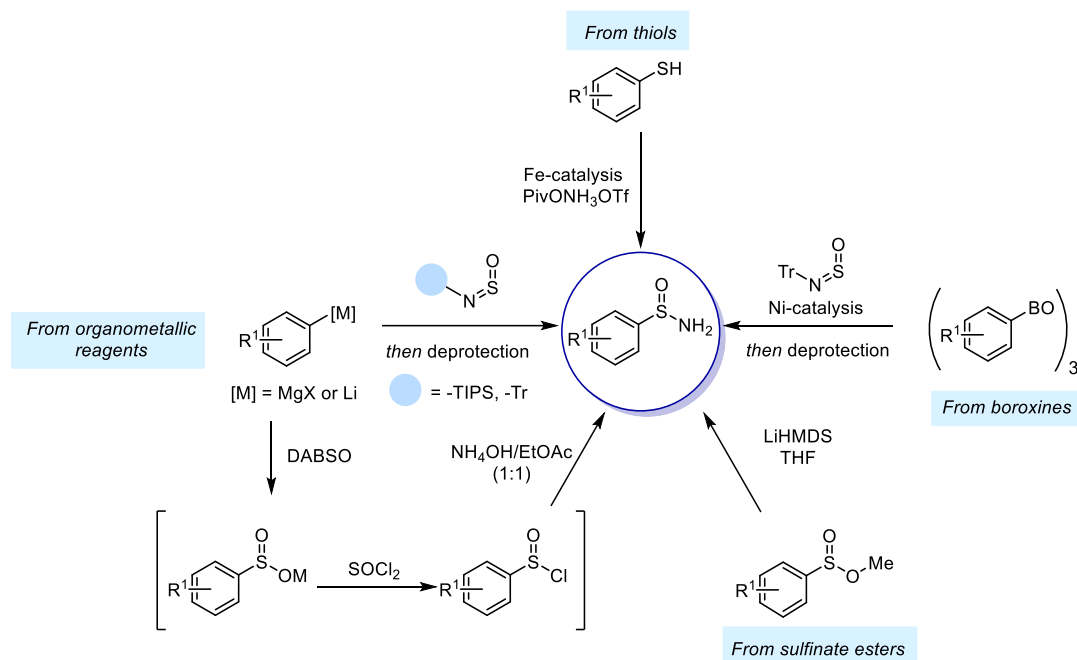
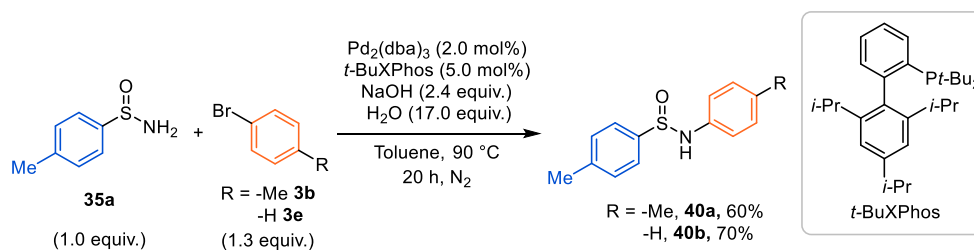


Figure 4.3 Selected routes for the synthesis of primary aryl sulfinamide reagents.

There is precedent for using primary aryl sulfinamides in metal-mediated C-N bond forming reactions.^[131, 151] Of particular interest is work by Zeng and co-workers demonstrating the Pd-catalysed reaction of primary sulfinamides with aryl bromides to form the *N*-functionalised sulfinamide products.^[131] Although the focus of the methodology was the use of C-alkyl sulfinamides, the authors reported two C-aryl examples **40a-b** in moderate to good yields (**Scheme 4.1**).



Scheme 4.1 Palladium-catalysed C-N bond forming reaction between primary aryl sulfinamides and aryl bromides reported by Zeng and co-workers^[131]

This methodology putatively proceeds *via* the same sulfinamide intermediate as the desired desulfinamidative reaction pathway (**Figure 4.4**), with subsequent *N*-arylation (**B**) favoured over desulfinamidative C-C bond formation (**A**). The authors do not discuss any observed selectivity issues between C-C or C-N bond formation. However, as the proposed desulfinamidative arylation is developed, controlling this chemoselectivity is essential. Encouragingly, this report from Zeng and co-workers suggests that transmetalation of sulfinamides can occur at 90 °C.

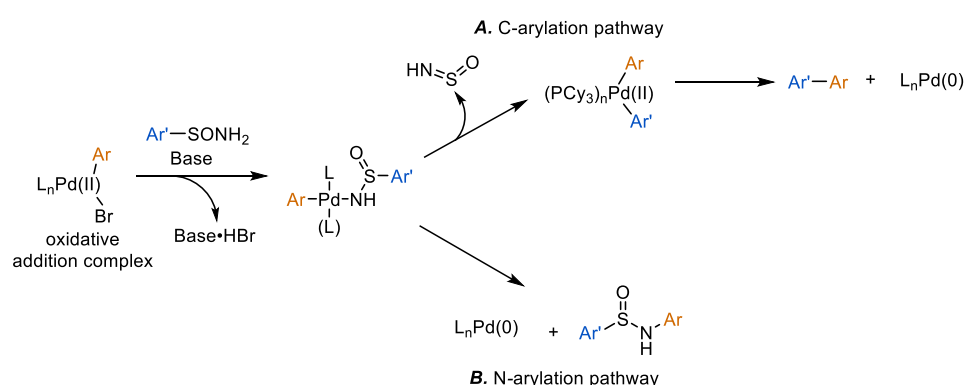


Figure 4.4 Two proposed divergent pathways for reductive elimination to give either the C-C or C-N bond formation products.

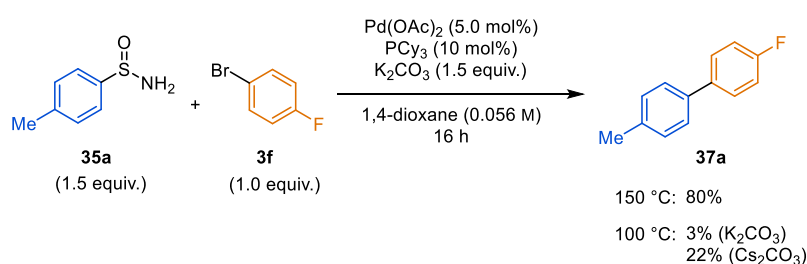
In this chapter the use of primary aryl sulfinamides as alternative sulfur(IV) nucleophilic coupling partners in Pd-catalysed desulfinylative cross-coupling reactions is investigated. The key aims of this research were to establish a proof of concept for desulfinamidative C-C bond formation, enable these transformations to occur at lower temperatures (<120 °C) and finally extend this approach to the synthesis of key 2-(hetero)arylpyridine motifs.

4.2. Optimisation of aryl sulfinamides in cross-coupling reactions

4.2.1. Preliminary results

The initial hit result and early screening of this system was performed by a previous DPhil student in the Willis group, Dr. Antoine de Gombert, and are fully reported in his DPhil thesis.^[152]

In the preliminary investigations by de Gombert, when *p*-tolylsulfinamide **35a** was combined with 1-bromo-4-fluorobenzene **3f** at 150 °C, using the conditions of the original sulfinate work,^[11] a high 80% HPLC yield of the biaryl **37a** was observed (**Scheme 4.2**). Use of the analogous sodium sulfinate under these reaction conditions gave 92% yield of biaryl **37a**. Lowering the temperature to 100 °C dramatically reduced the sulfinamide coupling to 3% yield. Using caesium carbonate instead of potassium carbonate was beneficial, likely due to the increased solubility of Cs₂CO₃ in polar aprotic solvents compared to K₂CO₃.^[153]



Scheme 4.2 First attempt at using primary aryl sulfinamides under Pd-catalysed conditions by de Gombert, all HPLC yields calculated using 1,3,5-trimethoxybenzene.

After screening various classes of ligands, de Gombert found that monodentate, bulky alkyl phosphines performed best, with P(*t*-Bu)₂Me•HBF₄ found to give the highest yield (**Table 4.1**, entry 1). Moreover, sterically encumbered, strongly σ -donating phosphine ligands are also optimum in Pd-catalysed desulfurative chemistry, as seen with the

reaction of sulfinate salts, allylsulfones, β -nitrilesulfones and β -estersulfones (**Chapter 2**).^[88, 90, 115] Key changes to the system were increasing the reaction concentration by two-fold (entry 1 vs. 2), and use of a larger excess of base in a 1:2 sulfinamide to base ratio (entry 3). Unlike metal sulfinate salts, sulfinamides are not charged species, and so a larger excess of base may be needed to account for the HBr by-product generated during transmetalation. Attempts to deprotonate the sulfinamide **35a** prior to use in the coupling reaction mixture caused a reduction in yield (entry 4). Ultimately, initial investigation gave a promising 49% yield of biaryl **37a** at 100 °C, under conditions alike the optimal conditions for the sulfinate salt and the allylsulfone couplings, albeit at a lower temperature of 100 °C.^[88, 90]

Table 4.1. Selected key results from de Gombert's initial optimisation (0.11 mmol scale).

Entry	Variation to equation above	Conc.	Yield ^[a] / %
0	<i>PCy₃</i> (10 mol%) instead	0.055 M	22
1	-	0.055 M	35
2	1,4-dioxane (0.11 M)	0.110 M	40
3	Cs ₂ CO ₃ (3.0 equiv.)	0.110 M	49
4	35a deprotonated first with <i>n</i> -BuLi	0.110 M	4

Reactions run on a 0.11 mmol scale by Dr. A. de Gombert.^[a] All HPLC yields calculated using 1,3,5-trimethoxybenzene as an internal standard.

4.2.2. Further optimisation

When I took up this project, in order to further optimise this system, the reaction of *p*-tolylsulfinamide **35a** and 1-bromo-4-fluorobenzene **3f** was run on a preparative scale (0.30 mmol, **Table 4.2**) instead of a screening scale (0.11 mmol, **Table 4.1**). The move to a preparative scale and increase in reaction concentration by a factor of 3 (0.11 M to

0.30 M), gave the best result seen for this cross-coupling yet, with an isolated 66% yield of biaryl **37a** (Table 4.2, entry 1). The reaction could not be concentrated further on this scale for practical reasons, such as maintaining efficient stirring and salt solubility. Unreacted sulfinamide **35a**, aryl bromide **3f** starting material, and homocoupling product, 4,4'-dimethyl-1,1'-biphenyl, accounted for the rest of the mass balance.

Next, trialkyl phosphine ligands with similar steric parameters to $P(t\text{-Bu})_2\text{Me}\cdot\text{HBF}_4$ were explored (entries 1 – 5), however no other ligand performed as well as $P(t\text{-Bu})_2\text{Me}\cdot\text{HBF}_4$. It was observed that a narrow range of spatial bulk was tolerated for good yields, with a reduction of yield observed when using either bulkier ligands, $P(t\text{-Bu})_2n\text{-Bu}\cdot\text{HBF}_4$ and $P(t\text{-Bu})_2n\text{-Hex}\cdot\text{HBF}_4$, or less bulky ligand $P(i\text{-Pr})_3\cdot\text{HBF}_4$ (for additional ligands run, see experimental section 6.4.1). There are a variety of steric descriptors that have been applied to phosphine ligands. Based on recent work by Doyle and co-workers,^[154] and the establishment of a discovery platform for organophosphorus ligands (*Kraken*),^[155] we chose to use the minimum percentage buried volume, %VBur(min). Percentage buried volume, %VBur, is a measure of steric bulk proximal to the metal centre, defined as percentage volume occupied by the ligand in the metal sphere (assuming a radius of 3.5 Å). The %VBur(min) parameter represents the smallest %VBur of all the energetically accessible conformers of a ligand.^[154] As a result %VBur is a better descriptor for comparing the sterics of a ligand class than Tolman cone angle. In the sulfinamide cross-coupling reaction, alkylphosphine ligands with %VBur(min) values within the approximate range 29.0 – 32.0 performed the best.

Table 4.2 Further optimisation of desulfinamidative cross-coupling on a preparative scale (0.30 mmol).

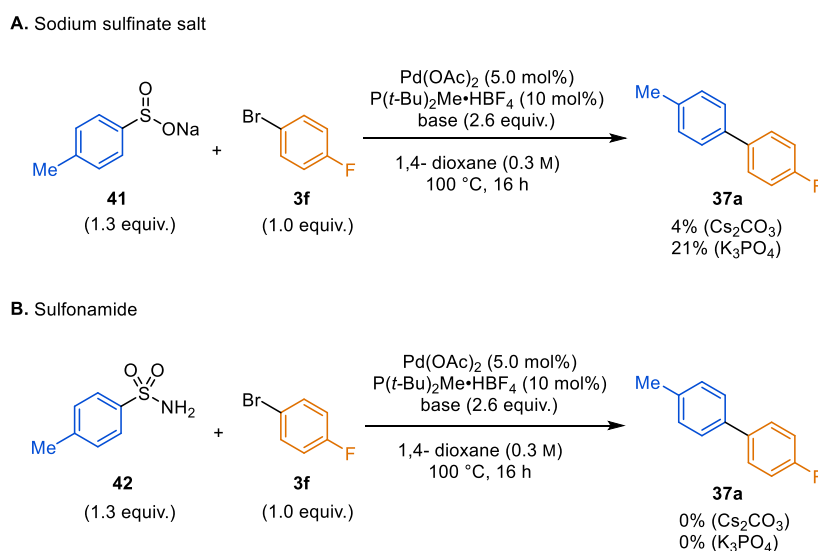
Entry	Base	Solvent	Ligand	%V _{bur(min)} ^[b]	Yield ^[a] / %
1			P(<i>t</i> -Bu) ₂ Me•HBF ₄	31.5	69 (66)
2			P(Cyp) ₃ •HBF ₄	29.3	65
3	Cs ₂ CO ₃	1,4-dioxane	P(<i>i</i> -Pr) ₃ •HBF ₄	29.0	61
4			P(<i>t</i> -Bu) ₂ <i>n</i> -Bu•HBF ₄	32.7	24
5			P(<i>t</i> -Bu) ₂ <i>n</i> -Hex•HBF ₄	-	19
6	Rb ₂ CO ₃				55
7	K ₃ PO ₄	1,4-dioxane	P(<i>t</i> -Bu) ₂ Me•HBF ₄		60
8	K ₃ PO ₄ (3.0 equiv.)				64 (61)
9		anisole			46
10		ethoxybenzene			30
11	K ₃ PO ₄	DMA	P(<i>t</i> -Bu) ₂ Me•HBF ₄		64
12		Cyrene			nr
13		Isoamyl acetate			2

^[a] Average HPLC yields calculated using 1,3,5-trimethoxybenzene and *p*-ditolyether as internal standards.

^[b] V_{Bur(min)} values were obtained from the *Kraken* database^[155] and further processed to get the percentage: %V_{bur(min)} = 100*(V_{bur(min)}/179.59). Isolated yields are in parentheses. nr = no reaction, due to polymerisation and decomposition of solvent.

Although Cs₂CO₃ performed well in the reaction, it is expensive and has a high molecular weight. Therefore, it was encouraging to see that Rb₂CO₃ and K₃PO₄ (entries 6 – 8) performed comparably well. The presence of thionylamide gas **36** (HNSO) was not measured as it is known to be unstable with regards to polymerisation and hydrolysis to form SO₂ and NH₃.^[134, 156] In analogy to the desulfonative (-SO₂) processes,^[89a] it was thought that the sulfinylamine gas was likely hydrolysed and sequestered by the carbonate or phosphate base. After a screen of solvents with high boiling points (>100 °C) (entries 9 – 13), only *N,N'*-dimethylacetamide (DMA) gave a comparable yield to 1,4-dioxane. However, due to the higher toxicity of DMA, 1,4-dioxane continued to be used as the reaction solvent.

Throughout the optimisation, the most promising conditions (**Table 4.2**, entries 1 and 7), were very similar to those employed in the Willis group's previous arylation reactions using sulfinate salts, albeit at a reaction temperature 20 – 50 °C lower. Nevertheless, when sodium *p*-tolylsulfinate **41** was combined with the same aryl bromide **3f** at 100 °C under these conditions, the yield of biaryl **37a** was drastically lower than that observed when using *p*-tolylsulfonamide; use of Cs₂CO₃ gave 4% vs. 69% and use of K₃PO₄ gave 21% vs. 60% (Scheme 4.3.a). This illustrates the superior activity of the sulfonamide **35a** coupling partner, over the analogous sulfinate salt **41** at a reaction temperature of 100 °C. Furthermore, using the primary sulfonamide **42**, gave none of the desired product and only unreacted starting material (**Scheme 4.3.b**).



Scheme 4.3 Use of analogous, alternative sulfur nucleophilic partners at 100 °C: (A) Sodium sulfinate salt **41**, (B) Sulfonamide reagent **42**.

Returning to the optimisation of the primary sulfonamide system, varying the reaction stoichiometry was next investigated (**Table 4.3**). Increasing the excess of base did improve the reaction yield (entries 1 – 2), however, also concurrently increasing the equivalents of sulfonamide did not greatly improve the yield (entries 4 – 5). Having an

excess of base relative to sulfinamide, in at least 2:1 ratio (Base: SONH₂), proved to be optimal. Markedly, doping the reaction with stoichiometric water (2.0 equiv.) did not attenuate the reaction efficacy (entry 3). Addition of water was essential in the Pd-mediated *N*-arylation of primary sulfinamides reported by Zeng and co-workers, however none in this case none of the *N*-arylation product was observed.^[131] Inverting the stoichiometry and using the aryl bromide in excess instead of the sulfinamide gave reduced, albeit moderate yields (entries 6 – 8). For Pd-catalysed coupling of sulfinate salts (RSO₂Na), reduction of the palladium (II) precatalyst to the active Pd(0) species is facilitated by homo-coupling of the sulfinate salt.^[89a] Analogously, excess sulfinamide may be necessary to similarly kickstart the palladium catalytic cycle.

Table 4.3 Optimisation of reaction stoichiometry and control reactions.

Entry	Equiv. (SONH ₂ :ArBr:B)	Base	Yield ^[a] / %
1	1.3: 1.0: 2.6	K ₃ PO ₄	60
2	1.3: 1.0: 3.0	K ₃ PO ₄	64
3	1.3: 1.0: 3.0	K ₃ PO ₄ (2.0 equiv. H ₂ O)	60
4	1.5: 1.0: 3.0	K ₃ PO ₄	63 (65)
5	2.0: 1.0: 3.0	K ₃ PO ₄	65 (64)
6	1.0: 2.0: 3.0	K ₃ PO ₄	52
7	1.0: 1.5: 3.0	K ₃ PO ₄	52 (46)
8	1.0: 2.0: 2.0	K ₃ PO ₄	39
9	1.3: 1.0: 3.0	Cs ₂ CO ₃	74 (74)
10	1.5: 1.0: 3.0	Cs ₂ CO ₃	77 (77)
11 ^[b]	1.5: 1.0: 3.0	Cs ₂ CO ₃	53
12 ^[c]	1.5: 1.0: 3.0	Cs ₂ CO ₃	71
13	1.5: 1.0: 0	no Cs ₂ CO ₃	0
14	1.5: 1.0: 3.0	Cs ₂ CO ₃ (no Pd)	0
15	1.5: 1.0: 3.0	Cs ₂ CO ₃ (no ligand)	3
16 ^[d]	1.5: 1.0: 3.0	Cs ₂ CO ₃	4

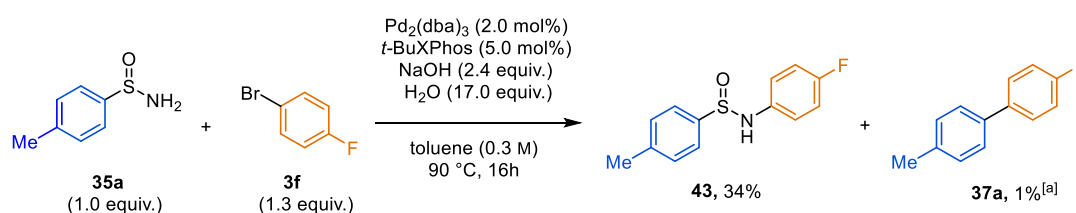
^[a] Average HPLC yields calculated using 1,3,5-trimethoxybenzene and *p*-ditolylether as internal standards. Isolated yields are in parentheses, ^[b] Reaction run at 90 °C, ^[c] Reaction run at 110 °C, ^[d] Reaction run in a 2-neck 25 mL round bottom flask with a condenser.

Although using potassium phosphate tribasic allowed us to obtain good yields >60%, ultimately use of caesium carbonate as the base was optimal, achieving yields over 70% of biaryl **37a** (entries 9 – 10). Using a stoichiometry of sulfinamide: arylbromide: base (1.5: 1.0: 3.0) gave a high 77% isolated yield of biaryl **37a** and was henceforth used as the optimum conditions (entry 10). Pleasingly, when the reaction was performed at 90 °C under these conditions a 53% yield could be obtained (entry 11). Additionally, raising the reaction temperature to 110 °C did not drastically improve the yield (entry 12). The reaction did not work well, or at all, if either base (entry 13), palladium (entry 14) or ligand (entry 15) were omitted. All the reactions reported in **Table 4.2** and **Table 4.3** were performed in sealed microwave tubes on 0.3 mmol scale. Therefore, we ran this reaction in a non-pressurised round bottom flask (rbf) with a condenser attached, to see how the chemistry translated across set-ups and the impact of increasing the volume of headspace (entry 16). Disappointingly, the reaction yield significantly reduced to 4%. The internal reaction temperature was measured by a temperature probe and found to be 95 – 99 °C throughout the course of the reaction. As observed when scaling up the base-activated latent sulfinate work (**Chapter 2, Section 2.5**), exploration of higher boiling solvents and stirring speeds may need to be investigated.

4.2.3. Investigation of the *N*-arylation pathway

In the previously discussed Pd-catalysed *N*-arylation of primary sulfinamides, reported by Zeng and co-workers, there is no mention as to whether any desulfinamidative biaryl product is formed. When *p*-tolylsulfinamide **35a** and 1-bromo-4-fluorobenzene **3f** were subjected to the reported *N*-arylation conditions, only trace amounts of biaryl **37a** was observed by HPLC analysis (**Scheme 4.4**). Instead, 34% yield of *N*-arylated sulfinamide

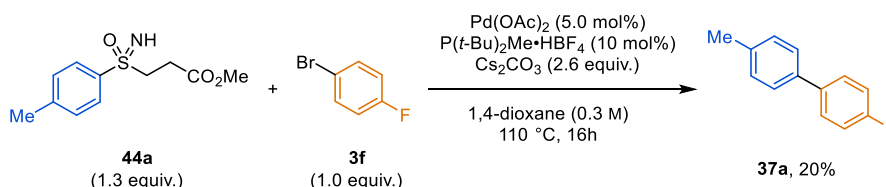
product **43** was obtained. In contrast, using the optimised conditions at 90 °C allowed the desired biaryl **37a** to be obtained in a 53% yield (**Table 4.3**, entry 11). Comparison of these results demonstrates that the reactivity of primary sulfinamides can be tailored between *N*-arylation and desulfinamidative C-arylation through choice of conditions, namely base, ligand and water additive. This chemo-divergence lends itself to further study in the future.



Scheme 4.4 Reaction of primary sulfinamide **35a** and 1-bromo-4-fluorobenzene **3f** under *N*-arylation conditions reported by Zeng and co-workers.^[131] ^[a] Yield determined by HPLC using *p*-ditolylether as an internal standard.

4.3. Phenyl sulfoximines as latent sulfinamide reagents

Analogous to the latent sulfinate approach (**Chapter 2**), it was of interest to investigate if masking the sulfinamide with a base-labile group on sulfur would improve the system. Thus, the use of β -methyl ester sulfoximine **44a** as a coupling partner was envisioned, which under the basic reaction conditions could release methyl acrylate and give the anionic sulfinamide *in situ* that could further react with palladium (**Scheme 4.5**).



Scheme 4.5 Initial hit reaction of the use of latent sulfinamide reagent **44a**.

As original attempts deprotonating the sulfinamide partner prior to cross-coupling had been unsuccessful (**Table 4.1**, entry 4), it was envisaged that masking the sulfinamide could allow controlled *in situ* formation of this anionic species, which could be favourable. The initial attempt was promising, giving a 20% of the desired biaryl **37a** and full consumption of the sulfoximine **44a** at 110 °C; no sulfinamide was observed by HPLC analysis, and the only other identified product was from the homocoupling of the aryl bromide **3f**. The *NH* of the sulfoximine is mildly basic ($\text{S}=\text{NH}$, $\text{p}K_{\text{a}} = 24$ in DMSO; $\text{S}=\text{NH}_2^+$, $\text{p}K_{\text{a}} = 2.7$),^[157] but could be deprotonating under the hot, basic conditions, hence additional equivalents of base may be necessary. In addition, the sulfinamide anion may not be soluble in the reaction solvent, impeding reaction success. Unlike sulfinate salts, sulfinamides are not charged and so masking sulfinamides as sulfoximines does not offer the same advantages as masked sulfonates. Thus, although this was a promising initial hit, greater success has been observed using primary sulfinamides directly as nucleophiles, and so this avenue of investigation was not pursued further. If this research was to be continued in the future, of particular interest would be investigation into the use *N*-substituted sulfoximines and the study of species evolution in this reaction over time.

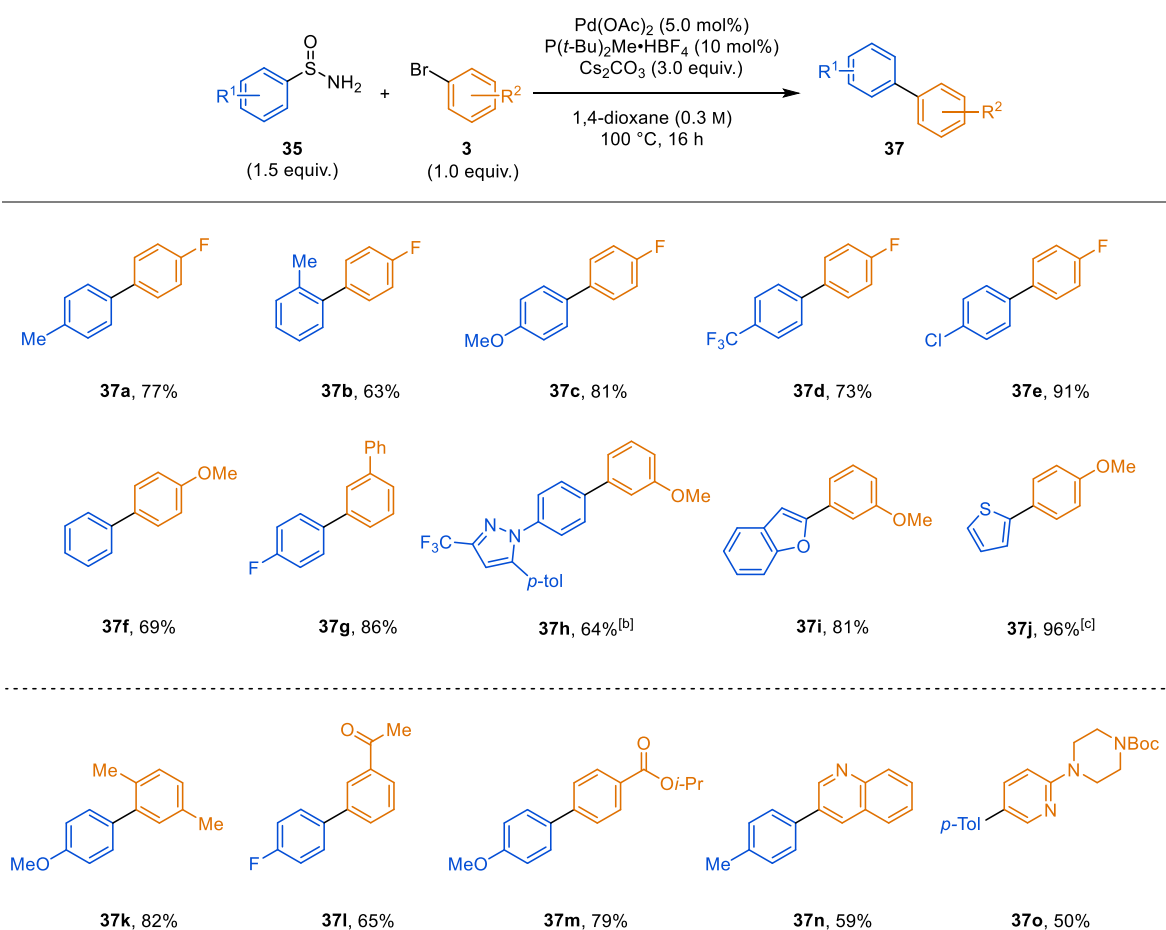
4.4. Reaction scope of desulfinamidative cross-coupling reaction

Due to their omnipresence in many areas of chemistry, from natural products to pharmaceuticals, to materials chemistry, there is an extensive range of methodologies for the synthesis of carbocyclic biaryls *via* Pd-catalysis.^[158] The most widely employed reaction being the Suzuki-Miyaura cross-coupling, which allows biaryl synthesis from organoboron reagents and aryl halides under mild, aqueous conditions (see **chapter 1**).^[20a, 158b] Nonetheless the use of aryl sulfinamides as nucleophiles in these

transformations is not known, and as such, exploration of the biaryl reaction scope of this desulfinamidative cross-coupling is still of fundamental interest. With the established, optimised reaction conditions (**Table 4.3**, entry 10), the investigation of the reaction scope commenced by first varying the sterics and electronics of the aryl sulfinamide reagent (**Table 4.4**).

Tolylsulfinamides substituted at different positions were compatible in the reaction (**37a** and **37b**). Although the yield was slightly reduced when using *ortho*-tolylsulfinamide (**37b**), likely due to increased steric hindrance directly adjacent to the reaction centre. Encouragingly, both electron-rich (**37c**) and electron-poor sulfinamide reagents (**37d**) underwent efficient coupling with 1-bromo-4-fluorobenzene **3f**, to give the respective biaryl product in 82% and 73% yield. 4-Chlorobenzenesulfinamide reacted chemoselectively under the reaction conditions to give a 91% of halogenated biaryl **37e**. Benzenesulfinamide and 4-fluorobenzenesulfinamides also coupled efficiently (**37f** and **37g**). Using a sulfinamide analogue of the sulfonamide containing COX-2 inhibitor drug Celecoxib,^[108] the drug-like scaffold **37h** was obtained in a 64% yield. Notably, this yield was achieved using a lower equivalence of the complex sulfinamide coupling partner (1.3 equiv. vs. 1.5 equiv.). Pleasingly, the reaction was tolerant of heteroaromatic sulfinamides giving high yields of benzofuran **37i** and thiophene **37j**, in 81% and 96% yields respectively.

Table 4.4 Reaction scope of the desulfenamidative cross-coupling of primary aryl sulfinamides and aryl halides.^[a]



^[a] Reaction conditions: sulfinamide (0.45 mmol, 1.5 equiv.), aryl bromide (0.3 mmol, 1.0 equiv.), Pd(OAc)₂ (0.015 mmol, 5.0 mol%), P(*t*-Bu)₂Me·HBF₄ (0.03 mmol, 10 mol%), Cs₂CO₃ (0.90 mmol, 3.0 equiv.), 1,4-dioxane (1.0 mL, 0.3 M), 100 °C, ^[b] Reaction run with sulfinamide (0.39 mmol, 1.3 equiv.), ^[c] Compound synthesised by C. Bell.

Following variation of the sulfinamide coupling partner, using different aryl halide electrophilic coupling partners was next explored. *Ortho*-substituted electrophiles were compatible with the reaction, giving 82% of biaryl **37k**. Moreover, the reaction has a reasonable functional group tolerance, achieving moderate to high yields using aryl bromides containing ketones, esters, functionalised pyridines and quinolines (**37l** - **37o**).

Inevitably, some substrates were less compatible under these reaction conditions (**Figure 4.5**). Disappointingly, the reaction was not tolerant of methyl 4-bromobenzoate, giving only 10% of ester **37p** and several co-eluting side-products. Additionally, poor reaction success was seen when using a sulfonamide analogue of the core of hypertension drug Sildenafil **37q**,^[159] likely due to unproductive deprotonation or co-ordination of the pyrimidinone NH. This may be attenuated by modification of the equivalents of base.

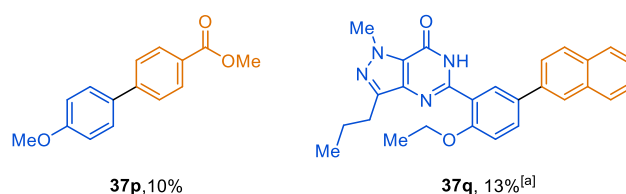


Figure 4.5 Poor-yielding substrates in the desulfonamidative cross-coupling. ^[a] Reaction run on a 0.15 mmol scale; half the scale of the scoping reactions in **Table 4.4**.

4.5. Use of 2-pyridyl sulfonamide coupling partners

In the previous sections, proof-of-concept has been established for the use of primary aryl sulfonamides as efficient nucleophilic coupling partners in Pd-catalysed arylation reactions. However, a noticeable gap in the reaction scope is the lack of 2-arylpyridines. Carbocyclic based biaryl structures, like many of those shown in our reaction scope (**37a** - **37o**), can be synthesised in a myriad of ways, notably the prolific Suzuki-Miyaura cross-coupling (SMC) reaction.^[20b, 160] As discussed throughout this thesis, important 2-(hetero)arylpyridines are hard to access *via* cross-coupling using 2-pyridyl nucleophilic coupling partners. Therefore, a key aim of this research is to extend our lower temperature, sulfonamide methodology to the cross-coupling of 2-pyridyl nucleophilic

coupling partners. Although desulfative chemistry has provided an efficient route, being able to access these important structures at 100 °C would prove an attractive alternative.

An initial attempt to couple 2-pyridylsulfonamide **35b** gave none of the desired 2-arylpyridine **45** at 100 °C (**Figure 4.6 a**). After 16 hours, both 2-pyridylsulfonamide and arylbromide starting materials were the primary reagents observed in the crude reaction mixture by HPLC analysis; the major by-product was the aryl bromide homo-coupling product.

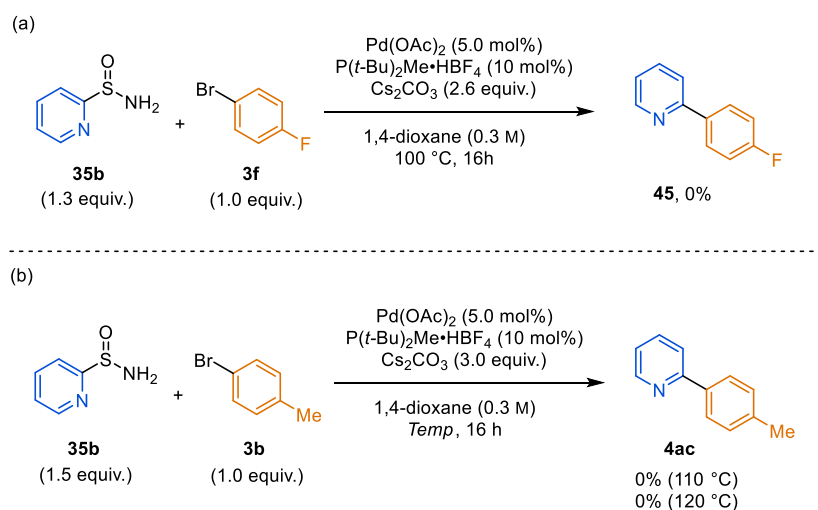


Figure 4.6 Investigation into the reaction of 2-pyridyl sulfonamide **35b** with aryl halides **3f** or **3b** (a) reaction at 100 °C, (b) increasing the reaction temperature. Reaction yield determined by HPLC analysis with *p*-ditolylether as the internal standard.

When studying the mechanism of desulfative cross-coupling, 2-pyridyl sulfinate salts were shown to strongly chelate the palladium metal centre in a $\kappa^2_{\text{N,O}}$ -mode, giving a five-membered ring palladacycle **46** (**Figure 4.7**).^[89a] To extrude SO₂ the Pd-*N*(pyridine) co-ordination needs to be overcome and the five-membered ring broken. This palladacycle does not form when carbocyclic sulfonates are used, resulting in a faster rate of SO₂ extrusion at lower temperature. Therefore, the lack of reaction and consumption of the nucleophilic reagent could be due to unproductive chelation of the 2-pyridylsulfonamide

35b to the palladium centre. To try and troubleshoot this, the reaction was performed at both 110 °C and 120 °C (**Figure 4.6 b**). However, again only starting material was observed and none of the desired product detected by HPLC analysis.

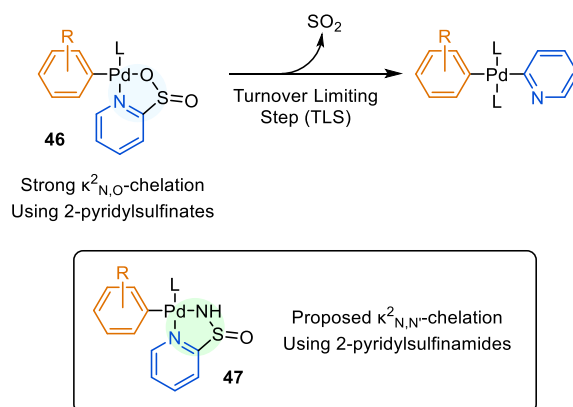


Figure 4.7 Palladacycle formed using 2-pyridyl sulfonates and proposed sulfonamide chelation.

The existence or the stability of the palladacycle formed using 2-pyridyl sulfonamide has not yet been studied. However, by analogy to the mechanism of 2-pyridyl sulfonates, it was theorized that the lack of reactivity of pyridyl sulfonamide **35b** is due to a stronger palladium chelate than formed when using pyridyl sulfonates **47**. Indeed, nitrogen-based ligands are more prevalent in Pd-catalysed reactions than oxygen-based,^[161] with (bis)pyridines and diamines regarded as privileged ligand structures.^[162] Sulfonamide containing ligands are also known, primarily for use in metal catalysed asymmetric transformations however.^[130a, 130b]

Regarding the coupling reaction of sulfinate salts, electron-withdrawing groups on the 2-pyridyl sulfinate reagents, or substitution at the 6-position, formed less thermodynamically stable chelates and resulted in higher cross-coupling yields in general.^[89a] Therefore, employing sulfonamides that have varied pyridine substitution patterns could further probe this reaction and the existence of the proposed chelate.

Furthermore, use of 3-pyridyl or 4-pyridyl primary sulfinamide reagents under these coupling conditions should also be explored to establish if poor reaction success is only seen with 2-pyridyl reagents, which would also help to elucidate the existence/nature of the suggested chelate. Additionally, isolation and study of the proposed Pd-sulfinamide palladacycle under the optimised desulfinamidative coupling conditions would offer insights into this challenging reaction.

The success of the base-activated latent 2-pyridyl sulfinates and the initial reactivity using phenylsulfoximines in coupling reactions (**Section 4.3**), led us to explore the use of 2-pyridyl sulfoximines as masked sulfinamide reagents (**Figure 4.8**). It was hypothesised that latent sulfinamides could enable a controlled release, and lower local concentration, of the sulfinamide, which in-turn could assist the coupling process in an analogous manner to latent sulfinates. 2-Pyridyl β -methylester sulfoximine **44b** was synthesised in 2-steps from the commercially available 2-mercaptopyridine *via* oxidation of the sulfide with ammonium carbonate using conditions reported by Bull and co-workers.^[163] To our disappointment, only trace amount of product was observed when sulfoximine **44b** was subjected to cross-coupling conditions at 110 °C (conditions *a*). Similarly, only 2% of the desired biaryl **4ac** were observed when the optimum conditions for the coupling of β -methylester sulfones at 130 °C were used (conditions *b*). Like the reaction of phenylsulfoximine **44a**, after 16 hours, no 2-pyridyl sulfoximine **44b** was observed in either reaction mixture by HPLC analysis; the sulfoximine reagent was fully consumed.

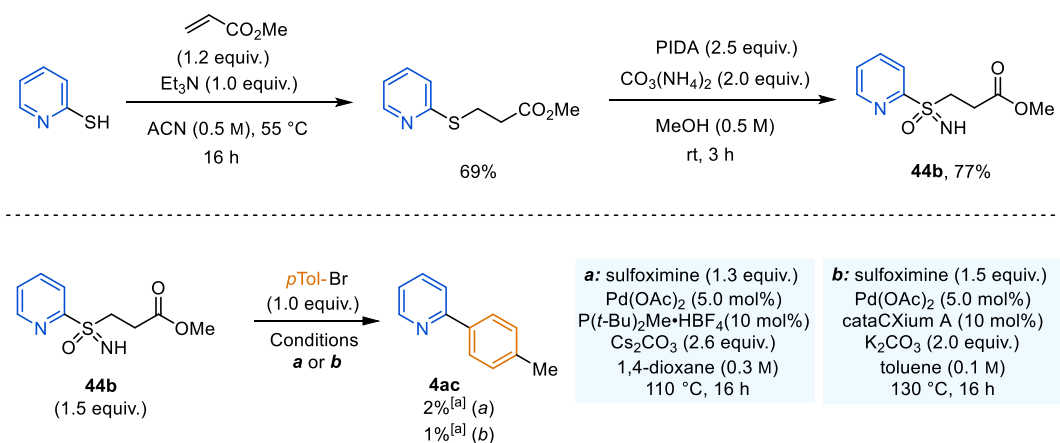


Figure 4.8 2-Pyridyl β-methylester sulfoximine **44b** as a latent sulfinamide reagent. PIDA = phenyliodine(III) diacetate.^[a] Yield determined by HPLC analysis using *p*-ditolyether as an internal standard.

4.6. Project summary and future work

In summary, the first example of Pd-catalysed desulfinamidative arylation using primary aryl sulfinamides and aryl bromides has been developed (**Figure 4.9**). The reaction has been optimised to run efficiently at 100 °C, which is lower than the reaction temperatures of previous desulfinative couplings using metal sulfinate salts as the active nucleophilic partner. This is hypothesised to be the result of sulfinamides being able to undergo transmetalation with the Pd catalytic metal centre with increased efficacy compared to sulfinate salts. However further study of the mechanism would be key to explaining this, in particular fostering a better understanding of how primary sulfinamide reagents operate *in situ*. A range of aryl sulfinamide coupling partners were successfully employed to prepare a representative scope of biaryls with varying steric and electronic properties. Notably, 2-benzofuran and 2-thiophenyl sulfinamides were successfully employed as nucleophilic reagents.

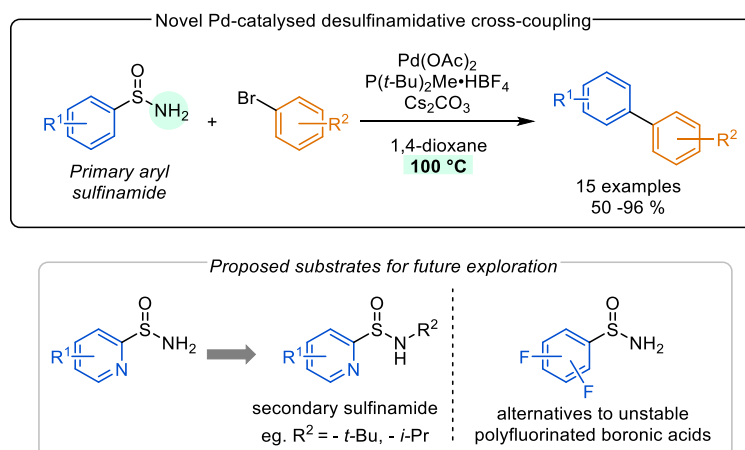


Figure 4.9 Summary of desulfamidative cross-coupling reaction and future work.

A current drawback of this methodology is that it is not optimised for the use of 2-pyridyl primary sulfonamides; no 2-arylpyridine product was observed at 100 – 120 °C. Extending this work to allow the use of 2-pyridyl sulfonamides and other nitrogen-rich heteroaromatics, would greatly improve the utility of this chemistry. Additionally, it would be interesting to use aryl sulfonamide nucleophiles to synthesise other frameworks that are challenging to access through SMC reactions due to boronic acid instability, such as polyfluorinated biaryls.^[22b] An advantage of sulfonamides compared to sulfonate salts, is the ability to tune the sulfonamide group through *N*-substitution. Therefore, further exploration of secondary (hetero)aryl sulfonamide reagents, varying the *N*-substituent, may allow development of a better reagent for 2-arylpyridine synthesis.

Moreover, initial exploration of the use of latent sulfonamide reagents, such as β -ester sulfoximine reagents, show promising reactivity for the formation of carbocyclic biaryls. Monitoring the behaviour of the sulfoximine reagents under cross-coupling conditions, and the release of the sulfonamide into the reaction mixture, would be key to informing the optimisation of this system. Further development of these reagents could build on

previous base-activated latent sulfinate work and provide an alternative nucleophilic reagent for desulfinamidative coupling.

Chapter 5. Conclusions and future work

In this thesis, the successful development and novel use of sulfur-based nucleophilic partners in palladium-catalysed sp^2 - sp^2 cross-coupling reactions has been described. This research contributes to the vast body of work focused on developing new methodologies to overcome the challenges in synthesising important biaryls, such as unsymmetrical bisazines and 2-arylpyridines.

To that effect, heteroaromatic β -nitrile and β -ester sulfones were developed as next-generation, base-activated latent sulfinates for use in desulfinative cross-coupling processes with (hetero)aryl bromides (**Figure 5.1 A**). The utility and robustness of these bench-stable reagents was demonstrated through both the synthesis of a wide range of 2-arylpyridines and other industrially relevant bi(hetero)aryls, and the successful multi-step elaboration of these masked sulfonates. Due to the efficacy of these reagents and the prevalence of the 2-pyridyl motif in a range of chemical fields, this methodology will likely find wide application in industrial and academic settings.

Inspired by the success of the base-activated latent sulfinates approach, the cross-electrophile coupling of two (hetero)aryl halides was explored, proceeding through the *in situ* generation of a masked sulfinates reagent (**Figure 5.1 B**). Although further optimisation is needed, initial investigation established the feasibility of a such a process, and a promising *c.a* 45% yield of the desired biaryl products was achieved when using electron-poor heteroaryl chlorides and SMOPS as the sulfinates transfer reagent. Future work should aim to improve the difficult formation of the masked sulfinates *in situ*, to enable further optimisation of the overall cross-electrophile coupling reaction.

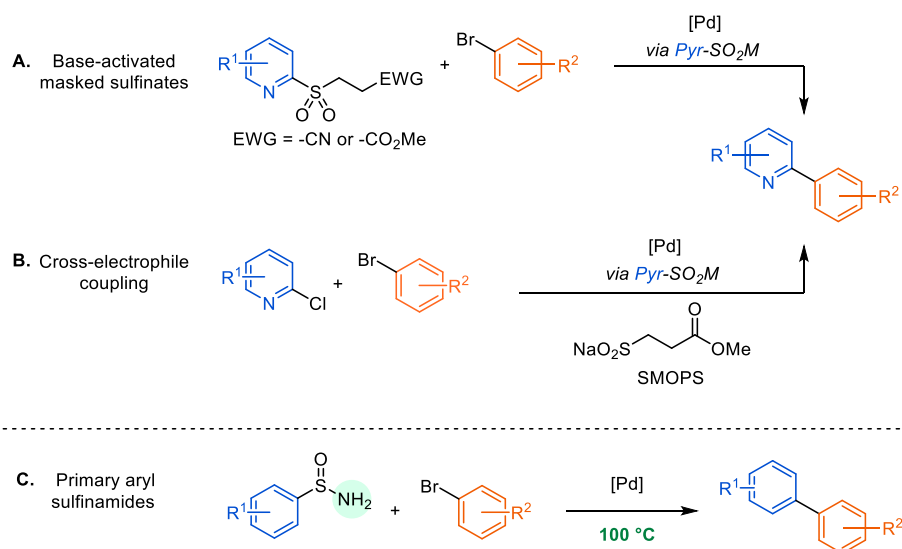


Figure 5.1 Overview of the research described in this thesis.

Finally, the first reported use of primary (hetero)aryl sulfinamides as nucleophilic partners in a palladium-catalysed desulfinamidative cross-coupling arylation was described (**Figure 5.1 C**). The reaction of (hetero)aryl sulfinamides and (hetero)aryl bromides was successfully optimised and was shown to give access to a good scope of biaryl products at 100 °C, a markedly lower reaction temperature than that required for sulfonates and masked sulfonate reagents. 2-Pyridyl and other azine sulfinamides are yet to be successfully employed, and future work will focus on extending this methodology to facilitate these key heteroaryl substrates.

Future development of new metal-catalysed methods to access more highly functionalised alkyl heteroaryl sulfones from heteroaryl halides would extend the accessibility, and thus improve the broader utility of these reagents in desulfonative cross-coupling processes (**Figure 5.2**). Additionally, this could be used in conjunction with desulfonative arylation conditions to enable cross-electrophile coupling, offering the potential for chemodivergent transformations. Such a methodology could also enable the development

of new masked sulfinate reagents as nucleophilic partners for desulfinative arylations, such as reagents with novel modes of activation (such as fluorine activated).

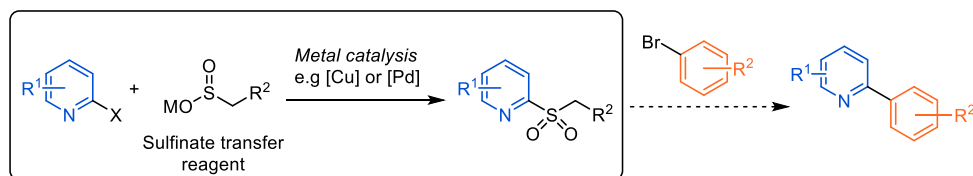


Figure 5.2 Metal-catalysed alkyl heteroaryl sulfone formation.

The sulfur-based nucleophiles developed for cross-coupling reactions operate under similar, but noticeably different reaction conditions, e.g. different temperatures, solvent polarities, and modes of sulfinate un-masking. In the future there is potential to exploit these differences in order to distinguish between different sulfur nucleophiles in the same reaction mixture. Taking inspiration from iterative Suzuki-Miyaura reactions, pyridines functionalised with different sulfur-based nucleophiles could therefore be used to synthesise oligopyridines through tandem, chemoselective desulfinylative reactions (**Figure 5.3**). Oligopyridines are important ligands, particularly in metallocsupramolecular chemistry, hence further tools for the synthesis of higher order 2-pyridine structures would be useful.

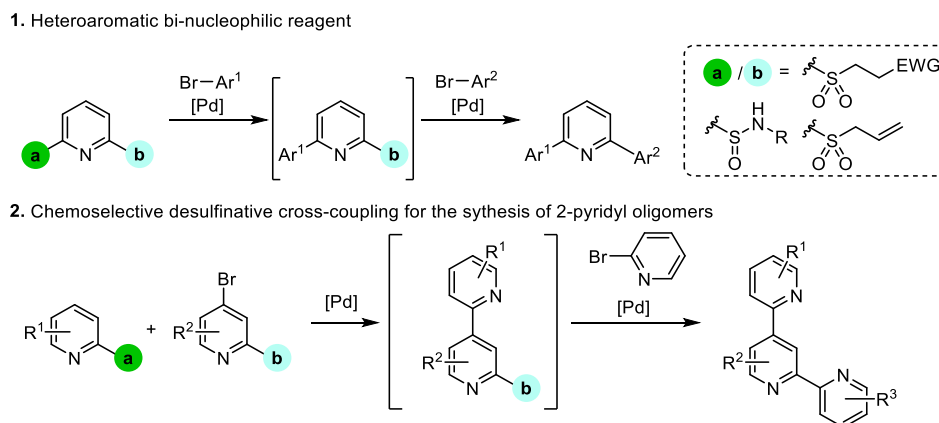


Figure 5.3 Tandem, chemoselective desulfinylative cross-coupling of 2-pyridyl sulfur nucleophiles.

Chapter 6. Experimental data and procedures

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6.1. General Considerations

All reactions were performed under an inert nitrogen atmosphere with anhydrous solvent and constant magnetic stirring, unless otherwise stated. All reactions were run using clean glassware that was oven dried at $>100\text{ }^{\circ}\text{C}$ for at least 2 hours and allowed to cool to room temperature (rt) under a positive pressure of nitrogen. All inert gases were sourced from the University of Oxford's internal supplies and dried through CaCl_2 drying columns. Reactions were monitored by thin-layer chromatography (TLC) until deemed to be complete. TLC was performed on Merck Kieselgel 60 PF254 pre-coated aluminium backed TLC sheets and visualized by UV lamp ($\lambda = 254\text{ nm}$) and/ or TLC staining by dipping in KMnO_4 , Dragendorff or vanillin solutions.

All reagents used were obtained from commercial sources and used without further purification, unless otherwise stated; commercial sources include Sigma Aldrich Chemical Co. Ltd., Fluorochem Ltd., Alfa Aesar, Insight Biotechnology Ltd., Acros Organics Ltd. and Strem Chemicals Inc. Phosphine ligands and salts (K_2CO_3 , Na_2CO_3 , Cs_2CO_3) were all stored under inert atmosphere and inside a desiccator. Salts were dried by heating at $180\text{ }^{\circ}\text{C}$ with stirring under high vacuum ($< 2\text{ mbar}$) for 18 h. Dry solvents were obtained from the University of Oxford internal solvent drying system (Innovative Technology Inc. PS-400-7). Solvents used in the desulfinative cross-coupling were degassed thoroughly by vigorously bubbling a stream of N_2 through the solvent for a minimum of 15 mins prior to use. Solvents that were used regularly (toluene, anisole, 1,4-dioxane and dimethylformamide) were stored under nitrogen, over activated 3 Å molecular sieves. Reagent grade solvents were used for purification. Use of 'Petrol' as a solvent, refers to the fraction of petroleum ether which boils within the range $40 - 60\text{ }^{\circ}\text{C}$. Flash column chromatography was performed by adsorbing the crude mixture onto celite and dry loading onto a slurried silica column. Flash columns used fluorochem silica gel

(60 A 40-63 u) and the indicated eluent system.

^1H , ^{19}F and ^{13}C NMR spectra were recorded on a Bruker AVIII400 Ultrashield spectrometer in deuterated solvent at the stated operating frequency. ^{13}C NMR spectra were recorded with ^1H broadband decoupling. Chemical shifts (δ) are reported in parts per million (ppm) and referenced relative to the residual solvent peak. ^{19}F NMR was referenced to CFCl_3 . Chemical shifts from ^1H NMR and ^{19}F NMR spectrometry are recorded to two decimal places, whereas chemical shifts from ^{13}C NMR spectrometry are recorded to one decimal place. Resonance multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), multiplet (m), broad (br.), apparent (app.), doublet of doublet (dd), etc. Coupling constants (J) are given in Hertz (Hz) and rounded to the nearest 0.5 Hz. Spectra assignments were deduced using chemical shifts, coupling constants, 2D-NMR spectra (COSY and HSQC) and/or by comparison to spectra of related compounds.

Low-resolution mass spectra were recorded on an Agilent 6120 Quadrupole spectrometer (ESI) using methanol: water: FA (90:10: 0.1). High resolution mass spectra were obtained *via* the in-house service at the Chemistry Research Laboratory, University of Oxford, utilizing a Bruker Daltronics MicroTOF spectrometer. Mass spectra samples were prepared as 1 mg/mL solutions in MeOH/MeCN. The m/z values are all recorded in Daltons to one decimal place for the low resolution spectrum and to four decimal places on the high resolution. For high resolution mass spectra, the mass found was compared to the mass calculated from the monoisotopic molecular formula, and all results were found to be within a tolerance of 5 ppm of the calculated values. Infrared spectra were determined neat using a Bruker Tensor 27 FT spectrometer with an internal range of 600-4000 cm^{-1} and all absorptions are given in wavenumbers to the nearest whole number

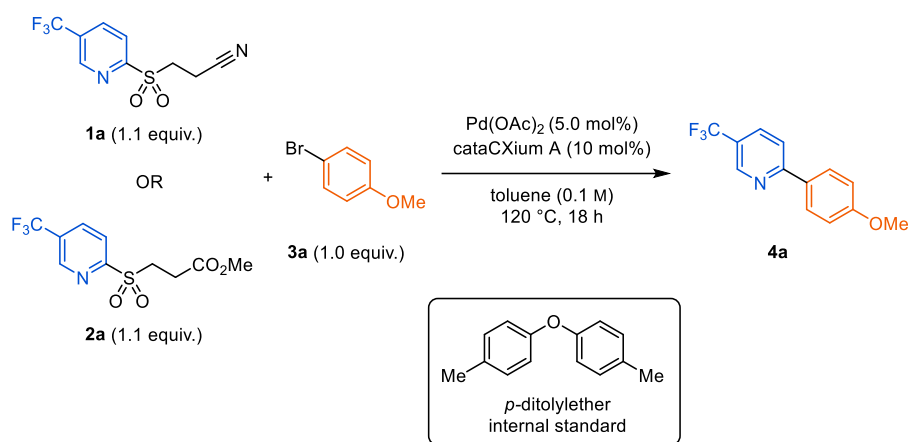
(cm⁻¹). Compound names are generated by PerkinElmer ChemDraw Professional.

Reaction temperatures refer to the temperature of the aluminium heating block or cooling bath. This was measured using a mercury thermometer for reactions heated above room temperature (20 – 200 °C), or with an ethanol low-temperature thermometer when reactions were cooled below room temperature (-80 – 19 °C). The exception being for the scaled-up chemistry where the internal reaction temperature of the solvent was recorded. Internal reaction temperatures were measured using a HANNA K-type thermometer (resolution of 0.1 °C, range: -149.9 – 999.9 °C) equipped with a customized K-type thermocouple probe coated in PTFE (2mm diameter X 150 mm length).

6.2. Data for Chapter 2

6.2.1. Monitoring the consumption of the sulfone starting material and formation of biaryl product.

To further investigate the effect of adding acetic acid into the system, the consumption of pyridine sulfone starting material (**1a** or **2a**) and formation of cross-coupled product (**4a**) (Scheme 6.1) was monitored under various cross-coupling conditions (Figure 6.1 a -e). To achieve this, the reaction was run according to general procedure F, with internal standard in the reaction mixture (15 mg, 0.076 mmol, 0.38 equiv., *p*-ditolyether). Aliquots of the reaction mixture were removed and quenched at specific interval and analysed by HPLC. The amount of starting sulfone and cross-coupled biaryl product present in the reaction mixture were monitored.



Scheme 6.1 Reaction of base-activated sulfones **1a** or **2a** and 4-bromoanisole **3a** to form biaryl **4a**, monitored over time by HPLC analysis using *p*-ditolyether as the internal standard.

On comparison of the plots showing the consumption of β - nitrile sulfone **1a** with AcOH additive in the system (Figure 6.1 a) to that without AcOH (Figure 6.1 b), it is evident that the presence of AcOH additive slows the rate of sulfone consumption, and therefore

the rate of sulfinatate release. With the presence of both K_2CO_3 and AcOH in the reaction medium, a mixture of salts could be generated *in situ*, such as $KHCO_3$ and KOAc. However, reaction of β - nitrile sulfone **1a** and arylbromide **3a** using a mixture of these salts, instead of a direct AcOH additive, gave a much slower consumption of sulfone starting material (**Figure 6.1 c** vs. **Figure 6.1 a**). Observation of slower rates of sulfone consumption with these salts suggests that their formation is not likely to occur at the start of the reaction, i.e AcOH does not react fully with K_2CO_3 on addition to the reaction. Use of AcOH additive in the reaction of β - ester sulfone **2a** with **3a** (**Figure 6.1 d**), results in a slower consumption of sulfone **2a**, and therefore slower release of sulfinatate salt, compared to when no AcOH additive is used (**Figure 6.1 e**). By comparing the plots showing the loss of β - nitrile sulfone **1a** under the conditions utilizing an AcOH additive (**Figure 6.1 a**) to that showing the loss of β - ester sulfone **2a** under the same conditions (**Figure 6.1 d**), we can see that β - ester sulfone **2a** is consumed at a slower rate than β - nitrile sulfone **1a**. In other words, under the cross-coupling conditions the β - nitrile sulfone **1a** and of β - ester sulfone **2a** are consumed, and release the sulfinatate salt, at different rates (**Figure 6.2**). Therefore, use of AcOH additive affects the rate of sulfinatate release from the corresponding masked sulfone (**1a** or **2a**) to different extents.

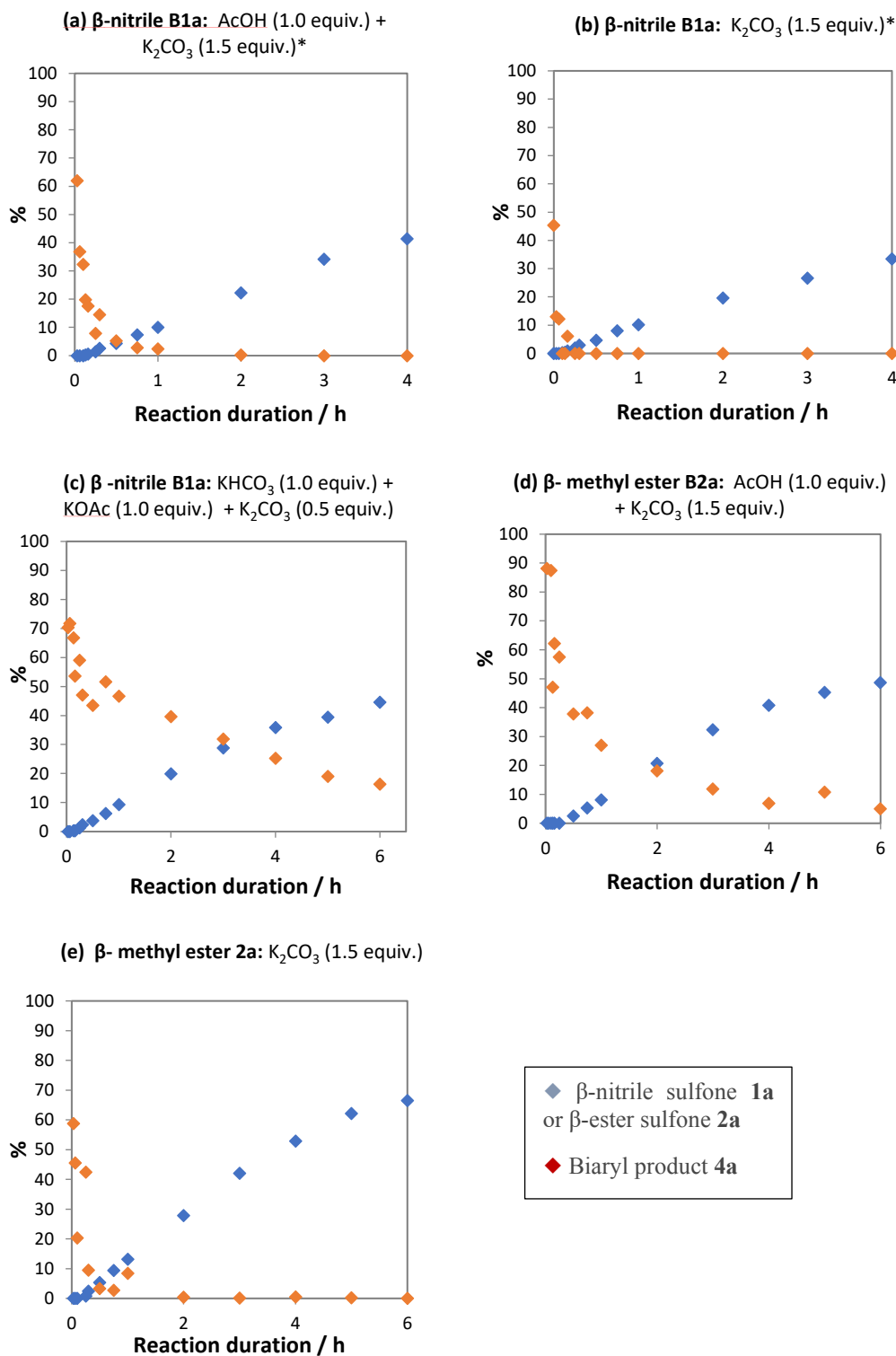


Figure 6.1 HPLC monitoring of the loss of starting material and the production of product in the reaction of β -nitrile pyridine sulfone (**1a**) or β -ester pyridine sulfone (**2a**) with 4-bromoanisole (**3a**). (a) Reaction of **1a** reaction containing AcOH (1.0 equiv.) and K_2CO_3 , (b) Reaction of **1a** with K_2CO_3 (1.5 equiv.) and no AcOH, (c) Reaction of **1a** reaction with a combination of $KHCO_3$ (1.0 equiv.), KOAc (1.0 equiv.) and K_2CO_3 (0.5 equiv.), (d) Reaction of **2a** reaction containing AcOH (1.0 equiv.) and K_2CO_3 (1.5 equiv.), (e) Reaction of **2a** with K_2CO_3 (1.5 equiv.) and no AcOH. The yield/consumption (%) is determined by HPLC using p-ditolylether as an internal standard. *These data sets were directly reproduced multiple times ($\times 3$).

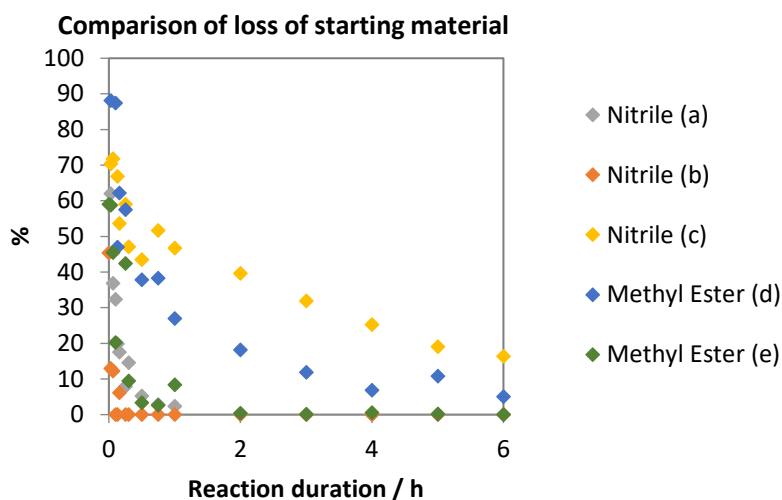
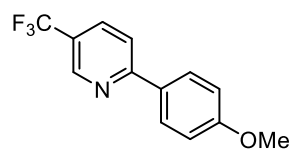


Figure 6.2 Comparison of the consumption of masked sulfonate starting material under varying cross-coupling conditions (overlay of **Figures 6.1 a-e**).

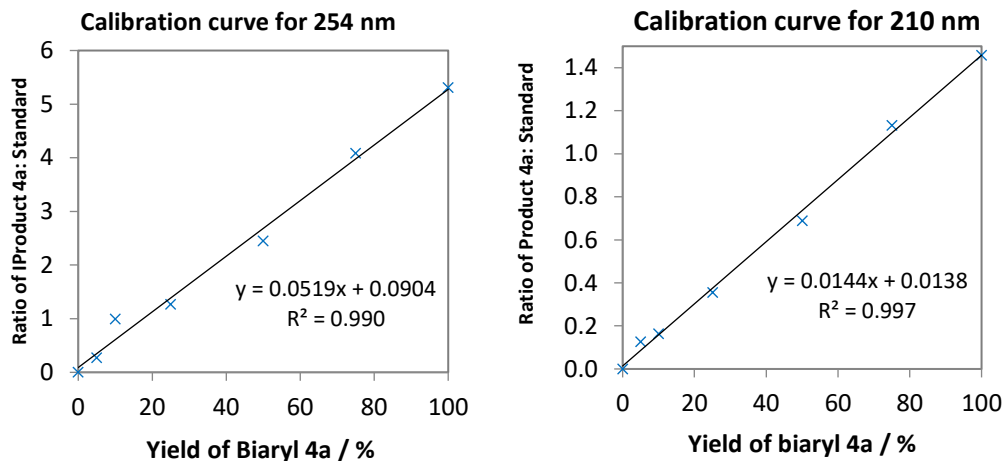
6.2.2. HPLC information and calibration curves

The HPLC data was obtained from an Agilent Technologies 1200 series HPLC Hypersol ODS, 5 μm column (100 $\times$ 4.0 MM) using an extended 12 min method H₂O (0.1 % v/v H₃PO₄): Acetonitrile (10-95% (9 min) to 100% (10.5 min) to 10% (12 min)). HPLC yields for the ligand screening were obtained *via* standard calibration curve using authentic desired product/starting material and *p*-ditoylether as an internal standard. Yields were calculated from two different wavelengths 254 nm and 210 nm and averaged. The method was verified by product isolation which gave a result $\pm$ 2%.

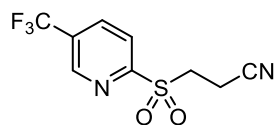
Calibration curves plotting yield of 2-(4-methoxyphenyl)-5-(trifluoromethyl)pyridine **4a** (retention time = 6.63 min), against the peak area ratio of product to internal standard, using *p*-ditoylether (retention time = 7.90 min) at either 210 nm or 254 nm.



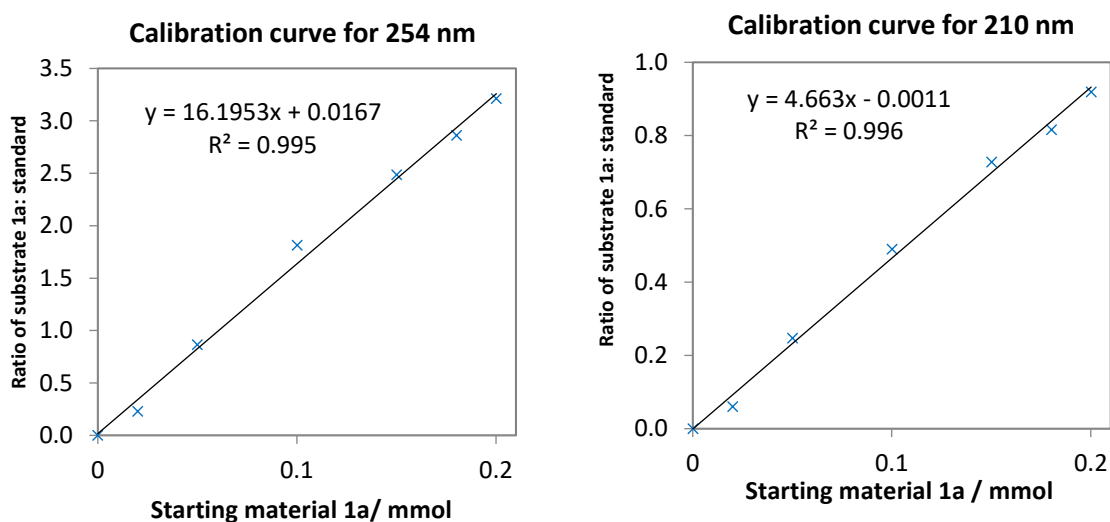
4a



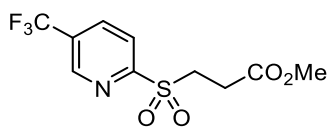
Calibration curves plotting yield of β -nitrile sulfone starting material **1a**, against the peak area ratio of product to internal standard, using *p*-ditoylether (retention time = 7.90 min) at either 210 nm or 254 nm.



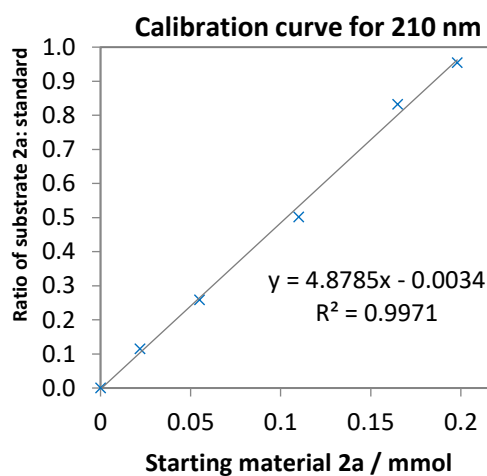
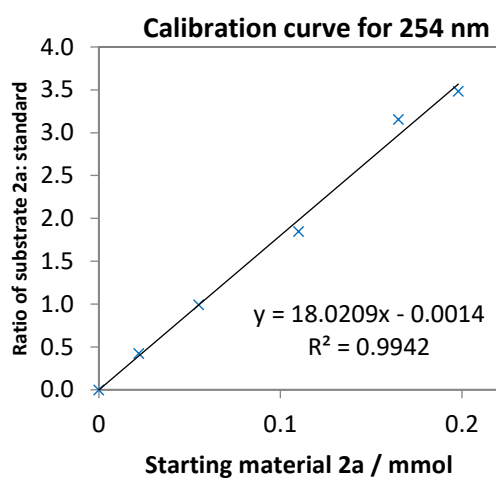
1a



Calibration curves plotting yield of β -ester sulfone starting material **2a**, against the peak area ratio of product to internal standard, using *p*-ditoylether (retention time = 7.90 min) at either 210 nm or 254 nm.



2a



6.2.3. Synthetic procedures and data

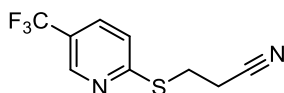
6.2.3.a Synthesis of heteroaromatic thioethers

General Procedure A:

Under N₂: Acrylonitrile (5.0 equiv.) *or* methyl acrylate (5.0 equiv.) was added dropwise to a stirring solution of pyridine thiol (1.0 equiv.) and Et₃N (1.0 equiv.) in acetonitrile (0.3 – 0.7 M). The resultant solution was heated to 40 – 45 °C for 18- 48 h. After which the reaction was allowed to cool to rt and concentrated *in vacuo* to remove the excess acrylonitrile/ methyl acrylate and Et₃N. The resultant crude residue was then purified by flash column chromatography on silica gel to give the desired compound.

General Procedure B: Modified procedure from the procedures detailed by Wei *et. al.*^[83]

Under N₂: Methyl-3-mercaptopropionate (1.5 equiv.) was added to a stirring suspension of heteroaryl chloride (1.0 equiv.) and K₂CO₃ (1.5 equiv.) in DMF (1.0 M). The reaction was stirred at rt for 24 h and monitored by TLC. The reaction mixture was then diluted with water and extracted with EtOAc thrice. The combined organic layers were then washed twice with 10% aqueous LiCl solution, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude residue was then purified by flash column chromatography on silica gel.

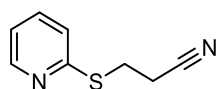


3-((5-(trifluoromethyl)pyridin-2-yl)thio)propanenitrile (*pre-1a*)

Following General procedure A, 5-(trifluoromethyl)pyridine-2-thiol (4.97 g, 27.7 mmol, 1.0 equiv.), acrylonitrile (9.20 mL, 139 mmol, 5.0 equiv.) and Et₃N (3.84 mL, 27.7 mmol, 1.0 equiv.) in acetonitrile (40.0 mL, 0.7 M) were heated at 40 °C for 23 h. The yellow

crude residue was purified by flash column chromatography (20% EtOAc in Petrol) to give the title compound as a colourless oil (4.06 g, 63%).

¹H NMR (400 MHz, CDCl₃) δ 8.69 – 8.67 (m, 1H, Ar-*H*), δ 7.71 (app. ddd, *J* = 8.5, 2.5, 0.5 Hz, 1H, Ar-*H*), δ 7.30 (app. dp, *J* = 8.5, 1.0 Hz, 1H, , Ar-*H*), 3.46 (t, *J* = 7.0 Hz, 2H, SCH₂), 2.87 (t, *J* = 7.0 Hz, 2H, CH₂CN); **¹³C NMR** (101 MHz, CDCl₃) δ 161.8, 146.5 (q, ³*J*_{C-F} = 4.5 Hz), 133.1 (q, ³*J*_{C-F} = 3.5 Hz), 123.7 (q, ¹*J*_{C-F} = 270.5 Hz), 123.1 (q, ²*J*_{C-F} = 33.5 Hz), 122.2, 118.4, 25.7, 18.6; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.22 (s); **LRMS** (ESI⁺) *m/z* 180.0 [M- C₃H₃N+H]⁺; **HRMS** (ESI⁺) found *m/z* 233.0357 [M+H]⁺, C₉H₈N₂F₃S requires *m/z* 233.0355; **IR** *v*_{max} (neat)/cm⁻¹ 3067, 2937, 2252, 1598, 1558, 1323, 1113, 1009, 832; **R_f** = 0.45 (20% EtOAc in Petrol).

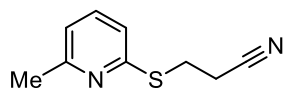


3-(pyridin-2-ylthio)propanenitrile (*pre-1b*)

Following General procedure A, 2-mercaptopyridine (1.11 g, 10.0 mmol, 1.0 equiv.), acrylonitrile (3.30 mL, 50.0 mmol, 5.0 equiv.) and Et₃N (1.39 mL, 10.0 mmol, 1.0 equiv.) in acetonitrile (15.0 mL, 0.6 M) was heated at 45 °C for 48 h. The yellow crude mixture was purified by flash column chromatography (20% EtOAc in Petrol) to give the title compound as a slightly yellow oil (696 mg, 42%).

¹H NMR (400 MHz, CDCl₃) δ 8.42 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, Ar-*H*), 7.50 (ddd, *J* = 8.0, 7.5, 2.0 Hz, 1H, Ar-*H*), 7.19 (dt, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 7.02 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, Ar-*H*), 3.42 (t, *J* = 7.0 Hz, 2H, SCH₂), 2.86 (t, *J* = 7.0 Hz, 2H, CH₂CN); **¹³C NMR** (101 MHz, CDCl₃) δ 156.3, 149.3, 136.0, 122.4, 119.7, 118.4, 25.3, 18.5; **LRMS** (ESI⁺) *m/z* 165.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 165.0482 [M+H]⁺, C₈H₉N₂S requires *m/z* 165.0481; **IR** *v*_{max} (neat)/cm⁻¹ 3048, 2918, 2250, 1578, 1557, 1455, 1415, 1291, 1123,

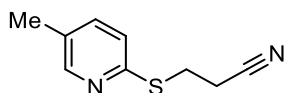
987, 759, 723; $R_f = 0.30$ (20% EtOAc in Petrol). Data consistent with literature: M. Gholinejad, H. Firouzabadi, *New J. Chem.* **2015**, 39, 5953-5959.^[164]



3-((6-methylpyridin-2-yl)thio)propanenitrile (*pre-15a*)

Following General procedure **A**, 6-methylpyridine-2-thiol (218 mg, 1.74 mmol, 1.0 equiv.), acrylonitrile (577 μ L, 8.70 mmol, 5.0 equiv.) and Et₃N (243 μ L, 1.74 mmol, 1.0 equiv.) in acetonitrile (5.0 mL, 0.3 M) was heated at 30 °C for 24 h. The yellow crude residue was purified by flash column chromatography (15% EtOAc in Petrol) to give the title compound as a slightly yellow oil (294 mg, 95%).

¹H NMR (400 MHz, CDCl₃) δ 7.39 (t, $J = 8.0$ Hz, 1H, Ar-*H*), 6.99 (d, $J = 8.0$ Hz, 1H, Ar-*H*), 6.87 (d, $J = 8.0$ Hz, 1H, Ar-*H*), 3.41 (t, $J = 7.0$ Hz, 2H, SCH₂), 2.86 (t, $J = 7.0$ Hz, 2H, CH₂CN), 2.49 (s, 3H, CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 158.8, 155.5, 136.7, 119.6, 119.4, 118.8, 25.7, 24.6, 18.8; **LRMS** (ESI⁺) m/z 179.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 179.0638 [M+H]⁺, C₉H₁₁N₂S requires m/z 179.0638; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 2981, 2361, 2248, 1580, 1566, 1438, 1317, 1288, 1258, 1161, 1146, 1087, 958, 906, 869, 778, 729, 677, 615; $R_f = 0.34$ (20% EtOAc in Petrol).

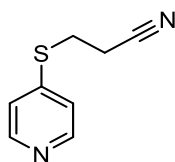


3-((5-methylpyridin-2-yl)thio)propanenitrile (*pre-1d*)

Following General procedure **A**, a solution of 5-methylpyridine-2-thiol (415 mg, 3.29 mmol, 1.0 equiv.), acrylonitrile (1.10 mL, 16.5 mmol, 5.0 equiv.) and Et₃N (459 μ L, 5.00 mmol, 1.0 equiv.) in acetonitrile (10.0 mL, 0.3 M) was heated at 45 °C for 24 h. The

resultant crude residue was purified by flash column chromatography (8-10% EtOAc in Petrol) to give the title compound as a slightly yellow oil (208 mg, 35%).

¹H NMR (400 MHz, CDCl₃) δ 8.26 – 8.25 (m, 1H, Ar-*H*), 7.33 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, Ar-*H*), 7.09 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 3.39 (t, *J* = 7.0 Hz, 2H, SCH₂), 2.83 (t, *J* = 7.0 Hz, 2H, CH₂CN), 2.27 (s, 3H, CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 153.2, 150.0, 137.3, 129.7, 122.4, 118.8, 25.8, 18.9, 18.0; **HRMS** (ESI⁺) found *m/z* 179.0638 [M+H]⁺, C₉H₁₁N₁S requires *m/z* 179.0637; **IR** *v*_{max} (neat)/cm⁻¹ 2925, 2250, 1593, 1557, 1464, 1421, 1367, 1317, 1292, 1222, 1145, 1112, 1025, 906, 820, 732, 620; **R_f** = 0.30 (10% EtOAc in Petrol).

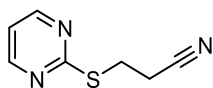


3-(pyridin-4-ylthio)propanenitrile (*pre-1e*)

Following General procedure A, 4-mercaptopyridine (500 mg, 4.50 mmol, 1.0 equiv.), acrylonitrile (1.49 mL, 22.0 mmol, 5.0 equiv.) and Et₃N (627 μL, 4.50 mmol, 1.0 equiv.) in acetonitrile (12.0 mL, 0.4 M) were heated at 40 °C for 24 h. The resultant crude residue was purified by flash column chromatography (100% EtOAc). The resultant orange crystalline solid was repurified by flash column chromatography (95% EtOAc in Petrol) to give the title compound as an off-white crystalline solid (211 mg, 29%).

¹H NMR (400 MHz, CDCl₃) δ 8.48 – 8.47 (m, 2H, Ar-*H*), 7.15 – 7.14 (m, 2H, Ar-*H*), 3.27 (t, *J* = 7.0 Hz, 2H, SCH₂), 2.74 (t, *J* = 7.0 Hz, 2H, CH₂CN); **¹³C NMR** (101 MHz, CDCl₃) δ 150.0, 146.0, 121.5, 117.5, 26.7, 18.0; **LRMS** (ESI⁺) *m/z* 165.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 165.0481 [M+H]⁺, C₈H₉N₂S requires *m/z* 165.0481; **IR** *v*_{max}

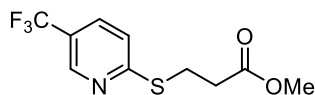
(neat)/cm⁻¹ 2361, 2341, 2251, 1576, 1541, 1484, 1409, 1323, 1288, 1223, 1109, 1066, 986, 904, 805, 711, 669; **mp** 59 – 61 °C (EtOAc); **R_f** = 0.17 (100% EtOAc).



3-(pyrimidin-2-ylthio)propanenitrile (*pre-1f*)

Following General procedure A, 2-mercaptopyrimidine (561 mg, 5.00 mmol, 1.0 equiv.), acrylonitrile (1.66 mL, 25.0 mmol, 5.0 equiv.) and Et₃N (697 µL, 5.00 mmol, 1.0 equiv.) in MeCN (12.5 mL, 0.4 M) were heated at 40 °C for 24 h. The resultant crude was purified by flash column chromatography (30% EtOAc in Petrol) to give the title compound as a pale-yellow oil (683 mg, 83%).

¹H NMR (400 MHz, CDCl₃) δ 8.54 (d, *J* = 5.0 Hz, 2H, Ar-*H*), 7.03 (t, *J* = 5.0 Hz, 1H, Ar-*H*), 3.38 (dd, *J* = 7.5, 7.0 Hz, 2H, SCH₂), 2.88 (dd, *J* = 7.5, 7.0 Hz, 2H, CH₂CN); **¹³C NMR** (101 MHz, CDCl₃) δ 170.7, 157.7, 118.5, 117.3, 26.7, 18.4; **LRMS** *m/z* 166.0 (100%, [M+H]⁺); **HRMS** (ESI⁺) found *m/z* 166.0436 [M+H]⁺, C₇H₈N₃S requires *m/z* 166.0433; **IR** ν_{max} (neat)/ cm⁻¹ 3020, 2980, 2975, 2350 (CN), 1556, 1420, 1381, 1328, 1195, 763; **R_F** = 0.33 (50% EtOAc in Petrol). Data consistent with literature: M. Gholinejad, H. Firouzbadi, *New J. Chem.* **2015**, 39, 5953-5959.^[164]



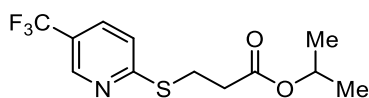
methyl 3-((5-(trifluoromethyl)pyridin-2-yl)thio)propanoate (*pre-2a*)

Following General procedure A, a solution of 5-(trifluoromethyl)pyridine-2-thiol (899 mg, 5.00 mmol, 1.0 equiv.), methyl acrylate (2.25 mL, 25.0 mmol, 5.0 equiv.) and Et₃N (697 µL, 5.00 mmol, 1.0 equiv.) in acetonitrile (7.2 mL, 0.7 M) was heated at 45 °C for 24 h. The resultant crude residue was purified by flash column chromatography (2%

EtOAc in Petrol) to give the title compound as a colourless liquid (998 mg, 75%). *On a 15 mmol scale the reaction gave a comparable 73% yield.*

Following General Procedure **B**, 2-chloro-5-(trifluoromethyl)pyridine (182 mg, 1.00 mmol, 1.0 equiv.), K₂CO₃ (207 mg, 1.50 mmol, 1.5 equiv.) and methyl 3-mercaptopropionate (166 μ L, 1.50 mmol, 1.5 equiv.) were combined in DMF (1.0 mL, 1.0 M) was added. The reaction mixture was stirred at rt for 18 h and then diluted with water. The reaction mixture was poured into a separating funnel and the aqueous layer was washed with EtOAc (15 mL $\times$ 4). The organic layers were combined and washed with 10% aqueous LiCl solution (50 mL $\times$ 2). The organic layers were then dried over MgSO₄, filtered and concentrated *in vacuo*. The yellow crude oil was then purified by flash column chromatography (5% EtOAc in Petrol) to give the title product as a colourless liquid (205 mg, 77%).

¹H NMR (400 MHz, CDCl₃) δ 8.67 – 8.65 (m, 1H, Ar-*H*), 7.67 – 7.64 (m, 1H, Ar-*H*), 7.26 – 7.23 (m, 1H, Ar-*H*), 3.71 (s, 3H, CO₂CH₃), 3.47 (t, *J* = 7.0 Hz, 2H, SCH₂), 2.80 (t, *J* = 7.0 Hz, 2H, CH₂CO₂Me); **¹³C NMR** (101 MHz, CDCl₃) δ 172.5, 163.5, 146.4 (q, ³*J*_{C-F} = 4.0 Hz), 132.7 (q, ³*J*_{C-F} = 3.5 Hz), 123.9 (q, ¹*J*_{C-F} = 272.0 Hz), 122.5 (q, ²*J*_{C-F} = 33.0 Hz), 121.9, 52.0, 34.3, 25.1; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.20 (s); **LRMS** (ESI⁺) *m/z* 266.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 266.0458 [M+H]⁺, C₁₀H₁₁O₂NF₃S requires *m/z* 266.0457; **IR** ν_{max} (neat)/cm⁻¹ 2928, 1606, 1563, 1481, 1458, 1384, 1327, 1165, 1129, 1083, 1015, 940, 851, 782, 753, 619; **R_f** = 0.37 (5% EtOAc in Petrol).

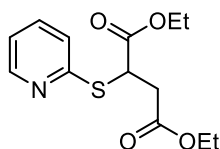


isopropyl 3-((5-(trifluoromethyl)pyridin-2-yl)thio)propanoate (*pre-2a-iPr*)

Note: Iso-propyl acrylate was made freshly via transesterification of methyl acrylate and then used directly as the crude in this reaction. Some methyl 3-((5-(trifluoromethyl)pyridin-2-yl)thio)propanoate side product was observed and isolated from this reaction.

Following General procedure A, a solution of 5-(trifluoromethyl)pyridine-2-thiol (179 mg, 1.00 mmol, 1.0 equiv.), crude iso-propyl acrylate in CH₂Cl₂ (12.0 mL, *c.a* 5.00 mmol, 5.0 equiv.) and Et₃N (140 μ L, 5.00 mmol, 1.0 equiv.) in acetonitrile (2.0 mL, 0.5 M) was heated at 45 °C for 24 h. The resultant crude residue was purified by flash column chromatography (2% EtOAc in Petrol) to give the title compound as a colourless oil (61.6 mg, 21%).

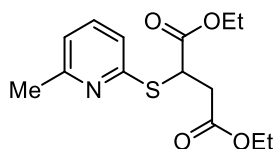
¹H NMR (400 MHz, CDCl₃) δ 8.68 – 8.62 (m, 1H, Ar-*H*), 7.66 – 7.62 (dd, *J* = 2.5, 8.5 Hz, 1H, Ar-*H*), 7.24 (dt, *J* = 8.5, 1.0 Hz, 1H, Ar-*H*), 5.04 (hept, *J* = 6.5 Hz, 1H, CO₂CH), 3.45 (t, *J* = 7.0 Hz, 2H, SCH₂), 2.74 (t, *J* = 7.0 Hz, 2H, CH₂CO₂Me), 1.23 (d, *J* = 6.5 Hz, 6H, C(CH₃)₂); **¹³C NMR** (101 MHz, CDCl₃) δ 171.5, 163.6, 146.4 (q, ¹*J*_{C-F} = 4.5 Hz), 132.7 (q, ¹*J*_{C-F} = 3.5 Hz), 123.9 (q, ³*J*_{C-F} = 271.0 Hz), 122.4 (q, ²*J*_{C-F} = 33.0 Hz), 121.9, 68.3, 34.8, 25.2, 22.0; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.21 (s); **LRMS** (ESI⁺) *m/z* 294.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 294.0772 [M+H]⁺, C₁₂H₁₅O₂NF₃S requires *m/z* 294.0770; **IR** ν_{max} (neat)/cm⁻¹ 2361, 2341, 1598, 1557, 1473, 1378, 1324, 1251, 1167, 1114, 1075, 1010, 939, 931, 746; **R_f** = 0.30 (5% EtOAc in Petrol).



diethyl 2-(pyridin-2-ylthio)succinate (*pre-8a*)

Following General procedure A, 2-mercaptopyridine (222.3 mg, 2.00 mmol, 1.0 equiv.), diethyl fumarate (1.64 mL, 10.0 mmol, 5.0 equiv.) and Et₃N (279 μ L, 2.00 mmol, 1.0 equiv.) in acetonitrile (3.0 mL, 0.7 M) was heated at 45 °C for 24 h. The resultant crude residue was purified by flash column chromatography (3% EtOAc in Petrol) to give the title compound as slightly yellow oil (479 mg, 84%).

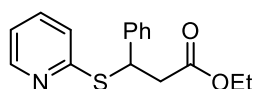
¹H NMR (400 MHz, CDCl₃) δ 8.42 – 8.39 (m, 1H, Pyr-*H*), 7.50 (app. td, J = 7.5, 2.0 Hz, 1H, Pyr-*H*), 7.20 (d, J = 8.0 Hz, 1H, Pyr-*H*), 7.03 – 6.99 (m, 1H, Pyr-*H*), 4.95 (dd, J = 8.5, 5.5 Hz, 1H, SCH), 4.24 – 4.11 (m, 4H, 2 $\times$ OCH₂CH₃), 3.14 (dd, J = 17.0, 8.5 Hz, 1H, CH_aH_bCO₂Et), 2.98 (dd, J = 17.0, 5.5 Hz, 1H, CH_aH_bCOOEt), 1.23 (dt, J = 12.0, 7.0 Hz, 6H, 2 $\times$ CH₂CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 171.3, 171.0, 156.5, 149.6, 136.4, 122.6, 120.3, 61.8, 61.0, 41.9, 37.3, 14.3, 14.1; **HRMS** (ESI⁺) found m/z 284.0950 [M+H]⁺, C₁₃H₁₈O₄N³²S requires m/z 284.0951; **IR** ν_{max} (neat)/cm⁻¹ 3048, 2017, 2936, 2936, 2841, 1729, 1578, 1558, 1455, 1416, 1371, 1326, 1300, 1235, 1204, 1175, 1121, 1096, 1028, 988, 858, 761; **R_f** = 0.41 (20% EtOAc in Petrol). Data is consistent with literature: T. Hideo, F. Misa and Y. Masataka, *Bulletin of the Chemical Society of Japan*, 1991, **64**, 57-67.^[165]



diethyl 2-((6-methylpyridin-2-yl)thio)succinate (*pre-8b*)

Following General procedure A, 6-methylpyridine-2-thiol (125.2 mg, 1.00 mmol, 1.0 equiv.), diethylfumarate (818.5 μ L, 5.00 mmol, 5.0 equiv.) and Et₃N (139.5 μ L, 1.00 mmol, 1.0 equiv.) in acetonitrile (2.0 mL, 0.5 M) was heated at 45 °C for 24 h. The resultant crude residue was purified by flash column chromatography (2 – 10% EtOAc in Petrol) to give the title compound as a colourless oil (207 mg, 70%).

¹H NMR (400 MHz, CDCl₃) δ 7.38 (t, J = 7.5 Hz, 1H, Pyr-*H*), 7.01 (d, J = 7.5 Hz, 1H, Pyr-*H*), 6.86 (d, J = 7.5 Hz, 1H, Pyr-*H*), 4.87 (dd, J = 8.5, 5.5 Hz, 1H, SCH), 4.17 (dq, J = 12.0, 7.0 Hz, 4H, 2 $\times$ OCH₂CH₃), 3.15 (dd, J = 17.0, 8.5 Hz, 1H, CH_aH_bCO₂Et), 2.97 (dd, J = 17.0, 5.5 Hz, 1H, CH_aH_bCO₂Et), 2.47 (s, 3H, Pyr-CH₃), 1.23 (dt, J = 12.0, 7.0 Hz, 6H, 2 $\times$ CH₂CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 171.4, 171.1, 158.6, 155.3, 136.7, 119.7, 119.6, 61.7, 61.0, 42.2, 37.3, 24.4, 14.3, 14.2; **LRMS** (ESI⁺) m/z 298.0 (50%, [M+H]⁺), 320.0 (50%, [M+Na]⁺); **HRMS** (ESI⁺) found m/z 298.1107 [M+H]⁺, C₁₄H₂₀O₄NS requires m/z 298.1108; **IR** ν_{max} (neat)/ cm⁻¹ 2983, 1732, 1580, 1567, 1439, 1371, 1162, 1030, 779; **R_f** = 0.47 (20% EtOAc in Petrol).

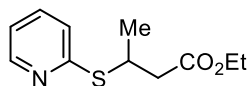


ethyl 3-phenyl-3-(pyridin-2-ylthio)propanoate (*pre-9*)

Following General procedure A, 2-mercaptopyridine (222.3 mg, 2.00 mmol, 1.0 equiv.), ethyl cinnamate (1.68 mL, 10.0 mmol, 5.0 equiv.) and Et₃N (279 μ L, 2.00 mmol, 1.0 equiv.) in MeCN (3.00 mL, 0.7 M) was heated at 80 °C for 24 h. Due to sluggish

reaction, the reaction temperature was raised to 100 °C for an additional 24 h. The resultant crude was purified by flash column chromatography (5% EtOAc in Petrol) to give the title compound as a yellow oil (207 mg, 36%).

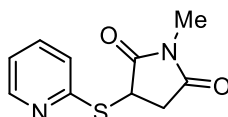
¹H NMR (400 MHz, CDCl₃) δ 8.46 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, Pyr-*H*), 7.48 – 7.42 (m, 3H, Ar-*H*), 7.33 – 7.27 (m, 2H, Ar-*H*), 7.26 – 7.20 (m, 1H, Pyr-*H*), 7.11 (dt, *J* = 8.0, 1.0 Hz, 1H, Pyr-*H*), 6.98 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, Pyr-*H*), 5.44 (dd, *J* = 9.5, 6.0 Hz, 1H, SCH), 4.03 (m, 2H, CH₂COOCH₂CH₃), 3.25 (dd, *J* = 16.0, 6.0 Hz, 1H, CH_aH_bCOOEt), 3.02 (dd, *J* = 16.0, 9.5 Hz, 1H, CH_aH_bCOOEt), 1.11 (t, *J* = 7.0 Hz, 3H, COOCH₂CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 170.9, 158.1, 149.8, 140.8, 136.2, 128.7, 128.0, 127.6, 122.7, 120.0, 60.7, 44.5, 41.5, 14.2; **HRMS** (ESI⁺) found for the methyl ester analogue (transesterification likely occurred in the preparative MS MeOH solution) *m/z* 274.0901 [M+H]⁺, C₁₅H₁₆O₂NS requires *m/z* 274.0896; **IR** *v*_{max} (neat)/ cm⁻¹ 3063, 3031, 2924, 2819, 1733, 1577, 1557, 1494, 1454, 1415, 1369, 1301, 1123, 1031, 868, 759, 724, 699; **R_F** = 0.22 (10% EtOAc in Petrol).



ethyl 3-(pyridin-2-ylthio)butanoate (*pre-10*)

Following a modified general procedure **A**, 2-mercaptopyridine (333.5 mg, 3.0 mmol, 1.0 equiv.), ethyl trans-2-butenate (449 μL, 3.6 mmol, 1.2 equiv.) and Et₃N (418 μL, 3.0 mmol, 1.0 equiv.) in acetonitrile (6.0 mL, 0.5 M) were heated to 55 °C for 16 h. The reaction mixture was then cooled to rt, concentrated *in vacuo* and purified by flash column chromatography (10 – 20% EtOAc in Petrol) to give the title compound as a colourless oil (96.5 mg, 14%).

¹H NMR (400 MHz, CDCl₃) δ 8.44 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, Pyr-*H*), 7.48 (ddd, *J* = 8.0, 7.5, 2.0 Hz, 1H, Pyr-*H*), 7.17 (dt, *J* = 8.0, 1.0 Hz, 1H, Pyr-*H*), 6.99 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, Pyr-*H*), 4.36 – 4.25 (m, 1H, SCH), 4.15 (q, *J* = 7.0 Hz, 2H, CH₂CH₃), 2.87 (dd, *J* = 15.5, 5.5 Hz, 1H, SCHCH_aH_b), 2.59 (dd, *J* = 15.5, 8.5 Hz, 1H, SCHCH_aH_b), 1.47 (d, *J* = 7.0 Hz, 3H, CH₃), 1.25 (t, *J* = 7.0 Hz, 3H, CH₂CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 171.4, 158.5, 149.5, 136.1, 122.8, 119.6, 60.5, 41.7, 35.9, 20.7, 14.2; **LRMS** *m/z* 226.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 226.0897 [M+H]⁺, C₁₁H₃₆O₂NS requires *m/z* 226.0896; **IR** ν_{max} (neat)/cm⁻¹ 29978, 1733, 1579, 1454, 1415, 1127, 760; **R_f** = 0.67 (30% EtOAc in Petrol).

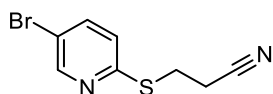


1-methyl-3-(pyridin-2-ylthio)pyrrolidine-2,5-dione (*pre-11*)

Following General procedure A, 2-mercaptopyridine (222.3 mg, 2.00 mmol, 1.0 equiv.), N-methyl maleimide (800 mg, 7.2 mmol, 3.6 equiv.) and Et₃N (279 μL, 2.00 mmol, 1.0 equiv.) in MeCN (3 mL, 0.7 M) was heated at 45 °C for 24 h. On heating the reaction turned from a dark orange solution to a vivid purple colour. The resultant crude was purified by flash column chromatography (25% EtOAc in Petrol) to give the title compound as a white solid (433 mg, 94%).

¹H NMR (400 MHz, CDCl₃) δ 8.24 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, Pyr-*H*), 7.51 (ddd, *J* = 8.0, 7.5, 2.0 Hz, 1H, Pyr-*H*), 7.19 (dt, *J* = 8.0, 1.0 Hz, 1H, Pyr-*H*), 7.00 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, Pyr-*H*), 4.31 (dd, *J* = 9.5, 5.0 Hz, 1H, SCH), 3.26 (dd, *J* = 18.5, 9.5 Hz, 1H, SCHCH_aH_b), 3.08 (s, 3H, N-CH₃), 2.95 (dd, *J* = 18.5, 5.0 Hz, 1H, SCHCH_aH_b); **¹³C NMR** (101 MHz, CDCl₃) δ 176.1, 175.5, 155.8, 149.2, 136.5, 122.1, 120.2, 40.6, 36.8, 25.3; **HRMS** (ESI⁺) found *m/z* 223.0537 [M+H]⁺, C₁₀H₁₁O₂N₂S requires *m/z* 223.0536; **IR**

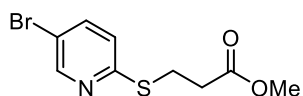
$\nu_{\max}$ (neat)/ cm^{-1} 3048, 2942, 2924, 2854, 1779, 1697, 1578, 1578, 1558, 1456, 1435, 1416, 1381, 1283, 1120, 988, 954, 760, 722, 694; R_F = 0.21 (30% EtOAc in Petrol).



3-((5-bromopyridin-2-yl)thio)propanenitrile (*pre-12a*)

Following General procedure A, 5-bromopyridine-2-thiol (380.1 mg, 2.00 mmol, 1.0 equiv.), acrylonitrile (663 μL , 10.0 mmol, 5.0 equiv.) and Et_3N (279 μL , 2.00 mmol, 1.0 equiv.) in acetonitrile (4.0 mL, 0.5 M) was heated at 45 $^\circ\text{C}$ for 22.5 h. The resultant crude residue was purified by flash column chromatography (10 – 20% EtOAc in Petrol) to give the title compound as a white solid (383.2 mg, 79%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.51 – 8.43 (m, 1H, Pyr-*H*), 7.61 (dt, J = 8.5, 2.0 Hz, 1H, Pyr-*H*), 7.12 – 7.05 (m, 1H, Pyr-*H*), 3.39 (t, J = 7.0 Hz, 2H, SCH_2), 2.83 (t, J = 7.0 Hz, 2H, CH_2CN); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 155.6, 150.5, 139.0, 123.8, 118.5, 116.8, 25.9, 18.7; **LRMS** (ESI^+) m/z 189.9 (50%, $[\text{M}-\text{CH}_2\text{CHCN}+\text{H}]^+$), 191.9 (50%, $[\text{M}-\text{CH}_2\text{CHCN}+\text{H}]^+$); **HRMS** (ESI^+) found m/z 242.9588 $[\text{M}+\text{H}]^+$, $\text{C}_8\text{H}_8\text{N}_2\text{S}^{35}\text{Br}$ requires m/z 242.9586; **IR** $\nu_{\max}$ (neat)/ cm^{-1} 3043, 2928, 2361, 1561, 1446, 1351, 1290, 1223, 1141, 1115, 1089, 1000, 906, 821, 726, 626; **mp** 77 – 79 $^\circ\text{C}$ (EtOAc); R_F = 0.42 (20% EtOAc in Petrol).

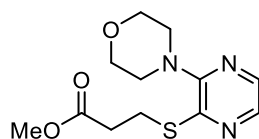


methyl 3-((5-bromopyridin-2-yl)thio)propanoate (*pre-12b*)

Following General procedure A, 5-bromopyridine-2-thiol (380.1 mg, 2.00 mmol, 1.0 equiv.), methyl acrylate (900 μL , 10.0 mmol, 5.0 equiv.) and Et_3N (279 μL , 2.00 mmol, 1.0 equiv.) in acetonitrile (4.0 mL, 0.5 M) was heated at 45 $^\circ\text{C}$ for 24 h. The

resultant crude residue was purified by flash column chromatography (5% EtOAc in Petrol) to give the title compound as a slightly yellow clear oil (481 mg, 87%).

¹H NMR (400 MHz, CDCl₃) δ 8.46 (dd, *J* = 2.5, 1.0 Hz, 1H, Pyr-*H*), 7.57 (dd, *J* = 8.5, 2.5 Hz, 1H, Pyr-*H*), 7.05 (dd, *J* = 8.5, 1.0 Hz, 1H, Pyr-*H*), 3.70 (s, 3H, CO₂Me), 3.39 (t, *J* = 7.0 Hz, 2H, SCH₂), 2.76 (t, *J* = 7.0 Hz, 2H, CH₂CO₂Me); **¹³C NMR** (101 MHz, CDCl₃) δ 172.5, 157.1, 150.4, 138.6, 123.6, 116.3, 51.9, 34.4, 25.3; **LRMS** (ESI⁺) *m/z* 189.9 (30%, [M-CH₂CHCO₂Me+H]⁺), 191.9 (30%, [M-CH₂CHCO₂Me+H]⁺), 276.0 (15%, [M+H]⁺), 278.0 (15%, [M+H]⁺); **HRMS** (ESI⁺) found *m/z* 275.9690 [M+H]⁺, C₉H₁₁NO₂S³⁵Br requires *m/z* 275.9688; **IR** *v*_{max} (neat)/ cm⁻¹ 2981, 2952, 2890, 1736, 1561, 1541, 1446, 1417, 1351, 1277, 1247, 1221, 1197, 1173, 1141, 1115, 1089, 1017, 999, 980, 945, 819, 726; **R_f** = 0.6 (20% EtOAc in Petrol).

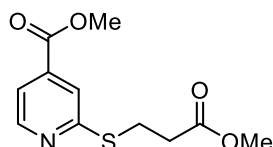


methyl 3-((3-morpholinopyrazin-2-yl)thio)propanoate (*pre-2d*)

Following general procedure **B**, 4-(3-chloropyrazin-2-yl)morpholine (399.3 mg, 2.00 mmol, 1.0 equiv.), K₂CO₃ (414.6 mg, 3.00 mmol, 1.5 equiv.) and methyl-3-mercaptopropanoate (332.3 μL, 3.00 mmol, 1.5 equiv.) were combined in dry DMF (2.0 mL, 0.1 M) to give a cloudy yellow suspension. The reaction was stirred at rt for 24 h and monitored by TLC (20% EtOAc in Petrol). The reaction mixture was worked up and purified by flash column chromatography (10% EtOAc in Petrol) to give the title product as a pale yellow oil (472 mg, 83%).

¹H NMR (400 MHz, CDCl₃) δ 8.00 (dd, *J* = 2.5, 1.0 Hz, 1H, Ar-*H*), 7.91 (dd, *J* = 2.5, 1.0 Hz, 1H, Ar-*H*), 3.88 – 3.82 (m, 4H, O(CH₂)₂), 3.71 (s, 3H, CO₂Me), 3.40 (t, *J* = 7.0, 2H, SCH₂), 3.31 – 3.23 (m, 4H, N(CH₂)₂), 2.77 (t, *J* = 7.0 Hz, 2H, CH₂CO₂Me); **¹³C NMR**

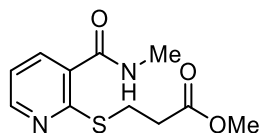
(101 MHz, CDCl₃) δ 172.6, 155.4, 148.9, 137.1, 136.6, 67.0, 51.9, 49.3, 34.3, 24.8; **LRMS** (ESI⁺) m/z 284.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 284.1063 [M+H]⁺, C₁₂H₁₈O₃N₃S requires m/z 284.1063; **IR** $\nu_{\max}$ (neat)/ cm⁻¹ 2962, 2854, 1741, 1591, 1557, 1509, 1441, 1408, 1366, 1323, 1287, 1267, 1246, 1188, 1141, 1116, 1069, 1043, 940, 845, 800, 761, 691, 621; **R_f** = 0.50 (20% EtOAc in Petrol).



methyl 2-((3-methoxy-3-oxopropyl)thio)isonicotinate (*pre-2e*)

Following general procedure **B**, methyl 2-chloroisonicotinate (514.7 mg, 3.00 mmol, 1.0 equiv.), K₂CO₃ (621.9 mg, 4.50 mmol, 1.5 equiv.) and methyl 3-mercaptopropionate (498.5 μ L, 4.50 mmol, 1.5 equiv.) were combined in dry DMF (3.0 mL, 1.0 M) to give a bright yellow suspension. The reaction was stirred at rt for 24 h and monitored by TLC (10% EtOAc in Petrol). The reaction mixture was then worked up and then purified by flash column chromatography (10% EtOAc in Petrol) to give the title product as a colourless oil (748 mg, 98%).

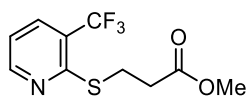
¹H NMR (400 MHz, CDCl₃) δ 9.00 (dd, J = 2.0, 1.0 Hz, 1H, Pyr-*H*), 8.02 (dd, J = 8.5, 2.0 Hz, 1H, Pyr-*H*), 7.20 (dd, J = 8.5, 1.0 Hz, 1H, Pyr-*H*), 3.92 (s, 3H, CO₂Me), 3.70 (s, 3H, CO₂Me), 3.47 (t, J = 7.0 Hz, 2H, SCH₂), 2.80 (t, J = 7.0 Hz, 2H, CH₂CO₂Me); **¹³C NMR** (101 MHz, CDCl₃) δ 172.5, 166.0, 164.1, 150.9, 136.5, 122.0, 121.6, 52.3, 51.9, 34.4, 25.1; **LRMS** (ESI⁺) m/z 256.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 256.0639 [M+H]⁺, C₁₁H₁₄O₄NS requires m/z 256.0638; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 2954, 2953, 1722, 1588, 1549, 1435, 1361, 1291, 1272, 1251, 1194, 1128, 1018, 980, 831, 767; **R_f** = 0.18 (10% EtOAc in Petrol).



methyl 3-((3-(methylcarbamoyl)pyridin-2-yl)thio)propanoate (*pre-2f*)

Following general procedure **B**, 2-chloro-N-methylnicotinamide (341.2 mg, 2.00 mmol, 1.0 equiv.), K₂CO₃ (414.6 mg, 3.00 mmol, 1.5 equiv.) and methyl 3-mercaptopropionate (332 µL, 3.00 mmol, 1.5 equiv.) were combined in dry DMF (2.0 mL, 1.0 M) to give a slightly yellow suspension. The reaction was stirred at rt for 24 h and monitored by TLC. The reaction mixture was worked up and then purified by flash column chromatography (60% EtOAc in Petrol) to give the title product as a bright white powdery solid (414.2 mg, 81%).

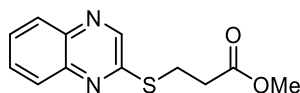
¹H NMR (400 MHz, CDCl₃) δ 8.47 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar-*H*), 7.81 (ddd, *J* = 7.5, 3.0, 1.5 Hz, 1H, Ar-*H*), 7.06 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, Ar-*H*), 6.29 (br. s, 1H, NH), 3.70 (s, 3H, CO₂Me), 3.47 (t, *J* = 7.0, 2H, SCH₂), 3.01 (d, *J* = 5.0, 3H, NHMe), 2.79 (t, *J* = 7.0 Hz, 2H, CH₂CO₂Me); **¹³C NMR** (101 MHz, CDCl₃) δ 172.7, 167.1, 156.2, 150.6, 136.5, 130.0, 119.3, 51.9, 34.4, 26.9, 25.5; **LRMS** (ESI⁺) *m/z* 277.0 [M+Na]⁺; **HRMS** (ESI⁺) found *m/z* 255.0799 [M+H]⁺, C₁₁H₁₅O₃N₂S requires *m/z* 255.0798; ; **IR** ν_{max} (neat)/cm⁻¹ 3069, 2951, 1735, 1639, 1578, 1556, 1438, 1410, 1394, 1359, 1318, 1255, 1243, 1226, 1171, 1137, 1086, 1063, 1017, 997, 979, 842, 817; **mp** 118 – 120 °C (EtOAc); **R_f** = 0.32 (80% EtOAc in Petrol).



methyl 3-((3-(trifluoromethyl)pyridin-2-yl)thio)propanoate (*pre-2g*)

Following general procedure **B**, 2-chloro-3-trifluoromethylpyridine (908 mg, 5.00 mmol, 1.0 equiv.), K₂CO₃ (1.04 g, 7.50 mmol, 1.5 equiv.) and methyl 3-mercaptopropionate (831 μ L, 7.50 mmol, 1.5 equiv.) were combined in dry DMF (5.0 mL, 1.0 M) to give a yellow suspension. The reaction was stirred at rt for 24 h and monitored by TLC. The reaction mixture was then worked up and then purified by flash column chromatography (15% EtOAc in Petrol) to give the title product as a colourless oil (898 mg, 68%).

¹H NMR (400 MHz, CDCl₃) δ 8.55 (ddd, J = 5.0, 2.0, 1.0 Hz, 1H, Pyr-*H*), 7.80 (ddd, J = 7.5, 1.5, 1.0 Hz, 1H, Pyr-*H*), 7.09 (ddd, J = 8.0, 5.0, 1.0 Hz, 1H, Pyr-*H*), 3.71 (s, 3H, CO₂Me), 3.50 (t, J = 7.0 Hz, 2H, CH₂CO₂Me), 2.79 (t, J = 7.0 Hz, 2H, SCH₂); ¹³C NMR (101 MHz, CDCl₃) δ 172.5, 157.7, 151.6, 134.5 (q, ³ J_{C-F} = 5.0 Hz), 123.9 (q, ² J_{C-F} = 33.0 Hz), 123.4 (q, ¹ J_{C-F} = 273.1 Hz), 118.5, 51.9, 34.4, 25.2; ¹⁹F NMR (377 MHz, CDCl₃) δ -63.36 (s); LRMS (ESI⁺) m/z 266.0 [M+H]⁺; HRMS (ESI⁺) found m/z 266.0457 [M+H]⁺, C₁₀H₁₁O₂NF₃S requires m/z 266.0457; IR $\nu_{\max}$ (neat)/ cm⁻¹ 3000, 2955, 2360, 1737, 1586, 1561, 1438, 1406, 1359, 1317, 1255, 1238, 1199, 1167, 1129, 1113, 1067, 1028, 981, 895, 807, 751, 717, 642; R_f = 0.24 (20% EtOAc in Petrol).

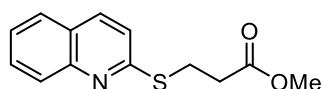


methyl 3-(quinoxalin-2-ylthio)propanoate (*pre-2h*)

Following general procedure **B**, chloroquinoxaline (329.2 mg, 2.00 mmol, 1.0 equiv.), K₂CO₃ (414.6 mg, 3.00 mmol, 1.5 equiv.) and methyl 3-mercaptopropionate (332 μ L, 3.00 mmol, 1.5 equiv.) were combined in dry DMF (2.0 mL, 1.0 M) to give a light brown

suspension. The reaction was stirred at rt for 24 h and monitored by TLC. The reaction mixture was then worked up and then purified by flash column chromatography (8 – 12% EtOAc in Petrol) to give the title product as a slightly yellow oil (440.5 mg, 89%).

¹H NMR (400 MHz, CDCl₃) δ 8.57 (s, 1H, Ar-*H*), 8.01 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar-*H*), 7.92 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar-*H*), 7.69 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Ar-*H*), 7.62 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H, Ar-*H*), 3.73 (s, 3H, CO₂Me), 3.59 (t, *J* = 7.0 Hz, 2H, SCH₂), 2.89 (t, *J* = 7.0 Hz, 2H, CH₂CO₂Me); **¹³C NMR** (101 MHz, CDCl₃) δ 172.5, 155.5, 144.9, 142.8, 140.1, 130.3, 129.4, 128.3, 128.0, 52.0, 34.0, 24.6; **LRMS** (ESI⁺) *m/z* 249.0 (52%, [M+H]⁺), 163.0 (48%, [M+H-C₄H₈O₂]⁺); **HRMS** (ESI⁺) found *m/z* 249.0695 [M+H]⁺, C₁₂H₁₃O₂N₂S requires *m/z* 249.0692; **IR** ν_{max} (neat)/cm⁻¹ 3061, 2999, 2951, 2846, 1737, 1542, 1487, 1437, 1359, 1248, 1223, 1197, 1174, 1152, 1125, 1086, 1016, 980, 962, 762; **R_f** = 0.39 (20% EtOAc in Petrol).



methyl 3-(quinolin-2-ylthio)propanoate (*pre-2i*)

Following general procedure **B**, 2-chloroquinoline (168.6 mg, 1.0 mmol, 1.0 equiv.), K₂CO₃ (207.3 mg, 1.5 mmol, 1.5 equiv.) and methyl-3-mercaptopropionate (166.1 μL, 1.5 mmol, 1.5 equiv.) were combined in dry DMF (1 mL, 0.1 M) to give a cloudy white suspension. The reaction was stirred at rt for 24 h and monitored by TLC (5% EtOAc in Petrol). The reaction mixture was worked up and purified by flash column chromatography (3% EtOAc in Petrol) to give the title product as a colourless oil (99.0 mg, 40%).

¹H NMR (400 MHz, CDCl₃) δ 7.93 (ddt, *J* = 8.5, 1.5, 1.0 Hz, 1H, Ar-*H*), 7.88 (dd, *J* = 8.5, 1.0 Hz, 1H, Ar-*H*), 7.71 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.64 (ddd, *J* = 8.5, 7.0, 1.5

Hz, 1H, Ar-*H*), 7.43 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H, Ar-*H*), 7.19 (d, $J = 8.5$ Hz, 1H, Ar-*H*), 3.72 (s, 3H, CO₂Me), 3.59 (t, $J = 7.0$ Hz, 2H, SCH₂), 2.90 (t, $J = 7.0$ Hz, 2H, CH₂CO₂Me); ¹³C NMR (101 MHz, CDCl₃) δ 172.9, 158.5, 148.5, 135.6, 129.8, 128.3, 127.8, 126.1, 125.5, 121.1, 51.9, 34.5, 24.9; LRMS (ESI⁺) m/z 248.0 [M+H]⁺; HRMS (ESI⁺) found m/z 248.07395 [M+H]⁺, C₁₃H₁₄O₂NS requires m/z 248.07398; IR $\nu_{\max}$ (neat)/ cm⁻¹ 3057, 3035, 2980, 2953, 2907, 2890, 1735, 1614, 1594, 1556, 1498, 1435, 1420, 1357, 1294, 1247, 1197, 1172, 1138, 1089, 1018, 979, 943, 861, 817, 781, 750, 630; R_f = 0.3 (5% EtOAc in Petrol).

6.2.3.b Synthesis of heteroaromatic sulfones (latent sulfinates)

General Procedure C:

Open to air: To a stirring solution of pyridine thioether (1.0 equiv.) in ethanol (0.7 M) was added Na₂WO₄•2H₂O (5.0 mol% or 10 mol%). A solution of hydrogen peroxide (30% w/w in water) (5.0 or 10.0 equiv.) was then added slowly as an exotherm may be observed. The reaction was stirred at rt overnight and the formation of the sulfoxide and sulfone were monitored by TLC analysis. After 16 h, three volumes of water relative to the reaction solvent (ethanol) was added to the reaction mixture and left to stir for 30 min. If a solid precipitated out of the reaction mixture on addition of water, the solid was collected by filtration, washed with copious amounts of water and dried *in vacuo* to give the product. If no precipitate was formed, then the solvent was removed under reduced pressure and the product was extracted from the aqueous layer with EtOAc thrice. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude residue was then purified by flash column chromatography on silica gel (EtOAc in Petrol).

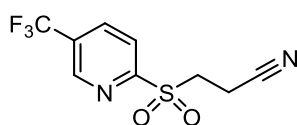
General Procedure D:

Open to air: To a solution of pyridine sulfinate (1.1 equiv.) in de-ionised water (0.4 M) was added acetic acid (1.1 equiv.) and either acrylonitrile (1.0 equiv.) or methyl acrylate (1.0 equiv.). The reaction mixture was then heated to reflux (115 °C) and monitored by TLC analysis. Upon completion, the reaction mixture was then cooled to rt and solid NaHCO₃ was added until the reaction mixture was $\approx$ pH 8. The aqueous layer was extracted with EtOAc ($\times$ 4). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude residue was then purified by flash column chromatography (EtOAc in Petrol) to give the desired product.

General procedure E: (Adapted from the literature procedure reported by Wang et. al^[78a])

Sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS reagent) was prepared according to Baskin and Wang,^[78a] or obtained from commercial sources.

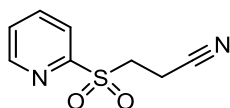
Under N₂: Iodopyridine *or* bromopyridine (1.0 equiv.) was added to a solution of CuI (3.0 – 5.0 equiv.) and sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS reagent) (3.0 – 5.0 equiv.) in DMSO (0.4 M). The reaction was stirred under nitrogen atmosphere at 110 °C for 16 h. The mixture was then cooled to rt, diluted with EtOAc and filtered through a pad of silica. The filtrate was washed with H₂O ($\times$ 2), brine, dried over MgSO₄ and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (EtOAc in Petrol) to give the desired sulfone product.



3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (**1a**)

Following general procedure **C**, 3-((5-(trifluoromethyl)pyridin-2-yl)thio)propanenitrile (4.00 g, 17.2 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (284 mg, 0.860 mmol, 5.0 mol%) and hydrogen peroxide solution (30% w/w in water) (8.80 mL, 86.1 mmol, 5.0 equiv.) in ethanol (25.0 mL, 0.7 M) was stirred at rt for 16 h. On diluting, a white solid precipitated out of the reaction mixture. The solid was collected by filtration, washed with copious amounts of water and dried *in vacuo*. The corresponding white solid was purified through hot recrystallisation using hexanes:EtOAc to give the title compound **1a** as iridescent flaky white crystals (3.87 g, 85%).

¹H NMR (400 MHz, CDCl₃) δ 9.03 – 9.02 (m, 1H, Ar-*H*), 8.30-8.25 (m, 2H, Ar-*H*), 3.79 (t, *J* = 7.5 Hz, 2H, SO₂CH₂), 2.98 (t, *J* = 7.5 Hz, 2H, CH₂CN); **¹³C NMR** (101 MHz, CDCl₃) δ 159.6, 147.5 (q, ³*J*_{C-F} = 4.0 Hz), 136.4 (q, ³*J*_{C-F} = 3.5 Hz), 130.9 (q, ²*J*_{C-F} = 35.0 Hz), 122.5 (q, ¹*J*_{C-F} = 274.0 Hz), 122.5, 115.9, 47.1, 12.3; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.68 (s); **HRMS** (ESI⁺) found *m/z* 287.0074 [M+Na]⁺, C₉H₇O₂N₂F₃NaS requires *m/z* 287.0073; **IR** ν_{max} (neat)/cm⁻¹ 3109, 3057, 2986, 2927, 2257, 1591, 1578, 1408, 1386, 1318 (SO₂), 1148 (SO₂), 1100, 1013, 867, 726, 700; **mp** 118 – 120 °C (hexanes:EtOAc); **R_f** = 0.42 (40% EtOAc in Petrol).



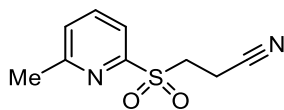
3-(pyridin-2-ylsulfonyl)propanenitrile (**1b**)

Following general procedure **C**, 3-(pyridin-2-ylthio)propanenitrile (644 mg, 3.92 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (64.7 mg, 0.20 mmol, 5.0 mol%) and hydrogen peroxide solution (30% w/w in water) (2.00 mL, 19.6 mmol, 5.0 equiv.) in ethanol (6.0 mL, 0.7 M) was stirred at rt for 16 h. On diluting, no precipitate was formed and the reaction was

worked up accordingly. The crude yellow oil was purified by flash column chromatography (50% EtOAc in Petrol) to give the title compound as an off-white solid (620 mg, 81%).

Following general procedure **D**, sodium pyridine-2-sulfinate (182 mg, 1.10 mmol, 1.1 equiv.), acrylonitrile (66.3 μ L, 1.00 mmol, 1.0 equiv.) and AcOH (57.2 μ L, 1.00 mmol, 1.0 equiv.) were refluxed in water (3.0 mL, 0.33 M) for 2.5 h. After workup, the crude residue was purified by flash column chromatography (60% EtOAc in Petrol) to give the title compound as a crystalline white solid (163 mg, 83%).

¹H NMR (400 MHz, CDCl₃) δ 8.76 (ddd, J = 4.5, 1.5, 1.0 Hz, 1H, Ar-*H*), 8.11 (dt, J = 8.0, 1.0 Hz, 1H, Ar-*H*), 8.02 (td, J = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.62 (ddd, J = 7.5, 4.5, 1.0 Hz, 1H, Ar-*H*), 3.73 (t, J = 7.5 Hz, 2H, SO₂CH₂), 2.95 (t, J = 7.5 Hz, 2H, CH₂CN); **¹³C NMR** (101 MHz, CDCl₃) δ 156.5, 150.5, 138.8, 128.3, 122.4, 116.1, 47.2, 12.3; **LRMS** (ESI⁺) m/z 197.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 197.0381 [M+H]⁺, C₈H₉O₂N₂S requires m/z 197.0379; **IR** ν_{max} (neat)/cm⁻¹ 3061, 3001, 2969, 2953, 2250, 1581, 1453, 1435, 1313 (SO₂), 1292, 1151 (SO₂), 1109, 993, 957, 902, 793, 747, 692; **mp** 50 – 51 °C (EtOAc:Petrol); **R_f** = 0.27 (60% EtOAc in Petrol).

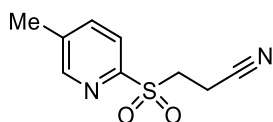


3-((6-methylpyridin-2-yl)sulfonyl)propanenitrile (**15a**)

Following general procedure **C**, 3-((6-methylpyridin-2-yl)thio)propanenitrile (290 mg, 1.63 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (27.0 mg, 0.08 mmol, 5.0 mol%) and hydrogen peroxide solution (30% w/w in water) (890 μ L, 8.70 mmol, 5.3 equiv.) in ethanol (2.5 mL, 0.7 M) was stirred at rt for 16 h. On diluting with water, a white solid precipitated out of the reaction mixture. The white solid was collected by filtration, washed with copious

amounts of water and dried *in vacuo* to give the title compound as a white solid (121 mg, 35%).

¹H NMR (400 MHz, CDCl₃) δ 7.93 – 7.85 (m, 2H, Ar-*H*), 7.46 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 3.72 (t, *J* = 7.5 Hz, 2H, SO₂CH₂), 2.95 (t, *J* = 7.5 Hz, 2H, CH₂CN), 2.67 (s, 3H, CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 160.7, 155.6, 138.6, 128.2, 119.5, 116.3, 47.0, 24.5, 12.3; **LRMS** (ESI⁺) *m/z* 211.0 (65%, [M+H]⁺), 232.9 (35%, [M+Na]⁺); **HRMS** (ESI⁺) found *m/z* 211.0538 [M+H]⁺, C₉H₁₁O₂N₂S requires *m/z* 211.0536; **IR** *v*_{max} (neat)/ cm⁻¹ 2962, 2361, 2252, 1593, 1557, 1454, 1420, 1313, 1254, 1177, 1149, 1117, 1087, 1036, 986, 956, 868, 798, 736, 717, 669; **mp** 68 – 70 °C (EtOH:H₂O); **R_f** = 0.18 (50% EtOAc in Petrol).

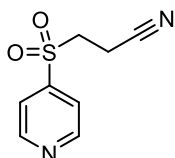


3-((5-methylpyridin-2-yl)sulfonyl)propanenitrile (1d)

Following general procedure C, 3-((5-methylpyridin-2-yl)thio)propanenitrile (201 mg, 1.13 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (18.6 mg, 0.056 mmol, 5.0 mol%) and hydrogen peroxide solution (30% w/w in water) (576 μL, 5.64 mmol, 5.0 equiv.) in ethanol (2.0 mL, 0.6 M) was stirred at rt for 20 h, then diluted with water. No precipitate was observed so the reaction mixture was extracted with EtOAc (20.0 mL × 3). The combined organic layers were then washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. The product was then purified by flash column chromatography (70% EtOAc in Petrol) to give the title compound as a crystalline white solid (187 mg, 79%).

¹H NMR (400 MHz, CDCl₃) δ 8.57 (app. dt, *J* = 2.0, 1.0 Hz, 1H, Ar-*H*), 7.99 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.79 (app. ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, Ar-*H*), 3.69 (t, *J* = 8.0, 2H, SO₂CH₂), 2.92 (t, *J* = 8.0 Hz, 2H, CH₂CN), 2.48 (s, 3H, CH₃); **¹³C NMR** (101 MHz,

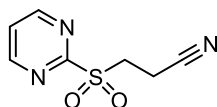
CDCl₃) δ 153.6, 151.1, 139.3, 138.8, 122.2, 116.2, 47.4, 18.8, 12.3; **LRMS** (ESI⁺) m/z 211.0 (60%, [M+H]⁺), 233.0 (40%, [M+Na]⁺); **HRMS** (ESI⁺) found m/z 211.0536 [M+H]⁺, C₉H₁₁O₂N₂S requires m/z 211.0536; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 2939, 2253, 1574, 1458, 1419, 1374, 1315, 1241, 1213, 1163, 1150, 1131, 1099, 1027, 956, 838, 782, 747, 712, 663, 644, 622; **mp** 66 °C (EtOAc); **R_f** = 0.11 (65% EtOAc in Petrol).



3-(pyridin-4-ylsulfonyl)propanenitrile (1e)

Following general procedure C, 3-(pyridin-4-ylthio)propanenitrile (320 mg, 1.95 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (64.6 mg, 0.20 mmol, 10 mol%) and hydrogen peroxide solution (30% w/w in water) (1.00 mL, 9.79 mmol, 5.0 equiv.) in ethanol (3.0 mL, 0.7 M) was stirred at rt for 16 h, and then diluted with water. No precipitate was observed so the reaction mixture was extracted with EtOAc (20 mL × 4). The combined organic layers were then washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo* to give the title compound as a white crystalline solid (306 mg, 80%). The compound was pure by ¹H NMR analysis and so was used without further purification.

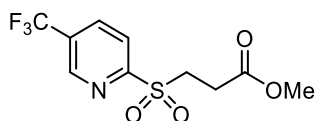
¹H NMR (400 MHz, CDCl₃) δ 9.02 – 8.95 (m, 2H, Ar-*H*), 7.84 – 7.79 (m, 2H, Ar-*H*), 3.43 (t, J = 7.5 Hz, 2H, SO₂CH₂), 2.88 (t, J = 7.5 Hz, 2H, CH₂CN); **¹³C NMR** (101 MHz, CDCl₃) δ 151.9, 145.9, 121.3, 115.6, 50.9, 11.9; **LRMS** (ESI⁺) m/z 197.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 197.0380 [M+H]⁺, C₈H₉O₂N₂S requires m/z 197.0379; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 3091, 2974, 2932, 2915, 2361, 2341, 2260, 1576, 1563, 1427, 1406, 1318, 1218, 1173, 1139, 1099, 1069, 966, 823, 751, 726, 684; **mp** 80 – 82 °C (EtOAc); **R_f** = 0.25 (100% EtOAc).



3-(pyrimidin-2-ylsulfonyl)propanenitrile (1f)

Following general procedure C, 3-(pyrimidin-2-ylthio)propanenitrile (673 mg, 4.07 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (134 mg, 0.41 mmol, 10 mol%), 30% hydrogen peroxide w/w water (2.08 mL, 20.4 mmol, 5.0 equiv.) in EtOH (5.0 mL, 0.7 M) was stirred at rt overnight for 24 h. On diluting with water, a white solid precipitated out of the reaction mixture. The solid was collected by filtration, washed with copious amounts of water. The resultant white solid was recrystallized (hot 80% EtOAc in Petrol) and dried *in vacuo* to give the title compound as thin needle-like crystals (183 mg, 23%).

¹H NMR (400 MHz, CDCl₃) δ 8.99 (d, *J* = 5.0 Hz, 2H, Ar-*H*), 7.64 (t, *J* = 5.0 Hz, 1H, Ar-*H*), 3.88 (t, *J* = 7.5 Hz, 2H, SO₂CH₂), 3.05 (t, *J* = 7.5 Hz, 2H, CH₂CN); **¹³C NMR** (101 MHz, CDCl₃) δ 165.0, 159.1, 124.6, 116.1, 46.7, 12.5; **HRMS** (ESI⁺) found *m/z* 220.0152 [M+Na]⁺, C₇H₇O₂N₃NaS requires *m/z* 220.0151; **IR** ν_{max} (neat)/ cm⁻¹ 2982, 2252 (CN), 1565, 1388, 1319, 1213, 1124, 989, 817, 699; **mp** 86–87 °C (EtOAc : Petrol); **R_F** = 0.15 (60% EtOAc in Petrol).



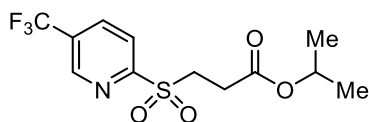
methyl 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoate (2a)

Following general procedure C, methyl 3-((5-(trifluoromethyl)pyridin-2-yl)thio)propanoate (974 mg, 3.67 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (60.5 mg, 0.18 mmol, 5.0 mol%) and hydrogen peroxide solution (30% w/w in water) (1.88 mL, 18.4 mmol, 5.0 equiv.) in ethanol (5.2 mL, 0.7 M) was stirred at rt for 16 h. On diluting

with water, a white solid precipitated out of the reaction mixture. The white solid was collected by filtration, washed with copious amounts of water and dried *in vacuo* to give the title compound as a crystalline white solid (989 mg, 91%). *When scaled up to a 15 mmol scale, gave a 90% yield.*

Alternative Synthesis: Following general procedure E, 2-bromo-5-(trifluoromethyl)pyridine (226 mg, 1.00 mmol, 1.0 equiv.), SMOPS (871 mg, 5.00 mmol, 5.0 equiv.) and CuI (952 mg, 5.00 mmol, 5.0 equiv.) were heated to 110 °C in DMSO (2.5 mL, 0.4 M) for 16h. The crude product was purified by flash column chromatography (20% EtOAc in Petrol) to give the title compound as a white crystalline solid (75.7 mg, 25%).

¹H NMR (400 MHz, CDCl₃) δ 8.99 – 8.98 (m, 1H, Ar-*H*), 8.26 – 8.21 (m, 2H, Ar-*H*), 3.81 – 3.76 (t, *J* = 7.5 Hz, 2H, SO₂CH₂), 3.69 (s, 3H, COOCH₃), 2.87 (t, *J* = 7.5 Hz, 2H, CH₂COOMe); **¹³C NMR** (101 MHz, CDCl₃) δ 170.4, 160.3, 147.4 (q, ³*J*_{C-F} = 4.0 Hz), 136.1 (q, ³*J*_{C-F} = 3.5 Hz), 130.3 (q, ²*J*_{C-F} = 34.5 Hz), 122.6 (q, ¹*J*_{C-F} = 273.0 Hz), 122.1, 53.2, 47.6, 27.4; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.68 (s); **LRMS** (ESI⁺) *m/z* 320.0 [M+Na]⁺; **HRMS** (ESI⁺) found *m/z* 298.0356 [M+H]⁺, C₁₀H₁₁O₄NF₃S requires *m/z* 298.0355; **IR** ν_{max} (neat)/cm⁻¹ 3061, 2956, 2360, 1744, 1732, 1594, 1578, 1325, 1149, 1099, 1073, 1014, 830; **mp** 75 – 76 °C (EtOH:H₂O); **R_f** = 0.55 (60% EtOAc in Petrol).



***Iso*-propyl 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoate (2a-*i*Pr)**

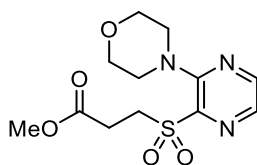
Following general procedure C, *iso*-propyl 3-((5-(trifluoromethyl)pyridin-2-yl)thio)propanoate (61.6 mg, 0.21 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (3.5 mg, 0.01 mmol, 5.0 mol%) and hydrogen peroxide solution (30% w/w in water) (107 μL, 1.05 mmol,

5.0 equiv.) in ethanol (300 μ L, 0.7 M) was stirred at rt for 19 h. On diluting with water, a white solid precipitated out of the reaction mixture. The white solid was collected by filtration, washed with copious amounts of water and dried *in vacuo* to give the title compound as a bright white solid (44.4 mg, 65%).

Alternative synthesis:

3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoic acid **2a-OH** (30 mg, 0.10 mmol, 1.0 equiv.) was dissolved in degassed *iso*-propanol (5.0 mL, 0.02 M) and conc. H₂SO₄ (1 drop) was added. The resultant cloudy suspension was heated to reflux for 4 h and then cooled to rt. The reaction mixture was then concentrated *in vacuo* to remove the solvent. The residue was dissolved in CH₂Cl₂ and poured into a separating funnel with water. The aqueous layer was basified with solid NaHCO₃ until it was *ca.* pH 8. The aqueous layer was washed with CH₂Cl₂ (15 mL $\times$ 3). The combined organic layers were dried over MgSO₄, concentrated *in vacuo* and purified by flash column chromatography (2 – 10% EtOAc in Petrol) to give the title compound as a crystalline white solid (26.6 mg, 82%).

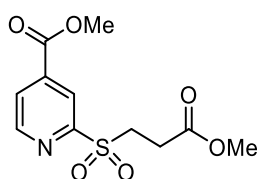
¹H NMR (400 MHz, CDCl₃) δ 9.00 (s, 1H, Ar-*H*), 8.25 – 8.22 (m, 2H, Ar-*H*), 4.99 (hept, J = 6.5 Hz, 1H, CH(CH₃)₂), 3.77 (t, J = 8.0 Hz, 2H, SO₂CH₂), 2.82 (t, J = 8.0 Hz, 2H, CH₂CO), 1.23 (d, J = 6.5 Hz, 6H, CH(CH₃)₂); **¹³C NMR** (101 MHz, CDCl₃) δ 169.4, 160.4, 147.4 (q, $^3J_{C-F}$ = 3.5 Hz), 136.0 (q, $^3J_{C-F}$ = 3.5 Hz), 130.3 (q, $^2J_{C-F}$ = 34.0 Hz), 122.6 (q, $^1J_{C-F}$ = 273.5 Hz), 122.1, 69.4, 47.7, 27.9, 21.8; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.69 (s); **HRMS** (ESI⁺) found m/z 326.0671 [M+H]⁺, C₁₂H₁₅O₄NF₃S requires m/z 326.0668; **IR** ν_{max} (neat)/cm⁻¹ 3104, 3061, 2983, 2933, 2361, 1726, 1323, 1254, 1238, 1162, 1142, 1127, 1101, 1073; **mp** 52 – 54 °C (EtOH:H₂O); **R_f** = 0.44 (30% EtOAc in Petrol).



methyl 3-((3-morpholinopyrazin-2-yl)sulfonyl)propanoate (2d)

Following general procedure C, methyl 3-((3-morpholinopyrazin-2-yl)thio)propanoate (458 mg, 1.62 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (26.6 mg, 0.08 mmol, 5.0 mol%) and hydrogen peroxide solution (30% w/w in water) (825 µL, 8.08 mmol, 5.0 equiv.) in ethanol (2.5 mL, 0.6 M) was stirred at rt for 20 h, then diluted with water. No precipitate was observed so the reaction mixture was extracted with EtOAc (20 mL × 4). The combined organic layers were then washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (55% EtOAc in Petrol) to give the title compound as a viscous yellow oil (418 mg, 82%).

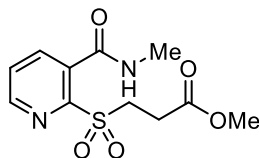
¹H NMR (400 MHz, CDCl₃) δ 8.26 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.95 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 3.88 – 3.81 (m, 6H, SO₂CH₂ and O(CH₂)₂), 3.74 – 3.70 (m, 7H, OCH₃ and (CH₂)₂N), 2.78 (t, *J* = 8.0 Hz, 2H, CH₂COOMe); **¹³C NMR** (101 MHz, CDCl₃) δ 170.9, 152.7, 144.6, 139.5, 132.5, 66.9, 52.5, 50.2, 48.8, 27.8; **LRMS** (ESI⁺) *m/z* 338.0 [M+Na]⁺; **HRMS** (ESI⁺) found *m/z* 316.0963 [M+H]⁺, C₁₂H₁₈O₅N₃S requires *m/z* 316.0962; **IR** ν_{max} (neat)/cm⁻¹ 2955, 2859, 1738, 1556, 1492, 1446, 1364, 1308, 1272, 1249, 1217, 1180, 1068, 1045, 980, 946, 855, 806, 718, 620; **R_f** = 0.18 (50% EtOAc in Petrol).



methyl 2-((3-methoxy-3-oxopropyl)sulfonyl)isonicotinate (2e)

Following general procedure C, methyl 2-((3-methoxy-3-oxopropyl)thio)isonicotinate (735.8 mg, 2.88 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (47.5 mg, 0.140 mmol, 5.0 mol%) and hydrogen peroxide solution (30% w/w in water) (1.47 mL, 14.4 mmol, 5.0 equiv.) in ethanol (4.1 mL, 0.7 M) was stirred at rt for 24 h, then diluted with water. No precipitate was observed so the reaction mixture was extracted with EtOAc (× 4). The combined organic layers were then washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (35-40% EtOAc in Petrol). However the product co-eluted with the sulfoxide. The mixed fractions were combined, concentrated *in vacuo* and dissolved in ethanol (3.0 mL, 0.7 M). To this stirring solution was added Na₂WO₄ · 2H₂O (33.0 mg, 0.10 mmol, 5.0 mol%) and hydrogen peroxide (30% w/w water) solution (1.0 mL, 10.0 mmol, 5.0 equiv.) and the reaction mixture was stirred at rt for 16 h. Upon addition of water (12 mL), a white precipitate formed. This precipitate was collected and purified by flash column chromatography (30% EtOAc in Petrol) to give the title compound as a white solid (191 mg, 23%).

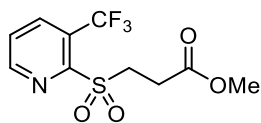
¹H NMR (400 MHz, CDCl₃) δ 9.29 (dd, *J* = 2.0, 1.0 Hz, 1H, Ar-*H*), 8.57 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar-*H*), 8.16 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 4.01 (s, 3H, CO₂Me), 3.77 (t, *J* = 8.0 Hz, 2H, SO₂CH₂), 3.69 (s, 3H, CO₂Me), 2.86 (t, *J* = 8.0 Hz, 2H, CH₂CO₂Me); **¹³C NMR** (101 MHz, CDCl₃) δ 170.5, 164.2, 160.2, 151.3, 139.7, 129.5, 121.8, 53.2, 52.5, 47.6, 27.5; **LRMS** (ESI⁺) *m/z* 310.0 [M+Na]⁺; **HRMS** (ESI⁺) found *m/z* 288.0537 [M+H]⁺, C₁₁H₁₄O₆NS requires *m/z* 288.0536; **IR** ν_{max} (neat)/cm⁻¹ 3736, 3622, 2924, 2855, 2361, 1733, 1459, 1371, 1296, 1165, 1122, 1023, 680; **mp** 104 – 105 °C (EtOAc); **R_f** = 0.22 (40% EtOAc in Petrol).



methyl 3-((3-(methylcarbamoyl)pyridin-2-yl)sulfonyl)propanoate (2f)

Following general procedure C, methyl 3-((3-(methylcarbamoyl)pyridin-2-yl)thio)propanoate (400 mg, 1.57 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (26.4 mg, 0.08 mmol, 5.0 mol%) hydrogen peroxide solution (30% w/w water) (1.60 mL, 15.7 mmol, 10.0 equiv.) in ethanol (2.5 mL, 0.6 M) was stirred at rt for 18 h, then diluted with water. No precipitate was observed so the reaction mixture was extracted with EtOAc (20 mL × 4). The combined organic layers were then washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (100% EtOAc) to give the title compound as a colourless oil that crystallised on standing to give a white solid (207 mg, 46%).

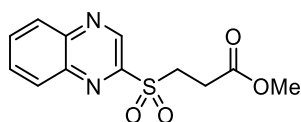
¹H NMR (400 MHz, CDCl₃) δ 8.66 (dd, *J* = 4.5, 2.0 Hz, 1H, Ar-*H*), 8.07 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.59 (dd, *J* = 8.0, 5.0 Hz, 1H, Ar-*H*), 6.69 (br. s, 1H, NH), 3.92 (t, *J* = 7.5 Hz, 2H, SO₂CH₃), 3.69 (s, 3H, CO₂CH₃), 3.01 (d, *J* = 5.0 Hz, 3H, NHCH₃), 2.90 (t, *J* = 7.5 Hz, 2H, CH₂CO₂Me); **¹³C NMR** (101 MHz, CDCl₃) δ 170.7, 165.5, 154.0, 149.7, 139.5, 132.3, 127.5, 52.5, 48.4, 27.7, 27.3; **LRMS** (ESI⁺) *m/z* 309.0 [M+Na]⁺; **HRMS** (ESI⁺) found *m/z* 287.0698 [M+H]⁺, C₁₁H₁₅O₅N₂S requires *m/z* 287.0696; **IR** ν_{max} (neat)/cm⁻¹ 3369, 3291, 3075, 2954, 2925, 2853, 1737, 1654, 1584, 1554, 1441, 1407, 1365, 1318, 1254, 1179, 1157, 1121, 1085, 1058, 979, 841, 767, 749, 707, 663, 524; **mp** 105 – 107 °C (EtOAc); **R_f** = 0.12 (100% EtOAc).



methyl 3-((3-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoate (2g)

Following general procedure C, methyl 3-((3-(trifluoromethyl)pyridin-2-yl)thio)propanoate (898.5 mg, 3.39 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (112 mg, 0.34 mmol, 10 mol%), hydrogen peroxide solution (30% w/w water) (3.46 mL, 33.9 mmol, 10.0 equiv.) in ethanol (5.0 mL, 0.6 M) was stirred at rt for 18 h, then diluted with water. No precipitate was observed so the reaction mixture was extracted with EtOAc (× 4). The combined organic layers were then washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (50% EtOAc in Petrol) to give the title compound as a pale yellow oil (310 mg, 31%).

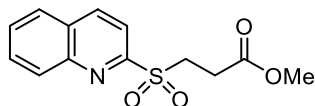
¹H NMR (400 MHz, CDCl₃) δ 8.82 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar-*H*), 8.26 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.71 (dd, *J* = 8.0, 5.0 Hz, 1H, Ar-*H*), 3.98 (t, *J* = 7.5 Hz, 2H, SO₂CH₂), 3.72 (s, 3H, OCH₃), 2.95 (t, *J* = 7.5 Hz, 2H, CH₂CO₂Me); **¹³C NMR** (101 MHz, CDCl₃) δ 170.8, 156.1, 151.2, 137.6 (q, ³*J*_{C-F} = 5.5 Hz), 127.1, 125.2 (q, ²*J*_{C-F} = 36.5 Hz), 121.9 (q, ¹*J*_{C-F} = 274.4 Hz), 52.5, 48.6, 27.9; **¹⁹F NMR** (377 MHz, CDCl₃) δ -58.00 (s); **HRMS** (ESI⁺) found *m/z* 298.0357 [M+H]⁺, C₁₀H₁₁O₄N₁F₃S requires *m/z* 298.0355; **IR** ν_{max} (neat)/cm⁻¹ 3060, 2956, 2360, 1739, 1586, 149, 1418, 1364, 1314, 1266, 1231, 1160, 1125, 1065, 1032, 981, 898, 817, 732, 702; **R_f** = 0.13 (40% EtOAc in Petrol).



methyl 3-(quinoxalin-2-ylsulfonyl)propanoate (2h)

Following general procedure **C**, methyl 3-(quinoxalin-2-ylthio)propanoate (429 mg, 1.73 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (28.5 mg, 0.087 mmol, 5.0 mol%), hydrogen peroxide solution (30% w/w water) (1.77 mL, 17.3 mmol, 10.0 equiv.) in ethanol (2.5 mL, 0.6 M) was stirred at rt for 18 h. On diluting with water, a white solid precipitated out of the reaction mixture. The white solid was collected by filtration, washed with copious amounts of water and dried *in vacuo* to give the title compound as a fine white solid (375 mg, 77%).

