

Methodology Development for Facile Access to Biphenyls and Multi-Arylated Heteroarenes *via* Pd-catalyzed Cross-Couplings

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Abstract

Methodology development for facile access to multi-arylated heteroarenes and biphenyls via Pd-catalyzed cross-couplings

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Multi-arylated heteroarenes and bi-phenyls are important motifs in a number of industries, such as organic semi-conductors and medicinal chemistry. Biphenyls are classically synthesized by transition metal catalyzed cross-couplings. Typically, non-symmetric, multi-arylated thiophenes and furans are prepared either by cyclization or transition metal catalyzed cross-coupling reactions. The latter strategy is more attractive as it allows for late stage functionalization and facilitates the synthesis of compound libraries. It is, however, more challenging to regioselectively functionalize each position on the heteroarene with cross-coupling. These synthetic steps tend to require a stoichiometric amount of organometallic reagent, and therefore generate heavy metallic waste, and can be impractical in terms of air- and moisture-sensitivity and long reaction times. To facilitate access to multi-arylated thiophenes and furans, we have developed cross-coupling methodologies that utilize the different facets of a carboxylic acid/ester functional group to regioselectively arylate thiophene and furan. This approach is both greener than previously reported methodologies and very practical in its relative simplicity. First, a double decarboxylative cross-coupling (DCC) route is devised as an effective strategy for quick access to non-symmetric, di-arylated thiophenes. Second, an expanded route utilizing directed halogenation, DCC, and Suzuki-Miyaura cross-couplings is developed in order to access tetra-arylated thiophene, tetra-arylated furan, as well as the various isomers of di- and tri-arylated thiophenes and furans. Of the cross-couplings utilized in these modular routes, DCC has the advantage of avoiding the use of organometallic reagents to generate the nucleophilic coupling partner. Unfortunately, this reaction is low yielding with un-activated benzoic acids, and requires hazardous solvents, high temperatures and long reaction times with these substrates. To access biphenyl bonds with a cross-coupling reaction that minimizes organometallic waste, avoids hazardous solvents and is done under relatively mild condition, a first-generation deselenative cross-coupling was also developed.

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List of Abbreviations

AIE	Aggregation Induced Emission
AIEgen	Aggregation Induced Emission Luminogen
BG	Blocking Group
BP2Tz	Bithiazole Co-oligomer
CBP	4,4'-Bis(N-carbazolyl)-1,1'-biphenyl
COX	Cyclooxygenase
DABSO	1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct
DCC	Decarboxylative Cross-Coupling
DG	Directing Group
DMA	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribose Nucleic Acid
DSSC	Dye Sensitized Solar Cell
ESI	Electrospray Ionization
eV	Electron Volt
GCMS	Gas Chromatography Mass Spectrometry
HFIP	Hexafluoroisopropanol
HOMO	Highest Occupied Molecular Orbital
HMF	Hydroxymethylfurfural
HRMS	High Resolution Mass Spectrometry
LA	Lewis Acid
LUMO	Lowest Unoccupied Molecular Orbital
MOF	Metal Organic Framework
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
NPB	N,N'-diphenyl-(1,1'-biphenyl)-4,4'-diamine

NSAID	Non-Steroidal Anti-Inflammatory Drug
OFET	Organic Field Effect Transistor
OLED	Organic Light Emitting Diode
OPV	Organic Photovoltaic
PTSA	<i>Para</i> -Toluene Sulfonic Acid
SMBHJ	Small Molecule Bulk Heterojunction
SMOPS	Sodium 1-methyl 3-sulfinopropanoate
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TM	Transition Metal
TMEDA	Tetramethylethylenediamine
TMB	Trimethoxybenzene
TMP	Tetramethylpiperidine
TMS	Trimethylsilyl
UV	Ultra-Violet

Chapter 1: Methodology Development for Bi-Aryl Carbon-Carbon Bond Formation

1.1 Methodology development in organic synthesis and the advent of green chemistry

Methodology development in organic synthesis involves the optimization of novel routes that facilitate access to high value chemical compounds. While the pursuit of efficiency is necessary for the continued optimization of materials and medicine, a cursory glance at any recent environmental findings gives credence to the growing global awareness that current industrial practices are not sustainable. Societal needs, buoyed for decades by the accessibility of polluting resources, will need to be addressed differently in the future. Recently, green chemistry has emerged as a discipline that focuses on eliminating the use and generation of hazardous substances within chemical industries.¹ In terms of methodology development, this entails the optimization of protocols that are safer, produce less waste, limit derivatization and avoid toxic reagents/solvents.

While there has been a steady rise in the number of publications that focus on developing greener protocols within organic synthesis, in practice, chemists tend to continue to use toxic reagents and solvents when it is more efficient to do so. So unless—and until—widely applicable, greener synthetic protocols are developed, inherently toxic materials will continue to be used. An important goal for methodology development within green chemistry should therefore be to find an intersection between practicality and environmental sustainability, as visually represented in Figure 1.

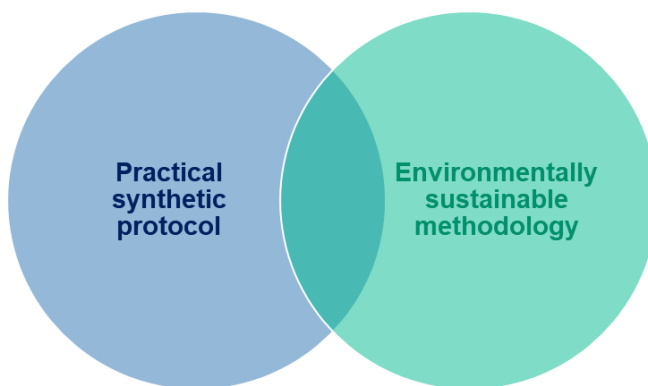


Figure 1: Target intersection between practicality and environmental sustainability for methodology development.

1.2 Prevalence of bi-aryl bonds

Bi-aryl bonds (sp^2 - sp^2 carbon-carbon bonds between two aromatic cycles) are some of the most common bonds within high-value target chemical compounds. This type of bond is ubiquitous within organic materials and therapeutic agents: Numerous commercially available drugs contain a bi-aryl bond, as do most opto-electronic materials, the breadth of which will be explored in the following sections.

1.2.1 Application of biphenyls as organic semi-conductors

Biphenyls and oligophenyls are widely utilized as molecular building blocks of organic semi-conductors,² as these materials have been shown to exhibit thermal stability and a wide range of electronic and optical properties.^{3–5} Organic semi-conductors are insulating carbon-based materials generally composed of sp^2 - sp^2 bonded moieties that become semi-conducting when charges are either injected from an electrode or by photoexcitation. This is due to the narrow energetic separation (2.5–4 eV) between the HOMO and LUMO of highly conjugated compounds.⁶ This gap, and therefore the energy required to induce conduction, can be readily tuned through chemical substitution and/or by varying the number of rings.^{7–10}

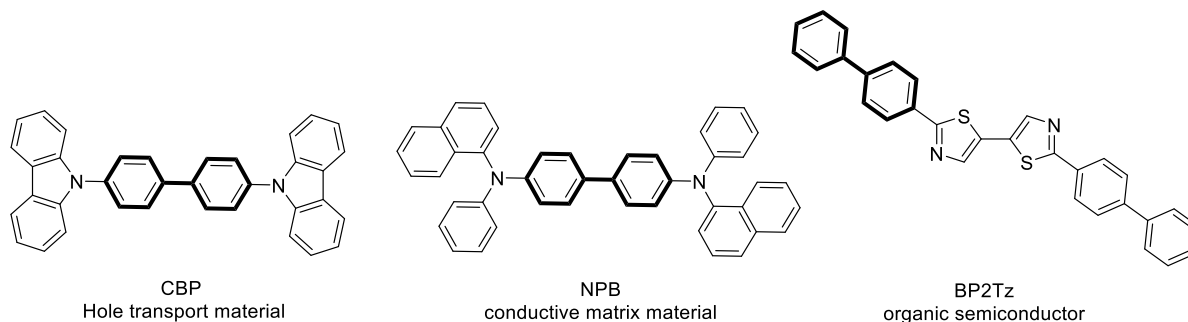


Figure 2: Biphenyl motif within organic semi-conductors.

Salient examples of biphenyls with semi-conducting properties are highlighted in Figure 2. 4,4'-Bis(N-carbazolyl)-1,1'-biphenyl (CBP) is a widely used hole-transport material in high-efficiency fluorescent and phosphorescent organic light-emitting diodes (OLEDs)¹¹ and electroluminescent Ir core dendritic complexes.¹² *N,N'*-Di(1-naphthyl)-*N,N'*-diphenyl-

(1,1'-biphenyl)-4,4'-diamine (NPB) is used intensively in OLEDs, as well as other organic electronic devices, such as organic photovoltaic (OPV)¹³ materials and perovskite solar cells,^{14,15} due to its hole transport capability. The biphenyl end-capped bithiazole co-oligomer, BP2Tz, is used to produce thin film field effect transistors.⁵ These examples exemplify the broad applicability of the biphenyl motif within organic semi-conductors.

1.2.2 Application of biphenyls in medicinal chemistry

Biphenyls are also largely considered a privileged substructure¹⁶ in medicinal chemistry, as this motif is a common substructure of biologically active compounds for a variety of receptors,¹⁷ such as the ubiquitous family of G-protein coupled receptors, due to their fit into in several binding pockets.¹⁸ Additionally, modified biphenyls have favorable drug-like physico-chemical properties¹⁹ and provide various aromatic and hydrophobic interactions with their target.²⁰ Selected examples of commercially available drugs with a biphenyl substructure are highlighted in Figure 3.

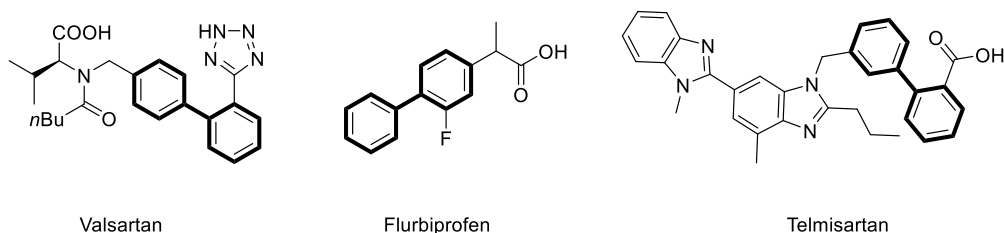


Figure 3: Biphenyl motif in medicinal chemistry.

Valsartan is a widely prescribed angiotensin II receptor blocker used to treat high blood pressure, heart failure, and diabetic kidney disease.²¹ Flurbiprofen is available worldwide as a non-steroidal anti-inflammatory drug (NSAID), with a similar mechanism of action as ibuprofen.²² Telmisartan is also an angiotensin II receptor blocker (with an even longer half-life than Valsartan and with a larger volume of distribution),²³ used to treat hypertension, diabetic kidney disease, and congestive heart failure.

1.2.3 Applications of arylated heteroarenes as organic semi-conductors

Arylated-heteroarene scaffolds are an even more widely represented class of compounds within organic semi-conductors. Thiophene, in particular, displays high charge

mobility^{24,25} due to the strong polarizability of the sulfur atom,²⁶ and arylated thiophenes exhibit opto-electronic properties that tend to be highly tunable.^{27–30} Thiophene is thus widely used within organic solar cells; as photosensitizers in dye-sensitized solar cells (DSSCs)^{31–35} and as small molecule bulk heterojunction (SMBHJ) donor materials for OPVs.^{26,36–38} Furan, the oxygen homolog of thiophene, has in some instances exhibited similar properties,^{39–41} but is up to date much less widely utilized.⁴² This can be attributed to furans being less stable, particularly in their susceptibility for light-induced decomposition,⁴³ which makes them somewhat more challenging to work with. However, furan-containing conjugated materials are expected to have smaller π - π stacking distances, increased conjugated lengths, and more quinoidal resonance structures, all of which can result in higher charge mobility.⁴⁴ Additionally, furan's larger dipole moment is also expected to improve solubility.⁴³

Selected examples of arylated heteroarenes with utility as organic semi-conducting materials are highlighted in Figure 4. As was previously mentioned, arylated thiophene motifs are exceedingly common within DSSCs, which typically follow a molecular pattern of donor/ π -bridging segment/acceptor. This structure is seen in the example of a thiophene photosensitizer (Figure 4A), where the carbazole moiety is the electron donor, the phenyl-thiophene is the π bridging segment, and the electron withdrawing cyano and carboxylic acid functional groups are as the electron acceptors.⁴⁵ Arylated thiophenes are also very common within organic field effect transistors (OFETs) and SMBHJ materials, as in the examples shown in Figures 4B⁴⁶ and 4C.²⁶ Arylated thiophenes have also found more niche applications, as their relative redox stabilities allow for use as photoswitches. The example presented in Figure 4D showed excellent stability and fatigue-resistance properties.⁴⁷ The branched furan compound Figure 4E is an example of an aggregation induced emission-based luminogens (AIEgen) with a furan core that exhibited more desirable properties (thermal and morphological stabilities, low turn-one voltage, high brightness, etc.) than its thiophene counterpart as part of a OLED device.⁴⁸

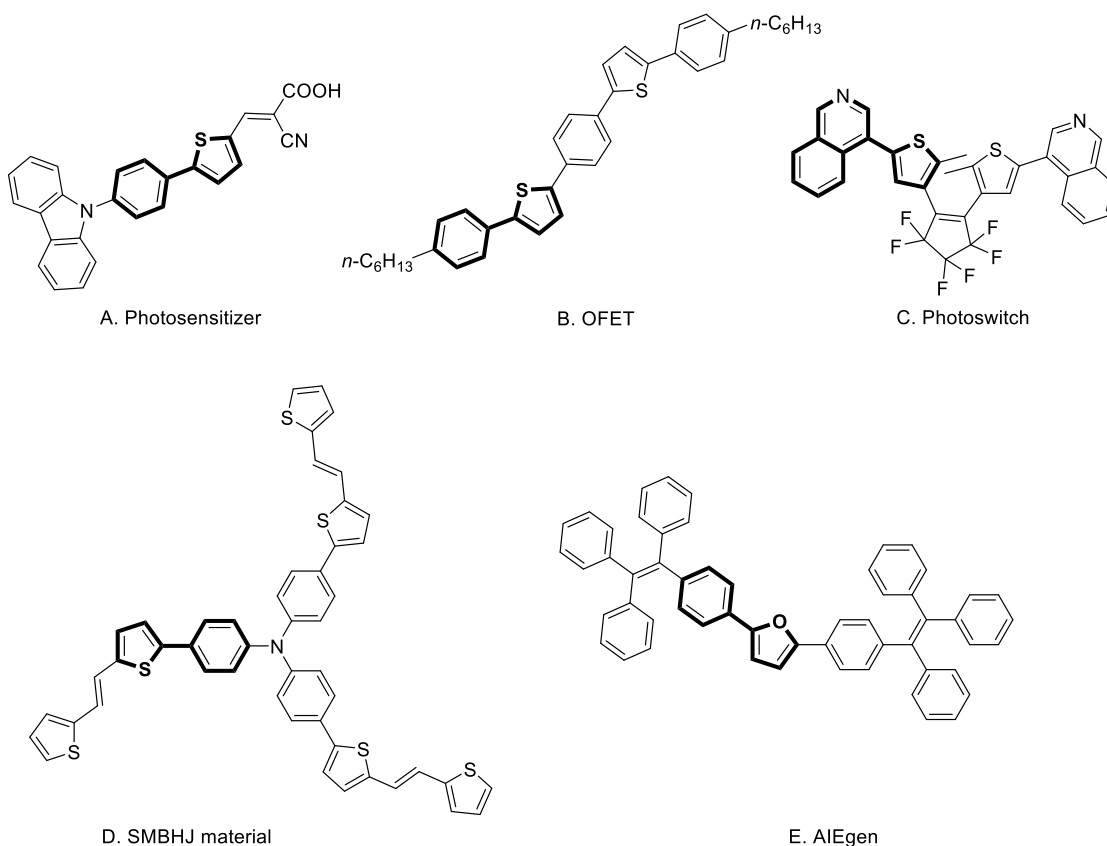


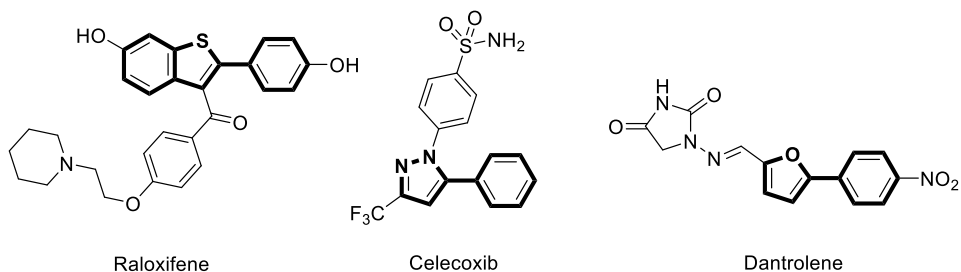
Figure 4: Arylated heteroarene motif within organic semi-conductors.

1.2.4 Application of arylated heteroarenes in medicinal chemistry

Heteroarenes are widely used molecules in medicinal chemistry. Salient examples of commercially available drugs with arylated heteroarenes are highlighted in Figure 5A. The arylated benzothiophene containing selective estrogen modulator Raloxifene⁴⁹ is used to prevent and treat osteoporosis and reduce the risk of invasive breast cancer in high-risk postmenopausal women. The arylated diazole containing COX-2 inhibitor Celecoxib in an NSAID used to treat pain or inflammation caused by many conditions such as arthritis, ankylosing spondylitis, and menstrual cramps.⁵⁰ The arylated furan containing ryanodine receptor agonist Dantrolene⁵¹ is a muscle relaxer that is used to treat muscle spasticity caused by conditions such as a spinal cord injury, stroke, cerebral palsy, hyperthermia, or multiple sclerosis.

Specifically, thiophene and furan are less ubiquitous within medicinal chemistry than phenyl groups, and other heteroarenes, such as pyridine and pyrrole. A potential reason for the underutilization of thiophene and furan is that these motifs can be susceptible to oxidation *via* cytochrome P450, leading to the formation of undesirable reactive metabolites.^{52,53} However, other metabolic biotransformation reactions are also possible *in vivo* (for example, *via* conjugation with glutathione), and so the presence of these rings alone is not enough to predict hepatotoxicity.^{52,53}

A) Commercially available drugs with arylated heteroarene motifs



B) Experimental drug candidates with arylated thiophene motifs

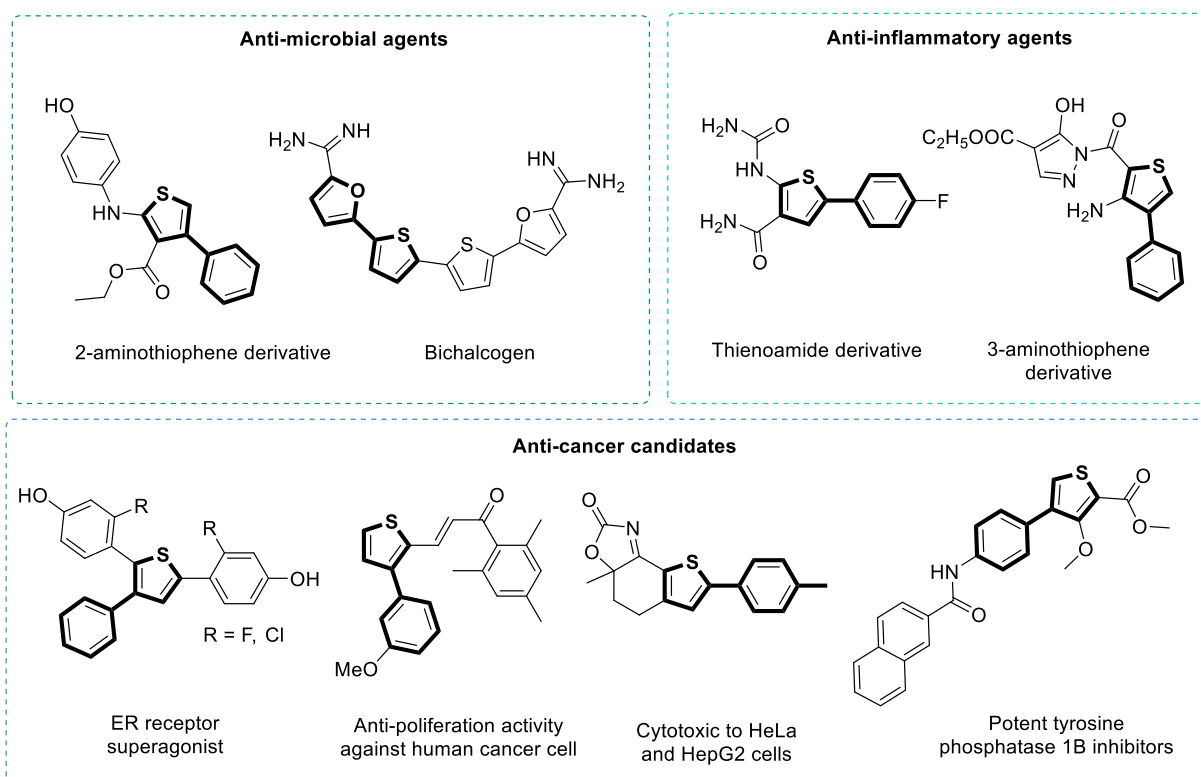


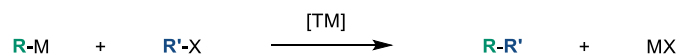
Figure 5: Examples of arylated heteroarenes in medicinal chemistry

Thiophene derivatives have more recently become important heteroarenes exhibiting remarkable applications in different disciplines of medicinal chemistry. For example, Duloxetine (Cymbalta) is a blockbuster antidepressant with a thiophene moiety that exhibits no toxicity due to reactive intermediates during biological metabolism.⁵³ So far, thiophene moieties have found utility in drugs candidates for the treatment of a number of ailments, such as malaria, microbial infection, fungal infection, depression, convulsions, cancer, viral infections, hypertension, and, most commonly, inflammation.⁵⁴ Figure 5B highlights salient examples of arylated thiophene molecules that have recently been studied for medicinal applications.

Several arylated thiophene compounds have found utility as potential therapeutic agents. A variety of 2-aminothiophene derivatives are currently being explored for their anti-microbial properties,⁵⁵ with arylated varieties also exhibiting excellent potency. Certain bichalcophenes demonstrate good anti-microbial activity due to their DNA binding and degradation abilities on both gram-positive and gram-negative microorganisms.⁵⁶ Arylated thiophene are also being explored as anti-inflammatory agents, with proposed modes of action similar to COX inhibitors, such as the thienoamide⁵⁷ and 3-aminothiophene⁵⁸ drug candidates presented in Figure 5B. Predominantly, however, arylated thiophene are becoming much more widely developed as anti-cancer agents. Certain classes of these derivatives have been found to exhibit superagonist activity when binding to estrogen receptors (ER),⁵⁹ which can be used to selectively target certain types of cancer that overexpress ERs. Arylated thiophenes have shown *in vitro* anti-proliferative activity against human colon cancer cell lines⁶⁰ and been reported as potent tyrosine phosphatase 1B inhibitors, exhibiting broad range anti-cancer activity.⁶¹ Arylated thiophenes have also been explored as part of a series of thiophene derivatives being developed for targeted damage to HeLa and Hep G2 (cancer) cells.⁶² While very toxic, these derivatives can be synthetically bound to folate receptor targeting nanocarriers for targeted delivery. It follows from these recent examples that both biphenyls and arylated heteroarenes are important motifs in synthetic organic chemistry, particularly within organic semi-conductors, and increasingly in medicinal chemistry as well.

1.3 Synthesis of bi-aryl bonds: Pd-catalyzed sp^2 - sp^2 cross-couplings

Bi-aryl bonds are habitually synthesized by carbon-carbon cross-coupling reactions. This reaction entails two fragments joined together with the aid of a transition metal catalyst, the driving force for which is the formation of a new sigma carbon-carbon bond, and at times, the precipitation of a salt. For the catalysis of carbon-carbon bond formation, transition metals are useful as they have a unique ability to activate various organic compounds.⁶³ The hybridization of these carbons can be a combinations of sp^3 , sp^2 or sp . For this type of reaction, an organometallic compound of the type R-M (R = organic fragment, M = activating metal group) reacts with an organic halide or a pseudohalide (R'-X) through a catalytic cycle on a transition metal (TM) for the formation of a new carbon-carbon bond (R-R'), as shown in Scheme 1.



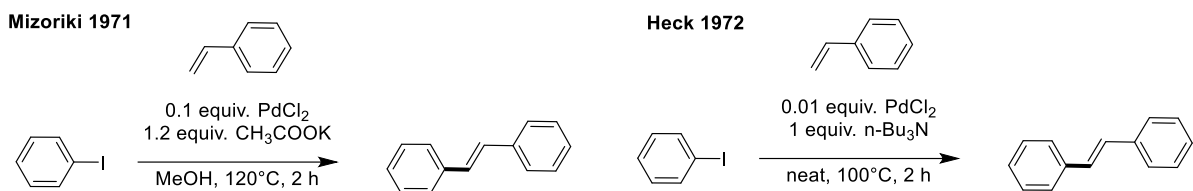
Scheme 1: General process of a cross-coupling reaction

1.3.1 Palladium-catalyzed cross-couplings

While palladium-catalyzed cross-couplings can generate new bonds between sp and sp^2 carbons (e.g. Sonogoshira cross-coupling),⁶⁴ as well as sp^3 and sp^2 carbons (e.g. Fukuyama cross-coupling),⁶⁵ a much larger body of work has led to the extensive development of Pd-catalyzed sp^2 - sp^2 bond formation. This approach is by far the most predominate method for the synthesis of biphenyls, and is among the most common for heteroarene-aryl bond formation.

1.3.1.1 The Mizoroki-Heck reaction

Tsutomu Mizoroki and Richard Heck pioneered the use of catalytic amounts of Pd for sp^2 - sp^2 cross-coupling with a reaction between iodobenzene and styrene to form stilbene, as shown in Scheme 2.

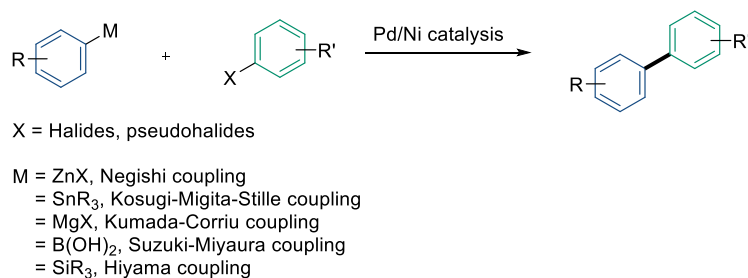


Scheme 2: Mizoriki and Heck cross-coupling reactions

Mizoriki published this reaction first in 1971,⁶⁶ which was built off of earlier work by Fujiwara⁶⁷ and Heck⁶⁸ on the arylation of olefins. Heck later published his version of the reaction in 1972,⁶⁹ reporting an even lower catalyst loading of Pd (0.01 vs. the 0.1 equivalents used for the Mizoriki version) and expanding the scope.

1.3.1.2 Subsequent Pd-catalyzed cross-coupling reactions for the synthesis of bi-aryls

The cross-coupling of two aryl substituents was then extensively developed in the 1970s by Ei-ichi Negishi (the Negishi cross-coupling), Masanori Kosugi, Migita Toshihiko,^{70,71} and John K. Stille⁷² (the Kosugi-Migita-Stille cross-coupling), Makoto Kumada⁷³ and Robert Corriu⁷⁴ (the Kumada-Corriu cross-coupling), as well as Norio Miyaura and Akira Suzuki (the Suzuki-Miyaura cross-coupling).⁷⁵ In the 1980s, Yasuo Hatanka and Tamejiro Hiyama also developed another type of C-C bond formation (the Hiyama cross-coupling), between aryl halides (or pseudohalides) and organosilanes.⁷⁶ These types of cross-coupling reactions are generally Pd-catalyzed (although significant work with Ni catalysis was also done). These approaches generally differ in the type of metal group (M) used to generate the nucleophilic aryl group needed to react with aryl halides (or pseudohalides) to form the corresponding bi-aryl under Pd catalysis, as shown in Scheme 3.



Scheme 3: Different types of classical Pd/Ni-catalyzed cross-coupling reactions for bi-aryl bond formation

The breadth of this and subsequent work in expanding these reactions demonstrates that Pd is one of the most useful catalysts for carbon-carbon bond formation, as it shows higher activity than other metal alternatives and functions efficiently with a high functional group tolerance.^{63,77,78} In recognition of the importance of these reaction, the Nobel Prize in Chemistry was awarded to Heck, Negishi and Suzuki for their work on classical Pd-catalyzed cross-couplings in organic synthesis in 2010.⁷⁹

1.3.2 General Pd catalysis mechanism

Generally, the accepted mechanisms for Pd-catalyzed cross-couplings consist of similar steps, regardless of the nucleophilic coupling partner. This mechanism begins with a zero-valent Pd (Figure 6, **A**) (which can be generated *in situ* from Pd(II) sources). After the loss of ligand(s) opens up an active site on the Pd metal, this species is able to undergo oxidative addition into the sp^2 carbon-halide bond of an aryl halide or pseudohalide (generally referred to as the electrophilic coupling partner) to generate Pd(II) intermediate **B**. Intermediate **B** can then transmetalate with an organometallic species (generally referred to as the nucleophilic coupling partner), resulting in both aryl groups on the Pd center in intermediate **C**.

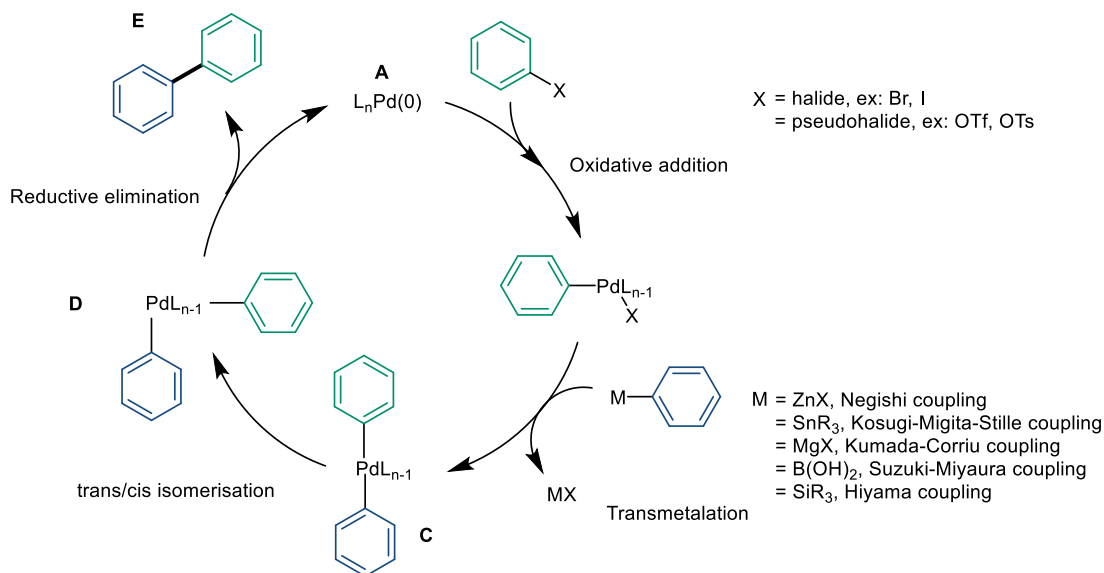


Figure 6: General mechanism for the Pd-catalyzed cross-coupling reaction.

At this stage, the coupling partners are *trans* to one another on the square planar Pd complex **C**. A cis/trans isomerization is therefore necessary to bring the groups adjacent to one other (intermediate **D**), after which it is possible to have a reductive elimination that forms a new carbon-carbon bond (**E**) and regenerates the zero-valent Pd species **A**. Depending on the constituents of the reaction, each of these steps can be the rate limiting step. For example, sterically larger ligands tend to increase the energy required for oxidative addition, while sterically smaller ligands tend to increase the energy required for reductive elimination.⁸⁰ With some nucleophilic coupling partners, transmetallation can be the more energetic step of this reaction as well.^{81,82}

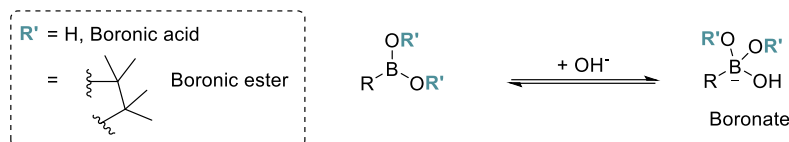
1.3.3 Current applications of classical Pd-catalyzed cross-coupling reactions

Since their initial development in the 1970s, the classical methods for Pd catalysis have been continuously improved upon, and these types of reactions continue to find application in modern organic synthesis. In particular, the Negishi cross-coupling,^{83,84} Kosugi-Migita-Stille cross-coupling,^{85,86} and Suzuki-Miyaura cross-coupling⁸⁷ are consistently employed in a variety of disciplines. A drawback of the two former reactions, however, is the need for unstable reagents and fully anhydrous reactions conditions, as organo-zincates and organotin compounds are very air and moisture sensitive. Additionally, organotin reagents are toxic to humans and the environment. The Suzuki-Miyaura cross-coupling reaction, which utilizes safe and relatively stable organoboranes, is by far the most broadly utilized classical Pd cross-coupling reaction in drug discovery⁸⁷ and in the synthesis of organic semi-conductors.⁸⁸

1.3.4 The Suzuki-Miyaura cross-coupling

Suzuki-Miyaura cross-couplings utilize boronic acids or boronic esters to generate the nucleophilic coupling partner. The great advantage of boronic acids and esters (as shown in Scheme 4) is that they are relatively bench stable, are generally insensitive to moisture and air, and, since their use has become widespread, are readily commercially available. These compounds are also reactive under relatively mild conditions. Due to the empty orbital on boron, boronic acid/ester moieties can be activated by a base, generating the boronate complex, as shown below in Scheme 4.⁸⁹ It is generally theorized that the

boronate complex is able to undergo transmetallation with the Pd complex **B** in Figure 6 (Suzuki-Miyaura cross-couplings do not occur in the absence of base).

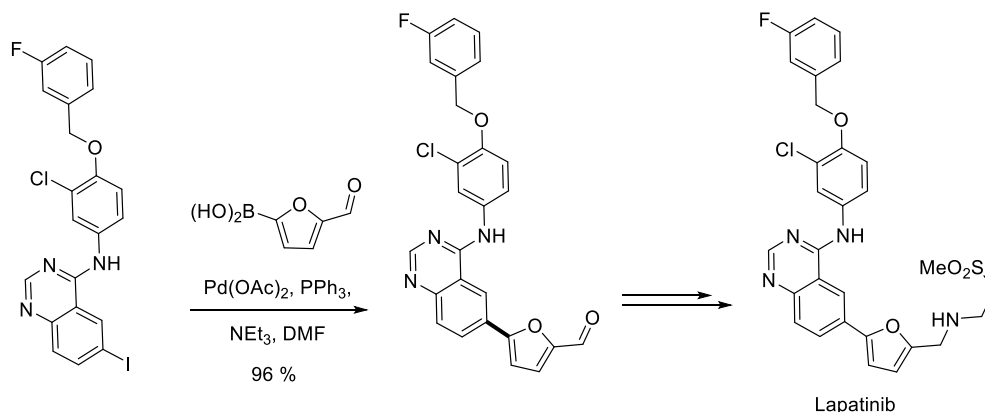


Scheme 4: Activation of the boronic acid with hydroxide base

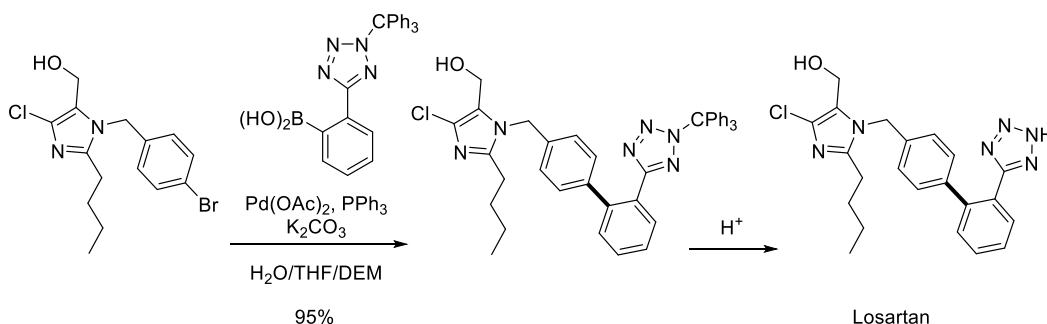
In 2014, it was reported that the Suzuki-Miyaura cross-coupling was one of the most utilized reactions in medicinal chemistry, second only to amide couplings.⁹⁰ For example, the bi-aryl bond in the GlaxoSmithKline synthesis of Lapatinib (Scheme 5A), a kinase inhibitor used in the treatment of solid tumors, such as those found in breast cancer, is synthesized with a Suzuki-Miyaura cross-coupling between a functionally complex iodinated quinoxaline and a furfural boronic acid with an excellent yield of 96 %.⁹¹

The angiotensin II receptor antagonist Losartan, used to treat high-blood pressure, is also commonly synthesized with a Suzuki-Miyaura cross-coupling between a imidazole benzyl bromide and a bi-aryl boronic acid with an excellent yield of 95 % (Scheme 5B).⁸⁷ The product of this cross-coupling reaction, a protected tetra-azole, can then be converted to Losartan in one acidic step to remove the trityl protecting group. These examples demonstrate the utility of the Suzuki-Miyaura coupling, as it is high yielding and chemoselective, making it very useful for the late stage synthetic steps. In terms of green chemistry, the Suzuki Miyaura coupling has many advantages. The reaction is atom economic given the size of the boron atom compared to other metals/metalloids. The relative safety of boronic acids compared to other organometallic reagents also promotes a less hazardous synthesis, and this reaction does at times use benign, aqueous solvents.

A. GlaxoSmithKline synthesis of Lapatinib



B. DuPont synthesis of Losartan



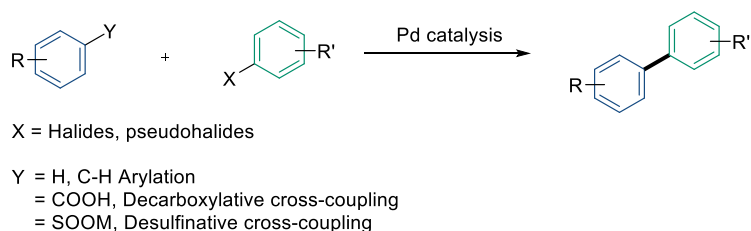
Scheme 5: Salient examples of Suzuki Miyaura cross-couplings in medicinal chemistry

1.3.4.1 Limitations of the Suzuki Miyaura cross-coupling

Despite their widespread application, there are some limitations to Suzuki Miyaura cross-couplings, in terms of utility and environmental sustainability. For example, the instability of some boronic acids, particularly 2-heteroaryl boronic acids,^{92,93} has at times limited their use for the formation of aryl-heteroarene bonds (although several examples exist, such as that shown in Scheme 5A). The cross-coupling of 2-pyridyl boronic acids and esters is particularly challenging, as these are prone to rapid proto-deboronation.⁹⁴ Despite the relative advantages of the Suzuki-Miyaura cross-coupling compared to the classical alternatives with air and moisture sensitive reagents, this approach still does require the use of a stoichiometric amount of an organometallic reagent.

1.3.5 Next generation Pd-catalyzed cross-couplings

More recently, alternative methodologies have been developed that allow for Pd-catalyzed cross-coupling without the need for a stoichiometric amount of metal/metalloid to generate the nucleophilic coupling partner. Prescient examples of these are the C-H arylation,⁹⁵ decarboxylative cross-coupling,⁹⁶ and desulfinative cross-coupling,⁹⁷ summarized in Scheme 6. For C-H arylation, a carbon-hydrogen bond is directly activated by a metal catalyst. While several mechanisms of Pd-catalyzed C-H arylation exists, generally, the metal center interacts with the electron pair in the sigma bond between carbon and hydrogen, forming a sigma complex,^{98,99} replacing the transmetallation step.

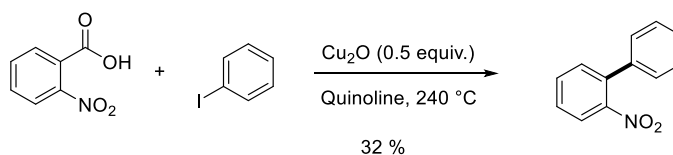


Scheme 6: Alternative cross-coupling reactions

The possibility of direct introduction of a new C–C bond *via* direct C–H bond transformation with C-H arylation is a highly attractive strategy in organic synthesis, as C-H bonds are ubiquitous and require no pre-functionalization.¹⁰⁰ Nevertheless, some drawbacks exist with the use of this method, mostly pertaining to the low reactivity of some compounds, requiring a large excess of reagent, and the issue of regioselectivity, as most molecules have multiple C-H bonds.¹⁰¹ For desulfinative cross-coupling, extrusion of SO₂ from an aryl sulfinate generates the nucleophilic coupling partner. For the decarboxylative cross-coupling, extrusion of CO₂ from aromatic carboxylic acids generates the nucleophilic coupling partner. As the carboxylic acid moiety is a common feature of natural products, and can also be added as a functional group to many molecules with relative ease,¹⁰² this reaction avoids the use of a stoichiometric amount of organometallic reagent while being regioselective and minimizing the need for extensive pre-functionalization.

1.3.5.1 Decarboxylative cross-coupling

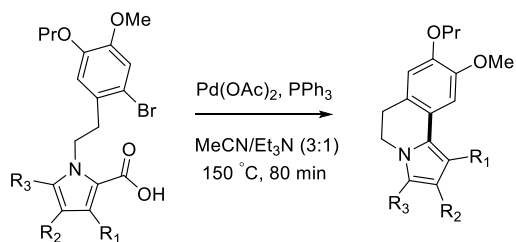
Decarboxylative cross-coupling entails the decarboxylation of a carboxylic acid to generate the nucleophilic coupling partner. In general, compared to other Pd-catalyzed cross-coupling reactions, aryl decarboxylative cross-couplings utilize reagents that are relatively inexpensive (carboxylic acids or their salts), and are far less air- and moisture-sensitive compared to most organometallic reagents, which can only be used in completely anhydrous environments.¹⁰³ This type of reaction was first devised by Martin Nilsson in 1966 with a bi-aryl synthesis between an *ortho*-nitro benzoic acid and iodobenzene using copper (Cu),¹⁰⁴ as shown in Scheme 7. It was surmised that this reaction proceeds *via* an Ullmann type mechanism, to generate the bi-aryl nitro compound.



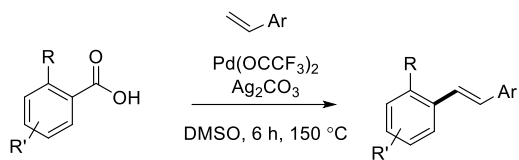
Scheme 7: Cu-catalyzed Nilsson decarboxylative cross-coupling

Since this time, several methodologies have been developed utilizing the decarboxylation of arenes for Pd-catalyzed cross-coupling reactions, salient examples of which are highlighted in Scheme 8. As previously mentioned, in these types of reactions, the extrusion of CO_2 gas is assumed to be the driving force for breaking a carbon-carbon bond,¹⁰⁵ however, this transformation still requires a lot of energy and is habitually done at relatively high temperatures ($>150\text{ }^\circ\text{C}$).

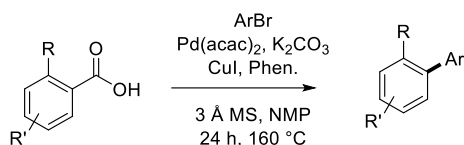
A. Steglich 2000



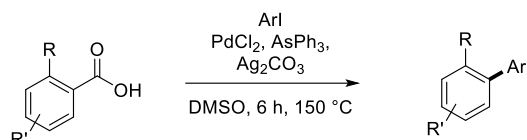
B. Myers 2002



C. Gooßen 2006



D. Becht 2007



Scheme 8: Selected examples of decarboxylative cross-coupling reactions for the formation of bi-aryl bonds

Notably, the first instance of a decarboxylative cross-coupling using Pd was published by Steglich⁹⁶ in his synthesis of Lamellarin L using a stoichiometric amount of Pd(OAc)₂ for an intramolecular reaction with a brominated pyrrole carboxylic acid (Scheme 8A). Afterwards, this reaction was adapted for Pd-catalysis by Myers,¹⁰⁶ Gooßen¹⁰⁷ and Becht,¹⁰⁸ among others. For the Myers reaction, an *ortho*-substituted carboxylic acid generates the electrophilic coupling partner, which reacts with an olefin (acryl and styrene derivatives) in a Heck-type cross-coupling employing stoichiometric amounts of Ag₂CO₃ (Scheme 8B).¹⁰⁶ In 2006, Gooßen and co-workers published a novel approach for the decarboxylation of *ortho*-substituted benzoic acids that employed a double Pd/Cu catalytic cycle (Scheme 9C).¹⁰⁷ Gooßen proposed the mechanism exhibited in Figure 7. While the steps within the Pd cycle are identical to that shown in Figure 6, there is an additional Cu catalytic cycle that generates the organocuprate (**G**) necessary for transmetalation to access di-aryl Pd complex **C**. Organocuprate **G** is generated *via* a decarboxylation after Cu co-ordinates the carboxylic acid in intermediate **F**. It was hypothesized that the *ortho*-substituent on the benzoic acid was necessary in order to displace the halide (X) going from intermediates **B** and **G** to **C** during transmetalation. Under these conditions (Scheme 8C), it was reported that in the absence of the *ortho* substituent on the benzoic acid, a stoichiometric amounts of Cu(II) carbonate and potassium fluoride are required.¹⁰⁹

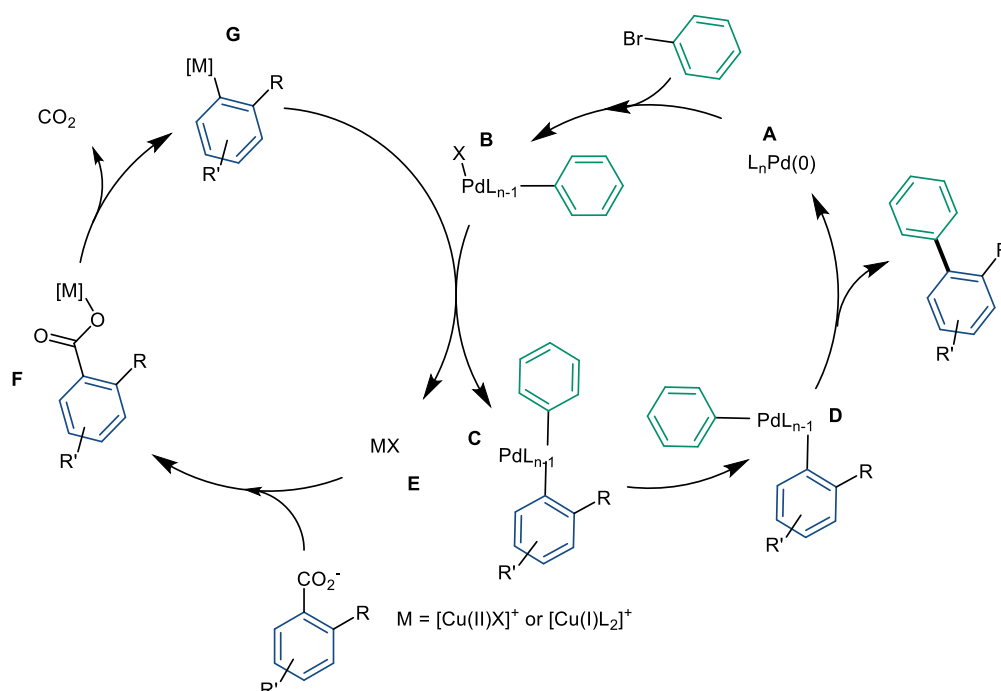


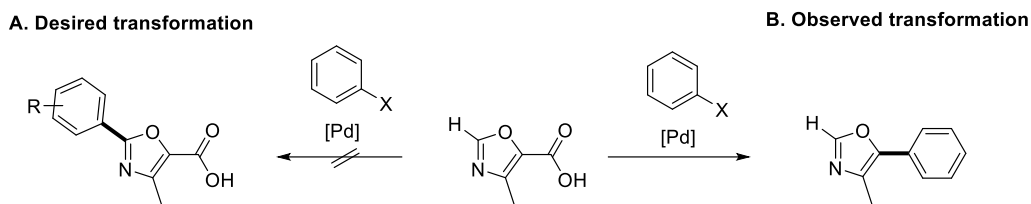
Figure 7: Proposed mechanism for the Pd/Cu-catalyzed decarboxylative synthesis of bi-aryls.

In 2007, Becht and co-workers developed a decarboxylative cross-coupling methodology between *ortho*-substituted benzoic acids and aryl iodides using silver carbonate as both the base and the co-catalyst, under relatively milder conditions (Scheme 8D).¹⁰⁸ Compared to Gooßen's conditions, however, Becht's protocol required a very high loading of Pd (30 mol%), and the use of triphenylarsine (60 mol%) as the ligand, in addition to three equivalents of silver carbonate. As was the case with Gooßen's conditions, *ortho*-substitution of the benzoic acid coupling partner was necessary, with either electron-donating or electron-withdrawing groups. Further optimization of this reaction by Gooßen and colleagues expanded the reaction scope to other electrophilic coupling partners such as aryl chlorides,¹¹⁰ aryl triflates,¹¹¹ and aryl tosylates.¹¹² Becht's protocol was also later expanded to include diaryliodonium triflates as the electrophilic coupling partner.¹¹³

1.3.5.2 The decarboxylative cross-coupling for aryl-heteroarene bond formation

While most optimization efforts have focused on optimizing decarboxylative cross-coupling for biphenyl synthesis, salient work has been done utilizing this reaction in the formation of arylated heteroarenes. In 2006, Forgione and Bilodeau published an

unexpected intermolecular Pd-catalyzed decarboxylative cross-coupling with heteroaromatic carboxylic acid.¹¹⁴ During drug discovery efforts, arylated oxazole compounds (such as that shown in Scheme 9A) were required, and an attempt was made to use C-H functionalization to generate this bond. As C-H functionalization can suffer from issues of regioselectivity, a carboxylic acid moiety was used as a blocking group to prevent reactivity at the undesired heteroarene position of the starting material.⁹²



Scheme 9: Unexpected Pd-catalyzed decarboxylative cross-coupling on an oxazole carboxylic acid.

The observed product of the reaction, however, was not the product from C-H arylation, but rather a chemoselective decarboxylative cross-coupling to generate an arylated oxazole (Scheme 9B). Forgione and co-workers expanded the scope of this reaction to other heteroaromatic carboxylic acids, including pyrrole, thiophene, furan, thiazole, and benzofuran, with a variety of aryl halides.^{114,115} The reaction mechanism for this type of reaction is thought to differ from that reported by Myers, Gooßen and Becht, in that it is a mono-metallic catalytic system. For the decarboxylative cross-coupling in this protocol, (and likely for Steglich's decarboxylative cross-coupling as well) delocalization of electrons from the heteroatom preclude the need for a secondary metal to generate the nucleophilic coupling partner. This approach thus further mitigates organometallic waste.

The proposed catalytic cycle for this reaction involves a C3 palladation (Figure 8) after oxidative addition *in lieu* of the transmetallation step to generate intermediate **C** after a nucleophilic attack of the heteroarene carboxylic acid onto Pd.

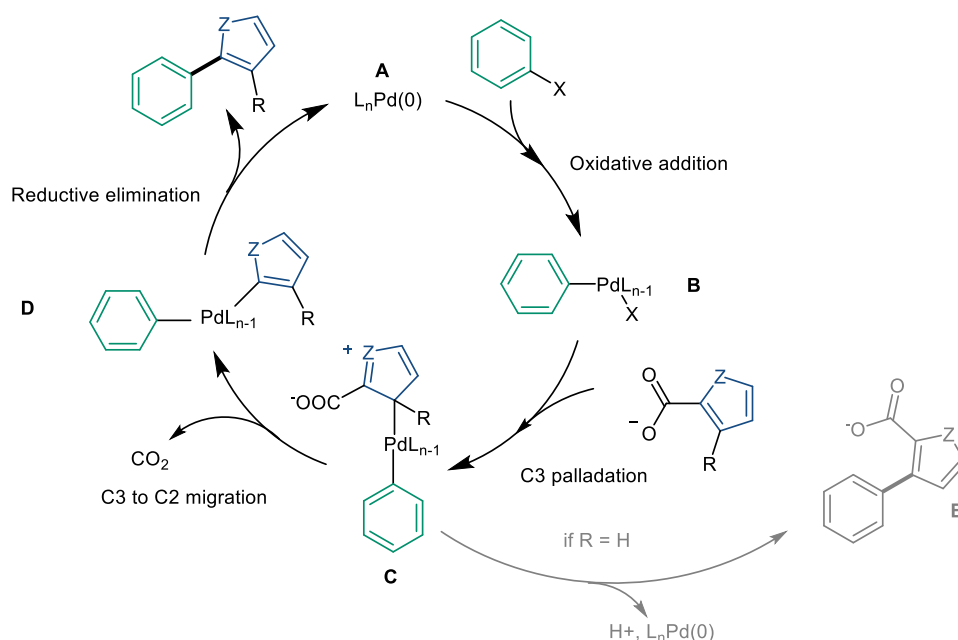
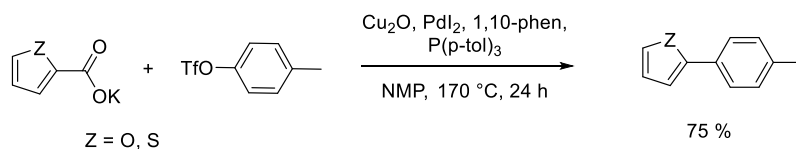
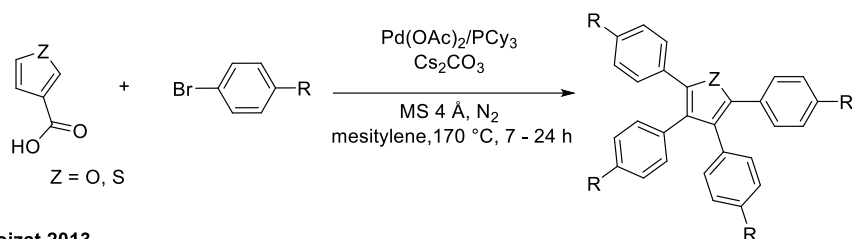
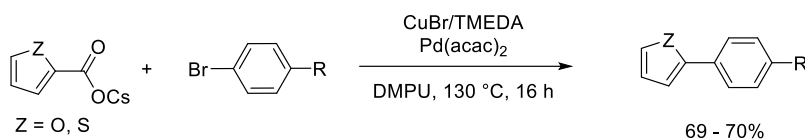


Figure 8: Possible catalytic cycle for decarboxylation cross-coupling of heteroaromatic carboxylic acids

From this intermediate, a C3 to C2 migration extrudes CO_2 and re-aromatized the ring to form intermediate **D**, from which a reductive elimination generates the desired aryl-heteroaryl bond. With some heterocycles, however, another pathway is thought to occur when R is a hydrogen. If this is the case, a deprotonation is possible to regenerate aromaticity on intermediate **C**. This intermediate can then undergo reductive elimination, coupling the aryl to the C3 position of the heterocycle, forming product **E**. As this compound still contains the carboxylic acid it is then free to re-enter the catalytic cycle where it can undergo a second cross-coupling at the C2 position. As was the case with the Myers, Gooßen and Becht reactions, it seems that once again functionalization *ortho* to the carboxylic acid is crucial for the high yielding formation of desired product. Interestingly, however, this was not found to be the case with pyrrole carboxylic acids.¹¹⁵

Since 2006, other groups have also developed protocols for the decarboxylative cross-coupling of heteroaromatic carboxylic acids, particularly thiophene and furan. Notable examples are highlighted below in Scheme 10.

A. Gooßen 2008**B. Miura 2008****C. Poizat 2013**

Scheme 10: Decarboxylative cross-couplings on heteroaryl carboxylates/carboxylic acids

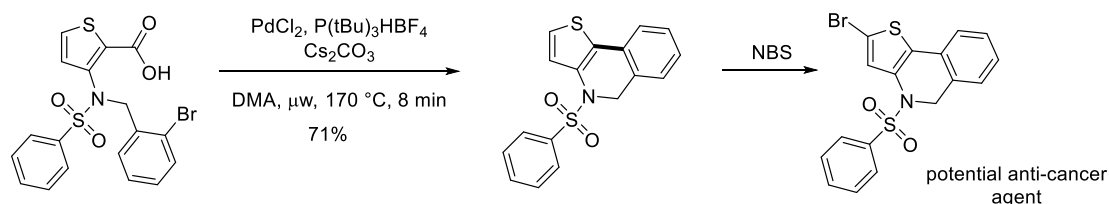
In 2008, Gooßen demonstrated that conditions for a bi-aryl synthesis from aromatic carboxylates and aryl triflates (Scheme 10A) could be expanded to include thiophene and furan carboxylates, producing arylated heteroarenes (thiophene and furan) with good yields of 75 %.¹¹¹ In the same year, Miura and Satoh reported the perarylation of 3-furan- and 3-thiophenecarboxylic acids with *para*-substituted bromoarenes to generate tetra-arylated thiophene (Scheme 10B), as well as the 3,4-diarylation of 2,5-diaryl-3-thiophenecarboxylic acid.¹¹⁶ In 2013, Poizat reported conditions for the decarboxylative cross-coupling of heteroaromatic cesium carboxylates with bromoarenes under considerable lower reaction temperatures (130°C vs. the usual $150 - 170^\circ\text{C}$) utilizing a Cu/Pd bi-metallic system and the diamine ligand TMEDA (Scheme 10C). Arylated thiophenes and furans were synthesized in good yields with these protocols, although the substrate scope is somewhat limited.¹¹⁷

1.3.5.3 Decarboxylative cross-couplings within medicinal chemistry

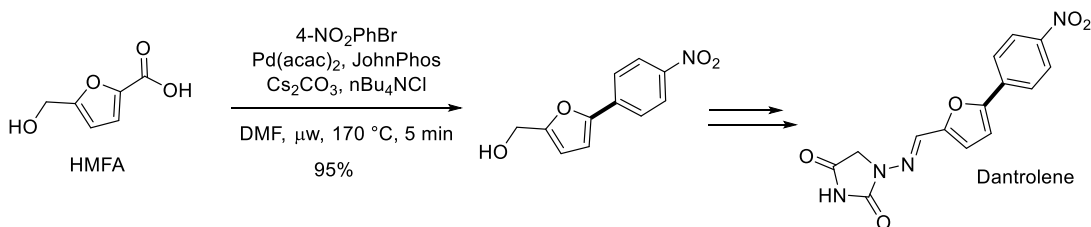
Decarboxylative cross-couplings have shown some utility within medicinal chemistry. Recently, a synthetic protocol that involved a late stage intramolecular decarboxylative

cross-coupling on a 2-thienoamine carboxylic acid to form a 2,3-thienoisquinolines was reported for access to a molecule that demonstrated anti-cancer activity (Scheme 11A).¹¹⁸

A. Synthesis of thienoisquinoline derivative



B. Synthesis of Dantrolene

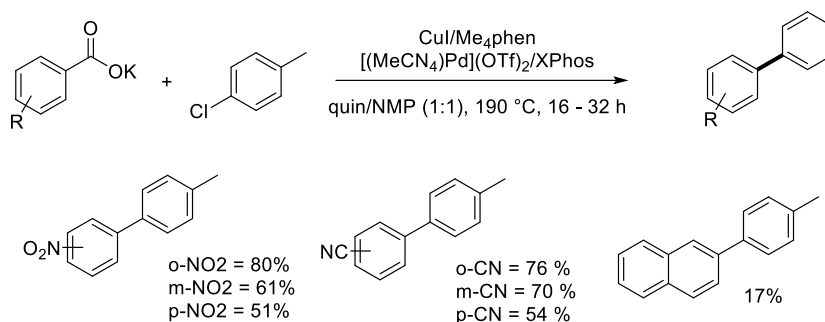


Scheme 11: Decarboxylative cross-couplings for the synthesis of drug molecules

A formal synthesis of the drug Dantrolene has also been reported utilizing a decarboxylative cross-coupling between biomass derived platform chemical hydroxymethylfurfuroic acid (HMFA) and 4-bromonitrobenzene to generate a necessary arylated furan intermediate (Scheme 11B).¹¹⁹

1.3.5.4 Limitation of decarboxylative cross-couplings for biphenyl synthesis

While decarboxylative cross-couplings are robust reactions that circumvent the need for a stoichiometric amount of organometallic reaction, there are some limitations in terms of substrate scope and the conditions necessary tend to be harsh (high temperatures). As previously discussed, for biphenyls, the bi-metallic reaction conditions reported by Gooßen and Becht generally require some activation of the benzoic acid for cross-coupling, either with *ortho*-substitution or with electron withdrawing/donating groups. In 2015, Gooßen reported an adaptation of his protocol to allow for decarboxylative cross-coupling without *ortho*-substitution using aryl chlorides and benzoates (selected scope shown in Scheme 12).¹²⁰



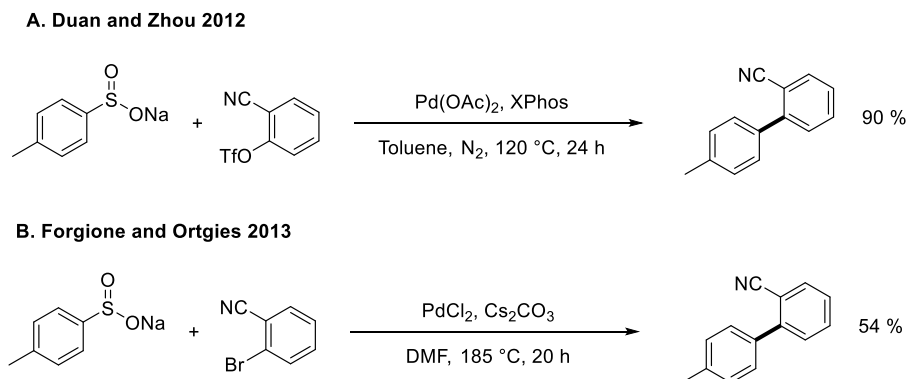
Scheme 12: Selected scope of decarboxylative cross-coupling with benzoate salts and aryl chlorides

Under the conditions reported in Scheme 12, decarboxylative cross-couplings are possible without *ortho*-substitution, however, these conditions are quite harsh (190 °C for up to 32 h) and the biphenyl product yields tend to decrease when substitution is moved from *ortho* to *meta* to *para*, as is shown with the selected examples. Only one cross-coupling was shown with an electron neutral group (2-chloro-naphthalene) and this afforded a relatively poor yield of 17%. While this work represents significant process towards expanding the versatility of decarboxylative cross-coupling for biphenyl synthesis, there does currently still remain some barriers of scope, generally pertaining to the need for electron withdrawing substitution on the benzoic acid/benzoate. Currently, there is no report of decarboxylative cross-coupling on unsubstituted benzoic acid.

1.3.5.5 Desulfonative cross-coupling

The desulfonative cross-coupling has the advantage of not needing an activating or *ortho* group on the nucleophilic coupling partner to obtain good yields. For this a type of cross-coupling, an aryl sulfonates acts as the nucleophilic coupling partner (although it is also possible to use sulfonates as the electrophilic coupling partner for Heck type aryl olefinations,¹²¹ Suzuki-Miyaura cross-couplings,¹²² and Hiyama cross-couplings¹²³). Similar to decarboxylative cross-coupling, it is surmised that the extrusion of SO₂ gas is a driving for the reaction. The first Pd-catalyzed desulfonative cross-coupling reaction between aryl triflates and aryl sulfonates was published in 2012¹²⁴ (although a patent with a similar reaction had been reported years prior¹²⁵). An example of this reaction is shown on Scheme 13A, where Pd acetate is used with the Buchwald ligand XPhos to catalyze the desulfonative cross-coupling between a *para*-tolyl sodium sulfinate and an *ortho*-cyanobenzotosylate with

a very good yield. Other un-activated (without electron withdrawing substitution) aryl sodium sulfinates also produced similarly good yields.¹²⁴ Since this time, the desulfinate cross-coupling has been more widely developed for both biphenyl bonds^{124,126–128} and heteroarene-aryl bonds.^{129–134} In 2013, Forgione and Orgies reported a ligand-free desulfinate cross-coupling with aryl bromides (Scheme 13B), which also produced decent yields with un-activated sulfinic salts, including toluene sodium sulfinate (a comparative example with both conditions is shown below). Compared to decarboxylative cross-coupling, the desulfinate cross-coupling is less limited in terms of scope to access a wide variety of biphenyls. Like the decarboxylative cross-coupling, desulfinate also avoids the use of a stoichiometric amount of organometallic reagents, and can be done either without base or without ligands, which greatly enhances the atom economy of the reaction.



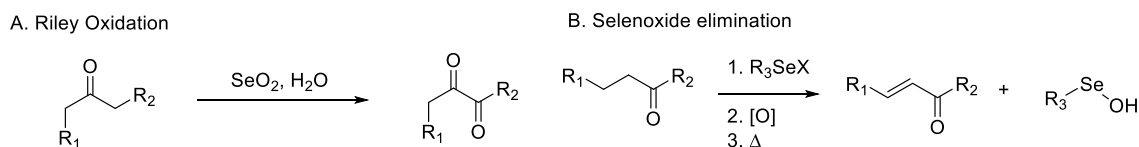
Scheme 13: Desulfinate cross-coupling on electron neutral aryl sulfinic salts

A drawback of the desulfinate cross-coupling, however, is a loss in practicality. Firstly, this pertains to the synthesis of aryl sodium sulfinate starting materials, which can be extensive,^{135,136} and usually necessitates either a stoichiometric amount of organometallic¹³² and/or an expensive reagent like SMOPS¹³⁵ or DABSO.¹³⁷ Secondly, the reactions themselves are lengthy in time and generally need to be done under anhydrous conditions. Additionally, as is the case with the decarboxylative cross-coupling, the solvents needed for this transformation tend to be less desirable, such as DMF, which is suspected of having reproductive toxicity, and toluene, which is suspected of having neurotoxicity and is highly flammable.¹³⁸

1.3.5.6 Deselenative cross-coupling

Selenium is a less commonly utilized element in synthetic organic chemistry, although several salient synthetic uses have been elucidated. Like sulphur, selenium is a group 16 non-metal, part of a group of elements referred to as the chalcogens (the oxygen family). Organo-selenium compounds are thus somewhat analogous to organo-sulfuric compounds, in that both central atoms have the same number of valence electrons, have the same stable oxidation states, and are reactive under similar conditions.¹³⁹

The main synthetic uses of selenium are the Riley oxidation, a selenium dioxide-mediated oxidation of methylene groups adjacent to carbonyls first reported by Riley and co-workers in 1932 (Scheme 14A).¹⁴⁰ Later, this reaction was expanded to include the oxidation the allylic position of olefins as well.¹⁴¹ Selenium compounds can also be used for β -hydrogen elimination (selenoxide elimination), in which a ketone is converted to an enone (Scheme 14B).¹⁴²



Scheme 14: Common organic transformations involving selenium reagents

Benzene seleninic acid was first used in the oxidation of hydrazines,¹⁴³ and more recently, has been utilized as a catalyst for a wide variety of oxidation reactions.¹⁴⁴ However, to date, no attempt has been made to utilize benzene seleninic acid a nucleophilic coupling partner for a Pd-catalyzed cross-coupling reaction. Building on the previous work done in desulfonative cross-coupling and decarboxylative cross-coupling, the potential to use aryl seleninic acids for cross-coupling reactions will be explored in Chapter 5.

1.4 Access to multi-arylated thiophene and furan via Pd-catalyzed cross-couplings

Currently, the synthetic approaches to access multi-arylated heteroarenes rely heavily on traditional cross-coupling reactions that tend to have poor atom economy, be linear, lengthy, and abundant in the production of solvent and heavy metal waste.²⁴⁻³¹ As such, there is an incentive for the development of greener, more modular, and more efficient

chemical methodologies for the synthesis of multi-arylated heteroarenes, to streamline the continued exploration for the various applications of this class of compounds.

Compared to the functionalization of phenyls, there are additional considerations when it comes to arylation, and especially multi-arylation, of heteroarenes. Thiophene and furan are moieties are similar to benzene in that they are aromatic, however, the electronics of the heteroatom alters reactivity and so the different positions of thiophene and furan are not equivalent. As shown in Figure 9, the 2 carbons adjacent to the heteroatom are referred to as the α -carbons. The protons at these carbon atoms are more acidic and the positions tend to be more reactive, particularly when it comes to C-H arylation and electrophilic aromatic substitution. The adjacent carbon atoms are referred to as the β -carbon. The numbering of the carbons on the five-membered heteroarene ring tend to vary depending on the substitution (the heteroatom is always 1), however, for the sake of clarity for this thesis, the number of the carbons will proceed according to the Figure 9, with the heteroatom pointing upright and the carbon numbering proceeding in the clockwise direction.

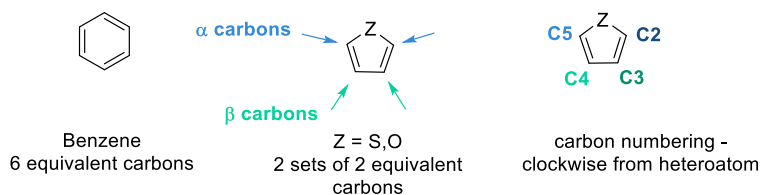


Figure 9: phenyl vs five membered heteroarenes thiophene and furan

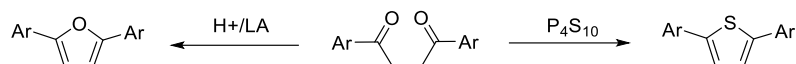
The methodologies for arylation at the α - and β -positions of heteroarenes thus differ, and various approaches are required to differentiate between the two α positions (C2 and C5), as well as the two β positions (C3 and C4).

1.4.1 Previously reported synthetic methodologies for access to arylation thiophene and furan

1.4.1.1 Cyclization approaches to multi-arylated heteroarenes

Unlike benzene, it is relatively easier to cyclize five membered heteroarenes *in situ*. That makes it possible to synthetically attach the desired groups at various positions of heteroarenes before the moiety is constructed. The most utilized method for the synthesis of thiophene and furan is the Paal-Knorr synthesis, a reaction that generates either furans,

pyrroles, or thiophenes from 1,4-diketones (furan and thiophene synthesis shown in Scheme 15).¹⁴⁵

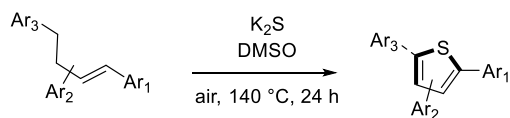


Scheme 15: Paal Knorr synthesis of thiophene and furan

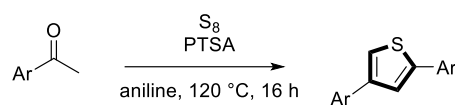
Arylated thiophenes can be made by reacting 1,4 di-ketones and an excess of either phosphorus pentasulfide or Lawesson's reagent at high temperatures.¹⁴⁶ Furan can be synthesized either using acid or a Lewis acid.¹⁴⁵ Several advancements have been made that build on this approach to access a wider variety of multi-arylated thiophene and furan under milder conditions. Selected recent examples are highlighted in the following sections.

Beyond the Paal Knorr synthesis, the cyclization of arylated thiophene can be done with a variety of substrates and sulfur sources. As shown in Scheme 16A, Chen and Yang have devised a strategy for the annulation of substituted buta-1-enes with potassium sulfide for access to multi-arylated thiophene.¹⁴⁷ This strategy can be used to access 2,4 di-arylated and 2,5 di-arylated thiophene. Huang and Li reported another procedure utilizing vinyl bromo-alkynes and potassium xanthate in the presence of the phase transfer catalyst tetrabutylphosphonium bromide (TBPB) to generate multi-arylated thiophene under aqueous conditions (Scheme 16B).¹⁴⁸ This strategy can be used to generate 2,4 di-arylated and 2,5 di-arylated thiophene, as well as 2,3,5 tri-arylated thiophene. Additionally, it is also possible to synthesize 2,3,5 tri-arylated thiophene with an iodine at the C4 position, which can then be used to generate tetra-aryl thiophene with a Suzuki-Miyaura cross-coupling. While highly modular, these strategies do necessitate extensive pre-functionalization for the synthesis of the necessary starting materials.

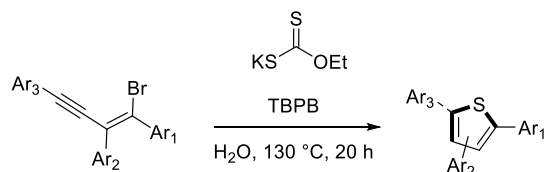
A. Chen and Yang 2018



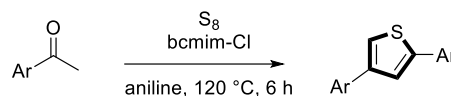
C. Nguyen and Retailleau 2018



B. Huang and Li, 2020



D. Gisbert and Paster 2020



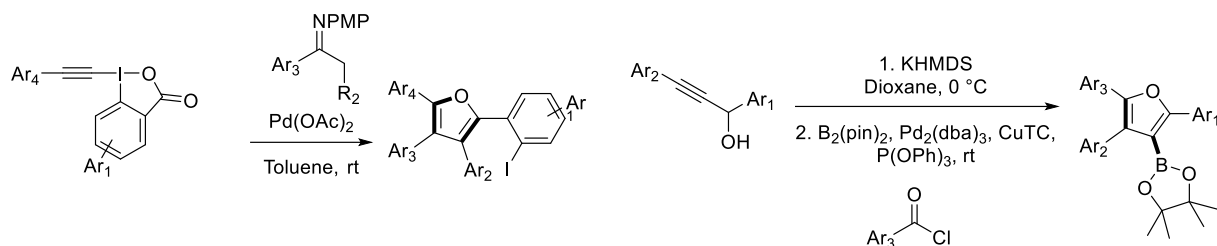
Scheme 16: Cyclization reactions to access multi-arylated thiophene

Another approach that needs less pre-functionalization was first reported by Nguyen and Retailleau utilizing *para*-toluene sulfonic acid (PTSA) to mediate the formation of C-C and C-S bonds to generate 2,4 di-arylated thiophene from acetophenones and elemental sulfur (Scheme 16C).¹⁴⁹ This approach was further expanded upon by Gilbert and Paster to use 1,3- bis(carboxymethyl)imidazolium chloride (bcmim-Cl) as a catalyst and allow the reaction to be done under non-anhydrous conditions, increasing the practicality (Scheme 16D).¹⁵⁰ Despite important advances, however, this approach remains limited in that there is a lack of regioselective control, and the aryl groups at the 2 and 4 positions of thiophene must be the same.

Certain advancements in the cyclization of furan have also expanded the potential to access a wide variety of multi-arylated furans. Salient examples are highlighted in Scheme 17. Notably, in 2014, Lu and Yoshikai devised a strategy for the Pd-catalyzed coupling reaction of ethynylbenziodoxolones and imines to afford several multi-substituted furans, a protocol which involves a unique condensation and fragmentation processes (Scheme 17A).¹⁵¹ More recently, Jin and Furstner have reported a route to multi-arylated furan boronic ester *via* a trans-carboboration strategy with a di-arylated alkyne and an aryl acyl chloride using Pd-catalysis (Scheme 17B).¹⁵² The resulting boronic ester at C3 can then be used for a subsequent Pd-catalyzed Suzuki-Miyaura cross-coupling to generate the tetra-arylated furan, and allow access to a wide variety of structures.

A. Lu and Yoshikai, 2014

B. Jin and Fürstner 2020



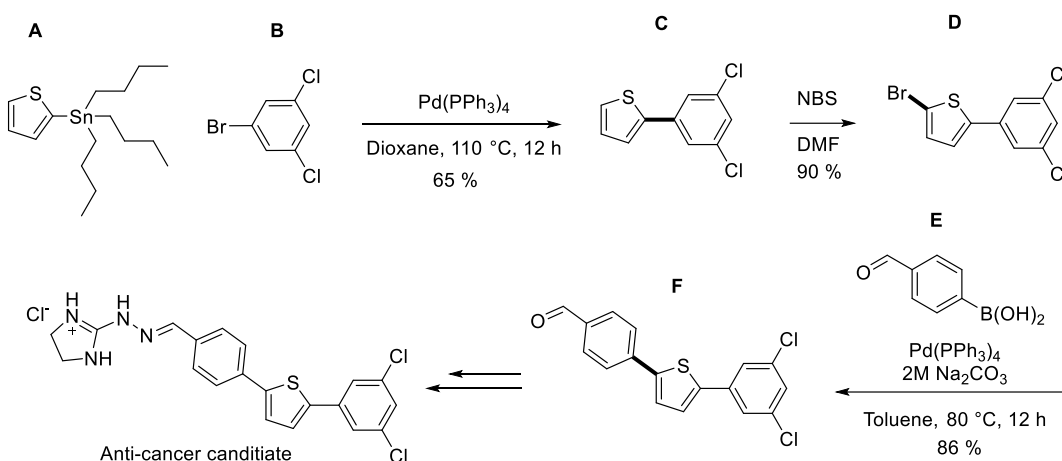
Scheme 17: Recent cyclization protocols to access multi-arylated furan

These strategies are highly modular, in that different aryl groups that can be accessed at the various positions of furan, however, as is was the case with the modular cyclization strategies to access multi-arylated thiophene, extensive pre-functionalization is required to access the necessary starting materials. Additionally, cyclizations strategies do not allow for late stage functionalization, a necessary aspect for efficient structure optimization, which is particularly necessary in drug discovery.

1.4.1.2 Cross-coupling approaches to multi-arylated heteroarenes

A cross-coupling approach to multi-arylated heteroarenes avoids the need for an extensive synthesis of functionally complex starting materials, and can allow for more efficient late state functionalization. While less extensively developed than cyclization approaches, several strategies toward developing this methodology have been previously reported, and are highlighted in the following sections.

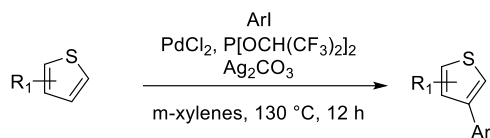
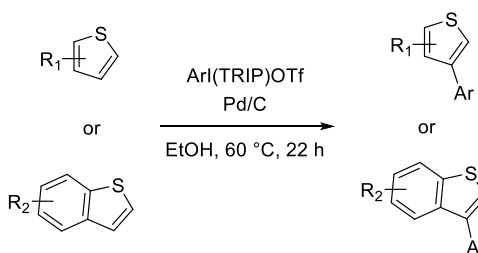
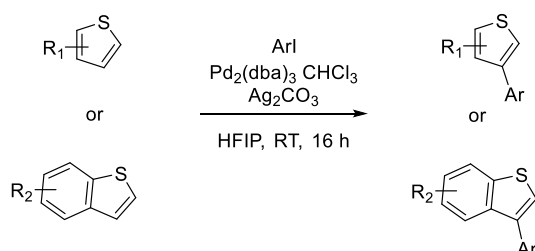
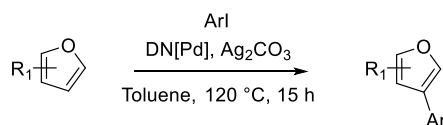
Planar 2,5 di-arylated thiophenes and furans are by far the most common motif of arylated heteroarenes. Arylation at these positions confer full conjugation of the molecule, and thus these compounds tend to exhibit desirable optoelectronic properties. Given the preferential reactivity of the α -positions of thiophene and furan, these motifs also tend to be the easiest to access synthetically. Countless examples of symmetric 2,5 di-arylated thiophene, and a significant amount of 2,5 di-arylated furan have been previously reported. Access to non-symmetric di-arylated heteroarenes, however, is somewhat more involved and these motifs are perhaps underrepresented in the literature to do this fact.³⁸ An example of a recently reported synthetic route towards a non-symmetric di-arylated thiophene with anti-proliferative activity against 60 cancer cell lines¹⁵³ is shown in Scheme 18.



Scheme 18: Synthesis of recently reported non-symmetric di-arylated thiophene with anti-cancer activity

The synthesis begins with Migita-Stille cross-coupling between a tin thiophene reagent (**A**) and an aryl bromide (**B**) to synthesize an arylated thiophene (**C**), followed by a bromination at the C5 position of the thiophene to generate bromide intermediate (**D**), and a subsequent Suzuki-Miyaura cross-coupling with benzaldehyde boronic acid (**E**) to access the aldehyde precursor (**F**). This derivative can then be converted to the desired thienylbenzamide anti-cancer candidate. While this strategy allows for modularity and later stage functionalization, it does really heavily on organometallic reagents and involves relatively long reaction times, which can be inconvenient if a library of compounds for a structure activity relation study is necessary.

An inherent challenge in the cross-coupling strategy for the multi-arylation of thiophene involves the selective arylation of the β -positions of thiophene and furan. For this, however, several strategies utilizing C-H arylation have been previously reported. Among other important work, salient examples are highlighted in Scheme 19. Itami and Yamaguchi first reported a methodology for selective β -arylation of mono- and di- substituted thiophenes with iodoarenes, where a cationic Pd catalytic system was used to obtain high regioselectivity (Scheme 19A).¹⁵⁴ In 2014, Tang and Glorius reported a C3-selective arylation of thiophenes (as well as benzothiophenes) using arylodonium triflates as the electrophilic coupling that was mediated by Pd/C under considerably mild conditions (Scheme 19B).¹⁵⁵

A. Itami 2010**B. Glorius 2014****C. Larrosa 2016****D. Tsukada 2017**

Scheme 19: Examples of selective beta-arylation of thiophene and furan

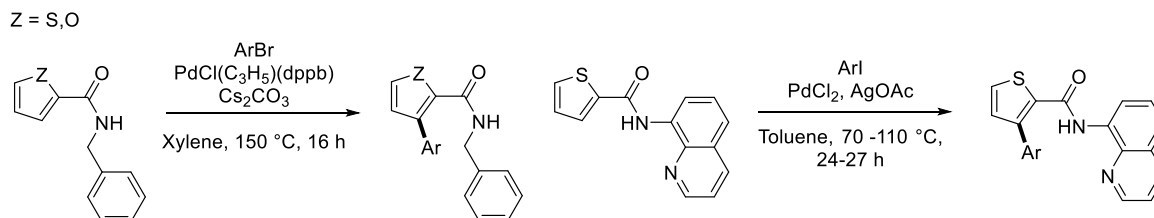
This was followed by work from Colletto and Larrosa that was able to achieve β -arylation of thiophenes (as well as benzothiophenes) with iodoarenes at room temperature, albeit utilizing a highly halogenated solvent, HFIP (Scheme 19C).¹⁵⁶ Goto and Tsukada reported a selective β -arylation of mono- and di-arylated furan with iodoarenes using a dinuclear Pd complex (DN[Pd]) (Scheme 19D).¹⁵⁶ Other important work towards this transformation have also reported using boronic acids,¹⁵⁷ organosilanes¹⁵⁸ and sulfonyl chlorides¹⁵⁹ as the electrophilic coupling partners. While reactions are often highly regioselective, they are generally dependent on the functionalization of thiophene and furan, and can be low yielding.

In order to achieve complete regioselectivity, directing groups can be used to target reactivity at the β positions of heteroarenes. Pyridines,¹⁶⁰ oxazolines,¹⁶¹ imines¹⁶² and amides¹⁶³ have all been used as directing groups for C-H activation, due to the strong coordinating abilities of nitrogen with transition metals. Miura first directed C-H bond arylation to the β carbon of thiophene using a carboxamide directing group.¹⁶⁴ Doucet expanded this work for regioselective access to either α or β positions, depending on the conditions used (Scheme 20A).¹⁶³ For selective access to β -arylation carboximide heteroarenes, a thiophene

or furan carboximide is reacted with an aryl bromide under Pd catalysis in xylene with Cs_2CO_3 as the base. Padmavathi and Babu later expanded on this work for thiophene carboximides that can be done under relatively milder conditions with aryl iodides (Scheme 20B).

A. Si Larbi and Doucet, 2012

B. Padmavathi and Babu, 2015

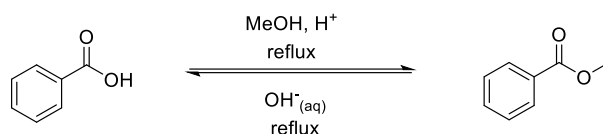


Scheme 20: Salient examples of directed C3 arylation

While the directing group approach greatly improves regioselectivity, these transformations can be operationally convoluted and include considerable derivatization when large directing groups are required.

1.4.2 The versatility of carboxylic acids/esters for reaction control in organic synthesis

Aryl carboxylic acids were previously shown to be able to generate the nucleophilic coupling partner for decarboxylative cross-coupling, but they also have several other synthetic utilities. Importantly, carboxylic acids are synthetic intermediates to other desirable groups such as aldehydes, alcohols, esters, amides, etc. The interconversion between a carboxylic acid and an ester is a trivial reaction (as shown with an example with benzoic acid on Scheme 21), which is particularly useful as under decarboxylative cross-coupling conditions, esters are unreactive. It is therefore relatively easy to shield carboxylic acids as esters. In terms of green chemistry, these reactions limit derivatization since methyl or ethyl esters (made *via* a condensation with methanol or ethanol) is an aqueous reaction with a very low weight protecting group that is environmentally benign.

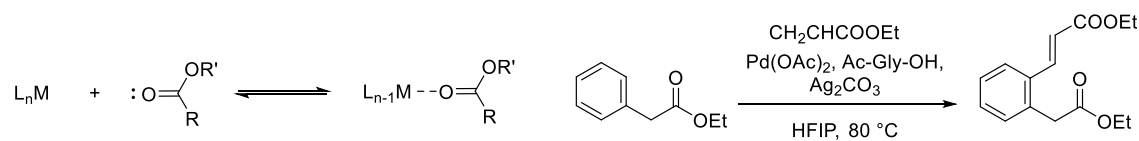


Scheme 21: Interconversion of benzoic acid to the corresponding methyl ester

Another salient aspect of carboxylic acids is their oxygen atoms, which confer two interesting properties. Firstly, since the electronegativity of oxygen is greater than that of carbon, the carbonyl carbon is electron poor and thus the entire group is electron withdrawing. Electronically, on conjugated systems like a phenyl ring, this makes carboxylic acids and esters deactivating *meta* directors for electrophilic aromatic substitution reactions. Secondly, the lone pairs on the oxygen atoms can also be used as a coordinating group with several electropositive metals (Scheme 22A). This facet can be used to direct chemistry, as was done in the example shown in Scheme 22B, where a distal ester moiety is used to direct olefination at the ortho position of a phenyl group.¹⁶⁵

A: Oxygen lone pair as metal ligand

B: Example of metal co-ordination used to direct chemistry (Yu, 2015)



Scheme 22: Metal coordination ability of carbonyl oxygen

1.5 Research goals and thesis organization

As has been demonstrated in the previous sections, arylated compounds, biphenyls and arylated heteroarenes, are important motifs within high value chemical compounds, particularly drug-like molecules and organic semi-conductors. The most predominant reactions devised to generate these bonds are Pd-catalyzed cross-coupling reactions. The research presented herein thus further expands this body of work, by devising innovative synthetic approaches that utilizes a variety of Pd-catalyzed cross-couplings to access these classes of compounds in a manner that is both practical and prioritizes environmental sustainability.

Described in Chapters 2-4 is methodology development for greener and more practical access to multi-arylated heteroarenes *via* site specific, ester controlled Pd-catalyzed cross-couplings. Chapter 2 is an adaptation of the article “Successive Pd-Catalyzed Decarboxylative Cross-Couplings for the Modular Synthesis of Non-Symmetric Di-Aryl-Substituted Thiophenes” by Cynthia Messina, Liam Z. Douglas, Jiang Tian Liu and Pat Forgione, *Eur. J. Org. Chem.* 2020, 5182–5191.¹⁶⁶ Research work and writing of the manuscript was conducted by the first author. L.Z. Douglas contributed to the purification of scope for Table 4. J.T. Liu contributed to the synthesis of carboxylic acid starting materials. Chapter 3 is an adaptation of the article “Programmed Synthesis of Tetra-Aryl Thiophenes with Stepwise, Ester-Controlled Regioselectivity” by Cynthia Messina, Xavier Ottenwaelder and Pat Forgione, *Org. Lett.* 2021, 23, 7348–7352. Research work and writing of the manuscript conducted by the first author. X. Ottenwaelder obtained the X-ray crystal structure and assisted with editing the manuscript. Chapter 4 is an adaptation of the article “Ester-Controlled Functionalization for Selective Access to Multi-Arylated Thiophenes and Furans” by Cynthia Messina, Keegan McKibbon, Karina Wong, Phil Prevost and Pat Forgione, currently in preparation. Research work and writing of the manuscript conducted by the first author. K. McKibbon, K. Wong and P. Prevost assisted in substrate scope synthesis, characterization and purification of compounds.

Chapter 5 reports the development of a novel type of Pd-catalyzed cross-coupling for bi-aryl synthesis under relatively mild conditions that avoids organometallic reagents. Chapter 5 is a portion of the article “First Generation Pd-catalyzed Deselenative Cross-Coupling for the Synthesis of Bi-Aryls with Un-Activated Benzene Seleninic acid and Aryl Iodides” by Cynthia Messina, Christopher Liczner, Keegan McKibbon, Christopher Wilds and Pat Forgione, currently in preparation. Research work and writing of the manuscript conducted by the first author. Christopher Liczner was an equal partner in the conceptualizing of this project and consulted during the optimization process, synthesized pyridine selenic acid and assisted in editing the manuscript. K. McKibbon assisted with substrate scope synthesis and purification of compounds.

Chapter 2: Successive Pd-Catalyzed Decarboxylative Cross-Couplings for the Modular Synthesis of Non-Symmetric Di-Aryl-Substituted Thiophenes

2.1 Introduction

Pd-catalyzed cross-couplings^{72–74,79,167} are among the most utilized reactions in transition metal-catalyzed carbon-carbon bond formation. Generally, the Stille-Migita and Suzuki-Miyura reactions are the most widely used for the preparation of many organic natural products,^{168,169} pharmaceuticals,¹⁷⁰ and agrochemicals.^{170,171} While heterocycles are ubiquitous in these fields, oligothiophenes have displayed particular importance in growing industries, such as organic photovoltaic,^{34,172–174} light-emitting diodes,^{28–30,175} fluorescence imaging,^{176–180} and other organic semi-conducting materials.^{181–184} In particular, oligothiophenes exhibit tunable conductance and light absorbance,¹⁸⁵ however, other five-membered heterocycles, such as pyrrole^{31,186–189} and furan,^{39,41,180,190,191} are also increasingly being incorporated as part of candidate organic semi-conductors.

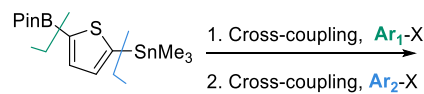
While the synthesis of repetitive and/or symmetric oligothiophenes can be effectively carried out by polymerization reactions,¹⁹² access to non-symmetric oligoheteroarenes involves a stepwise procedure that can be wasteful and synthetically time-consuming. As such, the prevalence of symmetry in the design of small molecule candidate organic semi-conductors may be due to a bias involving ease of synthesis.³⁸ A facile route to non-symmetric compounds is thus desirable to increase the library of possible structures that can be evaluated for improved properties, and to allow for increased synthetic modularity. Existing synthetic approaches for non-symmetric oligothiophenes involve a combination of Stille couplings,^{174,193–196} Kumada-Corriu type couplings,^{197–199} Suzuki-Miyura couplings,^{189,193,194,196,200–202} and/or C-H arylations^{198,201,203–207} (selected examples of previous work are highlighted in Scheme 23).

Among these, C-H arylation is the most atom-economic process and avoids the stoichiometric generation of heavy waste, but the reaction can require additional substrate functionalization to control regioselectivity.^{163,208–210} While organometallic cross-coupling reactions are chemoselective, accessing the required motifs for coupling requires wasteful pre-functionalization, and the reactivity of these groups poses a challenge for modular

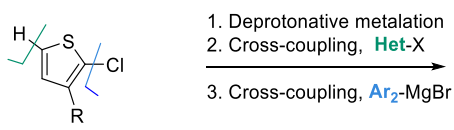
synthesis, as they are difficult to carry through several synthetic steps. Additionally, functional group incompatibility may make some targets challenging to access.

Selected examples of previous work

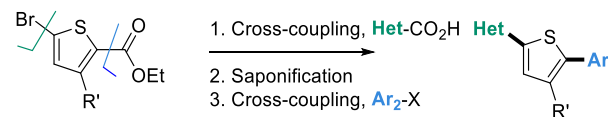
Staubitz³⁹



Mori⁴⁴

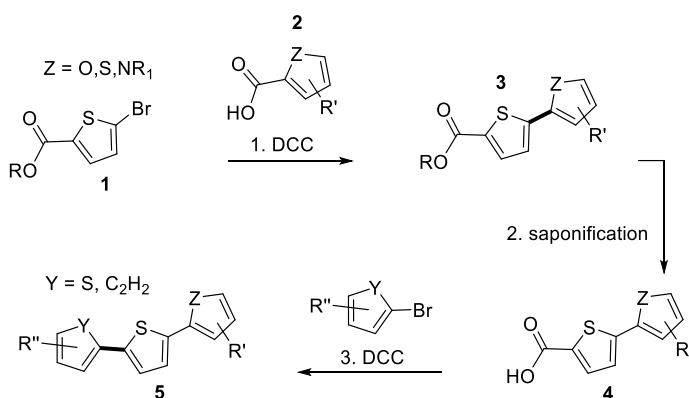


This work



Scheme 23: Selected reactions for the synthesis of non-symmetric 2,5 diarylated thiophene

In recent years, decarboxylative^{96,108,114,211–217} cross-coupling (DCC) has emerged as a versatile methodology for Pd-catalyzed carbon-carbon bond formation, with markedly wide applications for the coupling of heteroaromatics.^{115,204,218–221} Given the ubiquity of carboxylic acid functional groups, this reaction limits the need for extensive pre-functionalization. Additionally, carboxylic acids can be easily shielded as esters,²⁰⁷ allowing them to be carried through a multi-step synthesis and selectively exposed as required. Employing successive decarboxylative arylations thus provides a chemoselective, atom-economic, and tunable procedure for the synthesis of non-symmetric di-aryl-substituted thiophenes. We have thus developed an efficient protocol, summarized in Scheme 24, for facile access to a variety of di-aryl-substituted thiophenes with a donor/acceptor motif common to candidate organic semi-conductors, and compared their optical properties.



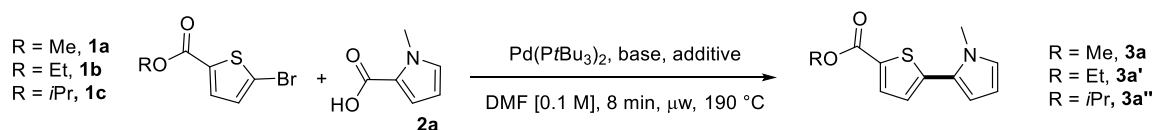
Scheme 24: General procedure for the three-step synthesis of non-symmetric di-aryl-substituted thiophenes

2.2 Results and Discussion

In order to develop an iterative route to di-aryl thiophenes, an initial decarboxylative cross-coupling was required that involves a heteroarene (**1**) containing an ester functional group. Conditions previously developed for the decarboxylative cross-coupling of heteraromatic carboxylic acids,¹¹⁵ however, were not initially tolerant of an ester functionality on the bromothiophene (Table 1, entry 1). An initial screening of esters and modified conditions was thus evaluated. 1-methyl-1*H*-pyrrole-2-carboxylic acid **2a** was employed as a model cross-coupling partner during optimization.

When the cross-coupling was performed with a methyl, ethyl or isopropyl ester (Table 1, entries 1-3), a significant by-product of this reaction was a transesterification with a butyl group of tetrabutylammonium chloride (*n*Bu₄NCl), an additive previously shown to increase the yield of certain decarboxylative cross-coupling reactions.¹¹⁵ In order to circumvent this issue, removal of the additive was evaluated. It was found that an improved yield could be obtained without *n*Bu₄NCl by increasing the temperature from 170 to 190 °C (Table 1, entries 4 and 5). A significant side-reaction for entries 1, 4 and 5 appears to be a transfers of the methyl chain from **1a** to the carboxylic acid **2a**, as methyl 1-methyl-1*H*-pyrrole carboxylate was observed as a major by-product. Additionally, homo-coupling was a significant product of the reaction with the isopropyl ester **1c** (Table 1, entry 7). Accordingly, the further screening was conducted with the ethyl ester **1b**. A screening of bases (Table 1, entries 6, 8 and 9) provided the corresponding product **3a'** in 88 % yield, with final conditions using KOH as a base (for the complete optimization see Table 14 in the supporting information for Chapter 2)

Table 1: Optimization of decarboxylative cross-coupling in the presence of an ester moiety



entry	thiophene halide	base	additive	product	yield, %
1*	1a	Cs ₂ CO ₃	<i>n</i> Bu ₄ NCl	3a	32 ^a
2*	1b	Cs ₂ CO ₃	<i>n</i> Bu ₄ NCl	3a'	27 ^a
3*	1c	Cs ₂ CO ₃	<i>n</i> Bu ₄ NCl	3a''	35 ^a
4*	1a	Cs ₂ CO ₃	-	3a	42 ^a

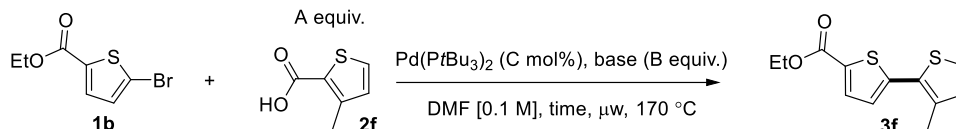
5	1a	Cs ₂ CO ₃	-	3a	48 ^α , 37 ^β
6	1b	Cs ₂ CO ₃	-	3a'	78 ^α
7	1c	Cs ₂ CO ₃	-	3a''	50 ^α
8	1b	KOH	-	3a'	91 ^α , 88 ^β
9	1b	Na ₂ CO ₃	-	3a'	60 ^α

* 170 °C, ^[α] yield estimated by ¹H NMR, ^[β] Isolated yield.

Conditions: 5-bromothiophene-2-ethyl ester (0.2 mmol), 1-methyl-1H-pyrrole-2-carboxylic acid (0.4 mmol), Pd(PtBu₃)₂ (0.01 mmol), base (0.3 mmol), anhydrous DMF (2 mL), 190 °C, μw, 8 min.

These adapted conditions, however, did not translate efficiently to couplings with thiophene carboxylic acids. When the reactions conditions were tested with 3-methylthiophene carboxylic acid **2f**, only a 21 % yield was obtained (Table 2, entry 1). A significant by-product of this reaction was a presumed ethyl chain transfer from the ethyl ester bromothiophene **1b** to the methyl thiophene carboxylic acid **2f**. As such, a further optimization was conducted for the decarboxylative cross-coupling of these substrates (see Table 2).

Table 2: Optimization of DCC with 3-methylthiophene carboxylic acid



entry	A	base	B	C	yield, %
1*	2.0	KOH	1.5	5.0	21 ^α
2	2.0	KOH	1.5	5.0	25 ^α
3	2.0	KOH	2.0	5.0	32 ^α
4	2.0	KOH	1.0	2.5	42 ^α
5	2.0	KOH	1.5	2.5	32 ^α
6	1.0	KOH	1.0	2.5	71 ^β
7	1.0	KOH	1.0	1.25	45 ^α
8	2.0	KOH	1.0	1.25	56 ^α
9	1.0	Cs ₂ CO ₃	1.0	2.5	90 ^β
10	1.0	Na ₂ CO ₃	1.0	2.5	82 ^α

* 190 °C, ^[α] yield estimated by ¹H NMR, ^[β] isolated yield.

Conditions: 5-bromothiophene-2-ethyl ester (0.2 mmol), 3-methyl thiophene carboxylic acid, Pd(PtBu₃)₂, base, anhydrous DMF (2 mL), 170 °C, μw, 8 min.

A reduction in reaction temperature did not significantly influence by-product formation (Table 2, entry 2), but altering the equivalents of thiophene carboxylic **2f**, base, and Pd catalyst helped mitigate this undesired reaction (entries 3-8). A combination of lowering the catalyst loading from 5 to 2.5 mol% and a reduction in the equivalents of base from 1.5 to 1.0 led to an improved yield of cross-coupling product (entry 4). Lowering the catalyst loading to 1.25 % rendered the reaction sluggish, and a significant amount of starting material remained (entries 7 and 8). Whereas previously, 2 equivalents of carboxylic acid **2f** to aryl halide **1b** were employed, using an equimolar amount of each reagent was shown to be significantly beneficial (entry 6). We surmise that limiting the excess of carboxylic acid to aryl halide mitigates the formation of non-desirable by-products and increases the yield for the desired product. Using the base Cs₂CO₃ (entry 9) also resulted in an improved yield compared with either KOH or Na₂CO₃, for a final optimized yield of 89% for this transformation. The altered conditions developed for thiophene carboxylic acid **2f** were also shown to be more effective when coupling with a furan carboxylic acids, although the suspected esterification by-product was not observed with this substrate.

These two sets of adapted decarboxylative cross-coupling conditions produced good to excellent yields with a variety of five-membered heteroaromatic coupling partners, as illustrated in Table 3. The pyrrole carboxylic acids used for this assessment of scope were synthesized according to existing methodologies, using either nucleophilic alkylation (**2a**, **2b** and **2e**), or Buchwald couplings (**2c** and **2d**).²²² Some of the thiophene and furan carboxylic acid starting materials are commercially available (**2f** and **2g**), while others were synthesized according to protocols previously developed (**2h**, **2i** and **2k**).^{223,224} All carboxylic acids screened are bench stable, non-volatile, and are easily manipulated open to an air atmosphere. This renders them more practical and safer to work with compared to the corresponding organometallic reagents necessary for comparable reactions, such as organotin or Grignard reagents.

Consistently good yields are achieved with pyrrole carboxylic acids **2a-e** (Table 3, entries 1-5), with either alkyl or aryl substitution at the N1-position. The reaction does not proceed with a free N1-H on the pyrrole, but encouragingly, works well with a *para*-methoxy benzyl (PMB) protecting group (entry 5), which can be removed if the free N1-H is required. Unfortunately, the reaction does not proceed with the more commonly used *tert*-butyl

carbonyl (BOC) protecting group. Good yields were also obtained with several thiophene carboxylic acids **2f**, **2h**, and **2i** (entries 6, 8 and 9), however, relatively lower for a thiophene without functionalization at the β -position (entry 7) and furan carboxylic acid **2j** (entry 11). We suspect that this is due to a competitive β (C3) palladation that can lead to non-desired by-products.³⁶ Encouragingly, a better yield was obtained with hydroxymethylfuroic acid (entry 11), a particularly interesting biomass-derived substrate.³⁹ Thermal conditions were also developed, to facilitate scale-up of these reactions, producing comparable yields for bi-aryl esters **3a** and **3g**. This was performed on a 1 mmol scale in a sealed round bottom flask at 140 °C for 6 h, using the same base and catalyst. It was also found that under this catalytic system, the reaction does not proceed 1-methyl-1H-pyrrole-3-carboxylic acid (entry 12) and is limited to heteroarenes with the carboxylic acid adjacent to the heteroatom.

Table 3: Substrate scope of the heteroaromatic coupling carboxylic acid.

entry	acid	conditions	product	yield, %
1		A		88/79 ^a
2		A		83
3		A		74
4		A		55

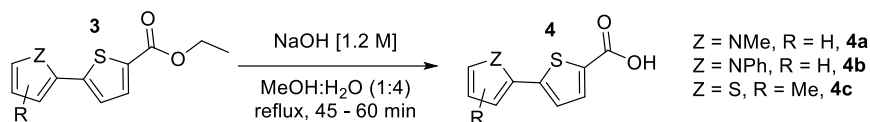
5		A		66
6		B		89/82 ^a
7		B		38
8		B		76
9		B		62
10		B		39
11		B		52
12		A/B		0

Conditions A: 5-bromothiophene-2-ethyl ester (1 mmol), acid (2 mmol), Pd(PtBu₃)₂ (0.025 mmol), KOH (1 mmol), DMF (5 mL), 190 °C, 8 min.

Conditions B: (variation): acid (1 mmol), Pd(PtBu₃)₂ (0.0125 mmol), Cs₂CO₃ (1 mmol), 170 °C. ^a reaction done thermally at 140 °C for 6 h

A saponification of esters **3a**, **3c**, and **3f** was then carried out to expose the carboxylic acid. This reaction is generally quantitative in methanol with aqueous sodium hydroxide under reflux for 45 – 60 minutes (Scheme 25). This step also allows for facile purification from the first cross-coupling *via* acid/base chemistry (see section 6.1.3), and

thus removes a column chromatography step. This facet of the route reduces the synthetic operations required to obtain final substrates, and minimizes the solvent waste.



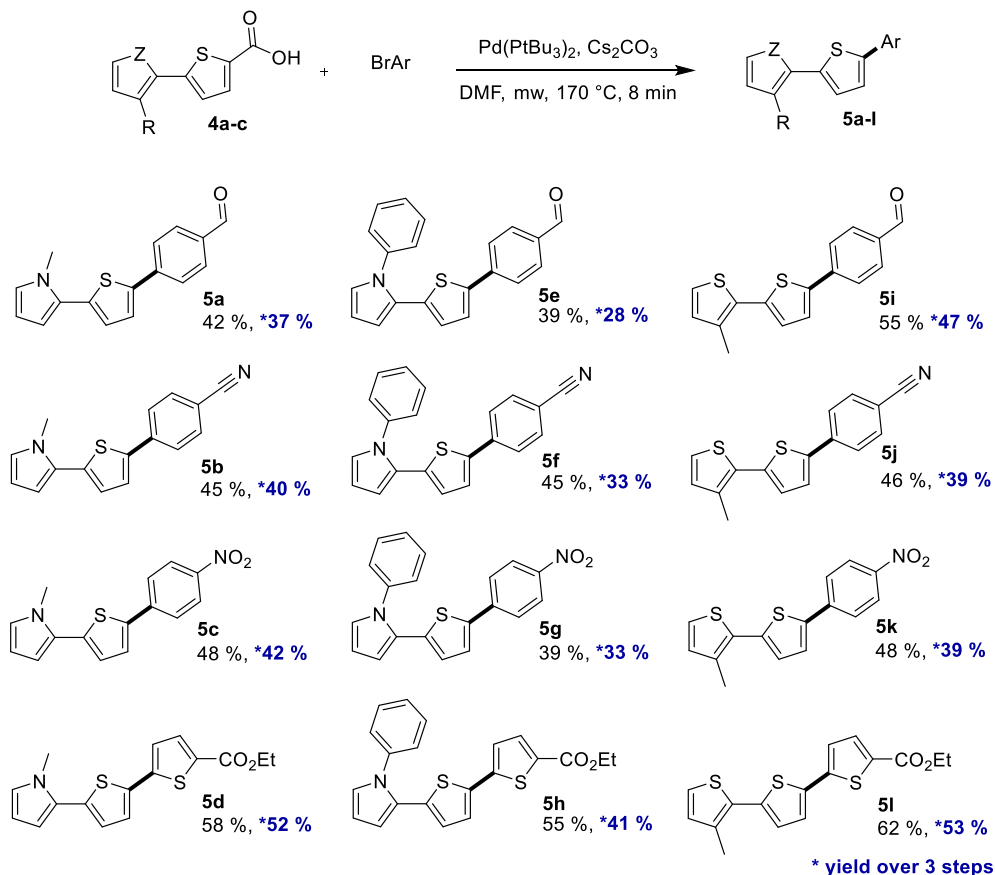
Scheme 25: General procedure for the saponification of bi-aryl esters.

Bi-aryl acids **4a**, **4b** and **4c** were then further functionalized *via* a second decarboxylative cross-coupling to yield a library of non-symmetric di-aryl-substituted thiophenes, with the donor/acceptor motif common in organic semi-conductors. As summarized in Table 4, yields for the second decarboxylative cross-coupling were relatively lower, with resulting moderate to good yields over three steps.

Optimization attempts revealed that no change in base, Pd source, ligand, temperature, or time made significant improvements to this decarboxylative cross-coupling step. It was found that the pressure/head space of the reaction was needed for reproducibility. Best yields were obtained when the vial was half filled, which translates to an approximate pressure of 2 bar upon microwave irradiation at 170 °C.

Several of the final compounds, particularly those with N-methyl pyrrole donor groups (**5a-d**), are suspected to be light sensitive and susceptible to degradation upon prolonged UV illumination. Despite these drawbacks, a variety of aryl halides with electron withdrawing functional groups underwent cross-coupling with bi-aryl acids for the construction of a small library of triaryls with a donor-acceptor motif. Final yields over three steps range from 28 to 47%. This route avoids the use of potentially unstable/reactive Grignard cross-coupling partners that would not be tolerated for examples highlighted through our method (Table 4, entries **5a**, **5d**, **5e**, **5h**, **5i** and **5l**). Furthermore, this approach avoids the generation of stoichiometric amounts of organometallic waste, which can be challenging to purify and may interfere in the electronic properties of the final compounds.^{225,226}

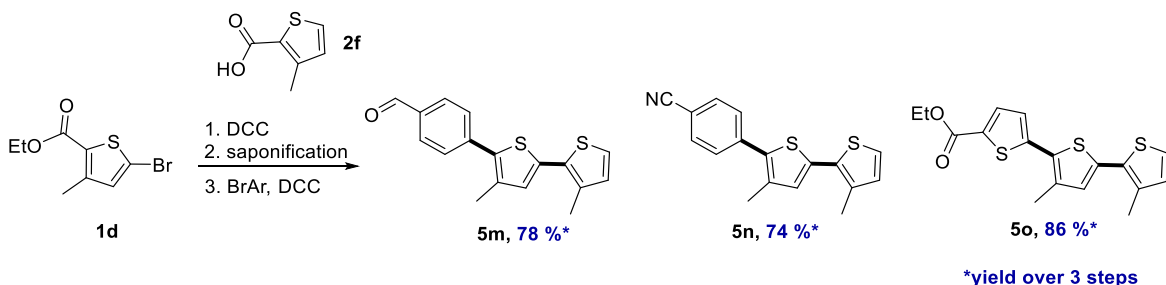
Table 4: Scope of non-symmetric di-aryl-substituted thiophene



Conditions: Ar-Br (0.4 mmol), bi-aryl acid (0.2 mmol), Pd(PtBu₃)₂ (0.005 mmol), Cs₂CO₃ (0.2 mmol), DMF (2 mL) in a 4 mL sealed microwave vial, 170 °C, μ w, 10 min.

Subsequently, we were interested in diversifying the starting substrate (bromothiophene ester **1**), to include substitution relevant to photoelectronic materials. Functionalization at the β position is an asset in terms of the applicability of organic semiconductors, as alkyl chains at branching positions assist with solubility.³⁸ Our developed synthetic route was evaluated employing the β -methylated bromothiophene ester **1d** (see Scheme 26). We hypothesized that, as was the case with the first decarboxylative cross-coupling step (see Table 3) functionalization at this position would increase yields by minimizing competing reactivity at C3. Preliminary results indicate that very good yields can be obtained utilizing this substrate (74-84% overall yields over three steps). The synthesis

was conducted with no intermediate purification step – small amounts of by-products from the first decarboxylative cross-coupling step (mostly homo-coupling of the bromothiophene) were removed by acid/base chemistry after the saponification.



Scheme 26: Synthetic route with β functionalized bromothiophene ester

This three-step procedure is thus efficient in terms of time and solvents used, in addition to its minimal use of organometallic reagents. The commercial cost of bromothiophene ester **1d**, however, is prohibitive, and we are currently developing a cost efficient synthesis of this starting material.

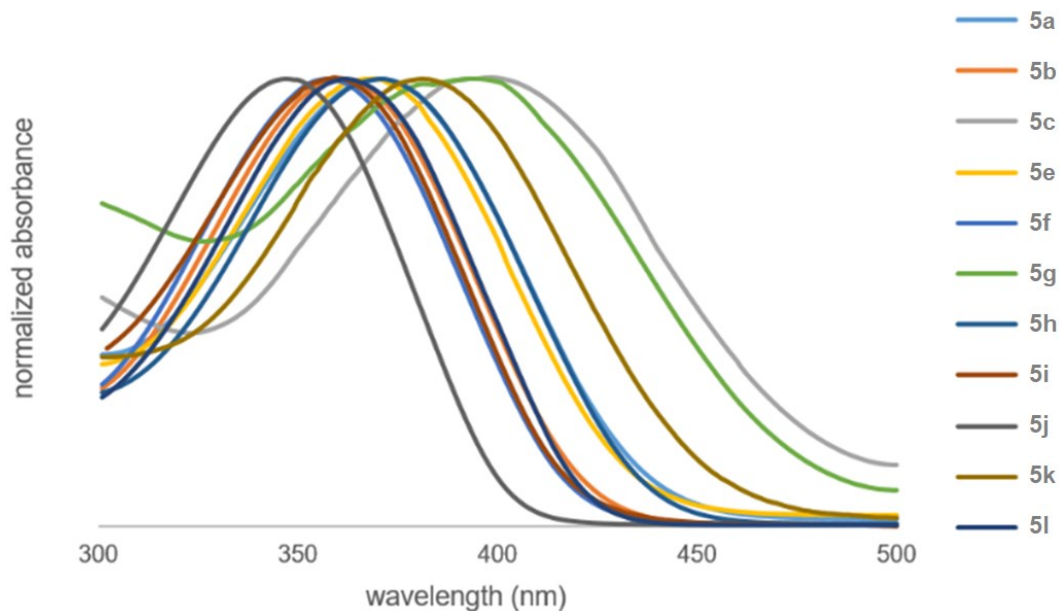


Figure 10: Absorption spectra of non-symmetric di-aryl-substituted thiophenes in acetonitrile

The UV/Vis absorption spectra of the oligoheteroarenes synthesized in Table 4, were also evaluated (Figure 10). As expected, the absorption profiles of these compounds appear to be influenced by the alteration of the donor (terminal heterocycle) and acceptor groups (terminal electron withdrawing group). Generally, the tri-aryls with the most bathochromic absorbance were those with pyrrole (**5a-c** and **5e-h**) rather than those with thiophene donors. Interestingly, tri-aryl compounds **5e-h**, with the N-phenyl pyrrole donor group, were blue shifted compared to compounds **5a-c**, with the N-methylated pyrrole donor. This implies that the phenyl group on the pyrrole is out of plane and does not contribute to molecular conjugation. The N-phenyl pyrrole series, however, was considerably less light sensitive compared to the N-methylated pyrrole, and did not display as much degradation upon UV illumination as the former (the thiophene donor series, **5i-l**, is light stable). In terms of acceptors, the nitro group consistently displayed the longest absorbance wavelength with all three donors (see nitro terminal tri-aryls **5c**, **5g** and **5k**), which suggests that this functional group has the stronger electron withdrawing ability than the other groups screened. This is particularly salient as nitro groups have potential as anchors for pigment molecules within dye-sensitized solar cells.²²⁷

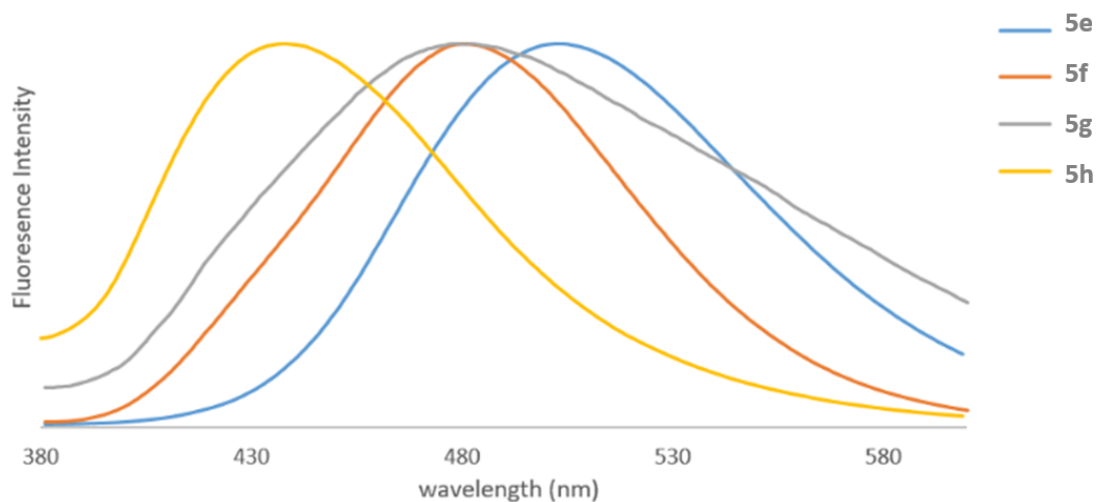


Figure 11: Photoluminescence emission of non-symmetric di-aryl-substituted thiophenes in acetonitrile, illuminated at their respective absorption maximum

All non-symmetric di-aryl-substituted thiophenes synthesized also exhibited photoluminescence, and so the emission spectra for each was also measured. Most of the compounds exhibit similar photoluminescence emissions around 470-495 nm. However, tri-

aryl compounds **5e-h**, with N1-phenyl pyrrole donor, did exhibit a marked variation in photoluminescence emission, from 426 to 495 nm λ_{max} emissions, highlighting the tunability of this particular series (see Figure 11). In the future, a modular library of tri-aryl compounds containing a larger variety of previously challenging to access derivatives will be constructed, in order to further assess the ability to tailor the properties of organic fluorophores.

