Nickel-Catalyzed Cross-Coupling Reactions to Access α-Aryl Nitriles

by

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Department of Chemistry
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Abstract

α-Aryl nitriles are medicinally and biologically relevant compounds that also provide a synthetic handle for further chemical diversification. This thesis focuses on the development of Ni-catalyzed cross-coupling to access α-aryl nitriles. The first methodology described is a Ni-catalyzed reductive decarboxylative cross-coupling of NHPI esters and aryl iodides. The reaction development and the scope of the reaction will be presented. The second methodology is a Ni-catalyzed decyanation and arylation of disubstituted malononitrile derivatives. In this Chapter, the key focus is on the development of a benzonitrile ligand for Ni catalysis. The reaction development, ligand design and optimization, and preliminary scope of the reaction will be discussed.

Acknowledgments

First and foremost, I would like to thank my supervisor, Professor Sophie Rousseaux who always believed in me and who always encouraged me to thrive for more. Sophie has been a tremendous mentor throughout my graduate studies, and I know she will continue to be my mentor and someone I look up to for the rest of my life. Her dedication towards her students and chemistry is unparalleled.

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I want to thank all the members of the Rousseaux group for supporting me throughout the years. They have become more than just labmates, they have become family and I know that I will always share a connection with them. When times were difficult and chemistry was even harder my lab family helped me every step of the way through late night fumehood conversations, coffee breaks, their infectious laughter, and so much more. I would like to especially thank Purvish, Mike, and Emily for their unending support and friendship.

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°C – degree Celsius

μL – microliter

Ac – acyl

Ar – aryl

BNAH –1-benzyl-1,4-dihydronicotinamide

bpy – 2,2'-bipyridine

COD – cyclooctadiene

di-tBubipy – 4,4′-di-tert-butyl-2,2′-dipyridyl

DMA – dimethylacetamide

DMAP – 4-(dimethylamino)pyridine

DMF – dimethylformamide

ee – enantiomeric excess

equiv – equivalent

Et – ethyl

EtOAc – ethyl acetate

FDA – food and drug administration

g – gram

hex – hexanes

h – hour

i-Pr – isopropyl

Me – methyl

mg – milligram

min – minute

mL – milliliter

MPMN – methyl phenyl malononitrile

mol – moles

NPhth – phthalimide

NBS – N-bromosuccinimide

NHPI – *N*-hydroxyphthalimide

NMR – nuclear magnetic resonance

Ph – phenyl

Ph. D. – doctor of philosophy

R – generic organic group

r.t. – room temperature

SET – single electron transfer

TDAE – tetrakis(dimethylamino)ethylene

temp. – temperature

THF – tetrahydrofuran

TLC – thin layer chromatography

TMEDA – tetramethylethylenediamine

TMS – trimethylsilyl

Chapter 1

1 An Introduction to α-Aryl Nitriles

1.1 The Importance of Nitriles

The nitrile pharmacophore is an important functional group found in agrochemicals and over 30 drugs prescribed for various diseases such as diabetes and breast cancer.[1] In the pharmaceutical industry nitriles have been shown to be useful functional groups in drugs because they can increase biocompatibility, are not readily metabolized, and can be used as hydrogen bond acceptors.[2–6] Nitriles have been show to act as ketone bioisostere engaging in polar interactions. The nitrile functional group also has the ability to optimize π– π interactions through the polarization of the aromatic ring. In addition to the advantages nitriles possess in final drug products, nitriles can also be used as synthetic handles to access amides, aldehydes, ketones, amidines, tetrazoles, and primary amines in drug development.[7] In fact, α-aryl nitriles have been used as a synthetic precursor to carboxylic acids after hydrolysis to access Ibuprofen commercially.[8]

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[1] Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902–7917.

[2] Murphy, S. T.; Case, H. L.; Ellsworth, E.; Hagen, S.; Huband, M.; Joannides, T.; Limberakis, C.; Marotti, K. R.; Ottolini, A. M.; Rauckhorst, M.; Starr, J.; Stier, M.; Taylor, C.; Zhu, T.; Blaser, A.; Denny, W. A.; Lu, G.-L.; Smaill, J. B.; Rivault, F. *Bioorg. Med. Chem. Lett.* **2007**, *17*), 2150–2155.

[3] Boyd, M. J.; Crane, S. N.; Robichaud, J.; Scheigetz, J.; Black, W. C.; Chauret, N.; Wang, Q.; Massé, F.; Oballa, R. M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 675–679.

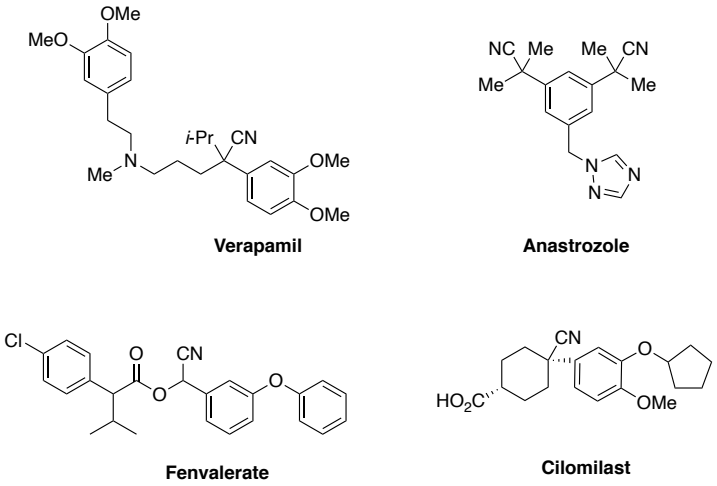
[4] Ziemniak, J. A.; Wynn, R. J.; Aranda, J. V.; Zarowitz, B. J.; Schentag, J. J. *Dev. Pharmacol. Ther.* **1984**, *7*, 30–38.

[5] Questel, J.-Y. L.; Berthelot, M.; Laurence, C. *J Phys Org Chem* **2000**, 13, 347–358

[6] Laurence, C.; Brameld, K. A.; Graton, J.; Le Questel, J.-Y.; Renault, E. *J. Med. Chem.* **2009**, *52*, 4073–4086.

[7] Larock, R. Interconversions of Nitriles in *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1990; Vol. 2, pp 1966-1994.

[8] Kukushkin, V. Yu.; Pombeiro, A. J. L. *Inorganica Chim. Acta* **2005**, *358*, 1–21.



Scheme 1-1 FDA-approved pharmaceuticals or agrochemicals that contain α-aryl nitriles.

Synthetic method development towards nitriles, specifically α-aryl nitriles has been a common research interest in academia.[9] They are an important class of nitriles in both the pharmaceutical industry and academic labs. Examples of FDA-approved pharmaceuticals that can be used in the treatment of several diseases and an agrochemical are shown in **Scheme 1-1**. Verapamil can be used to treat high blood pressure and angina, anastrozole is used in the treatment of breast cancer, cilomilast is used to treat respiratory diseases such as asthma and chronic obstructive pulmonary disease, and fenvalerate is an insecticide.[10–13]

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[9] Yan, G.; Zhang, Y.; Wang, J. *Adv. Synth. Catal.* **2017**, *359*, 4068–4105.

[10] McTavish, D.; Sorkin, E. M. *Drugs* **1989**, *38*, 19–76.

[11] Wiseman, L. R.; Adkins, J. C. *Drugs Aging* **1998**, *13*, 321–332.

[12] amble, E.; Grootendorst, D. C.; Brightling, C. E.; Troy, S.; Qiu, Y.; Zhu, J.; Parker, D.; Matin, D.; Majumdar, S.; Vignola, A. M.; Kroegel, C.; Morell, F.; Hansel, T. T.; Rennard, S. I.; Compton, C.; Amit, O.; Tat, T.; Edelson, J.; Pavord, I. D.; Rabe, K. F.; Barnes, N. C.; Jeffery, P. K. *Am. J. Respir. Crit. Care Med.* **2003**, *168*, 976–982.

[13] Maloney, S. E.; Maule, A.; Smith, A. R. *Appl. Environ. Microbiol.* **1988**, *54*, 2874–2876.

1.2 General Strategies to Access α-Aryl Nitriles

Traditional methods to synthesize α-aryl nitriles have been light mediated aromatic substitution and dehydration of amides (**Scheme 1-2a** and **b**).[14,15] However, light mediated aromatic substitution reactions have low functional group tolerance and substituted α-aryl amides can be difficult to synthesize for amide dehydration. Another simple method that has been used to access secondary α-aryl nitriles is the deprotonation of benzylic nitriles with the subsequent addition of alkyl iodides or other alkylating agents (**Scheme 1-2c**). However, due to its need for a strong base, this method can pose problems in terms of functional group compatibility and the propensity to over-alkylate the benzylic position.[16] An additional method to access α-aryl nitriles is the substitution of benzylic electrophiles using a toxic cyanide salts that can produce hazardous and potentially lethal hydrogen cyanide gas (**Scheme 1-2d**).[17] These problems have led to synthetic developments towards α-aryl nitriles through cross-coupling and other pathways.

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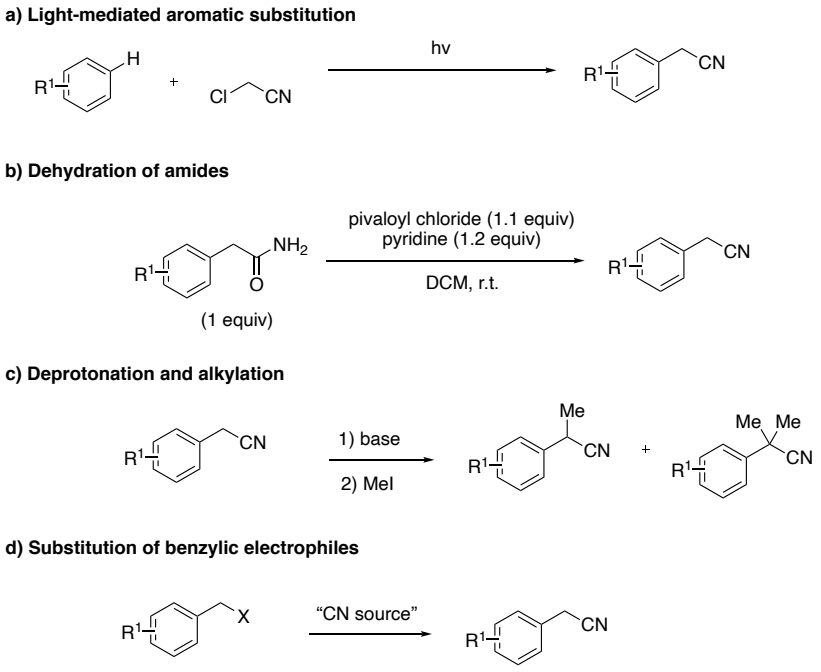
[14] Kurz, M. E.; Lapin, S. C.; Mariam, K.; Hagen, T. J.; Qian, X. Q. *J. Org. Chem.* **1984**, *49*, 2728–2733.

[15] Narsaiah, A. V.; Nagaiah, K. *Adv. Synth. Catal.* **2004**, *346*, 1271–1274.

[16] Kharasch, M. S.; Sosnovsky, G. *Tetrahedron* **1958**, *3*, 97–104..

[17] Fatiadi, A. J. Preparation and Synthetic Applications of Cyano Compounds. In *Triple-Bonded Functional Groups: Vol. 2 (1983)*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons, Ltd.: Chichester, UK, 1983; pp 1057–1303.



Scheme 1-2 Traditional methods to access α-aryl nitriles.

There were three main problems encountered in the early development of cross-coupling methods towards α-aryl nitriles. Firstly, in general a strong base is required for deprotonation of the α-proton of aryl nitriles limiting functional group compatibility. Secondly, due to the Lewis basic nature of nitriles, nitriles can form insoluble oligomers with the addition of main group reagents. Finally, due to the inductive effect of nitriles, reductive elimination can be slow in comparison to its ketone counterpart resulting in competing side product pathways.[18–23] Despite these problems, method development towards α-aryl nitriles continues to grow as explored in Sections 1.3 and 1.4.

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[18] Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541–555.

[19] Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4641–4642.

[20] Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330–9331.

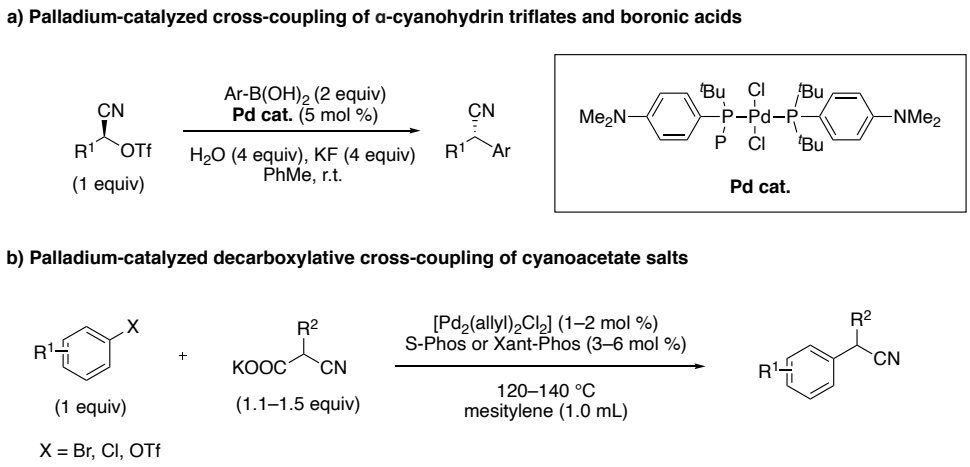
[21] You, J.; Verkade, J. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 5051–5053.

[22] You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003–8007.

[23] Tetsuya, S.; Jun-ichi, I.; Yoshiki, K.; Yuichiro, K.; Masahiro, M.; Masakatsu, N. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239–2246.

1.3 Synthesis of Secondary α-Aryl Nitriles

Starting from α-cyanohydrin triflates and aryl boronic acids, the Falck group was able to develop a stereospecific palladium-catalyzed cross-coupling to produce secondary α-aryl nitriles **(Scheme 1-3a)**.[24] This synthesis resulted in complete inversion of configuration of the final product with respect to the triflate starting material. To favour reductive elimination over the β-H elimination pathway to form the alkene byproduct, an electron-rich, bulky catalyst was used: $Pd(PtBu_3)_2$.



Scheme 1-3 Examples of palladium-catalyzed cross-couplings to access secondary α-aryl nitriles.

In addition, Liu reported the synthesis of secondary α-aryl nitriles through palladium-catalyzed decarboxylative coupling of substituted cyanoacetate salts with aryl chlorides, bromides, and triflates (**Scheme 1-3b).**[25] By decreasing the reaction temperature from 140 °C to 120 °C, aryl triflates could be used in the chemistry, which was inaccessible in previous reports of palladium-catalyzed α-arylation of α-silyl nitriles that will be seen later on in this chapter.[18–22,26,27] This

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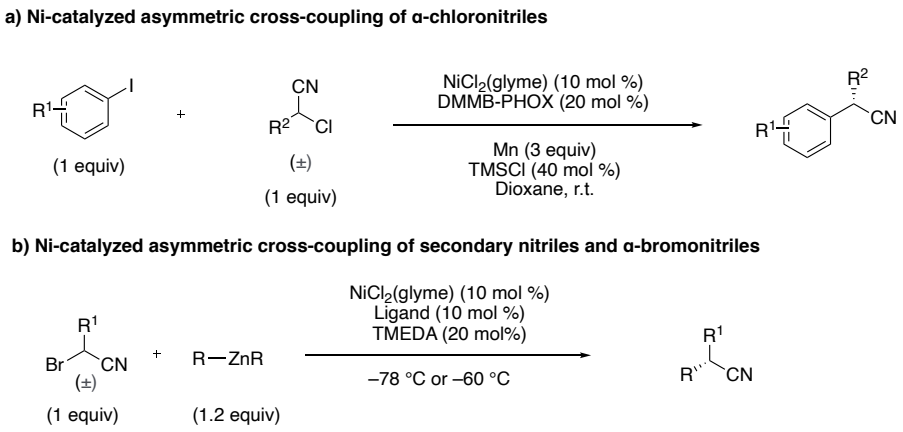
[24] He, A.; Falck, J. R. *J. Am. Chem. Soc.* **2010**, *132*, 2524–2525.

[25] Shang, R.; Ji, D.-S.; Chu, L.; Fu, Y.; Liu, L. *Angew. Chem.* **2011**, *123*, 4562–4566.

[26] Culkin, D. A.; Hartwig, J. F. **2003**, *36*, 234–245.

[27] Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824–15832.

method was also compatible with quaternary cyanoacetate salts that afforded the tertiary α-aryl nitriles.



Scheme 1-4 Examples of nickel-catalyzed cross-couplings to access secondary α-aryl nitriles.

Not only is palladium used to access secondary α-aryl nitriles but nickel-catalyzed cross-couplings have also been explored (**Scheme 1-4**). Reisman reported a Ni-catalyzed asymmetric reductive cross-coupling of α-chloronitriles with aryl iodides to afford enantioenriched secondary α-aryl nitriles (**Scheme 1-4a**).[28] This report demonstrated the first asymmetric Ni-catalyzed reductive cross-coupling that tolerated more Lewis basic heterocycles such as N-heterocyclic and S-heterocyclic coupling partners.

Fu has also demonstrated a Ni-catalyzed asymmetric cross-coupling of α-bromonitriles using Negishi type conditions with arylzinc or alkenylzinc reagents (**Scheme 1-4b**).[29] This was the first method developed that allowed the stereoconvergent cross-coupling of racemic α-halonitriles. However, the main disadvantage to this method in addition to the method described by Reisman with α-chloronitriles is that α-halonitriles can be difficult to synthesize.

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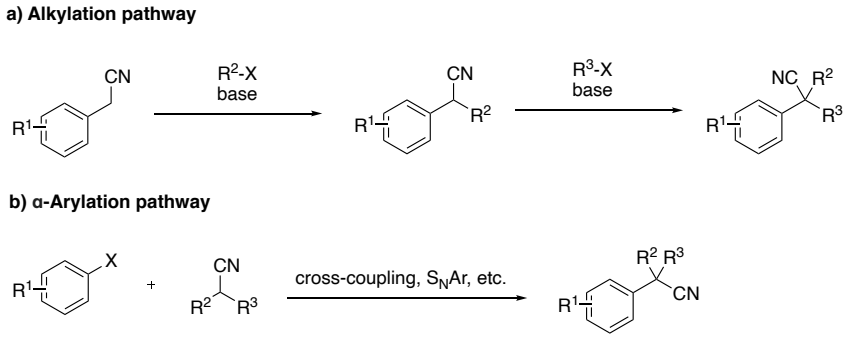
[28] Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 10480–10483.

[29] hoi, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 9102–9105.

1.4 Synthesis of Tertiary α-Aryl Nitriles

There are two main routes to afford tertiary α-aryl nitriles: alkylation and α-arylation (**Scheme 1-5a** and **b**). The vast majority of methods follow the alkylation pathway that begins with a benzylic nitrile that is deprotonated and trapped with an electrophile. The product is then deprotonated once again and trapped with another electrophile to afford the tertiary α-aryl nitrile. The second pathway is α-arylation that consists of several methods such as metal-catalyzed cross-coupling and nucleophilic aromatic substitution (S_NAr).



Scheme 1-5 General schemes to access tertiary α-aryl nitriles

An early account of α-arylation via metal-catalyzed cross-coupling was described by Hartwig and co-workers in 2002 where they explored both the structure and reactivity of arylpalladium cyanoalkyl complexes (**Scheme 1-6a**).[20] After the synthesis and characterization of 3 binding modes of the arylpalladium cyanoalkyl complex they were able to explore the reactivity of these complexes that led to the synthesis of tertiary α-aryl nitriles with aryl bromides. A year later, the Hartwig group further investigated this method in addition to the α-arylation of 2-cyanoacetate esters with aryl chlorides and bromides.[26] A strong base, $NaN(SiMe_3)_2$ was needed for the reaction to proceed, which resulted in limited functional group compatibility.

An additional method that does not require the use of a transition metal catalyst proceeds via S_NAr of aryl fluorides (**Scheme 1-6b**).[30] After deprotonation of secondary benzylic nitriles with

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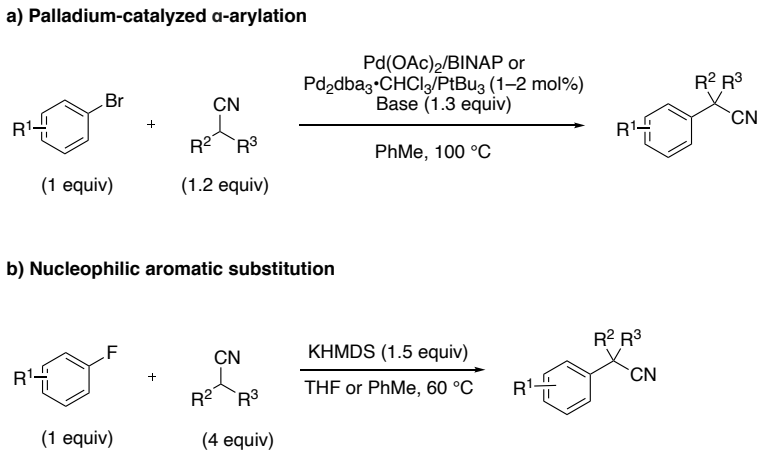
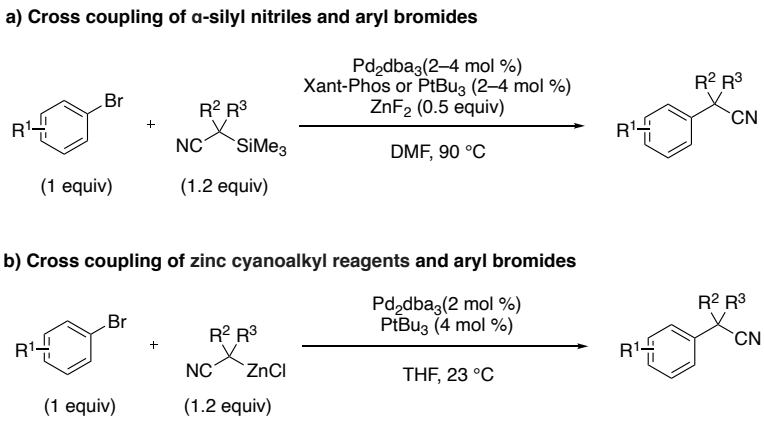
[30] Caron, S.; Vazquez, E.; Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712–713

KHMDS, addition of the secondary α-cyano anion to aryl fluorides can occur to afford tertiary α-aryl nitriles.



Scheme 1-6 Examples of methods to access tertiary α-aryl nitriles.

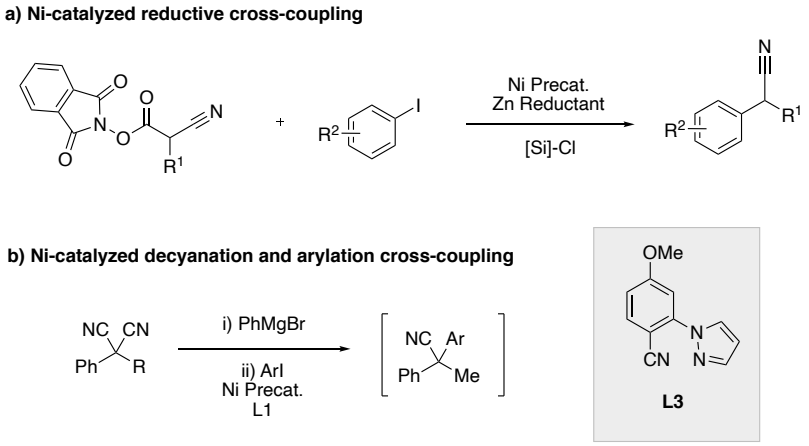
The Pd-catalyzed cross-coupling of aryl halides with α-silyl nitriles in the presence of ZnF_2 has also been reported for the synthesis of both secondary and tertiary α-aryl nitriles (**Scheme 1-7a**).[27] However, hindered secondary nitriles were incompatible with the aforementioned reaction conditions and a stronger base was necessary. To address the issue of functional group compatibility with the use of a stronger base, zinc cyanoalkyl reagents were explored (**Scheme 1-7b**). Using zinc cyanoalkyl reagents allowed the method to be extended to a broader range of functional groups such as esters and ketones.



Scheme 1-7 Examples of palladium-catalyzed cross-couplings to access tertiary α-aryl nitriles.

1.5 This Work

Due to the value and synthetic diversity of nitriles, and specifically of α-aryl nitriles, in both the pharmaceutical industry and academic labs, the Rousseaux group has made the development of new methodology towards nitriles synthesis a core research interest. This thesis will focus on two methodologies developed to synthesize secondary and tertiary α-aryl nitriles. The first project described herein (Chapter 2) is a nickel-catalyzed reductive cross-coupling to form secondary α-aryl nitriles from NHPI esters of cyanoacetic acid derivatives. The following project (Chapter 3) is the development of a benzonitrile ligand involved in the Ni-catalyzed decyanation and arylation of malononitriles to form tertiary α-aryl nitriles.



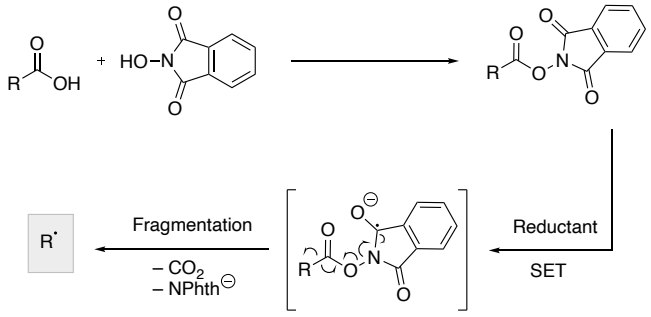
Scheme 1-8 General schemes of the work presented in this thesis.

Chapter 2
Nickel-Catalyzed Reductive Decarboxylative Cross-Coupling of α-Aryl Nitriles

2 Introduction

2.1 *N*-Hydroxyphthalimide Esters in Synthesis

Initially reported by Okada in 1988, redox active *N*-hydroxyphthalimide (NHPI) esters have the unique ability to accept an electron through a single electron transfer (SET) as seen in **Scheme 2-1**.[31] Once the electron is accepted to form a radical anion, a reductive fragmentation can take place that dispels CO_2 and a negatively charged phthalimide (NPhth) leaving a C(sp^3) radical species that can be used in several synthetic transformations. These NHPI esters are easily synthesized from the corresponding carboxylic acid and *N*-hydroxyphthalimide.[32]



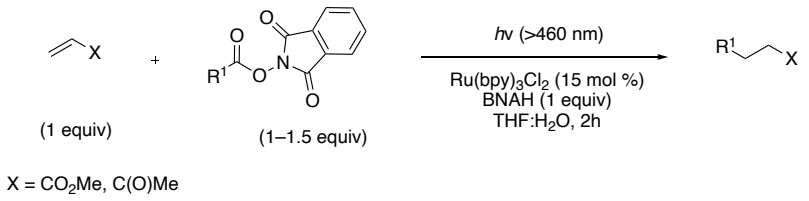
Scheme 2-1 Synthesis of NHPI esters and reductive decarboxylation to form alkyl radicals.

In the last decade there has been increasing interest in using these redox-active esters in C–C bond-forming reactions. Initial synthetic methods developed using NHPI esters were photoinduced requiring an external light source and photocatalyst to initiate the reductive decarboxylation. One of the first examples of this transformation's utility was reported in 1991

[31] Okada, Keiji.; Okamoto, Kazushige.; Oda, Masaji. *J. Am. Chem. Soc.* **1988**, *110* (26), 8736–8738.

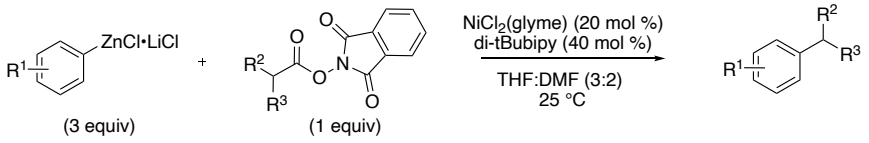
[32] Murarka, S. *Adv. Synth. Catal.* **2018**, *360* (9), 1735–1753.

by Okada and coworkers who demonstrated a photoinduced Giese reaction using NHPI esters as seen in **Scheme 2-2**.[33]



Scheme 2-2 Photoinduced Giese reaction using NHPI esters reported by Okada in 1991.

2.1.1 Nickel-Catalyzed Cross-Couplings Using *N*-Hydroxyphthalimides



Scheme 2-3 Ni-catalyzed cross-coupling of secondary NHPI esters reported by Baran in 2016.

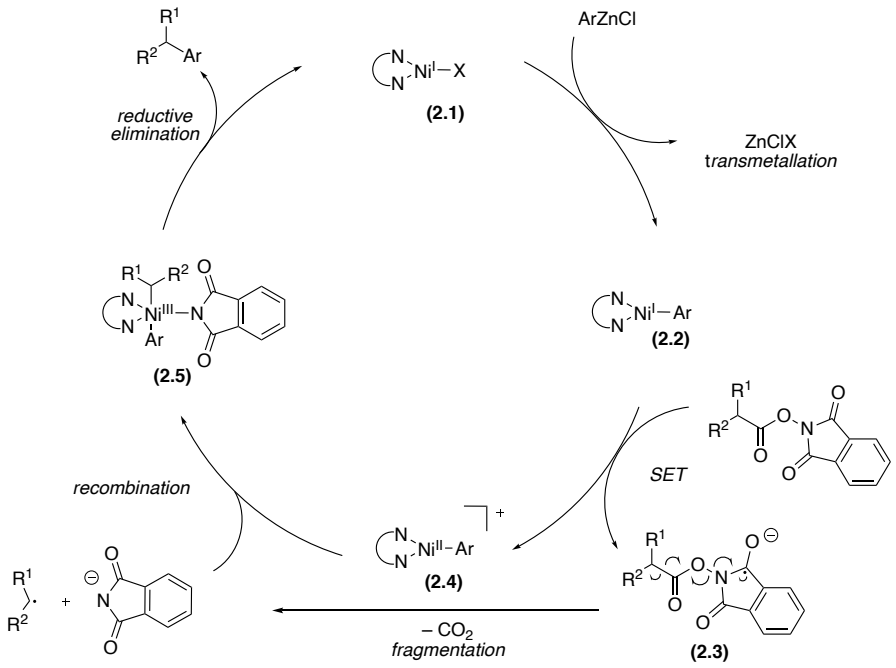
Seminal work in non-photocatalytic, nickel-catalyzed cross-couplings using NHPI esters was reported by both Baran and Weix in 2016 to form $C(sp^3)$–$C(sp^2)$ bonds.[34,35] These groups showed that low-valent nickel can reduce the NHPI ester, allowing the same fragmentation to the alkyl radical as described above in **Scheme 2-1**.

---

[33] Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M. *J. Am. Chem. Soc.* **1991**, *113*, 9401–9402.

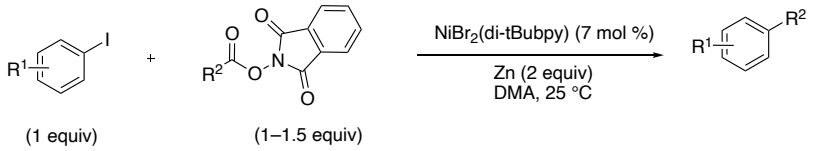
[34] Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 2174–2177.

[35] Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J. *J. Am. Chem. Soc.* **2016**, *138*, 5016–5019.



Scheme 2-4 Proposed catalytic cycle for the Ni-catalyzed cross-coupling reported by Baran in 2016.

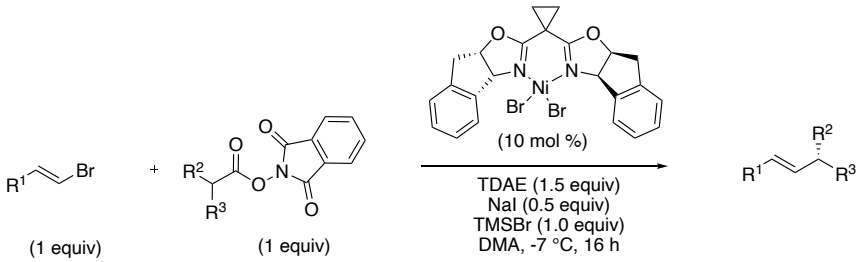
The Baran group reported the use of a secondary radical, derived from NHPI esters, coupled with arylzinc reagents as a nucleophilic partner for Negishi-type cross-coupling (**Scheme 2-3**).[34] The proposed catalytic cycle as described in **Scheme 2-4 b**egins with transmetallation of the Ni(I)–X complex **(2.1)** with the arylzinc reagent to generate a Ni(I)–aryl species **(2.2)**. This complex reduces the NHPI via SET to form **(2.3)**, allowing for decarboxylation and release of the secondary radical. Subsequently, the alkyl radical recombines with the Ni(II)–aryl complex **(2.4)** to form a Ni(III) complex **(2.5)** and reductive elimination forms the desired product.



Scheme 2-5 Ni-catalyzed reductive cross-coupling of NHPI esters reported by Weix in 2016.

In contrast, Weix reported the decarboxylative coupling of NHPI esters with aryl iodides using activated zinc powder as a reducing agent for the first reductive cross-coupling using NHPI esters.[35] Since the original report in 2016, Weix has demonstrated the use of decarboxylative

cross-electrophile couplings for aryl-alkyl and dialkyl ketone synthesis using NHPI esters and S-2-pyridyl thioesters.[36] Weix and co-workers have also demonstrated the formation of C(sp)–C(sp3) bonds via cross-electrophile coupling to form both terminal and internal alkynes from bromoalkynes.[37]



Scheme 2-6 Ni-catalyzed asymmetric reductive cross coupling of NHPI esters reported by Reisman in 2017.

In 2017, Reisman and co-workers reported an asymmetric Ni-catalyzed reductive cross-coupling of NHPI esters with vinyl bromides. This cross-coupling required the use of tetrakis(*N*,*N*-dimethylamino)ethylene as a homogeneous stoichiometric reductant.[38] This method showed a broad substrate scope for both the vinyl bromides and the NHPI esters furnishing products with high enantioselectivities. Initial studies were also done to show the ability to use α-methoxy NHPI esters under the same conditions to afford allylic ethers.

2.2 Results and Discussion

This work was done in collaboration with Nicholas Michel, a Ph.D. student, and Emmanuel Fagbola, a NSERC undergraduate student, in addition to Dr. Jonathan Hughes, Senior Scientist, and Dr. Louis-Charles Campeau, Executive Director, Head of Process Chemistry and Discovery Process Chemistry, from Merck & Co. Inc. Their contributions to the project are explicitly stated in the following text and the results presented are mine unless noted otherwise. My contributions to this project include the synthesis of starting materials and some of the reaction scope.

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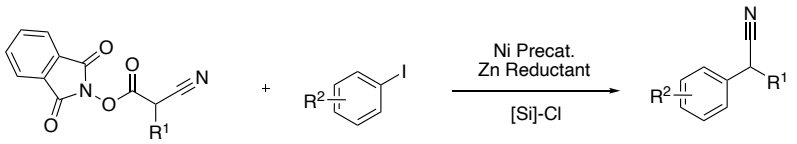
[36] Wang, J.; Cary, B. P.; Beyer, P. D.; Gellman, S. H.; Weix, D. J. *Angew. Chem. Int. Ed.* **2019**, *58*, 12081–12085.

[37] Huang, L.; Olivares, A. M.; Weix, D. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 11901–11905.

[38] Suzuki, N.; Hofstra, J. L.; Poremba, K. E.; Reisman, S. E. *Org. Lett.* **2017**, *19*, 2150–2153.

2.2.1 Reaction Design



Scheme 2-7 Proposed Ni-catalyzed reductive cross-coupling to form α-aryl nitriles using NHPI esters of cyanoacetic acid derivatives.

Inspired by the examples discussed in Section 2.1, we envisioned a reaction that would take advantage of these redox active esters in a Ni-catalyzed cross-coupling to form α-aryl nitriles. Traditional cross-coupling approaches using nitrile α-anions tend to require harsh conditions such as elevated temperatures and strong bases (**Scheme 2-8a).**[25,26,39] Radical processes using α-halonitrile sources is another viable route to from α-aryl nitriles but the synthesis to these α-halonitriles can be difficult due to stability concerns and oxidizing conditions (**Scheme 2-8b**).[28,29,40,41–42]

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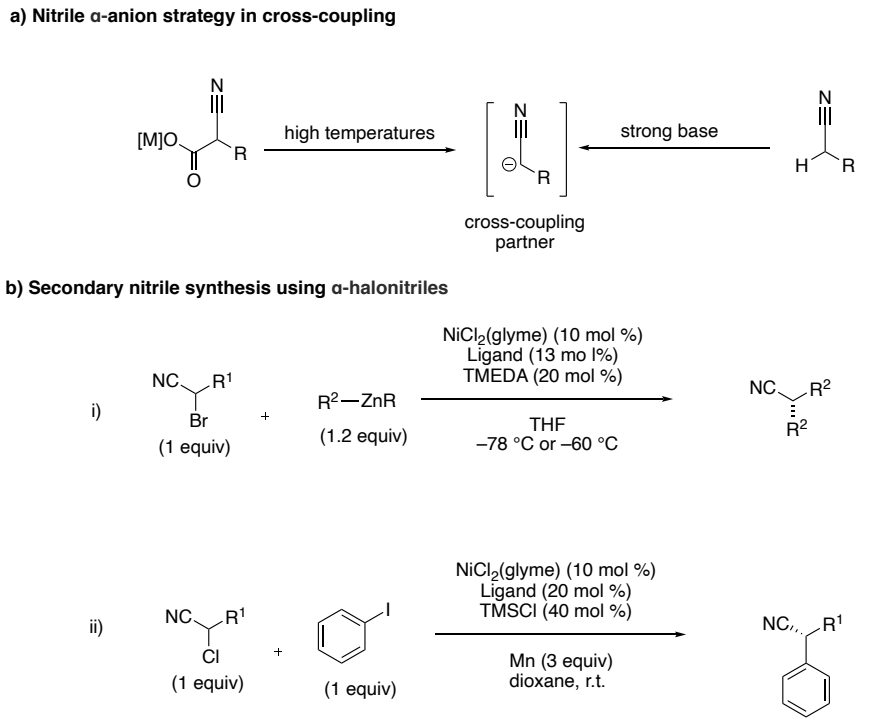
[39] Johansson, C. C. C.; Colacot, T. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 676–707.