¹H NMR (400 MHz, CDCl₃) δ 9.49 (s, 1H, Ar-*H*), 8.29 – 8.20 (m, 2H, Ar-*H*), 8.03 – 7.92 (m, 2H, Ar-*H*), 3.90 (t, *J* = 7.5 Hz, 2H, SO₂CH₂), 3.67 (s, 3H, CO₂Me), 2.96 (t, *J* = 7.5 Hz, 2H, CH₂CO₂Me); **¹³C NMR** (101 MHz, CDCl₃) δ 170.5, 151.5, 144.1, 141.3, 140.9, 133.4, 132.2, 130.3, 129.9, 52.6, 48.3, 27.5; **LRMS** (ESI⁺) *m/z* 303.0 [M+Na]⁺; **HRMS** (ESI⁺) found *m/z* 281.0592 [M+H]⁺, C₁₂H₁₃O₄N₂S requires *m/z* 281.0591; **IR** *v*_{max} (neat)/cm⁻¹ 3050, 3003, 2953, 2849, 1731, 1611, 1562, 1489, 1436, 1420, 1364, 1318, 1276, 1205, 1169, 1131, 1100, 1057, 965, 930, 870, 801, 782, 769, 708, 639; **mp** 105 – 107 °C (EtOAc); **R_f** = 0.11 (30% EtOAc in Petrol).

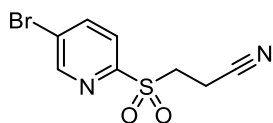


methyl 3-(quinolin-2-ylsulfonyl)propanoate (2i)

Following general procedure **C**, methyl 3-(quinolin-2-ylthio)propanoate (90 mg, 0.360 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (5.9 mg, 0.018 mmol, 5.0 mol%) and hydrogen

peroxide solution (30% w/w in water) (185 μ L, 1.82 mmol, 5.0 equiv.) in ethanol (1.0 mL, 0.35 M) was stirred at rt for 20 h, then diluted with water. No precipitate was observed so the reaction mixture was extracted with EtOAc (20 mL $\times$ 4). The combined organic layers were then washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (35% EtOAc in Petrol) to give the title compound as white crystalline solid (80.2 mg, 80%).

¹H NMR (400 MHz, CDCl₃) δ 8.45 (dd, *J* = 8.5, 1.0 Hz, 1H, Ar-*H*), 8.22 (dd, *J* = 8.5, 1.0 Hz, 1H, Ar-*H*), 8.12 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.98 – 7.92 (m, 1H, Ar-*H*), 7.87 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Ar-*H*), 7.73 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar-*H*), 3.90 (t, *J* = 7.5 Hz, 2H, SO₂CH₂), 3.67 (s, 3H, COOCH₃), 2.94 (t, *J* = 7.5 Hz, 2H, CH₂CO₂Me); **¹³C NMR** (101 MHz, CDCl₃) δ 170.8, 156.7, 147.3, 139.1, 131.5, 130.4, 129.6, 129.4, 128.1, 117.2, 52.4, 47.7, 27.7; **LRMS** (ESI⁺) *m/z* 302.0 [M+Na]⁺; **HRMS** (ESI⁺) found *m/z* 280.0638 [M+H]⁺, C₁₃H₁₄O₄NS requires *m/z* 280.0638; **IR** ν_{max} (neat)/cm⁻¹ 3005, 2957, 2161, 2033, 1727, 1616, 1580, 1498, 1367, 1313, 1275, 1237, 1200, 1180, 1163, 1124, 1097, 1054, 981, 945, 898, 856, 840, 802, 793, 772, 761, 705, 641, 615; **mp** 53 – 54 °C (EtOAc); **R_f** = 0.18 (30% EtOAc in Petrol). Data consistent with literature: B. Du, P. Qian, Y. Wang, H. Mei, J. Han and Y. Pan, *Org. Lett.*, 2016, **18**, 4144-4147.^[166]

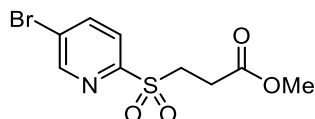


3-((5-bromopyridin-2-yl)sulfonyl)propanenitrile (12a)

Following general procedure C, 3-((5-bromopyridin-2-yl)thio)propanenitrile (348.2 mg, 1.43 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (46.2 mg, 0.140 mmol, 10 mol%), hydrogen peroxide solution (30% w/w water) (1.46 mL, 14.3 mmol, 10.0 equiv.) in ethanol (2.0 mL, 0.7 M) was stirred at rt for 18 h. On diluting with water, a white solid precipitated out of

the reaction mixture. The white solid was collected by filtration, washed with copious amounts of water and dried *in vacuo* to give the title compound as a white solid (305.4 mg, 78%).

¹H NMR (400 MHz, CDCl₃) δ 8.81 (dd, *J* = 2.5, 1.0 Hz, 1H, Pyr-*H*), 8.15 (dd, *J* = 8.5, 2.5 Hz, 1H, Pyr-*H*), 8.00 (dd, *J* = 8.5, 1.0 Hz, 1H, Pyr-*H*), 3.72 (t, *J* = 7.5 Hz, 2H, SO₂CH₂), 2.95 (t, *J* = 7.5 Hz, 2H, CH₂CN); **¹³C NMR** (101 MHz, CDCl₃) δ 154.8, 151.8, 141.4, 126.4, 123.6, 115.9, 47.3, 12.3; **HRMS** (ESI⁺) found *m/z* 274.9485 [M(⁷⁹Br)+H]⁺, C₈H₈O₂N₂S⁷⁹Br requires *m/z* 274.9485; **IR** ν_{max} (neat)/cm⁻¹ 3082, 3065, 2980, 2970, 2930, 2889, 2248, 1565, 1549, 1445, 1422, 1394, 1382, 1358, 1335, 1310, 1295; **mp** 97 – 99 °C (EtOAc); **R_f** = 0.37 (50% EtOAc in Petrol).

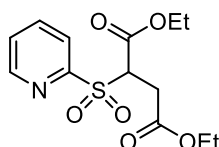


methyl 3-((5-bromopyridin-2-yl)sulfonyl)propanoate (12b)

Following general procedure **C**, methyl 3-((5-bromopyridin-2-yl)thio)propanoate (460.5 mg, 1.67 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (55.1 mg, 0.167 mmol, 10 mol%), hydrogen peroxide solution (30% w/w water) (1.70 mL, 16.7 mmol, 10.0 equiv.) in ethanol (2.4 mL, 0.7 M) was stirred at rt for 18 h. On diluting with water, a white solid precipitated out of the reaction mixture. The white solid was collected by filtration, washed with copious amounts of water and dried *in vacuo* to give the title compound as a bright white solid (531 mg, 99%).

¹H NMR (400 MHz, CDCl₃) δ 8.79 (dd, *J* = 2.0, 1.0 Hz, 1H, Pyr-*H*), 8.11 (dd, *J* = 8.5, 2.0 Hz, 1H, Pyr-*H*), 7.97 (dd, *J* = 8.5, 1.0 Hz, 1H, Pyr-*H*), 3.73 – 3.69 (m, 5H, SO₂CH₂ and CO₂Me), 2.84 (t, *J* = 7.5 Hz, 2H, CH₂CO₂Me); **¹³C NMR** (101 MHz, CDCl₃) δ 170.5, 155.5, 151.6, 141.0, 125.8, 123.6, 52.5, 47.9, 27.5; **LRMS** (ESI⁺) *m/z* 329.9 (50%, [M

($^{79}\text{Br}+\text{Na}^+$), 331.9 (50%, %, $[\text{M} (^{81}\text{Br})+\text{Na}]^+$); **HRMS** (ESI $^+$) found m/z 307.9587 $[\text{M}(^{79}\text{Br})+\text{H}]^+$, $\text{C}_9\text{H}_{11}\text{O}_4\text{N}^{79}\text{BrS}$ requires m/z 307.9587; **IR** ν_{max} (neat)/ cm^{-1} 3082, 3056, 2981, 2958, 2890, 1737, 1561, 1550, 1441, 1422, 1361, 1319, 1252, 1201, 1162, 1127, 1099, 1085, 1063, 1008, 979, 834, 806, 770, 711, 623; **mp** 58 – 60 °C (EtOAc); **R_f** = 0.42 (40% EtOAc in Petrol).

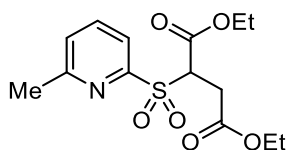


diethyl 2-(pyridin-2-ylsulfonyl)succinate (**8a**)

Following general procedure **C**, diethyl 2-(pyridin-2-ylthio)succinate (464 mg, 1.64 mmol, 1.0 equiv.), $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (54.0 mg, 0.16 mmol, 10 mol%) and hydrogen peroxide solution (30% w/w in water) (837 μL , 8.2 mmol, 5.0 equiv.) in ethanol (2.3 mL, 0.7 M) was stirred at rt for 20 h, then diluted with water. No precipitate was observed so the reaction mixture was extracted with EtOAc (20 mL $\times$ 4). The combined organic layers were then washed with brine (10 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (45% EtOAc in Petrol) to give the title compound as a white solid (305 mg, 59%).

^1H NMR (400 MHz, CDCl_3) δ 8.81 – 8.79 (m, 1H, Pyr-*H*), 8.07 (d, J = 7.5 Hz, 1H, Pyr-*H*), 7.98 (td, J = 7.5, 2.0 Hz, 1H, Pyr-*H*), 7.60 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H, Pyr-*H*), 5.05 (ddd, J = 10.5, 4.0, 1.0 Hz, 1H, SO_2CH), 4.21 – 4.14 (m, 2H, CO_2CH_2), 4.13 – 4.05 (m, 2H, CO_2CH_2), 3.31 (dd, J = 17.0, 11.0 Hz, 2H, $\text{SO}_2\text{CHCH}_a\text{H}_b$), 3.23 (dd, J = 17.0, 4.5 Hz, 2H, $\text{SO}_2\text{CHCH}_a\text{H}_b$), 1.26 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.06 (t, J = 7.0 Hz, 3H, CH_2CH_3); **^{13}C NMR** (101 MHz, CDCl_3) δ 169.9, 164.7, 156.4, 150.6, 138.2, 127.9, 123.3, 62.6, 61.7, 30.0, 14.2, 13.8; **HRMS** (ESI $^+$) found m/z 316.0852 $[\text{M}+\text{H}]^+$, $\text{C}_{13}\text{H}_{18}\text{O}_6\text{NS}$ requires m/z 316.0849; **IR** ν_{max} (neat)/ cm^{-1} 3066, 2990, 2941, 2870, 1736, 1580, 1453,

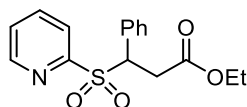
1428, 1372, 1325, 1215, 1165, 1110, 1083, 1026, 992, 857, 782, 747, 639; **mp** 77 – 78 °C (EtOAc); **R_f** = 0.13 (40% EtOAc in Petrol).



diethyl 2-((6-methylpyridin-2-yl)sulfonyl)succinate (8b)

Following general procedure C, diethyl 2-((6-methylpyridin-2-yl)thio)succinate (188.3 mg, 0.63 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (21.0 mg, 0.063 mmol, 10 mol%) hydrogen peroxide solution (30% w/w water) (647 µL, 6.33 mmol, 10.0 equiv.) in ethanol (1.0 mL, 0.6 M) was stirred at rt for 18 h. On diluting with water, a white solid precipitated out of the reaction mixture. The white solid was collected by filtration, washed with copious amounts of water and dried *in vacuo* to give the title compound as a white solid (115.1 mg, 55%).

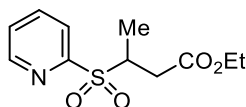
¹H NMR (400 MHz, CDCl₃) δ 7.87 (dd, *J* = 8.0, 1.5 Hz, 1H, Pyr-*H*), 7.83 (app. t, *J* = 7.5 Hz, 1H, Pyr-*H*), 7.42 (dd, *J* = 7.5, 1.5 Hz, 1H, Pyr-*H*), 5.04 (dd, *J* = 11.0, 4.0 Hz, 1H, SO₂CH), 4.22 – 4.03 (m, 4H, 2 × OCH₂), 3.30 (dd, *J* = 17.5, 11.0 Hz, 1H, SO₂CHCH_aH_b), 3.20 (dd, *J* = 17.5, 4.0 Hz, 1H, SO₂CHCH_aH_b), 2.67 (s, 3H, Pyr-*Me*), 1.27 (t, *J* = 7.0 Hz, 3H, CH₂CH₃), 1.06 (t, *J* = 7.0 Hz, 3H, , CH₂CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 170.0, 164.8, 160.6, 155.5, 138.0, 127.8, 120.3, 62.5, 62.4, 61.7, 30.0, 24.5, 14.2, 13.8; **LRMS** (ESI⁺) *m/z* 352.0 [M+Na]⁺; **HRMS** (ESI⁺) found *m/z* 330.1007 [M+H]⁺, C₁₄H₂₀O₆NS requires *m/z* 330.1006; **IR** ν_{max} (neat)/cm⁻¹ 2982, 2940, 2907, 1737, 1594, 1556, 1454, 1413, 1395, 1372, 1324, 1256, 1216, 1175, 1153, 1119, 1097, 1026, 991, 864, 836, 797, 735, 640; **mp** 70 – 71 °C (EtOAc); **R_f** = 0.26 (20% EtOAc in Petrol).



ethyl 3-phenyl-3-(pyridin-2-ylsulfonyl)propanoate (9)

Following general procedure C, methyl 3-phenyl-3-(pyridin-2-ylthio)propanoate (195 mg, 0.71 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (11.7 mg, 0.0355 mmol, 5.0 mol%), hydrogen peroxide (30% w/w water) solution (727 μ L, 7.12 mmol, 10.0 equiv.) in EtOH (1.0 mL, 0.7 M) was stirred at rt overnight for 24 h, then diluted with water. No precipitate was observed so the reaction mixture was extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were then washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (30-40% EtOAc in Petrol) to give the title compound as a colourless oil (165.8 mg, 73%).

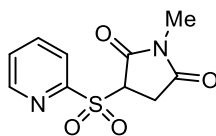
¹H NMR (400 MHz, CDCl₃) δ 8.77 (ddd, J = 5.0, 1.5, 1.0 Hz, 1H, Pyr-*H*), 7.74 (td, J = 7.5, 1.5 Hz, 1H, Pyr-*H*), 7.66 (dt, J = 8.0, 1.0 Hz, 1H, Pyr-*H*), 7.47 (ddd, J = 7.5, 4.5, 1.5 Hz, 1H, Pyr-*H*), 7.24 – 7.15 (m, 5H, Ar-*H*), 5.22 (dd, J = 10.5, 4.5 Hz, 1H, SO₂CH), 4.06 – 3.94 (m, 2H, CO₂CH₂), 3.47 (dd, J = 16.5, 4.5 Hz, 1H, SO₂CHCH_aH_b), 3.23 (dd, J = 16.5, 10.5 Hz, 1H, SO₂CHCH_aH_b), 1.10 (t, J = 7.0 Hz, 3H, CO₂CH₂CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 169.5, 155.8, 150.3, 137.8, 131.3, 130.0, 129.1, 128.6, 127.5, 124.0, 63.8, 61.3, 33.3, 14.1; **LRMS** m/z 342.0 (100%, [M+Na]⁺); **HRMS** (ESI⁺) found m/z 320.0951 [M+H]⁺, C₁₆H₁₈O₄NS requires m/z 320.0951; **IR** ν_{max} (neat)/ cm⁻¹ 3063, 3035, 2989, 2937, 2840, 1735, 1579, 1497, 1455, 1428, 1374, 1316, 1253, 1221, 1164, 1110, 1031, 992, 777, 745, 699, 630; **R_F** = 0.33 (60% EtOAc in Petrol).



ethyl 3-(pyridin-2-ylsulfonyl)butanoate (10)

Following general procedure C, ethyl 3-(pyridin-2-ylthio)butanoate (83.6 mg, 0.37 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (6.3 mg, 0.019 mmol, 5.0 mol%), hydrogen peroxide solution (30% w/w in water) (190 µL, 1.85 mmol, 5.0 equiv.) in ethanol (530 µL, 0.7 M) was stirred at rt for 16 h, then diluted with water. No precipitate was observed so the reaction mixture was extracted with EtOAc (× 4). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. With no further purification, the product was concentrated to give the title product as a colourless oil (88 mg, 92%).

¹H NMR (400 MHz, CDCl₃) δ 8.78 (ddd, *J* = 5.0, 1.5, 1.0 Hz, 1H, Pyr-*H*), 8.10 (dt, *J* = 8.0, 1.0 Hz, 1H, Pyr-*H*), 7.98 (td, *J* = 8.0, 1.5 Hz, 1H, Pyr-*H*), 7.57 (ddd, *J* = 7.5, 4.5, 1.2 Hz, 1H, Pyr-*H*), 4.17 – 4.05 (m, 3H, SO₂CH and CH₂CH₃), 3.09 (dd, *J* = 16.5, 4.0 Hz, 1H, CHCH_aH_b), 2.55 (dd, *J* = 16.5, 10.0 Hz, 1H, CHCH_aH_b), 1.36 (d, *J* = 7.0 Hz, 3H, CHCH₃), 1.25 (t, *J* = 7.0 Hz, 3H, CH₂CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 170.2, 156.0, 150.6, 138.3, 127.7, 123.6, 61.4, 53.6, 34.3, 14.3, 13.6; **HRMS** (ESI⁺) found *m/z* 258.0795 [M+H]⁺, C₁₁H₁₆O₄NS requires *m/z* 258.0795; **IR** ν_{max} (neat)/cm⁻¹ 2983, 1732, 179, 1456, 1428, 1350, 1162, 1081, 1030, 750; **R_f** = 0.26 (50% EtOAc in Petrol).

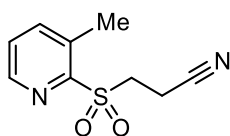


1-methyl-3-(pyridin-2-ylsulfonyl)pyrrolidine-2,5-dione (11)

Following general procedure C, 1-methyl-3-(pyridin-2-ylthio)pyrrolidine-2,5-dione (425 mg, 1.91 mmol, 1.0 equiv.), Na₂WO₄•2H₂O (31.7 mg, 0.096 mmol, 5.0 mol%),

hydrogen peroxide (30% w/w water) solution (1.46 mL, 14.3 mmol, 7.5 equiv.) in EtOH (3.0 mL, 0.7 M) was stirred at r.t overnight for 24 h, then diluted with water. No precipitate was observed so the reaction mixture was extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were then washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (40 – 50% EtOAc in Petrol) to give the title compound as a crystalline white solid (396 mg, 81%).

¹H NMR (400 MHz, CDCl₃) δ 8.78 (ddd, J = 5.0, 2.0, 1.0 Hz, 1H, Pyr-*H*), 8.09 (dt, J = 8.0, 1.0 Hz, 1H, Pyr-*H*), 8.03 (td, J = 8.0, 2.0 Hz, 1H, Pyr-*H*), 7.64 (ddd, J = 8.0, 5.0, 1.5 Hz, 1H, Pyr-*H*), 5.05 (dd, J = 10.0, 4.0 Hz, 1H, SO₂CH), 3.45 (dd, J = 19.0, 4.0 Hz, 1H, SO₂CHCH_aH_b), 3.14 (dd, J = 19.0, 10.0 Hz, 1H, SO₂CHCH_aH_b), 2.97 (s, 3H, NCH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 173.0, 168.6, 155.4, 150.4, 138.3, 128.1, 123.3, 59.5, 28.9, 25.5; **LRMS** m/z 255.0 (40%, [M+H]⁺), 277.0 (60%, [M+Na]⁺); **HRMS** (ESI⁺) found m/z 277.0253 [M+Na]⁺, C₁₀H₁₀O₄N₂SNa requires m/z 277.0253; **IR** ν_{max} (neat)/ cm⁻¹ 3126, 3100, 3077, 3063, 3034, 2990, 2974, 2942, 2936, 2842, 2821, 2246, 1605, 1515, 1481, 1447, 1422, 1344, 1297, 1277, 1243, 1210, 1164, 1131, 1105, 1062, 983, 935, 910, 808, 797, 771, 757; **mp** 98 – 100 °C (EtOAc); **R_F** = 0.30 (80% EtOAc in Petrol).

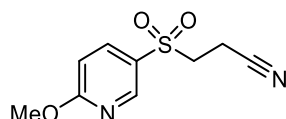


3-((3-methylpyridin-2-yl)sulfonyl)propanenitrile (1c)

Following general procedure **D**, lithium 3-methylpyridine-2-sulfinate (300 mg, 1.84 mmol, 1.0 equiv.), acrylonitrile (603 μ L, 9.2mmol, 5.0 equiv.) and AcOH (105 μ L, 1.84 mmol, 1.0 equiv.) were refluxed in water (3.5 mL, 0.5 M) for 16 h. After workup, the crude product was purified by flash column chromatography (20 – 30% EtOAc in

Petrol) and repurified by flash column chromatography (5 – 10% EtOAc in toluene) to give the title compound as a clear, colourless oil (213 mg, 55%).

¹H NMR (400 MHz, CDCl₃) δ 8.43 – 8.42 (m, 1H, Ar-*H*), 7.72 – 7.71 (m, 1H, Ar-*H*), 7.45 (dd, *J* = 7.5, 4.5 Hz, 1H, Ar-*H*), 3.95 – 3.87 (m, 2H, SO₂CH₂), 3.07 – 2.99 (m, 2H, CH₂CN), 2.69 (s, 3H, Pyr-CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 155.4, 146.0, 141.9, 133.2, 127.4, 116.7, 47.3, 17.7, 12.9; **LRMS** (ESI⁺) *m/z* 211.0 (50%, [M+H]⁺), 233.0 (50%, [M+Na]⁺); **HRMS** (ESI⁺) found *m/z* 211.0539 [M+H]⁺, C₉H₁₁O₂N₂S requires *m/z* 211.0536; **IR** *v*_{max} (neat)/cm⁻¹ 30003, 2974, 2941, 2361, 2341, 2252, 1563, 1452, 1423, 1399, 1303, 1242, 1205, 1151, 1123, 1094, 1040, 954, 824, 803, 751, 714, 668; **R_f** = 0.34 (60% EtOAc in Petrol) or **R_f** = 0.36 (20% EtOAc in toluene).

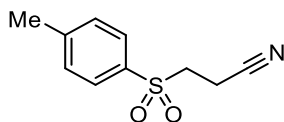


3-((6-methoxypyridin-3-yl)sulfonyl)propanenitrile (1g)

Following general procedure **D**, lithium 6-methoxypyridine-3-sulfinate (268.7 mg, 1.5 mmol, 1.1 equiv.), acrylonitrile (90.4 μL, 1.37 mmol, 1.0 equiv.) and AcOH (86.0 μL, 1.5 mmol, 1.1 equiv.) were refluxed in water (3.4 mL, 0.4 M) for 6 h. On addition of cold water (4 mL) and cooling, a white precipitate crashed out of the reaction mixture. The precipitate was collected by vacuum filtration, wash with water and dried to give the title compound as a white solid (258 mg, 84%).

¹H NMR (400 MHz, CDCl₃) δ 8.71 (dd, *J* = 2.5, 1.0 Hz, 1H, Ar-*H*), 8.00 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar-*H*), 6.91 (dd, *J* = 9.0, 1.0 Hz, 1H, Ar-*H*), 4.04 (s, 3H, OCH₃), 3.39 (t, *J* = 8.0 Hz, 2H, SO₂CH₂), 2.86 (t, *J* = 8.0 Hz, 2H, CH₂CN); **¹³C NMR** (101 MHz, CDCl₃) δ 168.0, 149.5, 138.1, 127.0, 116.0, 112.3, 54.8, 51.9, 12.2; **HRMS** (ESI⁺) found *m/z* 227.0487 [M+H]⁺, C₉H₁₁O₃N₂S requires *m/z* 227.0485; **IR** *v*_{max} (neat)/cm⁻¹ 2990, 2950,

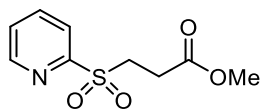
2246, 1734, 1593, 1560, 1486, 1461, 1434, 1377, 1322, 1289, 1244, 1172, 1150, 1128, 1095, 1012, 943, 847, 786, 768, 727; **mp** 122 – 124 °C (AcOH: H₂O); **R_f** = 0.21 (20% EtOAc in Petrol).



3-tosylpropanenitrile (1h)

Following general procedure **D**, sodium *p*-toluenesulfinate (196.0 mg, 1.1 mmol, 1.1 equiv.), acrylonitrile (65.5 μ L, 1.0 mmol, 1.0 equiv.) and AcOH (63.0 μ L, 1.1 mmol, 1.1 equiv.) were refluxed in water (4.0 mL, 0.25 M) for 2.5 h. The reaction was cooled to rt and a white precipitate formed. The solid was collected by vacuum filtration, washed with water and dried over vacuum to give the title compound as a white solid (153.2 mg, 73%).

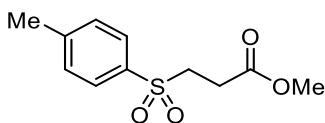
¹H NMR (400 MHz, CDCl₃) δ 7.81 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.42 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 3.37 (t, *J* = 8.0 Hz, 2H, SO₂CH₂), 2.81 (t, *J* = 8.0 Hz, 2H, CH₂CN), 2.48 (s, 3H, Ar-CH₃); **¹³C NMR** (101 MHz, CDCl₃) 146.2, 134.7, 130.6, 128.5, 116.1, 51.4, 21.9, 12.2; **HRMS** (ESI⁺) found *m/z* 232.0404 [M+Na]⁺, C₁₀H₁₁O₂NSNa requires *m/z* 232.0403; **IR** ν_{max} (neat)/cm⁻¹ 2991, 2946, 2247, 1596, 1496, 1422, 1303, 1292, 1245, 1168, 1139, 1085, 1019, 985, 828, 808, 780, 757, 637; **mp** 86 – 88 °C (H₂O); **R_f** = 0.24 (50% EtOAc in Petrol). Data is consistent with literature: W. Li, L. Gao, W. Zhuge, X. Sun and G. Zheng, *Org. Biomol. Chem.*, 2017, **15**, 7819-7823.^[167]



methyl 3-(pyridin-2-ylsulfonyl)propanoate (2b)

Following general procedure **D**, sodium pyridine-2-sulfinate (182 mg, 1.10 mmol, 1.1 equiv.), methyl acrylate (90 μ L, 1.00 mmol, 1.0 equiv.) and AcOH (57 μ L, 1.00 mmol, 1.0 equiv.) were refluxed in water (3.0 mL, 0.3 M) for 2.5 h. After workup, the crude product was purified by flash column chromatography (50% EtOAc in Petrol) to give the title compound as a clear, colourless oil (211 mg, 92%).

^1H NMR (400 MHz, CDCl_3) δ 8.75 (ddd, $J = 5.0, 2.0, 1.0$ Hz, 1H, Ar-*H*), 8.08 (app. dt, $J = 8.0, 1.0$ Hz, 1H, Ar-*H*), 7.98 (app. td, $J = 8.0, 2.0$ Hz, 1H, Ar-*H*), 7.57 (ddd, $J = 8.0, 5.0, 1.0$ Hz, 1H, Ar-*H*), 3.73 (t, $J = 8.0$ Hz, 2H, SO_2CH_2), 3.68 (s, 3H, COOCH_3), 2.84 (t, $J = 8.0$ Hz, 2H, $\text{CH}_2\text{CO}_2\text{Me}$); **^{13}C NMR** (101 MHz, CDCl_3) δ 170.6, 157.1, 150.4, 138.4, 127.7, 122.3, 52.5, 47.7, 27.5; **LRMS** (ESI^+) m/z 252.0 $[\text{M}+\text{Na}]^+$; **HRMS** (ESI^+) found m/z 252.0301 $[\text{M}+\text{Na}]^+$, $\text{C}_9\text{H}_{11}\text{O}_4\text{NNaS}$ requires m/z 252.0301; **IR** ν_{max} (neat)/ cm^{-1} 2955, 2349, 1736 (CO), 1579, 1428, 1365, 1315, 1252, 1201, 1164, 1110, 1083, 1044, 1017, 992, 900, 834, 809, 782, 752, 700, 617; **R_f** = 0.32 (60% EtOAc in Petrol).

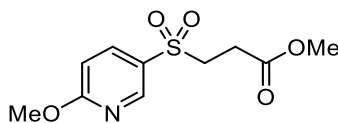


methyl 3-tosylpropanoate (2j)

Following general procedure **D**, sodium *p*-toluenesulfinate (196.0 mg, 1.10 mmol, 1.1 equiv.), methyl acrylate (90.1 μ L, 1.00 mmol, 1.0 equiv.) and AcOH (63.0 μ L, 1.10 mmol, 1.1 equiv.) were refluxed in water (4.0 mL, 0.25 M) for 2.5 h. The reaction was cooled to rt and a white precipitate was formed. The solid was collected by vacuum

filtration and dried over vacuum to give the title compound as a white solid (166.8 mg, 69%).

¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.36 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 3.64 (s, 3H, COOC), 3.41 (t, *J* = 7.5 Hz, 2H, SO₂CH₂), 2.75 (t, *J* = 7.5 Hz, 2H, CH₂COOMe), 2.46 (s, 3H, Ar-CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 170.7, 145.2, 135.7, 130.2, 128.4, 52.4, 51.7, 27.9, 21.8; **HRMS** (ESI⁺) found *m/z* 265.0507 [M+Na]⁺, C₁₁H₁₄O₄SNa requires *m/z* 265.0505; **IR** *v*_{max} (neat)/cm⁻¹ 3072, 3037, 2936, 2926, 2847, 2824, 1731, 1596, 1439, 1422, 1366, 1315, 1290, 1260, 1196, 1179, 1153, 1132, 1087, 1061, 985, 815, 768; **mp** 74 – 75 °C (H₂O); **R_f** = 0.31 (50% EtOAc in Petrol). Data is consistent with literature: H. E. Bartrum, D. C. Blakemore, C. J. Moody and C. J. Hayes, *Tetrahedron*, 2013, **69**, 2276-2282.^[168]

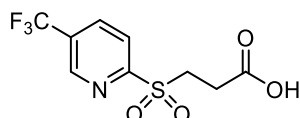


methyl 3-((6-methoxypyridin-3-yl)sulfonyl)propanoate (2k)

Following general procedure **D**, lithium 6-methoxypyridine-3-sulfinate (150.0 mg, 0.84 mmol, 1.1 equiv.), methyl acrylate (68.6 μL, 0.76 mmol, 1.0 equiv.) and AcOH (48.0 μL, 0.84 mmol, 1.1 equiv.) were refluxed in water (2.0 mL, 0.4 M) for 6 h. After workup, the product was concentrated *in vacuo* to give the title compound as a crystalline white solid (174 mg, 88%).

¹H NMR (400 MHz, CDCl₃) δ 8.63 (dd, *J* = 2.5, 1.0 Hz, 1H, Ar-*H*), 7.94 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar-*H*), 6.83 (dd, *J* = 9.0, 1.0 Hz, 1H, Ar-*H*), 3.98 (s, 3H, CH₃OAr), 3.61 (s, 3H, COOCH₃), 3.40 (t, *J* = 7.5 Hz, 2H, SO₂CH₂), 2.73 (t, *J* = 7.5 Hz, 2H, CH₂COOMe); **¹³C NMR** (101 MHz, CDCl₃) δ 170.4, 167.4, 149.0, 138.1, 127.8, 111.8, 54.5, 52.4, 52.0, 27.7; **LRMS** (ESI⁺) *m/z* 260.0 (50%, [M+H]⁺), 282.0 (50%, [M+Na]⁺); **HRMS** (ESI⁺)

found m/z 260.0589 $[M+H]^+$, $C_{10}H_{14}O_5NS$ requires m/z 260.0587; **IR** $\nu_{\max}$ (neat)/ cm^{-1} 2991, 2953, 2161, 1732, 1590, 1563, 1485, 1437, 1417, 1371, 1316, 1292, 1259, 1181, 1160, 1131, 1099, 1071, 1018, 1007, 989, 953, 902, 853, 825, 795, 777, 698, 669, 630; **mp** 80 – 84 °C (EtOAc); **R_f** = 0.31 (40% EtOAc in Petrol).

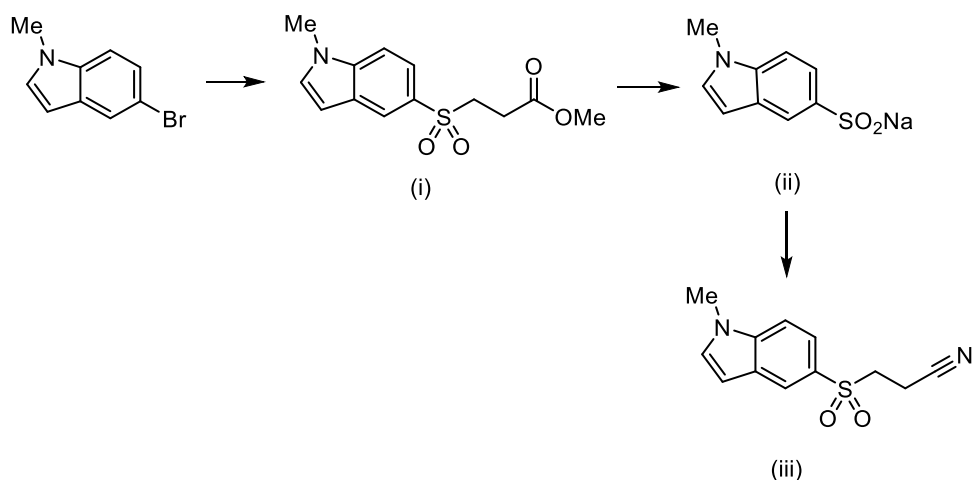


3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoic acid (2a-OH)

Following a modified version of general procedure **D**, sodium 5-(trifluoromethyl)pyridine-2-sulfinate (233 mg, 1.00 mmol, 1.0 equiv.), acrylic acid (137 μ L, 2.00 mmol, 2.00 equiv.) and AcOH (57.2 μ L, 1.00 mmol, 1.0 equiv.) were refluxed in water (4.0 mL, 0.25 M) for 5 h. The reaction was then cooled to rt on which a white precipitate formed (some precipitate may have been observed forming during the reaction). The precipitate was collected by vacuum filtration and washed with copious H_2O to give the title compound as a white solid (138 mg, 49%).

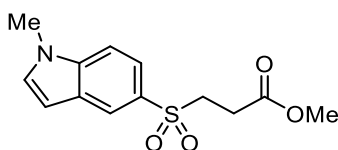
1H NMR (400 MHz, $MeOD-d^4$) δ 9.10 (d, J = 2.0 Hz, 1H, Ar- H), 8.48 (dd, J = 8.5, 2.0 Hz, 1H, Ar- H), 8.28 (d, J = 8.0 Hz, 1H, Ar- H), 3.78 (t, J = 7.5 Hz, 2H, SO_2CH_2), 2.79 (t, J = 7.5 Hz, 2H, CH_2COOH); **^{13}C NMR** (126 MHz, $MeOD-d^4$) δ 173.5, 161.6, 148.5 (q, $^3J_{C-F}$ = 4.0 Hz), 137.9 (q, $^3J_{C-F}$ = 4.0 Hz), 131.2 (q, $^2J_{C-F}$ = 34.0 Hz), 124.3 (q, $^1J_{C-F}$ = 272.0 Hz), 123.6, 49.0 (overlaps with solvent peak), 28.5; **^{19}F NMR** (377 MHz, $MeOD-d^4$) δ -64.23 (s); **LRMS** (ESI $^-$) m/z 281.9 $[M-H]^-$; **HRMS** (ESI $^+$) found m/z 306.0019 $[M+Na]^+$, $C_9H_8O_4NF_3NaS$ requires m/z 306.0018; **IR** $\nu_{\max}$ (neat)/ cm^{-1} 3104, 3066, 2994, 2361, 2341, 1710, 1596, 1581, 1298, 1167, 1153, 1128, 1102, 1074, 1014, 867; **mp** 141 – 143 °C (AcOH: H_2O); **R_f** = 0.38 (80% EtOAc in Petrol).

Telescope synthesis:



Route to synthesise 3-((1-methyl-1H-indol-5-yl)sulfonyl)propanenitrile (iii) (1i)

i)



methyl 3-((1-methyl-1H-indol-5-yl)sulfonyl)propanoate

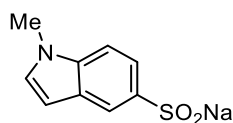
Following general procedure E, 5-bromo-1-methylindole (210.1 mg, 1.00 mmol, 1.0 equiv.), SMOPS reagent (522 mg, 3.00 mmol, 3.0 equiv.) and CuI (574 mg, 3.00 mmol, 3.0 equiv.) were heated at 110 °C in DMSO (2.0 mL, 0.5 M) for 16 h. The crude product was purified by flash column chromatography (20 – 50% EtOAc in Petrol) to the title compound as an off-white solid (262 mg, purity $\approx$ 80%, 75%).

The product was used in the next step without any further purification.

¹H NMR (400 MHz, CDCl₃) δ 8.22 (dd, J = 2.0, 0.5 Hz, 1H, Ar-*H*), 7.71 (dd, J = 8.5, 2.0 Hz, 1H, Ar-*H*), 7.45 (d, J = 9.0 Hz, 1H, Ar-*H*), 7.22 (d, J = 3.0 Hz, 1H, Ar-*H*), 6.65 (dd, J = 3.0, 1.0 Hz, 1H, Ar-*H*), 3.86 (s, 3H, NMe), 3.60 (s, 3H, CO₂Me), 3.45 (t, J = 8.0 Hz,

2H, SO₂CH₂), 2.75 (t, *J* = 8.0 Hz, 2H, CH₂CO₂Me); ¹³C NMR (101 MHz, CDCl₃) δ 170.7, 138.9, 131.5, 128.8, 128.0, 122.7, 120.6, 109.9, 102.9, 52.1, 52.0, 33.2, 28.0; LRMS (ESI⁺) *m/z* 304.0 [M+Na]⁺; HRMS (ESI⁺) found *m/z* 282.0794 [M+H]⁺, C₁₃H₁₆O₄N₁S requires *m/z* 282.0795; *R*_f = 0.23 (60% EtOAc in Petrol).

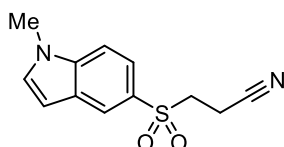
ii)



sodium 1-methyl-1H-indole-5-sulfinate

Following a modified literature procedure by Willis *et. al.*:^[11] To a stirring solution of crude methyl 3-((1-methyl-1H-indol-5-yl)sulfonyl)propanoate (250 mg, 0.89 mmol, 1.0 equiv.) in MeOH (1.0 mL, 1.0 M) was added NaOMe solution (25% in MeOH) (204 μL, 0.89 mmol, 1.0 equiv.). The reaction was monitored by TLC. After 30 min, the reaction mixture was concentrated *in vacuo* to give the crude title compound as a white solid. The crude product was used directly in the next step.

iii)

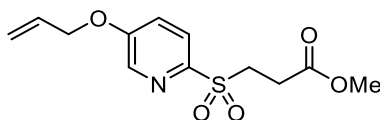


3-((1-methyl-1H-indol-5-yl)sulfonyl)propanenitrile (1i)

Following a modified version of general procedure **D**, crude sodium 1-methyl-1H-indole-5-sulfinate (193 mg, 0.890 mmol, 1.0 equiv.), acrylonitrile (88 μL, 1.34 mmol, 1.5 equiv.)

and AcOH (76 μ L, 1.34 mmol, 1.5 equiv.) were refluxed in water (2.0 mL, 0.4 M) for 7 h. After workup, the resultant crude product was purified by flash chromatography (40% EtOAc in Petrol) to give the title compound as a white solid (152 mg, 69%).

^1H NMR (400 MHz, CDCl_3) δ 8.22 (d, J = 2.0 Hz, 1H, Ar-*H*), 7.69 (dd, J = 9.0, 2.0 Hz, 1H, Ar-*H*), 7.47 (d, J = 9.0 Hz, 1H, Ar-*H*), 7.24 (d, J = 3.0 Hz, 1H, Ar-*H*), 6.66 (dd, J = 3.0, 1.0 Hz, 1H, Ar-*H*), 3.87 (s, 3H, N-*Me*), 3.39 (t, J = 8.0 Hz, 2H, SO_2CH_2), 2.78 (t, J = 8.0 Hz, 2H, CH_2CN); **^{13}C NMR** (101 MHz, CDCl_3) δ 139.4, 132.1, 128.4, 127.7, 123.0, 120.6, 116.4, 110.4, 103.2, 51.8, 33.4, 12.4; **HRMS** (ESI^+) found m/z 249.0693 $[\text{M}+\text{H}]^+$, $\text{C}_{12}\text{H}_{13}\text{O}_2\text{N}_2\text{S}$ requires m/z 249.0692; **IR** ν_{max} (neat)/ cm^{-1} 2990, 2943, 2518, 2247, 1735, 1606, 1517, 1482, 1423, 1344, 1297, 1260, 1240, 1210, 1165, 1131, 1105, 1062, 983, 911, 799, 771, 575, 737, 628, 616; **mp** 104 – 105 $^\circ\text{C}$ (EtOAc); **R_f** = 0.19 (50% EtOAc in Petrol).



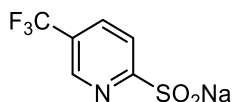
methyl 3-((5-(allyloxy)pyridin-2-yl)sulfonyl)propanoate (19)

Following General procedure E, and 5-(allyloxy)-2-bromopyridine (359.0 mg, 1.67 mmol, 1.0 equiv.), SMOPS reagent (435.4 mg, 2.50 mmol, 1.5 equiv.) and CuI (476.1 mg, 2.50 mmol, 1.5 equiv.) in DMSO (3.3 mL, 0.5 M) were heated at 110 $^\circ\text{C}$ for 24 h. The crude product was purified by flash column chromatography (30% EtOAc in Petrol) to give the title compound as a slightly yellow oil that crystallised on standing to an off-white crystalline solid (181.4 mg, 38%).

^1H NMR (400 MHz, CDCl_3) δ 8.40 (d, J = 3.0 Hz, 1H, Pyr-*H*), 8.02 (d, J = 8.5 Hz, 1H, Pyr-*H*), 7.34 (dd, J = 8.5, 3.0 Hz, 1H, Pyr-*H*), 6.03 (ddd, J = 17.0, 10.5, 5.5 Hz, 1H,

CH_aH_b=CH), 5.45 (d, J = 17.0 Hz, 1H, CH_aH_b=CH), 5.39 (d, J = 10.5 Hz, 1H, CH_aH_b=CH), 4.68 (app. dt, J = 5.5, 2.0 Hz, 2H, CH₂O), 3.70 – 3.63 (m, 5H, CH₃ and SO₂CH₂), 2.82 (t, 2H, J = 8.0 Hz, CH₂CO₂Me); ¹³C NMR (101 MHz, CDCl₃) δ 170.7, 157.7, 148.4, 139.6, 131.3, 124.2, 121.4, 119.5, 69.8, 52.4, 48.3, 27.6; LRMS (ESI⁺) m/z 308.0 [M+Na]⁺; HRMS (ESI⁺) found m/z 286.0740 [M+H]⁺, C₁₂H₁₆O₅NS requires m/z 288.0744; IR $\nu_{\max}$ (neat)/cm⁻¹ 3086, 3023, 2995, 2953, 2854, 1737, 1571, 1452, 1426, 1365, 1313, 1277, 1247, 1200, 1160, 1131, 1099, 1059, 1059, 1013, 932, 900, 835, 797, 773, 753; mp 26 – 28 °C (EtOAc); R_f = 0.2 (30% EtOAc in Petrol).

6.2.3.c Synthesis of sulfinates



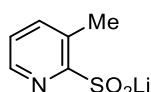
sodium 5-(trifluoromethyl)pyridine-2-sulfinate (48a)

Following a procedure adapted from Sato *et. al.*:^[169] (All other sulfinates used were commercial or were previously prepared using the same method)

Open to atmosphere: To a solution of NaOH (98.0 mg, 2.45 mmol, 0.98 equiv.) in 1:1 Ethanol: H₂O (22.0 mL, 0.1 M) was added 5-(trifluoromethyl)pyridine-2-thiol (899 mg, 5.00 mmol, 1.0 equiv.). Hydrogen peroxide solution (30% w/w H₂O) (382 μ L, 3.75 mmol, 1.5 equiv.) was added dropwise to the stirring yellow solution at rt and the reaction was stirred at rt for 18 h. The reaction mixture was then concentrated *in vacuo*. The resultant solid washed with EtOAc (15 mL $\times$ 5) and dried to give the title product as a white solid (441 mg, 77%).

¹H NMR (400 MHz, MeOD-*d*⁴) δ 8.85 – 8.81 (s, 1H, Ar-*H*), 8.26 – 8.21 (dd, J = 8.0, 2.0 Hz, 1H, Ar-*H*), 8.05 (d, J = 8.0 Hz, 1H, Ar-*H*); ¹³C NMR (126 MHz, MeOD-*d*⁴) δ 178.7, 146.7 (q, ³ J_{C-F} = 4.0 Hz), 136.4 (q, ³ J_{C-F} = 3.5 Hz), 128.1 (q, ² J_{C-F} = 33.0 Hz), 124.9 (q,

$^2J_{C-F}$ = 271.0 Hz), 119.1; ^{19}F NMR (377 MHz, MeOD- d^4) δ -63.85 (s); HRMS (ESI $^-$) found m/z 209.9837 [M-Na] $^-$, C₆H₃O₂NF₃S requires m/z 209.9842; IR ν_{max} (neat)/cm $^{-1}$ 3380, 1624, 1595, 1376, 1333, 1159, 1130, 1105, 1066, 1020, 1001, 984, 852, 767, 708, 623; mp >250 °C (EtOH: H₂O); R_f = 0.00 (60% EtOAc in Petrol). Data consistent with literature: T. Markovic, B. N. Rocke, D. C. Blakemore, V. Mascitti and M. C. Willis, *Chem. Sci.*, 2017, **8**, 4437-4442.^[11]

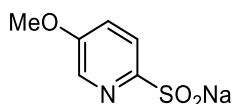


lithium 3-methylpyridine-2-sulfinate (48b)

Following a procedure adapted from Markovic *et. al.*:^[11]

n-BuLi solution (1.62 mL, 2.2 M in hexane, 3.60 mmol, 0.9 equiv.) was slowly added to a stirring solution of 2-bromo-3-methylpyridine (446 μL , 4.00 mmol, 1.0 equiv.) in THF (20.0 mL, 0.2 M) at -78 °C. The reaction mixture was stirred for 1 hour before TIMSO (514.5 μL , 4.0 mmol, 1.0 equiv., den: 1.16 g/cm³) was added dropwise. The reaction was then allowed to warm to room temperature. The crude product was collected by vacuum filtration. The product was then purified by washing with acetone and diethyl ether and drying under vacuum to yield the title compound as a pale yellow solid (552.1 mg, 94%).

^1H NMR (400 MHz, D₂O) δ 8.41 (d, J = 4.5 Hz, 1H, Pyr-*H*), 7.78 – 7.72 (dq, J = 7.5, 1.0 Hz, 1H, Pyr-*H*), 7.43 (dd, J = 7.5, 4.5 Hz, 1H, Pyr-*H*), 2.61 (s, 3H, Pyr-*Me*); ^{13}C NMR (101 MHz, D₂O) δ 165.7, 146.2, 141.0, 131.5, 125.4, 15.7; LRMS (ESI $^-$) m/z 155.9 [M-Li] $^-$; HRMS (ESI $^-$) found m/z 156.0117[M-Na] $^-$, C₆H₆O₂NS requires m/z 156.0125; IR ν_{max} (neat)/cm $^{-1}$ 3388, 2957, 2359, 1652, 1573, 1449, 1405, 1326, 1202, 1111, 976, 799, 754, 682, 642; mp decompose >250 °C.



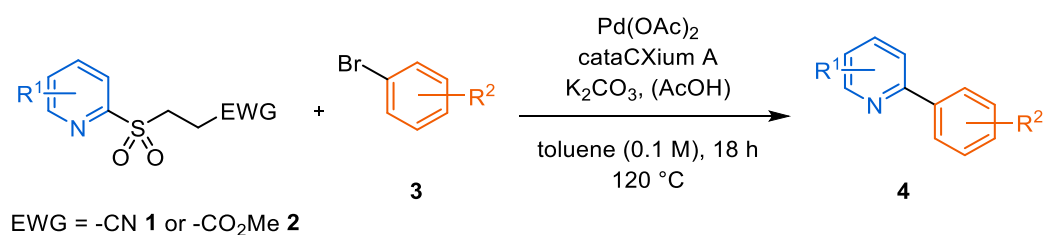
sodium 5-methoxypyridine-2-sulfinate (48c)

Following a modified literature procedure by Markovic et. al.:¹¹

To a stirring solution of crude methyl 3-((5-methoxypyridin-2-yl)sulfonyl)propanoate, (520 mg, 2.00 mmol, 1.0 equiv.) in MeOH (2.25 mL, 1.0 M) was added NaOMe solution (25% in MeOH) (457 μ L, 2.00 mmol, 1.0 equiv.) . The reaction was monitored by TLC (note: the by-product thiol has a strong odour). After 30 mins the reaction mixture was concentrated in vacuo to give the crude title compound as a white solid. The crude sulfinate product was used directly in the next step.

R_f = 0.0 (30% EtOAc in Petrol).

6.2.3.d Desulfonative cross-coupling of base-activated latent sulfonates



Caution: SO₂ is formed during the reaction.

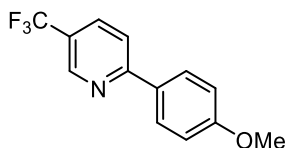
General Coupling procedure F or the pyridine β -nitrile sulfone **1** reagent with aryl halides: To an oven-dried microwave vial (10 mL) was added pyridine β -nitrile sulfone (0.22 mmol, 1.1 equiv.), aryl halide (if it is a solid) (0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A® (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.). The vial was capped and purged with N₂ for

10 mins. Dry toluene (2.0 mL, 0.1 M) was then added, followed by the addition of aryl halide (if it is a liquid) (0.20 mmol, 1.0 equiv.) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) with stirring. The reaction mixture was heated to 120 °C or 130 °C for 18 h. The reaction mixture was then allowed to cool to rt, filtered through a short pad of silica and washed with EtOAc. The resultant crude solution was concentrated *in vacuo*, adsorbed onto celite and purified by flash column chromatography (EtOAc in Petrol) to give the desired product.

General Coupling procedure G for the pyridine β -methylester sulfone reagent **2** with aryl halides:

To an oven dried microwave vial (10 mL) was added pyridine β -methylester sulfone (0.30 mmol, 1.5 equiv.), aryl halide (if it is a solid) (0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.). The vial was capped and purged with N₂ for 10 mins. Dry toluene (2.0 mL, 0.1 M) was then added, followed by the addition of aryl halide (if it is a liquid) (0.20 mmol, 1.0 equiv.) with stirring. The reaction mixture was heated to 120 °C or 130 °C for 18 h. The reaction mixture was then allowed to cool to rt, filtered through a pad of silica and washed with EtOAc. The resultant crude solution was concentrated *in vacuo*, adsorbed onto celite and purified by flash column chromatography (EtOAc in Petrol) to give the desired product.

Note: Biaryl substrates synthesised by Dr. Loïc Pantaine who collaborated on the base-activated latent sulfinate cross-coupling are indicated in the relevant scope tables in **Chapter 2**, and as such are not included in this experimental.



2-(4-methoxyphenyl)-5-(trifluoromethyl)pyridine (4a)

From the β -nitrile sulfone: Following general procedure **F**, 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (58.1 mg, 0.22 mmol, 1.1 equiv.), 4-bromoanisole (25 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (3% EtOAc in Petrol) to give the title product as a white solid (44.8 mg, 88%).

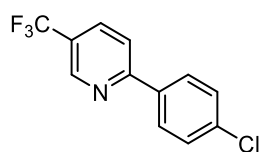
From the β -methylester sulfone (for comparison to the β -nitrile sulfone): Following general procedure **F**, methyl 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoate (65.4 mg, 0.22 mmol, 1.1 equiv.), 4-bromoanisole (25 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (3% EtOAc in Petrol) to give the title product as a white solid (36.0 mg, 71%).

From the β -methylester sulfone: Following general procedure **G**, methyl 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoate (89.2 mg, 0.30 mmol, 1.5 equiv.), 4-bromoanisole (25 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash purified by column chromatography on silica gel (3% EtOAc in Petrol) to give the title product as a white solid (44.4 mg, 87%).

From the diethyl succinate sulfone:

Following general procedure **G**, diethyl 2-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)succinate (115.0 mg, 0.30 mmol, 1.5 equiv.), 4-bromoanisole (25 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (3% EtOAc in Petrol) to give the title product as a white solid (42.1 mg, 83%). *When run at 130 °C, the reaction gave the title product in a 72% yield (36.5 mg).*

¹H NMR (400 MHz, CDCl₃) δ 8.89 (app. s, 1H, Pyr-*H*), 8.01 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.93 (dd, *J* = 8.5, 2.5 Hz, 1H, Pyr- *H*), 7.78 (d, *J* = 8.5 Hz, 1H, Pyr- *H*), 7.03 (app. dt, *J* = 9.0 Hz, 2H, Ar-*H*), 3.88 (s, 3H, OCH₃); **¹³C NMR** (101 MHz, CDCl₃) 161.5, 160.4, 146.6 (q, ³*J*_{C-F} = 4.0 Hz), 133.9 (q, ³*J*_{C-F} = 4.0 Hz), 130.6, 128.8, 124.2 (q, ²*J*_{C-F} = 34.0 Hz), 123.9 (q, ¹*J*_{C-F} = 272.0 Hz), 119.2, 114.5, 55.6; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.15 (s); **LRMS** (ESI⁺) *m/z* 254.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 254.0781 [M+H]⁺, C₁₃H₁₁ONF₃ requires *m/z* 254.0787; **IR** ν_{max} (neat)/cm⁻¹ 3031, 2970, 2043, 1598, 1319, 1299, 1283, 1249, 1114, 1084, 824, 774, 711; **mp** 111 – 113 °C (EtOAc); **R_f** = 0.44 (20% EtOAc in Petrol). Retention time on HPLC: 6.63 min. Data Consistent with literature: J. Wei, H. Liang, C. Ni, R. Sheng, J. Hu, *Org. Lett.*, 2019, **21**, 4, 937-940.^[83]

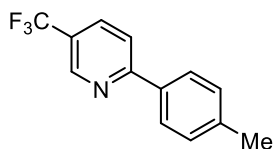


2-(4-chlorophenyl)-5-(trifluoromethyl)pyridine (4b)

From the β -nitrile sulfone: Following general procedure **F**, 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (58.1 mg, 0.22 mmol, 1.1 equiv.), 1-bromo-4-chlorobenzene (38.3 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (1% EtOAc in Petrol) to give the title product as an off-white crystalline solid (41.0 mg, 80%).

From the β -methylester sulfone: Following general procedure **G**, methyl 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoate (89.2 mg, 0.30 mmol, 1.5 equiv.), 1-bromo-4-chlorobenzene (38.3 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (1% EtOAc in Petrol) to give the title product as an off-white solid (36.5 mg, 71%).

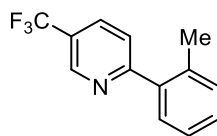
¹H NMR (400 MHz, CDCl₃) δ 8.95 – 8.92 (m, 1H, Pyr-*H*), 8.01 – 7.97 (m, 3H, Ar-*H* and Pyr-*H* overlap), 7.82 (d, *J* = 8.5 Hz, 1H, Pyr-*H*), 7.50 – 7.46 (m, 2H, Ar-*H*); **¹³C NMR** (101 MHz, CDCl₃) δ 159.5, 146.8 (q, ³*J*_{C-F} = 4.0 Hz), 136.5, 136.4, 134.2 (q, ³*J*_{C-F} = 4.0 Hz), 129.3, 128.7, 125.2 (q, ²*J*_{C-F} = 33.0), 123.8 (q, ¹*J*_{C-F} = 272.0), 119.9; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.28 (s); **LRMS** (ESI⁺) *m/z* 258.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 258.0292 [M+H]⁺, C₁₂H₈N³⁵ClF₃ requires *m/z* 258.0292; **IR** ν_{max} (neat)/cm⁻¹ 1595, 1477, 1379, 1337, 1134, 1092, 1014, 829, 768; **mp** 72 – 75 °C (EtOAc: Petrol); **R_f** = 0.53 (10% EtOAc in Petrol). Data is consistent with literature: Y. Xie, H. Chi, A. Guan, C. Liu, H. Ma, D. Cui. *J. Agric. Food Chem.* 2014, **62**, 52, 12491-12496.^[170]



2-(*p*-tolyl)-5-(trifluoromethyl)pyridine (4c)

From the β -nitrile sulfone: Following general procedure F, 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (58.1 mg, 0.22 mmol, 1.1 equiv.), 4-bromotoluene (34.2 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (1% EtOAc in Petrol) to give the title product as a white crystalline solid (38.0 mg, 80%). *When run at 130 °C, the reaction gave the title product in 89% yield (42.3 mg)*

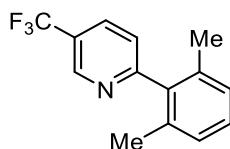
¹H NMR (400 MHz, CDCl₃) δ 8.93 – 8.91 (m, 1H, Pyr-*H*), 7.98 – 7.91 (m, 3H, Ar-*H* and Pyr-*H* overlap), 7.82 (d, J = 8.5 Hz, 1H, Pyr-*H*), 7.32 (d, J = 8.0 Hz, 2H, Ar-*H*), 2.43 (s, 3H, CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 160.8, 146.7 (q, $^3J_{C-F}$ = 4.0 Hz), 140.5, 135.3, 134.0 (q, $^3J_{C-F}$ = 3.5 Hz), 129.9, 127.3, 124.5 (q, $^2J_{C-F}$ = 32.0 Hz), 123.8 (q, $^1J_{C-F}$ = 272.0 Hz), 119.8, 21.5; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.18 (s); **LRMS** (ESI⁺) m/z 238.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 238.0839 [M+H]⁺, C₁₃H₁₁NF₃ requires m/z 238.0838; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 1713, 1599, 1332, 1224, 1124, 1014, 914, 823, 732; **mp** 101 – 103 °C (EtOAc); **R_f** = 0.53 (10% EtOAc in Petrol). Data is consistent with literature: T. Markovic, B. N. Rocke, D. C. Blakemore, V. Mascitti and M. C. Willis, *Chem. Sci.*, 2017, **8**, 4437-4442.^[11]



2-(*o*-tolyl)-5-(trifluoromethyl)pyridine (4e)

From the β -nitrile sulfone: Following general procedure F, 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (58.1 mg, 0.22 mmol, 1.1 equiv.), 2-bromotoluene (24.1 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (3% EtOAc in Petrol) to give the title product as a pale yellow oil (43.1 mg, 91%). *When run at 120 °C, the reaction gave the title product in a 56% yield (26.5 mg)*

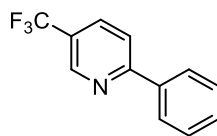
¹H NMR (400 MHz, CDCl₃) δ 8.97 (dq, J = 2.5, 1.0 Hz, 1H, Pyr-*H*), 7.99 (dd, J = 8.0, 2.5 Hz, 1H, Pyr-*H*), 7.55 (d, J = 8.0 Hz, 1H, Pyr-*H*), 7.43 – 7.28 (m, 4H, Ar-*H*), 2.39 (s, 3H, CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 163.7, 146.2 (q, $^3J_{C-F}$ = 4.0 Hz), 139.2, 136.0, 133.5 (q, $^3J_{C-F}$ = 4.0 Hz), 131.2, 129.8, 129.2, 126.2, 124.7 (q, $^2J_{C-F}$ = 33.0 Hz), 123.9 (q, $^1J_{C-F}$ = 273.0 Hz), 123.9, 20.4; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.21 (s); **LRMS** (ESI⁺) m/z 238.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 238.0838 [M+H]⁺, C₁₃H₁₁NF₃ requires m/z 238.0838; **IR** $\nu_{\max}$ (neat)/ cm⁻¹ 3065, 3025, 2928, 2927, 1605, 1564, 1480, 1457, 1384, 1324, 1271, 1238, 1163, 1123, 1081, 1014, 940, 850, 816, 785, 751, 721, 682, 637, 619; **R_f** = 0.46 (5% EtOAc in Petrol). Data is consistent with literature: J. Wei, H. Liang, C. Ni, R. Sheng, J. Hu, *Org. Lett.*, 2019, **21**, 14, 937-940.^[83]



2-(2,6-dimethylphenyl)-5-(trifluoromethyl)pyridine (4f)

From the β -nitrile sulfone: Following general procedure **F**, 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (58.1 mg, 0.22 mmol, 1.1 equiv.), 2-bromo-1,3-dimethylbenzene (26.6 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (2% EtOAc in Petrol) to give the title product as yellow oil (32.8 mg, 65%).

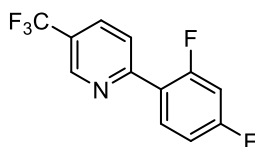
¹H NMR (400 MHz, CDCl₃) δ 9.01 (m, 1H, Pyr-*H*), 8.01 (app. ddd, J = 8.0, 2.5, 1.0 Hz, 1H, Pyr-*H*), 7.39 (app. dt, J = 8.0, 1.0 Hz, 1H, Pyr-*H*), 7.23 (dd, J = 8.0, 7.0 Hz, 1H, Ar-*H*), 7.13 (app. d, J = 7.5 Hz, 2H, Ar-*H*), 2.04 (s, 6H, (CH₃)CCC(CH₃)); **¹³C NMR** (101 MHz, CDCl₃) δ 163.9, 146.8 (q, $^3J_{C-F}$ = 4.0 Hz), 139.4, 135.7, 133.6 (q, $^3J_{C-F}$ = 3.5 Hz), 128.6, 127.9, 124.9 (q, $^2J_{C-F}$ = 33.0 Hz), 124.5, 123.8 (q, J^1_{C-F} = 272.5 Hz), 20.3; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.25 (s); **LRMS** (ESI⁺) m/z 252.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 250.0995 [M+H]⁺, C₁₄H₁₃NF₃ requires m/z 252.0995; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 3025, 2924, 2361, 1607, 1567, 1466, 1382, 1326, 1282, 1233, 1162, 1127, 1080, 1015, 940, 850, 771, 746, 698, 637; **R_f** = 0.33 (5% EtOAc in Petrol). Data is consistent with literature: T. Markovic, B. N. Rocke, D. C. Blakemore, V. Mascitt, M. C. Willis, *Org. Lett.* 2017, **19**, 22, 6033-6035.^[88]



2-phenyl-5-(trifluoromethyl)pyridine (4g)

From the β -nitrile sulfone: Following general procedure F, 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (58.1 mg, 0.22 mmol, 1.1 equiv.), bromobenzene (21.3 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude product was purified by flash column chromatography on silica gel (1% EtOAc in Petrol) to give the title product as a white crystalline solid (41.0 mg, 91%). *When run at 120 °C, the reaction gave the title product in a 54% yield (24.1 mg)*

¹H NMR (400 MHz, CDCl₃) δ 8.96 – 8.95 (m, 1H, Pyr-*H*), 8.06 – 8.02 (m, 2H, Ar-*H*), 7.99 (dd, J = 8.5, 2.5 Hz, 1H, Pyr-*H*), 7.85 (d, J = 8.5 Hz, 1H, Pyr-*H*), 7.56 – 7.45 (m, 3H, Ar-*H*); **¹³C NMR** (101 MHz, CDCl₃) δ 160.8, 146.8 (q, $^3J_{C-F}$ = 4.0 Hz), 138.1, 134.1 (q, $^3J_{C-F}$ = 3.5 Hz), 130.2, 129.1, 127.4, 125.0 (q, $^2J_{C-F}$ = 33.0 Hz), 123.9 (q, $^1J_{C-F}$ = 272.0 Hz), 120.1; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.21 (s); **LRMS** (ESI⁺) m/z 223.9 [M+H]⁺; **HRMS** (ESI⁺) found m/z 224.0681 [M+H]⁺, C₁₂H₉NF₃ requires m/z 224.0682; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 2925, 2923, 2360, 1711, 1601, 1481, 1449, 1387, 1337, 1238, 1165, 1123, 1087, 1013, 939, 839, 790, 739, 648; **mp** 64 – 66 °C (EtOAc); **R_f** = 0.50 (5% EtOAc in Petrol). Data is consistent with literature: J. Wei, H. Liang, C. Ni, R. Sheng, J. Hu, *Org. Lett.*, 2019, **21**, 4, 937-940.^[83]

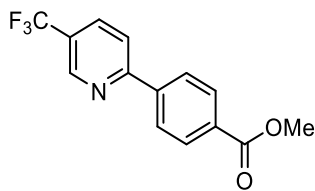


2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine (4h)

From the β -nitrile sulfone: Following general procedure F, 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (58.1 mg, 0.22 mmol, 1.1 equiv.), 1-bromo-2,4-difluorobenzene (22.6 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (1% EtOAc in Petrol) to give the title product as an off-white, crystalline solid (38.7 mg, 75%). *When run at 120 °C, the reaction gave the title product in a 68% yield (35.2 mg)*

¹H NMR (400 MHz, CDCl₃) δ 8.98 – 8.94 (m, 1H, Pyr-*H*), 8.10 (td, J = 9.0, 6.5 Hz, 1H, Ar-*H*), 7.99 (dd, J = 8.0, 2.5 Hz, 1H, Pyr-*H*), 7.90 (d, J = 8.0 Hz, 1H, Pyr-*H*), 7.07 – 7.01 (m, 1H, Ar-*H*), 6.95 (ddd, J = 11.0, 9.0, 2.5 Hz, 1H, Ar-*H*); **¹³C NMR** (101 MHz, CDCl₃) δ 164.0 (dd, J = 253.0, 12.5 Hz), 161.0 (dd, J = 252.5, 12.0 Hz), 155.9, 146.7 (q, $^3J_{C-F}$ = 4.0 Hz), 133.9 (q, $^3J_{C-F}$ = 3.5 Hz), 132.6 (dd, J = 10.0, 4.0 Hz), 125.3 (q, $^2J_{C-F}$ = 33.0 Hz), 123.7 (q, $^1J_{C-F}$ = 273.0 Hz), 123.8 (d, J = 11.0 Hz), 122.6 (dd, J = 11.0, 4.0 Hz), 112.4 (dd, J = 21.0, 3.5 Hz), 104.8 (dd, J = 27.0, 25.5 Hz); **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.40 (s, CF₃), -107.22 – -107.25 (m, CF), -112.06 – -112.09 (m, CF); **HRMS** (ESI⁺) found m/z 260.0493 [M+H]⁺, C₁₂H₇NF₅ requires m/z 260.0493; **IR** $\nu_{\max}$ (neat)/ cm⁻¹ 3095, 3035, 2920, 2852, 2183, 2152, 2027, 1987, 1908, 1702, 1602, 1571, 1511, 1488, 1430, 1389, 1333, 1295, 1266, 1243, 1217, 1177, 1133, 1108, 1084, 1018, 966, 913, 851, 820, 774, 739, 719, 641; **mp** 56 – 58 °C (EtOAc); **R_f** = 0.54 (5% EtOAc in Petrol). Data consistent

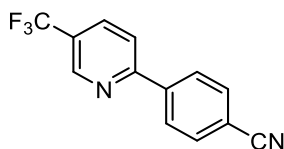
with literature: T. Rossolini, J. A. Leitch, R. Grainger, D. Dixon, *Org. Lett.* 2018, **20**, 21, 6794-6798.^[88]



methyl 4-(5-(trifluoromethyl)pyridin-2-yl)benzoate (4i)

From the β -methylester sulfone: Following general procedure **G**, methyl 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoate (89.0 mg, 0.30 mmol, 1.5 equiv.), methyl 4-bromobenzoate (43.0 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (2 – 3% EtOAc in Petrol) to give the title product as a white solid (44.4 mg, 79%).

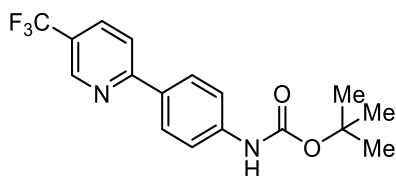
¹H NMR (400 MHz, CDCl₃) δ 8.97 – 8.96 (m, 1H, Ar-H), 8.16 (d, J = 8.5 Hz, 2H, Ar-H), 8.10 (d, J = 8.5 Hz, 2H, Ar-H), 8.01 (dd, J = 8.5 Hz, 2.0 Hz, 1H, Ar-H), 7.89 (d, J = 8.5 Hz, 1H, Ar-H), 3.95 (s, 3H, CO₂CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 166.8, 159.5, 146.9 (q, $^3J_{C-F}$ = 4.0 Hz), 142.0, 134.2 (q, $^3J_{C-F}$ = 3.5 Hz), 131.5, 130.3, 127.4, 125.7 (q, $^2J_{C-F}$ = 33.0 Hz), 123.7 (q, $^1J_{C-F}$ = 272.5 Hz), 120.6, 52.4; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.34 (s); **LRMS** (ESI⁺) m/z 282.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 282.0735 [M+H]⁺, C₁₄H₁₁F₃NO₂ requires m/z 282.0736; **IR** ν_{max} (neat)/cm⁻¹ 2928, 1722, 1606, 1343, 1281, 1129, 1014, 839, 752; **mp** 103 – 105 °C; **R_f** = 0.17 (5% EtOAc in Petrol). Data is consistent with literature: T. Markovic, B. N. Rocke, D. C. Blakemore, V. Mascitti and M. C. Willis, *Org. Lett.*, 2017, **19**, 22, 6033-6035.^[88]



4-(5-(trifluoromethyl)pyridin-2-yl)benzonitrile (4k)

From the β -nitrile sulfone: Following general procedure F, 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (58.1 mg, 0.22 mmol, 1.1 equiv.), 4-bromobenzonitrile (36.4 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (5% EtOAc in Petrol) to give the title product as an off-white solid (45.3 mg, 91%).

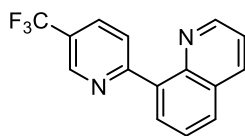
¹H NMR (400 MHz, CDCl₃) δ 8.98 (dq, J = 2.5, 1.0 Hz, 1H, Pyr-*H*), 8.17 (d, J = 9.0 Hz, 2H, Ar-*H*), 8.05 (dd, J = 8.5, 2.5 Hz, 1H, Pyr-*H*), 7.89 (d, J = 8.5 Hz, 1H, Pyr-*H*), 7.79 (d, J = 9.0 Hz, 2H, Ar-*H*); **¹³C NMR** (101 MHz, CDCl₃) δ 158.5, 147.1 (q, $^3J_{C-F}$ = 4.0 Hz), 142.0, 134.5 (q, $^3J_{C-F}$ = 3.5 Hz), 132.9, 128.0, 126.0 (q, $^2J_{C-F}$ = 33.0 Hz), 123.3 (q, $^1J_{C-F}$ = 127.0 Hz), 120.6, 118.6, 113.7; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.40 (s); **LRMS** (ESI⁺) m/z 249.3 [M+H]⁺; **HRMS** (ESI⁺) found m/z 249.0634 [M+H]⁺, C₁₃H₈N₂F₃ requires m/z 249.0640; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 304, 2924, 2360, 2226, 1718, 1601, 1581, 1560, 1485, 1413, 1386, 1325, 1297, 1244, 1171, 1142, 11201, 1083, 1032, 1013, 982, 951, 863, 834, 770, 740, 721; **mp** 95 – 102 °C (EtOAc); **R_f** = 0.23 (5% EtOAc in Petrol). Data is consistent with literature: T. Markovic, B. N. Rocke, D. C. Blakemore, V. Mascitti, M. C. Willis, *Org. Lett.* 2017, **19**, 22, 6033-6035.^[88]



***tert*-butyl (4-(5-(trifluoromethyl)pyridin-2-yl)phenyl)carbamate (4m)**

From the β -nitrile sulfone: Following general procedure F, 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (58.1 mg, 0.22 mmol, 1.1 equiv.), *tert*-butyl (4-bromophenyl) carbamate, (54.4 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (2 - 4% EtOAc in Petrol) to give the title product as an off-white solid (50.4 mg, 75%).

¹H NMR (400 MHz, CDCl₃) δ 8.92 – 8.87 (m, 1H, Pyr-*H*), 8.00 (d, J = 9.0 Hz, 2H, Ar-*H*), 7.93 (app. ddd, J = 8.5, 2.5, 1.0 Hz, 1H, Pyr-*H*), 7.80 (d, J = 8.5 Hz, 1H, Pyr-*H*), 7.51 (d, J = 9.0 Hz, 2H, Ar-*H*), 6.62 (br.s, 1H, NH), 1.54 (s, 9H, C(CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃) δ 160.1, 152.6, 146.6 (q, $^3J_{C-F}$ = 4.0 Hz), 140.5, 134.0 (q, $^3J_{C-F}$ = 4.0 Hz), 132.5, 128.2, 124.4 (q, $^2J_{C-F}$ = 33.0 Hz), 124.0 (q, $^1J_{C-F}$ = 272.3 Hz), 119.4, 118.6, 81.1, 28.5; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.20 (s); **LRMS** (ESI⁺) m/z 339.2 [M+H]⁺; **HRMS** (ESI⁺) found m/z 339.1316 [M+H]⁺, C₁₇H₁₈N₂O₂F₃ requires m/z 339.1315; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 3362, 2987, 2924, 2284, 1699, 1602, 1590, 1568, 1522, 1506, 1416, 1374, 1337, 1268, 1156, 1138, 1084, 832, 772, 716, 618; **mp** 159 – 162 °C (EtOAc); **R_f** = 0.35 (4% EtOAc in Petrol). Data is consistent with literature: T. Markovic, B. N. Rocke, D. C. Blakemore, V. Mascitt, M. C. Willis, *Org. Lett.* 2017, **19**, 22, 6033-6035.^[88]

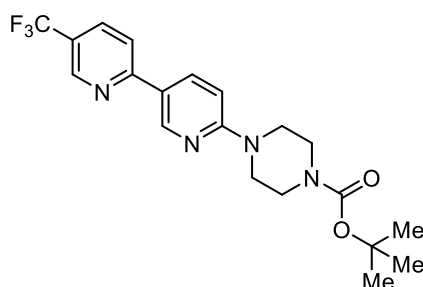


8-(5-(trifluoromethyl)pyridin-2-yl)quinolone (4n)

From the β -nitrile sulfone: Following general procedure F, 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (58.1 mg, 0.22 mmol, 1.1 equiv.), 8-bromoquinoline (41.6 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (8% EtOAc in Petrol). The product was then re-purified by flash column chromatography on silica gel (5% EtOAc in Petrol) to give the title product as an off-white, crystalline solid (40.5 mg, 74%).

¹H NMR (400 MHz, CDCl₃) δ 9.05 (dq, J = 2.5, 1.0 Hz, 1H, Pyr-*H*), 8.99 (dd, J = 4.0, 2.0 Hz, 1H, Quin-*H*), 8.31 (d, J = 8.5 Hz, 1H, Pyr-*H*), 8.27 (dd, J = 8.5, 2.0 Hz, 1H, Quin-*H*), 8.21 (dd, J = 7.0, 1.5 Hz, 1H, Quin-*H*), 8.04 (dd, J = 8.5, 2.5 Hz, 1H, Pyr-*H*), 7.95 (dd, J = 8.0, 1.5 Hz, 1H, Quin-*H*), 7.71 (dd, J = 8.0, 7.0 Hz, 1H, Quin-*H*), 7.48 (dd, J = 8.5, 4.0 Hz, 1H, Quin-*H*); **¹³C NMR** (101 MHz, CDCl₃) δ 160.5, 150.7, 146.5 (q, $^3J_{C-F}$ = 4.0 Hz), 145.6, 137.4, 137.0, 132.8 (q, $^3J_{C-F}$ = 3.5 Hz), 131.8, 129.9, 128.9, 126.8, 126.7, 125.0 (q, J^2_{C-F} = 33.5 Hz), 124.0 (q, $^1J_{C-F}$ = 272.0 Hz), 121.5; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.24 (s); **LRMS** (ESI⁺) m/z 275.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 275.0791 [M+H]⁺, C₁₅H₁₀ON₂F₃ requires m/z 275.0791; **IR** $\nu_{\max}$ (neat)/ cm⁻¹ 3057, 2924, 2854, 2108, 1926, 1823, 1739; 1600, 1560, 1327, 1190, 1156, 1130, 1103, 1079, 1026, 844, 825, 812, 794, 772; **mp** 67 – 70 °C (EtOAc); **R_f** = 0.18 (5% EtOAc in Petrol). Data

consistent with literature: T. Markovic, B. N. Rocke, D. C. Blakemore, V. Mascitti and M. C. Willis, *Chem. Sci.*, 2017, **8**, 4437-4442.^[11]

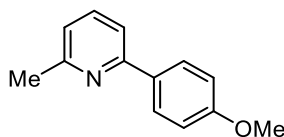


***tert*-butyl 4-(5-(trifluoromethyl)-[2,3'-bipyridin]-6'-yl)piperazine-1-carboxylate (4s)**

From the β -nitrile sulfone: Following general procedure F, 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (58.1 mg, 0.22 mmol, 1.1 equiv.), *tert*-butyl 4-(5-bromopyridin-2-yl)piperazine-1-carboxylate (68.5 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (15% EtOAc in Petrol) to give the title product as an off-white solid (65.3 mg, 80%).

¹H NMR (400 MHz, CDCl₃) δ 8.87 – 8.86 (m, 1H, Pyr-*H*), 8.84 (d, J = 2.5 Hz, 1H, Pyr-*H*), 8.23 (dd, J = 9.0, 2.5 Hz, 1H, Pyr-*H*), 7.91 (dd, J = 8.5, 2.5 Hz, 1H, Pyr-*H*), 7.74 (d, J = 8.5 Hz, 1H, Pyr-*H*), 6.73 (d, J = 9.0 Hz, 1H, Pyr-*H*), 3.69 – 3.64 (m, 4H, N(CH₂)₂), 3.57 (m, 4H, N(CH₂)₂), 1.49 (s, 9H, C(CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃) δ 159.7, 158.8, 154.9, 147.5, 146.8 (d, $^3J_{C-F}$ = 4.0 Hz), 136.5, 133.9 (d, $^3J_{C-F}$ = 4.0 Hz), 124.1 (q, $^2J_{C-F}$ = 33.0 Hz), 123.9 (q, $^1J_{C-F}$ = 273.0 Hz), 123.2, 118.3, 106.7, 80.2, 44.9, 28.6; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.19 (s); **LRMS** (ESI⁺) m/z 309.2 (25%, [M+H - C₄H₈]⁺), 353.0 (75%, [M+H - C₅O₂H₉]⁺); **HRMS** (ESI⁺) found m/z 409.1836 [M+H]⁺, C₂₀H₂₄O₂N₄F₃ requires m/z 409.1846; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 2986, 2926, 2854, 2359, 1687,

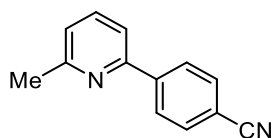
1598, 1421, 1336, 1166, 1128, 1088; **mp** 152 – 156 °C (EtOAc); **R_f** = 0.25 (20% EtOAc in Petrol).



2-(4-methoxyphenyl)-6-methylpyridine (4t)

From the β -nitrile sulfone: Following general procedure **F**, 3-((6-methylpyridin-2-yl)sulfonyl)propanenitrile (46.3 mg, 0.22 mmol, 1.1 equiv.), 4-bromoanisole (25 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (5% EtOAc in Petrol) to give the title product as a colourless, viscous oil that crystallised on standing (37.5 mg, 94%).

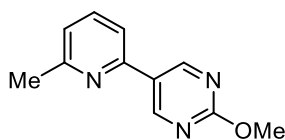
¹H NMR (400 MHz, CDCl₃) δ 7.97 – 7.92 (m, 2H, Ar-*H*), 7.59 (t, *J* = 8.0 Hz, 1H, Pyr-*H*), 7.45 (d, *J* = 8.0 Hz, 1H, Pyr-*H*), 7.04 (d, *J* = 8.0 Hz, 1H, Pyr-*H*), 7.01 – 6.96 (m, 2H, Ar-*H*), 3.86 (s, 3H, OCH₃), 2.61 (s, 3H, Pyr-CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 160.4, 158.3, 156.7, 136.9, 132.6, 128.4, 121.0, 117.0, 114.2, 55.5, 24.9; **LRMS** (ESI⁺) *m/z* 200.1 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 200.1069 [M+H]⁺, C₁₃H₁₄ON requires *m/z* 200.1070; **IR** ν_{max} (neat)/cm⁻¹ 2924, 1580, 1514, 1453, 1301, 1249, 1179, 1033, 839, 791, 645; **mp** 52 – 54 °C (EtOAc); **R_f** = 0.27 (10% EtOAc in Petrol). Data is consistent with literature: M. Zheng, P. Chen, W. Wu, H. Jiang, *Chem. Comm.*, 2016, **52**, 1, 84-87.^[171]



4-(6-methylpyridin-2-yl)benzonitrile (4u)

From the diethyl succinate sulfone: Following general procedure **G**, diethyl 2-((6-methylpyridin-2-yl)sulfonyl)succinate (98.8 mg, 0.30 mmol, 1.5 equiv.), 4-bromobenzonitrile (36.4 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (55.2 mg, 0.40 mmol, 2.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (5 – 10% EtOAc in Petrol) to give the title compound as a white solid (39.0 mg, 99%).

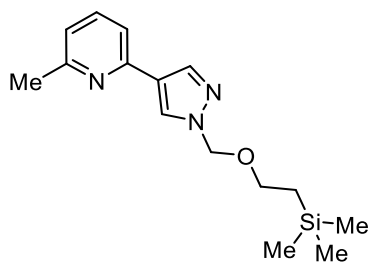
¹H NMR (400 MHz, CDCl₃) δ 8.11 (d, J = 8.5 Hz, 2H, Ar-H), 7.75 (d, J = 8.5 Hz, 2H, Ar-H), 7.69 (t, J = 8.0 Hz, 1H, Ar-H), 7.56 (d, J = 8.0 Hz, 1H, Ar-H), 7.18 (d, J = 7.5 Hz, 1H, Ar-H), 2.64 (s, 3H, Ar-CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 159.1, 154.8, 144.0, 137.3, 132.7, 127.7, 123.0, 119.1, 118.2, 112.3, 24.9; **LRMS** (ESI⁺) m/z 195.0 ([M+H]⁺); **HRMS** (ESI⁺) found m/z 195.0918 [M+H]⁺, C₁₃H₁₁N₂ requires m/z 195.0917; **IR** ν_{max} (neat)/cm⁻¹ 3057, 2927, 2854, 2229, 1591, 1455, 1160, 851, 792; **mp** 76 – 80 °C (CH₂Cl₂); **R_f** = 0.20 (10% EtOAc in Petrol). Data is consistent with literature: K. Cooper, M. J. Fray, M. J. Parry, K. Richardson and J. Steele, *J. Med. Chem.* 1992, **35**, 17, 3115-3129.^[172]



2-methoxy-5-(6-methylpyridin-2-yl)pyrimidine (4v)

From the β -nitrile sulfone: Following general procedure **F**, 3-((6-methylpyridin-2-yl)sulfonyl)propanenitrile (46.3 mg, 0.22 mmol, 1.1 equiv.), 5-bromo-2-methoxypyrimidine (37.8 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (30% EtOAc in Petrol) to give the title product as a white, crystalline solid (34.0 mg, 84%).

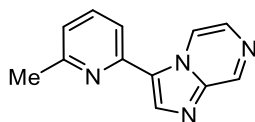
¹H NMR (400 MHz, CDCl₃) δ 9.10 (s, 2H, Pyrim-*H*), 7.66 (t, *J* = 8.0 Hz, 1H, Pyr-*H*), 7.45 (d, *J* = 8.0 Hz, 1H, Pyr-*H*), 7.14 (d, *J* = 8.0 Hz, 1H, Pyr-*H*), 4.08 (s, 3H, OCH₃), 2.61 (s, 3H, CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 165.9, 159.3, 158.0, 151.9, 137.3, 127.1, 122.5, 116.8, 55.3, 24.8; **LRMS** (ESI⁺) *m/z* 202.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 202.0975 [M+H]⁺, C₁₁H₁₂ON₃ requires *m/z* 202.0975; **IR** ν_{max} (neat)/cm⁻¹ 3017, 2956, 2924, 2854, 2472, 2349, 2163, 1992, 1728, 1653, 1575, 1479, 1455, 1359, 1336, 1315, 1280, 1241, 1440, 1192, 1170, 1108, 1037, 1025, 996, 960, 899, 875, 830, 804, 744; **mp** 79 – 81 °C (EtOAc); **R_f** = 0.14 (30% EtOAc in Petrol).



2-methyl-6-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-4-yl)pyridine (4x)

From the β -nitrile sulfone: Following general procedure F, 3-((6-methylpyridin-2-yl)sulfonyl)propanenitrile (46.3 mg, 0.22 mmol, 1.1 equiv.), 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (55.5 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (25% EtOAc in Petrol) to give the title product as a colourless oil (42.0 mg, 73%). *When run at 120 °C, the reaction gave the title product in 10% yield (5.8 mg).*

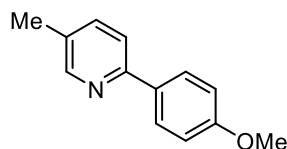
¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, J = 1.0 Hz, 1H, Pyraz-*H*), 8.00 (d, J = 1.0 Hz, 1H, Pyraz-*H*), 7.54 (t, J = 8.0 Hz, 1H, Pyr-*H*), 7.28 (d, J = 7.5 Hz, 1H, Pyr-*H*), 6.97 (d, J = 7.5 Hz, 1H, Pyr-*H*), 5.45 (s, 2H, NCH₂O), 3.62 – 3.55 (m, 2H, OCH₂), 2.55 (s, 3H, CH₃-Pyr), 0.95 – 0.89 (m, 2H, CH₂TMS), -0.03 (s, 9H, TMS); **¹³C NMR** (101 MHz, CDCl₃) δ 158.6, 151.2, 138.3, 136.9, 128.2, 125.1, 121.0, 116.8, 80.6, 67.0, 24.8, 18.0, -1.3; **LRMS** (ESI⁺) m/z 290.2 [M+H]⁺; **HRMS** (ESI⁺) found m/z 290.1687 [M+H]⁺, C₁₅H₂₄ON₃²⁸Si requires m/z 290.1683; **IR** ν_{max} (neat)/cm⁻¹ 2953, 2360, 1599, 1578, 1562, 1458, 1430, 1249, 1214, 1178, 1096, 978, 916, 859, 837, 791, 754, 694, 668; **R_f** = 0.25 (20% EtOAc in Petrol).



3-(6-methylpyridin-2-yl)imidazo[1,2-a]pyrazine (4y)

From the β -nitrile sulfone: Following general procedure **F**, 3-((6-methylpyridin-2-yl)sulfonyl)propanenitrile (46.3 mg, 0.22 mmol, 1.1 equiv.), 2-bromoimidazo[1,2-a]pyrazine (39.6 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (40 – 60% EtOAc in CH₂Cl₂) to give the title product as a white solid (39.8 mg, 94%).

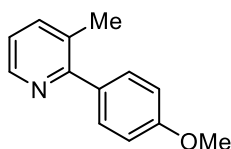
¹H NMR (400 MHz, CDCl₃) δ 9.85 (dd, J = 4.5, 1.5 Hz, 1H, Ar-*H*), 9.18 (d, J = 1.5 Hz, 1H), 8.26 (s, 1H, Ar-*H*), 8.02 (d, J = 4.5 Hz, 1H, Ar-*H*), 7.69 (t, J = 8.0 Hz, 1H, Pyr-*H*, Ar-*H*), 7.60 (d, J = 8.0 Hz, 1H, Pyr-*H*), 7.11 (d, J = 8.0 Hz, 1H, Pyr-*H*), 2.67 (s, 3H, CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 158.2, 148.9, 144.0, 142.3, 137.2, 135.7, 130.4, 124.9, 121.5, 120.7, 118.1, 24.7; **HRMS** (ESI⁺) found m/z 211.0979 [M+H]⁺, C₁₂H₁₁N₄ requires m/z 211.0978; **IR** ν_{max} (neat)/cm⁻¹ 3095, 2915, 2361, 1726, 1583, 1530, 1481, 1310, 1448, 1171, 1044, 847, 798; **mp** 130 – 132 °C (EtOAc); **R_f** = 0.09 (80% EtOAc in Petrol).



2-(4-methoxyphenyl)-5-methylpyridine (4z)

From the β -nitrile sulfone: Following general procedure F, 3-((5-methylpyridin-2-yl)sulfonyl)propanenitrile (46.3 mg, 0.22 mmol, 1.1 equiv.), 4-bromoanisole (25.0 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (8% EtOAc in Petrol) to give the title product as an off-white solid (30.8 mg, 77%). *When run at 130 °C, the reaction gave the title product in 86% yield (34.3 mg)*

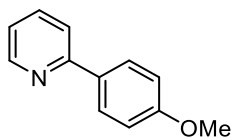
¹H NMR (400 MHz, CDCl₃) δ 8.48 – 8.46 (m, 1H, Pyr-*H*), 7.92 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.57 (dd, *J* = 8.0, 0.5 Hz, 1H, Pyr-*H*), 7.52 (ddd, *J* = 8.0, 2.5, 0.5 Hz, 1H, Pyr-*H*), 6.99 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 3.86 (s, 3H, OCH₃), 2.35 (s, 3H, CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 160.3, 154.7, 150.1, 137.4, 132.3, 130.9, 128.0, 119.4, 114.2, 55.5, 18.3; **LRMS** (ESI⁺) *m/z* 200.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 200.1071 [M+H]⁺, C₁₃H₁₄ON requires *m/z* 200.1071; **IR** ν_{max} (neat)/cm⁻¹ 3000, 2924, 2836, 2361, 1609, 1584, 1562, 1515, 1477, 1441, 1418, 1377, 1307, 1273, 1246, 1225, 1174, 1143, 1109, 1047, 1026, 848, 820, 791, 757, 750, 719, 668, 643; **mp** 53 – 55 °C (EtOAc); **R_f** = 0.10 (5% EtOAc in Petrol). Data is consistent with literature: C. Liu, W. Yang, *Chem. Comm.* 2009, **41**, 6267-6269.^[173]



2-(4-methoxyphenyl)-3-methylpyridine (4aa)

From the β -nitrile sulfone: Following general procedure **F**, 3-((3-methylpyridin-2-yl)sulfonyl)propanenitrile (46.3 mg, 0.22 mmol, 1.1 equiv.), 4-bromoanisole (25 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.) and AcOH (11.4 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (15% EtOAc in Petrol) to give the title compound as a colourless oil (37.7 mg, 95%). *When run at 120 °C, the reaction gave the title product in a 37% yield (15.0 mg).*

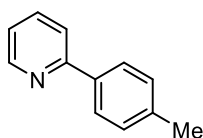
¹H NMR (400 MHz, CDCl₃) δ 8.51 (dd, J = 5.0, 1.5 Hz, 1H, Pyr-*H*), 7.55 (ddd, J = 8.0, 1.5, 1.0 Hz, 1H, Pyr-*H*), 7.49 (d, J = 8.5 Hz, 2H, Ar-*H*), 7.14 (dd, J = 8.0, 5.0 Hz, 1H, Pyr-*H*), 6.98 (d, J = 8.5 Hz, 2H, Ar-*H*), 3.86 (s, 3H, CO₂Me), 2.37 (s, 3H, Pyr-Me); **¹³C NMR** (101 MHz, CDCl₃) δ 159.5, 158.5, 147.1, 138.7, 133.3, 130.8, 130.4, 121.8, 113.7, 55.5, 20.4; **LRMS** (ESI⁺) m/z 200.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 200.1072 [M+H]⁺, C₁₃H₁₄ON requires m/z 200.1070; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 3047, 2957, 2933, 2915, 2836, 2361, 2341, 1610, 1580, 1514, 1460, 1442, 1422, 1302, 1246, 1176, 1109, 1043, 1025, 838, 791, 773; **R_f** = 0.14 (10% EtOAc in Petrol). Data is consistent with literature: W. Lin, J. Tang, S. Li, X. Zheng, M. Yuan, B. Xu, W. Jiang, H. Fu, R. Li, H. Chen, *Org. Lett.* 2020, 22, 20, 7814–7819.^[174]



2-(4-methoxyphenyl)pyridine (4ab)

From the β -nitrile sulfone: Following general procedure **F**, 3-(pyridin-2-ylsulfonyl)propanenitrile (43.2 mg, 0.22 mmol, 1.1 equiv.), 4-bromoanisole (25 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (12% EtOAc in Petrol) to give the title product as an off-white crystalline solid (27.3 mg, 74%).

¹H NMR (400 MHz, CDCl₃) δ 8.65 (ddd, J = 5.0, 2.0, 1.0 Hz, 1H, Pyr-*H*), 7.96 (d, J = 9.0 Hz, 2H, Ar-*H*), 7.71 (ddd, J = 8.0, 7.0, 2.0 Hz, 1H, Pyr-*H*), 7.66 (dt, J = 8.0, 1.0 Hz, 1H, Pyr-*H*), 7.17 (ddd, J = 7.0, 5.0, 1.0 Hz, 1H, Pyr-*H*), 7.00 (d, J = 9.0 Hz, 2H, Ar-*H*), 3.86 (s, 3H, OCH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 160.6, 157.3, 149.7, 136.8, 132.2, 128.3, 121.5, 119.9, 114.2, 55.5; **LRMS** (ESI⁺) m/z 186.1 [M+H]⁺; **HRMS** (ESI⁺) found m/z 186.0913 [M+H]⁺, C₁₂H₁₂ON requires m/z 186.0913; **IR** ν_{max} (neat)/ cm⁻¹ 2359, 2255, 2160, 2035, 1971, 1598, 1514, 1465, 1383, 1310, 1252, 1178; **mp** 49 – 51 °C (EtOAc); **R_f** = 0.27 (20% EtOAc in Petrol). Data is consistent with literature: T. Markovic, B. N. Roche, D. C. Blakemore, V. Mascitti and M. C. Willis, *Chem. Sci.*, 2017, **8**, 4437-4442.^[11]



2-(p-tolyl)pyridine (4ac)

From the β -nitrile sulfone: Following general procedure **F**, 3-(pyridin-2-ylsulfonyl)propanenitrile (43.2 mg, 0.22 mmol, 1.1 equiv.), 4-bromotoluene (34.2 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (6% EtOAc in Petrol) to give the title product as a colourless oil (28.0 mg, 83%). *When run at 120 °C, the reaction gave the title product in a 52% yield (17.6 mg)*

From the β -methylester sulfone: Following a stoichiometrically *modified* version of general procedure **F**, methyl 3-(pyridin-2-ylsulfonyl)propanoate (68.8 mg, 0.30 mmol, 1.5 equiv.), 4-bromotoluene (34.2 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.), AcOH (17.2 μ L, 0.30 mmol, 1.5 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (6% EtOAc in Petrol) to give the title product as a colourless oil (30.7 mg, 91%).

Following general procedure **G**, methyl 3-(pyridin-2-ylsulfonyl)propanoate (68.8 mg, 0.30 mmol, 1.5 equiv.), 4-bromotoluene (34.2 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene (2.0 mL) were heated at 130 °C

for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (6% EtOAc in Petrol) to give the title product as a colourless oil (9.7 mg, 29%).

Following general procedure **F**, methyl 3-(pyridin-2-ylsulfonyl)propanoate (50.4 mg, 0.22 mmol, 1.1 equiv.), 4-bromotoluene (34.2 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.02 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (6% EtOAc in Petrol) to give the title product as a colourless oil (22.6 mg, 67%). *When run at 130 °C, the reaction gave the title product in a 40% yield (13.5 mg).*

From the diethyl 2-(pyridin-2-ylsulfonyl)succinate (8a): Following general procedure **G**, diethyl 2-(pyridin-2-ylsulfonyl)succinate (94.6 mg, 0.30 mmol, 1.5 equiv.), 4-bromotoluene (34.2 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (6% EtOAc in Petrol) to give the title product as a colourless oil (32.4 mg, 96%). *When run at 120 °C, the reaction gave the title product in a 29% yield (9.8 mg)*

From the ethyl 3-phenyl-3-(pyridin-2-ylsulfonyl)propanoate (9): Following general procedure **G**, ethyl 3-phenyl-3-(pyridin-2-ylsulfonyl)propanoate (95.3 mg, 0.30 mmol, 1.5 equiv.), 4-bromotoluene (34.2 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 10 mol%) in toluene (2 mL) were heated at 130 °C for 18 h. Once cooled, the reaction mixture was

concentrated *in vacuo*. The crude was purified by flash column chromatography on silica gel (6% EtOAc in Petrol) to give the title product as a colourless oil (7.6 mg, 22%).

34% yield obtained using modified general procedure F; 30% yield obtained when anisole is used as a solvent instead of toluene.

From the ethyl 3-(pyridin-2-ylsulfonyl)butanoate (10): Following general procedure **G**, ethyl 3-(pyridin-2-ylsulfonyl)butanoate (77.2 mg, 0.30 mmol, 1.5 equiv.), 4-bromotoluene (34.2 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 5 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 10 mol%) in toluene (2 mL) were heated at 130 °C for 18 h. Once cooled, the reaction mixture was concentrated *in vacuo*. The crude was purified by flash column chromatography on silica gel (6% EtOAc in Petrol) to give the title product as a colourless oil (12.5 mg, 37%).

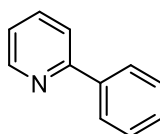
25% yield obtained when DMF is used as a solvent instead of toluene; 26% yield obtained with an acetic acid additive (1.5 equiv.).

From the 1-methyl-3-(pyridin-2-ylsulfonyl)pyrrolidine-2,5-dione (11): Following general procedure **G**, 1-methyl-3-(pyridin-2-ylsulfonyl)pyrrolidine-2,5-dione (76.3 mg, 0.30 mmol, 1.5 equiv.), 4-bromotoluene (34.2 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 5 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 10 mol%) in toluene (2 mL) were heated at 130 °C for 18 h. Once cooled, the reaction mixture was concentrated *in vacuo*. The crude was purified by flash column chromatography on silica gel (6% EtOAc in Petrol) to give the title product as a colourless oil (2.1 mg, 6%).

15% yield obtained when anisole is used as a solvent instead of toluene.

¹H NMR (400 MHz, CDCl₃) δ 8.69 – 8.67 (m, 1H, Pyr- *H*), 7.90 (d, *J* = 8.0 Hz, 2H, Tol- *H*), 7.75 – 7.67 (m, 2H, Pyr- *H*), 7.28 (d, *J* = 8.0 Hz, 2H, Tol- *H*), 7.20 (ddd, *J* = 6.5, 5.0,

2.0 Hz, 1H, Pyr-*H*), 2.41 (s, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 157.6, 149.7, 139.1, 136.8 (2C), 129.6, 126.9, 121.9, 120.4, 21.4; LRMS (ESI^+) m/z 170.0 $[\text{M}+\text{H}]^+$; HRMS (ESI^+) found m/z 170.0964 $[\text{M}+\text{H}]^+$, $\text{C}_{12}\text{H}_{12}\text{N}$ requires m/z 170.0964; IR ν_{max} (neat)/ cm^{-1} 3009, 2921, 2862, 2361, 2340, 1735, 1614, 1588, 1563, 1515, 1466, 1433, 1299, 1266, 1185, 1154, 1109, 1059, 1038, 1017, 989, 830, 773, 743, 722, 707, 678, 643, 621; R_f = 0.43 (20% EtOAc in Petrol). Data is consistent with literature: T. Markovic, B. N. Roche, D. C. Blakemore, V. Mascitti and M. C. Willis, *Chem. Sci.*, 2017, **8**, 4437-4442.^[11]



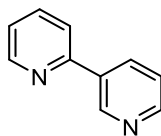
2-phenylpyridine (4ad)

From the β -nitrile sulfone: Following general procedure F, 3-(pyridin-2-ylsulfonyl)propanenitrile (43.2 mg, 0.22 mmol, 1.1 equiv.), bromobenzene (21 μL , 0.20 mmol, 1.0 equiv.), $\text{Pd}(\text{OAc})_2$ (2.2 mg, 0.010 mmol, 5.0 mol%), K_2CO_3 (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μL , 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 130 $^\circ\text{C}$ for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (8% EtOAc in Petrol) to give the title product as a colourless oil (18.4 mg, 59%).

^1H NMR (400 MHz, CDCl_3) δ 8.72 – 8.68 (m, 1H, Pyr-*H*), 8.01 – 7.97 (m, 2H, Pyr-), 7.78 – 7.71 (m, 2H, Ar-*H*), 7.52 – 7.38 (m, 3H, Ar-*H*), 7.23 (ddd, J = 6.5, 5.0, 2.0 Hz, 1H, Pyr-*H*); ^{13}C NMR (101 MHz, CDCl_3) δ 157.6, 149.8, 139.5, 136.9, 129.1, 128.9, 127.0, 122.2, 120.7; LRMS (ESI^+) m/z 156.0 $[\text{M}+\text{H}]^+$; HRMS (ESI^+) found m/z 156.0807 $[\text{M}+\text{H}]^+$, $\text{C}_{11}\text{H}_{10}\text{N}$ requires m/z 156.0808; IR ν_{max} (neat)/ cm^{-1} 3058, 3008, 2923, 2363, 2335, 1970, 1584, 1499, 1469, 1448, 1424, 1325, 1295, 1266, 1151, 1123, 1073, 990,

922, 799, 745, 694; R_f = 0.31 (20% EtOAc in Petrol). Data is consistent with literature:

J. Wei, H. Liang, C. Ni, R. Sheng, J. Hu, *Org. Lett.*, 2019, **21**, 4, 937-940.^[83]

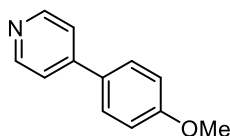


2,3'-bipyridine (4af)

From the β -nitrile sulfone: Following general procedure **F**, 3-(pyridin-2-ylsulfonyl)propanenitrile (43.2 mg, 0.22 mmol, 1.1 equiv.), 3-bromopyridine (19.3 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The reaction mixture was filtered through a silica plug, washing with copious EtOAc and MeOH, before being concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (75% EtOAc in Petrol) to give the title product as a pale yellow oil (28.9 mg, 93%). *When run at 120 °C, the reaction gave the title product in a 44% yield (13.7 mg).*

From the β -methylester sulfone: Following general procedure **G**, methyl 3-(pyridin-2-ylsulfonyl)propanoate (68.8 mg, 0.30 mmol, 1.5 equiv.), 3-bromopyridine (19.3 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (75% EtOAc in Petrol) to give the title product as a pale yellow oil (25.4 mg, 81%). *When run at 120 °C, the reaction gave the title product in a 36% yield (11.2 mg).*

¹H NMR (400 MHz, CDCl₃) δ 9.19 (d, *J* = 2.5 Hz, 1H, Pyr-*H*), 8.72 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H, Pyr-*H*), 8.65 (dd, *J* = 5.0, 2.0 Hz, 1H, Pyr-*H*), 8.32 (ddd, *J* = 8.0, 1.5, 2.0 Hz, 1H, Pyr-*H*), 7.82 – 7.72 (m, 2H, Pyr-*H*), 7.40 (dd, *J* = 8.0, 5.0 Hz, 1H, Pyr-*H*), 7.29 (ddd, *J* = 7.0, 5.0, 1.5 Hz, 1H, Pyr-*H*); **¹³C NMR** (101 MHz, CDCl₃) δ 154.9, 150.1, 150.0, 148.3, 137.1, 135.0, 134.4, 123.7, 122.9, 120.7; **LRMS** (ESI⁺) *m/z* 157.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 157.0761 [M+H]⁺, C₁₀H₉N₂ requires *m/z* 157.0760; **IR** *v*_{max} (neat)/cm⁻¹ 3053, 2928, 1588, 1461, 1433, 1407, 1334, 1285, 1192, 1156, 1097, 1068, 1050, 1017, 990, 823, 772, 744, 708, 654, 615; **R_f** = 0.15 (80% EtOAc in Petrol). Data consistent with literature: T. Markovic, B. N. Rocke, D. C. Blakemore, V. Mascitti and M. C. Willis, *Chem. Sci.*, 2017, **8**, 4437-4442.^[11]



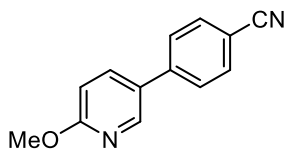
4-(4-methoxyphenyl)pyridine (4ag)

From the β-nitrile sulfone: Following general procedure **F**, 3-(pyridin-4-ylsulfonyl)propanenitrile (43.2 mg, 0.22 mmol, 1.1 equiv.), 4-bromoanisole (25 μL, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μL, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (35% EtOAc in Petrol) to give the title product as a white crystalline solid (18.3 mg, 49%).

From the β-methylester sulfone: Following general procedure **G**, methyl 3-(pyridin-4-ylsulfonyl)propanoate (68.8 mg, 0.30 mmol, 1.5 equiv.), 4-bromoanisole (25 μL, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene

(2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (35% EtOAc in Petrol) to give the title product as a white solid (33.0 mg, 89%).

¹H NMR (400 MHz, CDCl₃) δ 8.62 (dd, *J* = 4.0, 2.0 Hz, 2H, Pyr-*H*), 7.60 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.47 (dd, *J* = 4.5, 1.5 Hz, 2H, Pyr-*H*), 7.01 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 3.87 (s, 3H, OCH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 160.7, 150.3, 147.9, 130.5, 128.3, 121.2, 114.7, 55.5; **LRMS** (ESI⁺) *m/z* 186.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 186.0915 [M+H]⁺, C₁₂H₁₂ON requires *m/z* 186.0913; **IR** ν_{max} (neat)/cm⁻¹ 3080, 3023, 2965, 2927, 2846, 2360, 1738, 1605, 1579, 1542, 1523, 1489, 1287, 1257, 1228, 1094, 1035, 809; **mp** 74 – 76 °C (EtOAc); **R_f** = 0.15 (40% EtOAc in Petrol). Data is consistent with literature: T. Markovic, B. N. Rocke, D. C. Blakemore, V. Mascitti and M. C. Willis, *Chem. Sci.*, 2017, **8**, 4437-4442.^[11]

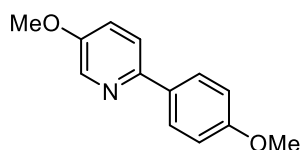


4-(6-methoxypyridin-3-yl)benzonitrile (4ah)

From the β-nitrile sulfone: Following general procedure F, 3-((6-methoxypyridin-3-yl)sulfonyl)propanenitrile (49.8 mg, 0.22 mmol, 1.1 equiv.), 4-bromobenzonitrile (36.4 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μL, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (4-5% EtOAc in Petrol) to give the title product as a white solid (40.1 mg, 95%).

From the β -methylester sulfone: Following general procedure **G**, methyl 3-((6-methoxypyridin-3-yl)sulfonyl)propanoate (77.8 mg, 0.30 mmol, 1.5 equiv.), 4-bromobenzonitrile (36.4 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (7% EtOAc in Petrol) to give the title product as a white solid (27.8 mg, 66%).

¹H NMR (400 MHz, CDCl₃) δ 8.40 (dd, J = 2.5, 1.0 Hz, 1H, Pyr-*H*), 7.79 (dd, J = 8.5, 2.65 Hz, 1H, Pyr-*H*), 7.75 – 7.71 (m, 2H, Ar-*H*), 7.65 – 7.60 (m, 2H, Ar-*H*), 6.85 (dd, J = 8.5, 1.0 Hz, 1H, Pyr-*H*), 3.99 (s, 3H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 164.6, 145.6, 142.6, 137.4, 132.9, 128.2, 127.2, 118.9, 111.5, 111.1, 53.9; LRMS (ESI⁺) m/z 211.3 [M+H]⁺; HRMS (ESI⁺) found m/z 211.0867 [M+H]⁺, C₁₃ H₁₁ON₂ requires m/z 211.0866; IR ν_{max} (neat)/cm⁻¹ 2943, 2359, 2224, 1604, 1573, 1483, 1430, 1416, 1372, 1288, 1251, 1175, 1142, 1042, 1042, 1017, 999, 934, 821, 664; mp 113 – 115 °C (EtOAc); R_f = 0.16 (5% EtOAc in Petrol). Data is consistent with literature: N. A. Isley, F. Gallou and B. H. Lipshutz, 2013, **135**, 17707-17710.^[175]

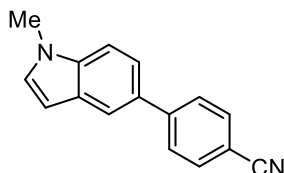


5-methoxy-2-(4-methoxyphenyl)pyridine (4ai)

From the β -methylester sulfone: Following general procedure **G**, methyl 3-((5-methoxypyridin-2-yl)sulfonyl)propanoate (77.8 mg, 0.30 mmol, 1.5 equiv.), 4-bromoanisole (25 μ L, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (55.3 mg, 0.40 mmol,

2.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (15% EtOAc in Petrol) to give the title compound as a crystalline white solid (26.5 mg, 62%). *When run at 120 °C, the reaction gave the title product in a 37% yield (16.0 mg).*

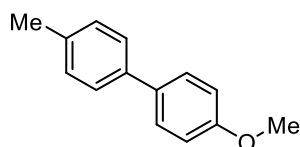
¹H NMR (400 MHz, CDCl₃) δ 8.35 (dd, *J* = 3.0, 1.0 Hz, 1H, Pyr-*H*), 7.86 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.59 (dd, *J* = 8.5, 1.0 Hz, 1H, Pyr-*H*), 7.24 (dd, *J* = 8.5, 3.0 Hz, 1H, Pyr-*H*), 6.98 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 3.88 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 160.0, 154.5, 150.1, 136.97, 132.0, 127.7, 121.6, 120.2, 114.2, 55.8, 55.5; **LRMS** (ESI⁺) *m/z* 216.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 216.1019 [M+H]⁺, C₁₃H₁₄NO₂ requires *m/z* 216.1019; **IR** *v*_{max} (neat)/cm⁻¹ 2964, 2942, 2841, 1607, 1480, 1262, 1247, 1181, 1050, 1016, 757; **mp** 111 – 115 °C (CH₂Cl₂); **R_f** = 0.27 (20% EtOAc in Petrol).



4-(1-methyl-1H-indol-5-yl)benzonitrile (4aj)

From the β-nitrile sulfone: Following general procedure F, 3-((1-methyl-1H-indol-5-yl)sulfonyl)propanenitrile (54.6 mg, 0.22 mmol, 1.1 equiv.), 4-benzonitrile (36.4 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.) and AcOH (11.4 μL, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (5% EtOAc in Petrol) to give the title compound as an off-white solid (29.4 mg, 63%).

¹H NMR (400 MHz, CDCl₃) δ 7.86 (dd, *J* = 2.0, 1.0 Hz, 1H, Indole-*H*), 7.77 – 7.69 (m, 4H, Ar-*H*), 7.47 (dd, *J* = 8.5, 2.0 Hz, 1H, Indole-*H*), 7.41 (dt, *J* = 8.5, 1.0 Hz, 1H, Indole-*H*), 7.12 (d, *J* = 3.0 Hz, 1H, Indole-*H*), 6.56 (dd, *J* = 3.0, 1.0 Hz, 1H, Indole-*H*), 3.84 (s, 3H, N-*Me*); **¹³C NMR** (101 MHz, CDCl₃) δ 147.3, 137.0, 132.6, 130.8, 130.2, 129.2, 127.9, 121.2, 120.0, 119.5, 110.0, 109.8, 101.8, 33.1; **LRMS** (ESI⁺) *m/z* 233.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 233.1073 [M+H]⁺, C₁₆H₁₃N₂ requires *m/z* 233.1073; **IR** *v*_{max} (neat)/cm⁻¹ 2960, 2927, 2359, 2343, 2225, 1712, 1600, 1513, 1335, 1172, 1160, 807, 799, 763, 734, 723; **mp** 185 – 187 °C (EtOAc); **R_f** = 0.25 (8% EtOAc in Petrol).



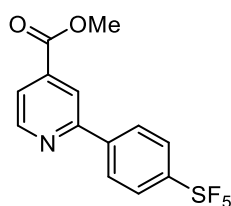
4-methoxy-4'-methyl-1,1'-biphenyl (4al)

From the β-nitrile sulfone: Following general procedure **F**, 3-tosylpropanenitrile (46.0 mg, 0.22 mmol, 1.1 equiv.), 4-bromoanisole (25 μL, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (41.4 mg, 0.30 mmol, 1.5 equiv.), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and AcOH (11.5 μL, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (0-1% EtOAc in Petrol) to give the title product as a white solid (25.3 mg, 64%).

From the β-methylester sulfone: Following general procedure **G**, methyl 3-tosylpropanoate (72.7 mg, 0.30 mmol, 1.5 equiv.), 4-bromoanisole (25 μL, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column

chromatography on silica gel (0-1% EtOAc in Petrol) to give the title product as a white solid (25.4 mg, 64%). *When run at 120 °C, the reaction gave the title product in a 43% yield (17.0 mg).*

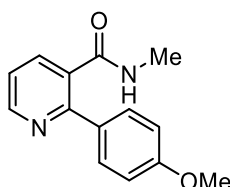
¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.46 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.23 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.98 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 3.85 (s, 3H, Ar-OCH₃), 2.39 (s, 3H, Ar-CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 159.1, 138.1, 136.5, 133.9, 129.6, 128.1, 126.7, 114.3, 55.5, 21.1; **HRMS** (APCI) found *m/z* 199.1121 [M+H]⁺, C₁₄H₁₅O requires *m/z* 199.1117; **IR** *v*_{max} (neat)/ cm⁻¹ 2926, 2839, 1609, 1401, 1290, 1247, 1177, 1040, 906, 842, 808, 129, 650; **mp** 96 – 98 °C (EtOAc); **R_f** = 0.37 (1% EtOAc in Petrol). Data is consistent with literature: C. Fricke, G. J. Sherborne, I. Funes-Ardoiz, E. Senol, S. Guven and F. Schoenebeck, *Angew. Chem. Int. Ed.*, 2019, **58**, 17788-17795. [176]



methyl 2-(4-(pentafluoro-16-sulfaneyl)phenyl)isonicotinate (4aq)

From the β-methylester sulfone: Following general procedure **G**, methyl 2-((3-methoxy-3-oxopropyl)sulfonyl)isonicotinate (86.2 mg, 0.30 mmol, 1.5 equiv.), 4-bromophenylsulfurpentoxide (56.6 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (1 – 5% EtOAc in Petrol) to give the title product as a white crystalline solid (54.6 mg, 80%).

¹H NMR (500 MHz, CD₃CN) δ 9.23 (dd, *J* = 2.0, 1.0 Hz, 1H, Pyr-*H*), 8.40 (dd, *J* = 8.5, 2.0 Hz, 1H, Pyr-*H*), 8.27 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 8.04 (dd, *J* = 8.5, 1.0 Hz, 1H, Pyr-*H*), 7.97 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 3.93 (s, 3H, CO₂Me); **¹³C NMR** (126 MHz, CD₃CN) δ 166.3, 158.9, 155.1 (p, *J* = 17.0 Hz), 151.6, 142.5, 139.1, 128.8, 127.4 (p, *J* = 4.5 Hz), 126.5, 121.7, 53.0; **¹⁹F NMR** (470 MHz, CD₃CN) δ 83.93 (p, *J* = 147.5 Hz), 62.18 (d, *J* = 147.5 Hz); **LRMS** (ESI⁺) *m/z* 340.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 340.0424 [M+H]⁺, C₁₃H₁₁NO₂SF₅ requires *m/z* 340.0425; **IR** ν_{max} (neat)/cm⁻¹ 2361, 1716, 1594, 1439, 1302, 1121, 1101, 1022, 976, 830, 783, 764, 739, 665; **mp** 138 – 140 °C (EtOAc); **R_f** = 0.18 (2% EtOAc in Petrol).

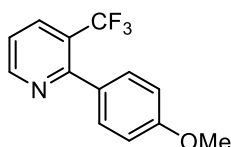


2-(4-methoxyphenyl)-N-methylnicotinamide (4ar)

From the β-methylester sulfone: Following general procedure **G**, methyl 3-((3-(methylcarbamoyl)pyridin-2-yl)sulfonyl)propanoate (85.9 mg, 0.30 mmol, 1.5 equiv.), 4-bromoanisole (25.0 μL, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (90-100% EtOAc in Petrol) to give the title compound as a colourless oil that crystallised to a white solid on standing (46.0 mg, 95%).

¹H NMR (400 MHz, CDCl₃) δ 8.59 (dd, *J* = 5.0, 2.0 Hz, 1H, Pyr-*H*), 7.87 (dd, *J* = 8.0, 2.0 Hz, 1H, Pyr-*H*), 7.59 – 7.50 (m, 2H, Ar-*H*), 7.22 (dd, *J* = 8.0, 5.0 Hz, 1H, Pyr-*H*),

6.98 – 6.88 (m, 2H, Ar-*H*), 5.70 (br. q, $J = 5.0$ Hz, 1H, CONH), 3.82 (s, 3H, OMe), 2.70 (d, $J = 5.0$ Hz, 3H, NHMe); ^{13}C NMR (101 MHz, CDCl_3) δ 169.5, 160.6, 155.5, 150.5, 137.3, 131.4, 131.0, 130.4, 121.6, 114.1, 55.5, 26.9; **LRMS** (ESI^+) m/z 243.0 $[\text{M}+\text{H}]^+$; **HRMS** (ESI^+) found m/z 243.1129 $[\text{M}+\text{H}]^+$, $\text{C}_{14}\text{H}_{15}\text{O}_2\text{N}_2$ requires m/z 243.1128; **IR** ν_{max} (neat)/ cm^{-1} 3061, 3047, 2936, 2454, 2360, 1634, 1609, 1466, 1253, 1178, 1148, 1107, 1041, 841, 782,; **mp** 136 – 138 °C (EtOAc); **R_f** = 0.14 (100% EtOAc in Petrol).

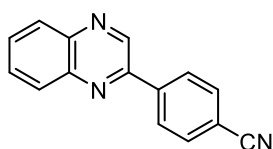


2-(4-methoxyphenyl)-3-(trifluoromethyl)pyridine (4as)

From the β -methylester sulfone: Following general procedure **G**, methyl 3-((3-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoate (89.2 mg, 0.30 mmol, 1.5 equiv.), 4-bromoanisole (25 μL , 0.20 mmol, 1.0 equiv.), $\text{Pd}(\text{OAc})_2$ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K_2CO_3 (55.2 mg, 0.40 mmol, 2.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (10% EtOAc in Petrol) to give the title compound as a pale yellow oil (50.1 mg, 99%).

^1H NMR (400 MHz, CDCl_3) δ 8.81 (d, $J = 5.0$ Hz, 1H, Pyr-*H*), 8.05 (d, $J = 8.0$ Hz, 1H, Pyr-*H*), 7.48 (d, $J = 8.5$ Hz, 2H, Ar-*H*), 7.36 (dd, $J = 8.0, 5.0$ Hz, 1H, Pyr-*H*), 6.98 (d, $J = 8.5$ Hz, 2H, Ar-*H*), 3.86 (s, 3H, OMe); ^{13}C NMR (101 MHz, CDCl_3) δ 160.3, 158.3 (d, $^4J_{\text{C-F}} = 2.0$ Hz), 151.9, 135.0 (q, $^3J_{\text{C-F}} = 5.0$ Hz), 131.9, 130.3 (q, $^4J_{\text{C-F}} = 2.0$ Hz), 124.8 (q, $^2J_{\text{C-F}} = 31.5$ Hz), 123.9 (q, $^1J_{\text{C-F}} = 273.0$ Hz), 121.4, 113.6, 55.4; ^{19}F NMR (377 MHz, CDCl_3) δ -57.41 (s); **LRMS** (ESI^+) m/z 254.0 $[\text{M}+\text{H}]^+$; **HRMS** (ESI^+) found m/z 254.0787 $[\text{M}+\text{H}]^+$, $\text{C}_{13}\text{H}_{11}\text{NOF}_3$ requires m/z 254.0787; **IR** ν_{max} (neat)/ cm^{-1} 3056, 3002,

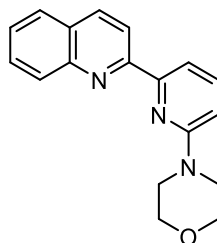
2961, 2934, 2917, 2840, 2359, 2340, 1609, 1588, 1580, 1566, 1515, 1437, 1320, 1301, 1250, 1226, 1161, 1111, 1089, 1043, 1026, 836, 814, 780, 716; **R_f** = 0.20 (10% EtOAc in Petrol). Data is consistent with literature: X. Lin, C. Hou, H. Li, Z. Weng, *Chem. Eur. J.* 2016, **22**, 2075-2084.^[177]



4-(quinoxalin-2-yl)benzonitrile (4at)

From the β -methylester sulfone: Following general procedure **G**, methyl 3-(quinoxalin-2-ylsulfonyl)propanoate (84.1 mg, 0.30 mmol, 1.5 equiv.), 4-bromobenzonitrile (36.4 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (15% EtOAc in Petrol) to give the title compound as a white solid (34.9 mg, 75%).

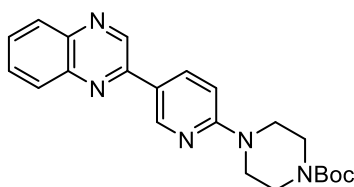
¹H NMR (400 MHz, CDCl₃) δ 9.36 (s, 1H, Quinox-*H*), 8.86 – 8.83 (m, 2H, Ar-*H*), 8.20 – 8.14 (m, 2H, Quinox-*H*), 7.90 – 7.85 (m, 2H, Ar-*H*), 7.85 – 7.81 (m, 2H, Quinox-*H*); **¹³C NMR** (101 MHz, CDCl₃) δ 149.7, 142.9, 142.4, 142.3, 141.0, 133.0, 131.0, 130.7, 130.0, 129.4, 128.2, 118.6, 113.9; **LRMS** (ESI⁺) *m/z* 232.0 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 232.0871 [M+H]⁺, C₁₅H₁₀N₃ requires *m/z* 232.0869; **IR** ν_{max} (neat)/ cm⁻¹ 2925, 2210, 1600, 1558, 1503, 1482, 1458, 1015, 1360, 1315, 1267, 1213, 1167, 1143, 1090, 1048, 1020, 959, 844, 765, 733, 669, 657; **mp** 178 – 180 °C (EtOAc); **R_f** = 0.27 (30% EtOAc in Petrol). Data is consistent with literature: A. Y. Dubovtsev, D. V. Dar'in, V. Y. Kukushkin, *J. Org. Chem.* 2020, **85**, 751.^[178]



4-(6-(quinolin-2-yl)pyridin-2-yl)morpholine (4au)

From the β -methylester sulfone: Following general procedure **G**, methyl 3-(quinolin-2-ylsulfonyl)propanoate (83.8 mg, 0.30 mmol, 1.5 equiv.), 2-bromo-6-morpholinopyridine (48.6 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (10% EtOAc in Petrol) to give the title product as a white solid (53.0 mg, 91%).

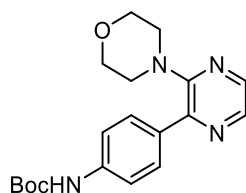
¹H NMR (400 MHz, CDCl₃) δ 8.53 (d, J = 8.5 Hz, 1H, Ar-*H*), 8.23 (d, J = 8.5 Hz, 1H, Ar-*H*), 8.16 (d, J = 8.5 Hz, 1H, Ar-*H*), 8.07 (d, J = 7.5 Hz, 1H, Ar-*H*), 7.84 (dd, J = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.75 – 7.68 (m, 2H, Ar-*H*), 7.53 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H, Ar-*H*), 6.74 (d, J = 8.5 Hz, 1H, Ar-*H*), 3.93 – 3.87 (m, 4H, (CH₂)₂), 3.68 – 3.62 (m, 4H, (CH₂)₂); **¹³C NMR** (101 MHz, CDCl₃) δ 159.2, 156.9, 154.4, 148.0, 138.7, 136.5, 129.9, 129.5, 128.3, 127.7, 126.6, 119.2, 111.9, 107.5, 67.0, 45.8; **HRMS** (ESI⁺) found m/z 292.1444 [M+H]⁺, C₁₈H₁₈ON₃ requires m/z 292.1444; **IR** ν_{max} (neat)/cm⁻¹ 3059, 2852, 2360, 2341, 1735, 1591, 1567, 1466, 1447, 1123, 984, 801, 786; **mp** 112 – 114 °C (EtOAc); **R_f** = 0.23 (20% EtOAc in Petrol).



tert-butyl 4-(5-(quinoxalin-2-yl)pyridin-2-yl)piperazine-1-carboxylate (4av)

From the β -methylester sulfone: Following general procedure **G**, methyl 3-(quinoxalin-2-ylsulfonyl)propanoate (84.1 mg, 0.30 mmol, 1.5 equiv.), tert-butyl 4-(5-bromopyridin-2-yl)piperazine-1-carboxylate (68.4 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (25% EtOAc in Petrol) to give the title compound as a yellow solid (45.9 mg, 59%).

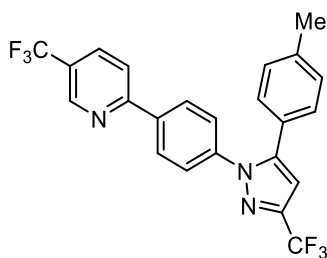
¹H NMR (400 MHz, CDCl₃) δ 9.25 (s, 1H, Ar-*H*), 9.00 (dd, *J* = 2.5, 1.0 Hz, 1H, Pyr-*H*), 8.38 (dd, *J* = 9.0, 2.5 Hz, 1H, Pyr-*H*), 8.07 (dt, *J* = 8.0, 2.0 Hz, 2H, Ar-*H*), 7.74 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Ar-*H*), 7.68 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Ar-*H*), 6.78 (dd, *J* = 9.0, 1.0 Hz, 1H, Pyr-*H*), 3.74 – 3.56 (m, 8H, N(CH₂)₂(CH₂)₂), 1.49 (s, 9H, C(CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃) δ 159.6, 154.9, 150.0, 147.6, 142.6, 142.5, 141.3, 136.6, 130.4, 129.3, 129.2, 129.0, 122.2, 107.0, 80.2, 44.8, 28.6; **LRMS** (ESI⁺) *m/z* 336.2 [M-CH₂C(CH₃)₂+H]⁺; **HRMS** (ESI⁺) found *m/z* 392.2081 [M+H]⁺, C₂₂H₂₆O₂N₅ requires *m/z* 392.2081; **IR** ν_{max} (neat)/cm⁻¹ 2975, 2928, 2856, 1686, 1604, 1420, 1241, 1172, 765; **mp** 105 – 107°C (EtOAc); **R_f** = 0.35 (50% EtOAc in Petrol).



tert-butyl (4-(3-morpholinopyrazin-2-yl)phenyl)carbamate (4aw)

From the β -methylester sulfone: Following general procedure **G**, methyl 3-((3-morpholinopyrazin-2-yl)sulfonyl)propanoate (94.6 mg, 0.30 mmol, 1.5 equiv.), *tert*-butyl (4-bromophenyl)carbamate (54.4 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (30% EtOAc in Petrol with 1% Et₃N) to give the title product as an off-white crystalline solid (71.2 mg, 99%).

¹H NMR (400 MHz, CDCl₃) δ 8.16 (d, J = 2.5 Hz, 1H, Pyrazine-*H*), 8.07 (d, J = 2.5 Hz, 1H, Pyrazine-*H*), 7.90 (d, J = 9.0 Hz, 2H, Ar-*H*), 7.46 (d, J = 9.0 Hz, 2H, Ar-*H*), 6.58 (br. s, 1H, NH), 3.72 – 3.68 (m, 4H), 3.19 – 3.15 (m, 4H), 1.54 (s, 9H, COO(CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃) δ 155.6, 152.7, 144.5, 139.4, 139.2, 136.4, 133.7, 128.6, 118.4, 80.8, 66.7, 49.0, 28.5; **LRMS** (ESI⁺) m/z 357.2 (20%, [M+H]⁺), 301.1 (80%, [(M-H₂C=C(CH₃)₂)+H]⁺); **HRMS** (ESI⁺) found m/z 357.19220 [M+H]⁺, C₁₉H₂₅N₄O₃ requires m/z 357.19212; **IR** ν_{max} (neat)/ cm⁻¹ 3305, 2975, 2854, 2360, 2341, 1727, 1594, 1520, 1419, 1367, 1314, 1265, 1241, 1159, 1117, 1053, 941, 839, 732, 641; **mp** 80 – 82 °C (EtOAc); **R_f** = 0.24 (40% EtOAc).

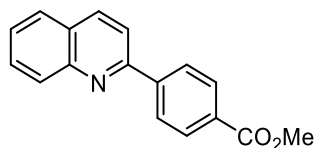


2-(4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-5-(trifluoromethyl)pyridine (4ay)

From the β -methylester sulfone: Following general procedure **G**, methyl 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoate (89.2 mg, 0.30 mmol, 1.5 equiv.), 1-(4-bromophenyl)-5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazole (76.2 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) and cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography on silica gel (5% EtOAc in Petrol) to give the title product as a white solid (73.4 mg, 83%).

¹H NMR (400 MHz, CDCl₃) δ 8.94 (app. dt, J = 2.5, 1.0 Hz, 1H, Pyr-*H*), 8.05 (d, J = 8.5 Hz, 2H, Ar-*H*), 8.00 (dd, J = 2.5, 8.0 Hz, 1H, Pyr-*H*), 7.85 (d, J = 8.5 Hz, 1H, Pyr-*H*), 7.47 (d, J = 8.5 Hz, 2H), 7.15 (br. s, 4H, Ar-*H*), 6.75 (s, 1H, Pyrazole-*H*), 2.36 (s, 3H, Ar-CH₃); **¹H NMR** (400 MHz, CD₃CN) δ 8.94 (dq, J = 2.5, 1.0 Hz, 1H, Pyr-*H*), 8.14 – 8.08 (m, 3H, Ar-*H* and Pyr-*H*), 7.99 (dt, J = 8.5, 1.0 Hz, 1H, Pyr-*H*), 7.43 (d, J = 9.0 Hz, 2H, Ar-*H*), 7.23 – 7.13 (m, 4H, Ar-*H*), 6.90 (s, 1H, Pyrazole-*H*), 2.31 (s, 3H, Ar-CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 159.4 (q, J_{C-F} = 2.0 Hz), 146.8 (q, J_{C-F} = 4.0 Hz), 145.1, 143.7 (q, J_{C-F} = 33.0 Hz), 140.8, 139.5, 137.7, 134.2 (q, J_{C-F} = 3.5 Hz), 129.7, 128.9, 128.1, 126.3, 125.8, 125.4 (q, J_{C-F} = 38.5 Hz), 123.9 (q, J_{C-F} = 271.5 Hz), 121.4 (q, J_{C-F} = 268.5 Hz), 120.2, 105.9 (q, J_{C-F} = 2.0 Hz), 21.4; **¹⁹F NMR** (377 MHz, CD₃CN) δ -62.72 (s), -62.86 (s); **HRMS** (ESI⁺) found m/z 448.1241 [M+H]⁺, C₂₃H₁₆N₃F₆ requires

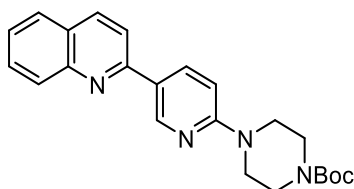
m/z 448.1243; **IR** $\nu_{\max}$ (neat)/ cm^{-1} 2926, 2361, 1603, 1472, 1329, 1236, 1163, 1130, 1014, 976, 834, 806; **mp** 98 – 100 °C (EtOAc); **R_f** = 0.22 (5% EtOAc in Petrol).



methyl 4-(quinolin-2-yl)benzoate (4az)

From the diethyl succinate sulfone: Following general procedure **G**, diethyl 2-(quinolin-2-ylsulfonyl)succinate (109.6 mg, 0.30 mmol, 1.5 equiv.), methyl 4-bromobenzoate (43.0 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) in toluene (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (3-5% EtOAc in Petrol) to give the title compound as a crystalline white solid (50.4 mg, 96%).

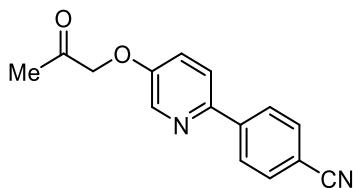
¹H NMR (400 MHz, CDCl₃) δ 8.29 – 8.23 (m, 3H, Ar-*H*), 8.23 – 8.17 (m, 3H, Ar-*H*), 7.91 (d, J = 8.5 Hz, 1H, Ar-*H*), 7.85 (dd, J = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.76 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H, Ar-*H*), 7.56 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H, Ar-*H*), 3.96 (s, 3H, CO₂Me); **¹³C NMR** (101 MHz, CDCl₃) δ 167.1, 156.2, 148.3, 143.8, 137.2, 130.8, 130.3, 130.1, 129.9, 127.7 (2C), 127.6, 127.0, 119.1, 52.4; **LRMS** m/z 264.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 264.1018 [M+H]⁺, C₁₇H₁₄O₂N requires m/z 264.1019; **IR** $\nu_{\max}$ (neat)/ cm^{-1} 2947, 1717, 1606, 1595, 1575, 1514, 1495, 1439, 1312, 1275, 1244, 1211, 1194, 1125, 1107, 1051, 1016, 940, 855, 825, 775; **mp** 148 – 150 °C (EtOAc); **R_f** = 0.23 (5% EtOAc in Petrol). Data is consistent with literature: S. Y. Lee and C-H. Cheon, *J. Org. Chem.*, 2018, **83**, 13036-13044.^[179]



tert-butyl 4-(5-(quinolin-2-yl)pyridin-2-yl)piperazine-1-carboxylate (4ba)

From the diethyl succinate sulfone: Following general procedure **G**, diethyl 2-(quinolin-2-ylsulfonyl)succinate (109.6 mg, 0.30 mmol, 1.5 equiv.), 4-Boc-1-(5-bromo-2-pyridyl)piperazine (68.5 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) in toluene (2.0) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (20% EtOAc in Petrol) to give the title compound as a pale yellow solid (37.8 mg, 48%).

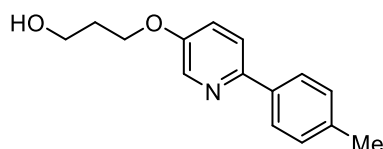
¹H NMR (400 MHz, CDCl₃) δ 8.94 (d, *J* = 2.5 Hz, 1H, Pyr-*H*), 8.42 (dd, *J* = 9.0, 2.5 Hz, 1H, Pyr-*H*), 8.15 (d, *J* = 8.5 Hz, 1H, Quin-*H*), 8.10 (d, *J* = 8.5 Hz, 1H, Quin-*H*), 7.82 – 7.75 (m, 2H, 2 × Quin-*H*), 7.69 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Quin-*H*), 7.48 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Quin-*H*), 6.77 (d, *J* = 9.0 Hz, 1H, Pyr-*H*), 3.68 – 3.55 (m 8H, 2 × N(CH₂)₂), 1.49 (s, 9H, C(CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃) δ 159.4, 155.2, 154.9, 148.4, 147.5, 136.9, 136.8, 129.8, 129.4, 127.6, 127.0, 126.0, 125.1, 117.9, 106.9, 80.2, 45.1, 28.6 (piperazine carbon environments appear at the same chemical shift); **LRMS** *m/z* 391.2 (60%, [M+H]⁺), 355.2 (40%, [M-C₄H₈+H]⁺); **HRMS** (ESI⁺) found *m/z* 391.2126 [M+H]⁺, C₂₃H₂₇O₂N₄ requires *m/z* 391.2129; **IR** ν_{max} (neat)/cm⁻¹ 2977, 2858, 1677, 1596, 1496, 1430, 1239, 1172, 933, 813, 731; **mp** 128 – 130 °C (EtOAc); **R_f** = 0.27 (30% EtOAc in Petrol)



4-(5-(2-oxopropoxy)pyridin-2-yl)benzonitrile (4bb)

From the β -methylester sulfone: Following general procedure **G**, methyl 3-((5-(2-oxopropoxy)pyridin-2-yl)sulfonyl)propanoate (45.2 mg, 0.15 mmol, 1.5 equiv.), 4-bromobenzonitrile (18.2 mg, 0.10 mmol, 1.0 equiv.), Pd(OAc)₂ (1.1 mg, 5.0 μ mol, 5.0 mol%), cataCXium A (3.6 mg, 0.010 mmol, 10 mol%) and K₂CO₃ (27.6 mg, 0.20 mmol, 2.0 equiv.) in toluene (1.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (35% EtOAc in Petrol) to give the title compound as a white solid (10.5 mg, 42%).

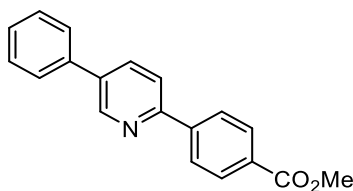
¹H NMR (400 MHz, CDCl₃) δ 8.42 (d, J = 3.0 Hz, 1H, Pyr-*H*), 8.07 – 8.03 (m, 2H, Ar-*H*), 7.75 – 7.70 (m, 3H, Ar-*H* and Pyr-*H*), 7.29 – 7.25 (dd, J = 8.5, 3.0 Hz, 1H, Pyr-*H*), 4.68 (s, 2H, CH₂O), 2.32 (s, 3H, COMe); **¹³C NMR** (101 MHz, CDCl₃) δ 203.7, 154.1, 148.8, 143.0, 138.3, 132.7, 127.0, 122.1, 121.5, 119.0, 112.0, 73.2, 26.7; **LRMS** m/z 253.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 253.0972 [M+H]⁺, C₁₅H₁₃O₂N₂ requires m/z 253.0972; **IR** ν_{max} (neat)/cm⁻¹ 2226, 1734, 1577, 1485, 1470, 1279, 1245, 1222, 1175, 1075, 823; **mp** 92 – 94 °C (EtOAc); **R_f** = 0.27 (50% EtOAc in Petrol).



3-((6-(p-tolyl)pyridin-3-yl)oxy)propan-1-ol (4bc)

From the β -methylester sulfone: Following general procedure **G**, methyl 3-((5-(3-hydroxypropoxy)pyridin-2-yl)sulfonyl)propanoate (91.0 mg, 0.30 mmol, 1.5 equiv.), 4-bromotoluene (34.0 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (96.7 mg, 0.70 mmol, 3.5 equiv.) in toluene: DMSO (1:1) (2.0 mL) were heated at 130 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (40% EtOAc in n-pentane) to give the title compound as a white solid (29.4 mg, 60%).

¹H NMR (400 MHz, CDCl₃) δ 8.39 (d, J = 3.0 Hz, 1H, Pyr-*H*), 7.83 (d, J = 8.5 Hz, 2H, Ar-*H*), 7.66 (d, J = 9.0 Hz, 1H, Ar-*H*), 7.33 (dd, J = 9.0, 3.0 Hz, 1H, Pyr-*H*), 7.29 – 7.26 (m, 2H, Ar-*H*), 4.22 (t, J = 6.0 Hz, 2H, CH₂O), 3.88 (t, J = 6.0 Hz, 2H, HOCH₂), 2.44 (br. s, 1H, OH), 2.39 (s, 3H, Ar-Me), 2.08 (p, J = 6.0 Hz, 2H, HOCH₂CH₂); **¹³C NMR** (101 MHz, CDCl₃) δ 154.1, 150.3, 138.3, 137.3, 136.3, 129.6, 126.4, 122.2, 120.8, 65.9, 59.7, 32.1, 21.3; **LRMS** (ESI⁺) m/z 244.2 [M+H]⁺; **HRMS** (ESI⁺) found m/z 244.1337 [M+H]⁺, C₁₅H₁₈O₂N requires m/z 244.1332; **IR** ν_{max} (neat)/cm⁻¹ 3356, 3026, 2926, 2878, 2360, 2340, 1469, 1276, 1220, 1059, 816; **mp** 72 – 74 °C (EtOAc); **R_f** = 0.24 (60% EtOAc in Petrol).

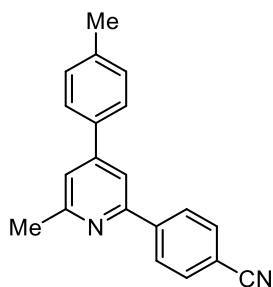


methyl 4-(5-phenylpyridin-2-yl)benzoate (14)

From the β -nitrile sulfone: Following general procedure **F**, 3-((5-phenylpyridin-2-yl)sulfonyl)propanenitrile (59.9 mg, 0.22 mmol, 1.1 equiv.), methyl 4-bromobenzoate (43.0 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%), K₂CO₃ (41.5 mg, 0.30 mmol, 1.5 equiv.) and AcOH (11.4 μ L, 0.20 mmol, 1.0 equiv.) in toluene (2.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (0 – 5% EtOAc in CH₂Cl₂) to give the title compound as a white crystalline solid (42.7 mg, 74%).

From the β -methylester sulfone: Following general procedure **G**, methyl 3-((5-phenylpyridin-2-yl)sulfonyl)propanoate (84.1 mg, 0.30 mmol, 1.5 equiv.), methyl 4-bromobenzoate (43.0 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) in toluene (2 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (0-5% EtOAc in CH₂Cl₂) to give the title compound as a white crystalline solid (55.2 mg, 95%).

¹H NMR (400 MHz, CDCl₃) δ 8.97 (d, J = 2.5, 1.0 Hz, 1H, PyrH), 8.19 – 8.11 (m, 4H, ArH), 8.00 (dd, J = 8.0, 2.5 Hz, 1H, PyrH), 7.88 (dd, J = 8.0, 1.0 Hz, 1H, PyrH), 7.67 – 7.63 (m, 2H, ArH), 7.54 – 7.48 (m, 2H, ArH), 7.46 – 7.41 (m, 1H, ArH), 3.96 (s, 3H, CO₂Me); **¹³C NMR** (101 MHz, CDCl₃) δ 167.1, 155.0, 148.5, 143.3, 137.5, 135.9, 135.4, 130.5, 130.3, 129.3, 128.4, 127.2, 126.9, 121.0, 52.4; **LRMS** (ESI⁺) m/z 290.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 290.1175 [M+H]⁺, C₁₉H₁₆O₂N requires m/z 290.1176; **IR** ν_{max} (neat)/cm⁻¹ 2949, 1719, 1607, 1556, 1471, 1438, 1407, 1371, 1312, 1280, 1194, 1181, 1111, 1014, 837, 763, 746, 698; **mp** 189 – 191 °C (EtOAc); **R_f** = 0.28 (100% CH₂Cl₂).



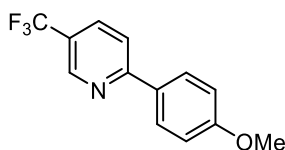
4-(6-methyl-4-(p-tolyl)pyridin-2-yl)benzonitrile (18)

From the β -methylester sulfone: Following general procedure **G**, methyl 3-((6-methyl-4-(p-tolyl)pyridin-2-yl)sulfonyl)propanoate (50.0 mg, 0.15 mmol, 1.5 equiv.), 4-bromobenzonitrile (18.2 mg, 0.10 mmol, 1.0 equiv.), Pd(OAc)₂ (1.1 mg, 5.0 μ mol, 5.0 mol%), cataCXium A (3.6 mg, 0.010 mmol, 10 mol%) and K₂CO₃ (27.6 mg, 0.20 mmol, 2.0 equiv.) in toluene (1.0 mL) were heated at 120 °C for 18 h. The crude reaction mixture was purified by flash column chromatography (3-5% EtOAc in Petrol) to give the title compound as a white solid (26.1 mg, 92%).

¹H NMR (400 MHz, CDCl₃) δ 8.16 (d, J = 8.5 Hz, 2H, Ar-*H*), 7.77 (d, J = 8.5 Hz, 2H, Ar-*H*), 7.74 (d, J = 1.5 Hz, 1H, Pyr-*H*), 7.58 (d, J = 8.0 Hz, 2H, Ar-*H*), 7.38 (d, J = 1.5 Hz, 1H, Pyr-*H*), 7.30 (d, J = 8.5 Hz, 2H, Ar-*H*), 2.69 (s, 3H, Pyr-*Me*), 2.43 (s, 3H, Ar-*Me*); **¹³C NMR** (101 MHz, CDCl₃) δ 159.4, 155.3, 149.9, 144.1, 139.5, 135.4, 132.6, 130.0, 127.8, 127.0, 120.9, 119.1, 116.4, 112.3, 24.9, 21.4; **LRMS** (ESI⁺) m/z 285.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 285.1383 [M+H]⁺, C₂₀H₁₇N₂ requires m/z 285.1386; **IR** ν_{max} (neat)/ cm⁻¹ 2923, 2362, 2226, 1734, 1601, 1548, 1507, 1457, 1389, 1114, 1019, 847, 815, 748, 626; **mp** 137 – 139 °C (EtOAc); **R_f** = 0.24 (5% EtOAc in Petrol).

6.2.3.e Scaled up desulfonative cross-coupling: Outside of a sealed reaction vessel

Note: Internal reaction temperature was measured using a customised K-type thermometer and thermocouple probe coated in PTFE. The probe was inserted through one of the necks of the multi-neck rbf (piercing through the suba-seal), to record to the temperature of the reaction solvent.



2-(4-methoxyphenyl)-5-(trifluoromethyl)pyridine (4a)

See above for characterisation data

From the β -nitrile sulfone:

On a 0.6 mmol scale:

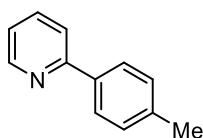
To an oven-dried two-neck round-bottom flask (25 mL) was added 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (237.8 mg, 0.90 mmol, 1.5 equiv.), Pd(OAc)₂ (6.7 mg, 0.030 mmol, 5.0 mol%), cataCXium A (21.5 mg, 0.060 mmol, 10 mol%) and K₂CO₃ (165.8 mg, 1.20 mmol, 2.0 equiv.). The flask was fitted with a condenser, sealed with a Suba-seal® and purged with N₂ for 30 mins. Degassed, dry anisole (6.0 mL, 0.1 M) was then added, followed by the addition of 4-bromoanisole (75.3 μ L, 0.60 mmol, 1.0 equiv.) and AcOH (51.5 μ L, 0.84 mmol, 1.5 equiv.) with stirring. The reaction mixture was then heated to 130 °C for 18 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The resultant crude residue was adsorbed onto celite and purified by flash column chromatography (3% EtOAc in Petrol) to give the title compound as a white solid (134.0 mg, 88%).