2.3 Conclusion

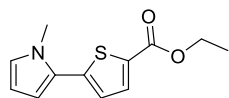
In summary, we have developed a facile and modular synthetic pathway towards non-symmetric di-aryl-substituted thiophenes utilizing successive Pd-catalyzed decarboxylative cross-coupling reactions, with an intermediate saponification step. This methodology allows for an efficient and atom economic approach towards this class of compounds. Ongoing work is being done to adapt this reaction to green solvents, as the use of DMF hinders the safety and sustainability of this protocol. Nevertheless, this strategy presents several advantages - it allows for the incorporation of electron-withdrawing groups that could be challenging to incorporate using existing methods, and avoids the use of stoichiometric amounts of organometallics, which are challenging to purify, particularly in terms of organotin,¹⁹² and could have undesired effects on opto-electronic properties. This protocol is also less energetically demanding and wasteful in terms of solvents used, as the total reaction time for the three-step synthesis is only 1.5 h, and requires a single flash column chromatography purification. Additionally, the synthetic approach developed is high yielding utilizing C3 methylated bromothiophene ester **1d**, with alkylation at this position being important for photoelectronic applications. Employing this protocol, we were able to study the absorbance and photoluminescence profiles of a small library of tri-aryls containing pyrrole and/or thiophene heteroaromatics. This methodology can thus be employed for rapid assessments of desired optoelectronic properties for the optimization of tri-aryl compounds with potential application as wide band gap organic semi-conductors and fluorophores.

2.4 Experimental section

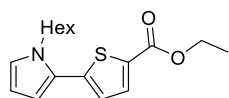
2.4.1 General procedure for decarboxylative cross-coupling with pyrrole carboxylic acids:

To an oven dried 20 mL microwave vial; pyrrole acid (2 mmol), ethyl 5-bromothiophene-2-carboxylate (1 mmol), Cs_2CO_3 (1 mmol), $\text{Pd}(\text{P}t\text{Bu}_3)_2$ (0.05 mmol) are added open to air and dissolved in 10 mL of anhydrous DMF. A stir bar is added and the vial is closed with a rubber seal and a metal cap. The reaction vessel is placed in a microwave reactor for 8 minutes at 190 °C. The reaction mixture is then filtered over celite, and diluted with 50 mL of water. The aqueous phase is extracted 3x with 30 mL of ethyl acetate. The combined organic layers are then washed with 1x saturated NaHCO_3 (aq) and 2x saturated NaCl, dried with Na_2SO_4 , evaporated under reduced pressure, and fully dried under high vacuum for 2 h. The product can then be purified by column chromatography, or the crude can be saponified directly.

For the synthesis of pyrrole carboxylic acid starting materials, see supporting information for Chapter 2.

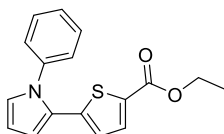


Ethyl 5-(1-methyl-1H-pyrrol-2-yl)thiophene-2-carboxylate (3a'): 1-methyl-1H-pyrrole-2-carboxylic acid (**2a**) (1 mmol) was reacted with ethyl 5-bromothiophene-2-carboxylate (**1b**) in a 20 mL vial. The reaction was purified by flash chromatography (98:2 hexane-EtOAc) to afford ethyl 5-(1-methyl-1H-pyrrol-2-yl)thiophene-2-carboxylate (**3a'**) as a yellow oil (199.5 mg, 84 %) Thermal conditions: 140 °C for 6 h (186.5 mg, 79 %) R_f : 0.40 (9:1 hexane-EtOAc) ^1H NMR (500 MHz, CDCl_3): 7.72 (d, J = 3.9 Hz, 1H), 7.00-6.99 (d, J = 3.9 Hz, 1H), 6.73-6.72 (dd, J = 2.7, 1.8 Hz, 1H), 6.45-6.44 (dd, J = 3.7, 1.8 Hz, 1H), 6.17-6.16 (dd, J = 3.7, 2.7 Hz, 1H) 4.37-4.33 (q, J = 7.1 Hz, 2H), 3.77 (s, 3H), 1.39-1.36 (t, J = 7.1 Hz, 3H) ^{13}C NMR (125 MHz, CDCl_3): δ 162.5, 142.3, 134.0, 131.5, 126.9, 125.8, 124.5, 111.4, 108.6, 61.3, 35.9, 14.6 HRMS (ESI): calculated for $[\text{C}_{12}\text{H}_{14}\text{NO}_2\text{S}]^{+1}$ = 236.07398, found = 236.07389 UV-Vis: λ_{max} = 324 nm

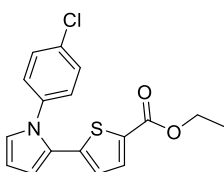


Ethyl 5-(1-hexyl-1H-pyrrol-2-yl)thiophene-2-carboxylate (3b): 1-hexyl-1H-pyrrole-2-carboxylic acid (**2b**) (1 mmol) was reacted with ethyl 5-bromothiophene-2-carboxylate (**1b**) in a 20 mL vial. The reaction was purified by flash chromatography (hexanes) to afford ethyl 5-(1-hexyl-1H-pyrrol-2-

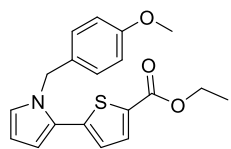
yl)thiophene-2-carboxylate (**3b**) as a black oil (125.8 mg, 83 %) R_f : 0.41 (95:5 hexanes-EtOAc) ^1H NMR (500 MHz, CDCl_3): δ 7.73 (d, J = 3.9 Hz, 1H), 6.98 (d, J = 3.9 Hz, 1H), 6.78 (dd, J = 2.7, 1.8 Hz, 1H), 6.40 (dd, J = 3.7, 1.8 Hz, 1H), 6.18 (dd, J = 2.7, 3.7 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 4.04 (t, 2H), 1.72-1.25 (m, 10H), 0.86 (t, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.32, 142.19, 133.65, 131.67, 125.86, 124.73, 124.26, 111.44, 108.36, 61.07, 47.86, 31.38, 31.29, 26.30, 22.47, 14.38. HRMS (ESI): calculated for $[\text{C}_{17}\text{H}_{24}\text{NO}_2\text{S}]^{+1}$ = 306.15223, found = 306.15207



Ethyl 5-(1-phenyl-1H-pyrrol-2-yl)thiophene-2-carboxylate (3c): 1-phenyl-1H-pyrrole-2-carboxylic acid (**2c**) (1 mmol) was reacted with ethyl 5-bromothiophene-2-carboxylate (**1b**) in a 20 mL vial. The reaction was purified by flash chromatography (98:2 hexanes - EtOAc) to afford ethyl 5-(1-phenyl-1H-pyrrol-2-yl)thiophene-2-carboxylate (**3c**) as a yellowish oil (112.1 mg, 75 %) R_f = 0.21 (95:5 Hexanes - EtOAc) ^1H NMR (500 MHz, CDCl_3) δ 7.49 (d, J = 3.9 Hz, 1H), 7.50- 7.39 (m, 3H), 7.29 – 7.20 (m, 2H), 6.90 (dd, J = 2.8, 1.7 Hz, 1H), 6.59 (dd, J = 3.7, 1.7 Hz, 1H), 6.42 (d, J = 3.9 Hz, 1H), 6.32 (dd, J = 2.8, 3.7 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H) ^{13}C NMR (125 MHz, CDCl_3): δ 162.22, 141.93, 139.59, 133.39, 131.01, 129.19, 127.91, 126.74, 126.59, 125.84, 124.49, 112.16, 109.61, 60.92, 14.31. HRMS (ESI): calculated for $[\text{C}_{17}\text{H}_{15}\text{NO}_2\text{S}]$ = 297.08180, found = 297.08199 UV-Vis: λ_{max} = 322 nm



Ethyl 5-(1-(4-chlorophenyl)-1H-pyrrol-2-yl)thiophene-2-carboxylate (3d): 1-(4-chlorophenyl)-1H-pyrrole-2-carboxylic acid (**2d**) (1 mmol) was reacted with ethyl 5-bromothiophene-2-carboxylate (**1b**) in a 20 mL vial. The reaction was purified by flash chromatography (98:2 hexanes:EtOAc) to afford ethyl 5-(1-(4-chlorophenyl)-1H-pyrrol-2-yl)thiophene-2-carboxylate (**3d**) as a yellowish oil (90.6 mg, 55 %) R_f = 0.17 (95:5 Hexanes – EtOAc) ^1H NMR (500 MHz, CDCl_3) δ 7.53 (d, J = 3.9 Hz, 1H), 7.38 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 6.88 (dd, J = 2.8, 1.7 Hz, 1H), 6.58 (dd, J = 3.7, 1.7 Hz, 1H), 6.47 (d, J = 3.9 Hz, 1H), 6.34 (dd, J = 3.7, 2.8 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 162.18, 141.45, 138.14, 133.43, 131.55, 129.43, 127.70, 125.71, 124.87, 112.61, 110.02, 61.05, 14.34. HRMS (ESI): calculated for $[\text{C}_{17}\text{H}_{15}\text{NO}_2\text{SCl}]^{+1}$ = 332.05065, found = 332.05074 UV-Vis: λ_{max} = 320 nm



Ethyl 5-(1-(4-methoxybenzyl)-1H-pyrrol-2-yl)thiophene-2-carboxylate

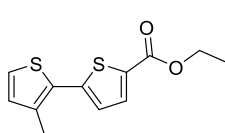
(3e): 4-methoxybenzyl-1H-pyrrole-2-carboxylic acid (**2e**) (1 mmol) was reacted with ethyl 5-bromothiophene-2-carboxylate (**1b**) in a 20 mL vial.

The reaction was purified by flash chromatography (98:2 hexanes - EtOAc) to afford ethyl 5-(1-(4-methoxybenzyl)-1H-pyrrol-2-yl)thiophene-2-carboxylate (**3e**) as a clear oil (112.5 mg, 66 %) $R_f = 0.16$ (95:5 Hexanes - EtOAc) ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, $J = 3.9$ Hz, 1H), 7.00 – 6.90 (m, 2H), 6.90 – 6.80 (m, 3H), 6.77 (dd, $J = 2.8, 1.8$ Hz, 1H), 6.47 (dd, $J = 3.7, 1.8$ Hz, 1H), 6.24 (dd, $J = 3.7, 2.8$ Hz, 1H), 5.20 (s, 2H), 4.33 (q, $J = 7.1$ Hz, 2H), 3.78 (s, 3H), 1.36 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 162.22, 159.03, 141.77, 133.67, 131.79, 129.82, 127.69, 126.34, 124.81, 114.20, 111.70, 108.96, 61.05, 55.25, 50.62, 14.35. HRMS (ESI): calculated for $[\text{C}_{19}\text{H}_{20}\text{NO}_3\text{S}]^{+1} = 342.11584$, found = 342.11568

2.4.2 General procedure for decarboxylative cross-coupling with thiophene carboxylic acids:

To an oven dried 20 mL microwave vial; thiophene acid (1 mmol), ethyl 5-bromothiophene-2-carboxylate (1 mmol), Cs_2CO_3 (1 mmol), $\text{Pd}(\text{P}t\text{Bu}_3)_2$ (0.025 mmol) are added open to air and dissolved in 10 mL of anhydrous DMF. A stir bar is added and the vial is closed with a rubber seal and a metal cap. The reaction vessel is placed in a microwave reactor for 8 minutes at 170 °C. The reaction mixture is then filtered over celite, and diluted with 50 mL of water. The aqueous phase is extracted 3x with 30 mL of ethyl acetate. The combined organic layers are then washed with 1x saturated NaHCO_3 (aq) and 2x saturated NaCl, dried with Na_2SO_4 and evaporated under reduced pressure, and fully dried under high vacuum for 2 h. The product can then be purified by column chromatography, or the crude can be saponified directly.

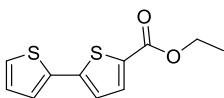
For the synthesis of thiophene carboxylic acid starting materials, see supporting information for Chapter 2.



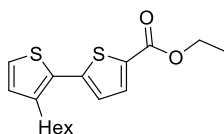
Ethyl 3'-methyl-[2,2'-bithiophene]-5-carboxylate (3f):

3-methylthiophene-2-carboxylic acid (**2f**) (1 mmol) was reacted with ethyl 5-bromothiophene-2-carboxylate (**1b**). The reaction was purified by flash chromatography (98:2 hexane-EtOAc) to afford ethyl 3'-methyl-[2,2'-bithiophene]-5-carboxylate (**3f**) as a clear oil (226.7 mg, 89 %) Thermal conditions: 140 °C for 6 h (208.1

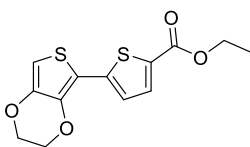
mg, 82 %) R_f : 0.14 (95:5 hexane-EtOAc) ^1H NMR (500 MHz, CDCl_3): 7.74-7.73 (d, J = 3.9 Hz, 1H), 7.21-7.20 (d, J = 5.4, 1H), 7.12-7.11 (d, J = 3.9 Hz, 1H), 6.91-6.90 (d, J = 5.4, 1H), 4.38-4.34 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 1.40-1.37 (t, J = 7.1 Hz, 3H) ^{13}C NMR (125 MHz, CDCl_3): δ 162.0, 143.3, 135.3, 133.4, 132.2, 131.5, 130.1, 125.2, 124.3, 60.91, 15.4, 14.1 HRMS (ESI): calculated for $[\text{C}_{12}\text{H}_{12}\text{O}_2\text{S}_2] = 252.02732$, found = 252.02742 UV-Vis: $\lambda_{\text{max}} = 322 \text{ nm}$



Ethyl [2,2'-bithiophene]-5-carboxylate (3g): thiophene-2-carboxylic acid (**2g**) (1 mmol) was reacted with ethyl 5-bromothiophene-2-carboxylate (**1b**). The reaction was purified by flash chromatography (98:2 hexane-EtOAc) to afford ethyl [2,2'-bithiophene]-5-carboxylate (**3g**) as a clear oil (88.6 mg, 38 %) R_f : 0.25 (9:1 Hexane-EtOAc) ^1H NMR (500 MHz, CDCl_3): 7.70-7.69 (d, J = 3.9 Hz, 1H), 7.31-7.28 (m, 2H), 7.15-7.14 (d, J = 3.9 Hz, 1H), 7.06-7.04 (dd, J = 5.1, 3.6 Hz, 1H), 4.38-4.34 (q, J = 7.1 Hz, 2H), 1.40-1.37 (t, J = 7.1 Hz, 3H) ^{13}C NMR (125 MHz, CDCl_3): δ 162.0, 148.3, 142.5, 139.7, 133.7, 131.4, 122.3, 111.8 107.0, 60.9, 14.1 HRMS (ESI): calculated for $[\text{C}_{11}\text{H}_{10}\text{O}_2\text{S}_2] = 238.01167$, found = 238.01173 UV-Vis: $\lambda_{\text{max}} = 319 \text{ nm}$

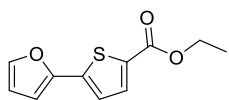


Ethyl 3'-hexyl-[2,2'-bithiophene]-5-carboxylate (3h): 3-hexylthiophene-2-carboxylic acid (**2h**) (1 mmol) was reacted with ethyl 5-bromothiophene-2-carboxylate (**1b**). The reaction was purified by flash chromatography (98:2 hexane-EtOAc) to afford ethyl 3'-hexyl-[2,2'-bithiophene]-5-carboxylate (**3h**) as a clear oil (122.4 mg, 76 %) ^1H NMR (500 MHz, CDCl_3) δ 7.74 (d, J = 3.9 Hz, 1H), 7.24 (d, J = 5.2 Hz, 1H), 7.10 (d, J = 3.9 Hz, 1H), 6.97 (d, J = 5.2 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 2.81 – 2.77 (m, 2H), 1.65 (p, J = 7.5 Hz, 2H), 1.39 (m, 5H), 1.31 (m, , 4H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.2, 143.3, 141.1, 133.6, 132.7, 130.3, 129.8, 126.0, 124.9, 61.2, 31.6, 30.5, 29.3, 22.6, 14.7, 14.1. HRMS (ESI): calculated for $[\text{C}_{17}\text{H}_{23}\text{O}_2\text{S}_2] = 323.11348$, found: 323.11339.



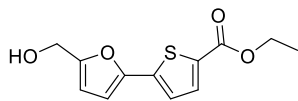
Ethyl 5-(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)thiophene-2-carboxylate (3i): 2,3-dihydrothieno[3,4-b][1,4]dioxine-5-carboxylic acid (**2i**) (0.5 mmol) was reacted with ethyl 5-bromothiophene-2-carboxylate (**1b**). The reaction was purified by flash chromatography (90:10 hexane-EtOAc) to afford ethyl ethyl 5-(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)thiophene-2-carboxylate (**3i**) as a white solid (91.8 mg, 76 %) R_f : 0.37 (9:1 hexane-EtOAc) ^1H NMR (500 MHz, CDCl_3): 7.69-7.68 (d,

$J = 4.0$ Hz, 1H), 7.17-7.15 (d, $J = 4.0$ Hz, 1H), 6.31 (s, 1H), 4.39-4.24 (m, 6H), 1.40-1.35 (t, $J = 7.1$ Hz, 3H) ^{13}C NMR (125 MHz, CDCl_3): δ 162.7, 142.1, 139.3, 133.7, 131.0, 122.8, 111.8, 99.1, 65.4, 64.8, 61.3, 14.6 HRMS (ESI): calculated for $\text{C}_{13}\text{H}_{12}\text{O}_4\text{S}_2 = 296.01715$, found = 296.01724 UV-Vis: $\lambda_{\text{max}} = 328$ nm.



Ethyl 5-(furan-2-yl)thiophene-2-carboxylate (3j): Following the general procedure for DCC with thiophene carboxylic acids, furoic acid (**2j**) (0.5 mmol) was reacted with ethyl 5-bromothiophene-2-carboxylate (**1b**). The

reaction was purified by flash chromatography (98:2 hexane-EtOAc) to afford ethyl 5-(furan-2-yl)thiophene-2-carboxylate (**3j**) as a clear oil (42.2 mg, 39 %) R_f : 0.18 (95:5 hexane-EtOAc) ^1H NMR (500 MHz, CDCl_3): 7.71 (d, $J = 3.9$ Hz, 1H), 7.46-7.45 (dd, $J = 1.8, 0.8$ Hz, 1H), 7.21-7.20 (d, $J = 3.9$ Hz, 1H), 6.65-6.64 (dd, $J = 3.4, 0.8$ Hz, 1H), 6.48-6.47 (dd, $J = 3.4, 1.8$ Hz, 1H), 4.38-4.34 (q, $J = 7.1$ Hz, 2H), 1.40-1.37 (t, $J = 7.1$ Hz, 3H) ^{13}C NMR (125 MHz, CDCl_3): δ 162.5, 148.9, 143.0, 140.2, 134.2, 131.9, 122.8, 112.3, 107.5, 61.4, 14.6 HRMS (ESI): calculated for $[\text{C}_{11}\text{H}_{11}\text{O}_3\text{S}]^{+1} = 223.04234$, found = 223.04239 UV-Vis: $\lambda_{\text{max}} = 257$ nm.



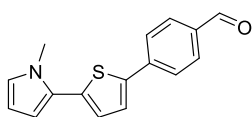
Ethyl 5-(5-(hydroxymethyl)furan-2-yl)thiophene-2-carboxylate (3k): Following the general procedure DCC with thiophene carboxylic acids, hydroxymethyl furoic acid (**2k**) (0.5 mmol) was reacted with ethyl 5-bromothiophene-2-carboxylate (**1b**). The reaction was purified by flash chromatography (9:1 hexane-EtOAc) to afford ethyl 5-(5-(hydroxymethyl)furan-2-yl)thiophene-2-carboxylate (**3k**) as a clear oil (65.4 mg, 52 %) R_f : 0.35 (9:1 hexane-EtOAc)

^1H NMR (500 MHz, CDCl_3): δ 7.68 (d, $J = 3.9$ Hz, 1H), 7.18 (d, $J = 3.9$ Hz, 1H), 6.57 (d, $J = 3.4$ Hz, 1H), 6.37 (d, $J = 3.4$ Hz, 1H), 4.64 (s, 2H), 4.34 (q, $J = 7.1$ Hz, 2H), 2.32 (s, 1H), 1.37 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 162.3, 154.5, 148.4, 139.7, 133.9, 131.6, 122.6, 110.1, 107.9, 61.2, 57.4, 14.3. HRMS (ESI): calculated for $[\text{C}_{12}\text{H}_{13}\text{O}_4\text{S}]^{+1} = 253.05291$, found = 253.05300 UV-Vis: $\lambda_{\text{max}} = 316$ nm

2.4.3 General procedure for decarboxylative cross-coupling with bi-aryl carboxylic acids:

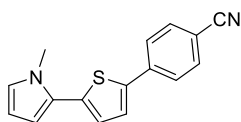
To an oven dried 4 mL microwave vial; bi-aryl acid (0.2 mmol), aryl halide (0.4 mmol), Cs_2CO_3 (0.2 mmol), and $\text{Pd}(\text{P}t\text{Bu}_3)_2$ (0.005 mmol) are added open to air and dissolved in 2 mL of anhydrous DMF. A stir bar is added and the vial is closed with a rubber seal and a

metal cap. The reaction vessel is placed in a microwave reactor for 8 minutes at 170 °C. The reaction mixture is then filtered over celite, and diluted with 50 mL of water. The aqueous phase is extracted 3x with 30 mL of ethyl acetate. The combined organic layers are then washed with 1x saturated NaHCO₃ (aq) and 2x saturated NaCl, dried with Na₂SO₄ evaporated under reduced pressure, and fully dried under high vacuum for 2 h.



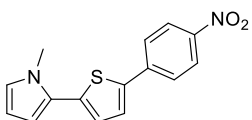
4-(5-(1-methyl-1H-pyrrol-2-yl)thiophen-2-yl)benzaldehyde (5a): 5-(1-methyl-1H-pyrrol-2-yl)thiophene-2-carboxylic acid (**4a'**) (0.2 mmol)

was reacted with 4-bromobenzaldehyde (0.4 mmol). The reaction was purified by flash chromatography (98:2 hexane-EtOAc) to afford 4-(5-(1-methyl-1H-pyrrol-2-yl)thiophen-2-yl)benzaldehyde (**5a**) as a yellow oil (22.5 mg, 42 %) R_f: 0.12 (9:1 Hexanes: EtOAc) ¹H NMR (500 MHz, CDCl₃) δ 10.00 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 3.8 Hz, 1H), 7.04 (d, *J* = 3.8 Hz, 1H), 6.74 (dd, *J* = 2.7, 1.8 Hz, 1H), 6.41 (dd, *J* = 3.9, 1.8 Hz, 1H), 6.19 (dd, *J* = 3.9, 2.7 Hz, 1H), 3.79 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 191.35, 140.82, 139.95, 136.84, 134.87, 130.47, 126.79, 125.55, 125.53, 125.44, 124.87, 110.49, 108.24, 35.46. HRMS (ESI): calculated for [C₁₆H₁₄NO₃]⁺ = 268.07906, found 268.07905. UV-Vis: λ_{max} = 370 nm Photoluminescence emission at λ_{max} = 487 nm



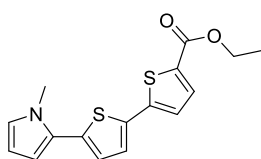
4-(5-(1-methyl-1H-pyrrol-2-yl)thiophen-2-yl)benzonitrile (5b): 5-(1-methyl-1H-pyrrol-2-yl)thiophene-2-carboxylic acid (**4a'**) (0.2 mmol) was

reacted with 4-bromobenzonitrile (0.4 mmol). The reaction was purified by flash chromatography (98:2 hexane-EtOAc) to afford 4-(5-(1-methyl-1H-pyrrol-2-yl)thiophen-2-yl)benzonitrile (**5b**) as a yellow solid, 23.8 mg, 45 %. R_f: 0.28 (95:5 Hexanes: EtOAc) ¹H NMR (500 MHz, CDCl₃) δ 7.66 (q, 4H), 7.37 (d, *J* = 3.8 Hz, 1H), 7.03 (d, *J* = 3.8 Hz, 1H), 6.74 (dd, *J* = 1.8, 3.7 Hz, 1H), 6.41 (dd, *J* = 3.7, 1.8 Hz, 1H), 6.19 (dd, *J* = 3.7, 2.7 Hz, 1H), 3.78 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 140.13, 138.50, 137.00, 132.72, 125.59, 125.53, 125.48, 124.94, 118.88, 110.58, 110.22, 108.27, 35.46. HRMS (ESI): calculated for [C₁₆H₁₂N₂S] = 264.07157, found 264.07182. UV-Vis: λ_{max} = 360 nm Photoluminescence emission at λ_{max} = 495 nm



1-methyl-2-(5-(4-nitrophenyl)thiophen-2-yl)-1H-pyrrole (5c): 5-(1-methyl-1H-pyrrol-2-yl)thiophene-2-carboxylic acid (**4a'**) (0.2 mmol) was reacted with 4-bromonitrobenzene (0.4 mmol). The reaction was

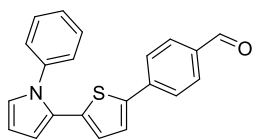
purified by flash chromatography (98:2 hexane-EtOAc) to afford 1-methyl-2-(5-(4-nitrophenyl)thiophen-2-yl)-1H-pyrrole (**5c**) as an orange solid (27.1 mg, 48 %) R_f : 0.22 (95:5 Hexanes: EtOAc) ^1H NMR (500 MHz, CDCl_3) δ 8.29 – 8.18 (m, 2H), 7.78 – 7.66 (m, 2H), 7.43 (d, J = 3.9 Hz, 1H), 7.05 (d, J = 3.9 Hz, 1H), 6.75 (dd, J = 2.7, 1.8 Hz, 1H), 6.43 (dd, J = 3.7, 1.8 Hz, 1H), 6.19 (dd, J = 3.7, 2.7 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 146.62, 140.71, 139.84, 137.99, 126.41, 125.85, 125.73, 125.38, 124.72, 110.99, 108.61, 35.77. HRMS (ESI): calculated for $[\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2\text{S}]$ = 284.06140, found 264.06137. UV-Vis: λ_{max} = 392 nm Photoluminescence emission at λ_{max} = 481 nm



Ethyl 5'-(1-methyl-1H-pyrrol-2-yl)-[2,2'-bithiophene]-5-carboxylate

(5d): 5-(1-methyl-1H-pyrrol-2-yl)thiophene-2-carboxylic acid (**4a'**) (0.2 mmol) was reacted with ethyl 5-bromothiophene-2-carboxylate (0.4 mmol). The reaction was purified by flash chromatography (98:2

hexane-EtOAc) to afford ethyl 5'-(1-methyl-1H-pyrrol-2-yl)-[2,2'-bithiophene]-5-carboxylate (**5d**) as a dark yellow oil (37.1 mg, 58 %). R_f : 0.42 (95:5 Hexanes: EtOAc) ^1H NMR (500 MHz, CDCl_3) δ 7.69 (m, J = 3.9 Hz, 1H), 7.22 (d, J = 3.7 Hz, 1H), 7.12 (d, J = 3.9 Hz, 1H), 6.94 (d, J = 3.7 Hz, 1H), 6.72 (dd, J = 2.7, 1.8 Hz, 1H), 6.38 (dd, J = 3.7, 1.8 Hz, 1H), 6.17 (dd, J = 3.7, 2.7 Hz, 1H), 4.34 (t, J = 7.1 Hz, 2H), 3.76 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.10, 143.96, 135.86, 134.82, 134.12, 131.48, 126.55, 125.47, 125.21, 124.84, 123.48, 110.52, 108.23, 61.19, 35.42, 14.35. HRMS (ESI): calculated for $[\text{C}_{16}\text{H}_{16}\text{NO}_2\text{S}_2]^+ = 318.06170$, found 318.06148.

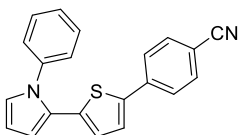


4-(5-(1-phenyl-1H-pyrrol-2-yl)thiophen-2-yl)benzaldehyde (5e): 5-

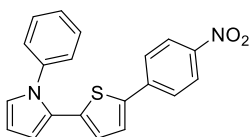
(1-phenyl-1H-pyrrol-2-yl)thiophene-2-carboxylic acid (**4b'**) (0.2 mmol) was reacted with 4-bromobenzaldehyde (0.4 mmol). The reaction was purified by flash chromatography (98:2 hexane-EtOAc) to afford 4-(5-

(1-phenyl-1H-pyrrol-2-yl)thiophen-2-yl)benzaldehyde (**5e**) as a yellow solid (29.7 mg, 45 %) R_f : 0.20 (95:5 Hexanes: EtOAc) ^1H NMR (500 MHz, CDCl_3) δ 9.95 (s, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.47 – 7.27 (m, 5H), 7.19 (d, J = 3.9 Hz, 1H), 6.91 (dd, J = 2.8, 1.7 Hz, 1H), 6.57 (dd, J = 3.7, 1.7 Hz, 1H), 6.49 (d, J = 3.9 Hz, 1H), 6.35 (dd, J = 3.7, 2.8 Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3) δ 191.56, 140.62, 140.21, 140.10, 137.03, 134.97, 130.63, 129.39, 128.02, 127.28, 126.89, 125.88, 125.65, 125.52, 125.47, 111.66, 109.75.

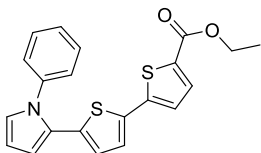
HRMS (ESI): calculated for $[C_{21}H_{15}NOS] = 329.08689$, found 329.08695. UV-Vis: $\lambda_{max} = 367$ nm Photoluminescence emission at $\lambda_{max} = 495$ nm



4-(5-(1-phenyl-1H-pyrrol-2-yl)thiophen-2-yl)benzonitrile (5f): 5-(1-phenyl-1H-pyrrol-2-yl)thiophene-2-carboxylic acid (**4b'**) (0.2 mmol) was reacted with 4-bromobenzonitrile (0.4 mmol). The reaction was purified by flash chromatography (98:2 hexane-EtOAc) to afford 4-(5-(1-phenyl-1H-pyrrol-2-yl)thiophen-2-yl)benzonitrile (**5f**) as a yellow solid (25.4 mg, 39 %) R_f: 0.26 (95:5 Hexanes: EtOAc) ¹H NMR (500 MHz, CDCl₃) δ 7.57 (q, 4H), 7.39 (m, 3H), 7.31 (m, 2H), 7.16 (d, $J = 3.9$ Hz, 1H), 6.92 (dd, $J = 2.8, 1.8$ Hz, 1H), 6.56 (dd, $J = 3.7, 1.7$ Hz, 1H), 6.50 (d, $J = 3.9$ Hz, 1H), 6.35 (dd, $J = 3.7, 2.8$ Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 140.07, 139.94, 138.76, 137.19, 132.88, 129.41, 128.07, 127.17, 126.92, 125.86, 125.71, 125.60, 125.49, 119.16, 111.72, 110.26, 109.77. HRMS (ESI): calculated for $[C_{21}H_{14}N_2S] = 326.08722$, found 326.08721. UV-Vis: $\lambda_{max} = 357$ nm Photoluminescence emission at $\lambda_{max} = 481$ nm

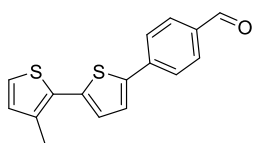


2-(5-(4-nitrophenyl)thiophen-2-yl)-1-phenyl-1H-pyrrole (5g): 5-(1-phenyl-1H-pyrrol-2-yl)thiophene-2-carboxylic acid (**4b'**) (0.2 mmol) was reacted with 4-bromonitrobenzene (0.4 mmol). The reaction was purified by flash chromatography (98:2 hexane-EtOAc) to afford 2-(5-(4-nitrophenyl)thiophen-2-yl)-1-phenyl-1H-pyrrole (**5g**) orange solid (32.0 mg, 46 %) R_f: 0.16 (95:5 Hexanes: EtOAc) ¹H NMR (500 MHz, CDCl₃) δ 8.21 – 8.16 (m, 2H), 7.63 – 7.58 (m, 2H), 7.46 – 7.39 (m, 3H), 7.32 (m, 2H), 7.21 (d, $J = 3.9$ Hz, 1H), 6.93 (dd, $J = 2.8, 1.8$ Hz, 1H), 6.58 (dd, $J = 3.7, 1.8$ Hz, 1H), 6.51 (d, $J = 3.9$ Hz, 1H), 6.36 (dd, $J = 3.7, 2.8$ Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 145.95, 140.20, 139.53, 138.87, 137.42, 128.94, 127.64, 126.44, 125.65, 125.42, 125.26, 125.07, 124.11, 111.35, 109.34. HRMS (ESI): calculated for $[C_{20}H_{14}N_2O_2S] = 346.07705$, found 346.07691. UV-Vis: $\lambda_{max} = 394$ nm Photoluminescence emission at $\lambda_{max} = 471$ nm

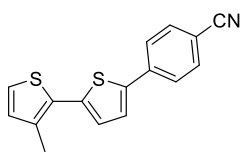


Ethyl 5'-(1-phenyl-1H-pyrrol-2-yl)-[2,2'-bithiophene]-5-carboxylate (5h): 5-(1-phenyl-1H-pyrrol-2-yl)thiophene-2-carboxylic acid (**4b'**) (0.2 mmol) was reacted with ethyl 5-bromothiophene-2-carboxylate (0.4 mmol). The reaction was purified by flash chromatography (98:2 hexane-EtOAc) to afford ethyl 5'-(1-phenyl-1H-pyrrol-2-yl)-[2,2'-bithiophene]-5-carboxylate

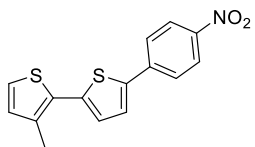
(5h) as an orange oil (41.7 mg, 55 %) R_f : 0.21 (95:5 Hexanes: EtOAc) ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, J = 3.9 Hz, 1H), 7.44 – 7.36 (m, 3H), 7.30 (m, 2H), 7.00 (dd, 2H), 6.90 (dd, J = 2.8, 1.8 Hz, 1H), 6.53 (dd, J = 3.7, 1.7 Hz, 1H), 6.41 (d, J = 3.9 Hz, 1H), 6.33 (dd, J = 3.7, 2.8 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.33, 144.28, 140.03, 136.04, 134.58, 131.47, 129.40, 128.05, 125.48, 123.55, 111.62, 109.73, 61.40, 14.59. HRMS (ESI): calculated for $[\text{C}_{21}\text{H}_{17}\text{NO}_2\text{S}_2] = 379.06952$, found 379.06957. UV-Vis: $\lambda_{\text{max}} = 370$ nm Photoluminescence emission at $\lambda_{\text{max}} = 426$ nm



4-(3'-methyl-[2,2'-bithiophen]-5-yl)benzaldehyde (5i): 3'-methyl-[2,2'-bithiophene]-5-carboxylic acid (**4c'**) (0.2 mmol) was reacted with 4-bromobenzaldehyde (0.4 mmol). The reaction was purified by flash chromatography (98:2 hexane-EtOAc) to afford 4-(3'-methyl-[2,2'-bithiophen]-5-yl)benzaldehyde (**5i**) as a yellow solid (32.7 mg, 55% yield). R_f : 0.24 (95:5 Hexanes: EtOAc) ^1H NMR (500 MHz, CDCl_3): δ 10.00 (s, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 3.9 Hz, 1H), 7.18 (2d, J = 3.9, 5.1 Hz, 2H), 6.92 (d, J = 5.1 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 191.12, 140.60, 139.73, 136.60, 134.64, 130.24, 126.55, 125.33, 124.62, 110.26, 108.00, 35.23, 29.44. HRMS (ESI): calculated for $[\text{C}_{16}\text{H}_{13}\text{OS}_2]^{1+} = 285.04023$, found 285.04018. UV-Vis: $\lambda_{\text{max}} = 358$ nm Photoluminescence emission at $\lambda_{\text{max}} = 488$ nm

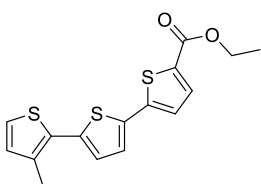


4-(3'-methyl-[2,2'-bithiophen]-5-yl)benzonitrile (5j): 3'-methyl-[2,2'-bithiophene]-5-carboxylic acid (**4c'**) (0.2 mmol) was reacted with 4-bromobenzonitrile (0.4 mmol). The reaction was purified by flash chromatography (98:2 hexane-EtOAc) to afford 4-(3'-methyl-[2,2'-bithiophen]-5-yl)benzonitrile (**5j**) as a yellow solid (26.1 mg, 46 %) R_f : 0.61 (9:1 Hexanes: EtOAc) ^1H NMR (500 MHz, CDCl_3): δ 7.68 – 7.58 (m, 4H), 7.35 (d, J = 3.9 Hz, 1H), 7.17 (d, J = 5.1 Hz, 1H), 7.12 (d, J = 3.9 Hz, 1H), 6.90 (d, J = 5.1 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 141.10, 138.75, 138.51, 134.88, 132.88, 131.83, 130.68, 126.66, 125.79, 125.68, 124.10, 119.03, 110.54, 15.75. HRMS (ESI): calculated for $[\text{C}_{16}\text{H}_{11}\text{NS}_2] = 281.03274$, found 281.03279. UV-Vis: $\lambda_{\text{max}} = 346$ nm Photoluminescence emission at $\lambda_{\text{max}} = 450$ nm



3-methyl-5'-(4-nitrophenyl)-2,2'-bithiophene (5k): 3'-methyl-[2,2'-bithiophene]-5-carboxylic acid (**4c'**) (0.2 mmol) was reacted with 4-bromonitrobenzene (0.4 mmol). The reaction was purified by flash

chromatography (98:2 hexane-EtOAc) to afford 3-methyl-5'-(4-nitrophenyl)-2,2'-bithiophene (**5k**) as an orange solid (28.9 mg, 48 %) R_f : 0.25 (95:5 Hexanes: EtOAc) ^1H NMR (500 MHz, CDCl_3): δ 8.25 (d, J = 8.9 Hz, 2H), 7.74 (d, J = 8.9 Hz, 2H), 7.45 (d, J = 3.9 Hz, 1H), 7.21 (d, J = 5.1 Hz, 1H), 7.17 (d, J = 3.9 Hz, 1H), 6.97 – 6.87 (d, J = 5.1 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 146.62, 140.71, 139.84, 137.99, 126.85, 126.41, 125.85, 125.73, 125.38, 110.99, 108.61, 35.77. HRMS (ESI): calculated for $[\text{C}_{15}\text{H}_{12}\text{NO}_2\text{S}_2]^{1+}$ = 302.03040, found 302.03017. UV-Vis: λ_{max} = 380 nm Photoluminescence emission at λ_{max} = 475 nm

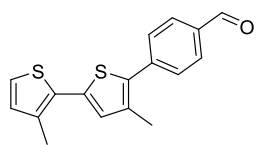


Ethyl 3''-methyl-[2,2':5',2''-terthiophene]-5-carboxylate (5l**):** 3'-methyl-[2,2'-bithiophene]-5-carboxylic acid (**4c'**) (0.2 mmol) was reacted with ethyl 5-bromothiophene-2-carboxylate (0.4 mmol). The reaction was purified by flash chromatography (98:2 hexane-EtOAc) to afford ethyl 3''-methyl-[2,2':5',2''-terthiophene]-5-carboxylate (**5l**) as a dark yellow oil (44.1 mg, 65 %) R_f : 0.32 (95:5 Hexanes: EtOAc) ^1H NMR (500 MHz, CDCl_3): δ 7.69 (d, J = 3.9 Hz, 1H), 7.22 (d, J = 3.8 Hz, 1H), 7.16 (d, J = 5.1 Hz, 1H), 7.13 (d, J = 3.9 Hz, 1H), 7.05 (d, J = 3.8 Hz, 1H), 6.89 (d, J = 5.1 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 146.62, 140.71, 139.84, 137.99, 126.85, 126.41, 125.85, 125.73, 125.38, 110.99, 108.61, 35.77. HRMS (ESI): calculated for $[\text{C}_{15}\text{H}_{12}\text{NO}_2\text{S}_2]^{1+}$ = 302.03040, found 302.03017. UV-Vis: λ_{max} = 361 nm Photoluminescence emission at λ_{max} = 475 nm

2.4.4 General procedure for the synthesis of di-arylated 3-methyl thiophene:

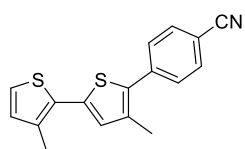
To an oven dried 4 mL microwave vial; 3-methyl thiophene carboxylic acid (**2f**) (0.2 mmol), ethyl 5-bromo-3-methylthiophene-2-carboxylate (**1d**) (0.2 mmol), Cs_2CO_3 (0.2 mmol), and $\text{Pd}(\text{PtBu}_3)_2$ (0.005 mmol) are added open to air and dissolved in 2 mL of anhydrous DMF. A stir bar is added and the vial is closed with a rubber seal and a metal cap. The reaction vessel is placed in a microwave reactor for 8 minutes at 170 °C. The reaction mixture is then filtered over celite, and diluted with 50 mL of water. The aqueous phase is extracted 3x with 30 mL of ethyl acetate. The combined organic layers are then washed with 1x saturated NaHCO_3 (aq) and 2x saturated NaCl, dried with Na_2SO_4 , evaporated under reduced pressure, and fully dried under high vacuum for 2 h. The crude is dissolved in 1 mL MeOH and mixed with a 4 mL aqueous solution of $\text{NaOH}_{(\text{aq})}$ [1.2 M] and heated under reflux for 60

minutes. The reaction mixture is evaporated under reduced pressure (to remove methanol). The aqueous solution is extracted once with EtOAc to remove impurities. The solution is then acidified to a pH of 2 with aqueous HCl [1 M]. The product is extracted 2x with EtOAc. The combined organic layers are washed with saturated NaCl_(aq), dried with Na₂SO₄ and evaporated under reduced pressure. This product is added to an oven dried 4 mL microwave vial, along with an aryl halide (0.4 mmol), Cs₂CO₃ (0.2 mmol), and Pd(PtBu₃)₂ (0.005 mmol), and dissolved in 2 mL of anhydrous DMF. A stir bar is added and the vial is closed with a rubber seal and a metal cap. The reaction vessel is placed in a microwave reactor for 8 minutes at 170 °C. The reaction mixture is then filtered over celite, and diluted with 50 mL of water. The aqueous phase is extracted 3x with 30 mL of ethyl acetate. The combined organic layers are then washed with 1x saturated NaHCO₃ (aq) and 1x saturated NaCl, dried with Na₂SO₄, evaporated under reduced pressure, and fully dried under high vacuum for 2 h.



4-(3',4-dimethyl-[2,2'-bithiophen]-5-yl)benzaldehyde (5m):

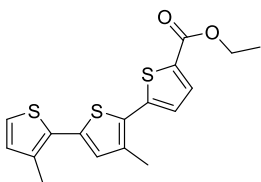
Following the general procedure for the synthesis of diaryl substituted 3-methyl thiophene, the product after the saponification step is reacted with bromobenzaldehyde (0.4 mmol). The reaction was purified by flash column chromatography (98:2 hexanes: EtOAc) to yield 4-(3',4-dimethyl-[2,2'-bithiophen]-5-yl)benzaldehyde (**5m**) as a yellowish oil (46.5 mg, 78 % yield over 3 steps). R_f: 0.56 (8:2 Hexanes: EtOAc) ¹H NMR (500 MHz, CDCl₃): δ 10.03 (s, 1H), 7.92 (m, 2H), 7.66 (m, 2H), 7.16 (d, *J* = 5.1 Hz, 1H), 7.00 (s, 1H), 6.90 (d, *J* = 5.1 Hz, 1H), 2.43 (s, 3H), 2.40 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 191.83, 140.94, 136.46, 136.07, 135.61, 134.91, 134.55, 131.80, 130.91, 130.27, 130.14, 129.09, 129.08, 123.77, 15.73. HRMS (ESI): calculated for [C₁₇H₁₅OS₂]¹⁺ = 299.05588, found 299.05575



4-(3',4-dimethyl-[2,2'-bithiophen]-5-yl)benzonitrile (5n):

Following the general procedure for the synthesis of diaryl substituted 3-methyl thiophene, the product after the saponification step is reacted with bromobenzonitrile (0.4 mmol). The reaction was purified by flash column chromatography (98:2 hexanes: EtOAc) to yield 4-(3',4-dimethyl-[2,2'-bithiophen]-5-yl)benzonitrile (**5n**) as a yellowish oil (44.1 mg, 74 % yield over 3 steps). R_f: 0.61 (9:1 Hexanes: EtOAc) ¹H NMR (500 MHz, CDCl₃): δ 7.70 – 7.66 (m, 2H), 7.58 (m, 2H), 7.16 (d, *J*

= 5.1 Hz, 1H), 6.99 (s, 1H), 6.89 (d, J = 5.1 Hz, 1H), 2.42 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 139.15, 136.37, 135.41, 135.05, 134.38, 132.33, 131.55, 130.48, 129.82, 128.88, 128.87, 123.61, 118.83, 110.32, 15.45, 15.35. HRMS (ESI): calculated for $[\text{C}_{17}\text{H}_{13}\text{NS}_2] = 295.04839$, found 295.04818



Ethyl 3',3''-dimethyl-[2,2':5',2''-terthiophene]-5-carboxylate (5o):

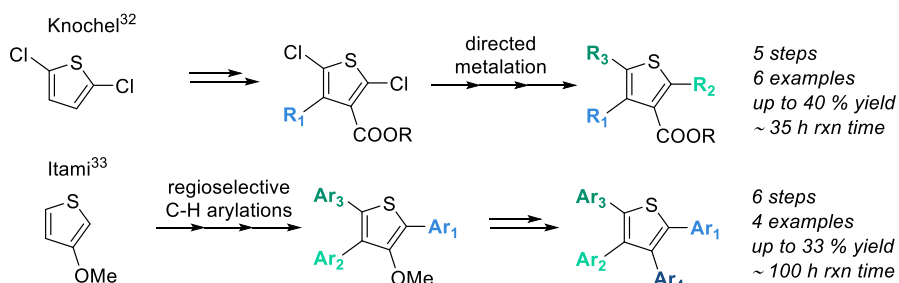
Following the general procedure for the synthesis of diaryl substituted 3-methyl thiophene, the product after the saponification step is reacted with ethyl 5-bromothiophene-2-carboxylate (0.4 mmol). The reaction was purified by flash column chromatography (98:2 hexanes: EtOAc) to yield ethyl 3',3''-dimethyl-[2,2':5',2''-terthiophene]-5-carboxylate (**5o**) as a yellowish oil (59.5 mg, 86 % yield over 3 steps). R_f : 0.25 (95:5 Hexanes: EtOAc) ^1H NMR (500 MHz, CDCl_3): δ 7.74 (d, J = 3.9 Hz, 1H), 7.15 (d, J = 5.1 Hz, 1H), 7.13 (d, J = 4.0 Hz, 1H), 6.94 (s, 1H), 6.88 (d, J = 5.1 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 2.44 (s, 3H), 2.42 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.22, 143.32, 135.90, 135.57, 134.48, 133.69, 132.23, 131.58, 130.44, 129.90, 129.78, 125.15, 123.64, 88.79, 77.26, 77.00, 76.75, 61.18, 15.86, 15.51, 14.38. HRMS (ESI): calculated for $[\text{C}_{17}\text{H}_{17}\text{O}_2\text{S}_3]^+ = 349.03852$, found 349.03851

Chapter 3: Programmed Synthesis of Tetra-Aryl Thiophenes with Stepwise, Ester-Controlled Regioselectivity

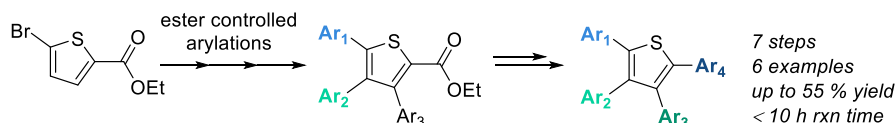
3.1 Introduction

Multi-arylated thiophenes have become ubiquitous motifs in a number of salient industries in the last two decades. Arylated thiophene analogues are recognized building blocks in drug-discovery, with derivatives used as estrogen receptor agonists⁵⁹ and A1 adenosine receptor agonists,²²⁸ anti-tumour agents,^{62,229,230} anti-microbial agents,^{56,231} as well as tyrosine phosphatase inhibitors,⁶¹ bacterial DNA gyrase inhibitors²³² and 15-lipoxygenase-1 inhibitors,²³³ among other applications.^{11–13} Tetra-aryl thiophenes, in particular, have emerged as compounds of interest for opto-electronic materials,^{237–243} energy storage,²⁴⁴ precursors to hexaarylbenzene p-channels,^{245,246} and polymeric materials.^{247–249} Currently, however, the range of methodologies for the complete and selective arylation of thiophenes is limited. In order to efficiently access this promising class of molecules, and further expand the range of applications, we report herein a programmed chemical controlled methodology for the regioselective synthesis of tetra-aryl thiophenes.

Previous work



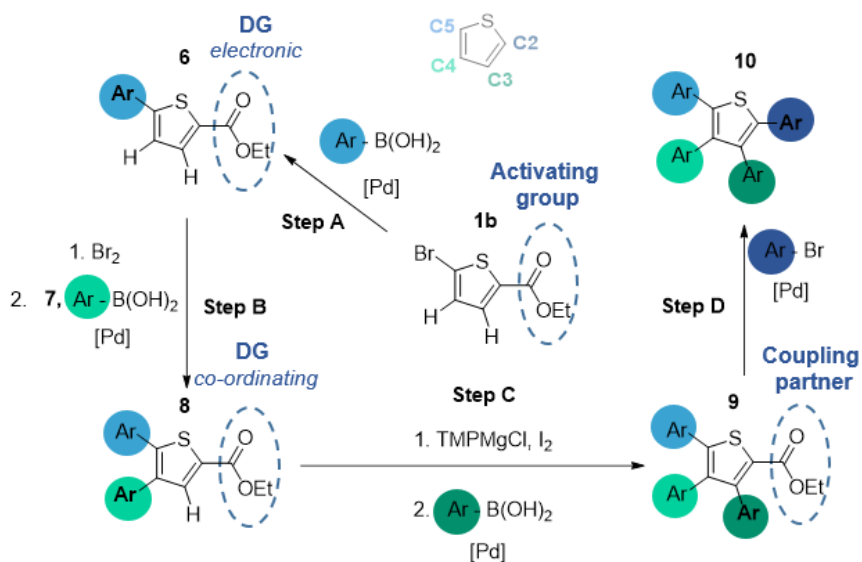
This work



Scheme 27: Syntheses of tetra-aryl thiophenes

In past literature reports, tetra-aryl thiophenes are either obtained by cyclization of the thiophene moiety or by substitutions on a thiophene backbone. Cyclization methods^{148,250–253} involve the lengthy synthesis of structurally complex starting materials and are not adapted for late-stage functionalization. Methods that involve stepwise arylation of a thiophene backbone are therefore more attractive, but face inherent challenges in the arylation of each position in a selective and controlled manner. Knochel *et al.* have reported the synthesis of tetra-substituted thiophenes by sequential directed metalation of dichlorothiophene with $\text{Mg}(\text{TMP})\text{Cl}\cdot\text{LiCl}$ (see Scheme 27).²⁵⁴

While this method is robust and can access a wide range of targets, the directing β -ester functional group remains in the final product for regioselectivity and the corresponding tetra-arylated thiophene was thus not reported. Pioneering work by Itami *et al.* led to the development of a programmed synthesis of tetra-aryl thiophenes *via* ligand-controlled regio-divergent C-H arylations of 3-methoxythiophene (Scheme 27).^{255,256} More than 10 years later, these routes remain the standard to access tetra-substituted thiophenes, among other noteworthy contributions.^{257–259}



Scheme 28: Programmed synthesis of tetra-arylated thiophenes via multi-faceted use of an ester group.

In the present work, we report an innovative approach to accessing tetra-aryl thiophenes that is both time-efficient and highly practical. This is achieved by selectively utilizing the

various facets of an ethyl ester moiety in four distinctive ways for site-specific Pd-catalyzed Suzuki-Miyaura^{75,260} and decarboxylative^{96,109,114} cross-couplings (Scheme 28).

The strategy presented here utilizes commercially available and inexpensive ethyl 2-bromothiophene-5-carboxylate (**1b**) as a generic starting material. The ester is first an activating group for an initial Suzuki-Miyaura coupling at C5 (Step A). It is then used as an electronic directing group (DG) to regioselectively brominate and then arylate the β -position at C4 (Step B). Next, the ester is employed as a co-ordinating directing group to regioselectively iodinate and then arylate the β -position at C3. Finally, the ester is saponified to reveal the carboxylic acid, which generates the nucleophilic partner for decarboxylative cross-coupling for the final C2 arylation to access the corresponding tetra-aryl thiophenes (Step D).

3.2 Results and Discussion

The first arylation is achieved with a Suzuki-Miyaura cross-coupling. Initial conditions were tried in DMF with the typical catalyst, Pd(PPh₃)₄ (Table 5, entry 1); however, this protocol failed to produce a good coupling yield. An increase in temperature (entry 2) only resulted in a very small improvement, and a change of catalyst to PdCl₂ (entry 6) was initially detrimental. A significantly better yield was obtained using a mixture of ethanol and water as the solvent, with no ligand on PdCl₂ (entry 4).

Table 5: Optimization of Suzuki-Miyaura coupling C5 arylation

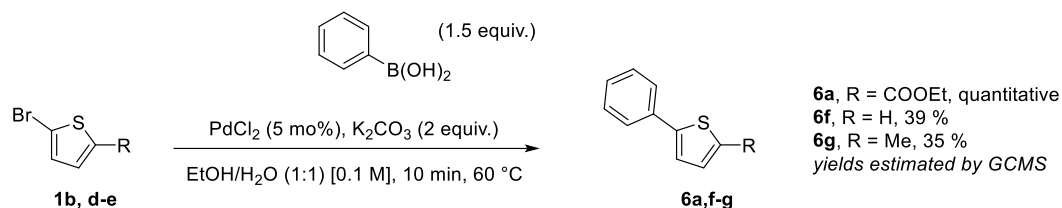
Entry	Pd	base	solvent	time, h	temp, °C	yield, %
1	Pd(PPh ₃) ₄	Na ₂ CO ₃	DMF	18	23	7
2	Pd(PPh ₃) ₄	Na ₂ CO ₃	DMF	18	40	10
3	PdCl ₂	Na ₂ CO ₃	DMF	18	23	5
4	PdCl ₂	Na ₂ CO ₃	EtOH:H ₂ O	6	23	45
5	PdCl ₂	Na ₂ CO ₃	EtOH	6	23	11
6	PdCl ₂	Na ₂ CO ₃	EtOH:H ₂ O	18	23	95 ^β
7	PdCl ₂	Cs ₂ CO ₃	EtOH:H ₂ O	18	23	92
8	PdCl ₂	K ₂ CO ₃	EtOH:H ₂ O	18	23	99 ^β
9	PdCl ₂	K ₂ CO ₃	EtOH:H ₂ O	2	23	99
10	PdCl ₂	K ₂ CO ₃	EtOH:H ₂ O	1	35	99

11 PdCl₂ K₂CO₃ EtOH:H₂O <0.1 60 99^β

Reaction conditions: **1** (0.2 mmol), phenyl boronic acid (0.3 mmol), base (0.4 mmol) and Pd source (0.01 mmol) in a round bottom flask in a silicon oil bath on a hot plate. Entries 7-12 open to atmosphere. Yields estimated by GCMS, ^β Isolated yields

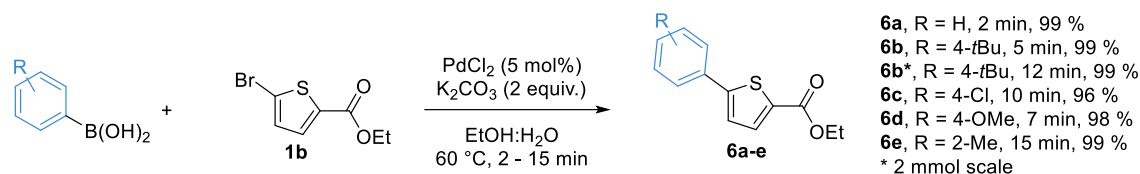
It was shown by entry 5 that the water was necessary for this product yield to occur. Aqueous conditions were then screened (1:1 mixture with EtOH) (entries 6-11) with ligandless PdCl₂. After 18 h with Na₂CO₃ as the base for this reaction, an almost quantitative yield was obtained (entry 6). Little change occurred with a change of base to the more expensive Cs₂CO₃ (entry 7), however, with K₂CO₃, the reaction went to completion in about 2 hours (entry 9). It was then found that under these conditions, with heating of the reaction to 60 °C that the reaction proceeds to completion in an impressively short amount of time (~2 mins) (entry 11).

A control experiment with various bromothiophenes as the aryl halide starting material confirms the activating nature of the ester, presumably by facilitating oxidative addition of Pd into the aryl-halide bond and reducing reaction time. While the reaction is quantitative after 10 minutes with bromothiophene ester **1b**, it is only 39 % complete when the ester is replaced with a proton (**6f**, Scheme 29) and 35 % complete with a methyl group in the place of the ester (**6g**, Scheme 29) in the same time period.



Scheme 29: Control experiments on bromothiophene substrates

As shown in Scheme 30, the Suzuki-Miyaura coupling reaction works exceedingly well with electron-neutral (**6a**), bulky (**6b**), *ortho*-functionalized (**6e**), electron-withdrawing (**6c**) and electron-donating (**6d**) groups on the phenyl boronic acid coupling partner. Additionally, purification by column chromatography is not required after this step since the only by-product, resulting from homocoupling of the boronic acid, does not hinder the subsequent reaction.



Scheme 30: Step A: Ester-activated Suzuki-Miyaura coupling of thiophene at C5

As the ester of arylated thiophene **6** is electron-withdrawing, it was then used to electronically direct remote bromination at C4 using an electrophilic aromatic substitution. This reaction required a significant optimization, as summarized in Table 8. Initially, a small high-through put screening (0.05 mmol scale) was conducted to identify the appropriate Lewis acid to catalyze this reaction with *n*-bromosuccinimide (NBS) in the common bromination solvent, chloroform (CHCl₃) (entries 1-6). It was found that ZnCl₂ produced the best yield (entry 4), and H₂SO₄ gave a relatively good yield (entry 5). However, when the reaction was scaled up to 0.2 mmol, the yields for both conditions depreciated significantly, even after 24 hours of reaction time (entries 7-9). An attempt was made to recreate reaction entry 4 and entry 5 in a sealed vial with degassed solvent (entries 10 and 11), but this seemed to hinder the yield even further. Repeating the conditions of entry 7 for 48 h produced a decent yield of 78 % (entry 12), but this was deemed too long of a reaction time to be practically viable. Recrystallizing the reagent NBS (entry 13) was not shown to be productive, and neither was conducting the reaction in the dark (entry 14). Heating the reaction to 35 °C somewhat improved the yield, to 20 % after 5 h, and 57 % after 24 h (entries 17 and 18, respectively). However, the reaction remained sluggish, and considerable amounts of starting material remained unconverted. Alternative conditions were thus tried in AcOH with FeCl₃ as the Lewis acid and Br₂ as the bromine source. This produced a moderate yield of 40% after 24 h, and 67 % after 48 h (entries 15 and 16, respectively). Heating these reaction conditions to 35 °C improved the yield to 59 % after 1 h, and 68 % after 2.5 h, but only 65 % after 24 h, which implies that the reaction would not proceed beyond a certain point (entries 19-21). Increasing the temperature to 45 °C under these conditions did not improve the yield, which remained 59 % after 18 h (entry 22). The conditions with AcOH as the solvent and Br₂ as the bromine source were then tried with ZnCl₂ as the Lewis acid at 45 °C, and this was found to be a beneficial alteration, with a yield of 84 % after 18 h (entry 23). Increasing the temperature to 60 °C produced a very good 87 % yield after only 3 h (entry 24). It was found that increasing the equivalents of

bromine to 1.5 produced an improved yield of 97 % after only 2 h (entry 25), and that if the equivalents of ZnCl₂ were increased to 1, the reaction went to completion in about 1 h (entry 26).

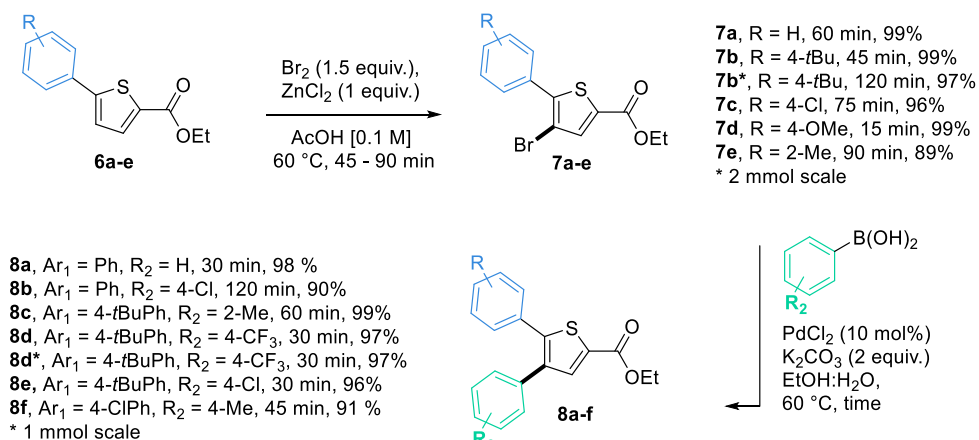
Table 6: Optimization of ester-directed bromination of C4

Entry	Br source	X	Additive	Y	Solvent	temp	time	yield
1 *	NBS	2	none	-	CHCl ₃	22 °C	3 h	0
2 *	NBS	2	AcOH	1.0	CHCl ₃	22 °C	3 h	> 5% ^β
3 *	NBS	2	(PhSe) ₂	0.5	CHCl ₃	22 °C	3 h	0
4 *	NBS	2	ZnCl ₂	0.5	CHCl ₃	22 °C	3 h	92 % ^β
5 *	NBS	2	H ₂ SO ₄	0.5	CHCl ₃	22 °C	3 h	63 % ^β
6 *	NBS	2	FeCl ₃	0.1	CHCl ₃	22 °C	3 h	> 5% ^β
7	NBS	2	ZnCl ₂	0.5	CHCl ₃	22 °C	3 h	60 %
8	NBS	1.1	ZnCl ₂	0.5	CHCl ₃	22 °C	24 h	55 % ^β
9	NBS	1.1	H ₂ SO ₄	0.5	CHCl ₃	22 °C	24 h	27 % ^β
10	NBS	1.1	ZnCl ₂	0.5	CHCl ₃ ^γ	22 °C	24 h	22 % ^β
11	NBS	1.1	H ₂ SO ₄	0.5	CHCl ₃ ^γ	22 °C	24 h	11 % ^β
12	NBS	1.1	ZnCl ₂	0.5	CHCl ₃	22 °C	48 h	78 %
13	NBS ^δ	1.1	ZnCl ₂	0.5	CHCl ₃	22 °C	24 h	42 % ^β
14 ^ε	NBS	1.1	ZnCl ₂	1.0	CHCl ₃	22 °C	48 h	68 % ^β
15	Br ₂	1.1	FeCl ₃	0.5	AcOH	22 °C	24 h	40 % ^β
16	Br ₂	1.1	FeCl ₃	0.5	AcOH	22 °C	48 h	67 % ^β
17	NBS	1.1	ZnCl ₂	0.5	CHCl ₃	35 °C	5 h	20 % ^β
18	NBS	1.1	ZnCl ₂	0.5	CHCl ₃	35 °C	24 h	57 % ^β
19	Br ₂	1.1	FeCl ₃	0.5	AcOH	35 °C	1 h	59 % ^β
20	Br ₂	1.1	FeCl ₃	0.5	AcOH	35 °C	2.5 h	68 % ^β
21	Br ₂	1.1	FeCl ₃	0.5	AcOH	35 °C	24 h	65 % ^β
22	Br ₂	1.1	FeCl ₃	0.5	AcOH	45 °C	18 h	59 % ^β
23	Br ₂	1.1	ZnCl ₂	0.5	AcOH	45 °C	18 h	84 % ^β
24	Br ₂	1.1	ZnCl ₂	0.5	AcOH	60 °C	3 h	87 % ^β
25	Br ₂	1.5	ZnCl ₂	0.5	AcOH	60 °C	2 h	97 %
26	Br ₂	1.5	ZnCl ₂	1.0	AcOH	60 °C	1 h	99 %

Reaction conditions: 2a (0.2 mmol) and acid/additive in a round bottom flask in [0.1 M] solvent open to air and stirred and/or heated in a silicon oil bath on a hot plate. Bromine source added subsequently. * reaction done on a 0.05 mmol scale in high throughput reactor wells, ^β yield estimated by ¹H NMR, ^γ sealed vial, degassed solvent, ^δ recrystallized reagent, ^ε Reaction done in the dark.

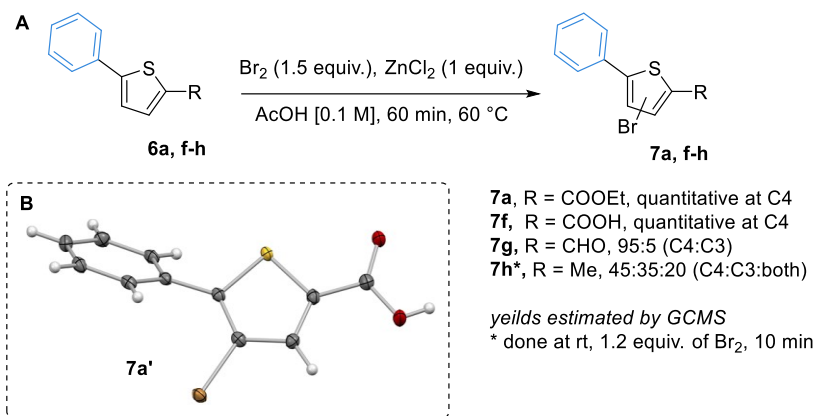
As shown in Scheme 31, the directed bromination reaction proceeds to completion in 1-1.5 hours for a number of substrates. Scaling up (tested up to 2 mmol) necessitates slightly longer reaction times, which are determined easily by TLC monitoring of this open-flask reaction. The reaction time is also greatly dependent on the electronics of the aryl group at C5; about 1 hour with electronically neutral groups (**7a**, **7b**), up to 90 minutes with a chlorinated (**7c**) substrate, and only 15 minutes with an electron-donating C5 aryl group (**7d**). Interestingly, increasing steric bulk around the C4 carbon does not hinder the regioselectivity of the reaction, notwithstanding the increased reaction time, as demonstrated with the *ortho*-arylated substrate (**7e**). Arylation at C4 is carried out by a second Suzuki-Miyaura cross-coupling, with excellent yields for a variety of functional groups (Scheme 31).

The bromination of arylated thiophene esters (**7a-e**) and subsequent Suzuki-Miyaura coupling is completely regioselective for C4 over C3 (when C5 is already functionalized). The regioselectivity of the bromination reaction (Step B) was confirmed with a crystal structure of thiophene carboxylic acid **7a'** obtained by saponification of thiophene ester **7a** (Scheme 32).



Scheme 31: Step B: Ester-directed "meta" bromination and sub-sequent arylation of thiophene at C4

This crystal structure of **7a'** also highlights why elevated temperatures are required: the bromine atom at C4 sterically hinders the planar conjugation of the two aromatic rings (see Figure 20 in the supporting information for Chapter 3 for a space filling model of **7a'**).



Scheme 32: Impact of the C2 ester directing group on regioselectivity of bromination. A: C4 halogenation on various 5-aryl thiophenes B: ORTEP at 50% ellipsoid probability of brominated thiophene acid **7a'**.

Control experiments were conducted to confirm that the C2 ester has a critical role in directing the regioselectivity of the reaction (Scheme 32A). It was shown that a quantitative yield of C4 bromination was obtained when a COOEt (**7a**) or COOH (**7f**) group is present at the C2 position of the arylated thiophene. Employing a C2-carboxaldehyde (**7g**) led to about 5% yield of the di-bromo isomer, likely because it is less sterically encumbering than the ester. However, employing a C2-methyl group (**7h**) resulted in a complex mixture of isomers. Overall, these results suggest that the electron-withdrawing properties of the ester moiety are paramount to the C4 regioselectivity in this bromination.

In step C, arylation at C3 on doubly arylated thiophene **8** utilizes the ester for directed *ortho*-metalation (Table 7). For this, the Hauser-Knochel base Mg(TMP)Cl·LiCl was used to deprotonate and subsequently iodinate the C3 position.²⁵⁴ The optimization of this reaction is shown in Table 7. While a metalation followed by a transmetalation to the zincate for a Negishi coupling was tried in order to do step C in one reaction, this strategy was found to be poor yielding. Directed deprotonation and iodination was first tried at -78 °C in THF (entry 1). This was not found to produce any yield, neither did an increase in temperature to -30 or -10 °C (entries 2 and 3). At 0 °C, there was some product yield of 11 % (entry 4) and at 25 °C, the yield increased slightly to 15 % (entry 5). Other bases were then screened

(*i*PrMgCl LiCl and *n*BuLi), but these were not found produce an appreciable amount of the desired product (entries 6-7). Using a mixture of THF and toluene as the solvent with Mg(TMP)Cl·LiCl as the base increased the yield of desired product somewhat to 23 % (entry 37). However, significant improvements were only made by increasing the concentration of the reaction (up to 0.5 M, entries 10-11) and by increasing the equivalencies of base to 2 (entry 12), which gave a decent yield of 75 % of the iodinate product after 75 minutes of reaction time with the iodine.

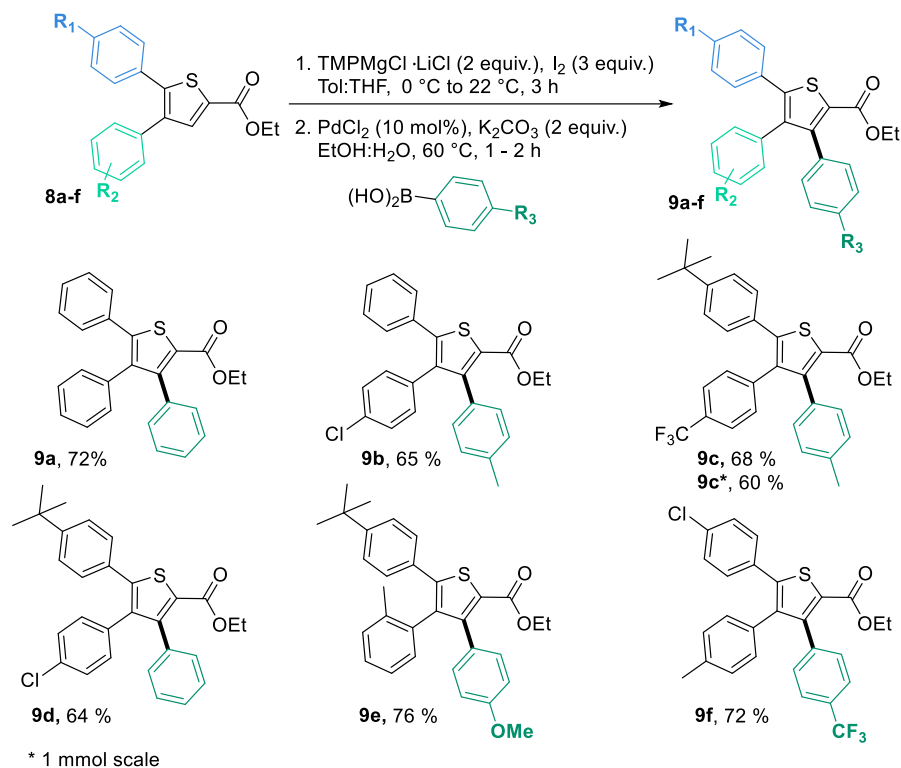
Table 7: Optimization of ester-directed iodination of C3

entry	base	X	solvent	M	temp, °C	2. time, min	yield, %
1	TMPMgCl LiCl	1.2	THF	[0.1]	-78	120	0
2	TMPMgCl LiCl	1.2	THF	[0.1]	-30	120	0
3	TMPMgCl LiCl	1.2	THF	[0.1]	-10	120	0
4	TMPMgCl LiCl	1.2	THF	[0.1]	0	120	11
5	TMPMgCl LiCl	1.2	THF	[0.1]	25	120	15
6	<i>i</i> PrMgCl LiCl	1.2	THF	[0.1]	-78	120	> 5
7	<i>n</i> BuLi	1.2	THF	[0.1]	-78	120	> 5
8	TMPMgCl LiCl	1.2	THF/Tol	[0.1]	25	120	23
9	TMPMgCl LiCl	1.2	THF/Tol	[0.25]	25	120	37
10	TMPMgCl LiCl	1.2	THF/Tol	[0.5]	25	75	45
11	TMPMgCl LiCl	1.5	THF/Tol	[0.5]	25	75	62
12	TMPMgCl LiCl	2.0	THF/Tol	[0.5]	25	75	75 ^β

Reaction conditions: **8a** (0.2 mmol) in a flame dried round bottom flask with a stir bar (either dissolved in THF or neat at 1 M solvent) is cooled to 0 °C in an ice bath, base is added dropwise. The reaction is lifted from the ice and left to react. After time 1, the round bottom flask with **8a*** is cooled in the ice bath to 0 °C and crushed I₂ is added as a powder under a stream of argon. Yields estimated by GCMS ^β yield estimated by ¹H NMR

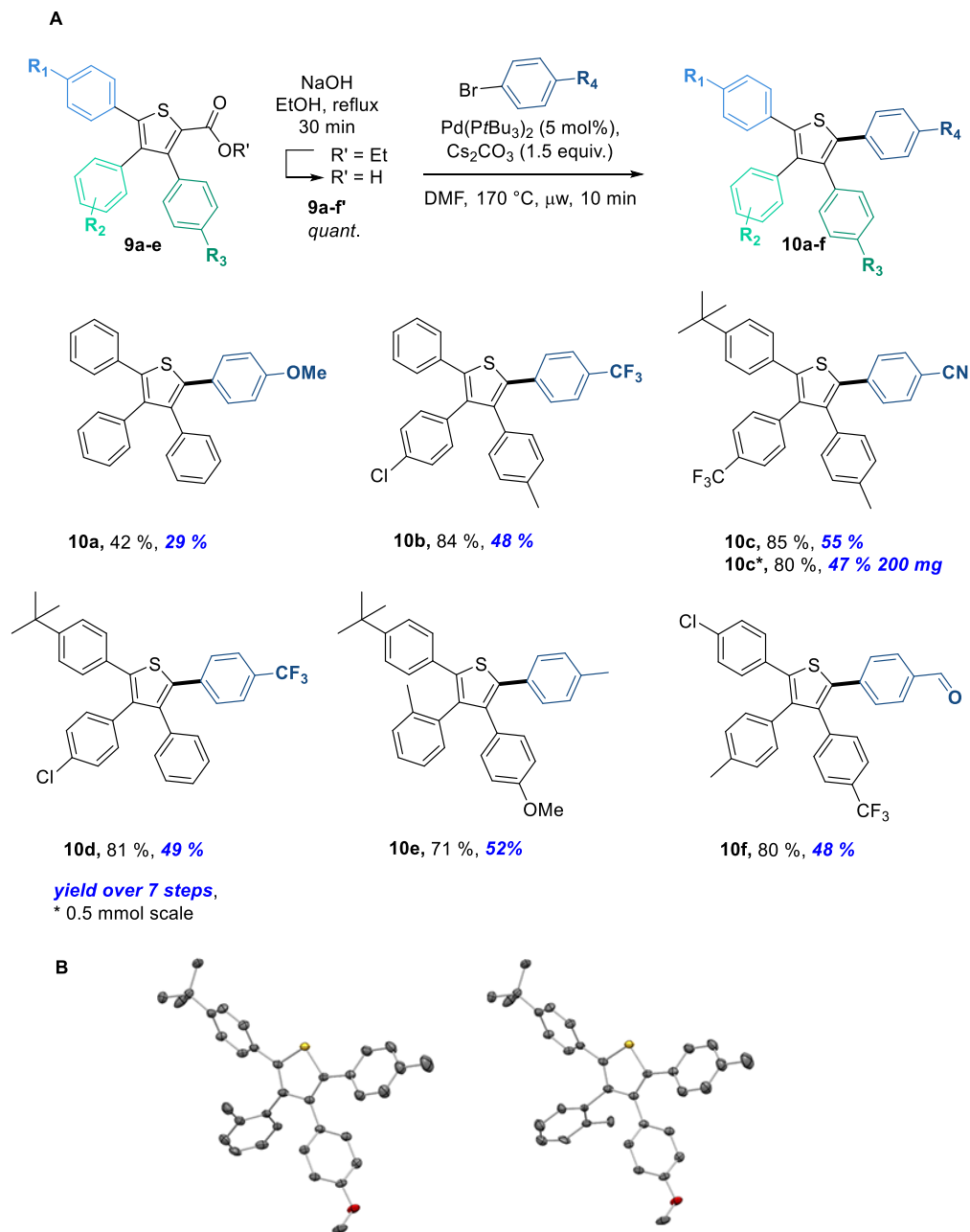
In this reaction, the ester directs *via* coordination rather than electronically. After filtration, the crude mixture is subjected to a third Suzuki-Miyaura cross-coupling to obtain tri-arylated thiophenes **9a-f** in good yields (Scheme 33). The overall yield for step C is limited by the deprotonation/iodination reaction, which did not proceed to completion (68-

85% yields of iodinated products **8'** as assessed by ^1H NMR). As **8'** could not be separated from residual starting material **8**, purification was performed on tri-arylated thiophenes **9**.



Scheme 33: Step C - Directed iodination at C3 and subsequent Suzuki-Miyaura cross-coupling

The final arylation (Step D) at C2 was performed by decarboxylative cross-coupling after saponification of the ester group in **9** (Scheme 34A). Reaction conditions for the decarboxylative cross-coupling only necessitated minor adjustments from previously reported conditions^{115,166} to produce very good yields with electron-deficient aryl bromides (**10b-d,f**, 81 to 85%), a good yield with an electron-neutral (**10e**, 71%), and a moderate yield with an electron-rich (**10a**, 42 %) aryl bromides. Crystallography of compound **10e** confirmed its chemical identity. Interestingly, it crystallizes as a 7:3 superposition of two diastereoisomers (rotation of the *o*-tol group) (as shown in Scheme 34B). This facet portends underlying atropisomerism, a concept that is relevant in drug development,²⁶¹ including the thiophene-based drug Telenzepine.²⁶² Tetra-arylated thiophene **10c** was also synthesized in a larger scale of 0.5 mmol with an overall yield of 47 % (200 mg), highlighting the potential of this methodology for the development of future applications of tetra-aryl thiophenes.



Scheme 34: A. Step D: Decarboxylative cross-coupling at C2 and formation of tetra-arylated thiophenes. B. ORTEP of 10e.

50% ellipsoid probability for the major (left) and minor (right) components of 10e. Hydrogen atoms were removed for clarity. Compound 11e crystallizes in the chiral P212121 space group, as a ca. 70:30 superposition of two diastereoisomers that differ by the position of the o-Me substituent with respect to the thiophene plane. The molecule displays planar chirality because of having 4 different substituents and a helical conformational arrangement of the aryl groups

While our synthetic pathway comprises 7 steps overall, it is considerably more time-efficient and higher yielding than previously reported routes. Thiophene **10b** (compound 7acgh),²⁶³ was previously synthesized by Itami *et al.* with their seminal 6-step route that includes specialized Pd and Rh catalytic systems for regioselective C-H arylations, with an overall yield of 25% and 76 h of total reaction time.²⁵⁵ This approach was later adapted to include a C4-arylation that was improved for air- and water-sensitivity and more easily scalable.²⁶⁴ With this, they obtained thiophene **10d** with an overall yield of 23 % after 116 h of reaction time. Comparatively, our approach produces compound **10b** in 53% overall yield in less than 10 h of reaction time and **10d** in 49% overall yield in 9 h of reaction time. Additionally, as all reactions are fully site-specific, there is no need for the often-challenging separation of regioisomers.

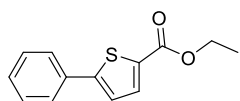
3.3 Conclusion

In summary, we have developed a programmed synthetic route to tetra-aryl thiophenes with complete regioselective control. This approach boasts simple and repetitive catalytic systems, short reactions times, easily scalable reactions, mostly bench-stable reagents, and only one water- and air-sensitive step. Six final compounds were synthesized with yields of 29-55 % over 7 steps, with approximately 10 h of total reaction time. The salient feature of this approach is the multi-faceted use of the ethyl ester functional group, first as an activating group, then as a directing group in two distinct fashions, and finally, as a cross-coupling partner after saponification to the corresponding carboxylic acid. The synthetic scope of this route can undoubtedly be expanded by taking advantage of the halogenated intermediates to access other motifs (e.g. alkyl chains, alkynes, amines, etc.). Overall, the methodology reported here provides practical access to previously synthetically challenging chemical space on thiophenes, which should facilitate further exploration of thiophene-based drug candidates and advanced materials.

3.4 Experimental section

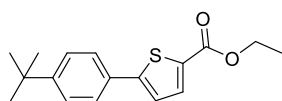
3.4.1 General Procedure for synthesis of C5 arylated thiophenes (6a-e):

To a solution of thiophene **1b** (purchased from AK Scientific, 0.5 mmol, 117.5 mg) in 1:1 H₂O/EtOH (5 mL, [0.1 M]) was added the corresponding aryl boronic acid (purchased from AK Scientific, 0.75 mmol), and K₂CO₃ (1 mmol, 136 mg) in a 25 mL round bottom flask. The reaction was heated to 60 °C open to atmosphere in a silicon oil bath on a hot plate. PdCl₂ (0.025 mmol, 4.4 mg) was added and the reaction was tracked by TLC to assess completion (product spot is easily identifiable as it glows blue when irradiated at 254 nm). Once complete, the reaction is cooled and transferred to a separatory funnel. 30 mL of water and 30 mL of EtOAc are added. The aqueous layer is extracted 2 more times with approximately 20 mL of EtOAc. The combined organic layers are washed with brine, dried with sodium sulfate and the solvent is evaporated under reduced pressure. The crude is purified by gravity column chromatography (silica gel, 95:5 hexanes/ethyl acetate) to afford **6a-e**. *The crude can also be re-suspended in 1:1 Hexanes/EtOAc and filtered through a silica plug to remove a black residue and carried through to following reactions without purification with no ill effect.



6a - ethyl 5-phenylthiophene-2-carboxylate: Thiophene **1b** is reacted with phenyl boronic acid; 2 minutes reaction time; clear oily solid (114.8 mg, 99 % yield); purified by gravity column chromatography (silica gel)

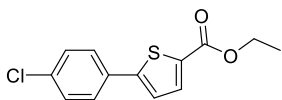
in 95:5 hexanes/ethyl acetate; R_f = 0.55; ¹H NMR (500 MHz, Chloroform-d) δ 7.76 (d, J = 3.9 Hz, 1H), 7.64 (m, 2H), 7.42 (m, 2H), 7.36 (m, 1H), 7.29 (d, J = 3.9 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H); ¹³C NMR (125 MHz, Chloroform-d) δ 162.3, 151.1, 134.2, 133.5, 132.6, 129.1, 128.7, 126.2, 123.6, 61.2, 14.4; HRMS (ESI) m/z : [M+H]⁺ calcd for [C₁₃H₁₃O₂S]⁺: 233.0631; Found 233.0631.



6b and 6b' - ethyl 5-(4-(tert-butyl)phenyl)thiophene-2-carboxylate: Thiophene **1b** is reacted with 4-tert-butylphenyl boronic acid; 5 minutes reaction time at 0.5 mmol scale, 12 minutes at 2

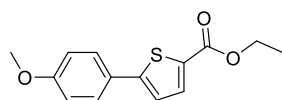
mmol scale; clear oil (143.0 mg, 99 % yield and 570.5 mg, 99% yield, respectively); purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate; R_f = 0.59; ¹H NMR (500 MHz, Chloroform-d) δ 7.75 (d, J = 3.9 Hz, 1H), 7.69 – 7.51 (m, 2H), 7.51 – 7.38

(m, 2H), 7.26 (d, $J = 3.8$ Hz, 1H), 4.37 (q, $J = 7.1$ Hz, 2H), 1.37 (m, 12H). ^{13}C NMR (125 MHz, Chloroform-d): δ 162.34, 152.07, 151.24, 134.23, 132.02, 130.71, 126.02, 125.94, 125.93, 123.16, 61.11, 34.72, 31.21, 14.39. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{17}\text{H}_{21}\text{O}_2\text{S}]^{+1}$: 289.1257; Found 289.1254.



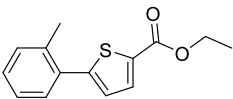
6c - ethyl 5-(4-chlorophenyl)thiophene-2-carboxylate:

Thiophene **1b** is reacted with 4-chlorophenyl boronic acid; 10 minutes reaction time; white solid (127.8 mg, 96 % yield); purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate; $R_f = 0.37$; ^1H NMR (500 MHz, Chloroform-d): δ 7.71 (d, $J = 3.9$ Hz, 1H), 7.53 – 7.46 (m, 2H), 7.35 – 7.29 (m, 2H), 7.20 (d, $J = 3.9$ Hz, 1H), 4.34 (q, $J = 7.1$ Hz, 2H), 1.37 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, Chloroform-d) δ 162.03, 149.49, 134.58, 134.17, 132.93, 131.92, 129.22, 129.22, 127.28, 127.26, 123.83, 61.24, 14.34; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{13}\text{H}_{12}\text{ClO}_2\text{S}]^{+1}$: 267.0241; Found 267.0241.



6d - ethyl 5-(4-methoxyphenyl)thiophene-2-carboxylate:

Thiophene **1b** is reacted with 4-methoxyphenyl boronic acid; 7 minutes reaction time, white solid (128.4 mg, 98 % yield); purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate; $R_f = 0.50$; ^1H NMR (500 MHz, Chloroform-d): δ 7.72 (d, $J = 3.9$ Hz, 1H), 7.57 – 7.51 (m, 2H), 7.15 (d, $J = 3.9$ Hz, 1H), 6.90 (m, $J = 2$ Hz), 4.35 (q, $J = 7.1$ Hz, 2H), 3.81 (s, 3H), 1.38 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, Chloroform-d): δ 162.32, 160.16, 151.19, 134.29, 134.28, 131.41, 127.46, 127.45, 126.22, 122.49, 114.45, 61.05, 55.33, 55.32, 14.37; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{14}\text{H}_{15}\text{O}_3\text{S}]^{+1}$: 263.0736; Found 263.0737.

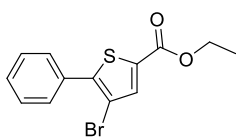


6e - ethyl 5-(o-tolyl)thiophene-2-carboxylate:

Thiophene **1b** is reacted with o-tolylboronic acid; 15 minutes reaction time, clear oily solid (122.5 mg, 99 % yield); purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate; $R_f = 0.72$; ^1H NMR (500 MHz, Chloroform-d): δ 7.77 (d, $J = 3.8$ Hz, 1H), 7.44 – 7.35 (m, 1H), 7.35 – 7.19 (m, 3H), 7.04 (d, $J = 3.8$ Hz, 1H), 4.37 (q, $J = 7.1$ Hz, 2H), 2.42 (s, 3H), 1.39 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, Chloroform-d): δ 161.28, 145.23, 139.36, 136.95, 131.98, 129.40, 129.21, 128.87, 107.60, 61.51, 21.35, 14.30; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{14}\text{H}_{14}\text{O}_2\text{S}]^{+1}$: 247.0787; Found 247.0787.

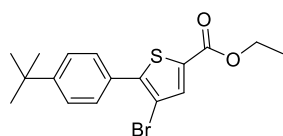
3.4.2 General procedure for the synthesis of C4 brominated aryl-thiophenes (7a-e):

To a solution of thiophene **6a-e** (0.4 mmol) in acetic acid (4 mL, [0.1 M]) was added ZnCl₂ (0.4 mmol, 54.4 mg, there is no need to use dry reagent) in a 35 mL round bottom flask. The reaction was heated to 60 °C open to atmosphere in a silicon oil bath on a hot plate. Br₂ (0.6 mmol, 31 µL) was added and the reaction was tracked by TLC to assess completion (product spot is easily identifiable as it considerably less blue coloured than the starting material **6a-e** when irradiated at 254 nm). Once complete, the reaction is cooled, quenched with aqueous sodium thiosulfate (about 10 mL), and transferred to a separatory funnel, after which 20 mL of water and 30 mL of EtOAc are added. The aqueous layer is extracted 2 more times with approximately 20 mL of EtOAc. The combined organic layers are washed with brine, dried with sodium sulfate and the solvent is evaporated under reduced pressure. The crude product is purified by gravity column chromatography (silica gel, 95:5 hexanes/ethyl acetate) to afford **7a-e**. *If acetic acid remains in the crude reaction after drying, this can be loaded directly onto the column with no ill effect. Purification at this point is crucial even if the crude is very clean, as we hypothesize that any residual zinc will hinder the yield of the next reaction.



7a - ethyl 4-bromo-5-phenylthiophene-2-carboxylate: ethyl 5-phenylthiophene-2-carboxylate (**6a**) is reacted for 60 minute reaction; clear oily solid (123.1 mg, 99 % yield); purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate; R_f = 0.64;

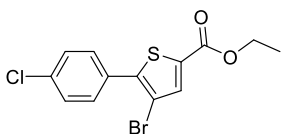
¹H NMR (500 MHz, Chloroform-d): δ 7.73 (s, 1H), 7.66 (m, 2H), 7.47 (m, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (125 MHz, Chloroform-d) δ 161.2, 145.0, 137.0, 132.4, 132.1, 130.5, 129.2, 129.0, 128.7, 128.7, 107.9, 61.6, 14.3; HRMS (ESI) *m/z*: [M+H]⁺ calcd for [C₁₃H₁₂BrO₂S]⁺: 310.9736; Found 310.9734.



7b and 7b* - ethyl 4-bromo-5-(4-(tert-butyl)phenyl)thiophene-2-carboxylate: ethyl 5-(4-(tert-butyl)phenyl)thiophene-2-carboxylate (**6b**) is reacted for 45 minutes at 0.4 mmol scale, and 120 minutes at

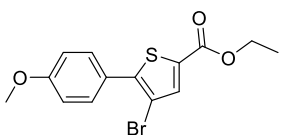
a 2 mmol scale*; clear, very thick oil (146.5 mg, 99 % yield and 706.4 mg, 97 % yield*, respectively); purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate; R_f = 0.68; ¹H NMR (500 MHz, Chloroform-d): δ 7.72 (s, 1H), 7.63 – 7.58 (m, 2H),

7.49 – 7.45 (m, 2H), 4.36 (q, $J = 7.1$ Hz, 3H), 1.37 (m, 12H); ^{13}C NMR (125 MHz, Chloroform- d) δ 161.3, 152.4, 145.2, 137.0, 132.0, 129.2, 128.6, 125.7, 107.5, 61.5, 34.8, 31.2, 14.3; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{17}\text{H}_{20}\text{BrO}_2\text{S}]^{+1}$: 367.0362; Found 367.0361.



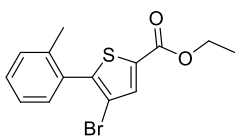
7c - ethyl 4-bromo-5-(4-chlorophenyl)thiophene-2-carboxylate:

ethyl 5-(4-chlorophenyl)thiophene-2-carboxylate (**6c**) is reacted for 75 minutes; white solid (132.8 mg, 96 % yield); purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate; $R_f = 0.49$; ^1H NMR (500 MHz, Chloroform- d): δ 7.70 (s, 1H), 7.58 (dd, $J = 8.4, 1.2$ Hz, 2H), 7.41 (dd, $J = 8.4, 1.2$ Hz, 2H), 4.36 (q, $J = 7.1$, 2H), 1.41 – 1.32 (t, $J = 7.1$ Hz 3H); ^{13}C NMR (125 MHz, Chloroform- d) δ 161.0, 143.5, 136.9, 135.4, 132.7, 130.5, 130.2, 123.0, 129.0, 108.3, 61.7, 14.3; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{13}\text{H}_{11}\text{BrClO}_2\text{S}]^{+1}$: 344.9346; Found 344.9344.



7d - ethyl 4-bromo-5-(4-methoxyphenyl)thiophene-2-carboxylate:

ethyl 5-(4-methoxyphenyl)thiophene-2-carboxylate (**6d**) is reacted for 15 minutes; off-white solid (136.5 mg, 99 % yield); purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate; $R_f = 0.064$; ^1H NMR (500 MHz, Chloroform- d): δ 7.71 (s, 1H), 7.61 (d, $J = 8.8$ Hz, 2H), 6.97 (d, $J = 8.8$ Hz, 2H), 4.36 (q, $J = 7.1$ Hz, 3H), 3.86 (s, 3H), 1.38 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, Chloroform- d) δ 161.3, 160.3, 145.1, 137.0, 131.6, 130.3, 124.5, 114.1, 107.3, 61.49, 55.4, 14.3; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{14}\text{H}_{14}\text{BrO}_3\text{S}]^{+1}$: 340.9842; Found 340.9839.

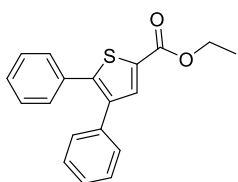


7e - ethyl 4-bromo-5-(o-tolyl)thiophene-2-carboxylate:

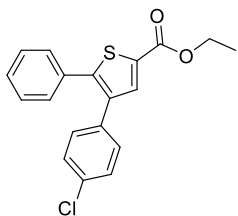
ethyl 5-(o-tolyl)thiophene-2-carboxylate (**6e**) is reacted for 90 minutes; clear oily solid (117.2 mg, 90 % yield); purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate; $R_f = 0.80$; ^1H NMR (500 MHz, Chloroform- d): δ 7.74 (s, 1H), 7.36 – 7.22 (m, 4H), 4.37 (q, $J = 7.1$ Hz, 3H), 2.26 (s, 2H), 1.39 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, Chloroform- d) δ 161.3, 145.1, 137.7, 135.7, 133.2, 131.4, 130.8, 130.8, 130.3, 129.6, 125.7, 110.6, 61.6, 20.1, 14.3; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{14}\text{H}_{14}\text{BrO}_2\text{S}]^{+1}$: 324.9892; Found 324.9890.

3.4.3 General procedure for the synthesis C4 arylated thiophene (8a-f):

To a solution of brominated thiophene **7a-e** (0.35 mmol) in 1:4 H₂O/EtOH (3.5 mL, [0.1 M]) in a 10 mL round bottom was added the corresponding aryl boronic acid (0.70 mmol) stirred heating at 60 °C in a silicon oil bath on a hot plate until all reagents are solubilized (heating to 80 °C is sometimes necessary, make sure to cool back to 60 °C before adding base to prevent saponification). Once the reaction solution is clear, add K₂CO₃ (0.7 mmol, 97 mg), then PdCl₂ (0.035 mmol, 6.2 mg). The reaction is done open to atmosphere and is tracked by TLC to assess completion (product spot is slightly below starting material in 9:1 hexanes/EtOAc). If the reaction becomes sluggish (a lot of starting material after 30 minutes), add 0.35 equivalents of the boronic acid and 3.1 mg of PdCl₂. Once complete, the reaction is cooled and transferred to a separatory funnel, after which 30 mL of water and 30 mL of EtOAc are added. The aqueous layer is extracted 2 more times with approximately 20 mL of EtOAc. The combined organic layers are washed with brine, dried with sodium sulfate and the solvent is evaporated under reduced pressure. The crude is purified by gravity column chromatography (silica gel, 98:2 hexanes/EtOAc) to afford **8a-f**.

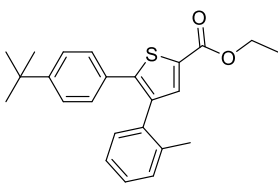


8a - ethyl 4,5-diphenylthiophene-2-carboxylate: Ethyl 4-bromo-5-phenylthiophene-2-carboxylate (**7a**) is reacted for 30 minutes with phenylboronic acid; clear oily solid (105.2 mg, 98 % yield); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; R_f = 0.64; ¹H NMR (500 MHz, Chloroform-d): δ 7.85 (s, 1H), 7.33 - 7.26 (m, 10H), 4.44 - 4.32 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1, 3H); ¹³C NMR (125 MHz, Chloroform-d) δ 162.26, 145.48, 138.83, 136.07, 135.58, 133.42, 129.25, 129.02, 128.62, 128.49, 128.35, 127.34, 61.23, 14.38; HRMS (ESI) m/z : $[M+H]^+$ calcd for [C₁₉H₁₇O₂S]⁺: 309.0944; Found 309.0944.



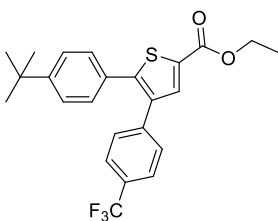
8b - ethyl 4-(4-chlorophenyl)-5-phenylthiophene-2-carboxylate: Ethyl 4-bromo-5-phenylthiophene-2-carboxylate (**7a**) is reacted for 120 minutes with 4-chlorophenylboronic acid; white solid (107.7 mg, 90 % yield); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; R_f = 0.59; ¹H NMR (500 MHz, Chloroform-d): δ 7.80 (s, 1H), 7.36 - 7.13 (m, 9H), 4.38 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H); ¹³C NMR (125 MHz, Chloroform-d) δ 162.11, 145.77, 137.43, 135.61, 134.00, 133.33, 133.09, 132.03,

130.27, 129.22, 128.75, 128.73, 128.55, 61.30, 14.36; HRMS (ESI) m/z : $[M+H]^+$ calcd for $[C_{19}H_{16}ClO_2S]^+1$: 343.0554; Found 343.0553.



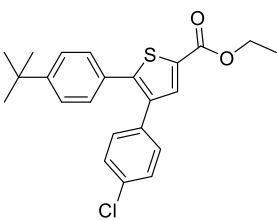
8c - ethyl 5-(4-(tert-butyl)phenyl)-4-(o-tolyl)thiophene-2-carboxylate:

Ethyl 4-bromo-5-(4-(tert-butyl)phenyl)thiophene-2-carboxylate (**7b**) is reacted for 60 minutes with o-tolyl boronic acid; clear oily solid (131.2 mg, 99 % yield); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; R_f = 0.72; ^1H NMR (500 MHz, Chloroform-d): δ 7.69 (s, 1H), 7.12 (s, 4H), 7.02 – 6.96 (m, 4H), 4.26 (q, J = 7.1 Hz, 2H), 2.22 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, Chloroform-d) δ 162.10, 143.42, 139.24, 137.34, 136.13, 134.34, 132.33, 132.07, 131.95, 130.44, 130.43, 129.35, 128.87, 128.82, 61.28, 21.19, 14.38; HRMS (ESI) m/z : $[M+H]^+$ calcd for $[C_{24}H_{27}O_2S]^+1$: 379.1726; Found 379.1726.



8d and 8d* - ethyl 5-(4-(tert-butyl)phenyl)-4-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate:

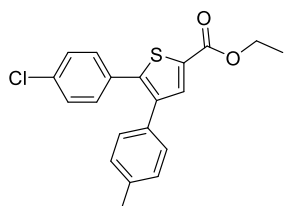
Ethyl 4-bromo-5-(4-(tert-butyl)phenyl)thiophene-2-carboxylate (**7b**) is reacted for 30 minutes at a 0.35 mmol scale, and for 65 minutes at a 1 mmol scale, with 4-trifluoromethylphenyl boronic acid; off-white oily solid (146.6 mg, 97 % yield and 409.8 mg, 97 % yield, respectively); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; R_f = 0.64; ^1H NMR (500 MHz, Chloroform-d): δ 7.82 (s, 0H), 7.58 – 7.53 (m, 2H), 7.42 – 7.37 (m, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, Chloroform-d) δ ^{13}C NMR (126 MHz, Chloroform-d) δ 162.07, 152.01, 146.82, 139.41, 136.75, 135.66, 131.91, 129.86, 129.39 (q, $^2J_{CF}$ = 32.5 Hz), 129.27, 128.79, 125.80, 125.43 (q, $^3J_{CF}$ = 3.8 Hz), 123.07, 61.31, 34.71, 31.18, 14.35; HRMS (ESI) m/z : $[M+H]^+$ calcd for $[C_{24}H_{24}F_3O_2S]^+1$: 433.1444; Found 433.1438.



8e - ethyl 5-(4-(tert-butyl)phenyl)-4-(4-chlorophenyl)thiophene-2-carboxylate:

ethyl 4-bromo-5-(4-(tert-butyl)phenyl)thiophene-2-carboxylate (**7b**) is reacted for 30 minutes with 4-chlorophenyl boronic acid; white solid (134.8 mg, 97 % yield); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; R_f = 0.64; ^1H NMR (500 MHz, Chloroform-d): δ 7.78 (s, 1H), 7.34 – 7.17 (m, 8H), 4.38 (q, J =

7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, Chloroform- d) δ 162.18, 151.78, 146.05, 137.08, 135.77, 134.25, 133.22, 131.57, 130.31, 130.09, 128.75, 128.74, 128.71, 128.70, 125.70, 61.24, 34.69, 31.20, 14.37; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{23}\text{H}_{24}\text{ClO}_2\text{S}]^{+1}$: 399.1180; Found 399.1180.



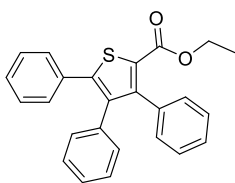
8f - ethyl 5-(4-chlorophenyl)-4-(p-tolyl)thiophene-2-carboxylate:

ethyl 4-bromo-5-(4-chlorophenyl)thiophene-2-carboxylate (**7c**) is reacted for 60 minutes with p-tolyl boronic acid; clear oily solid (113.5 mg, 91 % yield); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; R_f = 0.69; ^1H NMR (500 MHz, Chloroform- d): δ 7.69 (s, 1H), 7.12 (s, 4H), 7.02 – 6.96 (m, 4H), 4.26 (q, J = 7.1 Hz, 2H), 2.22 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, Chloroform- d) δ 162.10, 143.42, 139.24, 137.34, 136.13, 134.34, 132.33, 132.07, 131.95, 130.44, 130.43, 129.35, 128.87, 128.82, 61.28, 21.19, 14.38; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{20}\text{H}_{18}\text{ClO}_2\text{S}]^{+1}$: 357.0711; Found 357.0712.

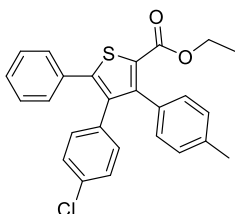
3.4.4 General procedure synthesis C3 arylated thiophene (towards 9a-f):

Di-arylated thiophene **8a-f** (0.30 mmol) in a flame dried 10 mL round bottom flask under argon is placed in an ice bath and a solution of 1M TMPMgCl LiCl (600 μL , 0.60 mmol) is added dropwise. After addition is complete, the round bottom is taken out of the ice and allowed to warm to room temperature (for oily substrates that stick to the stir bar, sonication or vortexing for a few minutes can help solubilisation and proper stirring). The solution is left to react for 75 minutes, after which it is cooled again in an ice bath. Crushed I_2 pellets (228 mg, 0.9 mmol) are added as a powder under a stream of argon. The reaction is allowed to warm to room temperature and react for 75 minutes, after which it is quenched with about 1 mL of aqueous sodium thiosulfate. The crude mixture is diluted with about 20 mL of EtOAc and 30 mL of water. The aqueous layer is extracted 2 more times with about 15 mL of EtOAc. The combined organic layers are washed with brine, dried with sodium sulfate and evaporated under reduced pressure. The crude mixture is re-suspended in about 10 mL of hexanes/EtOAc (1:1) and filtered through a silica plug to remove a bright yellow residue. This crude product is a mixture of starting material **4** and iodinated product **8'** (to the best of our abilities, these compounds are not isolatable by gravity column chromatography). The

conversion rate can be estimated by GCMS and/or ^1H NMR. The crude mixture is then evaporated under reduced pressure, and then dissolved in a 4:1 mixture of EtOH and water (3 mL, [0.1 M]) in a 10 mL round bottom flask and heated at 60 °C in a silicon oil bath on a hot plate. The boronic acid coupling partner (2 equiv.) is added to the solution, and when both reagents are fully dissolved, K_2CO_3 (0.6 mmol, 83 mg) and PdCl_2 (0.03 mmol, 5.3 mg) are added. The reaction is done open to air, and can be tracked by TLC (9:1 hexanes/EtOAc), the product spot being only slightly below the starting material. GCMS was used to assess completion of the reaction (full consumption of iodinated product **8'**). Once complete, the reaction is cooled and transferred to a separatory funnel. 30 mL of water and 30 mL of EtOAc are added. The aqueous layer is extracted 2 more times with approximately 20 mL of EtOAc. The combined organic layers are washed with brine, dried with sodium sulfate and the solvent is evaporated under reduced pressure. The crude is purified by gravity column chromatography (silica gel, 98:2 hexanes/ethyl acetate) to afford **9a-f**.

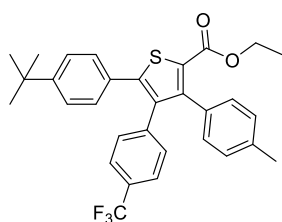


9a - ethyl 3,4,5-triphenylthiophene-2-carboxylate: Ethyl 4,5-diphenylthiophene-2-carboxylate (**8a**) is first iodinated to generate ethyl 3-iodo-4,5-diphenylthiophene-2-carboxylate (**8a'**). This compound is then reacted for 60 minutes with phenyl boronic acid; white solid (83 mg, 72 % yield over 2 steps); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; R_f = 0.59; ^1H NMR (500 MHz, Chloroform- d): δ 7.26 – 7.20 (m, 8H), 7.13 – 7.06 (m, 5H), 6.92 – 6.88 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, Chloroform- d) δ 162.1, 148.9, 144.8, 140.3, 135.9, 135.3, 133.6, 130.8, 129.9, 129.3, 128.4, 128.1, 127.9, 127.3, 127.3, 127.2, 126.9, 60.8, 14.0; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for iodinated intermediate **9a'** $[\text{C}_{19}\text{H}_{16}\text{IO}_2\text{S}]^{+1}$: 434.9910; Found 434.9911, HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for product **9a** $[\text{C}_{25}\text{H}_{21}\text{O}_2\text{S}]^{+1}$: 385.1257; Found 385.1256.

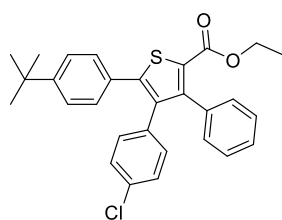


9b - ethyl 4-(4-chlorophenyl)-5-phenyl-3-(p-tolyl)thiophene-2-carboxylate: ethyl 4-(4-chlorophenyl)-5-phenylthiophene-2-carboxylate (**8b**) is first iodinated to generate ethyl 4-(4-chlorophenyl)-3-iodo-5-phenylthiophene-2-carboxylate (**8b'**). This compound is then reacted for 75 minutes with p-tolyl boronic acid; white solid (83.4 mg, 65 % yield over 2 steps); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; R_f = 0.55; ^1H NMR (500 MHz, Chloroform- d): δ 7.28 – 7.20 (m, 5H), 7.09 – 7.01 (m,

4H), 6.99 – 6.94 (m, 2H), 6.84 – 6.79 (m, 2H), 4.21 (q, $J = 7.1$ Hz, 2H), 2.32 (s, 3H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, Chloroform- d) δ 161.9, 148.9, 145.0, 138.8, 137.0, 133.9, 133.3, 132.9, 132.5, 132.1, 129.7, 129.3, 128.6, 128.4, 128.3, 128.2, 127.3, 60.9, 21.3, 14.1; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{26}\text{H}_{22}\text{ClO}_2\text{S}]^{+1}$: 433.1024; Found 433.1023.

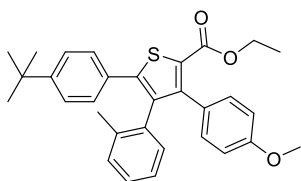


9c and 9c* - ethyl 5-(4-(tert-butyl)phenyl)-3-(p-tolyl)-4-(4-(trifluoromethyl)phenyl) thiophene-2-carboxylate: Ethyl 5-(4-(tert-butyl)phenyl)-4-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate (**8d**) is first iodinated to generate ethyl 5-(4-(tert-butyl)phenyl)-3-iodo-4-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate (**8d'**). This compound is then reacted with p-tolyl boronic acid; 75 minutes at 0.30 mmol scale and 120 minutes at a 1 mmol scale; white solid (106.2 mg, 68 % yield and 312.0 mg, 60 % yield, respectively, over 2 steps); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; $R_f = 0.59$; ^1H NMR (500 MHz, Chloroform- d): δ 7.37 – 7.34 (m, 2H), 7.28 – 7.25 (m, 2H), 7.12 (d, $J = 8.6$ Hz, 2H), 7.03 (m, 4H), 6.96 (d, $J = 8.1$ Hz, 2H), 4.21 (q, $J = 7.1$ Hz, 2H), 2.31 (s, 3H), 1.30 (s, 9H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, Chloroform- d) δ ^{13}C NMR (126 MHz, Chloroform- d) δ 161.9, 151.7, 148.9, 145.7, 139.5, 139.4, 138.2, 137.1, 132.4, 131.1, 130.1, 129.7, 128.9, 128.6 (q, $^2J_{\text{CF}} = 32.5$ Hz), 128.2, 127.1, 125.6, 124.8 (q, $^3J_{\text{CF}} = 3.7$ Hz), 60.9, 34.7, 31.2, 21.3, 14.1; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for iodinated intermediate **9d'** $[\text{C}_{24}\text{H}_{22}\text{F}_3\text{IO}_2\text{S}]^{+1}$: 559.0410; Found 559.0418; $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{31}\text{H}_{30}\text{F}_3\text{O}_2\text{S}]^{+1}$: 523.1913; Found 523.1912.



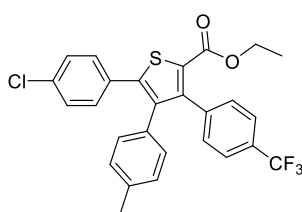
9d - ethyl 5-(4-(tert-butyl)phenyl)-4-(4-chlorophenyl)-3-phenylthiophene-2-carboxylate: Ethyl 5-(4-(tert-butyl)phenyl)-4-(4-chlorophenyl)thiophene-2-carboxylate (**8e**) is first iodinated to generate ethyl 5-(4-(tert-butyl)phenyl)-4-(4-chlorophenyl)-3-iodothiophene-2-carboxylate (**8e***). This compound is then reacted with phenyl boronic acid for 70 minutes; off-white solid (91.2 mg, 64 % yield over 2 steps); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; $R_f = 0.59$; ^1H NMR (500 MHz, Chloroform- d): δ 7.28 – 7.26 (m, 2H), 7.23 (dd, $J = 5.0, 1.9$ Hz, 3H), 7.15 (d, $J = 8.4$ Hz, 2H), 7.10 – 7.05 (m, 4H), 6.86 – 6.81 (m, 2H), 4.19 (q, $J = 7.1$ Hz, 2H), 1.30 (s, 9H), 1.17 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, Chloroform- d) δ 162.0, 151.5,

148.7, 145.3, 138.4, 135.8, 134.0, 132.8, 132.1, 130.2, 129.9, 128.8, 128.8, 128.2, 128.2, 127.7, 127.4, 127.3, 127.2, 126.7, 125.5, 60.8, 31.2, 14.0; HRMS (ESI) m/z: HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{29}H_{28}ClO_2S]^+1$: 475.1493; Found 475.1492.



9e - ethyl 5-(4-(tert-butyl)phenyl)-3-(4-methoxyphenyl)-4-(o-tolyl)thiophene-2-carboxylate: Ethyl 5-(4-(tert-butyl)phenyl)-4-(o-tolyl)thiophene-2-carboxylate (**8c**) is first iodinated to generate ethyl 5-(4-(tert-butyl)phenyl)-3-iodo-4-(o-tolyl)thiophene-2-

carboxylate (**8c'**). This compound is then reacted with 4-methoxyphenyl boronic acid for 70 minutes; clear oily solid (110.5 mg, 76 % yield over 2 steps); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; R_f = 0.49; ^1H NMR (500 MHz, Chloroform-d): ^1H NMR (500 MHz, Chloroform-d) δ 7.23 – 7.20 (m, 2H), 7.18 – 7.14 (m, 2H), 7.14 – 7.09 (m, 1H), 7.05 – 6.95 (m, 5H), 6.73 – 6.68 (m, 2H), 4.24 (dd, J = 7.1, 0.7 Hz, 2H), 3.74 (s, 3H), 1.87 (s, 3H), 1.27 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, Chloroform-d) δ 162.2, 158.7, 151.2, 149.2, 144.6, 139.5, 137.1, 135.6, 131.4, 130.9, 130.8, 129.9, 127.9, 127.9, 127.6, 126.1, 125.5, 125.5, 125.5, 112.6, 60.8, 55.0, 34.6, 31.2, 19.9, 14.2; HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{31}H_{33}O_3S]^+1$: 485.2145; Found 485.2143.

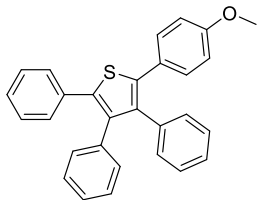


9f - ethyl 5-(4-chlorophenyl)-4-(p-tolyl)-3-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate: Ethyl 5-(4-chlorophenyl)-4-(p-tolyl)thiophene-2-carboxylate (**8f**) is first iodinated to generate ethyl 5-(4-chlorophenyl)-3-iodo-4-(p-tolyl)thiophene-2-carboxylate (**8f'**).

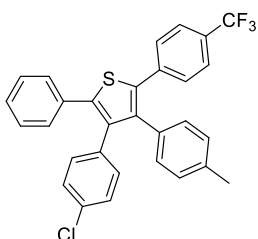
This compound is then reacted with 4-trifluoromethylphenyl boronic acid for 60 minutes; white solid (123.3 mg, 76 % yield over 2 steps); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; R_f = 0.59; ^1H NMR (500 MHz, Chloroform-d): δ 7.48 (d, J = 8.0 Hz, 2H), 7.26 – 7.13 (m, 6H), 6.91 (d, J = 7.7 Hz, 2H), 6.73 (d, J = 7.8 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 2.25 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, Chloroform-d) δ 161.7, 147.2, 143.6, 140.4, 139.7, 137.1, 134.3, 131.9, 131.4, 130.4, 130.3, 129.4, 129.2 ($^2J_{CF}$ = 32.3 Hz), 129.0, 128.8, 128.0, 124.3 ($^3J_{CF}$ = 3.7 Hz), 61.1, 21.2, 13.9.; HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{27}H_{21}ClF_3O_2S]^+1$: 501.0897; Found 501.0895.

3.4.5 General procedure for the C2 arylation of thiophene (10a-f):

To a solution of 0.15 mmols of tri-arylated thiophene **9a-f** in ethanol (1.5 mL, [0.1 M]) is added 1 mmol of NaOH (40 mg, 10 equiv.) to a 10 mL round bottom flask. The reaction is heated in a silicon oil bath on a hot plate under reflux for 30 minutes or until completion (all substrates shown were fully saponified after 30 minutes). The reaction is then cooled and acidified with 1M HCl until a pH of 2. The solution is diluted with about 20 mL of water and 30 mL of EtOAc. The aqueous is extracted 2 times with about 20 mL of EtOAc. The combined organic layers are washed with brine, dried with sodium sulfate and evaporated under reduced pressure. The white solid product (**9a'-f'**) is then used directly in the following reaction. To a solution of 0.15 mmol of tri-arylated thiophene acid **9a'-e'** in anhydrous DMF [0.1 M] (1.5 mL) in a conical microwave vial is added the aryl bromide coupling partner (0.225 mmol, 1.5 equiv.), Cs₂CO₃ (74 mg, 1.5 equiv.) and Pd(PtBu₃)₂ (3.8 mg, 5 mol%). The vial is sealed with a rubber septum and an aluminium cap, and reacted in a Biotage Initiator 2.3 build 6250 microwave system with a 400 W magnetron at 170 °C for 10 minutes. After cooling, the reaction mixture was filtered over celite, and diluted in about 20 mL EtOAc and 30 mL of water. The aqueous is extracted 2 times with about 20 mL of EtOAc. The combined organic layers are washed with brine (2x), dried with sodium sulfate and evaporated under reduced pressure. The crude is purified by gravity column chromatography (silica gel, 98:2 hexanes/ethyl acetate) to afford **10a-f**.

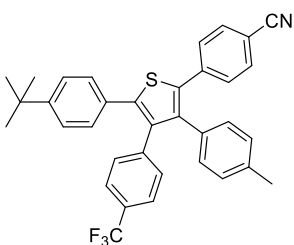


10a - 2-(4-methoxyphenyl)-3,4,5-triphenylthiophene: Ethyl 3,4,5-triphenylthiophene-2-carboxylate (**9a**) is first saponified and then reacted with 4-methoxybenzobromide; Oily white solid (17.1 mg, 42 % yield over 2 steps); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; R_f = 0.75; ¹H NMR (500 MHz, Chloroform-d): δ 7.26 – 7.16 (m, 5H), 7.15 – 7.10 (m, 8H), 6.97 (m, J = 4H), 6.81 (m, 2H), 3.70 (s, 3H); ¹³C NMR (126 MHz, Chloroform-d) δ 158.8, 139.4, 138.8, 138.5, 137.7, 136.6, 136.6, 134.3, 130.9, 130.9, 130.3, 129.2, 128.3, 127.8, 127.8, 127.1, 126.7, 126.5, 126.5, 113.8, 55.2; HRMS (ESI) m/z : $[M]^+$ calcd for [C₂₉H₂₂OS]⁺: 418.1386; Found 418.1386.