[40] Xiao, Y.; Liu, Z.-Q. *Org. Lett.* **2019**, *21*, 8810–8813.

[41] Pu, W.; Sun, D.; Fan, W.; Pan, W.; Chai, Q.; Wang, X.; Lv, Y. *Chem. Commun.* **2019**, *55*, 4821–4824.

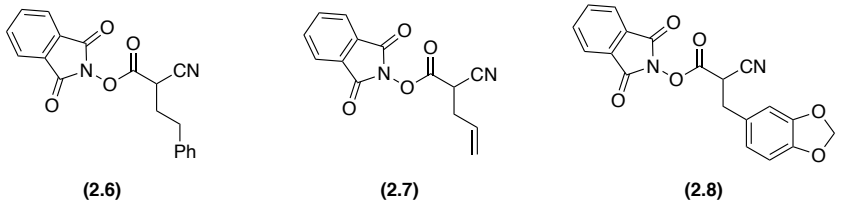
[42] Zheng, C.; Lu, F.; Lu, H.; Xin, J.; Deng, Y.; Yang, D.; Wang, S.; Huang, Z.; Gao, M.; Lei, A. *Chem. Commun.* **2018**, *54*, 5574–5577.



Scheme 2-8 Strategies to access α-aryl nitriles using an anion strategy or α-halonitriles in cross-couplings

To access α-aryl nitriles products under milder conditions, we decided to explore cyanoacetic acid derived NHPI esters. Our proposed method uses cyanoacetic acid as the nitrile precursor, which is a readily available, feedstock chemical.

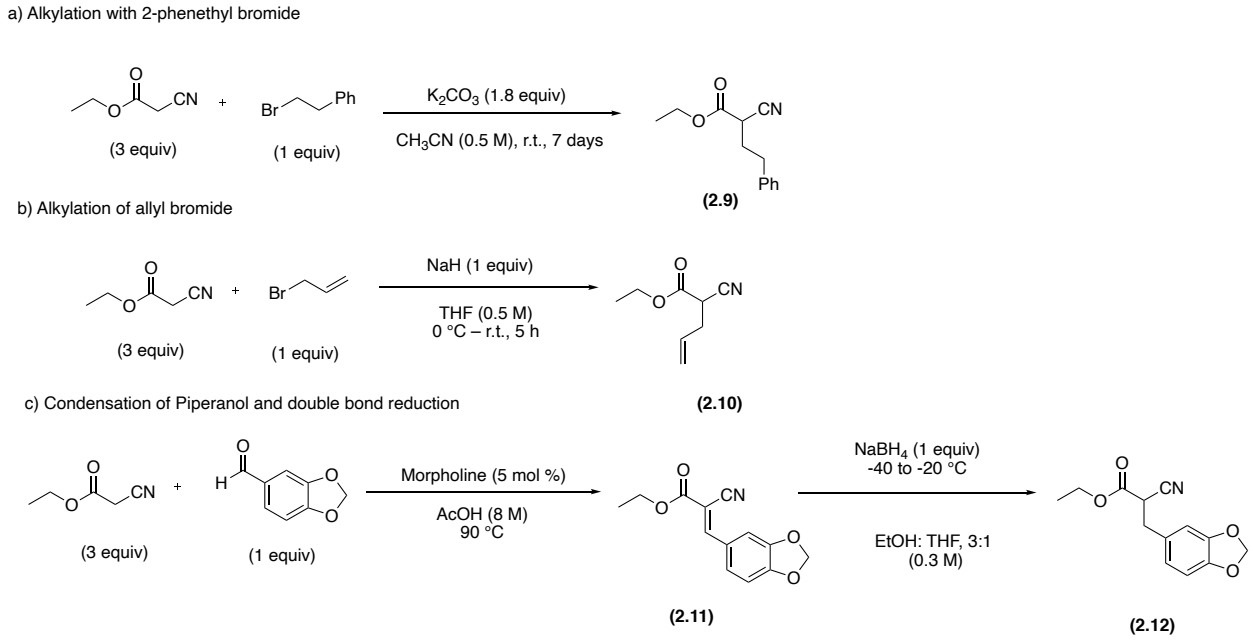
2.2.2 Synthesis of Starting Materials



Scheme 2-9 NHPI esters synthesized for the reductive coupling.

The NHPI esters (**2.6**, **2.7**, **2.8**) in **Scheme 2-9** were synthesized to evaluate the scope of the reaction. **Scheme 2-10** shows the first steps of the NHPI ester synthesis. Towards the synthesis of (**2.6**), ethyl cyanoacetate was treated with 2-phenylethyl bromide and K_2CO_3 in acetonitrile

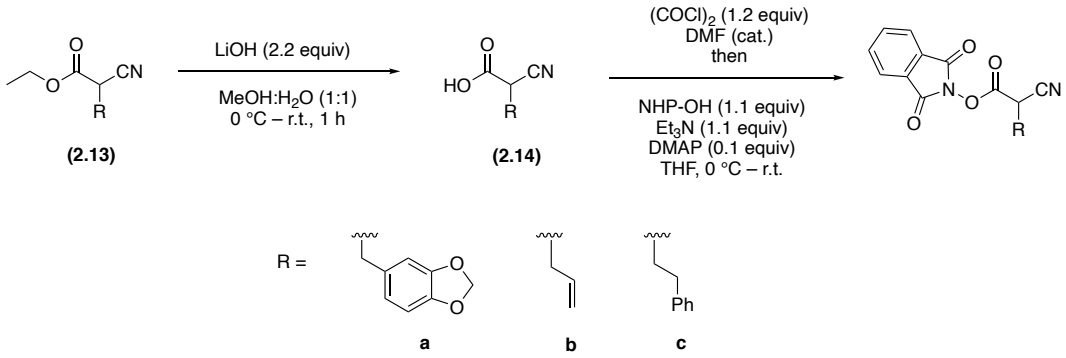
over 7 days (**Scheme 2-8a**). The long reaction time was due to the slow alkylation of the cyanoacetic ester and the propensity to favour the double alkylated product if the electrophile was added too quickly. The alkylation was also carried out with allyl bromide using NaH as the base in THF over 5 hours (**Scheme 2-8b**). Alkylation with allyl bromide under these conditions does not appear to be prone to double alkylation, and slow addition of the electrophile was not needed. The synthesis of (**2.8)** was initiated by the condensation of ethyl cyanoacetate and piperonal with morpholine as a catalyst in acetic acid. The condensed product was reduced by sodium borohydride at –40 °C in an ethanol/THF mixture to get the desired alkylated product. Separately all 3 products (**2.9**, **2.10**, **2.12**) were subjected to saponification conditions with lithium hydroxide in a MeOH:water mixture to afford the desired carboxylic acid as seen in **Scheme 2-11**.



Scheme 2-10 General scheme for the first steps of the synthesis of NHPI esters **2.6**, **2.7**, and **2.8**.

From the carboxylic acids, the NHPI esters were synthesized via acid chloride formation using 1.2 equivalents of oxalyl chloride with catalytic amounts of DMF (**Scheme 2-11**). After 1 hour the DCM was removed under reduced pressure and replaced with THF. The crude mixture was then subjected to a slight excess (1.1 equiv) of NHP–OH, triethylamine (1.1 equiv), and DMAP (10 mol %). To remove excess NHP-OH, the crude mixtures were passed through celite plugs and eluted with chloroform since NHP-OH is not soluble in chloroform and collected on the top

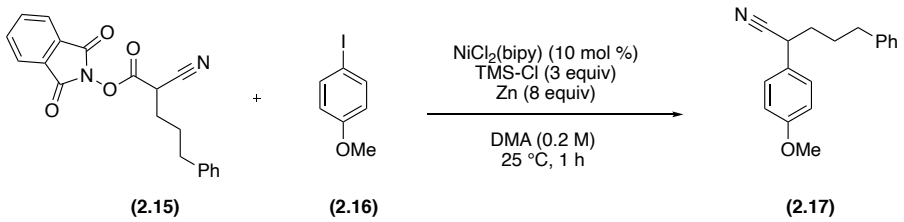
of the celite. The crude reaction mixture was subjected to flash column chromatography on silica gel to afford the desired products.



Scheme 2-11 General scheme for the last steps of the synthesis of NHPI esters.

2.2.3 Optimization of Reaction Conditions

Table 2-1 Initial reaction optimization of the reductive cross-coupling of NHPI esters derived from cyanoacetic acid derivatives.



Entry	Deviation from standard conditions	% Yield (3)
1	None	86
2	Zn (2 equiv)	65
3	NHPI (1.0 equiv), ArI (1.5 equiv), 0.1 M	43
4	No [Si]	-
5	No Ni	0
6	No bpy	0
7	No Zn	0

[a]All results in **Table 2-1** were done by Nick Michel

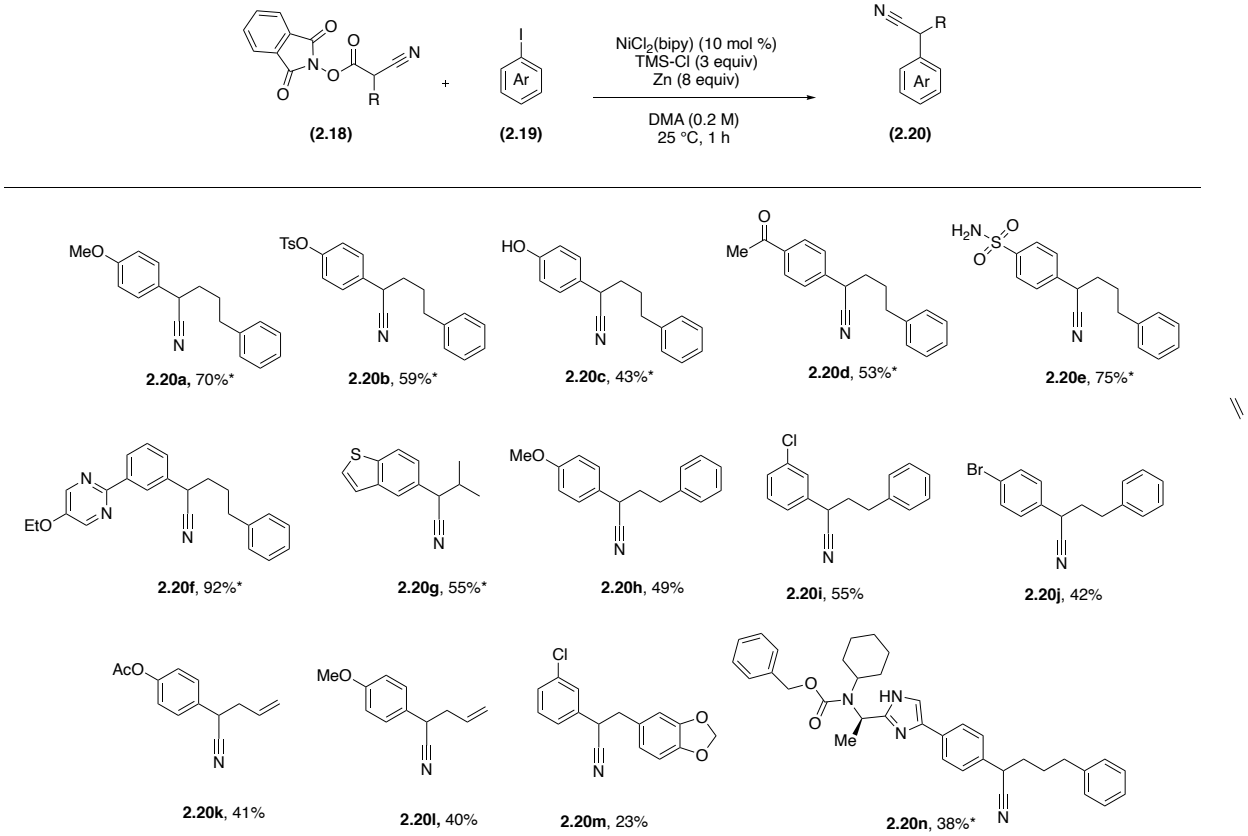
The initial optimization of this reaction was done by Nick Michel who explored nickel precatalysts, reductants, temperature, solvent, and additives in the reaction. Reaction

optimization revealed that relatively typical reductive cross-coupling conditions were ideal for our reaction. $NiCl_2$(bipy) at 10 mol % was the optimal precatalyst as shown in **Table 2-1,** entry 1. It should be noted that the optimized conditions require 8 equivalents of zinc (entry 1). However, 2 equivalents of zinc can be used in the reaction, although reduced yields are obtained (entry 2). An excess of NHPI ester (1.5 equivalents) relative to aryl iodide is required due to fast degradation of the NHPI ester starting material under the reaction conditions. Using the NHPI ester as the limiting reagent leads to a significant drop in product yield (entry 3). It was discovered that a chlorosilane additive was necessary for the reaction; without this additive, the desired product could not be detected (entry 4). The optimal chlorosilane was trimethylsilyl chloride (TMS-Cl) at 3 equivalents with several other bulky chlorosilanes working in the reaction but at reduced yields. The final parameters that were optimized were DMA as the solvent at 0.2 M and the reaction was run at room temperature for 1 h.

2.2.4 Scope of Reaction

With the optimized conditions for this reductive cross-coupling, we tested the functional group compatibility of the reaction with the synthesized NHPI esters and a diverse set of aryl iodides. Initial scope entries were done by Nick Michel denoted by the asterisks (*) as seen in **Table 2-2**. Aryl iodides are the favoured cross-coupling partner in comparison to aryl bromides (**2.20j**), aryl tosylates (**2.20b**), and aryl chlorides (**2.20m**) which remain untouched under the reaction conditions. The reaction works with a wide variety of functional groups that would not be traditionally be compatible with α-arylation strategies involving strong base such as a phenol (**2.20c**), sulfonamide (**2.20e**), and ketone (**2.20d**). More complex pharmaceutically relevant aryl iodides (**2.20n**) were subjected to the conditions and gave the desired product in modest yet synthetically useful yields.

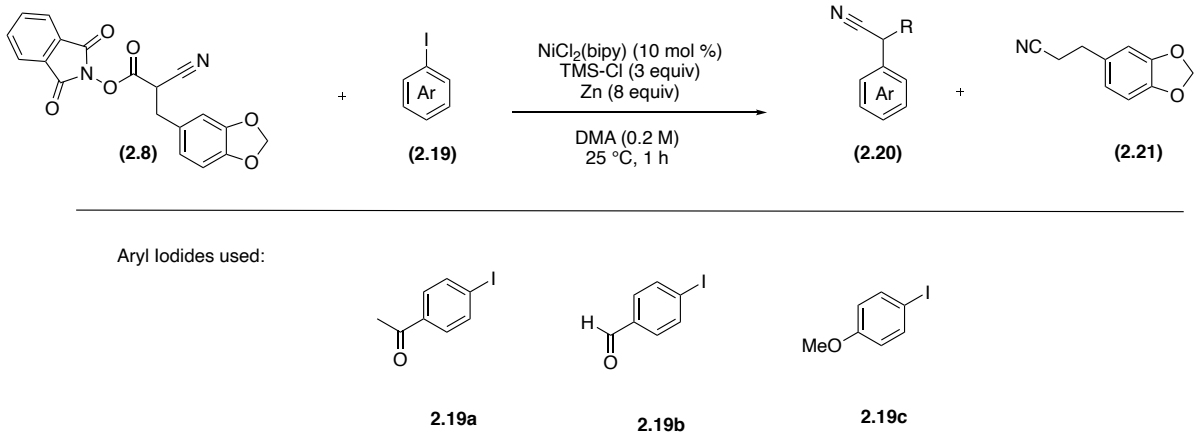
Table 2-2 Selected substrate scope.



*All results with (*) were obtained by Nick Michel

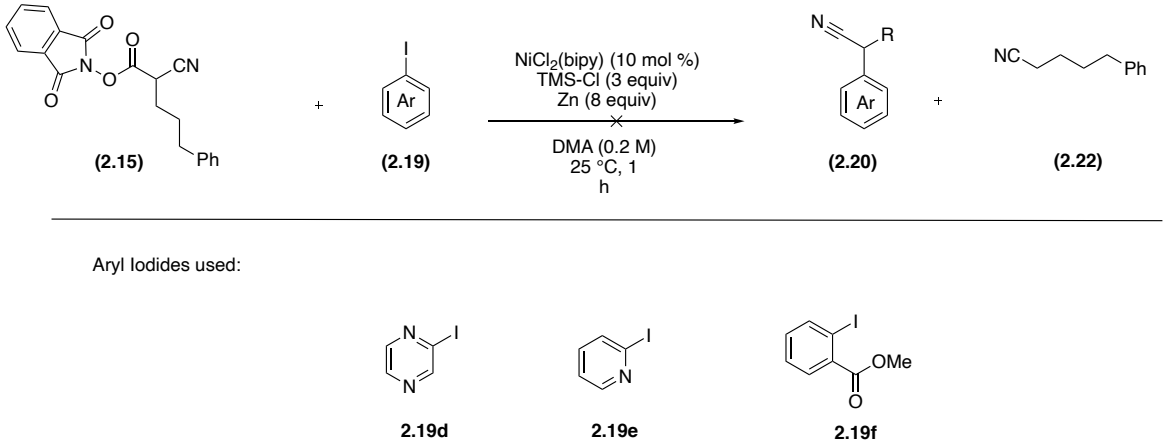
2.2.5 Incompatible Substrates

The major side-product obtained under the optimized reaction conditions is the decarboxylated reduced starting material (i.e. the simple alkyl–CN), an example being (**2.21**) in **Scheme 2-12.** A problem that was encountered during purification of the desired products (**2.20**) was direct co-elution of the desired product with the reduced side-product (**2.21**) during column chromatography. This overlap was seen in the coupling of (**2.8**) with select aryl iodides (**2.19a**, **2.19b**, **2.19c**) (**Scheme 2-12)**. After 2 columns with a slow gradient from 0–10% hexanes:EtOAc on either the Biotage or by manual column, there was no separation between the desired product and the side product. This overlap can be potentially avoided by repeating these reactions with aryl iodides that are more or less polar than the ones used.



Scheme 2-12 Aryl iodides that resulted in products that co-eluted with the decarboxylated NHPI ester.

Coupling NHPI ester (**2.15**) and aryl iodides (**2.19d**) and (**2.19e**) gave none of the desired product as determined by TLC or GC-MS; the majority of aryl iodide was recovered in these reactions. This finding could be due to catalyst poisoning, which completely shuts down reactivity. When (**2.19f**) was subjected to the reaction conditions, there was complete consumption of the aryl iodide, but the product was unable to be isolated for an unknown reason.



Scheme 2-13 NHPI esters with corresponding aryl iodides that were incompatible in the reductive cross-coupling.

2.2.6 Proposed Catalytic Cycle

A proposed mechanism for this reaction is depicted in **Scheme 2-14**. This proposed catalytic cycle is based on previous literature reports and mechanistic studies by Nick Michel that were

not mentioned in this thesis.[43–51] The catalytic cycle starts with the reduction of the Ni(II) catalyst to (**2.23**) that undergoes oxidative addition with the aryl iodide to generate (**2.24**). Subsequent reduction of (**2.24**) by SET from Zn(0) affords (**2.25**). Nick Michel has obtained strong evidence that TMS-Cl and zinc promote the reduction and fragmentation of the NHPI ester to the key radical (**2.26**) that recombines with (**2.25**) to form (**2.27**). Finally, reductive elimination affords the desired product.

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[43] Murarka, S. *Adv. Synth. Catal.* **2018**, *360*, 1735–1753.

[44] Ni, S.; Padial, N. M.; Kingston, C.; Vantourout, J. C.; Schmitt, D. C.; Edwards, J. T.; Kruszyk, M. M.; Merchant, R. R.; Mykhailiuk, P. K.; Sanchez, B. B.; Yang, S.; Perry, M. A.; Gallego, G. M.; Mousseau, J. J.; Collins, M. R.; Cherney, R. J.; Lebed, P. S.; Chen, J. S.; Qin, T.; Baran, P. S. *J. Am. Chem. Soc.* **2019**, *141*, 6726–6739.

[45] Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192–16197.

[46] Kaga, A.; Chiba, S. *ACS Catal.* **2017**, *7*, 4697–4706.

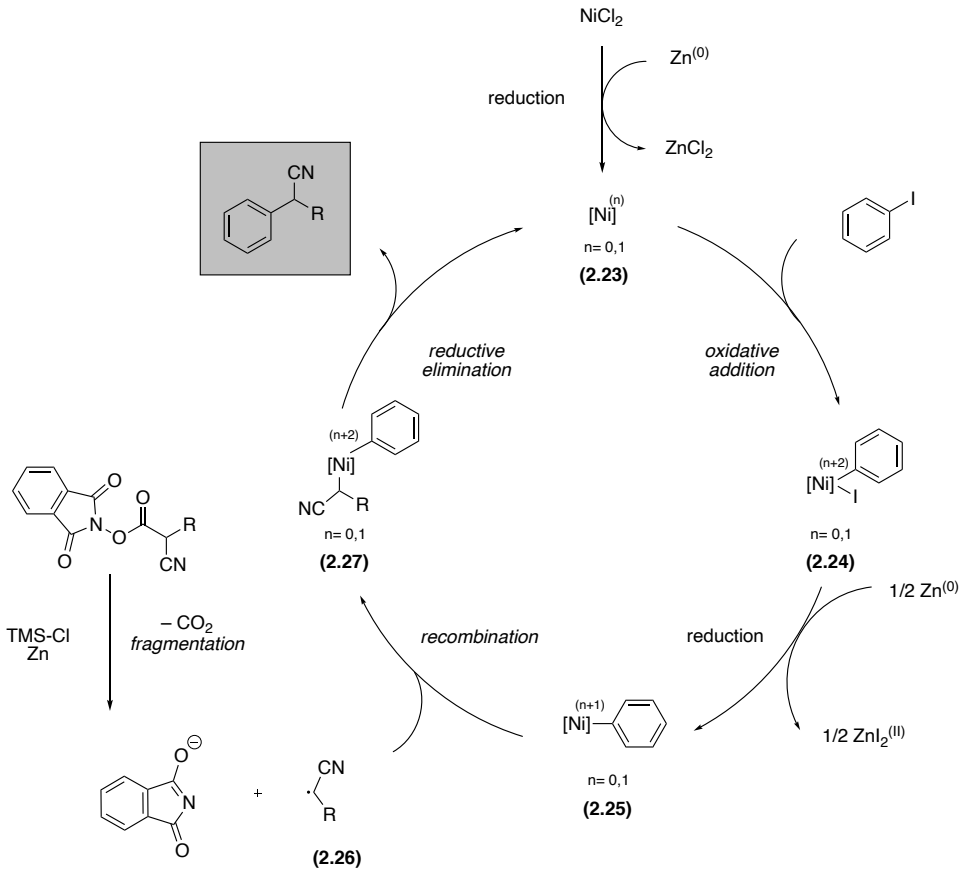
[47] Niu, P.; Li, J.; Zhang, Y.; Huo, C. *Eur. J. Org. Chem.* **2020**, *2020*, 5801–5814

[48] Poremba, K. E.; Dibrell, S. E.; Reisman, S. E. *ACS Catal.* **2020**, *10*, 8237–8246.

[49] Colon, I.; Kelsey, D. R *J. Org. Chem.* **1986**, *5*, 2627–2637.

[50] Ren, Q.; Jiang, F.; Gong, H. *J. Organomet. Chem.* **2014**, *770*, 130–135.

[51] Lin, Q.; Diao, T *J. Am. Chem. Soc.* **2019**, *141*, 17937–17948.



Scheme 2-14 Proposed catalytic cycle for the reductive cross-coupling.

2.3 Conclusion and Future Work

In conclusion, a new strategy towards tertiary α-aryl nitriles through a reductive cross-coupling of NHPI esters was developed. An interesting finding through the development of this reaction was the necessary role of the chlorosilane additive. Preliminary data shows that chlorosilanes are integral in the formation of the alkyl radical through the activation of the NHP ester with zinc. The scope of the reaction has proven to have a broad functional group tolerance and a wide range of products were synthesized that include functional groups that are incompatible with traditional anion nitrile methods in cross-coupling.

A project that is currently ongoing is the stereoselective α-arylation of esters under similar conditions as discussed in this chapter using NHPI esters derived from malonic acid half esters. Initial results have shown high ee of the reaction however with low yields of the desired enantioenriched product. Future goals of this project are to optimize the reaction conditions to

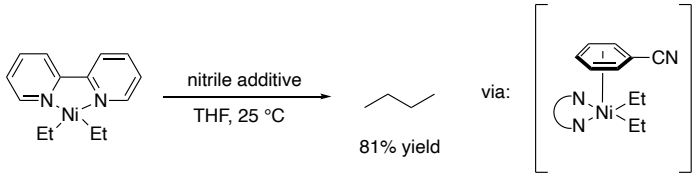
and take advantage of the new knowledge of the chlorosilane's effect on the stereoselective reaction.

Chapter 3
Development of a Benzonitrile Ligand for the Decyanation and Ni-catalyzed Arylation of Disubstituted Malononitriles

3 Introduction

3.1 Nitrile Ligand Effects in Cross-Coupling Reactions

Over the last 3 decades, various reports have described the effects of benzonitrile derivatives in Ni-catalyzed cross-coupling reactions. Yamamoto reported one of the first examples of benzonitrile affecting a cross-coupling reaction in 1997, followed by another report in 2002.[52,53] The preliminary study showed that the reductive elimination of *n*-butane from $NiEt_2(bpy)$ was promoted by electron-poor aromatic compounds, which included benzonitrile (**Scheme 3-1**). In the absence of an electron-poor additive, reductive elimination was not observed. However, with benzonitrile, *n*-butane was observed in 81% yield.



Scheme 3-1 Yamamoto and co-workers have shown that reductive elimination is promoted by benzonitrile derivatives.

Benzonitrile has also been shown to increase the rate of oxidative addition while also stabilizing Ni(0) intermediates in the catalytic cycle. Hartwig reported that, in the presence of benzonitrile, the Ni-catalyzed asymmetric α-arylation of 2-methyl-1-indanone with 4-chlorobenzotrifluoride occurs with full conversion of the indanone starting material. The desired product is obtained in 92% yield (**Scheme 3-2**).[54] This is in comparison to the same reaction without benzonitrile that afforded less than 5% of the desired product. In addition, it was shown that in the α-arylation of

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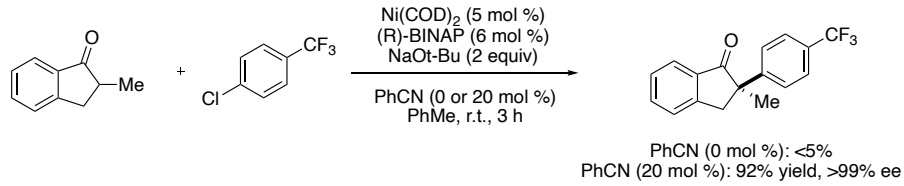
[52] Yamamoto, T.; Abla, M.. *J. Organomet. Chem.* **1997**, *535*, 209–211.

[53] Yamamoto, T.; Abla, M.; Murakami, Y. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1997–2009.

[54] Ge, S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 16330–16333.

ketones, the catalytic intermediate [(R)-BINAP)]Ni(η^2-NC-Ph) can rapidly add into arylchlorides and arylbromides at room temperature and reduces the decomposition pathway that leads to a less selective Ni(I) species.[54]



Scheme 3-2 Hartwig and co-workers have demonstrated an increased rate of oxidative addition with the addition of benzonitrile.

Schoenebeck and co-workers reported that nitrile additives are beneficial in the Ni-catalyzed coupling of SCF_3 derivatives with aryl chlorides.[55] Under the conditions shown in **Scheme 3-3**, the authors suggest that nitriles can displace COD ligands creating an equilibrium between the coordination of nitrile and COD to nickel. Where δGmax represents the free energy difference between the lowest and highest point of the reaction path that dictates the catalytic efficiency and reaction speed. Computational studies predict that the oxidative addition of [(dppf)Ni(0)(MeCN)] with PhCl has a lower activation free energy barrier of 9 kcal/mol in comparison to [(dppf)Ni(0)(COD)]. With the addition of benzonitrile, and thus a raised catalyst resting-state energy, the reaction afforded 70% of the desired product instead of trace amounts without any nitrile additive.

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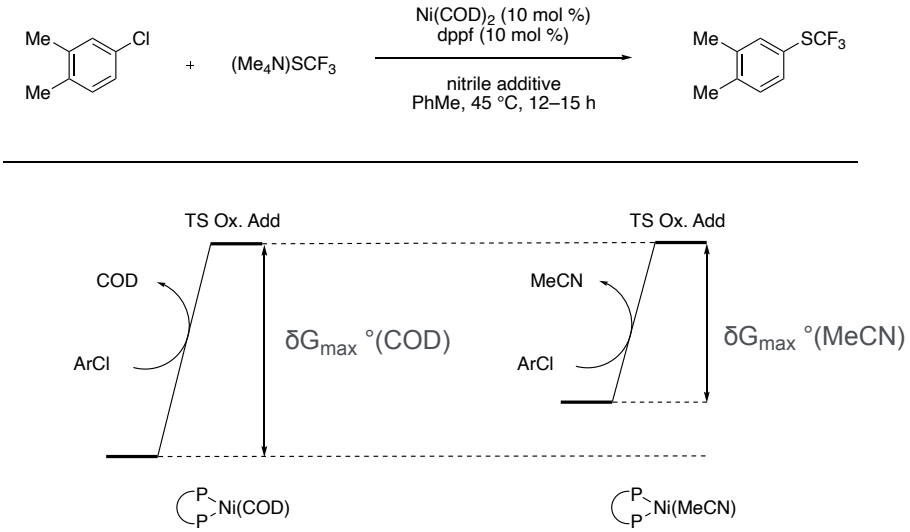
[55] Yin, G.; Kalvet, I.; Englert, U.; Schoenebeck, F. *J. Am. Chem. Soc.* **2015**, *137*, 4164–4172



Scheme 3-3 Schematic representation of the δGmax of [(dppf)Ni(cod] and [(dppf)Ni(MeCN)] of the trifluoromethylthiolation of aryl chlorides.

3.2 Results and Discussion

This work was done in collaboration with Dr. Reggie Mills, a recent Ph.D. graduate, and Nick Michel, a current Ph.D. student. Their contributions to the project are explicitly stated in the following text and the results presented are mine unless noted otherwise. My contributions to this project were the synthesis of benzonitrile ligand variations and preliminary exploration of the reaction scope.

3.2.1 Reaction Design and Optimization of Reaction Conditions

Malononitrile is an inexpensive chemical that can be easily diversified through alkylation and arylation. These disubstituted malononitriles can then be used as electrophilic nitrile sources to access α-aryl nitriles. Inspired by previous work by Reeves and co-workers, our group has explored the use of malononitrile derivatives as reagents for transnitrilation (i.e. nitrile-transfer) and as a nitrile building block.[56–59] Disubstituted malononitriles can undergo a retro-Thorpe

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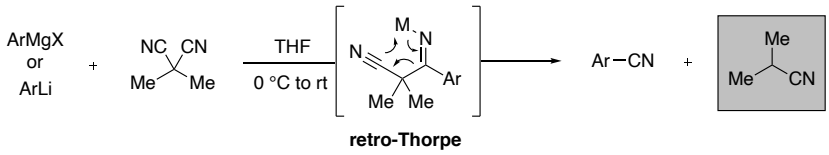
[56] Reeves, J. T.; Malapit, C. A.; Buono, F. G.; Sidhu, K. P.; Marsini, M. A.; Sader, C. A.; Fandrick, K. R.; Busacca, C. A.; Senanayake, C. H. *J. Am. Chem. Soc.* **2015**, *137*, 9481–9488.

[57] Mills, L. R.; Rousseaux, S. A. L. *Tetrahedron* **2019**, *75*, 4298–4306.

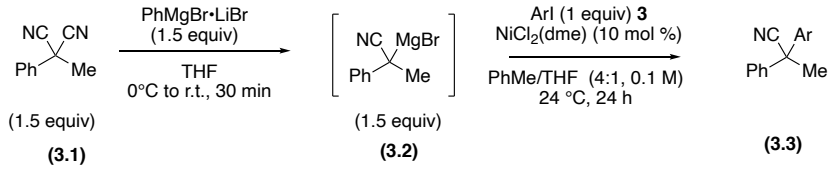
[58] Mills, L. R.; Graham, J. M.; Patel, P.; Rousseaux, S. A. L. *J. Am. Chem. Soc.* **2019**, *141*, 19257–19262.

reaction when subjected to a Grignard reagent or an aryl lithium (Scheme **3-4**). This process produces benzonitrile derivatives in addition to a byproduct that was initially discarded. We wanted to take advantage of this unused byproduct and investigate its utility in cross-coupling.



Scheme 3-4 Retro-Thorpe from a disubstituted malononitrile.

Dr. Reggie Mills, a recent Ph.D. graduate, carried the initial optimization of this reaction. The malononitrile derivative that was used in probing this reaction was methyl-phenyl-malononitrile (MPMN) (**3.1**) as seen in **Scheme 3-5**. MPMN (**3.1**) was subjected to 1.5 equivalents of PhMgBr in THF and refluxed for 30 minutes. After retro-Thorpe to obtain the α-nitrile anion byproduct (**3.2**), it was subjected to Ni-catalyzed cross-coupling conditions with aryl iodides



Scheme 3-5 Initial optimization of the Ni-catalyzed decyanation and arylation cross-coupling

3.2.2 Nitrile Additive Effect

A ligand screen was performed during reaction optimization with over 50 ligands examined including phosphines, NHCs, bipyridines, and other privileged ligands for Ni-catalyzed cross-couplings. However, a general trend that was seen was that ligands seemed to shut down the reactivity or have no effect in comparison to ligand-free conditions. More electron-rich ligands tended to poison the catalyst and electron-poor ligands tended to have little to no effect on the

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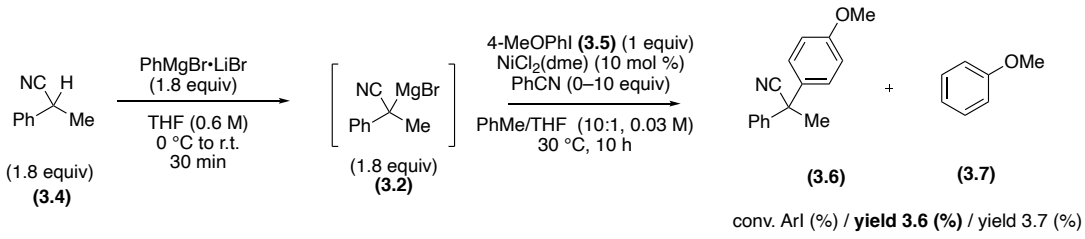
[59]Alazet, S.; West, M. S.; Patel, P.; Rousseaux, S. A. L. *Angew. Chem. Int. Ed.* **2019**, *58*, 10300–10304.

reaction. In addition, problems that were encountered throughout these screens were reproducibility issues.

Table 3-1 Probing the cross-coupling step with disubstituted malononitrile and α-arylated propionitrile derivatives.



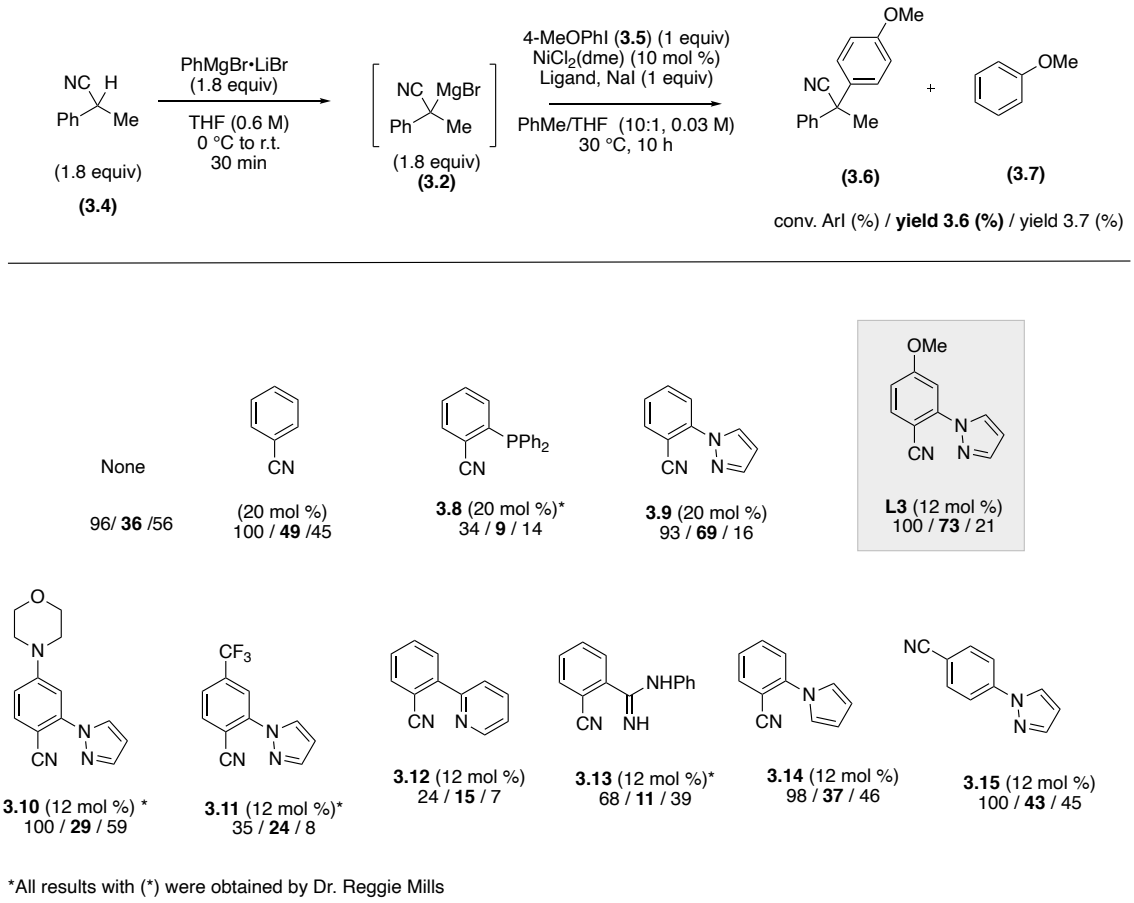
Entry	Conversion of **3.5** (%)	Yield **3.6** (%)[b]	Yield **3.7** (%)[b]
1	69–93	43-54	12-25
2	71	30	35

[a]All results in **Table 3-1** were done by Dr. Reggie Mills
[b]Calibrated GC-MS yields using n-dodecane as internal standard

To probe this reaction further, Reggie focused on the cross-coupling step and removed the variability of the decyanation step. This was done by using a 2-phenylpropanenitrile (**3.4**) seen in **Table 3-1**. Compound (**3.4**) was subjected to the reaction conditions for an initial deprotonation instead of the retro-Thorpe process. By removing the variability of the decyanation step, the reaction became much more reproducible as seen in entry 2, albeit with a decrease in yield by 15–25%. The key difference between these two conditions is that the decyanation of MPMN (**3.1**) produces 1 equivalent of benzonitrile as described previously in **Scheme 3-4**. To explore the effect of benzonitrile in the reaction, Reggie examined the effect of different amounts of benzonitrile in the reaction with (**3.4**). This study revealed that increased amounts of benzonitrile in the reaction resulted in increased yield of the desired product with lower yields of the reduced arene (**3.7**)

3.2.3 Ligand Optimization

Table 3-2 Benzonitrile ligand optimization.