On a 1.0 mmol scale:

To an oven-dried two-neck round-bottom flask (50 mL) was added 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (396.3 mg, 1.5 mmol, 1.5 equiv.), Pd(OAc)₂ (11.2 mg, 0.050 mmol, 5.0 mol%), cataCXium A (35.8 mg, 0.10 mmol, 10 mol%) and K₂CO₃ (276.4 mg, 2.0 mmol, 2.0 equiv.). The flask was fitted with a condenser, sealed with a Suba-seal® and purged with N₂ for 30 mins. Degassed, dry anisole (10 mL, 0.1 M) was then added, followed by the addition of 4-bromoanisole (125.5 µL, 0.60 mmol, 1.0 equiv.) and AcOH (85.9 µL, 1.5 mmol, 1.5 equiv.) with stirring. The reaction mixture was then heated to 130 °C for 18 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The resultant crude residue was adsorbed onto celite and purified by flash column chromatography (3% EtOAc in Petrol) to give the title compound as a white solid (245.8 mg, 97%).

From the β-methylester sulfone:**On a 1.0 mmol scale:**

To an oven-dried two-neck round-bottom flask (50 mL) was added methyl 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoate (445.9 mg, 0.90 mmol, 1.5 equiv.), Pd(OAc)₂ (11.2 mg, 0.050 mmol, 5.0 mol%), cataCXium A (35.8 mg, 0.10 mmol, 10 mol%) and K₂CO₃ (276.4 mg, 2.0 mmol, 2.0 equiv.). The flask was fitted with a condenser, sealed with a Suba-seal® and purged with N₂ for 30 mins. Degassed, dry anisole (10 mL, 0.1 M) and 4-bromoanisole (125.5 µL, 0.60 mmol, 1.0 equiv.) were added with stirring. The reaction mixture was then heated to 130 °C for 18 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The resultant crude residue was adsorbed onto celite and purified by flash column chromatography (3% EtOAc in Petrol) to give the title compound as a white solid (221.8 mg, 88%).



2-(*p*-tolyl)pyridine (4ac)

See above for characterisation data

From the β -nitrile sulfone:

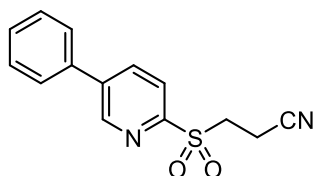
To an oven-dried two-neck round-bottom flask (50 mL) was added 3-(pyridin-2-ylsulfonyl)propanenitrile (294.3 mg, 1.5 mmol, 1.5 equiv.), 4-bromotoluene (171.0 mg, 1.0 mmol, 1.0 equiv.), Pd(OAc)₂ (11.2 mg, 0.050 mmol, 5.0 mol%), cataCXium A (35.8 mg, 0.10 mmol, 10 mol%) and K₂CO₃ (276.4 mg, 2.0 mmol, 2.0 equiv.). The flask was fitted with a condenser, sealed with a Suba-seal® and purged with N₂ for 30 mins. Degassed, dry anisole (10 mL, 0.1 M) was then added, followed by the addition of AcOH (85.9 μ L, 1.5 mmol, 1.5 equiv.) with stirring. The reaction mixture was then heated to 130 °C for 18 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The resultant crude residue was adsorbed onto celite and purified by flash column chromatography (5% EtOAc in Petrol) to give the title compound as a colourless oil (123.7 mg, 73%).

From the diethyl 2-(pyridin-2-ylsulfonyl)succinate:

To an oven-dried two-neck round-bottom flask (50 mL) was added diethyl 2-(pyridin-2-ylsulfonyl)succinate (473.0 mg, 1.5 mmol, 1.5 equiv.), 4-bromotoluene (171.0 mg, 1.0 mmol, 1.0 equiv.), Pd(OAc)₂ (11.2 mg, 0.050 mmol, 5.0 mol%), cataCXium A (35.8 mg, 0.10 mmol, 10 mol%) and K₂CO₃ (276.4 mg, 2.0 mmol, 2.0 equiv.). The flask was fitted with a condenser, sealed with a Suba-seal® and purged with N₂ for 30 mins. Degassed, dry anisole (10 mL, 0.1 M) was then added with stirring. The reaction mixture

was then heated to 130 °C for 18 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The resultant crude residue was adsorbed onto celite and purified by flash column chromatography (6% EtOAc in Petrol) to give the title compound as a white solid (88.0 mg, 52%).

6.2.3.f Derivatisations of the pyridine core of the masked sulfinate reagents



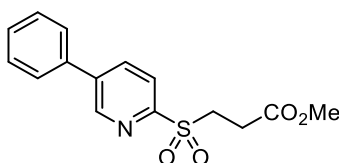
3-((5-phenylpyridin-2-yl)sulfonyl)propanenitrile (13a)

Following a modified Suzuki-Miyaura procedure reported by D. Hédou and A. S. Voisin-Chiret:^[110]

3-((5-Bromopyridin-2-yl)sulfonyl)propanenitrile (137.6 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (91.5 mg, 0.75 mmol, 1.5 equiv.), tris(dibenzylideneacetone)dipalladium(0) (22.9 mg, 0.025 mmol, 5.0 mol%), tetrabutylammonium bromide (TBAB, 16.1 mg, 0.05 mmol, 10 mol%) and tri(2-furyl)phosphine (tfp, 11.6 mg, 0.05 mmol, 10 mol%) were combined in a sealed tube and the reaction vessel was evacuated and flushed with N₂ three times. To the reaction mixture was then added THF (2.0 mL, 0.25 M) and K₂CO₃ (138.2 mg, 1.0 mmol, 2.0 equiv.) as a solution in water (0.5 mL). The reaction was heated to 40 °C for 18 h, before being cooled to rt and quenched with saturated aqueous NH₄Cl solution (5 mL). The product was then extracted with CH₂Cl₂ (2 × 10 mL), the organic layers combined and washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was then

purified through flash column chromatography on silica gel (12% EtOAc in toluene) to give the title compound as a white solid (98.3 mg, 72%).

¹H NMR (400 MHz, CDCl₃) δ 8.96 (t, J = 1.5 Hz, 1H, Pyr-*H*), 8.18 – 8.15 (m, 2H, overlapping Pyr-*H*), 7.65 – 7.60 (m, 2H, Ar-*H*), 7.58 – 7.49 (m, 3H, Ar-*H*), 3.76 (t, J = 7.5 Hz, 2H, SO₂CH₂), 2.99 (t, J = 7.5 Hz, 2H, CH₂CN); **¹³C NMR** (101 MHz, CDCl₃) δ 154.7, 149.1, 141.5, 136.6, 135.8, 129.8, 129.7, 127.7, 122.5, 116.2, 47.5, 12.3; **LRMS** (ESI⁺) m/z 273.0 (30%, [M+H]⁺), 295.0 (70%, [M+Na]⁺); **HRMS** (ESI⁺) found m/z 273.0692 [M+H]⁺, C₁₄H₁₃O₂N₂S requires m/z 273.0692; **IR** ν_{max} (neat)/ cm⁻¹ 3061, 2940, 2252, 1581, 1455, 1419, 1367, 1316, 1166, 1134, 1100, 1028, 1005, 953, 854, 811, 768, 748, 700, 672, 634; **mp** 108 – 110 °C (EtOAc); **R_f** = 0.23 (10% EtOAc in toluene).



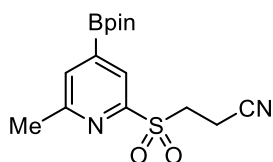
methyl 3-((5-phenylpyridin-2-yl)sulfonyl)propanoate (13b)

Following a modified Suzuki-Miyaura procedure reported by D. Hédou, A. S. Voisin-Chiret:^[110]

Methyl 3-((5-bromopyridin-2-yl)sulfonyl)propanoate (154.1 mg, 0.50 mmol, 1.0 equiv.), phenylboronic acid (91.5 mg, 0.75 mmol, 1.5 equiv.), tris(dibenzylideneacetone)dipalladium(0) (22.9 mg, 0.025 mmol, 5.0 mol%), tetrabutylammonium bromide (TBAB, 16.1 mg, 0.05 mmol, 10 mol%) and tri(2-furyl)phosphine (tfp, 11.6 mg, 0.05, 10 mol%) were combined in a sealed tube and the reaction vessel was evacuated and flushed with N₂ three times. To the reaction mixture was then added THF (2.0 mL, 0.25 M) and K₂CO₃ (138.2 mg, 1.00 mmol, 2.0 equiv.) as

a solution in water (0.5 mL). The reaction was heated to 40 °C for 22 h, before being cooled to rt and diluted with saturated aqueous NH₄Cl solution (5 mL). The product was then extracted with CH₂Cl₂ (2 × 10 mL), the organic layers combined and washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was then purified through flash column chromatography on silica gel (12% EtOAc in toluene) to give the title compound as a white solid (118.8 mg, 78%).

¹H NMR (400 MHz, CDCl₃) δ 8.95 (dd, *J* = 2.0, 1.0 Hz, 1H, Pyr-*H*), 8.15 (dd, *J* = 8.0, 1.0 Hz, 1H, Pyr-*H*), 8.13 (d, *J* = 2.0 Hz, 1H, Pyr-*H*), 7.63 – 7.60 (m, 2H, Ar-*H*), 7.57 – 7.46 (m, 3H, Ar-*H*), 3.77 (t, *J* = 7.5 Hz, 2H, SO₂CH₂), 3.70 (s, 3H, CO₂CH₃), 2.88 (t, *J* = 7.5 Hz, 2H, CH₂CO₂Me); **¹³C NMR** (101 MHz, CDCl₃) δ 170.7, 155.3, 148.9, 140.9, 136.3, 136.0, 129.62, 129.59, 127.6, 122.5, 52.5, 48.0, 27.6; **LRMS** (ESI⁺) *m/z* 328.0 [M+Na]⁺; **HRMS** (ESI⁺) found *m/z* 306.0794 [M+H]⁺, C₁₅H₁₆O₄NS requires *m/z* 306.0795; **IR** ν_{max} (neat)/ cm⁻¹ 3061, 2952, 1738, 1581, 1455, 1438, 1366, 1316, 1251, 1200, 1162, 1131, 1100, 1005, 853, 834, 768, 749, 699, 664; **mp** 102 – 104 °C (EtOAc); **R_f** = 0.18 (10% EtOAc in toluene).



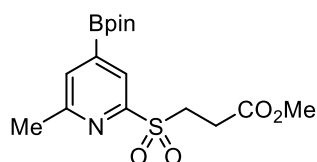
3-((6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)sulfonyl)propanenitrile (16a)

Following a modified Ir-catalysed borylation procedure reported by L. T. Pilarski and coworkers:^[111a]

Note: The B₂pin₂ was dried overnight under high vacuum at 60 °C before use.

To an oven-dried sealed tube equipped with a magnetic stirrer bar was added (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (8.3 mg, 0.0125 mmol, 2.5 mol%), B₂pin₂, (127 mg, 0.5 mmol, 1.0 equiv.) and 4,4'-Di-tert-butyl-2,2'-dipyridyl (dtbpy, 6.7 mg, 0.025 mmol, 5.0 mol%). The reaction vessel was evacuated under vacuum and flushed with N₂ (× 5) before the addition of anhydrous THF (2 mL). The reaction was stirred at rt for 30 mins (solution should go from a dark brown to a deep red colour). 3-((6-methylpyridin-2-yl)sulfonyl)propanenitrile (105 mg, 0.5 mmol, 1.0 equiv.) in a solution of THF (1.0 mL, 0.25 M) was added to the reaction mixture and reaction was heated to 60 °C for 18 h. The reaction was cooled to rt diluted with Et₂O and concentrated *in vacuo*. The crude product was then purified by triturating with minimal Et₂O and removing the solid impurities by filtering through filter paper (× 4). The residue was then dried overnight under vacuum at 60 °C to give the desired product as a pale orange oil (107.7 mg, 64%).

¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H, Pyr-*H*), 7.78 (s, 1H, Pyr-*H*), 3.69 (t, *J* = 8.0 Hz, 2H, SO₂CH₂), 2.92 (t, *J* = 8.0 Hz, 2H, CH₂CN), 2.65 (s, 3H, Pyr-CH₃), 1.35 (s, 12H, C(CH₃)₂C(CH₃)₂); **¹³C NMR** (101 MHz, CDCl₃) δ 159.9, 154.9, 133.5, 124.2, 116.3, 85.3, 47.1, 25.0, 24.2, 12.3; **HRMS** (ESI⁺) found *m/z* 337.1388 [M+H]⁺, C₁₅H₂₂O₄N₂BS requires *m/z* 337.1388; **mp** 90 – 92 °C (EtOAc); **IR** ν_{max} (neat)/ cm⁻¹ 2979, 2935, 2253, 1688, 1594, 1532, 1393, 1356, 1317, 1132, 911, 844; **R_F** = 0.10 (50% EtOAc in Petrol).



methyl 3-((6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)sulfonyl)propanoate (16b)

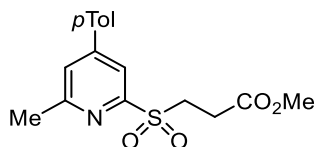
Following a modified Ir-catalysed borylation procedure reported by L. T. Pilarski and coworkers:^[111a]

Note: The B₂pin₂ was dried overnight under high vacuum at 60 °C before use.

To an oven-dried sealed tube equipped with a magnetic stirrer bar was added (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (8.3 mg, 0.0125 mmol, 2.5.0 mol%), B₂pin₂, (127 mg, 0.500 mmol, 1.0 equiv.) and 4,4'-di-tert-butyl-2,2'-dipyridyl (dtbpy, 6.7 mg, 0.0250 mmol, 5.0 mol%). The reaction vessel was evacuated under vacuum and flushed with N₂ (× 5) before the addition of THF (2 mL). The reaction was stirred at rt for 30 mins (solution should go from a dark brown to a deep red colour). Methyl 3-((6-methylpyridin-2-yl)sulfonyl)propanoate (121.6 mg, 0.500 mmol, 1.0 equiv.) in THF (1.0 mL, 0.5 M) was added to the reaction mixture and reaction was heated to 60 °C for 18 h. The reaction was cooled to rt, diluted with Et₂O and concentrated *in vacuo*. The crude product was then purified by triturating with minimal Et₂O and removing the solid impurities by filtering through filter paper (× 4). The residue was then dried overnight under vacuum at 60 °C to give the desired product as a pale orange oil (125.3 mg, 68%).

¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H, Pyr-*H*), 7.74 (s, 1H, Pyr-*H*), 3.72 – 3.66 (m, 5H, SO₂CH₂ and CO₂Me), 2.83 (t, *J* = 7.5 Hz, 2H, CH₂CO₂Me), 2.64 (s, 3H, Pyr-Me), 1.35 (s, 12H, C(CH₃)₂C(CH₃)₂); **¹³C NMR** (101 MHz, CDCl₃) δ 170.8, 159.7, 155.7, 133.0, 124.2, 85.2, 52.4, 47.6, 27.5, 25.0, 24.3; **HRMS** (ESI⁺) found *m/z* 369.1527

$[M+H]^+$, $C_{15}H_{25}O_6NBS$ requires m/z 369.1526; **IR** ν_{max} (neat)/ cm^{-1} 2979, 2954, 2361, 2342, 1741, 1593, 1533, 1436, 1393, 1373, 1128, 1060, 1019, 983, 965, 911, 898, 845, 827, 795, 742, 682; **R_f** = 0.16 (Spot drags off baseline - 80% EtOAc in Petrol).



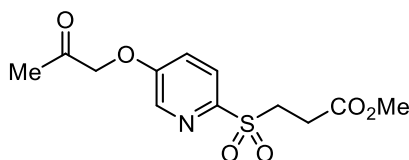
methyl 3-((6-methyl-4-(p-tolyl)pyridin-2-yl)sulfonyl)propanoate (17)

Following a modified Suzuki-Miyaura cross-coupling procedure reported by T. S.-B. Lou and M. C. Willis:^[112]

An oven-dried sealed tube containing 4-bromotoluene (34.2 mg, 0.20 mmol, 1.0 equiv.), methyl-3-((6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)sulfonyl) propanoate (110.8 mg, 0.30 mmol, 1.5 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 5.0 mol%) and XPhos (9.5 mg, 0.020 mmol, 10 mol%) was evacuated and backfilled with N_2 ($\times 5$). To the reaction vessel was added K_3PO_4 (84.9 mg, 0.40 mmol, 2.0 equiv.) as solution in water (400 μL) and then 1,4-dioxane (800 μL). The resulting bright orange suspension was heated at 70 $^{\circ}C$ for 18 h. The reaction mixture was then cooled to rt, diluted with EtOAc and anhydrous $MgSO_4$ was added directly. The reaction was filtered through a pad of celite (washing with EtOAc) and concentrated *in vacuo*. The crude residue was then purified by flash column chromatography (10% EtOAc in toluene) to give the title product as a cloudy colourless oil (41.3 mg, 62%).

1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 1.0 Hz, 1H, Ar-*H*), 7.61 – 7.53 (m, 3H, Ar-*H*), 7.31 (d, J = 8.0 Hz, 2H, Ar-*H*), 3.75 (t, J = 8.0 Hz, 2H, SO_2CH_2), 3.68 (s, 3H, CO_2CH_3), 2.87 (t, J = 8.0 Hz, 2H, CH_2CO_2Me), 2.68 (s, 3H, Pyr- CH_3), 2.42 (s, 3H, Ar- CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.8, 160.7, 156.8, 151.0, 140.5, 133.7, 130.2,

127.1, 124.7, 117.1, 52.4, 47.6, 27.5, 24.5, 21.4; **LRMS** (ESI⁺) *m/z* 356.0 [M+Na]⁺; **HRMS** (ESI⁺) found *m/z* 334.1102 [M+H]⁺, C₁₇H₂₀NO₄S requires *m/z* 334.1108; **IR** ν_{max} (neat)/cm⁻¹ 2953, 1740, 1599, 1537, 1518, 1437, 1388, 1313, 1250, 1163, 1120, 1020, 989, 908, 841, 817, 736, 719, 618; **R_f** = 0.25 (40% EtOAc in Petrol).



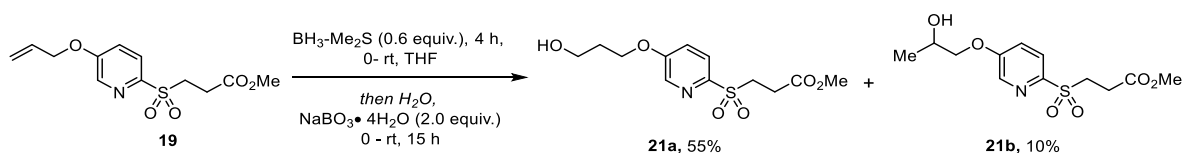
methyl 3-((5-(2-oxopropoxy)pyridin-2-yl)sulfonyl)propanoate (20)

Following a modified Wacker-like oxidation procedure reported by D. A. Chaudhari and R. A. Fernandes:^[180]

An oven-dried round bottom flask containing Pd(OAc)₂ (4.4 mg, 0.020 mmol, 10 mol%) and Dess-Martin periodinane (424.1 mg, 1.0 mmol, 5.0 equiv.) was purged with N₂ for 10 mins. Methyl 3-((5-(allyloxy)pyridin-2-yl)sulfonyl)propanoate (57.1 mg, 0.2 mmol, 1.0 equiv.) in MeCN (4.5 mL, 0.04 M) was added to the reaction vessel, followed by the addition of water (0.750 mL). The reaction was then heated to 50 °C for 18 h. On cooling to room temperature the reaction mixture was filtered through a pad of silica and washed with EtOAc. The filtrate was concentrated *in vacuo*, adsorbed onto celite and purified by flash column chromatography (60% EtOAc in Petrol) to give the title product as a clear oil that crystallised to a white solid on standing (26.4 mg, 44%).

¹H NMR (400 MHz, CDCl₃) δ 8.40 (dd, *J* = 3.0, 0.5 Hz, 1H, Pyr-*H*), 8.03 (dd, *J* = 8.5, 0.5 Hz, 1H, Pyr-*H*), 7.29 (dd, *J* = 8.5, 3.0 Hz, 1H, Pyr-*H*), 4.73 (s, 2H, CH₂OPyr), 3.70 – 3.64 (m, 5H, CO₂Me and SO₂CH₂), 2.85 – 2.80 (t, *J* = 8.0 Hz, 2H, CH₂CO₂Me), 2.32 (s, 3H, MeCO); **¹³C NMR** (101 MHz, CDCl₃) δ 202.1, 170.7, 156.9, 149.2, 139.3, 124.2, 121.5, 72.9, 52.5, 48.2, 27.6, 26.6; **LRMS** (ESI⁺) *m/z* 324.0 [M+Na]⁺; **HRMS** (ESI⁺)

found m/z 302.0691 $[M+H]^+$, $C_{12}H_{16}O_6NS$ requires m/z 302.0693; **IR** $\nu_{\max}$ (neat)/ cm^{-1} 2955, 2361, 1733, 1573, 1456, 1438, 1396, 1365, 1312, 1246, 1161, 1134, 1100, 1059, 1013, 977, 836, 754, 722; **mp** 62 – 64 °C (EtOAc); **R_f** = 0.23 (80% EtOAc in Petrol).



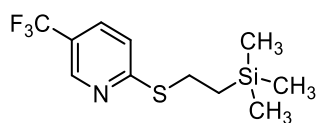
**methyl 3-((5-(3-hydroxypropoxy)pyridin-2-yl)sulfonyl)propanoate (21a) and
methyl 3-((5-(2-hydroxypropoxy)pyridin-2-yl)sulfonyl)propanoate (21b)**

Methyl 3-((5-(allyloxy)pyridin-2-yl)sulfonyl)propanoate (142.6 mg, 0.50 mmol, 1.00 equiv.) was dissolved in dry, degassed THF (2.5 mL, 0.2 M) under an argon atmosphere and the solution was cooled to 0 °C. Borane dimethyl sulfide complex solution (30.0 μ L, 0.32 mmol, 0.630 equiv.) was added dropwise to the stirring solution, after which the reaction mixture was allowed to warm to rt and stirred for 3.5 h. The reaction mixture was then cooled to 0 °C again and H_2O (2.0 mL) was added dropwise to the solution (gas release observed). Sodium perborate tetrahydrate (307.7 mg, 2.0 mmol, 4.0 equiv.) was then added in one portion, the reaction was allowed to warm to rt and stirred for 15 h. The reaction mixture was then diluted with EtOAc and the aqueous layer extracted with EtOAc (3 $\times$ 20 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography on silica gel (80% EtOAc in Petrol to 100% EtOAc) to give the anti-markovnikov product **21a** as a colourless oil (83.7 mg, 55%) and the markovnikov side product **21b** as a colourless oil (14.9 mg, 10%).

Anti-markovnikov product (21a): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.34 (dd, $J = 3.0, 0.5$ Hz, 1H, Pyr-*H*), 7.96 (dd, $J = 9.0, 0.5$ Hz, 1H, Pyr-*H*), 7.34 (dd, $J = 9.0, 3.0$ Hz, 1H, Pyr-*H*), 4.22 (t, $J = 6.0$ Hz, 2H, CH_2O), 3.82 (t, $J = 6.0$ Hz, 2H, HOCH_2), 3.65 (s, 3H, CO_2Me), 3.61 (t, $J = 8.5$ Hz, 2H, SO_2CH_2), 2.76 (t, $J = 8.5$ Hz, 2H, $\text{CH}_2\text{CO}_2\text{Me}$), 2.06 (p, $J = 6.0$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 170.7, 158.2, 147.8, 139.5, 124.3, 120.9, 66.1, 58.9, 52.4, 48.2, 31.7, 27.6; **LRMS** (ESI^+) m/z 326.0 $[\text{M}+\text{Na}]^+$; **HRMS** (ESI^+) found m/z 304.0849 $[\text{M}+\text{H}]^+$, $\text{C}_{12}\text{H}_{18}\text{O}_6\text{NS}$ requires m/z 304.0849; **IR** ν_{max} (neat)/ cm^{-1} 3519, 2953, 2361, 1736, 1572, 1453, 1366, 1309, 1278, 1250, 1201, 1160, 1131, 1098, 1054, 1013, 981, 949, 838, 753, 722, 670, 625; **R_f** = 0.23 (80% EtOAc in Petrol).

Markovnikov side- product (21b): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.41 (d, $J = 3.0$ Hz, 1H, Pyr-*H*), 8.03 (d, $J = 8.5$ Hz, 1H, Pyr-*H*), 7.37 (dd, $J = 8.5, 3.0$ Hz, 1H, Pyr-*H*), 4.26 (ddp, $J = 13.0, 6.5, 3.5$ Hz, 1H, MeCHOH), 4.06 (dd, $J = 9.5, 3.5$ Hz, 1H, CHCH_aH_b), 3.96 (dd, $J = 9.5, 7.5$ Hz, 1H, CHCH_aH_b), 3.70 – 3.63 (m, 5H, CO_2Me and SO_2CH_2), 2.81 (t, $J = 8.0$ Hz, 2H, $\text{CH}_2\text{CO}_2\text{Me}$), 1.34 (d, $J = 6.5$ Hz, 3H, MeCOH); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 170.7, 157.8, 148.6, 139.4, 124.2, 121.2, 74.2, 66.1, 52.5, 48.3, 27.6, 19.1; **LRMS** (ESI^+) m/z 326.0 $[\text{M}+\text{Na}]^+$; **HRMS** (ESI^+) found m/z 304.0849 $[\text{M}+\text{H}]^+$, $\text{C}_{12}\text{H}_{18}\text{O}_6\text{NS}$ requires m/z 304.0849; **IR** ν_{max} (neat)/ cm^{-1} 3501, 2953, 2360, 2341, 1738, 1573, 1450, 1368, 1315, 1280, 1252, 1201, 1162, 1133, 1099, 1062, 1021, 985, 934, 840, 800, 755, 724, 668, 625; **R_f** = 0.25 (80% EtOAc in Petrol).

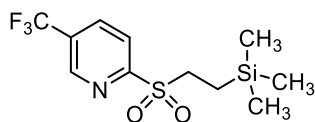
6.2.3.g Synthesis of fluoride-activated masked sulfinate reagent



5-(trifluoromethyl)-2-((2-(trimethylsilyl)ethyl)thio)pyridine (*pre-22*)

To a stirring solution of 5-(trifluoromethyl)pyridine-2-thiol (448 mg, 2.5 mmol, 1.0 equiv.) in THF (15.0 mL, 0.2 M) was added 2-(trimethylsilyl)ethan-1-ol (430 μ L, 3.0 mmol, 1.2 equiv.) and triphenyl phosphine (1.18 g, 4.5 mmol, 1.5 equiv.). The resultant bright yellow solution was cooled to 0 °C. Diisopropyl azodicarboxylate (DIAD) (886 μ L, 4.5 mmol, 1.5 equiv.) was added dropwise, causing a colour change from bright yellow to a colourless then pale yellow solution. The reaction mixture was then allowed to warm to rt overnight. After 16 h the reaction was stopped and adsorbed onto silica *in vacuo*. The yellow crude was purified by flash column chromatography (5% Et₂O in Petrol) to give the title compound as a clear and colourless oil (640 mg, 2.3 mmol, 92%).

¹H NMR (400 MHz, CDCl₃) δ 8.66 (dp, J = 3.0, 1.0 Hz, 1H, Ar-*H*), 7.70 – 7.60 (m, 1H, Ar-*H*), 7.22 (dt, J = 8.5, 1.0 Hz, 1H, Ar-*H*), 3.26 – 3.18 (m, 2H, SCH₂CH₂), 1.04 – 0.96 (m, 2H, SCH₂CH₂), 0.08 (s, 9H, Si(CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃) δ 165.5, 146.7 (q, $^3J_{C-F}$ = 4.3 Hz), 132.7 (q, $^3J_{C-F}$ = 3.5 Hz), 124.1 (q, $^1J_{C-F}$ = 271.0 Hz), 122.3 (q, $^2J_{C-F}$ = 34.4 Hz), 121.9, 26.9, 17.3, -1.31; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.1; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 2955, 1599, 1556, 1474, 1377, 1325, 1249, 1166, 1118, 1074, 1009, 858, 828, 747; **LRMS** (ESI) m/z 321.2 (100%, [M+MeCN+H]⁺); **HRMS** (ESI⁺) found m/z 280.07992 [M+H]⁺, C₁₁H₁₇NF₃SSi requires m/z 280.07976; **R_F** = 0.70 (20% Et₂O in Petrol).

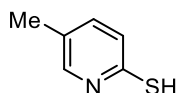


5-(trifluoromethyl)-2-((2-(trimethylsilyl)ethyl)sulfonyl)pyridine (22)

Open to atmospheric air: To a stirring solution of 5-(trifluoromethyl)-2-((2-(trimethylsilyl)ethyl)thio) pyridine (638 mg, 2.3 mmol, 1.0 equiv.) in EtOH (4.0 mL, 0.7 M) was added Na₂WO₄ (37.6 mg, 0.11 mmol, 0.05 equiv.). Then a solution of 30% hydrogen peroxide w/w water (1.16 mL, 11.4 mmol, 5.0 equiv.) was added slowly to form an off-white suspension. The reaction was stirred at r.t overnight and the formation of the sulfoxide and sulfone were monitored by TLC. After 16 h the reaction was quenched with three volumes of water relevant to solvent (12 mL) and stirred for 30 mins. On quenching, a white solid precipitated out of the reaction mixture. The solid was collected by filtration, washed with copious amounts of water, and dried *in vacuo* to give the title compound as a white solid (633.7 mg, 2.2 mmol, 89%).

¹H NMR (400 MHz, CDCl₃) δ 9.03 – 8.99 (m, 1H, Ar-*H*), 8.28 – 8.21 (m, 2H, Ar-*H*), 3.41 – 3.34 (m, 2H, SO₂CH₂), 0.97 – 0.90 (m, 2H, CH₂Si(CH₃)₃), 0.05 (s, 9H, Si(CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃) δ 160.5, 147.4 (d, ³*J*_{C-F} = 4.0 Hz), 135.8 (d, ³*J*_{C-F} = 3.7 Hz), 130.0 (q, ²*J*_{C-F} = 34.3 Hz), 122.6 (q, ¹*J*_{C-F} = 275.0), 122.4, 48.4, 8.4, -1.9; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.6; **LRMS** (ESI⁺) *m/z* 312.0 (100%, [M+H]⁺); **HRMS** (ESI⁺) found *m/z* 334.05165 [M+Na]⁺, C₁₁H₁₆O₂NF₃NaSSi requires *m/z* 334.05153; **IR** ν_{max} (neat)/ cm⁻¹ 3107m 3070, 2965, 2920, 2901, 1592, 1576, 1410, 1382 (SO₂), 1252 (Si(CH₃)₃), 1152 (SO₂); **mp** 115 – 116 °C (EtOH: H₂O); **R_F** = 0.45 (20% EtOAc in Petrol).

6.2.3.h Synthesis of miscellaneous building blocks



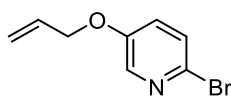
5-methylpyridine-2-thiol (49)

Following a modified procedure by Kanishchev *et.al.*:^[181]

Note: Due to the stench of Lawesson's reagent, it should be handled only inside a fumehood.

Under a N₂ atmosphere: 2-hydroxy-5-methylpyridine (1.09 g, 10.0 mmol, 1.7 equiv.) and Lawesson's reagent (6.50 g, 6.06 mmol, 1.0 equiv.) were combined in dry, degassed toluene (55 mL, 0.11 M). The resultant yellow suspension was stirred at reflux for 14 h. The reaction mixture was then transferred to a separating funnel containing aqueous NaOH solution (5.60 g in 60 mL H₂O). The aqueous layer was washed with Et₂O (30 mL). The organic layer was then discarded. The aqueous layer was then acidified with AcOH (45 mL). The aqueous layer was then washed with CH₂Cl₂ (3 × 25 mL). The organic layers were then combined and washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo* with additional toluene to remove all AcOH to give the crude title product as a bright yellow solid (442 mg, 35%). *The crude reaction product was used directly in the next step.*

¹H NMR (400 MHz, CDCl₃) δ 13.78 (s, 1H, SH), 7.48 (d, *J* = 9.0 Hz, 1H, Pyr-*H*), 7.42 (s, 1H, Pyr-*H*), 7.25 – 7.21 (m, 1H, Pyr-*H*), 2.18 (s, 3H, CH₃); **LRMS** (ESI⁺) *m/z* 126.1 [M+H]⁺. Data is consistent with the literature: O. S. Kanishchev and W. R. Dolbier, *Ang. Chem. Int. Ed.*, 2015, **54**, 280-284.^[181]



5-(allyloxy)-2-bromopyridine (50)

Following a modified allylation procedure reported J-X. Chen and coworkers:^[182]

Under a N₂ atmosphere: To a stirring solution of 6-bromopyridin-3-ol (348.0 mg, 2.0 mmol, 1.0 equiv.) in anhydrous DMF (4 mL, 2.0 M) was added NaH (60% in mineral oil, 88.0 mg, 2.2 mmol, 1.1 equiv.) at 0 °C. The resultant cloudy white suspension was allowed to warm to room temperature and stirred for 1 h. A solution of 3-bromoprop-1-ene (186 µL, 2.2 mmol, 1.1 equiv.) in DMF (1 mL) was added dropwise and the reaction heated to 70 °C for 1 h. The reaction was then cooled to rt and quenched with H₂O (2 mL). The aqueous layer was extracted with EtOAc, and the organic layer washed with brine (x3), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was then purified by flash column chromatography (5% EtOAc in Petrol) to give the title product as a colourless oil (359.1 mg, 84%).

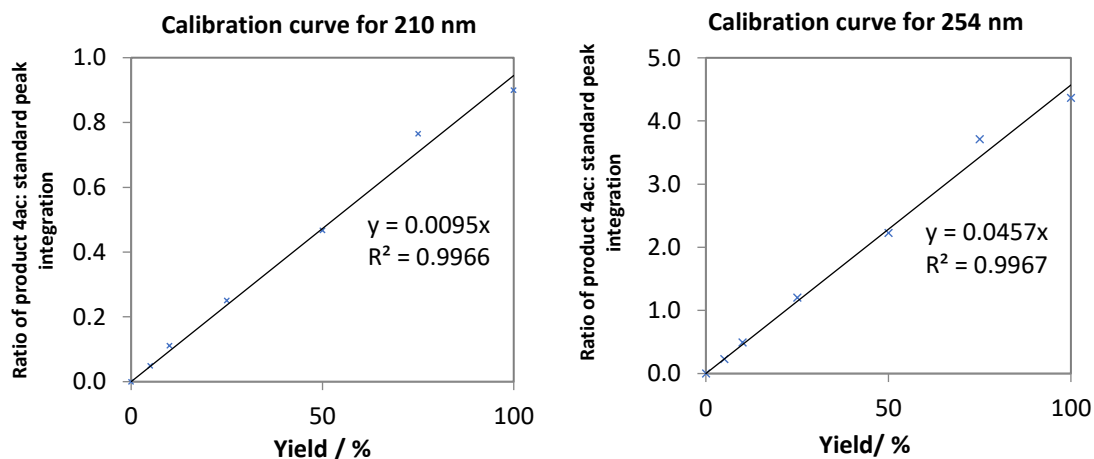
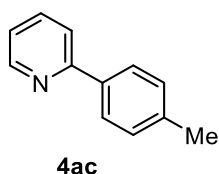
¹H NMR (400 MHz, CDCl₃) δ 8.07 (dd, *J* = 3.0, 0.5 Hz, 1H, Pyr-*H*), 7.36 (dd, *J* = 8.5, 0.5 Hz, 1H, Pyr-*H*), 7.10 (dd, *J* = 8.5, 3.0 Hz, 1H, Pyr-*H*), 6.01 (ddt, *J* = 17.5, 10.5, 5.5 Hz, 1H, CH^aH^b=CH), 5.41 (dq, *J* = 17.0, 1.5 Hz, 1H, CH^aH^b=CH), 5.33 (dq, *J* = 10.5, 1.5 Hz, 1H, CH^aH^b=CH), 4.56 (dt, *J* = 5.5, 1.5 Hz, 2H, OCH₂); **¹³C NMR** (101 MHz, CDCl₃) δ 154.6, 137.9, 132.4, 132.2, 128.3, 125.3, 118.8, 69.6; **LRMS** (ESI⁺) *m/z* 214.0 (50%, [M+H]⁺), 216.0 (50%, [M+H]⁺); **HRMS** (ESI⁺) found *m/z* 213.9864 [M(⁷⁹Br)+H]⁺, C₈H₉ON⁷⁹Br requires *m/z* 213.9862; **IR** ν_{max} (neat)/ cm⁻¹ 3084, 2867, 1650, 1577, 1564, 1449, 1424, 1367, 1269, 1223, 1120, 1089, 1011, 991, 928, 822, 721, 676, 622; **R_f** = 0.40 (10% EtOAc in Petrol).

6.3. Data for chapter 3

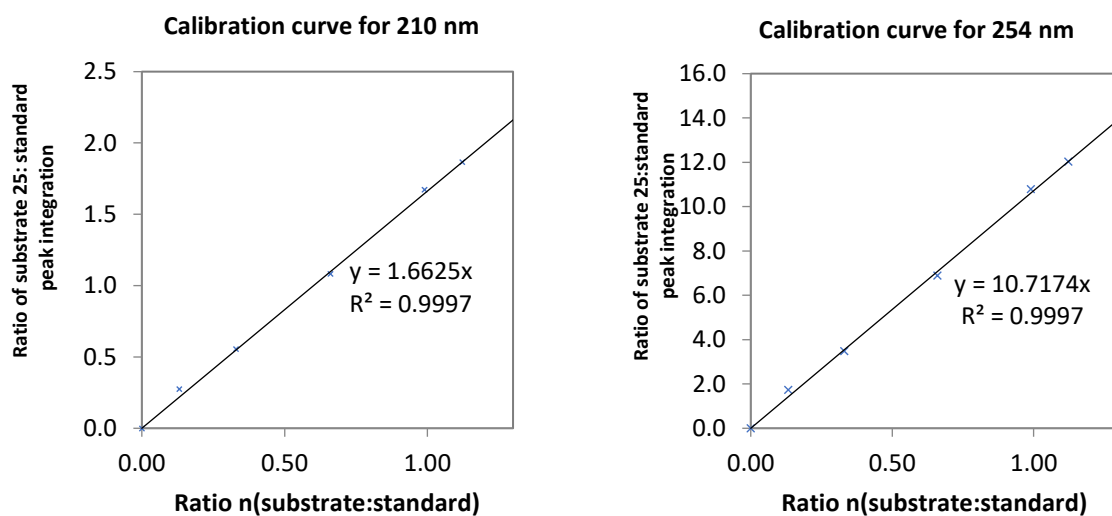
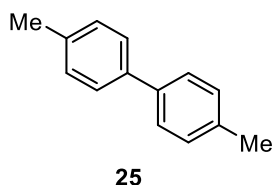
6.3.1. HPLC information and calibration curves

Using the same HPLC method as used for the HPLC analysis of results from Chapter 2. The HPLC data was obtained from an Agilent Technologies 1200 series HPLC Hypersol ODS, 5 μm column (100 $\times$ 4.0 MM) using an extended 12 min method H₂O (0.1 % v/v H₃PO₄): Acetonitrile (10-95% (9 min) to 100% (10.5 min) to 10% (12 min)). HPLC yields for the ligand screening were obtained *via* standard calibration curve using authentic desired product/starting material and *p*-ditoylether as an internal standard. Yields were calculated from two different wavelengths 254 nm and 210 nm and averaged. The method was verified by product isolation which gave a result $\pm$ 2%.

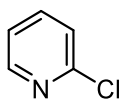
Calibration curves yield of 2-(*p*-tolyl)pyridine **4ac** (retention time = 1.98 min), against the peak area ratio of product to internal standard, using *p*-ditoylether (retention time = 7.93 min) at either 210 nm or 254 nm.



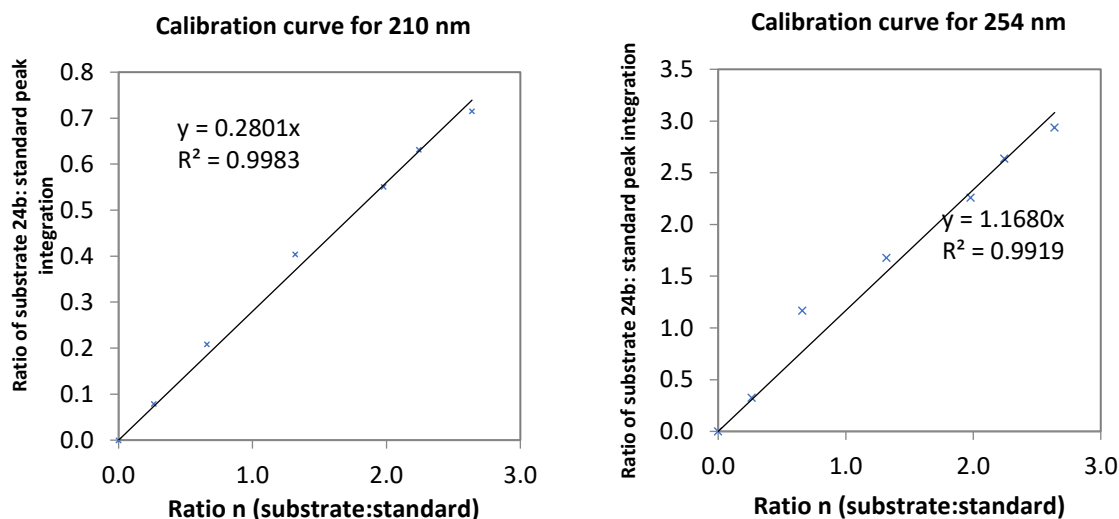
Calibration curves plot the mole ratio of by-product, 4,4'-dimethyl-1,1'-biphenyl **25** (retention time = 8.117 min) to *p*-ditoylether (retention time = 7.93 min), against the peak area ratio of by-product to internal standard, at either 210 nm or 254 nm.



Calibration curves plot the mole ratio of starting material 2-chloropyridine **24b** (retention time = 2.440 min) to *p*-ditoylether (retention time = 7.93 min), against the peak area ratio of by-product to internal standard, at either 210 nm or 254 nm.

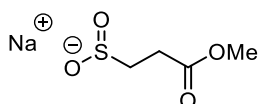


24b



6.3.2. Synthetic procedures and data

6.3.2.a Synthesis of sodium sulfinate reagents



sodium 4-methoxy-4-oxobutane-1-sulfinate (SMOPS) reagent (6)

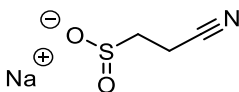
Caution: Exothermic reaction and evolution of H₂ gas

Open to air: To a rbf fitted with a CaCl₂ packed drying tube was added anhydrous MeOH (10 mL). To the stirring solvent was rapidly added hexane-washed, freshly cut sodium (115 mg, 5.00 mmol, 1.0 equiv.) in four equal portions. Once all the sodium had dissolved, dimethyl-3,3'-sulfonyldipropionate (1.19 g, 5.00 mmol, 1.0 equiv.) was added quickly and the reaction stirred for 2 h. The solvent was then removed *in vacuo* and the

resultant solid washed with EtOAc (50 mL), Et₂O (50 mL × 1) and dried under vacuum to give the title compound as a white solid (836 mg, 4.45 mmol, 89%).

¹H NMR (400 MHz, MeOD-*d*⁴) δ 3.67 (s, 3H, CO₂CH₃), 2.62 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 2H, CH₂), 2.49 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 2H, CH₂); **¹H NMR** (400 MHz, DMSO-*d*⁶) δ 3.56 (s, 3H), 2.41 (dd, *J* = 8.5, 7.0 Hz, 2H), 2.03 (dd, *J* = 8.5, 7.0 Hz, 2H); **¹³C NMR** (101 MHz, DMSO-*d*⁶) δ 173.9, 56.0, 51.2, 26.0; **HRMS** (ESI⁺) found *m/z* 151.00677 [M-Na]⁺, C₄H₇O₄S requires *m/z* 151.00705; **IR** ν_{max} (neat)/ cm⁻¹ 3435, 2954, 1735, 1441, 136, 1271, 1191, 1150, 1070, 1060, 986, 901, 806; **mp** >200 °C (EtOAc: Et₂O); **R_F** = 0.00 (100% EtOAc, with KMnO₄ staining).

Data is consistent with literature: J. M. Baskin and Z. Y. Wang, *Tetrahedron Lett.*, 2002, **43**, 8479-8483.^[78a]



sodium 2-cyanoethane-1-sulfinate (23)

Caution: Exothermic reaction and evolution of H₂ gas

Open to air: To a rbf fitted with a CaCl₂ packed drying tube was added anhydrous MeOH (40 mL). To the stirring solvent was rapidly added hexane-washed, freshly cut sodium (460 mg, 20.0 mmol, 1.0 equiv.) in four equal portions. Once all the sodium had dissolved, 3, 3'-sulfonyldipropionitrile (3.44 g, 20.0 mmol, 1.0 equiv.) was added quickly and the reaction stirred for 2 h. The solvent was then removed *in vacuo* and the resultant solid washed with EtOAc (50 mL × 2), Et₂O (50 mL × 1) and dried under vacuum to give the title compound as a white solid (2.51 g, 89%).

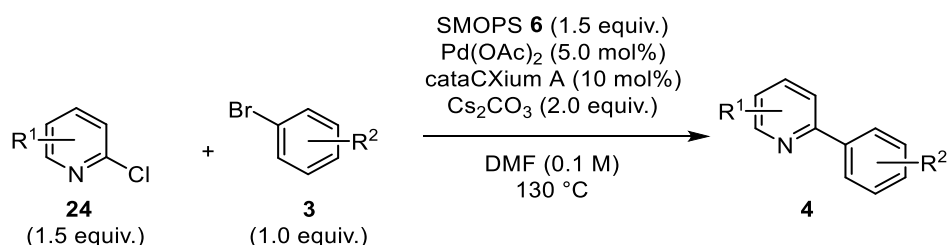
¹H NMR (400 MHz, MeOD-*d*⁴) δ 2.70 (t, *J* = 7.5 Hz, 2H, CH₂CN), 2.45 (t, *J* = 7.5 Hz, 2H, NaO₂SCH₂); **¹³C NMR** (101 MHz, CDCl₃) δ 120.7, 55.9, 10.2; **LRMS** *m/z* 118.0

(100%, [M-Na]⁺); **HRMS** (ESI⁺) found *m/z* 117.9967 [M-Na]⁺, C₃H₄O₂NS requires *m/z* 117.9968; **IR** ν_{max} (neat)/ cm⁻¹ 2953, 2920, 2250, 1422, 1050, 1029, 989, 770, 715, 692, 651; **mp** 167 – 169 °C (MeOH); **R_F** = 0.00 (100% EtOAc, staining with KMnO₄).

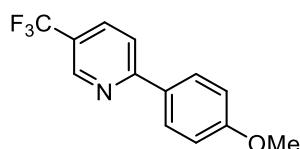
(Note: After two weeks the ¹H NMR spectrum of the sulfinate shows no decomposition when left out on bench)

Data is consistent with literature: J. McKnight, A. Shavnya, N. W. Sach, D. C. Blakemore, I. B. Moses, M. C. Willis, *Angew. Chem. Int. Ed.* **2022**, DOI: 10.1002/anie.202116775. ^[119]

6.3.2.b Cross-electrophile coupling procedure



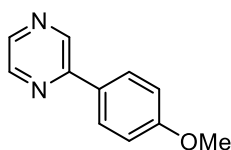
General Procedure H: To an oven dried microwave vial (10 mL) was added heteroaryl chloride (if it is a solid) (0.30 mmol, 1.0 equiv.), aryl bromide (if it is a solid) (0.20 mmol, 1.0 equiv.), SMOPS reagent (52.2 mg, 0.3 mmol, 1.5 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.). The vial was capped and purged with N₂ for 10 mins. Anhydrous DMF (2.0 mL, 0.1 M) was then added, followed by the addition of heteroaryl chloride (if it is a liquid) (0.30 mmol, 1.5 equiv.) or/and aryl bromide (if it is a liquid) (0.20 mmol, 1.0 equiv.) with stirring. The reaction mixture was heated to 130 °C for 18 h. The reaction mixture was then allowed to cool to rt, filtered through a pad of silica and washed with EtOAc. The resultant crude solution was concentrated in vacuo, adsorbed onto celite and purified by flash column chromatography on SiO₂ (EtOAc in Petrol) to give the desired product.



2-(4-methoxyphenyl)-5-(trifluoromethyl)pyridine (4a)

Following general procedure **H**, 2-Chloro-5-(trifluoromethyl)pyridine (54.5 mg, 0.3 mmol, 1.5 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) were combined in DMF (2.0 mL, 0.1 M). Next 4-bromoanisole (25.0 μ L, 0.20 mmol, 1.0 equiv.) was added. The reaction was heated at 130 °C for 18h. The crude residue was purified by flash column chromatography (8 – 20% EtOAc in Petrol) to give the title product as a white solid (22.6 mg, 45%).

Full characterisation data for this compound is reported in experimental section **6.2.3.d**.



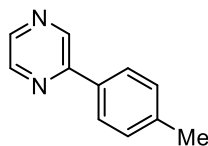
2-(4-methoxyphenyl)pyrazine (4bd)

Following general procedure **H**, Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) were combined in DMF (2.0 mL, 0.1 M). Next 2-chloropyridine (28.5 μ L, 0.30 mmol, 1.5 equiv.) and 4-bromoanisole (25.0 μ L, 0.20 mmol, 1.0 equiv.) were added. The reaction was heated at 130 °C for 18 h. The crude residue was purified by flash column chromatography (8 – 20% EtOAc in Petrol) to give the title product as a white solid (16.7 mg, 45%).

¹H NMR (400 MHz, CDCl₃) δ 8.98 (d, J = 1.5 Hz, 1H, Pyraz-*H*), 8.59 (dd, J = 2.5, 1.5 Hz, 1H, Pyraz-*H*), 8.44 (d, J = 2.5 Hz, 1H, Pyraz-*H*), 8.01 – 7.95 (m, 2H, Ar-*H*), 7.07 – 6.99 (m, 2H, Ar-*H*), 3.88 (s, 3H, OCH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 161.4, 152.7, 144.2, 142.2, 141.8, 129.0, 128.4, 114.6, 55.5; **LRMS** m/z 187.2 [M+H]⁺; **HRMS** (ESI⁺) found m/z 187.0866 [M+H]⁺, C₁₁H₁₁ON₂ requires m/z 187.0866; **IR** ν_{max} (neat)/cm⁻¹

2924, 2854, 2360, 2341, 1255, 826; **mp** 71 – 73 °C (EtOAc); **R_f** = 0.20 (20% EtOAc in Petrol).

Data consistent with literature: K. Tanimoro, M. Ueno, K. Takeda, M. Kirihata, S. Tanimori, *J. Org. Chem.* **2012**, 77, 7844-7849. ^[183]



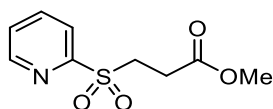
2-(p-tolyl)pyrazine (4be)

Following general procedure **H**, 4-bromotoluene (34.2 mg, 0.20 mmol, 1.0 equiv.), Pd(OAc)₂ (2.2 mg, 0.010 mmol, 5.0 mol%), cataCXium A (7.2 mg, 0.020 mmol, 10 mol%) and K₂CO₃ (55.3 mg, 0.40 mmol, 2.0 equiv.) were combined in DMF (2.0 mL, 0.1 M). Next 2-chloropyridine (28.5 μL, 0.30 mmol, 1.5 equiv.) was added. The reaction was heated at 130 °C for 18h. The crude residue was purified by flash column chromatography (7% EtOAc in Petrol) to give the title product as an off-white solid (16.0 mg, 47%).

¹H NMR (400 MHz, CDCl₃) δ 9.03 (s, 1H, Pyraz-*H*), 8.62 (s, 1H, Pyraz-*H*), 8.49 (s, 1H, Pyraz-*H*), 7.94 – 7.90 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.35 – 7.29 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 2.43 (s, 3H, CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 153.0, 144.3, 142.7, 142.1, 140.3, 133.7, 129.9, 127.0, 21.5; **LRMS** *m/z* 171.2 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 171.0918 [M+H]⁺, C₁₁H₁₁N₂ requires *m/z* 171.0917; **IR** *v*_{max} (neat)/cm⁻¹ 2920, 2856, 2361, 2342, 1017, 815; **mp** 37 – 37 °C (EtOAc); **R_f** = 0.15 (6% EtOAc in Petrol).

Data consistent with literature: X. Zhang, A. McNally, *Angew. Chem. Int. Ed.* **2017**, 56, 9833-9836. ^[184]

6.3.2.c Cu-mediated sulfone formation

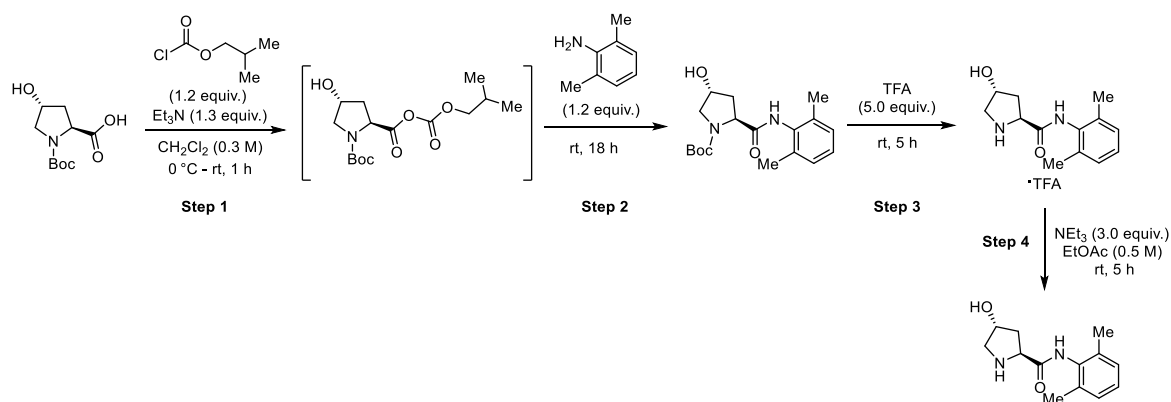


methyl 3-(pyridin-2-ylsulfonyl)propanoate (2b)

- (a) Following general procedure **E** (a modified procedure reported by Baskin and Wang),^[78a] sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS reagent, 52.2 mg, 0.3 mmol, 1.0 equiv.) and CuI (57.1 mg, 0.3 mmol, 1.0 equiv.) were combined in a reaction vial. The vial was purged and backfilled with N₂ (× 3), then DMSO (2.0 mL, 0.15 M) and 2-bromopyridine (28.5 μL, 0.3 mmol, 1.0 equiv.) were added and the reaction mixture heated at 130 °C for 16 h. The crude product was purified by flash column chromatography (50% EtOAc in Petrol) to give the title compound as a slightly yellow oil (55.4 mg, 81%).
- (b) Following a modified procedure reported by Lee and co-workers,^[121c] sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS reagent, 87.1 mg, 0.5 mmol, 1.0 equiv.), K₃PO₄ (106.1 mg, 0.5 mmol, 1.0 equiv.), DMPHPC (11.7 mg, 0.05 mmol, 10 mol%) and CuI (9.5 mg, 0.05 mmol, 10 mol%) were combined in a 10 mL round bottom flask. The flask was purged with N₂ for 20 mins, then DMSO (3.2 mL, 0.16 M) and 2-iodopyridine (106.0 μL, 1.0 mmol, 2.0 equiv.) were added. The reaction mixture was then heated at 35 °C for 18 h. The reaction mixture was then diluted with H₂O and extracted with EtOAc (× 3). The organic layers were combined, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (40 – 60% EtOAc in Petrol) to give the title product as a slightly yellow oil (24.3 mg, 21%).

Full characterisation data for this compound is reported in experimental section

6.2.3.b.



(2*S*,4*R*)-*N*-(2,6-dimethylphenyl)-4-hydroxypyrrolidine-2-carboxamide (DMPHPC)

(28)

Synthesis of DMPHPC ligand followed the synthetic route and procedure reported by Ma and co-workers,^[97a] however **step 4** was modified to allow free-basing in organic media, followed by trituration (ice cold EtOAc $\times$ 3) to give the title compound as a white crystalline solid (103 mg, 44%).

¹H NMR (400 MHz, DMSO) δ 9.94 (s, 1H, CONH), 9.23 (br. s, 1H, OH), 7.17 – 7.07 (m, 3H, Ar-*H*), 5.61 (d, J = 3.0 Hz, 1H, NH), 4.58 – 4.53 (m, 1H, (CH₂)₂CHOH), 4.51 (d, J = 3.0 Hz, 1H, NHCH), 3.39 (dd, J = 12.0, 4.0 Hz, 1H, NHCH_aH_b), 3.13 (d, J = 12.0 Hz, 1H, NHCH_aH_b), 2.45 (dd, J = 13.0, 7.0 Hz, 1H, NHCHCH_aH_b), 2.15 (s, 6H, 2 $\times$ CH₃), 2.05 (ddd, J = 13.0, 11.0, 4.5 Hz, 1H, NHCHCH_aH_b); **¹³C NMR** (101 MHz, DMSO) δ 166.7, 135.0, 133.7, 127.9, 127.0, 69.2, 58.3, 53.6, 38.9, 17.9; **LRMS** m/z 235.2 [M+H]⁺; **HRMS** (ESI⁺) found m/z 235.1439 [M+H]⁺, C₁₃H₁₉O₂N₂ requires m/z 235.1441; **IR** ν_{max} (neat)/cm⁻¹ 3734, 2360, 2342, 1684, 1559, 668; **R_f** = 0.35 (10% MeOH in EtOAc).

Data is consistent with previous literature reports: J. Zhao, S. Niu, X. Jiang, Y. Jiang, X. Zhang, T. Sun, D. Ma, *J. Org. Chem.* **2018**, *83*, 6589-6598.^[97a]

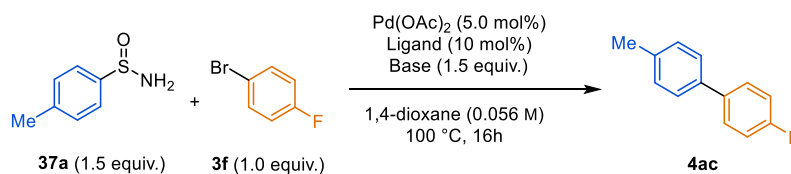
6.4. Data for chapter 4

6.4.1. Additional ligand and base screen for the cross-coupling of aryl sulfinamides and aryl bromides on a screening scale (0.11 mmol)

Additional phosphine ligands and bases that were screened during the initial optimisation of the cross-coupling of aryl sulfinamide **37a** and **3f** for the synthesis of **4ac** are documented in **Table 6.1**. Reactions were run on a smaller screening scale (0.11 mmol) before the reaction optimisation was moved to a preparative scale (0.30 mmol).

Poor results were observed when using phosphine ligands with %Vbur_(min) values outside the optimum range of 29.0 – 32.0. For example only 4% yield of biaryl product is observed when using P(*t*-Bu)₂Cy (entry 3) and only 8% yield when using P(*n*-Bu)₃•HBF₄ (entry 4). Caesium pivalate (entry 7) and potassium trimethylsilanolate (entry 8) did not perform as well as compared to caesium carbonate (entry 1).

Table 6.1 Additional ligands screened for the desulfinamidative cross-coupling on a 0.11 mmol scale.



Entry	Ligand	%Vbur (min)	Base	HPLC yield
1	P(<i>t</i> -Bu) ₂ Me•HBF ₄	31.5	Cs ₂ CO ₃	45%
2	P(Cy) ₂ Et•HBF ₄	28.2	Cs ₂ CO ₃	27%
3	P(<i>t</i> -Bu) ₂ Cy	34.3	Cs ₂ CO ₃	4%
4	P(<i>n</i> -Bu) ₃ •HBF ₄	24.2	Cs ₂ CO ₃	8%
5	P(Cyp) ₃ •HBF ₄	29.3	Cs ₂ CO ₃	33%
6	APhos	-	Cs ₂ CO ₃	8%
7	P(<i>t</i> -Bu) ₂ Me•HBF ₄	31.5	CsOPiv	5%
8	P(<i>t</i> -Bu) ₂ Me•HBF ₄	31.5	KOTMS	2%

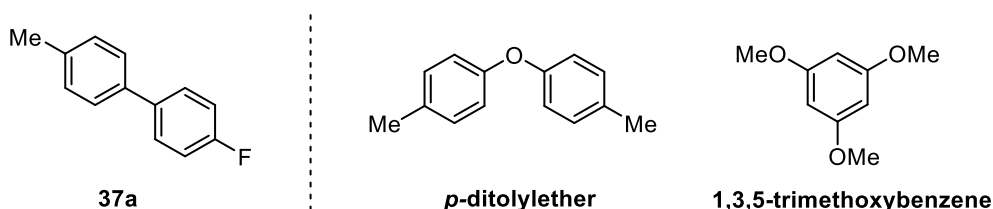
^[a] HPLC yield is the average yield calculated using 1,3,5-trimethoxybenzene and *p*-ditolylether.

Percentage buried volume, %V_{Bur}, is a measure of steric bulk proximal to the metal centre, defined as percentage volume occupied by the ligand in the metal sphere (assuming a radius of 3.5 Å). The %V_{Bur}(min) parameter represents the smallest %V_{Bur} of all the energetically accessible conformers of a ligand.^[154] V_{Bur}(min) values were obtained from the *Kraken* database^[155] and further processed to get the percentage: %V_{bur}(min) = 100*(V_{bur}(min)/179.59).

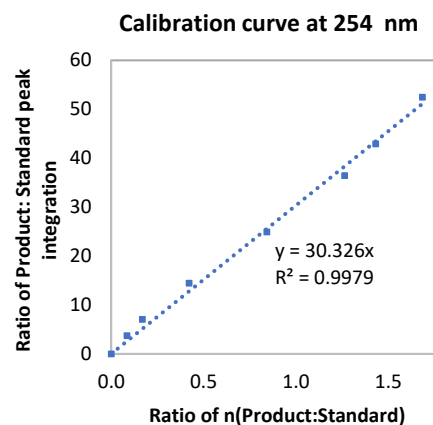
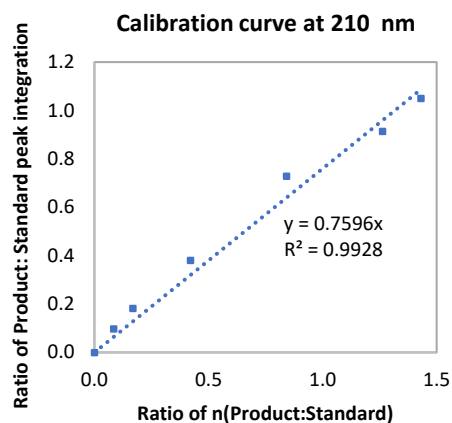
6.4.2. HPLC information and calibration curves

The HPLC data was obtained from an Agilent Technologies 1200 series HPLC Hypersol ODS, μ m column (100 $\times$ 4.0 MM) using a general 9 min method H₂O (0.1 % v/v H₃PO₄): Acetonitrile (10 – 95% (6.00 min) to 100% (6.01 – 7.50 min) to 10% (7.51 – 9.00 min)). HPLC yields for screening reactions were obtained via standard calibration curve using authentic desired product and an internal standard (1,3,5-trimethoxybenzene and *p*-ditolylether). Product yields were calculated from two different wavelengths 254 nm and 210 nm and averaged. The method was verified by product isolation which gave a result $\pm$ 5%.

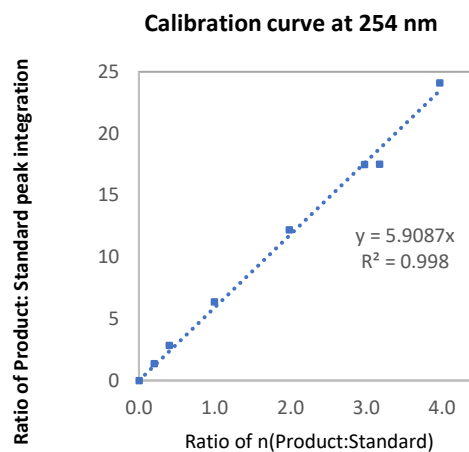
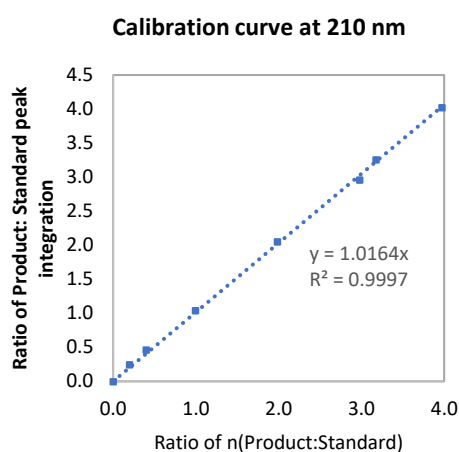
Calibration curves plot the mole ratio of biaryl product 4-fluoro-4'-methyl-1,1'-biphenyl **37a** (retention time = 5.64 min) to internal standards: (a) 1,3,5-trimethoxybenzene (retention time = 3.76 min) or (b) *p*-ditolylether (retention time = 5.87 min), against the peak area ratio of product to internal standard(s), at either 210 nm or 254 nm.



(a) Calibration curves of biaryl product **37a** with 1,3,5-trimethoxybenzene:



(b) Calibration curves of biaryl product **37a** with *p*-ditolylether:



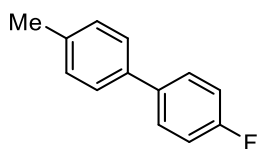
6.4.3. Synthetic procedures and data

All primary aryl sulfinamide reagents and phenyl sulfoximine reagent **44b** were kindly prepared and characterised by Charles Bell, a current DPhil student in the Willis group.

Sodium *p*-tolylsulfinate, sodium *p*-tolylsulfonate and 2-mercaptopyridine were sourced from commercial sources.

6.4.3.a Desulfinamidative cross-coupling reaction

General procedure I: Aryl sulfinamide (0.45 mmol, 1.5 equiv.), aryl bromide (if it is a solid) (0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol 5 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in an oven-dried microwave vial and sealed with a microwave cap. The reaction vial was evacuated and filled with N₂ (× 6). Anhydrous, degassed 1,4-dioxane (1.0 mL, 0.3 M) was then added, followed by the addition of aryl bromide (if it is a liquid) (0.30 mmol, 1.0 equiv.). The reaction was then heated at 100 °C for 16 h with fast magnetic stirring (>600 rpm), before being cooled to rt. The reaction solvent was removed *in vacuo* and the crude residue adsorbed onto celite and purified by flash column chromatography on silica gel to give the desired product.

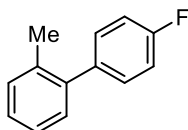


4-fluoro-4'-methyl-1,1'-biphenyl (37a)

Following general procedure I, 4-methylbenzenesulfinamide (69.8 mg, 0.45 mmol, 1.5 equiv.), 1-bromo-4-fluorobenzene (33.0 μ L, 0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 5.0 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (1% CH₂Cl₂ in hexanes) to give the title product as a white crystalline solid (43.2 mg, 77%).

¹H NMR (400 MHz, CDCl₃) δ 7.55 – 7.50 (m, 2H, Ar-*H*), 7.46 – 7.42 (m, 2H, Ar-*H*), 7.27 – 7.23 (m, 2H, Ar-*H*), 7.14 – 7.08 (m, 2H, Ar-*H*), 2.40 (s, 3H, CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 162.5 (d, ¹*J*_{CF} = 246.0 Hz), 137.5, 137.4 (d, ⁴*J*_{CF} = 3.5 Hz), 137.2, 129.7, 128.6 (d, ³*J*_{CF} = 8.0 Hz), 127.0, 115.7 (d, ²*J*_{CF} = 21.0 Hz), 21.2; **¹⁹F NMR** (377 MHz, CDCl₃) δ -116.32 (tt, *J* = 9.0, 5.5 Hz); **HRMS** (GC EI⁺) found *m/z* 186.0839 (M⁺), C₁₃H₁₁F requires *m/z* 186.0845; **IR** ν_{max} (neat)/cm⁻¹ 2923, 2361, 2341, 1499, 1237, 1159, 908, 810, 733; **mp** 61 – 62 °C (EtOAc); **R_F** = 0.59 (100% Petrol).

Data is consistent with literature: R. Cai *et. al.*, *Angew. Chem. Int. Ed.* **2015**, *54*, 8772 – 8776.^[185]



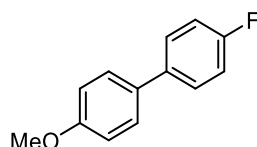
4'-fluoro-2-methyl-1,1'-biphenyl (**37b**)

Following general procedure **I**, 2-methylbenzenesulfinamide (69.8 mg, 0.45 mmol, 1.5 equiv.), 1-bromo-4-fluorobenzene (33.0 μL, 0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 5.0 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (100% hexanes) to give the title product as a colourless oil (35.3 mg, 63%).

¹H NMR (400 MHz, CDCl₃) δ 7.30 – 7.18 (m, 6H, Ar-*H*), 7.10 (t, *J* = 8.5 Hz, 2H, Ar-*H*), 2.25 (s, 3H, CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 162.1 (d, ¹*J*_{CF} = 245.0 Hz), 141.1, 138.0 (d, ⁴*J*_{CF} = 3.5 Hz), 135.5, 130.9 (d, ³*J*_{CF} = 8.0 Hz), 130.5, 130.0, 127.6, 126.0, 115.1 (d, ²*J*_{CF} = 21.5 Hz), 20.6; **¹⁹F NMR** (377 MHz, CDCl₃) δ -116.16 (tt, *J* = 6.0, 2.5 Hz);

HRMS (GC EI⁺) found m/z 186.0839 (M)⁺, C₁₃H₁₁F requires m/z 186.0845; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 2926, 2360, 2341, 1512, 1483, 1222, 1157, 838, 760, 730; **R_F** = 0.59 (100% Petrol).

Data is consistent with literature: G. J. Sherborne, A. G. Gevondian, I. Funes- Ardoiz, A. Dahiya, C. Fricke, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2020**, *59*, 15543–15548.^[186]

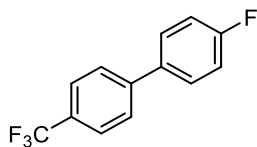


4-fluoro-4'-methoxy-1,1'-biphenyl (37c)

Following general procedure **I**, 4-methoxybenzenesulfonamide (77.0 mg, 0.45 mmol, 1.5 equiv.), 1-bromo-4-fluorobenzene (33.0 μ L, 0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 5.0 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (0 – 3% EtOAc in Petrol) to give the title product as a white solid (49.3 mg, 81%).

¹H NMR (400 MHz, CDCl₃) δ 7.52 – 7.44 (m, 4H, Ar-*H*), 7.10 (t, J = 9.0 Hz, 2H, Ar-*H*), 6.97 (d, J = 9.0 Hz, 2H, Ar-*H*), 3.85 (s, 3H, OCH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 162.3 (d, $^1J_{CF}$ = 245.0 Hz), 159.3, 137.1 (d, $^4J_{CF}$ = 3.0 Hz), 133.0, 128.4 (d, $^3J_{CF}$ = 8.0 Hz), 128.2, 115.7 (d, $^2J_{CF}$ = 21.5 Hz), 114.4, 55.5; **¹⁹F NMR** (377 MHz, CDCl₃) δ -116.75 (tt, J = 8.5, 5.0 Hz); **HRMS** (GC EI⁺) found m/z 202.0788 (M⁺), C₁₃H₁₁FO requires m/z 202.0794; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 2924, 2843, 2361, 1607, 1496, 1291, 1235, 1039, 826; **mp** 72 – 74 °C (EtOAc); **R_F** = 0.35 (2% EtOAc in Petrol).

Data is consistent with literature: R. Cai *et. al.*, *Angew. Chem. Int. Ed.* **2015**, 54, 8772 – 8776.^[185]

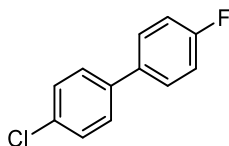


4-fluoro-4'-(trifluoromethyl)-1,1'-biphenyl (37d)

Following general procedure **I**, 4-(trifluoromethyl)benzenesulfonamide (94.1 mg, 0.45 mmol, 1.5 equiv.), 1-bromo-4-fluorobenzene (33.0 μ L, 0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 5.0 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (100% hexanes) to give the title product as a colourless oil (52.9 mg, 73%).

¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, J = 8.5 Hz, 2H, Ar-*H*), 7.65 (d, J = 8.5 Hz, 2H, Ar-*H*), 7.60 – 7.53 (m, 2H, Ar-*H*), 7.20 – 7.13 (m, 2H, Ar-*H*); **¹³C NMR** (101 MHz, CDCl₃) δ 163.1 (d, $^1J_{CF}$ = 247.5 Hz), 143.9, 136.0 (d, $^4J_{CF}$ = 3.0 Hz), 129.6 (q, $^2J_{CF}$ = 32.5 Hz), 129.1 (d, $^3J_{CF}$ = 8.0 Hz), 127.8, 125.9 (q, $^3J_{CF}$ = 4.0 Hz), 124.4 (q, $^1J_{CF}$ = 272.0 Hz), 116.1 (d, $^2J_{CF}$ = 22.0 Hz); **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.44 (s, 3F), -114.16 (tt, J = 8.5, 5.0 Hz, 1F); **HRMS** (GC EI⁺) found m/z 240.0557 (M⁺), C₁₃H₈F₄ requires m/z 240.0562; **IR** $\nu_{\max}$ (neat)/cm⁻¹ 2361, 2342, 1502, 1325, 1162, 1123, 1071, 1021, 824, 707; **R_F** = 0.46 (100% hexanes).

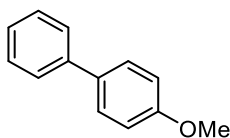
Data is consistent with literature: D. S. Casadio, S. Aikonen, A. Lenarda, M. Nieger, T. Hu, S. Taubert, D. Sundholm, M. Muuronen, T. Wirtanen, J. Helaja, *Chem. Eur. J.* **2021**, 27, 5283-5291.^[176]



4-chloro-4'-fluoro-1,1'-biphenyl (37e)

Following general procedure **I**, 4-chlorobenzenesulfonamide (79.0 mg, 0.45 mmol, 1.5 equiv.), 1-bromo-4-fluorobenzene (33.0 μ L, 0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 5.0 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (100% Petrol) to give the title product as a white solid (56.6 mg, 91%).

¹H NMR (400 MHz, CDCl₃) δ 7.56 – 7.43 (m, 4H, Ar-*H*), 7.40 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.16 – 7.09 (m, 2H, Ar-*H*); **¹³C NMR** (101 MHz, CDCl₃) δ 162.8 (d, ¹*J*_{CF} = 247.0 Hz), 138.9, 136.3 (d, ⁴*J*_{CF} = 3.5 Hz), 133.6, 129.1, 128.7 (d, ³*J*_{CF} = 8.0 Hz), 128.4, 115.9 (d, ²*J*_{CF} = 21.5 Hz); **¹⁹F NMR** (377 MHz, CDCl₃) δ -115.14 (tt, *J* = 8.5, 5.0 Hz); **HRMS** (GC EI⁺) found *m/z* 206.0293 (M⁺), C₁₂H₈ClF requires *m/z* 206.0299; **IR** ν_{max} (neat)/cm⁻¹ 2919, 2359, 1594, 1480, 1225, 1158, 1093, 1020, 909, 853, 817, 741; **mp** 69 – 71 °C (EtOAc); **R_F** = 0.66 (2% EtOAc in Petrol).



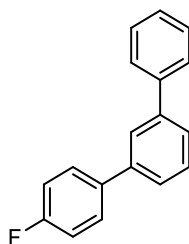
4-methoxy-1,1'-biphenyl (37f)

Following general procedure **I**, Benzenesulfonamide (63.5 mg, 0.45 mmol, 1.5 equiv.), 4-bromoanisole (37.5 μ L, 0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at

100 °C for 16 h. The crude residue was then purified by flash column chromatography (2 – 10% EtOAc in hexanes) to give the title product as a white crystalline solid (38.2 mg, 69%).

¹H NMR (400 MHz, CDCl₃) δ 7.58 – 7.51 (m, 4H, Ar-*H*), 7.42 (t, *J* = 7.5 Hz, 2H, Ar-*H*), 7.34 – 7.28 (m, 1H, Ar-*H*), 7.01 – 6.95 (m, 2H, Ar-*H*), 3.86 (s, 3H, OCH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 159.3, 141.0, 133.9, 128.9, 128.3, 126.9, 126.8, 114.4, 55.5; **HRMS** (GC EI⁺) found *m/z* 184.0882 (M⁺), C₁₃H₁₂O requires *m/z* 184.0888; **IR** ν_{max} (neat)/cm⁻¹ 2960, 2936, 2361, 2341, 1607, 1489, 1252, 1014, 834, 761, 690; **mp** 66 – 68 °C (EtOAc); **R_F** = 0.25 (100% Petrol).

Data is consistent with literature: R. Cai *et. al.*, *Angew. Chem. Int. Ed.* **2015**, 54, 8772 – 8776.^[185]

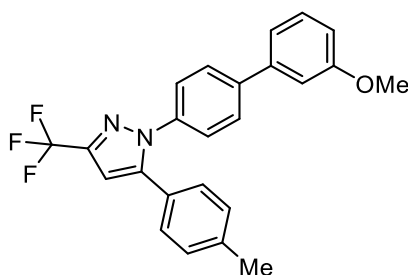


4-fluoro-1,1':3',1''-terphenyl (37g)

Following general procedure **I**, 4-fluorobenzenesulfinamide (71.6 mg, 0.45 mmol, 1.5 equiv.), 3-Bromobiphenyl (50.0 μL, 0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 5.0 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (100% hexanes) to give the title product as a white crystalline solid (64.4 mg, 86%).

¹H NMR (400 MHz, CDCl₃) δ 7.76 (s, 1H, Ar-*H*), 7.67 – 7.57 (m, 5H, Ar-*H*), 7.55 – 7.50 (m, 2H, Ar-*H*), 7.47 (t, *J* = 7.5 Hz, 2H, Ar-*H*), 7.38 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.15 (t, *J* = 8.5 Hz, 2H, Ar-*H*); **¹³C NMR** (101 MHz, CDCl₃) δ 162.7 (d, ¹*J*_{CF} = 246.5 Hz), 142.1, 141.2, 141.0, 137.4 (d, ⁴*J*_{CF} = 3.0 Hz), 129.4, 129.0, 128.9 (d, ³*J*_{CF} = 8.5 Hz), 127.6, 127.4, 126.3, 126.2, 126.1, 115.8 (d, ²*J*_{CF} = 21.5 Hz); **¹⁹F NMR** (377 MHz, CDCl₃) δ -115.58 (tt, *J* = 8.5, 5.5 Hz); **HRMS** (GC EI⁺) found *m/z* 248.0996 (M⁺), C₁₈H₁₃F requires *m/z* 248.1001; **IR** ν_{max} (neat)/cm⁻¹ 3061, 2981, 2361, 2341, 1604, 1513, 1474, 1228, 840, 798, 758, 700; **mp** 70 – 72 °C (EtOAc); **R_F** = 0.43 (100% Petrol).

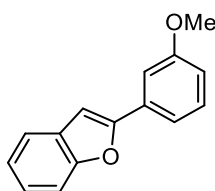
Data is consistent with literature: J. M. Antelo Miguez, L. A. Adrio, A. Sousa-Pedrares, J. M. Vila, K. K. Hii, *J. Org. Chem.*, **2007**, 72, 7771 – 7774. ^[187]



**1-(3'-methoxy-[1,1'-biphenyl]-4-yl)-5-(*p*-tolyl)-3-(trifluoromethyl)-1H-pyrazole
(37h)**

Following general procedure **I**, 4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfinamide (164.4 mg, 0.45 mmol, 1.5 equiv.), 3-bromoanisole (39.0 μL, 0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 5.0 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (1% EtOAc in Petrol) to give the title product as a crystalline white solid (78.5 mg, 64%).

¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.57 (m, 2H, Ar-*H*), 7.42 – 7.34 (m, 3H, Ar-*H*), 7.19 (dd, *J* = 1.5, 1.0 Hz, 1H), 7.17 (s, 4H, Ar-*H*), 7.12 (dd, *J* = 2.5, 1.5 Hz, 1H, Ar-*H*), 6.93 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, Ar-*H*), 6.75 (s, 1H, Pyraz-*H*), 3.87 (s, 3H, OCH₃), 2.37 (s, 3H, CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 160.2, 144.9, 143.4 (q, ²*J*_{CF} = 38.5 Hz), 141.4, 141.1, 139.3, 138.7, 130.1, 129.6, 128.8, 127.8, 126.4, 125.7, 121.5 (q, ¹*J*_{CF} = 269.0 Hz), 119.7, 113.2, 113.1, 105.6 (q, ³*J*_{CF} = 2.0 Hz), 55.5, 21.4; **¹⁹F NMR** (377 MHz, CDCl₃) δ -62.20; **LRMS** *m/z* 409.2 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 409.1520 [M+H]⁺, C₂₄H₂₀ON₂F₃ requires *m/z* 409.1522; **IR** ν_{max} (neat)/cm⁻¹ 2970, 2361, 2341, 1653, 1510, 1236, 1132, 1097, 977, 838; **mp** 95 – 97 °C (EtOAc); **R_F** = 0.22 (2% EtOAc in Petrol).



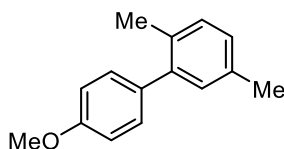
2-(3-methoxyphenyl)benzofuran (37i)

Following general procedure **I**, benzofuran-2-sulfonamide (81.5 mg, 0.45 mmol, 1.5 equiv.), 3-bromoanisole (38.0 μL, 0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 5.0 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (1% EtOAc in Petrol) to give the title product as a colourless oil that crystallised on standing to a white solid (54.8 mg, 81%).

¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.57 (m, 1H, Ar-*H*), 7.53 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-*H*), 7.47 (dt, *J* = 7.5, 1.5 Hz, 1H, Ar-*H*), 7.42 (dd, *J* = 2.5, 1.5 Hz, 1H, Ar-*H*), 7.36 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.32 – 7.27 (m, 1H, Ar-*H*), 7.24 (td, *J* = 7.5, 1.0 Hz, 1H, Ar-*H*),

7.03 (d, $J = 1.0$ Hz, 1H, Ar-*H*), 6.91 (ddd, $J = 8.0, 2.5, 1.0$ Hz, 1H, Ar-*H*), 3.90 (s, 3H, OCH₃); ¹³C NMR (101 MHz, CDCl₃) δ 160.1, 155.9, 155.0, 131.9, 130.0, 129.3, 124.5, 123.1, 121.1, 117.7, 114.6, 111.3, 110.3, 101.8, 55.5; LRMS m/z 225.0 [M+H]⁺; HRMS (ESI⁺) found m/z 225.0910 [M+H]⁺, C₁₅H₁₃O₂ requires m/z 225.0910; IR $\nu_{\max}$ (neat)/cm⁻¹ 2835, 2361, 2342, 1613, 1571, 1489, 1454, 1236, 1164, 1033, 779, 749; R_F = 0.41 (5% EtOAc in Petrol).

Data is consistent with literature: X. Qin, D. Sun, Q. You, Y. Cheng, J. Lan, J. You, *Org. Lett.* **2015**, *17*, 1762-1765.^[188]



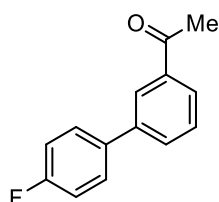
4'-methoxy-2,5-dimethyl-1,1'-biphenyl (37k)

Following general procedure **I**, 4-methoxybenzenesulfinamide (77.0 mg, 0.45 mmol, 1.5 equiv.), 2-bromo-1,4-dimethylbenzene (41.0 μL, 0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 5.0 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (0 – 3% EtOAc in Petrol) to give the title product as a colourless oil (52.2 mg, 82%).

¹H NMR (400 MHz, CDCl₃) δ 7.26 (d, $J = 9.0$ Hz, 2H, Ar-*H*), 7.16 (d, $J = 8.5$ Hz, 1H, Ar-*H*), 7.06 (d, $J = 6.5$ Hz, 2H, Ar-*H*), 6.95 (d, $J = 9.0$ Hz, 2H, Ar-*H*), 3.86 (s, 3H, OCH₃), 2.35 (s, 3H, CH₃), 2.24 (s, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 158.6, 141.5, 135.3, 134.7, 132.4, 130.8, 130.4, 127.8, 113.6, 55.4, 21.1, 20.2; HRMS (GC EI⁺) found m/z

212.1196 (M^+), $C_{15}H_{16}O$ requires m/z 212.1201; **IR** $\nu_{\max}$ (neat)/ cm^{-1} 2953, 2361, 2341, 1575, 1516, 1244, 1176, 1032, 834, 810; **R_F** = 0.35 (100% hexanes).

Data is consistent with literature: X. Yi, K. Chen, J. Guo, W. Chen, W. Chen, *Adv. Synth. Cat.* **2020**, 362, 4373–43.^[189]

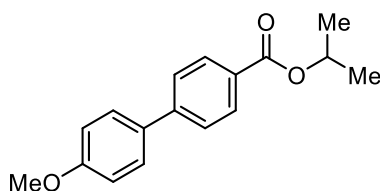


1-(4'-fluoro-[1,1'-biphenyl]-3-yl)ethan-1-one (37l)

Following general procedure **I**, 4-fluorobenzenesulfinamide (71.6 mg, 0.45 mmol, 1.5 equiv.), 1-(3-bromophenyl)ethan-1-one (39.5 μL , 0.30 mmol, 1.0 equiv.), $\text{Pd}(\text{OAc})_2$ (3.4 mg, 0.015 mmol, 5 mol%), $\text{P}(t\text{-Bu})_2\text{Me}\cdot\text{HBF}_4$ (7.4 mg, 0.030 mmol, 10 mol%) and Cs_2CO_3 (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (3 – 5% EtOAc in Petrol) to give the title product as a colourless oil (41.8 mg, 66%).

^1H NMR (400 MHz, CDCl_3) δ 8.13 (t, J = 2.0 Hz, 1H, Ar-*H*), 7.93 (ddd, J = 7.5, 2.0, 1.0 Hz, 1H, Ar-*H*), 7.74 (ddd, J = 7.5, 2.0, 1.0 Hz, 1H, Ar-*H*), 7.61 – 7.51 (m, 3H, Ar-*H*), 7.21 – 7.11 (m, 2H, Ar-*H*), 2.66 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, CDCl_3) δ 198.1, 162.9 (d, $^1J_{\text{CF}}$ = 247.5 Hz), 140.9, 137.8, 136.5 (d, $^4J_{\text{CF}}$ = 3.0 Hz), 131.7, 129.3, 129.0 (d, $^3J_{\text{CF}}$ = 8.0 Hz), 127.4, 126.9, 116.0 (d, $^2J_{\text{CF}}$ = 21.5 Hz), 26.9; **^{19}F NMR** (377 MHz, CDCl_3) δ -114.81 (tt, J = 8.5, 5.0 Hz); **HRMS** (GC EI^+) found m/z 214.0788 (M^+), $C_{14}H_{11}FO$ requires m/z 214.0794; **IR** $\nu_{\max}$ (neat)/ cm^{-1} 2980, 2924, 2360, 1685, 1605, 1515, 1235, 1160, 839, 795, 694; **R_F** = 0.32 (5% EtOAc in Petrol).

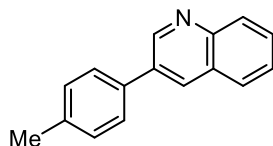
Data is consistent with literature: M. Kienle, P. Knochel, *Org. Lett.* **2010**, *12*, 2702–2705.^[190]



isopropyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (37m)

Following general procedure **I**, 4-methoxybenzenesulfonamide (77.0 mg, 0.45 mmol, 1.5 equiv.), isopropyl 4-bromobenzoate (73.0 mg, 0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (3% EtOAc in Petrol) to give the title product as a white crystalline solid (63.8 mg, 79%).

¹H NMR (400 MHz, CDCl₃) δ 8.08 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.61 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.57 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.00 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 5.27 (p, *J* = 6.5 Hz, 1H, OCH), 3.86 (s, 3H, OCH₃), 1.39 (d, *J* = 6.5 Hz, 6H, OCH(CH₃)₂); **¹³C NMR** (101 MHz, CDCl₃) δ 166.2, 159.9, 145.2, 132.7, 130.2, 129.2, 128.5, 126.5, 114.5, 68.4, 55.5, 22.1; **LRMS** *m/z* 293.1 [M+Na]⁺; **HRMS** (ESI⁺) found *m/z* 271.1329 [M+H]⁺, C₁₇H₁₉O₃ requires *m/z* 271.1329; **IR** ν_{max} (neat)/cm⁻¹ 2983, 2838, 2360, 1709, 1606, 1279, 1250, 1102, 909, 829, 774, 732; **mp** 83 – 85 °C (EtOAc); **R_F** = 0.26 (5% EtOAc in Petrol).

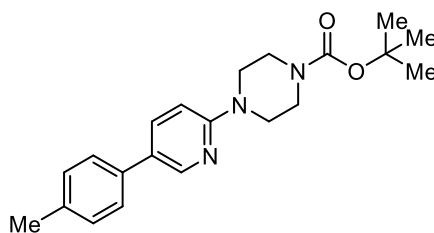


3-(*p*-tolyl)quinoline (37n)

Following general procedure **I**, 4-methylbenzenesulfinamide (69.8 mg, 0.45 mmol, 1.5 equiv.), 3-bromoquinoline (41.0 μ L, 0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (10 - 15% EtOAc in Petrol) to give the title product as a white solid (39.1 mg, 59%).

¹H NMR (400 MHz, CDCl₃) δ 9.18 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 8.29 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 8.14 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.88 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.72 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Ar-*H*), 7.63 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.58 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar-*H*), 7.34 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 2.44 (s, 3H, CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 150.0, 147.3, 138.3, 135.1, 134.0, 133.1, 130.1, 129.4, 129.3, 128.3, 128.1, 127.4, 127.1, 21.3; **LRMS** *m/z* 220.2 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 220.1120 [M+H]⁺, C₁₆H₁₄N requires *m/z* 220.1121; **IR** ν_{max} (neat)/cm⁻¹ 2920, 2360, 1518, 954, 910, 816, 751; **R_f** = 0.11 (10% EtOAc in Petrol).

Data is consistent with literature: R. Yan, X. Liu, C. Pan, X. Zhou, X. Li, X. Kang, G. Huang, *Org. Lett.* **2013**, *15*, 4876–4879.^[191]

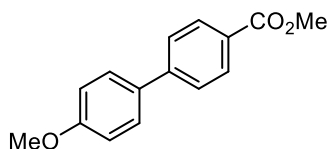


***tert*-butyl 4-(5-(*p*-tolyl)pyridin-2-yl)piperazine-1-carboxylate (37o)**

Following general procedure **I**, 4-methylbenzenesulfinamide (69.8 mg, 0.45 mmol, 1.5 equiv.), 4-Boc-1-(5-bromo-2-pyridyl)piperazine (102.7 mg, 0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (2 – 5 % EtOAc in toluene) to give the title product as a white solid (52.9 mg, 50%).

¹H NMR (400 MHz, CDCl₃) δ 8.44 (dd, *J* = 2.5, 1.0 Hz, 1H, Pyr-*H*), 7.71 (dd, *J* = 9.0, 2.5 Hz, 1H, Pyr-*H*), 7.41 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.23 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.70 (dd, *J* = 9.0, 1.0 Hz, 1H, Pyr-*H*), 3.57 (s, 8H, N(CH₂)₂(CH₂)₂N), 2.38 (s, 3H, CH₃), 1.50 (s, 9H, OC(CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃) δ 158.4, 154.9, 146.1, 136.7, 136.2, 135.4, 129.7, 126.8, 126.2, 107.1, 80.1, 45.3, 28.6, 21.2; **LRMS** *m/z* 298.2 [M-CH₂=C(CH₃)₂+H]⁺, 354.2 [M+H]⁺; **HRMS** (ESI⁺) found *m/z* 354.2177 [M+H]⁺, C₂₁H₂₈O₂N₃ requires *m/z* 354.2176; **IR** ν_{max} (neat)/cm⁻¹ 2981, 2361, 2342, 1678, 1603, 1492, 1419, 1366, 1241, 1174, 806, 730; **mp** 137 – 139 °C (EtOAc); **R_F** = 0.21 (10% EtOAc in toluene).

Poor yielding products from the sulfinamide cross-coupling



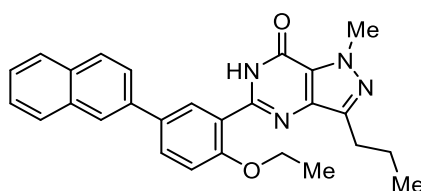
methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (37p)

Following general procedure **I**, 4-methoxybenzenesulfinamide (77.0 mg, 0.45 mmol, 1.5 equiv.), methyl 4-bromobenzoate (64.5 mg, 0.30 mmol, 1.0 equiv.), Pd(OAc)₂ (3.4 mg, 0.015 mmol, 5 mol%), P(*t*-Bu)₂Me·HBF₄ (7.4 mg, 0.030 mmol, 10 mol%) and Cs₂CO₃ (293.2 mg, 0.90 mmol, 3.0 equiv.) were combined in 1,4-dioxane (1.0 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (5 – 35 % EtOAc in Petrol) to give the title product as a crystalline white solid (7.4 mg, 10%).

¹H NMR (400 MHz, CDCl₃) δ 8.08 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.62 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.58 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.00 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 3.94 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 167.2, 160.0, 145.4, 132.6, 130.3, 128.6, 128.5, 126.6, 114.5, 55.5, 52.2; **HRMS** (ESI⁺) found *m/z* 243.1017 [M+H]⁺, C₁₅H₁₅O₃ requires *m/z* 243.1016; **IR** ν_{max} (neat)/cm⁻¹ 2924, 2854, 2361, 2341, 1719, 1604, 1292, 1201, 1114, 833, 772; **mp** 138 – 140 °C (EtOAc); **R_F** = 0.27 (10% EtOAc in Petrol).

Note: No 4-bromobenzoic acid or hydrolysed biaryl product is observed in the reaction mixture.

Data is consistent with literature: B. Xiong, Y. Li, Y. Wei, S. Kramer, Z. Lian, *Org. Lett.* **2020**, 22, 6334- 6338.^[192]

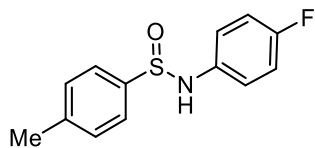


5-(2-ethoxy-5-(naphthalen-2-yl)phenyl)-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (37q)

Following general procedure **I** on half the scale (0.15 mmol), 4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzenesulfonamide (84.5 mg, 0.23 mmol, 1.5 equiv.), 2-bromonaphthalene (31.0 mg, 0.15 mmol, 1.0 equiv.), Pd(OAc)₂ (1.7 mg, 0.008 mmol 5 mol%), P(*t*-Bu)₂Me·HBF₄ (3.7 mg, 0.015 mmol, 10 mol%) and Cs₂CO₃ (146.6 mg, 0.45 mmol, 3.0 equiv.) were combined in dioxane (0.5 mL, 0.3 M) and heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (50% EtOAc in Petrol) to give the title product as an off-white solid (8.6 mg, 13%).

¹H NMR (400 MHz, CDCl₃) δ 11.12 (br. s, 1H, NH), 8.80 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 8.08 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.98 – 7.85 (m, 3H, Ar-*H*), 7.82 – 7.76 (m, 2H, Ar-*H*), 7.55 – 7.47 (m, 2H, Ar-*H*), 7.15 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 4.35 (q, *J* = 7.0 Hz, 2H, OCH₂CH₃), 4.29 (s, 3H, NCH₃), 2.99 – 2.93 (m, 2H, CH₂CH₂CH₃), 1.95 – 1.84 (m, 2H, CH₂CH₂CH₃), 1.64 (t, *J* = 7.0 Hz, 3H, OCH₂CH₃), 1.04 (t, *J* = 7.5 Hz, 3H, CH₂CH₂CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 156.1, 154.0, 148.5, 146.9, 137.4, 135.0, 133.8, 132.7, 131.3, 131.3, 130.0, 128.7, 128.3, 127.8, 126.6, 126.2, 125.7, 125.4, 124.7, 120.7, 113.7, 65.7, 38.4, 27.9, 22.5, 14.9, 14.2; **HRMS** (ESI⁺) found *m/z* 439.2127 [M+H]⁺, C₂₇H₂₇O₂N₄ requires *m/z* 439.2129; **IR** ν_{max} (neat)/cm⁻¹ 3304, 2960, 2360, 2342, 1695, 1494, 1243, 808; **mp** 129 – 131 °C (EtOAc); **R_F** = 0.61 (90% EtOAc in Petrol).

6.4.3.b Aryl sulfinamides under Pd-mediated *N*-arylation conditions



***N*-(4-fluorophenyl)-4-methylbenzenesulfinamide (43)**

Following a procedure adapted from a report from Zeng and co-workers.^[131]

4-methylbenzenesulfinamide (46.6 mg, 0.30 mmol, 1.0 equiv.), 1-bromo-4-fluorobenzene (43.0 μ L, 0.39 mmol, 1.3 equiv.), Pd₃(dba)₂ (5.5 mg, 0.006 mmol, 2 mol%), *t*-Bu XPhos (6.4 mg, 0.015 mmol, 5 mol%) and NaOH (28.8 mg, 0.72 mmol, 2.4 equiv.) were combined in a microwave reaction vial. The reaction vessel was purged and backfill with N₂ ($\times$ 6). Toluene (2.0 mL, 0.2 M) and H₂O (92.0 μ L, 5.10 mmol, 17.0 equiv.) were added and the flask was heated at 100 °C for 16 h. The crude residue was then purified by flash column chromatography (2 – 40% EtOAc in Petrol) to give the title product as an off-white solid (25.8 mg, 34%).

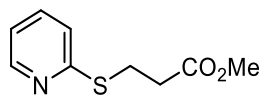
Note: Only 1% of the desulfinamidative biaryl product **37a** was observed by HPLC analysis of the crude reaction mixture.

¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, J = 8.5 Hz, 2H, Ar-*H*), 7.33 (dt, J = 8.0 Hz, 2H, Ar-*H*), 7.08 – 7.02 (m, 2H, Ar-*H*), 6.97 (dd, J = 9.0, 8.0 Hz, 2H, Ar-*H*), 5.96 (br. s, 1H, NH), 2.43 (s, 3H, Ar-CH₃); **¹³C NMR** (101 MHz, CDCl₃) δ 160.3 (d, $^1J_{CF}$ = 147.0 Hz), 142.2, 141.4, 136.3 (d, $^4J_{CF}$ = 2.5 Hz), 129.9, 125.6, 122.1 (d, $^3J_{CF}$ = 8.5 Hz), 116.3 (d, $^2J_{CF}$ = 22.5 Hz), 21.6; **¹⁹F NMR** (377 MHz, CDCl₃) δ -118.89 (ddd, J = 12.5, 8.0, 4.5 Hz); **LRMS** m/z 272.0 [M+Na]⁺; **HRMS** (ESI⁺) found m/z 250.0699 [M+H]⁺, C₁₃H₁₃ONFS

requires m/z 250.0696; **IR** $\nu_{\max}$ (neat)/ cm^{-1} 3083, 3050, 2360, 2342, 1505, 1210, 1091, 1054, 818; **R_F** = 0.44 (40% EtOAc in Petrol).

Data is consistent with literature: B. J. Austermuehle, E. S. Collins, C. G. Hamaker, S. R. Hitchcock, *Synth. Comm.* **2021**, *51*, 3483-3491.^[193]

6.4.3.c Synthesis of 2-pyridyl sulfoximine reagent

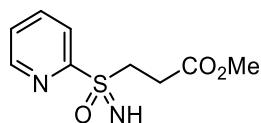


methyl 3-(pyridin-2-ylthio)propanoate (*pre-44b*)

Following general procedure **A**, 2-mercaptopyridine (333.5 mg, 3.0 mmol, 1.0 equiv.), methyl acrylate (325.0 μL , 3.6 mmol, 1.2 equiv.) and Et_3N (418.0 μL , 3.0 mmol, 1.0 equiv.) in acetonitrile (6.0 mL, 0.5 M) were heated to 55 °C for 16 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and purified by flash column chromatography (10% EtOAc in Petrol) to give the title compound as a colourless oil (408.9 mg, 69%).

¹H NMR (400 MHz, CDCl_3) δ 8.41 (ddd, J = 5.0, 2.0, 1.0 Hz, 1H, Pyr-*H*), 7.46 (ddd, J = 8.0, 7.5, 2.0 Hz, 1H, Pyr-*H*), 7.15 (dt, J = 8.0, 1.0 Hz, 1H, Pyr-*H*), 6.97 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H, Pyr-*H*), 3.69 (s, 3H, CH_3), 3.43 (t, J = 7.0 Hz, 2H, SCH_2), 2.79 (t, J = 7.0 Hz, 2H, $\text{CH}_2\text{CO}_2\text{CH}_3$); **¹³C NMR** (101 MHz, CDCl_3) δ 172.7, 158.3, 149.5, 136.1, 122.6, 119.6, 51.9, 34.6, 25.1; **LRMS** m/z 198.0 $[\text{M}+\text{H}]^+$; **HRMS** (ESI^+) found m/z 198.0585 $[\text{M}+\text{H}]^+$, $\text{C}_9\text{H}_{12}\text{O}_2\text{NS}$ requires m/z 198.0583; **R_f** = 0.53 (20% EtOAc in Petrol).

Data is consistent with literature reports: S. Greed, E. L. Briggs, F. I. M. Idiris, A. J. P. White, U. Lücking, J. A. Bull, *Chem. Eur. J* **2020**, 26, 12533-12538.^[103]



methyl 3-(pyridine-2-sulfonimidoyl)propanoate (44b)

Procedure adapted from a report by Bull and co-workers.^[163]

Open to air, methyl 3-(pyridin-2-ylthio)propanoate (389.2 mg, 1.97 mmol, 1.0 equiv.) and ammonium carbonate (379.6 mg, 3.95 mmol, 2.0 equiv.) were suspended in MeOH (4.0 mL, 0.5 M). To the stirring solution was added (diacetoxyiodo)benzene (1.59 g, 4.93 mmol, 2.5 equiv.) and the reaction was stirred at room temperature for 3 h. (*Note: after 30 min the cloudy white suspension became a clear, homogenous solution*). The reaction mixture was then concentrated *in vacuo*. The resultant crude residue was then purified by flash column chromatography (80 – 100% EtOAc in Petrol) to give the title compound as a pale-yellow oil (344.7 mg, 77%).

¹H NMR (400 MHz, CDCl₃) δ 8.74 (ddd, J = 5.0, 2.0, 1.0 Hz, 1H, Pyr-*H*), 8.15 (dt, J = 8.0, 1.0 Hz, 1H, Pyr-*H*), 7.96 (td, J = 8.0, 1.5 Hz, 1H, Pyr-*H*), 7.53 (ddd, J = 7.5, 4.5, 1.0 Hz, 1H, Pyr-*H*), 3.77 (t, J = 7.5 Hz, 2H, S(O)(NH)CH₂CH₂), 3.66 (s, 3H, CO₂CH₃), 2.96 – 2.68 (m, 3H, S(O)(NH)CH₂ and NH); **¹³C NMR** (101 MHz, CDCl₃) δ 171.0, 150.4, 138.4, 127.1, 122.5, 52.4, 49.6, 28.2; **LRMS** m/z 229.0 [M+H]⁺; **HRMS** (ESI⁺) found m/z 229.0643 [M+H]⁺, C₉H₁₃O₃N₂S requires m/z 229.0641; **IR** ν_{max} (neat)/cm⁻¹ 3544, 3278, 2954, 1733, 1578, 1426, 1364, 1229, 1085, 991, 780; **R_f** = 0.14 (100% EtOAc in Petrol).

7. References

- [1] a) X. A. F. Cook, A. de Gombert, J. McKnight, L. R. E. Pantaine, M. C. Willis, *Angew. Chem. Int. Ed.* **2021**, *60*, 11068-11091; b) E. C. Constable, C. E. Housecroft, *Molecules* **2019**, *24*, 3951.
- [2] A. Funk, P. V. Divekar, *Can. J. Microbiol.* **1959**, *5*, 317-321.
- [3] a) S. P. Curtis, B. Bockow, C. Fisher, J. Olaleye, A. Compton, A. T. Ko, A. S. Reicin, *BMC Musculoskel. Dis.* **2005**, *6*, 58; b) V. L. Keedy, T. M. Bauer, J. M. Clarke, H. Hurwitz, I. Baek, I. Ha, *J. Clin. Oncol.* **2018**, *36*, 1.
- [4] a) C. Coluccini, N. Manfredi, M. M. Salamone, R. Ruffo, M. G. Lobello, F. De Angelis, A. Abboto, *J. Org. Chem.* **2012**, *77*, 7945-7956; b) C. L. Fraser, A. P. Smith, *J. Polym. Sci. A1* **2000**, *38*, 4704-4716; c) L. Gao, J. Ni, M. Su, J. Kang, J. Zhang, *Dyes Pigments* **2019**, *165*, 231-238; d) F. Makoto, O. Katsuyuki, *Bull. Chem. Soc. Japan* **1996**, *69*, 1471-1482.
- [5] S. L. Hargreaves, B. L. Pilkington, S. E. Russell, P. A. Worthington, *Tetrahedron Lett.* **2000**, *41*, 1653-1656.
- [6] K. Teegardin, J. I. Day, J. Chan, J. Weaver, *Org. Process Res. Dev.* **2016**, *20*, 1156-1163.
- [7] R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845-5859.
- [8] George R. Newkome, Anil K. Patri, E. Holder, Ulrich S. Schubert, *Eur. J. Med. Chem.* **2004**, *2004*, 235-254.
- [9] L.-C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, 18020-18021.
- [10] D. Blakemore, in *Synthetic Methods in Drug Discovery: Volume 1, Vol. 1*, The Royal Society of Chemistry, **2016**, pp. 1-69.
- [11] T. Markovic, B. N. Rocke, D. C. Blakemore, V. Mascitti, M. C. Willis, *Chem. Sci.* **2017**, *8*, 4437-4442.
- [12] S. Schröter, C. Stock, T. Bach, *Tetrahedron* **2005**, *61*, 2245-2267.
- [13] a) A. Núñez, A. Sánchez, C. Burgos, J. Alvarez-Builla, *Tetrahedron* **2004**, *60*, 6217-6224; b) S. Yanagisawa, K. Ueda, T. Taniguchi, K. Itami, *Org. Lett.* **2008**, *10*, 4673-4676.
- [14] a) S. Yamada, K. Murakami, K. Itami, *Org. Lett.* **2016**, *18*, 2415-2418; b) B. Liu, Y. Huang, J. Lan, F. Song, J. You, *Chem. Sci.* **2013**, *4*, 2163.
- [15] a) C. Sambhagio, S. P. Marsden, A. J. Blacker, P. C. McGowan, *Chem. Soc. Rev.* **2014**, *43*, 3525-3550; b) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359-1469.
- [16] D. A. Everson, D. J. Weix, *J. Org. Chem.* **2014**, *79*, 4793-4798.
- [17] L. K. G. Ackerman, M. M. Lovell, D. J. Weix, *Nature* **2015**, *524*, 454-457.
- [18] K. Kang, N. L. Loud, T. A. DiBenedetto, D. J. Weix, *J. Am. Chem. Soc.* **2021**, *143*, 21484-21491.
- [19] M. Hapke, L. Brandt, A. Lützen, *Chem. Sov. Rev.* **2008**, *37*, 2782.
- [20] a) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451-3479; b) N. Miyaoura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457-2483; c) D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443-4458.
- [21] a) I. P. Beletskaya, F. Alonso, V. Tyurin, *Coordin. Chem. Rev.* **2019**, *385*, 137-173; b) A. J. J. Lennox, G. C. Lloyd-Jones, *Chem. Soc. Rev.* **2014**, *43*, 412-443.
- [22] a) P. A. Cox, A. G. Leach, A. D. Campbell, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2016**, *138*, 9145-9157; b) P. A. Cox, M. Reid, A. G. Leach, A. D. Campbell, E. J. King, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2017**, *139*, 13156-13165.
- [23] a) N. A. Jones, J. W. Antoon, A. L. Bowie Jr., J. B. Borak, E. P. Stevens, *J. Heterocyclic Chem.* **2007**, *44*, 363-367; b) C. Boos, D. M. Bowles, C. Cai, A. Casimiro-Garcia, X. Chen, C. A. Hulford, S. M. Jennings, E. Jason Kiser, D. W. Piotrowski, M. Sammons, R. A. Wade, *Tetrahedron Lett.* **2011**, *52*, 7025-7029; c) T. Ishiyama, K. Ishida, N. Miyaoura, *Tetrahedron* **2001**, *57*, 9813-9816.

- [24] J. Z. Deng, D. V. Paone, A. T. Ginnetti, H. Kurihara, S. D. Dreher, S. A. Weissman, S. R. Stauffer, C. S. Burgey, *Org. Lett.* **2009**, *11*, 345-347.
- [25] B. M. Crowley, C. M. Potteiger, J. Z. Deng, C. K. Prier, D. V. Paone, C. S. Burgey, *Tetrahedron Lett.* **2011**, *52*, 5055-5059.
- [26] A. J. J. Lennox, G. C. Lloyd-Jones, *Isr. J. Chem.* **2010**, *50*, 664-674.
- [27] Y. Yamamoto, M. Takizawa, X. Q. Yu, N. Miyaura, *Angew. Chem. Int. Ed.* **2008**, *47*, 928-931.
- [28] a) Y. Yamamoto, M. Takizawa, X. Q. Yu, N. Miyaura, *Heterocycles* **2010**, *80*, 359-368; b) S. Sakashita, M. Takizawa, J. Sugai, H. Ito, Y. Yamamoto, *Org. Lett.* **2013**, *15*, 4308-4311; c) K. Chen, R. Peterson, S. K. Math, J. B. LaMunyon, C. A. Testa, D. R. Cefalo, *Tetrahedron Lett.* **2012**, *53*, 4873-4876; d) K. Billingsley, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3358-3366; e) L. Ackermann, H. K. Potukuchi, *Synlett* **2009**, 2852-2856.
- [29] a) G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302-4314; b) G. A. Molander, B. Canturk, L. E. Kennedy, *J. Org. Chem.* **2009**, *74*, 973-980; c) G. A. Molander, J.-G. Ludvine, in *Org. Reactions*, **2013**, pp. 1-316.
- [30] W. Ren, J. Li, D. Zou, Y. Wu, Y. Wu, *Tetrahedron* **2012**, *68*, 1351-1358.
- [31] N. A. Isley, Y. Wang, F. Gallou, S. Handa, D. H. Aue, B. H. Lipshutz, *ACS Cat.* **2017**, *7*, 8331-8337.
- [32] P. B. Hodgson, F. H. Salingue, *Tetrahedron Lett.* **2004**, *45*, 685-687.
- [33] a) A. Lützen, C. Gütz, *Synthesis* **2010**, *2010*, 85-90; b) P. Gros, A. Doudouh, Y. Fort, *Tetrahedron Lett.* **2004**, *45*, 6239-6241.
- [34] E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 6716-6717.
- [35] D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961-+.
- [36] J. A. Gonzalez, O. M. Ogbay, G. F. Morehouse, N. Rosson, K. N. Houk, A. G. Leach, P. H. Y. Cheong, M. D. Burke, G. C. Lloyd-Jones, *Nat. Chem.* **2016**, *8*, 1067-1075.
- [37] a) J. W. B. Fyfe, C. P. Seath, A. J. B. Watson, *Angew. Chem. Int. Ed.* **2014**, *53*, 12077-12080; b) J. W. B. Fyfe, E. Valverde, C. P. Seath, A. R. Kennedy, J. M. Redmond, N. A. Anderson, A. J. B. Watson, *Chem. Eur. J* **2015**, *21*, 8951-8964; c) C. P. Seath, J. W. B. Fyfe, J. J. Molloy, A. J. B. Watson, *Angew. Chem. Int. Ed.* **2015**, *54*, 9976-9979.
- [38] G. R. Dick, E. M. Woerly, M. D. Burke, *Angew. Chem. Int. Ed.* **2012**, *51*, 2667-2672.
- [39] a) P. Guo, H. Zhang, J. Zhou, F. Gallou, M. Parmentier, H. Wang, *J. Org. Chem.* **2018**, *83*, 7523-7527; b) J. F. Mendes da Silva, A. F. Yepes Perez, N. Pinto de Almeida, *RSC Adv.* **2014**, *4*, 28148-28155; c) J. F. M. da Silva, A. F. Yepes Perez, N. P. de Almeida, *Synthetic Commun.* **2015**, *45*, 1995-2004; d) Y. Li, J. Wang, Z. Wang, M. Huang, B. Yan, X. Cui, Y. Wu, Y. Wu, *RSC Adv.* **2014**, *4*, 36262-36266.
- [40] a) M. Koyanagi, N. Eichenauer, H. Ihara, T. Yamamoto, M. Sugimoto, *Chem. Lett.* **2013**, *42*, 541-543; b) H. Noguchi, K. Hojo, M. Sugimoto, *J. Am. Chem. Soc.* **2007**, *129*, 758-759.
- [41] a) S. Kamio, I. Kageyuki, I. Osaka, H. Yoshida, *Chem. Commun.* **2019**, *55*, 2624-2627; b) H. Ihara, M. Koyanagi, M. Sugimoto, *Org. Lett.* **2011**, *13*, 2662-2665.
- [42] H. Yoshida, M. Seki, S. Kamio, H. Tanaka, Y. Izumi, J. Li, I. Osaka, M. Abe, H. Andoh, T. Yajima, T. Tani, T. Tsuchimoto, *ACS Cat.* **2020**, *10*, 346-351.
- [43] Y. Mutoh, K. Yamamoto, S. Saito, *ACS Cat.* **2020**, *10*, 352-357.
- [44] K. Murakami, S. Yamada, T. Kaneda, K. Itami, *Chem. Rev.* **2017**, *117*, 9302-9332.
- [45] W. Hagui, K. Periasamy, J.-F. Soule, *Eur. J. Org. Chem.* **2021**, *2021*, 5388-5402.
- [46] a) M. Ye, G.-L. Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19090-19093; b) P. Guo, J. M. Joo, S. Rakshit, D. Sames, *J. Am. Chem. Soc.* **2011**, *133*, 16338-16341.
- [47] A. M. Berman, J. C. Lewis, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 14926-14927.
- [48] S. R. Neufeldt, G. Jiménez-Osés, J. R. Huckins, O. R. Thiel, K. N. Houk, *J. Am. Chem. Soc.* **2015**, *137*, 9843-9854.
- [49] a) L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 3291-3306; b) M. P. Huestis, K. Fagnou, *Org. Lett.* **2009**, *11*, 1357-1360; c) J.-P. Leclerc,

- K. Fagnou, *Angew. Chem. Int. Ed.* **2006**, *45*, 7781-7786; d) D. J. Schipper, M. El-Salfiti, C. J. Whipp, K. Fagnou, *Tetrahedron* **2009**, *65*, 4977-4983.
- [50] H.-Y. Sun, S. I. Gorelsky, D. R. Stuart, L.-C. Campeau, K. Fagnou, *J. Org. Chem.* **2010**, *75*, 8180-8189.
- [51] a) S. Duric, F. D. Sypaseuth, S. Hoof, E. Svensson, C. C. Tzschucke, *Chem. Eur. J* **2013**, *19*, 17456-17463; b) S. Duric, C. C. Tzschucke, *Org. Lett.* **2011**, *13*, 2310-2313.
- [52] A. Larivée, J. J. Mousseau, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 52-54.
- [53] J. Xu, G. Cheng, D. Su, Y. Liu, X. Wang, Y. Hu, *Chem. Eur. J* **2009**, *15*, 13105-13110.
- [54] Y. Zeng, C. Zhang, C. Yin, M. Sun, H. Fu, X. Zheng, M. Yuan, R. Li, H. Chen, *Org. Lett.* **2017**, *19*, 1970-1973.
- [55] F. G. Mann, J. Watson, *J. Org. Chem.* **1948**, *13*, 502-531.
- [56] G. R. Newkome, D. C. Hager, *J. Am. Chem. Soc.* **1978**, *100*, 5567-5568.
- [57] a) Y. Uchida, K. Onoue, N. Tada, F. Nagao, H. Kozawa, S. Oae, *Heteroatom Chem.* **1990**, *1*, 295-306; b) Y. Uchida, K. Onoue, N. Tada, F. Nagao, S. Oae, *Tetrahedron Lett.* **1989**, *30*, 567-570; c) Y. Uchida, H. Kozawa, *Tetrahedron Lett.* **1989**, *30*, 6365-6368.
- [58] M. C. Hilton, X. Zhang, B. T. Boyle, J. V. Alegre-Requena, R. S. Paton, A. McNally, *Science* **2018**, *362*, 799-804.
- [59] B. T. Boyle, M. C. Hilton, A. McNally, *J. Am. Chem. Soc.* **2019**, *141*, 15441-15449.
- [60] a) N. Furukawa, T. Shibutani, H. Fujihara, *Tetrahedron Lett.* **1989**, *30*, 7091-7094; b) N. Furukawa, T. Shibutani, H. Fujihara, *Tetrahedron Lett.* **1987**, *28*, 5845-5848; c) T. Kawai, N. Furukawa, S. Oae, *Tetrahedron Lett.* **1984**, *25*, 2549-2552; d) S. Oae, T. Takeda, S. Wakabayashi, *Tetrahedron Lett.* **1988**, *29*, 4445-4448; e) J. Uenishi, T. Tanaka, S. Wakabayashi, S. Oae, H. Tsukube, *Tetrahedron Lett.* **1990**, *31*, 4625-4628.
- [61] a) M. Zhou, J. Tsien, T. Qin, *Angew. Chem. Int. Ed.* **2020**, *59*, 7372-7376; b) A. M. Horan, V. K. Duong, E. M. McGarrigle, *Org. Lett.* **2021**, *23*, 9089-9093; c) V. K. Duong, A. M. Horan, E. M. McGarrigle, *Org. Lett.* **2020**, *22*, 8451-8457.
- [62] A. G. Myers, D. Tanaka, M. R. Mannion, *J. Am. Chem. Soc.* **2002**, *124*, 11250-11251.
- [63] a) L. J. Goossen, N. Rodríguez, B. Melzer, C. Linder, G. Deng, L. M. Levy, *J. Am. Chem. Soc.* **2007**, *129*, 4824-4833; b) L. J. Goossen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662-664; c) B. Mu, Y. Wu, J. Li, D. Zou, J. Chang, Y. Wu, *Org. Biomol. Chem* **2016**, *14*, 246-250.
- [64] a) M. Font, J. M. Quibell, G. J. P. Perry, I. Larrosa, *Chem. Commun.* **2017**, *53*, 5584-5597; b) P. Lu, C. Sanchez, J. Cornella, I. Larrosa, *Org. Lett.* **2009**, *11*, 5710-5713.
- [65] X. Li, D. Zou, F. Leng, C. Sun, J. Li, Y. Wu, Y. Wu, *Chem. Commun.* **2013**, *49*, 312-314.
- [66] C. K. Haley, C. D. Gilmore, B. M. Stoltz, *Tetrahedron* **2013**, *69*, 5732-5736.
- [67] D. Hackenberger, P. Weber, D. C. Blakemore, L. J. Goossen, *J. Org. Chem.* **2017**, *82*, 3917-3925.
- [68] H. Malmberg, M. Nilsson, *Tetrahedron* **1986**, *42*, 3981-3986.
- [69] J.-B. Rouchet, C. Schneider, C. Spitz, J. Lefèvre, G. Dupas, C. Fruit, C. Hoarau, *Chem. Eur. J* **2014**, *20*, 3610-3615.
- [70] a) W. Borsche, W. Lange, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 2346-2356; b) S. Smiles, R. Le Rossignol, *J. Chem. Soc. Trans* **1908**, *93*, 745-762; c) S. Krishna, H. Singh, *J. Am. Chem. Soc.* **1928**, *50*, 792-798.
- [71] a) J. Aziz, A. Hamze, *Org. Biomol. Chem* **2020**, *18*, 9136-9159; b) J. Aziz, S. Messaoudi, M. Alami, A. Hamze, *Org. Biomol. Chem* **2014**, *12*, 9743-9759; c) D. Kaiser, I. Klose, R. Oost, J. Neuhaus, N. Maulide, *Chem. Rev.* **2019**, *119*, 8701-8780.
- [72] a) M. J. Tilby, M. C. Willis, *Expert Opin. Drug Disc.* **2021**, *16*, 1227 - 1231; b) K. A. Scott, J. T. Njardarson, *Top. Curr. Chem.* **2018**, *376*.
- [73] a) R. J. Reddy, A. H. Kumari, *RSC Adv.* **2021**, *11*, 9130-9221; b) S. Liang, K. Hofman, M. Friedrich, G. Manolikakes, *Eur. J. Org. Chem.* **2020**, *2020*, 4664-4676.
- [74] E. J. Emmett, M. C. Willis, *Asian J. Org. Chem.* **2015**, *4*, 602-611.
- [75] H. Woolven, C. González-Rodríguez, I. Marco, A. L. Thompson, M. C. Willis, *Org. Lett.* **2011**, *13*, 4876-4878.
- [76] a) E. J. Emmett, B. R. Hayter, M. C. Willis, *Angew. Chem. Int. Ed.* **2013**, *52*, 12679-12683; b) B. N. Rocke, K. B. Bahnck, M. Herr, S. Lavergne, V. Mascitti, C. Perreault, J.

- Polivkova, A. Shavnya, *Org. Lett.* **2014**, *16*, 154-157; c) A. S. Deeming, C. J. Russell, A. J. Hennessy, M. C. Willis, *Org. Lett.* **2014**, *16*, 150-153.
- [77] a) A. T. Davies, J. M. Curto, S. W. Bagley, M. C. Willis, *Chem. Sci.* **2017**, *8*, 1233-1237; b) A. Shavnya, S. B. Coffey, A. C. Smith, V. Mascitti, *Org. Lett.* **2013**, *15*, 6226-6229; c) P. K. T. Lo, Y. Chen, M. C. Willis, *ACS Cat.* **2019**, *9*, 10668-10673.
- [78] a) J. M. Baskin, Z. Y. Wang, *Tetrahedron Lett.* **2002**, *43*, 8479-8483; b) A. Shavnya, K. D. Hesp, A. S. Tsai, *Adv. Synth. Cat.* **2018**, *360*, 1768-1774; c) A. Shavnya, S. B. Coffey, K. D. Hesp, S. C. Ross, A. S. Tsai, *Org. Lett.* **2016**, *18*, 5848-5851; d) J. J. Day, D. L. Neill, S. Xu, M. Xian, *Org. Lett.* **2017**, *19*, 3819-3822.
- [79] W. Zhang, M. Luo, *Chem. Commun.* **2016**, *52*, 2980-2983.
- [80] a) K. Garves, *J. Org. Chem.* **1970**, *35*, 3273-3275; b) R. Selke, W. Thiele, *J. Prakt. Chem.* **1971**, *313*, 875-881.
- [81] D. H. Ortgies, A. Hassanpour, F. Chen, S. Woo, P. Forgione, *Eur. J. Org. Chem.* **2016**, *2016*, 408-425.
- [82] a) K. Cheng, S. Hu, B. L. Zhao, X. M. Zhang, C. Z. Qi, *J. Org. Chem.* **2013**, *78*, 5022-5025; b) K. Cheng, H.-Z. Yu, B. Zhao, S. Hu, X.-M. Zhang, C. Qi, *RSC Adv.* **2014**, *4*, 57923-57928; c) S. Chang, Y. B. Sun, X. R. Zhang, L. L. Dong, H. Y. Zhu, H. W. Lai, D. Wang, *Appl. Organometal. Chem.* **2018**, *32*, e3970.
- [83] J. Wei, H. M. Liang, C. F. Ni, R. Sheng, J. B. Hu, *Org. Lett.* **2019**, *21*, 937-940.
- [84] a) C. Zhou, Q. Liu, Y. Li, R. Zhang, X. Fu, C. Duan, *J. Org. Chem.* **2012**, *77*, 10468-10472; b) C. Zhou, Y. Li, Y. Lu, R. Zhang, K. Jin, X. Fu, C. Duan, *Chinese J. Chem.* **2013**, *31*, 1269-1273; c) D. H. Ortgies, A. Barthelme, S. Aly, B. Desharnais, S. Rioux, P. Forgione, *Synthesis* **2013**, *45*, 694-702; d) D. H. Ortgies, P. Forgione, *Synlett* **2013**, *24*, 1715-1721.
- [85] a) D. Mangel, C. Buonomano, S. Sevigny, G. Di Censo, G. Thevendran, P. Forgione, *Heterocycles* **2015**, *90*, 1228-1239; b) S. Sévigny, P. Forgione, *New J. Chem.* **2013**, *37*, 589-592; c) S. Sevigny, P. Forgione, *Chem. Eur. J.* **2013**, *19*, 2256-2260.
- [86] a) S. H. Gund, K. E. Balsane, J. M. Nagarkar, *Tetrahedron* **2016**, *72*, 5051-5056; b) J. Colomb, T. Billard, *Tetrahedron Lett.* **2013**, *54*, 1471-1474.
- [87] F. Lima, J. André, A. Marziale, A. Greb, S. Glowienke, M. Meisenbach, B. Schenkel, B. Martin, J. Sedelmeier, *Org. Lett.* **2020**.
- [88] T. Markovic, B. N. Rocke, D. C. Blakemore, V. Mascitti, M. C. Willis, *Org. Lett.* **2017**, *19*, 6033-6035.
- [89] a) A. de Gombert, A. I. McKay, C. J. Davis, K. M. Wheelhouse, M. C. Willis, *J. Am. Chem. Soc.* **2020**, *142*, 3564-3576; b) A. de Gombert, M. C. Willis, *Trends Chem.* **2020**, *2*, 865-866.
- [90] T. Markovic, P. R. D. Murray, B. N. Rocke, A. Shavnya, D. C. Blakemore, M. C. Willis, *J. Am. Chem. Soc.* **2018**, *140*, 15916-15923.
- [91] R. A. Sheldon, *Chem. Soc. Rev.* **2012**, *41*, 1437-1451.
- [92] a) B. M. P. Verbist, M. A. J. De Cleyn, M. Surkyn, E. Fraiponts, J. Aerssens, M. J. M. A. Nijssen, H. J. M. Gijssen, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2574-2579; b) H. Bladh, T. Klingstedt, J. Larsson, K. Lawitz, M. Lepistoe, H. Loenn, G. Nikitidis, WO2004043924 (A1), **2004**; c) H. Strobel, S. Ruf, D. Lesuisse, C. Nemecek, Y. El-Ahmad, J. Mauger, S. Guessregen, K. Ritter, J.-L. Malleron, WO2006010643 (A1), **2006**.
- [93] a) M. Janczyk, B. Appel, D. Springstube, H.-J. Fritz, S. Müller, *Org. Biomol. Chem.* **2012**, *10*, 1510; b) H. Saneyoshi, K. Ando, K. Seio, M. Sekine, *Tetrahedron* **2007**, *63*, 11195-11203.
- [94] a) A. G. M. Barrett, S. M. Cramp, A. J. Hennessy, P. A. Procopiou, R. S. Roberts, *Org. Lett.* **2001**, *3*, 271-273; b) M. Gilligan, A. C. Humpheries, T. Ladduwahetty, K. J. Merchant, S. (Merck, Dohme), WO2006095205A1, **2006**.
- [95] K. M. Maloney, J. T. Kuethe, K. Linn, *Org. Lett.* **2011**, *13*, 102-105.
- [96] G. Manolikakes, N.-W. Liu, S. Liang, *Synthesis* **2016**, *48*, 1939-1973.
- [97] a) J. Zhao, S. Niu, X. Jiang, Y. Jiang, X. Zhang, T. Sun, D. Ma, *J. Org. Chem.* **2018**, *83*, 6589-6598; b) W. Zhu, D. Ma, *J. Org. Chem.* **2005**, *70*, 2696-2700.

- [98] S. M. Hell, C. F. Meyer, A. Misale, J. B. I. Sap, K. E. Christensen, M. C. Willis, A. A. Trabanco, V. Gouverneur, *Angew. Chem. Int. Ed.* **2020**, *59*, 11620-11626.
- [99] N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci.* **2013**, *4*, 916-920.
- [100] J. Louie, J. F. Hartwig, *Angew. Chem. Int. Ed.* **1996**, *35*, 2359-2361.
- [101] A. J. J. Lennox, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2012**, *134*, 7431-7441.
- [102] a) D. G. Kananovich, A. Reino, K. Ilmarinen, M. Rõõmusoks, M. Karelson, M. Lopp, *Org. Biomol. Chem.* **2014**, *12*, 5634-5644; b) T. Yanagi, S. Otsuka, Y. Kasuga, K. Fujimoto, K. Murakami, K. Nogi, H. Yorimitsu, A. Osuka, *J. Am. Chem. Soc.* **2016**, *138*, 14582-14585; c) J.-M. Becht, A. Wagner, C. Mioskowski, *J. Org. Chem.* **2003**, *68*, 5758-5761.
- [103] S. Greed, E. L. Briggs, F. I. M. Idiris, A. J. P. White, U. Lücking, J. A. Bull, *Chem. Eur. J.* **2020**, *26*, 12533-12538.
- [104] a) N.-W. Liu, S. Liang, N. Margraf, S. Shaaban, V. Luciano, M. Drost, G. Manolikakes, *Eur. J. Org. Chem.* **2018**, *2018*, 1208-1210; b) W. Liu, W. Deng, S. Sun, C. Yu, X. Su, A. Wu, Y. Yuan, Z. Ma, K. Li, H. Yang, X. Peng, J. Dietrich, *Org. Lett.* **2019**, *21*, 9909-9913; c) X. Zheng, P. Bauer, T. Baumeister, A. J. Buckmelter, M. Caligiuri, K. H. Clodfelter, B. Han, Y.-C. Ho, N. Kley, J. Lin, D. J. Reynolds, G. Sharma, C. C. Smith, Z. Wang, P. S. Dragovich, J. Gunzner-Toste, B. M. Liederer, J. Ly, T. O'Brien, A. Oh, L. Wang, W. Wang, Y. Xiao, M. Zak, G. Zhao, P.-W. Yuen, K. W. Bair, *J. Med. Chem.* **2013**, *56*, 6413-6433; d) J. I. Higham, J. A. Bull, *Chem. Commun.* **2020**, *56*, 4587-4590.
- [105] G. Bravi, H. Hobbs, G. G. A. Inglis, S. Nicolle, P. Simon, WO2019115640 (A1), **2019**.
- [106] S. Das, L. A. Gharat, R. L. Harde, S. Y. Shelke, S. R. Pardeshi, A. Thomas, N. Khair-Atkar-Joshi, D. M. Shah, M. Bajpai, WO 2017/021879 A1, **2017**.
- [107] a) K. Heurling, A. Leuzy, E. R. Zimmer, M. Lubberink, A. Nordberg, *Eur. J. Nucl. Med. Mol. I.* **2016**, *43*, 362-373; b) T. G. Beach, D. R. Thal, M. Zanette, A. Smith, C. Buckley, *J. Alzheimer's Dis.* **2016**, *52*, 863-873.
- [108] R. C. Hubbard, R. J. Koepp, S. Yu, S. Talwalker, G. S. Geis, C. W. Wiesenhutter, W. S. Makarowski, H. A. Paulus, *Arthritis Rheum.* **1996**, *39*, 1188-1188.
- [109] a) C. Zhou, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 2302-2303; b) J.-C. Wan, J.-M. Huang, Y.-H. Jhan, J.-C. Hsieh, *Org. Lett.* **2013**, *15*, 2742-2745; c) J. Liu, X. Zhou, H. Rao, F. Xiao, C.-J. Li, G.-J. Deng, *Chem. Eur. J.* **2011**, *17*, 7996-7999; d) M. Behrends, J. Sävmarker, P. J. R. Sjöberg, M. Larhed, *ACS Catalysis* **2011**, *1*, 1455-1459.
- [110] D. Hédou, A. S. Voisin-Chiret, *Eur. J. Org. Chem.* **2020**, *2020*, 3640-3649.
- [111] a) E. Demory, K. Devaraj, A. Orthaber, P. J. Gates, L. T. Pilarski, *Angew. Chem. Int. Ed.* **2015**, *54*, 11765-11769; b) S. A. Sadler, H. Tajuddin, I. A. I. Mkhaliid, A. S. Batsanov, D. Albesa-Jove, M. S. Cheung, A. C. Maxwell, L. Shukla, B. Roberts, D. C. Blakemore, Z. Lin, T. B. Marder, P. G. Steel, *Org. Biomol. Chem.* **2014**, *12*, 7318-7327; c) M. A. Larsen, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 4287-4299.
- [112] T. S.-B. Lou, M. C. Willis, *Tetrahedron* **2020**, *76*, 130782.
- [113] a) S. Sato, T. Inokuma, N. Otsubo, D. R. Burton, C. F. Barbas, 3rd, *ACS Med. Chem. Lett.* **2013**, *4*, 460-465; b) I. A. I. Ali, W. Fathalla, *Heteroatom Chem.* **2006**, *17*, 280-288.
- [114] T. Chinnusamy, K. Feeney, C. G. Watson, D. Leonori, V. K. Aggarwal, in *Comprehensive Organic Synthesis (Second Edition)* (Ed.: P. Knochel), Elsevier, Amsterdam, **2014**, pp. 697- 699.
- [115] X. A. F. Cook, L. R. E. Pantaine, D. C. Blakemore, I. B. Moses, N. W. Sach, A. Shavnya, M. C. Willis, *Angew. Chem. Int. Ed.* **2021**, *60*, 22461-22468.
- [116] D. J. Weix, *Acc. Chem. Res.* **2015**, *48*, 1767-1775.
- [117] a) J.-M. Bégouin, C. Gosmini, *J. Org. Chem.* **2009**, *74*, 3221-3224; b) T.-F. Wu, Y.-J. Zhang, Y. Fu, F.-J. Liu, J.-T. Tang, P. Liu, F. D. Toste, B. Ye, *Chem* **2021**, *7*, 1963-1974; c) A. Krasovskiy, C. Duplais, B. H. Lipshutz, *J. Am. Chem. Soc.* **2009**, *131*, 15592-15593; d) B. K. Chi, J. K. Widness, M. M. Gilbert, D. C. Salgueiro, K. J. Garcia, D. J. Weix, *ACS Cat.* **2022**, *12*, 580-586.
- [118] X. Chen, W.-j. Li, S. Li, J. Tang, X. Du, X.-l. Zheng, M.-l. Yuan, H.-y. Fu, R.-x. Li, H. Chen, *J. Org. Chem.* **2020**, *85*, 622-632.

- [119] J. McKnight, A. Shavnya, N. W. Sach, D. C. Blakemore, I. B. Moses, M. C. Willis, *Angew. Chem. Int. Ed.* **2022**, n/a.
- [120] E. K. Reeves, E. D. Entz, S. R. Neufeldt, *Chem. Eur. J* **2021**, 27, 6161-6177.
- [121] a) J. M. Baskin, Z. Wang, *Org. Lett.* **2002**, 4, 4423-4425; b) X.-L. Chen, B.-C. Tang, C. He, J.-T. Ma, S.-Y. Zhuang, Y.-D. Wu, A.-X. Wu, *Chem. Commun.* **2020**, 56, 13653-13656; c) D.-K. Kim, H.-S. Um, H. Park, S. Kim, J. Choi, C. Lee, *Chem. Sci.* **2020**, 11, 13071-13078.
- [122] a) A. Ulman, E. Urankar, *J. Org. Chem.* **1989**, 54, 4691-4692; b) J. Zou, F. Li, F. G. Tao, *Chinese Chem. Lett.* **2009**, 20, 17-20.
- [123] T. R. Griffiths, D. C. Pugh, *Coordin. Chem. Rev.* **1979**, 29, 129-211.
- [124] S. Cacchi, G. Fabrizi, A. Goggiamani, L. M. Parisi, R. Bernini, *J. Org. Chem.* **2004**, 69, 5608-5614.
- [125] a) D. Bur, C. Grisostomi, O. Nayler, L. Remen, M. Vercauteren, R. Welford, WO2015075023A1, **2015**; b) D. Disalvo, D. Kuzmich, C. Mao, H. Razavi, C. Sarko, A. D. Swinamer, D. Thomson, Q. Zhang, **2009**; c) B. N. Cook, D. Kuzmich, C. Mao, H. Razavi, WO2011049917, **2011**; d) B. N. Cook, D. Disalvo, D. R. Fandrick, C. Harcken, D. Kuzmich, T. W.-H. Lee, P. Liu, J. Lord, C. Mao, J. Neu, B. C. Raudenbush, H. Razavi, J. T. Reeves, J. J. Song, A. D. Swinamer, Z. Tan, WO2010036632, **2010**; e) B. N. Cook, C. Harcken, T. W.-H. Lee, P. Liu, C. Mao, J. Lord, W. Mao, B. C. Raudenbush, H. Razavi, C. R. Sarko, A. D. Swinamer, WO2009137338, **2009**.
- [126] a) H. Suzuki, H. Abe, *Tetrahedron Lett.* **1995**, 36, 6239-6242; b) X. Ge, F. Sun, X. Liu, X. Chen, C. Qian, S. Zhou, *Mol. Cat.* **2018**, 449, 72-78.
- [127] a) M. Yang, H. Shen, Y. Li, C. Shen, P. Zhang, *RSC Adv.* **2014**, 4, 26295-26300; b) B. T. V. Srinivas, V. S. Rawat, K. Konda, B. Sreedhar, *Adv. Synth. Cat.* **2014**, 356, 805-817; c) M. Bian, F. Xu, C. Ma, *Synthesis* **2007**, 2007, 2951-2956.
- [128] D. J. Bernhardtson, D. W. Widlicka, R. A. Singer, *Org. Process Res. Dev.* **2019**, 23, 1538-1551.
- [129] a) R. G. Pearson, *J. Chem. Educ.* **1968**, 45, 643; b) R. G. Pearson, *J. Chem. Educ.* **1968**, 45, 581.
- [130] a) E. B. Benetskiy, C. Bolm, *Tetrahedron: Asymm.* **2011**, 22, 373-378; b) Z.-M. Zhang, P. Chen, W. Li, Y. Niu, X.-L. Zhao, J. Zhang, *Angew. Chem. Int. Ed.* **2014**, 53, 4350-4354; c) J. Solà, M. Revés, A. Riera, X. Verdager, *Angew. Chem. Int. Ed.* **2007**, 46, 5020-5023.
- [131] X. Sun, X. Tu, C. Dai, X. Zhang, B. Zhang, Q. Zeng, *J. Org. Chem.* **2012**, 77, 4454-4459.
- [132] H. Yu, Z. Li, C. Bolm, *Angew. Chem. Int. Ed.* **2018**, 57, 15602-15605.
- [133] T. Q. Davies, M. C. Willis, *Chem. Eur. J* **2021**, 27, 8918-8927.
- [134] R. L. DeKock, M. S. Haddad, *Inorg. Chem.* **1977**, 16, 216-217.
- [135] a) M. Carloti, G. Di Lonardo, G. Galloni, A. Trombetti, *J. Mol. Spectrosc.* **1980**, 84, 155-161; b) D.-L. Joo, H. Harjanto, D. J. Clouthier, *J. Mol. Spectrosc.* **1996**, 178, 78-83.
- [136] a) W. Srimontree, A. Chatupheeraphat, H.-H. Liao, M. Rueping, *Org. Lett.* **2017**, 19, 3091-3094; b) C. Liu, M. Szostak, *Angew. Chem. Int. Ed.* **2017**, 56, 12718-12722.
- [137] A. Dey, S. Sasmal, K. Seth, G. K. Lahiri, D. Maiti, *ACS Cat.* **2017**, 7, 433-437.
- [138] a) M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, 110, 3600-3740; b) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, 35, 984-995.
- [139] P. Dinér, A. Sadhukhan, B. Blomkvist, *Chem. Cat. Chem.* **2014**, 6, 3063-3066.
- [140] S. Otocka, M. Kwiatkowska, L. Madalińska, P. Kiełbasiński, *Chem. Rev.* **2017**, 117, 4147-4181.
- [141] a) S. Qin, S. Liu, Y. Cao, J. Li, C. Chong, T. Liu, Y. Luo, J. Hu, S. Jiang, H. Zhou, G. Yang, C. Yang, *Org. Lett.* **2018**, 20, 1350-1354; b) S. Qin, T. Liu, Y. Luo, S. Jiang, G. Yang, *Org. Chem. Front.* **2019**, 6, 732-735.
- [142] F. A. Davis, Y. Zhang, Y. Andemichael, T. Fang, D. L. Fanelli, H. Zhang, *J. Org. Chem.* **1999**, 64, 1403-1406.
- [143] a) F. A. Davis, *J. Org. Chem.* **2006**, 71, 8993-9003; b) P. Zhou, B.-C. Chen, F. A. Davis, *Tetrahedron* **2004**, 60, 8003-8030.
- [144] S. Mondal, S. Malakar, *Tetrahedron* **2020**, 76, 131662.

- [145] a) M. Funes Maldonado, F. Sehgelmeble, F. Bjarnemark, M. Svensson, J. Åhman, P. I. Arvidsson, *Tetrahedron* **2012**, 68, 7456-7462; b) O. G. Mancheño, C. Bolm, in *Beilstein J. Org. Chem.*, Vol. 3, **2007**, p. 25.
- [146] a) P. Mäder, L. Kattner, *J. Med. Chem.* **2020**, 63, 14243-14275; b) M. Andresini, A. Tota, L. Degennaro, J. A. Bull, R. Luisi, *Chem. Eur. J* **2021**, 27, 17293-17321; c) U. Lücking, *Angew. Chem. Int. Ed.* **2013**, 52, 9399-9408.
- [147] S. Chatterjee, S. Makai, B. Morandi, *Angew. Chem. Int. Ed.* **2021**, 60, 758-765.
- [148] L.-j. Ma, G.-x. Li, J. Huang, J. Zhu, Z. Tang, *Tetrahedron Lett.* **2018**, 59, 1600-1603.
- [149] a) P. K. T. Lo, G. A. Oliver, M. C. Willis, *J. Org. Chem.* **2020**, 85, 5753-5760; b) M. Ding, Z.-X. Zhang, T. Q. Davies, M. C. Willis, *Org. Lett.* **2022**.
- [150] P. K. T. Lo, M. C. Willis, *J. Am. Chem. Soc.* **2021**, 143, 15576-15581.
- [151] S. Qin, Y. Luo, Y. Sun, L. Tian, S. Jiang, J. Yan, G. Yang, *Tetrahedron Lett.* **2019**, 60, 151167.
- [152] A. De Gombert, University of Oxford (Oxford), **2021**.
- [153] J. A. Cella, S. W. Bacon, *J. Org. Chem.* **1984**, 49, 1122-1125.
- [154] S. H. Newman-Stonebraker, S. R. Smith, J. E. Borowski, E. Peters, T. Gensch, H. C. Johnson, M. S. Sigman, A. G. Doyle, *Science* **2021**, 374, 301-308.
- [155] T. Gensch, G. dos Passos Gomes, P. Friederich, E. Peters, T. Gaudin, R. Pollice, K. Jorner, A. Nigam, M. Lindner-D'Addario, M. S. Sigman, A. Aspuru-Guzik, *J. Am. Chem. Soc.* **2022**, 144, 1205-1217.
- [156] M. Beoke-Goehring, R. Schwarz, W. Spiess, *Z. Anorg. Allg. Chem.* **1958**, 293, 294-301.
- [157] N. A. Meanwell, *J. Med. Chem.* **2011**, 54, 2529-2591.
- [158] a) L. Yet, in *Privileged Structures in Drug Discovery* (Ed.: I. John Wiley & Sons), **2018**, pp. 83-154; b) I. Cepanec, in *Synthesis of Biaryls* (Ed.: I. Cepanec), Elsevier Science Ltd, Oxford, **2004**, pp. 139-207.
- [159] P. J. Dunn, *Org. Process Res. Dev.* **2005**, 9, 88-97.
- [160] N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, 20, 3437-3440.
- [161] A. Kumbhar, *J. Org. Chem.* **2017**, 848, 22-88.
- [162] K. M. Engle, J.-Q. Yu, *J. Org. Chem.* **2013**, 78, 8927-8955.
- [163] M. Zenzola, R. Doran, L. Degennaro, R. Luisi, J. A. Bull, *Angew. Chem. Int. Ed.* **2016**, 55, 7203-7207.
- [164] M. Gholinejad, H. Firouzabadi, *New J. Chem.* **2015**, 39, 5953-5959.
- [165] T. Hideo, F. Misa, Y. Masataka, *B. Chem. Soc. Jpn.* **1991**, 64, 57-67.
- [166] B. Du, P. Qian, Y. Wang, H. Mei, J. Han, Y. Pan, *Org. Lett.* **2016**, 18, 4144-4147.
- [167] W. Li, L. Gao, W. Zhuge, X. Sun, G. Zheng, *Org. Biomol. Chem* **2017**, 15, 7819-7823.
- [168] H. E. Bartrum, D. C. Blakemore, C. J. Moody, C. J. Hayes, *Tetrahedron* **2013**, 69, 2276-2282.
- [169] K. Sato, M. Hyodo, M. Aoki, X. Q. Zheng, R. Noyori, *Tetrahedron* **2001**, 57, 2469-2476.
- [170] Y. Xie, H. W. Chi, A. Y. Guan, C. L. Liu, H. J. Ma, D. L. Cui, *J Agric Food Chem* **2014**, 62, 12491-12496.
- [171] M. F. Zheng, P. Q. Chen, W. Q. Wu, H. F. Jiang, *Chem. Commun.* **2016**, 52, 84-87.
- [172] K. Cooper, M. J. Fray, M. J. Parry, K. Richardson, J. Steele, *J. Med. Chem.* **1992**, 35, 3115-3129.
- [173] C. Liu, W. B. Yang, *Chem. Commun.* **2009**, 6267-6269.
- [174] W. Li, J. Tang, S. Li, X. Zheng, M. Yuan, B. Xu, W. Jiang, F. Haiyan, R. Li, H. Chen, *Organic Letters* **2020**, 22, 7814-7819.
- [175] N. A. Isley, F. Gallou, B. H. Lipshutz, **2013**, 135, 17707-17710.
- [176] C. Fricke, G. J. Sherborne, I. Funes-Ardoiz, E. Senol, S. Guven, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2019**, 58, 17788-17795.
- [177] X. Lin, C. Hou, H. Li, Z. Weng, *Chem. Eur. J.* **2016**, 22, 2075-2084.
- [178] A. Y. Dubovtsev, N. V. Shcherbakov, D. V. Dar'In, V. Y. Kukushkin, *J. Org. Chem.* **2020**, 85, 745-757.
- [179] S. Y. Lee, C.-H. Cheon, *J. Org. Chem.* **2018**, 83, 13036-13044.
- [180] D. A. Chaudhari, R. A. Fernandes, *J. Org. Chem.* **2016**, 81, 2113-2121.
- [181] O. S. Kanishchev, W. R. Dolbier, *Angew. Chem. Int. Ed.* **2015**, 54, 280-284.