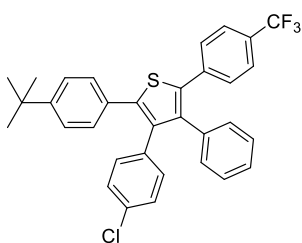
10b - 3-(4-chlorophenyl)-2-phenyl-4-(p-tolyl)-5-(4-(trifluoromethyl)phenyl)thiophene:

Ethyl 4-(4-chlorophenyl)-5-phenyl-3-(p-tolyl)thiophene-2-carboxylate (**9b**) is first saponified and then reacted with 4-bromobenzotrifluoride; White solid (42.4 mg, 84 % yield over 2 steps); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; $R_f = 0.82$; ^1H NMR (500 MHz, Chloroform- d): δ 7.46 (d, $J = 8.1$ Hz, 2H), 7.32 (d, $J = 8.1$ Hz, 2H), 7.22 (dd, $J = 6.8, 3.0$ Hz, 3H), 7.12 – 7.07 (m, 2H), 6.97 (d, $J = 7.7$ Hz, 2H), 6.91 – 6.86 (m, 2H), 6.82 (d, $J = 7.7$ Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, Chloroform- d) δ 140.4, 140.0, 138.4, 136.9, 136.6, 134.6, 133.7, 132.7, 132.6, 132.1, 130.4, 129.2, 129.2, 129.0, 128.5, 128.2, 127.7, 125.3 ($^3J_{\text{CF}} = 3.8$ Hz), 21.2; HRMS (ESI) m/z : $[\text{M}]^+$ calcd for $[\text{C}_{30}\text{H}_{20}\text{ClF}_3\text{S}]^{+1}$: 504.0921; Found 504.0918.



10c and 10c* 4-(5-(4-(tert-butyl)phenyl)-3-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)thio -phen-2-yl)benzo-nitrile:

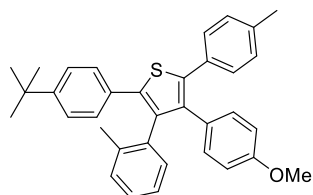
Ethyl 5-(4-(tert-butyl)phenyl)-3-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate (**9c**) is first saponified and then reacted with 4-bromobenzonitrile; White solid (47.1 mg, 85 % yield at 0.1 mmol scale and 207.4 mg, 75 % yield at a 0.5 mmol scale, over 2 steps); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; $R_f = 0.80$; ^1H NMR (500 MHz, Chloroform- d): δ 7.47 (d, $J = 8.3$ Hz, 2H), 7.38 (d, $J = 8.1$ Hz, 2H), 7.32 (d, $J = 8.1$ Hz, 2H), 7.28 – 7.24 (m, 2H), 7.12 (d, $J = 8.3$ Hz, 2H), 7.08 (d, $J = 8.0$ Hz, 2H), 6.97 – 6.93 (m, 2H), 6.81 (d, $J = 8.0$ Hz, 2H), 2.29 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, Chloroform- d) δ 141.38, 140.98, 138.92, 137.96, 137.21, 135.86, 132.31, 132.10, 131.10, 130.31, 130.23, 129.34, 129.33, 129.16, 128.72, 125.56, 124.83 ($^3J_{\text{CF}} = 3.8$ Hz), 118.80, 110.44, 34.62, 31.22, 31.20, 21.23; HRMS (EI): $[\text{M}]^+$ exact mass calculated for $[\text{C}_{35}\text{H}_{28}\text{F}_3\text{NS}]^{+1}$: 551.1889, found 551.1890.



10d - 2-(4-(tert-butyl)phenyl)-3-(4-chlorophenyl)-4-phenyl-5-(4-(trifluoromethyl)phenyl) thiophene:

Ethyl 5-(4-(tert-butyl)phenyl)-4-(4-chlorophenyl)-3-phenylthiophene-2-carboxylate (**9d**) is first saponified and then reacted with 4-bromobenzotrifluoride; Off-white solid (44.3 mg, 81 % yield over 2 steps); purified by gravity column chromatography (silica gel) in

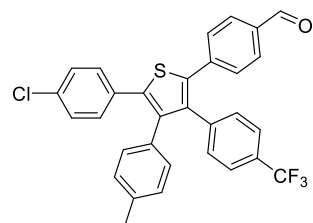
98:2 hexanes/ethyl acetate; $R_f = 0.80$; ^1H NMR (500 MHz, Chloroform- d): δ 7.46 (d, $J = 8.2$ Hz, 2H), 7.33 – 7.26 (m, 4H), 7.21 – 7.13 (m, 5H), 7.10 (d, $J = 8.2$ Hz, 2H), 6.95 (dd, $J = 7.6$, 1.7 Hz, 2H), 6.90 (d, $J = 8.2$ Hz, 2H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, Chloroform- d) ^{13}C NMR (126 MHz, Chloroform- d) δ 150.8, 140.4, 140.2, 137.9, 137.8, 135.8, 134.7, 132.7, 132.1, 130.6, 130.6, 129.1, 128.7, 128.2, 128.2, 127.1, 125.5, 125.3 ($^3J_{\text{CF}} = 3.8$ Hz), 34.6, 31.2; HRMS (ESI) m/z : $[\text{M}]^+$ calcd for $[\text{C}_{33}\text{H}_{26}\text{ClF}_3\text{S}]^{+1}$: 546.1390; Found 546.1385.



10e - 2-(4-(tert-butyl)phenyl)-4-(4-methoxyphenyl)-3-(o-tolyl)-5-(p-tolyl)thiophene: Ethyl 5-(4-(tert-butyl)phenyl)-3-(4-methoxyphenyl)-4-(o-tolyl)thiophene-2-carboxylate (**9e**) is first saponified

and then reacted with 4-bromotoluene; Clear solid (26.2 mg, 71 % yield over 2 steps); purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate; $R_f = 0.69$; ^1H NMR (500 MHz, Chloroform- d): δ 7.20 – 7.10 (m, 7H), 7.10 – 7.01 (m, 5H), 6.84 (d, $J = 8.7$ Hz, 2H), 6.60 (d, $J = 8.7$ Hz, 2H), 3.71 (s, 3H), 2.31 (s, 3H), 1.91 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (125 MHz, Chloroform- d) δ 158.0, 149.9, 138.9, 138.7, 137.7, 137.5, 137.3, 137.0, 136.7, 131.7, 131.6, 131.5, 131.3, 129.7, 129.0, 128.9, 128.9, 127.5, 127.2, 125.4, 125.3, 113.1, 55.0, 34.5, 31.2, 21.2, 20.0; HRMS (ESI) m/z : $[\text{M}]^+$ calcd for $[\text{C}_{35}\text{H}_{34}\text{OS}]^{+1}$: 502.2325; Found 502.2322.

* An additional purification by recrystallization in hexanes was necessary for this compound (the assumed proto-decarboxylation minor by-product has the same R_f value). Conditions reported in the crystallography section.



10f - 4-(5-(4-chlorophenyl)-4-(p-tolyl)-3-(4-(trifluoromethyl)phenyl)thiophen-2-yl) benzaldehyde: Ethyl 5-(4-chlorophenyl)-4-(p-tolyl)-3-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate (**9f**) is first saponified and then reacted with 4-bromobenzaldehyde; White solid (43.1 mg, 81 % yield over 2 steps); purified by gravity column chromatography (silica gel) in

98:2 hexanes/ethyl acetate; $R_f = 0.64$; ^1H NMR (500 MHz, Chloroform- d): δ 9.97 (s, 1H), 7.79 – 7.71 (m, 2H), 7.41 (d, $J = 8.0$ Hz, 2H), 7.37 – 7.29 (m, 2H), 7.24 – 7.18 (m, 2H), 7.18 – 7.13 (m, 2H), 7.07 (d, $J = 8.0$ Hz, 2H), 6.96 (d, $J = 7.8$ Hz, 2H), 6.84 – 6.73 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, Chloroform- d) δ 191.5, 140.0, 139.8, 139.4, 139.0, 137.8, 137.1, 135.1, 133.7, 132.2, 132.1, 131.0, 130.4, 130.3, 129.9, 129.6, 129.1, 128.7, 125.1 (q,

$^3J_{\text{CF}} = 3.8 \text{ Hz}$), 21.2.; HRMS (ESI) m/z : $[\text{M}]^+$ calcd for $[\text{C}_{31}\text{H}_{20}\text{ClF}_3\text{OS}]^{+1}$: 532.0870; Found 532.0865.

Chapter 4: Ester-Controlled Functionalization for Selective Access to Multi-Arylated Thiophenes and Furans

4.1 Introduction

Building complex molecules from readily available building blocks with simple, robust reaction conditions has long been a fundamental aim of organic synthetic chemistry. Arylated thiophenes and furans are molecules of interest in drug discovery and material. In particular, functionalization at the β -positions of heteroarenes is an emerging motif. Within photoelectronic materials, β -functionalization leads to increased tunability,^{265–267} and for drug candidates, this can break the planarity of otherwise conjugated systems, which has shown to be useful for drug efficacy,²⁶⁸ as well as for the AIE affect in photosensitizers and photodynamic therapy.²⁶⁸ While thiophene is more widely used motif, particularly in terms of photo-electronic materials, several recent reports are starting to expand on the benefits of furan over thiophene,^{39–41,48,190,191,269–271} An additional advantage of furan over thiophene in terms of green chemistry is that several furan derivatives can be biomass derived.²⁷²

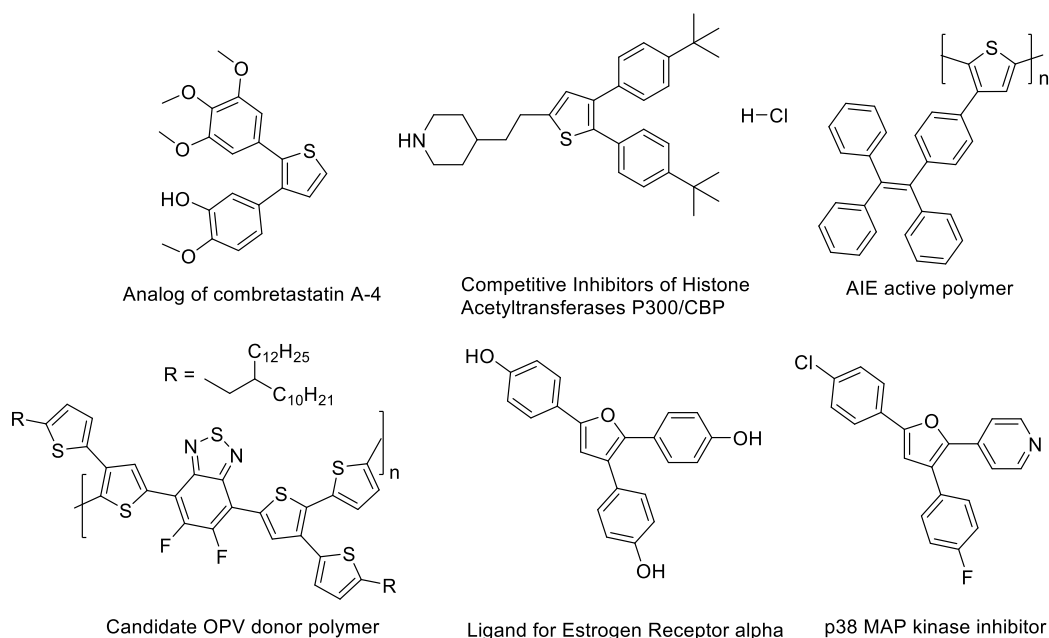
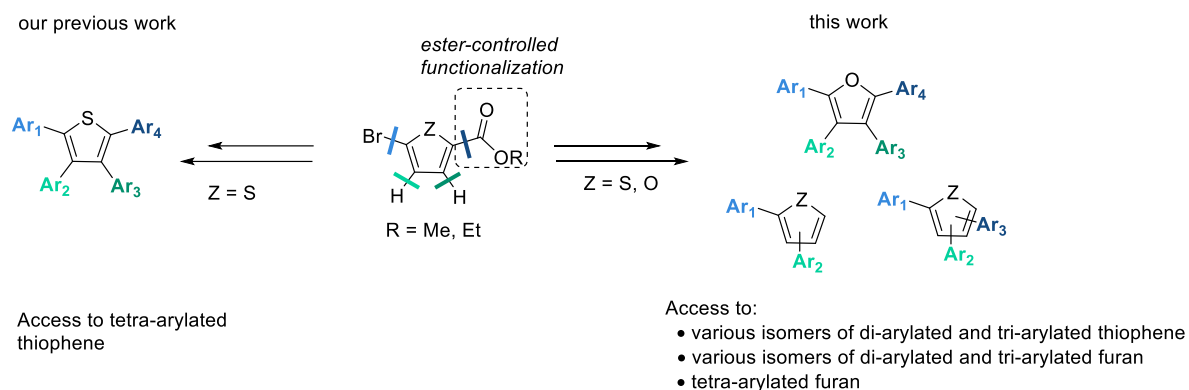


Figure 12: Examples of multi-arylated heteroarenes

Although a number of approaches have been developed for the synthesis of multi-arylated heteroarenes, it remains challenging to access this motif with a wide variety of substituent groups.^{273–281} Current methodologies commonly involve the cyclization of complex starting materials,^{235,282–288} which poses a synthetic challenge, and often requires complex catalytic systems and which don't allow for late stage functionalization. Figure 12 highlights recent examples of β -arylated thiophenes and furan in both medicinal and materials chemistry. As the utility of this class of compound warrants further exploration, easy and regioselective synthetic access to a variety of multi-arylated thiophene and furan is highly desirable.

Herein we adapt a previously reported methodology for the regioselective tetra-arylation of thiophene in order to access various isomers of di- and tri-arylated thiophenes in a programmed manner, utilizing a combination of ester-controlled reactions (summarized in Scheme 35). This methodology is also translated to the tetra-arylation of furan, and used to access the various isomers of di- and tri-arylated furan. This protocol is not only highly modular but exceedingly practical – boasting short reaction times, simple catalytic systems, and mostly air- and water-tolerant reactions. With facile access to a variety of di- and tri-arylated thiophenes and furans, we have assessed the relative optical properties of these molecules, showcasing their relative properties.



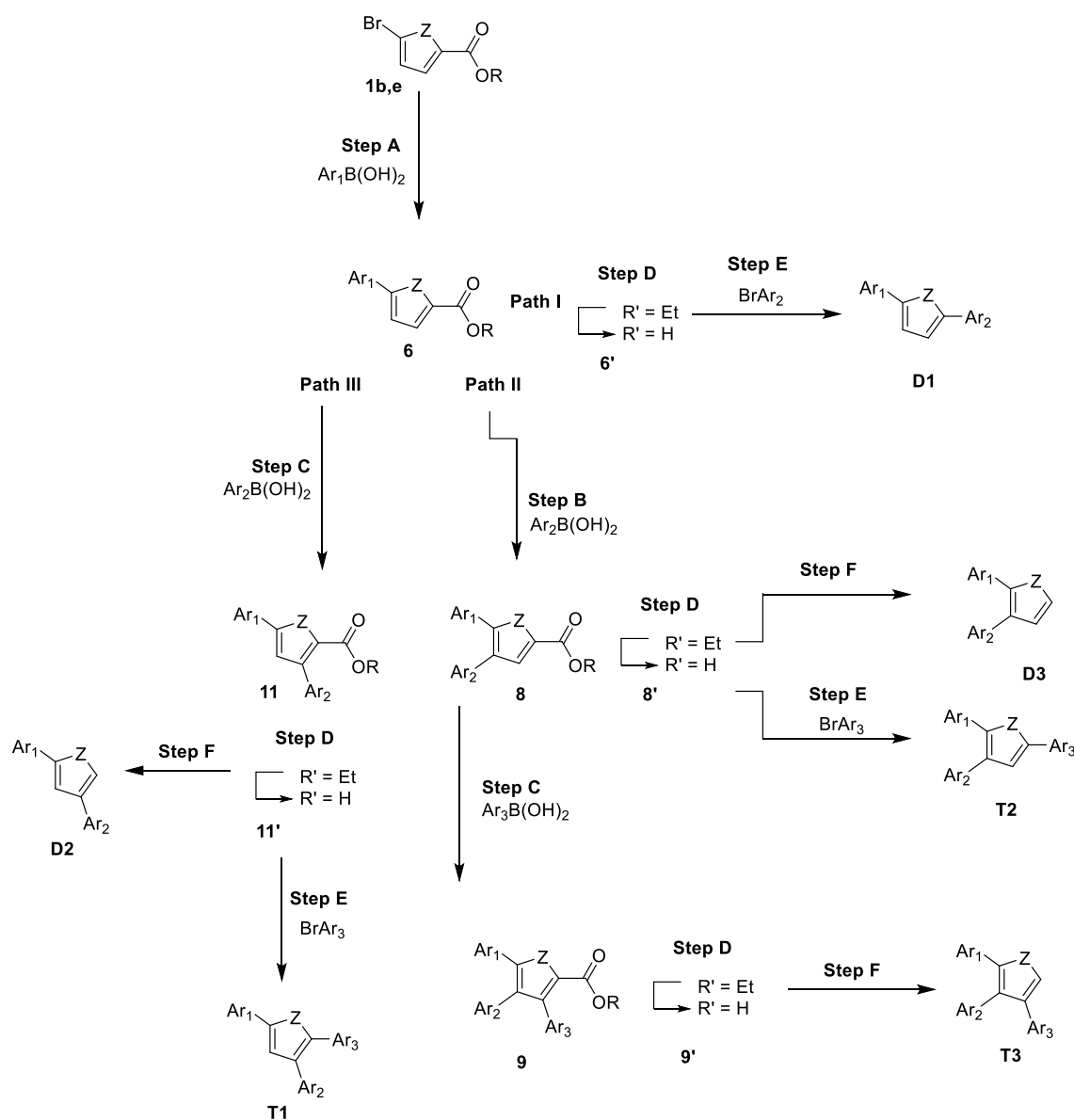
Scheme 35 : Previous work and this work towards multi-arylated heteroarenes

The salient aspect of this approach pertains to the regioselective control of β -functionalization permitted by the ester at C5. For C4 arylation, the ester is used to electronically direct bromination at C4. For C3 arylation, the ester is used for co-ordinated metallation/deprotonation and subsequent iodination at C3.

4.2 Results and Discussion

The general protocol for access to three isomers of di-arylated thiophene (2,5; 4,5 and 3,5) and for access to three isomers of tri-arylated thiophenes (2,3,5; 2,4,5 and 3,4,5) is summarized in Scheme 36. All synthetic routes begin with the same starting material, ethyl 5-bromothiophene 2- carboxylate (**1b**). The first reaction is the arylation at C5 using a rapid and quantitative, ester activated Suzuki-Miyaura cross-coupling (Step A) to get mono-arylated thiophene ester (**6**). From intermediate **6**, Path I leads to 2,5 di-arylated thiophene (**D1**) *via* a saponification (Step D) of the ester to the corresponding carboxylic acid, and a subsequent decarboxylative cross-coupling (Step E) with an aryl bromide. Alternatively, from intermediate **6** it is possible to take synthetic Path II towards 3 products; 5,4 di-arylated thiophene **D3**, 3,4,5 tri-arylated thiophene **T3** and 2,4,5 tri-arylated thiophene **T2**. The first step of Path II (Step B) constitutes an ester directed bromination of C3 (intermediate **7**, not shown in Scheme 36), followed by a second Suzuki-Miyaura cross-coupling to access di-arylated thiophene ester intermediate **8**. From intermediate **8**, it is possible to bifurcate in two different directions. A saponification of the ester (Step D) can be followed by either a silver carbonate catalyzed protodecarboxylation reaction²⁸⁹ (Step F) to access **D3**, or a decarboxylative cross-coupling (Step E) with an aryl bromide¹⁶⁶ to access **T2**.

Conversely, intermediate **8** can be iodinated at C3 using an ester directed metalation/deprotonation,²⁵⁴ followed by a Suzuki-Miyaura coupling (Step C) to produce tri-arylated thiophene ester (**9**). This intermediate can then be saponified (Step D) and proto-decarboxylated (Step F) for access to **T3**. **T1** and **D2** are accessible through synthetic Path III from mono-arylated intermediate **6** as well. First, intermediate **6** is iodinated at C3 using an ester directed metalation/deprotonation, followed by a Suzuki-Miyaura cross-coupling (Step C) to produce di-arylated thiophene ester **11**. A saponification of the ester (Step D) can be followed by either a silver carbonate catalyzed protodecarboxylation reaction (Step F) to access **D2**, or a decarboxylative cross-coupling (Step E) with an aryl bromide to access **T1**.

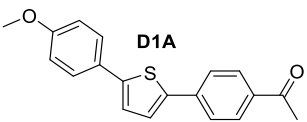
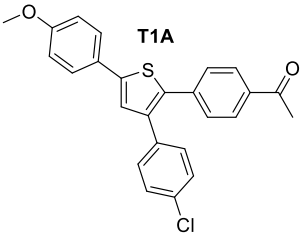
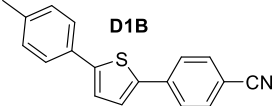
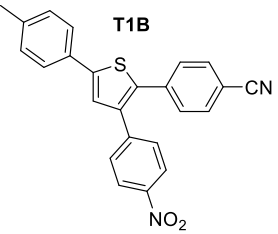
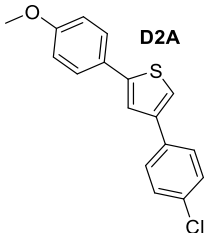
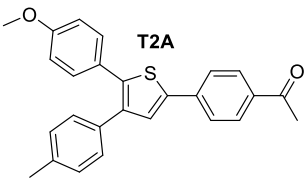
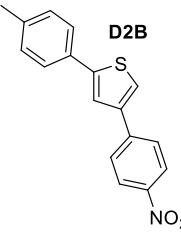
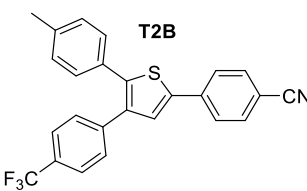
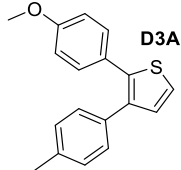
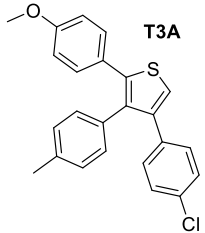


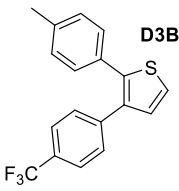
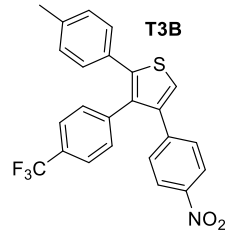
Scheme 36: Overview of branching pathways to access multi-arylated thiophene and furan

Two series (A and B) of multi-arylated thiophene were synthesized using this methodology, the results for which are summarized in Table 8 (for yields at every step, consult the experimental section). The 2,5 di-arylated thiophenes (**D1A** and **D1B**, entries 1 and 2) were synthesized in moderate yields of 45% and 46%, respectively, over 3 steps (for an average of 76% and 80% per step). Step E, the decarboxylative cross-coupling, is the yield limiting step in this protocol. As has previously been shown, the decarboxylative cross-coupling of a thiophene carboxylic acid is only moderately yielding when there is no

substitution at C3.¹⁶⁶ This is hypothesized to be due to competing reactivity at that position.¹¹⁵ Despite this lower yielding step, this protocol is still highly practical. The total reaction time to access these substrates is less than 1 h.

Table 8: Synthesis of various isomers of di- and tri-arylated thiophene (series A and B)

entry	structure	yield	entry	structure	yield
1		45 % over 3 steps	7		47, % over 5 steps
2		46, % over 3 steps	8		65, % over 5 steps
3		58, % over 5 steps	9		45, % over 5 steps
4		67, % over 5 steps	10		36, % over 5 steps
5		79, % over 5 steps	11		51, % over 7 steps

6	 D3B	75 % over 5 steps	12	 T3B	47, % over 7 steps
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The 3,5 di-arylated thiophenes (**D2A** and **D2B**, entries 3 and 4) were synthesized in good overall yields of 58 % and 67 %, respectively, over five steps (for an average of 89 % and 92% per step). The yield limiting step in this protocol is the ester directed iodination/arylated (Step C), as the necessary deprotonation does not proceed to completion under the reported conditions. However, this step was found to be completely regioselective in the absence of functionalization at C4, something that had not previously been shown.²⁹⁰ The total reaction time to access these substrates is approximately 7 h. the 4,5 di-arylated thiophenes (**D3A** and **D3B**, entries 5 and 6) were synthesized in excellent overall yields of 79 % and 75 %, respectively, over five steps (95 % and 94 % average per step). The total reaction time to access both substrates is under 7 h. the 2,3,5-tri-arylated thiophenes (**T1A** and **T1B**, Table 8, entries 7 and 8) were synthesized in very good overall yields of 47 % and 65 %, respectively, over 5 steps (for an average of 86 % and 92 % per step). The decarboxylative cross-coupling (step E) for these compounds was much higher yielding than was seen with the **D1** series, as these substrates have substitution at C3. The total reaction time to access both substrates is under 6 h. The 2,4,5-tri-arylated thiophene **T2A** and **T2B** (entries 9 and 10) were synthesized in moderate overall yields of 47 % and 36%, respectively, over five steps (for an average of 86 % and 82 % per step). As these substrates don't have substitution at C3, the yields for the decarboxylative cross-couplings are relatively lower (47 -53 %). The total reaction time to access both substrates is under 6 h. The 3,4,5 tri-arylated thiophenes **T3A** and **T3B** (entries 11 and 12) were synthesized in good overall yields of 51 % and 47 % respectively, over 7 steps (for an average of 91 % and 90 % per step). The total reaction time for these substrates is under 10 h. In summary, a variety of di- and tri-arylated thiophenes were accessed using a branching protocol with repetitive steps. These synthetic routes are highly modular, allow full regioselective control, and can boast short reaction times, repetitive catalytic systems, and few air- and moisture-sensitive steps.

The UVA/B spectra of thiophene series B is able to provide a good indication of the conjugation these compounds (the UVA/B spectra of thiophene series A exhibits similar trends, as seen in the supporting information for Chapter 4, Figure 21). As expected, **D1B** with di-arylation at C2 and C5 has the most red-shifted λ_{max} in the UVA/B region at 352 nm, as shown in Figure 13. This absorbance is to characteristic of a planar, di-arylated thiophene.

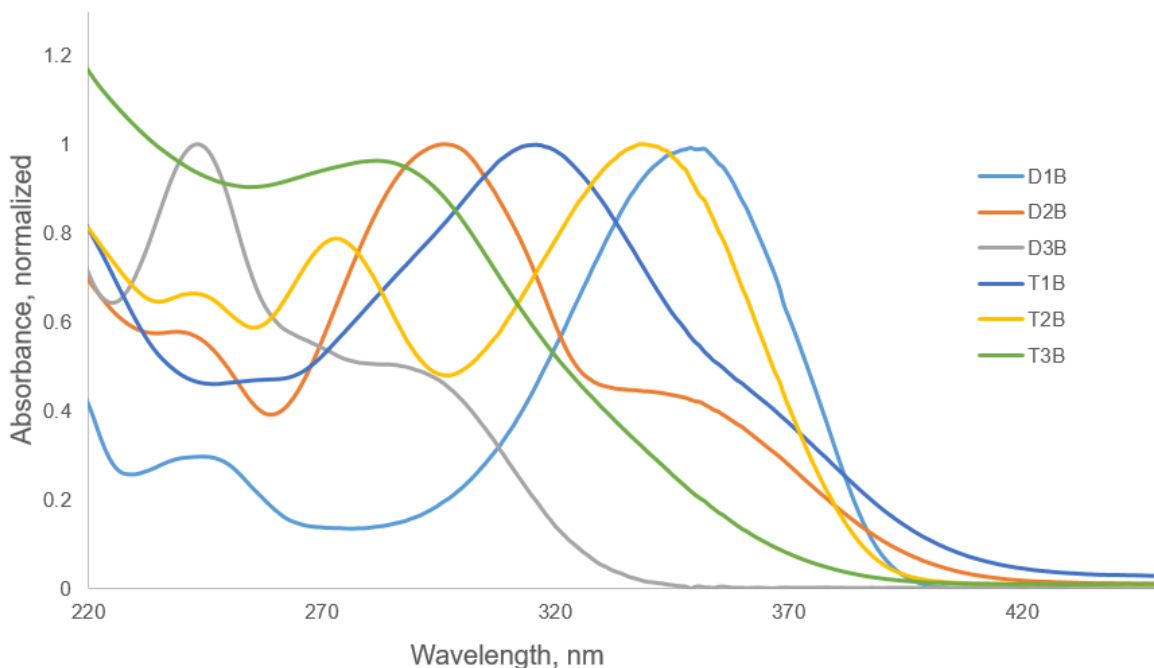


Figure 13: UVA/B spectrum of arylated thiophene series B

For the compound **D2B**, however, with the aryl groups at C5 and C3, while there is a small absorption maxima around 350 nm, the λ_{max} in the UVA/B region is significantly blue shifted at 298 nm. Likely, this is because there is no possible charge separated state across the thiophene core in this configuration, as there is with the 2,5 di-arylated isomer, and the molecule is therefore not as conjugated. The λ_{max} in the UVA/B region for **D3B** with the aryl groups at C5 and C4 is even more blue shifted, with a small absorption maxima at 296 nm and a λ_{max} at 245. Although the charge separated state across the thiophene core is theoretically possible in this configuration, the molecule would have to be planar for full conjugation. The absorption profile of this molecule suggest that, likely due the steric hindrance between the two adjacent rings, the aryl group rings are not in conjugation through the thiophene and are likely significantly tilted. For the tri-arylated compounds **T1B**

and **T2B**, the relatively high λ_{max} values (319 and 342 nm, respectively) seem to indicate that some conjugation between the C2 and C5 aryl groups and the thiophene core are retained, despite the steric hindrance of aryl groups at C3 and C4. **T1B** is significantly more blue shifted than **T2B**, which may be due to the strong electron withdrawing effect of the branching β aryl group (NO_2). **T1A** and **T2A** also have very similar λ_{max} values to **D1A** (351, 352 and 360 nm, respectively). Altogether, these results suggest that unless a very strong electron withdrawing group is present, aryl branching at the β positions of thiophene does not have a large effect on the bandgap of the molecule. For **T3B**, however, the λ_{max} is 291 nm, and suggests that the rings are not in conjugation with thiophene core and the structure has no planarity. These results agree with what would be expected from the crystal structure of tetra-arylated thiophene **10e** (Scheme 34), which found tetra-arylated thiophene to be propeller shaped.

Modular access to multi-arylated furans was also developed using an adaptation of the aforementioned methodology. Generally, there are even fewer reported routes to multi-arylated furan than thiophene, although important work has been done by Lu and Yoshikai,¹⁵¹ as well as, Furstner and Jin¹⁵² in this domain with a cyclization strategies, among other notable contributions.^{291–294} This may be due to the fact that furans are generally more challenging to work with in terms of their sensitivity to ring opening in aqueous acidic conditions.²⁹⁵ Nevertheless, there are advantages to using furan as the core heteroarene in multi-arylated compounds, due to unique optical properties,⁴⁸ and due to the important fact that unlike thiophene, several furan compounds, including furoic acids, can be derived from biomass.²⁹⁴ As we have previously reported, tetra-arylated thiophene can be synthesized using a combination of the aforementioned steps (Step A $\rightarrow$ Step B $\rightarrow$ Step C $\rightarrow$ Step D $\rightarrow$ Step E). Firstly, we adapted this synthetic route to access tetra-arylated furan, and secondly, we translated this modular methodology to access the various isomers of di- and tri-arylated furans, as was done with thiophene above. In a similar fashion, we are thus able to use an ester group to direct and control selective arylation of furan.

Encouragingly, only a few variations were necessary to translate Steps A and B from thiophene to furan. As with thiophene, the starting material to access tetra-arylated furan is a C5 brominated furan ester (Table 9, compounds **1e**). For this, it is hypothesized that the ester activates the heteroarene bromide and under the previously reported conditions for

Suzuki-Miyaura cross-coupling, the reaction is done exceedingly quickly. Table 9 summarized the few modifications that were needed. With the same conditions as those used with thiophene (entry 1), the reaction was complete under 10 minutes, however, with the furan substrate, a significant amount of saponification was observed at 60 °C, resulting in only a 76 % yield of desired arylated ester product **6l**.

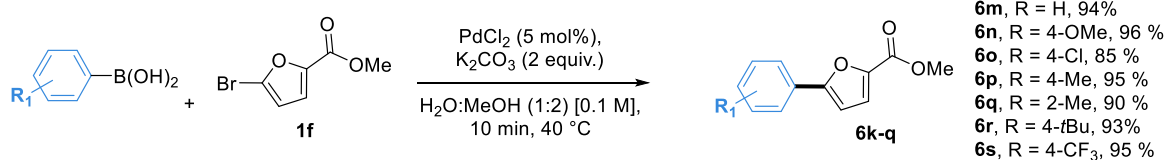
Table 9: Translation of Step A to furan starting material

entry	R	solvent	temp, °C	yield, %
1	Et	EtOH	60	76
2	Et	EtOH	55	90
3	Et	EtOH	50	95
4	Me	EtOH	50	75
5	Me	MeOH	50	94

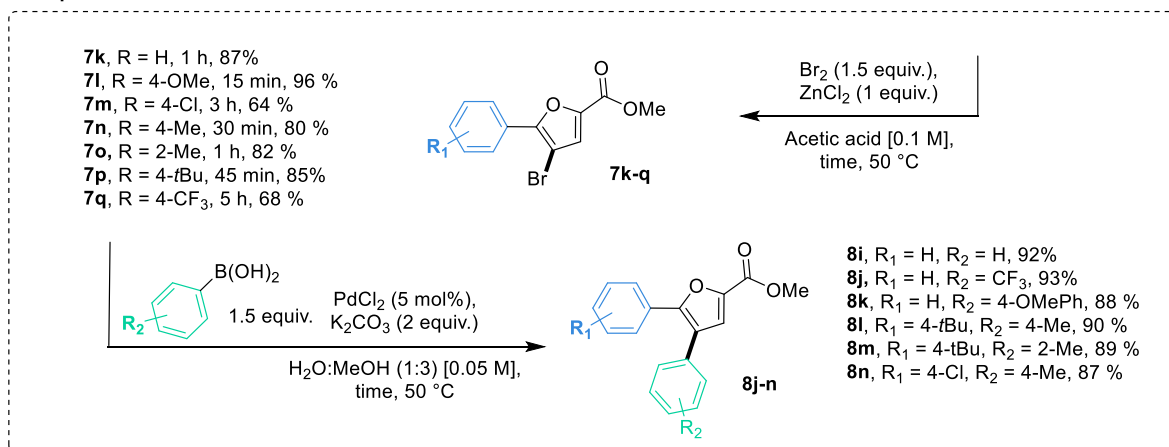
Conditions: 0.2 mmol of furan bromide (x) was dissolved in 1 mL of alcohol with 0.3 mmol of phenyl boronic acid. The reaction was heated and then 1 ml of H₂O, 0.3 mmol of K₂CO₃ and 0.01 mmol of PdCl₂ were added. The reaction was left for 10 minutes open to atmosphere.

This was mitigated by lowering reaction temperature (entries 2 and 3) to 50 °C, which was still very high yielding after 10 minutes, but avoided saponification. As the methyl ester of brominated furan (**1f**) was commercially available, the reaction conditions were also tried with this substrate. It was found, however, that in ethanol some trans-esterification occurred (entry 4), limiting the yield of the desired product **6m** for this reaction. However, the yield was still excellent when trading ethanol for methanol, preventing the transesterification product.

Step A



Step B



Scheme 37: Steps A and B to access mono- and di-arylated furan

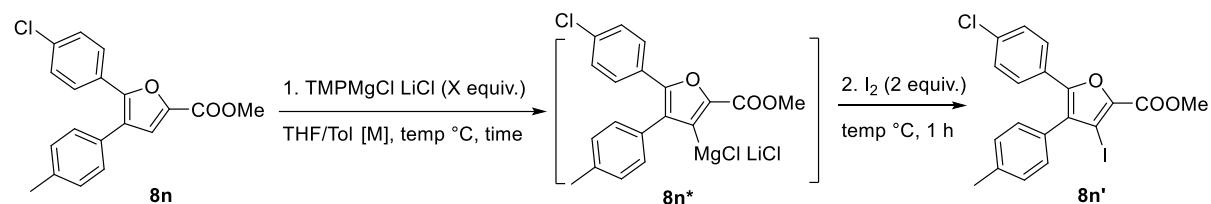
As summarized in Scheme 37, Step A, the Suzuki-Miyaura cross-coupling with furan **1f** was high yielding with a variety of aryl boronic acids, such as those with an electron donating group (**6n**), an electron withdrawing group (**6s**), and neutral groups (**6m**, **6p**, and **6r**), as well as with *ortho* methylation (**6q**) and was selective for the bromide over the chloride (**6o**).

For the first part of Step B, the ester directed bromination of C4, only a slight change in temperature (60 to 50 °C) was made from previously reported conditions to obtain the brominated products in good yields (Scheme 37, compounds **7k-q**). We were fully prepared to re-optimize this reaction to a different solvent - it had been assumed that reacting furan in acetic acid would have led to significant ring opening. Surprisingly, however, arylated furan appeared to be relatively stable in this reaction. As has been previously observed with the thiophene substrate,²⁸⁹ the reaction time and yield was highly dependent on the functionalization of the aryl group at C5. With an electron donating group at C5 (**7l**) the reaction was complete very quickly with a high yield. With electron withdrawing groups, the reaction took much longer (5 h with a CF₃ group, with only a 68% yield, **7q**). Likely this reaction proceeds *via* electrophilic aromatic substitution, and electron withdrawing groups

hinder the nucleophilicity of the furan ring. For the second part of Step B, a second Suzuki-Miyaura cross-coupling reaction was done to access the C4 arylated compounds **8j-n**. Similar conditions to the previous Suzuki-Miyaura cross-coupling afforded the desired di-arylated products in very good yields (87 – 93 %). The starting materials for this reaction (**7k-q**), however, proved to be markedly less soluble in mixed alcohol/aqueous solvent than the thiophene counterparts, and so the ratio of water to methanol was adjusted to 1:3 and the reaction needed to be diluted to a concentration of [0.05 M] to ensure full reagent solubilization. The reaction generally went to completion in under 2 h, although at larger scales the reaction did become sluggish and required an additional 5 mol% of PdCl₂ and 0.5 equivalents of boronic acid.

The arylation of di-arylated furans (**8j,l,n**) at C3 was also conducted *via* an ester-directed metalation/iodination (Step C), however, significant modifications were necessary. With the standard conditions optimized for thiophene substrates, the furan ring appeared to fully decompose (Table 10, entry 1). In order to prevent decomposition, optimization began with lower equivalents of base, shorter reaction times, and lower temperatures (entries 2-5). These alterations were found to mitigate starting material degradation. For entry 2 at 0 °C, there was a 100% conversion, but only a 22 % recovered yield. However, for entries 3 - 5, at -20, -40 and -78 °C, respectively, conversion was not complete, but very little degradation was observed. It was decided to continue optimization at -20 °C, as the reaction yield was not significantly different at lower temperatures.

Table 10: Optimization of Step C with di-arylated furan ester



entry	X	M	temp, °C	time, min	yield, %
1	2.0	[0.5]	25	75	trace
2	1.0	[1.0]	0	20	22 % ^a
3	1.0	[1.0]	-20	20	46 % ^a
4	1.0	[1.0]	-40	20	45 % ^a
5	1.0	[1.0]	-78	20	48 % ^a

6	1.0	[0.5]	-20	20	59 % ^a
7	1.2	[0.5]	-20	20	73 % ^a
8	1.3	[0.5]	-20	20	84 % ^a

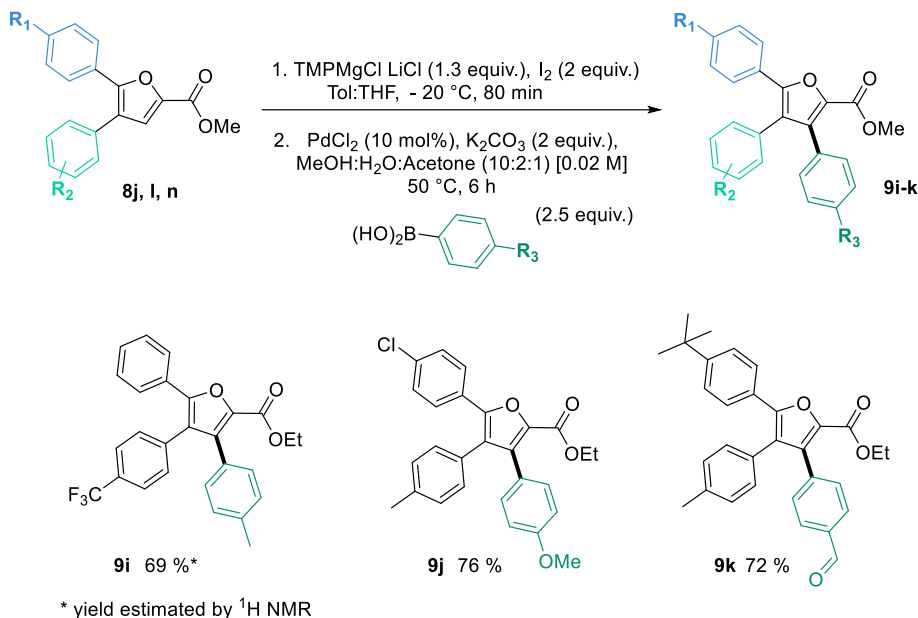
Reaction conditions: **8n** (0.2 mmol) in a flame dried round bottom flask with a stir bar (either dissolved in THF or neat at 1 M solvent) is cooled and the base is added dropwise. After time, crushed I₂ is added as a powder under a stream of argon. Yields estimated by GCMS^a

A major issue with this reaction at colder temperatures, however, was the stirring. Whereas with thiophene these reactions needed to be done at a high concentration of 1 M (only the base solution as solvent), for the furan substrates, this resulted in thick solutions that did not stir properly. A small amount of THF was thus added to help with solubilization, reducing the concentration to 0.5 M (Table 10, entry 6). This helped significantly with stirring and the conversion was improved. As there was a lot of residual starting material for entry 6, the equivalents of the base were raised to 1.2 and 1.3 for entries 7 and 8, which improved the yield to 73 % and 84 %, respectively (these yields are estimated by GCMS, as the iodinated product **8n'** is not isolatable from the starting material).

The subsequent Suzuki-Miyaura cross-coupling to obtain the C3 arylated furan (Step C, part 2) was then done on the unpurified (filtered) iodinated di-aryl furan **8n'**. A major issue with this step was the insolubility of the starting material. Whereas the previous Suzuki-Miyaura cross-couplings for the halogenated furans were done in 1:2 and 1:3 H₂O/methanol at [0.05 M], the di-arylated iodofuran **8n'** was not at all soluble in this solvent system and thus did not react with the boronic acids under Pd catalysis. It was found that a solvent system of 1:2:10 acetone/H₂O/methanol was needed to properly solubilize the substrate along with the K₂CO₃ base at 50°C (any increase in temperature led to saponification of the ester), at a very low concentration of 0.02 M. At this concentration, it was necessary to increase the Pd loading to 10 mol% and increase the equivalents of boronic acid to 2.5 for the reaction to reach completion after 6 h.

A small scope of products was tested for this modified reaction, as shown in Scheme 38. The yields over 2 steps are relatively good, with a 69 % yield for tri-arylated furan ester (**9i**) with electron neutral functionalization on the aryl boronic acid, a 72 % yield for tri-arylated furan ester (**9k**) with an electron withdrawing group on the aryl boronic acid, and a

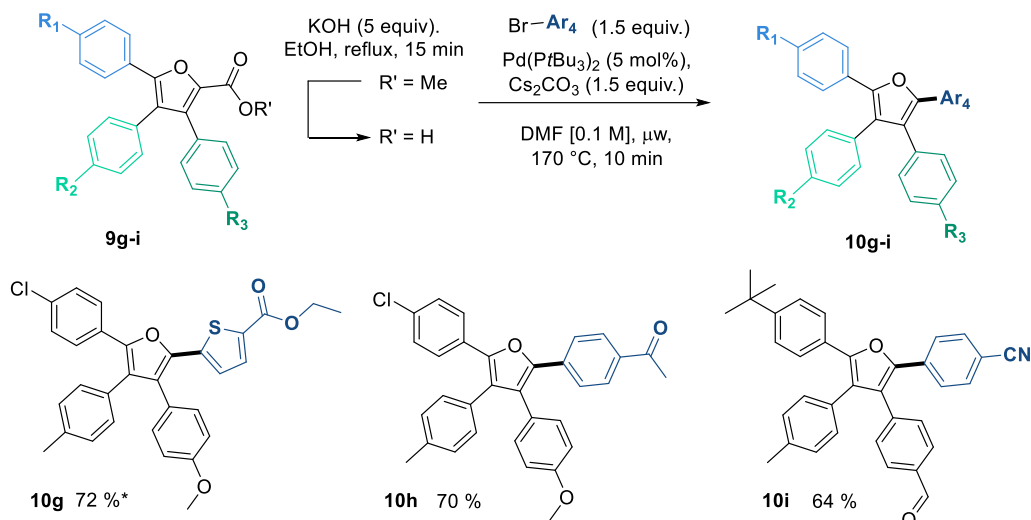
76 % yield with tri-arylated furan ester (**9j**) with an electron donating group on the aryl boronic acid.



Scheme 38: Scope of C3 arylation of furan with a modified Step C

For the last step towards tetra-aryl furan, the tri-aryl furan esters were then subjected to a saponification to access the corresponding carboxylic acids (as shown in Scheme 39). This reaction occurs rapidly (done in about 15 minutes) in ethanol at [0.1 M] with 5 equivalents of KOH at reflux (quantitative yields). With the tri-arylated furan carboxylic acids in hand, the compounds can then undergo a decarboxylative cross-coupling reaction to access the tetra-arylated species (Scheme 39). The first group that was attempted for this final cross-coupling was the bromothiophene ester substrate **1b**, as we wanted to show how chain extension might be possible. Unfortunately, while the crude ¹H NMR indicated that a significant amount of the desired product was formed (72% estimated yield), it was found that this compound (**10g**) readily degraded in ambient light on silica during attempted purifications. Unfortunately, this compound will need to be resynthesized and isolated in relative darkness in order to ascertain an isolated yield. The same tri-arylated carboxylic acid was then coupled with a different aryl bromide, 4-bromoacetophenone. It was found that while this compound (**10h**) was very sensitive to UV irradiation (readily degrades on the TLC plate), it was stable to ambient light and was able to be isolated with a relatively good yield of 70 %. The major by-product of this reaction appeared to be a competitive proto-

decarboxylation. A second tetra-arylated furan was successfully synthesized and isolated using tri-arylated furan carboxylic acid **9i'** with 4-bromobenzonitrile affording tetra-arylated furan **10i** with a 64 % yield.



* yield estimated by ^1H NMR

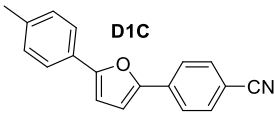
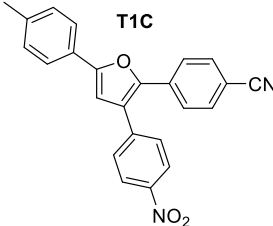
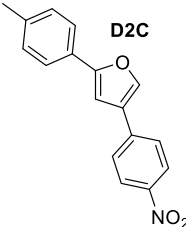
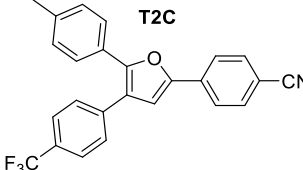
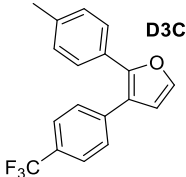
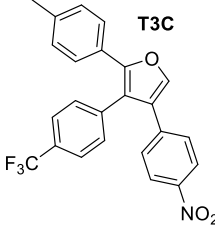
Scheme 39: Tetra-arylated furans synthesized with adapted programmed methodology

Despite some necessary modifications, the ester-controlled protocol to regioselectively arylate thiophene was shown to generally translate to furan. The overall yields for the tetra-arylated furans were 25 % for compound **10h** and 32 % for compound **10i**, which are good yields over 7 steps (for an average of 82 % and 87 % per step, respectively). Largely, the challenge in adapting the synthetic steps to furan related to some compound instability and issues with solubility. While some studies have report that multi-arylated furans have better solubility in organic solvent than multi-arylated thiophene,^{191,271,296} this was not the case for these furan substrates. Several steps of the reaction needed to be done at a higher dilution to avoid precipitation, and several compounds needed to be loaded as suspensions for column chromatography.

The modified route presented above to access tetra-aryl furans can also be utilized to access the various isomers of di-arylated furans and tri-arylated furans, as it was done with thiophene (summarized in Table 11, for yields at every step consult the experimental section). For comparative analysis, identical pathways and coupling partners were employed as with the thiophene series B (see Table 8). Markedly, the protodecarboxylation (Step F)

was found to be lower yielding on arylated furan carboxylic acids. As such, the final overall yields of final furan compounds including a proto-decarboxylation were lower than their thiophene counterparts; 62 %, 63 %, and 29 % for **D2C**, **D3C** and **T3C** (Table 11, entries 2, 3 and 6), compared to 67 %, 75 % and 47 % for **D2B**, **D3B** and **T3B** (Table 8, entries 4, 6 and 12), respectively. Interestingly, however, the decarboxylative cross-coupling (Step E) of arylated furan compounds with no substitution at C3 was much better yielding than with the thiophene substrates.

Table 11: Synthesis of various isomers of multi-arylated furan (series C, homolog of thiophene series B)

entry	structure	yield	entry	structure	yield
1		71, % over 3 steps	4		64, % over 5 steps
2		62, % over 4 steps	5		58, % over 5 steps
3		63, % over 5 steps	6		29, % over 7 steps

As such, the yields of final compounds **D1C** and **T2C** are 71 % and 58 %, (Table 11, entries 1 and 5) compared to the thiophene homologs at 46 % and 36 %, respectively (Table 8, entries 2 and 10). While some steps needed modification and resulted in varying yield, the various isomers of di- and tri-arylated furans were shown to be accessible through this route.

Comparing the UVA/B spectra of the various isomers of multi-arylated furan with those of the thiophene homolog can elucidate some of the optical/conformational similarities between the homologs. The overlaid spectra in Figure 14 suggests that when it comes to 2,5 di-arylated compounds, thiophene and furan have very nearly identical absorption profiles, with nearly the same λ_{max} for **D1C** and **D1B**, indicating that 2,5 di-arylated furan is planar and fully conjugated, as expected.

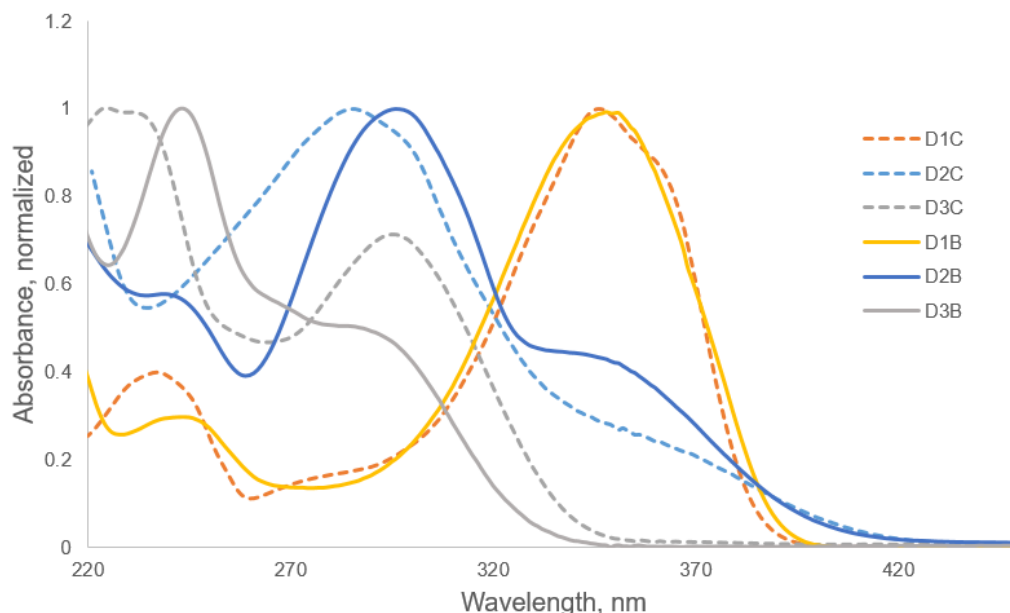


Figure 14: UVA/B spectra of di-arylated furans compared to di-arylated thiophenes

For the 5,3 di-arylated compounds **D2C** and **D2B**, the absorption profiles are also quite similar (with a slight blue shift in maximum absorption with the furan counterpart), however, the shoulder at 350 nm that was observed with thiophene is relatively reduced. When it comes to the 5,4-di-arylated compounds, however, the shoulder at 298 that was observed with thiophene compound **D3B** is actually more pronounced. This is perhaps due to the smaller exocyclic bond angle of furan relative to thiophene,²⁹⁷ causing less steric hindrance between the adjacent aryl rings.

For the tri-arylated compounds analyzed (Figure 15), the absorption spectra of the furan compared to thiophene compounds are also relatively similar. Interestingly, for the tri-

arylated furans with substitution at C2 and C5 (**T1C** and **T2C**), there is slight red shift in λ_{max} compared to the thiophene homologs.

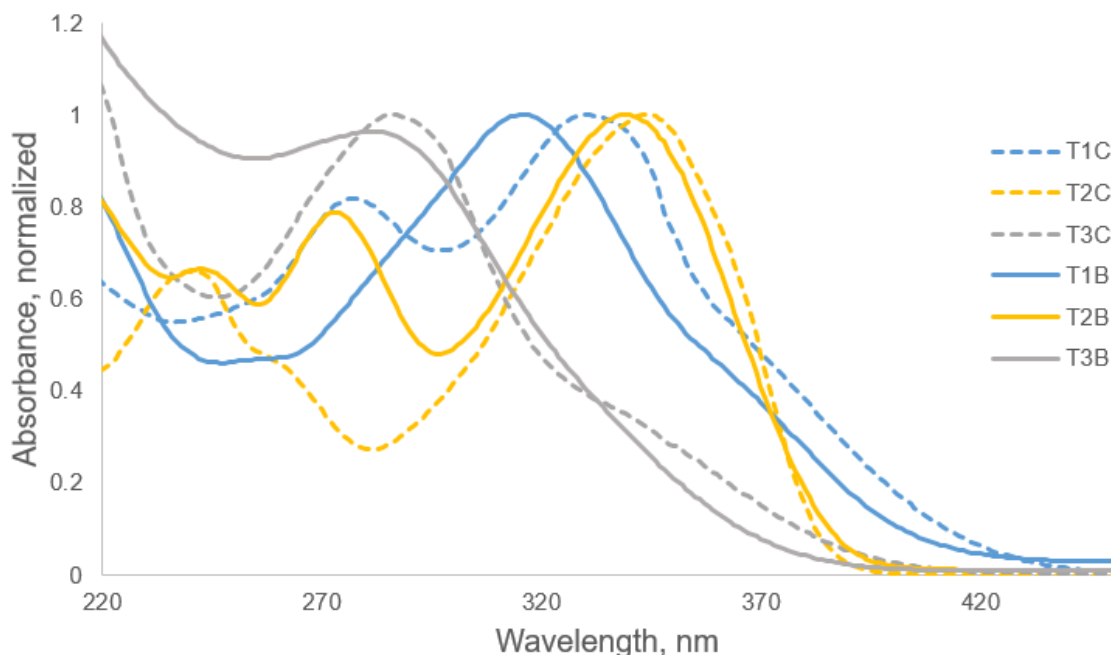


Figure 15: UVA/B spectra of the tri-arylated furans compared to tri-arylated thiophene

As was the case with the 3,4,5 tri-arylated thiophene (**T3B**), 3,4,5 tri-arylated furan (**T3C**) has a maximum absorbance close to the absorbance of un-substituted furan, suggested that none of the aryl groups are in conjugation with the furan. Altogether, these results suggest that although there may be small differences in the absorbance profiles, the optical properties of the various isomers of multi-arylated furan and multi-arylated thiophene are quite comparable. This is significant for the objective of supplanting petroleum derived thiophenes for biomass derived furan in certain industries that utilize thiophenes for their optical properties.

4.3 Conclusion

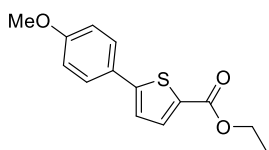
Presented herein is a branching methodology that allows for ester-controlled access to various isomers of di- and tri-arylated thiophenes and furans, as well as tetra-aryl furan, using a different combination of repetitive, practical, and generally high yielding steps. Additionally, inexpensive, commercially available bromide ester starting materials are

utilized. In terms of the thiophene substrates, this methodology provides facile access to a wide variety of highly utilized compounds. In terms of the furan substrates, this methodology provides facile access to a wide variety of structures whose utility has been significantly under-explored. UVA/B analysis of the various isomers of thiophene and furan was able to provide a good first impression of the three dimensional structures of these compounds. A comparative look at the various isomers of multi-arylated thiophene and furan is a good preliminary indicator of their similar optical properties.

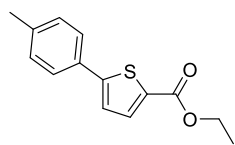
4.4 Experimental section

4.4.1 Synthesis of mono-arylated thiophene ester (Step A):

Refer to section 3.3.1 for reaction details



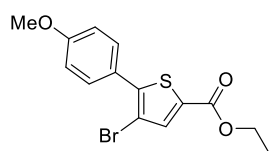
Ethyl 5-(4-methoxyphenyl)thiophene-2-carboxylate, 6j: Thiophene **1b** (1 mmol) is reacted with 4-methoxyphenyl boronic acid (1.5 mmol); white solid (256 mg, 98 % yield) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. Rf ^1H NMR (500 MHz, Chloroform- d) δ 7.72 (d, J = 3.9 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.15 (d, J = 3.9 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 1.38 (t, J = 7.1 Hz, 4H). ^{13}C NMR (125 MHz, Chloroform- d) δ 162.32, 160.16, 151.19, 134.29, 134.28, 131.41, 127.46, 127.45, 126.22, 122.49, 114.45, 61.05, 55.33, 55.32, 14.37. HRMS



Ethyl 5-(p-tolyl)thiophene-2-carboxylate, 6k: Thiophene **1b** (1 mmol) is reacted with 4-tolyl boronic acid (1.5 mmol); White solid (244 mg, 99 % yield) purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate. Rf ^1H NMR (500 MHz, Chloroform- d) δ 7.75 (d, J = 3.9, 1H), 7.52 (d, J = 7.2 Hz, 2H), 7.24 (dd, J = 3.9 Hz, 1H), 7.20 (d, J = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, Chloroform- d) δ 162.33, 151.35, 138.85, 134.24, 134.22, 131.93, 130.71, 129.75, 126.06, 123.06, 61.10, 21.26, 14.38.

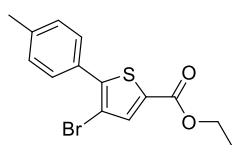
4.4.2 Synthesis of di-arylated thiophene ester (Step B)

Refer to sections 3.3.2 (bromination) and 3.3.3 (Suzuki-Miyaura coupling at C4) for reaction details



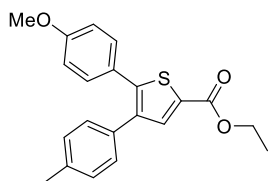
Ethyl 4-bromo-5-(4-methoxyphenyl)thiophene-2-carboxylate, 7i:

ethyl 5-(4-methoxyphenyl)thiophene-2-carboxylate **6j** (0.5 mmol) is reacted for 10 minutes; white solid (165.2 mg, 97% yield) purified by gravity column chromatography (silica gel) in 9:1 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.71 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 162.33, 151.35, 138.85, 134.24, 134.22, 131.93, 130.71, 129.75, 126.06, 123.06, 61.10, 21.26, 14.38.



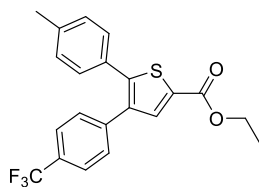
Ethyl 4-bromo-5-(p-tolyl)thiophene-2-carboxylate, 7j:

Ethyl 5-(p-tolyl)thiophene-2-carboxylate **6k** (0.5 mmol) is reacted for 60 minutes; off-white solid (160.1 mg, 98 % yield) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.72 (s, 1H), 7.56 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 162.33, 151.35, 138.85, 134.24, 134.22, 131.93, 130.71, 129.75, 126.06, 123.06, 61.10, 21.26, 14.38.



Ethyl 5-(4-methoxyphenyl)-4-(p-tolyl)thiophene-2-carboxylate, 8g:

Ethyl 4-bromo-5-(4-methoxyphenyl)thiophene-2-carboxylate **7i** (0.45 mmol) is reacted with p-tolyl boronic acid (0.90 mmol) for 120 minutes; light yellow solid (150.1 mg, 93 % yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.82 (s, 1H), 7.54 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 2.36 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 162.09, 146.87, 139.29, 138.85, 136.78, 135.53, 131.91, 129.91, 129.56, 129.38, 129.23, 129.09, 125.48, 125.45, 125.42, 125.39, 61.33, 21.26, 14.36.

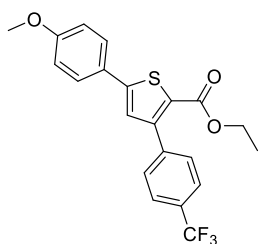


Ethyl 5-(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate, 8h: Ethyl 4-bromo-5-(p-tolyl)thiophene-2-carboxylate **7j** (0.45 mmol) is reacted with tri-fluoromethylphenyl boronic acid (0.90 mmol) for 100 minutes; white solid (168.5 mg, 96 % yield) purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl

acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.82 (s, 1H), 7.54 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 2.36 (s, 3H), 1.40 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 162.09, 146.87, 139.29, 138.85, 136.78, 135.53, 131.91, 129.91, 129.56, 129.38, 129.23, 129.09, 125.48, 125.45, 125.42, 125.39, 61.33, 21.26, 14.36.

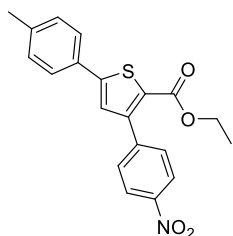
4.4.3 Synthesis of C3 arylated thiophene ester (Step C)

Refer to section 3.3.4 for reaction details



Ethyl 3-(4-chlorophenyl)-5-(4-methoxyphenyl)thiophene-2-carboxylate, 11a: Ethyl 5-(4-methoxyphenyl)thiophene-2-carboxylate **6j** (0.20 mmols) was first iodinated to generate ethyl 3-iodo-5-(4-methoxyphenyl)thiophene-2-carboxylate. This compound was then reacted with 4-chlorophenyl boronic acid for 60 minutes; white solid

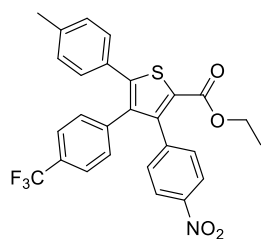
(61.4 mg, 80 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.61 – 7.56 (m, 2H), 7.45 – 7.42 (m, 2H), 7.40 – 7.36 (m, 2H), 7.14 (s, 1H), 6.94 (d, J = 8.8 Hz, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.95, 160.33, 148.71, 148.01, 134.37, 133.93, 130.56, 127.97, 127.46, 126.05, 125.80, 125.16, 114.51, 60.95, 55.40, 29.69, 14.17.



Ethyl 3-(4-nitrophenyl)-5-(p-tolyl)thiophene-2-carboxylate, 11b: ethyl 5-(p-tolyl)thiophene-2-carboxylate **6k** (0.20 mmol) was first iodinated to generate ethyl 3-iodo-5-(p-tolyl)thiophene-2-carboxylate. This compound was then reacted with 4-nitrophenyl boronic acid for 60 minutes; light orange solid (59.2 mg, 81 % yield over 2 steps) purified by

gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 8.11 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.08 (s, 4H), 7.02 – 6.98 (m, 2H), 4.22 (q, J = 7.1 Hz, 2H), 2.33 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 161.41, 147.11, 146.86, 145.75, 142.61, 139.02, 138.45, 137.64, 130.94, 129.52, 129.12, 125.25, 125.22, 122.79, 61.32, 21.22, 14.06.

Ethyl 3-(4-chlorophenyl)-5-(4-methoxyphenyl)-4-(p-tolyl)thiophene-2-carboxylate, 9g



Ethyl 3-(4-nitrophenyl)-5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)

thiophene-2-carboxylate, 9h : Ethyl 5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate **8h** (0.20 mmol) was first iodinated to generate ethyl 3-iodo-5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate. This compound was then reacted with 4-

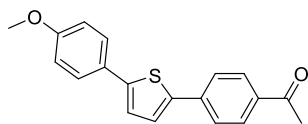
nitrophenyl boronic acid for 60 minutes; orange solid (77.1 mg, 75 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ¹H NMR (500 MHz, Chloroform-*d*) δ 8.14 – 8.08 (m, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.30 – 7.26 (m, 2H), 7.07 (s, 4H), 6.99 (d, *J* = 7.9 Hz, 2H), 4.22 (m, 2H), 2.33 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (125 MHz, Chloroform-*d*) δ 161.41, 147.11, 146.86, 145.75, 142.61, 139.02, 138.45, 137.64, 130.98, 130.94, 129.57, 129.52, 129.50, 129.48, 129.31, 129.12, 128.05, 125.28, 125.25, 125.22, 125.19, 124.95, 122.79, 61.32, 21.22, 14.06.

4.4.4 General procedure for the synthesis of arylated thiophene carboxylic acids (Step D)

Arylated thiophene esters are dissolved in ethanol [0.1 M] and heated to reflux. 5 equivalents of KOH are added and the reaction proceeds until completion (10 to 30 min, tracked by TLC). The reaction is then cooled and acidified to a pH of 2. The solution is extracted 2 times with ethyl acetate. The combined organic extractions are then washed 2x with brine, dried with sodium sulfate and evaporated under reduced pressure. These compounds are not purified before use in following reactions.

4.4.5 Synthesis of C2 arylated thiophene (Step E)

Refer to section for 3.3.5 for reaction conditions

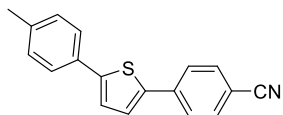


1-(4-(5-(4-methoxyphenyl)thiophen-2-yl)phenyl)ethan-1-one,

D1A: ethyl 5-(4-methoxyphenyl)thiophene-2-carboxylate **6j** (0.1 mmol) was saponified and then reacted with 4-

bromoacetophenone; light greenish solid (29.1 mg, 47 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.99 – 7.95 (m, 2H), 7.71 – 7.67 (m, 2H), 7.59 – 7.55 (m, 2H), 7.39 (d, *J* = 3.8 Hz, 1H), 7.21 (d, *J* = 3.8 Hz, 1H), 6.96 – 6.91 (m, 2H), 3.85 (s, 3H), 2.61 (s, 3H). ¹³C

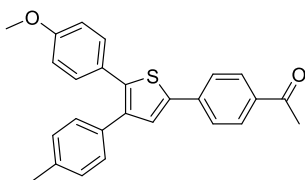
NMR (125 MHz, Chloroform-*d*) δ 197.25, 159.57, 145.48, 140.90, 138.82, 135.50, 129.13, 127.05, 126.78, 125.58, 125.14, 123.25, 114.39, 55.39, 26.55.



4-(5-(p-tolyl)thiophen-2-yl)benzonitrile: ethyl 5-(p-tolyl)thiophene-2-carboxylate **6k** (0.1 mmols) is first saponified and then reacted with 4-bromobenzonitrile; yellow solid (26.4 mg, 48 % yield over 2

steps) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate.

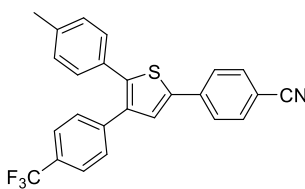
^1H NMR (500 MHz, Chloroform-*d*) δ 7.71 – 7.63 (m, 4H), 7.53 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 3.8 Hz, 1H), 7.28 (d, J = 3.8 Hz, 1H), 7.22 (d, J = 8.5 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 146.32, 140.38, 138.63, 138.21, 132.72, 130.92, 129.71, 126.05, 125.69, 125.61, 123.86, 118.91, 110.26, 21.23.



1-(4-(5-(4-methoxyphenyl)-4-(p-tolyl)thiophen-2-

yl)phenyl)ethan-1-one, T2A: Ethyl 5-(4-methoxyphenyl)-4-(p-tolyl) thiophene-2-carboxylate **8g** (0.1 mmols) is first saponified and then reacted with 4-bromoacetophene; light yellow solid (21.1

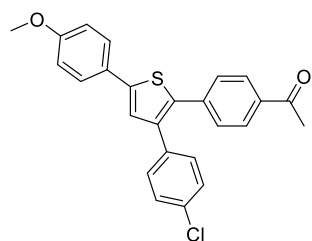
mg, 53 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 8.00 – 7.95 (m, 2H), 7.72 – 7.67 (m, 2H), 7.44 (s, 1H), 7.29 – 7.24 (m, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.12 (dt, J = 7.9, 0.7 Hz, 2H), 6.84 – 6.80 (m, 2H), 3.81 (s, 3H), 2.61 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 197.37, 159.01, 147.61, 146.64, 137.16, 135.24, 135.10, 133.31, 131.28, 130.01, 129.35, 129.33, 129.14, 128.63, 128.54, 127.34, 127.10, 126.05, 125.26, 124.64, 114.08, 55.14, 26.52, 21.28.



4-(5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)thiophen-2-yl)benzo

nitrile, T2B: Ethyl 5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl) thiophene-2-carboxylate **8h** (0.1 mmol) is first saponified and then reacted with 4-bromobenzonitrile; light orange solid (24.4 mg, 58 % yield over 2 steps) purified by gravity column chromatography

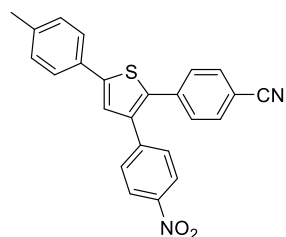
(silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (300 MHz, Chloroform-*d*) δ 7.76 – 7.65 (m, 4H), 7.57 (d, J = 8.0 Hz, 2H), 7.47 – 7.39 (m, 3H), 7.21 – 7.09 (m, 4H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 141.80, 140.20, 139.70, 138.43, 138.12, 137.51, 132.83, 130.10, 129.54, 129.37, 129.23, 129.11, 129.01, 127.80, 125.71, 125.51, 125.48, 125.45, 125.42, 123.05, 118.75, 110.80, 21.25.



1-(4-(3-(4-chlorophenyl)-5-(4-methoxyphenyl)thiophen-2-

yl)phenyl)ethan-1-one, T1A: Ethyl 4-bromo-5-(p-tolyl)thiophene-2-carboxylate **11a** is first saponified and then reacted with 4-bromoacetophenone; light yellow solid (33.4 mg, 80 % yield over 2 steps) purified by gravity column chromatography (silica gel) in

95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.89 – 7.84 (m, 2H), 7.57 (d, J = 8.8 Hz, 2H), 7.41 – 7.36 (m, 2H), 7.30 (d, J = 8.6 Hz, 2H), 7.27 – 7.23 (m, 3H), 6.95 (d, J = 9.0 Hz, 2H), 3.85 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 197.40, 159.69, 144.21, 138.97, 138.84, 135.66, 134.81, 133.33, 130.33, 128.91, 128.83, 128.65, 127.01, 126.38, 125.52, 125.50, 114.45, 55.41, 29.69, 26.56.



4-(3-(4-nitrophenyl)-5-(p-tolyl)thiophen-2-yl)benzonitrile, T1B:

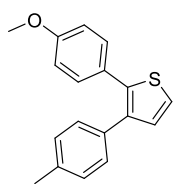
ethyl 3-(4-nitrophenyl)-5-(p-tolyl)thiophene-2-carboxylate **11b** is first saponified and then reacted with 4-bromobenzonitrile; orange solid (32.2 mg, 82 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR

(500 MHz, Chloroform-*d*) δ 8.20 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.35 (s, 1H), 7.25 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 147.03, 145.76, 142.58, 138.72, 138.16, 136.67, 132.56, 130.24, 129.86, 129.78, 129.52, 125.70, 125.57, 124.05, 118.44, 111.42, 21.27.

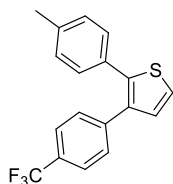
4.4.6 General procedure for the synthesis of decarboxylated heteroarenes (Step F)

Arylated thiophene carboxylic acids (0.1 mmol) are dissolved in DMSO (non-anhydrous) [0.1] and heated to 120 °C in a flask open to atmosphere. 0.01 mmols of Ag_2CO_3 are added and the solution is left to reaction until completion (tracked by TLC), taking between 1 and 3 h. It is very important for this reaction that vials and stir bars are washed with nitric acid or aqua regia prior as any residual Pd will lead to homocoupling. When the reaction is complete, the solution is cooled and diluted with 20 ml of water. The solution is then extracted 3 times with about 10 mL of ethyl acetate. The combined organic extractions are washed 2x with brine, dried with sodium sulfate and evaporated under reduced pressure.

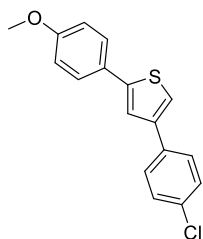
The crude mixture is purified by column chromatography with silica gel and 95:5 hexanes/ethyl acetate.



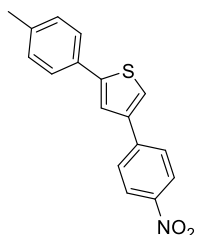
2-(4-methoxyphenyl)-3-(p-tolyl)thiophene, D3A: Ethyl 5-(4-methoxyphenyl)-4-(p-tolyl)thiophene-2-carboxylate **8g** is saponified and then protodecarboxylated; light yellow oily solid (27.8 mg, 99 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform- d) δ 7.26 (d, J = 5.3 Hz, 1H), 7.25 – 7.23 (m, 2H), 7.20 – 7.16 (m, 2H), 7.12 (d, J = 5.2 Hz, 1H), 7.11 – 7.07 (m, 2H), 6.84 – 6.79 (m, 2H), 3.80 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, Chloroform- d) δ 158.95, 138.12, 137.38, 136.35, 133.75, 130.48, 130.41, 129.06, 128.92, 126.92, 123.34, 113.87, 55.22, 21.17.



2-(p-tolyl)-3-(4-(trifluoromethyl)phenyl)thiophene, D3B: Ethyl 5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate **8h** is saponified and then protodecarboxylated; white solid (29.2 mg, 93 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform- d) δ 7.53 (dt, J = 8.1, 0.7 Hz, 2H), 7.39 (dt, J = 8.1, 0.8 Hz, 2H), 7.33 (d, J = 5.2 Hz, 1H), 7.18 – 7.13 (m, 3H), 7.10 (dt, J = 7.9, 0.7 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, Chloroform- d) δ 146.33, 140.39, 138.64, 138.21, 132.72, 130.93, 129.71, 126.05, 125.69, 125.62, 123.86, 118.90, 110.27, 21.23.

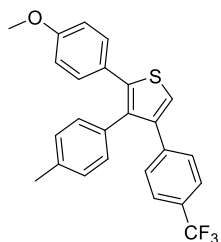


4-(4-chlorophenyl)-2-(4-methoxyphenyl)thiophene, D2A: Ethyl 4-bromo-5-(p-tolyl)thiophene-2-carboxylate **11a** is first saponified and protodecarboxylated; light yellow solid (29.7 mg, 99 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform- d) δ 7.59 – 7.52 (m, 4H), 7.43 (d, J = 1.5 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.30 (d, J = 1.5 Hz, 1H), 6.97 – 6.92 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, Chloroform- d) δ 159.45, 145.34, 141.76, 134.43, 132.95, 128.93, 127.51, 127.49, 127.15, 126.98, 121.04, 119.01, 114.34, 55.37.



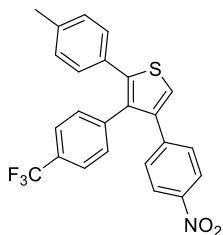
4-(4-nitrophenyl)-2-(p-tolyl)thiophene, D2B: Ethyl 3-(4-nitrophenyl)-5-(p-tolyl)thiophene-2-carboxylate **11b** is saponified and then protodecarboxylated (26.2 mg, 91 % yield over 2 steps) purified by gravity

column chromatography (silica gel) in 9:1 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 8.27 (d, J = 8.7 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.58 – 7.51 (m, 4H), 7.23 (d, J = 7.9 Hz, 2H), 2.39 (s, 4H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 146.67, 146.41, 141.98, 140.57, 138.17, 130.93, 129.72, 126.68, 125.82, 124.31, 121.97, 121.23, 21.21.



4-(4-chlorophenyl)-2-(4-methoxyphenyl)-3-(p-tolyl)thiophene, T3A:

Ethyl 3-(4-chlorophenyl)-5-(4-methoxyphenyl)-4-(p-tolyl)thiophene-2-carboxylate, **9g** (0.05 mmol) is saponified and then protodecarboxylated (19.1 mg, 98 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 9:1 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.23 (s, 1H), 7.19 – 7.11 (m, 4H), 7.05 – 6.97 (m, 4H), 6.87 (d, J = 8.1 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 158.86, 142.40, 140.50, 136.49, 136.40, 135.62, 132.76, 132.57, 130.64, 130.46, 130.21, 128.97, 128.11, 126.97, 121.41, 121.40, 113.72, 55.17, 29.69.

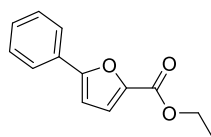


4-(4-nitrophenyl)-2-(p-tolyl)-3-(4-(trifluoromethyl)phenyl)thiophene, T3B:

ethyl 3-(4-nitrophenyl)-5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate **9h** (0.05 mmol) is saponified and then protodecarboxylated (19.2 mg, 88 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 9:1 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.74 – 7.65 (m, 4H), 7.56 (d, J = 8.1 Hz, 2H), 7.45 (s, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 146.68, 143.11, 142.93, 141.05, 139.22, 137.99, 135.01, 131.05, 130.40, 129.56, 129.33, 129.32, 129.22, 125.39, 124.03, 123.53, 29.69.

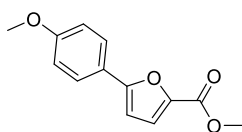
4.5 Synthesis of mono-arylated furans:

Refer to section 3.3.1 for reaction conditions. Minor modifications include the use of methyl 5-bromofuran-2-carboxylate as the starting material, methanol rather than ethanol for the solvent, and 50 °C rather than 60 °C as the reaction temperature.

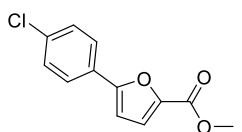


Ethyl 5-phenylfuran-2-carboxylate, 6l: Furan **1e** (0.5 mmols) is reacted with phenyl boronic acid; clear oil (95.3 mg, 94 % yield) purified by gravity

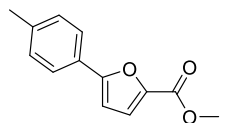
column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.80 (s, 2H), 7.41 (s, 2H), 7.35 (d, J = 17.3 Hz, 1H), 7.24 (s, 1H), 6.74 (d, J = 3.6 Hz, 1H), 4.43 – 4.34 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 158.86, 157.46, 143.89, 129.56, 128.87, 128.79, 124.82, 119.78, 106.78, 77.26, 77.01, 76.75, 60.87, 14.39



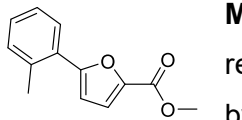
Methyl 5-(4-methoxyphenyl)furan-2-carboxylate, 6n: Furan **1f** (0.5 mmols) is reacted with 4-methoxyphenyl boronic acid; light yellow solid (111.2 mg, 96 % yield) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.72 – 7.66 (m, 2H), 7.21 (d, J = 3.6 Hz, 1H), 6.95 – 6.89 (m, 2H), 6.58 (d, J = 3.6 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 159.89, 158.90, 157.44, 142.55, 126.02, 122.05, 119.92, 113.88, 105.04, 54.94, 51.38.



Methyl 5-(4-chlorophenyl)furan-2-carboxylate, 6o: Furan **1f** (0.5 mmols) is reacted with 4-chlorophenyl boronic acid; white solid (100.5 mg, 85 % yield) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.69 – 7.64 (m, 2H), 7.38 – 7.33 (m, 2H), 7.21 (d, J = 3.7 Hz, 1H), 6.69 (d, J = 3.7 Hz, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 159.03, 156.33, 143.77, 134.75, 129.04, 127.93, 126.01, 119.97, 107.19, 107.18, 51.88.

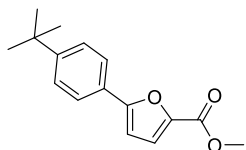


Methyl 5-(p-tolyl)furan-2-carboxylate, 6p: Furan **1f** (0.5 mmols) is reacted with p-tolyl boronic acid; white solid (102.5 mg, 95 % yield) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.66 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 3.6 Hz, 1H), 7.20 (d, J = 8.5 Hz, 2H), 6.66 (d, J = 3.6 Hz, 1H), 3.90 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 159.03, 156.33, 143.77, 134.75, 129.04, 127.93, 126.01, 119.97, 107.19, 107.18, 51.88.

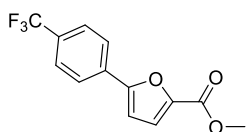


Methyl 5-(o-tolyl)furan-2-carboxylate, 6q: Furan **1f** (0.5 mmols) is reacted with o-tolyl boronic acid; white solid (95.8 mg, 90 % yield) purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.78 – 7.70 (m, 1H), 7.27 (td, J = 4.4, 3.9, 2.4 Hz, 4H), 6.63 (d, J = 3.6 Hz, 1H), 3.92 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-

d) δ 159.29, 157.41, 143.27, 135.56, 131.29, 128.97, 128.86, 127.96, 126.13, 119.59, 110.27, 51.84, 21.72.



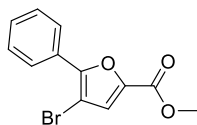
Methyl 5-(4-(tert-butyl)phenyl)furan-2-carboxylate, 6r: Furan **1f** (0.5 mmols) is reacted with 4-tert-butylphenyl boronic acid; clear oily solid (119.7 mg, 93 % yield) purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.74 – 7.69 (m, 2H), 7.46 – 7.41 (m, 2H), 7.24 (d, J = 3.5 Hz, 1H), 6.69 (d, J = 3.6 Hz, 1H), 3.91 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 159.28, 157.87, 152.26, 143.27, 126.77, 125.74, 125.74, 124.66, 120.12, 106.30, 51.80, 34.77, 31.18.



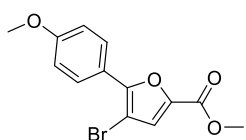
Methyl 5-(4-(trifluoromethyl)phenyl)furan-2-carboxylate, 6s: Furan **1f** (0.5 mmols) is reacted with 4-trifluoromethylphenyl boronic acid; white solid (128.2 mg, 95 % yield) purified by gravity column chromatography (silica gel) in 98:2 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.87 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 3.7 Hz, 1H), 6.83 (d, J = 3.7 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 158.97, 155.72, 144.45, 132.58, 132.57, 130.63, 125.87, 125.84, 125.81, 125.78, 124.98, 124.89, 122.82, 119.83, 108.52, 51.99.

4.5.1 Synthesis of brominated C5 aryl furans:

Refer to section 3.3.2 for reaction conditions. Minor modifications include a change in reaction temperature from 50 °C rather than 60 °C.

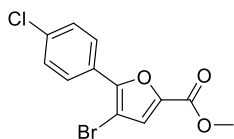


Methyl 4-bromo-5-phenylfuran-2-carboxylate, 7k: Ethyl 5-phenylfuran-2-carboxylate **6m** (0.4 mmol) is reacted for 1 h; white solid (109.2, 87 % yield) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 8.03 (d, J = 7.2 Hz, 2H), 7.46 – 7.35 (m, 3H), 7.23 (s, 1H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 158.31, 152.36, 142.67, 129.38, 128.60, 128.52, 126.37, 123.21, 97.09, 52.11.

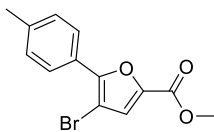


Methyl 4-bromo-5-(4-methoxyphenyl)furan-2-carboxylate, 7l: Methyl 5-(4-methoxyphenyl)furan-2-carboxylate **6n** (0.4 mmol) is reacted for 15

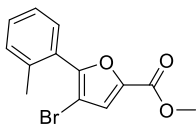
minutes (119 mg, 96 % yield) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.94 (d, J = 9.0 Hz, 2H), 7.19 (s, 1H), 6.92 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 160.38, 158.47, 153.08, 141.96, 127.98, 123.32, 121.22, 114.00, 95.54, 55.27, 52.04.



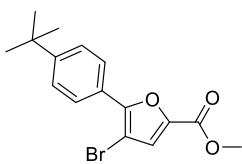
Methyl 4-bromo-5-(4-chlorophenyl)furan-2-carboxylate, 7m: Methyl 5-(4-chlorophenyl)furan-2-carboxylate **6o** (0.4 mmols) is reacted for 3 h; white solid (80.2 mg, 64 % yield) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.91 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.17 (s, 1H), 3.87 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 158.12, 151.13, 151.12, 142.78, 135.28, 131.48, 128.83, 128.81, 127.47, 127.44, 127.41, 127.39, 126.90, 123.12, 123.10, 97.44, 52.17.



Methyl 4-bromo-5-(p-tolyl)furan-2-carboxylate, 7n: Methyl 5-(p-tolyl)furan-2-carboxylate **6p** (0.4 mmols) is reacted for 30 min; white solid (94.3 mg, 80 % yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.94 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 3H), 3.91 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 158.44, 142.36, 139.64, 129.30, 126.38, 125.80, 123.27, 96.45, 52.09, 21.45.



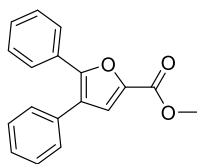
Methyl 4-bromo-5-(o-tolyl)furan-2-carboxylate, 7o: Methyl 5-(o-tolyl)furan-2-carboxylate **6q** (0.4 mmol) is reacted for 1 h; white solid (95.6 mg, 82 % yield)) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.49 (dd, J = 7.5, 1.5 Hz, 1H), 7.36 (td, J = 7.5, 1.5 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.26 (d, J = 0.9 Hz, 1H), 3.91 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 158.45, 154.92, 143.39, 138.11, 130.74, 130.39, 130.11, 127.52, 125.56, 121.82, 99.38, 52.13, 20.29.



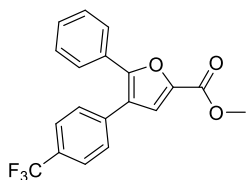
Methyl 4-bromo-5-(4-(tert-butyl)phenyl)furan-2-carboxylate, 7p: Methyl 5-(4-(tert-butyl)phenyl)furan-2-carboxylate **6r** (0.45 mmol) is reacted for 45 min; white oily solid (114.3 mg, 85 % yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 8.05 – 7.90 (m, 2H), 7.51 – 7.39 (m, 2H), 7.25 (s, 1H), 3.91 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 158.44, 152.73, 152.72, 142.43, 126.22, 125.78, 125.56, 123.25, 96.52, 52.08, 34.85, 31.14.

4.5.2 Synthesis of di-arylated furans:

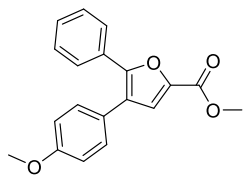
Refer to section 3.3.3 for reaction conditions. Minor modifications include the use of methanol rather than ethanol for the solvent, and 50 °C rather than 60 °C as the reaction temperature.



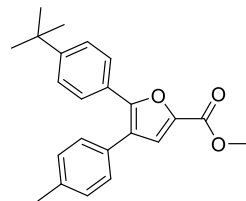
Methyl 4,5-diphenylfuran-2-carboxylate, 8i: Methyl 4-bromo-5-phenylfuran-2-carboxylate **7k** (0.1 mmol) is reacted with phenylboronic acid; white solid (25.6 mg, 92 % yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.63 – 7.59 (m, 2H), 7.42 – 7.35 (m, 5H), 7.34 – 7.30 (m, 4H), 3.94 (s, 3H). ¹³C NMR (125 MHz, Chloroform-*d*) δ 159.26, 152.25, 142.82, 132.93, 129.84, 128.87, 128.81, 128.65, 128.50, 127.78, 127.03, 124.19, 121.56, 51.95.



Methyl 5-phenyl-4-(4-(trifluoromethyl)phenyl)furan-2-carboxylate, 8j: Methyl 4-bromo-5-phenylfuran-2-carboxylate **7k** (0.30 mmol) is reacted with phenylboronic acid for 50 min; white solid (96.5 mg, 93 % yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 8.8 Hz, 2H), 7.58 – 7.55 (m, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.37 – 7.33 (m, 3H), 3.94 (s, 3H). ¹³C NMR (125 MHz, Chloroform-*d*) δ 159.05, 152.89, 143.27, 136.66, 129.95, 129.34, 129.33, 128.86, 128.70, 127.20, 125.80, 125.77, 122.69, 120.93, 120.92, 52.06, 52.04.

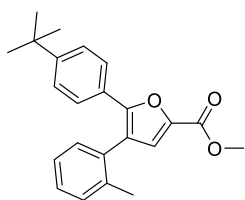


Methyl 4-(4-methoxyphenyl)-5-phenylfuran-2-carboxylate, 8k: Methyl 4-bromo-5-phenylfuran-2-carboxylate **7k** (0.1 mmol) is reacted with 4-methoxyphenyl boronic acid for 90 min; white solid (27.2 mg, 88 % yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.63 – 7.59 (m, 2H), 7.33 – 7.29 (m, 5H), 6.93 – 6.89 (m, 2H), 3.93 (s, 3H), 3.84 (s, 3H). ¹³C NMR (125 MHz, Chloroform-*d*) δ 159.29, 159.24, 151.90, 142.66, 130.00, 129.80, 128.72, 128.47, 128.45, 126.91, 125.13, 123.89, 121.65, 114.24, 55.28, 51.92.



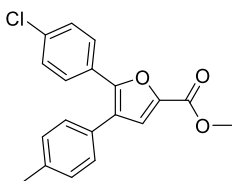
Methyl 5-(4-(tert-butyl)phenyl)-4-(p-tolyl)furan-2-carboxylate, 8l: Methyl 4-bromo-5-(4-(tert-butyl)phenyl)furan-2-carboxylate **7p** (0.3 mmol) is reacted with p-tolyl boronic acid for 80 min; clear oil (92.2 mg,

89 % yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform- d) δ 7.57 – 7.53 (m, 2H), 7.34 – 7.27 (m, 5H), 7.19 (m, 2H), 3.92 (s, 3H), 2.39 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, Chloroform- d) δ 159.33, 152.31, 151.97, 142.41, 137.45, 130.13, 129.46, 129.45, 128.55, 127.15, 126.56, 125.39, 123.68, 121.76, 51.86, 34.73, 31.16, 21.25.



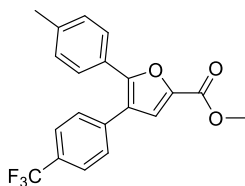
Methyl 5-(4-(tert-butyl)phenyl)-4-(o-tolyl)furan-2-carboxylate, 8m:

Methyl 4-bromo-5-(4-(tert-butyl)phenyl)furan-2-carboxylate **7p** (0.1 mmol) is reacted with o-tolyl boronic acid for 80 min; clear oil (31.5 mg, 90 % yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform- d) δ 7.42 – 7.39 (m, 2H), 7.34 – 7.28 (m, 2H), 7.27 – 7.22 (m, 3H), 7.17 (s, 1H), 3.93 (s, 3H), 2.14 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (125 MHz, Chloroform- d) δ 159.36, 152.43, 151.74, 142.10, 136.89, 132.94, 130.40, 130.16, 128.25, 127.18, 126.22, 125.47, 125.40, 122.70, 122.45, 51.87, 34.67, 31.11, 20.06.



Methyl 5-(4-chlorophenyl)-4-(p-tolyl)furan-2-carboxylate, 8n:

Methyl 4-bromo-5-(4-chlorophenyl)furan-2-carboxylate **7k** (0.3 mmol) is reacted with p-tolyl boronic acid for 80 min; clear oily solid (84.8 mg, 87 % yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform- d) δ 7.56 – 7.52 (m, 2H), 7.29 – 7.23 (m, 5H), 7.21 – 7.17 (m, 2H), 3.93 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, Chloroform- d) δ 150.84, 142.89, 137.86, 134.64, 129.62, 129.59, 128.75, 128.45, 128.40, 128.14, 124.61, 121.64, 51.97, 21.25.



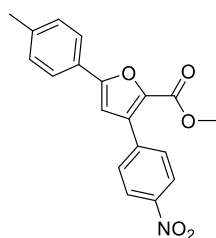
Methyl 5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)furan-2-carboxylate, 8o:

Methyl 4-bromo-5-(p-tolyl)furan-2-carboxylate **7n** (0.3 mmol) is reacted with 4-trifluoromethylphenyl boronic acid for 80 min; oily solid (107.1 mg, 99 % yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform- d) δ 7.62 (d, J = 7.8 Hz, 2H), 7.50 (d, J = 7.7 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.32 (s, 1H), 7.15 (d, J = 7.7 Hz, 2H), 3.94 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, Chloroform- d) δ 159.17, 153.30, 142.95, 139.59, 136.81, 129.40, 128.83, 127.15, 126.51, 125.75, 122.15, 120.98, 115.50, 52.03, 21.37.

4.5.3 General procedure for the synthesis of C3 arylated furans:

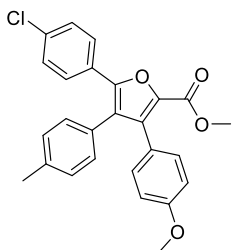
Arylated-furan esters is dissolved in mL dry THF [1.5 M] in a flame dried round bottom flask under argon, placed in a bath at -20 °C (dry ice and ethylene glycol) and sealed with a rubber septum. 1.3 equiv. of 1 M TMPMgCl LiCl is added dropwise. The solution is left to react for 20 minutes, after which the septum is opened under a stream of argon and crushed I₂ pellets (2 equiv.) are added as a powder. The reaction is left for 60 minutes, after which it is quenched with methanol (while remaining at -20 °C). The crude mixture is diluted with EtOAc and water. The aqueous layer is extracted 2 more times with EtOAc. The combined organic layers and washed with brine, dried with sodium sulfate and evaporated under reduced pressure. The crude mixture is resuspended in about 10 mL of hexanes/EtOAc (1:1) and filtered through a silica plug to remove a brown residue.

The crude mixture is then evaporated under reduced pressure, and then dissolved in a 10:2:1 mixture of methanol, water, and acetone [0.02 M] in a round bottom flask and heated at 50 °C in a silicon oil bath on a hot plate. The boronic acid coupling partner (2.5 equiv.) is added to the solution, and when both reagents are fully dissolved, K₂CO₃ (2 equiv.) and PdCl₂ (0.1 equiv.) are added. The reaction is done open to air, and can be tracked by TLC (9:1 hexanes/EtOAc), the product spot being only slightly below the starting material. Once complete, the reaction is cooled and transferred to a separatory funnel and diluted with water and EtOAc. The aqueous layer is extracted 2 more times with approximately EtOAc. The combined organic layers are washed with brine, dried with sodium sulfate and the solvent is evaporated under reduced pressure. The crude is purified by gravity column chromatography (silica gel, 98:2 hexanes/ethyl acetate) to afford C3 arylated furan esters.

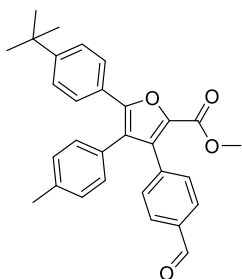


Methyl 3-(4-nitrophenyl)-5-(p-tolyl)furan-2-carboxylate, 11c: Methyl 5-(p-tolyl)furan-2-carboxylate **6p** (0.3 mmol) is first iodinated and then reacted with 4-nitrophenyl boronic acid; yellow solid (83.1 mg, 82% yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ¹H NMR (500 MHz, Chloroform-d) δ 8.38 – 8.34

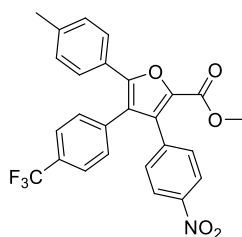
(m, 2H), 8.30 – 8.25 (m, 2H), 7.83 – 7.75 (m, 4H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.25 (m, 2H), 6.82 (s, 1H), 3.88 (s, 3H), 2.40 (s, 3H). ¹³C NMR (125 MHz, Chloroform-d) δ 159.26, 156.87, 148.05, 147.53, 144.96, 139.80, 138.82, 138.06, 134.42, 130.24, 129.67, 128.32, 126.09, 124.94, 124.37, 123.28, 108.12, 51.91, 51.90, 21.44.



Methyl 5-(4-chlorophenyl)-3-(4-methoxyphenyl)-4-(p-tolyl)furan-2-carboxylate, 9j: Methyl 5-(4-chlorophenyl)-4-(p-tolyl)furan-2-carboxylate **8n** (0.3 mmol) is first iodinated and then reacted with 4-methoxyphenyl boronic acid; white solid (98.5 mg, 76% yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform- d) δ 7.49 – 7.44 (m, 2H), 7.27 – 7.22 (m, 2H), 7.14 – 7.09 (m, 2H), 7.09 – 7.05 (m, 2H), 6.99 – 6.95 (m, 2H), 6.81 – 6.77 (m, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, Chloroform- d) δ 159.61, 159.12, 150.28, 138.19, 137.50, 136.28, 134.45, 131.43, 130.13, 129.46, 128.67, 128.61, 128.36, 127.95, 125.32, 122.93, 113.07, 55.09, 55.08, 51.69, 51.68, 21.29.



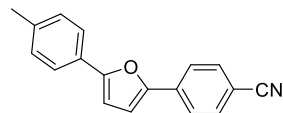
Methyl 5-(4-(tert-butyl)phenyl)-3-(4-formylphenyl)-4-phenylfuran-2-carboxylate, 9k: Methyl 5-(4-(tert-butyl)phenyl)-4-(p-tolyl)furan-2-carboxylate **8l** (0.3 mmol) is first iodinated and then reacted with 4-benzaldehyde boronic acid; white solid (96.9 mg, 72 % yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (300 MHz, Chloroform- d) δ 9.98 (s, 1H), 7.81 – 7.74 (m, 2H), 7.49 (d, J = 8.7 Hz, 2H), 7.41 – 7.28 (m, 4H), 7.11 – 7.03 (m, 2H), 6.98 (d, J = 8.1 Hz, 2H), 3.82 (s, 3H), 2.33 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, Chloroform- d) δ 192.03, 159.40, 152.09, 152.06, 138.02, 137.93, 137.57, 135.36, 135.26, 130.95, 130.15, 129.46, 128.91, 128.41, 126.69, 126.36, 125.43, 124.08, 51.73, 34.73, 31.13, 21.27.



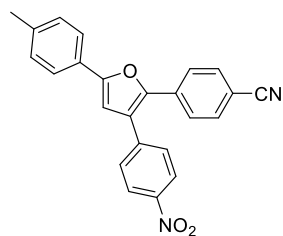
Methyl 3-(4-nitrophenyl)-5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)furan-2-carboxylate, 9l: Methyl 5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)furan-2-carboxylate, **8o** (0.1 mmol) is first iodinated and then reacted with 4-benzaldehyde boronic acid; white solid (66 % yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate.

4.5.4 Synthesis of C2 arylated furans:

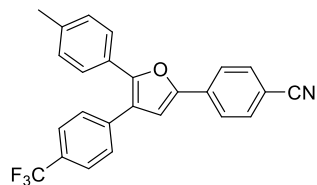
Refer to section 3.3.4 for reaction conditions.



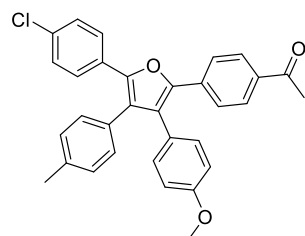
4-(5-(p-tolyl)furan-2-yl)benzonitrile, D1C: Methyl 5-(p-tolyl)furan-2-carboxylate **6p** (0.1 mmol) is first saponified and then reacted with 4-bromobenzonitrile; yellow solid (19.5 mg, 75 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.79 (d, J = 8.6 Hz, 2H), 7.72 – 7.61 (m, 4H), 7.23 (dd, J = 8.6, 0.8 Hz, 2H), 6.89 (d, J = 3.5 Hz, 1H), 6.72 (d, J = 3.5 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 155.36, 150.83, 138.14, 134.59, 132.59, 129.52, 127.42, 124.01, 123.66, 119.07, 110.48, 109.88, 106.96, 21.35.



4-(3-(4-nitrophenyl)-5-(p-tolyl)furan-2-yl)benzonitrile T1C: Methyl 3-(4-nitrophenyl)-5-(p-tolyl)furan-2-carboxylate **11c** (0.1 mmol) is first saponified and then reacted with 4-bromobenzonitrile; red/orange solid (32.2 mg, 85 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.29 (d, J = 8.8 Hz, 2H), 7.70 – 7.59 (m, 8H), 7.27 (d, J = 6.3 Hz, 2H), 6.80 (s, 1H), 2.41 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 155.08, 147.35, 146.25, 140.55, 138.83, 134.35, 132.49, 129.66, 129.43, 126.68, 126.17, 125.31, 124.30, 124.16, 118.64, 111.04, 108.48, 29.69, 21.40.

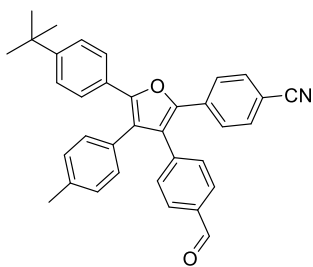


4-(5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)furan-2-yl)benzonitrile, T2C: Methyl 5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)furan-2-carboxylate **8o** (0.1 mmol) is first saponified and then reacted with 4-bromobenzonitrile; white solid (31.2 mg, 77 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.82 – 7.78 (m, 2H), 7.70 – 7.66 (m, 2H), 7.66 – 7.62 (m, 2H), 7.55 (dd, J = 8.7, 0.8 Hz, 2H), 7.48 – 7.44 (m, 2H), 7.18 (dd, J = 8.7, 0.8 Hz, 2H), 6.96 (s, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 150.66, 150.64, 150.62, 138.85, 137.45, 134.06, 132.66, 129.64, 129.45, 129.38, 128.79, 127.16, 126.59, 125.76, 125.73, 125.70, 125.67, 125.23, 123.85, 123.06, 122.86, 118.92, 111.70, 110.48, 21.36.



1-(4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-4-(p-tolyl)furan-2-yl)phenyl)ethan-1-one, 10h: Methyl 5-(4-chlorophenyl)-3-(4-methoxyphenyl)-4-(p-tolyl)furan-2-carboxylate **9j** (0.1 mmol) is first

saponified and then reacted with 4-bromoacetophenone; yellow/green oily solid (33.9 mg, 70 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.88 – 7.83 (m, 2H), 7.61 – 7.56 (m, 2H), 7.48 – 7.43 (m, 2H), 7.27 – 7.22 (m, 2H), 7.07 (dd, *J* = 8.5, 2.9 Hz, 4H), 7.04 – 7.00 (m, 2H), 6.85 – 6.79 (m, 2H), 3.81 (s, 3H), 2.57 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 197.37, 159.01, 147.61, 146.64, 137.16, 135.24, 135.10, 133.31, 131.28, 130.01, 129.35, 129.33, 129.14, 128.63, 128.54, 127.34, 127.10, 126.05, 125.26, 124.64, 114.08, 55.14, 26.52, 21.28.

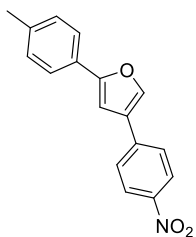


4-(5-(4-(tert-butyl)phenyl)-3-(4-formylphenyl)-4-(p-tolyl)furan-2-yl)benzonitrile, 10i: Methyl 5-(4-(tert-butyl)phenyl)-3-(4-formylphenyl)-4-phenylfuran-2-carboxylate **9k** (0.1 mmol) is first saponified and then reacted with 4-bromobenzonitrile; yellow solid (32.1 mg, 64 % yield over 2 steps) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H

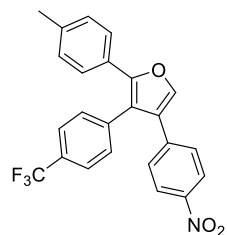
NMR (500 MHz, Chloroform-*d*) δ 10.00 (s, 1H), 7.83 – 7.78 (m, 2H), 7.54 (s, 4H), 7.49 – 7.43 (m, 2H), 7.36 – 7.30 (m, 4H), 7.09 – 7.04 (m, 2H), 7.04 – 6.99 (m, 2H), 2.34 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 191.78, 151.29, 149.81, 145.53, 139.33, 137.40, 135.45, 134.53, 132.32, 130.84, 130.07, 129.98, 129.42, 128.93, 127.24, 126.93, 125.75, 125.65, 125.46, 124.60, 118.84, 110.38, 34.69, 31.17, 21.28.

4.5.5 Protodecarboxylation of C2 arylated furan carboxylic acids:

Refer to section 4.4.6 for reaction conditions.



4-(4-nitrophenyl)-2-(p-tolyl)furan, D2C: Methyl 3-(4-nitrophenyl)-5-(p-tolyl)furan-2-carboxylate, **11c** (0.05 mmol) is first saponified and then protodecarboxylated; yellow solid (11.4 mg, 82 % yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform-*d*) δ 8.28 – 8.23 (m, 2H), 7.86 (s, 1H), 7.70 – 7.65 (m, 2H), 7.64 – 7.60 (m, 2H), 7.24 (d, *J* = 7.7 Hz, 2H), 6.93 (s, 1H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 156.12, 146.57, 139.19, 138.14, 129.51, 127.35, 126.58, 126.06, 124.32, 123.98, 102.58, 29.69.



4-(4-nitrophenyl)-2-(p-tolyl)-3-(4-(trifluoromethyl)phenyl)furan, T3C:

Methyl 3-(4-nitrophenyl)-5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl) furan-2-carboxylate, **9I** (0.05 mmol) is first saponified and then protodecarboxylated; yellow solid (14.4 mg, 66 % yield) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate.

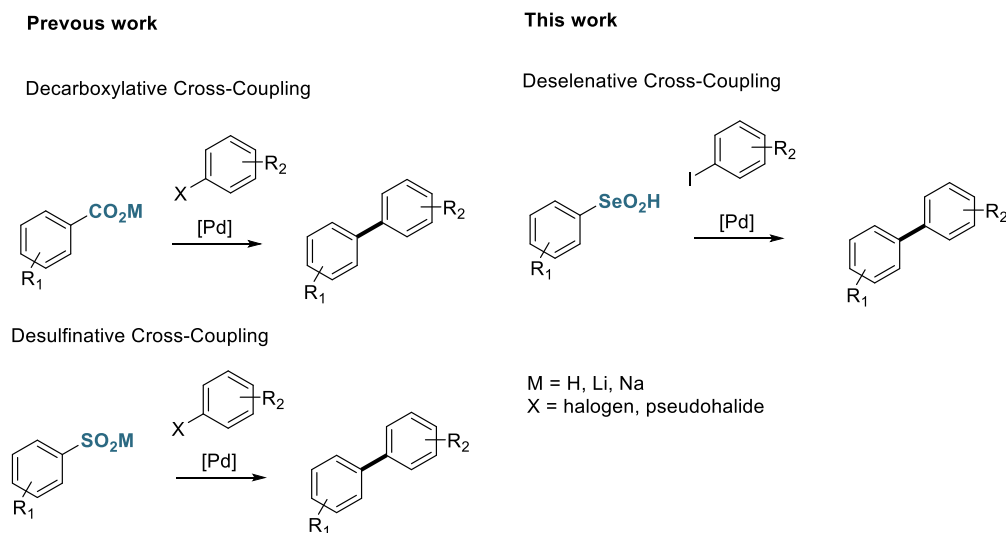
^1H NMR (500 MHz, Chloroform-*d*) δ 7.75 – 7.65 (m, 4H), 7.57 (d, J = 8.1 Hz, 2H), 7.45 (s, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.21 – 7.18 (m, 2H), 7.13 (d, J = 7.9 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 148.00, 144.43, 144.26, 142.37, 140.54, 139.31, 136.33, 132.37, 131.72, 130.88, 130.65, 130.64, 130.54, 126.71, 125.36, 124.85, 31.01.

Chapter 5: Pd-Catalyzed Deselenative Cross-Coupling for the Synthesis of Bi-Aryls with Un-Activated Benzene Seleninic Acid

5.1 Introduction

Pd-catalyzed cross-coupling reactions are generally the standard for the formation of sp^2 - sp^2 carbon-carbon bonds. While classical methods for Pd-catalyzed cross-coupling reactions have been extensively developed and have become widely used, these reaction have some drawbacks, such as the use of a stoichiometric amount of organometallic reagent. More recently, alternative methodologies, summarized in Scheme 40, have emerged that forego organometallic reagents.

The decarboxylative cross-coupling reaction is a robust alternative that utilizes ubiquitous carboxylic acids or carboxylate salts as a nucleophilic coupling partner. ^{109,113,114,120,223,298,299} Importantly, recent advances have been made that reduce the necessity for an activated aryl carboxylic acid coupling partner (i.e. with an electron withdrawing or donating group substitution) in the formation of biphenyls, although this facet remains necessary to obtain good yields. ^{120,299}



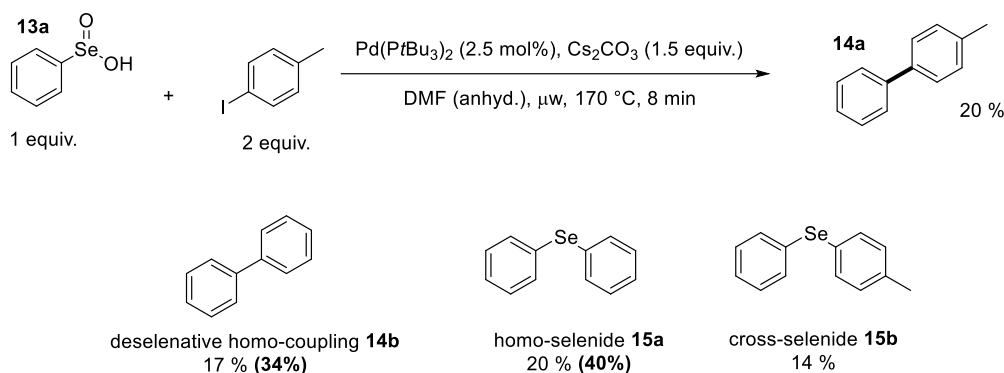
Scheme 40: Decarboxylative, desulfinate and deselenative cross-coupling

Comparatively, the desulfinate cross-coupling, while less extensively developed, produces much better yields on un-activated substrates.^{126,127,133,300} The disadvantage of sulfonates, however, involves the need for specialized reagents for their synthesis^{301,302} and their sometimes challenging purification.¹³⁶ Additionally, as is often the case with the decarboxylative cross-coupling, the desulfinate cross-coupling reaction is quite air- and moisture-sensitive.

Herein we propose an alternative route to bi-aryl synthesis – a first generation deselenative cross-coupling reaction that is both good yielding on un-activated substrates and practical in application. This reaction (summarized in Scheme 40) can be conducted in relatively milder conditions, uses a relatively green solvent (DMSO) and is highly tolerant of air and moisture. Organoselenides have previously been used as the electrophilic coupling partner in cross-coupling Suzuki-Miyaura, Kumada-Corriu, Negishi and Sonogoshira reactions.³⁰³ To the best of our knowledge, however, this is the first report of a seleninic acid being used as the nucleophilic coupling partner in a cross-coupling reaction.

5.2 Results and discussion

The initial conditions for deselenative cross-coupling were taken from conditions previously developed for decarboxylative cross-coupling,¹⁶⁶ as similar conditions have been shown to yield some coupling product for the desulfinate cross-coupling of un-activated arenes as well.¹²⁶ The results, summarized in Scheme 41, indicate that cross-coupling is possible with a seleninic acid coupling partner (**14a**, 20% yield), although several other by-products are also formed during the course of the reaction.

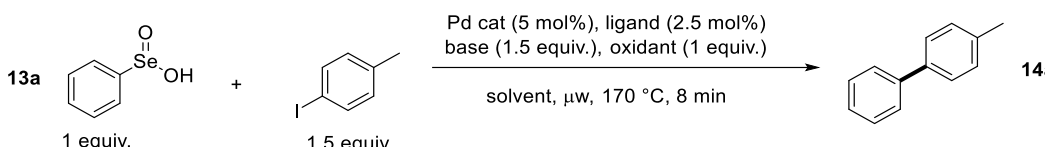


Scheme 41: Starting conditions for the deselenative cross-coupling and major by-products

Deselenative homocoupling (**14b**) and homo-selenide formation (**15a**) were the major contributors to the consumption of the limiting reagent, with a 17% and 20% yield, respectively (the yields in bold for the deselenative homo-coupling and homo-selenide represent the yield with respect to consumption of the limiting reagent, the benzene seleninic acid). A minor by-product was another selenide (**15b**), this one a cross-coupling with the iodotoluene. Some homo-coupling of the iodotoluene also occurs, but as much iodotoluene was left over in the reaction vessel (it was used in excess), this was not supposed to affect product formation.

A series of control experiments were conducted prior to optimization to ascertain how these by-products were being formed (see Scheme 55 in the supporting information for Chapter 5). From these experiments, we surmised that all by-product formation is Pd-catalyzed and that benzene seleninic acid (**13a**) is likely being partially reduced *in situ* to the diselenide. Cross-coupling product (**14a**) formation, however, is from the seleninic acid (**13a**) and not from the diselenide, as no product was observed in the absence of this reagent. Optimization was thus conducted with the congruent dual aims of preventing seleninic acid reduction and mitigating the formation of by-products **14b**, **15a** and **15b**. Results are summarized in Table 12.

Table 12: Optimization of deselenative cross-coupling under microwave irradiation^a

						
entry	base	conditions	Pd cat.	Solvent	[o]	Yield, ^b %
1	Ag ₂ CO ₃	-	Pd(PtBu ₃) ₂	DMF	-	29
2	KOtBu	-	Pd(PtBu ₃) ₂	DMF	-	10
3	AgNO ₃	-	Pd(PtBu ₃) ₂	DMF	-	10
4	AgOTf	-	Pd(PtBu ₃) ₂	DMF	-	7
5	none	-	Pd(PtBu ₃) ₂	DMF	-	nd
6	Ag ₂ CO ₃	Under argon atmosphere	Pd(PtBu ₃) ₂	DMF	-	>5
7	Ag ₂ CO ₃	Solvent saturated with Ar	Pd(PtBu ₃) ₂	DMF	-	nd
8	Ag ₂ CO ₃	Under O ₂ atmosphere	Pd(PtBu ₃) ₂	DMF	-	16
9	Ag ₂ CO ₃	Solvent saturated with O ₂	Pd(PtBu ₃) ₂	DMF	-	8

10	Ag ₂ CO ₃	Under dry air atmosphere	Pd(PtBu ₃) ₂	DMF	-	36
11	Ag ₂ CO ₃	Anhydrous solvent	Pd(PtBu ₃) ₂	DMA	-	27
12	Ag ₂ CO ₃	Anhydrous solvent	Pd(PtBu ₃) ₂	DMSO	-	24
13	Ag ₂ CO ₃	Undried solvent	Pd(PtBu ₃) ₂	DMSO	-	25
14	Ag ₂ CO ₃	Anhydrous solvent	Pd(PtBu ₃) ₂	NMP	-	13
15	Ag ₂ CO ₃	Anhydrous solvent	Pd(PtBu ₃) ₂	Cyrene	-	12
16	Ag ₂ CO ₃	Undried solvent	Pd(PtBu ₃) ₂	DMF	-	>5
17	Ag ₂ CO ₃	Undried solvent	Pd(PPh ₃) ₄	DMSO	-	17
18	Ag ₂ CO ₃	Undried solvent	PdCl ₂ , JohnPhos	DMSO	-	> 5
19	Ag ₂ CO ₃	Undried solvent	PdCl ₂ , MePhos	DMSO	-	> 5
20	Ag ₂ CO ₃	Undried solvent	PdCl ₂ , Phen	DMSO	-	> 5
21	Ag ₂ CO ₃	Undried solvent	PdCl ₂ , RuPhos	DMSO	-	> 5
22	Ag ₂ CO ₃	Undried solvent	PdCl ₂ , PoTol	DMSO	-	33
23	Ag ₂ CO ₃	Undried solvent	Pd(OAc) ₂ , PoTol ₃	DMSO	-	22
24	Ag ₂ CO ₃	Undried solvent	PdCl ₂ , PoTol ₃	DMSO	I ₂	21
25	Ag ₂ CO ₃	Undried solvent	PdCl ₂ , PoTol ₃	DMSO	H ₂ O ₂ (aq)	46
26	Ag ₂ CO ₃	Undried solvent	PdCl ₂ , PoTol ₃	DMSO	MCPBA	> 5

^aBenzene seleninic acid (0.1 mmol), iodotoluene (0.15 mmol), base (1.5 mmol), Pd source (5 mol%), dissolved with solvent in a 2 mL conical microwave sealed with a rubber septum and aluminium cap.

^bDetermined by GCMS with TMB as an internal standard.