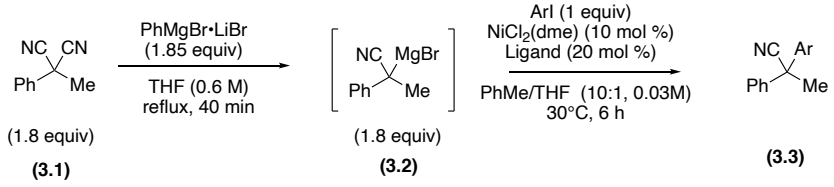


*All results with (*) were obtained by Dr. Reggie Mills

These findings were supported by previous reports discussed in the introduction of this chapter. To take advantage of this nitrile effect, we started designing a benzonitrile ligand. The initial design of the ligand was to have two coordination sites for nickel: the nitrile moiety tethered to a Lewis basic group. To determine the success of the ligand, the conversion of the aryl iodide, the yield of the desired product, and the yield of the reduced arene were monitored. The ligands prepared by Dr. Reggie Mills are denoted by an asterisks (*).

Without any additional ligand in the system the product yield was 36% while addition of 20 mol % benzonitrile increased the yield of desired product to 49%. Lewis basic coordination sites *ortho* to the nitrile were first investigated. We found that pyrazole (**3.9**) afforded the best results in terms of high conversion of the aryl iodide (93%), high yield of the desired product (69%) and minimal amounts of reduced arene (16%) resulting from undesired β-hydride elimination. In

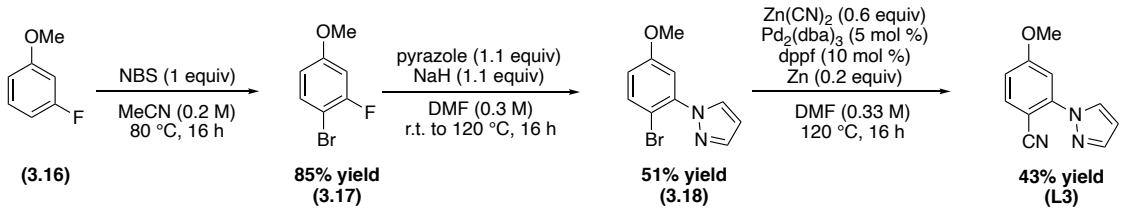
comparison, ligands containing phosphine (**3.8**), pyridine **(3.12),** and amidine **(3.13)** as Lewis basic substituents were all less effective. With the pyrazole derivative, the electronic properties of the ligand were explored with the addition of electron-donating (**L3**, **3.10**) and electron-withdrawing (**3.11**) groups *para* to the nitrile. We determined that (**L3)**, bearing a *p*-OMe group, was the ideal ligand in this reaction. To ensure that the Lewis basic group was imperative for the success of the ligand, a pyrrole derivative **(3.14)** was subjected to the reaction conditions. The pyrrole derivative resulted in reduced yields of the desired product and similar yields of the reduced arene to conditions without any ligand present. To probe whether the pyrazole group and the nitrile needed to be in close proximity to properly bind to the nickel catalyst, the pyrazole group was installed *para* to the nitrile in (**3.19**)**.** This led to reduced yields, similar to those in the reaction with "simple" benzonitrile. Overall, the optimal benzonitrile ligand (**L3**) afforded 100% conversion of the aryl iodide, 73% of the desired product, and 21% of the reduced arene. The addition of **L3** prevented β-H elimination of the aryl iodide in the catalytic cycle while favouring reductive elimination to the desired product. Using (**L3**), the reaction conditions were further optimized with the disubstituted malononitrile derivative (**Scheme 3-6**).



Scheme 3-6 Final reaction conditions for the decyanation and Ni-catalyzed arylation of malononitriles.

3.2.4 Synthesis of Benzonitrile Ligand

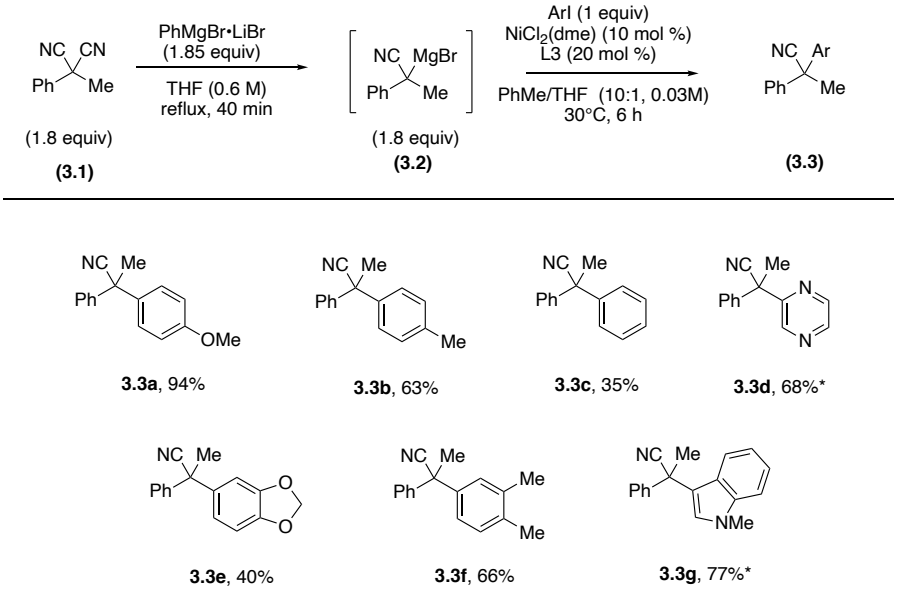
Dr. Reggie Mills developed the synthetic pathway to **L3** as described in **Scheme 3-7**. The synthesis starts with 3-fluoroanisole, which is commercially available. 3-Fluoroanisole (**3.16**) was brominated at the *para* position of the aromatic ring relative to the methoxy group with NBS to afford (**3.17**). After bromination, (**3.17**) was subjected to nucleophilic aromatic substitution to install the pyrazole group to afford (**3.18**). The last step in the synthesis is a palladium-catalyzed cross-coupling of (**3.18**) with $Zn(CN)_2$ to install the nitrile, which furnishes the desired product (**L3**).



Scheme 3-7 Synthesis of the benzonitrile ligand (**L3**).

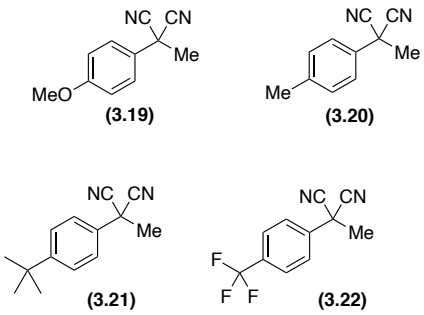
3.2.5 Preliminary Scope

Table 3-3 Selected reaction scope.



*All results with (*) were obtained by Dr. Reggie Mills

The preliminary scope of the reaction is shown in **Table 3-3**. With respect to the aryl iodide, various functional groups are tolerated including an electron-donating group (**3.3a**), heterocycles (**3.3d**, **3.3g**), and benzodioxole (**3.3e**). Currently, different malononitrile derivatives are being synthesized to vary both the electronic and steric effects of this starting material (**Scheme 3-8**). In addition, the alkyl group of the disubstituted malononitrile will be varied to test more than just methyl.



Scheme 3-8 Potential disubstituted malononitriles to try in the reaction.

3.3 Conclusion and Future Work

In conclusion, we have developed a benzonitrile ligand for the decyanation and Ni-catalyzed arylation of disubstituted malononitrile derivatives. Mechanistic experiments performed by Dr. Reggie Mills strongly suggest that the ligand prevents β-hydride elimination from occurring by promoting reductive elimination. Ongoing work on this project is focusing on further characterization of the nature of the (**L3**)-Ni interaction. The nature of the interaction will help understand the applicability of **L3** in other cross-coupling methods and increase the knowledge of benzonitrile additives in Ni catalysis. A potential new route that this project could explore is the development of a chiral ligand for the enantioselective desymmetrization of malononitriles. This would not only lead to highly valued tertiary α-aryl nitriles but hopefully chiral products as well.

Chapter 4

4 Experimental Section

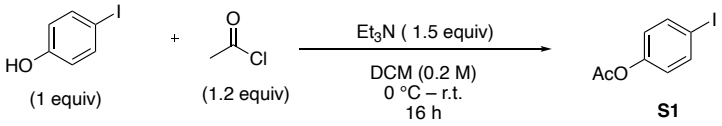
4.1 General Information

Unless otherwise noted, reactions were carried out on the benchtop and run under N_2 or Ar atmosphere using flame-dried glassware and anhydrous solvents. HPLC-grade DCM, Et_2O, PhMe and THF (inhibitor free) were purchased from Caledon or Sigma-Aldrich, were dried using PureSolv MD 5 solvent purification system and used without further manipulation. PhMe used for nickel-catalyzed reactions was degassed with an argon in addition to sonication under high vacuum for 15 min prior to use. THF was further dried over activated 3 Å molecular sieves for 3 days before use. DMA and DMF were purchased from Acros as Extra Dry over molecular sieves. DMA used in the reductive decarboxylative chemistry was further dried over activated 3 Å molecular sieves for 3 days before use. All other anhydrous solvents were purchased from Sigma–Aldrich in Sure/Seal bottles or from Acros in AcroSeal bottles and were used as received. $NiCl_2$(dme) was prepared from $NiCl_2$ and ethylene glycol dimethyl ether and was stored in a glovebox. All organometallic reagents were titrated before use using Knochel's protocol before use.[60]

GC-MS data was obtained on a Shimadzu GCMS-QP2010 SE; yields represent peak areas calibrated against each compound's response factor relative to *n*-dodecane internal standard. ^{1}H and ^{13}C NMR spectra were recorded on Varian MercuryPlus 400 MHz, Bruker AvanceIII 400, Agilent DD2 500 MHz spectrometers. TLC samples were run on EMD Millipore TLC Silica gel 60 F254 plates and were visualized by UV or by staining with KMnO4.

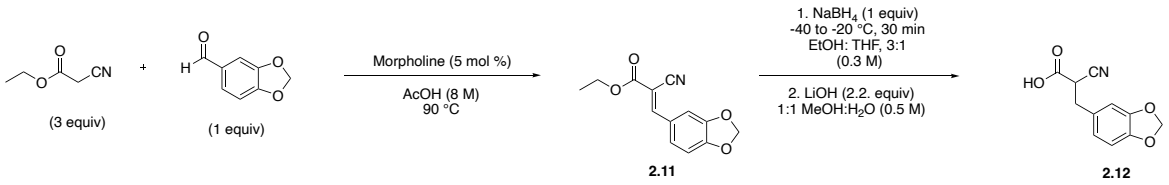
[60]Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *2006*, 0890–0891.

4.2 Synthesis of Aryl Iodides



4-Iodophenyl acetate (S1): A solution of iodophenol (2.2 g, 10 mmol, 1.0 equiv) in DCM (0.23 M) was cooled to 0 °C. Acetyl chloride (0.86 mL, 12 mmol, 1.2 equiv) and triethylamine (2.1 mL, 15 mmol, 1.5 equiv) were added and the solution was warmed to room temperature. The reaction was stirred for 16 h. Water was added to the reaction flask and extracted with DCM (x3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (gradient 0 – 20% EtOAc in hexanes) to afford 2.1 g (82% yield) of **S1** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.81–7.51 (m, 2H), 6.86 (d, J = 8.9 Hz, 2), 2.29 (s, 3H). **^{13}C NMR** (124 MHz, $CDCl_3$, 298 K): δ_C 169.0, 150.4, 138.4, 123.7, 89.8, 21.0. NMR data is consistent with previous literature reports.[61]

4.3 Synthesis of N hydroxyphthalimide Ester Starting Materials



Ethyl (*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)-2-cyanoacrylate (2.11): Ethylcyanoacetate (5.3 mL, 50 mmol, 1.0 equiv), piperonal (7.8 g, 52 mmol, 1.2 equiv), piperidine (0.25 mL, 2.5 mmol, 5.0 mol%) were added to a round bottom flask followed by acetic acid (8 M). The reaction was run at 90 °C until no starting material was detected by TLC. The reaction mixture was cooled to r.t., the solution solidified, and the crude product was recrystallized with hexanes and EtOAc to

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[61] Van der Born, D.; Sewing, C.; Herscheid, J. K. D. M.; Windhorst, A. D.; Orru, R. V. A.; Vugts, D. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 11046–11050.

afford 6.8 g (56% yield) of **2.11** as a yellow solid. **^{1}H NMR** (399 MHz, $CDCl_3$, 298 K): δ_H 8.12 (d, J = 0.6 Hz, 1H), 7.73–7.70 (m, 1H), 7.42 (ddd, J = 8.2, 1.9, 0.6 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H).**^{13}C NMR (**101 MHz, $CDCl_3$, 298 K): δ_C 182.9, 156.24, 154.3, 152.2, 129.6, 125.9, 115.9, 109.0, 108.8, 102.2, 99.8, 62.5, 14.1. NMR data is consistent with previous literature reports.[62]

Ethyl 3-(benzo[*d*][1,3]dioxol-5-yl)-2-cyanopropanoate: Step 1: Sodium borohydride (108 mg, 3.30 mmol, 1.00 equiv) was added to a mixture of THF (3 mL) and EtOH (8 mL) and cooled to –40 °C. In one portion **2.11** (690 g, 3.30 mmol, 1.0 equiv) was added and let the reaction stir for 1 h allowing the mixture to warm up to –20 °C. The reaction was quenched with 1M HCl and extracted with EtOAc (x3). The organic layers were combined and washed with brine, concentrated under reduced pressure, and dried with $MgSO_4$. No further purification was necessary to afford 477 mg (58% yield) of the desired compound as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K): δ_H 6.80–6.70 (m, 3H), 5.95 (s, 2H), 4.25 (t, J = 7.1, 0.9 Hz, 2H), 3.67 (t, J = 8.3, 5.8 Hz, 1H), 3.23–3.07 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H).**^{13}C NMR** (126 MHz, $CDCl_3$, 298 K): δ_C 165.4, 147.9, 147.2, 128.8, 122.3, 116.0, 109.3, 108.5, 101.1, 62.9, 39.9, 35.5, 13.9. NMR data is consistent with previous literature reports.[63]

3-(Benzo[*d*][1,3]dioxol-5-yl)-2-cyanopropanoic acid (2.12): Step 2: Ethyl 3-(benzo[*d*][1,3]dioxol-5-yl)-2-cyanopropanoate (1.8 g, 7.2 mmol, 1.0 equiv) was dissolved in MeOH (7.0 mL) and water (7.0 mL) in a round bottom flask and the mixture was cooled to 0 °C. LiOH (378 mg, 15.8 mmol, 2.20 equiv) was added in one portion and the mixture was warmed slowly to room temperature. Upon reaction completion (as determined by TLC, approx. 1 h), the reaction mixture was quenched with 1M HCl, and extracted with EtOAc (x3). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to yield 1.3 g (82% yield) of **2.12** as a yellow solid which was of sufficient purity for use in the next step.**^{1}H NMR** (500 MHz, $CDCl_3$, 298 K): δ_H 6.79–6.74 (m, 3H), 5.97 (s, 2H),

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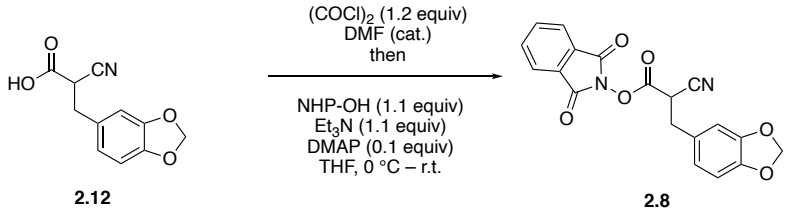
[62] Dakdouki, S. C.; Villemin, D.; Bar, N. *Eur. J. Org. Chem.* **2012**, *2012*, 780–784.

[63] Wang, J.; Song, G.; Peng, Y.; Zhu, Y. *Tetrahedron Lett.* **2008**, *49*, 6518–6520.

3.76–3.73 (dd, J = 8.3, 5.7 Hz 1H), 3.25–3.13 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K): δ_C 168.5, 148.0, 147.4, 128.3, 122.4, 115.4, 109.2, 108.6, 101.2, 39.6, 35.4.

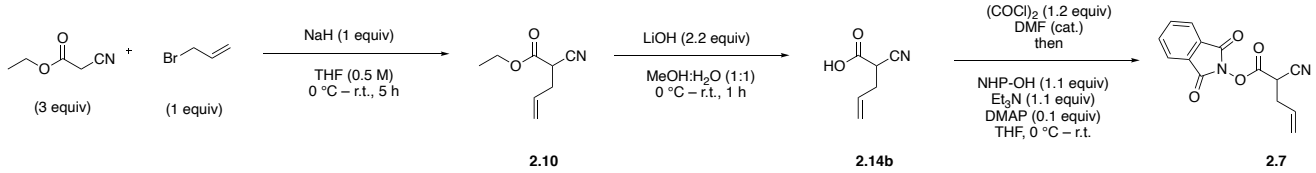


2.12 **2.8**

2.8: **2.12** (2.0 g, 9.1 mmol, 1.0 equiv) was dissolved in DCM (11 mL), and $(COCl)_2$ (0.92 mL, 10 mmol, 1.2 equiv) was added dropwise. 2-4 drops of DMF were then added and the mixture was left to stir at room temperature for 2 hours. Once bubbling ceased (approx. 2 hr), the reaction mixture was then concentrated under reduced pressure, and the brown oily residue was dissolved in THF (18 mL) and cooled to 0 °C. *N*-Hydroxyphthalimide (1.6 g, 10 mmol, 1.1 equiv), and DMAP[64] (100 mg, 0.900 mmol, 0.100 equiv) were added, followed by dropwise addition of NEt_3 (1.4 mL, 10 mmol, 1.1 equiv). The reaction mixture was warmed slowly to room temperature and stirred for 2 hours before being quenched with 1M HCl and extracted with EtOAc (x2). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude brown solid was suspended in $CHCl_3$, sonicated for 2 minutes before being passed through a plug of celite (eluting with $CHCl_3$) to remove excess N-hydroxyphthalimide, and finally concentrated under reduced pressure. The crude material was then passed through a short pad of silica gel eluting with dichloromethane (50–100 mL), followed by 1.5% MeOH in DCM (100 mL)[65] and concentrated under reduced pressure to afford 2.8 g (55% yield) of **2.8** a yellow solid. **^{1}H NMR** (399 MHz, $CDCl_3$, 298 K): δ_H 7.94–7.83 (m, 4H), 6.88–6.81 (m, 3H), 5.99 (s, 2H), 4.09 (dd, J = 8.0, 5.6 Hz, 1H), 3.44 – 3.20 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K): δ_C 162.5, 148.0, 147.5, 135.0, 128.5, 127.3, 124.2, 123.5, 122.7, 113.8, 109.3, 108.6, 101.2, 37.9, 35.8.

[64] The reaction also proceeded in the absence of DMAP

[65] In general the R_f for the TLC of NHPI esters in a solvent system of DCM or 1% MeOH/DCM was 0.9 – 0.95



Ethyl 2-cyanopent-4-enoate (2.10): To a flask containing sodium hydride (2.0 g, 50 mmol, 1.0 equiv) was added THF (100 mL) and the mixture was cooled to 0 °C in an ice bath. Ethylcyanoacetate (16 mL, 150 mmol, 3.0 equiv) was added dropwise, followed by allyl bromide (4.3 mL, 50 mmol, 1.0 equiv). Upon reaction completion (as determined by TLC, approx. 5 h) the reaction was quenched with water and extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (gradient 0 – 20% EtOAc in hexanes) to afford 5.30 g (69% yield) of **2.10** as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 5.87–5.76 (m, 1H), 5.31–5.18 (m, 2H), 4.31–4.22 (m, 2H), 3.55 (dd, J = 7.5, 6.1 Hz, 1H), 2.71–2.65 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H). **^{13}C NMR (**101 MHz, $CDCl_3$, 298 K): δ_C 165.5, 131.3, 120.0, 116.0, 62.8, 37.4, 33.8, 13.9. NMR data is consistent with previous literature reports.[66]

2-Cyanopent-4-enoic acid (2.14b): 2.10 (256 mg, 1.00 mmol, 1.00 equiv) was dissolved in MeOH (1 mL) and water (1 mL) and cooled to 0 °C. LiOH (53 mg, 2.2 mmol, 2.2 equiv) was added in one portion and the mixture was warmed slowly to room temperature. Upon reaction completion (as determined by TLC, approx. 1 hr), the reaction mixture was quenched with 1 M HCl, and extracted with EtOAc (x3). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to yield to afford 163 mg (74% yield) of **2.14b** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 5.84 (ddt, J = 17.0, 10.1, 7.0, 1.1 Hz, 1H), 5.39–5.19 (m, 2H), 3.66 (dd, J = 7.5, 6.0 Hz, 1H), 2.82 – 2.64 (m, 2H). **^{13}C NMR (**101 MHz, $CDCl_3$, 298 K): δ_C 170.2, 130.8, 120.5, 115.3, 37.4, 33.6. NMR data is consistent with previous literature reports.[67]

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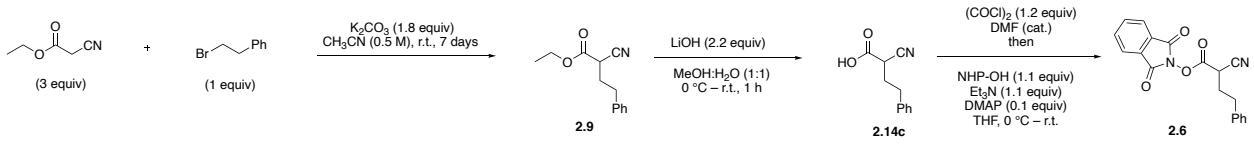
[66] Malmedy, F.; Wirth, T. *Eur. J. Org. Chem.* **2017**, *2017*, 786–789.

[67] Roudias, M.; Gilbert, A.; Paquin, J.-F. *J. Org. Chem.* **2019**, *2019*, 6655–6665.

2.7: **2.14b** (3.6 g, 28 mmol, 1.0 equiv) was dissolved in DCM (35 mL), and $(COCl)_2$ (3.0 mL, 35 mmol, 1.2 equiv) was added dropwise. 2-4 drops of DMF were then added and the mixture was left to stir at room temperature for 2 hours. Once bubbling had ceased (approx. 2 hr), the reaction mixture was then concentrated under reduced pressure, and the brown oily residue was dissolved in THF (60 mL) and cooled to 0 °C. *N*-Hydroxyphthalimide (5.22 g, 32 mmol, 1.10 equiv), and DMAP[64] (0.35 g, 2.9 mmol, 0.1 equiv) were added, followed by dropwise addition of NEt_3 (4.5 mL, 32 mmol, 1.1 equiv). The reaction mixture was warmed slowly to room temperature and stirred for 2 hours before being quenched with 1M HCl and extracted with EtOAc (x2). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude brown solid was suspended in $CHCl_3$, sonicated for 2 minutes before being passed through a plug of celite (eluting with $CHCl_3$) to remove excess *N*-hydroxyphthalimide, and finally concentrated under reduced pressure. The crude material was then passed through a short pad of silica gel eluting with dichloromethane (200 – 300 mL), followed by 1.5% MeOH in DCM (100 mL)[65] and concentrated under reduced pressure to afford 4.34 g (55% yield) of **2.7** a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.99–7.78 (m, 4H), 5.94 (ddt, J = 17.1, 10.2, 7.1 Hz, 1H), 5.51–5.34 (m, 1H), 3.98 (t, J = 6.6 Hz, 1H), 2.98–2.83 (m, 2H).**^{13}C NMR (**101 MHz, $CDCl_3$, 298 K): δ_C 162.6, 160.9, 135.0, 129.8, 128.5, 124.2, 121.5, 113.8, 35.5, 34.1.



Ethyl 2-cyano-4-phenylbutanoate (**2.9**): Ethylcyanoacetate (32 mL, 0.30 mol, 3.0 equiv) was added to a suspension of K_2CO_3 (24.9 g, 180 mmol, 1.80 equiv) in acetonitrile (200 mL) followed by a portion of (2-bromoethyl)benzene (6.9 mL, 50 mmol, 0.5 equiv) added dropwise. After near complete consumption of the alkyl bromide (as determined by ^{1}H NMR), another portion of (2-bromoethyl)benzene (6.9 mL, 50 mmol, 0.5 equiv)) was added. Upon complete consumption of the alkyl bromide (approx. 7 days), the reaction mixture was poured over 1M HCl, and extracted with EtOAc (x3). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was distilled to

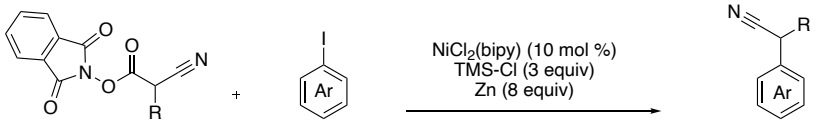
remove most of the ethylcyanoacetate and purified by column chromatography on silica gel (slow gradient 0–20% EtOAc in hexanes) to afford 11.7 g (54% yield) of **2.9**as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K): δ_H 5.87–5.21 (m, 1H), 5.33–5.18 (m, 2H), 4.26 (q, *J* = 7.1 2H), 3.55 (dd, *J* = 7.5, 6.1 Hz, 1H), 2.76 – 2.61 (m, 2H), 1.31 (t, *J* = 7.1, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K): δ_C 165.5, 131.3, 120.0, 116.0, 62.8, 37.4, 33.8, 13.9. NMR data is consistent with previous literature reports.[66]

2-Cyano-4-phenylbutanoic acid (2.14c): **2.9** (5.0 g, 1.0 mmol, 1.0 equiv) was dissolved in MeOH (23 mL) and water (23 mL) and cooled to 0°C. LiOH (52.7 mg, 2.20 mmol, 2.20 equiv) was added in one portion and the mixture was warmed slowly to room temperature. Upon completion (as determined by TLC, approx. 1 hr), the reaction mixture was quenched with 1M HCl, and extracted with EtOAc (x3). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to yield to afford 155 mg (82% yield) of **2.14b** as a yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K): δ_H 5.90–5.79 (m, 1 H), 5.33–5.27 (m, 2H), 3.66 (dd, *J* = 7.5, 6.0 Hz, 1H), 2.79–2.67 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K): δ_C 170.2, 130.8, 120.5, 115.3, 37.4, 33.6. NMR data is consistent with previous literature reports. NMR data is consistent with previous literature reports.[66]

2.6: **2.14c** (7.6 g, 49 mmol, 1.0 equiv) was dissolved in DCM (48 mL), and $(COCl)_2$ (4.1 mL, 48 mmol, 1.2 equiv) was added dropwise. 2-4 drops of DMF were then added and the mixture was left to stir at room temperature for 2 hours. Once bubbling had ceased (approx. 2 hr), the reaction mixture was then concentrated under reduced pressure, and the brown oily residue was dissolved in THF (80 mL) and cooled to 0 °C. *N*-Hydroxyphthalimide (7.22 g, 44.0 mmol, 1.10 equiv), and DMAP[64] (0.49 g, 4.0 mmol, 0.10 equiv) were added, followed by dropwise addition of NEt_3 (6.1 mL, 44 mmol, 1.1 equiv). The reaction mixture was warmed slowly to room temperature and stirred for 2 hours before being quenched with 1M HCl and extracted with EtOAc (x2). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude brown solid was suspended in $CHCl_3$, sonicated for 2 minutes before being passed through a plug of celite (eluting with $CHCl_3$) to remove excess N-hydroxyphthalimide, and finally concentrated under reduced pressure. The crude material was then passed through a short pad of silica gel eluting with dichloromethane (200 – 300 mL),

followed by 1.5% MeOH in DCM (100 mL)[65] and concentrated under reduced pressure to afford 5.46 g (41% yield) of **2.7** a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.95–7.80 (m, 4H), 7.39–7.27 (m, 5H), 3.86 (d, J = 7.1 Hz, 1H), 3.11–2.89 (m, 2H), 2.48 (dt, J = 8.1, 7.1 Hz, 2H). **^{13}C NMR (**126 MHz, $CDCl_3$, 298 K): δ_C 163.3, 161.0, 138.3, 135.1, 128.9, 128.6, 128.5, 127.0, 124.3, 114.1, 34.6, 32.3, 32.1.

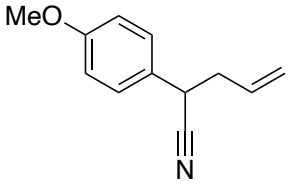
4.4 General Procedure for Ni-Catalyzed Reductive Decarboxylative Cross-Coupling



(2.18) **(2.19)** **(2.20)**

General Procedure A: Representative procedure for 0.20-mmol scale reaction. An 8 mL threaded culture tube was equipped with a stir bar, fit with a size 19 rubber septum, flame dried under vacuum, and cooled under N_2. NHPI ester (**2.18**) (0.30 mmol, 1.5 equiv), aryl iodide (**2.19**) (0.20 mmol, 1.0 equiv), Zn dust (105 mg, 1.60 mmol, 8.00 equiv), and $NiCl_2$bpy (5.8 mg, 0.020 mmol, 0.10 equiv) were added on the bench top. The tube was sealed with a septum and electrical tape and evacuated and backfilled with N_2 (x3). A solution of TMS-Cl (72 μL, 0.60 mmol, 3.0 equiv) in DMA (1.0 mL, 0.2 M) was then added to the tube containing the solids in one portion. After 1 h, the reaction was exposed to air, diluted with EtOAc, quenched with 1M HCl, and extracted with EtOAc (x2). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford the desired secondary α-aryl nitrile.

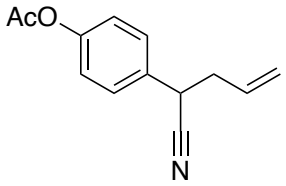
4.5 Synthesis of Secondary α-Aryl Nitriles



2.20l

2-(4-Methoxyphenyl)pent-4-enenitrile (2.20l):

According to General Procedure A, **2.20l** was prepared using the following amounts of reagent: NHPI ester **2.7** (81 mg, 0.30 mmol, 1.5 equiv), 4-iodoanisole (46.8 mg, 0.200 mmol, 1.00 equiv), Zn dust (104 mg, 1.60 mmol, 8.00 equiv), $NiCl_2$bpy (5.8 mg, 0.020 mmol, 0.10 equiv), and a solution of TMS-Cl (72 μL, 0.60 mmol, 3.0 equiv) in DMA (1.0 mL, 0.2 M). The crude residue was purified by flash column chromatography on silica gel (slow gradient of 0 – 10% EtOAc/Hexanes) to afford 24.8 mg of **2.20l** as a yellow oil (49%). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.28–7.23 (m, 2H), 6.93–6.87 (m, 2H), 5.79 (dd, J = 17.0, 9.9 Hz, 1H), 5.21–5.13 (m, 2H), 3.81 (s, 3H), 2.68–2.53 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K): δ_C 159.3, 132.7, 128.4, 127.1, 120.5, 119.2, 114.3, 55.3, 39.9, 36.7. $\mathbf{R}_f$ = 0.29 (9:1 Hexanes:EtOAc) $KMnO_4$ NMR data is consistent with previous literature reports.[68]



2.20k

2-(4-Acetylphenyl)pent-4-enenitrile (2.20k): According to General Procedure A, **2.20k** was prepared using the following amounts of reagent: NHPI ester **2.7** (81 mg, 0.30 mmol, 1.5 equiv), 4-iodophenyl acetate (52.4 mg, 0.200 mmol, 1.00 equiv), Zn dust (104 mg, 1.60 mmol, 8.00 equiv), $NiCl_2$bpy (5.8 mg, 0.020 mmol, 0.10 equiv), and a solution of TMS-Cl (72 μL, 0.60 mmol, 3.0 equiv) in DMA (1.0 mL, 0.2 M). The crude was purified by flash column chromatography on silica gel (slow gradient of 0 – 20% EtOAc/Hexanes) to afford 16.5 mg of **2.20k** as a thick white oil (41% yield). **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K): δ_H 7.99–7.93 (m, 2H), 7.46–7.41 (m, 2H), 5.82–5.71 (m, 1H), 5.21–5.13 (m, 2H), 3.93 (dd, J = 7.6, 6.7 Hz, 1H), 2.67–2.62 (m, 2H), 2.60 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K): δ_C 140.1, 136.8, 131.9, 129.0, 127.6, 123.5, 119.9, 119.6 39.5, 37.3, 26.6. $\mathbf{R}_f$ = 0.18 (9:1 Hexanes:EtOAc) $KMnO_4$

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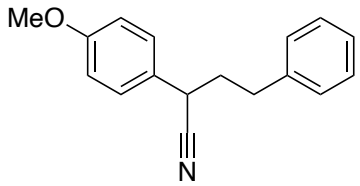
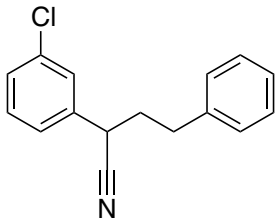
[68] Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070–1071.