- [182] P. Ye, Y. Shao, F. Zhang, J. Zou, X. Ye, J. Chen, *Adv. Synth. Catal.* **2020**, *362*, 851-857.
- [183] K. Tanimoro, M. Ueno, K. Takeda, M. Kiriata, S. Tanimori, *J. Org. Chem.* **2012**, *77*, 7844-7849.
- [184] X. Zhang, A. McNally, *Angew. Chem. Int. Ed.* **2017**, *56*, 9833-9836.
- [185] R. Cai, M. Lu, E. Y. Aguilera, Y. Xi, N. G. Akhmedov, J. L. Petersen, H. Chen, X. Shi, *Angew. Chem. Int. Ed.* **2015**, *54*, 8772-8776.
- [186] G. J. Sherborne, A. G. Gevondian, I. Funes-Ardoiz, A. Dahiya, C. Fricke, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2020**, *59*, 15543-15548.
- [187] J. M. Antelo Miguez, L. A. Adrio, A. Sousa-Pedrares, J. M. Vila, K. K. Hii, *J. Org. Chem.* **2007**, *72*, 7771-7774.
- [188] X. Qin, D. Sun, Q. You, Y. Cheng, J. Lan, J. You, *Org. Lett.* **2015**, *17*, 1762-1765.
- [189] X. Yi, K. Chen, J. Guo, W. Chen, W. Chen, *Adv. Synth. Cat.* **2020**, *362*, 4373-4377.
- [190] M. Kienle, P. Knochel, *Org. Lett.* **2010**, *12*, 2702-2705.
- [191] R. Yan, X. Liu, C. Pan, X. Zhou, X. Li, X. Kang, G. Huang, *Org. Lett.* **2013**, *15*, 4876-4879.
- [192] B. Xiong, Y. Li, Y. Wei, S. Kramer, Z. Lian, *Org. Lett.* **2020**, *22*, 6334-6338.
- [193] B. J. Austermeuhle, E. S. Collins, C. G. Hamaker, S. R. Hitchcock, *Synth. Comm.* **2021**, *51*, 3483-3491.

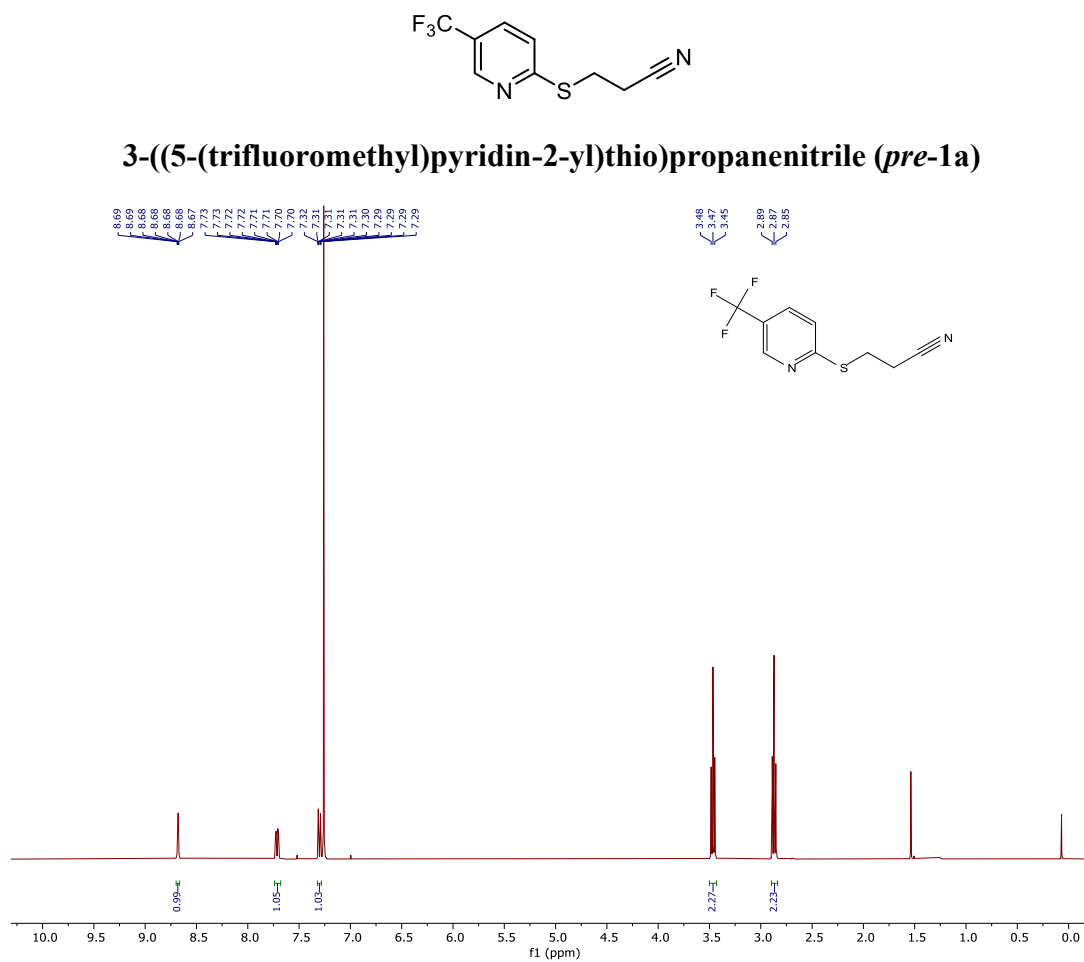
8. NMR spectra of compounds

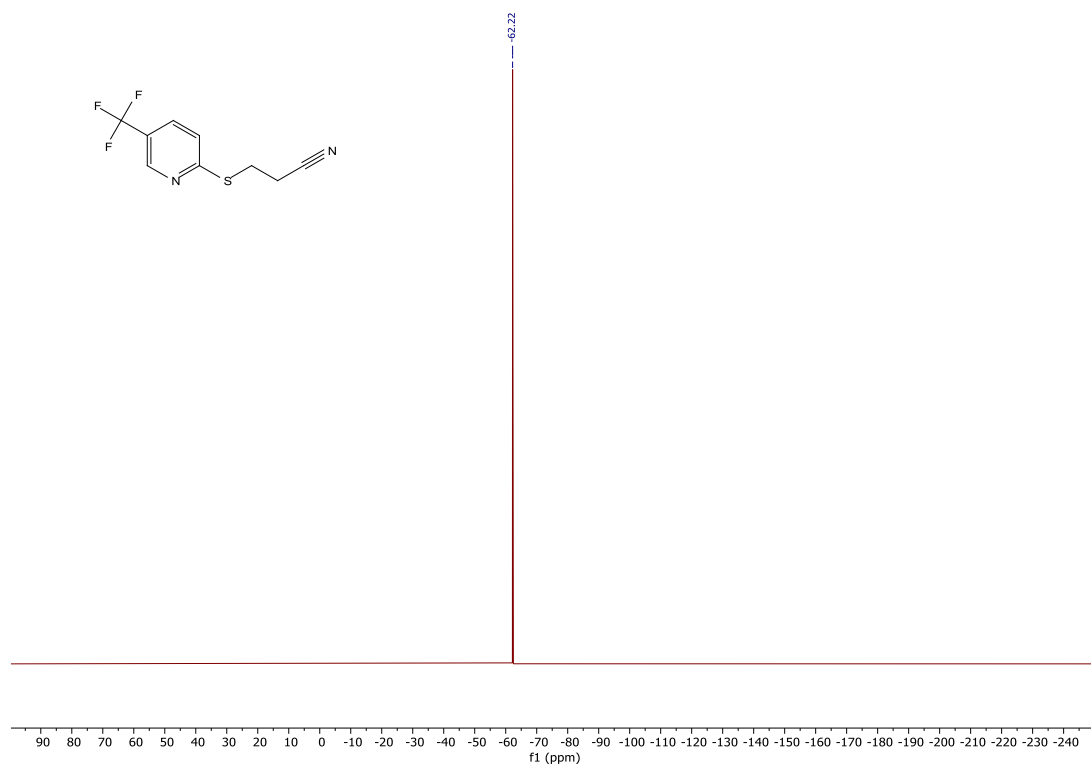
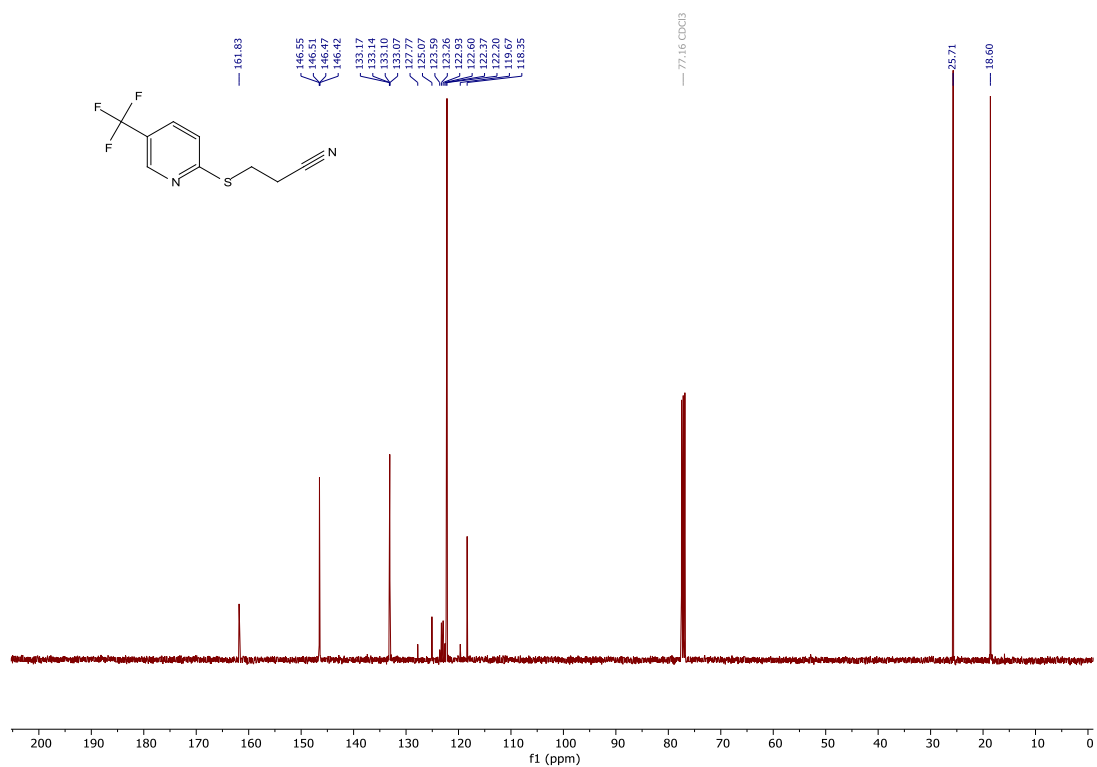
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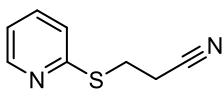
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8.1. NMR spectra for chapter 2

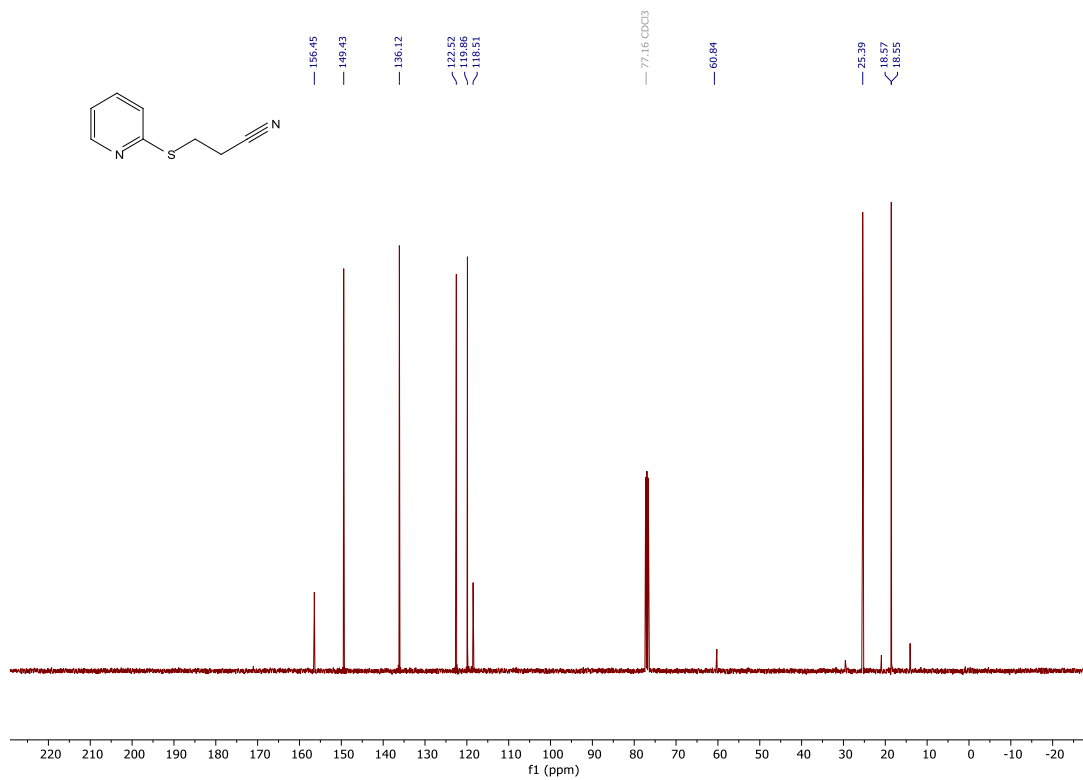
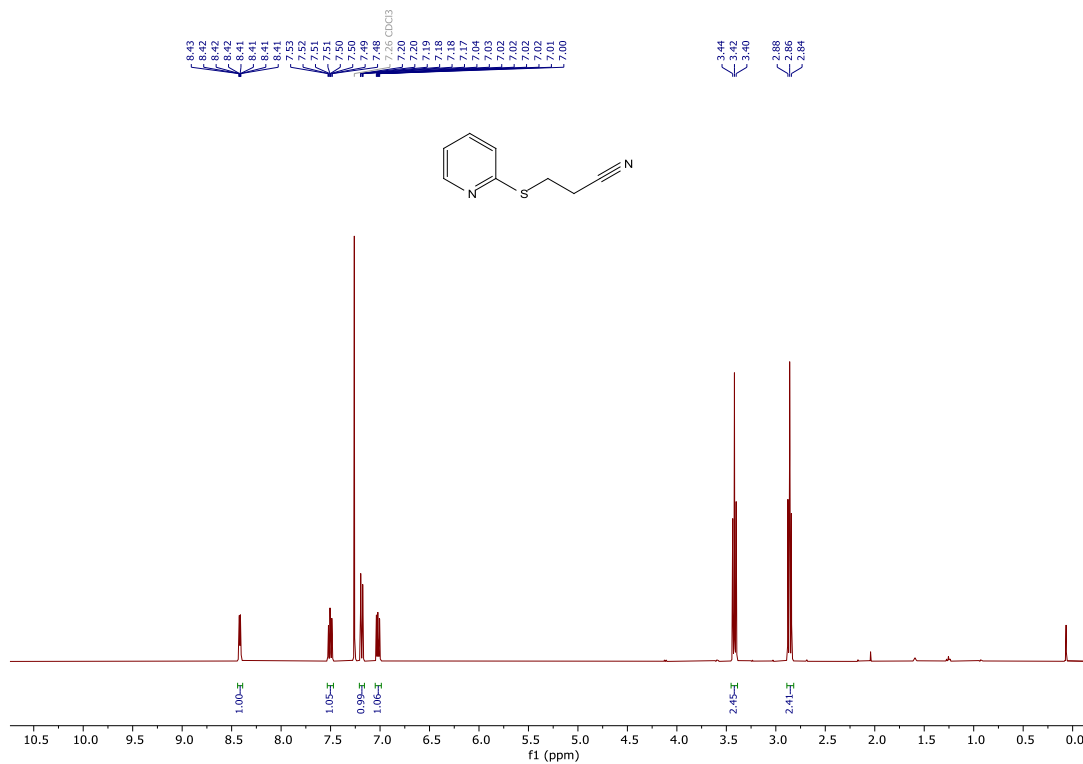
8.1.1. Sulfides

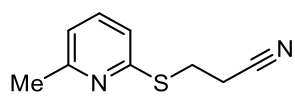




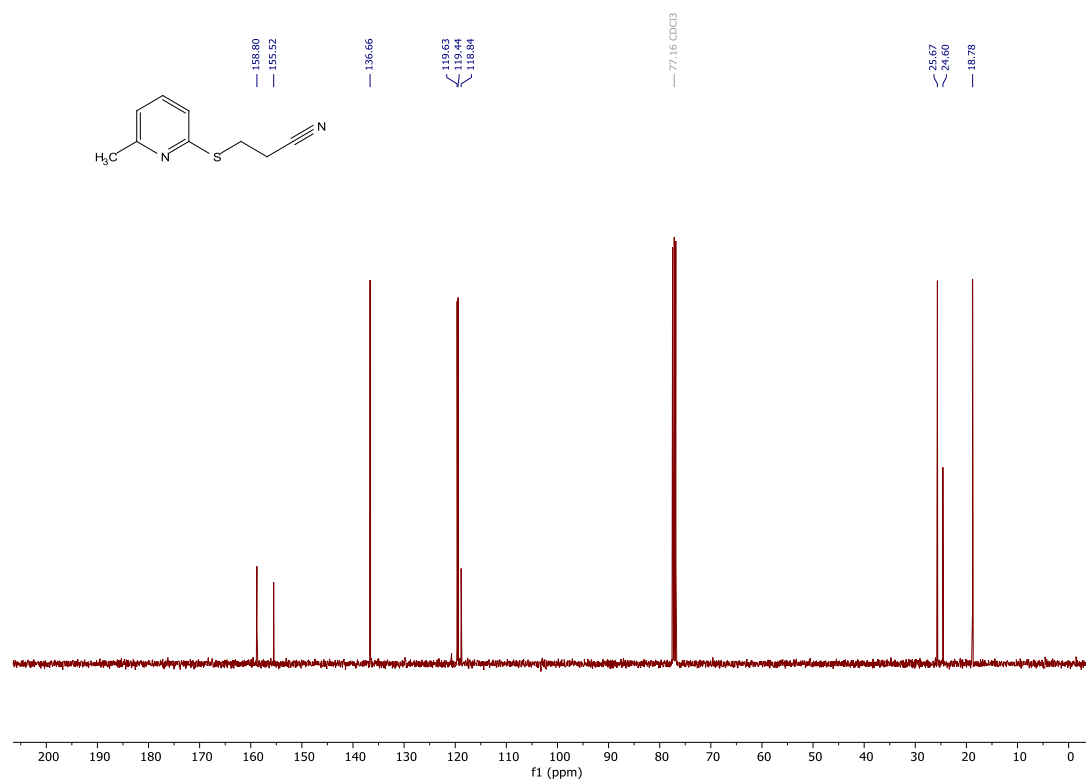
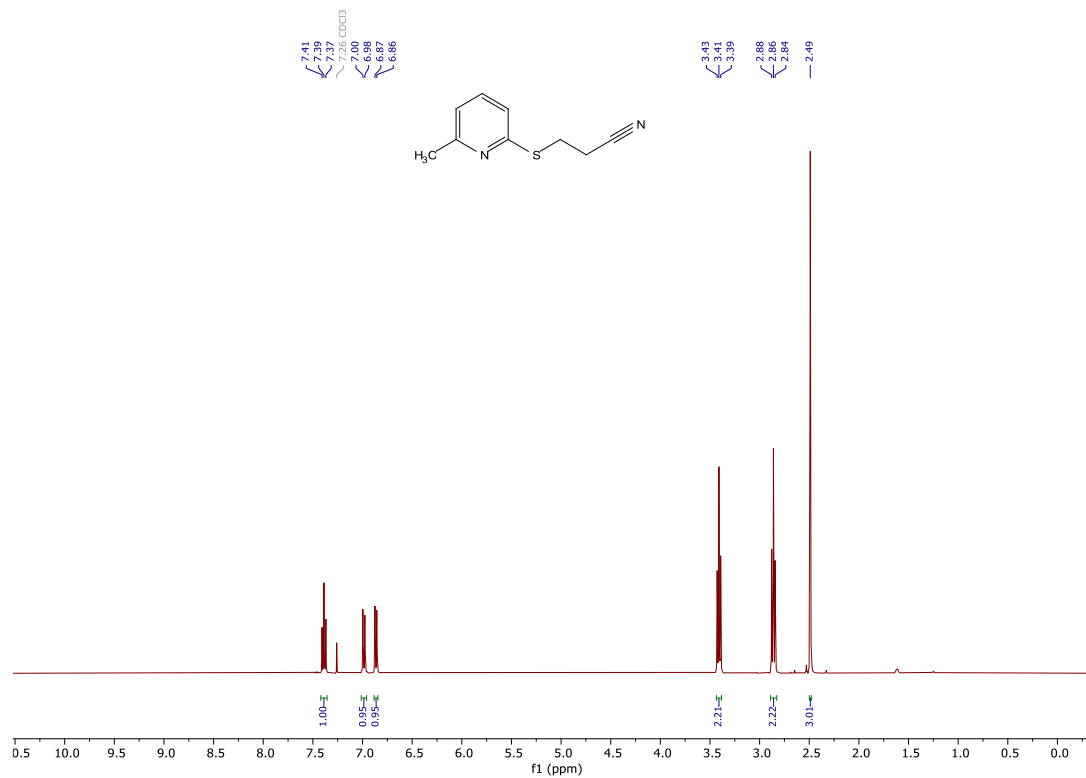


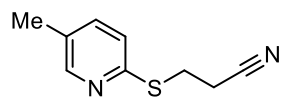
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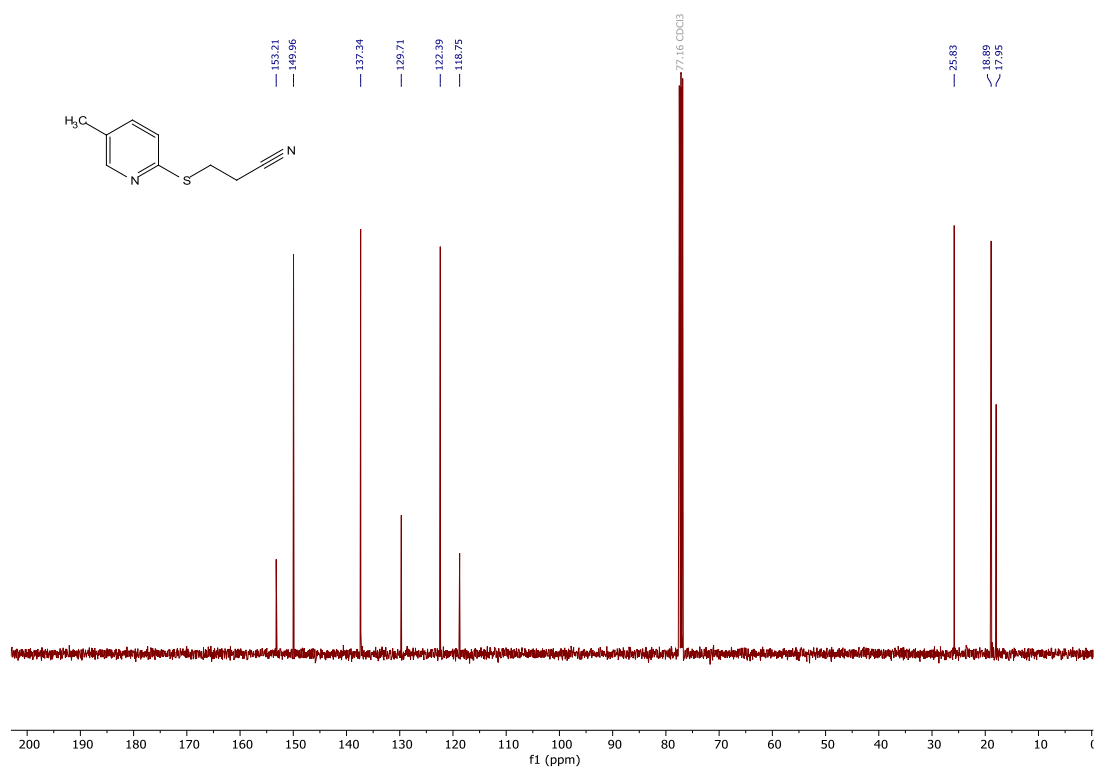
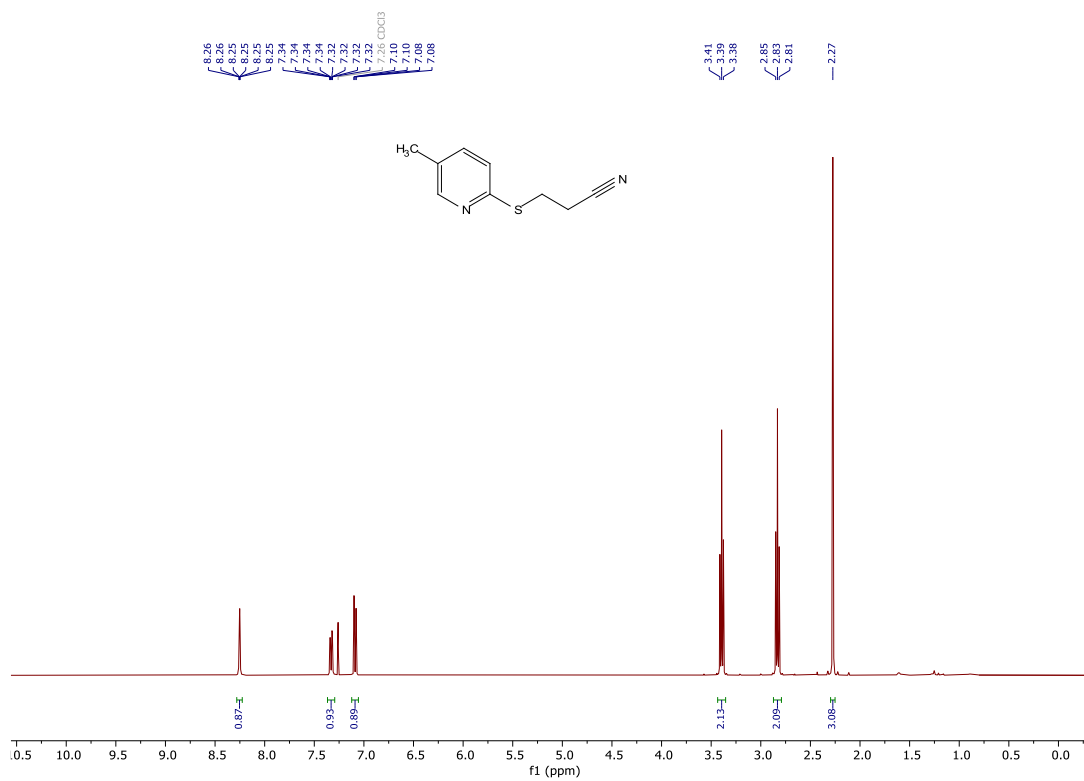


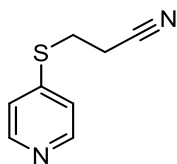
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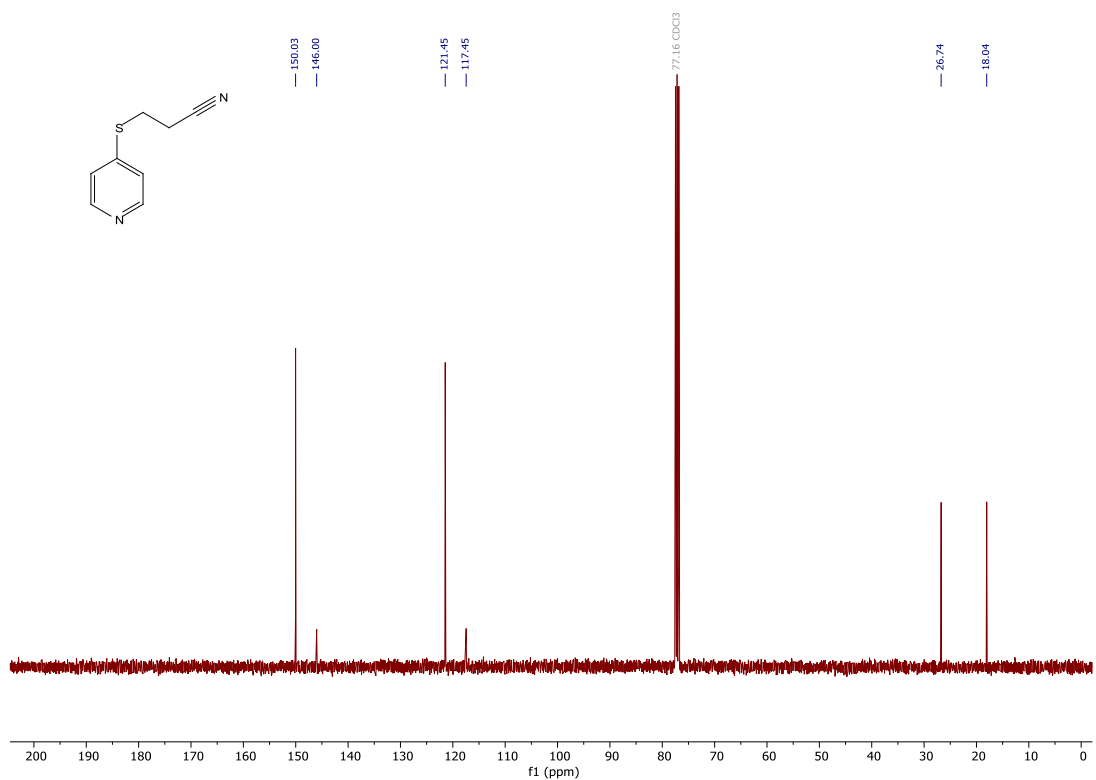
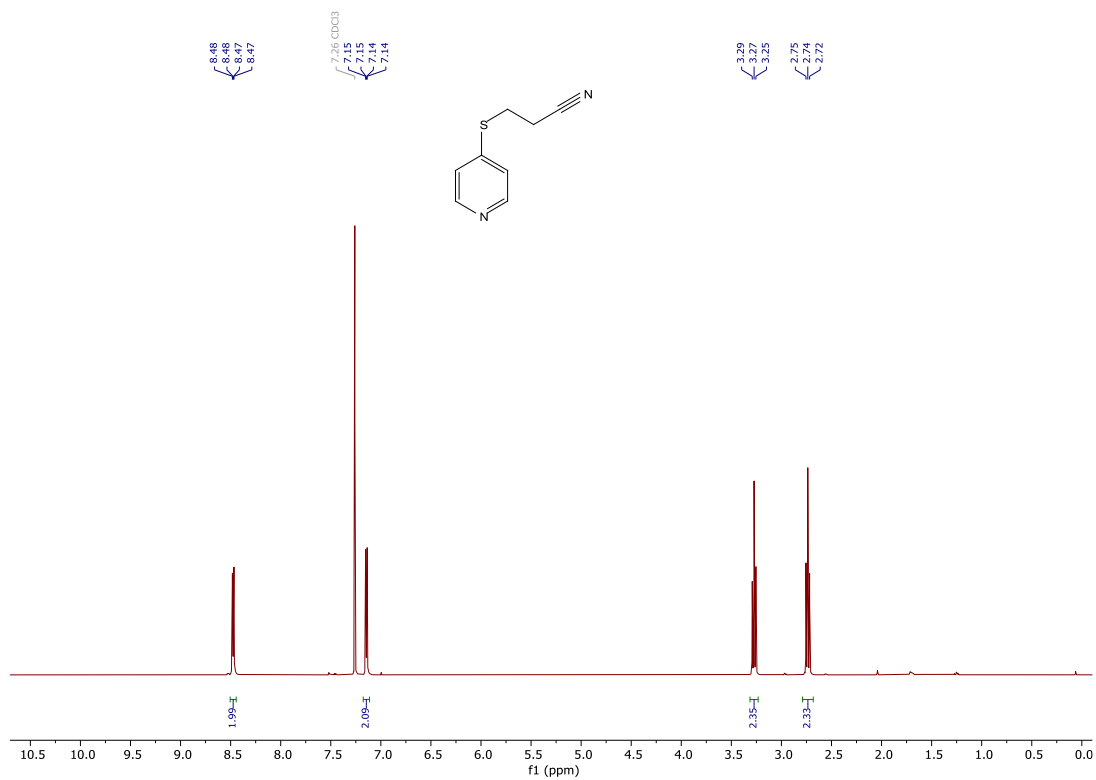


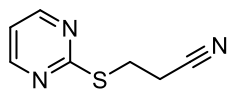
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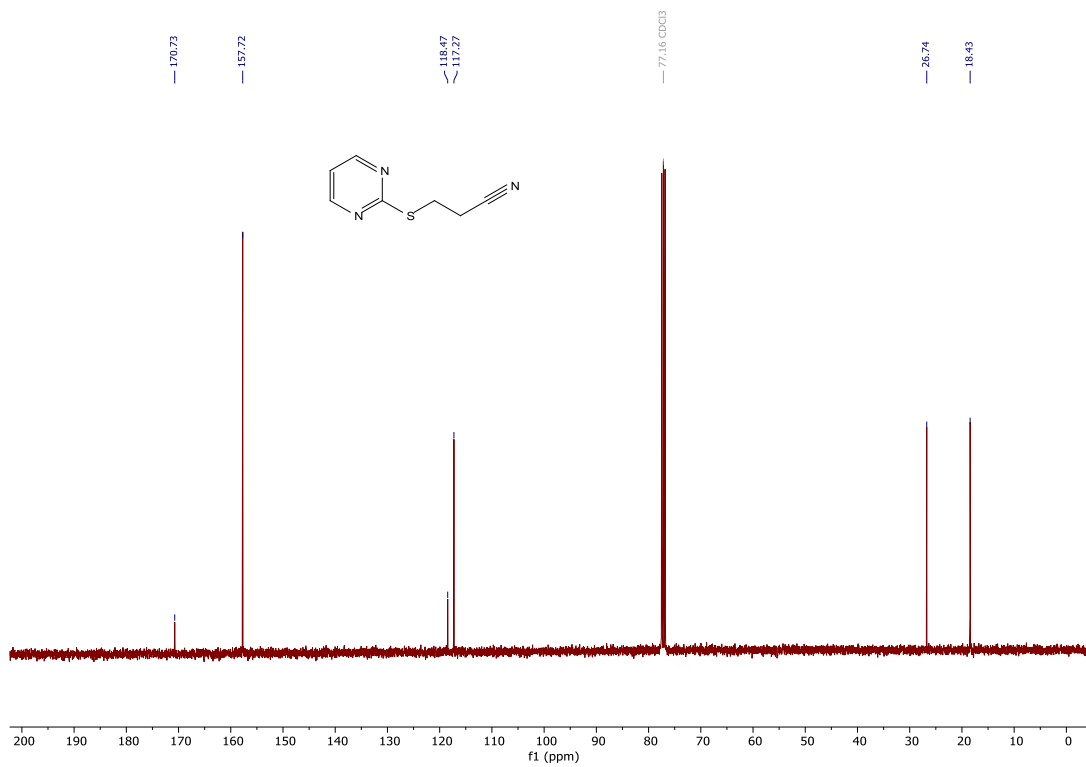
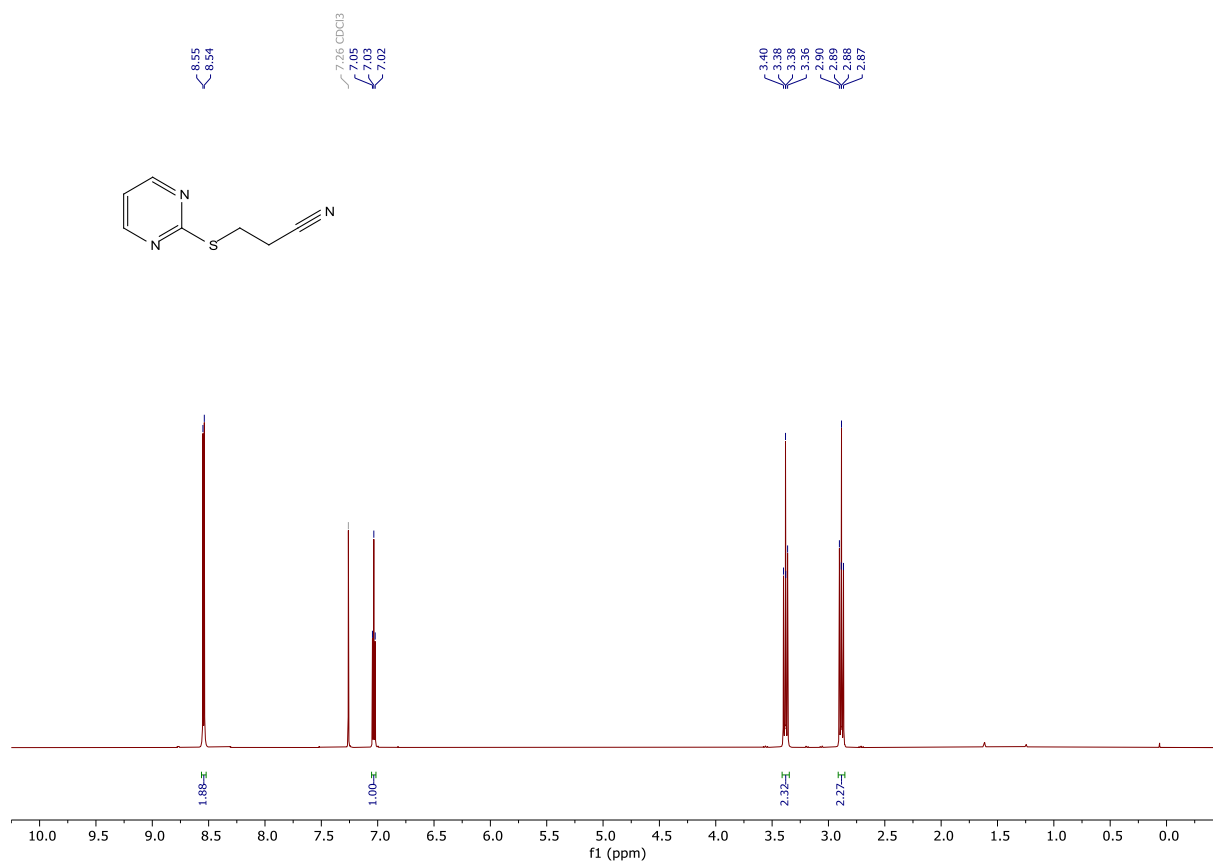


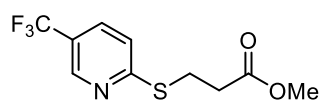
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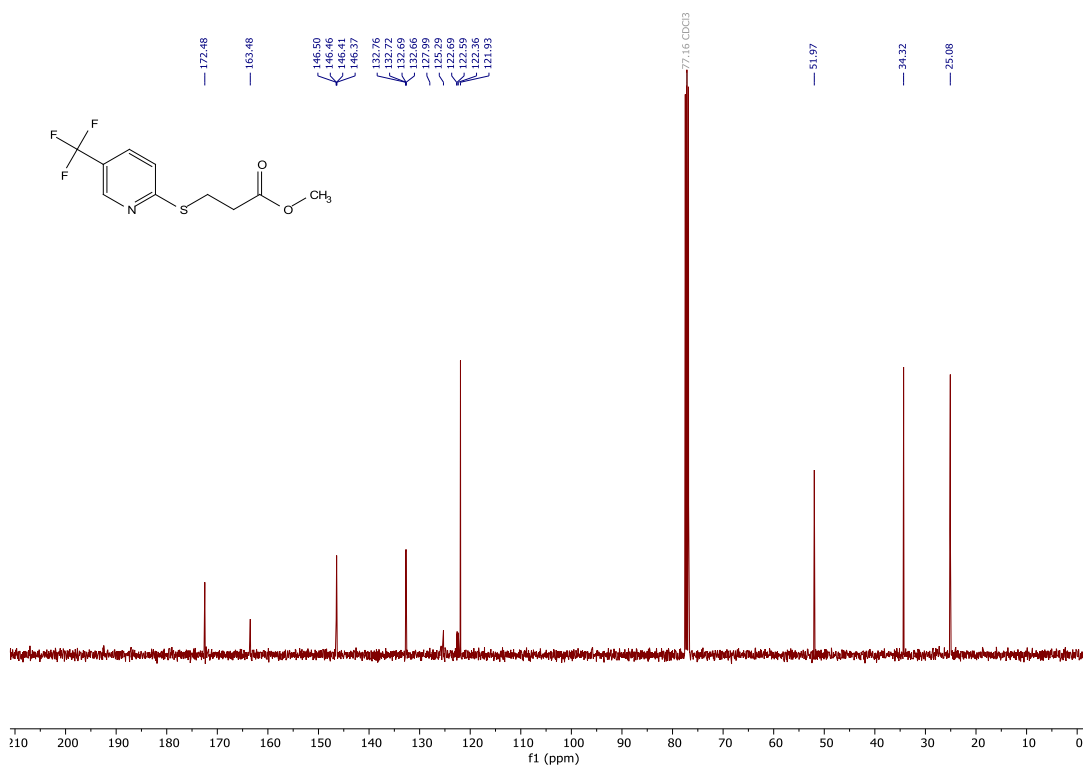
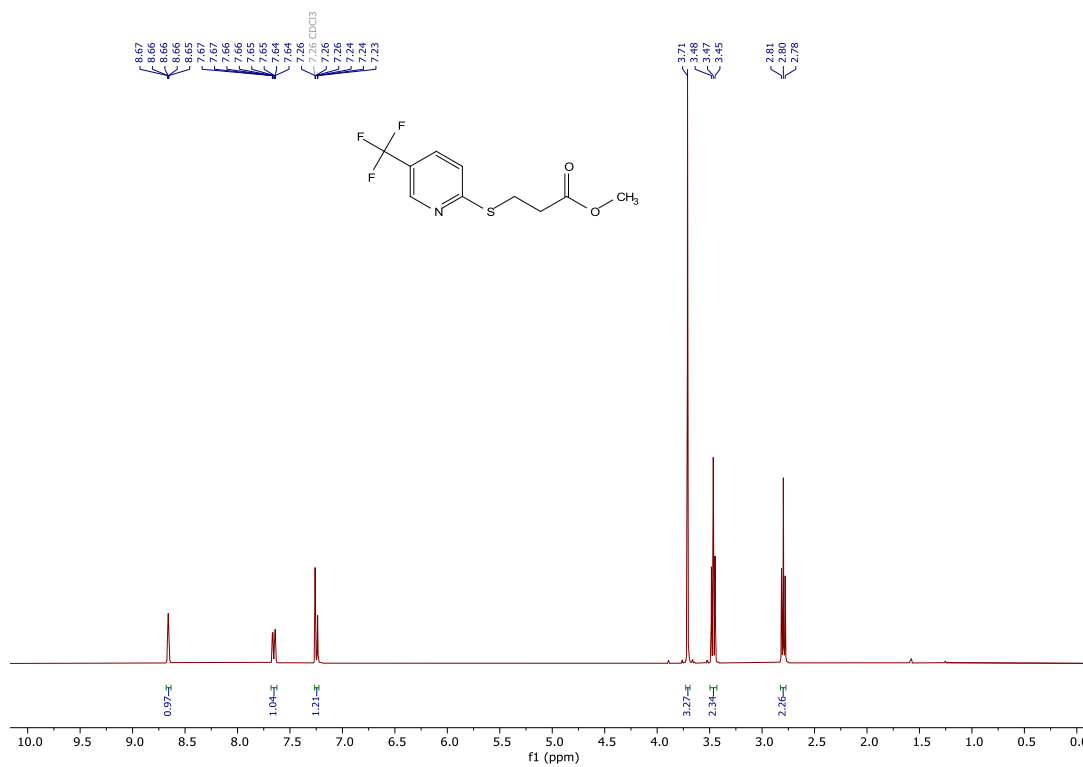


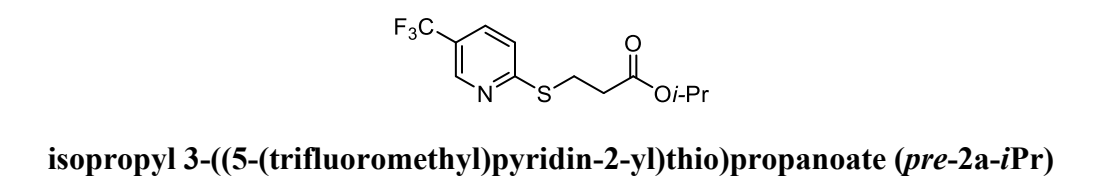
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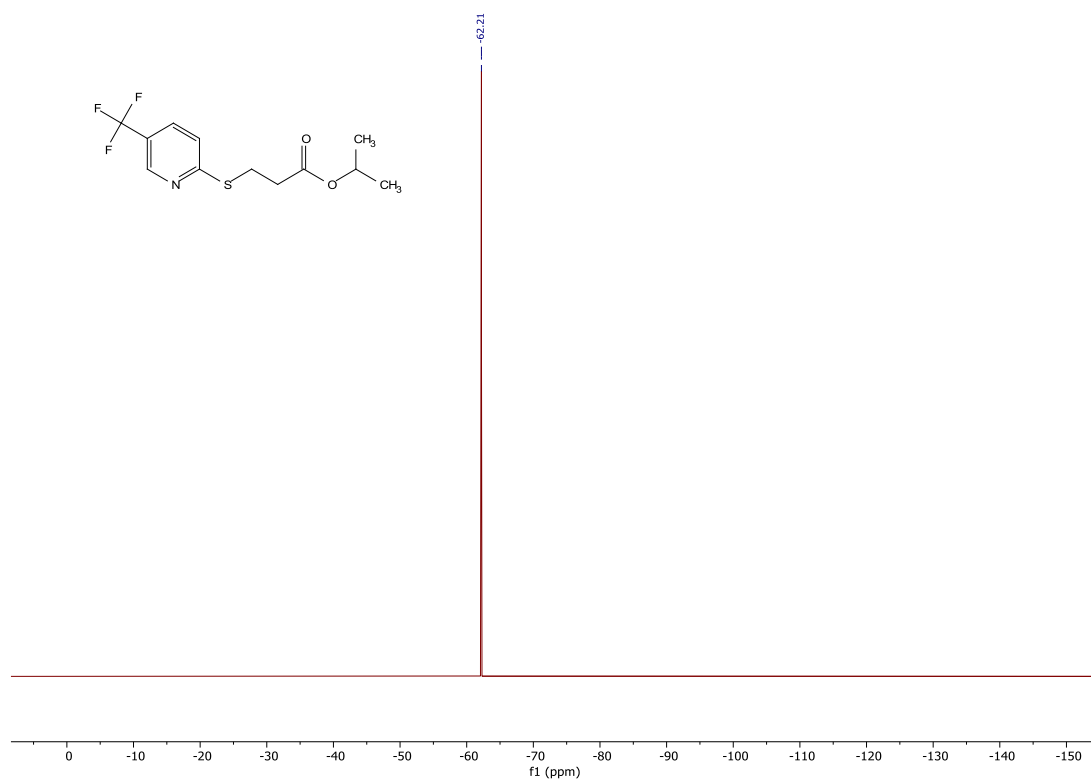
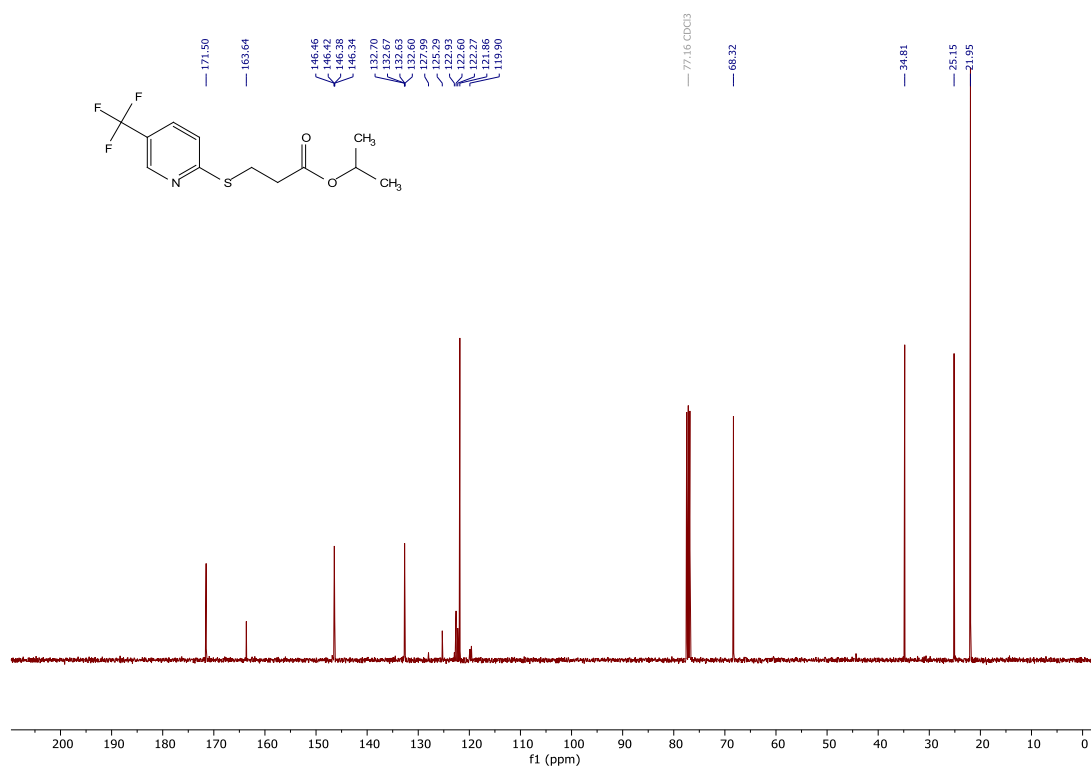


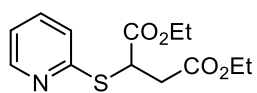


methyl 3-((5-(trifluoromethyl)pyridin-2-yl)thio)propanoate (*pre-2a*)

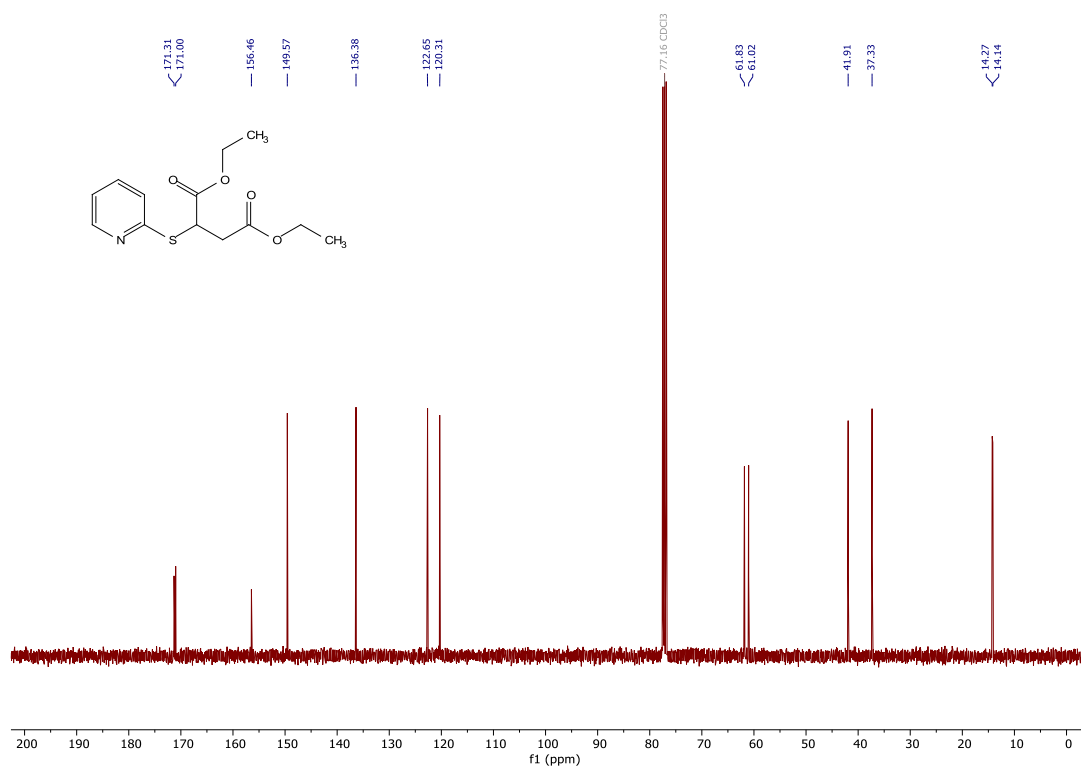
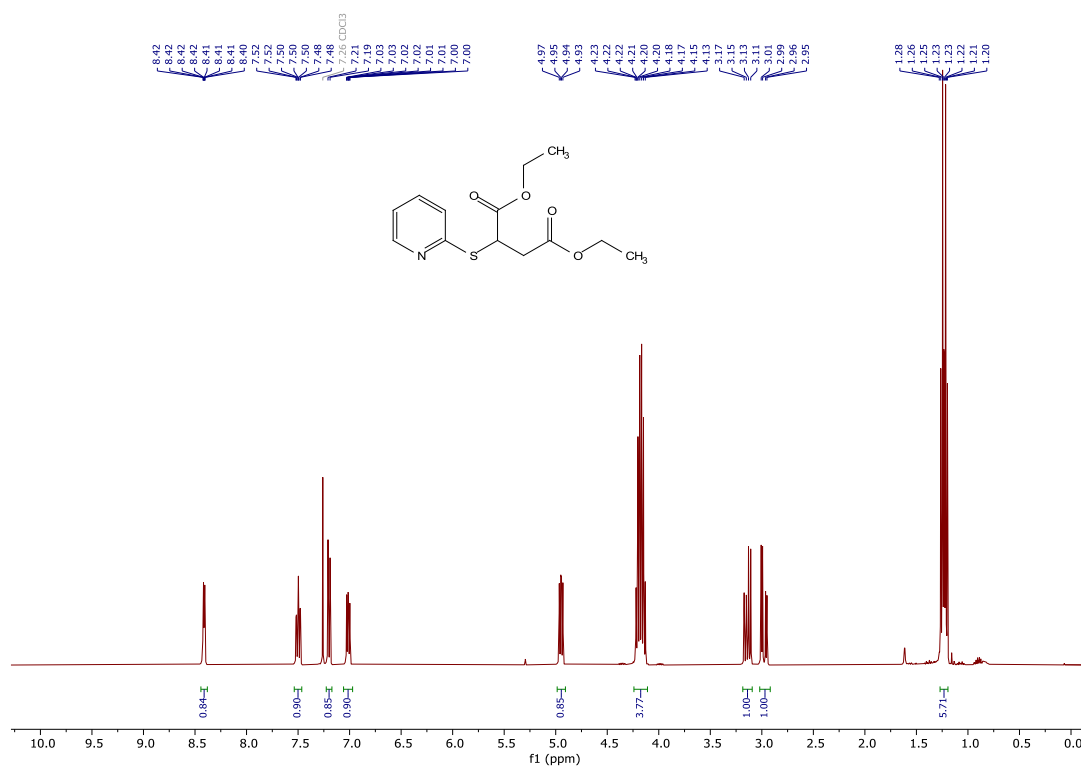


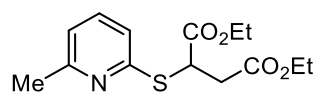




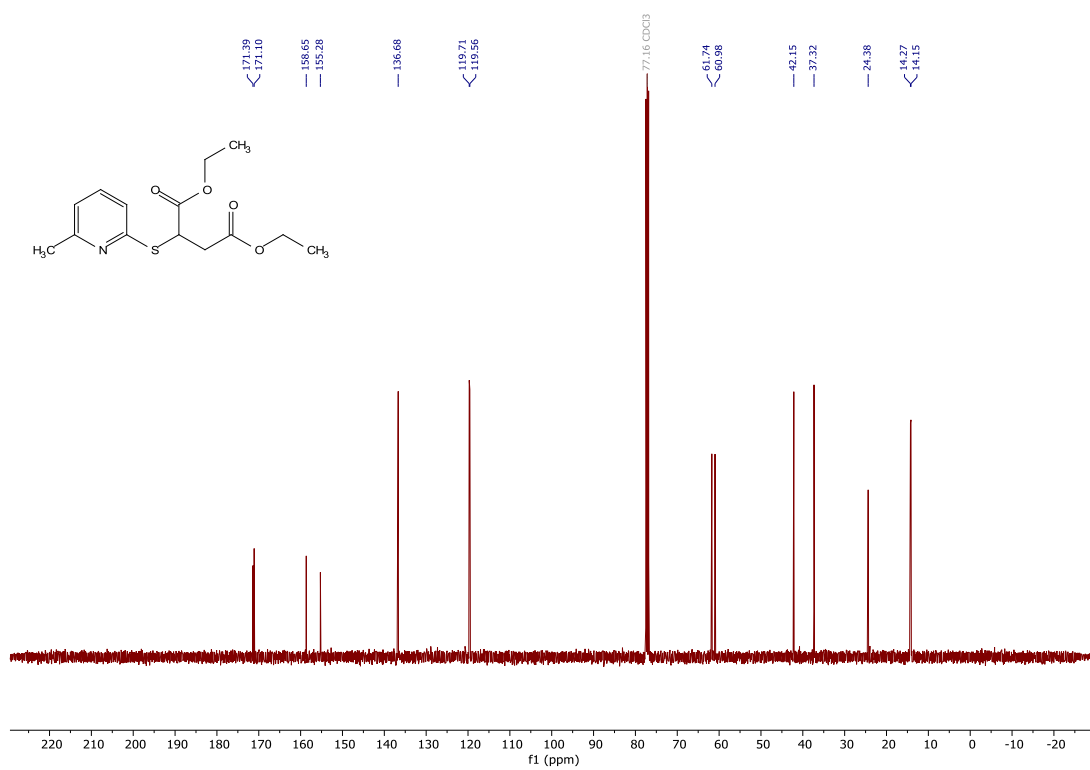
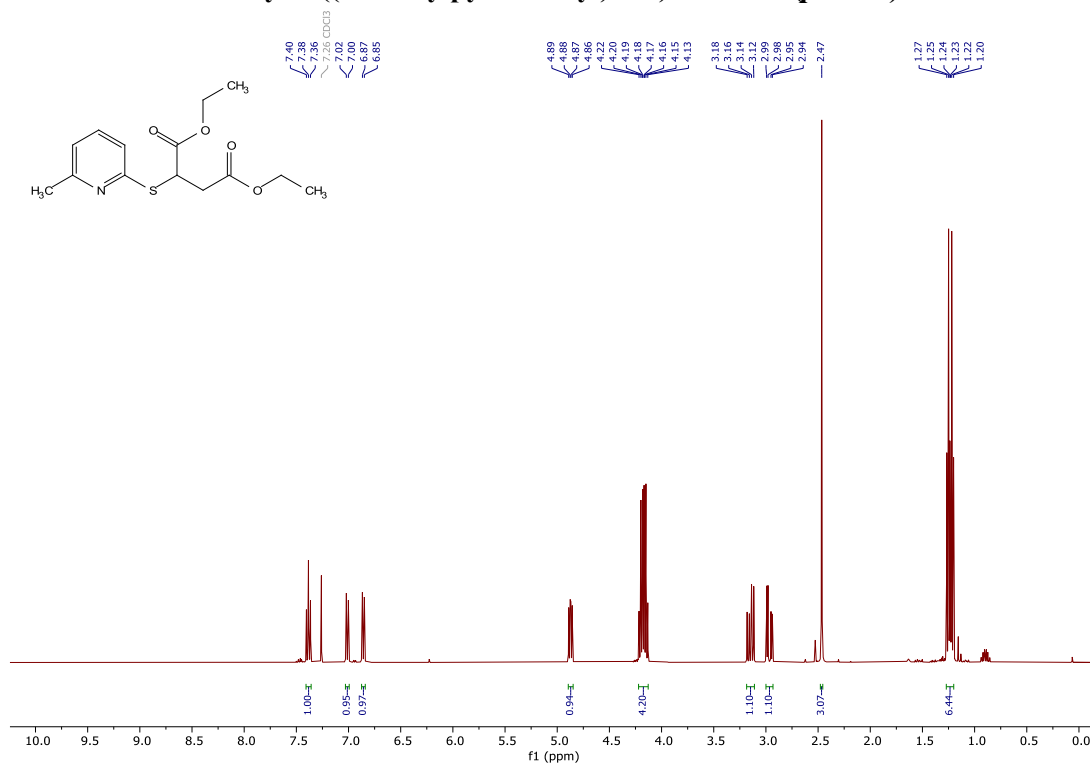


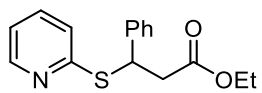
diethyl 2-(pyridin-2-ylthio)succinate (*pre-8a*)



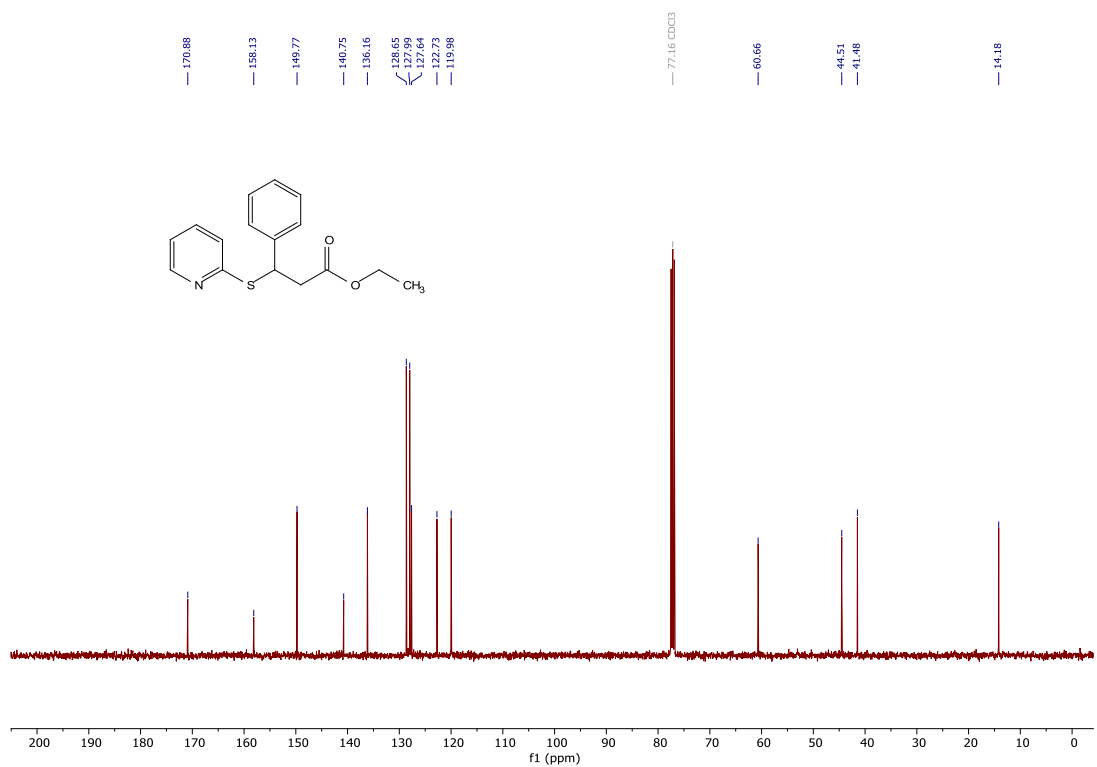
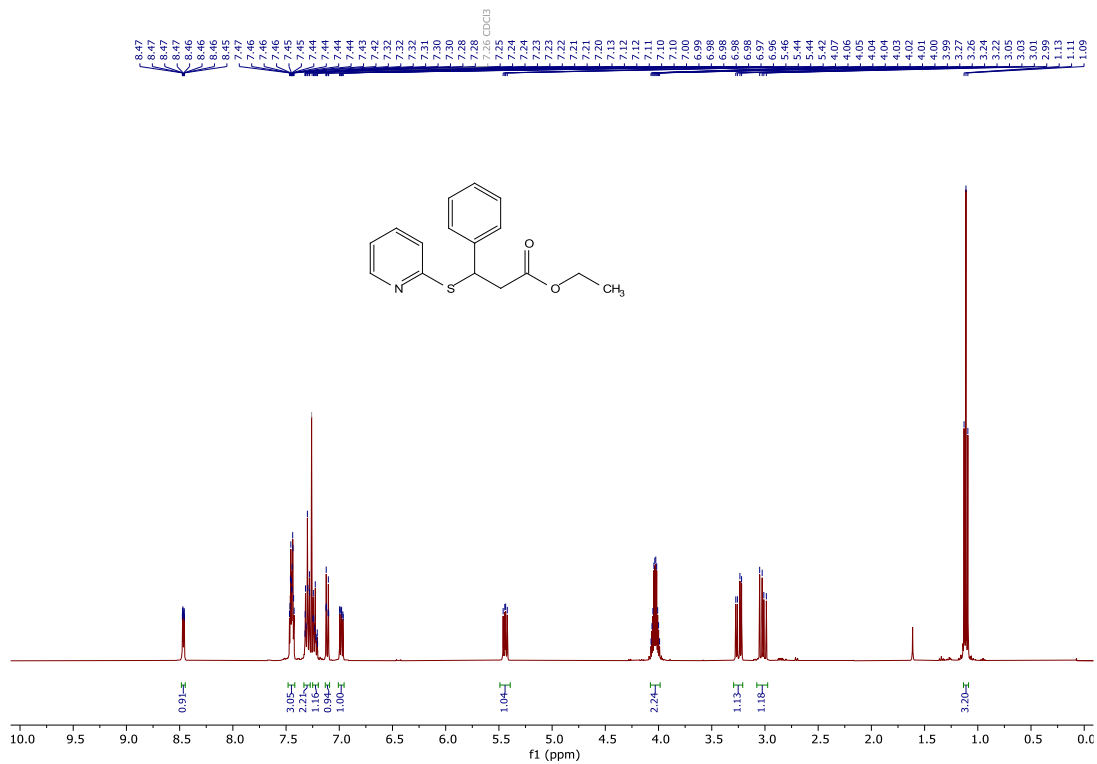


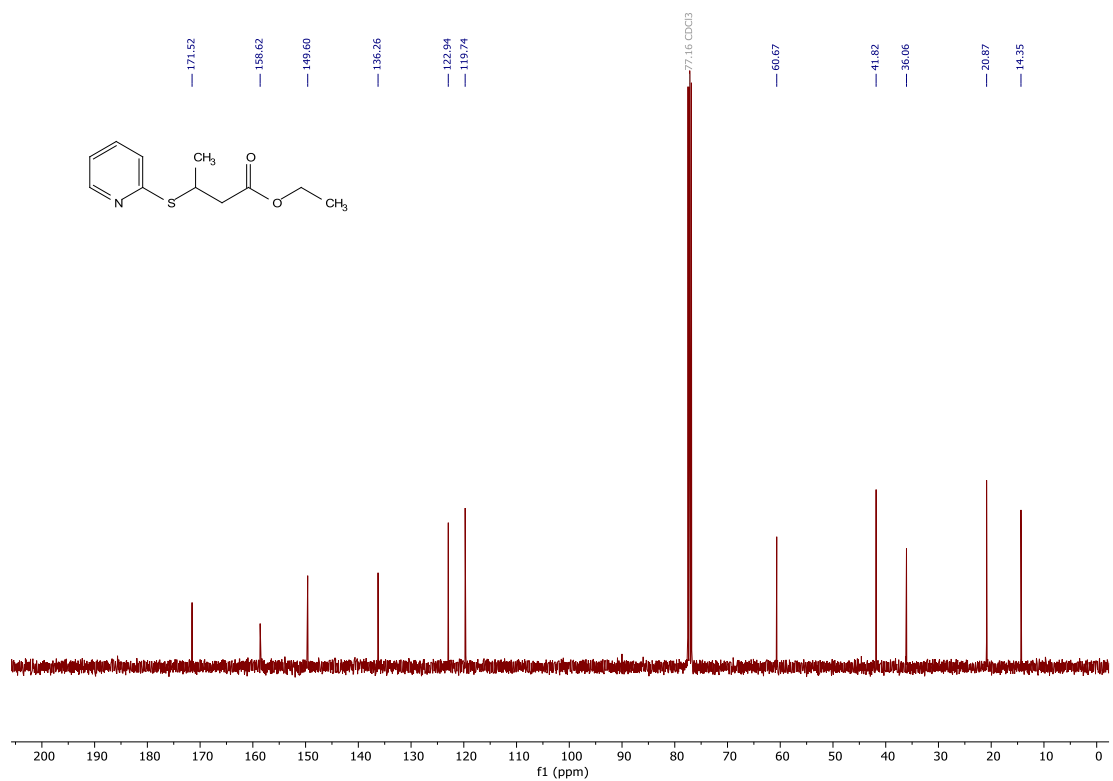
diethyl 2-((6-methylpyridin-2-yl)thio)succinate (*pre-8b*)

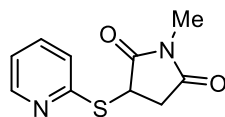




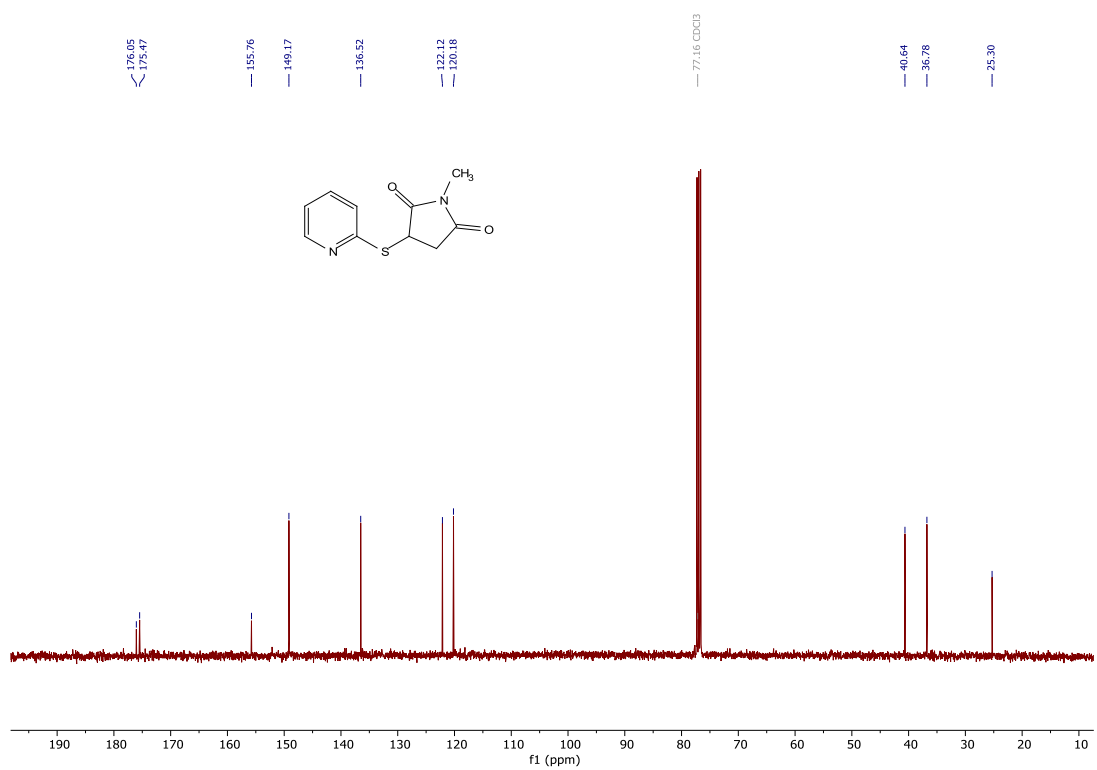
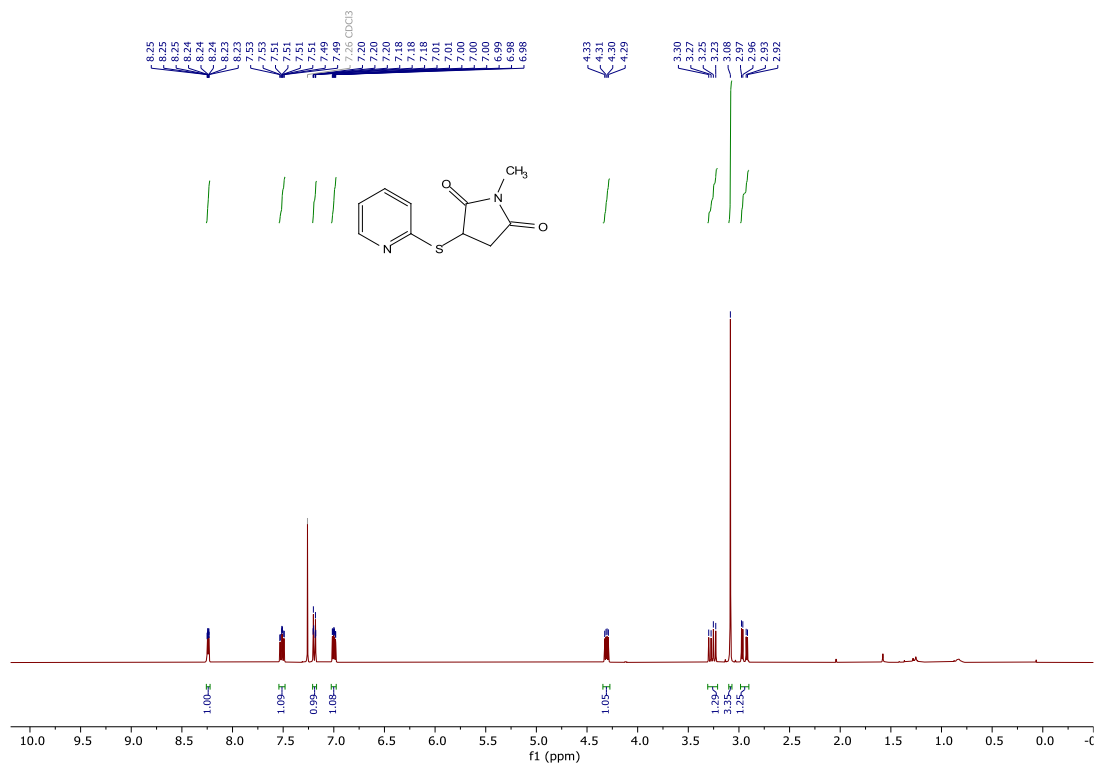
methyl 3-phenyl-3-(pyridin-2-ylthio)propanoate (*pre-9*)

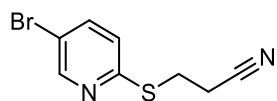




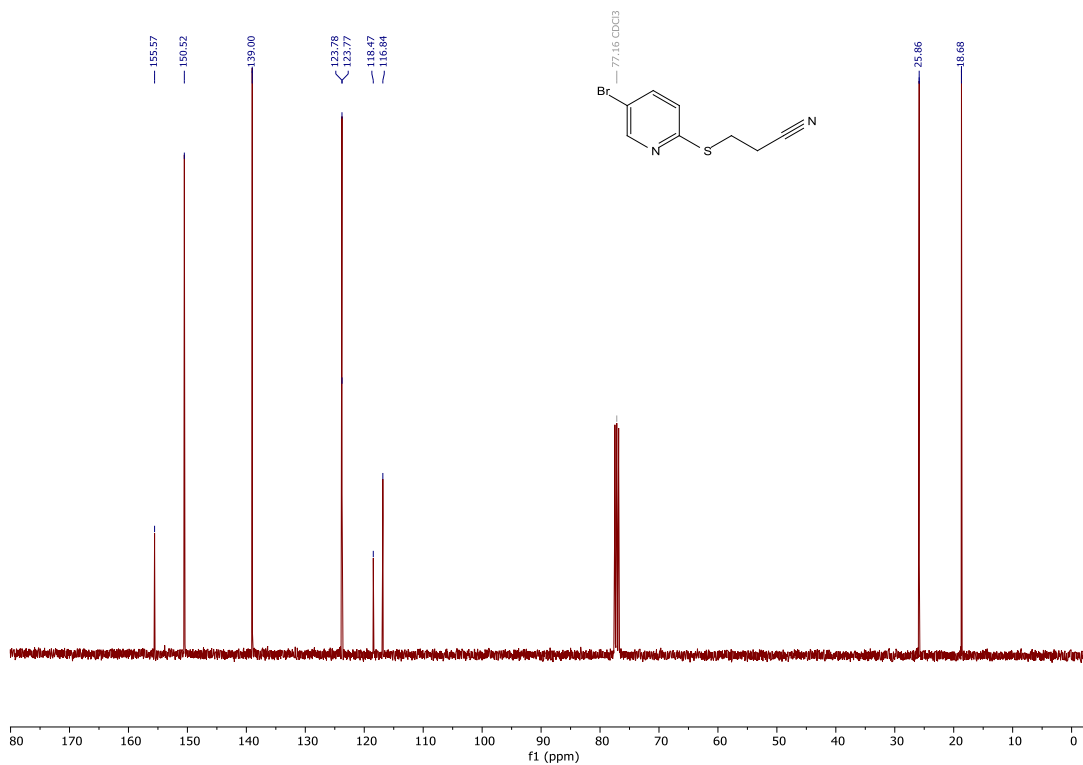
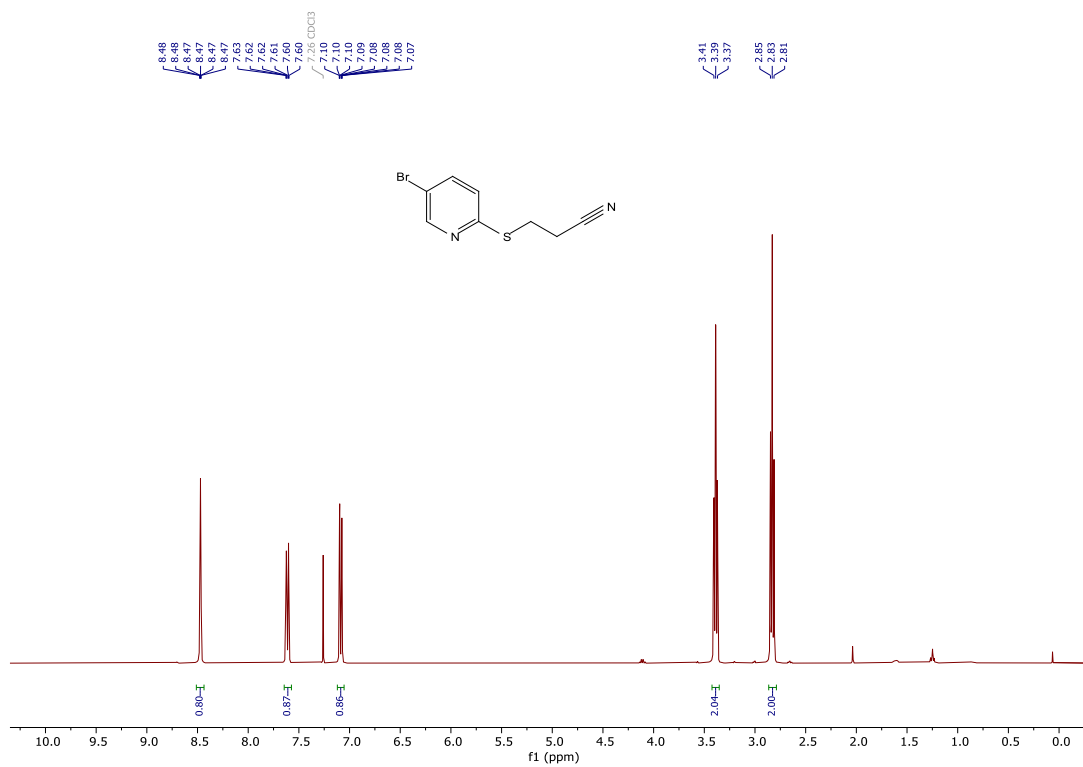


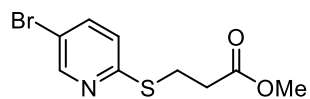
1-methyl-3-(pyridin-2-ylthio)pyrrolidine-2,5-dione (*pre* -11)



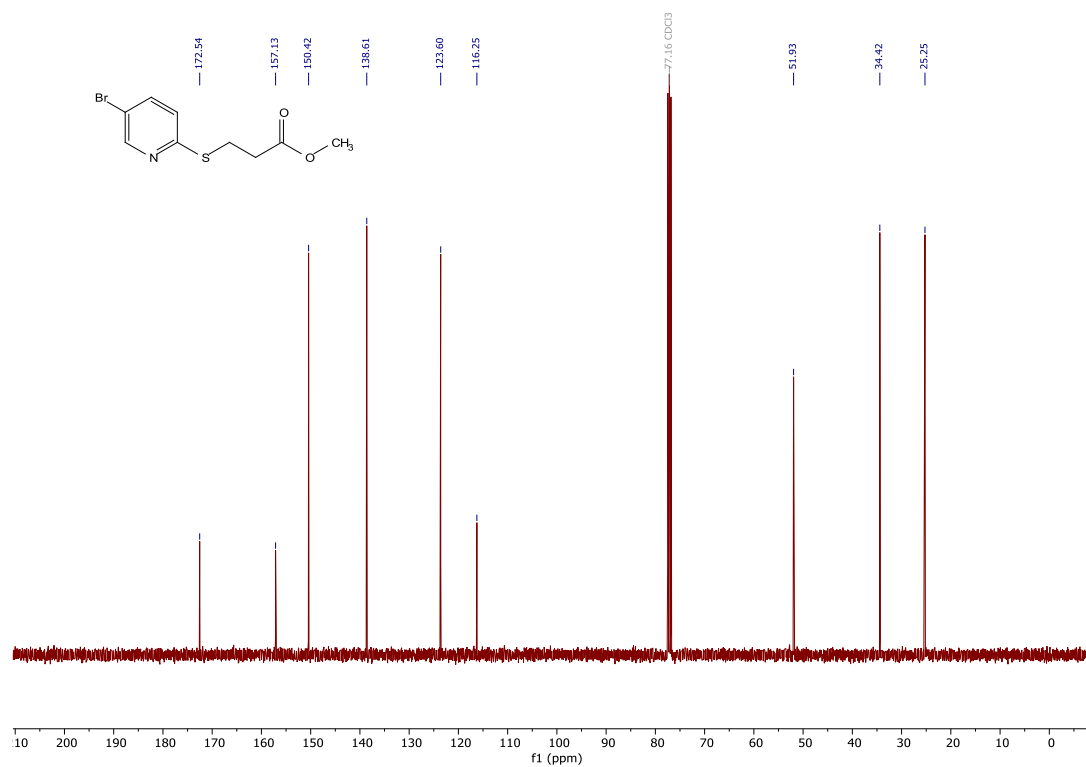
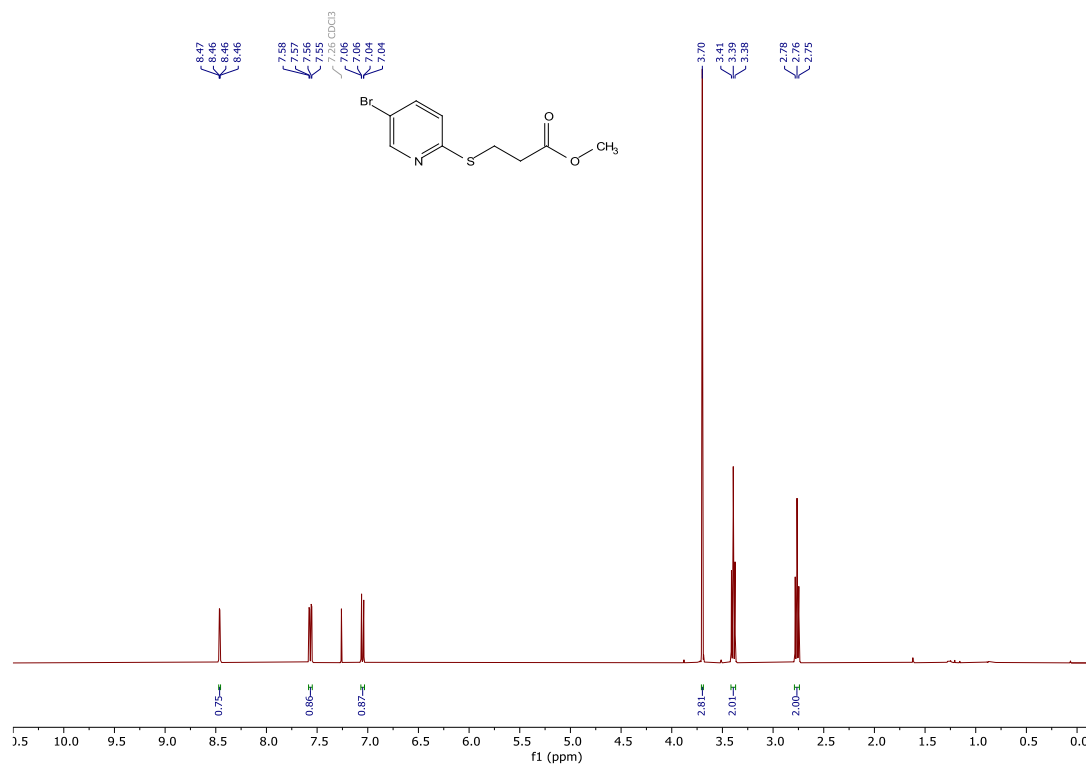


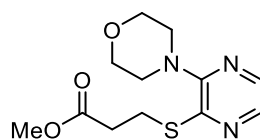
3-((5-bromopyridin-2-yl)thio)propanenitrile (*pre-12a*)



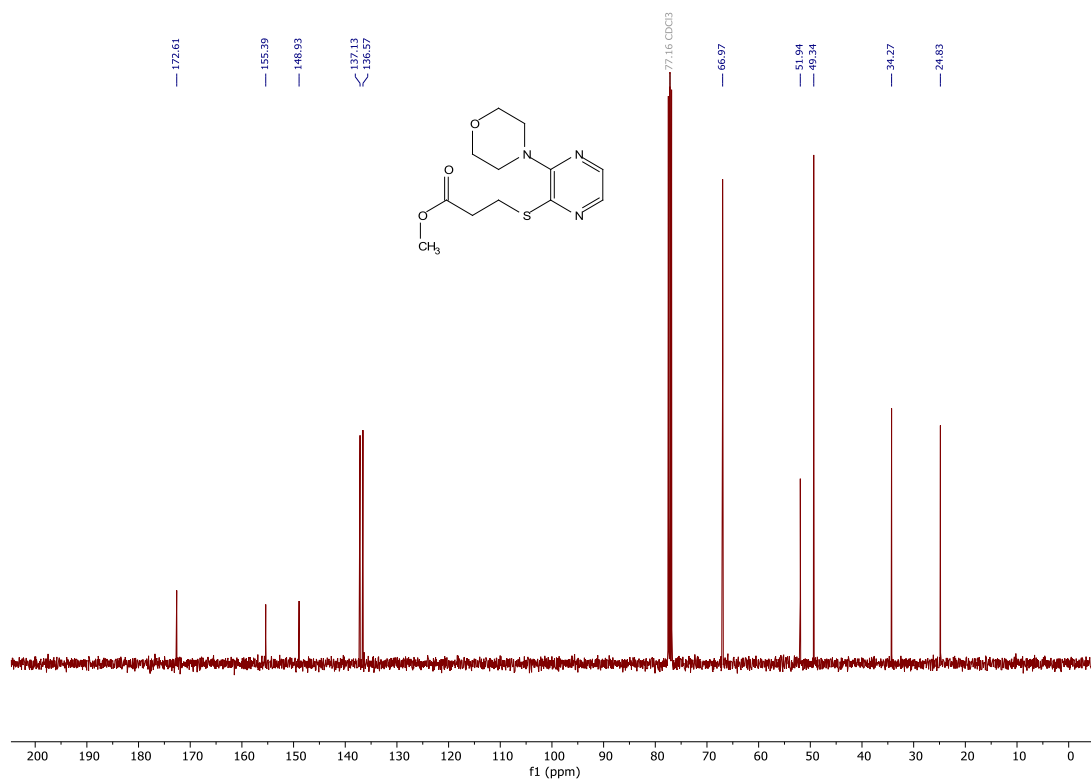
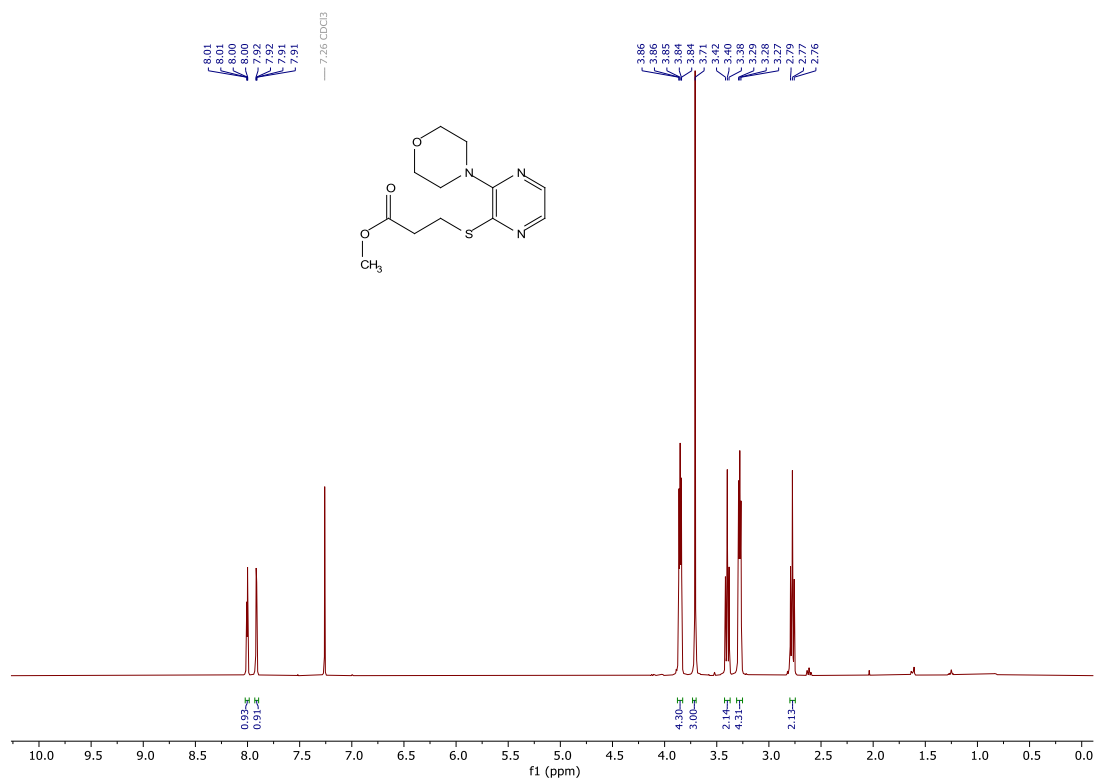


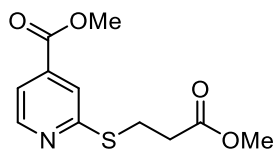
methyl 3-((5-bromopyridin-2-yl)thio)propanoate (*pre-12b*)



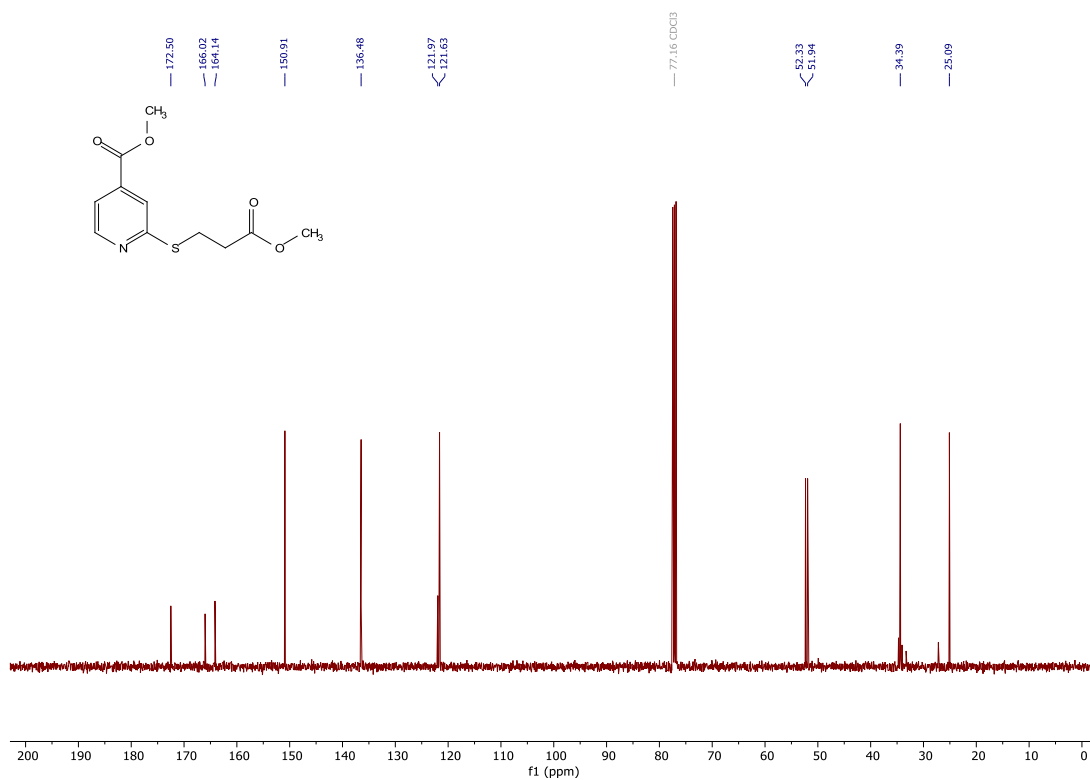
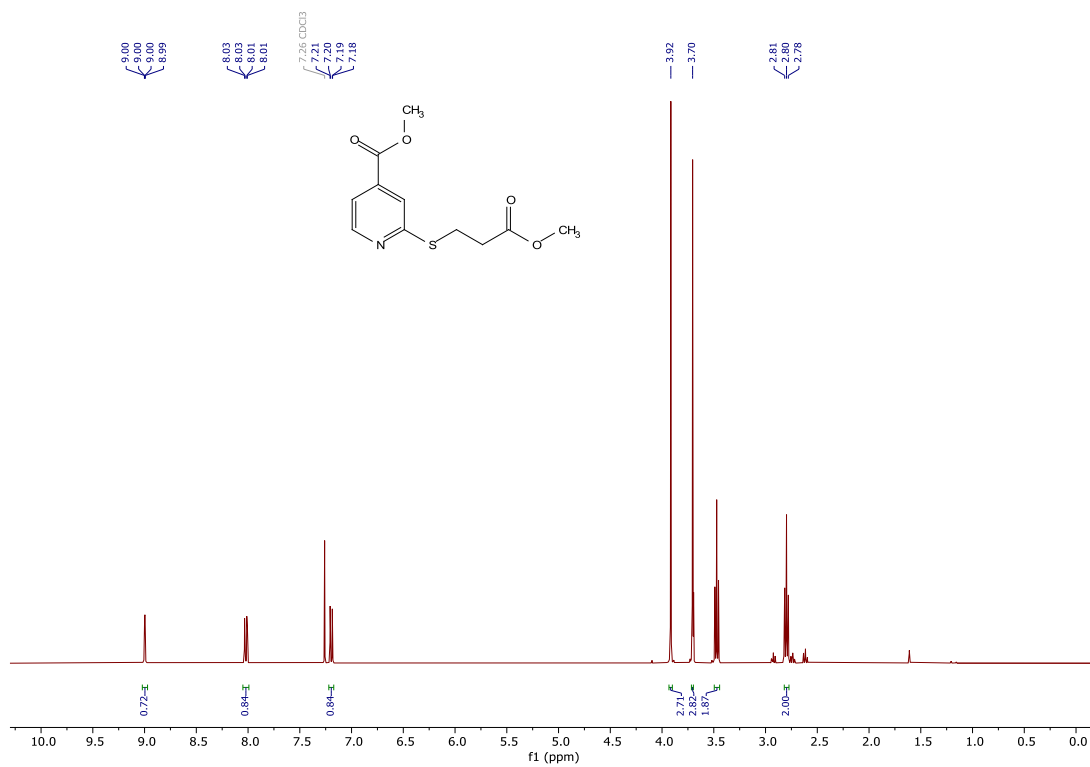


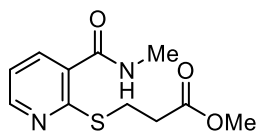
methyl 3-((3-morpholinopyrazin-2-yl)thio)propanoate (*pre-2d*)



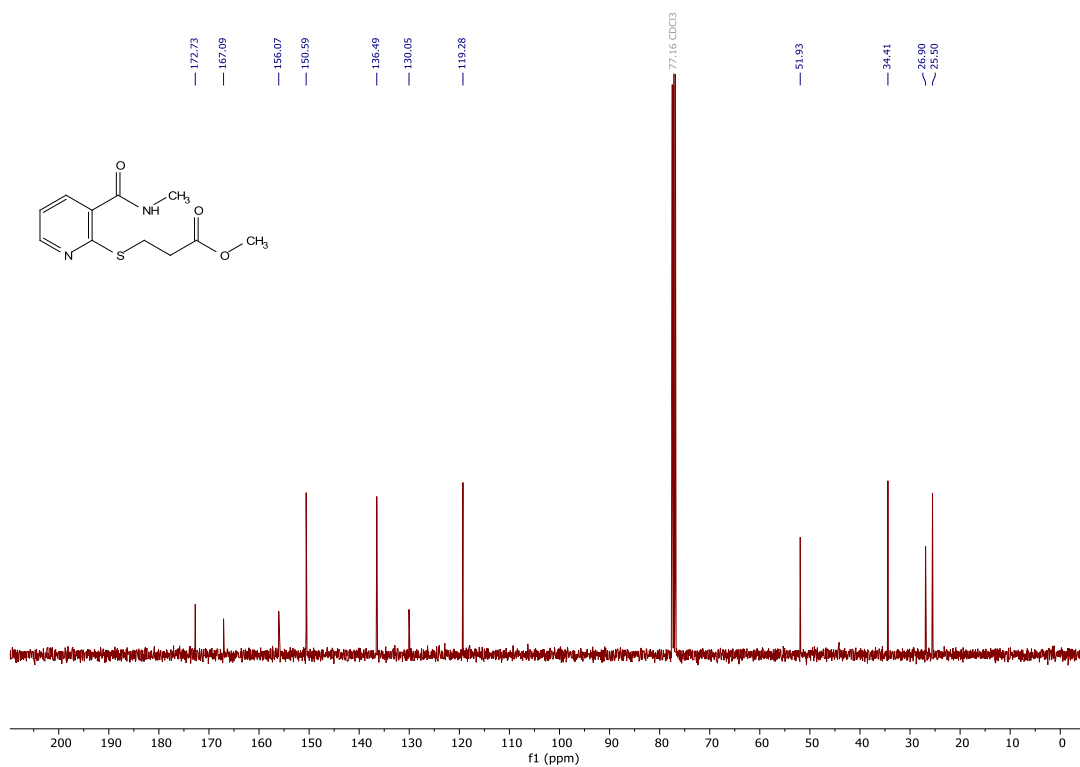
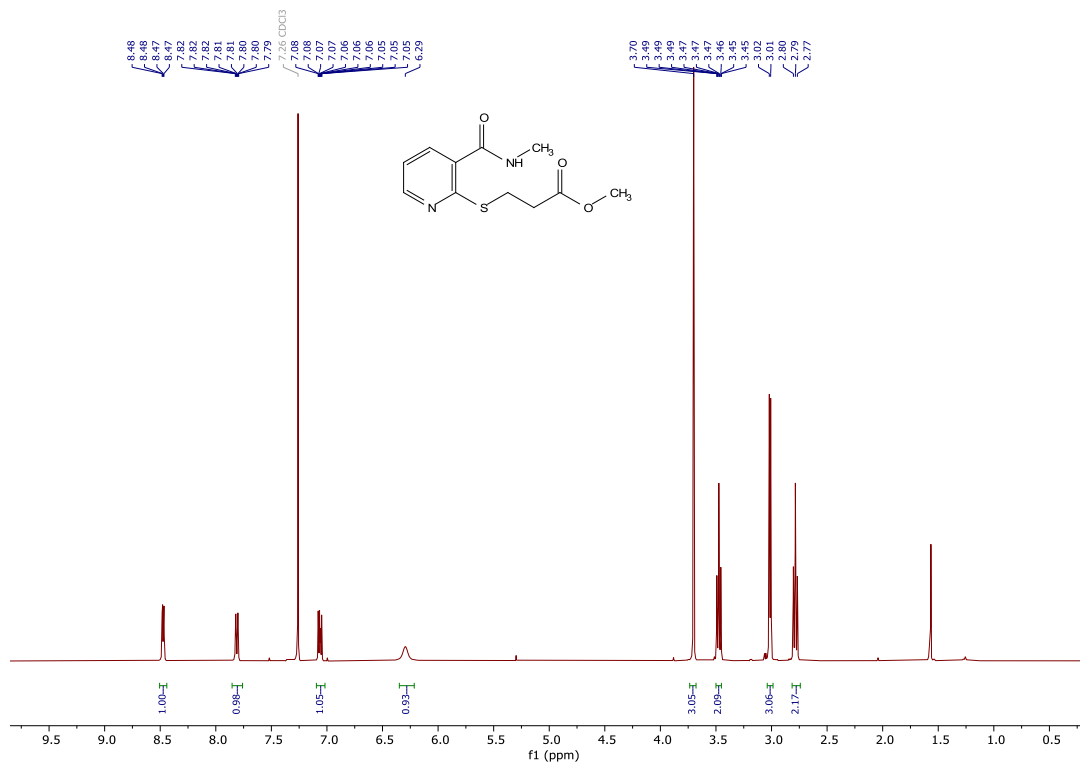


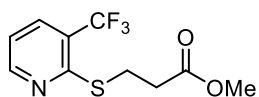
methyl 2-((3-methoxy-3-oxopropyl)thio)isonicotinate (*pre-2e*)



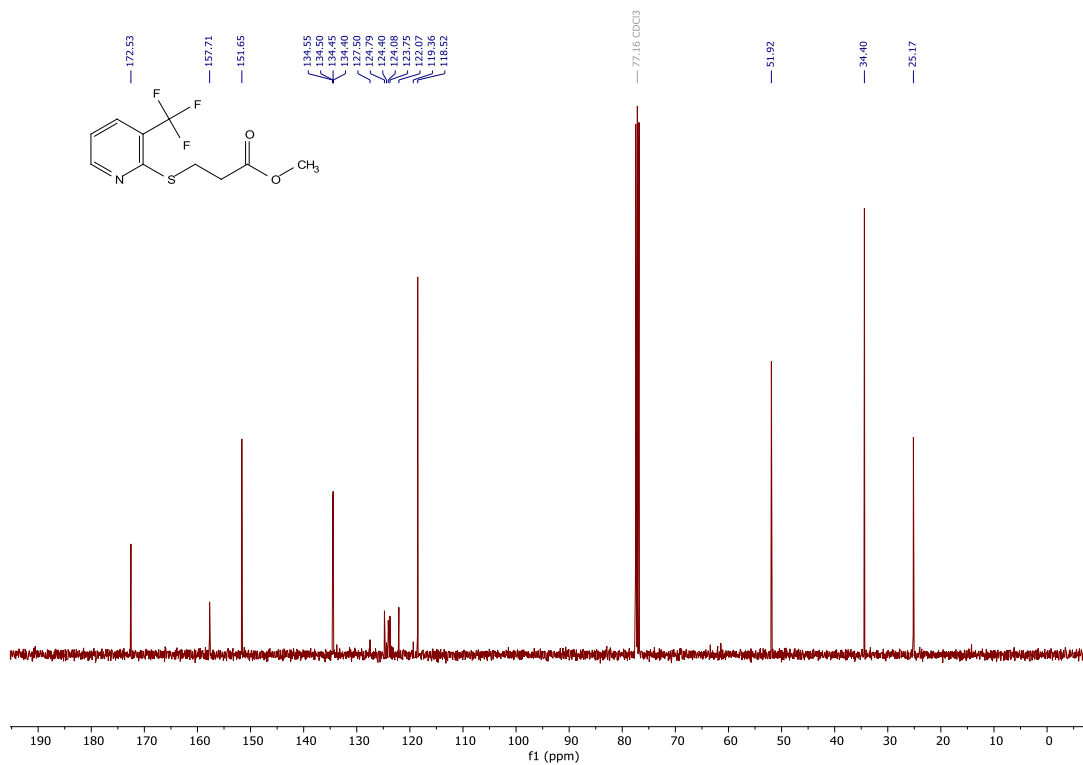
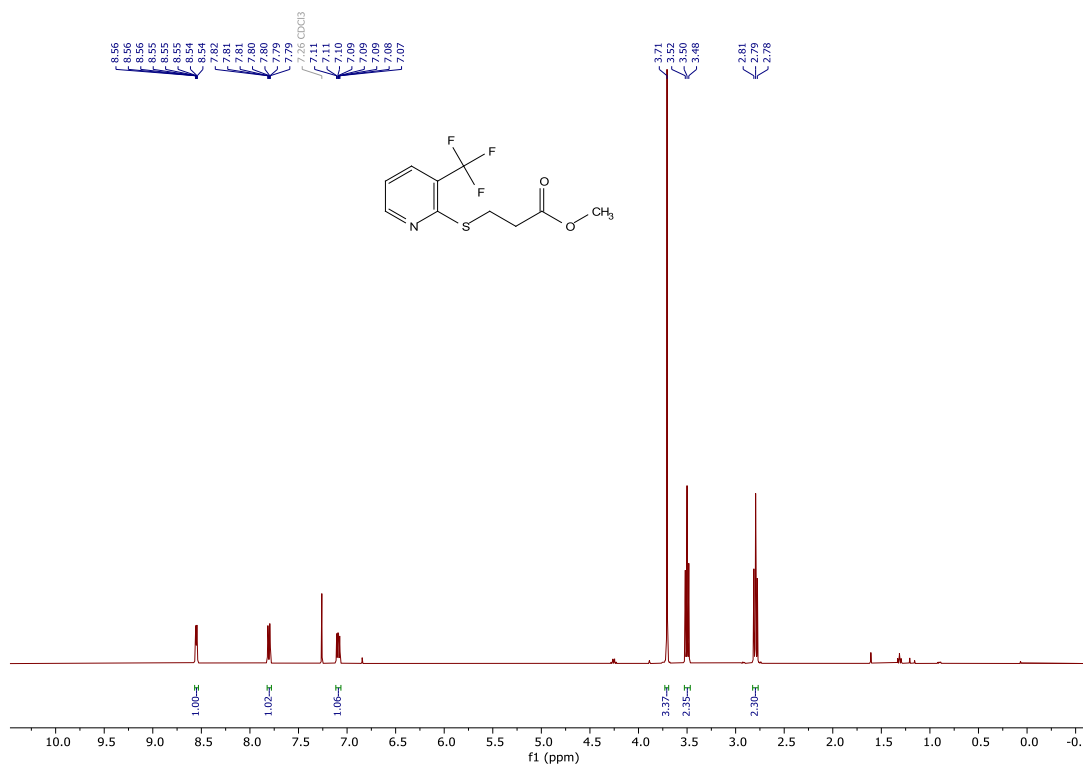


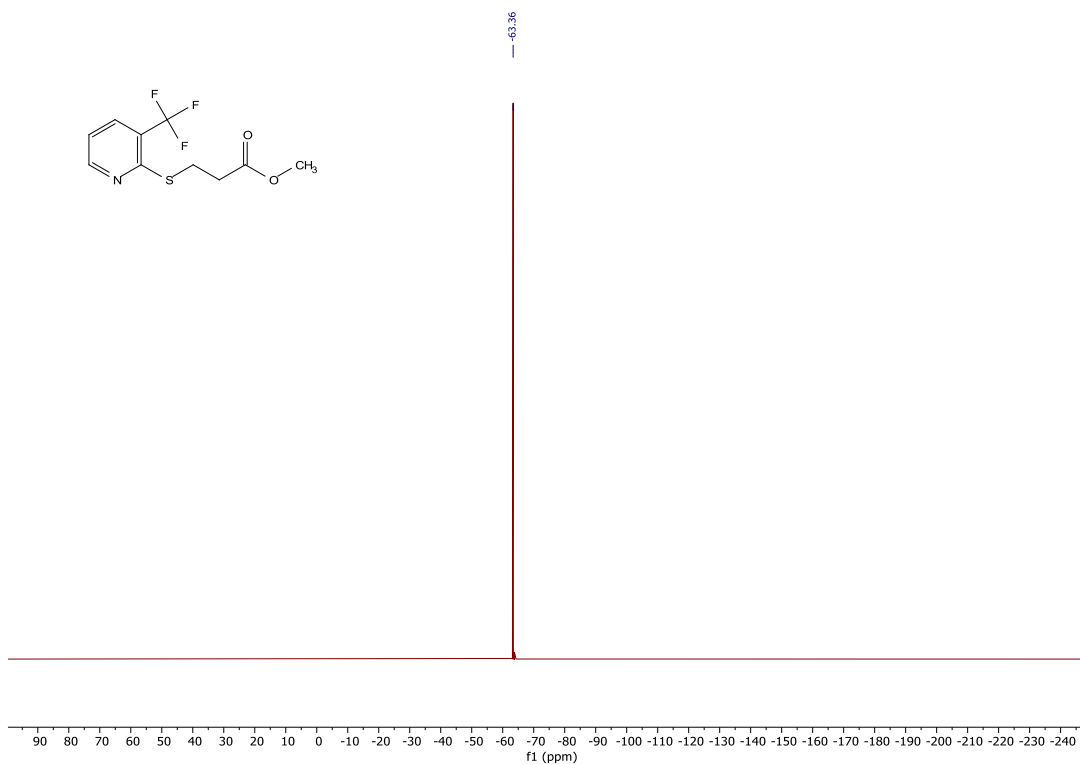
methyl 3-((3-(methylcarbamoyl)pyridin-2-yl)thio)propanoate (*pre-2f*)





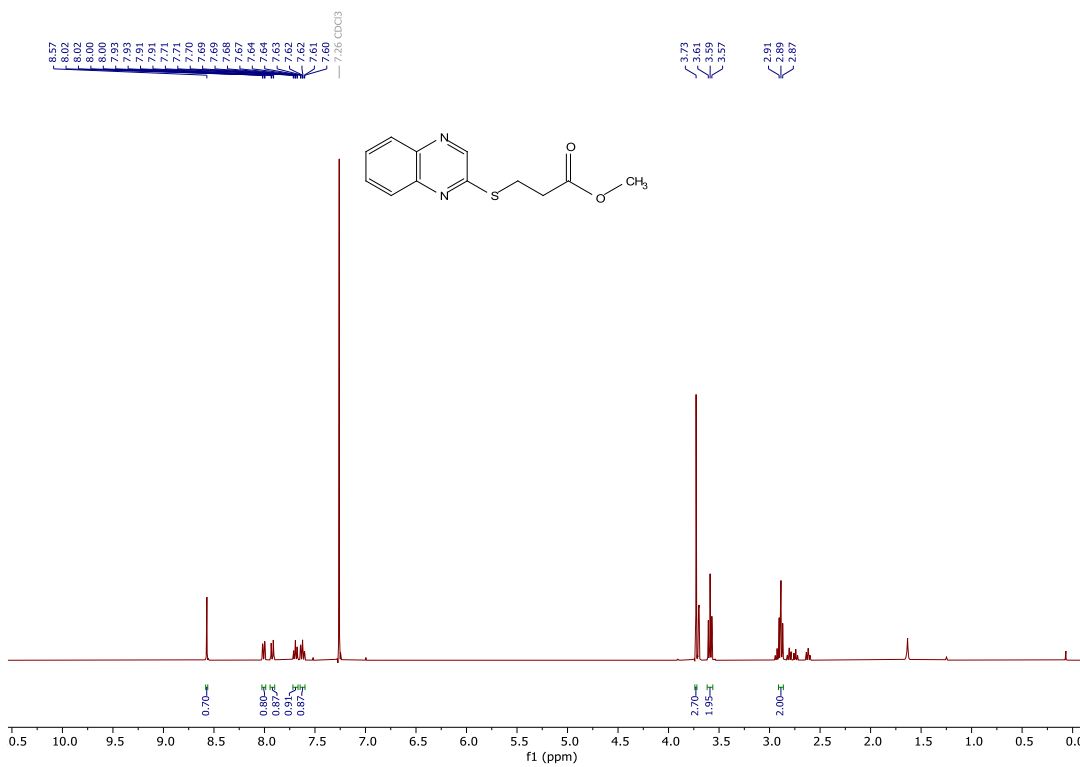
methyl 3-((3-(trifluoromethyl)pyridin-2-yl)thio)propanoate (*pre-2g*)

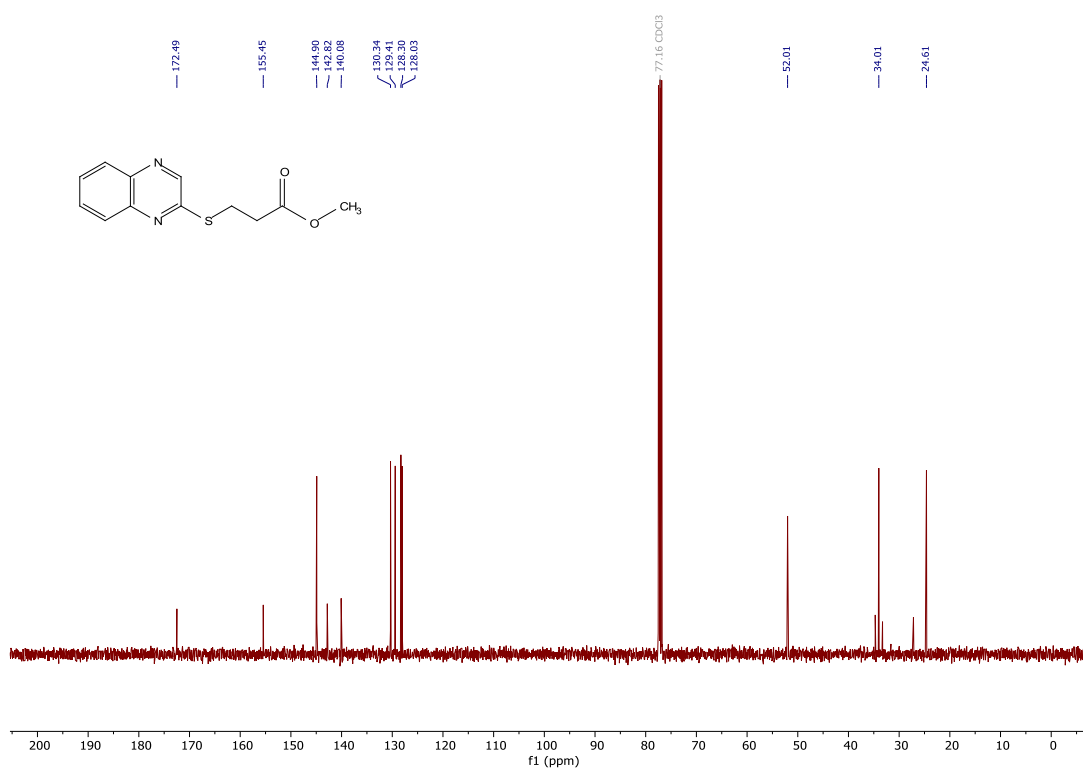




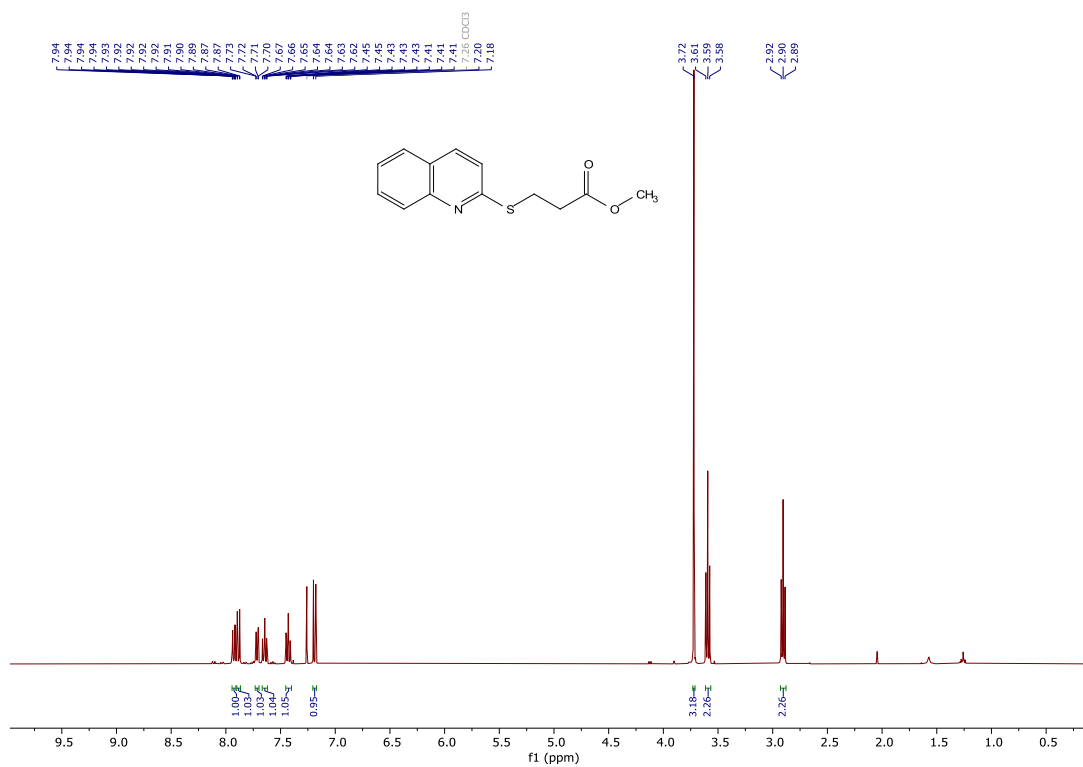
Chemical structure: CCOC(=O)CCSC1=CC2=C(N1)N=CN=C2

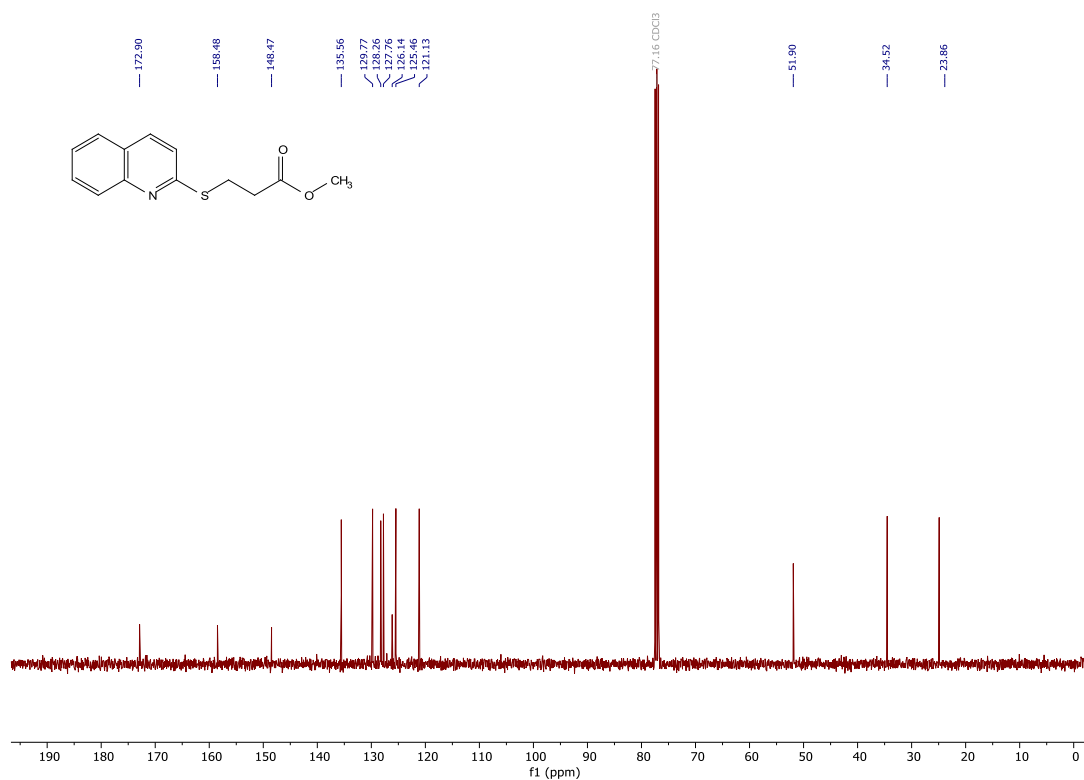
methyl 3-(quinoxalin-2-ylthio)propanoate (*pre-2h*)



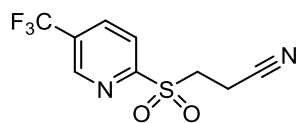


COC(=O)CCSC1=NC2=CC=CC=C2N=C1
methyl 3-(quinolin-2-ylthio)propanoate (*pre-2i*)

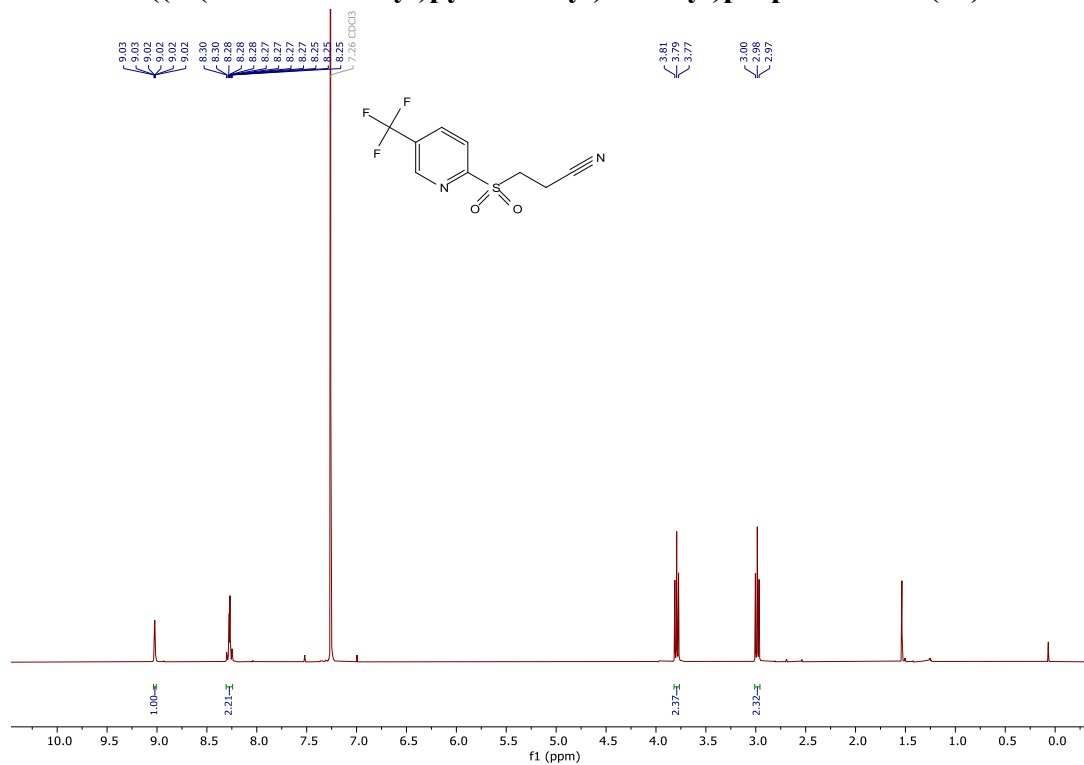


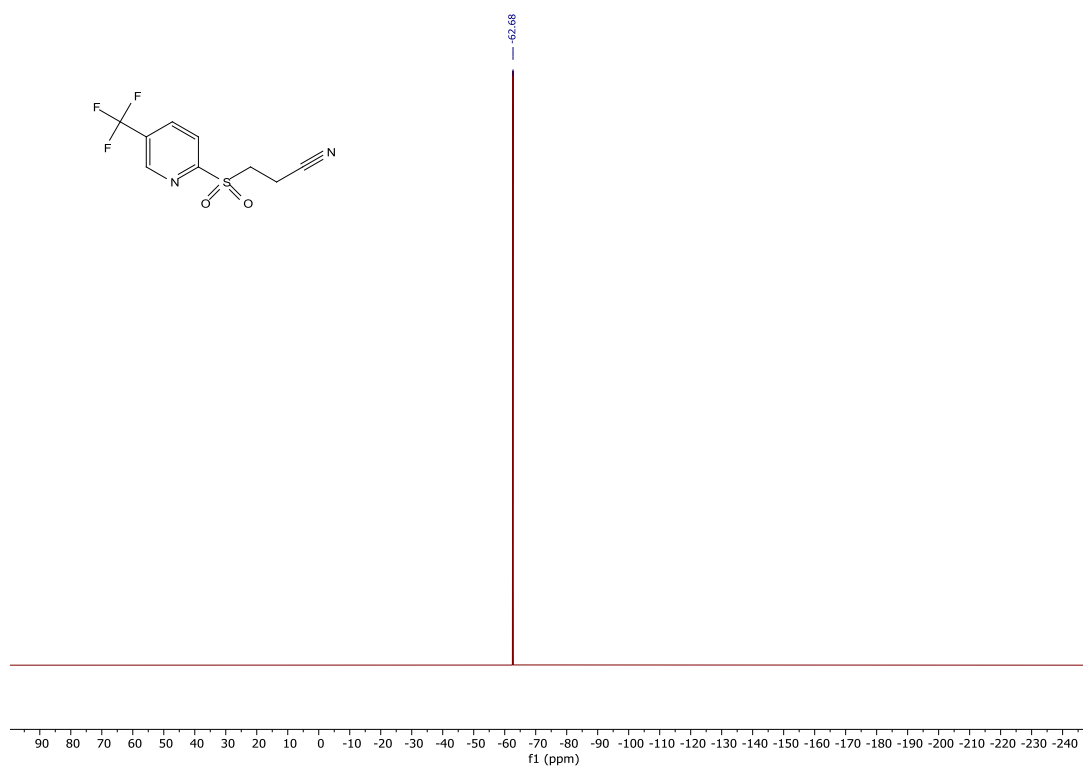
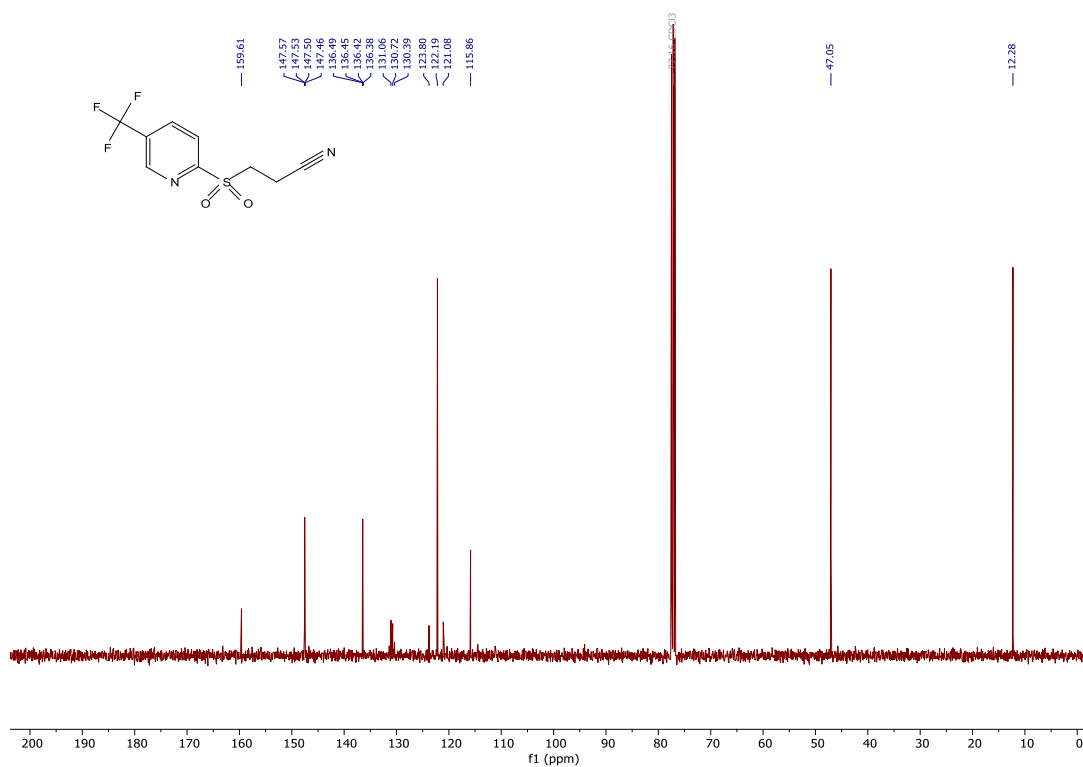


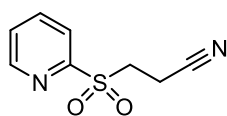
8.1.2. Sulfones



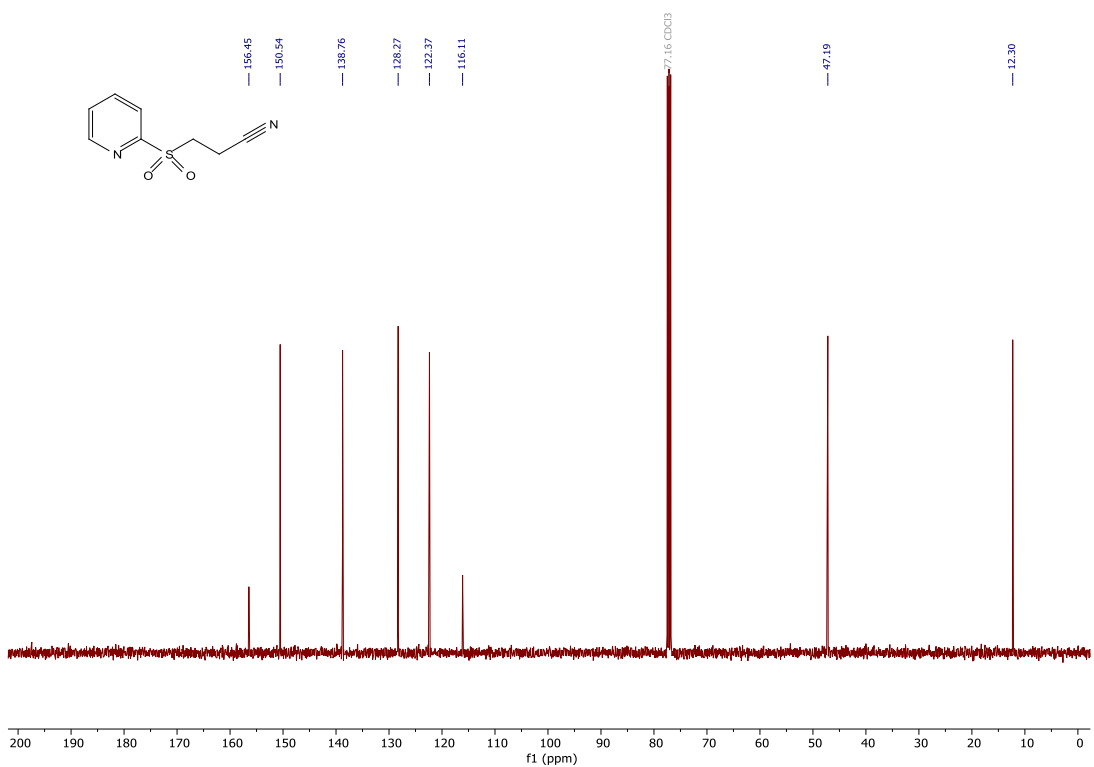
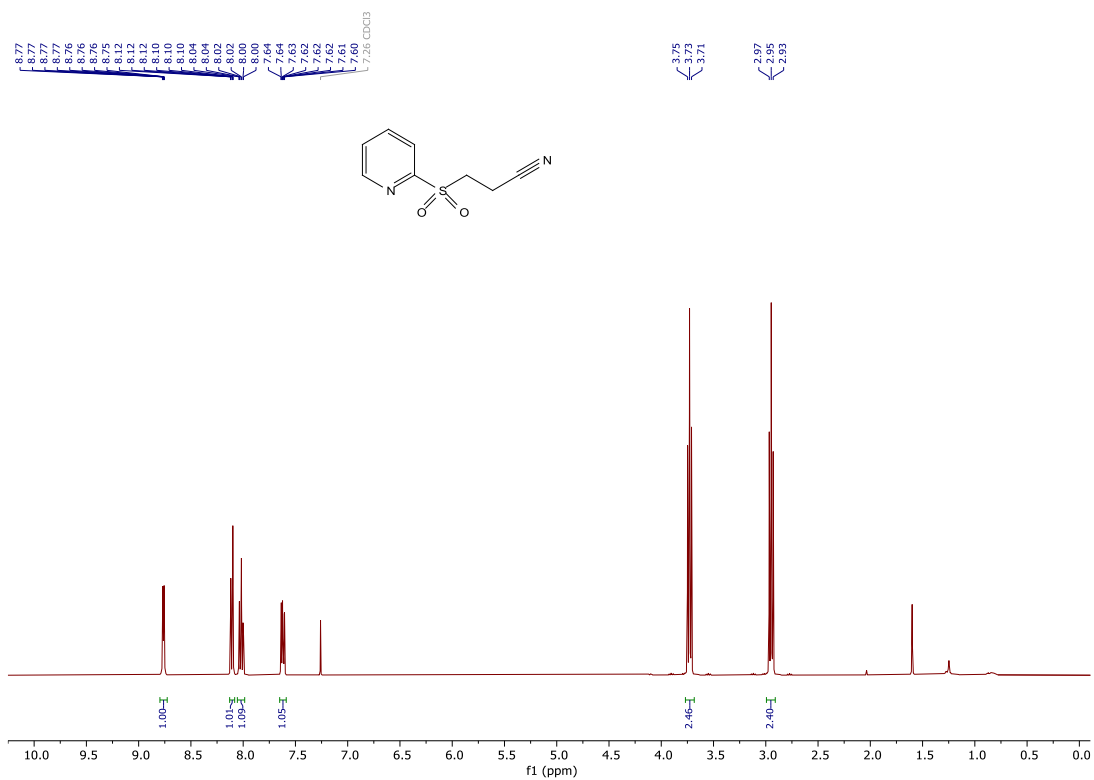
3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanenitrile (1a)

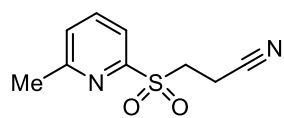




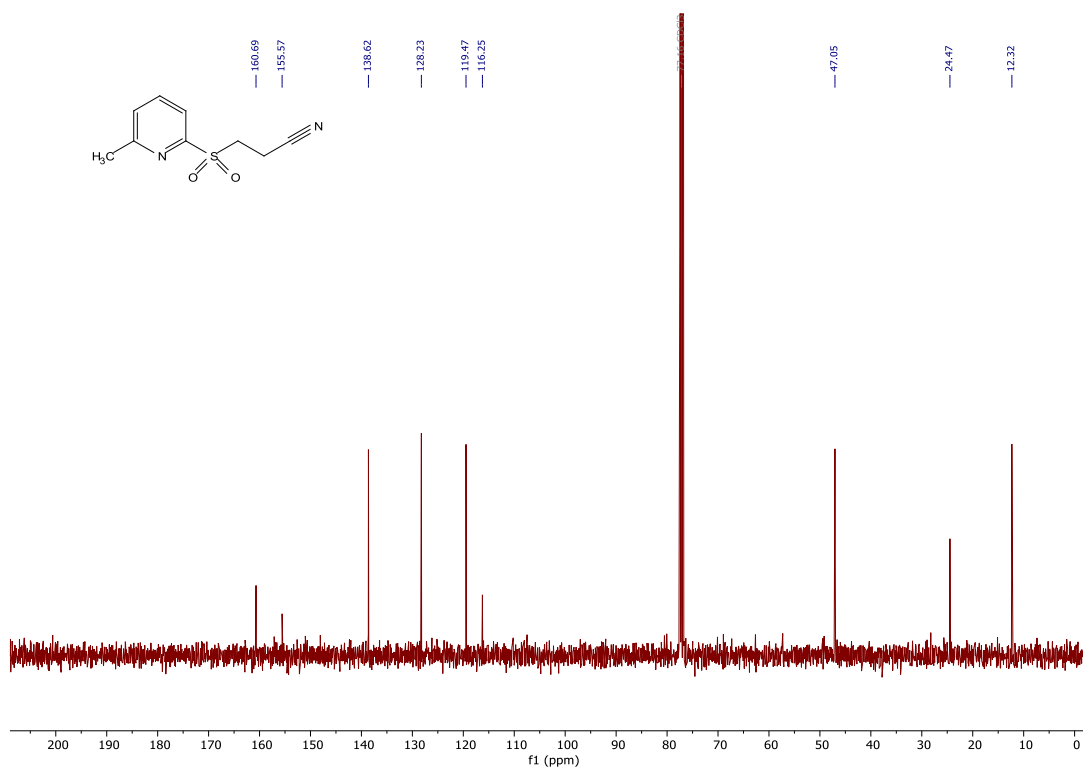
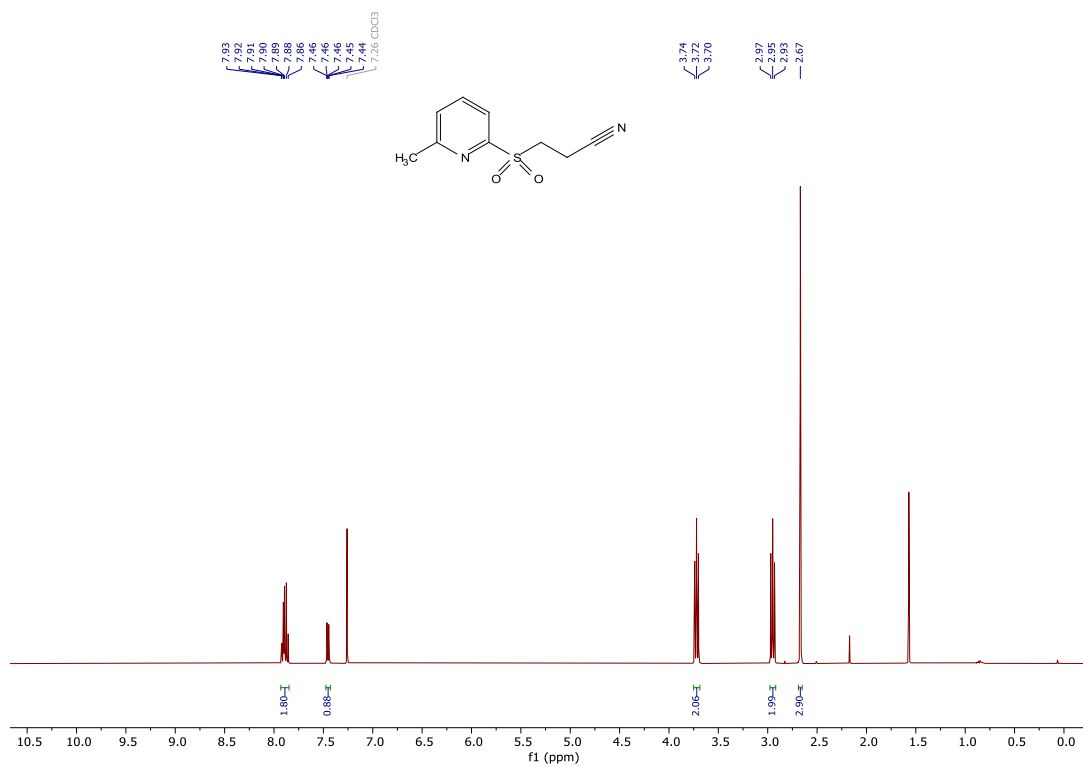


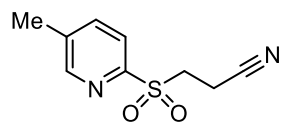
3-(pyridin-2-ylsulfonyl)propanenitrile (1b)



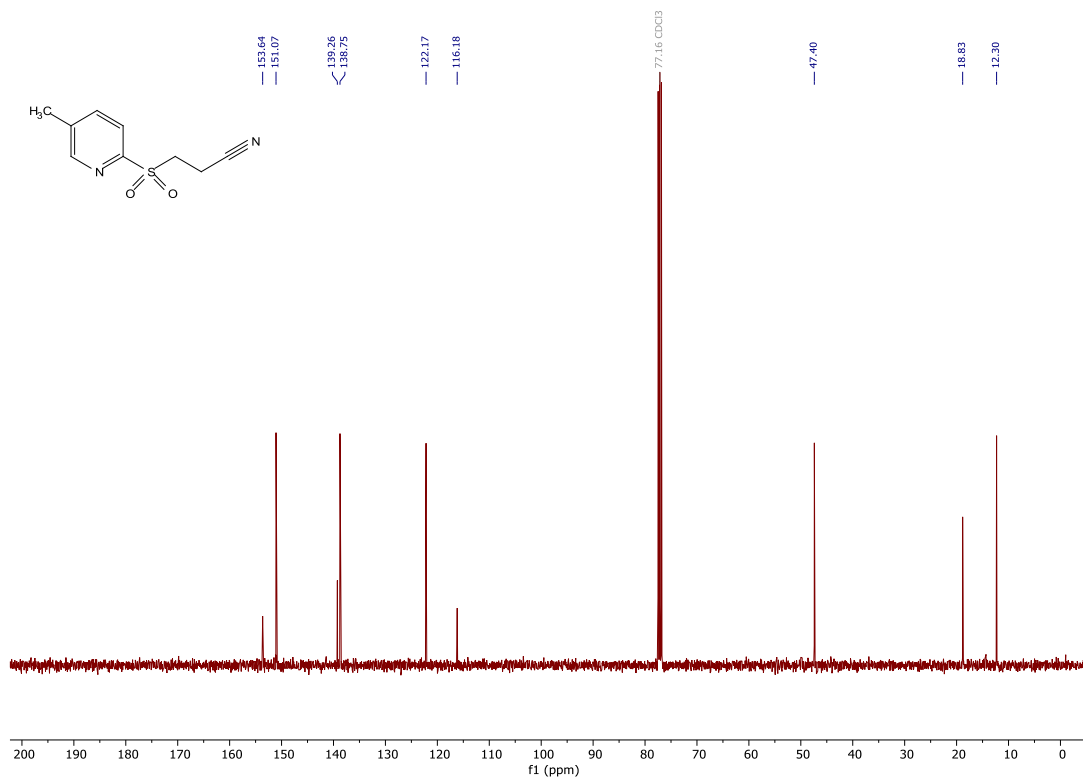
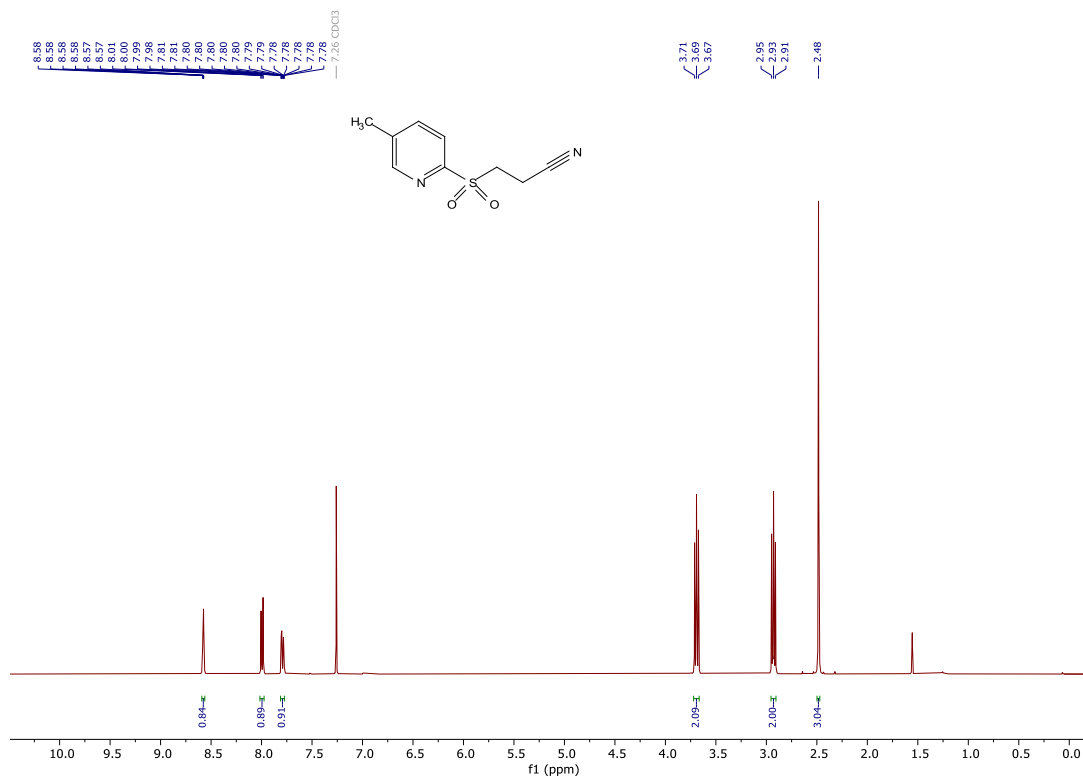


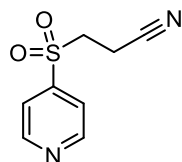
3-((6-methylpyridin-2-yl)sulfonyl)propanenitrile (15a)