The first condition screened was the base used for this reaction. It was found that changing the base from Cs₂CO₃ to Ag₂CO₃ improved the yield of desired product (Table 12, entry 1). Interestingly, other silver sources such as AgNO₃ and AgOTf (entries 3 and 4) showed a marked decrease in yield, indicating that the carbonate base may be of importance.

As most decarboxylative and desulfinate cross-coupling reactions are water sensitive, steps were taken to further exclude moisture. It was found, however, as shown in entry 6, that doing this reaction under argon led to significant decrease in product formation. Additionally, when the solvent was degassed with Ar, no product was observed at all (entry 7). This lead to the presumption that perhaps oxygen was an important part of the reaction mechanism. Accordingly, the reaction was then tried under an O₂ atmosphere (entry 8) and with the solvent saturated with O₂ (entry 9). To our disappointment, adding oxygen to the reaction did not improve the yield, and the homo-selenide (**15a**) was the major product in both cases. Doing the reaction under dried air (entry 10), did produce a slight increase in

yield of desired product to 36%. We can only surmise from these results that a slight, but not overly anaerobic atmosphere is necessary for this reaction to occur.

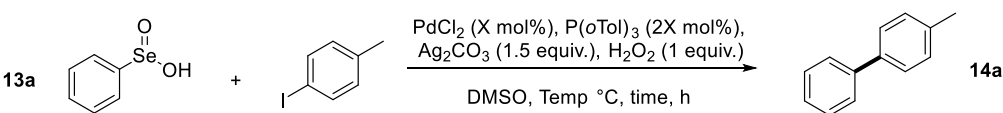
A screening of solvents was then conducted. It was found that the yield of desired product formation was approximately the same with anhydrous DMA and DMSO (entries 11 and 12). A lower yield was obtained with the anhydrous solvents NMP and Cyrene (entries 14 and 15). Interestingly, however, when the reaction was tried with undried DMSO straight from a long opened bottle kept in a regular cabinet, the yield was approximately the same (entry 13). This suggests that the reaction is not as moisture sensitive as previously supposed, since DMSO is known to be quite hygroscopic. To test this, the reaction was done with undried DMF (entry 16). With this solvent, however, the reaction yield plummeted significantly. It would seem from these results, somewhat puzzlingly, that the reaction is moisture sensitive in DMF, but not in DMSO.

Pd sources were screened next, with DMSO (undried) as the solvent, given the significant increase in practicality and safety provided by this option. The yields of **14a** was 17 % with $\text{Pd}(\text{PPh}_3)_4$ (entry 17), however, with almost all other catalyst/ligand combinations screened, there was almost no formation of desired product (entries 18-21). The ligand $\text{P}(\text{oTol})_3$, in combination with PdCl_2 , however, produced a relatively good yield of 33 % (entry 22). While still too low to be viable, this latter yield was encouraging as it further demonstrated that this reaction is feasible under less sensitive conditions (PdCl_2 and $\text{P}(\text{oTol})_3$ are relatively bench stable compared to the Pd zero complex $\text{Pd}(\text{P}^t\text{Bu}_3)_2$). By-product formation, however, remained high for this reaction, and as some of these are suspected to result from the reduction of benzene seleninic acid, additional oxidants were screened. As shown in entries 24-26, H_2O_2 (30% in water) appears to have the best effect on this reaction. One equivalent of H_2O_2 lead to a near elimination of both selenide product formation (**15a** and **15b**).

The formation of desulfinative homo-coupling (**14b**) by-product, however, appears to be independent of the population of diphenyl diselenide and was unaffected by oxidizing conditions. Presumably, this product is formed *via* the transmetallation of two Pd centers after 2 deselenation events, followed by a reductive elimination, As such, we surmised it might be possible to reduce its formation by either lowering catalyst loading, or by lowering the temperature of the reaction (as deselenation/transmetallation is presumably the most

energetic step). In testing lower temperatures, it was decided to continue optimization of this reaction thermally rather than by microwave irradiation. The results of this optimization under thermal conditions are reported in Table 13.

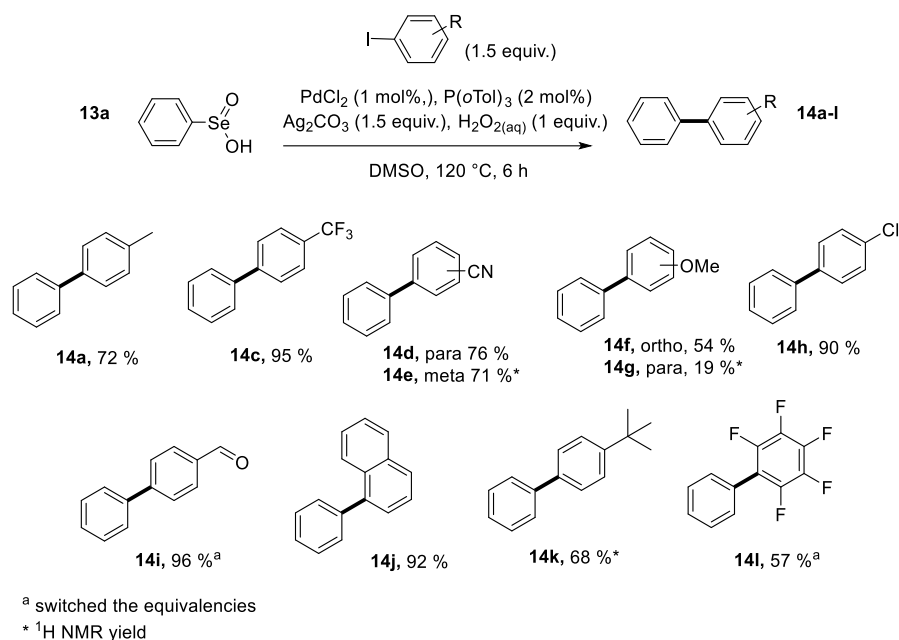
Table 13: Optimization of deselenative cross-coupling under thermal conditions

				
entry	x	T, °C	t, h	yield 2a ^b , %
1	5.0	140	3	55
2	2.5	140	3	63
3	1.0	140	3	65
4	1.0	130	3	68
5	1.0	120	6	75 (72 ^c)
6	1.0	110	6	22
7	1.0	110	24	40

^aBenzene seleninic acid (0.1 mmol), iodotoluene (0.15 mmol), Ag₂CO₃ (0.15 mmol), PdCl₂, P(oTol)₃, and H₂O₂(aq) weighed open to air, dissolved with undried DMSO in a 2 mL conical microwave sealed with a rubber septum and aluminium cap.

^bDetermined by ¹H NMR with TMB as an internal standard.
^c0.4 mmol scale, isolated yield

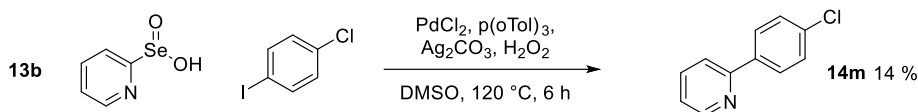
It was found that lowering the catalyst loading to either 2.5 % or 1 % hindered deselenative homo-coupling (**14b**) and increased the yield of our desired product (Table 13, entries 1-3), as did lowering the reaction temperature to 120 °C (a subsequent increase in reaction time to 6 h was also needed for the reaction to go to completion), as shown in entries 4-7, with a final moderate isolated yield of 72 % (entry 5). We surmise that the mechanism of this reaction proceeds in a similar manner to the desulfinative cross-coupling (proposed catalytic cycle in Figure 22 in the supporting information for Chapter 5), however, further mechanistic studies are needed to elucidate the intricacies of this reaction. With these optimized conditions, we proceeded to explore a small scope of aryl iodide coupling partners, as well as aryl seleninic acids, summarized below in Scheme 42.



Scheme 42: Scope of deselenative cross-coupling with benzene seleninic acid

The reaction generally works quite well with electron withdrawing groups on the aryl iodide, with excellent yields for deselenative cross-coupling with iodobenzotrifluoride (**14c**), iodobenzochloride (**14h**), and iodobenzaldehyde (**14i**). The reaction yield was good with iodobenzonitrile, both with the cyano at the *para* and the *meta* position (**14d** and **14e**). With the methoxy group, however, the yields significantly vary, with only a 19 % estimated yield with the OMe at the *para* position (**14g**) and a 54 % yield with the OMe at the *ortho* position (**14f**). The yields are moderate to good with more electron neutral substrates, ranging from 57 to 92 % for substrates **14a**, **14j**, **14k** and **14l**.

With these results in hand, we are looking to investigate the scope of the benzene seleninic acid. A substrate of particular interest is the 2-pyridyl compound, as 2-pyridine boronic acids tends to have poor reactivity due to de-borylation in solution. With the 2-pyridine seleninic acid, we only obtained a 14 % isolated yield of the cross-coupling product (as shown in Scheme 43). However, efforts to re-optimized reactions conditions to better suit this substrate are underway.



Scheme 43: First attempt at deselenative cross-coupling with a pyridine seleninic acid

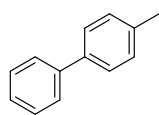
5.3 Conclusion

Biphenyl compounds were synthesized using a new methodology, the deselenative cross-couple reactions, which utilizes benzene seleninic acid as the nucleophilic coupling partner. As with the decarboxylative and desulfonative cross-coupling, this protocol avoids the need for a stoichiometric amount of organometallic reagent. The conditions for this reaction are very practical compared to other protocols, as it isn't air or moisture sensitive, uses a safe solvent, DMSO, and is done under relatively mild conditions (120 °C for 6 h).

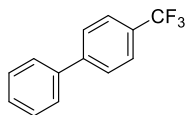
5.4 Experimental section

5.4.1 General procedure for the synthesis of biphenyls 14a-14l

Benzene seleninic acid (0.4 mmols) was mixed with 0.6 mmols of aryl iodide, 0.6 mmols of Ag_2CO_3 , 0.004 mmols of PdCl_2 and 0.008 mmols of P(oTol) and dissolved in DMSO (non-anhydrous) [0.1], after which 0.4 mmols of H_2O_2 (30% aqueous solution) was added. The flask is sealed and heated 120 °C for 6 h. When the reaction is complete, the solution is cooled and diluted with 20 ml of water. The solution is then extracted 3 times with about 10 mL of ethyl acetate. The combined organic extractions are washed 2x with brine, dried with sodium sulfate and evaporated under reduced pressure. The crude mixture is purified by column chromatography with silica gel and 98:2 hexanes/ethyl acetate.

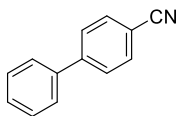


4-methyl-1,1'-biphenyl, 14a: Benzene seleninic acid is reacted with 4-iodotoluene; white solid (48.8 mg, 72% yield) purified by gravity column chromatography (silica gel) in 99:1 hexanes/ethyl acetate. ^1H NMR (300 MHz, Chloroform- d) δ 7.63 – 7.54 (m, 2H), 7.53 – 7.46 (m, 2H), 7.46 – 7.38 (m, 2H), 7.36 – 7.28 (m, 1H), 7.25 (d, J = 7.9 Hz, 2H), 2.40 (s, 3H).

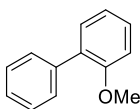


4-(trifluoromethyl)-1,1'-biphenyl, 14c: Benzene seleninic acid is reacted with 4-iodobenzotrifluoride; clear solid (81.5 mg, 95%) purified by gravity

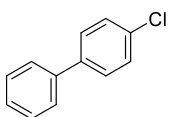
column chromatography (silica gel) in 99:1 hexanes/ethyl acetate. ^1H NMR (300 MHz, Chloroform- d) δ 7.69 (s, 4H), 7.63 – 7.56 (m, 2H), 7.52 – 7.36 (m, 3H).



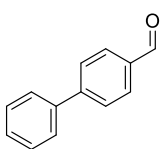
[1,1'-biphenyl]-4-carbonitrile, 14d: Benzene seleninic acid is reacted with 4-iodobenzonitrile; white solid (55.1 mg, 76%) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform- d) δ 7.75 – 7.67 (m, 4H), 7.61 – 7.56 (m, 2H), 7.51 – 7.46 (m, 2H), 7.45 – 7.41 (m, 1H).



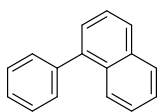
2-methoxy-1,1'-biphenyl, 14f: Benzene seleninic acid is reacted with 2-methoxyiodobenzene; white solid (39.4 mg, 54%) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (300 MHz, Chloroform- d) δ 7.58 – 7.52 (m, 2H), 7.42 (m, 2H), 7.38 – 7.30 (m, 3H), 7.08 – 6.98 (m, 2H), 3.82 (s, 3H).



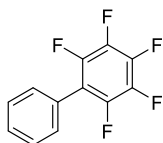
4-chloro-1,1'-biphenyl, 14h: Benzene seleninic acid is reacted with 4-chloriodobenzene; white solid (66.9 mg, 90%) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (300 MHz, Chloroform- d) δ 7.59 – 7.48 (m, 4H), 7.48 – 7.31 (m, 5H).



[1,1'-biphenyl]-4-carbaldehyde, 14i: Benzene seleninic acid is reacted with 4-iodobenzaldehyde; white solid (69.4 mg, 96%) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (300 MHz, Chloroform- d) δ 10.06 (s, 1H), 8.00 – 7.90 (m, 2H), 7.81 – 7.71 (m, 2H), 7.68 – 7.58 (m, 2H), 7.55 – 7.36 (m, 3H).

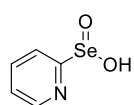


1-phenylnaphthalene, 14j: Benzene seleninic acid is reacted with 1-iodonaphthalene; white solid (75.0 mg, 92 %) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (300 MHz, Chloroform- d) δ 7.91 (m, 3H), 7.61 – 7.36 (m, 9H).



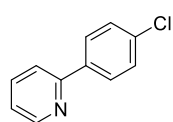
2,3,4,5,6-pentafluoro-1,1'-biphenyl, 14l: Benzene seleninic acid is reacted with 2,3,4,5,6-pentafluoriodobenzene; white solid (55.6, 57%) purified by gravity column chromatography (silica gel) in 97:3 hexanes/ethyl acetate. ^1H NMR (300 MHz, Chloroform- d) δ 7.69 (s, 4H), 7.63 – 7.56 (m, 2H), 7.52 – 7.36 (m, 3H).

5.4.2 Deselenative cross-coupling with pyridine seleninic acid



2-Pyridine seleninic acid, 13b: Iodopyridine is converted to 2-pyridine diselenide following the procedure from (REF) and then to the seleninic acid following the procedure from (REF). Off white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.67 (d, J = 4.0 Hz, 1H), 8.10 (td, J = 7.7, 1.8 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.60 (ddd, J = 7.5, 4.8, 1.3 Hz, 1H).

Coupling with pyridine seleninic acid, conditions same as for biphenyl synthesis, see section 5.4.1

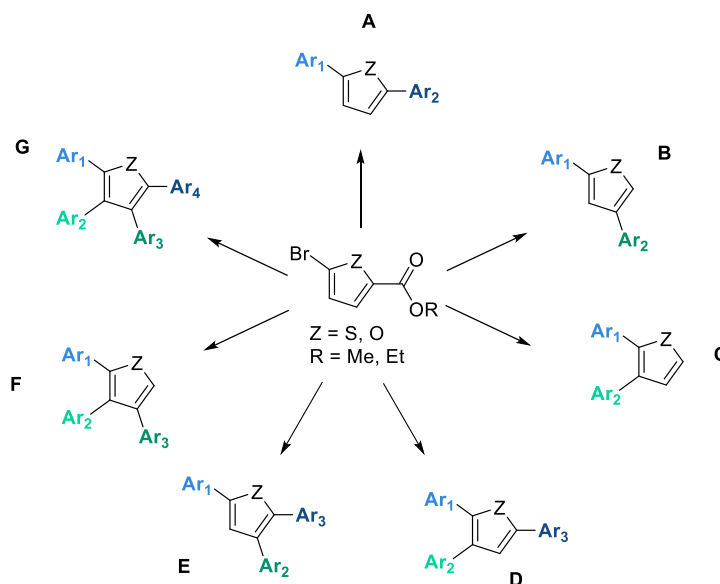


2-(4-chlorophenyl)pyridine, 14m: Pyridine seleninic acid (0.2 mmol) is reacted with 4-chloriodobenzene; white solid (5.3 mg, 14% yield) purified by gravity column chromatography (silica gel) in 95:5 hexanes/ethyl acetate. ^1H NMR (500 MHz, Chloroform- d) δ 8.69 (d, J = 5.0 Hz, 1H), 7.94 (d, J = 8.6 Hz, 2H), 7.79 – 7.73 (m, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 6.0 Hz, 1H).

Chapter 6: Conclusion and Future Work

6.1 Summary of presented work

Herein, we have presented novel methodologies that allow facile access to a wide variety of arylated compounds, with an emphasis on both practicality and environmental sustainability. These types of molecules are privileged structures in medicinal chemistry, as well as within organic semi-conductors, and thus there is great value in optimizing modular routes, particularly those that allow for late-stage functionalization. Green and practical synthetic approaches to access these compounds promotes the exploration of desired properties by facilitating the building of compound libraries.



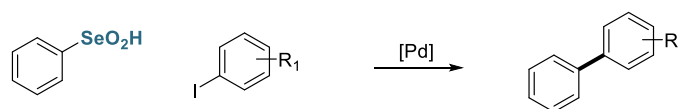
Scheme 44: Accessible structures from commercially available thiophene and furan starting materials

For multi-arylated heteroarene synthesis, simple protocols that begin with the same starting material and utilize the different facets of its carboxylic acid/ester functional group are devised to access various isomers of di-arylated (compounds **A**, **B** and **C**, Scheme 44) and tri-arylated (compounds **D**, **E** and **F**) thiophenes and furans, as well as tetra-arylated (compound **G**) thiophenes and furans. These approaches entail a combination of site

selective halogenations, Pd-catalyzed Suzuki-Miyaura cross-couplings, Pd-catalyzed decarboxylative cross-couplings, and Ag-catalyzed proto-decarboxylations.

The individual synthetic steps are exceedingly time efficient, generally high yielding, mostly air- and moisture-tolerant, predominately use greener solvents, and boast repetitive catalytic systems. In terms of the tenets of green chemistry, these routes emphasize minimizing waste (limited purification steps), atom economy (limited heavy metal use), benign solvents (mostly aqueous conditions, alcohols or DMSO is used), energy efficiency, reduced derivatization, and a predominant use of catalysis.

For biphenyl synthesis, a first generation deselenative cross-coupling is reported that allows for Pd-catalyzed cross-couplings with aryl iodides. This protocol minimizes organic metallic reagents used, and can be done under relatively mild conditions (undried DMSO, 120 °C for 6 h), summarized in Scheme 45.



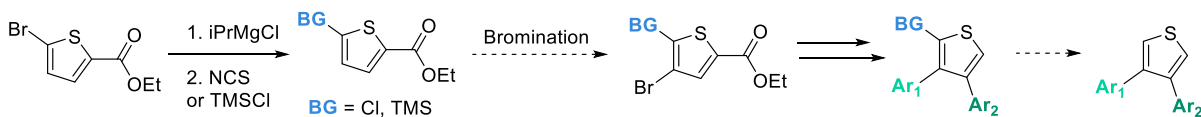
Scheme 45: First general deselenative cross-coupling

Preliminary results also seem to indicate that this reaction can be optimized for 2-pyridine seleninic acid (currently underway), which is encouraging as Suzuki-Miyaura cross-couplings are generally challenging with these substrates.⁹⁴

6.2 Future work

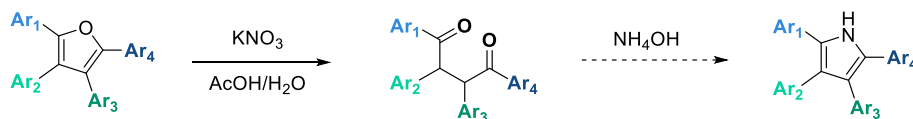
In terms of methodology development to access the various isomers of thiophenes and furans, there are additional avenues to be explored for further modulation of the previously reported routes. Firstly, it may be possible with an altered approach to access the 3,4 isomer of di-arylated thiophene and furan. We have been looking at several options to utilize a blocking group (BG) at C5 that can be removed at the end of the synthetic route (Scheme 46). For this, we have installed both Cl and TMS at the C5 position of thiophene using a magnesium/halogen exchange followed by treatment with an electrophile (NCS or TMSCl). For both options, however, there is an issue with the bromination step. With Cl on the C5 position, the bromination does not seem to proceed (less than 5% yield after 16 h using previously reported conditions). With the TMS on the C5 position, bromination occurs,

but there is a significant loss of the blocking group during the reaction. Future work entails screening for other blocking groups and/or optimizing different bromination conditions.



Scheme 46: Potential access to the 3,4 di-arylated isomer

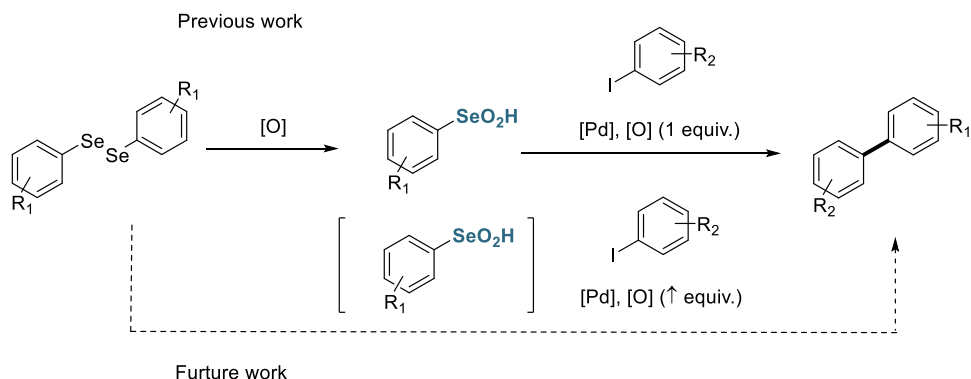
Secondly, as the multi-arylation of thiophene and furan routes go through halogen intermediates at C5, C4 and C3, the possible reactions to substitute these positions are not limited to arylations. Future routes for the project entails the optimizing of alternative substitution, such as olefination (Heck type cross-couplings), alkylation (sp^2 - sp^3 cross-couplings), alkynylation (Sonogoshira cross-couplings), and amination (Buchwald-Hartwig cross-couplings), all of which utilize halogen coupling partners. The carboxylic acid/ester at C2 is also a very versatile handle that can lead to a variety of functional groups, particularly amides, which are very useful for making bioconjugates. Lastly, there are several interesting synthetic routes that can be explored from tetra-arylated furan, which can be opened by oxidative hydrolysis to the 1,4-enedione.³⁰⁴ These compounds are desirable as they exhibit aggregation induced emission, but also, the 1,4-enedione can also be used to make tetra-aryl pyrrole by utilizing a Paal-Knorr ring closing synthesis (as represented in Scheme 47).¹⁵² This way, the stepwise tetra-arylation of pyrrole (which has significantly different reactivity than furan and thiophene and is therefore not accessible through a similar route), can potentially be achieved.



Scheme 47: Potential access to tetra-arylated pyrrole via tetra-arylated furan

For the deselenative cross-coupling, current work is being done screening a variety of substrates. Firstly, a variety of other phenyl-seleninic acids are being synthesized, and the substrate scope of this reaction will be further assessed. Secondly, as previously mentioned, we are optimizing the cross-coupling conditions for use with pyridine seleninic acid. Thirdly,

we are interested in adapting the reaction conditions in order to oxidize the aryl diselenide *in situ* (as shown in Scheme 48).



Scheme 48: Proposed deselenative cross-coupling with aryl diselenides

With this, aryl diselenide could be used directly in the reaction, rather than having to be oxidized to the seleninic acid, the product isolation for which can be challenging. Preliminary results only produced a 7 % estimated yield for the product with increasing equivalents of hydrogen peroxide (up to 4), but we contend it may be possible to further optimize this reaction by screening alternative conditions. This advance would render the novel cross-coupling more easily applicable and facilitate access to a wide range of biphenyls, as the diselenides can be catalytically made from aryl iodides and elemental selenium using CuO ³⁰⁵ or MOF-199.³⁰⁶ And lastly, our group aims to fully investigate the mechanism of this novel cross-coupling reaction.

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Appendices

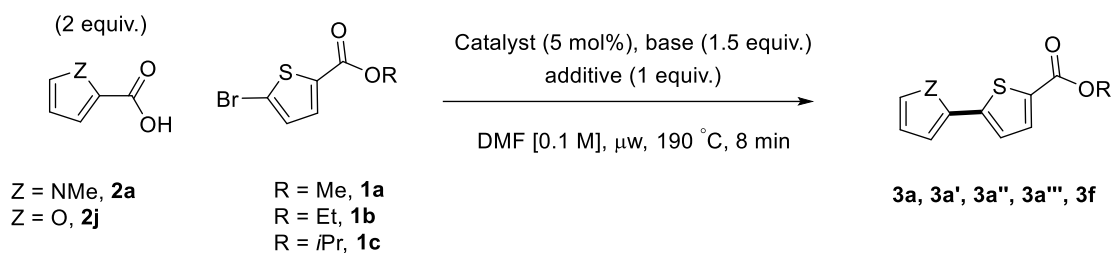
Supporting information for Chapter 2

General Conditions

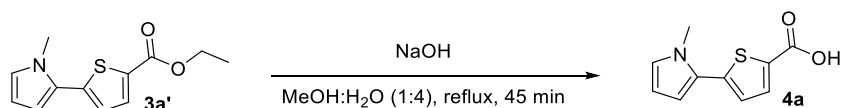
Reactions were carried out in regular glassware under air unless otherwise noted. Commercially available starting materials and reagents were purchased from Sigma-Aldrich and AK Scientific, and used without further purification. Palladium catalysts were stored under inert gas in the freezer at -10 degrees Celsius. All solvents were purchased from Fisher ACP chemicals and Sigma-Aldrich as ACS grade. Dimethylformamide (DMF) was dried using activated 3 Å molecular sieves and stored in an oven-dried Schlenk flask under argon atmosphere. Distilled water was obtained from an in-house distillery. Compounds were purified using column chromatography on silica-gel (Zeoprep 60 Eco, 40 – 63 µm, Zeochem AG). Microwave-assisted reactions were carried out using the Biotage Initiator™ 2.3 build 6250 microwave system with a 400 W magnetron. ¹H and ¹³C NMR data were measured on a Varian VNMR-500. High-resolution mass spectral data (HRMS) were collected using a LC-TOF ESI mass spectrometer operated in positive ion mode. UV/Vis was performed using an Agilent Technologies Cary 5000 Spectrophotometer, range 2500-320 nm, averaging time 0.033 s, data interval 1 nm, no source changeover, detector & grating changeover at 800 nm. Fluorescence spectra were acquired using a Cary Eclipse fluorescence spectrophotometer (Agilent Technologies). Spectra were acquired in a 1 cm quartz cuvette at λ_{ex} = 360–660 nm (5 nm intervals). The excitation and emission slits were set to a width of 5 nm with a PMT voltage at 600 V. All data were processed using Cary Eclipse software. Yield determination using ¹H NMR was done using trimethoxybenzene (TMB) as an internal standard.

Full optimization table for initial decarboxylative cross-coupling

Table 14: Initial optimization for decarboxylative coupling with aryl halide ester



Entry	Z	Catalyst	R	base	Additive	Yield [%]
1*	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Me	Cs_2CO_3	$n\text{Bu}_4\text{NCl}$	32 ^[a]
2* ⁱ	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Me	Cs_2CO_3	$n\text{Bu}_4\text{NCl}$	28 ^[a]
3* ⁱⁱ	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Me	Cs_2CO_3	$n\text{Bu}_4\text{NCl}$	15 ^[a]
4	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Me	Cs_2CO_3	$n\text{Bu}_4\text{NCl}$	35 ^[a]
5**	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Me	Cs_2CO_3	$n\text{Bu}_4\text{NCl}$	31 ^[a]
6	NMe	$\text{PdCl}_2, \text{HBF}_4\text{P}t\text{Bu}_3$	Me	Cs_2CO_3	$n\text{Bu}_4\text{NCl}$	30 ^[a]
7	NMe	$\text{PdCl}_2, \text{JohnPhos}$	Me	Cs_2CO_3	$n\text{Bu}_4\text{NCl}$	28 ^[a]
8	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Me	Ag_2CO_3	$n\text{Bu}_4\text{NCl}$	40 ^[a]
9	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Me	Cu_2CO_3	$n\text{Bu}_4\text{NCl}$	7 ^[a]
10	NMe	$\text{PdCl}_2, \text{AsPh}_3$	Me	Cu_2CO_3	$n\text{Bu}_4\text{NCl}$	20 ^[a]
11	O	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Me	Cs_2CO_3	-	31 ^[a]
12	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Me	Cs_2CO_3	$n\text{Bu}_4\text{NCl}$	30 ^[a]
13	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Et	Cs_2CO_3	$n\text{Bu}_4\text{NCl}$	27 ^[a]
14	O	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Et	Cs_2CO_3	-	41 ^[a]
15	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	iPr	Cs_2CO_3	$n\text{Bu}_4\text{NCl}$	35 ^[a]
16	O	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	iPr	Cs_2CO_3	-	21 ^[a]
17	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Me	Cs_2CO_3	-	48 ^[a] , 37 ^[b]
18	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Et	Cs_2CO_3	-	68 ^[a]
19	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	iPr	Cs_2CO_3	-	50 ^[a]
20	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Et	KOH	-	91 ^[a] , 88 ^[b]
21	O	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Et	KOH	-	28
22	NMe	$\text{Pd}(\text{P}t\text{Bu}_3)_2$	Et	Na_2CO_3	-	60 ^[a]



Scheme 50: Saponification of compound 3a'

Crude ^1H NMR of **4a** after acid/base extraction in CDCl_3 (300 MHz)

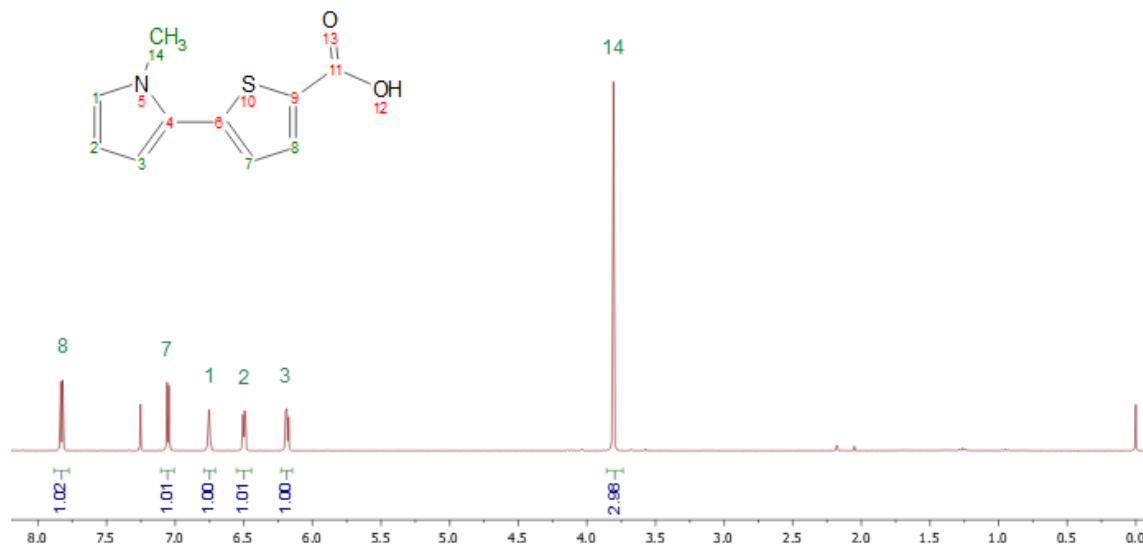
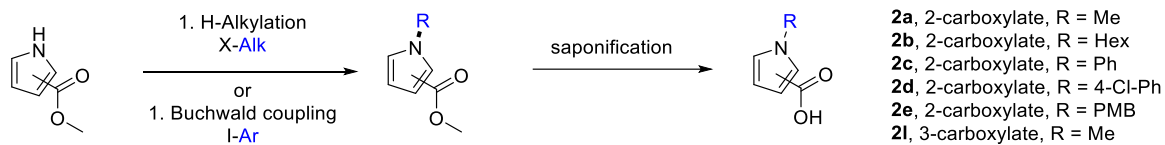


Figure 17: crude reaction after acid/base work up

Experimental Procedures and preparation of compounds

Eight of the starting materials (**2a-e**, **2h**, **2i**, **2k**, and **2l**) in Table 3 were synthesized (**2f**, **2g**, and **2j** were purchased).

Preparation of carboxylic acid starting materials



Scheme 51: Synthesis of pyrrole carboxylic acid starting materials

1-methyl-1H-pyrrole-2-carboxylic acid (2a): To an oven dried flask, 16 mmols of NaH was added to 15 ml of anhydrous DMF and the reaction was cooled to 0 °C. Under argon, 8 mmols of methyl 1H-pyrrole-2-carboxylate dissolved in 5 mL of anhydrous DMF was added dropwise. The reaction was brought up to room temperature and stirred for 30 minutes. The reaction was cooled to 0 °C once again and 10 mmols of iodomethane was added dropwise under argon. The reaction was brought up to room temperature and stirred for 4 hours, then quenched with 5 ml of aqueous NaHCO₃. The reaction mixture is then diluted with 50 mL of water. The aqueous phase is extracted 3x with 30 mL of ethyl acetate. The combined organic layers are then washed with 1x saturated NaHCO₃ (aq) and 1x saturated NaCl, dried with Na₂SO₄ and evaporated under reduced pressure (do not put this products under high vacuum, it is quite volatile) the product was purified by flash column chromatography in 9:1 hexanes: EtOAc, then saponified in a 25 mL of NaOH_(aq) [1.2 M] by heating under reflux for 45-60 minutes, yielding 1-methyl-1H-pyrrole-2-carboxylic acid as a grey solid (780 mg, 78 % yield over 2 steps). **¹H NMR (500 MHz, DMSO-d₆)** δ 12.12 (s, 1H), 7.03 (dd, *J* = 2.5, 1.9 Hz, 1H), 6.78 (dd, *J* = 3.9, 1.9 Hz, 1H), 6.05 (dd, *J* = 3.9, 2.5 Hz, 1H), 3.83 (s, 3H).

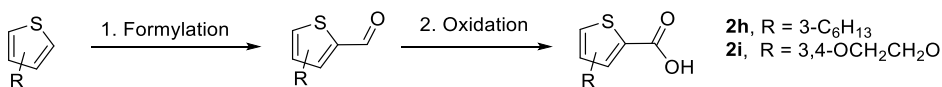
1-hexyl-1H-pyrrole-2-carboxylic acid (2b): To an oven dried flask, 1.6 mmols of NaH was added to 1.5 ml of anhydrous DMF and the reaction was cooled to 0 °C. Under argon, 0.8 mmols of methyl 1H-pyrrole-2-carboxylate dissolved in 0.5 mL of anhydrous DMF was added dropwise. The reaction was brought up to room temperature and stirred for 30 minutes. The reaction was cooled to 0 °C once again and 1 mmol of bromohexane was added dropwise under argon. The reaction was brought up to room temperature and stirred for 4 hours, then quenched with 1 ml of aqueous NaHCO₃. The reaction mixture is then diluted with 5 mL of water. The aqueous phase is extracted 3x with 3 mL of ethyl acetate. The combined organic layers are then washed with 1x saturated NaHCO₃ (aq) and 1x saturated NaCl, dried with Na₂SO₄ and evaporated under reduced pressure. The product is purified by flash column chromatography in 9:1 hexanes: EtOAc, then saponified in a 2.5 mL of NaOH_(aq) [1.2 M], by heating under reflux for 45-60 minutes, yielding 1-hexyl-1H-pyrrole-2-carboxylic acid as a black oil (103.5 mg, 66 % yield over two steps). **¹H NMR (300 MHz, CDCl₃)** δ 7.10 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.89 (dd, *J* = 2.5, 1.8 Hz, 1H), 6.15 (dd, *J* = 4.0, 2.5 Hz, 1H), 4.29 (t, *J* = 7.3 Hz, 2H), 1.77 (t, *J* = 10.4 Hz, 2H), 1.37 – 1.23 (m, 6H), 0.93 – 0.83 (m, 3H).

1-phenyl-1H-pyrrole-2-carboxylic acid (2c): Methyl 1-phenyl-1H-pyrrole-2-carboxylate is synthesized from methyl 1H-pyrrole-2-carboxylate (8 mmol) and iodobenzene according to Buchwald's protocol.²²² The product is purified by flash column chromatography in 9:1 hexanes: EtOAc, then saponified in a 25 mL of NaOH_(aq) [1.2 M], by heating under reflux for 45-60 minutes, yielding 1-(4-methoxybenzyl)-1H-pyrrole-2-carboxylic acid as a white solid (987 mg, 66 % yield over two steps). ¹H NMR (300 MHz, DMSO-d₆) δ 12.15 (s, 1H), 7.50 – 7.26 (m, 5H), 7.16 (dd, *J* = 2.7, 1.8 Hz, 1H), 6.98 (dd, *J* = 3.8, 1.8, 1H), 6.28 (dd, *J* = 3.8, 2.7 Hz, 1H).

1-(4-methoxybenzyl)-1H-pyrrole-2-carboxylic acid (2d): To an oven dried flask, 1.6 mmols of NaH was added to 1.5 ml of anhydrous DMF and the reaction was cooled to 0 °C. Under argon, 0.8 mmols of methyl 1H-pyrrole-2-carboxylate dissolved in 0.5 mL of anhydrous DMF was added dropwise. The reaction was brought up to room temperature and stirred for 30 minutes. The reaction was cooled to 0 °C once again and 1 mmol of PMBCl was added dropwise under argon. The reaction was brought up to room temperature and stirred for 4 hours, then quenched with 1 ml of aqueous NaHCO₃. The reaction mixture is then diluted with 5 mL of water. The aqueous phase is extracted 3x with 3 mL of ethyl acetate. The combined organic layers are then washed with 1x saturated NaHCO₃ (aq) and 1x saturated NaCl, dried with Na₂SO₄ and evaporated under reduced pressure. The product is purified by flash column chromatography in 9:1 hexanes: EtOAc, then saponified in a 2.5 mL of NaOH_(aq) [1.2 M], by heating under reflux for 45-60 minutes, yielding 1-(4-methoxybenzyl)-1H-pyrrole-2-carboxylic acid as a grey solid (164 mg, 89 % yield over two steps). ¹H NMR (300 MHz, CDCl₃) δ 7.13 (dd, *J* = 4.0, 1.8 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.90 (dd, *J* = 2.6, 1.8 Hz, 1H), 6.87 – 6.81 (m, 2H), 6.18 (dd, *J* = 4.0, 2.6 Hz, 1H), 5.47 (s, 2H), 3.77

1-(4-chlorophenyl)-1H-pyrrole-2-carboxylic acid (2e): Methyl 1-(4-chlorophenyl)-1H-pyrrole-2-carboxylate is synthesized from methyl 1H-pyrrole-2-carboxylate (8 mmol) and iodobenzene according to Buchwald's protocol.²²² The product is purified by flash column chromatography in 9:1 hexanes: EtOAc, then saponified in a 2.5 mL of NaOH_(aq) [1.2 M], by heating under reflux for 45-60 minutes, yielding 1-(4-methoxybenzyl)-1H-pyrrole-2-carboxylic acid as a white solid (973 mg, 52 % yield over two steps). ¹H NMR (300 MHz, CDCl₃) δ 7.53 (d, *J* = 3.9 Hz, 1H), 7.43 – 7.32 (m, 2H), 7.25 – 7.14 (m, 2H), 6.88 (dd, *J* = 2.8, 1.7 Hz, 1H), 6.58 (dd, *J* = 3.7, 1.7 Hz, 1H), 6.47 (d, *J* = 3.9 Hz, 1H), 6.34 (dd, *J* = 3.7, 2.8 Hz, 1H).

1-methyl-1H-pyrrole-3-carboxylic acid (2l): To an oven dried flask, 1 mmol of NaH was added to 1 ml of anhydrous DMF and the reaction was cooled to 0 °C. Under argon, 0.5 mmols of methyl 1H-pyrrole-3-carboxylate dissolved in 0.5 mL of anhydrous DMF was added dropwise. The reaction was brought up to room temperature and stirred for 30 minutes. The reaction was cooled to 0 °C once again and 0.6 mmols of iodomethane were added dropwise under argon. The reaction was brought up to room temperature and stirred for 1 hour, then quenched with 1 ml of aqueous NaHCO₃. The reaction mixture is then diluted with 5 mL of water. The aqueous phase is extracted 3x with 5 mL of diethyl ether. The combined organic layers are then washed with 1x saturated NaHCO₃ (aq) and 1x saturated NaCl, dried with Na₂SO₄ and evaporated under reduced pressure (do not put this products under high vacuum, it is quite volatile) the product was purified by flash column chromatography in 9:1 hexanes: EtOAc, then saponified in a 3 mL of NaOH_(aq) [1.2 M] by heating under reflux for 45 minutes, yielding 1-methyl-1H-pyrrole-3-carboxylic acid as a white solid (115 mg, 92 % yield over 2 steps). **¹H NMR (300 MHz, DMSO-d₆)** δ 11.69 (s, 1H), 7.37 (app. t, *J* = 2.5, 2.0 Hz, 1H), 6.78 (app. t, *J* = 2.5 Hz, 1H), 6.40 (dd, *J* = 2.8, 1.7 Hz, 1H), 3.69 (s, 3H).



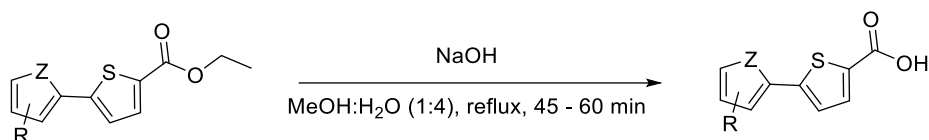
Scheme 52: General Scheme for the synthesis of thiophene carboxylic acid starting materials 2h and 2i

3-hexylthiophene-2-carboxylic acid (2h): Synthesized from 3-hexylthiophene (8 mmol) according to a previous protocol developed in the Forgione lab,²²³ yielding 3-hexylthiophene-2-carboxylic acid as a white powder (752 mg, 44 % yield over 2 steps). **¹H NMR (500 MHz, CDCl₃)** δ 12.01 (s, 1H), 7.49 (d, *J* = 5.0 Hz, 1H), 6.99 (d, *J* = 5.0 Hz, 1H), 3.10 – 2.95 (m, 2H), 1.70 – 1.58 (m, 2H), 1.41 – 1.32 (m, 2H), 1.36 – 1.24 (m, 4H), 0.97 – 0.83 (m, 3H).

2,3-dihydrothieno[3,4-b][1,4]dioxine-5-carboxylic acid (2i): Synthesized from 2,3-dihydrothieno[3,4-b][1,4]dioxine (8 mmol) according to a previous protocol developed in the Forgione lab²²³, yielding 2,3-dihydrothieno[3,4-b][1,4]dioxine-5-carboxylic acid as a white powder (260 mg, 14 % yield over 2 steps). **¹H NMR (500 MHz, DMSO-d₆)** δ 6.92 (s, 1H), 4.30 – 4.17 (m, 4H).

5-(hydroxymethyl)furan-2-carboxylic acid (2k): Synthesized from 5-(hydroxymethyl)furan-2-carbaldehyde (8 mmol) according to a previous protocol developed in the Forgione lab,²²⁴ yielding 5-(hydroxymethyl)furan-2-carboxylic acid as a yellow solid (556.6 mg, 98% yield) ¹H NMR (500 MHz, DMSO-d₆): δ 12.94 (bs, 1H), 7.15 (d, *J* = 3.4 Hz, 1H), 6.46 (d, *J* = 3.4 Hz, 1H), 5.45 (bs, 1H), 4.44 (s, 2H).

Saponification of arylated thiophene esters



Scheme 53: General Scheme for the saponification of bi-aryl esters

General Procedure for the saponification of bi-aryl esters: Bi-aryl ethyl esters (0.2 mmol) are dissolved in MeOH (1 mL) and mixed with an aqueous solution of NaOH_(aq) [1.2 M] (4 mL) and heated under reflux for 45-60 minutes. The reaction mixture is evaporated under reduced pressure (to remove methanol). The aqueous solution is extracted once with EtOAc to remove impurities. The solution is then acidified to a pH of 2 with aqueous HCl. The product is extracted 2x with EtOAc. The combined organic layers are washed with saturated NaCl_(aq), dried with Na₂SO₄ and evaporated under reduced pressure.

5-(1-phenyl-1H-pyrrol-2-yl)thiophene-2-carboxylic acid (4a): Following the procedure for the saponification of bi-aryl esters, ethyl 5-(1-phenyl-1H-pyrrol-2-yl)thiophene-2-carboxylate (0.5 mmol) is heated under reflux in 4:1 H₂O-MeOH for 60 min to afford 5-(1-phenyl-1H-pyrrol-2-yl)thiophene-2-carboxylic acid as a light brown solid (132.5 mg, 99 % yield). **R_f:** 0.25 (5:5 hexanes-EtOAc) **¹H NMR (500 MHz, DMSO d-6):** δ 12.95 (s, 1H), 7.50-7.47 (m, 4H), 7.34-7.31 (m, 1H), 7.10 (m, 1H), 6.69-6.68 (d, *J* = 3.9 Hz, 1H), 6.67-6.66 (dd, *J* = 3.7, 1.7 Hz, 1H), 6.32-6.31 (dd, *J* = 3.7, 2.8 Hz, 1 H) **¹³C NMR (125 MHz, DMSO d-6):** δ 162.8, 141.0, 139.0, 133.3, 131.8, 129.5, 128.3, 126.8, 126.5, 126.3, 124.7, 112.0, 109.7 **HRMS (ESI):** calculated for C₁₅H₁₂O₂NS¹⁺ = 270.05833, found = 270.05828 **UV-Vis:** λ_{max} = 301 nm

5-(1-methyl-1H-pyrrol-2-yl)thiophene-2-carboxylic acid (4b): Following the procedure for the saponification of bi-aryl esters, ethyl 5-(1-methyl-1H-pyrrol-2-yl)thiophene-2-carboxylate (0.5 mmol) is heated under reflux in 4:1 H₂O-MeOH for 45 min to afford 5-(1-methyl-1H-pyrrol-2-yl)thiophene-2-carboxylic acid as a greenish brown solid (98.4 mg, 95 % yield). **R_f:**

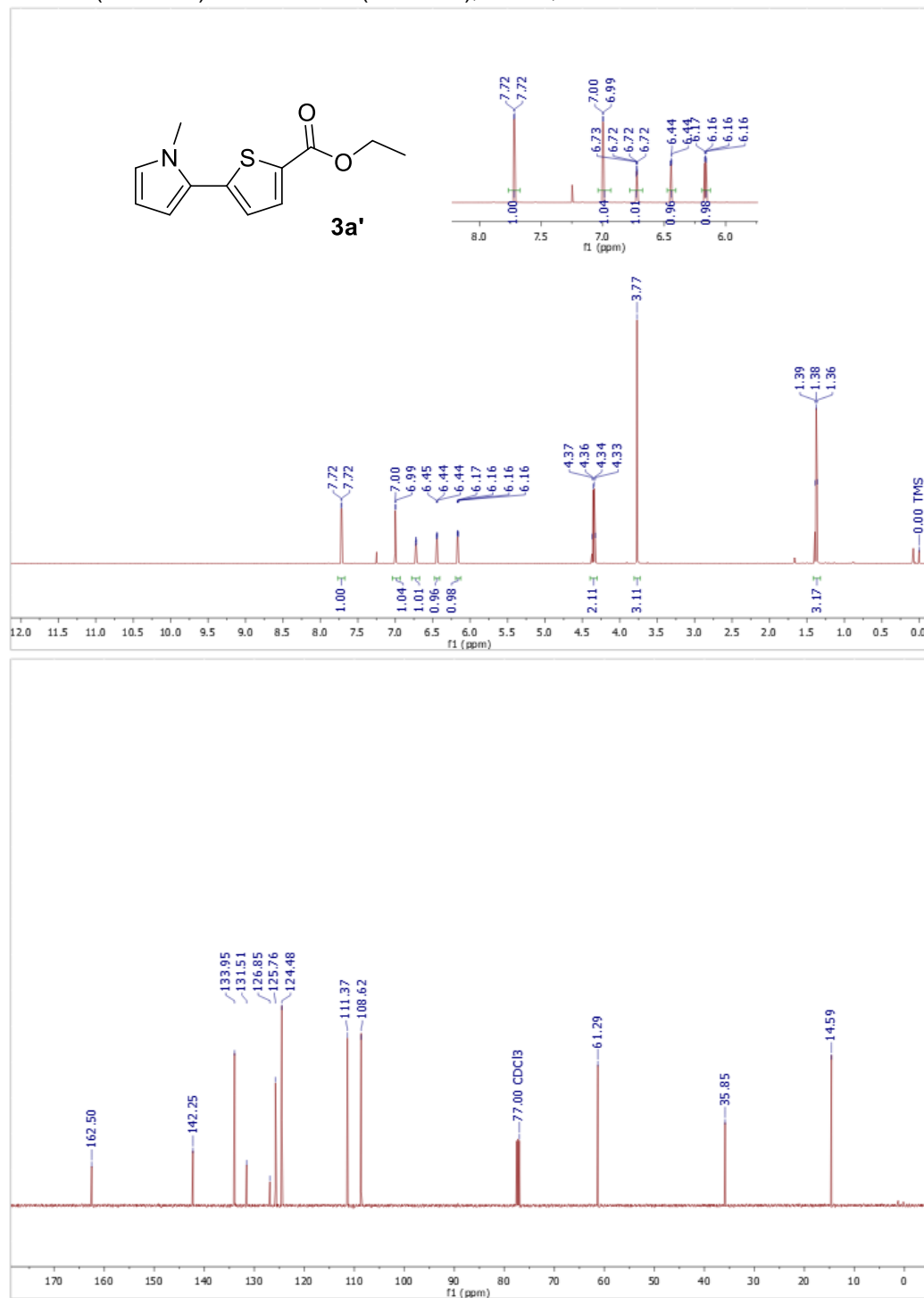
0.20 (5:5 hexanes-EtOAc) **¹H NMR (500 MHz, CDCl₃)**: δ = 7.83-7.82 (d, *J* = 3.9, 1H); 7.05 (d, *J* = 3.9, 1H), 6.76-6.75 (dd, *J* = 2.6, 1.9, 1H), 6.50-6.49 (dd, *J* = 3.7, 1.9, 1H), 6.19-6.18 (dd, *J* = 3.7, 2.6, 1H), 3.80 (3H, s) **¹³C NMR (125 MHz, CDCl₃)**: δ 167.6, 144.0, 135.5, 129.8, 126.5, 126.0, 124.4, 111.6, 108.6, 35.8 **HRMS (ESI)**: calculated for C₁₀H₁₁O₂NS¹⁺ = 208.04273, found = 208.05833 **UV-Vis**: λ_{max} = 317 nm

3'-methyl-[2,2'-bithiophene]-5-carboxylic acid (4c): Following the procedure for the saponification of bi-aryl esters, ethyl-3'-methyl-[2,2'-bithiophene]-5-carboxylate (2a) (0.5 mmol) is heated under reflux in 4:1 H₂O-MeOH for 45 min to afford 3'-methyl-[2,2'-bithiophene]-5-carboxylic acid as a bright yellow solid (108.5 mg, 97 % yield). **R_f**: 0.22 (5:5 hexanes-EtOAc) **¹H NMR (500 MHz, DMSO d-6)**: δ 13.17 (s, 1H), 7.71-7.70 (d, *J* = 3.9 Hz, 1H), 7.54-7.53 (d, *J* = 5.4 Hz, 1H), 7.26-7.25 (d, *J* = 3.9 Hz, 1H), 7.04-7.03 (d, *J* = 5.4 Hz, 1H), 2.38 (s, 3H) **¹³C NMR (125 MHz, DMSO d-6)**: δ 163.1, 142.9, 136.0, 134.3, 133.6, 129.8, 126.4, 126.1, 15.8 **HRMS (ESI)**: calculated for C₁₀H₈O₂S₂¹⁺ = 225.00385, found = 225.00391 **UV-Vis**: λ_{max} = 296 nm

Spectroscopic Data

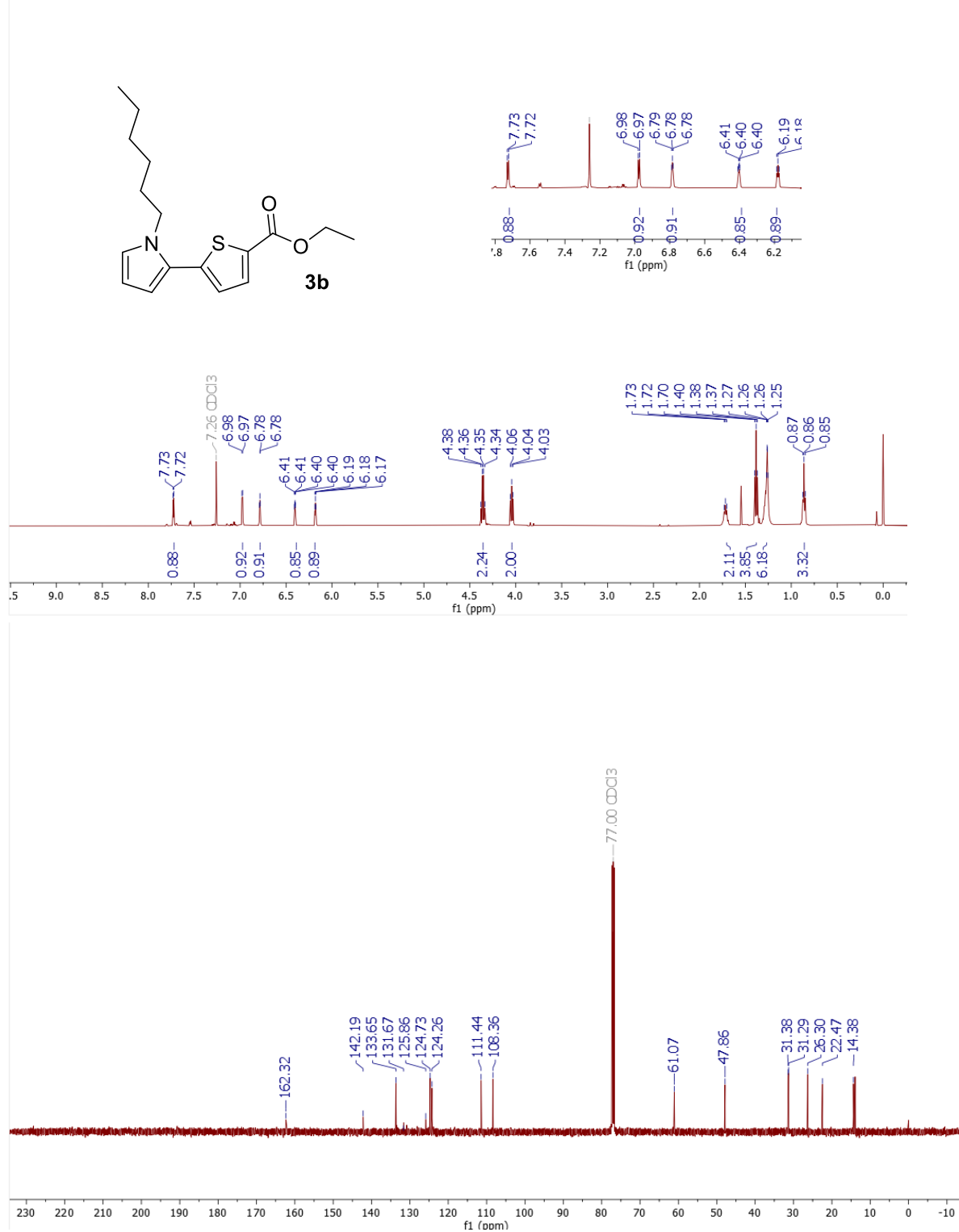
Ethyl 5-(1-methyl-1H-pyrrol-2-yl)thiophene-2-carboxylate (**3a'**)

¹H NMR (500 MHz) and ¹³C NMR (125 MHz), CDCl₃,



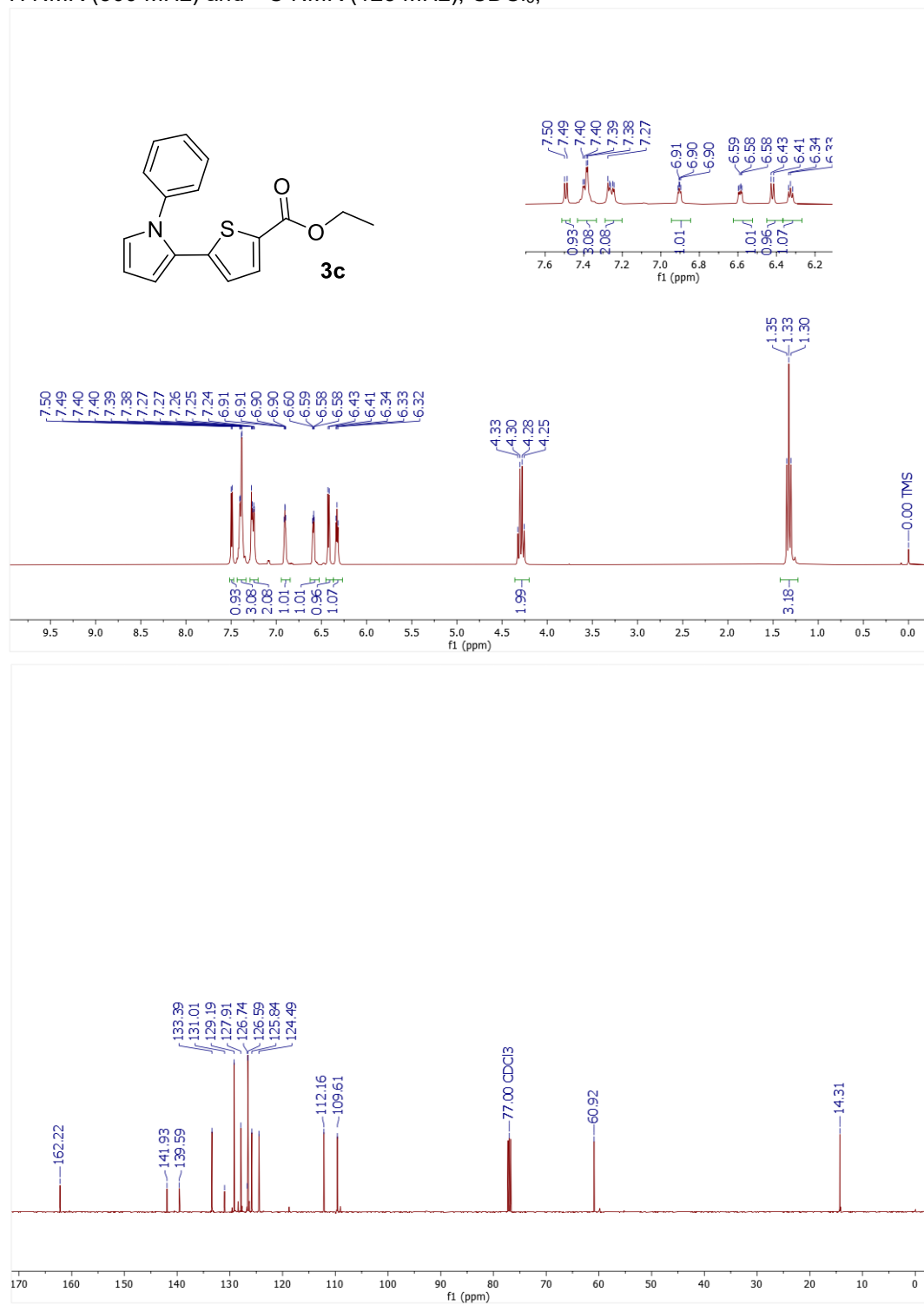
Ethyl 5-(1-hexyl-1H-pyrrol-2-yl)thiophene-2-carboxylate (3b)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3 ,



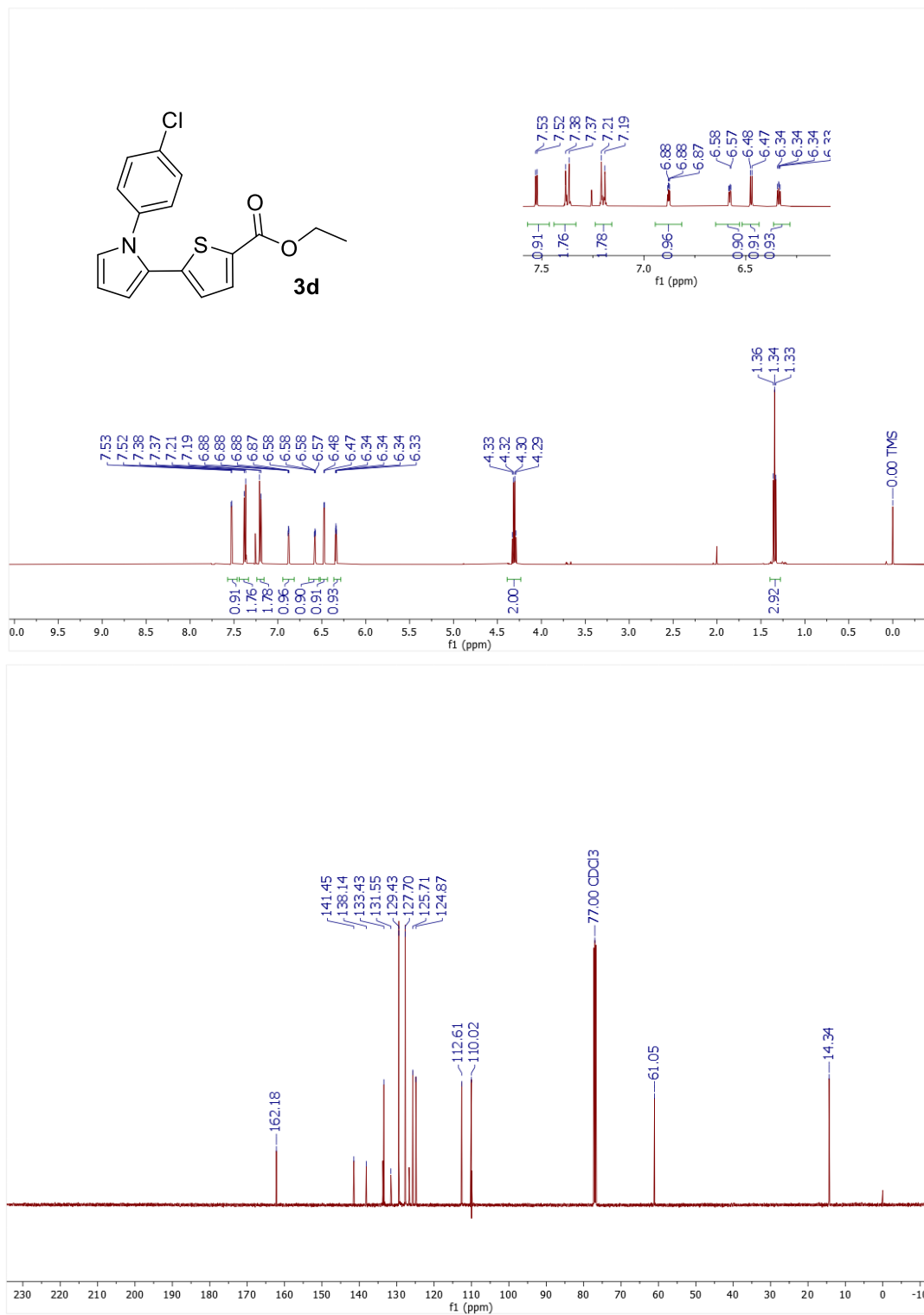
Ethyl 5-(1-phenyl-1H-pyrrol-2-yl)thiophene-2-carboxylate (3c)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3 ,



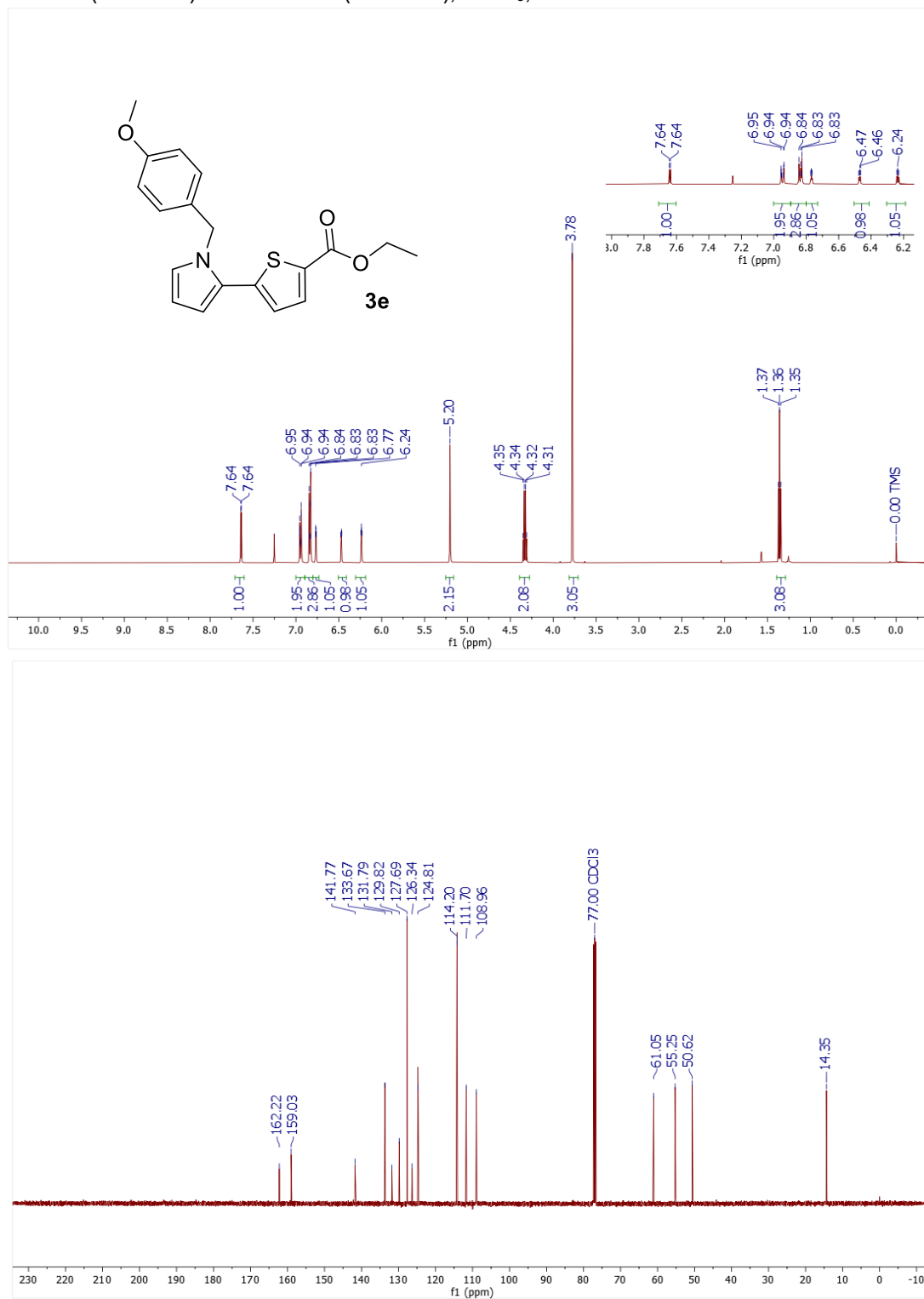
Ethyl 5-(1-(4-chlorophenyl)-1H-pyrrol-2-yl)thiophene-2-carboxylate (3d)

¹H NMR (500 MHz) and ¹³C NMR (125 MHz), CDCl₃,



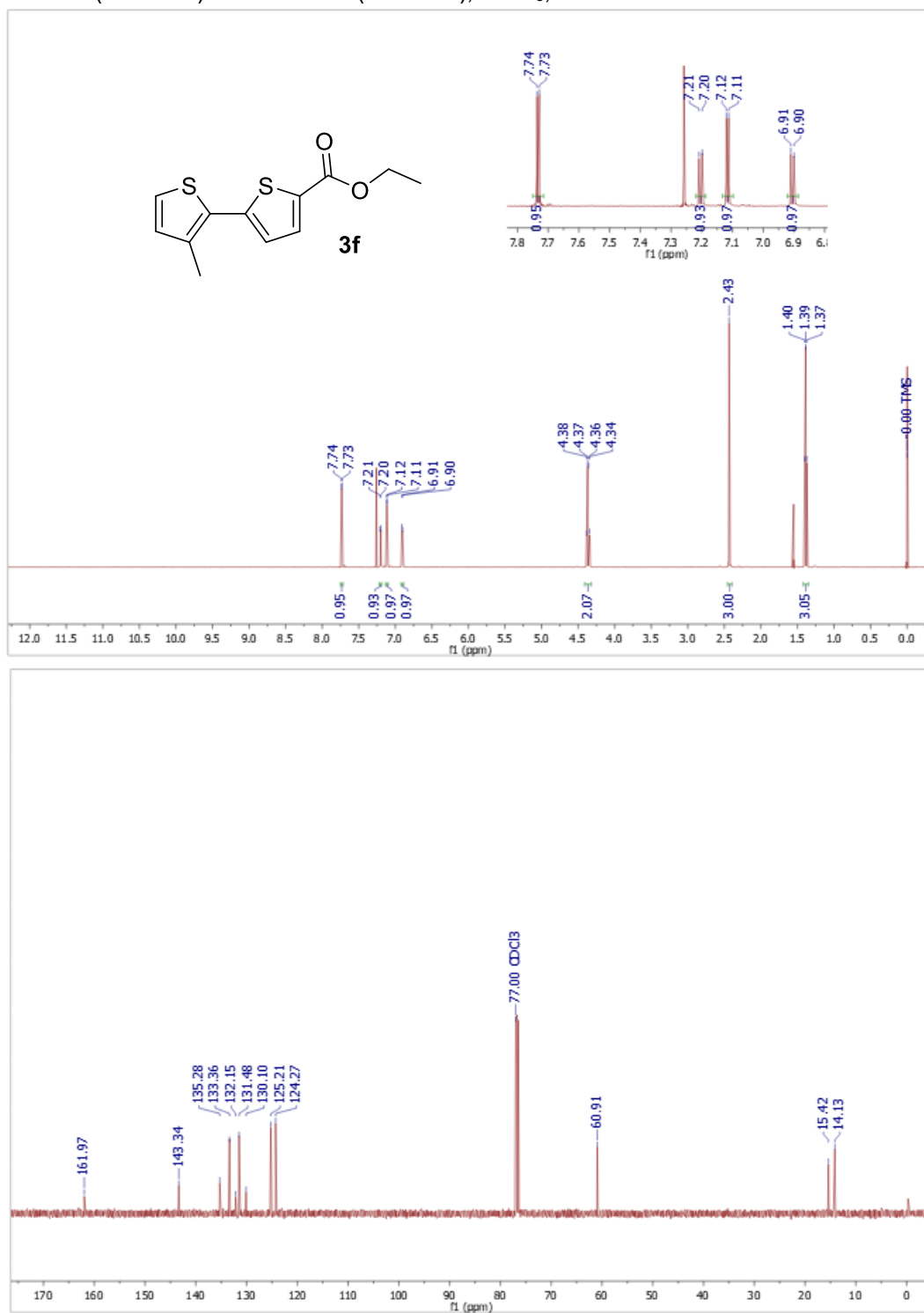
Ethyl 5-(1-(4-methoxybenzyl)-1H-pyrrol-2-yl)thiophene-2-carboxylate (3e)

¹H NMR (500 MHz) and ¹³C NMR (125 MHz), CDCl₃,



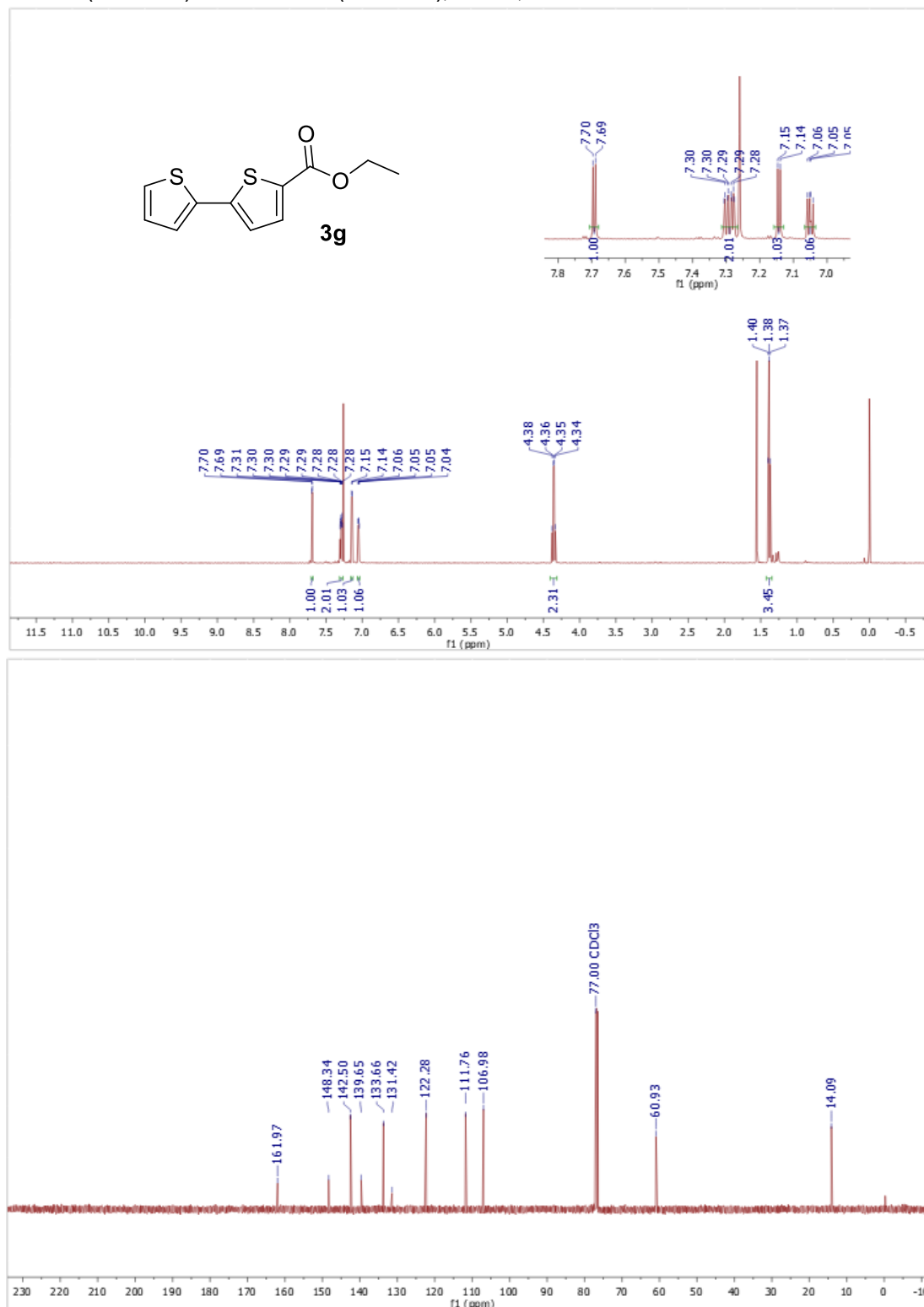
Ethyl 3'-methyl-[2,2'-bithiophene]-5-carboxylate (3f)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3 ,



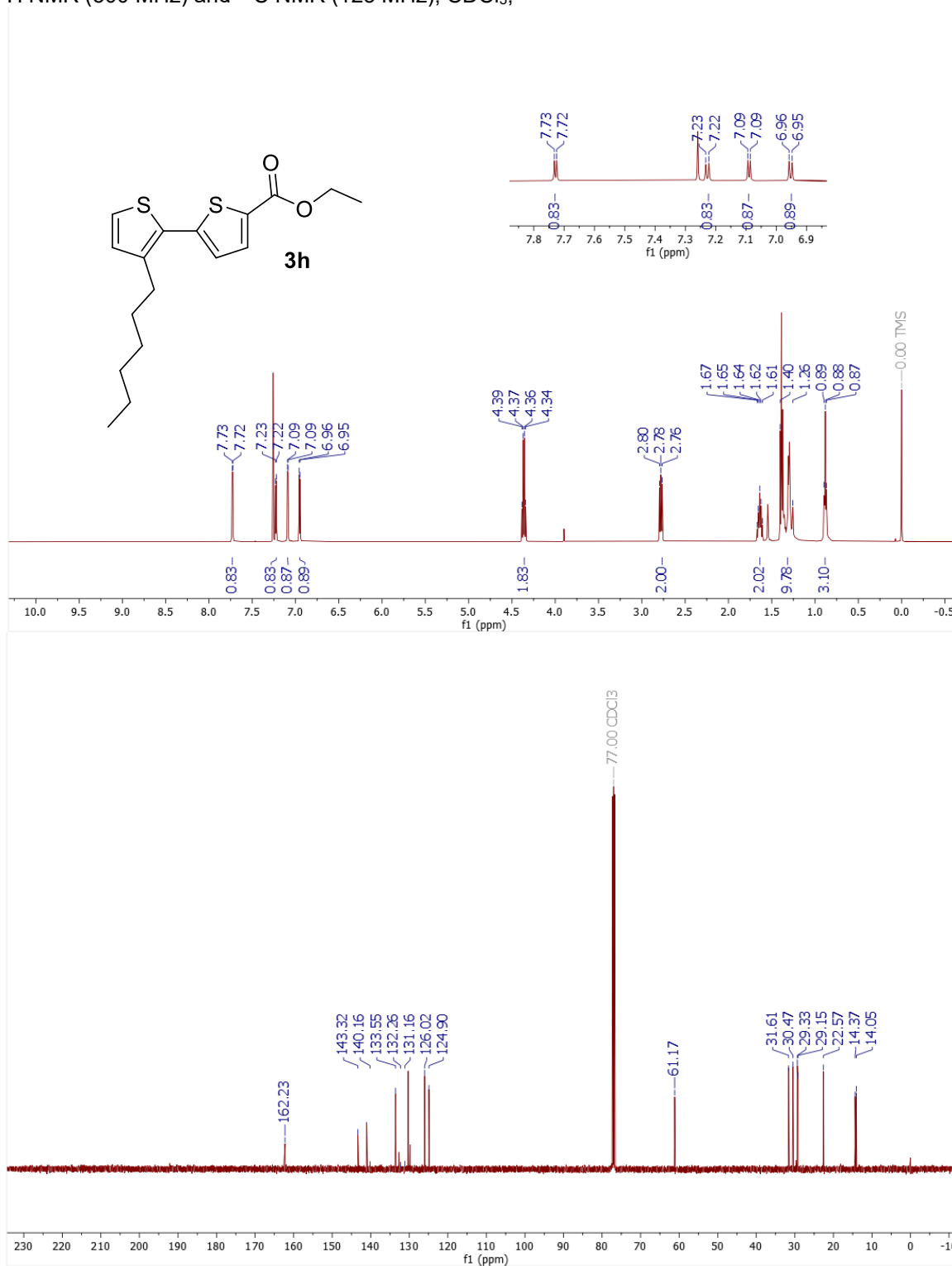
Ethyl [2,2'-bithiophene]-5-carboxylate (3g)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3 ,



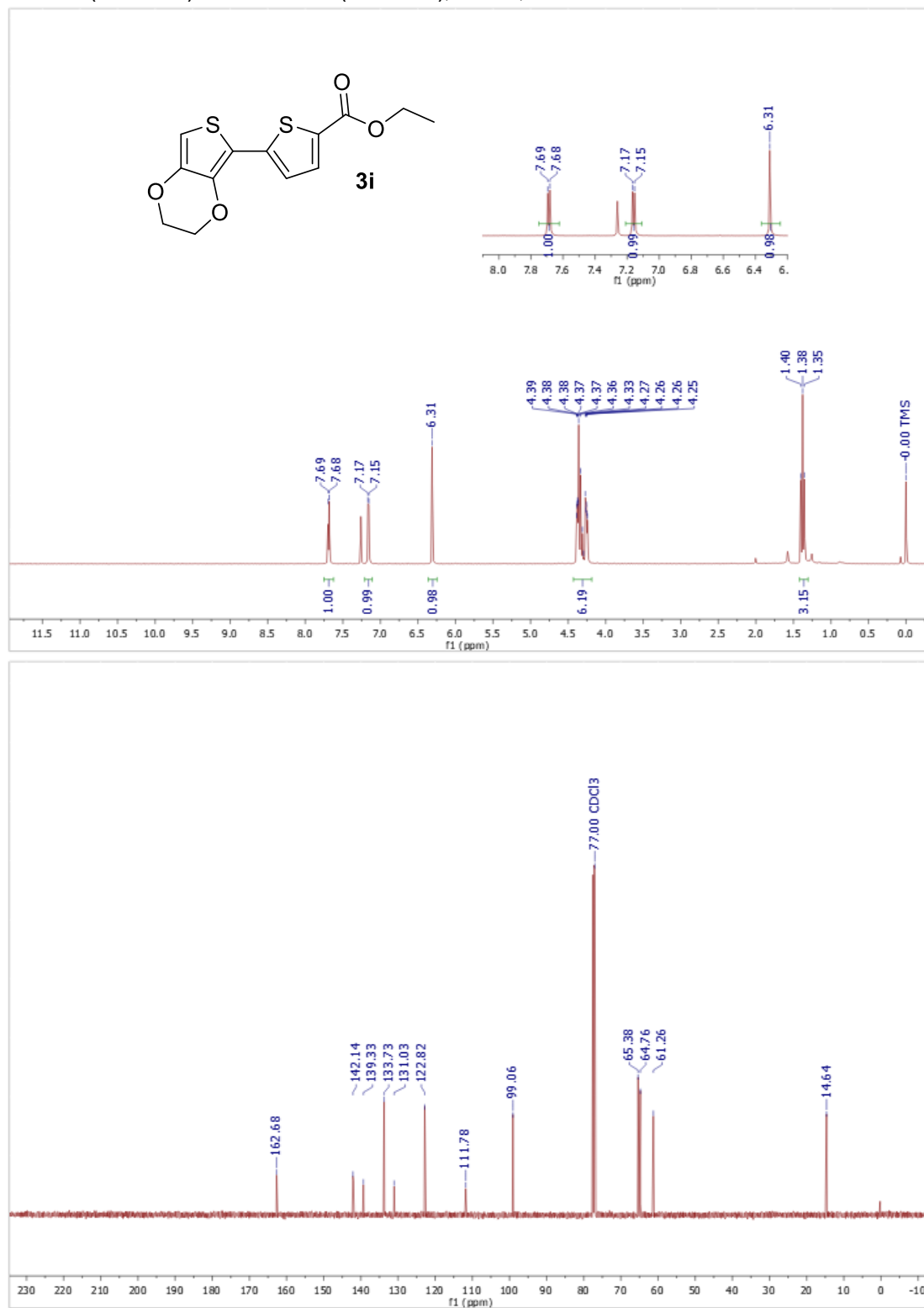
Ethyl 3'-hexyl-[2,2'-bithiophene]-5-carboxylate (3h)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3 ,

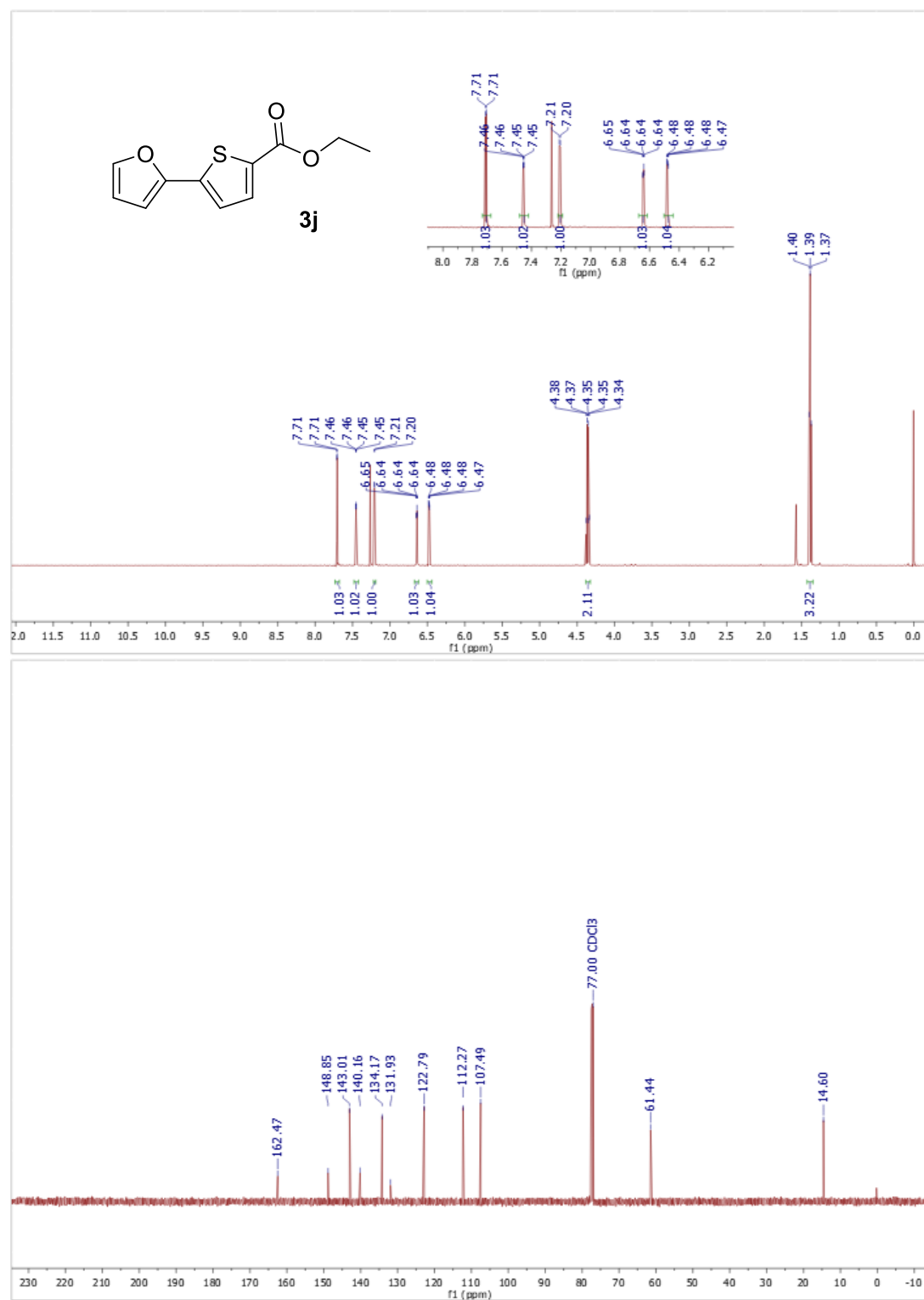


Ethyl 5-(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)thiophene-2-carboxylate (3i)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3 ,

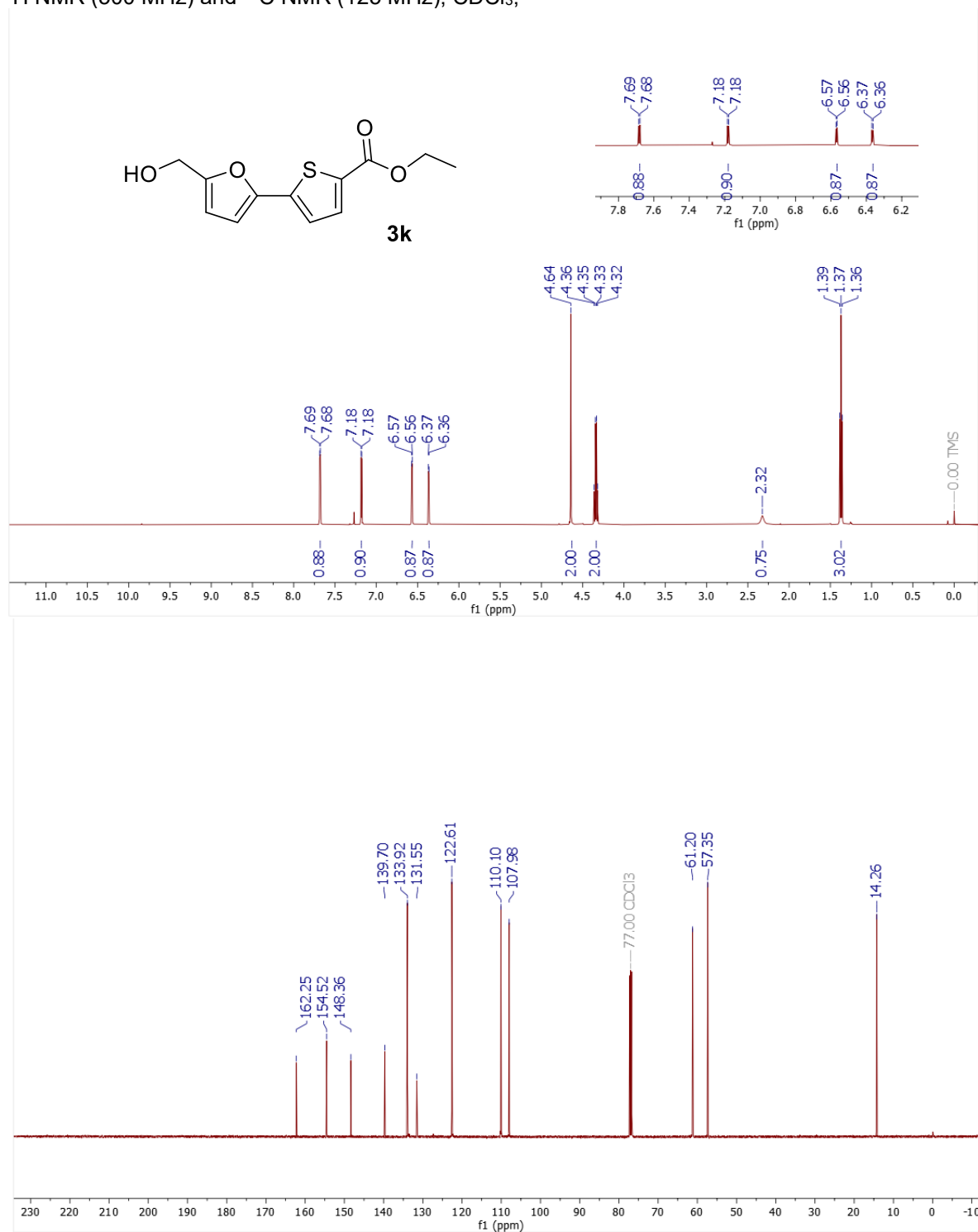


Ethyl 5-(furan-2-yl)thiophene-2-carboxylate (3j)
¹H NMR (500 MHz) and ¹³C NMR (125 MHz), CDCl₃,



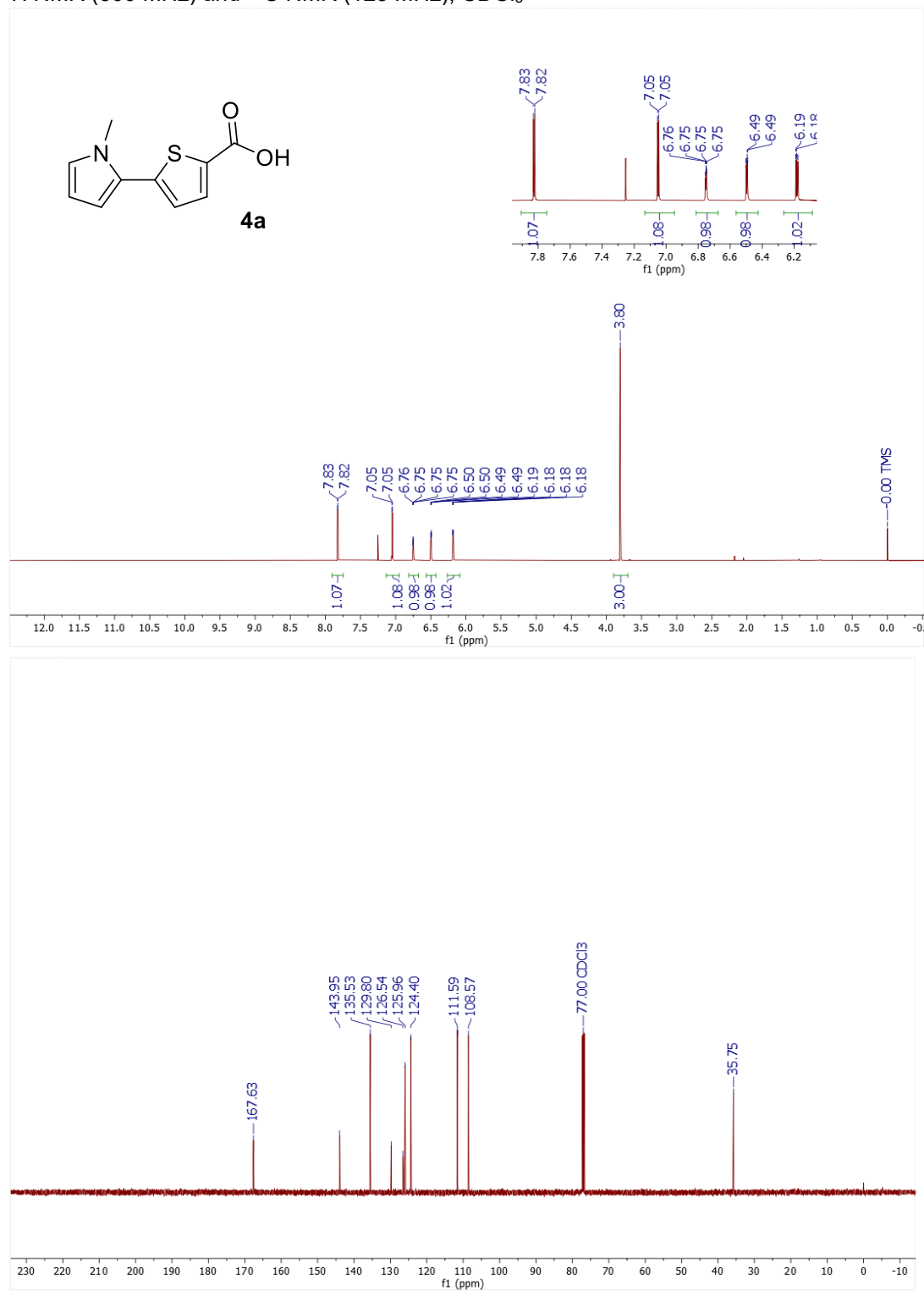
Ethyl 5-(5-(hydroxymethyl)furan-2-yl)thiophene-2-carboxylate (3k)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3 ,



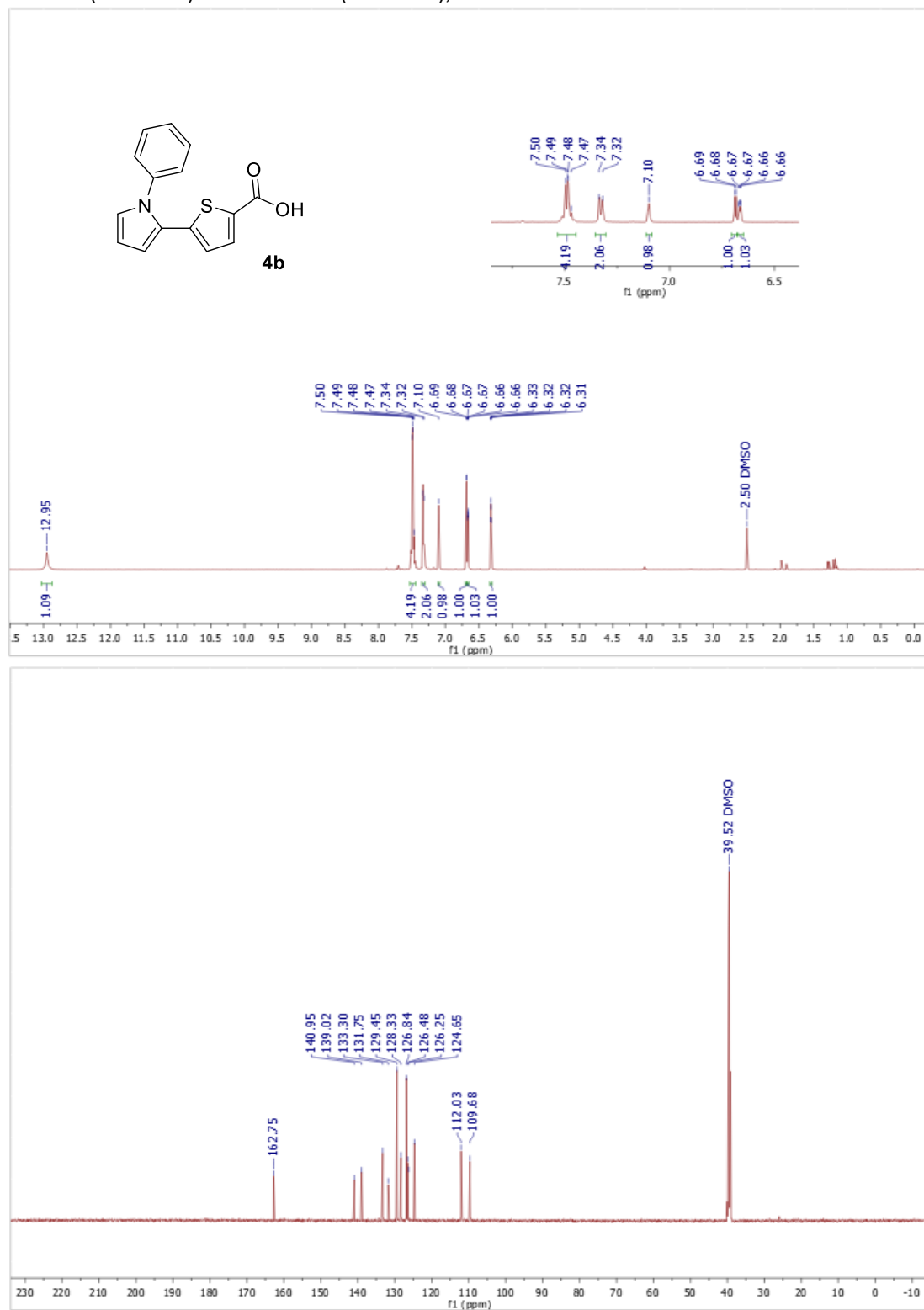
5-(1-methyl-1H-pyrrol-2-yl)thiophene-2-carboxylic acid (4a)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3

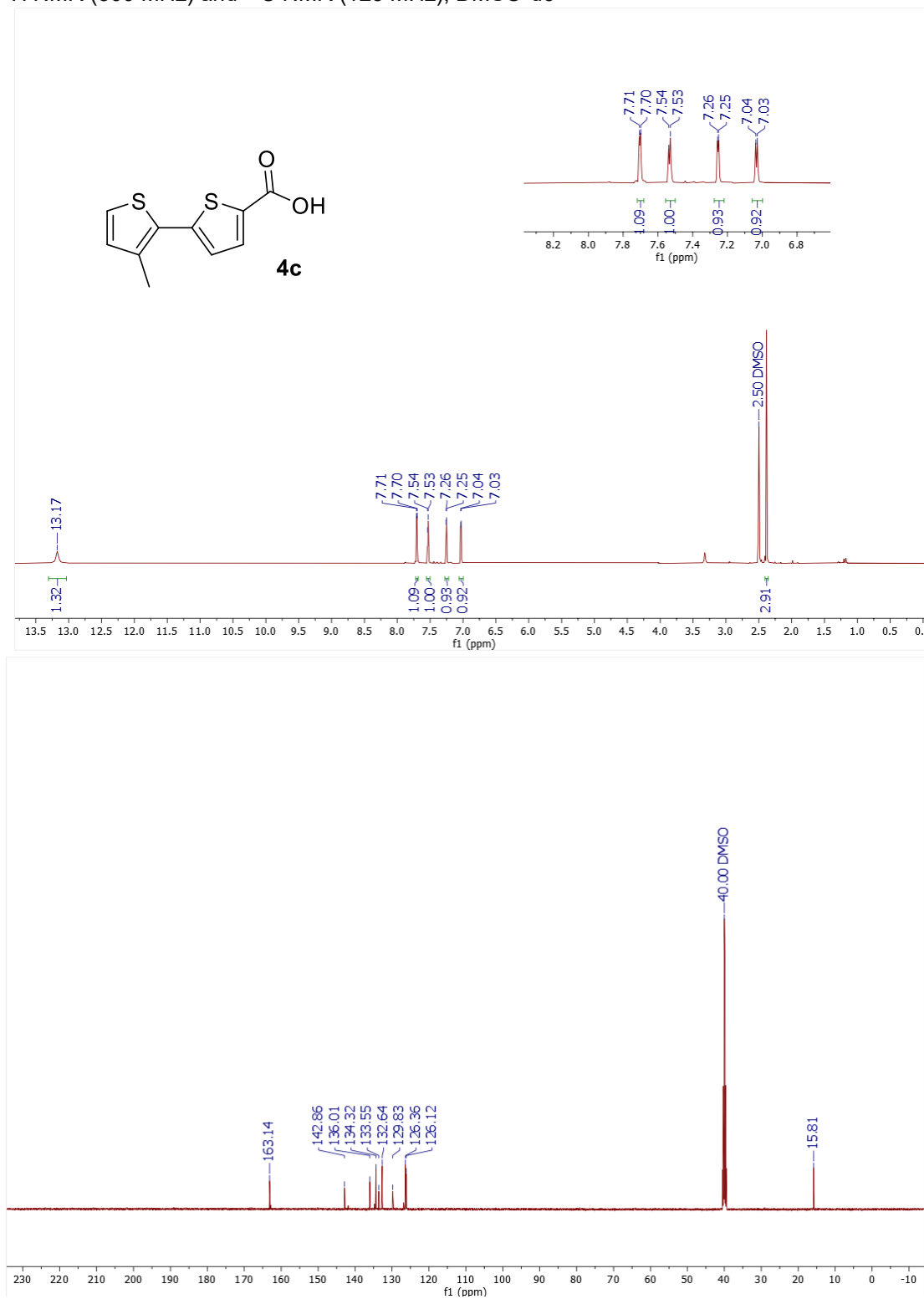


5-(1-phenyl-1H-pyrrol-2-yl)thiophene-2-carboxylic acid (4b)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), DMSO- d_6

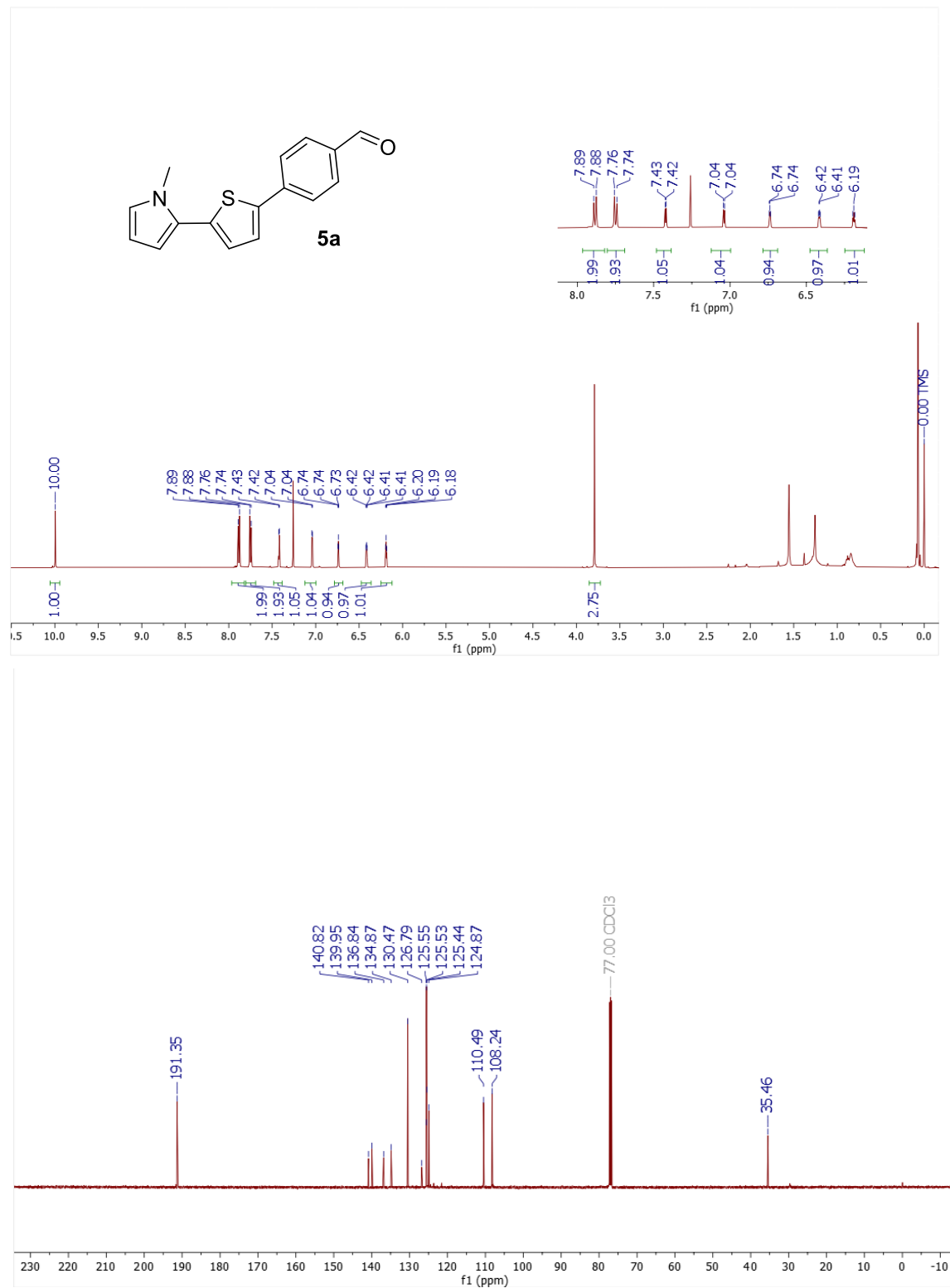


3'-methyl-[2,2'-bithiophene]-5-carboxylic acid (4c)
¹H NMR (500 MHz) and ¹³C NMR (125 MHz), DMSO-d₆



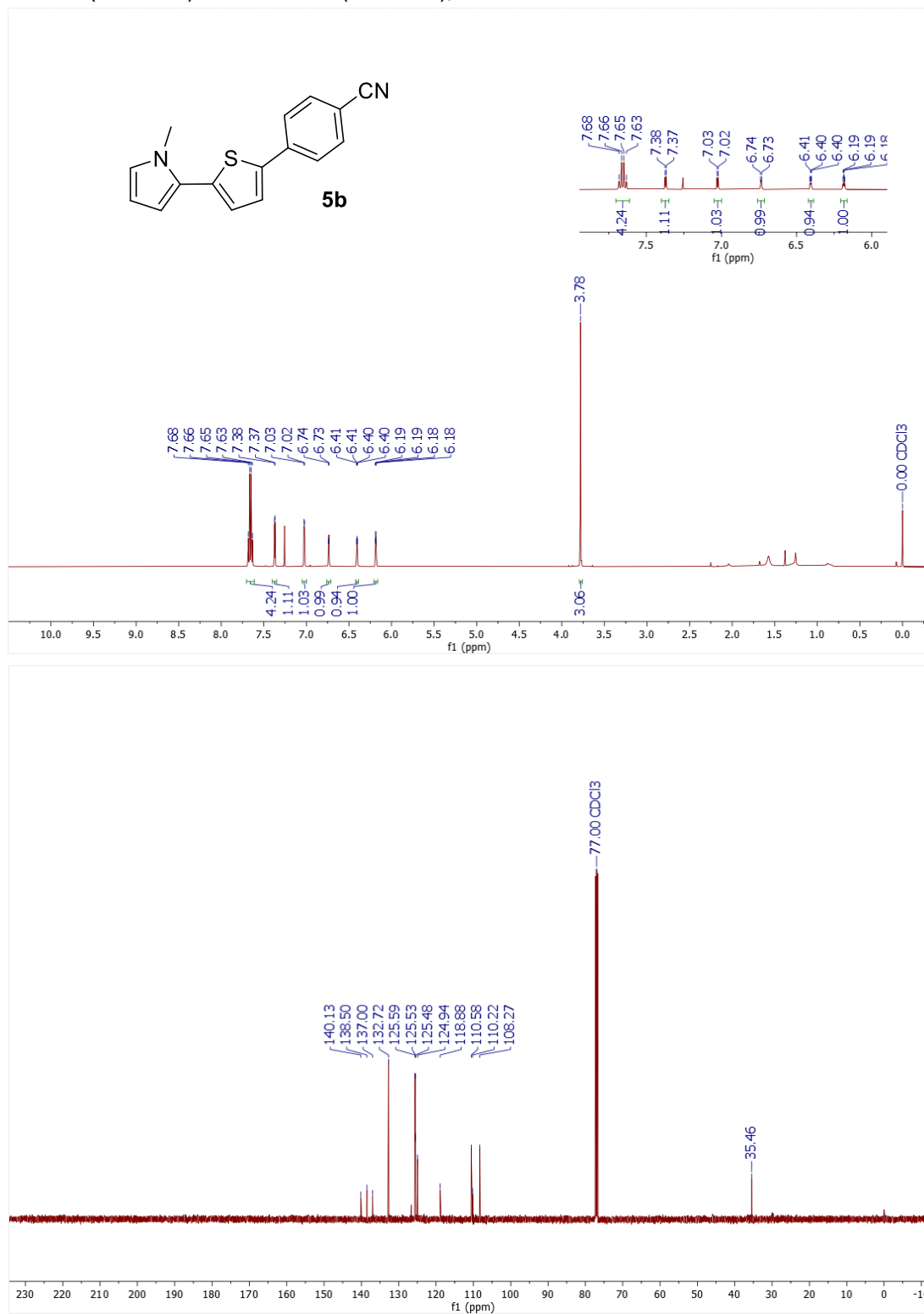
4-(5-(1-methyl-1H-pyrrol-2-yl)thiophen-2-yl)benzaldehyde (5a)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) CDCl_3



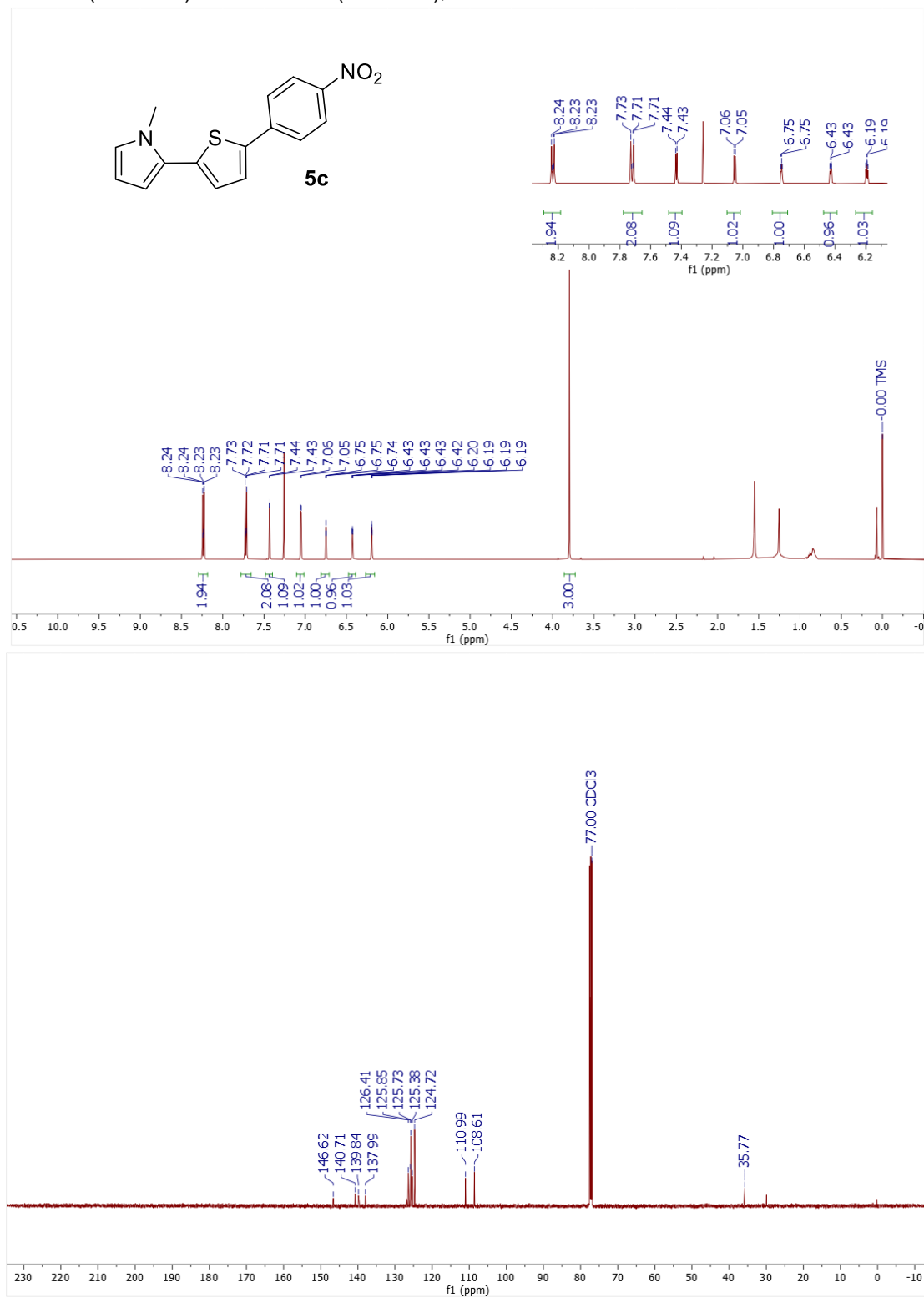
4-(5-(1-methyl-1H-pyrrol-2-yl)thiophen-2-yl)benzonitrile (5b)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3



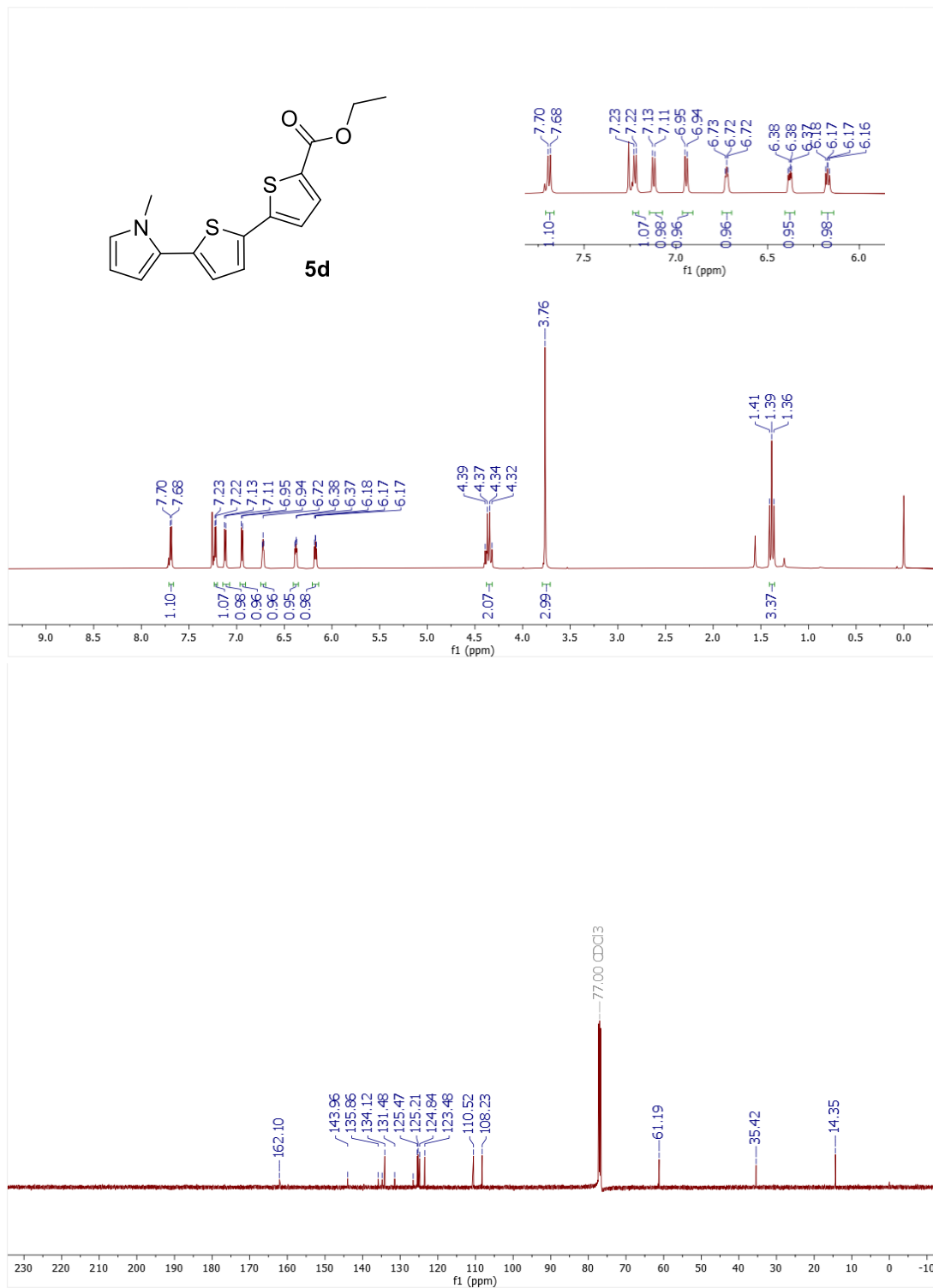
1-methyl-2-(5-(4-nitrophenyl)thiophen-2-yl)-1H-pyrrole (5c)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3