2.20h

2-(4-methoxyphenyl)-4-phenylbutanenitrile (2.20h): According to General Procedure A, **2.20h** was prepared using the following amounts of reagent: NHPI ester **2.6** (100 mg, 0.30 mmol, 1.5 equiv), 4-iodoanisole (46.8 mg, 0.200 mmol, 1.00 equiv), Zn dust (104 mg, 1.60 mmol, 8.00 equiv), $NiCl_2$bpy (5.8 mg, 0.020 mmol, 0.10 equiv), and a solution of TMS-Cl (72 μL, 0.60 mmol, 3.0 equiv) in DMA (1.0 mL, 0.2 M). The crude was purified by flash column chromatography on silica gel (slow gradient of 0 – 10% EtOAc/Hexanes) to afford 24.8 mg of **2.20h** as a yellow oil (49% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.36–7.30 (m, 2H), 7.28–7.20 (m, 5H), 6.95–6.90 (m, 2H), 3.82 (s, 3H), 3.71 (dd, J = 8.8, 6.2 Hz, 1H), 2.87–2.74 (m, 2H), 2.35–2.10 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K): δ_C 159.3, 139.9, 128.6, 128.4, 128.4, 127.6, 126.4, 120.9, 114.5, 55.3, 37.3, 35.7, 33.0. NMR data is consistent with previous literature reports.[69]



2.20i

2-(3-chlorophenyl)-4-phenylbutanenitrile (2.20i): According to General Procedure A, **2.20i** was prepared using the following amounts of reagent: NHPI ester **2.6** (100 mg, 0.30 mmol, 1.5 equiv), 1-chloro-3-iodobenzene (25 μL, 0.20 mmol, 1.0 equiv), Zn dust (104 mg, 1.60 mmol, 8.00 equiv), $NiCl_2$bpy (5.8 mg, 0.020 mmol, 0.10 equiv), and a solution of TMS-Cl (72 μL, 0.60 mmol, 3.0 equiv) in DMA (1.0 mL, 0.2 M). The crude was purified by flash column

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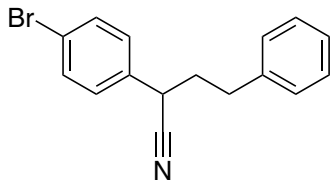
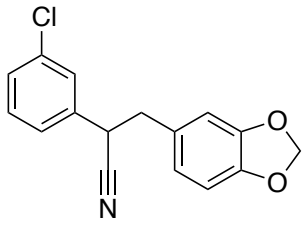
[69] Wu, G.; Deng, Y.; Wu, C.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 10510–10514.

chromatography on silica gel (slow gradient of 0 – 10% EtOAc/Hexanes) to afford 28.2 mg of **2.20i** as a clear oil (55% yield). **^{1}H NMR** (399 MHz, $CDCl_3$, 298 K): δ_H 7.30–7.24 (m, 5H), 7.22–7.12 (m, 4H), 3.66 (dd, *J* = 9.2, 6.0 Hz, 1H), 2.85–2.70 (m, 2H), 2.27–2.03 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 139.4, 137.5, 135.0, 130.4, 128.7, 128.4, 128.4, 127.5, 126.6, 125.4, 119.9, 37.2, 36.2, 32.9. $\mathbf{R}_f$ = 0.58 (9:1 Hexanes:EtOAc) $KMnO_4$



2.20j

2-(4-bromophenyl)-4-phenylbutanenitrile (2.20j): According to General Procedure A, **2.20j** was prepared using the following amounts of reagent: NHPI ester **2.6** (100 mg, 0.30 mmol, 1.5 equiv), 1-bromo-4-iodobenzene (56 mg, 0.20 mmol, 1.0 equiv), Zn dust (104 mg, 1.60 mmol, 8.00 equiv), $NiCl_2$bpy (5.8 mg, 0.020 mmol, 0.10 equiv), and a solution of TMS-Cl (72 μL, 0.60 mmol, 3.0 equiv) in DMA (1.0 mL, 0.2 M). The crude was purified by flash column chromatography on silica gel (slow gradient of 0 – 10% EtOAc/Hexanes) to afford 28.9 mg of **2.20j** as a clear oil (48% yield). **^{1}H NMR** (500 MHz $CDCl_3$, 298 K): δ_H 7.55–7.49 (m, 2H), 7.36–7.30 (m, 2H), 7.27–7.23 (m, 1H), 7.21–7.18 (m, 3H), 3.71 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.87–2.75 (m, 2H), 2.35–2.10 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K): δ_C 139.5, 134.6, 132.3, 129.0, 128.7, 128.4, 126.6, 122.2, 120.1, 37.2, 36.0, 32.9. $\mathbf{R}_f$ = 0.45 (9:1 Hexanes:EtOAc) $KMnO_4$

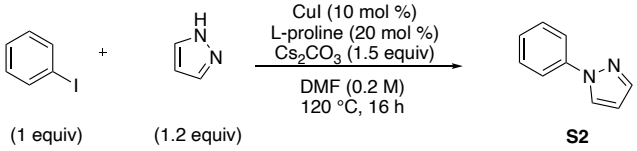


2.20m

3-(benzo[*d*][1,3]dioxol-5-yl)-2-(3-chlorophenyl)propanenitrile (2.20m): According to General Procedure A, **3m** was prepared using the following amounts of reagent: NHPI ester **2.8** (109 mg,

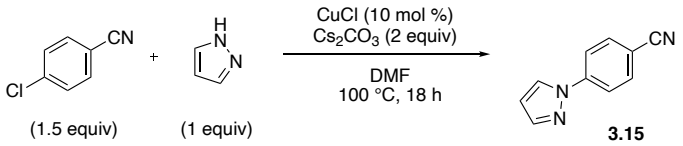
0.300 mmol, 1.50 equiv), 1-chloro-3-iodobenzene (25 µL, 0.20 mmol, 1.0 equiv), Zn dust (104 mg, 1.60 mmol, 8.00 equiv), $NiCl_2$bpy (5.8 mg, 0.020 mmol, 0.10 equiv), and a solution of TMS-Cl (72 µL, 0.60 mmol, 3.0 equiv) in DMA (1.0 mL, 0.2 M).The crude was purified by flash column chromatography on silica gel (slow gradient of 0 – 10% EtOAc/Hexanes) to afford 13.1 mg of **2.20m** as a white solid (23% yield). **^{1}H NMR** (500 MHz $CDCl_3$, 298 K): δ_H 7.35–7.25 (m, 3H), 7.18–7.12 (m, 1H), 6.73 (d, J = 7.9 Hz, 1H), 6.63–6.56 (m, 2H), 5.95 (s, 2H), 3.93 (dd, J = 8.3, 6.4 Hz, 1H), 3.14–3.00 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K): δ_C 147.8, 147.0, 136.9, 134.9, 130.2, 129.4, 128.5, 127.6, 125.7, 122.5, 119.7, 109.4, 108.4, 101.1, 41.7, 39.6, 29.7. $\mathbf{R_f}$ = 0.21 (9:1 Hexanes:EtOAc) $KMnO_4$

4.6 Synthesis of Benzonitrile Ligand

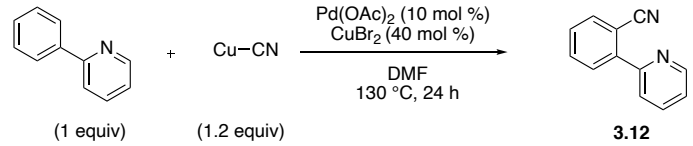


1-Phenyl-1H-pyrazole (S2): To a 100-mL flask were added iodobenzene (0.55 mL, 5.0 mmol, 1.0 equiv), pyrazole (0.41g, 6.0 mmol, 1.2 equiv), copper (I) iodide (95 mg, 0.50 mmol, 10 mol%), L-proline (0.12 g, 1 mmol, 20 mol%), Cs_2CO_3 (2.4 g, 7.5 mmol, 1.5 equiv), and DMF (25 mL, 0.20 M). The reaction was sealed under nitrogen and left to stir at 120 °C for 16 h. The solution was cooled to r.t., quenched with NH_4Cl, and extracted with EtOAc (x3). The organic fractions were combined, washed with brine (x1), dried over $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (gradient, 0-15% EtoAc/hexanes) to yield 0.21 g of **S2** as a dark brown oil (30% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298K): δ_H 7.76 (ddd, J = 7.8, 1.6, 0.5 Hz, 1H), 7.66 (ddd, J = 8.1, 7.6, 1.6 Hz, 1H), 7.46–7.36 (m, 2H), 7.13–7.09 (m, 2H), 6.42–6.40 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$, 298K): δ_C 141.0, 140.2, 129.4, 126.7, 126.4, 119.2, 107.6. $\mathbf{R_f}$ = 0.4 (8:2 hexanes/EtOAc; UV/$KMnO_4$) NMR data is consistent with previous literature reports.[70]

[70] Gair, J. J.; Grey, R. L.; Giroux, S.; Brodney, M. A. *Org. Lett.* **2019**, *21*, 2482–2487.

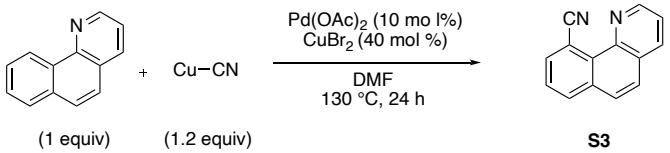


4-(1-Hpyrazol-1yl)benzonitrile (3.15): To a 50-mL flask were added 4-chlorobenzonitrile (2.3 g, 7.5 mmol, 1.5 equiv), pyrazole (0.34 g, 5.0 mmol, 1.0 equiv), copper chloride (50 mg, 0.50 mmol, 0.10 equiv), Cs_2CO_3 (3.3 g, 10 mmol, 2.0 equiv), and DMF (25 mL). The reaction was sealed under nitrogen and heated to 100 °C for 18h. The reaction was diluted with DCM, filtered through a pad of silica, extracted with brine (x3), dried over $MgSO_4$, and concentrated. The reaction was purified by column chromatography (gradient from 100% hexanes to 3:1:7 EtOAc/DCM/hexanes) to yield 0.82 g of **3.15** as a white solid (96% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298K): δ_H 7.99 (dd, J = 2.6, 0.6 Hz, 1H), 7.88–7.82 (m, 2H), 7.78–7.73 (m, 3H), 6.54 (dd, J = 2.6, 1.8 Hz, 1H) **^{13}C NMR** (100 MHz, $CDCl_3$, 298K): δ_C 142.6, 142.4, 133.6, 126.7, 118.9, 118.3, 109.6, 109.0. **R_f** = 0.39 (7:2:1 hexanes:EtOAc:DCM; UV) NMR data is consistent with previous literature reports.[58]

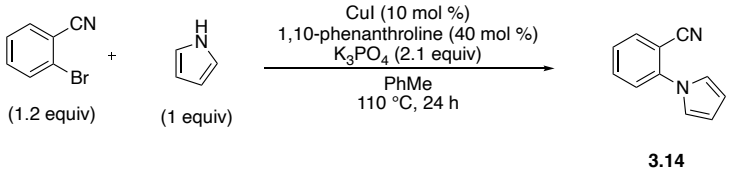


2-(Pyridine-2-yl)benzonitrile (3.12): To a 100-mL flask was added 2-phenylpyridine (1.4 mL, 10 mmol, 1.0 equiv), copper (I) cyanide (1.1 g, 12 mmol, 1.2 equiv), $Pd(OAc)_2$ (0.23 g, 1.0 mmol, 10 mol%), $CuBr_2$ (0.89 g, 4.0 mmol, 40 mol%), and DMF (50 mL). The flask was equipped with a condenser and heated at 130 °C (open to air) for 24 h. The solution was quenched with $NaHCO_3$, extracted with EtoAC (x3) and washed with brine (x3), dried over $MgSO_4$, and concentrated. The crude residue was purified with column chromatography (gradient, 0-50% EtOAc/DCM/hexanes; 3:2:5 as a final gradient) to yield 0.77 g of a yellow solid (42% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298K): δ_H 8.79 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H), 7.88 – 7.76 (m, 4H), 7.70 (td, J = 7.7, 1.4 Hz, 1H), 7.51 (td, J = 7.6, 1.3 Hz, 1H), 7.36 (ddd, J = 7.4, 4.8, 1.3 Hz, 1H) **^{13}C NMR** (100 MHz, $CDCl_3$, 298K): δ_C 148.5, 144.5, 136.3, 135.7, 134.3,

134.1, 132.7, 127.4, 127.2, 127.1, 127.00, 123.0. $\mathbf{R_f}$ = 0.32 (5:3:2 hexanes:EtOAc:DCM; UV). NMR data is consistent with previous literature reports.[71]



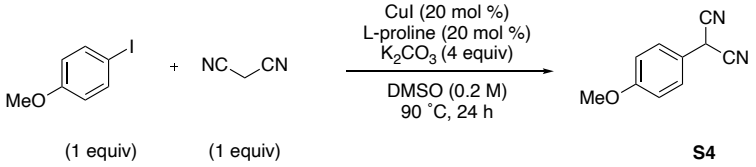
Benzo[h]quinoline-10-carbonitrile (S3): To a 50-mL flask were added benzo[h]quinolone (0.34 g, 2.0 mmol, 1 equiv), copper (I) cyanide (0.20 g, 2.2 mmol, 1.2 equiv), $Pd(OAc)_2$ (45 mg, 0.20 mmol, 10 mol%), copper (II) bromide (0.19 g, 0.44 mmol, 40 mol%), and DMF (10 mL). The flask was equipped with a condenser and was left open to air at 130 °C for 24 h. The solution was quenched with $NaHCO_3$, extracted with EtOAc (x3) and washed with brine (x3), dried over $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (gradient, 0-50% EtOAc/DCM/hexanes; 3:2:5 as a final gradient) to yield 0.77 g of a yellow solid (42% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298K): δ_H 9.15 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.24 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.16 (ddd, *J* = 15.5, 7.7, 1.3 Hz, 2H), 7.83 (q, *J* = 8.9 Hz, 2H), 7.75 (dd, *J* = 8.1, 7.4 Hz, 1H), 7.64 (dd, *J* = 8.1, 4.3 Hz, 1H) **^{13}C NMR** (100 MHz, CDCl3, 298K): δ_C 148.5, 144.5, 136.2, 135.7, 134.1, 132.7, 130.8, 127.3, 127.2, 127.1, 127.0, 123.0, 120.7, 109.0. $\mathbf{R_f}$ = 0.29 (7:2:1 hexanes:EtOAc:DCM; UV)



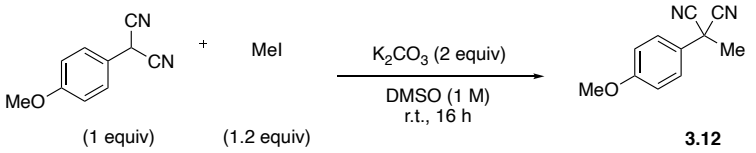
2-(1-*H*-Pyrrol-1-yl)benzonitrile (3.14): To a flame-dried 100-mL flask was added 2-bromobenzonitrile (2.2 g, 12 mmol, 1.2 equiv), pyrrole (0.69 mL, 10 mmol, 1.0 equiv), copper(I) iodide (0.19 g, 1.0 mmol, 10 mol %), 1,10-phenanthroline (0.72 g, 4.0 mmol, 40 mol %), and potassium phosphate (4.5 g, 21 mmol, 2.1 equiv). The flask was sealed and evacuated and backfilled with N_2 (×3) and PhMe (25 mL, 0.40 M) was added. The reaction was stirred at 110

[71] Jia, X.; Yang, D.; Zhang, S.; Cheng, J. *Org. Lett.* **2009**, *11*, 4716–4719.

ºC for 24 h. The solution was cooled to r.t., diluted with EtOAc, filtered through Celite, and the Celite pad was washed with EtOAc (×1). The filtrate was concentrated and the crude residue was purified by flash column chromatography (gradient of 0–30% EtOAc/hexanes) to yield 1.1 g of **3.14** as a light yellow oil (65% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.76 (ddd, J = 7.8, 1.6, 0 Hz, 1H), 7.66 (ddd, J = 8.1, 7.6, 1.6 Hz, 1H), 7.46–7.36 (m, 2H), 7.13–7.09 (m, 2H), 6.42–6.40 (m, 2H) **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 134.5, 134.3 133.9, 133.2, 127.6, 126.5, 125.1, 121.1, 116.9, 111.2, 106.9. **R_f** = 0.4 (8:2 hexanes/EtOAc; UV/$KMnO_4$) NMR data is consistent with previous literature reports.[72]



2-(4-Methoxyphenyl)malononitrile (S4): To a 250-mL flask was added malononitrile (2.0 g, 30 mmol, 1.0 equiv), copper iodide (0.38 g, 2.0 mmol, 20 mol%), L-proline (0.23 g, 4.0 mmol, 20 mol %), K_2CO_3 (5.5 g, 80 mmol, 4.0 equiv), 4-iodoanisole (2.3g, 10 mmol, 1.0 equiv), and DMSO (50 mL, 0.20 M). The flask was backfilled with N_2 (x3), sealed with a septum and electrical tape and left to stir at 90 °C for 16 h. The solution was cooled to r.t., quenched with NH_4Cl, and extracted with EtOAc (x3). The organic fractions were combined, washed with brine (x3), dried over $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (gradient, 0-20% EtOAc/hexanes) to yield 1.0 g (87% yield) of a pink solid pink solid. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.44–7.39 (m, 2H), 6.99 (d, J = 8.8 Hz, 2H), 5.00 (s, 1H), 3.85 (s, 3H) **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 161.01, 128.57, 117.83, 115.36, 111.96, 55.51, 27.45. NMR data is consistent with previous literature reports.[73]



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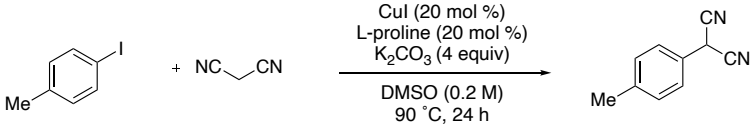
[72] Patra, T.; Agasti, S.; Akanksha; Maiti, D. *Chem. Commun.* **2013**, *49*, 69–71

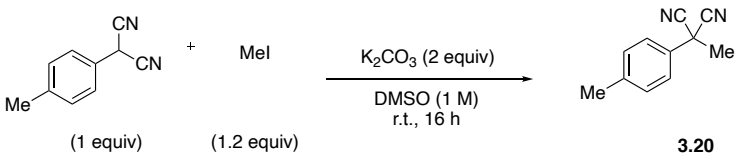
[73] Peterson, J. P.; Geraskina, M. R.; Zhang, R.; Winter, A. H. *J. Org. Chem.* **2017**, *82*, 6497–6501.

2-(4-Methoxyphenyl)-2-methylmalononitrile (3.12): To a 25-mL flask were added 2-(4-methoxyphenyl)malononitrile (0.8 g, 4.6 mmol, 1 equiv), K_2CO_3 (1.3 g, 9.2 mmol, 2.0 equiv), and DMSO (4.6 mL, 1.0 M). Methyl iodide (0.34 mL, 5.5 mmol, 1.2 equiv) was then added to the reaction. The reaction was left to stir at r.t. for 2 h and then quenched with NH_4Cl, and extracted with EtOAc (x3). The organic fractions were combined, washed with brine (x3), dried over $MgSO_4$, and concentrated to yield 0.85 g of a brown solid (99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.49 (d, 2H), 6.99 (d, 2H), 3.84 (s, 3H), 2.09(s, 3H) **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 160.6. 126.6, 124.8, 115.8, 115.0, 113.3, 55.5, 29.3.

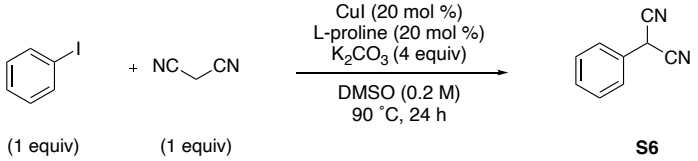


2-(*p*-Tolyl)malononotrile (S5): To a 100-mL flask was added malononitrile (0.99 g, 15 mmol, 1.0 equiv), copper iodide (0.19 g, 1.0 mmol, 20 mol %), L-proline (0.12 g, 1.0 mmol, 20 mol %), K_2CO_3 (0.55 g, 20 mmol, 4.0 equiv), 4-iodotoluene (1.1 g, 5.0 mmol, 1.0 equiv), and DMSO (25 mL, 0.20 M). The reaction was sealed with electrical tape and left to stir at 90 °C for 24 h. The solution was cooled to r.t., quenched with NH_4Cl, and extracted with EtOAc (x3). The organic fractions were combined, washed with brine (x3), dried over $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (gradient, 0-10% EtOAc/DCM/hexanes; 9:1:1) to yield 0.28 g of a yellow oil (36%). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.38 (d, J = 8.1 Hz, 2H), 7.30 (d, 2H), 5.01 (s, 1H), 2.40 (s, 3H). NMR data is consistent with previous literature reports.[74]

[74] Kawase, T.; Wakabayashi, M.; Takahashi, C.; Oda, M. *Chem. Lett.* **1997**, *26*, 1055–1056.

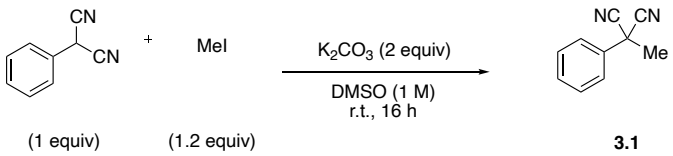


2-Methyl-2-(*p*-tolyl)malononitrile (3.20): To a 25-mL flask was added 2-(*p*-tolyl)malononitrile (0.2 g, 1.3 mmol, 1.0 equiv), K_2CO_3 (0.36 g, 2.6 mmol, 2.0 equiv), and DMSO (1.6 mL, 1.0 M). Methyl iodide (0.10 mL, 1.5 mmol, 1.2 equiv) was added to the reaction. The reaction was left to stir for 2 h and then quenched with NH_4Cl, and extracted with EtOAc (x3). The organic fractions were combined, washed with brine (x3), dried over $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (gradient, 0-10% EtOAc/DCM/hexanes; 9:1:1) to yield 0.22 g of **3.20** as an orange oil (99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.49–7.43 (m, 2H), 7.29 (m, 2H), 2.39 (s, 3H), 2.09 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 140.2, 130.4, 130.1, 125.1, 115.8, 36.1, 29.3, 21.0. NMR data is consistent with previous literature reports.[74]

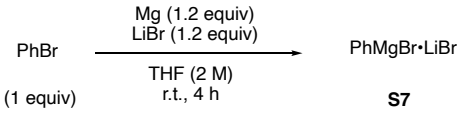


2-Phenylmalononitrile (S6): Copper iodide (1.9 g, 10 mmol, 20 mol %), L-proline (1.2 g, 10 mmol, 20 mol %), and potassium carbonate (28.0 g, 200 mmol, 4.00 equiv) were added to a flame-dried 500-mL flask. Then, malononitrile (9.90 g, 150 mmol, 3.00 equiv) was added and, swiftly, the flask was sealed, evacuated and backfilled with N_2 (×3), and DMSO was added (250 mL, 0.20 M). Iodobenzene (5.6 mL, 50 mmol, 1.0 equiv) was added and the reaction was stirred at 90 ºC for 72 h under nitrogen. The flask was cooled to 0 ºC, opened to air, and 1 M HCl was added to bring the solution to pH 2–3 (there is vigorous gas formation if HCl is added too quickly). The solution was extracted with EtOAc (×3) and the organic fractions were combined, washed with brine (×3), dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (gradient of 10–20% EtOAc/hexanes) to yield 4.1 g (65% yield) of **S6** as an off-white solid. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.52–7.51 (m, 5H), 5.06 (s,

1H). **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K: δ_C 130.4, 130.0, 127.2, 126.2, 111.7, 28.1. NMR data is consistent with previous literature reports.[75]



2-Methyl-2-phenylmalononitrile (3.1): To a 25-mL flask was added malononitrile **S8** (500 mg, 3.50 mmol, 1.00 equiv). The flask was evacuated and backfilled with N_2 (×3) and DMSO (3.5 mL, 1.0 M; reagent grade) was added. Iodomethane (0.26 mL, 4.2 mmol, 1.2 equiv) was added followed by potassium carbonate (967 g, 7.00 mmol, 2.00 equiv). The reaction was stirred at r.t. for 2 h. The reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc (×3). The organic fractions were combined, washed with brine (×3), dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (gradient of 5–20% EtOAc/hexanes) to yield 0.440 g (81% yield) of **3.1** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.63–7.44 (m, 5H), 2.12 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 133.1, 130.0, 129.8, 125.3, 115.6, 36.4, 29.4. NMR data is consistent with previous literature reports.[57]



Phenylmagnesium bromide–lithium bromide complex (S7): To a 50-mL round-bottom flask with stir bar was added magnesium turnings (1.5 g, 60 mmol, 1.2 equiv). The flask was flame-dried and cooled under vacuum and then backfilled with N_2. The flask was sealed, brought into a glovebox, and lithium bromide (5.2 g, 60 mmol, 1.2 equiv) was added. The flask was again sealed, removed from the glovebox, and THF (30 mL, 1.67 M) was added. The solution was stirred and the magnesium was activated with 1,2-dibromoethane (ca. 0.050 mL, 0.60 mmol). Bromobenzene (5.3 mL, 50 mmol, 1.0 equiv) was added dropwise until initiation was observed

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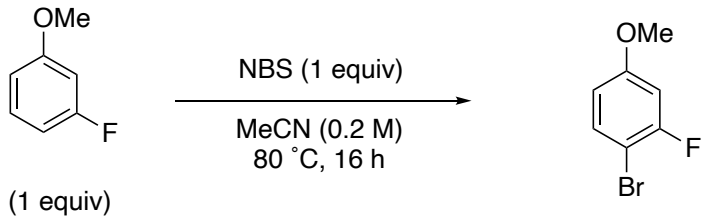
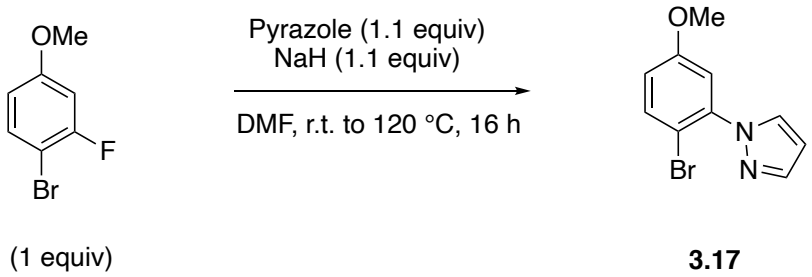
[75] Kawase, T.; Wakabayashi, M.; Takahashi, C.; Oda, M. *Chem. Lett.* **1997**, *26*, 1055–1056.

(ca. 0.50 mL added). The remainder of bromobenzene was added portionwise over 2 h at r.t. under N_2. The reaction was then stirred for an additional 4 h at r.t. under N_2 and was allowed to sit for 1 h before use. An aliquot was analyzed by GC-MS to confirm full consumption of bromobenzene. The solution was titrated with I_2 to give a concentration of 1.28 M (38 mmol, 76%). The solution was sealed using a septum covered with electrical tape and was stored in a fumehood at r.t. Titration (two trials) was performed immediately before use. Phenylmagnesium bromide–lithium bromide complex was prepared fresh every month.



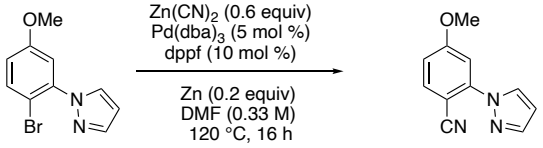
3.16

1-Bromo-2-fluoro-4-methoxybenzene (3.16): To a flame-dried 100 mL flask was added *N*-bromosuccinimide (2.0 g, 11 mmol, 1.0 equiv) and the flask was sealed with a septum and evacuated and backfilled with N_2 (×3). MeCN (30 mL, 0.20 M) was added followed by 3-fluoroanisole (1.1 mL, 10 mmol, 1.0 equiv). The reaction was left to stir at 80 °C for 16 h. The reaction was cooled to r.t., opened to air, and quenched with sat. aq. NH_4Cl. The solution was extracted with EtOAc (×3) and the organic fractions were combined, washed with brine (×1), dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (gradient of 0–3% EtOAc/hexanes) to yield 1.1 g of a colourless oil (85% yield). Approximately 20% of 1,5-dibromo-2-fluoro-4-methoxybenzene (dibrominated species) remained in the isolated product. **^{1}H NMR** (500 MHz, $CDCl_3$, 298 K): δ_H 7.40 (dd, J = 8.9, 8.0 Hz, 1H), 6.69 (dd, J = 10.4, 2.8 Hz, 1H), 6.66–6.55 (m, 2H), 3.79 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K): δ_C 160.4, 158.5, 133.3, 133.2, 111.3, 111.3, 111.3, 102.9, 99.3, 55.7. **^{19}F NMR** (375 MHz, $CDCl_3$, 298 K) δ_F -105.35 (dd, *J* = 10.7, 7.8 Hz).



(1 equiv) **3.17**

1-(2-Bromo-5-methoxyphenyl)-1*H*-pyrazole (3.17): To a flame-dried 50-mL flask with stir bar was added sodium hydride (0.68 g of a 60% w/w dispersion in mineral oil, 6.5 mmol, 1.1 equiv) and DMF (100 mL). Pyrazole (0.68 g, 6.1 mmol, 1.1 equiv) was dissolved in DMF (25 mL) and slowly added to the flask. The flask was sealed with a septum, evacuated and backfilled with N_2 (×3), equipped with a balloon of Ar and DMF (125 mL) was added. The reaction was stirred at r.t. for 30 min. Then, 1-bromo-2-fluoro-4-methoxybenzene (5.0 mL of a 1.82 M solution in DMF, 9.1 mmol, 1.0 equiv) was added. The reaction was stirred at 120 ºC for 16 h. The reaction was cooled to r.t., opened to air, and quenched with sat. aq. NH_4Cl. The solution was extracted with EtOAc (×3) and the organic fractions were combined, washed with brine (×2), dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (gradient of 5–20% EtOAc/hexanes) to yield 1.2 g of a colourless oil (51% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.87–7.85 (m, 1H), 7.75 (d, J = 1.8 Hz, 1H), 7.55 (d, J = 8.9 Hz, 1H), 7.08 (d, J = 3.0 Hz, 1H), 6.85 (dd, J = 8.9, 3.0 Hz, 1H), 6.49–6.45 (m, 1H), 3.82 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 159.5, 140.8, 140.3 134.1, 131.3, 116.3, 113.3, 108.3, 106.5, 55.7.

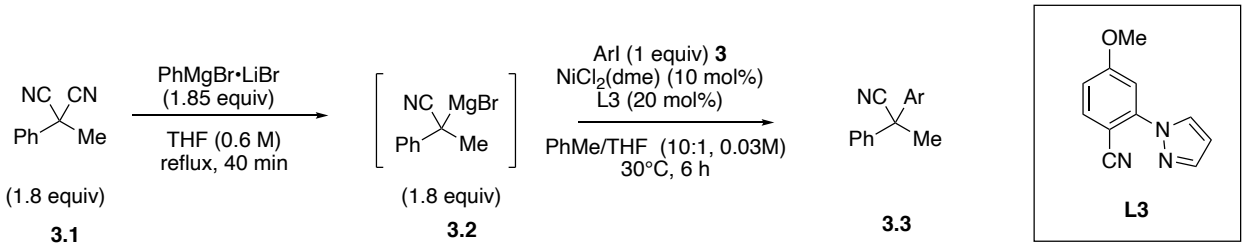


(1 equiv) **L3**

4-Methoxy-2-(1*H*-pyrazol-1-yl)benzonitrile (L3): To a flame-dried 25-mL round-bottom flask equipped with a stir bar were added zinc(II) cyanide (0.19 g, 1.6 mmol, 0.60 equiv), dipalladium(0) tris(dibenzylideneacetone) (0.12 g, 0.14 mmol, 5.0 mol %), dppf (0.15 g, 0.27 mmol, 10 mol %), and zinc(0) dust (35 mg, 0.54 mmol, 0.20 equiv). The flask was sealed, evacuated and backfilled with N_2 (×3), and 1-(2-bromo-5-methoxyphenyl)-1*H*-pyrazole (8.2 mL

of a 0.33 M solution in DMF, 2.7 mmol, 1.0 equiv) was added. The reaction was stirred at 120 °C for 16 h. The reaction was cooled to r.t., opened to air, and quenched with sat. aq. $NaHCO_3$. The solution was extracted with EtOAc (×3) and the organic fractions were combined, washed with H_2O (×1) and brine (×1), dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (gradient of 20–40% EtOAc/hexanes) to yield 0.23 g of a white solid (43% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 8.21 (d, J = 2.6 Hz, 1H), 7.80 (d, J = 1.8 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.33 (d, J = 2.5 Hz, 1H), 6.93 (dd, J = 8.7, 2.5 Hz, 1H), 6.54 (dd, J = 2.6, 1.8 Hz, 1H), 3.92 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 163.7, 142.1, 135.6, 129.7, 117.4, 114.0, 109.2, 108.4, 96.4, 95.0, 55.9.

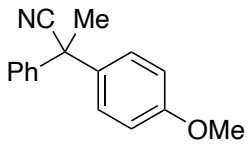
4.6.1 General Procedure for the Decyanation and Arylation Reaction



General Procedure B: *Step 1:* Nitrile α-anion solution was generally prepared in 10-fold excess, to run multiple cross-coupling reactions from a single stock solution. To a flame-dried 16-mL culture tube with a stir bar was added malononitrile **1** (7.2 mmol; 10×0.72 mmol, 10×1.8 equiv). The tube was sealed with a size 19 septum and electrical tape and was evacuated and backfilled with N_2 (×3). For a desired final nitrile α-anion solution concentration of 0.60 M, the total solution volume was calculated to be 12.0 mL. The required amount of phenylmagnesium bromide–lithium bromide complex was calculated to be 5.6 mL (5.6 mL of a 1.28 M solution in THF, 7.2 mmol; 10×0.72 mmol, 10×1.85 equiv). Thus, THF (6.4 mL) was added and the solution was stirred at r.t. Phenylmagnesium bromide–lithium bromide complex (6.4 mL) was added dropwise (total THF volume = 12.0 mL, 0.60 M). The solution was put into a pre-heated 70 ºC oil bath and was stirred at this temperature for 40 min (the total required nitrile transfer time may be longer depending on the substrate). The solution was removed from the oil bath and was quickly cooled to r.t. with a water bath. (N.B.: Nitrile α-anions sometimes displayed poor solubility and crashed out of solution if perturbed, so maintaining a smooth, high-rpm (>500 rpm) stir for nitrile transfer was optimal.)

Step 2: To a flame-dried 16-mL culture tube equipped with a stir bar was added **L3** (8.0 mg, 0.080 mmol, 20 mol %) and aryl iodide (if solid; 0.40 mmol, 1.0 equiv). The tube was sealed with a size 19 septum and electrical tape and was evacuated and backfilled with N_2 (×3). The tube was brought into a glovebox and $NiCl_2$(dme) (8.8 mg, 0.040 mmol, 10 mol %) was added. The tube was again sealed with a septum and electrical tape and was removed from the glovebox. PhMe (degassed; 12.0 mL) was added, followed by aryl iodide (if liquid; 0.40 mmol, 1.0 equiv). The solution was stirred for 20 s at r.t. to evenly mix the reaction components. Then, while stirring, nitrile α-anion (1.2 mL of a 0.60 M solution in THF, 0.72mmol, 1.8 equiv) was added (total reaction volume = 13.2 mL of a 10:1 PhMe/THF mixture, 0.030 M). The solution was stirred for another 20 s at r.t., during which time catalyst activation was achieved. During catalyst activation, the solution goes from yellow to red to black in a time-period of about 15 s. Immediately, the reaction was placed in a pre-heated 30 ºC oil bath and was stirred for 6 h at 1200 rpm (a high stir speed is required for efficient mixing of the dilute solution). The reaction was cooled to r.t., opened to air, and quenched with sat. aq. NH_4Cl. The solution was extracted with EtOAc (×2), and the organic fractions were combined, filtered through a plug of $MgSO_4$ and Celite, and concentrated. The crude residue was purified by flash column chromatography to yield α-arylnitrile.

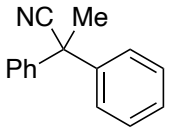
4.6.2 Synthesis of Tertiary α-aryl nitriles



3.3a

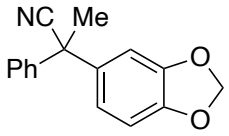
2-(4-Methoxyphenyl)-2-phenylpropanenitrile (3.3a): According to General Procedure B, **3.3a** was prepared using the following amounts of reagent: **L3** (15.9 mg, 0.080 mmol, 20 mol %), 4-iodoanisole (93.6 mg, 0.200 mmol, 1.00 equiv), $NiCl_2$(dme) (8.8 mg, 0.020 mmol, 10 mol %), PhMe (degassed; 12.0 mL), and nitrile α-anion (1.2 mL of a 0.60 M solution in THF, 0.72 mmol, 1.8 equiv). The crude material was purified by flash column chromatography on silica gel (slow gradient of 0 – 10% EtOAc/Hexanes) to afford 58 mg of white solid (61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.41–7.21 (m, 7H), 6.91–6.85 (m, 2H), 3.81 (s, 3H), 2.07 (s, 3H). **^{13}C**

NMR (100 MHz, $CDCl_3$, 298 K): δ_C 159.1, 141.7, 133.2, 128.8, 127.8, 127.8, 126.5, 123.6, 114.1, 55.3, 45.5, 28.3.



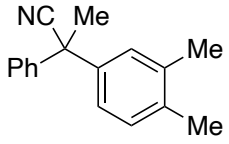
3.3c

2,2-Diphenylpropanenitrile (3.3c): According to General Procedure B, **3.3c** was prepared using the following amounts of reagent: **L3** (15.9 mg, 0.080 mmol, 20 mol %), iodobenzene (45 µL, 0.20 mmol, 1.0 equiv), $NiCl_2$(dme) (8.8 mg, 0.020 mmol, 10 mol %), PhMe (degassed; 12.0 mL), and nitrile α-anion (1.2 mL of a 0.60 M solution in THF, 0.72 mmol, 1.8 equiv). The crude material was purified by flash column chromatography on silica gel (slow gradient of 0 – 10% EtOAc/Hexanes) to afford 29 mg of a clear oil (35% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.41–7.27 (m, 10H), 2.10 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 141.2, 128.8, 127.8, 126.6, 123.4, 46.1, 28.1.



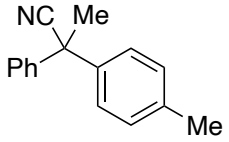
3.3e

2-(4-Methoxyphenyl)-2-phenylpropanenitrile (3.3e): According to General Procedure B, **3.3e** was prepared using the following amounts of reagent: **L3** (15.9 mg, 0.080 mmol, 20 mol %), 1-Iodo-3,4-methylenedioxybenzene (51 µL, 0.20 mmol, 1.0 equiv), $NiCl_2$(dme) (8.8 mg, 0.020 mmol, 10 mol %), PhMe (degassed; 12.0 mL), and nitrile α-anion (1.2 mL of a 0.60 M solution in THF, 0.72 mmol, 1.8 equiv). The crude material was purified by flash column chromatography on silica gel (slow gradient of 0 – 10% EtOAc/Hexanes) to afford 38 mg of white solid (35% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.41–7.35 (m, 5H), 6.91 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.80–6.76 (m, 2H), 5.96 (s, 2H), 2.05 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 135.1, 128.8, 128.0, 127.9, 127.6, 126.6, 126.4, 123.4, 119.9, 108.1, 107.5, 101.4, 45.8, 28.3.



3.3f

2-(3,4-Dimethylphenyl)-2-phenylpropanenitrile (3.3f): According to General Procedure B, **3.3f** was prepared using the following amounts of reagent: **L3** (15.9 mg, 0.080 mmol, 20 mol %), 1-Iodo-2,4-dimethylbenzene (57 μL, 0.20 mmol, 1.0 equiv), $NiCl_2$(dme) (8.8 mg, 0.020 mmol, 10 mol %), PhMe (degassed; 12.0 mL), and nitrile α-anion (1.2 mL of a 0.60 M solution in THF, 0.72 mmol, 1.8 equiv).The crude material was purified by flash column chromatography on silica gel (slow gradient of 0 – 10% EtOAc/Hexanes) to afford 36 mg of an oil (39% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.44–7.26 (m, 5H), 7.20–7.05 (m, 3H), 2.26 (s, 6H), 2.08 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ_C 141.6, 138.6, 137.1, 136.4, 130.0, 129.1, 128.8, 127.8, 127.7, 126.5, 123.8, 45.8, 28.1, 19.9, 19.3.