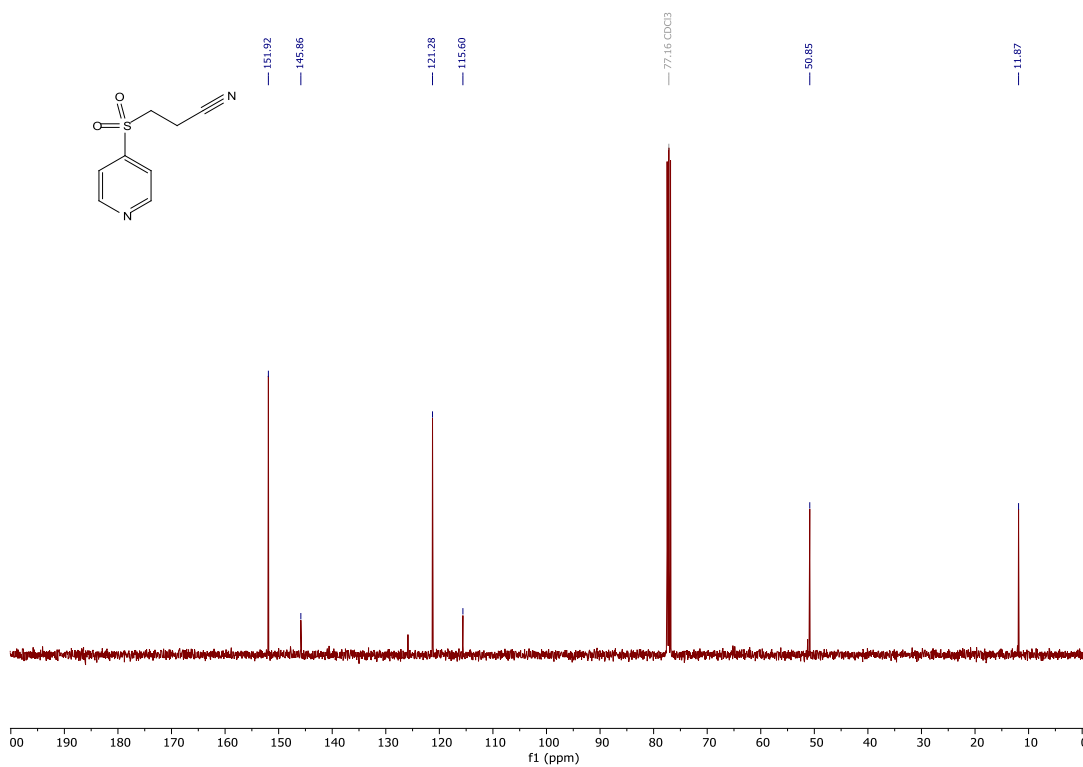
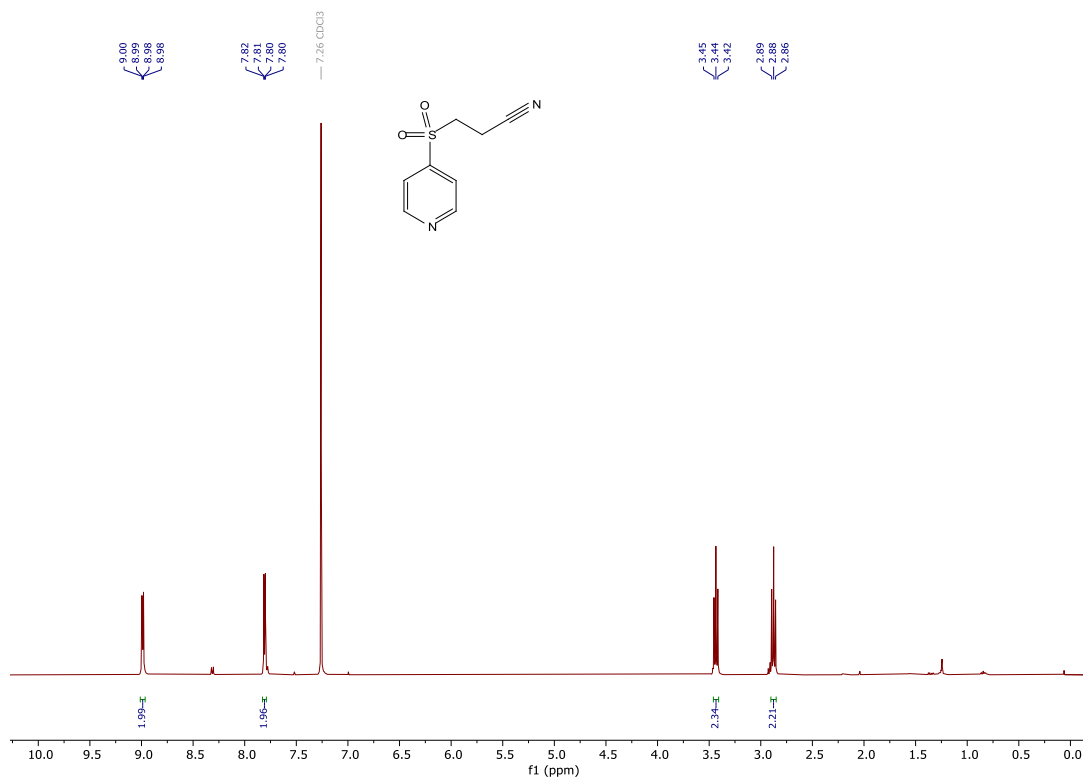


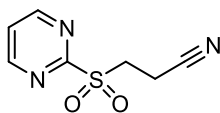
3-((5-methylpyridin-2-yl)sulfonyl)propanenitrile (1d)



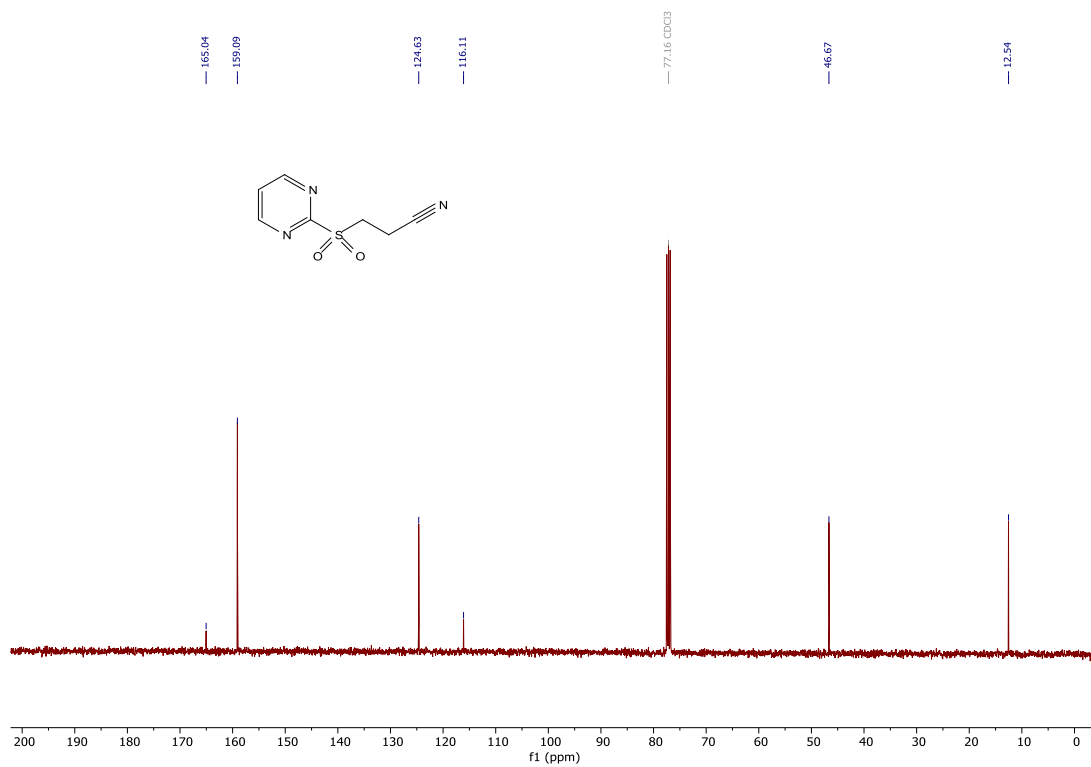
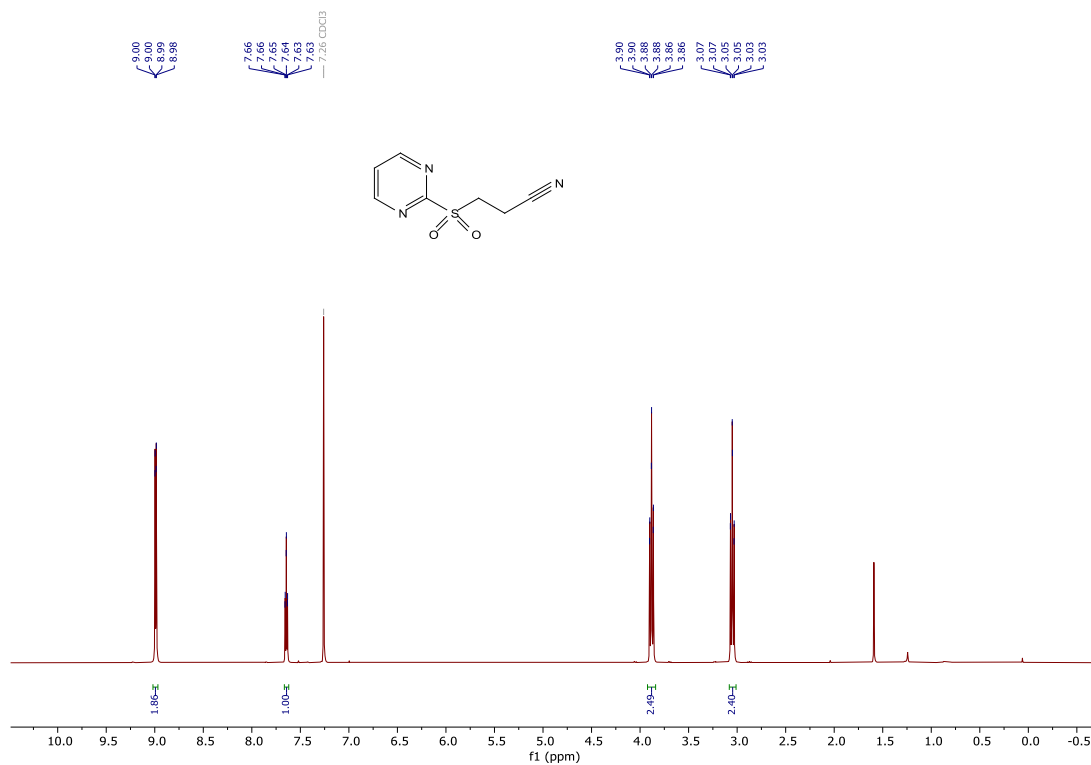


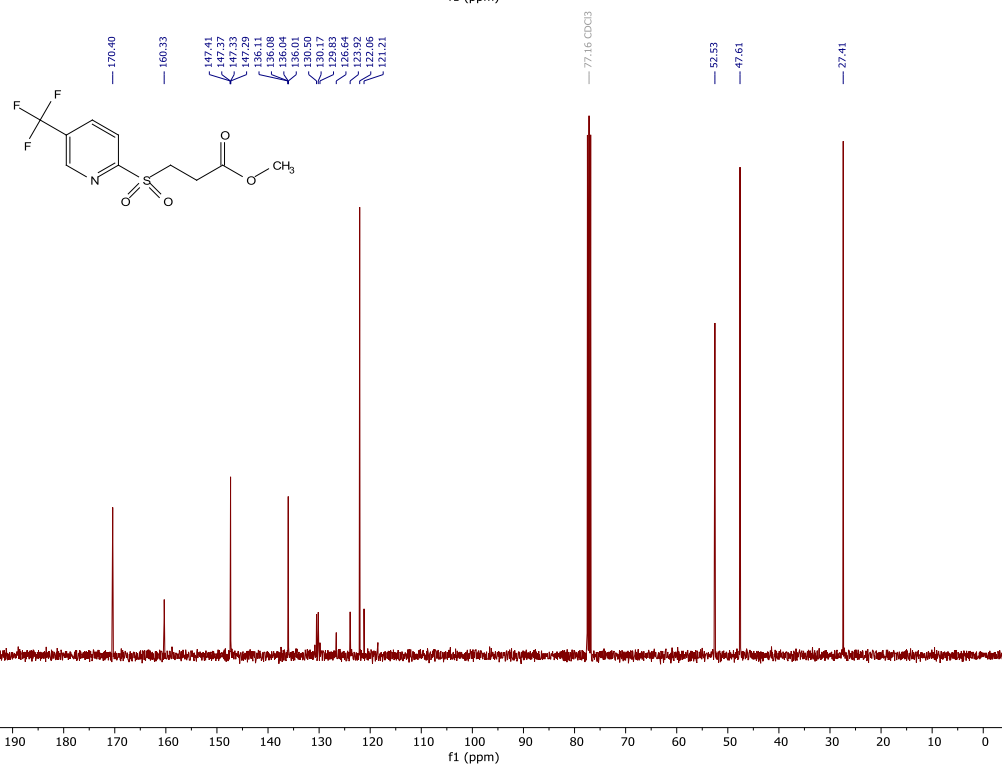
3-(pyridin-4-ylsulfonyl)propanenitrile (1e)

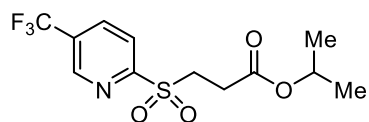
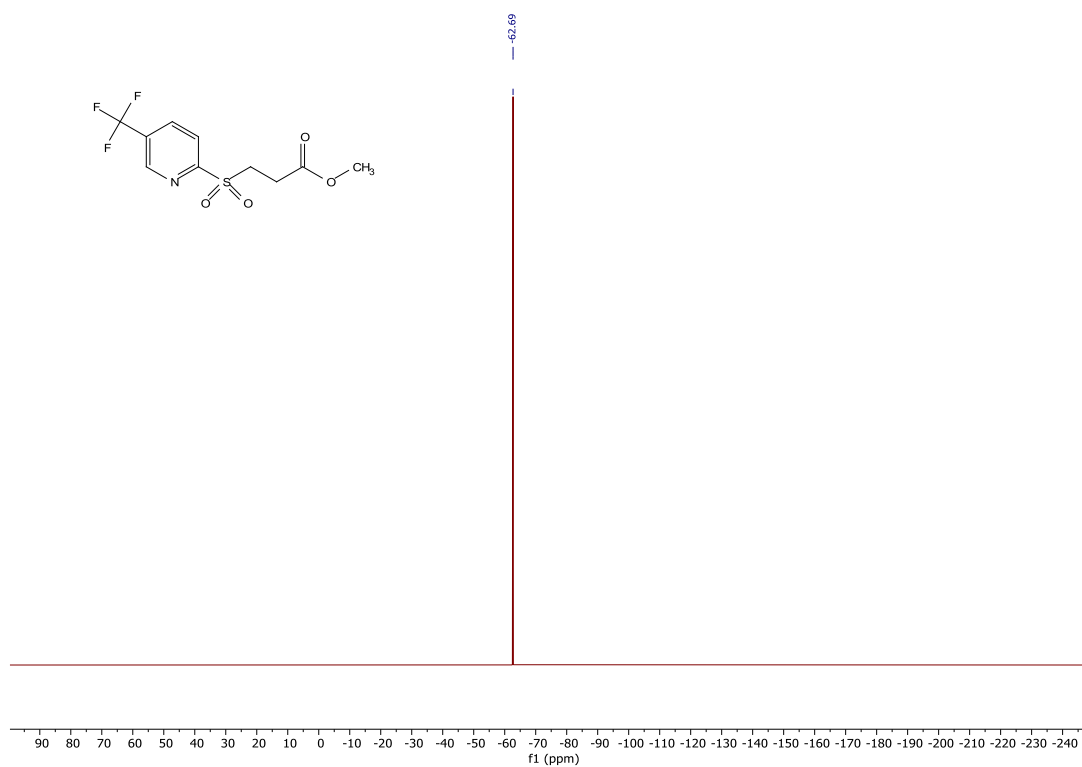




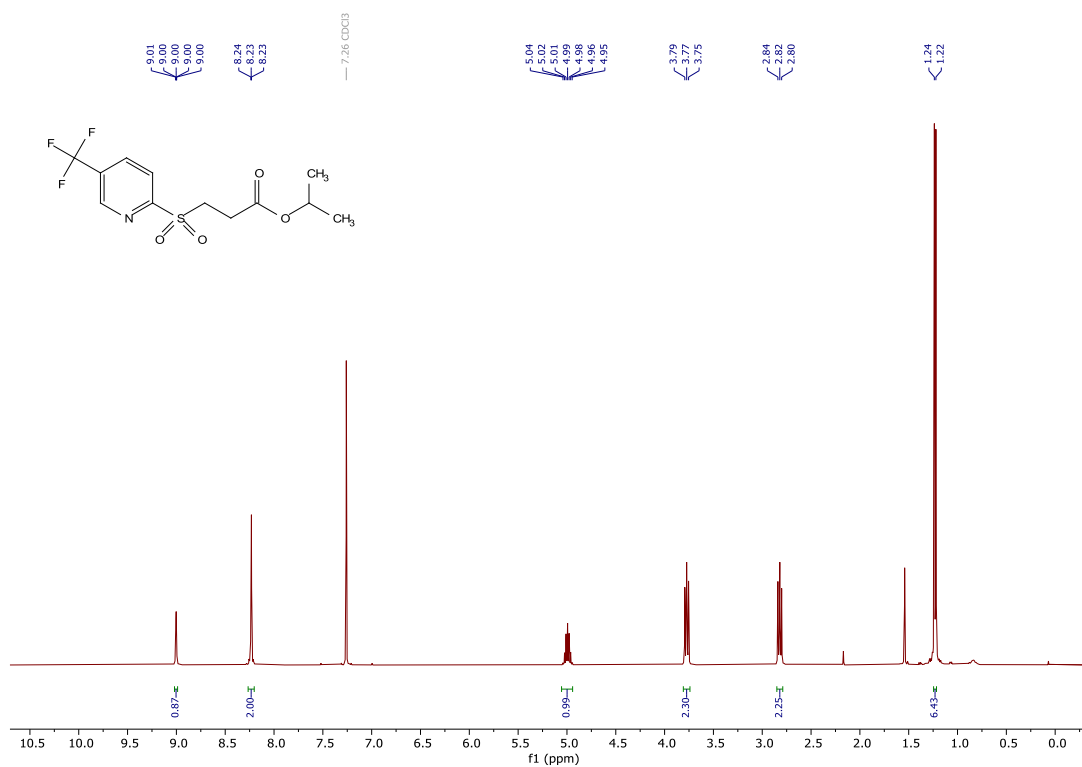
3-(pyrimidin-2-ylsulfonyl)propanenitrile (1f)

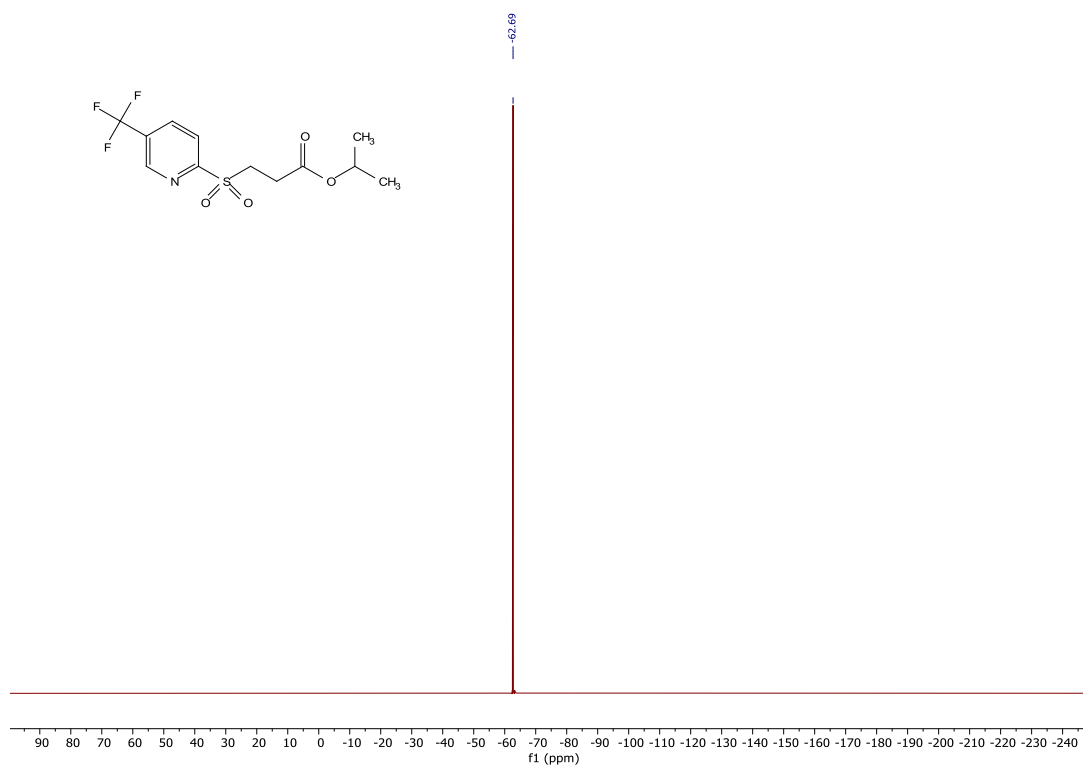
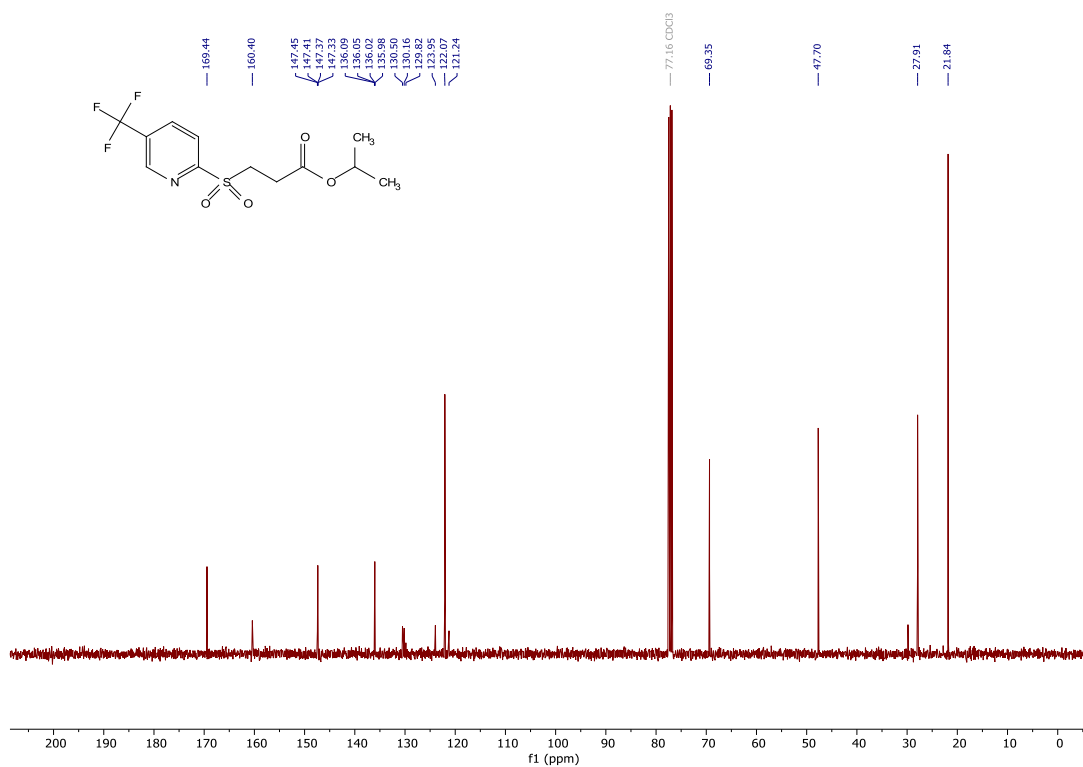


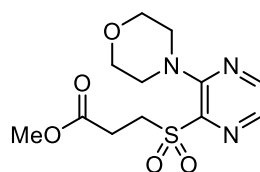




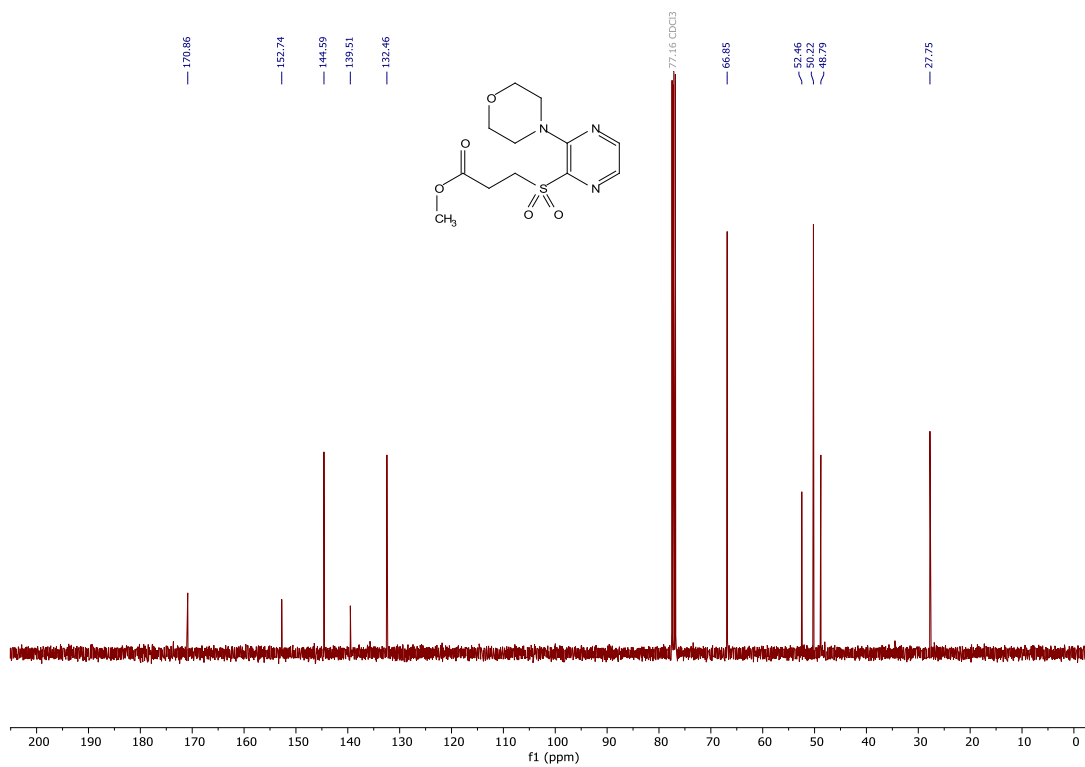
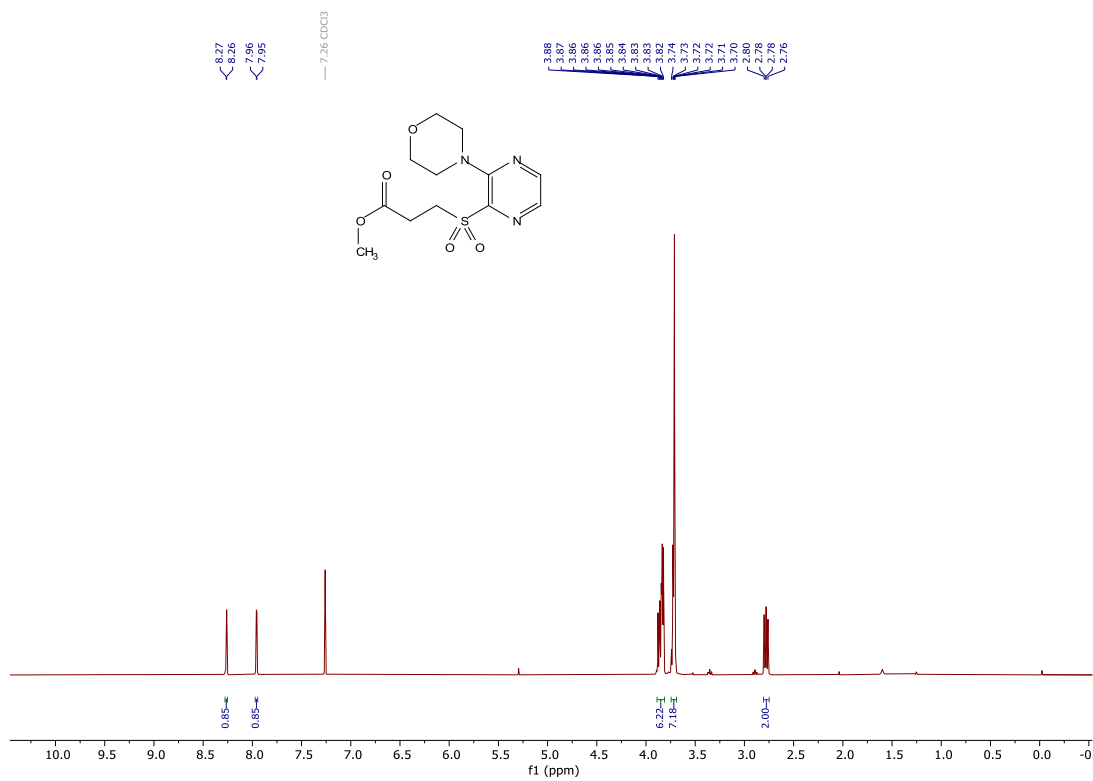
***Iso*-propyl 3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoate (2a-iPr)**

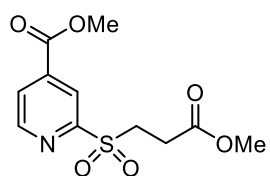




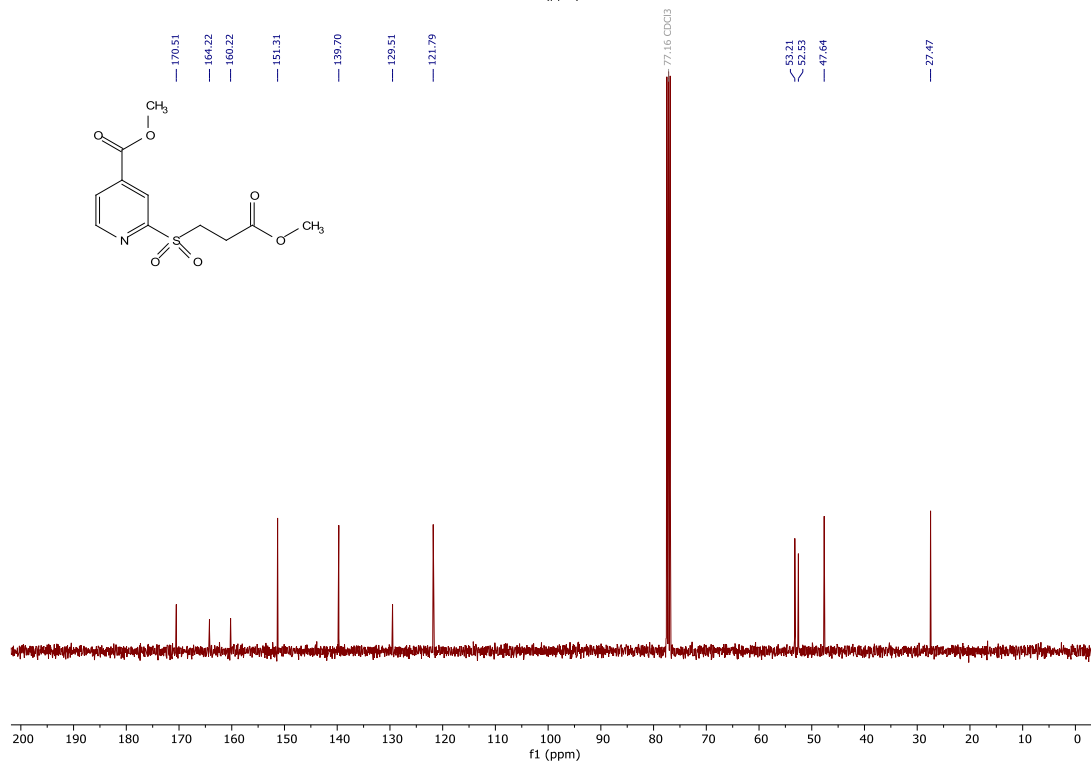
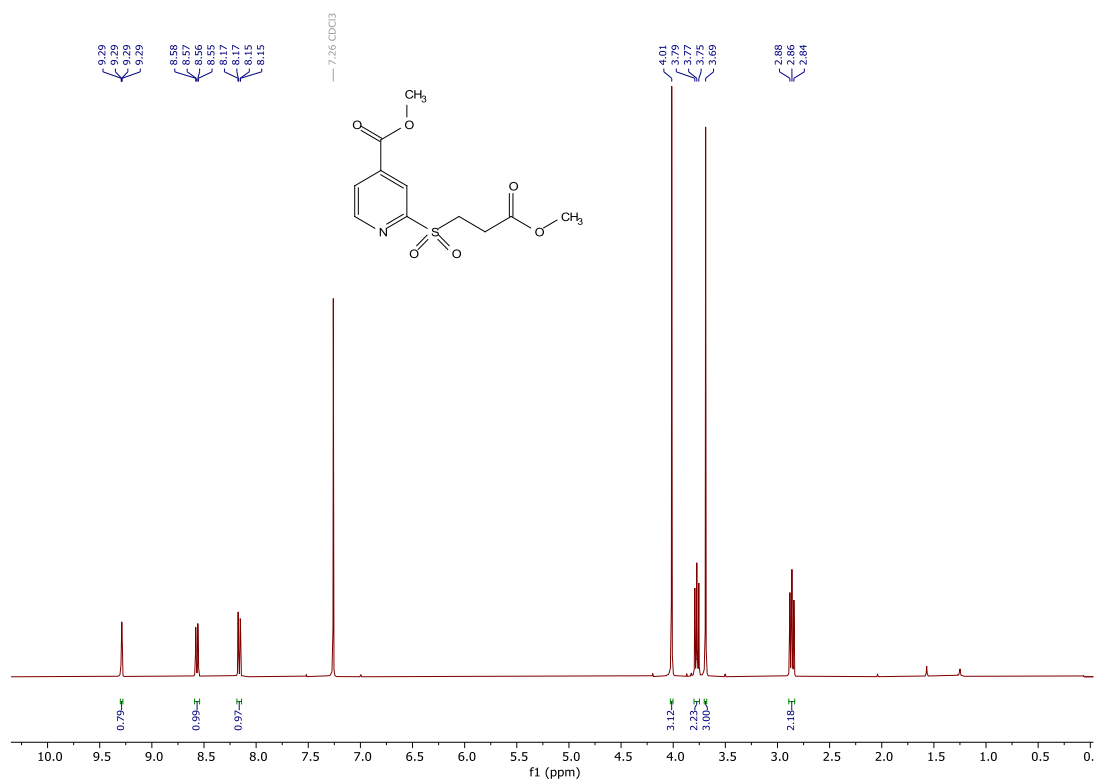


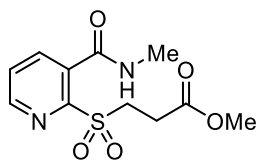
methyl 3-((3-morpholinopyrazin-2-yl)sulfonyl)propanoate (2d)



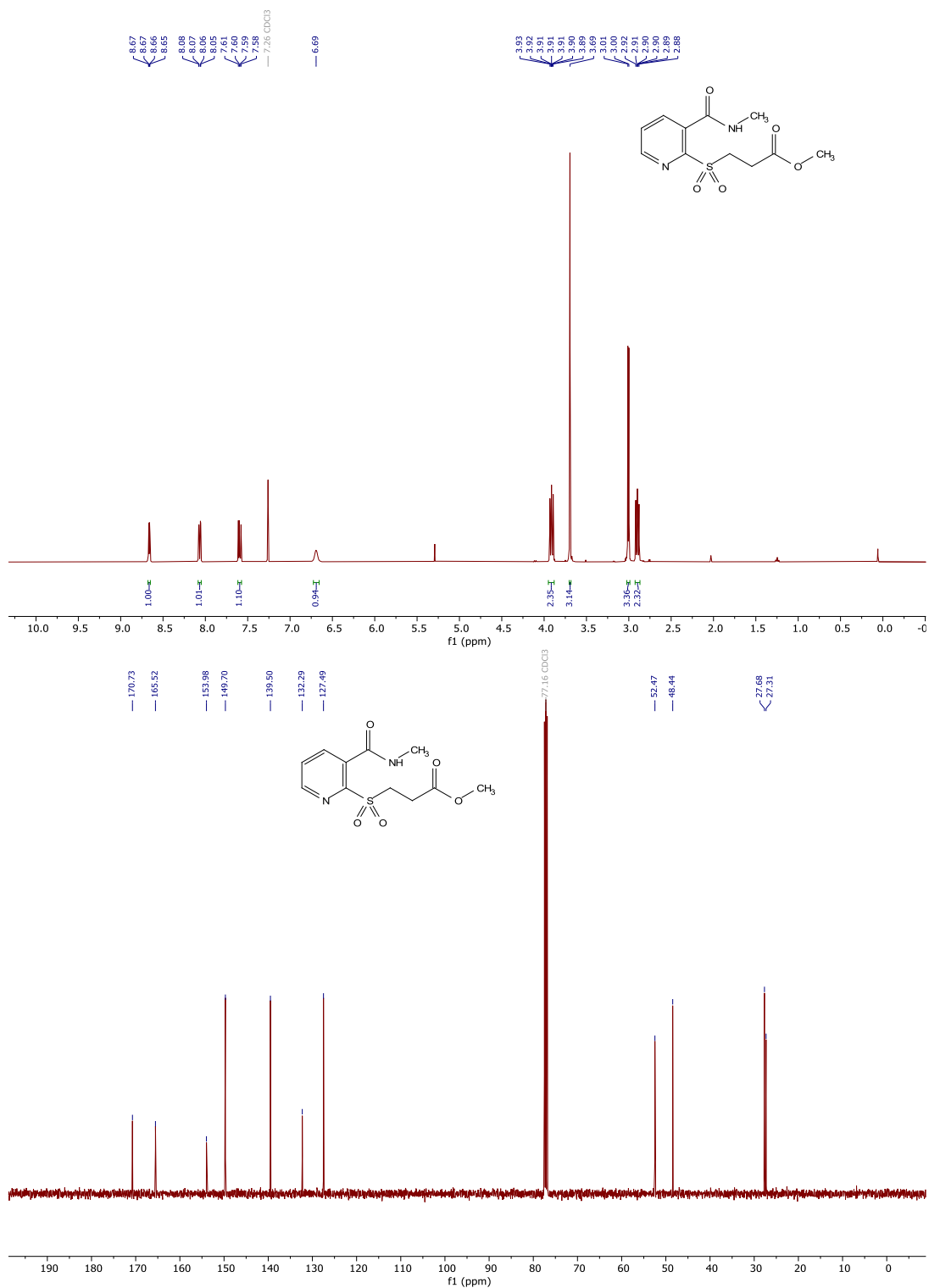


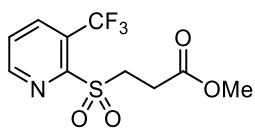
methyl 2-((3-methoxy-3-oxopropyl)sulfonyl)isonicotinate (2e)



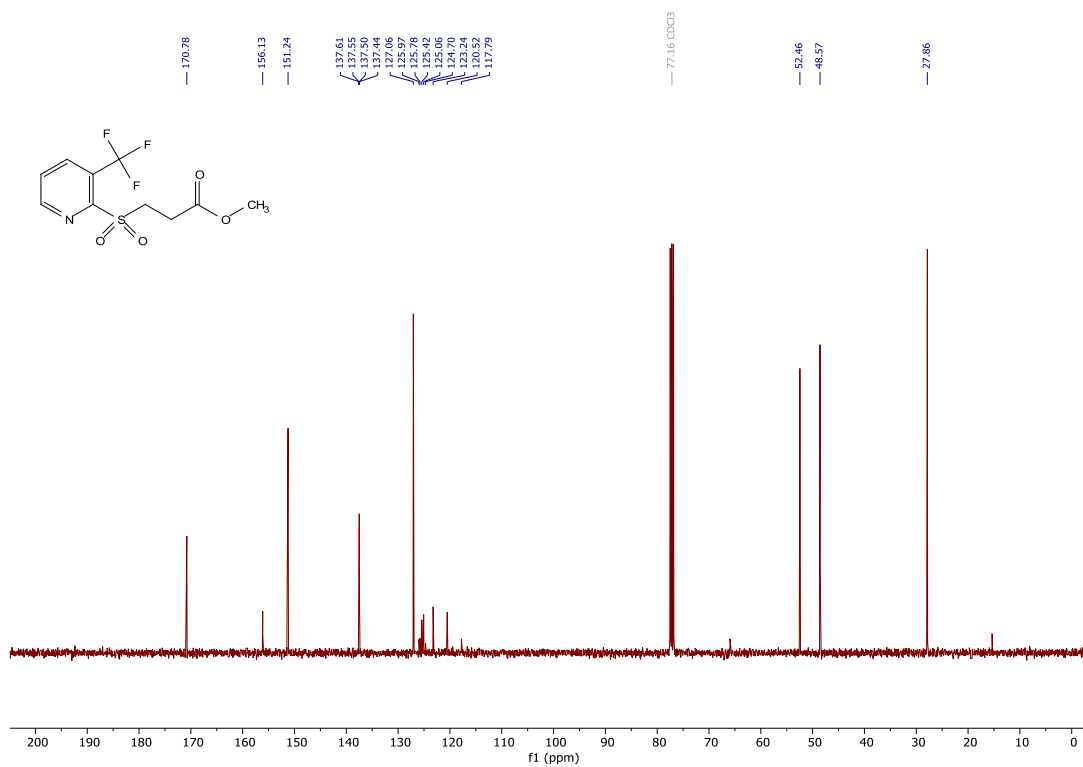
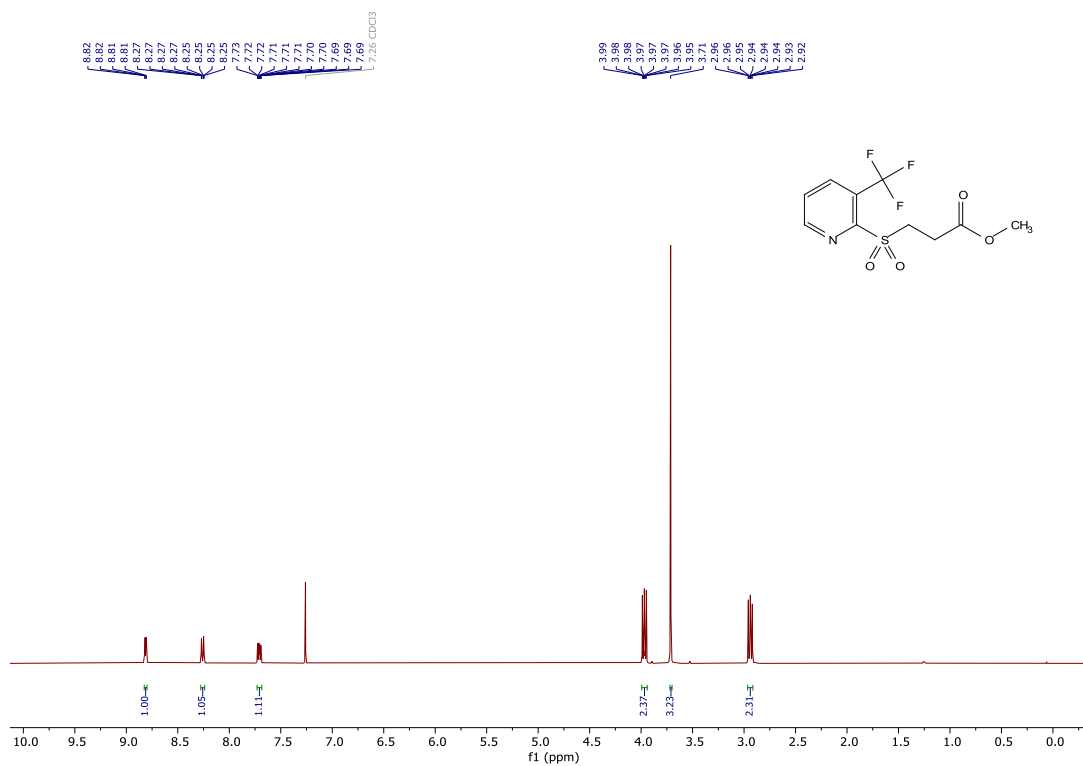


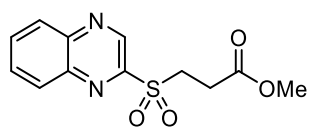
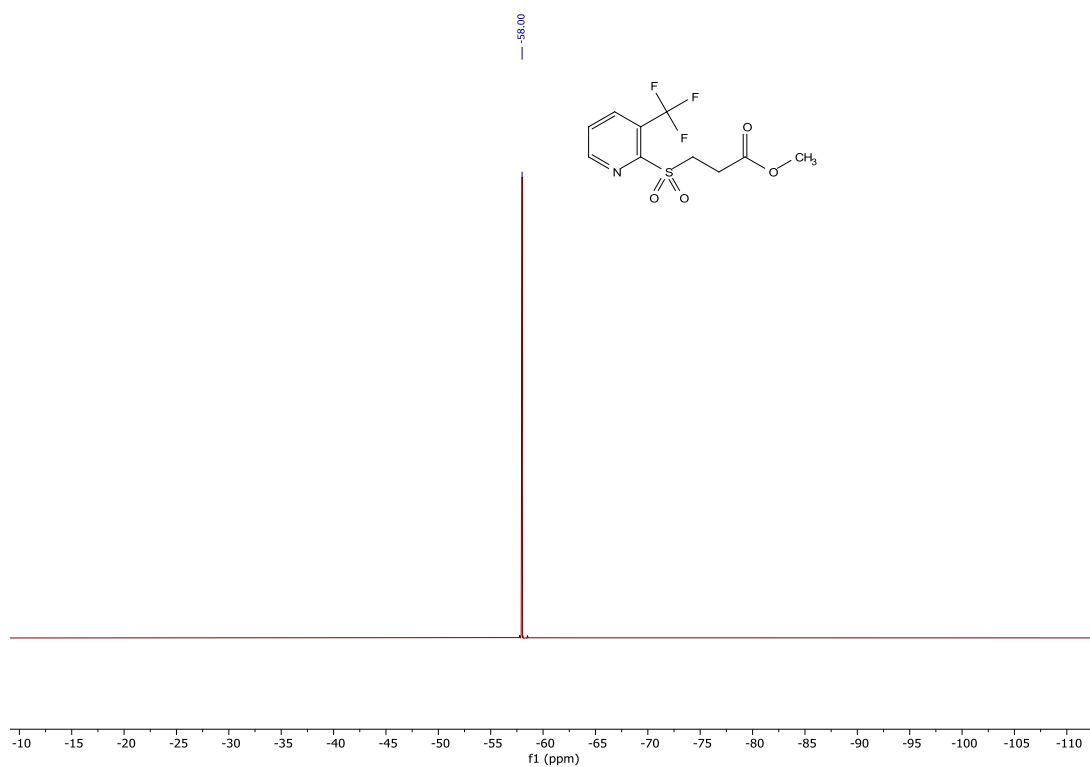
methyl 3-((3-(methylcarbamoyl)pyridin-2-yl)sulfonyl)propanoate (2f)



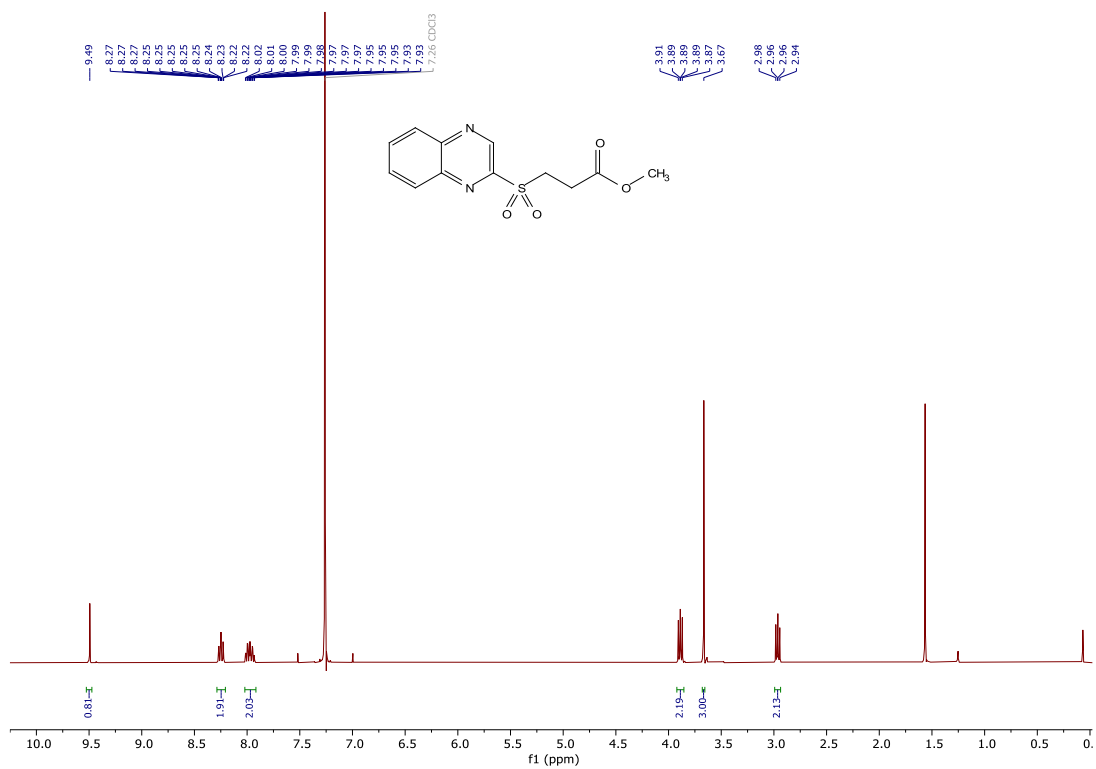


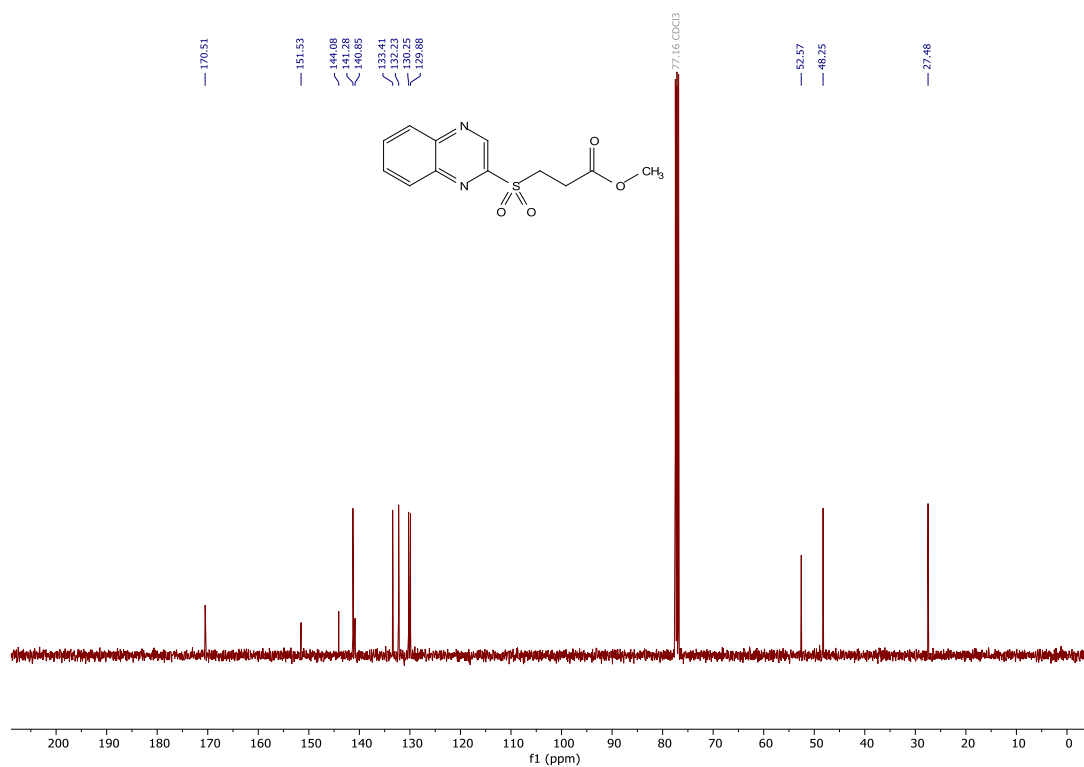
methyl 3-((3-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoate (2g)



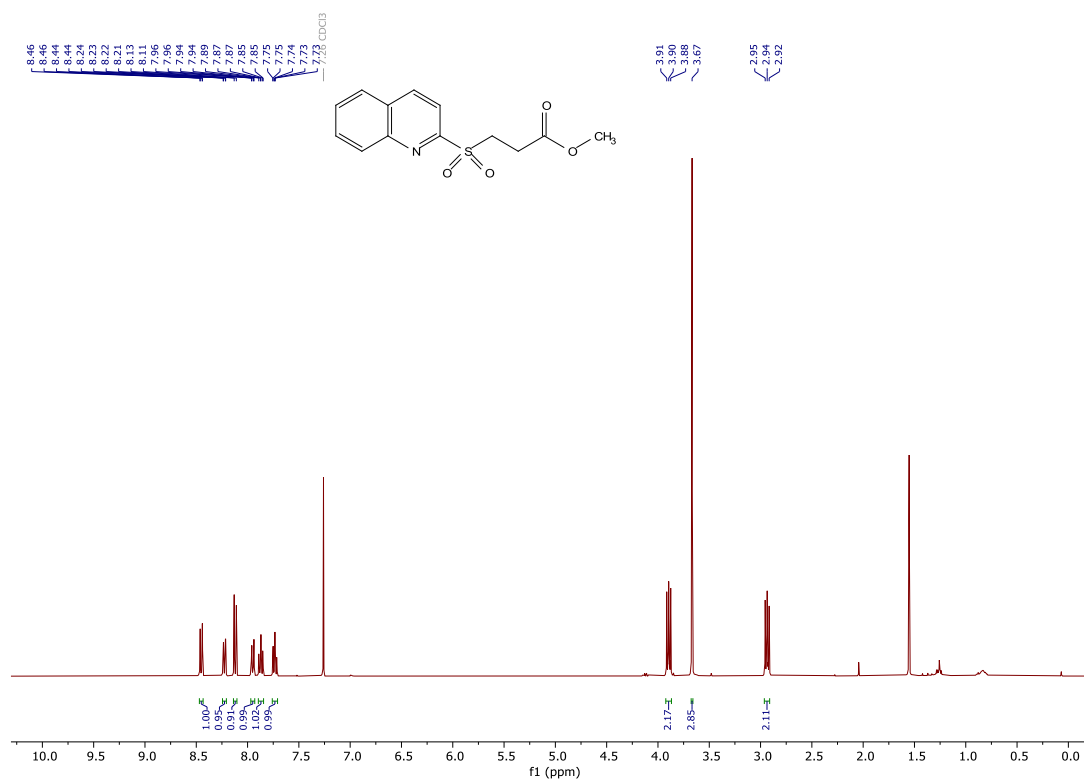


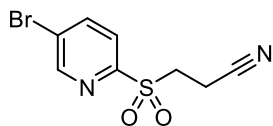
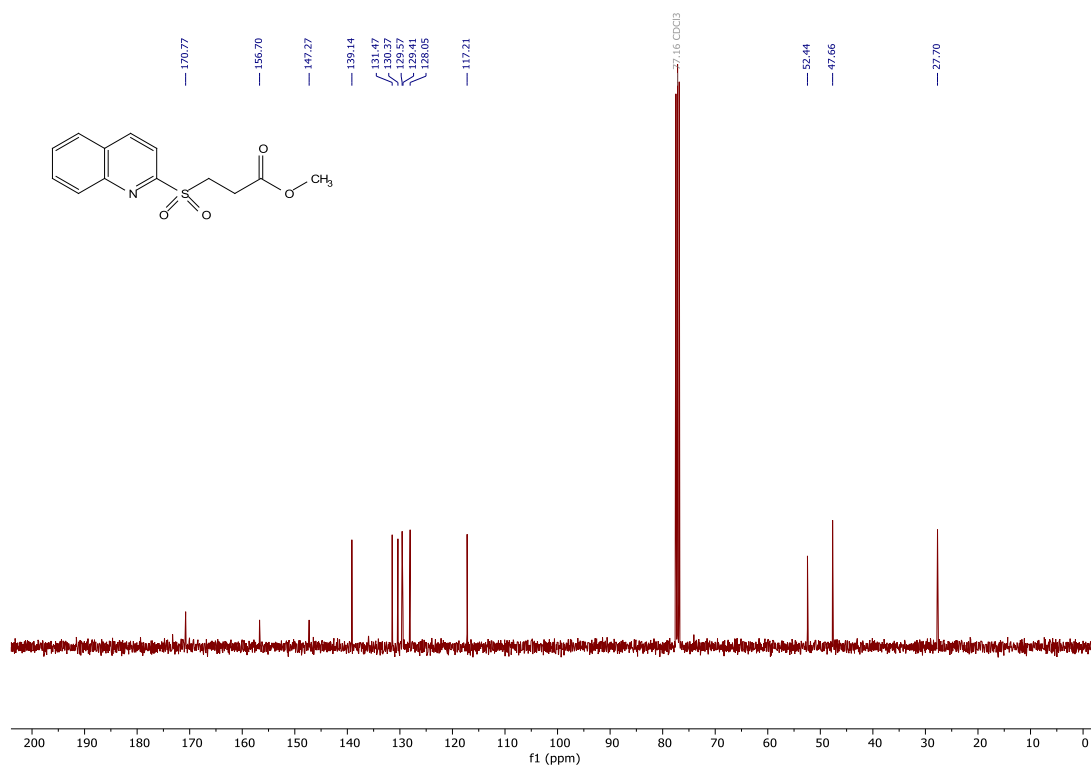
methyl 3-(quinoxalin-2-ylsulfonyl)propanoate (2h)



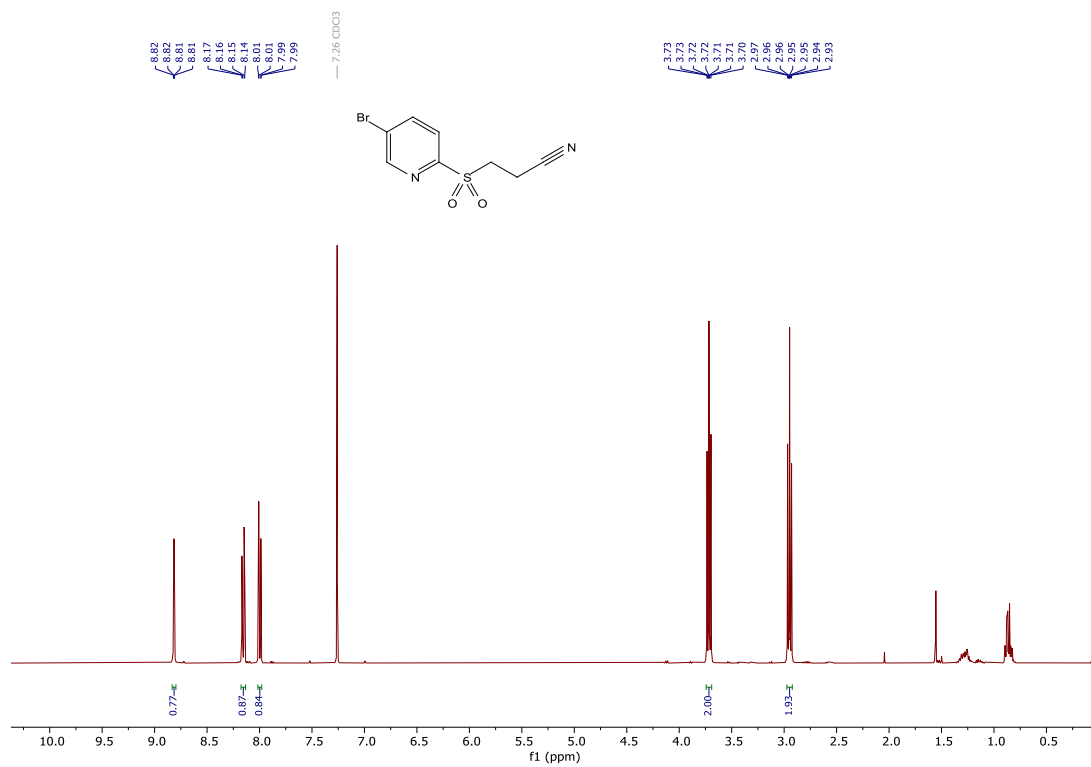


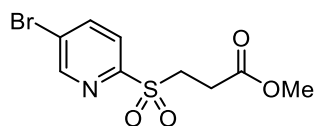
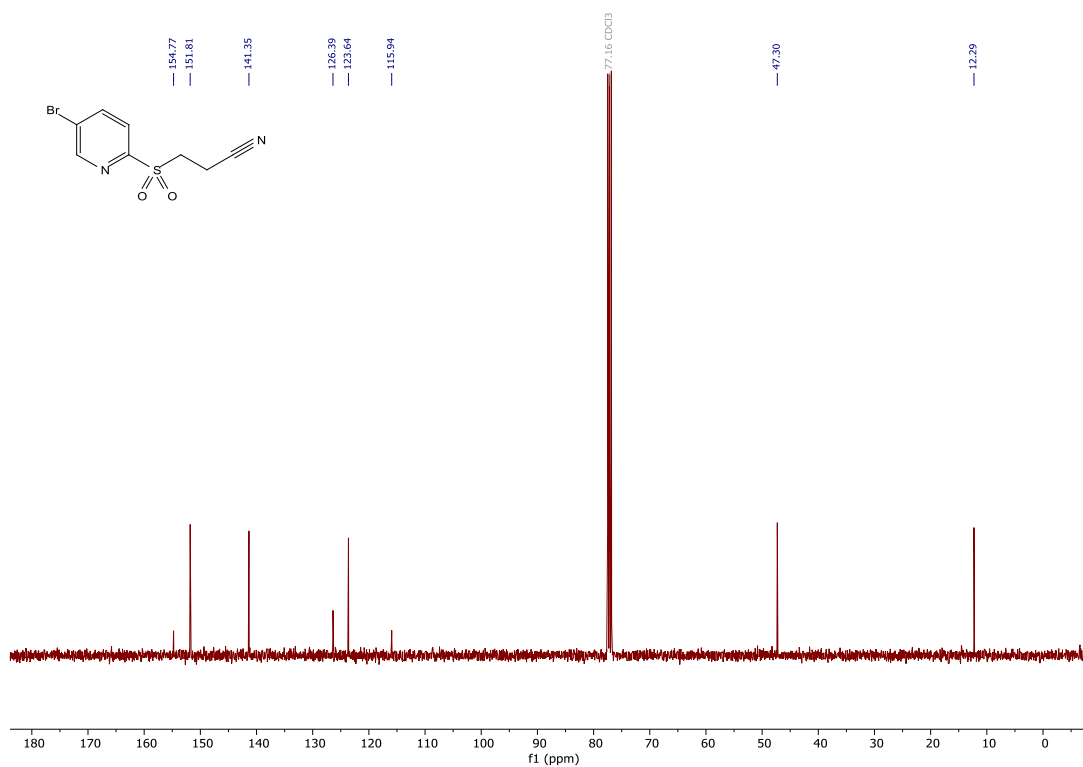
COC(=O)CCS(=O)(=O)c1ccc2ccccc2n1
methyl 3-(quinolin-2-ylsulfonyl)propanoate (2i)



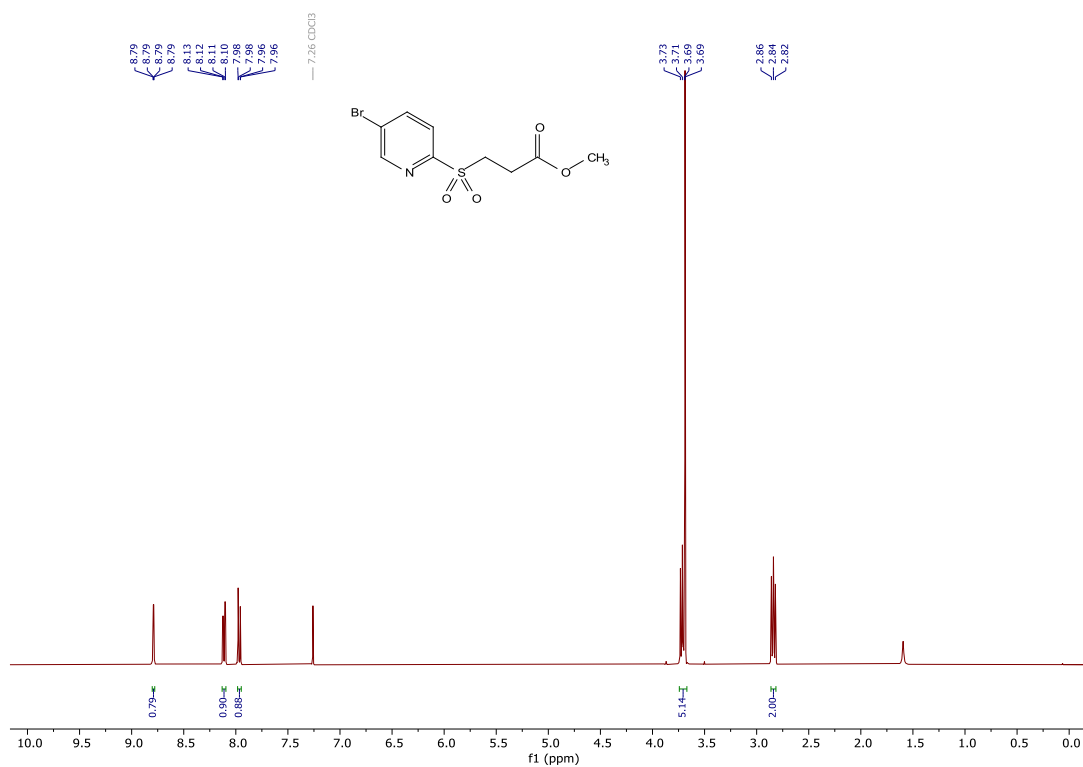


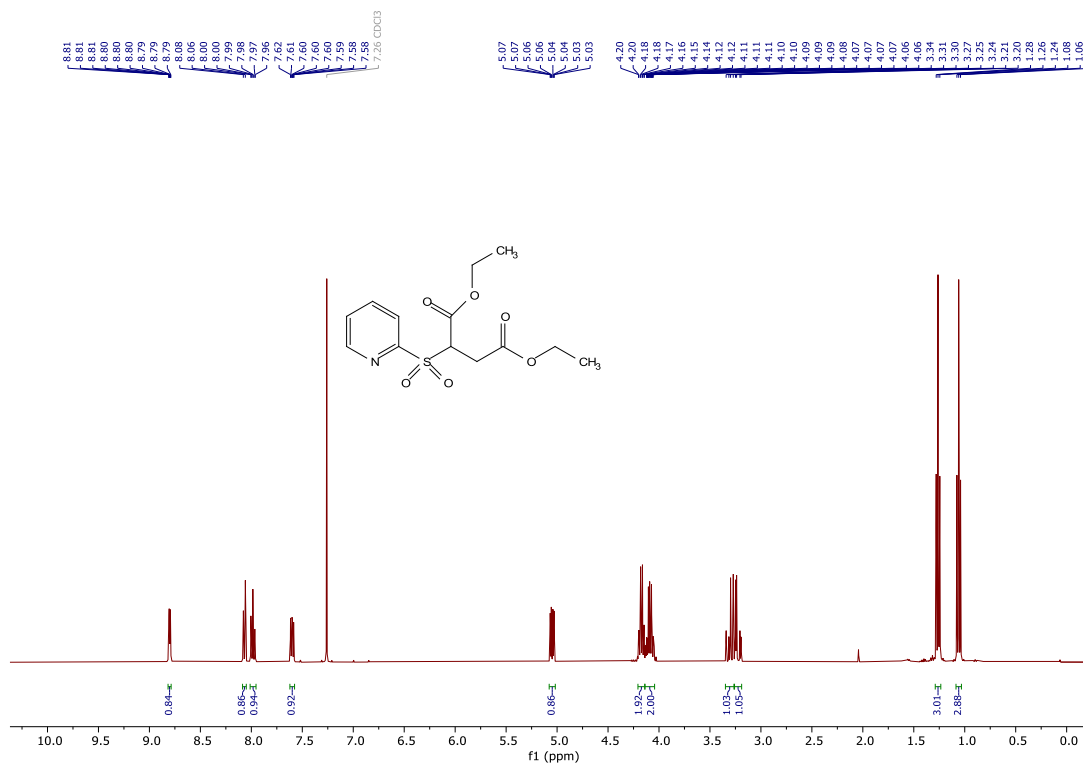
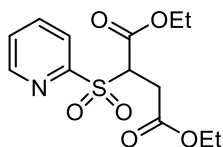
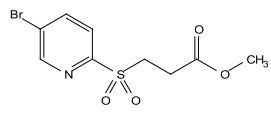
3-((5-bromopyridin-2-yl)sulfonyl)propanenitrile (12a)

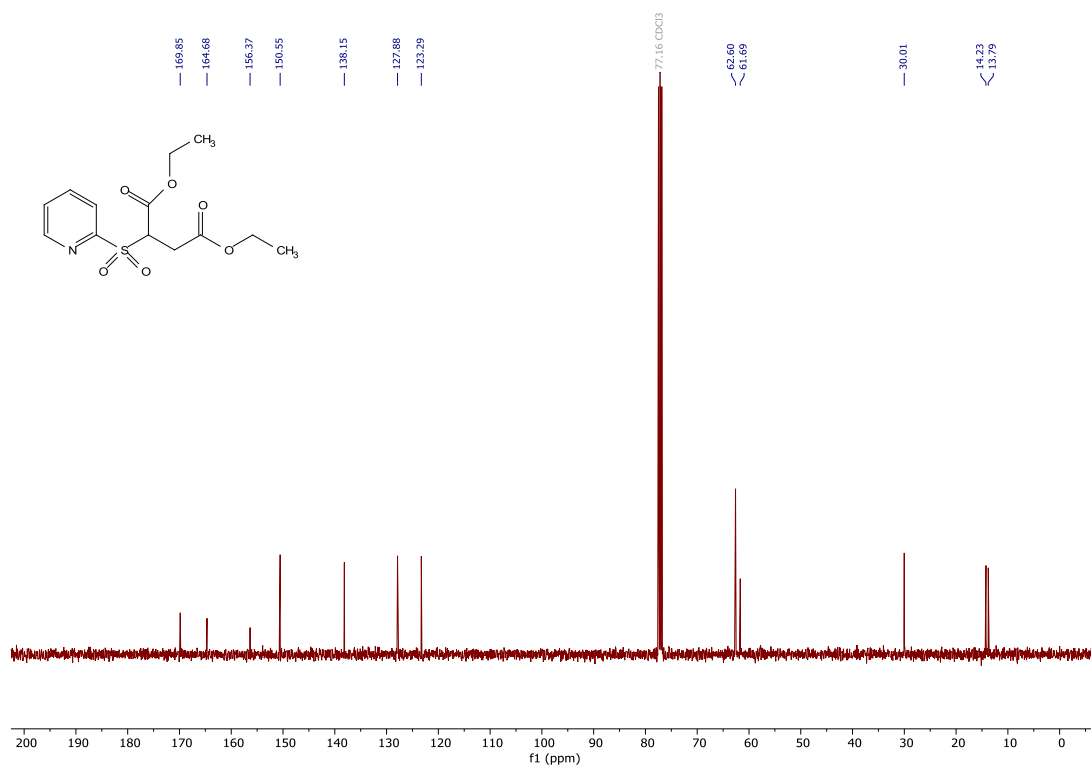




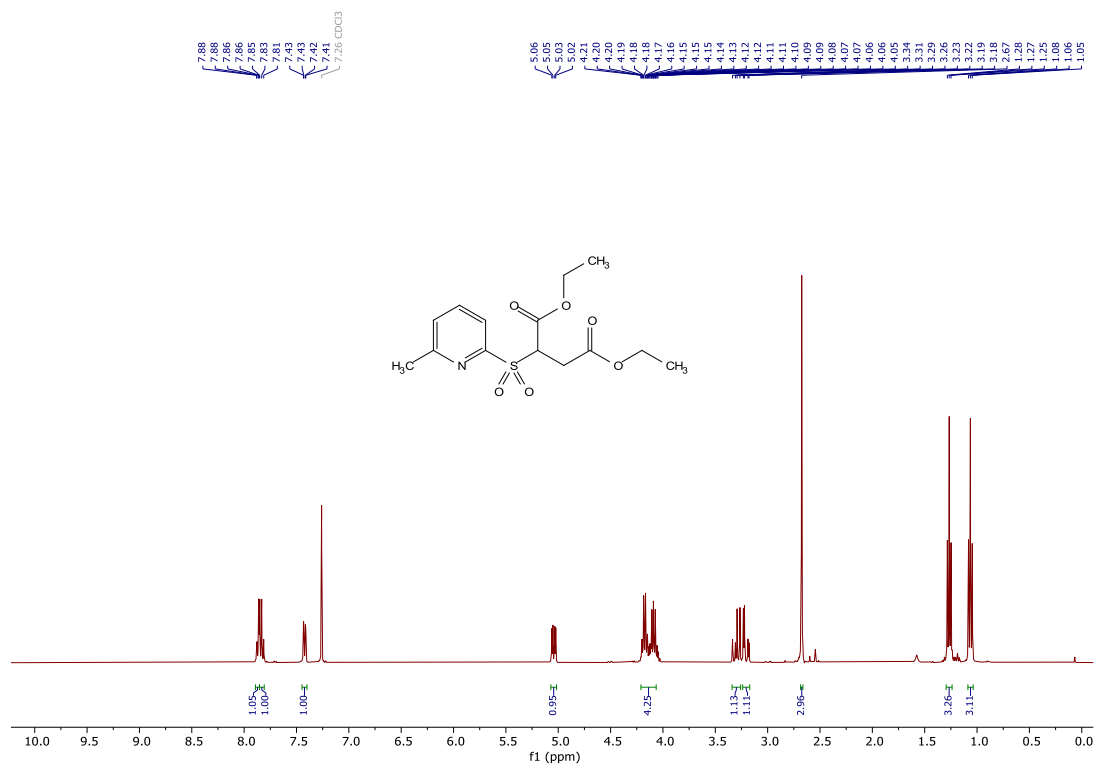
methyl 3-((5-bromopyridin-2-yl)sulfonyl)propanoate (12b)

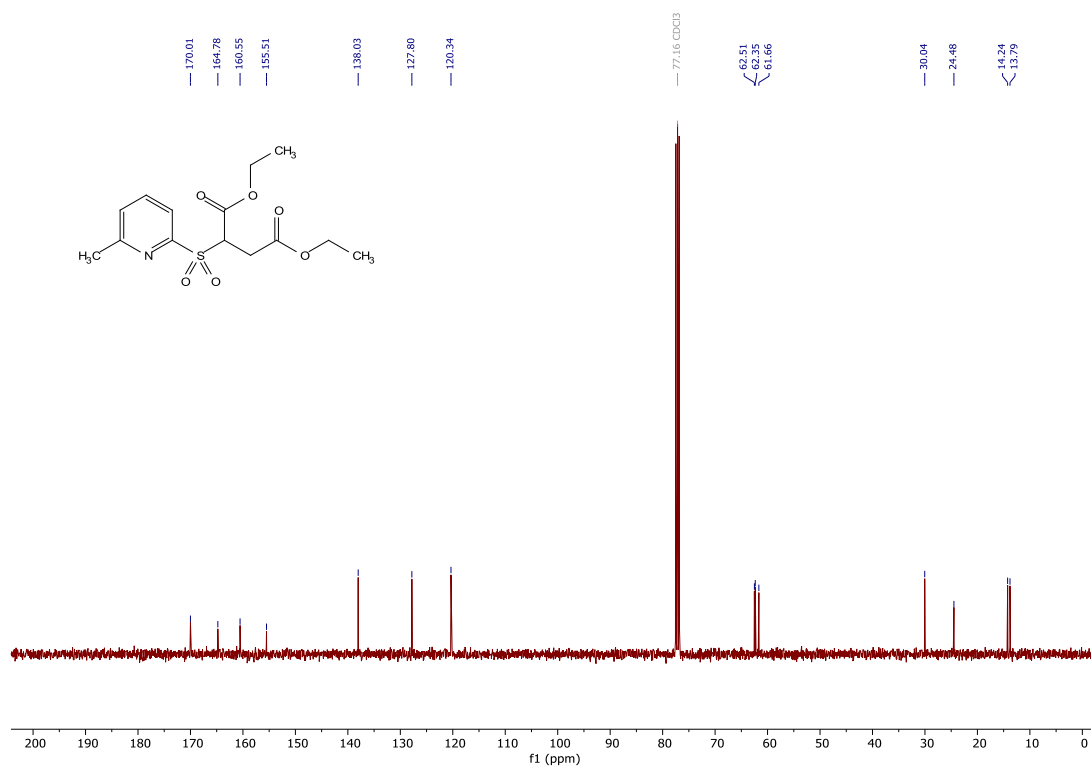




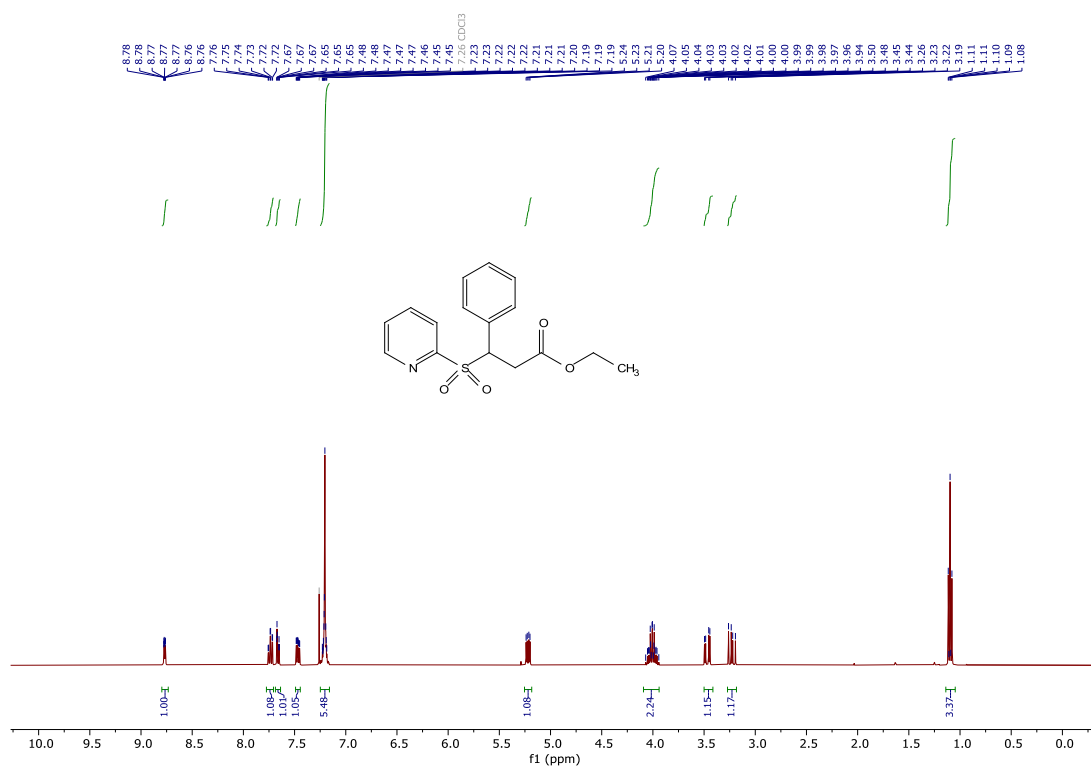


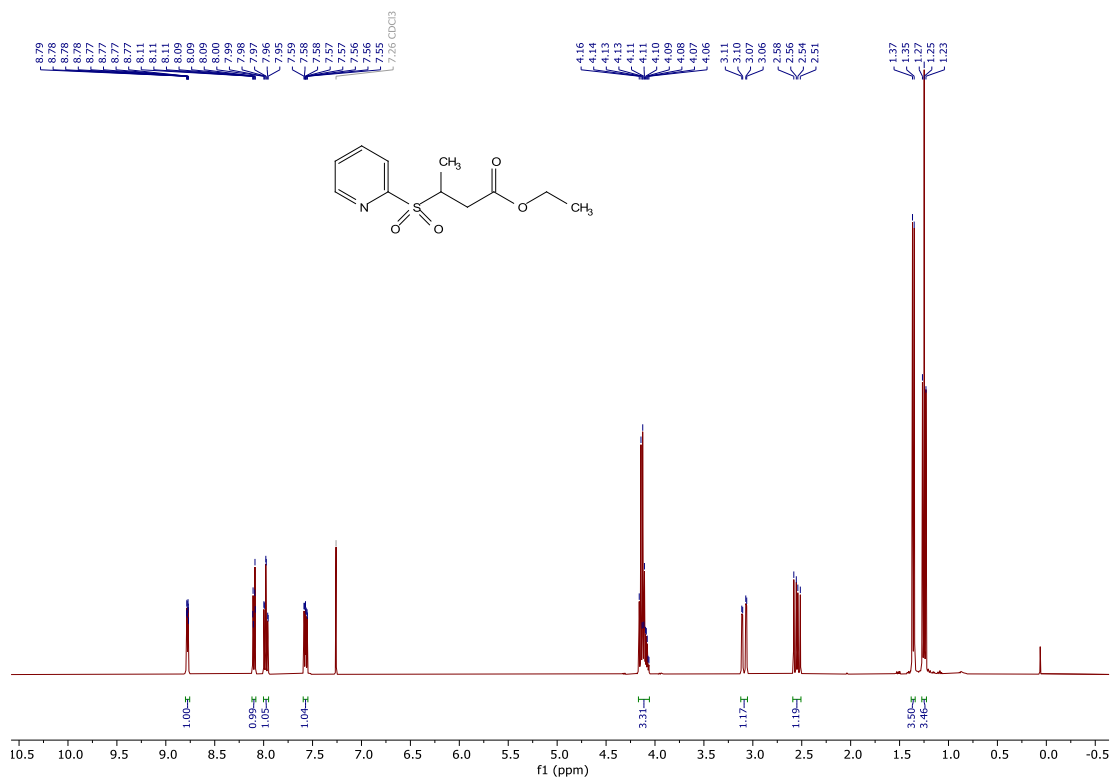
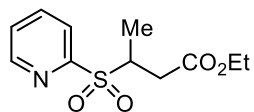
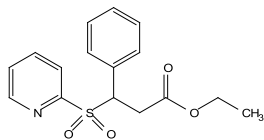
diethyl 2-((6-methylpyridin-2-yl)sulfonyl)succinate (8b)

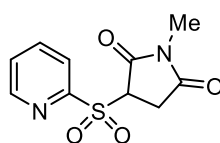
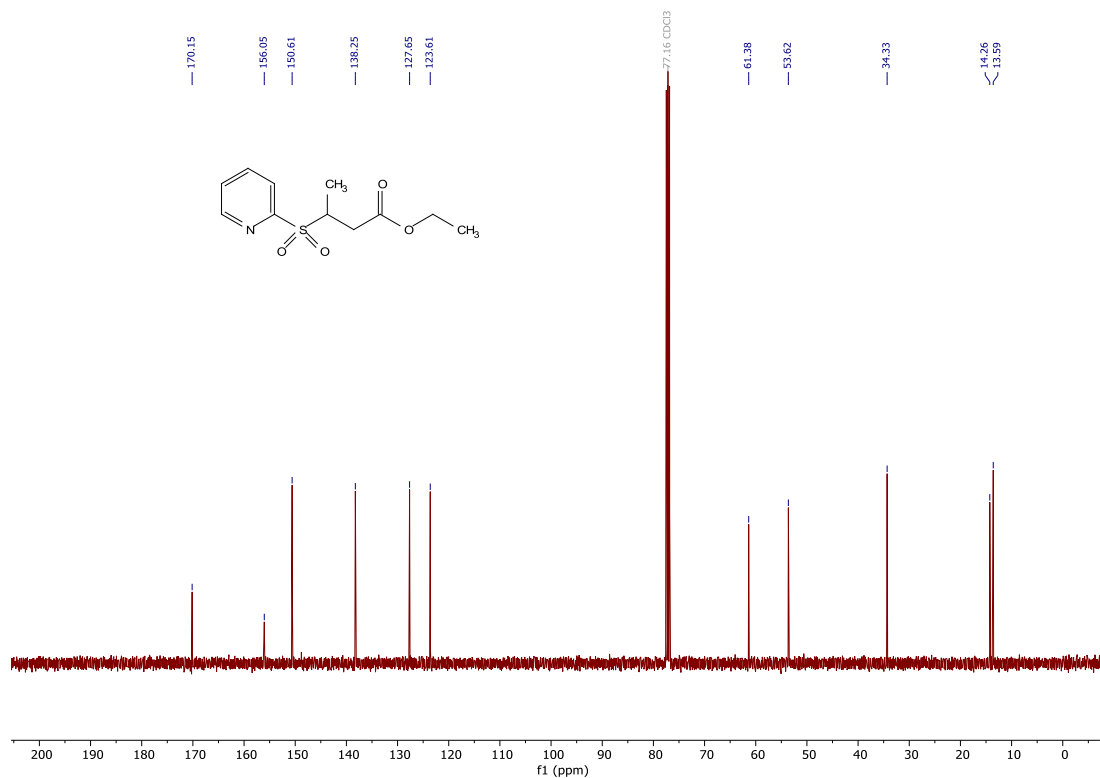




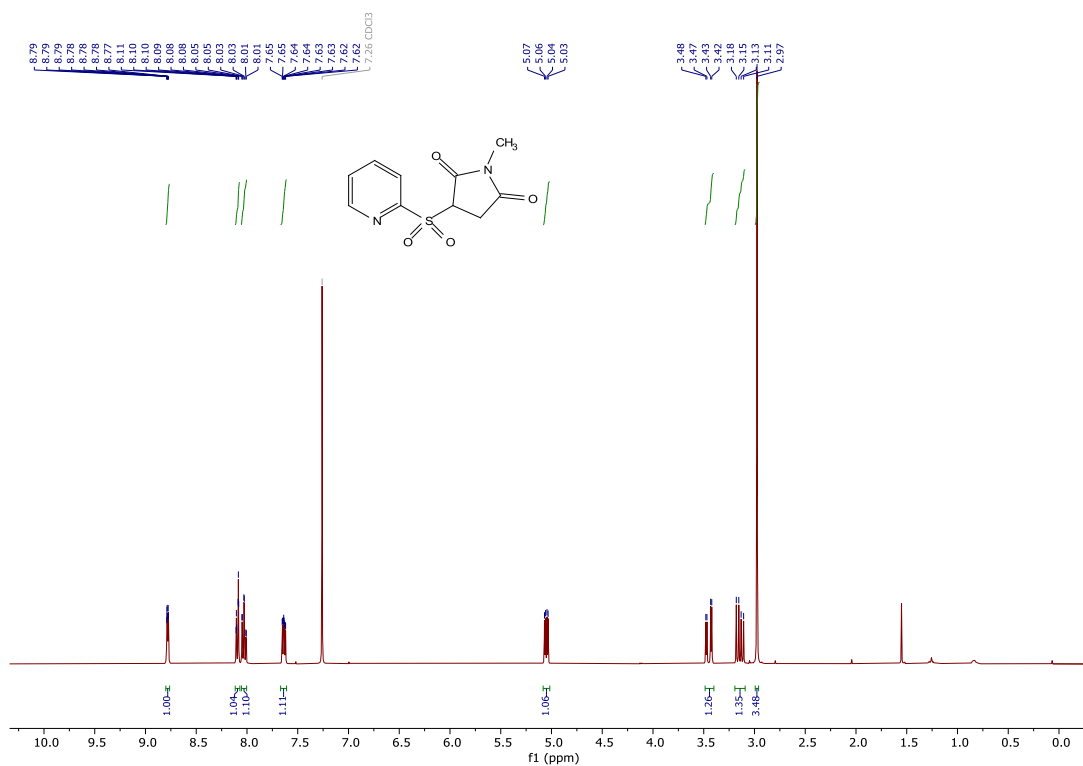
ethyl 3-phenyl-3-(pyridin-2-ylsulfonyl)propanoate (9)

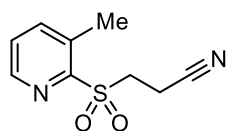
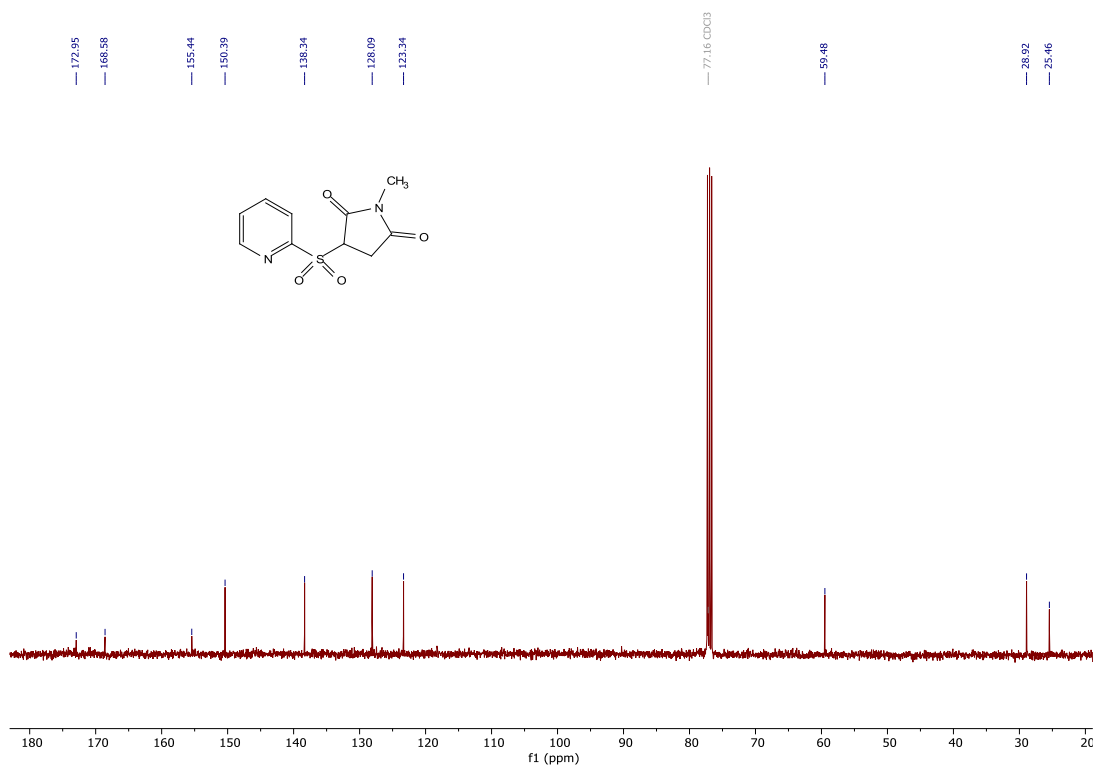




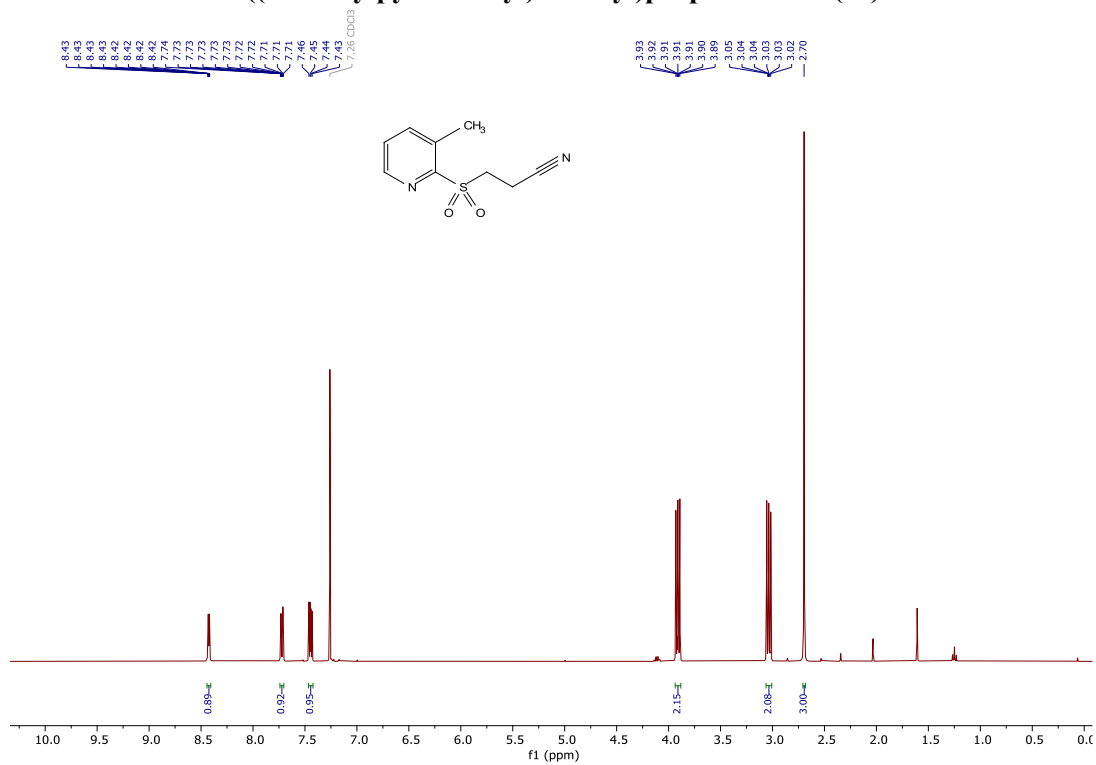


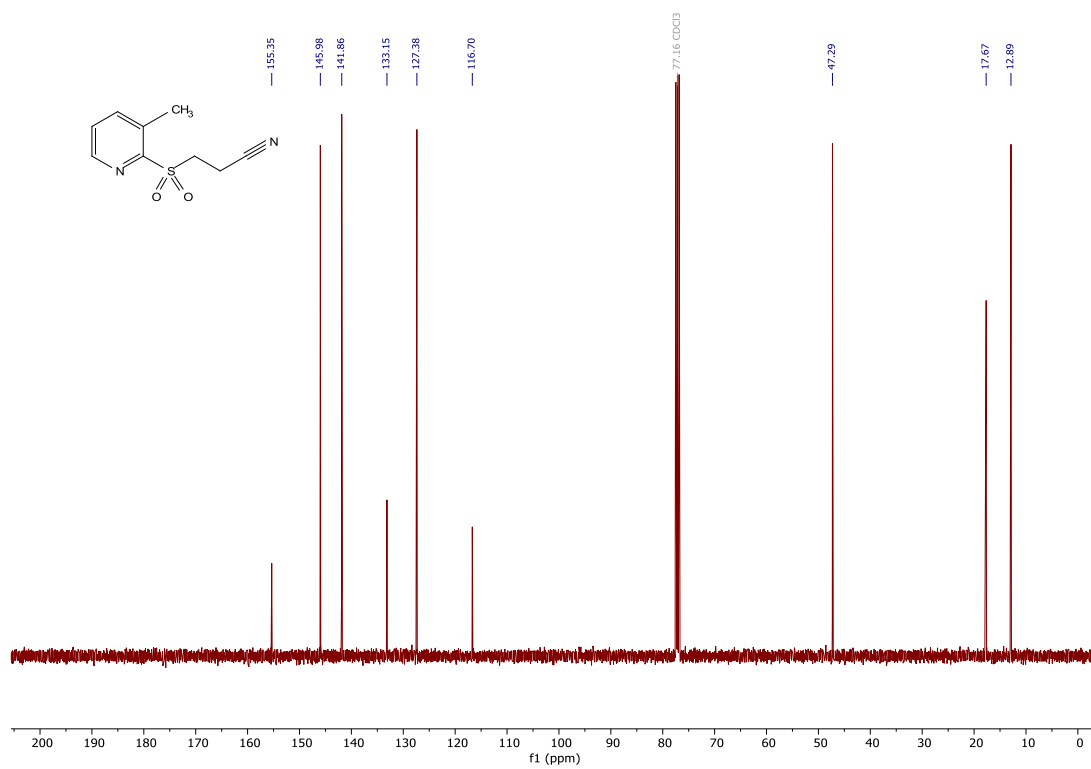
1-methyl-3-(pyridin-2-ylsulfonyl)pyrrolidine-2,5-dione (11)

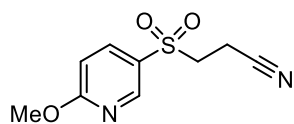




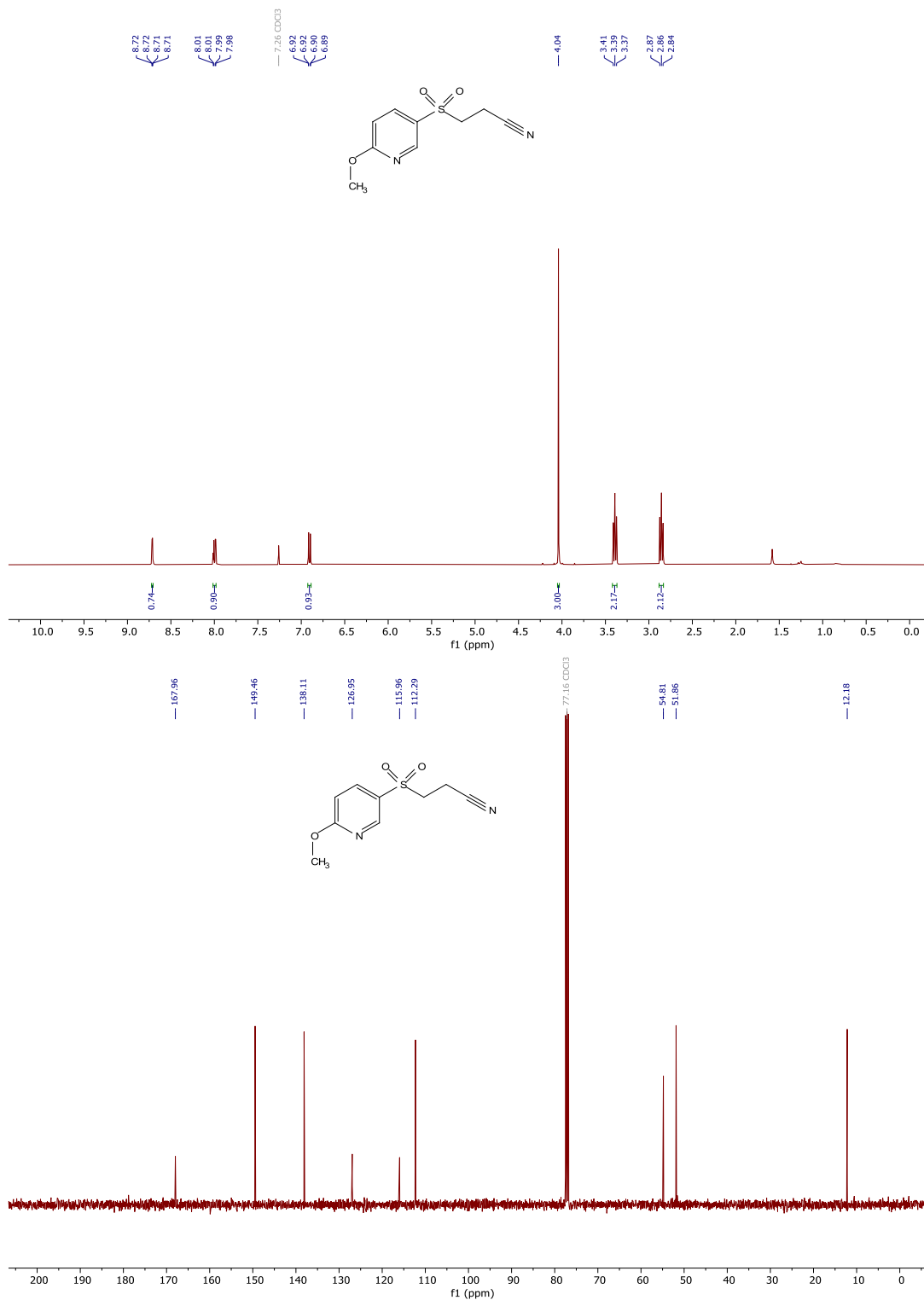
3-((3-methylpyridin-2-yl)sulfonyl)propanenitrile (1c)

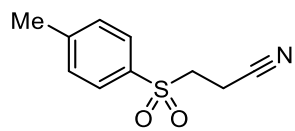




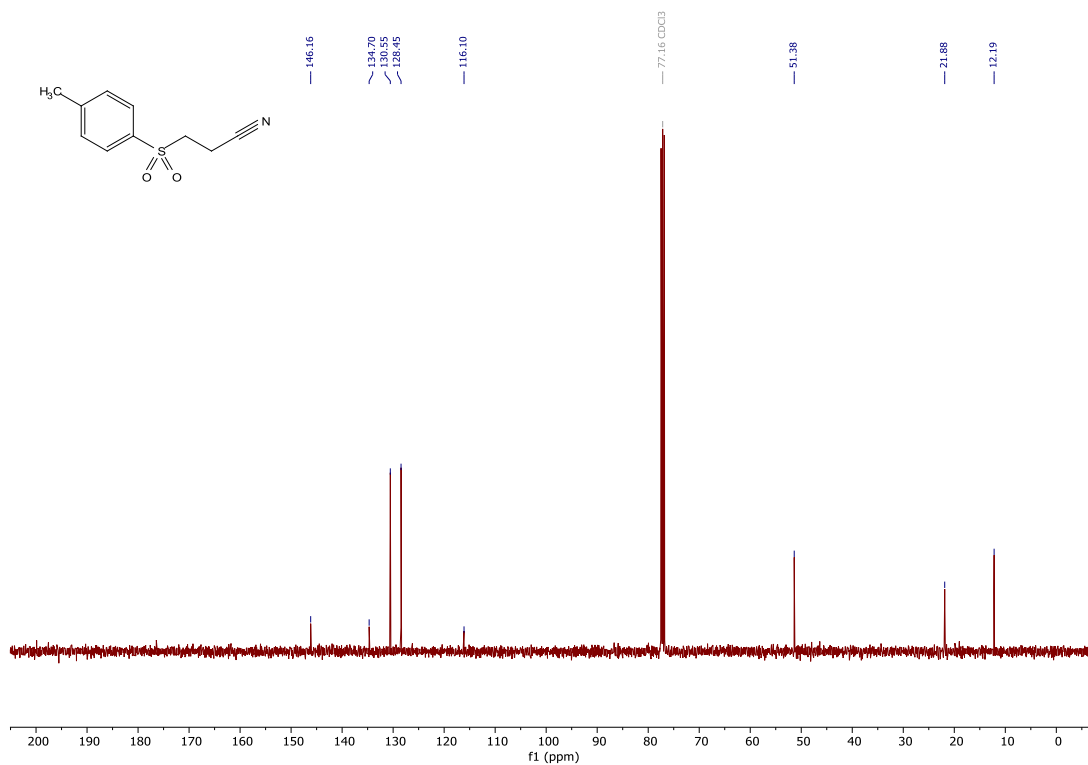
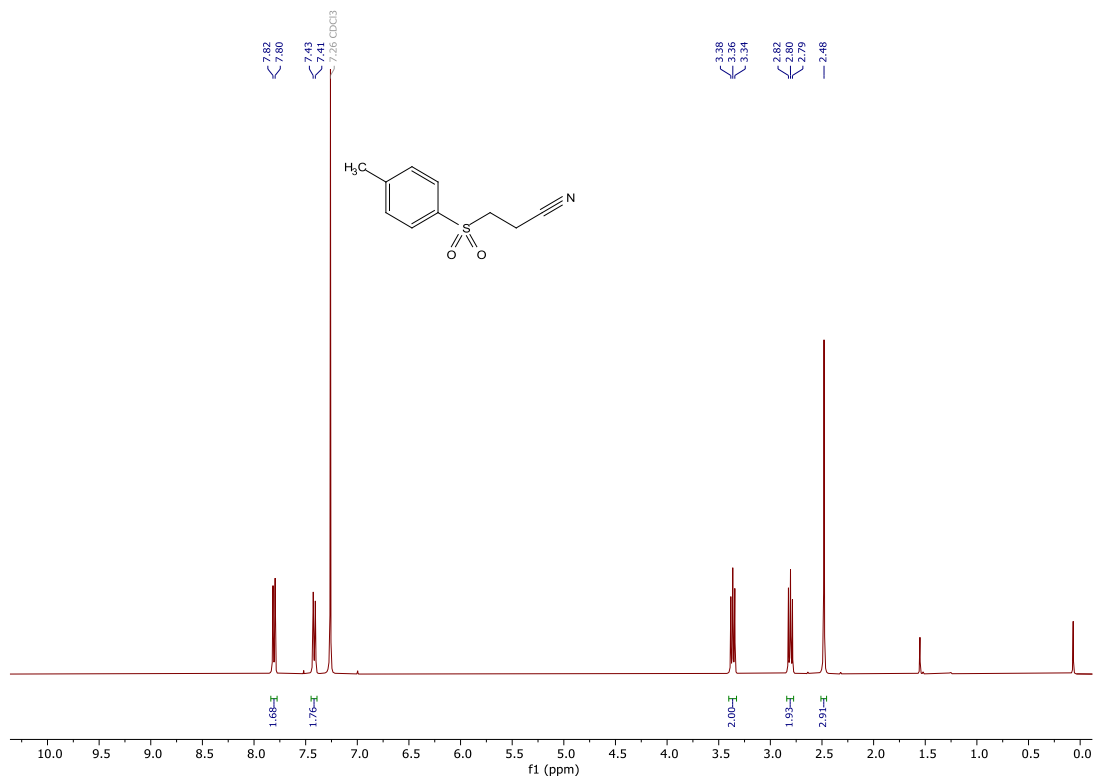


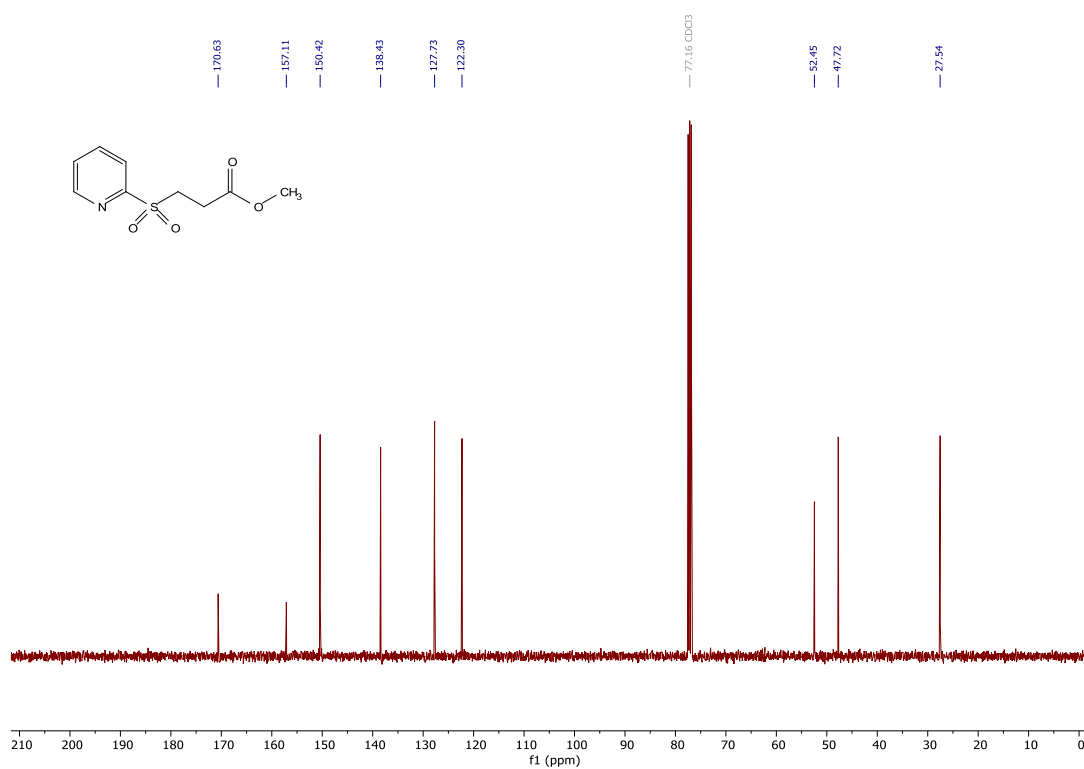
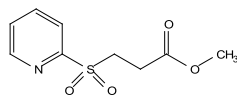
3-((6-methoxypyridin-3-yl)sulfonyl)propanenitrile (1g)

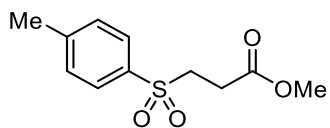




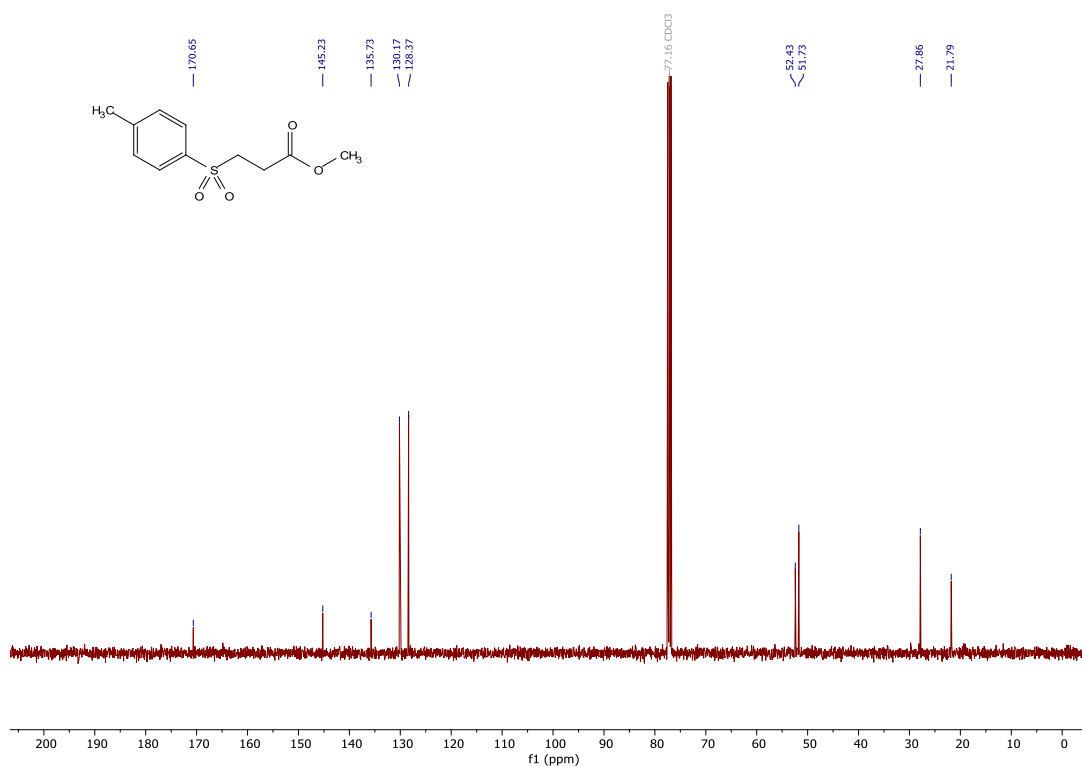
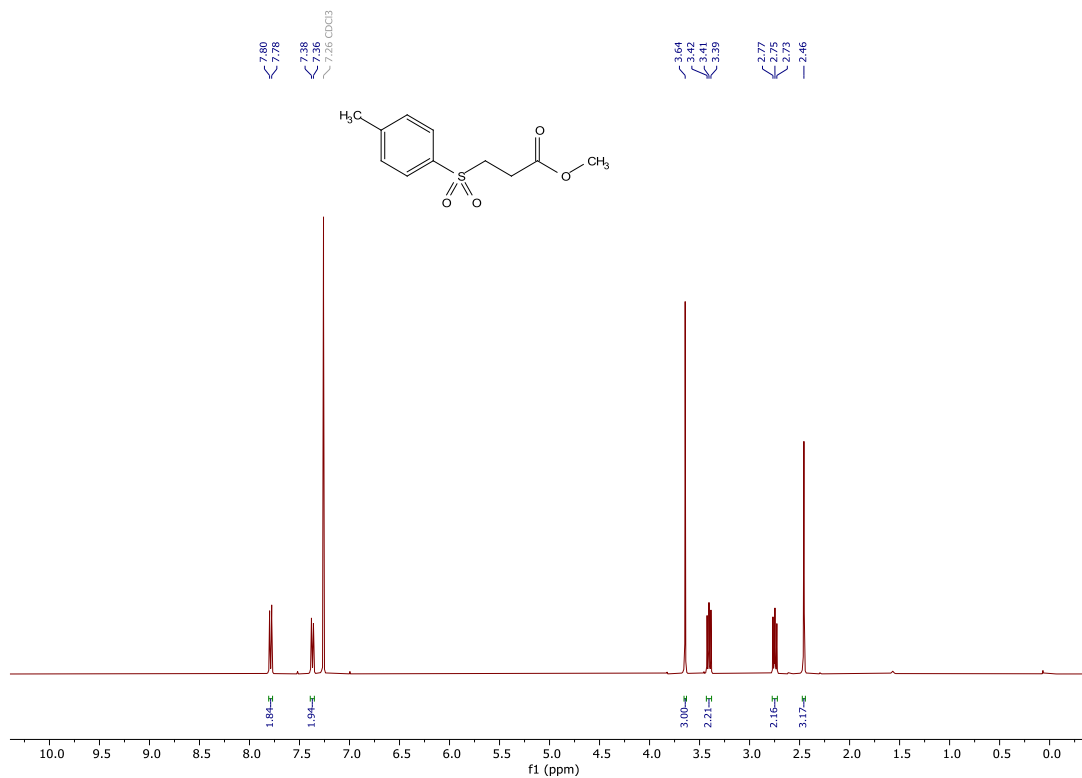
3-tosylpropanenitrile (1h)

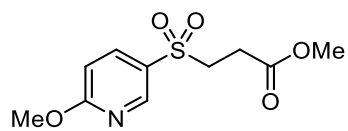




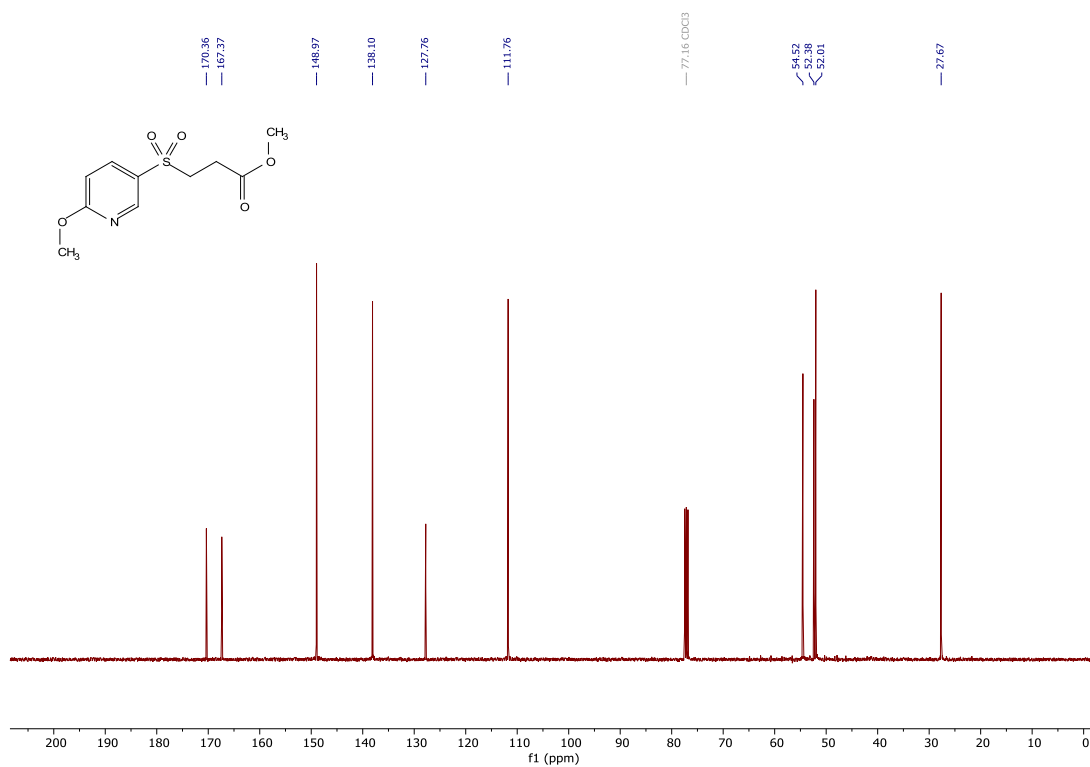
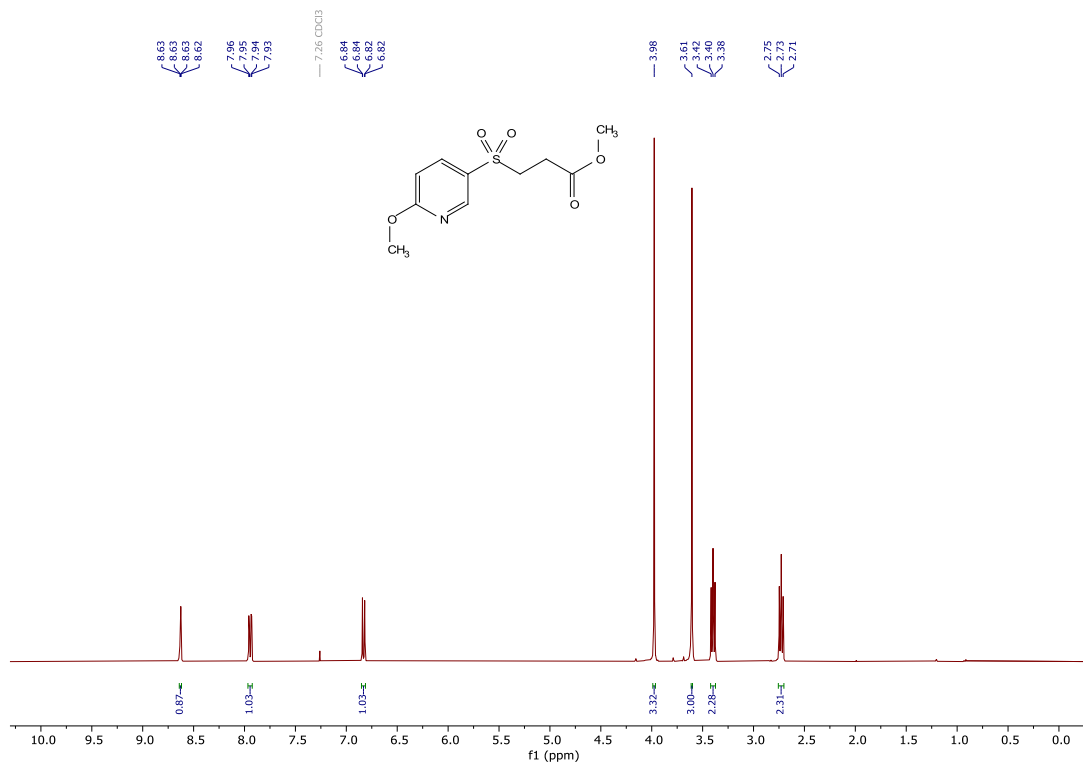


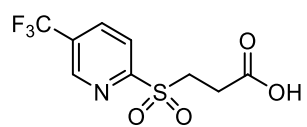
methyl 3-tosylpropanoate (2j)



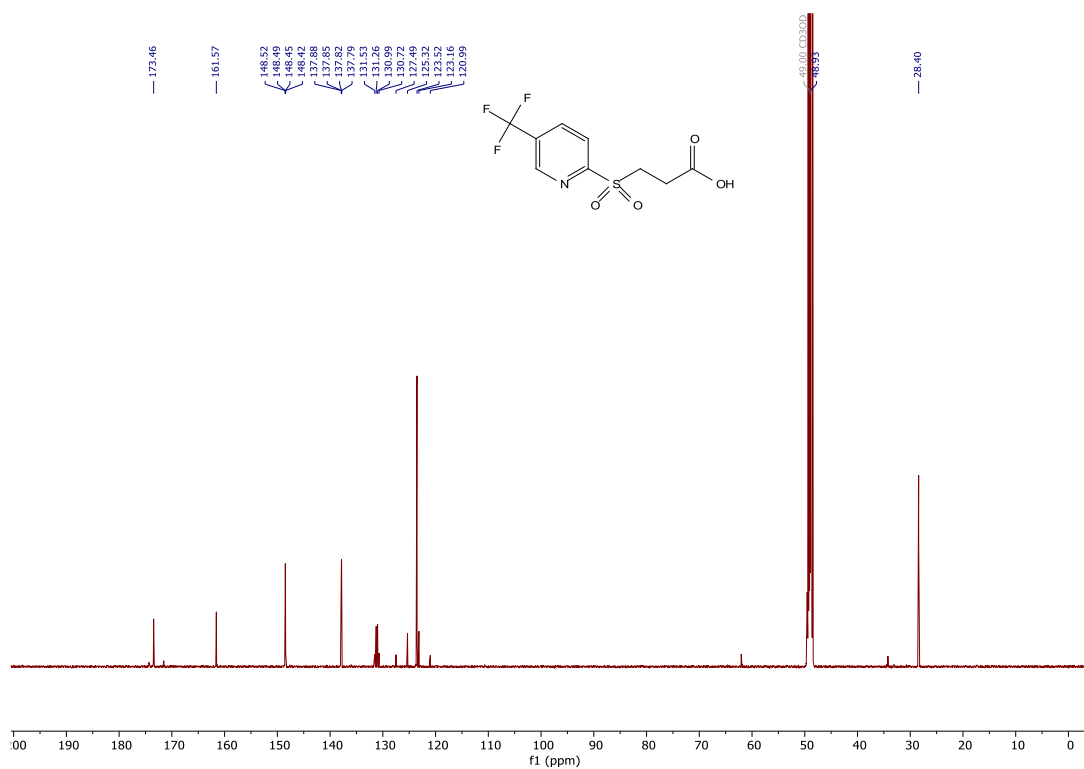
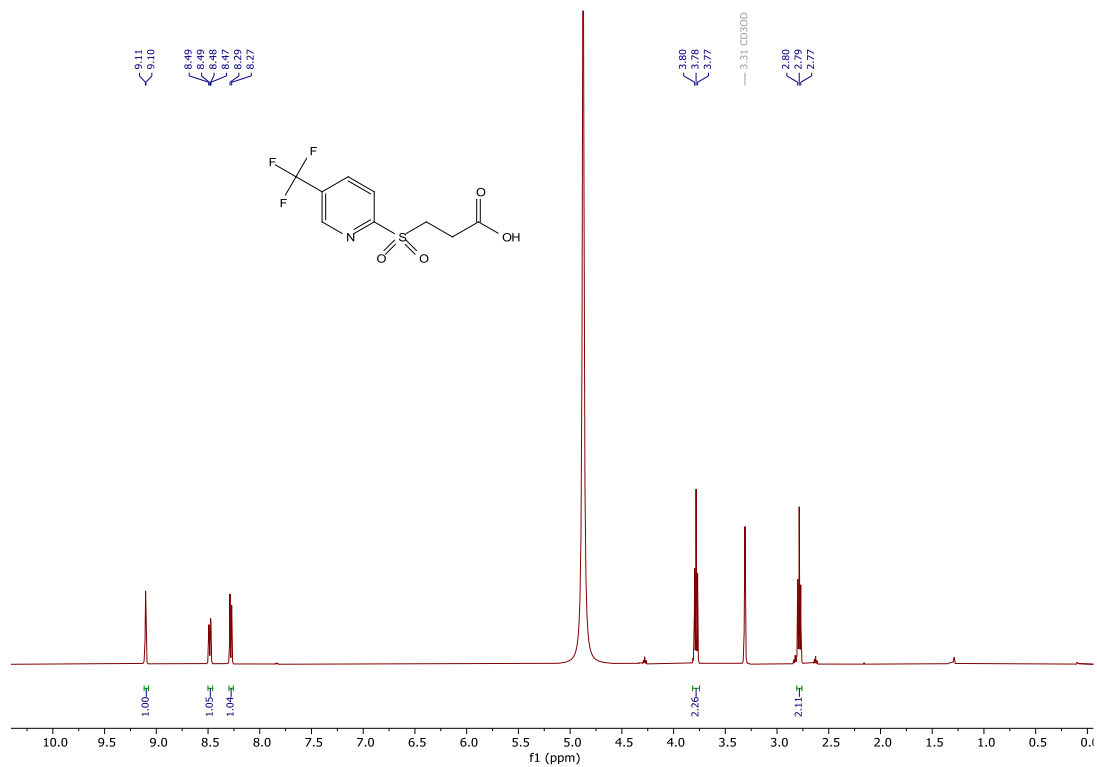


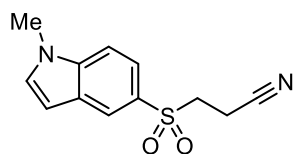
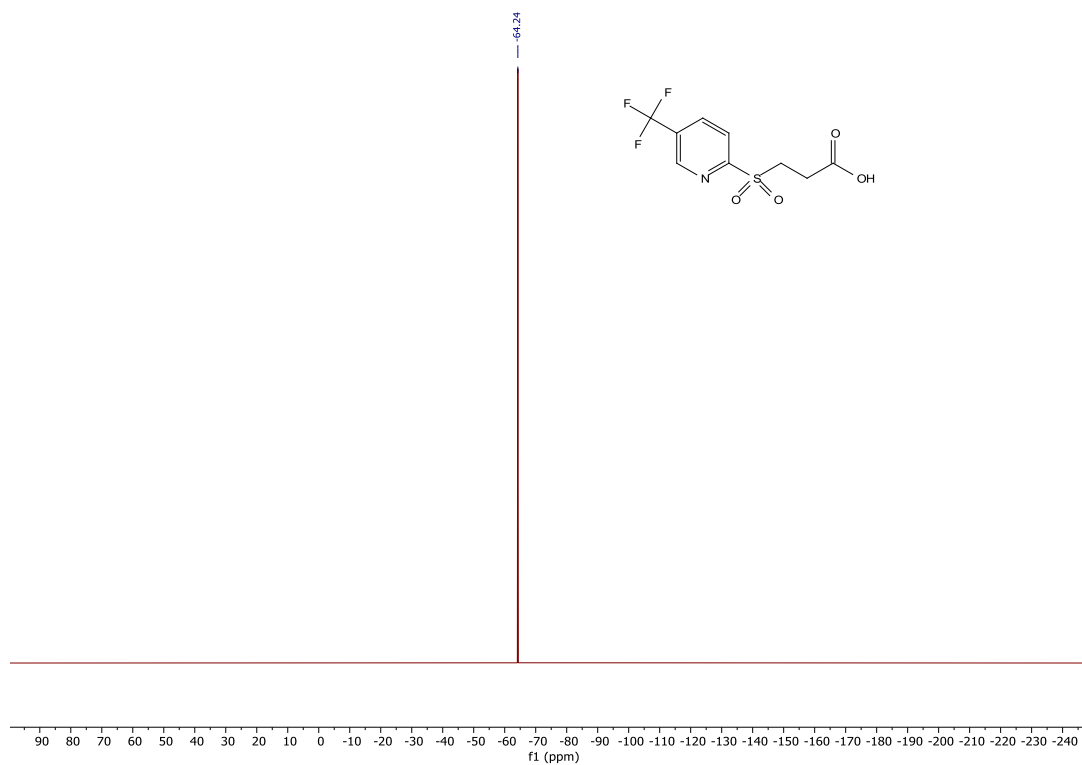
methyl 3-((6-methoxypyridin-3-yl)sulfonyl)propanoate (2k)



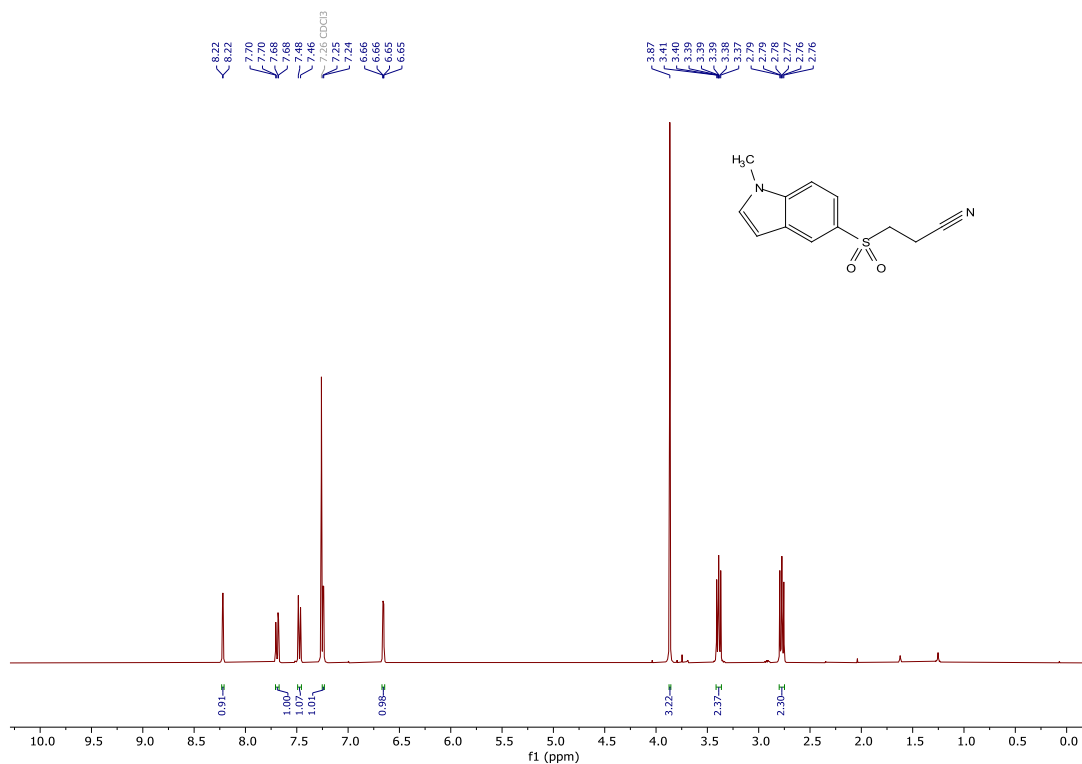


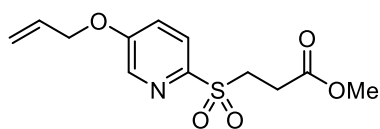
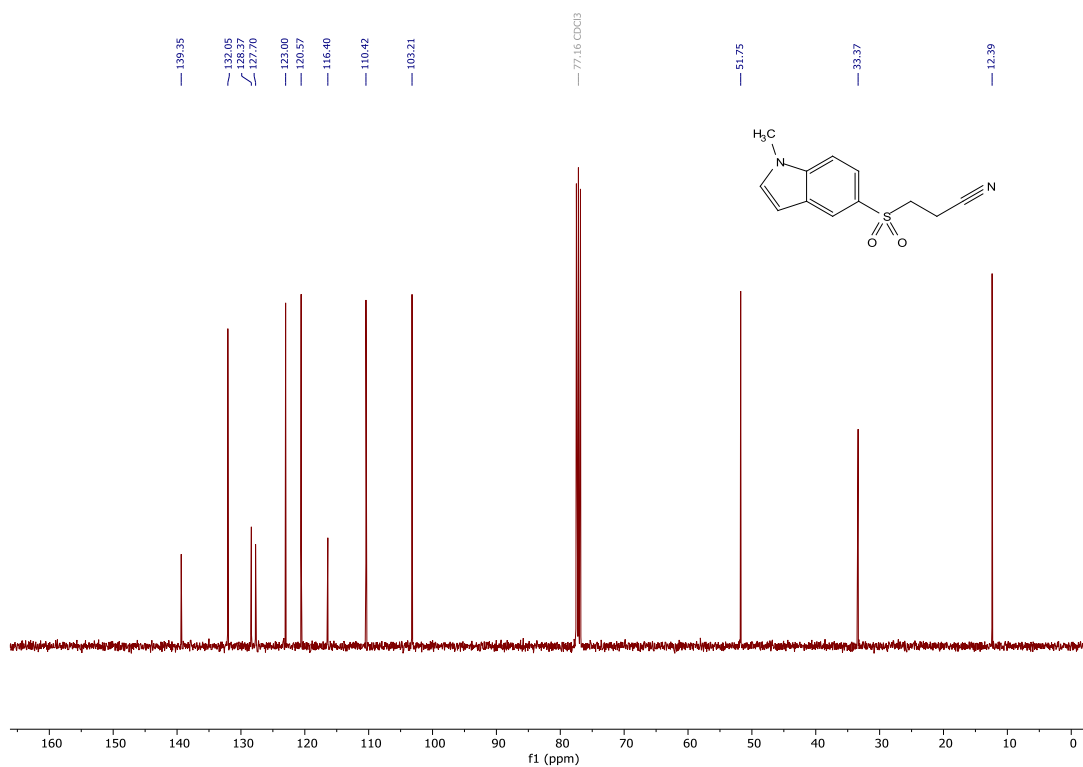
3-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)propanoic acid (2a-OH)



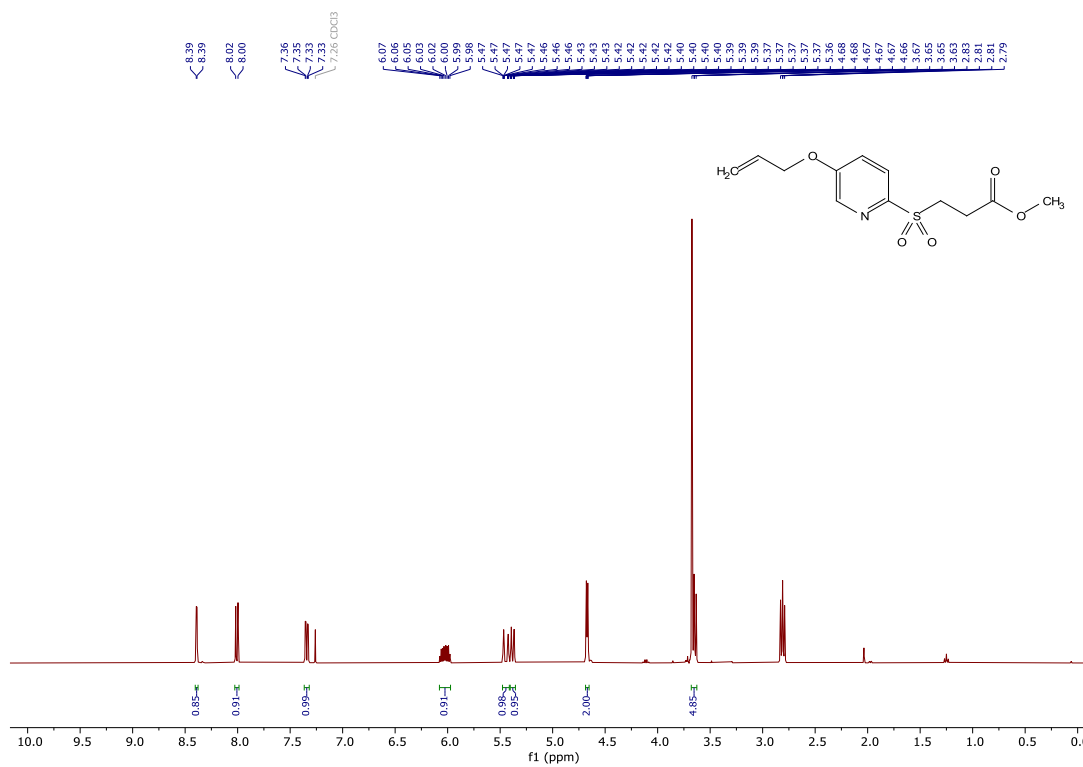


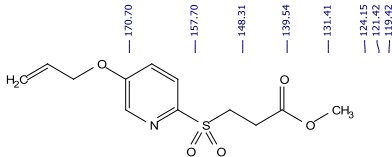
3-((1-methyl-1H-indol-5-yl)sulfonyl)propanenitrile (1i)



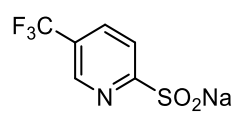


methyl 3-((5-(allyloxy)pyridin-2-yl)sulfonyl)propanoate (19)

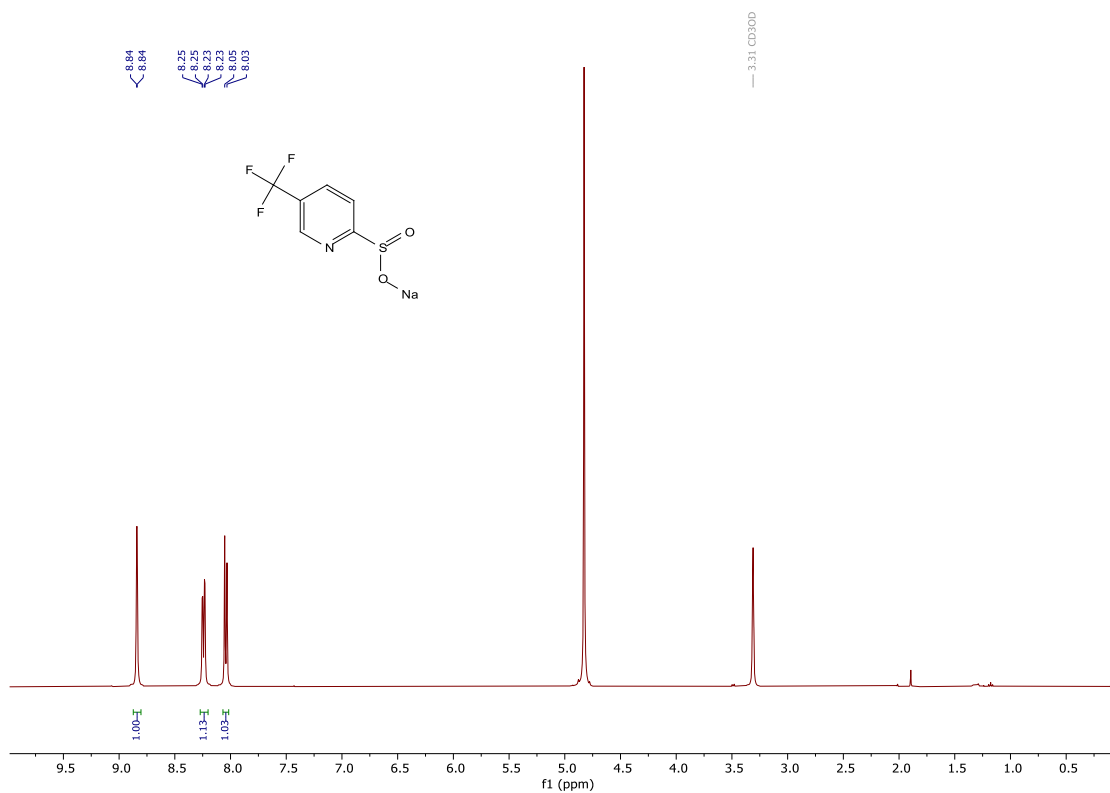


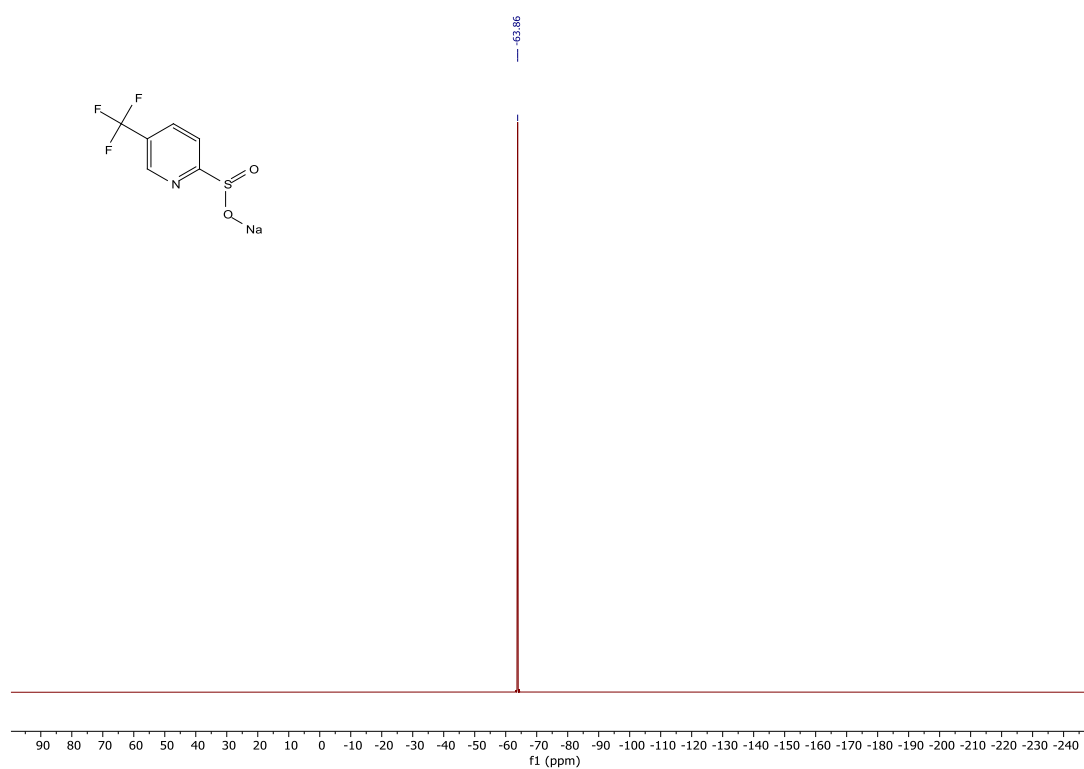
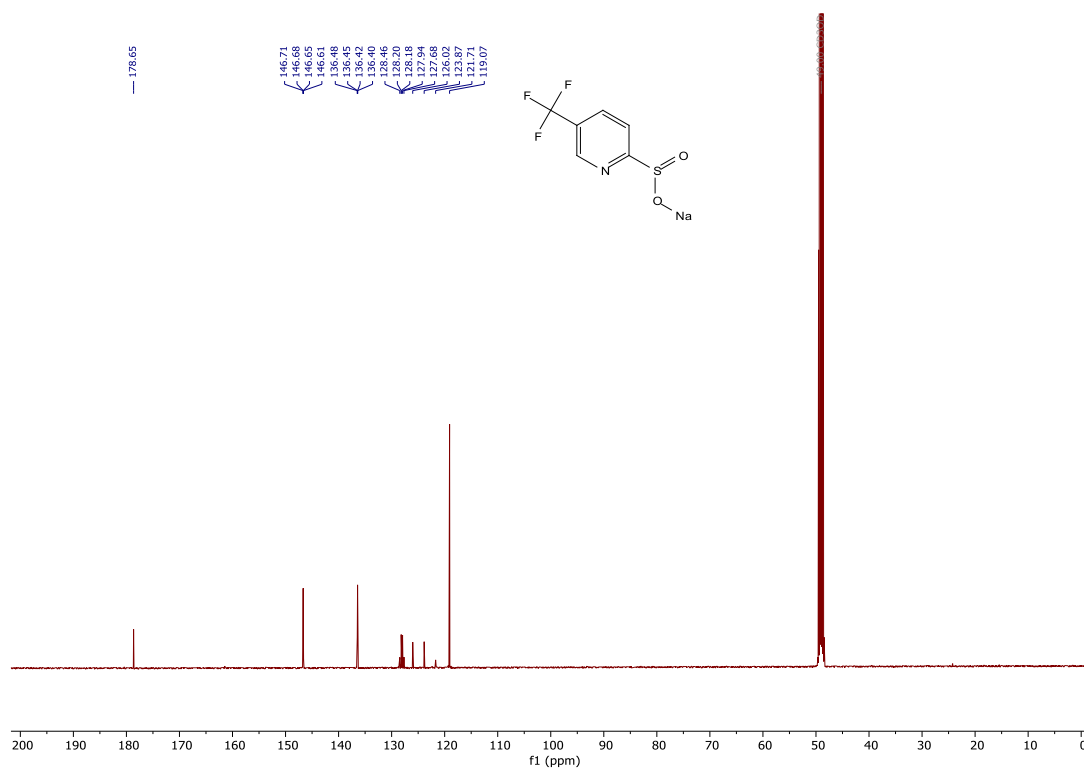


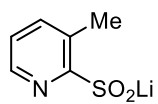
8.1.3. Sulfinate salts



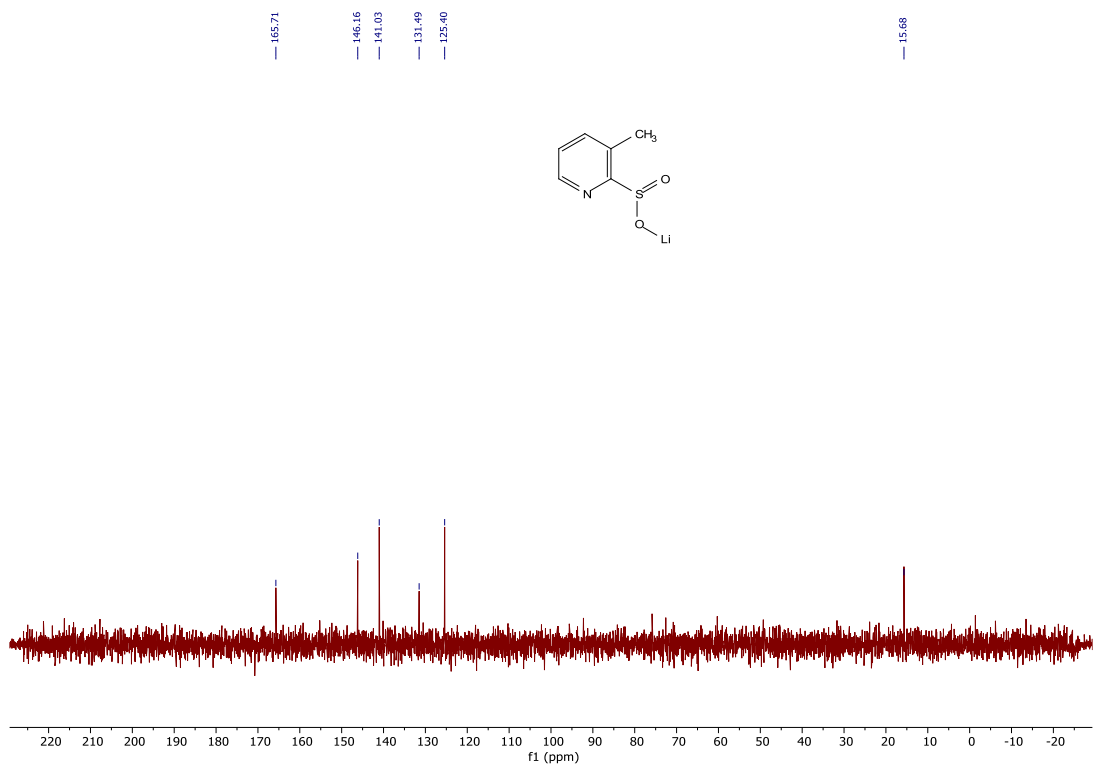
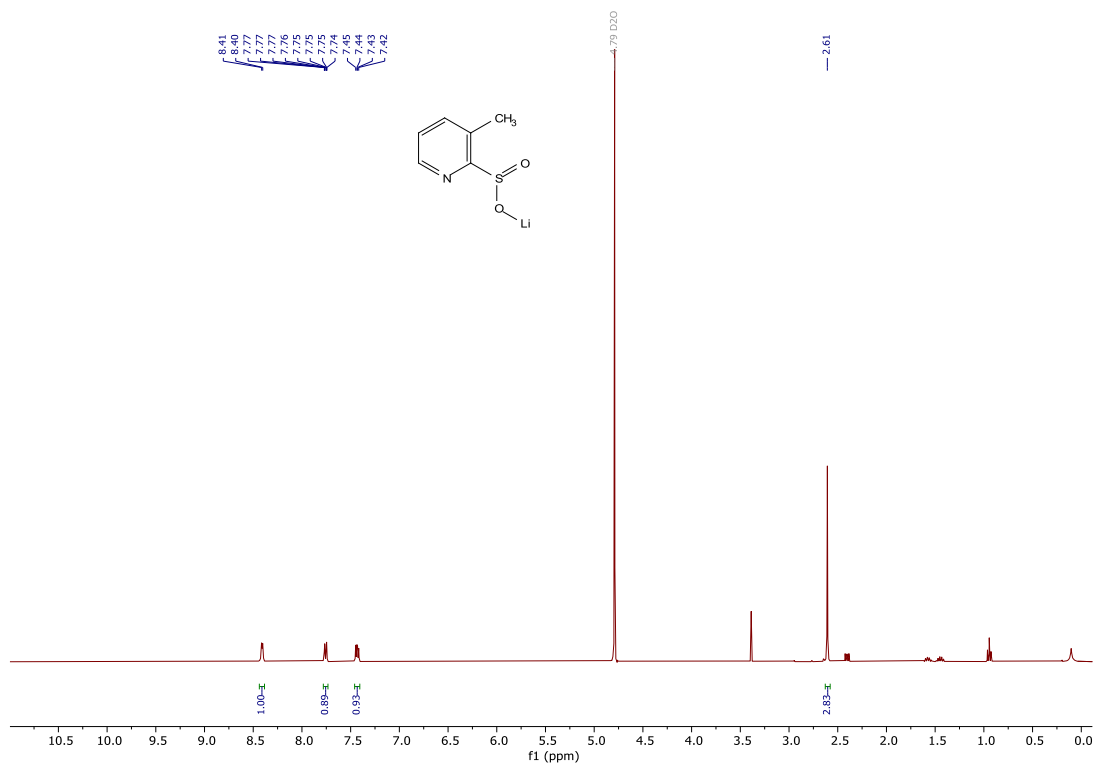
sodium 5-(trifluoromethyl)pyridine-2-sulfinate (48a)