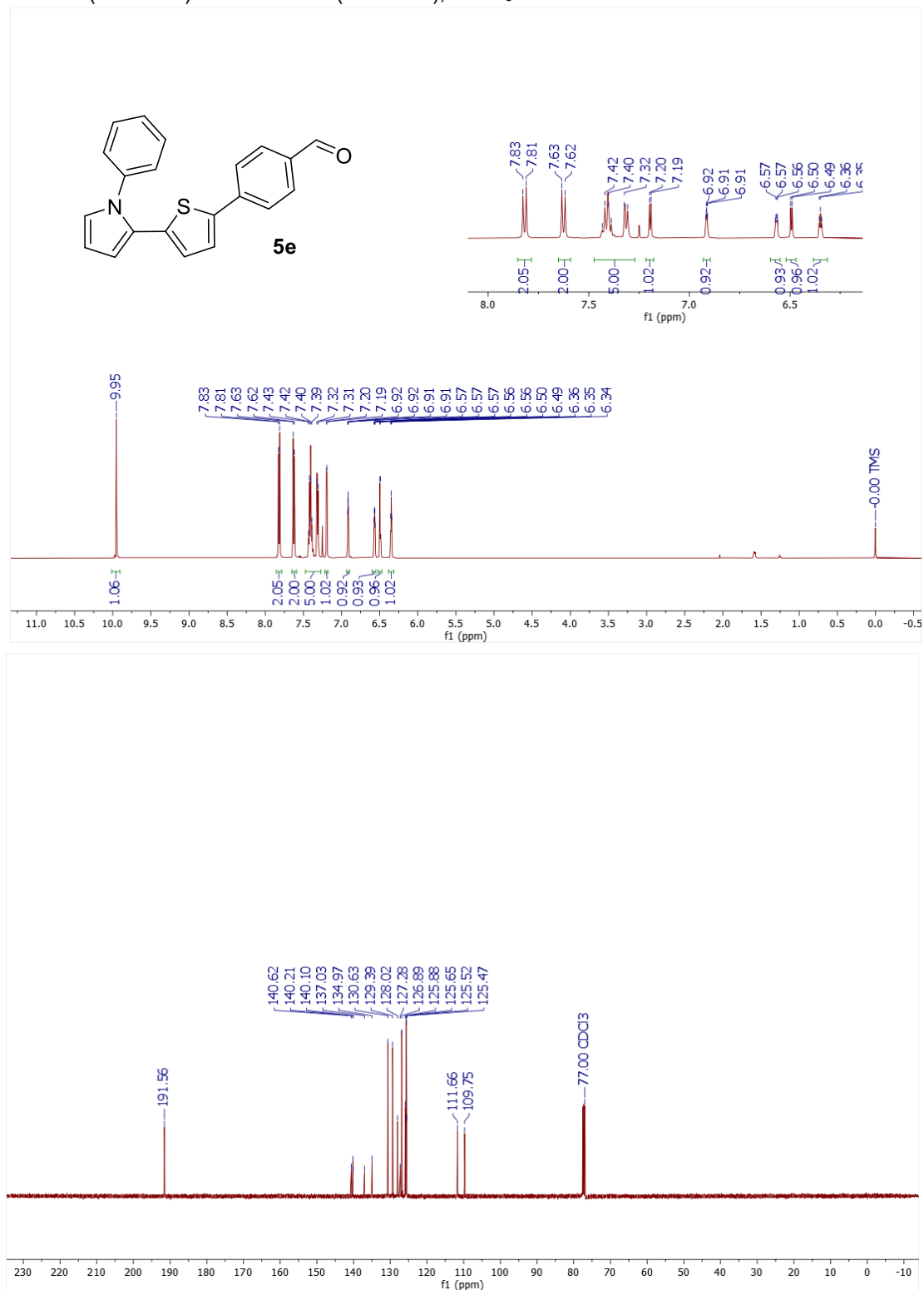
Ethyl 5'-(1-methyl-1H-pyrrol-2-yl)-[2,2'-bithiophene]-5-carboxylate (5d)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3



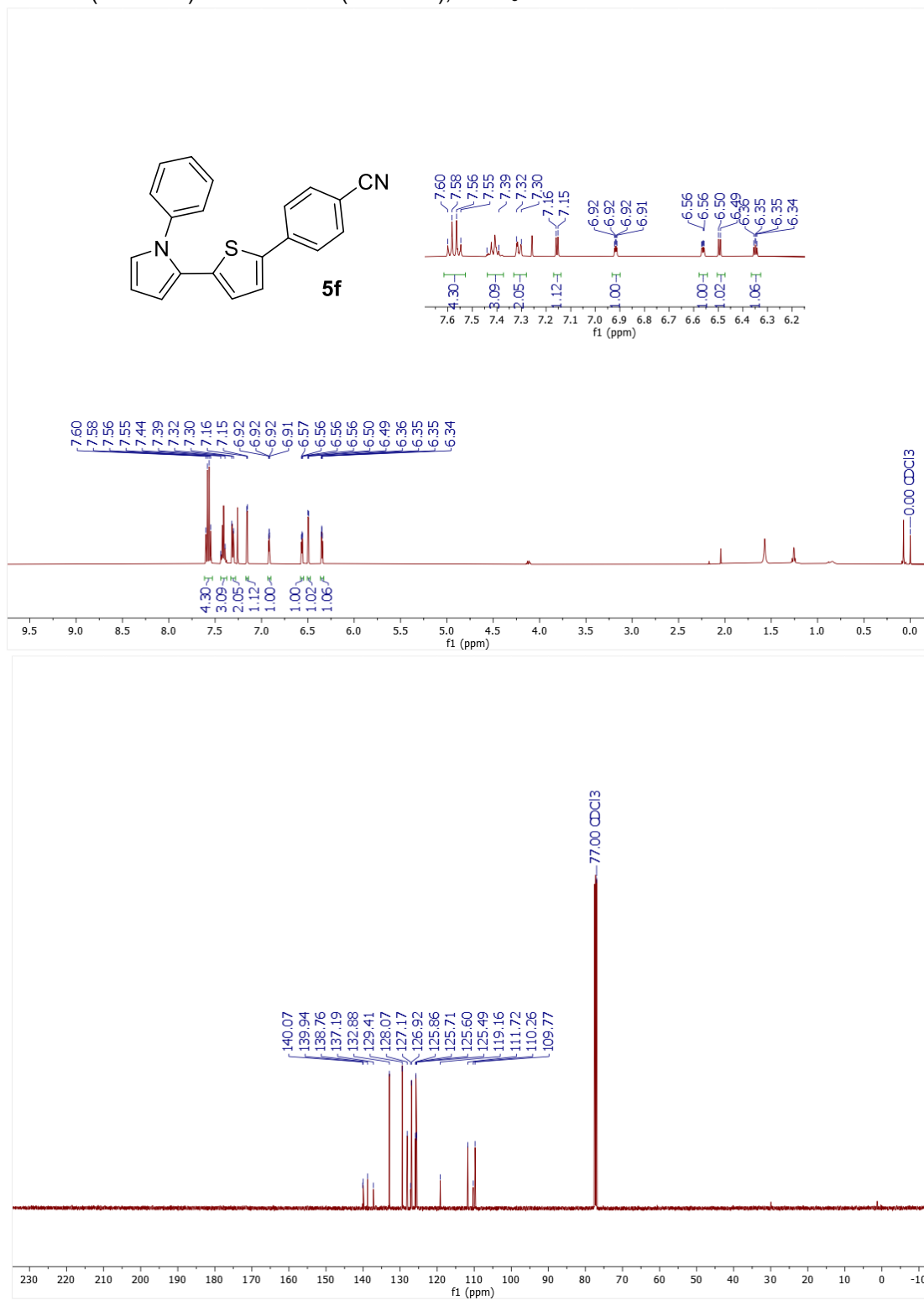
4-(5-(1-phenyl-1H-pyrrol-2-yl)thiophen-2-yl)benzaldehyde (5e)

¹H NMR (500 MHz) and ¹³C NMR (125 MHz), CDCl₃



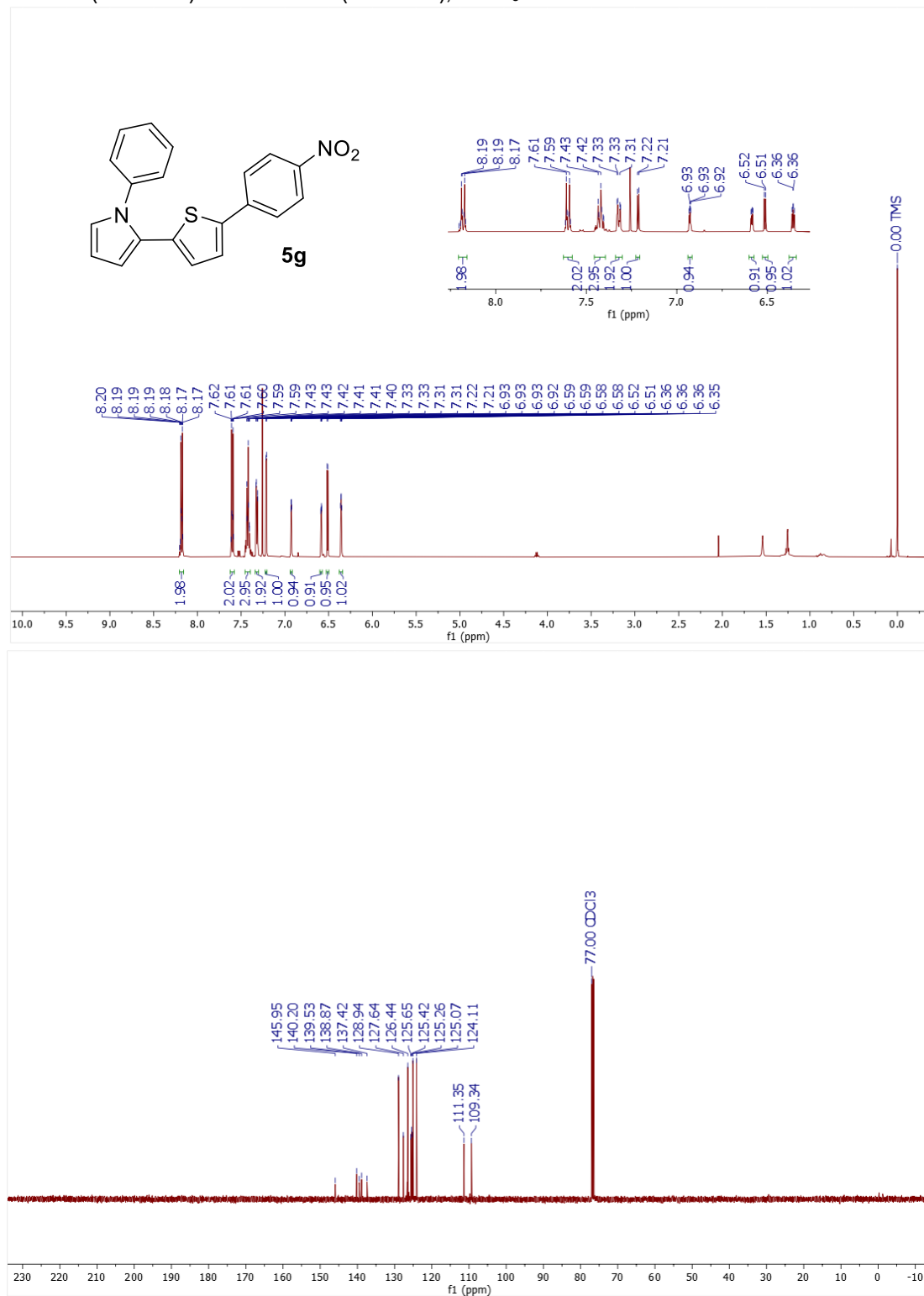
4-(5-(1-phenyl-1H-pyrrol-2-yl)thiophen-2-yl)benzonitrile (5f)

¹H NMR (500 MHz) and ¹³C NMR (125 MHz), CDCl₃



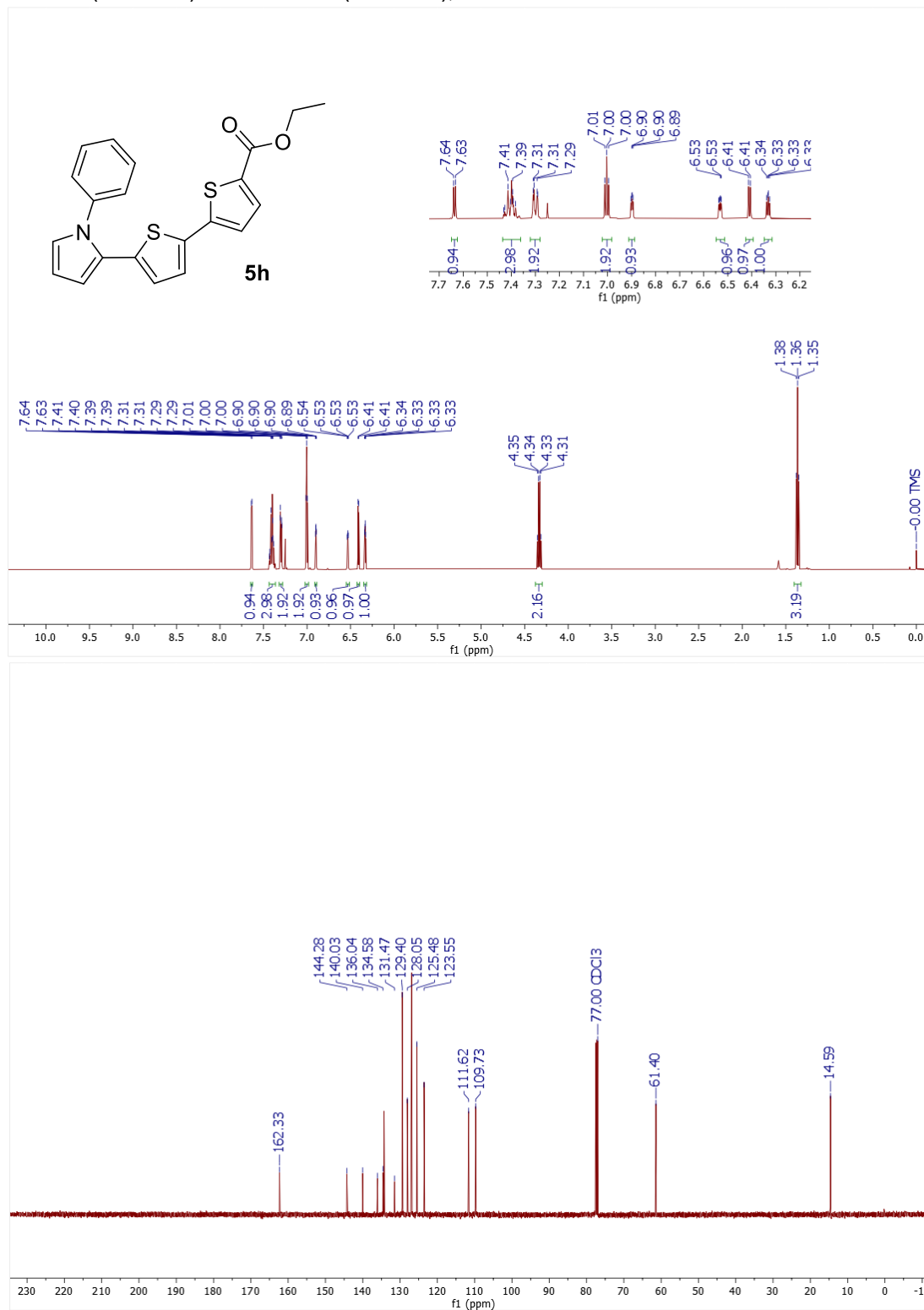
2-(5-(4-nitrophenyl)thiophen-2-yl)-1-phenyl-1H-pyrrole (5g)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3



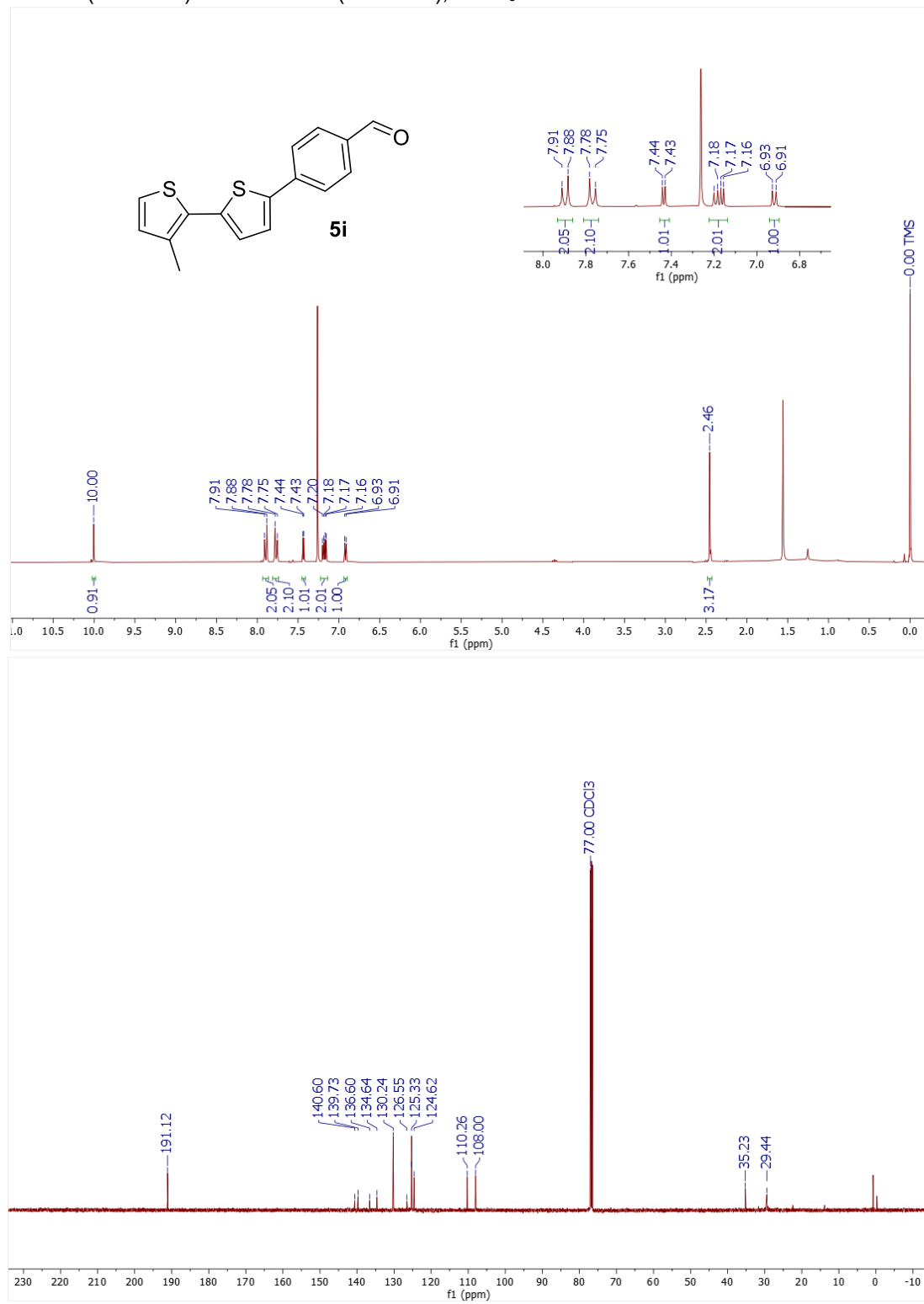
Ethyl 5'-(1-phenyl-1H-pyrrol-2-yl)-[2,2'-bithiophene]-5-carboxylate (5h)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3



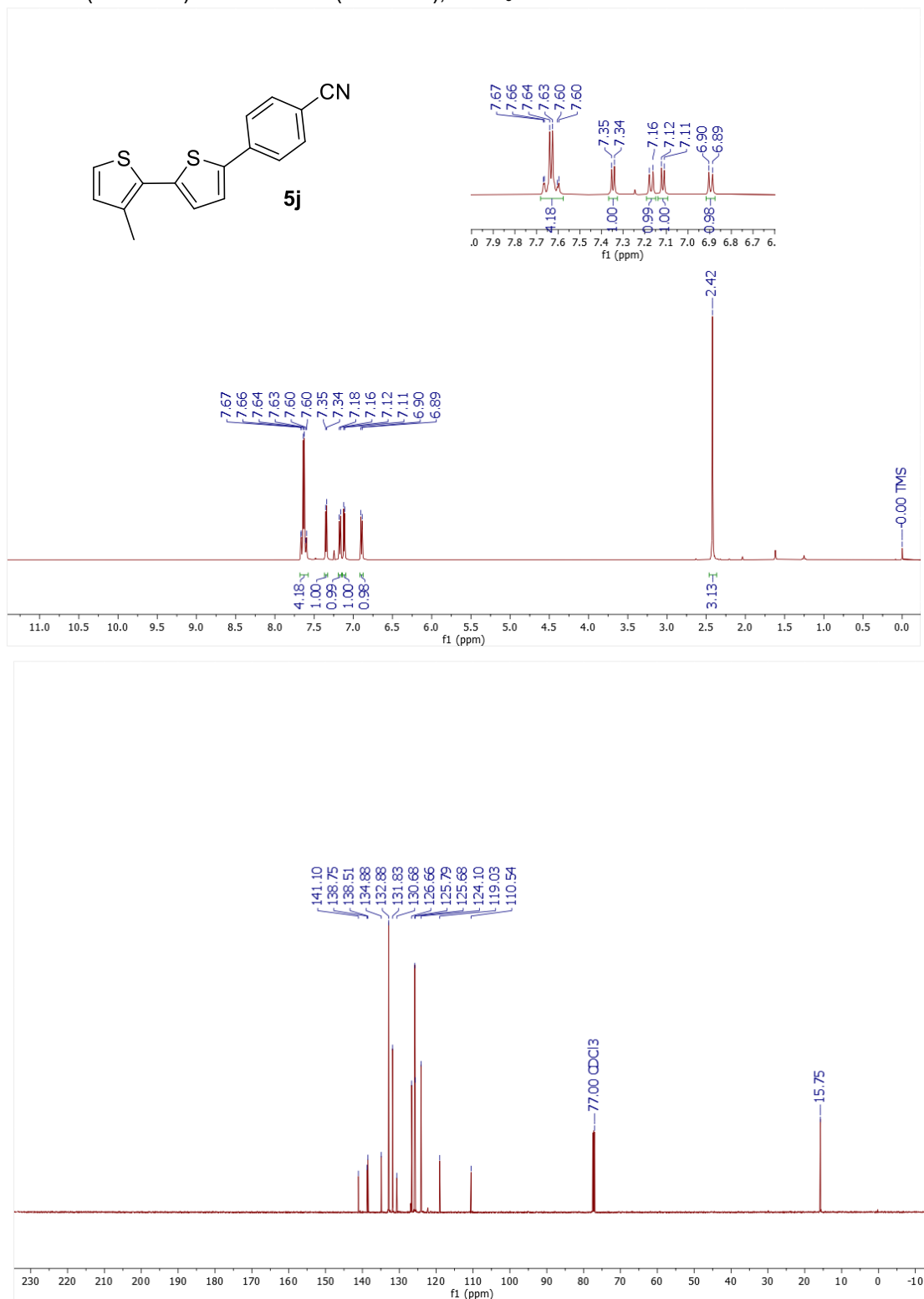
4-(3'-methyl-[2,2'-bithiophen]-5-yl)benzaldehyde (5i)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3



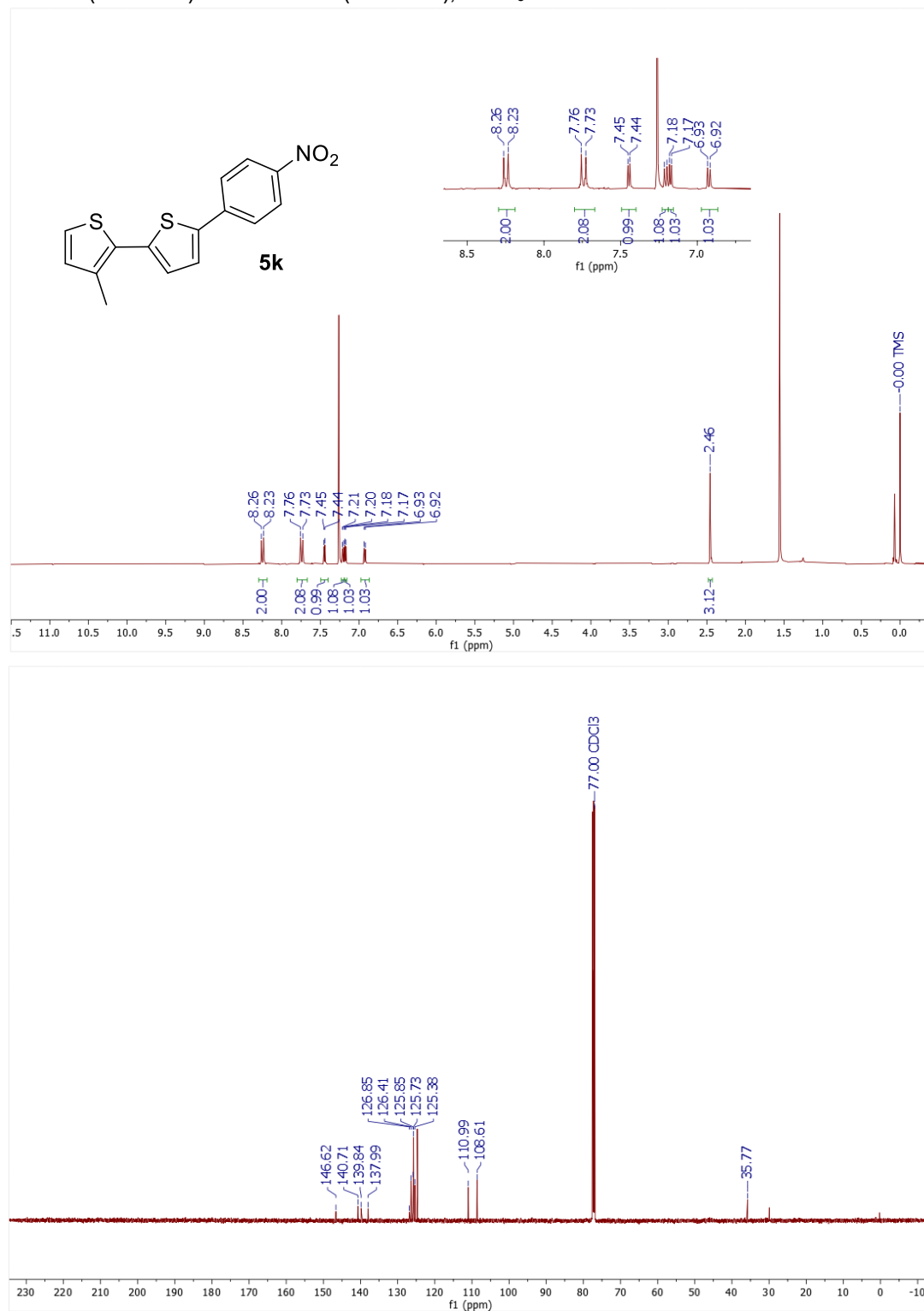
4-(3'-methyl-[2,2'-bithiophen]-5-yl)benzonitrile (5j)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3



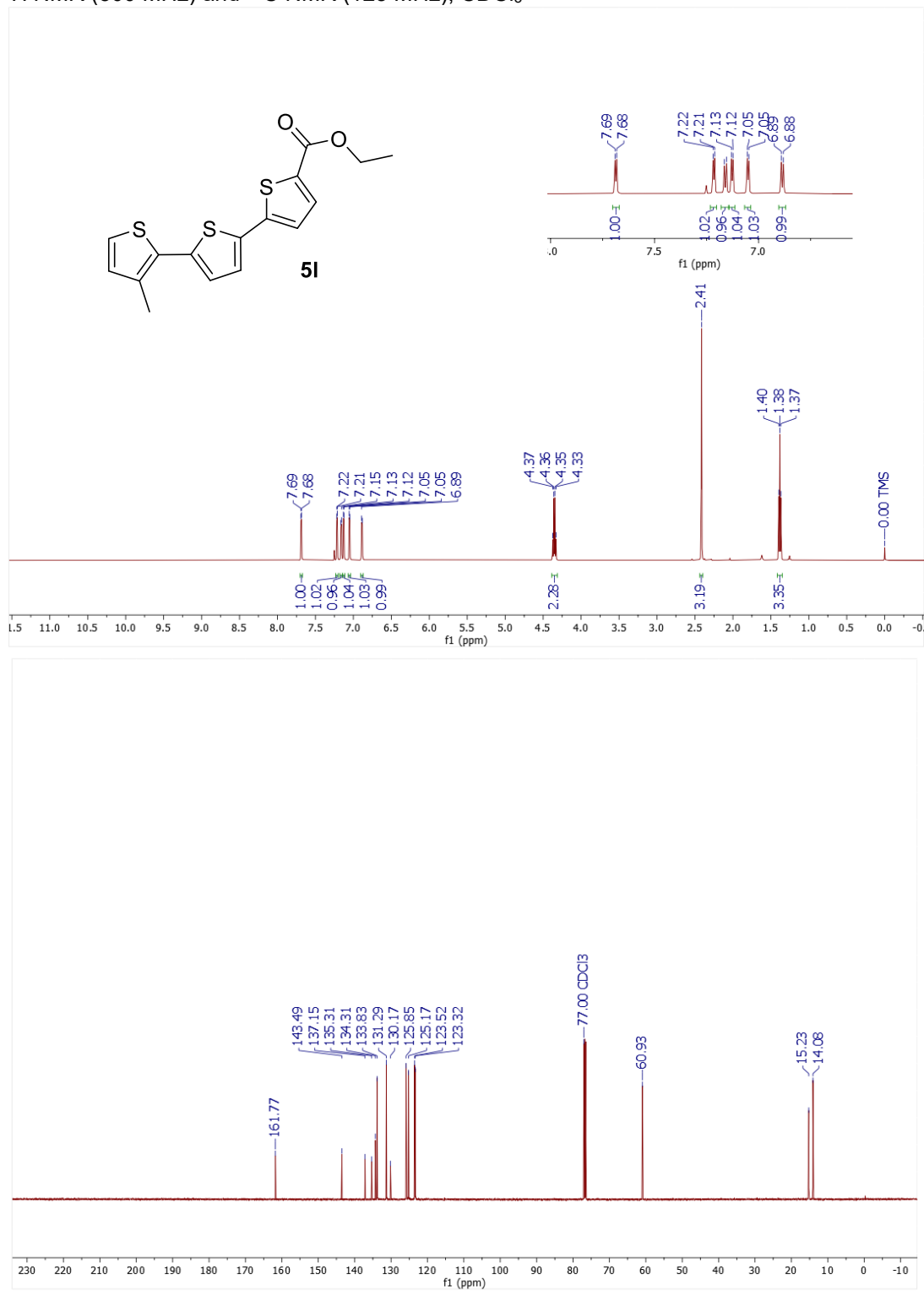
3-methyl-5'-(4-nitrophenyl)-2,2'-bithiophene (5k)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3



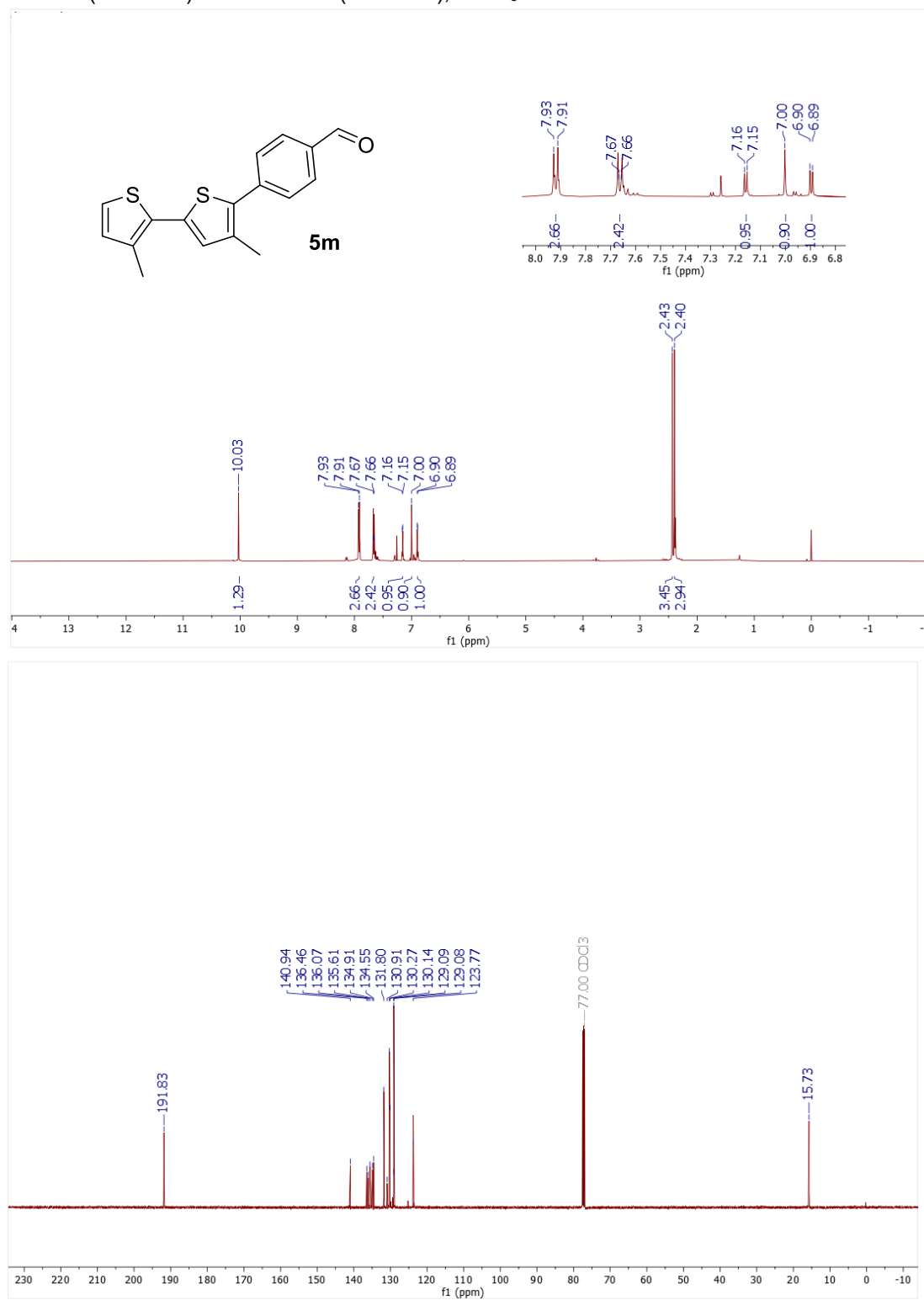
Ethyl 3''-methyl-[2,2':5',2''-terthiophene]-5-carboxylate (5I)

¹H NMR (500 MHz) and ¹³C NMR (125 MHz), CDCl₃



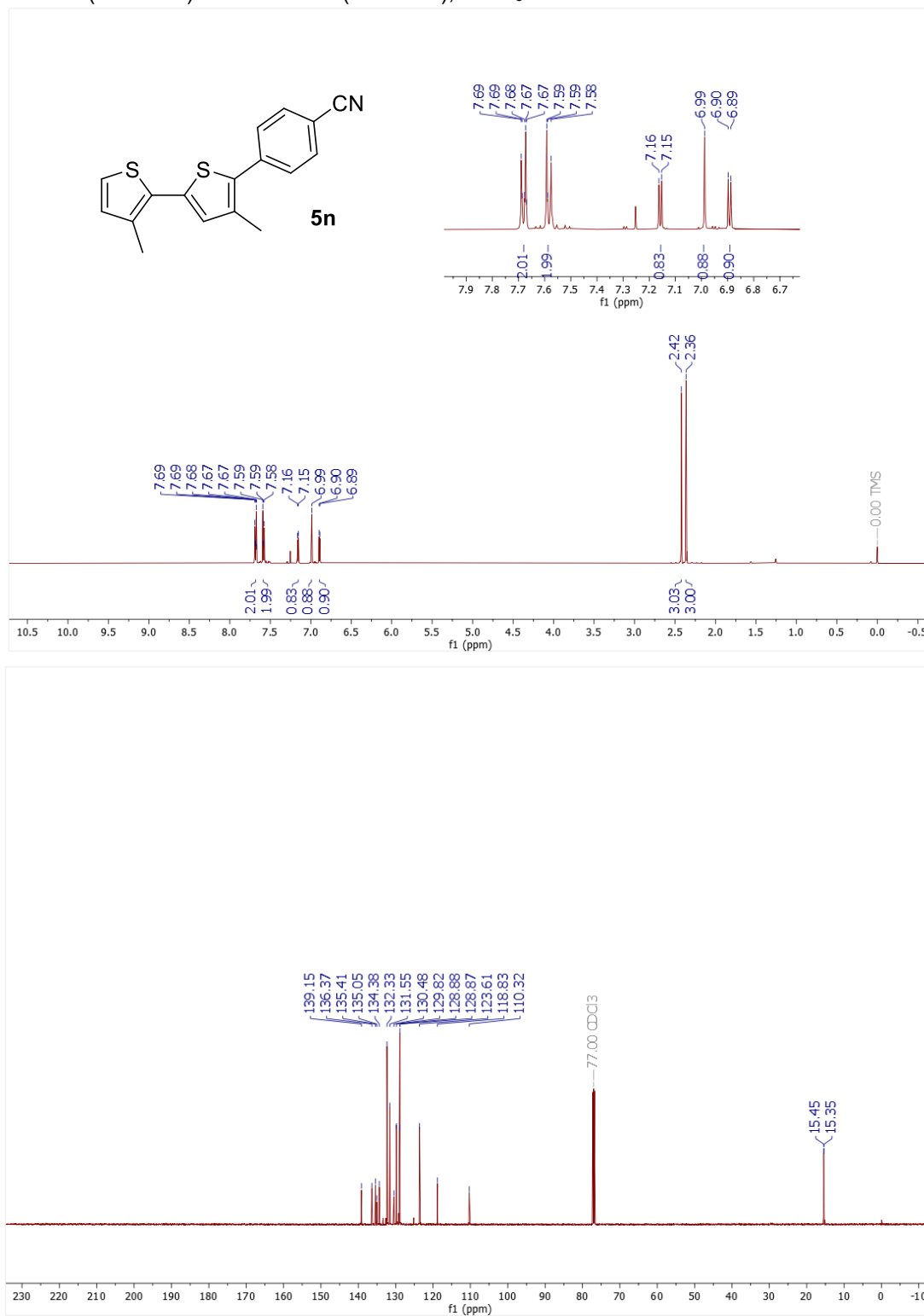
4-(3',4-dimethyl-[2,2'-bithiophen]-5-yl)benzaldehyde (5m)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3



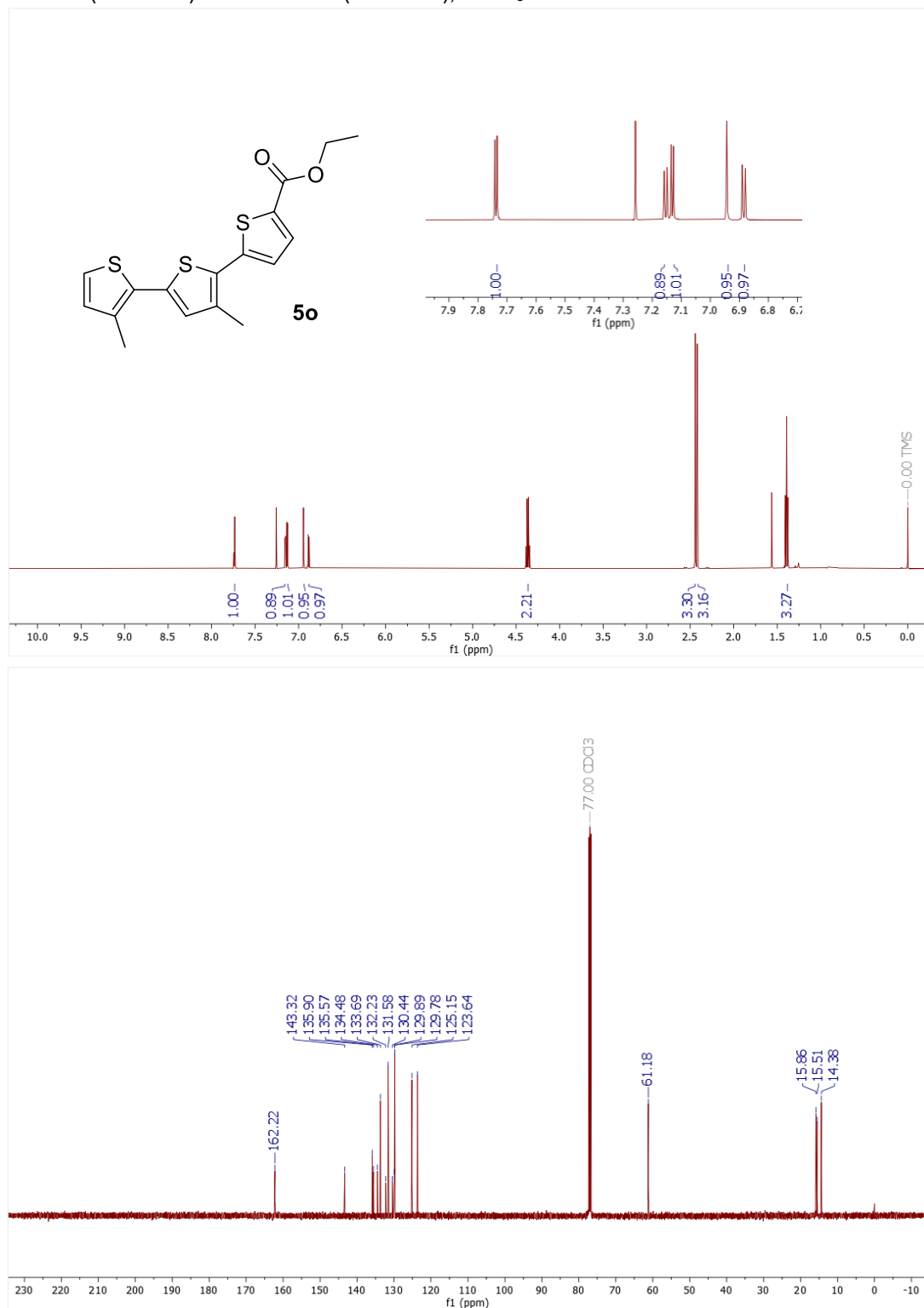
4-(3',4-dimethyl-[2,2'-bithiophen]-5-yl)benzonitrile (5n)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3



Ethyl 3',3"-dimethyl-[2,2':5',2"-terthiophene]-5-carboxylate (5o)

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz), CDCl_3



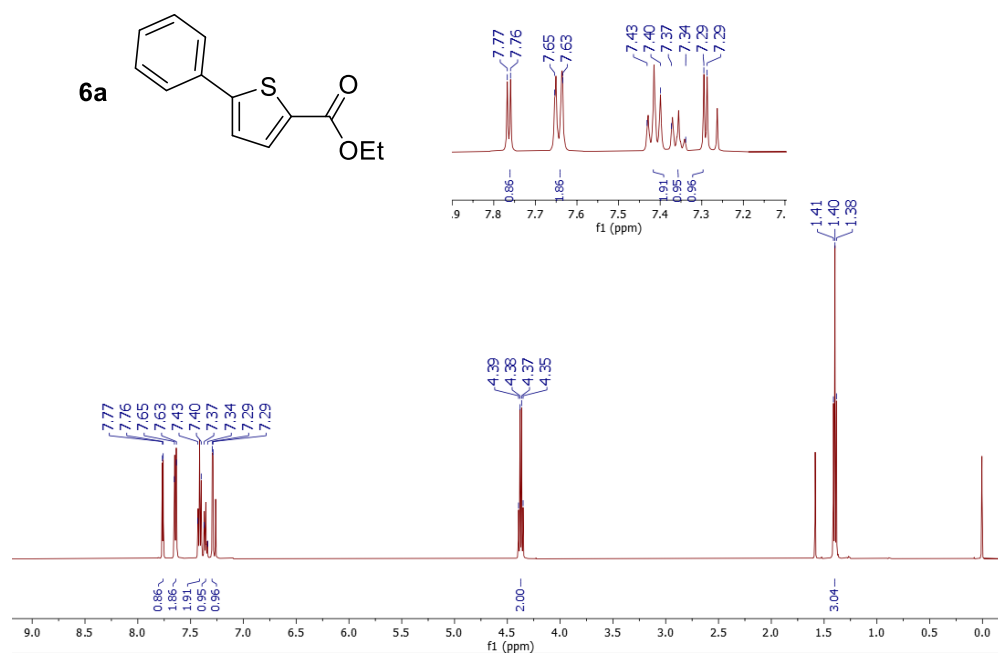
Supporting Information for Chapter 3

General conditions

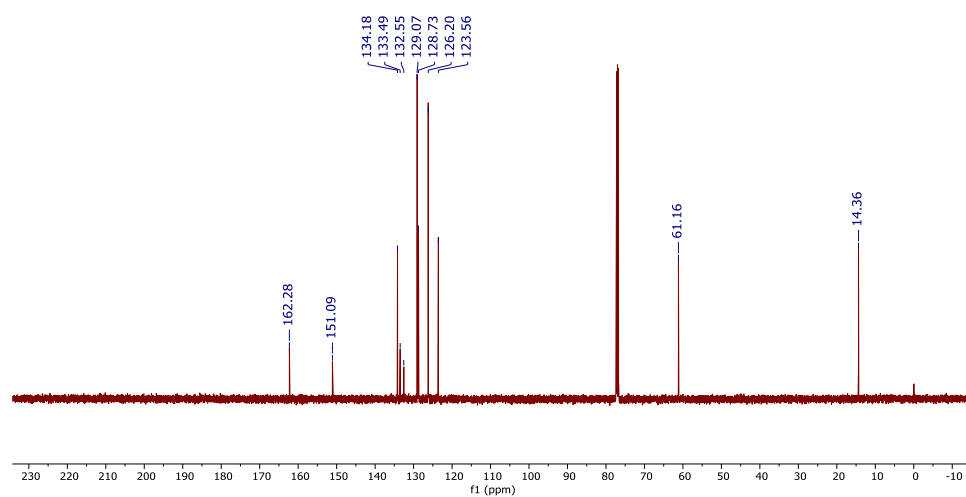
Reactions were carried out in regular glassware under air unless otherwise noted. Commercially available starting materials (thiophene ester **1**, all boronic acids and aryl halides) and reagents (K_2CO_3 , $ZnCl_2$, Cs_2CO_3 , NaOH and $TMPMgCl \cdot LiCl$) were purchased from Sigma-Aldrich and AK Scientific, and used without further purification. Palladium catalysts were purchased from STREM and stored under inert gas at room temperature ($PdCl_2$) or in the freezer at -10 degrees Celsius ($Pd(PtBu_3)_2$). All solvents were purchased from Fisher ACP chemicals and Sigma-Aldrich as ACS grade. Dimethylformamide (DMF) was dried using activated 3 Å molecular sieves and stored in an oven-dried Schlenk flask under argon atmosphere. Distilled water was obtained from an in-house distillery. Compounds were purified using column chromatography on silica-gel (Zeoprep 60 Eco, 40 – 63 μm , Zeochem AG). Microwave-assisted reactions were carried out using the Biotage Initiator™ 2.3 build 6250 microwave system with a 400 W magnetron – this instrument monitors temperature during the reaction time period and adjusts wattage accordingly. ^1H and ^{13}C NMR data were measured on a Varian VNMRs-500. High-resolution mass spectral data (HRMS) was collected using a LC-TOF ESI mass spectrometer operated in positive ion mode. Yield determination using ^1H -NMR was done using trimethoxybenzene (TMB) as an internal standard. X-ray crystallography was performed on a Bruker APEX-DUO diffractometer using the Cu K α microfocus source. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. Data were corrected for absorption effects using the multiscan method (SADABS). The structures were solved by SHELXT and refined using the APEX3 software package. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were generated in idealized positions, riding on the carrier atoms with isotropic thermal parameters.

Spectroscopic Data

6a - ethyl 5-phenylthiophene-2-carboxylate ^1H NMR (500 MHz, CDCl_3)

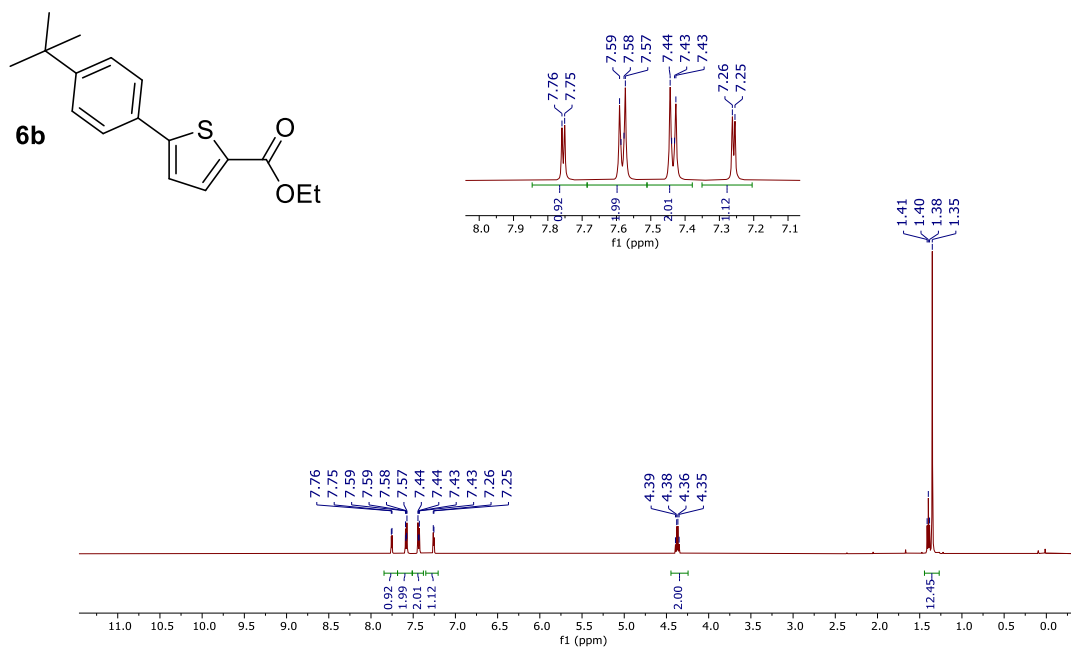


^{13}C NMR (125 MHz, CDCl_3)

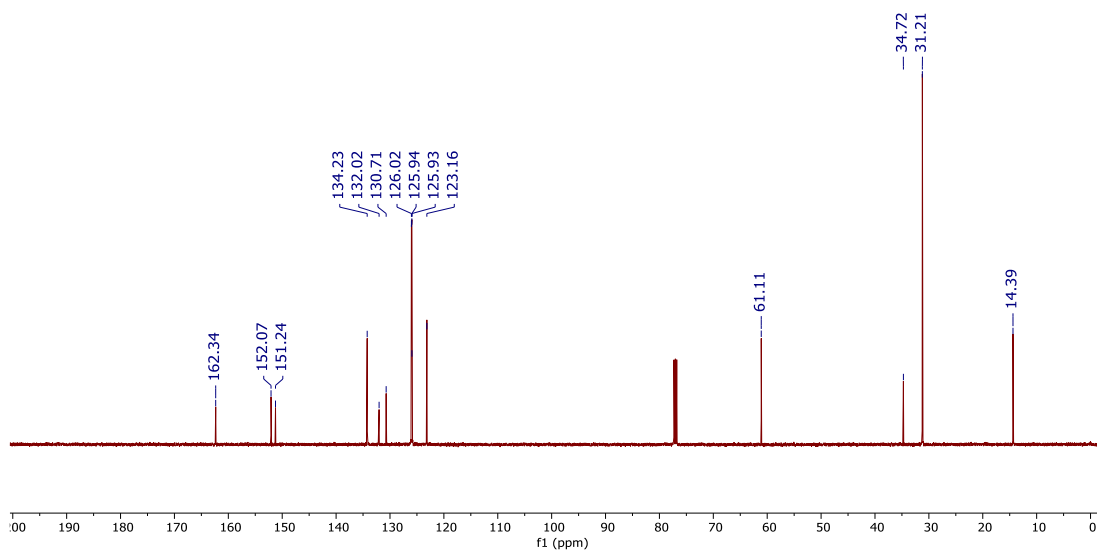


6b - ethyl 5-(4-(tert-butyl)phenyl)thiophene-2-carboxylate

¹H NMR (500 MHz, CDCl₃)

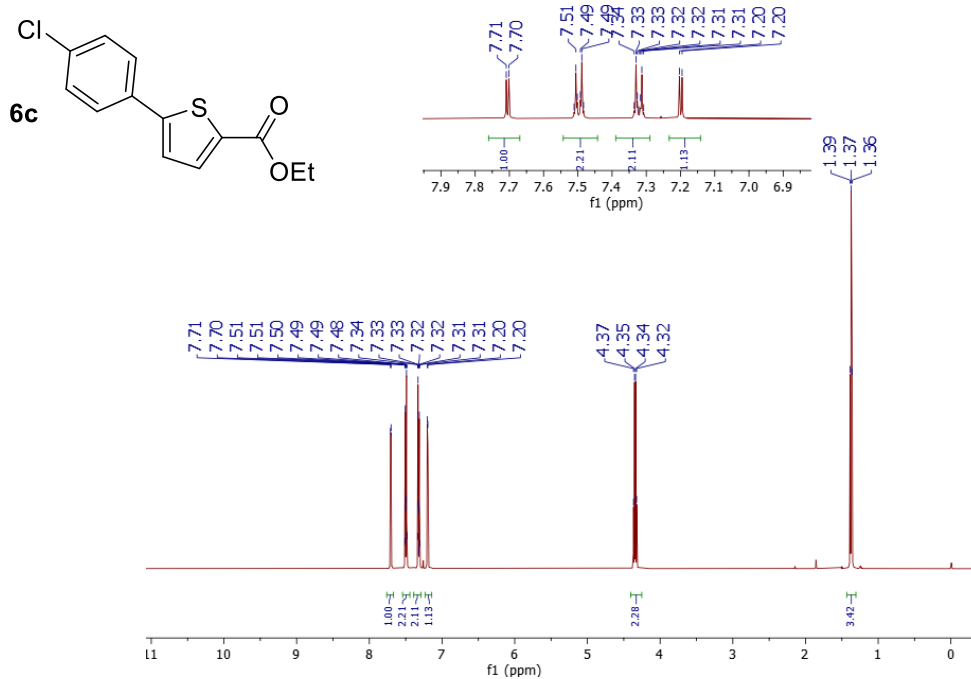


¹³C NMR (125 MHz, CDCl₃)

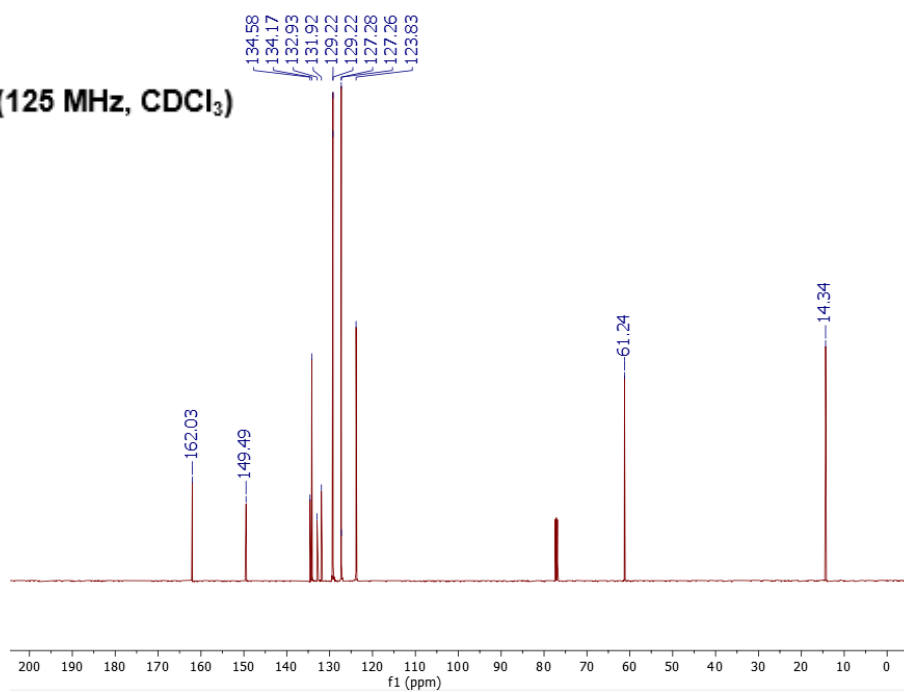


6c - ethyl 5-(4-chlorophenyl)thiophene-2-carboxylate

¹H NMR (500 MHz, CDCl₃)

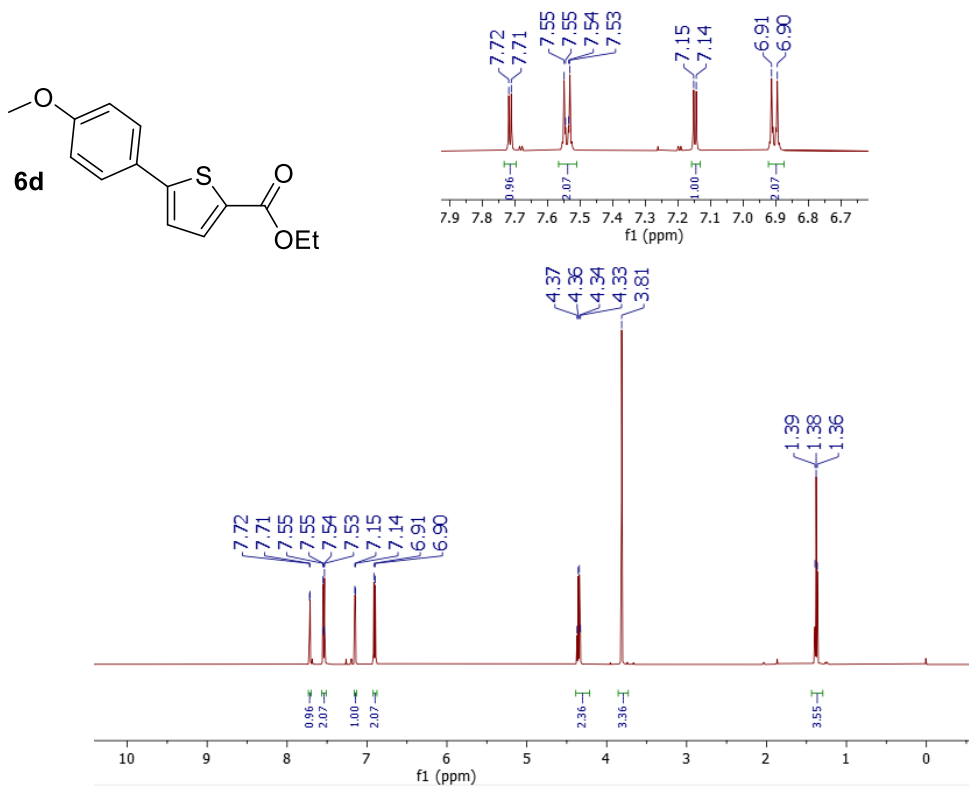


¹³C NMR (125 MHz, CDCl₃)

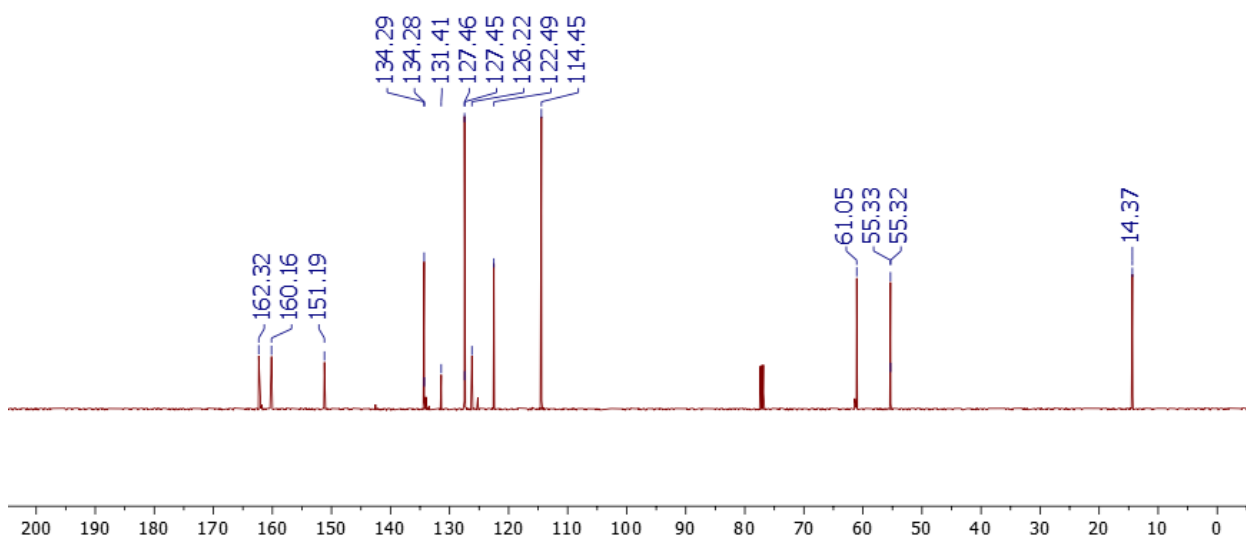


6d - ethyl 5-(4-methoxyphenyl)thiophene-2-carboxylate

¹H NMR (500 MHz, CDCl₃)

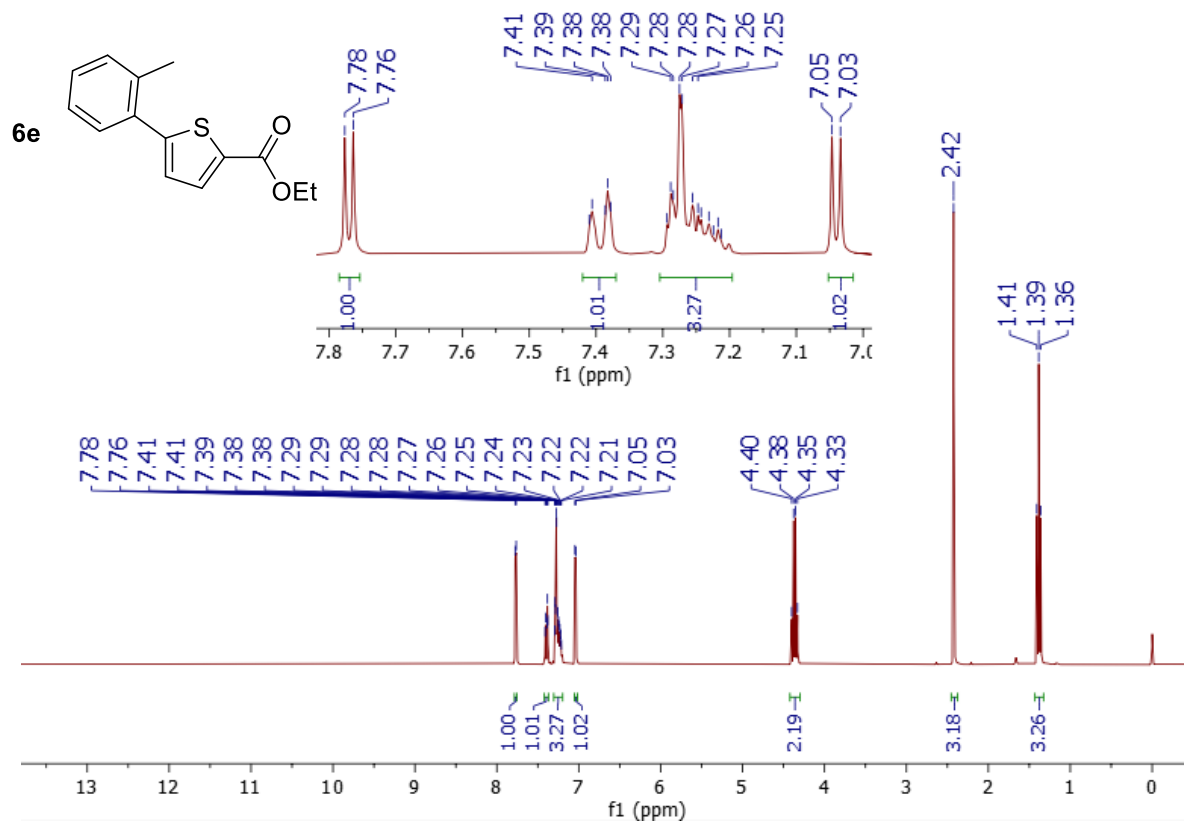


¹³C NMR (125 MHz, CDCl₃)

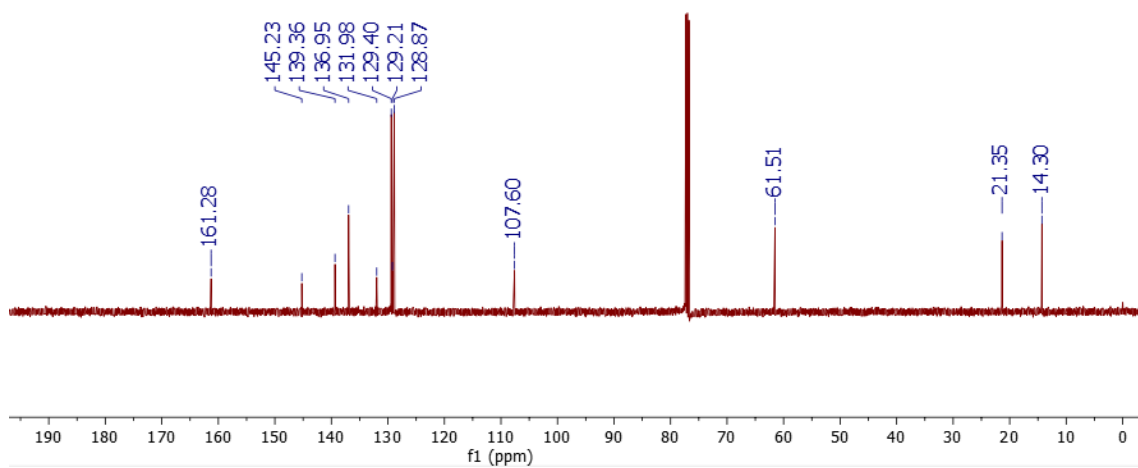


6e - ethyl 5-(4-methoxyphenyl)thiophene-2-carboxylate

¹H NMR (500 MHz, CDCl₃)

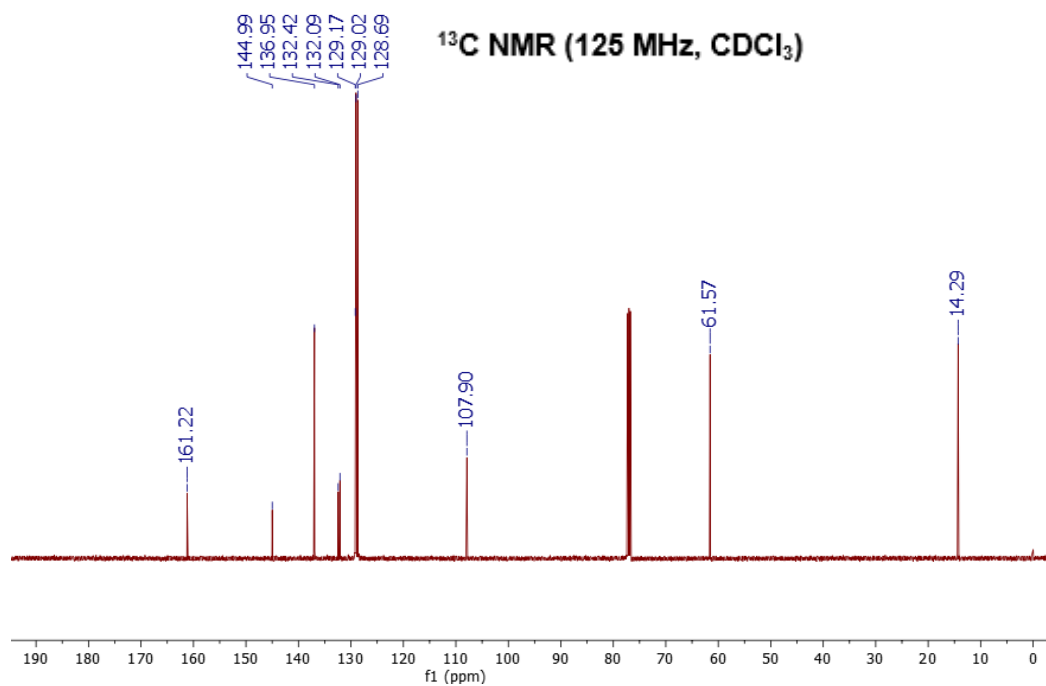
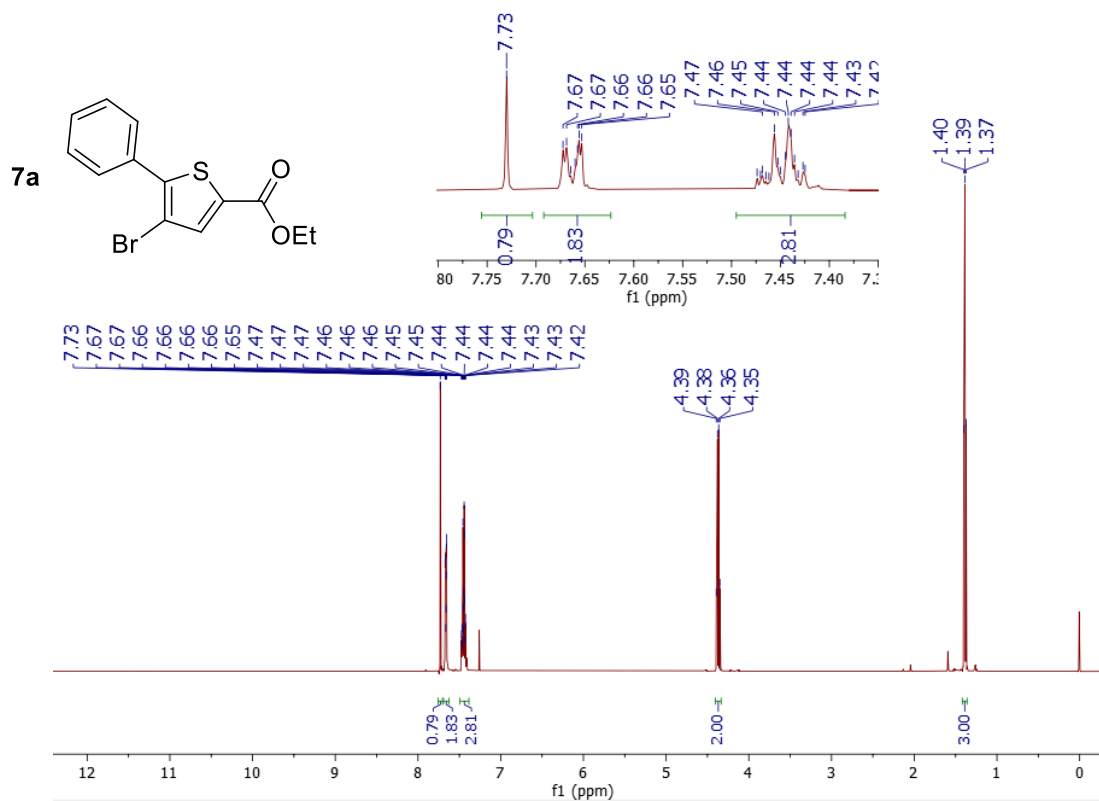


¹³C NMR (125 MHz, CDCl₃)



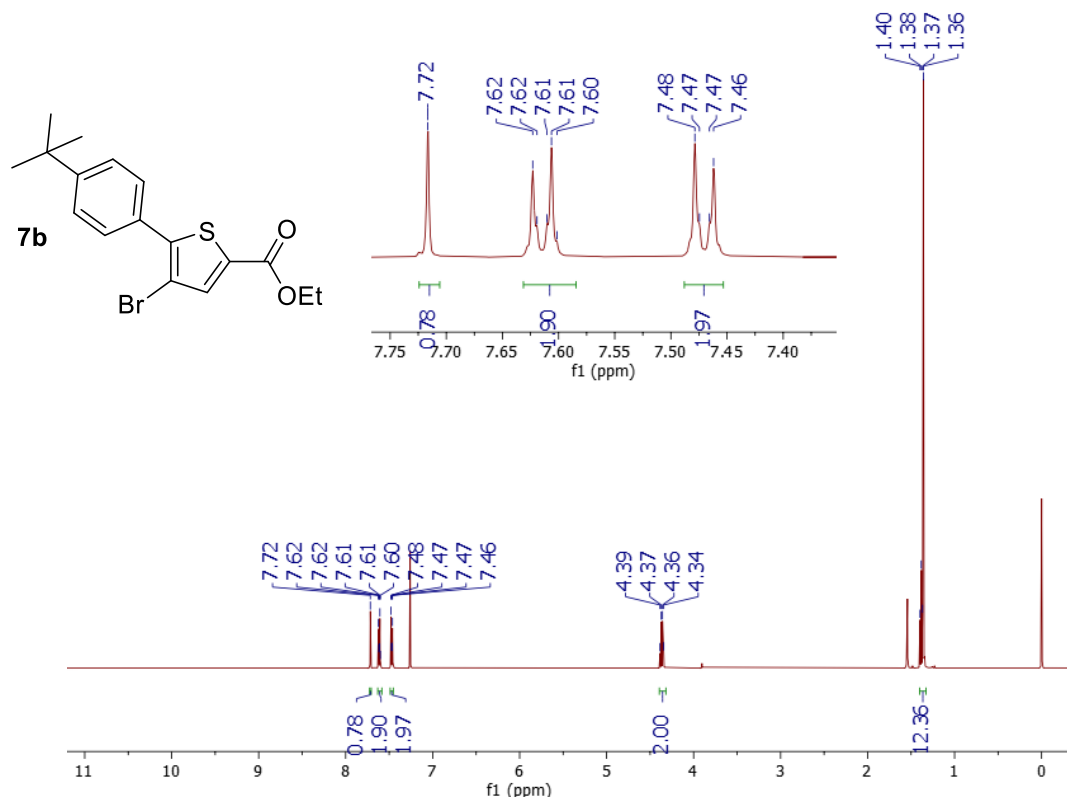
7a - ethyl 4-bromo-5-phenylthiophene-2-carboxylate

¹H NMR (500 MHz, CDCl₃)

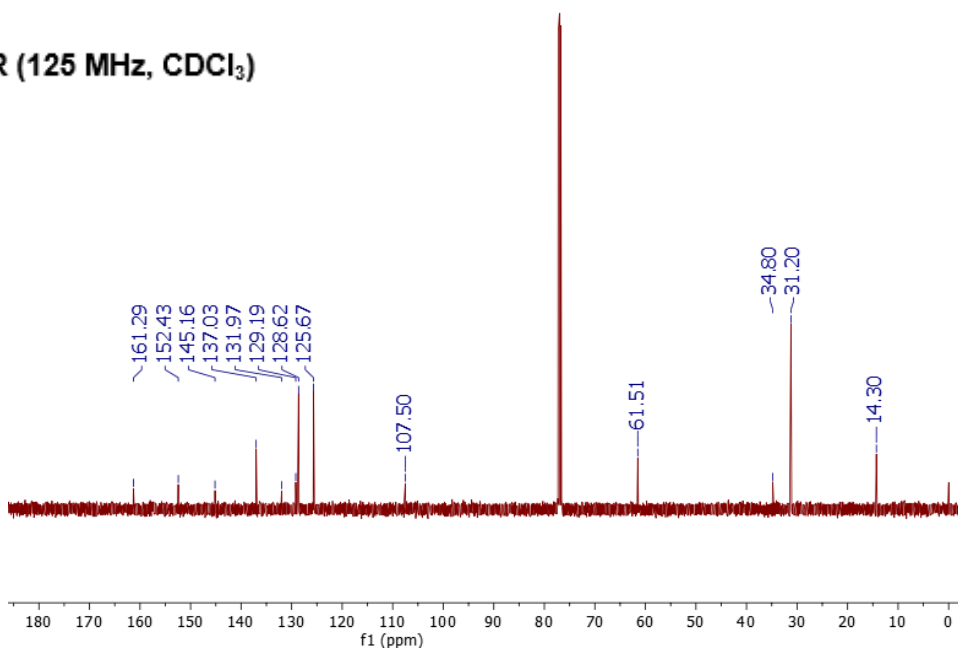


7b - ethyl 4-bromo-5-(4-(tert-butyl)phenyl)thiophene-2-carboxylate

¹H NMR (500 MHz, CDCl₃)

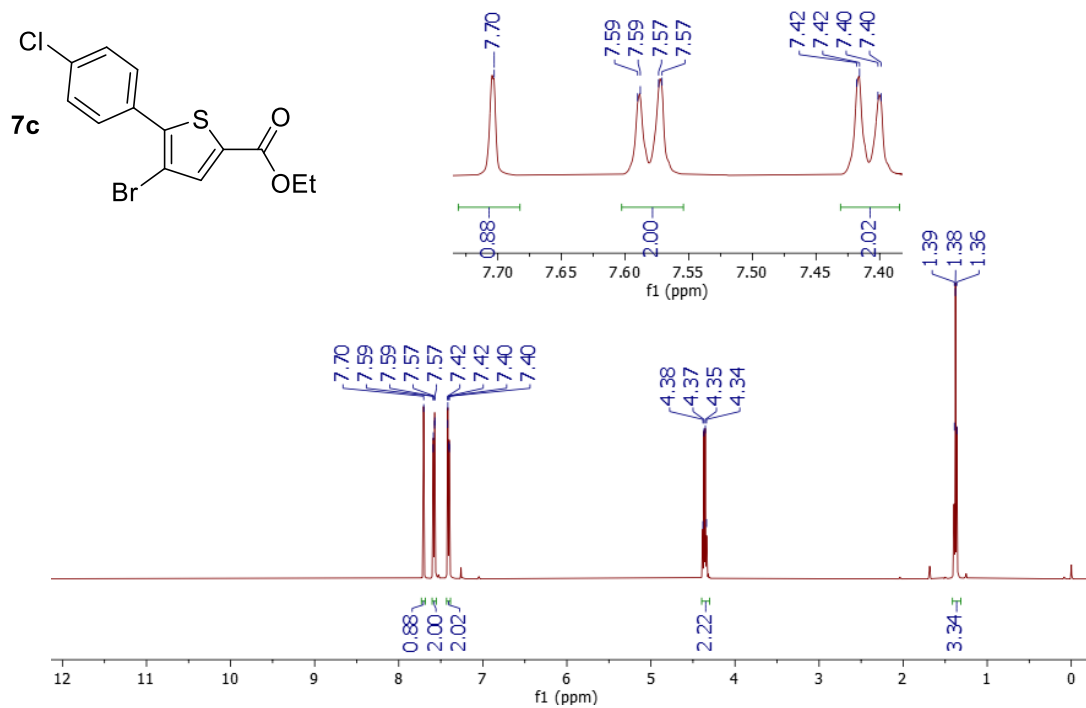


¹³C NMR (125 MHz, CDCl₃)

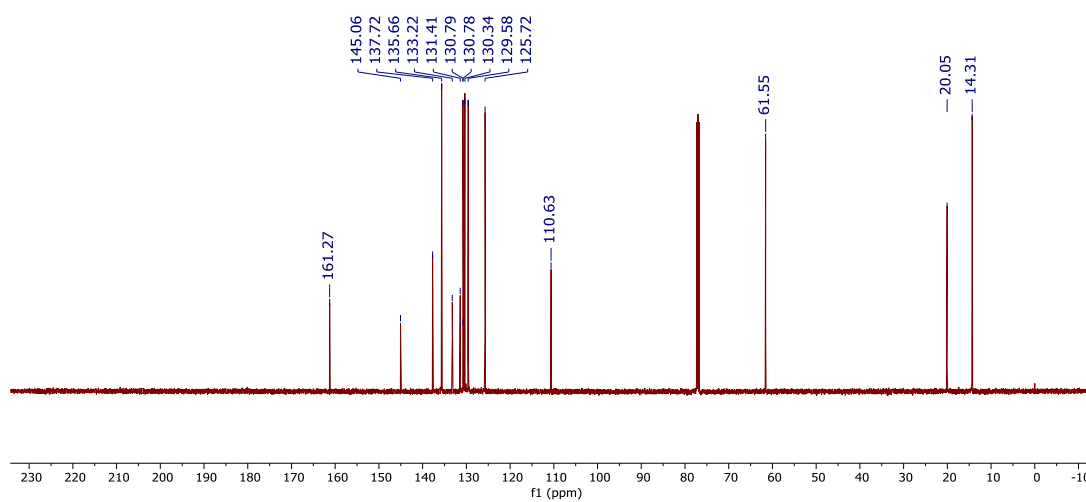


7c - ethyl 4-bromo-5-(4-chlorophenyl)thiophene-2-carboxylate

¹H NMR (500 MHz, CDCl₃)

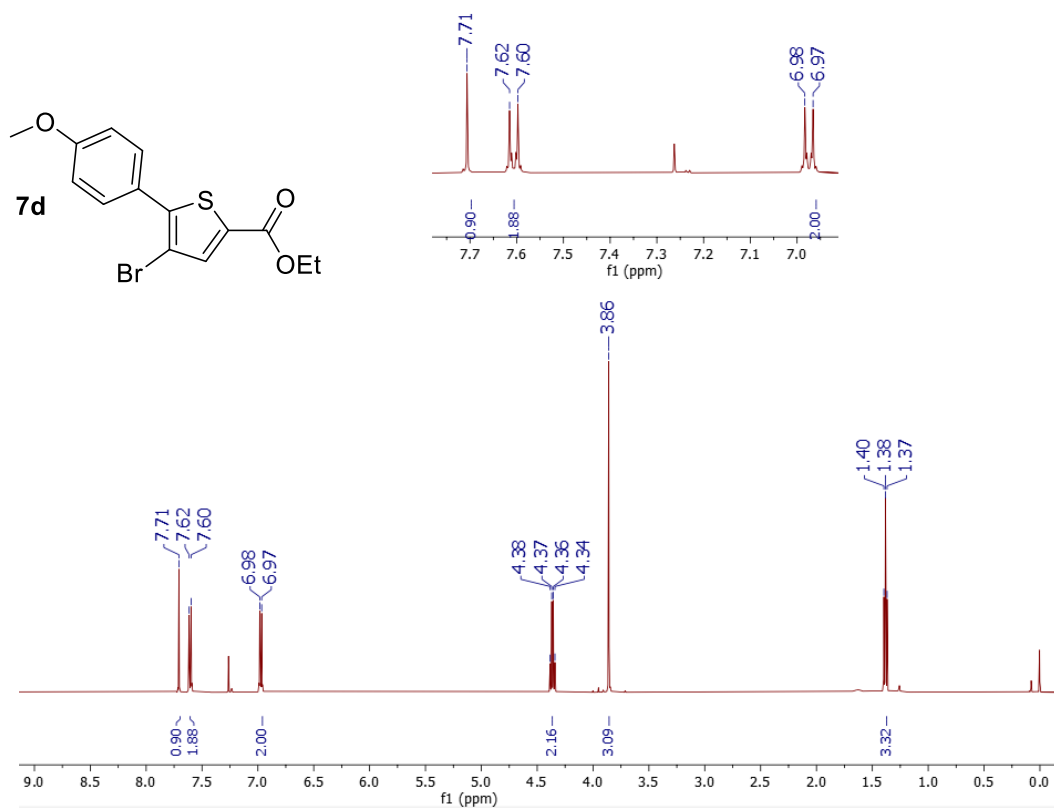


¹³C NMR (125 MHz, CDCl₃)

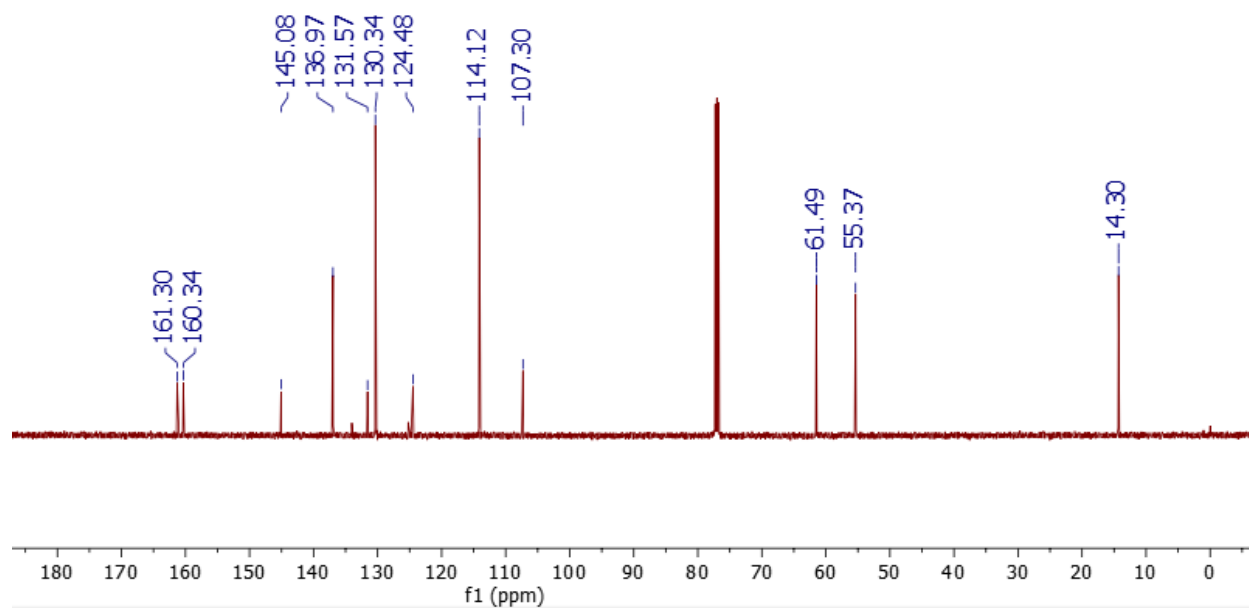


7d - ethyl 4-bromo-5-(4-methoxyphenyl)thiophene-2-carboxylate

¹H NMR (500 MHz, CDCl₃)

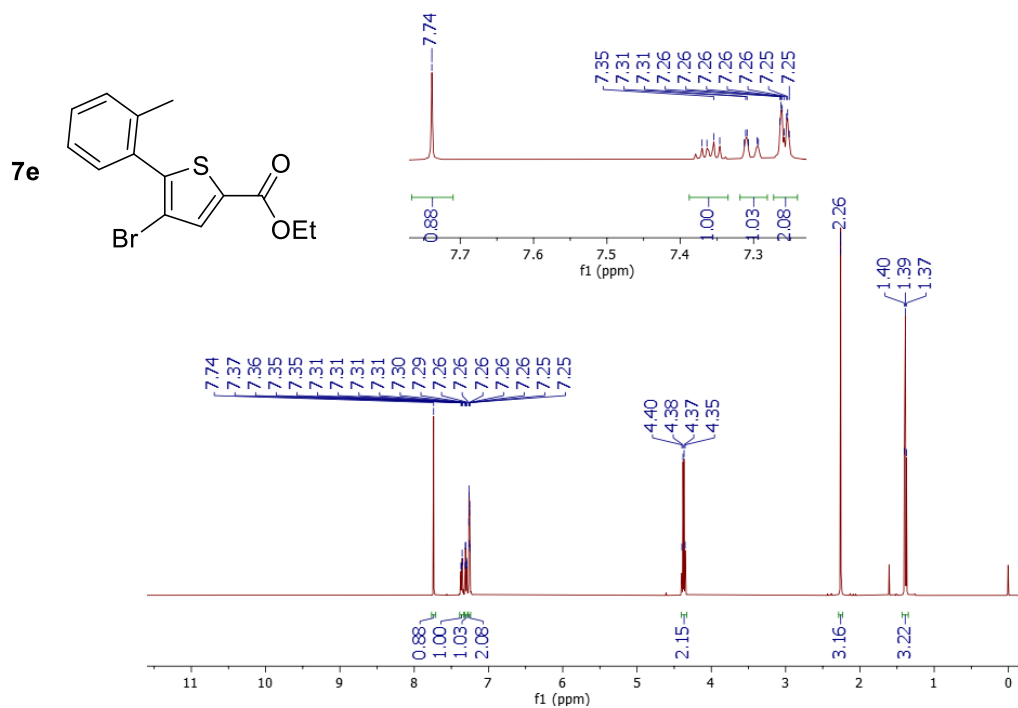


¹³C NMR (125 MHz, CDCl₃)

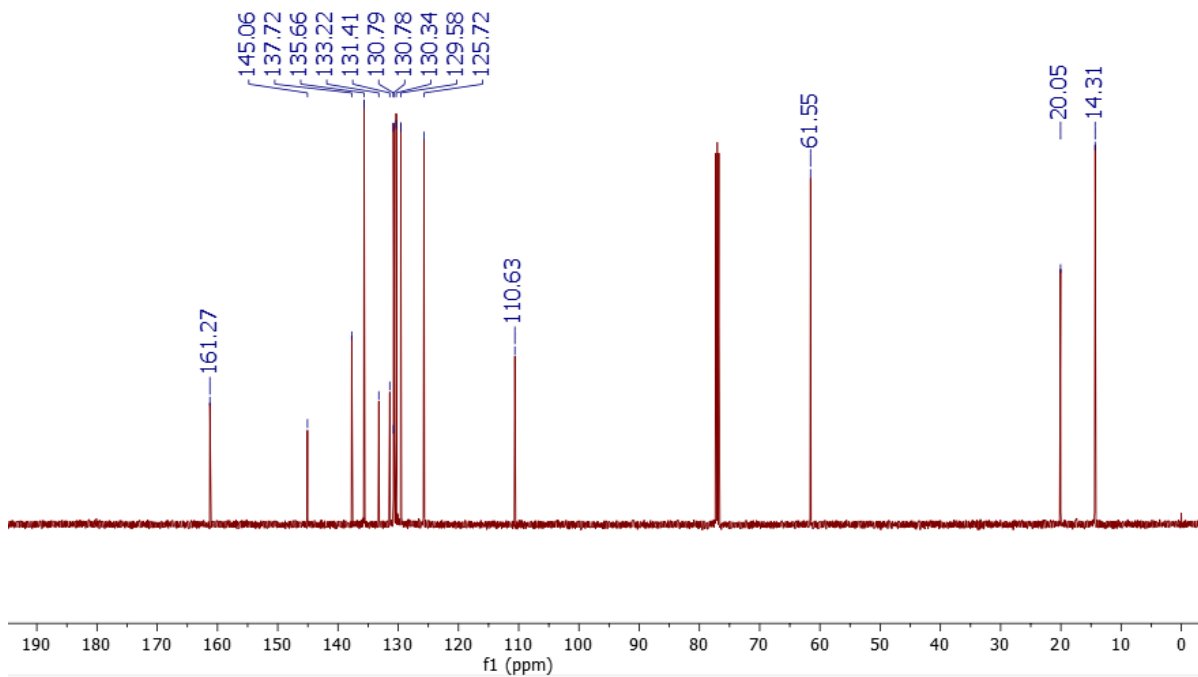


7e - ethyl 4-bromo-5-(o-tolyl)thiophene-2-carboxylate

¹H NMR (500 MHz, CDCl₃)

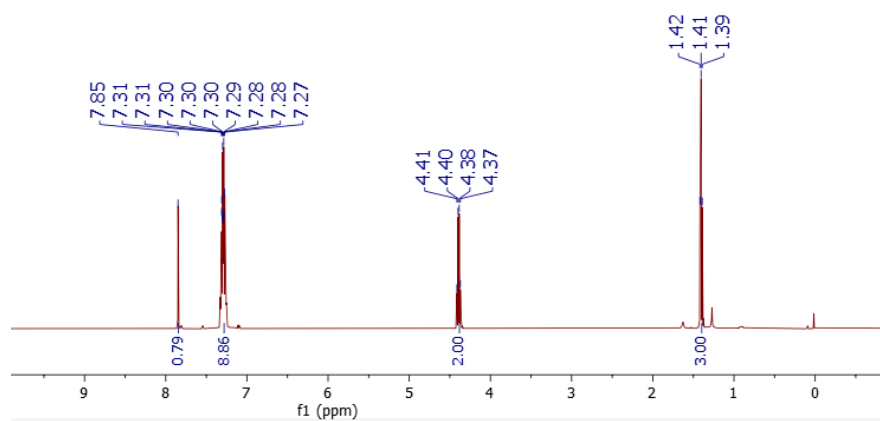
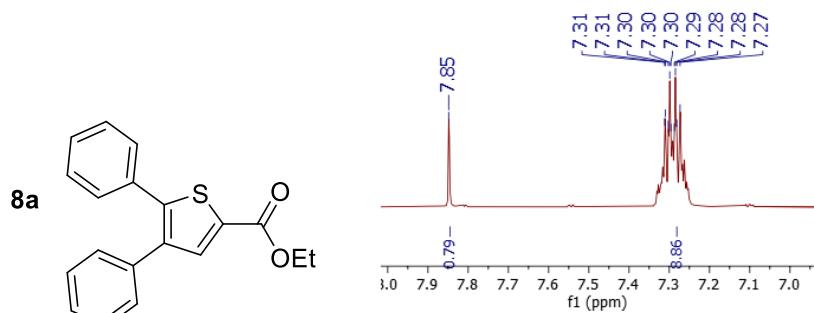


¹³C NMR (125 MHz, CDCl₃)

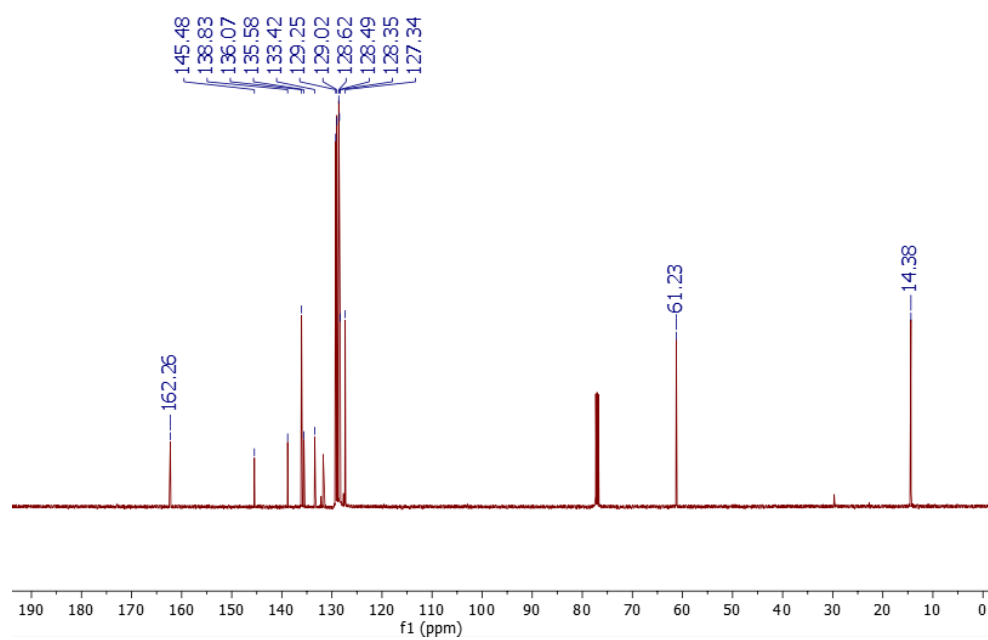


8a - ethyl 4,5-diphenylthiophene-2-carboxylate

¹H NMR (500 MHz, CDCl₃)

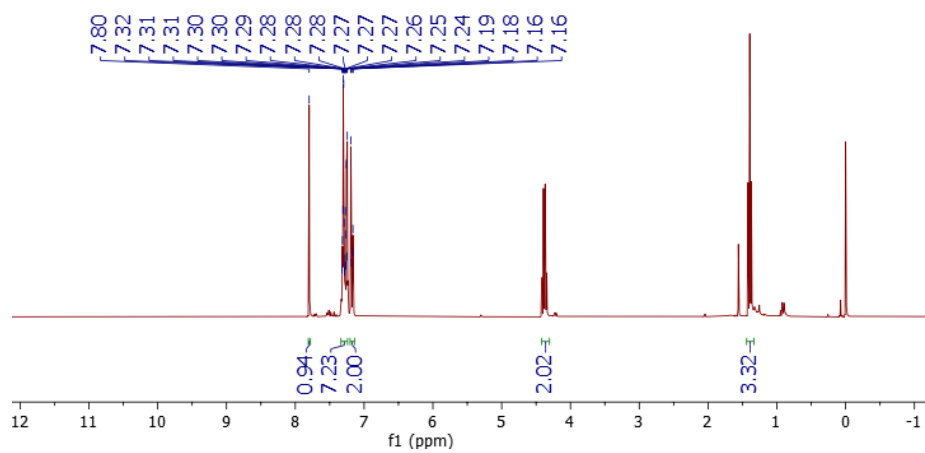
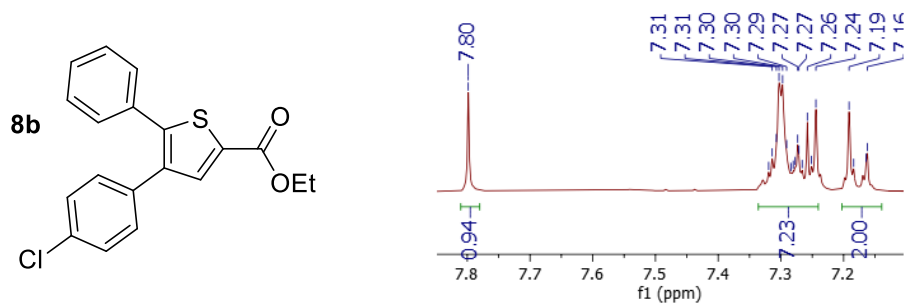


¹³C NMR (125 MHz, CDCl₃)

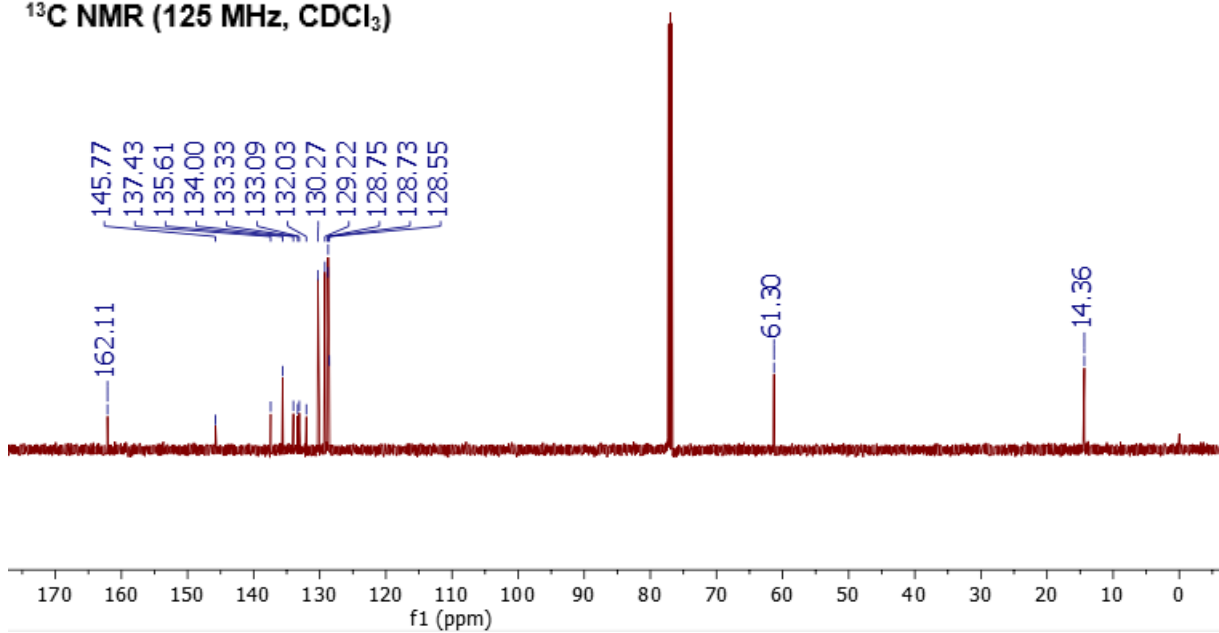


8b - ethyl 4-(4-chlorophenyl)-5-phenylthiophene-2-carboxylate

^1H NMR (500 MHz, CDCl_3)

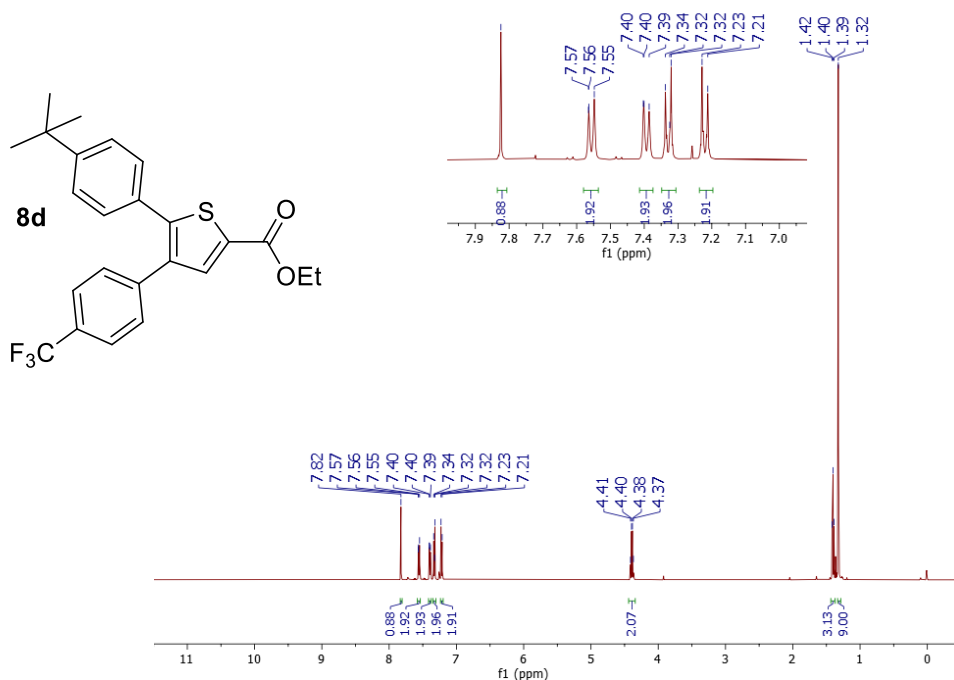


^{13}C NMR (125 MHz, CDCl_3)

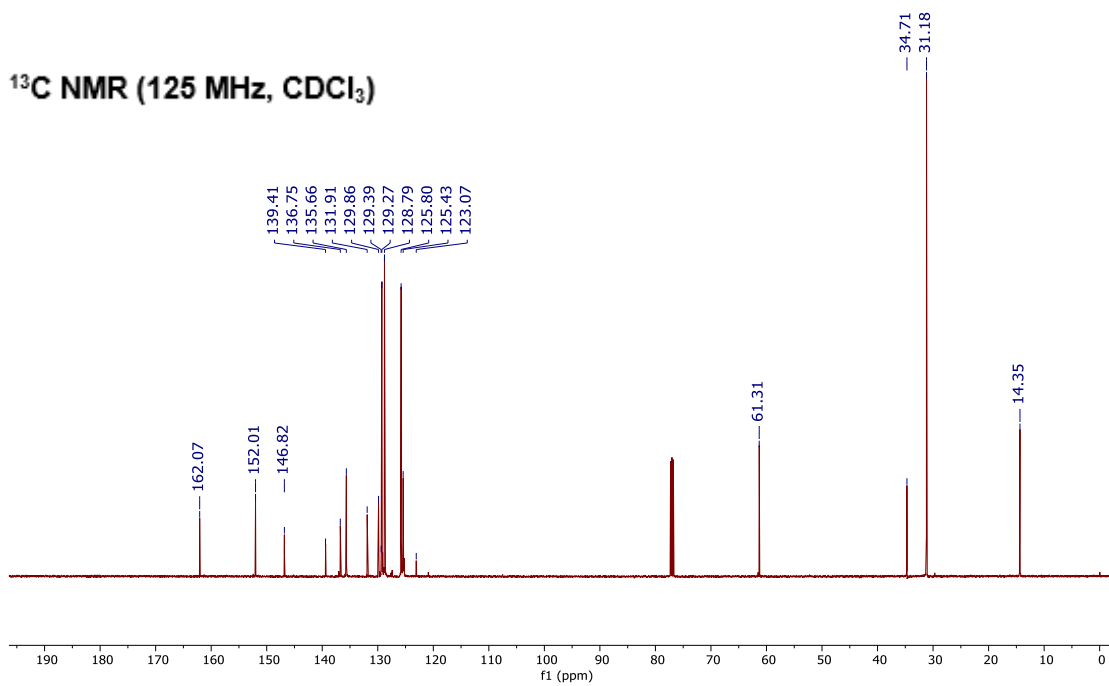


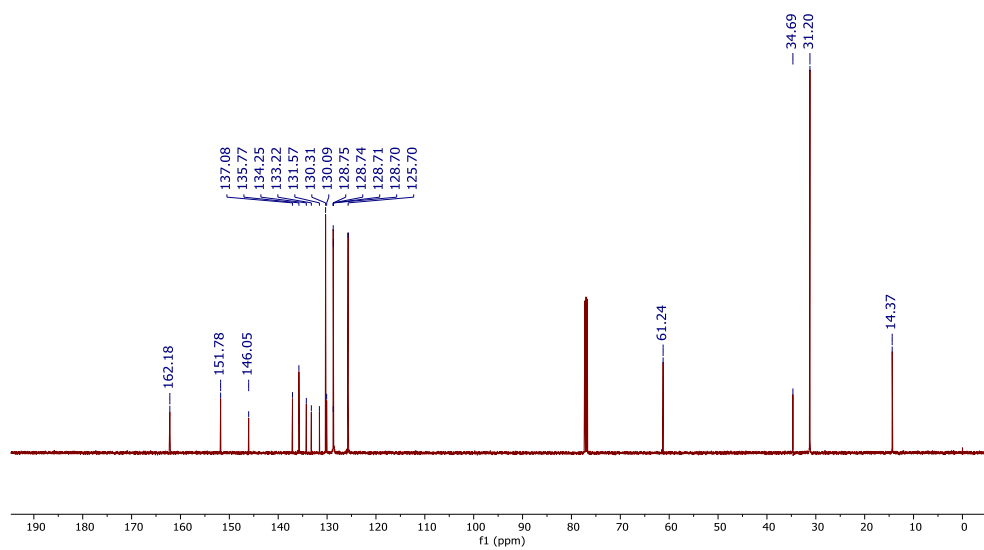
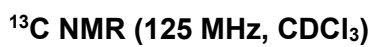
8d - ethyl 5-(4-(tert-butyl)phenyl)-4-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate

¹H NMR (500 MHz, CDCl₃)



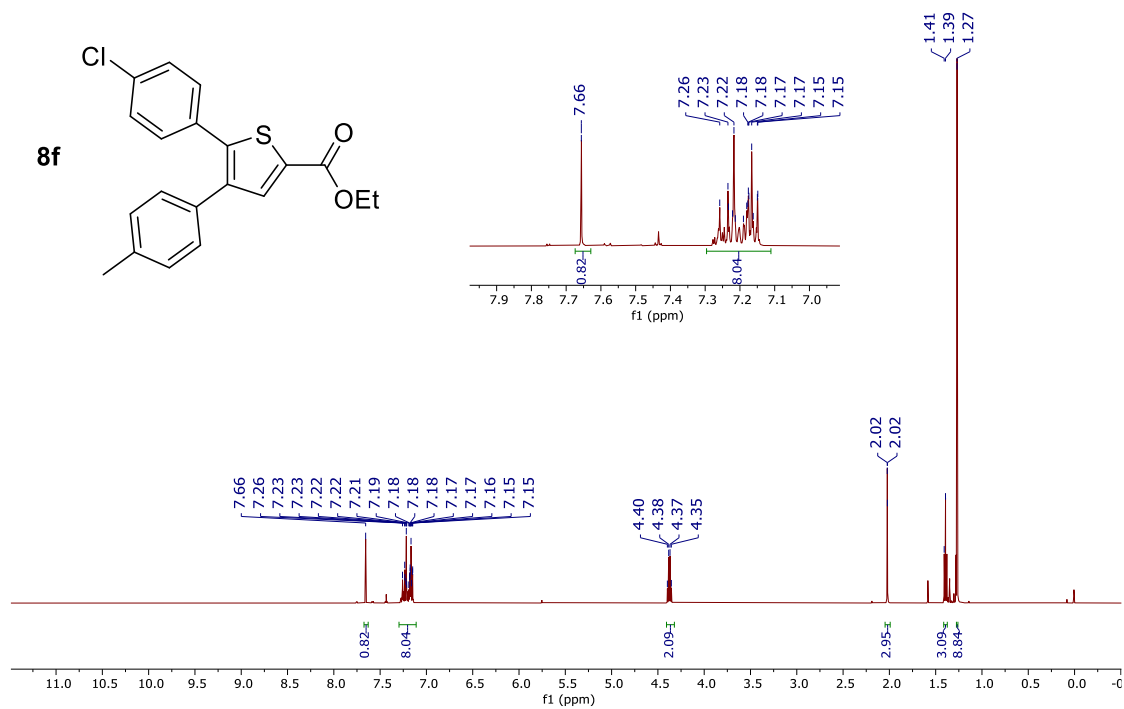
¹³C NMR (125 MHz, CDCl₃)



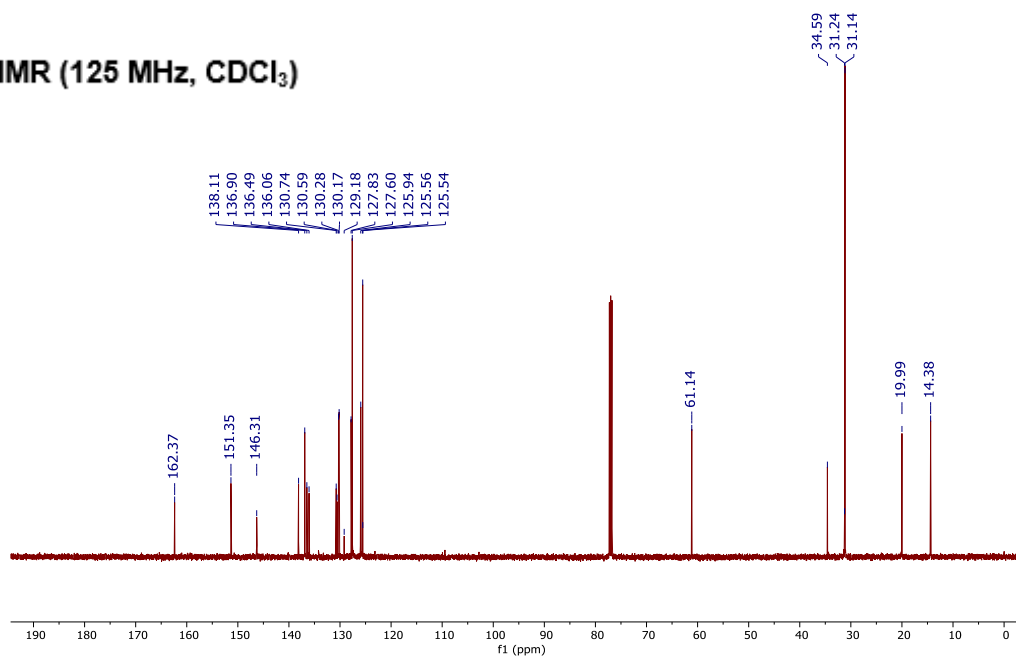
¹H NMR (500 MHz, CDCl₃)

8f - ethyl 5-(4-(tert-butyl)phenyl)-4-(o-tolyl)thiophene-2-carboxylate

¹H NMR (500 MHz, CDCl₃)

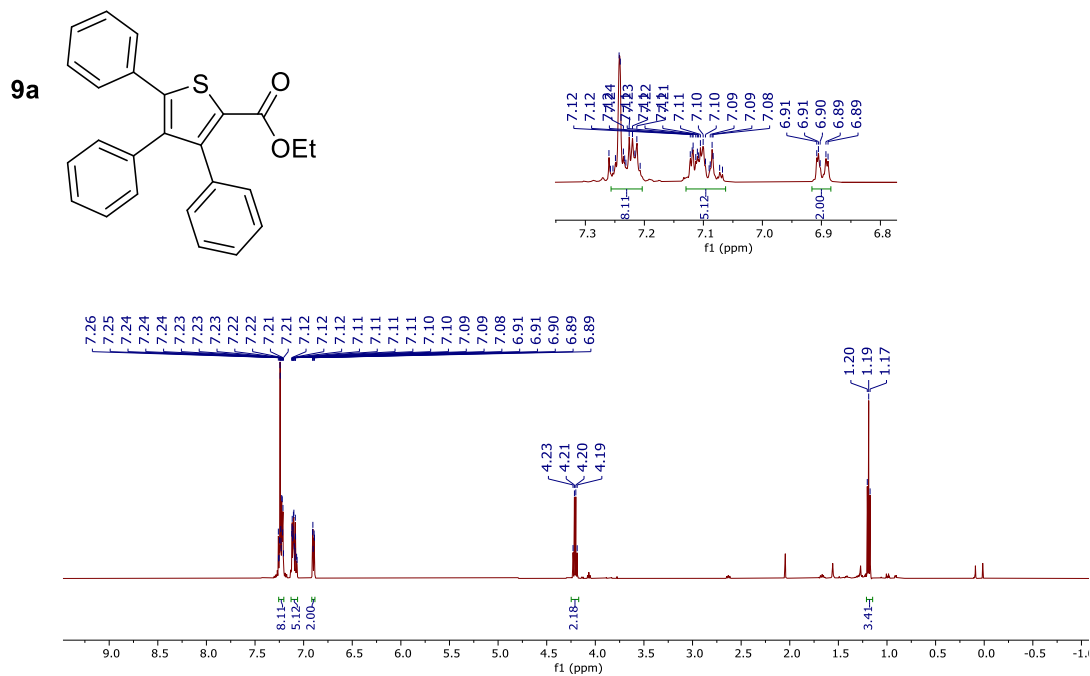


¹³C NMR (125 MHz, CDCl₃)

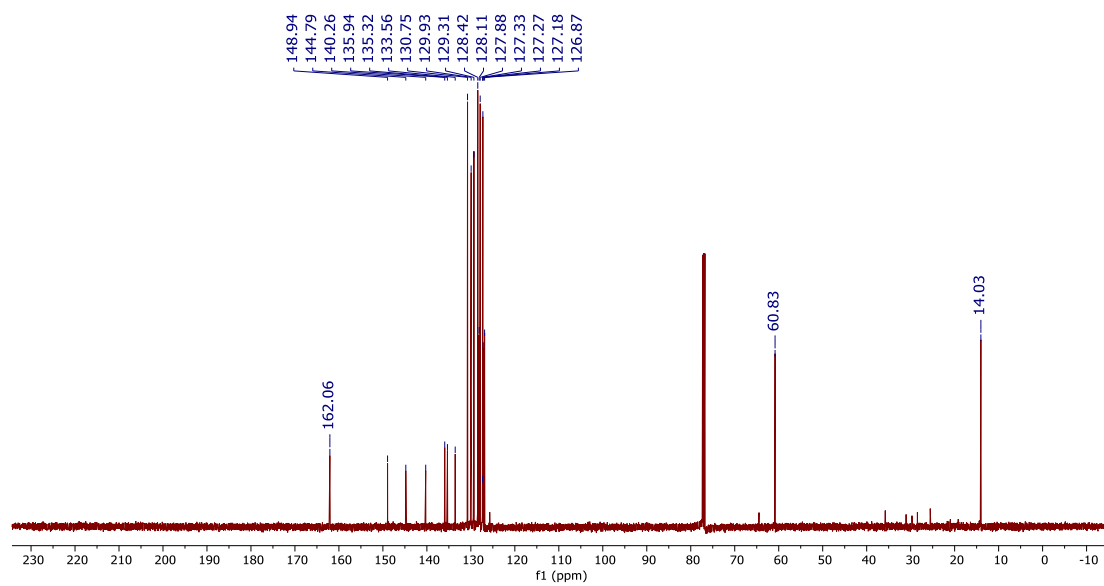


9a - ethyl 3,4,5-triphenylthiophene-2-carboxylate

¹H NMR (500 MHz, CDCl₃)