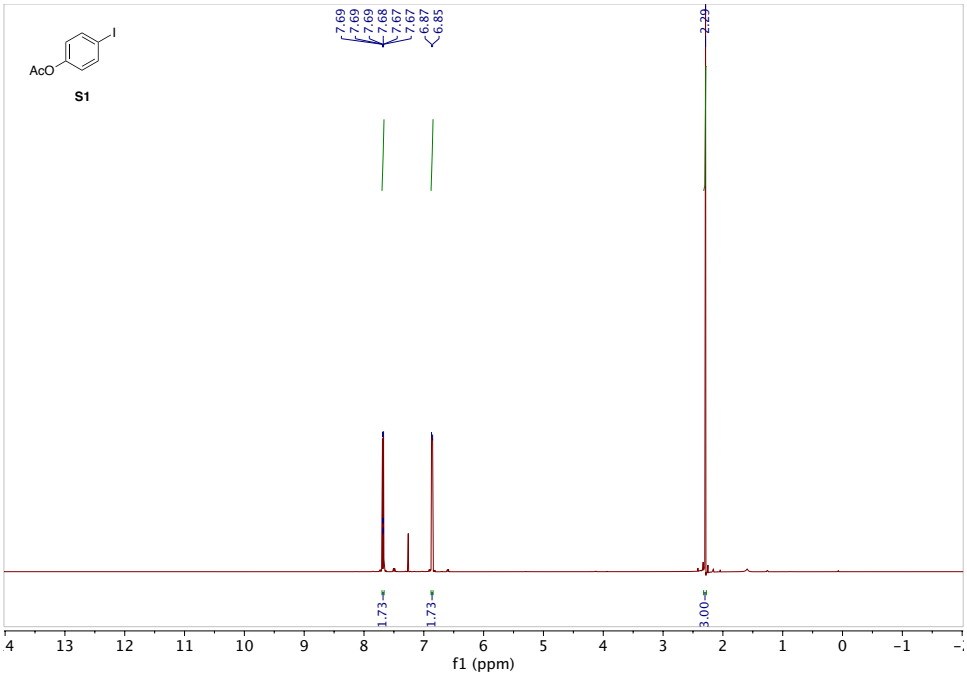


3.3b

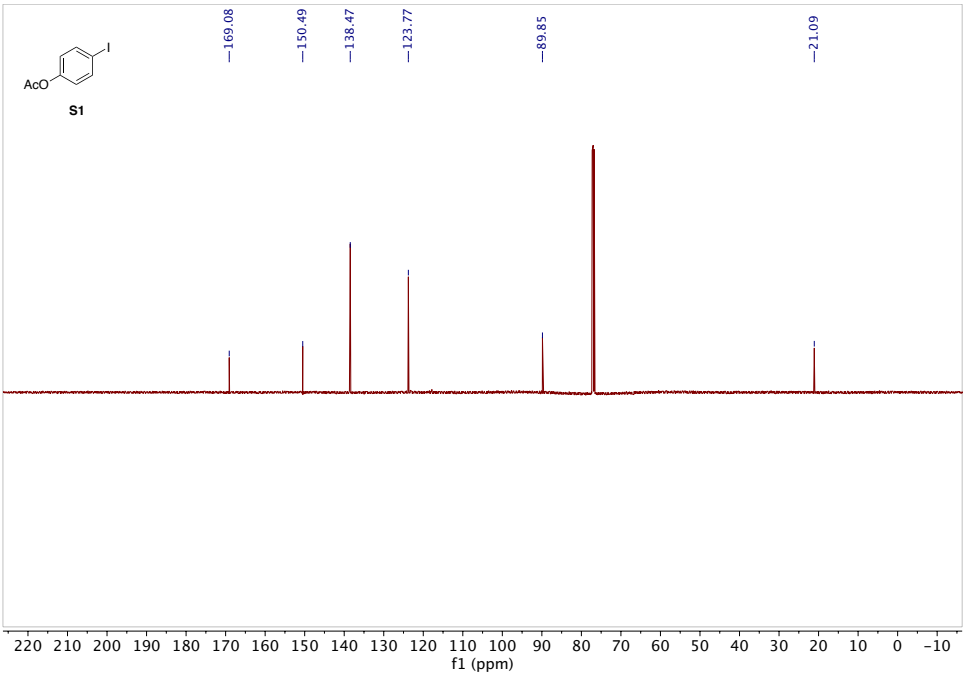
2-Phenyl-2-(*p*-tolyl)propanenitrile (3.3b): According to General Procedure B, **3.3b** was prepared using the following amounts of reagent: **L3** (15.9 mg, 0.080 mmol, 20 mol %), 4-iodotoluene (87.2 mg, 0.200 mmol, 1.00 equiv), $NiCl_2$(dme) (8.8 mg, 0.020 mmol, 10 mol %), PhMe (degassed; 12.0 mL), and nitrile α-anion (1.2 mL of a 0.60 M solution in THF, 0.72 mmol, 1.8 equiv).The crude material was purified by flash column chromatography on silica gel (slow gradient of 0 – 10% EtOAc/Hexanes) to afford 56 mg of a clear oil (63% yield). **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ_H 7.40–7.33 (m, 5H), 7.27 (d, J = 1.9 Hz, 1H), 7.25 (d, J = 2.1 Hz, 1H), 7.19 – 7.14 (m, 2H), 2.34 (s, 3H), 2.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K): δ_C 141.5, 138.3, 137.7, 130.0, 129.5, 128.8, 128.2, 127.8, 127.0, 126.5, 126.5, 123.5, 45.8, 28.1, 20.9.

4.7 NMR Spectra of Products

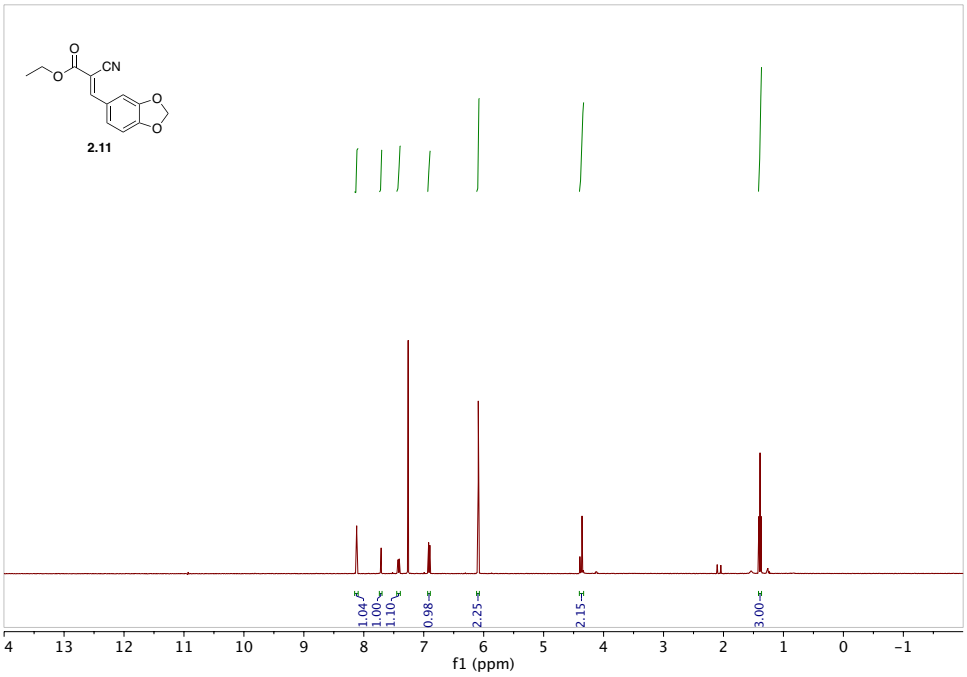
^{1}H NMR (399 MHz, $CDCl_3$, 298 K)



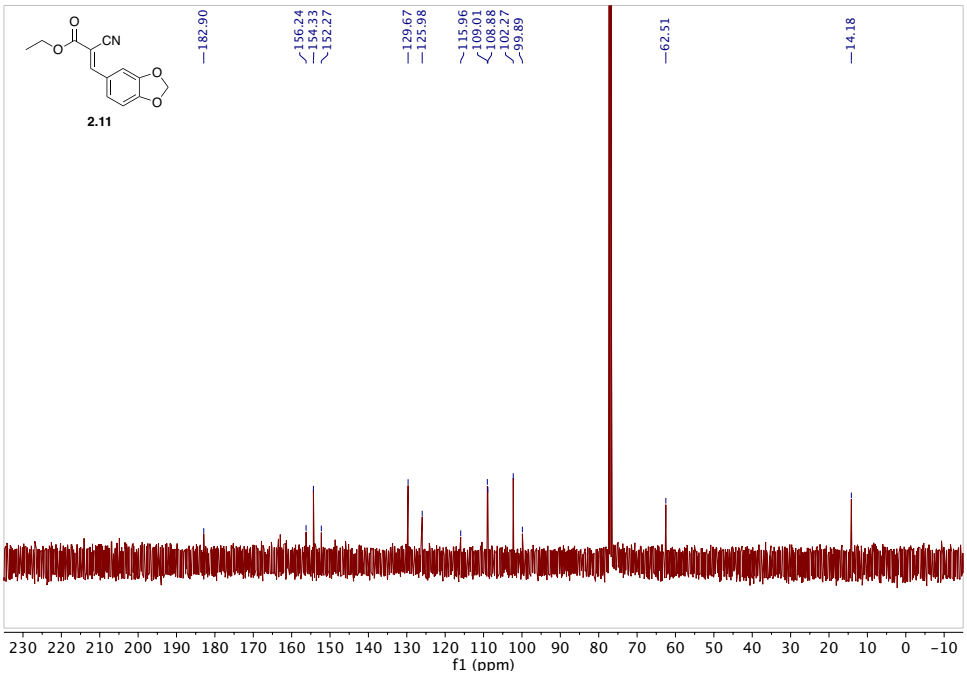
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



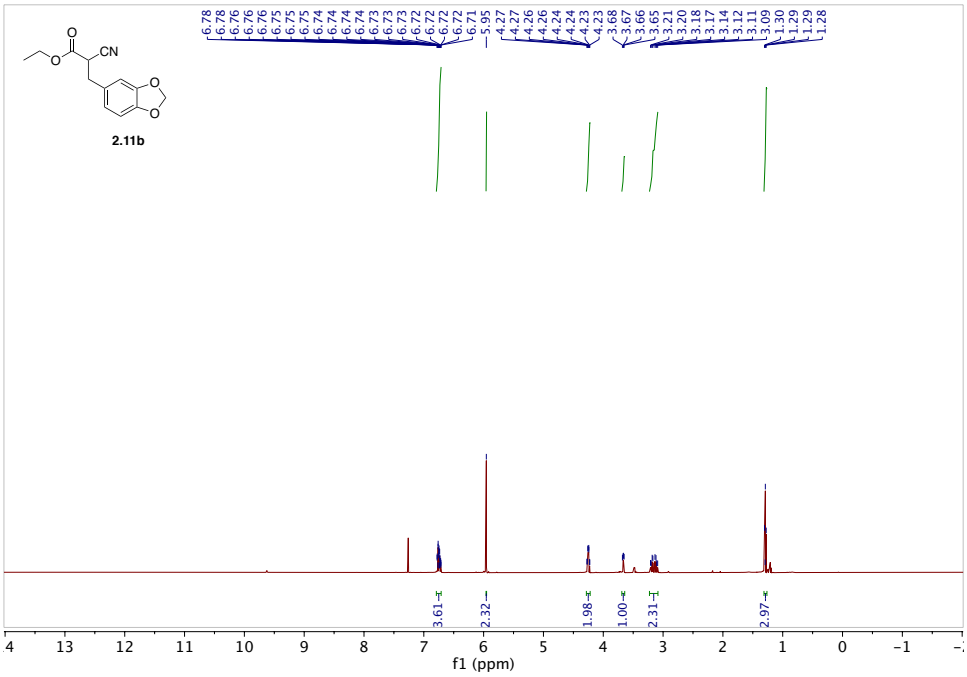
^{1}H NMR (399 MHz, $CDCl_3$, 298 K)



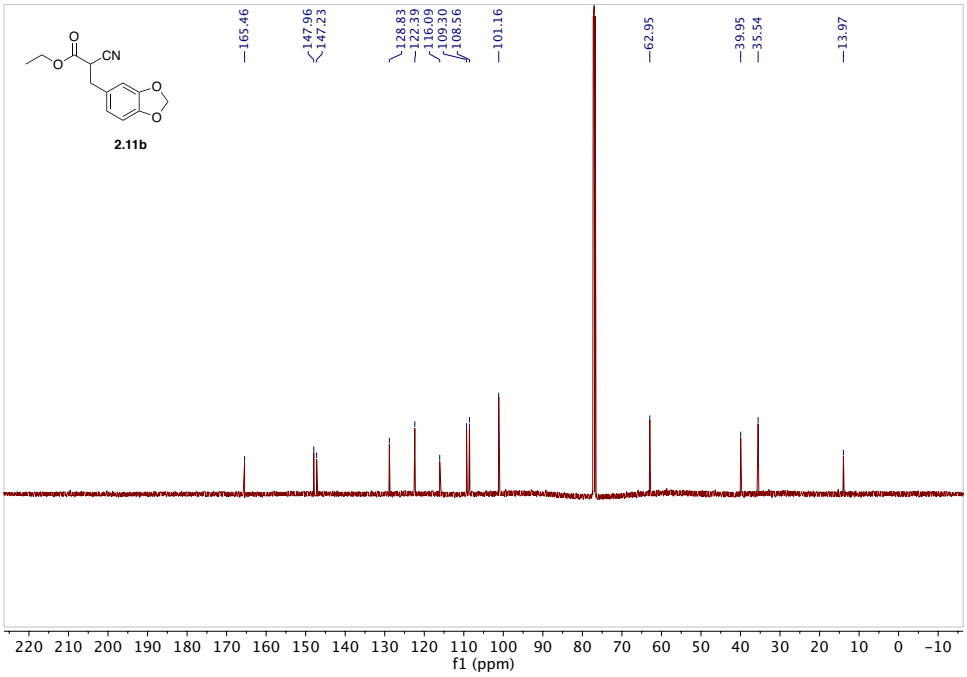
^{13}C NMR (101 MHz, $CDCl_3$, 298 K)



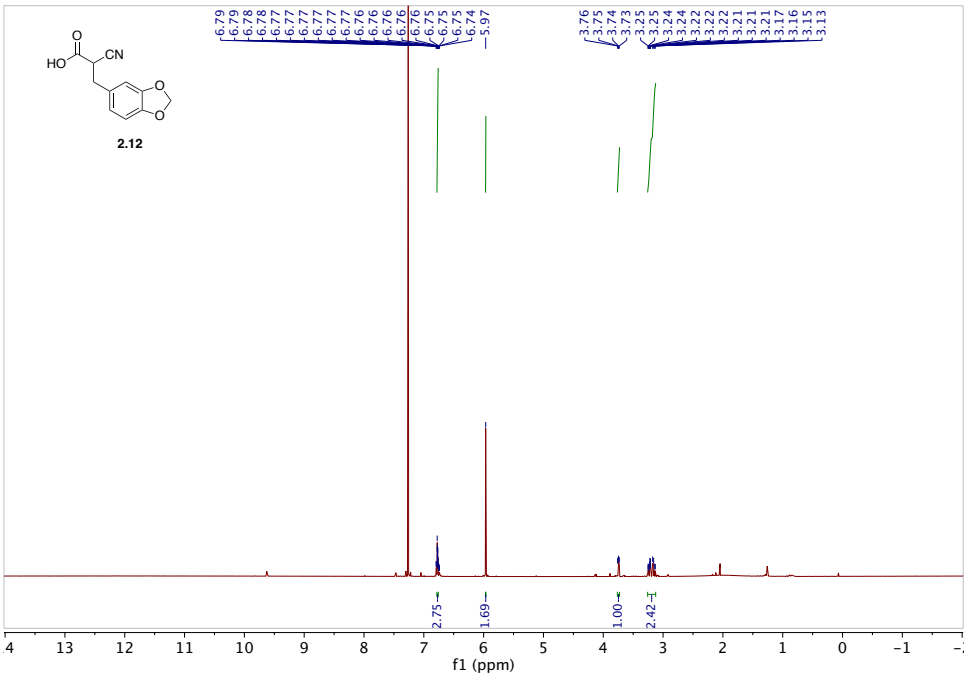
^{1}H NMR (500 MHz, $CDCl_3$, 298 K)



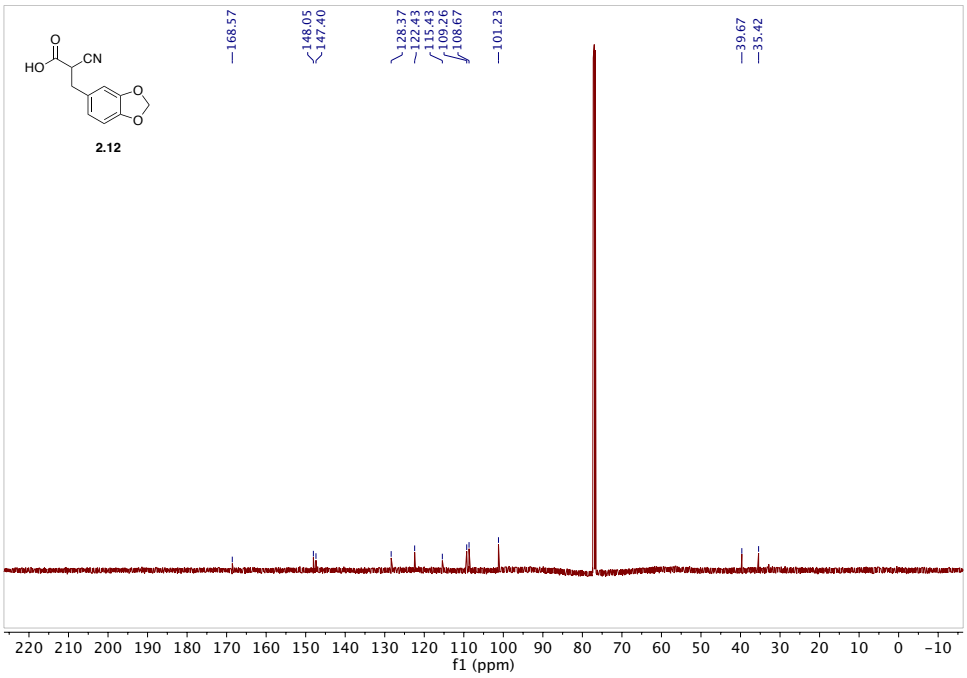
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



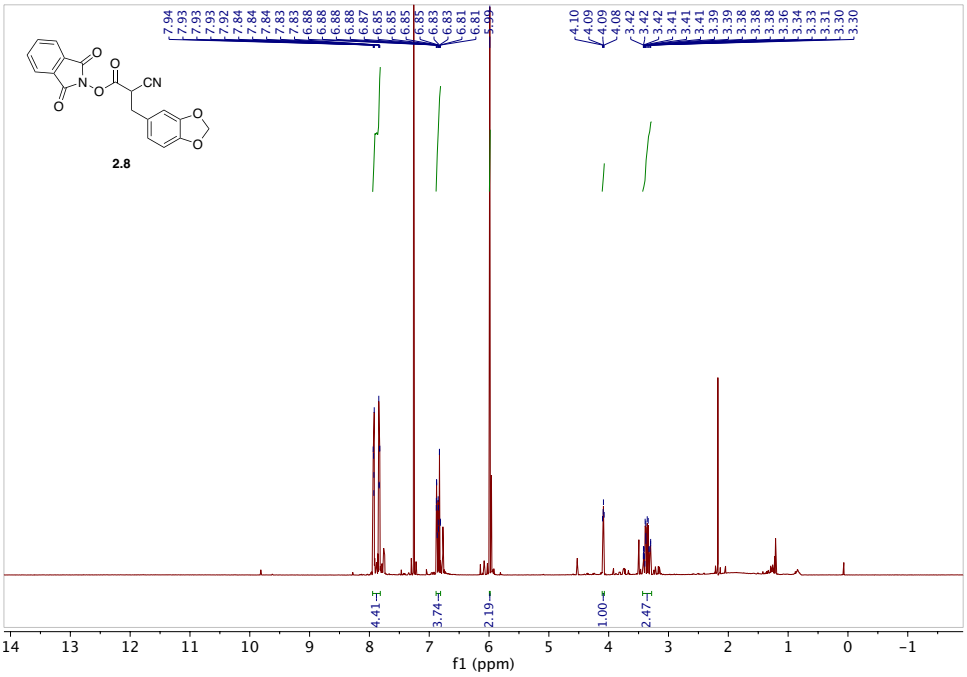
^{1}H NMR (500 MHz, $CDCl_3$, 298 K)



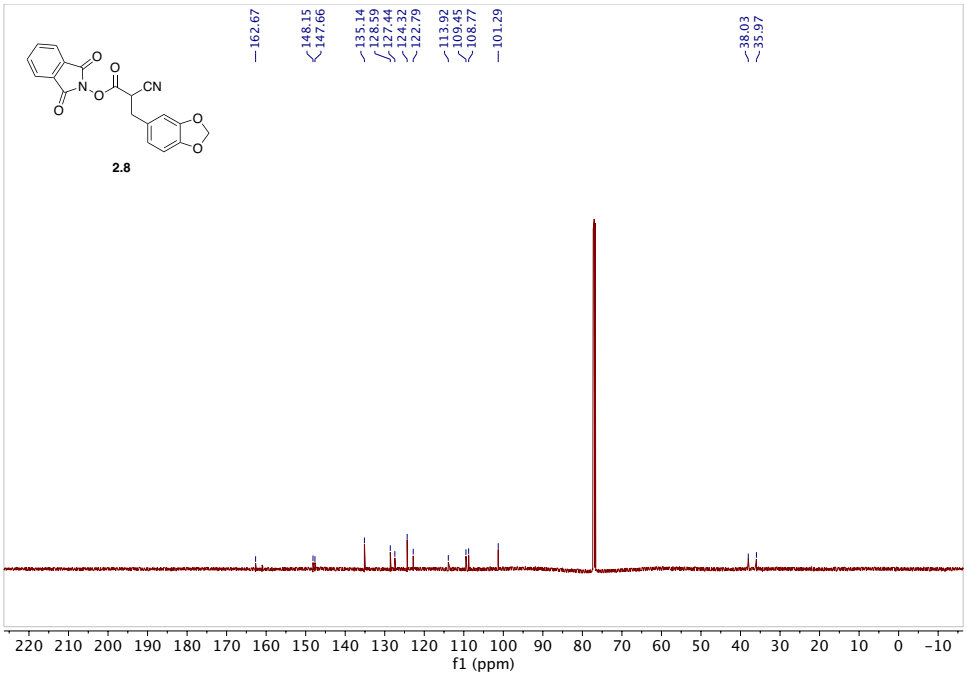
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



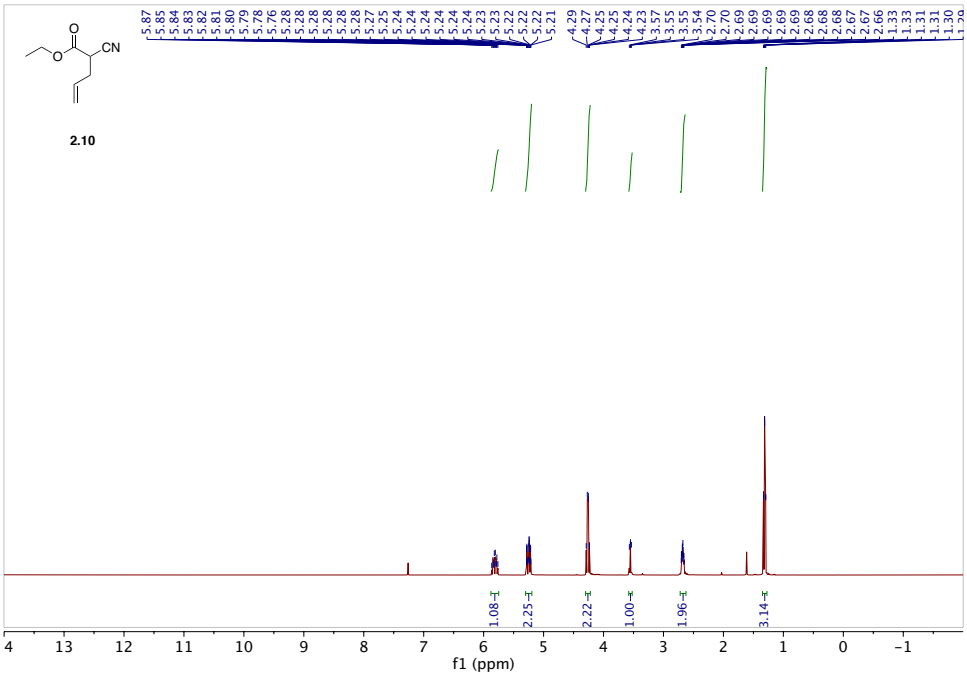
^{1}H NMR (399 MHz, $CDCl_3$, 298 K)



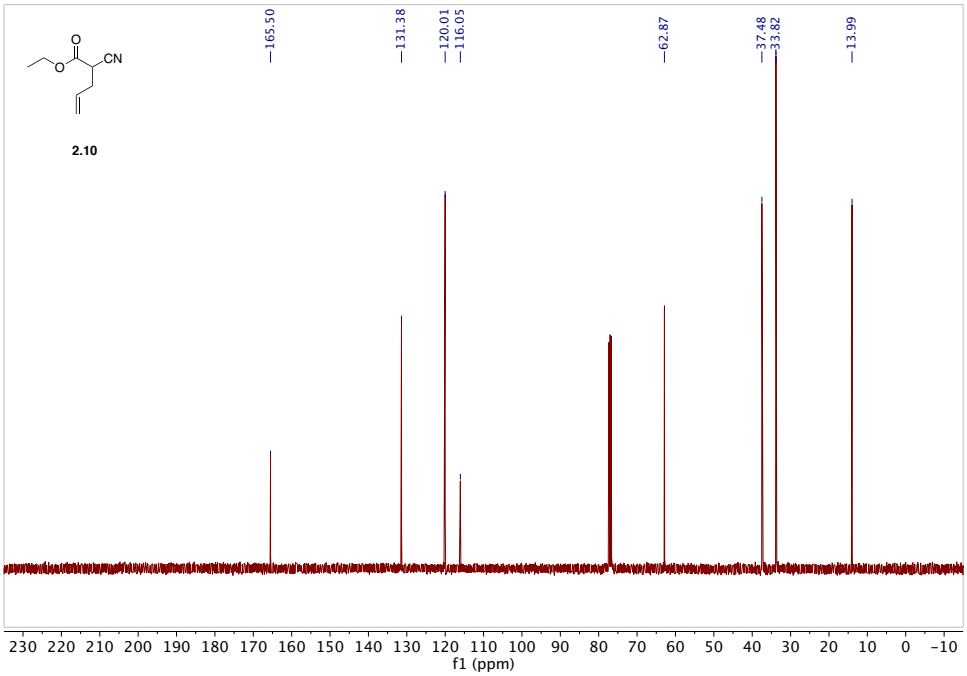
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



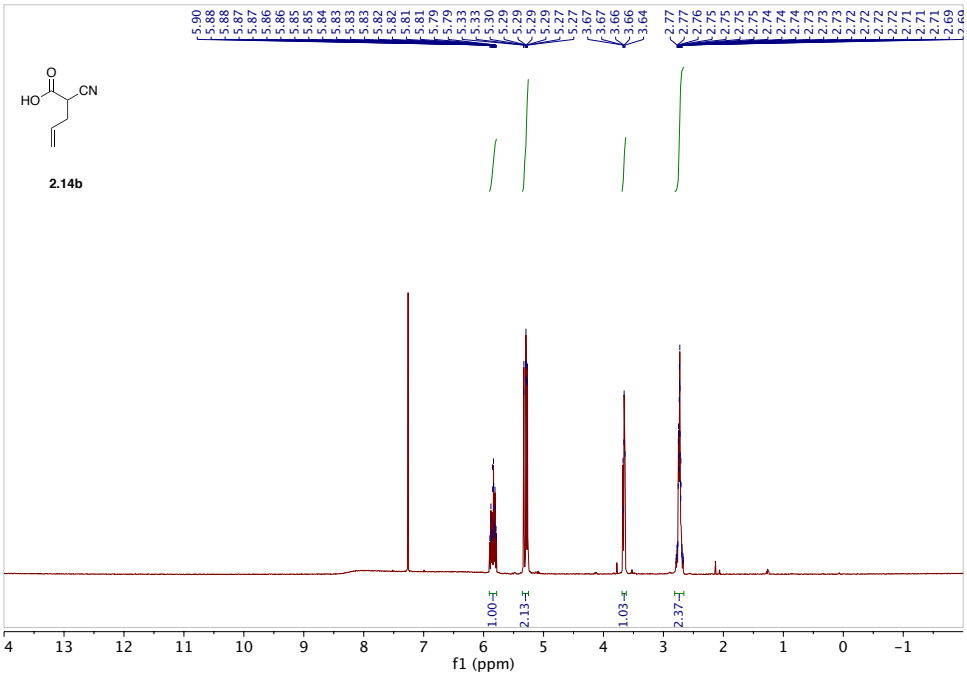
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



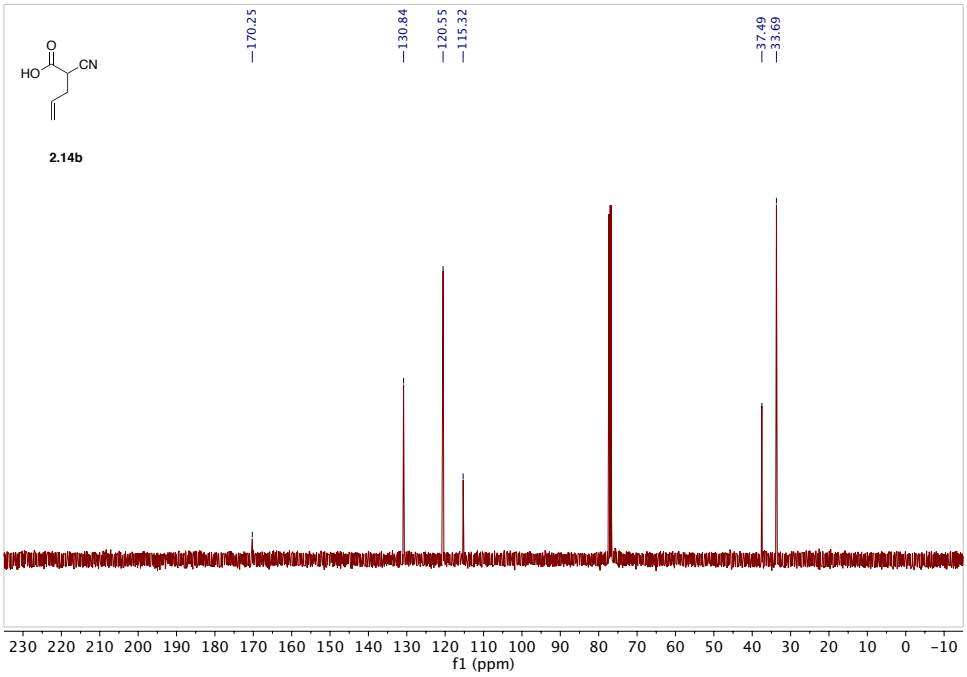
^{13}C NMR (101 MHz, $CDCl_3$, 298 K)



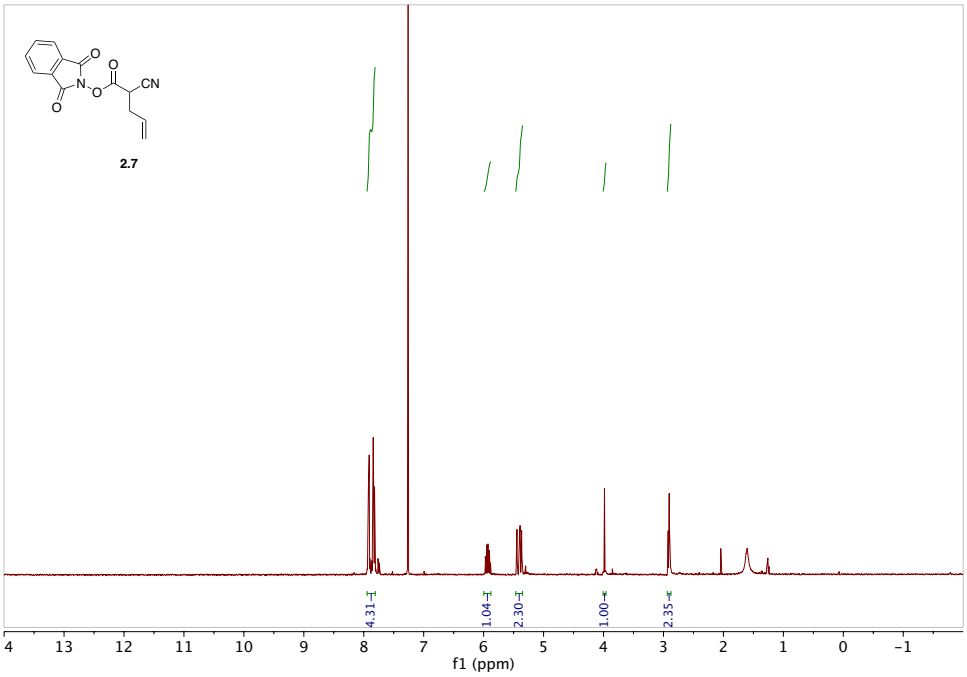
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



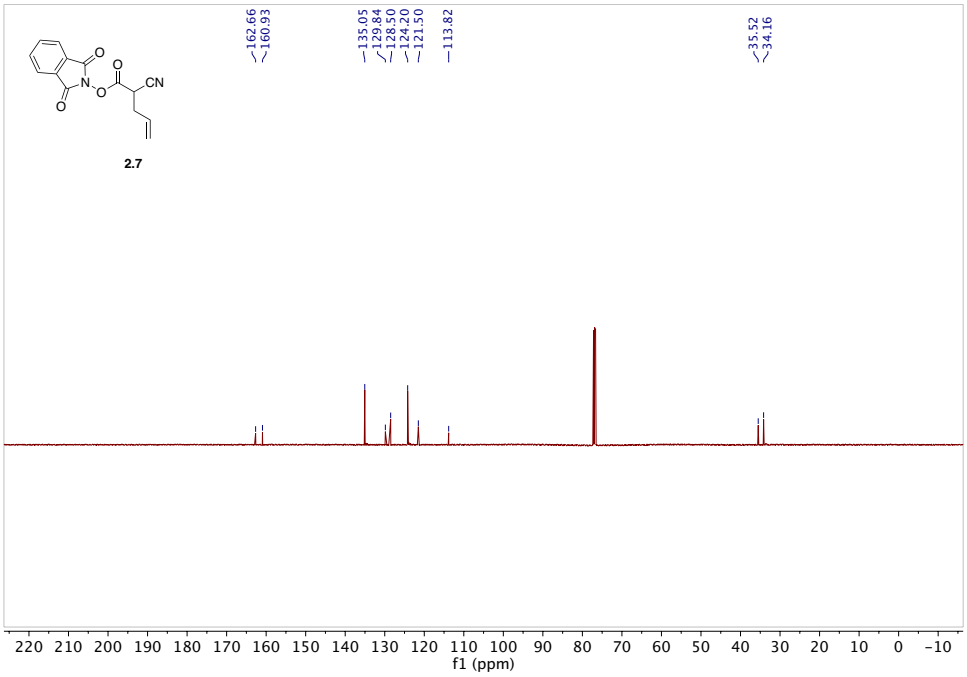
^{13}C NMR (101 MHz, $CDCl_3$, 298 K)



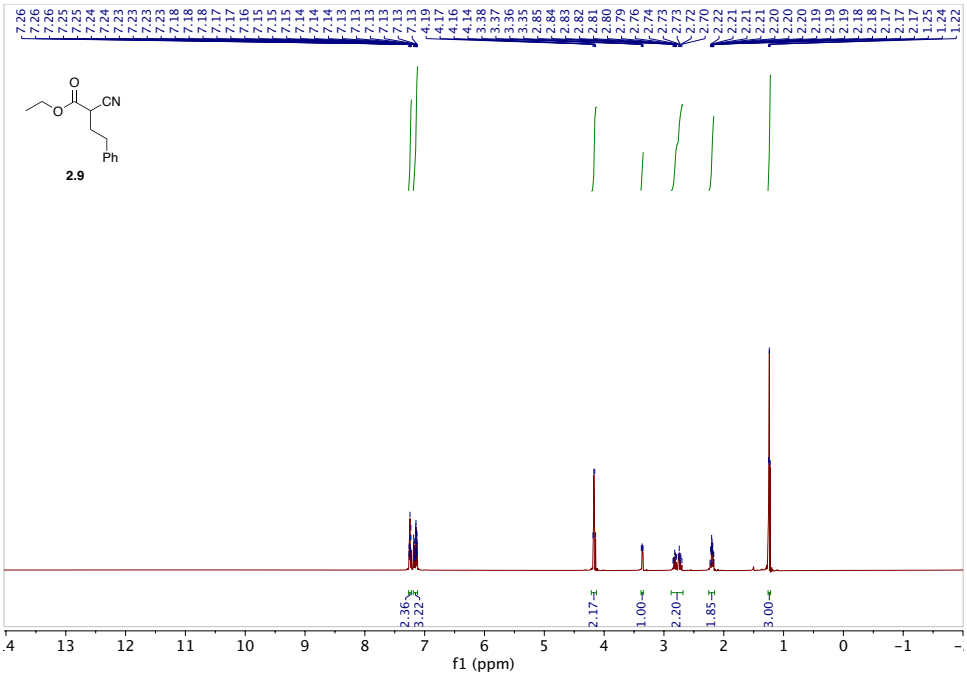
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



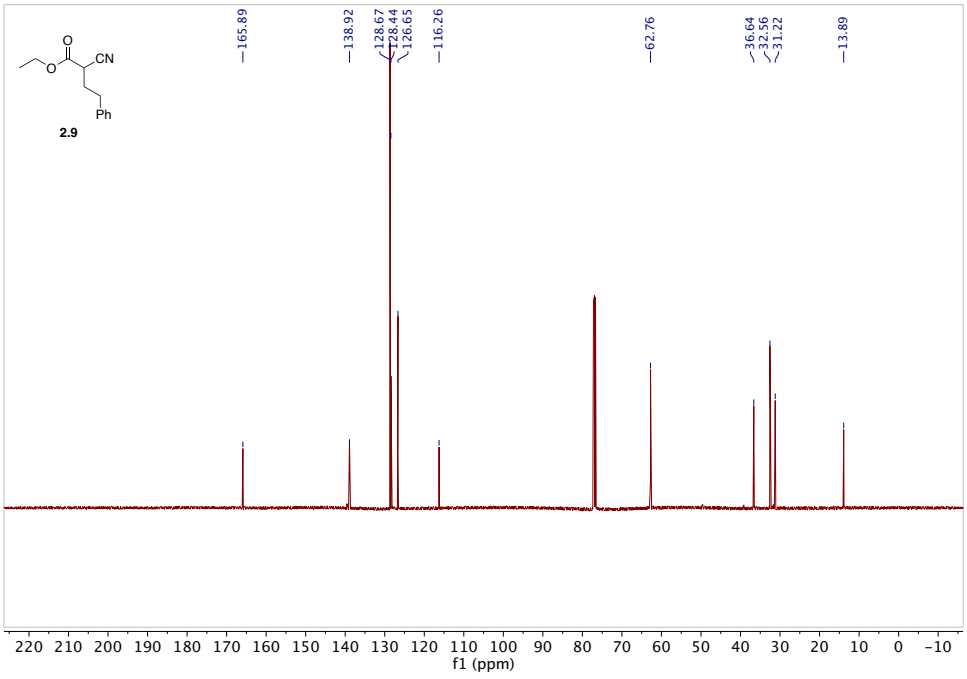
^{13}C NMR (101 MHz, $CDCl_3$, 298 K)