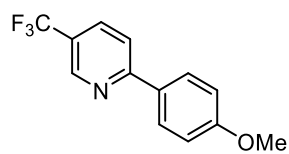




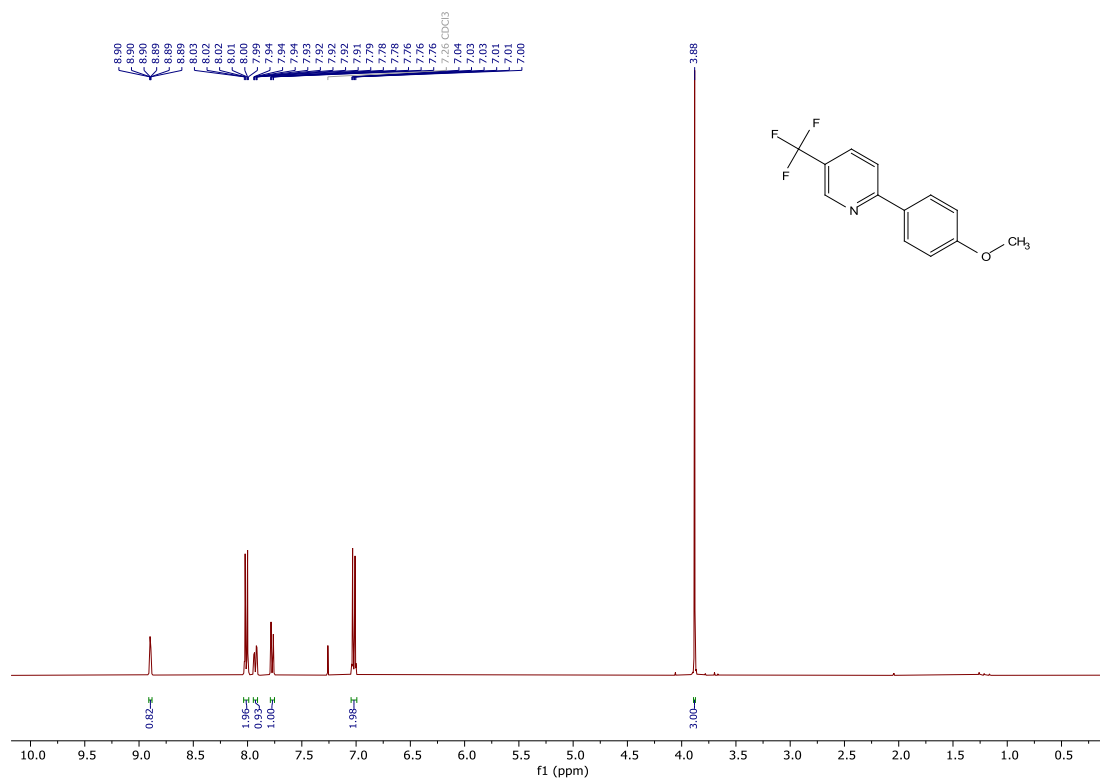
lithium 3-methylpyridine-2-sulfinate (48b)

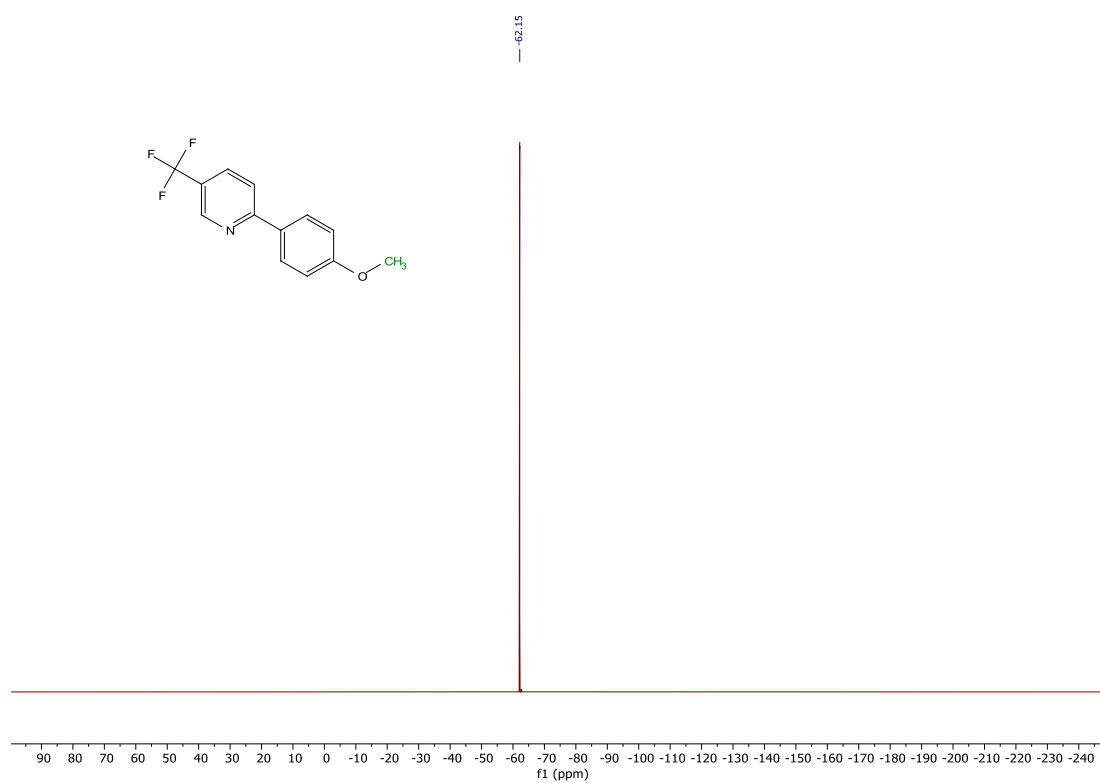
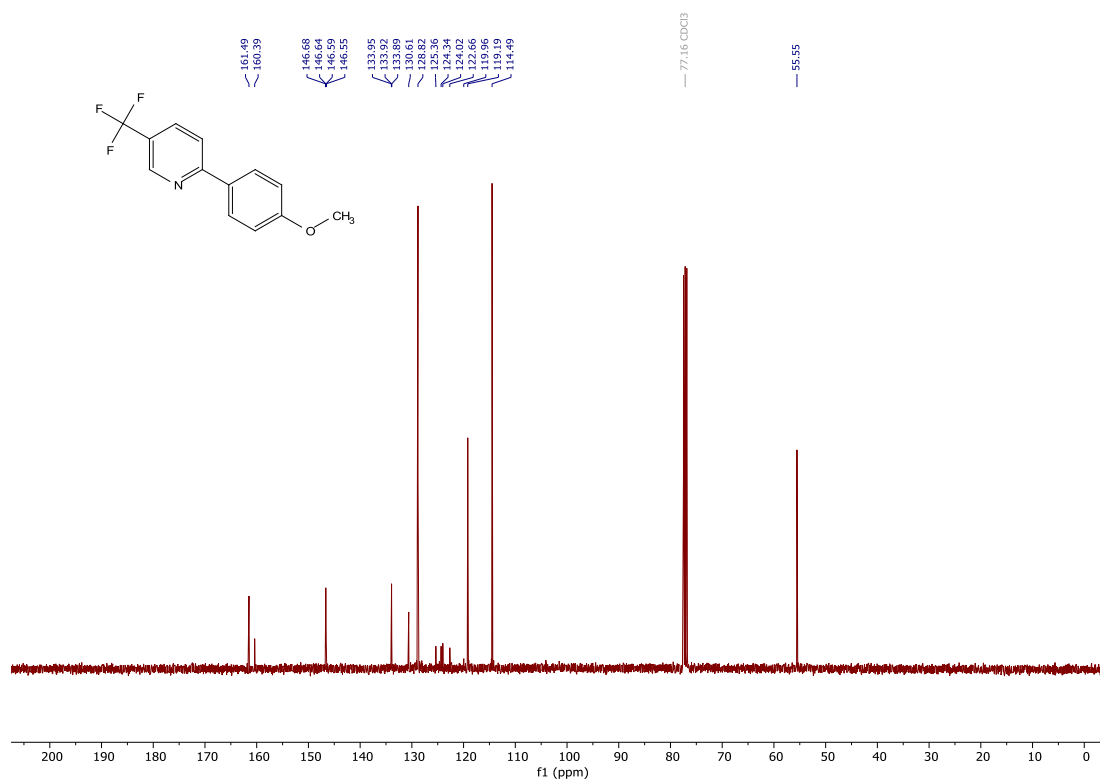


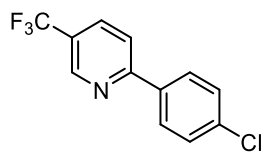
8.1.4. Biaryl products



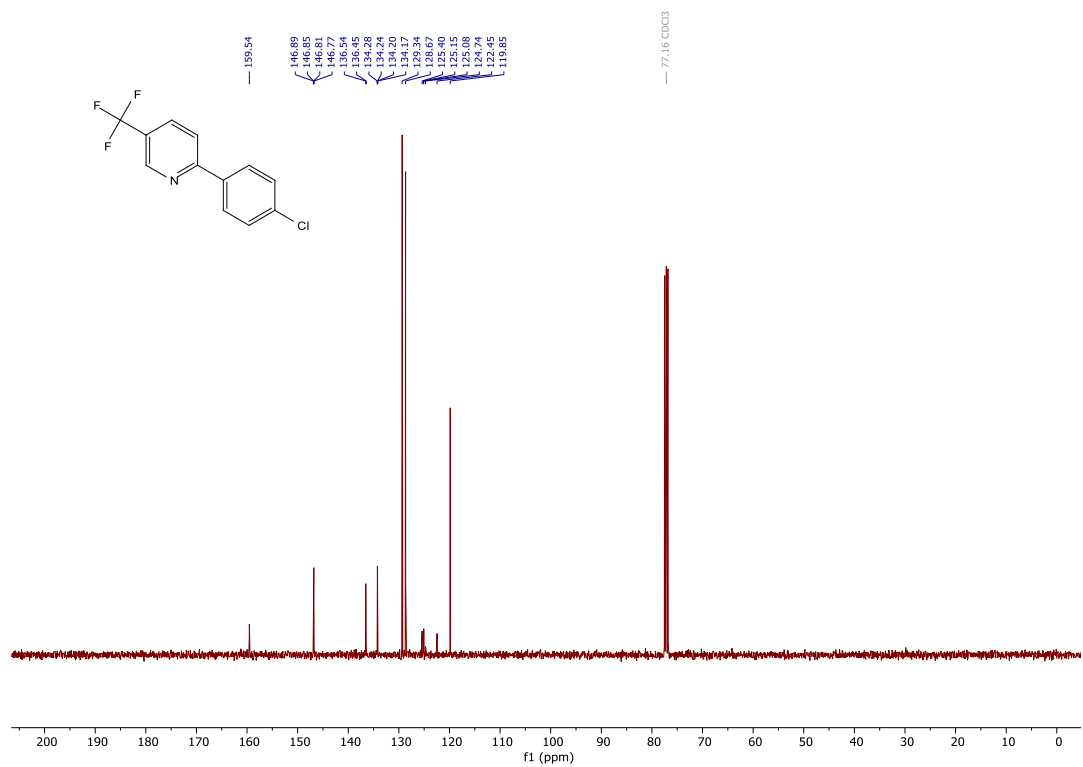
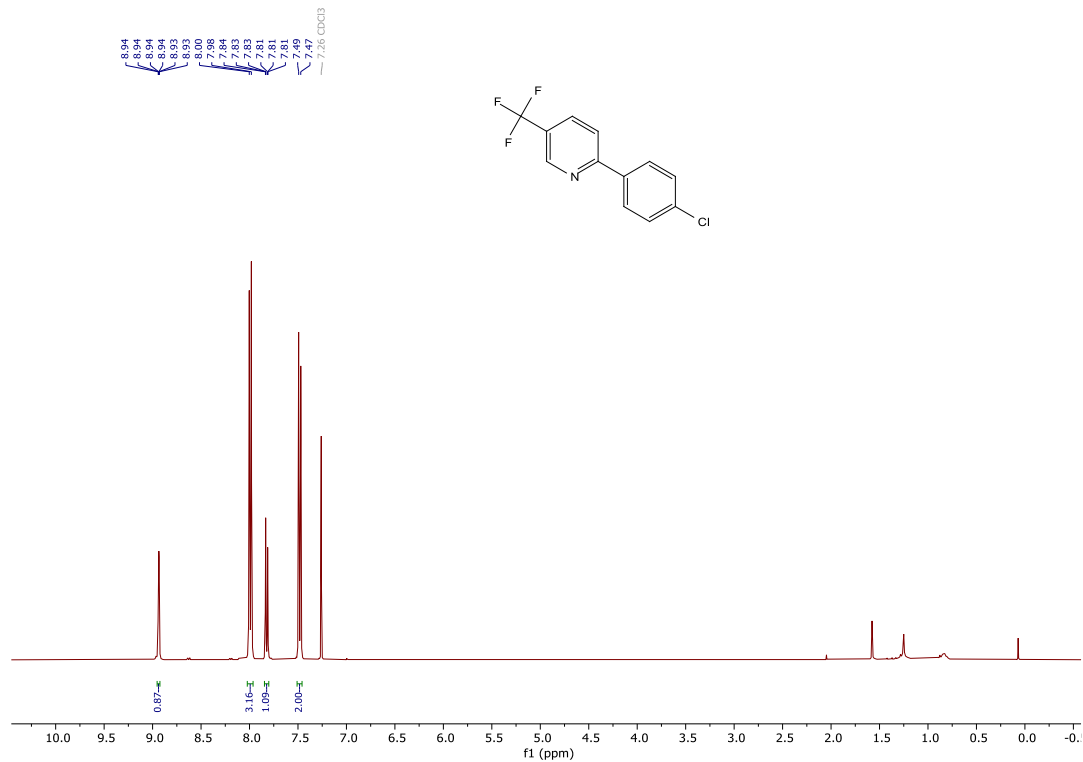
2-(4-methoxyphenyl)-5-(trifluoromethyl)pyridine (4a)

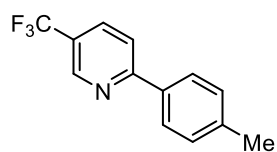
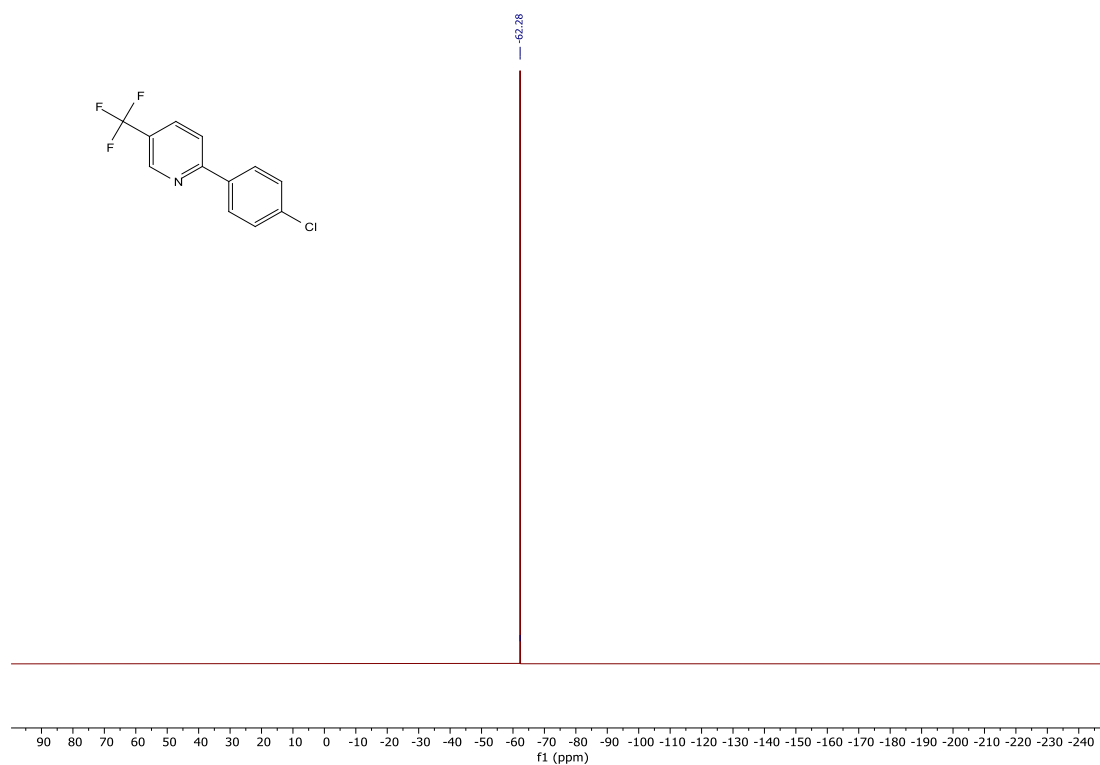




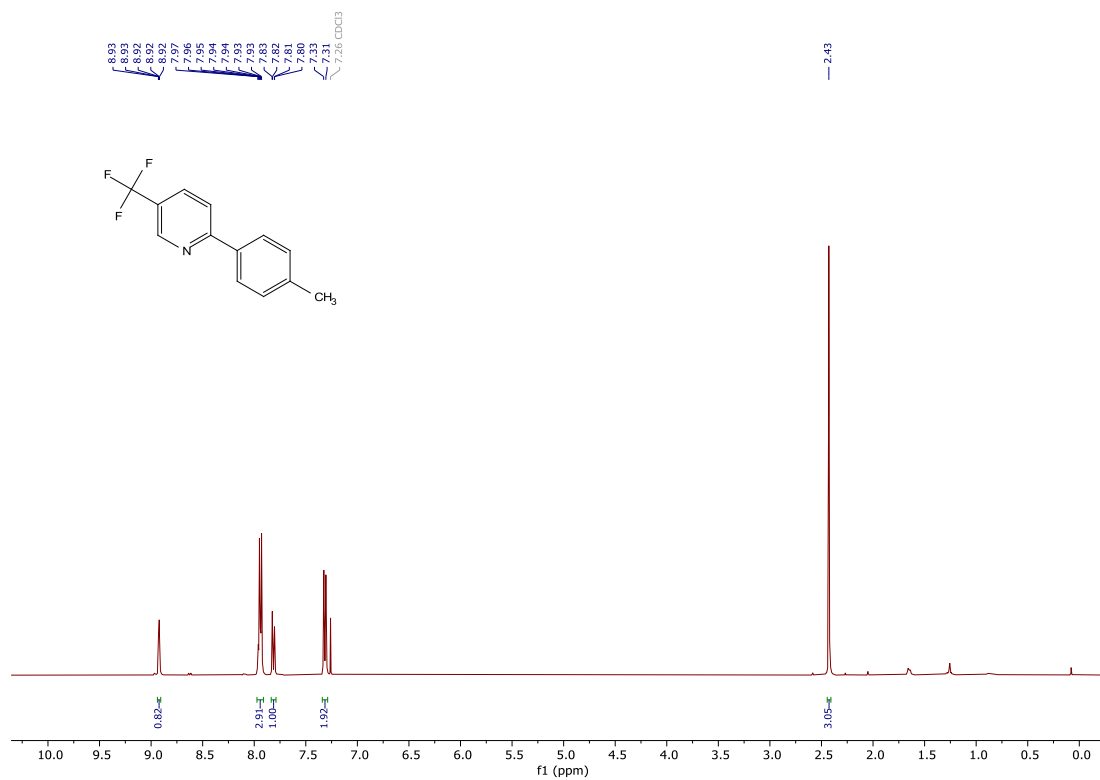


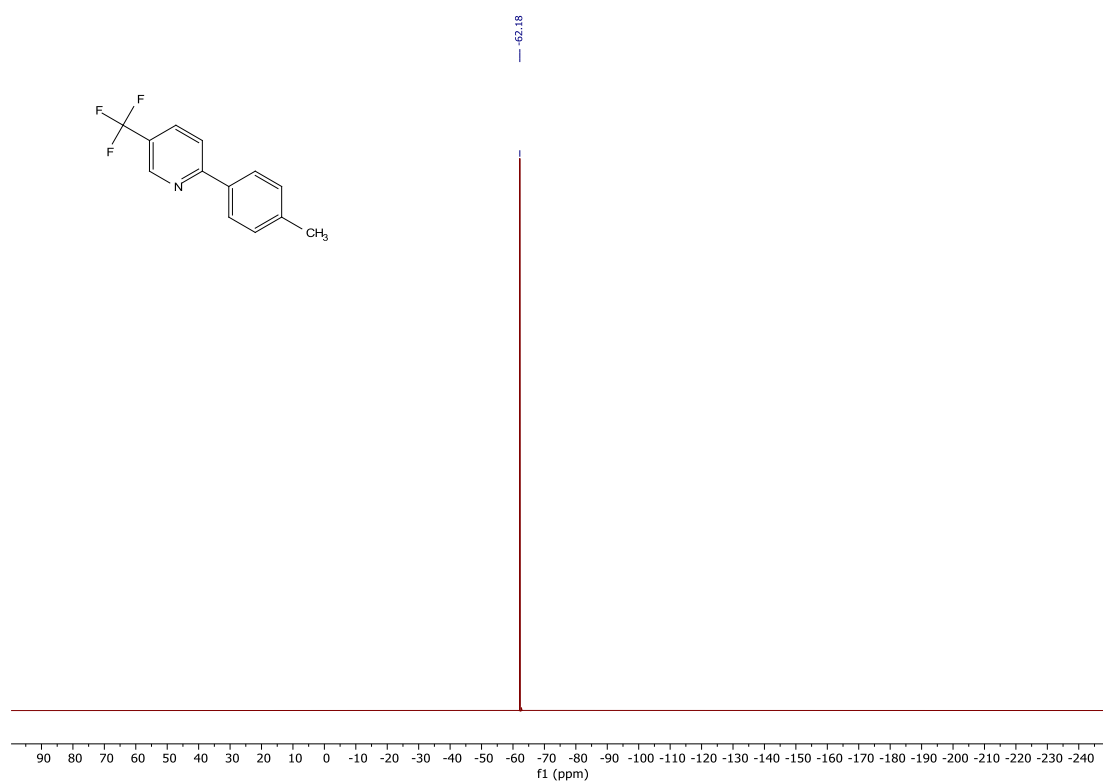
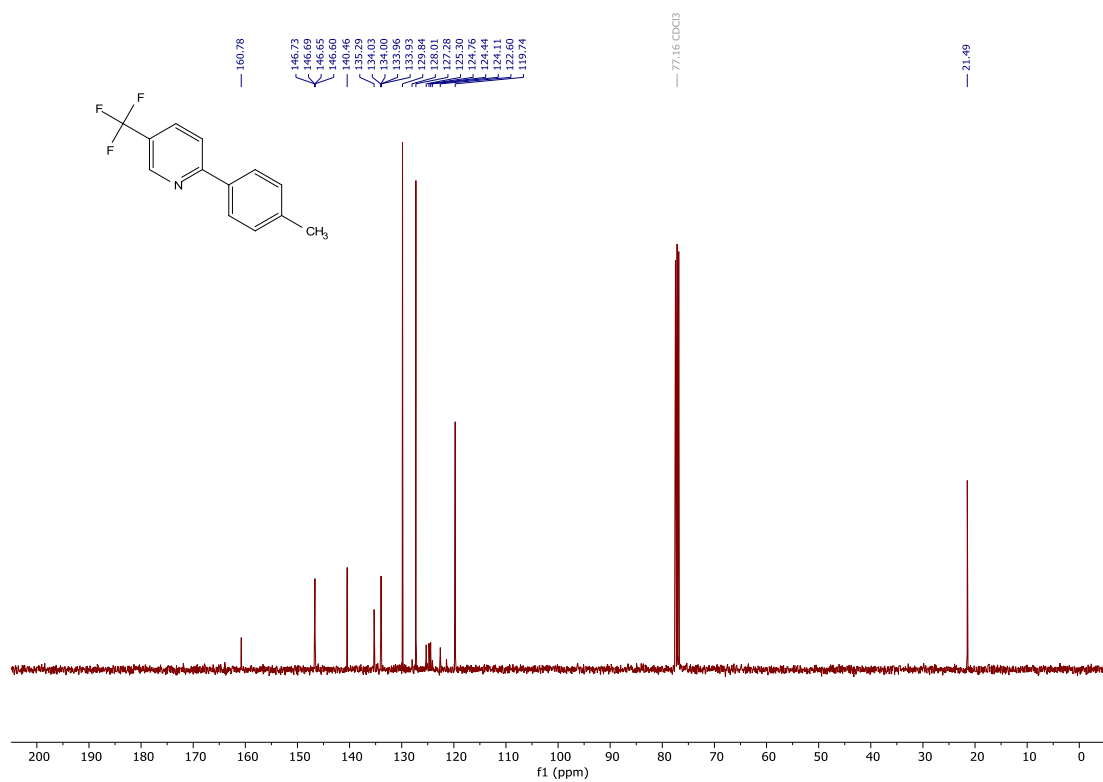
2-(4-chlorophenyl)-5-(trifluoromethyl)pyridine (4b)

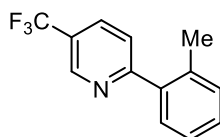




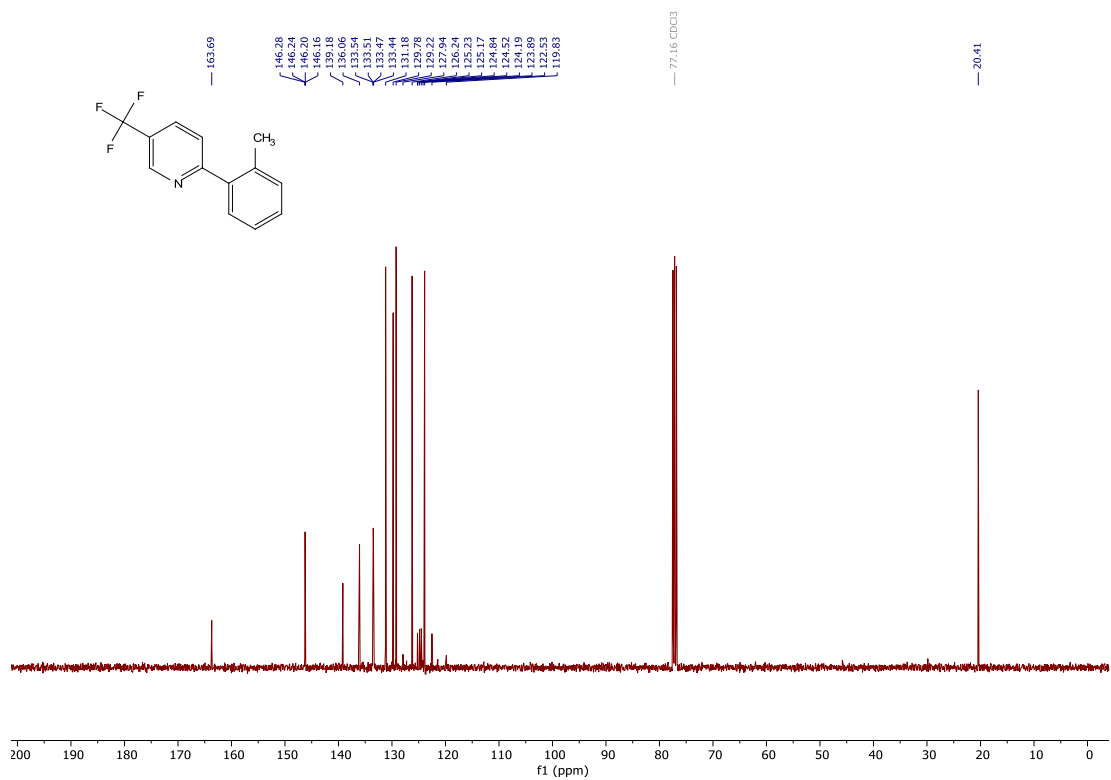
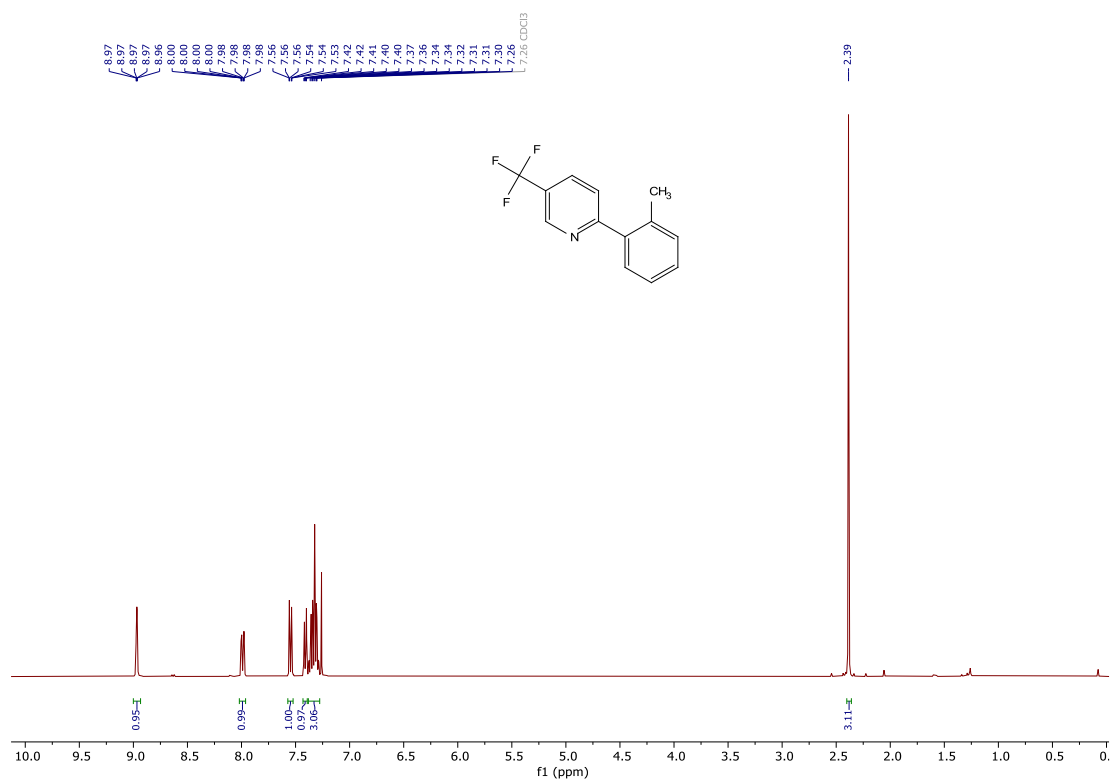
2-(p-tolyl)-5-(trifluoromethyl)pyridine (4c)

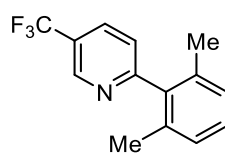
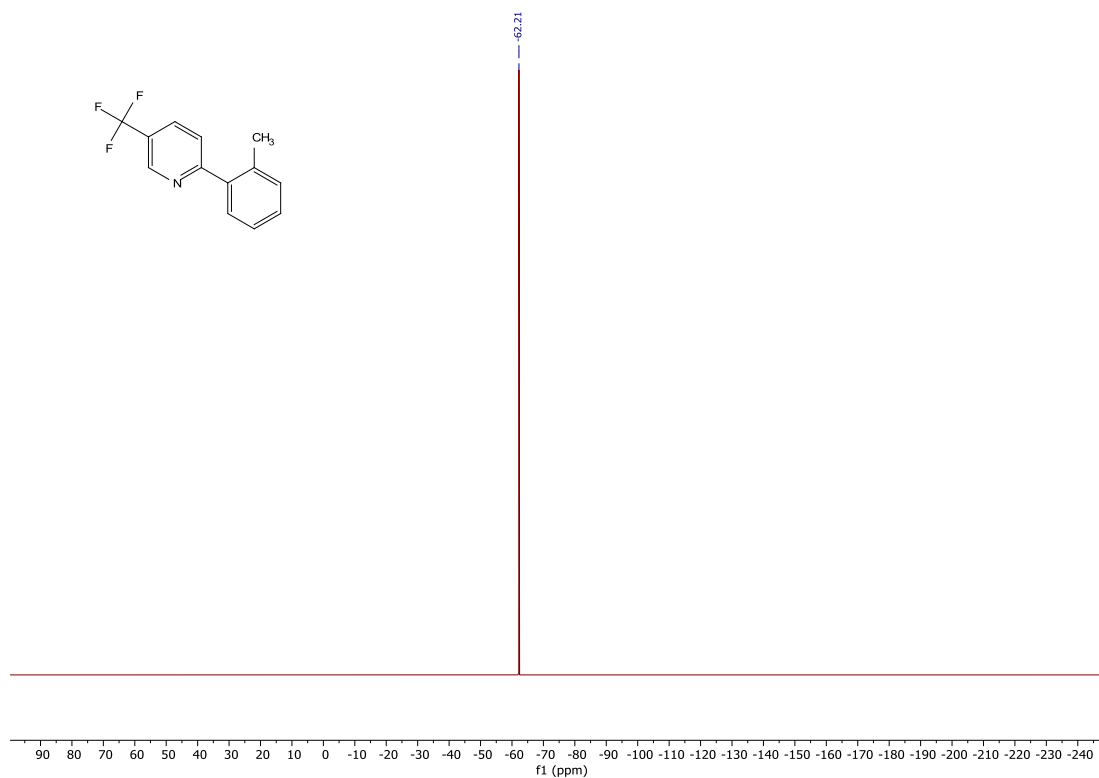




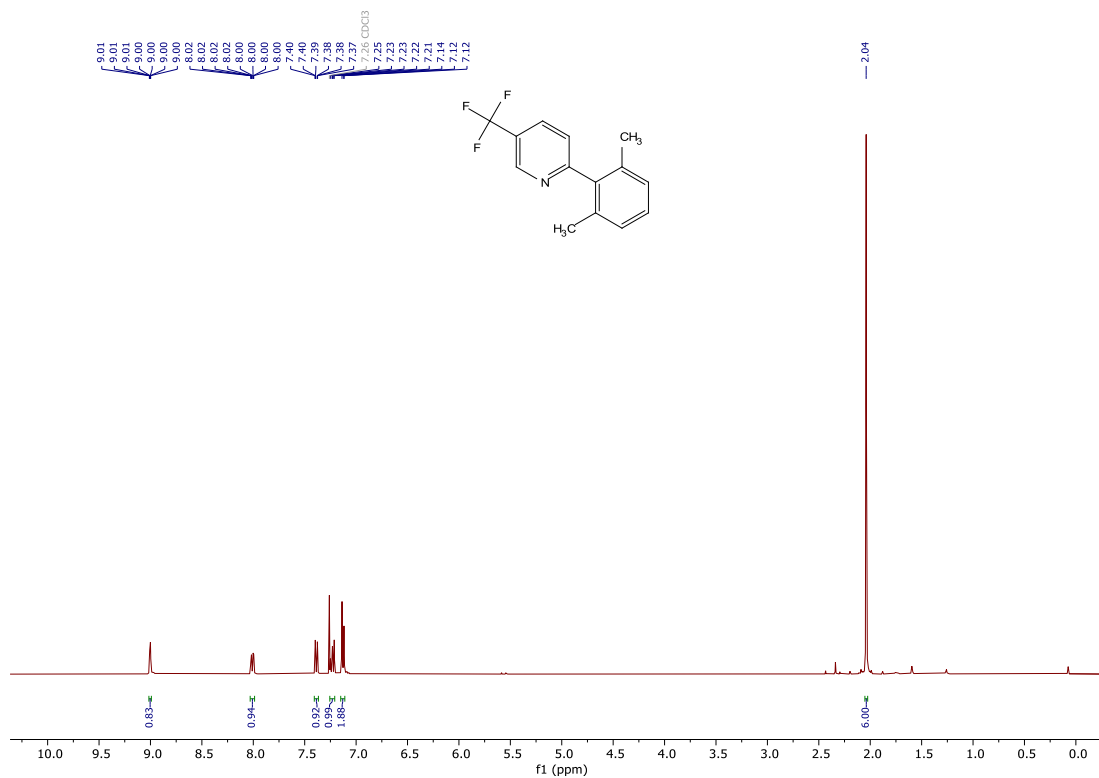


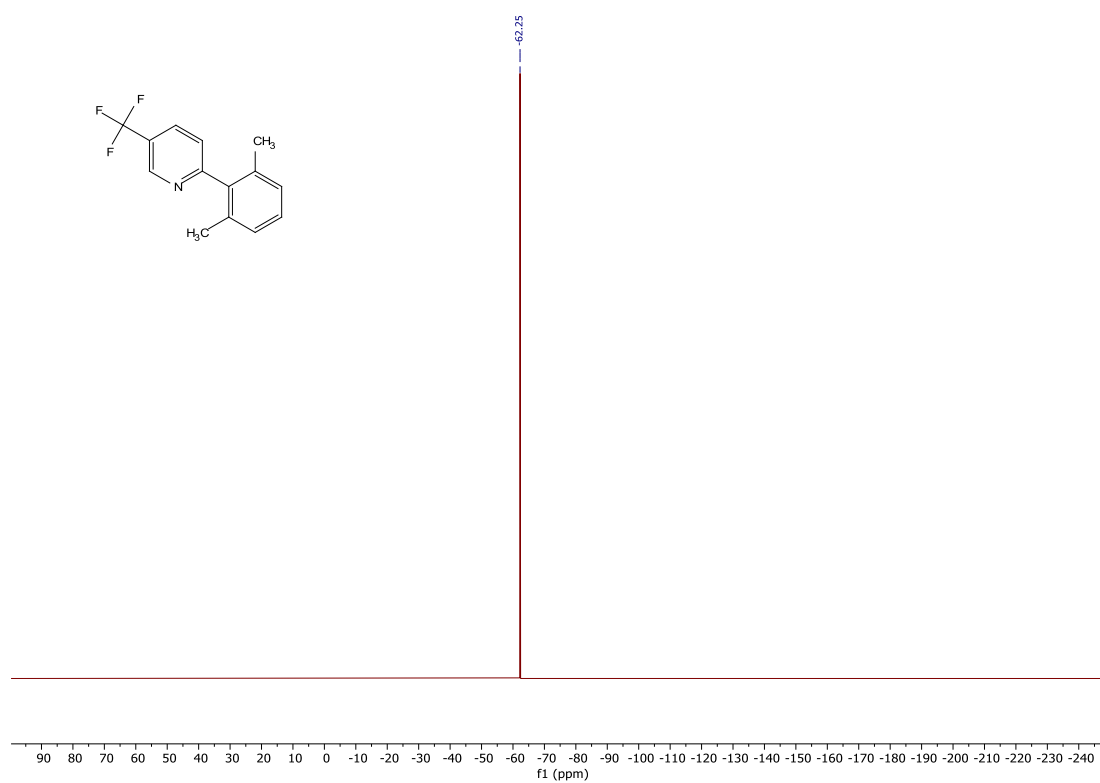
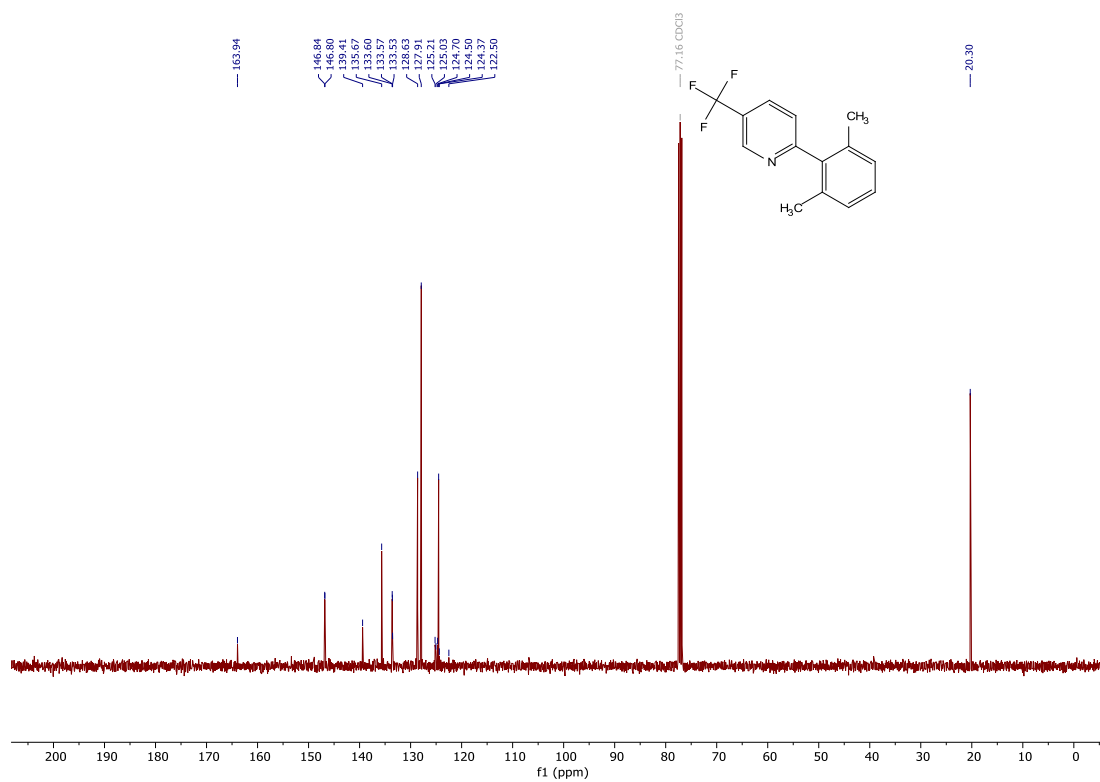
2-(o-tolyl)-5-(trifluoromethyl)pyridine (4e)

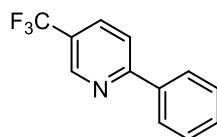




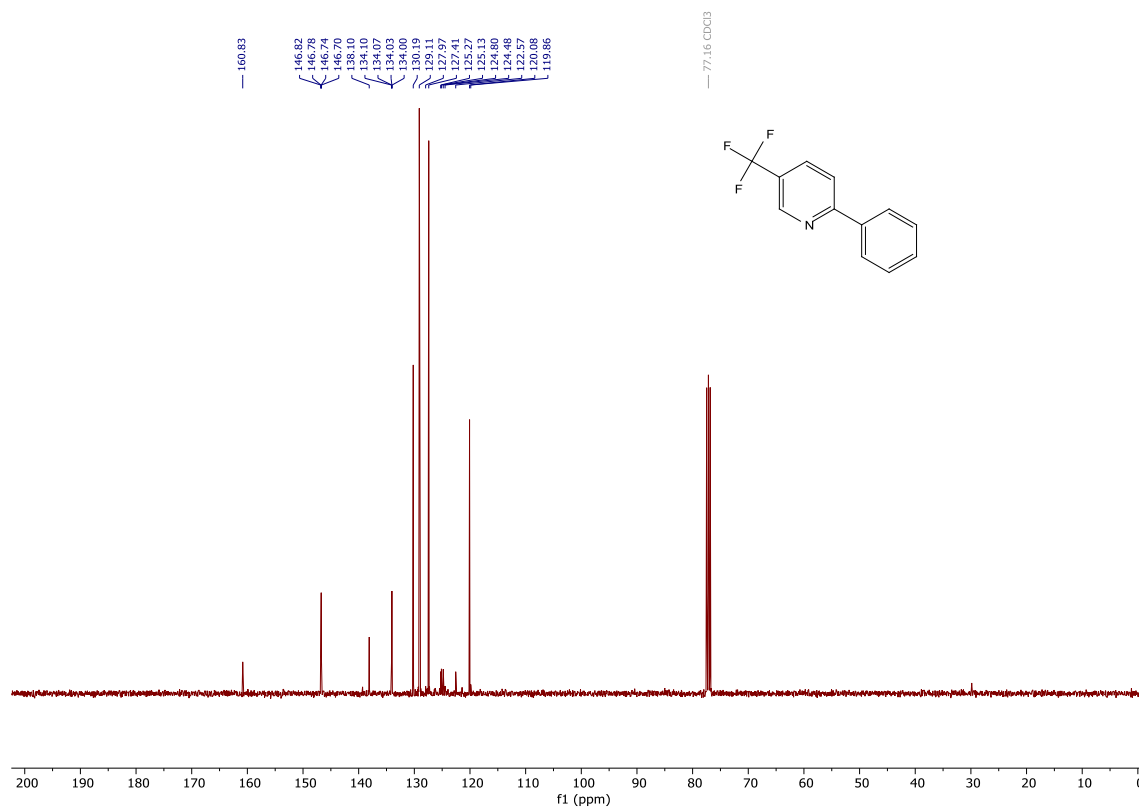
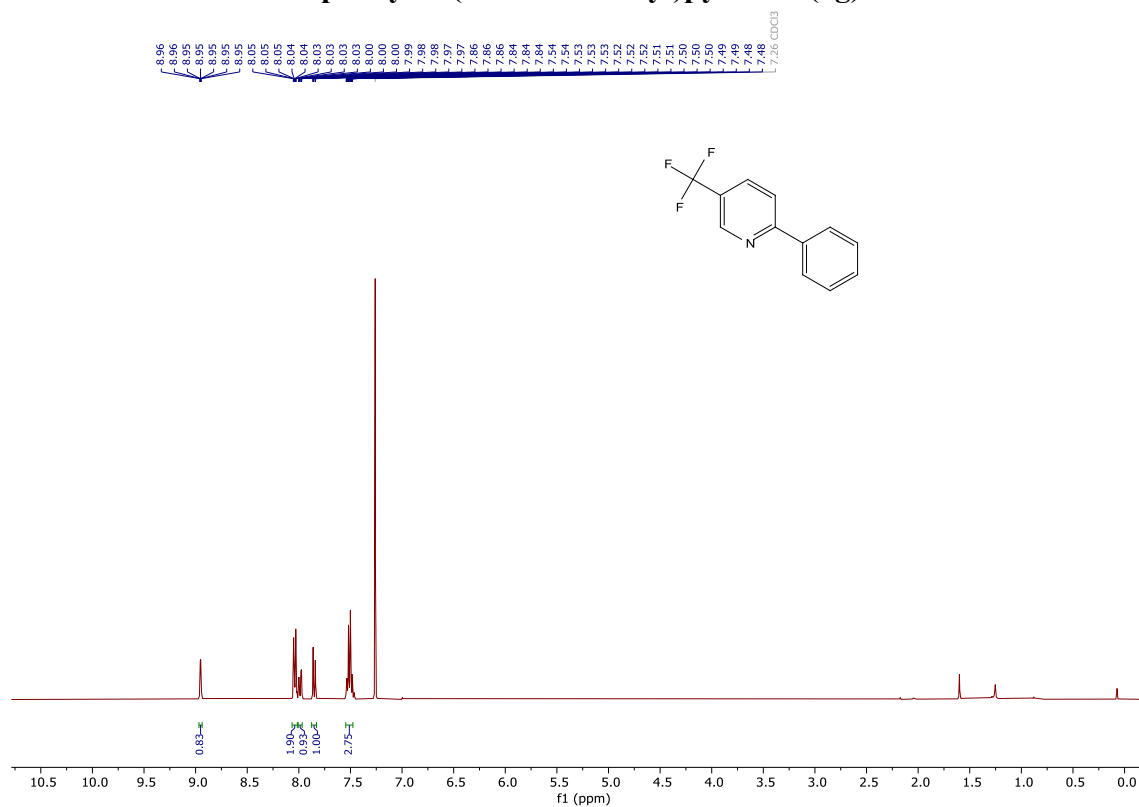
2-(2,6-dimethylphenyl)-5-(trifluoromethyl)pyridine (4f)

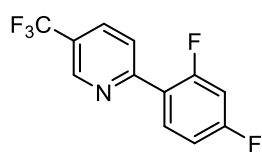
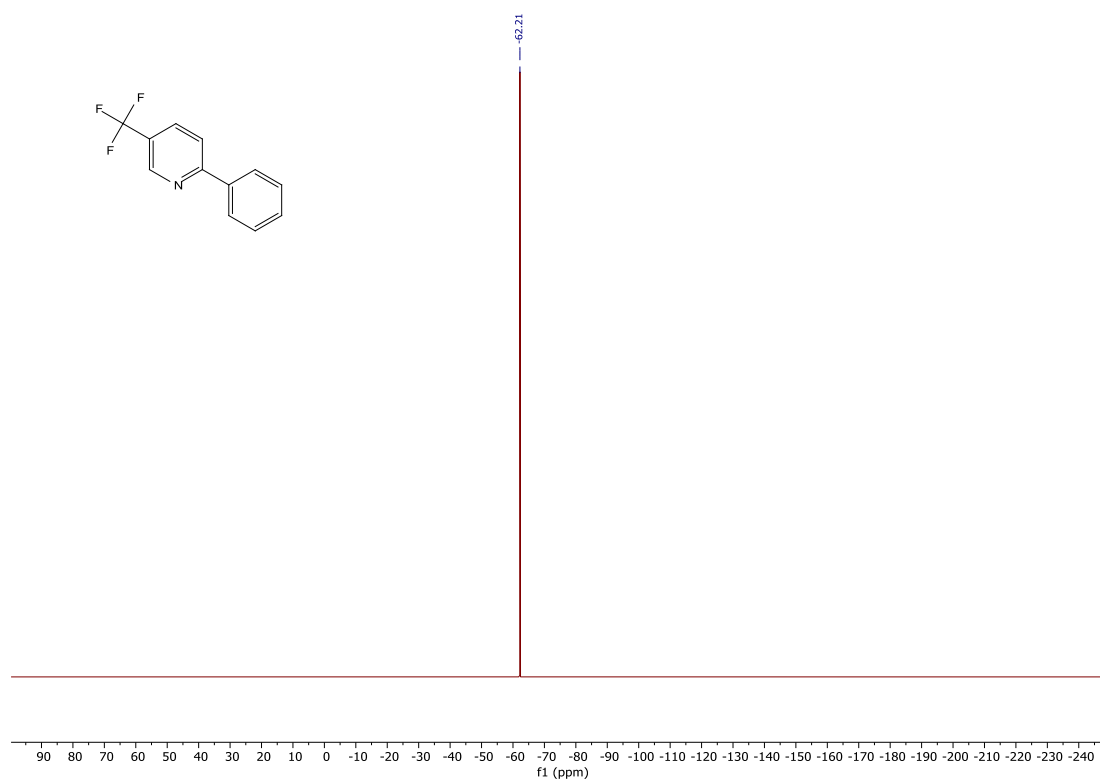




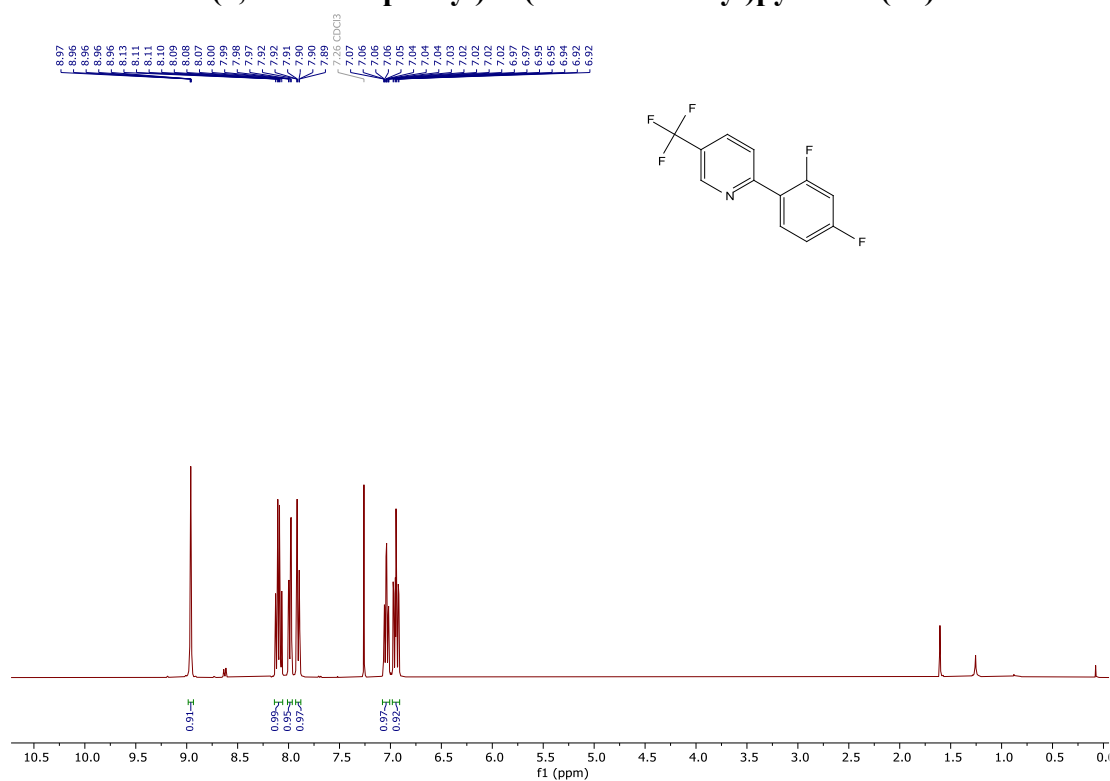


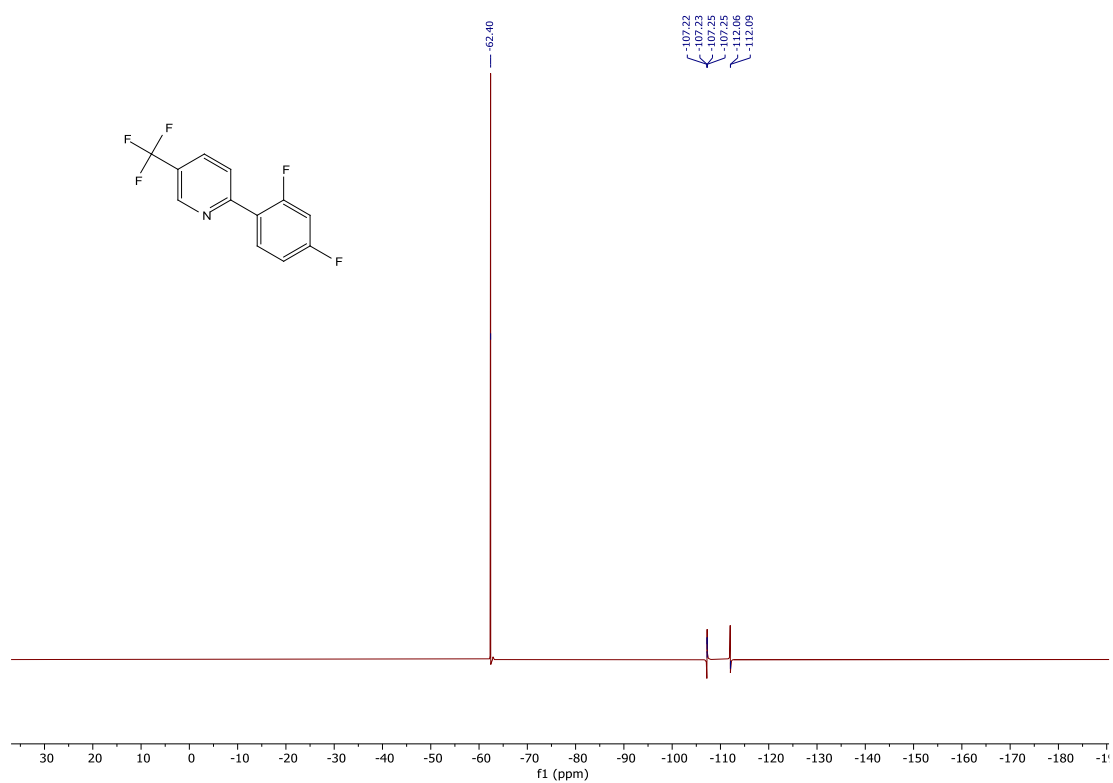
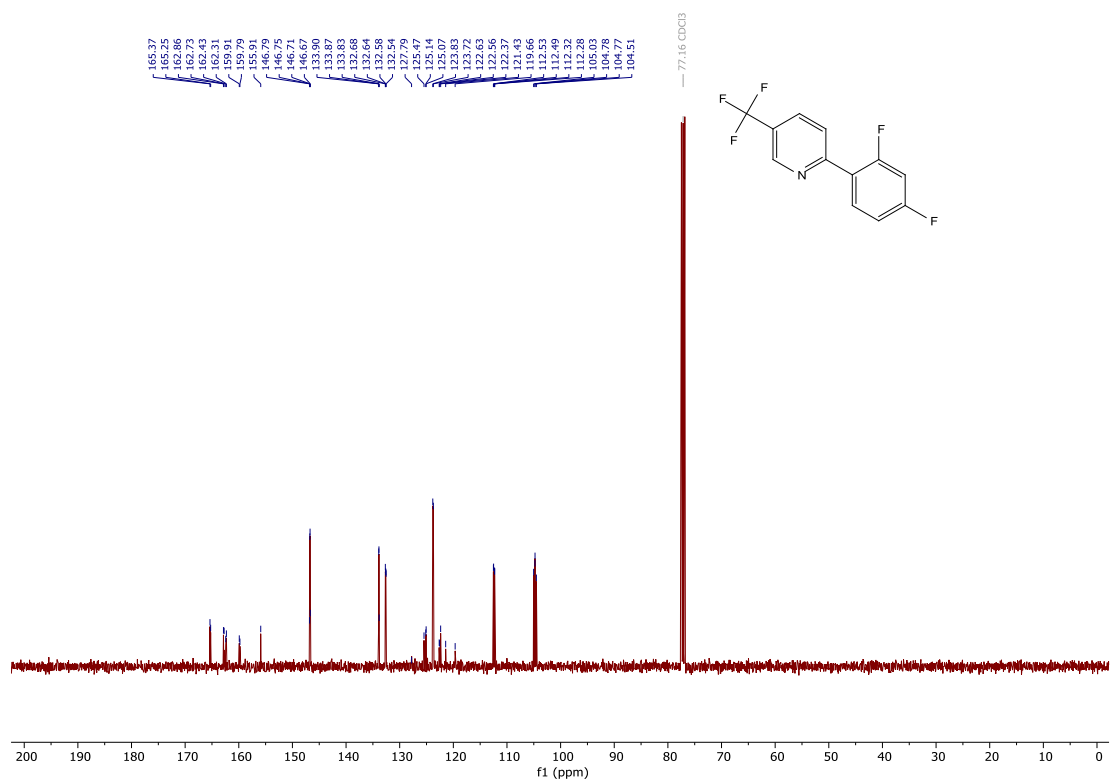
2-phenyl-5-(trifluoromethyl)pyridine (4g)

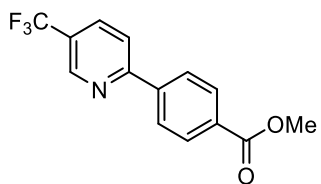




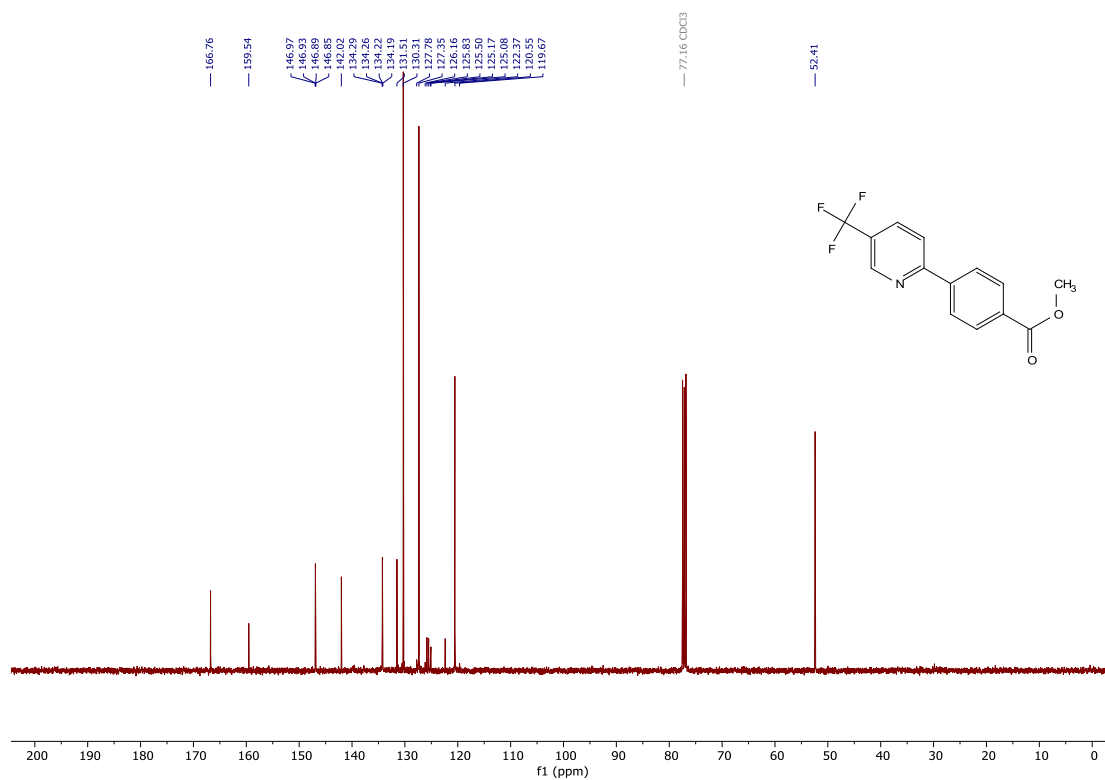
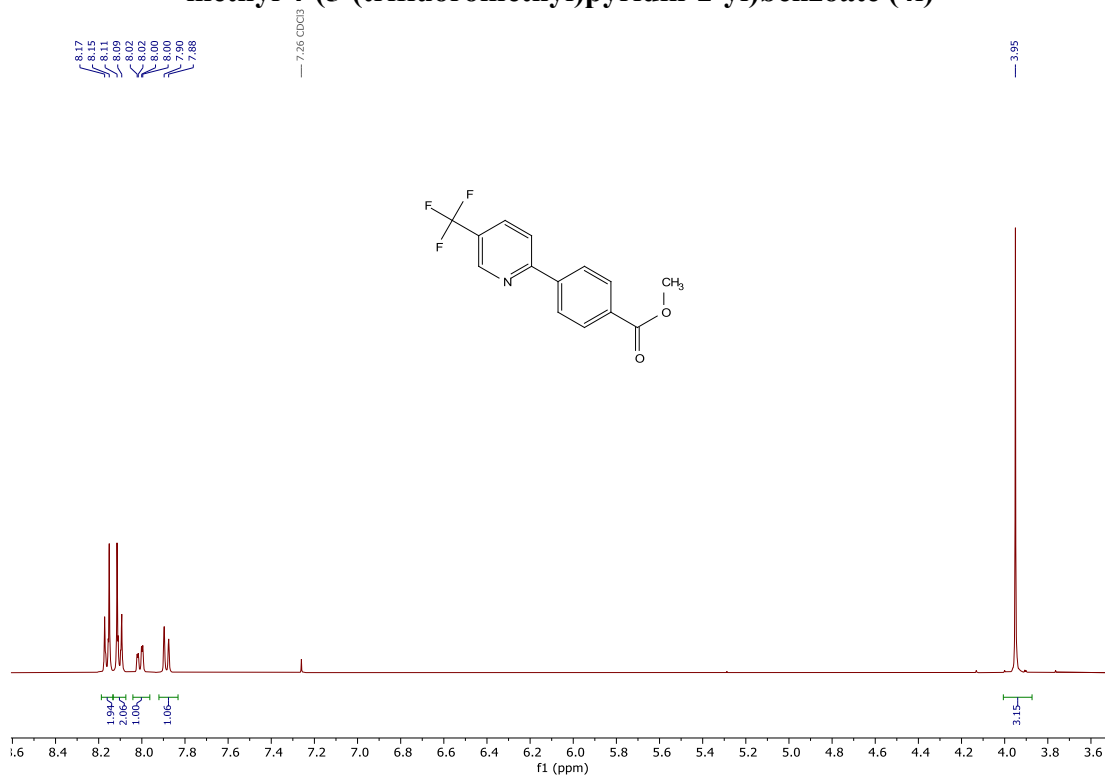
2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine (4h)

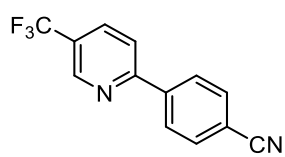
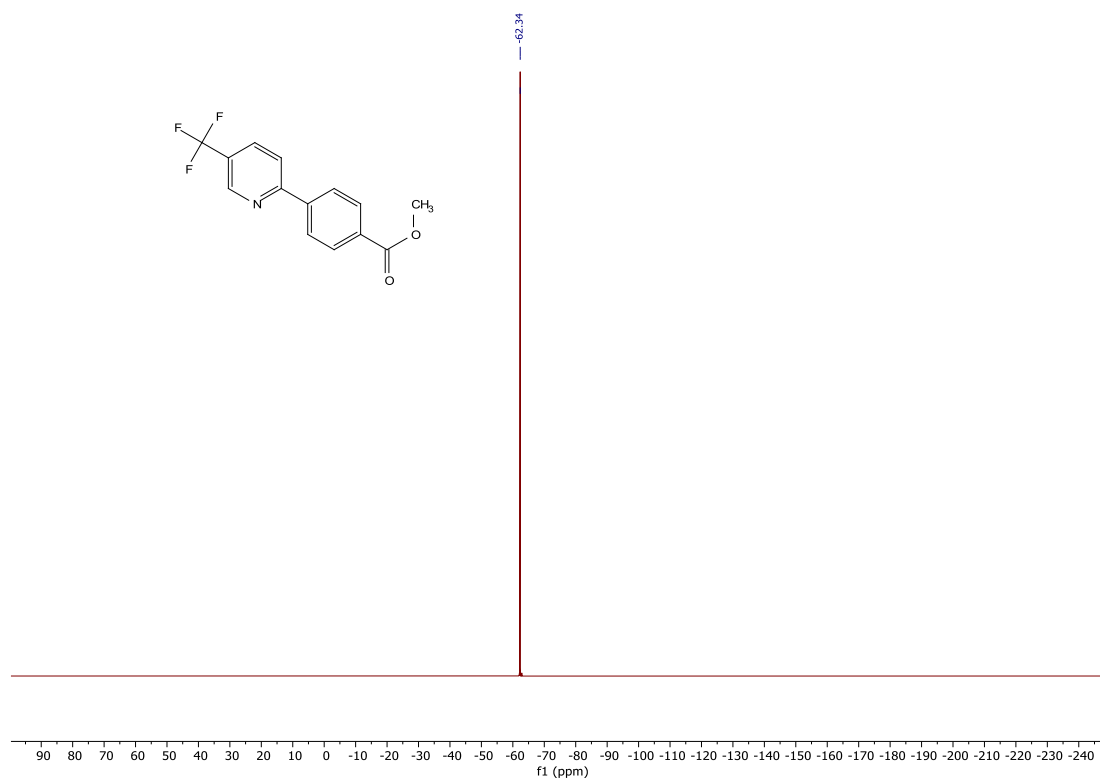




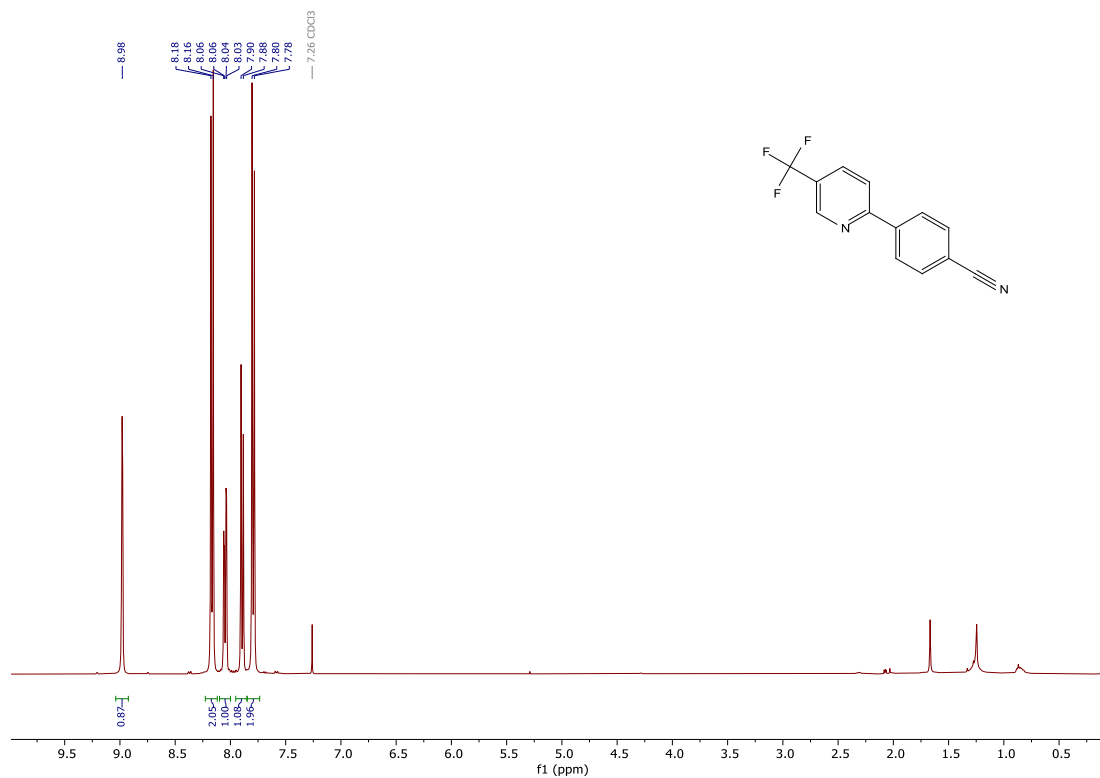


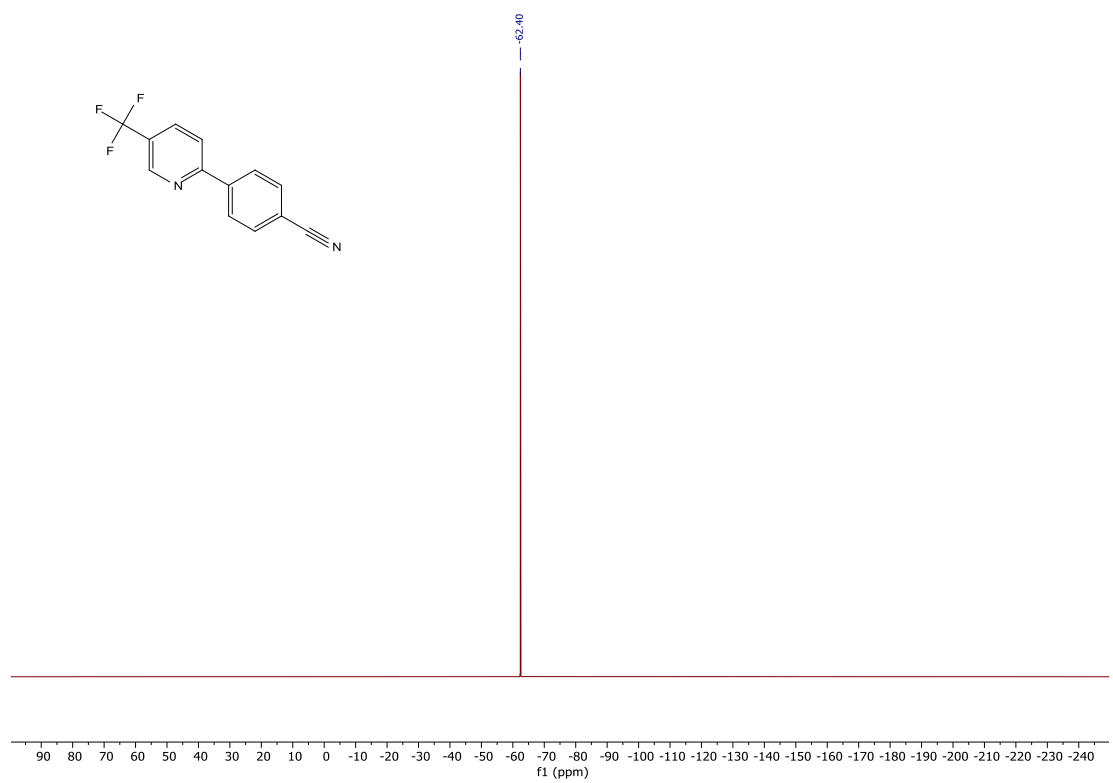
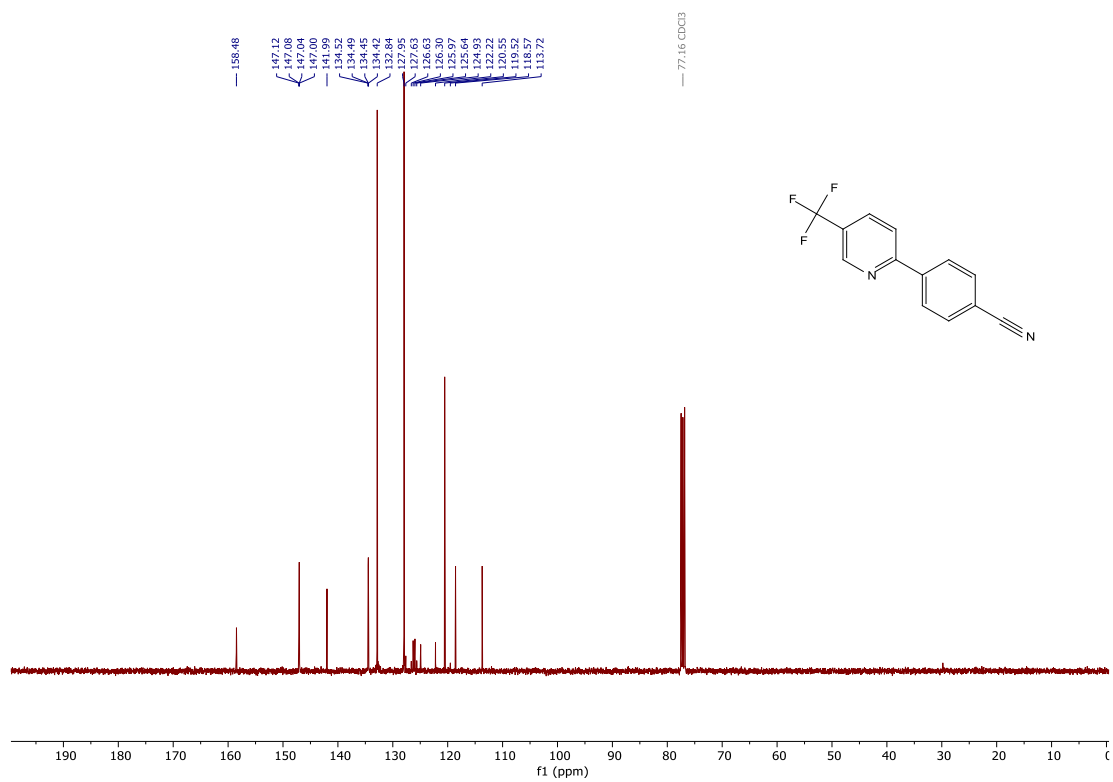
methyl 4-(5-(trifluoromethyl)pyridin-2-yl)benzoate (4i)

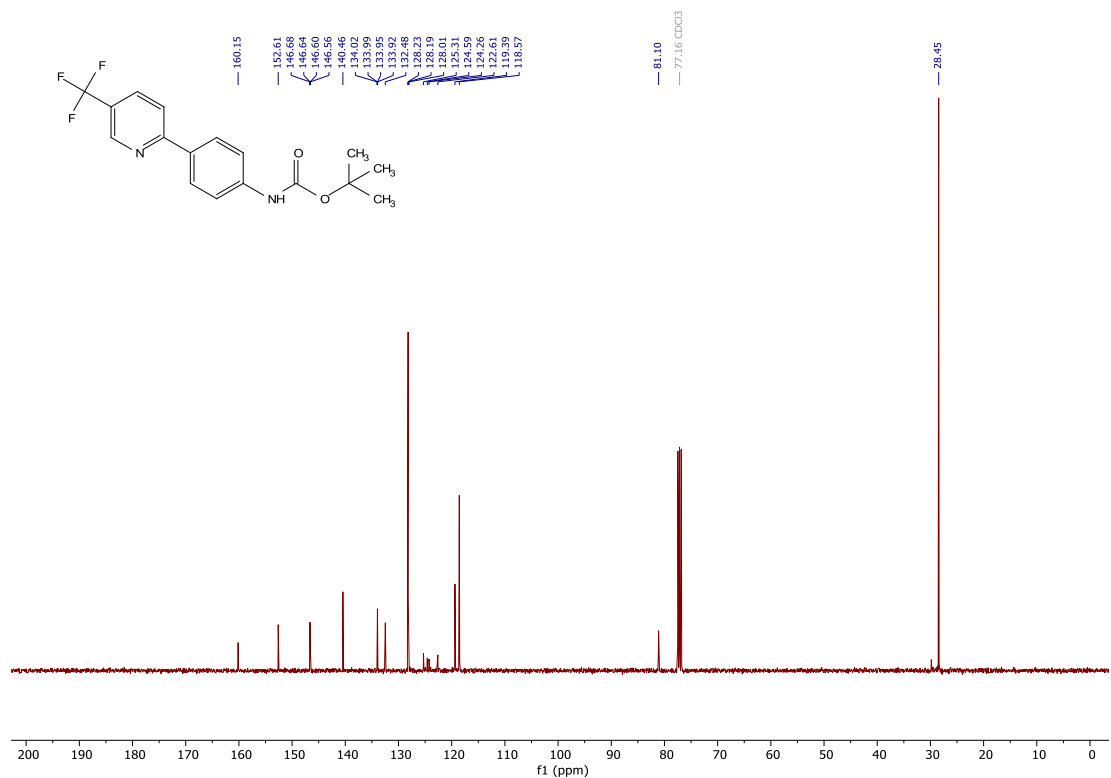


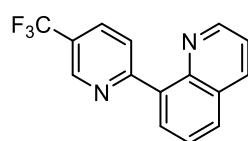
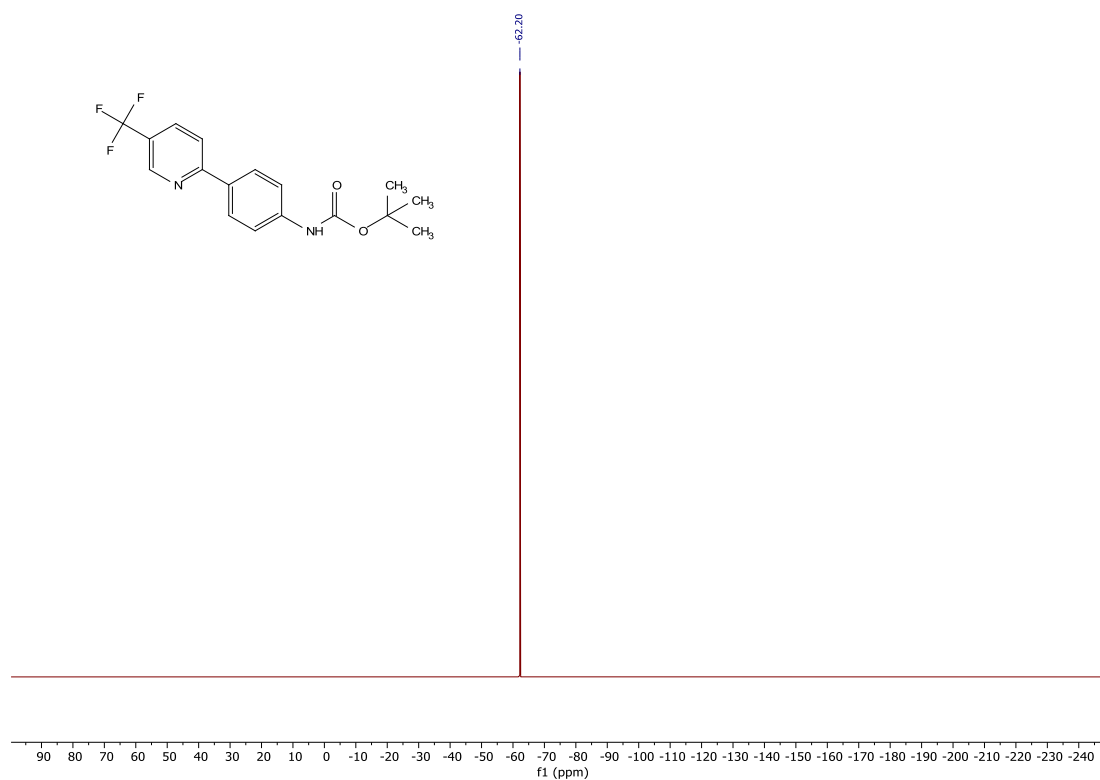


4-(5-(trifluoromethyl)pyridin-2-yl)benzonitrile (4k)

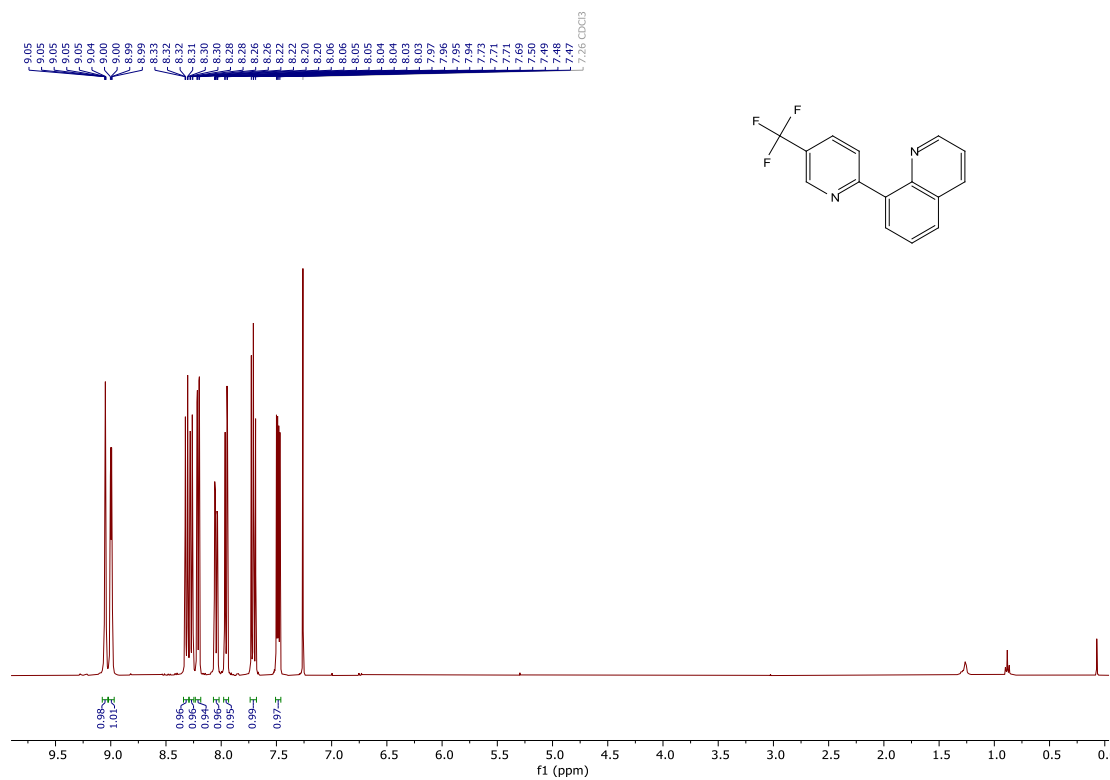


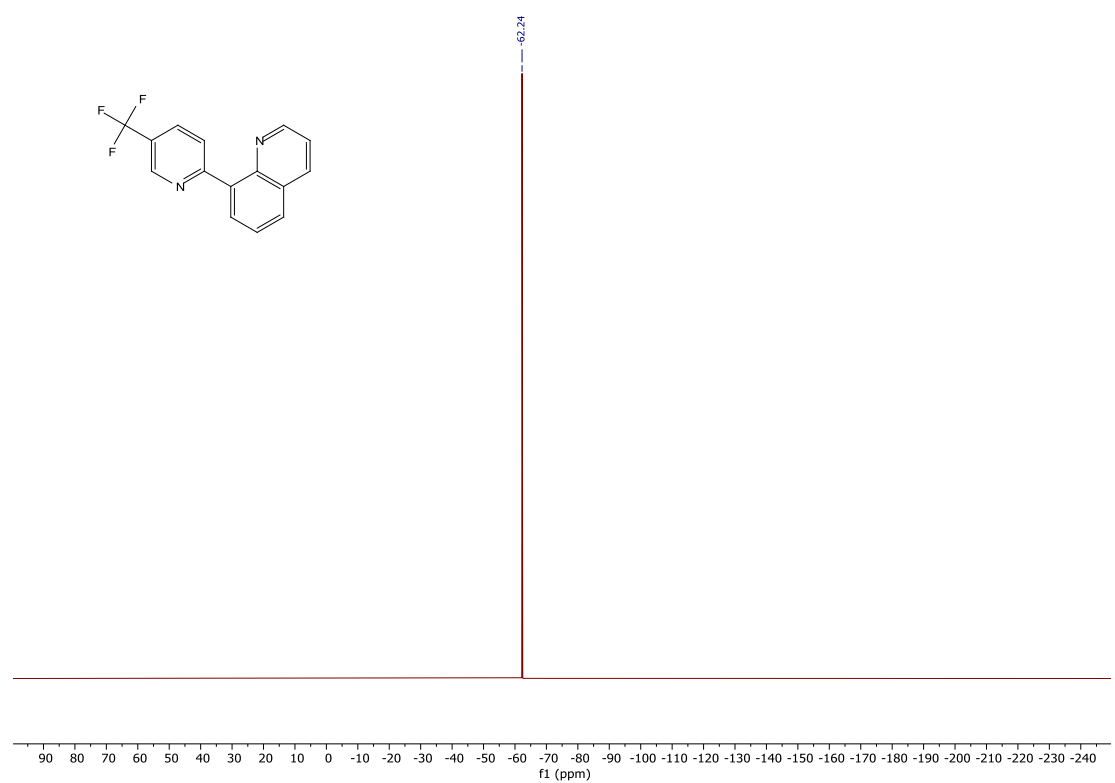
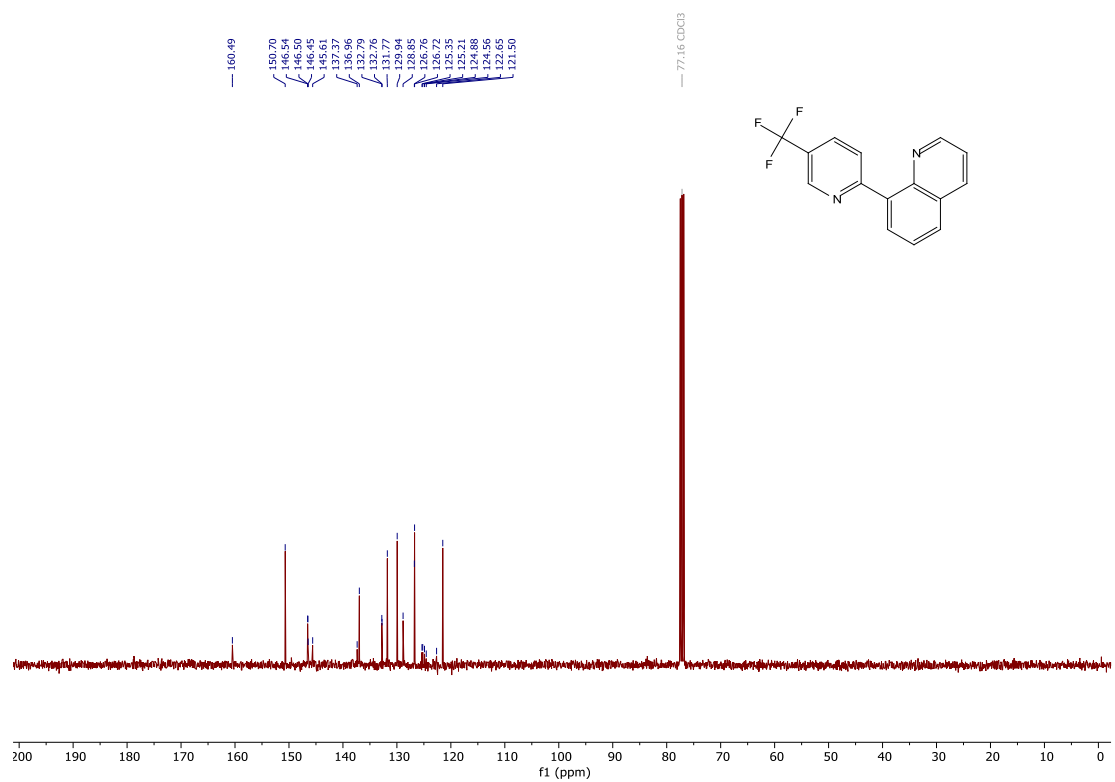


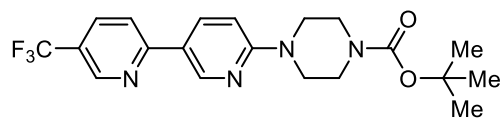




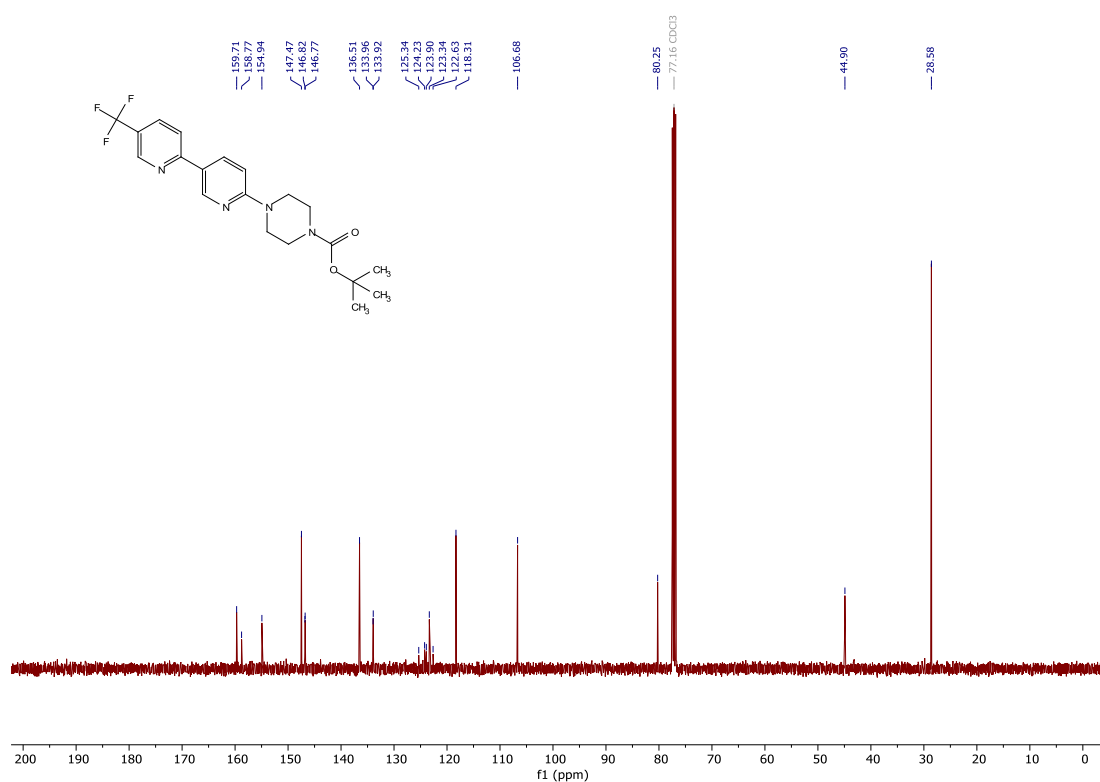
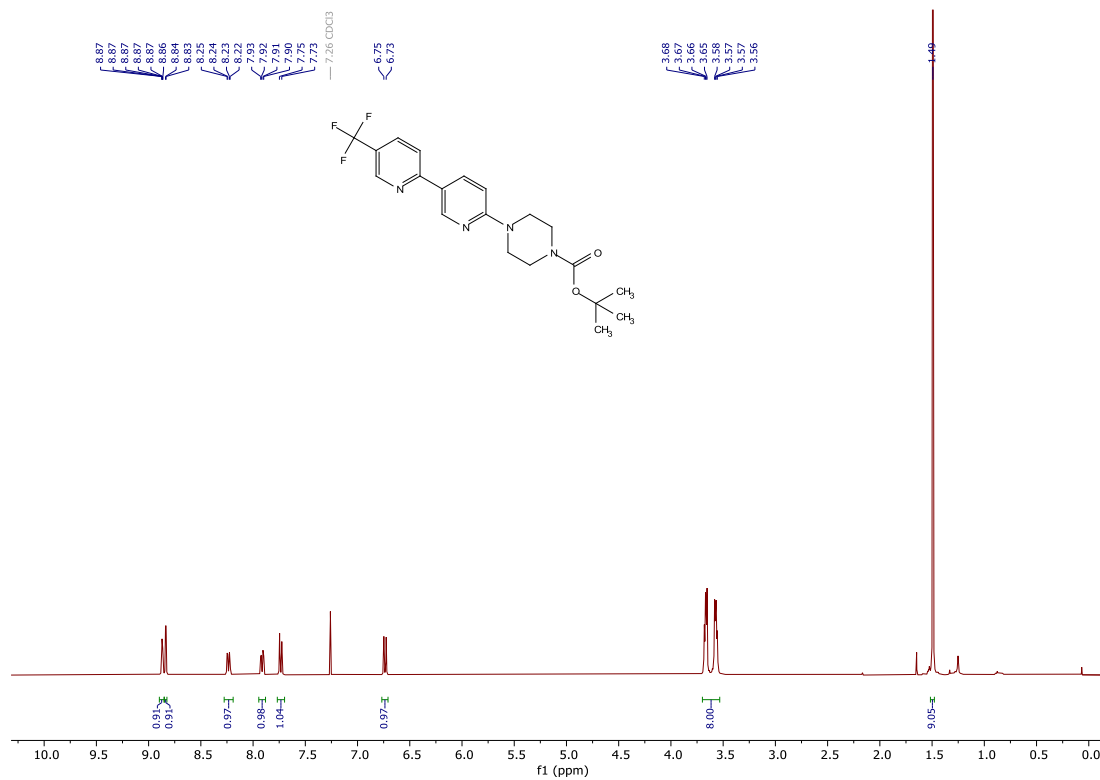
8-(5-(trifluoromethyl)pyridin-2-yl)quinoline (4n)

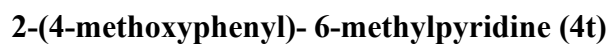
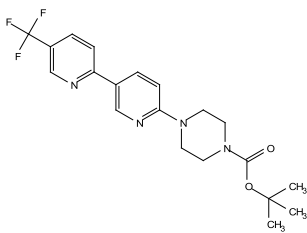


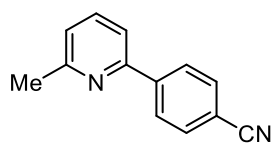
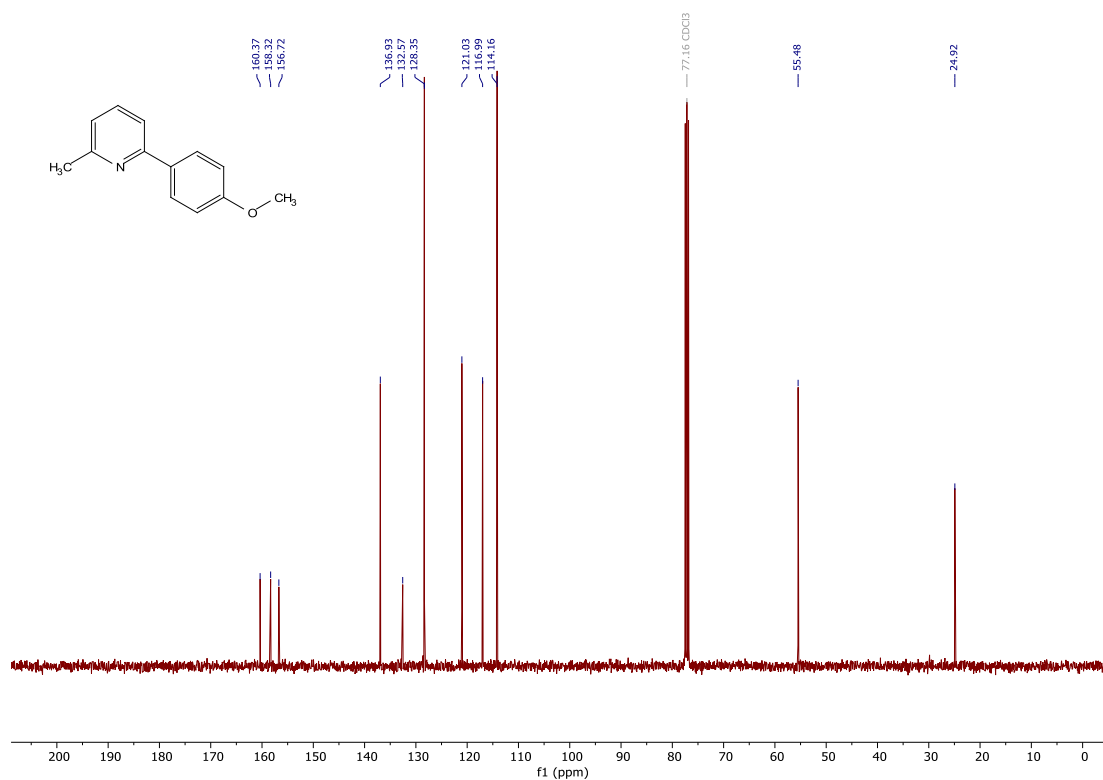




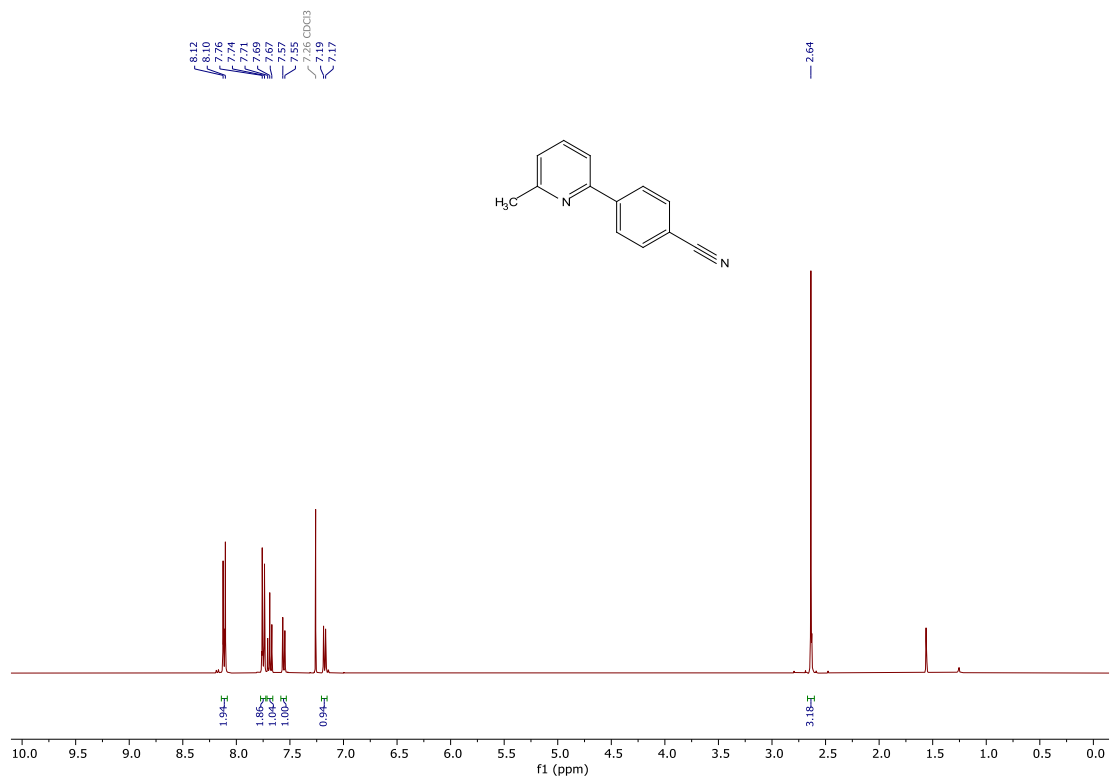
***tert*-butyl 4-(5-(trifluoromethyl)-[2,3'-bipyridin]-6'-yl)piperazine-1-carboxylate (4s)**

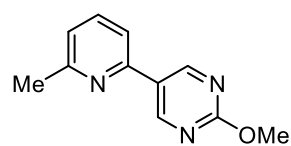
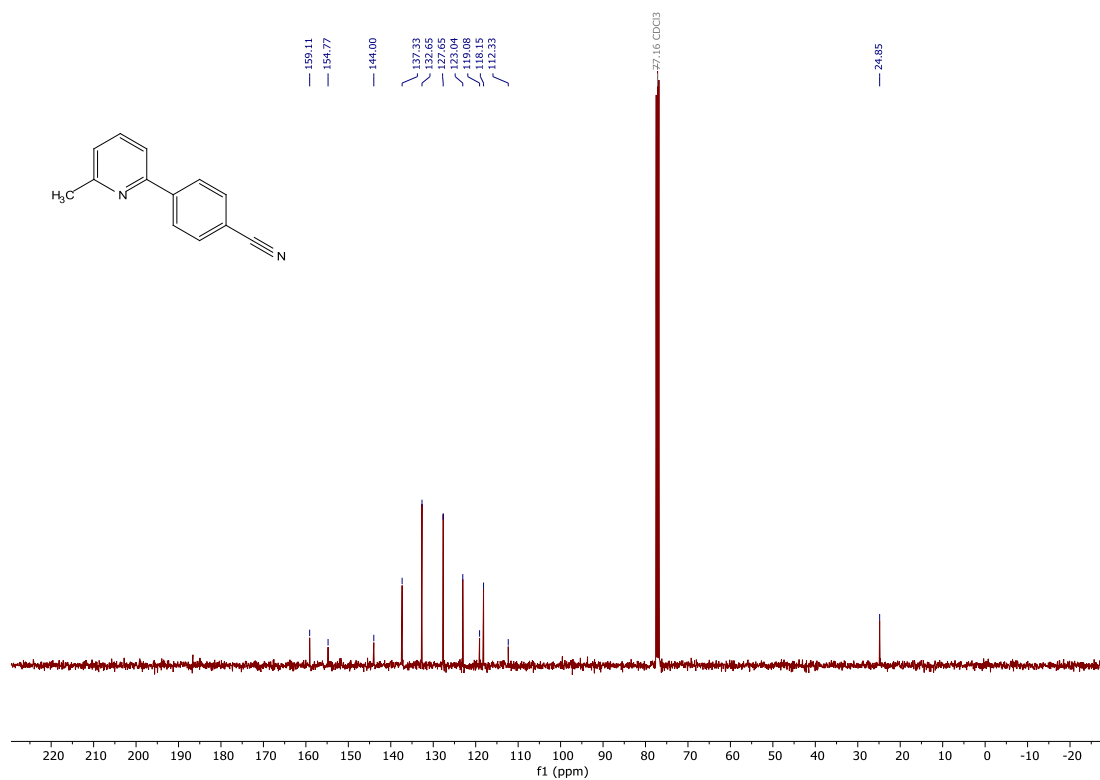




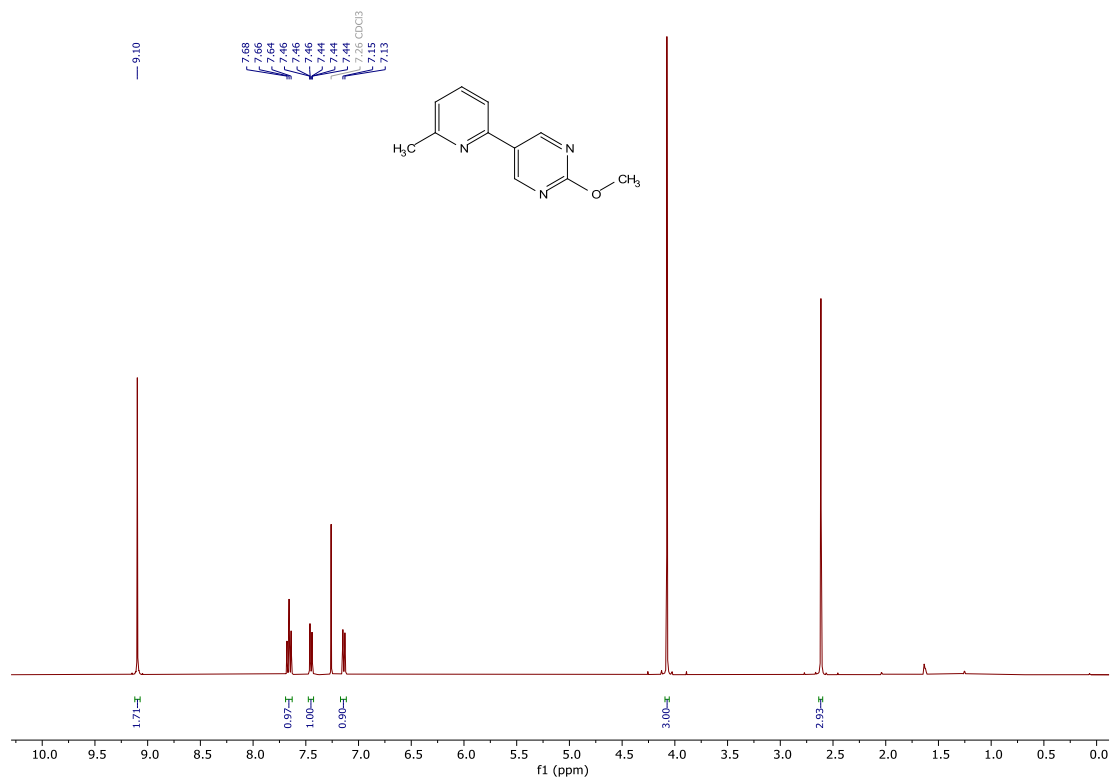


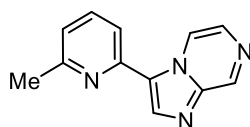
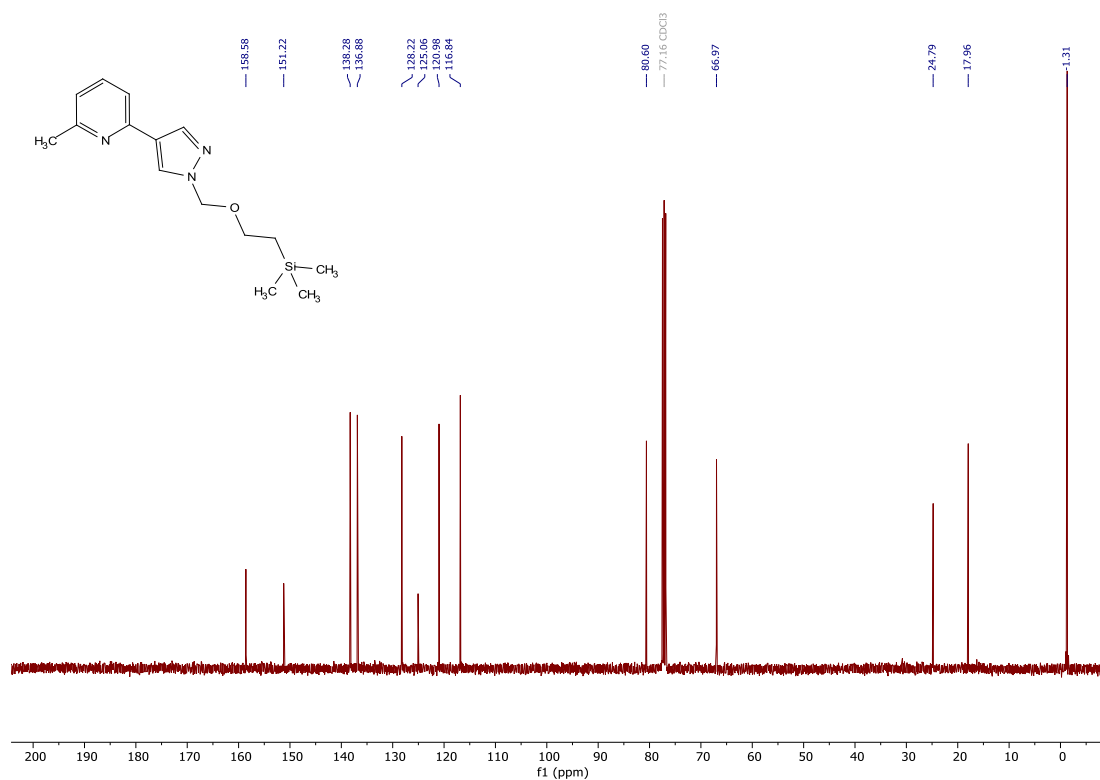
4-(6-methylpyridin-2-yl)benzonitrile (4u)



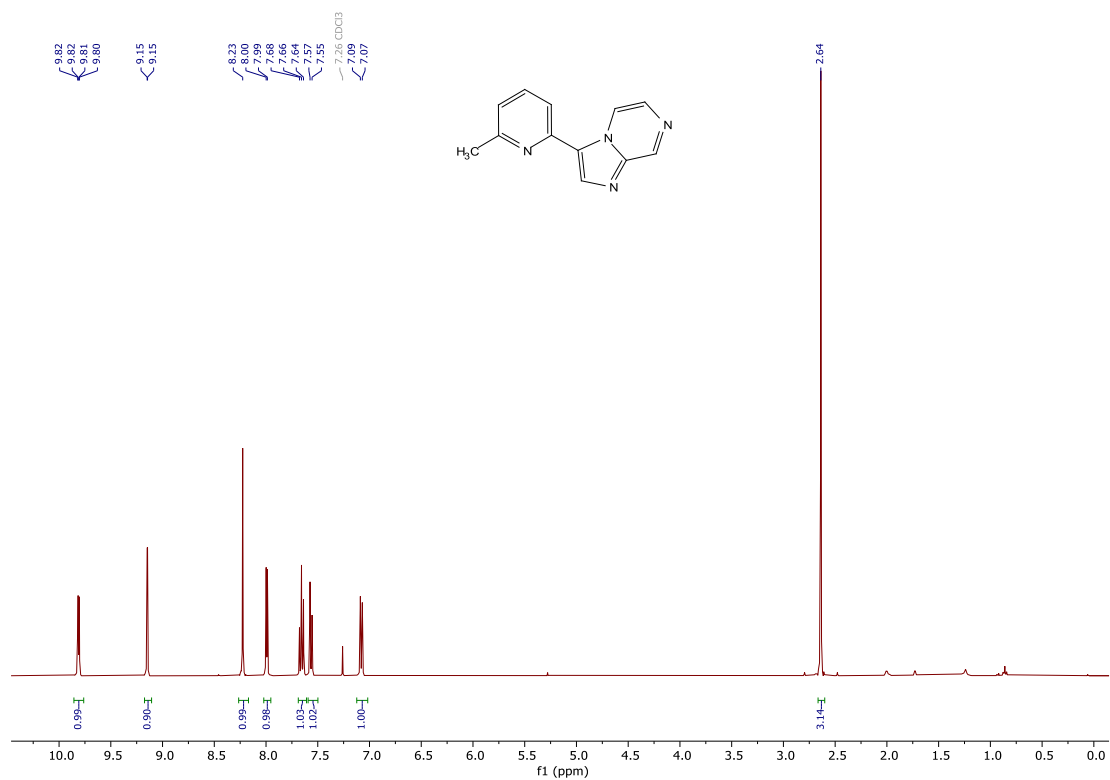


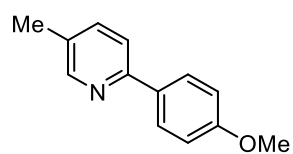
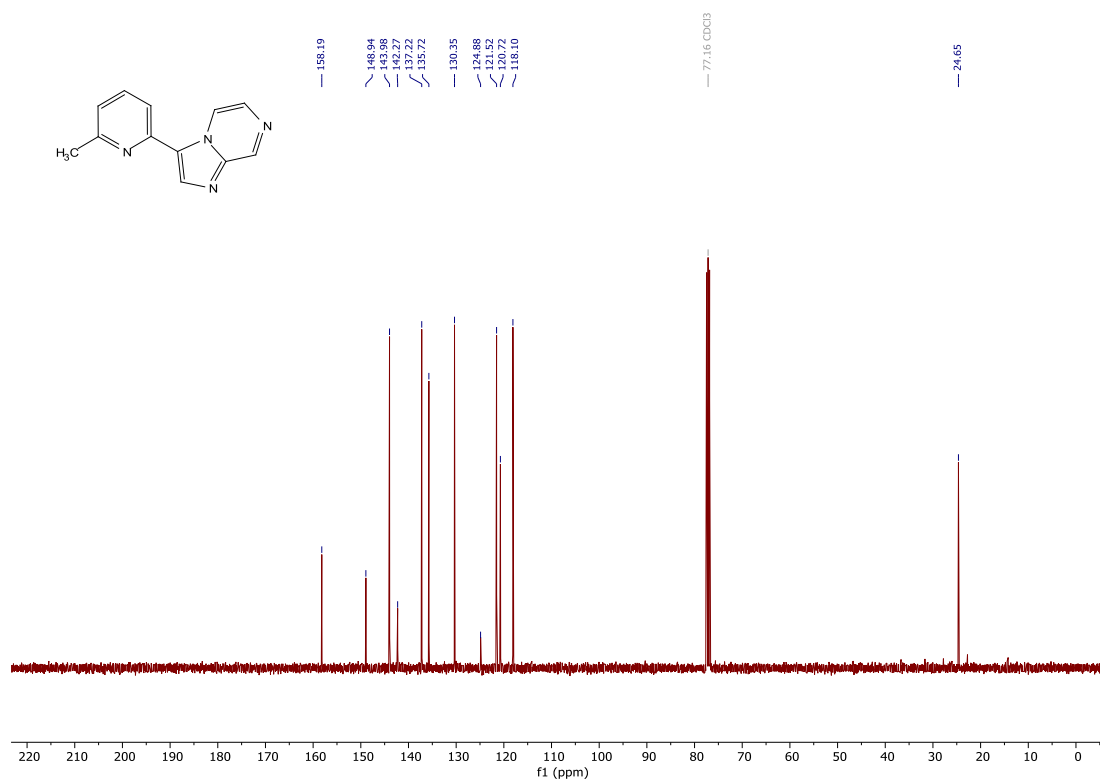
2-methoxy-5-(6-methylpyridin-2-yl)pyrimidine (4v)



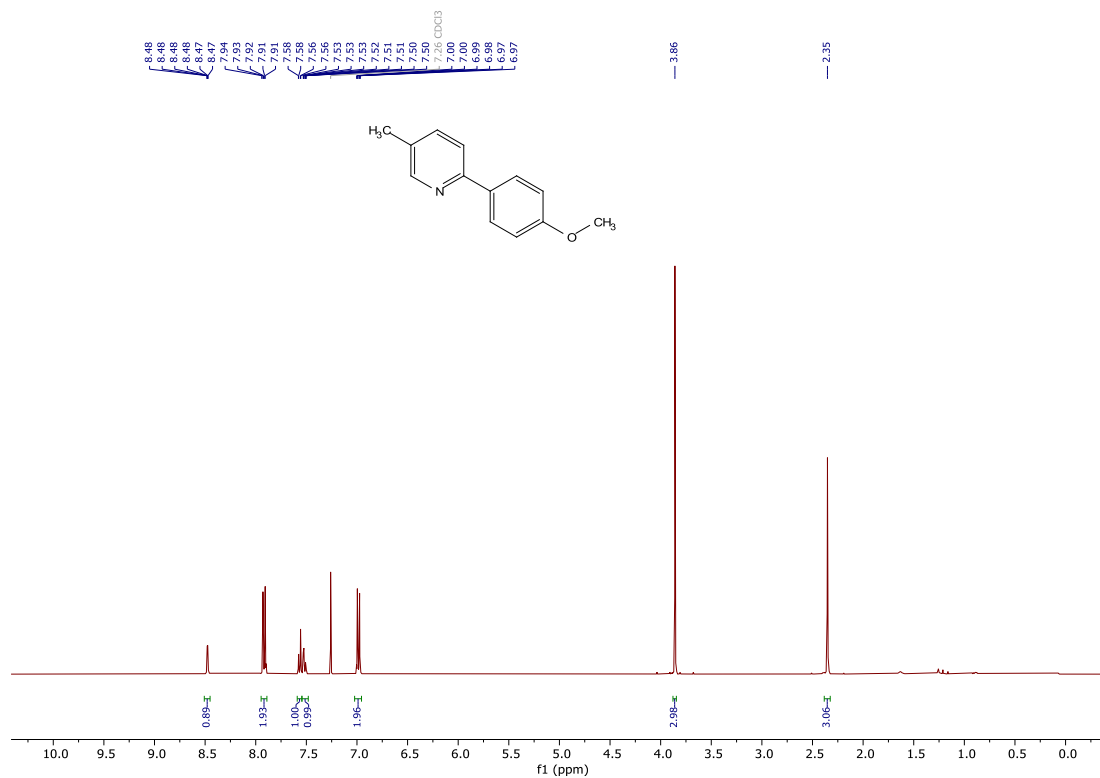


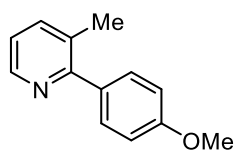
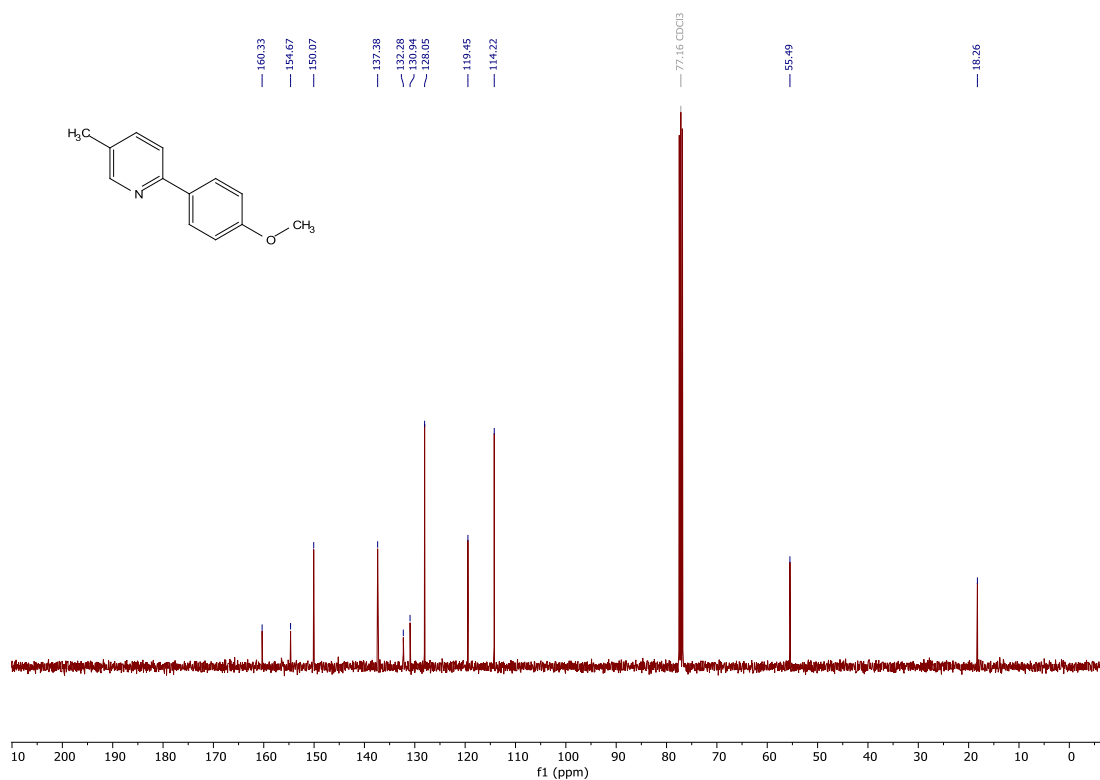
3-(6-methylpyridin-2-yl)imidazo[1,2-a]pyrazine (4y)



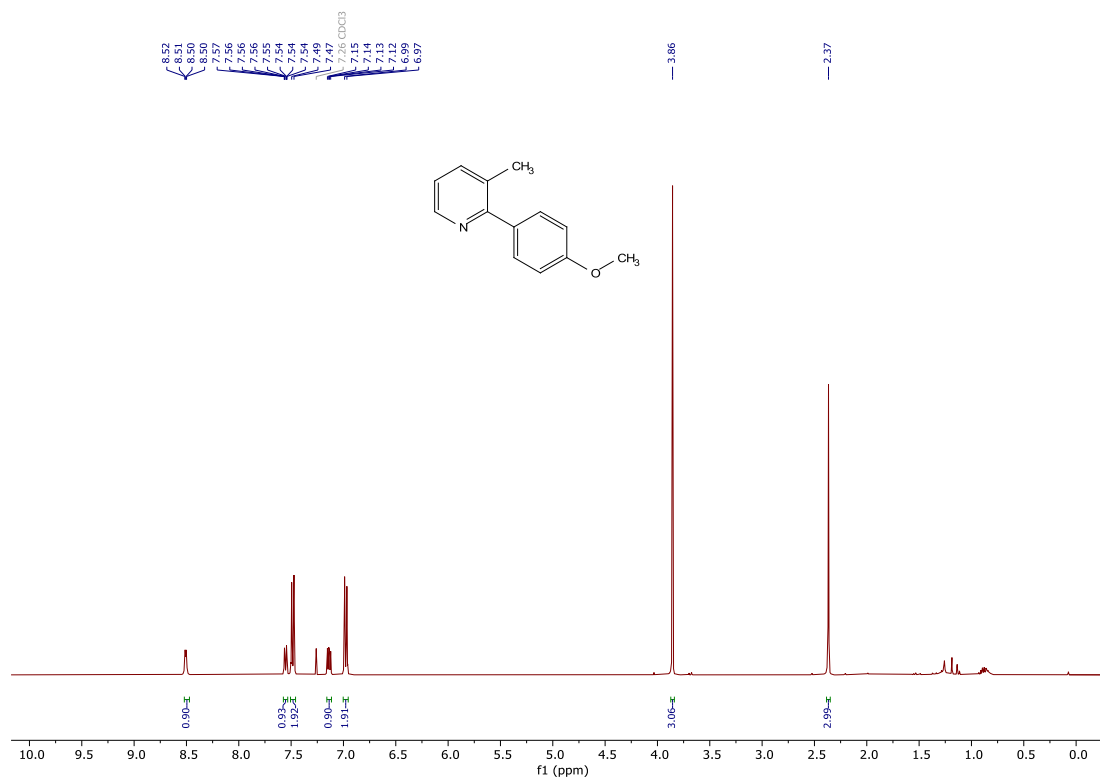


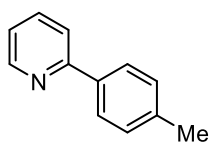
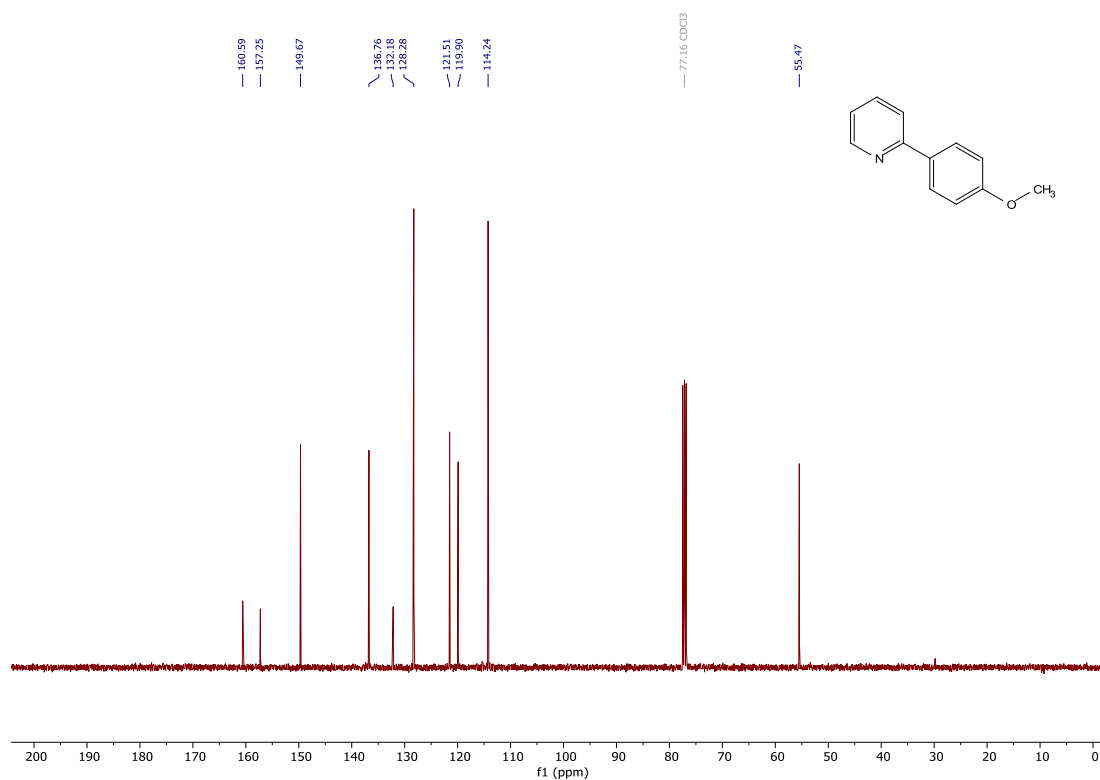
2-(4-methoxyphenyl)-5-methylpyridine (4z)



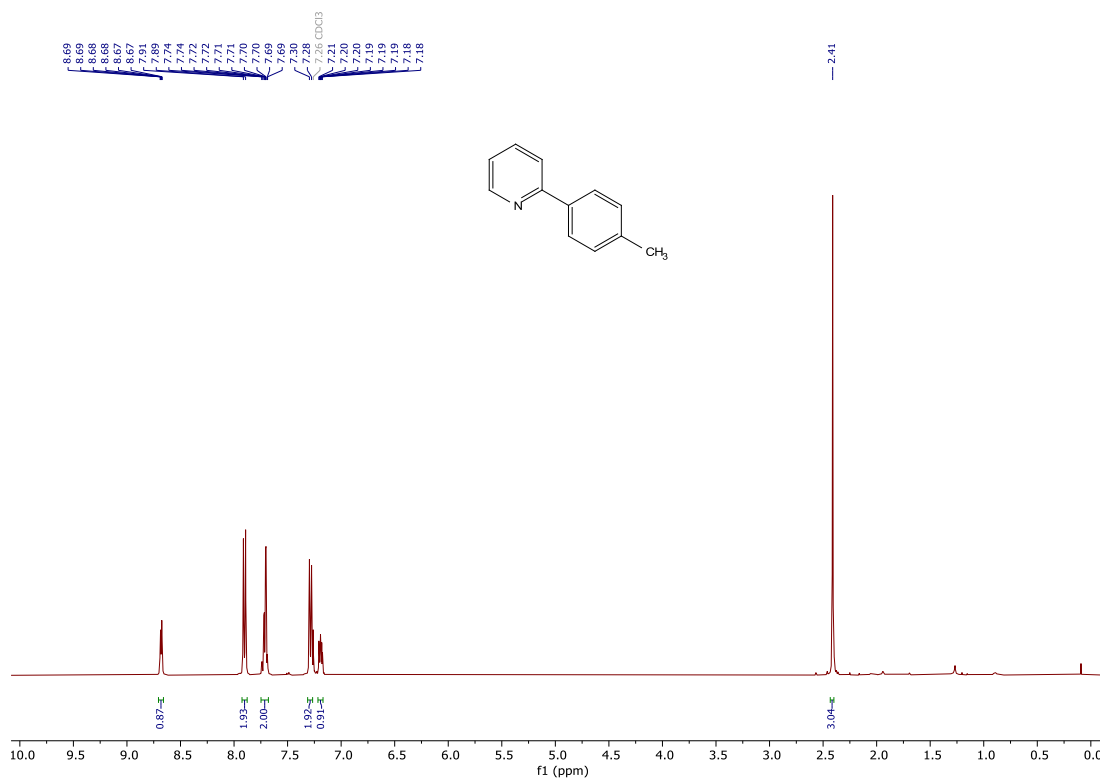


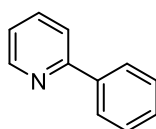
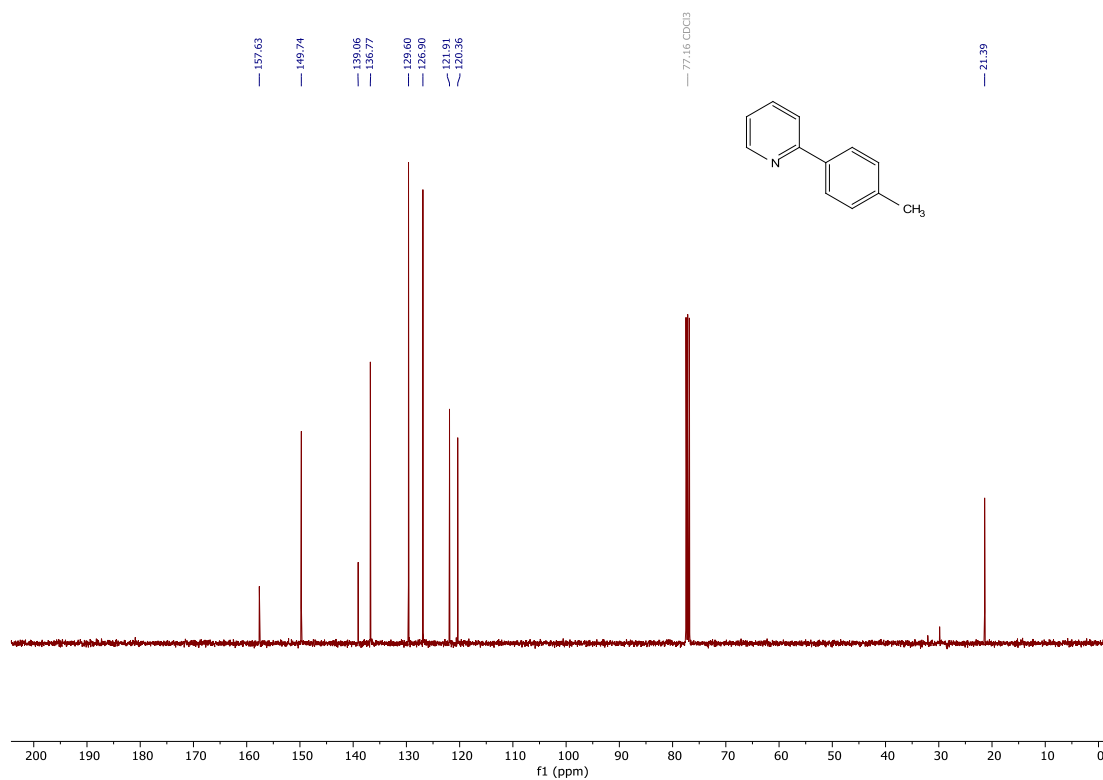
2-(4-methoxyphenyl)-3-methylpyridine (4aa)



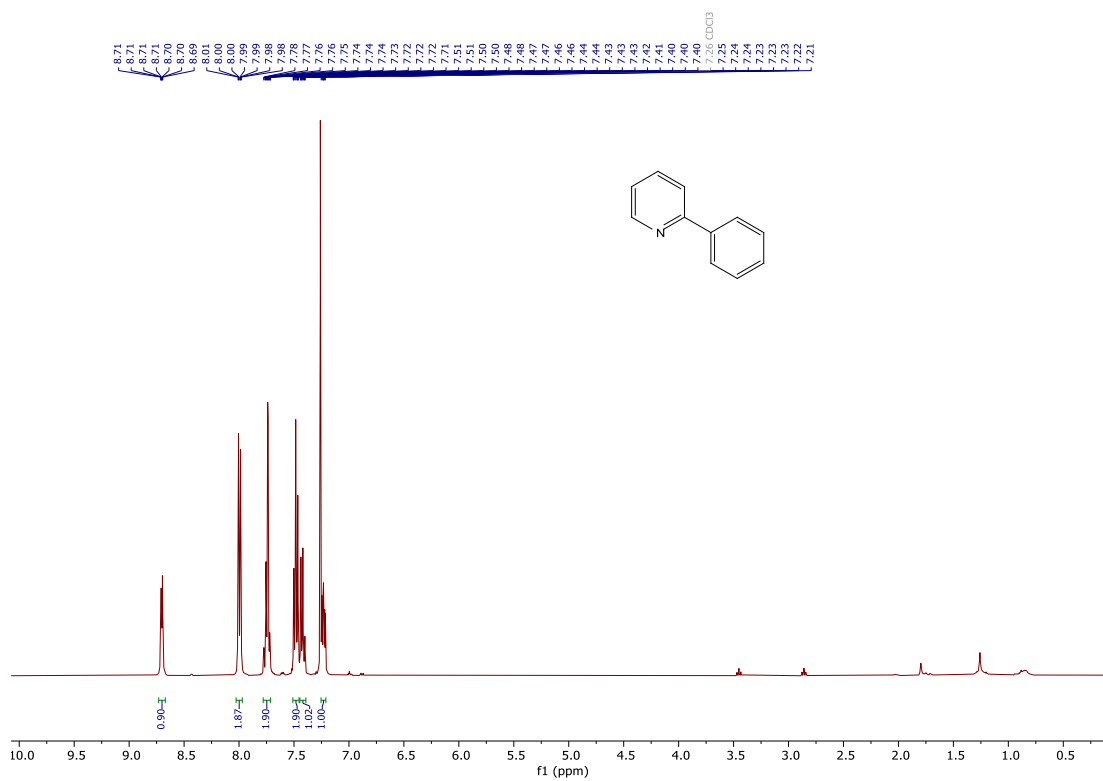


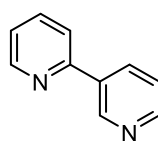
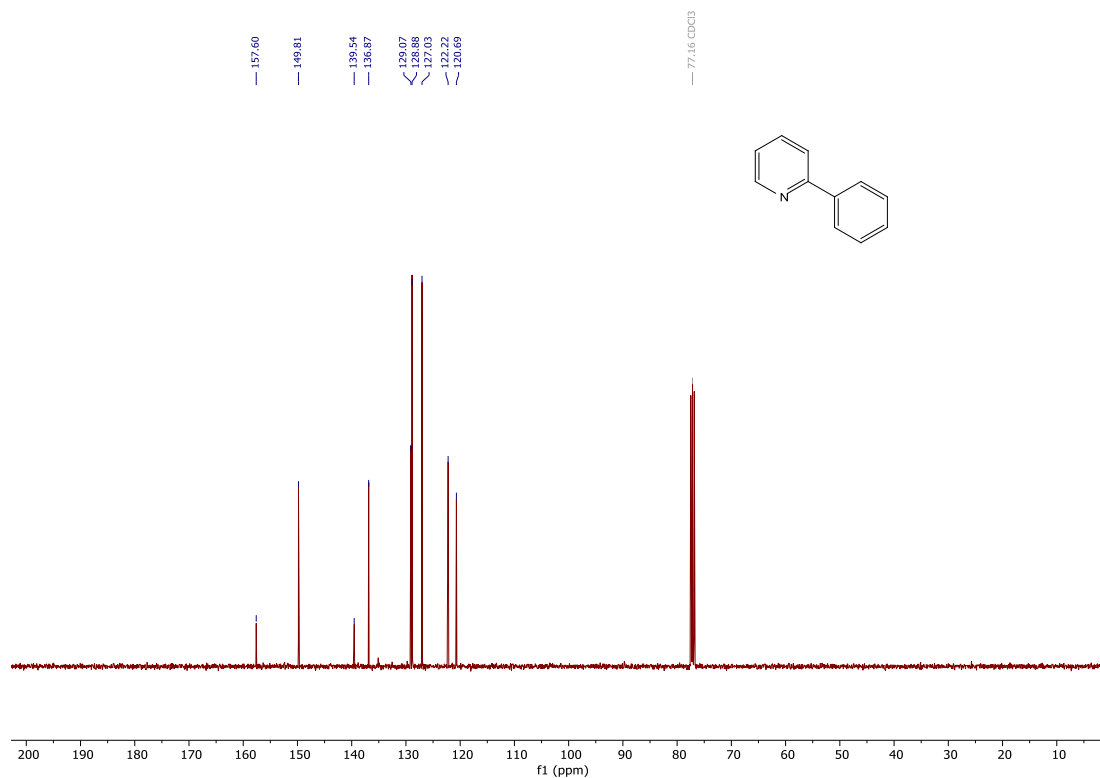
2-(p-tolyl)pyridine (4ac)



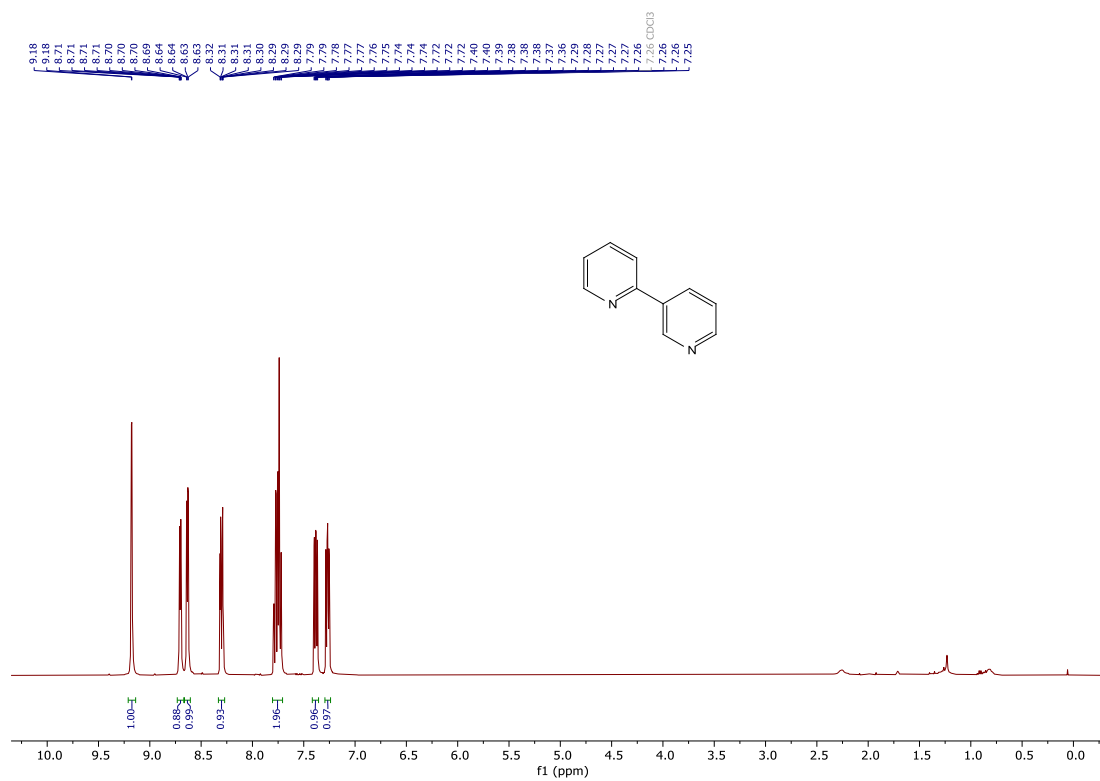


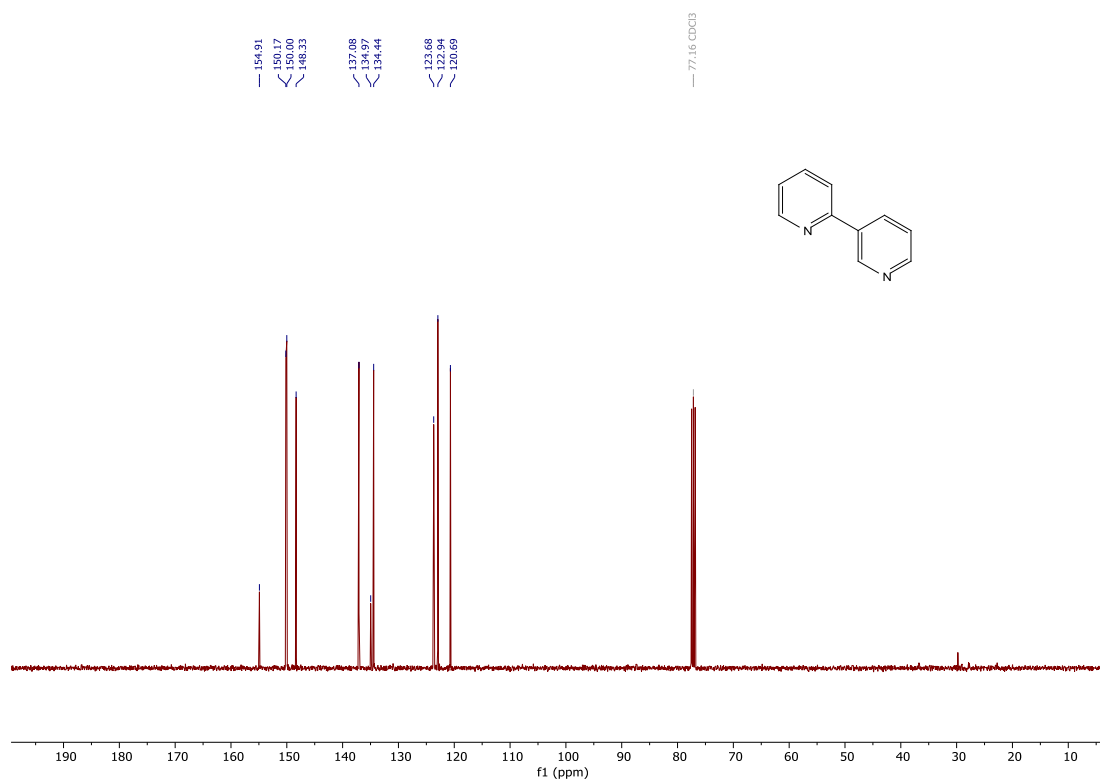
2-phenylpyridine (4ad)



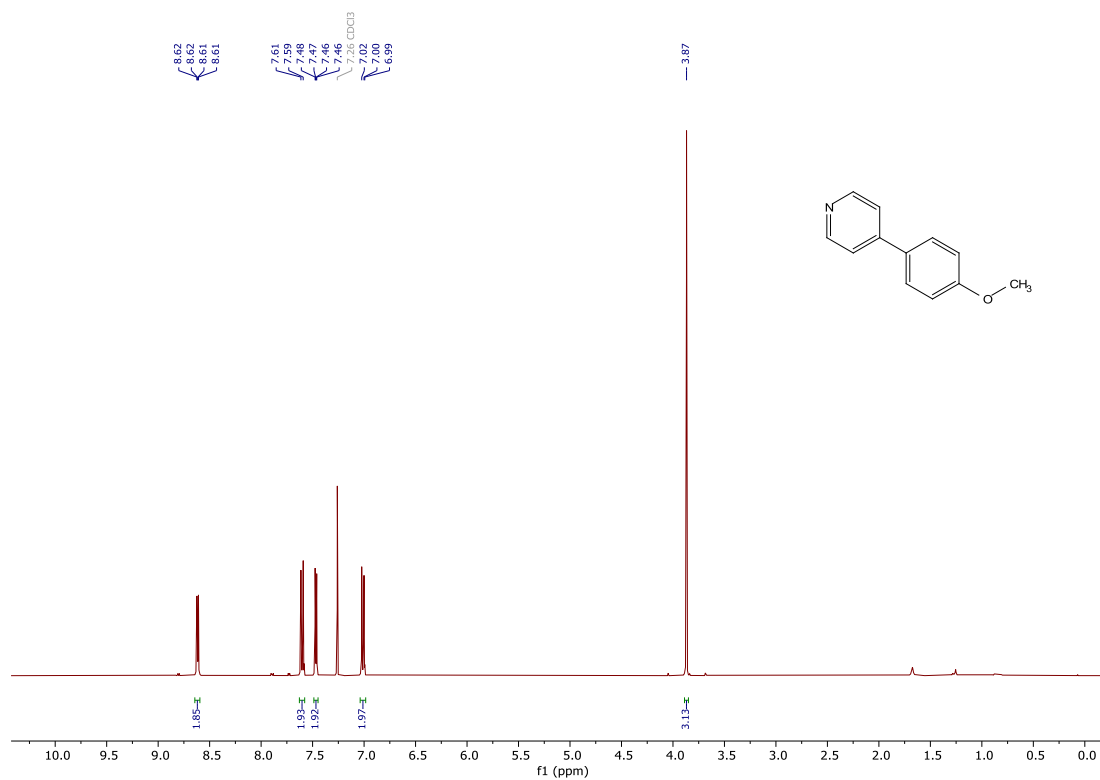


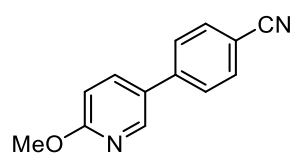
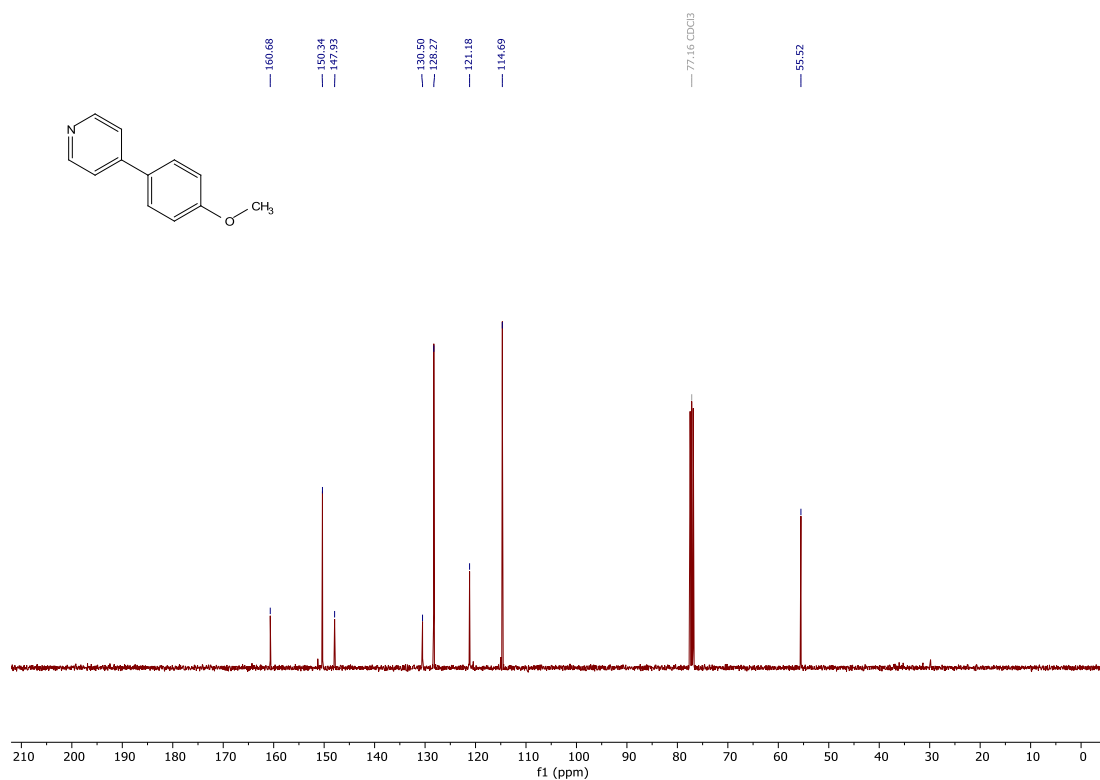
2,3'-bipyridine (4af)