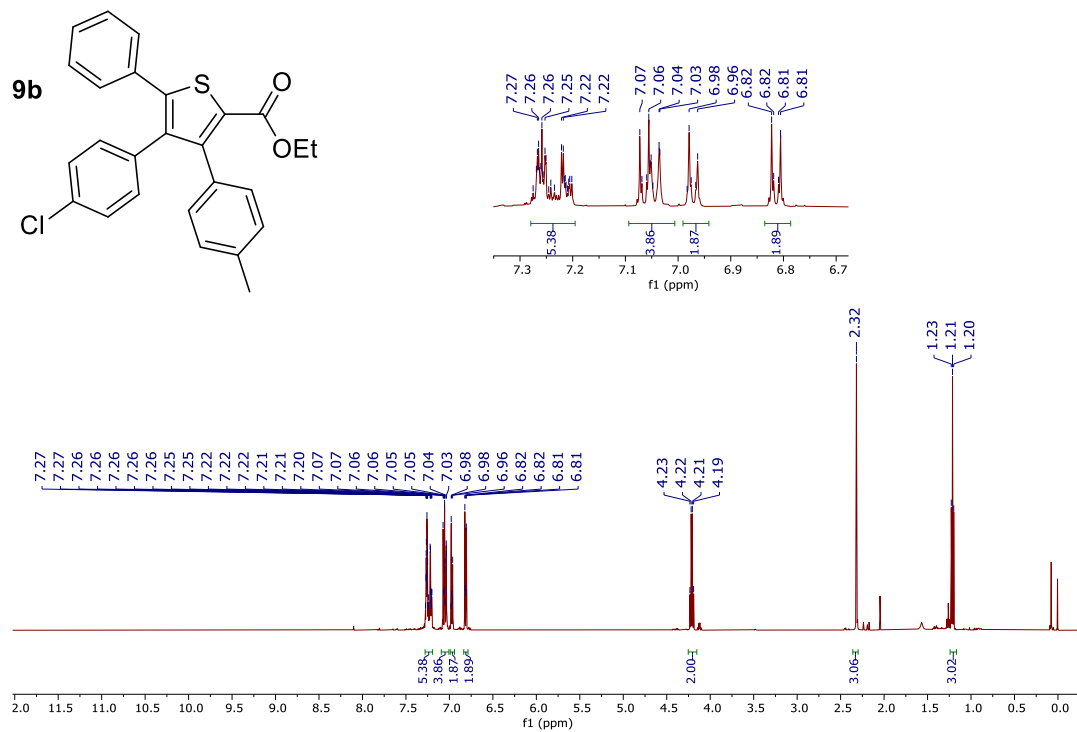


¹³C NMR (125 MHz, CDCl₃)

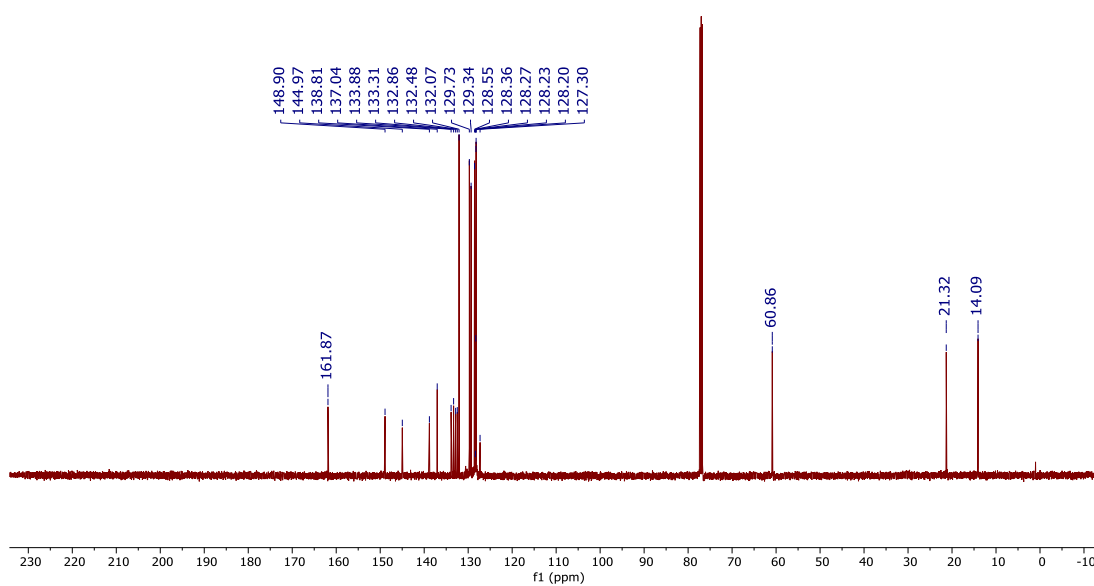


9b - ethyl 4-(4-chlorophenyl)-5-phenyl-3-(p-tolyl)thiophene-2-carboxyl

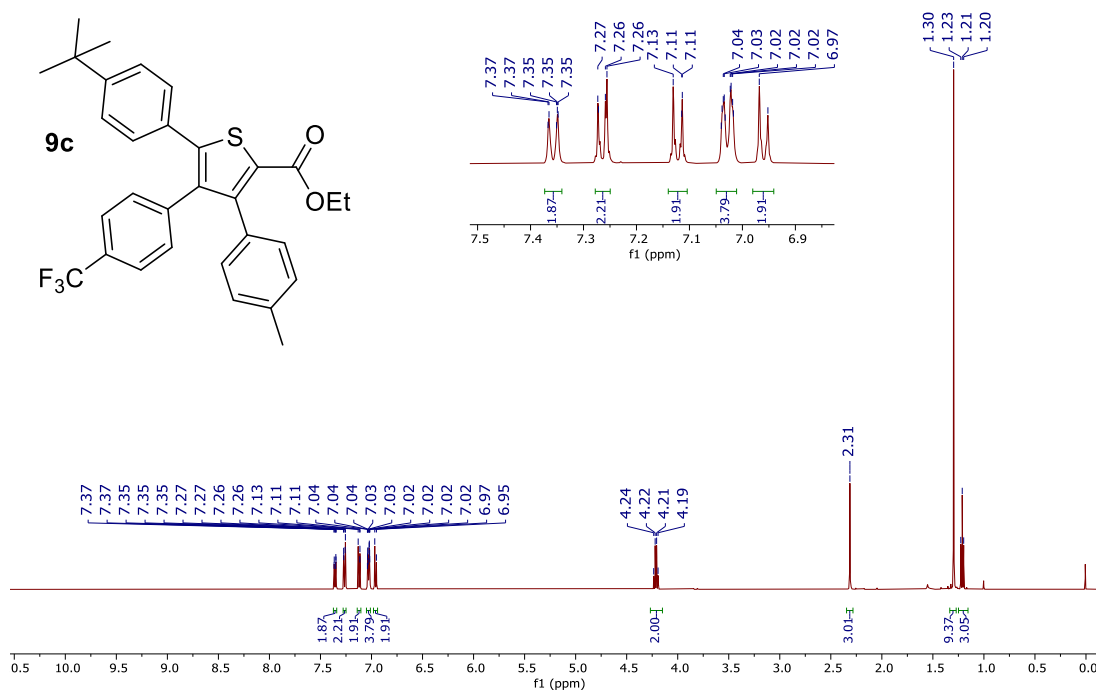
¹H NMR (500 MHz, CDCl₃)



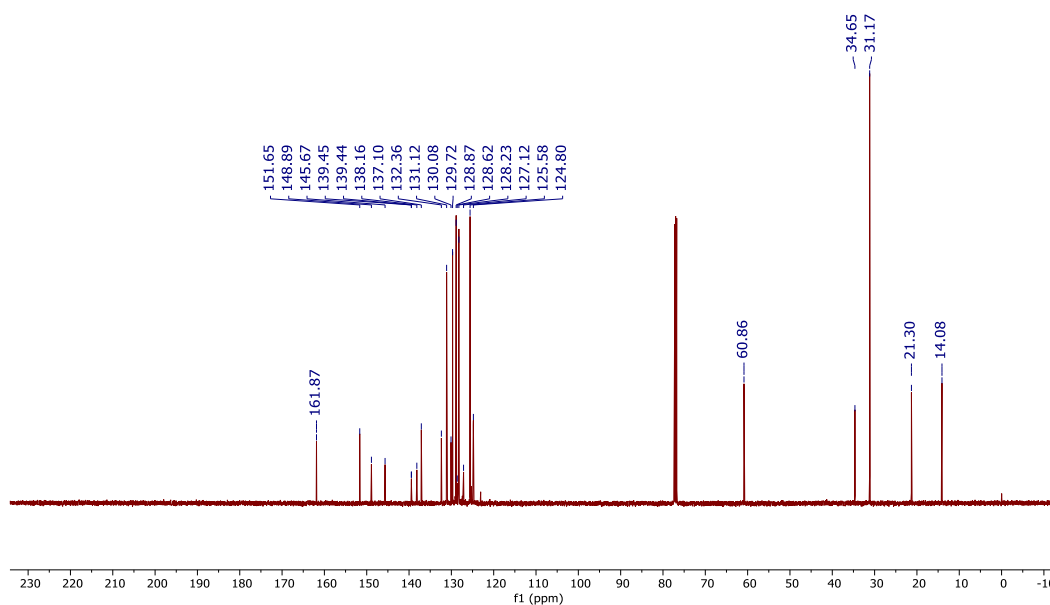
¹³C NMR (125 MHz, CDCl₃)



9c - ethyl 5-(4-(tert-butyl)phenyl)-3-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate
¹H NMR (500 MHz, CDCl₃)

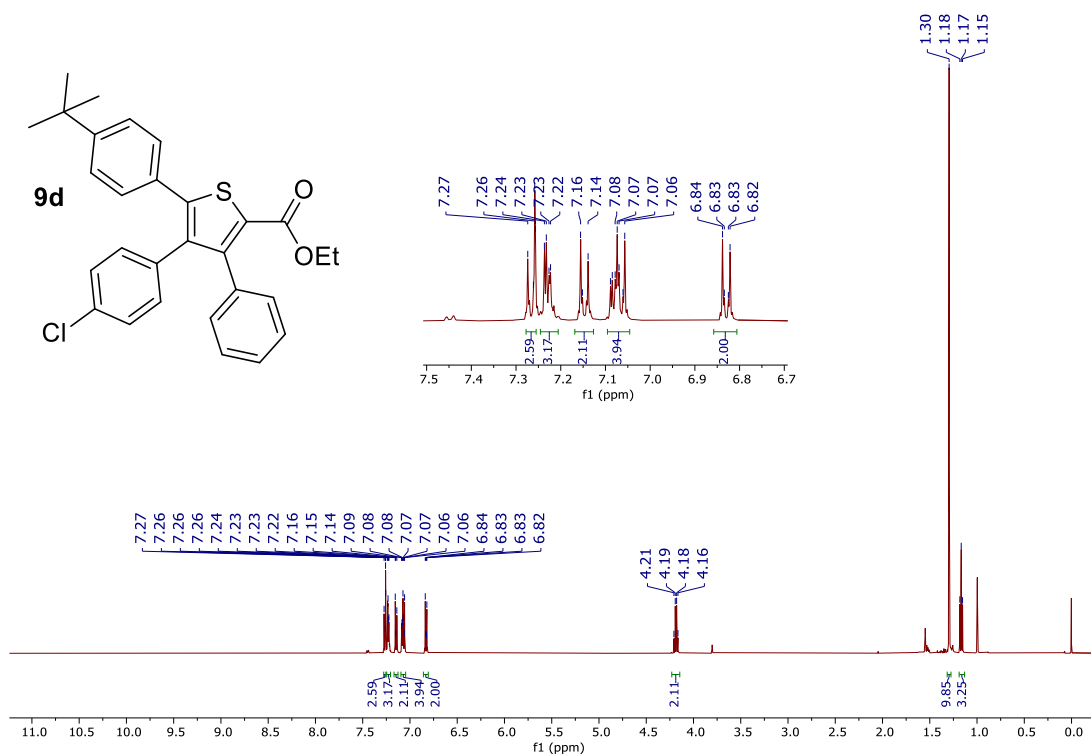


¹³C NMR (125 MHz, CDCl₃)

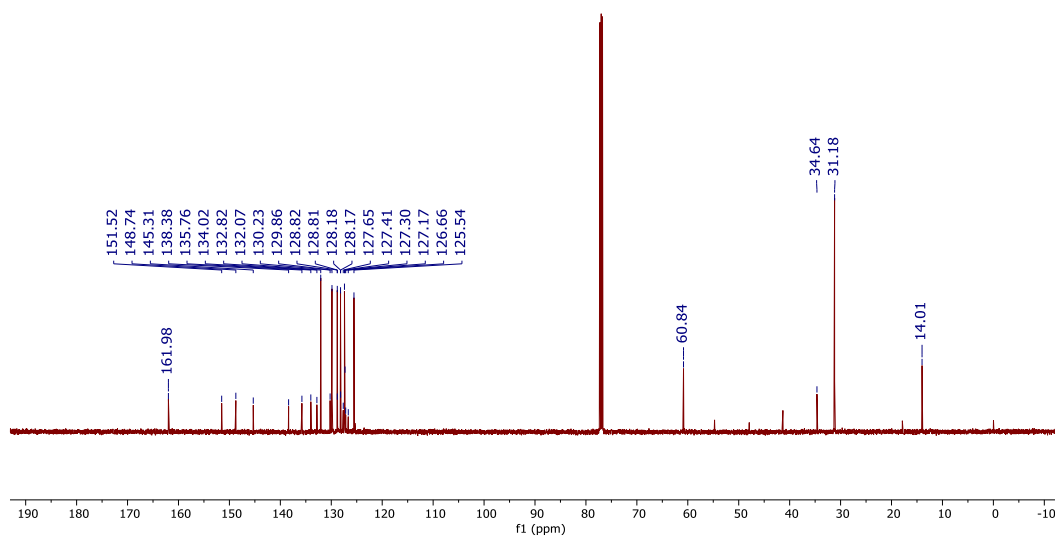


9d - ethyl 5-(4-(tert-butyl)phenyl)-4-(4-chlorophenyl)-3-phenylthiophene-2-carboxylate

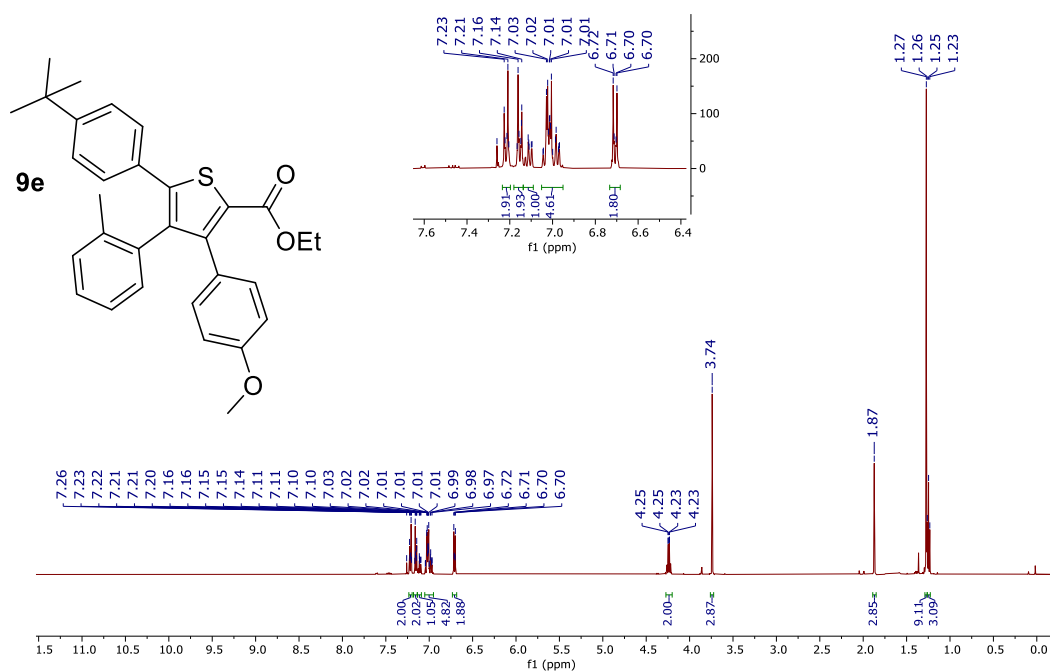
¹H NMR (500 MHz, CDCl₃)



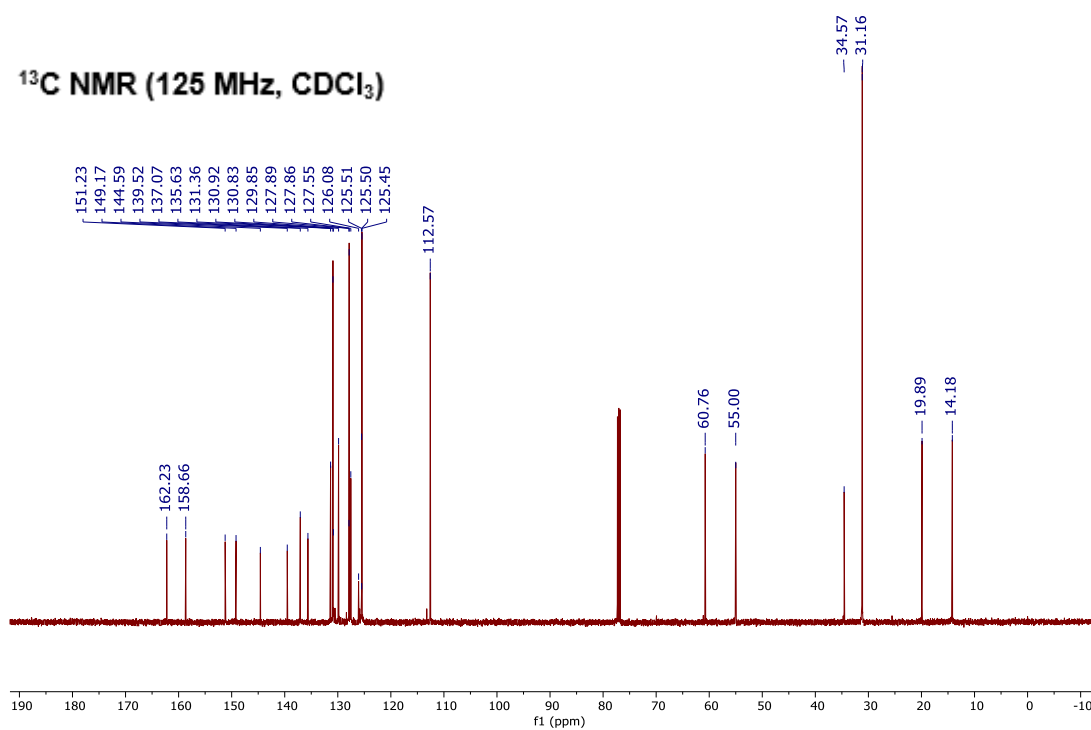
¹³C NMR (125 MHz, CDCl₃)



9e - ethyl 5-(4-(tert-butyl)phenyl)-3-(4-methoxyphenyl)-4-(o-tolyl)thiophene-2-carboxylate
¹H NMR (500 MHz, CDCl₃)

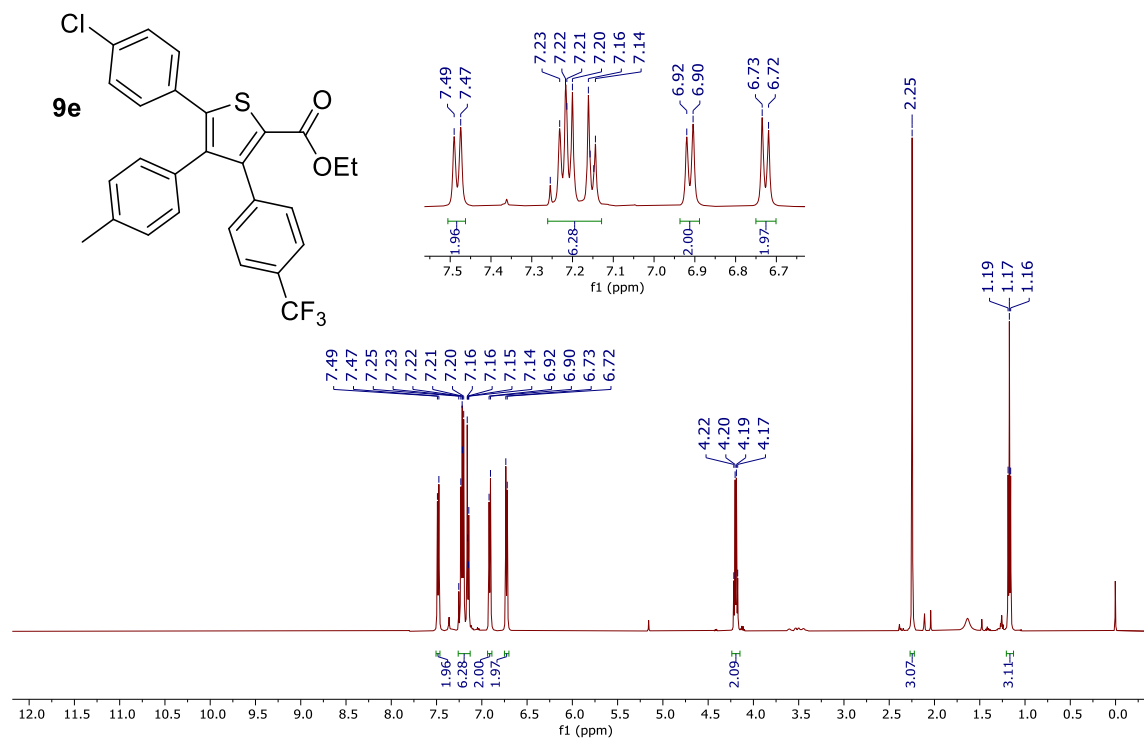


¹³C NMR (125 MHz, CDCl₃)

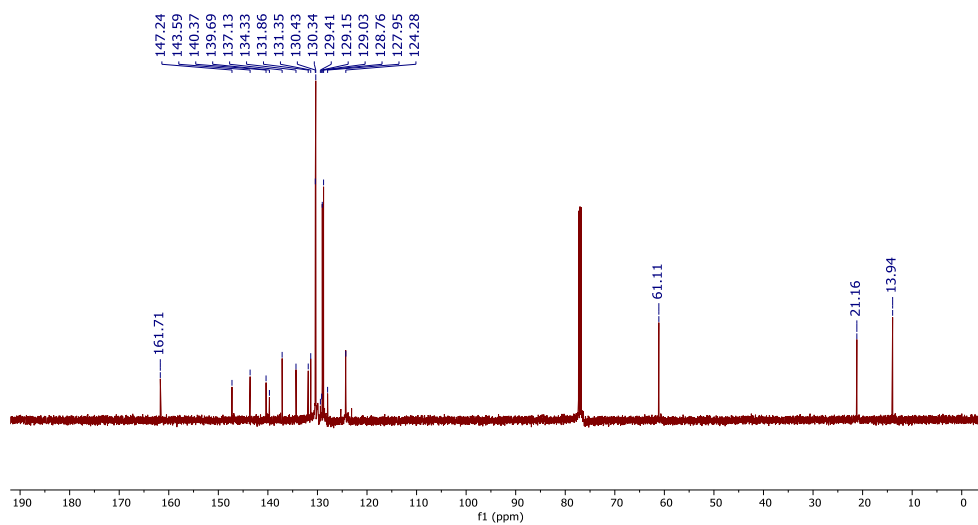


5f - ethyl 5-(4-chlorophenyl)-4-(p-tolyl)-3-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate

¹H NMR (500 MHz, CDCl₃)

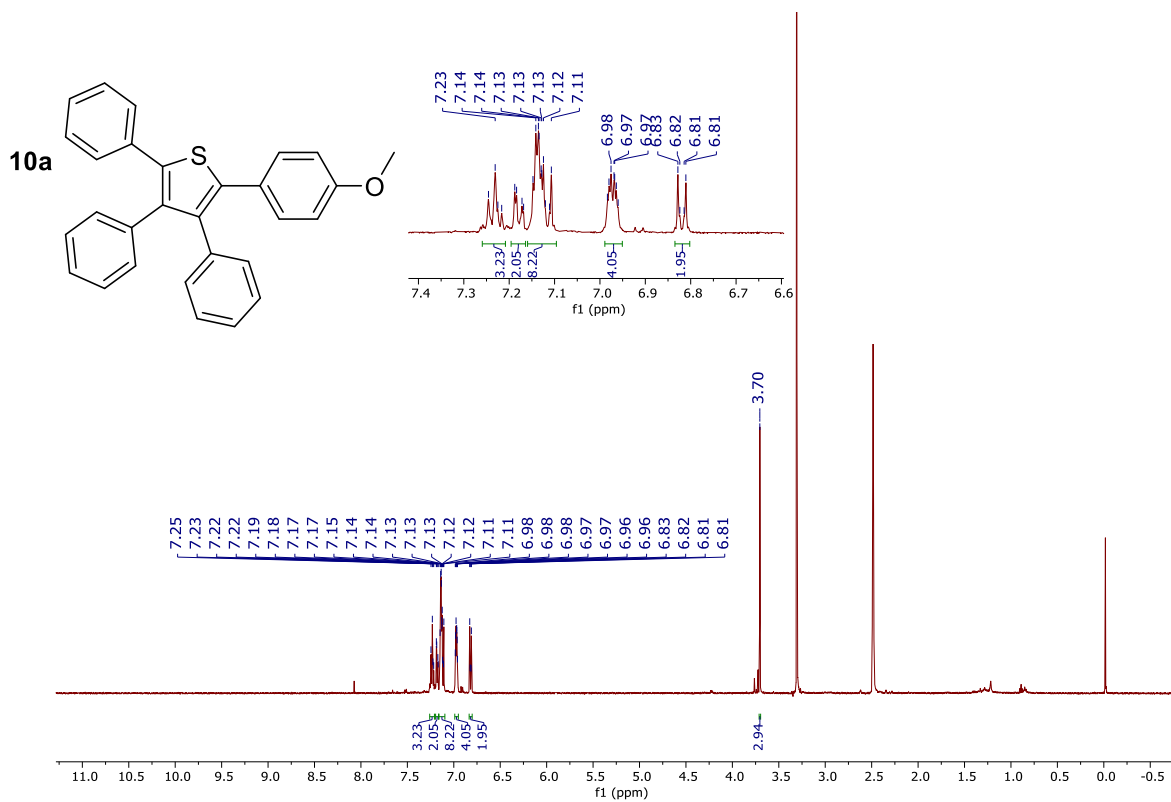


¹³C NMR (125 MHz, CDCl₃)

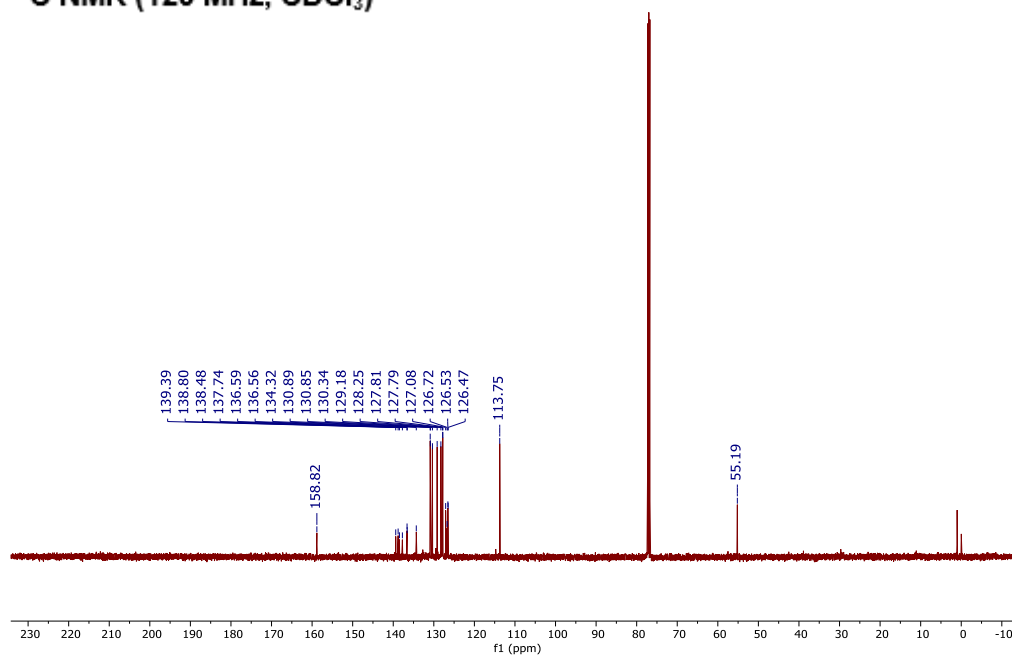


10a - 2-(4-methoxyphenyl)-3,4,5-triphenylthiophene

¹H NMR (500 MHz, DMSO δ -6)

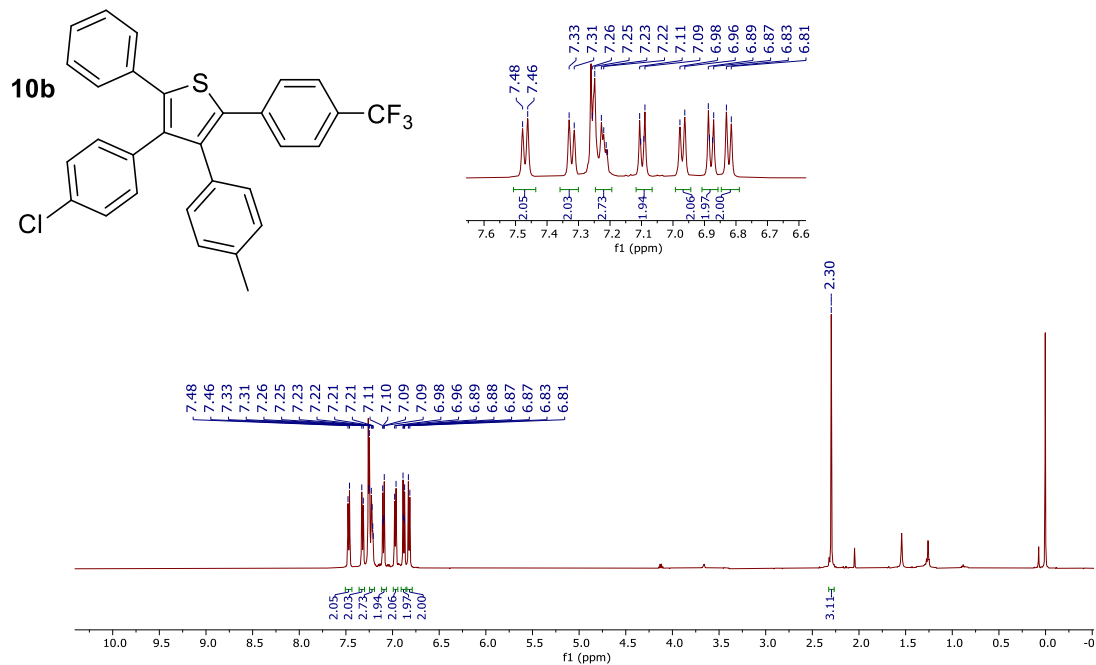


¹³C NMR (125 MHz, CDCl₃)

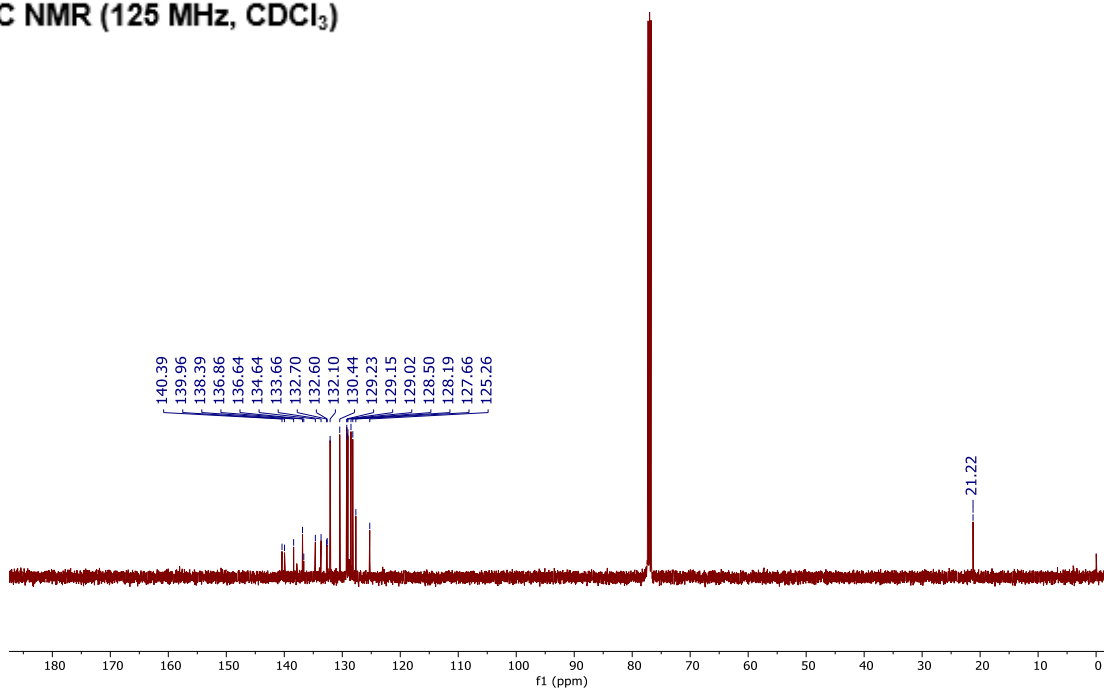


10b - 3-(4-chlorophenyl)-2-phenyl-4-(p-tolyl)-5-(4-(trifluoromethyl)phenyl)thiophene

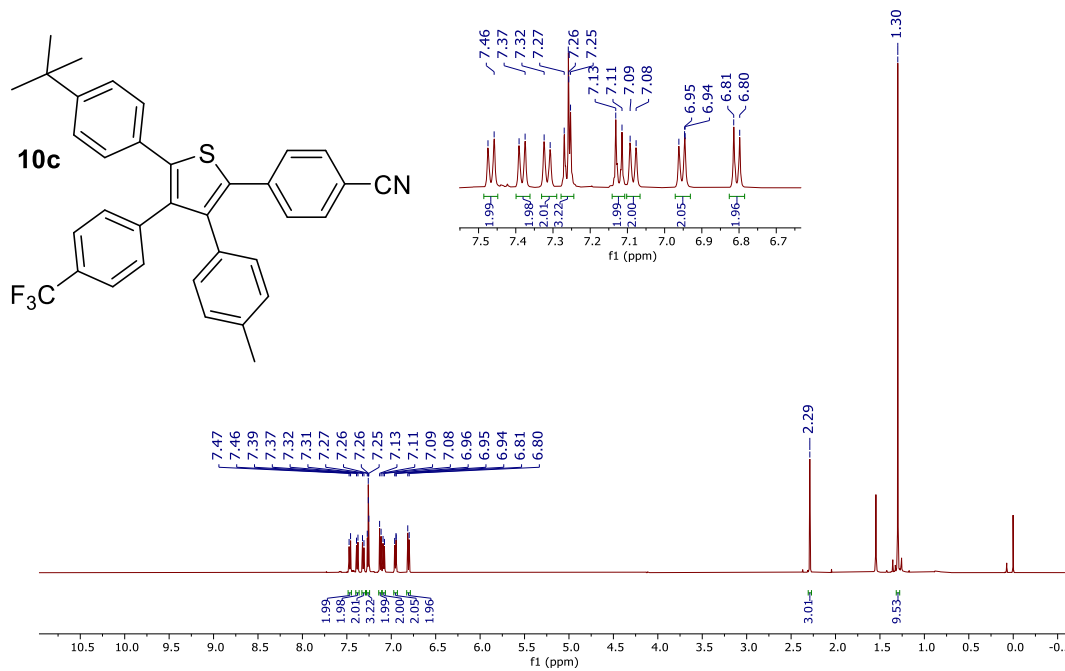
¹H NMR (500 MHz, CDCl₃)



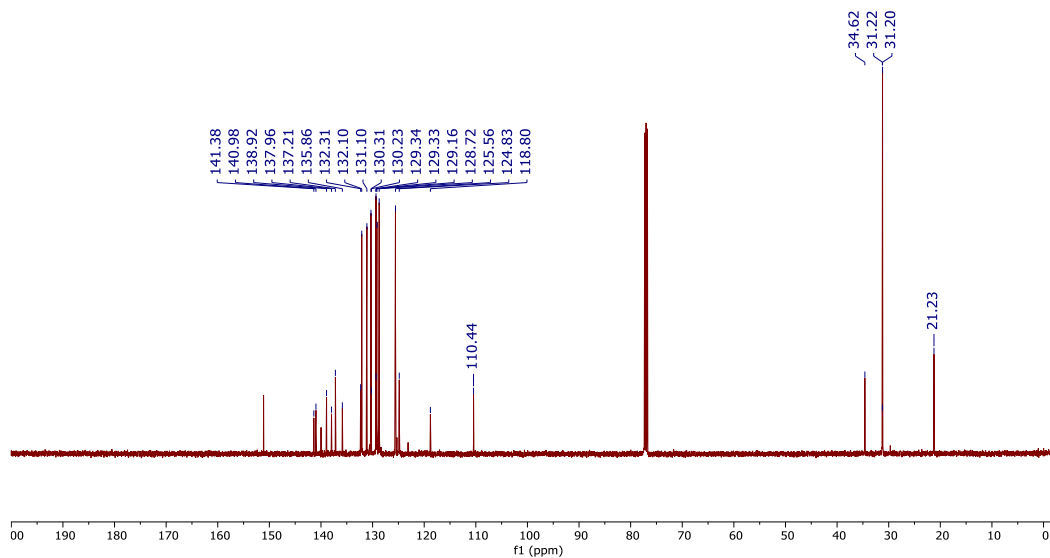
¹³C NMR (125 MHz, CDCl₃)



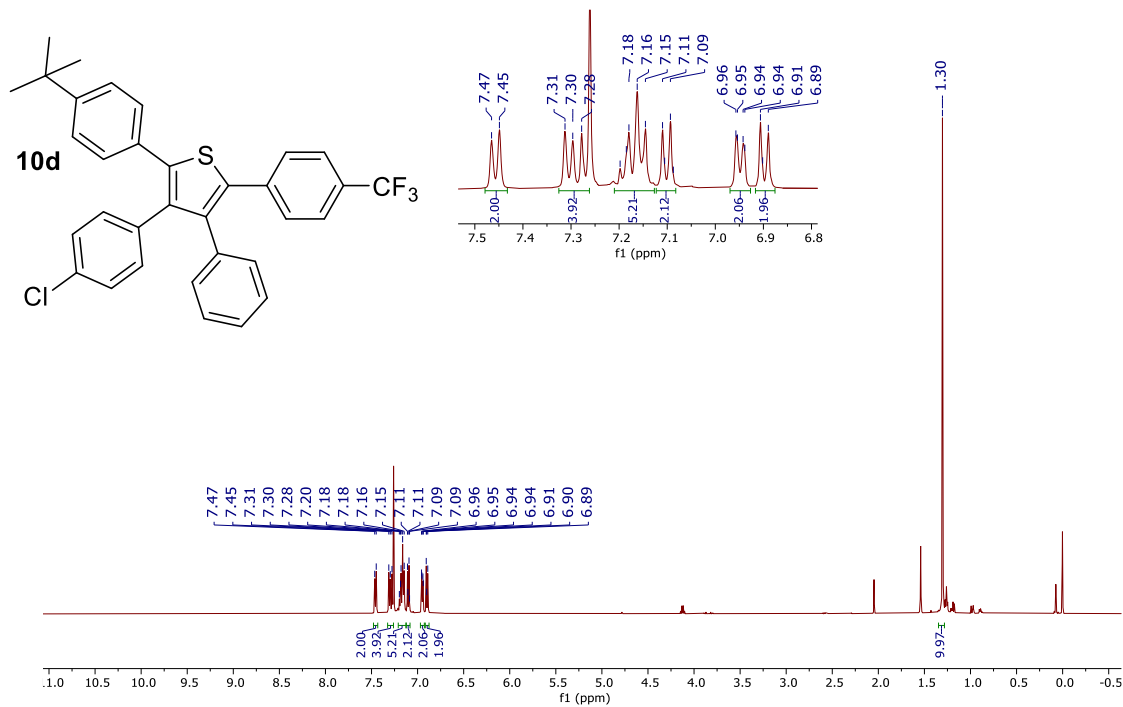
10c - 4-(5-(4-(tert-butyl)phenyl)-3-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)thiophen-2-yl)benzo-nitrile
¹H NMR (500 MHz, CDCl₃)



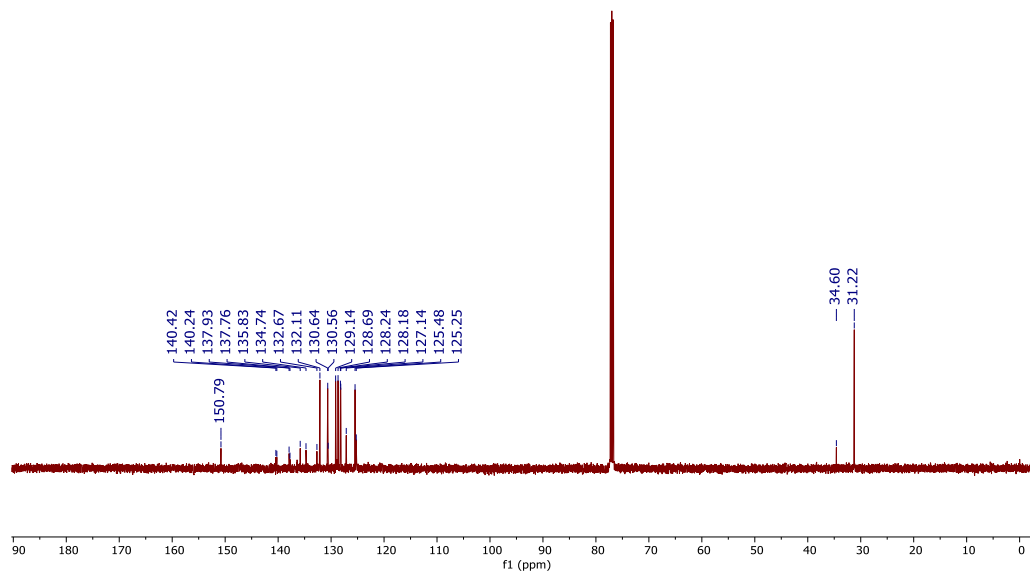
¹³C NMR (125 MHz, CDCl₃)



10d - 2-(4-(tert-butyl)phenyl)-3-(4-chlorophenyl)-4-phenyl-5-(4-(trifluoromethyl)phenyl)thiophene
¹H NMR (500 MHz, CDCl₃)

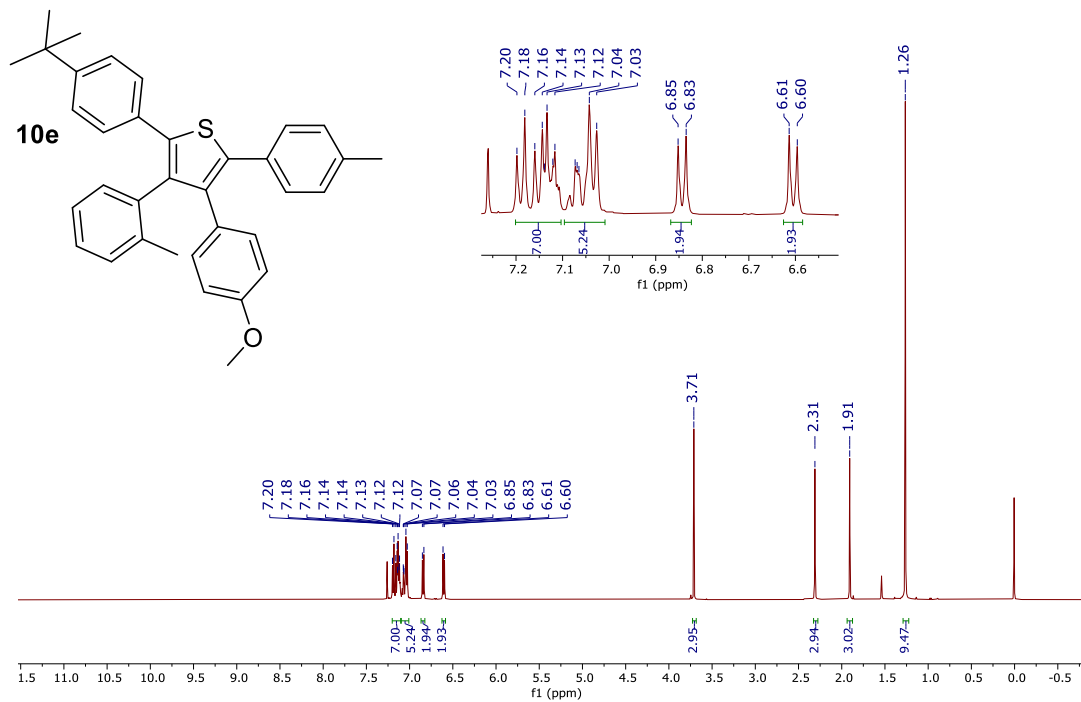


¹³C NMR (125 MHz, CDCl₃)

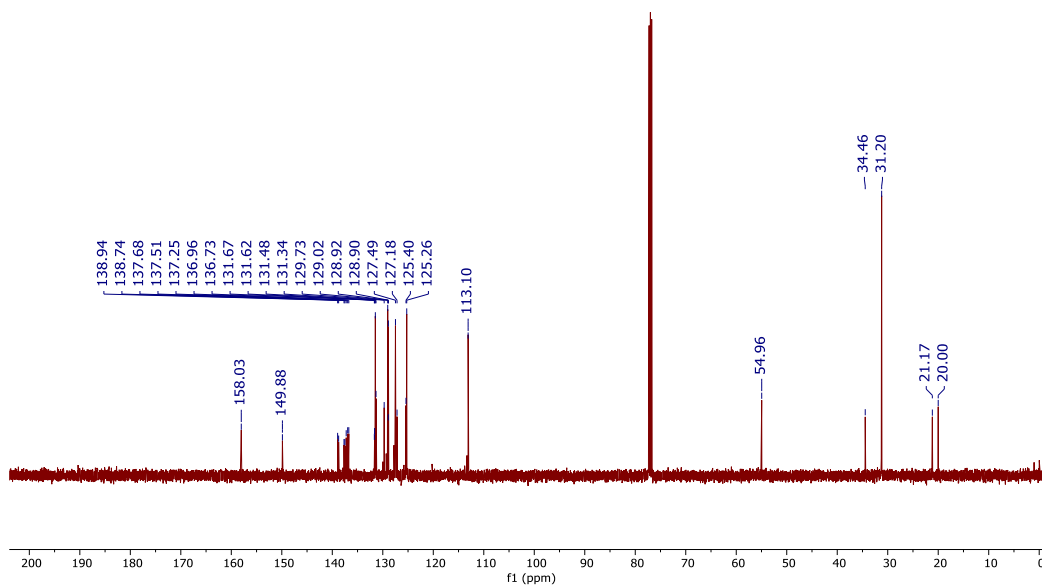


10e - 2-(4-(tert-butyl)phenyl)-4-(4-methoxyphenyl)-3-(o-tolyl)-5-(p-tolyl)thiophene

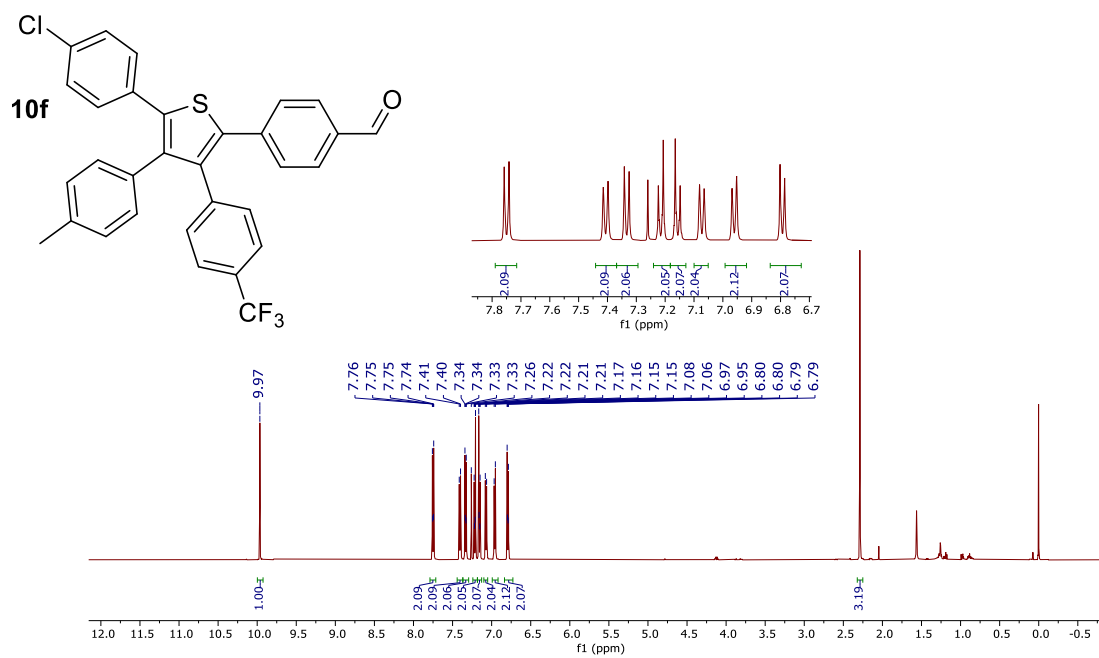
^1H NMR (500 MHz, CDCl_3)



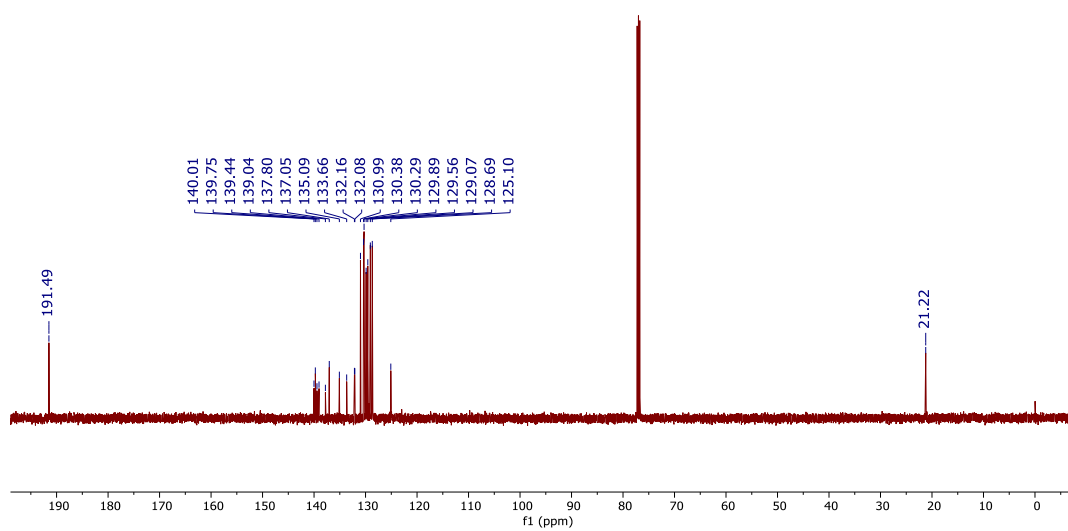
^{13}C NMR (125 MHz, CDCl_3)



10f - 4-(5-(4-chlorophenyl)-4-(p-tolyl)-3-(4-(trifluoromethyl)phenyl)thiophen-2-yl)benzaldehyde
¹H NMR (500 MHz, CDCl₃)

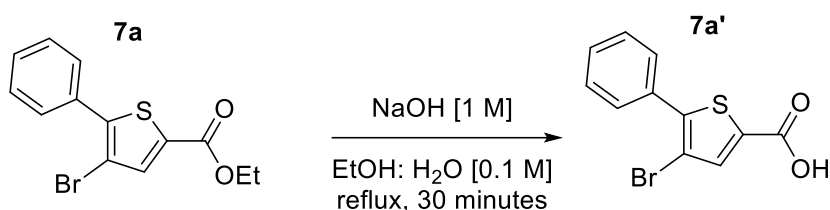


¹³C NMR (125 MHz, CDCl₃)



Crystallography information

Crystallization methods



Scheme 54: Saponification of 6a for crystallization

Conditions: Brominated thiophene ester **7a** (0.2 mmols) are dissolved in 1 mL of ethanol, 1 mmol of NaOH is dissolved in 1 mL of water. The two are mixed in a 10 mL round bottom flask and heated until reflux in an oil bath with a hotplate for 30 minutes. The reaction is then cooled, acidified with around 2 mL of 1M HCl in a separatory funnel and extracted with about 10 mL of EtOAc (2x). The combined organic layers are then washed with brine (2x), dried with sodium sulfate and evaporated under reduced pressure.

Initial crystallization set-up

Brominated thiophene carboxylic acid **7a'** (0.1 mmols, 31 mg) are dissolved in a small amount of ethyl acetate (about 1 mL) in a 4 mL glass vial. This vial is placed in a larger 20 mL glass vial, which is itself filled with hexanes. The larger vial is capped and left for 1 week.

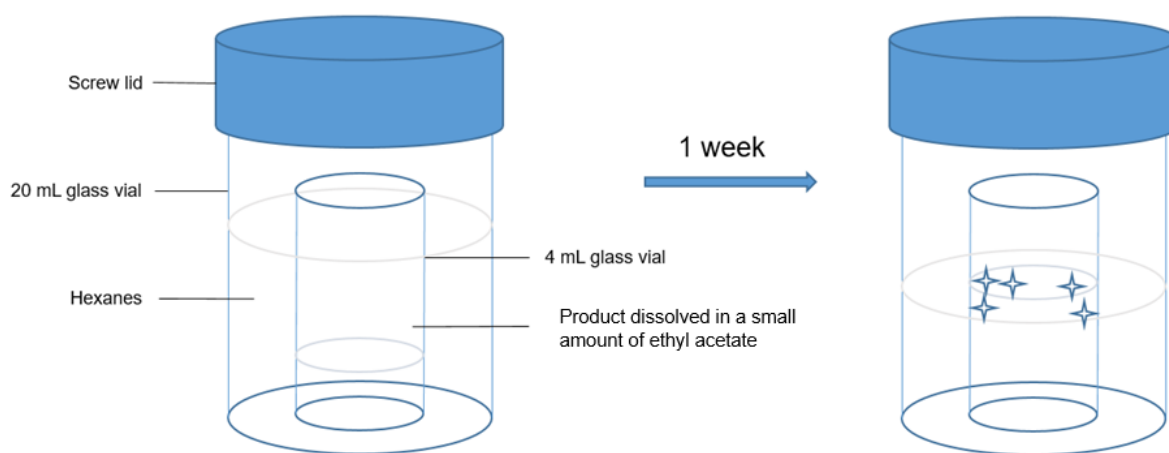


Figure 18: Crystallization set up for **7a'**

After 1 week, the interior vial is filling with hexanes, and white, filamentous crystals have formed near the solvent front. Conditions for crystallization: Product **10e**

0.15 mmols of product **10e** was dissolved in warmed hexanes (boiled and allowed to cool for a moment) in a 4 mL glass vial. The vial was closed with a plastic cap, and an 18 gauge needle was inserted into the cap. The vial was left to evaporate slowly to dryness over 5 days. Large clumps of needle-like (and some rod) crystals formed, and an oily residue was carefully rinsed off with cold hexanes.

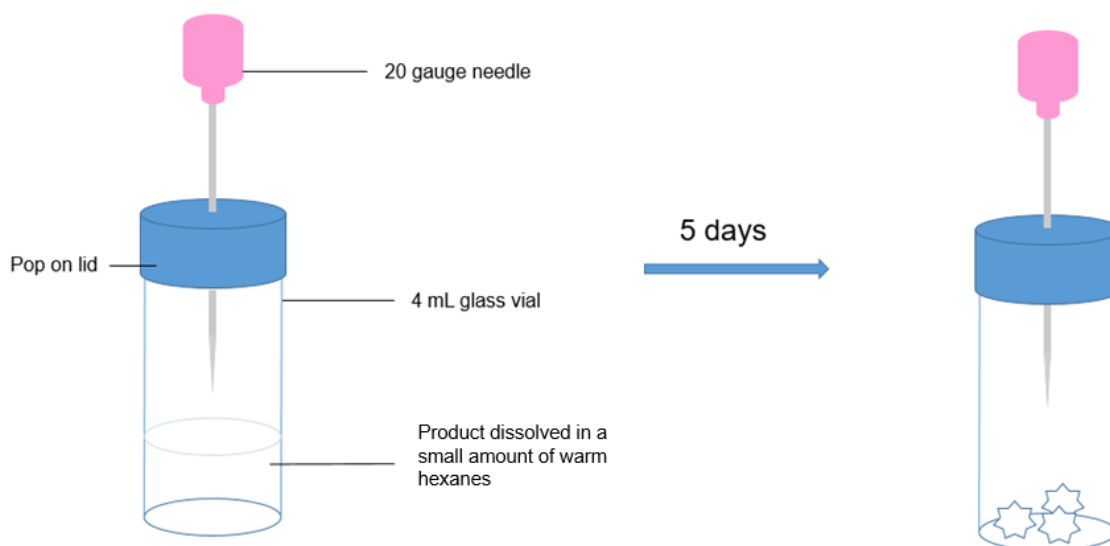


Figure 19: Crystallization set up for 10e

Crystallographic data and parameters

X-ray crystallography was performed on a Bruker APEX-DUO diffractometer using the Cu K α microfocus source. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. Data were corrected for absorption effects using the multiscan method (SADABS). The structures were solved by SHELXT and refined using the APEX3 software package. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were generated in idealized positions, riding on the carrier atoms with isotropic thermal parameters.

Table 15: Crystallographic data

	10e	7a'
CCDC code	2088565	2093162
Formula	C ₃₅ H ₃₄ OS	C ₁₁ H ₇ BrO ₂ S
F.W. (g mol ⁻¹)	502.68	283.14
<i>T</i> /K	110(2)	110(2)
Wavelength/Å	1.54178	1.54178
Size/mm ³	0.17×0.15×0.12	0.032×0.69×0.578
Crystal System	Orthorhombic	Monoclinic
Space Group	P2 ₁ 2 ₁ 2 ₁	C2/c
<i>a</i> /Å	10.3221(2)	23.9849(7)
<i>b</i> /Å	12.1695(2)	3.83080(10)
<i>c</i> /Å	22.1649(4)	23.9215(7)
α /°	90	90
β /°	90	109.8960(10)
γ /°	90	90
<i>V</i> /Å ³	2784.24(9)	2066.75(10)
<i>Z</i>	4	8
<i>D</i> _{calc.} / g cm ⁻³	1.199	1.820
μ /mm ⁻¹	1.213	7.111
ϑ_{min} /°	3.989	3.920

$\vartheta_{max}/^{\circ}$	68.364	68.327
Measured Reflections	41723	12535
Independent reflections	5126	1857
Reflexions with $I > 2\sigma(I)$	5074	1744
R_{int}	0.0479	0.0623
Parameters	406	137
Restraints	36	0
Largest Peak	0.136	1.759
Deepest Hole	-0.252	-1.571
Goodness of fit	1.088	1.320
wR_2 (all data)	0.0723	0.01321
wR_2	0.0721	0.01306
R_1 (all data)	0.0285	0.0528
R_1	0.0282	0.0509



Figure 20: Space filling model for 7a'

Supporting information for Chapter 4

General Condition

Reactions were carried out in regular glassware under air unless otherwise noted. Commercially available starting materials (thiophene ester **1b**, all boronic acids and aryl halides) and reagents (K_2CO_3 , $ZnCl_2$, Cs_2CO_3 , NaOH and $TMPMgCl \cdot LiCl$) were purchased from Sigma-Aldrich and AK Scientific, and used without further purification. Palladium catalysts were purchased from STREM and stored under inert gas at room temperature ($PdCl_2$) or in the freezer at -10 degrees Celsius ($Pd(PtBu_3)_2$). All solvents were purchased from Fisher ACP chemicals and Sigma-Aldrich as ACS grade. Dimethylformamide (DMF) was dried using activated 3 Å molecular sieves and stored in an oven-dried Schlenk flask under argon atmosphere. Distilled water was obtained from an in-house distillery. Compounds were purified using column chromatography on silica-gel (Zeoprep 60 Eco, 40 – 63 μm , Zeochem AG). Microwave-assisted reactions were carried out using the Biotage Initiator™ 2.3 build 6250 microwave system with a 400 W magnetron – this instrument monitors temperature during the reaction time period and adjusts wattage accordingly. ^1H and ^{13}C NMR data were measured on a Varian VNMRs-500. Yield determination using ^1H -NMR was done using trimethoxybenzene (TMB) as an internal standard.

Supplementary UV Vis Data

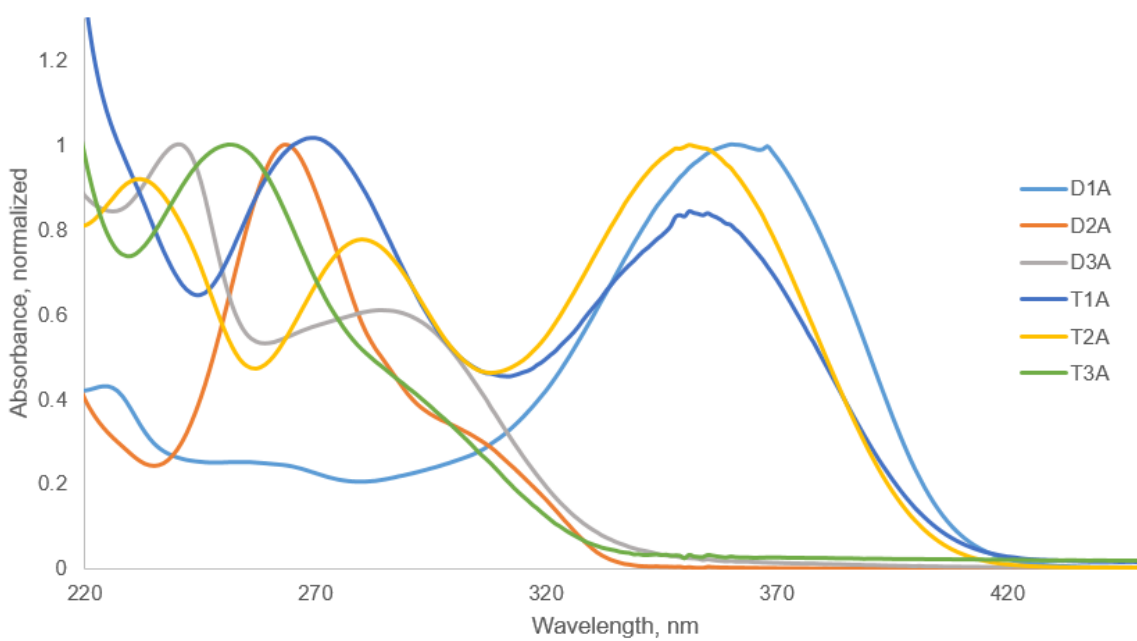
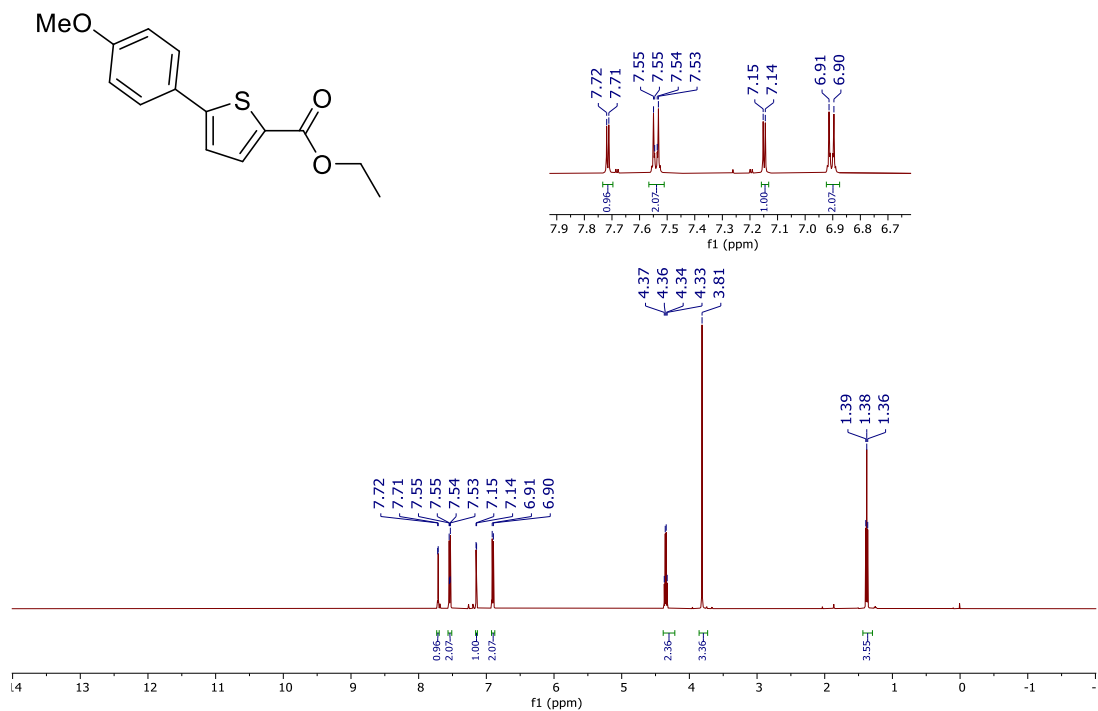


Figure 21: UV Vis spectra of thiophene series A in ACN

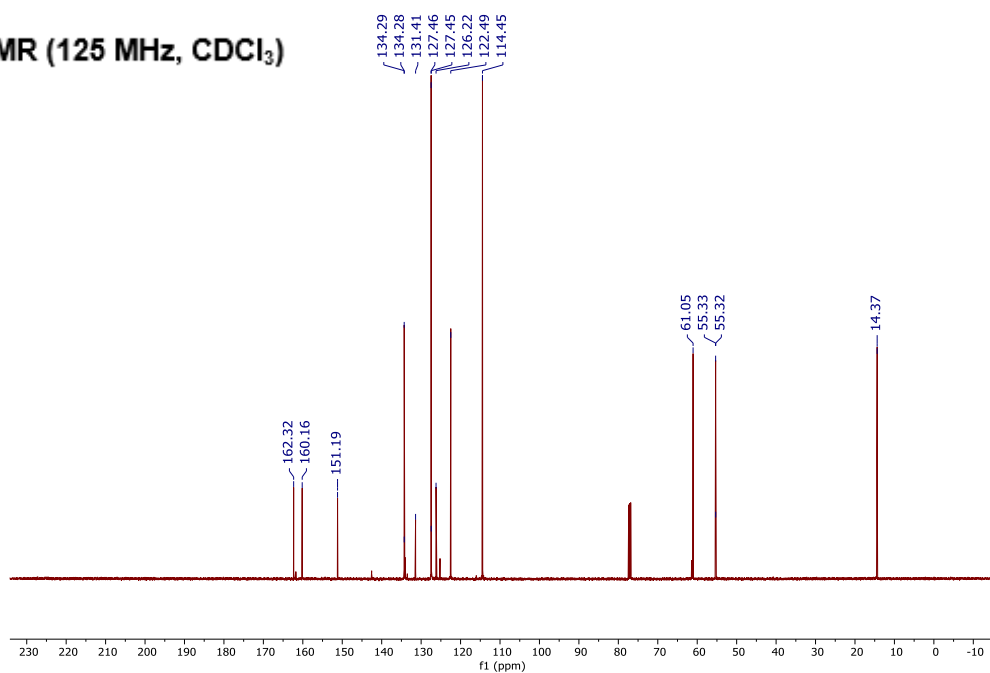
Spectroscopic Data

Ethyl 5-(4-methoxyphenyl)thiophene-2-carboxylate, 6j

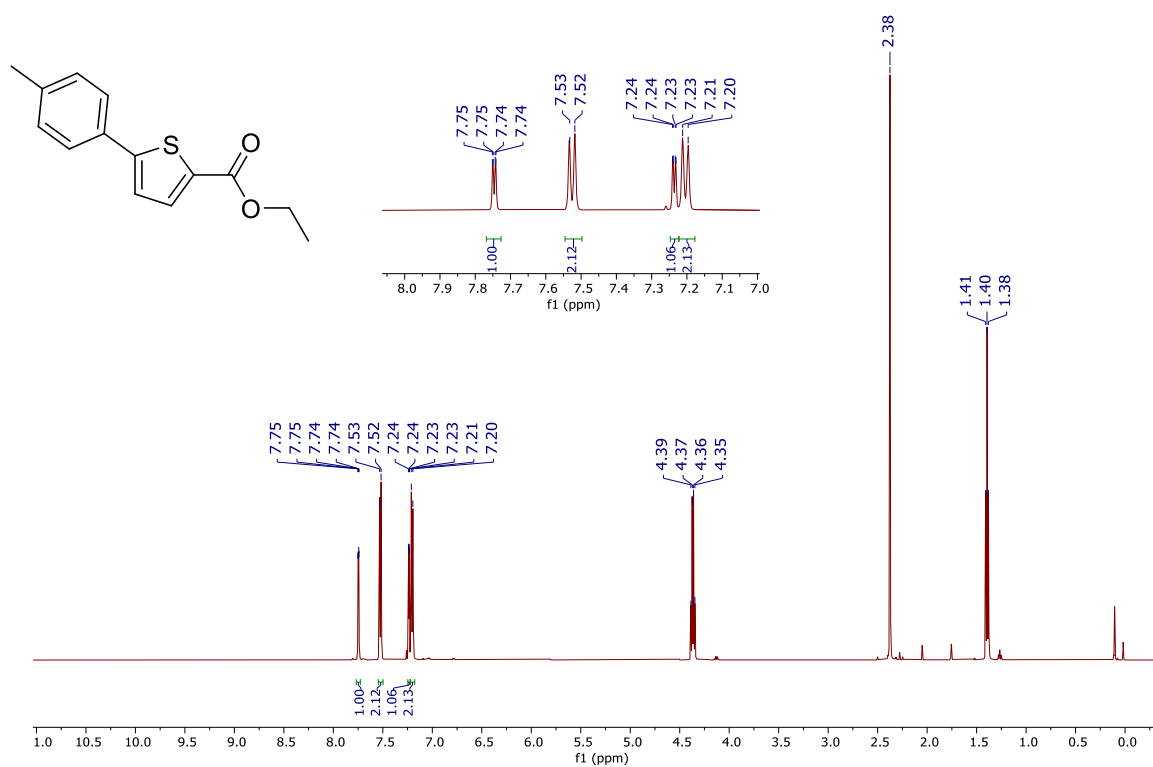
¹H NMR (500 MHz, CDCl₃)



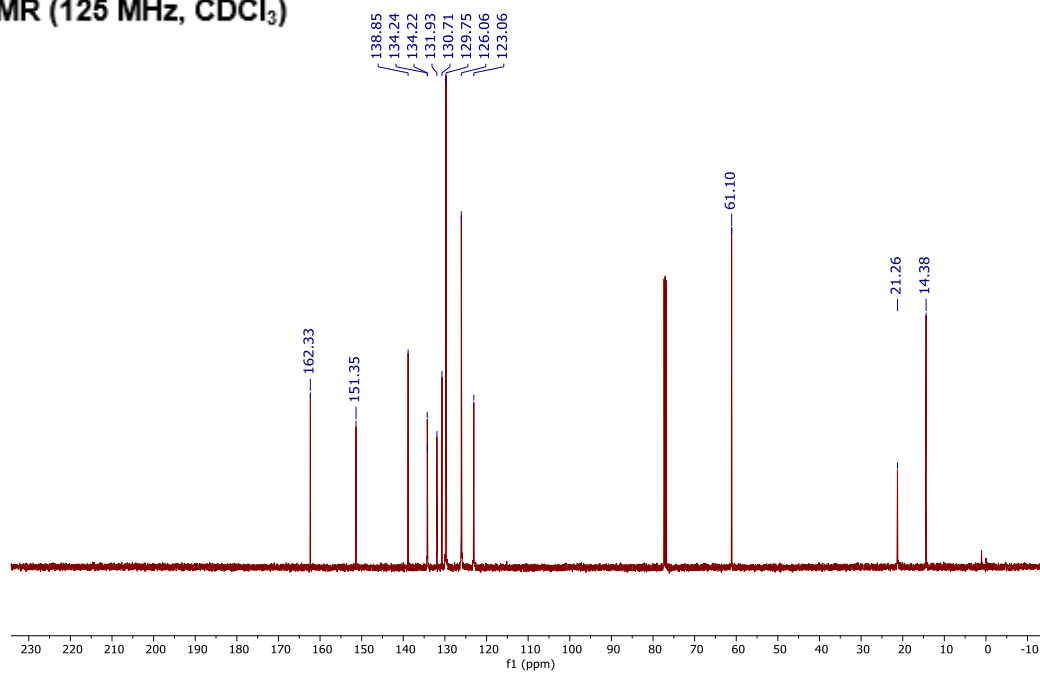
¹³C NMR (125 MHz, CDCl₃)



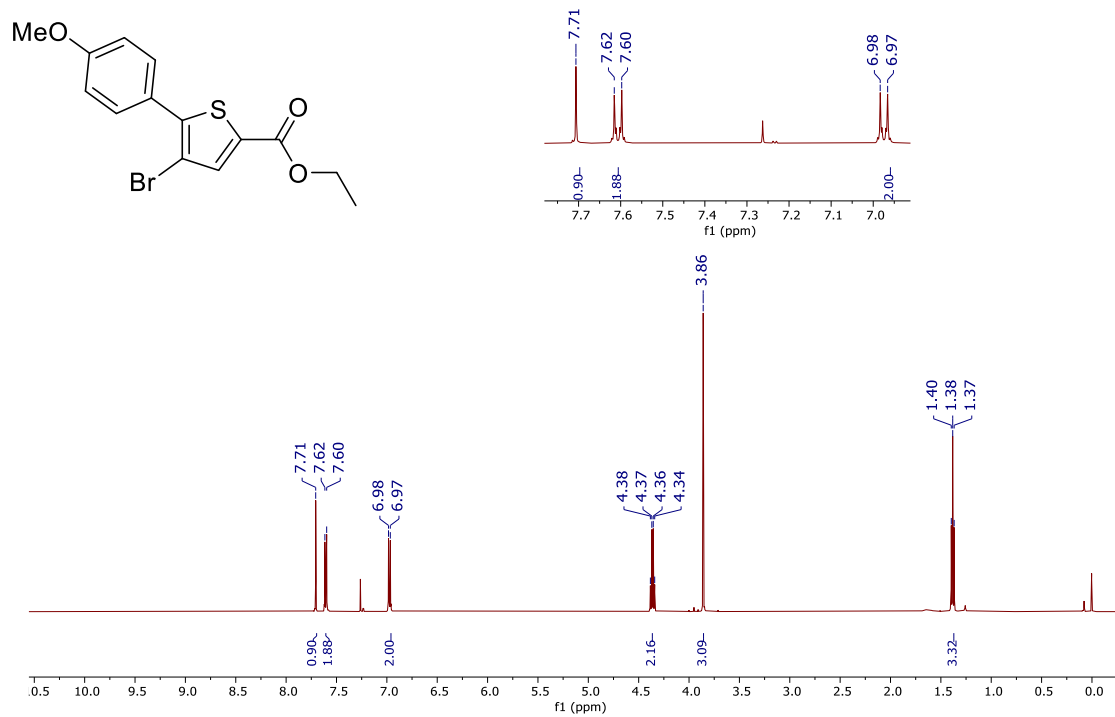
Ethyl 5-(p-tolyl)thiophene-2-carboxylate, 6k
¹H NMR (500 MHz, CDCl₃)



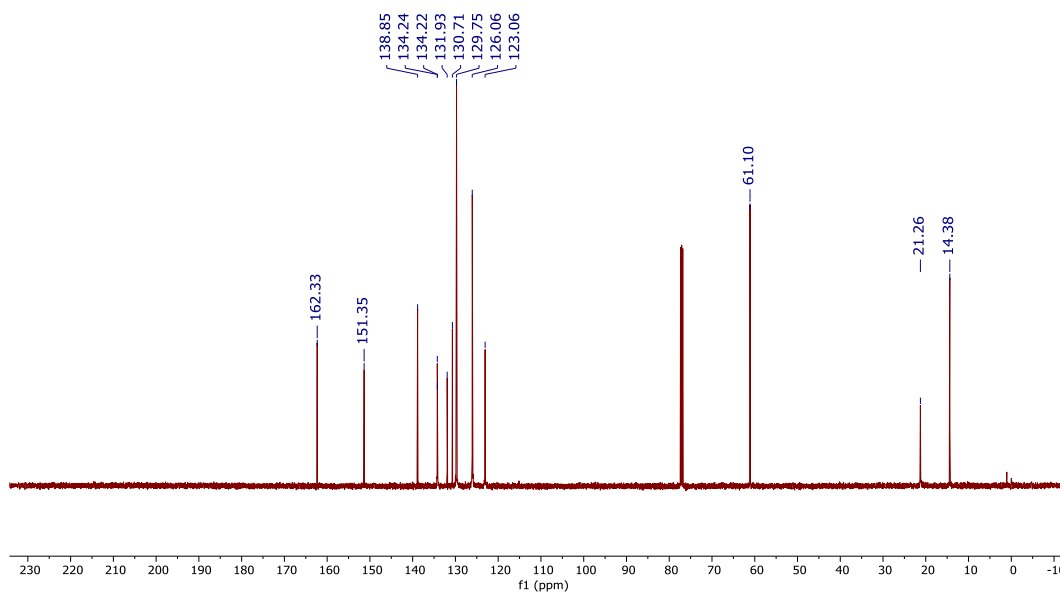
¹³C NMR (125 MHz, CDCl₃)



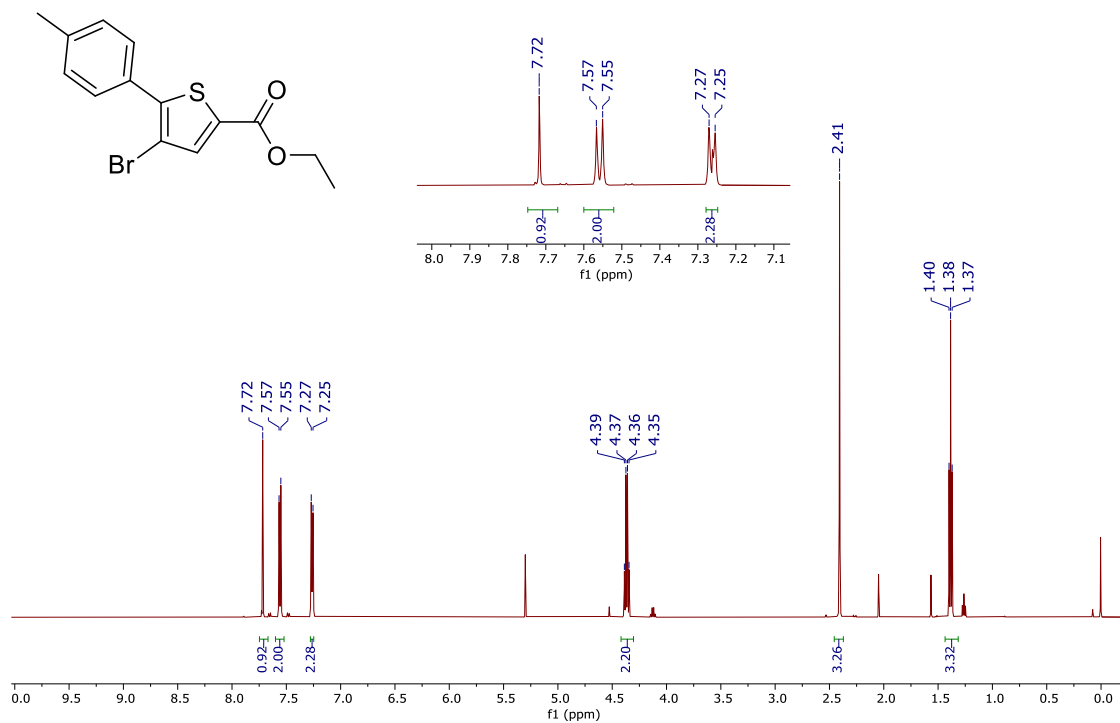
Ethyl 4-bromo-5-(4-methoxyphenyl)thiophene-2-carboxylate, 7i
¹H NMR (500 MHz, CDCl₃)



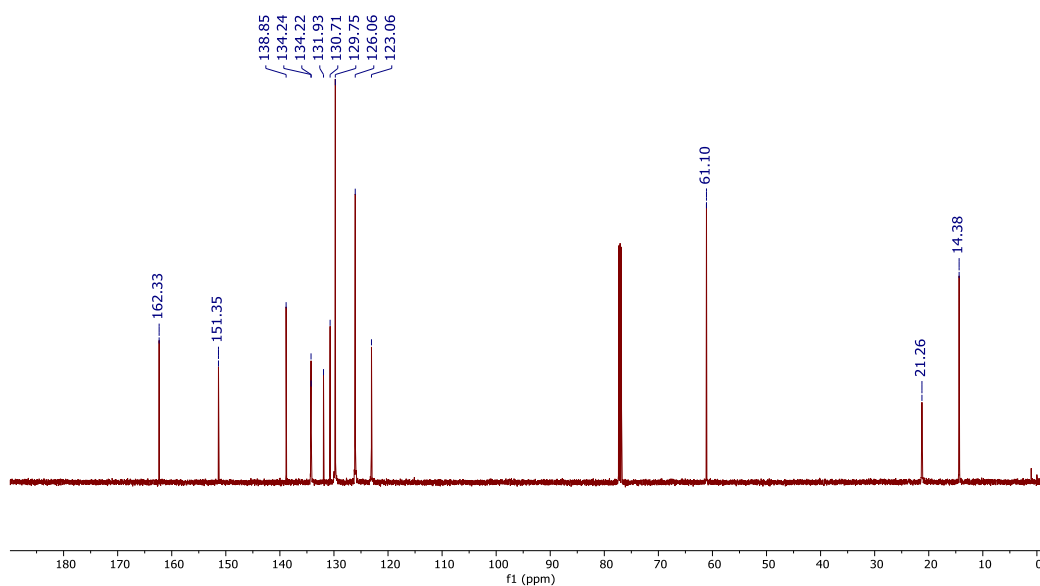
¹³C NMR (125 MHz, CDCl₃)



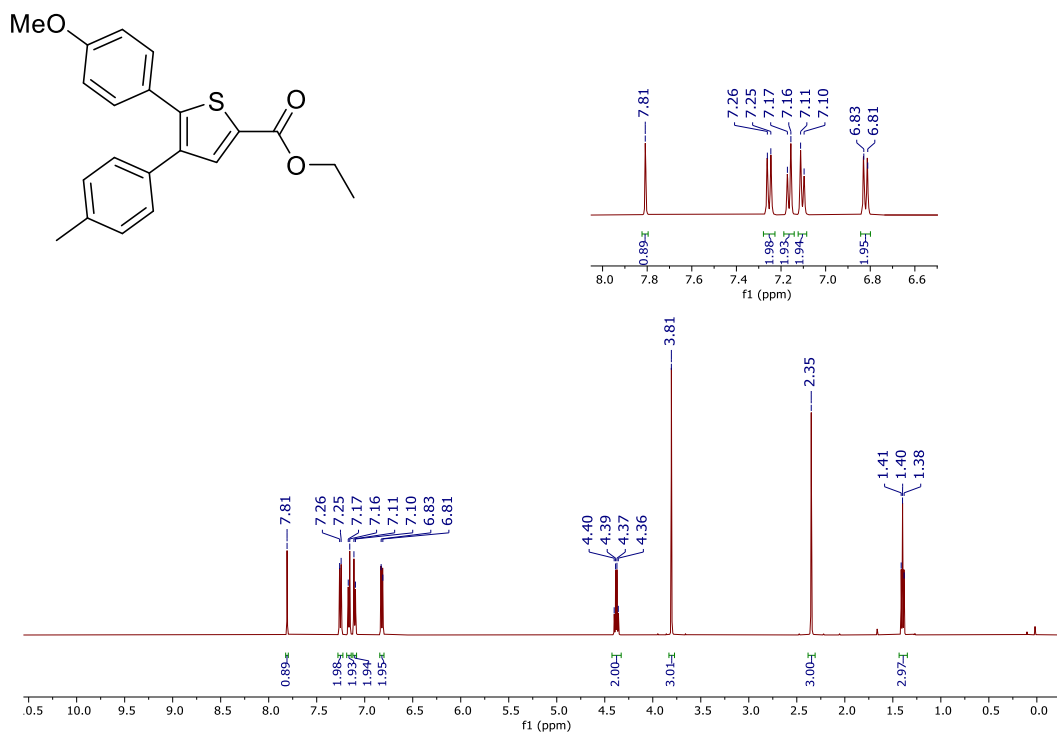
Ethyl 4-bromo-5-(p-tolyl)thiophene-2-carboxylate, 7j
¹H NMR (500 MHz, CDCl₃)



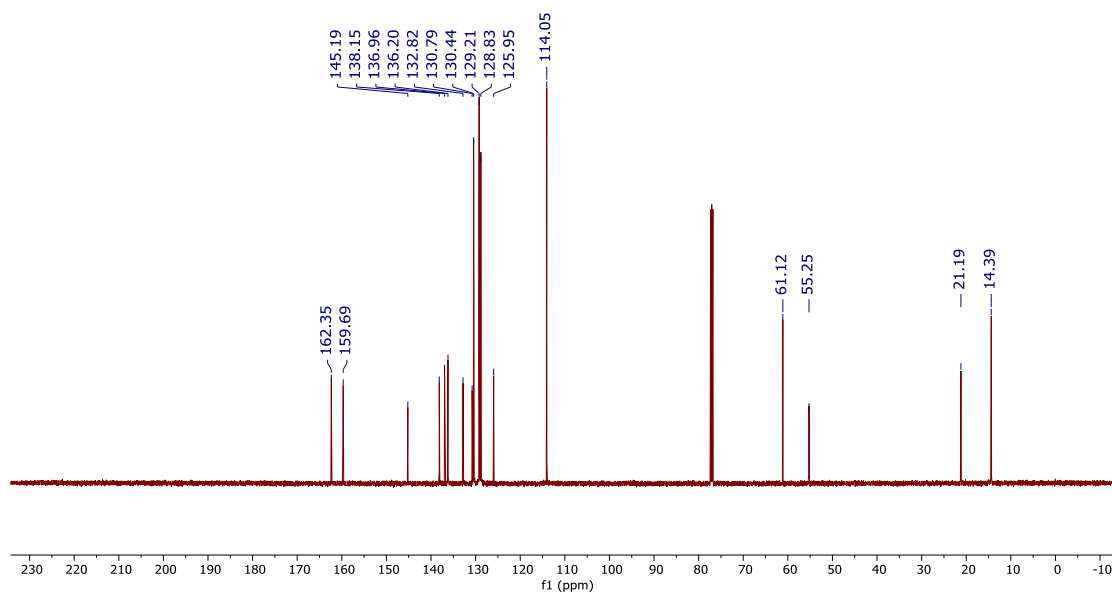
¹³C NMR (125 MHz, CDCl₃)



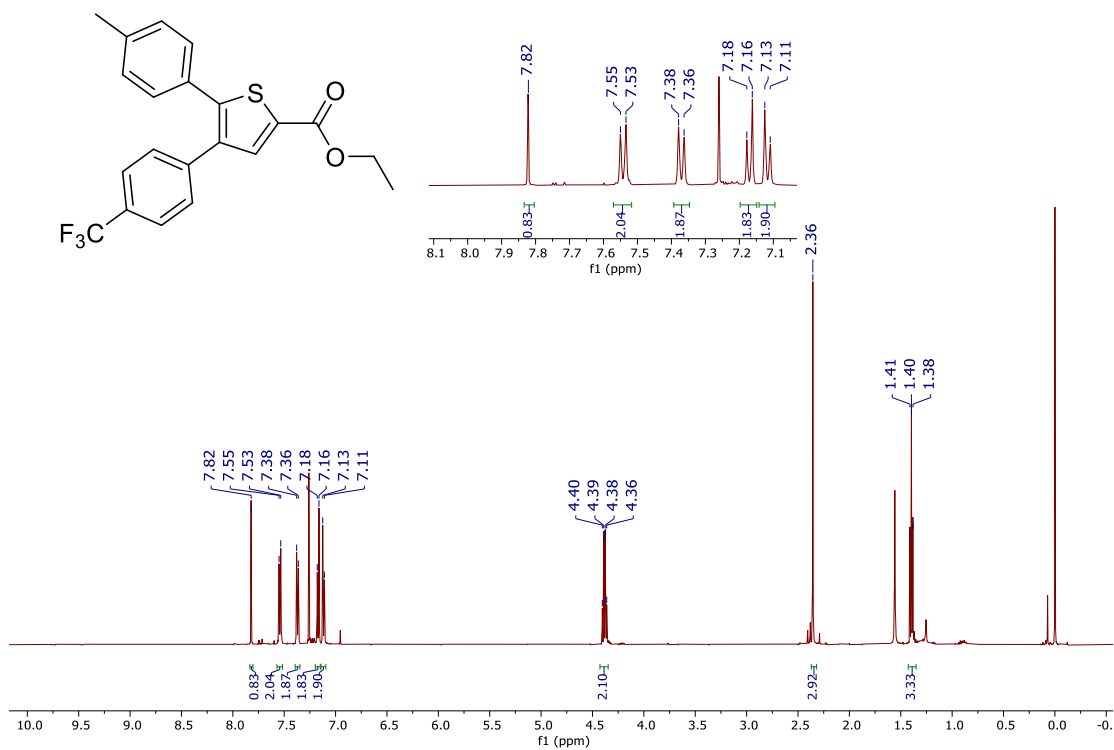
Ethyl 5-(4-methoxyphenyl)-4-(p-tolyl)thiophene-2-carboxylate, 8g
¹H NMR (500 MHz, CDCl₃)



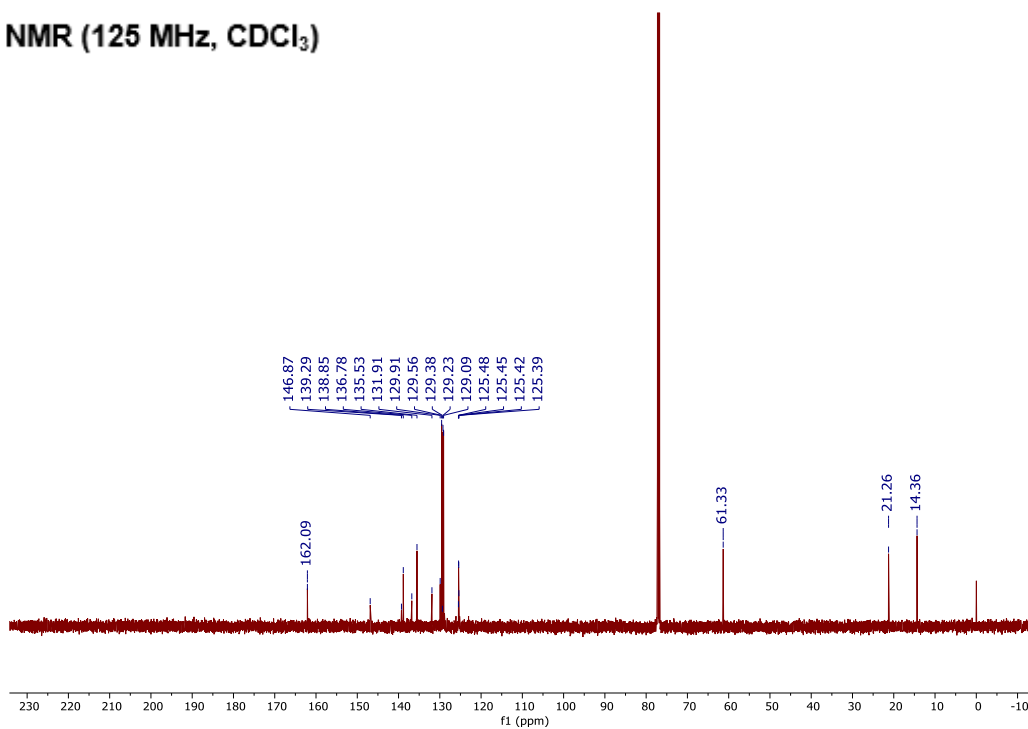
¹³C NMR (125 MHz, CDCl₃)



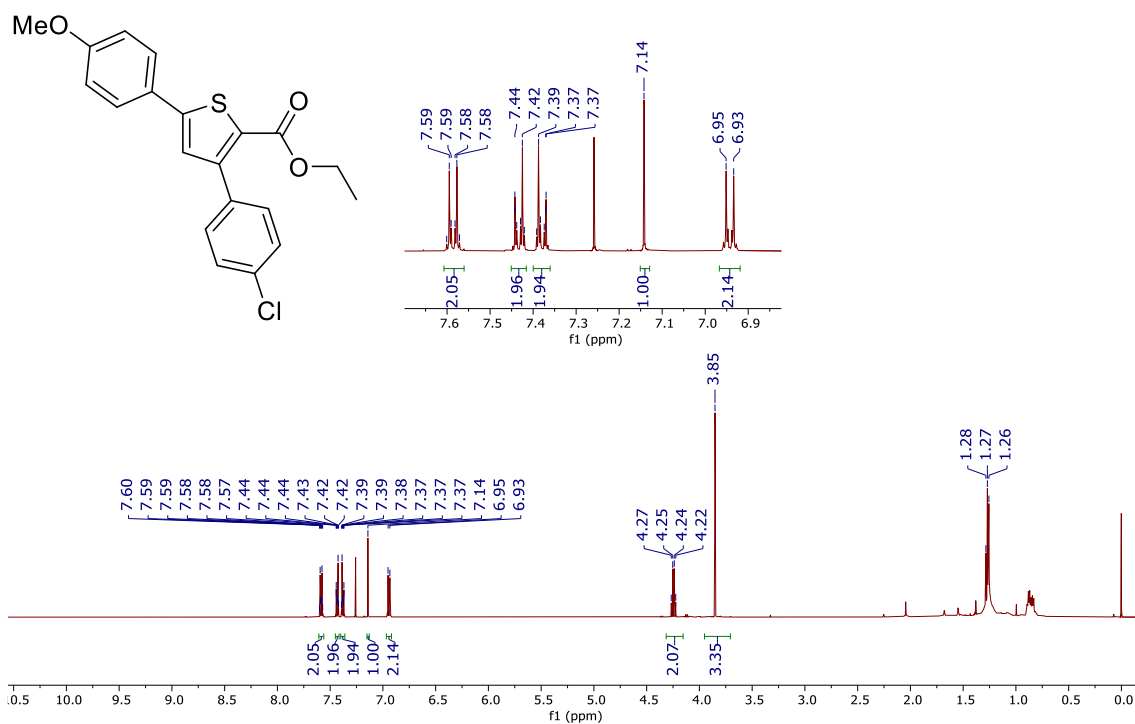
Ethyl 5-(4-methoxyphenyl)-4-(p-tolyl)thiophene-2-carboxylate, 8h
¹H NMR (500 MHz, CDCl₃)



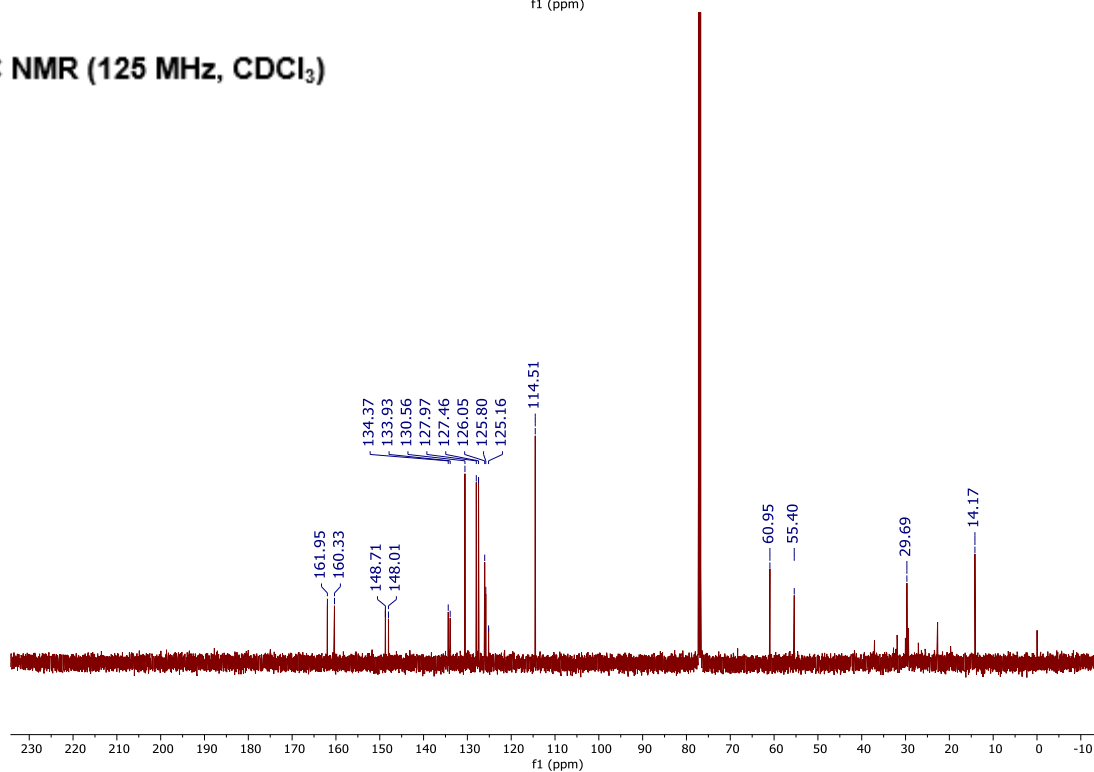
¹³C NMR (125 MHz, CDCl₃)



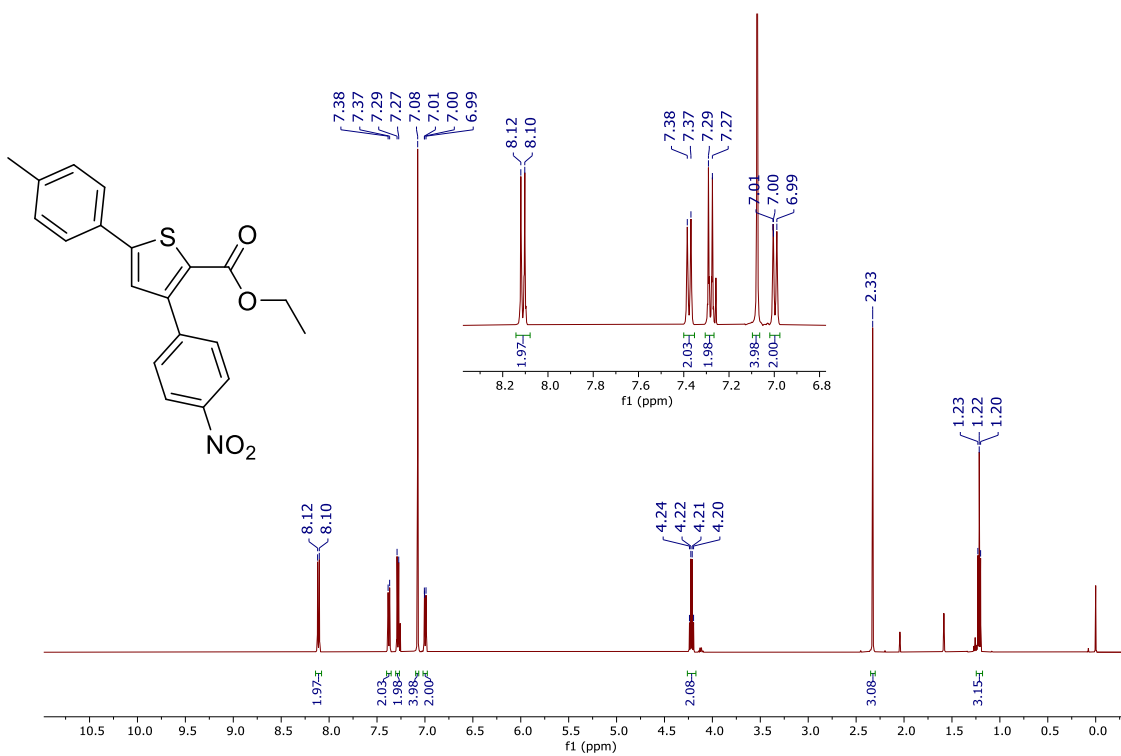
Ethyl 3-(4-chlorophenyl)-5-(4-methoxyphenyl)thiophene-2-carboxylate, 11a
¹H NMR (500 MHz, CDCl₃)



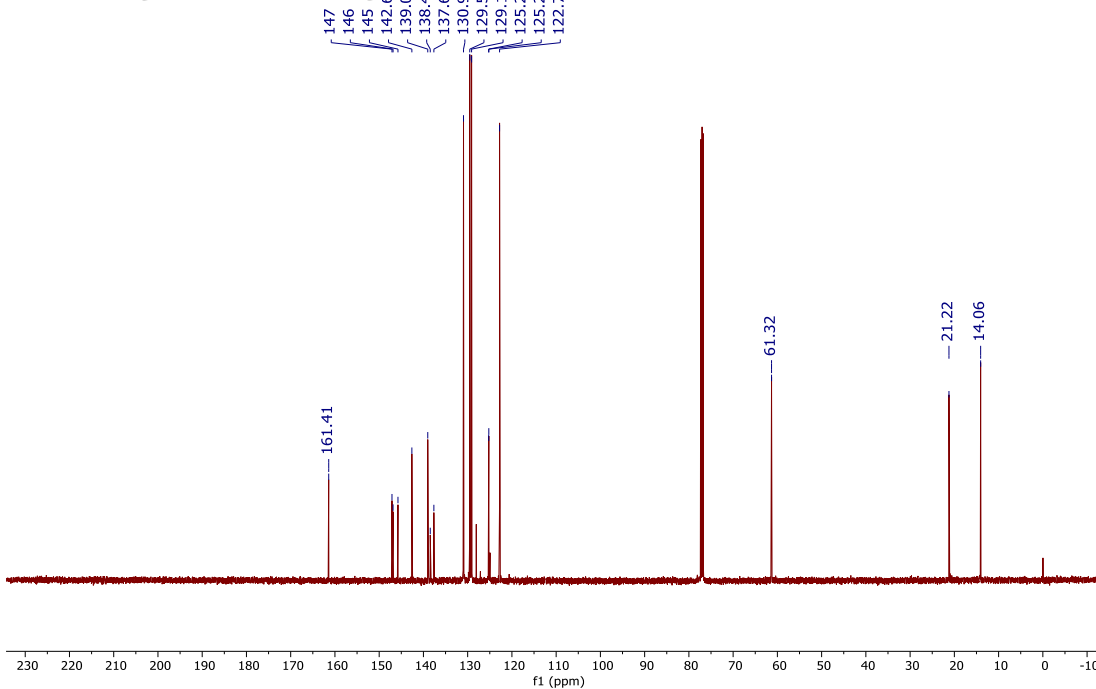
¹³C NMR (125 MHz, CDCl₃)



Ethyl 3-(4-nitrophenyl)-5-(p-tolyl)thiophene-2-carboxylate, 11b
¹H NMR (500 MHz, CDCl₃)

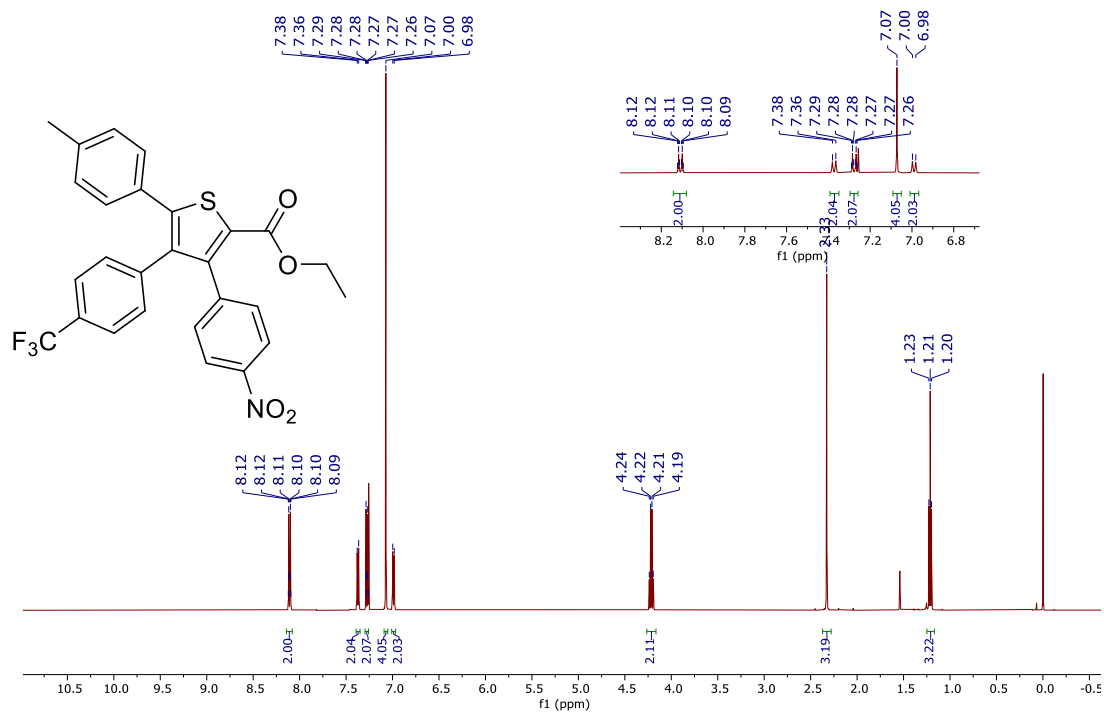


¹³C NMR (125 MHz, CDCl₃)

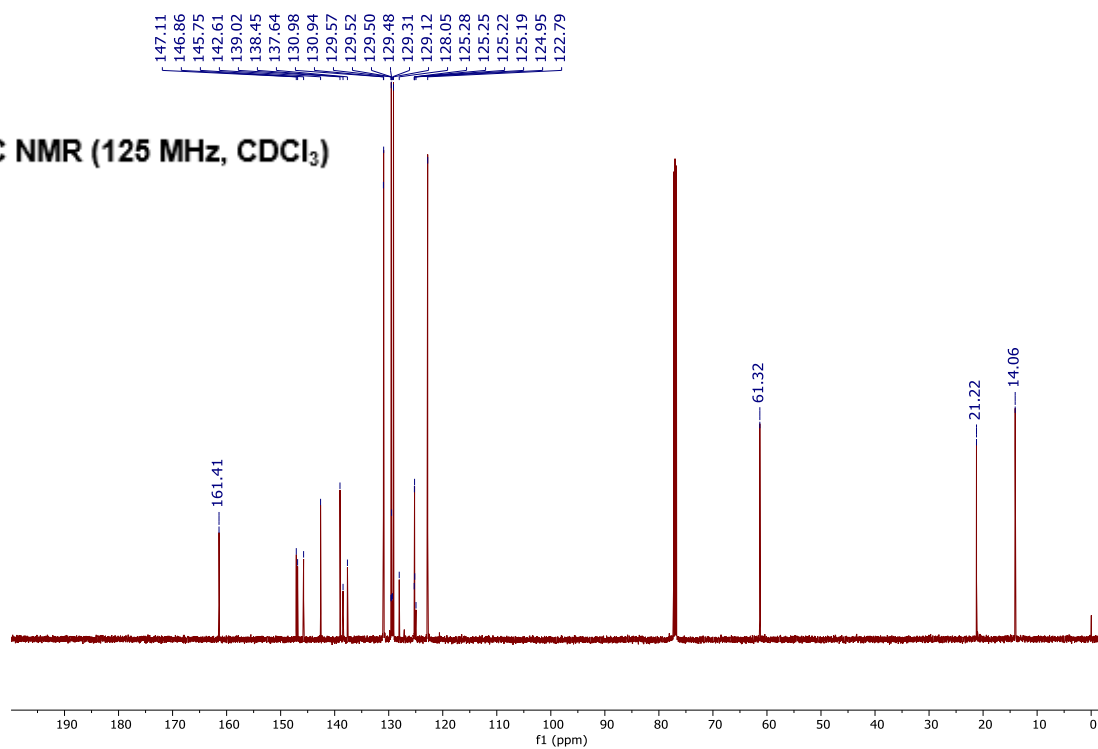


Ethyl 3-(4-nitrophenyl)-5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)thiophene-2-carboxylate
9h

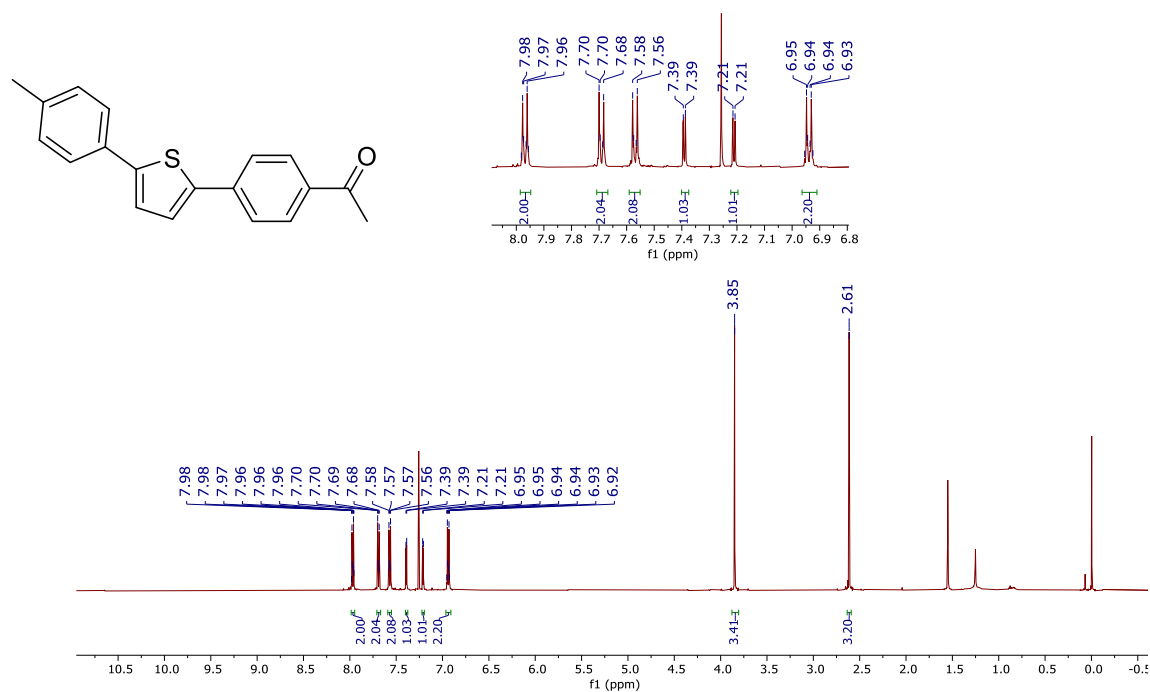
¹H NMR (500 MHz, CDCl₃)



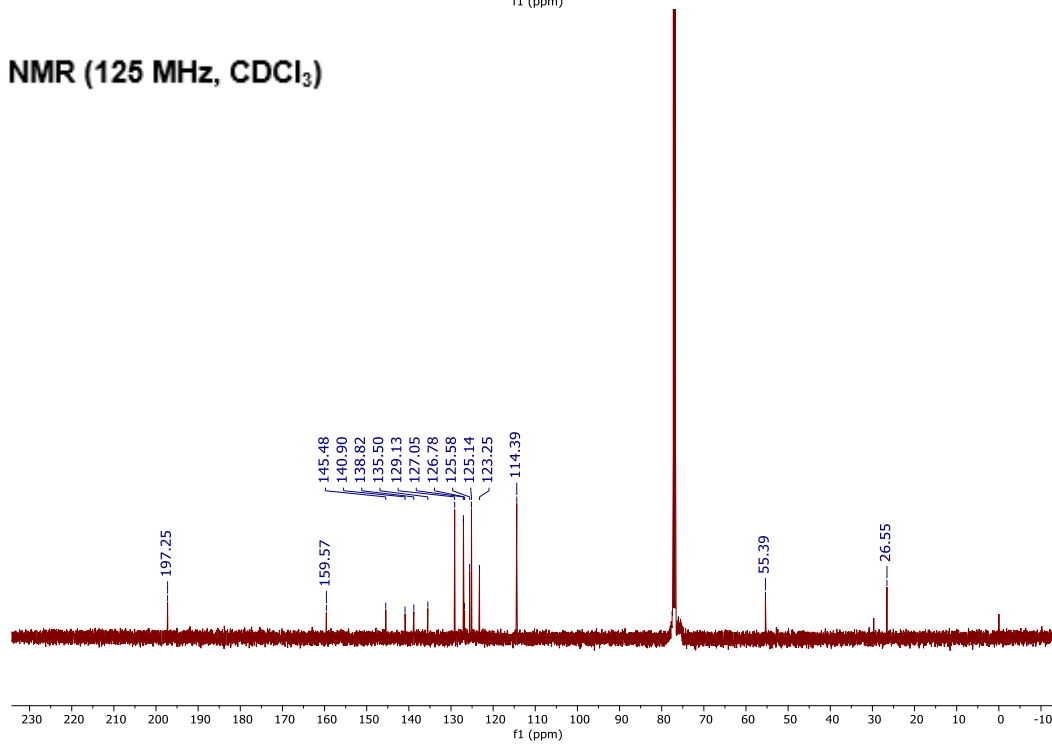
¹³C NMR (125 MHz, CDCl₃)



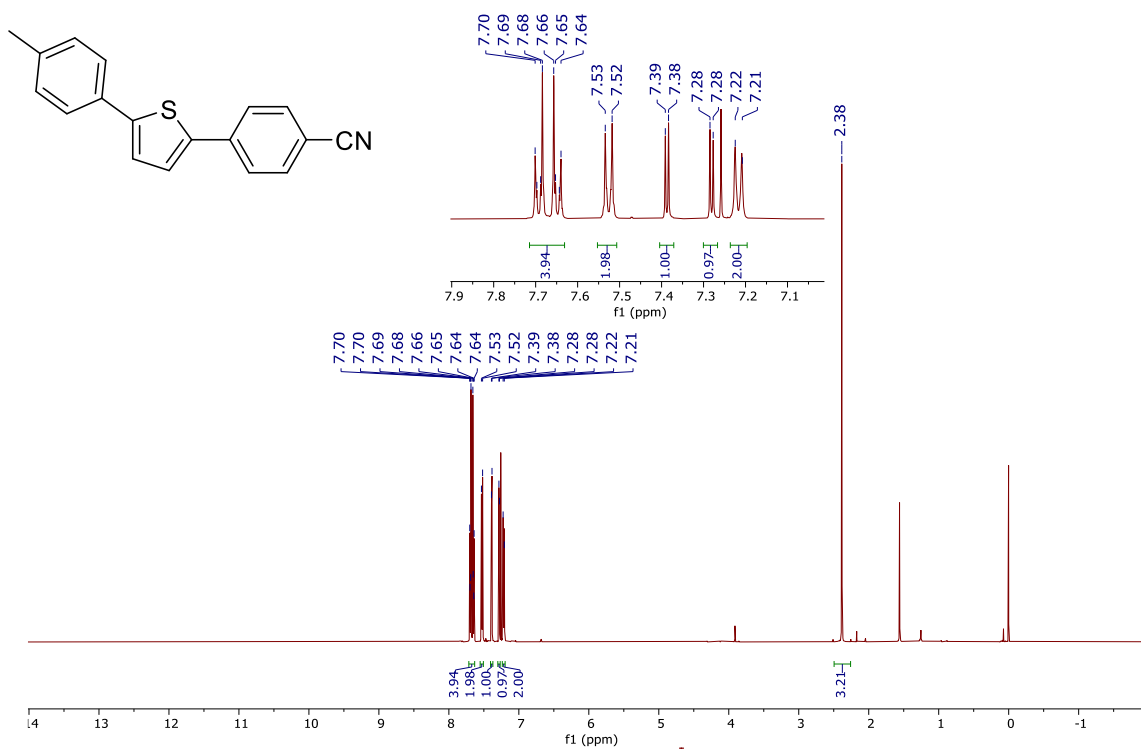
1-(4-(5-(4-methoxyphenyl)thiophen-2-yl)phenyl)ethan-1-one, D1A
¹H NMR (500 MHz, CDCl₃)



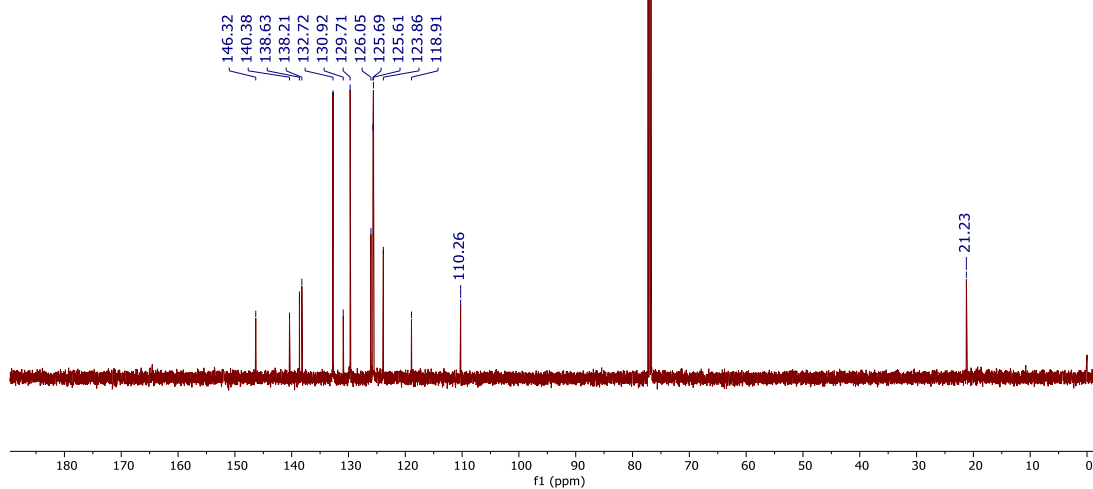
¹³C NMR (125 MHz, CDCl₃)