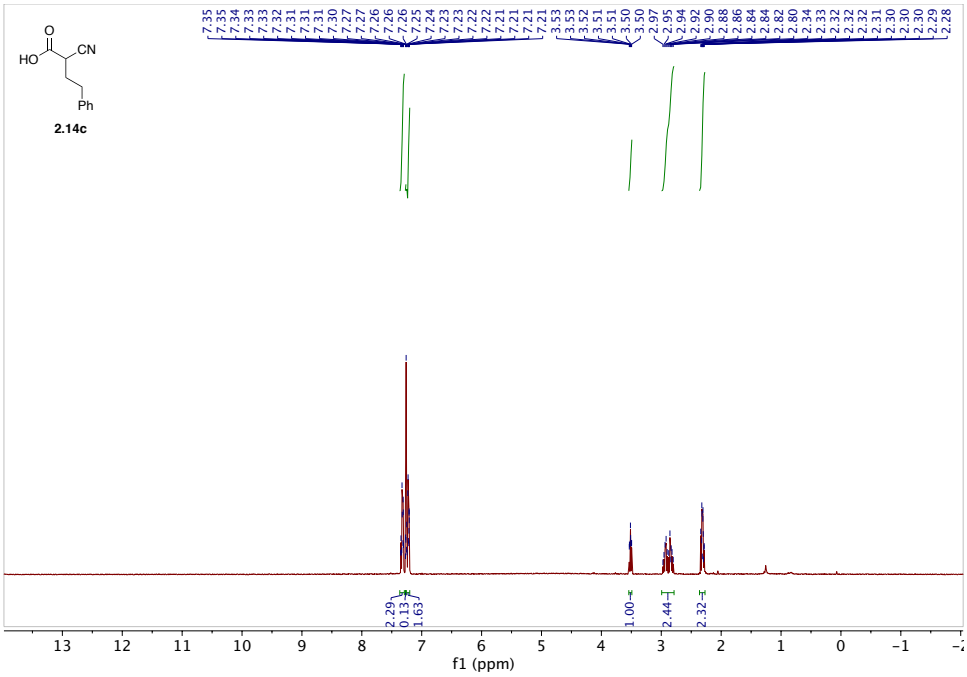
^{1}H NMR (500 MHz, $CDCl_3$, 298 K)



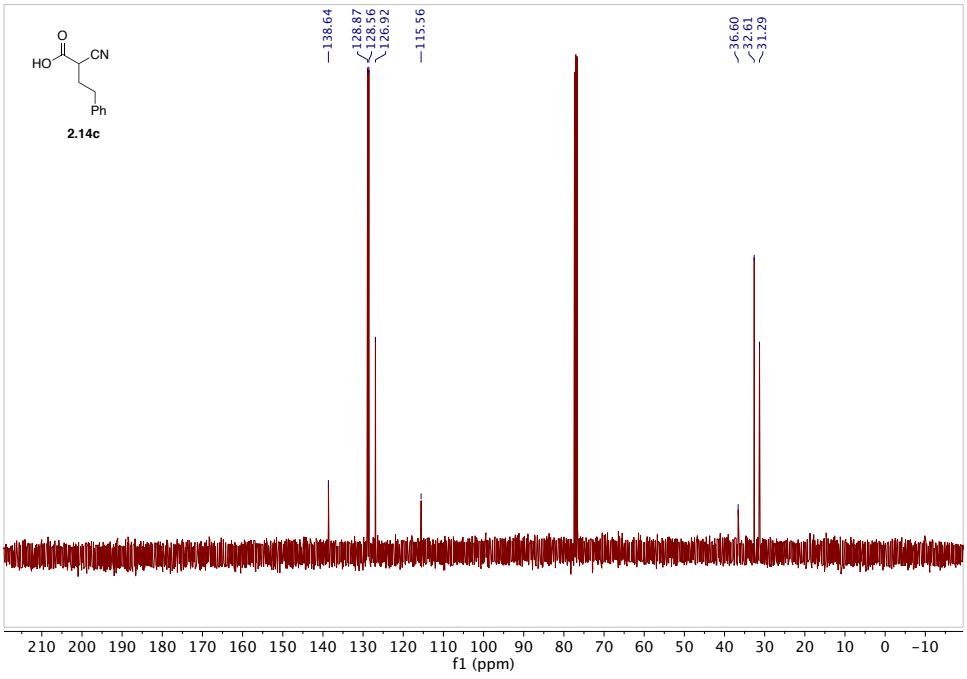
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



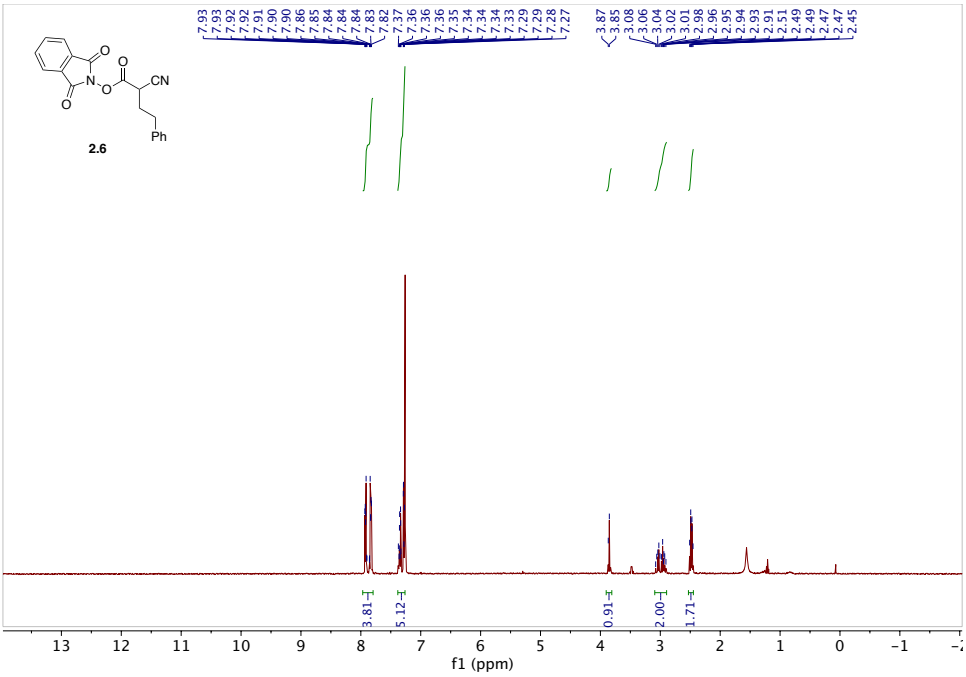
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



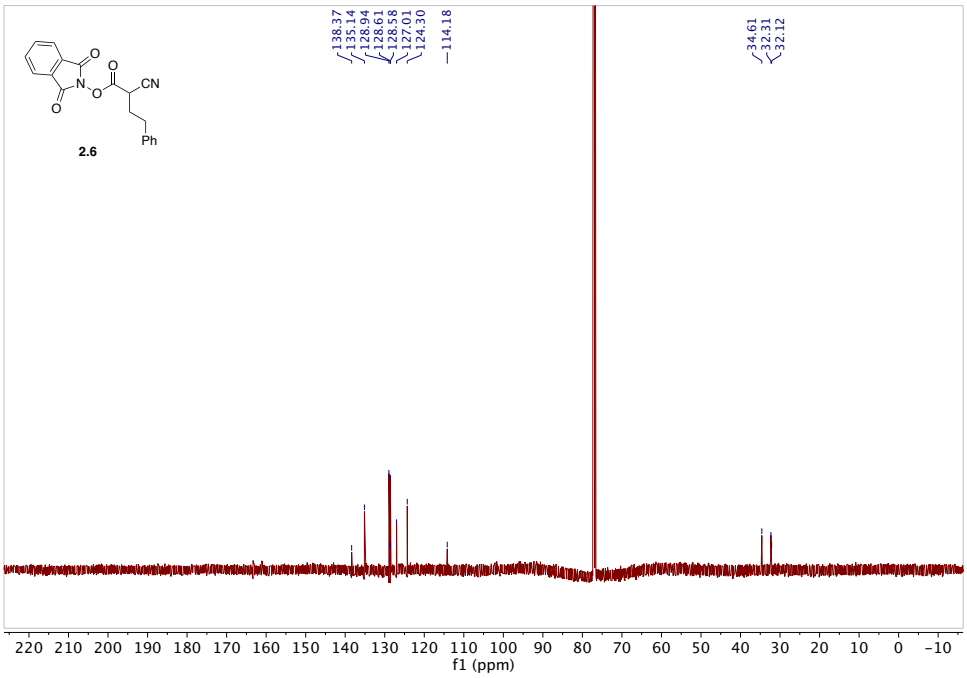
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



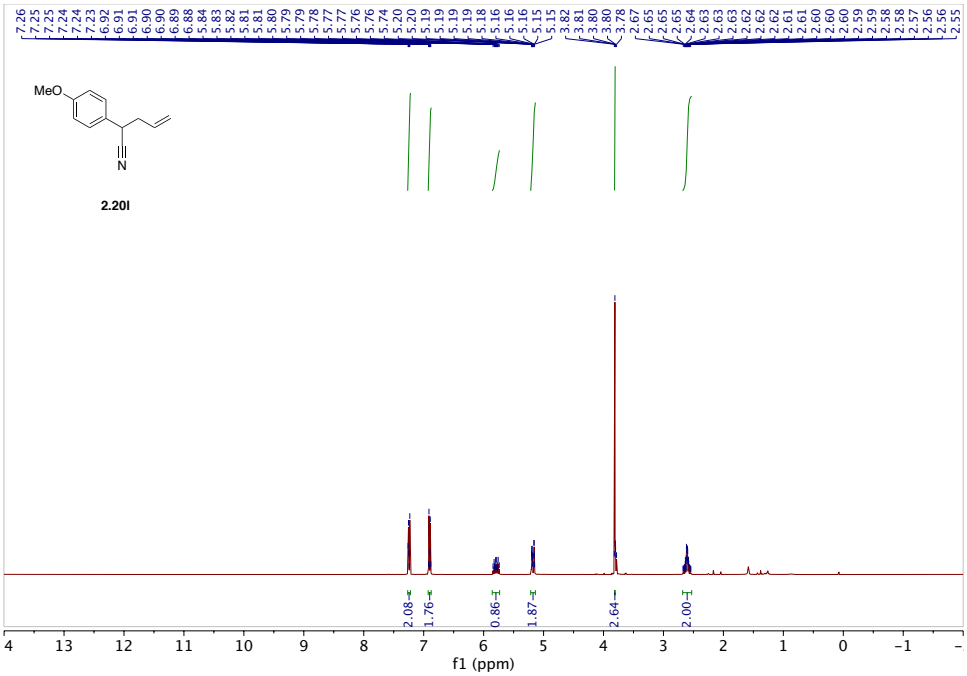
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



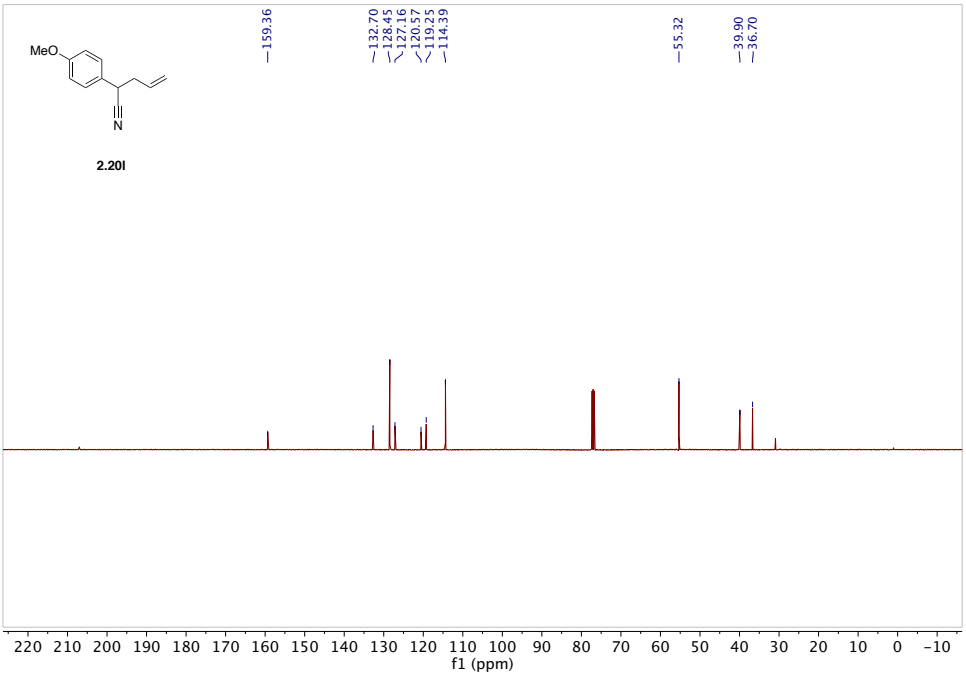
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



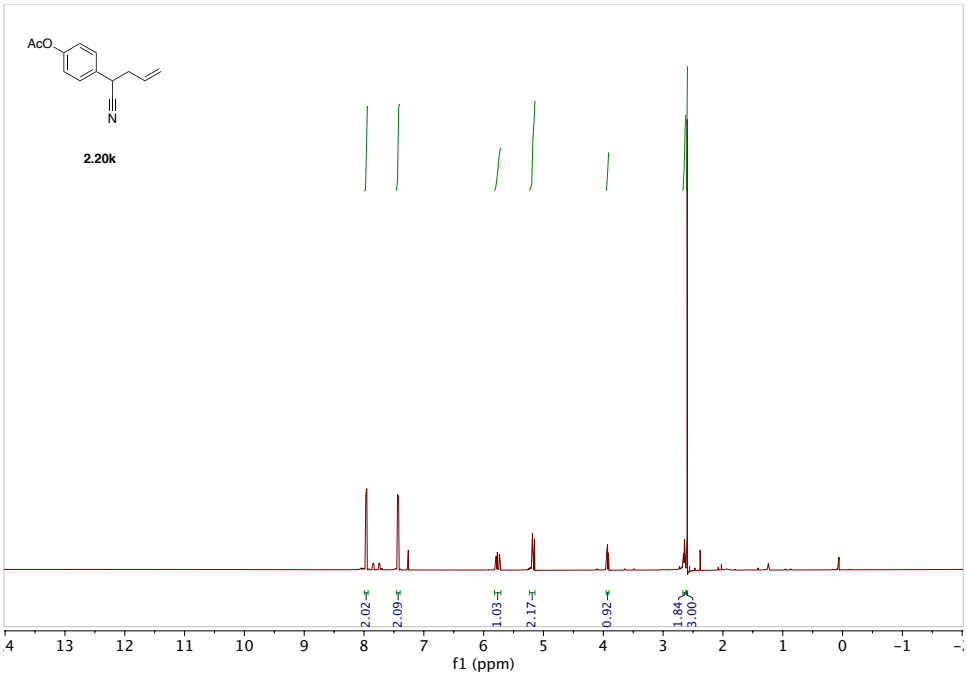
^{1}H NMR (500 MHz, $CDCl_3$, 298 K)



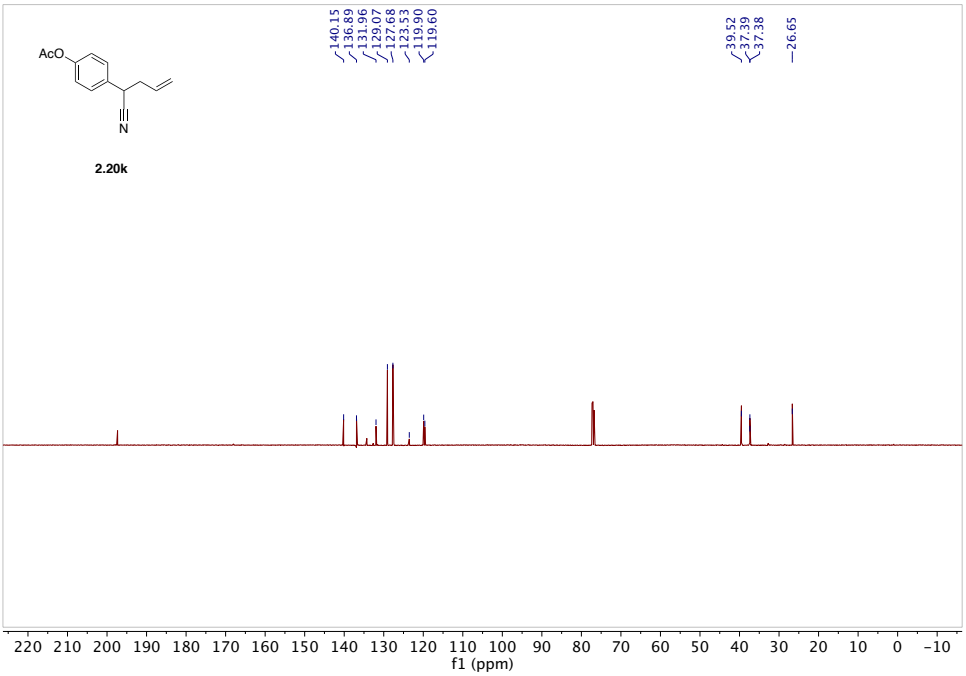
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



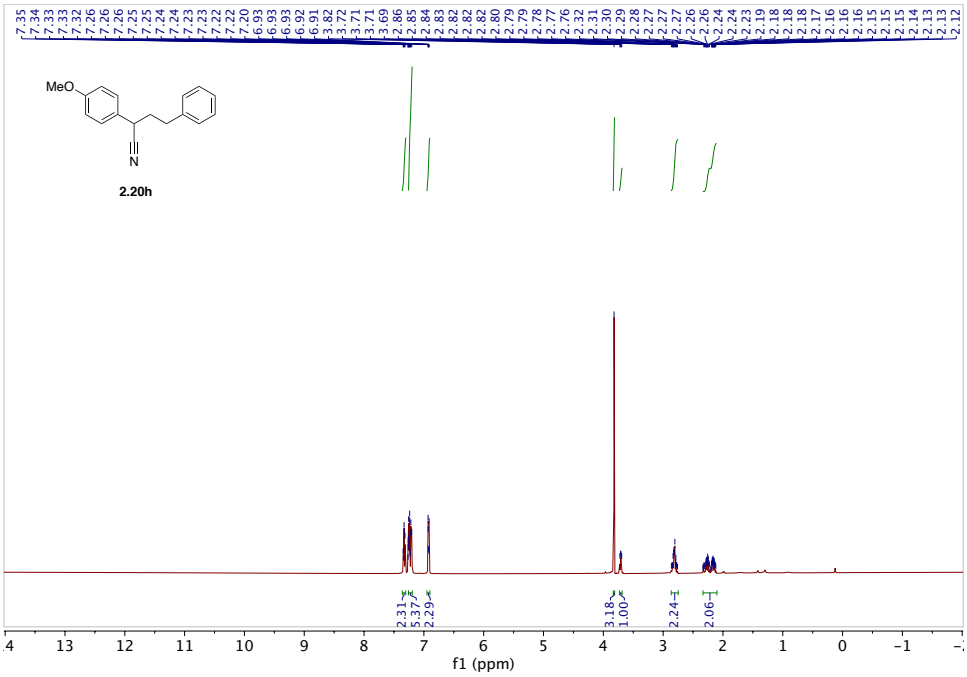
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



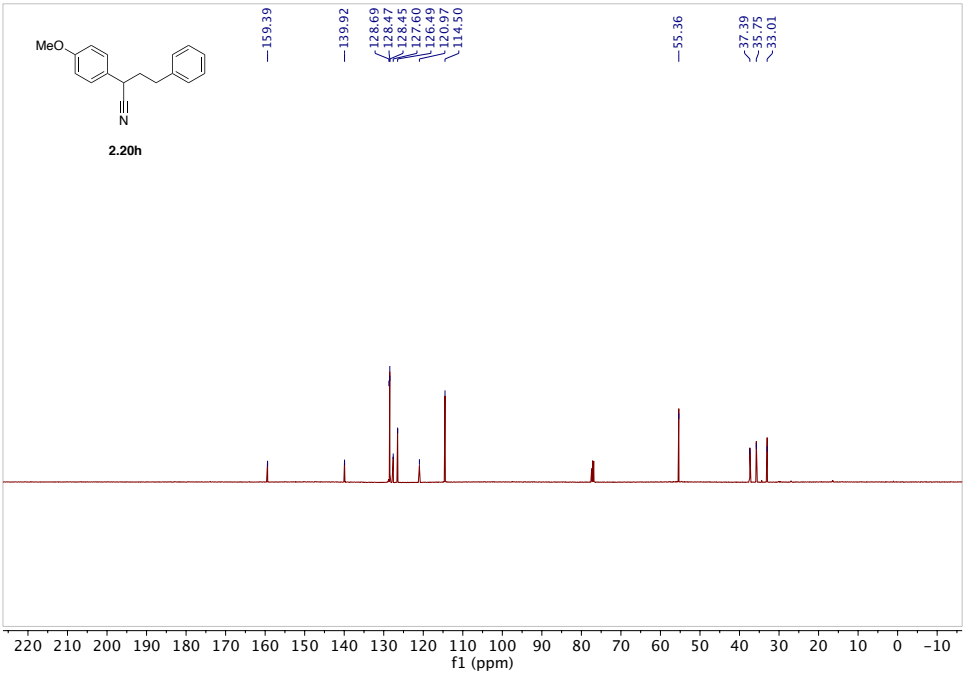
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



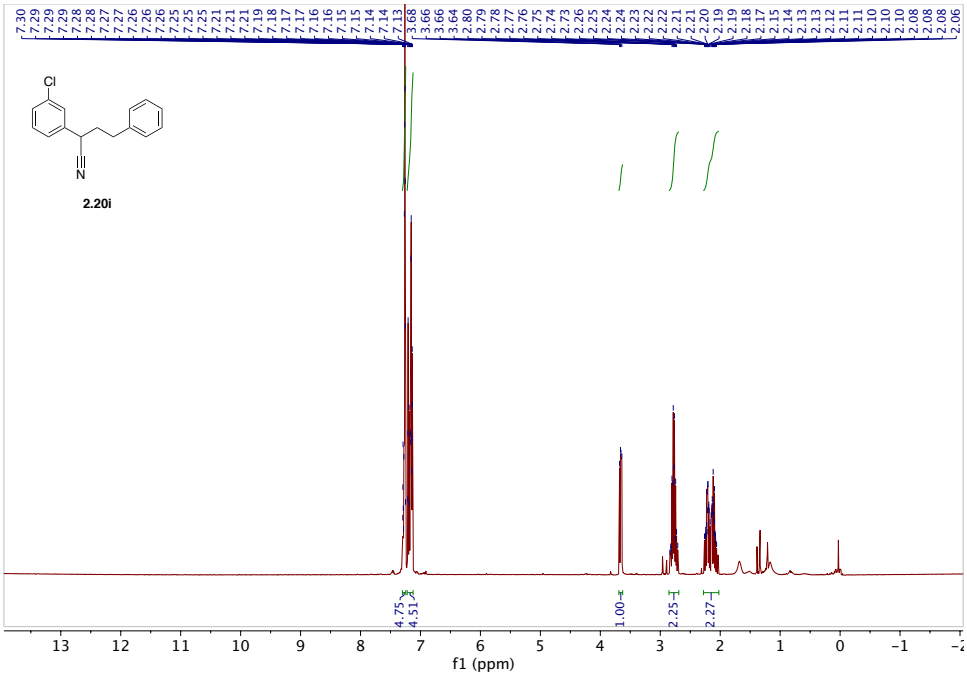
^{1}H NMR (399 MHz, $CDCl_3$, 298 K)



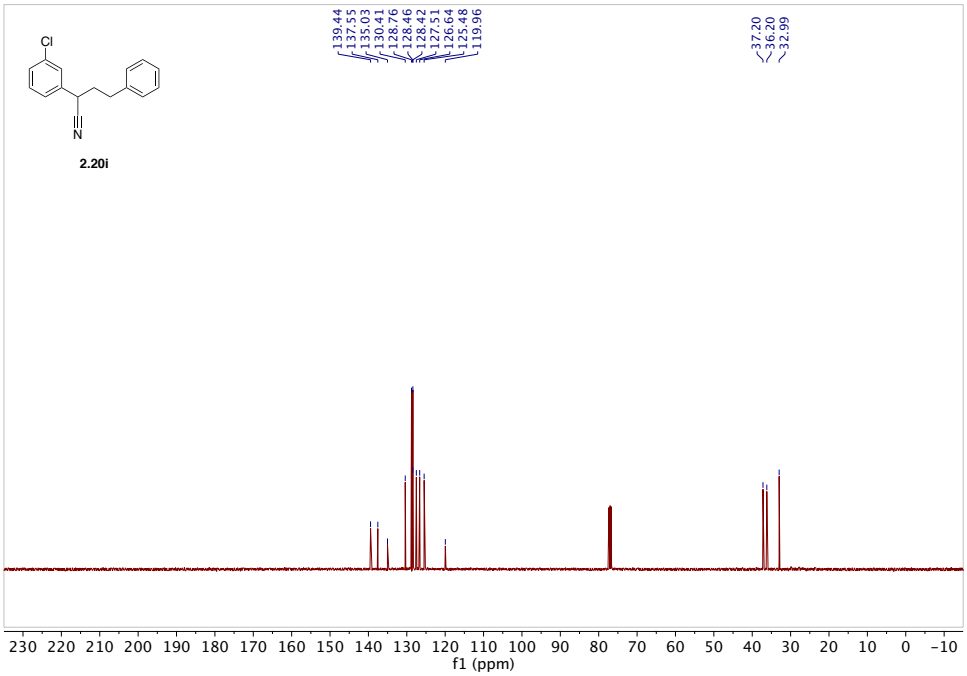
^{13}C NMR (100 MHz, $CDCl_3$, 298 K)



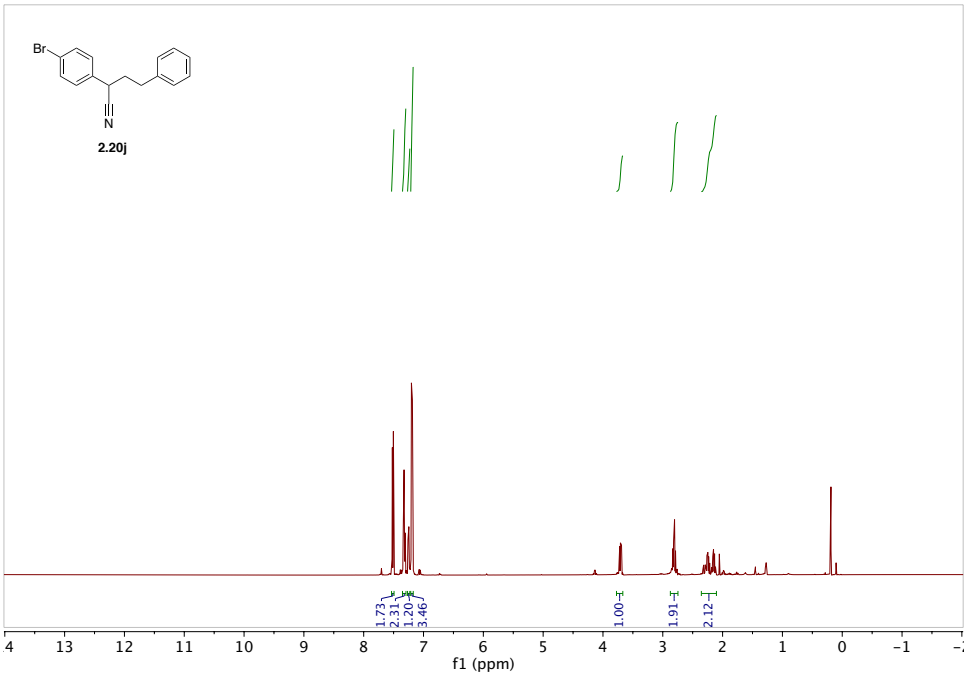
^{1}H NMR (500 MHz $CDCl_3$, 298 K)



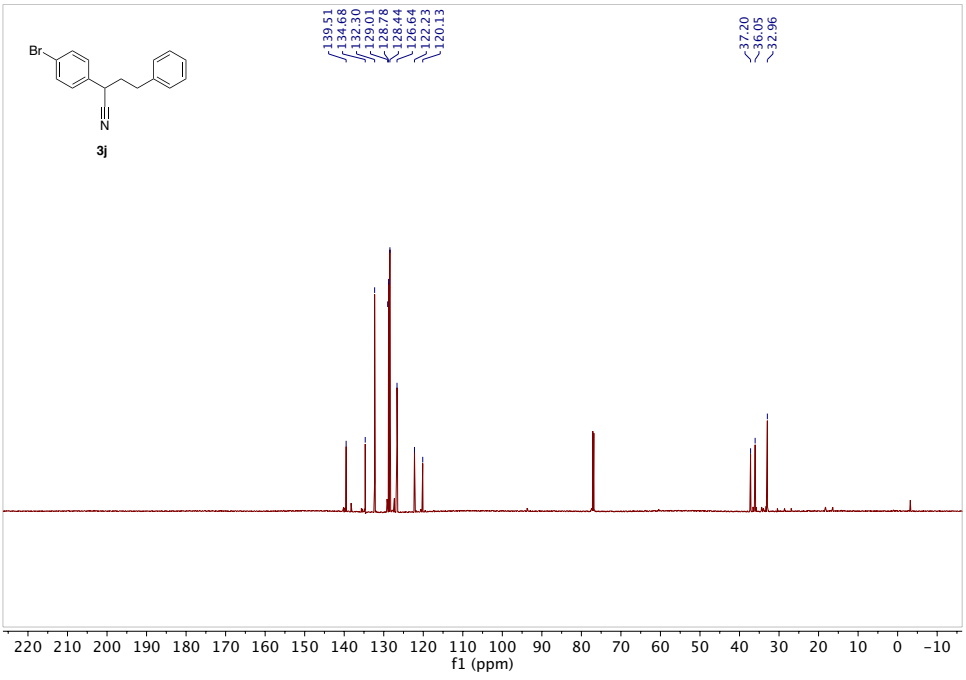
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



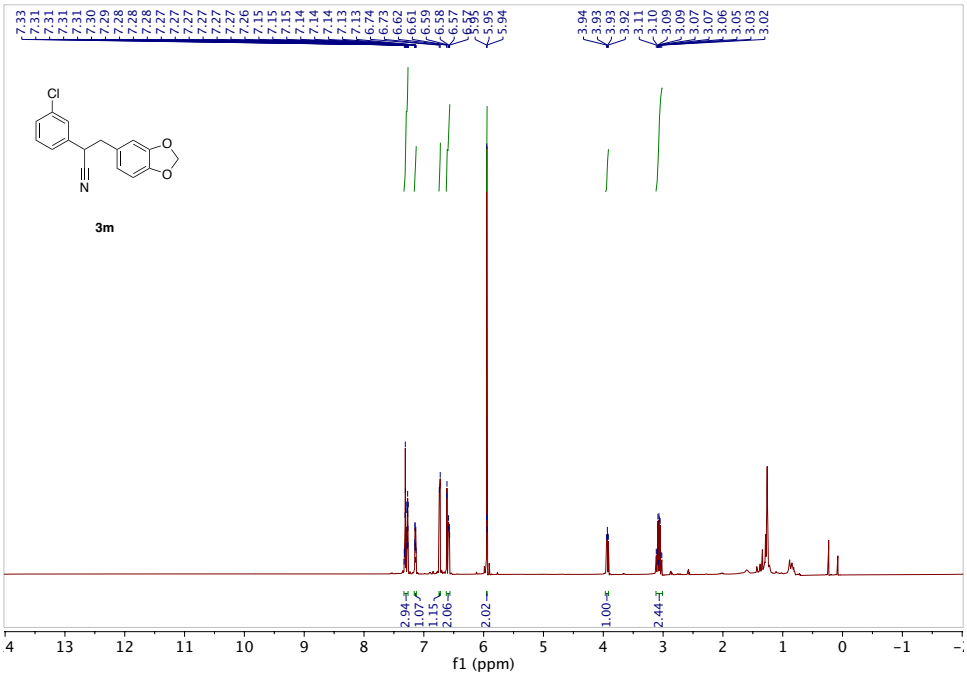
^{1}H NMR (500 MHz $CDCl_3$, 298 K)



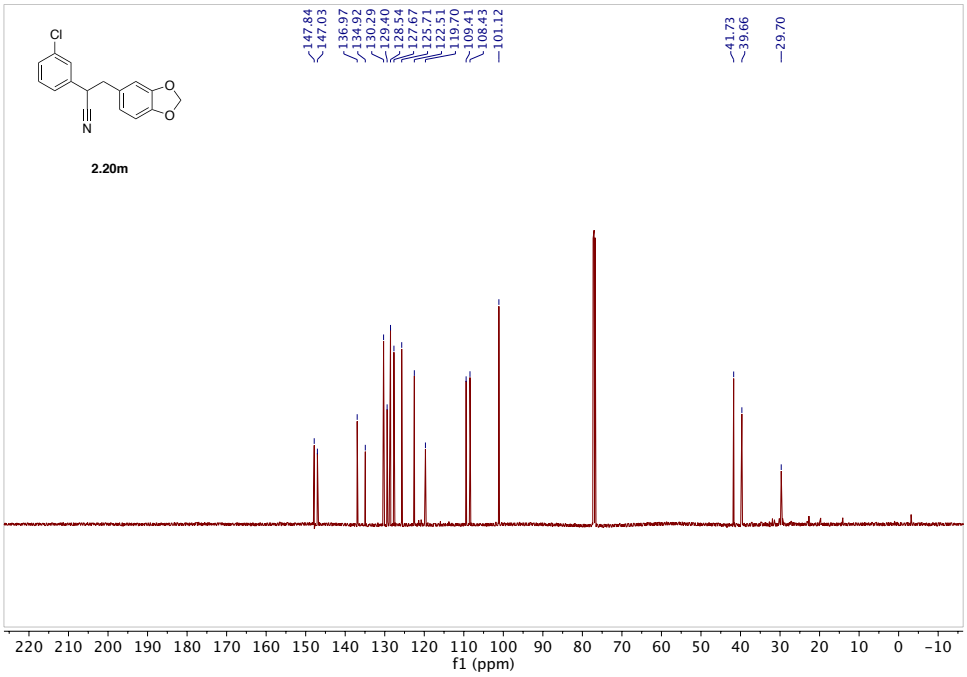
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



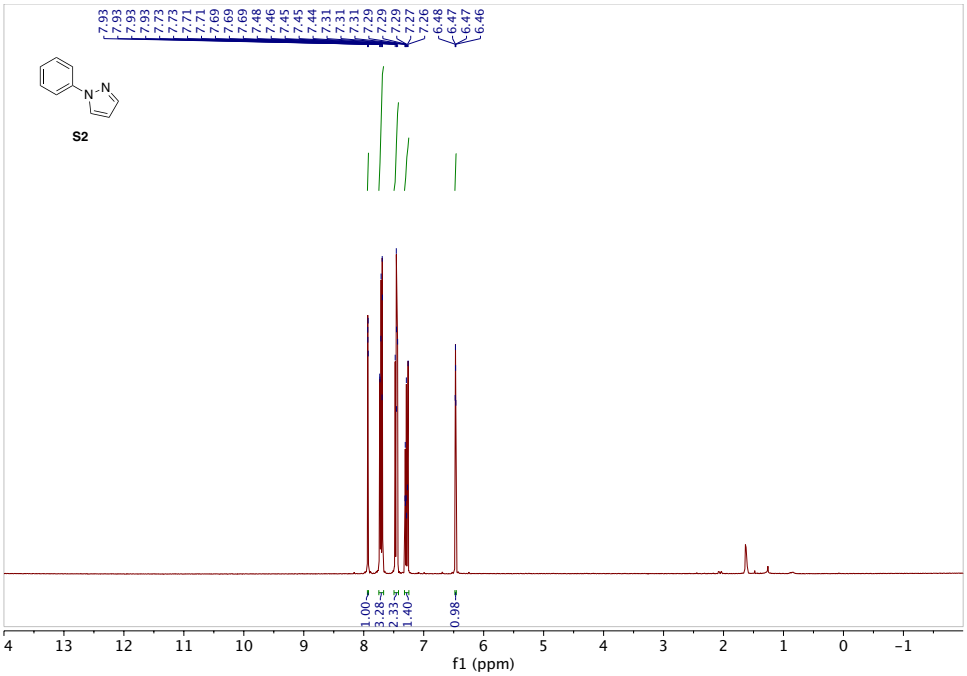
^{1}H NMR (500 MHz $CDCl_3$, 298 K)



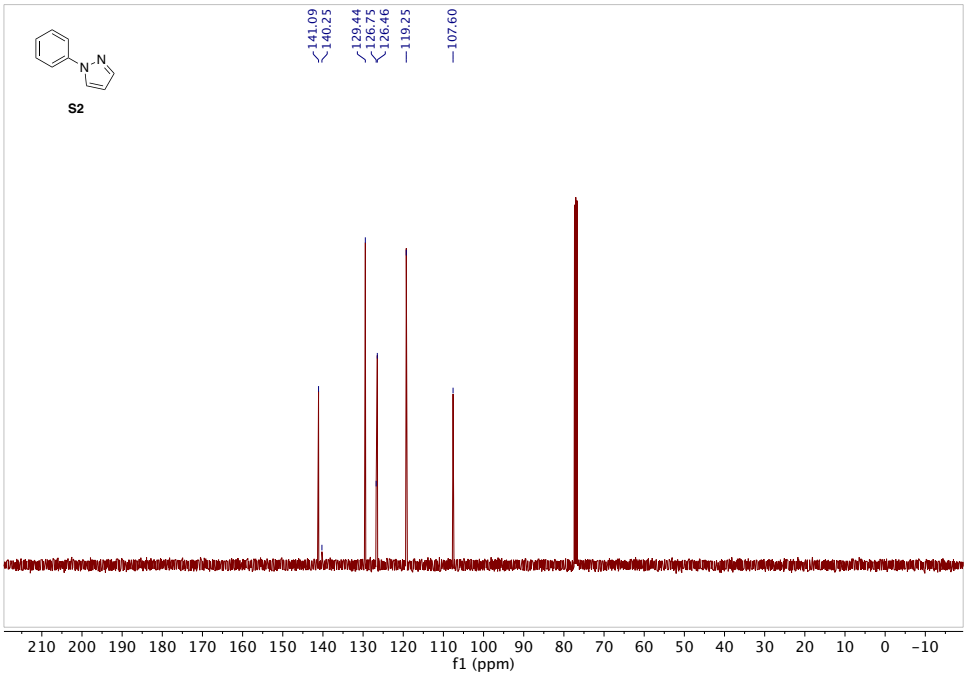
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