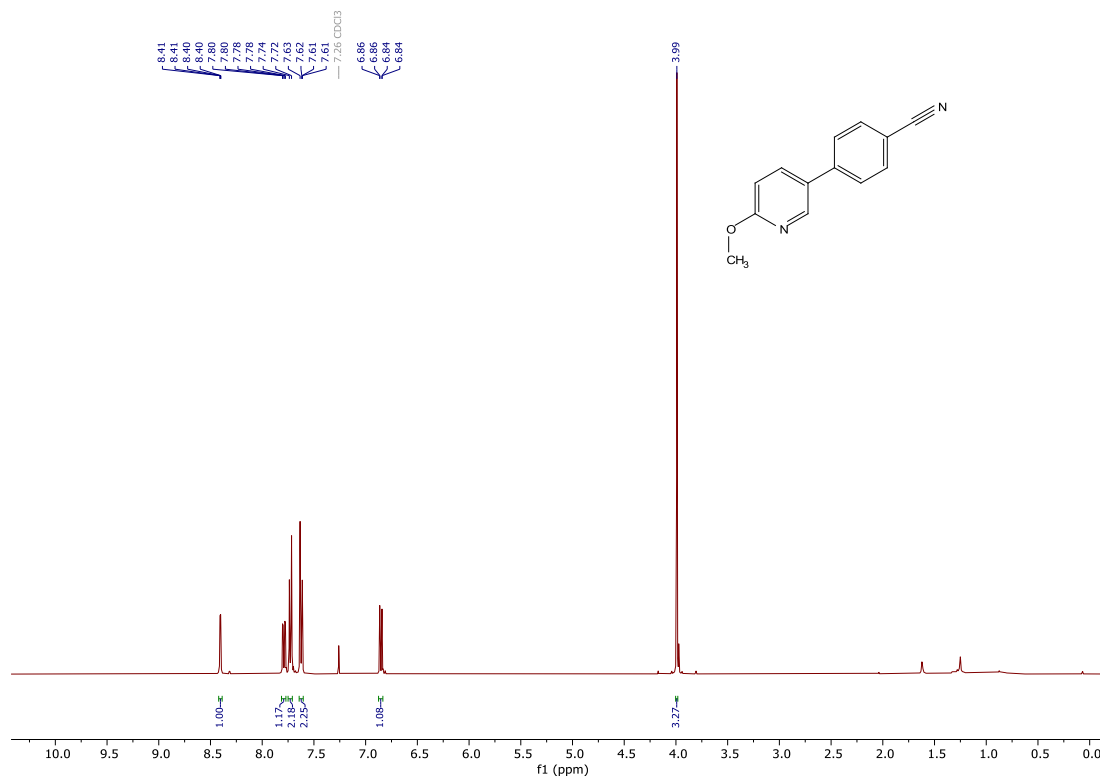


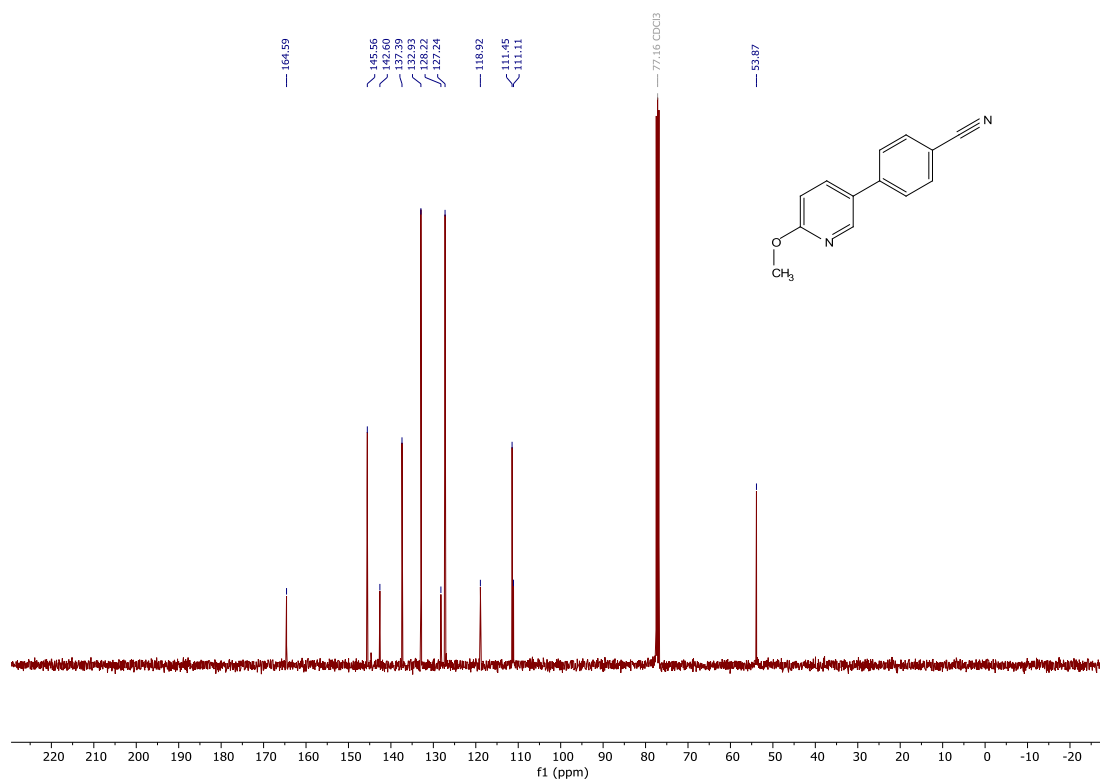
4-(4-methoxyphenyl)pyridine (4ag)



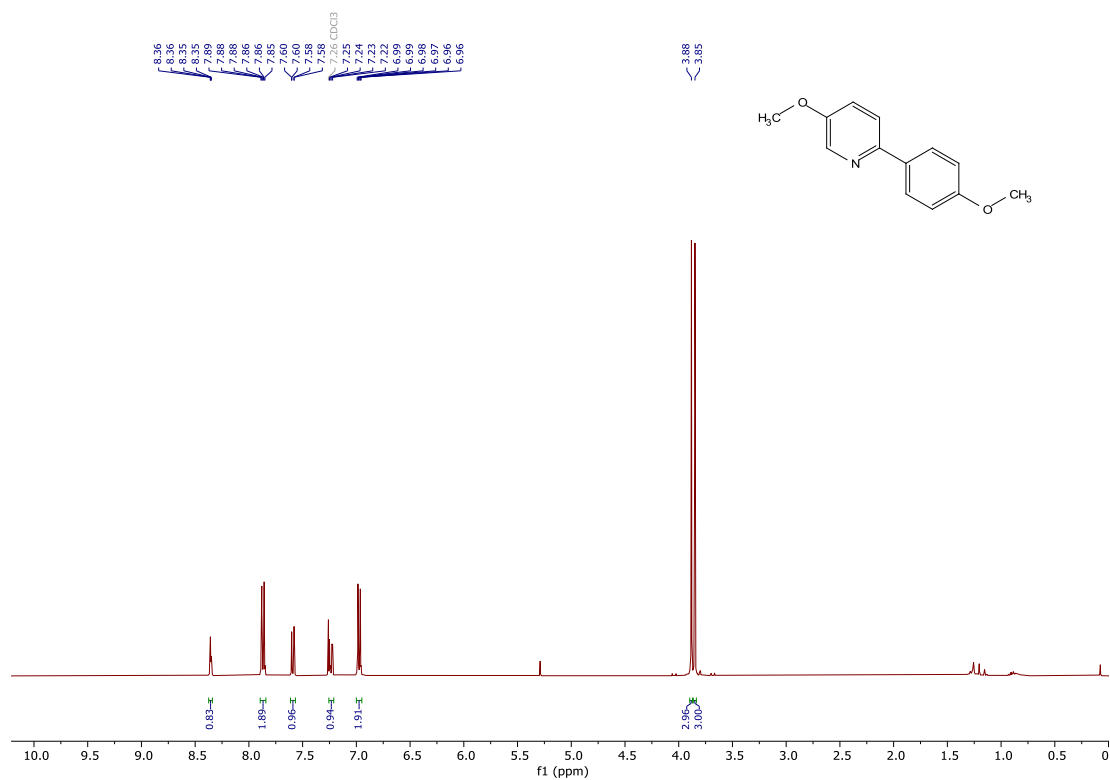


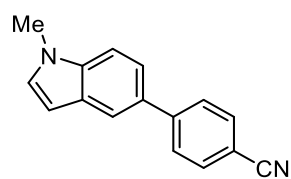
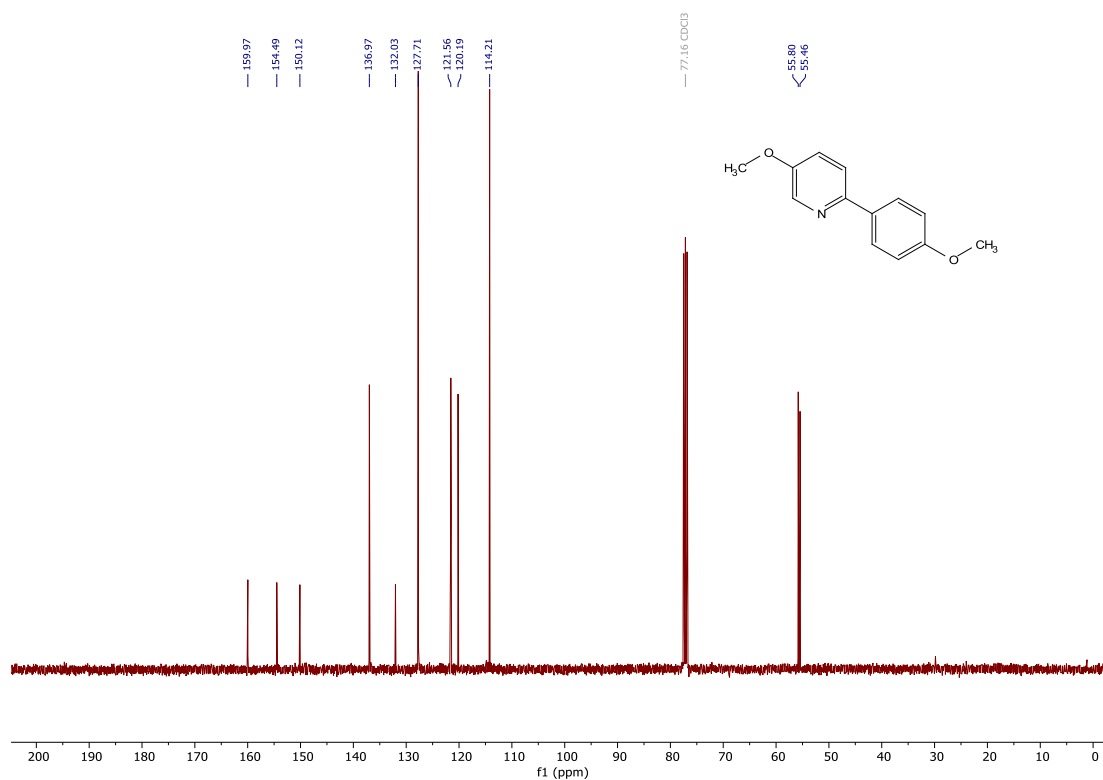
4-(6-methoxypyridin-3-yl)benzonitrile (4ah)



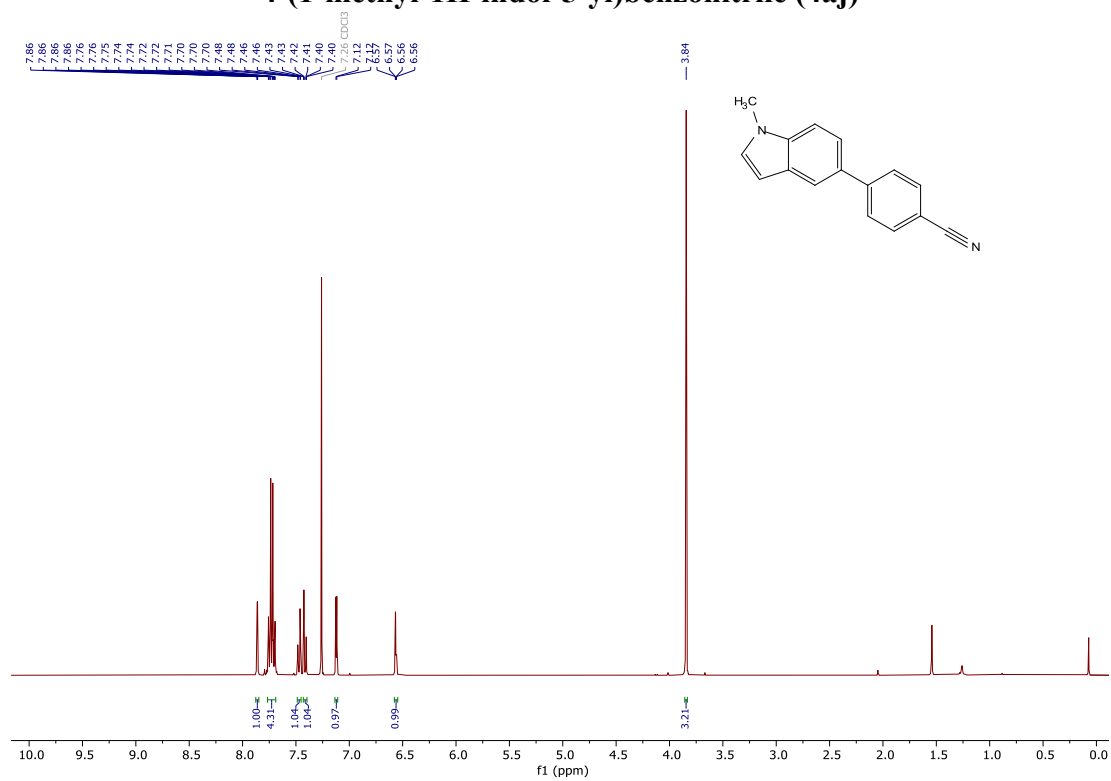


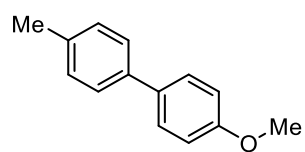
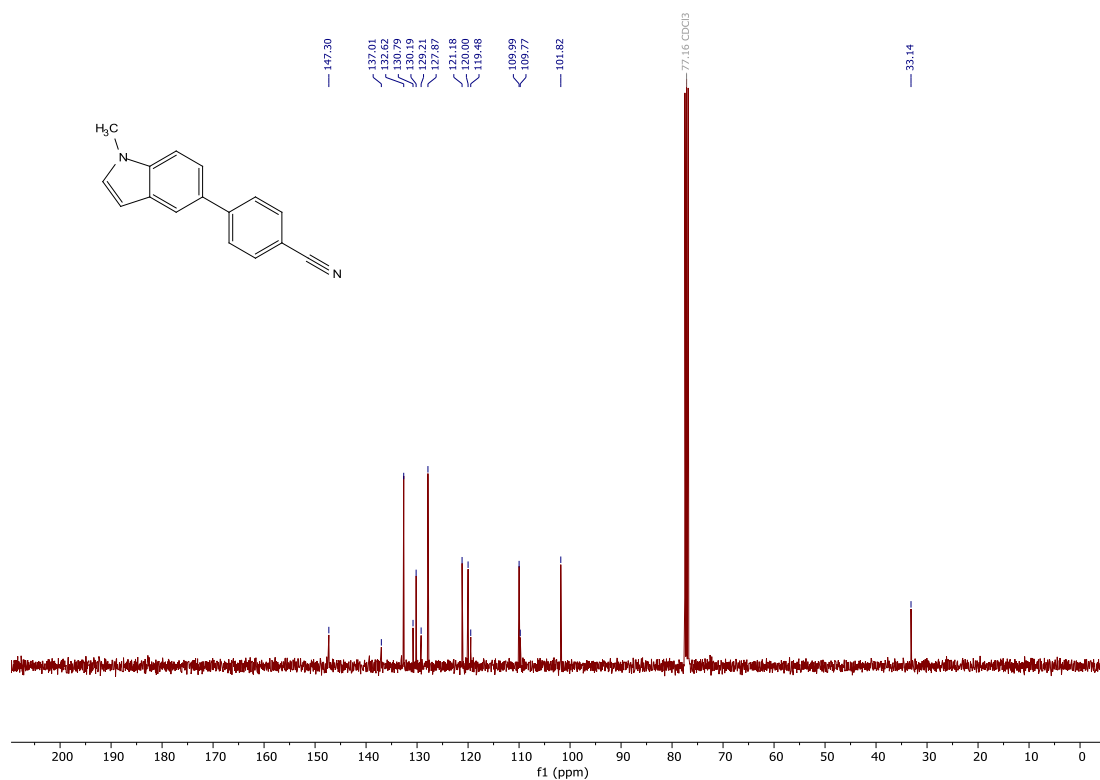
5-methoxy-2-(4-methoxyphenyl)pyridine (4ai)



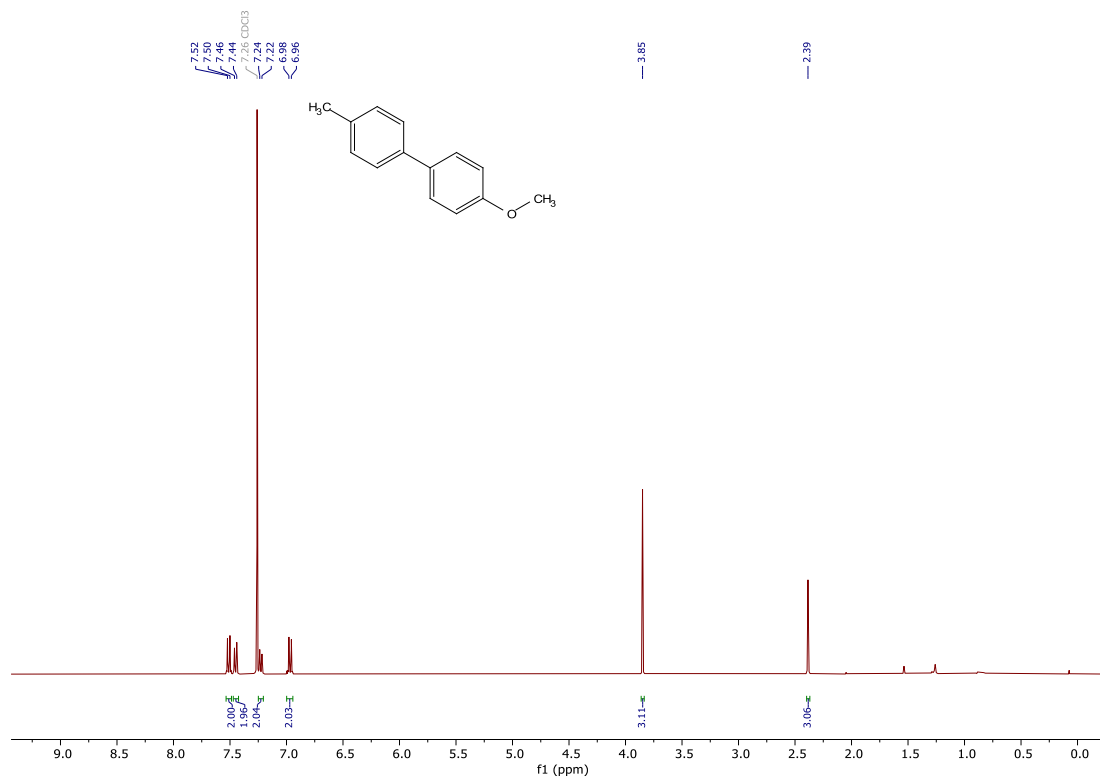


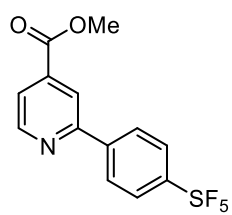
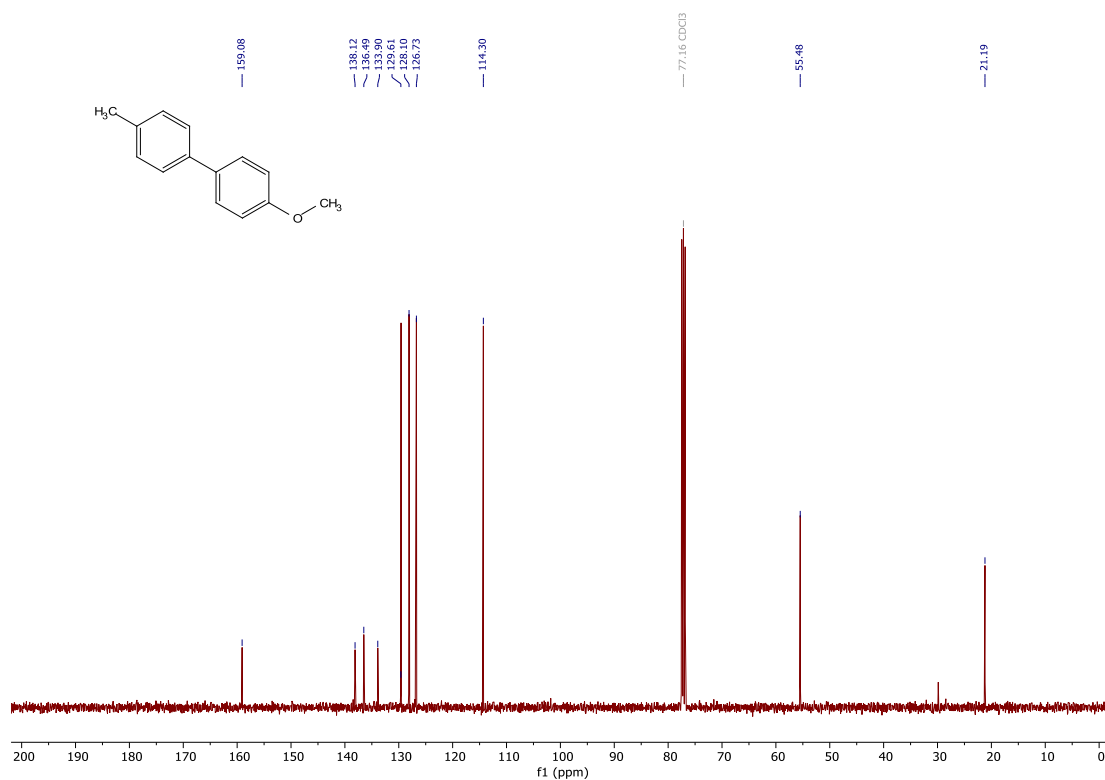
4-(1-methyl-1H-indol-5-yl)benzonitrile (4aj)



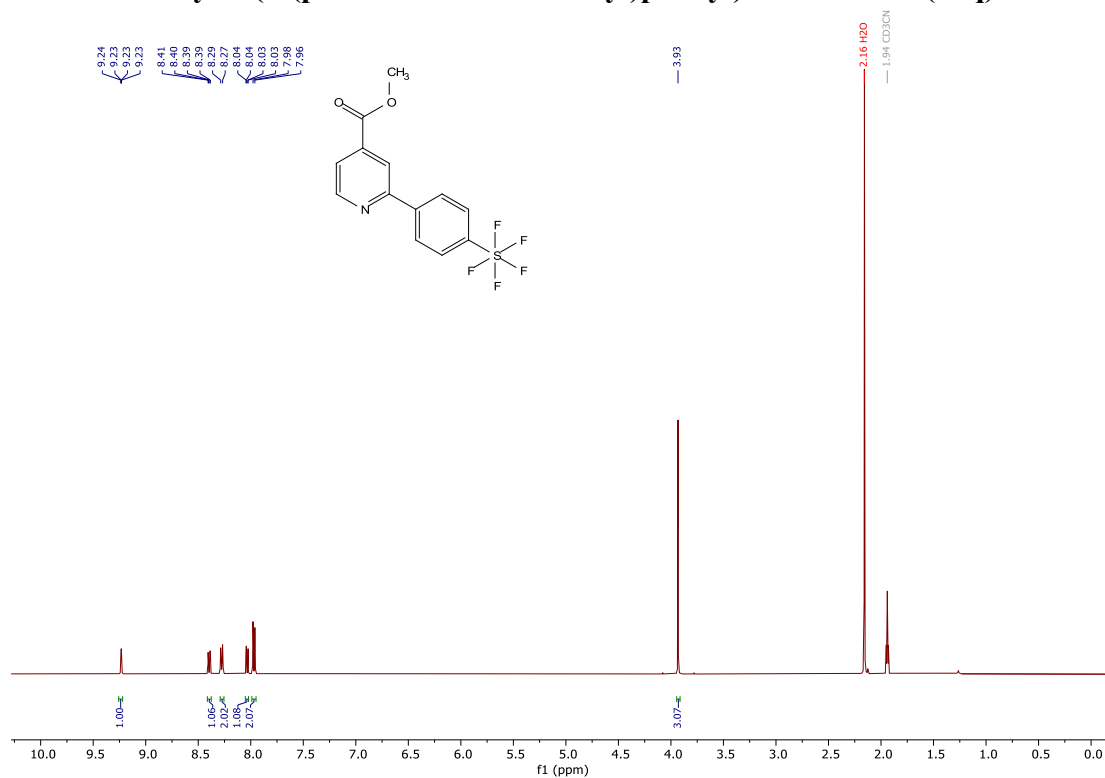


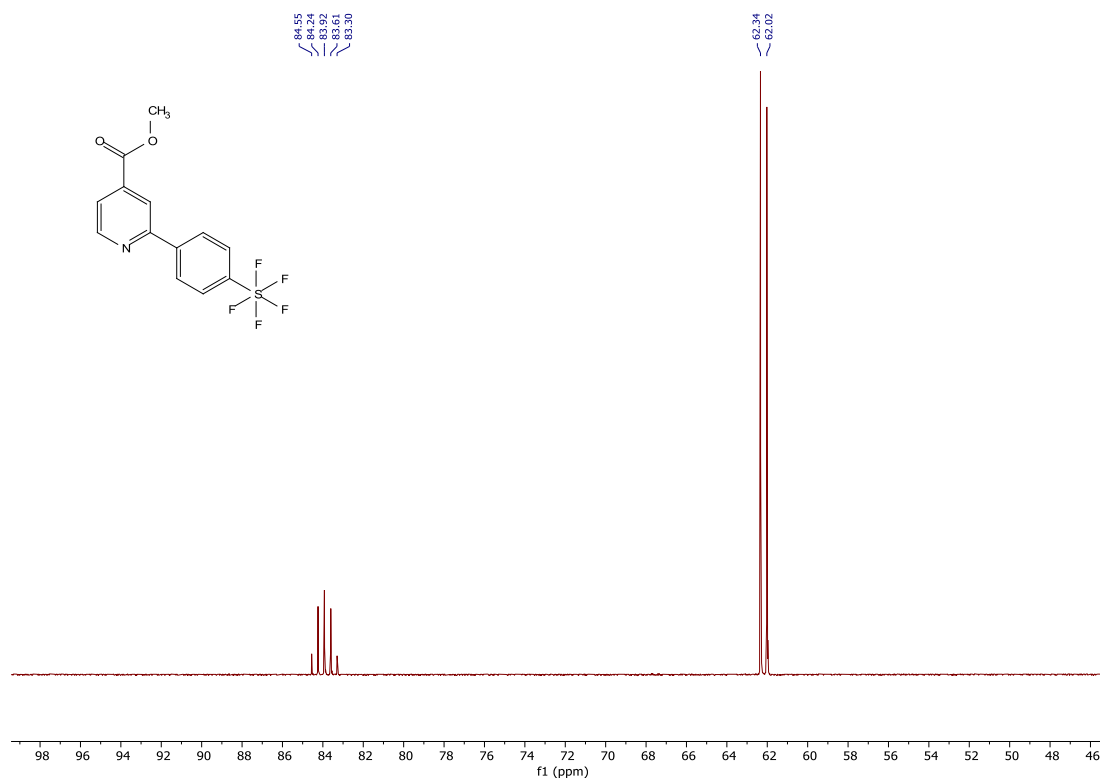
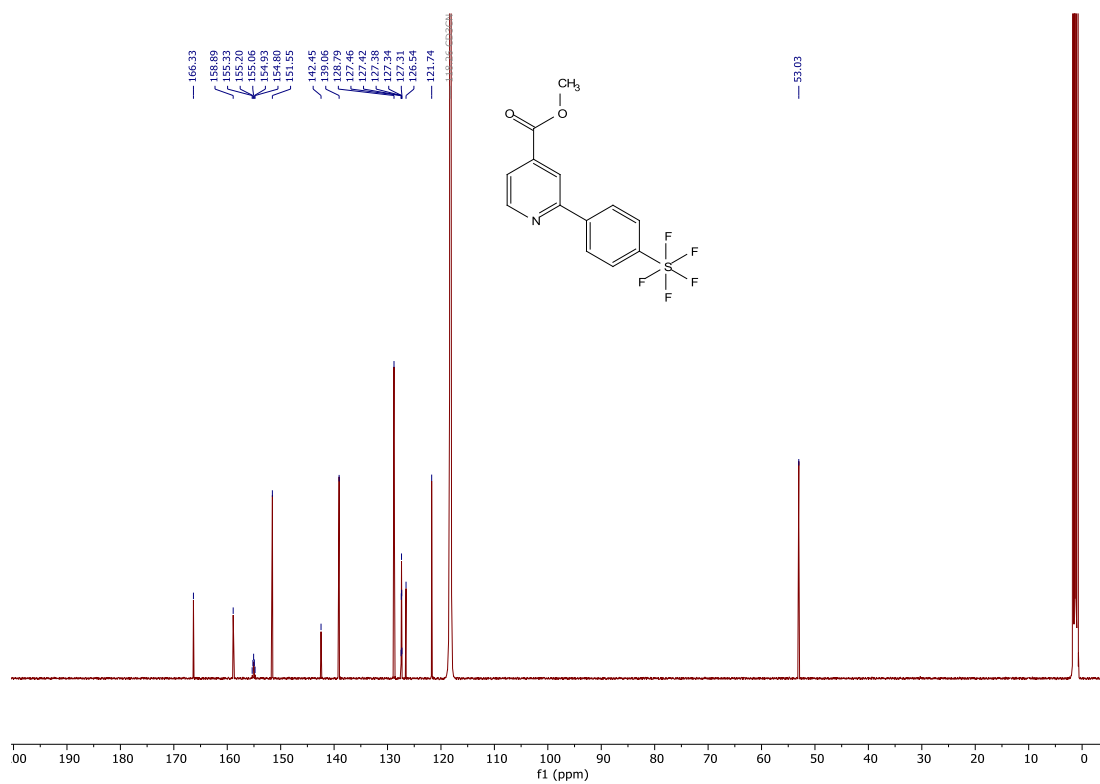
4-methoxy-4'-methyl-1,1'-biphenyl (4al)

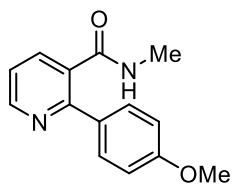




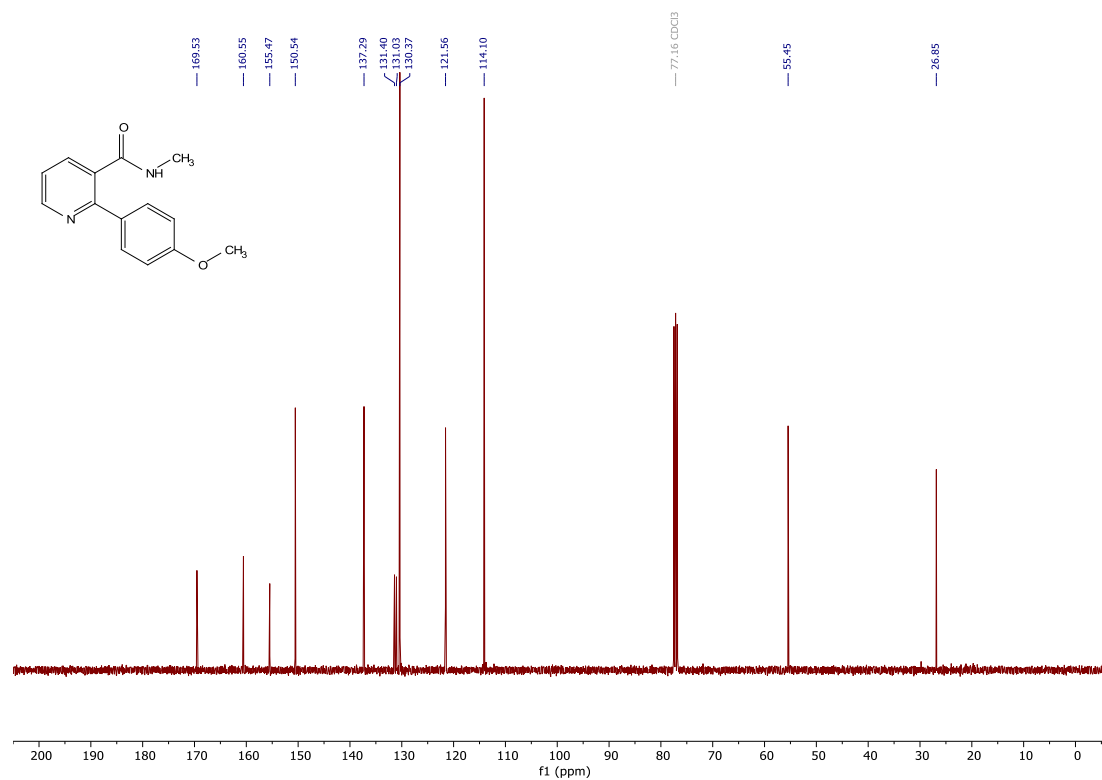
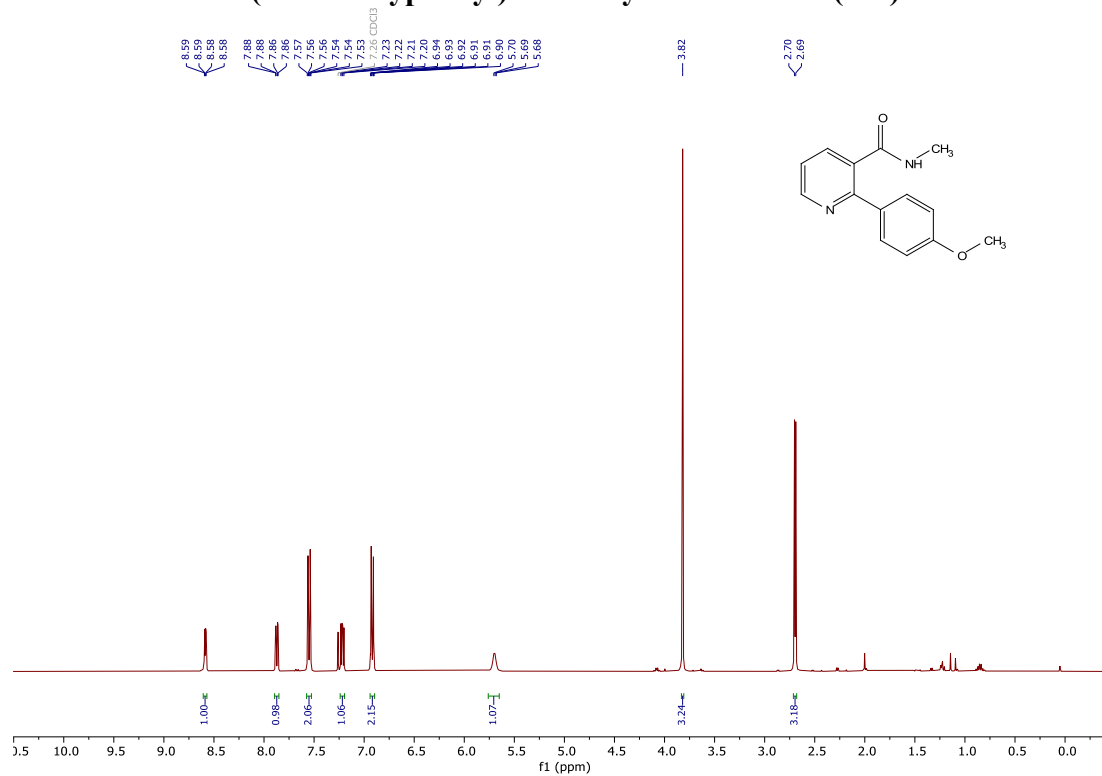
methyl 2-(4-(pentafluoro-1,6-sulfanyl)phenyl)isonicotinate (4aq)

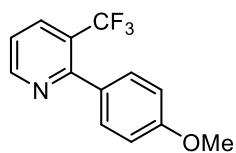




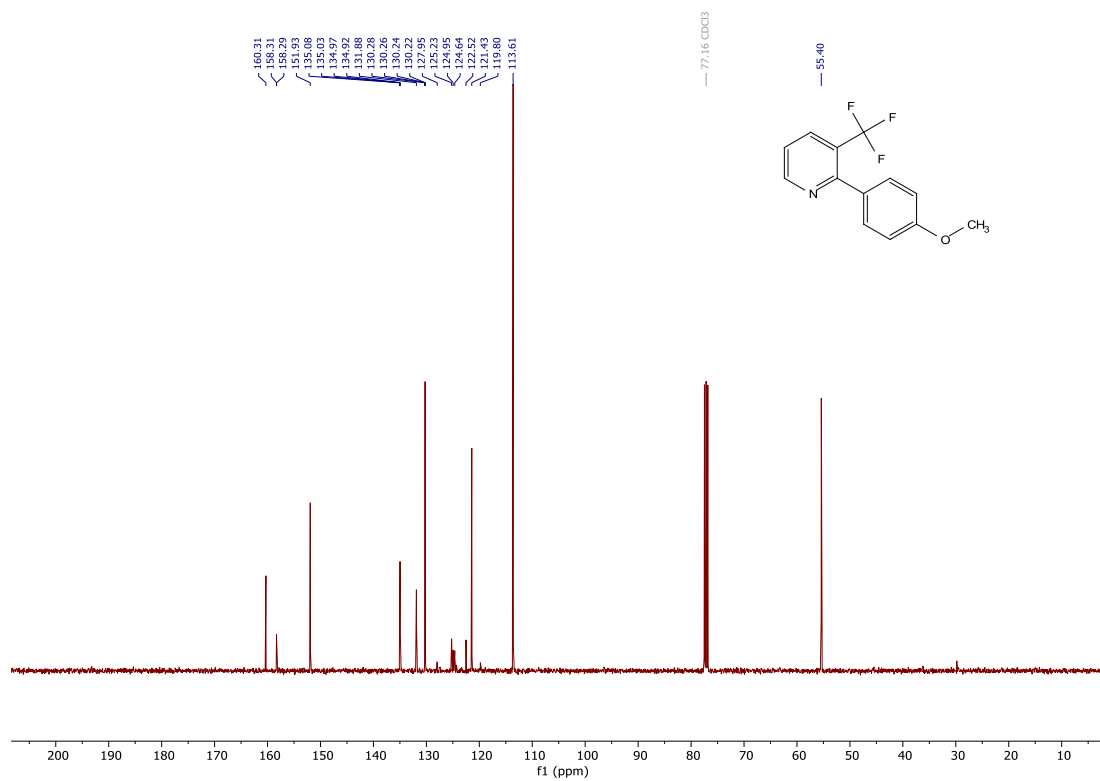
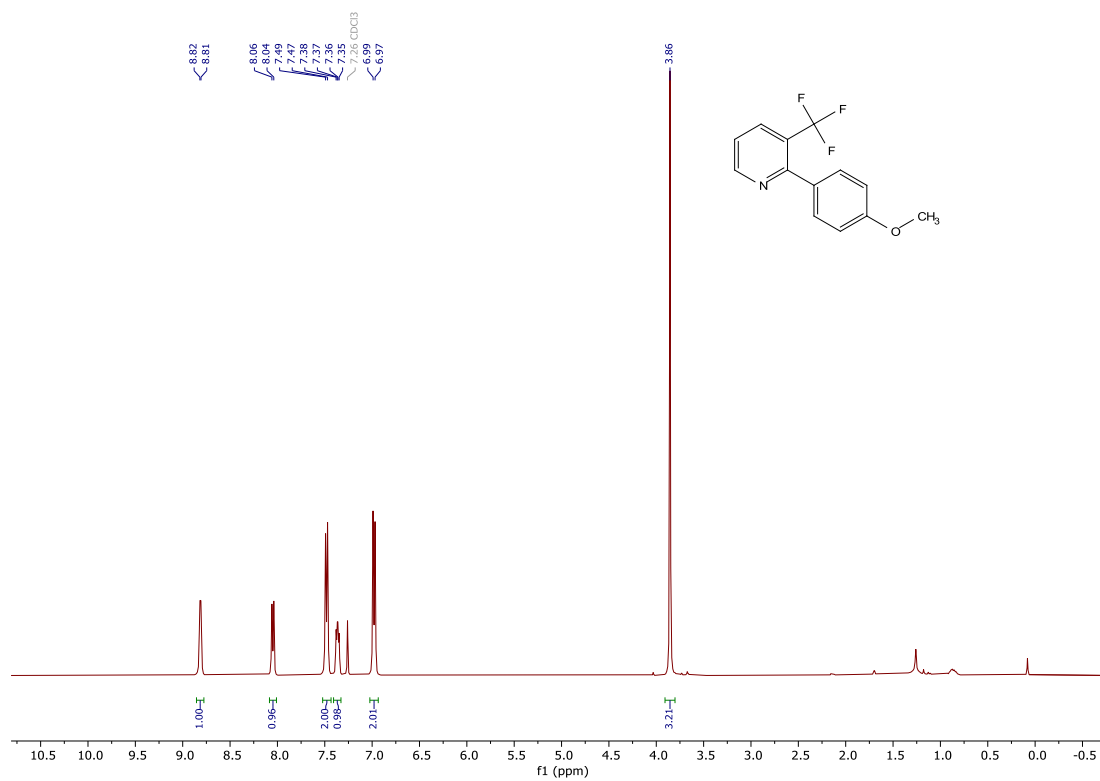


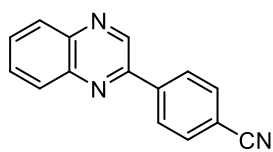
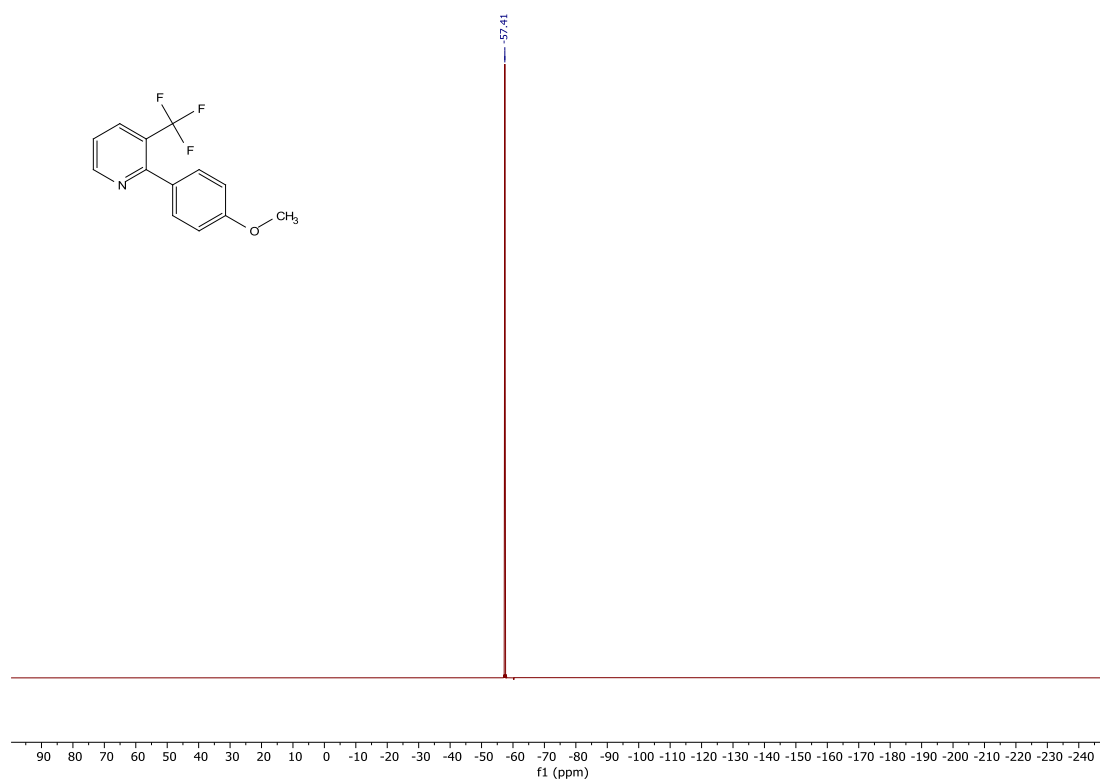
2-(4-methoxyphenyl)-N-methylnicotinamide (4ar)



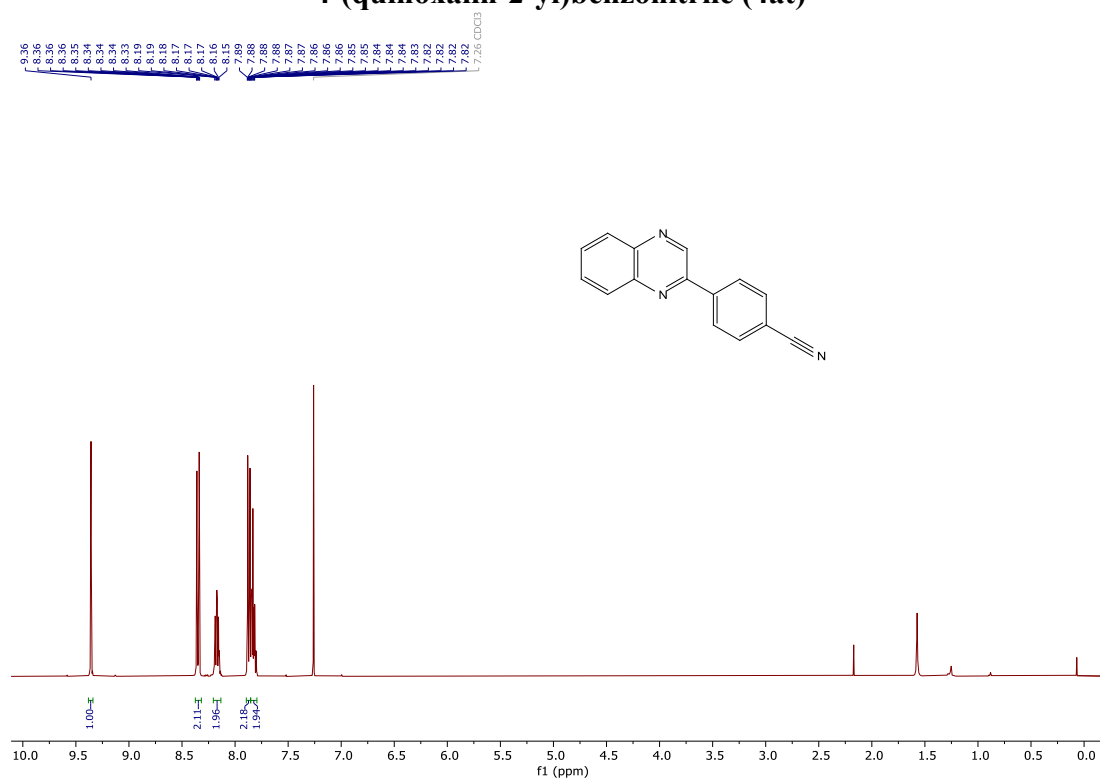


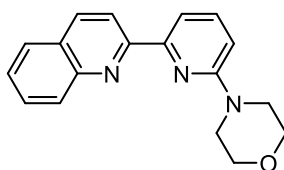
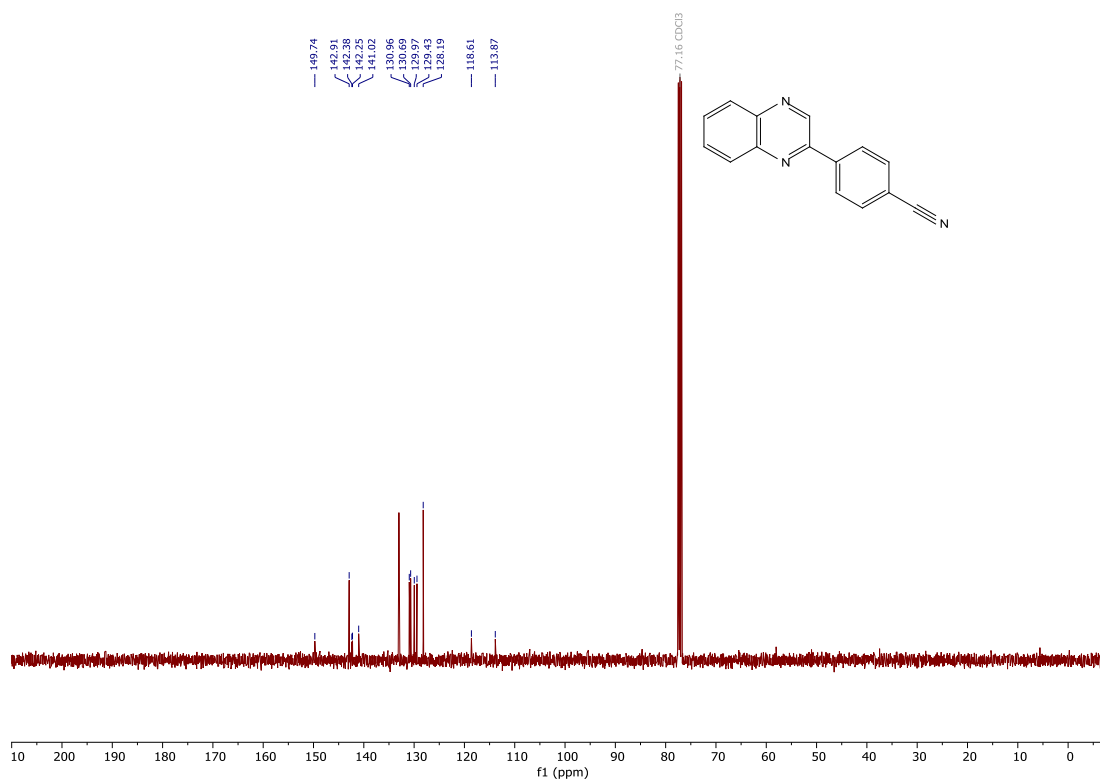
2-(4-methoxyphenyl)-3-(trifluoromethyl)pyridine (4as)



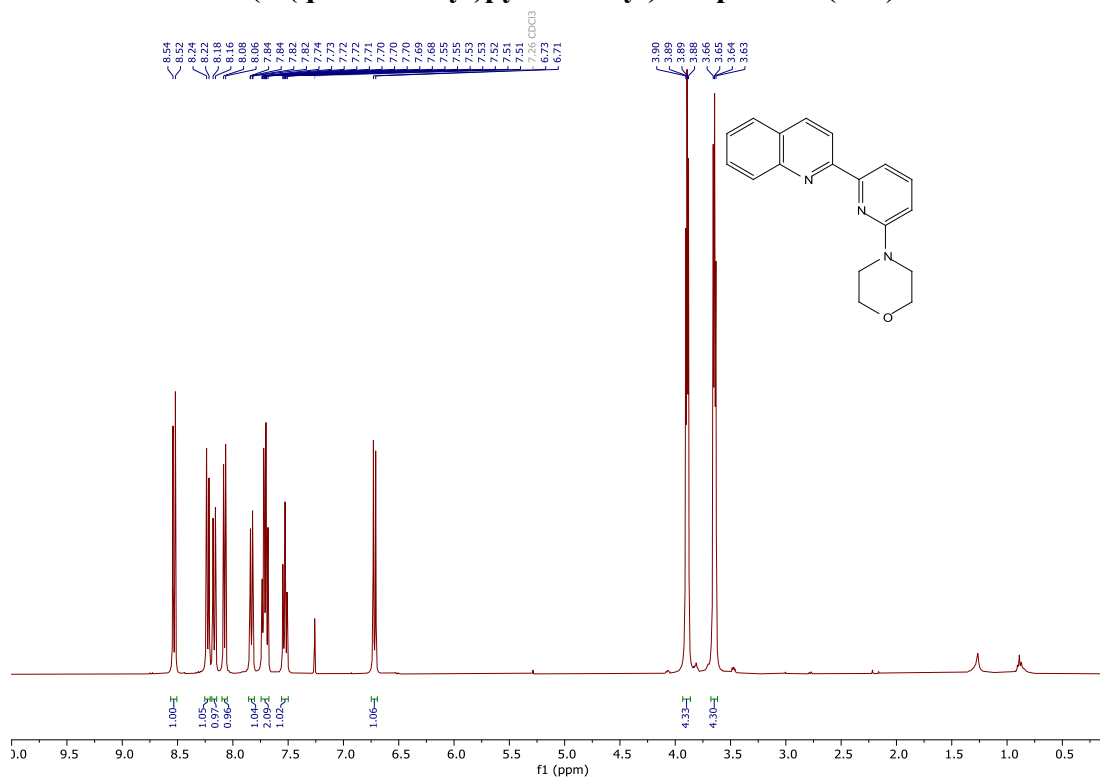


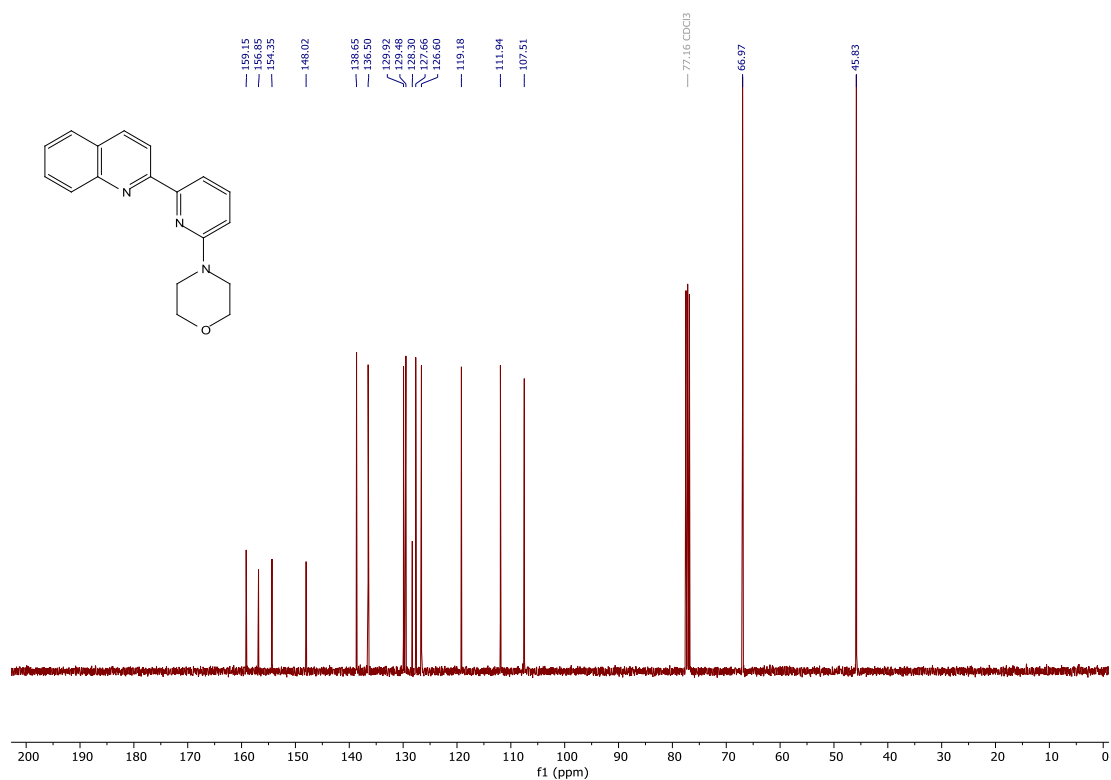
4-(quinoxalin-2-yl)benzonitrile (4at)



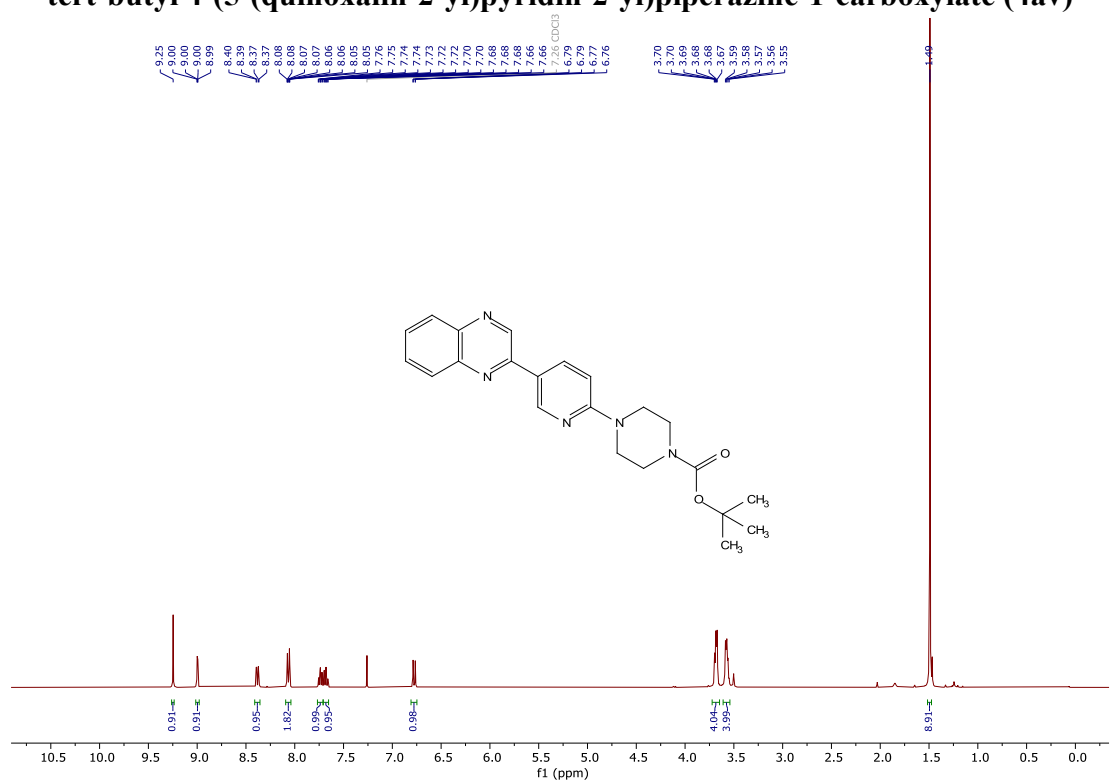


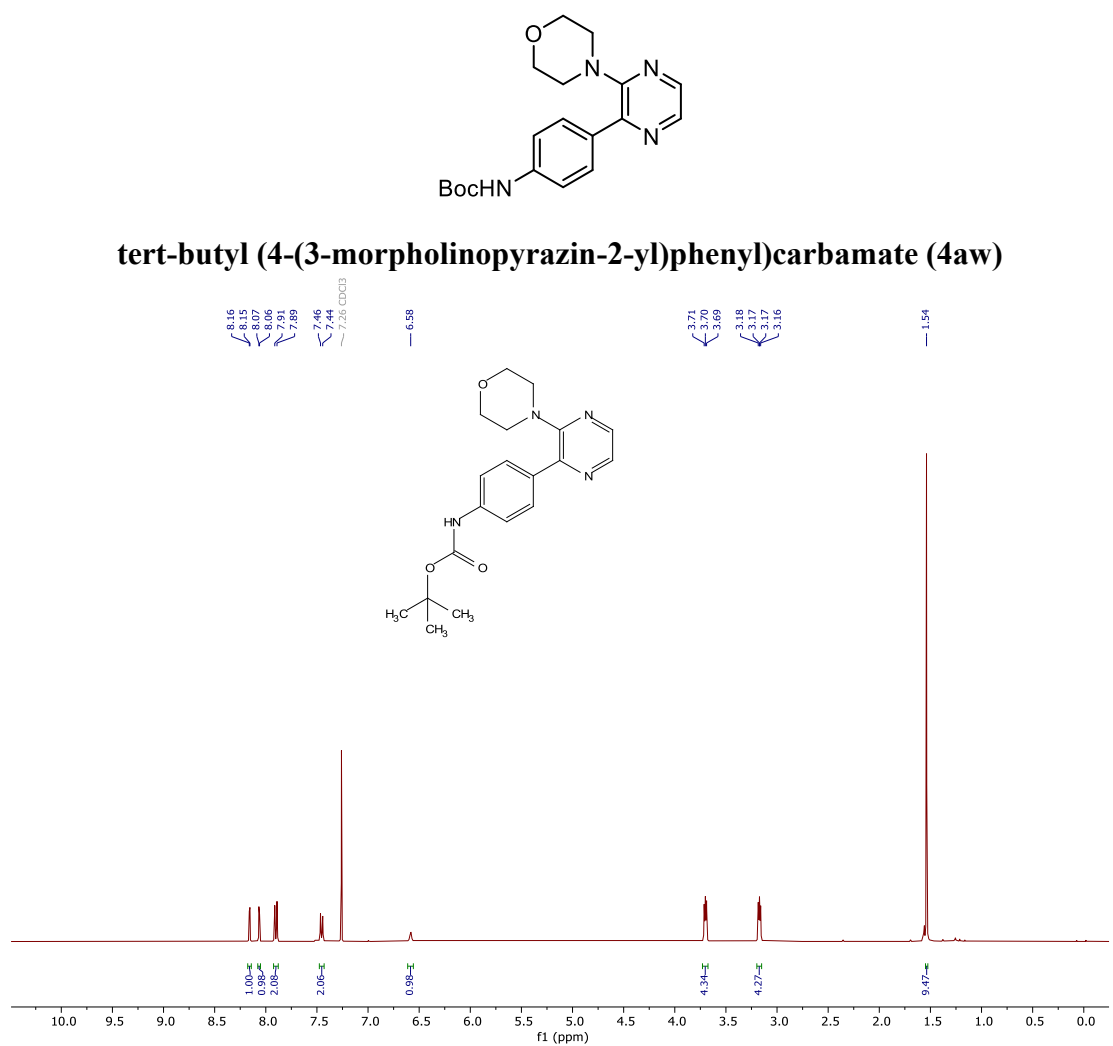
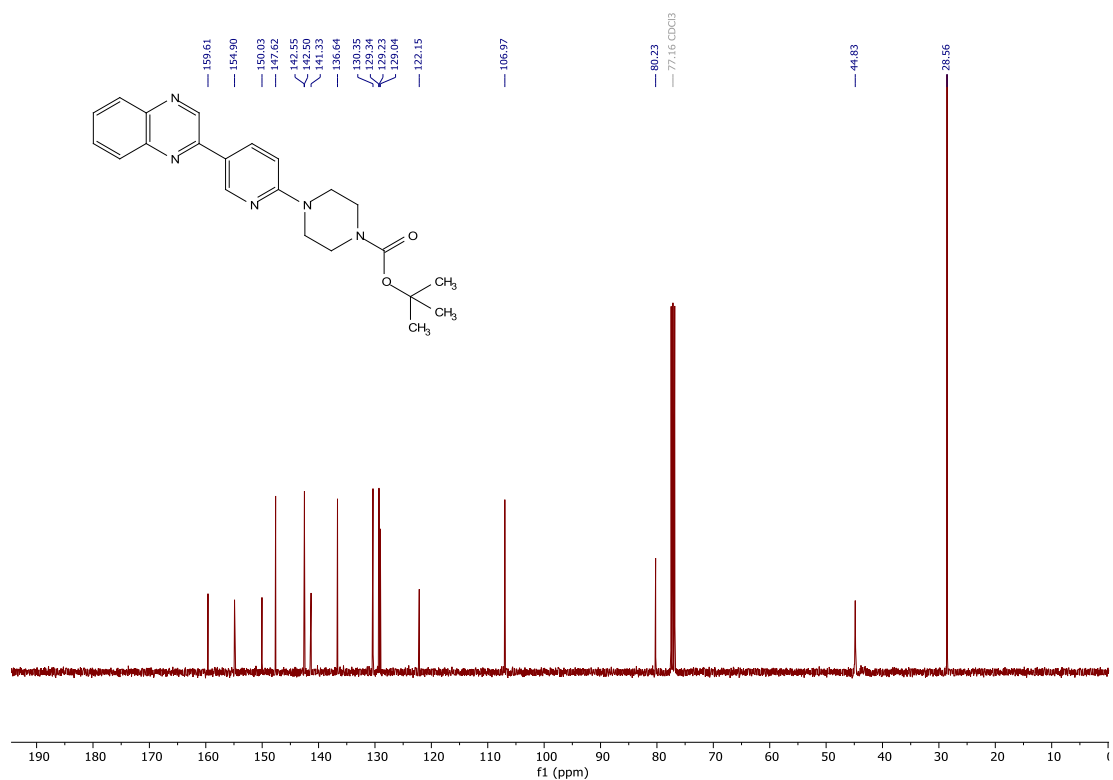
4-(6-(quinolin-2-yl)pyridin-2-yl)morpholine (4au)

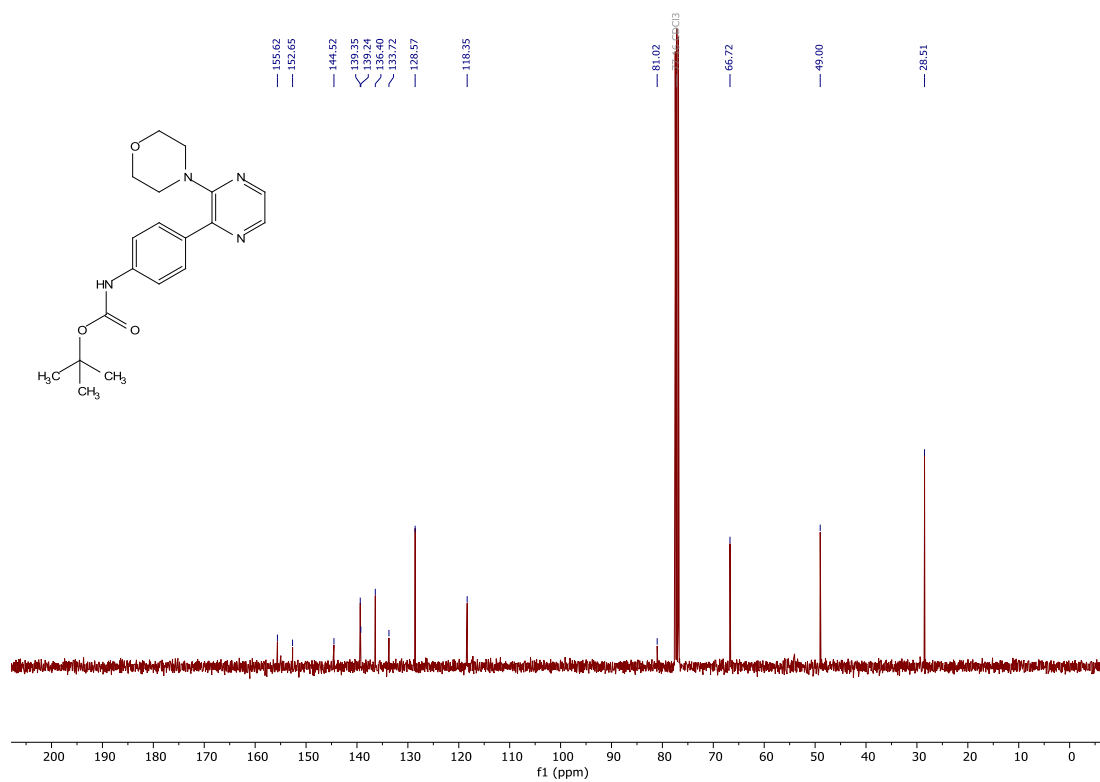




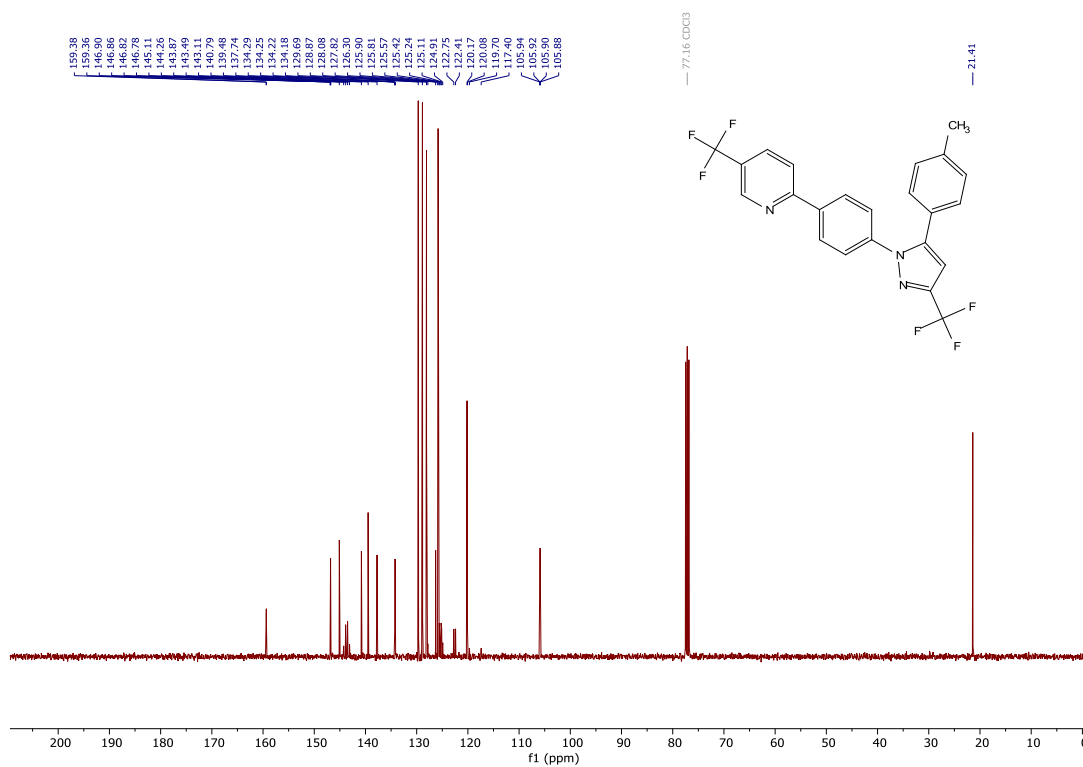
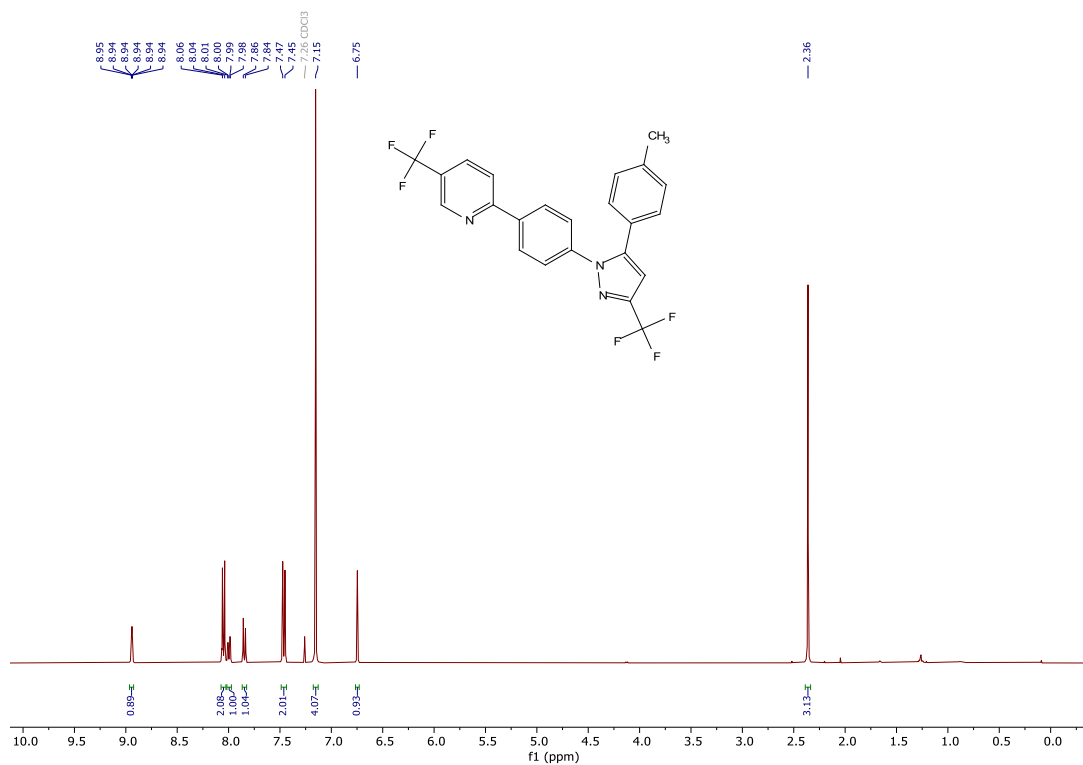
tert-butyl 4-(5-(quinoxalin-2-yl)pyridin-2-yl)piperazine-1-carboxylate (4av)



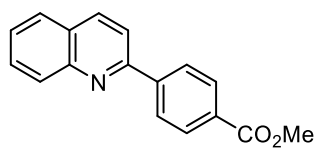




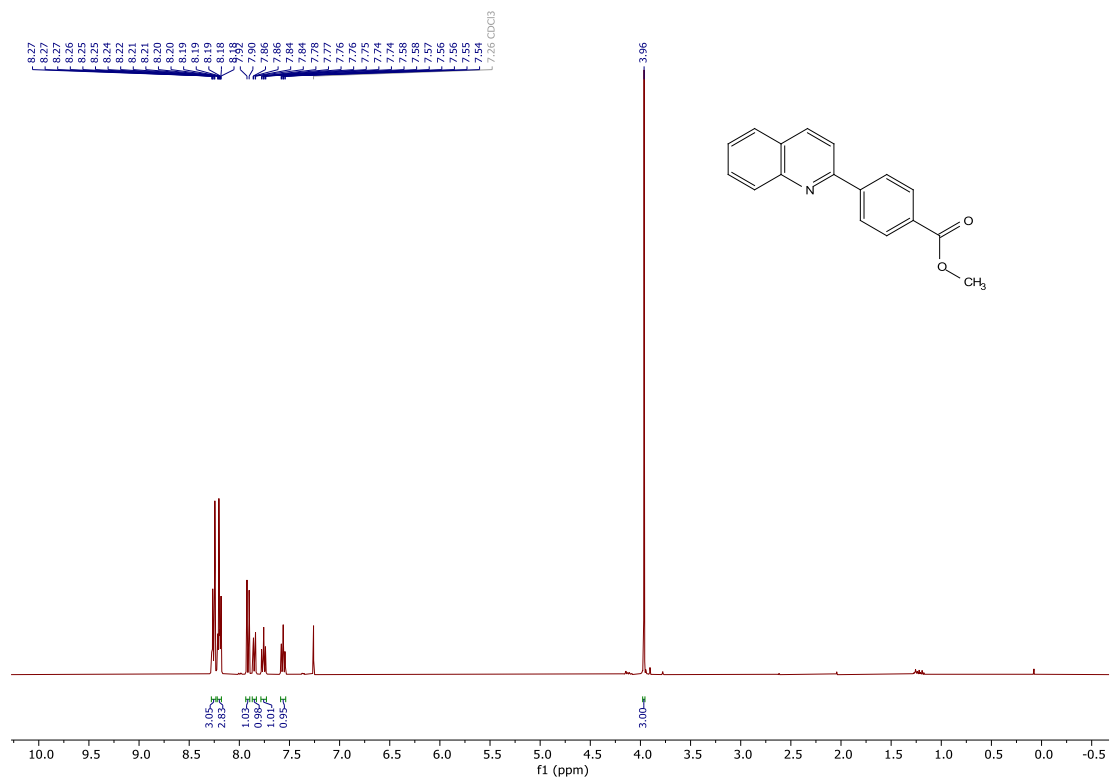
2-(4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-5-(trifluoromethyl)pyridine (4ay)

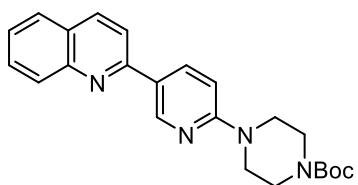




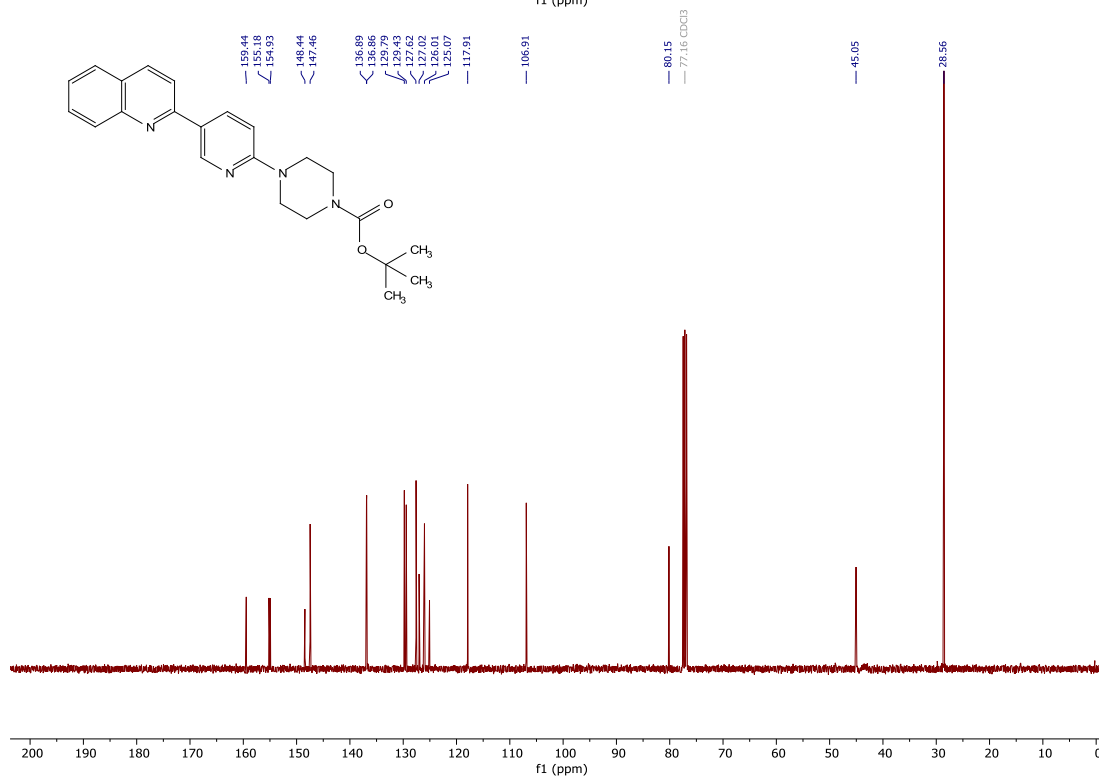
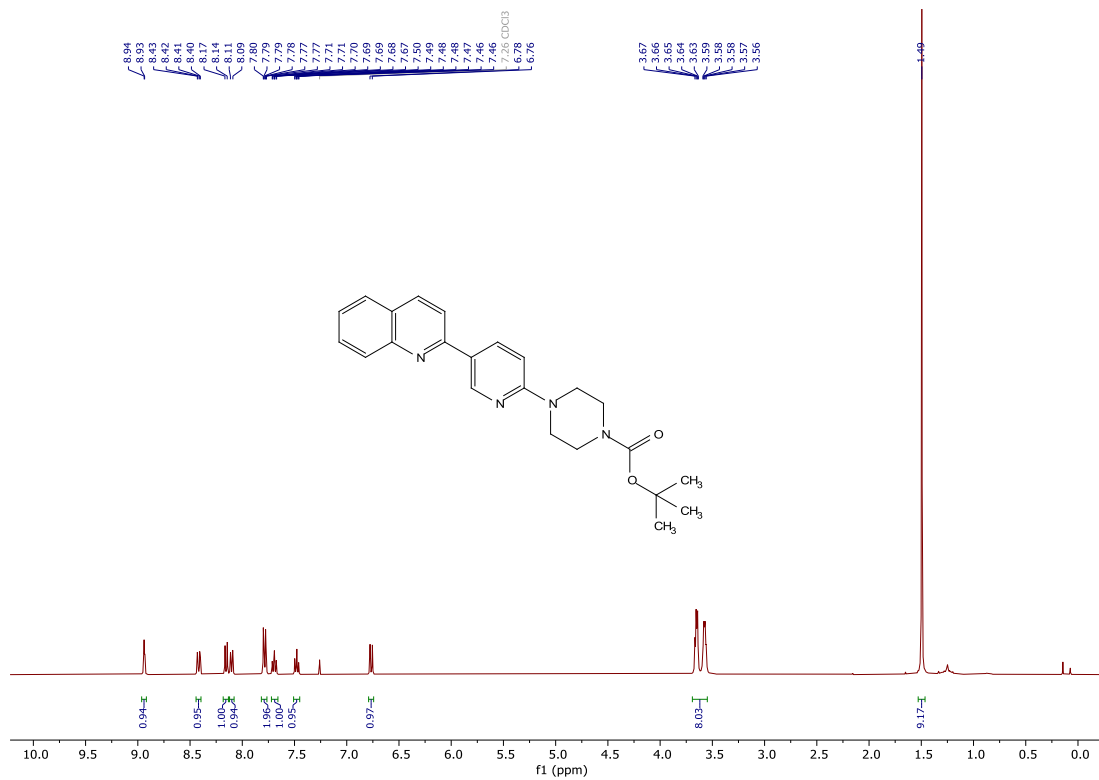


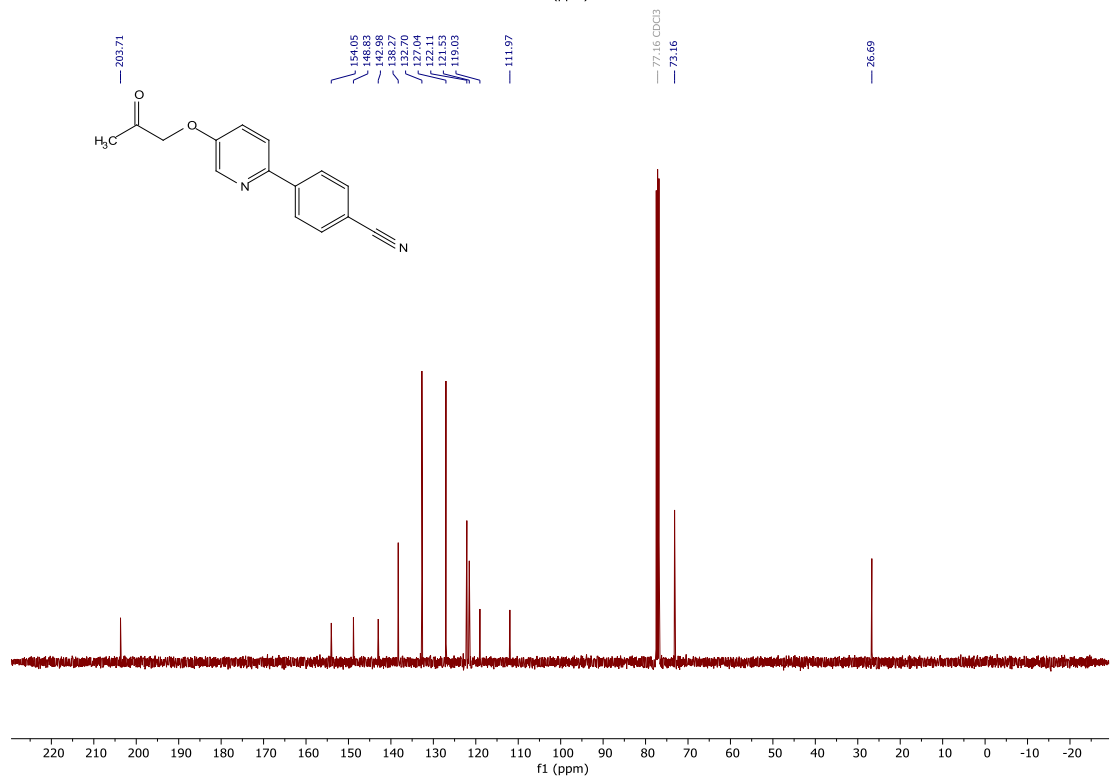
methyl 4-(quinolin-2-yl)benzoate (4az)

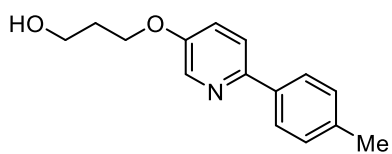




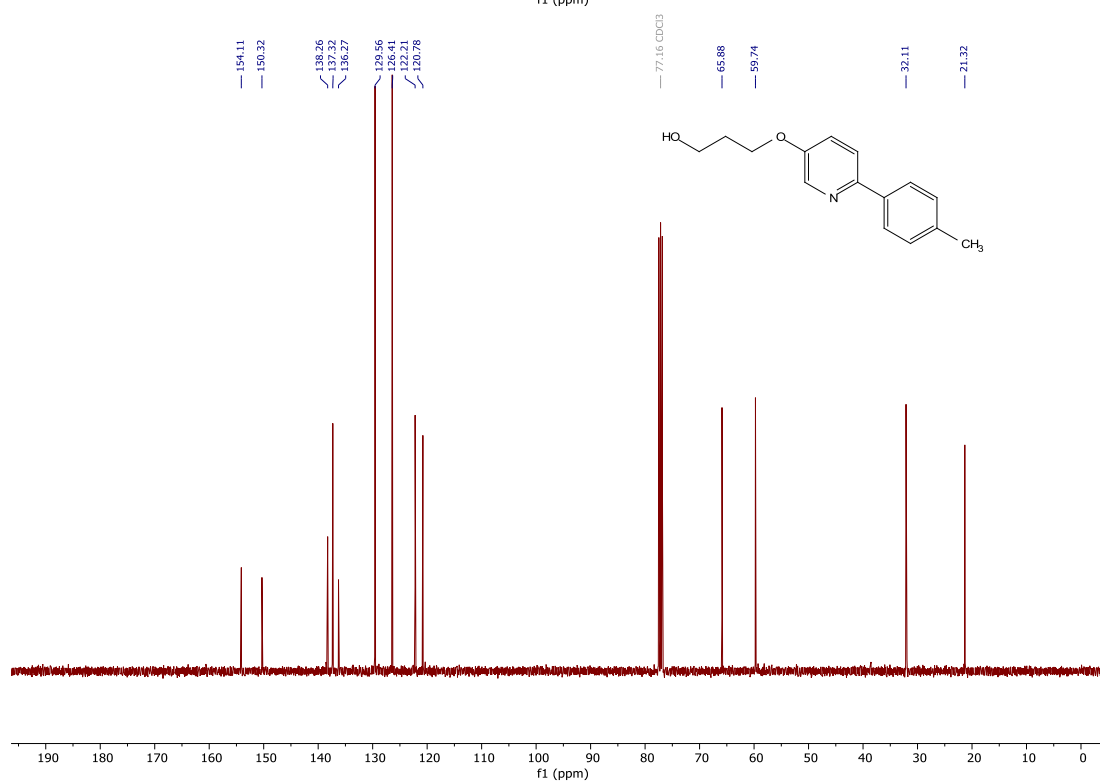
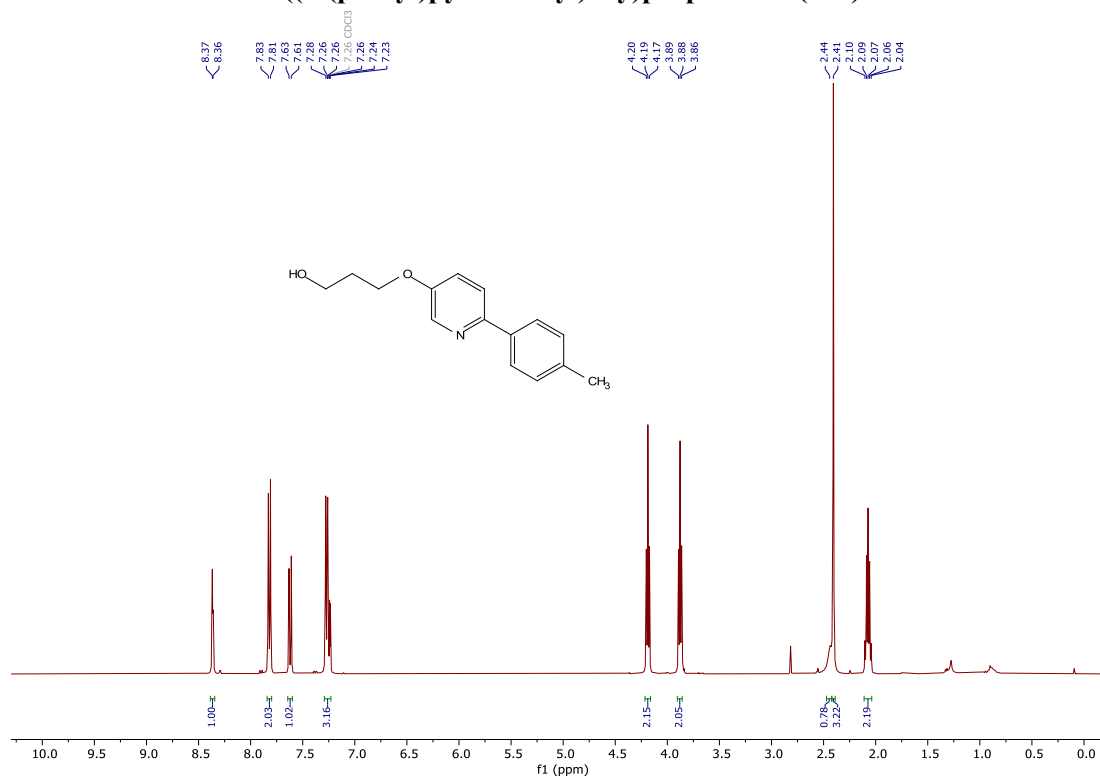
tert-butyl 4-(5-(quinolin-2-yl)pyridin-2-yl)piperazine-1-carboxylate (4ba)

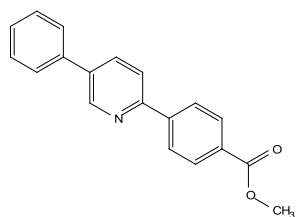
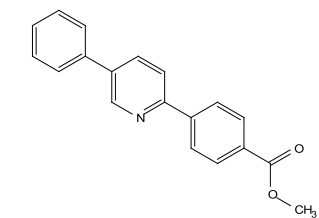


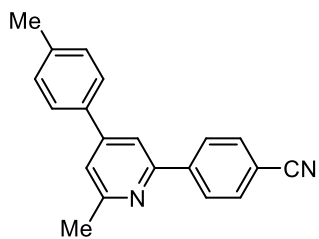




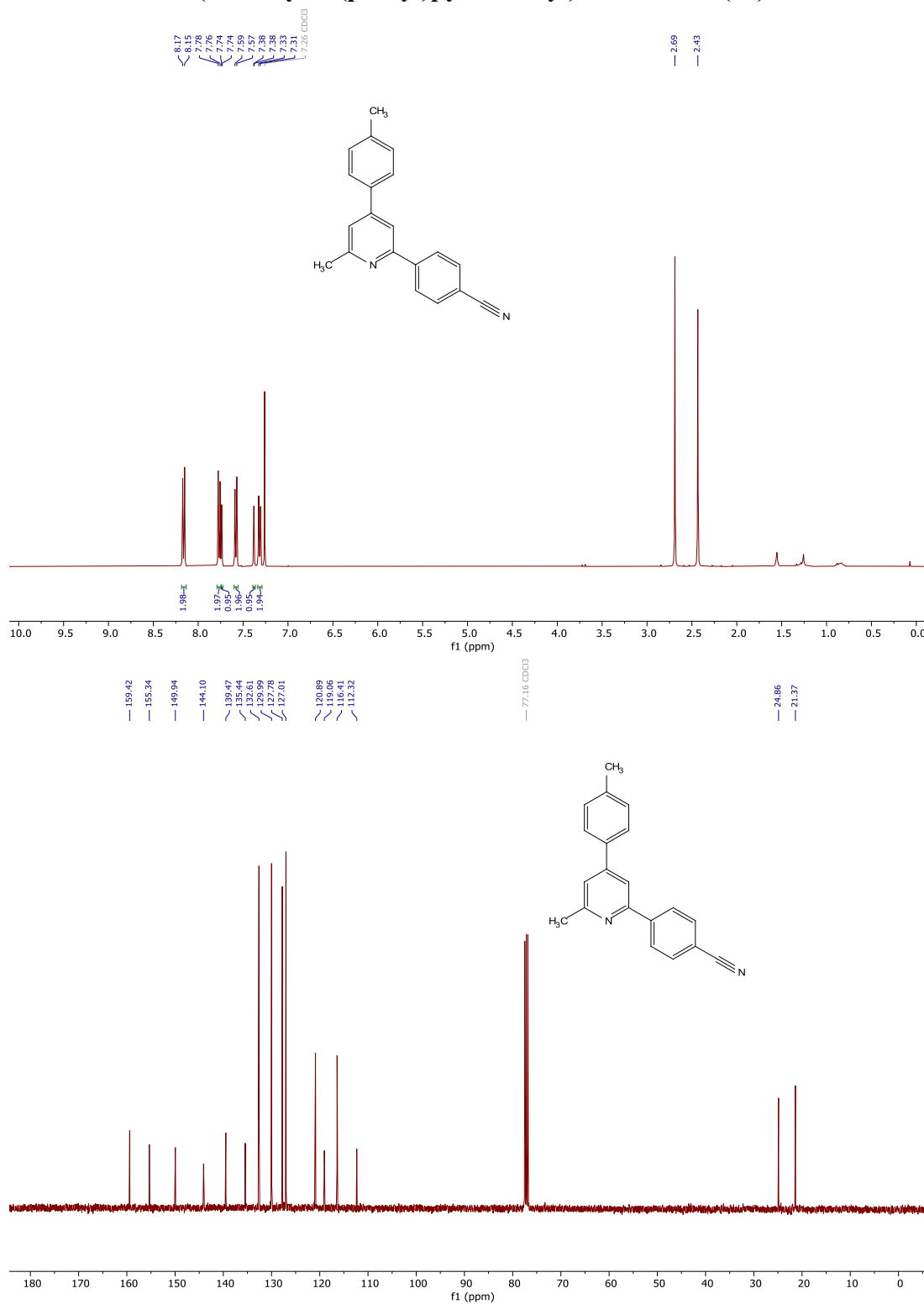
3-((6-(p-tolyl)pyridin-3-yl)oxy)propan-1-ol (4bc)



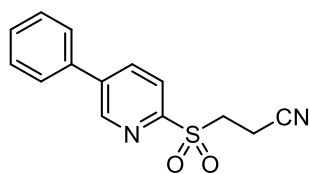




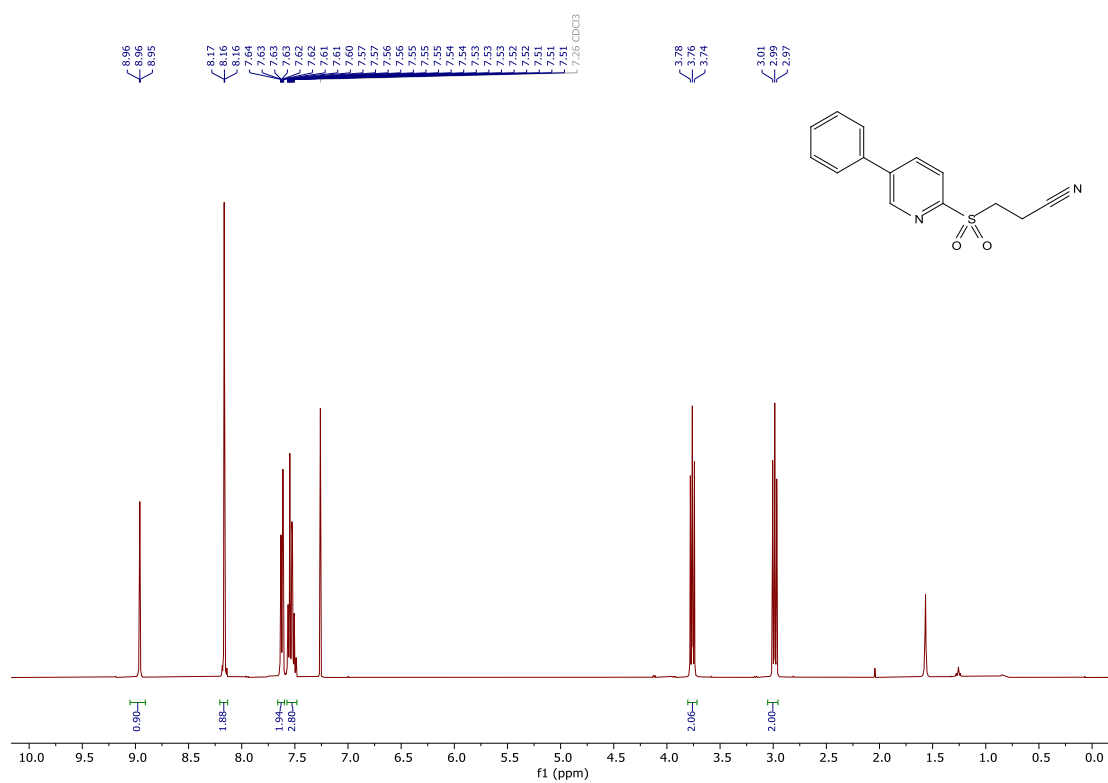
4-(6-methyl-4-(p-tolyl)pyridin-2-yl)benzonitrile (18)

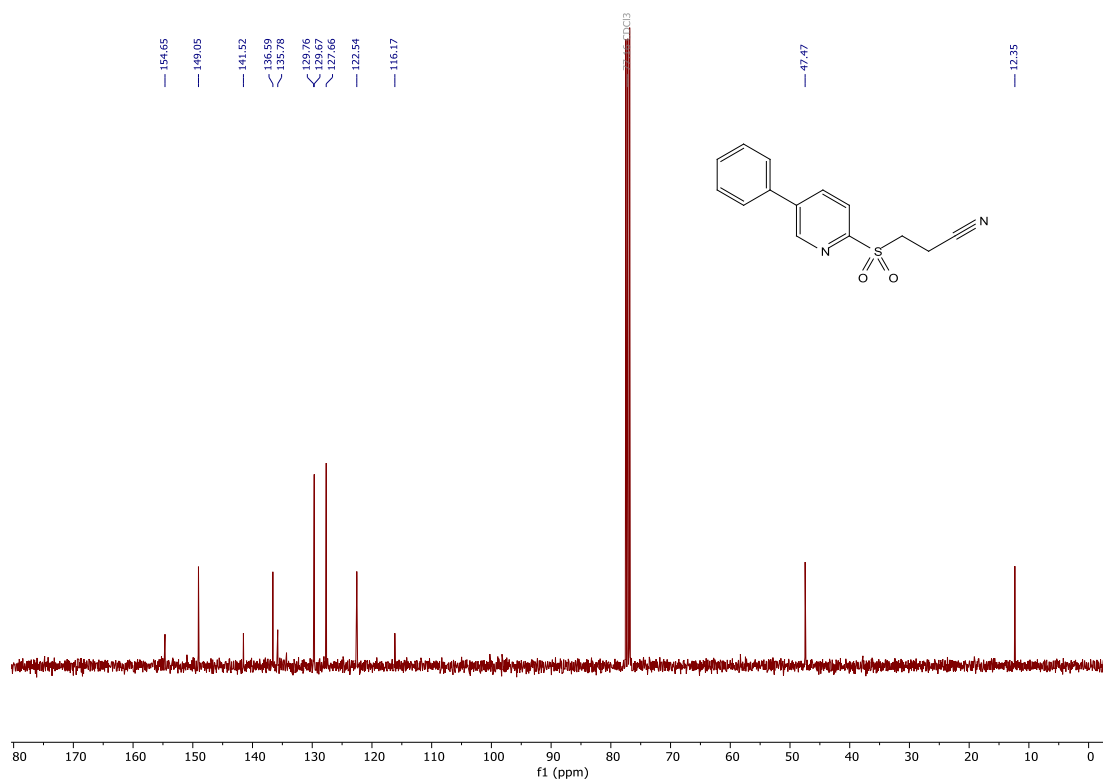


8.1.5. Multi-step elaboration products

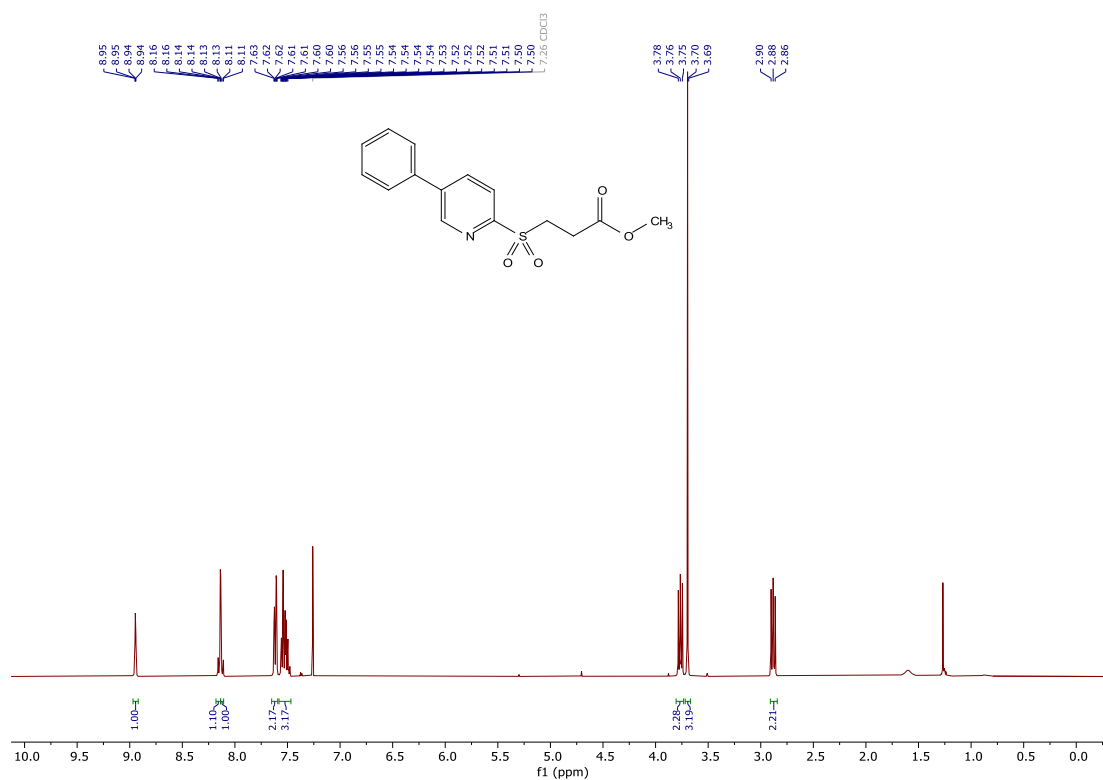


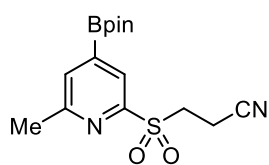
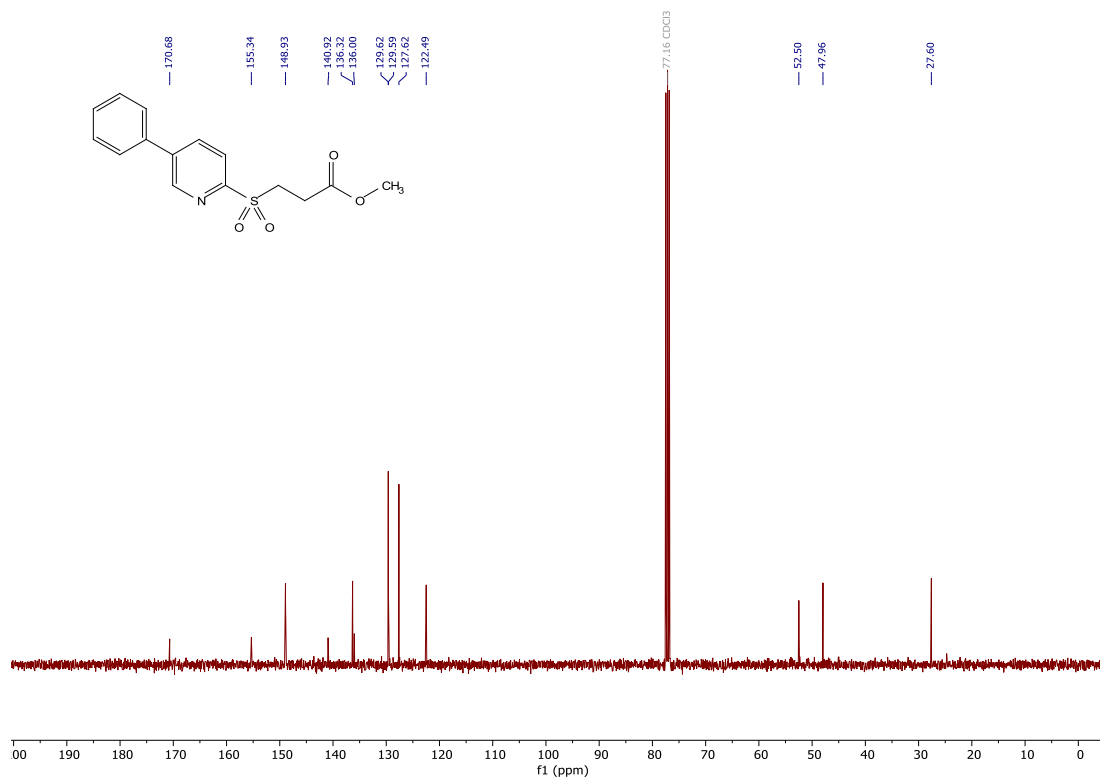
3-((5-phenylpyridin-2-yl)sulfonyl)propanenitrile (13a)



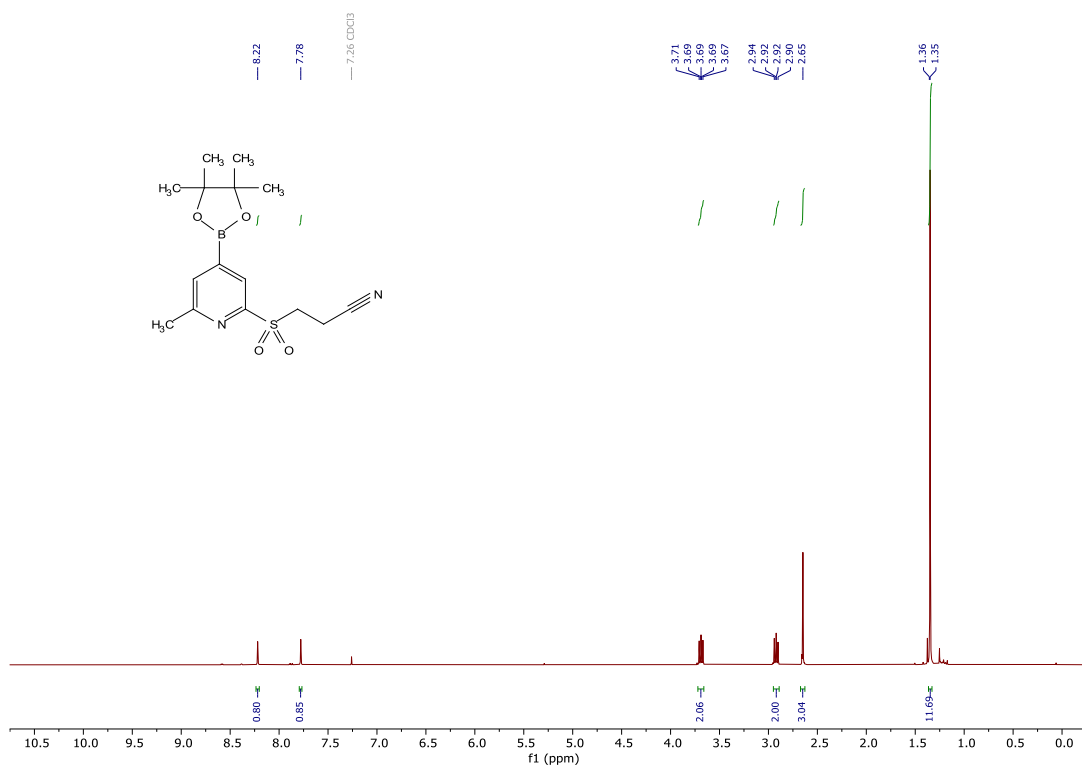


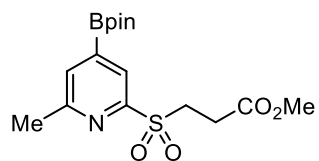
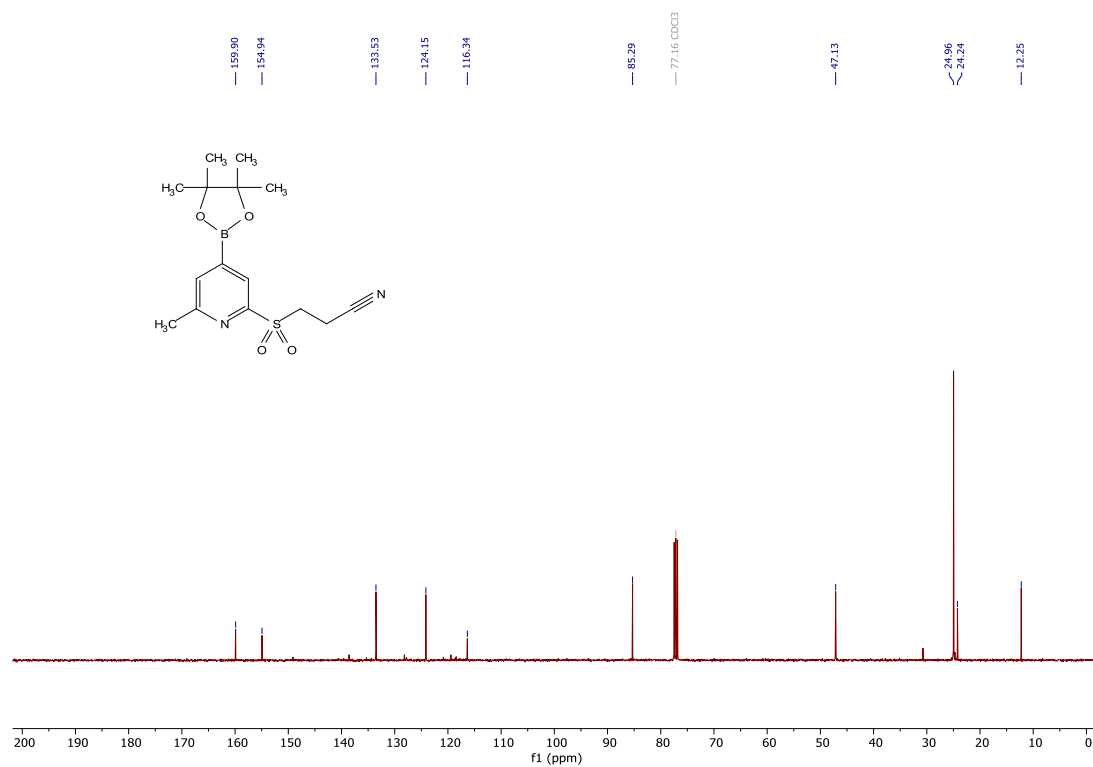
methyl 3-((5-phenylpyridin-2-yl)sulfonyl)propanoate (13b)



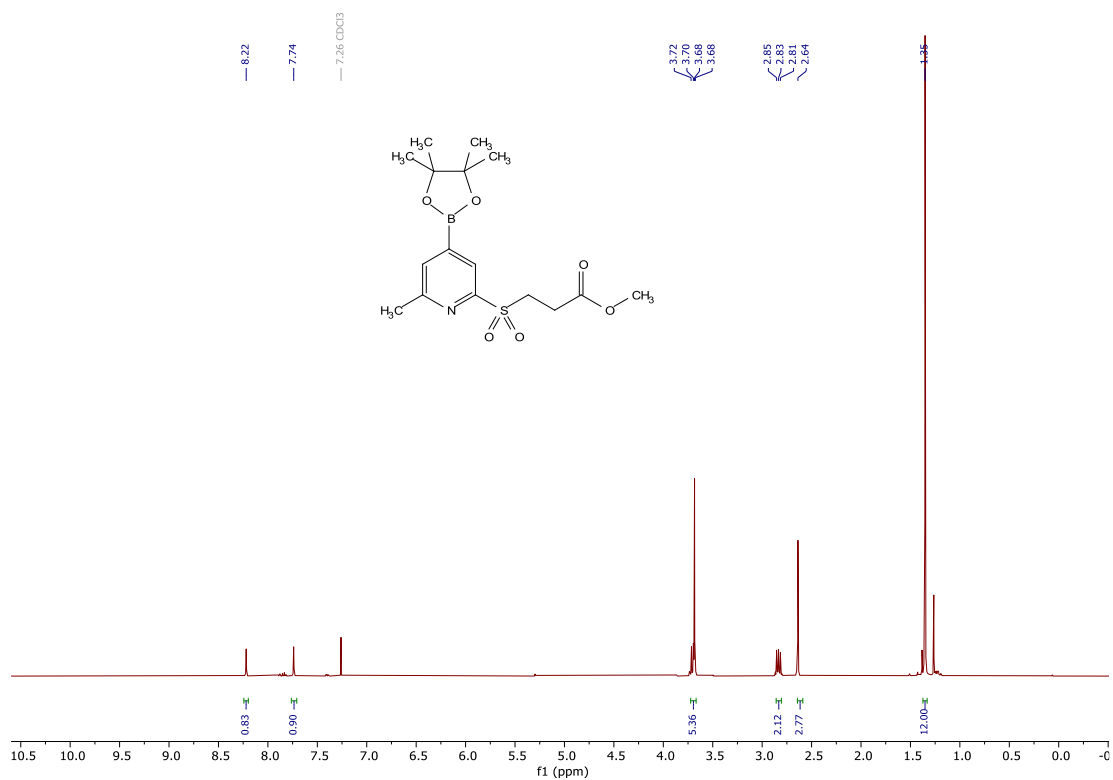


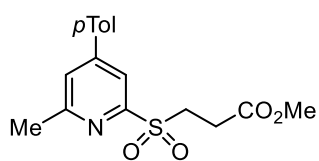
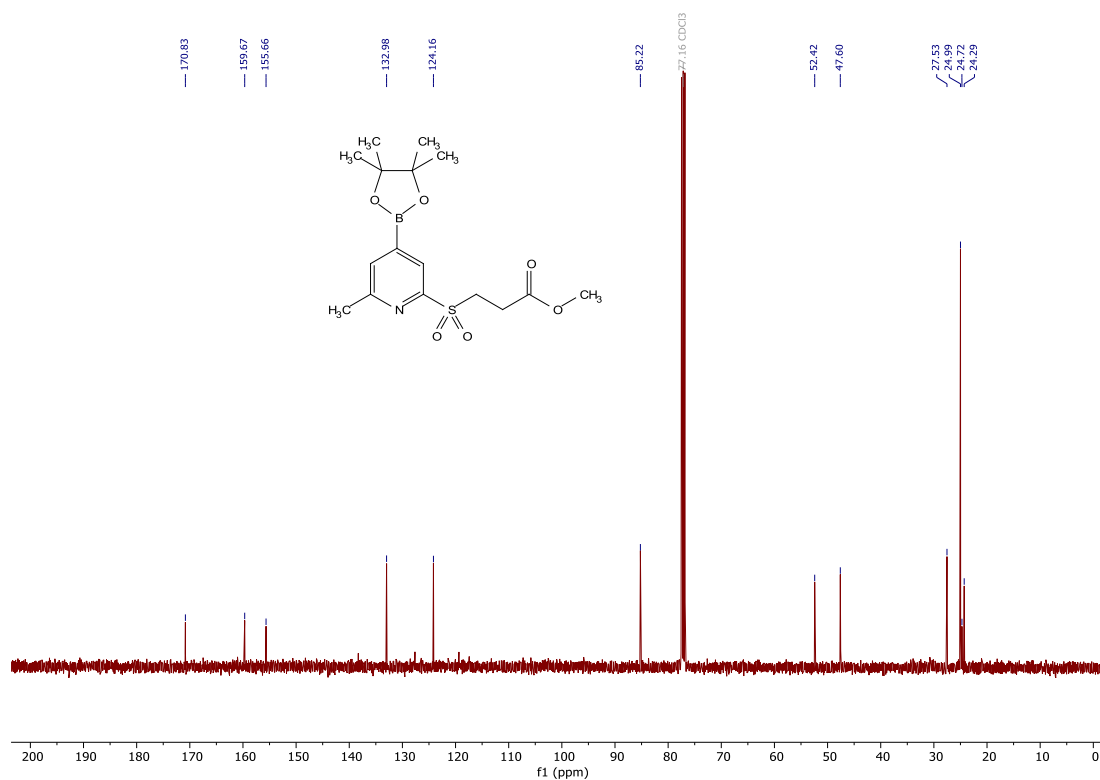
3-((6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)sulfonyl)propanenitrile (16a)



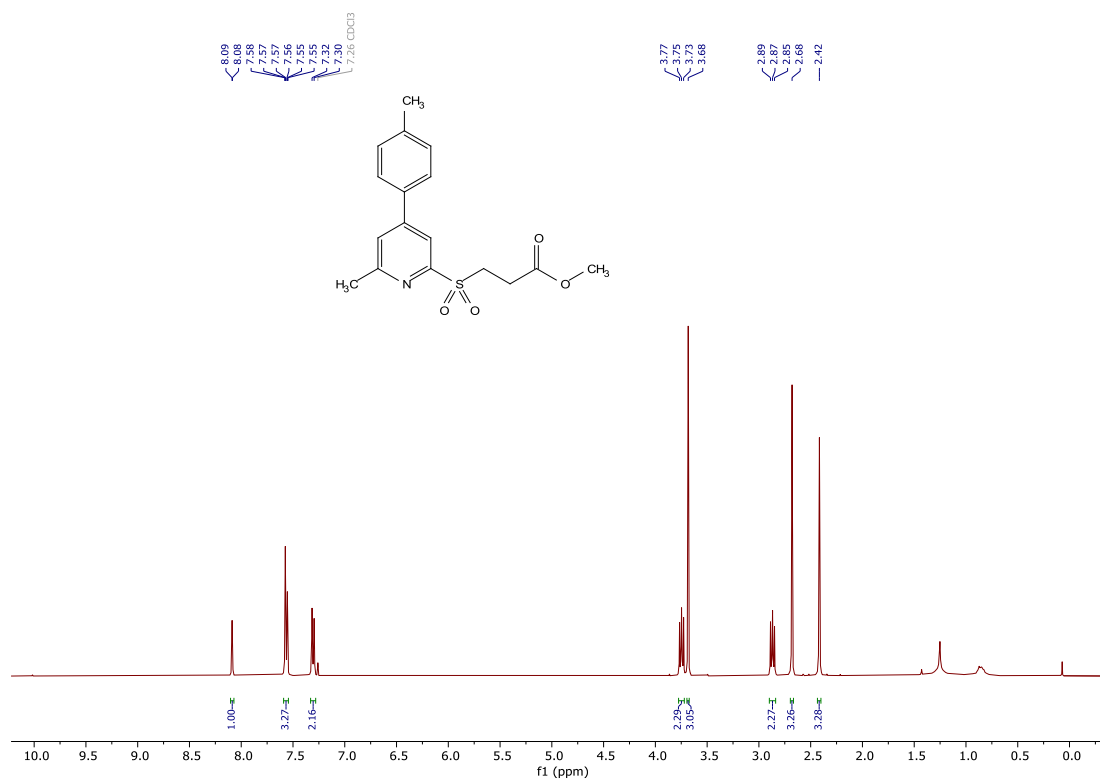


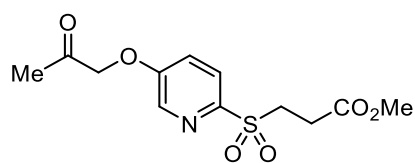
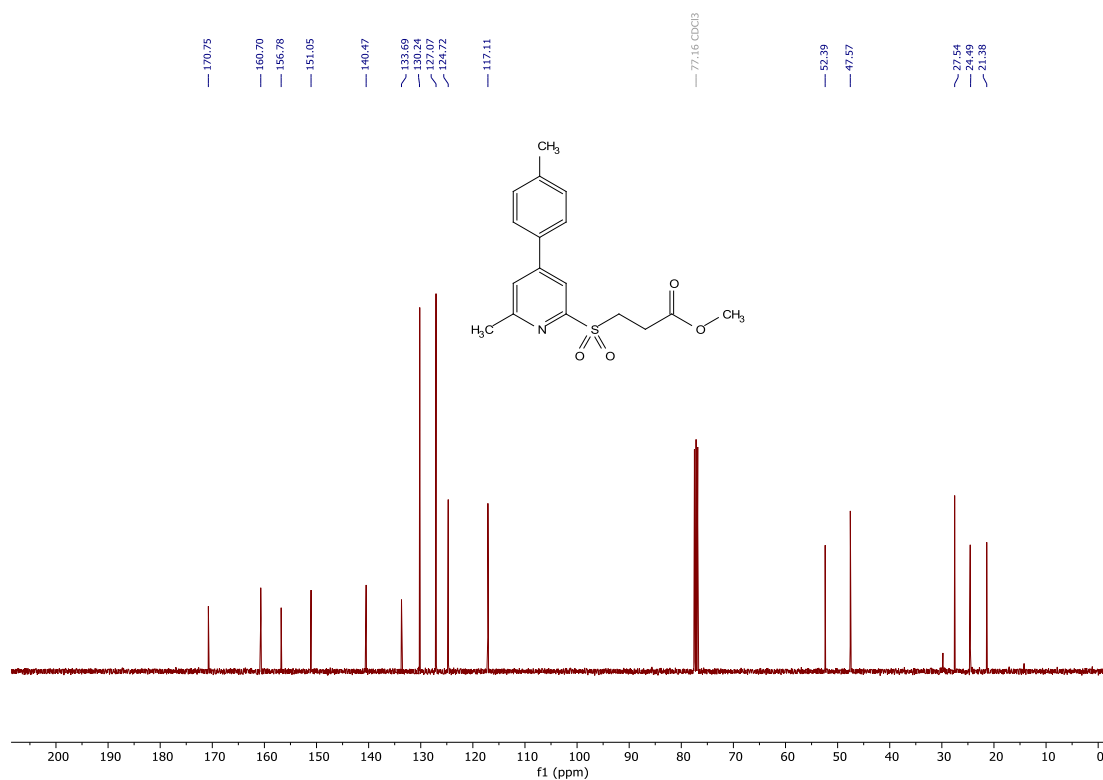
methyl 3-((6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)sulfonyl)propanoate (16b)



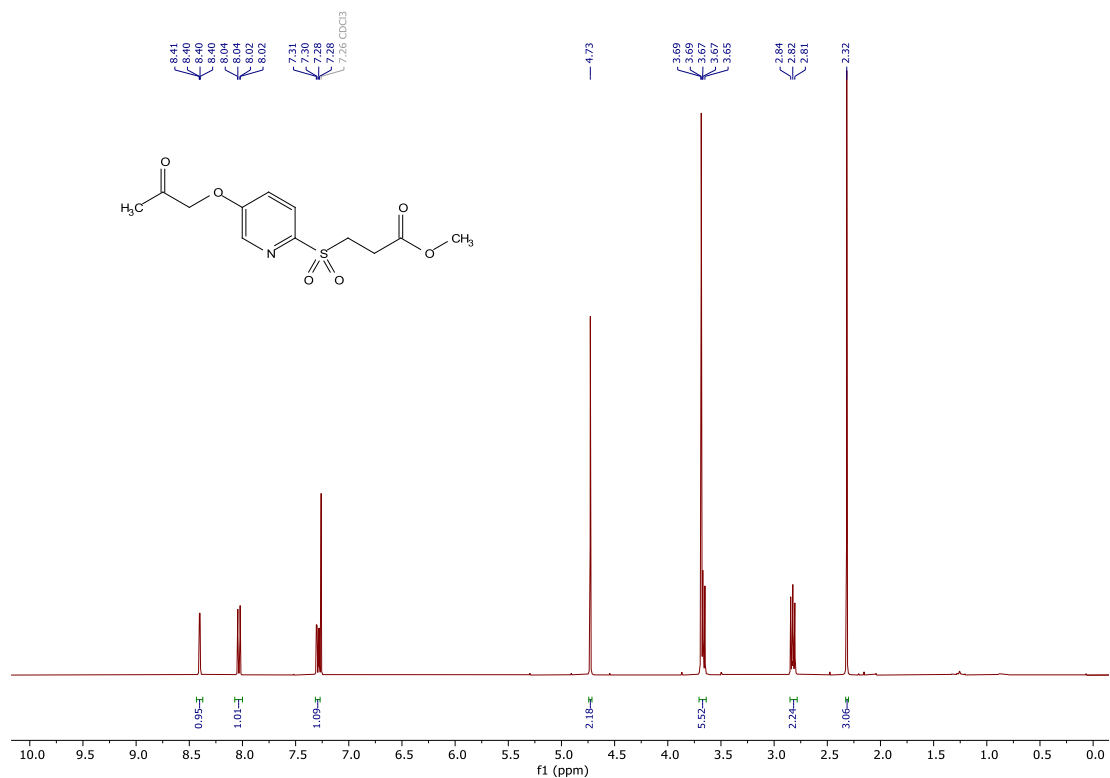


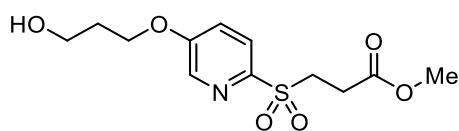
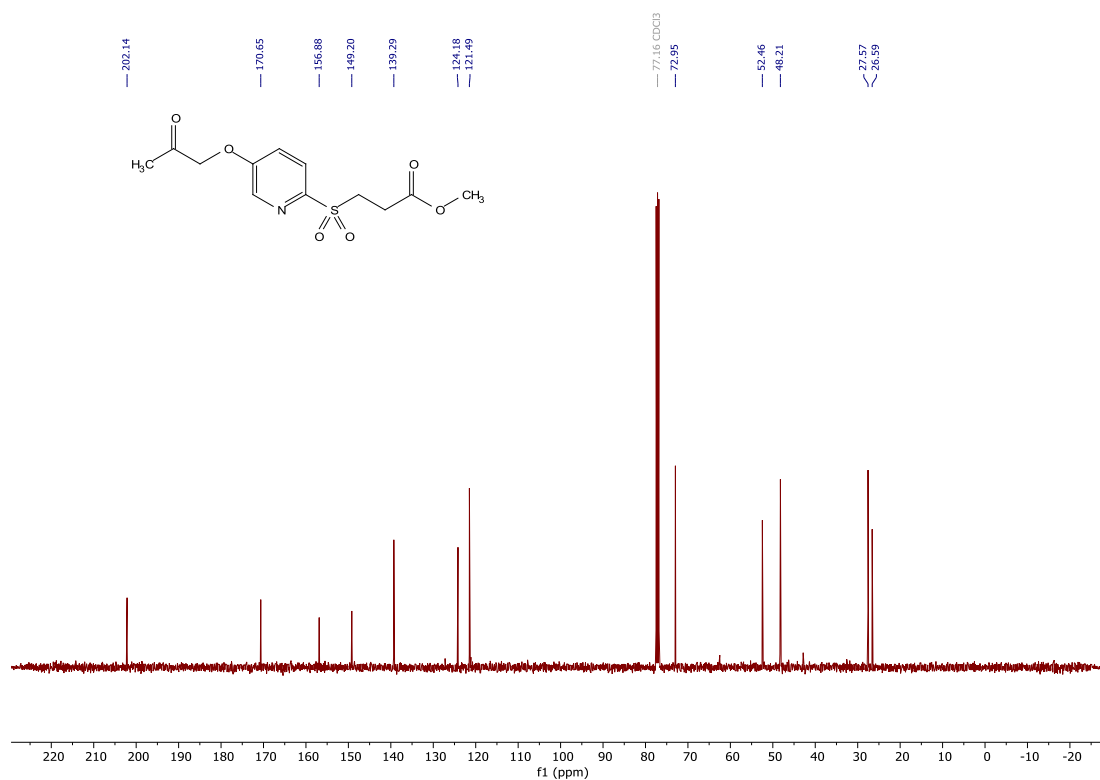
methyl 3-((6-methyl-4-(p-tolyl)pyridin-2-yl)sulfonyl)propanoate (17)



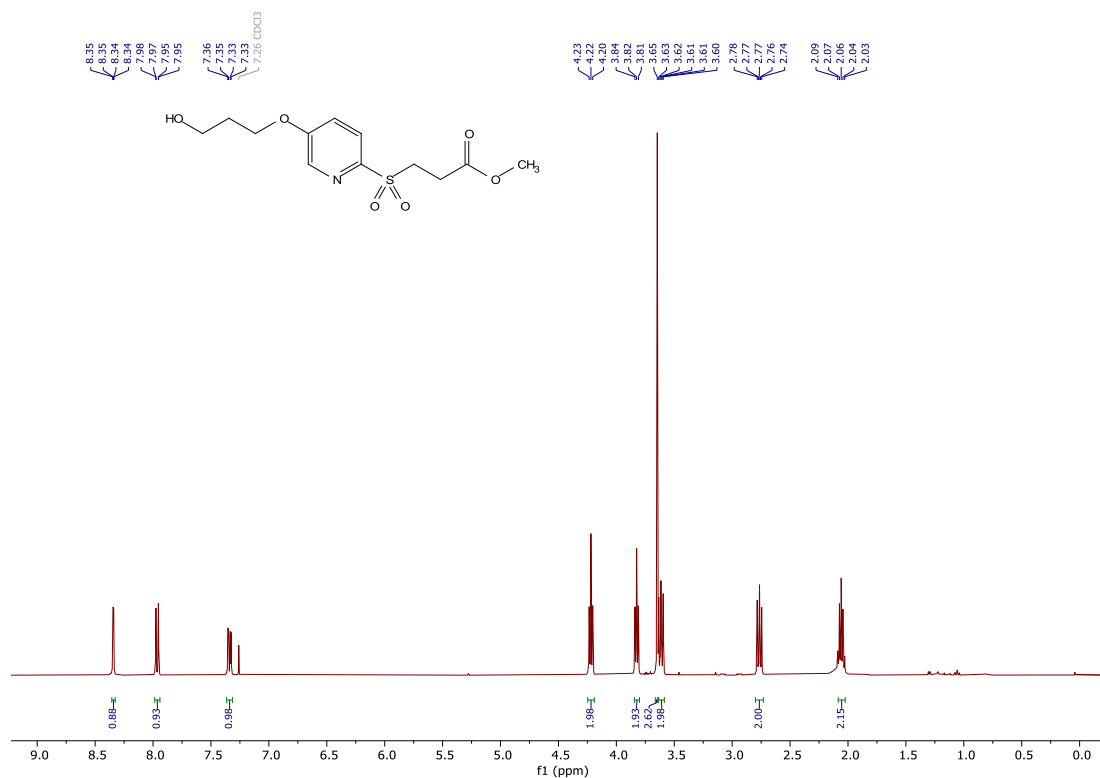


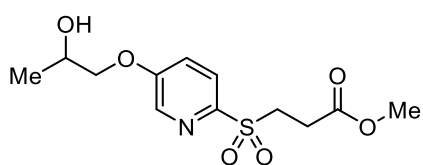
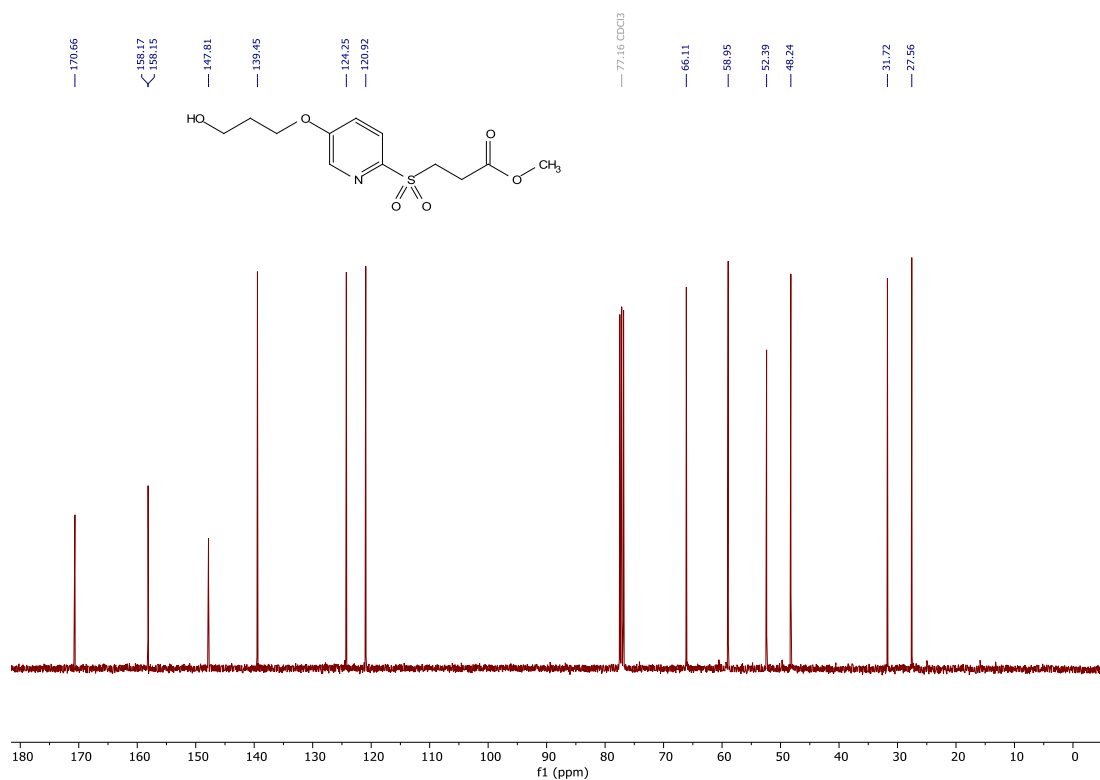
methyl 3-((5-(2-oxopropoxy)pyridin-2-yl)sulfonyl)propanoate (20)



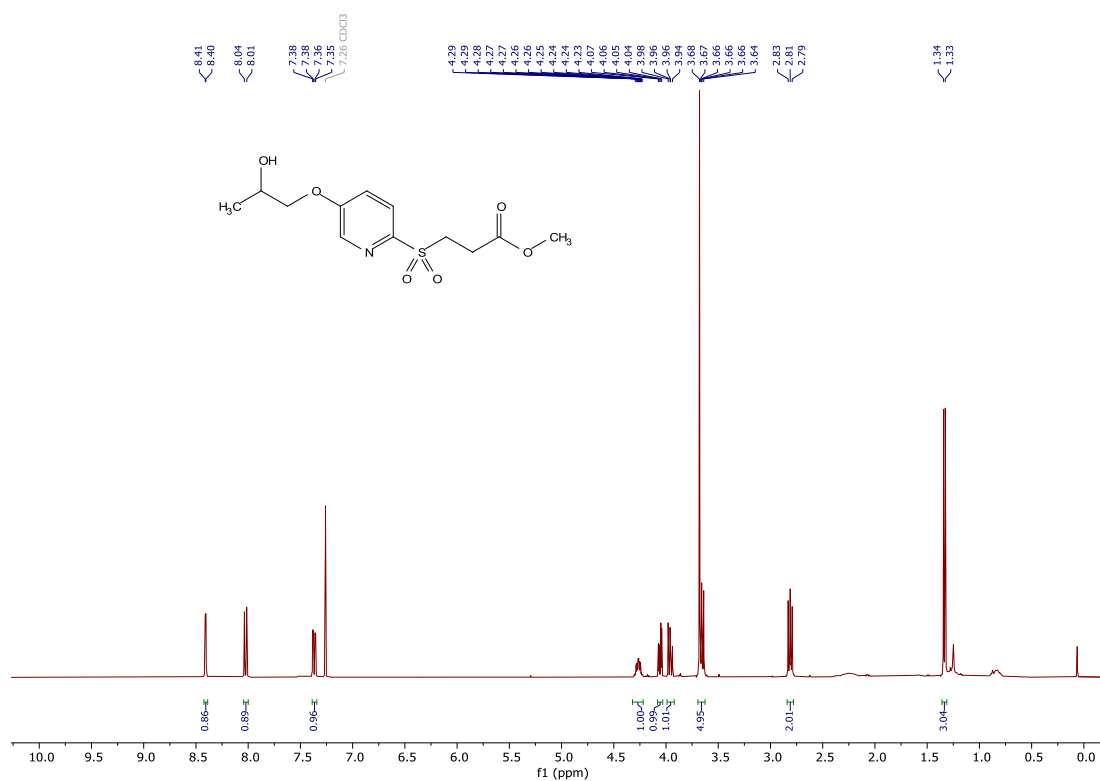


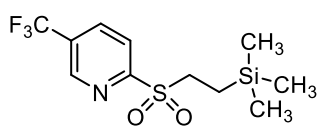
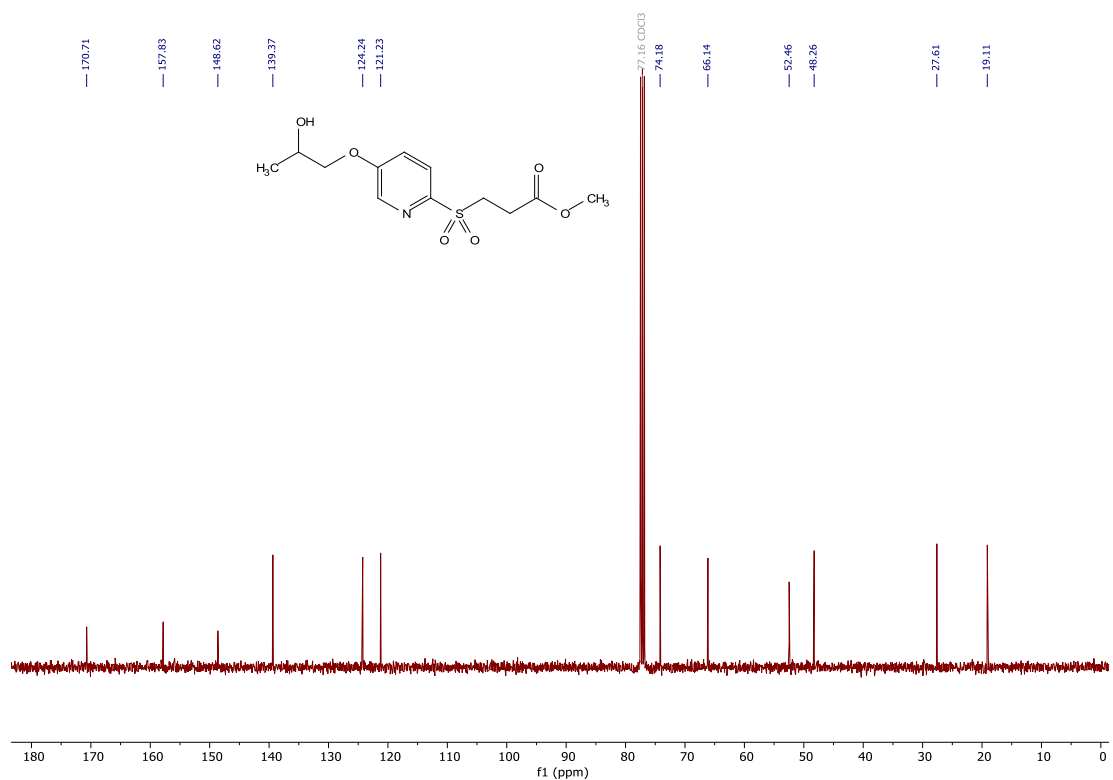
methyl 3-((5-(3-hydroxypropoxy)pyridin-2-yl)sulfonyl)propanoate (21a)



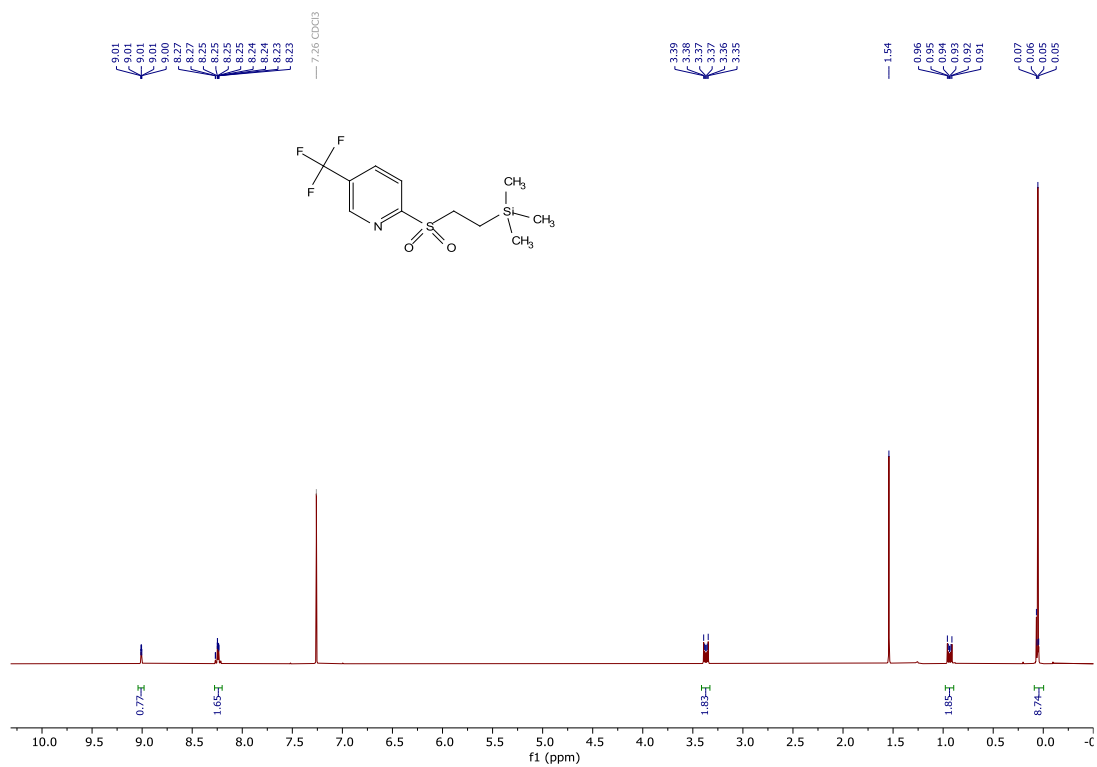


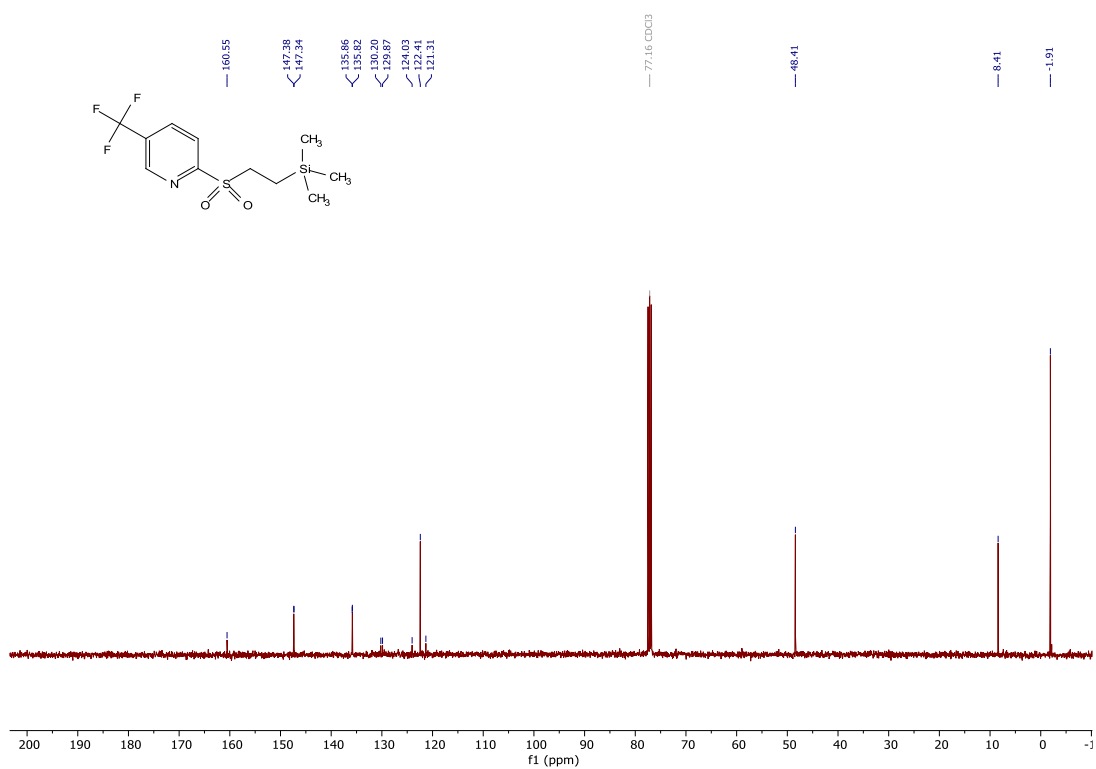
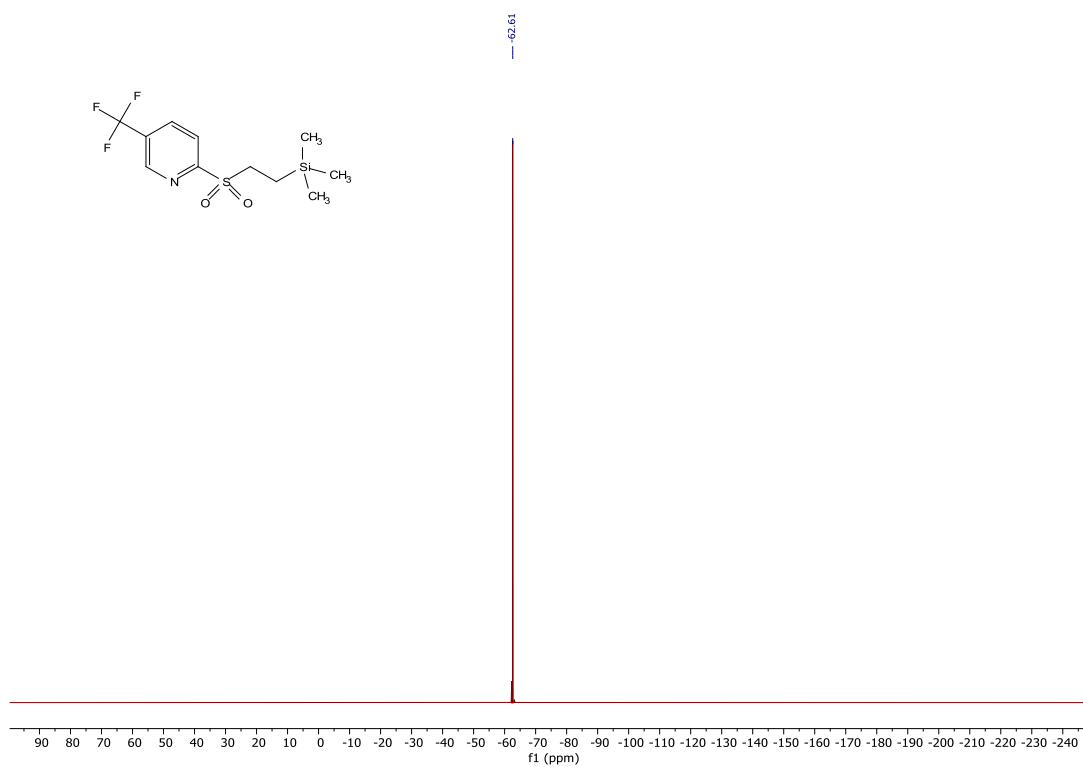
methyl 3-((5-(2-hydroxypropoxy)pyridin-2-yl)sulfonyl)propanoate (21b)