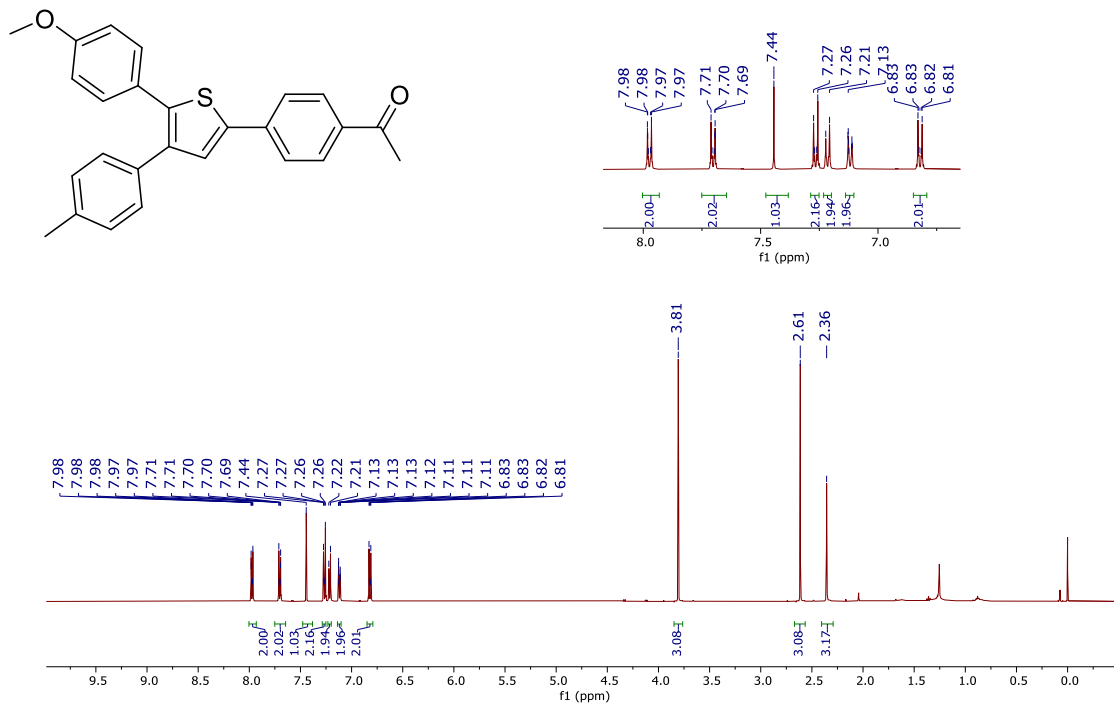
4-(5-(p-tolyl)thiophen-2-yl)benzonitrile, D1B
¹H NMR (500 MHz, CDCl₃)



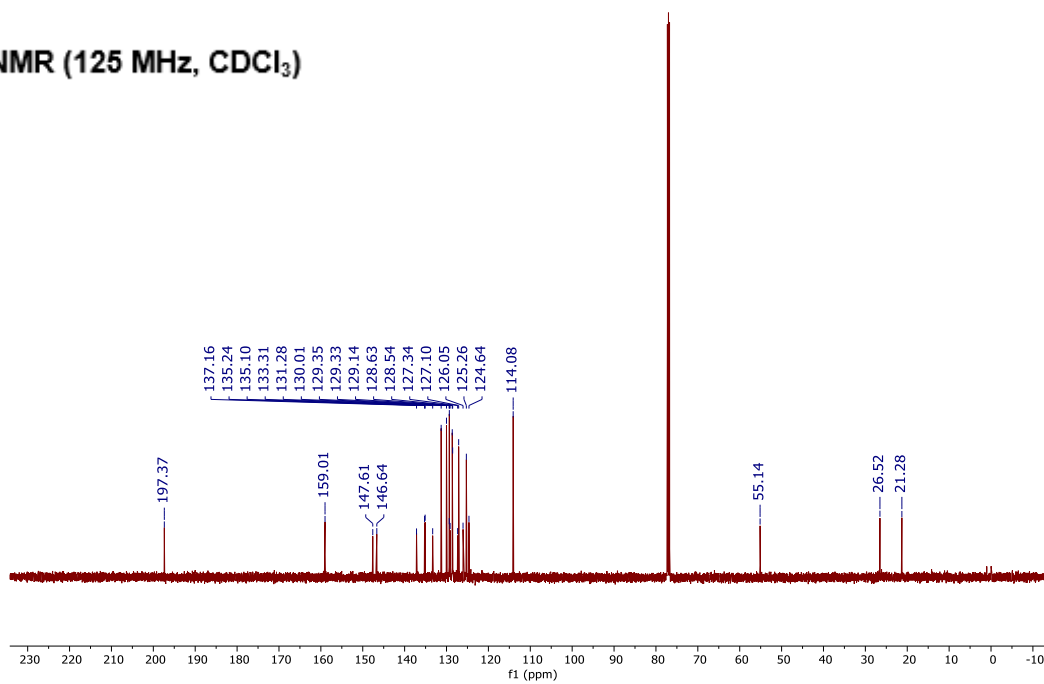
¹³C NMR (125 MHz, CDCl₃)



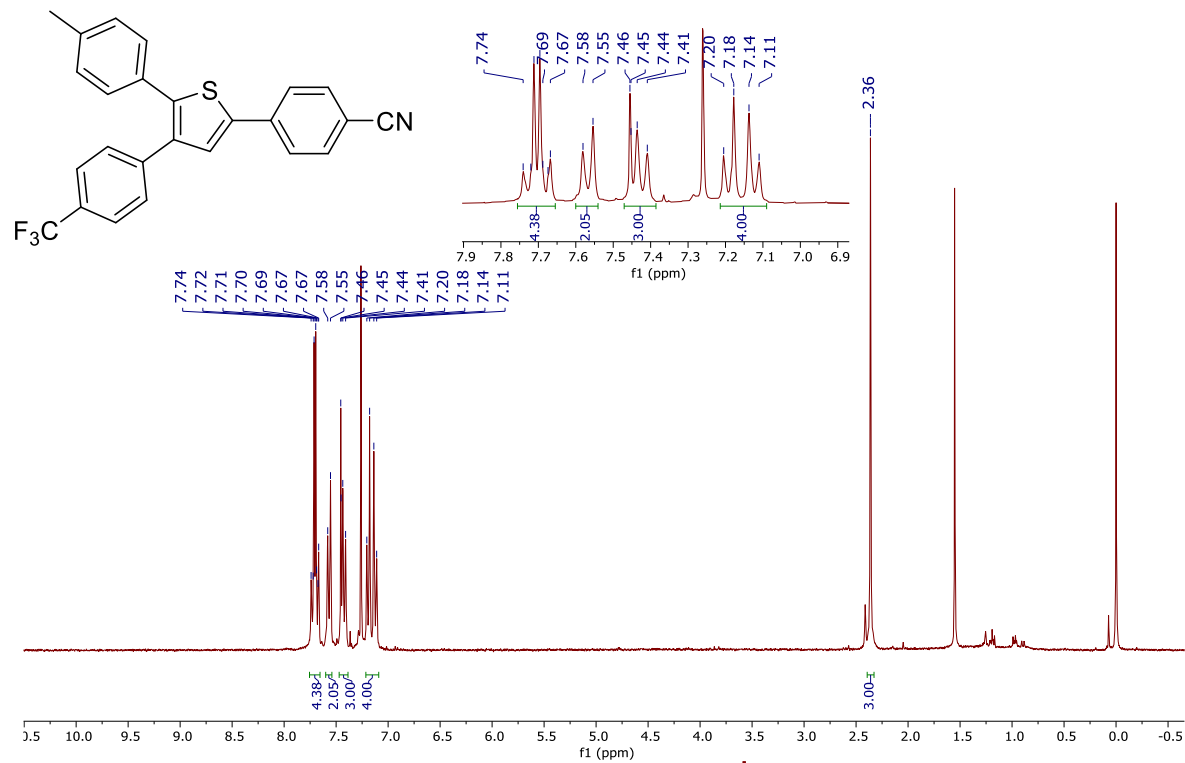
1-(4-(5-(4-methoxyphenyl)-4-(p-tolyl)thiophen-2-yl)phenyl)ethan-1-one, T2A
¹H NMR (500 MHz, CDCl₃)



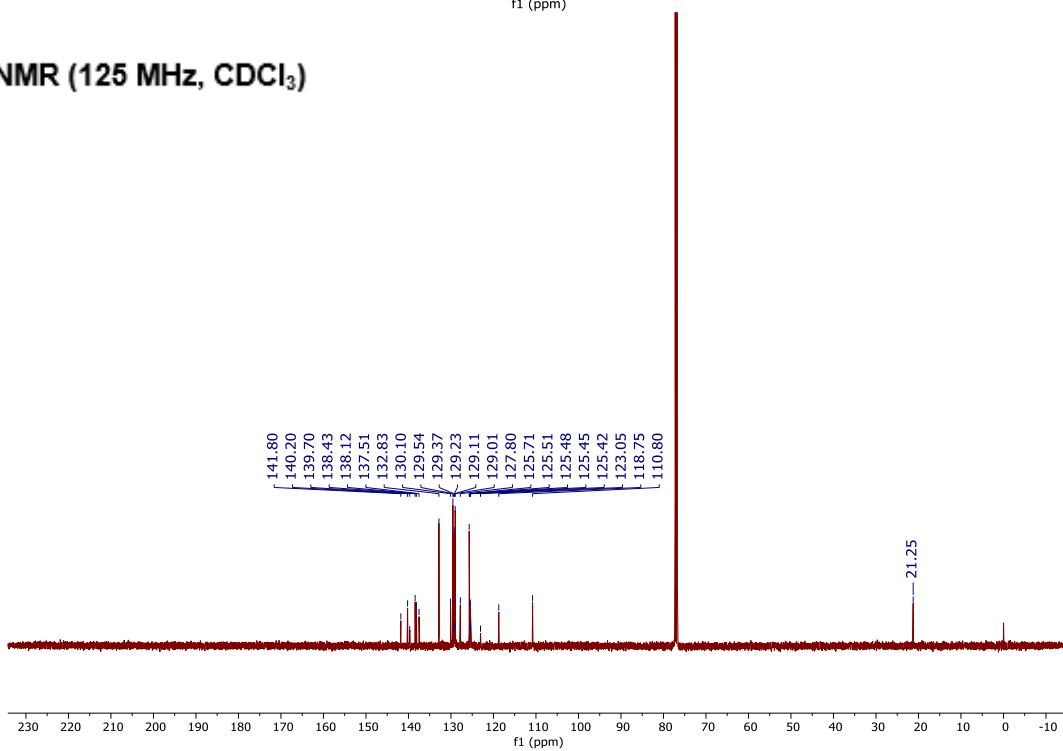
¹³C NMR (125 MHz, CDCl₃)



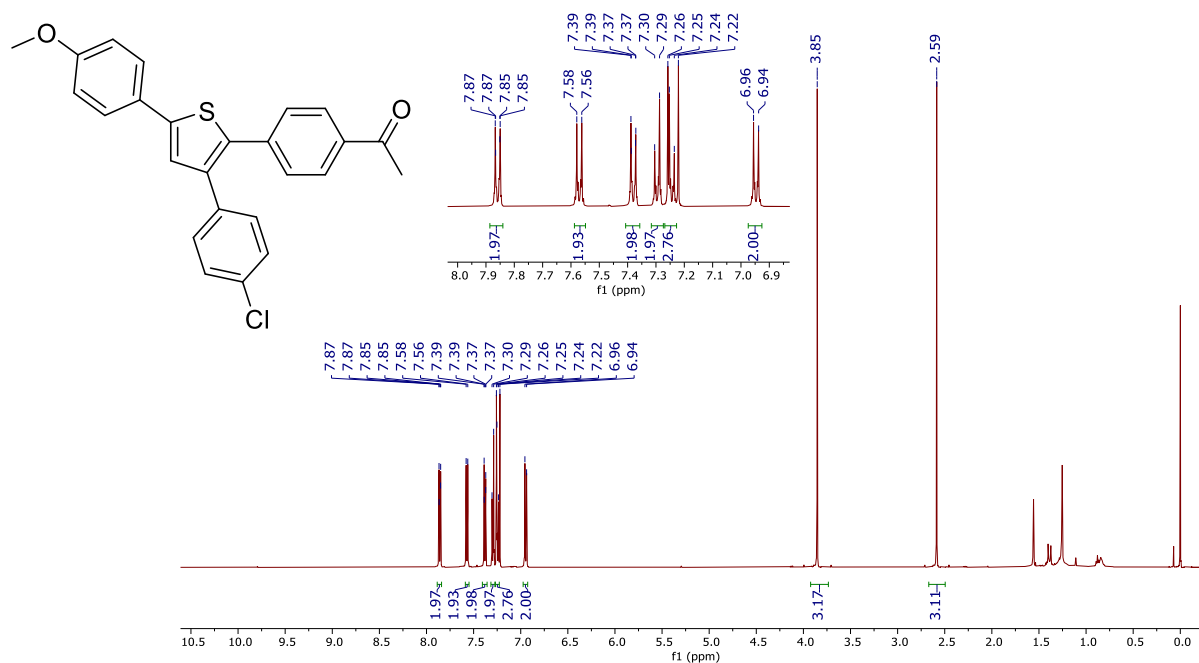
4-(5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)thiophen-2-yl)benzonitrile, T2B:
¹H NMR (500 MHz, CDCl₃)



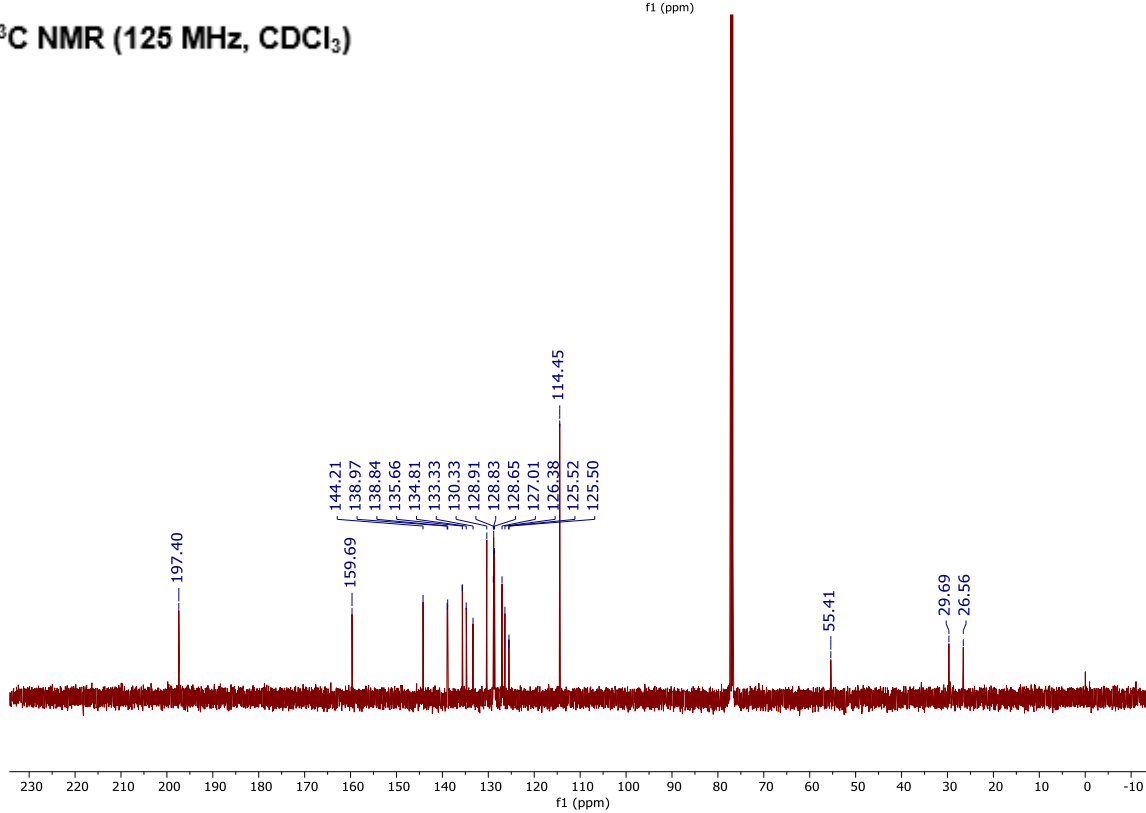
¹³C NMR (125 MHz, CDCl₃)



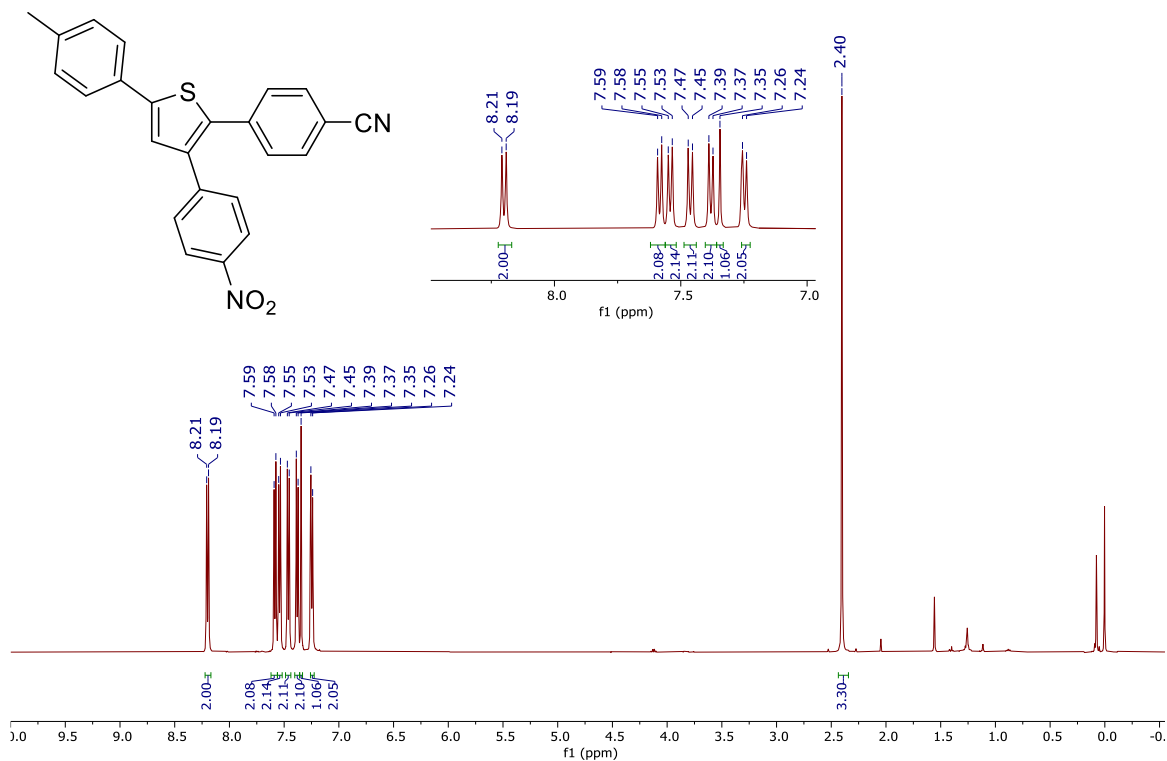
1-(4-(3-(4-chlorophenyl)-5-(4-methoxyphenyl)thiophen-2-yl)phenyl)ethan-1-one, T1A
¹H NMR (500 MHz, CDCl₃)



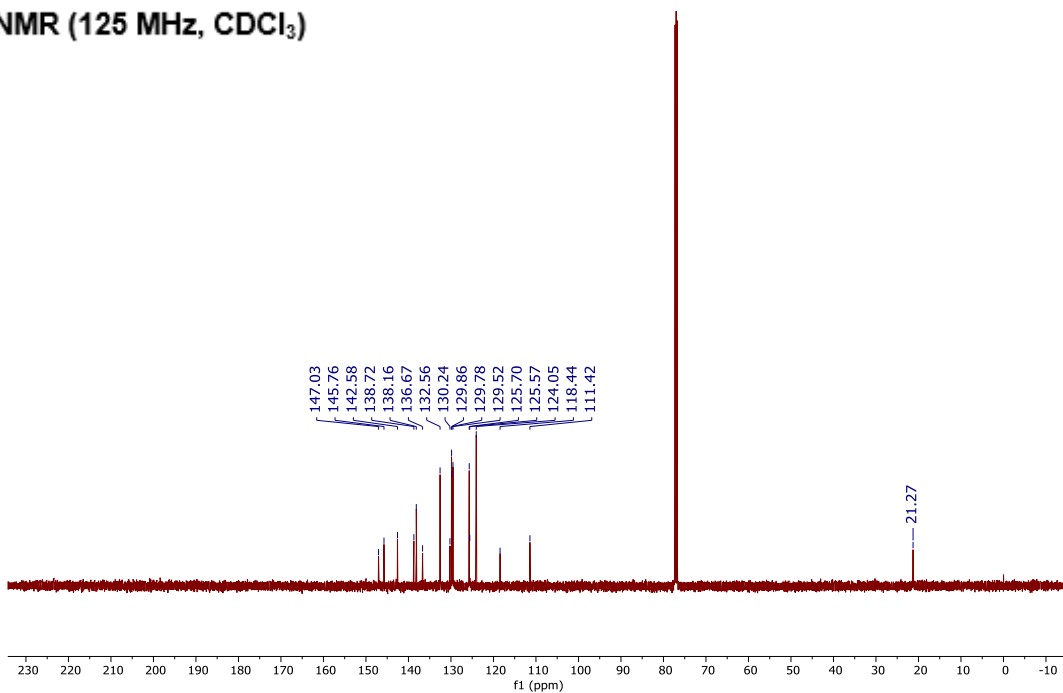
¹³C NMR (125 MHz, CDCl₃)



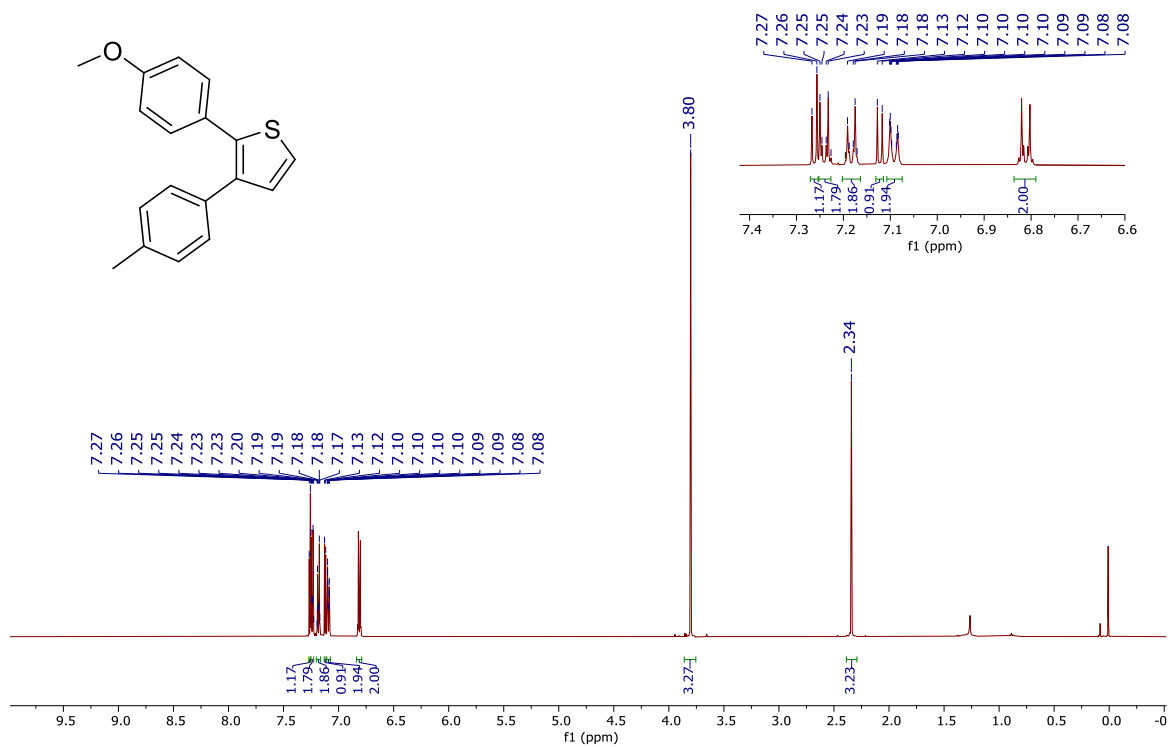
4-(3-(4-nitrophenyl)-5-(p-tolyl)thiophen-2-yl)benzonitrile, T1B
¹H NMR (500 MHz, CDCl₃)



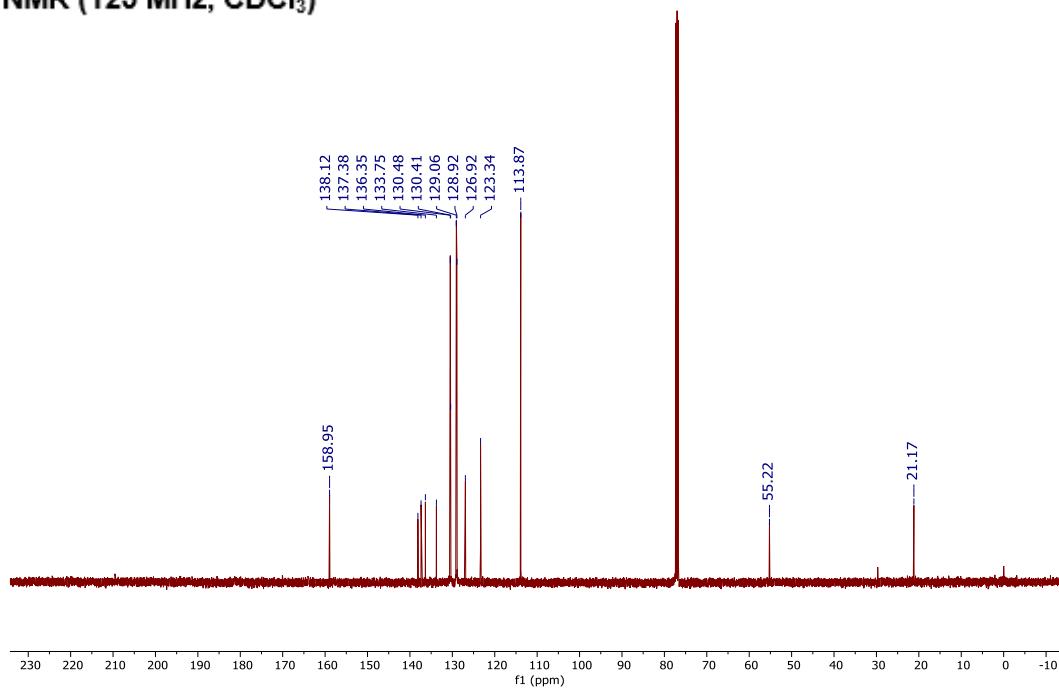
¹³C NMR (125 MHz, CDCl₃)



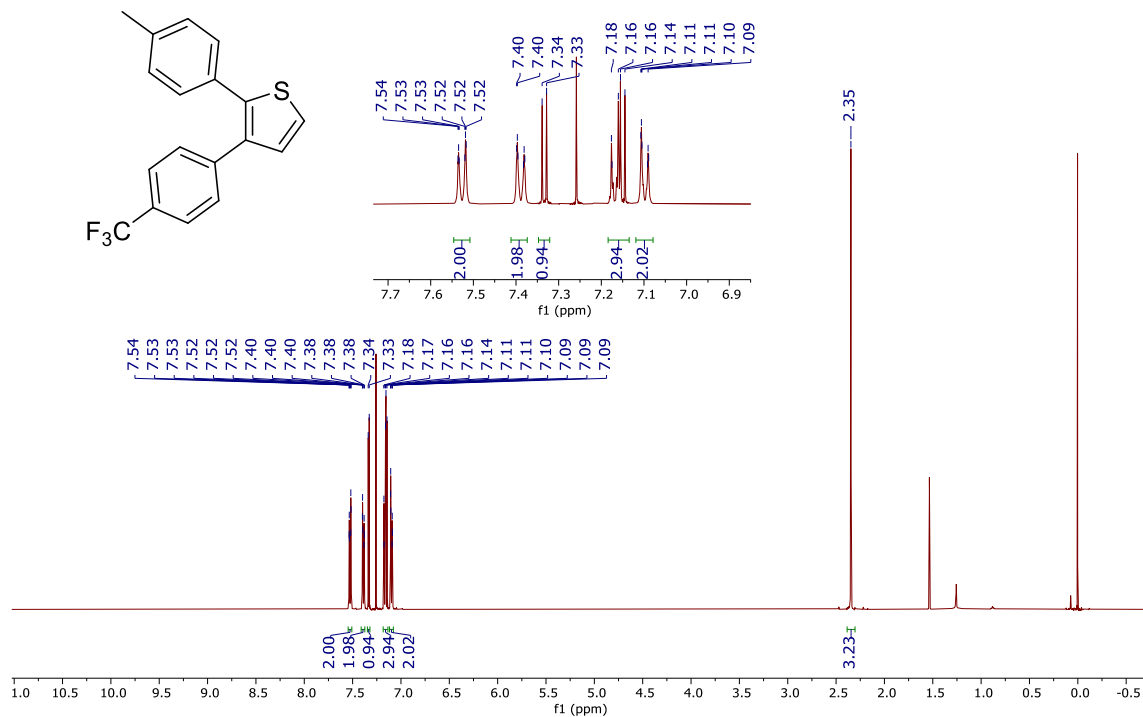
2-(4-methoxyphenyl)-3-(p-tolyl)thiophene, D3A
¹H NMR (500 MHz, CDCl₃)



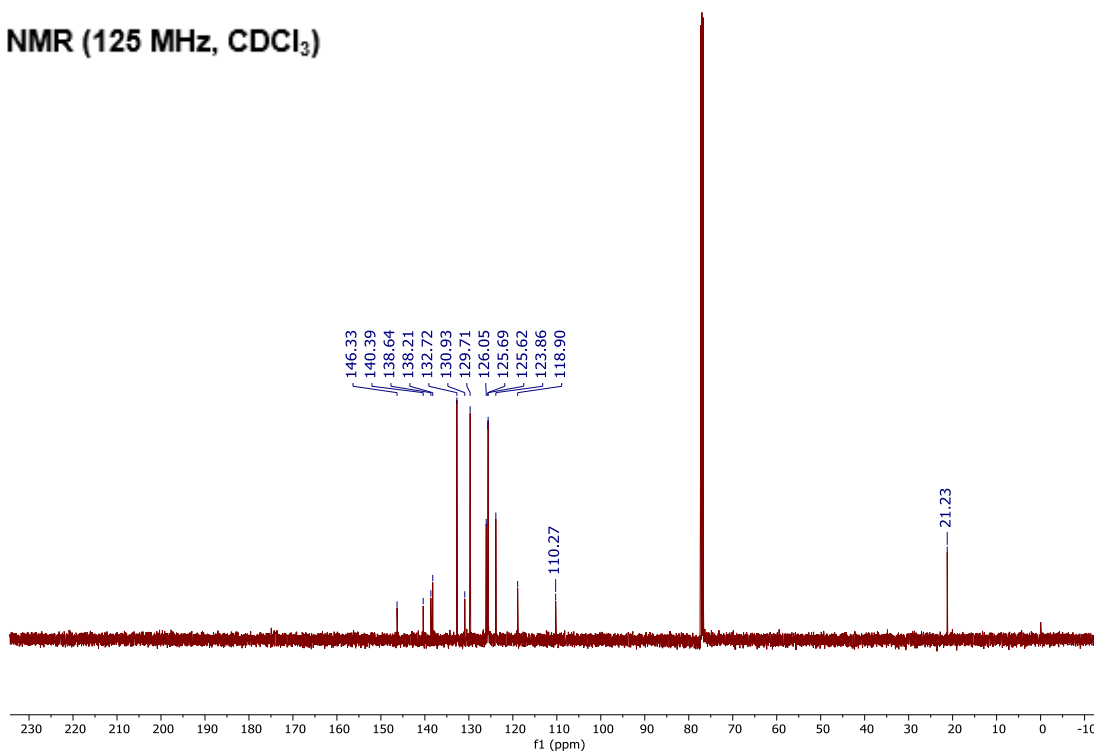
¹³C NMR (125 MHz, CDCl₃)



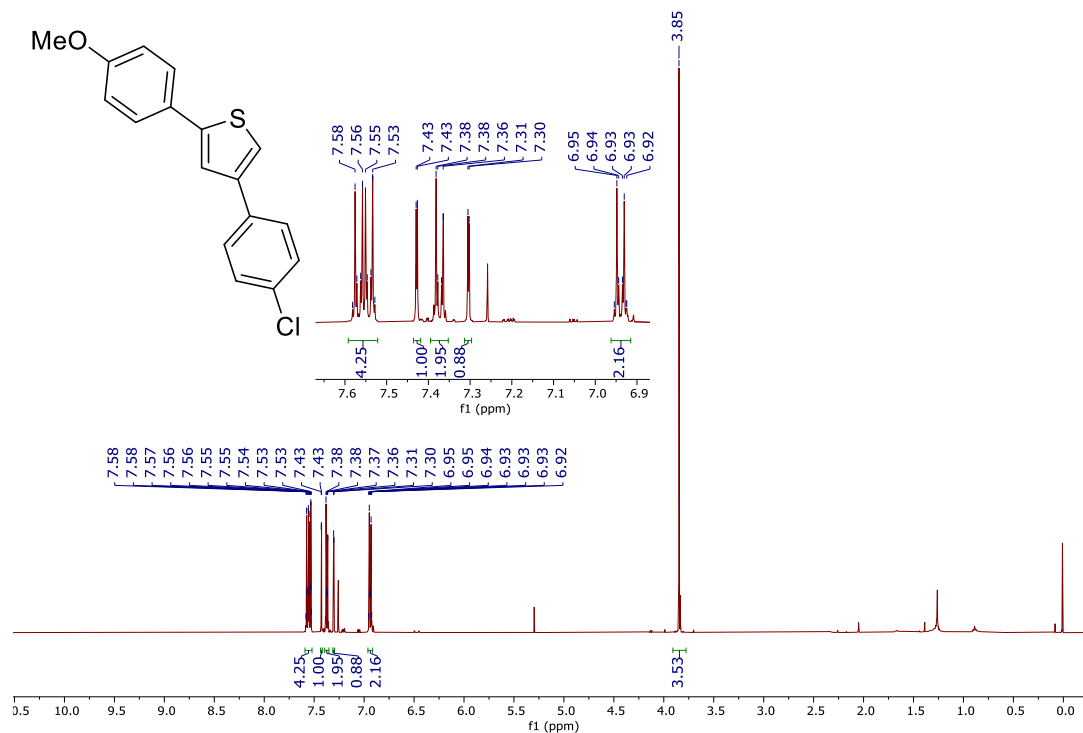
2-(p-tolyl)-3-(4-(trifluoromethyl)phenyl)thiophene, D3B
¹H NMR (500 MHz, CDCl₃)



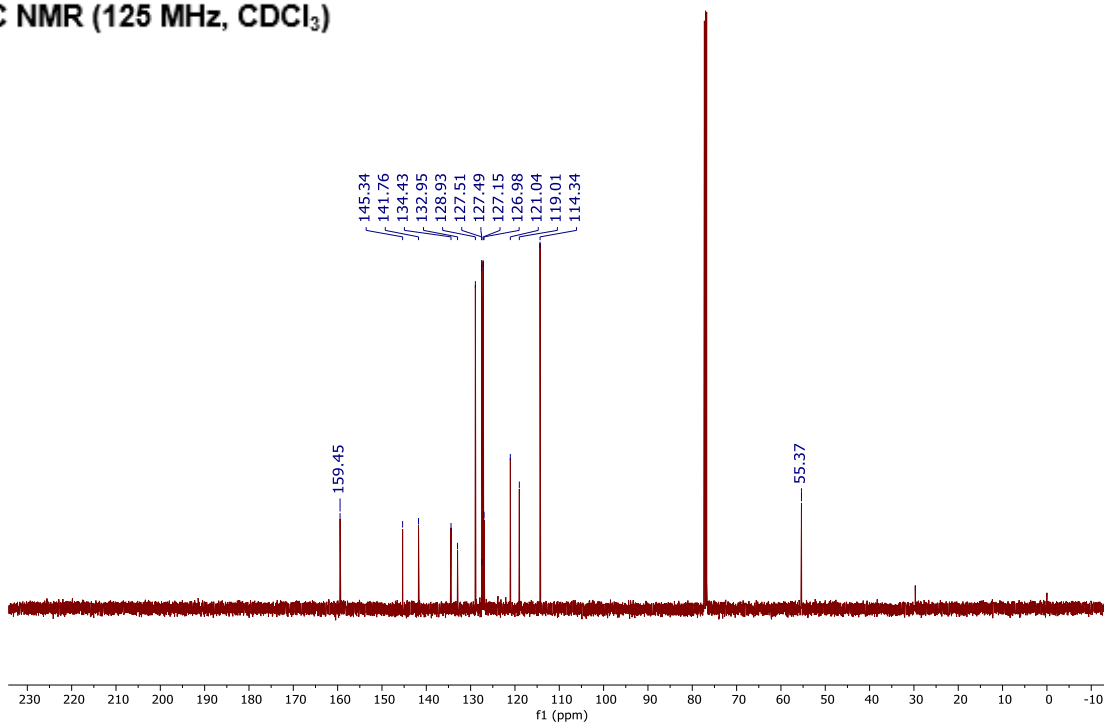
¹³C NMR (125 MHz, CDCl₃)



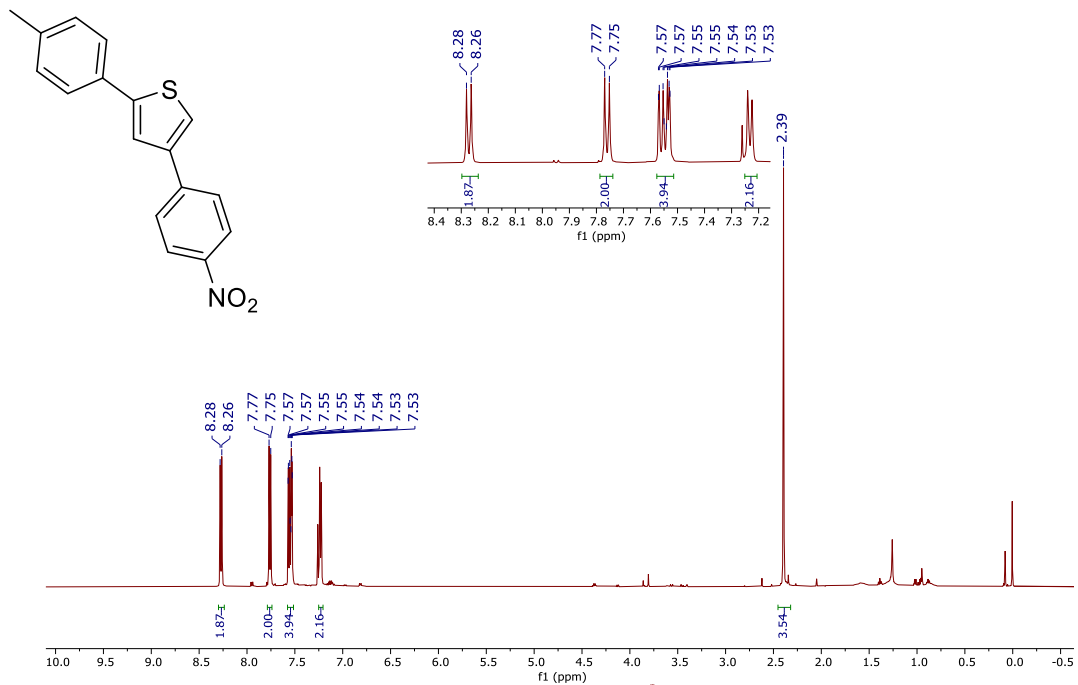
4-(4-chlorophenyl)-2-(4-methoxyphenyl)thiophene, D2A
¹H NMR (500 MHz, CDCl₃)



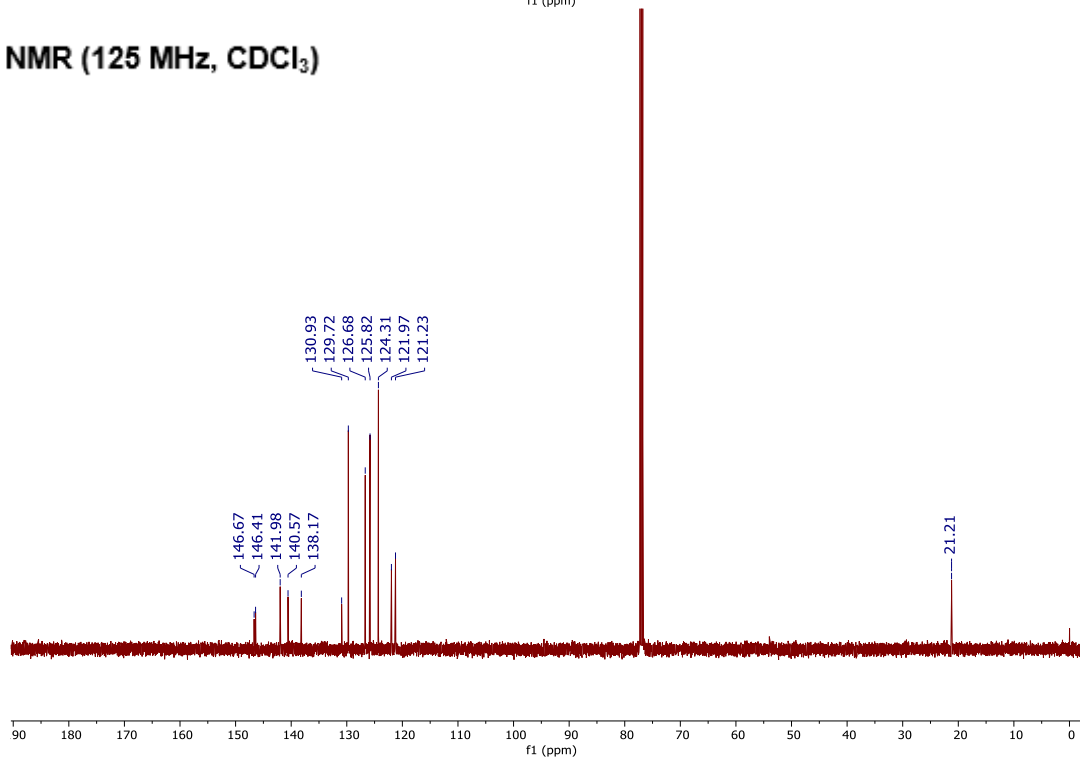
¹³C NMR (125 MHz, CDCl₃)



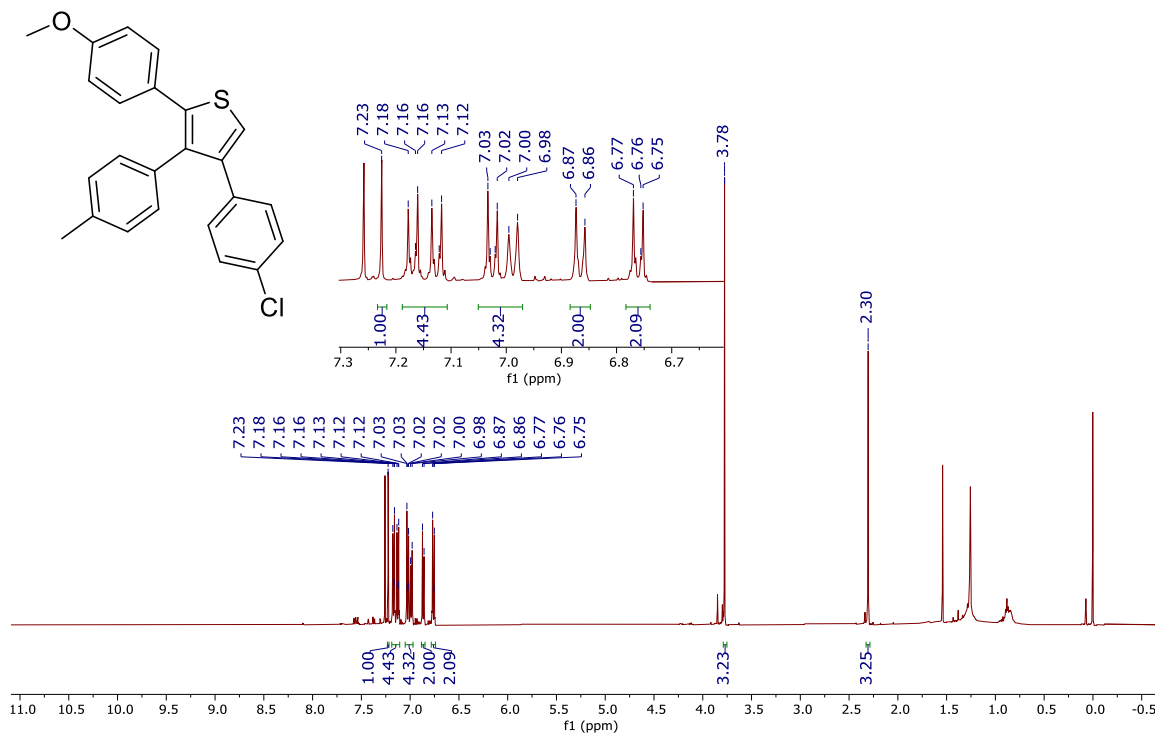
4-(4-nitrophenyl)-2-(p-tolyl)thiophene, D2B
¹H NMR (500 MHz, CDCl₃)



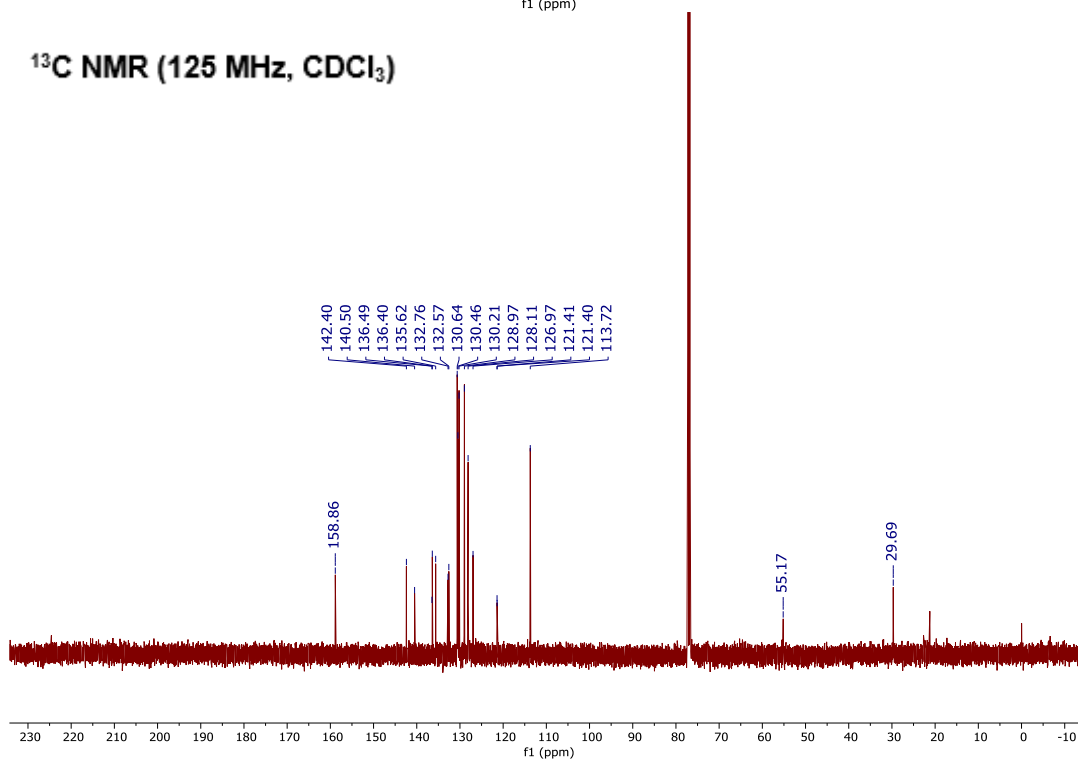
¹³C NMR (125 MHz, CDCl₃)



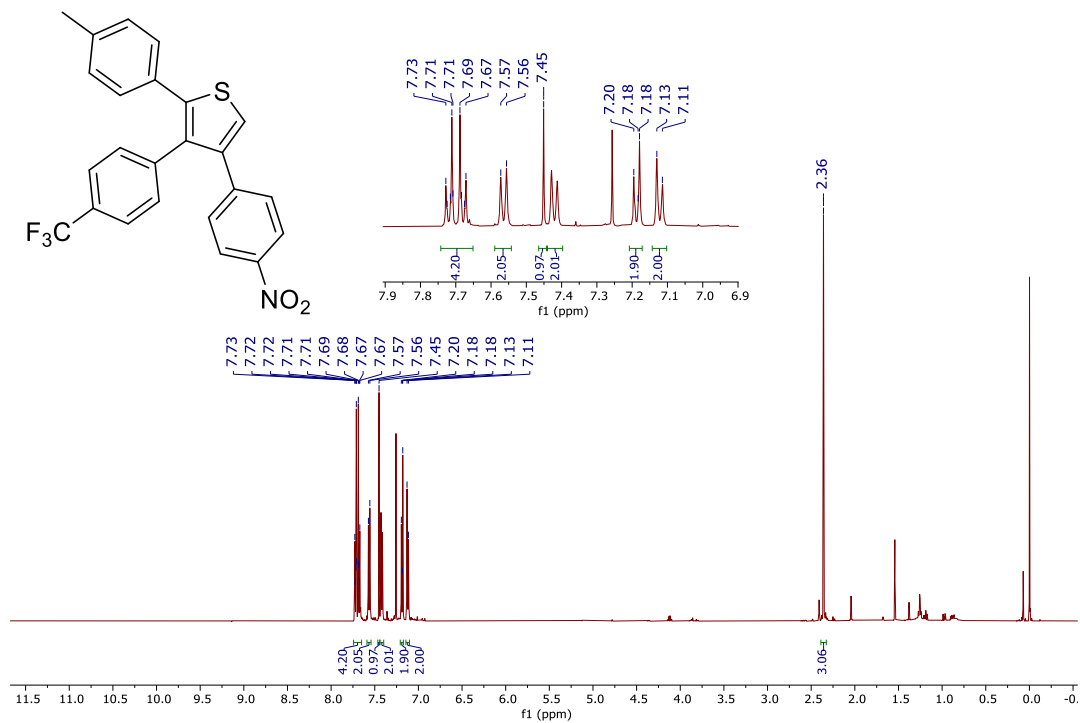
4-(4-chlorophenyl)-2-(4-methoxyphenyl)-3-(p-tolyl)thiophene, T3A
¹H NMR (500 MHz, CDCl₃)



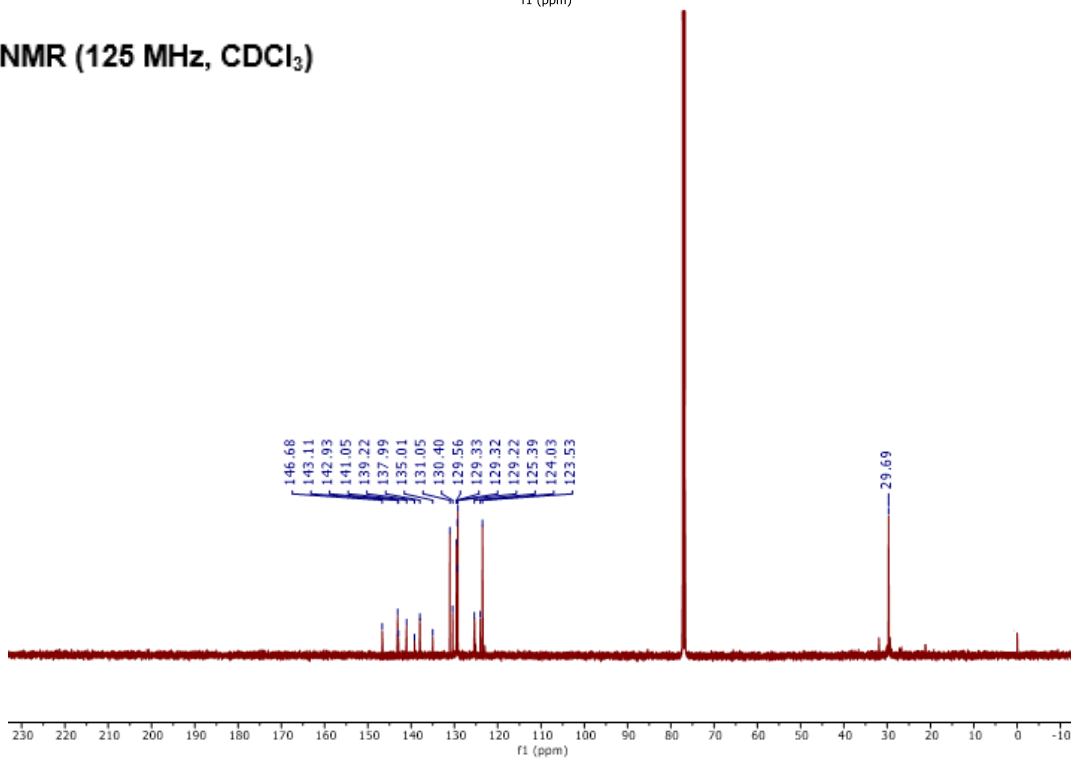
¹³C NMR (125 MHz, CDCl₃)



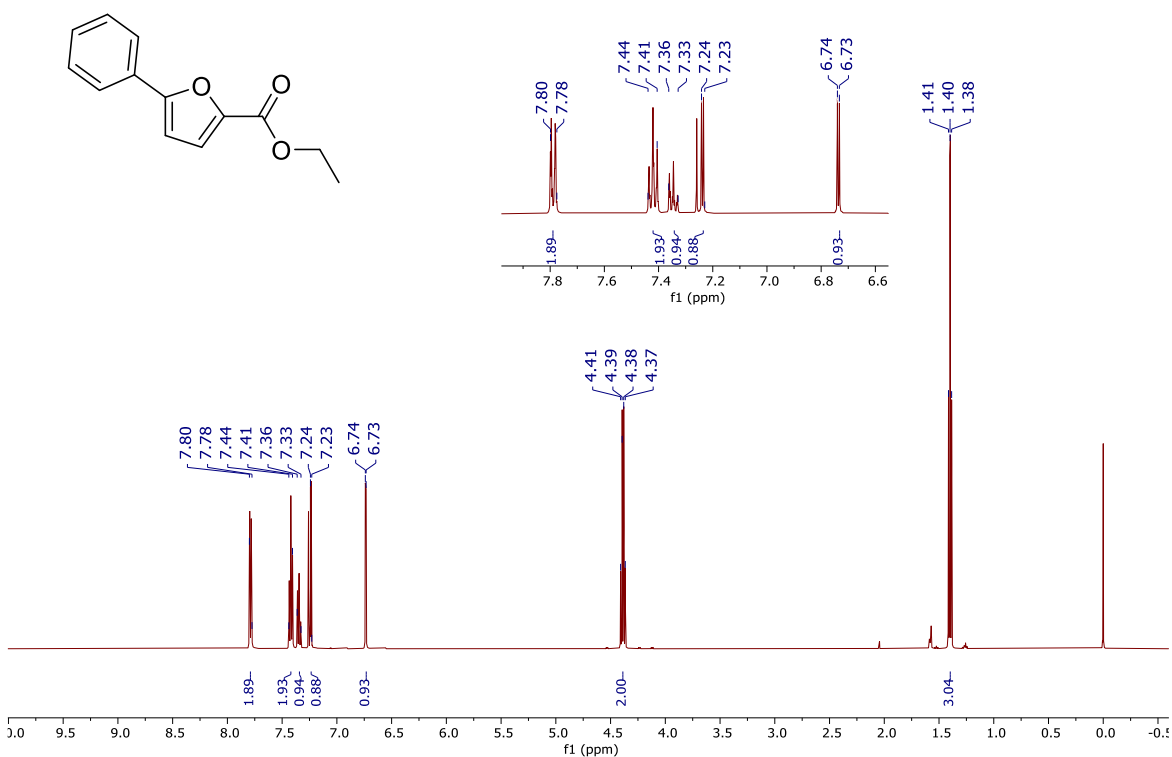
4-(4-nitrophenyl)-2-(p-tolyl)-3-(4-(trifluoromethyl)phenyl)thiophene, T3B
¹H NMR (500 MHz, CDCl₃)



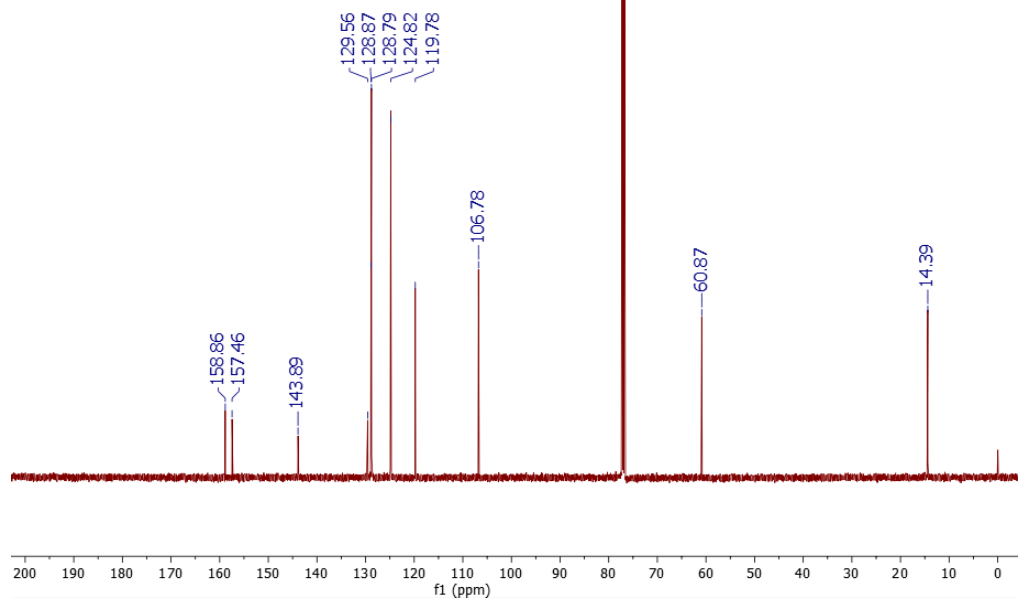
¹³C NMR (125 MHz, CDCl₃)



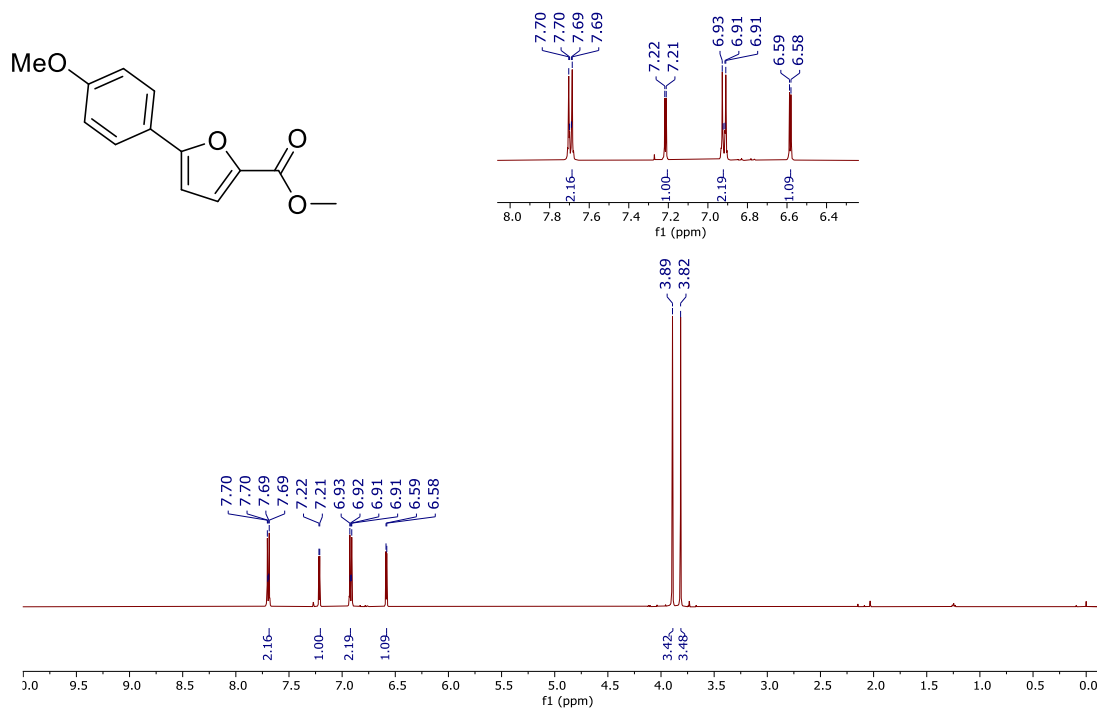
Ethyl 5-phenylfuran-2-carboxylate, 6l
 ^1H NMR (500 MHz, CDCl_3)



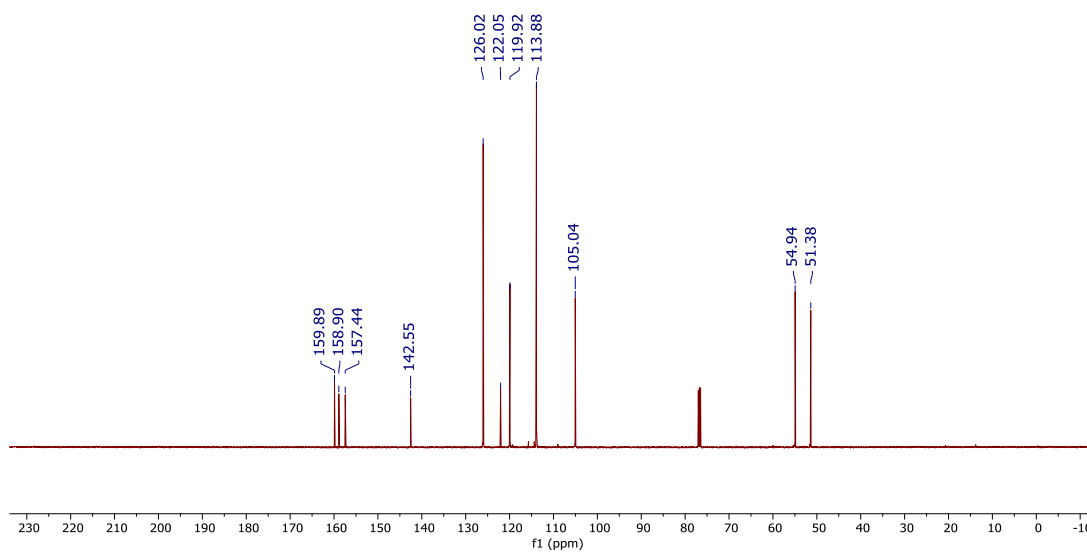
^{13}C NMR (125 MHz, CDCl_3)



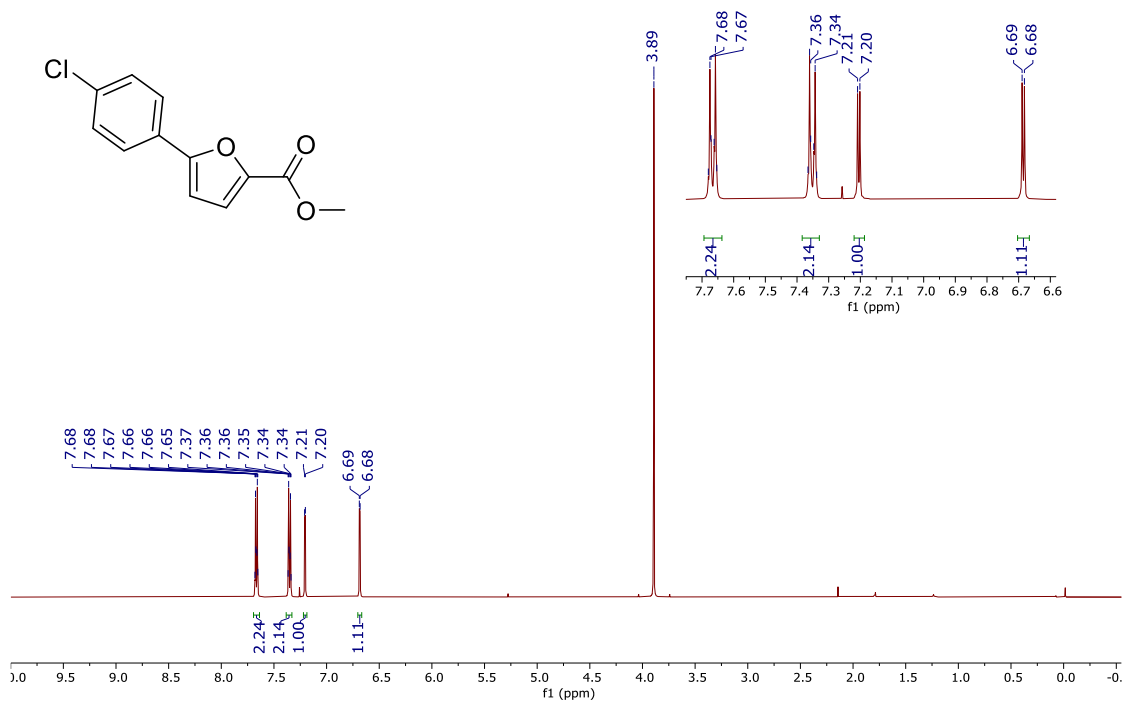
Methyl 5-(4-methoxyphenyl)furan-2-carboxylate, 6n
¹H NMR (500 MHz, CDCl₃)



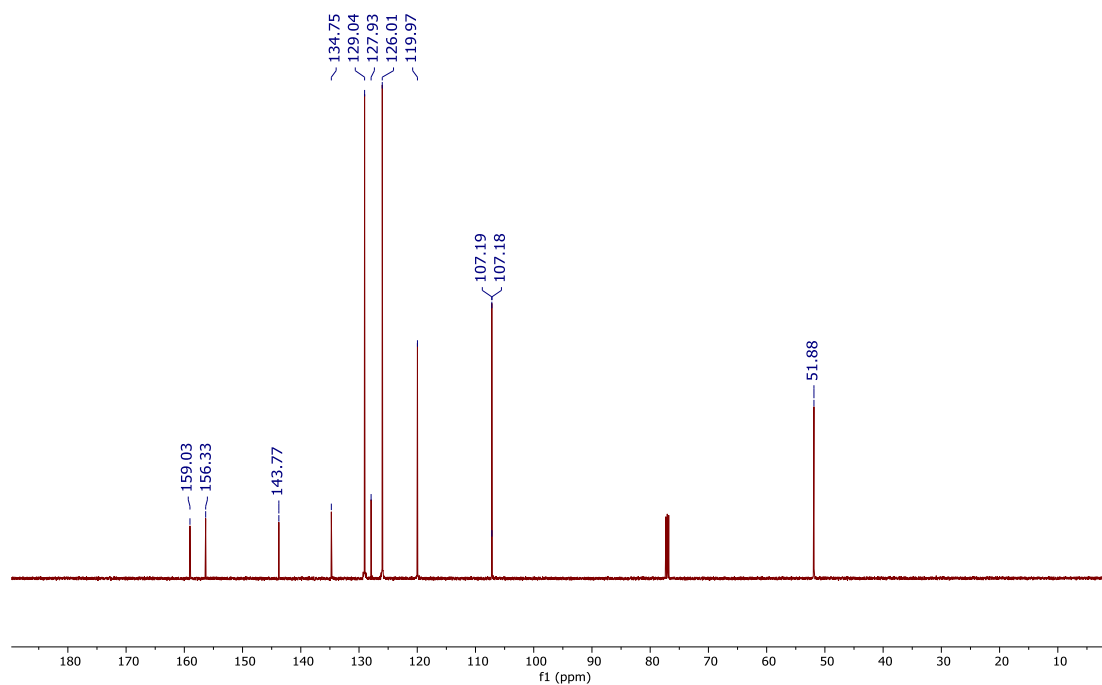
¹³C NMR (125 MHz, CDCl₃)



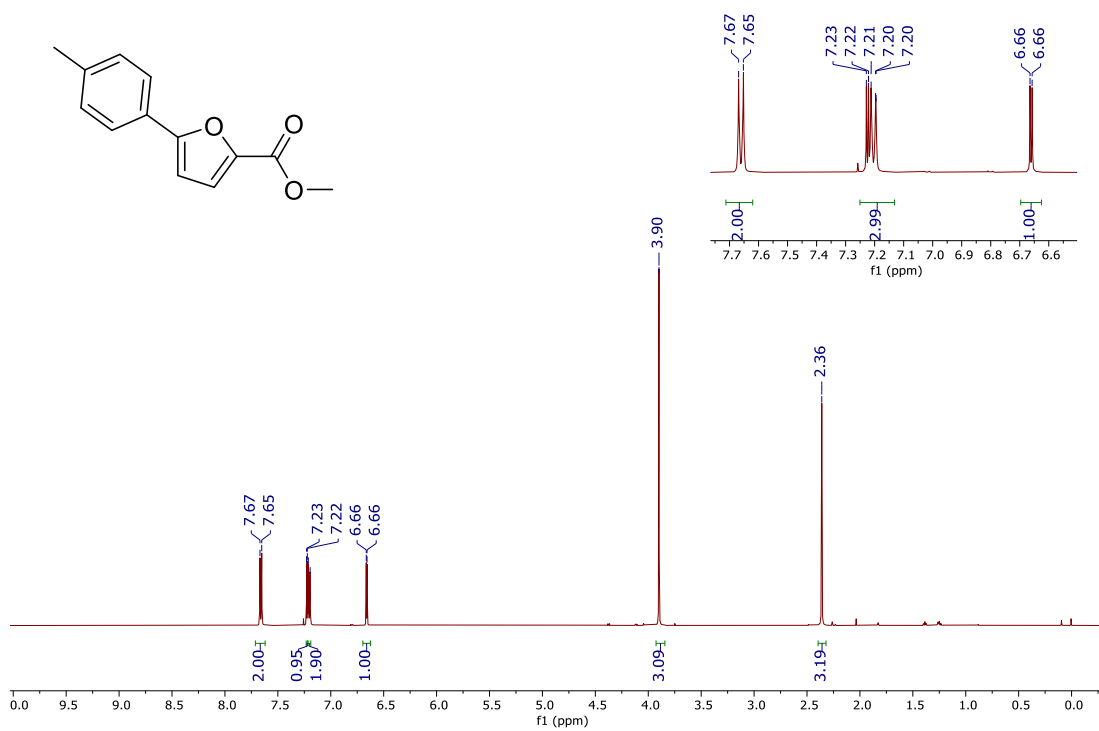
Methyl 5-(4-chlorophenyl)furan-2-carboxylate, 6o
¹H NMR (500 MHz, CDCl₃)



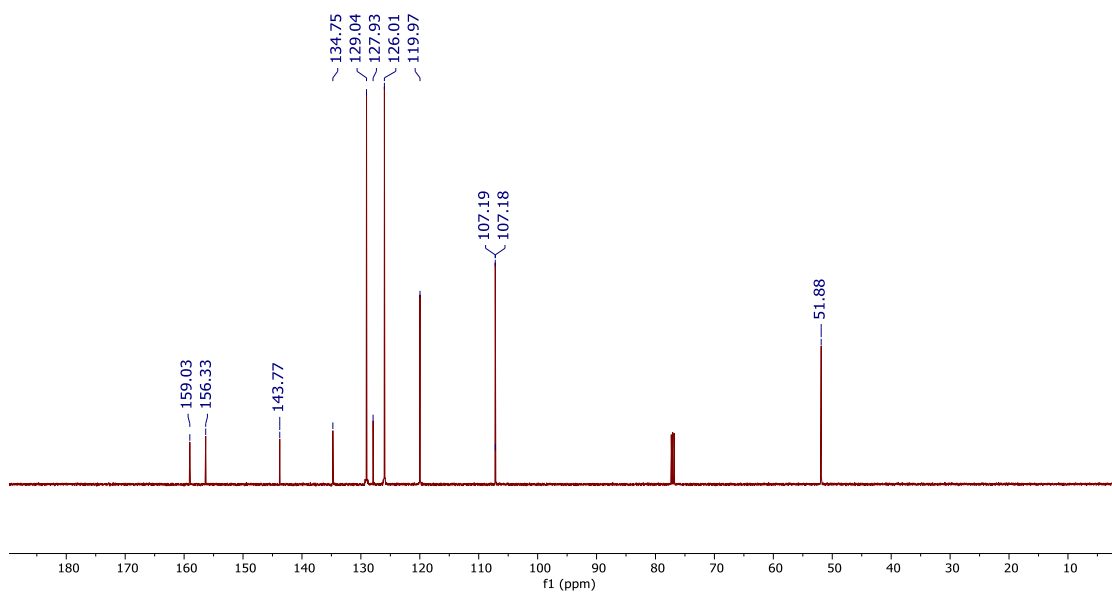
¹³C NMR (125 MHz, CDCl₃)



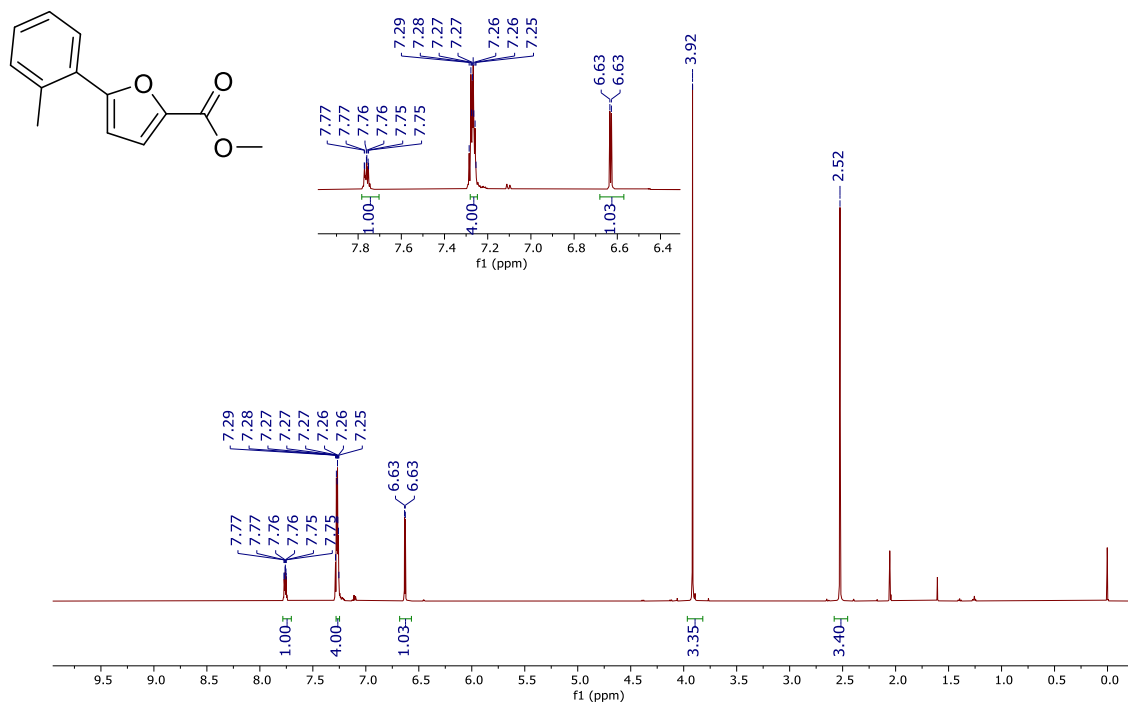
Methyl 5-(p-tolyl)furan-2-carboxylate, 6p
¹H NMR (500 MHz, CDCl₃)



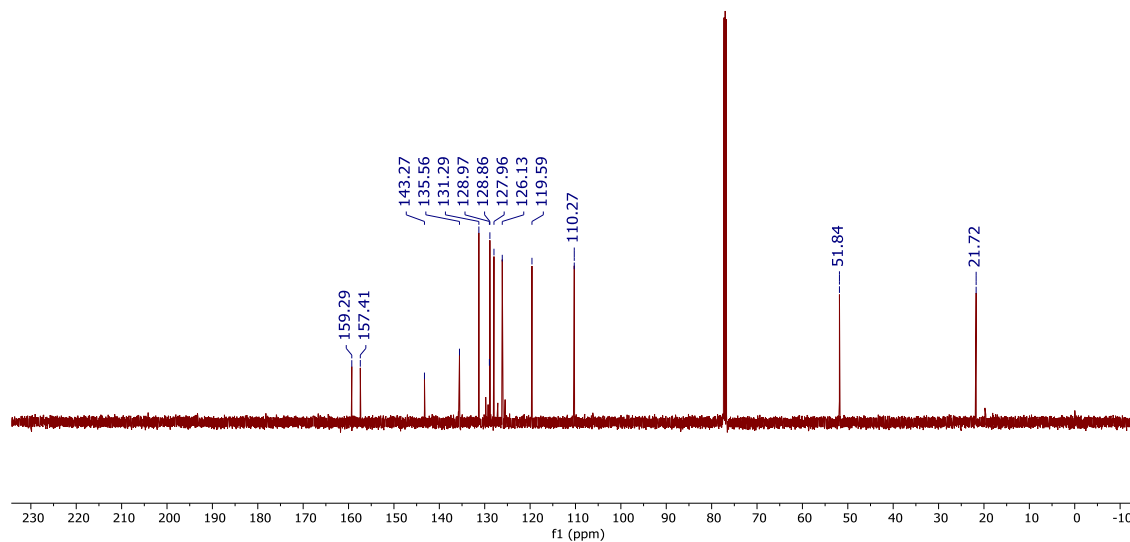
¹³C NMR (125 MHz, CDCl₃)



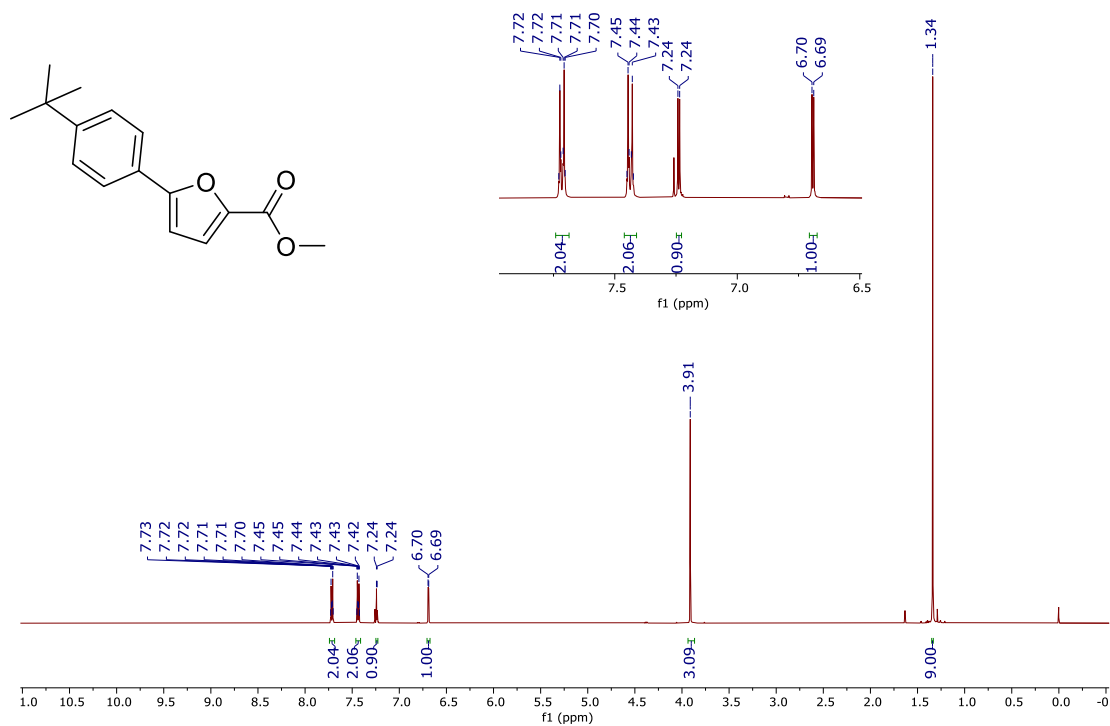
Methyl 5-(o-tolyl)furan-2-carboxylate, 6q
¹H NMR (500 MHz, CDCl₃)



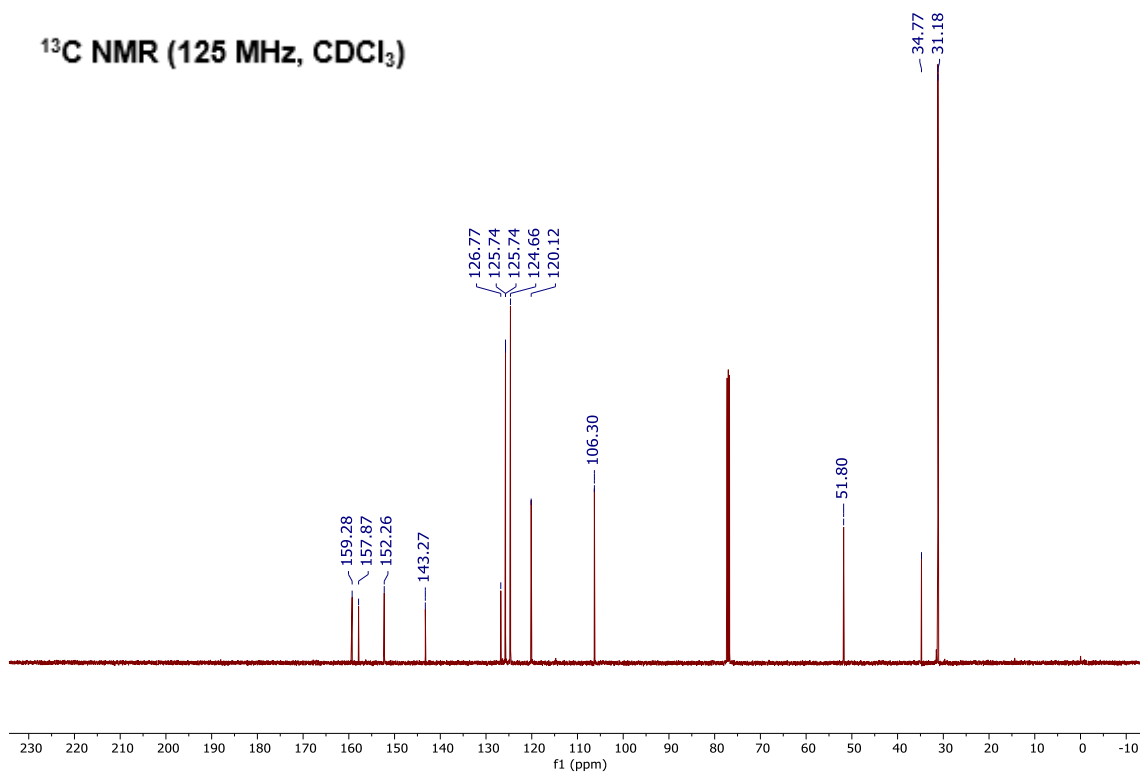
¹³C NMR (125 MHz, CDCl₃)



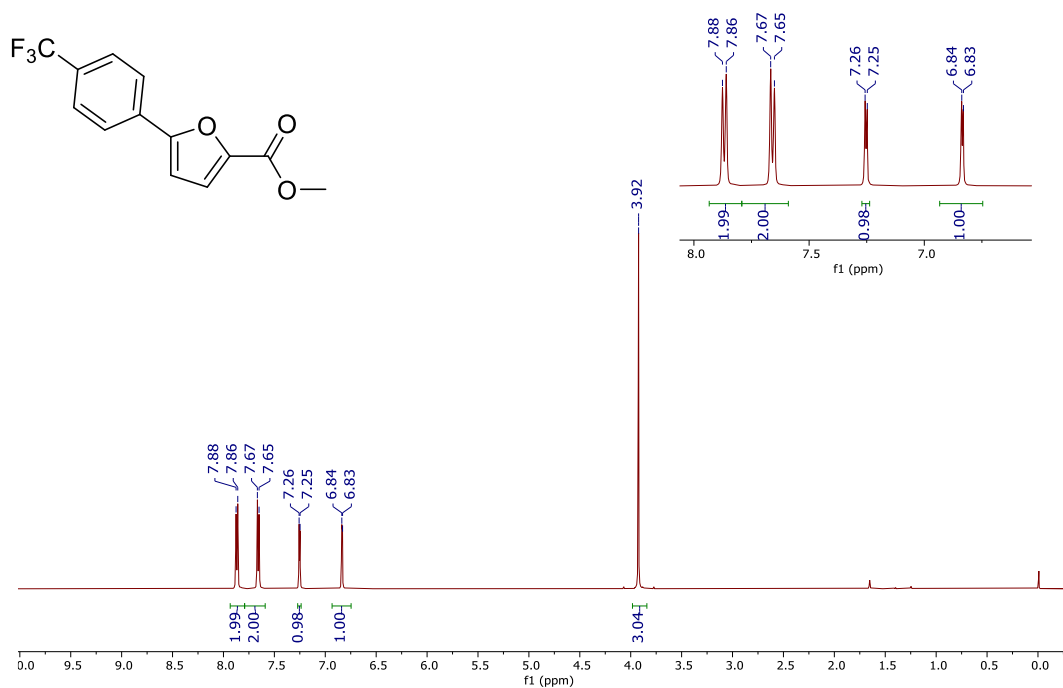
Methyl 5-(4-(tert-butyl)phenyl)furan-2-carboxylate, 6r
¹H NMR (500 MHz, CDCl₃)



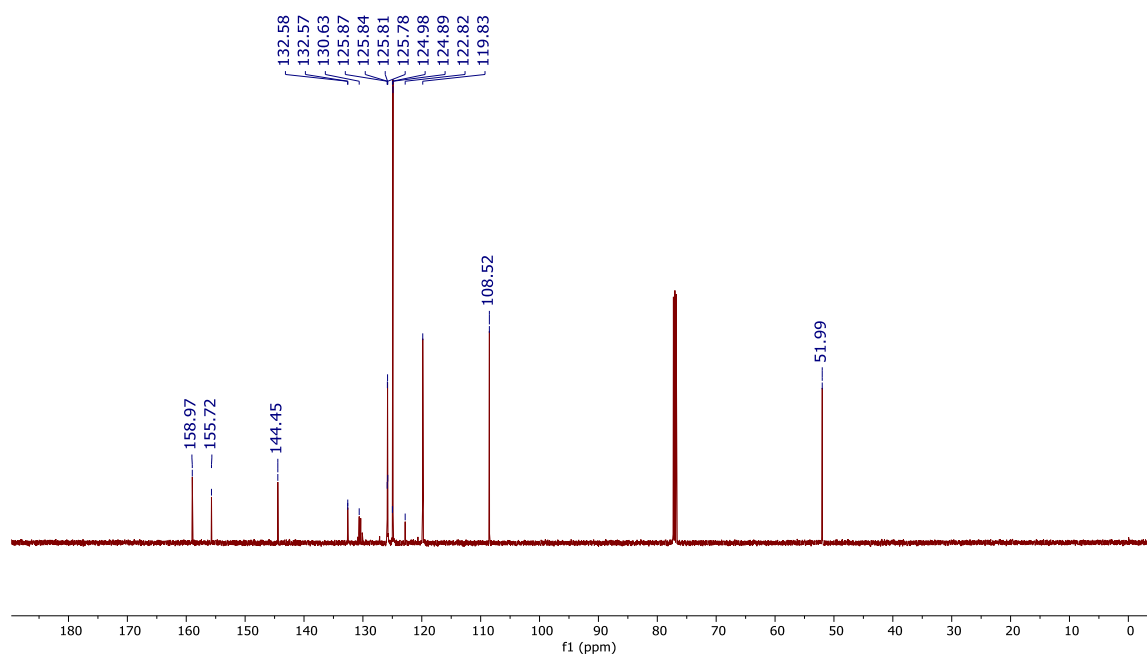
¹³C NMR (125 MHz, CDCl₃)



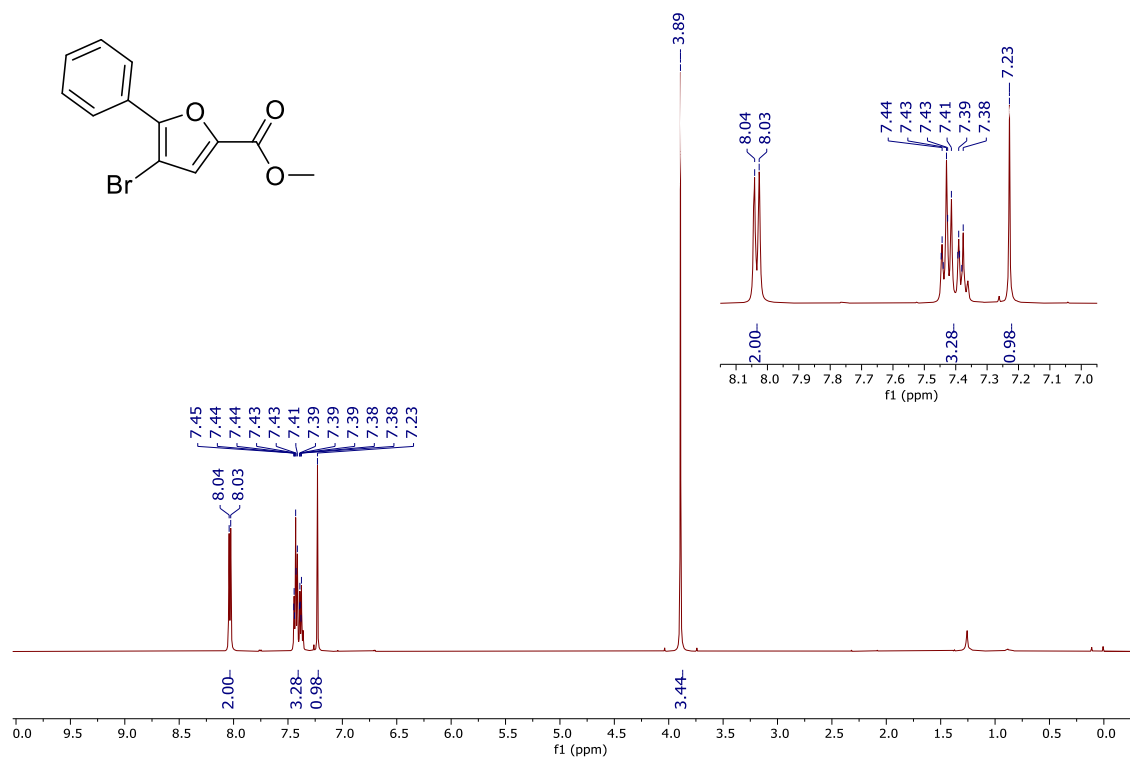
Methyl 5-(4-(trifluoromethyl)phenyl)furan-2-carboxylate, 6s
¹H NMR (500 MHz, CDCl₃)



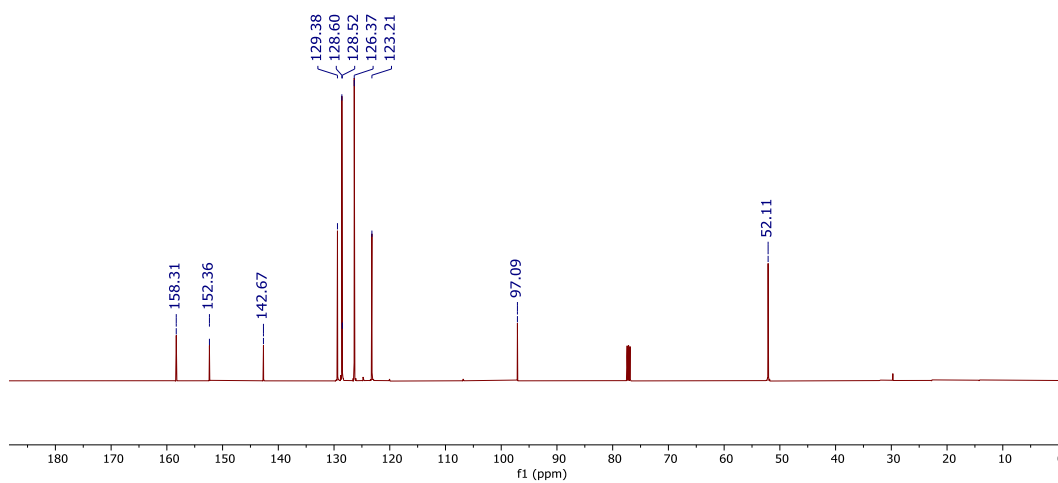
¹³C NMR (125 MHz, CDCl₃)



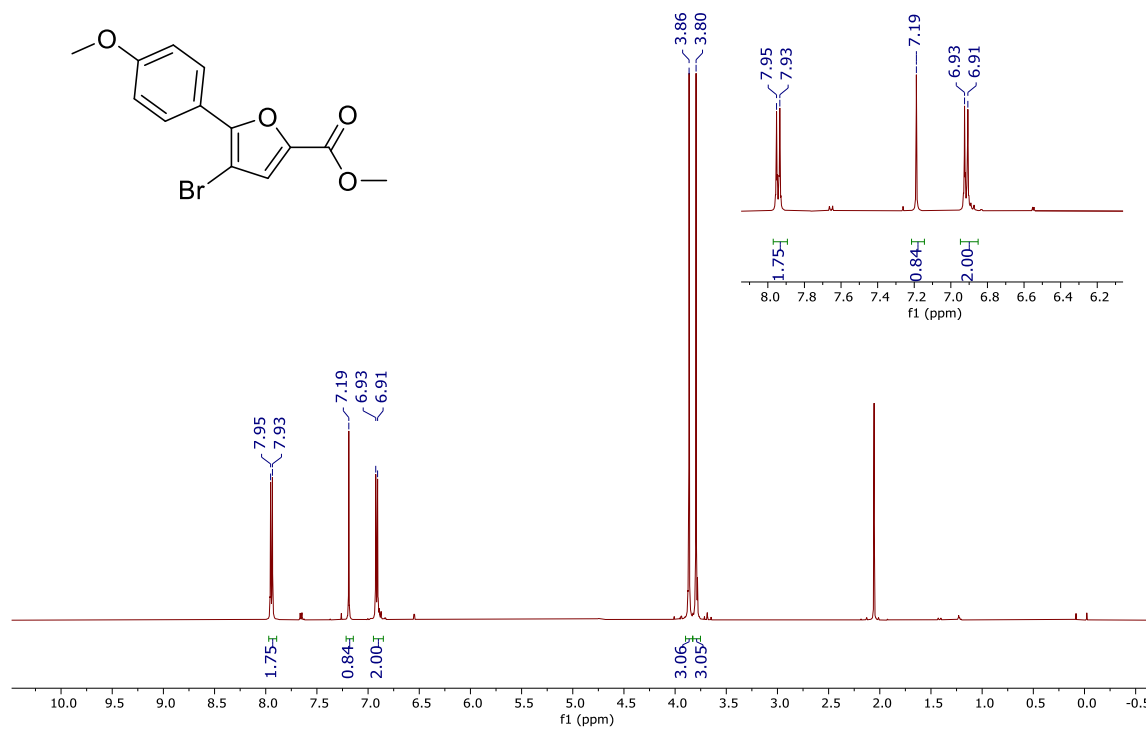
Methyl 4-bromo-5-phenylfuran-2-carboxylate, 7k
¹H NMR (500 MHz, CDCl₃)



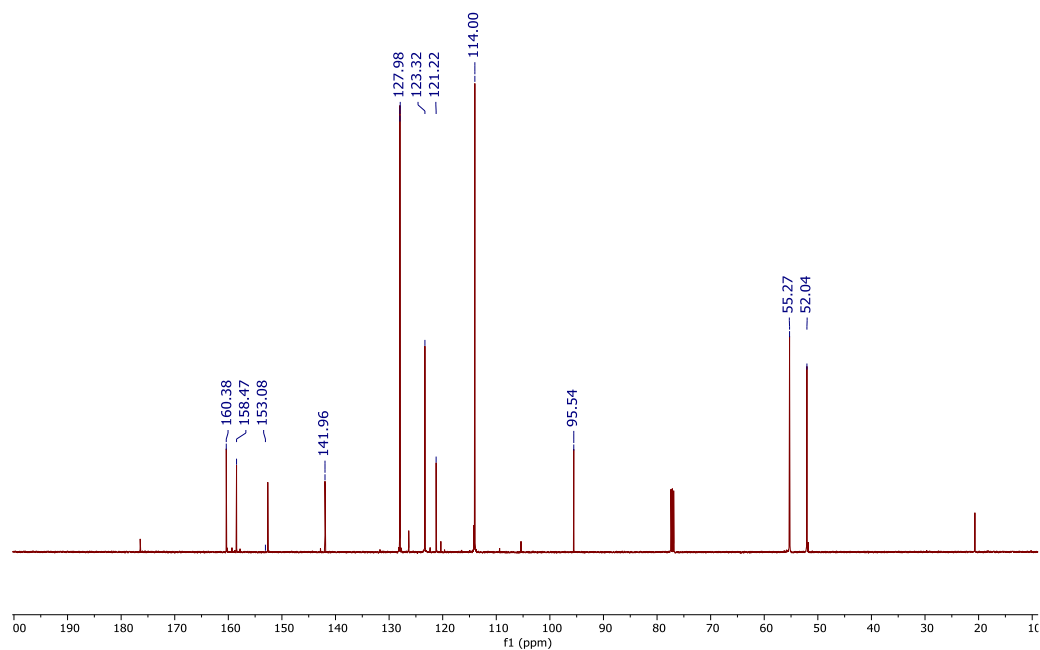
¹³C NMR (125 MHz, CDCl₃)



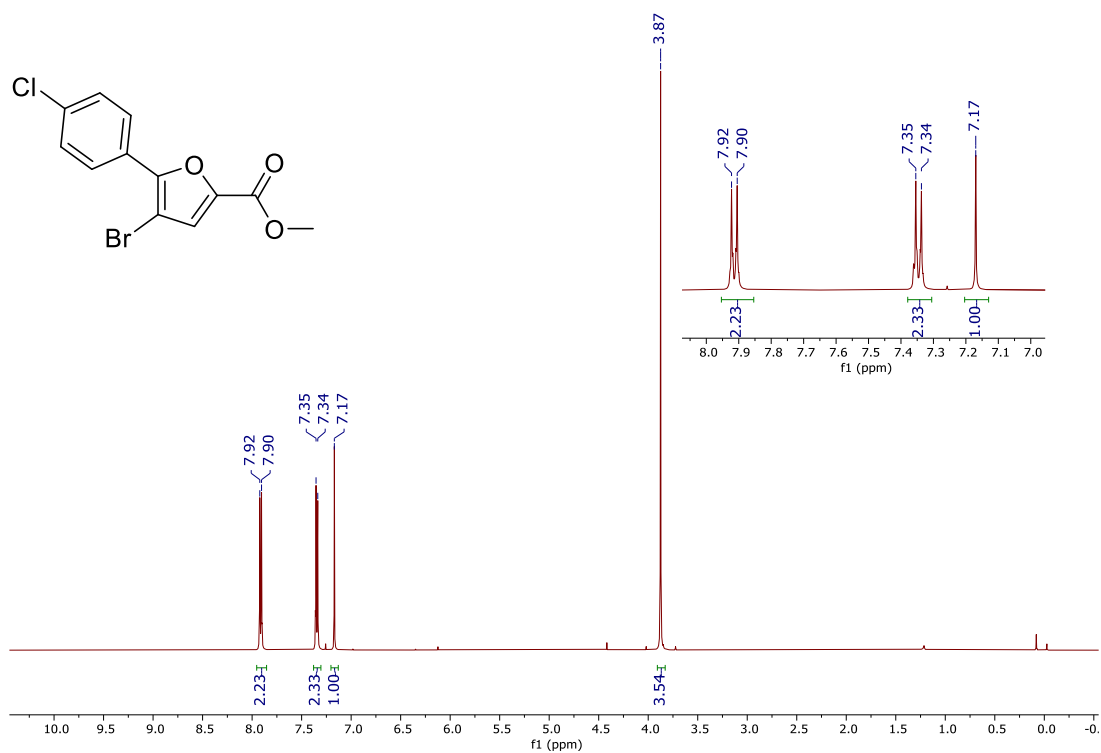
Methyl 4-bromo-5-(4-methoxyphenyl)furan-2-carboxylate, 7I
¹H NMR (500 MHz, CDCl₃)



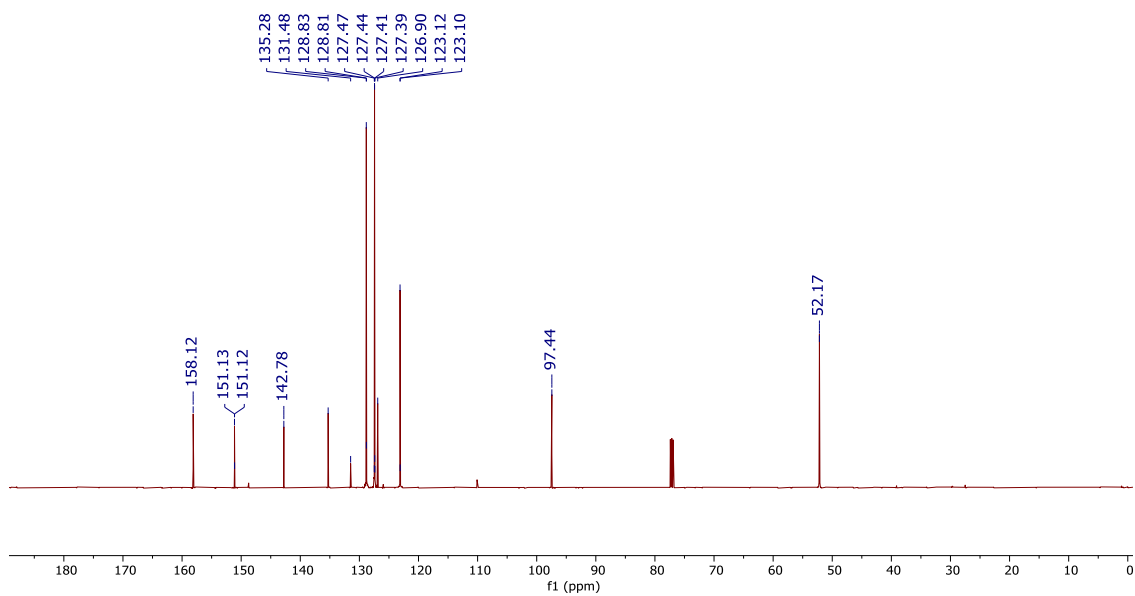
¹³C NMR (125 MHz, CDCl₃)



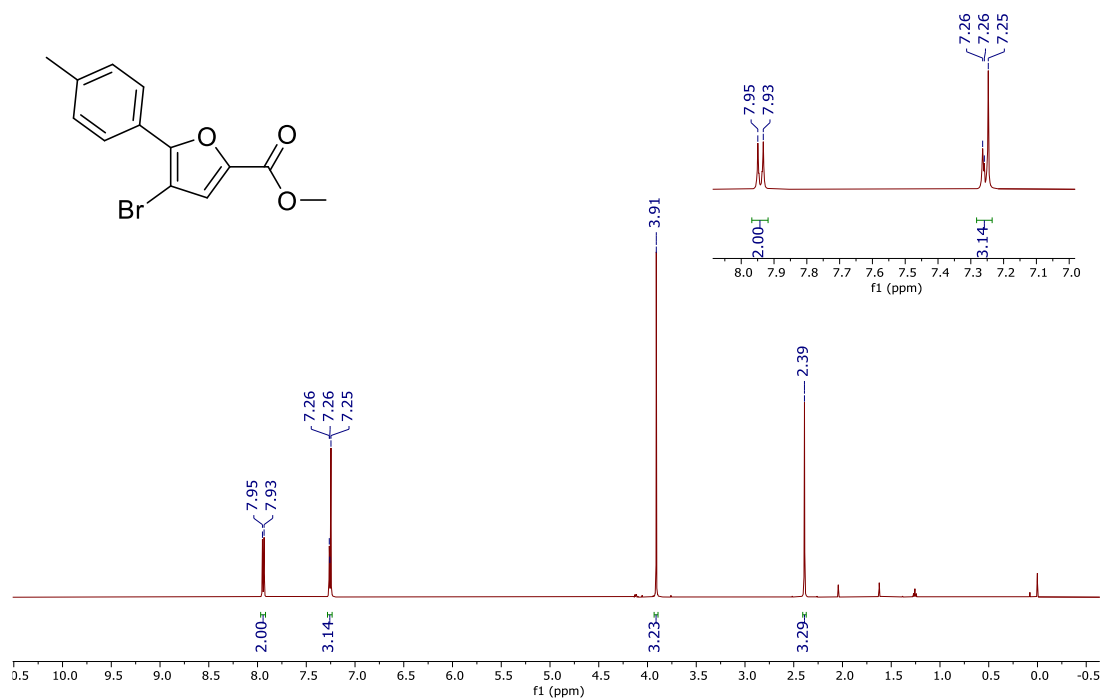
Methyl 4-bromo-5-(4-chlorophenyl)furan-2-carboxylate, 7m
¹H NMR (500 MHz, CDCl₃)



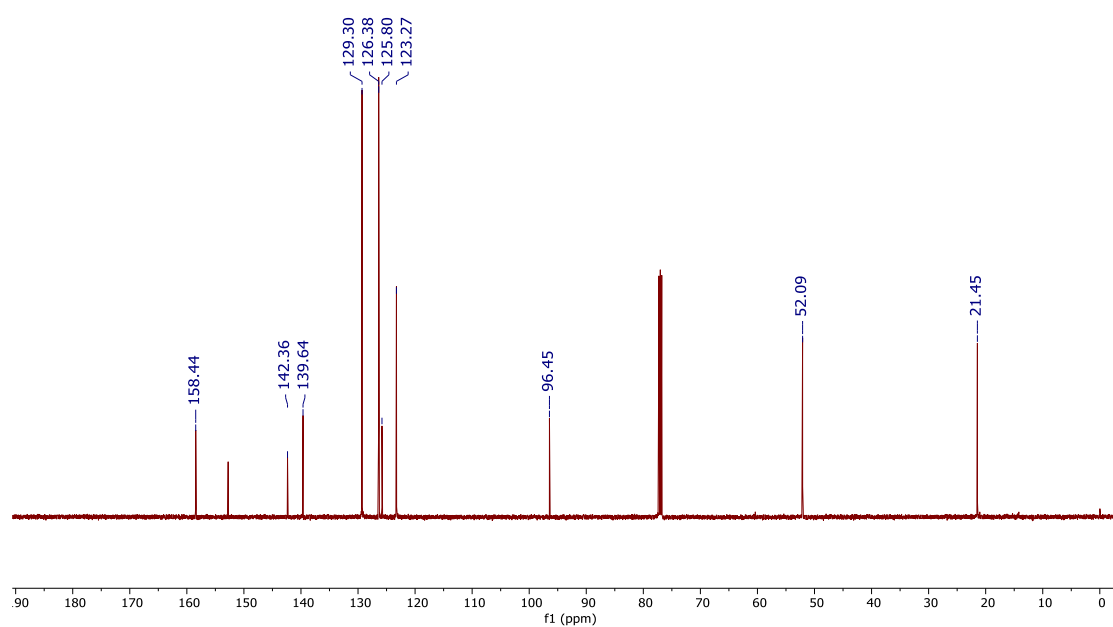
¹³C NMR (125 MHz, CDCl₃)



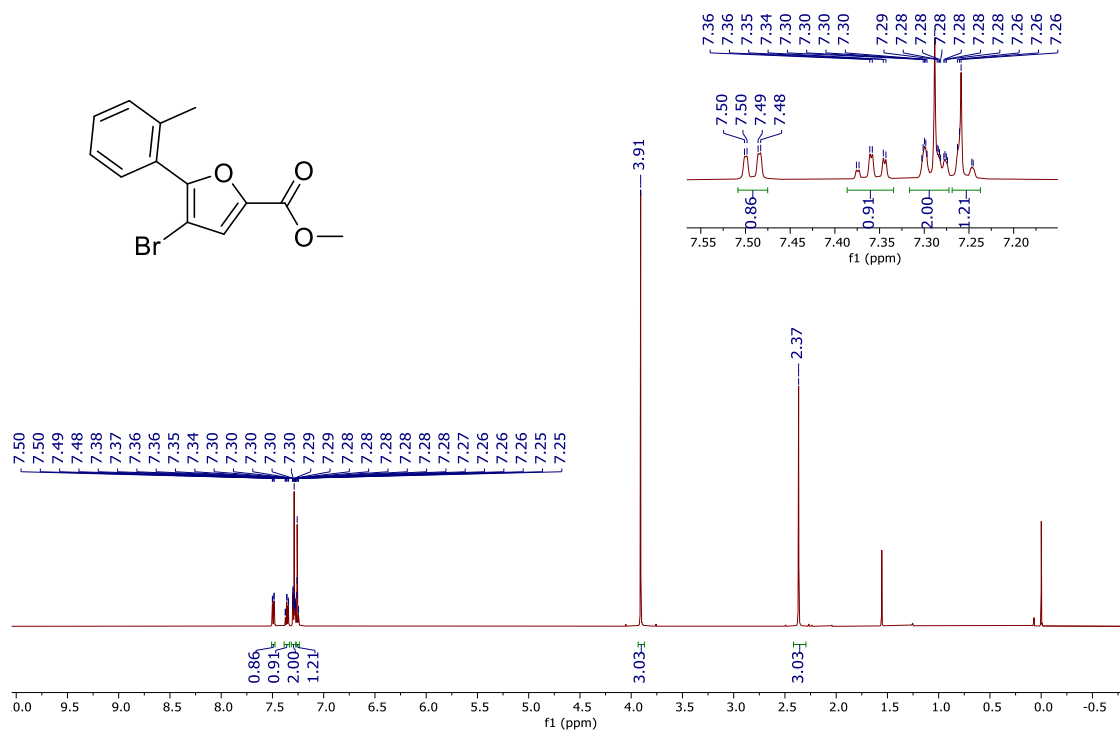
Methyl 4-bromo-5-(p-tolyl)furan-2-carboxylate, 7n
¹H NMR (500 MHz, CDCl₃)



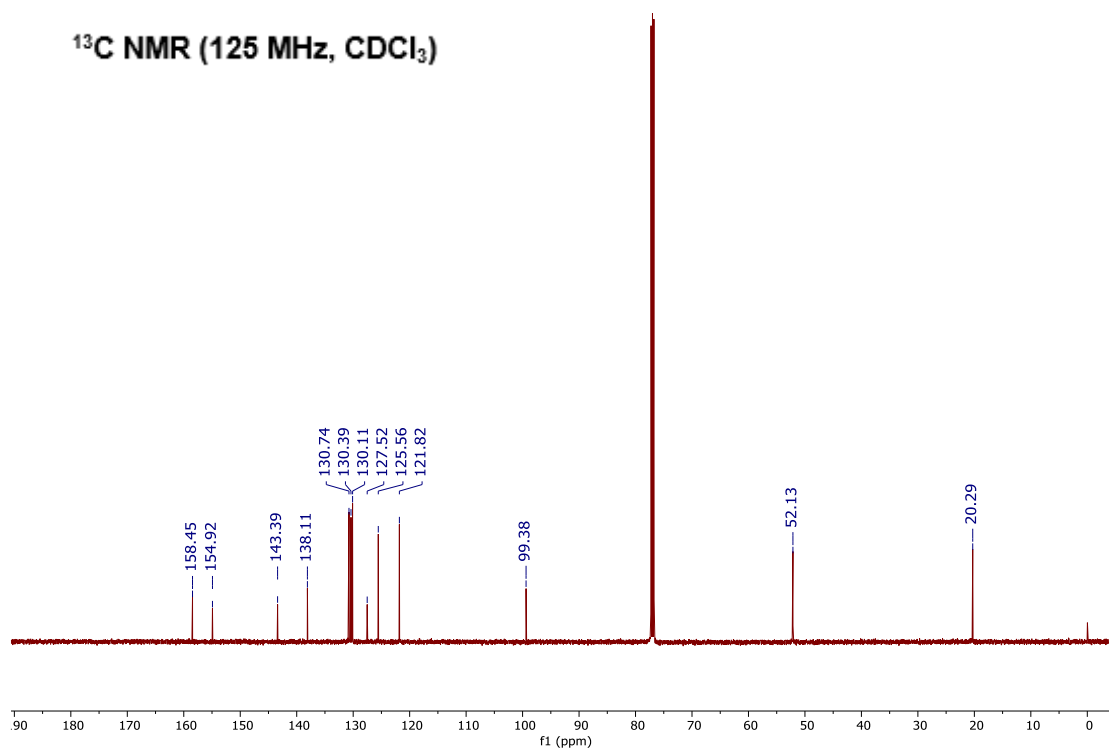
¹³C NMR (125 MHz, CDCl₃)



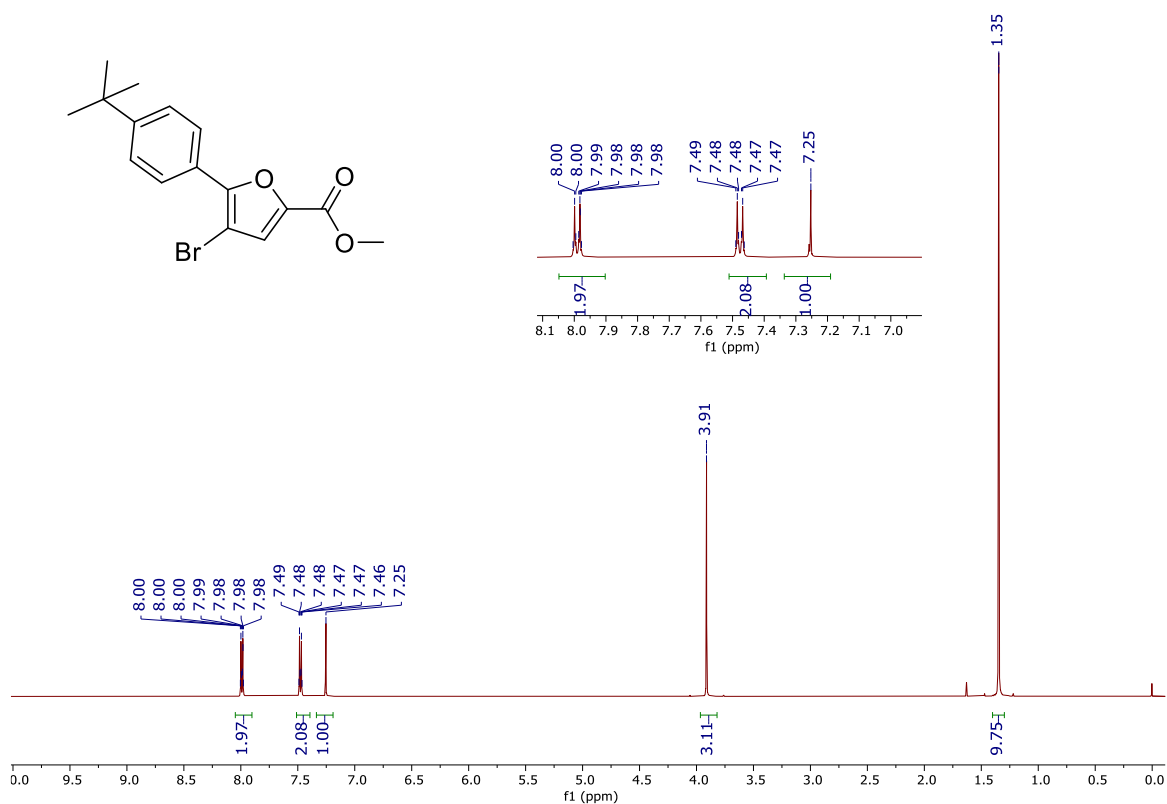
Methyl 4-bromo-5-(o-tolyl)furan-2-carboxylate, 7o
¹H NMR (500 MHz, CDCl₃)



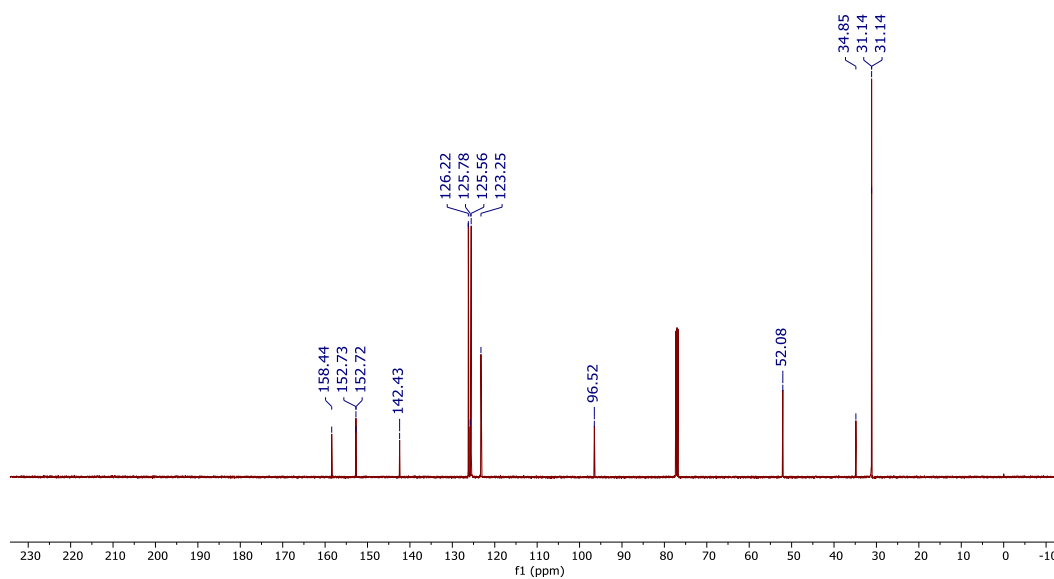
¹³C NMR (125 MHz, CDCl₃)