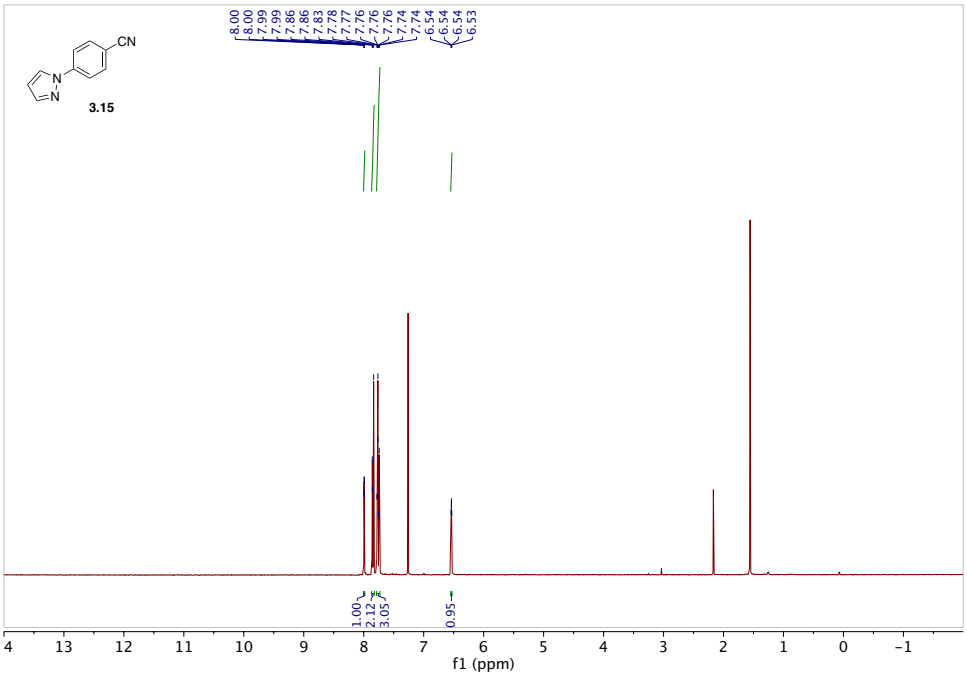
^{1}H NMR (400 MHz, $CDCl_3$, 298K)



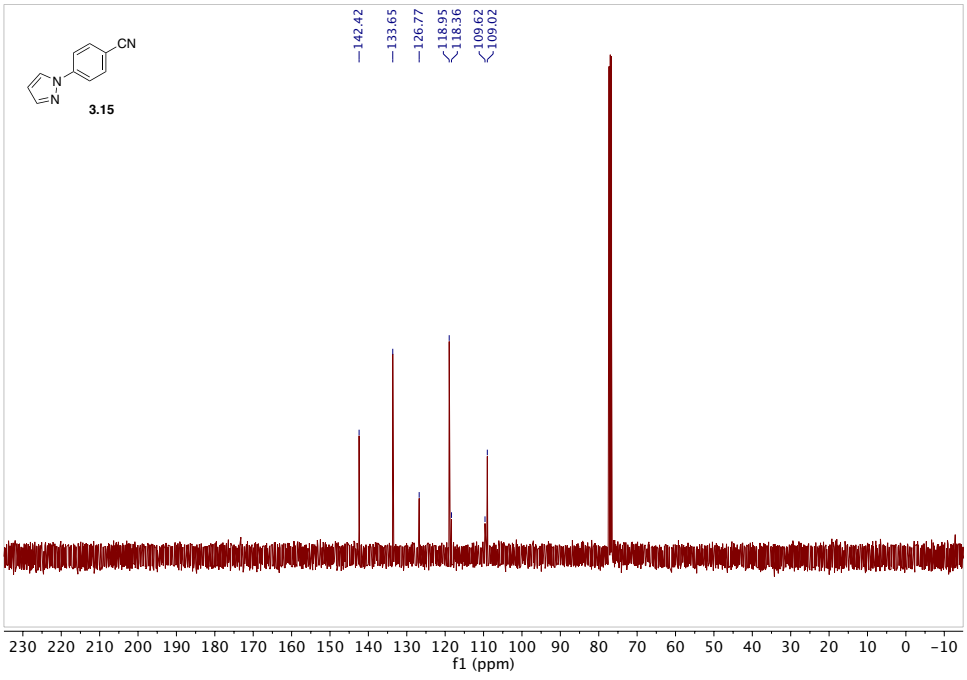
^{13}C NMR (100 MHz, $CDCl_3$, 298K):



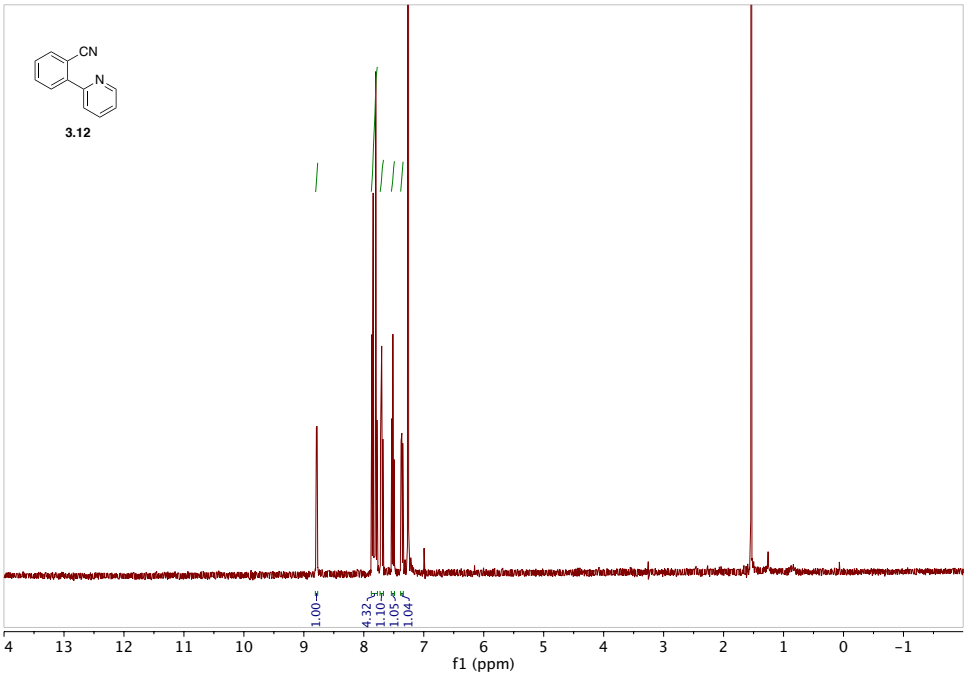
^{1}H NMR (400 MHz, $CDCl_3$, 298K)



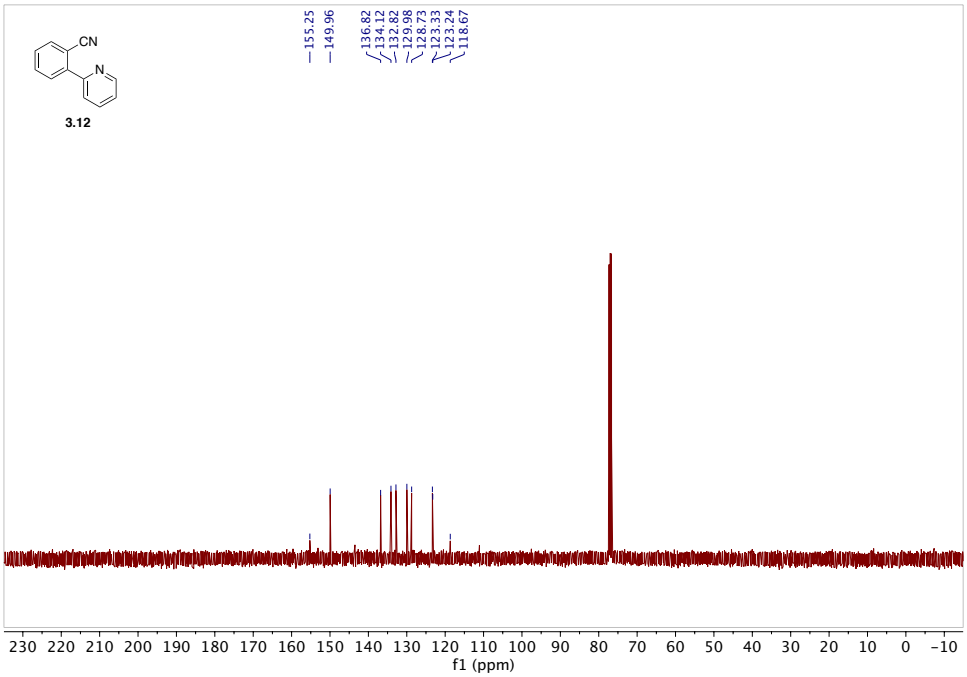
^{13}C NMR (100 MHz, $CDCl_3$, 298K)



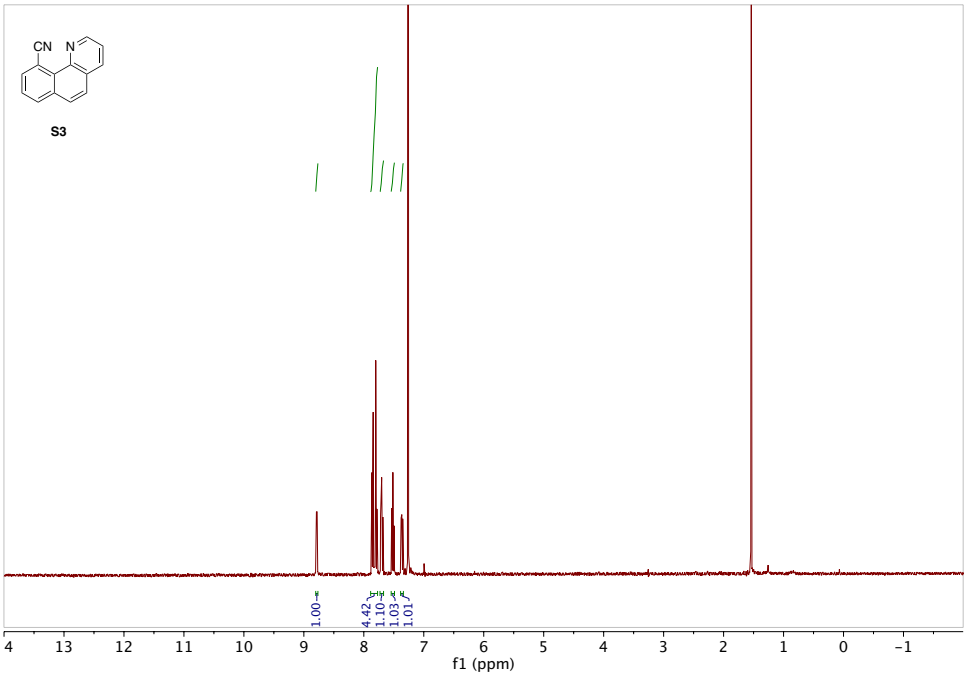
^{1}H NMR (400 MHz, $CDCl_3$, 298K)



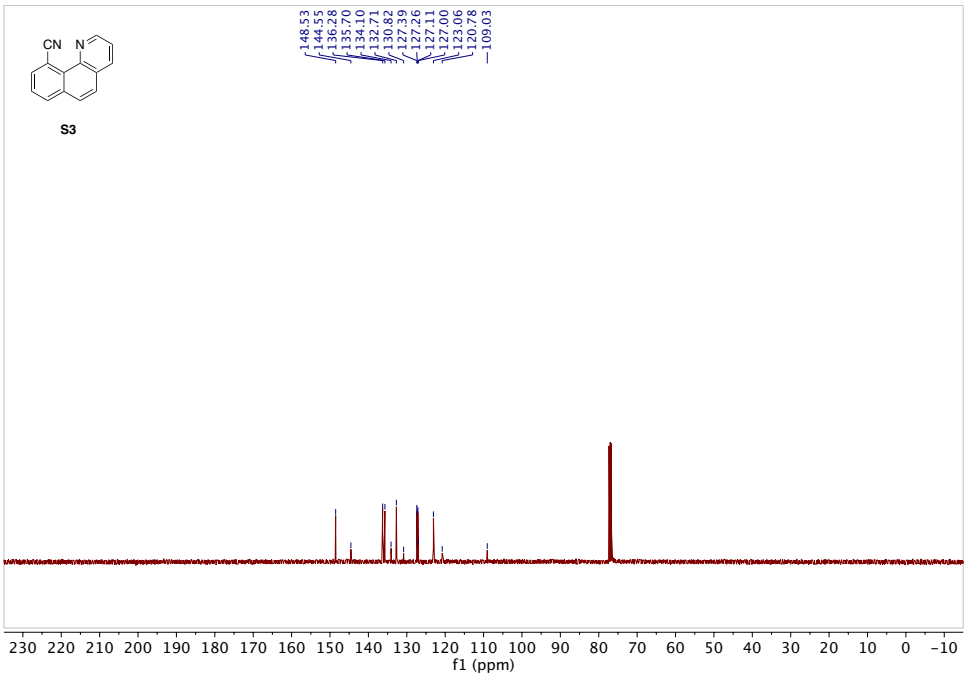
^{13}C NMR (100 MHz, $CDCl_3$, 298K)



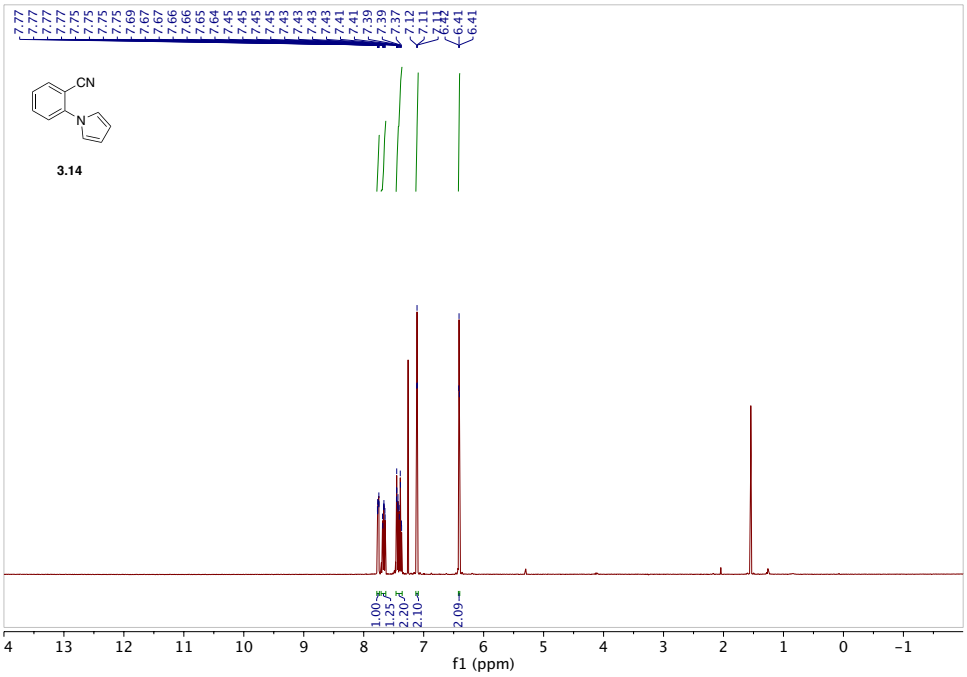
^{1}H NMR (400 MHz, $CDCl_3$, 298K)



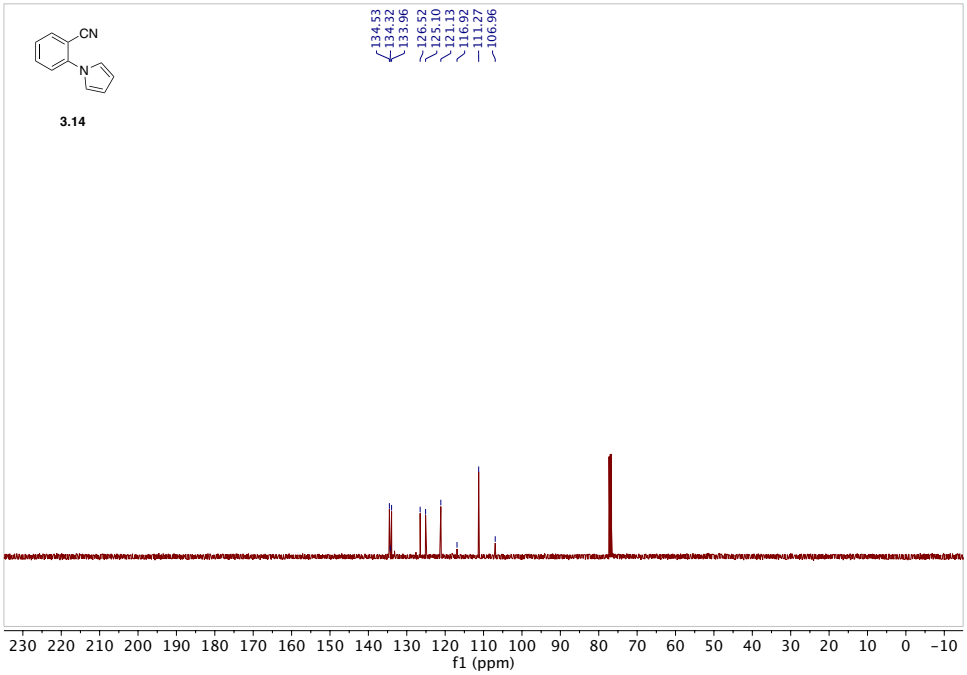
^{13}C NMR (100 MHz, CDCl3, 298K)



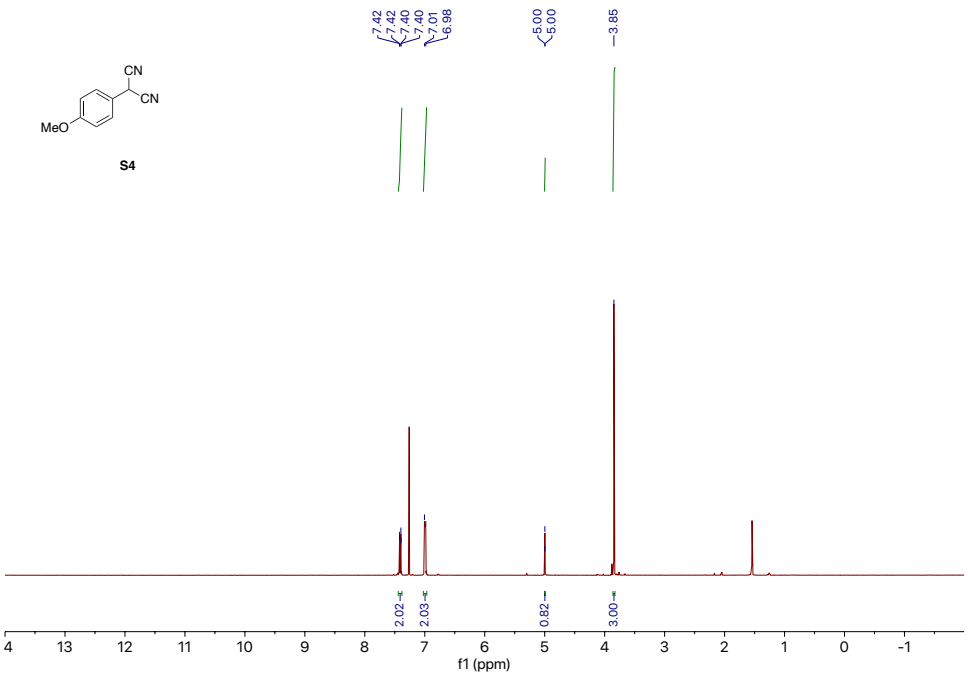
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



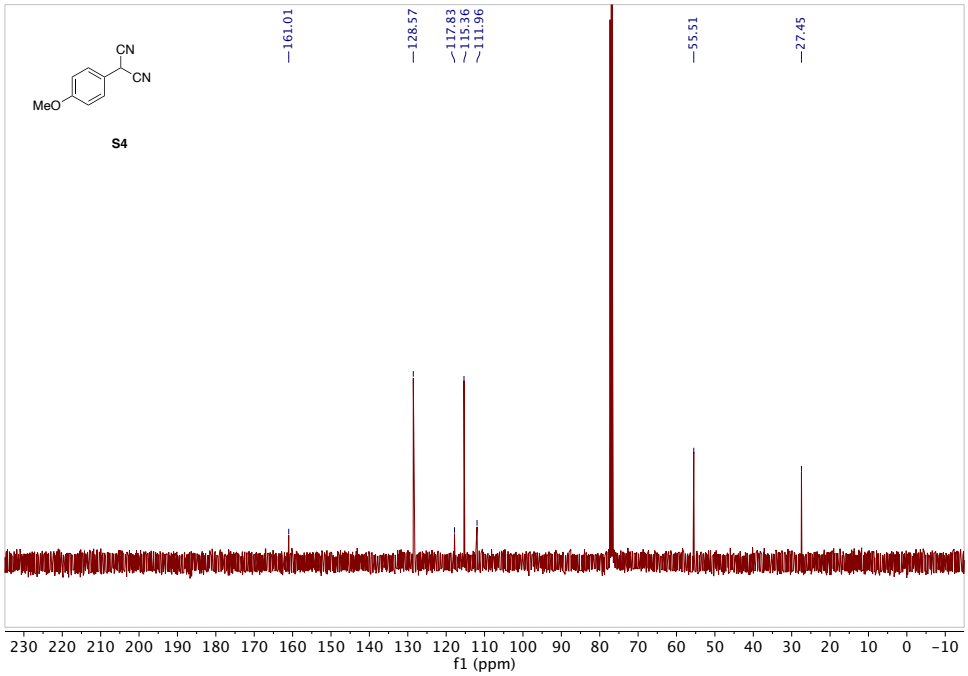
^{13}C NMR (100 MHz, $CDCl_3$, 298 K)



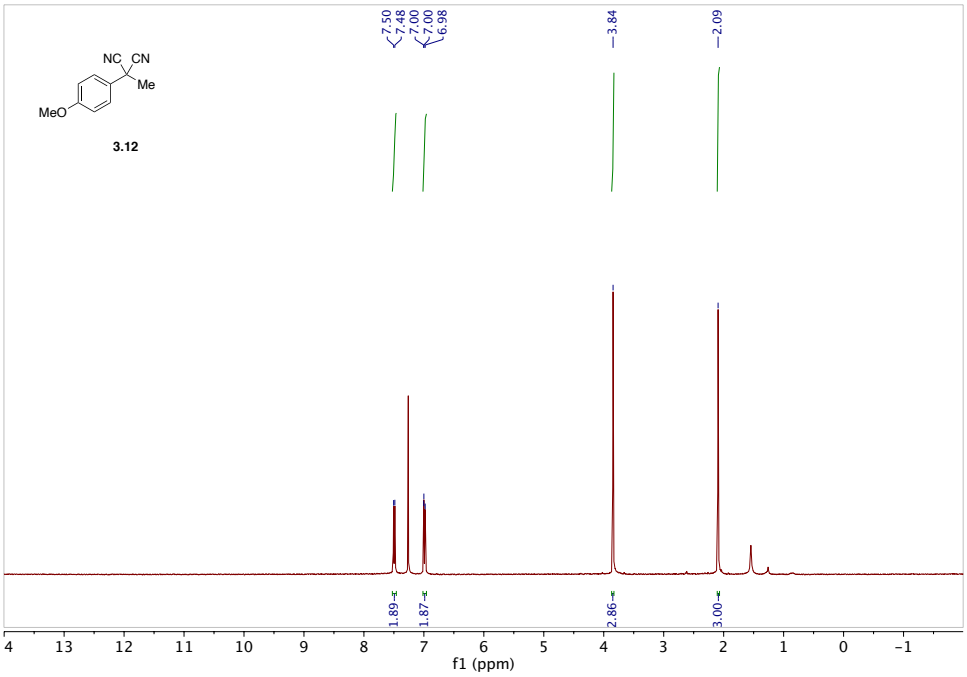
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



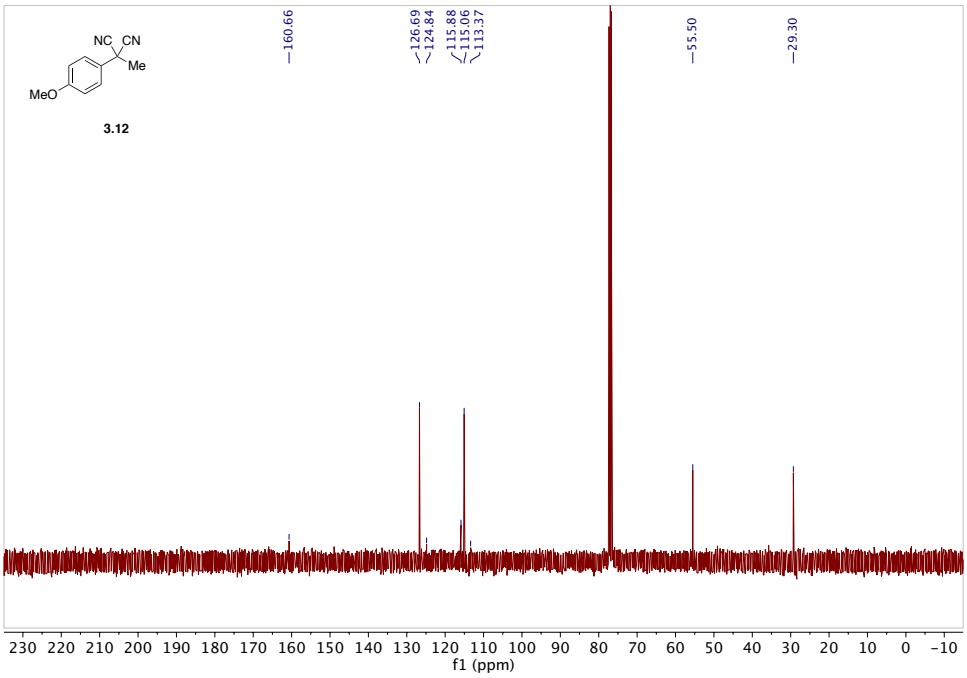
^{13}C NMR (100 MHz, $CDCl_3$, 298 K)



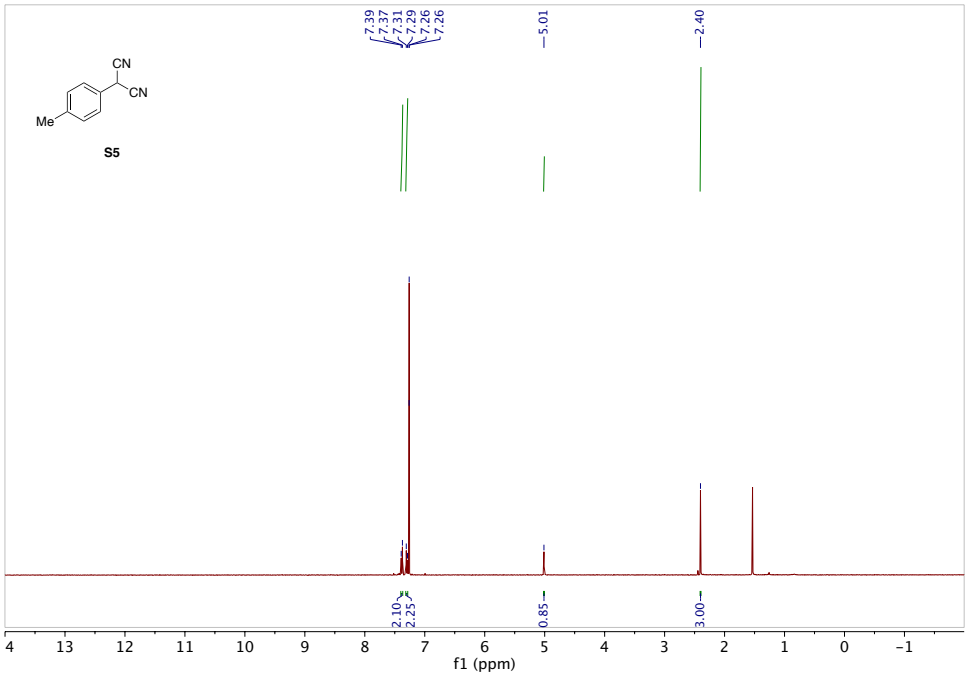
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



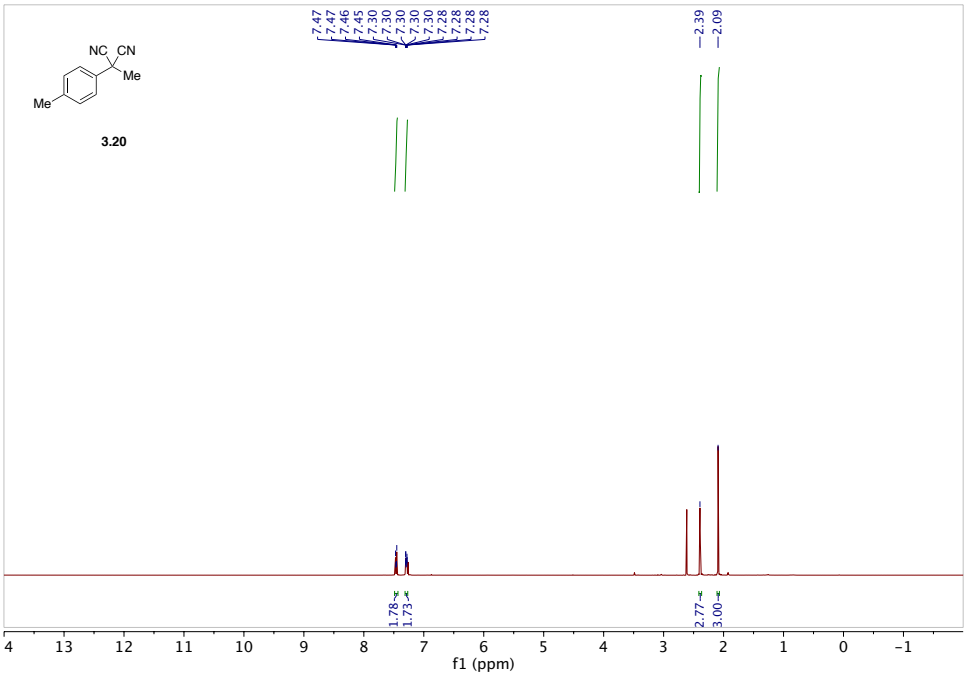
^{13}C NMR (100 MHz, $CDCl_3$, 298 K)



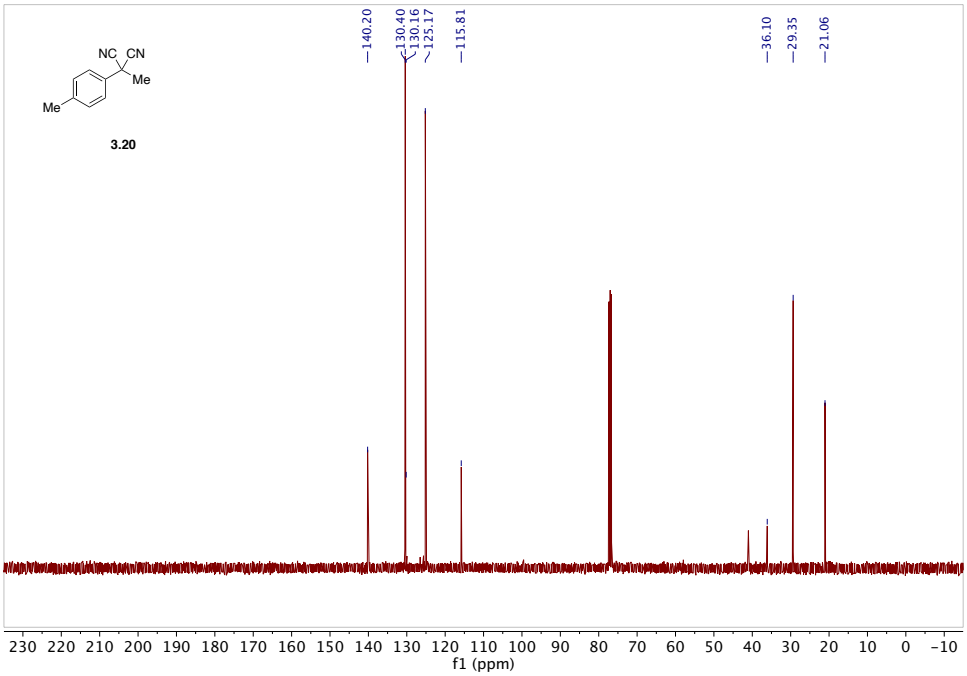
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



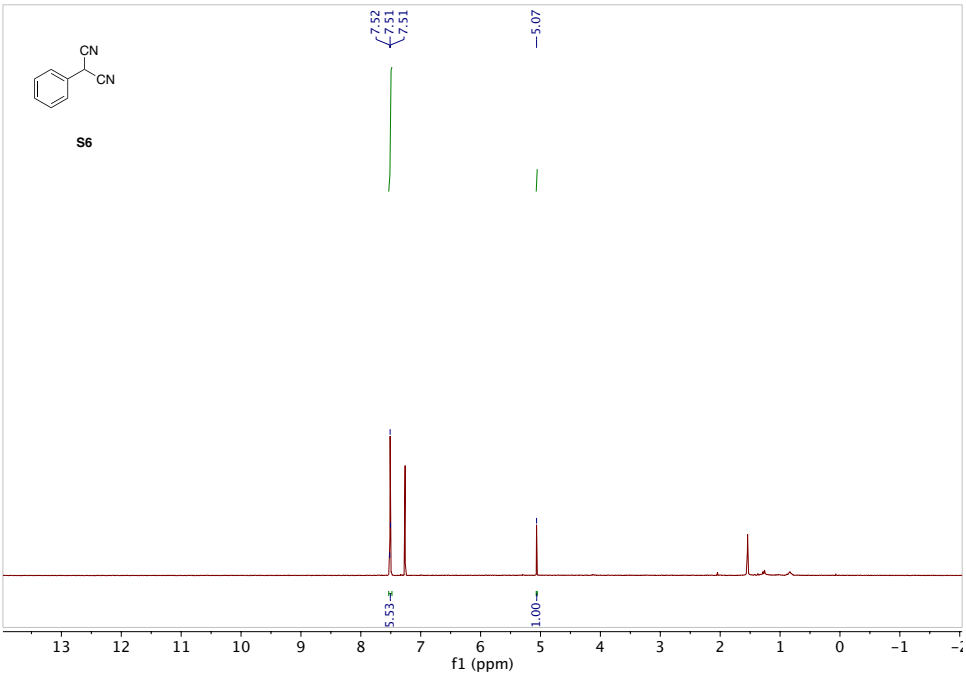
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



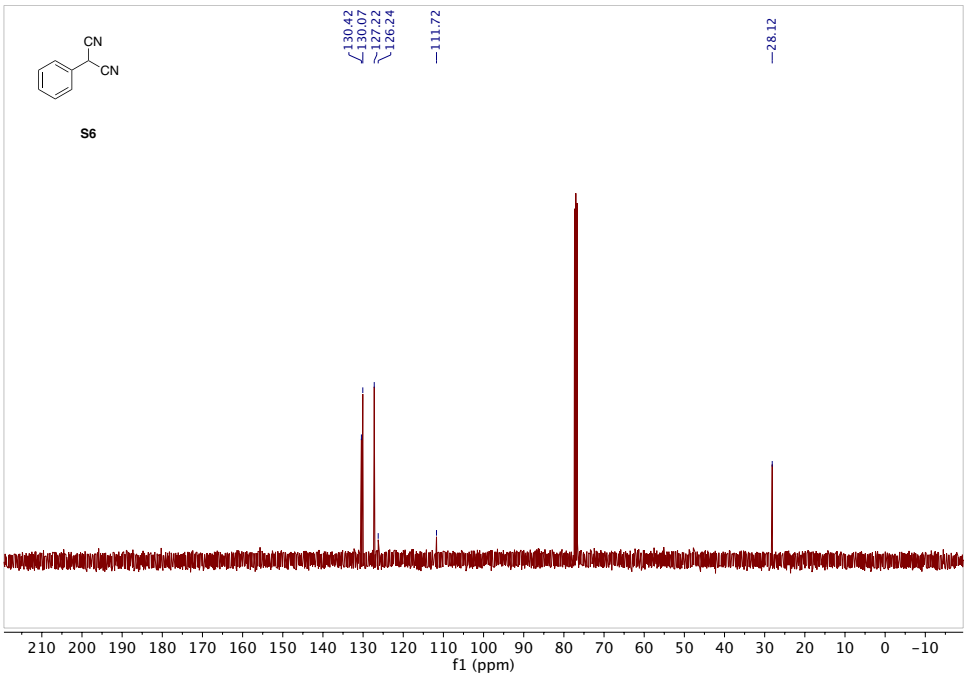
^{13}C NMR (100 MHz, $CDCl_3$, 298 K)