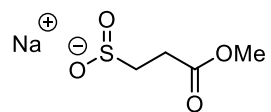
5-(trifluoromethyl)-2-((2-(trimethylsilyl)ethyl)sulfonyl)pyridine (22)



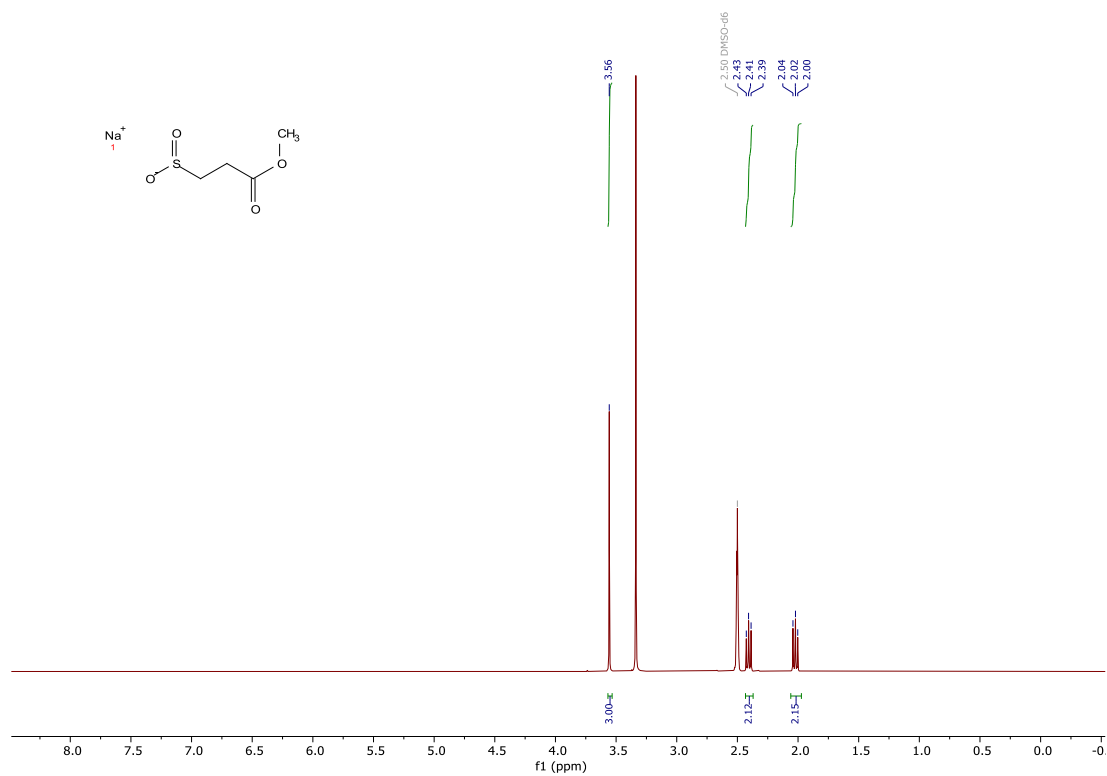


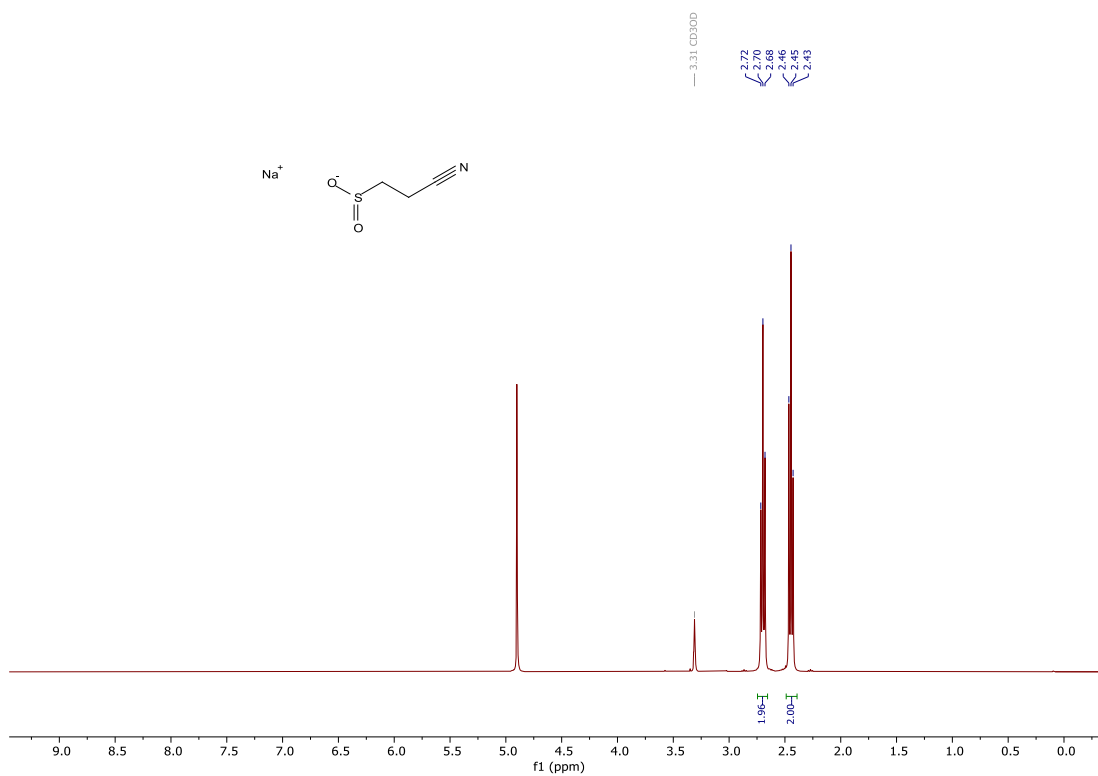
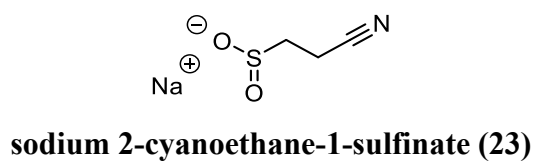
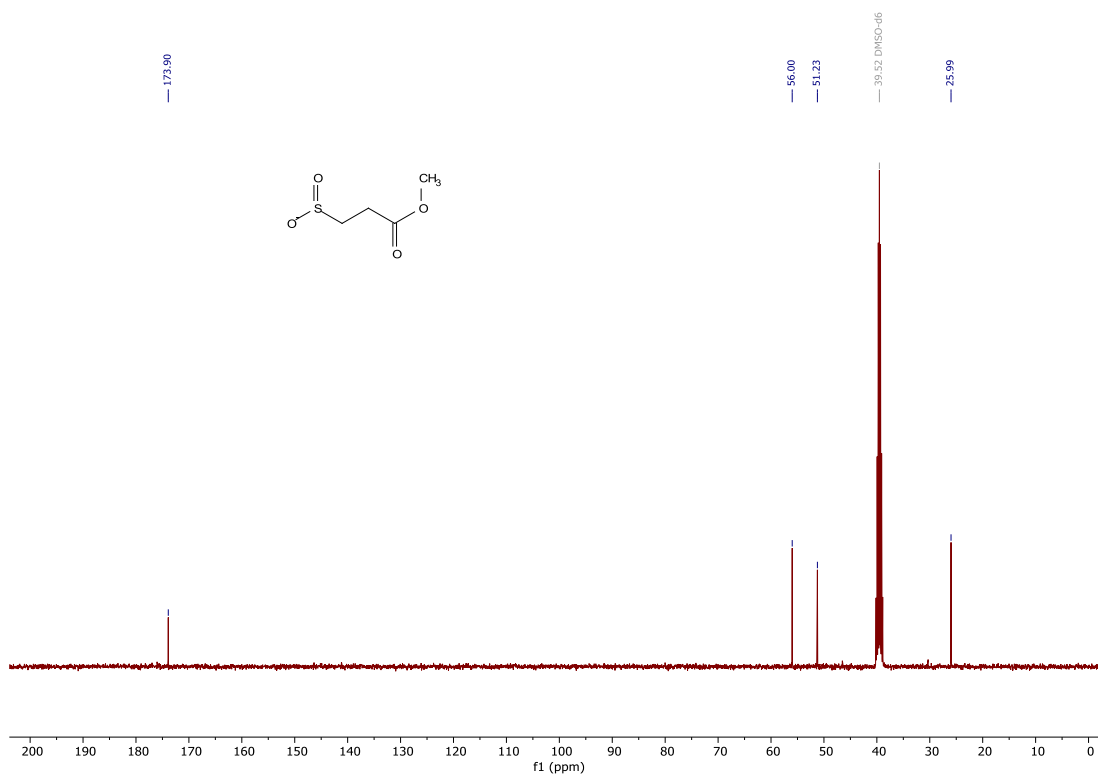
8.2. NMR spectra for chapter 3

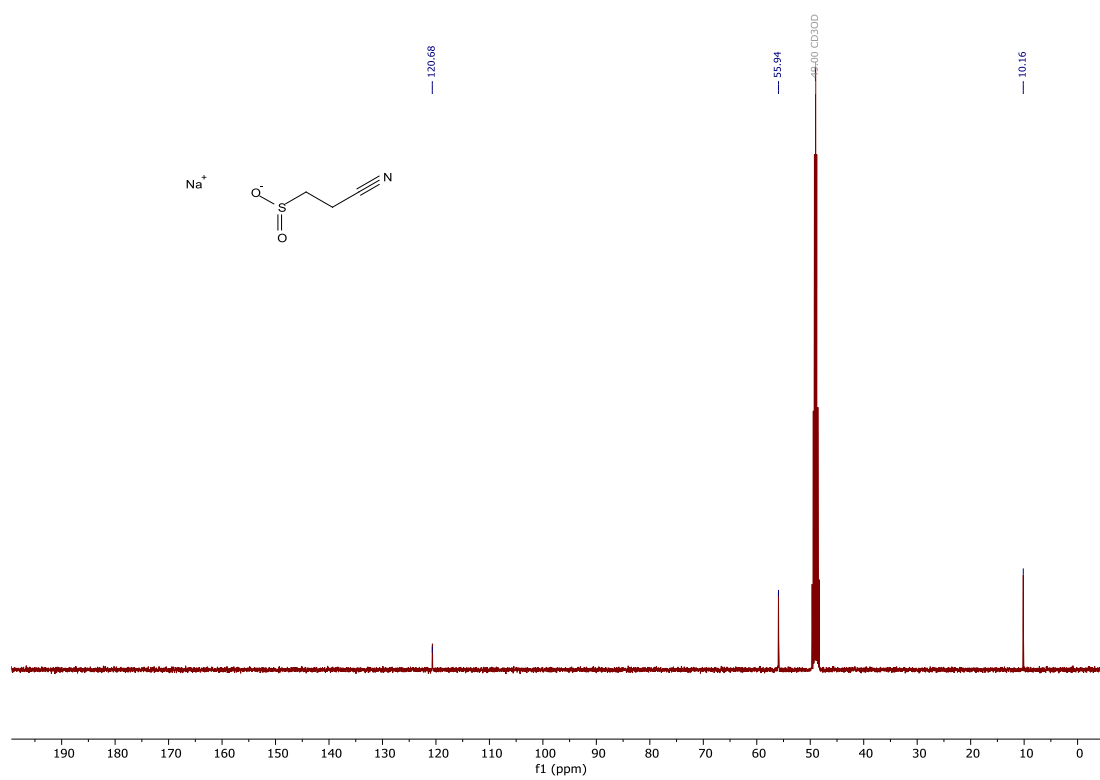
8.2.1. Sulfinate transfer reagents



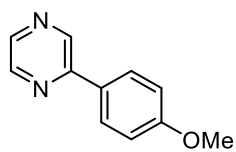
sodium 4-methoxy-4-oxobutane-1-sulfinate (SMOPS) reagent (6)



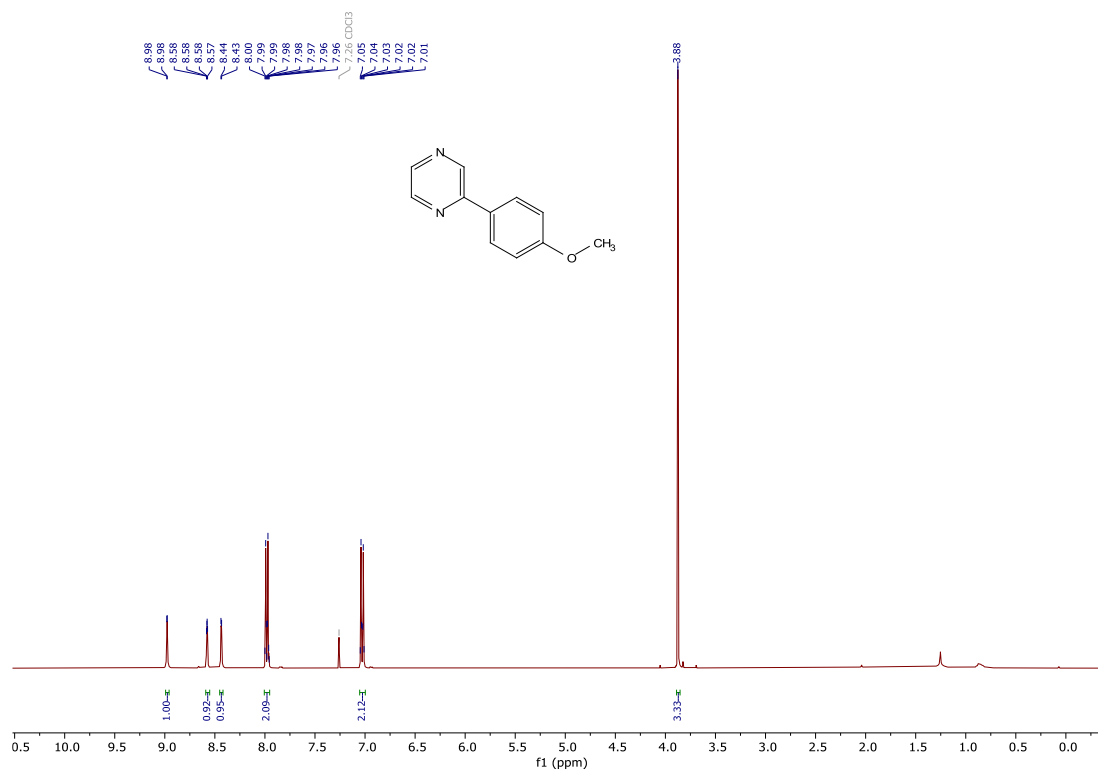


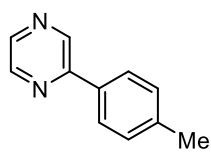
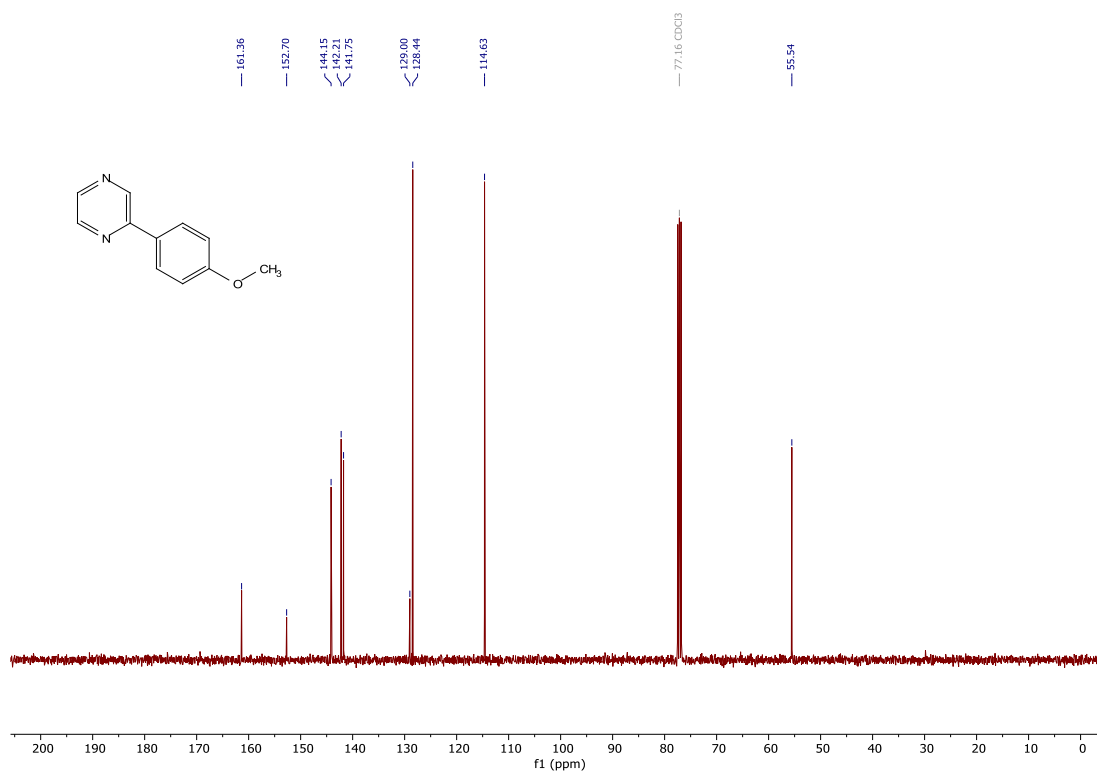


8.2.2. Biaryl products

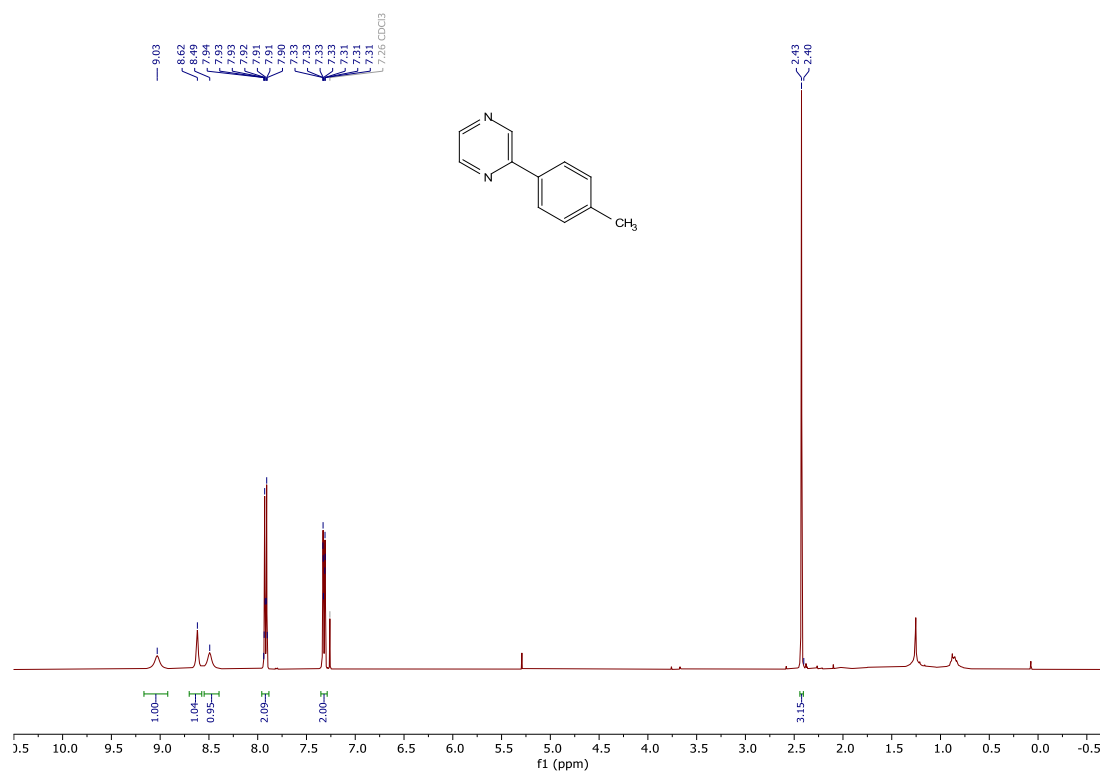


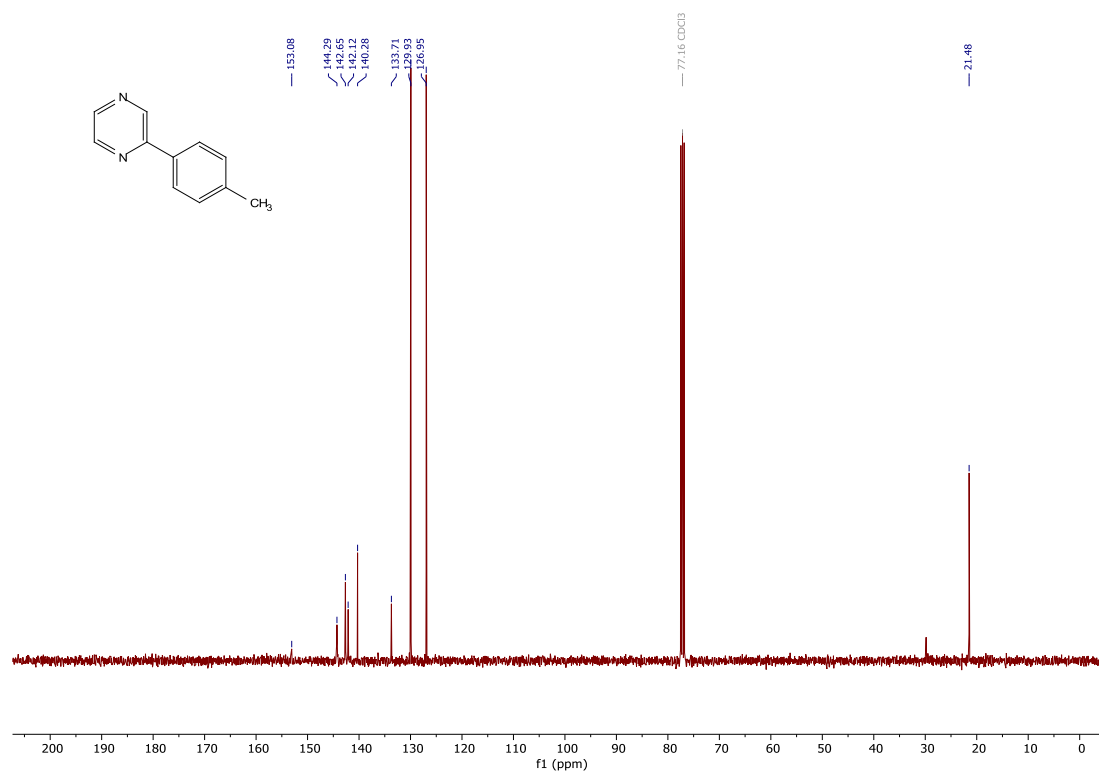
2-(4-methoxyphenyl)pyrazine (4bd)



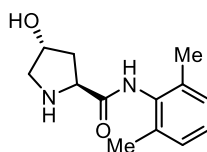


2-(*p*-tolyl)pyrazine (4be)

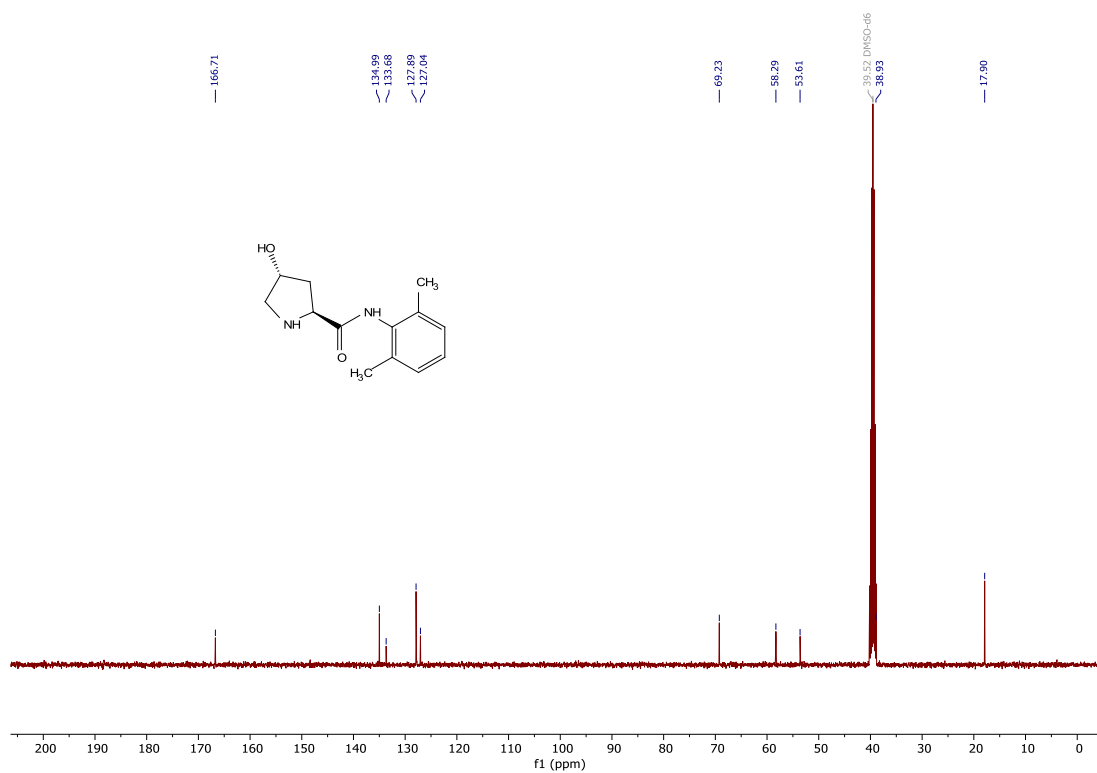
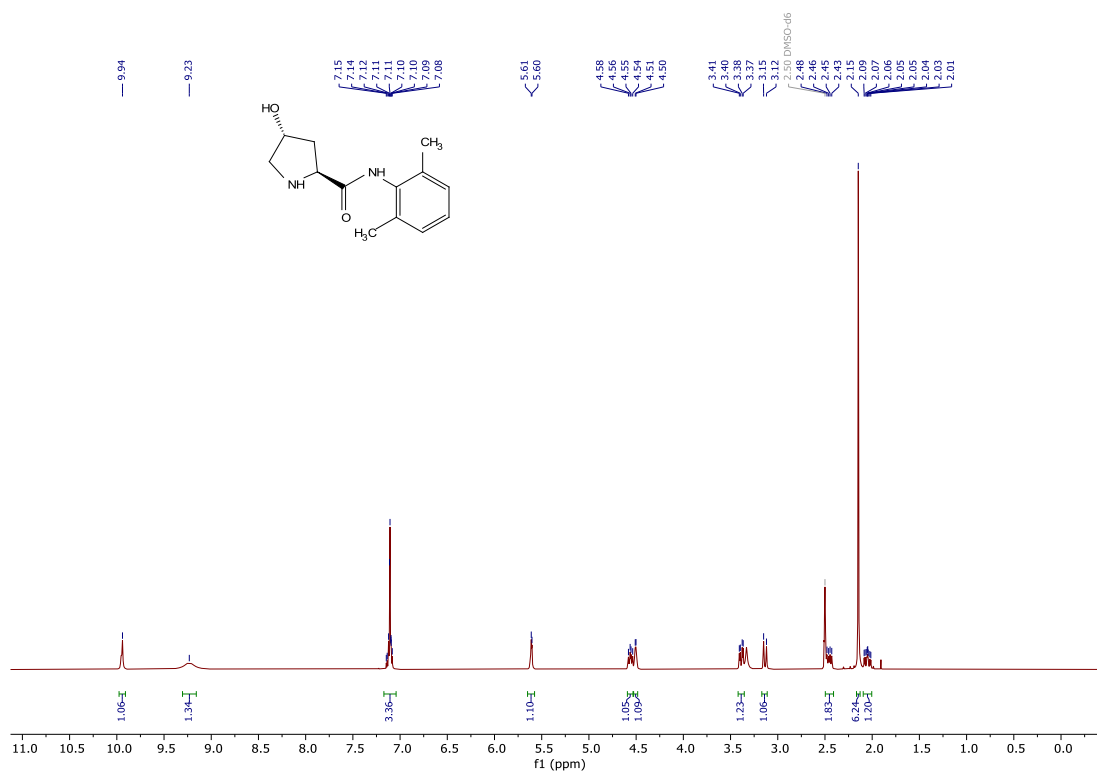




8.2.3. Materials for copper-mediated sulfone formation

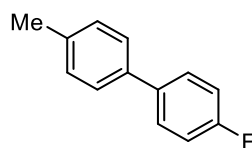


(2*S*,4*R*)-*N*-(2,6-dimethylphenyl)-4-hydroxypyrrolidine-2-carboxamide (28)

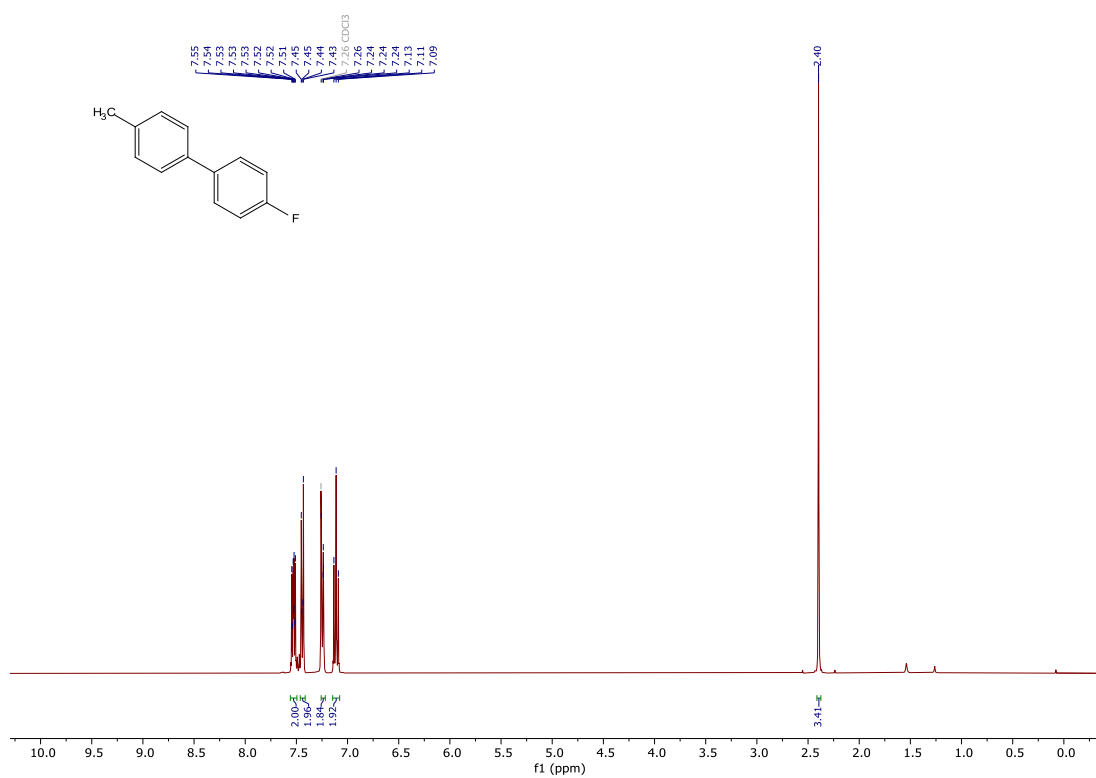


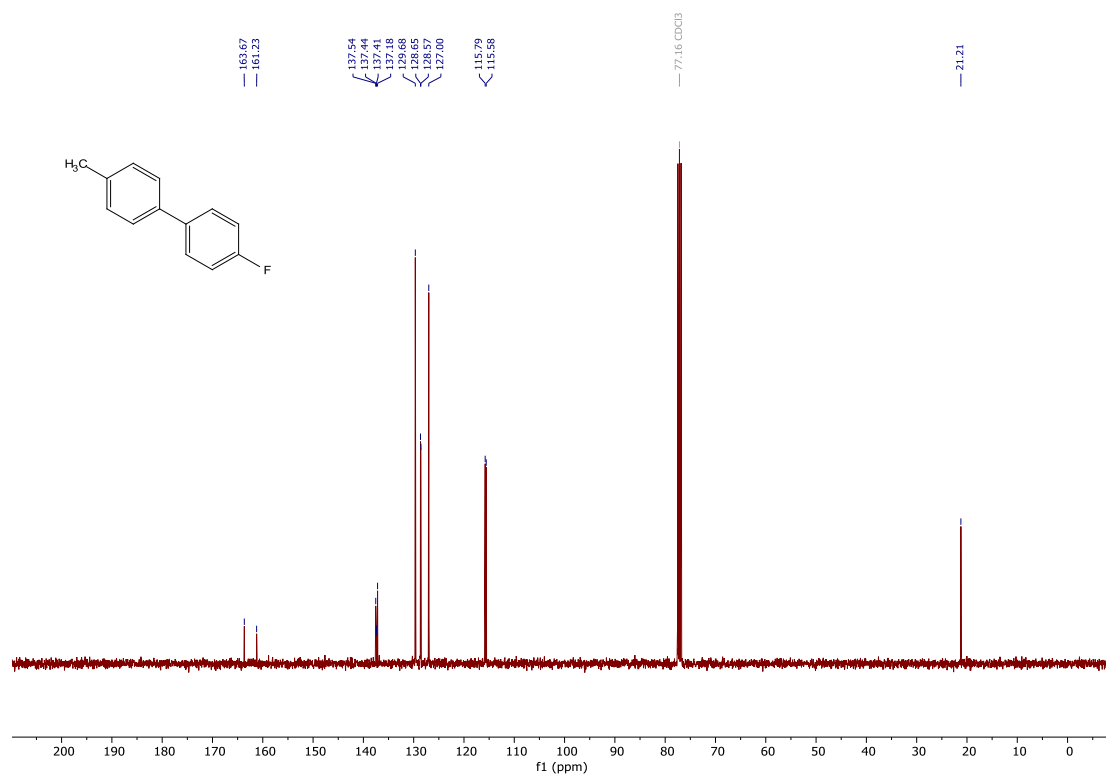
8.3. NMR spectra from chapter 4

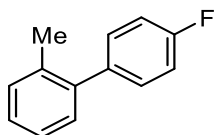
8.3.1. Biaryl products



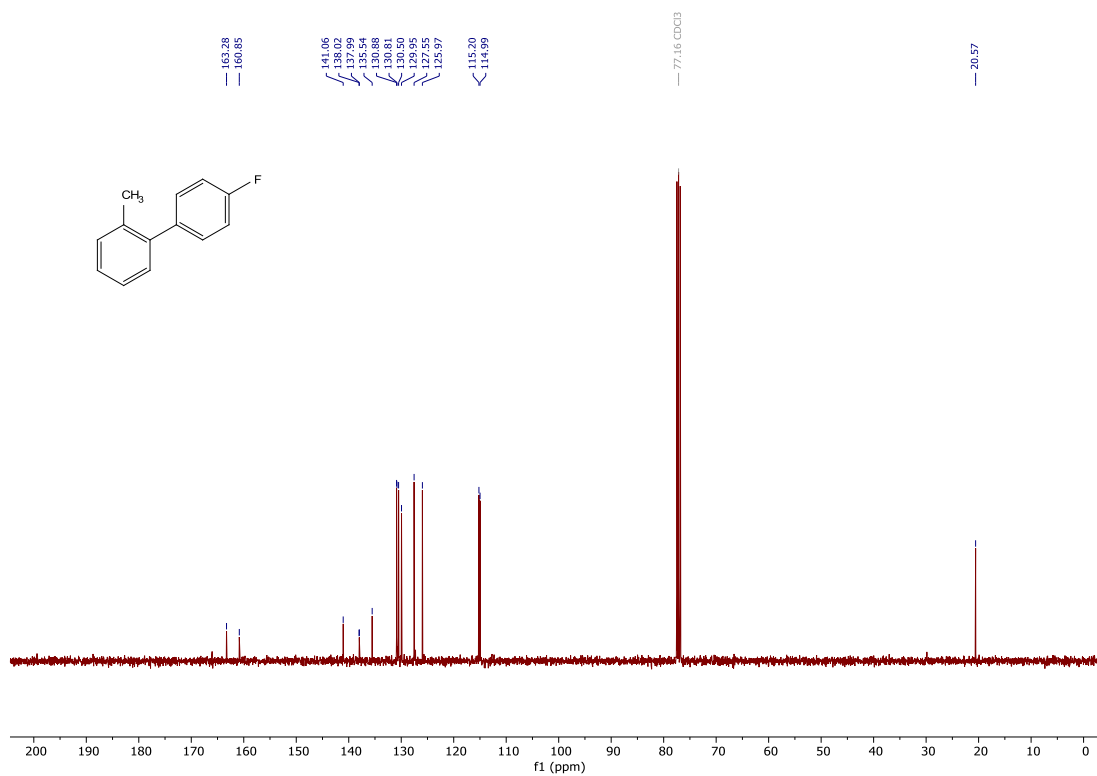
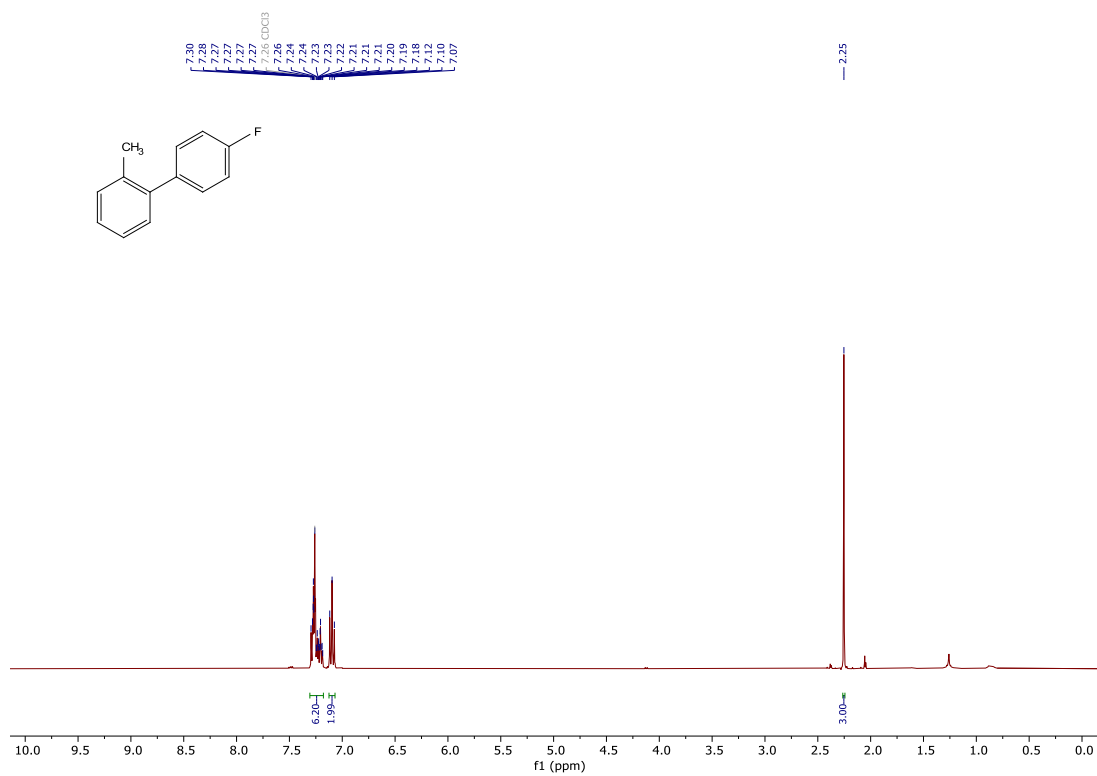
4-fluoro-4'-methyl-1,1'-biphenyl (37a)

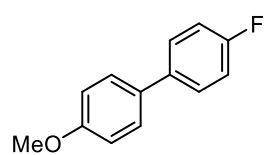
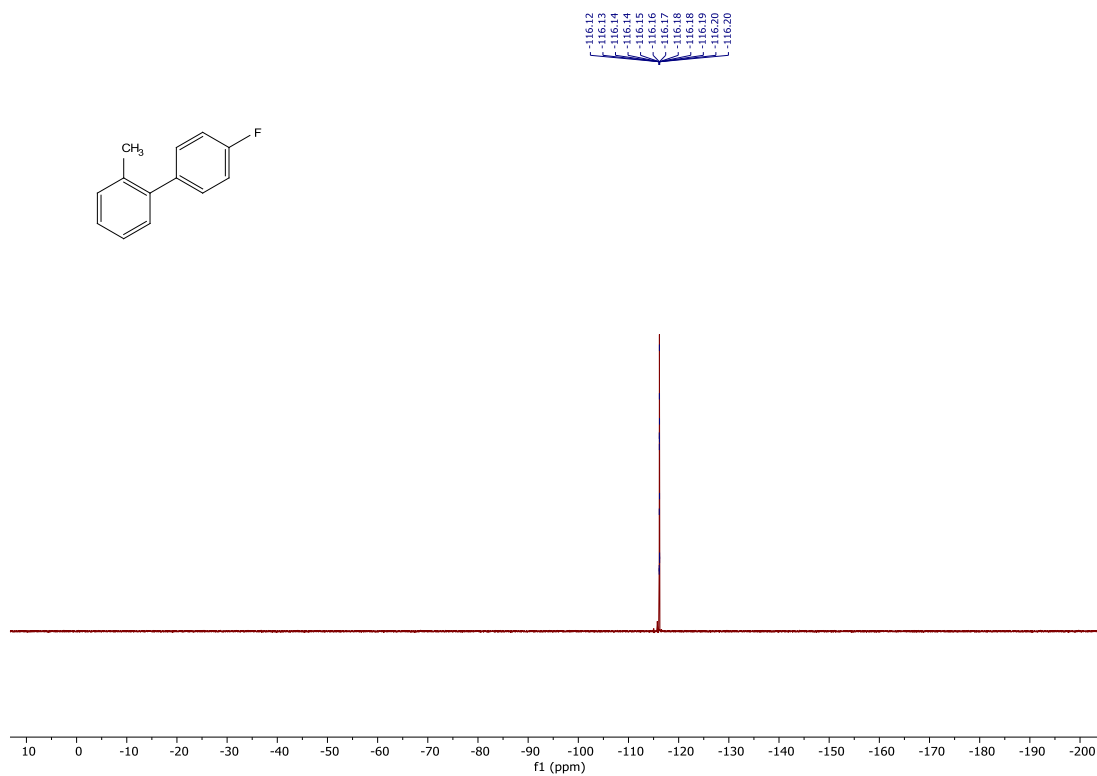




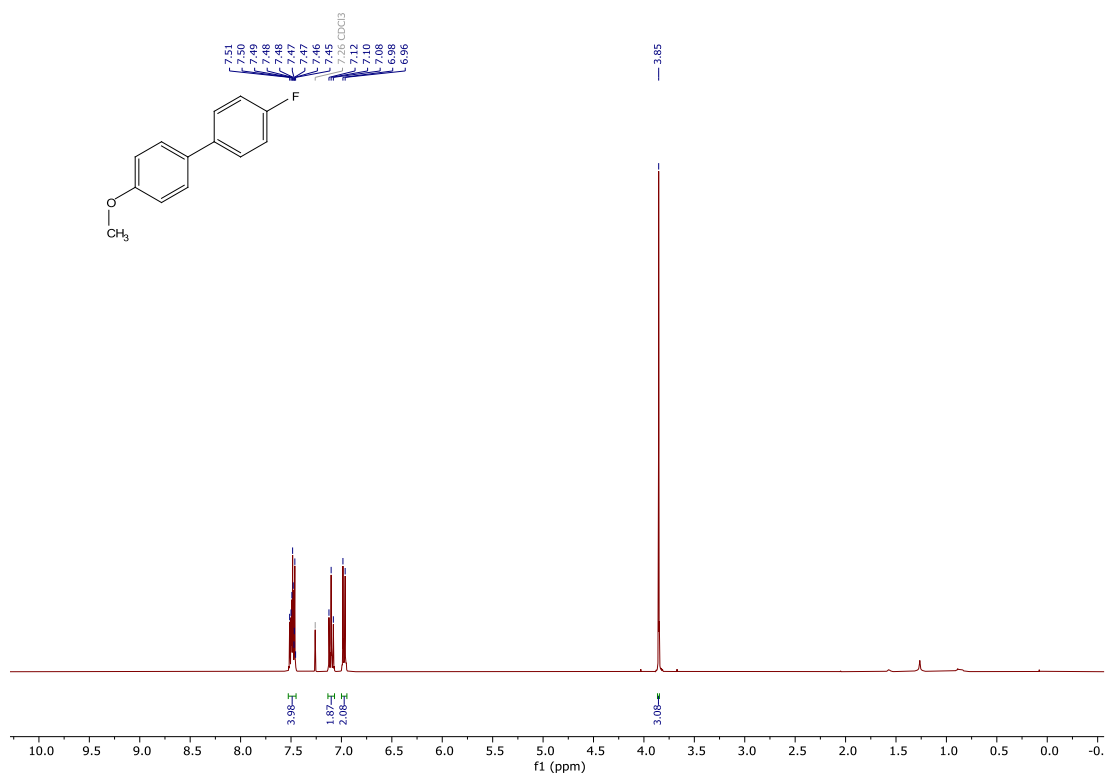


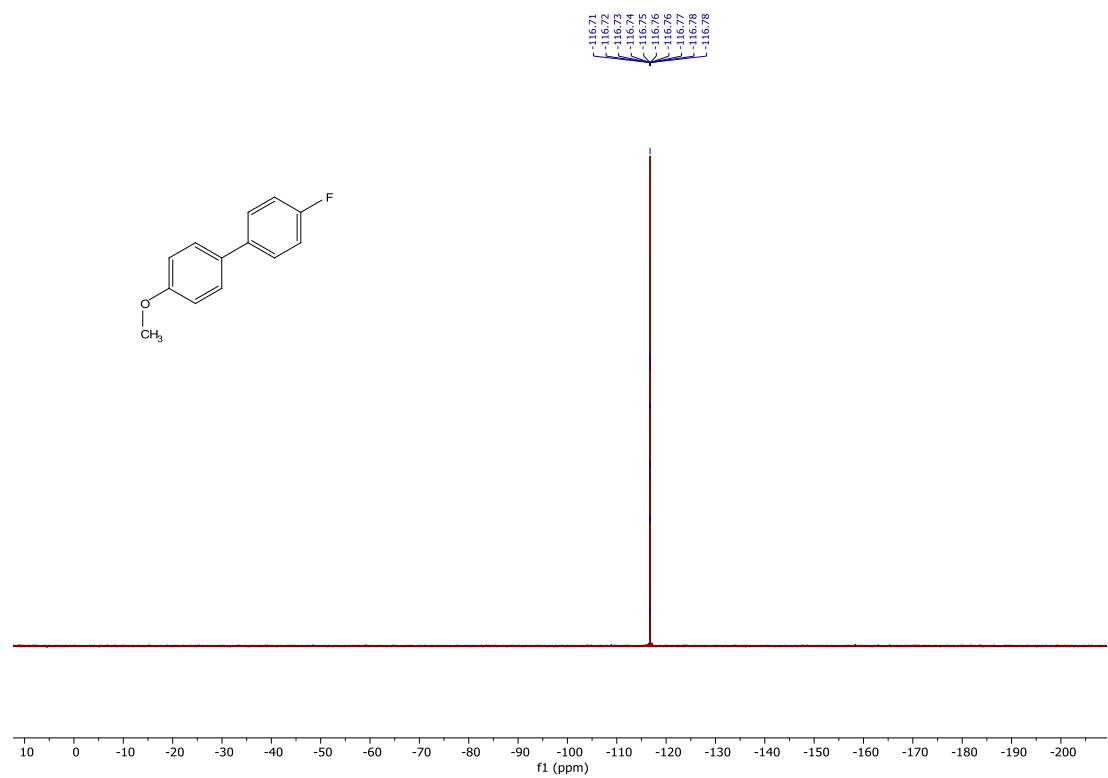
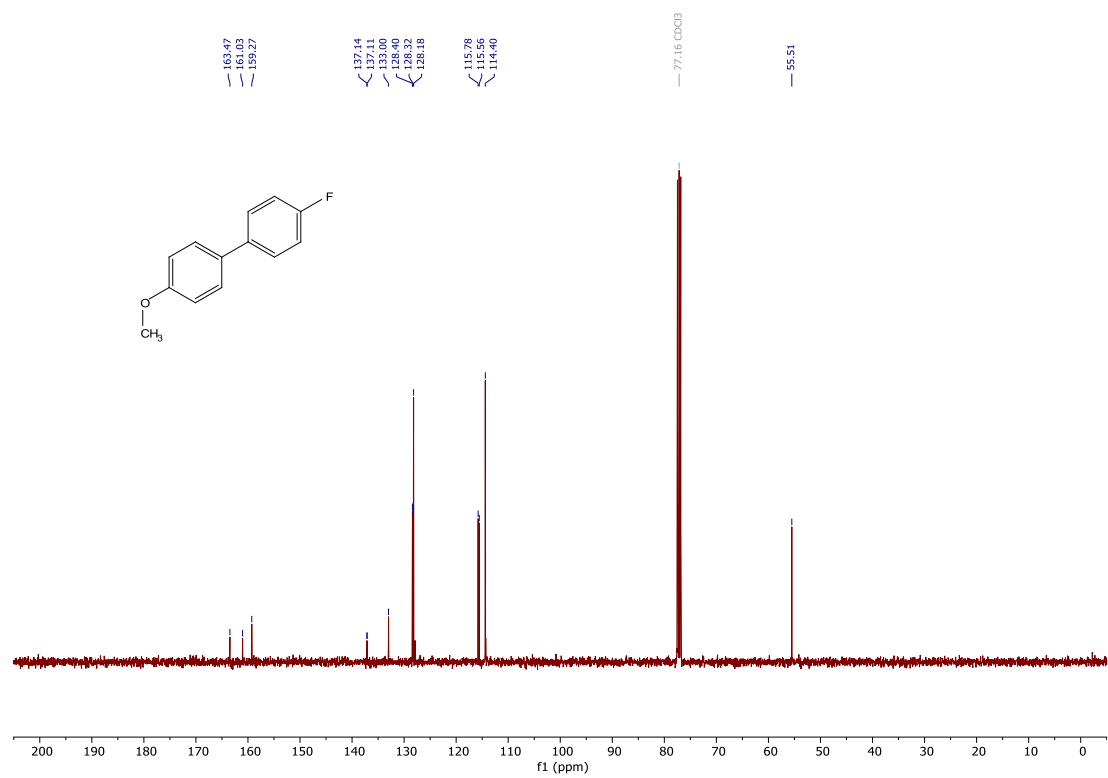
4'-fluoro-2-methyl-1,1'-biphenyl (37b)

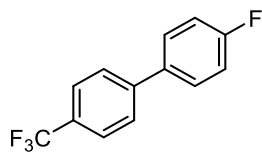




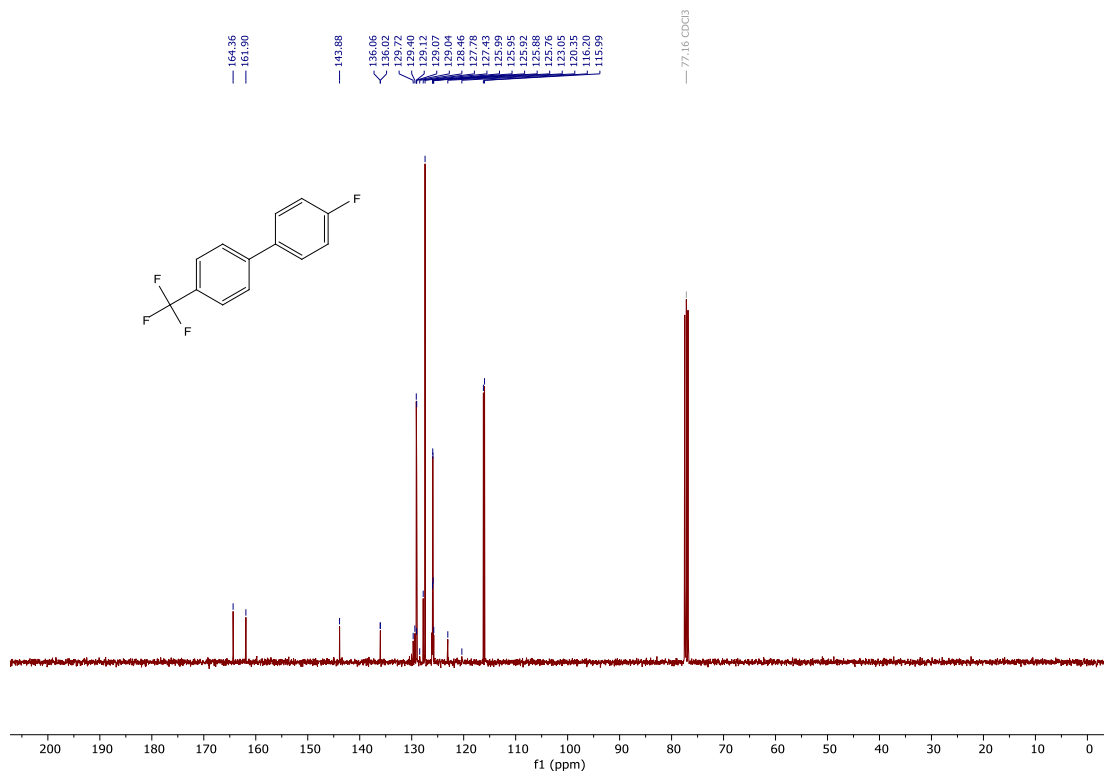
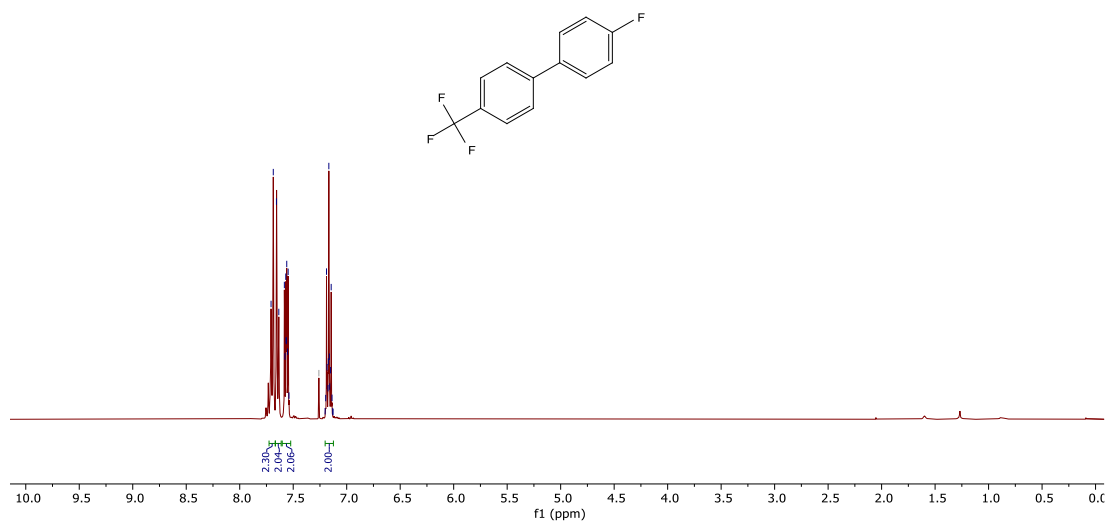
4-fluoro-4'-methoxy-1,1'-biphenyl (37c)

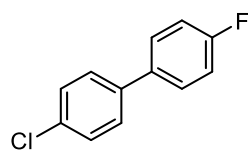
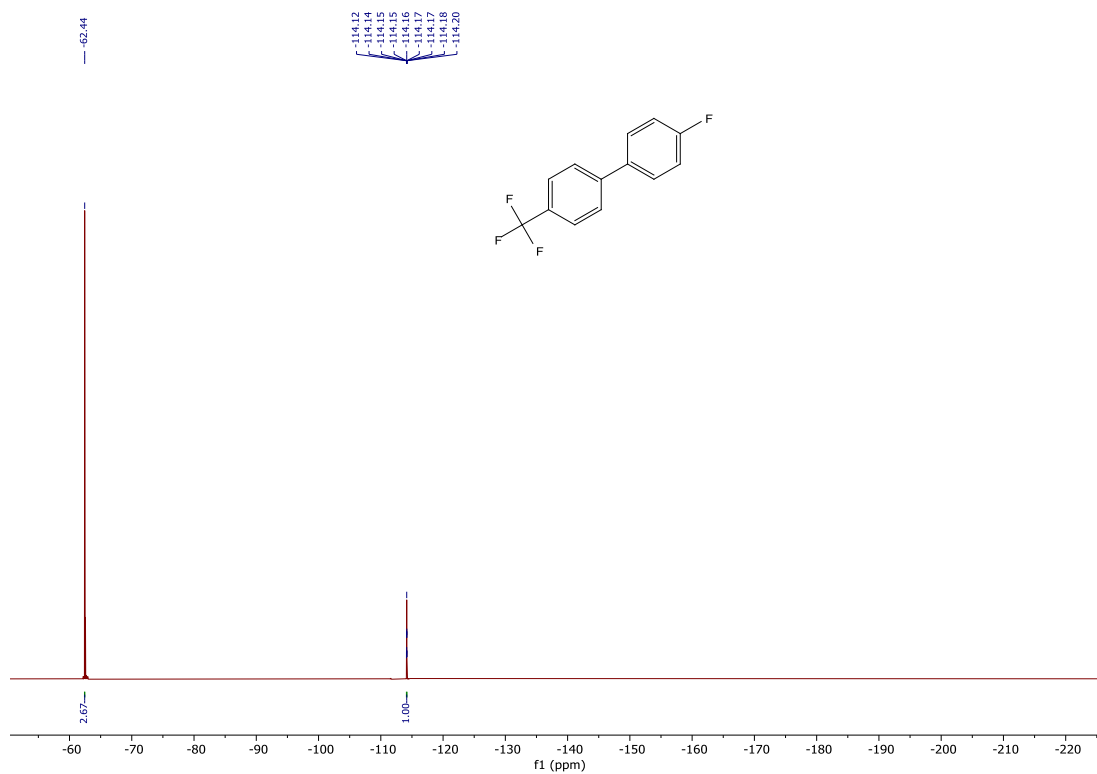




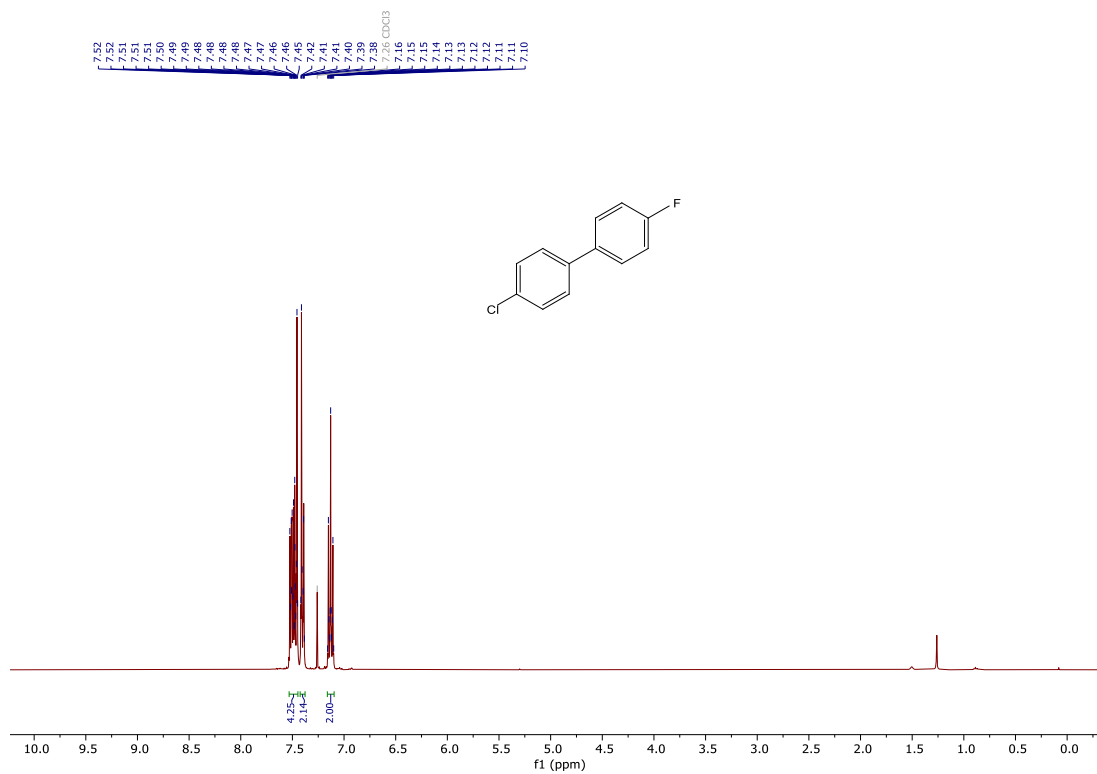


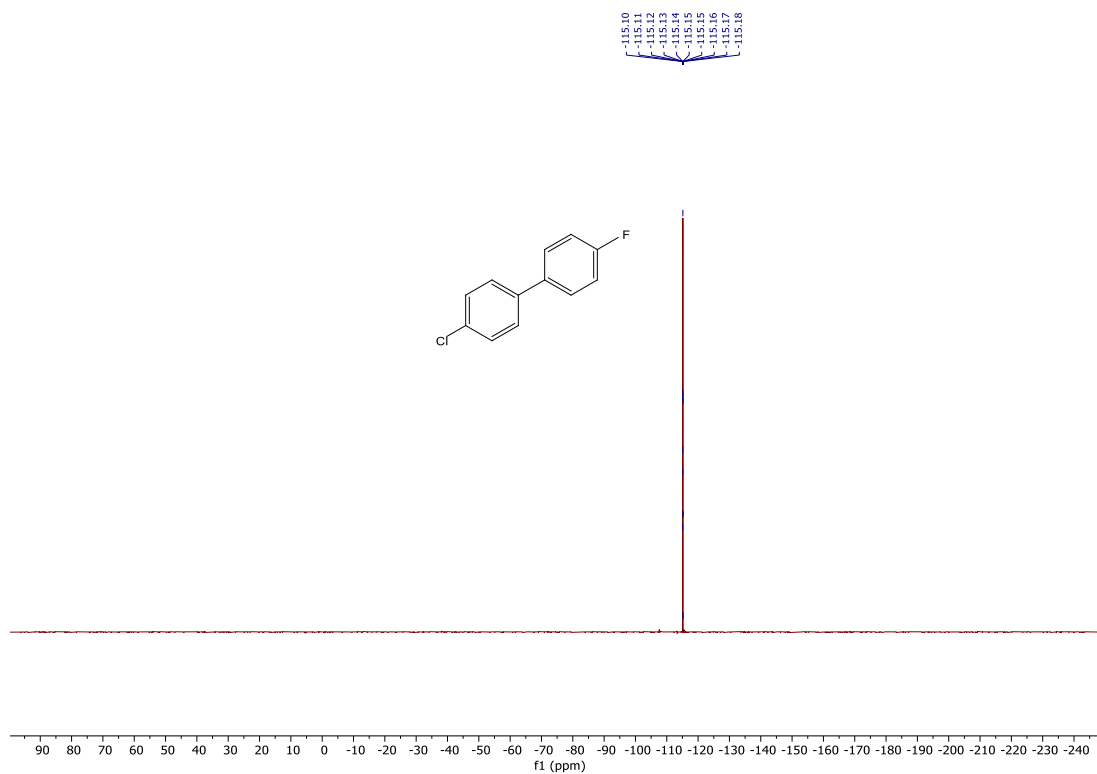
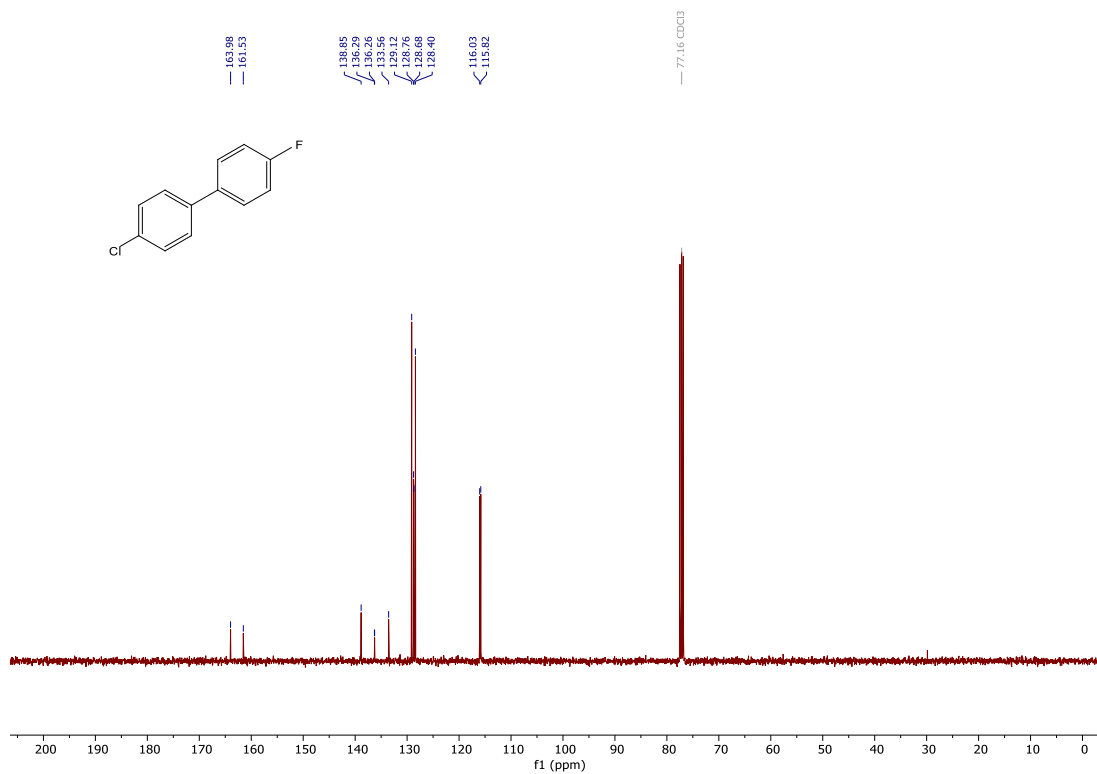
4-fluoro-4'-(trifluoromethyl)-1,1'-biphenyl (37d)

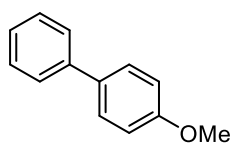




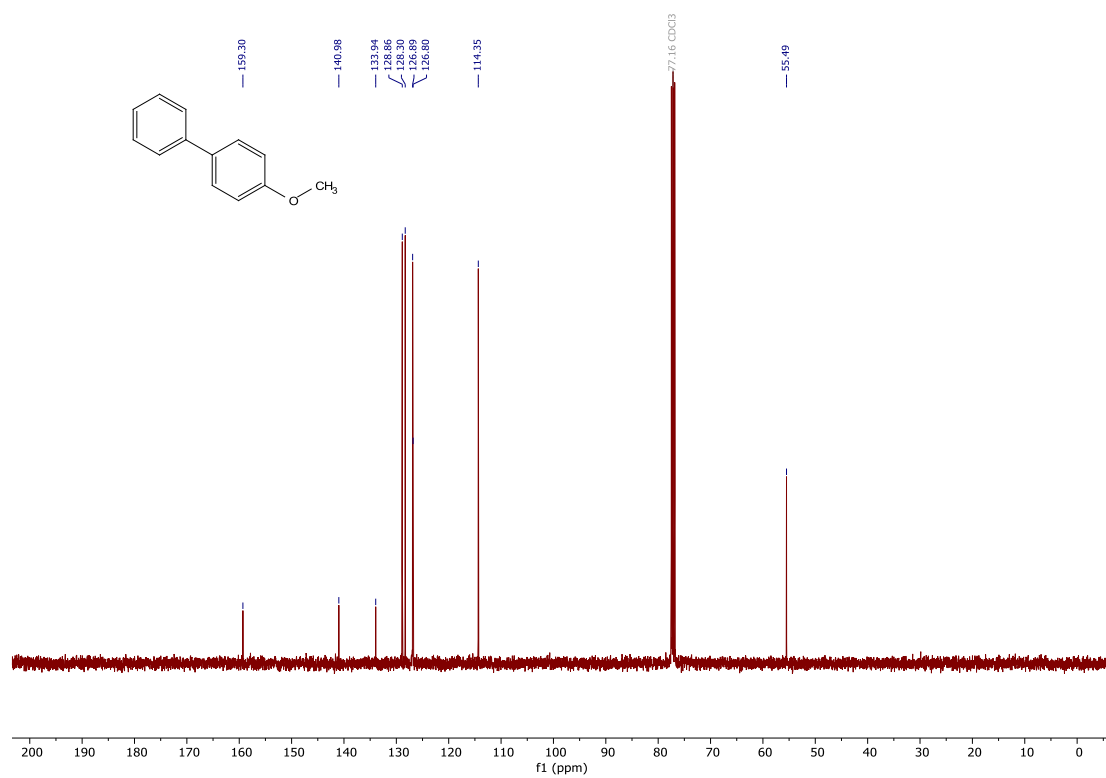
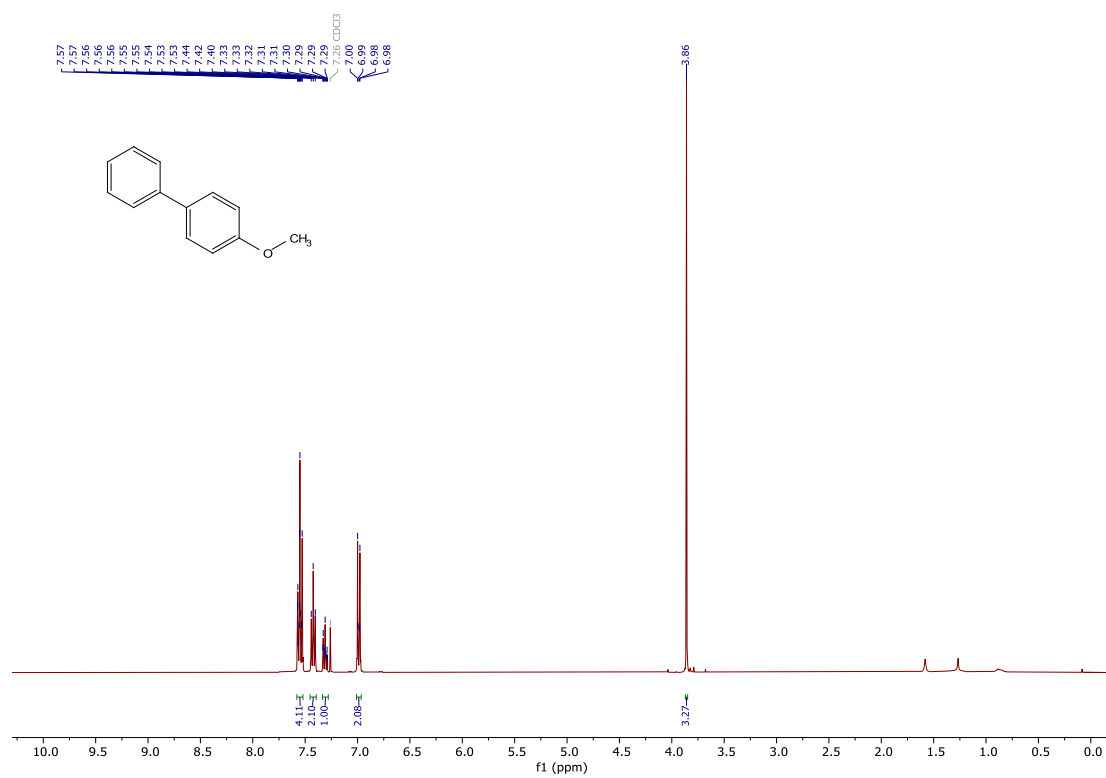
4-chloro-4'-fluoro-1,1'-biphenyl (3e)

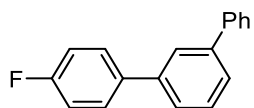




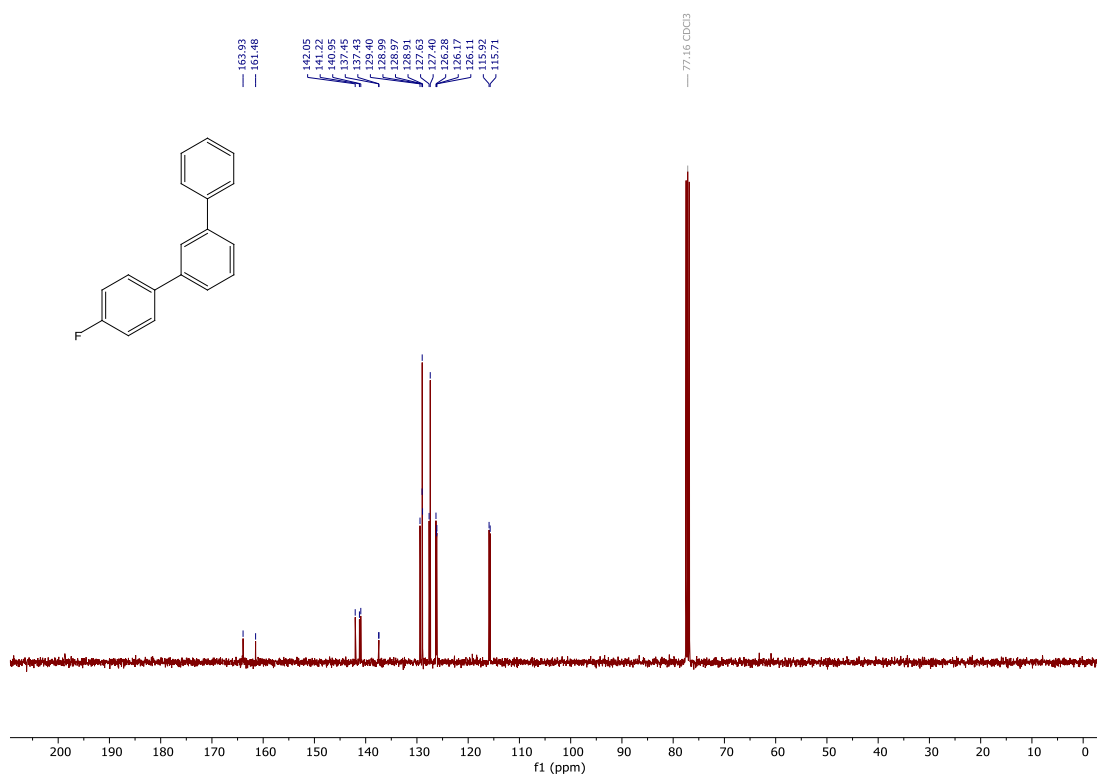
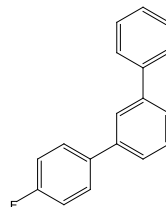
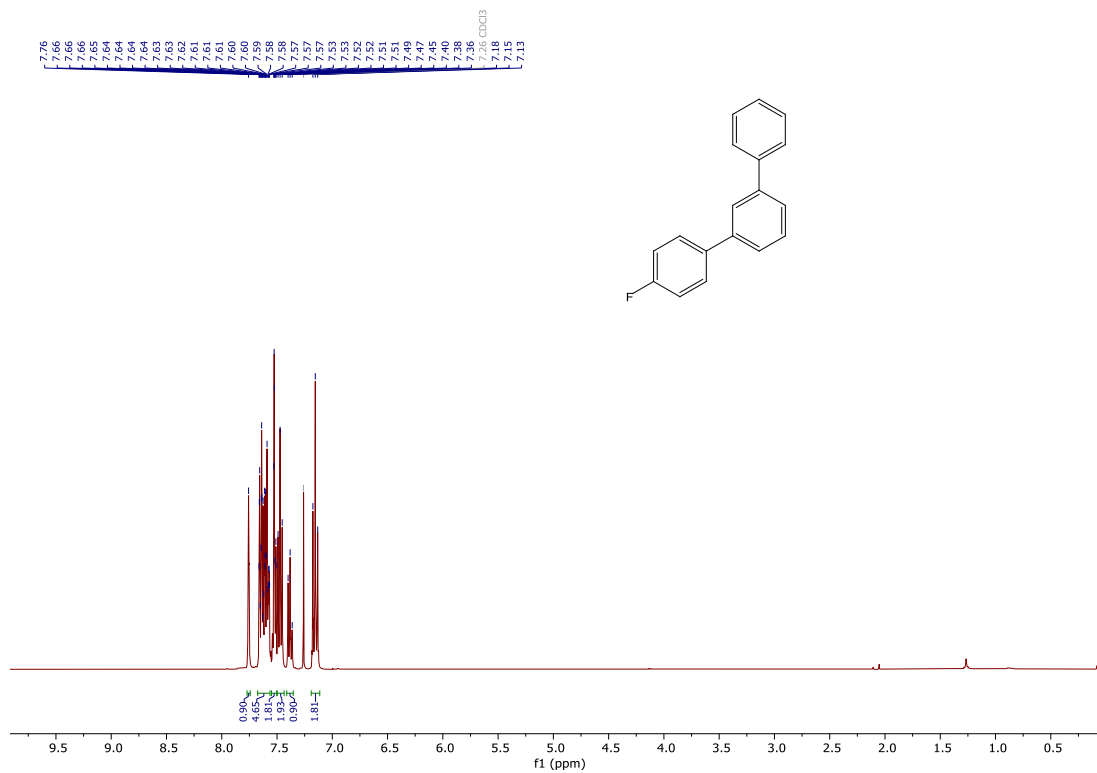


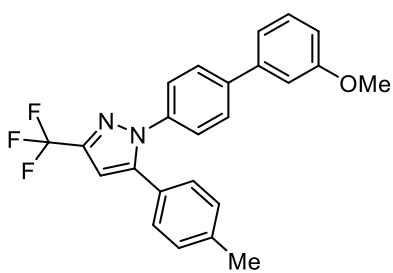
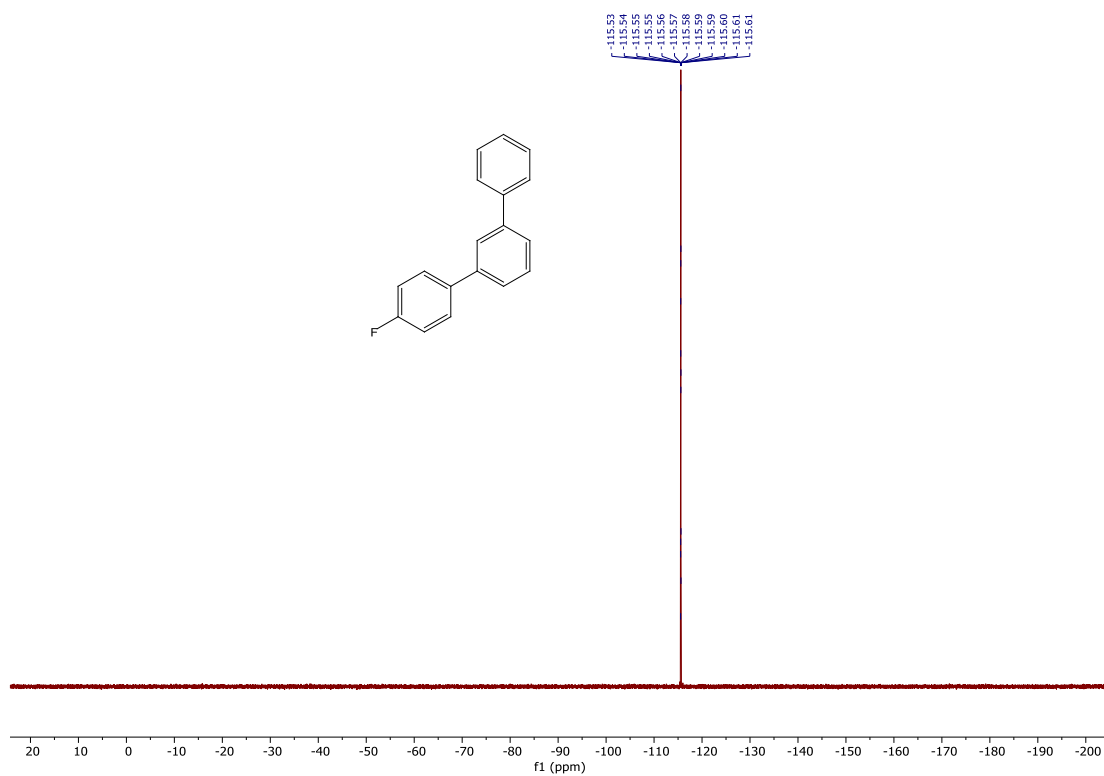
4-methoxy-1,1'-biphenyl (37f)



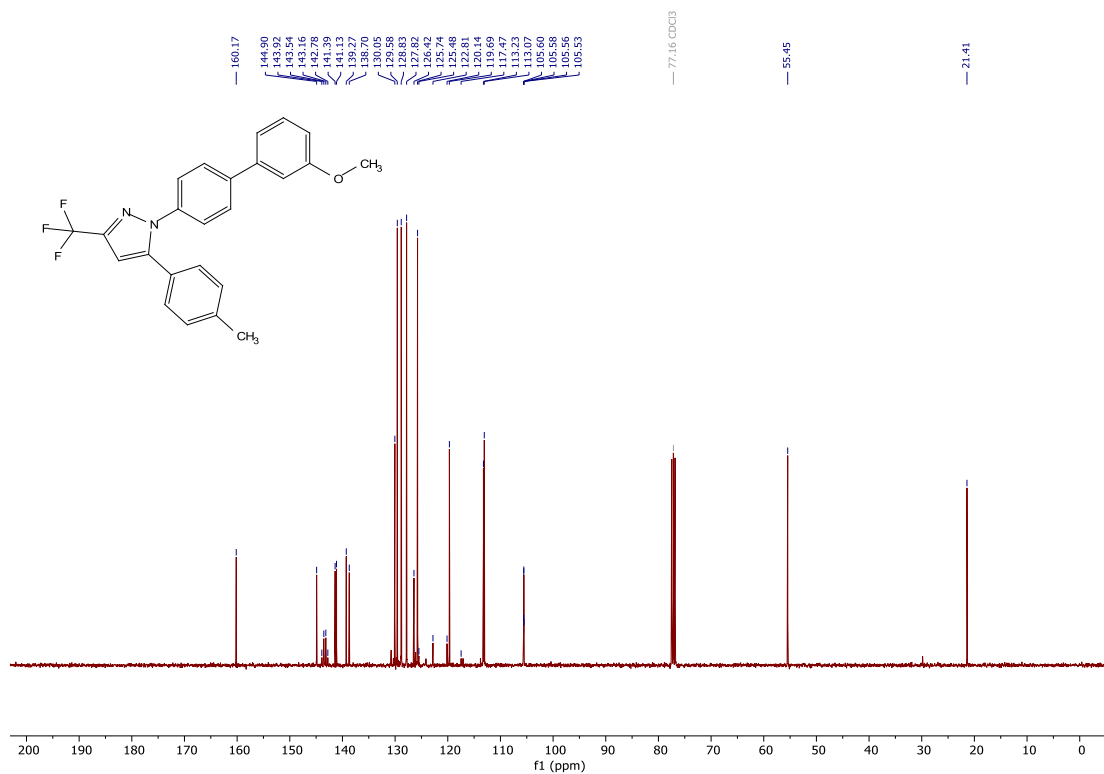
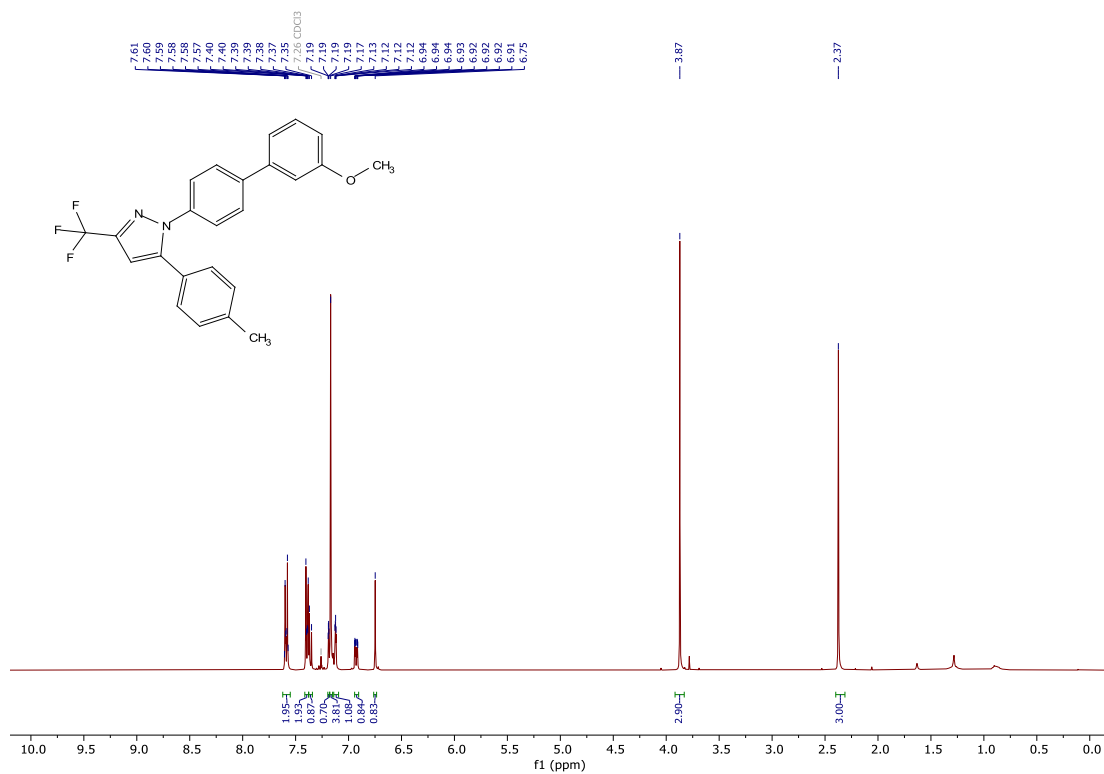


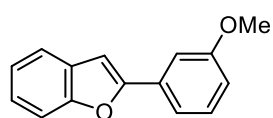
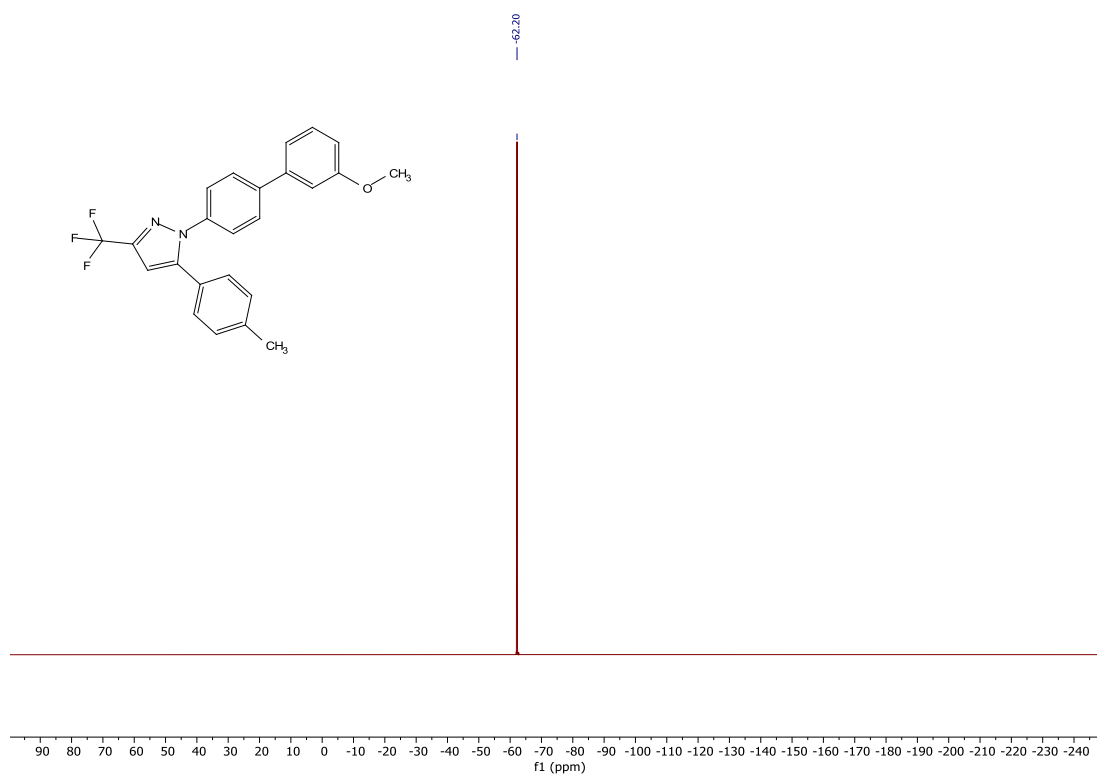
4-fluoro-1,1':3',1''-terphenyl (3g)



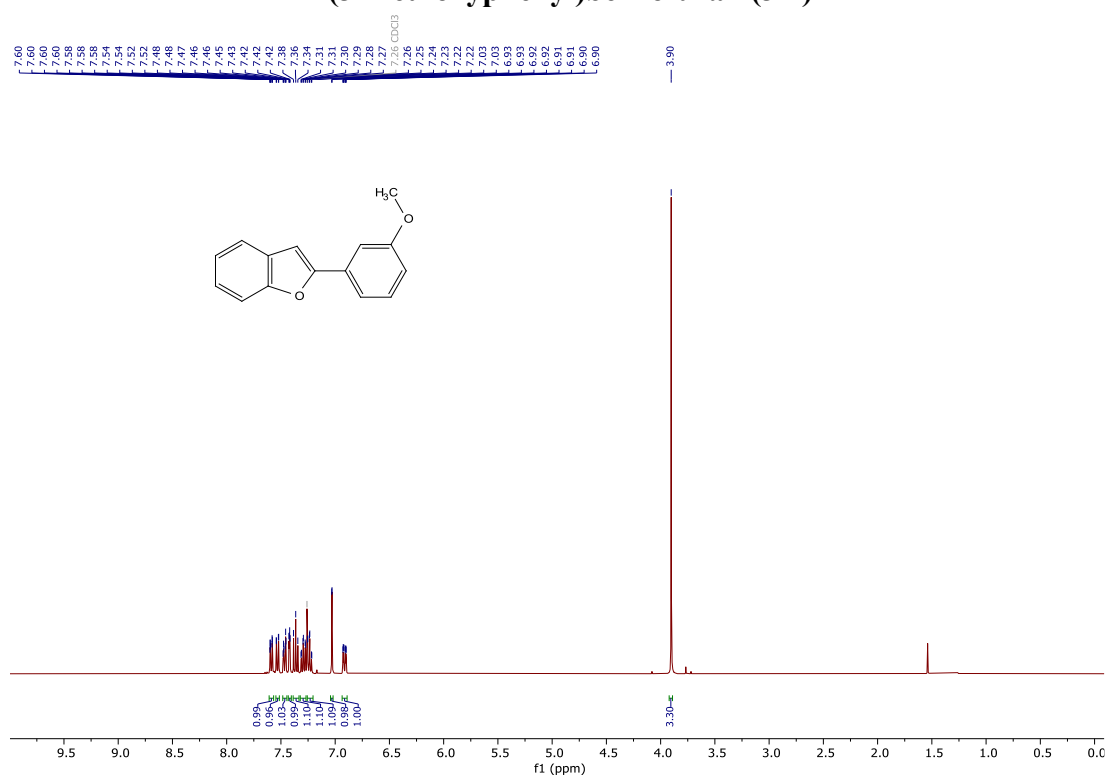


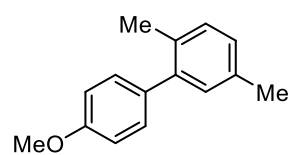
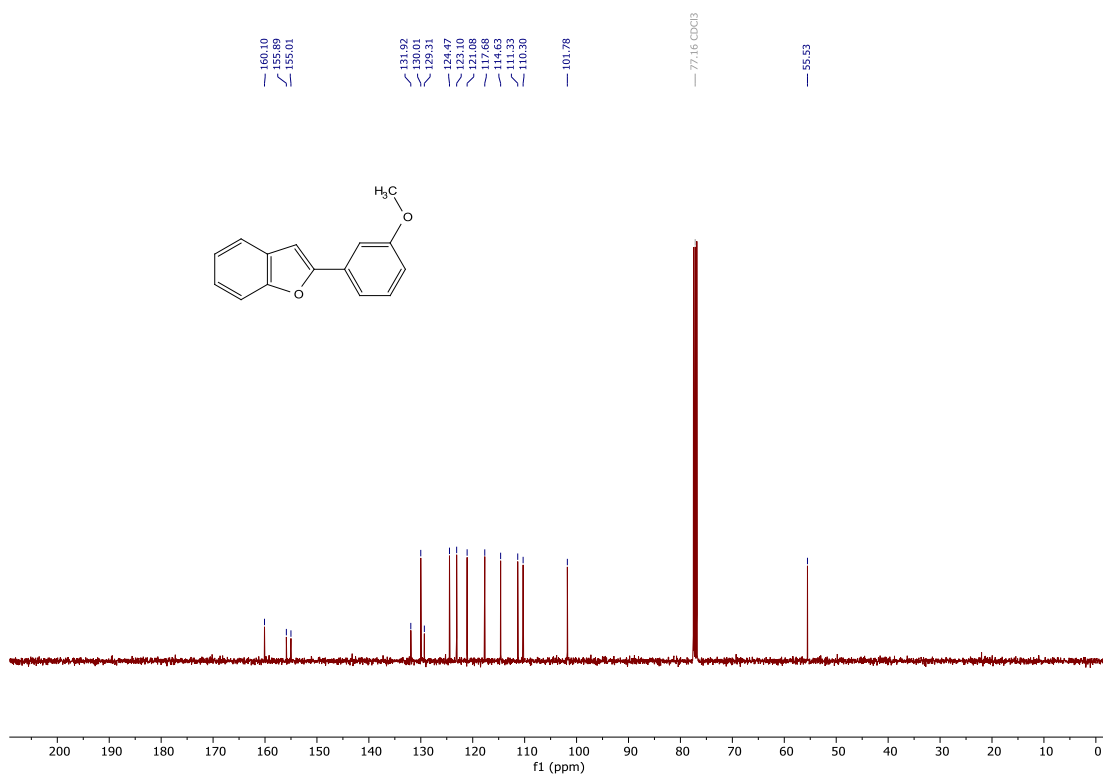
1-(3'-methoxy-[1,1'-biphenyl]-4-yl)-5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazole (37h)



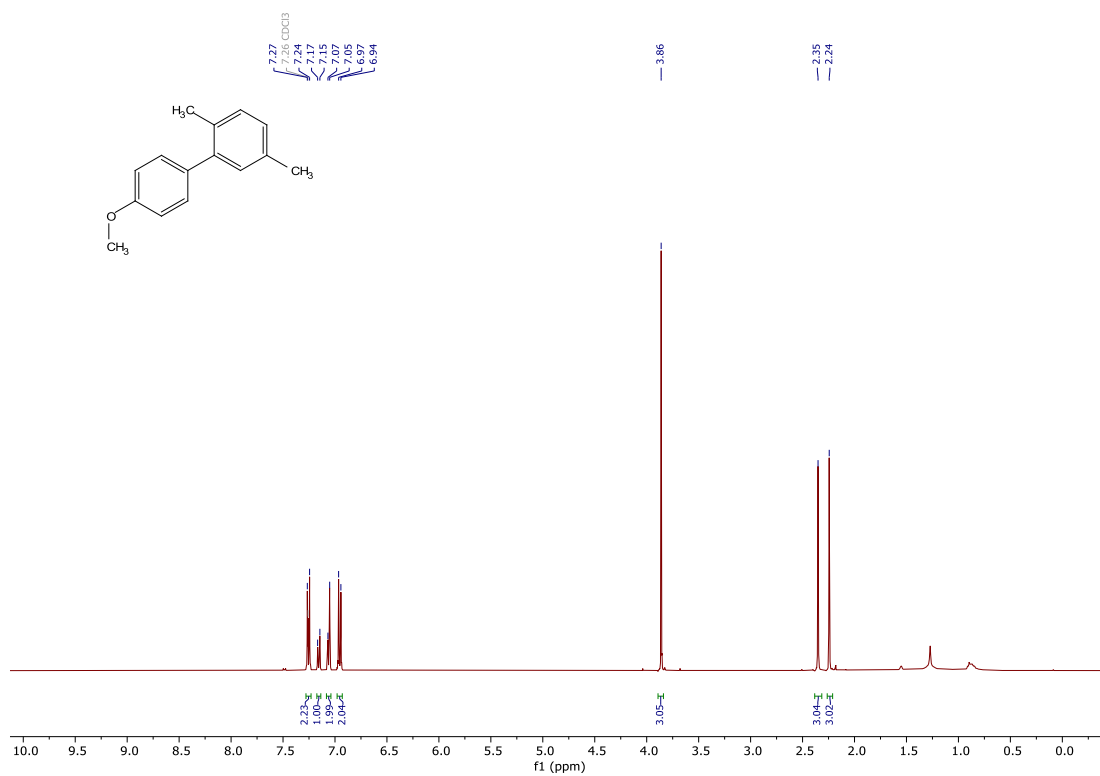


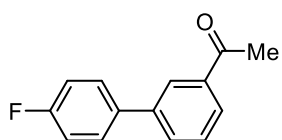
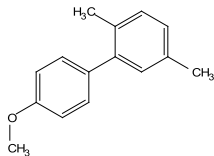
2-(3-methoxyphenyl)benzofuran (37i)





4'-methoxy-2,5-dimethyl-1,1'-biphenyl (37k)





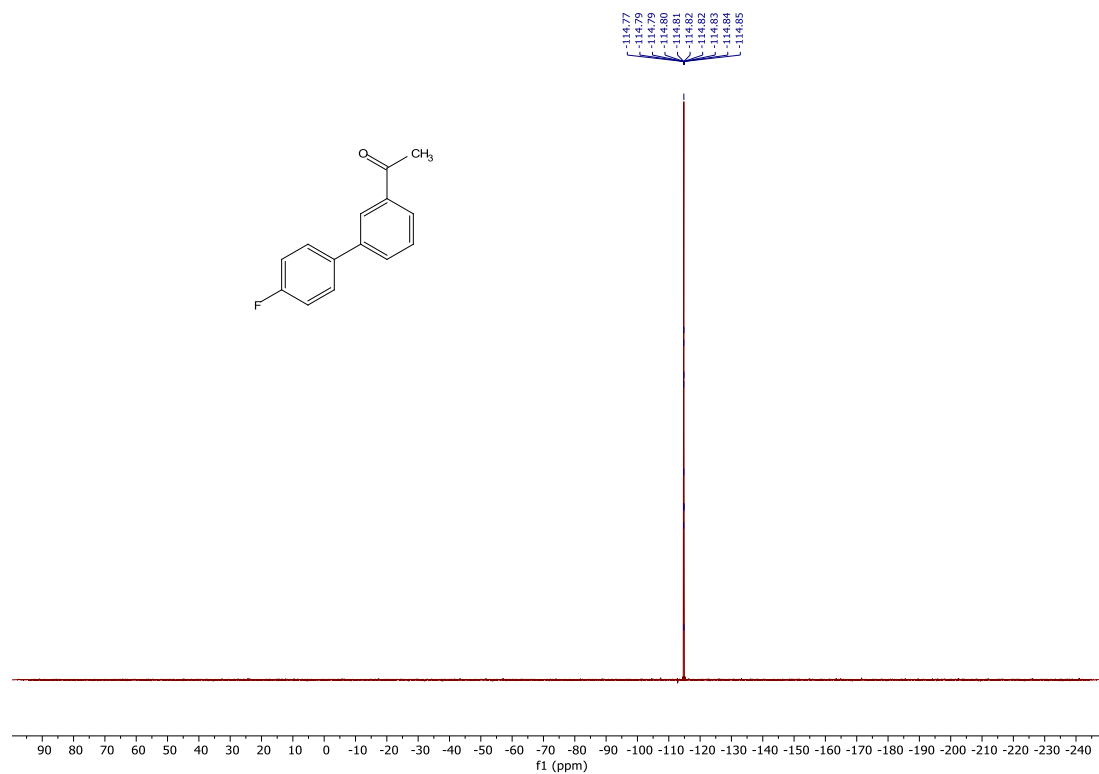
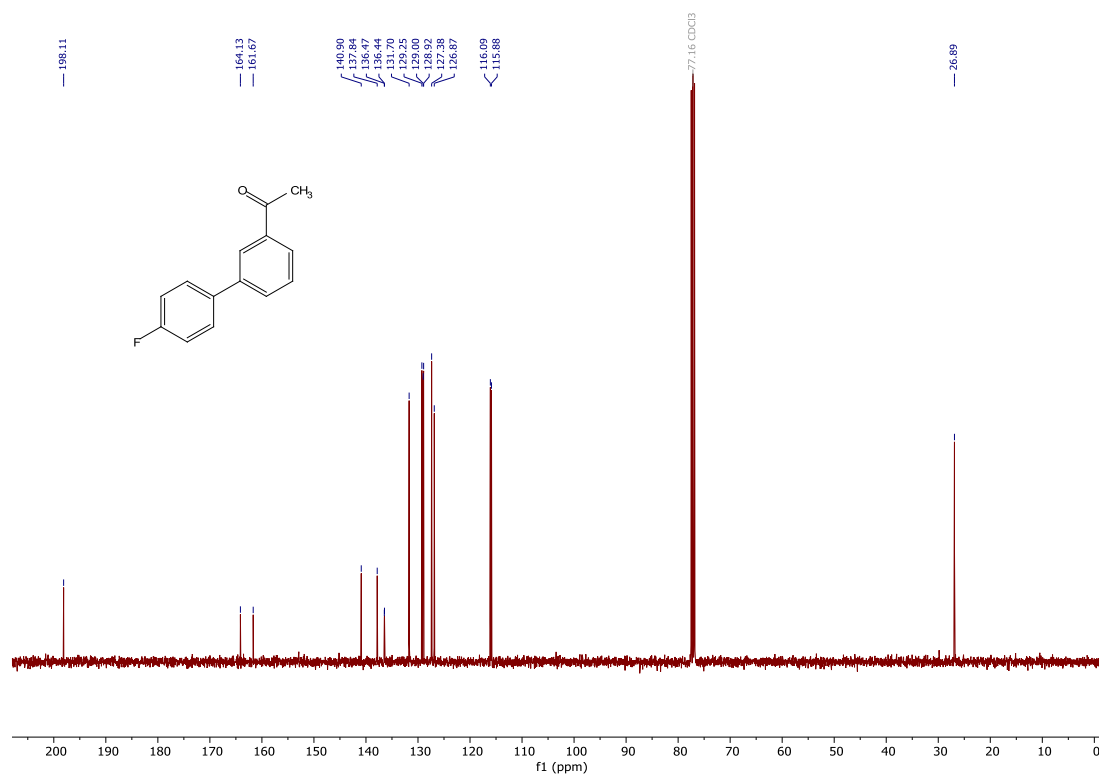
FC1=CC=C(C=C1)-C2=CC=C(C=C2)C(=O)O

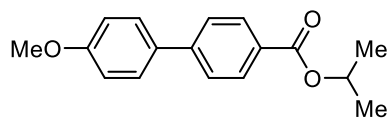
12.66

8.14, 8.13, 8.13, 7.94, 7.94, 7.94, 7.93, 7.92, 7.92, 7.92, 7.91, 7.75, 7.75, 7.75, 7.75, 7.74, 7.73, 7.73, 7.73, 7.73, 7.60, 7.59, 7.58, 7.58, 7.57, 7.57, 7.56, 7.56, 7.55, 7.54, 7.52, 7.52, 7.18, 7.18, 7.18, 7.17, 7.16, 7.16, 7.15, 7.15, 7.14, 7.14, 7.13, 7.13

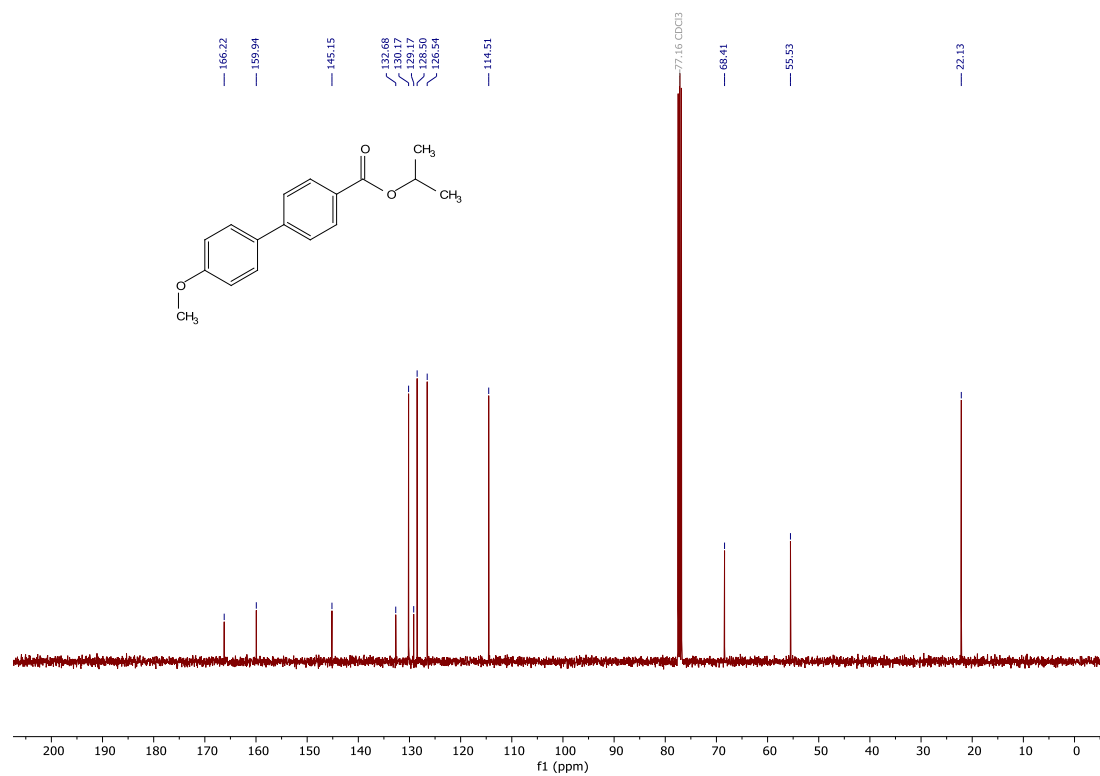
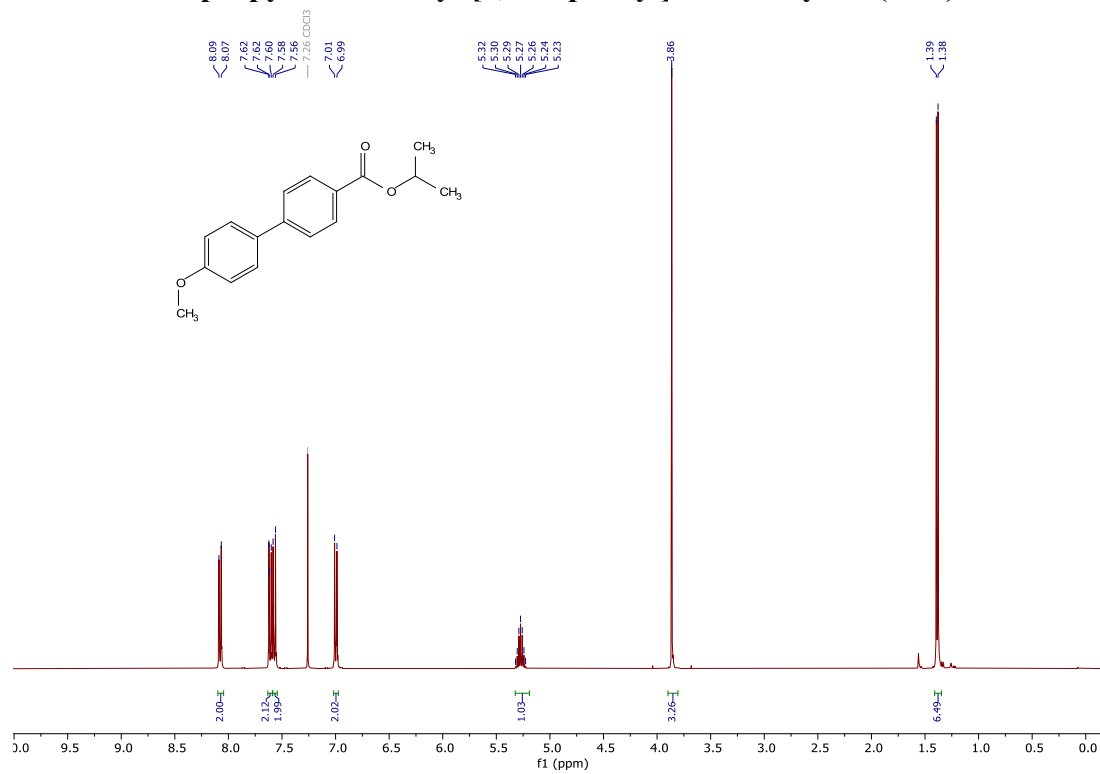
1.00, 1.05, 1.08, 3.32, 2.14, 3.40

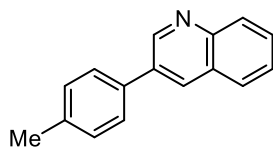
f1 (ppm)



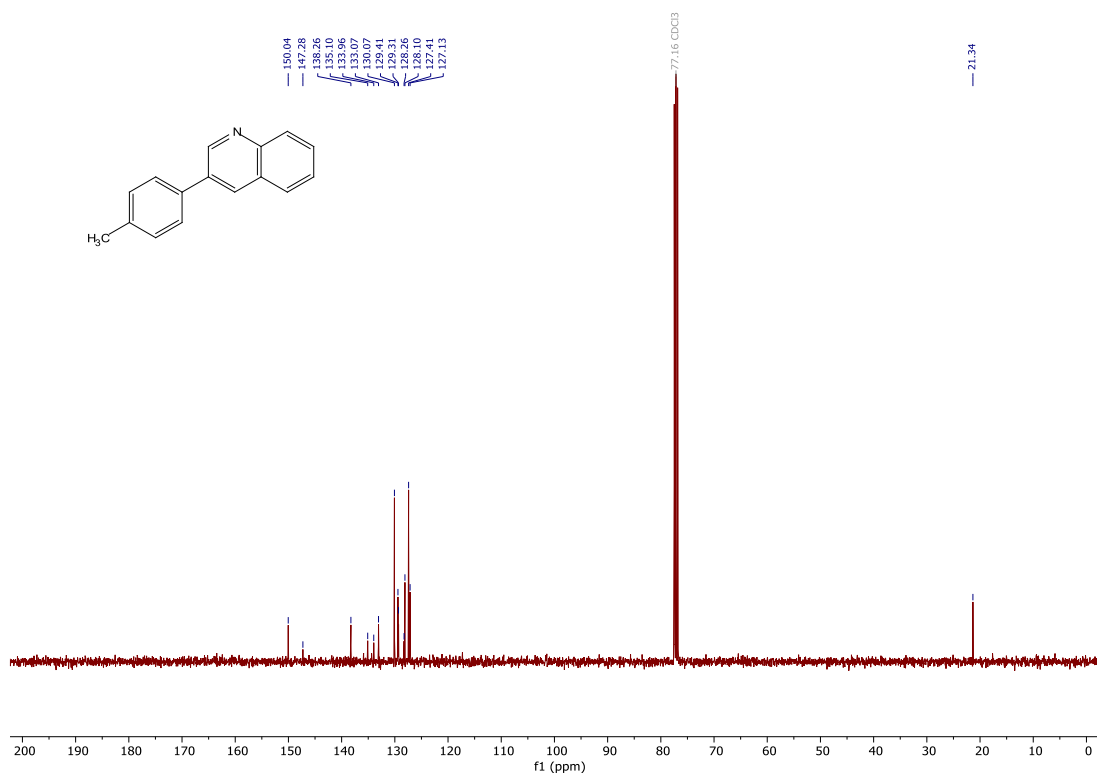
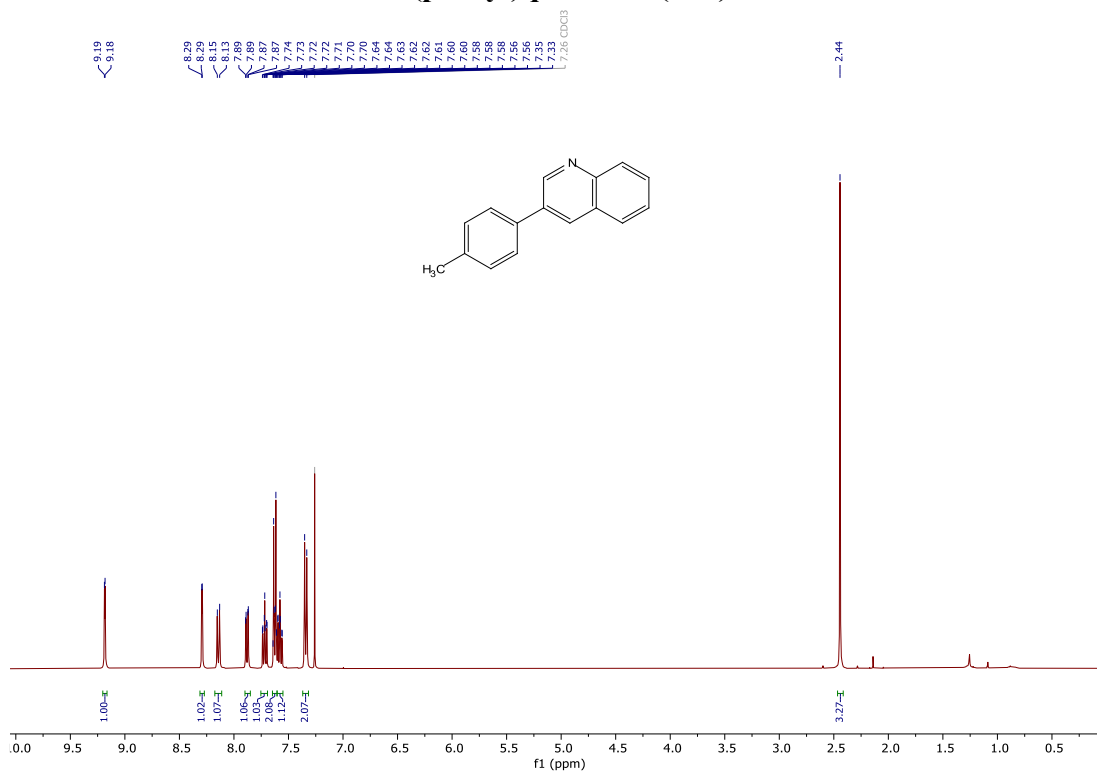


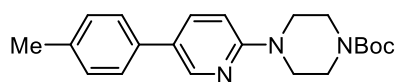
isopropyl 4'-methoxy- [1,1'-biphenyl]-4-carboxylate (37m)



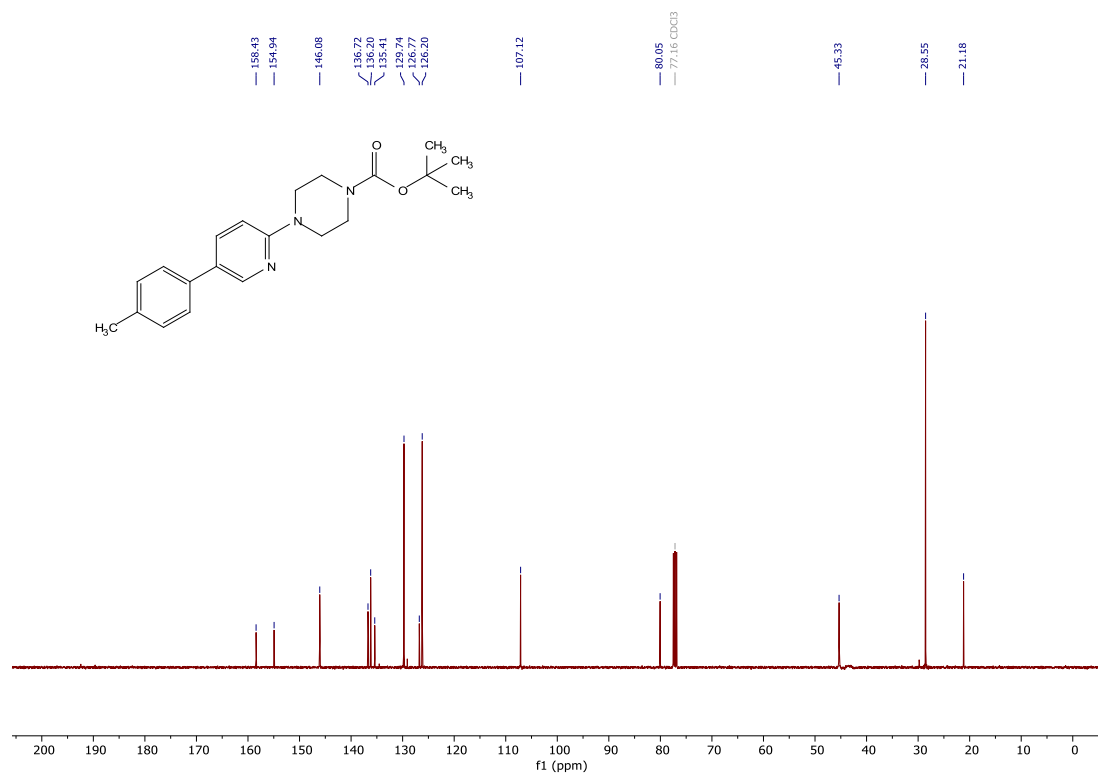


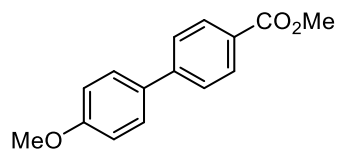
3-(p-tolyl)quinoline (37n)



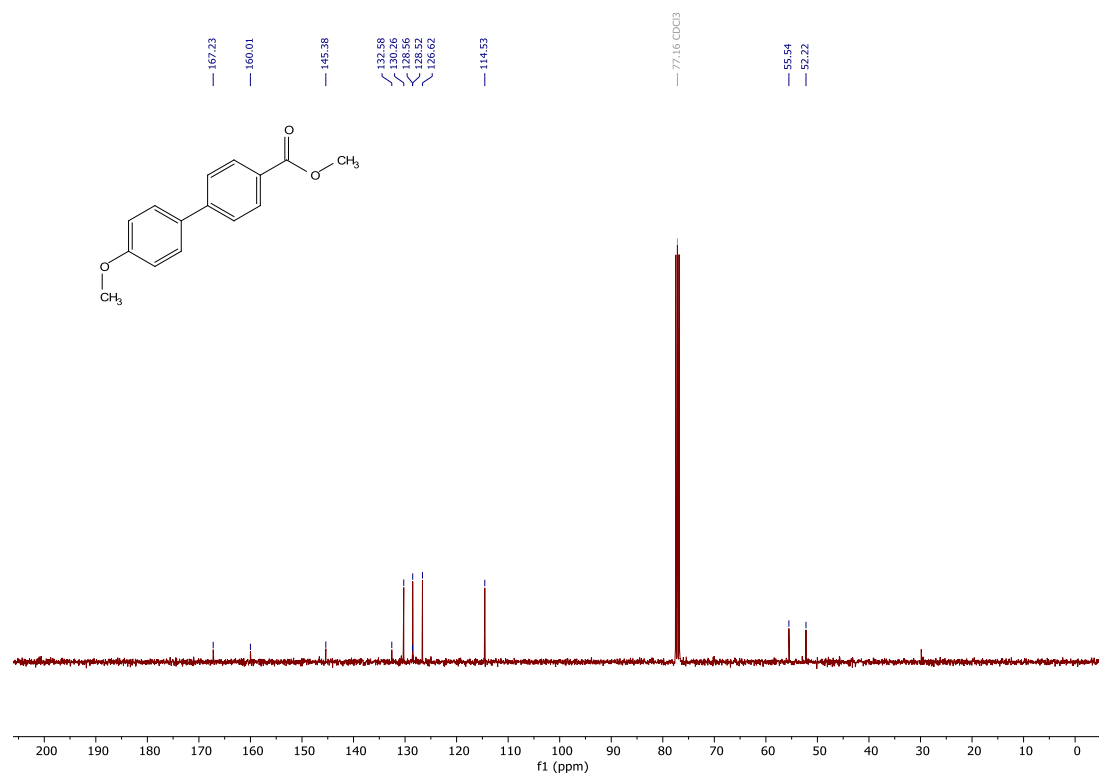
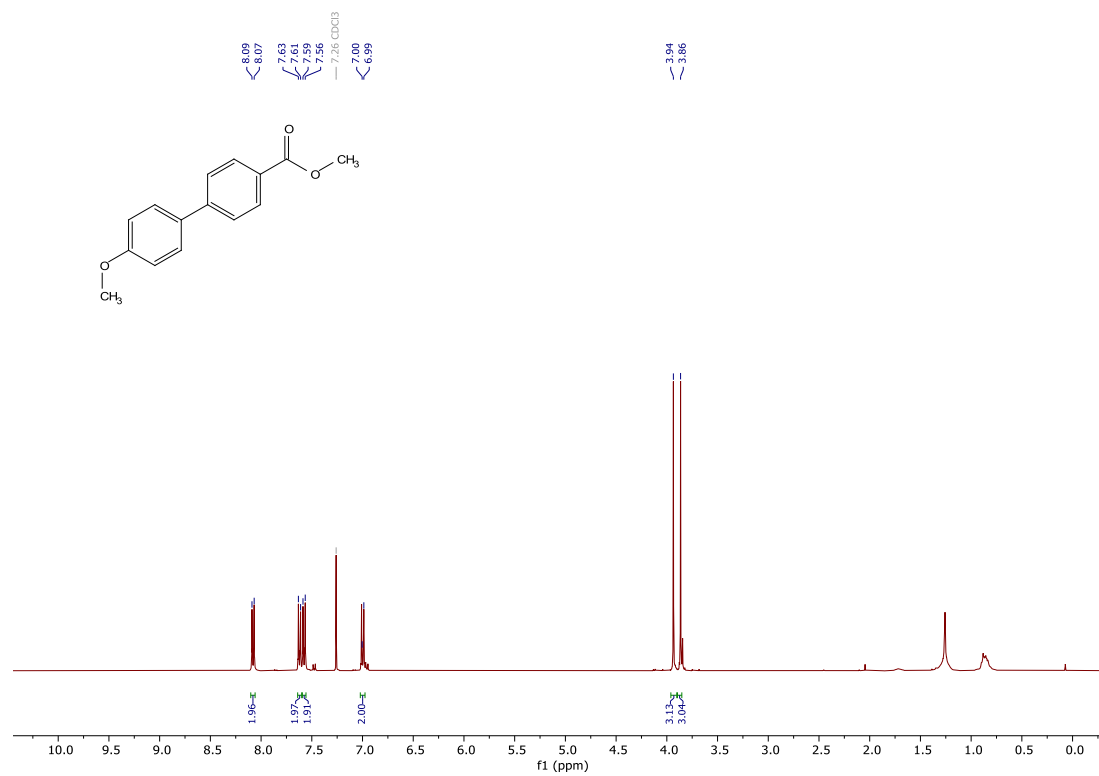


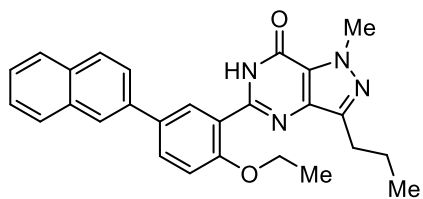
tert-butyl 4-(5-(p-tolyl)pyridin-2-yl)piperazine-1-carboxylate (37o)



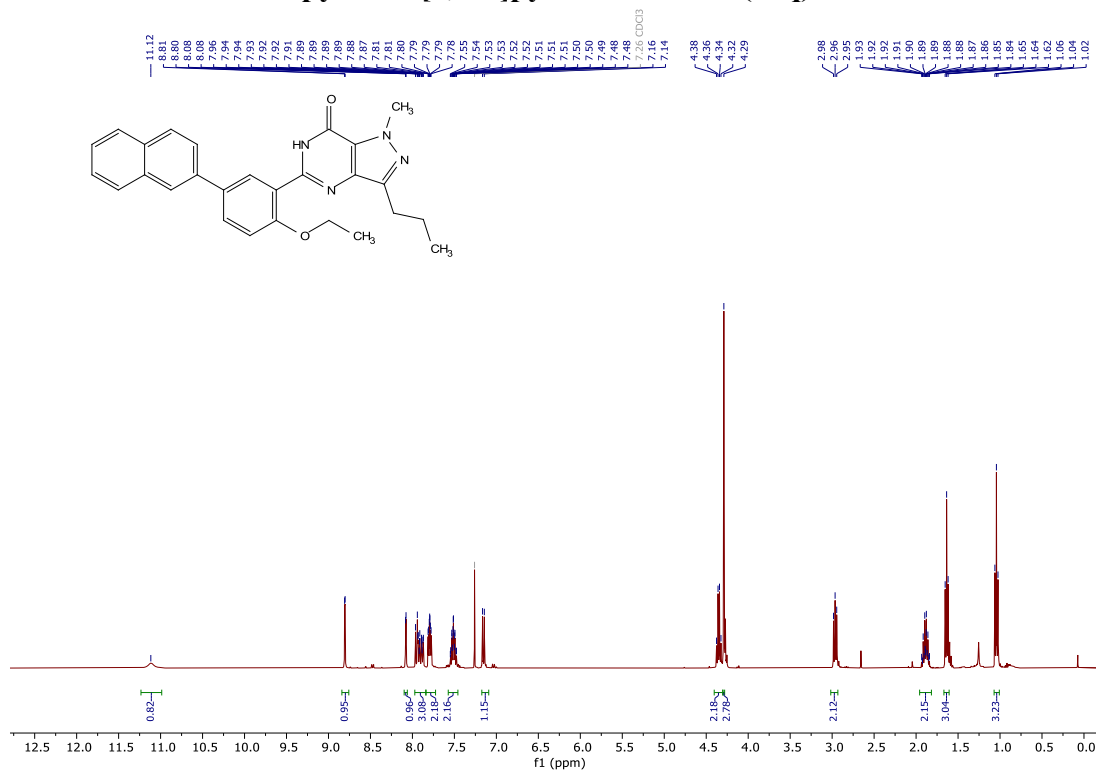


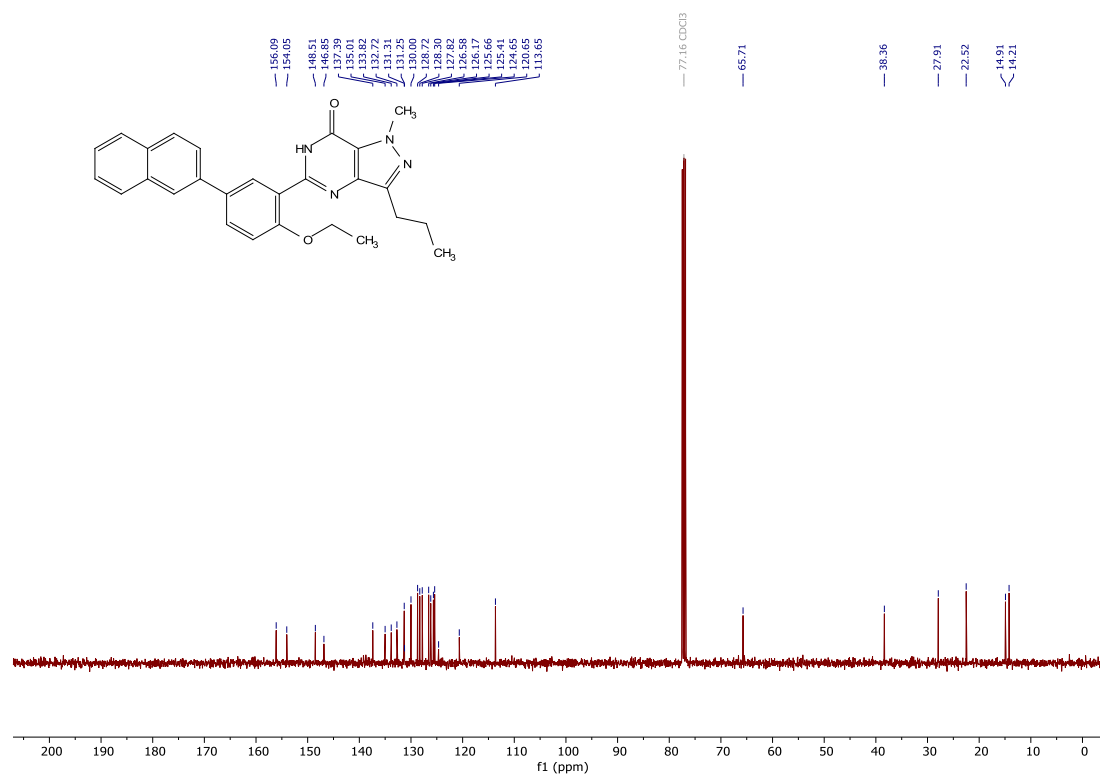
methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (37p)



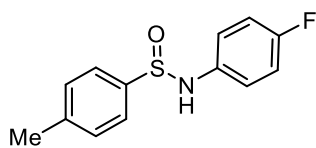


5-(2-ethoxy-5-(naphthalen-2-yl)phenyl)-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (37q)

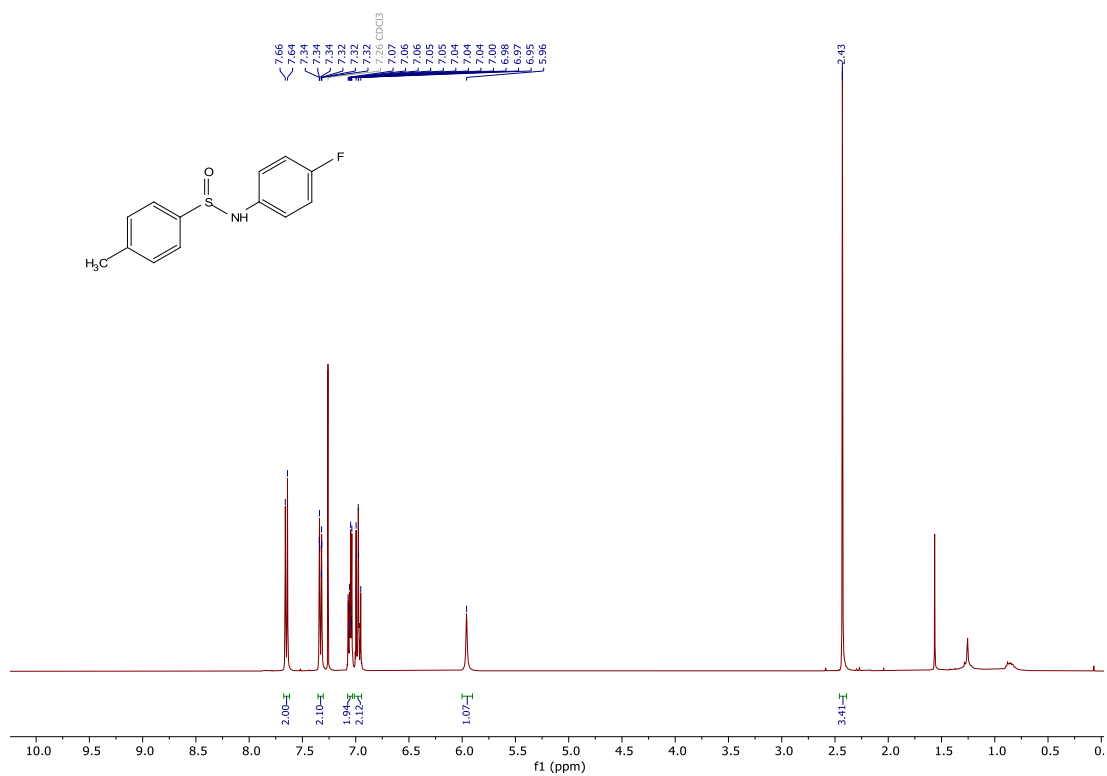


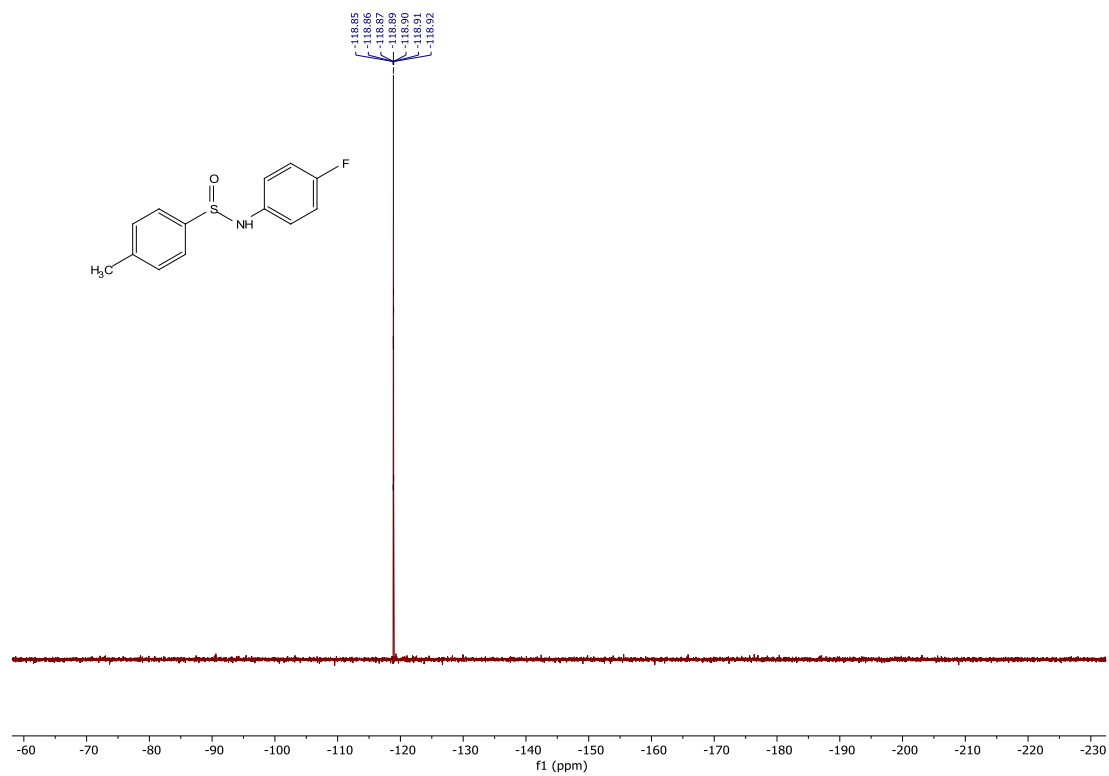
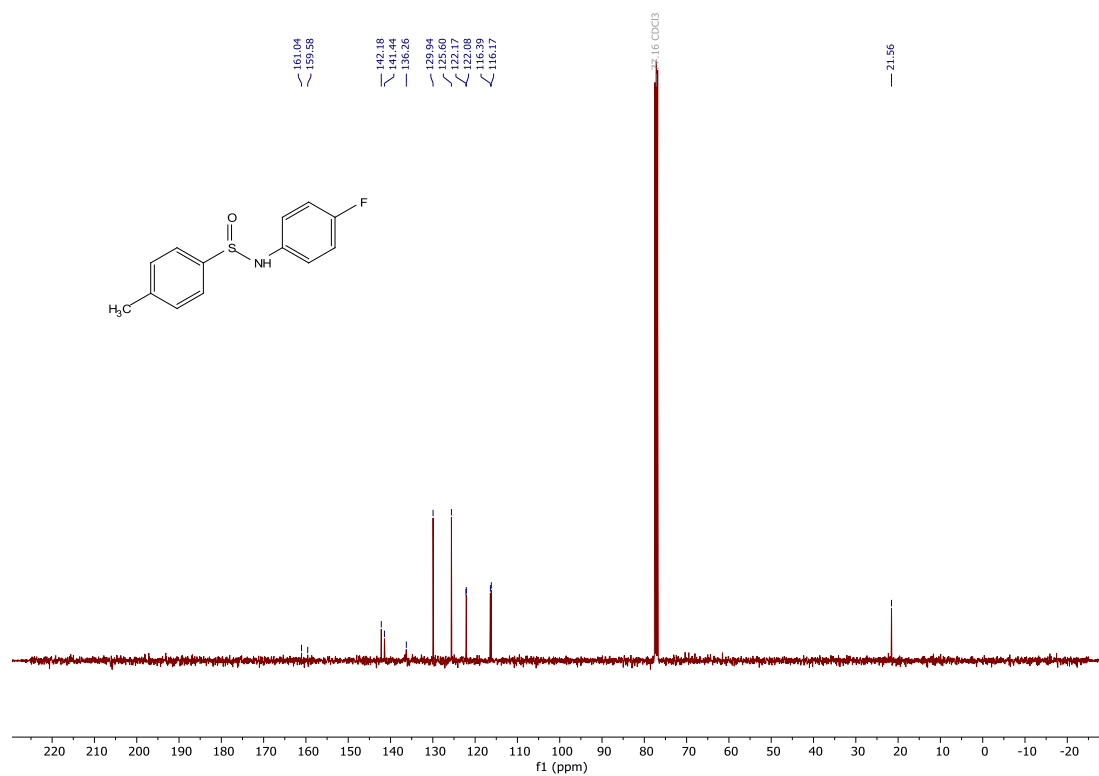


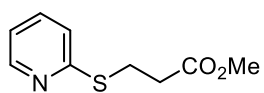
8.3.2. Sulfinamide and sulfoximine compounds



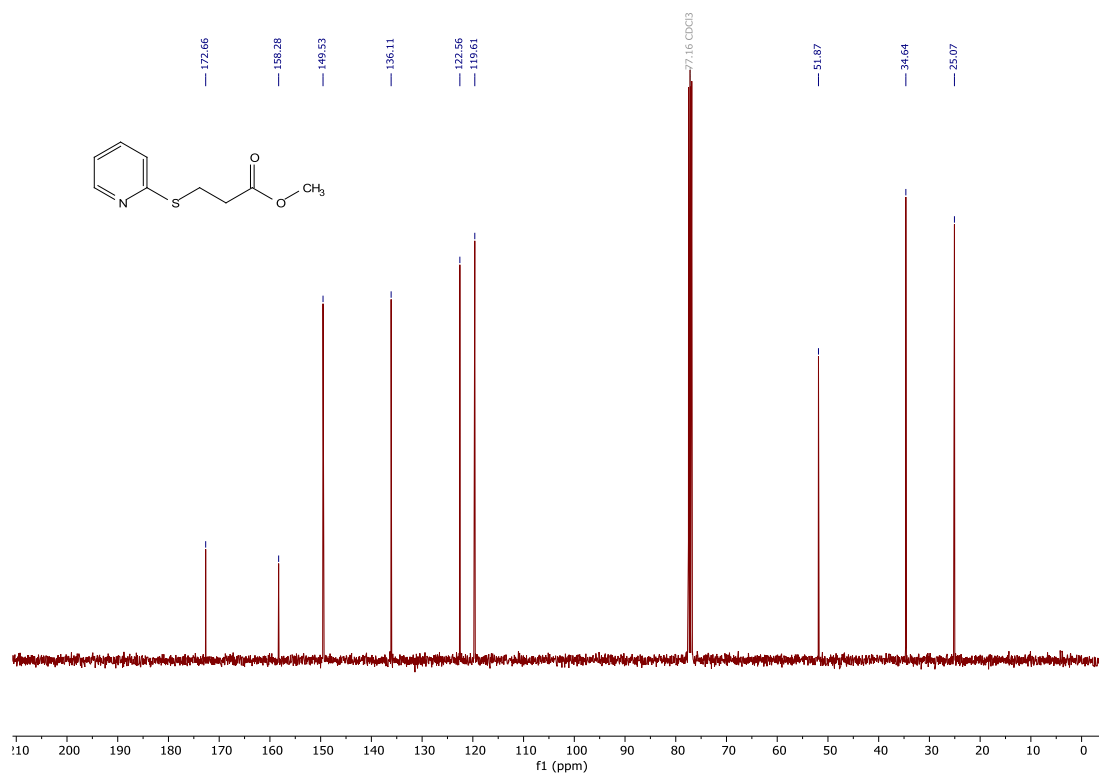
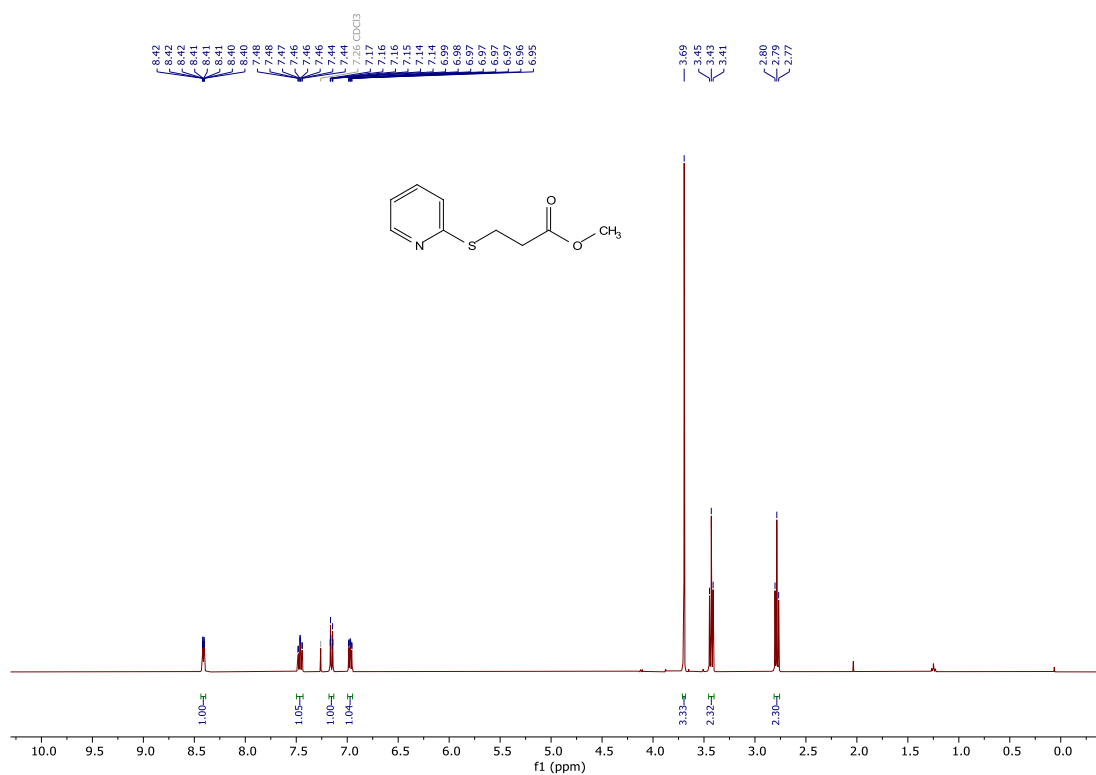
***N*-(4-fluorophenyl)-4-methylbenzenesulfonamide (43)**

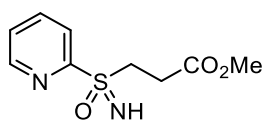






methyl 3-(pyridin-2-ylthio)propanoate (*pre-44b*)





methyl 3-(pyridine-2-sulfonimidoyl)propanoate (44b)