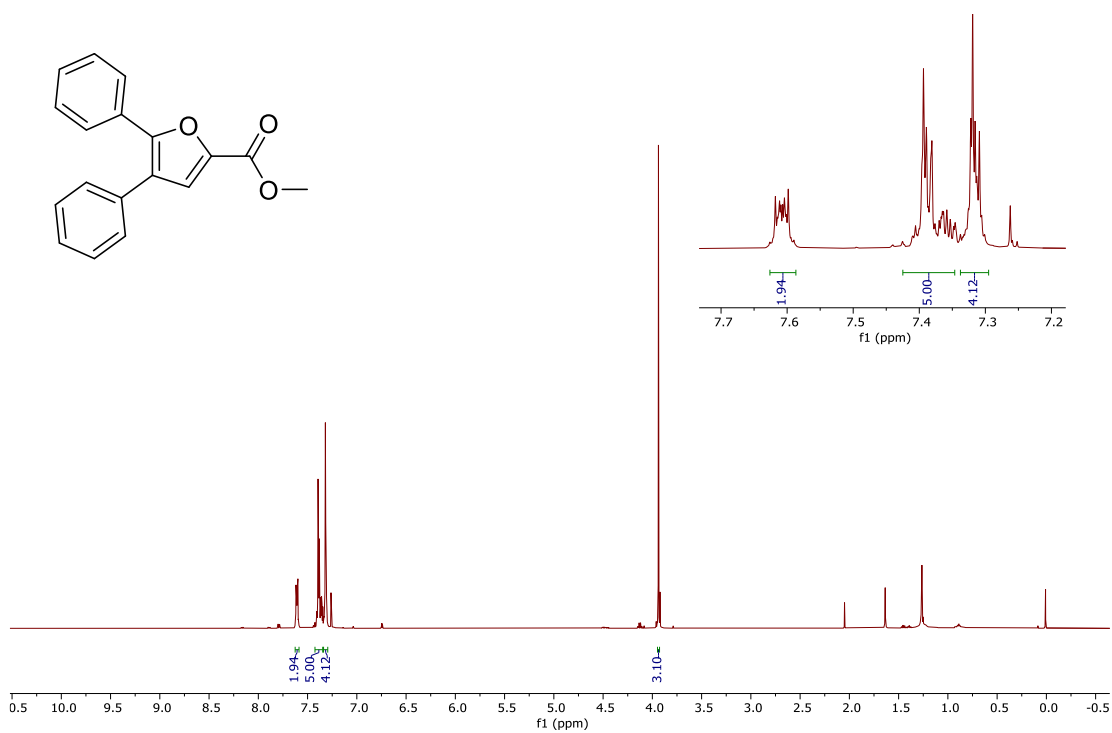
Methyl 4-bromo-5-(4-(tert-butyl)phenyl)furan-2-carboxylate, 7p
¹H NMR (500 MHz, CDCl₃)



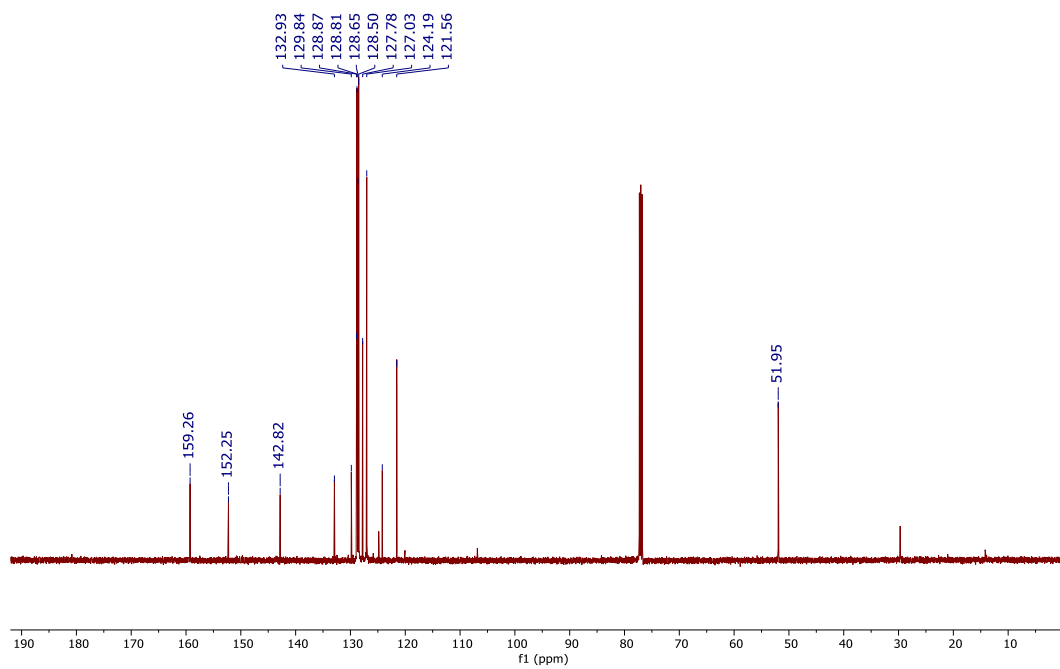
¹³C NMR (125 MHz, CDCl₃)



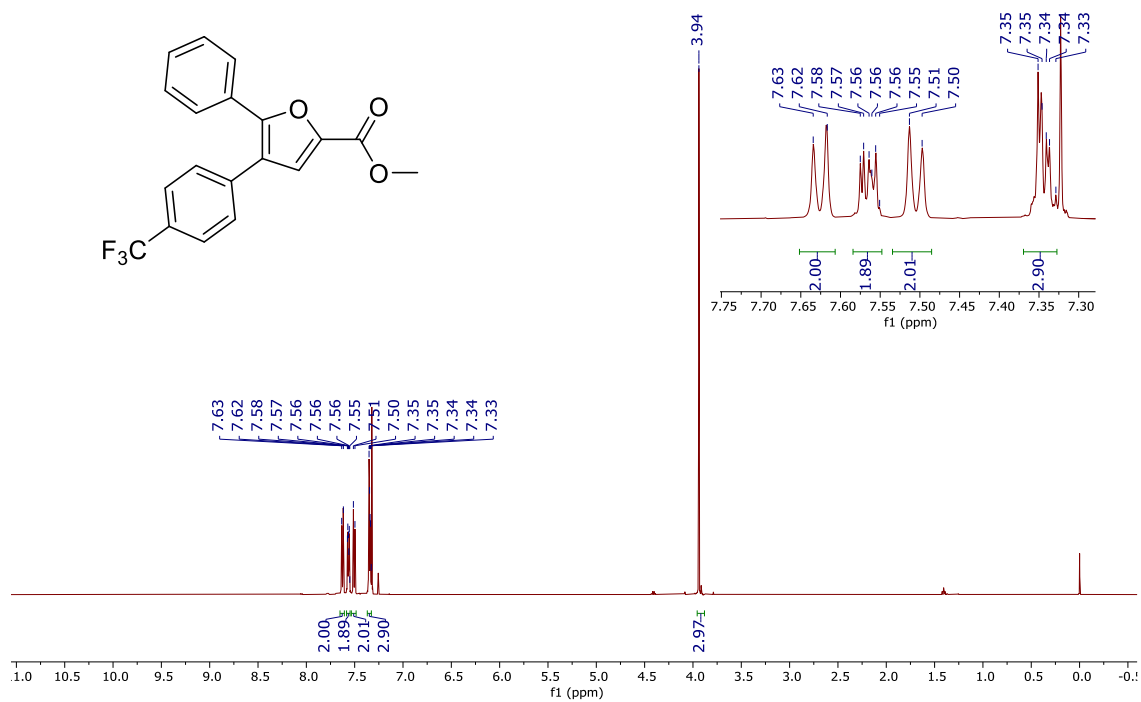
Methyl 4,5-diphenylfuran-2-carboxylate, 8i
¹H NMR (500 MHz, CDCl₃)



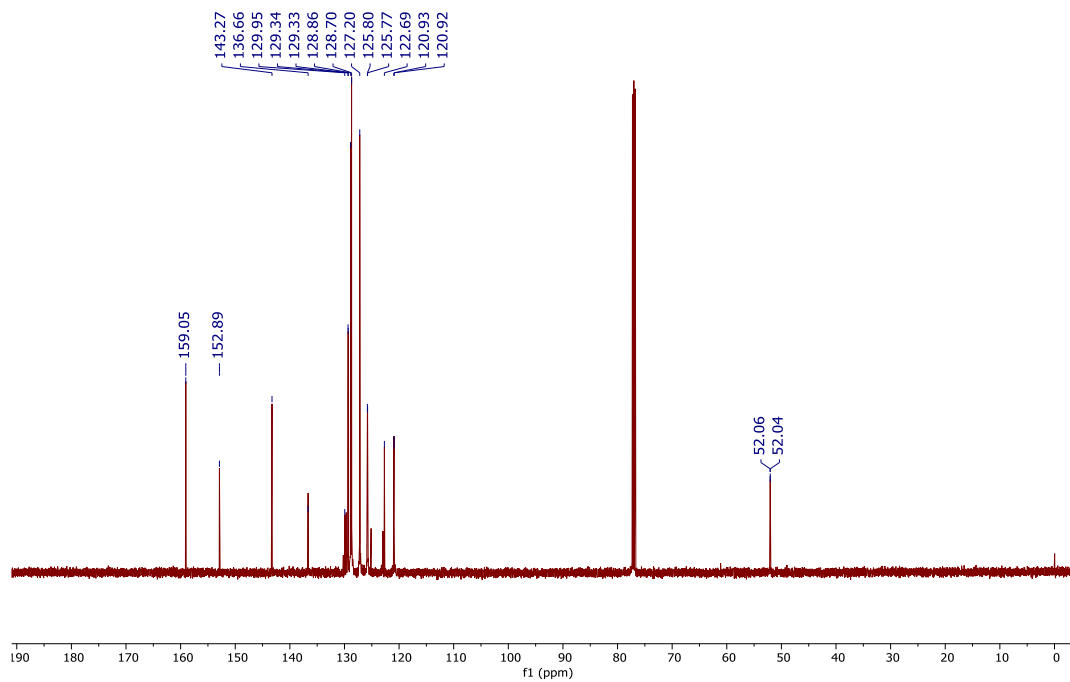
¹³C NMR (125 MHz, CDCl₃)



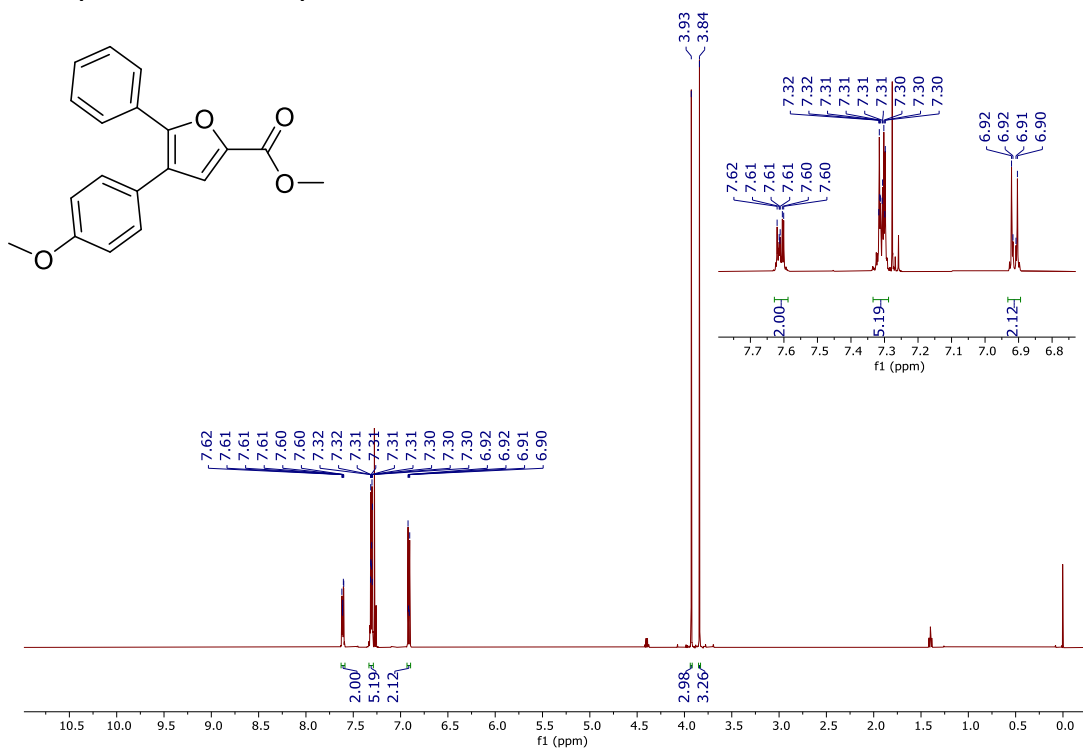
Methyl 5-phenyl-4-(4-(trifluoromethyl)phenyl)furan-2-carboxylate, 8j
¹H NMR (500 MHz, CDCl₃)



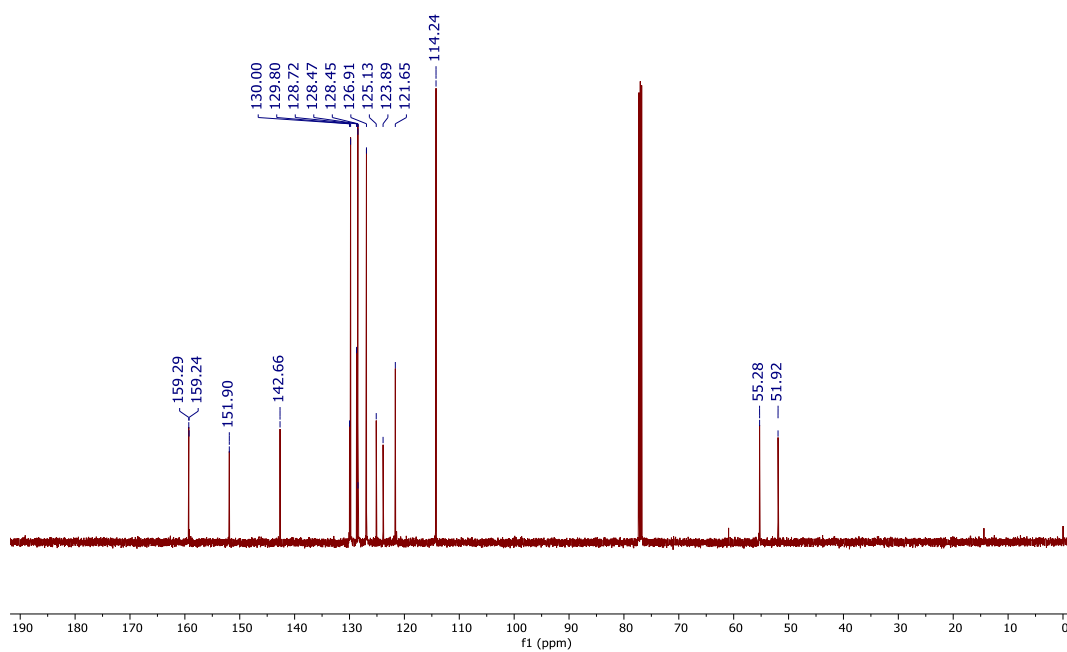
¹³C NMR (125 MHz, CDCl₃)



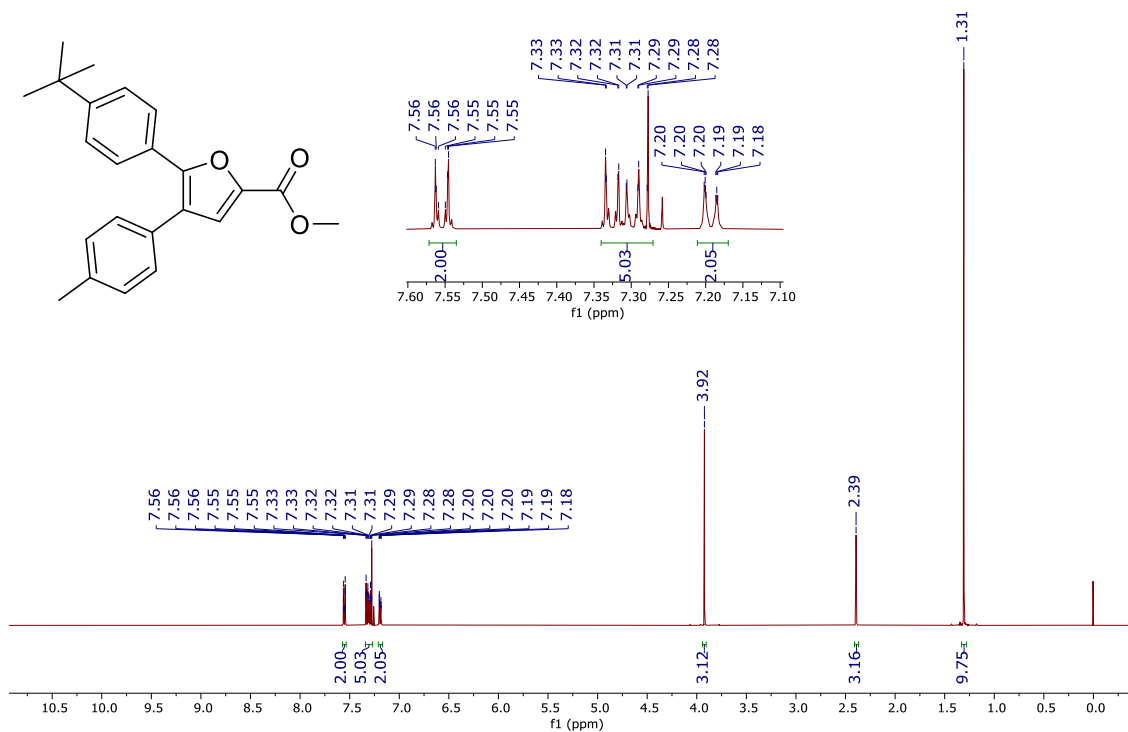
Methyl 4-(4-methoxyphenyl)-5-phenylfuran-2-carboxylate, 8k
¹H NMR (500 MHz, CDCl₃)



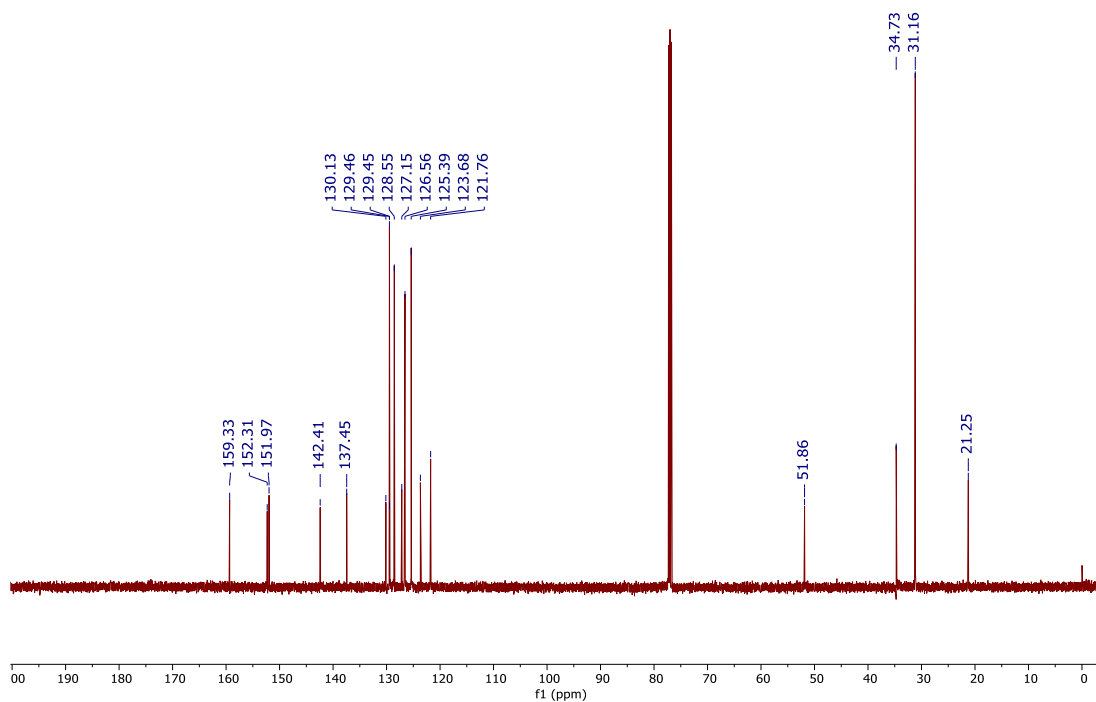
¹³C NMR (125 MHz, CDCl₃)



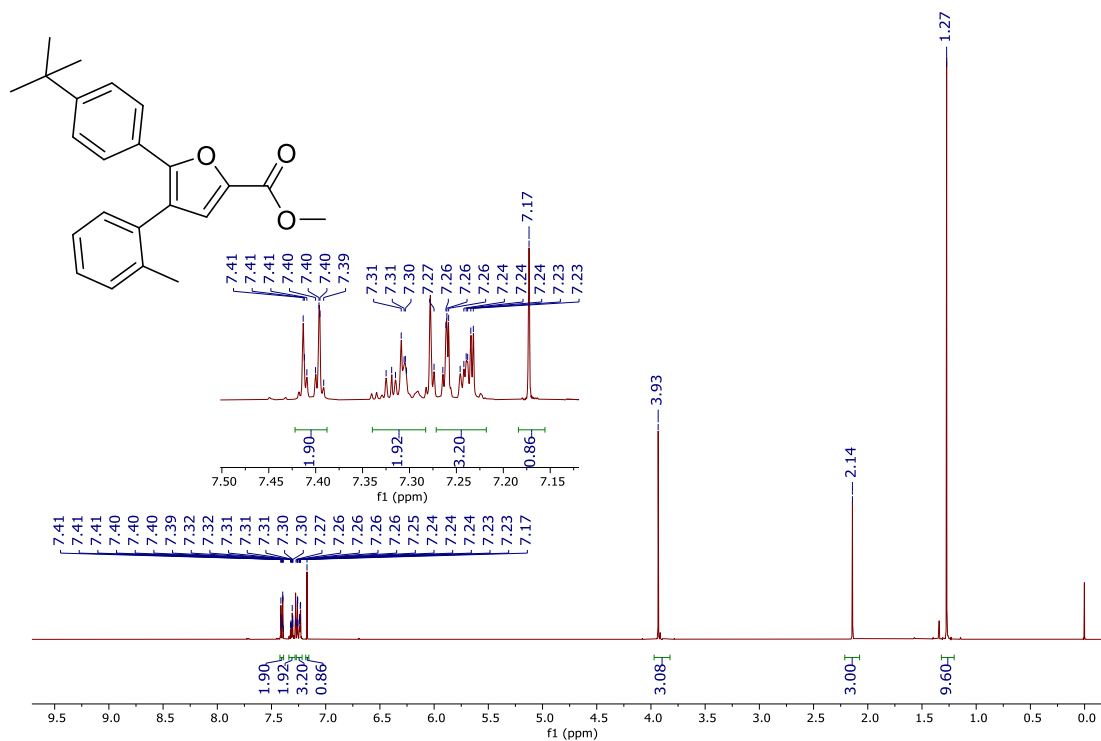
Methyl 5-(4-(tert-butyl)phenyl)-4-(p-tolyl)furan-2-carboxylate, 8l
¹H NMR (500 MHz, CDCl₃)



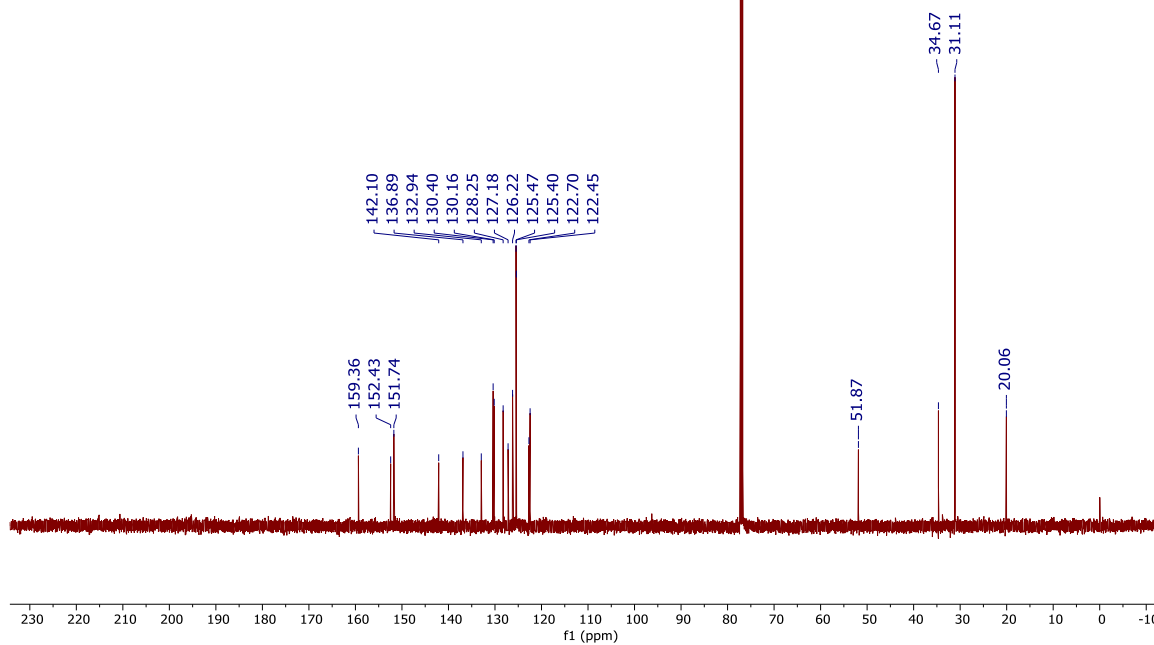
¹³C NMR (125 MHz, CDCl₃)



Methyl 5-(4-(tert-butyl)phenyl)-4-(o-tolyl)furan-2-carboxylate, 8m
¹H NMR (500 MHz, CDCl₃)

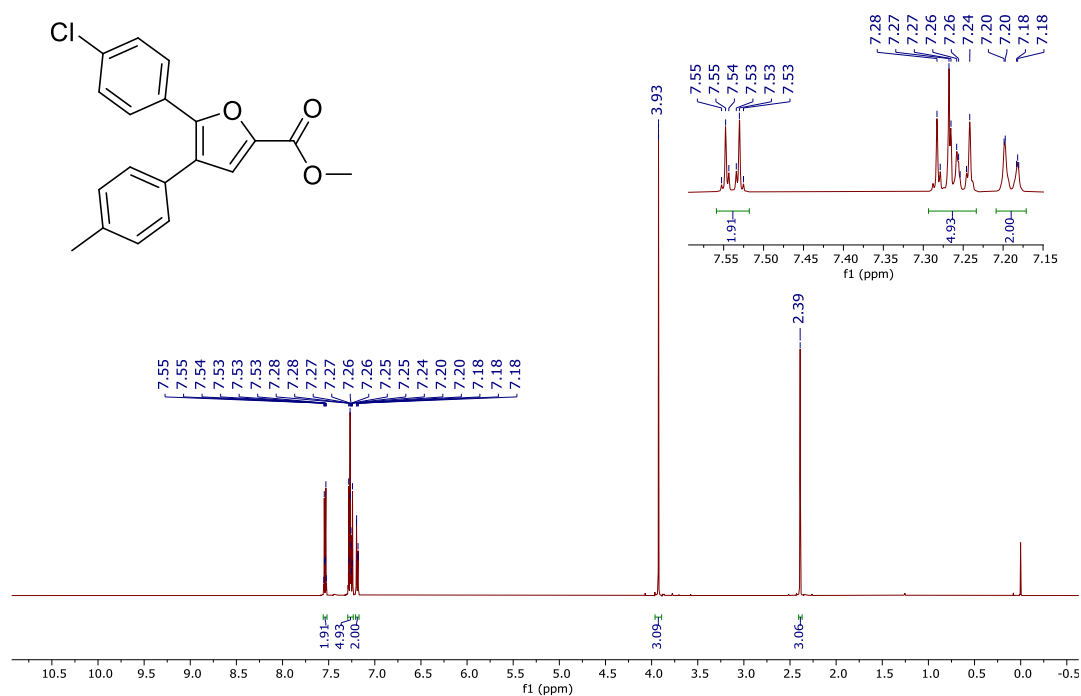


¹³C NMR (125 MHz, CDCl₃)

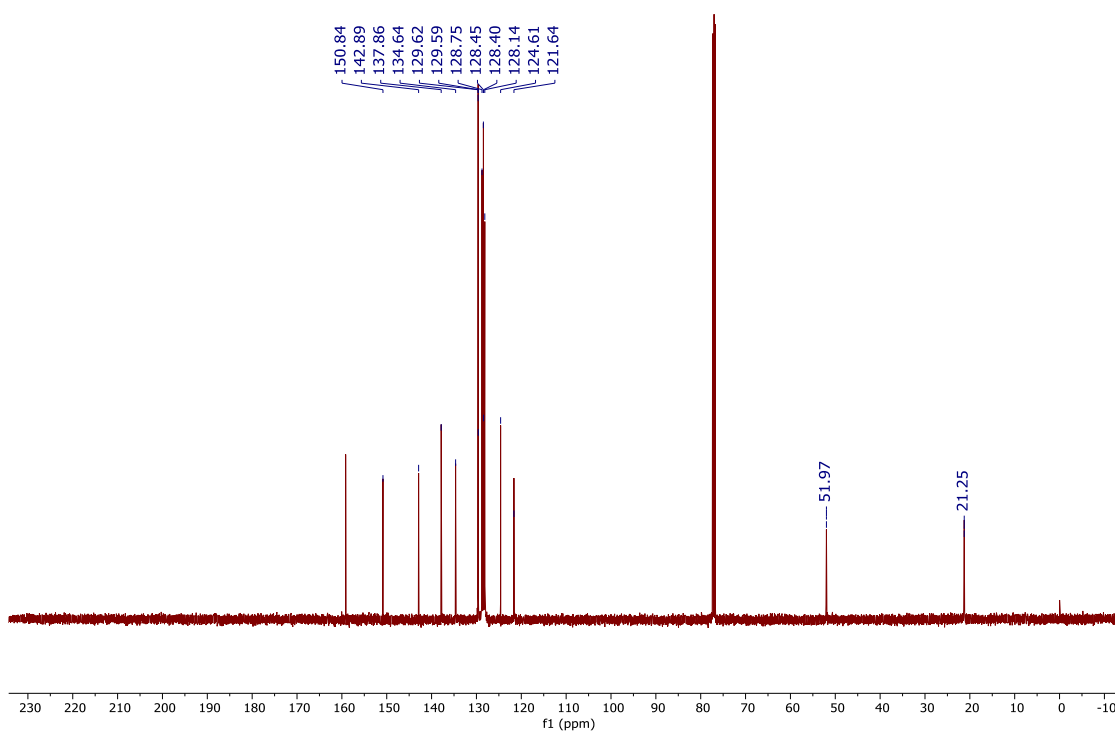


Methyl 5-(4-chlorophenyl)-4-(p-tolyl)furan-2-carboxylate, 8n

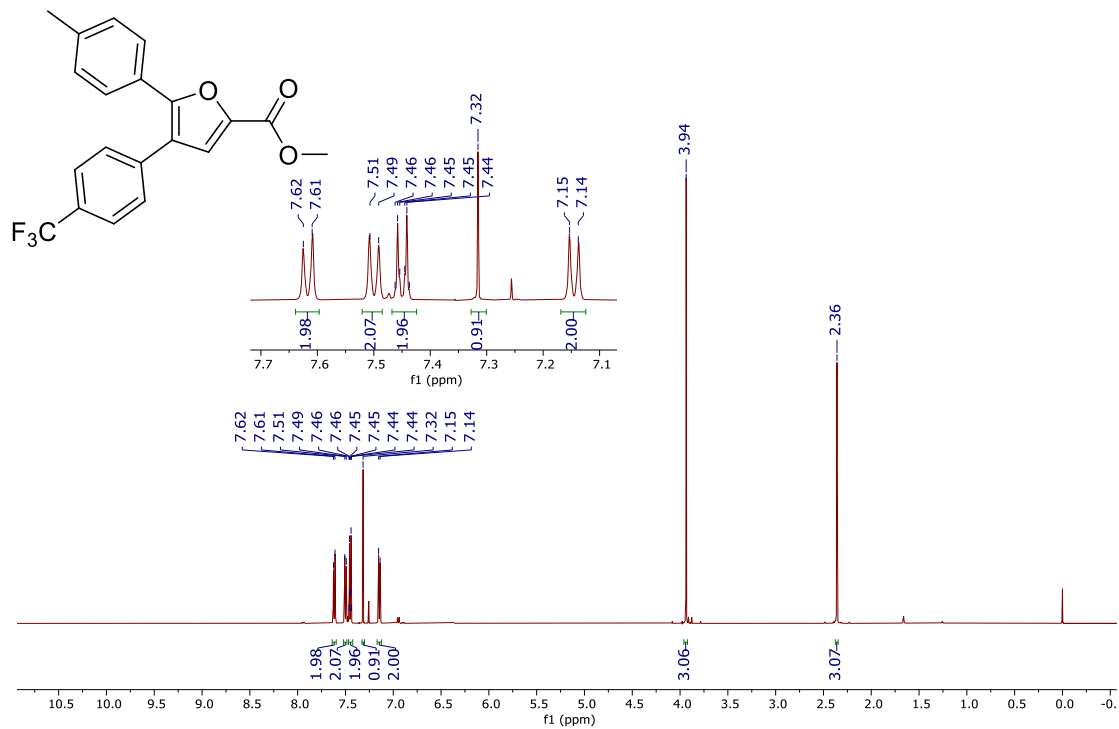
^1H NMR (500 MHz, CDCl_3)



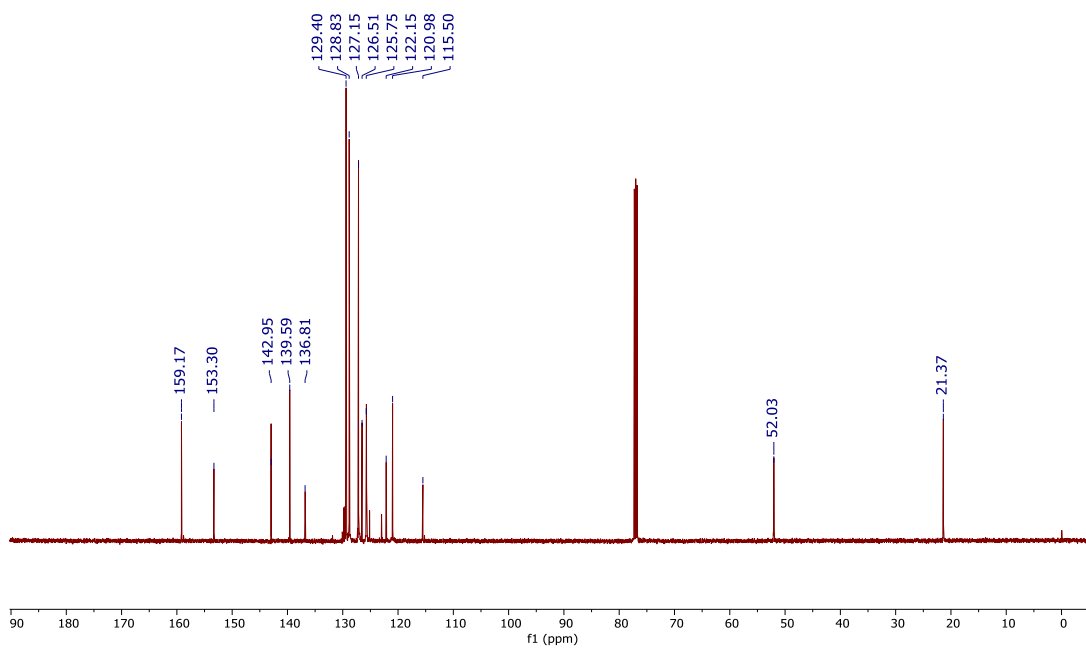
^{13}C NMR (125 MHz, CDCl_3)



Methyl 5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)furan-2-carboxylate, 8o
¹H NMR (500 MHz, CDCl₃)

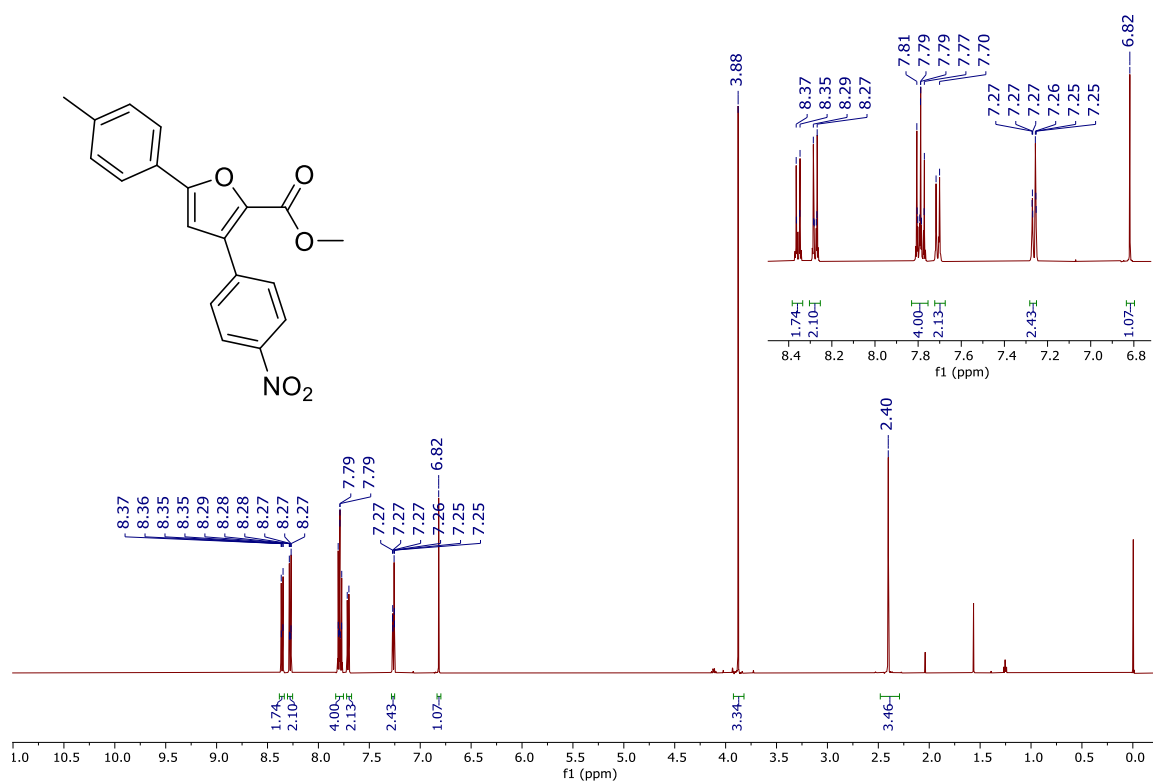


¹³C NMR (125 MHz, CDCl₃)

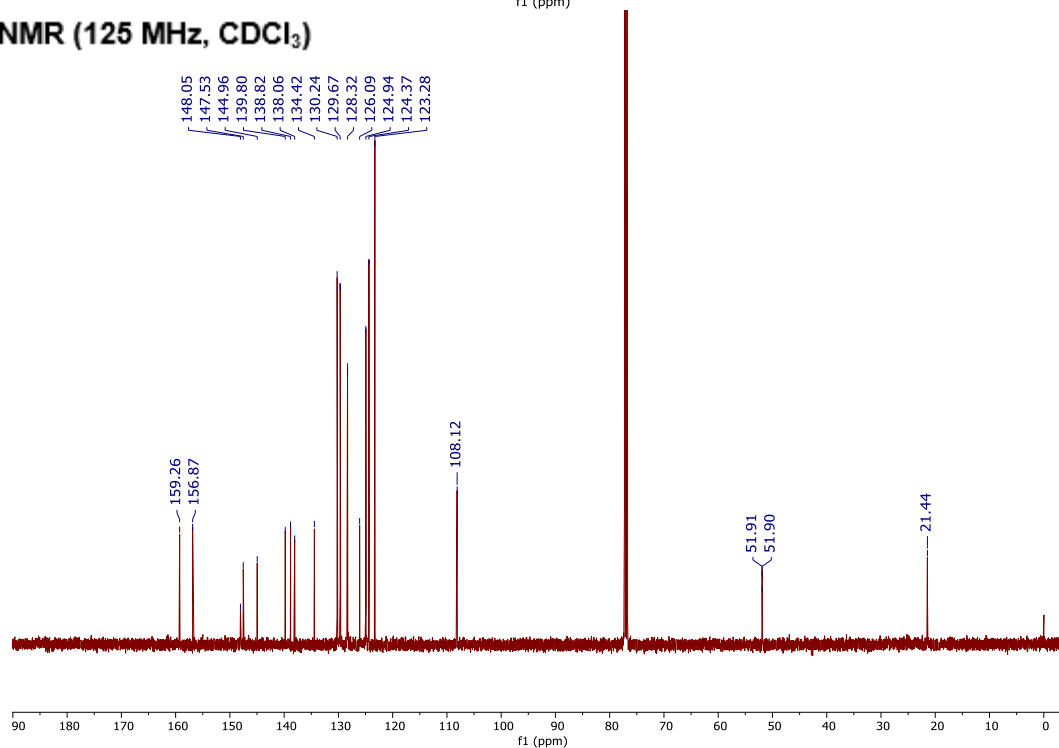


Methyl 3-(4-nitrophenyl)-5-(p-tolyl)furan-2-carboxylate, 11c

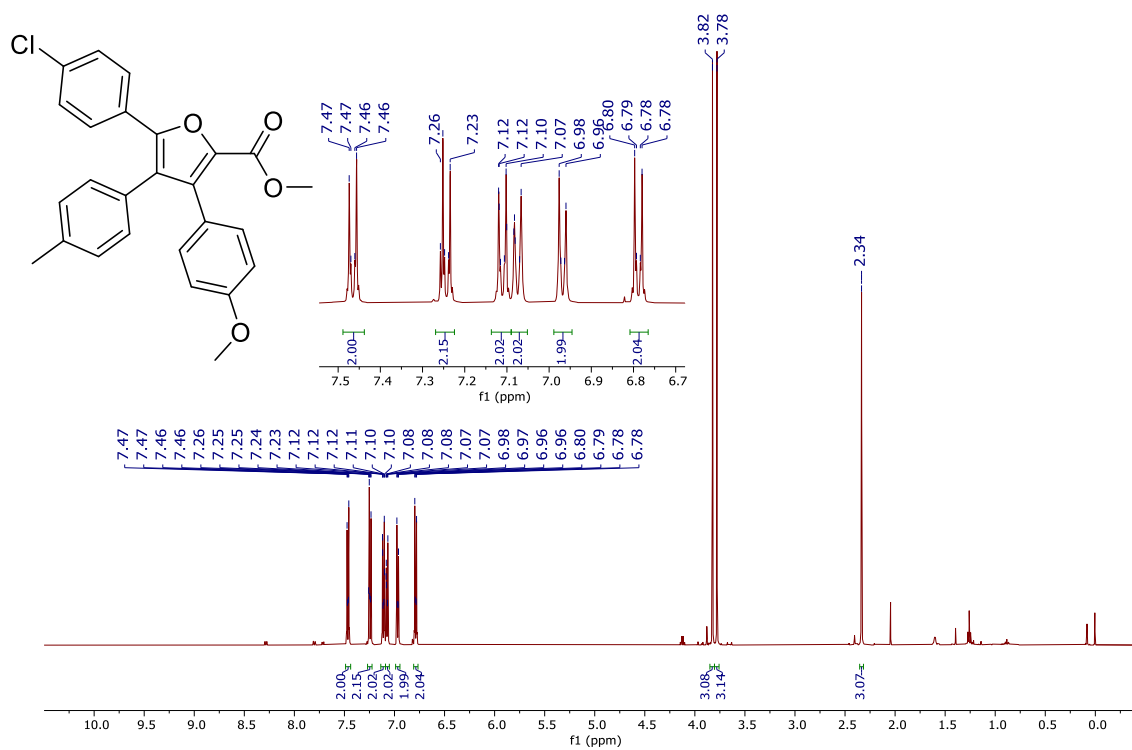
¹H NMR (500 MHz, CDCl₃)



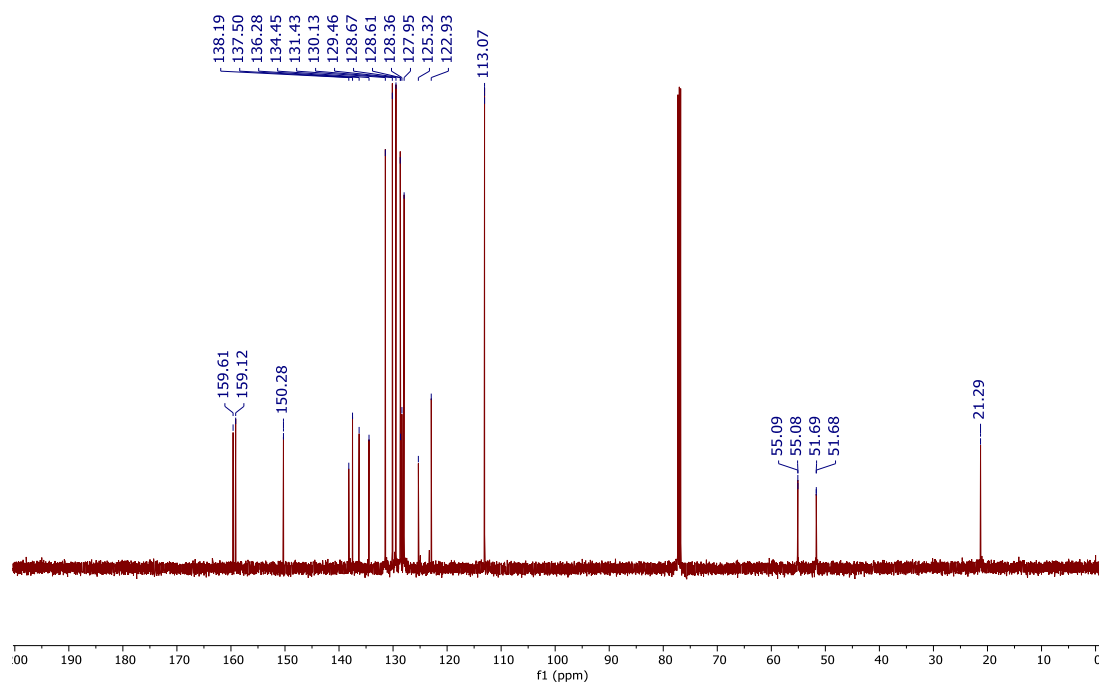
¹³C NMR (125 MHz, CDCl₃)



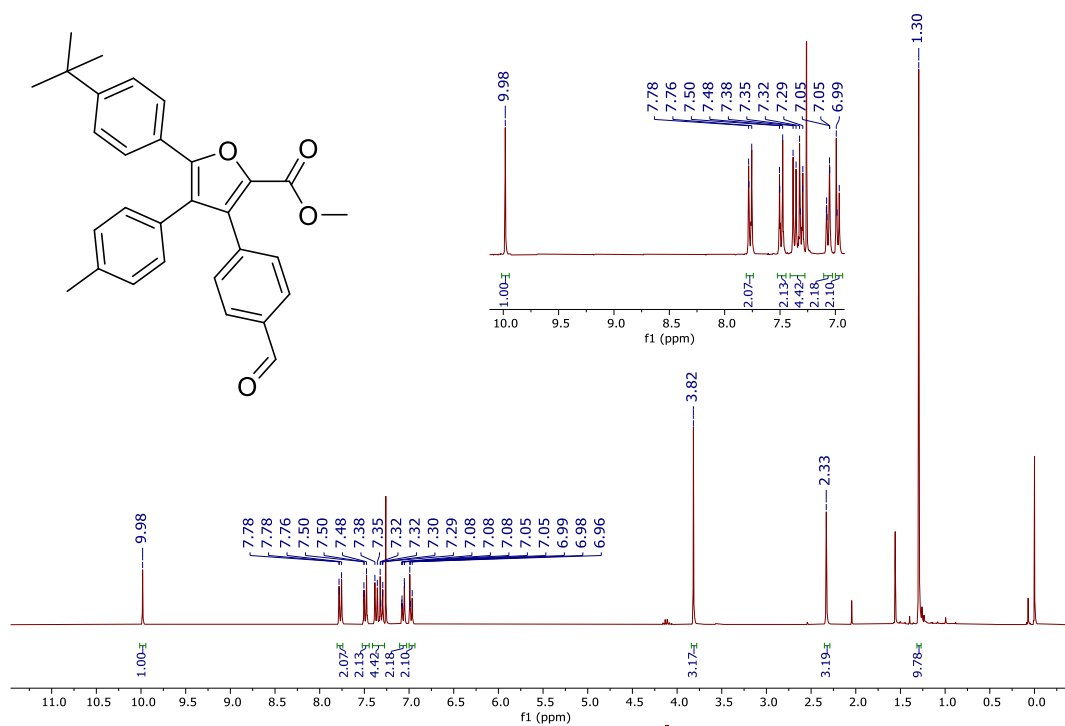
Methyl 5-(4-chlorophenyl)-3-(4-methoxyphenyl)-4-(p-tolyl)furan-2-carboxylate, 9j
¹H NMR (500 MHz, CDCl₃)



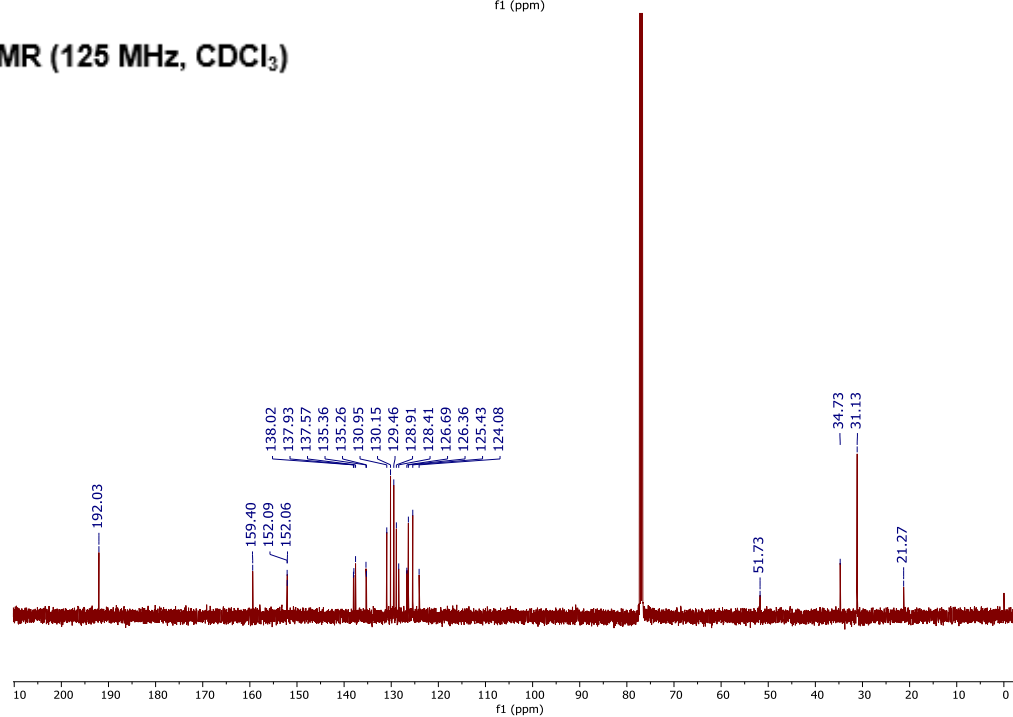
¹³C NMR (125 MHz, CDCl₃)



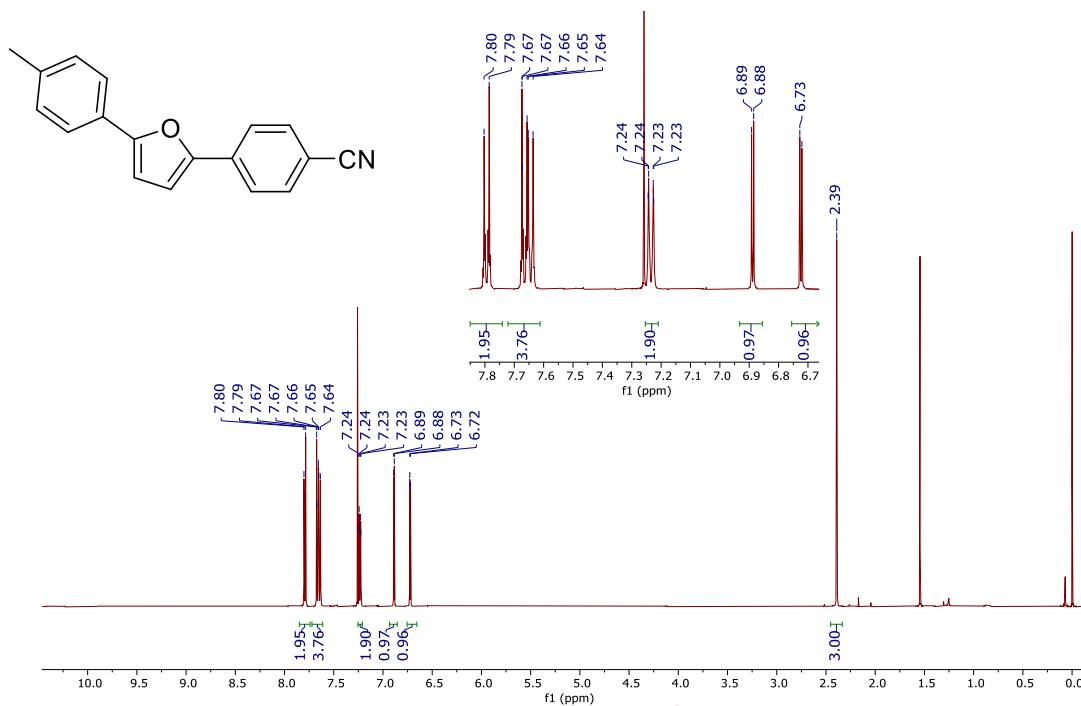
Methyl 5-(4-(tert-butyl)phenyl)-3-(4-formylphenyl)-4-phenylfuran-2-carboxylate, 9k
¹H NMR (500 MHz, CDCl₃)



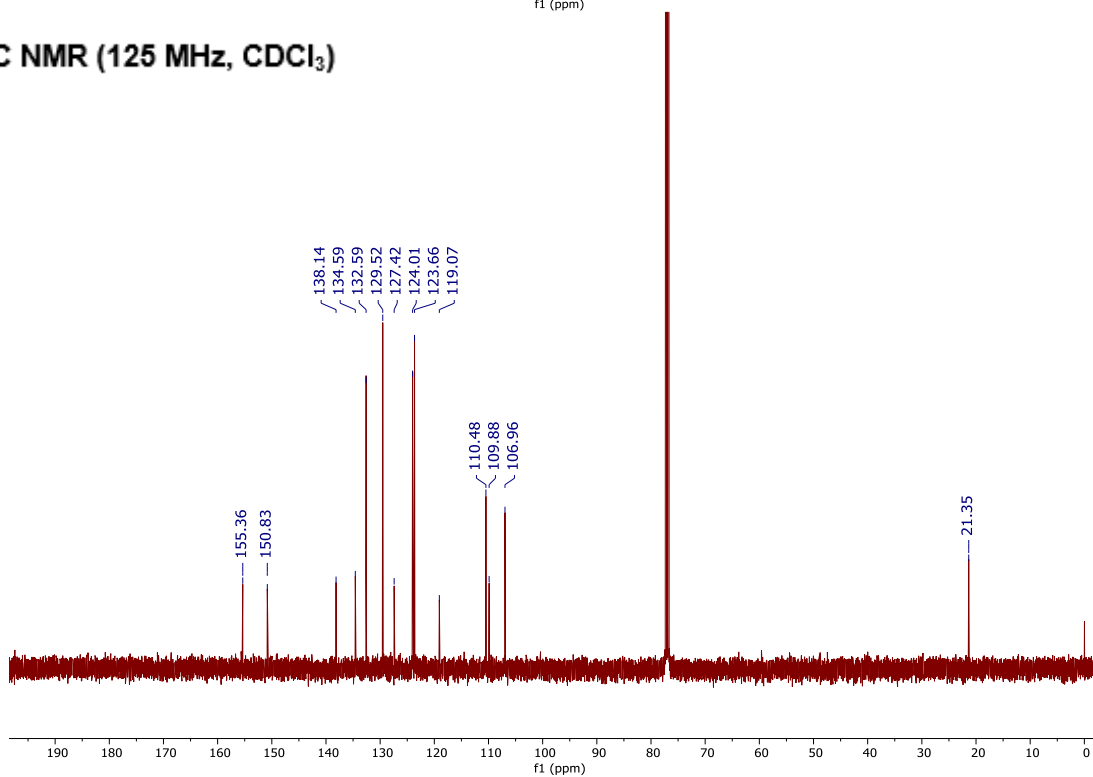
¹³C NMR (125 MHz, CDCl₃)



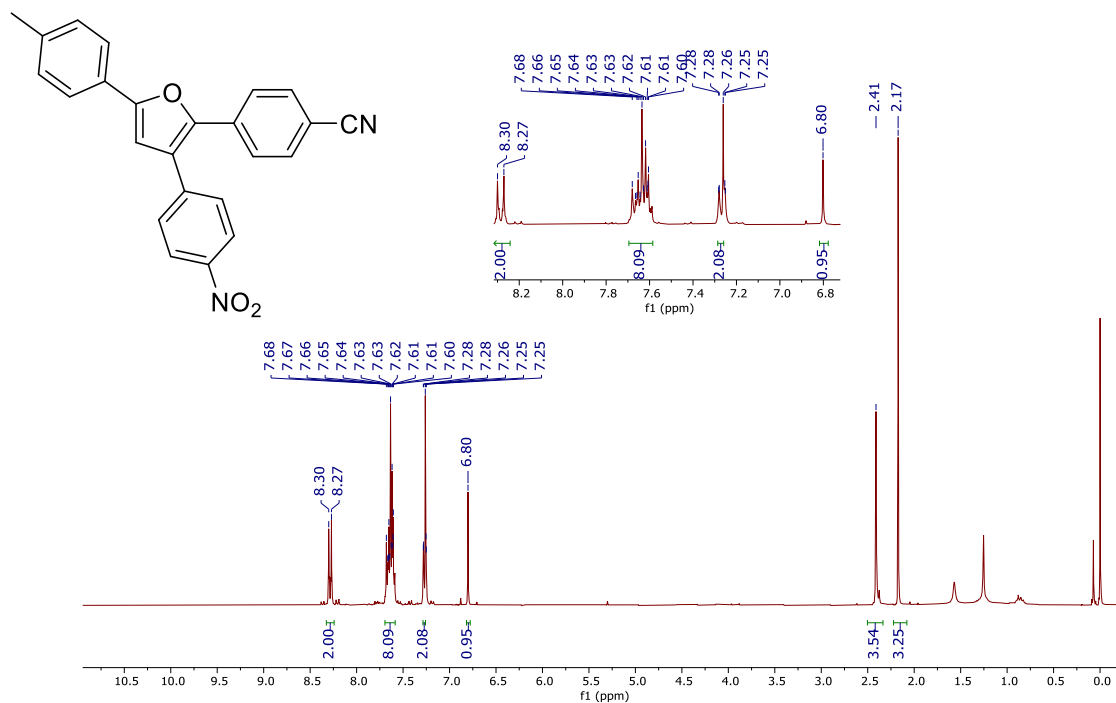
4-(5-(p-tolyl)furan-2-yl)benzonitrile, D1C
¹H NMR (500 MHz, CDCl₃)



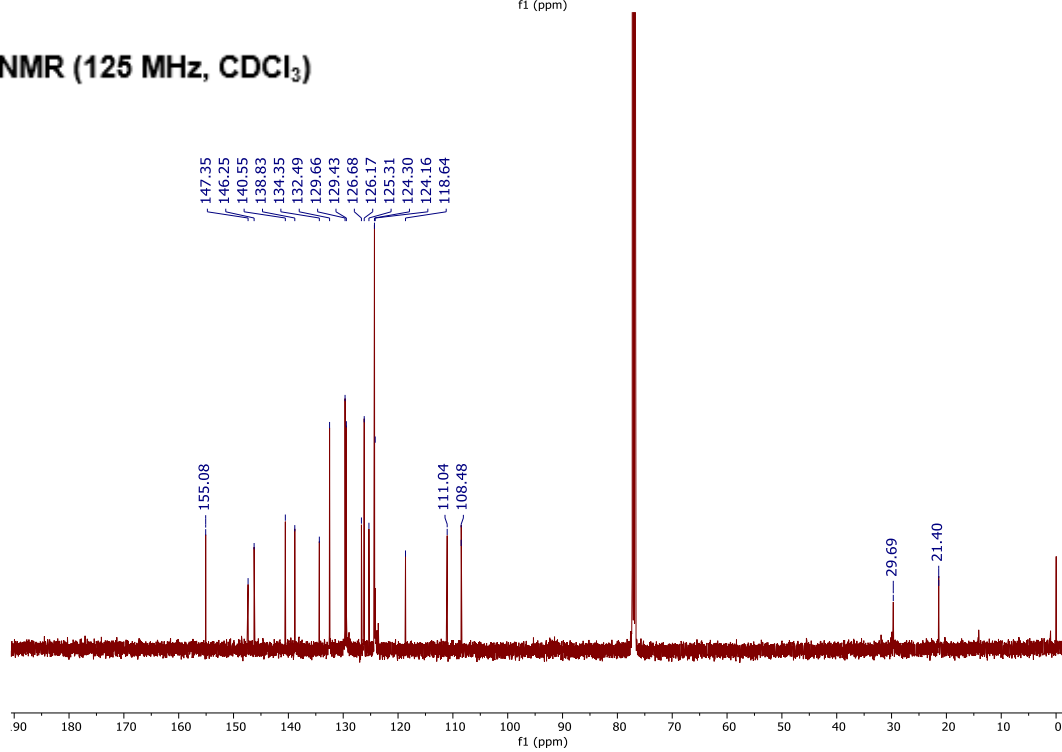
¹³C NMR (125 MHz, CDCl₃)



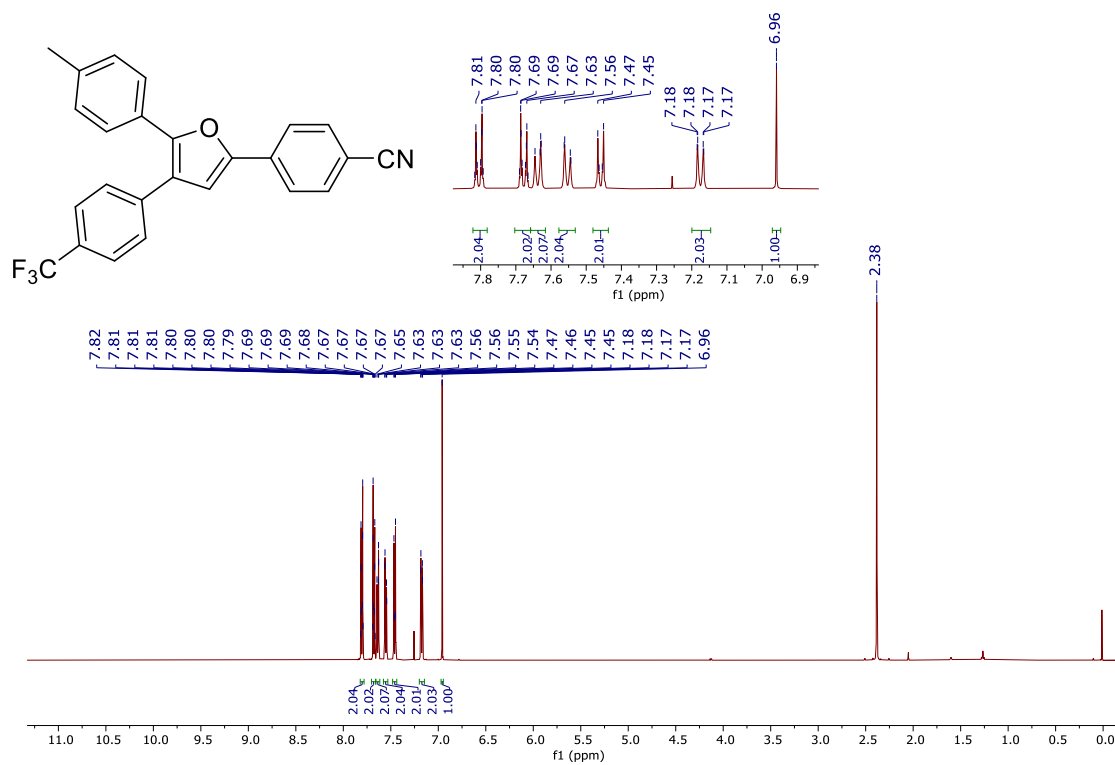
4-(3-(4-nitrophenyl)-5-(p-tolyl)furan-2-yl)benzonitrile, T1C
¹H NMR (500 MHz, CDCl₃)



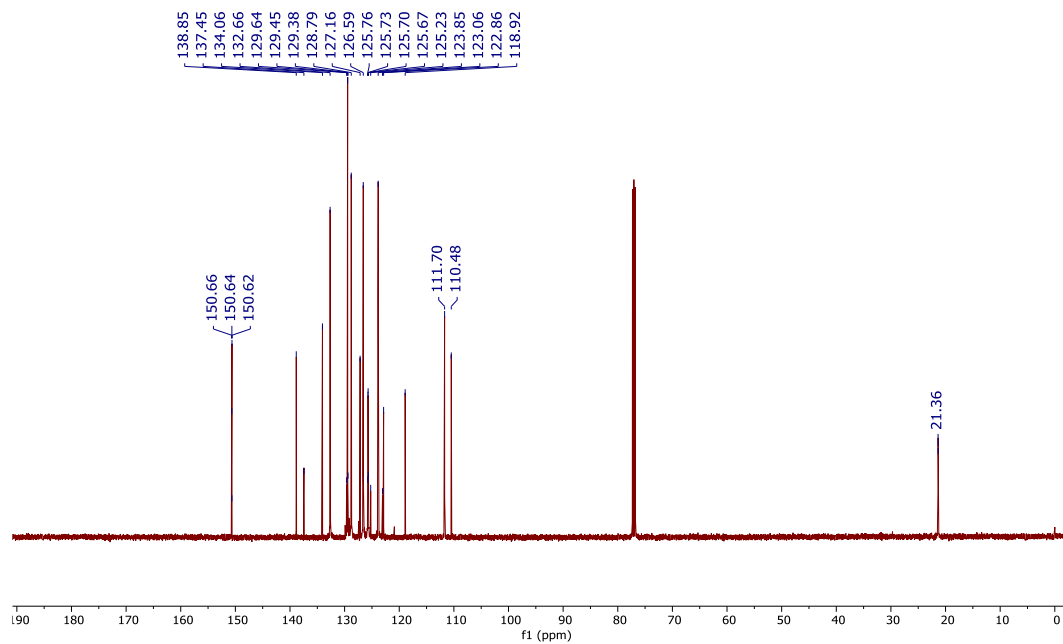
¹³C NMR (125 MHz, CDCl₃)



4-(5-(p-tolyl)-4-(4-(trifluoromethyl)phenyl)furan-2-yl)benzonitrile, T2C
¹H NMR (500 MHz, CDCl₃)

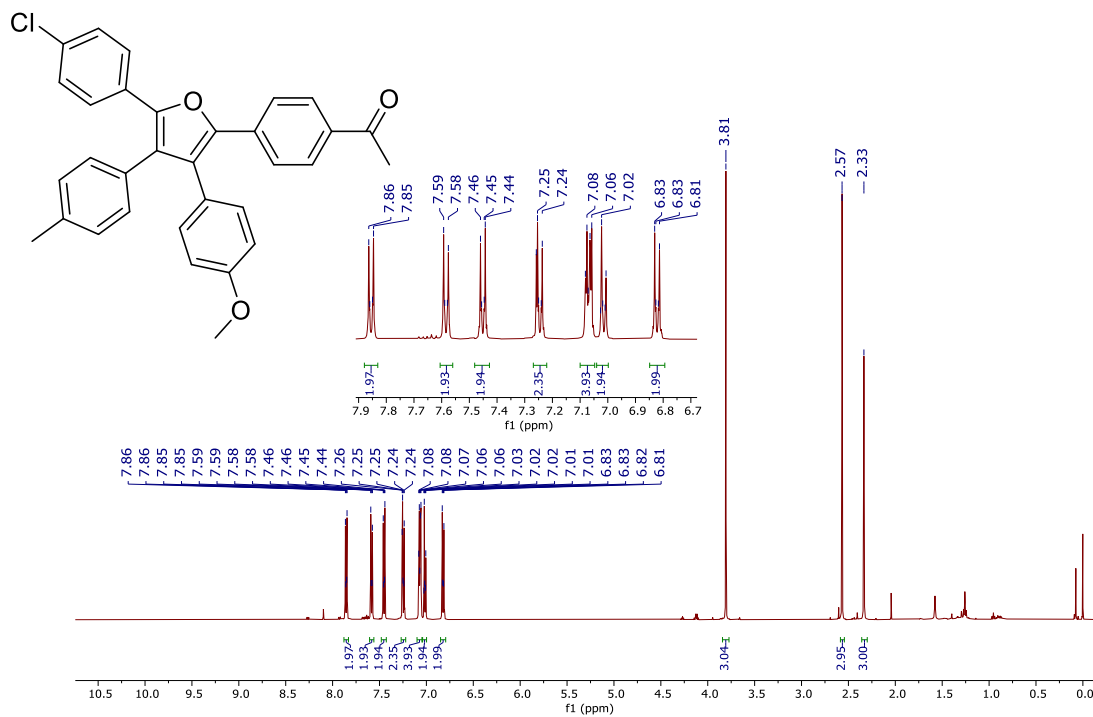


¹³C NMR (125 MHz, CDCl₃)

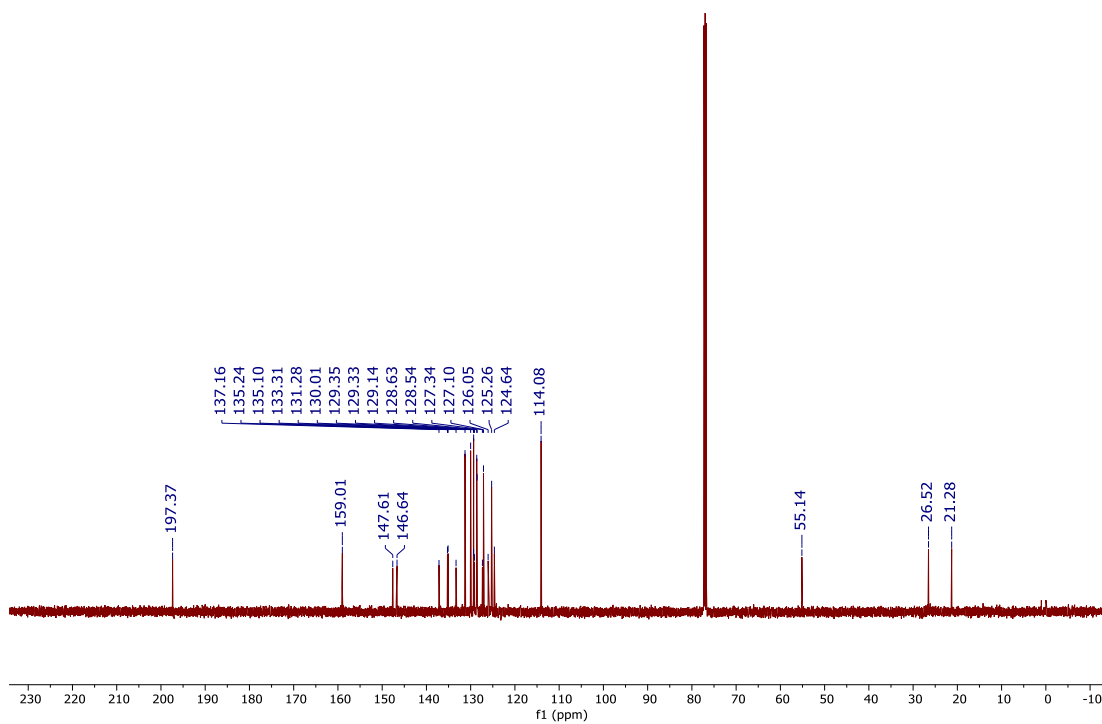


1-(4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-4-(p-tolyl)furan-2-yl)phenyl)ethan-1-one, 10h

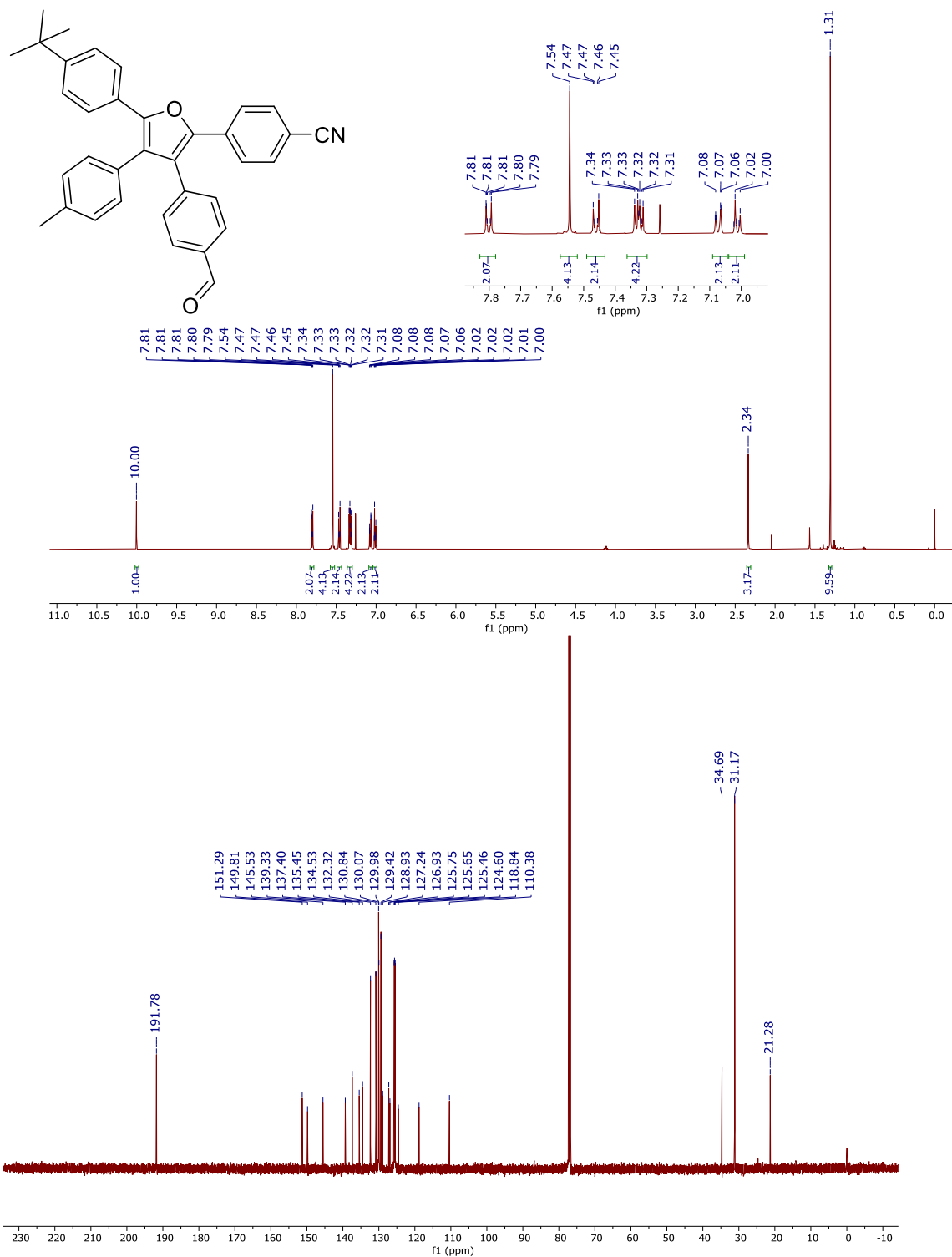
¹H NMR (500 MHz, CDCl₃)



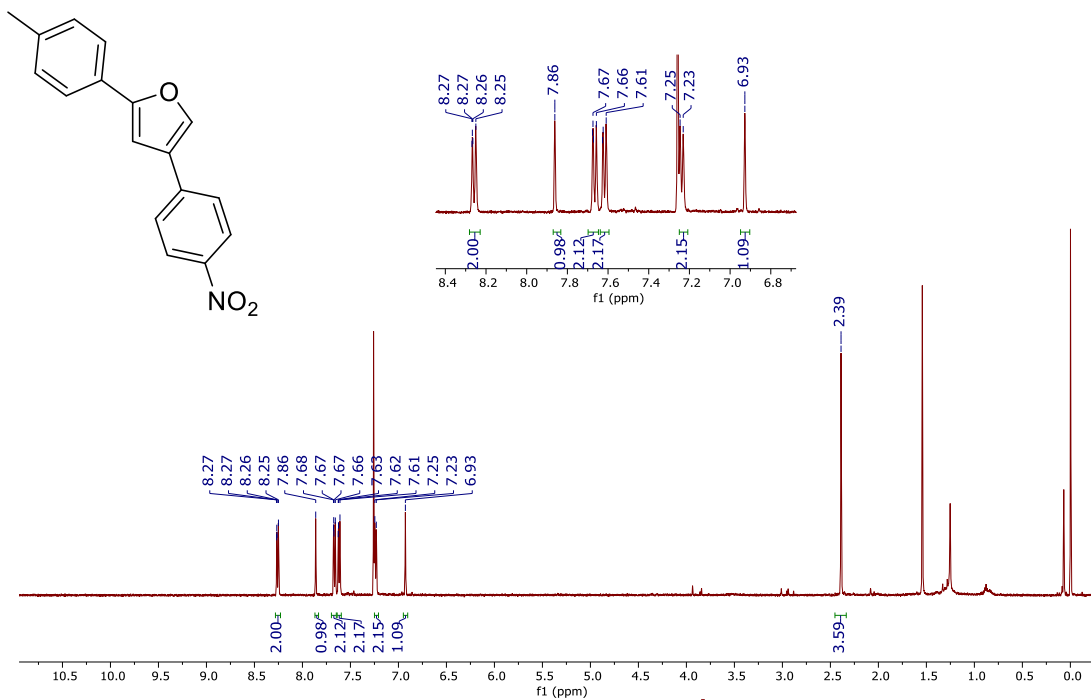
¹³C NMR (125 MHz, CDCl₃)



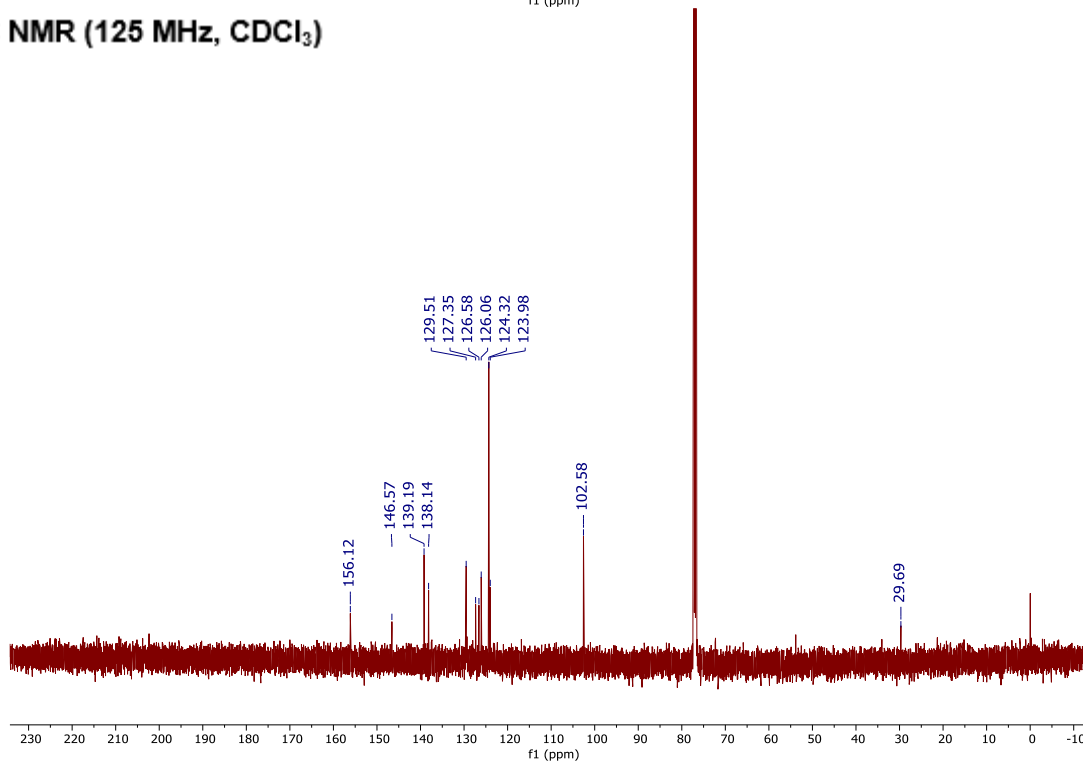
4-(5-(4-(tert-butyl)phenyl)-3-(4-formylphenyl)-4-(p-tolyl)furan-2-yl)benzonitrile, 10i
¹H NMR (500 MHz, CDCl₃)



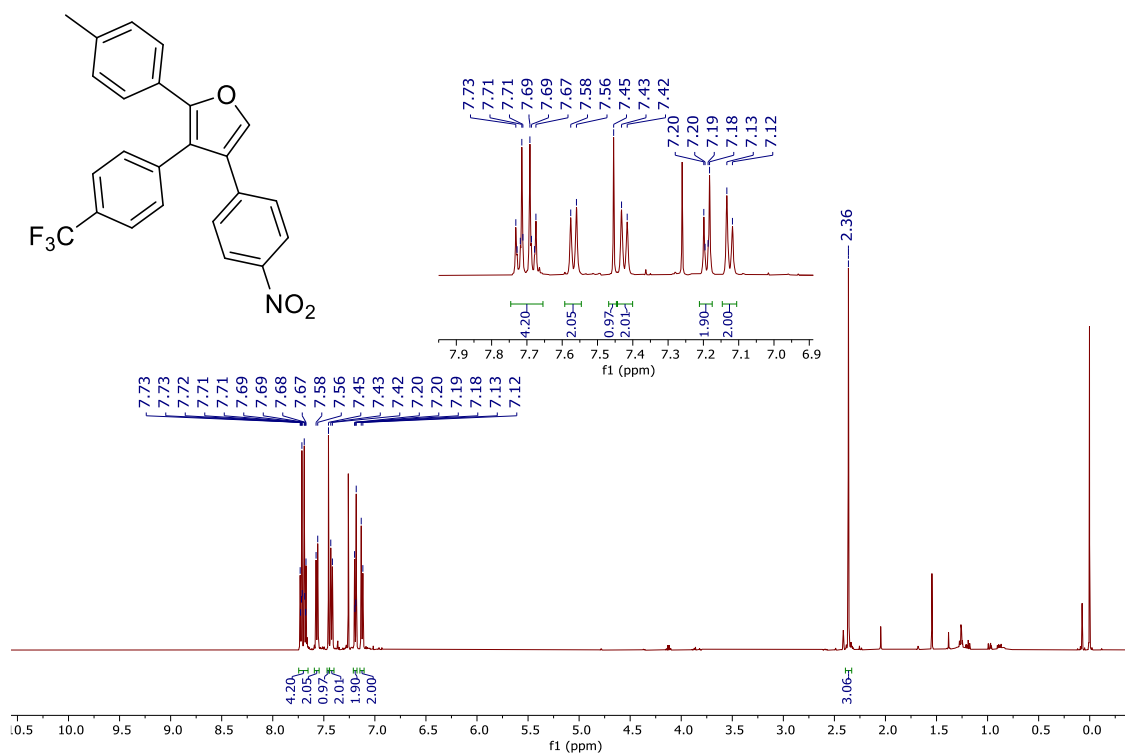
4-(4-nitrophenyl)-2-(p-tolyl)furan D2C
¹H NMR (500 MHz, CDCl₃)



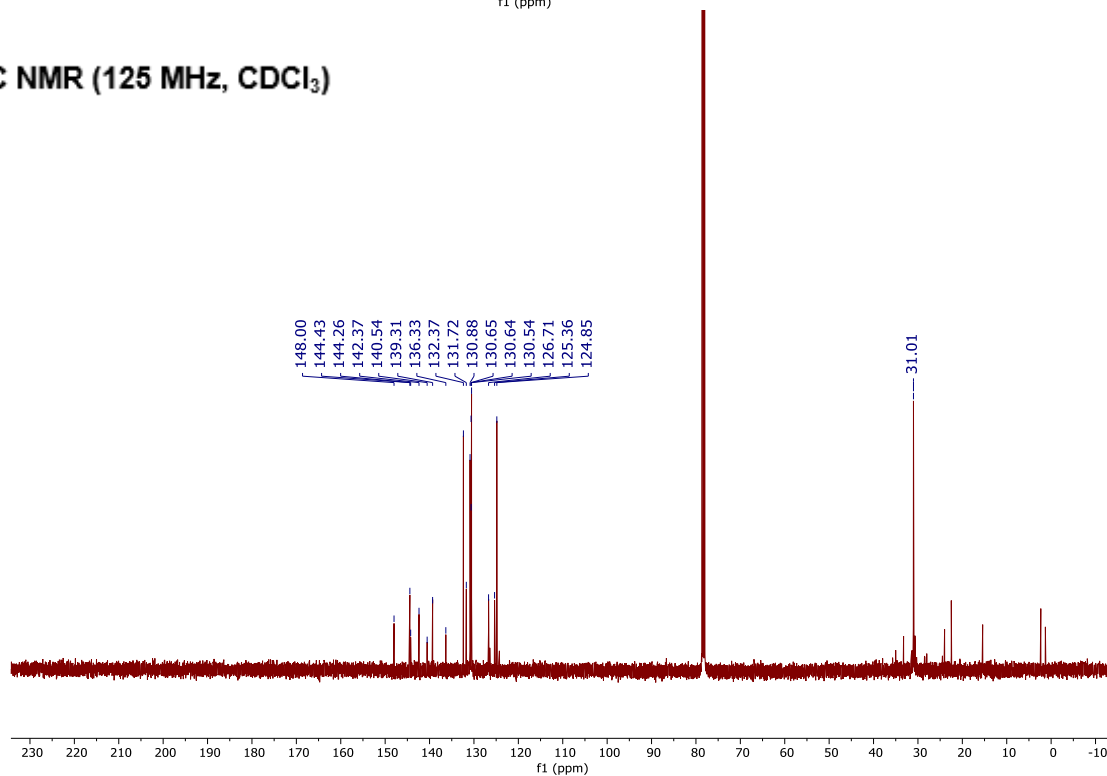
¹³C NMR (125 MHz, CDCl₃)



4-(4-nitrophenyl)-2-(p-tolyl)-3-(4-(trifluoromethyl)phenyl)furan, T3C
¹H NMR (500 MHz, CDCl₃)



¹³C NMR (125 MHz, CDCl₃)



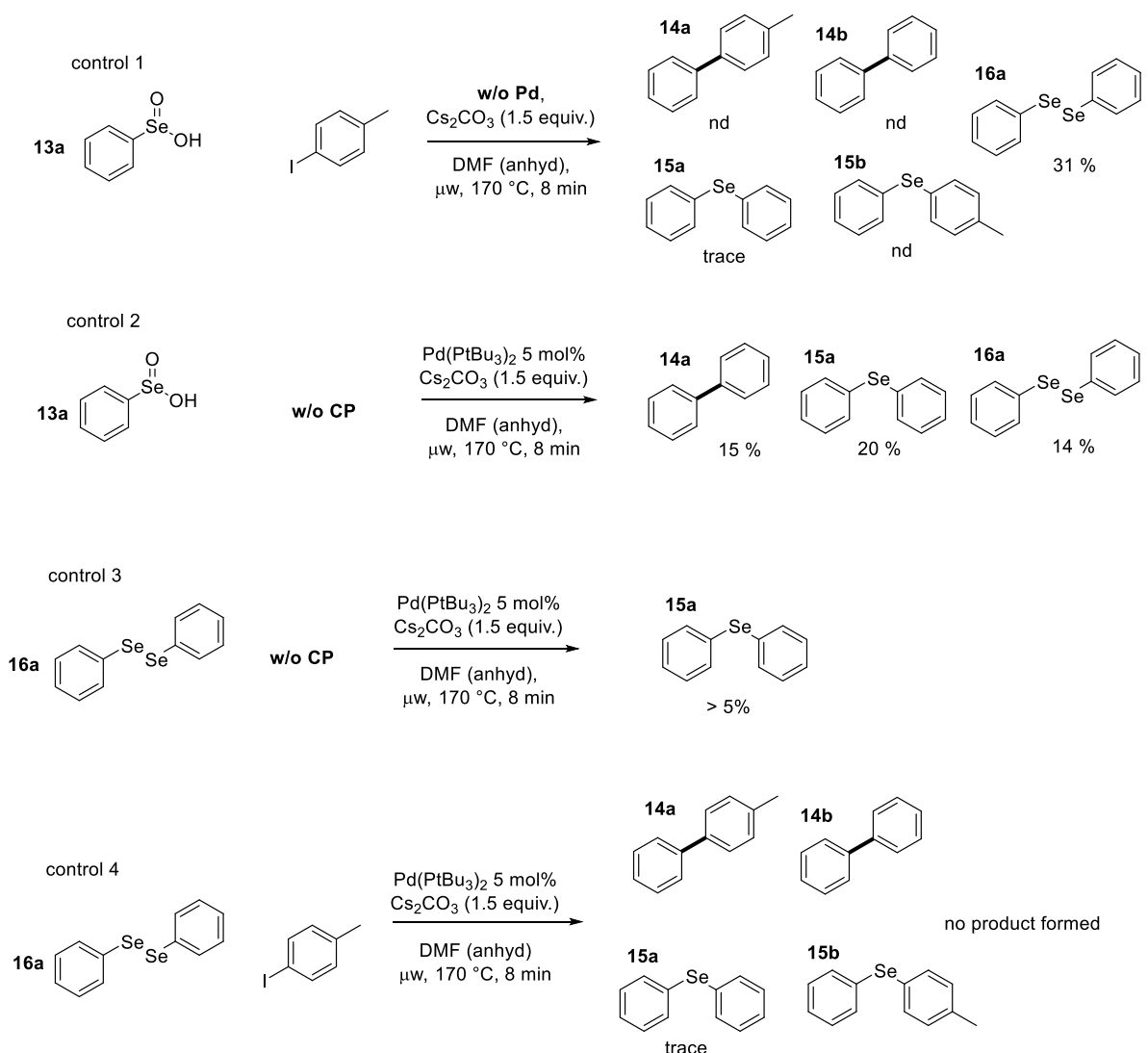
Supporting information for Chapter 5

General Conditions

Reactions were carried out in regular glassware under air unless otherwise noted. Commercially available starting materials and reagents were purchased from Sigma-Aldrich and AK Scientific, and used without further purification. Palladium catalysts were purchased from STREM and stored under inert gas at room temperature (PdCl_2) or in the freezer at -10 degrees Celsius ($\text{Pd}(\text{P}t\text{Bu}_3)_2$). All solvents were purchased from Fisher ACP chemicals and Sigma-Aldrich as ACS grade. Dimethylformamide (DMF) was dried using activated 3 Å molecular sieves and stored in an oven-dried Schlenk flask under argon atmosphere. Distilled water was obtained from an in-house distillery. Compounds were purified using column chromatography on silica-gel (Zeoprep 60 Eco, 40 – 63 μm , Zeochem AG). Microwave-assisted reactions were carried out using the Biotage Initiator™ 2.3 build 6250 microwave system with a 400 W magnetron – this instrument monitors temperature during the reaction time period and adjusts wattage accordingly. ^1H NMR data were measured on a Varian VNMR5-500. Yield determination using ^1H -NMR was done using trimethoxybenzene (TMB) as an internal standard.

Control experiments

A series of control experiments were conducted prior to optimization to ascertain how by-products were being formed. As shown in Scheme 55, control 1, subjecting the cross-coupling partners to reaction conditions without palladium does not result in the formation of any product. We can therefore surmise that all product and by-product formation is palladium-catalyzed. In the absence of palladium, the major product of is diphenyl diselenide, the reduced form of the benzene seleninic acid.



Scheme 55: Control reactions done before optimization of the deselenative cross-coupling

When benzene seleninic acid alone is reacted under standard conditions (control 2), there is approximately a 1:2 ratio of deselenative homo-coupling and homo-selenide. A subsequent control reaction with only di-phenyl di-selenide as the reactant produces no homo-coupling or homo-selenide formation (control 3) and a reaction with di-phenyl diselenide and iodotoluene results in no product formation or cross-selenide (control 4). This implies that benzene seleninic acid may be partially reduced *in situ* to the diselenide, and that the diselenide is not involved in the cross-coupling. However the diselenide may contribute to the formation of by-products 15a and 15b, as these appear to require a reduced selenium reagent.

Proposed catalytic cycle for the deselenative cross-coupling

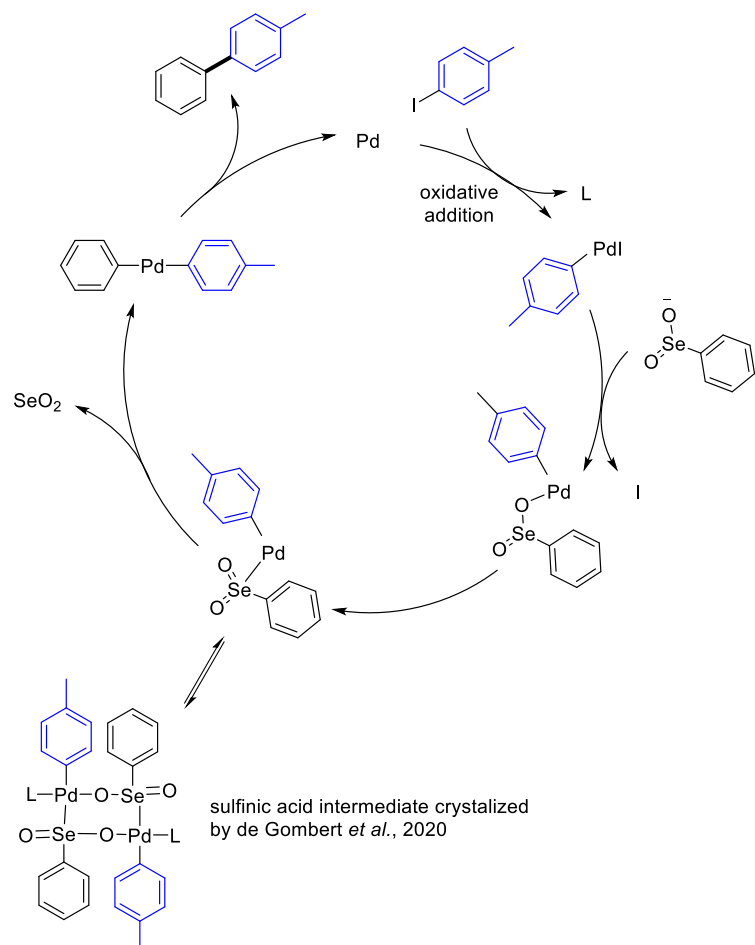
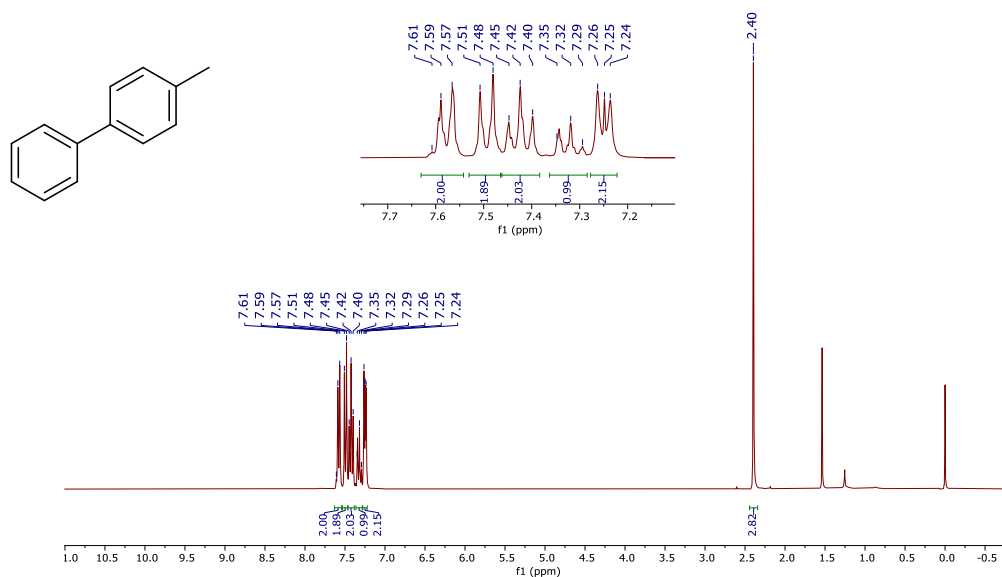


Figure 22: Proposed catalytic cycle for the deselenative cross-coupling reaction

Spectroscopic data

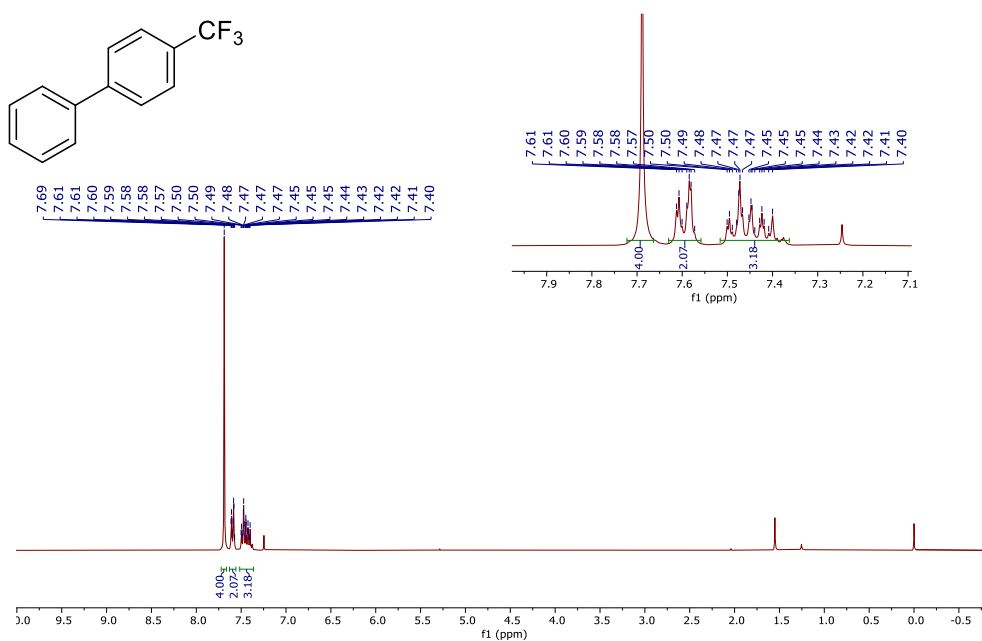
4-methyl-1,1'-biphenyl, 14a

¹H NMR (500 MHz, CDCl₃)

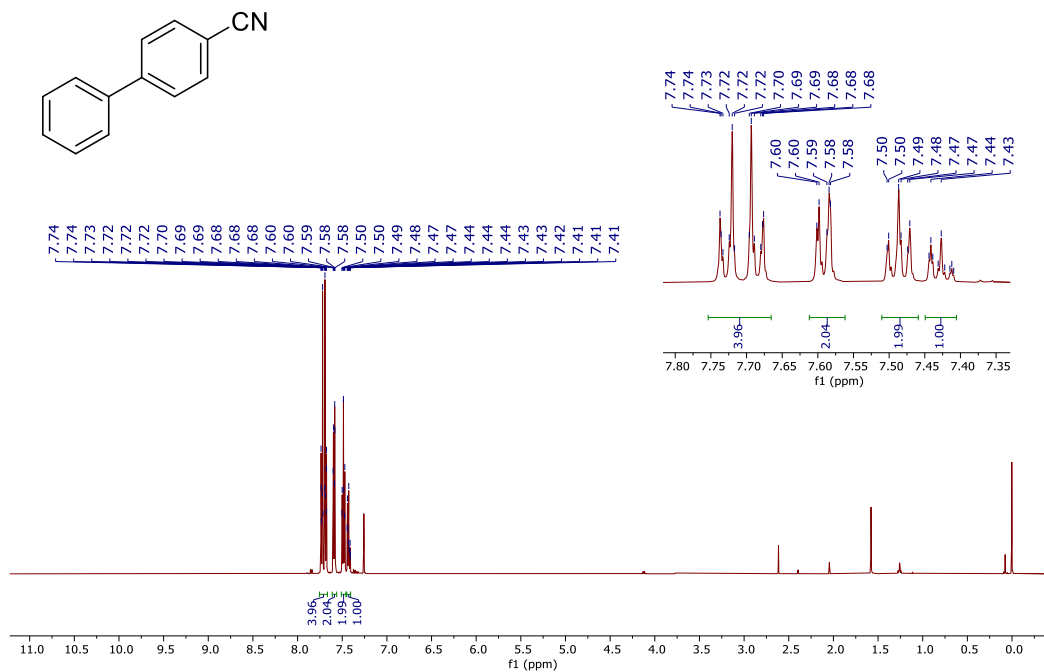


4-(trifluoromethyl)-1,1'-biphenyl, 14c

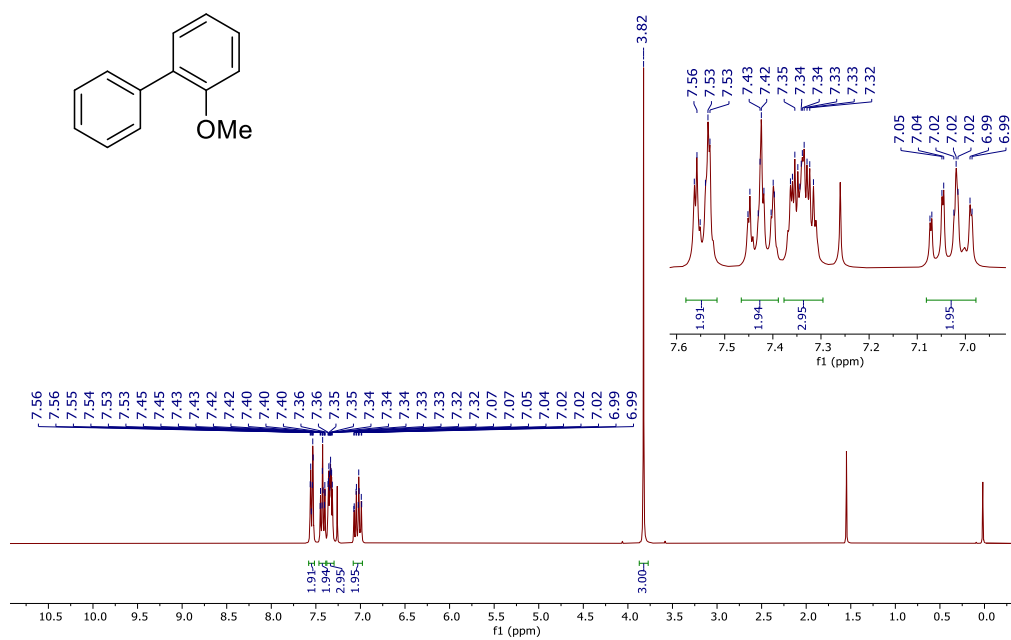
¹H NMR (500 MHz, CDCl₃)



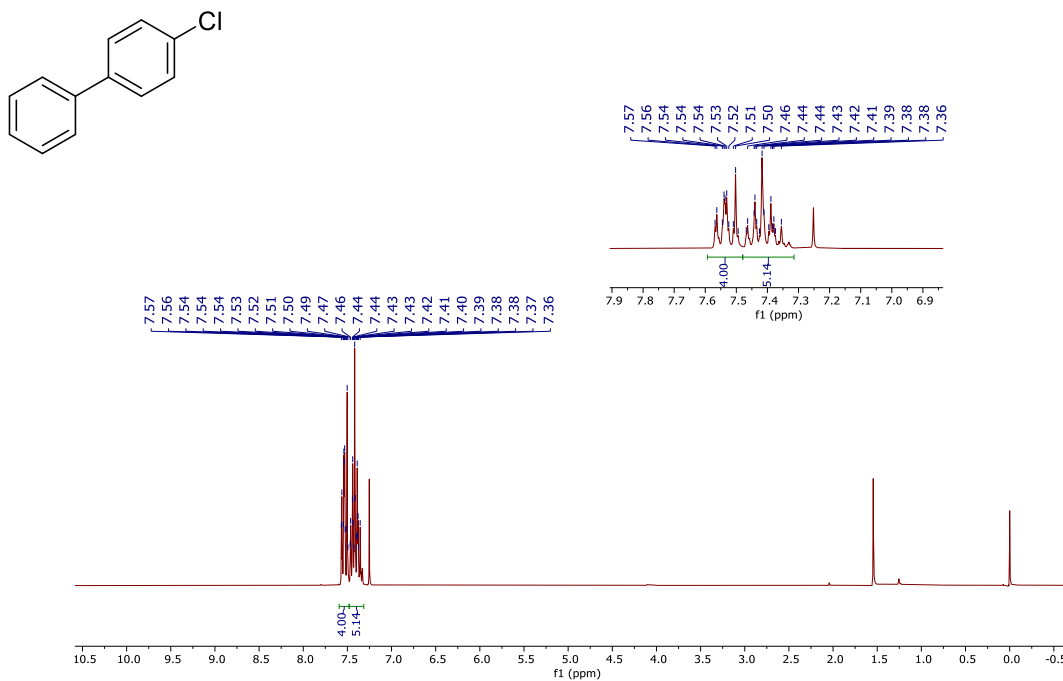
[1,1'-biphenyl]-4-carbonitrile, 14e
¹H NMR (500 MHz, CDCl₃)



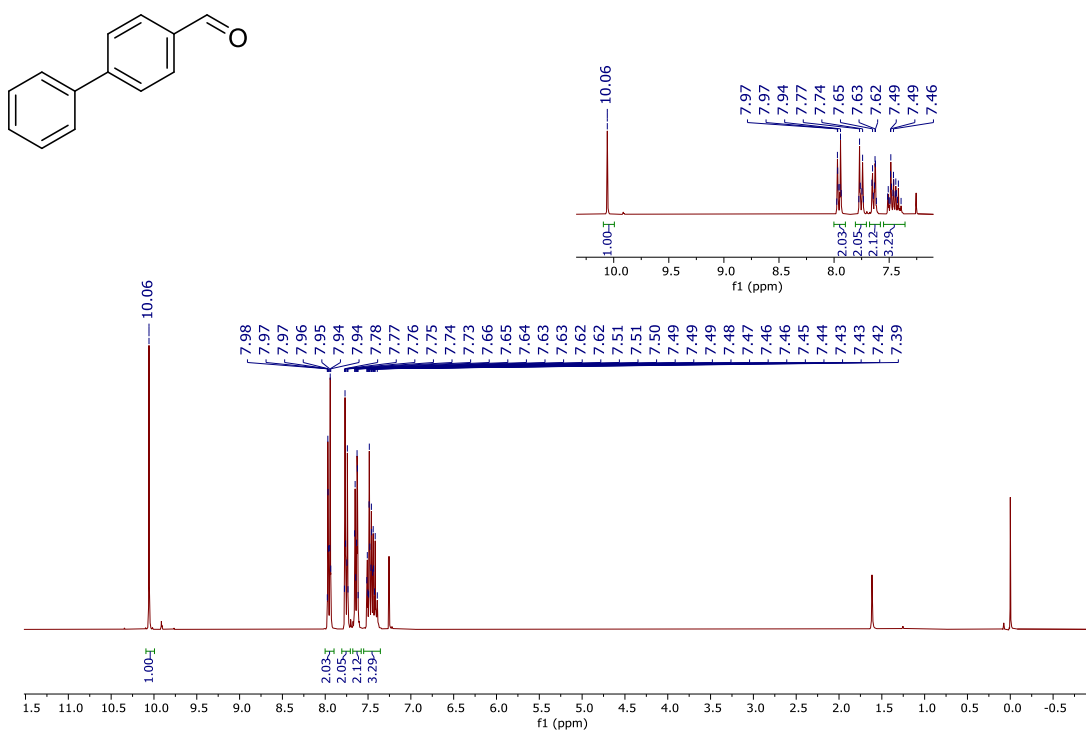
2-methoxy-1,1'-biphenyl, 14f
¹H NMR (500 MHz, CDCl₃)



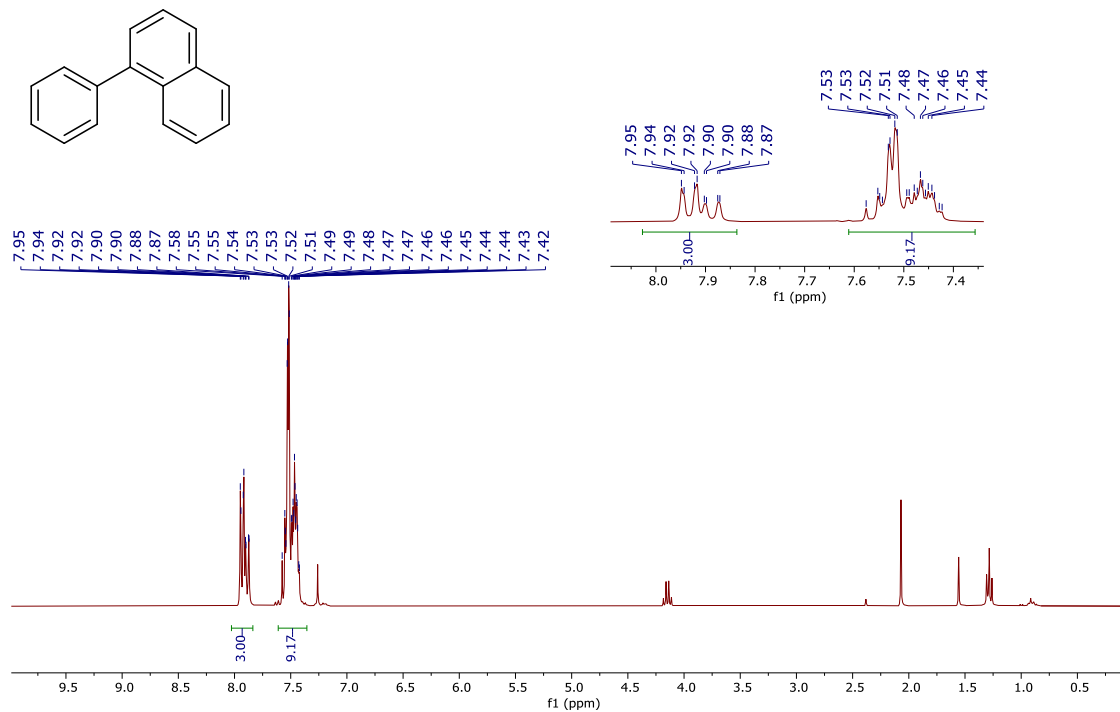
4-chloro-1,1'-biphenyl, 14h
¹H NMR (500 MHz, CDCl₃)



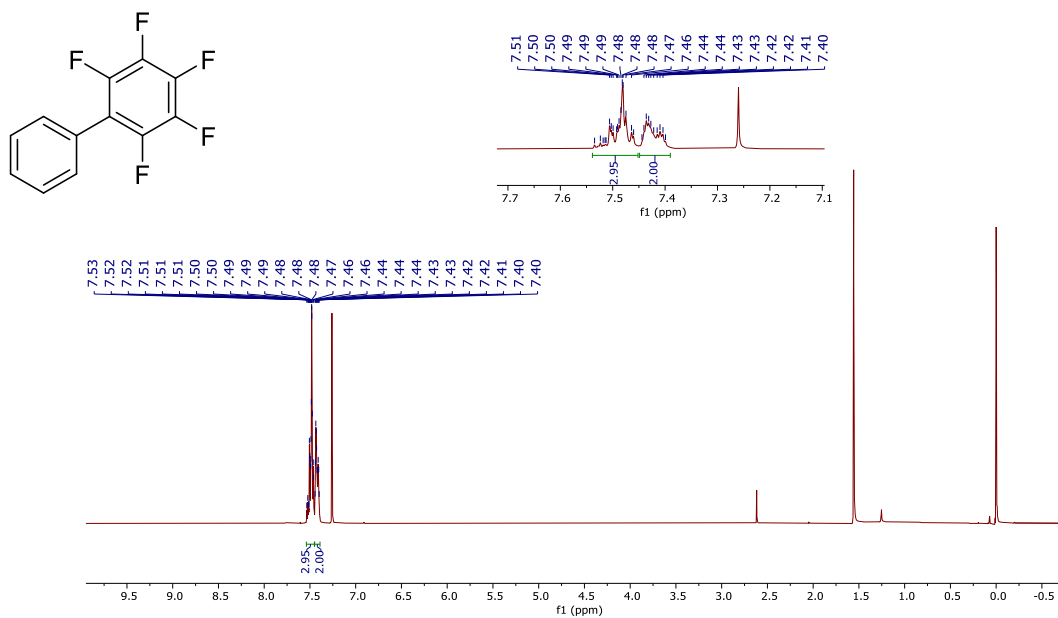
[1,1'-biphenyl]-4-carbaldehyde, 14i
¹H NMR (500 MHz, CDCl₃)



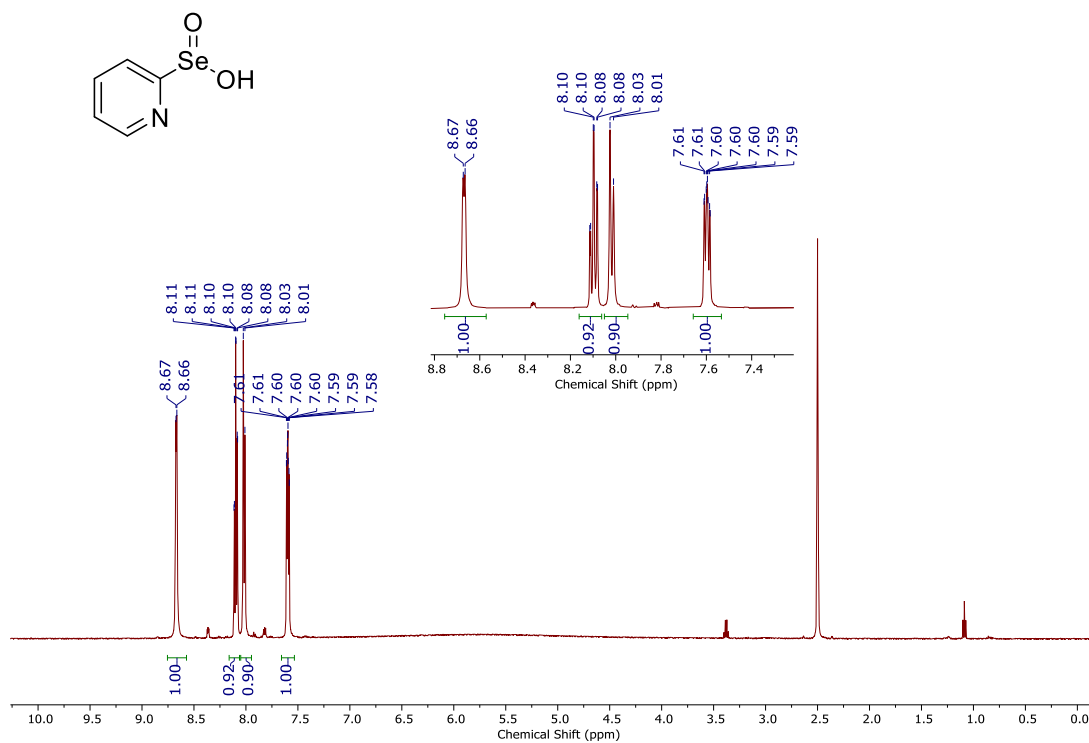
1-phenylnaphthalene, 14j
¹H NMR (500 MHz, CDCl₃)



2,3,4,5,6-pentafluoro-1,1'-biphenyl, 14l
¹H NMR (500 MHz, CDCl₃)



pyridine-2-seleninic acid, 13b
¹H NMR (500 MHz, DMSO-d₆)



2-(4-chlorophenyl)pyridine, 14m
¹H NMR (500 MHz, CDCl₃)