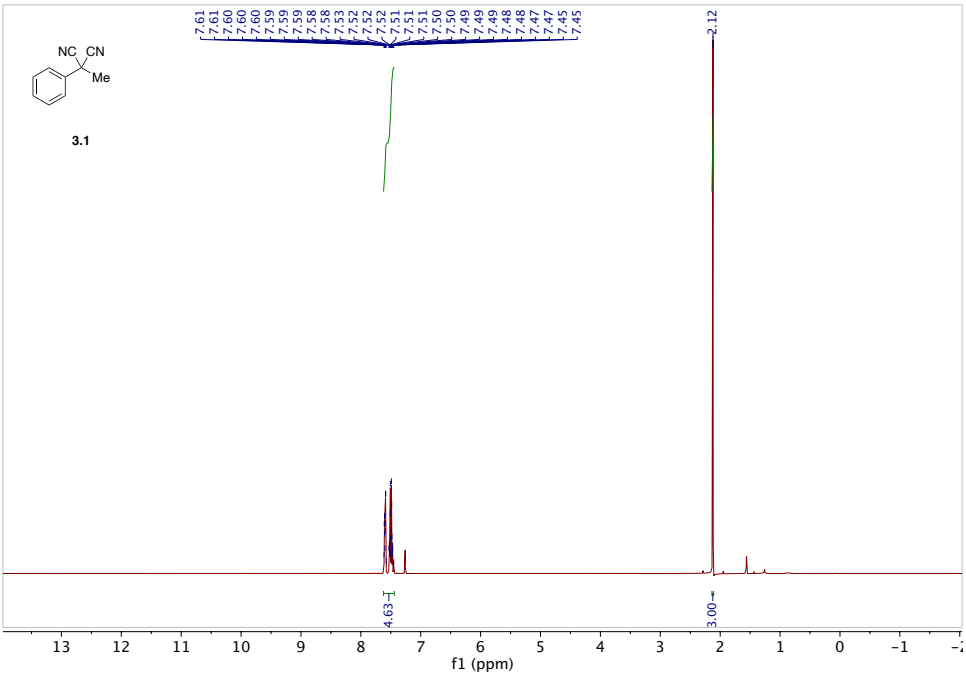
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



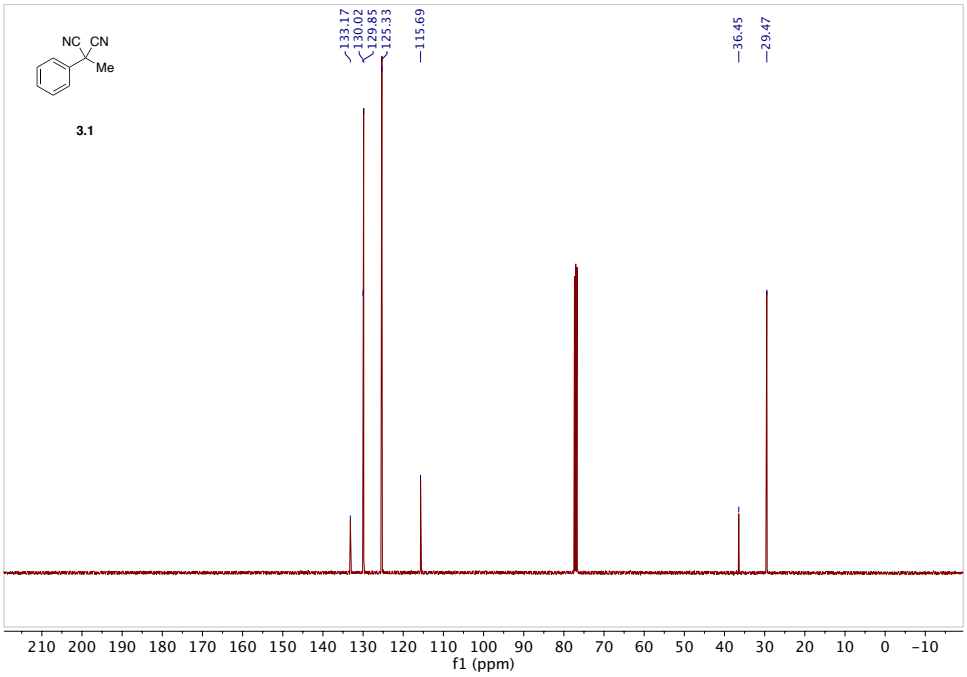
^{13}C NMR (100 MHz, $CDCl_3$, 298 K)



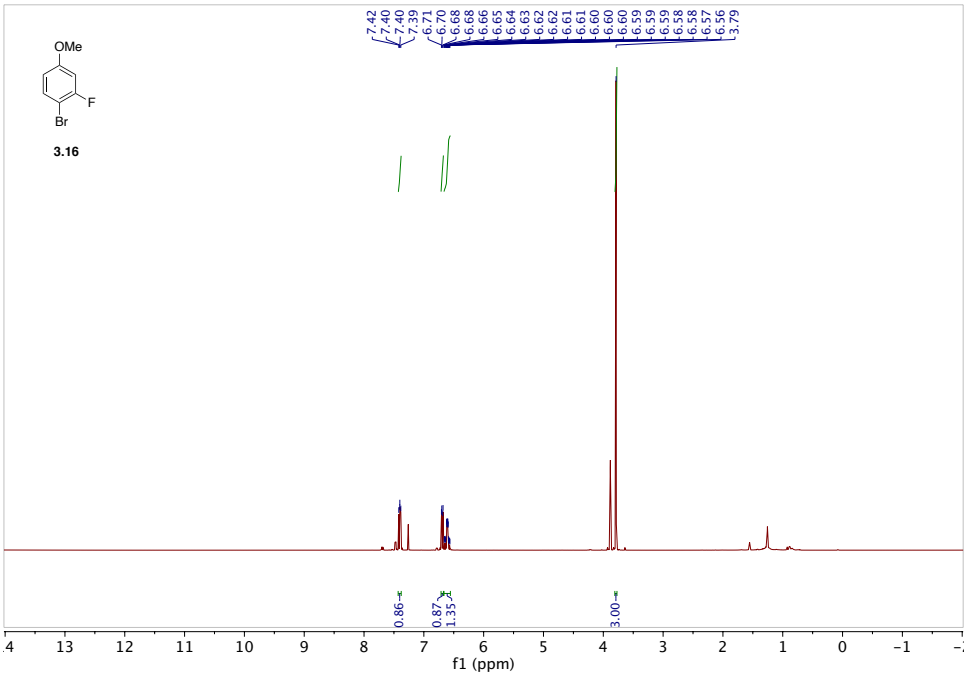
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



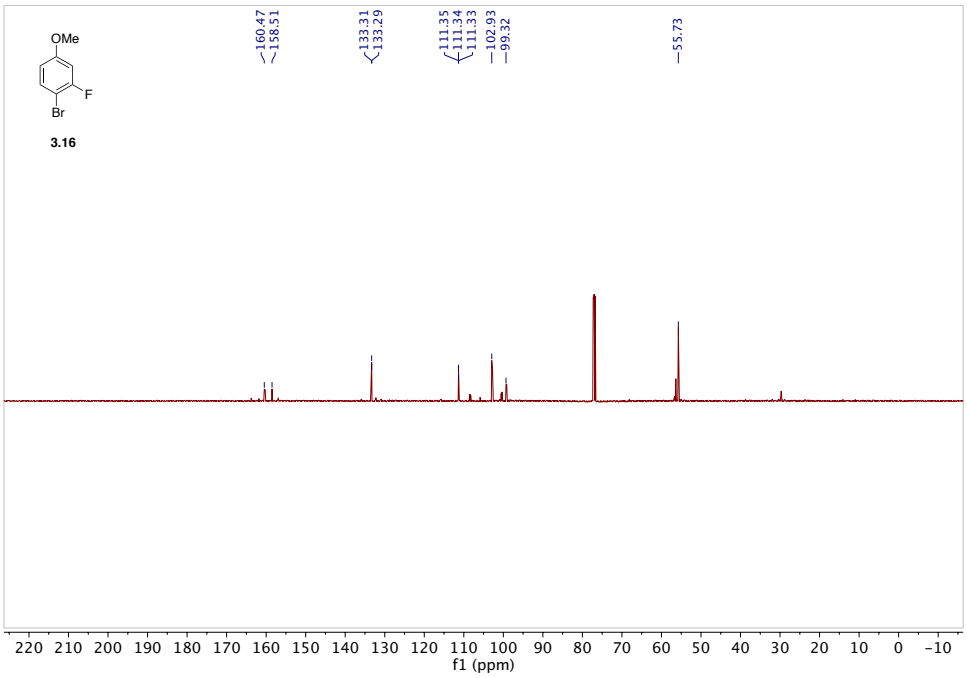
^{13}C NMR (100 MHz, $CDCl_3$, 298 K)



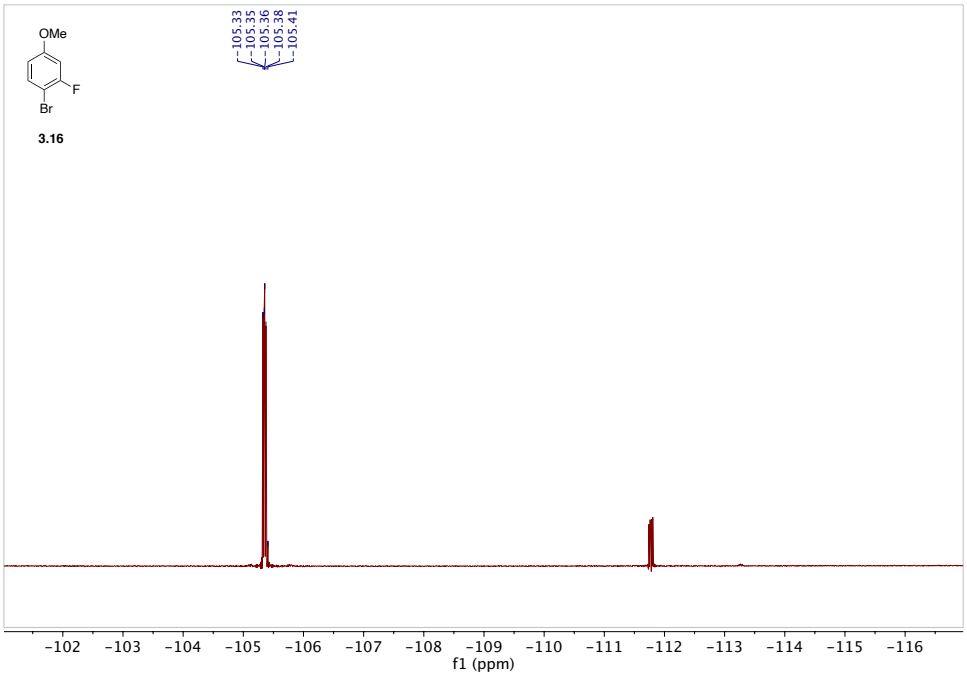
^{1}H NMR (500 MHz, $CDCl_3$, 298 K)



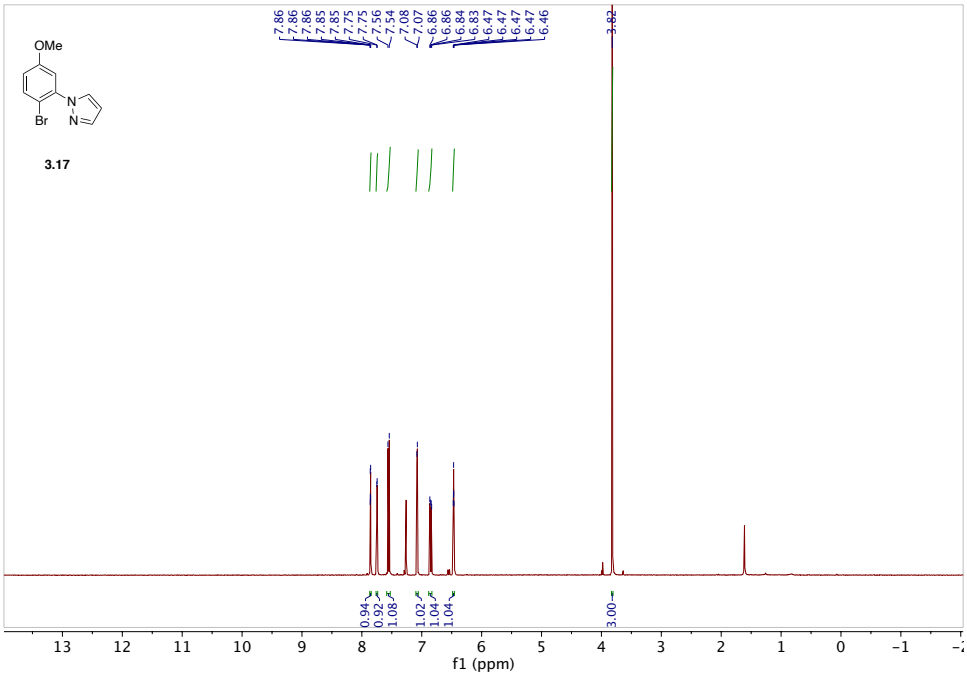
^{13}C NMR (126 MHz, $CDCl_3$, 298 K)



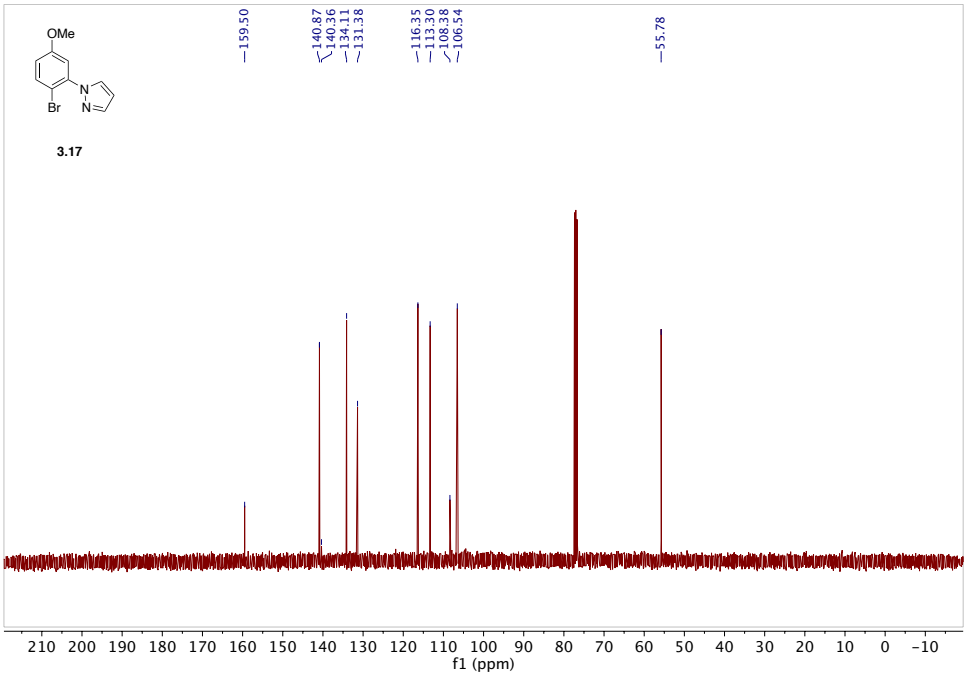
^{19}F NMR (375 MHz, $CDCl_3$, 298 K)



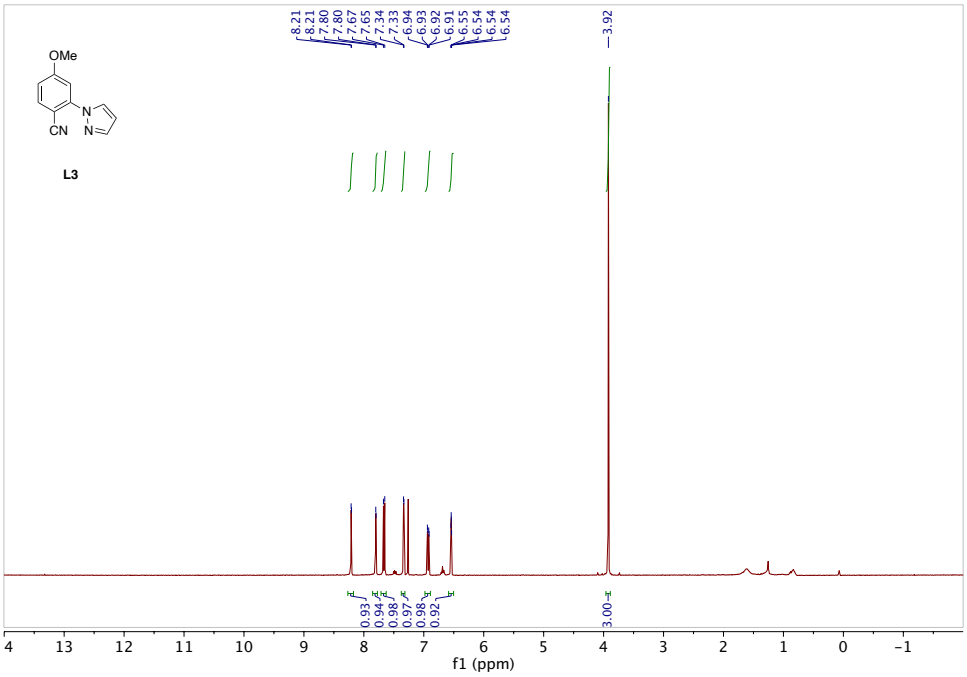
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



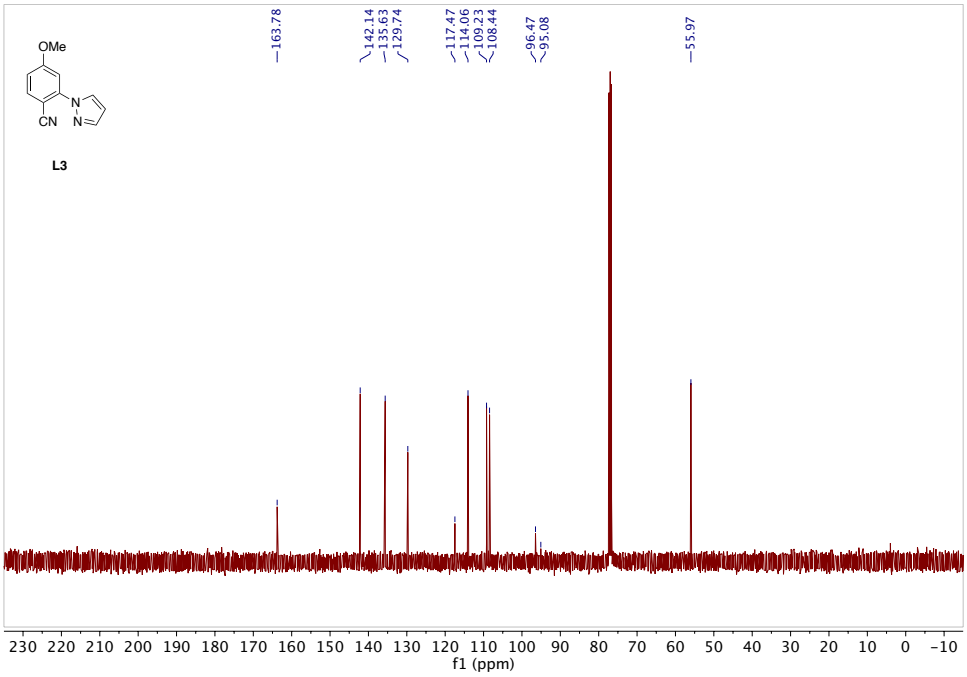
^{13}C NMR (100 MHz, $CDCl_3$, 298 K)



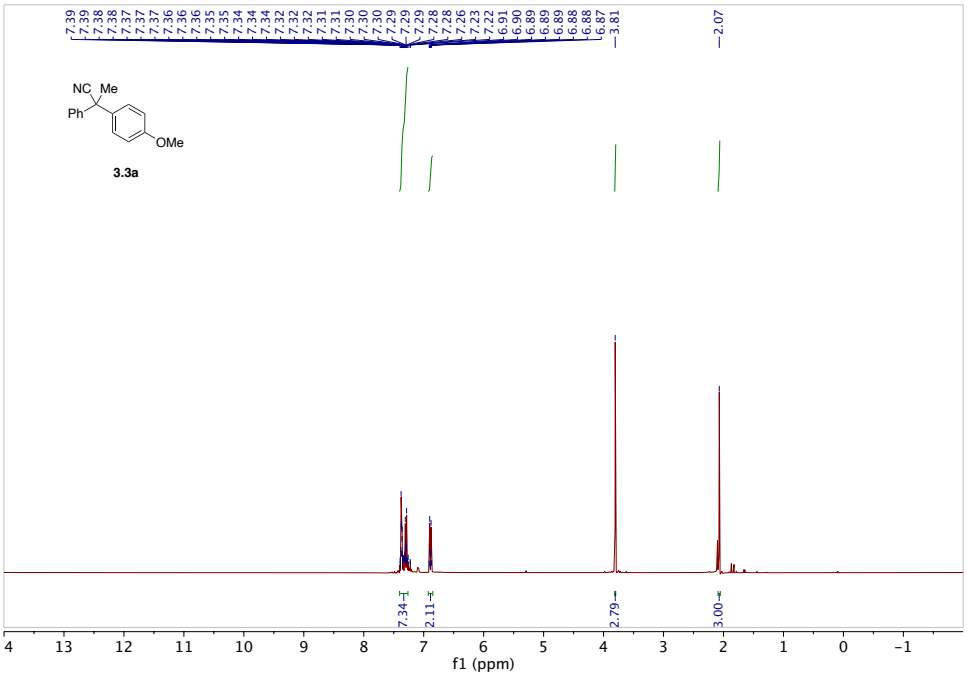
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



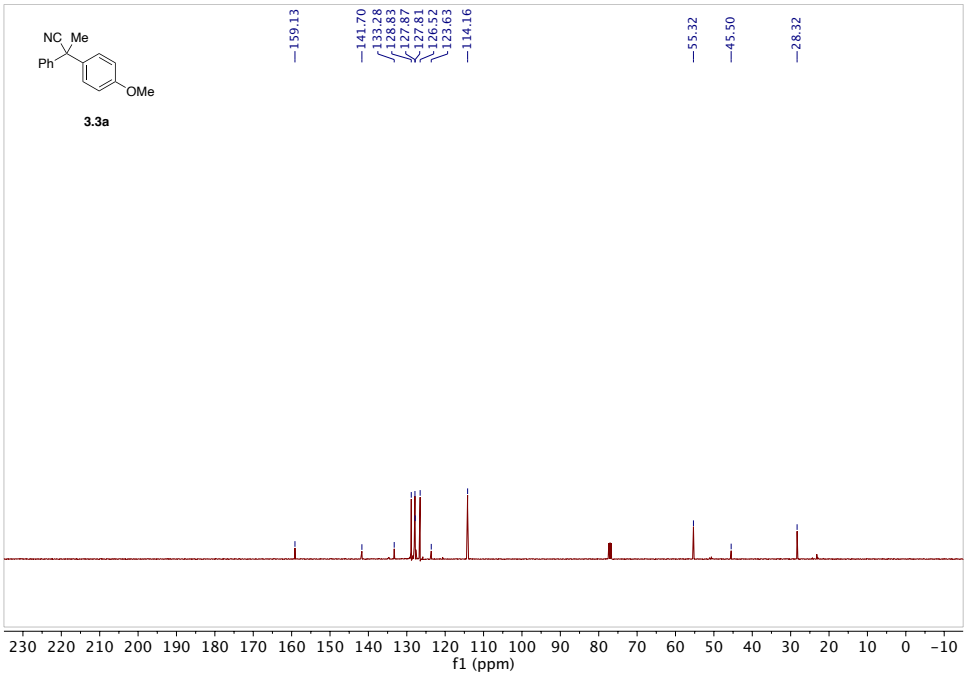
^{13}C NMR (100 MHz, $CDCl_3$, 298 K)



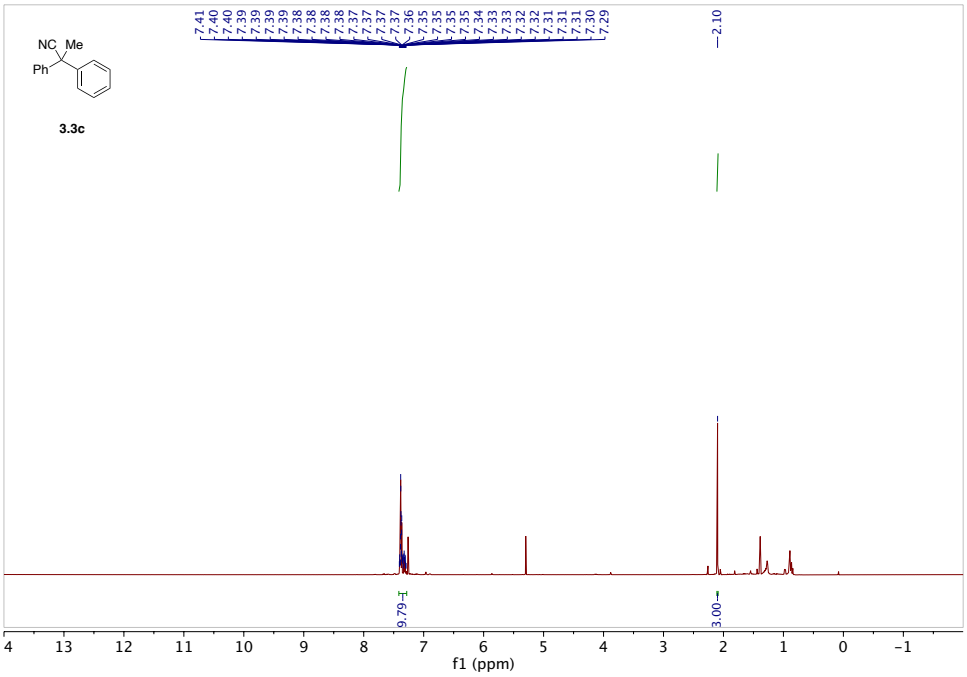
^{1}H NMR (400 MHz, $CDCl_3$, 298 K):



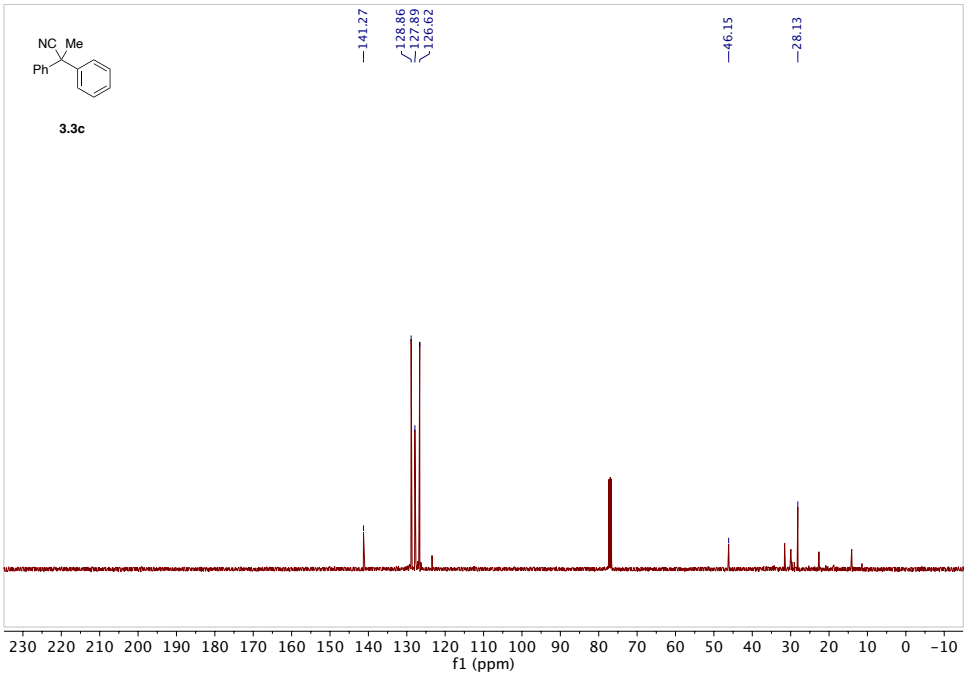
^{13}C NMR (100 MHz, $CDCl_3$, 298 K)



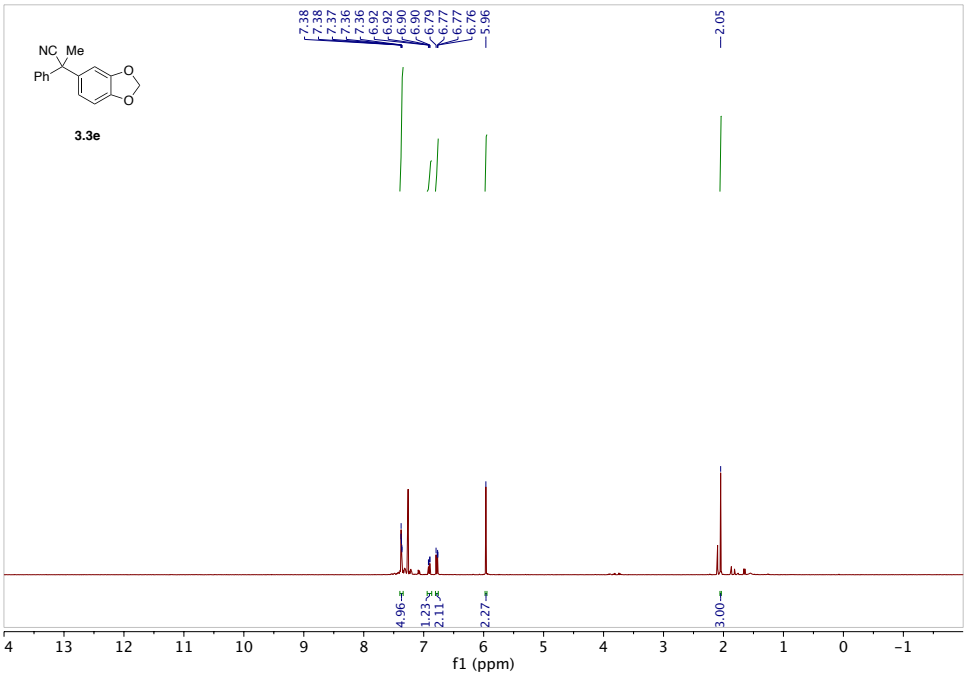
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



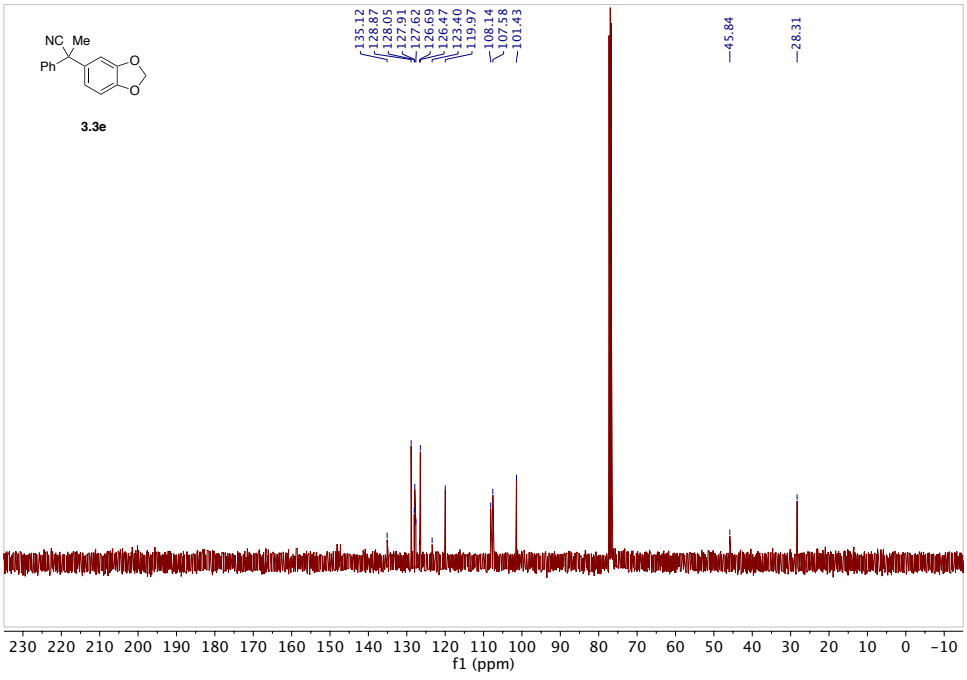
^{13}C NMR (100 MHz, $CDCl_3$, 298 K



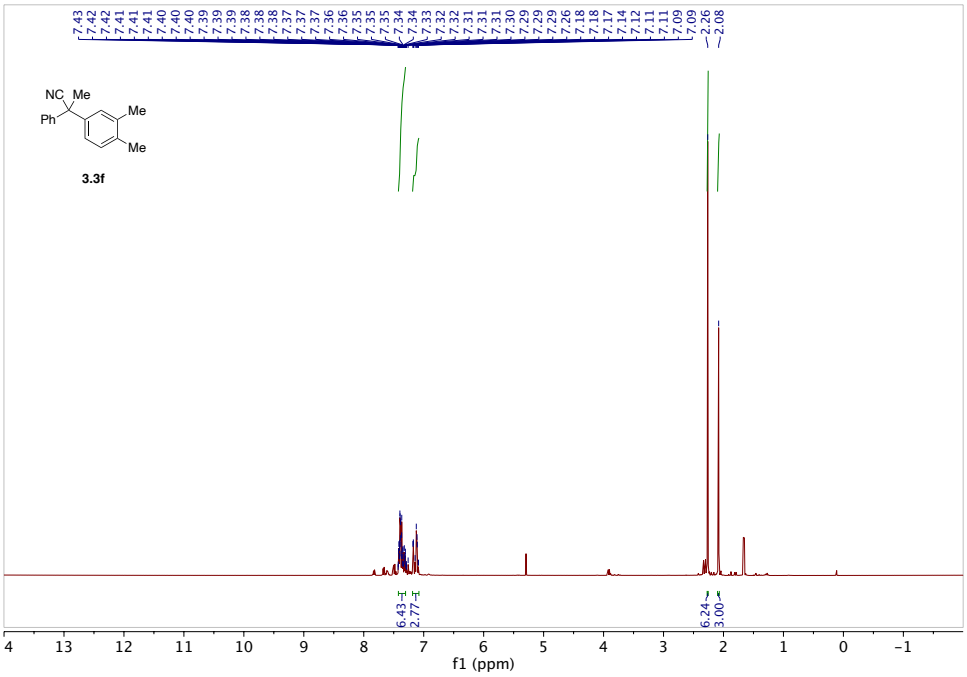
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



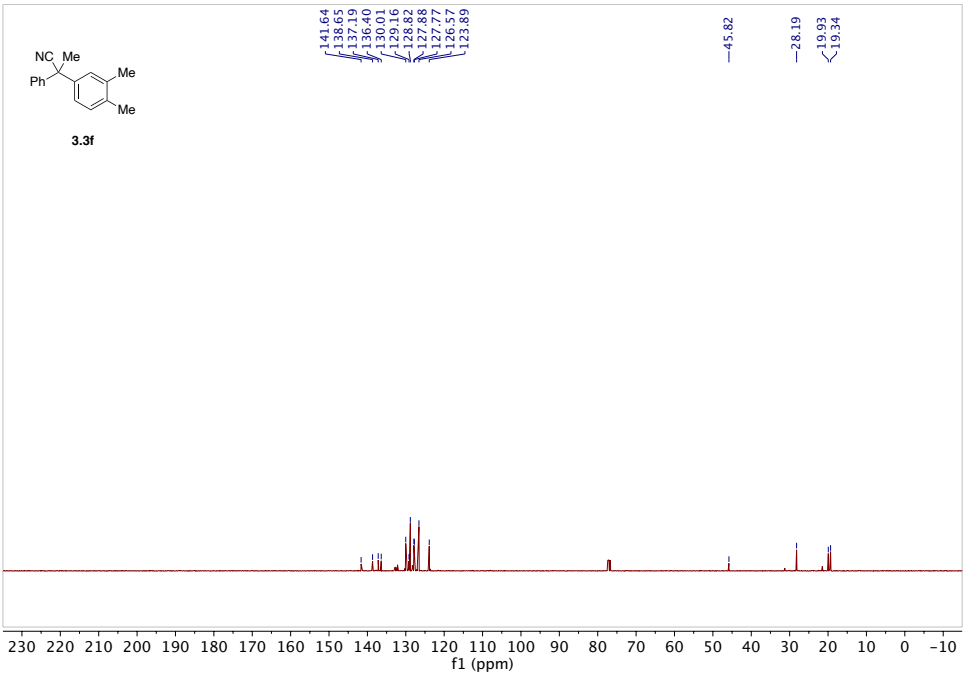
^{13}C NMR (100 MHz, $CDCl_3$, 298 K)



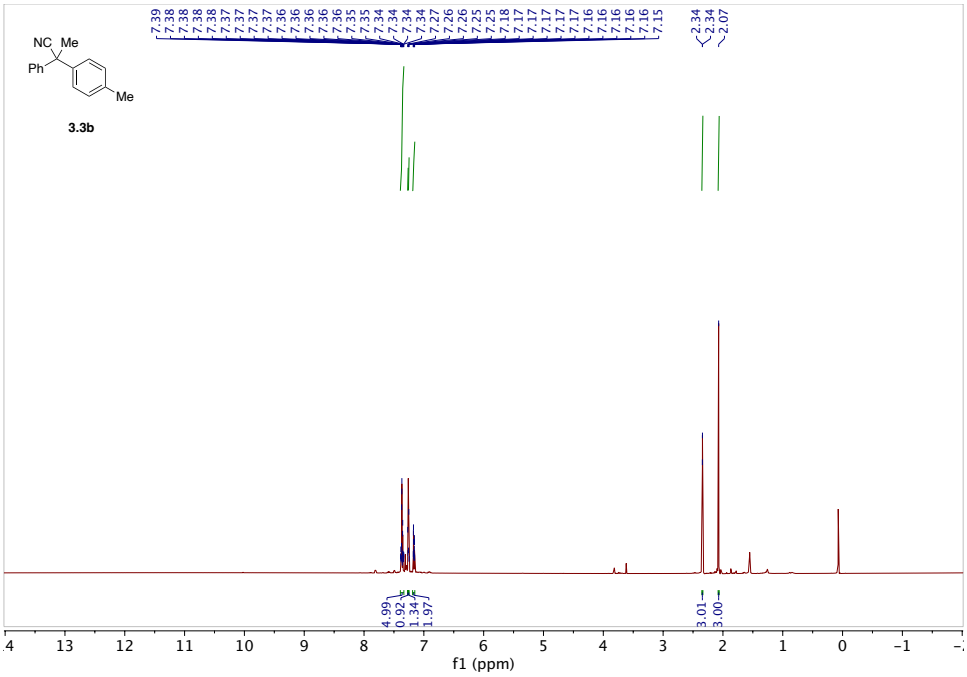
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



^{13}C NMR (100 MHz, $CDCl_3$, 298 K)



^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



^{13}C NMR (126 MHz, $CDCl_3$, 298 K)